### MINISTRY OF HEALTH OF UKRAINE National Pirogov Memorial Medical University, Vinnytsya

"AGREED"

Head of Department of Tuberculosis, Clinical Immunology and Allergy

Ass Prof Ludmila KULIK

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## A self-study module for medical students

Academic discipline	Phthisiology		
Module 1	Phthisiology		
Thematic module 4	Clinical management of tuberculosis		
Topic	Individual, standard, empirical treatment tuberculosis	of	
Course	4		
Faculty	General medicine		

The global struggle to eliminate tuberculosis, an infectious disease that kills over 1 mln people every year, has recently encountered a serious obstacle – an uprise of multidrug resistant (MDR) forms of Mycobacterium tuberculosis. Countries of the Eastern Europe account for the majority of MDR cases in WHO European Region. In 2020, Ukraine alone had 7 265 MDR-TB cases compared to 865 in all EU/EEA countries.

Globally, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years. There were an estimated 1.2 million (range, 1.1– 1.3 million) TB deaths among HIV-negative people in 2019 (a reduction from 1.7 million in 2000), and an additional 208 000 deaths (range, 177 000–242 000)6 among HIV-positive people (a reduction from 678 000 in 2000) (WHO, 2020).

Poor treatment outcomes including death, treatment failure, and lost to follow-up accounted for 30-40% of multidrug resistant (MDR) and 50-60% of extensively drug resistant (XDR) TB cases in 2020 worldwide [ECDC, 2020]. MDR/XDR-TB is caused by Mycobacterium tuberculosis strains harboring chromosomal mutations that convey antibiotics resistance. The number of new MDR/XDR -TB cases notified globally in 2019 reached 208 000 causing high economic burden due to direct and indirect costs of active case finding and clinical management. The treatment success rate for people newly enrolled on treatment in 2018 was 85% (WHO).

Without treatment, the mortality rate from TB is high. Studies of the natural history of TB disease in the absence of treatment with anti-TB drugs (conducted before drug treatments became available) found that about 70% of individuals with sputum smear-positive pulmonary TB died within 10 years of being diagnosed, as did about 20% of people with culture-positive (but smear-negative) pulmonary TB (WHO).

#### 2. Learning Objectives (main learning issues for self-study).

- 1. Be able to prescribe treatment of new TB patients.
- Be able to analyze the main advantages and disadvantages of using combined fixed dosage formulations in comparison versus standard single-drug formulations.

- 3. To study the indications for intermittent regimen during the intensive phase of drug-susceptible TB treatment.
- 4. To understand indications for adjuvant corticosteroids in tuberculosis management.
- 5. Choose the regimen for rifampicin-susceptible, isoniazid-resistant tuberculosis.
- 6. To master the most optimal interventions for the formation of adherence to treatment in patients with TB?
- 7. Be able to identify the main drugs and methods of active monitoring for the prevention and treatment of adverse reactions to anti-TB drugs.
- 8. To get practical skills required for TB case definitions according with WHO classification, formulate differential diagnosis and be competent at the basic principles of treatment.
- 9. To understand pathogenesis and mechanisms of TB transmission.
- 10. To be able differentiate latent TB infection from active TB disease, secondary and primary TB.

#### 3. INTERDISCIPLINARY INTEGRATION

Subjects	Required skills		
1. Human Anatomy	General structure of the lungs: basic lobar, mediastinal, and fissure anatomy. Anatomic relationships		
2. Normal physiology	Ventilation of the lungs and alveoli. Pulmonary function testing. Static and dynamic lung volumes. Gas transfer and arterial blood gas assessment		
3. Microbiology and Immunology	Study of infectious process. Mycobacteria (the causative agent of tuberculosis), structure, pathogenic factors. Types of mycobacteria and their epidemiological significance. Nontuberculous mycobacterial diseases		
4. Pharmacology	Pharmacokinetics of drugs. TB antibiotics, classification, dosage, administration.		
5. Radiology	Lung imaging. Lung CT.		

6. Pathologic
anatomy

# TB as an infectious disease. Granulomatous inflammation. Structure of specific granuloma in tuberculosis.

- 1. MDR-TB: TB caused by Mycobacterium Tuberculosis (M. tuberculosis) strains that are resistant to at least both rifampicin and isoniazid.
- 2. Extensively drug resistant TB (XDR-TB): TB that is resistant to any fluoroquinolone and to at least one of Group A drugs (linezolid or bedaquiline), in addition to multidrug resistance.
- 3. Longer multidrug-resistant TB (MDR-TB) regimens: used for treatment of multidrug- or rifampicinresistant TB (MDR/RR-TB), these regimens last 18 months or more, and are designed using a hierarchy of recommended medicines, including a minimum number of medicines considered to be effective based on drug-resistance patterns or patient history.
- 4. Shorter MDR/RR-TB regimen: a course of treatment for MDR/RR-TB lasting 9–12 months, which is largely standardized, and whose composition and duration follows closely the one for which there is documented evidence from different settings.
- 5. A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.

#### **Standards for Public Health Responsibilities**

All providers of care for patients with tuberculosis should ensure that persons (especially children under 5 years of age and persons with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations.

Children under 5 years of age and persons with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with M. tuberculosis and for active tuberculosis.

All providers must report both new and retreatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

#### **Theoretical questions:**

- 1 Monitoring patient response to MDR-TB treatment using culture.
- 2 Starting antiretroviral therapy in patients on second-line anti-TB regimens.
- 3 Surgery for patients on multidrug-resistant TB treatment.
- 4 Treatment administration options to patients on TB treatment:
  - a) Community- or home-based directly observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment
  - b) DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members or unsupervised treatment
  - c) Video-observed treatment (VOT) may replace DOT when the video communication technology is available, and it can be appropriately organized and operated by health care providers and patients.
- 5 Fixed-dose combinations of anti-TB drugs
- 6 Standard regimens for defined patient groups

For people with clinically suspected TB, a TB specialist should request rapid diagnostic nucleic acid amplification tests for rifampicin resistance on primary specimens if a risk assessment for multidrug resistance identifies any of the following risk factors:

history of previous TB drug treatment, particularly if there was known to be poor adherence to that treatment

contact with a known case of multidrug-resistant TB

birth or residence in a country in which the World Health Organization reports that a high proportion (5% or more) of new TB cases are multidrug-resistant (NICE, 2020)

#### Table Treatment regimen for people with TB that is resistant to 1 drug

Drug resistance	First 2 months (initial phase)	Continue with (continuation phase)
Isoniazid	Rifampicin, pyrazinamide and ethambutol	Rifampicin and ethambutol for 7 months (up to 10 months for extensive disease)

Pyrazinamide	Rifampicin, isoniazid (with pyridoxine) and ethambutol	Rifampicin and isoniazid (with pyridoxine) for 7 months
Ethambutol	Rifampicin, isoniazid (with pyridoxine) and pyrazinamide	Rifampicin and isoniazid (with pyridoxine) for 4 months
Rifampicin	As for multidrugresistant TB	

**NICE, 2020** 

## **New Classification WHO-2018**

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines	Levofloxacin <u>OR</u> Moxifloxacin	Lfx Mfx
(unless they cannot be used)	Bedaquiline <sup>1,4</sup>	Bdq
	Linezolid <sup>2</sup>	Lzd
Group B:	Clofazimine	Cfz
Add both medicines (unless they cannot be used)	Cycloserine <u>OR</u> Terizidone	Cs Trd
Group C:	Ethambutol	E
Add to complete the regimen and when	Delamanid <sup>3,4</sup>	Dlm
medicines from Groups A and B cannot be	Pyrazinamide <sup>5</sup>	Z
used	Imipenem-cilastatin <u>OR</u> Meropenem <sup>6</sup>	Ipm-Cln Mpm
	Amikacin ( <u>OR</u> Streptomycin) <sup>7</sup>	Am (S)
	Ethionamide <u>OR</u> Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

#### PRE-CLASS READING LIST

NICE Tuberculosis Clinical Guidancewww.nice.org.uk/search/guidancesearchresults.jsp? keywords=TUBERCULOSIS&searchType=guidance

European Respiratory Society ersnet.org

British Lung Foundation, www.lunguk.org

TB Alert, www.tbalert.org / www.thetruthabouttb.org

- 2. Centers for Disease Control and Prevention (CDC) TB Guidelines (listed by category or by date)http://www.cdc.gov/tb/pubs/mmwr/maj\_guide.htm
- 3. American Thoracic Society. Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis 1990; 142:725-735.
- 4. Institute of Medicine. Ending Neglect: the elimination of tuberculosis in the United States. Washington, DC: National Academy Press; 2000.

Self-study module established by

Associate Professor Dr Litvinyuk O. MD PhD

Self-study module approved at the meeting of the department "29" 08.2025 Protocol №1.

Head of the department Associate Professor Dr Kulyk L MD PhD