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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

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7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

COMPLIANCE OF INITIALLY PRESCRIBED ANTI-TUBERCULOSIS TREATMENT REGIMENS WITH COMPLETE DRUG SUSCEPTIBILITY TEST RESULTS AND ITS ASSOCIATION WITH TREATMENT OUTCOMES IN GEORGIA (2015-2020)

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Tuberculosis continues to be a public health crisis for whole world. Globally, an estimated 10.0 million people fell ill with TB in 2018. The burden of disease varies enormously among countries, from fewer than five to more than 500 new cases per 100 000 population per year, with the global average being around 130. There were an estimated 1.2 million TB deaths among HIV-negative people in 2018 and an additional 251 000 deaths among HIV positive people. TB affects people of both sexes in all age groups but the highest burden is in men (aged ≥15 years), who accounted for 57% of all TB cases in 2018. By comparison, women accounted for 32% and children (aged <15 years) for 11%. 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 [1].

According to the World Health Organization (WHO), in 2018, the total number of notified TB Cases in Georgia was 2 590 (incidence – 65 cases per 100 000 population). MDR-TB was diagnosed in 12% of new, and in 31% of previously treated cases. The treatment outcome was defined as successful in 84% of new and relapse cases registered in 2017 (cohort - 2351), in 65% of MDR/RR-TB and in 56% of XDR-TB cases started on second-line treatment in 2016 (cohorts – 339 and 55, respectively) [2].

In line with WHO recommendations, the Georgian algorithm for TB diagnosis recommends the GeneXpert MTB/RIF test and the line probe assays (LPAs) as the initial diagnostic tests for TB [3,4]. These rapid molecular genotypic drug susceptibility tests (gDSTs) can identify susceptibility to the one or two (Rifampicine or Isoniazid) key drugs out of four first-line anti-TB drugs which should be used in the DS-TB treatment regimens. The complete DST profile, such as susceptibility to all drugs, which may be included in the TB regimen, requires phenotypic DST (pDST), the results of which become available only two months after treatment initiation. Within this period only real DS-TB cases receives appropriate treatment. TB patients, who based on gDST started DS-TB treatment, but based on pDST are diagnosed as mono-, poly- or even as MDR- or XDR-TB cases, before pDST results are treated with first line drugs inappropriately.

A meta-analysis of previous studies shows that inaccurate DST by comparison to a reference standard led to under treatment of drug resistant tuberculosis and increased mortality. Rapid molecular DST of first- and second-line drugs at diagnosis is required to improve outcomes in patients with MDR-TB and pre-XDR/XDR-TB [5]. Comprehensive drug susceptibility testing (phenotypic and/or genotypic) is necessary to inform physicians about the best drugs to treat individual patients with tailor-made treatment regimens. Phenotypic drug resistance can now often, but with variable sensitivity, be predicted by molecular drug susceptibility testing based on e.g. whole genome sequencing (WGS), which in the future could become an affordable method for the guidance of treatment decisions, especially in high-burden/resource-limited settings [6]. Although commercial genotypic drug-susceptibility tests (DST) are close to the goal, they are still not able to detect all relevant DR-TB related mutations. WGS allows better comprehension of DR-TB with a great discriminatory power; it's able to provide all the relevant information about M. tuberculosis drug susceptibility in a single test; and also can detect a mutation in rpoB which is not covered by commercial genotypic DST [8]. Although, the WGS of *Mycobacterium tuberculosis* is rapidly progressed from a research tool to a clinical application for the diagnosis and management of tuberculosis [9], it's still not available for programmatic use in Georgia.

Currently available gDSTs and pDST in Georgia gives opportunity to identify susceptibility to the key anti-TB drugs in majority of cases. In 2019, 99% of bacteriologically confirmed new and 93% of previously treated TB cases were tested for rifampicin resistance; and 242 MDR/RR-TB cases were tested for resistance to any fluoroquinolone [2], but the rate of resistance to the other drugs, the proportion of initially registered DS-TB cases who in period between of gDST and pDST results receives treatment that is fully compliant with the individual DST profile and whether this compliance is associated with the treatment outcomes, was not assessed. A recent study was designed to determine these important data.

Material and methods. A retrospective cohort study was conducted with individual data of >18 years old patients who were registered in the National Tuberculosis Electronic Register as the DS-TB cases from 2015 to 2020, whose DST profile was known and for whom the treatment outcome was defined until August 2020.Considering the inclusion criteria, 8468 patients, initially registered as DS-TB cases (n=1877[2015 cohort] + n=1891[2016 cohort] + n=1710[2017 cohort] + n=1526[2018 cohort] + n=1399[2019 cohort] + n=65[2020 cohort]), with known DST and treatment outcomes were selected as study participants.

The study was conducted at the National Center for Tuberculosis and Lung Disease as part of the Georgian National Tuberculosis Programme.

During the study period TB laboratory networks in Georgia performed smear microscopy, Xpert MTB/RIF testing, culture on solid and liquid media, DST to the first- and second-line drugs by automated Mycobacteria Growth Indicator Tube (MGIT) and LPA methods.

The country uses a standardized electronic TB recording and reporting system. Case classification and definition of treatment category is provided using specialized TB surveillance services in line with the latest WHO recommendations [10].

Data variables were collected in relation to study objectives and included socio-demographic characteristics, laboratory data, data of drug susceptibility tests results and treatment outcomes. The primary outcome was appropriateness of treatment defined as full compliance of prescribed regimens with gDST and pDST results, compared to inappropriate treatment regimens, which before pDST results included resistant drug(s). TB treatment outcomes were categorized as successful (Cured and completed) or unsuccessful (Failure, Death, Lost to follow-up, Moved to category 4, Transfer out or Not evaluated).

The data collected were analyzed by using of EasyStat (https://easystat.app). A descriptive analysis was performed for

socio-demographic, behavioral and clinical characteristics. Bivariate and multivariate logistic regression analysis was used to measure the link between appropriateness of TB treatment and treatment outcome. Odds ratios and their 95% confidence intervals were calculated. All the variables significant at $p<0.05$ in the bivariate analysis were included in the adjusted model.

Permission to carry out the study was obtained from the National Center for Tuberculosis and Lung Diseases (NCTLD) in Georgia. Local ethics approval was obtained from the Ethics Review Board of the NCTLD.

Results and discussion. The data of 13994 TB patients initially registered as DS-TB cases from 2015 and 2020 cohorts were extracted from the National Tuberculosis Electronic Register. According to the inclusion criteria, 8468 TB patients with known DST results and treatment outcomes were selected as the study participants (Fig. 1). From this, at initial stage of TB diagnosis based on rapid molecular gDST results the appropriate treatment regimen was prescribed and later, within period of 8 weeks treatment, based on pDST results the appropriateness of this regimen was confirmed in 8284 (97.8%) cases. These patients were defined as the group, for whom in period between gDST and pDST results an appropriate treatment regimen was used. In 184 (2.2%) cases, based on pDST, resistance to the different first and second line anti-TB drugs and therefore non-appropriateness of initially prescribed 2 months treatment was identified. These patients were defined as the group for whom before pDST results an inappropriate treatment regimen was used.

As the first stage the socio-demographic and clinical characteristics of selected 8468 (100%) TB patients were summarized (Table 1). From the total 8468 (100%) patients, who initially were registered as the DS-TB cases, finally based on gDST and pDST results, the DS-TB was confirmed in 7451 (88%) cases; In 730 (8.6%) cases mono- and poly-resistance and in 287 (3.4%) cases Rifampicin, Multi- or Extensively drug resistant Tuberculosis (RR/MDR/XDR-TB) was detected.

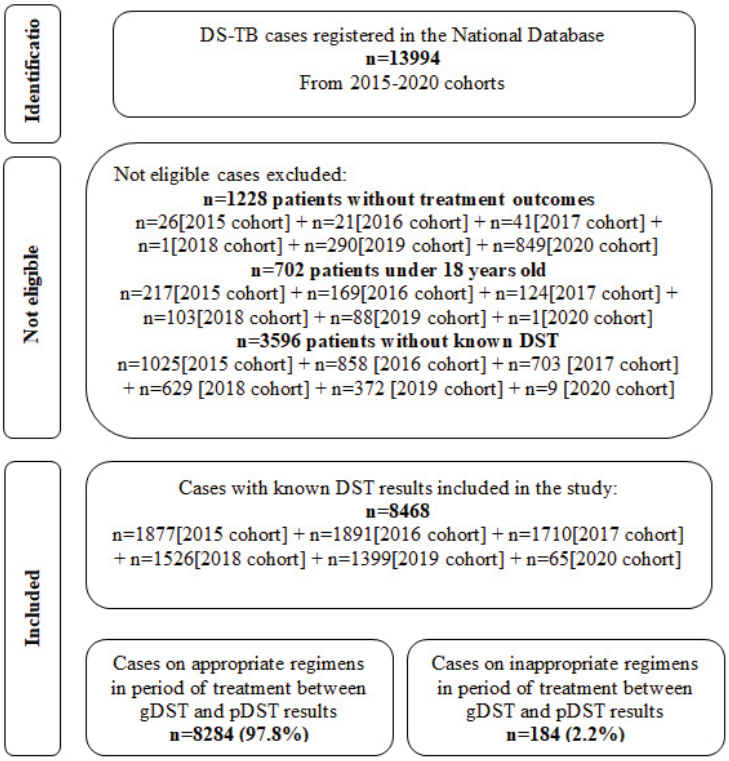


Fig. 1. Study flow chart

Table 1. Socio-demographic and clinical characteristics of the study participants, N=8468 (TB patients, initially diagnosed as DS-TB cases; Georgia; 2015–2020 cohorts)

Categories	Subcategories	Total N=8468
Gender (n,%)	Female	2220 (26.2%)
	Male	6248 (73.8%)
Age (n,%)	18-34	2662 (31.4%)
	35-54	3450 (40.7%)
	55	2356 (27.8%)
Region (n,%)	High	2622 (31%)
	Low	1633 (19.3%)
	Middle	4213 (49.8%)

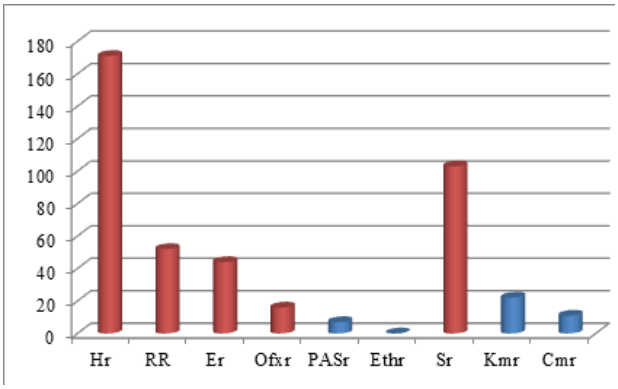
Categories	Subcategories	Total N=8468
Employment (n,%)	Employed	1057 (12.5%)
	Military	17 (0.2%)
	Minor	84 (1%)
	Unemployed	7040 (83.1%)
	Unknown	270 (3.2%)
HIV(+) (n,%)	No	6973 (82.3%)
	Unknown	1328 (15.7%)
	Yes	167 (2%)
HCV(+) (n,%)	No	1019 (12%)
	Unknown	7265 (85.8%)
	Yes	184 (2.2%)
TB Form (n,%)	EPTB	404 (4.8%)
	PTB	8064 (95.2%)
TB Case (n,%)	New Case	6552 (77.4%)
	Previously Treated Case	1916 (22.6%)
AFB(+) at diagnosis (n,%)	No	4057 (47.9%)
	Not Done	480 (5.7%)
	Yes	3931 (46.4%)
Xpert/MTB(+) (n,%)	No	400 (4.7%)
	No Result	78 (0.9%)
	Unknown	769 (9.1%)
	Yes	7221 (85.3%)
Xpert/RR(+) (n,%)	Indeterminate	102 (1.2%)
	No	6874 (81.2%)
	Unknown	1283 (15.2%)
	Yes	209 (2.5%)
Culture (+) (n,%)	No	664 (7.8%)
	Not done	37 (0.4%)
	Unknown	605 (7.1%)
	Yes	7162 (84.6%)
Bacteriological Confirmation (n,%)	C+Yes	1247 (14.7%)
	Xpert/C+Yes	5915 (69.9%)
	Xpert+Yes	1306 (15.4%)
DST type (n,%)	gDST	7074 (83.5%)
	pDST	1394 (16.5%)
Hr (n,%)	No	5651 (66.7%)
	Unknown	1976 (23.3%)
	Yes	841 (9.9%)
RR (notXpert) (n,%)	No	6331 (74.8%)
	Unknown	1965 (23.2%)
	Yes	172 (2%)

Categories	Subcategories	Total N=8468
Er (n,%)	No	6115 (72.2%)
	Unknown	2160 (25.5%)
	Yes	193 (2.3%)
Sr (n,%)	No	4076 (48.1%)
	Unknown	2714 (32.1%)
	Yes	1678 (19.8%)
Kmr (n,%)	No	150 (1.8%)
	Unknown	8250 (97.4%)
	Yes	68 (0.8%)
Cmr (n,%)	No	179 (2.1%)
	Unknown	8250 (97.4%)
	Yes	39 (0.5%)
Ofxr (n,%)	No	162 (1.9%)
	Unknown	8238 (97.3%)
	Yes	68 (0.8%)
Etor (n,%)	No	21 (0.2%)
	Unknown	8445 (99.7%)
	Yes	2 (0%)
PASr (n,%)	No	139 (1.6%)
	Unknown	8307 (98.1%)
	Yes	22 (0.3%)
Resistance type (n,%)	DS-TB	7451 (88%)
	Mono/PDR-TB	730 (8.6%)
	RR/MDR/XDR-TB	287 (3.4%)
Appropriateness of Regimen (n,%)	Appropriate regimen	8284 (97.8%)
	Inappropriate regimen	184 (2.2%)
AFB(+) at II month (n,%)	No	6040 (71.3%)
	Not done	380 (4.5%)
	Unknown	1284 (15.2%)
	Yes	764 (9%)
AFB(+) at III month (n,%)	No	778 (9.2%)
	Not done	267 (3.2%)
	Unknown	7204 (85.1%)
	Yes	219 (2.6%)
AFB(+) at V month (n,%)	No	5499 (64.9%)
	Not done	878 (10.4%)
	Unknown	1941 (22.9%)
	Yes	150 (1.8%)
AFB(+) at VI month (n,%)	No	5443 (64.3%)
	Not done	794 (9.4%)
	Unknown	2131 (25.2%)

Categories	Subcategories	Total N=8468
	Yes	100 (1.2%)
Treatment Outcome (n,%)	Successful	6833 (80.7%)
	Unsuccessful	1635 (19.3%)
Treament Outcome_1 (n,%)	Completed	990 (11.7%)
	Cured	5843 (69%)
	Default	783 (9.2%)
	Died	395 (4.7%)
	Failure	268 (3.2%)
	Moved To Cat Four	39 (0.5%)
	Not Evaluated	136 (1.6%)
	Transfer Out	14 (0.2%)

HIV – human immunodeficiency virus; RR-TB – rifampicin-resistant tuberculosis; MDR-TB – multidrug-resistant tuberculosis; pre-XDR-TB – pre-extensively drug-resistant tuberculosis; XDR-TB – extensively drug-resistant tuberculosis

From 184 patients, for whom between gDST and pDST results an inappropriate 2 month treatment was used, in majority of cases the resistance to the Isoniazid was detected (171 - 93%). Rifampicin resistance was detected in 52 (28%) cases, Ethambutol resitance in 44 (24%) cases, Ofloxacin - in 16 (9%) and Streptomycin resistance in 103 (56%) cases (Fig. 2).



Hr - Isoniazid resistance; RR –Rifampicin resistance; Er – Ethambutol resistance; Ofxr – Ofloxacin resistance; PASr - Para-aminosalicylic acid resistance; Etor – Ethionamide resistance; Sr - Streptomycin resistance; Kr –Kanamycin resistance; Cmr – Capreomycin resistance

Fig. 2. Detected resistance to the first and second line anti-TB drugs in patients on inappropriate treatment regimen (N=184)

At initial stage of TB diagnosis 3931 (46.4%) patients had the AFB(+) results. The same AFB(+) results were defined at the end of the II month treatment in 764 (9%) cases, at the end of III month in 219 (2.6%) cases, at the end of V month in 150 (1.8%) cases and at the end of treatment in 100 (1.2%) cases.

In all study participants (N=8468) TB was bacteriologically confirmed and DST profile of all patients was known. In 5915 (69.9%) cases TB was confirmed based on Xpert MTB/RIF test and culture examination together. In 1306 (15.4%) cases TB was confirmed based on Xpert tests only. In 1247 (14.7%) cases TB was confirmed based on culture (+) results only.

Based on study data discordance between Xpert MTB/RIF and culture tests were revealed. From all 7221 (85.3%) Xpert (MTB+) cases, only 5915 cases were culture positive too (in 37 cases culture was not done and in 605 cases culture results was unknown). All 400 (4.7%) patients with Xpert (MTB-) results, were Culture (+). In 664 cases with Xpert (MTB+) results, Culture was negative (Table 2).

The successful treatment outcome was defined in 6833 (80.7%) (“Cured” in 5843 (69%) and “Completed” in 990 (11.7%) cases) and unsuccessful outcome in 1635 (19.3%) cases (“Lost to follow-up” in 783 (9.2%), “Death” in 395 (4.7%), “Failure” in 268 (3.2%), “Not evaluated” in 136 (1.6%), “Moved to category four” in 39 (0.5%) and “Transfer out” in 14 (0.2%) cases).

All key factors were analyzed for association with the treatment outcomes. The adjusted analysis was used for factors defined as significantly associated with the treatment outcomes (Table 3).

Table 2. Discordance between Xpert MTB/RIF and Culture tests results

		Culture results			
Xpert MTB/RIF test results	**N=8468**	**No N=664**	**Not done N=37**	**Unknown N=605**	**Yes N=7162**
No	400 (4.7%)	0 (0%)	0 (0%)	0 (0%)	400 (5.6%)
No Result	78 (0.9%)	0 (0%)	0 (0%)	0 (0%)	78 (1.1%)
Unknown	769 (9.1%)	0 (0%)	0 (0%)	0 (0%)	769 (10.7%)
Yes	7221 (85.3%)	664 (100%)	37 (100%)	605 (100%)	5915 (82.6%)

Table 3. Factors associated with TB treatment outcomes
(TB patients, initially diagnosed as DS-TB cases; Georgia; 2015–2020 cohorts)

Categories	Subcatego-ries	Total N=8468	Successful N=6833	Unsuccess-ful N=1635	Bivariate			Multivariate		
					Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Gender (n,%)	Female	2220 (26.2%)	1925 (28.2%)	295 (18%)	**1.78**	**[1.55, 2.04]**	**<0.001**	**1.69**	**[1.47, 1.94]**	**<0.001**
	Male	6248 (73.8%)	4908 (71.8%)	1340 (82%)	1			ref.	ref.	ref.
Age (n,%)	18-34	2662 (31.4%)	2296 (33.6%)	366 (22.4%)	1	-	-			
	35-54	3450 (40.7%)	2724 (39.9%)	726 (44.4%)	0.6	[0.52, 0.69]	<0.001			
	55	2356 (27.8%)	1813 (26.5%)	543 (33.2%)	0.53	[0.46, 0.62]	<0.001			
Region (n,%)	High	2622 (31%)	2071 (30.3%)	551 (33.7%)	1	-	-	ref.	ref.	ref.
	Low	1633 (19.3%)	1358 (19.9%)	275 (16.8%)	**1.31**	**[1.12, 1.54]**	**<0.001**	0.7	[0.6, 0.83]	<0.001
	Middle	4213 (49.8%)	3404 (49.8%)	809 (49.5%)	1.12	[0.99, 1.26]	0.0681	0.84	[0.74, 0.95]	0.0059
HIV (n,%)	No	6973 (82.3%)	5812 (85.1%)	1161 (71%)	1	-	-			
	Unknown	1328 (15.7%)	915 (13.4%)	413 (25.3%)	0.44	[0.39, 0.51]	<0.001			
	Yes	167 (2%)	106 (1.6%)	61 (3.7%)	0.35	[0.25, 0.48]	<0.001			
HCV (n,%)	No	1019 (12%)	829 (12.1%)	190 (11.6%)	1	-	-			
	Unknown	7265 (85.8%)	5883 (86.1%)	1382 (84.5%)	0.98	[0.82, 1.15]	0.774			
	Yes	184 (2.2%)	121 (1.8%)	63 (3.9%)	0.44	[0.31, 0.62]	<0.001			
TB Form (n,%)	EPTB	404 (4.8%)	338 (4.9%)	66 (4%)	1.24	[0.94, 1.62]	0.121			
	PTB	8064 (95.2%)	6495 (95.1%)	1569 (96%)	1					
TB Case (n,%)	New Case	6552 (77.4%)	5498 (80.5%)	1054 (64.5%)	**2.27**	**[2.02, 2.55]**	**<0.001**	**2.15**	**[1.91, 2.42]**	**<0.001**
	Previously Treated Case	1916 (22.6%)	1335 (19.5%)	581 (35.5%)	1			ref.	ref.	ref.
DST type (n,%)	gDST	7074 (83.5%)	5685 (83.2%)	1389 (85%)	0.88	[0.76, 1.02]	0.0856			
	pDST	1394 (16.5%)	1148 (16.8%)	246 (15%)	1					
FL drugs Resistance (n,%)	No	5546 (65.5%)	4658 (68.2%)	888 (54.3%)	1	-	-			
	Unknown	1897 (22.4%)	1553 (22.7%)	344 (21%)	0.86	[0.75, 0.99]	0.0318			
	Yes	1025 (12.1%)	622 (9.1%)	403 (24.6%)	0.29	[0.25, 0.34]	<0.001			
SL drugs Resistance (n,%)	No	49 (0.6%)	24 (0.4%)	25 (1.5%)	1	-	-			
	Unknown	6724 (79.4%)	5536 (81%)	1188 (72.7%)	4.85	[2.76, 8.53]	<0.001			
	Yes	1695 (20%)	1273 (18.6%)	422 (25.8%)	3.14	[1.78, 5.56]	<0.001			

Categories	Subcategories	Total N=8468	Successful N=6833	Unsuccessful N=1635	Bivariate			Multivariate		
					Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Resistance type (n,%)	DS-TB	7451 (88%)	6212 (90.9%)	1239 (75.8%)	1	-	-			
	Mono/PDR-TB	730 (8.6%)	570 (8.3%)	160 (9.8%)	0.71	[0.59, 0.86]	<0.001			
	RR/MDR/ XDR-TB	287 (3.4%)	51 (0.7%)	236 (14.4%)	0.04	[0.03, 0.06]	<0.001			
TB Regimen (n,%)	Appropriate	8284 (97.8%)	6726 (98.4%)	1558 (95.3%)	**3.11**	**[2.31, 4.19]**	**<0.001**	**3.3**	**[2.43, 4.48]**	**<0.001**
	Inappropriate	184 (2.2%)	107 (1.6%)	77 (4.7%)	1			ref.	ref.	ref.

TB– tuberculosis; DS-TB – Drug susceptibility tuberculosis; HIV – human immunodeficiency virus; HCV- Hepatitis C virus; DST – Drug susceptibility testing; gDST – Genotypic Drug susceptibility testing; pDST – Phenotypic Drug susceptibility testing; FL – First line; SL – Second line; Mono DR-TB – Mono drug resistant tuberculosis; PDR-TB – Poly drug resistant tuberculosis; RR-TB – Rifampicin resistant tuberculosis; MDR-TB – multidrug-resistant tuberculosis; XDR-TB – extensively drug-resistant tuberculosis; ref. – reference category

In bivariate analysis, TB treatment success was positively associated with the appropriate treatment regimen (OR 3.11; 95% CI [2.31, 4.19]; p<0.001); female gender (OR 1.78; 95% CI [1.55–2.04]; p<0.001); new case (OR 2.27; 95% CI [2.02-2.55]; p<0.001); and with living in the region where TB prevalence is low (OR 1.31; 95% CI [1.12–1.54]; p<0.001).

Adjusted analysis shows significant association of a successful TB treatment outcome with the appropriate treatment regimen (adjusted OR 3.3, 95% CI: (2.43–4.48), p<0.001), female gender (adjusted OR 1.69, 95% CI: 1.47 – 1.94, p<0.001) and with new TB case (adjusted OR 2.15, 95% CI: 1.91–2.42, p<0.001).

According to the study data in majority of cases (8284 (97.8%)) appropriateness of initially prescribed regimen was confirmed. This means, that the treatment regimen prescribed based on initial gDSTs results, with high reliability is in line with pDST results and in majority of cases can lead to the successful outcome.

Based on the study data, in a small but significant number of patients (184 (2.2%)) pDST revealed inappropriateness of initially prescribed regimen and this inappropriateness in majority of cases (171 (93%)) was related with using of resistant Isoniazid in 2 month period before pDST results. Isoniazid is the key anti –TB drug and in case of Isoniazid mono- or poly-resistant TB cases specific Hr-TB regimen is recommended [11]. The possibility to prescribe this regimen in timely manner should be maximized by availability of rapid, highly sensitive gDSTs for maximum number of TB patients. This finding also addresses the need for timely detection of susceptibility to the other drugs to which resistance was less frequently detected, although it was still significant (Rifampicin resistance was detected in 52 (28%) cases, Ethambutol resitance in 44 (24%) cases and Ofloxacin resistance in 16 (9%) cases).

The main finding of our study confirms our initial hypothesis. The study results show a significant association between treatment with appropriate regimen and successful outcome (OR 3.11; 95% CI [2.31, 4.19]; p<0.001). This finding emphasizes the importance of drug susceptibility test results in guiding regimen selection. Therefore, there is urgent need for expansion of laboratory capacity to perform rapid drug susceptibility tests for all potentially used TB drugs.

Adjusted analysis show, that in parallel with "Appropriate treatment", the "Female gender" and the "New case" are significantly associated with successful TB treatment outcomes, which is in line with the results of previously conducted similar studies [12,13].

The separate discussion is needed due the discordance, which was revealed between GeneXpert and culture tests results. Unfortunately, based on the National Tuberculosis Electronic Register it's not possible to differentiate in which case the Xpert MTB/RIF and in which the Xpert MTB/RIF Ultra was used and therefore, based on our data, we were unable to compare Culture and Xpert or Xpert Ultra tests sensitivities. Farther studies are needed to assess degree, reasons and results of discordance between genotypic and phenotypic DSTs. However, even without these studies, based on existing data we can conclude that implementation of the new tests (e.g. WGS or others, depended on the available evidences and country decision) is needed for early and accurate identification of individual, complete DST profiles and successful treatment of TB patients.

Limitations of the study. Study data includes important information about injectable agents (Cm and Km), but it was not underlined and covered in the discussion, because, in line with latest WHO guidelines (2019), Cm and Km are no longer recommended for DR-TB treatment [11]. It would be interesting to review data about Pyrazinamide (one of the first line anti-TB drug), but due the insufficient reliability of currently available Pyrazinamide susceptibility testing, these data were not included in the study.

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SUMMARY

COMPLIANCE OF INITIALLY PRESCRIBED ANTI-TUBERCULOSIS TREATMENT REGIMENS WITH COMPLETE DRUG SUSCEPTIBILITY TEST RESULTS AND ITS ASSOCIATION WITH TREATMENT OUTCOMES IN GEORGIA (2015-2020)

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Georgia has countrywide access to the genotypic and phenotypic drug susceptibility testing (gDST and pDST), however identification of susceptibility to the different anti-Tuberculosis (TB) drugs in different time period, not in all cases gives us opportunity to simultaneously know susceptibility to the all anti-TB drugs and to build an appropriate treatment regimens based on complete individual DST profile in timely manner. Initial TB treatment regimen prescribed based on gDST results not in all cases may be compliant with complete DST profile, which may be detected based on pDST results within eight weeks only. It's important to know proportion of TB patients, who in period between gDST and pDST results are treated with regimens which is non-compliant with complete individual DST profile and how the use of these inappropriate treatment regimens may affect TB treatment outcome.

The aim of the study was to assess compliance of anti-TB treatment regimens with complete DST profile in period between gDST and pDST results and its association with treatment outcomes among patients who initially was registered as drug sensitive TB (DS-TB) cases in Georgia.

A retrospective cohort study was conducted among 8468 patients initially registered as DS-TB adult (18+) cases, from 2015 - 2020 cohorts, whose DST profiles and anti-TB treatment outcomes was known.

Adjusted analysis of the study participants data [8468 (100%)] shows significant association of a successful TB treatment outcome with the "appropriate treatment regimen" (adjusted OR 3.3, 95% CI: (2.43–4.48), p<0.001), "female gender" (adjusted OR 1.69, 95% CI: 1.47 – 1.94, p<0.001) and with "new TB case" (adjusted OR 2.15, 95% CI: 1.91–2.42, p<0.001).

From 184 patients, for whom between gDST and pDST results an inappropriate 2 month treatment was used, in 171 (93%) cases the resistance to the Isoniazid was detected (Rifampicin resistance in 52 (28%), Ethambutol resitance in 44 (24%) and Ofloxacin rsistance in 16 (9%) cases was detected).

Based on study data discordance between Xpert MTB/RIF and culture tests were revealed. From all 7221 (85.3%) Xpert (MTB+) cases, only 5915 cases were culture positive too. All 400 (4.7%) patients with Xpert (MTB-) results were Culture positive. In 664 cases with Xpert (MTB+) results, Culture was negative.

For successful outcomes, all efforts should be done to have the individual and complete DST profiles of all patients at initial stage of TB diagnosis. Otherwise, in case of delayed DST results anti-TB treatment for a certain period maybe inappropriate and can raise the risk of non-successful outcome.

Keywords: Tuberculosis, DS-TB, phenotypic and genotypic DST, susceptibility, resistance, compliance, treatment outcomes.

РЕЗЮМЕ

ОЦЕНКА СООТВЕТСТВИЯ РЕЖИМОВ ПРОТИВОТУБЕРКУЛЕЗНОГО ЛЕЧЕНИЯ ПОЛНОМУ ПРОФИЛЮ ТЕСТИРОВАНИЯ НА ЛЕКАРСТВЕННУЮ ЧУВСТВИТЕЛЬНОСТЬ И ЕГО СВЯЗЬ С ИСХОДАМИ ЛЕЧЕНИЯ БОЛЬНЫХ ТУБЕРКУЛЕЗОМ В ГРУЗИИ

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Генотипическое и фенотипическое тестирование на лекарственную чувствительность (ТЛЧ) проводится на всей

территории Грузии, однако выявление чувствительности к различным противоткберкулезным препаратам в разные периоды времени не во всех случаях позволяет одновременно иметь информацию о восприимчивости ко всем противотуберкулезным препаратам и своевременно строить соответствующие режимы лечения на основе полного индивидуального профиля ТЛЧ. Изначальный режим лечения туберкулеза, назначенный на основе результатов генотипического ТЛЧ, не во всех случаях может соответствовать полному профилю ТЛЧ, который на основе результатов фенотипического ТЛЧ может быть выявлен только в течение восьми недель. Важно знать долю пациентов с туберкулезом, которые в период между результатами генотипического и фенотипического ТЛЧ лечатся режимами, несоответствующими полному индивидуальному профилю ТЛЧ, и как использование этих несоответствующих режимов лечения может повлиять на результаты лечения туберкулеза.

Цель исследования - оценка соответствия режимов противотуберкулезного лечения полному профилю тестирования на лекарственную чувствительность в период между результатами генотипического и фенотипического тестирования и связь с результатами лечения пациентов, зарегистрированных как случаи лекарственно устойчивого туберкулеза в Грузии.

Ретроспективное когортное исследование проведено среди 8468 пациентов, первоначально зарегистрированных как взрослые (+18 лет) случаи лекарственно чувствительного туберкулеза с 2015 по 2020 гг., чьи профили ТЛЧ и исходы противотуберкулезного лечения были известны.

Анализ данных участников исследования показывает статистический значимую связь успешного исхода лечения туберкулеза с «соответствующим режимом лечения» (уточненное ОШ 3,3, 95% ДИ: (2,43-4,48), p<0,001), “женским полом” (уточненное ОШ 1,69, 95% ДИ: 1,47 - 1,94, p < 0,001) и с “новым случаем туберкулеза” (уточненное ОШ 2,15, 95% ДИ: 1,91-2,42, p<0,001).

Из 184 пациентов, для которых между результатами генотипического и фенотипического ТЛЧ использовано несоответствующее двухмесячное лечение, в 171 (93%) случае выявлена устойчивость к изониазиду, устойчивость к рифампицину - в 52 (28%), к этамбутолу - в 44 (24%) и к офлоксацину - в 16 (9%) случаях.

На основании данных исследования выявлено несоответствие между результатами Xpert MTB/RIF и культурального исследования. Из всех Xpert (MTB+) 7221 (85,3%) случая только в 5915 случаях выявлен культура-положительный результат. Все 400 (4,7%) пациентов с Xpert (MTB-) результатами были положительными по культуре. В 664 Xpert (MTB+) случаях результат культурального исследования был отрицательным.

Для успешного лечения туберкулеза необходимо на начальной стадии диагностики получить индивидуальные и полные профили ТЛЧ пациентов. В случае задержки результатов ТЛЧ противотуберкулезное лечение в течение определенного периода может быть несоответствующим и увеличить риск безуспешного лечения.

რეზიუმე

საწყისად დანიშნული ტუბსაწინააღმდეგო რეჟიმის შესაბამისობა მედიკამენტებისადმი მგრძნობელობის ტესტირების შედეგებთან და მისი ასოცირება მკურნალობის გამოსავალთან

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საქართველოში ქვეყნის მასშტაბით ხელმისაწვდომია მედიკამენტებისადმი მგრძნობელობის გენოტიპური და ფენოტიპური ტესტირება (gDST და pDST), თუმცა სხვადასხვა ტუბსაწინააღმდეგო მედიკამენტის მიმართ მგრძნობელობის სხვადასხვა დროს განსაზღვრა ყველა პაციენტთან მედიკამენტებისადმი მგრძნობელობის ერთდროულად განსაზღვრისა და სრულ, ინდივიდუალურ DST პროფილთან შესაბამის ადექვატური სამკურნალო რეჟიმის დროულად დანიშვნის შესაძლებლობას არ იძლევა. gDST-ის შედეგზე დაყრდნობით შერჩეული საწყისი ტუბსაწინააღმდეგო სამკურნალო რეჟიმი ყველა შემთხვევაში შეიძლება არ იყოს შესაბამისი იმ სრულ DST პროფილთან, რომელიც მხოლოდ pDST-ით 8 კვირის ვადაში ხდება ცნობილი. მნიშვნელოვანია განისაზღვროს იმ პაციენტთა წილი, რომლებიც gDST და pDST შედეგებს შორის პერიოდში სრულ, ინდივიდუალურ DST პროფილთან შეუსაბამო მკურნალობას ღებულობს და შეფასდეს არაადექვატური რეჟიმის გამოყენება მკურნალობის გამოსავალზე

კვლევის მიზანი - საქართველოში საწყისად სენსიტიური ტუბერკულოზის მქონე პაციენტებად დარეგისტრირებულ შემთხვევებთან, მედიკამენტებისადმი მგრძნობელობის გენოტიპური და ფენოტიპური ტესტირების შედეგების პერიოდში, ტუბსაწინააღმდეგო სამკურნალო რეჟიმის სრულ DST პროფილთან შესაბამისობის და ამ შესაბამისობის მკურნალობის გამოსავალთან ასოცირების შესწავლა.

რეტროსპექტული კოჰორტული კვლევა 2015-2020 წლების კოჰორტის, +18 ასაკობრივი ჯგუფის, საწყისად სენსიტიური ტუბერკულოზით დარეგისტრირებულ ისეთ 8468 პაციენტთან ჩატარდა, რომლების DST პროფილი და ტუბსაწინააღმდეგო მკურნალობის გამოსავალი ცნობილი იყო. კვლევის მონაწილეთა მონაცემების დაზუსტებულმა ანალიზმა აჩვენა, რომ ტუბსაწინაარმდეგო მკურნალობის წარმატებული გამოსავალი სარწმუნოდ ასოცირდება ადექვატური სამკურნალო რეჟიმით მკურნალობასთან (adjusted OR 3.3, 95% CI: (2.43–4.48), p<0.001), მდედრობით სქესთან (adjusted OR 1.69, 95% CI: 1.47 – 1.94, p<0.001) და „ახალ“ შემთხვევასთან (adjusted OR 2.15, 95% CI: 1.91–2.42, p<0.001).

184 პაციენტთაგან, რომლებსაც gDST და pDST შედეგებს შორის 2-თვიან პერიოდში არაადექვატური ტუბსაწინააღმდეგო რეჟიმი იყო დანიშნული, 171 (93%)-ს იზონიაზიდისადმი რეზისტენტობა გამოუვლინდა, რიფამპიცინისადმი რეზისტენტობა - 52 (28%)-ს, ეტამბუტოლისადმი - 44 (24%)-ს, ოფლოქსაცინისადმი - 16 (9%) პაციენტს.

კვლევის ფარგლებში გამოვლინდა შეუსაბამობა Xpert MTB/RIF და კულტურალური კვლევის შედეგებს შორის. ჯამში, სულ Xpert (MTB+) შედეგის მქონე 7221 (85.3%) პაციენტისგან, კულტურა-დადებითი შედეგი 5915 პაციენტთან დაფიქსირდა. Xpert (MTB-) შედეგის მქონე ყველა 400 (4.7%) პაციენტი აღმოჩნდა კულტურა-დადებითი. 664 Xpert (MTB+) შედეგის მქონე პაციენტთი იყო კულტურა-უარყოფითი.

დადებითი ტუბსაწინააღმდეგო მკურნალობის გამოსავალის მისაღწევად აუცილებელია ტუბერკულოზის საწყისი დიაგნოსტიკისთანავე ყველა პაციენტის სრული, ინდივიდუალური DST პროფილის გამოვლენა. მედიკამენტებისადმი მგრძნობელობის ტესტის გვიანი შედეგების პირობებში დანიშნული ტუბსაწინააღმდეგო რეჟიმი გარკვეული პერიოდის მანძილზე შესაძლოა არაადექვატური იყოს და გამოიწვიოს მკურნალობის წარუმატებელი გამოსავლის რისკის მატება.

DIAGNOSTICS AND TREATMENT OF GENITAL INVASION CAUSED BY TRICHOMONAS VAGINALIS AND POSSIBLY OTHER RELATED SPECIES (PENTATRICHOMONAS HOMINIS AND TRICHOMONAS TENAX) IN PATIENTS WITH IMMUNODEFICIENCY

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Trichomoniasis disease despite its intensive study is nowadays a considerable clinical problem in practice of dermatovenereologists, urologists and gynecologists. Trichomonas invasion has a negative influence on patient fertility and quality of life [11]. According to data of the World Health Organization in recent decades global incidence rate in urinary trichomoniasis (ICD-10, A59) is about 270 million people per year [17].

Until recently it has been believed that only *Trichomonas vaginalis* can exist in human genitourinary tract [18]. However, inclination of Protozoa to evolutionary changes and significant shift in patterns of sexual behaviour, in particular, frequent anal and oral sex practice resulted in the existence of other species of trichomonads in human genitourinary tract, namely, *Pentatrichomonas hominis* and *Trichomonas tenax* [12,13,18].

In Ukraine investigations on determination of *Pentatrichomonas hominis* and *Trichomonas tenax* in the genitourinary tract of patients with sexually transmitted infections (STI) were conducted for the first time in 2013-2017. The mentioned microorganisms were found in more than a third of patients with advanced progressive illness [9,13,19]. In the investigation the abstinence not less than 2 days was strictly observed that made it impossible to consider *Pentatrichomonas hominis* and *Trichomonas tenax* as a transitory microflora. Duration of the investigation minimized the probability of outer contamination. Persistence of chronic inflammation in the patients allowed us to suppose a certain ethiological role of *Pentatrichomonas hominis* and *Trichomonas tenax* in it. Moreover, detection of trichomonad species in genitourinary tract, their elimination, and certain behavioural modifications may play a decisive role in prevention of trichomonias recurrences or re-infections [20]. Besides, it should be also noted that phagocytic features are peculiar to all *Protozoa*, in particular, trichomonads. By phagocytosis carried out by any *Protozoa*, a part of microorganisms is not destroyed completely – they are preserved unhurt (incomplete phagocytosis) inside the cytozoon [3]. In case of incomplete phagocytosis of cocci, diplococci, mycoplasma, Chlamydia, bacillary forms, viruses passing out by death of trichomonads are able to support inflammatory process in urogenital tracts that is often considered to be "untreatable" trichomoniasis or "posttrichomonal" lesions [11]. That's why Protozoa, whereof direct pathogenicity on human urinary system has not been finally proved. First of all, we should consider *Trichomonas tenax* and *Pentatrichomonas hominis,* at least as disease-producing agents of STI. For this reason, eradication of *Trichomonas tenax* and *Pentatrichomonas hominis* from human urinary system should be required.

Thus, urgency of the issue of urinary trichomoniasis is connected with a high incidence of disease as well as possibility of colonization of the urinary system with "new" agents as a result of partial change of their biological properties [9,12,13]. Consideration of presence of the agents, which are morphologically similar to *Trichomonas vaginalis*, but different from them by taxonomic belonging, will present an opportunity of more accurate diagnostics of trichomoniasis and its more successful treatment and prevention.

As it is known from the literature, infectious affections of the urinary system often become chronically persistent or resistant to many treatments in the case of immunodeficiency [16]. Immunodeficiency (ICD-10, D80 – D89) may be determined as impairment of structure and function of any chain of the immune system, body's loss of ability to present resistance to any infections and recover impairments of its organs. Besides, the process of body rejuvenation slows down or stops at all by immunodeficiency [2].

Based on the above mentioned, we can come to the conclusion that it is necessary to develop a new effective treatment method for STI, in particular, trichomoniasis on the background of immunological disorders [15].

Nowadays, therapeutic methods including prescription of α and ß- defensin-containing drugs for the purpose of immunocorrection are one of the most promising. PROPES® drug developed by the Research and Development enterprise "NIP" (Ukraine) at the present time is the only registered in our country immu-