

Clinical standards for the management of adverse effects during treatment for TB

SUMMARY

BACKGROUND: Adverse effects (AE) to TB treatment cause morbidity, mortality and treatment interruption. The aim of these clinical standards is to encourage best practise for the diagnosis and management of AE.

METHODS: 65/81 invited experts participated in a Delphi process using a 5-point Likert scale to score draft standards.

RESULTS: We identified eight clinical standards. Each person commencing treatment for TB should: Standard 1, be counselled regarding AE before and during treatment; Standard 2, be evaluated for factors that might increase AE risk with regular review to actively identify and manage these; Standard 3, when AE occur, carefully assessed and possible allergic or hypersensitivity reactions considered; Standard 4, receive appropriate care to minimise morbidity and mortality associated

with AE; Standard 5, be restarted on TB drugs after a serious AE according to a standardised protocol that includes active drug safety monitoring. In addition: Standard 6, healthcare workers should be trained on AE including how to counsel people undertaking TB treatment, as well as active AE monitoring and management; Standard 7, there should be active AE monitoring and reporting for all new TB drugs and regimens; and Standard 8, knowledge gaps identified from active AE monitoring should be systematically addressed through clinical research.

CONCLUSION: These standards provide a person-centred, consensus-based approach to minimise the impact of AE during TB treatment.

KEY WORDS: tuberculosis; adverse effects; management; toxicity; drugs; safety

TB disease requires treatment with a combination of drugs over several months.^{1–3} Adverse effects (AE) are associated with poor treatment adherence, treatment interruption and treatment failure.^{4–8} Early identification and management of AE is essential to avoid the development of resistance or disease progression. In some cases, the drug and or regimen may need to be permanently discontinued and alternative drugs used. AE occur in 25–75% of people receiving treatment for TB.^{9–11} The incidence of AE varies across studies due to heterogeneity in definitions of an AE, reporting thresholds/criteria for defining causality, study design,^{12,13} population characteristics (including concomitant medications), medication formulations and administration regimens. When new symptoms or laboratory abnormalities appear during treatment, differentiation is needed between AE, a new disease process, or a paradoxical reaction (e.g., immune reconstitution inflammatory syndrome [IRIS]). When AE are thought likely to be related to TB drugs, the use of combination therapy may make it difficult to ascertain which drug in a regimen is responsible. There is limited evidence for strategies to manage AE during treatment for TB. The clinical standards presented here are based on expert opinion and the best available evidence available. New evidence will be considered as it emerges with periodic future updates planned. The manuscript also highlights key research needs for optimising AE management during

the treatment of drug susceptible (DS-) and drug-resistant (DR-) TB.

The IJTLD Clinical Standards for Lung Health complement existing WHO or other guidelines and integrate their recommendations to focus on person-centred care. The Standards are broad principles formulated with the understanding that they may have to be adapted and contextualised due to legal, organisational or economic reasons in diverse settings. We acknowledge differences in capacity but hope that these clinical standards will help to shape service development and facilitate access to additional resources to improve treatment outcomes for people with TB.

AIM OF THE CLINICAL STANDARDS

This consensus-based document describes the following standards:

Each person commencing treatment for TB should:

- 1 Be counselled regarding AE before and during treatment for TB.
- 2 Be evaluated for factors that might increase AE risk with regular review to actively identify and manage these.
- 3 When AE occur, be carefully assessed and possible allergic or hypersensitivity reactions considered.
- 4 Receive appropriate care to minimise the morbidity and mortality associated with AE.
- 5 Be restarted on TB drugs after a serious AE

according to a standardised protocol that includes active drug safety monitoring (aDSM);

In addition:

- 6 Healthcare workers (HCW) should be trained on AE including how to counsel people undertaking TB treatment, as well as active AE monitoring and management.
- 7 There should be active AE monitoring and reporting for all new TB drugs and regimens.
- 8 Knowledge gaps identified from active AE monitoring should be systematically addressed through clinical research.

Some elements relate to previously published standards^{14,15} and these are highlighted when relevant (e.g., therapeutic drug monitoring is discussed in detail in 'Clinical standards for the dosing and management of TB drugs'¹⁴).

METHODS

A panel of 81 global experts representing the main scientific societies, associations and groups active in TB was identified, and invited to participate. Two declined and 14 did not respond. The 65 respondents included TB clinicians ($n=37$), TB public health ($n=4$), TB paediatricians ($n=8$), TB pharmacologists ($n=13$), a methodologist ($n=1$), an immunologist ($n=1$) and an epidemiologist ($n=1$). Respondents were asked to comment using a Delphi process on an initial draft including eight standards developed by a core coordination team. A 5-point Likert scale was used (5: high agreement; 1: low agreement). At the first Delphi round, agreement was high, with a median value of 5 for all eight standards. Based on substantial agreement on the standards, a draft document was jointly developed by the coordination team. After two rounds of revisions, the document was approved by consensus (100% agreement).

STANDARD 1

Each person commencing treatment for TB should be counselled regarding AE before and during treatment for TB

Providing education and counselling to all people diagnosed with TB before and during their treatment is a core component of national and international treatment guidelines.^{15–17} Education and counselling should be person-centred and tailored appropriately considering the person's current health, health literacy, language, culture and planned treatment regimen^{18,19} Clinicians should consider including people from the person's support network (e.g., nominated family or friends). Health education and counselling is intended to empower people with TB to understand the disease, the benefits, and risks of the treatment and the importance of

treatment adherence, emphasising the benefits of optimal treatment to both the person with TB and their family and community. Education and counselling should cover the importance of regular clinic assessment for early detection of AE, non-harmful drug effects (e.g. red/orange discoloration of body fluids by rifampicin,²⁰ how to deal with symptoms including when and how to contact the treating team to report these and seek medical attention. Education and counselling should also include circumstances in which self-cessation of drugs should occur pending review, such as signs and symptoms of potentially life-threatening and/or irreversible AE (e.g., hepatotoxicity, visual impairment, or severe cutaneous AE). Educational materials about AE should be developed internationally and adapted locally involving stakeholders such as HCW (e.g., nurses, treating physicians, pharmacists), people affected by TB and their caregivers. Materials should be person-centred, include information about AE (as outlined in the previous paragraph) as well as general information about TB, the importance of treatment, adherence, and disease prevention. Digital resources may improve access to information and communication between HCW and people undergoing treatment for TB, including regarding AE.²¹

STANDARD 2

Each person commencing treatment for TB should be evaluated for factors that might increase AE risk with regular review to actively identify and manage these

Demographic, medical, social and behavioural characteristics have been associated with increased risk of AE during treatment for TB (Table 1).¹⁴ The association with increased risk may be related to factors such as age, genetics or alcohol use on drug pharmacokinetics. Other factors may cause morbidity or toxicity that overlap with AE, such as other causes of hepatitis and peripheral neuropathy (e.g., diabetes, substance use disorder). Pre-treatment clinical assessment should include evaluation for these risk factors. Identification of a risk factor should prompt clinicians to optimise management (e.g., nutrition, control of diabetes) and to follow up more closely/frequently for active monitoring. Baseline laboratory testing (before starting treatment) may identify additional risk factors and provide a reference to enable recognition of new changes that occur during treatment. All people with TB should undergo testing for HIV. Other recommended baseline tests if feasible and/or clinically indicated include liver function tests (LFT), kidney function (serum creatinine) and complete blood count and pregnancy test if relevant. Tests for hepatitis B virus (HBV) and hepatitis C virus (HCV) should be performed if there are epidemiologic risk factors or baseline LFT derangement.

Table 1 Risk factors for the development of AE during treatment for TB.

| Risk factor | Comments and references |
|---|---|
| Older age | Associated with hepatotoxicity ^{27,62,63} May be due to changes in body composition, reduced enzymatic activity and renal insufficiency ⁴³ |
| Family/personal history of AE, atopy or allergy | Associated with cutaneous AE and hypersensitivity ⁶⁴ |
| HIV | Data are mixed and systematic evidence is lacking, but trends for increased AE among people living with HIV, especially hepatotoxicity and hypersensitivity reactions have been described ^{1,65–67} Cotrimoxazole may play a role in toxicity ⁶⁸ |
| Viral hepatitis | Associated with hypothyroidism in children prescribed ETH and PAS ⁶⁹ Associated with increased hepatotoxicity ^{70–72} |
| Substance use disorders | Alcohol use was associated with higher risks of treatment interruption and unfavourable outcome ^{7,73} Smoking in combination with alcohol may further increase risk ^{74,75} |
| DM | Associated with four-fold or more increase in AE ⁷⁶ Increased risk of peripheral neuropathy/ocular neuropathy ^{13,77} In MDR-TB treatment, increased nephrotoxicity and hypothyroidism risk (older regimens) ^{73,78} |
| Renal impairment | Associated with ethambutol and CS ¹³ /terizidone, aminoglycoside and fluoroquinolone toxicity due to increased drug concentrations ^{73,79} |
| Pregnancy, early post-partum | Increased risk of hepatotoxicity, neuropathy ⁸⁰ |
| Low weight/BMI | Variable association of low weight with increased rates of AE ⁸¹ especially hepatotoxicity ⁸² |
| Malnutrition, hypoalbuminemia, anaemia | Malnutrition associated with increased risk of hepatotoxicity ^{83–86} Interferes with drug clearance which can lead to accumulation of drugs in the body and AE Anaemia was an independent risk factor associated with AE ^{87,88} Hypoalbuminemia was an independent risk factor for TB drug-induced hepatotoxicity, ⁸⁹ including in children ⁹⁰ |
| More advanced TB | Extrapulmonary TB in either people with TB or TB-HIV was an independent risk factor associated with AE ⁹¹ |
| MDR-TB | Higher rates of AE have been reported compared to treatment of DS-TB but many based on older regimens ^{49, 60} Relatively higher incidence of AE leading to medication discontinuation associated with use of injectable agents, CPM, PAS and also linezolid (lower risk with FQ, BDQ, CFZ) ⁹² |
| Concomitant medications/ polypharmacy | Drug interactions and overlapping AEs may be important Common in individuals with co-infections or dual disease, e.g., TB-HIV or TB-DM ^{93–96} Pharmacokinetics and/or pharmacodynamic drug–drug interactions may result in overlapping adverse drug reactions or synergy in the occurrence of AE ^{97,98} |

AE = adverse event(s); ETH = ethionamide; PAS = para-aminosalicylic acid; CS = cycloserine; DM = diabetes mellitus; MDR-TB = multidrug resistant TB; BMI = body mass index; DS-TB = drug-susceptible TB; CPM = capreomycin; BDQ = bedaquiline; CFZ = clofazimine.

The effect of pharmacogenomics (i.e., the way an individual's genetic makeup affects the response to therapeutic drugs) is more difficult to assess. Variations (polymorphisms) in the *N*-acetyltransferase 2 (*NAT2*) gene, responsible for the metabolism of isoniazid was significantly associated with the likelihood of experiencing TB drug related hepatotoxicity.²² A randomised controlled trial demonstrated that the risk of drug-induced liver injury due to isoniazid could be reduced in adult slow acetylators by a dose reduction to 2.5 mg/kg/day without early treatment failure.²³

In some cases where an AE is unable to be reliably detected or reported, an alternative agent may need to be substituted. For example, in the case of diminished visual acuity or colour blindness the clinician may decide not to use ethambutol (EMB) and/or linezolid, due to the as risk of optic neuropathy.

For all persons with TB, active surveillance for AE should occur according to a defined framework, including systematic and structured clinical assessment. As per Standard 1, pre-treatment counselling and education regarding when and how to access attention for symptoms that may appear during treatment and that may indicate the development of AE should be reinforced. The development of service structures that enables timely access to HCW review is

also important. Assessment of new symptoms should always include consideration of and assessment for other causes, e.g., viral hepatitis in the case of hepatitis. Periodic laboratory testing may help to identify early AE, but cost-benefit assessments have not been done.^{24,25} Repeat laboratory testing may be warranted during the intensive phase of treatment (when most AE occur) and is important if baseline tests were abnormal, in the case of risk factors (e.g., underlying liver or renal/kidney disease, concomitant medications), pregnancy/early post-partum, ongoing treatment with pyrazinamide (beyond intensive phase) or at any time in the case of presumed AE (Table 2).

In assessing AE, attention should be given to recognising reactions in which morbidity is likely and for which drug therapy may need to be withheld (Table 3). This will vary on a case-by-case basis depending on comorbidities and severity of TB disease. Use of first-line therapy for TB is associated with raised liver transaminases in about 20% of those treated, which spontaneously resolves over days to weeks without alteration in therapy.²⁶ All individual agents have been associated with hepatotoxicity aside from EMB.²⁷ Transaminase increases of over five times the upper normal limit (ULN) or three times the ULN in the presence of symptoms suggestive of hepatic toxicity (e.g., nausea, vomiting) should lead

Table 2 Assessment and monitoring for AE using active drug safety monitoring*.

| | Targeted clinical assessment | Tests | Additional assessments only if second-line drugs are used |
|------------------|--|--|--|
| Before treatment | <ul style="list-style-type: none"> • Presence of risk factors (see Table 1) • Extent of TB disease/dissemination • Pregnancy/breast feeding | <ul style="list-style-type: none"> • Colour vision,[†] visual acuity • Pregnancy (urinary/serum HCG) • Mental health/neuropsychiatric assessment[‡] • HIV • LFT (ALT), creatinine, CBC • Hepatitis B/C serology • HbA1c | <ul style="list-style-type: none"> • If QT prolonging agents (FQs, CFZ, BDQ, DLM), measure electrolytes (K⁺, Ca⁺⁺, Mg⁺⁺) and ECG • If DLM, measure albumin • If ETH or PAS, measure TSH • If aminoglycoside/CPM (now uncommon): assess hearing and bedside vestibular function. Formal pure tone audiometry for high frequency detection is optimal. |
| During treatment | <ul style="list-style-type: none"> • Gastrointestinal upset • Hepatotoxicity (e.g., anorexia, nausea, vomiting, fever, fatigue, pruritis, jaundice (icterus), abdominal discomfort, easy bruising/bleeding, hepatomegaly) • Joint pain/arthritis (gout) • Neuropathy (e.g., tingling, numbness, burning hands or feet), altered gait, refusal to walk • Blurry or altered vision (optic neuropathy) • Rash; characterise nature and location/extent (e.g., mucosal involvement), severity, systemic features (fever, nausea) • Pregnancy/breast feeding • Neuropsychiatric disorders, including depression, anxiety, hallucinations, delusions – assess severity, presence of suicidal ideation • Anaemia (tiredness, pallor shortness of breath) | <ul style="list-style-type: none"> • Symptoms should prompt further clinical assessment and relevant testing (e.g., colour vision[†]/visual acuity, mental health assessment, LFT) • Laboratory tests without symptoms or baseline abnormalities may not be needed unless risk factors are present (e.g., LFT in the presence of viral hepatitis or underlying cirrhosis) • Consider tests for other causes, e.g., LFT derangement, test for hepatitis A (especially children)⁹⁹ • Rash, if severe, assess for organ dysfunction: LFT/creatinine, eosinophils (DRESS syndrome) | <ul style="list-style-type: none"> • If QT prolonging agents (e.g., FQs, BDQ, CFZ, DLM), measure repeat electrolytes (serum K⁺, Ca⁺⁺, Mg⁺⁺) and ECG (QT interval) at 2w, 12w, 24w (or in case there are suggestive symptoms, e.g., dizziness, fainting, palpitations, syncope) • If LZD, measure monthly CBC • If ETH or PAS, monitor for hypothyroidism (every 2 months, additionally if clinically indicated) • If FQs, assess for arthralgia, arthritis, tendonitis; be aware of rare AEs, such as raised intracranial pressure (headache) • If CFZ, warn those undergoing treatment; monitor for skin discolouration, ichthyosis • If aminoglycoside/CPM (now rare), assess regularly (monthly, 3/6 months after completion) for renal function and ototoxicity (hearing, vestibular dysfunction) |

* During treatment the frequency of review should be tailored to the individual person, treatment regimen/drugs used and the likely risk. Early during treatment and particularly during the intensive phase when most AEs are likely to occur review should be more frequent (e.g., every 2–4 weeks). During all phases additional review in case of new symptom development or concern is important.

[†] For example, Ishihara testing to assess colour vision; charts are available online.¹⁰⁰

[‡] Mental health assessment tools that are accessible and assess the range of potential side effects across TB treatments are limited.¹⁰¹ Those that do exist may not be relevant and/or validated across populations (e.g., age, culture). Assessment should focus on AEs of the drug being used and use locally validated tools applicable to age.

AE = adverse effects; HCG = human chorionic gonadotropin; LFT = liver function test; ALT = alanine transaminase; CBC = complete blood count; HbA1c = glycated haemoglobin; FQ = fluoroquinolone; CFZ = clofazimine; BDQ = bedaquiline; DLM = delamanid; K⁺ = potassium; Ca⁺⁺ = calcium; Mg⁺⁺ = magnesium; ECG = electrocardiogram; ETH = ethionamide; PAS = para-aminosalicylic acid; TSH = thyroid stimulating hormone; LZD = linezolid; CPM = capreomycin; DRESS = drug reaction with eosinophilia and systemic symptoms; w = weeks.

to therapy being withheld (Table 3).²⁷ Treatment with rifamycins is associated with increased alkaline phosphatase and bilirubin concentrations without adverse consequences. Treatment should therefore continue if transaminases remain below these thresholds.²⁶ In people with miliary/disseminated TB, increased transaminases are frequently observed. They may be present prior to and improve with treatment. Decisions regarding withholding treatment due to LFT derangement should consider these possibilities, as well as the potential for worsening with treatment due to paradoxical reactions.

STANDARD 3

Each person commencing treatment for TB should, when AE occur, be carefully assessed and possible allergic or hypersensitivity reactions considered

A systematic approach is needed to assess possible AE, documenting the nature and severity and the

likelihood that it is related to TB drugs. Tools such as the Naranjo Scale may be used to assess the likelihood of a causal relationship with drug administration.²⁸ This scale includes the timing of onset and AE progression relative to drug administration, presence of other possible causes, including other prescription or over-the-counter medications, and whether there is objective confirmation of the AE (clinical assessment or laboratory testing). It is important to ascertain whether the AE has led to treatment modification (including self-initiated) or interruption and if so, the period and whether symptoms have changed. AE are most common soon after starting the drug; however, a time lag prior to their development (including allergic reactions) is also possible. More than 80% of AE are classified as 'Type A' reactions. Type A reactions are predictable from drug properties, may be recognised from previous reports and are sometimes referred to as 'augmented reactions'. They are usually dose-

Table 3 Identification and further assessment of 'red flag' symptoms (that may be associated with high risk of poor outcomes and necessitate withholding of medication), including criteria for identifying allergic/hypersensitivity reactions.

| Criteria | Additional information needed | Possible reaction |
|--|---|---|
| Timing of onset <1 h after dose administration* | Nature of reaction: urticarial rash, pruritis, with systemic features, e.g., flushing, angioedema of face, extremities or laryngeal tissues (e.g., throat tightness or stridor), wheezing, gastrointestinal symptoms and/or hypotension | Type I hypersensitivity reaction (may occur with any drug) |
| Petechial rash | Platelet count | Suggests thrombocytopenia from a rifamycin hypersensitivity |
| Moderate–severe rash or other severe cutaneous reaction | Blistering, mucosal involvement, systemic features (fever, nausea/vomiting) | Severe cutaneous adverse event, e.g., Steven's Johnson syndrome, drug reaction with eosinophilia and systemic symptoms ('DRESS') or toxic epidermal necrolysis (may represent Type IV hypersensitivity reaction). Most common with rifampicin |
| Loss of appetite, nausea, vomiting, abdominal pain, especially with jaundice | Examination for evidence of acute hepatitis (e.g., jaundice, RUQ tenderness) Liver tests (including transaminases, bilirubin, alkaline phosphatase) | Severe hepatotoxicity (AST/ALT > 5x ULN or >3x ULN with symptoms or underlying cirrhosis/liver disease) Pyrazinamide and INH are most commonly associated with hepatotoxicity (Standard 4) ¹⁰² |
| Visual change | Test colour vision (e.g., Ishihara plates) and visual acuity (e.g., Snellen chart), compare to baseline | Ocular toxicity including optic neuritis may be related to EMB, LZD or rarely INH |
| 'Fullness' in ears, hearing loss and vertigo/nystagmus | Otoscopy: rule out wax Audiometry assessment if available | Aminoglycosides/capreomycin (or streptomycin) related ototoxicity |
| Neuropsychiatric adverse effects | Seizures In case of depression, assess for severity – is suicidal ideation present? Psychosis In children: assess for hallucinations and night terrors | Seizures may be due to CS, ¹⁰³ FQs, LZD, INH, carbapenems; may also be symptoms of TB disease CS ¹⁰³ and ETH (less common INH/EMB) CS, FQs (less commonly INH) DLM, CS/terizidone, FQs |
| Renal failure | | Rifamycins, ^{104–106} aminoglycosides |

* Type I hypersensitivity reactions may be delayed if taken with food, with cases reported up to 6h after dosing.

DRESS = drug reaction with eosinophilia and systemic symptoms; RUQ = right upper quadrant; AST = aspartate transaminase; ALT = alanine aminotransferase; ULN = upper limit of normal (local range); EMB = ethambutol; LZD = linezolid; INH = isoniazid; CS = cycloserine; ETH = ethionamide; FQ = fluoroquinolone; DLM = delamanid

related (Table 3). Type A reactions can usually be managed symptomatically or by modification of treatment times or doses (Table 4). In case of dose adjustment, therapeutic drug monitoring (TDM) is a valuable tool but is infrequently available.¹⁴ 'Type B' reactions are idiosyncratic (unpredictable) and may occur even after a sub-therapeutic dose. Type B reactions include hypersensitivity reactions (those mediated by an immunologic or inflammatory mechanism). Allergic reactions are those in which an immunologic mechanism has been demonstrated. Information on Type B reactions is mainly from case reports and a few case series, therefore evidence of the relative frequency of Type B reactions between different drugs is limited.

Additional tests for possible drug hypersensitivity such as skin prick, intradermal, patch or in vitro tests²⁹ are used in some centres to further characterise reactions, but access to these tests and expertise on their use, is limited.^{30–33} Furthermore, research is needed to validate these tests and to establish non-irritant concentrations before they are more widely recommended. In vitro testing has also been explored,³⁴ but is unproven and inaccessible in most settings.

STANDARD 4

Each person commencing treatment for TB should receive appropriate care to minimise the morbidity and mortality associated with AE

Every person undergoing treatment for TB should also be provided with appropriate care to manage AE as part of routine free-of-charge TB care. People experiencing AE should be supported with strategies that allow safe continuation of treatment when possible. This may include alterations in drug formulation³⁵ (e.g., use of a dispersible or liquid) or administration (e.g., drugs taken at night rather than morning), as well as the use of ancillary therapies for symptomatic relief (Table 4). AE should be followed up to resolution or stabilisation as part of routine care.³⁶ Additional therapies for symptomatic relief may include anti-emetics, steroids, antihistamines, analgesia or other medications, as well as non-pharmacological interventions (Table 4). When starting new drugs, including those administered to manage symptoms, always check drug–drug interactions, especially when using rifamycins. Before adding ancillary medication, care should also be taken to alert the patient to possible additional AE associated with their use (e.g., anti-emetics, antihis-

Table 4 How to support people when continuing TB therapy in the context of mild–moderate AE*.

| Modality | Examples |
|-----------------------|---|
| Structural and timing | <ul style="list-style-type: none"> • Change timing of doses (for sleep disturbance or daytime nausea) • Split doses of medication (for pill burden or nausea) • Positioning (e.g., sit upright after doses to avoid reflux) |
| Psychological | <ul style="list-style-type: none"> • Contextualisation <ul style="list-style-type: none"> ◦ "Can you tolerate the joint discomfort knowing that pyrazinamide will stop in 2 weeks?" ◦ "In case you stop this drug, the treatment duration of other drugs will have to be prolonged?" • Reassurance ("The urine colour change is from your rifampicin, and isn't harmful") • Education ("Your cough is likely caused by TB rather than your medication") |
| Pharmacological | <ul style="list-style-type: none"> • Analgesia (for joint pain) • Anti-emetics (for nausea/vomiting), confirm that this is not caused by hepatotoxicity (LFT) • Antihistamines (for itch, non-severe rash) • Change of drugs within a class (e.g., moxifloxacin for levofloxacin) • Supplemental levothyroxine if hypothyroidism due to TB drugs • Management of peripheral neuropathy with (increased) vitamin B6 supplementation with INH (limited data) |
| Topical therapies | <ul style="list-style-type: none"> • Moisturisers and/or sunscreen (for dry skin) • Makeup or coloured skin products (for clofazimine discoloration) • Anti-acne topical medication (for acne associated with INH use, especially the face) |

* The table lists examples of possible adverse effects and management options – it is not intended to be comprehensive or proscriptive. LFT = liver function test; INH = isoniazid.

tamines and several other medications prolong QT interval). In children, HCWs should be aware of the possibility of neurologic AE related to administration of anti-emetics (dystonia, which may be interpreted as convulsions). The entire treating team should be aware of any alterations that are made to the treatment regimen. Psychological support is an important element of managing any AE. Some AE may be mild or self-limiting, and psychological support alone may be sufficient to enable successful continuation of therapy. Aligning discussion to individually motivating factors is an important element of providing person-centred care.³⁷

It is rarely appropriate to reduce doses of TB drugs in response to AE, as doing so may compromise effectiveness and increase the risk of drug resistance.¹⁴ Exceptions include where trial data have an established role, such as dose reduction of linezolid following onset of anaemia (myelosuppression) and cytopenia (Table 5).^{38,39} TDM may be useful, for example, to determine whether drug concentrations are suprathreshold (possibly toxic) or when dose modification is used to manage symptoms of presumed AE.¹⁴ In case of reducing doses, drug susceptibility information (phenotypic and genotypic, when available) and microbiological monitoring can also be useful to monitor for disease relapse and selection of resistance. Lower doses of TB drugs may sometimes be used as part of an established protocol for drug escalation, such as for re-introduction in the setting of intolerance or desensitisation for some hypersensitivity reactions (Supplementary Data).

In some cases, interruption or cessation of TB treatment will be needed to minimise morbidity, considering morbidity associated with TB that may result from delaying or inadequate treatment as well as morbidity associated with AE. In severe, miliary or central nervous system (CNS) TB, therapy may need to be continued using alternative (second-line) agents.

Indications for interruption or cessation of TB treatment include ocular toxicity, renal failure, severe hepatotoxicity, hypersensitivity reactions and some neuropsychiatric disorders. Accurate diagnosis is important, especially in the case of hypersensitivity reactions, as this will help to determine which strategies are appropriate for further assessment and possibilities for continuing with therapy, and in a few cases, identifying AE that preclude restarting the drug (uncommon) or the need for alternative agents/regimens (see Standard 3).

New medications such as bedaquiline and pretomanid are effective and well-tolerated in treatment of DR-TB,^{38,40} and may be considered as second-line therapy in the case of AE during the treatment of DS-TB. Their tolerability and efficacy substantially improve options in the management of AE, although price and availability remain limitations to their use.

STANDARD 5

Each person commencing treatment for TB should be restarted on TB drugs after a serious AE according to a standardised protocol that includes active drug safety monitoring

AE related to TB drugs can often be managed with counselling and education without discontinuing medications. Cessation of drugs may be indicated with serious and/or worsening AE (Table 3). For hepatotoxicity, consensus thresholds for cessation have been established,²⁷ while for many others assessment of severity and subjective evaluation of tolerability will guide timing of discontinuation. Optic neuritis, ototoxicity, severe acute nephrotoxicity, haemolytic anaemia, thrombocytopenic purpura, severe depression/suicidal ideation, psychosis, seizure or encephalopathy are examples of serious AE where treatment should be withheld and rechallenge may be contraindicated (see Table 3 for

Table 5 Proposed protocol for rechallenge of TB drugs after specific AE.^{1,3,27,29,32,41}

| Adverse reaction | Probable causative drug | Rechallenge protocol |
|--|--|---|
| Cutaneous AE (sometimes known as cutaneous adverse drug reactions or 'CADR') | An individual drug can cause multiple types of cutaneous AE and a specific type of AE can be due to any drug Most reported:* • Drug hypersensitivity: INH, RIF, SM, PZA • Stevens-Johnson syndrome; toxic epidermal necrolysis: RIF, PZA, INH, EMB, SM, CS, FQs | Rechallenge (drug provocation testing) is not recommended in severe cutaneous adverse events (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) or immediate hypersensitivity. Rechallenge after rash has substantially improved, starting the drugs individually at intervals of 2–3 days, in the following order: RIF, followed by INH, then EMB or PZA. If rash reappears, the last drug added is withdrawn. In cases where three drugs were reintroduced without rash, the fourth drug may not be reintroduced unless the rash was mild and that drug essential In drug hypersensitivity, rapid desensitisation may be useful, see Supplementary Data for suggested protocol. For rapid desensitisation protocol, see Supplementary Data |
| Drug fever | INH RIF (Differential diagnosis: LZD (serotonin syndrome)) | Body temperature is usually normal within 24 hours after drugs are withdrawn. Once afebrile, restart drugs as indicated for cutaneous AE |
| Optic/peripheral neuropathy | INH, LZD, CS ^{38,39} | Cease LZD INH/CS: vitamin B6 supplementation |
| Myelosuppression Hepatotoxicity | LZD Most common with PZA and INH | Reduce LZD dose to 300 mg daily ³⁹ Rechallenge if ALT levels <2x ULN, bilirubin normal and symptoms abated Start simultaneously with EMB and RIF, INH and PZA at usual doses, every 2–3 days Repeat LFT measurements before reintroducing a new drug If symptoms recur or ALT increases, the last drug reintroduced should be withdrawn Reintroduce full treatment over a period of up to 21 days [†] If RIF, EMB and INH were reintroduced without further increases in transaminases, PZA can be suspended, in which case TB treatment should be extended to 9 months (continuation phase extended from 4 to 7 months) |

* Information on Type B reactions is mainly from case reports and a few case series, therefore evidence regarding the relative frequency of Type B reactions between different drugs is limited.

[†] Time for reintroduction is uncertain. Minimising the time without effective therapy should be balanced against the risk/morbidity associated with AE-related toxicity.

AE = adverse effect; INH = isoniazid; RIF = rifampicin; SM = streptomycin; PZA = pyrazinamide; EMB = ethambutol; FQ = fluoroquinolone; LZD = linezolid; CS = cycloserine; ALT = alanine aminotransferase; ULN = upper limit of normal; LFT = liver function test.

attributable TB drugs).^{1,3,41} Reintroduction of the standard regimen should be sought whenever possible. It is important that this is clearly explained to the person and their support network/caregivers. The decision on whether to reintroduce the 'culprit' drug will depend on the severity of the AE and risk of a more severe reaction after rechallenging, and on the severity of TB disease vs. the risk of a less potent and/or longer treatment regimen. Sequential reintroduction is used in some cases (drugs reintroduced one at a time) and should always start with the drug with the least probability to produce the AE, and to follow in order of probabilities.

Persons with severe forms of TB generally require initiation of an alternative regimen during the time the drug(s) presumed to induce toxicity are withheld and the rechallenge has not been completed.^{1,3,41} If the drug cannot be reintroduced, the person should be managed as if they had "functional resistance" to the drug.

Drug-induced hepatotoxicity

Protocols for rechallenge of TB drugs are best described for cases of drug-induced hepatitis, although randomised controlled trials are needed to compare strategies for reintroducing drugs after hepatotoxicity. Most international guidelines^{1,3,27,41} follow the recommendation of reintroducing TB drugs after transaminase levels (especially alanine transaminase [ALT]) decrease to less than two times the ULN, bilirubin levels return to normal (for adults over 18 years old, normal total bilirubin is less than 1.2 mg/dL [20.5 micromol/L] of blood; in those aged <18 years, the upper limit is 1 mg/dL) and the person has no symptoms of hepatotoxicity. For those in whom there should be no treatment interruption (e.g., severe TB disease, CNS disease), three drugs not associated with hepatotoxicity may be administered while awaiting transaminase levels to decrease (Table 5). Sequential reintroduction of TB drugs at their usual doses should be done every 2–3 days (so that

Table 6 Items to be included when reporting a serious AE (adapted from⁵²)

| Item | Details |
|------------------|---|
| Person affected | <ul style="list-style-type: none"> Sex, date of birth/age Pregnancy or breastfeeding |
| Drug (s) | <ul style="list-style-type: none"> Name and daily dose Date started and stopped |
| Event | <ul style="list-style-type: none"> Date event started and stopped Seriousness of event (death, life-threatening event, hospitalisation or prolongation of hospitalisation, persistent or significant disability, congenital anomaly), other |
| Action taken | <ul style="list-style-type: none"> Medicine withdrawn, dose increased, dose reduced, dose not changed, unknown |
| Outcome of event | <ul style="list-style-type: none"> Recovered/resolved, recovering/resolving, recovered with sequelae, not recovered/not resolved, died, unknown |

transaminase measurements can be repeated) over a period of no more than 7–10 days, generally in the following order: EMB, rifampicin (which can be reintroduced at the same time as EMB), isoniazid. If all other agents are tolerated, then continuing treatment without pyrazinamide is a reasonable strategy. If pyrazinamide is not included during the intensive phase of therapy, the continuation phase would need to be extended from 4 to 7 months.^{3,13,42,43} If reintroduction of the drug triggers a hepatocellular AE similar to or of greater severity than the previous one, this drug should no longer be used in future regimens for this person.^{1,3,27,41} Sequential rechallenge may allow determination of which medication is the cause of the hepatotoxicity; however, in a randomised trial that excluded individuals at increased risk of hepatotoxicity, no increased hepatotoxicity was observed when drugs were restarted concurrently.^{44,45} Some guidelines recommend a graded rechallenge (with incremental dosing increase; however, there is no evidence to suggest that this is better than full-dose rechallenge.^{27,45,46}

Cutaneous AE due to TB drugs

In case of significant cutaneous reactions in presumed drug hypersensitivity (Table 3), all TB drugs should be stopped. Mild cutaneous reactions, such as small surface area urticaria, may permit continued therapy and observation with antihistamines if symptoms are tolerable. Judicious drug provocation testing may be used to exclude drugs deemed unlikely to cause the reaction by restarting. Sequential testing in inverse order of probability of causation (starting with the drug least likely to cause the reaction based on currently available evidence) is recommended. Drug provocation testing is undertaken where the risk/probability of a hypersensitivity reaction (HSR) to a drug is thought to be low, with the intention of demonstrating clinical tolerance based on clinical judgement; however, the benefit of this strategy has not been proven. Rechallenge protocols that are

frequently recommended for reintroduction of TB drugs after an AE are shown in Table 5.

Some authors propose desensitisation therapy for TB drugs after HSR using a carefully structured dosing administration schedule that starts with a very low dose of each drug under close clinical supervision (Supplementary Data).^{30,33} The aim of desensitisation is to alter the immune response to the drug resulting in temporary tolerance, allowing the person to safely receive an uninterrupted course of medication. If therapy is interrupted, the hypersensitivity to the medication returns.⁴⁷ Desensitisation may reacquire a drug option; however, success is not guaranteed. This strategy may be appropriate for immediate allergic reactions (Type 1 hypersensitivity) and non-severe delayed reactions, but clinical utility has not been validated in controlled studies. Desensitisation is not recommended in the case of severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.^{32,33,48} In all approaches, the risk of new, and possibly, fatal cutaneous AE must be balanced against the increased mortality risk due to TB treatment interruption.^{1,32} The procedure should include counselling of the person and members of their support network and/or caregivers regarding the possible risk of anaphylaxis or other systemic reaction, and for need for strict treatment compliance with continued medication doses as prescribed and without interruption following desensitisation.

STANDARD 6

Healthcare workers should be trained on AE including how to counsel people undertaking TB treatment, as well as active AE monitoring and management

Education of HCWs is a crucial component of TB treatment programmes and should include training in effective counselling methods, as well as information regarding treatment initiation, the nature of AE, the importance of adherence, common drug-drug interactions and recommended follow-up strategies and schedules. HCW education should emphasise the importance of a person-centred approach to TB care – the guiding principle for counselling about AE and TB treatment. It should include an explanation of the underlying mechanisms of common and important AE for each TB drug, with information about recommended surveillance for common AE, including investigations. Training on available and accessible tools and resources to support monitoring and management of AE should be provided to help build an effective system for active AE monitoring, reporting and management, and support for those undergoing treatment.

Education for HCW should also cover the principles and components of pharmacovigilance and

aDSM to ensure timely and accurate recording and reporting of AE during treatment. Training should emphasise the importance of timely, careful, detailed record of the investigation, management, and follow-up of AE. Education should include the recommended management algorithms that should ensue in the event of a particular reaction or symptoms suggestive of AE (Tables 3–5). During HCW training, the importance of assessing the impact of AE on adherence and the TB treatment course should be emphasized. Education of HCW should also include the importance of communication and collaboration with other colleagues involved in the care of people undergoing treatment for TB such as pharmacists and nursing staff as well as their support networks and caregivers. This is particularly important in treating those with TB who also have comorbidities, which require AE monitoring and collaborative management between HCW with different areas of expertise.

STANDARD 7

There should be active AE monitoring and reporting for all new TB drugs and regimens

aDSM and management has been introduced for newly approved drugs such as bedaquiline and delamanid. This provides a system for 1) detection, 2) management, and 3) reporting of presumed or confirmed AE using active and systematic clinical and laboratory assessment of people receiving treatment.^{49–53} Not only new TB drugs, but also novel regimens, are captured. By prospectively using agreed monitoring strategies, findings from different countries can be easily interpreted and data aggregated, allowing for a timely international/global response to observed and reported AE.⁵⁴ Findings from the analysis could result in immediate safety warnings or prompt alertness for specific AE. Data from an aDSM database should be combined with data from other sources such as the Eudravigilance and the WHO Global Individual Case Safety Report database (VigiBase).^{55,56} Active monitoring for AE (depending on the drugs used) should include visual and hearing assessment, neurological/psychiatric evaluation, renal and hepatic function, electrocardiograph (ECG) and electrolytes, lipase and amylase test, blood count, blood glucose and thyroid test.⁵²

Depending on available resources, TB programs can focus on 1) only serious AE (SAE), 2) SAE and specific AE, or 3) (ideally) all AE.^{57,58} It is of value to involve national medicines regulatory agencies, as they have a legal responsibility for monitoring the safety of the approved medicines. This also helps with making reporting more efficient as duplication of efforts in reporting AE was considered a major hurdle by HCWs.⁵⁹ When reporting a case, the information outlined in Table 6 should be included; person

characteristics, event characteristics, seriousness of the event, actions taken and outcome.⁵²

STANDARD 8

Knowledge gaps and signals identified from active AE monitoring should be systematically addressed through clinical research

Many AE identified by HCW are not reported to health authorities at local, national or global level. This underreporting may be due to lack of awareness, administrative burden (need to report to the country and to the aDSM system and to the drug manufacturer with different forms and multiple steps), confidentiality issues, the involvement of different sectors (e.g., public and private, prisons) and the fear of blame.^{49,60} An important issue that needs to be addressed in the classification of AE is the attribution of an AE to an individual drug (for establishing causal associations between drugs and AE, see Standard 3). For optimisation of these causal attributions, implementation of standard operating procedures to monitor AE, drug exposure and concomitant drugs need to be carried out and clinical and operational research undertaken. Note should be made of type B reactions, which could be causal, but are not related to dose (e.g., allergic reaction). To assess the relationship between AE and drug exposure (dosage and frequency of administration) pharmacokinetic analysis of the TB drugs may be carried out. For establishing pharmacokinetic exposure parameters, such as ‘area under the curve’ (AUC) values that predict toxicity, classification and regression tree analysis can be used.⁶¹ Variables related to concomitant medications, which could affect drug exposure, should be recorded.¹⁴ Because TB drugs are used for prolonged duration and in combination, the cumulative toxicity of a drug should be investigated as well.

CONCLUSION

Early identification and management of AE during treatment for TB is critical to optimise successful treatment completion. There remains great uncertainty regarding AE risk prior to treatment, and studies into genomic and other predictors should be investigated for developing tailored treatment and monitoring strategies. Programmatic approaches to safe reintroduction of medication after AE should be prioritised, as should evidence-based, person-centred strategies for supporting people with TB through AE safely, and optimal counselling strategies for education regarding AE and reporting.

K. P. Singh,^{1,2} A. C. C. Carvalho,³ R. Centis,⁴ L. D’Ambrosio,⁵ G. B. Migliori,⁴ S. G. Mpagama,^{6,7} B. C. Nguyen,⁸ R. E. Aarnoutse,⁹ A. Aleksa,¹⁰ R. van Altena,¹¹ P. K. Bhavani,¹² M. S. Bolhuis,¹³

S. Borisov,¹⁴ N. van't Boveneind-Vrubleuskaya,^{13,15} J. Bruchfeld,^{16,17} J. A. Caminero,^{18,19} I. Carvalho,²⁰ J. G. Cho,^{21,22,23} L. Davies Forsman,^{16,17,24} M. Dedicoat,²⁵ K. Dheda,^{26,27,28} K. Dooley,²⁹ J. Furin,³⁰ J. M. García-García,³¹ A. Garcia-Prats,^{32,33} A. C. Hesselning,³² S. K. Heysell,³⁴ Y. Hu,³⁵ H. Y. Kim,^{21,22,24} S. Manga,³⁶ B. J. Marais,^{21,37} I. Margineanu,¹³ A-G. Mårtson,³⁸ M. Munoz Torrico,³⁹ H. M. Nataprawira,⁴⁰ E. Nunes,^{41,42} C. W. M. Ong,^{43,44,45} R. Otto-Knapp,⁴⁶ D. J. Palmero,⁴⁷ C. A. Peloquin,⁴⁸ A. Rendon,⁴⁹ D. Rossato Silva,⁵⁰ R. Ruslami,^{51,52} A. M. I. Saktiawati,^{53,54} P. Santoso,⁵⁵ H. S. Schaaf,³² B. Seaworth,⁵⁶ U. S. H. Simonsson,⁵⁷ R. Singla,⁵⁸ A. Skrahina,⁵⁹ I. Solovic,⁶⁰ S. Srivastava,^{56,61,62} S. L. Stocker,^{24,63} M. G. G. Sturkenboom,¹³ E. M. Svensson,^{9,64} M. Tadolini,^{65,66} T. A. Thomas,³⁴ S. Tiberi,⁶⁷ J. Trubiano,^{1,68} Z. F. Udawadia,⁶⁹ A. R. Verhage,⁷⁰ D. H. Vu,⁷¹ O. W. Akkerman,^{72,73} J. W. C. Alffenaar,^{21,22,24} J. T. Denholm^{1,2,74}

KPS, ACCC, RC, LDA, GBH, SGM, BCN, OWA, JWCA and JTD comprised the core writing team.

OWA, JWCA and JTD were senior authors.

¹Department of Infectious diseases, University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, ²Victorian Infectious Disease Unit, Royal Melbourne Hospital, VIC, Australia; ³Laboratório de Inovações em Terapias, Ensino e Bioprodutos (LITEB), Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil; ⁴Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Tradate, Italy; ⁵Public Health Consulting Group, Lugano, Switzerland; ⁶Kilimanjaro Christian Medical University College, Moshi, ⁷Kibong'oto Infectious Diseases Hospital, Sanya Juu, Siha, Kilimanjaro, United Republic of Tanzania; ⁸Woolcock Institute of Medical Research, Viet Nam and University of Sydney, NSW, Australia; ⁹Department of Pharmacy, Research Institute for Medical Innovation, Radboud University Medical Center, Nijmegen, The Netherlands; ¹⁰Grodno State Medical University, Grodno, Belarus; ¹¹Asian Harm Reduction Network (AHRN) and Medical Action Myanmar (MAM), Yangon, Myanmar; ¹²Indian Council of Medical Research-National Institute for Research in Tuberculosis; ¹³Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; ¹⁴Moscow Research and Clinical Center for Tuberculosis Control, Moscow, Russia; ¹⁵Department of Public Health TB Control, Metropolitan Public Health Services, The Hague, The Netherlands; ¹⁶Departement of Medicine Solna, Division of Infectious Diseases, Karolinska

Institutet, Stockholm, Sweden; ¹⁷Departement of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; ¹⁸Department of Pneumology. University General Hospital of Gran Canaria "Dr Negrin", Las Palmas, Spain; ¹⁹ALOSA (Active Learning over Sanitary Aspects) TB Academy, Spain; ²⁰Paediatric Department, Vila Nova de Gaia Hospital Centre, Vila Nova de Gaia Outpatient Tuberculosis Centre, Vila Nova de Gaia, Portugal; ²¹Sydney Infectious Diseases Institute (Sydney ID), The University of Sydney, Sydney, NSW, Australia; ²²Westmead Hospital, Sydney, NSW, Australia; ²³Parramatta Chest Clinic, Parramatta, NSW, Australia; ²⁴School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; ²⁵Department of Infectious Diseases, Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; ²⁶Centre for Lung Infection and Immunity Unit, Department of Medicine, Division of Pulmonology and UCT Lung Institute, University of Cape Town, Cape Town, ²⁷South African Medical Research Council Centre for the Study of Antimicrobial Resistance, University of Cape Town, Cape Town, South Africa; ²⁸Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK; ²⁹Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, ³⁰Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; ³¹Tuberculosis Research Programme, SEPAR (Sociedad Española de Neumología y Cirugía Torácica), Barcelona, Spain; ³²Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Tygerberg, South Africa; ³³Department of Pediatrics, University of Wisconsin, Madison, WI, USA; ³⁴Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA, USA; ³⁵Department of Epidemiology, School of Public Health and Key Laboratory of Public Health Safety, Fudan University, Shanghai, China; ³⁶Tuberculosis Department Latin American Society of Thoracic Diseases, Lima, Peru; ³⁷Department of Infectious Diseases and Microbiology, The Children's Hospital at Westmead, Westmead, NSW, Australia; ³⁸Centre of Excellence in Infectious Diseases Research, Antimicrobial Pharmacodynamics and Therapeutics Group, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK; ³⁹Clinica de Tuberculosis, Instituto Nacional de Enfermedades Respiratorias, México City, Mexico; ⁴⁰Division of Paediatric Respiriology, Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin Hospital, Bandung, Indonesia; ⁴¹Department of Pulmonology of Central Hospital of Maputo, Maputo, ⁴²Faculty of Medicine of Eduardo

Mondlane University, Maputo, Mozambique; ⁴³Infectious Disease Translational Research Programme, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, ⁴⁴National University of Singapore Institute for Health Innovation & Technology (iHealthtech), Singapore, ⁴⁵Division of Infectious Diseases, Department of Medicine, National University Hospital, Singapore; ⁴⁶German Central Committee Against Tuberculosis (DZK), Berlin, Germany; ⁴⁷Hospital Muniz and Instituto Vaccarezza, Buenos Aires, Argentina; ⁴⁸Infectious Disease Pharmacokinetics Laboratory, College of Pharmacy and Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA; ⁴⁹Universidad Autonoma de Nuevo Leon, Facultad de Medicina, Neumología, CIPTIR, Monterrey, Mexico; ⁵⁰Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; ⁵¹TB/HIV Research Centre, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia; ⁵²Department of Biomedical Sciences, Division of Pharmacology and Therapy, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia; ⁵³Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; ⁵⁴Centre for Tropical Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; ⁵⁵Division of Respiriology and Critical Care, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/Hasan Sadikin General Hospital, Bandung, Indonesia; ⁵⁶University of Texas Health Science Center at Tyler, Tyler, TX, USA; ⁵⁷Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; ⁵⁸Department of TB & Respiratory Diseases, National Institute of TB & Respiratory Diseases, New Delhi, India; ⁵⁹Republican Research and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus; ⁶⁰National Institute of Tuberculosis, Lung Diseases and Thoracic Surgery, Faculty of Health, Catholic University, Ružomberok, Vyšné Hágy, Slovakia; ⁶¹Department of Medicine, The University of Texas at Tyler School of Medicine, TX, USA; ⁶²Department of Pharmacy Practice, Texas Tech University Health Science Center, Dallas, TX, USA; ⁶³Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW, Australia; ⁶⁴Department of Pharmacy, Uppsala University, Uppsala, Sweden; ⁶⁵Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico di Sant'Orsola, Bologna, Italy; ⁶⁶Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy; ⁶⁷Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of

London, London, UK; ⁶⁸Department of Infectious Diseases, Austin Hospital, Melbourne, VIC, Australia; ⁶⁹P. D. Hinduja National Hospital and Medical Research Centre, Mumbai, India; ⁷⁰Department of Paediatrics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; ⁷²Department of Pulmonary Diseases and Tuberculosis, Groningen, and ⁷³Tuberculosis Center Beatrxoord, University Medical Center Groningen, University of Groningen, Haren, the Netherlands; ⁷⁴Victorian Tuberculosis Program, Melbourne Health, VIC, Australia. Correspondence to: Kasha P Singh, Department of Infectious diseases, University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia. E-mail: kasha.singh@unimelb.edu.au

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R É S U M É

CONTEXTE : Les effets indésirables (AE) du traitement de la TB sont une cause de morbidité, de mortalité et d'interruption du traitement. L'objectif de ces normes cliniques est d'encourager une meilleure pratique en matière de diagnostic et de prise en charge des AE.

MÉTHODES : Ont participé 65/81 experts invités à un processus Delphi utilisant une échelle de Likert en 5 points pour évaluer des ébauches de normes.

RÉSULTATS : Nous avons identifié huit normes cliniques. Chaque personne commençant un traitement antituberculeux devrait : Norme 1, être informée des AE avant et pendant le traitement ; Norme 2, être évaluée afin de détecter tout facteur susceptible d'augmenter le risque d'AE et faire l'objet d'un examen régulier afin d'identifier et de prendre en charge ces facteurs de manière proactive ; Norme 3, en cas d'AE, être évaluée avec soin et tenir compte d'éventuelles réactions allergiques ou d'hypersensibilité ; Norme 4, recevoir

des soins appropriés pour minimiser la morbidité et la mortalité associées aux AE ; Norme 5, reprendre les médicaments antituberculeux après un AE grave selon un protocole standardisé avec une surveillance active de l'innocuité des médicaments ; Norme 6, les agents de santé doivent être formés aux AE, y compris à la manière de conseiller les personnes qui suivent un traitement antituberculeux, ainsi qu'à la surveillance et à la prise en charge actives des AE ; Norme 7 : tous les nouveaux médicaments et schémas antituberculeux doivent faire l'objet d'une surveillance active des AE et d'une notification ; et Norme 8 : les lacunes en matière de connaissances identifiées grâce à la surveillance active des AE doivent être systématiquement comblées par la recherche clinique.

CONCLUSION : Ces normes fournissent une approche centrée sur la personne et fondée sur le consensus afin de minimiser l'impact des AE pendant le traitement de la TB.
