Effect of smoking on drug-resistant tuberculosis treatment outcomes and exploring potential pathways: A multicountry cohort study

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ABSTRACT

People who smoke are at increased risk of unfavorable tuberculosis (TB) treatment outcomes compared with those who do not, but the pathways explaining this effect are unclear. We estimated the effect of smoking on a successful end-of-treatment outcome for multidrug-resistant and rifampicin-resistant (MDR/RR) TB and examined if intervening on loss to follow-up mitigates this effect.

The endTB Observational Study was a prospective cohort of people with MDR/RR-TB who were treated with longer regimens containing bedaquiline and/or delamanid. We used marginal standardization to examine the effect of smoking (≥1 cigarette daily at enrollment) on treatment success (cured/completed). To simulate intervening on lost to follow-up, we censored participants and applied inverse probability of censoring weights.

Among 1786 participants in 12 countries, 539 (30.2%) reported smoking. At the end of treatment, 73.5% of people who smoked and 80.3% of people who did not smoke had treatment success (risk difference in percentage points: -6.8, 95% CI: -11.1, -2.6). After adjusting for baseline confounders including demographics, social history, and comorbidities, the risk difference was similar (-5.2 percentage points) but 95% CIs were less precise (-14.1, 3.2). In a pseudopopulation without loss to follow-up, the risk difference was reduced (-1.9 percentage points; 95% CI: -10.2, 5.1).

People who smoked had less frequent MDR/RR-TB treatment success compared with those who did not smoke. A simulated intervention on loss to follow-up reduced this difference, suggesting that pathways related to retention in care were a driver of this effect.

Key words: Tobacco Smoking; Mycobacterium tuberculosis; Tuberculosis, Multidrug-Resistant; Treatment Adherence and Compliance; Lost to Follow-Up

INTRODUCTION

Tuberculosis (TB) and tobacco smoking are both major contributors to morbidity and mortality [1, 2]. Their intersection is also substantial with a higher prevalence of tobacco smoking in high TB burden countries and among populations that are disproportionately affected by TB, such as men, people living with HIV, incarcerated people, and mine workers [1, 2]. The dual burden of TB and smoking is not coincidental. Epidemiologic evidence has consistently supported that tobacco smoke increases the risk of TB infection and disease [3, 4]. Tobacco smoking has also been associated with more severe TB disease presentation, including greater sputum mycobacterial load, more cavitary lesions, and higher probability of disease requiring hospitalization [5-7], and worse TB treatment outcomes, specifically increased risk of delayed smear and culture conversion, unfavorable end-of-treatment outcomes, and recurrence [8-11].

A negative effect of smoking on TB treatment outcomes could plausibly be explained by direct biological effects of tobacco smoke. Tobacco smoke causes profound structural and functional damage to the respiratory tract [12] and impairs the pulmonary immune response to TB infection [13]. These changes favor the pathogen's survival, persistence, and proliferation, and thus could compromise the effectiveness of TB treatment. Another pathway to unfavorable treatment outcomes could include greater adherence challenges among people who smoke culminating in early discontinuation from treatment, i.e., loss to follow-up after treatment initiation [14]. This pathway is complex and related to multiple factors at different levels, e.g., competing economic responsibilities, lack of social support, negative experiences accessing care, and clinical evolution and adverse events on TB treatment [15-19]. The observed association between smoking and TB treatment outcomes may also be spurious, as smoking is frequently accompanied by other factors known to affect TB treatment outcomes, such as alcohol and other substance use [20-22].

Multidrug-resistant and rifampicin-resistant (MDR/RR) TB is more difficult to treat compared with drug-susceptible TB[1], and individuals often endure an extended duration of complicated drug regimens with multiple toxicities [23]. Impacts may be experienced by the individual as well as by their family and others around them [24-26]. Therefore, identifying areas for intervention that effectively increase treatment success is of high clinical and public health importance. Most of the evidence for the negative effect of smoking on TB treatment outcomes comes from studies enrolling people with drug-susceptible TB [8, 10, 11]. A meta-analysis focused on MDR/RR-TB reported that TB treatment outcomes were similar by smoking status; however, most of the studies defined smoking as ever smoking rather than current smoking at the time of treatment initiation and heterogeneity among the studies was very high [27]. Using epidemiologic methods rooted in causal inference, we estimate the effect of smoking on MDR/RR-TB end-of-treatment outcomes. To understand the contribution of different pathways of how smoking affects these outcomes, we simulate intervening on loss to follow-up.

METHODS

Setting and participants

We used data from the endTB Observational Study (ClinicalTrials.gov Identifier: NCT03259269), a prospective cohort of people with MDR/RR-TB who were treated with longer regimens containing bedaquiline and/or delamanid [28, 29]. Participants were enrolled from April 2015 through September 2018 in 17 countries. Details on study procedures are available elsewhere [28, 29]. The study protocol was approved by ethics committees for each consortium partner and in each country. Participants (or a guardian if the individual was a minor, as defined by local legal requirements) provided written informed consent and older minors provided assent. For these analyses, if individuals were treated multiple times during the study, we included only the first treatment regimen. We excluded individuals treated in the Democratic

People's Republic of Korea due to differences in clinical protocols and regimens, including their use of shortened treatments. Additional exclusion criteria are listed in **Figure 1**.

Variables

Exposure and outcome

Our exposure of interest was smoking status, which was assessed at the enrollment visit based on a yes/no response when participants were asked if they smoke ≥1 cigarette daily. End-of-treatment outcomes were assigned by the treating clinician based on World Health Organization (WHO) outcome definitions [30]. Successful treatment comprised an outcome of cured or completed. Unsuccessful treatment comprised an outcome of death, treatment failure, or lost to follow-up. Lost to follow-up was defined as a treatment interruption for ≥2 consecutive months.

Other variables

Demographics (country, sex, age) and social history variables (married or living with partner, employed, homeless in past year, if ever incarcerated, refugee/displaced person/migrant status, drinks alcohol, and drug use) were self-reported at enrollment. We categorized countries as a post-Soviet country or other country, in recognition of the higher proportion of participants who smoked in the former.

Comorbidities at enrollment included HIV; hepatitis B virus infection, based on a positive surface antigen; hepatitis C virus infection, based on a positive antibody, PCR, or viral load; diabetes, based on self-reported diagnosis, random plasma glucose >200 mg/dL (11.1 mmol/L), or hemoglobin A1C ≥6.5%; and underweight, defined as a body mass index <18.5 kg/m^2 using measured height and weight.

TB disease and treatment characteristics at enrollment included the presence of extrapulmonary TB; presence of bilateral disease, fibrosis, and cavitary disease based on chest

x-ray; sputum smear positive and grade; sputum culture positivity; known prior treatment with second-line TB drugs; drug susceptibility results categorized as to whether fluoroquinolone resistance was present or not; and baseline TB regimen composition, including the number of likely effective drugs.

Variables assessed during follow-up included indicators of TB disease severity (i.e., sputum smear positivity, sputum culture positivity, and presence of cavitary disease) and monthly TB treatment adherence. Adherence was computed for each month as the number of days all medications were taken as prescribed divided by the number of days those medications were prescribed. This monthly proportion was dichotomized as <80% and ≥80%. These variables were treated as time-varying so they could change throughout follow-up.

Statistical analyses

We used marginal standardization to compute risk differences and ratios for the effect of smoking on treatment success in an unadjusted model and a model adjusted for baseline confounders (**Figure 2a**). The bias-corrected and accelerated bootstrap with 1000 resamples was used to obtain 95% confidence intervals (CIs). We used the missing indicator method to account for missing data on baseline confounders. We used directed acyclic graphs (**Figure 2a-c**) to understand the underlying causal structure between smoking and MDR/RR-TB treatment outcome and identified potential baseline demographic, social, and clinical confounders *a priori*. In primary analyses, we assumed that baseline indicators of TB disease severity were a result of smoking and therefore part of the pathway through which smoking could impact TB treatment outcomes [5-7]. However, it may be that these characteristics coincide with, but are unrelated to smoking. We therefore conducted a sensitivity analysis that additionally adjusted for these characteristics.

To simulate intervention on loss to follow-up, we censored participants who were lost to follow-up and used time-varying stabilized inverse probability of censoring weights to create a

pseudopopulation in which no one was lost to follow-up. We computed weights by fitting a pooled logistic regression model to predict whether participants remained uncensored, conditional on smoking status; baseline demographics, social history, and comorbidities; baseline indicators of TB disease severity; and time-varying indicators of TB severity and monthly TB medication adherence (**Figure 2b, 2c; Table E1**). We carried observations forward for time-varying variables and used the missing indicator method for any remaining missing data. As with the other analyses, we used marginal standardization to estimate risk differences and ratios and bootstrapping for 95% CIs.

We used SAS 9.4 (SAS Institute, Cary, NC) and R version 4.4.2 (R Core Team, 2023) for analyses.

RESULTS

Description of selection of the analytic sample and participant characteristics

Of 2788 endTB observational study participants enrolled in 17 countries, 1002 were excluded (**Figure 2**), resulting in a final analytic sample of 1786 participants in 12 countries: Armenia (93 [5.2%]), Belarus (101 [5.7%]), Ethiopia (34 [1.9%]), Georgia (208 [11.7%]), Indonesia (61 [3.4%]), Kazakhstan (641 [35.9%]), Kyrgyzstan (13 [0.7%]), Myanmar (42 [2.4%]), Pakistan (262 [14.7%]), Peru (260 [14.6%]), South Africa (39 [2.2%]), and Vietnam (32 [1.8%]). Of the 1786 participants, 539 (30.2%) reported smoking cigarettes daily.

There were some notable differences in demographics, social history, comorbidities, and TB disease characteristics at enrollment by smoking status (**Table 1**). Compared with those who did not smoke, participants who smoked more commonly resided in post-Soviet countries (92.8% vs. 44.6%) and were more frequently male (89.1% vs. 52.6%), older (median age 41 years vs. 32 years), ever incarcerated (35.4% vs. 9.2%), and identified as a refugee, displaced person, or migrant (6.4% vs. 1.9%). They also more commonly drank alcohol (33.5% vs. 3.2%) and used drugs (12.9% vs. 2.4%). Regarding comorbidities, participants who smoked more

often had HIV (8.4% vs. 5.9%), hepatitis B (5.0% vs. 3.7%), and hepatitis C (28.8% vs. 7.3%) and less often had diabetes (11.2% vs. 14.7%) and were underweight (29.7% vs. 39.3%) compared with those who did not smoke. Participants who smoked more often had bilateral disease (71.4% vs. 64.3%), a positive sputum smear (61.8% vs. 53.8%), and a positive sputum culture (70.9% vs. 60.2%) compared with those who did not smoke. The number of likely effective drugs in the baseline TB treatment regimen was similar by smoking status (median of 4 for both smoking categories).

Frequencies of end-of-treatment MDR/RR-TB treatment outcomes

Overall, 1397 (78.2%) had a successful treatment outcome of cured or completed (**Table 2**). Regarding unsuccessful outcomes, 137 (7.7%) died, 97 (5.4%) had treatment failure, and 155 (8.7%) were lost to follow-up. The median (interquartile range) time from cohort enrollment until death was 5.6 (2.4, 11.5) months and until assigned lost to follow-up was 8.7 (5.7, 13.4) months. With regard to unsuccessful outcomes by smoking status, the frequency of death among participants who smoked was 5.0%, versus 8.8% in those who did not. Compared with participants who did not smoke, the frequencies of treatment failure (8.5% vs. 4.1%) and lost to follow-up (13.0% vs. 6.8%) were higher for participants who smoked, including frequencies of clinician-assigned reasons for both of these outcomes.

Effect of smoking on MDR/RR-TB treatment success and the potential impact of intervening on loss to follow-up

In the unadjusted model (**Table 3**), the risk of successful treatment outcome was 6.8 percentage points lower among participants who smoked (73.5%) versus those who did not (80.3%; 95% CI for risk difference: -11.1, -2.6) with a risk ratio of 0.92 (95% CI: 0.86, 0.97). When adjusting for baseline confounders related to demographics, social history, and comorbidities, the risk difference was -5.2 percentage points (95% CI: -14.1, 3.2) and the risk

ratio was 0.93 (95% CI: 0.82, 1.04). In the sensitivity analysis that also adjusted for baseline indicators of TB disease severity, the risk difference was -4.4 percentage points (95% CI: -12.7, 3.2) and the risk ratio was 0.94 (95% CI: 0.84, 1.04).

In the pseudopopulation which simulated intervening to eliminate loss to follow-up, the risk of successful treatment was (84.0%) among participants who smoked compared with (85.9%) in those who did not (risk difference -1.9 percentage points, 95% CI: -10.2, 5.1; risk ratio: 0.98, 95% CI: 0.88, 1.06).

DISCUSSION

Cigarette smoking was common at the start of MDR/RR-TB treatment, particularly in post-Soviet countries, and was frequently accompanied by a complex social history, including past incarceration and substance use, and infectious comorbidities, especially hepatitis C. We found evidence that people who smoked had a lower frequency of MDR/RR-TB treatment success compared with those who did not. In a pseudopopulation without loss to follow-up, this difference in treatment success by smoking status was reduced but not eliminated. This finding suggests that smoking may negatively impact MDR/RR-TB treatment outcomes both through complex adherence-related pathways leading to loss to follow-up and other pathways like the direct biological pathways leading to treatment failure.

In the model adjusted for baseline confounders, the risk difference of treatment success by smoking status was -5.2 percentage points, which is of clinically relevant magnitude and similar to that observed in other studies. For example, in a large prospective cohort from Hong Kong with 16,345 people who had drug-susceptible TB, the risk difference in treatment success by smoking status (current vs. never) was about -3.3 percentage points [7]. Although the CI was less precise, the adjusted risk difference was similar to the unadjusted risk difference. Therefore, baseline confounding did not appear to be a major driver of the observed association. Selection of confounders requires a clear understanding of directionality with regard

to the exposure, which may not always be known. For example, more advanced TB disease may result from smoking through direct biological effects, but may also coincide with smoking if people who smoke have delays in diagnosis (e.g., if they are less likely to identify TB symptoms as indicative of illness). In our sensitivity analysis, additionally adjusting for sputum smear and culture positivity, and presence of cavitary disease slightly attenuated the risk difference and did not lead to a different conclusion. Nevertheless, we advocate researchers examining the impact of smoking on TB outcomes to similarly examine the sensitivity of results to assumptions about why people who smoke present with more severe TB disease.

In a pseudopopulation simulating intervention to eliminate loss to follow-up, the risk difference in treatment success by smoking status decreased to -1.9 percentage points. This finding supports that complex adherence-related pathways leading to loss to follow-up were a driver of worse TB treatment outcomes among people who smoked. Although we observed a higher frequency of loss to follow-up among people who smoked, consistent with other studies [11, 31], intervening on this outcome was not guaranteed to increase treatment success. For example, if poor clinical evolution contributed to early treatment discontinuation, intervening on loss to follow-up may simply increase the number of observed treatment failures. Our analytic approach accounted for this potential scenario by including time-varying factors associated with loss to follow-up and unfavorable treatment outcomes (i.e., measures of TB disease severity and TB medication adherence) in our inverse probability of censoring weights. The attenuated risk difference when intervening on loss to follow-up suggests that interventions that facilitate retention in care could reduce the observed difference in TB treatment outcomes by smoking status. The reasons why people disengage from MDR/RR-TB treatment are complex [18, 32, 33], but evidence supports interventions providing psychosocial support throughout TB treatment, such as through counseling sessions and home visits by healthcare workers, as one possible way [34]. Although such interventions might be broadly beneficial, further research is

needed to understand how reasons for loss to follow-up might differ for specific groups (e.g., people who smoke) to optimize and better target interventions.

The remaining difference in TB treatment outcomes after eliminating loss to follow-up could plausibly be attributed to random variability or to a direct biological effect of smoking on TB treatment failure. Evidence from drug-susceptible TB supports that smoking cessation after a TB diagnosis and continuing not to smoke during treatment may increase treatment success and lower recurrence compared with those who continue to smoke [35, 36]. Recognizing the intersections in TB and lung health, the WHO recommends an integrated approach to care [37], for example implementing guideline recommendations on tobacco cessation [38] into the delivery of MDR/RR-TB treatment. Implementation research would be beneficial to inform how to optimally integrate services and should consider the multiple issues that face people with TB, not limited to complex social and economic contexts and comorbidities related to both physical and mental health.

Strengths of this work include applying a causal inference framework when designing the analysis, including the use of directed acyclic graphs to guide analysis decisions and weighting to appropriately account for baseline and on-treatment factors that predicted loss to follow-up. Our findings should also be interpreted in the context of limitations. The definition of smoking status is subject to potential misclassification, for example, due to underreporting of smoking, which we would expect to bias our findings towards the null. Since smoking was only assessed at enrollment, we do not know if individuals quit smoking during treatment. Despite analyzing a large cohort, we may not have had sufficient power to detect statistically significant differences in our adjusted analyses. However, since we aimed to estimate causal effects, our interpretation focused on the magnitude and precision of these effects instead. To provide further confidence in our findings, we would recommend replication in other cohorts. Most people who smoked were in post-Soviet countries, so although we leveraged a multicountry cohort, generalizability may still be limited. Despite our best efforts to identify and control for

potential confounders, residual confounding remains a possibility and some potential confounders were not measured, e.g., mental health symptoms, both of which might have resulted in bias.

People who smoked had a lower frequency of MDR/RR-TB treatment success compared with those who did not smoke. In a pseudopopulation simulating intervention on loss to follow-up, the difference in treatment success by smoking status was substantially reduced but not eliminated. This finding suggests that complex pathways related to retention in care were the main driver of this effect, although other pathways, such as those related to the direct biological effects of smoking, may also contribute. Implementing both interventions to reduce loss to follow-up and smoking cessation services could be key to improving MDR/RR-TB treatment outcomes among people who smoke.

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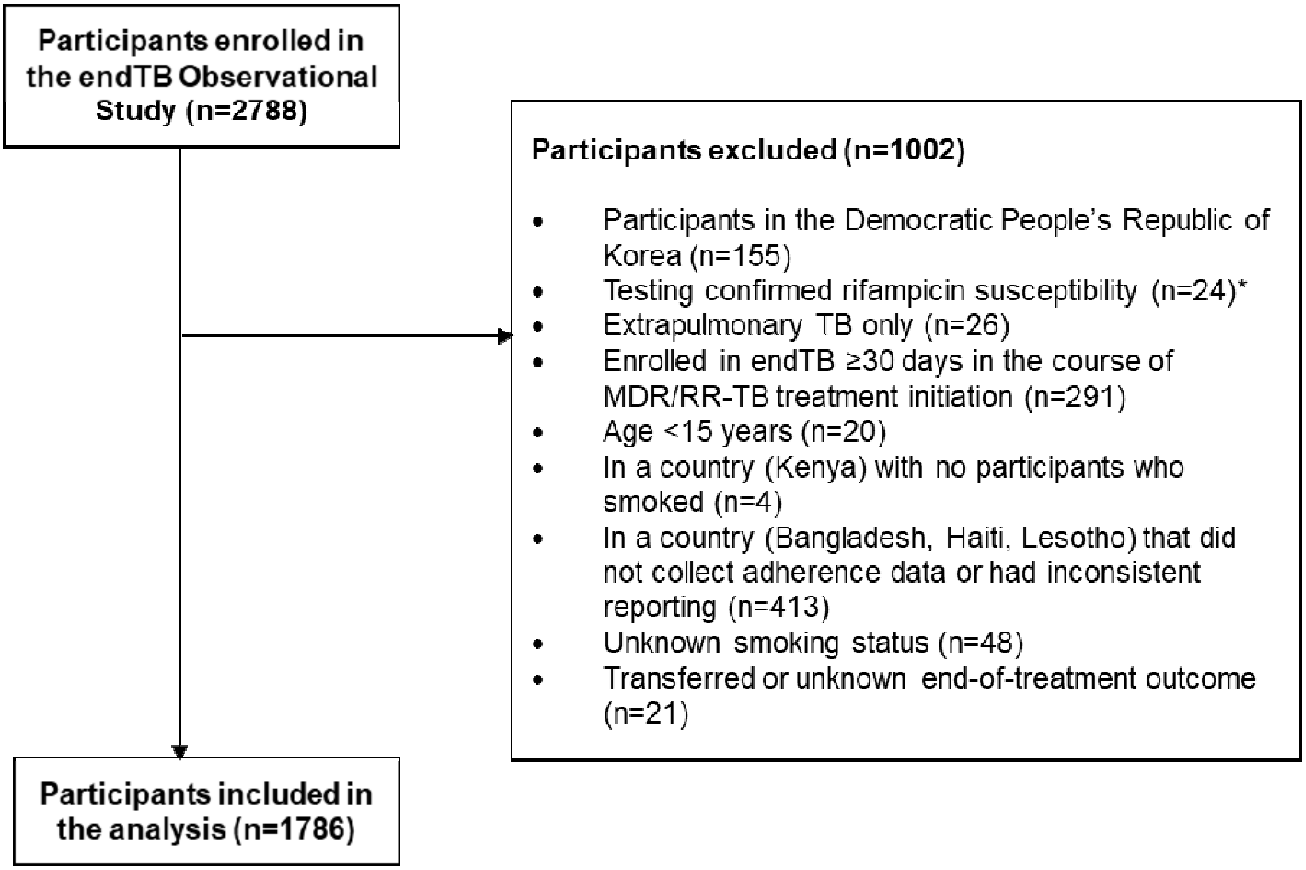

Figure 1. Flowchart of participants enrolled in the endTB Observational Study and their inclusion in this analysis

MDR/RR, multidrug-resistant or rifampicin-resistant; TB, tuberculosis.

*n=32 participants did not have rifampicin testing results and we were not excluded for this reason.

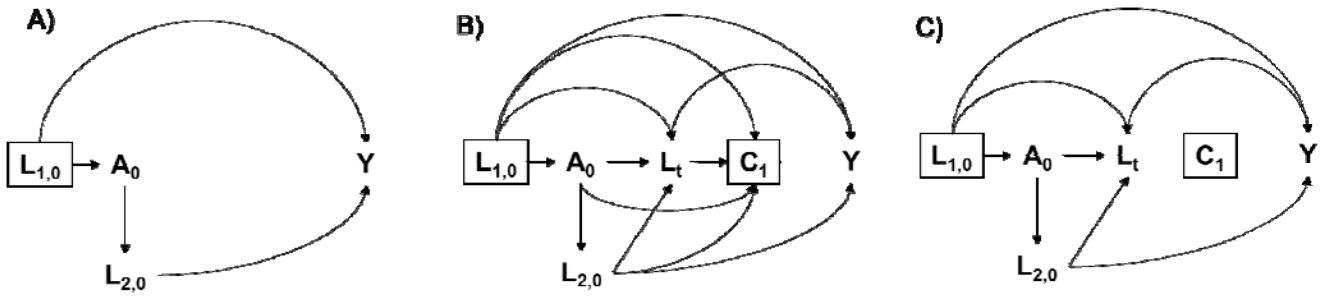

Figure 2. Directed acyclic graphs for the relationship between cigarette smoking and MDR/RR-TB end-of-treatment outcomes

$L_{1,0}$: Baseline confounders: demographics (country, sex, age), social history (ever incarcerated, refugee/displaced person/migrant, drinks alcohol, drug use), and comorbidities (HIV, hepatitis C, diabetes, underweight); **$L_{2,0}$:** Baseline indicators of TB disease severity (sputum smear and culture positivity, and cavitary disease); **A_0:** Cigarette smoking status at enrollment; **L_t:** On-treatment factors on the causal path from A_0 to Y: time-varying indicators of TB disease severity (sputum smear and culture positivity, cavitary disease) and monthly TB treatment adherence rate; **C_1:** Lost to follow-up; **Y:** Successful or unsuccessful MDR/RR-TB treatment outcome.

In A), the directed acyclic graph shows the hypothesized causal relationship between cigarette smoking status at enrollment (A_0) and a successful (cured/completed) or unsuccessful (treatment failure/death/lost to follow-up) MDR/RR-TB treatment outcome (Y). The analysis conditioned on baseline confounders ($L_{1,0}$), but not baseline indicators of TB disease severity ($L_{2,0}$) which are expected to be on the causal path between A_0 and Y as a mediator. We explored adjusting for $L_{2,0}$ in a sensitivity analysis, treating it as a potential confounder.

In B), the directed acyclic graph shows the causal relationship between A_0 and Y, but participants who were lost to follow-up (C_1) are censored. We also include additional time-varying variables (L_t) expected to be affected by smoking and associated with loss to follow-up and the MDR/RR-TB treatment outcome (Y).

In C), the directed acyclic graph depicts the causal relationship between A_0 and Y, applying stabilized inverse probability of censoring weights to uncensored individuals (i.e., those who were not lost to follow-up) that were conditional on A_0, $L_{1,0}$, $L_{2,0}$, and L_t. Applying these weights and additionally adjusting for $L_{1,0}$ in the final model effectively removed all of the arrows pointing to C_1, creating a pseudopopulation that would exist had loss to follow-up not happened.

Table 1. Characteristics at cohort enrollment among participants included in the analysis, overall and by cigarette smoking status

Characteristic at cohort enrollment	n	Overall, n=1786 n (%)	Smokes cigarettes? Yes, n=539 n (%)	No, n=1247 n (%)
Demographics				
Country	1786			
Post-Soviet country (Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan)		1056 (59.1)	500 (92.8)	556 (44.6)
Other country (Ethiopia, Indonesia, Myanmar, Pakistan, Peru, South Africa, Vietnam)		730 (40.9)	39 (7.2)	691 (55.4)
Male sex	1786	1136 (63.6)	480 (89.1)	656 (52.6)
Age in years, median (interquartile range; range)	1786	35 (27–46; 15–83)	41 (34–50; 17–70)	32 (25–43; 15–83)
Social history				
Married or living with partner	1780	919 (51.6)	259 (48.4)	660 (53.0)
Employed	1777	270 (15.2)	77 (14.4)	193 (15.5)
Homeless in past year	1727	69 (4.0)	24 (4.8)	45 (3.7)
Ever incarcerated	1485	273 (18.4)	185 (35.4)	88 (9.2)
Refugee, displaced person, or migrant	1757	57 (3.2)	33 (6.4)	24 (1.9)
Drinks alcohol	1762	216 (12.3)	177 (33.5)	39 (3.2)
Used non-prescribed illicit drugs and/or intravenous drugs in past year	1718	93 (5.4)	63 (12.9)	30 (2.4)
Comorbidities				
HIV	1785	118 (6.6)	45 (8.4)	73 (5.9)
Hepatitis B virus infection	1782	73 (4.1)	27 (5.0)	46 (3.7)
Hepatitis C virus infection	1782	246 (13.8)	155 (28.8)	91 (7.3)
Diabetes	1785	243 (13.6)	60 (11.2)	183 (14.7)
Underweight (body mass index <18.5 kg/m^2)	1777	647 (36.4)	159 (29.7)	488 (39.3)
TB disease characteristics				
Concurrent extrapulmonary disease	1786	30 (1.7)	13 (2.4)	17 (1.4)
Bilateral disease	1710	1137 (66.5)	377 (71.4)	760 (64.3)
Fibrosis	1646	1105 (67.1)	345 (67.9)	760 (66.8)
Cavitary disease	1676	1140 (68.0)	349 (67.1)	791 (68.4)
Positive sputum smear	1683	946 (56.2)	314 (61.8)	632 (53.8)
Sputum smear grade (among positive)	946			
Scanty		70 (7.4)	28 (8.9)	42 (6.7)
1+		420 (44.4)	155 (49.4)	265 (41.9)
2+		228 (24.1)	57 (18.2)	171 (27.1)
3+		228 (24.1)	74 (23.6)	154 (24.4)
Extensive disease (i.e., cavitary disease and smear grade 3+)	1582	172 (10.9)	53 (10.8)	119 (10.9)
Positive sputum culture	1656	1049 (63.4)	350 (70.9)	699 (60.2)
Known prior TB treatment with second-line drugs	1471	1282 (87.2)	405 (89.8)	877 (86.0)
Fluoroquinolone resistance	1701	1122 (66.0)	358 (68.9)	764 (64.7)
Initial TB treatment regimen characteristics				
Number of likely effective drugs in regimen,*	1786	4 (4–5; 0–8)	4 (4–5; 0–7)	4 (4–5; 0–8)

median (interquartile range; range)				
Number of WHO Group A drugs (moxifloxacin or levofloxacin; bedaquiline; linezolid), median (interquartile range; range)	1786	2 (2–3; 0–3)	2 (2–3; 0–3)	2 (2–3; 0–3)
Number of WHO Group B drugs (clofazimine; cycloserine or terizidone), median (interquartile range; range)	1786	1 (1–2; 0–2)	1 (1–2; 0–2)	1 (1–2; 0–2)

MDR/RR-TB, multidrug-resistant/rifampicin-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis

*A drug was considered likely effective if all reported resistance testing to that drug confirmed susceptibility, or, in the absence of drug susceptibility testing, the individual had not previously received the drug for one month or longer.

Table 2. Frequencies of clinician-assigned MDR/RR-TB end-of-treatment outcomes, overall and by cigarette smoking status

Outcomes	Overall, n=1786 n (%)	Smokes cigarettes? Yes, n=539 n (%)	No, n=1247 n (%)
Successful treatment	**1397 (78.2)**	**396 (73.5)**	**1001 (80.3)**
Cured	1299 (72.7)	368 (68.3)	931 (74.7)
Completed	98 (5.5)	28 (5.2)	70 (5.6)
Unsuccessful treatment	**389 (21.8)**	**143 (26.5)**	**246 (19.7)**
Death (and causes)	137 (7.7)	27 (5.0)	110 (8.8)
TB-related*	64 (3.6)	12 (2.2)	52 (4.2)
Non-TB-related	47 (2.6)	11 (2.0)	36 (2.9)
Unknown	26 (1.5)	4 (0.7)	22 (1.8)
Treatment failure (and reasons)†	97 (5.4)	46 (8.5)	51 (4.1)
Lack of sputum culture conversion	32 (1.8)	19 (3.5)	13 (1.0)
Bacteriological reversion	44 (2.5)	15 (2.8)	29 (2.3)
Adverse drug reaction	10 (0.6)	8 (1.5)	2 (0.2)
Other/Unknown	15 (0.8)	7 (1.3)	8 (0.6)
Lost to follow-up (and reasons)†	155 (8.7)	70 (13.0)	85 (6.8)
Participant refusal	71 (4.0)	27 (5.0)	44 (3.5)
Left region/country	32 (1.8)	21 (3.9)	11 (0.9)
Family, financial, or other social problems	35 (2.0)	12 (2.2)	23 (1.8)
Substance abuse	12 (0.7)	5 (0.6)	7 (0.6)
Other/Unknown	36 (2.0)	14 (2.6)	22 (1.8)

*TB was known to be an immediate or contributing cause of death, or death was related to surgery/treatment of TB.
†Participants may have more than one clinician-assigned reason for treatment failure (with the exception of simultaneous lack of sputum culture conversion and bacteriological reversion) or loss to follow-up.

Table 3. Effect of smoking status on a successful MDR/RR-TB end-of-treatment outcome and impact of intervening on loss to follow-up

Outcome and analysis*	Risk, percentage		Risk difference, percentage points (95% CI)	Risk ratio (95% CI)
	Participants who smoked	Participants who did not smoke		
Successful treatment (versus unsuccessful treatment)				
Unadjusted	73.5	80.3	-6.8 (-11.1, -2.6)	0.92 (0.86, 0.97)
Adjusted for baseline confounders[†]	73.8	79.0	-5.2 (-14.1, 3.2)	0.93 (0.82, 1.04)
Adjusted for baseline confounders[†] and baseline indicators of TB disease severity[‡] (sensitivity analysis)	74.5	78.9	-4.4 (-12.7, 3.2)	0.94 (0.84, 1.04)
Successful treatment (versus unsuccessful treatment, in a pseudopopulation intervening on loss to follow-up)				
IP weighted and adjusted for baseline confounders[†]	84.0	85.9	-1.9 (-10.2, 5.1)	0.98 (0.88, 1.06)

CI, confidence interval; IP, inverse probability; TB, tuberculosis.

*Generalized linear models with logit links were used to estimate risks separately by smoking status and risk differences and ratios were computed by standardizing mean predicted risks of the outcome. The bias-corrected and accelerated bootstrap with 1000 resamples was used to obtain 95% confidence intervals for the risk differences and ratios. The missing indicator method used to handle missing data on baseline confounders except for HIV status (n=1 [0.06%)], hepatitis C (n=4 [0.2%]), and diabetes (n=1 [0.06%)] for which we assumed the condition to be absent because the small number of missing observations precluded use of missing indicators.

[†]Demographics (country, sex, age), social history (ever incarcerated, refugee/displaced person/migrant, drinks alcohol, drug use), and comorbidities (HIV, hepatitis C, diabetes, underweight).

[‡]Sputum and culture positivity, and presence of cavitary disease.