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SORT IT TB Key Population

Treatment outcomes of drug-resistant tuberculosis in people living with HIV in Odesa province, Ukraine, 2014-2016

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Abstract

Introduction: Odesa province has the highest TB/HIV prevalence in Ukraine, exceeding the total prevalence in the country by 3 times. The objective of this study was to investigate the unfavorable treatment outcomes and associated factors in patient with drug-resistant (DR) TB in people living with HIV (PLH) in Odesa.

Methodology: A cohort study with secondary data analysis was conducted among 373 PLH with confirmed pulmonary DR TB for 2014-2016.

Results: About 2/3rd of the cohort were males from urban areas. Mean age and CD4 counts were 39 and 203, respectively. The overall treatment success was 44.2% with the most unfavorable treatment outcomes being observed in extensively and pre-extensively drug resistant (XDR and PreXDR) TB. The mean time between the results of GeneXpert (manufactured by Cepehid) and DR TB treatment based on GeneXpert was 1.3 days. However, the mean time between DR TB treatment based on GeneXpert and results of drug susceptibility test (DST) was 37.0 days referring to a late reporting of DST and to a late adjustment of previously prescribed treatment. The factors associated with the treatment unfavorable outcome included XDR and Pre-XDR TB, lack of antiretroviral treatment (ART), contrimoxazole preventive therapy (CPT) and CD4 test.

Conclusions: The rate of successful DR TB treatment in PLH in Odesa remains low. The delayed reporting of DST contributes to lack of timely adjusted treatments. XDR and Pre-XDR TB, lack of ART and CPT are associated with unfavorable treatment outcomes. Additional studies would help to understand the temporal relationship between CD4 test and treatment outcomes.

Key words: people living with HIV; treatment outcomes; tuberculosis; Ukraine.

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Introduction

Tuberculosis (TB) is the leading cause of death among people living with HIV (PLH) [1]. PLH have 19 times higher risk to develop TB disease than those who do not have HIV. In 2018 the total number of new cases of TB in PLH was estimated to be 862,000. In the same year 1.5 million died from TB worldwide, of which 251,000 PLH. The control of TB-HIV co-infection became more complicated due to the persisting problem of drug-resistant forms of TB. According to the World Health Organization (WHO) the estimated number of new TB cases with resistance to rifampicin (the most effective first-line drug) was 484,000 in 2018, of which 78% were cases of multidrug-resistant tuberculosis (MDR TB). In 2018, only 56% of MDR TB patients were successfully treated worldwide [2].

The total HIV prevalence among TB patients in Ukraine increased from 3.3% in 2005 to 13.3% in 2017. Odesa oblast (province) has the highest TB and HIV prevalence in the country. In 2017 the prevalence of TB/HIV co-infection among all registered TB cases was 41.9% which is about 3 times higher than the total prevalence of co-infection in Ukraine [3]. The problem of TB/HIV co-infection, which accounts for more than 70% of annual deaths among patients with AIDS in Ukraine, is further exacerbated by the development of DR TB. However, official data on prevalence of DR TB among PLH in Ukraine is lacking.

Despite the fact that the recommended goal of WHO for treatment success for MDR TB is at least 75% [4], the percentage of successful treatment outcome in all MDR TB in Ukraine is still low: it was 50.8% in Ukraine and particularly 61.5% in Odesa province in 2015 [3]. The DR TB treatment outcomes particularly for such a key vulnerable population as PLH are not officially reported or studied in Ukraine. Hence, the aim of this study is to identify the treatment outcome and risk factors associated with unfavorable treatment outcomes in PLH who received treatment for confirmed DR TB in Odessa province, Ukraine, from 2014 to 2016.

Methodology

Study design

A cohort study design with secondary data analysis, using standard clinical and surveillance data from the Odesa province was used for this study.

Study Setting and TB/HIV control

Ukraine is located in Central and Eastern Europe with 24 provinces and an autonomous Republic of Crimea that along with a part of the Donetsk and Luhansk provinces have the status of temporarily occupied territories. Ukraine is classified as a middle-income country. The health system is financed mainly by public funds. The total health care expenditure in the structure of GDP is 2.3% [5]. Odesa is the largest province in Ukraine, with a population of 2.4 million people nearly 40% living in Odesa city [6].

The issue of combating TB epidemic is one of the priorities of Ukrainian public health policy. The fight against TB is in line with WHO 2015 global TB control strategy and the TB control plan for the European Region for 2016-2020. Since 2002 Ukraine has been implementing 5-years TB control programs that included also measures for TB/HIV co-infection. The last program was carried out in the period of 2012-2017. The patients with TB/HIV co-infection are beneficiaries of separate TB and HIV programs. A local TB program in Odesa province was developed based on the National TB Program. One of the main focuses of the local TB program was TB/HIV co-infection.

The TB program is implemented through a network of specialized TB and primary health facilities. For patients with TB/HIV co-infection, the antiretroviral treatment (ART) and cotrimoxazole preventive therapy (CPT) are provided based on WHO guidelines according to which the treatment should be initiated within 2 weeks from TB diagnosis. The TB control is supposed to start with testing sputum via miscrosopy, GeneXpert and DST. After receiving the findings of microscopy and GeneXpert, a treatment is supposed to be prescribed and later adjusted after receiving the results of DST. Based on the DST results, TB disease is classified into the following groups: sensitive TB, multidrug-resistant TB (resistant to isoniazid and rifampicin), extensively drug-resistant tuberculosis (XDR TB) (resistance to isoniazid, rifampicin, aminoglycosides and fluoroquinolones), and PreXDR TB (resistance to isoniazid, or rifampicin either to fluoroquinolones). The treatment of different types of DR TB is administered based on the WHO-recommended standardized treatment guidelines.

Study population and sample size

All 373 PLH with confirmed pulmonary DR TB (MDR, PreXDR and XDR) from Odesa oblast for the period of 2014-2016 were included in the study. The inclusion criteria were age over 18, diagnosis of HIV at any time and in any region of Ukraine using standard HIV testing algorithm and WHO HIV clinical stage classification, receiving DR TB treatment and availability of DST profile to all first- and second-line TB drugs. The exclusion criterion was extrapulmonary TB.

Data source, management and analysis

Data on patients from Odesa oblast was taken from the national electronic registry (e-TB manager) and it was further enhanced with the help of local DR TB local database. Variables of the analysis included demographic and clinical characteristics of our study participants such as gender, age, residential area, type of TB resistance, type of DR TB, ART, CPT, DR TB treatment outcomes, availability of CD4 test, CD4 count, time between HIV diagnosis and ART, time between GeneXpert and DR TB treatment based on GeneXpert, time between DR TB treatment based on GeneXpert and results of DST. Statistical analysis was conducted using Microsoft Excel and EasySTAT online statistical application (http://easystat.app/) Data was summarized using percentages for categorical variables, means and standard deviations (SD) for variables with standard-distribution. Median and median difference were used only for the variable "time b/n HIV diagnosis" since it demonstrated non-standard distribution. The associations between the TB treatment outcome and risk factors with standard distribution were tested via χ^2 test and Student's t-test with significance level at 5%. For "time b/n HIV diagnosis" variable non-parametric Mann-Whitney U test was used to test the median difference.

Table 1. Characteristics of PLH on DR TB treatment in Odesa province, Ukraine, 2014-2016.

Variable		Total N = 373 N (%) / mean (+/-SD)
Gender	female	135 (36.2%)
	male	238 (63.8%)
Residential area	rural	132 (35.4%)
	urban	241 (64.6%)
Type of resistance	MDR TB	277 (74.3%)
	PreXDR TB	60 (16.1%)
	XDR TB	36 (9.7%)
Type of DR TB	new	264 (70.8%)
	relapsed	109 (29.2%)
ART	no	32 (8.6%)
	yes	341 (91.4%)
CPT	no	15 (4%)
	yes	358 (96%)
CD4 test	no	33 (8.8%)
	yes	340 (91.2%)
CD4 count		202.7 (± 201.4)
Age		39.4 (± 8.5)
Time b/n HIV diagnosis and ART initiation		339*
Time b/n GeneXpert and DR TB treatment based on GeneXpert		1.3 (± 4.8)
Time b/n DR TB treatment based on GeneXpert and results of DTS		37.0 (± 32.0)

ART: antiretroviral therapy, CPT: cotrimoxazole preventive therapy; DR TB: drug-resistant tuberculosis; DST: drug susceptibility test; LTFU: loss to follow-up; MDR TB: multidrug-resistant tuberculosis; PLH: people living with HIV; PreXDR TB– pre-extensively drug-resistant tuberculosis; SD: standard deviation; XDR TB TB– extensively drug-resistant tuberculosis; *median was reported for this variable since data demonstrated non-standard distribution.

Ethical considerations

Local ethical approval was obtained from the Institutional Ethics Review Board of Odesa Regional Center of Socially Significant Diseases.

Results

In the total group of 373 patients, the majority were males (63.8%) from urban areas (64.6%). The mean age of the study participants was 39 ± 8.5 years with no difference between men and women. Around 71.0% of study population were new DR TB cases and the rest were relapsed. The prevalence of MDR TB, PreXDR TB and XDR TB were 74.3%, 16.1% and 9.7%, respectively. The average CD4 count was about 203. During the entire period of the study, ART was provided to 91.4% of patients with the median duration of 339 days from HIV diagnosis to the ART initiation. The CPT coverage was 96%. The mean time between GeneXpert and DR TB treatment based on the results of GeneXpert was 1.3 ± 4.8 days while the mean time between DR TB treatment based on GeneXpert and results of DST was 37.0 ± 32.0 days (Table 1).

The total treatment success of DR TB treatment in PLH was 44.2%. Among all unfavorable treatment outcome for DR TB in PLH, 30.6% died during their treatment, 8.8% failed the treatment and 16.4% were lost to follow-up. When presented by the type of DR TB resistance, the treatment success was 49.8% for MDR and 28.1% for XDR and PreXDR TB. In the second combined group, the death outcome and the failure outcomes were statistically significantly higherover the same outcomes in the first group. Death in the XDR and PreXDR was 45.8% compared to 25.3% of death in MDR. In addition, the outcome of failure was13.5% in

Table 2. Treatment outcomes by type of resistance among PLH on DR TB treatment in Odesa province, Ukraine, 2014-2016

DR TB treatment outcome	Total (N = 373, %)	MDR TB (N = 277, %)	XDR & PreXDR TB (N = 96, %)
Successful	**165 (44.2%)**	**138 (49.8)**	**27 (28.1%)**
completed	28 (7.5%)	21 (7.6%)	7 (7.3%)
cured	137 (36.7%)	117 (42.2%)	20 (20.8%)
Unfavorable	**208 (55.8%)**	**139 (50.2%)**	**69 (71.8%)**
died	114 (30.6%)	70 (25.3%)	44 (45.8%)
failure	33 (8.8%)	20 (7.2%)	13 (13.5%)
LTFU	61 (16.4%)	49 (17.7%)	12 (12.5%)

DR TB: drug-resistant tuberculosis; LTFU: loss to follow-up; MDR TB: multidrug-resistant tuberculosis; PLH: people living with HIV; PreXDR TB: pre-extensively drug-resistant tuberculosis; XDR TB: extensively drug-resistant tuberculosis.

XDR and PreXDR versus 7.2% in MDR. Loss to follow-up (LTFU) was not statistically significantly different across these groups: 17.7% in MDR and 12.5% in XDR and PreXDR (Table 2).

The factors associated with DR TB unfavorable treatment outcome included PreXDR and XDR TB, lack of CD4 test, lack of ART and lack of CPT (Table 3). The odds of having unfavorable treatment outcome was 4.1 times higher for XDR compared to MDR (95% confidence interval 95% CI = 1.7-9.7, $p < 0.001$). All study participants who did not have ART and CPT had unfavorable treatment outcome ($p < 0.001$). Lack of CD4 test was another factor for unfavorable treatment outcome. Those who did not have CD4 test had 4.9 higher odds for unfavorable treatment outcome compared to those who had them (95% CI = 1.8-16.9, $p < 0.001$).

Discussion

DR TB in PLH is an alarming public health problem in Ukraine, with Odesa province having the highest rate of co-infection in the country. The largest prevalence of co-infection in this province perhaps could be explained by an active migration flow through the five biggest ports of Ukraine located in Odesa. Despite the alarming problem, the current treatment status of DR TB in PLH is not available partly because of the lack of official data and partly because of the lack of studies focusing on the co-infection in this province. This study was the first attempt to investigate the problem.

According to our data, less than half of DR TB in PLH (44.2%) had successful DR TB treatment outcome. Although the group of MDR TB patients had the highest treatment success (49.8%) compared to PreXDR and XDR (28.1%), it is still much lower than the WHO-recommended goal of 75% [4]. The treatment success of MDR TB in our cohort is similar to the pooled rate of success for MDR (49.9%) reported by a systematic review and meta-analysis [7]. When comparing the rate of LTFU in MDR TB in PLH with the WHO-recommended rate of LTFU for the same population (17.7% in our cohort versus 5% of WHO rate), it becomes evident that it is much higher: about one out of five patients in our cohort was lost before completing the DR TB treatment [4]. This rate is also close to the rate of MDR TB in PLH reported by the above mentioned systematic review and meta-analysis (16.1% pooled rate of LTFU) [7]. It is particularly

Table 3. Factors associated with DR TB treatment outcome among PLH on DR TB treatment in Odesa province, Ukraine, 2014-2016.

Variable	Level	Unfavorable outcome N = 208	Successful outcome N = 165	Odds Ratio/ Mean Difference	95% CI	p value
Gender	female	71 (34.1%)	64 (38.8%)	0.8	(0.5, 1.3)	0.353
	male	137 (65.9%)	101 (61.2%)	1		
Residential area	rural	74 (35.6%)	58 (35.2%)	1.0	(0.7, 1.6)	0.932
	urban	134 (64.4%)	107 (64.8%)	1		
Type of resistance	MDR TB	139 (66.8%)	138 (83.6%)	1	-	-
	PreXDR TB	40 (19.2%)	20 (12.1%)	2.0	(1.1, 3.6)	0.020**
	XDR TB	29 (13.9%)	7 (4.2%)	4.1	(1.7, 9.7)	< 0.001**
Type of DR TB	new	144 (69.2%)	120 (72.7%)	0.8	(0.5, 1.3)	0.461
	relapsed	64 (30.8%)	45 (27.3%)	1		
ART	no	32 (15.4%)	0 (0%)	ND†	(7.5, ND†)	< 0.001**
	yes	176 (84.6%)	165 (100%)	1		
CD4 test	no	28 (13.5%)	5 (3%)	4.9	(1.8, 16.9)	< 0.001**
	yes	180 (86.5%)	160 (97%)	1		
CPT	no	15 (7.2%)	0 (0%)	ND†	(3, ND†)	< 0.001**
	yes	193 (92.8%)	165 (100%)	1		
Age		39.3 (± 9.1)	39.6 (± 7.1)	0.3 (± 0.9)	(-2.0, 1.4)	0.73
CD4 count		186.6 (± 183.7)	220.7 (± 218.8)	-34.1 (±- 21.3)	(-77.5, 9.3)	0.123
Time b/n HIV diagnosis and ART initiation		205	507	-302*	NA	0.387
Time b/n GeneXpert and DR TB treatment based on GeneXpert		1.4 (± 6.4)	1.2 (± 0.8)	0.3 (±- 0.5)	(-0.6, 1.2)	0.534
Time b/n DR TB treatment based on GeneXpert and results of DTS		34.9 (± 26.2)	40.1 ± 39.0)	-5.2 (±- 3.5)	(-13.4, 3.1)	0.216

*median difference was reported for this variable since data demonstrated non-standard distribution; **statistically significant difference was found; † Not Defined as there is no enough information to estimate; ART: antiretroviral therapy, CI: confidence interval; CPT: cotrimoxazole preventive therapy; DR TB: drug-resistant tuberculosis; DST: drug susceptibility test; MD: mean difference; MDR TB: multidrug-resistant tuberculosis; NA: not applicable; OR: odds ratio; PLH: people living with HIV, PreXDR TB: pre-extensively drug-resistant tuberculosis; SD: standard deviation; XDR TB: extensively drug-resistant tuberculosis.

alarming that one third of DR TB patients in PLH die during their DR TB treatment. The rate of death in the group of XDR and PreXDR TB in PLH was almost twice as high (45.8%) as the same rate in the group of MDR TB patients (25.3%). The latter is higher than the death date of 18.1% documented for MDR TB in a systematic review and meta-analysis for Sub Saharan Africa [8]. Our findings show low success rate for DR TB patients among PLH in Odesa province in general and for those in the group of XDR and PreXDR TB in particular. Immediate measures are to be implemented to improve the treatment success for DR TB patients with special emphasis on patients with XDR and PreXDR TB (Table 1).

Another important implication of this study is that although the patients start their treatment based on the findings of GeneXpert in about 1.3 days after getting the results of GeneXpert, the result of DST is reported only 37.0 days after the start of the initial treatment. As a result, patients who need more adjusted treatment based on the findings of DST undergo non-adjusted treatment for about 5 weeks before they have a chance to get more case-specific treatment. This finding on the late adjustment echoes with the literature which suggests that delayed management of tuberculosis can lead to poor treatment outcomes [9].

The risk groups for unfavorable treatment outcome included patients with XDR and PreXDR, lack of ART, CPT and CD4 test. The WHO recommends joint TB-HIV management which included ART and CTP for PLH among other activities [10]. According to our study findings the coverage of ART and CPT are relatively high (both exceeding 90%). The administration of ART and CPT, in addition, could substantially improve the DR TB treatment outcome for PLH among those who lack those treatments. The importance of ART is in line with the results of systematic reviews from different settings [11,12] and so is the importance of CPT. A study showed that the mortality rate of TB among PLH in Botswana was higher for those who did not start CPT [13]. Hence, the administration of ART and CPT should be among the priorities of the HIV and TB care in Ukraine. As for CD4 test, it is hard to conclude from our data whether this factor itself led to poor treatment outcomes or if it was not possible to take CD4 test due to the early death and early loss. More targeted research is necessary to further analyze this association.

Being the first attempt to investigate the treatment outcomes of DR in PHL in Ukraine, our findings may have significant value for improving TB and HIV care in our study population. The fact that the manuscript was written in accordance with STROBE guideline ensures more systematic and comprehensive reporting of our findings. Our study used routinely collected data, which did not allow for more specific and detailed analysis, however, it allowed to receive a general picture of treatment success of DR TB in PLH in Odesa and to come up specific recommendations.

Conclusion

Despite the efforts contributing to the improvement of DR TB diagnosis and treatment such as introducing molecular genetic diagnostic methods, improving access to treatment, expanding HIV treatment programs, introducing directly observed therapy and CPT in Ukraine, the rate of successful DR TB treatment in PHL in Odesa province remains low with the poorest treatment outcomes being identified in patients with XDR and PreXDR TB. The delayed reporting of DST is a problem contributing to lack of timely adjusted treatments. Being an XDR and PreXDR patient and lack of ART and CPT are associated with the risk of unfavorable DR TB treatment outcomes. Additional studies would be helpful to investigate the temporal relationship between CD4 test and unfavorable treatment outcome in Odesa.

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Authors' contributions

Svitlana Yesypenko, Yulia Sereda and Olga Denisuk conceived the study aims; Svitlana Yesypenko, Oleksandr Postnov, Oleksandr Neduzhko, Liana Kovtunovich, Tatyana Rybak and Sergiy Antonyak led the data collection; Svitlana Yesypenko, Ruzanna Grigoryan, Oleksandr Neduzhko and Olga Denisuk designed and executed the analysis; Svitlana Yesypenko and Ruzanna Grigoryan wrote the first draft of the manuscript; All authors provided feedback to the first draft of the manuscript.

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