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DRUG-INDUCED LIVER INJURY IN HIV-INFECTED PATIENTS WITH ACTIVE TUBERCULOSIS: COMPARATIVE LABORATORY CHARACTERIZATION

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Abstract

Introduction. Co-infection with human immunodeficiency virus (HIV) and tuberculosis constitutes specific diagnostic and therapeutic problems and creates a significant burden on the health care system. Two microorganisms Mycobacterium tuberculosis and human immunodeficiency virus potentiate each other, accelerating the deterioration of immunological functions and lead to premature death in the absence of treatment. According to numerous data, tuberculosis is the direct cause of death in an average of 30% of patients with human immunodeficiency virus. Tuberculosis and the human immunodeficiency virus have profound effects on the immune system because they are able to suppress the host's immune responses.

The aim is to identify drug–induced liver lesions in a cohort of patients with human immunodeficiency virus infection and pulmonary tuberculosis.

Materials and methods. A prospective study, the study included 150 patients with human immunodeficiency virus with and without active tuberculosis. All patients underwent physical and laboratory examination. Statistical processing was performed using IBM SPSS Statistics 29.0.2.0.

Results. The patients were divided into three groups: The first group (I) included patients with HIV infection (n=31), the second (II) - with pulmonary tuberculosis (n=55); the third group (III) included patients with HIV tuberculosis (n=64)). In all groups, gender, age and laboratory indicators were assessed and their comparative analysis was carried out. At the next stage, the number of cases of drug-induced liver damage was assessed and their structure was presented.

Conclusions 1. The incidence of hepatotoxicity in group III (59.3%) was higher than in group I (22.5%) and II (43.6%).

2. ALT levels were higher in men of group III 45.0 (34.0; 66.0) compared to group I 36.0 (24. 75; 45.0) (p=0.015).

3. In male patients of group III, ALT and AST indicators were higher compared to similar indicators in patients of group II, ALT(III) - 45.0 (34.0; 66.0) and ALT(II) (34.0 (17.0; 45.0), respectively, p = 0.008; AST(III) - 48.0 (33.0; 78.0) and AST(II) 36.0 (22.0; 45.0), respectively, p=0.049).

The hemoglobin level was lower in patients of group III 110.0 (96.0; 120.0) compared to the same indicator in patients of group II - 130.0 (100.0; 145) diseases.0), respectively, p = 0.022);

4. Clinical signs such as cough, shortness of breath, and weakness were more often observed in patients of group III compared to groups I and II.

5. The average age of women in group III was 40.0 (37.0; 44.5), respectively, younger compared to the age of women in group I (51.0 (45.0; 53.5), p = 0.034).

Key words: *hepatotoxicity, tuberculosis, HIV, transaminases, antiretroviral therapy.*

Резюме

ЛЕКАРСТВЕННЫЕ ПОРАЖЕНИЯ ПЕЧЕНИ У ВИЧ-ИНФИЦИРОВАННЫХ ПАЦИЕНТОВ С АКТИВНЫМ ТУБЕРКУЛЕЗОМ: СРАВНИТЕЛЬНАЯ ЛАБОРАТОРНАЯ ХАРАКТЕРИСТИКА

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Введение. Ко-инфекция вирусом иммунодефицита человека (ВИЧ) и туберкулезом является диагностической и терапевтической проблемой и создает существенную нагрузку для системы здравоохранения. Два микроорганизма *Mycobacterium tuberculosis* и вирус иммунодефицита человека потенциируют друг друга, ускоряя ухудшение иммунологических функций и приводят к преждевременной смерти при отсутствии лечения. Согласно многочисленным данным, туберкулёз является непосредственной причиной смерти в среднем у 30% пациентов с вирусом иммунодефицита человека. Туберкулёз и вирус иммунодефицита человека оказывают глубокое воздействие на иммунную систему, поскольку они способны подавлять иммунные ответы хозяина.

Цель – изучить частоту лекарственных поражений печени в когорте пациентов с инфекцией вирусом иммунодефицита человека и туберкулёзом лёгочной локализации

Материалы и методы. Проспективное исследование, в которое были включены 150 пациентов с вирусом иммунодефицита человека с активным туберкулёзом и без него. Всем пациентам проводилось физикальное и лабораторное исследование. Статистическая обработка проводилась при помощи IBM SPSS Statistics 29.0.2.0.

Результаты. Пациенты были разделены на три группы: в первую группу (I) включены пациенты с ВИЧ инфекцией (n=31), во вторую (II) -с туберкулёзом легких (n=55); в третью группу (III) включены пациенты с ВИЧ + туберкулёз (n=64)). Во всех группах проведена оценка гендерных, возрастных и лабораторных показателей и проведен их сравнительный анализ. На следующем этапе проведена оценка количества случаев лекарственных поражений печени и представлена их структура.

Выводы. 1. Частота гепатотоксичности в III группе (59,3%) была выше, чем в I (22,5%) и II (43,6%) группах.

2. Уровень АЛТ был выше у мужчин III группы - 45,0 (34,0; 66,0) по сравнению с I группой - 36,0 (24,75; 45,0) (p=0,015).

3. У пациентов мужского пола III группы показатели АЛТ и АСТ были выше по сравнению со аналогичными показателями у пациентов II группы, АЛТ(III) - 45,0 (34,0; 66,0) и АЛТ(II) (34,0 (17,0; 45,0) соответственно, p=0,008; АСТ(III) - 48,0 (33,0; 78,0) и АСТ (II) 36,0 (22,0; 45,0) соответственно, p=0,049).

Уровень гемоглобина был ниже у пациентов III группы 110,0 (96,0; 120,0) в сравнении с аналогичным показателем у пациентов группы II- 130,0 (100,0; 145) заболеваний.0) соответственно, p=0,022);

4. Такие клинические признаки, как кашель, одышка и слабость, чаще наблюдались у пациентов III группы по сравнению с I и II группами.

5. Средний возраст женщин группы III составил 40,0 (37,0; 44,5), соответственно был моложе в сравнении с возрастом женщин I группы (51,0 (45,0; 53,5), p = 0,034).

***Ключевые слова**: гепатотоксичность, туберкулез, ВИЧ, трансаминазы, антиретровирусная терапия.*

Түйіндеме

БЕЛСЕНДІ ТУБЕРКУЛЕЗБЕН АУЫРАТЫН АИТВ ЖҰҚТЫРҒАН НАУҚАСТАРДА БАУЫРДЫҢ ДӘРІЛІК ЗАҚЫМДАНУЫ: САЛЫСТЫРМАЛЫ ЗЕРТХАНАЛЫҚ СИПАТТАМАСЫ

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Кіріспе. Адамның иммун тапшылығы вирусымен (АИТВ) және туберкулезбен Ко-инфекциясы нақты диагностикалық және емдік проблемаларды құрайды және денсаулық сақтау жүйесіне айтарлықтай жүктеме жасайды. Екі микроорганизм Mycobacterium tuberculosis және адамның иммун тапшылығы вирусы бір-бірін күшейтеді, иммунологиялық функциялардың нашарлауын тездетеді және емделмеген жағдайда мезгілсіз өлімге әкеледі. Көптеген мәліметтерге сәйкес, туберкулез адамның иммун тапшылығы вирусымен ауыратын науқастардың орта есеппен 30% өлімнің тікелей себебі болып табылады. Туберкулез және адамның иммун тапшылығы вирусы иммундық жүйеге қатты әсер етеді, өйткені олар иесінің иммундық жауаптарын басуға қабілетті.

Мақсаты. Адамның иммун тапшылығы вирусы инфекциясы және өкпе локализациясы туберкулезі бар пациенттер когортындағы бауырдың дәрілік зақымдану жиілігін зерттеу.Материалы и методы. Проспективное исследование, в которое были включены 150 пациентов с вирусом иммунодефицита человека с активным туберкулёзом и без него. Всем пациентам проводилось физикальное и лабораторное исследование. Материалдар мен тәсілдер. Белсенді туберкулезбен және туберкулезсіз адамның иммун тапшылығы вирусын жұқтырған 150 пациентті қамтитын перспективалық зерттеу. Барлық науқастар физикалық және зертханалық тексеруден өтті

Статистикалық өңдеу IBM SPSS Statistics 29.0.2.0 көмегімен жүргізілді.

Нәтижелер. Пациенттер үш топқа бөлінді: бірінші топқа (I) АИТВ инфекциясы бар науқастар (n=31), екінші топқа (II) -өкпе туберкулезі бар науқастар (N=55); үшінші топқа (III) АИТВ + туберкулезі бар науқастар (N=64) кіреді.) Барлық топтарда гендерлік, жас және зертханалық көрсеткіштер бағаланып, олардың салыстырмалы талдауы жүргізілді. Келесі кезеңде бауырдың дәрілік зақымдану жағдайларының саны бағаланды және олардың құрылымы ұсынылды.

Қорытындылар. 1. III топтағы гепатоуыттылық жиілігі 59,3% денгеінде байкалды, өзге топтарға қарағанда жоғары болды(I (22,5%) ; II (43,6%).

2. III топтағы ерлерде ALT деңгейі жоғары болды - 45,0 (34,0; 66,0), I топтағы ерлердин көрсеткиштеримен салыстырғанда-36,0 (24,75; 45,0) (p=0,015).

3. III топтағы ер пациенттерде ALT және AST көрсеткіштері II топтағы науқастардағы ұқсас көрсеткіштермен салыстырғанда жоғары болды, ALT(III) – 45,0 (34,0; 66,0) және ALT(II) (34,0 (17,0; 45,0), p = 0,008; AST(III) - 48,0 (33,0; 78,0) және AST(II) 36,0 (22,0; 45,0), сәйкесінше, p=0,049).

Гемоглобин деңгейі III топтағы науқастарда 110,0 (96,0; 120,0) II топтағы науқастардағы бірдей көрсеткішпен салыстырғанда төмен болды – 130,0 (100,0; 145) ауру.0), сәйкесінше, p = 0,022);

4. Жөтел, ентігу және әлсіздік сияқты клиникалық белгілер I және II топтармен салыстырғанда III топтағы науқастарда жиі байқалды.

5. III топтағы әйелдердің орташа жасы 40,0 (37,0; 44,5) құрады, сәйкесінше I топтағы әйелдердің жасымен салыстырғанда (51,0 (45,0; 53,5), p = 0,034) жастау болды.

Түйінді сөздер: *гепатоуыттылық, туберкулез, АИТВ, трансаминазалар, антиретровирустық терапия.*

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Relevance of the topic

The prevalence of human immunodeficiency virus as of December 31, 2021 was 1.56 million people [3]. Every hour, 8 people in Russia are infected with HIV. On average,200 young people are infected with the virus every day [12]. The incidence of tuberculosis in patients without HIV infection in 2017 was 48.3 per 100 thousandth of the population [7]. The prevalence of tuberculosis in the cohort of patients with HIV infection is high, amounting to 1,667. 4 per 100 thousand patients in Russia as of 2019 [10]. A recent study found no significant differences in the risk of liver cirrhosis and hepatocellular carcinoma in patients with and without HIV [6,8].

Given that both patients with HIV infection and tuberculosis need to constantly take a large number of drugs, this category is at risk for drug-induced liver damage. The high prevalence and mortality from co-infection HIV and tuberculosis co-infection, as well as the high risk of liver damage in diseases, predisposes us to study the types and structure of drug-induced liver damage in this cohort of patients.

Objective: to analyze the types and extent of drug-induced liver damage in patients with human immunodeficiency virus and pulmonary tuberculosis**.**

Materials and methods. Ethical approval and consent to participate. This study was approved by the Pirogov

Russian National Research Medical University of the Ministry of Health of the Russian Federation (Protocol No. 5 of December 20, 2020). The prospective study was conducted from January to July 2022. The study included 150 men and women infected with HIV with and without pulmonary tuberculosis aged 18-65 years. Patients were recruited to the study on the basis of the Federal State Budgetary Institution "National Medical Research Institute of Phthisiopulmonology" of the Ministry of Health of the Russian Federation. All patients signed an informed consent for the examination and publication of the results obtained. Inclusion criteria:

1. 150 men and women infected with HIV with and without pulmonary tuberculosis aged 18-65 years;

2. Patients who have provided informed consent for the examination and the publication of the results obtained. Criteria for non-inclusion:

3. Refusal to issue informed consent;

4. Tuberculosis process of extrapulmonary localization;

5. The presence of mental illness;

6. The presence of active drug addiction, substance abuse, alcoholism 12 weeks before inclusion in the study;

7. Pregnancy; breastfeeding.

As part of the study, an objective examination of patients was conducted to determine their medical history: laboratory and biochemical blood test, a general urinalysis, an assessment of the acid-base state, an X-ray or computed tomogram of chest organs, an ultrasound examination of the liver, seeding or polymerase chain reaction to detect Mycobacterium tuberculosis in sputum/blood/urine/feces, an assessment of the level of CD4+ lymphocytes, identification of human immunodeficiency virus ribonucleic acid. The severity of hepatotoxicity was assessed based on the criteria of severity of hepatotoxicity of the US National Cancer Institute. CIOMS [4] criteria were also used to assess the type of liver damage. All patients received antiretroviral therapy for HIV infection and antitubercular therapy for tuberculosis. The patients were divided into three groups: the first group (I) included patients with HIV infection (n=31), the second (II) - with pulmonary tuberculosis (n=55); the third group (III) included patients with HIV + tuberculosis (n=64)). Gender, age, and laboratory parameters were assessed and compared in all groups. At the next stage, an assessment of the number of cases of medicinal liver damage was carried out and their structure was presented. Статистическая обработка проводилась с использованием IBM SPSS Statistics 29.0.2.0. To describe quantitative variables with a normal distribution, the average value with a standard deviation was used. Nonparametric methods of statistical data processing were applied for some of the data that did not obey the law of normal distribution. Thus, quantitative variables with an abnormal distribution were expressed as the median with an interquartile range. The Mann-Whitney test was used to compare two independent groups. To determine the relationship between qualitative variables, the Pearson and Fisher chi-square test was used. The correlation was determined using Spearman's rank correlation coefficient. Categorical data was presented as a percentage frequency. Statistical hypotheses were tested at the significance level ($p<0.05$).

Results.

During the study, patients were divided into three groups: I- Patients with only human immunodeficiency virus (HIV), n=31; II- Patients with tuberculosis, n=55; III- Patients with a combination of these diseases (n=64). The gender distribution in the groups of patients showed that in two groups (with HIV and a combination of diseases), men predominated, while in tuberculosis patients, women/men were distributed in approximately equal proportions (men accounted for 52.7%). With HIV, the number of men was 77.4%, with a combination of HIV and tuberculosis 70.3%.

By ages, patients with tuberculosis were older in comparison with other groups, as shown in Figure 1.

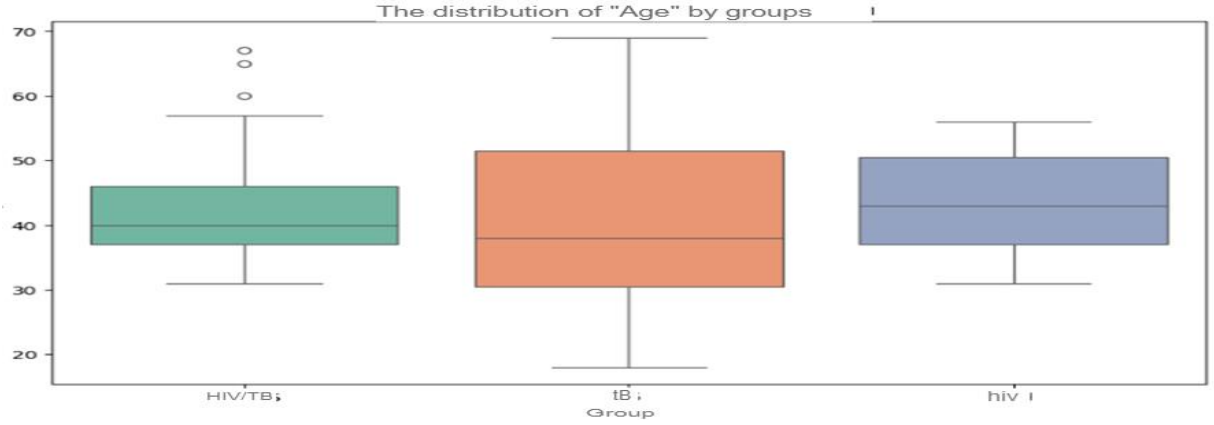

Figure 1. Age distribution of patients in the study groups

The main laboratory parameters in patients of the studied groups, depending on gender, a comparative analysis of laboratory parameters in patients with HIV and a combination of tuberculosis and HIV, depending on gender, showed the following results in table 1.

According to the table, it can be concluded that women with HIV were older in comparison with women with tuberculosis and HIV (51.0 (45.0; 53.5) and 40.0 (37.0; 44.5) respectively, p=0.034). Men differed in the ALT index- it was higher in tuberculosis combined with HIV and amounted to 45.0 (34.0; 66.0), while 36.0 (24.75; 45.0) in the presence of HIV (p=0.015). No differences are shown for other indicators.

Further, laboratory markers were analyzed in patients with a combination of HIV and tuberculosis and patients with tuberculosis in table 2.

Table 1.

Comparative analysis of laboratory parameters in HIV patients by gender.

Gender	Indicators, (Me, Q1; Q3)	HIV -	HIV+TB	P
Female	Age	51.0 (45.0; 53.5)	40.0 (37.0; 44.5)	0.034
	Hemoglobin	100.0 (88.5; 117.0)	108.0 (89.5; 125.0)	0.75
	Platelets	186.0 (93.5; 295.0)	190.0 (135.0; 236.5)	0.954
	the Number of erythrocytes	3.8 (3.35; 4.2)	4.3 (3.7; 5.15)	0.247
	the Number of leukocytes	3.85 (3.8; 5.7)	4.9 (3.3; 7.2)	0.588
	Total bilirubin	18.0 (10.0; 18.0)	8.0 (7.0; 13.0)	0.151
	Alkaline phosphatase	66.0 (56.0; 77.0)	80.0 (78.5; 271.5)	0.145
	aspartate aminotransferase (AST)	36.0 (27.5; 41.0)	34.0 (23.0; 82.0)	0.772
	alanine aminotransferase (ALT)	38.0 (23.5; 42.5)	45.0 (34.0; 53.0)	0.212
	Total protein	68.0 (67.0; 69.0)	67.0 (64.75; 76.0)	0.803
	Creatinine	59.0 (59.0; 59.0)	71.0 (67.0; 90.0)	0.484
Male	Age	43.0 (34.75; 47.75)	40.0 (37.0; 46.0)	0.865
	Erythrocytes	4.25 (3.725; 4.9)	4.2 (3.4; 4.5)	0.191
	Leukocytes	4.2 (3.6; 6.05)	4.35 (3.325; 6.85)	0.756
	Platelets	144.0 (89.75; 206.5)	145.0 (120.0; 234.0)	0.719
	Hemoglobin	99.0 (89.0; 131.5)	110.0 (96.0; 120.0)	0.738
	AST	45.0 (34.0; 46.75)	48.0 (33.0; 78.0)	0.183
	ALT	36.0 (24.75; 45.0)	45.0 (34.0; 66.0)	0.015
	Gamma-glutamyl transpeptidase (GGTP)	71.0 (54.25; 173.25)	54.0 (45.0; 83.0)	0.647
	Total bilirubin	12.0 (7.5; 17.5)	15.0 (7.0; 18.0)	0.731
	Alkaline phosphatase	77.5 (68.5; 129.5)	80.0 (70.0; 132.5)	0.887
	Total protein	65.0 (61.0; 69.0)	68.0 (65.0; 78.0)	0.064
	Creatinine	77.0 (66.5; 87.5)	89.0 (76.0; 90.0)	0.784

Table 2.

Analysis of laboratory parameters in patients with a combination of HIV and tuberculosis in comparison with patients with tuberculosis.

Gender	Parameters (Me, Q1; Q3)	TB	HIV+TB	p
Female	Age	36.0 (26.25; 53.25)	40.0 (37.0; 44.5)	0.382
	Erythrocytes	4.25 (3.875; 5.675)	4.3 (3.7; 5.15)	0.483
	Leukocytes	4.9 (3.9; 7.625)	4.9 (3.3; 7.2)	0.827
	Hemoglobin	120.0 (111.0; 130.0)	108.0(89.5; 125.0)	0.052
	Platelets	182.0(156.75; 270.75)	190.0(135.0; 236.5)	0.671
	Alkaline phosphatase	75.0 (52.5; 120.0)	80.0 (78.5; 271.5)	0.349
	GGTP	108.0 (79.0; 137.0)	56.0 (33.5; 85.5)	0.5
	Total bilirubin	12.0 (7.0; 15.0)	8.0 (7.0; 13.0)	0.355
	AST	44.5 (33.25; 52.75)	34.0 (23.0; 82.0)	0.589
	ALT	45.0 (25.75; 54.0)	45.0 (34.0; 53.0)	0.636
	Total protein	74.0 (67.25; 78.0)	67.0 (64.75; 76.0)	0.092
	Creatinine	68.2 (63.0; 76.5)	71.0 (67.0; 90.0)	0.702
Male	Age	39.0 (33.0; 49.0)	40.0 (37.0; 46.0)	0.3
	Hemoglobin	130.0 (100.0; 145.0)	110.0 (96.0; 120.0)	0.022
	Platelets	188.0 (112.5; 280.25)	145.0 (120.0; 234.0)	0.358
	Erythrocytes	4.2 (3.5 And 5.1)	4.2 (3.4; 4.5)	0.19
	Leukocytes	5.9 (4.3; 7.5)	4.35 (3.325; 6.85)	0.057
	Alkaline phosphatase	123.5 (104.0; 161.5)	80.0 (70.0; 132.5)	0.325
	GGTP	59.0 (51.5; 73.25)	54.0 (45.0; 83.0)	0.687
	Total bilirubin	15.0 (10.0; 17.0)	15.0 (7.0; 18.0)	0.98
	ALT	34.0 (17.0; 45.0)	45.0 (34.0; 66.0)	0.008
	AST	36.0 (22.0; 45.0)	48.0 (33.0; 78.0)	0.049
	Total protein	72.0 (69.0; 76.0)	68.0 (65.0; 78.0)	0.227
	Creatinine	90.0 (72.5; 90.0)	89.0 (76.0; 90.0)	0.666

In women, there were no differences in biochemical parameters and indicators of general blood analysis (p>0.05). In men, ALT and AST were shown to be higher in a combination of diseases compared to the group with only tuberculosis (ALT - 45.0 (34.0; 66.0) and 34.0 (17.0; 45.0), respectively, p=0.008; AST - 48.0 (33.0; 78.0) and 36.0 (22.0; 45.0), respectively, p=0.049). Hemoglobin was also lower in patients with a combination of diseases (110.0 (96.0; 120.0) and 130.0 (100.0; 145.0), respectively, p=0.022).

The study examined the presence of social factors such as disability and lack of work in groups. More than half of patients with both HIV, and tuberculosis (57.8%) have social factors. Also, 51.6% of patients with HIV alone and 66.6% of patients with tuberculosis alone have a disability or lack of work.

Among patient complaints, the most common is coughing in 81.3% of patients with tuberculosis and HIV; 98.2% of patients with tuberculosis; 9.7% of patients with HIV. In the second place, general weakness is most common: in 100% of patients with tuberculosis, in 93.8% with a combination of diseases, and in 51.6% with HIV infection. The severity of liver damage is shown in table 3.

Table 3.

The degree of drug-induced liver damage in patients.

Diagnosis	I degree		II degree		III degree		IV degree		n (%)
	n	%	n	%	n	%	n	%	
HIV + tuberculosis	27	42.19	7	10.94	3	4.69	1	1.56	(n=38) 59.38
HIV	5	16,13	1	3,23	1	3,23	-	-	(n=7) 22.58
Tuberculosis	15	27.27,27	5	9.09	3	5.45	1	1.82	(n=24) 43.64

As can be seen from the table, the majority of patients were distinguished by the presence of liver damage in 59.38% (with a combination of diseases). In tuberculosis, the lesion was found in 43.64%, while in HIV only in 22.58%. The most common type of lesion was grade 1 (Figure 2). Our data is the same as that of other authors. The study included 382 patients who had normal liver function and had not previously received antiretroviral therapy. After the start of antiretroviral therapy, liver damage was observed in 235 patients. Just as in our study, patients were more likely to have first-degree drug-induced liver damage [4,9] in figure 2.

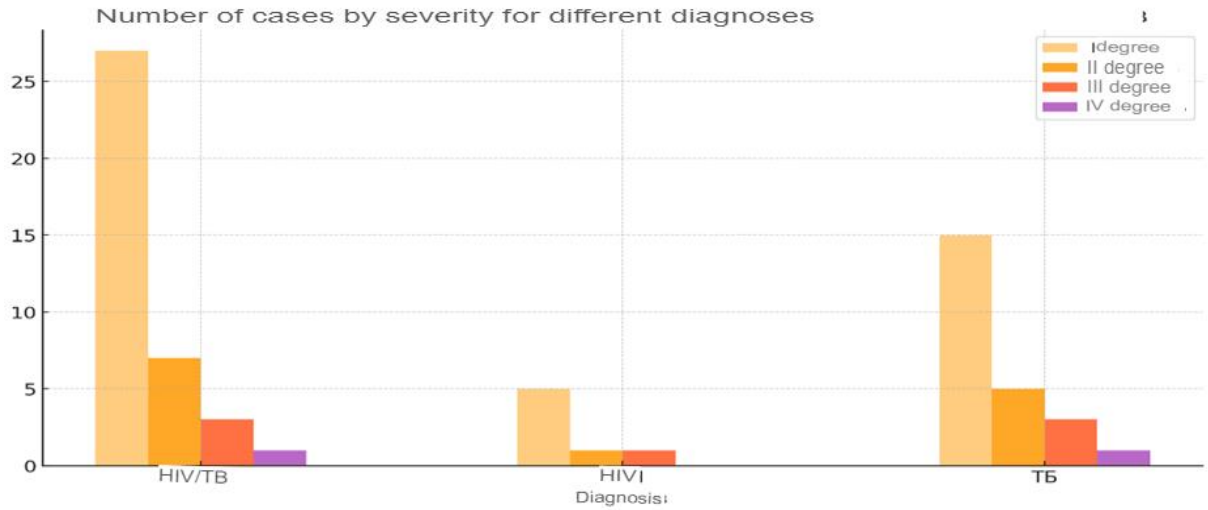

Figure 2. Number of cases by severity of liver damage in patients. [2]

The CIOMS-law was applied between male and female patients to compare the types of lesions among HIV+TB and HIV in table 4. The CIOMS-law was applied between male and female patients to compare the types of lesions among HIV+TB and TB in table 5.

Table 4.

Competitive types of liver damage among HIV+TB and TB.

Gender	CIOMS	HIV+TB (n=64)	HIV (n=31)	P
Female	No defeat	14 (73.7%)	7 (100.0%)	0,278
	Cholestatic	5 (26.3%)	0 (0.0%)	0,278
Male	No defeat	35 (77.8%)	21 (87.5%)	0,519
	Cholestatic	6 (13.3%)	2 (8.3%)	0,704
	Mixed	2 (4.4%)	1 (4.2%)	1
	Hepatocellular	2 (4.4%)	0 (0.0%)	0,54

Table 5.

Competitive types of liver damage among HIV+TB and HIV.

Gender	CIOMS	HIV+TB (n=64)	Tuberculosis (n=55)	p-value (Fisher's Exact Test)
Female	No defeat	14 (73.7%)	23 (88.5%)	0,253
	Cholestatic	5 (26.3%)	2 (7.7%)	0,114
	Mixed	0 (0.0%)	1 (3.8%)	1
Male	No defeat	35 (77.8%)	23 (79.3%)	1
	Cholestatic	6 (13.3%)	3 (10.3%)	1
	Mixed	2 (4.4%)	1 (3.4%)	1
	Hepatocellular	2 (4.4%)	2 (6.9%)	0,642

According to the tables, there were no differences in the groups by types of liver damage between male and female patients to compare HIV+TB with HIV and tuberculosis by CIOMS-law.

Discussion

According to our study, the gender distribution in the patient groups showed that men prevailed in two groups (with HIV and combined diseases), whereas in tuberculosis patients, women/men were distributed in approximately the same ratio (men accounted for 52.7%). With HIV, the number of men was 77.4%, with a combination of HIV and tuberculosis, 70.3%. Researchers *V.V. Pokrovsky and co-authors* (2017) also obtained data on the prevalence of HIV in men, which is associated with their frequent drug use compared to women, as well as the presence of same-sex relationships [8].

Women with HIV were older than women with tuberculosis and HIV (51.0 (45.0; 53.5) and 40.0 (37.0; 44.5) respectively, p=0.034). According to another source, the data differ - the peak incidence of both HIV and tuberculosis occurs at the age of 25-34 years, while the age of patients with HIV and a combination of diseases does not differ significantly [4]. In our opinion, this may be due to the fact that women initially from disadvantaged families develop tuberculosis, and subsequently HIV infection.

Men differed in the alanine aminotransferase index – with tuberculosis in combination with HIV, it was higher and amounted to 45.0 (34.0; 66.0), whereas 36.0 (24.75; 45.0) in the presence of HIV without tuberculosis (p=0.015). In men, AlT and AsT were shown to be higher with a combination of diseases compared with the group with only tuberculosis (AlT - 45.0 (34.0; 66.0) and 34.0 (17.0; 45.0), respectively, p=0.008; AsT - 48.0 (33.0; 78.0) and 36.0 (22.0; 45.0), respectively, p=0.049*). A.I. Dolgushina* and co-authors (2018) point to the hepatoxicity of drugs used in the treatment of tuberculosis, which can increase the level of liver enzymes [6]. Our data on the issue is consistent with other data – patients with a combination of diseases need to take more drugs that are hepatotoxic, which leads to liver damage. According to our data, the number of cases of hepatotoxicity in the HIV and tuberculosis group (59.3%) exceeds that of HIV (22.5%) and tuberculosis (43.6%). *Akhmedzhanova Z.I. and co-authors* (2020) talk about the presence of hepatotoxicity of drugs for the treatment of HIV infection, which confirms our data [2].

The hemoglobin level was lower in patients with a combination of diseases (110.0 (96.0; 120.0) and 130.0 (100.0; 145.0), respectively, p=0.022). The presence of anemia in patients with HIV infection has been noted in the literature. The incidence of anemia is 30% with an asymptomatic course and 80-90% at the stage of acquired immunodeficiency syndrome [5]. Tuberculosis also causes a decrease in serum iron content [11]. Probably, with a combination of diseases, there is a greater decrease in hemoglobin compared to the presence of HIV infection or tuberculosis alone. Thus, the results obtained do not contradict the literature data.

In tuberculosis, liver damage occurred in 43.64%, while in HIV only in 22.58%. The most common type of lesion was grade 1. Our data is consistent with the data of other authors. The study examined 382 patients who had normal liver function and had not previously taken antiretroviral therapy. After starting antiretroviral therapy, liver damage was observed in 235 patients. As in our study, patients were more likely to have drug-induced liver damage of the first degree [1].

According to our data, clinical signs in the form of cough, shortness of breath, and weakness were more often observed in patients with a combination of diseases. Tuberculosis causes lung damage, which leads to coughing and shortness of breath. The presence of general weakness in tuberculosis was also noted. Naturally, with a combination of diseases, general weakness increases.

Conclusions:

1. The incidence of hepatotoxicity in group III (59.3%) was higher than in group I (22.5%) and II (43.6%).

2. ALT levels were higher in men of group III 45.0 (34.0; 66.0) compared to group I 36.0 (24. 75; 45.0) (p=0.015).

3. In male patients of group III, ALT and AST were shown to be higher compared to group II, ALT - 45.0 (34.0; 66.0) and 34.0 (17.0; 45.0), respectively, p=0.008;

AST - 48.0 (33.0; 78.0) and 36.0 (22.0; 45.0), respectively, p=0.049). Hemoglobin was also lower in patients with a combination of 110.0 (96.0; 120.0) and 130.0 (100.0; 145) diseases.0), respectively, p=0.022);

4. Clinical signs such as cough, shortness of breath, and weakness were more often observed in patients of group III compared to groups I and II.

5. Women of group I were older compared to women of group III (51.0 (45.0; 53.5) and 40.0 (37.0; 44.5), respectively, p = 0.034).

Ethical approval and consent to participate

This study was approved by the Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation (Protocol No. 5 of December 20, 2020). All participants gave written informed consent before conducting the interview.

Availability of data and materials

Original data can be provided by the Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation.

Conflict of interest: *The authors declare that there is no conflict of interest.*

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