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Effectiveness of Alcohol Treatment Interventions Integrated into Routine Tuberculosis Care in Tomsk, Russia

Sonya Shin, MD, MPH^{1,2,3}, Viktoria Livchits, MD⁴, Hilary Smith Connery, MD, PhD^{1,5}, Alan Shields, PhD^{1,3,6,*}, Sergei Yanov, MD⁷, Galina Yanova, MD⁷, Garrett M. Fitzmaurice, ScD^{1,5}, Adrienne K. Nelson, MPH², and Shelly F. Greenfield, MD, MPH^{1,5} on behalf of On behalf of the Tomsk Tuberculosis Alcohol Working Group

¹Harvard Medical School, 25 Shattuck Street, Boston, MA 02115

²Division of Global Health Equity, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115

³Department of Infectious Diseases, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115

⁴Partners in Health Representative Office in Russian Federation, Trekhpudny per., 11/13 103001, Moscow, Russia

⁵McLean Hospital, 115 Mill Street, Belmont, MA, 02478 USA

⁶Mapi Consultancy, 180 Canal Street, Suite 503, Boston, MA 02114

⁷Tomsk Oblast Clinical Tuberculosis Hospital, Timiryazev, Novaya Str 1. Russian Federation, Tomsk 634009

Abstract

Aims—To test the feasibility and effectiveness of Brief Counseling Intervention (BCI) and Naltrexone integrated into tuberculosis (TB) care in Tomsk, Russia.

Design—Using factorial randomized controlled trial design, patients were randomized into: Naltrexone, Brief Behavioral Compliance Enhancement Therapy (BBCET), treatment as usual (TAU); BCI, TAU; Naltrexone, BBCET, BCI, TAU; TAU.

Setting and Participants—In the Tomsk Oblast, hospitalized TB patients diagnosed with Alcohol Use Disorders (AUDs) by the DSM-IV were referred upon the start of TB treatment. Of the 196 cohort, the mean age was 41 years and 82% were male. Severe TB (84.7% had cavitary disease), and smoking (92.9%) were common. The majority had a diagnosis of an AUD (63.0%). 27.6% reported nearly daily drinking and consumed a median of 16 standard drinks per day.

Measurements—Primary outcomes were “favorable” TB outcome (cured, completed treatment) and change in mean number of abstinent days in the last month of study compared with baseline. Change in mean number of heavy drinking days, defined as 4 drinks per day and 5 drinks per day for women and men respectively, and TB adherence, measured as percent of doses taken as prescribed under direct observation, were secondary outcomes. Analysis based on “intention to treat” was performed for multivariable analysis.

All correspondence to: Sonya Shin, Brigham and Women's Hospital, Division of Global Health Equity, 75 Francis Street, Boston, MA 02115, sshin@partners.org.

* At the time of study participation

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Findings—Primary TB and alcohol endpoints between naltrexone and no-naltrexone or BCI and no-BCI groups did not differ significantly. TB treatment adherence and change in number of heavy drinking days also did not differ significantly among treatment arms. Among individuals with a prior quitting attempt (n=111), naltrexone use was associated with an increased likelihood of favorable TB outcomes (92.3% versus 75.9%, $P=0.02$).

Conclusions—In Tomsk Oblast, Russia, tuberculosis patients with severe Alcohol Use Disorders who were not seeking alcohol treatment did not respond to naltrexone or behavioral counselling integrated into tuberculosis care; however, those patients with past attempts to quit drinking had improved tuberculosis outcomes.

Introduction

Delivery of evidence-based alcohol interventions to vulnerable populations continues to pose considerable challenges in both resourced and under-resourced settings. A common barrier to addressing alcohol use disorders (AUDs) is the lack of healthcare systems that can deliver alcohol care to individuals who do not readily seek addictions services. Individuals with AUDs who get care for other chronic diseases could potentially receive alcohol treatment if such services were integrated in a seamless fashion into the management of these medical conditions. Such a strategy might offer a service “platform” to provide alcohol treatment, and furthermore, could improve chronic disease management by reducing negative synergies – both biological and behavioral – between alcohol and other diseases (1, 2).

Given strong evidence that alcohol contributes substantial morbidity and mortality related to active tuberculosis (3–5), there has been growing interest in integrating alcohol care into tuberculosis management in a variety of resource-poor settings (6–8). In Tomsk Oblast of Western Siberia, we conducted a factorial randomized clinical trial to test the feasibility and assess the effectiveness of two alcohol interventions – brief counseling intervention (BCI) and naltrexone – for patients with co-occurring TB and AUDs. To our knowledge, this is the first controlled study to examine the effectiveness of alcohol care when delivered as part of routine TB care.

Methods

Study Setting

The study took place in Tomsk Oblast of Russia, an area of 316,900 km², comprising a population of 1,200,000. In 2010, TB incidence in Tomsk was 73.3 per 100,000 and TB mortality was 8.6 per 100,000 (9). While there are no reliable data on alcohol use in Tomsk, one study estimated 52% of total mortality for adults 15–54 years could be attributed to alcohol use.(10) As described elsewhere, Tomsk Oblast Tuberculosis Services (TOTBS) has collaborated with Partners in Health (PIH) and Brigham and Women’s Hospital (BWH) since 2000 to improve TB treatment outcomes among vulnerable patients, such as prisoners, individuals with multidrug-resistant tuberculosis (MDR-TB) and those with AUDs (8, 11). During the study period (2008–2010), overall cure/completed rate was 69.2% (12).

Routine care

Patients are evaluated for TB when they present with symptoms or through targeted fluoroscopy screening. Diagnosis is confirmed using radiographic, clinical and/or bacteriologic data. All active cases undergo screening for AUDs using the Alcohol Use Disorders Identification Test (AUDIT) (13); HIV screening using ELISA (enzyme-linked immunosorbant assay), and drug susceptibility testing of their infecting *M. tuberculosis* strain. Individuals are evaluated for alcohol detoxification prior to initiation of TB treatment.

Individuals with socio-economic or medical problems that could complicate therapy (including most individuals with AUDs) are admitted to the hospital to start treatment; patients are usually transitioned to ambulatory care once stable. TB treatment is provided free of charge and under direct observation; regimens and outcome criteria follow World Health Organization (WHO) guidelines (14). Alcohol services are provided by the Tomsk Narcology Services, requiring physician or self-referral and payment by the patient; however, a full-time addiction specialist (narcologist) employed at the TB hospital provides free services to inpatients. Standard of care for AUDs includes psychotherapy, disulfiram, and placebo implants; naltrexone is not readily available although it is approved for use in Russia for both alcohol and narcotic dependence (15).

Study protocol

The study design has been described elsewhere (16). Adults starting TB treatment were consecutively referred to the study and evaluated for alcohol abuse or dependence based on Diagnostic and Statistical Manual Fourth Edition (DSM-IV (17)) as measured by the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM (18)) (19). Inclusion criteria were as follows:

1. TB Diagnosis and registered for TB therapy with the TOTBS;
2. TB treatment initiation in one of the three study sites (inpatient hospital, polyclinic, day hospital); and
3. Diagnosis with alcohol abuse or dependence based on the CIDI-SAM).

Individuals were excluded if they:

1. Were under 18 years of age;
2. Had liver function tests more than three times upper limit of normal range. The participant could be retested after five days and enrolled if repeat liver function tests were less than three times upper limit of normal range;
3. Reported opioid use in the past month or a positive urine screen for opioids. The participant could be retested after five days and enrolled if the second urine screen was negative;
4. Was pregnant or breastfeeding;
5. Had inadequate understanding of the study after undergoing informed consent;
6. Had any co-occurring other medical or psychiatric condition that would make it impossible for them to comply with the study procedures;

Abstinence prior to enrollment was not required. Those who consented to participate in the study were stratified by assigned TB provider and block-randomized to receive one of four possible non-blinded interventions:

1. Brief Counseling Intervention (BCI) plus treatment as usual (i.e. standard referral to and management by a narcologist);
2. Naltrexone and Brief Behavioral Compliance Enhancement Treatment (BBCET) plus treatment as usual;
3. BCI plus naltrexone-BBCET plus treatment as usual;
4. Treatment as usual alone.

Non-blinded randomization assignment was generated by computer by the study team.

Study interventions

The NIH/NIAAA's *Helping Patients with Alcohol: A Health Practitioner's Guide* (20) was adapted for our study population, described elsewhere (21). BCI consisted of six 10–15 minute discussions delivered monthly by TB physicians embedded in their standard 45–60 minute TB appointments (22–25). Naltrexone was orally administered to patients as a daily single dose of 50 mg for six months, starting at the time of study enrollment, usually within two weeks of TB treatment start. TB staff administered naltrexone together with anti-tuberculosis medications under direct observation and recorded all doses on a naltrexone administration card. Monthly assessment included a structured interview for adverse events, liver and kidney function tests, and pregnancy or opioid test if indicated. TB physicians managed naltrexone side effects as well as treatment interruptions due to detoxification, opioid use (including surgery), and pregnancy.

All participants randomized to naltrexone also received brief adherence counseling adopted from the Brief Behavioral Compliance Enhancement Treatment (BBCET) used in the Topiramate Clinical Protocol (26), with permission from the authors. The BBCET was a focused intervention to enhance naltrexone adherence and promote changes in drinking behavior through goal-setting and naltrexone-specific feedback. BBCET differs from BCI in that it does not use counseling or motivational interviewing. Six 5–10 minute BBCET encounters were delivered monthly by TB physicians during standard follow-up appointments.

Due to the factorial study design, some participants were randomized to receive both BCI and naltrexone-BBCET. We created a BCI/BBCET manual which combined both behavioral interventions in a streamlined fashion, with each encounter lasting approximately 15–25 minutes.

Training and fidelity assessment

TB providers received training on naltrexone, including the mechanism of action, pharmacology, administration, dosing, side effect management, and contraindications. Training and fidelity procedures for behavioral interventions have been described elsewhere (21). Fidelity assessment was conducted throughout the study, via review of audio-taped sessions by our study team with standardized coding for fidelity and adherence. Scoring sheets provided quantitative and qualitative feedback to providers. 98% of BCI encounters reviewed met criteria for procedural adherence; for BBCET, 87% of encounters adhered to protocols, while 13% included counseling such as discussing events or goals not related to adherence or engaging in problem solving.

Data collection and analysis

Baseline and follow-up data were collected by trained TB providers, including chart review for sociodemographic information and co-morbidities. Baseline depression was measured using the Center for Epidemiologic Studies Depression Scale (CES-D) (27). Patients were interviewed about alcohol use with the Time Line Follow Back (TLFB) questionnaire with three-month recall at baseline, three and six months (28). We obtained TB bacteriologic, adherence and outcome data from the TOTBS registry.

We obtained approval from the Partners Healthcare IRB as well as the State Research Center Virology and Biotechnology, Novosibirsk Region and the Siberian State Medical University of the Federal Agency for Health care and Social Development, local IRB in Tomsk, Russia. The trial was registered with clinicaltrials.gov, registration number NCT00675961.

Study outcomes

We assessed both TB- and alcohol-related outcomes. The primary TB endpoint was “favorable outcome,” i.e. cure, completed treatment, while “poor outcomes” included treatment failure, death from any cause, or default. For those without a final outcome (including transfers and those still in treatment), individuals who achieved culture conversion (i.e. at least two consecutive monthly negative cultures) were considered to have a favorable outcome. TB treatment adherence defined as the percent of doses taken as prescribed under direct observation was also considered.

Our primary alcohol outcome was defined as the change in mean number of abstinent days in the last month of study period compared with pre-hospitalization baseline. The secondary alcohol endpoint was: the change in mean number of heavy drinking days (4 drinks per drinking day for women and 5 drinks per drinking day for men) (29) in the last month of the study compared with pre-hospitalization baseline. Additionally, because this was a non-treatment seeking group with long-standing AUDs, we hypothesized that the individuals with prior attempts to quit drinking may be more likely to respond to study interventions. We therefore performed a secondary analysis limited to individuals who reported any prior attempt to quit drinking alcohol.

Analytic approach

We compared binary outcomes using Chi-Square (or Fisher’s exact tests for expected cells < 5). Continuous variables were compared using t-test, and for variables with non-normal distribution, the Wilcoxon two-sample test. Logistic regression models were used to provide estimates of intervention effect on TB outcome controlling for baseline characteristics. We also tested for interactions between the treatment arms. We compared the change in alcohol endpoints between baseline and last month of the study period using a log-linear regression analyses, with the baseline measure as a covariate. We performed analysis based on “intention-to-treat”. To address missing data on alcohol endpoints, log-linear regression analyses were performed for multivariable analysis on datasets multiply imputed using Markov Chain Monte Carlo methods (30).

In designing the study, we calculated that a cohort of 280 participants would provide power of > 0.80 to detect a decrease from 35% to 20% in poor TB treatment response with a two-sided 5% significance level. This cohort would also achieve power of > 0.95 to detect a relative rate ratio of 1.14 or larger at a two-sided 5% significance level for change in number of abstinent days. The study was not powered to evaluate interactions between the effects of BCI and naltrexone-BBCET. Due to slow enrollment, we reduced the sample size to 200, which provided greater than 90% power to detect a relative rate ratio of 1.30 for the primary alcohol outcome and power of 0.62 to detect the anticipated effect size on the primary TB outcome. A blinded interim analysis was conducted mid-point through enrollment by our Data and Safety Monitoring Board to assess whether any intervention arm was superior or inferior to the treatment as usual arm.

Results

Enrollment and follow-up

From June 2007 through September 2011, a total of 411 TB patients were recruited (Figure 1). Of these, 131 were ineligible, and 80 eligible candidates declined enrollment. Two hundred individuals were randomized, of which four individuals were subsequently withdrawn because they were confirmed to have a diagnosis other than TB.

The remaining 196 individuals comprise the cohort for analysis. Individuals were randomized to receive BCI versus no BCI (98 versus 98) and to receive naltrexone versus no naltrexone (92 versus 104). Eleven individuals did not receive the standard intervention as allocated, largely due to participant refusal of naltrexone ($n=10$). Thirteen individuals withdrew from the study, due to participant preference ($n=6$), contraindication to naltrexone per treating physician due to naltrexone side effects or opioid use after enrollment (31), poor general health of the participant (31), and loss to follow-up (31). Study withdrawal was more common in the naltrexone versus no naltrexone arms (9 versus 4, $P=0.15$). Data were collected for 153 (78.1%) of alcohol endpoints and 194 (99.0%) of TB endpoints.

Baseline characteristics

Baseline characteristics of the study cohort are presented in Table 1. The mean age was 41 years, and 82% were male. Participants often presented with severe tuberculosis, reflected by a low body mass index in 29.1% and cavitary disease in 84.7% of participants. Smoking was almost ubiquitous (92.9%), while only 14 (7.1%) had a concomitant drug use disorder. Most individuals (63.0%) had a diagnosis of alcohol dependence, and consumption was heavy: 27.6% reported nearly daily drinking the past 12 months, with median of 16 standard drinks per drinking day. Depression, assessed only among study participants, was observed in 13.5% of the cohort.

Compared with study participants (Table 1), eligible candidates who declined were less likely to be married or living with a partner (53.8% v. 37.8%, $P=0.01$), and were less likely to be unemployed (63.8% versus 78.1%, $P=0.01$). In addition, those who declined tended to have less severe AUDs: they were less likely to have a diagnosis of alcohol dependence (39.7% versus 63.0%, $P<0.001$), reported less daily drinking in the past year (18.0% versus 27.6%, $P<0.001$) and fewer number of standard drinks (median 8.5 versus 16.0, $P=0.03$), and had lower average baseline AUDIT scores (16.0 versus 18.3, $P=0.03$) compared with study participants.

Baseline characteristics displayed in Table 1 did not differ significantly among individuals randomized to naltrexone versus no naltrexone. Individuals assigned to BCI versus no BCI were more likely to have a diagnosis of alcohol dependence (70.1% versus 55.8%, $P=0.04$), but did not differ significantly in other respects.

Intervention delivery

Participants randomized to naltrexone-BBCET received a median [first and third quartiles, Q1, Q3] of three [1, 5] BBCET encounters and 112 [39, 159] doses of naltrexone (74.7% of the total planned 150 doses). Five participants received no BBCET and an additional eight individuals received neither BBCET nor naltrexone. Those randomized to BCI received a median [Q1, Q3] of three BCI encounters [2, 5], and thirteen received no BCI.

Adverse events

Monthly assessment for adverse events yielded no significant difference in specific and overall (combined) adverse events among individuals assigned to naltrexone versus those not assigned to naltrexone. Likewise, the frequency of adverse events among individuals assigned to BCI versus no BCI did not significantly differ.

Study Outcomes

The overall rate of favorable response (cure or completed treatment) among study participants was 82.3%, compared to 69.2% in the overall TB treatment population in Tomsk during the study period. TB outcomes did not significantly differ among naltrexone versus no-naltrexone groups ($P=0.23$), nor among those receiving BCI versus no-BCI

($P=0.46$) (Table 2). TB treatment adherence did not differ among treatment arms (94.0% versus 93.3% among NTX versus no-NTX, $P=0.53$; 93.7% versus 93.8% among BCI versus no-BCI, $P=0.83$). In terms of alcohol outcomes, mean abstinent days and heavy drinking days did not differ by treatment arms (Table 2), and findings did not change when adjusting for baseline characteristics. We observed no significant interaction between the intervention arms on either favorable TB outcome (P -value for interaction term 0.94) or abstinence (P -value for interaction term 0.10).

Among the 111 individuals who reported at least one prior attempt to quit (Table 3), naltrexone was associated with an increased likelihood of a favorable TB outcome (92.3% versus 75.9%, $P=0.02$, adjusted $P=0.04$), but no significant difference in terms of abstinent days or heavy drinking days. Comparison of BCI versus no-BCI groups among individuals who previously attempted to quit, when adjusted for baseline differences in dependence, revealed a weak trend toward good TB outcome (88.1% versus 78.4%, P -value 0.17, adjusted $P=0.21$), but no impact on abstinence or heavy drinking days.

Discussion

Among TB patients with severe AUDs, we found that integrating free-of-charge evidence-based alcohol services into TB care did not have a significant impact on TB or alcohol outcomes. Possible explanations for this finding include the fact that individuals were by and large not alcohol treatment seeking and may not have been interested in changing their drinking behavior. Also, it is possible that the relatively low "dose" of BCI and/or BBCET (only half of the scheduled encounters) contributed to minimal impact of these interventions. There may have been some "contamination" between BBCET versus BCI encounters, resulting in less of a difference between study versus control arms, particularly given the factorial design. Furthermore, TB treatment outcomes in all study arms were better than programmatic outcomes during the study period, suggesting that intensive follow-up and support related to clinical trial participation may have improved outcomes and diminished the relative difference observed among treatment arms. Finally, our cohort was comparable to that of the Veterans Affairs Naltrexone Cooperative Study 425 Group (32) in terms of the duration and severity of their alcohol problems. Such a recidivistic group – typical of those treated for TB in Russia – may not be the ideal population for oral naltrexone or brief treatment interventions for AUDs, particularly when they are not specifically seeking treatment. Rather, these populations may require more intensive interventions, such as intensive outpatient or day treatment that focuses on the adverse effects of alcohol, the individual's motivation and skills to become abstinent, and relapse prevention strategies. In addition, it is not clear whether depot naltrexone might confer benefit as adherence to this regimen over a longer follow-up period would be more feasible because it obviates the need for oral dosing (33, 34).

Individuals who had made prior attempts to quit drinking appeared to benefit more from naltrexone than the general cohort. This may have been, in part, related to a modest decrease in the average amount consumed per drinking day among those receiving naltrexone in this subgroup (9.54 ± 1.22 standard drinks versus 14.16 ± 1.11 , $p=0.33$). Alternatively, receipt of naltrexone and BBCET may have had other positive benefits on TB outcome through mechanisms not related to decreased drinking, such as stronger patient motivation to continue treatment or improved TB management, e.g. ability to perform adjunctive surgery (35). We speculate that this group of individuals who were already in a contemplative state of change toward their drinking may have been more responsive to NTX, resulting in exceptional TB outcomes (92.3% favorable outcome, compared with 69.2% in the general TB population during this period).

Our study had several limitations. First, the cohort size was reduced during the course of the study due to slow enrollment. This smaller than expected sample size may have limited our ability to detect significant effects on study endpoints. In addition, our ability to obtain study completion data on alcohol outcomes was limited by social marginalization, geographic distances, and limited phone access to participants once they were released from the hospital. Nonetheless, we were able to obtain alcohol endpoint data in 78.1% of the cohort.

This clinical trial expands our understanding of how alcohol care could be effective when applied in resource-poor settings. We were able to demonstrate the feasibility of delivering alcohol interventions by non-specialist providers as part of management for a co-occurring chronic medical disease. In many resource-poor settings, addictions services and specialist care are scarce and essentially inaccessible for individuals without personal financial resources. Integrated management strategies may offer potential avenues for difficult-to-reach populations. Implementing pharmacologic interventions such as naltrexone may be more straight-forward than behavioral interventions which require more intensive training for non-specialist providers (35). Combining behavioral interventions with contingency management strategies (36, 37) may also be a strategy worth investigating for individuals who are not yet treatment seeking for their alcohol use disorder. In particular, long-acting medications for alcohol dependence, such as depot and implant formulations, merit further exploration as a strategy for increasing naltrexone adherence, particularly for patients who are transitioning from the inpatient to outpatient setting. We suggest further exploration into integrated programmatic utilization of evidence-based interventions, particularly naltrexone and other medications as well as more-intensive behavioral treatments, for individuals with co-occurring AUDs and other medical conditions such as TB.

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Figure 1.
CONSORT flow diagram for IMPACT trial

Table 1
 Characteristics of study participants versus eligible individuals who declined study, N=276

Variable (N, if not complete cohort)	Study participants N=196 n (%)	Declined enrollment, N=80 n (%)	p-value
Sociodemographic characteristics			
Age (Mean $\pm$ STD)	40.9 $\pm$ 11.2	40.9 $\pm$ 10.5	0.96
Male gender	161 (82.1)	69 (86.3)	0.41
Married or living together	74 (37.8)	43 (53.8)	0.01
Unemployed	153 (78.1)	51 (63.8)	0.01
Receiving disability pension	13 (6.6)	2 (2.5)	0.24
Prior incarceration	51 (26.3)	13 (16.3)	0.08
Clinical characteristics			
HIV, N=271	1 (0.5)	1 (1.3)	0.49
Diabetes mellitus	5 (2.6)	2 (2.5)	1.00
Cardio- or cerebro-vascular disorder	8 (4.1)	4 (5.0)	0.75
No prior TB treatment	125 (63.8)	58 (72.5)	0.16
Low body mass index, N=275	57 (29.1)	20 (25.3)	0.53
Cavitary abnormalities on chest radiograph	166 (84.7)	70 (87.5)	0.55
Substance use history			
Current smoker, N=274	182 (92.9)	69 (88.5)	0.24
Pack-years among ever-smokers (Median [Q1, Q3]), N=260	18.9 [10.0, 30.0]	20.0 [10.0, 30.0]	0.78
Drug use disorder by DSM criteria	14 (7.1)	2 (2.6)	0.25
DSM classification of alcohol use disorder			<0.001
Alcohol dependence disorder	121 (63.0)	27 (39.7)	
Alcohol abuse disorder	71 (37.0)	41 (60.3)	
Age at first alcoholic drink, N=274	15.0 $\pm$ 3.3	16.3 $\pm$ 3.0	0.49
Age of alcohol abuse onset, N=252	26.5 $\pm$ 8.9	25.7 $\pm$ 8.0	0.53
Age of alcohol dependence onset, N=146	31.3 $\pm$ 8.5	31.5 $\pm$ 9.8	0.92
Nearly daily drinking in past twelve months	54 (27.6)	14 (18.0)	<0.001

Variable (N, if not complete cohort)	Study participants N=196 n (%)	Declined enrollment, N=80 n (%)	p-value
Standard drinks per drinking day in past year (Median [Q1, Q3]), N=253	16.0 [8, 22]	8.5 [4.0, 16.0]	0.03
Number of serious attempts to quit (Median [Q1, Q3]), N=193	2 [0, 4]	0 [0, 3]	0.08
AUDIT score, N=274	18.3 ± 7.6	16.0 ± 7.8	0.03

b. Characteristics of study participants versus eligible individuals who declined study, N=276

Variable (N, if not complete cohort)	Study participants N=196 n (%)	Declined enrollment, N=80 n (%)	BCI N=53 n (%)	NTX N=47 n (%)	BCI+ NTX N=45 n (%)	TAU alone N=51 n (%)
Sociodemographic characteristics						
Age (Mean ± STD)	40.9 ± 11.2	40.9 ± 10.5	42.2 ± 10.3	41.5 ± 10.8	41.0 ± 10.4	40.0 ± 12.1
Male gender	161 (82.1)	69 (86.3)	43 (81.1)	41 (87.2)	34 (75.6)	43 (84.3)
Married or living together *	74 (37.8)	43 (53.8)	17 (32.1)	21 (44.7)	18 (40.0)	18 (35.3)
Unemployed *	153 (78.1)	51 (63.8)	43 (81.1)	39 (83.0)	30 (66.7)	41 (80.4)
Receiving disability pension	13 (6.6)	2 (2.5)	3 (5.7)	6 (12.8)	1 (2.2)	3 (5.9)
Prior incarceration	51 (26.3)	13 (16.3)	14 (26.4)	14 (30.4)	10 (22.7)	13 (25.5)
Clinical characteristics						
HIV, N=271	1 (0.5)	1 (1.3)	1 (1.9)	0	0	0
Diabetes mellitus	5 (2.6)	2 (2.5)	3 (5.7)	0	1 (2.2)	1 (2.0)
Cardio- or cerebro-vascular disorder	8 (4.1)	4 (5.0)	0	2 (4.3)	2 (4.4)	4 (7.8)
No prior TB treatment	125 (63.8)	58 (72.5)	32 (60.4)	29 (61.7)	31 (68.9)	33 (64.7)
Low body mass index, N=275	57 (29.1)	20 (25.3)	13 (24.5)	12 (25.5)	15 (33.3)	17 (33.3)
Cavitary abnormalities on chest radiograph	166 (84.7)	70 (87.5)	43 (81.1)	44 (93.6)	36 (80.0)	43 (84.3)
Substance use history						
Current smoker, N=274	182 (92.9)	69 (88.5)	50 (94.3)	43 (91.5)	41 (91.1)	48 (94.1)
Pack-years among ever-smokers (Median [Q1, Q3]), N=260	18.9 [10.0, 30.0]	20.0 [10.0, 30.0]	20.0 [12.5, 30.0]	20.0 [11.5, 30.0]	15.0 [9.0, 30.0]	15.0 [8.5, 30.0]
Drug use disorder by DSM criteria	14 (7.1)	2 (2.6)	3 (5.7)	4 (8.5)	2 (4.4)	5 (9.8)
DSM classification of alcohol use disorder [§]						
Alcohol dependence disorder	121 (63.0)	27 (39.7)	37 (69.8)	23 (50.0)	31 (70.5)	30 (61.2)

b. Characteristics of study participants versus eligible individuals who declined study, N=276						
Variable (N, if not complete cohort)	Study participants N=196 n (%)	Declined enrollment, N=80 n (%)	BCI N=53 n (%)	NTX N=47 n (%)	BCI+ NTX N=45 n (%)	TAU alone N=51 n (%)
Alcohol abuse disorder	71 (37.0)	41 (60.3)	16 (30.2)	23 (50.0)	13 (29.6)	19 (38.8)
Age at first alcoholic drink, N=274	15.0 ± 3.3	16.3 ± 3.0	14.6 ± 3.7	14.6 ± 3.1	15.0 ± 3.0	15.8 ± 3.3
Age of alcohol abuse onset, N=252	26.5 ± 8.9	25.7 ± 8.0	27.4 ± 8.9	29.8 ± 9.4	27.0 ± 8.0	24.4 ± 9.4
Age of alcohol dependence onset, N=146	31.3 ± 8.5	31.5 ± 9.8	32.3 ± 9.0	29.8 ± 6.4	32.3 ± 8.2	30.4 ± 9.7
Nearly daily drinking in past twelve months [§]	54 (27.6)	14 (18.0)	17 (32.1)	13 (27.7)	14 (31.1)	10 (19.6)
Standard drinks per drinking day in past year (Median [Q1, Q3]), N=253 [*]	16.0 [8, 22]	8.5 [4, 16]	16 [8, 32]	16 [8, 16]	16 [7, 16.5]	16 [8, 16]
Number of serious attempts to quit (Median [Q1, Q3]), N=193	2 [0, 4]	0 [0, 3]	1 [0, 3]	2 [0, 5]	2 [0, 4]	2 [0, 4]
AUDIT score, N=274 [*]	18.3 ± 7.6	16.0 ± 7.8	19.1 ± 7.9	18.8 ± 7.3	18.6 ± 7.6	16.6 ± 7.6

* Participants v. declined enrollment: $p < 0.05$

[§] Participants v. declined enrollment: $p < 0.001$

Table 2

Treatment comparisons of tuberculosis and alcohol endpoints, N=196

	NTX N=92 n (%)	No NTX N=104 n (%)	Unadjusted effect [¶] [95% CI]	Adjusted effect [§] [95% CI]
Primary outcomes				
Good TB outcome, N=195	80 (87.0)	83 (80.6)	1.60 [0.74, 3.50]	1.95 [0.65, 5.85]
Abstinent days [*]	24.51 ± 1.04	23.38 ± 0.86	1.01 [0.91, 1.11]	1.00 [0.90, 1.11]
Secondary outcome				
Heavy drinking days [*]	3.63 ± 0.78	4.05 ± 0.65	0.94 [0.68, 1.29]	0.97 [0.70, 1.36]
	BCI N=98 n (%)	No BCI N=98 n (%)	Unadjusted effect [¶] [95% CI]	Adjusted effect [§] [95% CI]
Primary outcomes				
Good TB outcome, N=195	83 (85.6)	80 (81.6)	1.33 [0.62, 2.86]	1.97 [0.68, 5.66]
Abstinent days [*]	24.03 ± 0.95	23.67 ± 0.93	1.00 [0.91, 1.11]	1.03 [0.92, 1.15]
Secondary outcomes				
Heavy drinking days [*]	3.52 ± 0.71	4.21 ± 0.70	1.05 [0.76, 1.44]	1.00 [0.71, 1.42]

^{*} Mean ± standard error, adjusted for baseline consumption.

[¶]Odds ratios for TB outcome; rate ratios for alcohol outcomes; note: alcohol endpoint data were imputed for 14% in TAU, 11% in BCI, 28% in NTX, and 38% in BCI+NTX groups.

[§] Adjusted for all baseline variables

Table 3

Treatment comparisons of tuberculosis and alcohol endpoints among those with prior attempts to quit, N=111

	NTX N=52 n (%)	No NTX N=59 n (%)	Unadjusted effect[¶] [95% CI]	Adjusted effect^{¶§} [95% CI]
Primary outcomes				
Good TB outcome, N=110	48 (92.3)	44 (75.9)	3.82 [1.17, 12.48]	3.74 [1.07, 13.13]
Abstinent days [*]	23.67 ± 1.21	24.07 ± 1.04	1.04 [0.92, 1.17]	1.03 [0.90, 1.17]
Secondary outcomes				
Heavy drinking days [*]	4.09 ± 0.83	4.03 ± 0.72	0.92 [0.63, 1.34]	0.98 [0.67, 1.44]
	BCI N=60 n (%)	No BCI N=51 n (%)	Unadjusted effect[¶] [95% CI]	Adjusted effect^{¶§} [95% CI]
Primary outcomes				
Good TB outcome, N=110	52 (88.1)	40 (78.4)	2.04 [0.73, 5.74]	2.07 [0.66, 6.50]
Abstinent days [*]	24.61 ± 1.08	23.11 ± 1.14	0.96 [0.86, 1.09]	0.97 [0.85, 1.12]
Secondary outcomes				
Heavy drinking days [*]	3.43 ± 0.74	4.76 ± 0.78	1.11 [0.76, 1.61]	1.15 [0.75, 1.75]

* Mean ± standard error, adjusted for baseline consumption

[¶]Odds ratios for TB outcome; rate ratios for alcohol outcomes[§] Adjusted for all baseline variables