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SORT IT TB Key Population

Antiretroviral therapy among patients with HIV in Almaty, Kazakhstan: the implication for HIV-associated tuberculosis control

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Abstract

Introduction: Antiretroviral therapy (ART) is an effective preventive strategy against tuberculosis (TB) in people living with HIV (PLWH). In Kazakhstan, according to the revised HIV treatment guideline (2017), ART should be initiated immediately after HIV diagnosis established, regardless of CD4+ count.

Aim: To evaluate the impact of early initiation of ART on TB infection in PLWH registered in the Center of Prevention and Control of AIDS, Almaty, Kazakhstan, between 2008 and 2018.

Methodology: A retrospective cohort study was conducted using the data of 4,053 patients from electronic HIV case management system (2008-2018) (EHCMS).

Results: The study revealed low rates (12.6%) of rapid ART (≤ 1 month after HIV diagnosis). Patients in the rapid ART initiation group were less likely to develop TB compared with those who started treatment >1 month after the HIV detection (odds ratio 1.6; 95% confidence interval [1.1, 2.2]; p = 0.00799). Interestingly, the risk for developing TB among patients receiving ART ≥ 1 month after HIV diagnosis was significantly higher compared with those not taking any treatment. The latter was explained by several confounding not addressed during the analysis, since ART was prescribed to patients with primarily deeper immunodeficiency, while the patients not receiving ART were less immunocompromised.

Conclusion: Despite the recently changed HIV treatment guideline in Kazakhstan, ART is still initiated based on the disease severity. In 2018, the initiation of ART during the first month after HIV diagnosis increased by 50%. However, it is necessary to reduce the time to initiation of ART for all patients.

Key words: HIV; tuberculosis; Kazakhstan; antiretroviral therapy; operational research; SORT IT.

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Introduction

Tuberculosis (TB) is the commonest opportunistic infection in people living with Human Immunodeficiency Virus (HIV) [1] According to Joint United Nations Programme on HIV/AIDS (UNAIDS) report, in 2016, there were more than one million (10% of all worldwide) TB cases among people living with HIV (PLWH) [2], and the risk of developing TB disease among PLWH was around 21 times higher compared to the rest of the world population [3]. The PLWH are at extremely high risk of TB due to the immunological impairment associated with HIV and deprived social conditions [3]. According to World Health Organization's (WHO) Global Tuberculosis Report (2018), there were about 300,000 deaths from TB among PLWH worldwide in 2017 [4]. Antiretroviral therapy (ART) among HIV infected TB patients can improve the TB treatment outcomes and improve the overall survival [3]. According to WHO recommendations HIV patients must receive ART regardless of their CD4+ count [5]. Unfortunately, this goal is still far from being achieved satisfactorily in most countries with an average coverage of 57% in 2012 at the global level [6].

Kazakhstan is one of the countries in the WHO European Region that has identified TB control as a key health priority. However, it is among the 30 countries with the highest burden of multidrug-resistant tuberculosis (MDR-TB) worldwide [7]. ART should be initiated immediately after HIV infection is diagnosed (regardless of CD4+ count is one of the biggest AIDS Centers in Kazakhstan. In 2017, there were 480 new

HIV cases diagnosed through ELISA and Western blot methods at the Almaty Center for AIDS Prevention and Control (population 1,751,300); to compare, 308 patients were diagnosed in 2008 [8]. The prevalence of HIV in 2017 constituted 0.35% in the age group 15-49 years, compared with 0.2% nationwide [8]. According to the Almaty Center for AIDS Prevention and Control's recent survey conducted in Kazakhstan, it was estimated that as of 2017, 75% of PLWH were aware of their HIV status, of which 59% received ART [2]. Delayed initiation of ART among HIV patients is one of the factors associated with its poor preventive effect on HIV-associated TB [3]. Findings from a South African research suggested that during long-term ART TB incidence remained greater among HIV population compared with local HIV uninfected population, regardless of the ART duration or maintenance of CD4 cell counts >700 cells/μL [9]. Other study showed that reduction in TB incidence during ART depended on CD4+ cell count; but after 3 years of treatment, rates were still 5- to 10-fold higher than among non-HIV-infected people [3].

The aim of the study was to evaluate the effect of rapid initiation of ART on developing of TB infection in HIV patients (occurrence of TB) registered in the Center of Prevention and Control of AIDS of Almaty between 2008 and 2018.

Specific objectives were:

1) To identify the sociodemographic characteristics of the study population
2) To measure time to TB development in the following groups:
   - ART not initiated
   - ART initiated within one month after HIV detection
   - ART initiated after one month after HIV detection.

Methodology

Study Design

A retrospective cohort study was designed to analyze the data from the Electronic HIV case management system (2008-2018).

Table 1. Sociodemographic and clinical characteristics of the HIV patients, stratified by TB status registered in Almaty, Kazakhstan, 2008-2018.

Variable	Level	Total N = 4053	TB status		OR or mean difference	95% CI	p value
			TB+ N = 406	TB- N = 3647			
ART groups by initiation time, n (%)	< 1 month	509 (12.6%)	41 (10.1%)	468 (12.8%)	1	-	-
	≥ 1 month	2440 (60.2%)	297 (73.2%)	2143 (58.8%)	1.6	[1.1, 2.2]	0.00799
	never started	1104 (27.2%)	68 (16.7%)	1036 (28.4%)	0.7	[0.5, 1.1]	0.159
Age, n (%)	18-30 years	1419 (35%)	100 (24.6%)	1319 (36.2%)	1	-	-
	31-59 years	2516 (62.1%)	299 (73.6%)	2217 (60.8%)	1.8	[1.4, 2.3]	< 0.001
	≥ 60 years	118 (2.9%)	7 (1.7%)	111 (3%)	0.8	[0.4, 1.8]	0.647
Gender, n (%)	female	1513 (37.3%)	89 (21.9%)	1424 (39%)	0.4	[0.3, 0.6]	< 0.001
	male	2540 (62.7%)	317 (78.1%)	2223 (61%)	1		
	missing	9 (0.2%)	0 (0%)	9 (0.2%)	-		
Education, n (%)	higher	994 (24.5%)	57 (14%)	937 (25.7%)	0.5	[0.4, 0.6]	< 0.001
	non-higher	3050 (75.3%)	349 (86%)	2701 (74.1%)	1		
	missing	3 (0.1%)	0 (0%)	3 (0.1%)	-		
Marital status, n (%)	married	1833 (45.2%)	164 (40.4%)	1669 (45.8%)	0.8	[0.7, 1.0]	0.0379
	single	2217 (54.7%)	242 (59.6%)	1975 (54.2%)	1		
ART first interruption, n (%)	no-interruption	2623 (64.7%)	311 (76.6%)	2312 (63.4%)	1	-	-
	interruption after first therapy	326 (8%)	27 (6.7%)	299 (8.2%)	0.7	[0.4, 1.0]	0.056
	not-started	1104 (27.2%)	68 (16.7%)	1036 (28.4%)	0.5	[0.4, 0.6]	< 0.001
Outcome, n (%)	on ART treatment	1734 (42.8%)	124 (30.5%)	1610 (44.1%)	1	-	-
	no ART	880 (21.7%)	70 (17.2%)	810 (22.2%)	1.1	[0.8, 1.5]	0.459
	unsuccessful	1439 (35.5%)	212 (52.2%)	1227 (33.6%)	2.2	[1.8, 2.8]	< 0.001
Age, mean ± SD		35.7 ± 10.2	36.7 ± 8.85	35.6 ± 10.39	1.1 ± 0.47	[0.1, 2.0]	0.0234 (< 0.001)
Time to death after HIV diagnosis, mean ± SD		32.6 ± 30.2	41.6 ± 32.01	30.1 ± 29.23	11.5 ± 1.66	[6.5, 16.4]	< 0.001 (< 0.001)
Time to TB infection after HIV diagnosis, mean ± SD		29.9 ± 31.6	29.9 ± 31.6	-	-	-	-

ART: antiretroviral therapy; CI: confidence interval; OR: odds ratio; SD: standard deviation; TB: tuberculosis.

Study Setting

Kazakhstan is a country in the Central Asian region. The population of the country is about 18.6 million, more than half of which lives in urban areas. The Almaty Center for AIDS Prevention and Control was established in 1991 to control the increasing incidence of HIV in the city.

Study population

The study population included all HIV-positive patients registered at the AIDS center during the period of 2008-2018 in Almaty, Kazakhstan.

Exclusion criteria for this study were:

- Foreign citizens and PLWH without any identification documents
- Patients who were diagnosed to have TB before the HIV detection
- Age under 18 years old.

The study variables are presented in Appendix 1.

Analysis and statistics

The data were obtained from the EHCMS and entered into MS Excel spreadsheet. Data analysis was done using SAS 9 statistics software and Easystat web-based statistical application (https://easystat.app/). Levels of significance were set at 5%. Descriptive statistics have been used to analyze the sociodemographic characteristics of the study population (frequencies, proportions, measures of central tendency (mean), and variation (standard deviation). Product-Limit Failure Curves analysis was applied to assess TB free survival after initiation of ART compared with those who did not receive any treatment.

Ethics approval

Permission for the study was granted by the Local ethical committee of the Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan.

Results

The study included 4,053 patients, mainly males (62.7%), and belonged to the age group between 31 and 59 years (62.1%). The socio-demographic and clinical characteristics of the study population are presented in Table 1. The median time interval from the HIV detection to ART initiation was 13 months in the group that initiated ART after one month (n = 2,440; 60.2%). Figure 1 represents the trends of ART initiation duration, starting from the moment that HIV was detected. Among the study population, only 509 (12.6%) patients initiated ART within the first month after HIV detection. About 10% (n = 406) of study population developed TB during the period of 2008-2018. Among those, ART was initiated within one month in 41 (10.1%) patients, n = 297 (73.2%) after one month, and n = 68 (16.7%) patients did not receive ART in the selected period. The group of all patients that received ART after one month and those who did not receive ART in the selected period were included in the survival analyses for getting TB over the period of time after the HIV diagnosis. In terms of treatment outcome,

Figure 1. Trends of the number and proportion of HIV patients registered in Almaty, Kazakhstan, stratified by status of starting antiretroviral therapy initiation duration categories, 2008-2018.

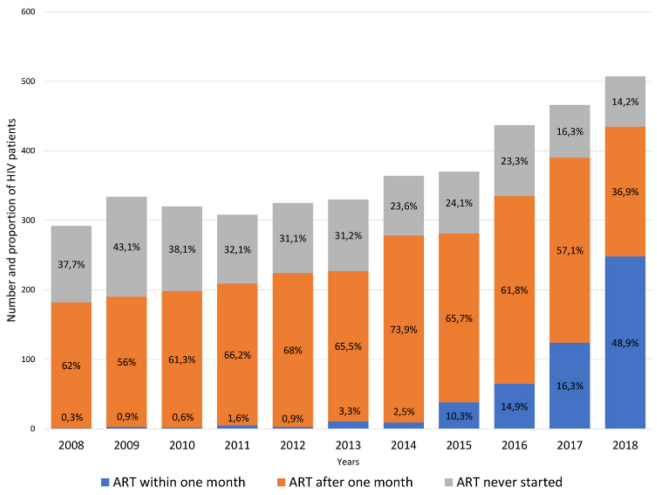
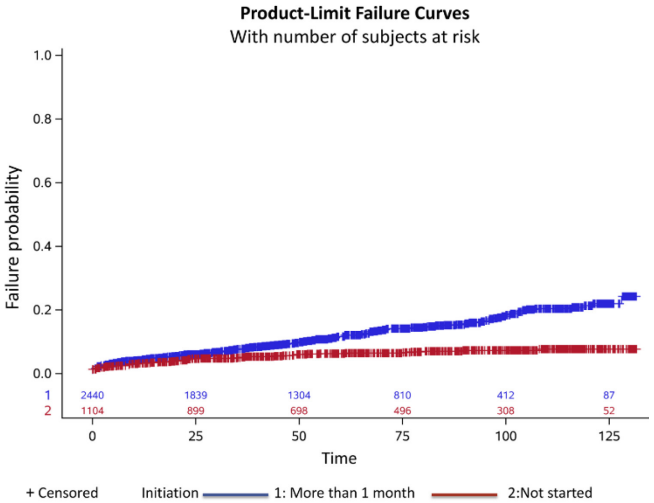


Figure 2. Product-Limit Failure Curves with number of subjects at the Risk for TB among the patients started antiretroviral therapy after >1 month of HIV diagnosis or not started.



Log rank p < 0.01, HR = 0.39 for those who are not taking medication.

1,439 patients (35.5%) had unsuccessful results (death/lost to follow-up). Among those, 212 were TB-positive (52.2% of all TB-positive cases). The PLWH in the 31-59 years age group appeared to be more likely to develop TB compared to those aged 18-30 years: odds ratio (OR) 1.8; 95% confidence interval (CI) [1.4, 2.3]. Females with HIV were 60% less likely to develop TB compared with males (OR 0.4; 95% CI [0.3, 0.6]). Those with higher educational level were 50% less likely to develop TB compared to those who do not have higher educational level (OR 0.5, 95% CI [0.4, 0.6]). The average duration of TB-free period after the HIV detection was 30 months. Among 2,440 (60.2%) patients, ART was initiated after one month from the HIV detection. Of these, 297 (73.2%) cases developed TB. The analysis revealed that those who initiated ART after one month were 60% more likely to develop TB compared with those in whom ART was started within the first month after the HIV diagnosis (OR 1.6; 95% CI [1.1, 2.2]; p = 0.00799). However, survival analysis showed a higher probability of developing TB among patients in the ART initiation after one month group compared to those who never started ART in the selected time period (Figure 2). Hazard ratio of having TB was about 60% lower among those who were NOT taking medication compared to those receiving ART.

Discussion

To our knowledge, this is the first study describing detailed sociodemographic characteristics of HIV/TB patient in Kazakhstan, and providing insight to the association of rapid initiation ART and developing of TB infection among the study population. In Kazakhstan, ART, since its inception in 2005 until May 2017, has been prescribed on the basis of CD4+ cell count or TB co-infection. According to the study findings, the median time for ART prescription was 13 months after HIV diagnosis, whereas TB was developed within 30 months on average since the time of HIV diagnosis. Our findings were consistent with those from Australia, which showed median time from diagnosis to ART ranging between 2.5-14 months in the period of 2011-2015 [10]. The higher likelihood of TB disease among males and those with lower educational level could be explained by the gender features and impact of social status, which was frequently, reported worldwide [11].

This study results indicated a quite low rates of early ART (≤ 1 month after HIV diagnosis) in the study population (12.6%). At the same time, in sub-Saharan countries after national adoption of "treat all" program and early ART initiation the compliance was as high as up to 81.6% [12].

One of the main findings of the study was the higher risk of developing TB disease among patients who started ART late, after one month of the HIV diagnosis compared to those with early ART (≤ 1 month after HIV diagnosis). This result was consistent with a large piece of literature evidence [13-15]. Interestingly, our results also demonstrated significantly higher risk for developing TB among patients receiving ART late (≥ 1 month after HIV diagnosis) compared with those not taking any ART. It is highly possible that the observed risk difference was due to several confounding not addressed during the analysis, since ART was prescribed to patients with primarily deeper immunodeficiency, while the patients not receiving ART were less immunocompromised. This finding together with the low rate of early ART in our study population supports the assumption that despite the recently changed HIV treatment guideline in Kazakhstan ART is still initiated rather late than early, based on the disease severity. In 2018, the initiation of ART during the first month after diagnosis of HIV increased by 50%. However, it is necessary to initiate ART as early as possible to for all patients.

Limitations: There are several limitations to this retrospective cohort study. First, ART compliance of patients was not assessed. Possibly, there were confounding factors, such as differences in severity of disease between patients in ART/no ART groups, which was not addressed during the analysis. Finally, odds ratio was used as a measure of association between ART and TB-risk. Considering the fact that TB was a common outcome in this study, the possible overestimation of the risk cannot be excluded. Another limitation of the study is that for the estimation of HR of getting TB over the time (Figure 2), we did not include patients with less than 1-month of getting TB, because the time of getting TB for this group is not considered to be accurate, since patients were diagnosed with TB at the time of HIV diagnose or even before.

Conclusion

The study results indicated quite low rates of early ART in the study population, and a higher probability of developing TB among patients with late ART initiation. Results of this study may affect the current health system's policy and practice on TB care for HIV positive individuals in Kazakhstan, consistently improving TB control among PLWHA and the broader community. Further research is recommended to

evaluate the sociodemographic factors associated with not initiating ART and understuingin the effect of early ART initiation on getting TB among the HIV patients.

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