

Human immunodeficiency virus and tuberculosis coinfection: clinical features and predictors of mortality

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Received: 12.06.2017 • Accepted/Published Online: 03.04.2018 • Final Version: 14.06.2018

Background/aim: This study was undertaken to identify subjects with human immunodeficiency virus and tuberculosis (HIV/TB) coinfection in a group of HIV-positive patients followed at five different healthcare centers, and to determine the demographic and clinical characteristics of these subjects as well as the predictors of mortality.

Materials and methods: A database search for subjects with TB coinfection was performed among 1475 HIV-positive adult patients and a total of 66 individuals were identified with HIV/TB coinfection.

Results: There were 66 patients (4.5%) with TB coinfection. Twenty-one percent (n = 14) of the patients with TB coinfection died during the study period and these patients had significantly lower baseline CD4 counts at the time of TB diagnosis (P = 0.005). None of the patients with CD4 count of ≥ 200 cells/mm³ died during follow-up and a low CD4 count at the time of TB diagnosis (<200 cells/mm³) was associated with poor survival (P = 0.012). However, none of the parameters emerged as significant independent predictors of survival in multivariate analysis.

Conclusion: Coexistence of TB and HIV infection is associated with many clinical challenges and a better understanding of patient characteristics as well as the parameters impacting the outcome will improve the quality of care provided for this group of patients.

Key words: Human immunodeficiency virus, tuberculosis, coinfection, mortality

1. Introduction

Human immunodeficiency virus (HIV) infection is associated with deterioration of cellular immune responses and increased risk of opportunistic infections via reduced CD4+ T lymphocyte count. According to the data provided by the World Health Organization, the global number of HIV-positive individuals reached 36.9 million in 2014 (http://www.who.int/hiv/data/epi_core_july2015.png?ua=1). Tuberculosis (TB) represents the second leading cause of mortality from infectious diseases following HIV infection. Furthermore, TB is the most common opportunistic infection in HIV-positive individuals and is a major cause of death (1).

TB prevalence in Turkey was estimated to be 21/100,000 in the general population in 2011 and its incidence has

been decreasing over the years (2). The prevalence of TB in the largest city, İstanbul, was slightly higher (36/100,000) than in the general population (2).

HIV infection is an important risk factor for the rapid development of TB after exposure (3–6) and HIV-positive subjects have an increased risk of reactivation of latent TB and active TB (7). Active treatment of latent TB infections carries clinical significance with respect to decreasing the TB-associated morbidity and mortality and reducing the risk of TB transmission (8,9).

In addition, active TB infection leads to a significantly increased HIV viral number (10), and TB has a negative impact on the course of HIV infection, leading to the development of acquired immune deficiency syndrome (AIDS), accelerated disease progression, and death

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(11,12). According to the 2014 Global Tuberculosis Report of the World Health Organization, among 9 million cases of TB diagnosed in the previous year, HIV was present in 1.1 million and of the 1.5 million deaths due to TB, 360,000 were HIV-positive individuals (http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1).

Although antiretroviral therapy (ART) leads to a dramatic drop in morbidity and mortality in TB/HIV coinfection, simultaneous administration of antiretroviral and antituberculous treatments may give rise to complications such as drug interactions, toxicity, or worsening of TB symptoms due to HIV/TB-associated immune reconstitution inflammatory syndrome (13). Thus TB/HIV coinfection requires a complex approach.

To date, only a few studies examined patients with HIV/TB coinfection or provided data on this condition in Turkey (14–16). This study was undertaken to identify subjects with HIV/TB coinfection in a group of HIV-positive patients followed at five different tertiary healthcare centers, and to determine the demographic and clinical characteristics of those subjects as well as the predictors of mortality.

2. Materials and methods

2.1. Patients

The database of the ACTHIVIST group was used for the study purposes. This group was established by the participation of 5 tertiary care institutions (3 university hospitals and 2 research and training hospitals) that maintain a registry of HIV-positive patients in İstanbul, a large metropolitan city with a high number of HIV-positive residents. The medical data of HIV-positive patients followed by the centers mentioned above are entered into a joint database. The study was conducted in accordance with the Declaration of Helsinki and relevant laws and guidelines, and the study protocol was approved by the local ethics committee (no. 2015/0065, dated 27 May 2015).

Among a group of 1475 HIV-positive adult patients (>18 years) with data entry between 1996 and 2015, those diagnosed with active TB based on clinical, microbiological, histopathological, or imaging studies any time during the specified time period were included in this study. All data were transferred to Excel files and were sent to the respective centers for data update, following the addition of extra columns to these files for missing information required for study analyses. The missing data were completed by each center using the information gathered from patient records, through telephone contact with the patient, or from the hospital database. Completed and updated data were used for statistical analyses. HIV-positive patients with no proper patient file or missing major data were excluded.

Age, gender, race, sexual identity, baseline CD4 T cell count and HIV RNA (at the time TB was diagnosed), timing of TB with respect to ART, mortality status, and the localization of TB (pulmonary vs. extrapulmonary) were recorded and assessed.

2.2. Statistical analysis

Study data were analyzed using the SPSS 21 for Windows (IBM Corp., Armonk, NY, USA). Categorical data were compared with Fischer's exact test, while the Mann-Whitney U test was used for continuous variables. Univariate comparisons for survival were done using the log-rank test. Survival was defined as the time elapsed between the diagnosis of TB and death from any cause, and patients alive at the last follow-up were censored. Potential predictors of survival were entered into a Cox proportional hazards model to identify independent predictors of mortality. Two-sided P-values of <0.05 were considered statistically significant.

3. Results

Within the total cohort of 1475 patients, TB was detected in 66 (4.5%). The Table shows the characteristics of HIV-positive patients with TB coinfection. More than two-thirds of the patients had a CD4 T lymphocyte count of less than 200 cells/mm³ at the time of TB diagnosis and about a quarter had less than 50 cells/mm³. In the majority of patients, HIV infection was presented with TB infection (72.7%). In only 12.1% of cases, TB developed when the patient was receiving ART. Forty-one patients (62%) had pulmonary and 25 (38%) had extrapulmonary TB. At least one comorbid condition was present in 18 patients (27.3%): hepatitis B virus infection (n = 3), cytomegalovirus infection (n = 3), *Pneumocystis jirovecii* pneumonia (n = 2), Kaposi's sarcoma (n = 2), syphilis (n = 2), esophageal candidiasis (n = 1), cryptococcal meningitis (n = 1), cerebral toxoplasmosis (n = 1), HIV encephalopathy (n = 1), psychosis (n = 2), depression (n = 1), coronary artery disease (n = 1), and chronic obstructive pulmonary disease (n = 1). Twenty-one percent (n = 14) of the patients with TB coinfection died during follow-up. A higher proportion of patients who died during follow-up had their HIV infection presenting with TB compared to those who developed TB after being diagnosed with HIV (93% vs. 65%, P = 0.040).

The mean survival of patients with coinfection was 191 ± 17 months (95% CI: 157–225 months). In univariate analysis with the log-rank test, age group (>40 vs. ≤40) (P = 0.443), gender (P = 0.939), sexual identity (P = 0.706), presence of comorbidity (P = 0.998), HIV RNA at the time of TB diagnosis (<100,000 vs. ≥100,000 copies/mL) (P = 0.753), presence of extrapulmonary TB (P = 0.249), race (P = 0.051), and presentation of HIV with TB (P = 0.062) did not have a significant effect on survival. However, a

Table. Patient characteristics (n = 66).

Age ¹ , years (mean ± SD)	38.7 ± 9.2
Male gender	57 (86.4%)
Race	
Caucasian	64 (97.0%)
Black	2 (3.0%)
Sexual identity	
Heterosexual	38 (57.6%)
Homosexual	12 (18.2%)
Bisexual	6 (9.1%)
Not specified	10 (15.2%)
Comorbidity present	18 (27.3%)
CD4 cell count ¹ (cells/mm ³)	
≤50	16 (24.2%)
>50; ≤200	30 (45.5%)
>200	20 (30.3%)
HIV RNA ¹ (copies/mL)	
<100,000	45 (68.2%)
≥100,000	11 (16.7%)
Data not available	10 (15.2%)
Extrapulmonary tuberculosis	25 (37.9%)
Timing of HIV, TB, and ART	
HIV presented with TB	48 (72.7%)
TB developed without ART	10 (15.2%)
TB developed under ART	8 (12.1%)
Death during follow-up ²	14 (21.2%)

Unless otherwise stated, data are presented as n (%). ¹At the time of TB diagnosis, ²long-term follow-up data available for 60 patients.

SD, Standard deviation; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; RNA, ribonucleic acid; TB, tuberculosis; ART, antiretroviral therapy.

low CD4 T cell count at the time of TB diagnosis (<200 cells/mm³) was associated with poor survival (P = 0.012). In addition, patients who died during follow-up had significantly lower CD4 T cell counts at the time of TB diagnosis compared to those who survived (66 ± 44 vs. 194 ± 169, P = 0.005). Although none of the patients with CD4 T cell count of ≥200 cells/mm³ died during follow-up, survival statistics could not be computed since all cases

were censored. None of the parameters were identified as independent significant predictors of survival in the Cox proportional hazard model.

4. Discussion

Based on recent reports, there were about 8200 HIV-positive individuals in Turkey by mid-2014 (http://www.hatam.hacettepe.edu.tr/veriler_Haziran_2014.pdf). Thus, our cohort represents nearly 15% of all HIV-positive cases in Turkey. To date, data on HIV/TB coinfection in Turkey have been very limited and have mostly been dependent on official figures based on notifications and on a few publications (14–17).

In this study, the prevalence rate of TB among HIV-positive individuals was 4.5%. According to the 2015 Global Tuberculosis Report of the World Health Organization, 1.2 million out of the 9.6 million global cases of TB (12%) were HIV-positive (http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1). In the same document, 9344 of the total 13,378 reported cases of TB from Turkey were reported to have a “known status” of HIV serology, with 45 cases (0.48%) being HIV-positive. Similarly, the most recent national report on TB reported an HIV positivity rate of 0.31% among individuals with TB for whom HIV test results were available (17). However, these data are based on official notifications. In a metaanalysis by Gao et al., 0.9% of TB patients were reported to have HIV coinfection, while the prevalence of TB among HIV-positive subjects was 7.2% (18). In another metaanalysis by the same authors, the coinfection prevalence for these two conditions in countries other than China was found to vary between 2.9% and 72.3%, with an average prevalence rate of 23.5% (19). The specific figures for geographic locations including African, Asian, European, and Latin America countries were 31.25%, 17.21%, 20.11%, and 25.06%, respectively, while a prevalence of 14.8% was reported for the United States (19). However, in that metaanalysis, studies looking at HIV positivity in patients with TB and those looking at TB coinfection in HIV-positive patients were considered jointly, with generally close figures for these two subset of individuals (19). A study from Turkey investigated mycobacterial infections among 383 HIV-infected patients and found mycobacterial infection in 6%, most of them being *Mycobacterium tuberculosis* infections (19 out of 24) (14). In another Turkish study, TB was the most common opportunistic infection (16.5%) among 115 HIV-positive individuals (15). On the contrary, TB was the third most frequent opportunistic infection (4%), preceded by oral candidiasis (15%) and *P. jirovecii* pneumonia (8%), in a study from the Cappadocia region of Turkey (16).

An HIV positivity rate of 0.31%–0.48% among TB patients in Turkey is relatively low. In addition,

coexistence of TB in 4.5% of the HIV-positive patients in this study is relatively lower than those studies from the world mentioned above and several studies from Turkey (14,15). While this may partly be explained by the lower prevalence of HIV as well as the lower and decreasing prevalence and burden of TB in Turkey (2,17,20), the low rate of HIV testing among TB patients, the common use of tuberculin skin testing and the use of prophylaxis for latent TB among HIV-positive individuals, and the unique profile of the İstanbul cohort (i.e. higher socioeconomic level, better healthcare access, better healthcare after diagnosis including earlier initiation of ART) might all have contributed to this relatively low frequency among our patients.

Low CD4 T cell counts were associated with a high risk of TB in a number of studies, with calculated relative risks of 15.7 and 3.2 for cell counts below 200 and between 200 and 350, respectively (21–23). Low CD4 T cell count was also associated with mortality (21), with a CD4 count below 200 cells/ μ L resulting in increased mortality (24). Similarly, in our study, those who survived had significantly higher CD4 T cell counts than those who died.

The mortality rate of 21% among our patients with HIV/TB coinfection is higher than that (12%) reported by Chu et al. in Uganda (25). In the metaanalysis of Straetemans et al., the all-cause mortality with TB coinfection was 2-fold higher as compared to that without TB coinfection, although in a subgroup analysis involving higher use of highly active ART, non-TB factors rather than TB were found to play a role in mortality, and no increased risk of mortality was observed for those patients with TB coinfection compared to those without (26). In another study including individuals with easy access to ART, TB coinfection was associated with a 4.5-fold increased risk of all-cause mortality (27). Considering the high number of cases (2/3) with a low CD4 T cell count in our study and the significant association between CD4 T cell count and mortality, the high mortality rate is not surprising.

A high mortality rate in our TB/HIV coinfecting patients and a lower baseline CD4 count in patients who died suggest a delay in the diagnosis of coinfection. Another reason for high mortality may be that the majority of the patients were not on ART at the time of TB diagnosis (either HIV patients presented with TB infection or were not receiving ART at the time of TB diagnosis).

Although the results of our study are consistent with previous reports in terms of increased mortality (21,24), this did not emerge as an independent predictor of mortality, probably due to the small sample size.

The predominance of male patients in the subgroup of patients with TB coinfection as in the overall cohort is consistent with many reports from different areas of Sub-Saharan Africa, where TB is highly endemic (21–23),

and in the TB/HIV Rio (ThRIo) cohort from Brazil (21). In 2011, of the newly diagnosed cases of TB in Turkey, 58.6% and 41.4% were male and female, respectively (http://tuberkuloz.thsk.saglik.gov.tr/Dosya/Dokumanlar/raporlar/turkiyede_verem_savasi_2013_raporu.pdf). The gender distribution in our group with HIV/TB coinfection more closely resembles the HIV-positive patients rather than the overall population of TB patients in Turkey. It is not surprising to observe a higher predominance of male patients with HBV/TB coinfection in a larger sample set with male predominance.

In a 2012 metaanalysis, a strong link between HIV infection and extrapulmonary TB was found, while a CD4 T cell count of less than 100 cells/ μ L was suggested to represent a significant factor for the development of extrapulmonary TB in a subgroup analysis (24).

Although pulmonary TB is the most common form of disease presentation irrespective of the stage of HIV infection, extrapulmonary TB occurs at a higher frequency among severely immunocompromised individuals as compared to HIV-negative individuals or HIV-positive individuals with intact immunity (28). In the present study, 62% and 38% of the patients had pulmonary and extrapulmonary TB, consistent with the overall figures from Turkey, where 59.3%, 36.8%, and 3.9% of the reported cases of TB had pulmonary, extrapulmonary, and both types of involvement, respectively (http://tuberkuloz.thsk.saglik.gov.tr/Dosya/Dokumanlar/raporlar/turkiyede_verem_savasi_2013_raporu.pdf). In other words, our observation is at odds with the expected increase in the occurrence of extrapulmonary TB in HIV-positive patients.

On the other hand, despite the numerically higher mortality among those with extrapulmonary TB (63% vs. 34%), the difference was not significant, probably due to the small sample size.

One limitation of our study is its small sample size. Most parameters did not reach significance for predicting mortality, which may be due to type II error caused by small sample size. Second, since a retrospective evaluation was performed on patient records with data entry prior to the study, missing data including data on treatments could not be completed in some patients. Third, this cohort represents the largest metropole of Turkey and patient characteristics may be different from those from other locations of the country and thus findings may not be generalized.

In conclusion, TB has always been an important infectious disease both globally and in Turkey, whereas the origination of HIV dates back to more recent times and HIV is a relatively new disease entity for Turkey. Cooccurrence of these two conditions is associated with a number of problems such as the coinciding adverse consequences,

multidrug use, drug toxicity, and drug resistance. In this cohort, the patient characteristics of individuals with TB/HIV coinfection were reviewed in order to shed light on

the overall status of such patients. Early diagnosis and treatment of HIV infection and TB carry great significance both for society and for individuals.

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