CONTENT ANALYSIS OF COMBINED ANTI-TUBERCULOSIS DRUGS

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Introduction

Tuberculosis (TB) remains one of the leading causes of death from infectious diseases in the world. The situation is complicated by the increasing prevalence of multidrug-resistant forms of the pathogen Mycobacterium tuberculosis against the background of covid, post-covid, long-covid disorders, which requires improving approaches to pharmacotherapy according to the requirements of ICD-11. According to the World Health Organization, more than ten million new cases of tuberculosis are registered in the world annually, while about one million three hundred thousand patients die [1-5].

Standard treatment of active tuberculosis, recommended by the World Health Organization, involves the use of a combination of at least three or four anti-tuberculosis drugs. This approach allows you to effectively combat the bacterial load, reduce the risk of developing drug resistance, shorten the duration of therapy, and reduce the frequency of relapses of the disease [6].

Fixed-dose combination drugs, which contain several active pharmaceutical ingredients in one dosage form, are designed to increase patient adherence to treatment and prevent dosing errors. These drugs are particularly relevant in countries with high tuberculosis incidence rates, where non-adherence to treatment regimens is common. Numerous studies have shown that fixed-dose combination drugs provide efficacy and safety comparable to single drugs, and reduce the risk of drug resistance [7, 8].

However, the use of fixed-dose combination drugs has certain limitations. Among patients with human immunodeficiency virus co-infection, pharmacokinetic interactions between anti-tuberculosis and antiretroviral drugs are possible. This can lead to changes in the concentration of active substances in the blood, reduced treatment efficacy, or increased toxicity [9]. In addition, the use of fixed-dose combination drugs may be inappropriate in cases of individual intolerance to one of the components or if dosage adjustment is necessary for a particular patient.

Thus, despite the advantages of fixed-dose combination anti-tuberculosis drugs, their use requires an individual approach and constant monitoring of the effectiveness and safety of therapy. The rational use of such drugs in national tuberculosis control programs is a key factor in the successful control of this global health problem [10].

Overcoming multidrug-resistant tuberculosis is a challenging task, as the bacteria that cause this infection can develop resistance to standard anti-TB drugs. However, combination antimycobacterial chemotherapy remains the mainstay of treatment. It involves the use of at least three anti-TB drugs to which the bacteria are still susceptible, and the duration of treatment is at least 6 months [11, 12].

The main principles of anti-TB chemotherapy are:

- Combination use of anti-TB drugs: The use of several drugs simultaneously reduces the risk of the development of resistance of TB bacteria to one of the drugs.
- Use of standard drug combinations: Certain combinations of anti-TB drugs are defined as standard and are used to treat patients with new cases of TB and relapses of the disease.
- Monitoring by healthcare professionals: Healthcare professionals should ensure that patients take their medications correctly and adhere to their treatment regimen.
- Avoid adding one anti-TB drug after treatment failure: If a patient does not respond to treatment, adding another anti-TB drug to the regimen may lead to further failure.

In addition, antimicrobial therapy is administered under the supervision of healthcare professionals, which allows for monitoring of drug use and prevention of potential complications.

Regarding the convenience of taking medications, the development of combination drugs that contain the active pharmaceutical ingredients necessary for pharmacotherapy can help patients to facilitate their treatment regimen, improve adherence to the therapy protocol, and ensure the quality of the drugs [12].

Overall, the fight against multidrug-resistant tuberculosis requires a comprehensive approach, active collaboration between healthcare professionals and patients, as well as continuous improvement of anti-TB strategies and the development of new drugs to treat this dangerous infection.

The purpose of the study was to conduct a content analysis of the modern range of combined anti-tuberculosis drugs registered on the pharmaceutical market of Ukraine, considering the current requirements of domestic legislation in the field of healthcare. Particular attention is paid to the study of the clinical feasibility of using fixed-dose combination drugs in the pharmacotherapy of tuberculosis in accordance with the provisions of the sixteenth edition of the State Formulary of Medicines, approved by the Order of the Ministry of Health of Ukraine dated March 12, 2024 No. 418 "On Approval and Implementation of the Sixteenth Edition of the State Formulary of Medicines". The work also analyzed current scientific sources on the effectiveness, safety, and impact of combined anti-tuberculosis pharmacotherapy on reducing the level of chemoresistance and increasing patient adherence to treatment.

DOI: 10.5281/zenodo.15662640

Materials and methods

The study is of a content analysis nature and is based on a comprehensive study of open information sources related to combined anti-tuberculosis drugs. The main information resources were: scientific publications from professional domestic and international medical and pharmaceutical journals, official documents of the World Health Organization, analytical materials of international initiatives to combat tuberculosis, as well as current regulatory legal acts of Ukraine in the field of health care.

The analysis of the range of combined anti-tuberculosis drugs registered in Ukraine was carried out using data from the State Register of Medicines of Ukraine. Particular attention was paid to drugs included in the sixteenth edition of the State Formulary of Medicines, approved by the Order of the Ministry of Health of Ukraine dated March 12, 2024 No. 418 “On Approval and Implementation of the Sixteenth Edition of the State Formulary of Medicines”. International non-proprietary names of active pharmaceutical ingredients, trade names of medicines, release forms, dosages, as well as their availability in state reimbursement programs were studied.

In the process of research, methods of content analysis of scientific literature, comparative analysis of regulatory sources, classification method, as well as elements of a statistical approach for quantitative assessment of the presence of combined drugs on the pharmaceutical market of Ukraine, previous studies of foreign and domestic scientists in the direction of content analysis, quality of drugs [13-20] were applied. Special attention was paid to comparing data on the advantages and disadvantages of combination therapy in the context of international and national clinical guidelines, [21-23].

The research of the article is a fragment of research works of Private Scientific Institution "Scientific and Research University of Medical and Pharmaceutical Law" and Danylo Halytsky Lviv National Medical University on the topic "Diagnosis, treatment, pharmacotherapy of inflammatory, traumatic and onco-thoracic pathology using instrumental methods" (state registration number 0125U000071, implementation period 2025-2031); Lviv Medical Institute on the topic of "Improving the system of circulation of drugs during pharmacotherapy on the basis of evidentiary and forensic pharmacy, organization, technology, biopharmacy and pharmaceutical law" (state registration number 0120U105348, implementation period 2021-2026); Private Scientific Institution "Scientific and Research University of Medical and Pharmaceutical Law" on the topic “Multidisciplinary research of post-traumatic stress disorders during war among patients (primarily combatants)” (state registration number 0124U002540, implementation period 2024-2028).

Results and discussion

The current state of use of fixed-dose combination anti-TB drugs demonstrates their high efficacy and safety in the treatment of tuberculosis. The study conducted by scientists showed that four-component combination drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) have efficacy comparable to individual drugs, while reducing the risk of drug resistance and improving patient adherence to treatment [24].

Additionally, a systematic review published in a European journal confirmed that fixed-dose combination drugs provide similar efficacy and safety compared to individual drugs, while simplifying the dosing regimen and reducing the number of medication errors [25].

In the context of Ukraine, according to the State Register of Medicines, several fixed-dose combination drugs are available on the market that meet international standards for the treatment of tuberculosis. Drugs containing combinations of rifampicin, isoniazid, pyrazinamide, and ethambutol are widely used in national tuberculosis control programs.

In addition, according to information published in a report by the World Health Organization, in 2024, the procurement of short-term four-month treatment regimens for children with uncomplicated tuberculosis, including pediatric formulations of fixed-dose combination drugs, was supported, which is an important step in improving access to treatment for pediatric patients [26].

Thus, the use of fixed-dose combination anti-tuberculosis drugs is an effective and safe approach to the treatment of tuberculosis, which helps to improve patient adherence to therapy and reduce the risk of developing drug resistance.

The combined use of anti-tuberculosis drugs is the main principle of antimicrobial therapy in patients with multidrug-resistant tuberculosis [27].

Multidrug-resistant tuberculosis occurs when the Mycobacterium tuberculosis bacteria that cause the disease become resistant to one or more of the anti-TB drugs commonly used in standard anti-TB therapy [28].

Combination therapy refers to the simultaneous use of multiple active pharmaceutical ingredients to treat tuberculosis. This is important because in multidrug-resistant tuberculosis, some drugs may not be effective due to the development of resistance in the bacteria. Combination therapy allows for more effective eradication of the bacteria and reduces the risk of further development of resistance [29].

This approach also reduces the risk of new mutations developing and helps improve treatment outcomes. Treatment of multidrug-resistant tuberculosis can be long-term (lasting several months or even years) and usually requires monitoring and regular use of the drugs to achieve successful results [30-37].

The international nonproprietary names (INN) and clinical-pharmacological groups of combination antituberculosis drugs are given in Table 1.

For the analysis, a proprietary drug selection methodology was first developed, which included 5 criteria, which are presented in Fig. 1.

DOI: 10.5281/zenodo.15662640

Table 1: International nonproprietary name and clinical-pharmacological groups of combination antituberculosis drugs

No.	INN	Clinical and pharmacological group
1.	Rifampicin + ethambutol + isoniazid	Antituberculosis drugs. ATC code J04A M 02
2.	Rifampicin + isoniazid + pyrazinamide + ethambutol	Combined antituberculosis drugs. ATC code J04A M06
3.	Sodium aminosalicylate + isoniazid	Combined antituberculosis drugs. ATC code J04A M.
4.	Rifampicin + isoniazide	Combined antituberculosis drugs. ATC code J04A M02

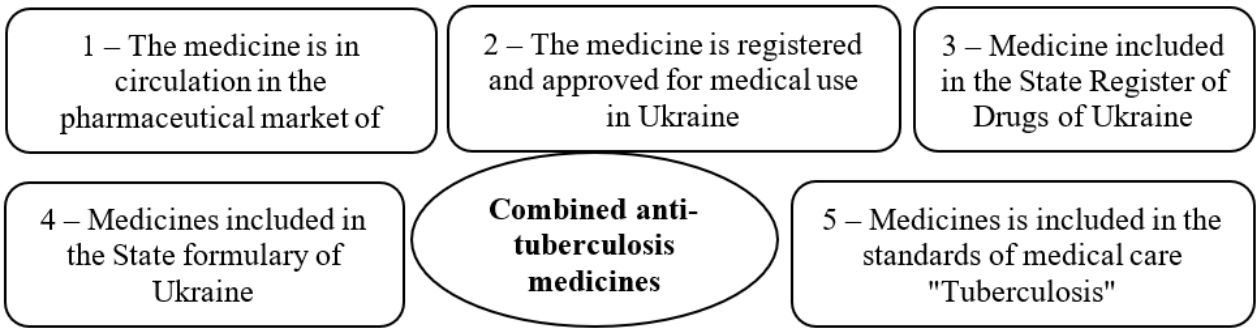

Figure 1. Criteria for selection of combined anti-tuberculosis drugs for the study
Source: own development

Content analysis was performed by grouping drugs by the indicator of the drug manufacturer. The grouping indicator was understood as the country of the manufacturer of the combined anti-tuberculosis drug, the products of which are registered in Ukraine.

Content analysis of drugs was performed by manufacturers by grouping them using the Sturges formula with subsequent construction of discrete series of variations and a distribution polygon. The Sturges formula used to calculate the number of drug groups has the following form:

$$n = 1 + 3.322 \lg N, \quad (1)$$

where n is the number of variations; N is the number of drug manufacturers.

The step limits of the specified drug groups were determined by the following formula:

$$h = \frac{X\max - X\min}{n}, \quad (2)$$

where h is the step size of the group;
X_{max} – the maximum number of manufacturers;
X_{min} – the minimum number of manufacturers [38-41].

The primary data for the content analysis were selected as combined anti-tuberculosis drugs approved for circulation in Ukraine, which, according to the State Register of Drugs of Ukraine as of January 2025, were registered and approved for circulation in health care institutions. After summarizing the processed data, a list of combined anti-tuberculosis drugs was compiled, which includes 9 drug names (Table 2).

Table 2: List of combined anti-tuberculosis drugs

No.	Trade name/Manufacturer/Country	Dosage form, weight, amount per unit
1.	Akurit-3 / Lupin Limited / India	Tablets, without coating, in blister pack / 150 mg / 275 mg
2.	Rifampicin + isoniazid + ethambutol hydrochloride / Lupin Limited / India	Tablets, without coating, in blister pack / 75 mg
3.	Rifampicin 150 mg / isoniazid 75 mg / pyrazinamide 400 mg / ethambutol hydrochloride 275 mg / Swissera Labs Private Limited / India	Coated tablets, peroral use, in blister pack / 150 mg / 275 mg
4.	Forecox trek / Mcleods Pharmaceuticals Limited / India	Tablets, without coating, in strip and blister pack / 75 mg
5.	Pas-izo / PJSC "Technolog" / Ukraine	Granules, for oral suspension, 100 g in package / 150 mg / 75 mg / 400 mg / 275 mg

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6.	Rifampin and isoniazid / Lupin Limited / India	Dispersible tablets in strip / 150 mg / 75 mg / 400 mg / 275 mg
7.	Rifampicin 150 mg / isoniazid 75 mg / Swissera Labs Private Limited / India	Tablets in blister pack / 0.8 g / 0.0233 g
8.	Rifampicin 75 mg and isoniazid 50 mg / Mcleods Pharmaceuticals Limited / India	Dispersible tablets in strip / 75 mg / 50 mg
9.	Rifampicin / isoniazid / Mcleods Pharmaceuticals Limited / India	Coated tablets, peroral use, in blister pack / 150 mg / 75 mg

For content analysis, the studied drugs were distributed according to the indicator for calculating the number of drug manufacturing countries.

For content analysis of drugs by manufacturers, primary data on manufacturers and the number of studied drugs from the list were selected and processed (Table 3).

Table 3: Primary data for content analysis of drugs from the list by manufacturers

No.	Manufacturer	Quantity of medicines
1.	Lupin Limited, India	3
2.	Mcleods Pharmaceuticals Limited, India	3
3.	PJSC "Technolog", Ukraine	1
4.	Swissera Labs Private Limited, India	2
	Total	**9**

From Table 3 it is seen that the products of 4 manufacturers are represented in circulation in the health care center. The number of drug names of these manufacturers is from 1 to 3 positions.

When calculating the number of drugs produced by different pharmaceutical manufacturers, according to formula 1, the number of groups was determined:

n=1+3,322·lgN= 1+3,322·lg4= 2,9

we take n=3 groups

and according to formula 2, the group step is determined

$$h = \frac{X\max - X\min}{n}$$

$$h = \frac{(3-1)}{3} = 0,6$$

we take h =1

The distribution of the step according to the groups is given in Table 4.

Table 4: Determination of the step limit of drug groups when generalizing by manufacturers

Group No.	Initial pitch value	Final pitch value
1	0	1
2	2	2
3	3	3

Source: own development

According to the calculations, the studied combined anti-tuberculosis drugs were distributed by 4 manufacturers into three groups, as indicated in Table 5.

Table 5: Manufacturer and number of names of combined anti-tuberculosis drugs

No.	Manufacturer, Country	Quantity of medicines
The 1st group		
1.	PJSC "Technolog", Ukraine	1
	Total	**1**
The 2nd group		
1.	Swissera Labs Private Limited, India	2
	Total	**2**
The 3rd group		
1.	Lupin Limited, India	3
2.	Mcleods Pharmaceuticals Limited, India	3
	Total	**6**

Source: own development

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Based on the data obtained in Table 5, we can conduct an analysis of the pharmaceutical market by drug manufacturers whose products are in demand in health care facilities. The first group includes one Ukrainian manufacturer PJSC "Technolog", whose drugs are in circulation in health care facilities in the range from 0 to 1 name.

The second group includes one Indian manufacturer of combined anti-tuberculosis drugs and 2 names of drugs.

Based on the data in Table 5, the third group includes two Indian manufacturers whose drugs are in circulation and have 6 names of drugs. This indicates that these manufacturers provide health care facilities with economically affordable combined anti-tuberculosis drugs and their products are in greater demand in health care facilities.

Based on the content analysis of drugs by manufacturers and by quantitative indicator, statistical processing of the research results was carried out by constructing discrete variation series and polygons of the distribution of the data obtained. Discrete variation series of drug distribution in Table 6.

Table 6: Discrete variation series

No.	Range of the group	Frequency, f_i
1	0-1	1
2	2-2	2
3	3-3	6

Source: own development

Discrete variation series is an ordered distribution of units of the studied population into groups (according to the results of grouping using the Sturges formula) according to a certain variable (the number of combined anti-tuberculosis drugs produced by pharmaceutical companies). The obtained discrete variation series of the distribution of drugs indicates that the studied quantitative indicator of drug manufacturers fluctuates within the third group (range from three to three) with the highest frequency (f_i=6). Graphically, the discrete variation series of the studied drugs is presented in Fig. 2 in the form of a distribution polygon.

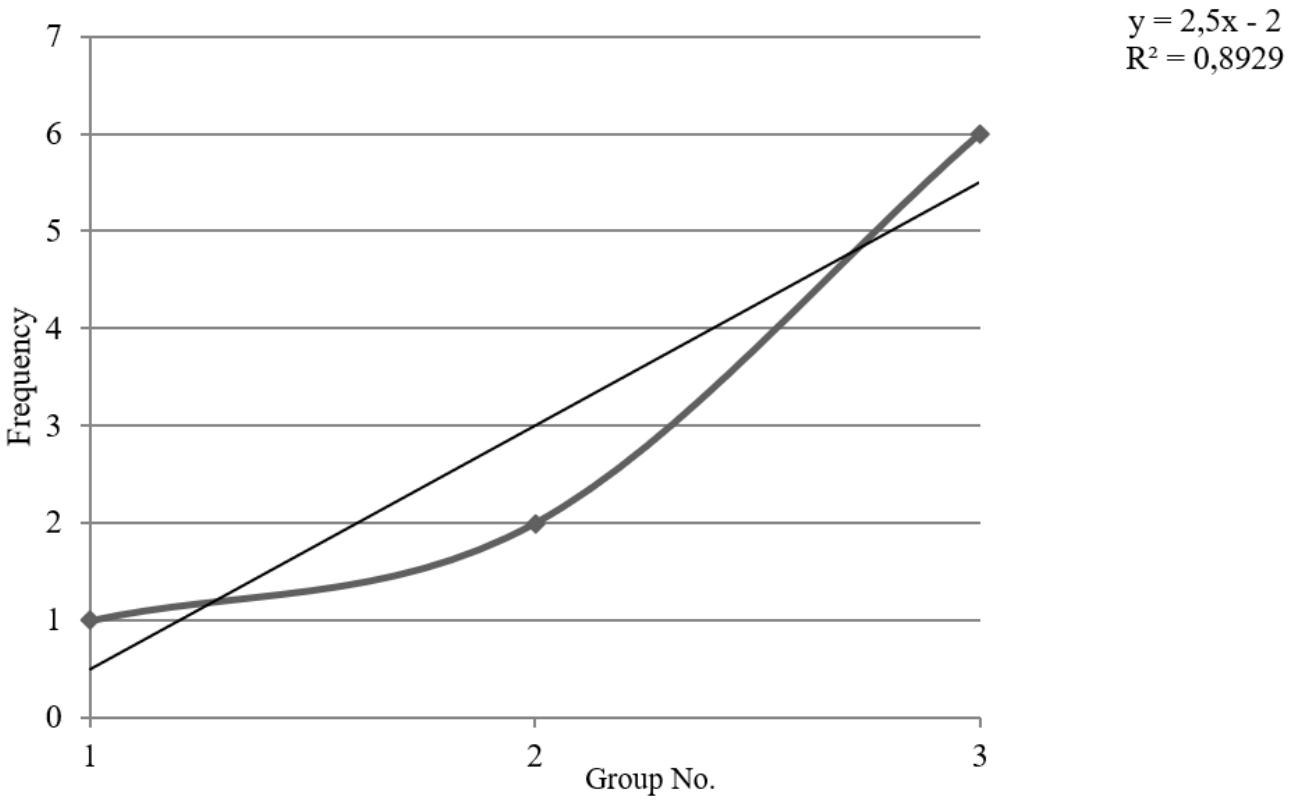

Fig. 2. Discrete variation series of the studied combined anti-TB drugs by manufacturers
Source: own development

The data of Fig. 2 show, however, that we have three groups of the studied drugs by manufacturers. The first group includes one Ukrainian manufacturer PrJSC "Technolog", which produces combined anti-TB drugs. The second group includes one Indian manufacturer of combined anti-TB drugs, which produces 2 names of drugs. The third group includes two Indian manufacturers, whose drugs are in circulation and have 6 names of drugs. This indicates that these manufacturers provide health care facilities with economically affordable combined anti-TB drugs and their products are in greater demand in health care facilities.

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Conclusions

In the context of the growing threat of multidrug-resistant tuberculosis, expanding the range and localization of production of combined anti-TB drugs in Ukraine is extremely relevant. The conducted content analysis showed that the pharmaceutical market of such drugs is currently dominated by foreign, mainly Indian, manufacturers. At the same time, the domestic segment is represented to a limited extent, the drug Pas-izo / PJSC "Technolog" / Ukraine.

To increase the effectiveness of the national response to the challenges of tuberculosis, it is advisable to stimulate the development of domestic production of fixed-dose combination drugs that will meet international standards of quality, safety, and effectiveness. Such an approach will contribute to increasing the accessibility of treatment, reducing the cost of pharmacotherapy, and strengthening the pharmaceutical sovereignty of the state.

In addition, research and development activities in the field of creating new combinations of anti-tuberculosis drugs, particularly those aimed at overcoming the multidrug resistance of the pathogen, need to be intensified. The introduction of modern combination therapy schemes considering national needs and global trends will allow to strengthen control over tuberculosis and ensure an adequate level of public health.

Declaration of conflict interest. Authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Authors confirm that they are the authors of this work and have approved it for publication. Authors also certify that the obtained clinical data and research were conducted in compliance with the requirements of moral and ethical principles based on medical and pharmaceutical law, and in the absence of any commercial or financial relationships that could be interpreted as potential conflict of interest.

Data availability statement. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Content analysis of combined anti-tuberculosis drugs

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Introduction. The fight against tuberculosis remains one of the main challenges in global public health. The emergence of multidrug-resistant tuberculosis (MDR-TB) has significantly complicated the effectiveness of standard anti-TB therapy. The use of combined fixed-dose drug formulations is a key approach to increase treatment adherence and therapeutic efficacy. **Materials and methods.** The study involved a content analysis of the assortment of combined anti-tuberculosis medicines registered in Ukraine. The data were grouped by manufacturers using Sturges' formula to create discrete variation series and a frequency polygon. The availability of drugs in the State Formulary and the national legislation was also analyzed as of the current edition approved by Order of the Ministry of Health of Ukraine dated March 12, 2024, No. 418. **Results and discussion.** The study found that the use of combined anti-tuberculosis drugs is critical for the treatment of MDR-TB. The analysis showed that fixed-dose combinations offer pharmacological benefits, improve patient compliance, and reduce the risk of developing resistance. The Ukrainian pharmaceutical market offers a limited number of such combinations, with a significant share represented by foreign manufacturers. The current State Formulary reflects the need to expand access to essential anti-tuberculosis drug combinations. **Conclusions.** The combined use of anti-tuberculosis drugs is an effective strategy in MDR-TB treatment. Ensuring availability and expanding the range of fixed-dose combinations in Ukraine is vital for improving treatment outcomes and aligning with WHO recommendations.

Keywords: tuberculosis, MDR-TB, fixed-dose combinations, anti-tuberculosis drugs, pharmaceutical market, treatment strategy.

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DOI: 10.5281/zenodo.15662640