

MANAGEMENT OF DIABETES MELLITUS-TUBERCULOSIS

A Guide to the Essential Practice

First Edition
2018

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Contents

Preface	6
Authorship and Acknowledgements	7
Abbreviations	8
Target audience	9
Executive summary and key recommendations	10
1 Tuberculosis	12
1.1 Summary statement	12
1.2 What is the burden of tuberculosis (TB)?	12
1.3 What is TB?	13
1.4 What is the natural history of TB?	15
1.5 Who is at higher risk of developing TB?	15
1.6 What is drug-resistant TB and how does it develop?	15
1.7 How should health care workers screen for TB?	16
1.8 Should the chest radiograph be used to screen for TB?	17
1.9 What are the common tools available for diagnosing TB at peripheral level?	17
1.10 What is the role of the National Reference Laboratory in diagnosing TB?	19
1.11 What should not be used for the diagnosis of active TB?	19
1.12 How are patients diagnosed with active TB disease classified?	20
1.13 How is latent TB Infection diagnosed?	20
2 Diabetes mellitus	22
2.1 Summary Statement	22
2.2 What is the burden of diabetes mellitus (DM)?	22
2.3 How does DM develop and how is it classified?	23
2.4 What health problems does DM cause?	24
2.5 What are the main symptoms of DM?	24
2.6 What are the key risk factors for DM?	25
2.7 How is DM and “Pre-DM” diagnosed?	25
2.8 What are the advantages and disadvantages of the three main tests for diagnosing DM?	27
2.9 Can point of care tests be used for diagnosing DM?	28
2.10 What should be done about patients with Pre-DM?	29

3	Impact of diabetes mellitus and tuberculosis on each other	30			
3.1	Summary statement	30			
3.2	Does diabetes mellitus (DM) increase the incidence and prevalence of tuberculosis (TB)?	30			
3.3	Does DM change the clinical presentation of TB?	31			
3.4	Does DM affect the response to TB treatment?	31			
3.5	Does active TB disease cause hyperglycaemia or DM?	32			
4	Screening people with tuberculosis for diabetes mellitus	34			
4.1	Summary statement	34			
4.2	Should all tuberculosis (TB) patients be routinely screened for diabetes mellitus (DM)?	34			
4.3	When should patients with TB be screened for DM?	35			
4.4	What are the best tools available for diagnosing DM among TB patients?	37			
4.5	Which is the best algorithm to use to screen TB patients for DM?	37			
4.6	Should there be a repeat diagnostic blood test to confirm the diagnosis of DM?	40			
5	Screening people with diabetes mellitus for tuberculosis	42			
5.1	Summary statement	42			
5.2	Should persons with diabetes mellitus (DM) be screened for tuberculosis (TB)?	42			
5.3	How should patients with newly diagnosed DM be screened for TB?	43			
5.4	Should patients with DM be screened for latent TB?	44			
6	Management of diabetes mellitus during anti-tuberculosis treatment	46			
6.1	Summary statement	46			
6.2	What are the aims and principles of diabetes mellitus (DM) management?	46			
6.3	Who should provide DM care for patients with DM and tuberculosis (TB)?	47			
6.4	What glucose control target should be aimed for in a patient with DM and TB and how should this be monitored?	48			
6.5	What glucose lowering drugs should be used in patients with TB?	49			
6.6	What should be done for a patient diagnosed with TB in a DM clinic?	51			
6.7	What should be done for a TB patient diagnosed in a TB clinic who is diagnosed with new DM or who is already receiving treatment for DM?	52			
6.8	What can be done to prevent and / or manage hypoglycaemia?	53			
6.9	How is cardiovascular risk assessed and managed?	53			
6.10	Should cardiovascular risk be assessed and managed in patients with newly diagnosed DM during TB treatment?	55			
6.11	How should DM be managed in patients with HIV-associated TB?	55			
6.12	What should be done at the end of TB treatment?	56			
7	Management of tuberculosis in persons with diabetes mellitus	58			
7.1	Summary statement	58			
7.2	What are the aims and principles of tuberculosis (TB) treatment?	58			
7.3	Drug-susceptible TB	59			
7.4	Where are diabetes mellitus (DM) patients who have active TB disease treated?	62			
7.5	How are DM patients who are being treated for drug-susceptible TB monitored?	62			
7.6	Are there special considerations in managing DM patients with drug-susceptible TB?	66			
7.7	Drug-resistant TB	68			
7.8	How is the treatment of MDR-TB / RR-TB monitored?	70			
8	Recording, reporting and cohort analysis	72			
8.1	Summary Statement	72			
8.2	What has been done so far with recording, reporting and cohort analysis for patients undergoing bi-directional screening for tuberculosis (TB) and diabetes mellitus (DM)?	72			
8.3	How to do recording and reporting on TB patients being screened for DM?	73			
8.4	How to do recording and reporting on persons with DM being screened for TB?	74			
9	Tuberculosis infection control and prevention of airborne transmission in diabetes clinics	76			
9.1	Summary statement	76			
9.2	What is the aim of tuberculosis (TB) infection control and prevention of airborne transmission in diabetes mellitus (DM) clinics?	76			
9.3	What is airborne transmission and how can it be prevented?	76			
9.4	Does airborne transmission of <i>M. tuberculosis</i> occur in DM clinics?	77			
9.5	What are administrative controls?	77			
9.6	What are environmental controls?	78			
9.7	What are personal protection measures?	79			
10	Collaborative services for tuberculosis and diabetes mellitus	80			
10.1	Summary statement	80			
10.2	What is the reason for collaboration?	80			
10.3	What are the objectives of collaborative services?	81			
10.4	How can collaboration be achieved?	81			
10.5	What should these joint coordinating bodies do?	82			
10.6	How should joint diabetes mellitus (DM) / tuberculosis (TB) activities be started?	83			
10.7	How should collaborative activities be monitored and evaluated?	85			
11	Further reading	86			
11.1	Useful documents (in chronological order)	86			
11.2	Useful scientific and review papers (in chronological order)	87			
	Annexes	90			

Tables and Figures

Tables		
2.1	Thresholds and cut-off points for Diabetes Mellitus (DM) and Pre-DM	26
4.1	Algorithm for the diagnosis of DM among TB patients	36
6.1	Targets for glycaemic control during TB treatment	49
6.2	Common glucose-lowering drugs used for managing DM in TB patients	50
6.3	Management of HbA1c or blood glucose at the start of TB treatment	53
6.4	Cardiovascular disease risk in patients with DM and TB	54
6.5	Special considerations when co-managing HIV, DM and TB	56
7.1	Recommended doses of first-line TB drugs for adults with DM	60
7.2	For patients with drug-susceptible TB, the number of FDC tablets to be given daily for adults on treatment according to weight bands and the contents of the tablets	61
7.3	The most common adverse effects from the four essential anti-TB drugs, their relationship to DM and the suggested management	63
7.4	Definitions of treatment outcomes for patients (excluding RR-TB or MDR-TB)	65
7.5	Considerations in treatment and care of patients with both TB and DM	66
7.6	Drugs recommended for the treatment of MDR-TB	69
7.7	Treatment outcomes for RR-TB/ MDR-TB/ XDR-TB using second line treatment	71
8.1	Quarterly Cohort Report of TB patients being screened for DM	73
8.2	Quarterly Cohort Report of DM patients being screened for TB	75
10.1	Quarterly Cohort Report of DM Screening in TB Patients	84
10.2	Quarterly Report of TB Screening in DM Patients	85
Figures		
1.1	Natural history of tuberculosis	14
4.2	Algorithm for the diagnosis of DM among TB patients	38
5.1	Algorithm for TB screening amongst persons with newly diagnosed DM in countries with high prevalence of TB (> 100 cases per 100,000 population)	45

Preface

In 2017, there were an estimated 425 million people living with diabetes mellitus (DM) globally, with numbers set to rise to nearly 629 million by 2045. Each year, another 10 million people develop new DM and up to 5 million persons may die from DM-related complications. DM is a global pandemic and it is out of control.

Tuberculosis (TB) is the world's leading cause of death due to a single infectious disease. Despite significant progress made in fighting this disease, with reductions in TB incidence and TB mortality, it remains a major public health problem. In 2016, an estimated 10.4 million new people developed TB worldwide, with 600,000 being multidrug-resistant (*Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampicin or rifampicin alone). Despite the fact that TB is potentially curable, there were 1.7 million TB deaths in 2016, 374,000 of which were associated with HIV.

The association between DM and TB has been known for many years but studies in the last 10-15 years have highlighted that DM (both type 1 and type 2) increases the risk of active TB and that patients with dual disease have worse TB treatment outcomes compared with those who have just TB alone. The rapidly growing epidemic of DM in low and middle income countries therefore threatens TB control efforts and might derail progress made towards achieving the Sustainable Development Goal of ending TB by 2030. Likewise TB may provoke hyperglycaemia and result in overt DM in susceptible persons.

In 2011, a collaborative framework for the care and control of DM and TB was launched by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (The Union). The framework provides the policy package for jointly managing the two diseases. However, up to now there has been no practical guidance for front line health workers who are responsible for the diagnosis, management and care of patients with these two diseases.

This guide has been developed to provide essential information for the practical and comprehensive management and care of persons with DM-TB. It draws on evidence from published research, expert opinion and practical experience.

We hope it will serve as a useful and practical resource for frontline health workers and help to achieve WHO's End TB Strategy targets and the United Nations Sustainable Development Goals for both ending the TB epidemic and reducing premature mortality from DM.

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Abbreviations and Acronyms

AFB	Acid fast bacilli
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
BG	Blood glucose
DM	Diabetes mellitus
DOT	Directly observed treatment
DOTS	Directly observed therapy, short-course
EPTB	Extra-pulmonary tuberculosis
FBG	Fasting blood glucose
GH	General hospital
HIV	Human immunodeficiency virus
HbA1c	Glycosylated haemoglobin
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant TB
NCD	Non-communicable disease(s)
NTP	National Tuberculosis Programme
OGTT	Oral glucose tolerance test
Pre-DM	Pre-diabetes
PLHIV	Person(s) living with HIV
RBG	Random blood glucose
TB	Tuberculosis
The Union	International Union Against Tuberculosis and Lung Disease
UVGI	Ultraviolet germicidal irradiation
WHO	World Health Organization

Target Audience

The immediate beneficiaries of this guide are frontline health care professionals in low- and middle-income countries working in TB diagnostic and treatment services, in DM / non-communicable disease clinics and in primary health care facilities where services may be more integrated. They include clinicians, nurses, public health workers and programme managers.

Executive summary and key recommendations

Executive summary

Diabetes mellitus (DM) increases the risk of tuberculosis (TB) by 2-3 times and increases the risk of adverse TB treatment outcomes. TB causes “stress-induced hyperglycaemia” and this can make the management of DM more difficult. A published “Collaborative Framework for the care and control of Tuberculosis and Diabetes” can guide policy makers and implementers in combatting the epidemics of both diseases.

This document provides practical clinical and programmatic advice to programme managers and front-line health workers in low- and middle-income countries on the implementation of bi-directional screening of TB and DM; the management and treatment of patients with both diseases; and the monitoring, recording and reporting that is needed to evaluate collaborative activities.

Key recommendations

- All adult TB patients should be offered screening for DM. If resources are limited, a targeted screening approach should be used (for example, screening TB patients more than 40 years of age).
- Fasting blood glucose and, if resources are available, HbA1c are the preferred diagnostic tests for DM in patients with TB. Although the oral glucose tolerance test is the gold standard for diagnosing DM, it is too cumbersome for routine use in busy TB clinics.
- DM patients should be offered systematic screening for TB only in high-TB burden countries where TB prevalence is greater than 100 per 100,000 people.
- In persons newly diagnosed with DM, systematic TB screening should be performed actively (i.e., it should be provider-initiated) using a TB symptom screen followed by Xpert MTB/RIF if there are suggestive TB symptoms. If resources are available, consideration can also be given to screening with a chest radiograph, and if there are any abnormalities on chest radiography further investigation can be carried out by Xpert MTB/RIF.

- In persons with already established DM, there should be a heightened index of suspicion of TB and health workers should have a low threshold for testing for TB if suggestive symptoms and signs are present.
- Treatment for drug-susceptible and drug-resistant TB is similar in persons with and without DM. Health workers should be vigilant about monitoring treatment response as treatment failure and recurrent TB are more common in persons with DM.
- People with both DM and infectious TB should be treated for at least the first two weeks and preferably the first two months just in the TB clinic and visits to the DM clinic should be avoided wherever possible to prevent the transmission of *Mycobacterium tuberculosis* to health workers and persons with DM in that setting. This may require consultancies from the DM clinic to the TB clinic to assist with complicated cases.
- *Metformin* is the first-line drug of choice for treating persons with DM if medication is needed to control elevated glucose levels. Insulin may have to be considered if blood glucose levels are very high or in those whose blood glucose levels are not controlled with oral hypoglycaemic drugs.
- People with DM and a history of previous cardiovascular disease should be offered low dose aspirin and a statin.
- Patients with DM and TB need to be counselled about appropriate lifestyle management (smoking cessation, good diet and physical activity).
- Standardised recording and reporting tools for bidirectional screening need to include numbers screened and numbers diagnosed with each condition.
- The first priority of a national joint coordinating body for DM and TB should be the development and launch of a national plan for joint collaborative activities which incorporates development of national guidelines and tools, resource mobilisation, monitoring and evaluation and operational research, pre-service and in-service training and advocacy, communication and social mobilisation.

1 Tuberculosis

1.1 Summary statement

From a clinical and public health point of view, there are two stages of tuberculosis (TB): latent TB infection and active TB disease. The three common tools available for diagnosing TB at the peripheral level are: sputum smear microscopy, WHO-approved rapid molecular assays, such as Xpert MTB/RIF, and the chest radiograph. Given the low sensitivity of sputum smear microscopy and its inability to diagnose drug resistance, WHO now recommends the rapid molecular assay, Xpert MTB/RIF, as the first diagnostic test of choice among all people with presumptive TB: this test diagnoses both TB and rifampicin resistance within 2 hours. A recent updated version, Xpert MTB/RIF Ultra, is more sensitive than the former and has been recently recommended for use by the WHO. Chest radiography is a useful complementary tool in the diagnosis of clinical TB. Therapeutic trials and serological tests should not be used for the diagnosis of active TB. The tools available for diagnosing latent TB infection are the tuberculin skin test (TST) and the interferon gamma release assay (IGRA). These are not helpful in differentiating infection from active disease or in predicting who will progress to active TB disease and they should not be used in the diagnosis of active TB disease, except in children where they are part of the diagnostic package.

1.2 What is the burden of TB?

Despite great progress over the years, TB remains a major global health problem. In 2016, an estimated 10.4 million people fell ill with TB and 1.7 million people died from the disease. In 2016, an estimated 1.03 million people living with HIV developed TB and 374,000 died from TB-related causes. In 2012, the population attributable fraction of diabetes mellitus (DM) in adult TB was estimated at 15%, with the number of adult TB patients associated with DM being 1.04 million, similar to HIV-associated TB. The other key challenge relates to drug-resistant TB. The burden is huge: in 2016, there were an estimated 490,000 new cases of multidrug-resistant TB (MDR-TB) and 110,000 new cases of Rifampicin Resistant TB (RR-TB) globally, the latter group managed in the same way as for MDR-TB. With an estimated pool of about 3 billion people with latent TB infection, the TB epidemic is far from over.

1.3 What is TB?

TB is an airborne infectious disease caused by a microorganism called *Mycobacterium tuberculosis* (*M. tuberculosis*). The micro-organisms usually enter the body by inhalation and spread from the initial location in the lungs to other parts of the body via the blood stream, the lymphatic system and the airways or by direct extension to other organs.

From a clinical and public health perspective, there are two stages: latent TB infection and active TB disease. In latent TB infection, the infection is dormant (the organisms are not detectable by culture-based or any other direct method) and the person is asymptomatic and does not transmit the disease to others. In active TB disease, the infection is active (organisms are usually detectable by culture-based or other molecular methods) and the patient usually has symptoms and can transmit the disease to others.

There are two major types of active TB disease: pulmonary TB (PTB - affecting the lung parenchyma) and extra-pulmonary TB (EPTB - affecting any organ other than lung parenchyma).

PTB is the most common form of the disease, comprising over 80% of cases. This can further be subdivided into two subtypes:

i) **bacteriologically confirmed TB**: this is where *M. tuberculosis* micro-organisms are in sufficient numbers to be detected in the sputum or other specimens by diagnostic tests and these patients are the most infectious;

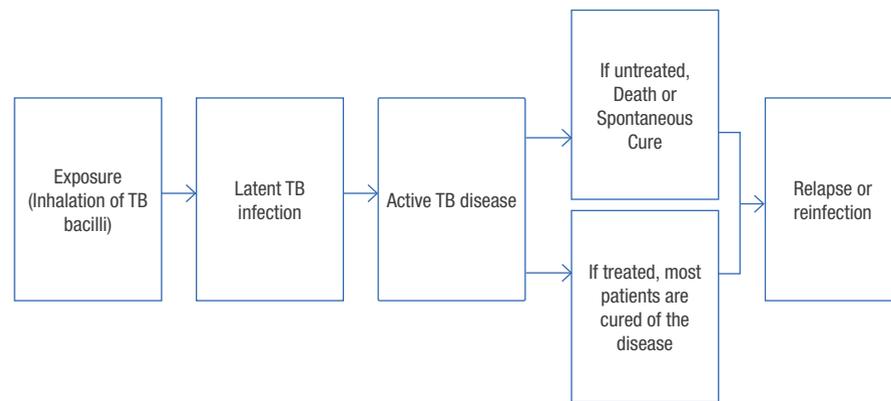
ii) **clinically diagnosed TB**: this is where *M. tuberculosis* micro-organisms cannot be detected in the sputum or other specimens but patients have persistent symptoms with chest radiograph shadows suggestive of TB disease. Such patients are relatively less infectious and the severity of their disease is usually less than that of bacteriologically confirmed patients.

EPTB affects organs other than the lung parenchyma, most frequently lymph nodes, pleura, pericardium, spine and other bones and joints, genitourinary tract, nervous system, abdomen or virtually any organ. EPTB patients are almost never infectious, unless they have PTB as well. If a patient has both types, then they are classified as 'pulmonary TB'.

1.4 What is the natural history of TB?

The natural history of TB is complex and not completely understood. The Figure below shows the key steps of progression from exposure to active disease and beyond.

Figure 1.1 Natural history of TB



The individual inhales droplet nuclei (small infectious respiratory particles of less than 5µm containing *M. tuberculosis*) which are spread into the air by infectious patients. The droplet nuclei which remain suspended in the air for long periods of time, especially in dark and poorly ventilated rooms, avoid bronchial defences and penetrate into the terminal alveoli of the lungs.

Exposure leads to one of two broad outcomes: elimination by the immune system or persistence of the micro-organisms. If the micro-organisms are not eliminated, they may persist in a dormant or quiescent state that is detectable by tuberculin skin test (TST) or Interferon Gamma Release Assays (IGRA). This stage is referred to as latent TB infection.

Among those who become infected and have latent TB infection, most will never become ill with active TB unless their immunity is compromised. Up to 10% of individuals, who become infected, however, subsequently develop active TB disease. While the likelihood of developing the disease is highest in the months immediately following infection, the risk remains throughout the person's life.

Active TB disease is frequently fatal if untreated, with approximately 70% dying within a period of ten years. But, if treated with the appropriate treatment regimens, more than 90% of those with active drug-susceptible TB disease can be cured. Latent TB infection

and active TB disease do not confer permanent immunity to re-infection. *M. tuberculosis*, which persists in a dormant state after treatment, may reactivate causing relapse or reinfection may occur with another strain of *M. tuberculosis* causing recurrent disease.

1.5 Who is at higher risk of developing TB?

There are several subgroups of people who are at a high risk of infection, such as those living in crowded conditions (especially migrants and refugees), living in poor housing, working in health care facilities or being household or other close contacts (especially children) of index TB patients. In terms of progressing from latent TB infection to active TB disease, HIV infection is the strongest known risk factor. Other risk factors include occupational exposure to silica dust, undernutrition, indoor air pollution, DM, tobacco smoking and excessive alcohol use.

1.6 What is drug-resistant TB and how does it develop?

Drug-resistant TB is caused by *M. tuberculosis* which is not responsive to treatment by one or more of the first-line TB drugs. Drug-resistant TB develops either from spontaneous, random mutations of the bacterial chromosome or as a result of inadequate treatment (bad prescribing practices, monotherapy, inadequate doses of drugs, non-adherence to recommended regimens or malabsorption of drugs).

Most TB patients (95%) have drug-susceptible disease and respond to the first-line TB drugs. However, about 5% of TB patients are resistant to first-line drugs and need to be treated with second-line and relatively toxic drugs. Drug resistance is classically divided into:

- **Primary resistance:** This is resistance in a patient who has never previously been treated for TB for as much as one month (new patients). It occurs when a patient develops TB after being infected by another patient who has resistant micro-organisms.
- **Acquired resistance:** This is mostly seen in patients who have previously been treated for TB for more than one month (previously treated patients). This is man-made and could be due to any of the factors mentioned above.

Drug resistance, whether primary or acquired, can be classified as follows:

- **Monoresistance:** Resistance to only one of the first line TB drugs (other than resistance to rifampicin).
- **Polyresistance:** Resistance to more than one of the first line TB drugs (other than resistance to rifampicin alone or resistance to isoniazid and rifampicin).
- **Multidrug-resistant tuberculosis (MDR-TB):** Resistance to at least isoniazid and rifampicin. This also includes patients diagnosed as “rifampicin-resistant” TB [RR-TB] by rapid molecular assays, such as Xpert MTB/RIF. WHO recommends that MDR-TB and RR-TB be regarded as multidrug-resistant TB and both types of disease need to be treated with the same MDR-TB treatment regimen.
- **Extensively drug-resistant tuberculosis (XDR-TB):** This is MDR-TB with added resistance to fluoroquinolones and one of the three injectable second line drugs (kanamycin, amikacin, capreomycin). About 10% of persons with MDR-TB are estimated to have XDR-TB. If there is just resistance to fluoroquinolones or one of the three injectable second line drugs, this is termed pre-XDR-TB.

1.7 How should health care workers screen for TB?

The most common, feasible and easiest way of screening for TB is to ask about symptoms suggestive of TB. The most frequent symptoms of pulmonary TB are:

- Cough for two weeks or more. In some patient groups, such as PLHIV and household contacts of TB patients, cough of any duration is important.
- Sputum production which may be blood-stained (haemoptysis), shortness of breath and chest pain; and
- Loss of appetite and loss of weight, a general feeling of illness (malaise) and tiredness (fatigue), night sweats and fever.

‘**Presumptive TB**’ refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect). WHO now recommends using the following four symptoms for screening: cough, fever, weight loss and night sweats. Patients with presumptive TB must submit two sputum specimens on the same day for examination if sputum smear microscopy will be performed. One sputum specimen is sufficient for Xpert MTB/RIF test.

Symptoms of EPTB depend on the organ involved. Chest pain from TB pleurisy, enlarged lymph nodes, joint pains, neck stiffness from meningitis and sharp angular deformity of the spine are some of the presenting symptoms and signs of EPTB. Specimens for

examination depend on the organ involved, for example, lymph node aspirate or biopsy for suspected TB lymphadenitis.

1.8 Should the chest radiograph be used to screen for TB?

With the END TB Strategy emphasising early diagnosis and treatment, chest radiography is being increasingly used in asymptomatic patients as a method of screening for TB because it is highly sensitive. Anyone found to have an abnormality suggestive of TB on chest radiography should be considered as having ‘presumptive TB’ and investigated further.

1.9 What are the common tools available for diagnosing TB at peripheral level?

There are three common technologies used for diagnosing active TB (drug-susceptible TB treated by first line TB drugs): sputum smear microscopy, the WHO approved rapid molecular tests, especially Xpert MTB/RIF, and the chest radiograph.

1. Sputum smear microscopy

This is still the most widely used tool for diagnosing TB in low- and middle-income countries. The examination consists of microscopic examination of a specimen of sputum that has been spread on a slide and stained by the Ziehl-Neelsen (ZN) or fluorescence method (smear microscopy). If micro-organisms (frequently referred to as acid-fast bacilli or AFB) are detected by this method, the patient is generally said to have smear-positive pulmonary TB. One positive smear result is sufficient to register the patient as having sputum smear-positive pulmonary TB and to start treatment.

Sputum smears are usually reported as positive, negative or not done. If AFB are present they can be recorded on a scale from scanty (< 9AFB per 100 high power fields) to 3+ (more than 10 AFB per high power field). In patients with PTB, AFB will only be detected on microscopy if there are 10,000 organisms or more per ml of sputum. The biggest advantage of smear microscopy is that this low-cost method identifies the most infectious forms of active TB disease.

2. Cartridge-Based Nucleic Acid Amplification Test (CB-NAAT)

One of the limitations of sputum smear microscopy is the poor sensitivity which ranges from 32%-97% in different settings and is especially low in PLHIV. Sputum smear microscopy cannot be used to diagnose drug-resistance.

The WHO recommends that the Xpert MTB/RIF test (a CB-NAAT based on automated GeneXpert technology from Cepheid, Sunnyvale, California, USA) be used as the first-line diagnostic test among all people with presumptive TB (both adults and children).

The Xpert MTB/RIF test has several advantages over smear microscopy: needs a single sputum specimen; a rapid turnaround of 2 hours; an automated method; high sensitivity; and the ability to detect rifampicin resistance. However, this test is also more expensive and has infrastructural and technical issues related to its deployment in peripheral settings. Recent developments, such as GeneXpert OMNI system (a portable, battery-operated, single-cartridge system), and Xpert MTB/RIF Ultra (an assay with higher sensitivity than Xpert MTB/RIF) address some of the limitations of the previous technology. In 2017, WHO recommended the use of Xpert MTB/RIF Ultra in all settings as a replacement for Xpert MTB/RIF.

3. Chest radiography

Chest radiography (including the latest advances, such as digital radiography and computer assisted radiography) is a useful complementary tool for the diagnosis of clinical TB. Patients with presumptive TB in whom the sputum smears or the Xpert MTB/RIF test result are negative should be reviewed by the clinician and a decision made about treating for clinical TB or not. Unfortunately, no chest radiographic pattern is absolutely diagnostic of TB, although upper lobe involvement, cavitation, fibrosis and bilateral disease are suggestive of TB. If the chest radiograph demonstrates changes suggestive of TB, one approach is to give a course of broad spectrum antibiotics (without anti-TB activity). If the symptoms persist after completion of the antibiotics, a second sputum examination may be performed and, if still negative, the clinician may then choose to treat the patient for TB and record the patient as a case of clinically diagnosed PTB.

1.10 What is the role of the National Reference Laboratory in diagnosing TB?

Generally, the National Reference Laboratory (NRL) is only used to confirm the pattern of drug-resistance in patients who are suspected of having MDR-TB or XDR-TB. Sputum specimens are transported from peripheral health centres to NRLs for this purpose.

Many NRLs use the traditional mycobacterial culture and phenotypic drug susceptibility testing. The usual culture medium is Lowenstein Jensen which can take several weeks to achieve mycobacterial growth, although newer and faster liquid culture systems (such as the Mycobacterium Growth Indicator Tube, MGIT) are being increasingly used. NRLs are also beginning to invest in different types of Line Probe Assay (LPA) that can detect resistance to isoniazid and rifampicin and also to second-line drugs through identification of specific gene mutations. LPAs allow a diagnosis of MDR-TB or XDR-TB within 3 days but for optimal use they require a good functioning and well-resourced laboratory with well trained and skilled laboratory technicians.

1.11 What should not be used for the diagnosis of active TB?

Serological tests:

Diagnostic tests for active TB based on the detection of antibodies (serological tests) have been commercially available for decades, although international guidelines do **NOT** recommend their use because the tests are inaccurate and imprecise. In 2011, WHO issued a strong recommendation against the use of all commercial serological tests for the diagnosis of TB disease and also called for countries to ban the use of serological tests to diagnose active TB disease.

Therapeutic trial of anti-TB treatment:

The 'trial of treatment' describes the response of a patient to a short course of TB treatment in order to decide whether or not the patient has TB. This is regarded as poor practice and should not be done.

1.12 How are patients diagnosed with active TB disease classified?

Patients are first classified according to whether active TB is bacteriologically confirmed or clinically diagnosed. They are then further classified according to:

- Anatomical site of disease: *PTB* or *EPTB*
- History of previous treatment: *new* or *previously treated TB* – this includes *relapse* or *recurrent TB*, *treatment after failure*, *treatment after loss to follow up*, *other previously treated*
- Drug resistance: *monoresistance*; *polyresistance*; *MDR-TB*; *pre-XDR-TB*; *XDR-TB*
- HIV status: *HIV-positive*, *HIV-negative* or *HIV unknown*

1.13 How is latent TB Infection diagnosed?

There are two tests available for diagnosing latent TB infection. These are the Tuberculin Skin Test (TST) and the Interferon Gamma Release Assay (IGRA). Both tests can be used for the diagnosis of latent TB infection but they are not useful in differentiating between latent TB infection and active TB disease and are poor in predicting who will progress to active TB. They should **not** be used for the diagnosis of active TB in adults.

2. Diabetes mellitus

2.1 Summary statement

Diabetes mellitus (DM) is increasing in every country in the world, with up to 95% of persons with DM having type 2 DM. In most low- and middle-income countries middle-aged or older people are at the highest risk of developing the disease although DM is starting to emerge at younger ages than previously recognised. The increase of type 2 DM is linked to globalisation and urbanisation with erosion of traditional diets, less physical activity and increased consumption of highly-processed, more energy-dense foods. Obesity, and especially central (abdominal) obesity, is a strong risk factor for type 2 DM. DM can lead to many serious health complications, especially microvascular and macrovascular, and the risk of infectious diseases, including TB, is also increased. DM is typically diagnosed in the routine setting by fasting blood glucose (FBG) or, if resources allow, by glycosylated haemoglobin (HbA1c) although by far the most sensitive test for DM is the oral glucose tolerance test (OGTT). The advantages and disadvantages of all three tests are discussed. In many resource limited settings, where laboratory facilities are not always widely available, DM is frequently diagnosed in practice using less optimal “screening” methods such as point of care (POC) finger prick (capillary) glucose tests. Repeated testing is advised to confirm any DM diagnosis, unless a patient has clear DM symptoms.

2.2 What is the burden of DM?

In 2017, there were an estimated 425 million people globally with DM, with numbers predicted to increase to 629 million by 2045. Each year, a further 10 million new people are estimated to develop DM and up to 5 million persons may die from DM-related complications. It is a global pandemic out of control. The Asian region is the most heavily affected, with China followed by India being the two countries with the highest numbers of people living with DM. DM prevalence is particularly high in the Pacific island groups (up to 30% among adults), the Middle East and Gulf states (between 12-29% of adults), as well as some parts of South Asia and the Western Pacific (about 11% in China), and the Caribbean (between 18-24% in Barbados). DM prevalence appears to be lower but still high at around 7% in sub-Saharan Africa. In all regions, DM is not necessarily a “disease of affluence” as DM prevalence in some rural areas has reached or exceeded that found in more affluent urban centres.

2.3 How does DM develop and how is it classified?

Diabetes (DM) is a serious and usually irreversible life-long health condition that occurs when the amount of glucose (sugar) in the blood is too high. There are two main types.

Type 1 DM:

This is an autoimmune condition where the insulin-producing cells of the pancreas are destroyed, meaning no insulin is produced. This condition usually develops rapidly and is fatal without insulin treatment. It mostly emerges during childhood but can develop at any age.

Type 2 DM:

This is a condition in which the body does not make enough insulin or becomes resistant to the effects of insulin, resulting in an increase in the blood glucose. The development of type 2 DM is not usually as rapid as with type 1 DM and the majority of patients can be managed without insulin at least in the initial phase of their disease. Type 2 DM is typically diagnosed in middle aged and older adults (over 40 years) though this varies by ethnicity. Age of onset and diagnosis can be in younger people in high risk ethnic groups, for example South Asians. Type 2 DM has been increasing in younger people and even children, coincident with rising levels of obesity at younger ages in many parts of the world.

It may be difficult to determine whether a patient has Type 1 or Type 2 DM, particularly in low- and middle-income countries. Age at onset and type of medication used after diagnosis are reasonably good proxy measures for deciding.

Other forms of DM:

There are other forms of DM, of which the most common is gestational DM (diagnosed in the 2nd or 3rd trimester of pregnancy).

“Pre-DM”:

This is a term used to describe patients who have blood glucose levels that are considered to be above normal but below the threshold for diagnosing DM. These patients are at higher risk of developing DM. Other names for this condition include “impaired fasting glucose (IFG)” and “impaired glucose tolerance (IGT).

DM in this guideline refers to type 2 DM unless specified otherwise.

2.4 What health problems does DM cause?

If left untreated or poorly controlled, high blood glucose levels can lead to a range of serious health complications. These are usually categorised as **microvascular** (damage to small blood vessels that particularly affects the kidneys [nephropathy], the eyes [retinopathy], the peripheral nervous system [neuropathy]; or **macrovascular disease** (damage to larger blood vessels resulting in cardiovascular disease, cerebrovascular disease and peripheral vascular disease). There is also a substantial risk of death due to infectious diseases globally in DM patients. Infections among DM patients (common bacterial, fungal and viral infections, infected foot ulcers and endemic infections such as melioidosis and dengue) may be more frequent, more severe, slower to resolve, and they may also have a big impact on quality of life and economic productivity.

2.5 What are the main symptoms of DM?

The classic symptoms of DM are:

- **Polyuria** - need to urinate frequently
- **Polydipsia** - increased thirst and fluid intake
- **Tiredness and fatigue**
- **Unexpected weight loss**

Other key symptoms of DM include blurred vision (or other visual changes), increased appetite and slow healing of wounds. Whilst these symptoms can help in the clinical recognition and diagnosis of DM, they are frequently absent, particularly at the earlier stages of DM progression. They have therefore not been widely used as part of routine screening programmes for DM, since the aim of screening is generally to identify DM at earlier stages, before symptoms become apparent or severe.

2.6 What are the key risk factors for DM?

The key non-modifiable risk factors for DM are age (risk increases with older age), sex (risk is usually higher in men), family history of DM (risk is higher if one or more first degree relatives e.g. parents, siblings and children are affected with the disease), genetic markers and ethnicity (risk is increased in Black African, Afro-Caribbean, Asian and Pacific Island groups). A personal history or isolated raised blood glucose in the past may also be an important risk factor and is most often identified in women who have had a previous pregnancy with gestational DM or who have delivered a very large baby (> 4kg at birth).

Major modifiable risk factors include overweight and obesity (particularly central obesity), physical inactivity, dietary factors, such as consumption of highly-processed foods, excess calorie intake along with diets low in fruits and vegetables and more complex carbohydrates, alcohol consumption and prenatal / early life influences.

2.7 How is DM and “Pre-DM” diagnosed?

DM is a progressive condition and its diagnosis is not straightforward even among people who are otherwise “healthy”. The thresholds or cut-off points for diagnosing DM on each diagnostic test are broadly based on the levels at which the risk of microvascular damage (e.g., retinopathy) and macrovascular complications start to increase.

WHO and the American Diabetes Association currently recommend three diagnostic tests for DM:

- i) oral glucose tolerance test (OGTT),
- ii) fasting blood glucose (FBG) and
- iii) glycosylated haemoglobin (HbA1c).

There is some disagreement between these two institutions about thresholds and cut-offs. **In this guidelines document, the WHO criteria for diagnosing DM and pre-DM will be used.** The exception is the diagnosis of “pre-DM” using glycosylated haemoglobin where WHO has not advised on any criteria: here the criteria set by an international expert committee and adopted in the UK and elsewhere will be used.

The thresholds or cut-off points for DM or pre-DM based mainly on the WHO criteria are shown in **Table 2.1**.

Table 2.1: Thresholds and cut-off points for DM and Pre-DM

Blood test	Diabetes mellitus	Pre-diabetes
2-hour plasma glucose after Oral Glucose Tolerance test (OGTT)	≥ 11.1 mmol/l ≥ 200 mg/dl	7.8 – 11.0 mmol/l 140 – 199 mg/dl
Fasting plasma glucose (FPG)	≥ 7.0 mmol/l ≥ 126mg/dl	6.1 – 6.9 mmol/l 110-125 mg/dl
Glycosylated haemoglobin (HbA1c)	≥ 6.5% ≥ 48 mmol/mol	6.0 – 6.4% 42-47 mmol/mol

Values are given in mmol/l, mg/dl or %

Values are based on plasma glucose (venous) samples

The diagnosis of DM is made using these thresholds and cut-off points based on whether the person investigated is *symptomatic* (for example, polyuria, polydipsia, unexplained weight loss) or *asymptomatic*.

- If symptomatic, then a single fasting plasma glucose ≥ 7.0 mmol/l (≥ 126mg/dl), a post-prandial plasma glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) or HbA1c ≥ 6.5% (≥ 48 mmol/mol) will suffice for diagnosis. A random blood glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) in persons with clear symptoms of DM is also diagnostic.
- If asymptomatic, then it is advisable to obtain a fasting plasma glucose ≥ 7.0 mmol/l (≥ 126mg/dl), a post-prandial plasma glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) or HbA1c ≥ 6.5% (≥ 48 mmol/mol) on two separate occasions.

2.8 What are the advantages and disadvantages of the three main tests for diagnosing DM?

Oral Glucose Tolerance Test (OGTT)

The OGTT is widely considered to be the ideal gold standard to diagnose DM, since it identifies many individuals who would be missed by fasting plasma glucose (FPG) or HbA1c tests. There is also some evidence that it may be the best predictor of future DM complications, particularly coronary heart disease.

The OGTT consists of two components: a fasting blood glucose test followed by post-prandial glucose challenge and a further blood glucose test 2 hours later. *Fasting* is defined as refraining from eating or drinking any liquids other than water for at least eight hours. This should be clearly communicated to patients who may have different cultural understandings of the term “fasting”.

The OGTT is difficult to use in routine practice due to its cumbersome nature, requiring both overnight fasting and a long clinic stay to measure the 2 hour challenge. The OGTT also has relatively poor reproducibility; repeated tests on the same individual can fluctuate from day to day. These features make the OGTT particularly problematic with TB patients –the OGTT has only occasionally been used in this patient group, mostly in research studies.

Fasting Plasma Glucose (FPG)

FPG is the test most widely used to diagnose DM because it is cheap and simple. However, for any patient, this generally requires a repeat clinic visit (as most people are not fasting on initial presentation). The requirements for fasting are the same as described above, i.e., not eating or drinking liquids other than water for at least an 8 hour period before the test. In reality, not all patients adhere to these criteria, even when the criteria are carefully explained.

The diagnosis of DM based on FPG misses about one third to one half of persons with DM compared with the OGTT. Like OGTT testing, FPG measurements lack reproducibility and can vary in the same individual from day to day. However, several screening programmes (for example, in India and China) have successfully introduced FPG tests as a standard to identify DM among TB patients.

Glycosylated Haemoglobin (HbA1c)

Use of HbA1c is increasing since it was first recognised and accepted for the diagnosis of DM by the WHO in 2011. In the context of TB, it has attractive features: it is relatively stable and does not require fasting. Therefore, it can be used in TB patients as soon as they are diagnosed and may be more convenient.

However, the HbA1c test is relatively expensive for both laboratory-based standardised methods and point of care (POC) versions. HbA1c may be less accurate in patients with anaemias, haemoglobinopathies and other illnesses that affect red blood cell turnover, such as malaria. For example, HbA1c may be increased in iron deficiency anaemia yet decreased in other anaemias. It is not recommended for use during pregnancy. Some medications, such as steroids and anti-psychotic drugs, may cause rapid glucose rises. HbA1c also misses up to one third or more of those diagnosed with DM on OGTT, so is much less sensitive than the OGTT test. This means that DM could still be present (on OGTT) for patients with HbA1c somewhat below the diagnostic threshold of 6.5%.

It should be noted that HbA1c is not recommended for diagnosing DM among children and younger people or those of any age suspected of having type 1 DM.

2.9 Can point of care tests be used for diagnosing DM?

Point of care (POC) test devices for blood glucose (often called glucometers) and HbA1c are very widely used although generally they have not been formally certified for the diagnosis of DM. Most of these tests are “near-patient” hand-held or sometimes desktop devices. Such POC tests have numerous potential advantages since they do not require laboratory infrastructure and resources. They can also produce immediate results to guide further management. The main disadvantages include the lower accuracy compared with laboratory analyses of venous samples.

POC blood glucose tests:

Most POC tests for blood glucose (glucometers) use finger prick (or capillary) blood samples. Capillary blood glucose results are approximately 12 per cent lower than plasma blood glucose, since the glucose content of whole blood is usually lower than that of plasma. Modern glucometers usually adjust for this automatically producing “plasma equivalent” (sometimes termed plasma-corrected or plasma-calibrated) results. Older glucometers and more simple devices do not and this difference can result in confusion.

It is important to know whether your meter produces plasma-adjusted or capillary results since the latter underestimate plasma blood glucose. If in doubt you can check your instruction book, contact the manufacturer of your meter or local DM services. There are a large number of different glucometers for measuring capillary (adjusted plasma) glucose: commonly used devices include Accu-Check (Roche, Switzerland), Free Style (Abbott Diabetes Care, US), One Touch (Lifescan, Johnson & Johnson, US).

POC tests for HbA1c:

POC HbA1c devices are usually slightly larger (desktop) devices. Those commonly used include DCA Vantage (Siemens Medical Diagnostics, US), Hemocue HbA1c 501 system (Infopia/Hemocue, Sweden), Quo Test (EFK, UK), A1CNow (PTS/Check Diagnostics, US). There can be disagreement between POC HbA1c and laboratory HbA1c tests, at least for some commonly used devices. This may be particularly problematic for individuals who are anaemic (Hb < 10g/dl) or with mildly raised or normal levels of HbA1c, at or just below the diagnostic cut-off points for DM. In the context of TB, there is the potential for error, particularly as severe anaemia may be common among TB patients.

Use of POC tests for glucose and HbA1c:

In summary, although POC tests have limitations, they may be the only practical choice in some TB clinics. In these settings, DM patients are often diagnosed with very high levels of HbA1c or FBG, well above the thresholds for diagnosis. Such significant hyperglycaemia is predictive of poor TB treatment outcomes and also more likely to be confirmed with laboratory testing for DM. POC tests can be used to screen for DM initially in TB clinics but any new diagnosis of DM should be confirmed using a laboratory test when feasible and certainly by the end of TB treatment. In some settings, this may be achievable by referral to DM services after the intensive phase of TB treatment has been completed.

2.10 What should be done about patients with Pre-DM?

There is evidence that pre-DM is an important predictor of future DM risk and DM complications (especially cardiovascular disease). In the context of TB, there have been only a few studies considering whether HbA1c and blood glucose in this “pre-DM” range is associated with active TB disease. The limited evidence indicates a possible modestly increased risk. Persons identified with FPG or HbA1c in the pre-DM range should be re-tested at the end of TB treatment and given information about the potential future risk of DM and its prevention.

3 Impact of diabetes mellitus and tuberculosis on each other

3.1 Summary statement

Diabetes mellitus (DM) increases the risk of active tuberculosis (TB) disease two- to three-fold and the increasing burden of DM worldwide may offset the global decrease in TB incidence. TB may present atypically with more frequent and severe symptoms and signs in those with dual disease. DM also adversely affects TB treatment outcomes by causing delays in microbiological responses and by being associated with increased rates of death, failure and relapse after completion of treatment. Long-term poor or inadequate glycaemic control appears to play a key role in the increased risk of TB and poor response to treatment. Likewise TB may provoke hyperglycaemia and may result in overt DM in susceptible persons, which may be difficult to control in the presence of active disease.

3.2 Does DM increase the incidence and prevalence of TB?

There is strong evidence that DM increases the risk of TB disease two- to three-fold. This association may be even stronger in the presence of other risk factors, such as HIV infection or cigarette smoking. The increased risk occurs in both type 1 DM and type 2 DM. However, type 2 DM accounts for over 95% of patients with DM worldwide and therefore the public health burden of comorbid disease from type 2 DM is much greater.

The increase risk of TB has mainly been described for patients with smear-positive and culture-confirmed pulmonary disease, with little published evidence so far associating risk with extra-pulmonary TB (EPTB). There is recent evidence to show that DM is an important risk factor for MDR-TB.

3.3 Does DM change the clinical presentation of TB?

Active TB disease may present atypically with altered symptoms and signs in those with DM. Among persons with DM, TB may progress faster, present with more chest and systemic symptoms and more frequent and higher grade smear and culture positivity. Severity at presentation seems to be related to the degree of uncontrolled hyperglycaemia.

The effects of DM on chest radiograph findings are inconsistent. Some studies have described more frequent isolated lower lung field lesions and an increase in consolidation and cavities in PTB in patients with DM, sometimes mimicking the pattern of radiographic TB seen in people living with HIV. No studies have yet reported on whether there are differences in presentation in patients with EPTB.

3.4 Does DM affect the response to TB treatment?

DM has several adverse effects on TB treatment.

Sputum bacteriological conversion:

There is some evidence that DM prolongs smear and culture positivity at 2-3 months of treatment. Poor glycaemic control may be an important factor in this delay.

Adverse drug reactions:

DM is probably associated with a higher risk of hepatitis and renal drug toxicity. It is also associated with gastrointestinal and other side effects that may overlap between TB drugs and glucose lowering drugs used by persons with DM.

TB treatment outcomes:

DM adversely affects TB treatment outcomes. The reasons are not completely understood but include the immunosuppressive effects of DM itself, drug-drug interactions, adverse effects from medications, suboptimal adherence to medication, reduced bio-availability of the drugs and other unlisted factors. The evidence points to an almost doubling of the risk of death during TB treatment among those with DM with the risk increasing to about five times when adjustments are made for age and other potential confounders. Cardiovascular deaths could explain an increased rate of deaths within months after starting TB treatment and the much higher death rates among DM patients who smoke.

DM also increases the risk of TB treatment failure and losses to follow-up. It is not clear whether the poorer TB treatment outcomes described among those with worse glycaemic control are due to existing DM-related complications or the hyperglycaemia itself. The risks of relapse and recurrent TB in those who have completed anti-TB treatment are also higher among those with DM compared with those without: whether this is due to reactivation of disease from the original *Mycobacterium tuberculosis* or reinfection from another strain of *Mycobacterium tuberculosis* is not known. Some preliminary evidence suggests that improving glycaemic control can lead to better TB treatment outcomes and reduced risk of relapse and recurrence.

Post-TB treatment complications

Extensive TB disease, late presentation to health services and delayed diagnosis and/or treatment initiation may increase the risk of post-TB complications such as chronic obstructive and chronic restrictive lung disease.

3.5 Does active TB disease cause hyperglycaemia or DM?

TB does not cause DM although it may unmask those at risk of DM in the future.

TB is associated with glucose intolerance and hyperglycaemia, both of which resolve automatically with TB treatment. In some studies, up to 50% of TB patients who have high blood glucose levels at the time of diagnosis have normal levels by the end of TB treatment. TB also impairs glycaemic control among patients with previously known DM. This impairment of blood glucose that occurs with TB and persists for a time during TB treatment is an example of stress-induced hyperglycaemia.

4 Screening people with tuberculosis for diabetes mellitus

4.1 Summary statement

Routine screening of adult patients with active tuberculosis (TB) disease for diabetes mellitus (DM) should be carried out in most countries and settings. The approach to screening should be standardised and is preferably done at the time of diagnosis and registration of TB. The first step is to ask TB patients whether they already have DM and in those who do not have DM, screen using a blood test. First, a single Random Blood Glucose (RBG) is performed and any patient whose plasma glucose ≥ 6.1 mmol/l (≥ 110 mg/dl) is at risk of DM and must have a second test. The second test is either a single Fasting Blood Glucose (FBG) (requiring the patient to return in a fasting state on the next or subsequent days) or a single glycosylated haemoglobin (HbA1c) test (which can be done on the same day), the latter being easier if the test is available. DM can be diagnosed if the HbA1c $\geq 6.5\%$ (≥ 48 mmol/l) or the fasting plasma glucose ≥ 7 mmol/l (≥ 126 mg/dl). Both these abnormal tests should be confirmed when anti-TB treatment is completed to avoid unnecessary, life-long labelling of the patient as having DM. The TB patient with already known DM must also have a single FBG or HbA1c test to assess glycaemic control.

4.2 Should all TB patients be routinely screened for DM?

The WHO and the International Union Against Tuberculosis and Lung Disease recommend that all adult TB patients should be screened for DM. This results in the diagnosis of many new, hitherto undiagnosed, persons with DM, thus allowing people to know about their disease and be referred to appropriate DM care.

If resources are tight, it may be more cost-effective to undertake targeted screening. Targeted screening means that DM testing is offered to selected sub-groups of TB patients and not to all TB patients. Decisions about which subgroups to screen should be based on local epidemiology. In general, the following sub-groups of TB patients may be considered:

- Those aged 40 years and above (the age threshold may be reduced in some countries of South Asia as DM tends to present at earlier ages)

- Those who are overweight or obese (with body mass index of 25 and above; the body mass index cut-off could be lower in the South Asian population)
- Those with a family history of DM
- Those who are known to consume excessive amounts of alcohol
- Those with previous gestational DM or previous pre-DM

National programmes need to make a judgement about targeted screening based on DM prevalence, availability of human resources, DM test kits and facilities for DM care and support.

4.3 When should patients with TB be screened for DM?

Blood glucose levels may be affected by TB (stress-related hyperglycaemia). In this regard, glycosylated haemoglobin is less affected than fasting blood glucose.

“Stress-related hyperglycaemia” makes the timing of DM testing particularly difficult and it remains one of the unresolved issues. Screening at the time of TB diagnosis and registration may result in many patients with stress-related hyperglycaemia being identified leading to unnecessary referrals and potential anxiety for patients. Furthermore, as the initial priority for patients with newly diagnosed TB may not be the diagnosis and subsequent management of DM, both physician and patient may prefer to delay such screening to concentrate initially on the treatment of TB. Screening at a later time may result in a more stable diagnosis but misses the opportunity for earlier intervention which may be critical given the evidence that DM might increase the risk of early TB mortality (within 100 days of diagnosis).

The advantages and disadvantages of DM testing at different times during TB treatment are shown in **Table 4.1**, overleaf.

Table 4.1: Algorithm for the diagnosis of DM among TB patients

<i>Timing of DM screening</i>	<i>Advantages</i>	<i>Disadvantages</i>
At the time of diagnosis or registration	Logistically, the easiest time to screen as the patients are still present and available at the health facility Early diagnosis of DM and the possibility of early initiation of appropriate DM care, thus resulting in better outcomes	The chances of a false-positive diagnosis of DM are increased due to the phenomenon of stress-induced “transient hyperglycaemia”. However, this transient hyperglycaemia may still need to be treated to improve TB treatment outcomes
During the intensive phase of treatment (2- 8 weeks)	Stress-induced hyperglycaemia much reduced. More stable diagnosis of DM and reduced likelihood of a false-positive diagnosis	Early interventions to treat DM and potentially improve treatment outcomes are lost Attempts to screen might be forgotten as the patient is often in the community and treated as an out-patient with attention focused on TB treatment
At the end of the continuation phase	The likelihood of a false-positive diagnosis of DM is almost zero	It is too late to have any effect on improving TB treatment outcomes if the patient does have DM Attempts to screen might be forgotten

Logistically, it is easier to screen TB patients at the time of diagnosis and registration as this increases the potential to identify and control DM at the start of TB treatment. There is also some evidence that any hyperglycaemia (even though transient) at the time of TB registration is associated with worse TB treatment outcomes with a higher risk of treatment failure or death.

Thus, the following recommendations are made:

- TB patients should be screened for DM at the time of diagnosis and registration.
- TB patients with blood glucose levels consistent with pre-DM or DM should all be re-tested at the end of TB treatment and a decision made at that time on future management. This will avoid unnecessary, life-long labelling of persons as having DM. Available evidence suggests that if DM is diagnosed at the time of registration with blood glucose levels that are significantly higher than the diagnostic threshold, then these patients will have high glucose levels at the end of treatment and will require long-term care for DM. Persons with TB who are diagnosed with DM with borderline values may see their hyperglycaemia resolve during the course of TB treatment.

It is possible that patients with transient hyperglycaemia whose blood glucose levels revert to normal during treatment may still be at higher risk of future DM (similar to gestational DM). Therefore, such patients should be counselled about this possibility and encouraged to follow healthy lifestyle advice to reduce their future risk of DM. This includes dietary changes, increased physical activity, smoking cessation and reducing consumption of alcohol.

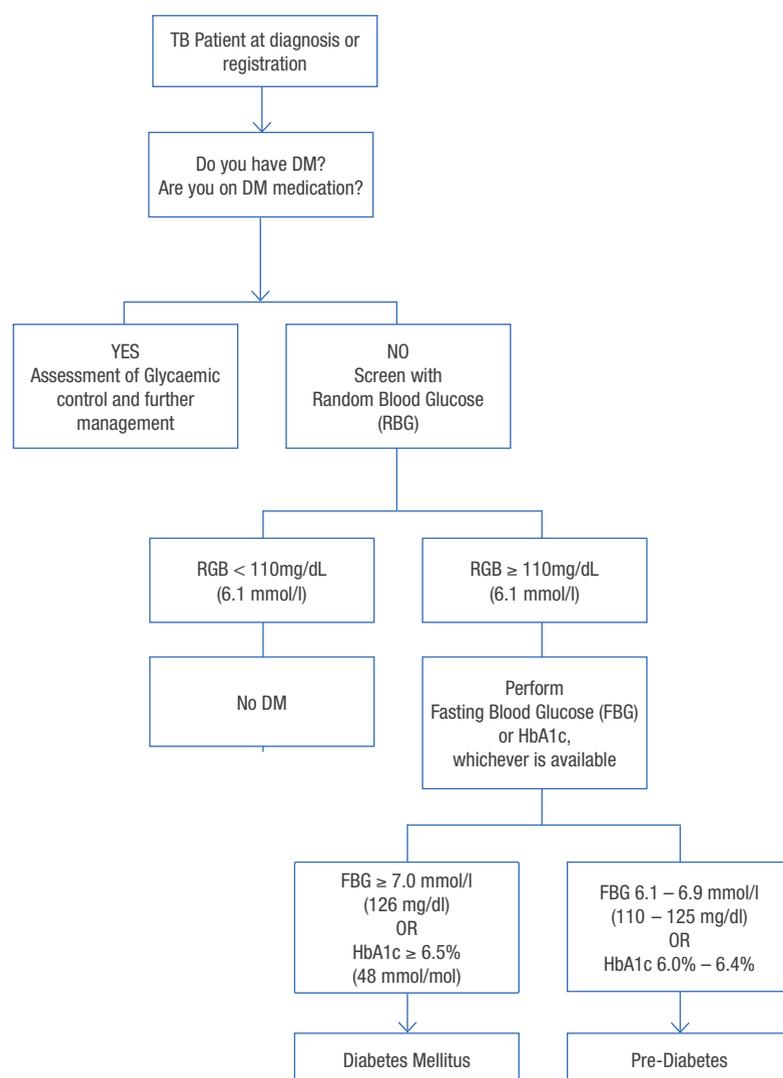
4.4 What are the best tools available for diagnosing DM among TB patients?

As previously discussed in Chapter 2, the **FBG** and **HbA1c** tests are the two diagnostic tools most suited for use in the programmatic setting. The OGTT, while considered the gold standard for diagnosing DM, is usually too cumbersome to use in busy TB clinics. It is also difficult to just use high random blood glucose levels for diagnosing DM as the symptoms and signs of DM often cannot be distinguished from those of TB.

4.5 Which is the best algorithm to use to screen TB patients for DM?

Based on experience in the field, the algorithm shown in **Figure 4.1** has been tried and tested in India and China and is recommended.

Figure 4.1: Algorithm for the diagnosis of Diabetes mellitus among Tuberculosis patients



At the time of diagnosis and registration, TB patients should first be asked about whether they are already known to have DM or whether they are taking any DM medication. These patients should have their glycaemic control assessed using HbA1c or FBG (whichever test is available and convenient) and managed further based on the results.

TB patients who state that they do not have DM should be offered a single RBG measurement at this time to identify those who are at risk and require further investigation with either FPG or HbA1c.

If the RBG is < 6.1 mmol/l (< 110 mg/dl):

The TB patient is at low risk of DM and no further investigation is required.

If the RBG is ≥ 6.1 mmol/l (≥ 110 mg/dl):

The TB patient requires further investigation. This can be done on the same day using a glycosylated haemoglobin test (HbA1c) or the patient will have to come back on another day in a fasting state for a FBG test.

If the HbA1c ≥ 6.5% (≥ 48 mmol/mol):

The patient is diagnosed as having DM and recorded as such.

If the FBG ≥ 7.0 mmol/l (≥ 126 mg/dl):

The patient is diagnosed as having DM and recorded as such.

Further immediate management based on the results of the screening:

If the TB patient is diagnosed with DM, we recommend (based on very low quality evidence) that he/she needs to be managed in the TB clinic for at least the first two weeks of TB treatment and if possible until the end of the initial intensive phase. This is to ensure that the TB patient is no longer infectious by the time he/she returns to the DM clinic. DM care should therefore be provided in the TB clinic. If the patient has severe hyperglycaemic symptoms with an FBG > 18 mmol/l (325 mg/dl) or HbA1c > 10% then urgent DM specialist advice needs to be obtained.

If the TB patient is found to have pre-DM, the patient is informed and the result is recorded but no further action is taken in terms of DM care or support.

If the TB patient is found to have a normal result, the patient is informed and the result is recorded and no further action is taken in terms of DM care or support.

4.6 Should there be a repeat diagnostic blood test to confirm the diagnosis of DM?

WHO guidance recommends that diagnostic blood tests be repeated in **asymptomatic persons** before a confirmed diagnosis of DM is made (see Chapter 2). Patients with TB are not asymptomatic. The challenge though is distinguishing the symptoms of DM (polyuria, polydipsia, polyphagia, unexplained weight loss, extreme tiredness, slow wound healing) from the symptoms of active TB disease. This is because some of the symptoms of DM may overlap or be explained by or be suppressed by TB.

In TB programme settings, it is not always feasible to recommend repeat DM diagnostic testing. This guide recommends that a single DM diagnostic test is done at the time of TB diagnosis and registration. Glucose values above the thresholds and cut-off points for diagnosing DM are taken as indicating the presence of DM and the patient is recorded as having DM. Field experience from India and elsewhere suggests that most persons with DM that were diagnosed by a single screening were confirmed by a repeat test done later at the DM clinic, provided the initial values were significantly above the diagnostic cut-offs and not borderline. As stated before, all patients diagnosed with DM at the start of TB treatment need to have a repeat test done at the end of TB treatment to confirm whether or not they have DM.

5 Screening people with diabetes mellitus for tuberculosis

5.1 Summary statement

Even though diabetes mellitus (DM) increases the risk of tuberculosis (TB), the numbers of patients with new active TB disease that can be identified in DM clinics is relatively small. Screening for TB should therefore only be considered in TB endemic settings. Preference is given to people newly diagnosed with DM in whom a one-off active TB case finding screen at the time of registration in the DM clinic is recommended. The screening should be done by actively enquiring about symptoms suggestive of TB and referring those with positive symptoms to the TB clinic for investigation. Given the association between DM and drug-resistant TB, we recommend that Xpert MTB/RIF be the diagnostic test. Persons with DM already in care should be educated about the risks of TB and the symptoms and signs of TB and be asked to present to the clinic or their physicians if they think they have active TB disease.

5.2 Should persons with DM be screened for TB?

Amongst persons with DM, the yield of screening for TB depends on the underlying prevalence of TB in the population, as well as the criteria for screening for TB. If TB prevalence is low, e.g., less than 100 per 100,000 population, then too many DM persons need to be screened to detect one additional case of TB. This is not cost-effective. In contrast, in high TB prevalence settings, screening may be cost effective with the numbers needing to be screened to yield one additional case being much lower. **Therefore, persons with DM should only be considered for systematic TB screening in countries with a TB prevalence of over 100 per 100,000 population.**

There appears to be a higher risk of TB in the initial months following DM diagnosis. Whether this is related to uncontrolled hyperglycaemia is not known, but this information suggests a practical way forward for screening. We therefore recommend the following:

- In countries with TB prevalence > 100 cases per 100,000 population, persons with DM should be screened for TB
- **Persons diagnosed with new DM** in high TB prevalence countries (> 100 cases per 100,000 population) should be systematically screened as a one-off process at the

time of diagnosis and registration in the DM clinic (*an active case finding approach*)

- **Persons already in DM care** in high TB prevalence countries (> 100 cases per 100,000 population) should be educated about their increased risk of new and recurrent TB as well as the symptoms and signs of TB, especially if they fall into one of the high risk categories such as being a smoker or having uncontrolled hyperglycaemia. Such persons should be asked to present to health care services or consult their physicians if they think they might have active TB disease (*a passive case finding approach*).

5.3 How should patients with newly diagnosed DM be screened for TB?

The algorithm shown in **Figure 5.1** on the next page is recommended for use.

Persons with newly diagnosed DM who are registered in the DM clinic should be first asked whether they are already on TB treatment. If they are on TB treatment, they are recorded as having TB, they are checked for their next scheduled appointments at the TB clinic and appropriate infection control measures are ensured.

If the person with newly diagnosed DM is not on TB treatment, he/she is asked if there are any symptoms related to TB. These symptoms include cough for two or more weeks, unexplained weight loss, fever and night sweats. The person should also be asked if he/she has any other symptoms or signs, such as swelling of glands in the neck (cervical lymphadenopathy) that might indicate extra-pulmonary TB.

If resources permit, consideration could be given for referring a person with newly diagnosed DM, regardless of symptoms and signs, for chest radiography. This has the advantage of having higher sensitivity than symptom screening for diagnosing TB.

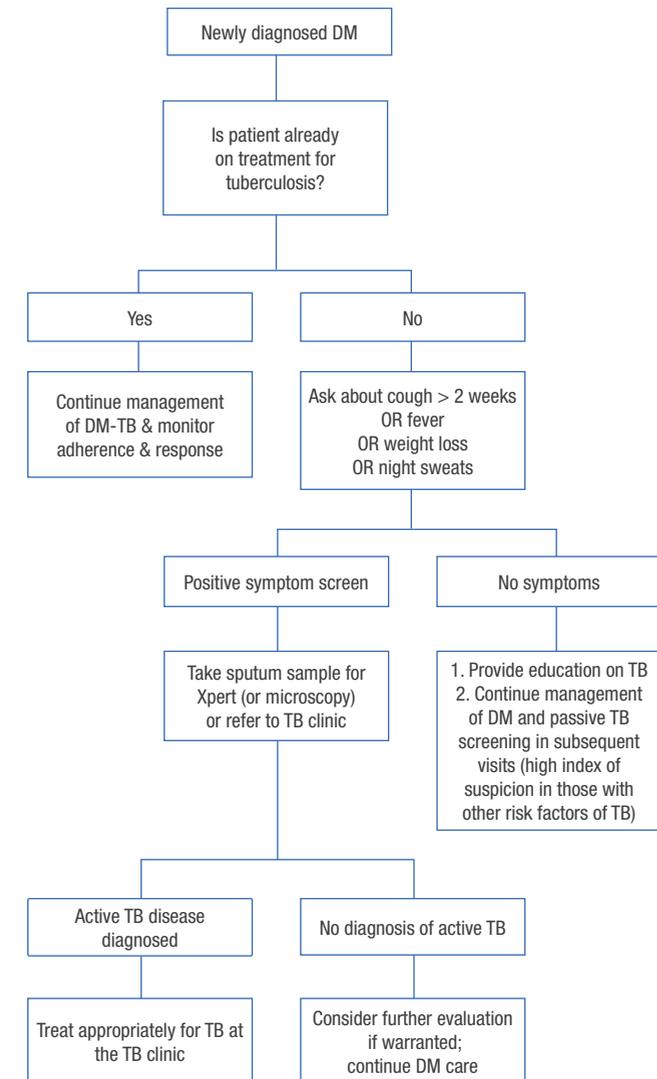
If there are any positive symptoms or signs suggestive of TB or the chest radiograph, if done, shows any lung parenchymal changes suggestive of TB the patient is classified as “presumptive TB” and either has sputum samples transported to the TB clinic/laboratory for Xpert MTB/RIF or the patient is actually referred to the TB clinic for further investigation. In this situation, it is important to set up mechanisms to ensure that patients reach the TB clinic and that the outcome of the investigation is also communicated to the DM clinic.

At the TB clinic, the first line recommended test on sputum or other samples is Xpert MTB/RIF in line with current WHO recommendations. If the assay is unavailable, then investigation by sputum smear microscopy is carried out.

5.4 Should patients with DM be screened for latent TB?

Currently, the WHO does not recommend screening for latent TB infection in DM clinics, and this guideline endorses this approach.

Figure 5.1: Algorithm for TB screening amongst persons with newly diagnosed DM in countries with high prevalence of TB (> 100 cases per 100,000 population)



6 Management of diabetes mellitus during tuberculosis treatment

6.1 Summary statement

The management of Diabetes mellitus (DM) during tuberculosis (TB) treatment is aimed at improving TB treatment outcomes and reducing DM-related morbidity and mortality. The key activities are optimizing glycaemic control (through dietary instructions and medication) and implementing measures to reduce the risk of cardiovascular disease. Metformin is the first choice oral glucose-lowering drug for TB patients. Sulphonylurea derivatives can be used as add-ons or in patients who cannot use metformin although drug-drug interactions with rifampicin limit their use. Insulin is effective in patients with severe hyperglycaemia but has several disadvantages limiting its use in TB patients in programmatic settings. In the first two weeks to two months of TB treatment, the infectious patients are preferably managed in the TB clinic and wherever possible visits to the DM clinic should be limited or postponed in order to prevent transmission of *Mycobacterium tuberculosis* within that setting. Cardiovascular risk assessment should be considered in TB-DM patients through counselling and prescription of anti-hypertensive, lipid-lowering and anti-platelet treatment with the aim of lowering early and long-term cardiovascular morbidity and mortality. Aspirin and statins should be considered early on in patients who have a previous history of cardiovascular disease. Healthy life styles need to be promoted.

6.2 What are the aims and principles of DM management?

The management of DM is in general aimed at reducing short-term and long-term complications such as cardiovascular disease, eye problems and foot amputations. DM management mainly consists of: life style counselling (diet, weight loss, physical activity, smoking cessation, avoiding excess alcohol); treatment with blood glucose lowering drugs; measures to reduce the risk of cardiovascular disease and associated complications that include anti-hypertensive drugs, lipid-lowering drugs and anti-platelet drugs if indicated; and management of specific complications like diabetic feet and eye problems.

Do these aims and principles apply to the management of persons with DM and TB?

In patients with DM and TB, the priority is to treat TB while at the same time keeping blood glucose levels under control. DM, and especially poorly controlled DM, is associated with adverse TB treatment outcomes and there is evidence suggesting that better DM control leads to better TB treatment outcomes. There is also evidence that poor lifestyle practices (for example, the continuation of cigarette smoking) can significantly increase the risk of death.

There are some considerations that need to be taken into account in the management of patients with dual disease:

- TB-associated inflammation can lead to temporary “stress-induced hyperglycaemia” which can be quite pronounced but will usually improve during TB treatment. If blood glucose levels are high they need to be treated to ensure optimal TB treatment outcomes.
- The initial priority lies with successful initiation of TB treatment and with optimising blood glucose control.
- Combined DM and TB treatment is associated with increased pill-burden, overlapping adverse effects and toxicity, and drug-drug interactions.
- Referral of TB patients to specialised DM services is not recommended in the early phases of anti-TB treatment because of the risk of transmission of *M. tuberculosis* to those working in or attending these clinics. With effective treatment patients with drug-susceptible TB are usually non-infectious after two weeks and almost certainly after two months. Patients with MDR-TB or RR-TB may take longer to become non-infectious. Good and regular consultation with DM health care practitioners may be needed if blood glucose levels are high.

6.3 Who should provide DM care for patients with DM and TB?

For DM patients in the DM clinic who are screened and diagnosed with TB:

DM care and treatment remains with the DM clinic. However, to limit the risk of possible transmission of *M. tuberculosis*, DM clinic visits during the first two weeks, and if possible the first two months, of TB treatment should be avoided. It is suggested that consultation with the DM clinic can be carried out remotely and medication pick-ups managed in as safe a manner as possible.

For TB patients in the TB clinic who are screened and diagnosed with already known DM:

In the first two months of TB treatment, DM management may have to be adjusted in the TB clinic, preferably in coordination with the DM practitioner. After this, DM care and treatment can be done by the DM clinic.

For TB patients in the TB clinic who are screened and diagnosed with new DM:

Initial DM management should preferably be done in the TB clinic. For patients with severe, symptomatic and uncontrolled DM, specialist DM advice should be sought and referral to the DM clinic preferably postponed for at least the first two weeks by which time the risk of infection should be minimal. Local circumstances in terms of training and expertise, availability of DM medications, glucometers and access to laboratories with glucose measuring capacity will guide the type of DM management that can be offered in a TB clinic.

6.4 What glucose control target should be aimed in a patient with DM and TB and how should this be monitored?

Targets for glucose control during TB treatment

The accepted target for glucose control in DM is an HbA1c < 7% (53 mmol/mol). This may be hard to achieve during TB treatment, especially in the first two months when TB may lead to stress-induced hyperglycaemia, and in the presence of severe or longstanding DM and limited resources. The benefit, the potential risks and the costs of additional efforts to achieve more stringent glucose control and reach the accepted target are currently unknown. Even less is known about targets using fasting blood glucose (FBG) measurements. However, evidence from other situations suggests that good blood glucose control is important when faced with high FBG or HbA1c during stress induced hyperglycaemia.

These guidelines recommend trying to achieve a consistent target of HbA1c < 8% or FBG < 10 mmol/l (180 mg/dl) during TB treatment (see Table 6.1), in line with those for DM management in persons with a significant co-morbidity.

Table 6.1: Targets for glycaemic control during TB treatment

<i>Measurement</i>	<i>Target</i>
Fasting blood (capillary) glucose	< 10 mmol/l (< 180 mg/dl)
HbA1c	< 8%

Monitoring of glucose control during TB treatment

Monitoring of glucose control during TB treatment is best done by measurement of FBG. HbA1c can be used but is generally not repeated within 2-3 months after starting DM treatment. The frequency of monitoring depends on DM severity. In mild cases (for example, HbA1c < 8% at baseline), blood glucose or HbA1c measurement can be repeated after 3 months. In more severe cases (for example, HbA1c > 10%), FBG measurements should be done more frequently, for example every one – two weeks until reasonable control is achieved. If FBG cannot be done because patients have come to the clinic in a non-fasting state, then post-prandial blood glucose measurements can be done with the aim of reaching glucose levels < 11.1 mmol/l (< 200 mg/dl). Use of insulin ideally requires self-monitoring of blood glucose.

6.5 What glucose lowering drugs should be used in patients with TB?

The documented experience of treating DM in TB patients is mostly limited to three types of drugs: metformin; sulphonylurea derivatives (SUs) and insulin. These three types of drugs are also the most widely available and they are described below.

Newer drugs for treating DM, such as incretin-based therapies (glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors) and sodium glucose transporter 2 inhibitors, are generally not available in resource-limited countries and will not be discussed in this guide.

The basic essentials of these three drugs are shown in Table 6.2.

Table 6.2: Common glucose-lowering drugs used for managing DM in TB patients

Characteristic	Metformin	Sulphonylurea derivatives	Insulin
Drug of choice	First choice	Add-on Used in case there is a contraindication or intolerance to metformin	Use if targets for HbA1c or FBG cannot be reached or if there is symptomatic hyperglycaemia
Risk of Hypoglycaemia	No	Yes	Yes
Starting dose (od = once a day; bid = twice a day)	500 mg od or bid, titrated to a maximum dose of 2000mg daily	Gliclazide 40-80mg OD Glibenclamide 2.5-5mg OD Glimepiride 1-2 mg OD Glipizide 5mg OD	10 units basal insulin per day as the starting point
Interaction with Rifampicin	Not clinically relevant	Yes, 30% - 80% lower efficacy with rifampicin	None
Main side effects	Gastrointestinal Lactic acidosis	Hypoglycaemia	Hypoglycaemia
Use in reduced kidney function (GFR = glomerular filtration rate)	Dose adjustment if eGFR < 45 ml/min Contraindication if eGFR < 30 ml/min *	Increased risk of hypoglycaemia Preference gliclazide	Can be safely used
Cardiovascular events	Recognised benefit	Neutral	Neutral

* if measurement of eGFR cannot be done, metformin should not be given to patients with known chronic kidney disease without approval from their treating physician.

eGFR = estimated glomerular filtration rate

Metformin:

This is the first choice glucose-lowering agent recommended in type 2 DM, including patients with TB. Its advantages include extensive experience in its use, extremely low risk of hypoglycaemia, effectiveness, low cost, beneficial effects on cardiovascular disease, lack of clinically relevant interaction with rifampicin and finally a potential benefit on TB itself. Its two main disadvantages are gastro-intestinal side effects and rarely, the development of lactic acidosis which may be fatal if unrecognised and untreated.

In resource-limited settings it is difficult to diagnose lactic acidosis, so this condition needs to be suspected in any patient with DM and TB receiving metformin who deteriorates during the course of TB treatment. The starting dose of 500 mg od/bid can be titrated to 1,000 mg bid or 500 mg bid for those with a renal clearance (eGFR) < 50ml/min.

Sulphonylurea derivatives:

These are second choice glucose-lowering agents which can be used as “add-ons” to metformin if metformin alone is ineffective or if there is intolerance or a contraindication to metformin. The most widely used sulphonylurea derivatives are gliclazide, glibenclamide, glimepiride and glipizide. The two main disadvantages are a) the risk of hypoglycaemia and b) strong interactions with rifampicin that show wide individual variation but result in their efficacy being reduced by 30% - 80%.

Insulin

This is the third choice, except for sick and hospitalised patients or patients already using insulin prior to a TB diagnosis. Insulin is indicated in case of severe hyperglycaemia (for example, HbA1c > 10% or FBG > 15 mmol/l (> 270 mg/dl) or if targets for glucose control cannot be reached using metformin and other oral medications. In well-resourced settings, the use of insulin is usually accompanied by the need for self-monitoring of blood glucose through glucometers.

6.6 What should be done for a patient diagnosed with TB in a DM clinic?

The following steps should be carried out:

- The patient should be referred to the TB clinic to start TB treatment. TB medicines should be administered and monitored from that clinic until successful completion of therapy.
- Attendance at the DM clinic should be avoided during the intensive phase of TB treatment (the first two months). If DM control is difficult, contact the DM clinic for advice without referring the patient. If the patient does have to visit the DM clinic in the intensive phase, he/she should wear a surgical mask.

- Before referral to the TB clinic,
 - Measure glycaemic control (either HbA1c or FBG) and consider stepping-up DM treatment (for example, increasing medication) at the time of TB diagnosis.
 - If the patient is on metformin, continue. If the patient is on other oral glucose-lowering drugs, consider switching to metformin which has no relevant drug-drug interactions with rifampicin.
 - Provide appropriate dietary instruction
 - If not yet prescribed, aspirin should be started for patients who have established cardiovascular disease or a prior history of heart attack or stroke.
 - Ensure that s/he understands that TB is curable and explain about infection control and prevention.

6.7 What should be done for a TB patient diagnosed in a TB clinic who is diagnosed with new DM or who is already receiving treatment for DM?

The following steps should be carried out:

- Glycaemic control should be assessed either by measurement of HbA1c or measurement of FBG. This assessment can be done in the TB clinic if blood glucose can be measured. If assessment has to be done at the DM clinic or a general health clinic, this is best postponed until at least two weeks or even 2 months of TB treatment have been completed. Guidance for newly diagnosed patients or those already receiving DM treatment is shown in **Table 6.3**.
- Document cigarette smoking status and counsel if still smoking.
- Ask about history of cardiovascular disease (myocardial infarction, stroke, peripheral arterial disease). If yes, then start/continue low-dose aspirin (75-150 mg once a day).
- After 8 weeks (at the end of the initial intensive phase of TB treatment for drug-susceptible TB), measure blood pressure and start / increase antihypertensive medication if systolic blood pressure \geq 140 mmHg and/or diastolic blood pressure \geq 90mm Hg, considering possible drug-interactions with rifampicin.
- After 8 weeks (at the end of the initial intensive phase of TB treatment for drug-susceptible TB), start/continue statin if age > 40 years or there is established cardiovascular disease.

Table 6.3: Management of HbA1c or blood glucose at the start of TB treatment

<i>HbA1c or FBG at the start of anti-TB treatment</i>	<i>Diagnosed with new DM</i>	<i>Already receiving treatment for DM</i>
If HbA1c < 8% or FBG < 10.0 mmol/l (180 mg/dl)	No further immediate action is taken; re-assess blood glucose levels at 2 months and again at the end of TB treatment	No further action is taken; the patient continues on current medication for DM
If HbA1c \geq 8% but less than 10% or FBG \geq 10 mmol/l (180 mg/dl) but less than 15 mmol/l (270 mg/dl)	Start metformin 500 mg once a day, reassess in two weeks and increase the dose to 500 mg twice a day or refer if blood glucose levels have not improved	Intensify current glucose lowering treatment and reassess one - two weeks later
If HbA1c \geq 10% or FBG \geq 15mmol/l (270 mg/dl)	Start metformin 500 mg twice a day and seek specialist advice.	Seek specialist advice and consider the need for hospital admission for better glucose control

6.8 What can be done to prevent and/ or manage hypoglycaemia?

Patients using sulphonylurea derivatives or insulin are at risk for hypoglycaemia. These patients and their family members should be counselled about the risks and symptoms of hypoglycaemia. Patients with DM and TB are advised not to fast during Ramadan because of an increased risk of hypoglycaemia or worsening of glucose control

In case of severe hypoglycaemia, if plasma glucose < 2.6 mmol/l (50 mg/dl) sugar water or glucose containing foods (biscuits or sugar granules) should be given. If the patient is unconscious, he/she should receive 20-50 ml intravenous glucose 50% in 1-3 minutes if possible. Once symptoms have resolved, it is good practice to recheck the blood glucose.

6.9 How is cardiovascular risk assessed and managed?

Atherosclerotic cardiovascular disease, including myocardial infarction, stroke and peripheral arterial disease, is the leading cause of morbidity and mortality for individuals with DM. Therefore, assessment and management of cardiovascular risk is important in DM. Cardiovascular risk assessment is focused on four possible interventions:

- Life style counselling (weight loss, physical activity, smoking cessation, reducing alcohol consumption)
- Antihypertensive treatment
- Lipid-lowering treatment (statins)
- Anti-platelet treatment (aspirin)

The targets, the interventions and the specific considerations in DM patients with TB are highlighted in **Table 6.4**.

Table 6.4: Cardiovascular disease risk in patients with DM and TB

<i>Cardiovascular risk</i>	<i>Target</i>	<i>Intervention</i>	<i>Specific considerations in TB patients</i>
Smoking	Stop smoking	Counselling for smoking cessation	Relevant for TB treatment outcomes
Obesity	Body Mass Index > 23 (Asian) or > 25 (other) kg/mm ²	Counselling (diet, physical activity)	Often ~10% weight gain as a result of TB treatment
Excessive alcohol consumption	Avoid alcohol intake during TB treatment	Counselling	Risk of liver dysfunction associated with anti-TB drugs
Hypertension	< 140/90 mmHg	Antihypertensive treatment	Rifampicin reduces efficacy of some anti-hypertensive drugs (calcium channel blockers and ACE-inhibitors) No interaction with thiazide diuretics
Hyperlipidaemia	LDL < 2.6 mmol/l (100 mg/dl)	Statins: - for those > 40 years; - for those with prior cardiovascular disease	Rifampicin reduces the efficacy of most statins
Established cardiovascular disease (previous myocardial infarct, stroke, peripheral arterial disease)	Secondary prophylaxis	Aspirin 80-100 mg daily Statin (simvastatin 20-40 mg daily or pravastatin 40-80 mg daily)	Risk of bleeding with haemoptysis

6.10 Should cardiovascular risk be assessed and managed in patients with newly diagnosed DM during TB treatment?

- **At the time of TB diagnosis**, the successful initiation of TB treatment and glucose control are of greater priority than the assessment and management of cardiovascular risk. Therefore, at the time of diagnosis, the only considerations are initiation of aspirin for those with established cardiovascular disease and counselling for smoking cessation and reduction of alcohol consumption
- **After completion of the initial intensive phase of TB treatment (at 8 weeks)**, patients should be counselled about other healthy life styles and antihypertensive medication and statin treatment may be started as indicated (Table 4).
- **At TB treatment completion**, patients should be counselled about continuing care for DM and cardiovascular disease and referred to other general or DM health care providers for further monitoring and treatment. DM-associated TB is associated with a higher rate of TB relapse. Patients need advice about what to do in case renewed cough, fever, night sweats or weight loss so that they return to care without delay.

6.11 How should DM be managed in patients with HIV-associated TB?

In patients with HIV-associated TB, there are a few issues which need special consideration (see **Table 6.5**, overleaf). Drug-drug interactions are even more probable in these patients and toxicity profiles and side-effects of HIV, TB, and DM drugs might overlap.

Table 6.5: Special considerations when co-managing HIV, DM and TB

<i>The Issue</i>	<i>Special Considerations</i>	<i>Action</i>
TB-associated immune reconstitution inflammatory syndrome (IRIS)	Corticosteroids may be given for IRIS which can increase levels of hyperglycaemia	Monitor blood glucose and initiate glucose-lowering treatment if indicated
Drug-drug interactions	<p>Many antiretroviral (ARV) drugs affect metabolism of glucose-lowering drugs, statins, antihypertensive drugs and antiplatelet drugs</p> <p>Metabolism of most antiretroviral drugs is increased by rifampicin</p> <p>Dolutegravir reduces metabolism of metformin</p>	<p>Seek specialist advice about drug- drug interactions between ARV drugs (www.hiv-druginteractions.org)</p> <p>Preferably use raltegravir/dolutegravir (in a double dose) or efavirenz (standard dose); avoid use of protease inhibitors</p> <p>Reduce metformin dose by 50%</p>

6.12 What should be done at the end of TB treatment?

At the end of TB treatment patients should be counselled about:

- the need for continued DM care and monitoring
- the increased risk and management of cardiovascular disease
- the increased risk of TB relapse and what to do in case of renewed cough, fever, night sweats or weight loss.

Efforts should be made for effective referral to appropriate services for continued DM care.

7 Management of tuberculosis in persons with diabetes mellitus

7.1 Summary statement

The standard treatment regimens recommended for drug-susceptible and drug-resistant tuberculosis (TB) remain unchanged with or without Diabetes mellitus (DM) as there is no strong evidence currently to support an alternative approach. Dosages should be given daily throughout both the initial and continuation phases. When the person with DM is diagnosed with TB, either through bidirectional screening in the TB clinic or through bidirectional screening in the DM clinic, the treatment should always be administered, supervised and monitored in a TB clinic where the drugs are available and where health care workers are trained in the management of the disease and patient-centred care. Because DM is associated with an increased risk of drug-resistant TB and worse TB treatment outcomes, patients need to be carefully assessed for drug resistance at the start of treatment (using Xpert MTB/RIF) and carefully monitored for failure during treatment and for relapse after treatment has been completed.

7.2 What are the aims and principles of TB treatment?

The aims of treatment of TB in a person with and without DM are:

- To cure the patient and restore quality of life and productivity
- To prevent death from TB or its late effects
- To prevent relapse of disease
- To reduce transmission of *Mycobacterium tuberculosis* to others
- To prevent the development and transmission of drug resistance

7.3 Drug-susceptible TB

This is defined as TB which is susceptible to essential first-line drugs. Globally, about 95% of patients diagnosed with TB have drug-susceptible disease.

What are the essential first-line TB drugs and the principles of their use?

There are four essential first line drugs currently in use (isoniazid, rifampicin, pyrazinamide and ethambutol). Isoniazid is the most potent bactericidal drug and kills most of the bacillary population during the first days of chemotherapy. Rifampicin is another good bactericidal drug. With these two powerful drugs, most patients with infectious pulmonary TB are rendered non-infectious after two weeks of treatment. Rifampicin is also active against semi-dormant bacilli and the drug is therefore a good sterilising agent and is effective in preventing relapse of disease. Pyrazinamide is another important sterilising drug which kills bacilli that are well protected in an acid medium inside cells and macrophages. Pyrazinamide is very effective for the first two months but there is limited benefit from more extended use and so the drug is not used beyond the initial phase of treatment. Ethambutol is mainly used to prevent the emergence of drug resistance to the other three first-line drugs.

Treatment of TB always involves an *intensive phase* which is designed to kill actively growing and semi-dormant bacilli, followed by a *continuation phase* designed to eliminate residual bacilli. The four essential first line drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) are used in the intensive phase. At the start of the continuation phase, there are low numbers of bacilli and less chance that drug-resistant mutants will be selected and therefore only rifampicin and isoniazid are used.

What is the standardised treatment for DM patients with drug-susceptible TB and how is it administered?

Patients with new TB: The six-month rifampicin based regimen (2HRZE/4HR) is the one recommended for treatment of those with new drug-susceptible or presumed drug-susceptible TB. The initial intensive phase of 2 months consists of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase of 4 months uses just two drugs, usually isoniazid and rifampicin, preferably given by direct observation.

Patients with previously treated TB: On the basis of the drug susceptibility profile (which all patients should have), the standard six-month rifampicin based regimen (2HRZE/4HR) can be repeated if no resistance is documented.

Patients with other types of TB: Some experts recommend 9-12 months treatment for tuberculous meningitis, given the serious risk of disability and mortality. They also recommend 9 months treatment for TB of the bones and joints because of the difficulties of assessing treatment response. Adjuvant corticosteroid therapy is recommended for tuberculous meningitis and tuberculous pericarditis; more frequent monitoring of blood glucose will be needed in these circumstances because of the deleterious effects of steroids on glucose metabolism.

HIV-associated TB: TB treatment regimens are similar, although some recommend 9-12 months treatment. More frequent monitoring of blood glucose will be needed if adjunctive corticosteroid therapy is given for the prevention or management of TB-associated IRIS (inflammatory immune reconstitution syndrome) in individuals with DM.

Dosages:

The essential drugs and recommended dosages based on body weight are shown in Table 7.1.

Table 7.1: Recommended doses of first-line TB drugs for adults with DM

Drug	Abbreviation	Recommended daily doses	
		Dose (range) in mg/kg	Maximum Mg
Isoniazid	H	5 (4-6)	300
Rifampicin	R	10 (8-12)	600
Pyrazinamide	Z	25 (20-30)	-
Ethambutol	E	15 (15-20)	-

Although, three times a week dosing is used in some National TB Programmes in the continuation phase, this may pose a risk for the development of acquired rifampicin resistance in patients with or without DM. It is thus recommended that dosing of drugs in both the intensive and continuation phases is DAILY.

Dosage standardisation by weight bands and FDCs:

To facilitate procurement, distribution and administration of treatment to patients, the daily dosage is usually standardised for three body weight bands –30-39 kg, 40-54 kg and more than 55 kg, as is done with the Global Drug Facility patient kits.

The use of fixed-dose combinations (FDCs) of TB drugs is also recommended over separate drug formulations because these limit the development of drug resistance,

prescription errors are less frequent and medication adherence is better. **Table 7.2** shows how treatment with FDCs is given according to weight bands.

Table 7.2: For patients with drug-susceptible TB, the number of FDC tablets to be given daily for adults on treatment according to weight bands and the contents of the tablets

Month of Treatment	Drug	Number of FDC tablets taken daily		
		30-39kg	40-55kg	> 55kg
1 – 2 Intensive Phase	RHZE (R150mg, H75mg, Z400 mg, E275 mg) combined tablets	2	3	4
3 – 6 Continuation Phase	RH (R150mg, H75mg) combined tablets	2	3	4

H= isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol

Patient treatment kits: Many National TB Programmes use patient kits. Each kit contains the full course of treatment for an individual patient and thus reassures the patient that his or her medicines will be available throughout treatment. The kit provides health workers with a container that has all the required medicines in the necessary strengths and quantities.

Medication supervision and DOT:

On starting treatment, all patients should be given health education about the disease and counselling on treatment adherence. The drugs in the initial intensive phase and the continuation phase, whether in FDCs or provided in kit form, should be given under direct observation (DOT), where someone watches and observes the patient actually taking medication.

Community or home-based DOT is recommended over health-facility-based DOT and within this structure DOT by trained community volunteers / workers or formal health care workers is recommended over DOT that is administered by family members. Where video communication technology is available and can be organised and operated by health care workers and patients, video observed treatment (VOT) can replace DOT.

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

a) where there is known high prevalence of isoniazid resistance in new patients, the information being obtained from previous drug-resistance prevalence surveys. In such cases, the patient may receive HRE in the continuation phase as an acceptable alternative to HR.

b) they have developed TB after a known contact with a patient documented to have drug-resistant TB. It is likely that such patients have a similar drug resistance pattern to the index patient. Drug sensitivity testing (DST) should be carried out before treatment and the patient treated initially with a regimen based on the DST results of the index patient until the results of their own DST are available.

7.4 Where are DM patients who have active TB disease treated?

DM patients with infectious TB disease should be comprehensively managed in the TB clinic for at least the first two weeks of TB treatment and if possible until the end of the initial intensive phase. Patients should preferably not be seen in the DM clinic until after this time and DM care should be administered from the TB clinic. If hyperglycaemia is difficult to control then consultation from DM health care practitioners to the TB clinic must be provided. The continuation phase of TB treatment should be supervised and completed from the TB clinic and at this stage with the patient no longer infectious, DM care can be provided if feasible from the DM clinic.

7.5 How are DM patients who are being treated for drug-susceptible TB monitored?

A proper monitoring and evaluation system, based on meticulous recording and reporting of cases, is essential to assess the effectiveness of the TB treatment and the particular TB programme's performance.

The patient's weight should be monitored every month. Although it is sometimes recommended that dosages be adjusted if weight changes, in the programmatic setting this rarely happens due to the FDCs and patient kits being administered from the time of registration with the dosages determined by the baseline weight.

Adverse effects from treatment need to be detected promptly and managed properly. In patients with bacteriologically confirmed pulmonary TB (smear-positive, culture-positive or diagnosed by a WHO approved rapid diagnostic test, e.g., Xpert MTB/RIF), sputum

smears are examined for acid-fast bacteria at 2 months, and again at 5 months and 6 months of therapy. For other TB patients, clinical monitoring is the usual guide to assess treatment response. Routine monitoring of treatment response by chest radiography is wasteful of resources and unnecessary, although chest radiography may be helpful at the end of the six months therapy, especially in smear-negative pulmonary patients.

Monitoring and recording of adverse effects:

Most TB patients complete their treatment without any significant adverse drug effects. However, a few patients do experience adverse effects and these need to be clinically monitored. Routine laboratory monitoring is not necessary. Health care workers must teach patients how to recognise symptoms and/or signs and urge them to report these if they develop.

The main adverse effects from the four first-line drugs are shown in **Table 7.3**. Some of these may be compounded by DM or by diabetes medications (see below).

Table 7.3: The most common adverse effects from the four essential anti-TB drugs, their relationship to DM and the suggested management

<i>Drug</i>	<i>Adverse effects</i>	<i>Considerations from DM</i>	<i>Management</i>
Isoniazid	Peripheral neuropathy Hepatitis	May be worsened by DM	Give pyridoxine Stop all medication
Rifampicin	Gastrointestinal Hepatitis Red urine	May be worsened by metformin	Symptomatic therapy Stop all medication Reassure
Pyrazinamide	Arthralgia Hepatitis	Arthralgia and hepatic toxicity may be more common in DM	Aspirin or NSAID Stop all medication
Ethambutol	Retro-bulbar neuritis	May be worsened by DM retinopathy	Stop all medication

NSAID = non-steroidal anti-inflammatory drugs

Sputum monitoring by smear microscopy in new pulmonary TB patients:

DM is known to be a risk factor for delayed sputum smear conversion at 2 months or at 5–6 months. The reasons include: i) the disease itself with some degree of immunosuppression; ii) poor adherence to treatment; iii) malabsorption of drugs, for example due to vomiting; iv) doses of anti-TB drugs that are below the recommended range especially if the patient is overweight or even obese; v) slow resolution of disease because the patient had extensive cavitation and an initial heavy bacterial load; and vi) the patient may have drug-resistant TB that is not responding to first-line therapy. Other reasons not related to DM include poor quality of anti-TB drugs and the presence of non-viable bacteria that still remain visible by microscopy.

Smear-positive at 2-months:*Action taken:*

The TB programme must first review whether drug susceptibility assessment was carried out at baseline using a WHO approved rapid diagnostic test, such as Xpert MTB/RIF, or line probe assay.

If drug susceptibility testing was done and the patient is known to have drug-susceptible TB, then a careful review must be done on the quality of the patient's support and supervision and necessary action must be taken if this is suboptimal. The patient is changed to the continuation phase with RH at the end of two months, but sputum smear microscopy is performed again at 3-months. If the sputum smear is still smear-positive at 3-months, then sputum culture and drug susceptibility testing is performed. The purpose of this step is to detect drug resistance without waiting until the fifth month to change to appropriate therapy.

If drug susceptibility assessment was not done at baseline, then a WHO approved rapid diagnostic test is carried out (Xpert MTB/RIF or line probe assay) to determine whether there is RR-TB or MDR-TB. If this is found, then the patient is changed to an MDR-TB regimen. If there is no evidence of RR-TB or MDR-TB, then management continues as above.

Smear-positive at 5-months or at 6-months:

If sputum smears are positive at 5-months or 6-months, the patient has failed treatment.

Action taken:

Sputum is obtained for culture and DST, the TB treatment card is closed (treatment outcome = failed) and a new treatment card is opened (with the patient registered as "treatment after failure"). With rapid molecular DST (e.g., line probe assays or Xpert MTB/RIF), MDR-TB can be confirmed or excluded within one to two days, thus allowing the DST results to guide the choice of the next regimen.

Recording and reporting on standardised treatment outcomes for drug-susceptible TB

At the end of the course of treatment for each patient, the treatment outcomes are recorded in the treatment card and TB register according to standardised definitions (see **Table 7.4**). If the patient is declared cured or treatment completed, this is deemed as treatment success and the patient is referred back to the DM clinic for further management of their DM.

Table 7.4: Definitions of treatment outcomes for patients (excluding RR-TB or MDR-TB)

<i>Outcome</i>	<i>Definition</i>
Cure	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because the tests were not done or because the results are unavailable.
Treatment failure	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment
Died	A TB patient who dies for any reason before starting or during the course of treatment
Lost to follow up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes patients "transferred-out" to another treatment unit as well as patients for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of <i>cured</i> and <i>treatment completed</i> .

Patients found to have RR-TB or MDR-TB at any point in time should be started on an adequate second-line drug regimen. These patients are excluded from the main TB cohort when calculating treatment outcomes (see below) and included only in the second-line TB treatment cohort analysis. If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from among those presented in **Table 7.4**.

In TB programmes, the group of patients diagnosed and registered in a specific time period (usually over three months) is called a “quarterly cohort”. Treatment outcomes are evaluated in this cohort, usually about three months after the last patient is judged to have finished treatment. This cohort analysis of treatment outcomes is a key management tool to evaluate the effectiveness of the programme at peripheral, district, regional and national levels.

This type of programmatic evaluation is especially important with patients who have both DM and TB as it allows an assessment within the routine setting of whether outcomes are worse in those with dual disease and whether impaired treatment success is due to death, failure or other reasons.

7.6 Are there special considerations in managing DM patients with drug-susceptible TB?

There are still uncertainties about the optimum TB treatment strategies in patients with dual disease, with some of the key issues being highlighted in **Table 7.5**.

Table 7.5: Considerations in treatment and care of patients with both TB and DM

<i>The issue</i>	<i>Intervention</i>	<i>Considerations</i>
Length of TB treatment	Currently 6 months for new drug-susceptible TB: rifampicin and isoniazid for six months combined with pyrazinamide and ethambutol for the first two months	Increased rates of treatment failure and relapse TB suggest the need to consider extended treatment: this should be evaluated in clinical trials. Reasons for increased failure and relapse /recurrent TB are not known and include: more extensive TB disease, altered immune response consequent on DM, reduced concentrations of anti-TB drugs. These reasons need to be studied

<i>The issue</i>	<i>Intervention</i>	<i>Considerations</i>
Drug-drug interactions leading to reduced drug concentrations in the treatment of DM	Rifampicin increases hepatic metabolism of all oral sulphonylurea derivatives, thus reducing their plasma concentrations and making dose adjustments difficult Little is known about the interaction of rifampicin with newer DM drug classes	Insulin and metformin are largely unaffected by rifampicin and should be strongly considered if drug treatment of DM is needed Weight-adjusted doses of anti-TB drugs might be needed, although this is difficult to implement in routine programmatic practice
Drug-drug toxicity	Isoniazid and DM Ethambutol and DM Metformin and anti-TB drugs	Peripheral neuropathy induced by both isoniazid and DM. Use adjunctive pyridoxine at the start to counteract effects of isoniazid Ethambutol-induced ocular effects and DM-induced retinopathy Gastrointestinal toxicity from metformin and anti-TB drugs. Metformin may rarely cause lactic acidosis which needs to be considered and diagnosed if a TB patient deteriorates on therapy – the action is to stop metformin
Adherence to medication	Adherence could be compromised from symptoms of both diseases, high pill counts, side effects of drugs	Appropriate patient education, use of fixed-dose combinations of anti-TB drugs, directly observed therapy
Use of corticosteroids	Adjunctive corticosteroids for TB meningitis, TB pericarditis or IRIS in HIV-associated TB can lead to or aggravate hyperglycaemia	More frequent monitoring of blood glucose and appropriate adjustment

7.7 Drug-resistant TB

How is drug-resistant TB treated in patients with DM?

Readers are referred to the WHO and Union guidelines for the management of MDR-TB (and XDR-TB) and the key drugs and concepts are briefly described below. Patients with MDR-TB and XDR-TB should be managed under the Programmatic Management of Drug-Resistant TB section of the National TB Programme, as expertise is needed. Currently, the treatment of MDR-TB and XDR-TB is similar in patients with and without DM.

The advice from WHO on longer and shorter MDR-TB regimens and on the groupings of second-line drugs for treating MDR-TB was changed in August 2018 and comprehensive guidance will follow by the end of the year.

Longer MDR-TB regimens:

The drugs have been regrouped into three categories and ranked based on the latest evidence for effectiveness and safety. The longer MDR-TB regimens usually last 18–20 months and may be standardised or individualised. These regimens are usually designed to include at least five drugs considered to be effective. The drugs are shown in **Table 7.6** according to three groups. Group A drugs are to be prioritised; Group B drugs are to be added next; Group C drugs are to be included to complete the regimens and when agents from Groups A and B cannot be used.

Note that kanamycin and capreomycin are no longer recommended and generally use of injectable medicines is discouraged.

Table 7.6: Drugs recommended for the treatment of MDR-TB

<i>Group</i>	<i>Name of Drug</i>	<i>Abbreviation</i>
Group A: Include all three drugs (unless they cannot be used)	Levofloxacin OR	Lfx
	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add both drugs (unless they cannot be used)	Clofazamine	Cfz
	Cycloserine OR	Cs
	Terizidone	Trd
Group C: Add to complete the regimen and when drugs from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin OR	Ipm-Cln
	Meropenem	Mpm
	Amikacin	Am
	(OR Streptomycin)	(S)
	Ethionamide OR	Eto
	Prothionamide	Pto
p-aminosalicylic acid	PAS	

Shorter MDR-TB Regimen:

In patients with MDR-TB who have not been treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a **shorter MDR-TB regimen of 9–12 months** may be used instead of a conventional, longer regimen. The regimen composition is as follows in the absence of sufficient evidence of replacing the injectable with bedaquiline or other oral agents:

Intensive phase 4–6 months: Am-Mfx-Pto(Eto)-Cfz-Z-E-H high-dose

Continuation phase 5 months: Mfx-Cfz-Z-E

In general:

Patients with MDR-TB should be treated using mainly patient-centred ambulatory care rather than hospital care. In patients with MDR/RR-TB, we recommend testing for second line drug resistance using LPA (wherever feasible) as this will help in identifying patients who may benefit from the shorter MDR-TB regimen.

7.8 How is the treatment of MDR-TB / RR-TB monitored?

General: Close monitoring during therapy is essential. The patient's weight must be measured monthly. Sputum smear and cultures should be performed monthly until smear and culture conversion – conversion is defined as two consecutive negative smears and cultures taken 30 days apart. After conversion, sputum smears should be performed monthly and sputum culture quarterly until successful completion of therapy.

Adverse effects: Second-line TB drugs have many more adverse effects than first-line TB drugs.

It follows that *active TB drug safety monitoring and management* (aDSM) is essential for all patients because adverse effects can be managed even in resource poor settings as long as they are recognised early. Some of these adverse effects may be worsened by DM or medications for DM. For example, aminoglycosides may be more toxic in DM. Neuropathy with linezolid is more common and fluoroquinolones may be associated with increased toxicity in DM. Please refer to national MDR-TB guidelines and PMDT Companion Handbook for more information.

Recording and reporting on standardised treatment outcomes for MDR-TB:

Standardised outcomes are shown in **Table 7.7**.

Table 7.7: Treatment outcomes for RR-TB/ MDR-TB/ XDR-TB using second line treatment

<i>Outcome</i>	<i>Definition</i>
Cure	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment failure	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: a) lack of conversion to two consecutive negative cultures by the end of the intensive phase, or b) bacteriological reversion in the continuation phase to two consecutive positive cultures after conversion in the intensive phase to negative cultures, or c) evidence of additional acquired resistance to fluoroquinolones or second line injectable agents or d) adverse drug reactions
Died	A patient who dies for any reason during the course of treatment
Lost to follow up	A patient whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A patient for whom no treatment outcome is assigned. This includes patients “transferred-out” to another treatment unit as well as patients for whom the treatment outcome is unknown to the reporting unit
Treatment success	The sum of <i>cured</i> and <i>treatment completed</i>

Treatment outcomes are evaluated in quarterly cohorts in the same way as for drug-susceptible TB and will usually take place about three months after the last patient is judged to have finished treatment.

8 Recording, reporting and cohort analysis

8.1 Summary statement

Recording and reporting and quarterly cohort analysis should be done at the facility level using treatment cards, registers and if available electronic medical record systems for bi-directional screening. The two basic indicators that need to be documented are the numbers (%) screened and the numbers (%) diagnosed with each disease.

8.2 What has been done so far with recording, reporting and cohort analysis for patients undergoing bi-directional screening for TB and DM?

Screening TB patients for DM:

The cornerstone of a good TB control programme is a standardised monitoring and evaluation system reporting quarterly on the number of patients registered for TB treatment, the types and categories of TB and the treatment outcomes of the patients registered one year earlier. It has thus been relatively easy to build into this system a monitoring and evaluation framework for DM screening in TB patients, similar to what is currently being done for HIV-related indicators and antiretroviral therapy.

Screening persons with DM for TB:

Recording the results of screening persons with DM for TB has been much more difficult largely because there are no globally established standardised patient recording and cohort reporting systems for patients with chronic non-communicable disease (NCD).

8.3 How to do recording and reporting on TB patients being screened for DM?

Recording:

For each TB patient registered, the programme will need to record at a minimum the following information:

- Whether the patient was screened for DM
- Whether the patient was diagnosed with DM

This can be done in the treatment card and in the TB patient register. Figure 8.1 and Figure 8.2 in the Appendices show how this information has been integrated into the TB treatment cards and TB patient registers in India after the country made a policy decision in 2012 to screen all TB patients for DM.

Reporting and cohort analysis:

The quarterly report on case finding can include the following information:

- Number of TB patients registered in the quarter
- Number screened for DM
- Number diagnosed with DM

An example is shown in **Table 8.1**.

Table 8.1: Quarterly Cohort Report of TB patients being screened for DM

<i>Characteristic being measured in the quarter</i>	<i>Number</i>
Number of TB patients registered	
Number screened for DM ^a	
Number diagnosed with DM ^b	

^a The number being screened for DM includes
i) all those asked about a previous diagnosis of DM and
ii) in those who did not receive a previous diagnosis of DM, all those who had a blood test carried out to determine the presence of new DM.

^b The number diagnosed with DM includes i) all those with a previous diagnosis of DM and ii) all those with a new diagnosis of DM as determined by screening in the TB clinic.

8.4 How to do recording and reporting on persons with DM being screened for TB?

New patients registered in the DM clinic and undergoing active case finding for TB

Recording:

It is recommended that new DM patients be proactively screened for TB if they live in a high TB burden country. For each new patient registered with DM, the DM clinic should record the following information:

- Whether the patient was investigated for TB (presumptive TB patient)
- Whether the patient was diagnosed with TB (diagnosed TB patient)

This information could be recorded in the case file, the treatment card, the DM register or an electronic medical register if there is one available in the clinic.

Reporting and cohort analysis:

The DM clinic could report on new case finding every quarter and this could include the following information:

- Number of new patients diagnosed with DM in the quarter
- Number investigated for TB (number of presumptive TB patients)
- Number diagnosed with TB (number of diagnosed TB patients)

An example is shown in **Table 8.2**.

Table 8.2: Quarterly Cohort Report of DM patients being screened for TB

<i>Characteristic being measured in the quarter</i>	<i>Number</i>
Number of new patients registered with DM	
Number investigated for TB (presumptive TB) ^a	
Number diagnosed with TB (diagnosed TB) ^b	

^a The number being screened / investigated for TB includes i) all those screened and investigated as a result of referral to TB services from the DM clinic and ii) all those screened and investigated as a result of referral to TB services from elsewhere.

^b The numbers diagnosed with TB includes a) all those diagnosed with TB as a result of referral to TB services from the DM clinic and b) all those diagnosed with TB as a result of referral to TB services from elsewhere during the quarter.

Persons already in DM care and undergoing passive case finding for TB

A record should just be made of the number of DM patients already in care who were investigated for TB and diagnosed with TB during the quarter.

9 Tuberculosis infection control and prevention of airborne transmission in diabetes clinics

9.1 Summary statement

The general principles of preventing hospital-acquired infection that are recommended for all types of health facilities should be applied to diabetes (DM) clinics. Standard procedures for airborne infection control need to be implemented in order to prevent patients with presumptive or diagnosed TB transmitting *Mycobacterium tuberculosis* (*M. tuberculosis*) to other persons with DM and health workers in the clinic. The key components include administrative controls, environmental controls and personal protection measures.

9.2 What is the aim of TB infection control and prevention of airborne transmission in DM clinics?

The aim of TB infection control in DM clinics is to prevent the transmission of *M. tuberculosis* (drug-susceptible or drug-resistant) in airborne droplets from a DM patient with TB to DM patients without TB, health care workers, family members, visitors or other persons attending the DM clinic.

9.3 What is airborne transmission and how can it be prevented?

M. tuberculosis is transmitted through droplet nuclei (infectious respiratory particles with a diameter of less than 5µm) which are spread into the air by infectious patients who cough, sneeze, talk, spit and sing. Droplet nuclei can remain suspended in the air for long periods of time. A single cough can produce 3,000 droplet nuclei. Direct sunlight kills *M. tuberculosis* in droplet nuclei in five minutes but they can survive in the dark and in poorly ventilated rooms for long periods of time. Such rooms provide a perfect setting for droplet nuclei to remain suspended and become inhaled by others. Droplet nuclei avoid bronchial defences and penetrate to the terminal alveoli where multiplication and infection begins. The spread of *M. tuberculosis* from a patient with active TB disease to others in

health care facilities is called *nosocomial* airborne transmission. Airborne transmission can be prevented or reduced by implementing infection control measures: administrative controls, environmental controls and personal protection measures.

9.4 Does airborne transmission of *M. tuberculosis* occur in DM clinics?

The simple answer is that we do not know and this is an important area for research. However, it is a strong possibility. For example, in Mexico, 20% of patients with DM with recurrent TB had re-infection with a different strain of *M. tuberculosis* rather than relapse from reactivation of improperly treated disease. It is possible that this recurrent disease might have resulted from inadvertent exposure to patients with undiagnosed TB in these DM clinics or elsewhere. A rapid assessment of ten DM clinics in China identified inadequate infection control measures, suggesting that the DM clinic might be a place for exposure to *M. tuberculosis*.

9.5 What are administrative controls?

Administrative controls are a series of policy measures that aim to reduce exposure of DM patients and health workers in the DM clinic to *M. tuberculosis*. The administrative control measures include the following managerial and work practices:

- 1 Develop an **infection control plan** and identify a focal person who is responsible for monitoring implementation of infection control measures. Large facilities should have an infection control committee to coordinate these measures.
- 2 Ensure health workers receive **training** on airborne infection control and understand their role in implementing infection control measures. This is particularly important in areas of the facility where transmission of *M. tuberculosis* is a risk, such as medical inpatient wards, TB wards and clinics and DM clinics.
- 3 Ensure that patients attending facilities, including those with DM, receive health education about "**cough etiquette**". This is particularly important among persons with cough. Such persons should be advised to cover their mouths and noses with a handkerchief or tissue paper when coughing or sneezing and turn their heads away from other patients or health workers when coughing. If surgical masks are available, they should be given to coughing patients.
- 4 Promptly **identify DM patients with a cough** and move them to a separated waiting area away from other patients. Such patients should be prioritised for obtaining

sputum specimens and implementing investigations so that appropriate treatment is started promptly and minimum time is spent in the outpatient setting.

- 5 Promote outpatient management wherever possible, especially in secondary and tertiary facilities through early hospital discharge or avoidance of hospitalisation altogether. When hospitalisation cannot be avoided, patients with a cough should be placed in a separate room. If this is not possible, it is important to pay attention to cough etiquette education and good ventilation (see below).
- 6 Be vigilant about the possibility of TB and ensure that persons with DM with a cough for 2-3 weeks are referred to the TB clinic for further investigation. For any person with DM who is diagnosed with TB, TB treatment is the top priority as this rapidly renders her/him non-infectious.
- 7 We recommend (based on very low quality evidence) that DM patients with TB should be managed in the TB clinic for at least the first two weeks of anti-TB treatment and if possible until the end of the intensive phase. Patients should not be referred to the DM clinic until after this time.

9.6 What are environmental controls?

Environmental controls consist of appropriate ways of improving ventilation by natural or mechanical means and considering ultraviolet germicidal irradiation (UVGI) in health facilities, including DM clinics.

Ventilation: Natural and mechanical ventilation allows fresh air to enter and circulate within the health facility which in turn removes or dilutes air contaminated with droplets containing *M. tuberculosis*. In resource-limited settings, the simplest and least expensive way to have good airflow is to use natural ventilation through open windows or skylights or a mixed approach that includes mechanical ventilation. Open windows may not be feasible in cold climates or seasons. The major obstacles to facilitate good natural ventilation are not related to the climate but awareness. Previously, health care workers have regarded DM as a non-communicable disease with no need to consider infection control as applied to the TB clinic. Even in warm seasons, most windows in DM clinics remain closed due to privacy, reasons of safety or because of air conditioning apparatus. In this regard, the assigned focal person needs to ensure that windows remain open throughout clinic hours.

Mechanical ventilation generally means the use of window fans and other exhaust ventilation measures. They are used to direct air flow to dilute and remove air or to

produce negative pressure in isolation rooms. If window fans are used, it is essential to keep the direction of air flow from health care worker to the patient to the outside, and not the other way round, that is, from the patient to the health care worker to the outside.

UVGI: this is often used in TB clinics and other facilities if resources permit. UVGI cleans the air by killing airborne *M. tuberculosis* in droplet nuclei. It is worth considering in the DM clinic if adequate ventilation is difficult to achieve. An UVGI device should be placed near the ceiling to irradiate the air in the upper part of the room. UVGI is suitable for most climates but its effectiveness can be reduced by high humidity above 70%. As the concentration of droplet nuclei that may carry *M. tuberculosis* in DM clinics is not as high as in TB clinics, an UVGI device may be used at night so as to avoid exposing persons with DM and the health care workers to ultraviolet light. If a UVGI device is used, the DM clinic or hospital manager must appoint a focal person to maintain and service the device to keep it functioning.

9.7 What are personal protection measures?

Personal protection measures are aimed at preventing the inhalation of aerosolised droplet nuclei. In situations where administrative and environmental control measures are not adequate to protect health care workers and persons with DM from exposure to *M. tuberculosis*, personal protection measures act as a third line of defence.

Personal protection equipment: this usually means a surgical mask or a respirator. The surgical mask is made of paper and should be used by persons with DM and with presumptive or diagnosed TB to 'cover their cough', that is, to prevent them from spreading infectious droplet nuclei into the air. Surgical masks are inexpensive but sometimes there is stigma attached to wearing them. Surgical masks are of no benefit to those exposed to a cough and do not protect the user in this situation from inhaling aerosolised droplet nuclei.

A personal respirator (for example, a N95 mask) is widely used by health workers to prevent inhalation of aerosolised droplet nuclei. These masks are expensive, they need to be properly applied and closely fitted to be effective and are uncomfortable to use in warm and humid settings. They are probably unnecessary in the DM clinic.

TB preventive therapy: if health care workers or persons with DM have been exposed in the DM clinic to an infectious TB patient, the issue of TB preventive therapy may arise. It will be important to determine whether the index patient has drug-susceptible or drug-resistant TB and guidance from the National TB Programme should be sought.

10 Collaborative services for tuberculosis and diabetes mellitus

10.1 Summary statement

In the same way as HIV and tuberculosis (TB) services have developed mechanisms for collaboration these need to be developed for diabetes mellitus (DM) and TB. Coordinated, integrated and patient centred services facilitate the concept of “*one patient – one health care worker – one health system – two (or more) diseases*”. The key step is to set up joint coordinating DM and TB bodies, especially at the national level, that take responsibility for the development of a national plan, its implementation and monitoring. The national plan includes the development of national guidelines and tools, resource mobilization, monitoring and evaluation and operational research, pre-service and in-service training and advocacy, communication and social mobilization.

10.2 What is the reason for collaboration?

Effective collaboration between TB and HIV programmes in the last two to three decades has helped to avoid unnecessary duplication of service delivery structures and has helped to promote optimal and coordinated use of scarce health care resources. As a result, the management and outcomes for patients being screened and treated for HIV-associated TB have greatly improved in countries. The vision for collaborative DM and TB services is based on this experience and applies the key elements to TB and DM. These elements could also be further applied to other risk factors for TB, for example, cigarette smoking, under-nutrition, alcohol dependency and substance abuse and associated co-morbidities.

10.3 What are the objectives of collaborative services?

The overall goal of the collaborative TB and DM services is to reduce the burden of TB among persons with DM and the burden of DM among patients with active TB. Specific objectives of these services are:

- To address issues of *primary prevention of both diseases* by tackling underlying risk factors and social determinants.
- To ensure *early diagnosis* of DM among TB patients and *the diagnosis of TB* among persons with DM.
- To *improve treatment outcomes* of both diseases through initiating anti-TB treatment and DM treatment for persons with both diseases.
- To *strengthen TB and DM surveillance*, including cohort analysis of treatment outcomes.
- To make health services ‘safer’ by implementing effective *infection prevention and control measures* for TB (and other airborne pathogens).
- To *strengthen health systems* through training; supportive supervision; the collection, analysis and use of routine TB-DM data at all levels; good supply chain management for essential consumables and drugs; and operational research.

10.4 How can collaboration be achieved?

Mechanisms for collaboration are well described in the WHO and Union Collaborative Framework for care and control of DM and TB.

National governments need to provide the leadership and political will to ensure sufficient resources for coordinated activities. Funding is necessary and should come mainly from domestic sources, and supported by international sources if necessary, based on a national strategic plan.

The first important step is to set up a **coordinating body** to ensure effective collaboration between existing programmes. As these programmes cut across communicable and non-communicable diseases, this coordinating body should also consider collaboration with other common co-morbidities, such as HIV, respiratory disease and malnutrition. If such a coordinating body already exists (for example, an HIV-TB coordinating body), the coordination of activities for DM and TB should be incorporated into its terms of

reference. Joint coordination should be established at national, provincial, regional, district and/or local levels (sensitive to country-specific factors), with representation from all relevant stakeholders.

10.5 What should these joint coordinating bodies do?

A key area for joint coordination is development of a joint plan for DM and TB activities, which is reflected in national strategic plans on TB and non-communicable diseases. The **national joint coordinating body** should take responsibility for drawing up the *joint national plan* which needs to encompass the following:-

- **Development of national guidelines and tools** for bi-directional screening of TB and DM and for management and treatment of patients with both diseases. These current generic guidelines for the care and control of DM and TB can serve as the framework for a more country-based and context-specific document. These guidelines should be comprehensive and include issues of governance, setting of standards and quality control assurance. Country-specific guidelines must take into account a) public-private partnerships, b) referral mechanisms between TB and DM clinics, and c) provision of long-term care for the person with DM after anti-TB treatment has been completed.
- **Resource mobilisation** focused on reliable supply chain management ensuring uninterrupted supplies of diagnostic consumables and drugs for the management of both diseases that are free for patients at the point of delivery (either through programme funding or through health insurance schemes)
- **Monitoring and evaluation** of collaborative activities for DM and TB
- **Promotion of operational research** so that local evidence can be generated about what works and what does not work as well as testing innovative ideas to streamline services at the community level
- **Pre-service and in-service training** that includes the development of training materials. Plans need to be developed to incorporate elements of this training into the curricula of medical, nursing and paramedical schools and into in-service training schedules and professional development seminars
- **Joint advocacy, communication and social mobilisation** addressing the needs of individual patients and communities for clinical care and prevention of both diseases. Basic facts about TB and DM should also be included into community care initiatives.

The coordination bodies at provincial, regional, district and/or local levels need to ensure that the national plan and national guidelines are disseminated to relevant implementers and stakeholders and they must help with the implementation, supervision and monitoring of collaborative DM and TB activities on the ground.

10.6 How should joint DM / TB activities be started?

Experience in the last decade has shown that it is easier to first set up services that allow the screening of TB patients for DM. Screening persons with DM for TB is a more difficult exercise and can be introduced later.

Setting up the screening of TB patients for DM at health facilities

Programme managers and implementers must first decide at what level of the health service they will implement the screening of TB patients for DM and whether testing for DM will be done in the TB clinic or elsewhere in the health facility. These decisions will be determined by the type of DM diagnostic test used (glycosylated haemoglobin [HbA1c] or random blood glucose [RBG]/fasting blood glucose [FBG]). They must also ensure that health care workers have been trained, consumables for glucose testing are in stock and treatment cards and registers are available for recording and reporting the activities and the findings. There are key indicators and data at the clinic level that need to be captured to assess the feasibility of the screening approach as well as provide sufficient information to inform about the prevalence of DM. At the end of every quarter, it is good practice to review the data, assess progress and take remedial measures if necessary. The parameters shown in **Table 10.1** can be used to monitor the pilot project and assess how each stage works. It might also be useful for clinics to record information about the severity of DM, and this could be stratified for example into those with HbA1c $\geq 6.5\%$ and $< 8.0\%$; $\geq 8.0\%$ and $< 10.0\%$; $\geq 10.0\%$ or the equivalent in FBG.

Table 10.1: Quarterly Cohort Report of Diabetes Screening in TB Patients

<i>Name of Treatment Unit:</i>		<i>Year:</i>	<i>Quarter:</i>
<i>Letter Code</i>	<i>Characteristic being measured</i>	<i>Number</i>	
A	Number of TB patients registered		
B	Number already known with Diabetes Mellitus (DM)		
C	Number not known to have DM at the time of screening (A-B)		
D	Of 'C', Number screened with Random Blood Glucose		
E	Of 'D', Number with Random Blood Glucose ≥ 6.1 mmol/l (≥ 110 mg/dl)		
F	Of 'E', Number screened with Fasting Blood Glucose (FBG) or HbA1c		
G	Of 'F', Number newly diagnosed with DM -FBG ≥ 7.0 mmol/l (≥ 126 mg/dl) OR with DM- HbA1c $\geq 6.5\%$ (≥ 48 mmol/mol)		
H	Total number of DM (B + G)		
I	Of 'H', Number who were referred to Diabetes Care		
J	Of 'I', Number who reached Diabetes Care		

Ensuring continued DM care for patients who have completed TB treatment

Efficient and timely referral of patients from one service to another is challenging in many settings. Public sector services for DM care may frequently be limited. In the absence of specialist DM clinics, specialists in medicine may be tasked to manage persons with DM. Task shifting or sharing may also be used, and consideration given to using paramedics and DM nurses. Mechanisms to ensure and measure efficient referral of patients between TB and DM/NCD clinics and bringing back patients who have not arrived at the receiving service within an agreed time period need to be developed. Community volunteers could play a role in strengthening the referral of patients.

Setting up the screening of persons with DM for TB at health facilities

It is unlikely that DM clinics are available at the most primary levels of the health system. They are more likely to operate at secondary or tertiary level hospitals. Once agreement has been reached about screening DM patients for TB, the program managers and implementers must also ensure that health care workers are trained, referral systems are in

place for the investigation and diagnosis of TB and that systems are in place for recording and reporting the activities and the findings.

Screening should follow the guidance provided in Chapters 1 and 5. Table 10.2 provides a template for reporting these parameters at quarterly intervals when setting up the pilot studies to assess whether screening, investigations and diagnoses are being made. More detail about the type of TB (bacteriologically confirmed TB or clinically diagnosed TB) could also be captured.

Table 10.2: Quarterly Report of Tuberculosis Screening in Diabetes Patients

<i>Treatment Unit</i>	<i>Year:</i>	<i>Quarter:</i>
<i>Characteristic being measured</i>	<i>Number</i>	
New DM patients:		
New DM patients registered in the quarter		
New DM patients screened for TB		
New DM patients identified with "Presumptive TB"		
New DM patients referred for TB investigations		
New DM patients diagnosed and registered with "active TB"		
Established DM patients:		
Persons with established DM seen in the quarter		
Persons with established DM diagnosed and registered with "active TB"		
Total DM patients diagnosed and registered with active TB		

10.7 How should collaborative activities be monitored and evaluated?

Monitoring and evaluation provides the means to regularly assess the quality, effectiveness, coverage and delivery of collaborative activities. Once collaborative activities have been started, decisions need to be made about scaling up, the level of detail required at national and other levels for monitoring and evaluating activities, the frequency of reporting (for example, quarterly) and to which body the reports are sent. Recording and reporting frameworks are discussed and presented in Chapter 8.

11 Further reading

11.1 Useful documents (in chronological order)

World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Summary of Technical Report and Recommendations. Geneva, Switzerland: WHO 2006.

World Health Organization. Treatment of Tuberculosis Guidelines, Fourth Edition. Geneva, Switzerland. WHO 2009. WHO/HTM/TB/2009.420.

World Health Organization and The International Union Against Tuberculosis and Lung Disease. Collaborative Framework for Care and Control of Tuberculosis and Diabetes. Geneva, Switzerland: WHO, 2011. WHO/HTM/TB/2011.15.

World Health Organization. 2011 Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation. Geneva, Switzerland: WHO 2011. HO/NMH/CHP/CPM/11.1.

World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. 2016 Update. Geneva, Switzerland. WHO 2016, WHO/HTM/TB/2016.04.

World Health Organization. Global Tuberculosis Report 2017. Geneva, Switzerland. WHO 2017. WHO/HTM/TB/2017.23.

World Health Organization. Treatment of Tuberculosis. Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 update. Geneva, Switzerland. WHO, 2017. WHO/HTM/TB/2017.05.

International Diabetes Federation. IDF Diabetes Atlas. Eighth Edition, 2017.

American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care 2017;40 (Supplement 1): S11-S24.

World Health Organization. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). August 2018. WHO/CDS/TB/2018.18.

11.2 Useful scientific and review papers (in chronological order)

Jeon CY & Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Medicine 2008; 5: e152.

Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med 2011; 9: 81.

Lin Y, Li L, Mi F, et al. Screening of patients with diabetes mellitus for tuberculosis in China. Trop Med Int Health 2012; 17: 1302 - 1308.

Li L, Lin Y, Mi F, et al. Screening of patients with tuberculosis for diabetes mellitus. Trop Med Int Health 2012; 17: 1294 - 1301.

India Diabetes Mellitus-Tuberculosis Study Group. Screening of patients with diabetes mellitus for tuberculosis in India. Trop Med Int Health 2013; 18: 646 - 654.

India Tuberculosis-Diabetes Study Group. Screening of patients with tuberculosis for diabetes mellitus in India. Trop Med Int Health 2013; 18: 636- 645.

Lönnroth K, Roglic G, Harries AD. Diabetes and tuberculosis 1: Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. Lancet Diabetes Endocrinol 2014; 2: 730 – 739.

Riza AL, Pearson F, Ugarte-Gil C, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrin 2014; 2: 740-753.

Lin Y, Harries AD. Tuberculosis infection control measures in diabetes clinics in China: a rapid assessment of 10 hospitals. Trop Med Int Health 2015; 20: 1196 – 1200.

Harries AD, Kumar AMV, Satyanarayana S, et al. Diabetes mellitus and tuberculosis: programmatic management issues. Int J Tuberc Lung Dis 2015; 19: 879 – 886.

Lo H-Y, Yang S-L, Lin H-H, et al. Does enhanced diabetes management reduce the risk and improve the outcomes of tuberculosis? Int J Tuberc Lung Dis 2016; 20: 376-382.

Liu Q, Li W, Xue M, et al. Diabetes mellitus and the risk of multidrug resistant tuberculosis: a meta-analysis. Scientific Reports 2017; 7: 1090.

Al-Rifai RH, Pearson F, Critchley J, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: a systematic review and meta-analysis. PLoS ONE 2017; 12: e0187967.

Koesoemadinata RC, Kranzer K, Livia R, et al. Computer-assisted chest radiography reading for tuberculosis screening in people living with diabetes mellitus. *Int J Tuberc Lung Dis* 2018; 22: 1088-1094.

Harries AD, Lin Y, Kumar AMV, Satyanarayana S, Zachariah R, Dlodlo RA. How can integrated care and research assist in achieving the SDG targets for diabetes, tuberculosis and HIV/AIDS? *Int J Tuberc Lung Dis* 2018; 22: 1117-1126.

ABOUT THE INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE (THE UNION)

The Union is a global scientific organisation with the mission to improve health among people living in poverty. We do that by conducting scientific research, working with governments and other agencies to translate research into better health for people around the world, and delivering projects directly in the field. The Union is made up of a global membership body of people who help to advance our mission, and a scientific institute that implements public health projects within countries. For close to 100 years, we have been leaders in the fight against some of the world's biggest killers, including tuberculosis, lung diseases and tobacco use.