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Assessment of TB-HIV co-infection according to the drug resistance profile

TB-HIV co-infected patients have a greater risk for multidrug-resistance, that in association with lower cure rates and higher mortality endanger disease control. ***Objective*** — to perform a comparative assessment of TB-HIV co-infected patients according to the first-line anti-tuberculosis drug resistance profile.

Materials and methods. A retrospective selective, descriptive study targeting risk factors, biological, social, epidemiological peculiarities, case-management, diagnosis radiological aspects and microbiological characteristics of 248 patients with TB/HIV co-infected registered in Chisinau city from 2010 to 2015 was performed distributed in a confirmed or presumptive drug-susceptible tuberculosis group of 161 patients and confirmed MDR-TB group of 87 patients.

Results and discussion. Two third of patients were men, had less than 45 years old and the most of them were from urban districts. One third of the total sample was detected by primary health care and one third by the pulmonologist. Symptomatic patients were the majority of the total sample and by annual screening were detected only a small number of cases. The prevalent high risk was the previous history of tuberculosis and the low rate of infectious contact demonstrated poor screening in high risk groups. The majority were treated according to the regimen of drug-susceptible TB, despite the differences in the drug resistance profile. Low treatment outcome in both groups and high rate of death demonstrated poor case-management of the TB/HIV co-infected patients.

Conclusions. Low treatment outcome in both groups and high rate of death demonstrated poor case-management of the TB/HIV co-infected patients.

Key words

HIV, tuberculosis, risk factors, outcome.

In 2014, there were registered 9.6 million new cases of tuberculosis, of which 1.2 million were among people living with HIV [7, 8]. The risk of developing tuberculosis is estimated to be between 26—31 times higher in HIV infected people. Infections (opportunistic and others) are the major cause of death in people living with HIV [2, 3]. The patients TB-HIV co-infected have a greater risk to acquire multidrug-resistance, that in association with lower cure rates and higher mortality endanger disease control [4]. In the Republic of Moldova there is a continuous worsening of the epidemiological indices of TB-HIV co-infection [1, 5, 6]. Between 2011 and 2015 the rate of HIV infection among tuberculosis new cases encreased in Chisinau and at the national level with 2.6 %: 2011 — 5.0 %, 2012 — 5.0 %, 2013 — 2.2 %, 2014 — 5.3 %, 2015 — 7.6 % in Chisinau and 2011 — 5.1 %, 2012 — 5.1 %, 2013 — 5.2 %, 2014 — 6.5 % and 2015 — 7.7 % in entire country. The rate of HIV infection in new and relapsed cases increased evidently in Chisinau with 2.3 %: 2011 — 4.6 %, 2012 — 4.4 %, 2013 — 2.9 %, 2014 — 5.5 % and 2015 — 6.9 % and with 2.9 % in the entire country: 2011 — 5.2 %, 2012 — 5.3 %, 2013 — 5.9 %, 2014 — 7.2 % and 2015 — 8.1 %. The rate of TB-HIV co-infected cases among died patients showed an increased tendecy in Chisinau with 4.2 %: 2011 — 11.9 %, 2012 — 13.8 %, 2013 — 9.2 %, 2014 — 16.0 % and 2015 — 16.1 % as well as in the entire country with 5.3 %: 2011 — 15.4 %, 2012 — 12.8 %, 2013 — 11.8 %, 2014 — 20.8 % and 2015 — 20.7 % [1]. Compared to drug-susceptible tuberculosis, MDR-TB shows differences in treatment outcome due to particular risk factors associated to each type of drug-resistance. The aim

of the study was to perform a comparative assessment of TB-HIV co-infected patients according to the first-line anti-tuberculosis drug resistance profile.

Objectives were: 1. Assessment of general, socio-economic and epidemiological risk factors of TB-HIV co-infected patients. 2. Evaluation of case-management, diagnosis, radiological aspects and microbiological characteristics of TB-HIV co-infected patients with susceptible and multidrug-resistant tuberculosis. 3. Establishement the factors influencing the final treatment outcome.

Materials and methods

It was performed a retrospective selective, descriptive study targeting social, demographic, economic and epidemiological pecualiarities, case-management, diagnosis radiological aspects and microbiological characteristics of 248 patients with tuberculosis-HIV co-infection registered in Chisinau city in the period 2010—2015. The electronic system for monitoring and follow-up of tuberculosis cases (SIME TB) was used for the patients selection. According to the national policy all tuberculosis patients were counseled and tested for HIV markers. The diagnosis and case-management of HIV infection was established by the referral specialist in infectious diseases. The inclusion criteria in the study were: age > 18 years old, tuberculosis diagnosed by the pulmonologist, HIV-infection diagnosed by the specialist in infectious diseases, patient hospitalized in the Clinical Municipal Hospital of Phtysiopneumology during the period 1.1.2010—31.12.2015, signed informed consent. The total sample was divided in two groups: 1st group was composed by 161 patients with non MDR-TB and the 2nd group included 87 MDR-TB patients. So, the rate of MDR-TB/HIV patients constituted 35.08 % of the total sample. The investigational schedule determined demographic, social and epidemiological data: sex (male/female ratio), age (distribution in age groups), demographic characterstics (urban/rural residence, homeless status), socio-economic status, health and social insurance status, migrational and detention history, presence of high risks, patient's case-management, treatment type, adverse drug reactions, final outcome. All selected patients were diagnosed and managed according to the national policy. Statistic analysis was carried out using the quantitative and qualitative research methods. Statistical survey was performed using Microsoft Excel XP soft.

Results and discussion

The total group distribution according to the microbiological results established that each third case was microscopic positive for acid-fast-bacilli (AFB) and each second patient had positive cultures on the conventional media. In one half of microscopic positive subgroup were identified till 9 AFB per microscopic field and one half of the total group had higher bacillarity. Repartition of culture positive results identified a similar distribution of all three positive results. No statistic difference was established between the rate of positive results on the microscopic examination and culture on the conventional media. A lower proportion had molecular genetic investigation performed due to its national implementation since 2014. In the 1st group were included patients with confirmed or presumed drug susceptible tuberculosis as well as a limited number of mono- and poliresistant tuberculosis (excluding rifampicine resistance). In the 2nd group were selected patients with confirmed drug resistance, two third being resistant to all 1st line anti-TB drugs: isonizid (H), rifampicin (R), streptomycin (S), ethambutol (E) and one fifth — to three anti-TB drugs (H, R, S). In 1 (1.15 %) case was identified extensive drug resistance.

Studying case-management was identified that primary health care detected 94 (37.91 %) patients and specialized level (pulmonologists) detected 89 (35.89 %) patients. Symptomatic patients were 154 (62.09 %) cases (table 1). From the total number of symptomatic patients one half of the subgroup was detected by the general practitioners and one half by pulmonologists. By screening method (annual chest X-ray) was identified a small rate of patients. Direct addressing to the specialized clinical services was used by each fifth patient, due to high proportion of retreated cases. Distribution in case-type according to the WHO definitions established that one third of patients (87 (35.08 %) cases) were included in re-treatment regimens, most of them being relapses and patients with previous therapeutic drop-up. A limited number of cases was diagnosed after death or transferred from other country during the anti-TB treatment (table 2).

Distributing TB/HIV patients in high risk groups it was established that the most prevalent epidemiological risk factor represents the history of a previous anti-TB treatment, followed by the history of detention, probably linked with the illicit drug use. The history of migration in last 12 months was identified in one fifth part of the group. Lack of health insurance and social security identified in the majority of patients demonstrated their social vulnerability associated to the unemployment. Social conventional income had only a small rate of the group, despite the fact that drug-resistant tuberculosis and advanced clinical stage of the AIDS allowed patients to receive the social income. Low rate of identified closed contacts showed poor qua-

Table 1. **Distribution of TB-HIV patients by microbiological features, p (%)**

Characteristics		Total sample (n = 248)	p_{value}
Microbio-logical test results	Microscopic positive, including:	80 (32.25)	> 0.05
	1—9 AFB/100 MF	44 (55.00)	
	1+	9 (11.25)	
	2+	8 (10.00)	
	3+	19 (23.75)	
	Culture positive	119 (47.98)	
	1+	38 (31.93)	
	2+	44 (36.97)	
	3+	37 (31.09)	
MGT test results	GeneXpert MTB/Rifampicine positive	48 (19.35)	> 0.05
	GeneXpert MTB/Rifampicine positive, resistant	26 (10.48)	
2nd group MDR-TB (n = 87)	HRSE resistance	66 (75.86)	N/A
	HRS resistance	19 (21.94)	
	HRE resistance	2 (2.29)	
1st group (n = 161)	HS resistance	5 (3.11)	
	H resistance	3 (1.86)	
	Confirmed 1st t drug-line susceptibility by DST	22 (13.66)	

Note. AFB — acid fast bacilli; MF — microscopic field; MGT — molecular genetic test, isonizid (H), rifampicin (R), streptomycin (S), ethambutol (E); DST — drug sensitivity testing; N/A — non available.

Table 2. **Case-management of TB-HIV patients, p (%)**

Health level	Detection ways	Total sample (n = 248)	p_{value}
PHC	Detected by GPs-symptomatics	78 (31.45)	> 0.05
	Detected by GPs-screening of HRG	36 (14.51)	
Specialised level	Detected by SP-symptomatics	76 (30.64)	
	Detected by SP-screening of HRG	13 (5.24)	
Hospital	Direct addressing	45 (18.14)	
New case	First time diagnosed	158 (63.71)	N/A
Retreatement	Relapse	40 (16.13)	
	After previous treatment failure	15 (6.05)	
	After treatment default	32 (12.91)	
Other	Post-mortem diagnosis	2 (0.81)	
	Transferred from abroad	1 (1.41)	

Note. Applied statistical test: paired simple T — test; P — probability; PHC — primary health care level; GPs — general practitioner; HRG — high risk groups.

lity of the epidemiological cross-examination, rather than to the lack of closed (family) contacts. So, the distribution of patients with TB/HIV established the primary target groups in frame of which must be performed awareness, education, and improvement of health behavior are social and economical vulnerable groups, migrants, homeless and individual with the history of epidemiological threatened (table 3).

Sex distribution identified that in the 1st group composed by non-MDR-TB/HIV patients the male-female ratio was 2.22/1 and in the 2nd group (MDR-TB/HIV) was 2/1. No statistic difference between groups was identified regarding the distribution of patients in age groups. It was identified the predominance of the 35—54 years group in both samples, following by the 18—34 years group. However patients from 18—34 years group were more frequent in the 2nd group and patients from 35—54 years group were more frequent in the 1st group. Distribution of patients according to the demographic characteristics identified that patients from urban districts predominated in both groups but a higher proportion was identified in the 2nd group. Homeless status was established in the each fifth patient of both groups. So, distributing patients according to the biological characteristics it was argued that HIV infected men had the same probability to get susceptible or resistant tuberculosis as women, but young individuals and those

Table 3. **Distribution of TB-HIV patients in high risk groups, p (%)**

Risk factors	Parametres	Total sample (n = 248)	p_{value}
Social-epidemiological	History of migration	35 (14.11)	> 0.05
	History of detention	48 (19.35)	
Epidemiological	Closed TB contact	14 (5.65)	
	Previous treated for TB	90 (36.29)	
Social	Lack of health and social insurance	219 (88.31)	N/A
	Disease disabled (conventional income)	33 (13.31)	
	Illicit drug use (in life history)	20 (8.06)	
	Homelessness	42 (16.93)	

Note. Applied statistical test: paired simple T — test; P — probability.

Table 4. **Distribution of TB-HIV patients by demographic data, p (%)**

Parametres		1st group (n = 161)	2nd group (n = 87)	p_{value}
Sex	Men	111 (68.94)	58 (66.67)	> 0.05
	Women	50 (31.05)	29 (33.33)	> 0.05
Age groups	18—34 years	55 (34.16)	41 (47.13)	> 0.05
	35—54 years	96 (59.62)	44 (50.57)	> 0.05
	> 55 years	10 (6.21)	2 (2.29)	> 0.05
Residence	Urban	126 (78.26)	74 (85.07)	> 0.05
	Rural	35 (21.74)	13 (14.94)	> 0.05
Other	Homeless	27 (16.77)	15 (17.24)	> 0.05

Note. Applied statistical test: paired simple T — test; P — probability.

from urban disctricts had higher frequence of drug-resistant tuberculosis (table 4).

Identifying the clinical radiological forms of pulmonary tuberculosis it was established that pulmonary tuberculosis was diagnosed in the majority of cases from both groups, but more frequently in the 2nd group. It is explained by the fact that multidrug-resistance is established by the conventional microbiological methods that are almost positive in sputum samples. Patients with extra-pulmonary tuberculosis were included in the 1st group due to the establishment of the presumptive drug-susceptible tuberculosis. It is important to note that one third of pulmonary tuberculosis cases had disseminated form identified as a hallmark of TB/HIV co-infection. A limited number of generalized tuberculosis was identified (table 5).

The majority of patients from the 1st group were treated with the 1st line anti-TB drugs according to the standard regimen for drug-susceptible tuberculosis and a lower proportion were treated according to the retreatment regimen. The successful outcome was registered in one half and died one third of the group. The most of patients from the 2nd group were treated starting with the onset till the availability of conventional culture drug sensitivity testing with: 1st line drugs. Only a limited number received from the onset an adequate treatment for MDR-TB. In 2 (2.29 %) patients were registered major drug adverse reaction. In consequence the successful ending was established in a lower proportion and death was registered in average one half of patients. Is continuing DOTS-Plus regimen for MDR-TB every fifth patient (table 6).

Conclusions

TB/HIV represents an important public health problem in the Republic in Moldova, due to the high rate of multidug resistance.

Microbiological positive patients constituted almost one half of the total sample of TB/HIV patients and one third was identified infected with multidrug resistant strains.

Two third of patients were men, had less than 45 years old and the most of them were from urban districts.

One third of the total sample was detected by primary health care staff and one third — by the specialists in pulmonology.

Sympotmatic patients were the majority of the total sample and by annual screening were detected only a small number of cases despite the fact that HIV-infected individuals are included in the high risk groups.

The major rate in the frame of high risk groups was established regarding previous history of tuberculosis.

Table 5. **Distribution of TB-HIV patients by forms of tuberculosis, p (%)**

Parametres	Type	1st group (n = 161)	2nd group (n = 87)	p_{value}
New case	First time diagnosed	110 (68.32)	43 (49.42)	> 0.05
Retreatement	Relapse	24 (14.91)	16 (18.39)	> 0.05
	After previous failure	6 (3.72)	9 (10.34)	> 0.05
	After treatment default	21 (13.04)	19 (21.84)	> 0.05
Forms of pulmonary TB (n = 142)	Pulmonary TB, including	142 (88.19)	84 (96.55)	> 0.05
	PIT	102 (71.83)	66 (78.57)	> 0.05
	PDT	39 (27.46)	14 (16.67)	> 0.05
	FCVT	1 (0.71)	4 (4.76)	> 0.05
	Generalised TB	3 (1.86)	1 (1.15)	> 0.05
Extrapulmonary TB (n = 16)	Extrapulmonary TB including	16 (9.94)	2 (2.29)	> 0.05
	TB pleuresy	3 (18.75)	1 (50.0)	N/A
	Tracheobronchic TB	1 (6.25)	1 (50.0)	N/A
	TPLN	2 (12.5)	0	N/A
	TILN	5 (31.25)	0	N/A
	CNST	4 (25.00)	0	N/A
	OAT	1 (6.25)	0	N/A

Note. Applied statistical test: paired simple T — test, P — probability; PIT — pulmonary infiltrative tuberculosis; PDT — pulmonary disseminated tuberculosis; FCVT — pulmonary fibro-cavernous tuberculosis; NT — nodular tuberculosis, tracheobronchic TB; TILN — tuberculosis of intrathoracic lymph nodes; TPLN — tuberculosis of peripheric lymph nodes; OAT — osteoarticular tuberculosis; CBST — central nervous system tuberculosis; N/A — non-available statistical assessment.

Table 6. **Distribution of TB-HIV patients by treatment types and final outcomes, p (%)**

Parametres	Type	1st group (n = 161)	2nd group (n = 87)	p_{value}
Treatment regimen	New case	130 (80.75)	54 (62.07)	< 0.01
	Retreatment	27 (16.77)	27 (31.03)	< 0.05
	DOTS-Plus	0	6 (6.89)	> 0.05
	Individualised	4 (2.48)	0	> 0.05
Treatment outcome	Success	85 (52.79)	14 (16.09)	< 0.001
	Died	50 (31.06)	37 (42.53)	> 0.05
	Failed	4 (2.48)	5 (5.74)	> 0.05
	Lost to follow-up	6 (3.72)	4 (4.59)	> 0.05
	Continue DOTS-Plus	0	20 (22.98)	N/A
	Continue individualized regimen	2 (1.24)	1 (1.15)	> 0.05
	Transferred/left the country	14 (8.69)	7 (8.05)	> 0.05

Note. Applied statistical test: paired simple T — test; P — probability.

Low rate of identified TB contact demonstrated low quality of the screening in high risk groups (both HIV-infected and contacts from the infectious clusters).

The majority of patients from both groups were treated according to the drug-susceptible regimen, despite the differences in the drug resistance profile.

Low treatment outcome in both groups and high rate of death demonstrated poor case-management of the TB/HIV co-infected patients.

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Оцінка ТБ/ВІЛ ко-інфекції відповідно до профілю лікарської стійкості

Пацієнти з коморбідністю ВІЛ/ТБ мають більший ризик для формування множинної лікарської стійкості, що в асоціації з нижчим показником ефективності лікування становить загрозу щодо ефективного подалання туберкульозної інфекції та впливає на зростання показника смертності.

Мета роботи — порівняльна оцінка формування резистентності до протитуберкульозних препаратів першого ряду у пацієнтів з поєднаною інфекцією ТБ/ВІЛ.

Матеріали та методи. Ретроспективне описове дослідження, спрямоване на фактори ризику, біологічні, соціальні, епідеміологічні особливості; управління реєстрацією віпадків; методи променевої діагностики, мікробіологічні характеристики 248 пацієнтів з коморбідністю ТБ/ВІЛ, зареєстрованих у місті Кишиневі з 2010 по 2015 рік. Були сформовані 2 групи: 161 пацієнт загальної вибірки з чутливим туберкульозом та група з 87 пацієнтів з мультирезистентним туберкульозом.

Результати та обговорення. Дві третини пацієнтів були чоловіки віком менше 45 років, і більшість з них були з міських районів. Одна третина від загальної вибірки була виявлена на етапі звертання у заклади первинної медико-санітарної допомоги та одна третина — пульмонологом. Пацієнти із симптомами становили більшість від загальної вибірки, і щорічним скринінгом була виявлена лише невелика кількість випадків. З переважно високим ризиком були пацієнти, які мали туберкульозний анамнез та низький рівень інфекційного контакту, що показує поганий скринінг у групах високого ризику. Контакт із хворими на туберкульоз становив групу високого ризику. Більшість лікувалися за схемою лікарсько-чутливого туберкульозу, незважаючи на відмінності в профілі лікарської стійкості. Низький результат ефективності лікування в обох групах і висока частота смерті вказує на погане прецедентне управління пацієнтами з коморбідністю ВІЛ/ТБ.

Висновки. Низький результат лікування в обох групах і високий рівень смертності продемонстрували поганий контроль щодо оцінки прогнозу формування коморбідності ТБ/ВІЛ у групах ризику.

Ключові слова: ВІЛ, туберкульоз, фактори ризику, результати лікування.

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Оценка ТВ/ВИЧ ко-инфекции соответственно профилю лекарственной устойчивости

Пациенты с коморбидностью ТБ/ВИЧ обладают большим риском формирования множественной лекарственной устойчивости, что в сочетании с более низким показателем эффективности лечения представляет угрозу для эффективного преодоления туберкулезной инфекции и влияет на рост показателя смертности.

Цель работы — сравнительная оценка формирования резистентности к противотуберкулезным препаратам первого ряда у пациентов с сочетанной инфекцией ТБ/ВИЧ.

Материалы и методы. Ретроспективное описательное исследование, направленное на факторы риска, биологические, социальные, эпидемиологические особенности; управление регистрацией случаев; методы лучевой диагностики, микробиологические характеристики 248 пациентов с коморбид-

ностью ТБ/ВИЧ, зарегистрированных в городе Кишиневе с 2010 по 2015 год. Были сформированы 2 группы: 161 пациент общей выборки с чувствительным туберкулезом и группа из 87 пациентов с мультирезистентным туберкулезом.

Результаты и обсуждение. Две трети пациентов были мужчины в возрасте менее 45 лет, и большинство из них были из городских районов. Одна треть от общей выборки были выявлены на этапе обращения в учреждения первичной медико-санитарной помощи и одна треть — пульмонологом. Пациенты с симптомами составляли большинство от общей выборки, и ежегодным скринингом было обнаружено лишь небольшое количество случаев. С преимущественно высоким риском были пациенты, которые имели туберкулезный анамнез и низкий уровень инфекционного контакта, что показывает плохой скрининг в группах высокого риска. Контакт с больными туберкулезом составил группу высокого риска. Большинство лечились по схеме врачебно-чувствительного туберкулеза, несмотря на различия в профиле лекарственной устойчивости. Низкий результат эффективности лечения в обеих группах и высокая частота смертности указывает на плохое прецедентное управление пациентами с коморбидностью ТБ/ВИЧ.

Выводы. Низкий результат лечения в обеих группах и высокий уровень смертности продемонстрировали плохой контроль относительно оценки прогноза формирования коморбидности ТБ/ВИЧ в группах риска.

Ключевые слова: ВИЧ, туберкулез, факторы риска, результаты лечения.

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