

## CHAPTER 4

# Definitions: case registration, bacteriology and treatment outcomes

### 4.1 Chapter objectives

This chapter establishes case definitions, patient registration categories, bacteriological terms, treatment outcome definitions and cohort analysis procedures for patients who meet WHO Category IV diagnostic criteria, defined as “chronic cases” (still sputum smear-positive after supervised re-treatment; proven or suspected MDR-TB) (1).

For definitions of diagnostic Categories I, II and III, see other WHO documents (1).

The categories, definitions and procedures defined in this chapter will facilitate the following:

- standardized patient registration and case notification,
- assignment to appropriate treatment regimens,
- case evaluation according to site, bacteriology and history of treatment,
- cohort analysis of registered Category IV patients and Category IV treatment outcomes.

### 4.2 General definitions of resistance

A patient is determined to have drug-resistant TB only through laboratory confirmation of in vitro resistance to one or more first-line antituberculosis drugs (see Chapter 6 for further information on laboratory requirements).

Antituberculosis drug resistance is classified according to the following three definitions:

- **Confirmed mono-resistance.** Tuberculosis in patients whose infecting isolates of *M. tuberculosis* are confirmed to be resistant in vitro to one first-line antituberculosis drug.
- **Confirmed poly-resistance.** Tuberculosis in patients whose infecting isolates are resistant in vitro to more than one first-line antituberculosis drug, other than both isoniazid and rifampicin.
- **Confirmed MDR-TB.** Tuberculosis in patients whose infecting isolates are resistant in vitro to at least isoniazid and rifampicin.

While laboratory confirmation of MDR-TB is being obtained, patients may be included in diagnostic Category IV **only** if representative DRS data indicate a very high probability of MDR-TB (see Chapter 5).

### 4.3 Site of drug-resistant tuberculosis disease (pulmonary and extrapulmonary)

In general, recommended treatment regimens for drug-resistant forms of TB are similar, irrespective of site. Defining site is important primarily for recording and reporting purposes.

- **Pulmonary tuberculosis.** Tuberculosis involving the lung parenchyma. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, therefore constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a pulmonary case.
- **Extrapulmonary tuberculosis.** Tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. The definition of an extrapulmonary case with several sites affected depends on the site representing the most severe form of disease.

### 4.4 Bacteriology

Bacteriological examinations used in patients with drug-resistant TB include sputum smear microscopy and culture. Sputum smear microscopy and culture should be performed and results reported according to international standards (2). These techniques should be used at the start of treatment to confirm TB disease and to identify the most infectious (sputum smear-positive) patients.

**Sputum conversion** is defined as two sets of consecutive negative smears and cultures taken 30 days apart. Both bacteriological techniques (smear and culture) are used to monitor patients throughout therapy (see Chapter 11).

Many programmes use the frequency and timing of smear and culture conversion among smear- and/or culture-positive patients receiving Category IV treatment as indicators of programme performance. In order for a patient to be considered culture- or sputum smear-positive at the start of treatment, the following criteria must be met: at least one pretreatment culture or smear was positive; the collection date of the sample on which the culture or smear was performed was less than 30 days before, or 7 days after, initiation of Category IV treatment.

Alternatively, some programmes will choose not to examine sputum conversion but rather to look at the proportion of patients who are smear- and culture-negative at one point in time (for example, 6 months after the start of treatment) to help in the interim evaluation of programme performance (see Chapter 18 and Form 08).

#### 4.5 Registration based on history of previous antituberculosis treatment

Before enrolling a patient in a Category IV regimen with second-line drugs, it is important to determine whether the patient has previously received antituberculosis treatment and, if so, to record the treatment outcome (see Chapter 18 and Form 01). It is also important to record whether the patient ever previously received second-line drugs. These registration groups are essential for epidemiological monitoring of the TB epidemic at the regional and country level and help to identify patients who may be at risk for failing a Category IV regimen.

The registration groups delineated below refer explicitly to previous treatment and do not purport to explain the reason(s) for resistance.<sup>1</sup> The groups are defined by the treatment history when the sputum was taken that showed MDR-TB or, in cases where MDR-TB is suspected, at the time the patient is registered as Category IV.

- **New Category IV patients.** Category IV patients who have never received antituberculosis treatment or who have received antituberculosis treatment for less than one month. (Note: patients who had DST at the start of a WHO Category I regimen and are then switched to a Category IV regimen because of resistance are placed in this group, even if they received more than one month of Category I treatment.)
- **Category IV patients previously treated with first-line drugs only.** Category IV patients who have been treated for one month or more with first-line drugs only.
- **Category IV patients previously treated with second-line drugs.** Category IV patients who have been treated for one month or more with one or more second-line drugs, with or without first-line drugs.
- **Transfer in.** Category IV patients who have been transferred from another register for treatment of drug-resistant TB to continue Category IV treatment. Their outcomes should be reported to the transferring unit so that it can report their outcomes in the cohort in which they originally started MDR-TB treatment.
- **Other.** Category IV patients who do not fit the above definitions. This group includes Category IV patients who were treated outside DOTS programmes.

<sup>1</sup> These guidelines do not use the terms “primary” and “acquired” drug resistance because these types of resistance cannot be distinguished in most programmes for control of drug-resistant TB. If DST is done before the start of the patient’s first antituberculosis treatment, any resistance documented is primary resistance. If new resistance is found when DST is later repeated and genetic testing confirms that it is the same strain, only then can it be concluded that the strain has acquired resistance.

Patients should be further classified according to the outcome of the most recent previous treatment: failed, defaulted and relapse, as defined in other WHO documents (1). If DST is carried out at the start of Category I, II or III treatment and the patient is later switched to a Category IV regimen because of resistance (without meeting the formal criteria of failure), he or she should be included in the outcome analysis of Category I, II and III – under the category Change to Category IV and noted as such in the District Tuberculosis Register. Programmes should keep track of the number of patients who do not meet the traditional definition of failure and are switched to Category IV regimens because of resistance. The Category IV Treatment Card provides for documentation of history of previous antituberculosis treatment and therefore facilitates the determination of the group registrations as described above (see Chapter 18 and Form 01).

#### 4.6 Treatment outcome definitions for Category IV treatment

The following are mutually exclusive Category IV outcome definitions (3) that rely on the use of laboratory smear and culture as a monitoring tool and will be reported in Forms 01, 02 and 09 (see Chapter 18). The outcomes should be applied to patients who are receiving Category IV regimens. They have been constructed to be parallel to the six DOTS outcomes for drug-susceptible TB (1, 3).

- **Cured.** A Category IV patient who has completed treatment according to the programme's protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture<sup>1</sup> is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.
- **Treatment completed.** A Category IV patient who has completed treatment according to the programme's protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
- **Died.** A Category IV patient who dies for any reason during the course of MDR-TB treatment.
- **Failed.** Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment

<sup>1</sup> A positive culture requires >10 colonies on solid media; two consecutive positive cultures must be obtained if <10 colonies are detected in the first culture; if the second culture also contains <10 colonies, the culture should be interpreted as positive.

early because of poor response or adverse events. These latter failures can be indicated separately for the purposes of sub-analysis.)

- **Defaulted.** A Category IV patient whose treatment was interrupted for two or more consecutive months for any reason.
- **Transferred out.** A Category IV patient who has been transferred to another reporting and recording unit and whose treatment outcome is unknown.

#### 4.7 Cohort analysis

A Category IV treatment cohort is defined as a group of patients who start Category IV treatment during a defined time period. The Category IV treatment cohort will consist of a subset of patients recorded in the Category IV Register, i.e. those who actually started Category IV treatment during the specified period of time. To allow adequate analysis of all patients who meet the criteria of diagnostic Category IV, three dates should be recorded (these dates are recorded in both Forms 01 and 02; see Chapter 18):

1. **Date of initial registration as a TB case** (most commonly obtained from the District Tuberculosis Register)
2. **Date of registration in Category IV**
3. **Date of starting Category IV treatment**

**Treatment cohort analysis** focuses on treatment outcomes among patients who actually started Category IV treatment. **Registration cohort analysis** focuses on the number of patients identified and the number who are placed on treatment. Programmes are encouraged to undertake cohort analysis for both treatment and registration.

The recommended time frame for Category IV treatment cohort analysis reflects the long duration of Category IV regimens. Cohort analyses should be carried out at 24 months and repeated at 36 months after the last patient starts treatment (see Chapter 18 and Form 09). The analysis is done at 24 months because most of the patients will have finished treatment, allowing preliminary assessment of cure rates. Since a few patients may be on treatment longer than 24 months, the cohort analysis is repeated at 36 months after the last patient starts treatment. The 36-month evaluation is considered the final treatment cohort analysis result.

All patients should be assigned the first outcome they experience for recording and reporting purposes. Programmes may wish to record subsequent outcomes among patients followed systematically. (For example, a patient defaults on the first Category IV treatment and then returns 14 months later to be re-registered and is cured with a second Category IV treatment. This patient should receive a final outcome of “defaulted” in the cohort in which he or she was first registered and “cured” in the second cohort.) Patients who

remain on treatment at the end of a designated cohort treatment period must be identified as “still on treatment”.

For each cohort, an interim status should be assessed at 6 months after the start of treatment to monitor programme progress (see Chapter 18 and Form 08).

## References

1. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).
2. *Laboratory services in tuberculosis control. Parts I, II and III*. Geneva, World Health Organization, 1998 (WHO/TB/98.258).
3. Laserson KF et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 2005, 9(6):640–645.