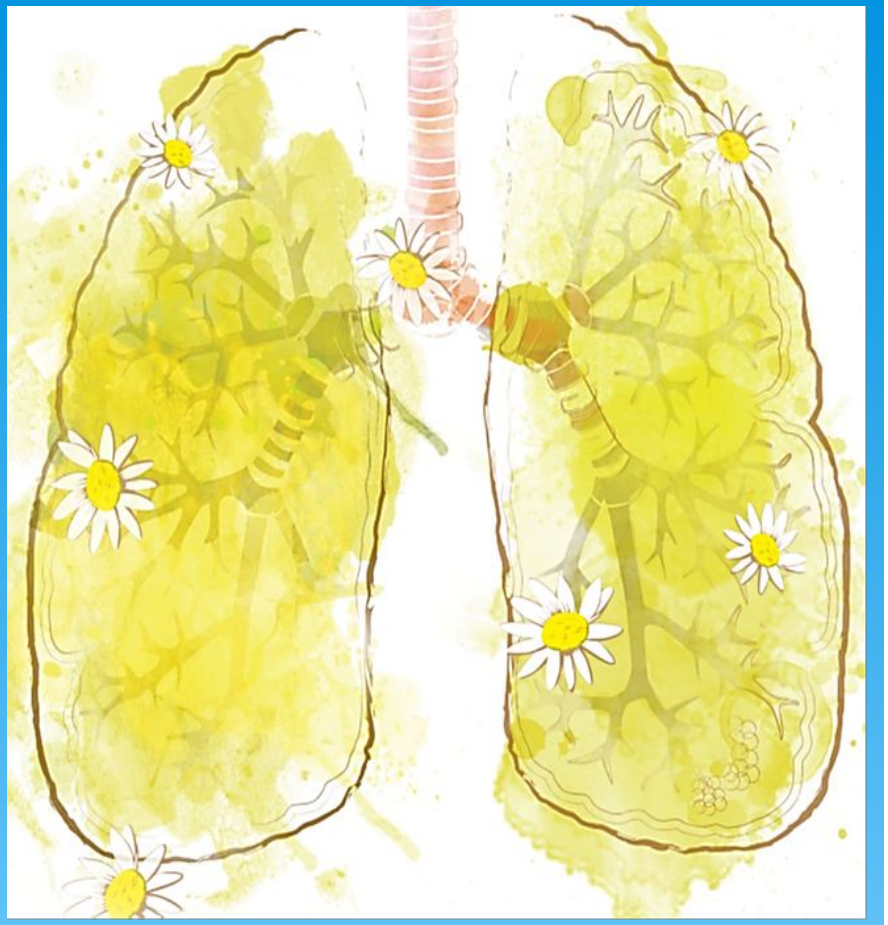
MULTI DRUG -RESISTANT TUBERCULOSIS (MDR-TB). TB/HIV CO-INFECTION



An estimated 2 billion people – one-third of the global population – are infected with tuberculosis (TB), and each year, 8.7 million people develop TB disease. TB kills more than 1.4 million people each year and is economically devastating to families and communities worldwide

Although TB is a global problem, its geographic distribution is drastically disproportionate. Ninety-five percent of all TB cases and 98 percent of all TB deaths occur in developing countries.

TB is one of the top killers of women and is responsible for 500,000 of their deaths each year

TB is a major killer among women of reproductive age and the leading cause of death in HIV-positive individuals.

Only 22 high-burden countries (HBCs) account for 80 percent of the global TB burden, with half of these countries located in Asia.

In Africa, 40 countries have an estimated TB prevalence rate greater than 100/100,000 compared to an estimated prevalence rate of <5/100,000 in the United States

The global resurgence of TB has been fueled by a combination of factors, including increasing rates of HIV/AIDS and multidrug resistance, inadequate investments in public health infrastructure, insufficient political commitment, limited awareness of TB, disparities in access to and quality of health care services, and inadequate investments in new tools, including drugs, diagnostics, and vaccines.

The disease threatens the poorest and most marginalized, disrupts the social fabric of society, and slows or undermines gains in economic development

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to, at least, isoniazid and rifampicin, the two most powerful, first-line (or standard) anti-TB drugs

Extensively drug-resistant TB (XDR-TB)
is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs.

Because XDR TB is resistant to the most potent TB drugs, patients are left with treatment options that are much less effective. XDR TB is of special concern for persons with HIV infection or other conditions that can weaken the immune system. These persons are more likely to develop TB disease once they are infected, and also have a higher risk of death once they develop TB

The global TB situation

	Estimated incidence, 2013	Estimated number of deaths, 2013
All forms of TB	• 9.0 million (8.6–9.4 million)	1.1 million (1.0–1.3 million)
HIV/TB	• 1.1 million (1.0–1.2 million)	360,000 (310,000–410,000)
MDR-TB	• 480,000 (350,000–610,000)	210,000 (130,000–290,000)

Globally in 2013, an estimated 480 000 people developed MDR-TB and there were an estimated 210 000 deaths from MDR-TB.

The number of people diagnosed with MDR-TB tripled between 2009 and 2013, and reached 136 000 worldwide. This was equivalent to 45% of the estimated MDR-TB cases among notified TB patients. Progress in the detection of drug-resistant TB has been facilitated by the use of new rapid diagnostics.

A total of 97 000 patients were started on MDR-TB treatment in 2013, a three-fold increase compared with 2009. However, 39 000 patients were on waiting lists, and the gap between diagnosis and treatment widened between 2012 and 2013 in several countries.

XDR-TB has been reported by 100 countries in 2013. On average, an estimated 9% of people with MDR-TB have XDR-TB.

HIV/AIDS and TB co-infection present special challenges to the expansion and effectiveness of DOTS programs and the Stop TB Strategy. TB accounts for one-quarter of AIDS deaths worldwide and is one of the most common causes of morbidity in people living with HIV and AIDS (PLWHA). Currently, approximately 34 million people are infected with HIV, and at least one-third of them are also infected with TB

The dual epidemics of TB and HIV are particularly pervasive in Africa, where HIV has been the most important contributing factor in the increasing incidence of TB over the last 10 years. In some countries in sub-Saharan Africa, up to 80 percent of individuals with active TB disease are also HIV-positive

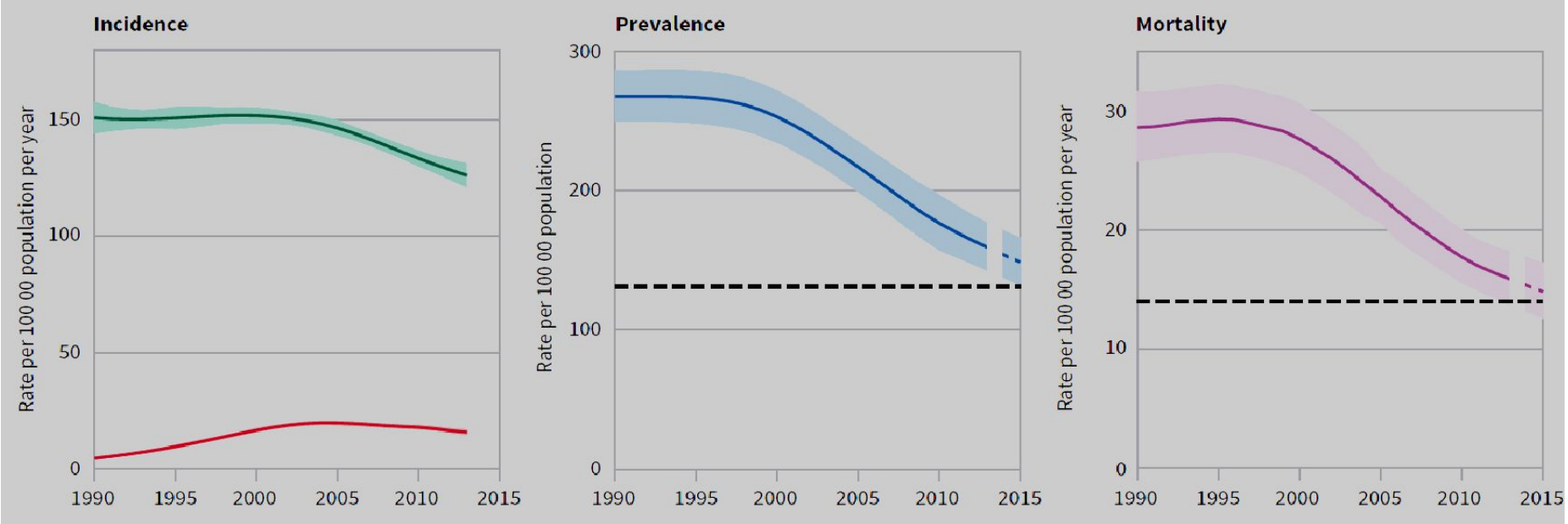
The dual epidemics are also of growing concern in Asia, where two-thirds of TB-infected people live and where TB now accounts for 40 percent of AIDS deaths. Eastern Europe and the former Soviet Union have the fastest growing HIV epidemic in the world, a factor further exacerbating the expanding problem of the multidrug-resistant TB (MDR-TB) epidemic in these regions

The overlap of TB-HIV co-infection with MDR-TB and extensively drug-resistant TB presents a tremendous challenge and threatens progress in controlling TB and HIV and AIDS and in eliminating the mortality associated with these diseases

Individuals co-infected with HIV and TB are 30 times more likely to progress to active TB disease. Infection with TB enhances replication of HIV and may accelerate the progression of HIV infection to AIDS. Fortunately, TB treatment under the DOTS programs is just as effective in individuals with HIV as it is in people who are HIV negative

In addition, clinical trials have shown that there are anti-TB regimens that can prevent or decrease the likelihood of TB infection progressing to active TB disease in an HIV-infected individual, making it an important intervention for increasing the length and quality of life for those co-infected and their families and communities

Global trends in estimated rates of TB incidence, prevalence and mortality



Global trends in estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red). The dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people

67th World Health Assembly, Geneva, May 2014

THE END TB STRATEGY

SIXTY-SEVENTH WORLD HEALTH ASSEMBLY WHA67.1

Agenda item 12.1 21 May 2014

Global strategy and targets for tuberculosis prevention, care and control after 2015

The Sixty-seventh World Health Assembly,

Having considered the report on the draft global strategy and targets for tuberculosis prevention, care and control after 2015;[1]

Acknowledging the progress made towards the achievement of Millennium Development Goal 6 (Combat HIV/AIDS, malaria and other diseases) for 2015 following the United Nations Millennium Declaration and related 2015 tuberculosis targets, through the adoption of the DOTS strategy, the Stop TB Strategy and the Global Plan to Stop TB 2006–2015, as well as the financing of national plans based on those frameworks, as called for, inter alia, in resolution WHA60.19 on tuberculosis control;

The End TB Strategy – Components

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION

A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and

high-risk groups

B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support

C. Collaborative tuberculosis/HIV activities, and management of co-morbidities

D. Preventive treatment of persons at high risk, and vaccination against tuberculosis

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS

A. Political commitment with adequate resources for tuberculosis care and prevention

B. Engagement of communities, civil society organizations, and public and private care providers

C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational

use of medicines, and infection control

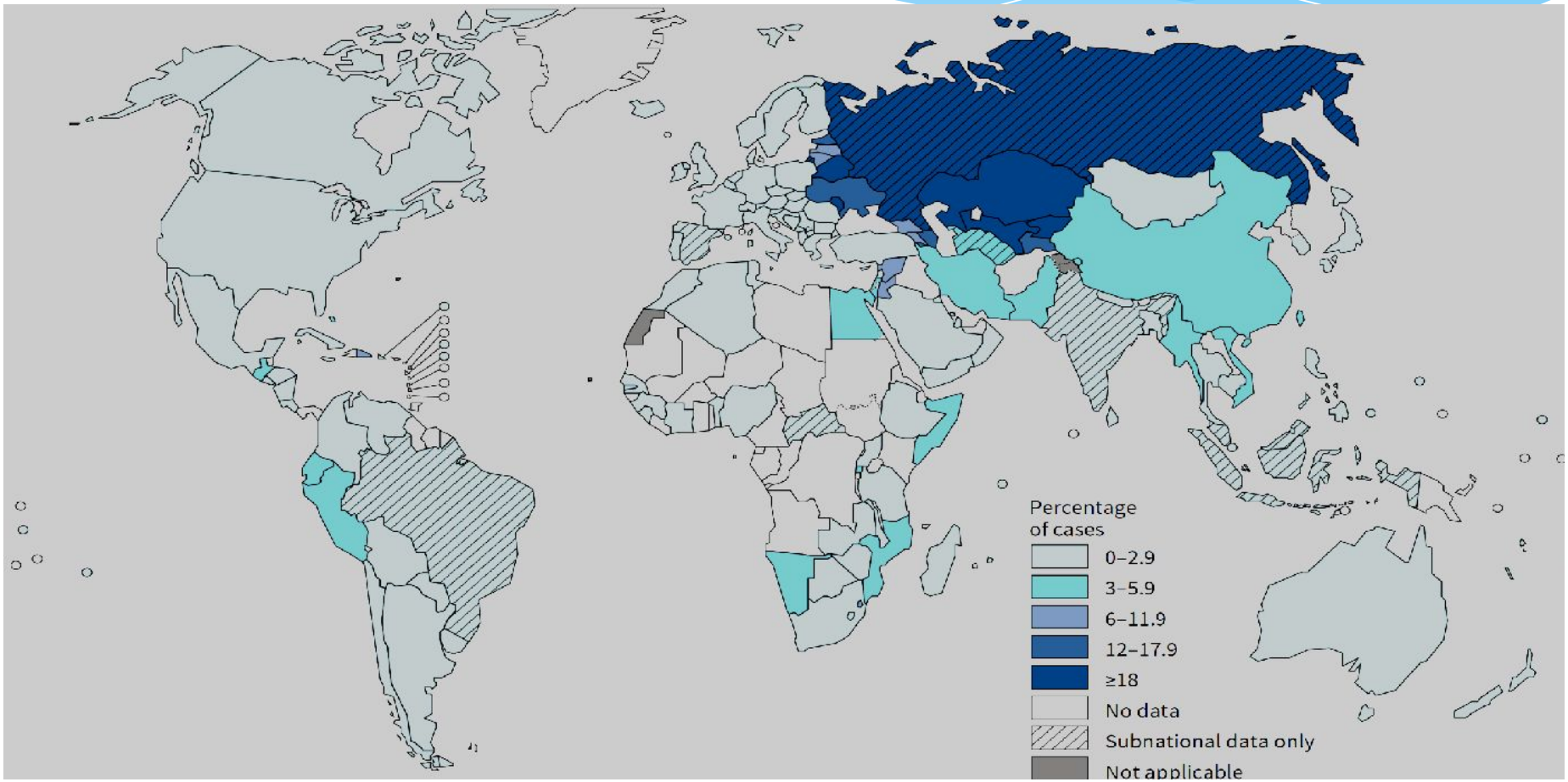
D. Social protection, poverty alleviation and actions on other determinants of tuberculosis

3. INTENSIFIED RESEARCH AND INNOVATION

A. Discovery, development and rapid uptake of new tools, interventions and strategies

B. Research to optimize implementation and impact, and promote innovations

Percentage of new TB cases with MDR-TB (WHO 2014)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries

Five priority actions to address the global MDR-TB crisis

Prevent the development of drug resistance through high quality treatment of drug-susceptible TB

Expand rapid testing and detection of drug-resistant TB cases

Provide immediate access to effective treatment and proper care

Prevent transmission through infection control

Increase political commitment with financing

Diagnosing drug-resistant TB

Since there are no specific clinical or radiographic features to distinguish HIV-infected patients with MDR-TB from those with drug-susceptible tuberculosis, the key to diagnosing MDR-TB is a high index of suspicion. Given the variability in the clinical and radiographic presentation of tuberculosis in HIV-infected patients, tuberculosis should always be included in the differential diagnosis of all pulmonary disease processes in such patients, and the work-up should include tests to detect M. tuberculosis.

Sputum and other clinical specimens – such as pleural or bronchoalveolar lavage fluid and tissue from transbronchial biopsy – should be stained and cultured for acid-fast bacilli. Blood cultures for acid-fast bacilli should also be obtained. Since M. tuberculosis is never part of a patient's normal flora, the finding of even one acid-fast organism should lead to empiric treatment for tuberculosis in essentially all clinical situations

At present, the rapid DST of choice in individuals suspected of MDR-TB is the **Xpert MTB/RIF** as it is the only platform that is quick, simple, and robust enough to be used outside reference laboratories. It can be used in peripheral laboratories and does not require sophisticated equipment and highly skilled personnel.

The **GeneXpert® System** consists of an instrument, personal computer, bar code scanner, and preloaded software, and uses single-use disposable cartridges containing lyophilized reagents, buffers, and washes

The Xpert MTB/RIF

- **The Xpert MTB/RIF is a cartridge-based, automated diagnostic test that can identify Mycobacterium tuberculosis (MTB)DNA and resistance to rifampicin (RIF)by nucleic acid amplification technique(NAAT**

The test is based on real-time polymerase chain reaction (PCR) technology targeting specific nucleic acid sequences in the M. tuberculosis complex genome, while simultaneously providing information about the most common mutations related to rifampicin resistance.

The GeneXpert® System and the Xpert MTB/RIF assay are currently the only mature technology representing a new generation of automated diagnostic platforms. There are others in the prototype stage

1. For TB detection, Xpert MTB/RIF is substantially more sensitive than microscopy.

- ✔ Sensitivity is close to 100 percent in smear-positive tuberculosis.
- ✔ Sensitivity is greater than 70 percent in smear-negative, culture-positive tuberculosis.
- ✔ Sensitivity is higher if the test is repeated.

2. For rifampicin resistance, the sensitivity compared with conventional DST on culture is greater than 95 percent. The test has a high negative predictive value, therefore rifampicin-susceptible results can be considered to be true susceptible.

3. Xpert MTB/RIF does not eliminate the need for conventional microscopy, culture, and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

4. Xpert MTB/RIF is not currently recommended for monitoring of response to TB treatment.

Testing for XDR-TB

1. Diagnosing XDR-TB is done through conventional phenotypic DST for the injectable drugs (kanamycin/amikacin and capreomycin) and a fluoroquinolone.

2. Commercially available LPA (e.g., GenoType® MTBDRsl) is starting to incorporate resistance mutations for second-line anti-TB drugs. However, the reliability of LPA for second-line DST has not been fully determined, and this cannot yet replace conventional phenotypic second-line DST:

- ✔ **LPA** for second-line DST can be used as an initial test on smear-positive specimens to guide the initial treatment in XDR-TB suspects while awaiting confirmatory results from conventional phenotypic testing.
- ✔ **LPA** that indicates genetic mutations associated with second-line drug resistance may be used to guide choice of second-line anti-TB drugs.
- ✔ **LPA** negative for second-line drug resistance does not rule out resistance. If suspicion is high, the strain should be assumed to have second-line resistance until confirmatory second-line DST results are known.

Diagnosis of MDR-TB in people living with HIV

Xpert MTB/RIF is the recommended test for drug resistance in every case of HIV-associated TB

- ✔ Untreated MDR-TB in an HIV-positive patient carries a high mortality. Many deaths from MDR-TB in HIV-positive patients occur before the diagnosis of MDR-TB

- ✔ In high HIV prevalence settings such as sub-Saharan Africa this means the majority of TB patients should be tested with Xpert MTB/RIF

Presumptive diagnosis of MDR-TB in HIV-positive patients

- ✔ Laboratory confirmation of MDR-TB may be difficult or impossible (e.g., extrapulmonary TB) for many coinfected patients, so empiric MDR-TB treatment is important
- ✔ Due to the high mortality of untreated MDR-TB in HIV-positive patients, empiric treatment with second-line drugs should be considered in patients who have a high risk for MDR-TB
- ✔ HIV-positive household contacts of known MDR-TB patients should be treated empirically for MDR-TB if they develop active TB. This is the same recommendation for all household contacts, but it is more urgent if the contact is HIV-positive
- ✔ Patients who meet the programmatic definition of failure to a standard first-line regimen (e.g., smear-positive at five months) should be started immediately on an MDR-TB regimen

MDR-TB is often confused for IRIS in patients being treated for presumed drug-susceptible TB

- ✔ Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated immune response to a previously undiagnosed opportunistic infection (unmasking IRIS) or an exacerbation of a partially or successfully treated opportunistic infection (paradoxical IRIS)

- ✔ TB-IRIS may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, or new extrapulmonary manifestations

- ✔ Mild to moderate TB-IRIS is relatively common, especially in severely immunosuppressed patients (**CD4 count < 50 cells/mm3**), but rare in its severe forms

- ✔ TB-IRIS can be indistinguishable from the unmasking of undiagnosed and untreated MDR-TB in a patient who is assumed to have drug-susceptible TB

- ✔ Patients suspected of TB-IRIS should have a diagnostic workup for other possible opportunistic infections, as well as diagnostic tests such as Xpert MTB/RIF to rule out MDR-TB

Principles of MDR-TB treatment

- ✔ The intensive phase should include at least four core second-line anti-TB drugs likely to be effective, plus pyrazinamide.
- ✔ If a drug does not meet the criteria of "likely to be effective," it should not be counted as one of the four core second-line anti-TB drugs, even if it used in the regimen.
- ✔ In the case of unclear evidence about the effectiveness of some drugs, the treatment regimen may include more than five drugs.
- ✔ A drug should not be used when patient is known to have a strong contraindication of usage (e.g., major drug-drug interactions, overlapping toxicities, history of severe allergic reaction, or pregnancy).

Programmatic considerations

- ✔ Each dose is given under directly observed therapy (DOT) throughout the treatment. A treatment card is marked for each observed dose.
- ✔ Ambulatory DOT can be either facility-based or home-based (often referred to as community-based).
- ✔ Treatment is given six or seven days a week. Six days a week is common in some outpatient settings where health workers are not available every day.

Empiric treatment

- ✔ Empiric refers to the initiation of treatment prior to determination of a firm diagnosis of DR-TB.
- ✔ Empiric regimens can be standardized or individualized.
- ✔ For example, an empiric XDR regimen refers to the use of a regimen designed to treat XDR-TB before the diagnosis of XDR-TB is made.

MDR-TB transmission and mortality in HIV-positive patients

- ✔ People living with HIV are vulnerable to MDR-TB infection and are at high risk of developing active MDR-TB once infected.
- ✔ HIV-positive patients are more likely to die from MDR-TB than HIV-negative patients.
- ✔ HIV-positive patients may experience delayed diagnosis of MDR-TB because they may more frequently be smear- or culture-negative at the outset.
- ✔ HIV-positive patients often die while waiting for laboratory confirmation of MDR-TB and before starting effective therapy. This was best illustrated by the rapid and deadly spread of XDR-TB among HIV-positive patients in South Africa.
- ✔ HIV-positive patients are more likely to die during MDR-TB treatment than HIV-negative patients, though mortality decreases once ART is started.

Start ART as soon as possible in MDR-TB patients

- ✔ MDR-TB patients who are already on ART should continue it.
- ✔ WHO recommends that MDR-TB patients who are not already on ART should start ART within the first eight weeks of starting effective MDR-TB treatment irrespective of CD4 count.
- ✔ Initiating ART with second-line anti-TB drugs may be challenging because of overlapping adverse effects and the high pill burden, but a well-trained clinical team can usually initiate ART within two weeks of starting MDR-TB treatment in stable patients.

A first-line ART regimen should include two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI).

The most commonly used ART regimen for MDR-TB patients infected with HIV is AZT + 3TC + EFV

- **AZT** (azt, retrovir) – a drug that suppresses the replication (reproduction) of HIV
- **EPIVIR 3TC** – leads to premature termination of replication and thus inhibit the synthesis of HBV DNA
- **Efavirenz (EFV)** - efavirenz is used to treat HIV infection. It is never used alone and is always given in combination with other drugs. The decision on when to start treatment should take into account CD4 count, HIV viral load, treatment history, resistance profiles and patient preference.

Infection control for MDR-TB

Administrative controls

Outpatient settings

- ✔ Patients should be screened for cough as they enter into the health care facility and receive basic education about TB.
- ✔ Patients with a cough of over two weeks should be sent to a separate, well-ventilated waiting area and fast-tracked to sputum examination.
- ✔ All coughing patients should receive tissues or face masks, and should be asked to cover their mouth and nose when they cough.

Inpatient settings

The circulation of visitors, patients, and their attendants in the hospital needs to be strictly controlled:

- ✔ Patients should be encouraged to spend as much time as possible outdoors.
- ✔ Visiting areas should be well-marked. Restricted areas should have signage forbidding visitors to enter.
- ✔ Encourage visits outside the building, in open air, especially for contagious patients.
- ✔ If visits outside are not possible, visitors should be provided masks while visiting with patients if the patient is contagious.

TB wards must be well-ventilated and separated from the other wards in the health structure compound:

- ✔ Ideally, patients may be placed in single rooms.
- ✔ If single rooms are not possible, cohort isolation must be implemented. Patients are separated by degree of contagiousness (smear/culture status), DST pattern, and immune status.
- ✔ Sputum smear-positive patients may be separated from less or noncontagious forms of TB: Smear-negative pulmonary TB, extrapulmonary TB, patients who have converted.
- ✔ Known or suspected MDR-TB patients may be separated from drug-susceptible TB patients, and XDR-TB patients may be separated from MDR-TB patients without XDR-TB.
- ✔ Immunosuppressed patients (such as HIV-positive patients) should be separated from contagious TB patients.

Environmental controls

Ventilation

- ✔ Ventilation is the most effective means for reducing the concentration of M. tuberculosis suspended in the air.
- ✔ Areas where TB transmission might occur should have a minimum ventilation rate of 6 to 12 air changes per hour (ACH).
- ✔ Natural ventilation relies on the movement caused by the wind and convection in order to achieve dilution and renewal of air.
- ✔ If natural ventilation alone is not sufficient, other mechanical devices can be used to augment it: simple propeller fans, wind-driven roof turbines, chimneys.
- ✔ When natural ventilation cannot reach adequate rates, centralized mechanical ventilation should be considered in some settings, such as cold climates.

Architectural considerations

- ✔ TB infection control should be considered during the planning stages of new health structures and those being modified.
- ✔ Building layouts and designs should maximize natural ventilation.
- ✔ Service areas with a high risk of M. tuberculosis transmission (e.g., waiting rooms) and procedures (e.g., sputum collection, sputum induction, etc.) should be relocated into more isolated, better ventilated areas.
- ✔ Layouts should allow patient flow to be manipulated to reduce exposure of at-risk patients to infectious patients (e.g., separate waiting rooms for different cohorts, one patient per room).
- ✔ For TB wards, spaces incorporating plenty of single rooms or small rooms with two to four beds allow for easier separation of different patient cohorts.
- ✔ General hospitals should also have isolation rooms available for TB suspects and contagious patients.
- ✔ Sputum collection and sputum induction areas may be established outside in open air where bacilli will naturally be dispersed by wind.
- ✔ In cold-climate regions, indoor rooms with UVGI and at least six ACHs could be an option.

Ultraviolet germicidal irradiation (UVGI)

- ✔ M. tuberculosis is sensitive to germicidal radiation of UV found in the UV-C portion of the ultraviolet spectrum. The UV-C radiation in natural light does not inactivate the TB bacillus, but UVGI lamps can provide an appropriate germicidal dose.

- ✔ UVGI lamps are reserved for high-risk areas (sputum collection, sputum induction areas, poorly ventilated spaces with less than six ACHs, etc.) where other environmental measures are not sufficient due to climatic (hot arid or cold regions) or structural constraints.

- ✔ UV lamp usage requires specific procedures and present several main challenges.

Personal protection

Respirators

- ✔ Respirators (also known as high-filtration masks, N95 masks, or FFP2 masks) provide a bacterial filtration efficiency of greater than 95 percent if challenged with 0.3-micron particles.
- ✔ M. tuberculosis is trapped in the filter of a mask, which will not be released with shaking or other physical movements of the mask. It eventually dies once outside the human body.
- ✔ These masks should be worn.

When to Wear the Respirator

(N95 masks)

- When entering a TB isolation area
- During contact with a patient with suspected or confirmed active TB
- During high risk procedures on high risk patient groups

A respirator may be re-used by the same person until it becomes wet or damaged.

- ✔ Attendants and visitors must wear a high-filtration mask (like those worn by staff) when entering a contagious TB patient's room.

- ✔ Respirators classified as disposable can be reused by the staff as long as they are not wet, or damaged in any way, and provided they do not have loosened straps. The filter materials remain functional for weeks or months, however, the fitting may decrease with frequent wearing.

- ✔ If the filter material is damaged or the mask has loose straps, the respirator should be discarded. There is no set limit of days of use, but if a respirator is used extensively for seven days, it may be discarded. If it is only used a few hours two to three times per week, it can be kept and reused for several weeks. Storage should not crush or damage the mask.

- ✔ Respirators can be disposed in normal waste and do not need to be incinerated. Masks should not be shared between staff.

Simple cloth masks and surgical masks

Contagious patients must wear a simple cloth, surgical, or face mask when they leave their rooms to go to another department or any other enclosed area. The mask is intended to prevent projection of M. tuberculosis by the patient

Waste management

- ✔ In wards, where patients are coughing regularly, sputum containers should be about 200 mL, sealable, nonsterile containers.
- ✔ Laboratory sputum containers are smaller (25-35 mL), with hermetic cap, nonsterile, and for single use.
- ✔ Used containers should be collected in a trash bag and incinerated. Do not reuse. Do not fill the containers with chlorine solution before incineration (this can produce toxic gases).
- ✔ Standard infectious health care waste treatment related to sharp and soft waste should be respected. There are no specific measures for TB services.

Thank you for your attention !