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Lolakhon Tashpulatova Date

Role of Comorbid Conditions Such as Diabetes, HIV, and Alcohol Abuse in Outcomes of TB Therapy
A Review of Literature

By

Lolakhon Tashpulatova
MPH

Hubert Department of Global Health
Rollins School of Public Health
Emory University

_____

Kenneth G. Castro, MD, FIDSA
Committee Chair

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Lolakhon Tashpulatova

M.D.
Tashkent Medical Academy
2011

Thesis Committee Chair: Kenneth G. Castro, MD, FIDSA

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Abstract

Role of Comorbid Conditions Such as Diabetes, HIV, and Alcohol Abuse in Outcomes of TB Therapy
A Review of Literature

By Lolakhon Tashpulatova

Tuberculosis (TB) is a worldwide infectious disease, which mostly affects lungs. Tuberculosis treatment strategy has been improved and modified continuously during the last 30 years. However, TB problem is still endemic and burden in low-income and developing countries. The major challenges in TB treatment are social-economic conditions and chronic health disorders. Diabetes mellitus (DM) and HIV are leading comorbid conditions for TB. The existing data suggest that, compared with TB cases who do not have diabetes, TBDM patients have a higher risk of poor treatment outcomes and of development of PTB if latently infected with *Mycobacterium tuberculosis* (MTB). One possible explanation advanced by an investigator is that DM patients may have a slower response rate to TB treatment, or limited absorption of key medications in the TB treatment regimen. Age over 45 years old, male sex, and birthplace in country with high DM rate were described as factors influencing developing DM among TB patients.

HIV infection is the most 'common' comorbid condition for TB worldwide. HIV is a leading death cause among TB patients. There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. The existing data suggest that HIV patients on ART have better TB treatment outcomes than those who never received ART. HIV and TB co-infection should be treated individually starting with early antiviral therapy and soon adding anti-TB treatment.

Alcohol use disorder (AUD) was also reported as a very frequent social risk factor among TB patients. The existing published observations suggest that alcohol consumption does not significantly influence TB treatment outcomes, but may affect TB screening process and represents an important factor for developing TB disease from latent TB infection.

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Problem Statement

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis* and spread from person-to-person by the airborne droplets generated during coughs or sneezes. *M. tuberculosis* can cause both latent infection and disease. When causing disease, it can affect any part of the body but most commonly affects the lungs (CDC, 2016). Drug resistant TB occurs when the drugs used to treat TB are misused or mismanaged, or when a person with drug resistant TB transmits it to close contacts (CDC, 2016). Multidrug resistant TB (MDR-TB) is defined as TB caused by strains of *M. tuberculosis* resistant to at least isoniazid and rifampin (the two principal drugs in the treatment regimen against TB). MDR-TB leads to enormous problems by relatively poor treatment outcomes and increasing the cost of care for TB worldwide (Gomez-Gomez et al., 2015).

WHO Global Report of 2016 reports that globally, 10.4 million persons were estimated to have TB disease and 1.8 million died in 2015. Of those estimated with TB disease, nearly 1/3 are not notified to health authorities and thus treatment outcomes for these persons remain unknown. Concerted efforts have been implemented in most countries to enhance the detection and treatment of people suffering with TB disease.

Among those notified, the treatment success rate is 83%. In contrast, treatment success rate for persons with MDR-TB is limited to 52%. MDR-TB treatment is longer and less successful than treatment of drug-susceptible TB (Farley et al., 2011). The factors affecting TB and MDR-TB may vary from social-economic conditions of the region to individual's health and presence of co-morbid conditions.

Frame A Research Question

Do social and other co-morbid conditions, such as diabetes or HIV infection, affect the outcome of patients treated for TB?

Problem Statement. Diabetes Mellitus among TB Patient Treatment Outcomes

Over 347 million people in the world have been diagnosed with diabetes mellitus (DM) (Ahmed et al., 2017). "In lower income countries, individuals with diabetes are more likely than non-diabetics to have TB [univariable odds ratio (OR): 2.39; 95% confidence interval (CI): 1.84–3.10; multivariable OR: 1.81; 95% CI: 1.37–2.39]. Increases in TB prevalence and incidence over time were more likely to occur when diabetes prevalence also increased (OR: 4.7; 95% CI: 1.0–22.5; OR: 8.6; 95% CI: 1.9–40.4). Large populations, prevalent TB and projected increases in diabetes make countries like India, Peru and the Russia Federation areas of particular concern" (Goldhaber-Fiebert et al., 2011). DM is the main co-morbid condition among TB patients in Mexico (Munoz-Torrico et al., 2017). In Mexico, the number of DM among TB patients was 9.2% in 2012 (Munoz-Torrico et al., 2017). Since 2000, DM "increases the risk of active TB three times" (Magee et al., 2015). Since 2000, DM has posed a global challenge for TB treatment outcomes (Chang et al., 2011). In addition to multiple other

social risk factors for TB, DM is one of the biggest and partly missed (Gomez-Gomez et al., 2015).

A research group in Taiwan conducted a clinical trial during November 2004-October 2005, among 129 new patients with pulmonary TB who were treated and prospectively followed for more than 1 year. Of these, 60 (31.2%) had diabetes mellitus and TB (DMTB) and 132 (68.8%) had TB in the absence of DM. All participants with DM had a fasting plasma glucose concentration test over 126 ml/Dl at two different time points, and those with MDR-TB had demonstrated resistance to isoniazid and rifampicin. HIV patients were excluded from the study. The participant age, race and health chronic conditions were not significantly different. All participants were treated with the same therapeutic regimen: 2-month intensive phase with pyrazinamide, rifampicin, isoniazid and ethambutol, followed by an additional 4 months with isoniazid, ethambutol and rifampicin. (Table 1).

Table 1.

	DMTB (*n* = 60)	TB (*n* = 132)	*p*
Cured and completed treatment[a], *n* (%)	50/60 (83)	119/132 (90)	0.177
Duration of treatment[b] (mo)	9.9 ± 1.8 (*n* = 50)	7.5 ± 1.8 (*n* = 119)	< 0.01
Treatment failure (at 5–6 mo), *n* (%)	10/60 (17)	2/132 (2)	< 0.01
culture/smear positive Sputum	8/2	2/0	
conversion (mo)	2.5 ± 3.0	1.6 ± 1.4	< 0.01
MDR-TB, *n* (%)	3/60 (5.0)	1/132 (0.8)	0.056

Note: The table "One-year outcomes of patients with newly diagnosed and regularly treated pulmonary tuberculosis" retrieved from "Journal of the Formosan Medical Association = Taiwan yi zhi" (Chang et al., 2011).

This same study documented the emergence of MDR-TB in 3/60 (5%) of DMTB patients, compared with 1/132(0.8%) in the TB group with no DM. This difference was of borderline statistical significance (P=0.056). A possible reason of the observed results

among the DMTB group may be a poor immune response by depression of IFN – gamma. Also, rifampicin plasma levels were lower in DMTB patients (53%) than in the comparison group (Chang et al., 2011).

The National Health Insurance Research Database in Taiwan (NHIRD) investigated the role of DM in pulmonary TB recurrence and "with special emphasis on the impact of anti-TB treatment duration and DOTs" (Wang JY et al., 2015). 12,688 DM cases (out of 55,883) were pulmonary TB cases that received 6-month and 9-month duration anti-TB therapy. The timeline for all anti-TB non-first line drugs was less than 14 days. The study outcome of 2-year TB recurrence rate for DM group was 2.20% (95% CI, 1.94%-2.45%) (279 recurrence cases) and for the group without DM was 1.38% (95% CI, 0.89%-1.25%) (597 recurrence cases). The recurrence rate was higher between 2002-2006 and decreased since DOTs was implemented in Taiwan in 2006. 5,459 patients (43%) out of 12,688 were DM diagnosed before 2006 (DOTs implementation), and 7,229 patients (57%) were diagnosed after 2006. The difference between the recurrence rates before and after DOTs implementation was significant: 2-year recurrence rate has decreased from 3.54% (95% CI, 3.21%-3.86%) to 1.19% (95% CI, 1.00%-1.38%) with $p<0.001$. All DM patients were split into two groups: 9-month with 4,506 patients (35.5%) and 6-month with 8,182 (64.5%) patients. Multivariate COX regression analysis calculated Hazard Ratio (HR) = 0.76 (95% CI, 0.59-0.97) for 9-month anti-TB treatment group. "The benefit disappeared at HR=0.69 (95% CI, 0.43-1.11) under DOTs" (Wang JY et al., 2015). The lower HR provides evidence that 9-month anti-TB treatment in Taiwan had decreased the recurrence rate among DM patients, and suggests that longer treatment may be necessary for patients with TB and DM (Wang JY et al., 2015).

A Sudanese case-control study in Hospital at Ribat University aimed at finding an association between Type 2 DM (T2DM) and pulmonary TB (PTB). For study group, the researchers selected 60 T2DM patients, and for control group, 60 non-diabetic patients were selected. All participants provided information about duration of DM, age, race, sex, socioeconomic status, HbA1c percentage and treatment type. 72 (60%) were males and 48 (40%) females. 14 (19.4%) males and 6 (12.5%) females had PTB. The collected data was analyzed by SPSS (Statistical Package Software). MTB genotype was detected by polymerase chain reaction (PCR), which used for DNA extraction from sputum. The results of sputum smears of Ziehl–Neelsen (ZN) staining were positive in 15 (12.5%) in comparison with 20 (16.7%) positive by PCR and 100 (83.3%) negative by PCR, with statistically significant difference P=0.000. (Table 2). The frequency of HbA1c among 58 patients with controlled DM was 24 (41.4%) and among patients with uncontrolled DM was 34 (58.6%). "12 out of 60 patients with diabetes had PTB with uncontrolled DM, with statistically significant difference (p=0.000)" (Ahmed et al., 2017). The data of the study showed that PTB in the diabetic group was higher than in non-diabetic: PCR positive was 12 in (20%) in diabetic group and 8 (13.3%) in non-diabetic group, P=0.232. Even though the statistical analysis was not significantly different (P=0.232), the results are suggestive of an association between DM and PTB. The research group recommended to confirm TB negative results of ZN smear by PCR test (Ahmed et al., 2017).

Nigeria is considered the third "among 30 countries with estimated highest burden TB" globally (Ekeke et al., 2017). A Nigerian study researched epidemiology of DM among TB patients. "The main objective of the study was to determine screening

efficacy, prevalence of DM and determinants of DM among TB patients (Ekeke et al., 2017). Newly TB diagnosed 2,094 patients participated in the study. One hundred ninety six out of 2,094 patients were found to have DM (9.4%, 95% CI 8.2-10.7). Newly diagnosed with DM were 115 (5.5%), while previously diagnosed were 81 (3.9%). "The prevalence of DM was 13.3% (95% CI 11.4–15.5) among rural residents compared to 5.7% (95% CI 4.5–7.2) among urban residents ($P < 0.001$). The prevalence of DM among TB patients who received care at a public facility was 6.6% (95% CI 5.4–8.1) compared to 14.0% (95% CI 11.8–16.6) among patients who received care at a private facility ($P < 0.001$)" (Ekeke et al., 2017). Participants over 40 years old, "rural residence and private health facility care" were factors increasing risk of DM among TB patients. (Table 3). Conversely, TB patients with vigorous activity occupations have lower chances to develop DM. "Screening among newly TB patients found undiagnosed DM in more than half" (Ekeke et al., 2017).

If current high increases of global TB cases as well as DM cases continue, 642 million people are anticipated to be infected by TB and DM by 2040 (Ekeke et al., 2017). Around 15% of all TB cases have comorbidity with diabetes (Bates et al., 2015). Girardi et al. suggests that migration could be a possibly associated with diabetes, tuberculosis, and poor treatment outcomes. Several studies in developed TB-DM high burden countries published the prevalence of cases among native and foreign-born patients (Girardi et al., 2017).

In a retrospective study in Rome, Italy, among 971 TB patients, 723 were foreign-born, and 63 (6.5%) of them had DM. "DM prevalence was 12.7% (8/63) among those born in countries with DM prevalence $\geqslant$ 8%, 4.7% (31/660) among patients from

countries with DM prevalence <8% and 9.7% among Italian patients (24/248)" (Caraffa et al., 2016). Patients born in high DM incidence countries, older age and male gender are more likely to develop DM among TB patients (Caraffa et al., 2016). In retrospective population-based analysis, among TB patients in California, during 2010-2012, the relative risk of tuberculosis among DM patients was calculated. The TB rate among foreign-born patients was 141.5/100,000 and among U.S. born was 12.0/100,000. The TB rate in foreign-born persons with diabetes was 12 times higher than in U.S. born without diabetes (Demlow et al., 2015). The authors conclude that an optimum treatment plan for foreign-born patients with diabetes would significantly decrease number of TB cases in California (Demlow et al., 2015).

In other publications, anti-TB treatment outcomes among DM patients had a successful rate in high-income countries (Uchimura et al., 2013). Japanese researchers studied pulmonary TB treatment outcomes among DM and HIV patients. A total of 33,699 smear positive PTB cases (out of 96,689 TB cases) reported to the Japanese tuberculosis surveillance data between 2007-2010 were analyzed. TB treatment outcome success in DM cases was 51.9% among male group (4,396) and 50.3% among females (1,226), compared with 54.0% (23,037) in all male patients and 59.3% (10,662) in all female patients studied (Uchimura et al., 2013).

In three DOTS centers in South India, a study was conducted among 60.4% (191) of participants. All participants were screened for fasting blood glucose test (FBG) before starting anti-TB treatment. The patients with FBG of beyond 110 mg/dL were screened for 2-hour plasma glucose test (2hPG) after 75 g oral glucose test (OGTT). DM was confirmed as diagnose for participants if 2hPG was ≥200 mg/dL. PTB and EPTB (extra-

pulmonary) group 39.6% (125). A total of 9.49% DM cases were diagnosed prior to TB among all participants (30/316) and the remaining 6.33% (20/316) at the time of screening. PTB patients had higher DM rate (19.4%) than EPTB patients (9.6%). DM patients reported more symptoms of dyspnea, chest pain and hemoptysis. The treatment plan started with 4 drugs in intensive phase (IP) and followed by 2 drugs in continuation phase (CP) for 4 additional months (2HRZE/4HR) (Siddiqui et al., 2016). "Microscopic examination of sputum samples at 2 months reveals higher sputum positivity in DM (27.8%) as compared to no-DM (24.7%) patients" (Siddiqui et al., 2016). One hundred seventy-seven out of 191 PTB patients completed DOTS treatment, while 125 out of 125 EPTB patients fully completed the treatment. The independent risk of unfair outcome among PTB patients associated with DM in this study was 1.176 (95% CI: 0.310–4.457). This study found that glycemic control during the IP of treatment should be strictly managed for successful treatment outcomes. TB patients should be actively screened for DM to prevent disease's complications (Siddiqui et al., 2016).

Table 2

Factor	PCR positive	PCR negative	Percentage	*P*
ZN smear positive	15	0	100	*P*=0.000
ZN smear negative	5	100	25	
Total	20	100	-	

PCR: Polymerase chain reaction, ZN: Ziehl-Neelsen

Comparison between polymerase chain reaction and Ziehl-Neelsen stain between polymerase chain reaction and Ziehl-Neelsen stain (Ahmed et al., 2017).

Table 3.
Prevalence of diabetes among TB patients in Southern Nigeria 2015 (n = 209)

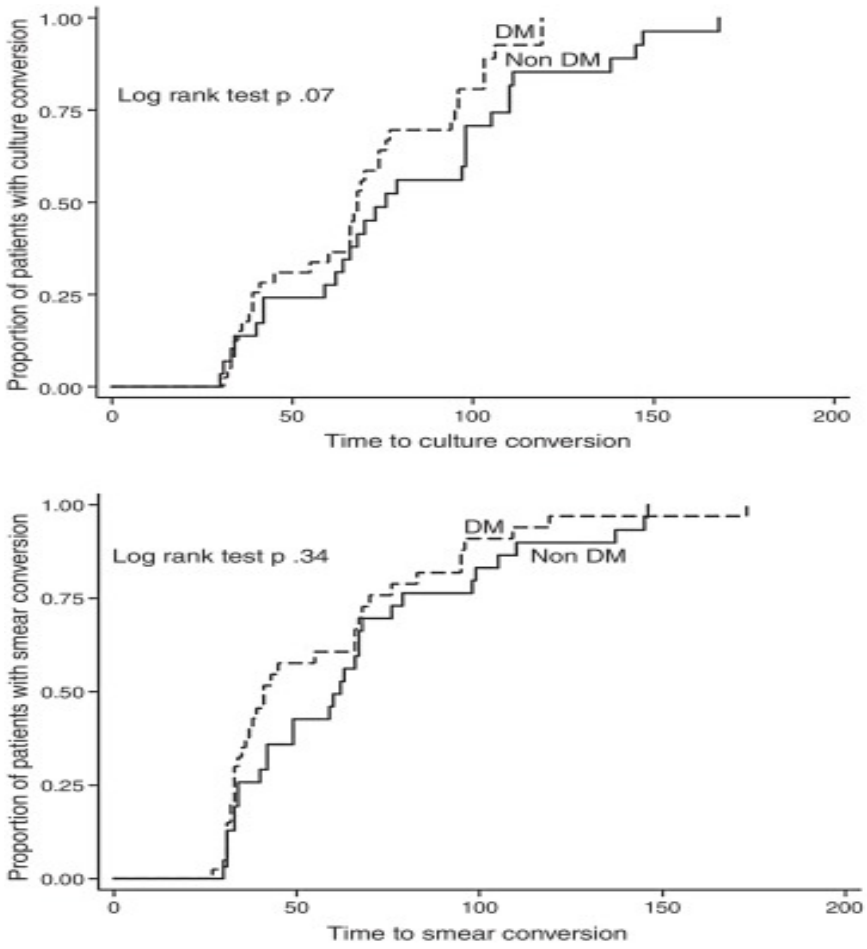
	Total TB patients evaluated for DM	**TB patients with DM**	**Prevalence of DM**	**P -value**
	N	**n**	**% (95%CI)**	
Total	2094	196	9.4 (8.2–10.7)	
Age (years)				<0.001
≤25	358	8	2.2 (1.1–4.4)	
26–35	585	44	7.5 (5.7–9.9)	
36–45	458	41	9.0 (6.7–11.9)	
46–55	305	46	15.1 (11.5–19.5)	
56–65	231	39	16.9 (12.6–22.3)	
>65	157	18	11.5 (7.4–17.4)	
Sex				0.93
Female	913	86	9.4 (7.7–11.5)	
Male	1181	110	9.3 (7.8–11.1)	
Residence				<0.001
Rural	1007	134	13.3 (11.4–15.5)	
Urban	1087	62	5.7 (4.5–7.2)	
Type of TB				0.26
EPTB	98	6	6.1 (2.8–12.7)	
PTB	1996	190	9.5 (8.3–10.9)	
Facility type				<0.001
Private	778	109	14.0 (11.8–16.6)	
Public	1316	87	6.6 (5.4–8.1)	
HIV status				0.33
Negative	1686	163	9.7 (8.3–11.2)	
Positive	408	33	8.1 (5.8–11.1)	
Current Smoker				0.87
No	1993	187	9.4 (8.2–10.7)	
Yes	101	9	8.9 (4.8–16.1)	
Physical activity				0.30
Sedentary	1042	106	10.2 (8.5–12.2)	
Moderate	689	55	8.0 (6.2–10.3)	
Vigorous	363	35	9.6 (7.0–13.1)	

TB: tuberculosis, HIV: human immunodeficiency virus, EPTB: extrapulmonary TB, PTB: pulmonary TB.
(Ekeke et al., 2017).

One of the main targets in Georgian cohort study was to determine the association between DM and anti-TB treatment (Magee et al., 2015). All participants had been newly diagnosed for TB and tested for DM and pre-DM by HbA1c test. Patients with both DM–TB "were more likely" than those without DM to develop hemoptysis, MDR-TB and positive baseline culture (Magee et al., 2015). The study first found that participants with DM, without previous TB diagnosed in their medical history, were more likely to develop MDR-TB with aOR=2.27. However, DM and TB patients didn't show a significantly higher risk if compared to TB patients exclusively: 28.1% vs. 23.6%. The researchers suggested the need to improve DM screening among TB patients (Magee et al., 2015).

The study in Mexico compared bacteriological conversion and treatment outcomes among 90 patients with MDR-TB with DM and MDR-TB without DM between 2010- 2015. All patients with DM and without DM in their medical history performed fasting glucose test, blood biometry, blood chemistry, HbA1c, and thyroid stimulating hormone. The treatment results among 77 patients (out of 90), included in the analysis (43 with DM and 34 without DM), suggested that TB patients without DM had better outcomes, but this difference was not statistically significant. Successful treatment exposure (AUC0–6 h) to rifampicin was 53% lower in Indonesian patients with TB and DM, compared with patients with TB only outcomes were not significantly different between DM MDR-TB 18/32 (56.3%) group and without DB MDR-TB group 19/24 (79.2%) (Munoz-Torrico et al., 2017). (Figure 1).

Figure 1.



Time to sputum smear and culture conversion (in days) among 40 DM and 31 non-DM MDR-TB cases in Mexico. TB: tuberculosis; DM: diabetes mellitus; MDR-TB: multidrug-resistant tuberculosis (Munoz-Torrico et al., 2017).

Conclusion

During last decades, the number of persons diagnosed with DM in various populations has increased (Wang Q. et al., 2017). The external reason for the increase may be inactive lifestyle, dietary (e.g., reliance of processed foods), and poor environmental conditions (Bates et al., 2015). The existing data suggest that, compared with TB cases who do not have diabetes, TBDM patients have a higher risk of poor

treatment outcomes and of development of PTB if latently infected with MTB. One possible explanation advanced by an investigator is that DM patients may have a slower response rate to TB treatment, or limited absorption of key medications in the TB treatment regimen. "Exposure (AUC0–6 h) to rifampicin was 53% lower in Indonesian patients with TB and DM, compared with patients with TB only." The higher bodyweight of diabetic patients may require a higher dose a rifampicin and individual treatment plan for better TB treatment outcomes (Nijland et al., 2006). Age over 45 years old, male sex, and birthplace in country with high DM rate were described as factors influencing developing DM among TB patients (Caraffa et al., 2016). "However, diabetes as a diagnosis by itself is not consistently found to adversely affect TB treatment outcomes" (Munoz-Torrico et al., 2017). All TB patients should be tested for blood glucose level. The treatment plan for DM patients should be framed with taking into account the level of glucose in blood. Another reason for routine DM screening of persons with TB is to prevent treatment complications. Glycemic control should be maintained during and after anti-TB treatment period (Siddiqui et al., 2016).

Problem Statement. HIV Infections in TB Patients and Treatment Outcomes

HIV infection is the most 'common' comorbid condition for TB worldwide. South Africa is one of the highest burden TB countries, where more than 30% of all TB infected population has HIV co-infection (Ali, Mavundla, Fantu, & Awoke, 2016). HIV status has been described as a leading condition for unfavorable TB treatment outcomes (Ali et al., 2016). "In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among

women and 1.0 million (10%) among children. People living with HIV accounted for 1.2 million (11%) of all new TB cases. There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015." (WHO, 2017). People living with HIV are 29 times more likely to develop active TB disease than those who are not HIV infected (Liu et al., 2015). (Figure 4).

Does HIV status and associated immunosuppression significantly affect TB treatment outcomes? What other external factors may influence the health status of persons with HIV/TB co-infection?

An open-label randomized controlled trial was conducted in Durban, South Africa to determine optimal timing for antiretroviral therapy (ART) among TB patients (Abdool Karim et al., 2010). From June 2005 to July 2008, starting ART at three points in time (SAPiT) while patients were also treated for TB was assessed in the largest ambulatory center in Durban. A total of 642 TB-HIV patients participated in the study. All enrolled population initiated on the standard TB treatment regimen and had a CD4+ count <500 cells/mm3. Participants were randomized to one of three treatment arms in 1:1:1 ratio: "Arm 1 - ART to be initiated within 4 weeks of starting tuberculosis treatment (early integrated treatment arm), Arm 2 - ART to be initiated within 4 weeks of completing the intensive phase of tuberculosis treatment (late integrated treatment arm) and Arm 3 - ART to be initiated within 4 weeks after completing tuberculosis treatment (sequential treatment arm). Participants received adherence counselling, cotrimoxazole prophylaxis, and the same once daily ART regimen; didanosine (250mg if weight <60kg and 400mg if

weight >60kg), lamivudine (300mg) and efavirenz (600mg)" (Abdool Karim et al., 2010). In the integrated treatment arm, 25 deaths occurred with a mortality rate of 5.4 per 100 person-years, compared to 27 deaths in the sequential treatment arm with a mortality rate of 12.1 per 100 person-years (HR=0.44, p=0.003) (Abdool Karim et al., 2010).

"ART adherence by pill count was 97.2% and 97.6% in the integrated and sequential treatment arms, respectively. Tuberculosis treatment outcomes were similar in both study arms for first episode and retreatment cases. The proportion with suppressed HIV RNA level was higher in the integrated compared to sequential treatment arm at 12-month post-enrolment (90.0% vs 77.8%; respectively p=0.006). However, proportion with suppressed HIV RNA 6 months after ART initiation was similar in both arms" (Abdool Karim et al., 2010). ART delay leads to mortality rise: from 5.4 per 100 person-years to 12.1 per 100 person-years in this study (Abdool Karim et al., 2010).

Figure 2.

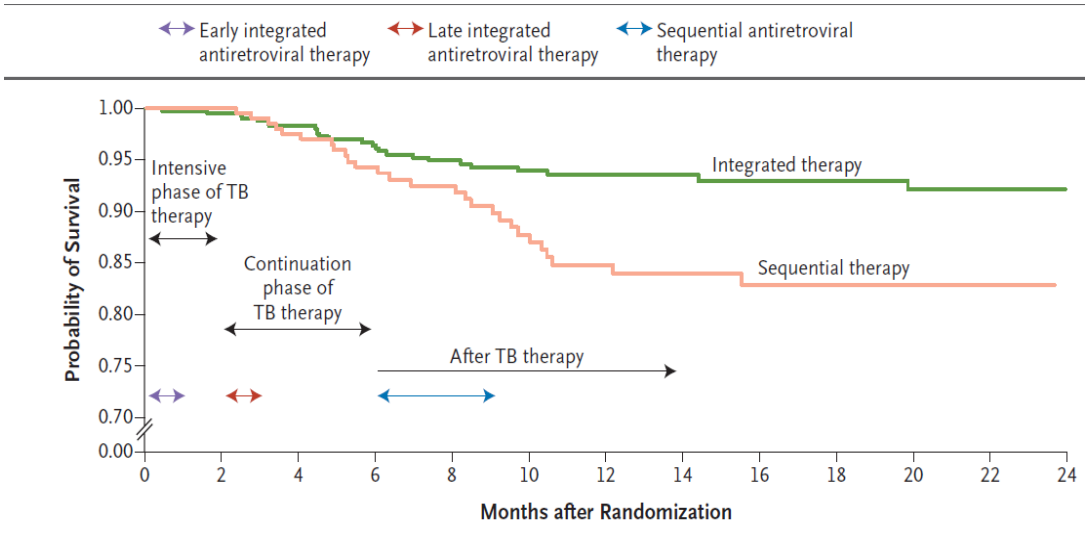


Figure 2. Kaplan–Meier Survival Curves.

(Abdool Karim et al., 2010)

During 2004-2012, a prospective cohort study in Dar es Salaam, Tanzania, demonstrated that ART significantly reduced the incidence of active TB among HIV patients. The final sample size was 67,686 patients. Among them 53,056 (78%) were found eligible for and initiated ART during follow-up, the remaining 14,630 (22%) patients remained on care and monitoring services (ART naive). Every participant assessed to individual ART plan, stratified by CD4+ cell count <350 or <200 cells/uL (Liu et al., 2015) "Standard first-line ART regimens included 2 nucleoside reverse-transcriptase inhibitors (NRTI) [lamivudine (3TC) or emtricitabine (FTC), plus stavudine (d4T) or zidovudine (AZT) or Tenofovir (TDF)], and 1 nonnucleoside reverse-transcriptase inhibitor (NNRTI) [efavirenz (EFV) or nevirapine (NVP)]" (Liu et al., 2015). Incident TB cases were confirmed as newly diagnosed by sputum smear or chest X-ray (Liu et al., 2015).

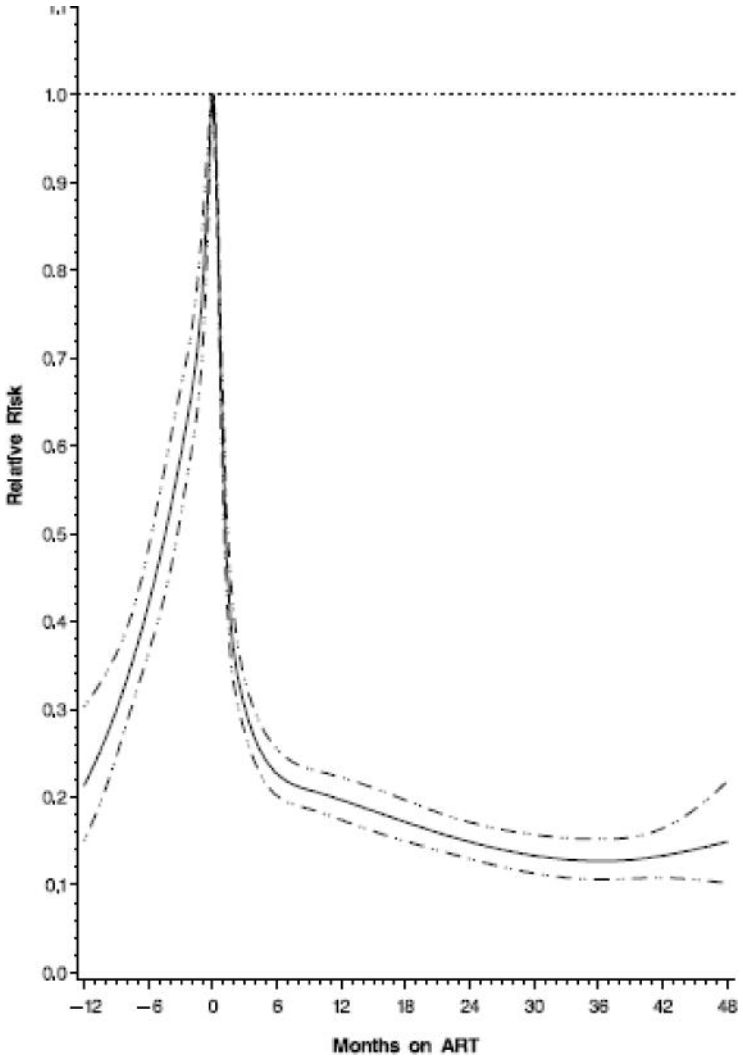
The authors stated: "53,056 of 67,686 patients initiated ART, and the median time between enrollment and ART initiation was 31 (Inter Quartile Range (IQR), 16–158) days. During a median follow-up of 24 (IQR, 8–49) months, 7,602 of 67,686 patients developed incident TB. The incidence rate was 7.9 (95% CI, 7.6–8.2)/100 person-years for patients on care and monitoring (ART naïve), and 4.4 (95%CI, 4.2–4.4)/100 person-years for patients on ART" (Liu et al., 2015).

During the analyses, male patients had a 53% significantly higher risk of developing TB than females [Hazard Ratio (HR), 1.53; 95%CI, 1.45–1.60]. Participants nutritional status was also associated with TB risk. Patients with BMI<17.0 had a 2-fold increased risk of TB than patients with BMI > 18. The patients, who were overweight or obese had 36% and 45% reduced risk to develop TB (Liu et al., 2015).

"Lower CD4+ cell counts and advanced WHO HIV disease stage were significantly associated with a higher risk of developing TB. Compared with patients with CD4+ ≥350 cells/uL, those with CD4+ <200 cells/uL had a significantly 5% to 20% higher risk of TB (Liu et al., 2015).

ART treatment regimens affect TB incident risk (Figure 3). Compared to patients receiving d4T-contaning regimens, those receiving AZT- or TDF-containing regimens had 35% (HR:0.65, 95%CI: 0.60–0.70) and 10% (HR:0.90,95%CI:0.77–1.05) reduced risks of incident TB, respectively; compared to patients receiving EFV-containing regimens, those receiving NVP-containing regimens had a 64% (HR:0.36,95%CI:0.34–0.39) reduced risk of incident TB" (Liu et al., 2015). The risk of TB was observed during the raining season: May, June and November. A possible explanation may be more indoor time, leading to vitamin D deficiency. Previously, another study reported vitamin D deficiency harmful effects on the immune response to mycobacterial infection (Martineau, 2012).

Figure 3.



Hazard Ratio of incident tuberculosis by duration on ART (with zero as reference) among HIV-infected individuals in Dar es Salaam, Tanzania. Note: The horizontal dot line shows where the hazard ratio equal to 1; the solid line shows hazard ratio; the dot-dash lines show the 95% confidence intervals for hazard ratios; negative times represent time before ART initiation, only patients who have started ART during the follow-up were included to create the graph (Liu et al., 2015).

A cross-sectional analysis conducted in Ethiopia among 575 TB patients with 29.4% HIV positive status. The study revealed a significantly higher risk of unfavorable

treatment outcomes among HIV/TB when compared to non-HIV-infected TB patients (11.8% vs. 6.4%, P =0.03) (Ali et al., 2016). (Table 4).

Table 4.
"Comparison of TB treatment success based on HIV status (*N* = 529)"

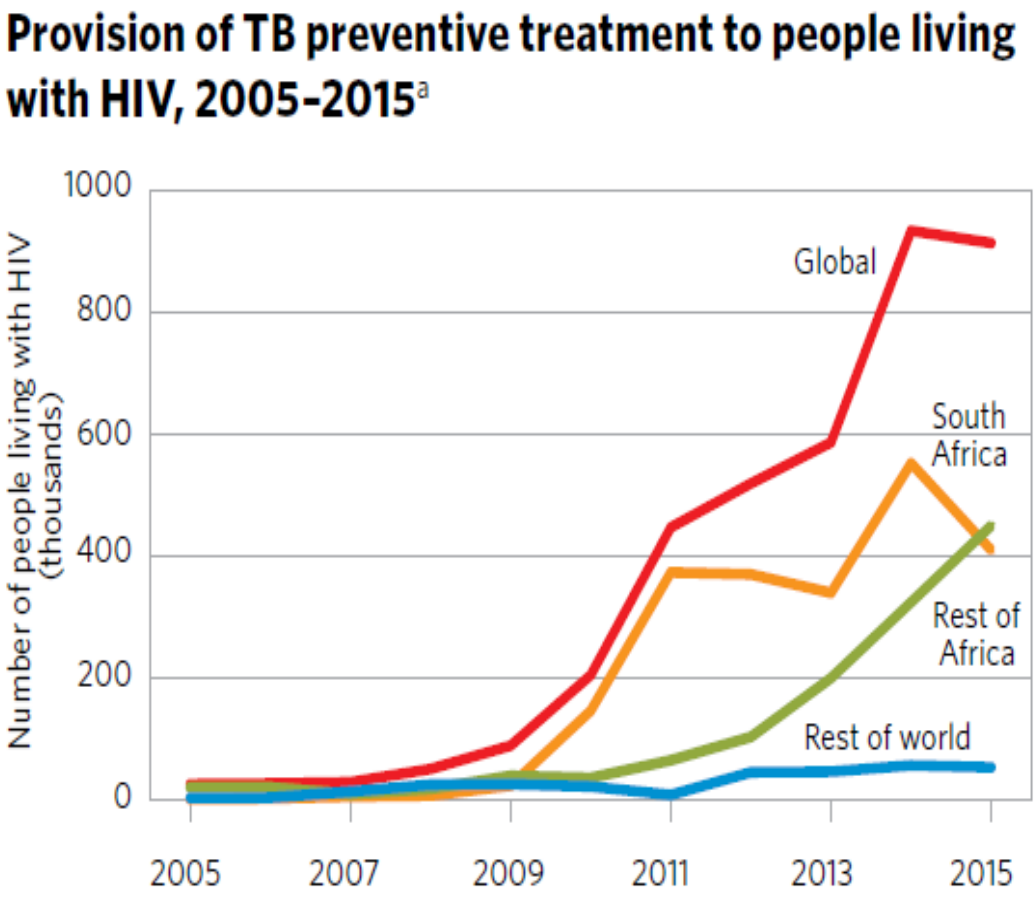
TB treatment outcome	**HIV status**		**Total**
	HIV negative	**HIV positive**	
Unfavourable outcome	23 (6.4 %)	20 (11.8 %)	43 (8.1 %)
Favourable outcome (treatment success)	337 (93.6 %)	149 (88.2 %)	486 (91.9 %)
Total	360 (100.0 %)	169 (100.0 %)	529 (100.0 %)

Note: Table retrieved from " Outcomes of TB treatment in HIV co-infected TB patients in Ethiopia: a cross-sectional analytic study", BMC Infection Diseases (Ali et al., 2016).

In retrospective study in rural KwaZulu-Natal, in South Africa, TB and HIV treatment outcomes were evaluated at district hospital level or "were down-referred" to decentralized primary health clinics. HIV/TB patients, who received treatment at district hospital level, had 82.2% treatment success rate (Jacobson, Moll, Friedland, & Shenoi, 2015). A low CD4+ T-lymphocyte count (< 200 cells/mm3) was associated with one case fatality among the participants of this study. More than 70 % of all patients had not previously taken the antiretroviral therapy, which the authors proposed as a possible reason for improved TB treatment outcomes. An appropriate antiviral therapy may prevent TB or lead to the improvement of TB treatment results (Jacobson et al., 2015). Similar results were described from a study in India, which supports the evidence of antiviral therapy (ART) to positively influence favorable treatment outcomes among TB patients (Shastri, Naik, Shet, Rewari, & De Costa, 2013). More than 23% of all TB cases in the world are reported from India. National TB and HIV programs conducted the

current research study in 61-million population province Karnataka. 6,480 reports from the National HIV Control programs were analyzed during the study. The participants in this cohort were co-infected patients on ART and co-infected patients who were not on ART. The results demonstrated that TB treatment success was much higher among patients on ART (80%) than patients who never take ART (54%) before the study (Shastri et al., 2013).

Figure 4.



(WHO, 2017)

Timing of HIV treatment among HIV-TB patients would be another factor influencing the TB treatment outcomes (Gadoev et al., 2015). Interesting results were described in a recent study in Myanmar. A total of 1708 patients were split in two treatment groups: the majority of participants (92%) started anti-TB treatment therapy (ATT) and the rest of participants (8%) started on ART. MDR-TB patients were excluded from the study. The median time to start ART, for the patients began treatment with ATT, was 8.6 weeks. The second group of patients, who began treatment with ATT, had the median time of 21.6 weeks for ART. The group started with ATT first (1565 patients) had unfavorable outcome of 20% with anemia as the main predictor. Poor immune recovery and delayed sputum conversion were caused by anemia. The group which was started on ART had unsuccessful treatment outcome of 12%. In this group, the treatment outcome was associated with CD4 count. Patients with CD4>100/mm3 had lower risk of an unfavorable treatment outcome than patients with CD4<100/mm3. A lower mortality rate was demonstrated among patients who started ART first, with initiation of ATT in the next 8 weeks. These results may be explained by CD4 counts, which rise after ART initiation (Thi et al., 2016). (Table 5).

Table 5.
"ART initiation and ATT outcomes of all patients with TB-HIV initiated on ART in the IHC programme, Mandalay, Myanmar, 2011–2014."

Variable	All patients with TB-HIV *n* (%)	Started ATT first *n* (%)	Started ART first *n* (%)
Total	1708 (100)	1565 (100)	143 (100)
ART initiation			
ATT first			
ART within 8 weeks	735 (43)	735 (47)	—
ART after 8 weeks	830 (49)	830 (53)	—
ART first			
ATT within 3 months	56 (3)	—	56 (39)
ATT after 3 months	87 (5)	—	87 (61)
TB outcome			
Cured	32 (2)	27 (2)	5 (4)
Completed	1555 (91)	1434 (92)	121 (85)
Treatment failure	6 (0)	5 (0)	1 (1)
Death	107 (6)	91 (6)	16 (11)
Loss to follow-up	8 (1)	8 (1)	—
TB final outcome*			
Successful	1587 (93)	1461 (93)	126 (88)
Unsuccessful	121 (7)	104 (7)	17 (12)

* Successful outcome includes cured and completed; unsuccessful outcome includes treatment failure, death or loss to follow-up.
ART = antiretroviral therapy; ATT = anti-tuberculosis treatment; TB = tuberculosis; HIV = human immunodeficiency virus; IHC = Integrated HIV Care.

Note: The table retrieved from "Timing of antiretroviral therapy and TB treatment outcomes in patients with TB-HIV in Myanmar" Public Health Action (Thi et al., 2016).

Conclusion

The existing data suggest that HIV patients on ART have better TB treatment outcomes than those who never received ART. HIV and TB co-infection should be treated individually starting with early antiviral therapy and soon adding anti-TB treatment. Updated WHO guidelines for optimal HIV/TB therapy should be followed by health facilities (WHO, 2016). Several other studies provide data on longer-term effects of ART, among TB and PTB patients (Low et al., 2016). "It can be explained by the occurrence of tuberculosis across a wide range of CD4 counts, with less of a protective effect of early immune restoration, and because of the significant rate of unmasking immune reconstitution inflammatory syndrome (IRIS) in the first months after ART

initiation" (Low et al., 2016). "Potential explanations for an association between vitamin D deficiency and active TB include both causality (i.e. vitamin D deficiency impairs host immune response to MTB and causes susceptibility) and reverse causality (i.e. active TB causes vitamin D deficiency, due to anorexia, decreased exposure to sunlight in debilitated patients, or MTB-induced dysregulation of vitamin D metabolism)" (Martineau, 2012). An appropriate duration and timing of ART therapy among HIV/TB patients influence anti-TB treatment outcomes (Shastri, 2013). Poor immune recovery and delayed sputum conversion associated with anemia is another factor potentially influencing anti-TB treatment (Thi, 2016).

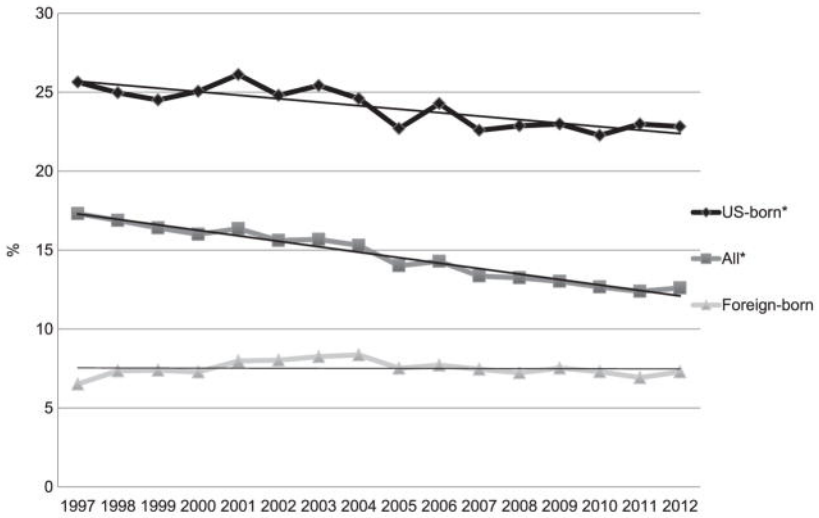
Problem Statement. Alcohol Consumption as a Factor Affecting TB Treatment Outcomes

One of the targets of WHO Sustainable Development Goals is "Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol" (WHO, 2016). Alcoholism is one of the most important social risk factors among TB patients. A systematic literature review by Lonnroth et al. suggests the prevalence range of alcohol abuse 10% -50% among diagnosed TB patients. The prevalence was calculated by studies results in Russia, Canada, Switzerland, Australia and the US. The cut-off level for alcoholism in the current literature review study was 40g (50 ml) alcohol per day (Lonnroth, Williams, Stadlin, Jaramillo, & Dye, 2008).

Alcohol usage among TB patients is noticeably high in the US (Oeltmann, Kammerer et al., 2009). Alcohol consumption affects immune system, which may influence TB disease progression from latent TB infection (Zhang et al., 2002). A U.S. research team analyzed alcohol consumption and TB treatment outcomes using

multivariate logistic regression (Volkmann et al., 2015). The researchers used data from the National Tuberculosis Surveillance System (NTSS) in the period of 1997-2012 (Volkmann et al., 2015). Authors describe 31,207 out of 207,307 TB cases as excess alcohol consumers: "15.1%; yearly range 12.4–17.3) (data not shown); 22,733 (72.8%) were born in the United States (US-born) and 8,474 (28.2%) outside the United States (foreign-born). For 1997–2012, the prevalence of excess alcohol use differed significantly between US-born and foreign-born patients (24.3%, range 22.8–25.6 vs. 7.5%, range 6.5–8.4; P < 0.001)" (Volkmann et al., 2015). (Figure 5).

Figure 5.



A proportion of excess alcohol use in confirmed TB cases aged ≥15 years reported to the National TB Surveillance System, United States, 1997–2012 (n = 207 307).* Trend P < 0.0001 (Volkmann et al., 2015).

Alcohol users were more among males at the age group of 45-64. "Excess alcohol use was associated with a positive sputum smear result (aOR 1.23, 95%CI 1.18–1.28) and death during treatment (vs. completion of treatment) (aOR 1.16, 95%CI 1.10–1.22). The rate of culture conversion was higher among patients without excess alcohol use (adjusted hazard ratio 1.20, 95%CI 1.18–1.23)" Volkmann et al., 2015). "When the

adjusted analysis was stratified by therapy, the rate of conversion among those without excess alcohol use was significantly higher for those treated with DOT (aHR 1.22, 95%CI 1.19–1.25), but not for those who underwent SAT (self-administrated therapy) (aHR 1.11, 95%CI 0.99–1.25)" (Volkmann et al., 2015). The study suggests that alcohol usage among TB patients "has been linked to TB transmission" and poor treatment outcomes (Volkmann et al., 2015).

The cross-sectional study in Chennai, South India, suggests that alcoholism leads to TB by two plausible mechanisms: alcohol influenced health conditions (liver dysfunction, immune stress disorders, psychiatric and neurologic diseases) and specific social environment, where usually alcoholism place individuals in congregate settings. Chronic alcohol consumption is a potential risk to anti-tuberculosis-drug-induced hepatotoxicity (anti-TB-DIH). Direct toxicity of alcohol has been described as "primary compound affecting hepatocytes, biliary epithelial cells, and/or liver vasculature" (Wondwossen et al., 2016).

Anti-TB-DIH increases the level of aspartate transaminase (AST) or alanine transaminase (ALT) to five times higher than normal (Wondwossen et al., 2016). A South Ethiopian prospective study was "aimed to determine the incidence of anti-TB-DIH and identify the possible risk factors of anti-TB-DIH among TB patients" (Wondwossen et al., 2016). A total of 124 newly diagnosed TB-patients were observed for 2 months. Every week during 2-month period, blood samples and physical exams were reported from the participants. None of the patients were taking hepatotoxic drugs. "13 of 124 participants were taking different antibiotics during the study period, of which nine (69%) were males and four (31%) were females. Among 124 participants, eight (6.5%)

were reported to be alcoholics, of whom six (75%) were females and two (25%) were males. Smear-positive pulmonary TB accounted for 99 (79.8%) of all cases, and extrapulmonary TB accounted for about 25 (20.2%) cases" (Wondwossen et al., 2016).

During the study period from May to October 2014, 10 out of 124 patients developed anti-TB drug hepatotoxicity. ALT and AST levels, total bilirubin were five times higher than Upper Level Norm (ULN) with or without symptoms. "Patients with anti-TB-DIH had their ALT, AST, and bilirubin total values (mean ± SD) were 22.70 ± 9.71 U/L, 21.60 ± 6.67 U/L, and 0.34 ± 0.21 mg/dL, respectively, at baseline measurement, and their peak values during treatment were 304.80 ± 93.67 U/L, 261.80 ± 66.07 U/L, and 1.86 ± 0.91 mg/dL, respectively" (Wondwossen et al., 2016). Alcohol consumption was found to be significantly associated with the incidence of anti-TB-DIH (crude odds ratio = 9.343, 95% confidence interval 1.8–47.3) (Wondwossen et al., 2016). (Table 6).

Table 6.
Association of predictors with incidence of antituberculosis-drug-induced hepatotoxicity in patients taking antituberculosis drugs in Dawro Zone Tercha Hospital and five health centers, Southern Ethiopia, from May 2014 to October 2014.

Variables		COR	95% CI	*p*
Gender	Male	1.3	.36–5.04	.65
	Female	.74	.12–2.34	.56
Age (y)	10–19	.11	.4–3.76	.838
	20–49	.818	.15–4.27	.81
	>50	.474	.039–5.7	.556
BMI (kg/m^2)	<18.5	161,547,162	0	.999
	18.5–25	11,643,038	0	.99
	>25	1,454,367	0	.999
Extent of disease	Pulmonary	1.792	.42–7.4	.424
	Extrapulmonary	.76	.11–1.54	.89
Alcohol status	Alcoholic	9.3	1.8–47.3	.007
	Nonalcoholic	.064	.13–7.5	.92

Note: BMI = body mass index; CI = confidence interval; COR = crude odds ratio; y = year.

The participants of Chennai study were patients in Tuberculosis Units (TB units) of Chennai Corporation. The patients from four zones (TB units) were randomly selected and screened for AUDIT scale alcohol consumption test. Among 490 participants, 66% were men, women did not report usage of alcohol. Of all male participants, 191 (29%) were diagnosed as alcohol consumers. These data demonstrate the importance of alcohol screening among TB patients. Alcohol diagnostic tests in combination with alcoholism treatment among TB patients would lead to favorable TB treatment outcomes (Suhadev et al., 2011).

TB is one of the 10 diseases which lead to poor health outcomes, such as chronic disability and death. In this setting, alcoholism worsened TB outcomes (Przybylski et al., 2014). The study in Poland targeted social risk factors among TB patients. Alcoholism is the most common TB risk factor in Poland. "Particular attention was given to alcohol abuse among the TB patients, as alcohol abuse is a major social problem in Poland. The number of people abusing alcohol in Poland is estimated at about 2.8–3.5 million, including 0.6–0.9 million addicts. Poland has the highest rate of consumption of spirits in the world, and our consumption is rising" (Przybylski et al., 2014).

The retrospective study researched the epidemiological data in the Regional Centre of Pulmonology in Bydgoszcz among 2,025 patients during the period of 2001-2010. All patients in the study were received directly observed treatment (DOT), which included receiving pyrazinamide, isoniazid, rifampicin, ethambutol or streptomycin for the first two months. Participants with TB and adverse drug reaction (ADR) were stratified into the three groups: "1. toxicity-like serious or potentially life-threatening

reactions; 2. Patients with adverse effects (hepatitis, kidney failure, allergic reactions, etc.); 3. Unpleasant reaction that are not damaging for health (bloating, photosensitivity, etc.)" (Przybylski et al., 2014). The results were 89.5 % of participants had favorable outcomes. The other 10.5 % had unfavorable treatment outcomes. However, ADR was registered in 780 (38%) patients: hepatotoxicity 25.8%, hematological disturbance 19.0%, gastrointestinal disturbance 14.0 %, and psychiatric disorders 11.75%. The suggested reason for such a low risk (10.5%) in the results may be that all participants were hospitalized and strictly supervised by clinicians (Przybylski et al., 2014).

Alcohol use disorder (AUD) was also reported as the most frequent risk social factor among TB patients (Cavanaugh et al., 2012). First cohort study in Tomsk, Siberia, reported that women with TB had the same number of alcohol consumptions as men. Out of 374 TB participants, only 92 were women. 28 % of women were diagnosed with AUD. The results of the study show that the alcohol consumption is the leading social risk factor among TB women patients. While for the men, it was smoking with $p<0.0001$. Also, the average drink per day was not significantly different between women and men with $p=0.29$ (12.7 vs. 16.2) (Shin et al., 2010).

A research team from Scotland suggests that alcohol misusers most likely to develop pulmonary TB - 92% (out of 2419 participants) versus 61%, $P<0.001$. A treatment completion rate was 77% among alcohol misusers and 79% among other TB patients, with $P <0.34$ (de la Haye et al., 2012). The same study suggests that the alcohol consumption placed people into socio-economic deprivations, where they could be infected by TB (de la Haye et al., 2012).

Conclusion

According to the existing published observations, alcohol consumption does not significantly influence TB treatment outcomes, but may affect TB screening process (Suhadev et al., 2011). The US study shows that alcohol consumption may affect TB outcomes depending of treatment options, age group, and place of birth (Volkmann et al., 2015). The reviewed literature supports that alcohol consumption is an important factor developing TB disease from latent TB infection (de la Haye et al., 2012; Volkmann et al., 2015). US-born TB patients have a higher rate of alcohol consumption than non-US born (Volkmann et al., 2015). Age over 45 years old and males are most likely to be heavy alcohol consumers among TB population (Cavanaugh, 2012). The risk to develop anti-TB DIH is higher among alchohol consumers due to high alcohol toxicity affect to the lever and gastro-intestinal system (Wondwossen, 2016).

The existing literature review demonstrates that social and health risk factors do not appear to consistently and significantly affect TB treatment outcomes. On the other hand, poor health and "social-economic deprivation" environment may be associated with development of TB and MDR-TB (de la Haye et al., 2012).

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