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SORT IT KB Key Population

The survival rate of tuberculosis patients in HIV-treated cohort of 2008-2018 in Almaty, Kazakhstan

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Abstract

Introduction: HIV/TB comorbidity is responsible for 1.6 million deaths worldwide. HIV/TB control and patients' survival are still among priorities of the national HIV and TB programs. We aimed to evaluate the HIV/TB survival in connection with TB treatment outcomes and factors influencing life duration of the cohort 2008-2018 in Almaty, Kazakhstan.

Methodology: This retrospective cohort study extracted data for all HIV and pulmonary TB adults coinfected during 2008-2018 in Almaty from national registries to apply descriptive, Kaplan-Meier estimation, and Cox proportional hazards regression model. Survival function for the TB treatment outcomes and factors predicting the probability of survival were tested and described.

Results: The cohort population (n = 521) mean age was 37.4 years with 405 (77.7%) males and 210 (40.3%) marrieds. More than one TB treatment had 181 (34.7%) patients, 291 (55.9%) were smear-positive (SS+), and 423 (81.2%) were on antiretroviral therapy with mean CD4 count 254.22cells/μL. Probability to live longer was higher (128 versus 37 months, p = 0.003; 95% confidence interval (CI) 71.65, 184.35) for those who succeeded in TB treatment compared to "lost to follow-up" and "failed" treatment outcomes. Adjusted Cox regression model death hazard showed association with missing ART treatment (HR: 1.699, 95%CI 1.164, 2.481, p = 0.006) and having CD4 count < 499 (HR 2.398, 95%CI 1.191, 4.830, p < 0.014).

Conclusion: TB treatment outcomes, ART treatment, and the CD4 count of HIV/TB coinfected population substantially influence their life duration. The medical decision- and policy-makers should take this into consideration when implementing targeted improvements in the national HIV and TB programs.

Key words: tuberculosis; HIV; survival; SORT IT.

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Introduction

Tuberculosis (TB) is ranked among top 10 diseases causing death globally [1]. The chance of developing TB disease increases among people infected with HIV leading to poorer treatment outcomes [1]. Despite the fact that the number of HIV/TB deaths has fallen by 44% since 2000 and by 20% since 2015, in 2017, HIV/TB comorbidity was still responsible for 1.6 million deaths worldwide, counting 57% males and 43% females [1]. The Sustainable Development Goals (SDGs) and WHO's End TB Strategy include the global targets and milestones for reducing number of TB deaths compared to 2015 equal to 95% and 75% for 2030 and 2025, respectively, by management of comorbidities and implementation of collaborative TB/HIV activities [1].

Kazakhstan is a high burden country for multidrug-resistant TB (MDR-TB), counting 26% for newly diagnosed cases and 44% for previously treated TB cases [1]. While the TB and HIV rates in Kazakhstan during the last five years have a favorable trend: declining in 35.5% for TB and remaining the same for HIV [2], the TB/HIV control and patients' survival remain a challenge. In Kazakhstan in 2017, the HIV/TB mortality rate reported to be 0.2 per 100,000 population [2].

Reducing mortality, preventing drug resistance and morbidity associated with TB is among essential goals of national TB/HIV collaborative activities of the country to meet SDGs. Kazakhstan follows the WHO recommendations for Antiretroviral Therapy (ART). International studies showed that with the initiation of ART, the life expectancy of people with HIV is

dramatically increases [3]. Almost all HIV-positive TB patients in Kazakhstan are prescribed for ART within the first two months of the TB treatment start. The number of HIV-positive TB patients on ART has dramatically grown in Kazakhstan in recent years: from 72% to 90.3% [2], equivalent to high TB/HIV burden countries coverage (85%) [1].

Health services in the Republic of Kazakhstan are covered by the state funds for entire population, including both HIV and TB services. The republic has 14 regions and 3 biggest cities with structures equal to regional level [4]. The 24% of the country's population have a low socio-economic status [4]. Almaty city is one of the biggest financial, economic and cultural centers of the country with 1.8 million population [4].

One of the effective ways of identifying and evaluating the disease-related patterns and estimating the likelihood of death due to the specific health conditions, including TB and HIV, is the survival rates analysis. This information is of interest to a large audience, including, clinicians, public health specialists, researchers, patients, public, and policy makers. It helps to make informed policy decisions and to improve health of the population. Limited research conducted worldwide shows that the mortality rates among HIV-positive population are highly associated with TB coinfection irrespective of the country resource level, availability of ART, gender, and age [5].

This study aims to evaluate the survival of HIV/TB patients in regards to their TB treatment outcomes and the factors influencing life duration of the cohort 2008-2018 in Almaty, Kazakhstan.

Methodology

Study design

This was a retrospective cohort study based on an analysis of the national Electronic HIV Case Management System database. It included 1) abstraction of data from records and databases, 2) survival analyses of the target population data on their TB treatment success, and 3) identifying clinical, behavioral and demographic risk factors associated with life duration among HIV/TB coinfected patients.

Settings and data abstraction

In Almaty, the HIV services, including blood sampling for detection of HIV infection are performed in all medical centers with a testing of serum. The Republic AIDS center laboratory gives final confirmation of the results. Specialized TB services are performed in a center of pulmonology that conducts sputum smear microscopy, culture, and drug susceptibility testing. Ambulatory treatment of TB patients is done in 40 outpatient TB centers located in the primary health care facilities. According to the national guidelines, TB screening and 6 months' Isoniazid treatment is recommended for all HIV-diagnosed patients [6]. Also, those diagnosed with TB first, undergo the HIV testing [7].

We abstracted the data for this research from multiple registries of the national Electronic HIV Case Management System. Data from HIV/AIDS Patients register, TB Patients register, Patients Receiving ART register, and HIV/AIDS Patients' death register were linked to create a comprehensive database to use in this study. No personal identifiers such as name, phone number, and address of participants were recorded to comply with the data protection principles. Matching was conducted using a unique IDs assigned to each patient in the national database across the different registries.

Study population

This census included data of all adult patients over 18 years of age with HIV and pulmonary TB co-infection registered in the electronic databases for the period of 2008-2018 in Almaty. Patients entered the cohort upon first recorded HIV/TB coinfection diagnosis and left at date last seen for HIV/TB care prior 31 December 2018 or date of death (if applicable). All remaining observations were censored at the end of 2018.

Statistical analyses

Statistical analyses were conducted using IBM SPSS statistics 21, and SAS statistical software version 9.2. We applied basic descriptive statistics (means, medians, standard deviations, and frequencies) to describe socio-demographic, behavioral, and clinical characteristics of the study population. Significance tests were performed with t-tests for parametric and Fisher's exact tests for nonparametric data. Proportions were compared with chi square.

For time-to-event analysis we used nonparametric Kaplan-Meier estimator to define the survival function for the TB treatment outcomes among HIV/TB coinfected patients [8,9].

To compare the survival probabilities and to test the difference between two groups, we identified "treatment success" as combination of "cured" and "treatment completed" cases, following the WHO classification and considered "treatment non-success" as combination of "treatment failed" and "lost-to-follow-up" cases. Excluding TB treatment outcome

"died" from the survival analysis helped to prevent the data misinterpretation.

The Cox proportional hazards (PH) regression model was used to estimate adjusted clinical, behavioral and demographic hazard functions associated with patients' life duration predicting the probability of survival in each group, while keeping the other covariates fixed at their mean values [9,10]. We consider magnitude of hazard ratios (HR) and the width of their confidence intervals (CI) to decide whether associations were clinically, as well as statistically significant. Level of significance was set at 5% for all models.

Ethical approval

The study protocol received a waiver from the Institutional Review Board on Human Research within the Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan due to the nature of the data used: secondary data analysis and absence of a new data collection with the human subjects' involvement.

Table 1. Sociodemographic, behavioral, and clinical characteristics of HIV/TB co-infected patients' cohort 2008-2018, Almaty.

Variables	N = 521 n (%) or mean ± SD
Age, years	37.4 ± 9.12
Gender, male/female, n (%)	405/116 (77.7%/22.3%)
Education:	
school (≤ 11 years), n (%)	358 (68.7%)
higher (> 11 years), n (%)	163 (31.3%)
Married, n (%)	210 (40.3%)
HIV transmission:	
parenteral, n (%)	353 (67.8%)
sexual, n (%)	165 (31.7%)
not identified, n (%)	3 (0.6%)
History of drug use, n (%)	353 (67.8%)
History of incarceration, n (%)	235 (45.1%)
Sputum smear:*	
positive, n (%)	291 (55.9%)
negative, n (%)	224 (43%)
Type of TB:*	
new, n (%)	332 (63.7%)
retreatment, n (%)	181 (34.7%)
Treatment outcome:	
cured, n (%)	7 (1.3%)
completed, n (%)	297 (57.0%)
lost to follow-up, n (%)	31 (6.0%)
failure, n (%)	6 (1.2%)
TB-related death, n (%)	143 (27.4%)
On ART treatment, n (%)	423 (81.2%)
CD4 count, cells/μL, mean ± SD	254.22 ± 217.29
Viral intensity, mean ± SD	434,460.61 ± 1,186,686.30

*Data for few cases were missing; ART – AntiRetroviral Therapy; SD – Standard Deviation; TB – Tuberculosis.

Results

General descriptive

Table 1 shows the sociodemographic, behavioral, and clinical characteristics of the TB/HIV coinfected cohort. The cohort consisted of 521 patients diagnosed with HIV/TB coinfection for the 10 years' period (2008 - 2018) with a mean follow-up time of 1.1 years and a median of 1.4 years. Almost 78% (n = 405) of patients were men. The mean age at HIV/TB coinfection diagnosis was 37.4±9.12 years. Less than half were married and about two-third had ≤ 11 years of education (see Table 1).

Among 521 HIV/TB patients, 81.2% (n = 423) were on ART. The overall mean CD4 count and viral intensity of the total cohort were 254.22 cells/μL and 434,460.61, respectively. The 76% of patients (n = 396) were firstly diagnosed with TB and then HIV, with mean 15 days between these two diagnoses. Among those who received ART, the successful TB treatment outcomes after the standard course of TB treatment were observed in 71.4% of patients. Compared with those having non-successful treatment ("failed", "lost-to-follow-up", and "died") the TB treatment-succeeded cohort comprised a higher proportion of married people (p = 0.05), persons not having a history of drug use (p = 0.03), primary TB cases (p = 0.01), those having higher CD4 count (p = 0.009) and lower viral intensity (p = 0.02). A total of 248 (47.6%) persons died from any cause during follow-up, of whom 143 (27.4%) were TB-related. Most deaths occurred during the first two years of follow-up.

Survival

The survival rate for all patients was 82.6% at 1 year and 56.1% at 5 years. The number of patients at risk at different time points for two groups of patients having "successful" and "non-successful" TB treatment outcomes is displayed on the Figure 1. The Kaplan-Meier survival function estimated that the median survival time (the time by when the event has occurred in 50% of cases) for HIV/TB coinfected patients was 128 months for those who had successful TB treatment outcome and 37 months for those who "failed" or "lost to follow-up" in TB treatment with statistically significant difference between the groups (p = 0.003, 95%CI 71.648, 184.352).

In the multivariable Cox proportional hazard model (Table 2), those not being on ART treatment had 1.7 times higher hazard of death than those who received

ART. Patients with CD4 count less than 499, were at 2.4 times greater risk for death than those with CD4 above or equal to 500. (Table 2).

We tested also for other sociodemographic, behavioral, and clinical characteristics but did not find significant evidence of effect modification between exposure variables.

Discussion

We conducted survival analyses among patients living with HIV/TB coinfection in a middle resource country with free and accessible HIV and TB services. Our findings show that between 2008 and 2018 there were two main factors affecting survival. These include receiving ART treatment and patients' CD4 count level. Longer survival of patients receiving ART treatment closely connected to their level of CD4 count. It is likely that TB patients with high CD4 count would have better treatment outcome leading to higher survival. The cutting point for CD4 count that significantly affect the survival was found to be 500. These findings are

Figure 1. Probability of surviving among TB/HIV coinfected patients (N = 521) after care initiation separately for groups with successful and non-successful TB treatment outcomes, cohort 2008-2018, Almaty.

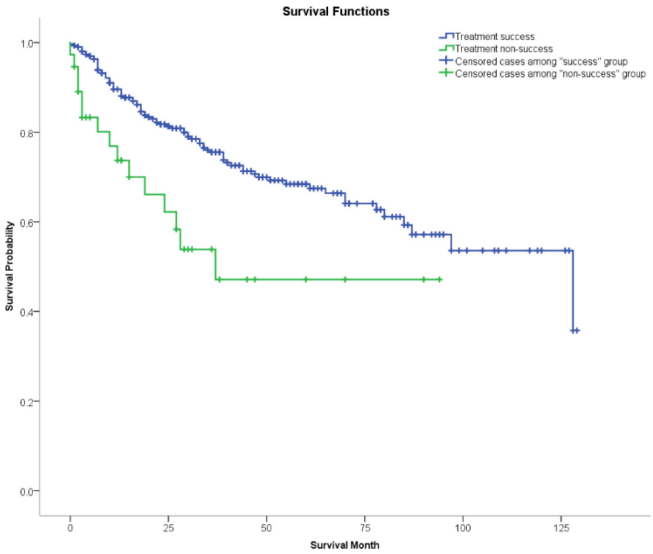

Table 2. Multivariable Cox regression analysis of all-cause mortality in the national HIV/TB coinfected patients' cohort (N = 521) 2008-2018, Almaty.

Variable	Hazard Ratio	95% CI	p value
Age	1.015	0.999; 1.032	0.069
Gender			
female	1		
male	1.194	0.776; 1.836	0.420
Education			
higher (> 11 years)	1		
school (≤ 11 years)	0.958	0.663; 1.385	0.820
Marital status			
married	1		
not married	0.795	0.561; 1.125	0.195
History of drug use			
no	1		
yes	1.384	0.034; 57.003	0.864
History of incarceration			
no	1		
yes	0.805	0.534; 1.213	0.299
Sputum smear			
negative	1		
positive	0.995	0.977; 1.014	0.620
Type of TB			
new	1		
retreated	1.004	0.992; 1.015	0.542
On ART treatment			
yes	1		
no	1.699	1.164; 2.481	0.006*
CD4 count			
≥ 500	1		
< 499	2.398	1.191; 4.830	0.014*
Viral intensity	1.000	1.000; 1.000	0.130

*Statistically significant finding; ART – AntiRetroviral Therapy; CI – Confidence Interval; TB – Tuberculosis.

consistent with the studies conducted in UK and elsewhere [11,12].

Most deaths in our cohort occurred within the first two years, in contrast to previous studies [11] with the similar design, where it happened within the first year. This difference might be due to the implemented mandatory ART initiation for all coinfected TB and HIV patients in Kazakhstan, regardless of their CD4 count. While other studies reported late or non-start of ART initiation for large proportion of individuals with very low CD4 count at diagnosis [11-13]. The importance of early ART initiation among TB coinfected patients has been demonstrated elsewhere [12,14] and recommended by the current guidelines [15].

We observed that HIV screening recommended for all patients diagnosed with TB is routinely implemented in Almaty health facilities, making the majority of HIV and TB diagnoses almost simultaneously (15 days of mean difference).

The impact of successful TB treatment outcome on survival identified in our cohort demonstrates that for patients with treatment success probability to leave longer is substantially higher ($p = 0.003$) than for those who left the TB treatment incomplete ("lost to follow-up") or "failed". Importantly, the HIV/TB coinfected patients whose TB treatment outcomes were "successful" represented persons having families, not using drugs and not being TB retreated. These socio-behavioral characteristics more likely assure person's compliance to TB treatment resulting on outcome success. The observations of studies conducted in other countries also support this hypothesis.

This study has the following limitations. Results of the multivariate analyses depend on the availability of information collected through routine surveillance. Though the completion rates for the used databases were generally high, some information was difficult to extract or was missing. For example, the factors such as other comorbidities are routinely collected in the national surveillance system of Kazakhstan, however they are recorded with the special codes that impossible to disclose without a corresponding key list. Moreover, data on whether patients were drug-susceptible or -resistant were missing from the registries. Therefore, we were not able to include information on patients' other comorbidities and drug-resistance in the survival multivariable model to test their impact.

Conclusion

The results of this cohort study demonstrate high rates of HIV/TB coinfection and consequent mortality in people living with HIV and TB. These results might inform the medical decision- and policy-makers in the Almaty's HIV and TB national programs about specific issues that need to be improved through changes in policy and practice resulting to improve national TB and HIV programs performance in Kazakhstan.

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Authors' contributions

AZ and NT conceived the study aims. AZ led the data collection. AZ, NT and ES designed and executed the analysis. AZ wrote the first draft of the manuscript. All authors provided feedback to the first draft of the manuscript.

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