Republic of Rwanda
Ministry of Health

Rwanda Biomedical Centre
Healthy People, Wealthy Nation

TUBERCULOSIS HANDBOOK

Edition 2020

INSTITUTE OF HIV/AIDS, DISEASE PREVENTION&CONTROL (IHDPC)
TUBERCULOSIS & OTHER RESPIRATORY COMMUNICABLE DISEASES DIVISION

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FOREWORD

Worldwide, tuberculosis (TB) continues to be the most important cause of death from a single infectious microorganism. Globally, an estimated 10.0 million people fell ill with TB in 2018, a number that has been relatively stable in recent years[1]. Despite being a preventable and curable disease, there were an estimated 1.2 million TB deaths among HIV-negative people in 2018 (a 27% reduction from 1.7 million in 2000), and an additional 251 000 deaths among HIV positive people (a 60% reduction from 620 000 in 2000). TB affects people of all age groups with 57% in men (aged ≥ 15 years), 32% in women and 11% in children (aged less than 15 years). Among all TB cases, 8.6% were people living with HIV (PLHIV). Africa accounted for 24% of the world's cases. Drug-resistant TB continues to be a public health threat. In 2018, there were about half a million new cases of rifampicin-resistant TB of which 78% had multidrug resistant TB (MDR-TB).

In Rwanda, the incidence rate of tuberculosis - new cases and relapses- was estimated at 59 cases per 100,000 inhabitants in 2018, lower than the global average and that of the AFRO region which were respectively 96 and 231. Estimated treatment coverage was 80%. Mortality has been on a consistent decline since 2010 to the current level of 4.5 per 100,000 population. Among the 5,822 incident cases notified in 2018, children (<15 years) represented 6%, males 65% and women 29%. The proportion of TB patients infected with HIV remains stable each year, between 21-25 %. MDR-TB burden is relatively low (1.5% in new cases; 10.7% in previously treated cases) and there is no established resistance to any second-line TB agent[2].

Rwanda, as a member of the World Health Assembly, adopted the END TB strategy that aims at ending the global TB epidemic by 2035 by markedly reducing death and incidence and eliminating the social and economic burden of this disease. The strategy encompasses a package of interventions organized around the three pillars of integrated patient-centered care and prevention, bold policies and supportive systems and intensified research and innovation.

This manual compiles all the technical and operational guidelines to be applied in all health facilities in the country with the aim of eliminating tuberculosis by 2035 (less than 10 cases per 100.000 inhabitants). These guidelines have been updated to comply with the latest scientific evidence and WHO recommendations, while adapting them to the national context.

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[1] Global tuberculosis report 2019 (WHO/CDS/TB/2019.23). Geneva: World Health Organization 2019.
[2] TB drug resistance survey conducted in 2015/2016

We strongly recommend this excellent tool to all those involved in the fight against tuberculosis at all levels of health facilities, health sciences institutes and to all those who support the Ministry of Health in the fight to reduce the morbidity and mortality due to tuberculosis in our country.

We take this opportunity to thank all those who contributed to updating this handbook and to those who work together on a daily basis with the Ministry of Health through its different health facilities levels and in their communities..

Dr. NGAMIJE M. Daniel

Minister of Health

This handbook is intended to provide guidance to professional health care workers on the management of people with tuberculosis as well as those co-infected with HIV. The development of these guidelines has been collaboration and contribution of different actors, partners and medical doctors working in referral and district hospitals.

MAIN CHANGES IN THESE GUIDELINES

- **Chapter 2: Tuberculosis control in Rwanda**
  - Rwanda medical supply (RMS) is substituting MPPD with the mandate of managing end-to-end health supply chain, including district pharmacies.
- **Chapter 3: Detection and diagnosis**
  - New risk groups have been added for enhanced case finding: malnourished individuals, post-partum women, mine workers, urban slum dwellers**.**
  - The urine lipoarabinomannan (LF-LAM) assay is a rapid test newly introduced in Rwanda to assist in the diagnosis of tuberculosis in PLHIV with advanced disease.
  - Rifampicin resistance detected in specimens with low or very low bacillary load, must be confirmed by a second Xpert test**.**
  - The diagnostic algorithm has been revised to incorporate these recommendations.
  - The use of the Xpert test is recommended for the diagnosis of TB meningitis and other forms of extrapulmonary tuberculosis (EPTB).
- **Chapter 4: Treatment and patient management**
  - Patients diagnosed with MTB+/RIF+ on a sample of low/very low bacillary load and MTB+/RIF- by the repeated Xpert test should be enrolled on first-line treatment and closely monitored at month 1 and month 2 through XPert, culture and DST. The treatment regimen will be reassessed based on the results.
  - Patients who fail first-line treatment and are susceptible to rifampicin should benefit from a “therapeutic drug monitoring” (TDM) test. The latter can detect an insufficient plasma dosage of drugs which may be caused by malabsorption and may require dose adjustment.
  - Patient's nutritional status should be assessed at the start of antituberculosis treatment. Those who have a BMI $\leq$ 18.5 should be treated for malnutrition and tuberculosis and receive nutritional support in order to reduce the risk of death and relapse.

- New guidelines are being developed by the TB&ORD Division regarding the tuberculosis preventive treatment (TPT) indications for contacts ≥ 5 years of age and the use of short TPT regimens containing rifampicin or rifapentine.

- **Chapter 5: TB/HIV coinfection**
  - LF-LAM test should be used to assist in the diagnosis of active TB in PLHIV with an advanced disease (CD4 count <200 cells/mm3 or stage 3 and 4) and with signs or symptoms of TB (new test).
  - Co-trimoxazole is indicated only for HIV+ children under 5 years of age, new PLHIV aged ≥ 5 years with baseline CD4 count <200 cells/mm3, and PLHIV aged ≥ 5 years with unsuppressed viral load (≥ 200 copies/ml).
  - ART regimens are changed in line with the national HIV guidelines.
- **Chapter 9: TB surveillance, supervision, monitoring and evaluation**
  - For any TB case, all data relating to TB notification, initiation, follow-up and termination of TB treatment should be introduced routinely in the electronic TB case-based surveillance system (e-TB).
  - The e-TB is completed by the TB focal person of the health facility that has received the patient as presumptive TB, whether it is a CDT or a CT.
  - Transferred patients are transferred with their original treatment card and they are also electronically transferred through the e-TB. The transferring health facility keeps a copy of the treatment card. The receiving health facility will search for the patient file in the e-TB system and complete the new data collected at the various stages until the end of the treatment stage.
- **Chapter 10: Management of anti-tuberculosis products**
  - The report and requisitions are made via e-LMIS; paper forms are no longer used.
  - All data on consumption, quantities received, stocks available, data on expiration etc. must be kept up to date in the e-LMIS system.
- **Fourth part: Laboratory**
  - A section has been added on FNA technique.

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ABBREVIATIONS

AFB	Acid fast bacilli
AIDS	Acquired immuno-deficiency syndrome
ART	Anti-retroviral treatment
BCC	Behaviour change communication
BCG	Bacillus of Calmette and Guérin
BMI	Body mass index
CBC	Complete blood count
CDT	Centre for diagnosis and treatment of tuberculosis
CHU	University teaching hospital (centre hospitalier universitaire)
CHW	Community health worker
CPC	Cetyl Pyridinium Choride
CSF	Cerebrospinal fluid
CT	Treatment centre (for TB)
CXR	Chest X-ray
DOT	Directly observed treatment
DH	District hospital
DP	District pharmacy
DQA	Data quality audit
DR-TB	Drug resistant TB
DST	Drug susceptibility test
EFV	Efavirenz
EPTB	Extrapulmonary tuberculosis
e-LMIS	Electronic logistic management information system for health products
e-TB	Electronic TB register
FDC	Fixed-dose combination
FM	Fluorescence microscopy
FNA	Fine needle aspiration
HC	Health center
HCW	Health care worker
HF	Health facility
HIV	Human Immunodeficiency Virus
IC	Infection control
IEC	Information, Education and Communication
IGRA	Interferon-gamma release assay
IHDPC	Institute of HIV/AIDS, Disease Prevention&Control
IMCI	Integrated management of childhood illnesses
INH	Isoniazid

IPC	Infection prevention and control
IPT	INH preventive treatment
IRIS	Immune reconstitution syndrome
LED	Light emitting diode
LF-LAM	Lateral flow urine lipoarabinomannan assay
LPA	Line probe assay
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant tuberculosis
MDR/RR-TB	Multidrug- or rifampicin-resistant tuberculosis
MTB	*Mycobacterium tuberculosis* complex bacteria
NCD	Non-communicable disease
NRL	National Reference Laboratory
NSAIDs	non-steroidal anti-inflammatory drugs
NSP	National Strategic Plan
NTM	Non-tuberculous mycobacteria
NVP	Nevirapin
PCR	Polymerase chain reaction
PLHIV	People living with HIV
PMTCT	Prevention of mother to child transmission of HIV
PPD	Purified protein derivative (used for the tuberculin skin test)
PTB	Pulmonary tuberculosis
RBC	Rwanda Biomedical Center
(RH)	Fixe dose combination of Rifampicin and Isoniazid
(RHZ)	Fixe dose combination of Rifampicin, Isoniazid and Pyrazinamide
(RHZE)	Fixe dose combination of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol
RR-TB	Rifampicin-resistant tuberculosis
RSQA	Rapid service quality assessment
TB	Tuberculosis
TB/HIV	HIV-associated TB
TB&ORD	Tuberculosis and Other Respiratory Communicable Diseases
TDM	Therapeutic drug monitoring of anti-tuberculosis drugs in the plasma
TPT	TB preventive treatment
TST	Tuberculin skin test (for the diagnosis of LTBI)
UTI	Urinary tract infection
WHO	World Health Organization
XDR-TB	Extensively drug-resistant TB

SUMMARY OF RECOMMENDATIONS

1. Detection of TB

- Presume TB in patients who have cough for 2 weeks or more, which can be accompanied, but not necessarily, by fever, night sweats, loss of appetite, weight loss (poor weight gain in children), sputum production, chest pain, fatigue, hemoptysis.
- Presume TB in HIV+ patients who have one or more of the following signs or symptoms regardless of their duration:
  - Adult: current cough, fever, weight loss, night sweats.
  - Children: current cough, fever, poor weight gain, TB contact.
- Enhance case finding through systematic screening for TB signs and symptoms among the following high-risk groups: PLHIV, contacts of a confirmed pulmonary TB or MDR-TB case, prisoners, children <15 years of age, adults ≥ 55 years, diabetics, health care workers and community health workers, refugees in camps. **Include new risk groups**: malnourished individuals, post-partum women, mine workers, urban slum dwellers, people addicted to alcohol, tobacco or drugs.
- Perform symptomatic and radiological screening during detection campaigns in prisons, for TB contacts and for newly diagnosed HIV-positive patients.

2. Diagnosis

- Request Xpert MTB/RIF as initial test to detect MTB and rifampicin resistance in:
  - All patients with presumptive TB who are at high-risk for TB or for DR-TB
  - All presumptive TB cases from high-burden districts (Kigali and other districts specified by the TB&ORD Division)
  - All patients with presumption of TB meningitis or other extrapulmonary TB.
- Request an Xpert MTB/RIF test for all cases diagnosed with a positive sputum smear to rule out possible resistance to rifampicin.
- Request a drug-susceptibility test (DST) for all patients at high risk of DR-TB. This includes all previously treated cases (failures, lost to follow up, relapses), contacts of a M/XDR TB case, patients with a positive control smear during first-line treatment.
- In the event of resistance to rifampicin detected in a sample with low or very low bacillary load, repeat XPert MTB/RIF on a new specimen.
- Request microscopy examination for:

- Patients with presumptive TB who are not eligible for XPert
- Follow-up examinations during treatment.

- Consider using urine lipoarabinomannan (LF-LAM) assay to assist in the diagnosis of active TB in PLHIV with advanced disease. **(new test being introduced)**
- Perform chest X-ray when pulmonary tuberculosis cannot be confirmed bacteriologically, particularly in people infected with HIV and children.

3. TB treatment

- Treat with the standard first-line regimen (2RHZE/4RH) the following cases:
  - Bacteriologically confirmed TB cases susceptible to rifampicin, new and retreatment.
  - Clinically diagnosed cases, pulmonary and extrapulmonary.
- If rifampicin resistance is detected, take into account the bacillary load of the sample tested (**new guidelines):**
  - If the bacillary load is low or very low, repeat Xpert MTB/RIF test and choose the regimen according to the 2nd result.
  - If the bacillary load is medium or high, refer the patient for second-line regimen.
- Treat TB meningitis with the first-line regimen for 12 months (2RHZE/10RH) and add prednisolone to reduce the risk of hydrocephalus.
- Treat osteoarticular TB with the first-line regimen for 12 months (2RHZE/10RH).
- Administer the treatment under observation (DOT) with a patient-centred approach and observance support. DOT by family members is not recommended except for young children.
- Assess patient's nutritional status at the start of antituberculosis treatment; those who have a BMI $\leq$ 18.5 should be treated for malnutrition and tuberculosis and receive nutritional support in order to reduce the risk of death and relapse.

4. First-line treatment follow-up

- Perform sputum smear examination at the end of month 2, 5 and 6 for bacteriologically confirmed TB cases.

- Ensure special monitoring of patients on first-line treatment who were diagnosed with MTB+/RIF+ on a low/very low bacillary load sample and MTB/RIF- at the repeat test by performing Xpert, culture and DST at month 1 and 2 **(new guidelines).**
- Send any smear-positive sputum at C2, C5 or C6 to the reference laboratory for culture and DST.
- Declare failure if C5 or C6 is smear-positive (confirmed by a 2nd positive smear after 15 days). Request XPert, culture and DST. Start retreatment based on rifampicin sensitivity according to Xpert result. Reassess the regimen upon receipt of culture and DST results.
- Consider performing a "therapeutic drug monitoring" (TDM) test in patients who fail in first-line treatment and are susceptible to rifampicin in order to detect possible insufficient plasma dosage of drugs which may be due to malabsorption. and which may require dosage adjustment. **(TDM is a new test, soon available at the NRL).**
- Check for any side effects of treatment at each follow-up visit and manage them promptly.
- Conduct contact investigation for all bacteriologically confirmed TB cases and for children diagnosed with TB by using the algorithm of TB contact investigation; repeat contact investigation at the end of treatment of the index case.

5. Tuberculosis preventive treatment (TPT)

- Offer TPT to the following high-risk groups:
    - Contacts aged <5 years of bacteriologically confirmed pulmonary TB cases
    - Contacts aged $\geq$ 5 years eligible according to the instructions to be published shortly by the TB&ORD Division
    - HIV+ adults and children aged $\geq$ 1 year (whether or not taking ART),
    - HIV+ infants aged <1 year who are contact of a bacteriologically confirmed TB case.
- Rule out TB before starting TPT based on the algorithm of contact investigation and the screening algorithm for PLHIV, respectively.
- Use the isoniazid preventive regimen (6H) or a shorter regimen containing rifampicin or rifapentine, in accordance with guidelines being developed by the TB&ORD Division.

6. TB/HIV coinfection

- Screen for TB any person living with HIV at enrolment in the ARV program and at each follow-up visit, using the TB screening algorithm for PLHIV.
- Request Xpert MTB/RIF as initial diagnostic test for any PLHIV who screen positive.
- Consider using LF-LAM test to assist in the diagnosis of active TB in PLHIV with an advanced disease (CD4 count <200cells/mm^3 or stage 3 and 4) and with signs or symptoms of TB **(new test being introduced**).
- Treat TB in priority and use the same antituberculosis regimen as for HIV-negative patients.
- Replace Rifampicin with Rifabutin for TB/HIV patients over 15 years of age who are taking a PI-based regimen boosted with ritonavir.
- Start ART in all TB/HIV patients as soon as possible within the first 2-8 weeks of anti-TB treatment (within the first 2 weeks if CD4 cell count $\leq$ 50/mm^3) and use the ART regimens updated by the HIV program.
- Give Co-trimoxazole to eligible TB/HIV patients:
    - All HIV+ children under 5 years of age
    - New PLHIV aged $\geq$ 5 years with baseline CD4 count < 200 cells/mm^3
    - PLHIV aged $\geq$ 5 years with unsuppressed viral load ($\geq$ 200 copies/ml)

  (new guidelines).
- Give pyridoxine to all TB/HIV patients for prevention of peripheral neuropathy.
- Provide integrated care and treatment of TB/HIV patients in the "One-Stop TB-HIV service".
- Offer TPT to eligible PLHIV whose TB screening is negative (refer to section 5 above).

7. TB in children

- Presume TB in children who present cough or fever for more than 14 days despite broad-spectrum antibiotic treatment, negative malaria smear and negative evaluation for other infectious diseases including urinary tract infection (UTI), poor weight gain, contact with a bacteriologically confirmed TB patient.
- Screen for TB in children under 5 years of age who consult the health facility by using the IMCI algorithm and registers.
- Start antituberculosis treatment in children who present any indication for treatment according to the pediatric poster, i.e. a positive bacteriological test or a combination of clinical signs, risk factors and/or additional tests supporting the diagnosis of TB.

- When a child is diagnosed with TB, conduct a family and school contact investigation using the algorithm for contact investigation.
- Administrate TPT to eligible children (see section 5 above).

8. TB infection control in health facilities

- Triage people with cough or suffering from tuberculosis and separate people with presumed or confirmed TB from other people, especially PLHIV and other immunocompromised patients. This should be done at the entrance to the health facility, in waiting areas, OPD, wards, emergency service, etc.).
- Educate patients with presumed or confirmed TB on cough hygiene.
- Minimize the time spent in the health facility by people with presumed or confirmed TB by ensuring prompt diagnosis and early initiation of treatment.
- Administer TB treatment on an outpatient basis unless admission is clinically indicated.
- Maximize natural ventilation within the health facility by keeping doors and windows open as much as possible.
- Wear a particulate respirator when caring for M/XDR-TB patients.
- Encourage coughing patients with presumptive or confirmed TB to wear a surgical mask when they are in contact, indoors, with other people or during specialized examination.

9. BCC

- Provide any patient eligible for antituberculosis treatment or preventive treatment with adequate information before starting treatment and during treatment, with emphasis on treatment adherence.
- Develop a BCC calendar including talks on tuberculosis in the health facility and in the community and keep a register of their execution.

10. TB surveillance

- Any case diagnosed with TB must be notified by the HF where he was received as presumptive TB case, whether or not TB treatment has started.
- Enter routinely in the e-TB, the TB register and the TB treatment card all information relating to TB notification, initiation, follow-up and termination of TB treatment.
- To transfer a patient:
    - The transferring health facility (HF) gives the patient the original treatment card, keeps a copy, and performs the transfer in the e-TB system.

- The HF to which the patient is transferred does not have to notify him/her a second time but to look for his/her file in the e-TB system in order to complete the new information collected until the end of the treatment.

11. Management of health products

- The “Rwanda Medical Supply (RMS)” is substituting the MPPD with the mandate of managing end-to-end health supply chain, including district pharmacies.
- Have a stock card for each product (drug, reagent, material) and regularly complete the input and output quantities.
- Make the report and requisitions via the e-LMIS system.
- Regularly update in the e-LMIS all data on consumption, quantities received, stocks available and expiration dates (at least once a week).

1ST PART. GENERAL INFORMATION

CHAPTER 1. TUBERCULOSIS

1.1. ETIOLOGY OF THE DISEASE

Tuberculosis (TB) is an infectious disease caused in the majority of cases by the *Mycobacterium tuberculosis* (Koch's bacillus). The bacilli enter the body by inhalation and reach the lungs, from where they may spread to other parts of the body via the blood stream, the lymphatic system, the airways or by direct extension to other organs.

Pulmonary tuberculosis is the most common form of the disease and is the only one that is contagious. Extrapulmonary tuberculosis can affect any organ and may even become disseminated. This type of tuberculosis is usually not infectious.

Infection by *Mycobacterium bovis* affects cattle and may be transmitted to people by drinking raw infected milk. However, its contribution to the global morbidity in Rwanda is minimal.

Characteristics of *Mycobacterium tuberculosis*:

- It is a micro-organism with bacillary shape, acid-fast bacillus (AFB), characteristic on which sputum smear microscopy is based.
- It is strictly aerobic, this the reason why it affects more the upper parts of the lungs where oxygen pressure is the highest.
- *M. tuberculosis* is rapidly destroyed when exposed to sunlight and their concentration in the air is reduced by good ventilation. On the contrary, bacilli excreted in an enclosed and poorly ventilated space may remain contagious for a longer period of time.
- Its multiplication is slow (12 to 24 hours) and this is why it takes 2 to 8 weeks to get results from culture. This slow growth also explains why it is not necessary to administer drugs several times a day.
- The bacilli may remain latent in the body for long periods of time and reactivate with a decline in immunity.

Tuberculosis affects the human body in two main stages. The first stage occurs when an individual is exposed to bacilli excreted by a person with an infectious form of tuberculosis

and becomes infected. In the second stage, the person falls ill and manifests various symptoms and signs that indicates that s/he has developed the disease.

1.2. TRANSMISSION AND RISK OF INFECTION

Tuberculosis is transmitted from an infectious pulmonary tuberculosis patient through aerosols with tiny droplets containing viable bacilli while coughing, talking, spitting, sneezing, laughing or singing. These droplets dry before reaching room surfaces and can become droplet nuclei, which are small (1 to 5 microns) and light enough to remain suspended in-room air for several hours. If inhaled by an individual, they can reach the pulmonary alveoli where the bacilli begin to multiply and generate TB infection.

The risk of TB infection is the probability that a person exposed to an infectious TB case will become infected. It depends on factors such as:

- The infectiousness of the source patient. Smear-positive tuberculosis cases are the most contagious and, if left untreated, infect an average of 10 to 20 people a year. The risk of infection from a person with smear-negative tuberculosis is low, but not null if the culture is positive. Patients with extrapulmonary tuberculosis are not contagious, except in case of simultaneous pulmonary involvement. In general, children are less contagious than adults since they have a lower bacillary load. The contagiousness of patients enrolled on treatment decreases rapidly (within a few days) as long as they take it correctly.
- The frequency, proximity and duration of contact with a contagious case as well as the immune response of the exposed person.
- Environmental factors. The risk of infection is particularly high for people who share confined and poorly ventilated accommodation with a contagious patient, as well as in penitentiary institutions and boarding schools. Conversely, the transmission is less active in a sunny outdoor environment.

1.3. LATENT TUBERCULOSIS INFECTION

The majority (90%) of persons with tuberculosis infection will not develop the disease, unless their immunity is compromised (HIV, etc.). The bacilli can remain latent in the body for an extended period of time. These people have a “latent tuberculosis infection” (LTBI), which is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB. About a quarter of the world’s population is estimated to be infected with *M. tb*, and the vast majority have no signs or symptoms of TB disease and are not infectious, although they are at risk for

active TB disease and for becoming infectious. The only sign of TB infection is a positive reaction to the tuberculin skin test (TST).

1.4. EVOLUTION TO TUBERCULOSIS DISEASE

On average, 5 to 10% of individuals infected with TB will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection. The development of TB disease can occur as a result of the infection or later by reactivation of the latent infection due to a weakened immune system. The main risk factors for developing active TB are:

- HIV infection
- Being a child contact less than 5 years of age
- Low body weight or malnutrition
- Diabetes mellitus
- Excessive alcohol and substance use, including tobacco use
- Silicosis or other occupational lung diseases
- Prolonged corticosteroid therapy
- Cancers, immune-modulation treatment, severe kidney disease, physical or emotional stress.
- Poverty is always strongly associated with tuberculosis as it promotes promiscuity and therefore transmission of TB from infectious patients is very likely. It can also limit access to healthcare, which prolongs the period of contagiousness and increases the risk of infection for people around.

Table 1 . Characteristics of tuberculous infection and tuberculosis disease

Characteristic	Tuberculous infection	Tuberculosis disease
Symptoms	None	Most present with cough, weight loss, fever, night sweats
Tuberculin skin test	Positive	Usually positive
Interferon-gamma release assay (IGRA)	Positive	Usually positive
Sputum bacteriological tests	Negative	Usually positive
Chest radiograph	Normal	Usually abnormal
Infectiousness	No	Often infectious (pulmonary TB before treatment)
Tuberculosis case	No	Yes
Preferred treatment	Preventive treatment	Antituberculosis treatment

1.5. DEVELOPMENT OF DRUG RESISTANCE

Drug resistance is due to the selection of bacilli which have acquired resistance to anti-TB drugs through mutations. Drug resistance is often a problem created by humans and may result of the following actions:

- Administration of an inappropriate treatment (insufficient dosage or duration or poor adherence)
- Poor management of supplies and quality of TB medicines (stock-outs, use of medicines that are not quality-assured, poor storage conditions)
- Airborne transmission of already resistant bacilli, especially among contacts of a drug-resistant TB patient.
- Inadequate infection controls in the health facilities, congregate settings (prisons, boarding schools, etc.) and public places.

The best prevention of DR-TB is the administration of high-quality treatment to patients with drug-susceptible TB.

1.6. PROGNOSIS

- The risk of death depends on the location and type of disease as well as the promptness of diagnosis and initiation of adequate chemotherapy.
- After 5 years and without treatment, 50-60% of individuals with contagious tuberculosis and not infected with HIV will be dead, 20-25% will be cured thanks to their strong immune system and 20-25% will have chronic contagious tuberculosis. Similar lethality is found in patients with untreated extrapulmonary or smear-negative TB. With appropriate treatment, the lethality of tuberculosis is greatly reduced and should be less than 5%.
- Tuberculosis in PLHIV not treated with ARVs is almost always fatal without treatment for tuberculosis. Even on ART, the lethality remains higher than for patients not infected with HIV.
- A first infection does not prevent the risk of subsequent reinfection and of developing a new episode of the disease, even in patients who have recovered from tuberculosis.

CHAPTER 2. TUBERCULOSIS CONTROL IN RWANDA

2.1. COORDINATION

TB control activities are conducted by the Tuberculosis and Other Respiratory Communicable Diseases (TB&ORD) Division under Rwanda Biomedical Center (RBC). It comprises four hierarchy levels:

- Central level (strategic level),
- District level (operational level),
- Peripheral level for implementation (health facilities)
- Community support.

2.2. MISSION

To contribute to ending the global tuberculosis epidemic by promoting universal and equitable access to quality diagnosis and effective treatment of TB, MDR-TB, and TB/HIV coinfection and by enhancing prevention of the disease.

2.3. OBJECTIVES

Rwanda goal is to end the TB epidemic by 2035, i.e. reduce the annual incidence rate to 10 cases per 100 000 population or less (new and relapses).

The strategies to achieve this goal are detailed in the National Strategic Plan (NSP) for Tuberculosis Control. The current NSP covers the period 2019-2024 and has set the following targets for mid-2024 as compared to 2015:

- 35% reduction in TB incidence rate
- 55% reduction in TB death rate
- 20% reduction of affected families facing catastrophic costs due to TB.

The 2019-2024 TB NSP strategies are shown below.

Tuberculosis National Strategic Plan 2019-2024

PILLAR I: PATIENT-CENTRED CARE
1.1. CONSIDERING THE PATIENT PATHWAY FOR TUBERCULOSIS
Specific Objective: 1.1.1. Accelerating early screening and appropriate diagnosis of TB
Specific Objective: 1.1.2. Quality of care and ensuring cure, ADSM and patient support
Specific Objective: 1.1.3. Promoting care seeking and prevention through community engagement

1.2 TARGETED EPIDEMIOLOGY AND POPULATIONS
Specific Objective: 1.2.1 Enhancing Programmatic Management of Drug -Resistant Tuberculosis
Specific Objective: 1.2.2. Ensuring prevention, diagnosis and treatment of Childhood Tuberculosis

Specific Objective: 1.2.3 Strengthening management of TB / HIV and other co-morbidities
Specific Objective: 1.2.4 Ensuring diagnosis and management of Lung health diseases
Specific Objective: 1.2.5. Promote intensified screening and diagnosis among high-risk group (HRG) populations

PILLAR II. BOLD POLICIES AND SUPPORTIVE SYSTEMS
2.1. PROGRAMMEMATIC MANAGEMENT, MULTI-SECTORAL COLLABORATION & ENGAGING ALL CARE PROVIDERS
Specific Objective:2.1.1. Promote political commitment with adequate resources for tuberculosis care and prevention
Specific Objective:2.1.2. Strengthen good services quality in management of TB care and prevention
Specific Objective:2.1.3. Engaging civil society organizations, and public and private care providers in the fight against TB
Specific Objective:2.1.4. Strengthening Migrant and cross border TB control
Specific Objective:2.1.5. Reinforcing TB infection control measures in health care and congregate settings

2.2. UNIVERSAL HEALTH COVERAGE, SOCIAL PROTECTION, HUMAN RIGHTS & NUTRITION
Specific Objective: 2.2.1. Strengthen Universal Health Coverage and Social protection mechanisms for TB control
Specific Objective: 2.2.2. Strengthen the Supply chain management of TB drugs, diagnostics and other commodities
Specific Objective: 2.2.3. Rational use of medicine

Pillar III: RESEARCH AND INNOVATION
Specific Objective: 3.1 Data for programmatic monitoring and planning
Specific Objective: 3.2 Research priorities

2.4. ORGANIZATION OF THE FIGHT AGAINST TUBERCULOSIS

2.4.1. ATTRIBUTIONS OF THE CENTRAL LEVEL

2.4.1.1. TB&ORD DIVISION

- Develop policy and guideline related to tuberculosis control in Rwanda.
- Monitor and evaluate tuberculosis control in line with the national health policy;
- Mobilize resources to fight TB and others respiratory disease in Rwanda
- Manage all human, material and financial resources of the programme;
- Promote national and international inter-sectoral collaboration;
- Strengthen collaboration with other services in the Health sector, including partners, civil society, communities and the private sector.
- Develop Behaviour Change Communication (BCC) in collaboration with Rwanda Health Communication Centre (RHCC).
- Promote research on TB and other respiratory diseases in Rwanda.

2.4.1.2. NATIONAL REFERENCE LABORATORY (NRL)

The Mycobacteriology section of the NRL is responsible for:

- Develop TB diagnostic algorithm
- Coordinate and ensure the quality control of diagnostic techniques
- Train and supervise the laboratory staff in health facilities
- Perform culture and drug susceptibility tests (DST) for 1st and 2nd line TB treatment
- Conduct and participate in research related to tuberculosis and other respiratory diseases.

2.4.1.3. RWANDA MEDICAL SUPPLY (RMS)

The RMS is a state-owned enterprise with the mandate of managing end-to-end health supply chain for Rwanda. RMS goals are to ensure the quality and timely availability of all health products to the public across the country through a cost-efficient, sustainable and effective supply chain.

2.4.2. ATTRIBUTIONS OF THE DECENTRALIZED LEVEL

2.4.2.1. DISTRICT PHARMACY

District pharmacies are distribution centers, merged into RMS, responsible for facilitating access by health facilities to medicines. Their role is to:

- Quantify the drugs, reagents and consumables needed for the management of tuberculosis
- Ensure recording and reporting on TB health logistic data in e-LMIS
- Place regular order through e-LMIS to ensure regular supply of drugs, reagents and consumables
- Keep good storage conditions of TB commodities
- Conduct physical inventory to maintain stock on hand between minimum and maximum level;
- Ensure distribution of TB commodities to health facilities
- Avail TB management tools (Lab forms, registers etc.)
- Build capacity of store managers of health facilities in pharmaceutical management
- Conduct supervision of health facilities to ensure rational use of TB medicines.

2.4.2.2. HOSPITAL LEVEL

- Plan and carry out TB activities within hospital catchment areas in line with national health policy
- Correctly manage drug stocks, equipment, reagents, and recording tools and ensure regular supply from District pharmacy.
- Train health care providers in collaboration with the TB &ORD Division of RBC;

- Supervise every quarter the management of TB at health center
- Perform quarterly quality control of TB diagnosis by health centers
- Coordinate the quarterly evaluation meeting of TB control activities within the catchment area.
- Evaluate the TB indicators related to performance based financing.
-

2.4.2.3. HEALTH CENTERS (CDT AND CT):

- Provide information, education and communication sessions
- Screen for TB
- Collect sputum specimen, perform sputum smearing and HIV testing
- Perform the sputum smear microscopy examination (at CDT only)
- Initiate appropriate treatment for all diagnosed tuberculosis cases
- Provide care and monitor TB patients according to guidelines
- Conduct contact tracing for all bacteriologically confirmed patients
- Ensure integrated care and treatment for all TB/HIV patients according to the TB/HIV policy.
- Train and supervise regularly community health workers (CHW)
- Ensure the availability of drugs, reagents and consumables
- Ensure timely recording and reporting of TB accurate data
- Implement TB infection control measures (CDT and CT).

2.4.3. COMMUNITY HEALTH WORKERS (CHW)

- Collaborate with local administrative authorities and community leaders in order to inform the community about the disease
- Screen and refer presumptive tuberculosis cases to the health center
- Provide supervised treatment to patients sent from the CDT for community DOT
- Record each dose on the community treatment card
- Accompany patients to the CDT for monthly control tests
- Request necessary drugs before stock out of supply
- Find irregular patients and motivate them to continue treatment
- Ensure that contact investigation is carried out for all bacteriologically confirmed patients
- Refer patients to the health center in case of side effects
- Keep confidentiality related to tuberculosis patients.

2D PART. DETECTION AND MANAGEMENT

CHAPTER 3. TUBERCULOSIS DETECTION AND DIAGNOSIS

The global priority for TB care and control is to find more cases and earlier, in order to provide them with effective treatment and to stop the transmission of the disease. This includes smear-negative cases which are often associated with HIV infection and young age. Another priority is to enhance the capacity to diagnose drug-resistant TB by expanding the use of molecular tests and promoting universal access to drug-susceptibility testing (DST) for all patients diagnosed with TB.

3.1. DETECTION OF TB

Any patient with signs or symptoms suggestive of TB is a "presumptive case of tuberculosis" and should be evaluated promptly to ensure early diagnosis of the disease.

3.1.1. SIGNS AND SYMPTOMS OF PRESUMPTIVE TB

- Pulmonary TB should be suspected in any patient with cough for 2 weeks or more. This can be accompanied, but not necessarily, by fever, night sweats, loss of appetite, weight loss (poor weight gain in children), sputum production, chest pain, fatigue, hemoptysis.
- TB should be suspected in any patient infected with HIV who exhibits one or more of the following signs or symptoms regardless of their duration:
  - HIV+ adults: current cough, fever, weight loss, night sweats.
  - HIV+ children: current cough, fever, poor weight gain [3], TB contact of a bacteriologically confirmed TB case.
- TB can be suspected from an abnormal chest x-ray with images consistent with TB.
- Extrapulmonary TB should be suspected in various clinical situations, such as meningeal signs, cervical adenopathies, deformity of the spine, swelling of a joint, etc.

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

3.1.2. STRATEGIES FOR DETECTING TB IN RWANDA

In Rwanda, two screening strategies are used to identify presumptive TB:

- Passive case finding is done among people attending the health facility (HF) with signs or symptoms suggestive of TB
- Enhanced case finding targets people at high risk of developing TB. It can be done systematically in health facilities (for example, screening for TB among PLHIV at each consultation) or by special activities (for example, active case finding campaigns in prisons and hot spot areas of TB). Enhanced case finding is done with a clinical algorithm and may include, for some groups, a chest X-ray (see table 2).

In addition, all health facilities should strengthen complementary strategies including:

- Behaviour change communication in all health facilities and community (schools, prisoners, villages, traditional healers, PLHIV) See chapter 8.
- The implementation of a triage system for patients with cough in health facilities for early detection of TB presumptive cases (see chapter 7). This should be done as a priority at the OPD, the antenatal care department, the IMCI clinic, the ART service, the emergency room and the hospitalization.

3.1.3. GROUPS AT RISK OF DEVELOPING TUBERCULOSIS

Evidence from routine surveillance data and from the national TB prevalence survey conducted in 2012 identified several population groups at higher risk of TB that should be targeted with enhanced case finding.

Table 2. High-risk groups targeted with enhanced TB case finding

Groups	Symptom screening	CXR screening*	When and where to screen them?
People living with HIV	X X	X	• all new PLHIV at diagnosis • all PLHIV at each follow up visit
Contacts of bacteriologically confirmed TB cases and contacts of pediatric cases	X X	X	• at the beginning of treatment of the index case • at the end of treatment of the index case
Prisoners and prison staff	X X X	 X X	• at entry in prison and before leaving the prison • if they are close contact of a contagious TB case • during active case finding campaigns
Children <15 years	X X		• at the IMCI clinic • at the malnutrition management service

People ≥ 55 years Diabetics	X X		• at the OPD • at the non-communicable disease clinic (NCD)
Malnourished individuals	X X		• at the OPD • at the internal medicine wards
Health care workers (HCWs) and community health workers (CHWs)	X X		• at the OPD • routinely, twice per year
Post-partum women	X		• at the post-natal care
Mine workers, refugees in camps, urban slum dwellers	X X	 X	• in consultation • during active case finding campaigns
Persons using alcohol, tobacco, or drugs	X		• at the general and specialized consultation

*CXR is strongly recommended (whenever possible)

3.1.4. GROUPS AT RISK FOR DRUG-RESISTANT TB (DR-TB)

The following groups of patients have higher risk of developing DR-TB:

- All patients in whom treatment failed (first-line treatment failures) and other previously treated patients who require retreatment (lost to follow-up and relapses)
- Close contacts of M/XDR-TB cases with presumptive TB
- Patients who have a positive smear microscopy control during first-line treatment
- New smear-positive patients who are prisoners, health care workers, patients who are diagnosed in Kigali CDT have higher exposure risk to DR-TB.
- HIV is not considered to be a risk factor for drug-resistant TB. However, all TB/HIV patients should have a drug susceptibility test to avoid high rates of mortality due to unrecognized drug-resistant TB in these patients.

3.2. DIAGNOSTIC TESTS FOR TUBERCULOSIS

For persons with signs or symptoms consistent with TB, performing prompt clinical evaluation is essential to ensure early and rapid diagnosis. This should include investigating patient's medical history and TB risk factors, performing a medical examination and additional tests. Diagnostic investigation should be conducted according to the TB diagnostic algorithm (section 3.3)

3.2.1. BACTERIOLOGICAL TESTS

Patients with suspected pulmonary TB will be asked to provide at least one sputum sample for testing for TB bacilli. For extrapulmonary TB disease, samples of affected body fluids or tissues can be tested. Although WHO recommends rapid molecular tests as initial diagnostic tests for people with presumptive TB rather than microscopy and

culture, this recommendation cannot yet be fully implemented in Rwanda and microscopy is still necessary for the diagnosis of TB.

3.2.1.1. XPERT MTB/RIF (REAL-TIME PCR)

The Xpert MTB/RIF test is a cartridge-based fully automated rapid molecular assay that can be performed easily in a peripheral laboratory. It allows rapid and simultaneous detection of TB and rifampicin resistance (within 2 hours). Rifampicin resistance can be used as a proxy for MDR-TB. Sensitivity of Xpert MTB/RIF is close to that of culture and its specificity is high. Rwanda aims to provide universal access to rapid test to detect TB and rifampicin resistance and has therefore gradually expanded **Xpert MTB/RIF indications as follows**:

- The Xpert MTB/RIF test should be used as initial diagnostic test to all presumptive TB cases in the following groups:
  - PLHIV
  - Prisoners
  - Children under 15 years
  - People aged 55 years and above
  - Contacts of a bacteriologically confirmed TB cases or MDR-TB cases
  - Diabetics
  - Health care workers
  - Presumptive TB cases from districts of Kigali City and other districts with high TB prevalence, according to indications of the TB&ORD Division
  - Presumptive TB meningitis cases (CSF samples)
  - Presumptive extrapulmonary TB cases
- The Xpert MTB/RIF assay should be performed to detect rifampicin resistance in the following TB cases:
  - All previously treated cases before starting retreatment (after failure, after loss to follow-up, relapses)
  - All cases diagnosed by a positive sputum smear (SS+ TB)
  - All contacts of a MDR-TB case
- Others medical reasons.

Collection of samples for Xpert MTB/RIF (sputum and extra pulmonary fluids or tissues can be tested, except blood or a sample mixed with blood):

- the minimum quantity of sample is 2 ml.
- a single sample is sufficient and must be kept cool.
- the sample must be sent to the geneXpert laboratory within 24 hours.

Test procedure and results' interpretation: see 4th Part on Laboratory, section 7.

The test should be repeated in case of:

- Rifampicin resistance (MTB+/RIF+) detected in a specimen that has a low or very low bacillary load (it could be a false positive RIF+).
- Indeterminate rifampicin resistance (MTB+/RIF indeterminate): it is usually attributed to a low bacillary load.
- Invalid test or error or no result.

The test will be repeated on a fresh sample at the same laboratory and the result of the repeat test will be used for the clinical decision.

If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid, fluoroquinolones and second-line injectable agents (first- and second-line LPAs) should be promptly performed to inform treatment of the MDR or XDR-TB. Susceptibility to other drugs should also be tested (culture and DST, sequencing test).

3.2.1.2. SPUTUM SMEAR MICROSCOPY.

Sputum smear microscopy is a simple, quick and inexpensive method to diagnose pulmonary tuberculosis. It helps identifying contagious cases to be treated as a priority in order to reduce the sources of infection. However, it has relatively low sensitivity as it requires a minimum of 5,000 bacilli per ml of sputum to be positive. It is often negative in patients with extrapulmonary tuberculosis, children and PLHIV. Sputum microscopy cannot distinguish between *M. tuberculosis* and non-tuberculous mycobacteria (NTM), nor between viable and non-viable bacilli. It also does not distinguish drug-sensitive strains from drug-resistant strains. Every sputum exam, whether for diagnosis or treatment follow-up, is free of charge in public, faith based and private health facilities.

Collection of sputum specimens: any suspected case of pulmonary tuberculosis should give 2 sputum samples within 2 days. The first sample is collected immediately, on the spot and under supervision, and the second, the next morning. In practice it is necessary:

- Explain to the patient how to produce adequate sputum instead of saliva (see 4th part on laboratory, section 3).
- Give him a sputum container to collect the second sample at home.
- Completely fill the TB lab exam form, especially the patient's name, full address, and phone number so that you can find them if positive and do not show up for the results.
- In CT, the laboratory technician will collect the 2 samples, prepare the smears and send them to the nearest CDT, along with the TB lab form. However, if a relapse is suspected or if the XPert MTB/RIF test is indicated as the initial test, the sputum sample should be sent and not the smears.

Staining method: M. *tuberculosis* is an acid-fast bacillus (AFB), that is, once colored, it is not discolored by acids or alcohol. This characteristic is used to demonstrate the bacillus, either by Ziehl-Neelsen staining or by auramine staining. This last technique requires a LED fluorescence microscope and is used in all CDTs in Rwanda because it is faster and more sensitive than the Ziehl technique.

Result: the test is positive when there is at least one AFB in one of the two smears. This is a case of sputum smear positive pulmonary tuberculosis. Results should be communicated and returned immediately to the health care provider who examined the patient (within 48 hours for CDT and 72 hours for CT from the time of sampling).

3.2.1.3. CULTURE

Culture is the gold standard for diagnosing TB. It is more sensitive than microscopy and can give a positive result from 10 to 100 bacilli per ml of sample. Due to the slow growth of *M. tuberculosis*, it takes several days to get the result. It is a complex technique that can only be performed in reference laboratories. Culture can be done in solid medium (Löwenstein Jensen) or in liquid medium (Bactec). Liquid culture is faster and has higher sensitivity, but it cannot be used for samples transported in CPC preservative media.

False-negative or false-positive can be the result of several factors including specimen quality, laboratory handling, cross-contamination, laboratory administrative errors, etc. Therefore, culture results should be always correlated with the patient's clinical conditions and the test should be repeated if necessary.

Most of the mycobacterial isolates are *M. tuberculosis*. However, non-tuberculous mycobacteria (NTM) can also be found, particularly in PLHIV. It is therefore essential to perform an identification test of mycobacteria.

Culture is recommended for the following groups:

- All previously treated TB cases (relapse, failure and lost to follow up)
- Any positive sputum smear during antituberculosis treatment
- Rifampicin resistant cases at Xpert test
- Rifampicin indeterminate cases at Xpert test
- All cases with positive sputum microscopy but MTB not detected at Xpert test
- All contacts of MDR-TB cases with presumptive TB
- All extrapulmonary specimens except blood
- Other cases as needed by the clinician.

3.2.1.4. DRUG-SUSCEPTIBILITY TESTING (DST)

DST determines whether a strain is susceptible or resistant to particular anti-TB agents, indicating the likely success or failure of treatment with those drugs.

- Phenotypic methods (also called conventional methods) involve culturing MTB in the presence of anti-tuberculosis drugs to detect growth (which indicates resistance) or inhibition of growth (which indicates susceptibility). Their reliability is high for rifampicin and isoniazid, less for pyrazinamide and ethambutol.
- Genotypic methods are used for the diagnosis of TB through amplification of bacillus DNA or RNA (PCR) and for the diagnosis of drug resistance by identifying molecular mutations associated with resistance against individual anti-tuberculosis drugs.

3.2.1.5. LINE PROBE ASSAYS (LPAS).

LPAs are molecular strip-based tests that rapidly detect mutations associated with drug resistance. They are carried out by reference laboratories (NRL and CHUs) since they require adequate infrastructure, equipment, biosafety precautions and well trained staff. They are also called Hain tests.

- First-line LPA (FL-LPA) detects MTB and resistance to rifampicin and isoniazid (MDR-TB) in sputum smear-positive specimens (direct testing) and in cultured isolates of MTBC (indirect testing). It provides results in 2 days. For smear-negative specimens, a culture is required, which increases the time to result.
- Second-line LPA (SL-LPA) detects resistance to fluoroquinolones and 2nd-line injectables (XDR-TB) in MDR or RR-TB patients.

FL-LPA is recommended as the initial test to detect resistance to rifampicin and isoniazid. However, culture and phenotypic DST remain necessary to monitor response to treatment and to detect additional resistance to other drugs.

3.2.1.6. LATERAL FLOW URINE LIPOARABINOMANNAN ASSAY (LF-LAM)

This test is based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine. The currently available urinary LAM assay has suboptimal sensitivity and is therefore not suitable as general diagnostic test for TB. However, it has improved sensitivity for the diagnosis of TB among PLHIV with advanced disease (low CD4 cell count, stage 3 or 4). The LF-LAM test is a strip-test that can be used in peripheral laboratories.

3.2.1.7. SEQUENCING TESTS

Targeted deep sequencing is a powerful tool to detect accurately most clinically relevant mutations on clinical specimens, thus providing a rapid full drug susceptibility profile. This information is crucial for clinicians to make prompt decisions regarding the best therapy to adopt for treatment of M/XDR-TB. A targeted deep sequencing is being implemented at the NRL as a “high-performing DR-TB diagnostic."

3.2.2. IMAGING TECHNIQUES

3.2.2.1. CHEST X-RAY

Chest x-ray (CXR) has high sensitivity to detect pulmonary tuberculosis. In Rwanda, it is used as a screening tool among HIV-positive individuals, TB contacts and prisoners, where it is possible. CXR is also used as a diagnostic tool when pulmonary tuberculosis cannot be confirmed bacteriologically, particularly in PLHIV and children.

Radiological images suggestive of TB are not specific and it may be difficult to distinguish active lesions from sequelae of tuberculosis. All patients with x-ray images suggesting TB (cavitation, infiltrate, lymphadenopathy, pleurisy, miliary) should be evaluated with a bacteriological diagnostic test. Before concluding with clinically diagnosed tuberculosis, all the elements (history, clinical signs, bacteriological results and x-ray) must be carefully analyzed and discussed by the medical staff.

Table 3. Summary of characteristics of diagnostic tests

Test	Characteristics	Disadvantages	Indications
Xpert MTB/RIF	- Rapid and automated assay detecting MTB and resistance to rifampicin in < 2 hours - Accurate, reliable, highly sensitive - Available in peripheral laboratories (hospitals and some HF)	- Expensive - May give false RIF resistant result on a specimen with low /very low bacillary load. - Does not distinguish viable/non-viable bacilli and is not useful for follow-up of treatment	- High-risk presumptive TB cases - Presumptive TB in Kigali/high TB burden districts - LCR and other extrapulmonary samples - Previously treated cases - New smear-positive TB cases
Microscopy (fluorescence LED)	- Easy, quick, inexpensive - Detect the most infectious cases of TB - Available in most health facilities	- Low sensitivity: misses TB cases excreting low numbers of bacilli (HIV+, children) - Cannot distinguish viable/non-viable bacilli, drug-sensitive/resistant strains, MTB/NTM	- Low risk presumptive TB cases who are not from Kigali or high TB burden districts - Bacteriological follow-up of first-line and 2nd line treatments
Culture on solid or liquid media	- Diagnostic 'Gold standard' detecting viable MTB - Liquid culture is faster and more sensitive than solid culture - Can differentiate MTB / NTM by an identification test	- Complex technique available only at referral lab. - Results in 6-8 weeks for solid culture and 2-3 weeks for liquid culture - Liquid culture cannot be performed on samples transported in CPC - May give false+ or false- results	- All previously treated TB cases - Any smear+ during treatment - Any MTB+/R+ at Xpert test - Rif indeterminate at Xpert test - Smear+ TB case with MTB not detected at Xpert - TB presumptive contacts of MDR-TB - Extrapulmonary samples except blood - Bacteriological follow-up of 2d-line treatment
Line-probe assays (LPA) first-line (FL) and second-line (SL)	- Rapid tests giving the results in 2 days for sputum smear-positive sample - FL-LPA detect resistance to R and H - SL-LPA detect resistance to FQ and SL injectable agents.	- Requires specialized equipment - Available only at referral laboratories - Can be performed only on smear+ or culture+ specimen; smear-negative specimen need to be cultivated before doing the test	FL-LPA: - Rifampicin resistance (RR) detected at Xpert - Previously treated TB cases - Contacts of drug-resistant TB SL-LPA: RR. and MDR-TB cases
DST (phenotypic or genotypic)	- Detect resistance to particular anti-TB drugs - PCR detects mutations associated with resistance	- Complex technique available at referral lab. - Results in 6 weeks for DST on solid media and 2 weeks on liquid media	- All smear+ during treatment - All culture + - DR-TB detected by XPert or LPA
LF-LAM	- Rapid test detecting lipoarabinomannan (LAM) antigen in the urine	- Adequate sensitivity only in PLHIV - A positive test should be confirmed by bacteriological tests (if possible) .	- To assist in the diagnosis of TB in PLHIV with advanced disease (CD4 cell count <200 cells/mm3, stage 3 and 4) with signs and symptoms of TB.
Sequencing test	- High-performing DR-TB diagnostic providing a rapid full drug susceptibility profile by detecting most mutations associated to DR-TB	- Complex technique available only at NRL	- To make prompt decisions regarding the best therapy to adopt for treatment of M/XDR-TB
X-ray	- High sensitive technique detecting early images suggestive of TB in asymptomatic or bacteriologically negative patients	- Low specificity, difficult to distinguish active lesions from TB sequelae - Does not confirm the diagnosis	- Screening of TB in high-risk groups - Diagnostic of TB, especially in children, PLHIV, presumptive TB cases with negative bacteriological tests
Tuberculin skin test (TST)	- Diagnosis of Latent TB infection (LTBI)	- Cannot differentiate between LTBI/active TB - Requires a trained nurse and 2 visits - May give false+ or false- results	- To support the diagnosis of TB in children - To test for LTBI before TB preventive treatment, if indicated by the TB&ORD Division

3.2.2.2. ULTRASOUND

- Ultrasound is helpful in confirming pleural effusion.
- Ultrasound is very useful for the diagnosis of pericarditis because it can confirm a pericardial effusion that is suspected on the x-ray.
- Abdominal ultrasound can detect abdominal lymphadenopathies, however these can be caused by other diseases, particularly HIV infection. Ultrasound can also detect thickening of the intestinal wall suggestive of TB.

3.2.3. TESTING FOR LATENT TUBERCULOSIS INFECTION (LTBI)

LTBI can be confirmed by a tuberculin skin test or by an interferon gamma release test (IGRA). These tests cannot predict which persons will develop active tuberculosis disease.

3.2.3.1. TUBERCULIN SKIN TEST (TST)

- The tuberculin skin test, also known as intradermal reaction (IDR) or Mantoux test, is mainly used as a tool to screen children for LTBI. Tuberculin is a purified protein derivative (PPD) of *M. tuberculosis*.
- Intradermal injection of 2 units of PPD RT23 tuberculin (or 5 units of PPD-S) causes a delayed hypersensitivity reaction if the person is infected with *M. tuberculosis*. This is manifested by an indurated papule whose diameter should be measured 48 to 72 hours after the injection (only the diameter of the induration of the skin is measured and not the redness at the injection site).
- The test is positive if the induration is:

  ≥10 mm in diameter for HIV negative children and

  ≥ 5 mm for HIV positive or severely malnourished children.
- A positive test identifies people infected with *M. tuberculosis* but cannot predict the course of the disease. False positive may occur in case of infection with a non-tuberculous mycobacterium (NTM) or following BCG (induration generally does not exceed 15 mm).
- A negative test does not rule out tuberculosis infection or tuberculosis disease. Indeed, false negative may occur in case of:
  - recent tuberculosis infection (4-8 weeks are necessary for the test to become positive).

- immunosuppression (severe tuberculosis, severe malnutrition, infection with HIV/AIDS, measles, chickenpox or severe infection)
- administration or reading error.

- Tuberculin is not readily available, it is expensive, has a short duration of use and should be kept away from heat and light. Its administration and interpretation require good technique.

3.2.3.2. INTERFERON-GAMMA RELEASE ASSAY (IGRA).

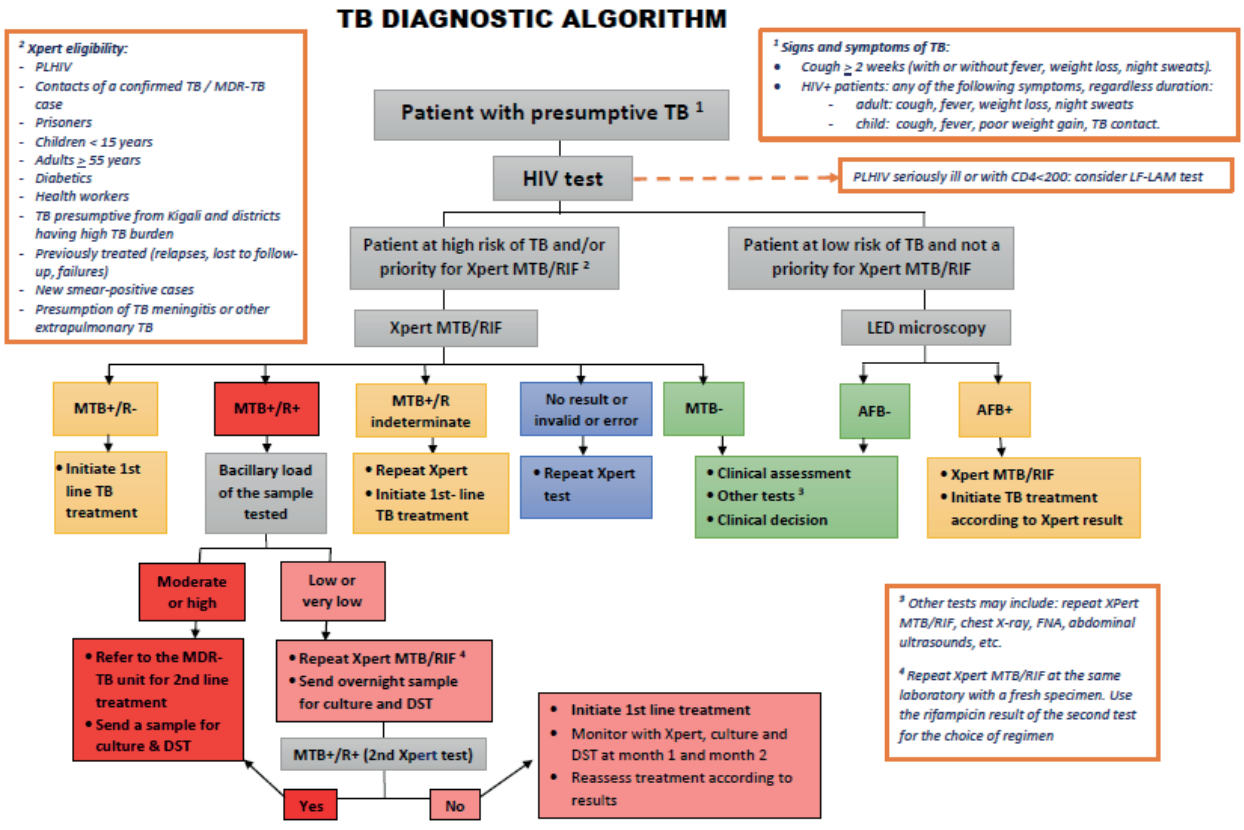
- These are whole blood tests that can help diagnose TB infection. They are based on stimulation of lymphocytes and macrophages by a group of *M. tuberculosis* antigens followed by measurement of the gamma interferon produced.
- Like TST, IGRAs cannot differentiate between TB infection and TB disease.
- IGRAs are more specific than TST due to the lack of cross-reaction to BCG and NTM, but may also give false positive results.
- It needs sophisticated laboratory equipment, highly skilled laboratory personnel to perform and interpret test results and is more expensive than TST.

3.3. RWANDA TB DIAGNOSTIC ALGORITHM

For persons with signs or symptoms consistent with TB, performing prompt diagnostic investigation is essential to ensure early and rapid diagnosis. This includes:

- Investigating patient's medical history and TB risk factors (especially history of previous TB treatment and co-morbidities)
- Assess whether the patient is eligible for Xpert MTB/RIF as initial test.
- Follow the tuberculosis diagnostic algorithm to interpret test results and select the appropriate treatment.

Figure 1. TB diagnostic algorithm



3.4. CASE DEFINITIONS

Any case diagnosed with TB must be properly classified in order to prescribe the correct treatment and to ensure adequate follow up.

Table 4 . Case definitions for registration

Classification based on diagnostic method	
Bacteriologically confirmed TB case (TB+)	A bacteriologically confirmed TB case is one from whom a biological specimen is positive • by smear microscopy, • culture or • WHO approved rapid test (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.
Clinically diagnosed TB case	A clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes • cases diagnosed on the basis of X-ray abnormalities or suggestive histology and • extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.
Classification based on anatomical site of disease	
Pulmonary tuberculosis (PTB)	Pulmonary tuberculosis refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. • Miliary TB is classified as PTB because there are lesions in the lungs. • A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.
Extra Pulmonary tuberculosis (EPTB)	Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. • Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, are cases of EPTB.
Classification based on history of previous TB treatment	
New patient	New patients have never been treated for TB or have taken anti-TB drugs for less than 1 month.
Relapse patients	Relapse patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

Treatment after failure patients	Treatment after failure patients are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.
Treatment after loss to follow-up patients	Treatments after loss to follow-up patients have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment.
Other previously treated patients	Other previously treated patients are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.
Patients with unknown previous TB treatment history	Patients with unknown previous TB treatment history do not fit into any of the categories listed above.
Classification based on drug resistance	
Drug-susceptible TB case	TB case in which a DST indicates that the strain is not resistant to any first-line anti-TB drugs.
Drug-resistant TB case	TB case in which a DST indicates that the strain is resistant to one or more first-line anti-TB drugs.
Monoresistance	Resistance to one first-line anti-TB drug only
Polydrug resistance	Resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
Multidrug resistance	Resistance to at least both isoniazid and rifampicin
Extensive drug resistance	Resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance
Rifampicin resistance	Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.
Classification based on HIV status	
HIV-positive TB patient	TB case who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started.

HIV-negative TB patient	TB case who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.
HIV status unknown TB patient	TB case who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

Note:

- These definitions are used in the monitoring and evaluation tools.
- New and relapses cases are incident TB cases.

3.5. EXTRAPULMONARY TUBERCULOSIS.

Extrapulmonary tuberculosis (EPTB) may occur at any age and affect any organ or tissue outside the lungs. Young children and patients with HIV infection are more likely to develop an EPTB. About 20% of all TB cases present an extrapulmonary form. EPTB present with various clinical features, depending on the organs affected. However, their common characteristics are an insidious evolution, deterioration of the general condition and the absence of response to symptomatic or non-specific anti-infectious treatments. EPTB may be accompanied by lung localization.

EPTB should be suspected in any patient presenting with one or more of the following signs:

- Cough for two or more weeks.
- Weight loss and night sweats.
- Temperature >37.5 °C
- Dyspnea (pleural effusion/ pericarditis).
- Cervical or axillary adenopathies
- Chest X-ray findings:
  - Miliary.
  - Pleural effusion.
  - Enlarged lymph nodes inside the chest.
  - Enlarged heart, especially if symmetrical and rounded (pericarditis)
- Chronic headache and mental deterioration (tuberculous meningitis)
- Disseminated tuberculosis should be suspected in PLHIV who experience rapid or marked weight loss, fever and night sweats. These patients are at high risk for deterioration and rapid death. An EPTB in an HIV-positive individual indicates WHO stage 4 (advanced AIDS).

Correct diagnosis of EPTB is difficult, especially in peripheral health facilities where diagnostic resources are limited. Often these patients are treated on the basis of presumptive clinical and radiological criteria.

- The Xpert MTB/RIF test increases the possibilities of bacteriological confirmation of EPTB. It must be used as an initial diagnostic test for cerebrospinal fluid (CSF) specimens when tuberculous meningitis is suspected. It should also be used as the initial diagnostic test rather than smear microscopy, culture and histopathology in other extrapulmonary samples (lymph node aspiration fluid or biopsy material, pleural fluid, pericardial fluid, peritoneal fluid, synovial fluid or urine specimen). The sensitivity and specificity of the Xpert MTB/RIF assay varies depending on the type of specimen. If there is a strong clinical suspicion of EPTB (especially in children), TB treatment should be initiated even if the result of an Xpert MTB/RIF test is negative or if the test is not available.
- Pleural, peritoneal, and pericardial fluids may be analyzed for protein and glucose (compared with simultaneous serum total protein and glucose). Cell and differential counts should be obtained. A high protein (> 50% of the serum protein concentration), a low glucose, and lymphocytosis are usually found in tuberculous infections, but neither their presence nor their absence is diagnostic.
- Adenosine deaminase (ADA), a purine-degrading enzyme that is necessary for the maturation and differentiation of lymphoid cells, can be measured on pleural fluid, peritoneal fluid, pericardial fluid and cerebrospinal fluid. According to a number of studies, ADA level is elevated when TB involves these sites. This test does not provide a definitive diagnosis of EPTB but rather supporting evidence that must be interpreted in the wider clinical setting.
- Sputum examination is necessary in people with EPTB so as not to miss a bacillary case which requires regular bacteriological monitoring, active contact tracing and adequate infection prevention and control measures.

3.5.1. PLEURAL TUBERCULOSIS

Pleural TB is the most likely cause of unilateral pleural effusion in countries with a high tuberculosis burden. Pleural TB is commonly related to HIV infection and also related to high mortality during the first two months of TB treatment.

The main signs of pleural tuberculosis are:

- Dry cough and fever
- Unilateral chest pain increasing with cough
- Dull percussion and absence or reduction of vesicular murmur
- Unilateral pleural opacity on radiography.

Diagnosis and management of pleural TB include the following key steps:

- Confirm pleural effusion by chest radiography and ultrasound and ensure immediate aspiration of fluid whenever possible, placing a sample of aspirated liquid into one plain to observe its aspect and clotting. Place another sample into one plain with anticlotting to count white blood cells and protein rate.
- A clear fluid, straw-coloured, with visible clots within a few minutes, confirms the high protein content of the fluid (exudate), which indicates tuberculosis.
- Calculate Light's criteria:
  - Fluid protein/ serum protein > 0.5
  - Fluid LDH/ serum LDH >0.6
  - Fluid LDH> to one third of the upper limit of serum LDH

  One or more of the above light's criteria define pleural effusion as exudate.

- Leucocytes: lymphocytes >50% are more likely to be related to TB although polymorphonuclear cells may predominate in the early stages.
- Regardless of the method used, pleural fluid is not a good sample for bacteriological confirmation of pleural tuberculosis. The microscopy is most often negative. The Xpert MTB/RIF test performed on a sample of pleural fluid has low sensitivity (50%, specificity 99%).
- Pleural biopsy with anatomo-pathological study and bacteriological tests has a high diagnostic yield. However, it is not recommended in routine care because it is unnecessarily invasive and has the potential to cause a diagnostic delay.
- Any patient with pleural effusion type exudate should be started on anti-TB treatment immediately (with absence of other signs suggesting other disease).
- Patients with unusual findings, such as bilateral effusions, cloudy or bloody aspirates should undergo the additional investigations.

3.5.2. LYMPH NODE TUBERCULOSIS.

In countries where TB is endemic, this is the most frequent cause of adenopathies. Tuberculous lymphadenitis should be suspected in any patient with enlarged lymph nodes that are firm, asymmetric, more than 2 cm in diameter, painless, cold, progressing chronically to fistula. It is usually accompanied with weight loss. The cervical lymph nodes are most often affected and it can be difficult to clinically distinguish them from other causes of lymphadenopathy such as HIV-associated lymphadenopathy, lymphoma and other infectious adenitis which are also common.

Diagnosis is done through bacteriological examination of secretions, aspiration fluid or biopsy. Fine needle aspiration (FNA) with bacteriological and cytological examination of the aspirated material can confirm more than 85% of tuberculous adenitis and should be performed at the first consultation in these patients. The Xpert MTB/RIF test should be

used as the initial diagnostic test rather than microscopy and culture. Cytology can identify the other most important causes of enlarged lymph nodes, including malignancies and other infections. Tuberculosis treatment should be started immediately if lymph node TB is considered to be the most likely clinical diagnosis.

3.5.3. OSTEOARTICULAR TUBERCULOSIS

Pott disease affects the vertebrae and intervertebral discs, causing destruction and angular deformation of the spine. The dorsal localization is the most frequent, followed by the lumbar and lumbosacral localization. Localized pain can precede the onset of radiological signs by several months. Pott disease may be accompanied by a cold paravertebral abscess and neurological complications (radicular pain, medullary compression, etc.).

Tuberculous arthritis is most often a monoarthritis that begins insidiously, with little or no pain, but causes joint destruction. It mainly affects the hip, knee, elbow or wrist.

Tuberculous osteitis is less common. It affects the long bones (chronic osteomyelitis) and is sometimes accompanied by cold abscess. Like arthritis, it is distinguished from bacterial infections by discreet clinical signs and severe bone destruction seen on x-rays.

These forms of TB are common in children. The diagnosis is based on clinical and radiological signs.

3.5.4. TUBERCULOUS MENINGITIS

It is one of the most serious forms mainly affecting young children. Its incidence has decreased due to BCG immunization. The beginning is slow with fever for more than 2 weeks, vomiting, headache, lethargy, behavior changes, irritability, photophobia, neck stiffness (hypotonia in infants), convulsions and coma. Tuberculous meningitis is an emergency and any delay in diagnosis or treatment can cause irreversible neurological damage. Left untreated, it is usually fatal.

Diagnosis is done by lumbar puncture. Given the urgency of rapid diagnosis, Xpert MTB/RIF must be used as the initial diagnostic test for all CSF specimens from patients being evaluated for TB meningitis. The CSF pressure is increased, the fluid is clear and colorless, but some dandruff or cobweb appears when left to settle down. The proteins level is high (0.6-2 g/L), glucose is low (< 50% of glycaemia simultaneously measured), leucocytes in moderate numbers (<500 per mm^3) with predominance of lymphocytes.

3.5.5. PERICARDIAL TUBERCULOSIS

Tuberculosis is the cause of about 90% of pericardial effusions in HIV positive individuals compared with 50 to 70% in HIV negative individuals. Tuberculous pericarditis causes chest pain, dyspnea, signs of cardiac decompensation (tachycardia, low blood pressure, peripheral edema, ascites), and pericardial friction on auscultation. Diagnosis involves radiography (enlarged heart), ECG and echocardiography.

3.5.6. PERITONEAL TUBERCULOSIS

Signs

- Fever and abdominal pain
- Ascites and malnutrition (especially in children)
- Palpable abdominal masses (mesenteric adenopathies)
- Sometimes obstructive syndrome by gland masses adhering to intestines
- Sometimes fistula between the intestine, bladder and intestinal wall.

Diagnosis

- Ultrasound: presence of ascites, enlarged mesenteric or retroperitoneal glands
- Puncture of ascites fluid: exudate, positive culture in 50% of cases (late)
- It is a presumptive diagnosis, peritoneal biopsy being inaccessible.

3.5.7. UROGENITAL TUBERCULOSIS

Renal tuberculosis can remain asymptomatic for a long time before the onset of genitourinary symptoms: dysuria (pain when urinating), urinary frequency, nocturia, hematuria, lumbar, abdominal or pelvic pain. Urinary sediment shows sterile pyuria unresponsive to broad-spectrum antibiotic therapy and often micro- or macroscopic hematuria.

Genital tuberculosis in women can cause inconstant and nonspecific signs such as abdominal pain, metrorrhagia, leucorrhoea. It can cause infertility. In men, it manifests as epididymitis with scrotal pain.

3.5.8. CUTANEOUS TUBERCULOSIS

Tuberculosis can cause one or more chronic, painless, non-pathognomonic skin lesions, papule-like or large tuberculoma. The diagnosis is based on bacteriological examinations from a biopsy.

3.6. TUBERCULOSIS IN HIV-POSITIVE PEOPLE

Tuberculosis can be the first sign of HIV infection. In the early stages of HIV infection, it presents as in HIV negative patients. In the advanced stages of HIV infection, immunity

deteriorates, clinical signs and radiography are atypical, and sputum smear-negative, disseminated and extrapulmonary forms are more common. In pulmonary tuberculosis, fever and weight loss are the predominant signs, while cough and hemoptysis are less common than in HIV-negative patients. Microscopy is often negative, hence the need to use more sensitive diagnostic tools such as the Xpert MTB/RIF test.

Table 5. Characteristics of TB according to the status of HIV infection.

Characteristics	Early HIV infection	Late HIV infection
Clinical forms	- Pulmonary TB	- Disseminated TB, EPTB, sputum smear-negative PTB - Predominating general signs (fever, weight loss)
Sputum bacteriological tests	- Often positive	- Positive or negative
Chest radiography	- Cavitary PTB is frequent	- Opacities, infiltrations without cavitation

3.7. MILIARY TUBERCULOSIS OR DISSEMINATED TB.

This is a massive hematogenous dissemination of bacilli. Many tiny tubercles similar to millet grains (≤ to 3mm) are found in all organs. This form especially affects children and immuno-depressed persons.

Symptoms are not specific. The onset is sometimes abrupt but most often insidious with a gradual deterioration of the general condition: weight loss, fever, headache, adenopathies, possible splenomegaly, cough and dyspnea signaling pulmonary involvement, gastro-intestinal complaints. Malnourished children and HIV-positive patients may not present any signs of tuberculosis. Miliary tuberculosis is frequent but often undiagnosed in HIV-positive patients presenting a wasting syndrome.

The diagnosis is confirmed by a miliary image on the chest x-ray and the presence of millet grains or choroid tubercles in the fundus. The sputum examination is negative. The tuberculin skin test may be false negative. In children, a lumbar puncture should be performed because of the high risk of meningeal involvement. Miliary TB is a medical emergency.

3.8. DUAL BURDEN OF TUBERCULOSIS AND COVID 19

TB and COVID-19 are both infectious diseases that attack primarily the lungs. They have similar symptoms such as cough, fever and difficulty breathing. TB, however, has a longer incubation period with a slower onset of disease. The Covid-19 epidemic significantly disrupts TB case detection and could lead to a rise in tuberculosis-related deaths. TB patients should take precautions advised by the health authorities to be protected from COVID-19 and they should continue their TB treatment as prescribed.

CHAPTER 4. TB TREATMENT AND PATIENT MANAGEMENT

As soon as diagnosis of tuberculosis is made, treatment must be initiated without delay and correct follow-up must be carried out in order to ensure the patient is completely cured. Inappropriate treatment can create drug resistance and increase the number of contagious cases in the community.

4.1. Basic principles for treatment

- Treatment of tuberculosis has the following objectives:
  - To cure tuberculosis patients, restore their quality of life and productivity
  - Prevent death and long-term sequelae of TB
  - Prevent relapses of TB
  - Reduce the transmission of TB
  - Prevent the development and transmission of resistance to anti-TB drugs.
- Treatment of tuberculosis is based on a correct polychemotherapy:
  - Including an appropriate and standardized association of at least four (4) drugs against tuberculosis, in order to avoid resistance
  - Prescribed in adequate dosage for a sufficient duration
  - Administered with supportive measures to patients, including information about the disease and its treatment, direct observation of treatment (DOT) and encouragement to complete treatment and achieve cure.

4.2. TREATMENT REGIMENS

4.2.1. First-line treatment

- The most important drugs for the treatment of drug-susceptible TB are isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E).
- Fixed-dose combinations (FDC) contain 2, 3 or 4 anti-tuberculosis drugs in the same tablet, which has the advantage of reducing the number of pills to be taken each day by the patient, reducing the risk of resistance and facilitating drug management (table 6).
- Pediatric formulations are child-friendly medicines suitable for children weighing less than 25 kg. The tablets do not need to be cut or crushed to obtain a suitable dose as they are dispersible in water in seconds and moreover, they have a pleasant taste. Each tablet should be put in a small amount of water (50 ml) to ensure that the child drinks

all the quantity and takes the exact doses s/he needs. Children weighing 25 kg and above are treated with adult dosage and formulations.

Table 6. Fixed-dose combinations for the treatment of drug-susceptible TB

Adults and children ≥ 25 kg		
(RHZE)	(R 150 mg + H 75 mg + Z 400 mg + E 275 mg)	Intensive phase
(RH)	(R 150 mg + H 75 mg)	Continuation phase
Pediatric formulations (children < 25 kg):		
(RHZ)	(R 75mg + H 50 mg+ Z 150mg)	Intensive phase
E	Ethambutol 100mg	Intensive phase
(RH)	(R 75 mg + H 50 mg)	Continuation phase

- Rwanda uses the standard first-line regimen recommended by WHO for drug-susceptible TB. It is a 6-month regimen including the intensive phase of 2 months with isoniazid, rifampicin, pyrazinamide and ethambutol followed by the continuation phase of 4 months with isoniazid and rifampicin. The medicines are taken once a day.
- This regimen is written 2(HRZE) /4(HR), according to the international codification. The number preceding the letters indicates the duration of the phase in months and the backslash (/) separates the intensive phase from the continuation phase. A number after the parenthesis indicates the number of doses per week. No number or the number "7" indicates daily treatment.
- For patients who require TB retreatment (relapses, treatment after failure, treatment after interruption), the category II regimen (8 months) should no longer be prescribed. An XPert MTB/RIF test should be performed to guide the choice of treatment regimen (see section 4.3).
- First-line regimen is indicated for:
  - all bacteriologically confirmed cases, new and retreatments, which are susceptible to rifampicin (Xpert result: MTB+/ RIF-).
  - clinically diagnosed cases, pulmonary and extrapulmonary.
- The standard first-line treatment is extended up to 12 months in case of tuberculous meningitis and osteoarticular TB. The intensive phase is unchanged (2 months) and the continuation phase is extended to 10 months (2RHZE/10RH).

- The daily dosage is based on weight bands to facilitate medication management and administration to patients.
- Treatment should be started as soon as possible after bacteriological confirmation of the disease. That is why any nurse previously trained in TB is authorized to prescribe and administer treatment for bacteriologically confirmed TB patients.

I. TREATMENT OF ADULTS and children ≥ 25 kg: 2 (RHZE) / 4 (RH)

Indicated for all new and previously treated cases who are susceptible to rifampicin and for clinically diagnosed, pulmonary and extrapulmonary TB.

Phase	Months / No doses	Drug	25-39 kg	40-54 kg	≥ 55 kg
Intensive	2 months (56 doses)	($R_{150}H_{75}Z_{400}E_{275}$)	2 Tab	3 Tab	4 Tab
Continuation	4 months (112 doses)	($R_{150}H_{75}$)	2 Tab	3 Tab	4 Tab

II. TREATMENT OF CHILDREN: 2 ($R_{75}H_{50}Z_{150}$) E100 / 4 (RH)

Indicated for all children weighing < 25 kg (new cases and previously treated).

Phase	Months / No doses	Drug	4-7 kg	8-11 kg	12-15 kg	16-24 kg	≥ 25kg
Intensive	2 months (56 doses)	($R_{75}H_{50}Z_{150}$)	1 Tab	2 Tab	3 Tab	4 Tab	Use the adult dosage and tablets
		E_{100}	1 Tab	2 Tab	3 Tab	4 Tab	
Continuation	4 months (112 doses)	($R_{75}H_{50}$)	1 Tab	2 Tab	3 Tab	4 Tab	

Infant with weight below 4 kg: calculate the dose according to the table below.

DOSAGE		
Drug	**Children <25 kg**	**Adults and children ≥ 25 kg**
Rifampicin (R)	15 mg/kg (10 to 20 mg/kg), max 600 mg/day	10 mg/kg (8 to 12 mg/kg), max 600 mg/day
INH (H)	10 mg/kg (7 to 15 mg/kg), max 300 mg/day	5 mg/kg (4 to 6 mg/kg), max 300 mg/day
Pyrazinamide (Z)	35 mg/kg (30 to 40 mg/kg)	25 mg/kg (20 to 30 mg/kg)
Ethambutol (E)	20 mg/kg (15 to 25 mg/kg)	15 mg/kg (15 to 20 mg/kg)

III. TB MENINGITIS AND OSTEOARTICULAR TB (new and retreatment): total duration **12 months**:

- Adults and children ≥ 25 kg: 2 (RHZE) / 10 (RH)
- Children < 25 kg: 2 (RHZ)E / 10 (RH)

Figure 2. First-line TB treatment dosage and indications

4.2.2. Second-line treatment regimen

- MDR/RR-TB patients require a second-line treatment regimen. In line with WHO recommendations, Rwanda is introducing fully oral treatment regimens which are effective, less toxic and easier to take by patients then regimens containing injectables.

Table 7. Second-line drugs used for DR-TB treatment in Rwanda

Group name	Anti-TB agent	Abbreviation
Fluoroquinolones	levofloxacin moxifloxacin	Lfx Mfx
New drugs	bedaquilin delamanid	Bdq Dlm
Oral bacteriostatic second-line anti-TB drugs	ethionamide prothionamide cycloserine p-aminosalicylic acid	Eto Pto Cs PAS
Other drugs	clofazimine linezolid	Cfz Lzd
Second-line injectable agents (aminoglycosides)	kanamycin amikacin capreomycin	Km Amk Cm

- Standard second-line regimens include a short regimen and a long regimen.

Table 8. Treatment regimens for DR-TB

INDICATION	REGIMEN	DURATION
Short treatment for: - newly diagnosed RR- and MDR-TB	6 Bdq-4 Lfx-Pto-Cfz-Z-E-$H_{high-dose}$/ 5 Mfx-Cfz-Z-E	9-11 months depending on the month of culture conversion
Long treatment regimen for: - previously treated MDR-TB - pre-XDR with resistance to aminoglycosides - XDR-TB	6 Bdq-Lzd-Lfx-Cfz or Cs/ 12 Lfx-Lzd-Cfz or Cs	18 months
Long treatment regimen for: - MDR-TB with resistance to FQ - XDR-TB	6 Bdq-Dlm-Lzd-Cfz-Cs / 12 Lzd-Cfz-Cs-Bdq or Dlm (depending on tolerance]	18 months

- For details and dosage, see the RBC manual on “programmatic management of drug-resistant tuberculosis”.

- Pyridoxine (Vitamin B6) is used in the short treatment regimen and in the long regimen if cycloserine is used. Dosage: 25 to 50 mg/day.

4.2.3. Mono and polyresistance

- Patients with isoniazid resistance and confirmed sensitivity to rifampicin should receive a treatment regimen with rifampicin, ethambutol, pyrazinamide and levofloxacin, with or without isoniazid, for a duration of 6 months: 6REZ-Lfx or 6(H)REZ-Lfx.
- Patients with poly-resistant tuberculosis, should receive an individualized regimen depending of the susceptibility profile.

4.3. Choice of TB treatment regimen

Reminder: all cases diagnosed with a positive sputum smear must have an Xpert MTB/RIF test. The choice of the appropriate regimen is based on the Xpert result, as follows:

- Patients susceptible to rifampicin (MTB+/RIF-), new and retreatment: treat with 2 RHZE/4RH.
- Patients with resistance to rifampicin (MTB+/RIF+):
  - If the bacillary load of the specimen tested is medium or high, refer the patient to a specialized MDR-TB center for 2d-line treatment. Send a specimen to the reference laboratory for LPA 1st and 2d line, culture and DST.
  - If the bacillary load is low or very low, repeat the Xpert test at the same laboratory with a fresh specimen and collect another specimen for culture and DST.
    - If rifampicin resistance is confirmed by the repeat test, refer the patient for 2d-line treatment.
    - If rifampicin resistance is not confirmed by the repeat test, start first-line treatment and monitor with Xpert, culture and DST at month 1 and month 2. Reassess the regimen upon receipt of results.
- Patients with MTB+/RIF indeterminate: repeat the XPert test, start 2RHZE/4RH and send a good quality sputum sample to the reference laboratory for culture and DST. Re-evaluate the regimen upon receipt of results.
- Clinically diagnosed, pulmonary and extrapulmonary cases: give first-line regimen (2RHZE/4RH.)
- TB meningitis and osteoarticular TB: 2RHZE/10RH (total duration 12 months).

4.4. Administration of treatment

- Directly observed treatment (DOT) is recommended for all patients to ensure that they are taking treatment completely and to prevent the development of drug resistance.
  - Each dose is given under the observation by a trained community health worker (CHW) or by a nurse at the health facility.
  - The DOT provider gives the medication to the patient, observes the ingestion of the tablets and places a check mark on the treatment card. And this for all the doses, throughout the treatment.
  - DOT administered by family members is not recommended. An exception is made for children because it can be difficult for them to receive their medicine from an unfamiliar DOT provider.
  - For more details on DOT performed at community level, refer to the RBC community DOTS manual.
- First-line treatment
  - Patients are usually treated on an outpatient basis, which prevents the transmission of bacilli within health facilities.
  - All tablets should be taken together, preferably in the morning on an empty stomach. In case of nausea, heartburn or stomach pain, a light meal or porridge may be taken shortly before taking the medication.
  - Hospital admission may be clinically indicated:
    - When the patient's clinical condition is critical: acute forms (miliary), bedridden or severely malnourished patients, meningitis, abundant pleural effusion, severe hemoptysis, pneumothorax, etc.
    - In the event of severe drug toxicity.
    - When there are associated pathologies likely to influence the course of treatment: unbalanced diabetes, digestive ulcer, renal failure, heart failure, mental illness, AIDS during acute complication period, etc.
  - Smear-positive patients who need hospitalization must be separated from other patients, particularly from HIV-positive patients (see chapter 7).
- Second-line treatment

- In Rwanda, MDR-TB patients are admitted in a specialized MDR-TB centre to initiate second-line treatment.
- When they get two consecutive negative smears and one negative culture, they are referred to continue outpatient treatment at the health facility closest to their home.
- To facilitate administration of treatment under DOT, medication is given once a day whenever possible.
- Patients receive free holistic care, including treatment for drug-resistant TB, psychosocial and nutritional support, as well as outpatient transport costs.
- A standardized calendar of treatment monitoring is observed by all health facilities caring for DR-TB patients.
- For details, see the RBC manual on "programmatic management of drug-resistant tuberculosis".

4.5. Promote treatment compliance

- The best way to guarantee success of treatment is regularity. Conversely, when the patient is irregular, the risk to develop resistance to antituberculosis drugs is high.
- A patient-centred approach should be used in order to promote treatment adherence, improve quality of life, and alleviate suffering. To this end, DOT should be delivered as close to the patient's home as possible. The patient should be involved in the decision to take DOT at the health center or in the community and should receive counselling and encouragement several times during treatment (see chapter 8). In the event of the patient's particular needs and to the extent possible, social support will be offered by mobilizing social assistance, government social programs, NGOs, churches, etc.

Table 9. Interventions to encourage adherence to treatment.

Interventions	Description
Patient education	Advice on tuberculosis and its treatment, the consequences of irregular or incomplete treatment (drug resistance, more severe disease later).
Staff education	Patient-centered approach

	Awareness in order to adopt a welcoming, respectful, and motivating attitude towards patients Written or visual aids for patient education (essential messages, flipchart) Algorithms for decision making
Material support to mitigate the consequences of loss of income due to illness.	Nutritional assistance, transport vouchers. Coordination with national and local partners
Psychological support	Counseling sessions or peer support groups
Communication with the patient	Home visits Communication by mobile phone (SMS or phone calls)

- Many patients quickly feel better after starting treatment and do not understand that they need to continue treatment. Emphasis should be placed on the importance of completing treatment and the consequences of incomplete treatment, such as the onset of drug resistance or more severe disease later.
- DOT enables the early identification of irregular patients and those lost to follow-up. Measures must be taken immediately for their recovery, such as appointing them to the health center, making a home visit to investigate the cause of the interruption and encourage continuation of treatment. In case of repeated irregularity or refusal to continue treatment, involve the family, or the chief of village or any other person having administrative or moral authority on the patient.
- As recuperation of patients lost to follow-up is sometimes laborious, it is always necessary to note on the patient's card and in the TB register their full address, telephone number, the address of a family member, chief of village and nearest CHW.
- The attitude of caregivers towards patients contributes to compliance with treatment. A warm welcome, rapid administration of medicines with a few words of encouragement are crucial in making them feel confident and able to express any doubts or difficulties.

<u>What to do in case of treatment interruption?</u>

- Patients who have stopped treatment for less than 8 consecutive weeks should restart or continue treatment, depending on the duration of the interruption and the phase of treatment during which the interruption occurs (see Table 10).

- Patients who have already taken at least 1 month of treatment and have interrupted for 8 consecutive weeks or more are declared "lost to follow-up". These patients should have an XPert MTB/RIF test before resuming treatment in order to check susceptibility to rifampicin.

Table 10. Managing treatment after interruption

Duration of interruption	When did interruption occur?	Test	Decision on treatment	Record result of treatment	Record again as...
< 2 weeks	-	-	Continue treatment and complete 168 doses	(a)	-
2 to 8 weeks	Intensive phase	-	Restart 1st line regimen	(a)	-
	Continuation phase	-	Continue treatment and complete 168 doses	(a)	-
≥ 8 consecutive weeks	< 1 month of treatment	-	Restart 1st line regimen	(a)	-
	> 1 month of treatment	Xpert MTB+/ RIF-	Restart 1st line treatment	Lost to follow up	Treatment after loss to follow up
		MTB+/ RIF+	Refer to MDR-TB unit for 2d line treatment.	Lost to follow up	Treatment after loss to follow up

(a): Use the same treatment card and the same line in the TB case register. The treatment result will be the final result.

- In some cases, such as prolonged interruption at the end of treatment or in a clinically diagnosed TB patient, the physician will decide whether to restart, continue or stop treatment, based on the clinic and additional examinations. These cases will be

monitored clinically and new examinations will be performed in the event of resumption of symptoms. The result of treatment will be “lost to follow up”.

4.6. Treatment of tuberculosis in particular situations

It is important to identify particular situations and comorbidities likely to influence the response to TB treatment and to manage them properly.

4.6.1. Pregnancy and breast-feeding

- First-line antituberculosis drugs may be administered during pregnancy and are safe for the baby. Any pregnant woman who has been diagnosed with tuberculosis should be informed of the importance of taking anti-tuberculosis treatment for a successful pregnancy.
- Second-line drugs have potential teratogenic effects, particularly injectable agents (kanamycin, amikacin) which may cause deafness to the baby and should be replaced by linezolid. The risks and benefits of treatment should be carefully evaluated by the physician and considered with the goal to protect the health of the mother and the child. Contraception is strongly recommended for all non-pregnant women of childbearing age during the whole duration of second-line treatment.
- In case of bacteriologically confirmed tuberculosis during breast-feeding, the mother should immediately receive the adequate treatment regimen in order to prevent transmission of TB to the infant. All first-line and second-line anti-tuberculosis drugs recommended for pregnant women may be administered to her. She will continue breast-feeding and if contagious, she should use a surgical mask until she becomes negative (smears and culture if MDR-TB). The baby will receive TB preventive treatment (see sections 4.10.2 and 6.6).

4.6.2. Contraceptive pill

- Rifampicin may reduce the efficacy of the contraceptive pill. A higher dose pill should be prescribed (containing 50 μg of estrogen) or another method of contraception may be used.
- Patients who vomit after taking an oral contraceptive can be at risk of decreased drug absorption and therefore of decreased TB treatment efficacy. These patients should be advised to take their contraceptives apart from the anti-TB medicines and to use a barrier method until the contraceptive tablets are tolerated.

4.6.3. Diabetes mellitus

- Diabetes increases the risk of tuberculosis two- to three-fold. People with diabetes have worse tuberculosis treatment outcomes than people who do not have diabetes. Tuberculosis may impair glycemic control in people with diabetes.
- The 6-month standard regimen (2RHZE/4RH) is recommended for people with diabetes and drug-susceptible TB. Diabetes may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy.
- Pyridoxine should be provided for prevention of neuropathy (25 mg/day) or for its treatment (100 mg/day).
- Comprehensive treatment of diabetes includes counselling about increased physical activity, diet, and the administration of a glucose-lowering drug, metformin being the drug of choice. Diabetes must be managed closely throughout the TB treatment, in consultation with the diabetes expert.
- Infection control measures should be carefully implemented to reduce the risk of transmission of TB bacilli within the diabetes services (see chapter 7)

4.6.4. Renal failure

- Avoid drugs which are eliminated by kidneys: ethambutol, and among second-line drugs: kanamycin, capreomycin and cycloserine.
- Alternative first-line regimen: 2RHZ / 4 RH
- Great care should be taken in the administration of second-line drugs in patients with renal insufficiency. The dose and/or the interval between dosing should be adjusted for some second-line drugs when the creatinine clearance is <30 ml/min or for patients receiving hemodialysis.

4.6.5. Liver disorders

- Pyrazinamide, isoniazid and rifampicin are toxic for the liver. Pyrazinamide is the most hepatotoxic and rifampicin the least, although rifampicin is associated with cholestatic jaundice.
- Among the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs.
- Standard regimens may be used in case of previous history of viral hepatitis or in case of alcoholism, except in the event of severe chronic liver disease. These cases should be referred to a university hospital which will establish an alternative regimen.
- In the case of jaundice or hepatitis (transaminases above 3 times the normal value), stop antituberculosis drugs until jaundice disappears and transaminases decrease to less than 3 times the normal value; then reintroduce one anti-TB drug at a time with single tablets at progressive dose. (see table 12).

4.6.6. Malnutrition

- Patient's nutritional status should be assessed at the start of treatment.
- Patients with a body mass index (BMI) $\leq$ 18.5 have an increased risk of death and relapse. These patients should be treated for malnutrition and tuberculosis. Administration of treatment in a health facility (HC or hospital) is desirable in order to ensure close clinical monitoring and adequate management of malnutrition.
- Nutritional support should be provided to patients with a BMI $\leq$ 18.5 until they recover to a satisfactory nutritional state and to all patients under second-line treatment to foster treatment adherence.

4.6.7. Use of corticosteroids

Corticosteroids should be used in addition to anti-TB treatment only in a limited number of cases:

- In patients with tuberculous meningitis, to reduce the risk of hydrocephalus.
- In patients with tuberculous pericarditis, to reduce the risk of death and constrictive pericarditis and facilitate treatment adherence.
- In case of miliary tuberculosis, to relieve the patient.
- In a child with hilar adenopathy with bronchial compression, to reduce the risk of atelectasis.

4.7. Management of side effects

- The occurrence of adverse events during antituberculosis treatment can contribute to additional morbidity, treatment interruption or failure, emergence of drug resistance, reduced quality of life, and/or death.

- Close monitoring of patients is necessary so that side effects of anti-TB drugs are recognized quickly. One of the main advantages of directly observed therapy (DOT) over self-administration is the ability to monitor patients for side effects on a daily basis.

- Patients on anti-TB treatment should be informed about the possible adverse effects of the anti-TB medicines and the importance of reporting them.

- The majority of side effects are easy to recognize. The DOT provider must systematically check for their occurrence by using an appropriate checklist of symptoms (such as the one on the treatment card).

- Any serious adverse event (SAE) should be reported and managed promptly.
- Second-line anti-TB drugs have many more adverse effects than the first-line drugs. Active drug-safety monitoring (ADSM) should apply in priority for M/XDR-TB patients treated with new medicines, such as bedaquiline or delamanid, or with new regimens.
- The laboratory has an important place in the detection of side effects.
    - Patients on first-line regimen should have biological tests at start of treatment, including complete blood count (CBC), liver and renal tests.
    - These tests should be repeated in the event of clinical signs suggestive of severe toxicity such as jaundice or repeated vomiting.
    - For patients on second-line treatment, laboratory screening is invaluable for the early detection of certain adverse effects often not detectable by the patient and the DOT provider, such as renal or liver toxicities or electrolytes disorders.

Table 11. Management of the adverse effects of first-line anti-tuberculosis drugs

Minor side effects	Potential responsible drugs	Treatment
Anorexia, nausea, abdominal pain	Rifampicin	- Take tablets along with a light meal - Symptomatic treatment
Joint pain	Pyrazinamide	Aspirin or Paracetamol
Numbness, prickling, burning sensation on hands and feet (peripheral neuropathy)	Isoniazid	- Neuropathy: Pyridoxine (Vit B6): 100mg/day until improvement, then 25mg/day - Prevention: Pyridoxine 25mg/day or Vit B complex, for patients at risk of neuropathy: TB/HIV patients, diabetics, malnutrition, renal failure, alcoholism.
Red-orange urine (tears, sweating)	Rifampicin	Reassure patient
Mild itching without eruption or light eruption	Rifampicin, Isoniazid	- Symptomatic treatment and monitoring. - Seek other causes
Interaction with other drugs (corticosteroids, drugs against epilepsy, oral diabetes drugs, ARV)	Rifampicin	Adjust dosage of other drugs
Reduction of efficiency of oral contraceptives	Rifampicin	Use an alternative method or a pill containing 50 µg of estrogen
Drowsiness and lethargy	Isoniazid	Reassure patient

Major side effects	Stop treatment and refer patient	
Hypersensitivity to drugs: Itching with severe rash or mucosal involvement (peeling dermatitis in the most severe cases)	All drugs, mainly R and H	- Stop antituberculosis drugs - Give anti-histaminic and corticosteroid - Refer for identification of responsible drug, to be stopped permanently
Hepatitis: anorexia, nausea, vomiting, jaundice, confusion (patient at risk: cirrhotic, alcoholics)	Pyrazinamide Isoniazid Rifampicin	- Stop anti-TB drugs until the jaundice disappears and transaminases decrease (<3 times the normal value) - Gradually reintroduce anti-TB drugs
Vision problems: colour-blindness, potential blindness	Ethambutol	- Stop Ethambutol permanently - Refer for an ophalmologic examination
General reaction: shock, purpura, acute renal failure	Rifampicin	- Give treatment for shock - Refer to hospital - Stop antituberculosis drugs - Identify responsible drug and stop it permanently.
Psychosis	Isoniazid	- Psychiatric assessment - Antipsychotic treatment and pyridoxine
Convulsions	Isoniazid	- Stop isoniazid until the convulsions resolve - Look for other possible causes of seizures

REINTRODUCTION OF THE REGIMEN AFTER HYPERSENSITIVITY REACTION OR JAUNDICE/ HEPATITIS

- After disappearance of hypersensitivity reaction or jaundice/hepatitis (decrease of transaminases to less than 3 times the normal value), reintroduce one drug at a time, with progressive increasing doses. When the patient does not present any reaction, the drug will be administered with normal dosage and another drug will be introduced in the same manner (see table 12).
- In case of reappearance of hypersensitivity signs or jaundice, the drug which was introduced the last is likely the responsible and should be replaced.
- In practice, isoniazid and rifampicin are first introduced. Single medicines are available at the central level (RMS).

Table 12. Dosage for reintroduction of TB drugs after hypersensitivity reaction or hepatitis.

Day Drug	1	2	3	4	5	6	7	8	9	10	11	12
INH Tab 100 mg	50 mg	100 mg	300 mg	Full dose	Full dose	Full dose	Full dose	Full dose	Full dose	Full dose	Full dose	Full dose
RIFAMPICINE Tab 150 mg				75 mg	300 mg	Full dose	Full dose	Full dose	Full dose	Full dose	Full dose	Full dose
Z Tab 400 mg							200 mg	800 mg	Full dose	Full dose	Full dose	Full dose
E Tab 400 mg										100 mg	400 mg	Full dose

- In the event of a very strong allergic reaction, the starting doses will be halved.
- Full doses are established according to patient's weight and should never be exceeded.

Table 13. Maximum doses of 1st line drugs by weight groups

DOSE max/ day	29 - 37 kg	38 - 54 kg	55-70 kg	≥ 71 kg
INH	150 mg	200 mg	300 mg	300 mg
Rifampicin	300 mg	450 mg	600 mg	600 mg
Pyrazinamide	800 mg	1200 mg	1600 mg	2000 mg
Ethambutol	600 mg	800 mg	1200 mg	1600 mg

4.8. Monitoring response to treatment

Monitoring response to treatment is done through regular clinical and bacteriological follow-up.

4.8.1. Clinical follow-up

- History taking should focus on TB symptoms (cough, sputum production, fever, and weight loss) which usually improve within the first few weeks of treatment.
- Weight measurement should be performed every two weeks in the intensive phase and every month during the continuation phase and reported on the treatment card. If a patient changes weight category, the dosage of medicines should be adjusted.
- A medical examination is recommended at the start of treatment, at the end of the intensive phase and at the end of treatment. Also in case of appearance of side effects, aggravation of the general condition or associated pathology.

4.8.2. Bacteriological follow-up of first-line treatment

- A sputum smear examination should be performed at the end of the 2nd, 5th and 6th months of treatment.
- For controls, a single sputum sample is sufficient, preferably in the morning.
- Sputum microscopy usually becomes negative in the first 2 months of treatment.
- If C2 is positive, check compliance with the treatment and remind the patient of the importance of taking it regularly.

  Note: the sample should never be destroyed before knowing the smear result because if positive, the same sample should be sent to the reference laboratory for culture and DST.
- Do not prolong the intensive phase (56 doses), proceed to the continuation phase.
- A positive control in C5 or C6 should raise suspicion of resistance. Send the same positive sample, within 48 hours, to the reference laboratory.

  Repeat microscopy examination after 15 days; if it is also positive, confirm the failure. Perform the Xpert MTB/RIF test to exclude rifampicin resistance and choose the appropriate regimen for retreatment (see section 4.3).
- If a failure case is susceptible to rifampicin, investigate whether the cause of failure is poor adherence to treatment or poor absorption, resulting in low plasma drug levels and ineffective therapy. Low absorption can be demonstrated by the "therapeutic drug monitoring" test (TDM) that will soon be available at the NRL for rifampicin, isoniazid and pyrazinamide. In case of low absorption of the drugs, the doses should be adjusted.
- The C6 control must be carried out 5 days before the end of treatment:
  - If C6 is negative: complete the continuation phase (112 doses). The patient is declared cured if he was also smear-negative on at least one previous occasion.
  - If C6 is positive: do the same as for C5 positive.
- Emphasize to the patients to do the controls in a timely manner. In case of positive result, take action as indicated in the following table and algorithm.

Table 14. Bacteriological follow-up of confirmed TB patients under 1st -line treatment

Reminder : at diagnosis	- For all cases diagnosed AFB+ (sputum smear-positive), perform an Xpert test to exclude rifampicin resistance
If positive at the end of the intensive phase (C2)	- Send the same AFB+ sample to the reference laboratory for culture and DST - Proceed with the continuation phase - Check if treatment is correctly supervised and regularly taken.
If positive at the end of the 5th month (C5) or at the end of treatment (C6)	- Send the same AFB+ sputum sample to the reference laboratory for culture and DST - Do another sputum smear examination after 15 days and if positive, declare the failure. - Perform Xpert MTB/RIF to exclude rifampicin resistance and start retreatment accordingly. - Consider doing a TDM test if rifampicin susceptible. - Reassess the treatment regimen according to culture and DST results

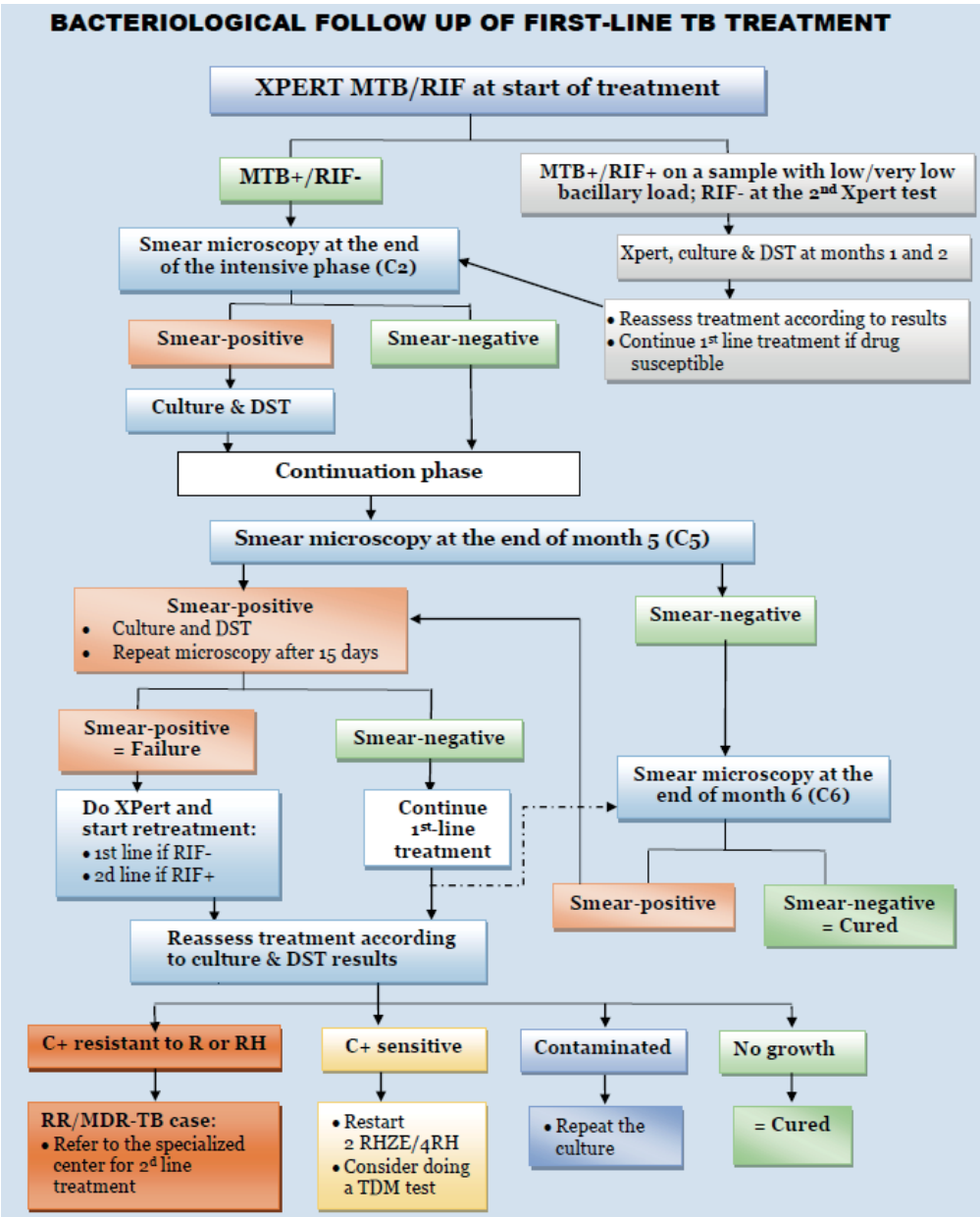


Figure 3. Algorithm for bacteriological follow-up of 1st-line treatment

Notes:

- Never declare failure before the end of the 5th month. A positive smear may be due to the intermittent excretion of dead bacilli and should be repeated before declaring the failure. A positive culture in C5 or C6 indicates the presence of live bacilli and therefore confirms the failure of the treatment.
- In case of rifampicin resistance detected on a specimen with low bacillary load but not confirmed by the repeat Xpert test, patients are treated with 2 RHZE/4RH. These patients should be monitored with Xpert, culture and DST at month 1 and 2 and the regimen should be reassessed upon receipt of results.

MONITORING OF CLINICALLY DIAGNOSED TB CASES

- Response to treatment is assessed primarily through clinical monitoring.
- Bacteriological monitoring is recommended by performing sputum smear examination at the end of the 2nd, 5th and 6th months of treatment. The results are analyzed in the same way as for bacteriologically confirmed cases.

4.8.3. Monitoring of second-line treatment

- Monitoring of DR-TB treatment includes regular history taking, physical examination, biological and bacteriological tests, ECG and chest X-ray. Smear microscopy and culture are done every 2 weeks during hospitalization, monthly on ambulatory phase and every 6 months during the first year post-treatment. Chest x-ray is performed every 6 months. (See the RBC manual on programmatic management of drug-resistant tuberculosis)

4.9. Treatment outcomes

There are 6 possible results; each has a well-standardized definition:

Table 15. First-line treatment outcomes

Outcome	Definition
Cured	- 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 (C6) and on at least one previous occasion (C2 or C5).

Treatment completed	- A TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment without evidence of failure but cannot be classified as cured or failed, either because the tests (smear or culture) were not done in the last month of treatment and at least once before, or because results are unavailable. - A patient with clinically diagnosed, pulmonary or extrapulmonary TB, who has completed treatment.
Treatment failed	- 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: - Patient "transferred out" to another treatment unit for whom the treatment outcome is unknown to the reporting unit. - Patient whose treatment was stopped for serious reaction or misdiagnosis.

Notes:

- As soon as a patient completes the treatment, record the outcome on the patient's treatment card, in the tuberculosis register (enter the date in the corresponding column) and in the e-TB system.
- Patients who are successfully treated = the sum of cured patients and patients who completed their treatment.
- All patients found to have an RR-TB or MDR-TB strain at any point in time should be started on the adequate second-line regimen. When calculating treatment outcome (cohort analysis) these cases are excluded from the drug-susceptible cohort and included only in the second-line TB cohort analysis.
- Second-line treatment outcome definitions differ from those of first-line treatment (see the RBC manual on programmatic management of DR-TB).

4.10. Contact investigation and preventive treatment

4.10.1. Contact investigation

- Contact investigation must be done:
    - for any bacteriologically confirmed TB case

- for any child diagnosed with TB in order to identify and treat the index case who infected the child, often an adult within the family.

- The highest priority contacts are those:
  - with signs or symptoms suggestive of TB
  - aged < 5 years
  - HIV-positive (or with another immunocompromising condition)
  - contacts of an M/XDR-TB case.

- Contact investigation should be done preferably during a home visit at the beginning of treatment of the index case and must be recorded on the patient' card. Contact investigation should be repeated at the end of treatment of the index case.

- The contact investigation should start with information about the importance of contact screening and how it is done.

- Contact investigation should follow the following algorithm:

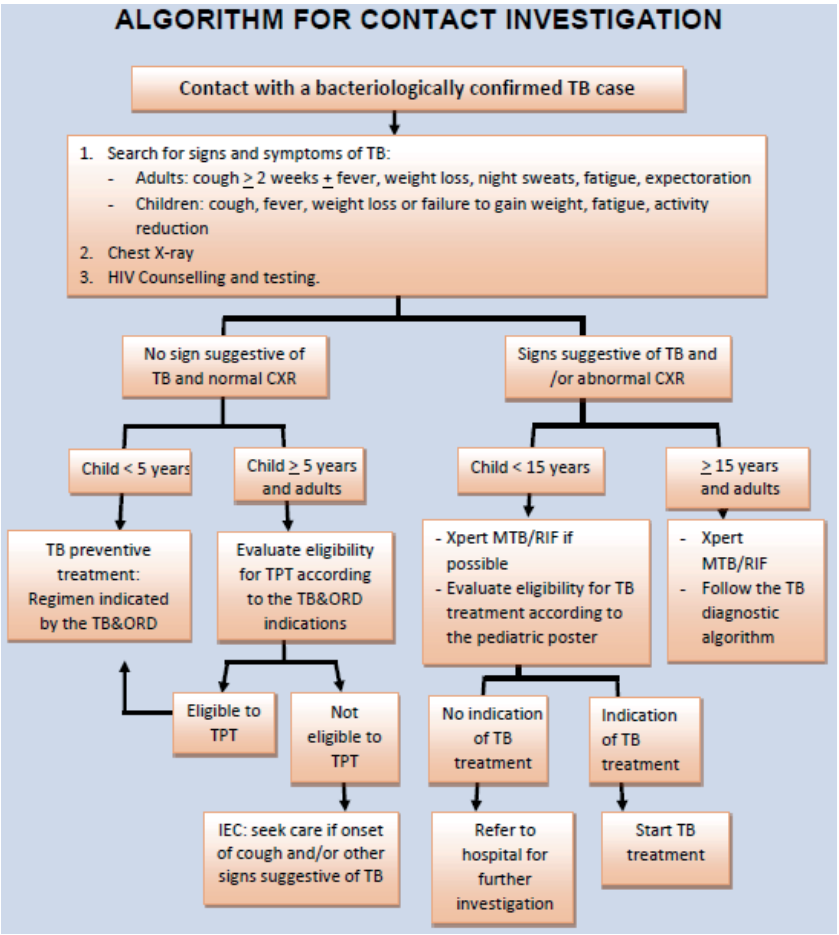


Figure 4. Algorithm for contact investigation

Reminder: all contacts with presumptive TB should have Xpert MTB/RIF as initial diagnostic test and should be managed according to the TB diagnostic algorithm for adults (figure 1 in section 3.3) or the pediatric poster (figure 8 in chapter 6).

4.10.2. TB preventive treatment (TPT) for contacts

TPT is one of the key interventions recommended by WHO to prevent to development of active TB disease.

Indications:

TPT is indicated, after exclusion of active TB through the algorithm of contact investigation, for:

- Contacts aged <5 years of bacteriologically confirmed pulmonary TB case
- Contacts ≥ 5 years according to the instructions that will be published in due course by the TB & ORD Division.

Notes:

- Chest X-ray is recommended for screening of contacts but it is not a requirement for initiating TPT.
- Testing for LTBI (by TST or IGRA) is not required to initiate TPT in household contacts aged <5 years. It is recommended for contacts ≥ 5 years old to limit unnecessary administration of TPT to those not infected with *M. tuberculosis.* However, unavailability of the test should not be a barrier to give TPT to people at higher risk for TB.

Contraindications:

- Presumption of tuberculosis
- Active hepatitis (acute or chronic)
- Concomitant use of hepatotoxic drugs
- Regular and heavy consumption of alcohol
- Symptoms of peripheral neuropathy
- History of hypersensitivity to INH, rifampicin or rifapentine.

Counselling:

- People eligible for TPT should receive information regarding TB infection, the benefits of TPT, duration, frequency of follow-up visits, signs of onset of active tuberculosis and possible side effects, importance of taking the treatment until completion for it to be effective.

TPT regimens:

- The classic regimen is isoniazid monotherapy, every day for 6 months. The dosage in children is presented in Table 19, section 6.6.
- New regimens include rifampicin or rifapentine and have the advantage of reducing the duration of treatment, making it easier to complete it. However, these regimens

may interact with ARVs, immunosuppressants, other medications, and contraceptives.

- The choice of the TPT regimen will depend on availability of appropriate formulations and considerations of age, safety, drug interactions and adherence. The TB&ORD Division will issue the corresponding instructions shortly.

Table 16. TPT regimens

TPT regimen	Comment
6 H : daily isoniazid for 6 months	- Availability of dispersible tablets for children - Availability of combined tablets of isoniazid, pyridoxine and sulfamethoxazole/ trimethoprim. - Preferred regimen for HIV+ children on PIs-based regimen, nevirapine, or integrase inhibitors (dolutegravir) due to potential drug-drug interactions.
4 R : daily rifampicin for 4 months	- Used if isoniazid is contraindicated
3 HR: daily isoniazid and rifampicin for 3 months	- Particularly suitable for children due to the availability of dispersible tablets (R75H50)
3 HP: isoniazid and rifapentine weekly for 3 months (12 doses)	- Can be used for children ≥ 2 years and adults. - Availability of a FDC (HP-300/300) - No child-friendly formulation currently available
1 HP: isoniazid and rifapentine daily for one month (28 doses)	- Can be used for children > 12 years and adults.

TPT administration and follow-up:

- TPT is delivered monthly for self-administration at home.
- Anyone on TPT must be monitored monthly in order to:
  - Identify without delay the appearance of active tuberculosis
  - Quickly detect any adverse effects of the treatment
  - Repeat educative messages to ensure treatment adherence and completion.

CHAPTER 5. TB/HIV COINFECTION

HIV infection is a major challenge in the fight against tuberculosis. HIV infection increases the risk of developing active tuberculosis and TB is the leading cause of preventable death among people with HIV, accounting for about a third of AIDS deaths. Routine screening for TB in anyone living with HIV, rapid diagnostic investigation and early treatment are among the most effective ways to prolong their life. Rwanda is implementing the WHO-recommended TB/HIV collaborative framework to mitigate the double burden of TB/HIV in populations at risk of or affected by both diseases. Strong collaboration between TB and HIV programs is essential for the implementation of joint strategies for the prevention, detection and management of TB/HIV co-infection. Likewise, in health facilities, TB and HIV detection and treatment services need to work closely together so that co-infected patients are treated in an integrated manner.

Framework of collaborative TB/HIV activities [4,5]:

A. Establish and strengthen the mechanisms for delivering integrated TB and HIV services

A.1. Set up and strengthen a coordinating body for collaborative TB/HIV activities functional at all levels
A.2. Determine HIV prevalence among TB patients and TB prevalence among people living with HIV
A.3. Carry out joint TB/HIV planning to integrate the delivery of TB and HIV services
A.4. Monitor and evaluate collaborative TB/HIV activities

B. Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy (the *Three I's for HIV/TB*)

B.1. Intensify TB case-finding and ensure high quality antituberculosis treatment
B.2. Prevent tuberculosis by ensuring universal access to early antiretroviral treatment and preventive treatment for tuberculosis
B.3. Ensure control of TB infection in health-care facilities and congregate settings

C. Reduce the burden of HIV in patients with presumptive and diagnosed TB

C.1. Provide HIV testing and counselling to all patients with presumptive and diagnosed TB
C.2. Promote HIV prevention interventions for patients with presumptive and diagnosed TB
C.3. Provide co-trimoxazole preventive therapy for all eligible TB/HIV patients
C.4. Ensure HIV prevention interventions, treatment and care for TB/HIV patients

[4] *WHO policy on collaborative TB/HIV activities. Guidelines for national programmes and other stakeholders. 2011*
[5] *RBC/IHDPC. Policy statement on TB/HIV collaborative activities. Update 2011.*

The essential guidelines are detailed in the following sections.

5.1. DETECTION OF HIV IN TB PATIENTS

- HIV testing should be routinely offered to all patients with presumptive TB and those who have been diagnosed with TB, respecting the principles of consent, confidentiality, counselling, correct test results and connection to care and treatment.
- Testing for HIV is important because treatment for tuberculosis may be less effective in TB/HIV co-infected patients. It is also an opportunity to provide advice on risky behavior and precautions to prevent HIV infection. In the event of a positive result, patients will be able to access the chain of HIV and TB prevention, care, support and treatment services.
- Partners and family members of HIV-positive TB patients should also be offered voluntary counselling and HIV testing.

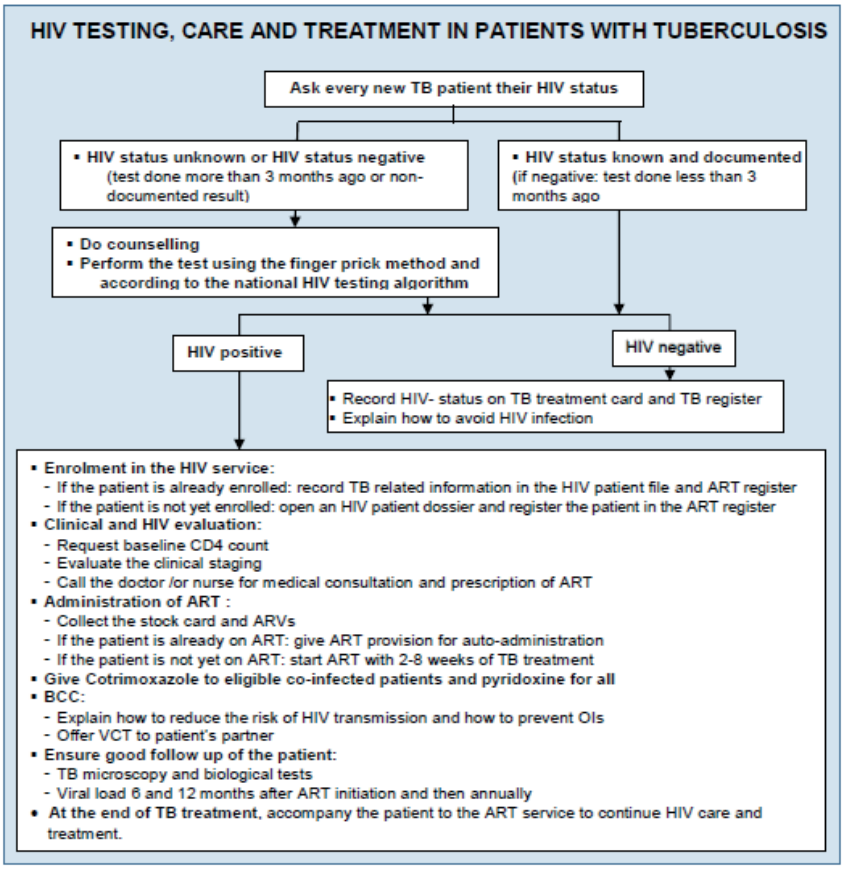


Figure 5. HIV testing, care and treatment in patients with tuberculosis

5.2. TB SCREENING IN PLHIV

- Screening for active TB should be systematic for any PLHIV at enrolment in ART program and at each follow-up visit, using the clinical algorithm in figure 6.
- TB screening includes looking for clinical signs or symptoms suggestive of TB, regardless of their duration and, for any new HIV-positive individual, a chest X-ray.
- The objective of routine screening for TB in PLHIV is twofold:
    - Detect and treat early any PLHIV with active TB in order to reduce mortality
    - Identify PLHIV eligible for preventive treatment of tuberculosis (TPT).

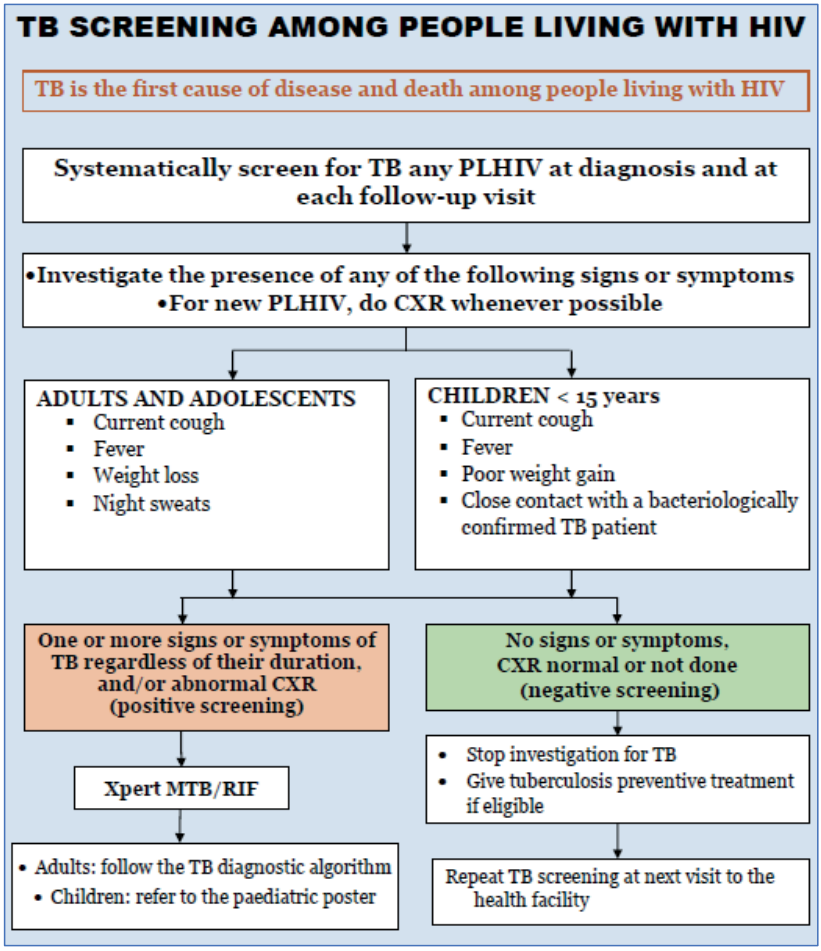


Figure 6. TB screening algorithm for PLHIV

5.3. DIAGNOSIS OF TUBERCULOSIS IN PLHIV

- Xpert MTB/RIF test:
  - All PLHIV with signs and symptoms of pulmonary TB who are capable of producing sputum should submit at least one sputum specimen

- Xpert MTB/RIF should be used as the initial diagnostic test for all PLHIV with presumptive TB, because it improves the sensitivity and speed of diagnosis for both drug-sensitive and drug-resistant TB.

- Xpert MTB/RIF should be used for the diagnosis of TB meningitis and other forms of extrapulmonary TB. According to WHO last recommendations, it may be used in blood for diagnosis of disseminated TB in HIV-positive patients.

- The urine lipoarabinomannan (LF-LAM) test is recommended by WHO to assist in the diagnosis of active TB for in-patients' HIV-positive adults, adolescents and children with:

  - Signs and symptoms of TB

  - Advanced disease or seriously ill

  - CD4 count <200 cells/mm3 irrespective of signs and symptoms of TB.

  LF-LAM test may be especially useful for patients unable to produce a sputum specimen. If LF-LAM is positive and no bacteriological test can be performed, clinicians may consider initiating TB treatment based on the positive LF-LAM and their clinical judgment.

- CXR is an important diagnostic tool in HIV-positive patients with presumptive TB and negative bacteriological tests and in patients unable to provide a sputum sample.

5.4. MANAGEMENT OF TUBERCULOSIS AND HIV

The management of tuberculosis and HIV is integrated. Treatment of TB is the priority, it should be started as soon as possible after the diagnosis of TB is established and it should be supervised. Antiretroviral therapy (ART) should be started in all TB/HIV co-infected patients, regardless of CD4 cell count.

5.4.1. ONE STOP TB/HIV SERVICE

The care and treatment of TB patients infected with HIV should be provided in an integrated manner in the TB service for both diseases. This has the advantage of reducing the number of patient appointments, reducing the risk of exposure to TB in HIV services, and finally improving the quality of care since patients are seen by the same providers for TB and HIV in one service.

The following tasks should be carried out at the One stop TB/HIV service:

- Administration of anti-TB drugs

- HIV counselling and testing by the TB nurse
- Enrolment into HIV care and treatment (or shift HIV file to TB service)
- Prescription of cotrimoxazole for eligible TB/HIV patients and pyridoxine for all
- Blood sampling for baseline CD4 cell count and biological tests for new PLHIV; viral load 6 and 12 months after ART initiation and then every year.
- Medical consultation and evaluation of clinical status of the patient
- Prescription and dispensation of ART:
    - If the patient is already on ART: give ART provision for auto-administration
    - If the patient is newly starting ART: initiate ART within 2-8 weeks following the start of anti-TB drugs
    - Filling of pharmacy tools (ART and cotrimoxazole stock cards);
- At the end of the antituberculosis treatment, referral of the patient with his HIV file to the ART clinic for subsequent follow-up.

  (see figure 5)

5.4.2. TUBERCULOSIS TREATMENT

- Treatment of tuberculosis is the priority and must be supervised (DOT)
- First and second-line TB regimens are the same for HIV-positive and HIV-negative patients.
- Rifabutin replaces Rifampicin for TB/HIV patients who are on the protease inhibitors based regimen with ritonavir such as:

    - Lopinavir/ritonavir or Kaletra
    - Atazanavir/ritonavir
    - Darunavir/ritonavir

  Rifabutin dosage is 150mg per day; it is prohibited for patients under 15 years old.
- The response to TB treatment for the co-infected TB/HIV patient is similar and sputum becomes negative as quickly as for HIV non-infected TB patients. However, HIV infected TB patients run a higher risk for:

    - Drug related toxicity.
    - Mortality during the treatment (often linked to other causes)
    - Relapse and re-infection.
- Given the fact that gastro-intestinal disorders are frequent with HIV-positive patients, malabsorption should be considered when tuberculosis persists despite appropriate treatment. A therapeutic drug monitoring test (TDM) can help to identify this issue.

- Side-effects are more frequent in HIV-positive than in HIV-negative TB patients. Their incidence is still higher in DR-TB patients due to the use of multiple second-line medicines with recognized high toxicities which are given in combination with ART.
- All TB/HIV co-infected patients, adult and children, should receive Pyridoxine for prevention of INH-related peripheral neuropathies as they are more common in PLHIV:
  - 1 tablet of pyridoxine of 25 mg per day for patients on first-line TB treatment
  - 1 tablet of pyridoxine of 100mg per day for MDR-TB patients on second-line treatment
  - This medication is available in the program.

5.4.3. ANTI-RETROVIRAL THERAPY FOR ADULTS WITH TB

- ART should be started in all TB patients living with HIV regardless of their CD4 cell count. ART will be provided at the One-Stop TB/HIV service during TB treatment.
- TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of TB treatment considering the clinical condition of the patient, as follows:
  - CD4 cell count $\leq$ 50: within 2 weeks
  - CD4 cell count > 50: between 2-8 weeks.
- The following table provides a summary of ART regimens for adults and the adjustments needed when they are given at the same time as anti-TB drugs. For children, refer to the last version of the National Guidelines for Prevention and Management of HIV.

Table 17. ART for adults on antituberculosis treatment

ART regimens	ART regimen adjustment
TDF or ABC/3TC/DTG	DTG should be dosed twice daily (50mg BID) if rifampicin is used
TDF or ABC/3TC + EFV	No adjustment (EFV remains 600mg daily)
TDF or ABC or AZT/3TC + ATV/r or LPV/r	Substitute rifampicin with rifabutin
ETV + DRV/r + DTG/RAL	Substitute rifampin with rifabutin

TDF: tenofovir ; ABC: abacavir ; 3TC: lamivudine ; DTG: dolutegravir; ; EFV: efavirenz; AZT: zidovudine; ATV/r: atazanavir/ritonavir; LPV/r: lopinavir/ritonavir; ETV: Etravirine ; DRV/r: darunavir/ritonavir; RAL: raltegravir

- After initiating ARV treatment, some co-infected patients may present with deterioration in clinical condition and signs such as high fever, respiratory symptoms and increased lymphadenopathy. This may be an immune reconstitution syndrome

(IRIS) due to an inflammatory response to an opportunistic infection and should not be considered as a clinical failure. Antituberculosis treatment should be maintained and the patient referred to the doctor in charge of HIV for appropriate treatment.

- Some toxicities are common to both anti-TB treatment and ART, which may result in added rates of adverse events. See figure 7 and annex 6.

5.4.4. PREVENTION OF OPPORTUNISTIC INFECTIONS WITH COTRIMOXAZOLE

Co-trimoxazole is a combination of sulfamethoxazole (SMX) and trimethoprim (TMP).

Indications: Co-trimoxazole should be administered to:

- All HIV+ children < 5 years old.
- New HIV+ patients aged > 5 years with baseline CD4 cell count < 200 cell/mm3
- Existing HIV+ patients aged > 5 years with unsuppressed viral load (> 200 copies/ml)

Dosage:

- Adults: one tablet of 960 mg or two tablets of 480 mg per day.
- Children: see table 18

Duration:

- Children < 5 years: until 5 years of age; then stop if virally suppressed.
- Children > 5 years and adults: until viral load suppression (VL <200 copies/ml)

Table 18. Simplified dosing of cotrimoxazole prophylaxis in children

Presentation	**Number of tablets or ml of Cotrimoxazole by weight band once daily**			
	3.0-5.9 kg	**6.0-13.9 kg**	**14-24.9 kg**	**25-34.9 kg**
Suspension 200/40 mg per 5 ml	2.5 ml	5 ml	10 ml	-
Tablets (dispersible) 100/20 mg	1	2	4	-
Tablets (scored) 400/80 mg	-	0,5	1	2
Tablets (scored) 800/160 mg	-	-	0,5	1

Adverse effects:

- Nausea: take drug with some food
- Generalized skin rash
- Medullary aplasia with pallor, hemoglobin < 8 g/L
- Jaundice, hepatitis

} Stop treatment and refer patient

INTEGRATED MANAGEMENT OF TB-HIV PATIENTS

1. Treat TB in priority and use the same antituberculosis regimens as for HIV-negative patients.
2. Start ART in all TB/HIV patients regardless of their CD4 cell count and as soon as possible within the first 2-8 weeks of anti-TB treatment (within the first 2 weeks if CD4 cell ≤ 50/mm3).

ART regimens	ART regimens adjustment
TDF or ABC/3TC/DTG	DTG should be dosed twice daily (50mg BID) if rifampicin is used
TDF or ABC/3TC + EFV	No adjustment (EFV remains 600mg daily)
TDF or ABC or AZT/3TC + ATV/r or LPV/r	Substitute rifampicin with rifabutin
ETV + DRV/r + DTG/RAL	Substitute rifampicin with rifabutin

ART for children: refer to the National Guidelines for Prevention and Management of HIV.

3. Replace Rifampicin with Rifabutin for TB/HIV patients over 15 years of age who are taking a protease inhibitor based regimen with ritonavir (rifabutin: 150 mg once per day).
4. Give Co-trimoxazole preventive treatment to:
   - HIV-positive children under 5 years of age,
   - New PLHIV aged ≥ 5 years with baseline CD4 cell count < 200/mm3
   - Patients aged ≥ 5 years with unsuppressed viral load (≥ 200 copies/ml)
5. Give pyridoxine for the prevention of peripheral neuropathies (25 mg/day)
6. Provide integrated care and treatment of TB and HIV in the "One-Stop TB-HIV service".
7. Pay attention to the potential additive toxicities of ARVs and anti-TB agents

Toxicity	ARV	Anti-TB	Management
Hepatotoxicity	NVP, EFV, all PIs (RTV > other PI), all NRTIs, DTG, RAL	Z, H, R, E, PAS, Eto/Pto, FQ, BDQ	- Stop anti-TB drugs until the hepatitis resolves, - Then gradually reintroducing one drug at a time
Peripheral neuropathy	D4T, ddI DdC	Lzd, Cs, H aminoglycosides, Eto/Pto, E	- Pyridoxine 100-200 mg/day (25 mg/day for prevention) - Replace the ARV with a less neurotoxic agent
Central nervous system (CNS) toxicity, depression	EFV	Cs, H, Eto/Pto, FQ	- Concomitant use of EFV and CS is accepted but requires frequent monitoring of CNS toxicity. - Stop temporarily Cs and give antipsychotic treatment or antidepressant. Consider substituting CS or EFV.
Headache	AZT, EFV	Cs, BDQ	- Ibuprofen, paracetamol, adequate hydration - Usually spontaneous resolution
Skin rash Hypersensitivity reaction	ABC, NVP, EFV, D4T, RAL, DTG, ETV, DRV/r	H, R, Z, PAS FQ and others	- Moderate reaction: antihistamine - Severe reaction: stop anti-TB drugs and gradually reintroduce one drug at a time; remove the responsible agent.
Renal toxicity, electrolyte disturbances	TDF (rare)	S, Km, Am, Cm	- Monitor creatinine clearance and adjust ARV and anti-TB dosages if necessary. - Or give the injectable 3 times a week.
Optic neuritis	ddI	E, Lzd, Eto/Pto, Cfz, rifabutin, H, S	- Stop and permanently replace the responsible agent
Lactic acidosis	D4T, ddI, AZT, 3TC, TDF	Lzd	- Replace the responsible agent
Pancreatitis	D4T, ddI, ddC LPV/r	Lzd	- Avoid using these agents together. If pancreatitis, permanently stop the responsible agent; do not use D4T, ddI or ddC.

Figure 7. Integrated management of TB-HIV patients

5.5. PREVENTION OF TUBERCULOSIS IN PLHIV

5.5.1. TUBERCULOSIS PREVENTIVE TREATMENT (TPT)

According to WHO, a systematic review of randomized controlled trials found that TPT for PLHIV reduced the overall risk of developing tuberculosis by 33%.

Indications:

- PLHIV, adults and children ≥ 1 year of age, in whom active tuberculosis has been excluded using the screening algorithm for PLHIV (figure 6 in section 5.2).
- Children under 1 year infected with HIV who are contact of a bacteriologically confirmed TB case (after exclusion of an active TB).

Contraindications:

- Presumption of tuberculosis
- Active hepatitis (acute or chronic)
- Concomitant use of hepatotoxic drugs
- Regular and heavy consumption of alcohol
- Symptoms of peripheral neuropathy
- History of hypersensitivity to INH, rifampicin or rifapentine.

Counselling should be provided to any PLHIV eligible for TPT and should cover the following information:

- The relationship between HIV and tuberculosis: the risk of developing active TB during their lifetime is estimated at 50% in PLHIV compared with 5-10% in HIV-negative people.
- What is TB? (cause, transmission, general signs and symptoms)
- The difference between latent and active TB
- Who qualifies for TPT?
- Potential benefits and the minimal risk of TPT
- TPT regimen, side effects and the importance of adherence

This information is essential to ensure that PLHIV eligible for TPT are able to accept or decline treatment based on a clear understanding of its potential advantages or disadvantages.

TPT regimens: see table 16 in section 4.10.2

- Isoniazid monotherapy, daily for 6 months (6H) is the preferred regimen when shorter regimens with rifampicin or rifapentine cannot be used.
- Tablets containing a combination of isoniazid, pyridoxine and sulfamethoxazole/ trimethoprim (HPST-300 mg/25 mg/800 mg/160 mg) are preferably used.

  Dosage of HPST: 1 tablet daily for adults
  ½ tablet for children ≥5 years and
  ¼ tablet for children <5 years of age.

- Regimens containing rifampicin or rifapentine should not be given to people taking protease inhibitors or nevirapine. Dolutegravir should be dosed twice daily if a TPT regimen with rifampicin is used.

5.5.2. OTHER INTERVENTIONS FOR PREVENTION OF TB

- All HIV+ individuals should be protected from contact with TB patients and be informed of situations that increase the risk of contracting TB. Therefore, health facilities should implement infection control measures and ensure that patients infected with HIV are separated from presumed and confirmed cases of pulmonary TB (see chapter 7).
- Universal access to early ART helps prevent tuberculosis. PLHIV are significantly less likely to develop TB and dying from TB if they begin ART before their immune system is severely affected.
- The BCG vaccine protects against severe forms of TB. It is applied to HIV positive children, except those with AIDS or malnourished or weighing less than 2.5kg.

5.6. PREVENTION OF HIV TRANSMISSION

- All TB patients should receive information about preventive measures against HIV infection including the reduction of the number of sexual partners, the correct and consistent use of condoms, the treatment of sexually transmitted infections and the use of disposable syringes and needles for each injection.
- Universal access to early ART reduces viral load and therefore transmission of HIV to partners.

CHAPTER 6. TUBERCULOSIS IN CHILDREN.

6.1. EPIDEMIOLOGY

- Children are usually infected by an adult in their family who has pulmonary tuberculosis bacteriologically confirmed. The best prevention is therefore the early detection and treatment of infectious TB patients.
- Children can get TB at any age. Extrapulmonary tuberculosis is more frequent among children than in adults, but pulmonary forms remain the majority of cases.
- The younger the child is infected, the more likely he is to develop tuberculosis, and they usually do so within one year of infection. Therefore, TB in children is an indicator of recent and ongoing transmission of *M. tuberculosis* in the community. In infants, the interval between infection and disease may be as little as 6 to 8 weeks.
- The main risk factors for tuberculosis in children are:
  - Close contact with a recently diagnosed bacteriologically confirmed TB case
  - Age < 5 years
  - HIV infection
  - Malnutrition.
- Children below five years of age who are household contacts of TB patients have significantly higher risk of acquiring TB infection and progressing rapidly to TB disease. Children below two years of age are also at greater risk for severe and disseminated forms of TB (TB meningitis and miliary TB) with very high risk of morbidity and mortality. That is the reason why every child under 5 years, in close contact with a bacteriologically confirmed TB patient, must be given TB preventive treatment if s/he has no signs or symptoms of active TB.
- A depression of the immune system (infection by HIV, malnutrition, whooping cough and measles, etc.) speeds up progression of tuberculosis infection to tuberculosis disease.
- Children can be infected by *M. Bovis*, by taking non boiled cow milk. They can then develop tuberculosis of the cervical lymph nodes, intestinal tuberculosis or even a pulmonary form or a disseminated form.
- Tuberculous pleurisy is the most frequent cause of sero-fibrinous pleurisy in teenagers. Adolescents are also at risk of developing adult type disease, i.e. often sputum smear-positive and highly infectious.

6.2. SIGNS AND SYMPTOMS

- Pulmonary tuberculosis should be presumed when a child has been sick for 2 weeks or more and presents with at least one of the following symptoms:

  - Cough ≥ 14 days, despite broad-spectrum antibiotic treatment
  - Fever ≥ 14 days despite broad-spectrum antibiotic treatment, with negative malaria smear and negative evaluation for other infectious diseases including urinary tract infection (UTI)
  - Loss of weight or failure to gain weight
  - Contact with a bacteriologically confirmed TB patient.

Extrapulmonary tuberculosis should be suspected in a child with:

  - Headache and irritability, occasional vomiting; the child wants to be alone and is less reactive during 2-3 weeks (presumption of tuberculous meningitis).
  - Stiffness and malformation of the backbone which might be signs of Pott's disease.
  - Swelling of an articulation or a bone, pain while walking (in the absence of a trauma)
  - Painless, hard or soft, sometimes fistulized, cervical lymphadenopathies
  - Swollen abdomen, ascites, and persistent abdominal mass after anti-parasitic treatment.

- TB in HIV-infected children:
  - As for the adult, TB presentation depend on the phase of the infection by HIV. At an early stage, when immunity is still good, symptoms are similar to those in a child not infected by HIV. As immunity declines, disseminated forms become more frequent, such as tuberculous meningitis, miliary and lymphatic tuberculosis.
  - HIV makes it difficult to diagnose pulmonary tuberculosis in children because other pulmonary infections associated to HIV have the same symptomatology. In addition, they can develop serious tuberculosis at any stage of their disease, with few clinical, radiological signs and a negative skin test reaction.

- Screening for TB in children under 5 years has been integrated into the IMCI (integrated management of childhood illnesses) and in the ICCM (integrated community case management) approaches. Thus, in Rwanda, any child under 5 years of age consulting a health center must be screened for TB using the algorithm and IMCI registers.

6.3. DIAGNOSIS

Diagnosis of pulmonary tuberculosis is difficult in children because they usually have paucibacillary forms with negative bacteriology and they cannot give adequate sputum samples. In addition, clinical signs are often not specific to tuberculosis. Therefore, the diagnosis of TB in children is often made clinically on the basis of a combination of signs and symptoms, risk factors and results of complementary tests. This requires a thorough assessment of all elements supporting the diagnosis of tuberculosis:

- Clinical signs and symptoms consistent with TB (see previous section) as well as unsatisfactory growth.
- Contact with a contagious TB case: carefully investigate the presence of cough among the living or recently deceased contacts of a child with presumptive TB. Contact with a contagious case makes tuberculosis infection more likely, but absence of contact does not exclude tuberculosis.
- HIV infection increases the likelihood of tuberculosis.
- Radiological abnormalities such as unilateral or bilateral adenopathies (hilar or mediastinal) and/or opacity in one lobe, atelectasis, miliary signs or a cavity (although rare in children) should always raise the suspicion of tuberculosis. Chest radiography is useful in the diagnosis of tuberculosis in children but the images are difficult to interpret, not specific and should never constitute the diagnosis on their own.
- Positive bacteriological tests of sputum or any other fluid.
    - Xpert MTB/RIF must be used as the initial diagnostic test for any child under 15 years who presents signs of presumptive pulmonary TB, tuberculous meningitis or other extrapulmonary TB. However, the majority of children will have negative results with all of the available bacteriological tests; therefore, a **negative test result does not rule out TB in children**.
    - If the child is unable to produce a sputum sample of sufficient quality and quantity, gastric aspiration may be done in the hospital, in the morning upon awakening.
- A positive tuberculin skin test (TST) or intradermoreaction:
    - The TST is positive if:

        the induration is ≥10 mm in diameter for HIV-negative children

        the induration is ≥ 5 mm for HIV-positive or malnourished children.
    - A positive TST may aid in the diagnosis of TB in children who have signs or symptoms of presumption, however it does not confirm the disease. It can be

positive in an asymptomatic child, in a sick child or in a child vaccinated with BCG.

- **A negative TST does not exclude TB.** The test may give a false-negative result in case of recent tuberculosis infection (4 to 8 weeks are necessary for the test to become positive) or in case of immunosuppression (severe tuberculosis, malnutrition, infection with HIV/AIDS, measles or severe infection).

6.4. TREATMENT OF TUBERCULOSIS IN CHILDREN UNDER 15 YEARS

6.4.1. TREATMENT INDICATIONS

- Children with bacteriologically confirmed TB
- Children presenting one of the following combinations of elements supporting the diagnosis of tuberculosis:
  - Cough or fever ≥ 14 days despite broad-spectrum antibiotic treatment, with negative malaria smear and negative evaluation for other infectious diseases including UTI and 1 additional test in favor of TB:
    - CXR suggestive of TB
    - TST positive.
  - Cough or fever ≥ 14 days despite broad-spectrum antibiotic treatment, with negative malaria smear and negative evaluation for other infectious diseases including UTI and 2 risks factors among the following:
    - Contact with a bacteriologically confirmed TB case
    - HIV infection
    - Severe malnutrition.
- Severely malnourished children presenting one of the following indications:
  - Cough ≥ 14 days despite appropriate antibiotic treatment for at least 7 days.
  - Fever ≥ 14 days despite appropriate antibiotic treatment for at least 7 days, negative smear for malaria and a negative evaluation for other infections including septicemia.

- The child is HIV-positive or is contact of a contagious TB case and presents at least one of the following results:
    - Chest X-ray suggestive of TB
    - TST ≥ 5 mm
- No clinical improvement after 4 weeks of nutritional rehabilitation according to the national guidelines.

NB: in the presence of one of these indications, nurses trained in TB management are allowed to initiate antituberculosis treatment in children without the intervention of a medical doctor. However, if the indication for treatment is doubtful, the child should be referred to the hospital.

6.4.2. FIRST-LINE TREATMENT REGIMEN

- The treatment regimen of drug-susceptible TB regimen is identical to that for adults (2 RHZE/4RH) but the dosage of first-line antituberculosis drugs in children < 25 kg is higher than in adults (see figure 2 in section 4.2.1).
- Pediatric formulations (R75H50Z150 and R75H50) are indicated for children < 25 kg. They contain the appropriate doses of drugs in combination. Tablets are dispersible in water and have a pleasant taste, which makes it easier for children to take. Put each tablet in 50 ml of water to ensure that the child drinks the full amount. Ethambutol is not included in the pediatric FDC; single tablets of E100 are administered with RHZ.
- Treatment is taken daily and should be directly observed in children as in adults.
- For children with tuberculous meningitis and children with osteoarticular tuberculosis (new cases and retreatment), the duration of treatment is 12 months: 2 months of intensive phase and 10 months of continuation phase: 2 (RHZ)E/10(RH). The recommended doses are the same as for pulmonary tuberculosis. These children should be treated in a hospital that can analyze CSF and do a chest x-ray.
- In children with tuberculous meningitis, Prednisolone should be administered to reduce the risks of hydrocephalus, at a rate of 2 mg/kg/day (4 mg/kg/day in severe cases, maximum 60 mg/day) for 4 weeks, then gradually reduction in 2-4 weeks.
- Infants aged 0–3 months with TB should be promptly treated with the standard treatment regimen. Dose adjustments may be necessary, given the risk of toxicity in younger infants.
- Streptomycin is no longer used for the first-line TB treatment.

6.4.3. SECOND-LINE TREATMENT REGIMEN

- Children with drug-resistant TB generally have initial resistance transmitted from an index case with drug-resistant TB.
- Treatment regimen should be guided by DST results or, if not available, by the resistance profile of the index case.
- For details see RBC manual on programmatic management of DR-TB.

6.5. CONTACT INVESTIGATION

- When a child is diagnosed with TB, always look for the TB case that infected him/her. Most often it is an adult living in the same household, sometimes undiagnosed. Contact investigation should therefore be done for the whole family of children with tuberculosis at the start and end of treatment.
- If a child diagnosed with TB is attending school, contact investigation should also be done among students and teachers. It is the same for orphanages and other closed environments.
- Any child in contact with a bacteriologically confirmed pulmonary TB case should be examined since the risk of infection and progression to a severe form of the disease is high.
- Follow the algorithm for contact investigation (figure 4 in section 4.10.1).

6.6. TUBERCULOSIS PREVENTIVE TREATMENT

- TPT is indicated, after exclusion of active TB, for children at high-risk of developing TB:
    - Contacts aged 0-4 years of a bacteriologically confirmed TB case
    - Contacts aged $\geq$ 5 years: according to the instructions which will be published shortly by the TB&ORD Division.
    - HIV+ children aged $\geq$ 1 year.
    - HIV+ infants aged < 1 year: only if they are contact of a confirmed TB case.
- The most suitable TPT regimens for children are daily isoniazid for 6 months and daily RH for 3 months since dispersible tablets are available.

- INH dosage:
    - Children < 10 years or <25 kg: 10 mg/kg/day (range 7-15)
    - Children ≥ 10 years or ≥ 25 kg: 5 mg/kg/day (range 4-6)

Table 19. Dosage of INH preventive treatment in children

< 7 kg	7-11kg	12-15 kg	16-24 kg	25-39 kg
½ tablet of 100 mg	1 tablet of 100 mg	1½ tablets of 100 mg	2 tablets of 100 mg	½ tablet of 300 mg

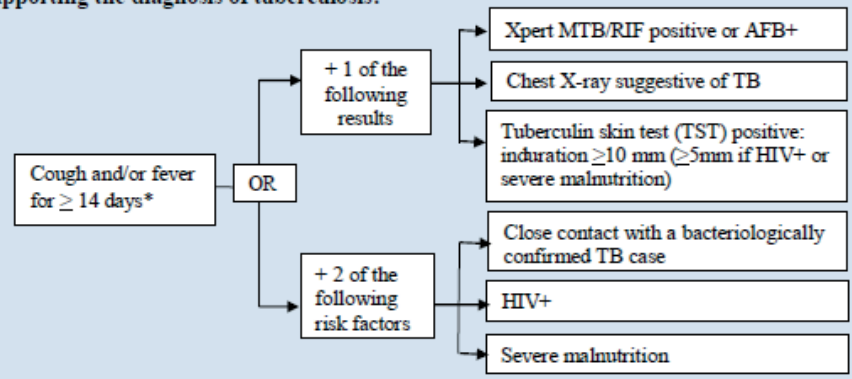
- A monthly follow-up is carried out during which the doses are given to the parents for administration at home.
- Newborn and infants whose mothers have a contagious tuberculosis should receive INH preventive therapy (after excluding active TB). The mother should continue breastfeeding the infant, wear a surgical mask when caring for the baby, and observe cough hygiene measures. After the end of the TPT, the infant should be revaccinated with BCG since the protective effect of the vaccine administered at birth may be decreased by the preventive therapy.

6.7. BCG VACCINE

- The BCG (Bacillus of Calmette and Guérin) is a live attenuated vaccine derived from *M. bovis.*
- The vaccine does not prevent infection by the *M. tuberculosis* but it protects against the most severe forms of disseminated tuberculosis, such as miliary and tuberculous meningitis, to which infants and young children are particularly susceptible. BCG therefore reduces infant mortality associated to tuberculosis.
- Vaccination by BCG is compulsory to all new-born children and is under the responsibility of the Extended Program of Immunization (EPI).
- BCG can be administered to newborns and infants exposed to HIV as long as they are asymptomatic. BCG is contra-indicated in infants who present signs and symptoms of clinical AIDS (stage 4, persistent severe malnutrition, severe septicemia, severe pneumonia, oral candidiasis after the age of one month).
- BCG should be postponed in premature babies and newborns with a weight < 2,5 kg.

TUBERCULOSIS IN CHILDREN LESS THAN 15 YEARS OF AGE

- **Think in tuberculosis if a child has:**
  - Cough ≥ 14 days, despite broad-spectrum antibiotic treatment,
  - Fever ≥ 14 days despite broad-spectrum antibiotic treatment, negative malaria smear and negative evaluation for other infectious diseases including urinary tract infection.
  - Loss of weight or failure to gain weight
  - Contact with a bacteriologically confirmed TB patient.
  - Headache and irritability, occasional vomiting (TB meningitis); painless cervical adenopathies; deformation of the spine; swelling of an articulation or a bone; etc.
- **Do the relevant investigations:**
  - Xpert MTB/RIF on sputum, CSF or other extrapulmonary specimens
  - Chest x-ray
  - HIV test
  - Tuberculosis skin test
- **Start anti-TB treatment if the child has any of the following combinations of elements supporting the diagnosis of tuberculosis:**



**despite broad spectrum antibiotic treatment, negative malaria smear and negative investigation for other infectious diseases including UTI*

- Refer children with presumptive TB if the diagnosis is doubtful.
- **For any child with TB, conduct contact investigation** in the family and school if applicable.
- **Administer TB preventive treatment, after having excluded active TB, to children at high-risk of developing TB:**
  - Contacts aged 0-4 years of a bacteriologically confirmed TB case
  - Contacts aged ≥ 5 years, according to the instructions of the TB&ORD Division.
  - HIV+ children aged ≥ 1 year.
  - HIV+ infants aged < 1 year: only if they are contact of a confirmed TB case.

Figure 8. Diagnosis and treatment in children less than 15 years old

CHAPTER 7. TB INFECTION CONTROL IN HEALTH FACILITIES

TB infection control measures aim to minimize the exposure of uninfected people, especially those who are immunocompromised, to contagious TB patients and to prevent the transmission of tuberculosis bacilli in health facilities. These measures should be prioritized in accordance with an infection control plan specific to each health facility and should prioritize services and procedures that put people at high risk of TB infection.

7.1. RISK OF TB INFECTION WITHIN HEALTH FACILITIES

- People with cough who have presumptive TB or sputum smear positive TB are the most infectious. Patients with smear negative but with a positive culture may be infectious, but with less probability compared to patients with smear positive.
- The risk of active transmission of TB infection in a particular ward within a health facility is rated as low, medium, high and very high based on the following factors:
  - the probability of exposure to suspected or bacteriologically confirmed TB cases
  - the potential number of such cases
  - the duration of exposure
  - the vulnerability of exposed people
  - the probability of generating aerosols loaded with tubercle bacilli given the procedures carried out in this service.

Table 20. Risk of TB infection according to services

Services available within the health care facilities	Low risk	Medium risk	High risk	Very high risk
Administrative areas	X	X		
Maternity and pediatrics		X	X	
Consultations (waiting rooms and clinics)		X	X	
Emergency rooms		X	X	
Intensive care and medical admission wards			X	
ARV clinic (outpatient consultations)			X	
TB service (DOT) (out patients services)			X	
TB admission wards			X	
MDR-TB ward			X	X
XDR-TB ward				X

- Low-risk services are those where the presence of TB patients is rare or the likelihood of exposure to TB bacilli is very low.
- Medium risk services are those where the presence of infectious TB patients is short duration and the likelihood of exposure is low.
- High and very high risk services and procedures are those where presumptive or confirmed TB patients may be present or are undergoing procedures very likely to emit TB bacilli. In these services, there may also be a high concentration of HIV patients, vulnerable persons (children and others), as well as MDR- or XDR-TB presumptive or confirmed TB patients.

Table 21. Risk of TB infection according to procedures

Procedures	Low risk	Medium risk	High risk	Very high risk
Direct microscopy of sputum	X	X		
Surgery on a patient neither suspected nor confirmed TB	X	X		
X-ray		X	X	
Intubation			X	
Bronchoscopy			X	
Culture, drug susceptibility test and molecular tests			X	X
Sputum collection			X	X
Sputum induction			X	X

- Microscopy examination and Xpert MTB/RIF are low risk procedures but sputum collection is a high risk procedure. Smear preparation can also generate *M. tuberculosis* aerosols if proper precautions are not respected.

7.2. INFECTION PREVENTION AND CONTROL (IPC)

TB infection prevention and control (IPC) include a combination of measures designed to minimize the risk of transmission of *M. tuberculosis* within populations. There are three types of measures, in order of priority, administrative measures, environmental measures and respiratory protection. To be efficient, these measures should be implemented as an integrated package of interventions. To this end, each health facility should conduct the following activities:

- Develop an IPC plan, proper to the health facility, which indicates areas at risk, the path of presumptive and confirmed TB cases, human resources, policies and procedures to ensure proper implementation of the IPC controls. This may require reorganization of the use of available spaces as well as renovation or construction work.

- Appoint a focal point (or a small team) responsible for the implementation of the infection control plan and create a committee responsible for the control of tuberculosis infection.
- Train healthcare workers, general staff and key stakeholders on the IPC measures defined in the plan and the signs and symptoms of presumptive TB; provide an annual refresher training.
- Monitor practices, processes and outcomes, and provide timely feedback.

7.2.1. ADMINISTRATIVE MEASURES

They are the first and most important measures to be implemented in any health facility to reduce exposure to infectious TB cases and transmission of the bacilli.

They include triage and separation of people with symptoms of TB, promoting cough hygiene, and minimizing the time spent by TB patients (presumptive or confirmed) in the health facility.

- Triage of people with cough or with TB disease should be done at the entrance to the health facility. For this purpose, a staff ("cough monitor") will ask all people who come to the health facility, whatever the reason (consultation, dressing, antenatal care, VCT, etc.) if they have cough and its duration, if they are undergoing diagnostic tests for TB or taking TB treatment. Patients with cough or with TB disease will be separated and placed in a well ventilated area, preferably outdoors. They will be informed about cough hygiene and will have priority for any service they need (registration, laboratory, etc.) to minimize the time they spend in the health facility.
- Separation of people with presumed or confirmed TB is recommended to reduce the transmission of *M. tuberculosis* to health workers or other persons attending health care facilities, especially PLHIV and other immunocompromised patients.
  - Any presumptive TB case requiring hospitalization should be hospitalized separately from other patients, especially immunocompromised patients and confirmed TB cases.
  - Hospital wards for bacteriologically confirmed TB patients should be located away from wards where there are often immunosuppressed patients (internal medicine and pediatrics). Similarly, medical emergency rooms should be designed to avoid exposure of immunocompromised patients to suspected or confirmed TB patients.
  - TB/HIV patients who require hospitalization should be admitted to a specific room or, if this is not possible, in a room with few bacteriologically confirmed patients.
  - Presumptive or confirmed MDR-TB or XDR-TB patients must be separated or isolated from other patients, including TB patients.
  - The usual hygiene rules must apply for the cleaning and disinfection of the isolation room and the equipment. Special measures for the patient's dishes and personal items are not necessary.

- Sputum collection should be done outside and away from other people.

- Education on cough hygiene covers the following good practices:
  - You should cover your mouth and nose when you cough or sneeze so that you do not spread TB or other illnesses to those around you. You can use a mask, tissue, your sleeve, bent elbow, or hand
  - Spit in a container with a cover and close it
  - Wash hands after every contact exposing to respiratory secretions
  - If you use paper tissues, dispose them after usage in a dustbin and close the cover
  - Frequently open windows in your home to let in fresh air and sunlight.
- Display posters in the most visited areas of health facilities to indicate the cough hygiene rules which should be followed by patients, staff and visitors.
- Install waste baskets with a top cover to collect contaminated material to be incinerated (tissues, sputum containers).
- Minimize time spent in the health facility by presumptive or confirmed TB cases by ensuring:
  - Prompt diagnostic investigation (smear microscopy results must be obtained within two days at most and Xpert results within 24 hours).
  - Prompt initiation of effective treatment of people diagnosed with TB.
  - Administration of TB treatment on an outpatient basis. If hospitalization is necessary, its duration should be reduced as much as possible.
- Implement surveillance of TB and HIV among health workers:
  - Health workers should screen for TB twice a year and at any time if signs of presumptive TB appear. Screening should be recorded in the TB screening register among health personnel of the health facility.
  - Any TB case among health workers should be recorded in the TB case register and reported quarterly in HMIS.
  - Health staff should be encouraged to do voluntary HIV testing. Those who test positive will benefit from the full package of prevention, treatment and care for both diseases. They will not have to care for patients with known or suspected TB and they will be transferred to a service at low risk of TB exposure.

7.2.2. ENVIRONMENTAL MEASURES

Environmental measures are designed to maximize ventilation and reduce the concentration of infectious droplet nuclei in the air. Environmental measures are the second priority for all health facilities given their lower efficiency in absence of prior administrative measures. They include the following:

- Natural ventilation should be maximized by keeping doors and windows open permanently.
- Wards dedicated to presumptive or bacteriologically confirmed TB cases should be equipped with wide windows on opposing walls. If a ward is split into other small wards, all air exchange between the different rooms must be avoided.
- Mechanical ventilation system (fans, air extractors) should be used in areas of higher risk of transmission where natural ventilation is inadequate in order to drain outside the contaminated air.
- Upper-room germicidal ultraviolet (GUV) systems can be used to disinfect the air in areas of higher risk of transmission where natural ventilation is inadequate. They need regular monitoring and maintenance to prevent side effects associated with UV overexposure (painful eye and skin irritation).
- Laboratories performing high risk procedures such as *M. tb* culture and DST should be equipped with a biosafety cabinet.
- Regular cleaning and maintenance of ventilation devices and biosafety hoods should be ensured.

7.2.3. RESPIRATORY PROTECTION

Personal protection measures are the third and last priority for any health facility. They should be used together with administrative and environmental measures in situations where the risk of transmission is high. They aim to reduce the spread of droplet nuclei from bacteriologically confirmed TB patients and to prevent inhalation of TB bacilli by uninfected persons.

- Particulate respirators should be worn by health workers and visitors for any indoor contact with a contagious MDR- or XDR-TB patient and for any very high risk procedure (bronchial endoscopy). Particulate respirators are equipped with a filter preventing inhalation of TB bacilli as long as they are properly applied on the face. Staff using particulate respirators should be trained in its proper use and a fit test should be performed periodically.
- Surgical masks should be used by patients with presumptive or confirmed TB, MDR or XDR-TB, when they are in contact, indoors, with other people or during specialized examination (CXR). Surgical masks reduce the expulsion of respiratory secretions by people with cough or sneezing but do not prevent inhalation of TB bacilli and infection.

Table 22. Basic infection control measures to be applied in all health facilities

1. The health facility has an infection control plan an IC focal point or team.
2. Health facility workers are regularly trained in TB infection control plan and measures.
3. Triage of coughing patients and TB cases is done at the entrance to the HF. They are separated in an adequately ventilated waiting area and promptly receive the service they need.
4. Bacteriologically confirmed TB patients requiring hospitalization are placed in a separate ward. Presumptive MDR-TB patients are separated from other bacteriologically confirmed TB cases.
5. Presumptive TB patients requiring hospitalization are separated from other patients and from bacteriologically confirmed TB cases.
6. Cough hygiene is reinforced during educational sessions and by posters which are displayed in all services likely to receive presumptive or confirmed TB patients.
7. Natural ventilation is optimized in all services likely to receive presumptive or confirmed TB patients (windows and doors kept open).

CHAPTER 8. BCC AND PSYCHOSOCIAL CARE FOR TB PATIENTS

The fight against tuberculosis in Rwanda faces significant challenges to achieve the targets defined in the national strategic plan in line with the global End TB strategy. Behavior change communication (BCC) is an essential component of the strategy and includes a series of activities that must be planned and carried out in all health facilities. The key message is that the best prevention of tuberculosis is the early detection and appropriate treatment of the disease.

8.1. BCC FOR THE COMMUNITY

Objectives:

- Increase general knowledge of tuberculosis, the mode of transmission and preventive measures in order to reduce new cases of tuberculosis
- Reduce the stigma linked to tuberculosis and the TB/HIV association
- Increase early detection of the disease by emphasizing the importance of seeking care if signs of tuberculosis appear
- Inform that tuberculosis is a curable disease and that anti-tuberculosis drugs are available and free in all health facilities in the country
- Promote hygiene rules that help reduce transmission of the disease.

8.2. EDUCATION AND PSYCHOSOCIAL CARE FOR TB PATIENTS

Education and psychosocial care play an important role in the treatment of tuberculosis, in particular with regard to adherence to treatment. These activities are the responsibility of the provider in charge of patients with tuberculosis (TB focal point).

8.2.1. EDUCATION

Any patient eligible for antituberculosis treatment should receive an educational session before starting treatment. Key messages should be repeated during treatment and a final interview should take place at the end of treatment.

- Objectives:
  - Encourage patient's adherence to the treatment until its end by explaining the possible consequences of the irregularity or the interruption of treatment (MDR-TB, death and other related complications).
  - Inform the patient of the possible side effects of the treatment and the action to be taken.

- Promote measures to prevent the transmission of tuberculosis.
- Insist on the importance of the contact investigation and ensure its realization.
- Encourage patients to give testimony of their cure.

- Initial interview with the patient

  - The first interview is fundamental to give the patient confidence and ensure compliance with treatment.
  - The information must be medically correct. It is recommended to use the flip chart developed by the TB&ORD Division to convey the key messages in simple terms.
  - Barriers can hinder effective communication with the patient, such as ignorance of the disease and its curability, excessive fear of TB and its association with HIV, fear of the social stigma associated with these two diseases, fear of appear ignorant when asking questions. To overcome these barriers, the nurse should adopt an empathic attitude and encourage the patient to ask the questions that concern him. It is advisable to invite a family member so that he understands the importance of supporting the patient throughout the treatment.

- Content of educational messages:

  - Tuberculosis, its transmission and prevention measures.
  - The importance of contact investigation.
  - Treatment: show the medicines corresponding to each phase, indicate the number of tablets per dose, how to take them and for how long.
  - The importance of the clinical and bacteriological monitoring to assess the response to treatment; the frequency of controls.
  - Possible side effects of medicines and the importance of reporting them promptly.
  - The need for strict compliance with treatment to cure.
  - Directly observed treatment (DOT) either by a trained community health worker or by a nurse at the health center, depending on the patient's preference.
  - The frequent association of TB and HIV infection and routine HIV testing.

- Key messages should be repeated frequently during treatment:

  - Patients must take their treatment correctly and completely.
  - People who cough or sneeze should cover their mouth and nose.
  - Do not spit on the ground but in a box or sputum container and keep it closed. Bury or burn the contents at the end of the day and disinfect the container.
  - Frequently ventilate the house where you live.
  - Take a complete and balanced diet, do not drink alcohol or do not smoke.

- Interview with the patient at the end of treatment:

  - Congratulate patients who are cured. Motivate them to give testimony of their cure and to sensitize any person with persistent cough to seek care to the health centre.
  - Advise them to consult promptly if signs of TB reappear.
  - Write the date of the end of treatment on their identification card and recommend keeping it carefully for presentation to the physician in case of recurrence of symptoms. Likewise advise them to keep any X-ray performed.

8.2.2. PSYCHOSOCIAL CARE FOR PATIENTS WITH TUBERCULOSIS

Patient education alone may not be sufficient to ensure treatment success. The health care provider should also assess:

- The psychological state of the patient in order to detect any sign of depression or anxiety disorder requiring referral of the patient to the mental health service. These signs include loss of interest or pleasure in doing things, sadness, depression, hopelessness, fatigue, lack of energy, insomnia or too much sleep, personal depreciation.

- The social conditions and the economic situation of the patient through the following questions:

  - Does the patient or caregiver have a job?
  - Is the schedule of school or job facilitating the time to take the medication?
  - How does the patient arrive to the health center? Does s/he have transport fees from home to health facility?
  - How is her/his accommodation? Does s/he access to clean water and sanitation? How many members of the family do live in the household?
  - How is the patient's accommodation? Is there access to clean water and sanitation? How many family members live in the household?
  - Does the patient have medical insurance?

- If the patient needs special support, the health provider should advocate with the community and available social services.

8.3. PREPARATION OF BCC SESSIONS

- One health education session must concern a very precise theme and must be short (fifteen minutes or less in the case of a Health Centre).

- Each session will be tailored to the target group, their knowledge and interests.

- Procure the teaching material available at the TB&ORD Division (flip chart, patient flyers, handbook for trainers and for community health workers).

- Suggestions for the formulation of messages:
  - Treat only one topic per session
  - Repeat the key message many times and surely at the end of the session
  - Use common words and sentences. Get informed beforehand about names used locally for tuberculosis.
  - Give concrete examples related to daily life.
  - Introduce patients giving testimony about their own experience.
  - Avoid interpretations and judgments on concrete cases.
  - Use a personal style and avoid indefinite terms such as “they, one must” etc.
- Evaluation of the session:
  - Ask questions at the end of the session to verify if the message is understood correctly.
  - Ultimately, analysis of behavior will make it possible to verify if the message was followed by a change in behavior.

8.4. PLANNING OF BCC SESSIONS AND FOLLOW UP OF THEIR EXECUTION

- Each health facility should elaborate a calendar of BCC talks including tuberculosis and indicating the dates of the talks, the name of the responsible staff, the duration and the subject, the targeted public and the location.
- An BCC register will be kept up to date and indicate the subject, the responsible of the talk, the location and the number of participants.
- BCC talks must be done in all services within the health facility and in the community, schools, military camps, prisons, etc.

3D PART. PROGRAM MANAGEMENT

CHAPTER 9. TB SURVEILLANCE, SUPERVISION, MONITORING AND EVALUATION

To assess the achievement of tuberculosis control objectives and adjust practical approaches if necessary, it is essential to have an adequate, reliable and simple disease surveillance system in place. Supervision at all levels of health services, as well as monitoring and evaluation, have the role of ensuring the proper use of the resources allocated to the program, the timely execution of activities and the achievement of expected results.

9.1. TB SURVEILLANCE

A good surveillance system involves: data collection, management, analysis, interpretation, reporting, dissemination, and use for appropriate decision making. This process must be applied at each level of the health system, from the peripheral to the central level, and scrupulously respected. It must also be verifiable at all times, in particular during various controls by evaluators and users.

9.1.1. TB DATA COLLECTION

The collection of individual data is done on a routine basis and through special surveys. Health facilities collect routine TB data in two ways, using printed tools and the electronic TB case-based surveillance system.

Printed tools

- They include registers, forms and patient cards (see table 23 and annexes 1 to 5).
- They contain detailed information on presumptive and diagnosed TB cases, people enrolled on tuberculosis preventive treatment (TPT), diagnostic tests, infection control, and management of pharmaceutical products.
- For details on how to fill out these tools, see the TB&ORD Division Procedures Manual.

Table 23. Printed tools used for collecting TB data in Rwanda.

Topic	Data	Tools
Detection and diagnosis	1. Presumptive TB cases by level (CHW, CT, CDT) and HIV status. 2. Diagnostic techniques (microscopy, Xpert, culture). 3. Culture and Xpert results. 4. Detection of TB in high-risk groups.	1. Laboratory request form 2. Laboratory register 3. OPD register, 4. ARV register 5. Medical dossier

		6. TB screening register at entry in prison 7. IMCI register
Notification of TB cases	1. TB cases by sex, age categories, HIV status, case definition. 2. Cascade TB/HIV: HIV status, CTX and ARV among co-infected.	1. Laboratory register. 2. TB case register.
Treatment outcomes	1. Final treatment outcome of drug-susceptible TB by sex, all ages, children 0-14, case category, HIV status, and for patients under community DOT. 2. Interim results of MDR-TB cases 3. Final treatment outcome of MDR-TB cases by regimen, sex and HIV status.	1. TB case register 2. TB treatment card 3. MDR-TB case register 4. MDR-TB treatment card
TB preventive treatment (TPT)	1. Enrolment on TPT by sex, age (under-5 or ≥ 5), TB contact, HIV status, others risk factors 2. TPT outcomes	1. TPT register for PLHIV 2. TPT register for TB contacts
Infection control (IC)	1. Implementation of the basic IC measures package 2. Triage of people with cough in HF 3. Screening of TB among HCW and CHW.	1. Register of triage 2. TB screening register 3. Evaluation grid of basic IC measures package 4. Register of TB screening in HCW and CHW.
Management of pharmaceutical products	1. Availability of drugs, reagents and consumables 2. Number of days out of stock of drugs, reagents and consumables.	1. Stock cards 2. *Reports and orders through e-LMIS*

The electronic TB case-based surveillance system (e-TB):

- Is used to register, for any TB case, all information relating to TB notification, initiation, follow-up and termination of TB treatment.
- It contains 7 stages that are completed in real time, once the TB case is notified and at every time the information is available to be filled in different stages. These stages are related to: 1) baseline information, 2) treatment initiation, 3) drug susceptibility testing, 4) bacteriological follow-up, 5) contact investigation, 6) monitoring adverse events and 7) treatment outcome.
- The e-TB system is completed by the TB focal person of the health facility that received the patient as presumptive TB, whether it is a CDT or a CT.
- It is completed by using information from the TB treatment card, the TB laboratory register and the TB case register.
- For details on data sources and how to fill out the stages in the e-TB, see the TB&ORD Division Procedures Manual.

9.1.2. TB DATA MANAGEMENT AND REPORTING

Quarterly and annual reports on tuberculosis are produced based on the data collection tools identified in the previous section, while using the standard reporting form provided by the TB&ORD division.

The quarterly reporting form is filled out in two ways:

- The aggregated tables related to TB notification and treatment outcomes are generated automatically from the e-TB system.
- The other tables, on presumptive TB, lab tests and other data, are produced manually by aggregating the data as follows:
  - The data manager distributes the sections (tables) of the reporting format to the various service managers for filling. The various completed sections are compiled by the data manager before being validated in collaboration with the TB focal point of the CDT or CT.
  - Once validated the report is entered into the HMIS electronic system by the data manager within the first five days of the month following the reported quarter.

Data entered by the health facilities in the quarterly report and in the e-TB system are controlled and validated during the quarterly TB evaluation meetings by HF staff in collaboration with central level staff (TB & ORD Division) under the coordination of the district hospital.

For details on data sources and how to fill out the report tables, see the TB&ORD Division Procedures Manual.

9.1.3. TRANSFERRED CASES

When a patient is transferred from the health facility where s/he was registered to another health facility to continue treatment, it is essential to respect the following rules so as not to count the same patient twice in the e-TB system and in the reports:

- Transferred patients are registered by the heath facility that received them as TB presumptive case.
- The patient is transferred with the original treatment card and is also electronically transferred through the e-TB system. The transferring health facility keeps a copy of the treatment card.
- The health facility to which the patient has been transferred will complete in the e-TB register the new information collected at the various stages until the end of the treatment stage. To this end, they should not register again the patient but search for him/her in the system.

- Treatment outcome of a transferred patient is evaluated in the cohort of the health facility that registered the patient and not in the health facility where s/he completed treatment.
- If the patient has not physically arrived at the destination health facility, s/he will be classified as "lost to follow-up" or if the treatment outcome is not known, as "not evaluated". Both results have a negative effect on the treatment success rate of the health facility of registration.
- Recording the transfer in the TB case register is as follows:
  - The transferring HF indicates in the observation column: Transfer out to … (the name of the destination HF and date of transfer).
  - The receiving HF records the transferred patient in the TB case register with a new order number and add it on the patient treatment card. The name of the transferring HF is indicated in the observation column of the TB register: Transfer in from ….

9.1.4. TB DATA ANALYSIS

The analysis of surveillance data in Rwanda makes it possible to measure the achievement of the objectives set in the TB strategic plan as well as the performance of the program. The analysis should also assess the trend of these indicators over time, places and identified key groups and produce trend figures.

Main analyzes to be carried out for the surveillance of Tuberculosis

- Tuberculosis case registration: evaluate the trend of TB cases by comparing it with the cases recorded in the previous four quarters if it is the quarterly report or in previous years if it is the annual report; calculate the percentages by case categories, age groups and male/female ratio.
- HIV testing among TB cases: calculate the proportion of TB cases tested for HIV, the proportion of HIV + cases among those tested, the proportions of co-infected TB/HIV cases on cotrimoxazole prophylaxis and on ARVs.
- HIV testing among presumptive TB cases: calculate the proportion of presumptive TB cases tested for HIV and the proportion of HIV + among those tested.
- Detection of TB among people at risk: assess the proportion of TB cases among different high-risk groups.
- TB treatment outcomes: assess the therapeutic success of the cohort of cases recorded the previous year by different categories of cases and the percentage of TB/HIV co-infected cases who received ARVs during TB treatment.
- Presumption process for MDR-TB:

- Calculate the proportion of new cases and retreatment cases with a drug sensitivity test result by Xpert or LPA.
- Calculate the proportion of the results available in relation to the samples sent for culture.

9.2. SUPERVISION / MENTORSHIP

Supervision is a systematic and permanent process, aimed at improving the performance of the health personnel by developing their knowledge, by improving their skills and by increasing their motivation.

- Mentorship, also called "Rapid Service Quality Assessment (RSQA)" or formative supervision, is carried out using a standard template. It focuses on tuberculosis control activities, namely: tuberculosis infection control measures, screening, diagnosis, overall management of tuberculosis, as well as management of tuberculosis at different levels of the health system.

  Supervision/mentorship ensures that TB control activities are carried out correctly, in concordance with current guidelines and procedures. If necessary, additional training is provided (mentorship). Supervision/mentorship of TB control activities is carried out at the 3 levels of the health services:

  - From the central level (TB & ORD Division, LNR), to the intermediate level (DH and selected HCs), once per semester.
  - From the intermediate level (DH), to the peripheral level, at least once per quarter per health center (HC).
  - From the peripheral level (HC), to the community (CHW who give DOT), monthly.

- Data Quality Audit (DQA)

  DQA is the confirmation of the accuracy, completeness, reliability and timeliness of data. This is done by verifying and comparing data between different sources of information to ensure data reliability and improve data quality.

  DQA is carried out at two levels, namely:
  - From the central level (TB & ORD Division, LNR, etc.) to the intermediate level (HD), once per semester.
  - From the intermediate level (HD) to the peripheral level (HC), at least once a quarter.

- For details on performing mentorship/RSQA and DQA, see the TB&ORD Division Procedures Manual.

9.3. MONITORING

Monitoring consists of making sure that activities are carried out in accordance with the action plan. It allows quick identification of problems and appropriate solutions. It is carried out through observation during supervision visits and indirectly by analyzing reports.

Health facilities are encouraged to monitor TB control activities, especially those to be strengthened to achieve program objectives. This can be done as follows (non-exhaustive list):

- Compare the laboratory register with the TB case register and check if all diagnosed cases are registered and have started treatment. Take necessary measures to trace those who are not registered.
- Review treatment cards and identify irregular patients. If not yet done, take necessary measures to recuperate them.
- Check whether all bacteriological controls and treatment results are up to date in the TB case register and in the e-TB system.
- Check whether Xpert MTB/RIF and culture were done according to the norms.
- Identify transferred out cases for which treatment result must be looked for.
- Check whether all information related to TB cases is up to date in the e-TB system.
- Follow up of TB infection control measures (check register of coughing patients triage, check ventilation).
- Check execution of the BCC calendar and planned activities.

9.4. EVALUATION

Evaluation is a periodical analysis of results achieved compare to objectives. It involves analysis of indicators and is carried out at sufficiently long intervals in order to measure results. For more information on program indicators and targets, see the TB-NSP monitoring and evaluation plan.

Evaluation activities include:

- Quarterly evaluation and data validation meetings organized by the district hospitals and the central level with participation of all health facilities within the hospital's coverage area. (see the TB&ORD Division procedures manual).
- The annual assessment of TB activities with various stakeholders involved in TB control
- External assessments of program components (MDR-TB, drug management, TB surveillance)
- Mid-term and/or final evaluation of the NSP and the Global Fund project.
- Periodic surveys aim at measuring the impact of TB control activities, such as the national TB prevalence survey that was conducted in 2012 and the national drug-resistance TB surveys conducted in 2007 and 2015/2016.

CHAPTER 10. MANAGEMENT OF ANTI-TUBERCULOSIS PRODUCTS

The DOTS strategy includes treatment with multidrug therapy and the uninterrupted supply of anti-tuberculosis drugs, reagents and laboratory materials, as well as the provision of information materials.

10.1. PARTICULARITIES OF THE MANAGEMENT OF ANTI-TUBERCULOSIS DRUGS

Special rules have been established for the management of anti-tuberculosis drugs in order to avoid the emergence of resistance. This is particularly important given the limited number of drugs available to treat tuberculosis, including multidrug-resistant tuberculosis. These rules include:

- The use of specific standardized treatment protocols depending on the case category.
- The use of fixed-dose combinations of drugs (FDC) to prevent patients from selecting certain molecules and taking monotherapy.
- The quantification of needs based on the number of cases recorded during a determined period, the quantity available at the end of the period considered and the delivery of complete cures in order to guarantee each patient who begins a treatment that s/he will receive all necessary medicines until the end of treatment.
- Free treatment in order to avoid discontinuation that would be linked to the cost of treatment.
- The non-commercialization of anti-TB drugs which are reserved exclusively for the treatment of tuberculosis, in order to avoid their irrational use for other pathologies.
- The administration of the treatment under direct observation (DOT) by a health care provider or community health worker to ensure that the patient is actually taking all the drugs prescribed, at the correct dose and for the duration necessary.

10.2. MANAGEMENT TOOLS FOR TB PRODUCTS

- Controlling the use of anti-tuberculosis drugs must be very rigorous and requires the use of management tools designed for the different operations.

Operation	Management tool
Report and product order	e-LMIS
Product delivery	Product delivery form
Stockage and inventory	Stock card by product
Supervision	Integrated supervision grid

10.3. QUANTIFICATION OF TB DRUGS AND LABORATORY SUPPLIES

- Quantification of needs for anti-tuberculosis drugs is based on the number of cases registered during the previous quarter and takes into account the stock available at the time of the order, the average cure and the number of patients per treatment regimen.
- The need = No of cases x average cure + buffer stock* - current amount in stock.

  ** 25 % for the district pharmacy and for the CDT*
- The average cure is the average number of tablets required for a complete treatment.
- Quarterly needs in sputum containers, slides and reagents are estimated based on the number of sputum examinations done during the previous quarter.
- An adequate quantification is essential to avoid stock outs which can lead to the interruption of treatments.

10.4. RULES FOR ORDERING TB PRODUCTS

- Drug orders are made at the beginning of each quarter, after having completed the quarterly report on TB case registration.
- However, to address potential stock outs, emergency orders are accepted.
- Requests are made via the electronic logistics management information system for health products (e-LMIS).
- Any order of drugs and laboratory products from the health facilities must be validated by the district pharmacy manager and that of the districts by the TB&ORD Division.

10.5. RULES FOR STOCKING TB DRUGS

- Medicines must be arranged on shelves according to the family of medicines(anti-TB), pharmaceutical form (tablets, syrups, injectables) and alphabetical order in order to facilitate their identification.
- Laboratory equipment and consumables must be grouped by category (injection equipment, sputum containers, slides, reagents, etc.).
- Each anti-TB drug must be identified with a label specifying the name of the product, the form and the dosage.
- Always put expiring products in front in order to use them first. This storage makes it possible to quickly identify drugs at risk of being out of stock or currently out of stock.

- Apply the same rules for the pharmacy cupboard (distribution stock).

10.6. STOCK CARD

- It is used to identify and record for a given product all the input and output quantities, and to calculate the number of months of theoretical stock available. It indicates the lot number and the expiration date.
- A stock card must exist for every product (drugs, reagents and materials). Different presentations or dosages of the same product will each be subject to an individual card.
- The "in use" stock cards are placed with the corresponding drugs.
- When entering the quantities of the product with different batches on the stock card, all the batch numbers must be entered on the stock card while respecting the principle of first expiry, first outgoing.
- The full stock cards are archived and new ones are opened for each of the drugs in stock.
- To ensure the traceability of TB products within the health facility, drug stock cards must be available at the dispensing level (One stop TB-HIV Service) and laboratory product stock cards must be available at the laboratory. They must be filled in regularly.

10.7. MONTHLY INVENTORY

- At the end of each month, the staff responsible for the anti-TB drug stock must count the physical stock and check whether the quantities counted are equal to the quantities reported on the stock cards. This should also be done by the person responsible for dispensing anti-TB drugs and by the head of the laboratory service.
- The differences must be explained and the stock cards must be corrected.
  - A counted quantity greater than the quantity indicated on the form may be due to a calculation error, an unregistered delivery or return.
  - A counted quantity lower than the quantity indicated on the card may be due to a calculation error, breakage, expired, theft, transcription error.
- All HCs must report in the e-LMIS the quantities in stock at the end of the quarter.

10.8. REPORT AND REQUISITION

- The report and requisitions are made via the e-LMIS; paper forms are no longer used.
- The e-LMIS indicates the needs based on the consumption recorded in the system. However, the quantities to order must be adjusted according to the number of TB cases recorded during the previous quarter and are calculated on an excel file.

- All data on products' consumption, quantities received, stocks available, expiration must be kept up to date in the e-LMIS. In particular, all HCs should introduce in the system the amounts consumed, preferably daily, or at least once a week.

10.9. AVAILABILITY OF DRUGS AT PERIPHERAL LEVEL

To avoid the risk of expiration, the TB & ORD Division recommends the following:

- District pharmacies and CDT-hospitals must have medicines for adults and children in stock even if there is no tuberculosis case.
- CDT-health centers must have the drugs for adults at all times, even if there are no tuberculosis patients. Pediatric drugs are ordered on a case-by-case basis at the district pharmacy, which must deliver them to the CDT as quickly as possible within 24 hours.
- CTs do not have a stock of anti-TB drugs and order them on a case-by-case basis at the district pharmacy which must deliver them as quickly as possible within 24 hours.
- Second-line drugs are delivered on a case-by-case basis for periods of 3 months because they have a short shelf life. Excess drugs at the end of treatment should be returned to the TB unit.

10.10. MANAGING EXPIRED PRODUCTS

Monthly inventory allows identification of expired products or close to expiration (products that will expire within 6 months).

- Expired products will be removed from stock (indicate on the stock card the quantity removed and "expired" in the observation column).
- Indicate on the boxes in a very legible way (with a marker) "expired" in large characters. Store them apart from other medications while awaiting incineration arranged by the District Pharmacy and / or RMS.
- Fill the medication return format and return excess stocks and expiring drugs to the district pharmacy and/or RMS so that they can be redistributed to services with a high number of cases. On the stock card, indicate the date, the recipient of the return, the exact quantity returned and in the observation "Return".
- Expired products or returned excess products must be accompanied by the delivery form indicating the batch number corresponding to these drugs.

4TH PART. LABORATORY

1. INTRODUCTION

- Sputum smear microscopy examination is a simple, fast and reliable method to diagnose tuberculosis. The principle is based on detection of acid-fast bacilli (AFB) after staining with Ziehl-Neelsen or fluorescent dye (auramine O) and decolorisation with alcohol-acid solution. Light Emitting Diode Fluorescence microscopy (LED-FM) is used in all CDT in Rwanda (hospitals and health centers) because this technique has both better sensitivity and speed of reading than conventional Ziehl-Neelsen microscopy. There is one TB microscopy laboratory (CDT) per 50,000 to 100,000 inhabitants on average. Health centers not designated as CDTs are sputum collection units and tuberculosis treatment centers (CTs). They collect sputum, prepare the smears and send them to the nearest CDT for staining and reading.
- The Xpert MTB/RIF test, a molecular amplification technique (polymerase chain reaction, PCR) allowing the rapid and simultaneous detection of mycobacteria and resistance to rifampicin within a few hours, is currently available in all district hospitals and some health centers.
- The culture of mycobacteria on solid or liquid media and drug susceptibility testing (DST) are essential techniques for the diagnosis and monitoring of drug resistance. These techniques are currently carried out at NRL and in the university teaching hospitals (CHUs).
- Other techniques including the mycobacteria identification test and rapid tests detecting the resistance to isoniazid and rifampicin (first-line LPA) which) and to fluoroquinolones and injectables (second-line LPA) are also carried out at NRL and CHUs.
- A targeted deep sequencing is being implemented at NRL as a high-performing drug-resistance TB diagnostic.
- The lateral flow urine lipoarabinomannan assay (LF-LAM) can help in diagnosing TB in HIV-infected patients with advanced disease.

2. BIOSAFETY INSTRUCTIONS FOR TECHNICIANS IN TB LABORATORY

The laboratory technician is responsible for his own safety, that of their colleagues and the environment. Tuberculosis is a contagious disease and the degree of infectiousness of patients is directly related to the quantity of bacilli in the sputum. A richly sputum can contain more than 10 million AFB per ml. Creation of infectious aerosols can be done by the following actions:

- When the patient spits
- When opening the sputum container
- When preparing smears
- During sterilizing of the wire loop to the flame

Laboratory technicians/technologists must take a number of precautions:

- Collect sputum outdoors and stay behind the patient while s/he spits.
- Ensure adequate and frequent ventilation in the laboratory.
- Put the sputum containers on the metal tray reserved for this purpose.
- Disinfect the tray and the work surface with 10% Dettol[6] or 10% bleach.
- Do not place the wire loop directly on the table or the bench; after flaming the wire head, put it on a support.
- Do not leave sputum containers and other contaminated material within the reach of the public who could recover them for use for other purposes. Disinfect and remove them correctly (see paragraph 4.8).
- If a sputum container is accidentally spilled, disinfect the place, preferably with Dettol or bleach solution (see SOP for spills management).
- Wash hands carefully when entering or leaving the laboratory and after handling sputum.
- Always wear personnel protective equipment in the laboratory.
- DO NOT EAT, DRINK OR SMOKE IN THE LABORATORY
- DO NOT SUCK YOUR PEN OR PENCIL

3. COLLECTION OF SPUTUM SPECIMENS

- To increase the chance of finding AFB, purulent or mucopurulent sputum specimen from the deepest part of the respiratory system should be collected.
- To reduce the risk of infection by TB bacilli, sputum specimen should be collected outdoors and away from other people.
- For the diagnosis: 1 sputum sample will be tested with Xpert MTB/RIF as an initial test for eligible patients. For the others, 2 sputum samples must be taken in 2 consecutive days and will be examined by LED fluorescence microscopy. A single positive result is sufficient to conclude that a patient has smear positive pulmonary tuberculosis.

[6] *Dettol is a phenol composite.*

- For treatment follow-up: 1 sample is sufficient, taken in the morning upon waking. It is examined under fluorescence microscopy.
- All positive sputum specimens at the end of the intensive phase (2nd month) or later will be processed by culture and drug susceptibility will be tested.

Collection of sputum (procedure):

- Put the patient at ease by explaining the reason for the examination.
- Write the name of the patient and the sample number (1st or 2nd) on the wall of the sputum container (not on the lid).
- Explain and demonstrate to the patient:
  - How to open and close the container;
  - How to hold it close to the mouth and expectorate in it
  - How to breathe deeply, cough vigorously, and expectorate the material produced into the sputum container
- Give the sputum container to the patient and accompany him outdoor to collect the sample.
- Check if the volume is sufficient (at least 3 ml), and whether it contains mucopurulent particles. If not, encourage the patient to cough again until the result is satisfactory.
- Close and tighten the sputum container, then wash your hands.
- If the patient cannot spit, consider the sputum container as having served and destroy it.

What if the patient cannot spit?

- First, explain what is expected from the patient.
- Then ask the patient to breathe deeply several times, then to exhale deeply. Usually, patients with lung disease avoid deep breathing, as this triggers coughing.
- If the patient's condition allows, we can also ask him to do some exercises, such as getting up and down fast enough many times, or run slowly around the health center for example. You must explain to the patient to spit in the sputum container if cough occurs during exercise.
- When the patient is too weak, let him lying on his stomach for 10 minutes, the body inclined at 30-40o with the head down so as to facilitate the drainage of secretions.
- If it is not possible to obtain a good sputum sample, gastric tubage may be done to aspirate the secretions that the patient has unconsciously swallowed while sleeping. This is done in the hospital in the morning, on an empty stomach.
- Bronchoalveolar lavage may also be helpful.

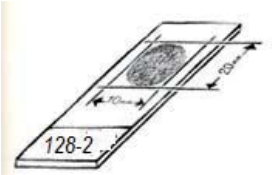
Very important points:

- Real purulent sputum is the key for TB diagnosis. It is better to spend 10 minutes collecting good quality sputum than a half hour to look for AFB on a salivary smear.
- All sputum specimens must be examined as they are likely to yield a positive result, even if they are salivary.

4. FLUORESCENCE MICROSCOPY

4.1. SLIDE IDENTIFICATION

- Always use new slides
- Write on the left edge of the slide, upper side (same side as the smear), the following information with a diamond pencil:
    - Patient's order number in the lab register
    - Number of the sputum sample (1 or 2).

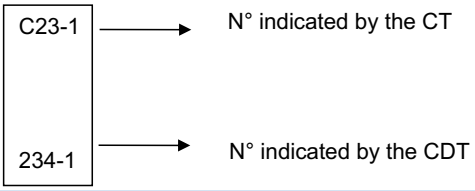


Example:

128 identifies the patient's number in the laboratory register

2 indicates that it is the 2nd sample produced

- If it is a control, indicate C2, C5 or C6 after the order number.
  Example: 128/C2, means that this is the patient whose order number in the register is 128 and that this is the control at the end of the 2nd month.
- For slides received from CT:



4.2. SMEAR PREPARATION

In order to increase the probability of finding AFB, the smear should be prepared from purulent particles of the sputum.

- Open the sputum container carefully to avoid aerosols.
- Pass the wire loop to the flame and let it cool for a few seconds. Do not use the wire loop still reddened by fire, as this may damage AFB and their staining quality.
- Pick a portion on the purulent part of the sputum and put it in the centre of the slide
- Make a smear approximately 20 mm long by 10 mm wide, carefully spreading the portion in the center of the slide.

4.3. SMEAR STAINING BY AURAMINE O FLUORESCENCE TECHNIQUE

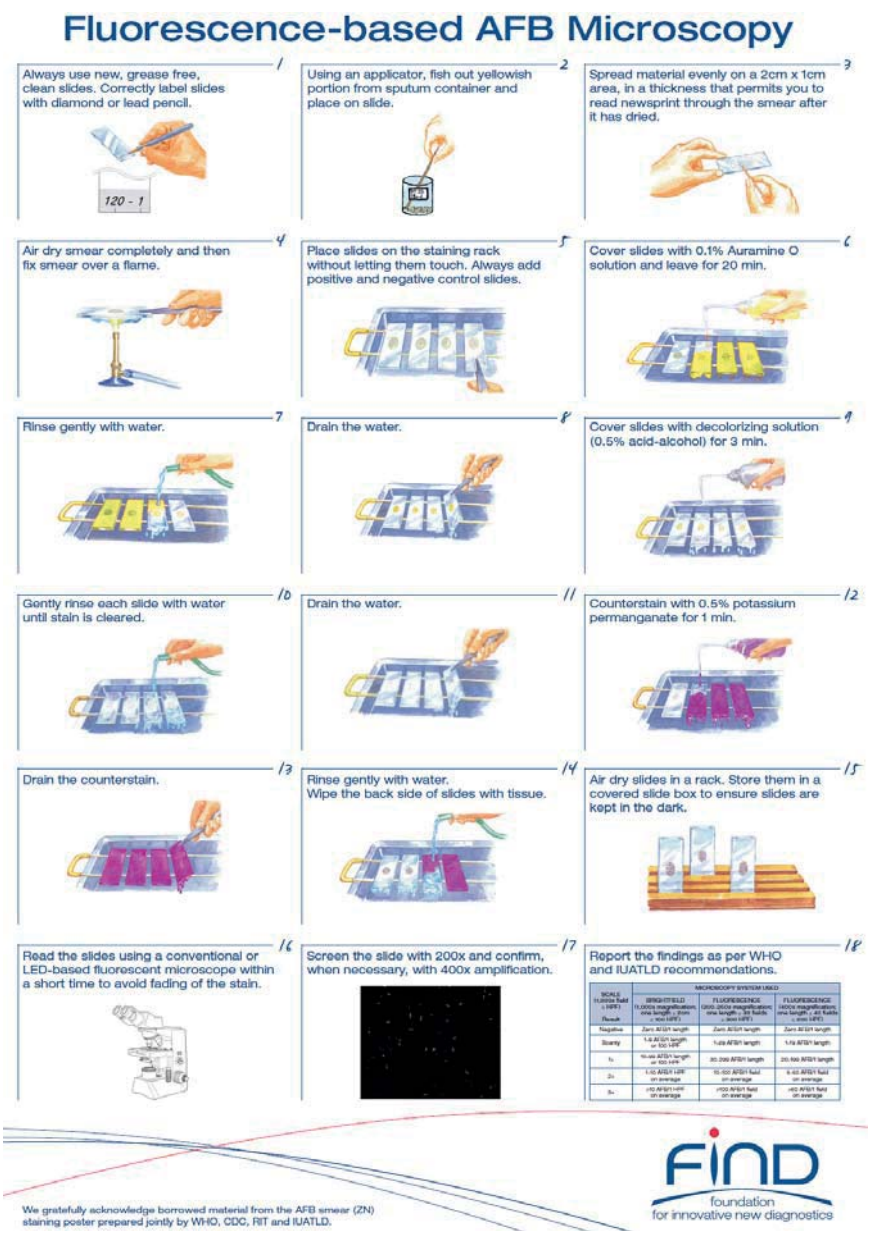


Figure 9. Staining auramine method

4.4. INTERNAL QUALITY CONTROL FOR REAGENTS AND FOR STAINING TECHNIQUE

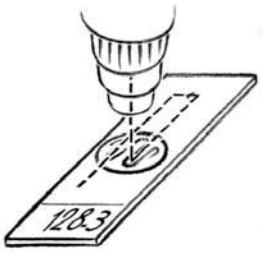
- Quality control should be performed upon receipt of reagents and with each set of slides to be stained. This is done by including control slides.
- Control slides' preparation: periodically prepare and fix twenty smears from sputum which you have identified as positive or negative. Identify the slides and store them separately (one smear positive box and one smear negative box) protected from light.
- Systematically add in each staining set one control positive slide and one control negative slide and read them before the others. If you obtain the expected results, it means the technique and the quality of reagents is acceptable and the microscope is in good condition.
- All reagents must be stored away from light, the reagents used for fluorescence technique are deteriorated by light
- All reagents should be used before the expiration date specified by the manufacture.

4.5. SLIDE READING

- After complete drying, the smear should be read on the same day because weakly stained bacilli lose the stain and may not be found.
- Focus and smear screening is done with the 20x to 25x objective. A more powerful objective (x40) is used to confirm typical morphological characteristics of the bacillus.

Smear examination technique

- The reading is done on perfectly dry smears. If the staining is done correctly, the AFB will appear bright yellow green (fluorescent) on a black background.
- Examination of the smear should be systematic and standardized in the following manner:



- Begin with the left edge of the smear and read one line moving the smear to the right;
- Then adjust to the front and read another line from right to left;
- When necessary, read a 3rd line from left to right.

- It takes about 2 minutes to read a 20 mm smear line (approximately 30 microscopic fields).
- When the smear is negative, take sufficient time and read at least 90 fields on fluorescence before concluding that the smear is negative. Indeed, a false negative

result means that a contagious patient continues to spread the infection in the community and the patient may die.

- Read the smears according to their order number and record the result for each smear immediately after examining it.
- After completing the reading session, protect the microscope from dust by keeping it in a box or by covering it.
- Keep all slides in a box for smear rechecking.

4.6. GRADING OF POSITIVE SMEAR

The number of bacilli observed during smear examination provides important information, as it reflects the degree of infectiousness of the patient and the severity of the disease. It also reports on the favorable evolution during treatment when the number of AFB observed decreases.

Table 24. Grading scale of LED-FM smears

Number of AFB seen	**Report value**
Fluorescence 400 – 450 x 60 fields	***WHO***
Zero AFB / 3 lengths	Negative
1-19 AFB / 1 length	Actual count
20 – 199 AFB / 1 length	1+
5 – 50 AFB / field	2+
> 50 AFB / field	3+

4.7. RECORDING AND REPORTING OF RESULTS

- Record the results on the laboratory request form and laboratory register (including results of internal quality control).
- Record the positive results in red pen.
- The appearance of sputum is important information to be reported. A negative result from salivary specimen indicates that the result is unreliable and it is better to repeat the examination.
- In the laboratory register:
  - Use one line per patient to record information from the laboratory request form and the results obtained
  - The address is absolutely necessary information in order to be able to locate positive patients who do not come for their results
  - Indicate whether it is a diagnostic examination or a follow up (control) and in this case, indicate the month of treatment.

- Any presumptive TB with at least one positive smear (with 1 AFB or more) is a smear-positive pulmonary tuberculosis case; immediately report the smear positive result to the responsible clinician.
- If a patient with presumptive TB is positive and does not come for his result, inform the TB focal point in order to immediately search for the respective patient.

4.8. ELIMINATION OF SPUTUM CONTAINERS AND OTHER CONTAMINATED MATERIAL

- After recording the results of smears, verify if the specimen is eligible for further testing (culture or Xpert MTB/RIF test) in which case it cannot be discarded.
- Collect used sputum containers in a bin for contaminated materials. The bin must be equipped with a lid and it must be kept closed.
- According to different possibilities, eliminate sputum containers as follows:
  - Bury them (first put bleach and close the sputum containers)
  - Sterilize them in an autoclave (do not disinfect them with bleach)
  - Incinerate them (do not disinfect them with bleach as the vapors are toxic).

5. QUALITY CONTROL FOR TB MICROSCOPY (SLIDE RECHECKING)

Slide rechecking is an essential component of any TB program in order to guarantee the quality and reliability of tests as well as the credibility of laboratories. Slide rechecking aims to quickly detect laboratories with problems in order to correct them.

5.1. GUIDELINES

- CDT must keep all smears in boxes by ordering them according to their number in the laboratory register.
- District hospitals are responsible for collecting and controlling slide samples from their respective CDTs. The NRL collects and controls slide samples from hospitals.
- The sample should not be selected by the laboratory technician of the controlled laboratory.
- The TB&ORD Division and the NRL define the sample size to be collected quarterly in each CDT using the stratified method. The sample to be checked quarterly consists of 8 follow-up slides and 7 diagnostic slides. For details refer to the NRL standard operating procedures on “the Quality Control for TB Microscopy Slides Re-testing”.
- All smears identified with discrepancy results by the DH first controller should be sent to the NRL for the second control. Discordant smears waiting to be sent at NRL should be kept in dark area to minimize fading due to heat and moisture.

5.2. ESSENTIAL PRINCIPLES FOR SMEAR RE-READING

- The controller must be a different person from the one who collected the smear.
- The controller must examine the smears blindly. He cannot know the results of the peripheral laboratory he is controlling.
- The controller must re-stain all smears before reading them; staining is fading quickly and a slide seen positive at the CDT may then appear negative by the controller.
- All discordant smears identified by the first controllers must be checked by a second NRL controller. NRL will give the final result and corrective action.
- The district hospital cannot give a discordant result because it must always be validated by the NRL.

5.3. CLASSIFICATION OF ERRORS

- Errors are classified as major and minor. Major errors represent a potential problem that requires investigation and subsequent intervention to improve performance. Minor errors are probably random, unless they are repetitive.
- It is expected to find 5 to 10% of errors in rechecking. Otherwise the quality of rechecking might not be reliable.

Table 25. Classification of errors from results of slide rechecking

Error classification			CDT	LNR
MAJOR	High false positive	HFP	1+,2+ or 3+	Negative
	High false negative	HFN	Negative	1+,2+ or 3+
MINOR	Low false positive	LFP	1 - 9 AFB per 100 fields	Negative
	Low false negative	LFN	Negative	1 - 9 AFB per 100 fields
	Quantification error	QE	1+	3+
			3+	1+
			1 - 9 AFB per 100 fields	2+ or 3+
			2+ or 3+	1 - 9 AFB per 100 fields

- Laboratories with poor performances (more than 1 HFP or 1 HFN or several LFP or LFN) should be supervised by a TB microscopy expert from NRL for problem investigation and to provide corrective measures.

False positive possible causes	False negative possible causes
- Re-use of slides - Slide contamination (by the loop, too many slides stained together, uncleaned objective) - Incorrect identification and recording of the smears (discordance between the rechecking form and the TB lab register) - AFB have faded since original report (no re-staining)	- Spreading of saliva instead of muco-purulent sputum - Incorrect smear (too thin or too thick) - Staining problem (pale AFB, insufficient contrast background, insufficient staining time) - Insufficient time spent in reading smear - Incorrect identification and recording of the smears - Defective microscope.

6. CULTURE AND DRUG SUSCEPTIBILITY TEST

- Indications: see section 3.2.1.3
- Samples for culture and drug susceptibility testing must be fresh.

Table 26. Procedures for sending samples to culture and DST laboratories

	Can the sample reach the LNR or CHUs laboratory within 48 hours of sputum collection?	
	YES	**NO**
Specimen preservation	- In a 50-ml conic tube without CPC - In the fridge (4 to 8 degrees C)	- In a 50-ml conic tube containing equal volume of CPC-NaCl* - At room temperature, not refrigerated
Transportation to the culture	- In a cool box at 4°C - Same day of collection up	- At room temperature, - Box without cold ice
laboratory	to 48 hours	- Within 7 days

*CPC (cetyl pyrimidine chloride) is a transport medium that helps maintain the viability of bacilli for 6-7 days

- Culture results are reported as follows:

0	No growth reported
(1-9)	< 10 colonies (report the number of colonies)
+	10-100 colonies
++	> 100 colonies
+++	Innumerable or confluent growth
C	contaminated

7. XPERT MTB/RIF TEST

- The Xpert MTB/RIF assay is the first of a new generation of molecular tests that integrates sample processing, amplification, and detection in a closed, single-use cartridge, thereby minimizing DNA contamination risk and biosafety requirements.
- In Rwanda, Xpert MTB/RIF test has been implemented in all hospitals and some health centers in order to increase TB cases detection and early identification of rifampicin resistant patients. Currently it cannot be performed for all people with presumptive TB, but only for high-risk patients and those for whom microscopy has low sensitivity (children, PLHIV, extrapulmonary samples). See categories of patients eligible in section 3.2.1.1.
- Types of samples that can be tested with Xpert MTB/RIF: sputum and extra pulmonary fluids/tissues except blood or a sample mixed with blood.

7.1. XPERT MTB/RIF TEST PROCEDURE

- Label each Xpert MTB/RIF cartridge with the sample identification (write on the side of the cartridge or affix a label). Do not put the label on the lid of the cartridge; do not hide the cartridge barcode.
- Add 2:1 of Xpert MTB/RIF reagent to sputum specimen.
- Shake vigorously 20 times then stand for 10 minutes. After 10 min, shake 20 times then stand for 5 min.
- Use the sterile pipette provided with the cartridge kit to aspirate the liquefied sample to above the minimum mark.
- Transfer the sample to the cartridge and make sure that the transferred liquid does not contain air bubbles, as this can cause errors.
- Double-click on the Xpert MTB/RIF® Dx shortcut located on the computer desktop, log into the software using your username and password.
- In the Xpert MTB/RIF® Dx software toolbar, click on the create test icon.
- Depending on your lab protocols scan the patient barcode then the cartridge barcode and the system fills the other boxes automatically i.e. select assay, reagent lot I.D, cartridge serial number (SN) and expiration date.
- If your lab does not identify patients' using barcodes, then proceed to enter their patient identification manually.
- Click on start test box. Type your username and password in the dialog box that appears.

- Open the instrument module door with the blinking green light and load the cartridge. Close the door. The module door latches shut. Once the test starts, the green light stops blinking. When the test finishes, the light goes off.
- Wait until the system releases the door lock then, open the module door and remove the cartridge.

7.2. XPERT MTB/RIF RESULTS

- The results of the test are displayed on the computer screen and their interpretation is done as shown in the following table.

Table 27. Xpert MTB/RIF results

Xpert® MTB/RIF Readout	Interpretation	Report* (Suggested Minimal Language)
MTB DETECTED; RIF Resistance DETECTED	MTB target is detected within sample. A mutation in the *rpoB* gene has been detected. A full first and second line drug panel should be conducted.	MTBC detected. rpoB mutation detected; likely rifampin resistance; Confirmatory testing in progress OR isolate has been forwarded to a reference laboratory for confirmatory testing.
MTB DETECTED; RIF Resistance NOT DETECTED	MTB target is detected within sample. A mutation in the *rpoB* gene has not been detected.	MTBC detected. No *rpoB* mutation detected; likely rifampin susceptible.
MTB DETECTED; RIF Resistance INDETERMINATE	MTB target is detected within sample. A mutation in the *rpoB* gene could not be determined due to insufficient signal detection.	MTBC detected. Insufficient MTB in the sample to allow determination of *rpoB* mutation result.
MTB Not Detected	MTB target is not detected within the sample.	MTBC not detected.

RIF Results should be reported prior to culture confirmation.

- Results are written: MTB+RIF+; MTB+RIF-; MTB+RIF indeterminate; MTB- (in the same order as in the table above)

The following results require repeating the test:

- **Invalid:** result indicates that the SPC (Internal Control) failed. The PCR was inhibited due to PCR inhibitors (pus, blood or food particles).
- **Error 5006/5007/5008:** the Probe Check control failed. This is mainly due to the viscosity and/or volume of the sputum; the reaction tube being filled improperly, or probe integrity problem detected.
- **Error 2008:** pressure exceeds the maximum pressure allowed or geneXpert module failure. If this happens randomly, this is mostly linked to the sample viscosity.
- **No result:** indicates that insufficient data were collected. For e.g., the test in progress has been stopped voluntarily or due to electrical failure.

8. FINE NEEDLE ASPIRATION (FNA)

Fine needle aspiration (FNA) enables rapid, safe, relatively painless, and inexpensive sampling of lymph nodes. It is used for the diagnosis of lymphoid or metastatic malignancies, infectious diseases and reactive lymphadenopathy.

FNA specimens may be submitted as smeared slides or fluid specimens. For suspicion of TB lymphadenitis, XPert MTB/RIF should be used as the initial diagnostic test rather than microscopy, culture and histopathology.

FNA technique:

- Use a sterile technique on all patients.
- Use a 10-20 ml disposable syringe attached to a 22-gauge needle (preferably).
- Move the needle back and forth into different parts of the lymph node several times before withdrawal.
- Prepare smeared slides by expelling the contents of the syringe and needle are onto glass slides.
- Fix immediately one (or more) Superfrost Plus slide in 95% ethanol with 2% acetic acid (or equivalent) for at least 15 minutes to preserve cellular morphology.
- Stain these slides with Papanicolaou stain and/or hematoxylin and eosin (H&E) stain.
- Other slides (plain slides) are air dried and immediately stained by the Diff-Quik method and Auramine stain for *M. tuberculosis*.
- Rinse the needle and syringe and process the fluid specimens with the Xpert MTB/RIF assay and/or culture.

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ANNEXES

ANNEX 1 : LABORATORY REQUEST FORM

REPUBLIQUE DU RWANDA / MINISTERE DE LA SANTE / RBC / IHDPC / TB & ORD Division-NRL

BON D'EXAMEN DE LABORATOIRE DE TUBERCULOSE

Adresse de la FOSA : District : ..... Fosa : ..... Service : .....
Identification du patient : Nom et prénom: .....
Age : ..... Sexe : [__] Masculin [__] Féminin
Adresse du patient : District:..... Secteur: .....
Cellule:..... ..... Umudugudu .....
N° tel .....
Nº de C.I : [___] / [___] [___] [___] [___] / [___] / [___] [___] [___] [___] [___] [___] [___] / [___] / [___] [___].
N° Registre consultation externe ou Dossier d'hospitalisation ou Dossier ARV :.....

Facteurs de risque : (*cocher tout ce qui est applicable*)

- [__] Contact avec un cas TPB+
- [__] Employé d'une FOSA
- [__] Prisonnier actuellement
- [__] Antécédents de Prisonnier les 5 dernières années
- [__] Employé d'une Prison
- [__] Réfugié/déplacé vivant dans un camp
- [__] Habitat collectif (camp, écoles, Transit Center ;etc)
- [__] Autre (Préciser) : ..... (*Indoor air pollution*) ?
- [__] Diabète non contrôlé (≥130 mg/dl)
- [__] Fume le tabac
- [__] Travaille dans une mine (mineur de fond)
- [__] PVVIH
- [__] Consomme l'alcool
- [__] Index de mass corporel bas (≤ 18.5)

Nature de l'échantillon : [__] Pulmonaire
[__] ExtraPulmonaire (spécifier) : .....

Date du 1er prélèvement : ...../...../.....

Examen demandé

[__] **Bacilloscopie**
Motif: [__] Diagnostic.
[__] Contrôle : [__] C2 [__] C5 [__] C6 [__] C.... Pour TB MR
Présumé traité pour TB auparavant: [__] Non [__] Oui
Patient Présumé par : [__] CDT [__] CT [__] ASC

Demandez l'examen de **GeneXpert** pour :

1. Tout cas présumé de TB avec VIH+
2. Cas NTPM+, traitement après échec, Rechute, Traitement après avoir été perdu de vue
3. Présumé de TB parmi les prisonniers
4. Contact présumé de TB autour d'un cas TB bactériologiquement confirmé ou d'un cas TB MR
5. Présumé de TB parmi les enfants de moins de 15 ans.
6. Présumé de TB parmi les personnes âgées de ≥ 55 ans.
7. Présumé de TB diabétique
8. Présumé de TB prestataire de soins
9. Présumé de TB dans les Districts de Kigali
10. Autres cas Jugé par le médecin

Demandez un échantillon pour **culture** pour :

1. Tout cas résistant à la Rifampicine au test GeneXpert.
2. Tout cas qui a un examen microscopique positif au cours du traitement (C5)
3. Tout cas présumé de TB parmis les contacts d'un cas TB-MR
4. Tout cas de retraitement
5. Rifampicine indéterminé au test de Genexpert
6. Tout cas à microscopie positive avec test genexpert négatif
7. Tout échantion pour la TB extrapulmonaire à l'exception du sang
8. Autres cas Jugé par le médecin

Note : Envoyez au Laboratoire de référence le même crachat qui a été positif à la FOSA.
Préciser chaque fois la sensibilité à la Rifampicine (Xpert) :
[__] Sensible [__] Résistant [__] Indéterminé [__] Non-fait

[__] **Test VIH.** Date du dernier test VIH : : ...../...../..... Résultat VIH : [__] Négatif [__] Positif [__] Non Connu

Nom et signature du demandeur : .....
Téléphone du demandeur : .....
Date de demande de l'examen : ...../...../.....

Résultats Microscopie

N° de série ..... Technique : [__] Ziehl Nelsen [__] Fluorescence

Date de lecture de la lame	Echantillon	Apparence (*Mucopurulent Salive,Sang*)	Nég	1-9	+	++	+++
...../...../.....	1						
...../...../.....	2						

FOSA examinateur :
Noms du laborantin examinateur : ..... Signature.....
Labo : ..... Date de résultat : ...../...../.....
FOSA demandeur : Date de réception de résultats : ...../...../..... Reçu par : ..... Signature : .....

ANNEX 2 : TB LABORATORY REGISTER

Mois de: ..... **Année:** .....

REPUBLIQUE DU RWANDA
RWANDA BIOMEDICAL CENTRE

REGISTRE DE LABORATOIRE DE LA TUBERCULOSE POUR CDT

N° d'ordre	N° série labo.	N° registre consultation externe / Dossier d'hospitalisation ou ARV	Date de réception de l'échantillon	Nom et prénom du patient	N° CI	Sexe (M/F)	Age	Adresse (district, secteur, cellule, quartier)	Facteur de risque (écrire le numéro correspondant, voir notes de bas de page)	TB Présumé Par :			Traité pour TB auparavant		Co-ntroie	Résultats microscopie		Technique microscopique		GXP (Date et Résultat)	Date résultat et Noms laborantin	Statut VIH		Culture		Commentaire
										CDT	ABC	TP	Non	Oui	C...	1	2	ZN	LED			PVV déjà connu (oui/non)	VIH Date / résultat	Date d'e envoi	Résultat et date de résultat au CDT	
1																										
2																										
3																										
4																										
5																										
6																										
7																										
8																										
9																										
10																										

Facteurs de risque : (*cocher tout ce qui est applicable*) 1. Contact avec un cas TPB+ 2. Employé d'une FOSA 3. Prisonnier actuellement 4. Antécédents de Prisonnier les 5 dernières années 5. Employé d'une Prison 6. Réfugié/déplacés vivant dans un camp 7. Habitat collectif (caserne, écoles, etc) 8. Diabète non contrôlé (≥130 mg/dl) 9. Fume le tabac 10. Travaille dans une mine (mineur de fond) 11. PVVIH 12. Consomme l'alcool 13. Index de mass corporel bas (≤ 18.5) 14. Autre (Préciser) : .....

Traité pour TB auparavant : Non = suspicion d'un nouveau cas de TB, Oui = suspicion de rechute ou reprise après abandon. Contrôle : indiquer le mois de contrôle, exemple C2 = contrôle au 2ème mois, C5 = contrôle au 5ème mois, etc.

Date résultat = date à laquelle le résultat de la série est disponible.

Technique d'examen : ZN = Ziehl Neelsen ; LED = microscopie en fluorescence GXP : genexpert.

Résultats GXP : **MTB+RIF+ (**MTb detected very low OU MTb detected low OU MTb detected medium OU MTb detected high; ET Rif Resistance detected**); MTB+RIF- (**MTb detected very low OU MTb detected low OU MTb detected medium OU MTb detected high; ET Rif Resistance not detected**); MTB-RIF- (**MTb not detected ET Rif Resistance not detected**); Invalid; Error.**

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ANNEX 3 : TRIAGE REGISTER

IDENTIFICATION					TB SCREENING							High risk group				TB Presumptive case		Tuberculin Skin Test done	Laboratory result Smear or Genexpert			Observations
					BY SYMPTOMS (Answer Yes or No)					By chest X-ray*												
Date	N°	Names	Age	Sex	COUGH		Fever	Night sweat	Weight loss	result	Not done	TB Contact	HIV+		Prisoner	Yes	No	Induration in mm	Pos	NEG	Not done	
						Duration (If Yes)							New	Old case								

NB: TST is indicated for the children under fifteen years

1. **Interpretations: TST Positive: ≥ 5mm**: children PLHIV or malnourished children
   ≥ 10mm: children **without** HIV or malnutrition

2. **Chest X-Ray done result**: Mentione **N** if Normal Chest X-ray or **ABN** if Abnormal Chest X-ray

ANNEX 4 : TB TREATMENT CARD

REPUBLIQUE DU RWANDA — N° TB : … …. …./…. …. (NOM DU CDT : ……CODE :……)
RWANDA BIOMEDICAL CENTER — N° TB : … …. …./…. …. (NOM DU CDT : ……CODE :……)
RBC/IHDPC/TB & ORD DIVISION — N° TB : … …. …./…. …. (NOM DU CDT : ……CODE :……)

FICHE DE TRAITEMENT DE LA TUBERCULOSE

Identification du patient							
Nom			**Prénom**				
Nº CI	[__] / [__] [__] [__] [__] / [__] / [__] [__] [__] [__] [__] [__] [__] / [__] / [__] [__].						
Sexe	[_] Masculin [_] Féminin	Date de naissance	[__] [__]./.[__][__] / [__] [__] [__] [__]			**Téléphone**	
Facteurs de risque (*cocher tout ce qui est applicable*)	[_] Employé d'une FOSA [_] Antécédents de Prisonnier les 5 dernières années [_] Réfugié/déplacés vivant dans un camp [_] Contact avec un cas TPB+ [_] Fume le tabac [_] Consomme l'alcool [_] Autre (Préciser) : …… [_] Prisonnier actuellement [_] Employé d'une Prison [_] Habitat collectif (Camp, écoles, transit center, etc) [_] Diabète non contrôlé (≥130 mg/dl) [_] Travaille dans une mine (mineur de fond) [_] Index de mass corporel bas (≤ 18.5)						
District		**Secteur**		**Cellule**		**Village**	
N°Dossier malade (Registre consultation, hospitalisation ou ARV)							
Noms de la Personne à contacter						**Telephone**	

Catégorisation du cas	
Définition de cas (*cocher une seule option*)	[_] Cas confirmé bactériologiquement [_] Cas diagnostiqué cliniquement
Site anatomique de la maladie (*cocher une seule option*)	[_] Tuberculose pulmonaire [_] Tuberculose extra-pulmonaire
Antécédents de traitement anti-tuberculeux (*cocher une seule option*)	[_] Nouveau patient [_] Patient en rechute [_] Patient traité après un échec thérapeutique [_] Patient traité après avoir été Perdu de Vue [_] Autre patient déjà traité [_] Patient sans antécédents connus de traitement anti-tuberculeux
Susceptibilité aux médicaments TB de 1ere ligne (*cocher une seule option*)	[_] Non-connu (test non fait) [_] Non-connu (résultat test non disponible) [_] Susceptible [_] Résistant à la rifampicine [_] TB MR
Infection VIH (*cocher une seule option*)	[_] Négatif [_] Positif [_] Non-connu

Gestion d'Infection VIH		
Test VIH	**Date du test** (jj/mm/aaaa):	
Si résultat positif :	N°du dossier : ……	Lieu : ……
Chargé Viral	Au moment du dg TB	/mm³
	A la fin du TTT TB	/mm³
CTX	Oui [_] Non [_] Si oui, Date début : ……/……/……	
ARV	Oui [_] Non [_] Si oui, Date début : ……/……/…… Régime :	

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	Bacilloscopie			GXP (résultat et date)	Culture et DST			Radiographie Thorax (au moment du Dg TB)
	Date échantillon	Résultat Bacilloscopie			Date d'envoi en culture	Résultat Culture	Résultat DST	
D								☐ Normale ☐ Adénopathies médiastinales ☐ Caverne(s) unilatérale ☐ Caverne(s) bilatérales ☐ Infiltrat unilatéral ☐ Infiltrat bilatéral ☐ Epanchement pleural ☐ Miliaire ☐ Autres : ……
C2								
C5								
C6								

Schéma de traitement et posologie (*Indiquer le nb de comprimés à administrer par jour*)			
SCHEMA / PHASE	Adultes	Enfants de 0-14 ans	
	$2(R_{150}H_{75}Z_{400}E_{275})_7$ / $4(R_{150}H_{75})_7$	Enfants 0-14 ans : $2[(R_{75}H_{50}Z_{150}) + E_{100}]_7$ / $4(R_{75}H_{50})_7$	
INTENSIVE	RHZE	$R_{75}H_{50}Z_{150}$	E_{100}
Date : …/……/……			
Date : …/……/……			
CONTINUATION	$R_{150}H_{75}$	$R_{75}H_{50}$	
Date : …/……/……			
Date : …/……/……			
Méningite TB ou TB osseuse : ❑ Adultes: $2(R_{150}H_{75}Z_{400}E_{275})_7$ / $10(R_{150}H_{75})_7$ ❑ Enfants de 0-14 ans : $2[(R_{75}H_{50}Z_{150}) + E_{100}]_7$ / $10(R_{75}H_{50})_7$			

Prise quotidienne de médicaments antituberculeux																													
Jour / Mois	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Indiquez **X** si la dose est prise sous supervision, **0** si le malade n'a pas pris sa dose de médicaments, **-** si la dose est auto-administrée

→ Flèche couvrant les doses confiées à l'animateur de santé.

Examen de contacts (*Si plus de 12 personnes, utilisez une feuille supplémentaire de même format*)											
	Contacts à examiner			Au début du traitement				A la fin du traitement			
	Nom et prénom	Sexe (M/F)	Age	Examiné (Oui/Non)	Présumé TB (Oui/Non)	Cas TB (Oui/Non)	Conduite à tenir (Tt TB / INH / IEC)	Examiné (Oui/Non)	Présumé TB (Oui/Non)	Cas TB (Oui/Non)	Conduite à tenir (Tt TB /IEC)
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											

Suivi clinique et para-clinique du malade			
DATE	**Évolution cliniques et para-clinique de la TB**	**Surveillance des effets secondaires**	**CONDUITE A TENIR**
Début traitement	Poids (kg) : .... Taille (cm) : .... Test de grossesse* : .... NFS* : .... SGPT* : .... SGOT* : .... ɣ GT* : .... Urée* : .... Créatinine* : .... Autre :	[__] Neuropathies [__] Ictère [__] Pâleur des conjonctives [__] Arthralgies [__] Vertiges [__] Perte acuité auditive [__] Perte acuité visuelle [__] Eruptions cutanées [__] Aucun	
	Poids (kg) : .... Autre :	[__] Neuropathies [__] Ictère [__] Pâleur des conjonctives [__] Arthralgies [__] Vertiges [__] Perte acuité auditive [__] Perte acuité visuelle [__] Eruptions cutanées [__] Aucun	
	Poids (kg) : .... Autre :	[__] Neuropathies [__] Ictère [__] Pâleur des conjonctives [__] Arthralgies [__] Vertiges [__] Perte acuité auditive [__] Perte acuité visuelle [__] Eruptions cutanées [__] Aucun	
	Poids (kg) : .... Autre :	[__] Neuropathies [__] Ictère [__] Pâleur des conjonctives [__] Arthralgies [__] Vertiges [__] Perte acuité auditive [__] Perte acuité visuelle [__] Eruptions cutanées [__] Aucun	
	Poids (kg) : .... Autre :	[__] Neuropathies [__] Ictère [__] Pâleur des conjonctives [__] Arthralgies [__] Vertiges [__] Perte acuité auditive [__] Perte acuité visuelle [__] Eruptions cutanées [__] Aucun	
	Poids (kg) : .... Autre :	[__] Neuropathies [__] Ictère [__] Pâleur des conjonctives [__] Arthralgies [__] Vertiges [__] Perte acuité auditive [__] Perte acuité visuelle [__] Eruptions cutanées [__] Aucun	
	Poids (kg) : .... Autre :	[__] Neuropathies [__] Ictère [__] Pâleur des conjonctives [__] Arthralgies [__] Vertiges [__] Perte acuité auditive [__] Perte acuité visuelle [__] Eruptions cutanées [__] Aucun	
Fin traitement	Poids (kg) : .... Autre :	[__] Neuropathies [__] Ictère [__] Pâleur des conjonctives [__] Arthralgies [__] Vertiges [__] Perte acuité auditive [__] Perte acuité visuelle [__] Eruptions cutanées [__] Aucun	

* : répéter ce test si nécessaire.

Résultat du traitement antituberculeux		**Malade transféré**		**Malade transféré pour traitement 2ème ligne**
Date de fin du traitement : [__] [__]./.[__][__] / [__] [__] [__] [__]		Date de transfert : [__] [__]./.[__][__] / [__] [__] [__] [__]		
Résultat du traitement	[__] Guérison [__] Traitement terminé [__] Echec thérapeutique [__] Décès [__] Perdu de vue [__] Non évalué	Vers FOSA de	....	Date : _____ / ______ / __________
		District de la FOSA	....	
		Adresse du malade au lieu de transfert	District:	Centre spécialisé
			Secteur:	[__] Kabutare
			Cellule:	[__] Kibagabaga
			Village:	[__] Kibungo

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ANNEX 5 : TB CASE REGISTER

REGISTRE DE CAS DE TUBERCULOSE POUR CDT *(page de gauche)*

ENREGISTREMENT								CATEGORISATION DU CAS																							TRAITEMENT			
Date d'enregistrement	N° registre TB	N° de alerte labo	Nom et prénoms	sexe	Age	Adresse District Administratif, Secteur, Cellule, Village	Définition de cas (Choisir une seule réponse)		Site de la maladie (Choisir une seule réponse)		Histoire de traitement TB (Choisir une seule réponse)						Susceptibilité aux antituberculeux (Choisir une seule réponse)						Test VIH : Résultat connu ... a (Choisir une seule réponse)			Date de début du traitement	Catégorie de traitement (I ou II)	Unité de traitement (FOSA, ASC)	Nom de l'ASC et date de début du suivi par ASC
							Confirmé bactériologiquement	Diagnostiqué cliniquement	Pulmonaire	Extra Pulmonaire	Nouveau	Rechute	Traitement après échec	Traitement après avoir été perdu de vue	autres patients déjà traités	patients sans antécédents connus de traitement antituberculeux	RR	TB-MR	Susceptible	Non connu (Résultat indisponible)	Non connu (Test non fait)	Non connu (Non éligible au test)	Positif	Négatif	Non connu				

REGISTRE DE CAS DE TUBERCULOSE POUR CDT (page de droite)

RESULTATS BACILLOSCOPIE						AUTRES EXAMENS						DATE ET RESULTAT DE TRAITEMENT						TEST VIH	PRISE EN CHARGE VIH (si positif)						Contacts									observations
Diagn.	C2	C3	C5	C6	C8	RX (date, résultat)	GXP		Culture		Test de sensibilité		Guéri	TT	E	Décédé	Perdu de vue	Non-évalué	Date du test	Unité PEC VIH	Sous-CTX (oui/non et date début si oui)	CD4 (Norme:)		Sous-ARV		Nb de contacts dans l'entourage du malade TPB+		Nb de contacts/Personnes dans l'entourage du malade TPB+		____ à ____ / Année Nb cas TB présumés parmi les contacts		Nb cas TB parmi les contacts		Nb Effs «Sans» parmi les contacts mis sous INH	
							Date de réception de résultat	Résultat	Date de réception de résultat	Résultat	Date de réception de résultat	Résultat								n° dossier		Au Dg TB	A la fin TT TB	oui/non (date début si oui)	Régime	≥ 5 ans d'âge	< 5 ans d'âge	≥ 5 ans d'âge	< 5 ans d'âge	≥ 5 ans d'âge	< 5 ans d'âge	≥ 5 ans d'âge	< 5 ans d'âge		

ANNEX 6. OVERLAPPING AND POTENTIAL ADDITIVE TOXICITIES OF ART AND ANTI-TB AGENTS

Toxicity	ARV	Anti-TB	Management	Comment
Peripheral neuropathy	D4T, ddI DdC	Lzd, Cs, H aminoglycosides, Eto/Pto, E	- Avoid using Cs or Lzd in combination with D4T, ddI, ddC - If peripheral neuropathy develops, replace the ARV with a less neurotoxic agent - Pyridoxine: 100-200 mg / day; (25 mg / day for prevention) - Amitriptyline, NSAIDs, acetaminophen	- Increased risk in patients with comorbidities (HIV, diabetes, alcoholism) - The neuropathy may be irreversible, but many patients improve when the offending agents are withheld. - Linezolid-associated neuropathy is common after prolonged use and often permanent. Stop linezolid.
Depression	**EFV**	**Cs,** H, Eto/Pto, FQ	- Stop temporarily Cs and give antipsychotic treatment (haloperidol) or antidepressant. - Reintroduce Cs at reduced dosage or replace.	- Severe depression can be seen in 2.4% of patients receiving EFV. Consider substituting EFV. - The severe socioeconomic circumstances of many patients with chronic disease can also contribute to depression.
Central nervous system (CNS) toxicity	**EFV**	**Cs,** H, Eto/Pto, fluoroquinolones	- Concomitant use of EFV and CS is accepted but requires frequent monitoring of CNS toxicity.	- EFV has a high rate of CNS adverse effects (confusion, impaired concentration, depersonalization, abnormal dreams, insomnia and dizziness) in the first 2–3 weeks, which usually resolve spontaneously.
Headache	**AZT, EFV**	Cs, BDQ	- Ibuprofen, paracetamol - Adequate hydration	- Rule out other more serious causes of headache (bacterial or cryptococcal meningitis / CNS toxoplasmosis) - Usually spontaneous resolution.
Hepatotoxicity	**NVP, EFV, all PIs** (RTV > other PIs), **all NRTis, DTG, RAL**	**Z, H, R, E,** PAS, Eto/Pto, Fluoroquinolones **BDQ**	- Stop anti-TB drugs until the hepatitis resolves, then gradually reintroducing one drug at a time - or exclude the responsible agent	- Usually reversible with discontinuation of the responsible drug - Also consider TMP/SMX as a cause of hepatotoxicity - Also rule out viral causes of hepatitis (Hepatitis A, B, C, and CMV).

Skin rash	**ABC, NVP, EFV, D4T,** RAL, DTG, ETV, DRV/r	**H, R, Z, PAS** FQ and others	- Moderate reaction: antihistamines - Severe reaction: corticosteroids and antihistamines ; stop anti-TB drugs and gradual reintroduce one drug at a time; remove the responsible agent.	- Do not re-challenge with ABC (can result in life-threatening anaphylaxis) or with any agent that caused Stevens-Jonhson syndrome. - TMP/SMX is also a possible cause of a rash
Renal toxicity, electrolyte disturbances	TDF (rare)	**Aminoglycosides (Km, Am), Capreomycin**	- Adjust the dosage of ARVs and anti-TB according to creatinine clearance. - Replace Km by Cm / stop the responsible agent / or reduce the frequency to 3 times a week. - Replace the electrolytes as needed	- TDF can cause renal damage and should be used with caution in patients receiving aminoglycosides or Cm; monitor creatinine and electrolytes. - Diarrhea and vomiting can cause electrolyte disturbances - Even without concomitant use of TDF, PLHIV have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.
Bone marrow suppression	AZT	**Lzd,** R, Rfb, H	- Monitor blood counts regularly. - Replace AZT if bone marrow suppression develops. - Consider suspension of Lzd.	- Also consider TMP/SMX as a cause if the patient is receiving this medication. - Consider adding folinic acid supplements, especially if receiving TMP/SMX.
Nausea and vomiting	**RTV, D4T,** NVP and most others	**Eto/Pto, PAS, H, E, Z** and others **BDQ**	- Check if dehydration - Antiemetic treatment - Decrease or replace the suspected drug if this does not compromise the treatment	- Common adverse effects. - Persistent vomiting and abdominal pain may be a result of developing lactic acidosis and/or hepatitis secondary to medications.
Abdominal pain	**All ART treatments**	**Cfz, Eto/Pto, PAS**	-	- Abdominal pain is a common adverse effect and often benign - however, abdominal pain may be an early symptom of severe adverse effects such as pancreatitis, hepatitis or lactic acidosis.
Pancreatitis	D4T, ddI, ddC	Lzd	- Avoid use of these agents together. - If pancreatitis, permanently stop the	- Also consider gallstones or alcohol as a potential cause of pancreatitis.

	LPV/r		responsible agent; exclude ARVs that may cause pancreatitis (D4T, ddI or ddC).	
Diarrhea	**All PI, ddI**	**Eto/Pto, PAS**, FQ	- Check hydration, - Loperamide	- Common adverse effect. - Also consider opportunistic infections as a cause of diarrhea
Hypothyroidism	D4T	**PAS, Eto/Pto**	- Administer thyroxine	- Frequent with PAS and Pto, especially in combination. Reversible. - Subclinical hypothyroidism associated with ARVs (stavudine).
Dysglycemia (disturbed blood sugar regulation)	**Protease inhibitors (IPs)**	**Gatifloxacin,** Eto/Pto	- Avoid Gatifloxacin given the possible glycemia disorders	- Protease inhibitors tend to cause insulin resistance and hyperglycaemia. - Eto/Pto tend to make insulin control in diabetics more difficult, and can result in hypoglycemia and poor glucose regulation
Optic neuritis	ddI	**E, Lzd,** Eto/Pto, Cfz, rifabutin, H, S	- Stop and permanently replace the responsible agent.	- The most common causative drug is ethambutol. - Serious and irreversible if the medication is not stopped immediately. - Loss of color vision (green color first)
Lactic acidosis	**D4T, ddI, AZT, 3TC,** TDF	**Lzd**	- Replace the responsible agent with one less likely to cause lactic acidosis.	
Hyperlipidemia	**IP, EFV**	None	- See ART guidelines	- No overlapping toxicities
Lipodystrophy	NRTIs (especially D4T and ddI)	None	- See ART guidelines	- No overlapping toxicities

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