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Table 3.1 RECOMMENDED DOSES OF FIRST-LINE ANTITUBERCULOSIS DRUGS FOR ADULTS

Drug	Recommended dose			
	Daily		3 times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	15 (15–20)	–	30 (25–35)	–
Streptomycin <sup>a</sup>	15 (12–18)		15 (12–18)	1000

<sup>a</sup> Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reduction of the dose to 10 mg/kg per day in patients in this age group (2). Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily (*WHO Model Formulary 2008*, [www.who.int/selection\\_medicines/list/en/](http://www.who.int/selection_medicines/list/en/)).

All anti-TB drugs should be quality-assured, and management of anti-TB drugs should be incorporated into the management of other essential medicines by the ministry of health.

Annex 1 provides additional information on the essential anti-TB drugs, including contraindications, precautions, use in pregnancy, adverse effects, and drug interactions. Intermittent dosing schedules are discussed in section 3.5.1 below.

### 3.3.1 Fixed-dose combinations of anti-TB drugs

While evidence on fixed-dose combinations (FDCs) of anti-TB drugs was not systematically reviewed for this fourth edition, WHO continues to recommend their use, as does Standard 8 of the ISTC (3). FDCs are thought to prevent acquisition of drug resistance due to monotherapy, which may occur with separate (“loose”) drugs. With FDCs, patients cannot be selective in the choice of drugs to ingest. Prescription errors are likely to be less frequent because dosage recommendations are more straightforward, and adjustment of dosage according to patient weight is easier. The number of tablets to ingest is smaller and may thus encourage patient adherence.

While there is ecological evidence of the benefits of FDCs in relation to drug resistance in early studies of DOTS programmes, there is limited direct evidence of improved adherence with FDCs (4). A recent multicentre trial found FDCs to have equivalent efficacy to single pills and to be more acceptable to patients (5). However, assessment of cure and relapses was based on smear microscopy and not on culture. A multicentre trial (The Union Study C) evaluating the efficacy, acceptability and toxicity of a four-drug FDC compared with loose pills given in the intensive phase

Recommended regimens for different patient registration groups are shown in Tables 3.2, 3.3 and 3.4. More details on the evidence and judgements underlying the recommended regimens are described in Annex 2.

### 3.5 New patients

New patients are defined as those who have no history of prior TB treatment or who received less than 1 month of anti-TB drugs (regardless of whether their smear or culture results are positive or not) (see section 2.6).

#### 3.5.1 New patients presumed or known to have drug-susceptible TB

New patients are presumed to have drug-susceptible TB with two exceptions:

- Where there is a high prevalence of isoniazid resistance in new patients (see section 3.5.2).
- or*
- If they have developed active TB after known contact with a patient documented to have drug-resistant TB; they are likely to have a similar drug resistance pattern to the source case (6), and DST should be carried out at the start of treatment. While DST results of the patient are awaited, a regimen based on the DST of the presumed source case should be started.

The 2-month rifampicin regimen (2HRZE/6HE) is associated with more relapses and deaths than the 6-month rifampicin regimen (2HRZE/4HR) (7). WHO therefore recommends the following for new patients presumed or known to have drug-susceptible TB. (See also Standard 8 of the ISTC (3).)

#### ■ Recommendation 1.1

**New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR**

(Strong/High grade of evidence)

*Remark a:* Recommendation 1.1 also applies to extrapulmonary TB except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy (see Chapter 8).

*Remark b:* WHO recommends that national TB control programmes provide supervision and support for all TB patients in order to ensure completion of the full course of therapy.

*Remark c:* WHO recommends drug resistance surveys (or surveillance) for monitoring the impact of the treatment programme, as well as for designing standard regimens.

### ■ Recommendation 1.2

**The 2HRZE/6HE treatment regimen should be phased out**

(Strong/High grade of evidence)

In terms of dosing frequency for HIV-negative patients, the systematic review found little evidence of differences in failure or relapse rates with daily or three times weekly regimens (7). However, patients receiving three times weekly dosing throughout therapy had higher rates of acquired drug resistance than patients who received drugs daily throughout treatment. In patients with pre-treatment isoniazid resistance, three times weekly dosing during the intensive phase was associated with significantly higher risks of failure and acquired drug resistance than daily dosing during the intensive phase. (Treatment regimens for TB patients living with HIV are discussed in detail in Chapter 5.)

### ■ Recommendation 2.1

**Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy**

(Strong/High grade of evidence)

There are two alternatives to Recommendation 2.1:

#### ■ Recommendation 2.1A

**New patients with pulmonary TB may receive a daily intensive phase followed by three times weekly continuation phase [2HRZE/4(HR)<sub>3</sub>] provided that each dose is directly observed**

(Conditional/High or moderate grade of evidence))

#### ■ Recommendation 2.1B

**Three times weekly dosing throughout therapy [2(HRZE)<sub>3</sub>/4(HR)<sub>3</sub>] is another alternative to Recommendation 2.1, provided that every dose is directly observed and the patient is NOT living with HIV or living in an HIV-prevalent setting**

(Conditional/High or moderate grade of evidence))

*Remark a:* Treatment regimens for TB patients living with HIV or living in HIV-prevalent settings are discussed in Recommendation 4 and Chapter 5.

*Remark b:* In terms of dosing frequency for HIV-negative patients, the systematic review found little evidence of differences in failure or relapse rates with daily or three times weekly regimens (7). However, rates of acquired drug resistance were higher among patients receiving three times weekly dosing throughout therapy than among patients who received daily drug administration throughout treatment. Moreover, in patients with pretreatment isoniazid resistance, three times weekly dosing during the intensive phase was associ-

ated with significantly higher risks of failure and acquired drug resistance than daily dosing during the intensive phase.

There is insufficient evidence to support the efficacy of twice weekly dosing throughout therapy (7).

### ■ Recommendation 2.2

**New patients with TB should not receive twice weekly dosing for the full course of treatment unless this is done in the context of formal research**

(Strong/High grade of evidence)

*Remark:* The available evidence showed equivalent efficacy of daily intensive-phase dosing followed by two times weekly continuation phase (7). However, twice weekly dosing is not recommended on operational grounds, since missing one dose means the patient receives only half the regimen.

Tables 3.2a and 3.2b present standard treatment regimen and dosing frequency for new TB patients.

Table 3.2a **STANDARD REGIMENS FOR NEW TB PATIENTS**  
(presumed, or known, to have drug-susceptible TB)

Intensive phase treatment	Continuation phase
2 months of HRZE <sup>a</sup>	4 months of HR

<sup>a</sup> WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative PTB or EPTB who are known to be HIV-negative. In tuberculous meningitis, ethambutol should be replaced by streptomycin.

H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin

Table 3.2b **DOSING FREQUENCY FOR NEW TB PATIENTS**

Dosing frequency		Comment
Daily	Daily	Optimal
Daily	Three times per week	Acceptable alternative for any new TB patient receiving directly observed therapy
Three times per week	Three times per week	Acceptable alternative provided that the patient is receiving directly observed therapy and is not living with HIV or living in an HIV-prevalent setting (See Chapter 5)

*Note:* Daily (rather than three times weekly) intensive-phase dosing may help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance (see section 3.5.2).

### 3.5.2 Settings with high levels of isoniazid resistance in new patients

When new patients with isoniazid-resistant TB start their treatment, outcomes are worse than for patients with isoniazid-susceptible TB, even with the 6-month rifampicin regimen (7). The global weighted mean of any isoniazid resistance (excluding MDR) is 7.4% in new patients (8). Thus, a significant proportion of the new TB cases in many regions of the world have a risk of poor treatment outcomes because of their pretreatment isoniazid resistance.

The following weak recommendation applies to countries where isoniazid susceptibility testing in new patients is not done (or results are not available) before the continuation phase begins.

#### ■ Recommendation 3

**In populations with known or suspected high levels of isoniazid resistance, new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR**

(Weak/Insufficient evidence, expert opinion)

Given the potential benefit (9) and low risk of toxicity from ethambutol, the pressing need to prevent MDR warrants this recommendation. However, the recommendation is conditional, for the reasons explained in more detail in Annex 2. The most effective regimen for the treatment of isoniazid-resistant TB is not known. There is inadequate evidence to quantify the ability of ethambutol to “protect rifampicin” in patients with pre-treatment isoniazid resistance. The evidence for ocular toxicity from ethambutol was not systematically reviewed for this revision, but the risk of permanent blindness exists. Further research (see Annex 5) is therefore urgently needed to define the level of isoniazid resistance that would warrant the addition of ethambutol (or other drugs) to the continuation phase of the standard new patient regimen in TB programmes where isoniazid drug susceptibility testing is not done (or results are not available) before the continuation phase begins.

Daily (rather than three times weekly) intensive-phase dosing may also help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance. The systematic review (7) found that patients with isoniazid resistance treated with a three times weekly intensive phase had significantly higher risks of failure and acquired drug resistance than those treated with daily dosing during the intensive phase.

Table 3.3 presents standard treatment regimens for new patients in settings with high isoniazid resistance.

**Table 3.3 STANDARD REGIMENS FOR NEW TB PATIENTS**  
(in settings where the level of isoniazid resistance among new TB cases is high and isoniazid susceptibility testing is not done (or results are not available) before the continuation phase begins)

Intensive phase treatment	Continuation phase
2 months of HRZE	4 months of HRE

### 3.6 Previously treated patients and multidrug resistance

Previous TB treatment is a strong determinant of drug resistance (10), and previously treated patients comprise a significant proportion (13%) of the global TB notifications in 2007.

Of all the forms of drug resistance, it is most critical to detect multidrug resistance (MDR) because it makes regimens with first-line drugs much less effective (11) and resistance can be further amplified (12). Prompt identification of MDR and initiation of MDR treatment with second-line drugs gives a better chance of cure and prevents the development and spread of further resistance. Because of its clinical significance, MDR (rather than any drug resistance) is used to describe the retreatment patient groups below.

At the global level, 15% of previously treated patients have MDR (8), which is five times higher than the global average of 3% in new patients (Figure 3.1). Even in Africa, the WHO region thought to have the lowest level of MDR in retreatment patients, a significant proportion (6%) of retreatment patients have MDR-TB (8).<sup>1</sup> If their MDR is not detected and treated with second-line drugs, these patients will suffer poor outcomes and spread MDR in their communities.

WHO surveillance data from 10 countries found the level of MDR to be 32% in patients returning after defaulting or relapsing and significantly higher (49%) in patients whose prior treatment has failed (Figure 3.2).<sup>2</sup> Other studies show MDR levels of up to 80–90% in patients whose prior treatment courses have failed (10–16). Modelling described in Annex 2 predicts that, when a first course of treatment containing 6 months of rifampicin fails, 50–94% of patients have MDR-TB (compared with 4–56% of patients upon failure of a regimen containing 2 months of rifampicin).

Many factors influence the level of MDR in previously treated patients, and levels are likely to vary widely by setting. Assignment of the retreatment patient groups to medium vs high likelihood of MDR may therefore need to be modified according to country-specific data on similar groups of patients, as well as other factors discussed in section 3.8 below.

<sup>1</sup> Of 46 countries in Africa, 6 have reported drug resistance data since 2002; 22 countries (representing 72% of the region's cases) have reported data since 1994 (5, p. 90).

<sup>2</sup> These are the only 10 countries that reported drug resistance surveillance data by subcategory of retreatment cases since 1997.

Table 3.4 STANDARD REGIMENS FOR PREVIOUSLY TREATED PATIENTS depending on the availability of routine DST to guide the therapy of individual retreatment patients

DST	Likelihood of MDR (patient registration group <sup>a</sup> )	
Routinely available for previously treated patients	High (failure <sup>b</sup> )	Medium or low (relapse, default)
Rapid molecular-based method	DST results available in 1–2 days confirm or exclude MDR to guide the choice of regimen	
Conventional method	While awaiting DST results: <sup>c</sup>	
	Empirical MDR regimen <i>Regimen should be modified once DST results are available.</i>	2HRZES/HRZE/5HRE <i>Regimen should be modified once DST results are available.</i>
None (interim)	Empirical MDR regimen <i>Regimen should be modified once DST results or DRS data are available.</i>	2HRZES/HRZE/5HRE for full course of treatment. <i>Regimen should be modified once DST results or DRS data are available.</i>

<sup>a</sup> The assumption that failure patients have a high likelihood of MDR (and relapse or defaulting patients a medium likelihood) may need to be modified according to the level of MDR in these patient registration groups, as well considerations discussed in section 3.8.

<sup>b</sup> And other patients in groups with high levels of MDR. One example is patients who develop active TB after known contact with a patient with documented MDR-TB. Patients who are relapsing or returning after defaulting from their second or subsequent course of treatment probably also have a high likelihood of MDR.

<sup>c</sup> Regimen may be modified once DST results are available (up to 2–3 months after the start of treatment).

*Notes:*

1. A country's standard MDR regimen is based on country-specific DST data from similar groups of patients (see Chapter 7).
2. In the country's standard regimens, the 8-month retreatment regimen should not be "augmented" by a fluoroquinolone or an injectable second-line drug; this practice jeopardizes second-line drugs that are critical treatment options for MDR patients. Second-line drugs should be used only for MDR regimens and only if quality-assured drugs can be provided by DOT for the whole course of therapy. In addition, there must be laboratory capacity for cultures to monitor treatment response, as well as a system for detecting and treating adverse reactions (see section 3.8.3 on the Green Light Committee Initiative) before embarking on MDR-TB treatment.

should they have MDR-TB. Some programmes recommend DST for HIV-infected TB patients with CD4 counts below 200 cells/mm<sup>3</sup> (6).

- Persons who develop active TB after known exposure to a patient with documented MDR-TB.
- All new patients in countries where the level of MDR-TB in new patients is >3% (23).



programme managers and staff can institute appropriate action to overcome them and improve programme performance. Evaluation of the outcomes of treatment and trends must be done at peripheral, district, regional and national levels to allow any necessary corrective action to be taken. It can also identify districts or units that are performing well and allows for positive feedback to be provided to staff; successful practices can then be replicated elsewhere.

Table 4.1 DEFINITIONS OF TREATMENT OUTCOMES<sup>a</sup>

Outcome	Definition
Cure	A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion <sup>b</sup>
Treatment failure	A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.
Died	A patient who dies for any reason during the course of treatment.
Default	A patient whose treatment was interrupted for 2 consecutive months or more.
Transfer out	A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.
Treatment success	A sum of cured and completed treatment <sup>c</sup>

<sup>a</sup> These definitions apply to pulmonary smear-positive and smear-negative patients, and to patients with extrapulmonary disease. Outcomes in these patients need to be evaluated separately.

<sup>b</sup> The sputum examination may not have been done or the results may not be available.

<sup>c</sup> For smear- or culture-positive patients only.

The district/local TB officer should perform cohort analysis of treatment outcome every quarter-year and at the end of every year. A typical cohort consists of all TB patients registered during a quarter. New patients and subcategories of previously treated patients (relapses, return after default, failures) should be analysed as separate cohorts because they have different characteristics and expected results. Evaluation of outcome at the end of treatment should be undertaken as soon as possible after the last patient in the cohort completes treatment.<sup>1</sup>

This information is transmitted in quarterly reports. After local review, district re-

<sup>1</sup> Outcomes are routinely evaluated at the beginning of the quarter following the completion of treatment by the last patient in that cohort.

Table 4.2 SYMPTOM-BASED APPROACH TO MANAGING SIDE-EFFECTS OF ANTI-TB DRUGS

Side-effects	Drug(s) probably responsible	Management
<i>Major</i>		<i>Stop responsible drug(s) and refer to clinician urgently</i>
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin
<i>Minor</i>		<i>Continue anti-TB drugs, check drug doses</i>
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily (3)
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration (3)

# Co-management of HIV and active TB disease

## 5.1 Chapter objectives

This chapter describes WHO recommendations for:

- HIV testing and counselling of all patients known or suspected to have TB;
- HIV prevention for TB patients;
- treatment of TB in people living with HIV;
- providing co-trimoxazole preventive therapy to all HIV-positive TB patients;
- when to start antiretroviral therapy (ART) and what antiretroviral agents to use;
- drug susceptibility testing and patient monitoring;
- ensuring comprehensive HIV care and support services.

Implementing these recommendations requires collaboration between TB and HIV/AIDS programmes at all levels (1, 2) and will help to reduce the burden of HIV in people diagnosed with TB. Similarly, collaboration is essential to reduce the burden of TB in people living with HIV. (While outside the scope of this chapter, see: *Three I's for reducing the burden of TB in persons living with HIV: Intensified case-finding (ICF), Isoniazid preventive therapy (IPT) and TB Infection control (IC) for people living with HIV* (3).)

People living with HIV are more likely to present with extrapulmonary or sputum smear-negative TB, especially as immunosuppression advances (4, 5). This can result in misdiagnosis or delays in diagnosis and, in turn, higher morbidity and mortality. Implementation of the WHO-recommended algorithms to diagnose pulmonary and extrapulmonary TB in HIV-prevalent settings is therefore crucial (6). (The treatment of extrapulmonary TB is discussed in Chapter 8.)

## 5.2 HIV testing and counselling for *all* patients known or suspected to have TB

Irrespective of epidemic setting, WHO recommends HIV testing for patients of all ages who present with signs or symptoms that suggest tuberculosis (7), whether TB is suspected or already confirmed. (See also Standard 14 of the ISTC (8).) TB is often the first clinical indication that a person has underlying HIV infection, and TB services can be an extremely important entry point to HIV prevention, care and treatment (1). In addition, the HIV status of TB patients makes a difference to their TB treatment. (See section 5.4, which includes the new recommendation for daily intensive-phase dosing of anti-TB drugs for HIV-positive TB patients.)

Detecting HIV infection in a TB patient is also critical for the TB patient's household members: HIV-positive TB patients may have household members who are also living with HIV. Testing and counselling should be recommended for children and other immediate family members of all people living with HIV, in cases where horizontal or vertical transmission may have occurred. Within a family-centred approach to HIV testing, once a family member is identified as having HIV, health workers should encourage and actively facilitate HIV testing for other family members. This could be done, where possible and appropriate, through couples or family testing and counselling services (9).<sup>1</sup> Serodiscordant partnerships (in which one partner is HIV-positive and the other is HIV-negative) provide an important opportunity for prevention of HIV transmission (10, 11).

Household contacts of an infectious TB case are a high priority for TB screening and treatment, especially if they are living with HIV (2, 12, 13), and those who are found to have active TB disease need prompt treatment. Among household contacts, people living with HIV (and children, regardless of their HIV status) who do not have active TB are candidates for isoniazid treatment to prevent the development of active TB (3). (See also Standards 16, 18 and 19 of the ISTC (8).)

WHO recommends “provider-initiated” testing, which means that the health care provider recommends HIV testing and counselling as a standard component of care (7). For patients known or suspected to have TB, provider-initiated HIV testing can be done at the same time the sputum samples or chest radiographs are obtained. This is more efficient, and more likely to result in patients learning their HIV status, than referring them elsewhere for HIV testing and counselling (12).

As in the case of client-initiated HIV testing, informed consent, counselling and confidentiality are essential. WHO recommends that providers use “opt-out” approaches (7), meaning that individuals must specifically decline the HIV test after receiving pretest information if they do not want the test to be performed.

The provision of HIV testing by the same health worker who provides the TB treatment (or the provision of HIV testing in the same facility) has been shown to facilitate HIV testing for TB patients (14, 15). If this is not possible, NTPs should take responsibility for ensuring that any referred individual actually goes for a test.

An HIV testing service using rapid assays offers several programmatic advantages. Rapid assays are easy to use and can be carried out by any health care worker who has received appropriate training. Most rapid HIV test kits can be stored at room temperature (up to 30 °C) and can be used for a single test without compromising the integrity of the remaining part of the test kit. Moreover, the diagnostic performance of high-quality rapid assays is comparable to that of traditional enzyme immunoassays, and the short turnaround time ensures that individuals receive their test results quickly. These rapid assays do not require specialized equipment and can be

<sup>1</sup> [http://www.who.int/hiv/pub/priority\\_interventions\\_web.pdf](http://www.who.int/hiv/pub/priority_interventions_web.pdf)

performed outside the traditional laboratory setting (7). The visibility of the test (to the person being tested) and its speed increase confidence in results and help to avoid clerical errors.

As with conventional HIV assays, a reactive result from the first, highly sensitive, rapid assay requires confirmation by a second, more specific test, typically another rapid assay. If the second test yields non-reactive or indeterminate results, a third test may be performed; if the result is reactive, follow-up HIV testing should be performed on a specimen collected 4 weeks after the initial test. The follow-up testing would rule out possible seroconversion at the time of the initial test as the cause of discrepant testing results and would reveal most technical or clerical errors. The use of rapid assay should be undertaken only with functional quality assurance in place and conducted according to the country's nationally validated testing algorithm. Appropriate post-test counselling should be ensured, with a strong focus on HIV prevention; this will also help prevent the spread of TB.

For more information, see WHO's *Scaling up HIV testing and counselling services: a toolkit for programme managers* (2005), which is available online at: [www.who.int/hiv/topics/vct/toolkit/en/](http://www.who.int/hiv/topics/vct/toolkit/en/)

### 5.3 HIV prevention in TB patients

National TB control programmes should develop and implement comprehensive HIV prevention strategies for their patients. Appropriate prevention messages and methods should be provided to patients with confirmed or suspected TB, according to their HIV status and local knowledge of the modes of transmission or assessment of risk (1). Harm-reduction measures for TB patients who are injecting drug users should be provided, either by NTPs or through referral linkages to HIV programmes (2).

### 5.4 TB treatment in people living with HIV

Among treated TB patients, death rates are higher in HIV-positive than in HIV-negative patients. Case-fatality is higher in people living with HIV with smear-negative pulmonary and extrapulmonary TB, as these patients are generally more immunosuppressed than those with smear-positive TB (6). The case-fatality rate is reduced in patients who receive concurrent ART (see section 5.6 below).

The first priority for HIV-positive TB patients is to initiate TB treatment, followed by co-trimoxazole and ART (16) (see sections 5.5 and 5.6 below). For TB diagnosed in a person already taking ART, see section 5.9.

New TB patients<sup>1</sup> living with HIV should be treated with the regimens given in Tables 3.2 and 3.3. However, the three times weekly intensive phase is no longer an

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<sup>1</sup> New TB patients are those who have had no prior TB treatment or who have been receiving TB treatment for less than 1 month.

option. This new recommendation is based on a systematic review showing that the incidence of relapse and failure among HIV-positive TB patients who were treated with intermittent TB therapy throughout treatment was 2–3 times higher than that in patients who received a daily intensive phase (17). In addition, a study in India showed that HIV-positive patients with pulmonary TB are at higher risk of acquired rifampicin resistance, when failing a three times weekly short-course intermittent regimen (18).

#### ■ Recommendation 4.1

**TB patients with known positive HIV status and all TB patients living in HIV-prevalent settings<sup>1</sup> should receive daily TB treatment at least during the intensive phase**

(Strong/High grade of evidence)

#### ■ Recommendation 4.2

**For the continuation phase, the optimal dosing frequency is also daily for these patients**

(Strong/High grade of evidence)

#### ■ Recommendation 4.3

**If a daily continuation phase is not possible for these patients, three times weekly dosing during the continuation phase is an acceptable alternative**

(Conditional/High or moderate grade of evidence)

In terms of duration of therapy, some experts recommend prolonging TB treatment in persons living with HIV in certain circumstances (19). A systematic review found lower relapse rates in people living with HIV treated with 8 or more months of rifampicin-containing regimens compared with the current recommendation of 6 months. However, the data quality of the studies included in the review was low, and different durations of TB treatment for HIV-positive and HIV-negative individuals would be operationally difficult in resource-constrained and HIV-prevalent settings (17).

#### ■ Recommendation 4.4

**It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients**

(Strong/High grade of evidence)

HIV-positive TB patients who have been previously treated for TB should receive the same retreatment regimens as HIV-negative TB patients (see Table 3.5).

<sup>1</sup> Countries, subnational administrative units, or selected facilities where the HIV prevalence among adult pregnant women is  $\geq 1\%$  or among TB patients is  $\geq 5\%$ .

Rifampicin induces the activity of hepatic enzymes, leading to sub-therapeutic concentrations of some antiretroviral drugs. This is discussed in section 5.6.1 below.

### 5.5 Co-trimoxazole preventive therapy

In all HIV-positive TB patients, co-trimoxazole preventive therapy should be initiated as soon as possible and given throughout TB treatment. (See also Standard 15 of the ISTC (8).) Co-trimoxazole preventive therapy substantially reduces mortality in HIV-positive TB patients (16, 20). The exact mode of activity is not clear but co-trimoxazole is known to prevent *Pneumocystis jirovecii* and malaria and is likely to have an impact on a range of bacterial infections in HIV-positive TB patients.

A system for providing co-trimoxazole preventive therapy to all people living with HIV who have active TB should be established by TB and HIV programmes. Continuation after TB treatment is completed should be considered in accordance with national guidelines.

For co-trimoxazole dosages, contraindications, and side-effects and their management, see reference 20.

### 5.6 Antiretroviral therapy

Antiretroviral therapy improves survival in HIV-positive patients (16). In addition, antiretroviral therapy reduces TB rates by up to 90% at an individual level, by 60% at a population level and it reduces TB recurrence rates by 50% (21–22). ART should be initiated for *all* people living with HIV with active TB disease irrespective of CD4 cell count. TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of starting TB treatment (23).

#### 5.6.1 What ART regimens to start?

Standardized, simplified ART regimens are used to support HIV treatment programmes so they can reach as many people living with HIV as possible. For the most up-to-date WHO guidance on ART regimens, reference should be made to [www.who.int/hiv/pub/guidelines/en](http://www.who.int/hiv/pub/guidelines/en)

WHO recommends that the first-line ART regimen contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI). These are efficacious, relatively less expensive, have generic and FDC formulations, do not require a cold chain, and preserve a potent new class of agents (protease inhibitors) for second-line regimens. The preferred NRTI backbone is zidovudine (AZT) or tenofovir disoproxil fumarate (TDF), combined with either lamivudine (3TC) or emtricitabine (FTC). For the NNRTI, WHO recommends either efavirenz (EFV) or nevirapine (NVP) (23).

The recommended first-line ART regimens for TB patients are those that contain efavirenz (EFV), since interactions with anti-TB drugs are minimal. In several cohort

studies, ART with standard-dose efavirenz and two nucleosides was well tolerated and highly efficacious in achieving complete viral suppression among patients receiving concomitant rifampicin-based TB treatment (24).

Because of concerns related to teratogenicity, efavirenz should not be used in women of childbearing potential without adequate contraception, nor should it be used for women who are in the first trimester of pregnancy. Alternatives are also needed for patients who are intolerant to efavirenz or are infected with a strain of HIV that is resistant to NNRTIs. For those who are unable to tolerate EFV or who have contraindications to an EFV-based regimen, AZT +3TC + NVP or TDF +3TC or FTC + NVP or a triple NRTI regimen (AZT+3TC+ABC or AZT+3TC+TDF) is recommended; the choice of regimen should be based on available regimens within countries. In countries where rifampicin is available, the lead-in dose of nevirapine is not necessary.

In individuals who need TB treatment and who require an ART regimen containing a boosted protease inhibitor (PI), it is recommended to give a rifabutin-based TB treatment. If rifabutin is not available, the use of rifampicin and a boosted antiretroviral regimen containing lopinavir or saquinavir with additional ritonavir dosing is recommended; this regimen should be closely monitored.

### 5.6.2 When to start ART?

While the optimal time to start ART in relation to the start of TB therapy is not yet clear, one randomized controlled trial provides some evidence for early initiation of antiretroviral therapy in terms of reduced all-cause mortality, improved TB outcomes and reduced incidence of immune reconstitution inflammatory syndrome (IRIS) (25). The recommendations of WHO in 2009 are that TB treatment should be commenced first and ART subsequently commenced, as soon as possible and within the first 8 weeks of starting TB treatment. In this rapidly evolving field, updated information and guidance on antiretroviral therapy is provided by WHO (see: <http://www.who.int/hiv/pub/guidelines/en>).

The rationale for starting ART soon after TB diagnosis is that case-fatality among HIV-TB patients occurs mainly in the first 2 months of TB treatment (16). However, early initiation of ART (within a few weeks of starting TB treatment) means a large number of tablets to ingest, which may discourage treatment adherence; there may also be complications – adverse effects, drug–drug interactions and IRIS.

Mild to moderate IRIS is relatively common in patients with TB started on ART: it has been reported in up to one-third of patients in some studies. However, it is relatively rare in its severe forms (24, 26). The syndrome can present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, or exacerbation of inflammatory changes at other sites. It generally presents within 3 months of the start of ART and is more common when CD4 cell count is low (<50 cells/mm<sup>3</sup>). Most cases resolve without intervention and ART can be safely continued (24).



IRIS is a diagnosis of exclusion. Patients with advanced AIDS may show clinical deterioration for a number of other reasons. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening. IRIS can also be confused with TB treatment failure. In addition, HIV-positive TB patients may be demonstrating progression of TB disease due to TB drug-resistance. IRIS is not a reason to switch patients to second-line ART, although the ART treatment regimen may need to be adjusted to ensure compatibility with the TB treatment (6).

### 5.7 Drug susceptibility testing

High mortality rates have been reported among people living with HIV who have drug resistant-TB (26), and rates can exceed 90% in patients coinfecting with extensively drug-resistant TB (XDR-TB) and HIV (27, 28). Prompt initiation of appropriate TB treatment (and subsequent initiation of ART) can reduce mortality among people living with HIV who have drug-resistant TB (28).

WHO recommends that NTPs undertake DST at the start of TB therapy in all HIV-positive TB patients, to avoid mortality due to unrecognized drug-resistant TB (25), and strongly encourages the use of rapid DST in sputum smear-positive persons living with HIV (26).

If the country is introducing DST, but does not yet have the resources to test all HIV-positive TB patients, initial NTP policy should be to target DST at the start of TB treatment for patients with previously treated TB, who are very likely to be multidrug-resistant (see section 3.8.1). This group includes patients whose prior TB treatment has failed, who have relapsed or who are returning from default. NTP managers may also choose to target DST for those HIV-positive TB patients with lower CD4 counts (e.g. less than 200 cells/mm<sup>3</sup>) given their very high risk of death due to unrecognized drug-resistant TB (26).

### 5.8 Patient monitoring during TB treatment

(See also Chapter 4.)

Adverse drug effects are common in HIV-positive TB patients, and some toxicities are common to both ART and TB drugs (16). Overlapping toxicities between ART, TB therapy and co-trimoxazole include rash (and, more rarely, hepatic dysfunction), and vigilant monitoring of side-effects is therefore essential (20, 26).

### 5.9 Considerations when TB is diagnosed in people living with HIV who are already receiving antiretroviral therapy

When TB is diagnosed in patients already receiving ART, TB treatment should be started immediately. There are two issues to consider in such cases: whether ART needs to be modified because of drug–drug interactions or to reduce the potential for

overlapping toxicities, and whether the presentation of active TB in a patient on ART constitutes ART failure that requires a change in the ART regimen. Diagnosis and management of ART failure are covered in another WHO document (29).

## 5.10 HIV-related prevention, treatment, care and support


The recommended package of HIV-related prevention, treatment, care and support services and support for people living with HIV should be provided either by TB programmes or by referral to HIV/AIDS programmes (12, 16). To improve treatment success, the special needs of particular groups (e.g. drug users, prisoners, migrant populations, other marginalized groups) should be assessed and addressed; their care should be integrated with other services.

A comprehensive AIDS care strategy includes clinical management (prophylaxis, early diagnosis, treatment and follow-up care for opportunistic infections), nursing care (including hygiene promotion and nutritional support), palliative care, home care (including education for care providers and patients' relatives, promoting universal precautions), counselling and social support (1, 9). This package of care includes a core set of effective interventions, listed below, that are simple and relatively inexpensive, can improve the quality of life, prevent further transmission of HIV and, in some cases, delay progression of HIV disease and prevent mortality. In addition to ART, these interventions promote health, reduce the risk of HIV transmission to others, and address diseases that most impact the quality and duration of life of adults and adolescents with HIV (3):

- reducing the burden of TB via intensified TB case-finding, infection control, and isoniazid preventive therapy;
- psychosocial counselling and support;
- disclosure of HIV status, partner notification and testing and counselling;
- co-trimoxazole prophylaxis;
- preventing fungal infections;
- preventing sexually transmitted and other reproductive tract infections;
- preventing malaria;
- providing selected vaccines (hepatitis B, pneumococcal, influenza, and yellow fever);
- nutrition;
- family planning;
- preventing mother-to-child transmission of HIV;
- needle/syringe programmes and opioid substitution therapy; and water, sanitation and hygiene.

Through the GLC Initiative, NTPs have access to:

- expertise in programmatic management of drug-resistant TB based on best available evidence and collective experience;
- high-quality drugs to treat drug-resistant TB at concessional prices;
- support through a wide network of technical partners;
- peer support and knowledge-sharing with other GLC-approved programmes;
- independent external monitoring and evaluation.



# **Guidelines for the programmatic management of drug-resistant tuberculosis**

**2011 update**



**World Health  
Organization**

For the scope of question 1 (Table 1), the discussion leading to the recommendations the term rapid tests to those providing a diagnosis within two days of specimen testing, thereby including only tests using molecular techniques (line probe assay and Xpert MDR/RIF<sup>1</sup>). The different groups of drugs referred to in the text are composed of the agents shown in Table 3. In the analyses of data for questions 3–5, streptomycin was found to be used but it is generally considered a first-line drug. Later-generation fluoroquinolones included levofloxacin (750mg/day or more), moxifloxacin, gatifloxacin and sparfloxacin. Ciprofloxacin, ofloxacin and levofloxacin (up to 600mg/day) were considered earlier-generation fluoroquinolones for this analysis.

**Table 3. Groups of second-line anti-tuberculosis agents referred to in these guidelines**

Group name	Anti-tuberculosis agent	Abbreviation
Second-line parenteral agent (injectable anti-tuberculosis drugs)	kanamycin	Km
	amikacin	Amk
	capreomycin	Cm
Fluoroquinolones	levofloxacin	Lfx
	moxifloxacin	Mfx
	gatifloxacin	Gfx
	ofloxacin	Ofx
Oral bacteriostatic second-line anti-tuberculosis drugs	ethionamide	Eto
	prothionamide	Pto
	cycloserine	Cs
	terizidone	Trd
	<i>p</i> -aminosalicylic acid	PAS
Group 5 drugs	clofazimine	Cfz
	linezolid	Lzd
	amoxicillin/clavulanate	Amx/Clv
	thioacetazone	Thz
	clarithromycin	Clr
	imipenem	Ipm

NB. Other drugs not generally considered as second-line anti-tuberculosis agents were also used to treat drug-resistant TB in some of the cohorts included in this analysis. These included the parenteral agent *viomycin*, the fluoroquinolones *ciprofloxacin* and *sparfloxacin*, as well as *azithromycin*, *roxithromycin*, *high-dose isoniazid* and *thioridazine*, which were included under the Group 5.

### Assessment of evidence and its grading

The evidence review teams assessed the evidence for the questions and their outcomes through a series of systematic literature reviews following an approved methodology that was documented (Annex 1). Titles, abstracts and full text of potentially relevant literature were screened using key subject words and text words. The search was not limited by study type or time period. Authors in the field and members of the Guideline Development Group were contacted to identify missing studies or studies in progress. Case-based data

<sup>1</sup> Xpert MTB/RIF refers to the currently available methodology that employs an automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance.



# 1. Rapid drug susceptibility testing for early start of appropriate treatment

## Recommendation

**Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation, ⊕○○○/very low quality evidence).**

## Evidence

The evidence used to determine the optimal timing of DST and the method of testing to be used relied on simulations from modelling work (9). There are inherent limitations when using models, which are linked to the underlying assumptions. Sensitivity analyses, however, showed fairly consistent results when epidemiological conditions and costs were varied.

For the purposes of the recommendation, the group considered a rapid test as one providing a diagnosis of resistance to isoniazid and rifampicin or rifampicin alone within two days of specimen testing. Only molecular tests can detect resistance so fast, of which two technologies – line probe assay and Xpert MTB/RIF – are currently recommended for use by WHO. Conventional DST of cultured mycobacteria typically provides results within 1–3 months.

Outcomes of interest were reduced mortality, increased likelihood of cure, decreased development of additional resistance, and reduced likelihood of failure and relapse, expressed as the cost per DALY averted. The model did not take into consideration ongoing transmission that may occur if diagnosis of resistance is delayed.

## Summary of findings

Performing DST in all patients before treatment using a rapid test that detects resistance to isoniazid and rifampicin was the best strategy for averting deaths and preventing acquired MDR-TB. The modelling work showed that rapid testing of both isoniazid and rifampicin at the time of diagnosis was the most cost effective testing strategy for any patient group or setting, even at very low levels of resistance among TB patients (MDR-TB in >1% and isoniazid resistance (other than MDR-TB) in >2%). For previously untreated patients, DST at the start of treatment was a better strategy than waiting to

test only those patients who remained sputum-smear positive later in the course of their first-line treatment.

Rapid DST of rifampicin alone did not have the same benefit as rapid testing of both isoniazid and rifampicin resistance. This is because DST of rifampicin alone could not prevent the acquisition of additional resistance in patients resistant to isoniazid only.

## Benefits

A short time to diagnosis may influence the composition of a patient's initial treatment and increase the likelihood of starting appropriate treatment early. The likely benefits of rapid DST therefore include increased cure rates, decreased mortality, reduced development of additional drug resistance, and a reduced likelihood of failure and relapse.

The detection of rifampicin resistance by Xpert MTB/RIF usually suffices to start a patient on a second-line TB regimen (10), subject to confirmatory testing in situations with low rifampicin resistance (see also under Risks).

Use of rapid tests to detect resistance to both rifampicin and isoniazid would have better outcomes than tests to detect resistance to rifampicin alone. The detection of patients with isoniazid resistance alone may provide an opportunity to initiate effective treatment before additional acquisition of resistance to rifampicin develops. The model assumptions included appropriate treatment for non-MDR-TB isoniazid-resistant TB. The optimal regimen for the treatment of isoniazid-resistant strains has not been determined, and benefits may be less if suboptimal regimens are used.

The influence on secondary transmission of resistant strains was not included in the model and therefore estimates of reduction in mortality and morbidity from early detection and treatment are likely to be conservative. The increased costs of using the diagnostic test may be offset by a reduction in the requirement of conventional TB laboratory capacity which may be substantial.

## Risks

The harms of rapid DST include false-positive results leading to wasted resources, and increased toxicity to the patient from unnecessary administration of second-line medications. Awareness of these potential harms is particularly important in patient groups in which rifampicin resistance is rare. Rifampicin resistance detected by Xpert MTB/RIF in such a situation will have a low predictive value and results need to be confirmed by phenotypic DST or line probe assay (10). Another potential harm from placing all rifampicin-resistant patients on an MDR-TB regimen is the exclusion of isoniazid from their treatment, thus depriving them of a safe and useful bactericidal drug.

## 2. Monitoring the response to MDR-TB treatment

### Recommendation

The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment (conditional recommendation, ⊕○○○/very low quality evidence).

### Evidence

The evidence used to assess how best to monitor treatment in MDR-TB patients using sputum smear microscopy and culture in settings with reliable direct microscopy was based on data pooled from 10 published observational studies (12–19). Monthly monitoring by culture was used as the reference in all the analyses. Random-effects Cox proportional hazards models were used to estimate the hazard ratio of failure, comparing monthly culture to alternative monitoring strategies.

### Summary of findings

Performing monthly sputum smear microscopy and culture was the best strategy in identifying failures earlier. Sputum smear microscopy alone resulted in delayed detection of failure: when done at monthly rather than two monthly intervals it increased the detection of failure slightly (not significantly). In patients who were smear-negative at the start of treatment, monthly smear monitoring (compared with culture) resulted in a statistically significantly greater risk of delayed detection of failure compared with smear-positive patients. Stratified estimates by HIV serostatus, body mass index, and extent of disease on chest radiograph, were not significantly different ( $P > 0.05$ ).

The related end-points of drug resistance, initiation of appropriate treatment and the acquisition of resistance were not measured. There was no information about reversion or reinfection and no data were available to assess the quality of culture and smear testing. Other methods of evaluating response to treatment such as clinical indicators or chest radiography were not evaluated.

### Benefits

Concomitant use of sputum smear microscopy and culture test results helps identify patients whose bacteriology remains positive or reverts to positive following initial



## 3. Composition of second-line anti-tuberculosis regimens

### Recommendations

- 3.1 In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, ⊕○○○/very low quality evidence).
- 3.2 In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, ⊕○○○/very low quality evidence).
- 3.3 In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, ⊕○○○/very low quality evidence).
- 3.4 In the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase<sup>3</sup> (conditional recommendation, ⊕○○○/very low quality evidence).
- 3.5 In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (*p*-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, ⊕○○○/very low quality evidence).

### Evidence

The evidence used to address the questions on which drugs to include (with or without information on their DST patterns) and the number of drugs to be used in regimens for MDR-TB patients was based on studies published in three major systematic reviews (27–29). All three reviews searched EMBASE and MEDLINE databases as well as the Cochrane Library and the ISI Web of Science. Studies published before 1970 and those including only XDR-TB cases were excluded. The reviewers then pooled individual patient data from studies which had featured in the systematic reviews for a meta-analysis.

The meta-analysis included 32 studies with more than 9000 treatment episodes for which the authors could be contacted and were willing to share their data (30). Patients

<sup>3</sup> The intensive phase is the initial part of a course of treatment during which a parenteral (injectable) agent is used.

The recommended composition of second-line regimens for MDR-TB patients has changed from those in the 2008 emergency update (3) (Table 7). The previous guidelines had likewise recommended designing regimens based on known drug resistance patterns in the country or patient, the history of previous treatment by the patient, and the drugs commonly used in the country. The inclusion of at least four drugs with either certain, or almost certain, effectiveness was previously recommended. The previous recommended regimen was composed of pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic drugs. Resort to antibiotics from Group 5 was only recommended if additional drugs were needed to bring the total to four. More drugs were recommended in the case of extensive disease or uncertain effectiveness.

**Table 7. Changes to the recommendations on regimen composition between the 2008 and 2011 updates of the guidelines**

2008 emergency update (3)	2011 update
Include at least four anti-tuberculosis drugs with either certain, or almost certain, effectiveness during the intensive phase of treatment.	Include at least four second-line anti-tuberculosis drugs likely to be effective as well as pyrazinamide during the intensive phase of treatment.
Consider adding more drugs in patients with extensive disease or uncertain effectiveness.	No evidence found to support the use of more than four second-line anti-tuberculosis drugs in patients with extensive disease. Increasing the number of second-line drugs in a regimen is permissible if the effectiveness of some of the drugs is uncertain.
The regimen should include pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic anti-tuberculosis drugs (no preference of oral bacteriostatic second-line anti-tuberculosis drug was made).	The regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and cycloserine, or else PAS if cycloserine cannot be used.
Ethambutol may be considered effective and included in the regimen if DST shows susceptibility.	Ethambutol may be used but is not included among the drugs making up the standard regimen.
Treatment with Group 5 drugs is recommended only if additional drugs are needed to bring the total to four.	Group 5 drugs may be used but are not included among the drugs making up the standard regimen.

## Benefits

The recommendations contained in this section aim to increase the likelihood of cure and reduce the risk of failure, relapse and death. The decision to recommend an additional drug to the regimen during the intensive phase of treatment – from the minimum of four inferred from the analysis – was based on expert opinion. It is intended



## 4. Duration of second-line anti-tuberculosis regimens

### Recommendations

- 4.1 In the treatment of patients with MDR-TB, an intensive phase of at least 8 months' duration is recommended (conditional recommendation, ⊕○○○/very low quality evidence).**
- 4.2 In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, ⊕○○○/very low quality evidence).**

### Evidence

The evidence used to derive recommendations on the duration of treatment was based on an analysis of the same individual patient data collected and described in Section 3 above. All data were from observational studies, and the quality of evidence was classified as very low. Attempts to control for selection bias and confounding in this review are unlikely to have adjusted for all important factors, and patients who receive longer therapy may be those who are more sick. Patients with XDR-TB were also excluded from the analysis. The findings may not be generalizable to all populations in settings with high or low prevalence of drug resistance or with different levels of resources.

### Summary of findings

The analysis provided evidence for an association between treatment success and the total length of treatment and the length of the intensive phase. The trend in relative risk for cure over successive months of treatment was studied to determine the optimal minimum duration for both total treatment and the intensive phase. The adjusted relative risk for cure peaked at an intensive phase lasting between 7.1 and 8.5 months (see also Table 8 and Annex 2). For total treatment duration, the peak occurred between 18.6 and 21.5 months for patients who had no previous MDR-TB treatment. The peak occurred later in patients who had been treated for MDR-TB (27.6–30.5 months), but no clear incremental trend was observed in these patients and the number of observations was far fewer than for those who had no previous MDR-TB treatment.

# Treatment of extrapulmonary TB and of TB in special situations

## 8.1 Chapter objectives

This chapter describes:

- the treatment of extrapulmonary TB;
- important drug interactions;
- the treatment of TB in pregnancy and breastfeeding;
- the treatment of patients with pre-existing liver disease, renal failure or renal insufficiency.

## 8.2 Treatment of extrapulmonary TB

Although TB most commonly affects the lungs, any organ or tissue can be involved. In countries with comprehensive diagnostic and reporting systems, extrapulmonary TB accounts for 20–25% of reported cases. Globally, extrapulmonary cases (without concurrent pulmonary involvement) comprised 14% of notified cases (new and relapse) in 2007. Of specific forms of EPTB, lymphatic, pleural, and bone or joint disease are the most common, while pericardial, meningeal and disseminated (miliary) forms are more likely to result in a fatal outcome.

As discussed in Chapter 5, provider-initiated HIV testing is recommended as part of the evaluation of all TB patients and patients in whom the disease is suspected. HIV testing is especially important in persons with or suspected of having EPTB because of the increased frequency of extrapulmonary involvement in persons with immunosuppression. Extrapulmonary TB is considered to be WHO clinical stage 4 HIV disease (1). (More details on the treatment of TB in persons living with HIV are provided in Chapter 5.)

For WHO guidance on the prompt diagnosis of EPTB, see reference 1.

Pulmonary and extrapulmonary disease should be treated with the same regimens (see Chapter 3).<sup>1</sup> Note that some experts recommend 9–12 months of treatment for TB meningitis (2, 3) given the serious risk of disability and mortality, and 9 months of treatment for TB of bones or joints because of the difficulties of assessing treatment response (3). Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis (1–4). In tuberculous meningitis, ethambutol should be replaced by streptomycin.

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<sup>1</sup> This fourth edition no longer includes the option of omitting ethambutol during the intensive phase of treatment for patients with extrapulmonary disease who are known to be HIV-negative.

Although sometimes required for diagnosis, surgery plays little role in the treatment of extrapulmonary TB. It is reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis and neurological involvement from Pott's disease (spinal TB). For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage appear beneficial (3).

### 8.3 Important drug interactions

Many TB patients have concomitant illnesses. At the start of TB treatment, all patients should be asked about medicines they are currently taking. The most important interactions with anti-TB drugs are due to rifampicin. Rifampicin induces pathways that metabolize other drugs, thereby reducing the concentration and effect of those drugs. To maintain a therapeutic effect, dosages of the other drug(s) may need to be increased. When rifampicin is discontinued, its metabolism-inducing effect resolves within about 2 weeks, and dosages of the other drug(s) will need to be reduced (3).

More information on TB drug interactions is available in Annex 1 and on the web sites of the Global Drug Facility and the WHO Essential Medicines Library ([www.stoptb.org/gdf/drugsupply/drugs\\_available.asp](http://www.stoptb.org/gdf/drugsupply/drugs_available.asp) and [www.who.int/emlib/Medicines.aspx](http://www.who.int/emlib/Medicines.aspx)).

Rifampicin substantially reduces the concentration and effect of the following drugs (for recommendations on dosage adjustment and on clinical or therapeutic drug monitoring, see reference 3):

- anti-infectives (including certain antiretroviral drugs discussed in section 5.6.1, mefloquine, azole antifungal agents, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol);
- hormone therapy,<sup>1</sup> including ethinylestradiol, norethindrone, tamoxifen, levothyroxine;
- methadone;
- warfarin;
- cyclosporin;
- corticosteroids;
- anticonvulsants (including phenytoin);
- cardiovascular agents including digoxin (among patients with renal insufficiency), digitoxin, verapamil, nifedipine, diltiazem, propranolol, metoprolol, enalapril, losartan, quinidine, mexiletine, tocainide, propafenone;
- theophylline;
- sulfonylurea hypoglycaemics;

<sup>1</sup> Rifampicin interacts with oral contraceptive medications leading to lowered protective efficacy. A woman receiving oral contraception may choose between two options while receiving treatment with rifampicin: following consultation with a clinician, an oral contraceptive pill containing a higher estrogen dose (50 µg), or another form of contraception.

- hypolipidaemics including simvastatin and fluvastatin;
- nortriptyline, haloperidol, quetiapine, benzodiazepines (including diazepam, triazolam), zolpidem, buspirone.

### 8.4 Treatment regimens in special situations

The treatment of TB in pregnancy and breastfeeding, liver disorders, and renal failure is discussed below.

#### 8.4.1 Pregnancy and breastfeeding

Women of childbearing age should be asked about current or planned pregnancy before starting TB treatment. A pregnant woman should be advised that successful treatment of TB with the standard regimen is important for successful outcome of pregnancy. With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy: streptomycin is ototoxic to the fetus and should not be used during pregnancy.

A breastfeeding woman who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby. Mother and baby should stay together and the baby should continue to breastfeed. After active TB in the baby is ruled out, the baby should be given 6 months of isoniazid preventive therapy, followed by BCG vaccination (5).

Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid (see section 4.8).

#### 8.4.2 Liver disorders

This section covers TB treatment in patients with pre-existing liver disease; for detection and management of hepatitis induced by anti-TB drugs, see section 4.10.2.

Patients with the following conditions can receive the usual TB regimens provided that there is no clinical evidence of chronic liver disease: hepatitis virus carriage, a past history of acute hepatitis, current excessive alcohol consumption. However, hepatotoxic reactions to anti-TB drugs may be more common among these patients and should therefore be anticipated (see section 4.10.2).

In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment, if possible. If the serum alanine aminotransferase level (6) is more than 3 times normal before the initiation of treatment,<sup>1</sup> the following regimens should be considered (also discussed in section 4.10.2).<sup>2</sup> The more unstable or severe the liver disease is, the fewer hepatotoxic drugs should be used.

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<sup>1</sup> Note that TB itself may involve the liver and cause abnormal liver function.

<sup>2</sup> In some cases of concurrent acute (i.e. viral) hepatitis not related to TB or TB treatment, it may be possible to defer TB treatment until the acute hepatitis has resolved.

Possible regimens include:

- Two hepatotoxic drugs (rather than the three in the standard regimen):
  - 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented);
  - 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;
  - 6–9 months of rifampicin, pyrazinamide and ethambutol.
- One hepatotoxic drug:
  - 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.
- No hepatotoxic drugs:
  - 18–24 months of streptomycin, ethambutol and a fluoroquinolone.

Expert consultation is advisable in treating patients with advanced or unstable liver disease.

Clinical monitoring (and liver function tests, if possible) of all patients with pre-existing liver disease should be performed during treatment.

### 8.4.3 Renal failure and severe renal insufficiency

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin. Isoniazid and rifampicin are eliminated by biliary excretion, so no change in dosing is necessary. There is significant renal excretion of ethambutol and metabolites of pyrazinamide, and doses should therefore be adjusted. Three times per week administration of these two drugs at the following doses is recommended: pyrazinamide (25 mg/kg), and ethambutol (15 mg/kg) (3, 7). These are the same mg/kg doses as those listed under Daily in Table 3.1.

While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy (see section 4.8).

Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. If streptomycin must be used, the dosage is 15 mg/kg, two or three times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored.

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[www.who.int/tb/challenges/hiv/en/index.html](http://www.who.int/tb/challenges/hiv/en/index.html)

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# Key recommendations

- 1 Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

*Strong recommendation, moderate quality of evidence<sup>1</sup>*

- 2 Adults and adolescents living with HIV and screened with a clinical algorithm for TB, and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

*Strong recommendation, moderate quality of evidence*

- 3 Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

*Strong recommendation, high quality of evidence*

- 4 Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT.<sup>2</sup> IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

*Conditional recommendation, moderate quality of evidence<sup>3</sup>*

- 5 TST is not a requirement for initiating IPT in people living with HIV.

*Strong recommendation, moderate quality of evidence*

- 6 People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.

*Strong recommendation, high quality of evidence*

<sup>1</sup> A **strong recommendation** is one for which the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

<sup>2</sup> The considerations for implementation should include the local context such as the epidemiology of TB and HIV, and settings with the highest rates of prevalence and transmission of TB among people living with HIV.

<sup>3</sup> A **conditional recommendation** is one for which the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects and data to support the recommendation are scant. Therefore, the recommendation is only applicable to a specific group, population or setting, or new evidence may result in changing the balance of risk to benefit, or the benefits may not warrant the cost or resource requirements in all settings.

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**7** Providing IPT to people living with HIV does not increase the risk of developing isoniazid (INH)-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

*Strong recommendation, moderate quality of evidence*

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**8** Children living with HIV who do not have poor weight gain,<sup>4</sup> fever or current cough are unlikely to have active TB.

*Strong recommendation, low quality of evidence*

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**9** Children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, such children should be offered IPT regardless of their age.

*Strong recommendation, low quality of evidence*

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**10** Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.

*Strong recommendation, moderate quality of evidence*

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**11** In children living with HIV who are less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.

*Strong recommendation, low quality of evidence*

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**12** All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.

*Conditional recommendation, low quality of evidence*

<sup>4</sup> **Poor weight** gain is defined as reported weight loss, **or** very low weight (weight-for-age less than –3 z-score), **or** underweight (weight-for-age less than –2 z-score), **or** confirmed weight loss (>5%) since the last visit, **or** growth curve flattening,

## 2.2.5 Patients previously treated for TB (secondary prophylaxis)

The Guidelines Group reviewed the evidence and discussed IPT as secondary prophylaxis for people who have previously been successfully treated for TB. GRADE assessment of the evidence from four studies including three randomized controlled trials [24–26] and one observational study [27] showed the value of providing IPT immediately after successful completion of TB treatment (Annex 7). The Guidelines Group strongly recommends that adults and adolescents living with HIV who successfully complete their TB

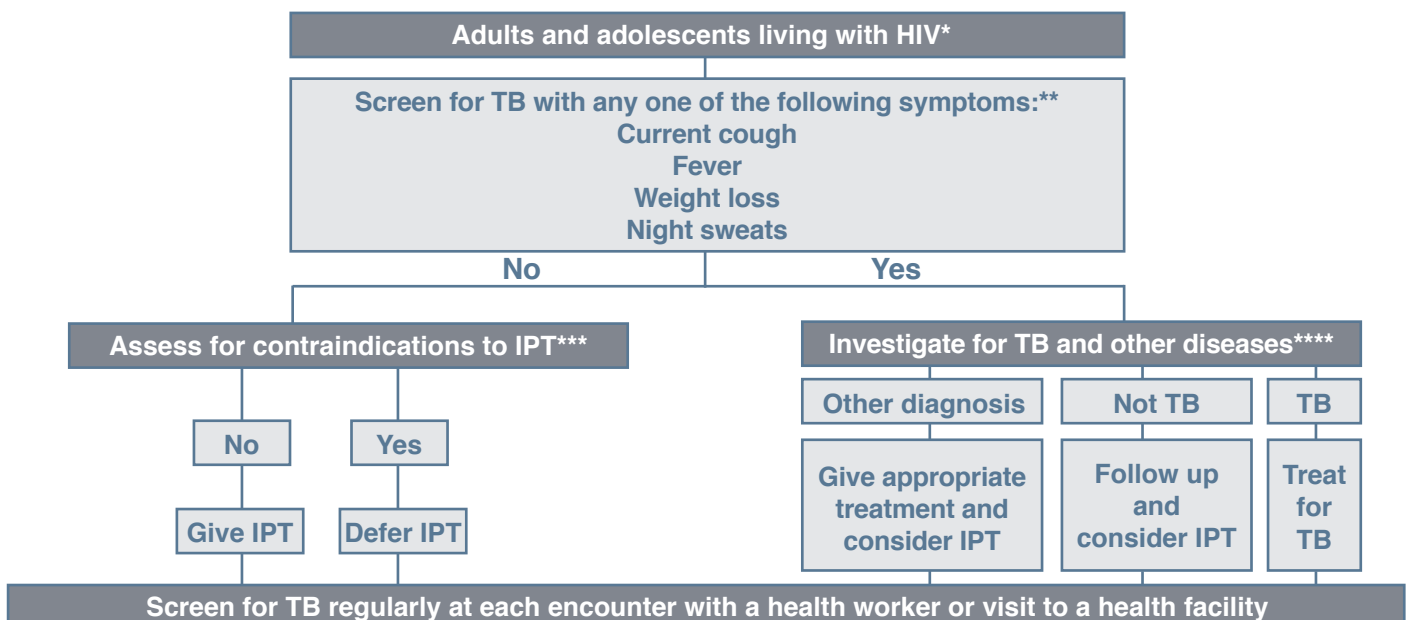
treatment should continue receiving INH for another six months and should conditionally receive it for 36 months based on the local situation (e.g. high rates of TB prevalence and transmission) and existing national guidelines. There was no evidence on the potential role of IPT for those who had successfully completed treatment for multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB. Therefore, the Guidelines Group did not make any recommendation on the use of IPT after successful treatment for MDR or XDR TB.

## 2.2.6 Special populations

People living with HIV in congregate settings, such as prisons and centres for refugees or internally displaced persons, have a higher risk for and incidence of TB, HIV infection and drug use.[2] Special attention has to be paid to ensure screening for TB and provision of IPT for these groups. Injecting drug users have a higher risk of coinfections with HIV, TB and hepatitis causing viruses. Screening

for TB and providing IPT for injecting drug users should be combined with harm reduction measures, including the provision of testing for hepatitis B and hepatitis C infection, and referral for positive cases. [28] Sound clinical judgement is required to weigh the benefits of IPT among injecting drug users with hepatitis coinfection. IPT should not be provided in the presence of active hepatitis.

## 2.2.7 Figure 1. Algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



### FOOTNOTES TO ALGORITHM FOR ADULTS

\* Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce *M. tuberculosis* transmission in all settings that provide care.

\*\* Chest radiography can be done if available, but is not required to classify patients into TB and non-TB groups. In high HIV-prevalence settings with a high TB prevalence among people living with HIV (e.g. greater than 10%), strong consideration must be given to adding other sensitive investigations.

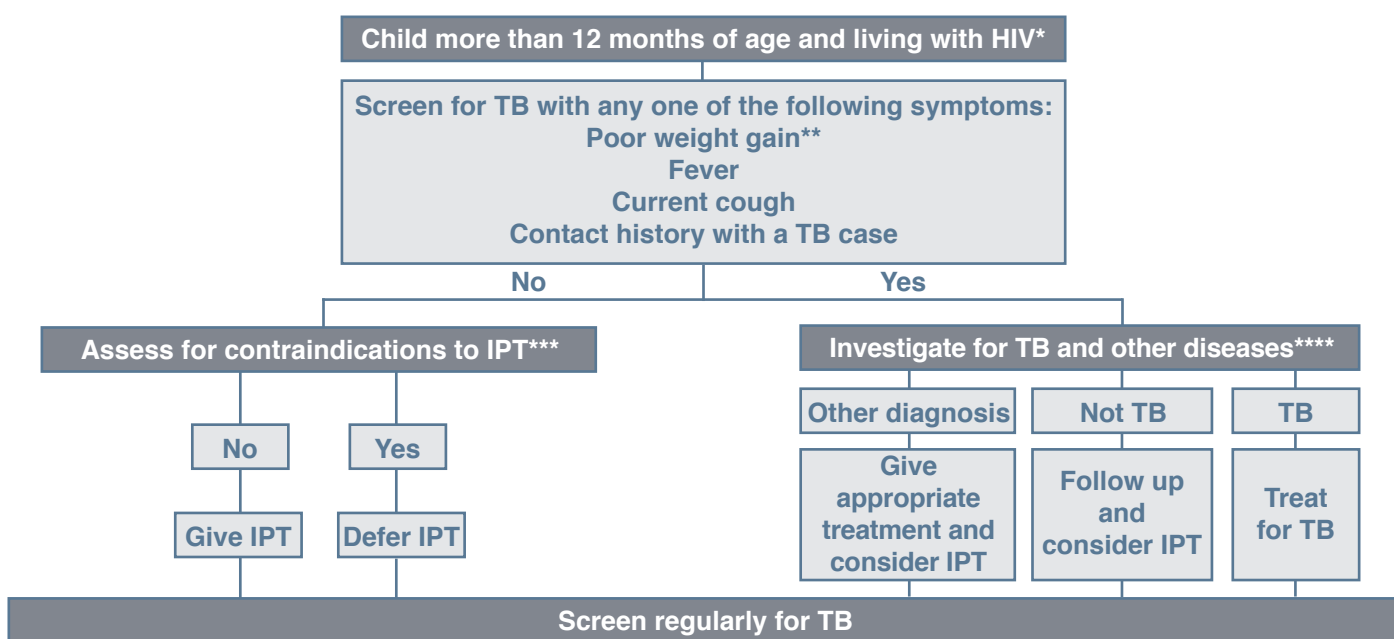
\*\*\* Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption, and symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for starting IPT. Although not a requirement for initiating IPT, TST may be done as a part of eligibility screening in some settings.

\*\*\*\* Investigations for TB should be done in accordance with existing national guidelines.

Encouraging data show that IGRA are more sensitive than TST in HIV-infected children, including those with a low CD4 count and/or malnutrition.[50–52]. In addition, excellent specificity for *M. tuberculosis* infection has been reported and, unlike TST, IGRA are unaffected by prior BCG vaccination or exposure to environmental mycobacteria. However, more evidence is needed and implementation issues

affecting most HIV-prevalence settings (cost, specific laboratory equipment and the need for a venous blood sample) have to be addressed. Therefore, the Guidelines Group strongly recommends that there is currently insufficient evidence to support the use of IGRA to identify children eligible for IPT outside research settings with laboratory-validated procedures.[53]

### 3.5 Figure 2: Algorithm for TB screening in children more than one year of age and living with HIV



#### FOOTNOTES TO ALGORITHM FOR CHILDREN

\* All children and infants less than one year of age should be provided with IPT if they have a history of household contact with a TB case.

\*\* Poor weight gain is defined as reported weight loss, **or** very low weight (weight-for-age less than -3 z-score), **or** underweight (weight-for-age less than -2 z-score), **or** confirmed weight loss (>5%) since the last visit, **or** growth curve flattening.

\*\*\* Contraindications include: active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. Past history of TB should not be a contraindication for starting IPT. Although not a requirement for initiating IPT, TST may be done as a part of eligibility screening in some settings.

\*\*\*\* Investigations for TB must be done in accordance with existing national guidelines.