DRUG USE REVIEWS

A Practical Strategy to Ensure the Rational Use of Anti-Tuberculosis Medicines

NOVEMBER
2014




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Drug Use Reviews—A Practical Strategy to Ensure the Rational Use of Anti-Tuberculosis Medicines

November 2014

This report is made possible by the generous support of the American people through the US Agency for International Development (USAID), under the terms of cooperative agreement number AID-OAA-A-11-00021. The contents are the responsibility of Management Sciences for Health and do not necessarily reflect the views of USAID or the United States Government.

About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

Recommended Citation

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SIAPS. 2014. *Drug Use Reviews—A Practical Strategy to Ensure the Appropriate Use of Anti-Tuberculosis Medicines.* Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health.

Key Words

Multidrug-resistant tuberculosis drug therapy; multidrug-resistant tuberculosis prevention and control, Anti-tubercular agent administration and dosage; drug use review; rational drug use.

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ABBREVIATIONS AND ACRONYMS

AMR	anti-microbial resistance
DOTS	core approach underpinning the Stop TB strategy for TB control
DR-TB	drug-resistant tuberculosis
DS-TB	drug susceptible tuberculosis
DST	drug susceptibility testing
DUR	drug use review
FDC	fixed-dose combination
HIV	human immunodeficiency virus
IV	intravenous
IM	intramuscular
MDR-TB	multidrug-resistant tuberculosis
M&E	monitoring and evaluation
MSH	Management Sciences for Health
NPV	National Pharmacovigilance Center
NTP	National Tuberculosis Program
NSAID	non-steroidal anti-inflammatory drug
OR	operations research
PPM	public-private mix
STG	standard treatment guidelines
TB	tuberculosis
XDR-TB	extensively drug resistant tuberculosis
WHO	World Health Organization

ACKNOWLEDGMENTS

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FOREWORD

This welcome publication brings together two themes in public health. The first is the problem of multiple drug-resistant tuberculosis (MDR-TB) and the second is the irrational and often irresponsible use of medicines to treat TB. One of the main reasons we face the global threat of MDR-TB has been the incorrect or inadequate treatment of drug sensitive TB. This has always been a difficult condition to treat but now with the long treatment regimens for MDR-TB, all health systems are challenged.

Drug utilization review (DUR) has existed for many years but has rarely been applied to the treatment of TB. Most TB programs have been rigid in their use of standard TB treatment guidelines. These may well still be appropriate for uncomplicated sensitive TB. But once a health system makes the choice to treat MDR-TB, DUR should become an essential element of the overall program.

This publication serves as an important resource for decision makers, program managers, and pharmacists who will be asked to manage these MDR-TB programs. The detailed four phase outline of how to conduct a DUR for MDR-TB programs provides a roadmap for action. In addition, the multiple annexes provides the needed pharmaceutical resources to make well informed decisions to guide the national or institutional programs.

Behind this publication are years of field work and experiences of multiple MSH country programs. The experiences distilled in these chapters are a resource for MDR-TB program managers to implement DUR as an integral part of any treatment program. In time I would hope to see the experiences gained with this manual extended to be used for national non-communicable diseases programs.

Finally I would like to encourage whoever uses this manual to report their results. Contact the authors at SIAPS but also publish in the TB journals, as well as the international pharmacy and health system journals. By documenting experiences, health workers, particularly pharmacists, can gain confidence to undertake DURs in differing circumstances.

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October 2014

HOW TO USE THIS RESOURCE

This document may seem intimidating, but you do not need to read it from cover to cover. It is divided into two sections, Methodolgy and Annexes.

The following features make the material accessible to readers looking for information in specific areas.

Methodology
This section lists and describes the various steps involved in implementing an Anti-TB Drug Use Review (DUR) Strategy in detail.

Annexes
Annexes provide a compendium of information to complement information provided in the methodology section.

Annex A. Published Criteria for Anti-Tuberculosis Treatment
Annex B. Sample Data Collection Forms
Annex C. Sample DUR Results Summary Report
Annex D. Sample Drug Use Review Activity Tracker
Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines
Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs
Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents
Annex H. Tyramine- and Histamine-Containing Foods
Annex I. Managing Drug Interactions with Antiretrovirals and Rifampicin
Annex J. Managing Drug Interactions with Antiretrovirals and Rifabutin
Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes

Electronic Editable Versions
The following documents can be opened with Microsoft Word and edited for your program specific drug use review

Methodology
Annex A. Published Criteria for Anti-Tuberculosis Treatment
Annex B. Sample Data Collection Forms
Annex C. Sample DUR Results Summary Report
Annex D. Sample Drug Use Review Activity Tracker

This resource is also available on http://siapsprogram.org/publication/dur-anti-tb-medicines/
We would be happy to hear from you. Please send comments to siaps@msh.org.

OVERVIEW

Drug use review (DUR)—sometimes referred to as drug use evaluation or medication use evaluation—is an **ongoing**, systematic process designed to maintain the appropriate and effective use of medications.

This manual is intended as to aid national tuberculosis program (NTP) managers, national pharmacovigilance center managers (NPV), tuberculosis (TB) service delivery providers, health care providers (physicians, pharmacists, nurses, public health officers and other health care professionals), academic institute staff, nongovernmental organizations, researchers, and any other staff working in organizations or individuals who are interested or involved in monitoring and improving medicine use to provide high quality treatment for susceptible tuberculosis (DS-TB) and particularly for drug-resistant tuberculosis (DR-TB).

The manual lists and describes the various steps involved to conduct a DUR. It also provides detailed drug information on World Health Organization's (WHO) recommended medicines for the treatment of DS-TB and (DR-TB. [1–4] Additionally, the manual provides criteria for reviewing medicines used for TB treatment and also some suggested performance benchmarks or targets for illustrative purposes. Generic data collection forms are also included for local adaptation and use.

Planning overambitious and extensive DURs can lead to challenges, delays, and frustration. During the initial periods of starting the DUR process, it is best to focus only on those few selected aspects of treatment or drug use that contribute to poor quality DR-TB treatment.

Treatment Factors Contributing to Poor Quality DR-TB Treatment

Inappropriate guidelines
Non-compliance with guidelines
Absence of guidelines
Poor training
Financial disincentives
Poor patient education
No monitoring of treatment
Poor management of adverse drug reactions
Poor treatment support
Poorly organized or funded TB control programs

Institutionalization of an on-going DUR strategy aims to be sustainable and to strengthen health systems. It supports the various building blocks of health systems through:

- Ensuring access to effective treatment for all forms of TB[5]
- Using systematic data collection procedures, both qualitative and quantitative, to accumulate evidence-supporting informed decision making
- Improving service delivery (effective, safe, cost-efficient) achieved as a result of review and improvement in practices

- Building operations research capacity for human resources involved in TB treatment as a result of their involvement in the design, implementation, interpretation and results dissemination from the DUR
- Improving information management systems as a result of generation, reporting, and use of TB medicine and treatment data
- Monitoring and evaluating effective risk prevention and management,[6] and pharmacovigilance systems
- Enhancing stewardship and governance as a result of audit and feedback, transparency in the patterns of drug use practice, and coordination and collaboration among the various TB stakeholders
- Using findings to advocate for financial and human resources

Parts of these guidelines are based on a previous work by Management Sciences for Health (MSH) entitled *Guidelines for Implementing Drug Utilization Review Programs in Hospitals*.[7] They have been reworked to focus on principles and content expressly for anti-TB drug use reviews.

Most of the recommendations provided in this manual are generic, describe general principles, and provide a comprehensive, step-by-step explanation of:

1. Developing context specific DUR criteria according to best available evidence
2. Collecting and analyzing existing available data
3. Providing feedback and taking action based on DUR findings when indicated
4. Reviewing the DUR strategy to identify opportunities for program improvement to provide high quality treatment

These guidelines are intended to be modified according to national or regional specific regulations and treatment practices so they can be used by national TB control programs and their administrative divisions.

Although multiple aspects of drug use and criteria for review are given in the annexes of this manual, implementers need to identify which of these are most critical, relevant, and feasible in their local contexts.

As the involved stakeholders gain experience and as the process matures, the methodology described here could be further adapted and then applied to ancillary medicines used to manage adverse drug reactions of DR-TB treatment, TB/HIV co-infected patients, patients with other co-morbidities (e.g., diabetes), and new drugs developed, approved, and introduced to treat DR-TB.

BACKGROUND

The Problem of Drug Resistance in Tuberculosis

TB continues to remain one of the biggest problems of global public health. A critical challenge to scaling up TB care and control is to prevent the emergence of antimicrobial resistance (AMR) and to ensure that every person with TB has access to an accurate diagnosis, effective treatment, and a cure.[8] AMR is a rapidly growing global problem that contributes to the burden of infectious diseases and diabetes, and TB is disproportionately affected with widespread occurrence of multidrug-resistant TB (MDR-TB) and, more recently, extensively drug-resistant TB (XDR-TB). In most countries with a high burden of MDR-TB, less than 25% of the people estimated to have MDR-TB were detected in 2012; of the estimated 450,000 people who developed MDR-TB, there were an estimated 170,000 deaths.[9] Treatment for MDR-TB is 50 to 200 times more expensive than DS-TB and requires a much longer treatment period than DS-TB;[3] also, cure rates are much lower. Additionally, the reserve drugs used for resistant cases are often less potent and more toxic. Several countries also have high rates of TB and human immunodeficiency virus (HIV) co-infection, which further complicates care, treatment, and outcomes.

From the perspective of the US Centers for Disease Control and Prevention's Global Disease Detection Operations Center, XDR-TB is one of the top five global infectious disease threats.[10] When XDR-TB develops, it becomes extremely difficult to treat and is associated with very high mortality rates. In South Africa, for example, an outbreak of XDR-TB killed 52 of 53 patients co-infected with tuberculosis and HIV in a rural area within a few weeks.[11] At least one case of extensively drug-resistant TB (XDR-TB) had been reported by 92 countries by the end of 2012.[9] Some countries (India,[12] Iran,[13] and Italy[14]) have even reported cases resistant to all anti-TB drugs tested and are described by new (not defined by WHO) terms like "extremely drug resistant" (XXDR-TB), "super XDR-TB," and "totally drug-resistant TB" (TDR-TB).

In 2001, the threat of AMR led to the establishment of the WHO Global Strategy on AMR.[15] Recently a resolution from the 2014 World Health Assembly detailed ten actions member states must take to combat AMR.[16] As outlined in the policy package, health providers and administrators must regulate and promote the rational medicines use. The 1985 Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya, established the following definition of rational use, "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community." The rational use of antibiotics/AMR has attracted world-wide attention and was selected as the topic of World Health Day in 2011.[17]

Problems with Anti-Tuberculosis Medicine Use

Irrational medicine use is a key driver for developing drug-resistant infections, including DR-TB. Every year, nearly three million people affected by TB are neither diagnosed nor treated according to international guidelines.[18] It is estimated that 450,000 new cases of MDR-TB emerge annually due to inadequate treatment and subsequent transmission of resistant organisms.[19] It is likely that only a minority of MDR-TB cases which occur in the world are treated according to WHO guidelines.

In addition to non-standard diagnosis and treatment of TB, treatment outcomes are compromised and contribute to the emergence and transmission of drug resistance[2] through—

- Unregulated availability of over-the-counter anti-TB drugs in the private sector
- Drug shortages in health facilities
- Lack of strategies to ensure patient adherence to treatment
- Drug quality assurance issues
- Inadequate laboratory support
- Poor infection control practices
- Inadequate human and financial resources at health facilities
- Patient's inability to pay for medicines

Many of these issues occur because of service inefficiencies stemming from weak infrastructure and health systems.

WHO international TB treatment guidelines provide NTPs and medical professionals with standardized, up-to-date, evidence-based recommendations on how to manage TB.[20] While many countries have adopted these guidelines, issues with inappropriate TB treatment persist. Inappropriate treatment regimens are those in which the treatment duration is too short or the regimen contains too few drugs, doses of regimen medicines are inadequate or contain incorrect drug combinations. Similarly, treatment regimens that are too long and contain an excessive medicine dose or too many drugs are also considered inappropriate. Anti-TB drugs must be prescribed and used appropriately to preserve their effectiveness, prevent the development of drug resistance, and minimize unnecessary adverse drug reactions to patients.[21]

A key impediment to the rational use of anti-TB drugs is the generally insufficient level of knowledge of TB guidelines among health care workers in various settings, particularly for DR-TB treatment. A systematic review of 31 studies from 14 countries assessed the knowledge of appropriate TB treatment regimens among public and private sector health care workers.[20] Most of the health care workers surveyed had insufficient knowledge of treatment dosages and reported prescribing too many drugs for a too long duration of therapy. These findings suggest that the lack of knowledge about standard treatment guidelines among health care workers would be associated with prescribing inappropriate treatment regimens. In fact, these studies are consistent with other studies measuring actual prescribing practices of primary care doctors. In one study from India, 45.2% of primary care doctors made prescription errors related to treatment regimen, 64.5% made errors related to treatment duration, and 30% made errors related to dosage.[22] A second study from Pakistan found that only 3.7% of prescriptions (N = 53) were written in accordance with national TB treatment guidelines.[23] Further, a systematic review of 37 studies from most continents found that inappropriate treatment regimens were prescribed in 67% of studies, and between 0.4% and 100% of patients received inappropriate TB treatment regimens.[21,24]

There is strong evidence to support the claim that incomplete or inadequate treatment can lead to the development of MDR-TB.[25,26] A review of two high quality studies concluded that receiving inappropriate treatment regimens increased the risk of developing MDR-TB 27-fold.[21,24] With the advent of new drugs to treat TB, it is crucial to encourage the monitoring of drug use.

While TB therapy requires good compliance, the onset of adverse drug reactions carries important implications for patient adherence. At least 70% of patients being treated for DR-TB report adverse drug reactions during therapy.[27,28] Adverse drug reactions are associated with treatment loss to follow-up.[29] For cases of TB/HIV co-infection, treatment regimens are particularly challenging due to serious drug interactions and a greater risk of adverse drug reactions—as many as 86% of patients on concurrent MDR-TB/HIV treatment may develop adverse drug reactions.[30] The most effective way to reverse this alarming statistic is to thoroughly train TB health care professionals on how to recognize and properly manage TB.[29] Close, timely monitoring and management of adverse drug reactions and drug interactions is crucial to recognizing issues as soon as they surface. If problems are not recognized in time, they can lead to treatment loss to follow-up or compromise a patient's life.[31]

The development of new drugs requires special focus on optimal drug combinations and rational use to treat all forms of TB.[32] For example, fluoroquinolones as well as several highly promising new drugs in the pipeline may become important components of future TB treatment regimens. With an increased need to develop new anti-TB drugs, as well as with those already in the pipeline, it is critical that health care providers receive comprehensive training on the rational use of old and new anti-TB drugs. It is also critical that policy makers put approaches and systems in place for close monitoring of the use of these new drugs. Active pharmacovigilance is recommended by WHO when new drugs (e.g., bedaquiline) and novel regimens (e.g., shorter MDR-TB regimen) are introduced.[33–35] In the absence of effective mechanisms to monitor and correct for inappropriate use, adverse drug reactions, and drug interactions, such precious new anti-TB drugs may soon become useless because of resistance.

More information is needed on prescribing practices in the private sector, where facilities operate in a largely unregulated manner.[36] In some resource-limited countries, a large proportion of TB patients get treated in the private sectors. Based on evidence of inconsistent and incomplete treatment regimens, studies show that private practitioners seldom comply with standard treatment guidelines.[21] This is worrisome in a country like India, where 86% of patients sought treatment at a private facility, and private practitioners prescribed excessive doses.[36]

To respond to this problem, WHO and The Stop TB Partnership strongly recommend a public-private mix (PPM) to support the core approach underpinning the Stop TB strategy for TB control that is known as DOTS. Treating patients with DOTS calls for direct observation of patients receiving medicines and limiting the length of treatment to a short-time period. implementation, which links the private sector to public sector treatment and notification recommendations.[36] Several countries have shown that effective PPM increases TB case notifications and treatment success rates.[37] The key is to involve all stakeholder groups, but such inclusiveness does not always occur. While PPM is useful, most countries have yet to establish effective PPMs, and of those who have, only a small fraction of private providers have been engaged. It is thus crucial to enhance and mobilize this PPM platform to monitor for inappropriate use of TB medicines in both public and the private sectors.

TB is one of the top 10 causes of death among children around the world;[38] however, pediatric TB has received little attention on a global and national scale. WHO estimates that the annual global burden of TB in children (under the age of 15) in 2012 was approximately 530,000 cases (or 6% of global TB burden), and that up to 74,000 children died from TB that year.[9] Treatment recommendations for children with TB need to be improved considerably. Current treatment regimens are lengthy and involve a mix of at least three to four different tablets that are difficult for children to swallow. Lack of suitable pediatric formulations represents a major gap area in the management of TB in children. While some liquid formulations do exist and are easier to

administer, they are often expensive.[38] Though backed by policies and scientific evidence, there has been slow progress to revise and make available fixed-dose combinations (FDC) for children. WHO revised recommendations for dosages of first-line anti-TB drugs in children in 2010; however, currently available FDCs are incompatible with these revised recommendations.[39] In the context of these new dose recommendations by WHO, in addition to other formulation and FDC-related challenges, the use of anti-TB drugs in children in various local settings should be monitored closely.

Drug Use Review of Anti-Tuberculosis Medicines

The facts and figures above indicate that TB treatment still has significant problems and that irrational prescribing and use of TB medicines is common. Establishing a system to monitor TB drug use and drug resistance is a key measure for promoting internationally recognized treatment and care guidelines.[40]

A Drug Use Review is a quality assurance intervention that, in a step-by-step manner, identifies and remedies problems related to drug use by collecting, analyzing, and interpreting data through organized, ongoing, systematic, and criteria-based reviews.

It is a well-proven intervention[41] that supports the monitoring, evaluation, and improvement of medicine use.

DURs serve as a continuous quality improvement[42] approach that leads to incremental improvements through an iterative or cyclical review process.

Implementing DURs can help policy-makers and program managers devise better TB control program planning and implementation strategies. When a problem is identified, the timely dissemination of results to TB care providers and administrators, coupled with the implementation of an improvement plan, should detect and minimize irrational drug use, adverse drug reactions, harmful drug interactions, and drug resistance; improve treatment outcomes; and in some cases reduce total treatment costs. Implementing a DUR strategy for pediatric TB is also aligned with key actions set out in the WHO Stop TB Strategy.[43] Monitoring drug use will improve detection, diagnosis, and management of TB in children. DURs of dosing aspects of pediatric TB medicine use will be able to identify the extent of dosing inappropriateness that still persists following WHO revisions to FDC dosing guidelines.[39]

Rational use of TB treatment and successful outcomes largely depend on the ability of a physician and other health care providers to:

- Accurately diagnose the type of TB (drug-susceptible or drug-resistant)
- Select the correct drug regimen, dosage forms, and routes of administration
- Foresee probable adverse drug reactions and drug interactions
- Prevent unnecessary or incomplete therapy
- Perform close clinical follow-up of patients during treatment

These steps need to be followed within the context of standard treatment guidelines and peer-reviewed medical literature.

Successful treatment outcomes depend on the performance of the pharmacy and nursing departments' ability to prepare and administer drugs, and the capacity of the entire TB care team to ensure patient adherence to the prescribed treatment regimen. These performance standards are the basis for establishing criteria to select for review, and the indicators measure whether the standard has or has not been achieved.

Selected key indicators (e.g., percentage of new smear-positive patients with pulmonary TB who were prescribed correct drugs in correct dosages with correct duration, based on the standard treatment guidelines) should be developed and included in TB program monitoring and evaluation plan.[44]

HOW TO IMPLEMENT A DRUG USE REVIEW STRATEGY

The process of a DUR strategy is laid out in four phases: plan the DUR strategy, conduct the DUR, implement the improvement plan, and assess effectiveness of the intervention strategy. Listed below are the steps involved in each phase. The phases and steps are also presented graphically in Figure 1. Each of these steps is described in detail in the subsequent sections of the manual.

Phase 1. Plan the DUR Strategy

Step 1. Establish responsibility for the DUR process
Step 2. Develop procedures
Step 3. Define all services where anti-TB drugs are used
Step 4. Orient TB staff to the process
Step 5. Prepare data collection forms
Step 6. Orient data collectors

Phase 2. Conduct the DUR

Step 7. Collect data
Step 8. Tabulate data
Step 9. Interpret data

Phase 3. Implement an Improvement Plan

Step 10. Make recommendations for improvement
Step 11. Disseminate results and discuss the improvement plan
Step 12. Implement the improvement plan

Phase 4. Assess Effectiveness of the Strategy

Step 13. Conduct a follow-up DUR
Step 14. Review and discuss follow-up data
Step 15. Evaluate the strategy
Step 16. Plan and implement the next cycle

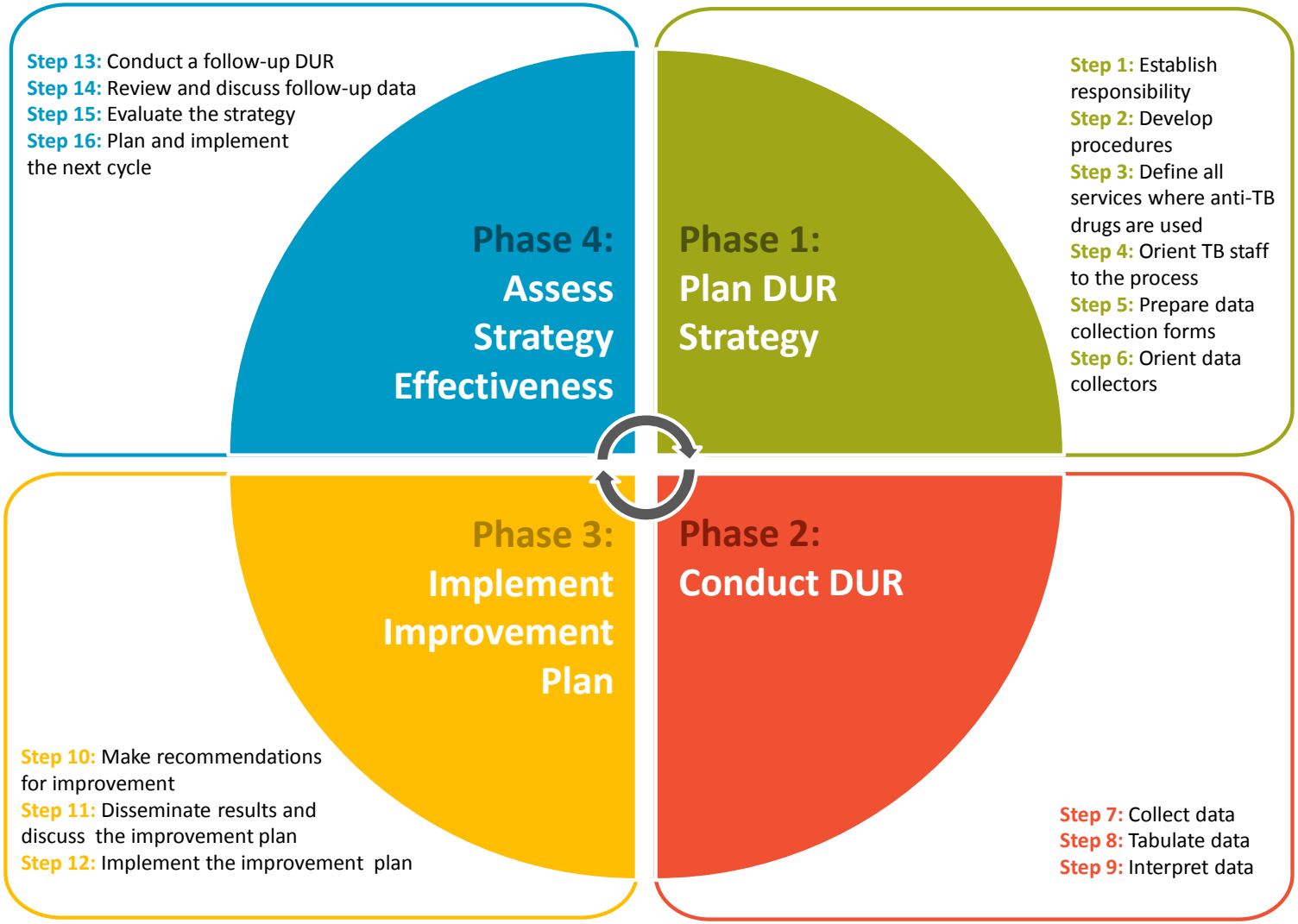


Figure 1. Phases and Steps for Implementing a Drug Use Review Strategy

Phase 1. Plan the DUR Strategy

During the planning phase, decisions are made about what needs to be done, and who does what, when, and where. The following six steps will help to plan for a successful strategy.

Step 1. Establish Responsibility for the DUR Process

DURs are primarily a medical staff function, with pharmacists and nurses providing expertise. In most countries, national tuberculosis programs (NTPs) are responsible for implementation of standard treatment guidelines (STGs) for TB to ensure rational medicine use for TB and DR-TB treatment and national pharmacovigilance centers (NPV) are responsible for patient safety. Therefore, NTPs in collaboration with NPVs are in the best position to lead anti-TB DUR activities.

DUR strategies can be executed by forming a DUR committee or working group within the NTP and NPV at the national level or at a regional or facility level depending on feasibility, motivation, workload, and available expertise. Whether a DUR committee is formed at the national, regional, or sub-regional level, the committee will assume a supervisory role and visit public and private TB treatment facilities where the reviews would be conducted in a participatory manner.

In some settings, a Drug and Therapeutics Committee (DTC) or a DUR sub-committee at TB hospitals or at general hospitals with TB wards can take responsibility for DUR activities at these facilities. However, their work must be communicated to the NTP and NPV, so they can then take these results and experience to improve and strengthen efforts in program advocacy, quality improvement, and expansion at the national level.

Regardless of its structure, the body responsible for DURs should be composed of professionals with an interest in improving drug therapy at treatment facilities, and have ready access to experts and other resources to facilitate the DUR initiative. The committee may require input from a variety of TB and other medical specialists in this step. Pharmacists should be included as full integral members of the committee.

The DUR Committee is responsible for the initial establishment of DUR procedures, and the planning and implementation of all DUR activities. Data collection may or may not be the direct responsibility of the committee members. However, the committee would need to ensure that data collectors are qualified and adequately oriented.

The most important tasks of the DUR Committee are:

- Set the objectives or purpose of the DUR
- Define the cohort to evaluate (e.g., DR-TB patients, pediatric TB patients)
- Select the medicines or regimens to evaluate
- Develop or select criteria and thresholds for evaluation
- Oversee the implementation of interventions (if needed)
- Measure TB program improvement
- Ensure the DUR activity remains an ongoing, systematic process designed to maintain the appropriate and effective use of medications for treating TB and DR-TB

Step 2. Develop Procedures

Prior to conducting the DUR, the NTP or DUR committee should draft and approve procedures that will govern its work. Inclusion of a clear statement of the goals and major activities of the committee is important because dissemination of the procedures may be used as a means of educating medical personnel about the strategy.

Designation as a "Process"

The DUR procedures should specify that DUR is a **continuous** process**.** It is not a one-off project. Formal approval of the process by the NTP or through an institutional approval process is recommended so that health care providers whose practices are under review understand that the institute is committed to ensuring safe and effective drug use, and the review is not intended as a punitive activity that takes place on an ad hoc basis after problems are identified.

Mission Statement and Goals

Below are a sample mission statement and a typical list of objectives of a DUR Committee. Any NTP or treatment facility (if DUR is conducted by selected treatment facility) should discuss and arrive at its own mission statement and goals, and determine the types of activities that are needed or possible in its own setting.

"The mission of the Drug Use Review (DUR) Committee is to enhance quality of patient care by assuring appropriate drug therapy, optimal patient treatment, and education for health care providers through the development and maintenance of a systematic, ongoing, criteria-based review."

Listed below are examples of DUR Committee goals[45] along with ideas for discussion when defining the purpose of the review.

- Promote optimal medication therapy according to the national treatment guidelines
  - What are the key issues with following the treatment guidelines?
  - What percentage of cases have DST performed according to the guidelines?
  - Are patients receiving the correct regimen, at the correct dose, administered at the correct frequency, for the correct duration (both intensive phase and continuation phase), and are they switching to the continuation phase according to the guidelines?

- Evaluate the effectiveness and safety (pharmacovigilance) of medication therapy
  - What is the loss to follow-up rate for DR-TB patients and why?
  - What is the treatment success rate for DR-TB patients and why?
  - How can the DUR find reasons for loss to follow-up?
  - How can DUR identify unmet needs to address treatment success rate?

- Evaluate the safety (pharmacovigilance) of medication therapy
  - Are adverse drug reactions properly recorded, reported?
  - Are anticipated adverse drug reactions properly managed?
  - Are trends in adverse drug reaction incidents identified and addressed?

- Prevent errors and minimize adverse effects to patients associated with medication therapy
  - Are patients receiving baseline and follow-up evaluations according to the STGs?
  - Are adverse events being managed according to the STGs?
  - Are patients receiving adequate counseling about their medications and managing adverse drug reactions?

- Establish interdisciplinary consensus on medication use processes
  - Who is in the TB treatment working group?
  - Are prescribers, pharmacists, nurses, laboratorians, audiologists, psychologists, administrators, and patients involved in the process?

- Stimulate improvements in medication-use processes
  - Once unmet needs are identified, who is responsible for deciding on the interventions needed and ensuring they are implemented?

- Stimulate standardization in medication-use processes
  - Who is responsible for maintaining, updating, distributing, and training on the STGs?

- Minimize procedural variations that contribute to suboptimal outcomes of medication use
  - Who is responsible for standardizing procedures (e.g., laboratory testing, record keeping) across treatment facilities?

- Identify areas in which further information and education for health care providers may be needed
  - Do all treatment facilities have a copy of the new guidelines?
  - Has key staff been trained on the guidelines?
  - Once unmet needs are identified, who is responsible for providing information and education?

- Meet or exceed internal and external quality standards
  - Are there monitoring and evaluation mechanisms in place?
  - Are there opportunities to exceed quality standards?

Committee Makeup

The makeup of the committee should be defined. Depending on the scope of the NTP, its organizational structure and feasibility the DUR committee can be organized within the NTP. In some cases, DUR committees can be organized at TB facilities. Normally, a DUR committee consists of authoritative representatives responsible for drug use in the treatment of adult and pediatric TB patients, TB specialists, pharmacists, nursing, and patient safety specialists.

Other key stakeholders involved in TB control (e.g., medicine regulatory authorities; pharmacovigilance centers; institutions; people affected by TB; TB control managers in penitentiary systems; and academic, research, and training representatives) may be invited to participate in developing criteria, data evaluation, and designing and implementing interventions.

Committee members can be flexible in sharing these duties among themselves.

The following table summarizes the composition of a DUR committee by position, role, estimated level of effort, and possible affiliation(s).

Table 1. Sample Composition of a DUR Committee

Position	Role	Estimated Level of Effort	Organization
Focal Person(s) TB health care providers	• Coordinate committee activities • Provide leadership on DUR guidelines, procedures, and objectives • Develop or select criteria and thresholds for monitoring and evaluation then implementing interventions	One to three days per month	NTP – one or two representatives Usually a TB specialist is chair and a pharmacist is secretary for the committee.
Advisors, nongovernmental organizations (NGO), faith- based organizations (FBO), and other stakeholders	• Provide technical assistance to the committee during implementation • Support country ownership to adopt the system	One day per month	NGO FBO Stakeholders
Biostatistician	• Consult with the Committee on statistical requirements for DUR activities • Prepare statistical data for analysis and inclusion in reports	One day per month and five days after data collection	MOH, Academic Institute, or NPV
Clinical pharmacist	• Consult with the committee on medication safety and appropriate medication use • Maintain drug information current in the guidelines	One to three days per month	NPV National TB Center
Health care provider Expert working group	• Consult with the committee on DUR objectives • Consult with the committee on criteria and thresholds for monitoring and evaluation • Assist the focal person(s) with guidelines and procedures	One day per month	A prescriber, pharmacist, and nurse from TB hospitals, clinics, or community providers
Ad hoc working group members	• Consult the committee on specific improvement efforts	Variable	Varies, depending on expertise required

Frequency of Meetings

The frequency of meetings will largely depend on the scope of the strategy, which is determined by the available resources and clinical need. The schedule should minimally include a yearly planning meeting; and meetings for selecting, revising, and approving criteria; interpreting data; designing interventions; and reviewing the strategy. Initially, monthly meetings may be necessary to discuss start-up problems and make corrections in the process. Later, quarterly or semi-annual meetings may be sufficient.

Work-planning and budgeting

Planning and conducting a DUR is demanding and time consuming. However, it is a powerful tool to improve quality of care and to achieve the best possible outcomes.

The DUR should be a combination of Operations Research (OR) and Monitoring and Evaluation (M&E). OR comprises one-off studies with a defined start and an end and can be conducted periodically (e.g., quarterly or annually). The monitoring element of M&E is generally a continuous process of collecting and analyzing routine data whereas the evaluation element is periodic and takes a longer and more holistic view.

Process Cycle

A DUR cycle should include the following major activities:

- Planning (including selection of drugs to be targeted through the DUR, their criteria and thresholds)
- Implementation (data collection and interpretation)
- Interventions
- Evaluation

A yearly cycle is strongly recommended.

Conducting DURs annually allows the DUR Committee to identify trends and assess the impact of interventions for the use of anti-TB drugs over time.

The DUR should have its own strategic plan (e.g., five years) and should be part of the national TB, OR, and M&E strategic plans. In addition, an annual operational plan should be prepared. The strategic and operational plans should include resource (budget) requirements estimates and should show the expected sources of funds (e.g., donors, MOH). The plans should use a standard format—a sample with a few suggestions is provided in Table 2.

NTPs that manage program data using electronic systems with data quality assurance processes in place[48] may be able to obtain data for DURs from data regularly collected electronically. Advantages of using an electronic-based system over a paper-based system include:

- Data quality is assured because of data-entry edit checks that prevent the input of invalid or incomplete data
- Cost efficiencies are generated by regularly collecting DUR data electronically
- The time to retrieve the data is much shorter

Table 2. DUR planning, costing and financing framework

Goal and activities	Respon-sible	Frequency	Data source	Length of time	Resource needs	Cost	Funding source
Improve effectiveness and safety of medication therapy	NTP manager						NTP
Determine loss to follow-up		Every six months	TB Information System	1 week	3 days of M&E Officer	No extra cost	
Determine treatment success rate			TB Information System				WHO
Identify reasons for loss to follow-up			OR Interviews				WHO
Identify reasons for treatment success rate			OR Interviews				
Plan improvement of loss to follow-up			Discussion				
Plan improvement of treatment success rate			Discussion				

Each activity in the strategic and operational plans should be analyzed for resource requirements. This includes estimates of supplies, travel, and the time needed by employees and required for technical assistance (see Table 3). In the strategic plans these should be broken out by year. After the time demands have been quantified, it will be important to conduct a feasibility check to see if staff will actually have to time available to do the work.

If funding is not sufficient, the activities may have to be reduced and prioritization will be important. One example of prioritizing could be reducing an analysis from twice a year to once a year. Once the planed activities are in line with the available funding, the plan and budget are complete.

Table 3. Illustrative Examples of Budget Items for a Drug Use Review Strategy[1]

DUR Costs	Implementation or Strategy Costs	Institutional Costs
• Personnel including all staff, data collectors, data managers, statisticians, etc., as well as consultants who could provide short-term technical support • Supplies and materials including printing of data collection instruments, notepads, pens, etc. • Equipment such as computers, printers, cell phones and airtime. • Travel and transportation • Per diems or travel allowances • Dissemination costs including renting halls for seminars or attending conferences	• Job aids for health care providers • Training programs for implementers • Commodities needed for intervention which are not already being provided by the existing program (e.g., electrocardiogram and audiology equipment, laboratory commodities) which are not already being provided by the existing program	Overhead costs or basic operating costs ranging from electricity to support staff. Most institutes have a standard overhead charge as operating costs are difficult to itemize directly.

[1] Adapted from The Framework for Operations and Implementation Research in Health and Disease Control Programs[47]

Financing for a DUR should be provided primarily by government and supplemented by donors where necessary. Some costs, such as staffing and shared equipment, will be covered by the routine government budget, others can fit in the TB program's M&E or OR budgets. Specific donors can fund other costs, preferably under a multi-year agreement.

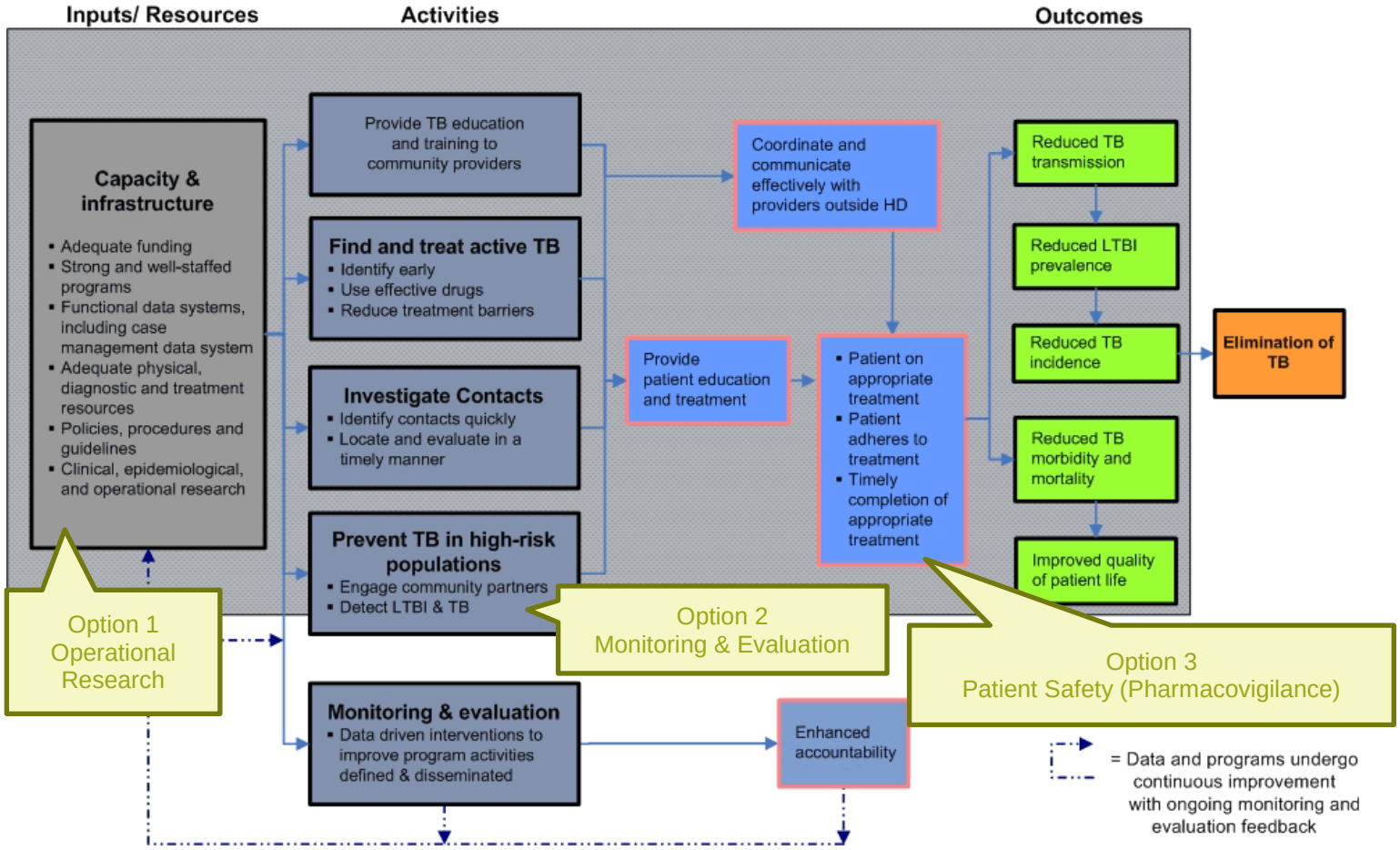
Evidence-based advocacy will be important to show the achieved benefits of the DUR—for costs and benefits, examples would be cure rates or treatment cost savings.

Across the public sector, the average amount budgeted for M&E is around 5%. Programs are encouraged by agencies such as the Global Fund to Fight AIDS, Tuberculosis and Malaria to spend 5 to 10% of their grant budgets on M&E, which could include spending on relevant OR.[46] As any research such as a DUR that produces practical useful knowledge (evidence, findings, information) that can improve program implementation (effectiveness, efficiency, safety, quality, access, scale-up, sustainability) regardless of the type of research (design, methodology, approach) falls within the boundaries of OR[47] , then it follows that funding for DUR activities can fall within the M&E budget.

Operations research is crucial to building the evidence base that allows new tools to be introduced in program settings, as well as to improve current strategies and optimize existing tools. Based on financial data reported to WHO by 32 low- and 67 middle-income countries, the estimated proportion of operational research in total national TB program expenditures (funding received) was about 1% in 2009 and 2010.[43]

Figure 2 shows three options where a DUR strategy could fit into an NTP's TB elimination plan.

Figure 2. Where can a DUR strategy fit into your TB Elimination Plan—three options for discussion[2]



[2] Adapted from the US Centers for Disease Control.[53]

Step 3. Elements of Drug Use Reviews

Drug use must be measured to be assessed. Measuring drug use can be divided into the three components criteria, indicators, and performance thresholds, which are described in detail below.

Criteria

Criteria are predetermined measureable aspects of drug prescribing and use. The DUR committee determines whether guidelines are being followed in actual practice. Three aspects of criteria for appropriate drug use are justification for use, process (or method of use), and outcome.

Justification for use. This is the drug's indication or the standard condition under which the medicine is being evaluated should be prescribed. The indication for all TB treatment medicines in this document should be consistent with on the WHO case definitions based on drug resistance.[19] Persons responsible for establishing the criteria may choose to revise the indication definition based on national standard treatment guidelines.

Process (or method of use). This is the standard that describes various elements of how a drug that is being evaluated is used, and should be monitored during therapy. The main elements are[49]

- Dosage and administration—recommended dosage, starting dose, dose range, and critical differences among population subsets
- Drug interactions——a list of other drugs (or classes of drugs) or foods that interact or are predicted to interact in clinically significant ways with the drug along with practical instructions for preventing or decreasing the likelihood of the interaction
- Contraindications—situations in which the drug should not be used because the risk clearly outweighs any possible therapeutic benefit
- Adverse drug reactions—a listing of the most frequently occurring adverse drug reactions that are important for reasons other than frequency (e.g., leading to discontinuation of drug or dosage adjustments) and how they are best managed
- Monitoring—recommendations for laboratory tests and treatment monitoring to ensure safe use of the drug
- Patient counseling information—important information regarding patient drug regimens, weight-based dosing, adverse drug reactions, treatment monitoring, and duration of treatment to be shared with the patients to engage and empower them in the decision-making process
- Storage and handling—When applicable and important, special storage or handling information (e.g., need for refrigeration, reconstitution prior to drug administration)

Traditionally, the cost of medicines is also monitored (e.g., choosing an expensive oral hypoglycemic to treat type-2 diabetes when a less expensive oral hypoglycemic would have been just as effective with the same number or fewer adverse drug reactions). These guidelines do not include the cost of anti-TB medicines as the predominant criterion for choosing anti-TB medicines is the patient's drug-resistance profile, and choices for alternatives are very limited. Additionally, cost is not an overwhelming consideration because the overriding public health importance of effectively treating all forms of TB to prevent transmission of virulent organisms.

Outcome. The standard anticipated results of anti-TB drug therapy (e.g., cured, treatment completed, treatment failed, died, lost to follow-up, not evaluated, or treatment success— the sum of cured and treatment completed).

As successful TB treatment outcomes can only be attributed to a complete regimen rather than any one individual drug in the regimen, outcome is not included as a criterion provided for the individual drugs in a treatment regimen in Annex A.

Annex A provides sample criteria for anti-TB drug use reviews. They are comprehensive and some criteria may not be relevant within your program's context. The intent of Annex A is to provide a complete, valid, and reliable list of criteria from which the users of these guidelines can select a meaningful subset of criteria and adapt them to focus on identifying medication errors, preventable adverse drug reactions, toxicity, or signs of treatment failure for their specific needs. An example of select criteria for cycloserine appears in Figure 3.

Figure 3. Select criteria for a cycloserine DUR

	II. ***Process criteria*** to consider when prescribing cycloserine
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent Patient history has been reviewed for: • Cycloserine or terizidone allergy • Epilepsy • Depression, severe anxiety, or psychosis • Severe renal insufficiency • Excessive concurrent use of alcohol HIV status is documented in case records Cycloserine was available for the duration of treatment
Dose and frequency	Appropriate cycloserine dosing for adult • 15 to 20 mg/kg daily Not to exceed 1,000 mg daily
	Appropriate cycloserine dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 250 mg once daily or 500 mg/dose three times per week • Cycloserine should be administered following dialysis on dialysis days • The use of cycloserine is not recommended in patients with creatinine clearance 50 mL/minute unless they are on hemodialysis
	Appropriate cycloserine dosing for pediatric patients • 10 to 20 mg/kg once or twice daily Not to exceed 1,000 mg daily

Selecting Criteria

The most important task of the NTP or DUR committee is to develop or select criteria and thresholds that serve as the basis for program monitoring and evaluation, then implementing interventions (if needed).

Not every criterion presented in Annex A will apply to every treatment setting. Reviewing all criteria will make the DUR a difficult and lengthy process and hinder success of the strategy. Too many criteria create information overload and become burdensome to maintain while too few criteria may only provide a partial picture of medicine use at the facility. Between one and five criteria that are meaningful for the facility can strike a balance between undue burden on human and financial resources and provide results.

The DUR committee could decide to use the criteria exactly as published in Annex A or the committee may wish to modify them to reflect existing national standards for appropriateness at the treatment center because of differences in laboratory capabilities or budgets, or different administrative level requirements.

Procedures that use drug use criteria different than those established in Annex A should be developed and updated as new information becomes available. Suggested resources include peer-reviewed medical literature (that is, scientific, medical, and pharmaceutical publications in which original manuscripts are published only after having been critically reviewed by unbiased independent experts), compendia (e.g., American Hospital Formulary Service Drug Information, United States Pharmacopeia-Drug Information, British National Formulary, WHO International Formulary, Vidal, and Martindale: The Extra Pharmacopeia), package inserts, WHO guidelines, TB specialists, and clinical staff. The list of references used in developing criteria should also be included with the procedures. What ever criteria are developed, they should be shared with the NTP, NPV, and WHO.

It is recommended to begin a DUR by conducting a small pilot DUR using a majority of the criteria for three to five cases, then use that experience to prioritize DUR criteria and include for review by the committee.

Indicators

Indicators are the means to measure achievement and track performance by determining if performance thresholds are being met.

For example, in a TB program indicators could be:

1. Percentage of DR-TB patients receiving a treatment regimen in accordance with national approved STGs
2. Percentage of DR-TB patients who had documented DST results at the time of diagnosis
3. Percentage of DR-TB patients treated with kanamycin with documented DST results prior to starting treatment

Performance Thresholds

A performance threshold (also known as tolerance level or targets) defines a minimum acceptable standard that identifies the point at which non-compliance with drug use review criteria is of such magnitude to warrant an intervention.

An example of a performance threshold of 95% means that problem exists if less than 95% of the data collected for a given criterion shows compliance. If serious consequences could result from noncompliance with a given criterion, the threshold should be 100%.

For example, the threshold for correct dosing and administration of all treatment must be 100%, since prescribing incorrectly can lead to further drug resistance, poor treatment outcomes, avoidable adverse effects, and waste of health care resources.

Although a threshold of 100% is ideal, it is not realistic for every criterion. A threshold for documenting results of drug susceptibility testing may be 90%, as the DUR Committee may determine that some deviations may be due to occasional problems at the laboratory, or that deviations are random occurrences that do not signify an ongoing problem.

A smaller threshold percentage may be more appropriate for a new laboratory test that is not yet customarily performed (e.g., second-line drug resistance testing), then gradually increased as the laboratory test become routine for all cases. Table 4 shows thresholds for example indicators.

Table 4. Examples of Performance Thresholds for Different Indicators

Indicator	Threshold
Percentage of DR-TB patients receiving a treatment regimen in accordance with national approved standard treatment guidelines	100%
Percentage of DR-TB patients who were with documented DST results at the time of diagnosis	80%
Percentage of DR-TB patients treated with kanamycin with documented DST results prior to starting treatment	50%, increase by 10% each quarter

Ethics Approval

As DURs are considered a TB program evaluation or operations research activity and the participants are those who provide a service for the program rather than patients, it is of negligible risk to patients and may not require human ethics review.

However, laws, regulations, and guidelines that govern human subjects differ from country to country, thus the DUR Committee is responsible for contacting their Human Ethics Advisory Group for advice in this regard prior to collecting any data for the DUR.

Ethics approval will be required if the intent of the DUR Committee is to create knowledge and evidence to inform policy or generalize findings beyond its own program. Additionally, many journals require that every research article (including operations research) submitted to them contain a statement that the research obtained ethics approval or a statement that it was not

required. (**Note:** Items in the DUR Results Summary form presented in Annex C can be modified to provide information required for most ethics review boards.)

Dissemination of Information

The results of M&E are disseminated first to appropriate treatment center personnel. This step is important because it will help prevent the perception among the personnel that problems identified are based on anecdotal information, or that interventions are unnecessary or chosen arbitrarily.

Types of Interventions

A document should be developed that specifies procedures for the major types of interventions to be employed to correct drug use problems. Such interventions might include:

- In-service and continuing education programs
- Written guidelines for drug use
- Development of special drug prescription forms
- Changes in treatment center policies and procedures
- Formulary additions and deletions
- Prescribing restrictions or reviews
- Formal and informal counseling

The procedures should also emphasize that the interventions are aimed at improving performance and not punitive. Educational interventions address knowledge deficits, but unfortunately some prescribers know what they should do but for a variety of reasons do not.

Strategy Evaluation

Procedures should specify that the DUR strategy be evaluated at the end of each cycle to make improvements and to assess the clinical and economic impact to the treatment center.

Step 4. Define All Services Where Anti-TB Drugs are Used

As a starting point in designing a **comprehensive** DUR strategy, the committee identifies all areas where patients are treated with anti-TB drugs (e.g., inpatient wards, out-patient clinics, or community based). The DUR strategy can only be comprehensive when it addresses anti-TB drug use in all areas where TB services are provided. Also identify sources of data such as medical, laboratory, and pharmacy records.

Orient TB Staff to the Process

Prior to data collection in the first process cycle, medical and pharmacy staff should be oriented to the objectives of the DUR strategy, and build support for the process and get review and input. Informal meetings with TB opinion leaders may be needed to build support. Medical staff orientation may best be accomplished by disseminating all or part of DUR procedures; this includes the monitoring and evaluation schedule, and criteria for each medicine for the staff members review and input. Dissemination may be done by various methods (e.g., print—memo or newsletter, electronic—text, e-mail, or website).

Organizing a staff meeting is recommended so staff members can interact and discuss the subject matter. These meetings may be formal, but are often better when held informally over breakfast, lunch, or tea. Participation tends to increase when food and beverages are served.

Before subsequent DUR cycles, distribution of the monitoring schedule and criteria may be sufficient, but the medical staff should always be informed about changes in DUR procedures.

Step 5. Prepare Data Collection Forms

Before the actual monitoring and evaluation of a drug begins, the NTP or DUR committee must establish methodology for data collection including data elements, data sources, forms to use, persons responsible, cohort definition, and number of cases to review.

Data elements: Describe each data element that must be collected during the evaluation. For example, drug name, drug dose, amount prescribed, and duration of therapy. Data elements will vary with criteria. See Annex A for examples.

Data sources: Indicate on a source data table where the selected data elements can be found, such as in patient histories, laboratory records, pharmacy records, and standard WHO recording and reporting forms.

Forms: Once the data elements are selected, modify the forms provided to be consistent with those data. See Annex B for examples.

Persons responsible: Indicate the persons who will be responsible for collecting, verifying, organizing, and reporting the data.

Cohort: A group of patients in whom TB has been diagnosed and who were registered for treatment during a specified time.

Number of cases to review (size of cohort): Decide how many patient charts to review, after considering the following aspects:

- Objectives of the evaluation
- Dates to be evaluated
- Time, personnel, and financial resources available

A facility with less than 30 patients should review all cases, facilities with more than 30 patients should review at least 30 cases or 5% of cases to a maximum of 100 cases, whichever is greater.[50]

Patient Confidentiality: NTP and medical facilities must ensure that throughout the DUR process confidentiality of medical records is maintained. Each patient's identifiable private information or information related to the patient's past, present or future medical condition, treatment or payment for care must be protected according to the national laws.

Prospective DUR: A prospective review compares drug prescriptions with criteria and conducting the intervention before the patient receives the drug. Its main advantage is its preventive potential, and it should be used when significant non-compliance with criteria has been identified. The impact of this approach is noticeable immediately, and physicians may

become accustomed to formal monitoring as a "double check." Various drug use problems can be detected and prevented from occurring with prospective monitoring, such as:

- Incorrect dosage
- Inappropriate dosage form
- Incorrect route of administration
- Incorrect duration of therapy
- Drug-drug interactions
- Drug-disease contraindications
- Drug-allergy and other adverse drug reactions
- Incorrect laboratory orders
- Incorrect therapy monitoring orders

A prospective DUR is most useful for short-term therapy, and does not usually apply to tuberculosis therapy.

The clinical team should routinely perform prospective DURs in their daily practice (but not collect drug use criteria data) when evaluating a patient's planned treatment regimen before the patient starts drug therapy.

This kind of review can be done as a part of the pharmacy's review of new patient's medicine orders. Its success is dependent on a number of factors, including access to full pharmacy records, sufficient workforce, and appropriate knowledge base of potential drug- and disease-drug interactions.

Concurrent DUR: A concurrent review involves comparing drug use with the same criteria as prospective reviews during therapy. The main difference between the two types is that with concurrent monitoring, interventions are corrective.

For example, criteria may be established stating that kanamycin dosage and frequency of administration should be adjusted based on renal function and audiometry tests. The criteria are checked regularly by the clinical team and the prescriber is notified when dosage adjustments may be needed.

Concurrent DUR data collection is similar to prospective in that it may be done in the pharmacy, or at the facility. It differs from prospective in that the data collection does not have to occur prior to administration of a first dose.

A concurrent DUR is beneficial at the facility level as this type of review allows a patient's treatment to be altered if necessary without delay. The clinical team routinely performs concurrent DURs in their daily practice (but drug use criteria data are not collected) when they assess the ongoing therapy of their patients and, when necessary, intervene to modify the patient's regimen.

Retrospective DUR: A retrospective review involves reviewing prescribed drugs **after** they are dispensed to the patient. Its main drawback is that interventions cannot be made to correct drug use irregularities for patients who have completed treatment, but can be effective for patients who are still on treatment. It can be used to monitor the same aspects of drug use listed for prospective DUR, as well as:

- Comparing drug prescribing among different physicians
- Comparing drug prescribing to standard treatment guidelines

Example, a treatment center performs a DUR on kanamycin, and one of the criteria under review is that its use is contraindicated in renal failure. Records for newly diagnosed cases over from the previous three months are reviewed. The review may show that a prescribing problem exists. The medical staff decides to do a more intensive review of all aminoglycosides, with similar results. An education program is conducted for the entire medical staff on aminoglycoside use in renal failure.

Since almost all required data elements are contained in case histories, data collectors typically work in cooperation with the medical records department. Retrieval of data elements that are not contained in the case history, such as treatment preparation, may require visits to the pharmacy or laboratory.

The method of data collection will vary greatly with the approaches (prospective, concurrent or retrospective) chosen. In all cases, forms will be necessary for documenting results. Retrospective DURs will be used in most cases by NTPs as they will usually be incorporated into routine supervision and support visits, and most patient records reviewed during the visit will be cases on treatment or have completed treatment. Also, retrospective DURs present the fewest problems with data collection, and therefore is often the method of choice for NTPs.

The data collection forms presented in Annex B are based on the corresponding criteria in Annex A. If the committee modifies the drug specific criteria to accommodate administrative level or treatment center specific needs, then the data collection forms must be adapted to be consistent with the modified criteria.

Figures 4, 5, and 6 show an example of data collection forms based on selected drug criteria on the example of evaluating the use of kanamycin.

Figure 4. Kanamycin Drug Use Review—Patient Information Cover Page

Page 1 of 3 Kanamycin Drug Retrospective Use Review [Name of TB Treatment Center]					
Case Reviewed	**1**	**2**	**3**	**4**	**5**
Patient Unique Identifier	SC	RK	HW	LH	PD
Health Service Setting (enter one) I—In-patient O— Out-patient C - Community	O	O	O	O	I
Gender	M	M	M	M	F
Age at start of treatment (years and months)	28	52	36	44	37
Weight at start of treatment (kg)	65	59.7	59	61.2	42
Date treatment initiated	20 Oct 11	27 Oct 11	01 Nov 11	11 Nov 11	11 Nov 11
Planned Treatment Duration Intensive Phase (months)	6	7	6	6	6
Planned Treatment Duration Continuation Phase (months)	18	17	18	18	18

Have these patient records been previously inspected during this DUR cycle? If yes enter last month of treatment reviewed	Y 6	Y 3	Y 3	N	N
Enter the last month of treatment inspected today	18	17	18	18	18
Data collector's initials	VK	VK	VK	VK	VK
Date of data collection	25 Feb 13	25 Feb 13	25 Feb 13	25 Feb 13	25 Feb 13

Figure 5. Kanamycin Drug Use Review—Selected Criteria Page

Kanamycin Drug Use Review [Name of TB Treatment Center]						Page 2 of 3
Case Reviewed		**1**	**2**	**3**	**4**	**5**
	Threshold %	Yes (Y), No (N), or Not Applicable (NA)				
1. HIV status is documented prior to starting treatment	100	N	N	N	Y	Y
2. Pregnancy status is documented for female patients of childbearing potential prior to starting treatment	100	N	N	N	Y	Y
3. Audiometric testing conducted prior to starting treatment	95	Y	Y	N	Y	Y
4. Renal function testing conducted prior to starting treatment	100	N	N	Y	Y	N
5. Serum potassium testing conducted prior to starting treatment	100	N	N	Y	Y	N
6. Serum potassium testing conducted at least monthly during treatment	100	N	N	Y	Y	N
7. Patient has not been coadministered or sequentially administered potentially nephrotoxic, neurotoxic, or ototoxic drugs (Annex F)	100	Y	Y	N	Y	Y

Figure 6 Kanamycin Drug Use Review—Comments Pages

Page 3 of 3 Kanamycin Drug Use Review [Name of TB Treatment Center] Comments Page	
Data collector Comments Sign and date each entry Patient 3 was taking furosemide (self-medicated). Patient complained of ringing in the ears. Furosemide was stopped. No antihypertensive was required. *VK 25 Feb 13*	DUR Committee Comments

Step 6. Orient Data Collectors

It is essential to have useful and reliable data, thus the role of data collectors is important in the process.

Data collection for DURs is usually carried out by physicians, pharmacists, or nurses. Pharmacy interns are often used to do the data collection. Data collectors should be chosen carefully, and should be familiar with how information is arranged in the patient's history, since data are often collected from the case history. Knowledge of the national TB STGs is important. Depending on their availability, physicians, pharmacists, and nurses not directly affiliated with the treatment facility avoid the potential for bias.

Ideally, data collection will be conducted during the routine NTP supervision visits. If data collection for DURs is incorporated into routine supervision and support visits, supervisors will need an orientation to the DUR process and data collection forms even though they are experienced staff, and quite familiar with the data sources (e.g., patient charts, dispensing records, medication administration records, laboratory reports, electronic records, and standard WHO DR-TB recording and reporting forms).

The objectives of data collector's orientation are to:

- Understand the rationale for DURs
- Discuss the overall DUR process
- Become familiar with the data collection instrument
- Become familiar with acceptable sources of data
- Practice skills required to use the instrument effectively
- Develop a plan for field implementation
- Clarify the logistical issues related to field implementation
- Appreciate that when appropriately collected, the information derived can facilitate NTP decision-making and enhance the program

The duration of orientation will depend on the data collector's experience level, the number of medical records to review, number of drugs to be reviewed, and number of working hours per day. The schedule should be flexible enough to allow for a few extra days in case for any reason, the facilities are not ready for data collection.

Phase 2: Conduct the DUR

This phase is when the DUR is executed, or the plans from Phase 1 become reality. The following three steps describe activities to operationalize the DUR.

Step 7. Collect Data

The quality of the information that the DUR generates depends on the accuracy of data collection. The DUR Committee has overall responsibility for the quality of the data, though all data collectors have a role to play in ensuring the accuracy of the data collected.

The following items will help to ensure greater accuracy.

- Thorough preparation and orientation is the first step in minimizing errors.
- A trial run of the forms for three to five patients before collecting data from all patients will be helpful to ensure the forms and instructions for completion are accurate and understood.
- Make sure that each data collector has enough copies of and is familiar with all the data collection instruments they will need for the site(s) for which that person is responsible
- Give a copy of explicit, written instructions for using the data collection forms to each data collector.
- Supplies such as pens, notebooks, bags for carrying forms, cell phone airtime and so on should also be given to each data collector.
- Make sure that all the site visits have been approved and scheduled by the NTP.
- Data collectors should be given copies of letters of introduction that confirm their identity and authorization to evaluate that site.
- Establish procedures to check for data completeness, consistency, plausibility and legibility in the field when it is still possible to correct errors or to fill in missing information.
- At the end of the day the supervisor should randomly check the quality and completeness of data collection if feasible. The supervisor should return to randomly selected TB facilities to collect the same data so as to check the accuracy of the data collected earlier, or if a team of supervisors is conducting a visit, one of the supervisors can check the accuracy of data collected.
- Develop a system for collecting, grouping, and storing completed data collection forms.

NTPs that are using web-based MIS systems, such as e-TB Manager or OpenMRS, may be able to collect some of the data remotely.

Step 8. Tabulate Data

Now you would like to see the results of your work. As information is collected from a small number of patient records (usually not more than 30) it can be tabulated by hand or with an Excel® spreadsheet.

For larger volumes of data, a variety of free software packages are available to download and install on computers for stand-alone (offline, non-web-based) forms development, data entry, and analysis. Examples include Epi-Info[51] and EpiData.[52]

A sample data summary table is presented in Figure 7 below.

Figure 7. Levofloxacin Drug Use Review Summary

NUMBER OF PATIENT RECORDS REVIEWED: 120					
DATE(S) DATA COLLECTED: 08 AUGUST 14					
CRITERIA	**TOTAL NUMBER MET**		**THRESHOLD MET**		**COMMENTS**
	YES	**NO**	**Target %**	**Observed %**	
1. TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)	**120**	**0**	**100**	100	
2. Laboratory drug susceptibility testing (DST) a. DST documents the organism resistance pattern includes at least rifampicin and susceptible to isoniazid alone	**100**	**0**	**100**	100	
b. Organism resistance pattern confirms at least rifampicin and isoniazid	**20**	**0**			
3. Documentation that patient history has been reviewed for: a. levofloxacin allergy b. quinolone antimicrobial allergy	**92**	**28**	**95**	77	
4. Adult patients were administered 500-1000 mg	**108**	**12**	**100**	90	
5. Levofloxacin was administered daily at least six times per week	**99**	**21**	**100**	83	
6. Serum glucose of diabetic patients is monitored at least monthly	12	3	**95**	80	
7. Documentation that at least once a month patients are advised to drink plenty of beverages	***100***	***20***	***95***	83	Patient information sheets are not available at the clinic. Check if there is a problem with providing information or documenting providing information
8. Patient experienced diarrhea	***44***	***76***	***Not Applicable***		
9. Diarrhea was managed by: • Assessing dehydration • Rehydration initiated (if indicated) • Anti-diarrheal therapy was initiated (e.g., loperamide)	***39***	***5***	**100**	89	

Step 9. Interpret Data

Data interpretation is one of the most critical steps in the DUR process. Conclusions drawn from data interpretation could result in changes in treatment, policies, formulary additions or deletions, prescribing restrictions, and counseling of treatment center staff. Information must be carefully aggregated when determining if thresholds were met or exceeded. Whenever feasible, a DUR committee member should review the data collection forms for completeness, and verify questionable data with the case history, or other treatment center records.

If a threshold set at 100% is met (indicating complete compliance with the criteria), it is usually sufficient to simply report the results to the DUR committee.

If a threshold is set at less than 100% (e.g., 80%) and that threshold is not met or exceeded (e.g., 63%), the DUR committee should decide if it is necessary to review those cases that were not in compliance with the criteria. The main purpose of any such review is to determine if there was a justifiable reason for non-compliance. It is not uncommon for a DUR committee to justify cases of non-compliance. In this case, they may decide to change the criteria prior to re-evaluation of the medicine. If non-compliance is determined, a recalculation of the threshold percentage can be considered.

A threshold that is not met may indicate a drug use problem. As above, cases of non-compliance should be reviewed to determine if drug use was actually appropriate. If the committee determines that a drug use problem does exist, the data should be evaluated to determine if the problem is widespread or limited to a few individuals, if the problem is localized to a particular ward or department, and even if the problem occurs on one particular treatment center shift. A common finding is that the notes are incomplete or illegible.

Phase 3: Implement an Improvement Plan

Phase 3 is the key phase to achieve improvement. It consists of using findings from Phase 2 to identify areas that need improvement and schedule interventions to address any TB programmatic management deficiencies.

The following steps describe activities for administering TB programmatic management change.

Step 10.Make Recommendations for Improvement

The DUR findings should be discussed at the committee meeting and reported to all stakeholders. When the DUR is conducted by the NTP, the findings also can be discussed at support and supervision visits. When the DUR committee determines that a drug use problem exists, it recommends one or more activities (interventions) that will result in improved drug use. Interventions can be educational or operational and can target groups, or only those individuals whose performance was not in compliance with drug use criteria. Some possible interventions are listed below.

Educational interventions can include the following:

- Educational meetings (e.g., conferences, lectures, workshops, or trainings
- Informal and formal counseling
- Letters to health care providers
- Newsletters, drug use guidelines, and other informational materials
- Clinical literature
- E-mail and text alerts
- Clinical mentoring
- Patient counseling
- Audit and feedback
- Reminders (specific information, provided verbally, on paper, or on a computer, which is designed or intended to prompt a health care provider to recall information)

Operational interventions can include the following:

- Development of drug prescriptions forms with systematic review
- Changes in treatment center policies and procedures
- Formulary additions and deletions
- Prescribing restrictions based on level of prescriber's credentials
- Counter signing patient medicine orders
- Implementing or revising STGs
- Improved record keeping
- Purchasing new equipment
- Skill mix changes (changes in number, type, or qualification of staff members)
- Supervisory changes

Step 11.Disseminate Results and Discuss the Improvement Plan

The results of the review and the strategy for improvement are disseminated to appropriate treatment center staff or national policymakers. This step is important because it will help prevent the perception among the medical staff that problem identification was based on anecdotal information, or that interventions are unnecessary or chosen arbitrarily.

The most common dissemination formats are oral presentations at staff meetings, fact sheets, slide or computer presentations, and written reports. Visual aids such as tables, charts, graphs, and photographs can be used effectively to summarize information and add a visual aspect to a written report or oral presentation.

Step 12.Implement the Improvement Plan

Identify the Target Audience

The target audience for an intervention depends primarily on the extent of the problem. If non-compliance with criteria is widespread, the intervention may be aimed at the entire medical staff, or at groups of specialists (e.g., laboratory, nursing, pharmacy, or prescribers). If a small number of prescribers or staff members are non-compliant, interventions may be directly aimed at only those who did not meet the criteria. Those who were fully compliant should be recognized and involved in follow on activities.

Assign Responsibility for Designing and Carrying Out Intervention

Interventions may be designed and carried out by a combination of committee members, treatment center staff, or outside experts. The committee chair is usually responsible for sending letters and counseling activities. Other interventions, such as writing an informational newsletter, or drafting new policies, may be assigned to specialists on the committee or on the treatment center staff. Outside experts may be used to conduct seminars for treatment center staff. The chief TB physician may be involved if intervention requires hiring additional staff, or purchasing equipment.

Phase 4: Assess Effectiveness of the Intervention

Phase 4 is a crucial step for reviewing the entire cycle of the DUR process and for developing long-term plans to ensure that improvement is sustained and progresses.

The last four steps describe how to evaluate the impact of the DUR strategy on TB programmatic management and how to improve and sustain it.

Step 13. Conduct a Follow-up DUR

Typically, a re-review is done 6 to 12 months after an intervention was put in place, and involves collecting the same data as in the original DUR evaluation from later records. If a comprehensive evaluation with a large number of criteria reviewed revealed a small number of deficiencies, the committee may decide to narrow the focus of the re-review to target only the criteria where results showed that the threshold was not met.

Step 14.Review and Discuss Follow-up Data

At the DUR committee meeting (or post-supportive supervisory meetings) assess the effectiveness of the intervention and document any improvements or remaining deficiencies. When the results show improvement it is important to communicate that success to the appropriate treatment center staff or national policymakers. When results indicate deficiencies remain, criteria and thresholds may need to be adjusted for the next cycle, or a new corrective action plan may need to be implemented.

Step 15. Evaluate the Strategy

At the end of each cycle, the DUR Committee should review the process to identify opportunities for its improvement, and if necessary, make procedural changes to reflect actual practices, or to facilitate desired changes.

Considerations for evaluation include:

- Were criteria developed according to procedures?
- Were thresholds appropriate?
- Were problems identified and appropriately addressed?
- Were interventions appropriate?
- Were drug use problems solved?
- Are there any remaining deficiencies that need corrective action?
- Did the DUR have an impact on the incidence of inadequate clinical follow-up, adverse drug reactions, drug-drug, drug-food, drug-disease, or drug-laboratory interactions, or medication administration errors?
- Were results disseminated according to procedures?
- Are additional resources (human or financial) required to improve TB program performance?

Step 16. Plan and Implement the Next Cycle

Once procedural changes have been made and the guidelines have been updated, plan activities for the next cycle in order to continue improving the use of anti-TB drugs, and to measure the impact of the DUR activities on the TB program or treatment center over the duration of the TB program. A Sample activity tracker is provided in Annex D.

CONCLUSION

Providing patients with the correct treatment regimen for the entire treatment time is fundamental to preventing the development of drug resistant, multidrug resistant, or extensively drug resistant TB. With new anti-TB drugs becoming available in the TB control armamentarium, rational and responsible drug use is also critical to prolonging a new drug's useful lifespan.

Strategies to ensure the rational and responsible use of anti-TB medicines should be an intrinsic part of national TB programs and implementing and using DURs is an excellent strategy. NTP managers, NPV managers, clinicians, health care providers, patients, educators, donors, and pharmaceutical companies all contribute to preventing the development of DR-TB, MDR-TB, or XDR-TB, and optimizing patient outcomes. The experience these individuals and groups gain in implementing and using these guidelines will provide valuable recommendations for local adaptation and improvement of future editions.

When DUR activities are carried out, all prescribing and record keeping is likely to improve even if the intervention did not target all areas. Prescribers and operational managers do not know what will be reviewed next and so, if they know what they should do, they are likely to do so.

ANNEX A. PUBLISHED CRITERIA FOR ANTI-TUBERCULOSIS TREATMENT

First-Line Drugs

Please be aware of the following when using information in this annex.

Although the drug information in this document is extensive, it is not intended to replace national standard treatment guidelines, package inserts, or other printed material that may be available or accompany a particular drug.

Only medicines on the WHO Model Essential Medicines Lists[53,54] are referenced in this document. Ancillary medicines or concomitant medicines on National Essential Medicine Lists that do not appear on the WHO Model Lists should be checked for

- Interactions with anti-TB medicines
- Contraindications for coadministration with anti-TB medicines
- Correct dose and administration for treatment of adverse drug reactions

These should be added to the information in Annex A.

Children older than 12 years of age can be managed as adults.[55]

Consult with a TB specialist or clinical pharmacist about the clinical use of **any** medicine administered to a patient.

Criteria for Ethambutol [1,4,56–60]			
I. ***Justification criteria*** for prescribing ethambutol			
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)		
	Clinically diagnosed by a TB medical provider (e.g., X-ray abnormalities or suggestive histology)		
	Laboratory drug susceptibility testing (DST) documents that the organism is susceptible to ethambutol		
	According to national TB treatment guidelines		
II. ***Process criteria*** to consider when prescribing ethambutol			
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent		
	Patient history has been reviewed for • Hypersensitivity to ethambutol • Optic neuritis • Inability to appreciate and report visual adverse drug reactions or changes in vision (e.g., young children, unconscious patients) • Liver disease • Previous discontinuation of ethambutol		
	HIV status is documented in case records		
	Ethambutol was available for the duration of treatment		
Dose and frequency	Appropriate dosing for adult patients • 15 mg/kg per day (15 to 20 mg/kg per day) or 15 mg/kg (25 to 30 mg/kg) per dose three times a week		
	Appropriate dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 15 to 25 mg/kg per dose three times per week		
	Administer ethambutol following dialysis on dialysis days		
	Appropriate dose for pediatric patients • 15 to 25 mg/kg/day Not to exceed 2,000 mg daily		
Administration	For oral use only		
Duration	Drug susceptible TB	Intensive phase	2 months

Criteria for Ethambutol [1,4,56–60]	

Patient monitoring	Prior to treatment and then at least monthly during treatment:
	• Weight (and every 2 weeks for the first 3 months of treatment)
	• Pregnancy testing—according to standard clinical protocol
	• Liver function
	  ○ AST (SGOT)
	  ○ ALT (SGPT)
	  ○ Total bilirubin
	• Renal function
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Complete blood count with differential
	
	Ophthalmologic function
	• Ophthalmoscopy
	• Finger perimetry
	• Acuity testing (Snellen chart)
	• Color discrimination (Ishihara tests)
	
	HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—ethambutol blood levels	Recommended only for patients suspected of having malabsorption or treatment failure Draw a peak serum concentration 2 to 3 hours after the dose; a second sample 6 hours post-dose could be obtained if there is concern about late absorption and to estimate the serum half-life Peak concentrations of 2 to 6 mcg/mL are expected with daily dosing See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration

Criteria for Ethambutol [1,4,56–60]	
Drug interactions	Aluminium hydroxide may delay and decrease absorption and serum concentrations of ethambutol Uricosuric doses may need to be increased, since ethambutol competes with uric acid for its renal excretion Disulfiram may increase the risk for ocular toxicity Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents. Hepatotoxic and neurotoxic drugs • May potentiate toxicities • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs.
Patient counseling	Advise patient: • Take ethambutol two hours before or four hours after taking antacids with aluminum hydroxide • Ethambutol can be taken with or without food Advise patient to contact a health care provider immediately if they experience: • Any eye problems: vision changes, blurring, color blindness, trouble seeing, or eye pain • Swelling of face • Rash, hives, or trouble breathing • Numbness, pain, or tingling in hands or feet • Joint pain • Fever or chills • Nausea, vomiting, poor appetite, or abdominal pain • Headache or dizziness Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Ethambutol [1,4,56–60]	
III. ***Complications*** that could occur during therapy with ethambutol, and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis) Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole) Stop ethambutol for short periods of time (e.g., one to seven days) Discontinue ethambutol if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Hypersensitivity, mild (skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., Stevens-Johnson syndrome, eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, lupoid reactions, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Ethambutol [1,4,56–60]	
Nausea or vomiting	Give with small meals and advise patient to swallow pills slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Decrease frequency of ethambutol administration Discontinue ethambutol if this can be done without compromising regimen—rarely necessary
Optic neuritis	Stop ethambutol Refer patient to an ophthalmologist In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions. In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult Modify regimen according to national TB treatment guidelines
Anorexia	Give with small meals and advise patient to swallow pills slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration; initiate rehydration if indicated Decrease frequency of ethambutol administration Discontinue ethambutol if this can be done without compromising regimen—rarely necessary
Arthralgias	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Decrease frequency of ethambutol administration Discontinue ethambutol if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines

Criteria for Ethambutol [1,4,56–60]	
Central nervous system-related adverse drug reactions (dizziness; mental confusion, disorientation, and possible hallucinations)	Generally occurs during first few weeks of therapy Reassure patient that symptoms will subside as treatment progresses Suspect drug-induced acute liver failure if there is jaundice Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Treat dizziness with cyclizine **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Consider reducing the frequency of ethambutol administration to five times or even three times per week Discontinue ethambutol if this can be done without compromising regimen—rarely necessary
Fever	Rule out other causes Paracetamol or ibuprofen can be given to lower the temperature **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Fluids may be given by mouth or IV to prevent dehydration, if necessary
Headache (e.g., meningitis or other central nervous system infections)	Rule out other causes Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of ethambutol administration to five times or even three times per week

Criteria for Ethambutol [1,4,56–60]	
Hematological abnormalities (e.g., thrombocytopenia, leukopenia, or neutropenia)	Stop all therapy pending resolution of toxicity Eliminate other potential causes of toxicity Consider suspending most likely agent permanently Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non-hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis), and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential, consider not reintroducing it Once resolved, monitor liver function monthly
Hyperuricemia	Monitor uric acid levels If accompanied by acute gouty arthritis discontinue or reduce the frequency of administration, and monitor serum levels of uric acid Modify regimen according to national TB treatment guidelines

Criteria for Ethambutol [1,4,56–60]	
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes
	Correct any vitamin or nutritional deficiencies
	Administer pyridoxine 200 to 300 mg per day
	Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily)
	Consider paracetamol and NSAIDs (or both) for pain relief
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Consider neurology consultation
	Consider administering carbamazepine
	Decrease frequency of ethambutol administration
	Discontinue ethambutol
	Modify regimen according to national TB treatment guidelines
Pulmonary infiltrates, with or without eosinophilia	Treat with corticosteroids according to standard clinical protocol
	Discontinue ethambutol
	Modify regimen according to national TB treatment guidelines
Overdosage	Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion
	Subsequently, hemo- or peritoneal dialysis may be of value
	There is no specific antidote and treatment is supportive

Criteria for Isoniazid [1,4,49,58,60–64]	
I. ***Justification criteria*** for prescribing isoniazid	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Clinically diagnosed by a TB medical practitioner provider (e.g., X-ray abnormalities or suggestive histology)
	Laboratory drug susceptibility testing (DST) documents that the organism is susceptible to isoniazid
	High-dose isoniazid—when isoniazid minimum inhibitory concentration (MIC) is less than 1 mg/L (possibly beneficial when isoniazid MIC is less than 5 mg/L)
	According to national TB treatment guidelines
II. ***Process criteria*** to consider when prescribing isoniazid	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Hypersensitivity to isoniazid • Liver disease • Excessive concurrent use of alcohol • Previous discontinuation of isoniazid • Peripheral neuropathy or conditions predisposing to neuropathy • G6PD deficiency
	HIV status is documented in case records
	Isoniazid was available for the duration of treatment

Criteria for Isoniazid [1,4,49,58,60–64]			
Dose and frequency	Appropriate dosing for adult patients with drug-susceptible TB • 5 (4 to 6) mg/kg daily Not to exceed 300 mg per day **or** 10 (8 to 12) mg/kg three times per week Not to exceed 900 mg per day Appropriate dosing for renal dysfunction (Creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 300 mg once daily, or 900 mg two or three times per week Isoniazid should be administered following dialysis on dialysis days Appropriate dose for pediatric patients • 10 to 15 mg/kg/day Not to exceed 300 mg per day High-dose isoniazid • Adults—10 mg/kg per day (when the isoniazid MIC is less than or equal to 1 mg/L **or** 16 to 20 mg/kg three times per week (when isoniazid MIC is more than 1 to 5 mg/L) • Pediatrics—20 to 30 mg/kg per dose two or three times a week Appropriate dosing for adult patients with drug-susceptible TB		
Administration	For oral use • Give by mouth on an empty stomach, one hour before or two hours after meals Parenteral administration: May be given intravenously, or intramuscularly if patient cannot tolerate oral medication • If administered intravenously, recommend administering dose slowly as an undiluted bolus injection (other methods have been employed) • Store at room temperature 15°C to 25°C • Protect from light Administer pyridoxine (vitamin B6) for peripheral neuropathy prophylaxis • Adult dose—100 mg daily • Pediatric dose— 1 to 2 mg/kg daily, with a usual range of 10 to 50 mg daily		
Duration	Drug susceptible TB	Intensive phase	2 months
		Continuation phase	4 months
	High dose for low level isoniazid resistance and XDR-TB	Intensive phase Continuation phase	According to national TB treatment guidelines

Criteria for Isoniazid [1,4,49,58,60–64]	

Patient Monitoring	Prior to treatment and then at least monthly during treatment
	
	Appropriate dose for pediatric patients
	• Weight (and every 2 weeks for the first 3 months of treatment)
	• Pregnancy testing—according to standard clinical protocol
	• Liver function
	  ○ AST (SGOT)
	  ○ ALT (SGPT)
	  ○ Total bilirubin
	• HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—isoniazid blood levels	Recommended only for patients suspected of having malabsorption or treatment failure Peak concentrations should be drawn at 1 and 4 hours If other drug concentrations are being submitted, collect blood for peak serum concentrations 2 hours after a dose (and if desired at 6 hours after a dose to calculate half-life) Peak concentration is expected to be 3 to 5 mcg/ml after daily dose Peak concentration is expected to be 9 to 15 mcg/ml after thrice weekly dose or high dose for DR-TB. See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance in how to adjust dose based on serum concentration.

Criteria for Isoniazid [1,4,49,58,60–64]	

Drug interactions	The dose of isoniazid may need to be increased when coadministered with the following drugs or classes of drugs
	• Phenytoin
	
	The dose of isoniazid may need to be decreased when coadministered with the following drugs or classes of drugs
	• Carbamazipine
	• Cycloserine
	• Dexamethasone
	• Haloperidol
	• Loratadine
	
	The dose of the following drugs or classes of drugs may need to be decreased when coadministered with isoniazid
	• Benzodiazepines (e.g., midazolam, lorazepam)
	• Carbamazepine
	• Ergot alkaloids (e.g., ergometrine)
	• Hemostatics (e.g., coagulation factors)
	• Hydantoin antiepileptics (e.g., phenytoin)
	• Opioid analgesics (e.g., codeine)
	• Oral anticoagulants (e.g., warfarin)
	• Statins (e.g., simvistatin)
	• Valproic acid
	• Vinca alkaloids (vincristine, vinblastine)
	
	The dose of the following drugs or classes of drugs may need to be increased when coadministered with isoniazid:
	• Azole antimycotics (e.g., fluconazole)
	• Opioid analgesics (e.g., codeine)
	• Tamoxifen
	
	Additional patient monitoring maybe required when coadministered with the following drugs
	• Oral anticoagulants
	  ○ Prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant
	• Antiepileptics
	  ○ Monitor patient for changes in therapeutic effect and adverse events
	• Tamoxifen
	  ○ Monitor patient for changes in therapeutic effect and adverse events
	
	Severe paracetamol toxicity may occur when coadministered with isoniazid
	• If necessary to coadminister, monitor adverse drug reactions carefully
	
	Hepatotoxic and Neurotoxic drugs
	• May potentiate toxicities

Criteria for Isoniazid [1,4,49,58,60–64]	
	• If necessary to coadminister, monitor adverse drug reactions carefully Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.
Patient counseling	Advise patients to • Take isoniazid one hour before or two hours after food with a full glass of water • Take isoniazid with a snack if patients have an upset stomach • Take antacids (if needed) one hour before or two hours after isoniazid • Avoid tyramine- and histamine-containing foods which may cause exaggerated response (e.g., headache, sweating, palpitations, flushing, and hypotension) Refer to Annex H. Tyramine- and Histamine-Containing Foods • Keep the liquid preparation at room temperature 15°C to 25°C, not in the refrigerator • Avoid alcohol while taking isoniazid Advise patients to contact a health care provider immediately if they experience: • Loss of appetite that continues for more than a few days • Fatigue weakness • Moderate stomach pain, nausea, or vomiting • Numbness or tingling of the fingers or toes • Blurred vision, eye pain • Yellow skin or eyes or dark-colored urine • Flushing, sweating, or headaches when eating certain cheeses or fish • Refer to Annex H. Tyramine- and Histamine-Containing Foods Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk Advise patients who are breastfeeding: • Most drugs used to treat TB cross into the breast milk at low levels • The amount of anti-TB drugs that babies receive through the breast milk will not treat or prevent TB in the infant

Criteria for Isoniazid [1,4,49,58,60–64]	
III. ***Complications*** that could occur during therapy with isoniazid, and how to respond if the complication presents, as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Alopecia	Encourage patients to tolerate this side effect Resolution occurs after treatment is stopped
Anemia	Determine cause of anemia (i.e., iron deficiency, hydroxocobalamin (vitamin B12) deficiency, chronic disease, bleeding) Supplement with iron, hydroxocobalamin (vitamin B12), folate (vitamin B9) , ascorbic acid (vitamin C) as appropriate
Arthralgias	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Decrease frequency of isoniazid administration Discontinue isoniazid if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Isoniazid [1,4,49,58,60–64]	
Depression	Assess and address underlying socioeconomic issues
	Assess for substance abuse and refer to treatment if appropriate
	Rule out other causes and if identified, treat according to standard clinical protocol
	Rule out adverse drug reactions of concomitant medications (e.g., cycloserine, amoxicillin/clavulanate, penicillin, benzodiazepines)
	Refer to psychologist or psychiatrist for assessment
	Initiate group (if patient is sputum smear and culture negative) or individual psychological therapy
	Initiate anti-depressant therapy (e.g., amitriptyline, fluoxetine)
	Only after group or individual psychological therapy initiated
	Use with caution when there is a history of convulsions
	Caution: Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes
	Decrease frequency of isoniazid administration
	Discontinue isoniazid
	Modify regimen according to national TB treatment guidelines
Diarrhea, cramping, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of isoniazid administration
	Discontinue isoniazid if this can be done without compromising regimen—rarely necessary
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis)
	Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole)
	Stop isoniazid for short periods of time (e.g., one to seven days)
	Discontinue isoniazid if this can be done without compromising the regimen
	Modify regimen according to national TB treatment guidelines

Criteria for Isoniazid [1,4,49,58,60–64]	
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal)	With or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting) Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal)	With or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting) Stop all hepatotoxic medicines Continue with three non-hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis), and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Hypersensitivity, mild (skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Isoniazid [1,4,49,58,60–64]	
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, lupoid reactions, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Nausea or vomiting	Administer with small meals and advise patient to swallow tablets slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration; if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Decrease frequency of isoniazid administration Discontinue isoniazid if this can be done without compromising regimen—rarely necessary
Optic neuritis	Refer patient to an ophthalmologist In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult

Criteria for Isoniazid [1,4,49,58,60–64]	
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes
	Correct any vitamin or nutritional deficiencies
	Administer pyridoxine 200 to 300 mg per day
	Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily)
	Consider paracetamol and NSAIDs (or both) for pain relief
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function
	Consider neurology consultation
	Consider administering carbamazepine
	Decrease frequency of isoniazid administration
	Discontinue isoniazid
	Modify regimen according to national TB treatment guidelines
Psychotic symptoms	Stop isoniazid for a short period of time (1 to 4 weeks) while psychotic symptoms are brought under control
	Initiate antipsychotic therapy (haloperidol, chlorpromazine, risperidone [consider biperiden to prevent extrapyramidal effects])
	If patient is at risk of self harm, hospitalize patient under expert psychiatric care
	Reduce frequency of isoniazid administration
	Reduce isoniazid dose
	If symptoms do not improve, discontinue isoniazid
	Modify regimen according to national TB treatment guidelines
Seizures	Suspend isoniazid pending resolution of seizures
	Suspend other seizure-inducing medicines (e.g., cycloserine, fluoroquinolones)
	Initiate anticonvulsant therapy (e.g., phenobarbital, phenytoin, carbamazepine, valproic acid)
	Administer pyridoxine 200 to 300 mg daily
	Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium, and chloride
	Once seizures have resolved, restart medications one at a time
	Reduce frequency of isoniazid administration
	Discontinue isoniazid if seizures do not resolve
	Modify regimen according to national TB treatment guidelines

Criteria for Isoniazid [1,4,49,58,60–64]	
Blood glucose disturbances	Monitor blood glucose until stabilized (and at least monthly for DR-TB patients)
	Initiate or adjust oral hypoglycemic agent or insulin—according to standard clinical protocol
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue isoniazid if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines
Hematological abnormalities (e.g., agranulocytosis, thrombocytopenia)	Stop all therapy pending resolution of toxicity
	Eliminate other potential causes of toxicity
	Consider suspending most likely agent permanently
	Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Metabolic acidosis	Monitor serum electrolytes and arterial blood gasses
	Initiate sodium hydrogen carbonate therapy—according to standard clinical protocol
Paracetamol toxicity	Treat according to standard clinical protocol
Pellagra	Initiate niacin (B3) replacement therapy—according to standard clinical protocol
Porphyria	Discontinue isoniazid
	Consider dosing 2 to 3 times a week if drug is essential to the regimen
	Provide symptomatic therapy, high carbohydrate intake and intravenous administration of hematin
	Modify regimen according to national TB treatment guidelines
Pyridoxine deficiency	Administer pyridoxine 200 to 300 mg daily
	Improve diet, possibly by admission to hospital
	Stop alcohol consumption
Overdosage	Untreated or inadequately treated cases of gross isoniazid overdosage, 80 mg/kg to 150 mg/kg, can cause neurotoxicity and death, but good response has been reported in most patients brought under adequate treatment within the first few hours after drug ingestion

Criteria for Isoniazid [1,4,49,58,60–64]

For the Asymptomatic Patient

Absorption of drugs from the GI tract may be decreased by giving activated charcoal

Gastric emptying should also be employed in the asymptomatic patient

Safeguard the patient's airway when employing these procedures

Patients who acutely ingest more than 80 mg/kg should be treated with intravenous pyridoxine on a gram per gram basis equal to the isoniazid dose

If an unknown amount of isoniazid is ingested, consider an initial dose of 5 grams of pyridoxine given over 30 to 60 minutes in adults, or 80 mg/kg of pyridoxine in children

For the Symptomatic Patient

Ensure adequate ventilation, support cardiac output, and protect the airway while treating seizures and attempting to limit absorption

If the dose of isoniazid is known, the patient should be treated initially with a slow intravenous bolus of pyridoxine, over 3 to 5 minutes, on a gram per gram basis equal to the isoniazid dose

If the quantity of isoniazid ingestion is unknown, then consider an initial intravenous bolus of pyridoxine of 5 grams in the adult or 80 mg/kg in the child

If seizures continue, the dosage of pyridoxine may be repeated. It would be rare that more than 10 grams of pyridoxine would need to be given. The maximum safe dose for pyridoxine in isoniazid intoxication is not known

If the patient does not respond to pyridoxine, diazepam may be administered

Phenytoin should be used cautiously, because isoniazid interferes with the metabolism of phenytoin

General

Obtain blood samples for immediate determination of gases, electrolytes, BUN, glucose, etc.

Type and cross-match blood in preparation for possible hemodialysis if procedure is available

Criteria for Pyrazinamide [1,4,59,60,64–66]			
I. ***Justification criteria*** for prescribing pyrazinamide			
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)		
	Clinically diagnosed by a TB medical provider (e.g., X-ray abnormalities or suggestive histology)		
	Laboratory drug susceptibility testing (DST) documents that the organism is susceptible to pyrazinamide		
	According to national TB treatment guidelines		
II. ***Process criteria*** to consider when prescribing pyrazinamide			
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent		
	Patient history has been reviewed for: • Hypersensitivity to pyrazinamide, ethionamide, prothionamide, isoniazid, niacin (nicotinic acid), or other chemically related medications • Liver disease • Renal failure • Acute gout • Diabetes mellitus • Porphyria • Previous discontinuation of pyrazinamide		
	HIV status is documented in case records		
	Pyrazinamide was available for the duration of treatment		
Dose and frequency	Appropriate dosing for adult patients • 25 mg/kg (20 to 30 mg/kg) daily or 35 mg/kg (30 to 40 mg/kg) per dose three times a week Not to exceed 2,000 mg daily		
	Appropriate dosing for renal dysfunction (Creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 25 to 35 mg/kg per dose three times per week		
	Administer pyrazinamide following dialysis on dialysis days		
	Appropriate dose for pediatric patients • 30 to 40 mg/kg daily Not to exceed 2,000 mg daily		
Administration	For oral use only		
Duration	Drug susceptible TB	Intensive phase	2 months
	Drug resistant TB	Intensive phase	at least 8 months
		Continuation Phase	at least 12 months

Criteria for Pyrazinamide [1,4,59,60,64–66]	

Patient Monitoring	Prior to treatment and then at least monthly during treatment
	• Weight (and every 2 weeks for the first 3 months of treatment)
	• Pregnancy testing—according to standard clinical protocol
	• Liver function
	  ○ ALT (SGPT)
	  ○ AST (SGOT)
	  ○ Total bilirubin
	• Serum Uric Acid
	• HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—pyrazinamide blood levels	Recommended only for patients suspected of having malabsorption or treatment failure Peak concentrations should be drawn at 2 and 6 hours for therapeutic drug monitoring Peak concentrations of 20 to 40 mcg/mL are expected after a daily dose Pyrazinamide can be found in the urine all day long and can be an indication of adherence to therapy. See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration.
Drug interactions	Pyrazinamide antagonizes the action of uricosuric agents (e.g., allopurinol) Pyrazinamide may increase the effects of ciclosporin Pyrazinamide may increase the toxic effects of rifampicin Rifampicin may increase the toxic effects of pyrazinamide Ofloxaxin, levofloxacin, moxifloxacin co-administration potentiates adverse drug reactions (hepatic, gastrointestinal, musculoskeletal) • If necessary to coadminister, monitor adverse drug reactions carefully Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents. Hepatotoxic drugs • May potentiate hepatotoxicity • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs Pyrazinamide has been reported to interfere with ACETEST® and KETOSTIX® urine tests to produce a pink-brown color

Criteria for Pyrazinamide [1,4,59,60,64–66]	
Patient counseling	Advise patient: • Pyrazinamide may be taken with or without food • Pyrazinamide may cause a rash after sun exposure; limit sun exposure Advise patient to contact a health care provider immediately if they experience • Skin rash, severe itching, or hives • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual fatigue or loss of appetite Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with pyrazinamide and how to respond if the complication presents as follows:[1]	
Severe or common toxicities are indicated by **bold** font	
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis) Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole) Stop pyrazinamide for short periods of time (e.g., one to seven days) Discontinue pyrazinamide if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Pyrazinamide [1,4,59,60,64–66]	
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol induced hepatitis); and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Pyrazinamide [1,4,59,60,64–66]	
Hypersensitivity, severe (e.g., Stevens-Johnson syndrome, eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, lupoid reactions, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Hyperuricemia (gout)	Can be considered as a parameter for therapeutic drug monitoring Monitor uric acid levels Discontinue and do not resume if accompanied by acute gouty arthritis Allopurinol is not effective in treating pyrazinamide-associated hyperuricaemia Modify regimen according national TB treatment guidelines
Nausea or vomiting	Administer with small meals and advise patient to swallow tablets slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Decrease frequency of pyrazinamide administration Discontinue pyrazinamide if this can be done without compromising regimen—rarely necessary

Criteria for Pyrazinamide [1,4,59,60,64–66]	
Photosensitivity/ phototoxicity	Mild Instruct patient to use sunscreens and avoid excessive exposure to sun or UV light exposure Initiate therapy with cool compresses and hydrocortisone cream Severe Eliminate pyrazinamide from regimen Modify regimen according to national TB treatment guidelines
Acne	Provide supportive care If acne is bothersome to the patient, topical acne treatments may be administered
Anorexia	Give with small meals and advise patient to swallow pills slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration; initiate rehydration if indicated Decrease frequency of pyrazinamide administration Discontinue pyrazinamide if this can be done without compromising regimen – rarely necessary
Dysuria	Provide supportive care If dysuria is bothersome to the patient, administer phenazopyridine 100 to 200 mg three times a day for 24 to 48 hours Phenazopyridine turns urine red-orange; patients should be cautioned not to confuse this effect with progression of infection or hematuria
Fever	Rule out other causes Paracetamol or ibuprofen can be given to lower the temperature **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity Exercise caution with use and monitor renal function Fluids may be given by mouth or IV to prevent dehydration, if necessary
Flushing	Usually mild and resolves without therapy If flushing is bothersome to the patient, an antihistamine (e.g., loratadine) may be administered to treat or prevent the reaction **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Pyrazinamide [1,4,59,60,64–66]	
Hematological abnormalities (decreased blood platelets, thrombocytopenia, vacuolation of erythrocytes, increased serum iron concentration, clotting disorders)	Stop all therapy pending resolution of toxicity Eliminate other potential causes of toxicity Consider suspending most likely agent permanently Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Interstitial nephritis	Stop all therapy pending resolution of interstitial nephritis Rule out other potential causes of interstitial nephritis Reintroduce drugs, individually with the least nephrotoxic agent first Monitor renal function Consider dosing 2 to 3 times a week if drug is essential to the regimen Adjust all anti-tuberculosis medications according to the creatinine clearance Discontinuation of pyrazinamide should strongly be considered
Musculo-skeletal Pain	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Decrease frequency of pyrazinamide administration Discontinue pyrazinamide if this can be done without compromising regimen—rarely necessary
Porphyria	Discontinue pyrazinamide Consider dosing 2 to 3 times a week if drug is essential to the regimen and patient can tolerate Provide symptomatic therapy, high carbohydrate intake and intravenous administration of hematin Modify regimen according to national TB treatment guidelines
Sideroblastic anemia	Administer pyridoxine 50 to 300 mg per day to maintain hemoglobin level
Overdosage	Clinical monitoring and supportive therapy should be employed There is no known antidote Pyrazinamide is dialyzable

Criteria for Rifabutin [4,59,60,64,67,68]	
I. ***Justification criteria*** for prescribing rifabutin	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Clinically diagnosed by a TB medical provider (e.g., X-ray abnormalities or suggestive histology)
	Laboratory drug susceptibility testing (DST) documents that the organism is susceptible to rifabutin
	Chronic multidrug-resistant pulmonary tuberculosis in the presence of rifampicin resistant, rifabutin-sensitive *M. tuberculosis* strains
	Patient is HIV immunodeficient and being treated with ritonavir-boosted protease inhibitor or protease-inhibitor-containing antiretroviral therapy
	Patient is rifampicin intolerant (e.g., hepatic impairment, hepatically based drug interactions)
	According to national TB treatment guidelines
II. ***Process criteria*** to consider when prescribing rifabutin	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Previous discontinuation of rifabutin • Hypersensitivity to rifabutin or other rifamycins • Anterior uveitis and other eye disorders • Impaired liver function • Impaired kidney function • History of diabetes • Excessive concurrent use of alcohol • Porphyria
	HIV status is documented in case records
	Rifabutin was available for the duration of treatment
Dose and Frequency	Appropriate dosing for adult patients • 300 to 450 mg once a day
	Appropriate dose for HIV-positive adult patients treated with ritonavir boosted protease inhibitors (e.g., lopinavir) • 150 mg three times a week or 150 mg every other day
	Appropriate dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • Monitor drug concentrations to avoid toxicity Administer rifabutin following dialysis on dialysis days • 5 to 10 mg/kg/day Not to exceed 300 mg daily

Criteria for Rifabutin [4,59,60,64,67,68]			
Administration	For oral use only May be administered without regard to food In pregnancy, phytomenadione (Vitamin K) should be administered at birth to the infant of a mother taking rifabutin because of the risk of postnatal hemorrhage		
Duration	Drug susceptible TB	Intensive phase	2 months
		Continuation phase	4 months
	Drug resistant TB	Intensive phase	at least 8 months
		Continuation phase	at least 12 months

Patient monitoring	Prior to treatment and then at least monthly during treatment:
	
	Weight (and every 2 weeks for the first three months of treatment)
	
	Pregnancy testing—according to standard clinical protocol
	
	Liver function
	• AST (SGOT)
	• ALT (SGPT)
	• Total bilirubin
	
	Note: For patients with impaired liver function—prior to therapy and then every 2 to 4 weeks during therapy
	
	Renal function
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Complete blood count with differential
	
	Platelet count
	
	Ophthalmologic function
	• Ophthalmoscopy
	• Finger perimetry
	• Acuity testing (Snellen chart)
	• Color discrimination (Ishihara tests)
	
	Therapeutic response of interacting medications		

Criteria for Rifabutin [4,59,60,64,67,68]	
Patients with diabetes	Prior to therapy and then at least daily until stabilized during therapy Blood glucose HIV testing—according to standard clinical protocol
Therapeutic drug monitoring—rifabutin blood levels	Recommended only for patients suspected of having malabsorption, treatment failure, or administered reduced doses in renal disease Peak concentrations should be obtained 2 hours after a dose, and if delayed absorption is considered, a concentration at 6 hours should also be collected Peak concentrations of 0.3 to 0.9 mcg/ml are expected Dose increase should be strongly considered for low concentrations (but not for delayed absorption), as rifampicin exhibits a dose response in treatment of TB See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance in how to adjust dose based on serum concentration
Drug interactions	The dose of rifabutin may need to be decreased when coadministered with the following drugs or classes of drugs • Antimycotics—imidazole and triazole derivatives (e.g., fluconazole—reduce rifabutin by half) • Calcium channel blockers (e.g., verapamil) • Chloramphenicol • Fluoroquinolones (e.g., levofloxacin) • Clarithromycin (reduce rifabutin dose by half) • Other macrolide antibiotics (e.g., azithromycin, erythromycin) • Indinavir (reduce rifabutin dose by half) • Other protease inhibitors (do not coadminister ritonavir or saquinavir) • Sulfamethoxazole • Trimethoprim
	The dose of rifabutin may need to be increased when coadministered with the following drugs or classes of drugs: • Carbamazepine • Mifepristone

Criteria for Rifabutin [4,59,60,64,67,68]	

	The dose of the following drugs or classes of drugs may need to be increased when coadministered with rifabutin
	• Anticonvulsants (e.g., carbamazepine, ethosuximide, phenytoin, valproic acid)
	• Antimycotics—azole derivatives (e.g., fluconazole)
	• Barbiturates (e.g., phenobarbital)
	• Benzodiazepines (e.g., diazepam, midazolam)
	• Beta blockers (e.g., propranolol)
	• Calcium channel blockers (e.g., verapamil)
	• Cardiac glycosides (e.g., digoxin)
	• Ciclosporin
	• Clarithromycin
	  ○ Other macrolide antibiotics (e.g., azithromycin, erythromycin)
	• Corticosteroids (e.g., dexamethasone, hydrocortisone, prednisolone)
	• Coumarin anticoagulants (e.g., warfarin)
	• Dapsone
	• Indinavir
	  ○ Other protease inhibitors (do not coadminister ritonavir or saquinavir)
	• Lidocaine
	• Non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine; do not coadminister delavirdine)
	• Nucleoside and nucleotide reverse transcriptase inhibitors (e.g., zidovudine)
	• Estrogens
	• Opiate analgesics (e.g., morphine)
	• Oral hypoglycemics (e.g., metformin)
	• Sulfamethoxazole
	• Trimethoprim
	• Vincristine

	If co-infected with HIV, patient is not coadministered non-nucleoside reverse transcriptase inhibitor delavirdine
	If co-infected with HIV, patient is not coadministered protease inhibitors ritonavir or saquinavir
	Patient is not coadministered halothane

Criteria for Rifabutin [4,59,60,64,67,68]

Additional patient monitoring maybe required when coadministered with the following drugs
• Oral anticoagulants
  ○ prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant
• Oral hypoglycemic agents (sulfonylureas)
  ○ glucose monitoring may be performed as frequently as necessary to establish and maintain the required dose of anti-diabetic agent or alternative glucose control therapy
• Clarithromycin (or other macrolides)
  ○ monitor patient for uveitis
• Fluconazole (and related compounds)
  ○ monitor patient for uveitis
• Indinavir (and related compounds)
  ○ monitor patient for increase in rifabutin adverse drug reactions

Antacids may reduce the absorption of rifabutin • Administer rifabutin at least 1 hour before the ingestion of antacids
Rifampicin impairs the effectiveness of oral contraceptives • Recommend the use of another form of contraception during treatment and four to eight weeks after stopping treatment
Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents. Adjust doses as described in Annex J. Managing Drug Interactions with Antiretrovirals and Rifabutin [115]
Hepatotoxic and nephrotoxic drugs • May potentiate toxicities • If necessary to coadminister, monitor adverse drug reactions carefully Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs
May cause false-positive urine opiate screening test results • Confirm with gas chromatography/mass spectrometry
May inhibit microbiological assays for serum folate (Vitamin B9) and hydroxocobalamin (Vitamin B12) • Consider alternate assay methods
May case abnormalities in liver function tests (LFTs) and reduce excretion of gall bladder contrast media • Conduct LFTs and gall bladder imaging prior to morning dose of rifabutin

Criteria for Rifabutin [4,59,60,64,67,68]	
Patient Counseling	Advise patient • Rifabutin may be taken with or without food • Rifabutin may produce a reddish coloration of the urine, stools, tears, saliva, sweat, semen and sputum; contact lenses and clothing may be permanently stained • Rifabutin may affect the reliability of oral or other systemic hormonal contraceptives and patient should consider using non-hormonal contraceptive measures during treatment and four to eight weeks after stopping treatment
	Advise patient to contact a health care provider immediately if they experience: • Eye pain, change in vision, or sensitivity to light • Fever or chills • Sore throat • Pain or swelling of the joints • Yellowish discoloration of the skin and eyes • Nausea or vomiting • Unusual fatigue or loss of appetite • Severe abdominal upset • Diarrhea • Darkened urine
	Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category B • Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women • No proven risk in humans
	Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Rifabutin [4,59,60,64,67,68]	
III. ***Complications*** that could occur during therapy with rifabutin and how to respond if the complication presents as follows:[1]	
Severe or common toxicities are indicated by **bold** font	
Anterior uveitis and other eye toxicities (e.g., optic neuritis, corneal deposits)	Refer patient to an ophthalmologist In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult
Arthralgias	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Decrease frequency of rifabutin administration Discontinue rifabutin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Hypersensitivity, mild (skin itching, redness, rash, swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Rifabutin [4,59,60,64,67,68]	
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, bronchospasm, angioedema, exfoliative dermatitis, stomatitis, shortness of breath, edema of face and extremities, hypotension, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Reddish coloration of body fluids (e.g., urine, stools, tears, saliva, sweat, semen, and sputum)	Counsel patients to expect discoloration Advise patients that contact lenses may be stained Reassure patient that symptoms are harmless and will subside as treatment progresses
Aphthous stomatitis	Instruct patient to: Avoid hot beverages and foods Avoid salty, spicy, and citrus-based foods Gargle with cool water or suck on ice pops Administer non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
Blood glucose disturbances	Monitor blood glucose Initiate or adjust oral hypoglycemic agent or insulin—according to standard clinical protocol

Criteria for Rifabutin [4,59,60,64,67,68]	
Central nervous system related adverse drug reactions (confusion)	Generally occurs during first few weeks of therapy
	Reassure patient that symptoms will subside as treatment progresses
	Suspect drug-induced acute liver failure if there is jaundice
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Consider reducing the frequency of rifabutin administration to five times or even three times per week
	Discontinue rifabutin if this can be done without compromising regimen— rarely necessary
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue rifabutin
	Modify regimen according to national TB treatment guidelines
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of rifabutin administration
	Discontinue rifabutin if this can be done without compromising regimen—rarely necessary
Ergocalciferol (Vitamin D) deficiency	Check Vitamin D
	If Vitamin D is low, also check for hypocalcaemia, hypophosphotaeimia, and elevated parathyroid hormone
	Initiate Vitamin D therapy—according to standard clinical protocol

Criteria for Rifabutin [4,59,60,64,67,68]	
Fever	Rule out other causes Paracetamol or ibuprofen can be given to lower the temperature **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Fluids may be given by mouth or IV to prevent dehydration, if necessary
Flu-like syndromes (e.g., fever, chills and malaise)	Change from intermittent to daily rifabutin Provide symptomatic treatment as listed for individual
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis) Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole) Stop rifabutin for short periods of time (e.g., one to seven days) Discontinue rifabutin if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of rifabutin administration to five times or even three times per week

Criteria for Rifabutin [4,59,60,64,67,68]	
Hematological abnormalities (e.g., **leukopenia**, **thrombocytopenia**)	Stop all therapy pending resolution of toxicity Eliminate other potential causes of toxicity Consider suspending most likely agent permanently Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Hepatitis and other **hepatotoxicity** (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other **hepatotoxicity** (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non-hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis); and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential, consider not reintroducing it Once resolved, monitor liver function monthly
Menstrual disturbances	Reported when used with hormonal contraceptives Consider non-hormonal contraceptive measures
Metabolic acidosis	Monitor serum electrolytes and arterial blood gasses Initiate sodium hydrogen carbonate therapy—according to standard clinical protocol
Myalgia	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Decrease frequency of rifabutin administration Discontinue rifabutin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines

Criteria for Rifabutin [4,59,60,64,67,68]	
Nausea, vomiting, or anorexia	Administer with small meals and advise patient to swallow tablets slowly with small sips of water
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Assess for dehydration, electrolyte disturbances, hepatitis
	Initiate rehydration if indicated
	Initiate antiemetic therapy (e.g., metoclopramide, ondansetron)
	Decrease frequency of rifabutin administration
	Discontinue rifabutin if this can be done without compromising regimen—rarely necessary
Nephrotoxicity or renal failure	Consider dosing two or three times a week if drug is essential to the regimen
	Monitor creatinine closely
	Adjust all anti-TB medications according to the creatinine clearance
	Discontinue rifabutin if serum creatinine is greater than 100 mcg/mL
	Modify regimen according to national TB treatment guidelines
Porphyria	Discontinue rifabutin
	Consider dosing 2 to 3 times a week if drug is essential to the regimen and patient can tolerate
	Provide symptomatic therapy, high carbohydrate intake, and intravenous administration of hematin
	Modify regimen according to national TB treatment guidelines
Purpura	Suspect thrombocytopenia
	Discontinue rifabutin as soon as purpura occurs
	Cerebral hemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura
	Modify regimen according to national TB treatment guidelines

Criteria for Rifabutin [4,59,60,64,67,68]	
Overdosage	Intensive support measures should be instituted and individual symptoms treated as they arise The airway should be secured and adequate respiratory exchange established Since nausea and vomiting are likely to be present, gastric lavage within the first 2 to 3 hours after ingestion is probably preferable to induction of emesis Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract Antiemetic medication may be required to control severe nausea and vomiting Active diuresis (measuring intake and output) will help promote rifabutin excretion For severe cases, extracorporeal hemodialysis may be required. If this is not available, peritoneal dialysis can be used along with forced diuresis

Criteria for Rifampicin [1,4,59,60,64,69]	
I. ***Justification criteria*** for prescribing rifampicin	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics) Clinically diagnosed by a TB medical provider (e.g., X-ray abnormalities or suggestive histology) Laboratory drug susceptibility testing (DST) documents that the organism is susceptible to rifampicin According to national TB treatment guidelines
II. ***Process criteria*** to consider when prescribing rifampicin	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent Patient history has been reviewed for: • Previous discontinuation of rifampicin • Hypersensitivity to rifampicin or other rifamycins • Impaired liver function • Impaired kidney function • History of diabetes • Excessive concurrent use of alcohol • Porphyria HIV status is documented in case records Rifampicin was available for the duration of treatment
Dose and frequency	Appropriate dosing for adult patients • 10 mg/kg (8 to 12 mg/kg) daily Not to exceed 600 mg daily • Appropriate dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • No adjustment necessary Administer rifampicin following dialysis on dialysis days Appropriate dose for pediatric patients • 10 to 20 mg/kg daily Not to exceed 600 mg daily

Criteria for Rifampicin [1,4,59,60,64,69]			

Administration	For oral use
	• Give by mouth on an empty stomach, one hour before or two hours after meals
	• May be given with a small amount of food if it irritates the stomach
	• For parenteral use—May be administered intravenously if patient cannot tolerate oral medication
	• Must not be administered intramuscularly or subcutaneously
	• The reconstituted solution is stable at room temperature 15 to 25°C, for 24 hours
	• Rifampicin can be added to the following diluents for infusion:
	  ○ glucose 5% for injection (stable at room temperature for up to 4 hours)
	  ○ normal saline (stable at room temperature for 24 hours)
	• Administer 500 mL infusion over 3 hours, or 100 mL infusion over 30 minutes
	• Store vials of powder at 25°C excursions permitted to 15 to 30°C
	• Avoid temperatures above 40°C
	• Protect from light
	
	In pregnancy, phytomenadione (vitamin K) should be administered at birth to the infant of a mother taking rifampicin because of the risk of postnatal hemorrhage		

Duration	Drug susceptible TB	Intensive phase	2 months
		Continuation phase	4 months

Criteria for Rifampicin [1,4,59,60,64,69]	

Patient monitoring	Adults—Prior to treatment and then at least monthly during treatment
	• Weight
	• Pregnancy testing—according to standard clinical protocol
	• Liver function
	  ○ AST (SGOT)
	  ○ ALT (SGPT)
	  ○ Total bilirubin
	
	Note: for patients with impaired liver function**—** Prior to treatment and then every 2 to 4 weeks during treatment:
	
	Renal function
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Complete blood count with differential
	
	Platelet count
	
	Pediatrics—none required unless a complicating condition is known or clinically suspected
	
	Patients with diabetes—Prior to therapy and then at least daily until stabilized during therapy:
	• Blood glucose
	
	HIV testing —according to standard clinical protocol

Therapeutic drug monitoring—rifampicin blood levels	Recommended only for patients suspected of having malabsorption or treatment failure Peak concentrations should be obtained 2 hours after a dose, and if delayed absorption is considered, a concentration at 6 hours should also be collected Peak concentrations of 8 to 24 mcg/ml are expected Dose increase should be strongly considered for low concentrations (but not for delayed absorption), as rifampicin exhibits a dose response in treatment of TB. See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration.

Criteria for Rifampicin [1,4,59,60,64,69]	

Drug interactions	The dose of rifampicin may need to be decreased when coadministered with the following drugs or classes of drugs
	• Antimycotics—azole derivatives (e.g., fluconazole—reduce rifampicin by half)
	• Calcium channel blockers (e.g., verapamil, enalapril)
	• Chloramphenicol
	• Clarithromycin (reduce rifampicin dose by half)
	  ○ Other macrolide antibiotics (e.g., azithromycin, erythromycin)
	• Fluoroquinolones (e.g., levofloxacin)
	• Haloperidol
	• Indinavir (reduce rifampicin dose by half)
	  ○ Other protease inhibitors (do not coadminister ritonavir or saquinavir)
	• Levothyroxine
	• Progestins (e.g., norethindrone enantate)
	• Pyrazinamide
	• Sulfamethoxazole
	• Sulfasalazine
	• Tricyclic antidepressants (e.g., amitriptyline)
	• Trimethoprim
	• Zidovudine

	The dose of rifampicin may need to be increased when coadministered with the following drugs or classes of drugs: • Carbamazepine • Mifepristone • Omeprazole • Quinine

Criteria for Rifampicin [1,4,59,60,64,69]	
	The dose of the following drugs or classes of drugs may need to be increased when coadministered with rifampicin • Anticonvulsants (e.g., carbamazepine, ethosuximide, phenytoin, valproic acid) • Antimycotics—azole derivatives (e.g., fluconazole) • Barbiturates (e.g., phenobarbital) • Benzodiazepines (e.g., diazepam, midazolam) • Beta blockers (e.g., propranolol) • Calcium channel blockers (e.g., verapamil) • Cardiac glycosides (e.g., digoxin) • Ciclosporin • Clarithromycin • Other macrolide antibiotics (e.g., azithromycin, erythromycin) • Corticosteroids (e.g., prednisolone, methylprednisolone) • Coumarin anticoagulants (e.g., warfarin) • Dapsone • Indinavir ○ Other protease inhibitors (do not coadminister ritonavir or saquinavir) • Lidocaine • Mifepristone • Non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine; do not coadminister delavirdine) • Nucleoside and nucleotide reverse transcriptase inhibitors (e.g., zidovudine) • Estrogens • Opiate analgesics (e.g., morphine) • Oral hypoglycemics (e.g., metformin) • Praziquantel • Pyrazinamide • Sulfamethoxazole • Trimethoprim • Vincrisinte
	If co-infected with HIV, patient is not coadministered ritonavir-boosted protease inhibitors ritonavir or saquinavir
	Patient is not coadministered halothane
	Rifampicin impairs the effectiveness of oral contraceptives • Recommend the use of another form of contraception
	Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents. • Adjust doses as described in Annex I. Managing Drug Interactions with Antiretrovirals and Rifampicin

Criteria for Rifampicin [1,4,59,60,64,69]	
	Hepatotoxic and nephrotoxic drugs • May potentiate toxicities • If necessary to coadminister, monitor adverse drug reactions carefully Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs
	May cause false-positive urine opiate screening test results • Confirm with gas chromatography/mass spectrometry
	May inhibit microbiological assays for serum folate (vitamin B9) and hydroxocobalamin (vitamin B12) • Consider alternate assay methods
	May case abnormalities in liver function tests (LFTs) and reduce excretion of gall bladder contrast media • Conduct LFTs and gall bladder imaging prior to morning dose of rifampicin
Patient counseling	Advise patient • Rifampicin may produce a reddish coloration of the urine, tears, saliva, sweat, semen, and sputum; contact lenses and clothing may be permanently stained • Rifampicin may affect the reliability of oral or other systemic hormonal contraceptives and should consider using non-hormonal contraceptive measures during treatment and four to eight weeks after stopping treatment • Take rifampicin one hour before or two hours after food or antacids with a full glass of water Advise patient to contact a health care provider immediately if they experience • Unusual fatigue or loss of appetite • Severe abdominal upset • Fever or chills • Nausea or vomiting • Darkened urine • Yellowish discoloration of the skin and eyes • Pain or swelling of the joints Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Potential benefit should outweigh the potential risk Advise patients who are breastfeeding • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Rifampicin [1,4,59,60,64,69]	
III. ***Complications*** that could occur during therapy with rifampicin and how to respond if the complication presents as follows:[1]	
Severe or common toxicities are indicated by **bold** font	
Flu-like syndrome (e.g., fever, chills and malaise)	Change from intermittent to daily rifampicin Provide symptomatic treatment as listed for individual
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis) Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole) Stop rifampicin for short periods of time (e.g., one to seven days) Discontinue rifampicin if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol induced hepatitis); and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Rifampicin [1,4,59,60,64,69]	
Hypersensitivity, mild (skin itching, redness, rash, swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, shortness of breath, edema of face and extremities, hypotension, anaphylactic shock, Stevens-Johnson syndrome)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson syndrome)
Reddish coloration of body fluids (e.g., urine, stools, tears, saliva, sweat, semen, and sputum)	Counsel patients to expect discoloration Advise patients that contact lenses may be stained Reassure patient that symptoms are harmless and will subside as treatment progresses
Blood glucose disturbances	Monitor blood glucose Initiate or adjust oral hypoglycemic agent or insulin—according to standard clinical protocol
Central nervous system-related adverse drug reactions (confusion)	Generally occurs during first few weeks of therapy Reassure patient that symptoms will subside as treatment progresses Suspect drug-induced acute liver failure if there is jaundice Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Consider reducing the frequency of rifampicin administration to five times or even three times per week Discontinue rifampicin if this can be done without compromising regimen— rarely necessary

Criteria for Rifampicin [1,4,59,60,64,69]	
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue rifampicin
	Modify regimen according to national TB treatment guidelines
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of rifampicin administration
	Discontinue rifampicin if this can be done without compromising regimen— rarely necessary
Ergocalciferol (Vitamin D) deficiency	Check Vitamin D
	If Vitamin D is low also check for hypocalcemia, hypophosphatemia, and elevated parathyroid hormone
	Initiate Vitamin D therapy—according to standard clinical protocol
Fever	Rule out other causes
	Paracetamol or ibuprofen can be given to lower the temperature
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity Exercise caution with use and monitor renal function
	Fluids may be given by mouth or IV to prevent dehydration, if necessary

Criteria for Rifampicin [1,4,59,60,64,69]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity Exercise caution with use and monitor renal function Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of rifampicin administration to five times or even three times per week
Hematological abnormalities (e.g., **thrombocytopenia**, disseminated intravascular coagulation, leukopenia, **acute hemolytic anemia**, decreased hemoglobin, agranulocytosis)	Stop all therapy pending resolution of toxicity Eliminate other potential causes of toxicity Consider suspending most likely agent permanently Reintroduce remaining drugs, one at a time with the least myelotoxic agents first, while frequently monitoring hematology
Menstrual disturbances	Reported when used with hormonal contraceptives Consider non-hormonal contraceptive measures
Metabolic acidosis	Monitor serum electrolytes and arterial blood gasses Initiate sodium hydrogen carbonate therapy—according to standard clinical protocol

Criteria for Rifampicin [1,4,59,60,64,69]	
Nausea, vomiting, anorexia	Administer with small meals and advise patient to swallow tablets slowly with small sips of water
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Assess for dehydration, electrolyte disturbances, hepatitis
	Initiate rehydration if indicated
	Initiate antiemetic therapy (e.g., metoclopramide, ondansetron)
	Decrease frequency of rifampicin administration
	Discontinue rifampicin if this can be done without compromising regimen—rarely necessary
Nephrotoxicity or renal failure	Consider dosing two or three times a week if drug is essential to the regimen
	Monitor creatinine closely
	Adjust all anti-TB medications according to the creatinine clearance
	Discontinue rifampicin if serum creatinine is greater than 100 mcg/mL
	Modify regimen according to national TB treatment guidelines
Porphyria	Discontinue rifampicin
	Consider dosing 2 to 3 times a week if drug is essential to the regimen and patient can tolerate
	Provide symptomatic therapy, high carbohydrate intake, and intravenous administration of hematin
	Modify regimen according to national TB treatment guidelines
Purpura	Suspect thrombocytopenia
	Discontinue rifampicin as soon as purpura occurs
	Modify regimen according to national TB treatment guidelines
	Cerebral hemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura
Visual disturbances	Generally occurs during first few weeks of therapy
	Reassure patient that symptoms will subside as treatment progresses
	Refer to ophthalmologist if condition persists

Criteria for Rifampicin [1,4,59,60,64,69]	
Overdosage	Intensive support measures should be instituted and individual symptoms treated as they arise The airway should be secured and adequate respiratory exchange established Since nausea and vomiting are likely to be present, gastric lavage within the first 2 to 3 hours after ingestion is probably preferable to induction of emesis Following evacuation of the gastric contents, instilling activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract Antiemetic medication may be required to control severe nausea and vomiting Active diuresis (measuring intake and output) will help promote rifampicin excretion For severe cases, extracorporeal hemodialysis may be required. If this is not available, peritoneal dialysis can be used along with forced diuresis

Criteria for Streptomycin [1,4,58–60,70,71]	
I. ***Justification criteria*** for prescribing streptomycin	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Clinically diagnosed by a TB medical provider (e.g., X-ray abnormalities or suggestive histology)
	Laboratory drug susceptibility testing (DST) documents that the organism is susceptible to streptomycin
	According to national TB treatment guidelines
II. ***Process criteria*** to consider when prescribing streptomycin	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Hypersensitivity to streptomycin • Hypersensitivity to other aminoglycocides (e.g., kanamycin, gentamicin) • G6PD deficiency • Previous discontinuation of streptomycin • Pregnancy status
	HIV status is documented in case records
	Streptomycin was available for the duration of treatment

Criteria for Streptomycin [1,4,58–60,70,71]		
Dose and frequency	Appropriate dosing for adult patients • 15 mg/kg (12 to 18 mg/kg) daily or 15 mg/kg (12 to 18 mg/kg) 2 or 3 times weekly Not to exceed 1,000 mg per day Adults over 59 years of age • 10 mg/kg daily Not to exceed 750 mg daily Appropriate dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis, pre-renal azotemia, nitrogen retention) • 12 to 15 mg/kg per dose two or three times per week Not to exceed 1,000 mg daily Administer streptomycin following dialysis on dialysis days Adjust frequency of administration to three times a week if appropriate for patients with a history of • Hearing disorders • Vestibular disorders • Neuromuscular disorders such as myasthenia gravis, Parkinson's Disease, or infant botulism Appropriate dose for pediatric patients • 20 to 40 mg/kg/day Not to exceed 1,000 mg daily	
Administration	For parenteral use • Reconstitute with water for injection • Deep intramuscular injection preferred • Intravenous injection given slowly as an undiluted bolus injection, although other methods may be employed Rotate injection sites to avoid local discomfort Sterile reconstituted solutions may be stored at room temperature (15 to 25°C) for one week Store ampoules of solution under refrigeration (2 to 8°C) Store vials of powder at controlled room temperature before reconstitution Protect from light	
Duration	Mono-resistant TB	at least 6 months

Criteria for Streptomycin [1,4,58–60,70,71]	
Patient monitoring	Prior to treatment and then at least monthly during treatment Weight (and every 2 weeks for the first 3 months of treatment) Pregnancy testing—according to standard clinical protocol Eighth cranial nerve function • Audiometric or caloric stimulation testing Renal function One or more of the following laboratory measurements: • Blood ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN) ○ Serum creatinine concentration (preferred over BUN) ○ Blood urea nitrogen (BUN) ○ Non-protein nitrogen (NPN) • Urine ○ Proteinuria ○ Presence of cells and casts ○ Specific gravity Liver function • AST (SGOT) • ALT (SGPT) • Total bilirubin Signs of neurotoxicity HIV testing—according to standard clinical protocol
Therapeutic drug monitoring—streptomycin blood levels	To assure adequate levels avoid troughs below 10 mcg/mL To avoid potentially toxic levels avoid prolonged peak concentrations above 35 mcg/mL See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration

Criteria for Streptomycin [1,4,58–60,70,71]	
Drug interactions	Potent diuretics (e.g., furosemide or mannitol) enhance the ototoxic effect of streptomycin • Adjust dosage as appropriate Streptomycin prolongs the action of non-depolarizing muscle relaxants (e.g., vecuronium) • Decrease dosage of the muscle relaxant as appropriate • Monitor neuromuscular function closely Beta-lactam-type antibiotics (penicillins or cephalosporins) may result in a significant mutual inactivation when coadministered with streptomycin • Adjust dosage as appropriate The following medicines may increase the effects of streptomycin • Amphotericin B • Capreomycin • Cephalosporins (e.g., cefalexin) • Cisplatin • Loop diuretics (e.g., furosemide) • NSAIDs • Vancomycin • BCG vaccine (avoid coadministration) Streptomycin may increase or prolong the effects of • Carboplatin • Ciclosporin • Opioid analgesics • Halogenated hydrocarbon inhalation anesthetics Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents. Hepatotoxic, Nephrotoxic, Neurotoxic and Ototoxic drugs • May potentiate toxicities • If necessary to coadminister or sequentially administer, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs. Streptomycin may cause false-positive results in urine glucose determinations using cupric sulfate solution (Benedict's reagent, Clintest®)

Criteria for Streptomycin [1,4,58–60,70,71]	
Patient counseling	Advise patient to contact a health care provider immediately if they experience • Problems with hearing, dizziness, or balance • Rash or swelling of the face • Trouble breathing • Decreased urination • Watery or bloody diarrhea • Swelling, pain, or redness at the injection site • Muscle twitching or weakness Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category D • There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans • Potential benefits may warrant use of the drug in pregnant women despite potential risks Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with streptomycin and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Electrolyte disturbances (e.g., dark urine, irregular heartbeat, fatigue, bowel irregularities muscle weakness or pain, changes in mood or coherence, headache)	Check potassium If potassium is low, also check magnesium (and calcium if hypocalcaemia is suspected) Replace electrolytes as needed Dose oral electrolytes apart from fluoroquinolones as they and interfere with fluoroquinolone absorption
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

[1] For mild reactions, encourage the patient to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Streptomycin [1,4,58–60,70,71]	
Hypersensitivity, severe (e.g., Stevens-Johnson syndrome, eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, lupoid reactions, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Injection site reactions (e.g., localized trauma, minor discomfort and pain, bleeding, bruising)	Maintain light pressure to prevent bruising If a bruise does appear, don't use that injection site again until the bruise is gone An affected limb should be elevated to minimize inflammation An anti-inflammatory cream or gel can be directly applied to the area Anti-inflammatory analgesics can be prescribed to treat both the inflammation and the pain associated with the reaction **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function
Optic neuritis (blurred vision, visual disturbances, scotomas, and enlargement of the blind spot dysfunction of the optic nerve)	Refer patient to an ophthalmologist In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions. In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult

Criteria for Streptomycin [1,4,58–60,70,71]	
Ototoxicity, auditory (any loss of hearing, ringing or buzzing, a feeling of fullness in the ears)	Conduct audiometry and compare with baseline Consider reducing the frequency of streptomycin administration to two or three times a week Discontinue streptomycin if hearing loss continues despite regimen modification **Note:** The risk of further hearing loss should be weighed against the risk of stopping streptomycin. The provider should consult with the patient regarding the desired course of action Modify regimen according to national TB treatment guidelines
Ototoxicity, vestibular (clumsiness, dizziness, nausea, vomiting, unsteadiness)	Document events and compare with prior to starting treatment Initiate anti-emetics (e.g., metoclopramide, ondansetron) if appropriate Initiate cyclizine for dizziness if appropriate Decrease frequency of streptomycin administration to two or three times a week Discontinue streptomycin if symptoms worsen **Note:** The risk of toxicity should be weighed against the risk of stopping streptomycin. The provider should consult with the patient regarding the desired course of action. Modify regimen according to national TB treatment guidelines
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes Correct any vitamin or nutritional deficiencies Administer pyridoxine 200 to 300 mg per day Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily) Consider paracetamol and NSAIDs (or both) for pain relief **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Consider neurology consultation Consider administering carbamazepine Decrease frequency of streptomycin administration Discontinue streptomycin Modify regimen according to national TB treatment guidelines

Criteria for Streptomycin [1,4,58–60,70,71]	
Renal failure or nephrotoxicity	Discontinue streptomycin
	Adjust dose of all drugs according to the creatinine clearance
	Rule out other causes (e.g., other medications, diabetes, congestive heart failure, urinary obstruction), and if identified, treat according to standard clinical protocol
	Consider dosing three times a week and monitor creatinine clearance every one to two weeks
	If creatinine clearance does not stabilize, permanently discontinue streptomycin
	Modify regimen according to national TB treatment guidelines
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue streptomycin if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of streptomycin administration
	Discontinue streptomycin if this can be done without compromising regimen—rarely necessary

Criteria for Streptomycin [1,4,58–60,70,71]	
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis), and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Neuromuscular blockade (e.g., difficulty in breathing, drowsiness, weakness)	If blockage occurs, calcium salts may reduce these phenomena but mechanical respiratory assistance may be necessary
Overgrowth of non-susceptible organisms	Discontinue streptomycin and institute appropriate therapy if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines

Criteria for Streptomycin [1,4,58–60,70,71]	
Renal irritation	Casts, white or cells, albumin • Increase hydration Decreased creatinine clearance; decreased urine specific gravity; increased BUN, creatinine or oliguria • Decrease frequency of streptomycin administration Increased azotemia or decrease in urinary output • Decrease frequency of streptomycin administration • Discontinue streptomycin if this can be done without compromising the regimen • Modify regimen according to national TB treatment guidelines
Overdosage	For most aminoglycoside overdosages, supportive symptomatic therapy, maintenance of life support measures (airway, breathing, circulation), and administration of sufficient fluids to maintain a urine flow of 3 to 6 mL/kg/hr are adequate. Caution must be exercised to avoid fluid overload and pulmonary edema, especially when overaggressive therapy is administered to patients with renal insufficiency. Intravenous calcium gluconate may be useful in treatment of neuromuscular paralysis Eight cranial nerve function (auditory, vestibular) must be carefully monitored in the period (weeks or months) after an aminoglycoside overdosage

Second-Line Drugs

Please Be Aware of the Following When Using Information in this Annex.

At this time, routine DST of drugs in groups 4 (ethionamide, protionamide, cycloserine, terizidone, p-aminosalicylic acid) is not recommended as reliability and reproducibility of laboratory testing cannot be guaranteed.[72]

Although the drug information in this document is extensive, it is not intended to replace National Standard Treatment Guidelines, package inserts, or other printed material that may be available or accompany a particular drug.

Only medicines on the WHO Model Essential Medicines Lists [53,54] are referenced in this document.

Ancillary medicines or concomitant medicines on National Essential Medicine Lists that do not appear on the WHO Model Lists should be checked for:

- interactions with anti-TB medicines
- contraindications for co-administration with anti-TB medicines
- correct dose and administration for treatment of adverse drug reactions

This information should be added to the information in Annex A.

Children older than 12 years of age can be managed as adults.[55]

Consult with a TB specialist or clinical pharmacist about the clinical use of **any** medicine administered to a patient.

Criteria for Amikacin [2–4,58,60,71,73–75]	
I. ***Justification criteria*** for prescribing amikacin	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents that the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available
	Patient is allergic to isoniazid or rifampicin
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin
	Organism is susceptible to amikacin (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing amikacin	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Amikacin allergy • Aminoglycoside allergy • Sodium bisulfate allergy • Possibility of pregnancy
	HIV status is documented in case records
	Amikacin was available for the duration of treatment

Criteria for Amikacin [2–4,58,60,71,73–75]			
Dose and frequency	Appropriate amikacin dosing for adult patients • 15 to 20 mg/kg daily Not to exceed 1,000 mg daily Adults over 59 years old • 10 mg/kg daily or 15 mg/kg three times per week Not to exceed 750 mg daily Appropriate amikacin dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 12 to 15 mg/kg per dose two or three times per week Amikacin should be administered following dialysis on dialysis days Appropriate amikacin dosing for pediatric patients • 15 to 22.5 mg/kg daily Not to exceed 1,000 mg daily Adjust dosing if appropriate for patients with a history of • Hearing disorders • Vestibular disorders • Neuromuscular disorders such as myasthenia gravis, Parkinson's Disease, or infant botulism		
Administration	For parenteral administration • Reconstitute with 0.9% sodium chloride injection • Deep intramuscular injection preferred • Administer IV injections over 2 to 3 minutes • Administer intermittent IV infusions ○ For adults over 30 to 60 minutes ○ For infants over 1 to 2 hours ○ May be divided into either 2 or 3 equally-divided doses at equally-divided intervals Rotate injection sites to avoid local discomfort Maintain adequate hydration to prevent irritation of the renal tubules Store vials at controlled room temperature, 15 to 25°C Amikacin is stable for 24 hours at room temperature and 2 days at refrigeration (2 to 8°C) at concentrations of 0.25 and 5.0 mg/mL in the following solutions • 5% glucose injection • 0.9% sodium chloride Injection • Sodium lactate, compound solution		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months

Criteria for Amikacin [2–4,58,60,71,73–75]	

Patient Monitoring	Prior to treatment and then at least monthly during treatment:
	• Weight (and every 2 weeks for the first 3 months of treatment)
	• Pregnancy testing—according to standard clinical protocol
	• Eighth cranial nerve function
	  ○ Audiometric or caloric stimulation testing
	• Renal function
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Liver function
	• Monitor in patients with severe liver disease
	  ○ AST (SGOT)
	  ○ ALT (SGPT)
	  ○ Total bilirubin
	
	Serum potassium
	• If low, check magnesium and calcium
	
	Signs of neurotoxicity
	
	HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—amikacin blood levels	To assure adequate therapeutic levels avoid troughs lower than 5 mcg/mL To avoid potentially toxic levels avoid peaks above 35 mcg/mL See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration

Criteria for Amikacin [2–4,58,60,71,73–75]	
Drug interactions	Potent diuretics (e.g., furosemide or mannitol) enhance the ototoxic effect of amikacin • Adjust dosage as appropriate Amikacin prolongs the effect of non-depolarizing muscle relaxants (e.g., vecuronium) • Decrease dosage of the muscle relaxant as appropriate • Monitor neuromuscular function closely Beta-lactam-type antibiotics (penicillins or cephalosporins) may result in a significant mutual inactivation when coadministered with amikacin • Adjust dosage as appropriate Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents. The following medicines may increase the effects of amikacin • Amphotericin B • Capreomycin • Cephalosporins (e.g., cefalexin) • Cisplatin • Loop diuretics (e.g., furosemide) • NSAIDs • Vancomycin • BCG vaccine (avoid coadministration) Amikacin may increase or prolong the effects of • Carboplatin • Ciclosporin • Halogenated hydrocarbon inhalation anesthetics • Opioid analgesics Hepatotoxic, nephrotoxic, neurotoxic and ototoxic drugs • May potentiate toxicities If necessary to coadminister, or sequentially administer, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs Amikacin may cause false-positive results in urine glucose determinations using cupric sulfate solution (Benedict's reagent, Clintest®)

Criteria for Amikacin [2–4,58,60,71,73–75]	
Patient counseling	Advise patient to contact a health care provider immediately if they experience • Problems with hearing, dizziness, or balance • Rash or swelling of the face • Trouble breathing • Decreased urination • Watery or bloody diarrhea • Swelling, pain, or redness at the injection site • Muscle twitching or weakness Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category D • There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans • Potential benefits may warrant use of the drug in pregnant women despite potential risks Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with amikacin and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Electrolyte disturbances (e.g., dark urine, irregular heartbeat, fatigue, bowel irregularities muscle weakness or pain, changes in mood or coherence, headache)	Check potassium If potassium is low, also check magnesium (and calcium if hypocalcaemia is suspected) Replace electrolytes as needed Dose oral electrolytes apart from fluoroquinolones as they interfere with fluoroquinolone absorption
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Amikacin [2–4,58,60,71,73–75]	
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Injection site reactions (e.g., localized trauma, minor discomfort and pain, bleeding, bruising)	Maintain light pressure to prevent bruising If a bruise does appear, don't use that injection site again until the bruise is gone An affected limb should be elevated to minimize inflammation An anti-inflammatory cream or gel can be directly applied to the area Anti-inflammatory analgesics can be prescribed to treat both the inflammation and the pain associated with the reaction **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
Ototoxicity, auditory (any loss of hearing, ringing or buzzing, a feeling of fullness in the ears)	Conduct audiometry and compare with baseline Consider reducing the frequency of amikacin administration to two or three times a week Discontinue amikacin if hearing loss continues Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin **Note:** The risk of further hearing loss should be weighed against the risk of stopping amikacin The provider should consult with the patient regarding the desired course of action

Criteria for Amikacin [2–4,58,60,71,73–75]	
Ototoxicity, vestibular (clumsiness, dizziness, nausea, vomiting, unsteadiness)	Document events and compare with prior to starting treatment
	Initiate anti-emetics (e.g., metoclopramide, ondansetron) if appropriate
	Initiate cyclizine for dizziness if appropriate
	Decrease frequency of amikacin administration to two or three times a week
	Discontinue amikacin if symptoms worsen
	Change amikacin to capreomycin if patient has documented susceptibility to capreomycin
	Note: The risk of toxicity should be weighed against the risk of stopping amikacin. The provider should consult with the patient regarding the desired course of action.
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue amikacin if this can be done without compromising regimen
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of amikacin administration
	Discontinue amikacin if this can be done without compromising regimen—rarely necessary

Criteria for Amikacin [2–4,58,60,71,73–75]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of amikacin administration to five times or even three times per week
Malabsorption syndrome	Assess for • Increase in fecal fat • Decrease in serum carotene • Reduced xylose absorption • Reduced iron absorption • Abnormal small bowel pattern on x-ray • Villus atrophy Initiate nutritional replacement therapy—according to standard clinical protocol
Nausea or vomiting	Administer with small meals and advise patient to swallow tablets slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Consider reducing the frequency of amikacin administration to five times or even three times per week Decrease frequency of amikacin administration Discontinue amikacin if this can be done without compromising regimen—rarely necessary

Criteria for Amikacin [2–4,58,60,71,73–75]	
Neuromuscular blockade (e.g., difficulty in breathing, drowsiness, weakness)	If blockage occurs, calcium salts may reduce these phenomena but mechanical respiratory assistance may be necessary
Overgrowth of non-susceptible organisms	Discontinue amikacin and institute appropriate therapy if this can be done without compromising the regimen
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes Correct any vitamin or nutritional deficiencies Administer pyridoxine 200 to 300 mg per day Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily) Consider paracetamol and NSAIDs (or both) for pain relief **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Consider neurology consultation Consider administering carbamazepine Decrease frequency of amikacin administration Discontinue amikacin Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin
Renal failure or **nephrotoxicity**	Discontinue amikacin Adjust dose of all drugs according to the creatinine clearance Rule out other causes (e.g., other medications, diabetes, congestive heart failure, urinary obstruction), and if identified, treat according to standard clinical protocol Consider dosing three times a week and monitor creatinine clearance every one to two weeks If creatinine clearance does not stabilize, permanently discontinue amikacin Consider use of capreomycin if patient has documented susceptibility to capreomycin

Criteria for Amikacin [2–4,58,60,71,73–75]	
Renal irritation	Casts, white or cells, albumin • Increase hydration Decreased creatinine clearance; decreased urine specific gravity; increased BUN, creatinine, or oliguria • Decrease frequency of amikacin administration Increased azotemia or decrease in urinary output • Decrease frequency of amikacin administration • Discontinue amikacin if this can be done without compromising the regimen
Overdose and life-threatening toxicity	In the event of overdosage or toxic reaction, hemodialysis, or peritoneal dialysis will aid in the removal of amikacin from the blood. In the newborn infant, exchange transfusion may also be considered.

Criteria for Capreomycin [2–4,59,60,71,76]	
I. ***Justification criteria*** for prescribing capreomycin	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented: • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available
	Patient is allergic to isoniazid or rifampicin
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin
	Organism is susceptible to capreomycin (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing capreomycin	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Capreomycin allergy • Possibility of pregnancy
	HIV status is documented in case records
	Capreomycin was available for the duration of treatment

Criteria for Capreomycin [2–4,59,60,71,76]			
Dose and frequency	Appropriate capreomycin dosing for adult patients up to 59 years of age • 15 to 20 mg/kg daily Not to exceed 1000 mg daily Appropriate capreomycin dosing for adult patients 59 years of age and older • 10 mg/kg daily Not to exceed 750 mg daily Appropriate capreomycin dosing for renal dysfunction (Creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 12 to 15 mg/kg per dose two or three times per week Capreomycin should be administered following dialysis on dialysis days Appropriate capreomycin dosing for pediatric patients • 15 to 30 mg/kg daily Not to exceed 1,000 mg daily Adjust dosing if appropriate for patients with a history of • Hearing disorders • Vestibular disorders • Neuromuscular disorders such as myasthenia gravis, Parkinson's Disease, or infant botulism		
Administration	For parenteral administration • Reconstitute with 0.9% sodium chloride injection or sterile water for injection • Deep intramuscular injection preferred • Intravenously—reconstituted capreomycin should be diluted in 100 mL of 0.9% sodium chloride injection and administered over 60 minutes Rotate injection sites to avoid local discomfort Maintain adequate hydration to prevent irritation of the renal tubules Store vials at controlled room temperature 15 to 25°C before reconstitution After reconstitution, all solutions of capreomycin may be stored for up to 24 hours under refrigeration (2 to 8°C)		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months

Criteria for Capreomycin [2–4,59,60,71,76]	

Patient monitoring	Prior to treatment and then at least monthly during treatment:
	• Weight (and every 2 weeks for the first three months of treatment)
	• Pregnancy testing—according to standard clinical protocol
	• Eighth cranial nerve function
	  ○ Conduct audiometric or caloric stimulation testing
	• Renal function
	
	One or more of the following laboratory tests:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Serum potassium levels
	• If low, check magnesium and calcium
	• Electrolyte disturbances are more common with capreomycin than with other injectable agents
	
	Liver function
	• AST (SGOT)
	• ALT (SGPT)
	• Total bilirubin
	
	HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—capreomycin blood levels	To assure adequate therapeutic levels avoid troughs below 5 mcg/mL To avoid potentially toxic levels avoid prolonged peak concentrations above 35 mcg/mL See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration

Criteria for Capreomycin [2–4,59,60,71,76]	
Drug interactions	Patient is not administered other parenteral anti-tuberculosis agents (e.g., streptomycin, viomycin) Potent diuretics (e.g., furosemide or mannitol) enhance the ototoxic effect of capreomycin • Adjust dosage as appropriate Capreomycin may prolong the effects of non-depolarizing muscle relaxants (e.g., neostigmine) • Decrease dosage of the muscle relaxant as appropriate • Monitor neuromuscular function closely Capreomycin may increase or prolong the effects of: • Halogenated hydrocarbon inhalation anesthetics • Opioid analgesics Beta-lactam-type antibiotics (penicillins or cephalosporins) may result in a significant mutual inactivation when coadministered with capreomycin • Adjust dosage as appropriate Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents. Hepatotoxic, Nephrotoxic, Neurotoxic, and Ototoxic drugs • May potentiate toxicities • If necessary to coadminister, or sequentially administer, monitor adverse drug reactions carefully Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs Capreomycin may cause false-positive results in urine glucose determinations using cupric sulfate solution (Benedict's reagent, Clinitest)

Criteria for Capreomycin [2–4,59,60,71,76]	
Patient Counseling	Advise patient to • Store capreomycin at controlled room temperature, 15 to 25°C Advise patient to contact a health care provider immediately if they experience: • Problems with hearing, dizziness, or balance • Rash or swelling of the face • Fever or chills • Bleeding or bruising • Trouble breathing • Decreased urination • Watery or bloody diarrhea • Swelling, pain, or redness at the injection site • Muscle twitching or weakness Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with capreomycin and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Electrolyte disturbances (e.g., dark urine, irregular heartbeat, fatigue, bowel irregularities muscle weakness or pain, changes in mood or coherence, headache)	Check potassium If potassium is low, also check magnesium (and calcium if hypocalcaemia is suspected) Replace electrolytes as needed Dose oral electrolytes apart from fluoroquinolones as they interfere with fluoroquinolone absorption

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Capreomycin [2–4,59,60,71,76]	
Hypersensitivity, mild (skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Injection site reactions (e.g., localized trauma, minor discomfort and pain, bleeding, bruising)	Maintain light pressure to prevent bruising If a bruise does appear, don't use that injection site again until the bruise is gone An affected limb should be elevated to minimize inflammation An anti-inflammatory cream or gel can be directly applied to the area Anti-inflammatory analgesics can be prescribed to treat both the inflammation and the pain associated with the reaction **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity Exercise caution with use and monitor renal function
Ototoxicity, auditory (any loss of hearing, ringing or buzzing, a feeling of fullness in the ears)	Conduct audiometry and compare with baseline Decrease frequency of capreomycin administration to two or three times a week Discontinue capreomycin if hearing loss continues **Note:** The risk of further hearing loss should be weighed against the risk of stopping capreomycin. The provider should consult with the patient regarding the desired course of action. Modify regimen according to national TB treatment guidelines

Criteria for Capreomycin [2–4,59,60,71,76]	
Ototoxicity, vestibular (clumsiness, dizziness, nausea, vomiting, unsteadiness)	Document events and compare with prior to starting treatment Initiate anti-emetics (e.g., metoclopramide, ondansetron) if appropriate Initiate cyclizine for dizziness if appropriate Decrease frequency of capreomycin administration to two or three times a week Discontinue capreomycin if symptoms worsen **Note:** The risk of toxicity should be weighed against the risk of stopping capreomycin The provider should consult with the patient regarding the desired course of action Modify regimen according to national TB treatment guidelines
Peripheral Neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes Correct any vitamin or nutritional deficiencies Administer pyridoxine 200 to 300 mg per day Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily) Consider paracetamol and NSAIDs (or both) for pain relief **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Consider neurology consultation Consider administering carbamazepine Decrease frequency of capreomycin administration Discontinue capreomycin Modify regimen according to national TB treatment guidelines
Leukocytosis, leukopenia, and eosinophilia (more than 5%)	Reduce dosage of capreomycin to 2 or 3 g weekly
Neuromuscular blockade (e.g., difficulty in breathing, drowsiness, weakness)	If blockage occurs, calcium salts may reduce these phenomena but mechanical respiratory assistance may be necessary

Criteria for Capreomycin [2–4,59,60,71,76]	
Renal failure or **nephrotoxicity**	Discontinue capreomycin Adjust dose of all drugs according to the creatinine clearance Rule out other causes (e.g., other medications, diabetes, congestive heart failure, urinary obstruction), and if identified, treat according to standard clinical protocol Consider dosing three times a week and monitor creatinine clearance every one to two weeks If creatinine clearance does not stabilize, permanently discontinue capreomycin Modify regimen according to national TB treatment guidelines
Renal irritation	Casts, white or cells, albumin • Increase hydration Decreased creatinine clearance; decreased urine specific gravity; increased BUN, creatinine or oliguria • Decrease frequency of capreomycin administration (e.g., three times a week) Increased azotemia or decrease in urinary output • Decrease frequency of capreomycin administration • Discontinue capreomycin if this can be done without compromising regimen • Modify regimen according to national TB treatment guidelines
Thrombocytopenia	Monitor hematology Decrease frequency of capreomycin administration Discontinue capreomycin if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines Rarely the spleen may need to be removed

Criteria for Capreomycin [2–4,59,60,71,76]	
Overdose and life-threatening toxicity	Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal. Patients who have received an overdose of capreomycin and have normal renal function should be carefully hydrated to maintain a urine output of 3 to 5 mL/kg/h. Fluid balance, electrolytes, and creatinine clearance should be carefully monitored. Hemodialysis may be effectively used to remove capreomycin in patients with significant renal disease.

Criteria for Cycloserine [2–4,58–60,77,78]	
I. ***Justification criteria*** for prescribing cycloserine	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics) Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available Patient is allergic to isoniazid or rifampicin Patient has documented serious adverse drug reaction to isoniazid or rifampicin Organism is susceptible to cycloserine (if DST is available) According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing cycloserine	
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent Patient history has been reviewed for: • Cycloserine or terizidone allergy • Epilepsy • Depression, severe anxiety, or psychosis • Severe renal insufficiency • Excessive concurrent use of alcohol HIV status is documented in case records Cycloserine was available for the duration of treatment
Dose and frequency	Appropriate cycloserine dosing for adult • 15 to 20 mg/kg daily Not to exceed 1,000 mg daily
	Appropriate cycloserine dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 250 mg once daily or 500 mg/dose three times per week • Cycloserine should be administered following dialysis on dialysis days • The use of cycloserine is not recommended in patients with creatinine clearance 50 mL/minute unless they are on hemodialysis
	Appropriate cycloserine dosing for pediatric patients • 10 to 20 mg/kg once or twice daily Not to exceed 1,000 mg daily

Criteria for Cycloserine [2–4,58–60,77,78]			
Administration	For oral use only Best taken one hour before or two hours after meals Peripheral neuropathy prophylaxis • Adults—administer pyridoxine 50 mg for every 250 mg of cycloserine daily • Pediatric patients—administer pyridoxine 1 to 2 mg/kg per day with a range of 10 to 50 mg per day		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months
		continuation phase	at least 12 months

Patient monitoring	Prior to treatment and then at least monthly during treatment:
	Weight (and every 2 weeks for the first 3 months of treatment)
	Pregnancy testing—according to standard clinical protocol
	Beck Depression Index (or similar tool to monitor depression)
	Complete blood count with differential
	• Liver function
	  ○ AST (SGOT)
	  ○ ALT (SGPT)
	  ○ Total bilirubin
	Renal function
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	Pregnancy testing—according to standard clinical protocol		

Criteria for Cycloserine [2–4,58–60,77,78]	
Therapeutic drug monitoring—cycloserine blood levels	To ensure adequate therapeutic levels monitor weekly for patients • With reduced renal function • Receiving a daily dosage greater than 500 mg • Showing signs and symptoms suggestive of toxicity For all patients • To ensure adequate therapeutic increase the dose if the peak is less than 15 mcg/mL • To avoid potential toxicities keep peak concentration below 35 mcg/mL If the dose is adjusted, repeat the peak concentration after at least three to four days. See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentrations.
Drug interactions	Ethanol • May enhance the neurotoxic effects of cycloserine specifically the risk for seizures Isoniazid • Concurrent administration with isoniazid may result in increased incidence of central nervous system effects • Dosage adjustments may be necessary Ethionamide • Concurrent administration with ethionamide may result in increased incidence of central nervous system effects • Dosage adjustments may be necessary Hepatotoxic, nephrotoxic, and neurotoxic drugs • Concurrent administration may potentiate toxicities If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs. Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.

Criteria for Cycloserine [2–4,58–60,77,78]	
Patient counseling	Advise patients to: • Take this medicine on an empty stomach, with juice, or antacids. If food is taken, avoid a large fatty meal • Avoid alcohol • Patient must also take a high-dose pyridoxine (Vitamin B6) supplement while on this medicine Advise patients to contact a health care provider immediately if they experience: • Seizures • Shakiness or trouble talking • Depression or thoughts of hurting oneself • Anxiety, confusion, or loss of memory • Personality changes, such as aggressive behavior • Rash or hives • Headache Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk Advise patients who are breastfeeding • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Cycloserine [2–4,58–60,77,78]	
III. ***Complications*** that could occur during therapy with cycloserine and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Central nervous system related adverse drug reactions (e.g., inability to concentrate, lethargy, vertigo, hyper-reflexia, paresis, hyperirritability, dysarthria, drowsiness, somnolence, confusion disorientation, loss of memory)	Administer pyridoxine maximum daily dose (200 to 300 mg per day) Reassurance Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Cycloserine [2–4,58–60,77,78]	
Depression	Hospitalize patients with suicidal ideation for 24-hour surveillance
	Assess and address underlying socioeconomic issues
	Assess for substance abuse and refer to treatment if appropriate
	Rule out other causes and treat
	If identified, treat specific cause according to standard clinical protocol
	Rule out adverse drug reactions of concomitant medications (e.g., cycloserine, amoxicillin/clavulanate, penicillin, benzodiazepines)
	Refer to psychologist or psychiatrist for assessment
	Initiate group (if patient is sputum smear and culture negative) or individual psychological therapy
	Initiate anti-depressant therapy (e.g., amitriptyline, fluoxetine) • Only after group or individual psychological therapy initiated • Use with caution when there is a history of convulsions
	Caution: Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval.
	Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes.
	Reduce dose of cycloserine to 500 mg daily
	Decrease frequency of cycloserine administration
	Discontinue cycloserine
	Modify regimen according to national TB treatment guidelines

Criteria for Cycloserine [2–4,58–60,77,78]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Start at lower doses of 250 to 500 mg then gradually increase over one to two weeks to target dose Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Confirm patient on adequate dose of pyridoxine Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity Exercise caution with use and monitor renal function. Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of cycloserine administration to five times or even three times per week
Hypersensitivity, mild (e.g., lichenoid eruptions, skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Cycloserine [2–4,58–60,77,78]	
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, lupoid reactions, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Hypersensitivity, severe (Stevens-Johnson syndrome)	Stop cycloserine Requires immediate therapy Provide fluid replacement and nutritional supplement Provide wound care Consult dermatologist if any question of diagnosis Provide supportive care (analgesic, antihistamine, antibiotic, systemic steroid, and immunoglobulin treatment—according to standard clinical protocol) Modify regimen according to national TB treatment guidelines

Criteria for Cycloserine [2–4,58–60,77,78]	
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes
	Correct any vitamin or nutritional deficiencies
	Administer pyridoxine 200 to 300 mg per day
	Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily)
	Consider paracetamol and NSAIDs (or both) for pain relief
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Consider neurology consultation
	Consider administering carbamazepine
	Decrease frequency of cycloserine administration
	Discontinue cycloserine
	Modify regimen according to national TB treatment guidelines
Psychotic Symptoms	Stop cycloserine for a short period of time (1 to 4 weeks) while psychotic symptoms are brought under control
	Initiate antipsychotic therapy (haloperidol, chlorpromazine, risperidone [consider biperiden to prevent extrapyramidal effects])
	If patient is at risk of self harm, hospitalize patient under expert psychiatric care
	Reduce frequency of cycloserine administration
	Reduce cycloserine dose to 500 mg daily
	If symptoms do not improve discontinue cycloserine
	Modify regimen according to national TB treatment guidelines
Seizure, convulsions, coma	Suspend cycloserine pending resolution of seizures
	Suspend other seizure inducing medicines (e.g., fluoroquinolones, isoniazid)
	Initiate anticonvulsant therapy (e.g., phenobarbital, phenytoin, carbamazepine, valproic acid)
	Administer pyridoxine 200 to 300 mg daily
	Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium, and chloride
	Once seizures have resolved, restart medications one at a time
	When restarting cycloserine with a dose one weight band lower
	Reduce frequency of cycloserine administration
	Discontinue cycloserine if seizures do not resolve
	Modify regimen according to national TB treatment guidelines

Criteria for Cycloserine [2–4,58–60,77,78]	
Suicidal Ideation	Hospitalize patients with suicidal ideation for 24 hour surveillance Discontinue cycloserine Modify regimen according to national TB treatment guidelines Request psychiatric consultation Initiate antidepressant therapy **Caution:** Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes
Anemia	Determine cause of anemia (e.g., iron deficiency, hydroxocobalamin (Vitamin B12) deficiency, chronic disease, bleeding) Supplement with iron, folate (Vitamin B9), hydroxocobalamin (Vitamin B12), ascorbic acid (Vitamin C) as appropriate Monitor complete blood counts weekly until stabilized
Congestive heart failure	Sudden development of congestive heart failure in patients receiving 1 to 1.5 g of cycloserine daily has been reported Treat according to standard clinical protocol
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly

Criteria for Cycloserine [2–4,58–60,77,78]	
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis); If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Tremor	Reassurance Maintain treatment if the tremor is mild and does not interfere with daily activities Initiate anticholinergic therapy (e.g., biperiden) if tremor is severe
Overdose and life-threatening toxicity	Acute toxicity can occur if more than 1 g is ingested by an adult. Chronic toxicity is dose related and can occur if more than 500 mg is administered daily. Symptomatic and supportive therapy is recommended Protect the patient's airway and support ventilation and perfusion Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes Activated charcoal may be more effective in reducing absorption than emesis or lavage In adults, many neurotoxic effects can be both treated and prevented with pyridoxine Hemodialysis removes cycloserine from the bloodstream but should be reserved for life-threatening toxicity

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
I. ***Justification criteria*** for prescribing ethionamide	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics) Laboratory drug susceptibility testing (DST) documents the organism resistance pattern to at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available Patient is allergic to isoniazid or rifampicin Patient has documented serious adverse drug reaction to isoniazid or rifampicin Organism is susceptible to ethionamide (if DST is available) According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing ethionamide	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent Patient history has been reviewed for: • Ethionamide or prothionamide allergy • Severe hepatic impairment • Porphyria • Excessive concurrent use of alcohol HIV status is documented in case records Ethionamide was available for the duration of treatment
Dose and frequency	Appropriate ethionamide dosing for adult patients • 15 to 20 mg/kg daily • Usually 500 to 75 mg/kg daily in two divided doses or a single daily dose Not to exceed 1,000 mg daily
	Appropriate ethionamide dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • No adjustment necessary • Ethionamide is not cleared by dialysis, so it may be administered irrespective of dialysis schedule and post-dialysis doses are not necessary
	Appropriate ethionamide dosing for pediatric patients • 15 to 20 mg/kg daily, usually divided into two or three daily doses Not to exceed 1,000 mg daily

Criteria for Ethionamide [2–4,58–60,64,71,79–82]			
Administration	For oral use only Administer pyridoxine (Vitamin B6) for peripheral neuropathy prophylaxis • Adult dose—100 mg daily • Pediatric dose— 1 to 2 mg/kg daily, with a usual range of 10 to 50 mg daily		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months
		continuation phase	at least 12 months
Patient monitoring	Prior to treatment and then at least monthly during treatment: Weight (and every 2 weeks for the first 3months of treatment) Pregnancy testing—according to standard clinical protocol Liver function: • AST (SGOT) • ALT (SGPT) • Total bilirubin Serum glucose Thyroid function Ophthalmologic function • Ophthalmoscopy • Finger perimetry • Acuity testing (Snellen chart) • Color discrimination (Ishihara tests) HIV testing—according to standard clinical protocol		
Therapeutic drug monitoring—ethionamide blood levels	Conduct when malabsorption is suspected To assure adequate therapeutic levels target peak concentrations of 1 to 5 mcg/mL, see Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration.		

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
Drug interactions	Ethanol • Monitor for psychotic reactions Ethionamide may temporarily raise serum concentrations of isoniazid • Monitor liver function tests and clinical signs and symptoms of hepatotoxicity Other anti-tuberculosis drugs • Monitor for potential overlapping adverse events of especially cycloserine (convulsions) Hepatotoxic and neurotoxic drugs • Concurrent administration may potentiate toxicities • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs. Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.
Patient counseling	Advise patients • Take this medicine with food • Patient must also take a high-dose pyridoxine (Vitamin B6) supplement while on this drug
	Advise patients to contact a health care provider immediately if they experience • Any problems with their eyes such as eye pain, blurred vision, color blindness, or trouble seeing • Numbness, tingling, or pain in their hands or feet • Unusual bruising or bleeding • Personality changes such as depression, confusion, or aggression • Yellowing of the skin or eyes • Dark-colored urine • Nausea or vomiting • Dizziness • Swollen breasts (in men)
	Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
	Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with ethionamide and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Alopecia	Encourage patients to tolerate this side effect Resolution occurs after treatment is stopped
Blood glucose disturbances	Monitor blood glucose at least monthly Initiate or adjust oral hypoglycemic agent or insulin—according to standard clinical protocol
Depression	Assess and address underlying socioeconomic issues Assess for substance abuse and refer to treatment if appropriate Rule out other causes, and if identified, treat specific cause according to standard clinical protocol Rule out adverse drug reactions of concomitant medications (e.g., cycloserine, amoxicillin/clavulanate, penicillin, benzodiazepines) Refer to psychologist or psychiatrist for assessment Initiate group (if patient is sputum smear and culture negative) or individual psychological therapy Initiate anti-depressant therapy (e.g., amitriptyline, fluoxetine) • Only after group or individual psychological therapy initiated • Use with caution when there is a history of convulsions **Caution:** Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. Decrease dose of ethionamide to 500 mg daily Decrease frequency of ethionamide administration Discontinue ethionamide Modify regimen according to national TB treatment guidelines

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of ethionamide administration
	Discontinue ethionamide if this can be done without compromising regimen—rarely necessary
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis)
	Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole)
	Stop ethionamide for short periods of time (e.g., one to seven days)
	Discontinue ethionamide if this can be done without compromising the regimen
	Modify regimen according to national TB treatment guidelines
Gynecomastia	Rule out other causes
	Reduce frequency of administration
	Encourage patients to tolerate this side effect
	Resolution occurs after treatment is stopped
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly
	Once resolved, monitor liver function monthly

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis); and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Hypersensitivity, mild (skin itching, redness, rash, swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization. **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Hypothyroidism	Monitor thyroid function every one to two months until stabilized Initiate thyroxine therapy according to standard clinical protocol

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
Nausea, vomiting, or anorexia	Administer with small meals and advise patient to swallow pills slowly with small sips of water
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Assess for dehydration, electrolyte disturbances, hepatitis
	Initiate rehydration if indicated
	Initiate antiemetic therapy (e.g., metoclopramide, ondansetron)
	Decrease frequency of ethionamide administration
	Discontinue ethionamide if this can be done without compromising regimen—rarely necessary
Optic neuritis	Refer patient to an ophthalmologist
	In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions
	In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult
Sense of taste disturbance	Encourage the patient to tolerate this adverse reaction
	Sucking on lemon drops or other hard candy or chewing gum can be helpful
	Normal taste returns when treatment is stopped
Suicidal ideation	Hospitalize patients with suicidal ideation for 24 hour surveillance
	Decrease dose of ethionamide to 500 mg daily until the patient is stable
	Request psychiatric consultation
	Initiate antidepressant therapy
	Caution: Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes.
Acne	Provide supportive care
	If acne is bothersome to the patient, topical acne treatments may be administered

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
Central nervous system related adverse drug reactions (e.g., drowsiness, dizziness, restlessness, postural hypotension)	Ensure patient is administered an adequate dose of pyridoxine Reassurance Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) If identified, treat specific cause according to standard clinical protocol Treat dizziness with cyclizine if appropriate **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Clostridium difficile-associated diarrhea	Bowel rest Appropriate fluid and electrolyte management Protein supplementation Antibiotic treatment of *C. difficile* Surgical evaluation should be instituted as a last resort, if clinically indicated Discontinue ethionamide if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Erectile dysfunction	Rule out other causes of, or contributors to the erectile dysfunction (ED) Screen for thyroid dysfunction Postpone specific treatment of ED in patients with thyroid dysfunction until euthyroidism has been reached for at least 6 months If caused by thyroid dysfunction, and all other causes and contributors have been ruled out, administer thyroxine therapy according to standard clinical protocol

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections)
	Ensure patient is administered an adequate dose of pyridoxine
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Encourage adequate fluid intake
	Treat with ibuprofen, paracetamol, or aspirin
	Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Address stressors potentially contributing to tension-related headaches
	Consider administering amitriptyline 50 to 150 mg at night
	Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine)
	Consider neurology consultation
	Consider reducing the frequency of ethionamide administration to five times or even three times per week
Hematological abnormalities	Stop all therapy pending resolution of toxicity
	Eliminate other potential causes of toxicity
	Consider suspending most likely agent permanently
	Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Hypersalivation	Tooth brushing and rinsing with alcohol-containing products will produce drying effects
Menstrual irregularity	Rule out other causes of, or contributors to, the irregularity
	Screen for thyroid dysfunction
	Initiate thyroid therapy for thyroid dysfunction, if all other causes and contributors have been ruled out

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes Correct any vitamin or nutritional deficiencies Administer pyridoxine 200 to 300 mg per day Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily) Consider paracetamol and NSAIDs (or both) for pain relief **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Consider neurology consultation Consider administering carbamazepine Decrease frequency of ethionamide administration Discontinue ethionamide Modify regimen according to national TB treatment guidelines
Photosensitivity/ phototoxicity	Mild • Instruct patient to use sunscreen and avoid excessive exposure to sun or UV light • Initiate therapy with cool compresses and hydrocortisone cream Severe • Eliminate ethionamide from regimen • Modify regimen according to national TB treatment guidelines
Porphyria	Discontinue ethionamide Consider dosing 2 to 3 times a week if drug is essential to the regimen Provide symptomatic therapy, high carbohydrate intake, and intravenous administration of hematin Modify regimen according to national TB treatment guidelines
Psychotic symptoms	Stop ethionamide for a short period of time (1 to 4 weeks) while psychotic symptoms are brought under control Initiate antipsychotic therapy (haloperidol, chlorpromazine, risperidone [consider biperiden to prevent extrapyramidal effects]) If patient is at risk of self harm, hospitalize patient under expert psychiatric care Reduce frequency of ethionamide administration Reduce ethionamide dose If symptoms do not improve, discontinue ethionamide Modify regimen according to national TB treatment guidelines

Criteria for Ethionamide [2–4,58–60,64,71,79–82]	
Overdose and life-threatening toxicity	No specific information is available on the treatment of overdosage with ethionamide If it should occur, standard procedures to evacuate gastric contents and to support vital functions should be employed.

Criteria for Kanamycin [2–4,58–60,71,83]	
I. ***Justification criteria*** for prescribing kanamycin	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics) Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available Patient is allergic to isoniazid or rifampicin Patient has documented serious adverse drug reaction to isoniazid or rifampicin Organism is susceptible to kanamycin (if DST is available) According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing kanamycin	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent Patient history has been reviewed for: • Kanamycin allergy • Aminoglycoside allergy • Sodium bisulfate allergy • Possibility of pregnancy HIV status is documented in case records Kanamycin was available for the duration of treatment

Criteria for Kanamycin [2–4,58–60,71,83]			
Dose and frequency	Appropriate kanamycin dosing for adult patients • 15 to 20 mg/kg daily Not to exceed 1000 mg daily Adults over 59 years of age • 10 mg/kg/day Not to exceed 750 mg daily Appropriate kanamycin dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 12 to 15 mg/kg per dose two or three times per week Kanamycin should be administered following dialysis on dialysis days Appropriate kanamycin dosing for pediatric patients • 15 to 30 mg/kg daily Not to exceed 1,000 mg daily Adjust dosing if appropriate for patients with a history of • Hearing disorders • Vestibular disorders • Neuromuscular disorders such as myasthenia gravis, Parkinson's Disease, or infant botulism		
Administration	For parenteral administration • Deep intramuscular injection preferred • Administer IV injections over 2 to 3 minutes • Administer intermittent IV infusions ○ For adults over 30 to 60 minutes ○ For infants over 1 to 2 hours ○ May be divided into either 2 or 3 equally-divided doses at equally-divided intervals Rotate injection sites to avoid local discomfort Maintain adequate hydration to prevent irritation of the renal tubules Store vials at controlled room temperature, 15 to 25 °C Kanamycin is stable for 24 hours at room temperature in the following solutions: • Glucose 5% in sodium chloride 0.9% • Glucose 5 or 10% in water • Sodium chloride 0.9% • Sodium lactate, compound solution		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months

Criteria for Kanamycin [2–4,58–60,71,83]	

Patient monitoring	Prior to treatment and then at least monthly during treatment
	
	Weight (and every 2 weeks for the first 3 months of treatment)
	
	Pregnancy testing—according to standard clinical protocol
	Eighth cranial nerve function
	• Audiometric or caloric stimulation testing
	
	Renal function
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Liver function
	• Monitor in patients with severe liver disease
	  ○ AST (SGOT)
	  ○ ALT (SGPT)
	  ○ Total bilirubin
	
	Serum potassium
	• If low, check magnesium and calcium
	
	Signs of neurotoxicity
	
	HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—kanamycin blood levels	To assure adequate therapeutic levels avoid troughs below 5 mcg/mL To avoid potentially toxic levels avoid prolonged peak concentrations above 35 mcg/mL See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance in how to adjust dose based on serum concentration
Drug Interactions	Potent diuretics (e.g., furosemide or mannitol) enhance the ototoxic effect of kanamycin • Adjust dosage as appropriate Kanamycin prolongs the action of non-depolarizing muscle relaxants (e.g., vecuronium) • Decrease dosage of the muscle relaxant as appropriate • Monitor neuromuscular function closely Beta-lactam-type antibiotics (penicillins or cephalosporins) may result in a significant mutual inactivation when coadministered with kanamycin • Adjust dosage as appropriate

Criteria for Kanamycin [2–4,58–60,71,83]

The following medicines may increase the effects of kanamycin

- Amphotericin B
- Capreomycin
- Cephalosporins (e.g., cefalexin)
- Cisplatin
- Loop diuretics (e.g., furosemide)
- NSAIDs
- Vancomycin
- BCG vaccine (avoid coadministration)

Kanamycin may increase or prolong the effects of

- Carboplatin
- Ciclosporin
- Halogenated hydrocarbon inhalation anesthetics
- Opioid analgesics

Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered

If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.

Hepatotoxic, nephrotoxic, neurotoxic and ototoxic drugs

- May potentiate toxicities
- If necessary to coadminister, or sequentially administer, monitor adverse drug reactions carefully.

Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs

Kanamycin may cause false-positive results in urine glucose determinations using cupric sulfate solution (Benedict's reagent, Clintest®).

Criteria for Kanamycin [2–4,58–60,71,83]	
Patient counseling	Advise patient to contact a health care provider immediately if they experience: • Problems with hearing, dizziness, or balance • Rash or swelling of the face • Trouble breathing • Decreased urination • Watery or bloody diarrhea • Swelling, pain, or redness at the injection site • Muscle twitching or weakness Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category D • There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans • Potential benefits may warrant use of the drug in pregnant women despite potential risks Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with kanamycin and how to respond if the complication presents as follows:[1]	
Severe or common toxicities are indicated by **bold** font	
Electrolyte disturbances (e.g., dark urine, irregular heartbeat, fatigue, bowel irregularities muscle weakness or pain, changes in mood or coherence, headache)	Check potassium If potassium is low, also check magnesium (and calcium if hypocalcaemia is suspected) Replace electrolytes as needed Dose oral electrolytes apart from fluoroquinolones as they interfere with fluoroquinolone absorption

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Kanamycin [2–4,58–60,71,83]	
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Injection site reactions (e.g., localized trauma, minor discomfort and pain, bleeding, bruising)	Maintain light pressure to prevent bruising If a bruise does appear, don't use that injection site again until the bruise is gone An affected limb should be elevated to minimize inflammation An anti-inflammatory cream or gel can be directly applied to the area Anti-inflammatory analgesics can be prescribed to treat both the inflammation and the pain associated with the reaction **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.

Criteria for Kanamycin [2–4,58–60,71,83]	
Ototoxicity, auditory (any loss of hearing, ringing or buzzing, a feeling of fullness in the ears)	Conduct audiometry and compare with baseline Consider reducing the frequency of kanamycin administration to two or three times a week Discontinue kanamycin if hearing loss continues Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin **Note:** The risk of further hearing loss should be weighed against the risk of stopping kanamycin. The provider should consult with the patient regarding the desired course of action.
Ototoxicity, vestibular (clumsiness, dizziness, nausea, vomiting, unsteadiness)	Document events and compare with prior to starting treatment Initiate anti-emetics (e.g., metoclopramide, ondansetron) if appropriate Initiate cyclizine for dizziness if appropriate Decrease frequency of kanamycin administration to two or three times a week Discontinue kanamycin if symptoms worsen Change kanamycin to capreomycin if patient has documented susceptibility to capreomycin **Note:** The risk of toxicity should be weighed against the risk of stopping kanamycin. The provider should consult with the patient regarding the desired course of action.
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes Correct any vitamin or nutritional deficiencies Administer pyridoxine 200 to 300 mg per day Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily) Consider paracetamol and NSAIDs (or both) for pain relief **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Consider neurology consultation Consider administering carbamazepine Decrease frequency of kanamycin administration Discontinue kanamycin Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin

Criteria for Kanamycin [2–4,58–60,71,83]	
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue kanamycin if this can be done without compromising regimen
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of kanamycin administration
	Discontinue kanamycin if this can be done without compromising regimen—rarely necessary
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections)
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Encourage adequate fluid intake
	Treat with ibuprofen, paracetamol, or aspirin
	Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Address stressors potentially contributing to tension-related headaches
	Consider administering amitriptyline 50 to 150 mg at night
	Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine)
	Consider neurology consultation
	Consider reducing the frequency of kanamycin administration to five times or even three times per week

Criteria for Kanamycin [2–4,58–60,71,83]	
Malabsorption syndrome	Assess for • Increase in fecal fat • Decrease in serum carotene • Reduced xylose absorption • Reduced iron absorption • Abnormal small bowel pattern on x-ray • Villus atrophy Initiate nutritional replacement therapy—according to standard clinical protocol
Nausea or vomiting	Administer with small meals Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Consider reducing the frequency of kanamycin administration to five times or even three times per week Discontinue kanamycin if this can be done without compromising regimen—rarely necessary
Neuromuscular blockade (e.g., difficulty in breathing, drowsiness, weakness)	If blockage occurs, calcium salts may reduce these phenomena but mechanical respiratory assistance may be necessary
Overgrowth of non-susceptible organisms	Discontinue kanamycin and institute appropriate therapy if this can be done without compromising the regimen
Renal failure or **nephrotoxicity**	Discontinue kanamycin Adjust dose of all drugs according to the creatinine clearance Rule out other causes (e.g., other medications, diabetes, congestive heart failure, urinary obstruction), and if identified, treat according to standard clinical protocol Consider dosing three times a week and monitor creatinine clearance every one to two weeks If creatinine clearance does not stabilize, permanently discontinue kanamycin Consider use of capreomycin

Criteria for Kanamycin [2–4,58–60,71,83]	
Renal irritation	Casts, white or cells, albumin • Increase hydration Decreased creatinine clearance; decreased urine specific gravity; increased BUN, creatinine, or oliguria • Decrease frequency of kanamycin administration Increased azotemia or decrease in urinary output • Decrease frequency of kanamycin administration • Discontinue kanamycin if this can be done without compromising the regimen
Overdose and life threatening toxicity	In the event of overdosage or toxic reaction, hemodialysis or peritoneal dialysis will aid in the removal of kanamycin from the blood In the newborn infant, exchange transfusion may also be considered

Criteria for Levofloxacin [2–4,58–60,84,85]
I. ***Justification criteria*** for prescribing levofloxacin
TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics) Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented: • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines Regimen is adjusted if DST results become available Patient is allergic to isoniazid or rifampicin Patient has documented serious adverse drug reaction to isoniazid or rifampicin Organism is susceptible to levofloxacin (if DST is available) According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing levofloxacin
Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent Patient history has been reviewed for: • Levofloxacin allergy • Quinolone antimicrobial allergy • Nalidixic acid allergy • QT interval prolongation • Torsade de Pointes • Hypothyroidism • Bradyarrhythmias • Uncompensated heart failure • Serum calcium, magnesium, or potassium levels below the lower limits of normal • Heart disease • Ventricular arrhythmias • Myasthenia gravis • G6PD deficiency HIV status is documented in case records Levofloxacin was available for the duration of treatment

Criteria for Levofloxacin [2–4,58–60,84,85]			
Dose and frequency	Appropriate levofloxacin dosing for adult patients • 500 to 1,000 mg by mouth daily Not to exceed 1,000 mg daily Appropriate levofloxacin dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 750 to 1,000 mg per dose three times per week Levofloxacin is not cleared by dialysis, so it may be administered irrespective of dialysis schedule and post-dialysis doses are not necessary Appropriate levofloxacin dosing for pediatric patients • 7.5 to 10 mg/kg daily Not to exceed 750 mg daily		
Administration	For oral administration • Tablets can be taken with food or on an empty stomach • Administer the oral solution 1 hour before or 2 hours after eating Parenteral form is for intravenous use only • IV doses less than 500 mg should be infused over 60 minutes every 24 hours • IV doses 750 mg or greater should be infused over 90 minutes every 24 hours • Avoid rapid or bolus intravenous infusion of levofloxacin to prevent hypotension Maintain adequate hydration to prevent the formation of highly concentrated urine Store ampoules of solution at controlled room temperature 15°C to 30°C Levofloxacin is stable 3 days at 25 °C and 14 days at 5 °C in the following solutions • 0.9% sodium chloride injection for 3 days at 25°C and 14 days at 5°C • 5% glucose injection • 5% glucose/0.9% sodium chloride injection		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months
		continuation phase	at least 12 months
Patient monitoring	Weight—every 2 weeks for the first three months of treatment then monthly Monitor serum glucose of diabetic patients according to standard clinical protocol HIV testing—according to standard clinical protocol Pregnancy testing—according to standard clinical protocol		

Criteria for Levofloxacin [2–4,58–60,84,85]	
Therapeutic drug monitoring—levofloxacin blood levels	To assure adequate therapeutic levels target peak concentrations of 8 to 12 mcg/mL for usual adult oral dosing, see Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration. Monitor patients with a known or suspected central nervous system disorder (e.g., severe cerebral arteriosclerosis, epilepsy) that may predispose them to seizures or lower the seizure threshold or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). Monitor patients for signs of tendinitis and tendon rupture (e.g. pain, swelling, inflammation, snap or pop in a tendon area) Monitor patients with low blood levels of potassium or magnesium, a slower-than-normal heart rate, or the use of certain drugs used to treat arrhythmias for abnormal changes in the electrical activity of the heart according to standard clinical protocol
Drug interactions	BCG vaccine decreases the effects of levofloxacin • Do not coadminister Live typhoid vaccine may be inactivated by levofloxacin • Do not coadminister Drugs that prolong the QT interval (e.g., mifepristone, azithromycin, amiodarone, and chloroquine) may have additive effects on levofloxacin induced QT interval prolongation • Avoid coadministration of QT interval prolonging drugs. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. Iron, calcium, zinc, or magnesium can attach to levofloxacin and decrease its absorption • Administer oral doses at least 2 hours before or 2 hours after antacids containing aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution Levofloxacin may enhance the effects of warfarin • Monitor prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation test when warfarin is coadministered with levofloxacin, as well as for evidence of bleeding • Adjust warfarin dose as appropriate Levofloxacin may cause blood glucose abnormalities • Diabetic patients receiving concomitant levofloxacin and anti-diabetic therapy (e.g., insulin, metformin) may experience altered blood glucose concentrations and symptomatic hyperglycemia or hypoglycemia • Careful monitoring of blood glucose concentrations recommended • Discontinue levofloxacin if a hypoglycemic reaction occurs • Modify regimen according to national TB treatment guidelines

Criteria for Levofloxacin [2–4,58–60,84,85]
NSAIDs coadministered with levofloxacin in may increase the risk of central nervous system stimulation (tremors, restlessness, agitation, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia suicidal thoughts or acts), and seizures • Monitor for central nervous system stimulation and convulsive seizures
Corticosteroids coadministered with levofloxacin increases the risk of severe tendon disorders (e.g., tendinitis, tendon rupture), especially in patients older than 60 years of age • Monitor for signs of signs of tendinitis and tendon rupture (e.g., pain, swelling, inflammation, snap or pop in a tendon area) and consider alternative to corticosteroid therapy • Consider using an alternative agent for management of hyperphosphatemia
Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • Levofloxacin may decrease levels of didanosine • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.
Hepatotoxic and neurotoxic drugs • May potentiate toxicities • If necessary to coadminister, monitor adverse drug reactions carefully.
Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs
Levofloxacin may produce false-positive urine screening results for opiates using commercially available immunoassay kits • Confirmation of positive opiate screens by more specific methods may be necessary
Injection not coadministered with any solution containing multivalent cations, (e.g., magnesium, through the same intravenous line)
IV line flushed before and after infusion of levofloxacin with an infusion solution compatible with levofloxacin and with any other drug(s) administered via this common line
IV form administered as a single agent without admixtures

Criteria for Levofloxacin [2–4,58–60,84,85]	
Patient counseling	Advise patients • To avoid caffeinated foods and beverages while taking this medicine • Can be taken with food or on an empty stomach • Drink plenty of beverages • Do not take milk-based products, antacids (especially aluminum containing), or multivitamins within 2 hours of this medication. • This medicine may cause sun sensitivity; use sunscreen. • Do not undertake new strenuous activities. • Educate patient on signs and symptoms of hypo- and hyperglcycaemia
	Advise patient to contact a health care provider immediately if they experience: • Pain, swelling or tearing of a tendon (such as the back of the ankle, elbow, etc.) • Muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing, or tightness in the chest • Diarrhea • Yellow skin or eyes • Anxiety, confusion, or dizziness
	Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk
	Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Levofloxacin [2–4,58–60,84,85]	
III. ***Complications*** that could occur during therapy with levofloxacin and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Arthralgias	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Decrease frequency of levofloxacin administration Discontinue levofloxacin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Blood glucose disturbances	Monitor blood glucose until stabilized and at least monthly Initiate or adjust oral hypoglycemic agent or insulin—according to standard clinical protocol
Depression	Assess and address underlying socioeconomic issues Assess for substance abuse and refer to treatment if appropriate Rule out other causes, and if identified, treat according to standard clinical protocol Rule out adverse drug reactions of concomitant medications (e.g., cycloserine, amoxicillin/clavulanate, penicillin, benzodiazepines) Refer to psychologist or psychiatrist for assessment Initiate group (if patient is sputum smear and culture negative) or individual psychological therapy Initiate anti-depressant therapy (e.g., amitriptyline, fluoxetine) • Only after group or individual psychological therapy initiated • Use with caution when there is a history of convulsions **Caution:** Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes Decrease frequency of levofloxacin administration Discontinue levofloxacin Modify regimen according to national TB treatment guidelines

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Levofloxacin [2–4,58–60,84,85]	
Dizziness	Conduct a clinical evaluation to determine whether the dizziness is vestibular or non-vestibular in origin Conduct a clinical evaluation to determine whether the dizziness is peripheral or central in origin If identified, treat specific cause according to standard clinical protocol If cause cannot be identified treat cyclizine **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis) Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole) Stop levofloxacin for short periods of time (e.g., one to seven days) Discontinue levofloxacin if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of levofloxacin administration to five times or even three times per week
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Levofloxacin [2–4,58–60,84,85]	
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Nausea, vomiting, or bloating	Administer with small meals and advise patient to swallow tablets slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Decrease frequency of levofloxacin administration Discontinue levofloxacin if this can be done without compromising regimen—rarely necessary

Criteria for Levofloxacin [2–4,58–60,84,85]	
Peripheral Neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes
	Correct any vitamin or nutritional deficiencies
	Administer pyridoxine 200 to 300 mg per day
	Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily)
	Consider paracetamol and NSAIDs (or both) for pain relief
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Consider neurology consultation
	Consider administering carbamazepine
	Decrease frequency of levofloxacin administration
	Discontinue levofloxacin
	Modify regimen according to national TB treatment guidelines
Prolongation of the QT interval	Obtain an electrocardiogram and initiate treatment according to standard clinical protocol
	Correct electrolyte imbalances (calcium, potassium, magnesium)
	Discontinue levofloxacin if risk of torsades de pointes outweighs the benefits of the drug
	Modify regimen according to national TB treatment guidelines
Psychotic Symptoms	Stop levofloxacin for a short period of time (1 to 4 weeks) while psychotic symptoms are brought under control
	Initiate antipsychotic therapy (haloperidol, chlorpromazine, risperidone [consider biperiden to prevent extrapyramidal effects])
	If patient is at risk to harm him/herself, hospitalize patient under expert psychiatric care
	Reduce frequency of levofloxacin administration
	Reduce levofloxacin dose
	If symptoms do not improve discontinue levofloxacin
	Modify regimen according to national TB treatment guidelines

Criteria for Levofloxacin [2–4,58–60,84,85]	
Seizures	Suspend levofloxacin pending resolution of seizures Suspend other seizure inducing medicines (e.g., cycloserine, isoniazid) Initiate anticonvulsant therapy (e.g., phenobarbital, phenytoin, carbamazepine, valproic acid) Administer pyridoxine 200 to 300 mg daily Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium, and chloride Once seizures have resolved, restart medications one at a time Reduce frequency of levofloxacin administration Discontinue levofloxacin if seizures do not resolve Modify regimen according to national TB treatment guidelines
Sense of taste disturbance	Encourage the patient to tolerate this side effect Sucking on lemon drops or other hard candy or chewing gum can be helpful Normal taste returns when treatment is stopped
Tendonitis and Tendon Rupture	If significant inflammation of tendons or tendon sheaths occur • Consider stopping levofloxacin • Treat with non steroidal anti-inflammatory drug (e.g., ibuprofen) • Rest the joint **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. If treatment failure is likely without levofloxacin • Decrease frequency of levofloxacin administration • Ensure joint is strictly rested • Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of levofloxacin
Vaginitis	Topical antifungal agents or short-course oral antifungal drugs are helpful Exclude other diseases if response to treatment is not prompt
Anxiety	If severe, initiate therapy with anxiolytic drugs (e.g., diazepam, midazolam) Decrease frequency of levofloxacin administration Discontinue levofloxacin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines

Criteria for Levofloxacin [2–4,58–60,84,85]	
Central nervous system related adverse drug reactions (e.g., confusion or hallucinations)	Generally occurs during first few weeks of therapy Reassure patient that symptoms will subside as treatment progresses Suspect drug-induced acute liver failure if there is jaundice
Central nervous system related adverse drug reactions (e.g., **insomnia,** restlessness, agitation, **tremors**)	Initiate sedative therapy with cyclizine Reassurance Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Decrease frequency of levofloxacin administration Discontinue levofloxacin if this can be done without compromising regimen
Clostridium difficile-associated diarrhea	Bowel rest Appropriate fluid and electrolyte management Protein supplementation Antibiotic treatment of *C. difficile* Surgical evaluation should be instituted as a last resort, if clinically indicated Discontinue levofloxacin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Constipation	Treat with stool softeners
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence Encourage fluid intake Assess for dehydration; initiate rehydration if indicated Assess for electrolyte disturbances; initiate replacement therapy if indicated Initiate anti-diarrheal therapy (e.g., loperamide) Administer lactobacillus or encourage foods such as yogurt Evaluate for *C. difficile* and other infections Decrease frequency of levofloxacin administration Discontinue levofloxacin if this can be done without compromising regimen—rarely necessary

Criteria for Levofloxacin [2–4,58–60,84,85]	
Hematological abnormalities (e.g., agranulocytosis, thrombocytopenia)	Stop all therapy pending resolution of toxicity Eliminate other potential causes of toxicity Consider suspending most likely agent permanently Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis), and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Increased intracranial pressure (pseudotumor cerebri)	Discontinue levofloxacin and institute appropriate therapy Modify regimen according to national TB treatment guidelines

Criteria for Levofloxacin [2–4,58–60,84,85]	
Photosensitivity/ Phototoxicity	Mild • Instruct patient to use sunscreen and avoid excessive exposure to sun or UV light. • Initiate therapy with cool compresses and hydrocortisone cream Severe • Eliminate levofloxacin from regimen • Modify regimen according to national TB treatment guidelines
Renal failure or nephrotoxicity	Discontinue levofloxacin Adjust dose of all drugs according to the creatinine clearance Rule out other causes (e.g., other medications, diabetes, congestive heart failure, urinary obstruction), and if identified, treat according to standard clinical protocol Consider dosing three times a week and monitor creatinine clearance every one to two weeks If creatinine clearance does not stabilize, permanently discontinue levofloxacin Modify regimen according to national TB treatment guidelines
Overdosage	In the event of an acute overdosage, the stomach should be emptied The patient should be observed and appropriate hydration maintained Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis

Criteria for Moxifloxacin [2–4,58–60,86,87]	
I. ***Justification criteria*** for prescribing moxifloxacin	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented: • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available
	Patient is allergic to isoniazid or rifampicin
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin
	Organism is susceptible to moxifloxacin (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing moxifloxacin	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Moxifloxacin allergy • Quinolone antimicrobial allergy • Nalidixic acid allergy • QT interval prolongation • Torsade de Pointes • Hypothyroidism • Bradyarrhythmias • Uncompensated heart failure • Serum calcium, magnesium, or potassium levels below the lower limits of normal • Heart disease • Ventricular arrhythmias • Myasthenia gravis • G6PD deficiency
	HIV status is documented in case records
	Moxifloxacin was available for the duration of treatment

Criteria for Moxifloxacin [2–4,58–60,86,87]			
Dose and frequency	Appropriate moxifloxacin dosing for adult patients • 400 mg daily Appropriate moxifloxacin dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • No adjustment necessary Moxifloxacin is not cleared by dialysis, so it may be administered irrespective of dialysis schedule and post-dialysis doses are not necessary Appropriate moxifloxacin dosing for pediatric patients • 7.5 to 10 mg/kg daily Not to exceed 400 mg daily		
Administration	May be administered without regard to food • Tablets can be taken with food or on an empty stomach Parenteral form is for intravenously use only • Administer IV preparations in 250 mL over 60 minutes every 24 hours by direct infusion or through a Y-type intravenous infusion set which may already be in place • Avoid rapid or bolus intravenous infusion of moxifloxacin to prevent hypotension Maintain adequate hydration to prevent the formation of highly concentrated urine Store ampoules of solution at 25°C ; excursions permitted to 15°C to 30°C **DO NOT REFRIGERATE - PRODUCT PRECIPITATES UPON REFRIGERATION** Moxifloxacin is compatible in the following solutions for immediate use—**Discard any unused portion** • 0.9% sodium chloride injection • 5% glucose injection • 10% glucose injection • Sterile water for injection		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months
		continuation phase	at least 12 months

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Patient Monitoring	Weight—every 2 weeks for the first 3 months of treatment then monthly Pregnancy testing—according to standard clinical protocol Monitor serum glucose of diabetic patients—according to standard clinical protocol Monitor patients with a known or suspected central nervous system disorder (e.g., severe cerebral arteriosclerosis, epilepsy) that may predispose them to seizures or lower the seizure threshold or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction) Monitor patients for signs of tendinitis and tendon rupture (e.g. pain, swelling, inflammation, snap or pop in a tendon area) Monitor patients with low blood levels of potassium or magnesium, a slower-than-normal heart rate, or the use of certain drugs used to treat arrhythmias for abnormal changes in the electrical activity of the heart according to standard clinical protocol HIV testing—according to standard clinical protocol
Therapeutic drug monitoring—moxifloxacin blood levels	To assure adequate therapeutic levels target peak concentrations of 3 to 4 mcg/mL for usual adult oral dosing, see Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentration.
Drug interactions	BCG vaccine decreases the effects of moxifloxacin • Do not coadminister Live typhoid vaccine may be inactivated by moxifloxacin • Do not coadminister Drugs that prolong the QT interval (e.g., mefepristone, azithromycin, amiodarone, and chloroquine) may have additive effects on moxifloxacin induced QT interval prolongation Avoid co-administration of QT interval prolonging drugs. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. Iron, calcium, zinc, or magnesium can attach to moxifloxacin and decrease its absorption • Administer oral doses at least 2 hours before or 2 hours after antacids containing aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution Moxifloxacin may enhance the effects of warfarin • Monitor prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation test when warfarin is coadministered with moxifloxacin, as well as for evidence of bleeding • Adjust warfarin dose as appropriate

Criteria for Moxifloxacin [2–4,58–60,86,87]

Moxifloxacin may cause blood glucose abnormalities

- Diabetic patients receiving concomitant moxifloxacin and anti-diabetic therapy (e.g., insulin, metformin) may experience altered blood glucose concentrations and symptomatic hyperglycemia or hypoglycemia
- Careful monitoring of blood glucose concentrations recommended
- Discontinue moxifloxacin if a hypoglycemic reaction occurs
- Modify regimen according to national TB treatment guidelines

NSAIDs coadministered with moxifloxacin in may increase the risk of central nervous system stimulation (tremors, restlessness, agitation, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia suicidal thoughts or acts) and seizures

- Monitor for central nervous system stimulation and convulsive seizures

Corticosteroids coadministered with moxifloxacin increases the risk of severe tendon disorders (e.g., tendinitis, tendon rupture), especially in patients older than 60 years of age

- Monitor for signs of signs of tendinitis and tendon rupture (e.g., pain, swelling, inflammation, snap or pop in a tendon area) and consider alternative to corticosteroid therapy

Hepatotoxic and neurotoxic drugs

- May potentiate toxicities
- If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs

Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered

- Moxifloxacin may decrease levels of didanosine
- If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.

Moxifloxacin may produce false-positive urine screening results for opiates using commercially available immunoassay kits

- Confirmation of positive opiate screens by more specific methods may be necessary

Administration of moxifloxacin may require confirmation of positive opiate screens by more specific methods may be necessary

Injection not coadministered with any solution containing multivalent cations, (e.g., magnesium, through the same intravenous line)

IV line flushed before and after infusion of moxifloxacin with an infusion solution compatible with moxifloxacin and with any other drug(s) administered via this common line

IV form administered as a single agent without admixtures

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Patient Counseling	Advise patients • To avoid caffeinated foods and beverages while taking this medicine • Tablets can be taken with food or on an empty stomach • Drink plenty of beverages • Do not take milk-based products, antacids (especially aluminum-containing), or multivitamins within 2 hours of this medication • This medicine may cause sun sensitivity; use sunscreen. • Do not undertake new strenuous activities • Educate patient on signs and symptoms of hypo- and hyperglcycaemia
	Advise patient to contact a health care provider immediately if they experience • Pain, swelling or tearing of a tendon (such as the back of the ankle, elbow, etc.) • Muscle or joint pain • Rashes, hives, bruising or blistering • Trouble breathing or tightness in the chest • Diarrhea • Yellow skin or eyes • Anxiety, confusion, or dizziness
	Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk
	Advise patients who are breastfeeding • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Moxifloxacin [2–4,58–60,86,87]	
III. ***Complications*** that could occur during therapy with moxifloxacin and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Arthralgias	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Decrease frequency of moxifloxacin administration Discontinue moxifloxacin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Blood glucose disturbances	Monitor blood glucose at least monthly Initiate or adjust oral hypoglycemic agent or insulin—according to standard clinical protocol
Depression	Assess and address underlying socioeconomic issues Assess for substance abuse and refer to treatment if appropriate Rule out other causes, and if identified, treat according to standard clinical protocol Rule out adverse drug reactions of concomitant medications (e.g., cycloserine, amoxicillin/clavulanate, penicillin, benzodiazepines) Refer to psychologist or psychiatrist for assessment Initiate group (if patient is sputum smear and culture negative) or individual psychological therapy Initiate anti-depressant therapy (e.g., amitriptyline, fluoxetine) • Only after group or individual psychological therapy initiated • Use with caution when there is a history of convulsions **Caution:** Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. Decrease frequency of moxifloxacin administration Discontinue moxifloxacin Modify regimen according to national TB treatment guidelines

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Diarrhea, Flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of moxifloxacin administration
	Discontinue moxifloxacin if this can be done without compromising regimen—rarely necessary
Dizziness	Conduct a clinical evaluation to determine whether the dizziness is vestibular or non-vestibular in origin
	Conduct a clinical evaluation to determine whether the dizziness is peripheral or central in origin
	Treat specific cause if it can be identified
	If cause cannot be identified, treat with cyclizine
	Initiate anti-emetics (e.g., metoclopramide, ondansetron) if appropriate
	Note: Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis)
	Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole)
	Stop moxifloxacin for short periods of time (e.g., one to seven days)
	Discontinue moxifloxacin if this can be done without compromising the regimen
	Modify regimen according to national TB treatment guidelines

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections)
	Encourage adequate fluid intake
	Treat with ibuprofen, paracetamol, or aspirin
	Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Address stressors potentially contributing to tension-related headaches
	Consider administering amitriptyline 50 to 150 mg at night
	Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine)
	Consider neurology consultation
	Consider reducing the frequency of moxifloxacin administration to five times or even three times per week
Hypersensitivity, mild (skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion
	Note: Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g. eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone)
	Note: Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
	Stop all therapy under cover of antihistamines
	Stop all therapy until reaction resolves
	Modify regimen according to national TB treatment guidelines
	Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol
	Rechallenge cutaneous hypersensitivity reactions with or without desensitization
	DO NOT attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Nausea or Vomiting	Administer with small meals and advise patient to swallow tablets slowly with small sips of water
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Assess for dehydration, electrolyte disturbances, hepatitis
	Initiate rehydration if indicated
	Initiate antiemetic therapy (e.g., metoclopramide, ondansetron)
	Decrease frequency of moxifloxacin administration
	Discontinue moxifloxacin if this can be done without compromising regimen—rarely necessary
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes
	Correct any vitamin or nutritional deficiencies
	Administer pyridoxine 200 to 300 mg per day
	Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily)
	Consider paracetamol and NSAIDs (or both) for pain relief
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Consider neurology consultation
	Consider administering carbamazepine
	Decrease frequency of moxifloxacin administration
	Discontinue moxifloxacin
	Modify regimen according to national TB treatment guidelines
Prolongation of the QT interval	Obtain an electrocardiogram and initiate treatment according to standard clinical protocol
	Correct electrolyte imbalances (calcium, potassium, magnesium)
	Discontinue moxifloxacin if risk of torsades de pointes outweighs the benefits of the drug
	Modify regimen according to national TB treatment guidelines

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Psychotic symptoms	Stop moxifloxacin for a short period of time (1 to 4 weeks) while psychotic symptoms are brought under control Initiate antipsychotic therapy (haloperidol, chlorpromazine, risperidone [consider biperiden to prevent extrapyramidal effects]) If patient is at risk of self harm, hospitalize patient under expert psychiatric care Reduce frequency of moxifloxacin administration Reduce moxifloxacin dose If symptoms do not improve discontinue moxifloxacin Modify regimen according to national TB treatment guidelines
Seizures	Suspend moxifloxacin pending resolution of seizures Suspend other seizure inducing medicines (e.g., cycloserine, isoniazid) Initiate anticonvulsant therapy (e.g., phenobarbital, phenytoin, carbamazepine, valproic acid) Administer pyridoxine 200 to 300 mg daily Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium, and chloride Once seizures have resolved, restart medications one at a time Reduce frequency of moxifloxacin administration Discontinue moxifloxacin if seizures do not resolve Modify regimen according to national TB treatment guidelines
Sense of taste disturbance	Encourage the patient to tolerate this side effect Sucking on lemon drops or other hard candy or chewing gum can be helpful Normal taste returns when treatment is stopped
Tendonitis and tendon rupture	If significant inflammation of tendons or tendon sheaths occur: • Consider stopping moxifloxacin • Treat with non-steroidal anti-inflammatory drug (e.g., ibuprofen) • Rest the joint **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. If treatment failure is likely without moxifloxacin • Decrease frequency of moxifloxacin administration • Ensure joint is strictly rested • Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of moxifloxacin
Vaginitis	Topical antifungal agents or short-course oral antifungal drugs are helpful Exclude other diseases if response to treatment is not prompt

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Anxiety	If severe, initiate therapy with anxiolytic drugs (e.g., diazepam, midazolam) Decrease frequency of moxifloxacin administration Discontinue moxifloxacin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Central nervous system-related adverse drug reactions (e.g., confusion or hallucinations)	Generally occurs during first few weeks of therapy Reassure patient that symptoms will subside as treatment progresses Suspect drug-induced acute liver failure if there is jaundice
Central nervous system related adverse drug reactions (insomnia, restlessness, agitation)	Initiate sedative therapy with cyclizine Reassurance Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Decrease frequency of moxifloxacin administration Discontinue moxifloxacin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Clostridium difficile-associated diarrhea	Bowel rest Appropriate fluid and electrolyte management Protein supplementation Antibiotic treatment of *C. difficile* Surgical evaluation should be instituted as a last resort, if clinically indicated Discontinue moxifloxacin if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Constipation	Treat with stool softeners
Hematological abnormalities (e.g., agranulocytosis, thrombocytopenia)	Stop all therapy pending resolution of toxicity Eliminate other potential causes of toxicity Consider suspending most likely agent permanently Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis); and if identified, treat according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Increased intracranial pressure (pseudotumor cerebri)	Discontinue moxifloxacin Institute appropriate therapy Modify regimen according to national TB treatment guidelines

Criteria for Moxifloxacin [2–4,58–60,86,87]	
Photosensitivity/ Phototoxicity	Mild • Instruct patient to use sunscreen and avoid excessive exposure to sun or UV light • Initiate therapy with cool compresses and hydrocortisone cream Severe • Eliminate moxifloxacin from regimen • Modify regimen according to national TB treatment guidelines
Renal failure or nephrotoxicity	Discontinue moxifloxacin Adjust dose of all drugs according to the creatinine clearance Rule out other causes (e.g., other medications, diabetes, congestive heart failure, urinary obstruction), and if identified, treat according to standard clinical protocol Consider dosing three times a week and monitor creatinine clearance every one to two weeks If creatinine clearance does not stabilize, permanently discontinue moxifloxacin Modify regimen according to national TB treatment guidelines
Overdosage	In the event of an acute overdosage, the stomach should be emptied The patient should be observed and appropriate hydration maintained Moxifloxacin is not efficiently removed by hemodialysis or peritoneal dialysis

Criteria for *p*-aminosalicylic acid [2–4,59,60,88–91] or *p*-aminosalicylic acid sodium	
I. ***Justification criteria*** for prescribing *p*-aminosalicylic acid	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics) Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented: • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available Patient is allergic to isoniazid or rifampicin Patient has documented serious adverse drug reaction to isoniazid or rifampicin Organism is susceptible to *p*-aminosalicylic acid (if DST is available) According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing *p*-aminosalicylic acid	
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent Patient history has been reviewed for: • *p*-aminosalicylic acid allergy or allergy to any of its components (dibutyl sebacate, hydroxypropyl methyl cellulose, methacrylic acid copolymer, microcrystalline cellulose, or talc) • Salicylic acid allergy • Renal failure • G6PD deficiency HIV status is documented in case records *p*-aminosalicylic acid was available for the duration of treatment
Dose and Frequency	Appropriate *p*-aminosalicylic acid dosing for adult patients • 8 to 12 g daily in 2 or 3 divided doses Not to exceed 12 g per day Appropriate *p*-aminosalicylic acid dosing for renal dysfunction (Creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 4 g twice daily • To be administered after hemodyalisis Appropriate *p*-aminosalicylic acid dosing for pediatric patients • 200 to 300 mg/kg daily in 2 to 4 divided doses Not to exceed 10 g per day

Criteria for *p*-aminosalicylic acid [2–4,59,60,88–91] or *p*-aminosalicylic acid sodium			
Administration	For oral use only Administer granules by • Sprinkling on acidic foods such as apple sauce or yogurt or by suspension in a fruit drink which will protect the coating • The granules sink and will have to be swirled • The coating will last at least 2 hours in either system • All juices tested to date have been satisfactory; tested juices include tomato, orange, grapefruit, grape, cranberry, apple, and fruit punch **Note:** *p*-aminosalicylic acid to be stored below 5°C (in a refrigerator or freezer) *p*-aminosalicylate sodium to be stored at room temperature (15°C to 25°C)		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months
		continuation phase	at least 12 months

Patient monitoring	Prior to treatment and then at least monthly during treatment:
	
	Weight (and every 2 weeks for the first three months of treatment)
	
	Pregnancy testing—according to standard clinical protocol
	
	Renal function
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations- preferred—over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Liver function:
	• AST (SGOT)
	• ALT (SGPT)
	• Total bilirubin
	
	Thyroid function
	
	Complete blood count with differential
	
	Electrolytes
	
	HIV testing—according to standard clinical protocol		

Criteria for *p*-aminosalicylic acid [2–4,59,60,88–91] or *p*-aminosalicylic acid sodium	
Therapeutic drug monitoring—*p*-aminosalicylic acid blood levels	To ensure adequate therapeutic levels peak concentrations are expected to be 20 to 60 mcg/mL To avoid potential toxicities avoid prolonged peaks greater than to 60 mcg/mL See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance in how to adjust dose based on serum concentrations
Drug Interactions	Isoniazid effects are decreased when coadministered with *p*-aminosalicylic acid Ethionamide • possible increase in liver toxicity when coadministered with *p*-aminosalicylic acid • monitor liver enzymes Hydroxocobalamin (Vitamin B12) absorption has been reduced 55% by 5 grams of *p*-aminosalicylic acid with clinically significant erythrocyte abnormalities developing after depletion Digoxin levels may decrease when coadministered with *p*-aminosalicylic acid Hepatotoxic and nephrotoxic drugs • Concurrent administration may potentiate toxicities • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs. Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents. *p*-aminosalicylic acid has been reported to interfere technically with the serum determinations of • Albumin by dye-binding • AST (SGOT) by the azoene dye method *p*-aminosalicylic acid has been reported to interfere technically with qualitative urine tests for • Ketones • Bilirubin • Urobilinogen • Porphobilinogen

Criteria for *p*-aminosalicylic acid [2–4,59,60,88–91] or *p*-aminosalicylic acid sodium	

Patient Counseling	Advise patients
	• *p*-aminosalicylic acid sodium packets may be stored at room temperature
	• Administer granules by
	  ○ Sprinkling on acidic foods such as apple sauce or yogurt or by suspension in a fruit drink which will protect the coating
	  ○ The granules sink and will have to be stirred
	  ○ The coating will last at least two hours in either system
	  ○ All juices tested to date have been satisfactory; tested are: tomato, orange, grapefruit, grape, cranberry, apple, “fruit punch”
	• Do **NOT** chew the granules
	• Take with food if desired
	• Do not use the packet if swollen or if the granules are discolored
	• Gastrointestinal discomfort and diarrhea usually improve over time
	• The shells of the granules may be seen in the stool—this is normal

	Advise patients to contact a health care provider immediately if they experience • Skin rash, severe itching, or hives, often followed by fever • Severe abdominal pain, nausea, vomiting, or diarrhea • Unusual fatigue or loss of appetite • Black stools or bleeding
	Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk
	Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for *p*-aminosalicylic acid [2–4,59,60,88–91] or *p*-aminosalicylic acid sodium	
III. ***Complications*** that could occur during therapy with *p*-aminosalicylic acid and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of *p*-aminosalicylic acid administration
	Discontinue *p*-aminosalicylic acid if this can be done without compromising regimen— rarely necessary
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis)
	Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole)
	Stop *p*-aminosalicylic acid for short periods of time (e.g., one to seven days)
	Discontinue *p*-aminosalicylic acid if this can be done without compromising the regimen
	Modify regimen according to national TB treatment guidelines
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly
	Once resolved, monitor liver function monthly

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for *p*-aminosalicylic acid [2–4,59,60,88–91] or *p*-aminosalicylic acid sodium	
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis) If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., drug fever, rash, skin eruptions of various types, including exfoliative dermatitis, infectious mononucleosis-like, or lymphoma-like syndrome, leucopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, jaundice, hepatitis, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Leoffler's syndrome, vasculitis and a **reduction in prothrombin**)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)

Criteria for *p*-aminosalicylic acid [2–4,59,60,88–91] or *p*-aminosalicylic acid sodium	
Hypothyroidism (increased risk with concomitant use of ethionamide)	Monitor thyroid function Initiate thyroxine therapy according to standard clinical protocol
Nausea or vomiting	Administer with small meals and advise patient to sallow tablets slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Decrease frequency of *p*-aminosalicylic acid administration Discontinue *p*-aminosalicylic acid if this can be done without compromising regimen— rarely necessary
Clostridium difficile-associated diarrhea	Bowel rest Appropriate fluid and electrolyte management Protein supplementation Antibiotic treatment of *C. difficile* Surgical evaluation should be instituted as a last resort, if clinically indicated Discontinue *p*-aminosalicylic acid if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Crystalluria	Maintain urine at a neutral or an alkaline pH as prophylaxis
Erythrocyte abnormalities	Initiate hydroxocobalamin (Vitamin B12) therapy
Fever	Rule out other causes Paracetamol or ibuprofen can be given to lower the temperature **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity Exercise caution with use and monitor renal function Fluids may be given by mouth or IV to prevent dehydration, if necessary
Malabsorption syndrome	• Assess for ○ Increase in fecal fat ○ Decrease in serum carotene ○ Reduced xylose absorption ○ Reduced iron absorption ○ Abnormal small bowel pattern on x-ray ○ Villus atrophy Initiate replacement therapy—according to standard clinical protocol

Criteria for *p*-aminosalicylic acid [2–4,59,60,88–91] or *p*-aminosalicylic acid sodium	
Overdose and life-threatening toxicity	Overdosage has not been reported

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
I. ***Justification criteria*** for prescribing prothionamide	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented: • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available
	Patient is allergic to isoniazid or rifampicin
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin
	Organism is susceptible to prothionamide (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing prothionamide	
	Administer in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Prothionamide or ethionamide allergy • Severe hepatic impairment • Porphyria • Excessive concurrent use of alcohol
	HIV status is documented in case records
	Prothionamide was available for the duration of treatment

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]			
Dose and frequency	Appropriate prothionamide dosing for adult patients • 15 to 20 mg/kg daily • Usually 500 to 75 mg/kg daily in two divided doses or a single daily dose Not to exceed 1,000 mg daily Appropriate prothionamide dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • No adjustment necessary • Prothionamide is not cleared by dialysis, so it may be administered irrespective of dialysis schedule and post-dialysis doses are not necessary Appropriate prothionamide dosing for pediatric patients • 15 to 20 mg/kg daily, usually divided into two or three daily doses Not to exceed 1,000 mg daily		
Administration	Administer pyridoxine (Vitamin B6) for peripheral neuropathy prophylaxis • Adult dose—100 mg daily • Pediatric dose—1 to 2 mg/kg daily, with a usual range of 10 to 50 mg daily		
Duration	Multidrug-resistant TB	intensive phase	at least 8 months
		continuation phase	at least 12 months
Patient Monitoring	Prior to treatment and then at least monthly during treatment: Weight (and every 2 weeks for the first three months of treatment) Pregnancy testing—according to standard clinical protocol Liver function: • AST (SGOT) • ALT (SGPT) • Total bilirubin Serum glucose Thyroid function Ophthalmologic function • Ophthalmoscopy • Finger perimetry • Acuity testing (Snellen chart) • Color discrimination (Ishihara tests) HIV testing—according to standard clinical protocol		
Therapeutic drug monitoring—prothionamide blood levels	Conduct when malabsorption is suspected To assure adequate therapeutic levels target peak concentrations of 1 to 5 mcg/mL, see Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance in how to adjust dose based on serum concentration.		

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
Drug interactions	Ethanol • Monitor for psychotic reactions Prothionamide may temporarily raise serum concentrations of isoniazid • Monitor liver function tests and clinical signs and symptoms of hepatotoxicity Other anti-tuberculosis drugs • Monitor for potential overlapping adverse events of especially cycloserine (convulsions) Hepatotoxic and neurotoxic drugs • Concurrent administration may potentiate toxicities • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs. Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.
Patient Counseling	Advise patients: • Take this medicine with food • Patient must also take a high-dose pyridoxine (Vitamin B6) supplement while on this medicine
	Advise patients to contact a health care provider immediately if they experience: • Any problems with their eyes such as eye pain, blurred vision, color blindness, or trouble seeing • Numbness, tingling, or pain in their hands or feet • Unusual bruising or bleeding • Personality changes such as depression, confusion, or aggression • Yellowing of the skin or eyes • Dark-colored urine • Nausea or vomiting • Dizziness • Swollen breasts (in men)
	Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
	Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with prothionamide and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Alopecia	Encourage patients to tolerate this side effect Resolution occurs after treatment is stopped
Blood glucose disturbances	Monitor blood glucose until stabilized Modify oral hypoglycemic agent or insulin—according to standard clinical protocol
Depression	Assess and address underlying socioeconomic issues Assess for substance abuse and refer to treatment if appropriate Rule out other causes If identified, treat specific cause according to standard clinical protocol Rule out adverse drug reactions of concomitant medications (e.g., cycloserine, amoxicillin/clavulanate, penicillin, benzodiazepines) Refer to psychologist or psychiatrist for assessment Initiate group (if patient is sputum smear and culture negative) or individual psychological therapy Initiate anti-depressant therapy (e.g., amitriptyline, fluoxetine) • Only after group or individual psychological therapy initiated • Use with caution when there is a history of convulsions **Caution:** Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. Decrease dose of prothionamide to 500 mg daily Decrease frequency of prothionamide administration Discontinue prothionamide Modify regimen according to national TB treatment guidelines

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of prothionamide administration
	Discontinue prothionamide if this can be done without compromising regimen—rarely necessary
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis)
	Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole)
	Stop prothionamide for short periods of time (e.g., one to seven days)
	Discontinue prothionamide if this can be done without compromising the regimen
	Modify regimen according to national TB treatment guidelines
Gynecomastia	Rule out other causes
	Reduce frequency of administration
	Encourage patients to tolerate this side effect
	Resolution occurs after treatment is stopped
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly
	Once resolved, monitor liver function monthly

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non-hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol induced hepatitis); If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Hypersensitivity, mild (e.g., skin itching, redness, rash, swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Hypothyroidism	Monitor thyroid function every one to two months until stabilized Initiate thyroxine therapy according to standard clinical protocol

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
Nausea, vomiting, or anorexia	Administer with small meals and advise patient to swallow pills slowly with small sips of water
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Assess for dehydration, electrolyte disturbances, hepatitis
	Initiate rehydration if indicated
	Initiate antiemetic therapy (e.g., metoclopramide, ondansetron)
	Decrease frequency of prothionamide administration
	Discontinue prothionamide if this can be done without compromising regimen—rarely necessary
Optic neuritis	Refer patient to an ophthalmologist
	In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions
	In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult
Sense of taste disturbance	Encourage the patient to tolerate this adverse reaction
	Sucking on lemon drops or other hard candy or chewing gum can be helpful
	Normal taste returns when treatment is stopped
Suicidal Ideation	Hospitalize patients with suicidal ideation for 24 hour surveillance
	Decrease dose of prothionamide to 500 mg daily until the patient is stable
	Request psychiatric consultation
	Initiate antidepressant therapy
	Caution: Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval.
	Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes.
Acne	Provide supportive care
	If acne is bothersome to the patient, topical acne treatments may be administered

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
Central nervous system-related adverse drug reactions (e.g., drowsiness, dizziness, restlessness, postural hypotension)	Ensure patient is administered an adequate dose of pyridoxine Reassurance Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Rule out other causes If identified, treat specific cause according to standard clinical protocol Treat dizziness with cyclizine if appropriate **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Clostridium difficile-associated diarrhea	Bowel rest Appropriate fluid and electrolyte management Protein supplementation Antibiotic treatment of *C. difficile* Surgical evaluation should be instituted as a last resort, if clinically indicated Discontinue prothionamide if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines
Erectile Dysfunction	Rule out other causes of, or contributors to the erectile dysfunction (ED) Screen for thyroid dysfunction Postpone specific treatment of ED in patients with thyroid dysfunction until euthyroidism has been reached for at least 6 months If caused by thyroid dysfunction, and all other causes and contributors have been ruled out, administer thyroxine therapy according to standard clinical protocol

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections)
	Ensure patient is administered an adequate dose of pyridoxine (200 to 300 mg per day)
	Encourage adequate fluid intake
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Treat with ibuprofen, paracetamol, or aspirin
	Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Address stressors potentially contributing to tension-related headaches
	Consider administering amitriptyline 50 to 150 mg at night
	Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine)
	Consider neurology consultation
	Consider reducing the frequency of prothionamide administration to five times or even three times per week
Hematological abnormalities	Stop all therapy pending resolution of toxicity
	Eliminate other potential causes of toxicity
	Consider suspending most likely agent permanently.
	Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Hypersalivation	Tooth brushing and rinsing with alcohol-containing products will produce drying effects
Menstrual irregularity	Rule out other causes of, or contributors to the irregularity
	Screen for thyroid dysfunction
	Initiate thyroid therapy for thyroid dysfunction, if all other causes and contributors have been ruled out

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes Correct any vitamin or nutritional deficiencies Administer pyridoxine 200 to 300 mg per day Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily) Consider paracetamol and NSAIDs (or both) for pain relief **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Consider neurology consultation Consider administering carbamazepine Decrease frequency of prothionamide administration Discontinue prothionamide Modify regimen according to national TB treatment guidelines
Photosensitivity/ phototoxicity	Mild • Instruct patient to use sunscreen and avoid excessive exposure to sun or UV light • Initiate therapy with cool compresses and hydrocortisone cream Severe • Eliminate prothionamide from regimen • Modify regimen according to national TB treatment guidelines
Porphyria	Discontinue prothionamide Consider dosing 2 to 3 times a week if drug is essential to the regimen Provide symptomatic therapy, high carbohydrate intake, and intravenous administration of hematin Modify regimen according to national TB treatment guidelines
Psychotic Symptoms	Stop prothionamide for a short period of time (1 to 4 weeks) while psychotic symptoms are brought under control Initiate antipsychotic therapy (haloperidol, chlorpromazine, risperidone [consider biperiden to prevent extrapyramidal effects]) If patient is at risk of self harm, hospitalize patient under expert psychiatric care Reduce frequency of prothionamide administration Reduce prothionamide dose If symptoms do not improve discontinue prothionamide Modify regimen according to national TB treatment guidelines

Criteria for Prothionamide [2–4,58,59,64,71,81,82,92,93]	
Overdose and life-threatening toxicity	No specific information is available on the treatment of overdosage with prothionamide If it should occur, standard procedures to evacuate gastric contents and to support vital functions should be employed

Criteria for Terizidone [2–4,58,59,94,95]	
I. ***Justification criteria*** for prescribing terizidone	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Presumptively diagnosed by DR-TB specialists if one or more of the following are documented: • Failure of retreatment regimens with first-line drugs • Patient has had close contact with DR-TB patients and has developed TB • Failure of new regimens with first-line drugs according to national DR-TB treatment guidelines • Regimen is adjusted if DST results become available
	Patient is allergic to isoniazid or rifampicin
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin
	Organism is susceptible to terizidone (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing terizidone	
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Terizidone or cycloserine allergy • Epilepsy • Depression, severe anxiety, or psychosis • Severe renal insufficiency • Excessive concurrent use of alcohol
	HIV status is documented in case records
	Terizidone was available for the duration of treatment
Dose and Frequency	Appropriate terizidone dosing for adult • 10 to 15 mg/kg daily Not to exceed 1,000 mg daily
	Appropriate terizidone dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • Recommendations not available • Terizidone should be administered following dialysis on dialysis days • The use of terizidone is not recommended in patients with creatinine clearance 50 mL/minute unless they are on hemodialysis
	Appropriate terizidone dosing for pediatric patients • 10 to 20 mg/kg once or twice daily in divided doses Not to exceed 1,000 mg daily

<table>
<tr><th colspan="4">Criteria for Terizidone [2–4,58,59,94,95]</th></tr>
<tr><td>Administration</td><td colspan="3">For oral use only

Best taken one hour before or two hours after meals

Peripheral neuropathy prophylaxis
• Adults—administer pyridoxine 50 mg for every 250 mg of cycloserine daily
• Pediatric patients—administer pyridoxine 1 to 2 mg/kg per day with a usual range of 10 to 50 mg per day</td></tr>
<tr><td>Duration</td><td>Multidrug-resistant TB</td><td>intensive phase
continuation phase</td><td>at least 8 months
at least 12 months</td></tr>
<tr><td>Patient Monitoring</td><td colspan="3">Prior to treatment and then at least monthly during treatment:

Weight (and every 2 weeks for the first 3 months of treatment)

Pregnancy testing—according to standard clinical protocol

Beck Depression Index (or similar tool to monitor depression)

Complete blood count with differential

Liver function
• AST (SGOT)
• ALT (SGPT)
• Total bilirubin

Renal function

One or more of the following laboratory measurements:
• Blood
○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient’s age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
○ Serum creatinine concentration (preferred over BUN)
○ Blood urea nitrogen (BUN)
○ Non-protein nitrogen (NPN)
• Urine
○ Proteinuria
○ Presence of cells and casts
○ Specific gravity

HIV testing—according to standard clinical protocol</td></tr>
<tr><td>Therapeutic drug monitoring—terizidone blood</td><td colspan="3">To ensure adequate therapeutic levels monitor weekly for patients
• With reduced renal function
• Receiving a daily dosage greater than 500 mg
• Showing signs and symptoms suggestive of toxicity</td></tr>
</table>

Criteria for Terizidone [2–4,58,59,94,95]	
levels	For all patients • To ensure adequate therapeutic increase the dose if the peak is less than 15 mcg/mL • To avoid potential toxicities keep peak concentration below 35 mcg/mL • If the dose is adjusted, repeat the peak concentration after at least three to four days See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentrations
Drug interactions	Ethanol • May enhance the neurotoxic effects of terizidone specifically the risk for seizures Isoniazid • Concurrent administration with isoniazid may result in increased incidence of central nervous system effects • Dosage adjustments may be necessary Ethionamide • Concurrent administration with ethionamide may result in increased incidence of central nervous system effects • Dosage adjustments may be necessary Hepatotoxic, nephrotoxic, and neurotoxic drugs • May potentiate toxicities If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs. Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.

Criteria for Terizidone [2–4,58,59,94,95]	
Patient Counseling	Advise patients to • Take this medicine on an empty stomach, with juice, or antacids. If food is taken, avoid a large fatty meal • Avoid alcohol • Patient must also take a high-dose pyridoxine (Vitamin B6) supplement while on this medicine Advise patients to contact a health care provider immediately if they experience • Seizures • Shakiness or trouble talking • Depression or thoughts of hurting oneself • Anxiety, confusion, or loss of memory • Personality changes, such as aggressive behavior • Rash or hives • Headache Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk Advise patients who are breastfeeding: • Most drugs used to treat TB cross into the breast milk at low levels • The amount of anti-TB drugs that babies receive through the breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with terizidone and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Terizidone [2–4,58,59,94,95]	
Central nervous system related adverse drug reactions (e.g., inability to concentrate, lethargy, vertigo, hyper-reflexia, paresis, hyperirritability, dysarthria, drowsiness, somnolence, confusion disorientation, loss of memory)	Administer pyridoxine maximum daily dose (200 to 300 mg per day) Reassurance Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
Depression	Assess and address underlying socioeconomic issues Assess for substance abuse and refer to treatment if appropriate Rule out other causes If identified, treat specific cause according to standard clinical protocol Rule out adverse drug reactions of concomitant medications (e.g., cycloserine, amoxicillin/clavulanate, penicillin, benzodiazepines) Refer to psychologist or psychiatrist for assessment Initiate group (if patient is sputum smear and culture negative) or individual psychological therapy Initiate anti-depressant therapy (e.g., amitriptyline, fluoxetine) • Only after group or individual psychological therapy initiated • Use with caution when there is a history of convulsions **Caution:** Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. • Decrease dose of terizidone to 500 mg daily • Decrease frequency of terizidone administration • Discontinue terizidone • Modify regimen according to national TB treatment guidelines
Hypersensitivity, mild (lichenoid eruptions, skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Terizidone [2–4,58,59,94,95]	
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, lupoid reactions, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Hypersensitivity, severe (Stevens-Johnson syndrome)	Stop terizidone Requires immediate therapy Provide fluid replacement and nutritional supplement Provide wound care Consult dermatologist if any question of diagnosis Provide supportive care (analgesic, antihistamine, antibiotic, systemic steroid, and immunoglobulin treatment—according to standard clinical protocol) Modify regimen according to national TB treatment guidelines

Criteria for Terizidone [2–4,58,59,94,95]	
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes
	Correct any vitamin or nutritional deficiencies
	Administer pyridoxine 200 to 300 mg per day
	Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily)
	Consider paracetamol and NSAIDs (or both) for pain relief
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function
	Consider neurology consultation
	Consider administering carbamazepine
	Decrease frequency of terizidone administration
	Discontinue terizidone
	Modify regimen according to national TB treatment guidelines
Psychotic Symptoms	Stop terizidone for a short period of time (1 to 4 weeks) while psychotic symptoms are brought under control
	Initiate antipsychotic therapy (haloperidol, chlorpromazine, risperidone [consider biperiden to prevent extrapyramidal effects])
	If patient is at risk of self harm, hospitalize patient under expert psychiatric care
	Reduce frequency of terizidone administration
	Reduce terizidone dose to 500 mg daily
	If symptoms do not improve, discontinue terizidone
	Modify regimen according to national TB treatment guidelines
Seizure, convulsions, coma	Suspend terizidone pending resolution of seizures
	Suspend other seizure inducing medicines (e.g., fluoroquinolones, isoniazid)
	Initiate anticonvulsant therapy (e.g., phenobarbital, phenytoin, carbamazepine, valproic acid)
	Administer pyridoxine 200 to 300 mg daily
	Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium, and chloride
	Once seizures have resolved, restart medications one at a time
	When restarting terizidone with a dose one weight band lower
	Reduce frequency of terizidone administration
	Discontinue terizidone if seizures do not resolve
	Modify regimen according to national TB treatment guidelines

Criteria for Terizidone [2–4,58,59,94,95]	
Suicidal ideation	Hospitalize patients with suicidal ideation for 24 hour surveillance
	Discontinue terizidone
	Modify regimen according to national TB treatment guidelines
	Request psychiatric consultation
	Initiate antidepressant therapy
	Caution: Certain SSRIs, SNRIs, and tricyclic antidepressants may prolong the QT interval
Anemia	Determine cause of anemia (i.e., iron deficiency, hydroxocobalamin (Vitamin B12) deficiency, chronic disease, bleeding)
	Supplement with iron, hydroxocobalamin (Vitamin B12), folate (Vitamin B9), ascorbic acid (Vitamin C) as appropriate
	Monitor complete blood counts weekly until stabilized
	Best taken one hour before or two hours after meals
Congestive Heart Failure	Sudden development of congestive heart failure in patients receiving 1 to 1.5 g of cycloserine (chemically related to terizidone) daily has been reported
	Treat according to standard clinical protocol
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections)
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Encourage adequate fluid intake
	Confirm patient on adequate dose of pyridoxine
	Treat with ibuprofen, paracetamol, or aspirin
	Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity Exercise caution with use and monitor renal function.
	Address stressors potentially contributing to tension-related headaches
	Consider administering amitriptyline 50 to 150 mg at night
	Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine)
	Consider neurology consultation
	Consider reducing the frequency of terizidone administration to five times or even three times per week

Criteria for Terizidone [2–4,58,59,94,95]	
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis, If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Tremor	Reassurance Maintain treatment if the tremor is mild and does not interfere with daily activities Initiate anticholinergic therapy (e.g., biperiden) if tremor is severe
Overdose and life-threatening toxicity	Acute toxicity can occur if more than 1 g is ingested by an adult. Chronic toxicity is dose related and can occur if more than 500 mg is administered daily. Symptomatic and supportive therapy is recommended Protect the patient's airway and support ventilation and perfusion Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes Activated charcoal may be more effective in reducing absorption than emesis or lavage In adults, many neurotoxic effects can be both treated and prevented with pyridoxine Hemodialysis removes terizidone from the bloodstream but should be reserved for life-threatening toxicity

Group 5 Drugs

Please be aware of the following when using information in this Section of the Annex

At this time, routine drug susceptibility testing (DST) of drugs in group 5 (clofazimine, linezolid, amoxicillin/clavulanate, clarithromycin,[1] imipenem) is not recommended as reliability and reproducibility of laboratory testing cannot be guaranteed.[72]

Although the drug information in this document is extensive, it is not intended to replace national tuberculosis treatment guidelines, Package Inserts or other printed material that may be available or accompany a particular drug.

Only medicines on the WHO Model Essential Medicines Lists [53,54] are referenced in this document.

Ancillary medicines or concomitant medicines on National Essential Medicine Lists that do not appear on the WHO Model Lists should be checked for:

- Interactions with anti-TB medicines
- Contraindications for co-administration with anti-TB medicines
- Correct dose and administration for treatment of adverse drug reactions

and added to the information in Annex A. Published Criteria for Anti-Tuberculosis Treatment.

Children older than 12 years of age can be managed as adults.[55]

Consult with a TB specialist or clinical pharmacist about the clinical use of **any** medicine administered to a patient.

[1] Clarithromycin is not included in this section of the annex as further studies are needed to establish the effectivness of clarithromycin in the treatment of TB.

Criteria for Amoxicillin/Clavulanate [2–4,49,60,96,97]	
I. ***Justification criteria*** for prescribing amoxicillin/clavulanate	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes isoniazid and rifampicin
	DST document the organism resistance pattern includes any fluoroquinolone
	DST document the organism resistance pattern includes at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin or second-line drug(s)
	Organism is susceptible to amoxicillin/clavulanate (if DST is available) According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing amoxicillin/clavulanate	
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Amoxicillin allergy • Clavulanate allergy • Penicillin allergy • Cephalosporin allergy • Cholestatic jaundice • Hepatic dysfunction • Mononucleosis ○ A high percentage of patients with mononucleosis who receive amoxicillin develop an erythematous skin rash
	HIV status is documented in case records
	Amoxicillin/clavulanate was available for the duration of treatment
Dose and frequency	Appropriate amoxicillin/clavulanate dosing for adult patients • 1,000/125 mg twice or three times a day Not to exceed 3,000 mg and 375 mg clavulanate daily
	Appropriate amoxicillin/clavulanate dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • For creatinine clearance 10 to 30 mL/min, administer 1,000 mg as amoxicillin component twice daily • For creatinine clearance less than 10 mL/min, administer 1,000 mg as amoxicillin component once daily • Administer after dialysis on dialysis days
	Appropriate amoxicillin/clavulanate dosing for pediatric patients • 80 mg/kg/day divided twice daily of the amoxicillin component Not to exceed 4,000 mg amoxicillin and 500 mg clavulanate daily

Criteria for Amoxicillin/Clavulanate [2–4,49,60,96,97]	
Administration	For oral use only
Duration	According to national DR-TB treatment guidelines
Patient Monitoring	Weight (and every 2 weeks for the first three months of treatment) Pregnancy testing—according to standard clinical protocol HIV testing—according to standard clinical protocol
Therapeutic drug monitoring—amoxicillin blood levels	To ensure adequate therapeutic levels and avoid toxicities Time to peak oral concentration is 60 to 90 minutes Peak concentrations are expected to be 17 mcg/mL of amoxicillin following a 2,000 mg (as amoxicillin) dose See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentrations
Drug Interactions	Live typhoid vaccine may be inactivated by amoxicillin/clavulanate • Avoid co-administration BCG vaccine may be inactivated by amoxicillin/clavulanate • Avoid co-administration Isoniazid effects are decreased when coadministered with amoxicillin/clavulanate • Tetracycline and its derivatives' effects are decreased when coadministered with amoxicillin/clavulanate Amoxicillin/clavulanate may increase the prolongation of prothrombin time when coadministered with anticoagulants Coadministration with allopurinol increases the risk of rash Amoxicillin/clavulanate may increase methotrexate blood levels Amoxicillin/clavulanate may reduce efficacy of oral contraceptives • Recommend the use of another form of contraception Hepatotoxic drugs • Concurrent administration may potentiate hepatotoxicity • If necessary to coadminister, monitor adverse drug reactions carefully Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs May result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution, or Fehling's Solution • Use glucose tests based on enzymatic glucose oxidase reactions

Criteria for Amoxicillin/Clavulanate [2–4,49,60,96,97]	
Patient Counseling	Advise patients: • Take with food or milk Advise patients to contact a health care provider immediately if they experience: • Rash or swelling • Trouble breathing • Severe diarrhea Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category B • Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. • No proven risk in humans Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant
III. ***Complications*** that could occur during therapy with amoxicillin/clavulanate and how to respond if the complication presents as follows[1]:	
Severe or common toxicities are indicated by **bold** font	
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence Encourage fluid intake Assess for dehydration; initiate rehydration if indicated Assess for electrolyte disturbances; initiate replacement therapy if indicated Initiate anti-diarrheal therapy (e.g., loperamide) Administer lactobacillus or encourage foods such as yogurt Evaluate for *C. difficile* and other infections Decrease frequency of amoxicillin/clavulanate administration Discontinue amoxicillin/clavulanate if this can be done without compromising regimen—rarely necessary

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Amoxicillin/Clavulanate [2–4,49,60,96,97]	
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis) Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole) Stop amoxicillin/clavulanate for short periods of time (e.g., one to seven days) Discontinue amoxicillin/clavulanate if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., drug fever, rash, skin eruptions of various types, including exfoliative dermatitis, infectious mononucleosis-like, or lymphoma-like syndrome, leucopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, jaundice, hepatitis, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Leoffler's syndrome, vasculitis and a reduction in prothrombin)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)

Criteria for Amoxicillin/Clavulanate [2–4,49,60,96,97]	
Nausea or vomiting	Administer with small meals and advise patient to swallow tablets slowly with small sips of water Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Decrease frequency of amoxicillin/clavulanate administration Discontinue amoxicillin/clavulanate if this can be done without compromising regimen—rarely necessary
Central nervous system related adverse drug reactions (e.g., agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity)	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Rule out other causes If identified, treat specific cause according to standard clinical protocol Treat dizziness with cyclizine if appropriate **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Consider reducing the frequency of amoxicillin/clavulanate administration to five times or even three times per week Discontinue amoxicillin/clavulanate if this can be done without compromising regimen —rarely necessary
Clostridium difficile-associated diarrhea	Bowel rest Appropriate fluid and electrolyte management Protein supplementation Antibiotic treatment of *C. difficile* Surgical evaluation should be instituted as a last resort, if clinically indicated Discontinue amoxicillin/clavulanate if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines

Criteria for Amoxicillin/Clavulanate [2–4,49,60,96,97]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Confirm patient on adequate dose of pyridoxine Treat with ibuprofen, paracetamol or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of amoxicillin/clavulanate administration to five times or even three times per week Lower the dose of amoxicillin/clavulanate if this can be done without compromising the regimen
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly

Criteria for Amoxicillin/Clavulanate [2–4,49,60,96,97]	
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis) If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Nephrotoxicity or renal failure	Consider dosing two or three times a week if drug is essential to the regimen Monitor creatinine closely Adjust all anti-tuberculosis medications according to the creatinine clearance Discontinue amoxicillin/clavulanate if serum creatinine is greater than 100 mcg/mL Modify regimen according to national TB treatment guidelines
Overgrowth of non-susceptible organisms	Discontinue amoxicillin/clavulanate and institute appropriate therapy if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Tooth discoloration (e.g., brown, yellow, or gray staining)	Explain tooth discoloration is a benign and reversible condition Remove with professional dental cleaning (manual descaling)
Vaginitis	Topical antifungal agents or short-course oral antifungal drugs are helpful Exclude other diseases if response to treatment is not prompt
Overdose and life-threatening toxicity	Discontinue medication Treat specific symptomatically according to standard clinical protocol Institute supportive measures Maintain adequate fluid intake and diuresis to reduce the risk of amoxicillin/clavulanate potassium crystalluria Amoxicillin/clavulanate potassium may be removed from circulation by hemodialysis

Criteria for Clofazimine [2–4,49,60,98]	
I. ***Justification criteria*** for prescribing clofazimine	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes isoniazid and rifampicin
	DST document the organism resistance pattern includes any fluoroquinolone
	DST document the organism resistance pattern includes at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin or second-line drug(s)
	Organism is susceptible to clofazimine (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing clofazimine	
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Clofazimine allergy • Severe hepatic insufficiency • Gastrointestinal problems (e.g., abdominal pain, diarrhea) • QT interval prolongation • Possibility of pregnancy
	HIV status is documented in case records
	Clofazimine was available for the duration of treatment
Dose and frequency	Appropriate clofazimine dosing for adult patients • A regimen of 200 mg daily for 4 to 6 weeks, followed by 100 mg daily has been used • In the event of adverse drug reactions reduce the 200 mg dose to 100 mg daily
	Appropriate clofazimine dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • No adjustment necessary • Administer clofazimine after dialysis on dialysis days
	Appropriate clofazimine dosing for pediatric patients • Children 25 kg and over 3 to 5 mg/kg daily • Children less than 25 kg 100 mg every second day Not to exceed 200 mg daily

Criteria for Clofazimine [2–4,49,60,98]	
Administration	For oral use only Administer with food or milk
Duration	According to national DR-TB treatment guidelines
Patient monitoring	Prior to treatment and then at least monthly during treatment: • Weight (and every 2 weeks for the first 3 months of treatment) • Pregnancy testing—according to standard clinical protocol • HIV testing—according to standard clinical protocol HIV co-infected patients: • Complete blood count with differential
Therapeutic drug monitoring—clofazimine blood levels	When feasible, to ensure adequate therapeutic levels and avoid toxicities peak concentrations 2 to 3 hours after a dose are expected to be 0.5 to 2.0 mcg/mL Peak concentrations occur at 4 to 8 hours when given with food See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentrations
Drug interactions	May decrease absorption rate of rifampicin Isoniazid increases clofazimine serum and urine concentrations and decreases skin concentrations Ingestion of clofazimine with orange juice resulted in a modest reduction in clofazimine bioavailability Drugs that prolong the QT interval (e.g., mifepristone, azithromycin, amiodarone, and chloroquine) may have additive effects on levofloxacin induced QT interval prolongation • Avoid co-administration of QT interval prolonging drugs. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. Hepatotoxic drugs • Concurrent administration may potentiate hepatotoxicity • If necessary to coadminister, monitor adverse drug reactions carefully Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.

Criteria for Clofazimine [2–4,49,60,98]	
Patient counseling	Advise patients • Take with food to avoid stomach upset and improve absorption • Clofazimine may discolor your skin and body secretions (conjunctivae, lacrimal fluid, sweat, sputum, urine, and feces) pink, red, or brownish-black. This should go away after stopping the medicine, but may take several months or years to disappear. • Avoid the sun or UV light exposure and use strong sunscreen Advise patients to contact a health care provider immediately if they experience • Abdominal pain or distress such as severe nausea, vomiting, abdominal pain, cramps, or burning (caused by crystal depositions and can present as an acute abdomen) • Bloody or black stools or diarrhea • Yellowing of skin or eyes • Depression or thoughts of self-harm Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out Advise patients who are breastfeeding • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant • Breastfeeding is not recommended during therapy with clofazimine

Criteria for Clofazimine [2–4,49,60,98]	
III. ***Complications*** that could occur during therapy with clofazimine and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence Encourage fluid intake Assess for dehydration; initiate rehydration if indicated Assess for electrolyte disturbances; initiate replacement therapy if indicated Initiate anti-diarrheal therapy (e.g., loperamide) Administer lactobacillus or encourage foods such as yogurt Evaluate for *C. difficile* and other infections Decrease frequency of clofazimine administration Discontinue clofazimine if this can be done without compromising regimen—rarely necessary
Gastritis and abdominal pain	Rule out other causes (e.g., pancreatitis, lactic acidosis, hepatitis) Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole) Stop clofazimine for short periods of time (e.g., one to seven days) Lower dose of clofazimine from 200 mg daily to 100 mg daily in adults Discontinue clofazimine if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Clofazimine [2–4,49,60,98]	
Hypersensitivity, severe (e.g., drug fever, rash, skin eruptions of various types, including exfoliative dermatitis, infectious mononucleosis-like, or lymphoma-like syndrome, leucopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, jaundice, hepatitis, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Leoffler's syndrome, vasculitis and a reduction in prothrombin)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Ichthyosis or xerosis	Apply oil or moisturizers to the skin and mucous membranes Apply hydrocortisone cream or calamine lotion for areas that get very inflamed and itchy
Optic neuritis	Refer patient to an ophthalmologist In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult
Photosensitivity	Mild • Instruct patient to use sunscreens and avoid excessive exposure to sun or UV light • Initiate therapy with cool compresses and hydrocortisone cream Severe • Eliminate clofazimine from regimen • Modify regimen according to national TB treatment guidelines

Criteria for Clofazimine [2–4,49,60,98]	
Pink or red discoloration of skin, conjunctiva, cornea, and body fluids (e.g., sweat, tears, saliva, urine, stools)	Counsel patients to expect discoloration Instruct patient to use sunscreens and avoid excessive exposure to sun or UV light Advise patients that contact lenses may be stained Reassure patients that symptoms are harmless Inform patients that the discoloration, although reversible, may take several months or years to disappear after the conclusion of therapy with clofazimine
Prolongation of the QT interval	Obtain an electrocardiogram and initiate treatment according to standard clinical protocol Correct electrolyte imbalances (calcium, potassium, magnesium) Discontinue clofazimine if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Severe abdominal distress—potentially fatal (e.g., crystal depletion in the wall of small bowel mesenteric lymph nodes, liver and spleen, acute abdomen, splenic infarction, gastrointestinal bleeding, and bowel obstruction)	Discontinue clofazimine Modify regimen according to national TB treatment guidelines
Anorexia	Give with small meals and advise patient to swallow pills slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration; initiate rehydration if indicated Decrease frequency of clofazimine administration Discontinue clofazimine if this can be done without compromising regimen—rarely necessary

Criteria for Clofazimine [2–4,49,60,98]	
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue clofazimine if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines
Decreased tear and sweat production	Assess for dehydration; initiate rehydration if indicated
	Treat specific cause according to standard clinical protocol
Dizziness	Conduct a clinical evaluation to determine whether the dizziness is vestibular or non-vestibular in origin
	Conduct a clinical evaluation to determine whether the dizziness is peripheral or central in origin
	Rule out other causes
	If identified, treat specific cause according to standard clinical protocol
	If cause cannot be identified, treat with cyclizine
	Note: Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections)
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Encourage adequate fluid intake
	Treat with ibuprofen, paracetamol, or aspirin
	Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function
	Address stressors potentially contributing to tension-related headaches
	Consider administering amitriptyline 50 to 150 mg at night
	Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine)
	Consider neurology consultation
	Consider reducing the frequency of clofazimine administration to five times or even three times per week

Criteria for Clofazimine [2–4,49,60,98]	
Retinopathy	Refer patient to an ophthalmologist In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult
Sense of taste disturbance	Encourage the patient to tolerate this side effect Sucking on lemon drops or other hard candy or chewing gum can be helpful Normal taste returns when treatment is stopped
Overdose and life-threatening toxicity	No specific data are available on the treatment of overdosage with clofazimine However, in case of overdose, the stomach should be emptied by inducing vomiting or by gastric lavage, and supportive symptomatic treatment should be employed

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	
I. ***Justification criteria*** for prescribing imipenem and cilastatin	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes isoniazid and rifampicin
	DST document the organism resistance pattern includes any fluoroquinolone
	DST document the organism resistance pattern includes at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin or second-line drug(s)
	Organism is susceptible to imipenem and cilastatin (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing imipenem and cilastatin	
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Imipenem allergy • Cilastatin allergy • Penicillin allergy • Cephalosporin allergy • Carbapenem allergy (e.g., meropenem) • Local anesthetic or lidocaine allergy • Meningitis co-infection (use meropenem rather than imipenem) • Central nervous system disorders (e.g., brain lesions or history of seizures) • Compromised renal function • Heart block • Recent antibiotic associated colitis
	HIV status is documented in case records
	Imipenem and cilastatin was available for the duration of treatment
Dose and frequency	Appropriate imipenem and cilastatin dosing for adult patients • 500 mg IV two or three times a day or 1,500 to 2,000 mg every 12 hours
	Appropriate imipenem and cilastatin dosing for renal dysfunction • For creatinine clearance 20 to 40 mL/min, administer 750 mg every 8 hours • For creatinine clearance less than 20 mL/min, administer 500 mg every 12 hours • Administer after dialysis on dialysis days

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	
	Appropriate imipenem and cilastatin dosing for pediatric patients • Meropenem preferred: 20 to 40 mg/kg/dose IV every 8 hours Not to exceed 2 grams per dose
Administration	May be given by intravenous infusion (not push) or intramuscularly Rotate injection sites to avoid local discomfort Total intramuscular doses of more than 1.5 gm/day are not recommended; therefore not very practical for treatment of drug-resistant TB Each 125 mg, 250 mg, or 500 mg dose should be given by intravenous administration over 20 to 30 minutes Each 750 mg or 1,000 mg dose should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed. Imipenem and cilastatin for injection should not be mixed with or physically added to other antibiotics Imipenem and cilastatin can be added to the following diluents: • 0.9% sodium chloride injection • 5% glucose injection Vials of powder should be kept at room temperature, 15 to 25°C Reconstituted suspension should be kept no more than 4 hours at room temperature Reconstituted suspension should be kept no more than 24 hours refrigerated, 2 to 8°C **Note**: Clavulanic acid increases the efficacy of imipenem/cilastatin
Duration	According to national DR-TB treatment guidelines

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	

Patient Monitoring	Prior to treatment and then at least monthly during treatment:
	
	Weight (and every 2 weeks for the first 3 months of treatment)
	
	Pregnancy testing—according to standard clinical protocol
	
	Liver function
	• AST (SGOT)
	• ALT (SGPT)
	• Total bilirubin
	
	Renal function
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Complete blood count with differential
	
	HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—imipenem blood levels	When feasible, to ensure adequate therapeutic levels and avoid toxicities peak concentrations Peak concentrations occur: • Immediately after IV infusion • 1 hour after IM infusion Peak concentrations of 30 to 40 mcg/mL See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentrations

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	
Drug Interactions	Valproic acid effects are decreased when coadministered with imipenem and cilastatin Live typhoid vaccine may be inactivated by imipenem and cilastatin • Delay vaccine until at least 4 days after imipenem and cilastatin course complete or Complete vaccine at least 4 days before the first imipenem and cilastatin dose BCG vaccine may be inactivated by imipenem and cilastatin • Avoid coadministration Hepatotoxic and nephrotoxic drugs • Co-administration may produce additive toxicities. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs.
Patient Counseling	Advise patients • Report use of any other medications, especially Antiretrovirals and antiepileptics Advise patients to contact a health care provider immediately if they experience: • Fast or irregular heartbeat • Seizures (convulsions) • Severe diarrhea (watery or bloody) • Skin rash, hives, or itching; severe blistering, peeling, and red skin rash • Swelling in the face, throat, or lips • Wheezing or trouble breathing • Confusion, hallucinations • Feeling light-headed, fainting • Flu symptoms • Dark urine, jaundice (yellowing of the skin or eyes) Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out • Potential benefit should outweigh the potential risk Advise patients who are breastfeeding • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	
III. ***Complications*** that could occur during therapy with imipenem and cilastatin and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence Encourage fluid intake Assess for dehydration; initiate rehydration if indicated Assess for electrolyte disturbances; initiate replacement therapy if indicated Initiate anti-diarrheal therapy (e.g., loperamide) Administer lactobacillus or encourage foods such as yogurt Evaluate for *C. difficile* and other infections Decrease frequency of imipenem and cilastatin administration Discontinue imipenem and cilastatin if this can be done without compromising regimen —rarely necessary
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis) If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential, consider not reintroducing it Once resolved, monitor liver function monthly
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Hypersensitivity, severe (e.g., drug fever, rash, skin eruptions of various types, including exfoliative dermatitis, infectious mononucleosis-like, or lymphoma-like syndrome, leucopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, jaundice, hepatitis, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Leoffler's syndrome, vasculitis and a reduction in prothrombin)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamines may in regimens with aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	
Nausea or vomiting	Administer with small meals and advise patient to swallow tablets slowly with small sips of water
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Assess for dehydration, electrolyte disturbances, hepatitis
	Initiate rehydration if indicated
	Initiate antiemetic therapy (e.g., metoclopramide, ondansetron)
	Decrease frequency of isoniazid administration
	Discontinue imipenem and cilastatin if this can be done without compromising regimen—rarely necessary
Seizures	Suspend imipenem and cilastatin pending resolution of seizures
	Suspend other seizure inducing medicines (e.g., cycloserine, fluoroquinolones, isoniazid)
	Initiate anticonvulsant therapy (e.g., phenobarbital, phenytoin, carbamazepine, valproic acid)
	Administer pyridoxine 200 to 300 mg daily
	Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride
	Once seizures have resolved, restart medications one at a time
	Reduce frequency of imipenem and cilastatin administration
	Discontinue imipenem and cilastatin if seizures do not resolve
	Modify regimen according to national TB treatment guidelines
Central nervous system related adverse drug reactions (e.g., dizziness, somnolence, confusional states, myoclonic activity)	Events usually resolve with discontinuation of the drug
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Rule out other causes
	If identified, treat specific cause according to standard clinical protocol
	Treat dizziness with cyclizine if appropriate
	Note: Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
	Suspect drug-induced acute liver failure if there is jaundice
	Decrease frequency of imipenem and cilastatin administration
	Discontinue imipenem and cilastatin if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue imipenem and cilastatin if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines
Hematological abnormalities (e.g., pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, hemolytic anemia)	Stop all therapy pending resolution of toxicity
	Eliminate other potential causes of toxicity
	Consider suspending most likely agent permanently
	Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Hemorrhagic colitis	Discontinue imipenem and cilastatin
	Modify regimen according to national TB treatment guidelines
	Evaluate for *C. difficile* and other infections
	Assess for dehydration; initiate rehydration if indicated
Hypotension	Monitor blood pressure
	Initiate or adjust cardiac stimulant agents or
	Adjust antihypertensive agents—according to standard clinical protocol
Injection site reactions (e.g., localized trauma, minor discomfort and pain, bleeding, bruising)	Maintain light pressure to prevent bruising
	If a bruise does appear, don't use that injection site again until the bruise is gone
	An affected limb should be elevated to minimize inflammation
	An anti-inflammatory cream or gel can be directly applied to the area
	Anti-inflammatory analgesics can be prescribed to treat both the inflammation and the pain associated with the reaction
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
Overgrowth of non-susceptible organisms	Discontinue imipenem and cilastatin
	Institute appropriate therapy if this can be done without compromising the regimen
	Modify regimen according to national TB treatment guidelines

Criteria for Imipenem and Cilastatin [2–4,49,60,63,71,97,99]	
Overdose and life-threatening toxicity	Discontinue imipenem and cilastatin
	Treat symptomatically according to standard clinical protocol
	Institute supportive measures as required
	Imipenem-cilastatin sodium is hemodialyzable; however, usefulness of this procedure in the overdosage setting is questionable

Criteria for Linezolid [2–4,49,58,60,97,100]	
I. ***Justification criteria*** for prescribing linezolid	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes isoniazid and rifampicin
	DST document the organism resistance pattern includes any fluoroquinolone
	DST document the organism resistance pattern includes at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin) for presumptive XDR-TB
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin or second-line drug(s)
	Organism is susceptible to linezolid (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing linezolid	
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Linezolid allergy • Oxazolidinones hypersensitivity (e.g., cycloserine) • Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) • Seizures or risk factors for seizures • Uncontrolled hypertension • Hypoglycemia • Pheochromocytoma • Thyrotoxicosis • Symptoms of neuropathy (pain, numbness, tingling, or weakness in the extremities) • Symptoms of visual impairment • Current catheter-related bloodstream or catheter-site infections
	HIV status is documented in case records
	Linezolid was available for the duration of treatment
Dose and frequency	Appropriate linezolid dosing for adult patients • Usual adult dose is 600 mg daily • In the event of adverse drug reactions, reduce dose to 300 mg daily • After sputum culture conversion, reduce dose to 300 mg daily

Criteria for Linezolid [2–4,49,58,60,97,100]	
	Appropriate linezolid dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • No dose adjustment is necessary • However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal impairment should be weighed against the potential risks of accumulation of these metabolites. • Linezolid should be given after hemodialysis
	Appropriate linezolid dosing for pediatric patients • 10 mg/kg dose twice daily for children younger than 10 years of age • 300 mg daily for children 10 years of age and older Not to exceed 600 mg per day

Administration	For oral use only
	
	No dose adjustment is necessary when switching from intravenous to oral administration
	
	For intravenous administration
	• Keep the infusion bags in the overwrap until ready to use
	• Once opened, use immediately
	• Discard any unused solution
	• Flush line with 5% glucose injection, or 0.9% sodium chloride injection before and after infusing linezolid
	• Intravenous doses are administered over 30 to 120 minutes
	• Linezolid is compatible with the following IV solutions
	  ○ 5% glucose injection
	  ○ 0.9% sodium chloride injection
	• Store infusion bags 25 °C; excursions permitted from 15 to 30°C
	
	Administer pyridoxine (Vitamin B6) to prevent peripheral neuropathy and cytopenias
	• Adult dose—100 mg daily
	• Pediatric dose— 1 to 2 mg/kg daily, with a usual range of 10 to 50 mg daily

Duration	According to national DR-TB treatment guidelines

Criteria for Linezolid [2–4,49,58,60,97,100]	
Patient Monitoring	Prior to treatment and then at least monthly during treatment: Weight (and every 2 weeks for the first 3 months of treatment) Pregnancy testing—according to standard clinical protocol Complete blood count with differential • Monitor CBC weekly during the initial period, then monthly, and then as needed based on symptoms Ophthalmologic function • Ophthalmoscopy • Finger perimetry • Acuity testing (Snellen chart) • Color discrimination (Ishihara tests) For patients with hypertension, pheochromcytoma, or thyrotoxicosis • Monitor blood pressure regularly until well controlled For patient with diabetes • Monitor blood glucose regularly until well controlled and at least monthly HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—linezolid blood levels	To ensure adequate therapeutic levels and avoid toxicities
	• Peak concentrations are achieved
	  ○ 1 to 1.5 hours after an oral dose
	  ○ 0.5 hours after an IV dose
	• Peak concentrations should be drawn
	  ○ 2 hours after an oral dose
	  ○ After the end of an IV infusion
	• A 6 hour post dose concentration can be used to calculate half-life
	• Peak concentrations are expected to be 12 to 24 mcg/mL
	
	See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentrations

Criteria for Linezolid [2–4,49,58,60,97,100]	
Drug Interactions	Isoniazid effects are decreased when coadministered with linezolid Linezolid may interact with serotonergic agents (e.g., fluoxetine) • Discontinue serotonergic agent • Monitor patient for symptoms of serotonin syndrome or neuroleptic malignant syndrome-like two weeks (five weeks if fluoxetine was taken) or until 24 hours after the last dose of linezolid, whichever comes first • Symptoms of serotonin syndrome or neuroleptic malignant syndrome-like reactions include hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that include extreme agitation progressing to delirium and coma • Monitor for discontinuation symptoms of the antidepressant (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms) Medications with potential for increases in blood pressure (e.g., directly and indirectly acting sympathomimetic agents [e.g., ephedrine], vasopressive agents [e.g., epinephrine], dopaminergic agents [e.g., dopamine]) • Monitor blood pressure according to standard clinical protocol Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g., isoniazid) • Discontinue isoniazid at least two weeks prior to starting linezolid Linezolid may increase the effects of insulin or oral hypoglycemics • Monitor blood glucose according to standard clinical protocol Selected myelosuppressive agents (e.g., clozapine) • Concurrent administration may potentiate toxicities Neurotoxic drugs • Concurrent administration may potentiate toxicities • If necessary to coadminister, monitor adverse drug reactions carefully Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered If necessary to coadminister, monitor adverse drug reactions carefully. Refer to Annex G. Potentially Overlapping Toxicities of Antiretrovirals and Anti-Tuberculosis Agents.

Criteria for Linezolid [2–4,49,58,60,97,100]	
Patient counseling	Advise patients • Linezolid may be taken with or without food • Try taking it with food if it bothers your stomach • Avoid food and drinks that contain tyramine: aged cheeses, dried meats, sauerkraut, soy sauce, tap beers, and red wines. Refer to Annex H. Tyramine- and Histamine-Containing Foods. • May cause tongue and oral mucosal discoloration which is reversible • Tell your heath care provider if you're taking medicines for colds, congestion, or depression Advise patients to contact a health care provider immediately if they experience • Pain, numbness, tingling or weakness in the extremities • Vision changes • Black, tarry stools or severe diarrhea • Watery and bloody stools (with or without stomach cramps and fever) • Unusual bleeding or bruising • Unusual fatigue or weakness • Headache, nausea, or vomiting • Hypoglycemic reactions Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category C • Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans • Risk cannot be ruled out Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Linezolid [2–4,49,58,60,97,100]	
III. ***Complications*** that could occur during therapy with linezolid and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide) if indicated
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of linezolid administration
	Discontinue linezolid if this can be done without compromising regimen—rarely necessary
Hematological abnormalities (e.g., anemia, myelosuppression)	Determine cause of anemia (i.e., iron deficiency, hydroxocobalamin (Vitamin B12) deficiency, chronic disease, bleeding)
	Supplement with iron, hydroxocobalamin (Vitamin B12), folate (Vitamin B9), ascorbic acid (Vitamin C) as appropriate
	Monitor complete blood counts weekly until stabilized
	Reduce frequency of linezolid if this can be done without compromising regimen
	Lower linezolid dose
	Consider administering transfusions for severe anemia
	Discontinue linezolid if myelosuppression occurs
	Consider restarting with a lower dose if myelosuppression resolves and if linezolid is essential to the regimen
	Modify regimen according to national TB treatment guidelines
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion
	Note: Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Linezolid [2–4,49,58,60,97,100]	
Hypersensitivity, severe (e.g., Stevens-Johnson syndrome, drug fever, rash, skin eruptions of various types, including exfoliative dermatitis, infectious mononucleosis-like, or lymphoma-like syndrome, leucopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, jaundice, hepatitis, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Leoffler's syndrome, vasculitis and a reduction in prothrombin)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Lactic acidosis	Evaluate patients who develop recurrent nausea or vomiting, unexplained acidosis, or low bicarbonate levels Monitor lactic acid levels according to standard clinical protocol Discontinue linezolid in patients who develop clinical symptoms or signs with or without laboratory findings Modify regimen according to national TB treatment guidelines
Nausea or vomiting	Give with small meals and advise patient to swallow tablets slowly with small sips of water Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Decrease frequency of linezolid administration Discontinue linezolid if this can be done without compromising regimen—rarely necessary

Criteria for Linezolid [2–4,49,58,60,97,100]	
Optic neuritis	Refer patient to an ophthalmologist
	In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions
	In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult
Peripheral Neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes
	Correct any vitamin or nutritional deficiencies
	Administer pyridoxine 200 to 300 mg per day
	Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily)
	Consider paracetamol and NSAIDs (or both) for pain relief
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function
	Consider neurology consultation
	Consider administering carbamazepine
	Decrease frequency of linezolid administration
	Discontinue linezolid
	Modify regimen according to national TB treatment guidelines
Blood glucose disturbances	Monitor blood glucose at least monthly
	Initiate or adjust oral hypoglycemic agent or insulin according to standard clinical protocol
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue linezolid acid if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines

Criteria for Linezolid [2–4,49,58,60,97,100]	
Dizziness, vertigo	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Rule out other causes If identified, treat specific cause according to standard clinical protocol If cause cannot be identified treat with cyclizine **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Fungal infection, oral moniliasis, vaginal moniliasis	Treat with topical or short-course oral antifungal medications according to standard clinical protocol
Gastritis and abdominal pain	Rule out other causes (e.g., lactic acidosis, hepatitis) Conduct lipase levels to rule out pancreatitis Treat with H2-blockers (e.g., ranitidine), or proton-pump inhibitors (e.g., omperazole) Stop linezolid for short periods of time (e.g., one to seven days) Discontinue linezolid if this can be done without compromising the regimen Modify regimen according to national TB treatment guidelines
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of linezolid administration to five times or even three times per week

Criteria for Linezolid [2–4,49,58,60,97,100]	
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Continue with three non hepatotoxic medications (e.g., the injectable agent, fluoroquinolone, and cycloserine) If hepatitis does not resolve, stop all medications Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis) If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Hypertension	Monitor blood pressure Initiate or adjust antihypertensive agents according to standard clinical protocol
Seizures	Suspend linezolid pending resolution of seizures Suspend other seizure inducing medicines (e.g., cycloserine, fluoroquinolones, isoniazid) Initiate anticonvulsant therapy (e.g., phenobarbital, phenytoin, carbamazepine, valproic acid) Administer pyridoxine 200 to 300 mg daily Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride Once seizures have resolved, restart medications one at a time Reduce frequency of linezolid administration Discontinue linezolid if seizures do not resolve Modify regimen according to national TB treatment guidelines

Criteria for Linezolid [2–4,49,58,60,97,100]	
Sense of taste disturbance	Encourage the patient to tolerate this side effect Sucking on lemon drops or other hard candy or chewing gum can be helpful Normal taste returns when treatment is stopped
Serotonin syndrome or neuroleptic malignant syndrome-like reactions (e.g., hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that include extreme agitation progressing to delirium and coma)	Discontinue linezolid Provide supportive treatment Modify regimen according to national TB treatment guidelines
Tongue and oral mucosal discoloration	Explain tongue discoloration is a benign and reversible condition Encourage the patient to tolerate this side effect
Tooth discoloration	Explain tooth discoloration is a benign and reversible condition Remove with professional dental cleaning (manual descaling)
Visual disturbances (e.g., changes in visual acuity, changes in color vision, blurred vision, or visual field defect)	Stop linezolid Refer patient to an ophthalmologist In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult Modify regimen according to national TB treatment guidelines
Overdose and life-threatening toxicity	In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration Hemodialysis may facilitate more rapid elimination of linezolid Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion

Criteria for Meropenem [4,49,59,63,71,97,101]	
I. ***Justification criteria*** for prescribing meropenem	
	TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes isoniazid and rifampicin
	DST document the organism resistance pattern includes any fluoroquinolone
	DST document the organism resistance pattern includes at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)
	Patient has documented serious adverse drug reaction to isoniazid or rifampicin or second-line drug(s)
	Organism is susceptible to meropenem (if DST is available)
	According to national DR-TB treatment guidelines
II. ***Process criteria*** to consider when prescribing meropenem	
	Administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent
	Patient history has been reviewed for: • Meropenem allergy • Penicillin allergy • Cephalosporin allergy • Carbapenem allergy (e.g., imipenem) • Central nervous system disorders (e.g., brain lesions or history of seizures) • Liver disease
	HIV status is documented in case records
	Meropenem was available for the duration of treatment
Dosing	Appropriate meropenem dosing for adult patients • 1,000 mg IV two or three times daily Not to exceed 6,000 mg per day
	Appropriate meropenem dosing for renal dysfunction • For creatinine clearance 20 to 40 mL/min, administer 750 mg every 12 hours • For creatinine clearance less than 20 mL/min, administer 500 mg every 12 hours • Administer meropenem for injection (IV) after dialysis on dialysis days
	Appropriate meropenem dosing for pediatric patients • 20 to 40 mg/kg IV Not to exceed 6,000 mg per day

Criteria for Meropenem [4,49,59,63,71,97,101]	
Administration	For intravenous use Reconstitute with sterile water for injection Shake to dissolve and let stand until clear May be given by IV infusion over 15 to 30 minutes May be given by IV bolus (up to 50 mg/mL of meropenem) over 3 to 5 minutes Long-term IV access recommended Meropenem for injection should not be mixed with or physically added to other antibiotics Meropenem for infusion can be added to the following diluents • Sodium chloride injection 0.9% • Glucose injection 5% • Glucose injection 10% • Glucose and sodium chloride injection 5%/0.9% • Glucose and sodium chloride injection 2.5%/0.45% • Potassium chloride in glucose injection 0.15%/5% • Sodium hydrogen carbonate in glucose injection 0.02%/5% • Sodium hydrogen carbonate injection 5% • Sodium lactate, compound solution The dry powder should be stored at controlled room temperature 15°C to 25°C Injection vials constituted with sterile water for injection for bolus administration (up to 50 mg/mL of meropenem) may be stored for up to 2 hours at controlled room temperature Infusion vials constituted with Sodium Chloride for Injection 0.9% (Meropenem concentrations ranging from 2.5 to 50 mg/mL) are stable for up to 2 hours at controlled room temperature or for up to 18 hours at 4° C Infusion vials constituted with glucose Injection 5% (meropenem concentrations ranging from 2.5 to 50 mg/mL) are stable for up to 1 hour at controlled room temperature or for up to 8 hours at 4°C **Note**: Clavulanic acid increases the efficacy of meropenem
Duration	As directed by national TB treatment guidelines

Criteria for Meropenem [4,49,59,63,71,97,101]	

Patient Monitoring	Prior to treatment and then at least monthly during treatment:
	
	Weight (and every 2 weeks for the first 3 months of treatment)
	
	Pregnancy testing—according to standard clinical protocol
	
	Liver function
	• AST (SGOT)
	• ALT (SGPT)
	• Total bilirubin
	
	Renal function
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	Complete blood count with differential
	
	HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—meropenem blood levels	When feasible, to ensure adequate therapeutic levels and avoid toxicities peak concentrations Peak concentrations occur: • Immediately after IV infusion • 1 hour after IM infusion Peak concentrations of 20 to 25 mcg/mL are expected See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentrations
Drug Interactions	Compatibility of meropenem with other drugs has not been established • Do not mix with or add to solutions containing other drugs Valproic acid effects are decreased when coadministered with meropenem

Criteria for Meropenem [4,49,59,63,71,97,101]	
Patient Counseling	Advise patients • Report use of any other medications, especially antiretrovirals and antiepileptics • If you experience side effects that might affect your ability to concentrate and react (e.g., headache and tremor, do not drive or use machines Advise patients to contact a health care provider immediately if they experience • Fast or irregular heartbeat • Seizures (convulsions) • Severe diarrhea (watery or bloody) • Skin rash, hives, or itching; severe blistering, peeling, and red skin rash • Swelling in the face, throat, or lips • Wheezing or trouble breathing • Confusion, hallucinations • Feeling light-headed, fainting • Flu symptoms • Dark urine, jaundice (yellowing of the skin or eyes) Advise patients who are pregnant or planning to become pregnant of the potential risks and potential benefits of starting TB treatment • US Food and Drug Administration Pregnancy Category B • Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. • No proven risk in humans Advise patients who are breastfeeding: • Most drugs used to treat TB cross into breast milk at low levels. • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Meropenem [4,49,59,63,71,97,101]	
III. ***Complications*** that could occur during therapy with meropenem and how to respond if the complication presents as follows[1]	
Severe or common toxicities are indicated by **bold** font	
***Clostridium difficile*-associated diarrhea**	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
	Discontinue meropenem if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of meropenem administration
	Discontinue meropenem if this can be done without compromising regimen—rarely necessary
Hematological abnormalities (e.g., thrombocytopenia, anemia)	Stop all therapy pending resolution of toxicity
	Eliminate other potential causes of toxicity
	Consider suspending most likely agent permanently
	Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely

Criteria for Meropenem [4,49,59,63,71,97,101]	
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol induced hepatitis) If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days, and if the most likely agent is not essential consider not reintroducing it Once resolved, monitor liver function monthly
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Meropenem [4,49,59,63,71,97,101]	
Hypersensitivity, severe (e.g., drug fever, rash, skin eruptions of various types, including exfoliative dermatitis, infectious mononucleosis-like, or lymphoma-like syndrome, leucopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, jaundice, hepatitis, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Leoffler's syndrome, vasculitis and a reduction in prothrombin)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Nausea or vomiting	Administer with small meals and advise patient to swallow tablets slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) Decrease frequency of meropenem administration Discontinue meropenem if this can be done without compromising regimen – rarely necessary

Criteria for Meropenem [4,49,59,63,71,97,101]	
Seizures	Suspend meropenem pending resolution of seizures
	Suspend other seizure inducing medicines (e.g., cycloserine, fluoroquinolones, isoniazid)
	Initiate anticonvulsant therapy (e.g., phenobarbital, phenytoin, carbamazepine, valproic acid)
	Administer pyridoxine 200 to 300 mg daily
	Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride
	Once seizures have resolved, restart medications one at a time
	Reduce frequency of meropenem administration
	Discontinue meropenem if seizures do not resolve
	Modify regimen according to national TB treatment guidelines
Apnea	Treat according to standard clinical protocol
Bleeding events (e.g., gastrointestinal hemorrhage, melena, expistaxis, hemoperitoneum)	Treat according to standard clinical protocol
	Assess for dehydration; initiate rehydration if indicated
	Evaluate for *C. difficile* and other infections
	Decrease frequency of meropenem administration
	Discontinue meropenem if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines
Central nervous system related adverse drug reactions (e.g., dizziness, somnolence, confusional states, myoclonic activity)	Events usually resolve with discontinuation of the drug
	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Rule out other causes
	If identified, treat specific cause according to standard clinical protocol
	Treat dizziness with cyclizine if appropriate
	Note: Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
	Decrease frequency of meropenem administration
	Discontinue meropenem if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines
Constipation	Treat with stool softeners

Criteria for Meropenem [4,49,59,63,71,97,101]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity Exercise caution with use and monitor renal function Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation Consider reducing the frequency of meropenem administration to five times or even three times per week
Injection site reactions (e.g., localized trauma, minor discomfort and pain, bleeding, bruising)	Maintain light pressure to prevent bruising If a bruise does appear, don't use that injection site again until the bruise is gone An affected limb should be elevated to minimize inflammation An anti-inflammatory cream or gel can be directly applied to the area Anti-inflammatory analgesics can be prescribed to treat both the inflammation and the pain associated with the reaction **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function
Overgrowth of non-susceptible organisms	Discontinue meropenem Institute appropriate therapy if this can be done without compromising the regimen
Sepsis	Treat according to standard clinical protocol
Shock	Treat according to standard clinical protocol
Overdose and life-threatening toxicity	Symptomatic treatments should be considered In individuals with normal renal function, rapid renal elimination takes place Meropenem and its metabolite are readily dialyzable and effectively removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdosage

New Drugs

Please be aware of the following when using information in this Annex. Although the drug information in this document is extensive, it is not intended to replace National Standard Treatment Guidelines, package inserts, or other printed material that may be available or accompany a particular drug.

Only medicines on the WHO Model Essential Medicines Lists [53,54] are referenced in this document.

Ancillary medicines or concomitant medicines on National Essential Medicine Lists that do not appear on the WHO Model Lists should be checked for

- interactions with anti-TB medicines
- contraindications for co-administration with anti-TB medicines
- correct dose and administration for treatment of adverse drug reactions
-

They should also be added to the information in Annex A. Published Criteria for Anti-Tuberculosis Treatment.

Children older than 12 years of age can be managed as adults.[55]

Consult with a TB specialist or clinical pharmacist about the clinical use of **any** medicine administered to a patient.

Criteria for Bedaquiline [4,33,49,102]	
I. ***Justification criteria*** for prescribing bedaquiline	
	Patient is 18 years or older Administered to patients under 18 if national tuberculosis treatment guidelines permit TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics) Documented evidence that an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed because of • In vitro resistance • Known adverse drug reactions • Poor tolerance • Contraindication • Unavailability or lack of supply of a drug in the WHO recommended regimen Organism is susceptible to bedaquiline (if DST is available) Used in combination with at least 3 other drugs to which the organism has been shown to be susceptible in vitro or if DST is unavailable, used in combination with at least 4 other drugs to which the organism is likely to be susceptible Clinical protocol has been approved by the national ethics authority Initiated and monitored by a physician experienced in the management of DR-TB

Criteria for Bedaquiline [4,33,49,102]	
II. ***Process criteria*** to consider when prescribing bedaquiline	
	Administered as a component of starting a new treatment regimen (i.e., not added alone to a failing regimen) Patient has provided written informed consent to be treated with bedaquiline ensuring that the patient: • Is aware of the novel nature of bedaquiline • Appreciates the reason why the drug is being proposed to be included in the regimen • Recognizes the benefits and potential harms Patient history has been reviewed for: • Bedaquiline allergy • QT interval prolongation • Torsade de Pointes • Hypothyroidism • Bradyarrhythmias • Uncompensated heart failure • Serum calcium, magnesium, or potassium levels below the lower limits of normal • Heart disease • Ventricular arrhythmias • Hepatic dysfunction • Renal dysfunction • Diabetes • Malignancies • Alcohol use • Substance use HIV status is documented in case records Pregnancy status is documented in the case records Bedaqualine was available for the duration of treatment
Dose and frequency	Appropriate bedaquiline dosing for adult patients • 100 mg twice daily for 24 weeks followed by 200 mg three times per week (at least 48 hours apart) for the remaining 22 weeks • Treatment with an appropriate combination regimen should continue after completion of the bedaquiline treatment period according to WHO guidelines Appropriate bedaqualine dosing for renal dysfunction • No adjustment necessary in patients with mild to moderate renal impairment • Use with caution in patients with severe renal impairment Appropriate bedaquiline dosing for pediatric patients • According to national TB treatment guidelines

Criteria for Bedaquiline [4,33,49,102]	
Administration	For oral use only Swallow tablets whole with water Administer with food If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From week 3 onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the 3 times a week regimen
Duration	Not to exceed six months

Patient monitoring	Prior to treatment and as specified during treatment
	
	Weight (and every 2 weeks for the first 3 months of treatment)
	
	Pregnancy testing—according to standard clinical protocol
	
	Drug resistance testing and again prior to switching to another regimen
	
	Electrocardiogram and at least 2, 12, and 24 weeks after starting treatment
	
	Serum potassium, calcium, and magnesium, then monthly, and if QT prolongation is detected
	
	Liver function tests and at least monthly during treatment
	• ALT (SGPT)
	  ○ more than three times the upper limit of normal should be followed by repeat testing within 48 hours
	• AST (SGOT)
	  ○ more than three times the upper limit of normal should be followed by repeat testing within 48 hours
	• Alkaline phosphatase
	• Bilirubin
	
	Renal function tests and at least monthly during treatment
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations - preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	HIV testing—according to standard clinical protocol

Criteria for Bedaquiline [4,33,49,102]	
Therapeutic drug monitoring—bedaquiline blood levels	To ensure adequate therapeutic levels and avoid toxicities • Peak concentrations 2 to 3 hours after a dose are expected to be 0.5 to 2.0 mcg/mL • Peak concentrations occur at 4 to 8 hours when given with food See Annex E. Therapeutic Drug Monitoring of Anti-TB Medicines for guidance on how to adjust dose based on serum concentrations
Drug interactions	Clofazimine may increase the risk of cardiotoxicity Fluoroquinolones (e.g., moxifloxacin) and macrolide antibacterial drugs (e.g., erythromycin) may increase the risk of cardiotoxicity Drugs that prolong the QT interval (e.g., azithromycin, amiodarone, and chloroquine) may have additive effects on levofloxacin induced QT interval prolongation • Avoid coadministration of QT interval prolonging drugs. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. Rifampicin and rifabutin or other strong cytochrome P3A4 inducers (e.g., carbamazepine) may decrease the effects of bedaquiline Strong cytochrome P3A4 inhibitors (e.g., chloramphenicol, clarithromycin) may increase the therapeutic and adverse effects of bedaquiline Hepatotoxic and nephrotoxic drugs • Coadministration may produce additive toxicities. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs. Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • Consult with HIV clinicians and ART specialists

Criteria for Bedaquiline [4,33,49,102]	
Patient counseling	Advise patients: • Do not crush or chew, swallow tablets whole with water • Take with food to avoid stomach upset and improve absorption • Avoid alcohol use while on treatment • Avoid paracetamol while on treatment • Avoid herbal products while on treatment Advise patients to contact a health care provider immediately if they experience • Change in heartbeat (a fast or irregular heartbeat) • Chest pain • Fainting or near fainting • Unexplained symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual fatigue, loss of appetite • Light colored bowel movements • Dark colored urine • Yellowing of the skin or whites of eyes Advise patients who are pregnant or planning to become pregnant • US Food and Drug Administration Pregnancy Category B • Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. • No proven risk in humans Advise patients who are breastfeeding • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant • Breastfeeding is not recommended during therapy with bedaquiline
III. ***Complications*** that could occur during therapy with bedaquiline and how to respond if the complication presents as follows:[1]	
Severe or common toxicities are indicated by **bold** font	
Arthralgias	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Decrease frequency of bedaqualine administration Discontinue bedaqualine if this can be done without compromising regimen Modify regimen according to national TB treatment guidelines

[1] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely.

Criteria for Bedaquiline [4,33,49,102]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation
Hepatic-related adverse drug reactions (e.g., new or worsening liver dysfunction (including clinically significant elevation of aminotransferases or bilirubin or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly)	If serum aminotransferases increase to more than three times the upper limit of normal • Test for viral hepatitis • Discontinue other hepatotoxic medications • Discontinue bedaquiline if: • Aminotransferase elevations are accompanied by total bilirubin elevation more than twice the upper limit of normal • Aminotransferase elevations are more than eight times the upper limit of normal • Aminotransferase elevations persist beyond two weeks
Hypersensitivity, mild (skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Bedaquiline [4,33,49,102]	
Hypersensitivity, severe (e.g., eosinophilia, drug fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, lupoid reactions, and anaphylactic shock)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Nausea, vomiting, or anorexia	Give with small meals and advise patient to swallow pills slowly with small sips of water Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Initiate antiemetic therapy (e.g., metoclopramide, ondansetron) if indicated
Prolongation of the QT interval	Obtain an electrocardiogram; initiate treatment—according to standard clinical protocol Correct electrolyte imbalances (potassium, magnesium) Monitor ECGs frequently to confirm that the QTc interval has returned to baseline Discontinue bedaquiline if significant ventricular arrhythmia develops Discontinue bedaquiline if a QTcF interval more than 500 ms develops (confirmed by repeat ECG)

Criteria for Bedaquiline [4,33,49,102]	
Abdominal pain	Conduct lipase levels to rule out pancreatitis
	For severe abdominal pain stop bedaquiline for short periods of time (one to seven days)
	Lower bedaqualine dose
	Decrease frequency of administration
	Discontinue bedaqualine if patient is diagnosed with pancreatitis or if abdominal pain is severe and does not subside
	Modify regimen according to national TB treatment guidelines
Chest pain	Obtain an ECG to detect QT
	Treat according to standard clinical protocol
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence
	Encourage fluid intake
	Assess for dehydration; initiate rehydration if indicated
	Assess for electrolyte disturbances; initiate replacement therapy if indicated
	Initiate anti-diarrheal therapy (e.g., loperamide)
	Administer lactobacillus or encourage foods such as yogurt
	Evaluate for *C. difficile* and other infections
	Decrease frequency of bedaquiline administration
	Discontinue bedaquiline if this can be done without compromising regimen—rarely necessary
Dizziness	Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs)
	Rule out other causes
	If identified, treat specific cause according to standard clinical protocol
	Treat specific cause if it can be identified
	If cause of dizziness cannot be identified treat with cyclizine
	Note: Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Bedaquiline [4,33,49,102]	
Hemoptysis	Treat according to standard clinical protocol
Myalgia	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
Syncope	Obtain an ECG to detect QT prolongation Treat according to standard clinical protocol
Overdose and life-threatening toxicity	There is no experience with the treatment of acute overdose with bedaqualine General measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) should be taken in case of deliberate or accidental overdose Removal of unabsorbed bedaquiline may be achieved by gastric lavage or aided by the administration of activated charcoal Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma
IV. **Adverse drug reaction recording and reporting**	
	Active pharmacovigilance system is in place All adverse drug reaction have been reported at the country level

Criteria for Delamanid [4,58,103]	
I. ***Justification criteria*** for prescribing delamanid	
	Patient is 18 years or older
	Administered to patients under 18 if national TB treatment guidelines permit
	Pulmonary TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)
	Documented evidence that an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed because of • In vitro resistance • Known adverse drug reactions • Poor tolerance • Contraindication • Unavailability or lack of supply of a drug in the WHO recommended regimen
	Organism is susceptible to delamanid (if DST is available)
	Used in combination with at least 3 other drugs to which the organism has been shown to be susceptible in vitro or if DST is unavailable, used in combination with at least 4 other drugs to which the organism is likely to be susceptible
	Treatment protocol has been approved by the national ethics authority Initiated and monitored by a physician experienced in the management of DR-TB

Criteria for Delamanid [4,58,103]
II. ***Process criteria*** to consider when prescribing delamanid
Administered as a component of starting a new treatment regimen (i.e., not added alone to a failing regimen) Patient has provided written informed consent to be treated with delamanid ensuring the patient: • Is aware of the novel nature of delamanid • Appreciates the reason why the drug is being proposed to be included in the regimen • Recognizes the benefits and potential harms Patient history has been reviewed for: • Delamanid allergy • Diabetes • Malignancies • Alcohol abuse • Substance abuse • Moderate to severe hepatic impairment • Severe renal impairment • Serum albumin less than 2.8 g/dL • QTcF more than 500 ms • History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia • Severe hypertension • Left ventricular hypertrophy (including hypertrophic cardiomyopathy) • Congestive cardiac failure accompanied by reduced left ventricle ejection fraction • Electrolyte disturbances, particularly hypokalemia, hypocalcaemia or hypomagnesaemia • Taking medicines that are known to prolong the QTc interval. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes. • Torsade de Pointes • Rare hereditary problems of galactose intolerance • Lapp lactase deficiency • Glucose-galactose malabsorption HIV status is documented in case records Pregnancy status is documented in the case records Delamanid was available for the duration of treatment

Criteria for Delamanid [4,58,103]	
Dose and frequency	Appropriate delamanid dosing for adult patients • 100 mg twice daily for 6 months • Treatment with an appropriate combination regimen should continue after completion of the 6 month delamanid treatment period according to WHO guidelines Appropriate delamanid dosing in renal dysfunction • Recommendations not available Appropriate delamanid dosing for pediatric patients • As per national TB treatment guidelines
Administration	For oral use only Swallow tablets whole with water Administer with food
Duration	Not to exceed 24 weeks

Criteria for Delamanid [4,58,103]	

Patient monitoring	Drug resistance testing and again prior to switching to another regimen
	
	Prior to treatment and at least monthly during treatment:
	
	Weight (and every 2 weeks for the first 3 months of treatment)
	
	Pregnancy testing—according to standard clinical protocol
	
	Electrocardiogram (ECG)
	• Delamanid discontinued if QTcF is more than 500 ms
	• Conduct ECG more frequently if QTc interval duration exceeds 450 to 470 ms
	
	Serum potassium, calcium, and magnesium
	• Conduct if QT prolongation is detected
	
	Serum albumin
	• Conduct ECG more frequently if serum albumin falls below 3.4 g/dL
	
	Liver function tests
	• AST (SGOT)
	• ALT (SGPT)
	• Total bilirubin
	
	Renal function tests
	
	One or more of the following laboratory measurements:
	• Blood
	  ○ Creatinine clearance rate (either carefully measured or estimated from published nomograms or equations based on patient's age, sex, body weight, and serial creatinine concentrations—preferred over BUN)
	  ○ Serum creatinine concentration (preferred over BUN)
	  ○ Blood urea nitrogen (BUN)
	  ○ Non-protein nitrogen (NPN)
	• Urine
	  ○ Proteinuria
	  ○ Presence of cells and casts
	  ○ Specific gravity
	
	HIV testing—according to standard clinical protocol

Therapeutic drug monitoring—delamanid blood levels	Data not yet published

Criteria for Delamanid [4,58,103]	
Drug Interactions	Coadministration with ethambutol significantly increases steady state plasma concentrations of ethambutol by approximately 25% Coadministration of strong cytochrome CYP3A4 inducers (e.g., carbamazepine) may decrease the effects of delamanid Coadministration of strong cytochrome P3A4 inhibitors (e.g., lopinavir/ritonavir) may prolong the QTc interval • If coadministered frequently, monitor ECGs throughout the full delamanid treatment period Coadministration with fluoroquinolones (e.g., moxifloxacin) may prolong the QTc interval • If coadministered frequently, monitor ECGs throughout the full delamanid treatment period Drugs that prolong the QT interval (e.g., mifepristone, azithromycin, amiodarone, and chloroquine) may have additive effects on levofloxacin induced QT interval prolongation • Avoid co-administration of QT interval prolonging drugs. Refer to Annex K. Drugs That Prolong the QT Interval or Induce Torsades de Pointes Hepatotoxic and nephrotoxic drugs • Co-administration may produce additive toxicities. Refer to Annex F. Hepatotoxic, Nephrotoxic, Neurotoxic, And Ototoxic Drugs. Antiretrovirals may have additive or synergistic toxicities, or cause sub-therapeutic levels when coadministered • Consult with HIV clinicians and ART specialists • Co-administration of lopinavir/ritonavir may increase the effects of delamanid

Criteria for Delamanid [4,58,103]	
Patient counseling	Advise patients • If they experience side effects, they should talk to their health care provider • If they experience side effects that might affect their ability to concentrate and react (e.g., headache and tremor), they should not drive or operate machinery Advise patients to contact a health care provider immediately if they experience • Change in heartbeat (a fast or irregular heartbeat) • Fainting • Unexplained symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual fatigue, loss of appetite • Light colored bowel movements • Dark colored urine • Yellowing of the skin or whites of eyes Advise patients who are pregnant or planning to become pregnant • Pregnancy Category—not yet classified by the US Food and Drug Administration • There are very limited data on the use of delamanid in pregnant women. Studies in animals have shown reproductive toxicity • Not recommended in pregnant women • Women of childbearing potential should be using a reliable form of contraception Advise patients who are breastfeeding: • Breastfeeding is not recommended during therapy with delamanid • Most drugs used to treat TB cross into breast milk at low levels • The amount of anti-TB drugs that babies receive through breast milk will not treat or prevent TB in the infant

Criteria for Delamanid [4,58,103]	
III. ***Complications*** that could occur during therapy with delamanid and how to respond if the complication presents as follows[26]	
Severe or common toxicities are indicated by **bold** font	
Dizziness	Conduct a clinical evaluation to determine whether the dizziness is vestibular or non-vestibular in origin Conduct a clinical evaluation to determine whether the dizziness is peripheral or central in origin Rule out other causes If identified, treat specific cause according to standard clinical protocol Treat specific cause if it can be identified If cause cannot be identified, treat with cyclizine **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo
Electrolyte disturbances (e.g., dark urine, irregular heartbeat, fatigue, bowel irregularities muscle weakness or pain, changes in mood or coherence, headache)	Check potassium If potassium is low, also check magnesium (and calcium if hypocalcaemia is suspected) Replace electrolytes as needed Dose oral electrolytes apart from fluoroquinolones as they and interfere with fluoroquinolone absorption

[26] For mild reactions, encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely.

Criteria for Delamanid [4,58,103]	
Headache	Rule out other causes (e.g., meningitis or other central nervous system infections) Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Encourage adequate fluid intake Treat with ibuprofen, paracetamol, or aspirin Treat migraine headaches with analgesics, low-dose beta-blockers, supportive measures **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Address stressors potentially contributing to tension-related headaches Consider administering amitriptyline 50 to 150 mg at night Consider administering mild opiate-containing analgesics (e.g., paracetamol with codeine) Consider neurology consultation
Hypersensitivity, mild (e.g., skin itching, redness, rash, or swelling)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo

Criteria for Delamanid [4,58,103]	
Hypersensitivity, severe (e.g., drug fever, rash, skin eruptions of various types, including exfoliative dermatitis, infectious mononucleosis-like, or lymphoma-like syndrome, leucopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, jaundice, hepatitis, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Leoffler's syndrome, vasculitis, and a reduction in prothrombin)	Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone) **Note:** Concurrent antihistamine administration with regimens containing aminoglycocides may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo Stop all therapy under cover of antihistamines Stop all therapy until reaction resolves Modify regimen according to national TB treatment guidelines Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, according to standard clinical protocol Rechallenge cutaneous hypersensitivity reactions with or without desensitization **DO NOT** attempt drug desensitization with severe skin, mouth, or mucous membrane reactions (e.g., exfoliative dermatitis and Stevens-Johnson Syndrome)
Hypoalbuminaemia	Conduct ECG more frequently if serum albumin falls below 3.4 g/dL
Peripheral neuropathy (e.g., burning of the feet, numbness, tingling)	Rule out other causes Correct any vitamin or nutritional deficiencies Administer pyridoxine 200 to 300 mg per day Initiate therapy with low-dose tricyclic antidepressant (e.g., amitriptyline daily) Consider paracetamol and NSAIDs (or both) for pain relief **Note**: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function. Consider neurology consultation Consider administering carbamazepine Decrease frequency of delamanid administration Discontinue delamanid Modify regimen according to national TB treatment guidelines

Criteria for Delamanid [4,58,103]	
Prolongation of the QT interval	Obtain an electrocardiogram and initiate treatment according to standard clinical protocol
	Correct electrolyte imbalances (potassium, magnesium)
	Monitor ECGs frequently to confirm that the QTc interval has returned to baseline
	Discontinue delamanid if significant ventricular arrhythmia develops
	Discontinue delamanid if a QTcF interval is more than 500 ms develops (confirmed by repeat ECG)
Tremor	Reassurance
	Maintain treatment if the tremor is mild and does not interfere with daily activities
	Initiate anticholinergic therapy (e.g., biperiden) if tremor is severe—rarely necessary
Anemia	Determine cause of anemia (i.e., iron deficiency, hydroxocobalamin (Vitamin B12) deficiency, chronic disease, bleeding)
	Supplement with iron, hydroxocobalamin (Vitamin B12), folate (Vitamin B9), ascorbic acid (Vitamin C) as appropriate
	Monitor complete blood counts weekly until stabilized
Arthralgias	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen)
	Note: NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
	Decrease frequency of delamanid administration
	Discontinue delamanid if this can be done without compromising regimen
	Modify regimen according to national TB treatment guidelines
Chest pain	Obtain an ECG to detect QT prolongation
	Treat according to standard clinical protocol
Clostridium difficile-associated diarrhea	Bowel rest
	Appropriate fluid and electrolyte management
	Protein supplementation
	Antibiotic treatment of *C. difficile*
	Surgical evaluation should be instituted as a last resort, if clinically indicated

Criteria for Delamanid [4,58,103]	
Diarrhea, flatulence	Encourage patients to tolerate some degree of loose stools and flatulence Encourage fluid intake Assess for dehydration; initiate rehydration if indicated Assess for electrolyte disturbances; initiate replacement therapy if indicated Initiate anti-diarrheal therapy (e.g., loperamide) Administer lactobacillus or encourage foods such as yogurt Evaluate for *C. difficile* and other infections Decrease frequency of delamanid administration Discontinue delamanid if this can be done without compromising regimen—rarely necessary
Hematological abnormalities (e.g., agranulocytosis, thrombocytopenia)	Stop all therapy pending resolution of toxicity Eliminate other potential causes of toxicity Consider suspending most likely agent permanently Reintroduce remaining drugs, one at a time with the least hemotoxic agents first, while frequently monitoring hematology
Hemoptysis	Treat according to standard clinical protocol
Hepatitis and other hepatotoxicity (less than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Monitor liver function tests and bilirubin weekly Once resolved, monitor liver function monthly

Criteria for Delamanid [4,58,103]	
Hepatitis and other hepatotoxicity (more than five times the upper limit of normal) with or without jaundice (greatly increased or decreased frequency of urination or amount of urine, increased thirst, loss of appetite, nausea, vomiting)	Stop all hepatotoxic medicines Rule out other potential causes of hepatitis (e.g., viral hepatitis, alcohol-induced hepatitis If identified, treat specific cause according to standard clinical protocol Reintroduce drugs, individually with the least hepatotoxic agent first while monitoring liver function every three days; and if the most likely agent is not essential, consider not reintroducing it Once resolved, monitor liver function monthly
Myalgia	Initiate therapy with non-steroidal anti-inflammatory drugs (e.g., ibuprofen) **Note:** NSAIDs, such as ibuprofen, may contribute to renal toxicity. Exercise caution with use and monitor renal function.
Nausea or vomiting	Administer with small meals and advise patient to swallow tablets slowly with small sips of water Give medication at a time of day to minimize the effects (consult the patient as to timing of drugs) Assess for dehydration, electrolyte disturbances, hepatitis Initiate rehydration if indicated Initiate antiemetic therapy (e.g., metoclopramide, ondansetron)
Nephrotoxicity or renal failure	Discontinue delamanid
Syncope	Obtain an ECG to detect QT prolongation Treat according to standard clinical protocol
Overdose and life-threatening toxicity	There is no experience with the treatment of acute overdose with delamanid General measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) should be taken in case of deliberate or accidental overdose
IV. **Adverse drug reaction recording and reporting**	
	Active pharmacovigilance system is in place All adverse drug reaction have been reported at the country level

Regimens

Example of Possible Criteria for Regimens		
Justification Criteria		
TB is microbiologically confirmed (e.g., smear, culture, WHO-approved rapid diagnostics)		
Laboratory drug susceptibility testing (DST) documents the organism resistance pattern includes at least rifampicin and isoniazid or rifampicin alone or Clinically diagnosed by DR-TB specialists if consumption of first-line treatment can be objectively documented		
Patient is allergic to isoniazid or rifampicin		
Organism is susceptible to all medicines in the regimen (if DST is available)		
According to national DR-TB treatment guidelines		
Process Criteria		
Patient was prescribed the correct regimen according to national treatment guidelines		
All medicines in the regimen were prescribed at the correct dose according to national treatment guidelines		
All medicines in the regimen were administered at the correct frequency according to national treatment guidelines		
All medicines in the regimen were administered for the correct duration of the intensive phase according to national treatment guidelines		
All medicines in the regimen were administered for the correct duration of the continuation phase according to national treatment guidelines		
Adverse Drug Reactions		
Indicate if the patient experienced selected expected adverse drug reactions (e.g., ototoxicity for aminoglycosides, dysglycemia for fluoroquinolones)		
Outcome		
Indicate the treatment outcome		
a. Cure b. Treatment completed c. Died d. Treatment failure e. Default f. Transfer Out	**OR**	a. Cured b. Treatment completed c. Died d. Treatment failed e. Lost to follow-up f. Not evaluated

ANNEX B. SAMPLE DATA COLLECTION FORMS

Kanamycin Retrospective Drug Use Review Adult Patients **[Name of Treatment Center]**			**Page 1 of ___**
Case Reviewed	**Patient 1**	**Patient 2**	**Patient 3**
DR-TB Case Number			
Health Service Setting (enter one) I—Inpatient O—Outpatient C—Community			
Diagnosis	DR-TB	DR-TB	DR-TB
Gender			
Age at start of treatment (years and months)			
Weight at start of treatment (kg)			
Date Treatment Initiated			
Planned Treatment Duration Intensive Phase (months)			
Planned Treatment Duration Continuation Phase (months)			
Have these chart notes been previously inspected during this Drug Use Review cycle? If yes, enter last month of treatment inspected.	No	No	No
Enter the last month of treatment inspected today.			
Data Collector's initials			
Date Data collected			

Kanamycin Retrospective Drug Use Review For Adult Patients **[Name of Treatment Center]**				**Page ___ of ___**
Case Reviewed		**Patient 1**	**Patient 2**	**Patient 3**
DR-TB Case Number	Threshold, %	Y (Yes), N (No), ND (Not Documented), NA (Not applicable)		
Justification Criteria				
1. TB is microbiologically confirmed (e.g., smear, culture, WHO- approved rapid diagnostics)	100			
2. Laboratory drug susceptibility testing (DST) documents the organism resistance is resistant to rifampicin and isoniazid	100			
3. Laboratory drug susceptibility testing (DST) documents the organism resistance is susceptible to kanamycin	100			
Process Criteria				
1. Past medical history documents screening for a. Kanamycin allergy	100			
b. Aminoglycoside allergy	100			
c. Possibility of pregnancy (if applicable)	100			
d. Hearing disorders	100			
e. Vestibular disorders	100			
f. Neuromuscular disorders (e.g., myasthenia gravis or Parkinson's Disease)	100			
2. HIV status is documented in case records	100			
3. Audiometric or caloric stimulation testing conducted prior to starting treatment	100			
4. Renal function testing conducted prior to starting treatment	100			
5. Liver function testing conducted prior to starting treatment	100			
6. Serum potassium testing conducted prior to starting	100			

Kanamycin Retrospective Drug Use Review For Adult Patients **[Name of Treatment Center]** **Page ___ of ___**				
Case Reviewed		**Patient 1**	**Patient 2**	**Patient 3**
DR-TB Case Number	Threshold, %	Y (Yes), N (No), ND (Not Documented), NA (Not applicable)		
treatment				
7. Patient has not been coadministered or sequentially administered potentially nephrotoxic, neurotoxic, or ototoxic drugs (Annex F)	100			
8. Patient has been advised to contact a health care professional if they experience problems with hearing, dizziness, or balance	100			
9. Patients who are pregnant or planning to become pregnant have been advised of the potential risks and potential benefits of starting TB treatment	100			
10. Patient's weight is documented prior to starting treatment and at least monthly	100			
11. Patent's weight has changed since initiation of treatment	NA			
12. Appropriate kanamycin dosing for **adult** patients • 15 to 20 mg/kg **OR** Appropriate kanamycin dosing for renal dysfunction (creatinine clearance less than 30 mL/min or patients receiving hemodialysis) • 12 to 15 mg/kg per dose • Two or three times per week • After dialysis if administered on dialysis days	95			
13. Kanamycin dose is less than or equal to 1,000 mg	100			
14. Kanamycin was administered for at least 8 months				

Kanamycin Retrospective Drug Use Review For Adult Patients **[Name of Treatment Center]** **Page ___ of ___**				
Case Reviewed		**Patient 1**	**Patient 2**	**Patient 3**
DR-TB Case Number	Threshold, %	Y (Yes), N (No), ND (Not Documented), NA (Not applicable)		
15. Kanamycin is administered at least six times per week	95			
16. Audiometric or caloric stimulation testing conducted monthly	75			
17. Liver function testing conducted at least monthly	100			
18. Renal function testing at least monthly	100			
19. Serum potassium testing conducted at least monthly	100			
20. HIV-positive patients are monitored for potentially overlapping antiretroviral toxicities (See Annex G)	100			
a. Ototoxicity (e.g., clumsiness, dizziness, nausea, vomiting, unsteadiness, any loss of hearing, ringing or buzzing, a feeling of fullness in the ears)	100			
• Management – Document events and compare with prior to starting treatment – Decrease frequency (e.g., three times a week)	100			
b. Nephrotoxicity	100			
• Management – Consider dosing 2 to 3 times a week if drug is essential to the regimen – Monitor creatinine daily	100			
c. Peripheral Neuropathy (burning of face or mouth, numbness, tingling)	100			

Kanamycin Retrospective Drug Use Review For Adult Patients **[Name of Treatment Center]** **Page ___ of ___**				
Case Reviewed		**Patient 1**	**Patient 2**	**Patient 3**
DR-TB Case Number	Threshold, %	Y (Yes), N (No), ND (Not Documented), NA (Not applicable)		
• Management – Administer pyridoxine 200 to 300 mg per day	100			
d. Injection site reactions	100			
• Management – Rotate injection sites	100			
e. Hypersensitivity, mild (skin itching, redness, rash, or swelling)	100			
• Management – Initiate antihistamine therapy (e.g., loratadine); corticosteroids (e.g., prednisolone, methylprednisolone), and hydrocortisone cream or calamine lotion	100			
f. Hypersensitivity, severe (eosinophilia, fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock)	100			
• Management – Eliminate kanamycin from regimen	100			

Kanamycin Retrospective Drug Use Review **Adult Patients** **[Name of Treatment Center]** **Page ___ of ___**	
Data Collector Comments **Sign and Date each comment**	**DUR Committee Comments**

Retrospective Drug Use Review – Regimen A
8 Z - Km - Lfx - Eto - Cs / 12 Z - Lfx - Eto - Cs[27]
Adult Patients

[Name of TB Treatment Center] **Page 1 of ____**

Case Reviewed	**Patient 1**	**Patient 2**	**Patient 3**
DR-TB Case Number			
Health Service Setting (enter one) I—Inpatient O—Outpatient C—Community			
Diagnosis	MDR-TB	MDR-TB	MDR-TB
Gender			
Age at start of treatment (years and months)			
Weight at start of treatment (kg)			
ate Treatment Initiated			
Planned Treatment Duration Intensive Phase (months)			
Planned Treatment Duration Continuation Phase (months)			
Have these chart notes been previously inspected during this Drug Use Review cycle? If yes, enter last month of treatment inspected.	No	No	No
Enter the last month of treatment inspected today.			
Data collector's initials			
Date data collected			

[27] Pyrazinamide (Z), kanamycin (K), levofloxacin (Lfx), ethionamide (Eto), cycloserine (Cs)

Retrospective Drug Use Review – Regimen A 8 Z - Km - Lfx - Eto - Cs / 12 Z - Lfx - Eto – Cs Adult Patients						
[Name of TB Treatment Center]					**Page ____ of ____**	
Case Reviewed	**Threshold %**	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
		Y (Yes), N (No), N/A (Not Applicable), N/D (Not Documented)				
Justification Criteria						
1. DR-TB is diagnosed by a. Line probe assay or Xpert MTB/RIF OR b. DR-TB specialist's clinical diagnosis						
2. Patient was 15 years of age or older at the start of the initiation phase						
3. Organism resistance pattern is to isoniazid and rifampicin						
Process Criteria						
1. Date intensive phase started	NA					
2. Weight at start of intensive phase	NA					
3. Patient was prescribed Z-Km-Lfx-Eto-Cs at initiation of the intensive phase						
4. Pyrazinamide was dosed at • 25 mg/kg (20 to 30 mg/kg) at initiation of the intensive phase						
5. Pyrazinamide was administered at least six times per week during the intensive phase						
6. Kanamycin was dosed at • 15 to 20 mg/kg at initiation of the intensive phase						
7. Kanamycin was administered at least six times per week during the intensive phase						

Retrospective Drug Use Review – Regimen A 8 Z - Km - Lfx - Eto - Cs / 12 Z - Lfx - Eto – Cs Adult Patients						
[Name of TB Treatment Center]					**Page ____ of ____**	
Case Reviewed	**Threshold %**	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
		Y (Yes), N (No), N/A (Not Applicable), N/D (Not Documented)				
8. Levofloxacin was dosed at • 500 to 1000 mg at initiation of the intensive phase						
9. Levofloxacin was administered at least six times per week during the intensive phase						
10. Ethionamide was dosed at • 15 to 20 mg/kg at initiation of the intensive phase						
11. Ethionamide was administered at least six times per week during the intensive phase						
12. Cycloserine was dosed at 15 to 20 mg/kg at initiation of the intensive phase						
13. Cycloserine was administered at least six times per week during the intensive phase						
14. Date continuation phase started	NA					
15. Weight at start of continuation phase	NA					
16. Patient was prescribed Z-Lfx-Eto-Cs at initiation of the continuation phase						
17. Pyrazinamide was dosed at • 25 mg/kg (20 to 30 mg/kg) at initiation of the continuation phase						
18. Pyrazinamide was administered at least six times per week during the continuation phase						
19. Levofloxacin was dosed at • 500 to 1000 mg at initiation of the continuation phase						

Retrospective Drug Use Review – Regimen A 8 Z - Km - Lfx - Eto - Cs / 12 Z - Lfx - Eto – Cs Adult Patients						
[Name of TB Treatment Center]					**Page ____ of ____**	
Case Reviewed	**Threshold %**	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
		Y (Yes), N (No), N/A (Not Applicable), N/D (Not Documented)				
20. Levofloxacin was administered at least six times per week during the continuation phase						
21. Ethionamide was dosed at • 15 to 20 mg/kg initiation of the continuation phase						
22. Ethionamide was administered at least six times per week during the continuation phase						
23. Cycloserine was dosed at • 15 to 20 mg/kg at initiation of the continuation phase						
24. Cycloserine was administered at least six times per week during the continuation phase						
25. Date treatment ended	NA					
26. Weight at the end of treatment	NA					
27. Patient was administered Z-Lfx-Eto-Cs on the last day of treatment						
28. Pyrazinamide was dosed at • 25 mg/kg (20 to 30 mg/kg) on the last day of treatment						
29. Levofloxacin was dosed at • 500 to 1,000 mg on the last day of treatment						
30. Ethionamide was dosed at • 15 to 20 mg/kg on the last day of treatment						
31. Cycloserine was dosed at • 15 to 20 mg/kg on the last day of treatment						

Retrospective Drug Use Review – Regimen A 8 Z - Km - Lfx - Eto - Cs / 12 Z - Lfx - Eto – Cs Adult Patients						
[Name of TB Treatment Center]					**Page ____ of ____**	
Case Reviewed	**Threshold %**	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
		Y (Yes), N (No), N/A (Not Applicable), N/D (Not Documented)				
32. Z-Km-Lfx-Eto-Cs were the only anti-TB medicines prescribed during treatment. If **NO,** list any additional anti-TB medicines prescribed on the comments page						
Adverse Drug Reactions[28]						
1. The patient experienced liver function tests five times greater than upper limit of normal during treatment						
2. The patient experienced hearing loss during treatment						
3. The patient experienced dysglycemia during treatment						
4. The patient experienced gynecomastia during treatment						
5. The patient experienced psychiatric disturbances during treatment						

[28] These ADRs were chosen for illustrative purposes only, additional or other ADRs may be included

COMMENTS PAGE
Retrospective Drug Use Review – Regimen A
8 Z - Km - Lfx - Eto - Cs / 12 Z - Lfx - Eto - Cs
Adult Patients

[Name of TB Treatment Center] **Page ____ of ____**

Data Collector Comments **Sign and Date each comment**	**DUR Committee Comments**

Data Collection Form (DCF) Completion Instructions

General

All entries on the DCF must be **accurate**, **legible,** and **verifiable with the source documents**. Examples of source documents are: progress notes, nursing notes, clinic notes, laboratory reports, pharmacy records, and correspondence from the patient or the patients' primary care or specialist physician(s).

Record only what you observe has been documented.

If the data are interpretations by field personnel rather than the "hard" data provided in the patient chart notes, the validity of the data may be questioned.

If you have a comment about how the patient was managed, enter the response to the data item as observed, and then write a comment in the comment section.

Example

	Patient 1	Patient 2	Patient 3
1. Liver function testing conducted prior to starting treatment	N	Y	Y

Drug Use Review **Name of Institute**	
Data collector comment **Sign and date each comment** Patient 1 A blood draw was conducted for baseline LFT, but the results could not be found in the patient's chart notes, so I responded ND for Procedure Criteria Item 1. AK 25 June 2013	**DUR Committee Comments**

If you are uncertain about how to respond for a specific item, or if an item on the form is not clear, please contact SIAPS for clarification.

SIAPS Contacts:

Global Contact:	Antonia Kwiecien	AKwiecien@msh.org
Local Contact:	[enter name]	[enter contact information]

Forms Completion

- Complete the DCF using a **black ballpoint pen.**
- Ensure all entries are complete and legible.
- Ensure that the patient DR-TB Number is entered on each page of the DCF
- Ensure that all fields are completed on each page or an explanation for missing data is recorded on the comments page
- Where information is not applicable, write **NA** in the relevant boxes
- Where information is not available, write **ND** in the relevant boxes
- Complete all dates as day, month, year (i.e., 13 NOV 2008). Partial dates should be recorded as NK/NOV/2008 (NK = not known)
- A supplemental comments page has been provided.
  - Enter the case number and DR-TB number at the top of the page
  - Enter the page number and total of page numbers at the bottom of the page
- A blank cover page has been provided for sites that are completing forms for more than three patients.
  - Enter the case number and DR-TB number at the top of the page
  - Complete the total of page numbers at the bottom of the page
- Any change or corrections to entries on the DCF must be initialled and explained (if necessary). The original entry should be crossed out with a single line and must not be obscured. The data correction must be written down as near to original entry as possible. See examples below.
- **Do not use correction fluid.**

Example: Correct Technique

	Threshold %	Patient 1	Patient 2	Patient 3
1. Renal function testing conducted prior to starting treatment	80	Y	~~Y~~ AK ~~N~~	N

Example: Incorrect Technique

	Threshold %	Patient 1	Patient 2	Patient 3
1. Renal function testing conducted prior to starting treatment	80	Y *obliterating, not initialed*	N *overwriting, not initialed*	N

Completing Previously Completed DUR Information

- This section is to gather information on data collected from previously conducted DURs so that the data collector does not duplicate work, and duplicate data is not collected for analysis.
- If this is the first time a DUR is conducted for a particular patient's chart notes, NO will be entered for you on the form (see example below).
- If this is a successive DUR you will be provided with a list of patient's chart notes that have been previously inspected (see example below).
- Enter the last month of treatment that appears on the list
- When you have completed the DUR, enter the last month of treatment notes that you inspected in the space provided.

Example: First DUR

Patient Reviewed	Patient 1	Patient 2	Patient 3
Have these chart notes been previously inspected during this Drug Use Review cycle? If yes, enter last month of treatment inspected.	No	No	No
Enter the last month of treatment inspected today.	18	12	5
Data collector's initials	AS	AS	AS
Date data collected	22 AUG 13	22 AUG 13	22 AUG 13

Example: Subsequent DUR

Patient Reviewed	Patient 1	Patient 2	Patient 3
Have these chart notes been previously inspected during this Drug Use Review cycle? If yes, enter last month of treatment inspected.	18	12	5
Enter the last month of treatment inspected today.	24	24	17
Data collector's initials	SK	SK	SK
Date data collected	17 JAN 14	17 JAN 14	17 JAN 14

SAMPLE DUR DATA COLLECTION TRACKING SHEET						
Site One						
Case Number	**First Treatment Month Reviewed**	**Last Month Reviewed**	**Data Collectors Initials**	**Date Sent to MSH**	**Date Received at MSH**	**Review Complete**
1	1	18	AS	15 JUL 13	17 JUL 13	N
2	1	12	AS	15 JUL 13	17 JUL 13	N
3	1	5	AS	15 JUL 13	17 JUL 13	N
1	19	24	SK	18 JAN 14	22 JAN 14	Y
2	13	24	SK	18 JAN 14	22 JAN 14	Y
3	6	17	SK	18 JAN 14	22 JAN 14	N

ANNEX C. SAMPLE DUR RESULTS SUMMARY REPORT

Name of Drug or Review	
Date of Report	
Total Number of Patient Charts Reviewed	
Date Reported to NTP or DUR Committee	
Person Responsible for the Review	

1. Objective(s)or Hypothesis:
   a. What are the objective(s) of the review?

2. Design:
   a. Define the timeframe (patient cohort) for data collection or date range for which historical data will be captured if appropriate.

3. Identify patient selection:
   a. How many charts will be reviewed (i.e., all patients or a defined representative sample of patients in the cohort)?

4. Data to be collected:
   a. Include a set of data collection forms.
   b. Define data sources.

5. References:
   a. Cite any references used to define the DUR (e.g., DUR Guidelines, local national TB treatment guidelines, published drug reference literature).

6. Results:
   a. How long did it take to obtain the data?
   b. Complete the table below.

DUR Data Summary Criteria [enter name of drug or regimen]	Total Number Met		Threshold Met		**Specific** Comments
	YES	NO	Target %	Observed %	
[list criteria selected for review] **Justification for Drug Being Prescribed**					
Process Criteria					
Adverse Drug Reaction Criteria					
Other Criteria					
Total Number of Charts Reviewed [enter total number reviewed]					

7. Conclusions:
   a. What conclusions can be made from the data collected?
   b. Does the review fulfill the objectives under the DUR?
   c. List any unforeseen issues pertaining to the current DUR.

8. Limitations:
   a. What was difficult to ascertain during data collection?
   b. Were there any unexpected challenges in the process of analysis?
   c. Was there data that was not obtainable?

9. Recommendations:
   a. What interventions can be made to improve the drug use process?
   b. Identify specific actions that will affect the results/conclusions identified.
   c. Identify a plan for conducting a follow-up DUR to determine if intervention was successful.
   d. Set a reasonable timeframe for follow-up.

ANNEX D. SAMPLE DRUG USE REVIEW ACTIVITY TRACKER

Sample DUR Activity Tracker

Done?	Task	Assigned To	Start By	Due By	Notes
	Discuss with NTP or Partner Focal Person			First Quarter	
	Define DUR objectives or hypothesis				
	Adapt generic guidelines for the local setting				Translation?
	Implementing Partner meeting (two days)				
	Confirm objectives				
	Define cohort				
	Select sample size				
	Select facilities				
	Select data collectors				
	Select medicines or regimen for review				
	Select criteria for each medicine or regimen				
	Select threshold for each criterion				
	Define roles and responsibilities				
	Finalize timeline				
	Discuss ethics approval				
	Plan three-day data collector workshop			Second Quarter	
	Conduct three-day data collector workshop				
	Revise DUR forms based on workshop feedback				
	Obtain NTP sign off				
	Obtain ethics approval				
	Prepare pilot data collection forms				
	Pilot data collection				
	Revise Criteria, Thresholds, and Forms based on the forms used in the pilot (if needed)				

Sample DUR Activity Tracker

Done?	Task	Assigned To	Start By	Due By	Notes
	Orient facility staff to the DUR process			Second and Third Quarters	
	Collect data at facilities				
	Tabulate and analyze data				
	Interpret data				
	Make recommendations			Third Quarter	
	Disseminate results				
	Publish results				
	Discuss improvement plan				
	Implement improvement plan			Fourth Quarter	
	Plan for country ownership				
	Conduct follow-up DUR			Year 2 First Quarter	
	Review and discuss follow-up data				
	Evaluate DUR program				
	Publish results				
	Continue with remaining steps in the cycle				

ANNEX E. THERAPEUTIC DRUG MONITORING OF ANTI-TB MEDICINES

Please Be Aware of the Following When Using Information in This Annex

This annex provides an overview of dosage adjustments and therapeutic drug monitoring for aminoglycosides. It should not be relied upon as a substitute for adequate training in dosing of the drugs involved, obtaining the samples, measuring the concentrations, using the results appropriately, or the consultation of an experienced clinical pharmacologist.

The goal of therapeutic drug monitoring (TDM) is to use serum drug concentrations to manage a patient's medication regimen to ensure adequate therapeutic drug levels and minimize adverse drug reactions.

While TDM for anti-tuberculosis drugs is still not widely available, its use is valuable in several circumstances:

- Aminoglycoside and capreomycin serum concentrations to minimize the risk of ototoxicity and renal impairment
- Cycloserine concentrations to minimize risk of CNS toxicity and to safely use optimal dose
- Ethambutol concentrations in patients with significant renal impairment
- Known or suspected malabsorption

A multidisciplinary team (e.g., physicians, clinical pharmacologists, clinical pharmacists, nurses, and clinical laboratorians) is involved with the various elements of TDM. Failure to properly carry out any one of the components of TDM can severely affect the usefulness of measuring serum drug concentrations to minimize adverse drug reactions and optimize patient outcomes.

As an introduction to TDM, four published methods for adjusting extended interval dosing (EID) aminoglycosides are presented in this annex.

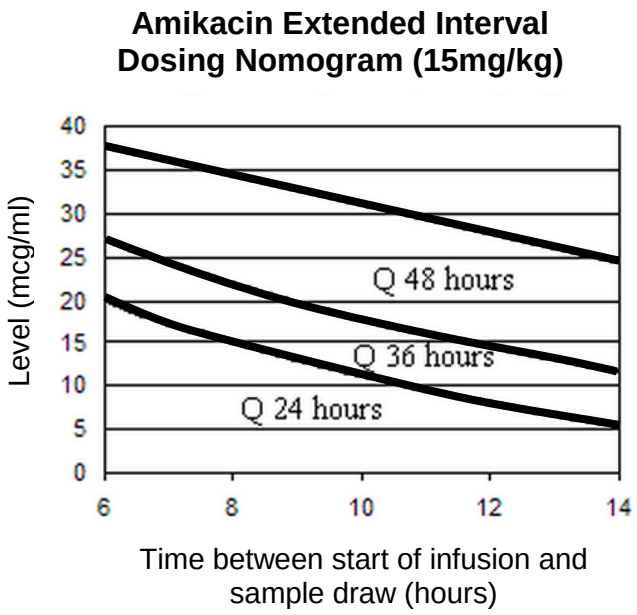
Method 1. Dosing Modifications Based on Percentage of Usual Dose

Table E - 1. Reduction of initial daily dose in case of decreased renal function[104]

Estimated creatinine clearance rate (mL/min)	Percentage of standard dose
Less than **90**	**100**
90	**90**
80	**88**
70	**84**
60	**79**
50	**74**
40	**66**
30	**57**

Method 2 Dosing Modifications Based on Serum Levels (Hartford Hospital)

Figure E - 1. Hartford Nomogram[105]



Practical Example

Patient Characteristics— Mr. JD a 23 year old, male DR-TB patient, weighs 55 kg, and has an estimated creatinine clearance (eCrCl) of 40 mL/min.

According to the DR-TB STG, the patient would receive amikacin 825 mg every 24 hours (15 mg/kg x 55 kg = 825 mg).

Ten hours after the first dose was given, the serum amikacin concentration is 40 mg/L.

According to the graph contained in the nomogram, the dosage interval should be changed to greater than once every 48 hours.

The new dose is 825 mg every 72 hours.

Method 3. Sawchuk and Zaske [106,107]

Patient specific parameters are calculated using the proven Sawchuk and Zaske pharmacokinetic dosing method are summarized in Table E - 2.

A legend for the symbols used in the equations is found in Table E - 3.

Table E - 2. Sawchuk-Zaske Method Equations

Steps	Equation	Comment
1. Find elimination rate constant (k)	$k = \frac{\ln C_1 - \ln C_2}{\text{time between samples}}$	Commonly used Dettli equation $k = 0.00293(\text{eCrCl}) + 0.014$ [108]
2. Find volume of distribution (V_D)	$V_D = \frac{(D/T)(1 - e^{-kT})}{k(C_{max} - C_{min}e^{-kT})}$	Approximate value of VD for aminoglycocides can be calculated with the following equation [108] VD = 0.24 (L/kg) * IBW (kg)
3. Determine ideal dosing interval (τ)	$\tau = \frac{[\ln C_{max,ss} - \ln C_{min,ss}]}{k} + T$	For Extended Interval Dosing the minimum τ = 24 hours
4. Calculate ideal maintenance dose (IMD)	$IMD = TkV_DC_{max,ss}\frac{(1 - e^{-}_{kT})}{(1 - e^{-}_{kT})}$	Round dose to the nearest 5 to 10 mg

Table E - 3. Sawchuk-Zaske Equation Symbols Legend

Symbol	Meaning
k	Elimination constant (hr^{-1})
C	Concentration (mg/L)
C_{min}	Trough Concentration (mg/L)
C_{max}	Peak Concentration (mg/L)
$C_{min,ss}$	Trough Concentration (mg/L) at steady state
$C_{max,ss}$	Peak Concentration (mg/L) at steady state
D	Dose (mg)
τ	Ideal Dosing interval (hr)
T	Dose infusion plus waiting time (1 hour for aminoglycosides)
V_D	Volume of distribution (L)
e	e^x calculated using http://www.eeweb.com/toolbox/calculator

Equations to estimate creatinine clearance required for calculations are presented below.

- **Adults—**Creatinine clearance is estimated (eCrCl) using the Cockroft-Gault equation

$$\text{eCrCl} = \frac{(140 - \text{age})(\text{IBW})}{(72)(\text{SCr})} \quad (0.85 \text{ if female})$$

- **Pediatrics—**Creatinine clearance is estimated using Schwartz's equation

eCrCl (mL/min) = /serum creatinine (micromol/liter)

$$\text{eCrCl} = \frac{\text{K x Length (cm)}}{\text{serum creatinine (mmol/L)}}$$

Table E - 4. Proportionality Constant for Calculating Creatinine Clearance

Where K = Constant of proportionality that is age specific

Age	K
Preterm infants up to 1 year	0.33
Full-term infants up to 1 year	0.45
1-12 years	0.55
13-17 years female	0.55
13-17 years male	0.70

Procedures for adjusting the maintenance dose for extended interval aminoglycoside dosing in patients with normal renal function

1. Determine dosing body weight (kg)

   Dose based on actual body weight (ABW), unless:
   - If patient is more than 20% over ideal body weight (IBW), use dosing body weight (DBW)
   - IBW_{Male} = (0.9 x height in cm) - 88
   - IBW_{Female} = (0.9 x height in cm) - 92
   - DBW = IBW + [0.4 (ABW – IBW)]

2. Determine initial dose (adults) according to according to national TB treatment guidelines
   - Amikacin: 15 to 20 mg/kg once daily to a maximum of 1,000 mg
   - Kanamycin: 15 to 20 mg/kg once daily to a maximum of 1,000 mg
   - Streptomycin: 12 to 18 mg/kg once daily to a maximum of 1,000 mg

3. Determine dosing interval according to half-life
   - Dosing for patients with DR-TB and normal renal function is every 24 hours according to national TB treatment guidelines
   - When calculating the dosage interval for patients with impaired renal function the interval should be rounded to a clinically accepted value (e.g., every 24, 36, or 48 hours)

4. Serum sampling
   - For extended interval dosing, the peak sample should be drawn between 6 and 14 hours post dose
   - The trough sample should be obtained 30 minutes prior to the dose, but trough levels are irrelevant in once daily dosing

      1. If $C_{max,ss}$ is outside goal range, adjust dose

$$\text{Dose} = T k V_D C_{max,ss} \frac{1 - e^{-k\tau}}{1 - e^{-k\tau}}$$

Practical Example

To illustrate how the nomogram is used, the same patient example used previously will be repeated for this dosage approach.

Patient Characteristics— Mr. JD, a 23-year-old, male DR-TB patient, weighs 55 kg, and has an estimated creatinine clearance (eCrCl) of 40 mL/min.

On 14 November 2013, he began a regimen of 6 Z-Km-Lfx-Eto-Cs/18 Z-Lfx-Eto-CS.

During his monthly clinical evaluation in January 2014, Mr. DE complained of ringing in his ears. The clinician ordered serum kanamycin levels in addition to his regular blood work.

His current dose of kanamycin is 825 mg IM every 24 hours.

His serum creatinine was 0.8 mg/dL.

Peak kanamycin serum concentration was 40 mg/L.

Adjust the kanamycin dose so the peak kanamycin concentration is less than 35 mg/L.

Steps to solve

1. Estimated creatinine clearance can be estimated using the Cockroft-Gault equation where

$$eCrCl = \frac{(140 - age)(IBW)}{(72)(SCr)}$$

$$eCrCl = \frac{(140 - 45)(55)}{(72)(0.8)}$$

$$eCrCl = 90.71 \text{ mL/min}$$

2. The elimination rate constant can be found using the Dettli equation where

$$k = 0.00293(eCrCl) + 0.014$$

$$k = 0.00293(90.71) + 0.014$$

$$k = 0.2798 \ (h^{-1})$$

3. Volume of distribution can be found by using the aminoglycoside approximation equation where

$$V_D = 0.24 \text{ (L/kg)} * IBW \text{ (kg)}$$

$$V_D = 0.24 \text{ (L/kg)} * 55 \text{ (kg)}$$

$$V_D = 0.24 \text{ (L/kg)} * 55 \text{ (kg)}$$

$$V_D = 13.2 \text{ L}$$

4. The dosing interval (τ) is 24 hours.

5. Dose infusion plus waiting time (T) is 1 hour.

6. The ideal maintenance dose can be calculated using the Sawchuk-Zaske equation where

$$IMD = T k V_D C_{max,ss} \frac{(1 - e^{-kT})}{(1 - e^{-kT})}$$

$$IMD = \frac{(1\ hr)\ (0.2798/h)(13.2\ L)(35\ mg/L)(1 - e^{-0.2798 \times 24\ h})}{(1 - e^{0.2798 \times 1h})}$$

$$IMD = \frac{129.27\ (1 - e^{-6.72})}{(1 - e^{-0.2798})}$$

$$IMD = \frac{129.27\ (1 - 0.0012)}{(1 - 0.7559)}$$

$$IMD = \frac{129.27\ (0.988)}{(0.2441)}$$

IMD = 523.22

IMD = 525 mg every 24 hours

Method 4 Bayesian Method for PK Parameter Estimation [109]

Although only one serum drug sample is needed for this method, it is mathematically complicated, requiring specialized staff experienced with computer software packages such as OSP-Fit, PopED and POPT. This method is not practical in middle- and low-income settings, thus not presented in this annex.

ANNEX F. HEPATOTOXIC, NEPHROTOXIC, NEUROTOXIC, AND OTOTOXIC DRUGS

Hepatotoxic Drugs

Liver Injury and Its Patterns [110]

HEPATOCELLULAR (Elevated Alanine Aminotransferase [ALT])	MIXED (Elevated alkaline phosphatase [ALP] + Elevated ALT)	CHOLESTATIC (Elevated ALP + Total Bilirubin)
Acarbose	Amitriptyline	Amoxicillin–clavulanic acid
Acetaminophen (paracetamol)	Azathioprine	Anabolic steroids
Allopurinol	Captopril	Chlorpromazine
Amiodarone	Carbamazepine	Clopidogrel
Baclofen	Clindamycin	Oral contraceptives
Buproprion	Cyproheptadine	Erythromycins
Fluoxetine	Enalapril	Estrogens
Haart drugs	Flutamide	Irbesartan
Herbals: kava kava and germander	Nitrofurantoin	Mirtazapine
Isoniazid	Phenobarbital	Phenothiazines
Ketoconazole	Phenytoin	Terbinafine
Lisinopril	Sulfonamides	Tricyclics
Losartan	Trazodone	
Methotrexate	Trimethoprim–Sulfamethoxazole	
NSAIDS	Verapamil	
Omeprazole		
Paroxetine		
Pyrazinamide		
Rifampicin		
Risperidone		
Sertraline		
Statins		
Tetracyclines		
Trazodone		
Trovafloxacin		
Valproic acid		

Note: This table is not a complete list of hepatotoxic medicines. There may be others, and patients and prescribers should be aware that many drugs have off-label uses.

Nephrotoxic Drugs

Commonly Encountered Nephrotoxic Medicines and Exposures [111]

Drug Class or Type of Exposure	Drug Sub-class	Examples
Antimicrobial	Aminoglycosides	tobramycin gentamicin kanamycin neomycin amikacin netilmicin sisomicin dibekacin ribostamycin isepamicin arbekacin bekanamycin
	Polymixin	colistin
	Sulfonamides	sulfadiazine
	Fluroquinolone	ciprofloxacin
Antiviral agents		cidofovir adefovir dipivoxil tenofovir acyclovir
Antifungal agents		amphotericin B
Anti-neoplastic agents	Platinum compounds	cisplatin carboplatin oxaliplatin polyplatillen satraplatin
	Other anti-neoplastic agents	Ifosfamide
		mitomycin
		gemcitabine
		methotrexate
		pentostatin
		imatinib gefitinib erlotinib sunitinib sorafenib
Immunostimulant		interleukin-2

Drug Class or Type of Exposure	Drug Sub-class	Examples
Analgesics	Non-steroidal anti-inflammatory drugs	diclofenac ibuprofen indomethacin naproxen
	Selective COX-2 inhibitors	celecoxib valdecoxib rofecoxib
	Other	phenacetin methoxyflurane
Intestinal anti-inflammatory agent		mesalazine
Immunosuppressants		sirolimus cyclosporine tacrolimus
Cardiovascular System	Angiotensin-converting enzyme inhibitors	captopril enalapril lisinopril
	Angiotensin-receptor blockers	losartan eprosrtan valsartan
	Lipid modifying agents - statins	atorvastatin fluvastatin lovastatin pitavastatin pravastatin simvastatin rosuvastatin
Anti-epileptics		topiramate zonisamide
Drugs for the treatment of bone diseases		pamidronate zolendronate
Anti-obesity medications		orlistat
Diagnostic agents		Gadolinium (in high dose)
	Colonoscopy prep	Oral sodium phosphate solution
	Radio contrast	High osmolar
		Low osmolar
		Iso-osmolar
Other		sucrose hydroxyethyl starch mannitol

Drug Class or Type of Exposure	Drug Sub-class	Examples
Alternative Products	Herbal remedies	aristolochic acid Ephedra sp. Glycyrrhiza sp. Datura sp. Taxus celebica Uno degatta Cape aloes
	Adulterants	mefenamic acid dichromate cadmium phenylbutazone melamine
Environmental Exposures	Heavy metals	lead mercury cadmium uranium copper bismuth
	Solvents	hydrocarbons (e.g., benzene, kerosene, diesel fuel)
	Other toxins	silicon germanium

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Note: This table is not a complete list of nephrotoxic medicines. There may be others, and patients and prescribers should be aware that many drugs have off-label uses.

Neurotoxic Drugs

Charcot-Marie-Tooth Foundation Medicial Alert [112]

Populations at greater risk include those with critical illness, renal function dysfunction, prior neurological disease, the elderly, and pediatrics.

Generic Name	Brand Name(s)	Labeled Uses	Method(s) of Administration
Definite High Risk			
Vincristine sulfate	Oncovin Vincasar PFS Vincristine Sulfate Injection	Acute leukemia; malignant lymphomas and carcinomas	Intravenous
Moderate to Significant Risk			
Amiodarone HCL	Cordarone	Ventricular arrhythmias (fibrillation and tachycardia	Oral Intravenous
Auranofin	Ridaura	Rheumatoid arthritis	Oral
Aurothioglucose	Solganal	Rheumatoid arthritis	Intramuscular
Bortezomib	Velcade	Multiple myeloma (bone cancer)	Intravenous
Cisplatin	Cisplatin Injection Platinol-AQ	Bladder, ovarian, and testicular carcinomas	Intravenous
Colchicine* *risk with extended use	Colchicine Tablets Colchicine Injection Probenecid and ColchicineTablets	Gout prevention; gouty arthritis; (unlabeled use: hepatic cirrhosis due to alcohol)	Oral Intravenous
Dapsone	Dapsone Tablets	Bullous herpetiformis dermatitis; leprosy	Oral
Didanosine; Dideoxyinosine (ddI)	Videx	HIV infection	Oral
Dichloroacetate (DCA)	Investigational Drug	Experimental chronic lactic acidosis treatment	Oral
Disulfiram	Antabuse	Alcoholism	Oral
Docetaxel	Taxotere	Breast and prostrate carcinomas; lung cancer	Intravenous
Eribulin Mesylate	Halaven	Metastatic breast cancer (patients who have received two prior chemotherapy regimens)	Intravenous

Generic Name	Brand Name(s)	Labeled Uses	Method(s) of Administration
Gold Salts (see specific drug names)			
Gold Sodium Thiomalate	Aurolate	Rheumatoid arthritis	Intramuscular
Ixabepilone	Ixempra	Metastatic or locally advanced breast cancer	Intravenous
Leflunomide	Arava	Rheumatoid arthritis	Oral
Metronidazole* *risk with extended use	Flagyl	Intestinal, vaginal and other bacterial infections; septicemia; peritonitis; endocarditis	Oral, Intravenous* *also a topical application in some formulations
Misonidazole* *risk with extended use	MISO	Cancer treatment radiotherapy	Oral Intravesical
Nitrofurantoin Macrodantin	Nitrofurantoin Capsules Macrobid Furadantin	Urinary tract infections	Oral
Nitrous Oxide* *risk with inhalation abuse or vitamin B12 deficiency	Nitronox	General anesthesia	Inhalation
Oxaliplatin	Eloxatin	Colorectal carcinoma	Intravenous
Perhexiline *	Pexsig	Angina pectoris	Oral
Pyridoxine* *risk with megadoses	Vitelle Nestrex	Vitamin B6 deficiency; antidote to drug-induced neuropathy	Oral, Intravenous
Stavudine (d4T)	Zerit	HIV infection	Oral
Suramin	Germanine Antrypol	African sleeping sickness; river blindness; experimental cancer treatment (prostate)	Intravenous
Paclitaxel	Onxol Paclitaxel Injection Taxol	Breast, lung, ovarian and esophageal carcinomas	Intravenous
Taxols (see specific drug names)			
Thalidomide	Thalomid	Erythema (reddening of the skin); nosodum leprosum (a rash associated with treatment of leprosy); many other off-label uses (mainly autoimmune disease and chemotherapy)	Oral

Generic Name	Brand Name(s)	Labeled Uses	Method(s) of Administration
Zalcitabine; Dideoxycytidine (ddC)	Hivid	HIV infection	Oral
Uncertain			
5-Fluorouracil; (5-FU)	Adrucil Fluorouracil injection	Breast, colorectal, gastric and pancreatic carcinomas	Intravenous
Adriamycin (Doxorubicin HCL)	Adriamycin Adriamycin RDF	Leukemia; lymphomas; carcinomas	Intravenous
Almitrine	Vectarion	Acute respiratory failure	Oral Intravenous
Atorvastatin	Lipitor	Elevated LDL cholesterol	Oral
Ciprofloxacin	Cipro	Bacterial infections	Oral Intravenous
Chloroquine	Aralen	Amebiasis Malaria	Oral Intravenous
Cytarabine Cytabine liposomal* *risk with high doses	Cycosar-U DepoCyt	Leukemias Lymphomatous meningitis	Oral Intravenous
Enoxacin	Penetrex	Urinary tract infections; gonorrhea	Oral
Ethambutol	Ethambutol Tablets Myambutol	Tuberculosis	Oral
Etoposide (VP-16)	Etoposide Capsules VePescid Etoposide for Injection Toposar VePescid Etopophos	Small cell lung carcinoma Refractory testicular neoplasm	Oral Intravenous
Fluoroquinolones (see specific drug names)			
Fluvastatin	Lescol	Elevated LDL cholesterol	Oral
Gatifloxacin	Tequin Tequin Injection	Pneumonia and bronchitis; sinus, respiratory tract, and urinary tract infections; sexually transmitted diseases	Oral, Intravenous
Gemcitabine	Gemzar	Non-small cell lung cancer; pancreatic carcinoma	Intravenous
Griseofulvin	Grifulvin V Fulvicin U/F Gris-PEG	Tineas (ringworm infections) of the skin, hair, and nails	Oral

Generic Name	Brand Name(s)	Labeled Uses	Method(s) of Administration
Hexamethylmelamine (Altretamine)	Hexalen	Ovarian cancer	Oral
Hydralazine	Apresoline Hydra-zide Apresazide Marpres	Hypertension	Oral Intravenous
Ifosfamide	Ifex	Testicular germ cell carcinoma; bone and soft tissue sarcomas	Intravenous
Infliximab	Remicade	Rheumatoid arthritis; Crohn's disease	Intravenous
Isoniazid	Nydrazid Lniazid	Tuberculosis	Oral Intravenous
Lansoprazole	Prevacid	Ulcers; gastroesophageal reflux disease (GERD); Zolliger- Ellison Syndrome	Oral
Levofloxacin	Levaquin	Infections, including skin, respiratory, and urinary tract infections; venereal diseases	Oral Intravenous
Lomefloxacin	Maxaquin	Bronchitis and urinary tract infections	Oral
Lovastatin	Lovastatin Mevacor Altocor	Elevated LDL cholesterol	Oral
Mefloquine	Lariam	Prevention and treatment of malaria	Oral
Moxifloxacin	Avelox	Skin and respiratory tract infections	Oral Intravenous
Norfloxacin	Noroxin	Urinary tract infections; prostatitis; gonorrhea	Oral
Ofloxacin	Floxin	Urinary tract, skin, bone, and heart infections	Oral Intravenous
Omeprazole	Prilosec Zegerid	Ulcers; gastroesophageal reflux disease (GERD); Zolliger- Ellison Syndrome	Oral
Penicillamine	Cuprimine Depen	Rheumatoid arthritis; Wilson's Disease (accumulation of copper in liver and other organs); cystinuria (kidney stones)	Oral
Phenytoin	Dilantin Phenytoin Sodium Injection	Epilepsy; convulsions; seizures	Oral Intravenous

Generic Name	Brand Name(s)	Labeled Uses	Method(s) of Administration
Sparfloxacin	Zagam	Lower respiratory tract infections	Oral
Trovafloxacin (Alatrofloxain)	Trovan	Pneumonia; abdominal, pelvic, and skin infections	Oral Intravenous
Podophyllin resin* *high risk with excessive time exposure or unintended route (oral; deep injection)	Podocon	Removal of benign growths and warts, esp. external genital and perianal exophytic warts caused by human papillomavirus (HPV)	Topical
Pravastatin	Pravachol Pravigard	Elevated LDL cholesterol	Oral
Rosuvastatin	Crestor	Elevated LDL cholesterol	Oral
Sertraline	Zoloft	Depression; panic attacks; obsessive-compulsive disorder; PTSD; social disorder	Oral
Simvastatin	Zocor	Elevated LDL cholesterol	Oral
Statins (see specific drug names)	Note: Statins are generally prescribed to control cholesterol and triglyceride levels and to prevent coronary events.		
Tacrolimus (FK506)	Prograf	Prevention of liver, kidney, and other organ transplant rejection	Oral Intravenous
Zimeldine (withdrawn from global market)	Normud Zelmid	Depression	Oral
α-Interferon	Roferon Intron Rebetron Infergen Alferon	Hepatitis B and C; warts caused by human papillomavirus (HPV); Kaposi's sarcoma; renal cell carcinoma; multiple myeloma (bone cancer); malignant melanoma (skin cancer); Non-Hodgkin's lymphoma	Intramuscular Intralesional Subcutaneous injection
Negligible or Doubtful Risk			
Allopurinol	Zyloprim Aloprim	Gout; gouty arthritis; kidney and urinary tract stones	Oral, Intravenous
Amitriptyline	Elavil	Depression	Oral
Chloramphenicol	Cloramphenicol Sodium Succinate Chloromycetin	Meningitis; typhoid fever	Intravenous
Chlorprothixene	Taractan	Psychosis	Oral, Intramuscular

Generic Name	Brand Name(s)	Labeled Uses	Method(s) of Administration
Cimetidine	Tagamet Cimetadine Hydrocloride Injection	Gastric and duodenal ulcers; gastroesophageal reflux	Oral Intravenous
Clioquinol	Clioquinol is an ingredient in numerous formulations (often in combination with hydrocortisone) used to treat bacterial and fungal infections of the skin	Dermatitis; folliculitis; eczema; athlete's foot; jock itch; ringworm	Topical (powders, creams, ointments)
Clofibrate	Atromid	Hyperlipidaemias (high cholesterol and triglyceride levels)	Oral
Cyclosporin A	Sandimmune; Neoral/Novartis	Prevention of rejection of organ transplants; severe cases of psoriasis and rheumatoid arthritis	Oral Intravenous
Enalapril	Vasotec/Biovail; Enalaprilat Injection	Hypertension; congestive heart failure	Oral Intravenous
Gluthethimide	Superceded by other drugs; not currently in use	Insomnia	Oral
Lithium	Lithium Carbonate Lithobid Eskalith	Bipolar disorder (manic/depressive disorder)	Oral
Phenelzine	Nardil	Depression	Oral
Propafenone	Propafenone HCL Rythmol	Atrial fibrillation; ventricular arrhythmias	Oral
Sulfacetamide	Numerous brand names and manufacturers	Acne; seborrheic dermatitis; eye and vaginal infections	Topical
Sulfabenzamide	Numerous brand names and manufacturers	Vaginitis	Topical
Sulfadiazine	Sulfadiazine Tablets	Toxoplasmosis	Oral

Generic Name	Brand Name(s)	Labeled Uses	Method(s) of Administration
Sulphasalazine	Azulfidine	Rheumatoid arthritis; ulcerative colitis	Oral
Sulfathiazole	Numerous brand names and manufacturers	Vaginitis	Topical
Sulphamethoxazole	Proloprim; Septra; Trimpex	Urinary tract infections; otitis media (middle ear infection)	Oral Intravenous
Sulfisoxazole (sulfafurazole)	Gantrisin	Urinary tract infections; otitis media (middle ear infection)	Oral
Sulfonamides (see specific drug names)	Note: Although listed here, the use of sulfonamides to treat infections has decreased due to the increase in drug-resistant bacteria		

Note: This table is not a complete list of neurotoxic medicines. There may be others, and patients and prescribers should be aware that many drugs have off-label uses.

Ototoxic Drugs

Avoid concurrent use of potent diuretics as they increase risk of ototoxicity

- Ethacrynic acid
- Tienilic acid
- Furosemide
- Bumetanide
- Piretanide
- Torsemide
- Muzolamine
- Etozolin
- Azosemide
- Ozolinone
- Indacrinone

Ototoxic Drug Index [113]

In this index the active principles are listed in alphabetical order, each with a numerical reference to the relevant type of side effect. Whenever possible according to data available to us, believing it to be very useful, we indicated the side effect frequency for each drug using a grading scale from a to e going from “very common” to “very rare”.

Pharmaceutical company indications about side effect frequency are normally expressed as follows:

a Very common (≥ 10%)
b Common (≥ 1% e < 10%)
c Uncommon (≥ 0,1% e <1%)
d Rare (≥ 0,01% e < 0,1%)
e Very rare (< 0,01%)
f Unknown, because available data is insufficient

It must be said that this grading is sometimes not published or known by the manufacturers so we haven’t assigned a grading letter to drugs with missing data.

1. Ototoxic drugs (ototoxicity may include both the possible associated symptomatology of labyrinthical alteration vertigo and the possible generation of tinnitus);
2. Drugs tinnitus-generating (there is no mention of ototoxicity);
3. Drugs vertigo-generating (there is no mention of ototoxicity);
4. Drugs with possible audiologic effects, indicated as “hearing disturbances” (drugs with aspecific otologic adverse drug reactions).

Drugs	***ADR numbers***
Abacavir + Lamivudine	3
Abacavir	3
Abacvir + Lamivudine + Zidovudine	3
Acebutolol	3b
Aceclidine + Timolol Maleate	2,3
Aceclofenac	2e,3e
Acetazolamide	3,4
Acetylsalicylic Acid	1
Acetylsalicylic Acid + Magnesium	1
Acyclovir	3
Adalimumab	3b
Adrenaline	3
Agalsidase Alfa - Beta	2,3
Alfacalcidol	3
Alfentanil	3
Alfuzosin Hydrochloride	3
Alizapride Hydrochloride	3
Allopurinol	3
Almotriptan	2c,3b
Alpha 1 Antitrypsin	3
Alprazolam	3b
Alprostadil	3
Amantadine Hydrochloride	3
Ambroxol Hydrochloride	3
Amifostine	3
Amikacin	1
Amikacin Sulphate	1
Amiloride And Hydrochlorothiazide	2,3
Amiodarone Hydrochloride	3
Amisulpride	3
Amitriptyline Chlordiazepoxide	2,3
Amitriptyline Hydrochloride	2,3
Amitriptyline Hydrochloride + Perphenazine	2,3
Amlodipine	2,3
Amoxycillin + Clavulanate	3
Amphotericin B	1
Anagrelide	3b
Aniracetam	3d

Drugs	***ADR numbers***
Aprepitant	2,3
Aproclonidin	3c
Aripiprazole	3b
Articaine + Adrenaline	2,3
Atazanavir	3c
Atenolol + Diuretics	3
Atenolol	3
Atomoxetine	3
Atorvastatin	2,3
Atosiban	3b
Atropine Sulphate	3
Azathioprine	3
Azithromycin	1,3d
Aztreonam	3
Bacitracin + Neomycin	1
Baclofen	3
Benazepril + Hydrochlorothiazide	2c,3b
Benazepril Hydrochloride	2,3
Betamethasone + Bekanamicin + Tetryzoline	1
Betamethasone + Tetryzoline	3
Betamethasone	3
Betamethasone + Clorfenamin	2,3
Bezafibrate	3
Biperiden Hydrochloride	3
Bisoprolol Fumarate + Diuretics	3c
Bisoprolol Fumarate	3b
Botulinum Toxin A	3b
Brimonidine Tartrate + Timolol	3c
Brimonidine Tartrate	3b
Brinzolamide	3c
Bromazepam	3
Bromocriptine Mesylate	3
Bromperidol	3
Brotizolam	3
Buflomedil Hydrochloride	3e
Bupivacaine + Adrenaline	3
Bupivacaine Hydrochloride	3
Buprenorphine	2d,3b

Drugs	ADR numbers
Bupropion	2c,3b
Buserelin	3,4
Buspirone Hydrochloride	3b
Butizide + Canrenoate Potassium	3e
Butylscopolamine Bromide	3
Buxamine	3
Buxamine + Fenobarbital + Fenitoine	3
Buxamine + Diazepam	3
Cabergoline	3b
Cadralazine	3
Calcitriol	3
Calcium Carbonate + Cholecalciferol (Vitamin D3)	3
Calcium Channel Blockers	3
Candesartan + Diuretics	3
Candesartan Cilexetil	3
Captopril + Diuretics	3
Captopril	3
Carbamazepine	3a
Carboplatin	1
Carvedilol	3a
Cefaclor	3d
Cefadroxil	3
Cefazolin Sodium	3
Cefepime	2d,3d
Cefixime	3
Cefonicid Disodium	3
Cefoperazone Sodium	3d
Cefotaxime	3
Cefpodoxime	3
Cefprozil	3c
Ceftazidime	3c
Ceftibutene	2,3d
Ceftizoxime Sodium	3
Ceftriaxone	3d
Cefuroxime	3
Celecoxib	2c,3c
Celiprololo Hydrochloride	3
Cephalexin	3

Drugs	*ADR numbers*
Cephradin	3
Cetuximab	3a
Chlordiazepoxide	3
Chloroquine	1
Chlorpheniramine Maleate	2b
Chlorthalidone	3
Cholecalciferol	3
Chondroitin Sulphate	3
Cilazapril + Diuretics	3
Cilazapril	3b
Cimetidine	3
Cimetropium Bromide	3
Cinacalcet	3b
Cinoxacin	1,2c,3b
Ciprofloxacin + Hydrocortisone	2b,3c,4d
Ciprofloxacin	2d,3c,4d
Cisplatin	1a
Citalopram	2b,3b
Clarithromicin	1e,2d,3e
Clidinium Bromide + Chlordiazepoxide	3
Clobazam	3
Clomiphene Citrate	3c
Clomipramine Hydrochloride	2b,3a
Clonazepam	3
Clonidine Hydrochloride	3
Clopidogrel Bisulfate	3d
Clorazepate Dipotassium	3
Clotiazepam	3
Cocarboxyilase + Pyridoxine + Hydroxocobalamin	3
Codeine + Pheniramine	3
Codeine Phosphate + Ivy	3e
Colistin	3
Cyclobenzaprine Hydrochloride	2,3
Cyclopentolate Hydrochloride	3
Cyproterone + Ethinyl Estradiol	3d
Danazol	3e
Dantrolene Sodium	3b
Daptomycin	3c

Drugs	ADR numbers
Dasatinib	2c,3d
Deferoxamine Mesylate	3,4
Defibrotide	3
Deflazacort	3
Delapril	3d
Delapril + Indapamide	3d
Delorazepam	3
Desipramine Hydrochloride	2b,3b
Dexamethasone	3
Dexamethasone + Neomycin	1
Dexamethasone + Netilmicin	1
Dexamethasone + Tobramycin	1
Dexibuprofene	2c,3b
Dexketoprofene	2e,3c
Diazepam	3
Diclofenac + Misoprostol	2,3
Diclofenac Epolamine	2e,3e
Diclofenac Potassium	2e,3e
Diclofenac Sodium	2e,3e
Diclofenamide (Sodium)	2,3
Didanosine	3
Digitoxin	3
Digoxin	3
Dihydrocodeine	3e
Dihydrocodeine + Benzoic Acid	3e
Dihydrocodeine + Pentetrazol	3e
Dihydroergokryptine Mesylate	3
Dihydroergotamine Mesylate	3
Dihydroquinidine Hydrochloride	1
Dihydrotachysterol	3
Diltiazem Hydrochloride	3
Dinoprostone	3
Diosmin	3
Diosmin + Hesperidin	3
Diphtheria, Tetanus Vaccine Adsorbed	3d
Dipyridamole	3e
Dolasetron Mesylate	3
Donepezil Hydrochloride	3b

Drugs	***ADR numbers***
Dorzolamide	3
Dorzolamide + Timolol	3c
Dosulepin Hydrochloride	2b,3b
Doxazosin	3b
Doxycycline	2
Duloxetine	3c
Dydrogesterone	3
Efavirenz	3c
Eletriptan	2c,3b
Emtricitabine + Tenofovir	3a
Emtricitabine	3b
Enalapril + Diuretics	2c,3c
Enalapril Maleate	2c,3c
Enfuvirtide	3b
Entacapone	3b
Entecavir	3b
Eprosartan	3d
Ergocalciferol	3
Ergometrine Maleate	2,3
Ergotamine Tartrate	3
Ertapenem	3
Erythromycin	1
Escitalopram	3b
Esmolol Hydrochloride	3
Esomeprazole	3c
Estazolam	3
Estradiol + Progestin	3c
Estradiol	3c
Estriol	3
Estrogens Conjugated + Progestin	3
Ethacrynic Acid	1
Ethinylestradiol	3c
Ethosuximide	3
Etizolam	3
Etonogestrel + Ethinylestradiol	3c
Etoposide	1
Etoricoxib	2c,3c
Exemestane	3b

Drugs	ADR numbers
Famciclovir	3d
Famotidine	3b
Felbamate	3c
Felodipine	3c
Fenofibrate	3
Fentanyl Citrate	3
Flavoxate Hydrochloride + Propyphenazone	3
Flavoxate Hydrochloride	3d
Flecainide Acetate	2b,3b
Fluconazole	3b
Flucytosine	3
Fluocinolone Acetonide + Neomycin	1
Fluorometholone + Gentamycin	1
Fluoxetine	3b
Fluphenazine/Nortriptyline	2,3
Flurazepam	3
Flurbiprofen Sodium	2,3
Flurbiprofen	2,3
Flurithromycin Ethylsuccinate	3
Flutamide	3d
Fluvoxamine Maleate	3b
Fondaparinux	3d
Fosamprenavir	3b
Foscarnet Sodium	3
Fosinopril	3c
Fosinopril + Diuretics	3
Frovatriptan	2c,3c
Furosemide	1d,2d
Gabapentin	2,3
Galantamine	2,3b
Gancyclovir	1,3b
Ganirelix	3
Gemeprost	3e
Gemfibrozil	3e
Gentamycin	1
Glipizide	3
Goserelin	3
Griseofulvin	3d

Drugs	***ADR numbers***
Haemophilus B (Meningococcal Protein Conjugate) Hepatitis B Vaccine Recombinant	3d
Halcinonide + Salicylic Acid	1
Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine	3d
Hepatitis B Vaccine (Rdna)	3d
Homatropine Bromhydrate	3
Human Coagulation Factor IX	3c
Human Coagulation Factor VIII	3
Human Cytomegalovirus Immunoglobulin For Intravenous Administration	3
Hydrochlorotiazide	3
Hydrochlorotiazide + Spironolactone	3
Hydrocortisone	3
Hydrocortisone + Neomycin + Cloramfenicol	1
Hydroxichloroquine Sulphate	1
Hydroxocobalamin	3
Hydroxyprogesterone Caproate	3
Ibuprofen	2d,3d
Icodextrin + Sodium Chloride + Sodium Lactate + Calcium Chloride + Magnesium Chloride	3b
Idebenone	3
Idroxine Hydrochloride	2,3
Imatinib	2c,3c
Imiglucerase	3c
Imipenem + Cilastatin	1
Imipramine Hydrochloride	2,3
Indapamide	3
Indinavir	3a
Indomethacin	2,3
Indomethacin + Caffeine + Proclorperazina	2,3,4
Infliximab	3b
Inosine Pranobex	3
Irbesartan + Diuretics	2e,3e
Irbesartan	2
Iron Sucrose Injection	3
Isoniazid + Ethambutol + Pyridoxine	3
Isoniazid	3
Isosorbide Dinitrate	3

Drugs	ADR numbers
Isosorbide Mononitrate	3e
Isotretinoin	4e
Isoxsuprine Hydrochloride	3
Isradipine	3
Itraconazole	3c
Ketazolam	3
Ketoconazole	3
Ketoprofen	2,3e
Ketorolac Tromethamine	3,4
Ketotifen	3
Lacidipine	3
Lamivudine	3
Lamotrigine	3
Lansoprazole	3
Leflunomide	3b
Lercanidipine Hydrochloride	3b
Lertapenem	3c
Letrozole	3b
Leuprorelin Acetate	3
Levetiracetam	3b
Levobupivacaine Hydrochloride	3b
Levodopa + Benserazide	3
Levodopa + Carbidopa	3c
Levodopa + Carbidopa + Entacapone	3c
Levodropropizine	3
Levofloxacin	3c,4e
Levonorgestrel	3b
Levosimendan	3b
Lidocaine + Adrenaline	3
Lidocaine + Cetrimonium Bromide	3
Lidocaine + Hydrocortisone	3
Lidocaine + Nor Adrenaline	3
Lidocaine Hydrochloride	3
Lincomycin Hydrochloride	2e,3e
Linezolid	2c,3c
Lisinopril	3b
Lisinopril+ Diuretics	3b
Lisuride Maleate	3e

Drugs	*ADR numbers*
Lodoxamide	3
Lomefloxacin Hydrochloride	1b,2b,3b
Loperamide Hydrochloride	3e
Lopinavir + Ritonavir	3d
Lorazepam	3b
Lormetazepam	3
Losartan Potassium	3b
Losartan Potassium + Diuretics	3b
Lysine Acetyl Salicylate	1b,2b,3b
Manidipine Hydrochloride	3
Measles, Mumps And Rubella Virus Vaccine Live Attenuated	1e
Meclofenamate Sodium	2,3
Medroxyprogesterone + Estrogens Conjugated	3
Medroxyprogesterone Acetate	3
Mefenamic Acid	2,3
Mefloquine	2,3b
Megestrol Acetate	3
Meloxicam	2c,3c
Memantine Hydrochloride	3b
Meningococcal Acwy Vaccine	3
Meningococcal Group C Polysaccharide Conjugate Vaccine	3e
Mepivacaine + Adrenaline	2,3
Mepivacaine Hydrochloride	2,3
Meprobamate	3
Metformin + Glybenclamide	3
Metformin Hydrochloride	3b
Methadone Hydrochloride	3b
Methyl Dopa + Hydrochlorotiazide	3e
Methyl Dopa	3
Methylergometrine Maleate	2e,3e
Methylpranolol + Pilocarpine Hydrochloride	3
Methylprednisolone	3
Methylprednisolone + Lidocaine	3
Metilphenidate Hydrochloride	3
Metixene Hydrochloride	3
Metoprolol + Diuretics	3e
Metoprolol Tartrate	3b
Metotrexate	3

Drugs	***ADR numbers***
Metronidazole	3e
Mexiletine Hydrochloride	3d
Mianserin Hydrochloride	2,3
Midazolam	3e
Midodrine Hydrochloride	3
Miglustat	3a
Minocycline	1,3d
Mirtazapine	3b
Misoprostol	3
Modafinil	3c
Moexipril + Diuretics	2d,3d
Moexipril Hydrochloride	2e,3e
Montelukast	3d
Moroctocog Alfa	3
Morphine Hydrochloride	3
Morphine Hydrochloride + Atropine Sulphate	3
Moxifloxacin	3b,4d
Moxonidine	3b
Muromonab - Cd3	1
Mycophenolic Acid	3b
Nabumetone	2d,3d
Nadolol	3e
Naltrexone Hydrochloride	3b
Naproxen	2b,3d
Natalizumab	3b
Nebivolol	3b
Neomycin + Antibiotics	1
Neomycin + Corticosteroid	1
Neomycin + Dexamethasone + Gramicidin + Tetryzoline	1
Neomycin + Dexamethasone +Phenylephrine	1
Neomycin + Fluocinolone Acetonide	1
Neomycin Sulphate	1
Neostigmine Methylsulfate	3d
Netilmicin	1e
Nicardipine Hydrochloride	2,3e
Nicergoline	3d
Niclosamide	3
Nicotine Drug Facts	2,3b

Drugs	*ADR numbers*
Nifedipine	3d
Nifedipine + Atenolol	3
Nimesulide	3c,4e
Nimesulide Beta – Dex	3e,4e
Nisoldipine	3
Nitrazepam	3
Nitroglycerin	3
Nizatidine	3
Nordazepam	3
Norethisterone + Estradiol	3
Norethisterone Acetate	3
Norethisterone	3
Norfloxacin	2e,3b,4e
Nortriptyline	2,3
Octatropine Methyl Bromide and Diazepam	3d
Ofloxacin	3e,4e
Olanzapine	3b
Olmesartan Medoxomil + Diuretics	3b
Olmesartan Medoxomil	3e
Olopatadine	3c
Omalizumab	3c
Omega-3 Acid Ethyl Esters	3
Omeprazole	3c
Ondansetrone	3d
Oral Cholera Vaccine	3d
Orphenadrine Hydrochloride	3
Oseltamivir	3b,4b
Otilonio Bromide	3
Otilonio Bromide + Diazepam	3e
Oxaliplatin	1c
Oxaprozin	2e,3e,4e
Oxazepam	3
Oxcarbazepine	3b
Oxibutynin Hydrochloride	3
Oxprenolol + Diuretics	3
Oxycodone Hydrochloride	3c
Palonosetron	2c,3b
Pamidronate	3c

Drugs	ADR numbers
Pantoprazole	3d
Paracetamol + Chlorphenamine	2,3
Paracetamol + Codeine Phosphate	3
Parathyroid Hormone	3b
Paricalcitol	3c
Paromomycin Sulphate	1e
Paroxetine	3b
Pefloxacin Mesylate	3
Pegaptanib Sodium	1c,3c
Pegvisomant	3b
Pentamidine Isethionate	3
Pentazocine	3b
Pentoxifylline	3
Pergolide	3a
Perindopril	3b
Perindopril + Diuretics	3c
Pethidine Hydrochloride	3
Phenobarbital	3
Phenytoin	3
Phenytoin Sodium	3e
Pilocarpine Hydrochloride	3b
Pindolol	3b
Pioglitazone + Metformin	3
Pioglitazone	3b
Pipemidic Acid	3
Piperazine	3
Piretanide	3
Piroxicam	2d,3d
Pizotifen	3
Polimyxyn B Sulphate + Neomycin Sulphate + Lidocaine Hydrochloride+ Hydrocortisone	1
Polymyxin B Sulphate + Neomycin Sulphate + Lidocaine Hydrochloride	1
Polymyxin	1
Posaconazole	3c,4d
Pramipexole	3b
Prasterone + Estradiol Valerate	3d
Pravastatin Sodium	3d

Drugs	*ADR numbers*
Prazepam	3
Prednisolone + Neomycin	1
Pregabalin	3a,4d
Prifinium Bromide	3
Primidone	3e
Progesterone	3d
Progestogen Oral Contraceptive	3
Proguanil Hydrochloride + Atovaquone	3
Propafenone Hydrochloride	3e
Propantheline Bromide	3d
Propofol	3
Propranolol Hydrochloride	3
Propyphenazone + Butalbital + Caffeine	3
Propyphenazone + Codeine	3d
Pyrantel Pamoate	3
Pyrimethamine + Sulfamethoperazine	2,3
Quetiapine	3a
Quinapril + Diuretics	3b
Quinapril	3b
Quinine	2,4
Quinupristin + Dalfopristin	3c
Rabbit Anti-Human Thymocyte Immunoglobulin	3
Rabeprazole Sodium	3b
Ramipril	3d
Ramipril + Diuretics	3d
Ranitidine	3d
Raubasine	3d
Reboxetine	3b
Remifentanil	3
Resagiline	3b
Reserpine + Chlorthalidone	3
Reserpine + Dihydroergocristine + Clopamide	3
Ribavirin	2b,3b
Rifampicin	3
Rifampicin + Isoniazid	3
Riluzole	3c
Risedronate	2,3
Risperidone	3c

Drugs	ADR numbers
Ritonavir	3b
Rivastigmine	3a
Rizatriptan	3b
Ropinirole	3b
Rosiglitazone Maleate	3b
Rosuvastatin	3b
Roxatidine Acetate Hydrochloride	3e
Roxithromycin	3e
Rufloxacin Hydrochloride	3b
Salmeterol	3
Salmon Calcitonin	3c
Salt Morphine	3d
Saquinavir	3
Scopolamine Hydrobromide	3d
Scopolamine Methylbromide/ Diazepam	3
Selegiline Hydrochloride	3b
Sertraline	3a
Sildenafil	3b
Simvastatin + Ezetimibe	3d
Simvastatin	3d
Sodium Neridronate	3b
Sodium Nitroprusside	3
Sodium Oxybate	3b
Sodium Stibogluconate	3
Somatostatin	3
Sorafenib	2b
Sotalol Hydrochloride	3b
Spectinomycin Hydrochloride	3
Stavudine	3b
Streptomycin	1
Sucralfate	3c
Sulfadiazine	2,3
Sulfametoxazolo + Trimethoprim	2e,3e
Sulfasalazine	2d,3d
Sulindac	2b,3b
Sumatriptan	3b
Sunitinib	3b
Tacrolimus	3b,4b

Drugs	***ADR numbers***
Tadalafil	3
Tamsulosin Hydrochloride	3b
Teicoplanin	1e,2e,3e
Telithromycin	3c
Telmisartan + Diuretics	3b
Telmisartan	3c
Temazepam	3
Tenofovir Disoproxil	3a
Tenoxicam	2,3c
Terazosin	3b
Terbinafine	3
Teriparatide	3b
Terlipressin	3
Tetanus Vaccine	3e
Thiamine + Pyridoxine +Hydroxocobalamin	3
Thiopental Sodium	3
Thyrotropin Alfa	3b
Tiagabine	3a
Tiaprofenic Acid	2,3
Tibolone	3e
Ticlopidine Hydrochloride	3
Tigecicline	3b
Timolol + Pilocarpine Hydrochloride	2
Timolol Maleate	2,3
Tinidazole + Nystatin	3
Tinidazole	3
Tiotropium	3c
Tipranavir	3c
Tizanidine	3
Tobramycin	1
Tobramycin + Dexamethasone	1
Topiramate	3b
Toremifene	3d
Torsemide	1e,2e
Tramadol	3a
Trandolapril	3
Trandolapril + Calcium Channel Blockers	3b
Tranexamic Acid	3

Drugs	***ADR numbers***
Tranylcypromine + Trifluoperazine	3
Trapidil	3e
Trastuzumab	3b
Trazodone Hydrochloride	2e,3e
Tretinoin	3a,4a
Triamcinolone	3
Triazolam	3
Trihexyphenidyl Hydrochloride	3
Trimetazidine Dihydrochloride	3e
Trimipramine	2b,3b
Triptorelin	3
Tropicamide	3
Tropisetron	3
Urapidil Hydrochloride	3e
Valacyclovir	3c
Valgancyclovir	3b
Valsartan + Diuretics	2c,3d
Vancomycin	1d
Vardenafil	3b
Varenicicline	2,3
Varicella Virus Vaccine Live	3e
Venlafaxine	2b,3b
Verapamil Hydrochloride	3b
Vigabatrin	3
Viminol-P-Hydroxybenzoate	3e
Vinblastine Sulphate	1d
Vincristine Sulphate	1
Vindesine Sulphate	1
Vinorelbine	1
Voriconazole	2d,3b,4d
Warfarin Sodium	3d
Zaleplon	3c,4c
Zidovudine	3
Zidovudine + Lamivudine	3d
Zoledronate	3c
Zolmitriptan	3b
Zolpidem Tartrate	3,4
Zonisamide	3a

Drugs	***ADR numbers***
Zopiclone	3

Note: This table is not a complete list of ototoxic medicines. There may be others, and patients and prescribers should be aware that many drugs have off-label uses.

ANNEX G. POTENTIALLY OVERLAPPING TOXICITIES OF ANTIRETROVIRALS AND ANTI-TUBERCULOSIS AGENTS

Potentially Overlapping Toxicities of Antiretovirals and Anti-Tuberculosis Agents [3,102,103]

Potential Toxicity	Antiretroviral therapy	Anti-tuberculosis therapy
Peripheral neuropathy	stavudine didanosine	cycloserine/terizidone isoniazid ethambutol fluoroquinolones streptomycin kanamycin amikacin capreomycin viomycin ethionamide/prothionamide linezolid
Psychiatric symptoms	efavirenz	cycloserine/terizidone isoniazid fluoroquinolones ethionamide/prothionamide
Hepatitis	nevirapine ritonavir-boosted protease inhibitors efavirenz etravirine maraviroc	pyrazinamide isoniazid rifampicin/rifabutin *p*-aminosalicylic acid fluoroquinolones bedaquiline
Gastrointestinal intolerance	zidovudine protease inhibitors didanosine	ethionamide/prothionamide *p*-aminosalicylic acid pyrazinamide isoniazid rifampicin ethambutol clofazimine bedaquiline
Renal toxicity	tenofofvir indinavir	streptomycin kanamycin capreomycin amikacin viomycin rifampicin
Bone marrow toxicity	zidovudine	linezolid rifampicin/rifabutin
Lactic acidosis	stavudine didanosine zidovudine	linezolid
Stevens-Johnson syndrome	nevirapine efavirenz	thioacetazone cycloserine/terizidone

Potential Toxicity	Antiretroviral therapy	Anti-tuberculosis therapy
	etravirine	linezolid ethambutol streptomycin
Arrhythmias/QT prolongation	atazanavir/ritonavir saquinavir/ritonavir lopinavir/ritonavir	fluoroquinolones bedaquiline
Rash/pruritus	nevirapine efavirenz etravirine abacavir	rifampicin/rifabutin pyrazinamide

ANNEX H. TYRAMINE- AND HISTAMINE-CONTAINING FOODS

Tyramine and Histamine Containing Foods [114]

TYPE OF FOOD	FOODS ALLOWED	FOODS RESTRICTED
MILK AND MILK PRODUCTS	• Plain pasteurized milk from any animal (most of us do best with Skim or Lactose Free Milk, Coconut Milk, or Goat Milk) • Milk products made without microbial cultures such as: - - Panir - Mascarpone* - Ricotta* **Read the labels carefully to ensure no microbial cultures are included* • Ice cream free from any restricted ingredient • Cream	• Fermented milk products from any animal, such as: - - Cheese of all types - Cottage cheese - Processed cheeses - Cream cheese - Sour cream - Buttermilk - Yogurt - Kefir • And any other fermented milk products • Foods made with milk products other than those allowed
GRAINS, CEREALS, BREADS, & OTHER BAKED PRODUCTS	• Any pure, unbleached flour or grain • Baking-powder-leavened products such as - Biscuits - Quick breads - Soda bread - Scones - Muffins • Homemade or purchased baked goods made with allowed ingredients • Crackers without yeast, such as Triscuits™ • Breakfast cereals with allowed ingredients including any grain without artificial colours or preservatives	• Yeast-risen breads and baked products such as: - - Bread - Pizza Dough - Buns - Pita Bread - Croissants - English Muffins - Crumpets - Crackers With Yeast (Read Labels) Such As Ritz, Saltines • Products made with Restricted Ingredients, such as:- - Anise - Artificial Flavours and/or Colours - Bleached Flour - Cheese - Chocolate - Cinnamon

TYPE OF FOOD	FOODS ALLOWED	FOODS RESTRICTED
GRAINS, CEREALS, BREADS, & OTHER BAKED PRODUCTS ***continued…***		- Cloves - Cocoa - Margarine - Preservatives - Restricted Fruit Including Jams And Jellies Made With These Fruits • Baking Mixes • Dry Dessert Mixes • Any Food made with or cooked in Oils With hydrolyzed lecithin, BHA, BHT • Breakfast Cereals containing Restricted Ingredients
VEGETABLES	• All pure, fresh, or frozen vegetables and their juices except those in the "restricted" columns	• Potato • Avocado • Broad Beans • Green Beans • Eggplant (Aubergine) • Pumpkin • Sauerkraut • Spinach • Sweet Potato • Tomato • Over-ripe vegetables • Pickled vegetables • Packaged salad mixes • Packaged peeled vegetables • Most commercial salad dressings with vinegar, artificial colour, flavour, or preservatives
FRUIT	• All pure, fresh, or frozen fruit and their juices except those in the "restricted" column • Allowed fruits include: - - Melons such as cantaloupe (rock melon), honeydew, watermelon • Other fruits such as: - - Apple - Pear - Fig - Kiwi - Mango - Passion fruit - Rhubarb - Starfruit - Longans - Lychees • Fruit dishes made with allowed ingredients	• Lemon AND/OR Lime • The following fresh, frozen, and canned fruits and their juices:- - **Berries** such as cranberries, blueberries, blackberries, gooseberries, loganberries, raspberries and strawberries - **Stone fruits** such as apricots, cherries, nectarines, peaches, plums, prunes - **Citrus fruits** such as oranges and grapefruits - **Other fruits** such as bananas, grapes, currants, dates, papayas (pawpaws), pineapples, raisins • Fruit dishes, jams, or juices made with restricted ingredients • Any over-ripe fruit

TYPE OF FOOD	FOODS ALLOWED	FOODS RESTRICTED
MEAT, POULTRY, AND FISH	• Pure, freshly cooked meat or poultry except those in the "restricted" column • Any freshly caught, gutted, and cooked fish EXCEPT those in "restricted" • If raw meat is not cooked immediately, store it in the freezer • Cooked meat uneaten should be immediately frozen. Histamine rises while cooked foods are resting or refrigerated. Freezing halts histamine rising in cooked foods.	• ALL Shellfish, roe, and caviar • Any fish that has not been gutted and cooked immediately after being caught • Commercially canned fish • All processed meats such as:- - Pepperoni - Salami - Bologna - Weiners (hot dog) • All pickled meats, eggs, fish
LEGUMES	• All plain legumes (except those in the "restricted" list) such as: – - Lima beans • Dried beans and peas, such as: - - Chickpeas (Garbanzo Beans) - Pinto Beans - White Beans - Navy Beans - Black-Eyed Peas - Black Beans - Lentils (Red, Yellow, Brown) - Split Peas - Peanuts - Pure Peanut Butter	• Green peas • Sugar or Sweet peas • Red beans • Soybeans • Tofu • Fermented soy products such as - - Soy Sauce - Fermented Bean Curd - Soybean Paste - Shrimp Paste - Chili Soybean Paste - Miso
NUTS AND SEEDS	• All plain nuts and seeds and their flours and butters *EXCEPT those in the "restricted" column*	• Walnuts • Pecans
FATS AND OILS	• All cold-pressed oils, such as:- - Extra Virgin Olive Oil - Coconut oil - Flaxseed oil - Sunflower oil - Jojoba oil	• Processed oils containing preservatives such as BHA and BHT
SPICES AND HERBS	• All fresh, frozen, or dried herbs and spices *EXCEPT those in the "restricted" column*	• Anise • Cinnamon • Cloves • Curry Powder • Hot Paprika (Cayenne) • Nutmeg • Seasoning Packets With Restricted Ingredients • Commercial Packaged Foods Labeled With "Spices" Or "Flavoring"

TYPE OF FOOD	FOODS ALLOWED	FOODS RESTRICTED
SWEETS AND SWEETENERS	• Pasteurized Honey, Sugar • Icing Sugar • Maple Syrup • Corn Syrup • Pure Jams, Jellies, Marmalade, And Conserves Made With Allowed Ingredients • Plain, Artificial Sweeteners • Homemade Sweets With Allowed Ingredients	• Unpasteurized Honey • Chocolate • Cocoa Beans • Cocoa • Flavoured Syrups • Prepared Dessert Fillings • Prepared Icings, Frostings • Spreads With Restricted Ingredients • Cake Decorations • Confectionery • Commercial Candies
BEVERAGES	• Plain Milk • Pure Juices Of Allowed Fruits And Vegetables • Plain And Carbonated Mineral Water • Coffee **not recommended due to tachycardia masto symptoms. Patients report Maxwell House coffee as less problematic than other brands.*	• Fruit Drinks And Cocktails With Restricted Ingredients • Cola Type Carbonated Drinks • Apple Cider • All Teas, Including Green Tea • All Alcoholic Beverages • Nonalcoholic Beers And Wines • All Drinks With "Flavor" Or "Spices" On The Label
OTHER	• Baking Powder • Baking Soda • Cream Of Tartar • Plain Gelatin • Homemade Relishes With Allowed Ingredients	• Baker's Yeast • All Vinegars • Prepared Pickles, Relishes, Ketchup, And Mustard Containing Vinegar • Flavoured Gelatin (eg. Jello) • Chocolate And Cocoa • Mincemeat • Yeasts Of The Species *Saccharomyces* • Brewer's Yeast • Nutritional Yeast • Yeast And Meat Extracts (eg.) Bovril, Marmite, Oxo, Vegemite

ANNEX I. MANAGING DRUG INTERACTIONS WITH ANTIRETROVIRALS AND RIFAMPICIN [115]

Table 2a. Recommendations for coadministering antiretroviral drugs with rifampin in adults – 2013

	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Non-nucleoside reverse transcriptase inhibitors			
Efavirenz	None; some clinicians may increase the dose to 800mg in persons weighing >50kg.	No change (600 mg/day)	Effect on efavirenz AUC is highly variable. Efavirenz should not be used during the 1st trimester of pregnancy.
Nevirapine	Initiate at a dose of 200 mg twice daily rather than 200 mg once daily (use the same maintenance dose of 200 mg twice daily)	No change (600 mg/day)	Efavirenz is preferred, but if nevirapine must be used, lead-in dosing at 200 mg once-daily should be avoided, as this may increase risk of virologic failure. Because of this risk, monitoring of adherence and viral load is recommended. If available, consider therapeutic drug monitoring.
Rilpivirine	Rifampin and rilpivirine should not be used together		Rilpivirine AUC ↓ by 80%, Cmin decreased 89%
Etravirine	Etravirine and rifampin should not be used together		Marked decrease in etravirine predicted, based on data on the interaction with rifabutin
Single protease inhibitors			
	Recommended change in dose of antiretroviral drug	**Recommended change in dose of rifampin**	**Comments**
Atazanavir	Rifampin and atazanavir should not be used together		Atazanavir AUC ↓ by >95%. Increasing the dose to 300 mg twice daily or 400 mg twice daily still resulted in subtherapeutic atazanavir concentrations.
Ritonavir-boosted protease inhibitors			
	Recommended change in dose of antiretroviral drug	**Recommended change in dose of rifampin**	**Comments**
Lopinavir / ritonavir (Kaletra™)	Lopinavir 800 mg plus ritonavir 200 mg twice daily (double dose)	No change (600 mg/day)	Use with caution; this combination resulted in hepatotoxicity in all adult healthy volunteers in an initial study. It was better-tolerated among adult patients already taking lopinavir/ritonavir based ART with increase to 600 mg/150 mg after one week, then 800 mg/200 mg one week later.
"Super-boosted" lopinavir / ritonavir (Kaletra™)	Lopinavir 400 mg plus ritonavir 400 mg twice daily (super boosting)	No change (600 mg/day)	Use with caution; this combination resulted in hepatotoxicity among adult healthy volunteers. It has not been adequately tested in patients with HIV.
Atazanavir / ritonavir	Rifampin and atazanavir/ritonavir should not be used together.		Atazanavir trough concentration ↓ by > 90%. Doubling the dose to 300/100 twice daily resulted in hepatotoxicity in healthy volunteers.
Darunavir / ritonavir	Rifampin and darunavir/ritonavir should not be used together		No drug interaction studies of darunavir and rifampin have been conducted.
Fosamprenavir/ ritonavir	Rifampin and fosamprenavir/ritonavir should not be used together		Fosamprenavir Cmax decreased by 70%, AUC decreased 82%, trough decreased 92%
Saquinavir / ritonavir	Rifampin and saquinavir/ritonavir should not be used together.		The combination of saquinavir (1000 mg twice-daily), ritonavir (100 mg twice-daily), and rifampin caused unacceptable rates of hepatotoxicity among healthy volunteers. In tuberculosis patients, 400/400 twice daily caused similar rates of hepatotoxicity.

Table 2b. Recommendations for coadministering antiretroviral drugs with rifampin in children – 2013

Antiretroviral drug regimen choices*	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
"Super-boosted" lopinavir / ritonavir + 2 NRTIs	Pediatric weight-adjusted dosing for lopinavir/ ritonavir* (Kaletra™) PLUS added ritonavir to reach mg to mg parity of lopinavir and ritonavir doses	No change	Preferred.
Zidovudine/lamivudine/ abacavir	None (standard pediatric weight-adjusted dosing*)	No change	Alternative for children <3 years
Efavirenz + 2 NRTIs	None (standard pediatric weight-adjusted dosing*)	No change	Efavirenz AUC ↓ by 20-30% on average, though effect is highly variable [illegible] alternative for children age 3-5 years. Careful monitoring of virologic response; therapeutic drug monitoring of efavirenz levels if available

* For pediatric dosing see: Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 11, 2011; pp 1-268. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf.

ANNEX J. MANAGING DRUG INTERACTIONS WITH ANTIRETROVIRALS AND RIFABUTIN [115]

Non-nucleoside reverse-transcriptase inhibitors			
	Antiretroviral dose change	**Rifabutin dose change**	**Comments**
Efavirenz	No change	↑ to 600 mg (daily or thrice-weekly)	If efavirenz is used, the rifamycin of choice is rifampin. Efavirenz reduces rifabutin concentrations, so if rifabutin is to be used, increasing rifabutin dose to 600 mg may compensate for the inducing effect of efavirenz. Employ caution as this strategy has not been tested among patients taking rifabutin daily or thrice-weekly. Efavirenz should not be used during the 1st trimester of pregnancy.
Nevirapine	No change	No change (300 mg daily)	Rifabutin and nevirapine AUC not significantly changed.
Rilpivirine	Rifabutin and rilpivirine should not be used together		Rilpivirine AUC ↓ by 46%; and Cmin ↓ by 49%.
Etravirine	No change	No change (300 mg daily)	No clinical experience; etravirine Cmin ↓ by 35% and rifabutin AUC reduced 17%; these changes are unlikely to be clinically relevant, so no dose adjustment is necessary. Since ritonavir-boosted darunavir and saquinavir also diminish etravirine concentrations, the combination of these boosted PIs, etravirine, and rifabutin is not recommended.
Single protease inhibitors			
	Antiretroviral dose change	**Rifabutin dose change**	**Comments**
Atazanavir	No change	↓ to 150 mg once daily	No published clinical experience.
Dual protease inhibitor combinations			
	Antiretroviral dose change	**Rifabutin dose change**	**Comments**
Lopinavir / itonavir (Kaletra™)	No change	↓ to 150 mg once daily	In patients with HIV taking lopinavir/ritonavir, 150 mg once daily of rifabutin produces favorable rifabutin pharmacokinetics. Clinical safety data are limited. Monitor closely for potential rifabutin toxicity – uveitis, hepatotoxicity, and neutropenia.
Fosamprenavir/ritonavir	No change	↓ to 150 mg once daily	In healthy volunteers, a dose of 150 mg every other day of rifabutin given together with standard dose boosted fosamprenavir resulted in an increase in amprenavir AUC and Cmax by 35% and no change in Cmin. Limited clinical data among patients with HIV. Monitor closely for uveitis, hepatotoxicity, and neutropenia.
Ritonavir (any dose) with saquinavir, indinavir, amprenavir, fos-amprenavir, atazanavir, tipranavir or darunavir	No change	↓ to 150 mg once daily	Rifabutin AUC ↑ and 25-O-des-acetyl rifabutin AUC ↑, by varying degrees. Monitor closely for uveitis, hepatotoxicity, and neutropenia.
CCR-5 receptor antagonists			
Maraviroc	No change	No change	No clinical experience; a significant interaction is unlikely, but this has not yet been studied
Integrase inhibitors			
Raltegravir	No change	No change	When given with standard-dose rifabutin (300 mg daily), raltegravir AUC increased 19%, C_{min} decreased 20%, and C_{max} increased 39%. These changes are unlikely to be clinically-significant.
Elvitegravir co-formulated with cobicistat, tenofovir, and emtricitabine (Stribild™)	Stribild™ and rifabutin should not be used together		When given with rifabutin 150 mg thrice-weekly, elvitegravir Cmin reduced 64%, cobicistat Cmin reduced 71%, and 25-O-desacetylrifabutin AUC increased 6-fold.

*Pediatric formulation and pharmacokinetic data are not available in children.

ANNEX K. DRUGS THAT PROLONG THE QT INTERVAL OR INDUCE TORSADES DE POINTES

Drugs That Prolong the QT Interval or Induce Torsades de Pointes[116]

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CREDIBLEMEDS®

Crediblemeds.org is your trusted partner providing reliable information on medicines. This is a combined list of drugs that CredibleMeds has concluded either 1) have a risk of TdP, 2) prolong QT and therefore have a possible risk of TdP or 3) have a risk of TdP under certain conditions such as overdose, drugdrug interactions or when administered to certain high-risk individuals (e.g. congenital long QT syndrome).

Generic Name	Brand Name
Alfuzosin	Uroxatral®
Amantadine	Symmetrel® and others
Amiodarone	Cordarone® and others
Amisulpride	Solian® and others
Amitriptyline	Elavil® (Discontinued 6/13) and others
Amoxapine	Asendin® and others
Anagrelide	Agrylin® and others
Apomorphine	Apokyn® and others
Aripiprazole	Abilify® and others
Arsenic trioxide	Trisenox®
Astemizole (Off US mkt)	Hismanal®
Atazanavir	Reyataz®
Azithromycin	Zithromax® and others
Bedaquiline	Sirturo®
Bepridil (Off US mkt)	Vascor®
Bortezomib	Velcade® and others
Bosutinib	Bosulif®
Chloral hydrate	Aquachloral® and others
Chloroquine	Aralen®
Chlorpromazine	Thorazine® and others
Ciprofloxacin	Cipro® and others
Cisapride (Off US mkt)	Propulsid®
Citalopram	Celexa® and others
Clarithromycin	Biaxin® and others
Clomipramine	Anafranil®
Clozapine	Clozaril® and others
Cocaine	Cocaine
Crizotinib	Xalkori®
Dabrafenib	Tafinlar®
Dasatinib	Sprycel®

Generic Name	Brand Name
Desipramine	Pertofrane® and others
Dexmedetomidine	Precedex® and others
Dihydroartemisinin+piperaquine	Eurartesim®
Diphenhydramine	Benadryl® and others
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Dolasetron	Anzemet®
Domperidone (Not on US mkt)	Motilium® and others
Doxepin	Sinequan® and others
Dronedarone	Multaq®
Droperidol	Inapsine® and others
Eribulin	Halaven®
Erythromycin	E.E.S.® and others
Escitalopram	Cipralex® and others
Famotidine	Pepcid® and others
Felbamate	Felbatol®
Fingolimod	Gilenya®
Flecainide	Tambocor® and others
Fluconazole	Diflucan® and others
Fluoxetine	Prozac® and others
Foscarnet	Foscavir®
Fosphenytoin	Cerebyx® and others
Furosemide (Frusemide)	Lasix® and others
Galantamine	Reminyl® and others
Gatifloxacin (Off US mkt)	Tequin®
Gemifloxacin	Factive®
Granisetron	Kytril® and others
Grepafloxacin (Off market worldwide)	Raxar®
Halofantrine	Halfan®
Haloperidol	Haldol® (US & UK) and others

Generic Name	Brand Name
Hydrochlorothiazide	Apo-Hydro® and others
Ibutilide	Corvert®
Iloperidone	Fanapt® and others
Imipramine (melipramine)	Tofranil®
Indapamide	Lozol® and others
Isradipine	Dynacirc®
Itraconazole	Sporanox® and others
Ivabradine (Not on US mkt)	Procoralan® and others
Ketoconazole	Nizoral® and others
Lapatinib	Tykerb® and others
Levofloxacin	Levaquin® and others
Levomethadyl (Off US mkt)	Orlaam®
Lithium	Eskalith® and others
Mesoridazine (Off US mkt)	Serentil®
Methadone	Dolophine® and others
Metronidazole	Flagyl® and many others
Mifepristone	Korlym® and others
Mirabegron	Myrbetriq®
Mirtazapine	Remeron
Moexipril/HCTZ	Uniretic® and others
Moxifloxacin	Avelox® and others
Nelfinavir	Viracept®
Nicardipine	Cardene®
Nilotinib	Tasigna®
Norfloxacin	Noroxin® and others
Nortriptyline	Pamelor® and others
Ofloxacin	Floxin®
Olanzapine	Zyprexa® and others
Ondansetron	Zofran® and others
Oxytocin	Pitocin® and others

If list is printed, check website for updates: www.crediblemeds.org •Please see Disclaimer and list continued

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CREDIBLEMEDS®

Crediblemeds.org is your trusted partner providing reliable information on medicines. This is a combined list of drugs that CredibleMeds has concluded either 1) have a risk of TdP, 2) prolong QT and therefore have a possible risk of TdP or 3) have a risk of TdP under certain conditions such as overdose, drugdrug interactions or when administered to certain high-risk individuals (e.g. congenital long QT syndrome).

Generic Name	Brand Name
Paliperidone	Invega® and others
Pantoprazole	Protonix® and others
Paroxetine	Paxil® and others
Pasireotide	Signifor®
Pazopanib	Votrient®
Pentamidine	Pentam®
Perflutren lipid microspheres	Definity®
Pimozide	Orap®
Piperaperone (Not on US Mkt)	Dipiperon (E.U) and others
Posaconazole	Noxafil® and others
Probucol (Off US mkt)	Lorelco®
Procainamide (Oral off US mkt)	Pronestyl® and others
Promethazine	Phenergan®
Protriptyline	Vivactil®
Quetiapine	Seroquel®
Quinidine	Quinaglute® and others
Quinine sulfate	Qualaquin®
Ranolazine	Ranexa® and others
Rilpivirine	Edurant® and others
Risperidone	Risperdal®
Ritonavir	Norvir®
Roxithromycin (Not on US Mkt)	Rulide® and others
Saquinavir	Invirase® (combo)
Sertindole (Not on US mkt)	Serdolect® and others
Sertraline	Zoloft® and others
Sevoflurane	Ulane® and others

Generic Name	Brand Name
Solifenacin	VESIcare®
Sorafenib	Nexavar®
Sotalol	Betapace® and others
Sparfloxacin (Off US mkt)	Zagam®
Sulpiride (Not on US Mkt.)	Dogmatil® and others
Sunitinib	Sutent®
Tacrolimus	Prograf® and others
Tamoxifen	Nolvadex® (discontinued 6/13) and others
Telaprevir	Incivek® and others
Telavancin	Vibativ®
Telithromycin	Ketek®
Terfenadine (Off US mkt)	Seldane®
Tetrabenazine (Orphan drug in US)	Nitoman® and others
Thioridazine	Mellaril® and others
Tizanidine	Zanaflex® and others
Tolterodine	Detrol® and others
Toremifene	Fareston®
Trazodone	Desyrel® (discontinued 6/13) and others
Trimethoprim-Sulfa	Septra® and others
Trimipramine	Surmontil® and others
Vandetanib	Caprelsa®
Vardenafil	Levitra®
Vemurafenib	Zelboraf®
Venlafaxine	Effexor® and others
Voriconazole	VFend®
Vorinostat	Zolinza®
Ziprasidone	Geodon® and others

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checkingthe website at crediblemeds.org for the most up-todate information. There may be many additional brand names that are not listed on this form.

Disclaimer and Waiver: The information presented is intended solely for the purpose of providing general information about health-related matters. It is not intended for any other purpose, including but not limited to medical advice and/or treatment, nor is it intended to substitute for the users relationships with their own health care providers. To that extent, by use of this website and the information it contains, the user affirms the understanding of the purpose and releases AZCERT, Inc. from any claims arising out of his/her use of the website and its lists. The absence of drugs from these lists should not be considered an indication that they are free of risk of QT prolongation or TdP. Many medicines have not been tested for this risk in patients, especially those with congenital long QT syndrome.

Generated: October 21, 2014. List last revised: September 26, 2014

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