Factors associated with screening failure and study withdrawal in a clinical trial of multidrug-resistant tuberculosis

Alvaro Schwalb[1], Rodrigo Cachay[1], Alicia Wright[2], Patrick PJ Phillips[3], Pawandeep Kaur[4], Andreas H. Diacon[5], César Ugarte-Gil[1], Carole D. Mitnick[6], Timothy R. Sterling[2], Eduardo Gotuzzo[1], C. Robert Horsburgh Jr[4]

[1]*Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru;* [2]*Vanderbilt University Medical Center, Vanderbilt Tuberculosis Center, Nashville, TN, United States of America;* [3]*University of California San Francisco Center for Tuberculosis, San Francisco, CA, United States of America;* [4]*Boston University, Departments of Epidemiology, Biostatistics, Global Health and Medicine, Boston, MA, United States of America;* [5]*TASK Applied Science and Stellenbosch University, Cape Town, South Africa;* [6]*School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru;* [6]*Harvard Medical School, Department of Global Health & Social Medicine, Boston, MA, United States of America*

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Summary:

Setting: Multidrug-resistant tuberculosis (MDR-TB) clinical trial in Lima, Peru and Cape Town, South Africa.

Objective: To identify baseline factors associated with screening failure and study withdrawal in an MDR-TB clinical trial.

Design: We screened patients for a randomized, blinded, phase II trial which assessed culture conversion over the first six months of treatment with varying doses of levofloxacin plus an optimized background regimen (ClinicalTrials.gov: NCT01918397). We identified factors for screening failure and study withdrawal using Poisson regression to calculate prevalence ratios (PR) and Cox proportional hazard regression to calculate hazard ratios (HR), respectively. We adjusted for factors with p-value < 0.2.

Results: There were 255 patients screened, of whom 144 (56.5%) failed screening. The most common reason for screening failure was an unsuitable resistance profile on sputum-based molecular susceptibility testing (105; 72.9%). No significant baseline predictors of screening failure were identified in the multivariable model. Of the 111 who were enrolled, 33 (30%) failed to complete treatment mostly for non-adherence and consent withdrawal. No baseline factors predicted study withdrawal in the multivariable model.

Conclusion: No baseline factors were independently associated with either screening failure or study withdrawal in this secondary analysis of a TB-MDR clinical trial.

Introduction:

Randomized clinical trials (RCTs) are considered a gold standard for biomedical research, providing reliable evidence on efficacy and safety of an intervention.[1] Abundant efforts and resources are placed in RCTs to ensure that they are conducted in a manner that ultimately leads to an answer to the stipulated research question. The process of selecting suitable participants will generally be limited by exclusions before and after randomization. Eligibility criteria of the trial will dictate exclusions occurring prior to group assignment, and after enrolment protocol deviations, late discovery of participant ineligibility, and mainly loss to follow-up will reduce the trial population.[2] Poor participant selection and attrition threaten to affect the statistical power, the internal validity and, consequently, the generalizability of the trial.[2–4]

Tuberculosis (TB) prevention and care greatly benefits from the results of clinical trials. To reach the 2035 End TB Strategy targets, the development and uptake of new treatments will be key.[5] However, TB clinical trials often require long follow-up periods to adequately determine participants' treatment outcomes. The treatment period is usually even greater for trials evaluating treatments for drug-resistant TB (DR-TB); additionally, drugs used for DR-TB are likely to cause more adverse events and lead to loss of follow-up.[6,7] While alternative designs are implemented to adapt to the challenges currently posed by the DR-TB epidemic,[8] robust participant recruitment and study retention are markers of study quality.

Previous studies have assessed factors associated with trial non-completion in the context of TB, but the experience of trials for multidrug-resistant tuberculosis (MDR-TB) is limited.[9–12] Additionally, while ineligibility is an issue related to protocol design independently specific to each study, it is worth exploring as many trials struggle to meet their planned sample size.[13] Therefore, we evaluated baseline factors associated with screening failure and study withdrawal in an MDR-TB clinical trial.

Methods:

Study design:

We evaluated screening failures and study withdrawal in participants in a pulmonary MDR-TB clinical trial (ClinicalTrials.gov: NCT01918397). Tuberculosis Trials Consortium (TBTC) Study

32 (Opti-Q) was a randomized, blinded, phase II clinical trial which assessed culture conversion over the first 6 months of treatment with varying doses of levofloxacin (11, 14, 17, and 20 mg/kg/day) plus an optimized background regimen; the latter was selected at the discretion of the investigators to conform to local guidelines.[14] The trial was conducted in three clinical sites (two in Lima, Peru and one in Cape Town, South Africa) from December 2014 to June 2017. At the start of the study, guidelines for empirical treatment of MDR-TB in Lima included a fluoroquinolone plus kanamycin, pyrazinamide, ethambutol, and cycloserine. In Cape Town, terizidone was used regularly, while ethambutol and cycloserine were not.[14] The Opti-Q study protocol and informed consent forms are available online.[14]

Participant eligibility

Potential participants were identified from the community health centers where, within the TB Program, patients evaluated (due to poor treatment response, treatment failure, etc. in TB episode) or confirmed of MDR-TB were treated. Patients newly registered to initiate MDR-TB treatment were asked to participate. Eligible participants consisted of adults with smear-positive pulmonary MDR-TB, confirmed as isoniazid and rifampicin-resistant by GenoType MTBDRplus Line Probe Assay (Hain Lifescience GmbH, Nehren, Germany) and fluoroquinolone-susceptible by GenoType MTBDRsl Line Probe Assay (Hain Lifescience GmbH, Nehren, Germany). Exclusion criteria included: poorly controlled diabetes mellitus (HbA1c >9%), concurrent use of known QT-prolonging drugs, known glucose-6-phosphate dehydrogenase deficiency, current pregnancy, or breastfeeding, anticipated surgical intervention for pulmonary TB treatment, among others.[14]

Statistical analysis

Baseline characteristics for all screened participants were obtained from the study database. Data included demographic information, risk factors for DR-TB (history of TB, drug use, unemployment, homelessness), and comorbidities such as diabetes mellitus and HIV serostatus. The Karnofsky Performance Score was used to classify participants according to their functional impairment; scores > 80 indicate the ability to perform normal activities, including work, without special care.[15] Prior treatment outcomes of participants who reported a history of active TB were either positive (cure/completed), or negative (treatment failure, or loss to follow-up). Screening failure was defined as not fulfilling all inclusion criteria, or meeting any of the exclusion criteria.

Enrolled participants were divided further according to per protocol treatment completion; participants were considered to have completed treatment if they received a minimum of 168 doses (24 weeks of treatment) within 200 days of initiation of the study regimen.

For the analysis, we presented categorical variables with frequencies and percentages, and continuous variables with medians and interquartile ranges. We identified baseline factors associated with screening failures using Poisson regression with robust variance, calculating crude prevalence ratios (cPR) in the bivariable analysis. We executed the multivariable analysis and presented adjusted prevalence ratios (aPR) by controlling for factors that were found to have p-value < 0.2 in the bivariable analysis. We identified baseline factors associated with study withdrawal using Cox proportional hazards regression calculating crude hazard ratios (cHR) in the bivariable analysis. Likewise, we executed the multivariable analysis and presented adjusted hazard ratios (aHR) by controlling for factors that had a p-value < 0.2 in the bivariable analysis. For all PR and HR, 95% confidence intervals (CIs) were calculated. Statistical analyses were done using Stata SE 16.1 (StataCorp, US).

Results:

Throughout the enrolment period, 255 potential participants were screened, of whom 163 (63.9%) were males and the median age was 31 years old (IQR:22-43). A history of active TB was reported in 104 (40.8%) screened patients; of those, 32 (30.8%) reported a negative treatment outcome from a previous TB episode. HIV infection and diabetes were reported in 60 (23.8%) and 12 (4.7%) patients, respectively; other demographic characteristics can be seen in **Table 1.** Overall, 111 participants (43.5%) were enrolled.

There were 144 (56.5%) screening failures. The main reason for failing screening was susceptibility to isoniazid and/or rifampicin or resistance to fluoroquinolones detected in the participant's baseline sputum (105; 72.9%). The rest of the reported reasons for screening failure are listed in **Figure 1**. In the bivariable analysis, there was weak evidence of an association between screening failure with a prior TB episode which resulted in cure or treatment completion (cPR:1.35; 95%CI:1.08-1.69) and older age (cPR:1.31; 95%CI:1.05-1.64). Additionally, there was some evidence of an association between screening failures with diabetes (cPR:1.51; 95%CI:1.14-

1.99). In the multivariable model, fitted with all the factors that met the < 0.2 p-value threshold in the bivariable analysis, no factor presented robust evidence of an association with screening failures **(Table 2)**.

Of 111 enrolled participants, 33 (29.7%) did not complete the minimum required doses; the reasons are listed in **Figure 1**. Non-adherence and consent withdrawal were the main reported reasons, contributing to 13 (39.4%) study withdrawals. In the bivariable analysis, there was some evidence of the association between non-intravenous drug use with study withdrawal (cHR:2.53; 95%CI:1.17-5.46). In the multivariable analysis, no factors were associated with higher hazard of study withdrawal **(Table 3)**. The proportional-hazards assumption was tested based on Schoenfeld residuals after fitting the multivariable model, resulting in a p-value of 0.673, therefore, the assumption holds for the model.

Discussion:

In this secondary data analysis of an MDR-TB clinical trial, no baseline factors were independently associated with either screening failure or study withdrawal. Identification of such factors would aid in the development of future studies directed at the same population to facilitate participant accrual and retention. Despite the lack of conclusive findings, several discussion points are raised.

Regarding participant retention, the importance of finding ways to retain participants with a history of an unsuccessful prior treatment outcome is essential, since this is common among patients with MDR-TB. According to the WHO Global Tuberculosis Report, while there have been increases in treatment cure rates for drug-resistant TB, these are still unacceptably low; in 2017 Africa and the Americas reported rates of 64% and 59%, respectively.[16] Furthermore, loss-to-follow up, as an unsuccessful treatment outcome, contributes to 13% and 22% of such outcomes, respectively, in these regions.[16] When there is loss to follow-up in a clinical trial, not only is the integrity of the trial jeopardized, but if the trial demonstrates that the regimen being studied works among patients with a history of a prior unsuccessful treatment outcome, it could result in underperformance of the regimen in a real-world scenario. Additionally, exclusion of these patients would prove to be an obstacle in completing trial recruitment on a reasonable timeline. Previous lessons from MDR-TB trials have reported intensive efforts to retain participants.[11]

While our findings failed to identify that prior TB episodes are an important risk factor for the development of MDR-TB, other studies suggest the opposite.[17] For some patients, non-adherence or treatment non-completion might be embedded in the pathway towards resistance and, therefore, under a more complex, lengthy, and arduous treatment course, similar outcomes are likely.[11] Distrust in the TB Program and its healthcare workers could also arise if despite treatment completion patients ultimately develop resistance.[11] Baseline factors could provide insight on participants who might require closer monitoring during the conduct of the trial to increase retention and ensure trial completion. Preventing loss to follow-up is critically important, as outcome information is frequently not attainable or not very descriptive of the participant's reason for withdrawal, as in the case of our study.[2] A qualitative approach, such as an open question, might encompass more reasons for withdrawal than a few pre-specified options.

In the bivariable analysis, some factors were found to have association with the outcomes of interest; nonetheless, some results might be spurious. For instance, our findings suggest that there was some evidence that prior history of TB – particularly with a successful outcome – was to be associated to screening failures. Eligible participants for this trial ideally shared this characteristic, as other studies have identified previous episodes of TB as a strong determinant for the development of MDR-TB .[17–19] Therefore, our results are contradictory and might be explained by a limited ability to control for confounding, as the sample size was inadequate. Furthermore, stronger evidence was found with a previous successful treatment, which again is counterintuitive and raises the issue of the small sample of participants. Similarly, while the presence of diabetes does entail a higher likelihood of screening failure as uncontrolled HbA1c is an exclusion criterion, it is difficult to conclude on the association between non-IV drug use and study withdrawal, due to low numbers and high potential for confounders. If the results had been conclusive, suggesting that participant selection be limited to patients who do not share these characteristics would lead to heavily affected patient accrual and generalizability. Other lessons from MDR-TB trials have shown that restricting criteria for participation greatly reduces the population pool,[20] which would equally negatively impact the study if the desired sample size is not reached. Moreover, the conduction of clinical trials in low-resource settings are crucial for some patient's well-being, since

potential participants benefit from baseline tests, such as line probe assays, that are otherwise not available through the public health system.[20]

Our study had some limitations. While ineligibility is not predictable as it is dependent on study design, TB trials (and in particular MDR-TB trials) dictate certain "fixed" inclusion/exclusion criteria that can be associated with participant characteristics. Exploring screening failures is important as these visits demand effort and can be costly.[21] Another significant limitation of the study was that there was no further investigation of the reasons for study participant withdrawal through the use of questionnaires of patient interviews. This secondary analysis of a clinical trial database provides partial understanding of the factors at play with withdrawal, including change of personal/work circumstances, mental health, and the effect of adverse events. The frequency and severity of adverse events were likely a non-trivial factor in the pathway to study withdrawal which were not explored in this study. Due to the continuous experience of adverse effects or due to delivery mode (some older background regimens included the daily use of injectable drugs), participants are likely to be lost to follow-up.[11] With the move to an all-oral regimen, the pain, inconvenience, and side effects of the injectable agents will be avoided, hopefully resulting in fewer withdrawals due to unrecognized drug intolerance. Moreover, explicit reasons for withdrawing were not always provided by the participants, although study staff suspected a combination of psychological factors.[16] Potentially, there was also information bias in the ascertainment of risk factors for MDR-TB, particularly drug use and alcoholism. Furthermore, the sample size was less than desired to ascertain an adequate power of these secondary analyses. The trial setting is a strength of the study; both Peru and South Africa are included in the WHO high MDR-TB burden countries list so they provide a representative sample of MDR-TB patients.[16]

Conclusions:

No baseline factors were independently associated with either screening failure or study withdrawal in this secondary analysis of a TB-MDR clinical trial. In lieu of the identification of study withdrawal predictors in this study, we suggest that MDR-TB clinical trials ensure ample patient follow-up and adequate management of adverse events or drug toxicities could improve retention. Revaluation and modification of study procedures should take place after concluding a clinical trial to improve participant support in future studies. Collection and analysis of individual

data, in the form of questionnaires or interviews, in other MDR-TB treatment trials may reveal a clearer picture of predictors for study withdrawal.

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References:

1 Schulz K F, Grimes D A. The Lancet handbook of essential concepts in clinical research. Lancet, 2006.

2 Schulz K F, Grimes D A. Sample size slippages in randomised trials: exclusions and the lost and wayward. Lancet 2002; 359(9308): 781–785.

3 Kadam R A, Borde S U, Madas S A, Salvi S S, Limaye S S. Challenges in recruitment and retention of clinical trial subjects. Perspect Clin Res 2016; 7(3): 137–143.

4 Fewtrell M S, Kennedy K, Singhal A, et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child 2008; 93(6): 458–461.

5 WHO. WHO End TB Strategy. World Health Organization. https://www.who.int/tb/End_TB_brochure.pdf?ua=1 (2014).

6 Lan Z, Ahmad N, Baghaei P, et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med 2020; 8(4): 383–394.

7 Merid M W, Muluneh A G, Yenit M K, Kassa G M. Treatment interruption and associated factors among patients registered on drug-resistant tuberculosis treatment in Amhara regional state, Ethiopia: 2010-2017. PLoS One 2020; 15(10): e0240564.

8 Phillips P P J, Mitnick C D, Neaton J D, Nahid P, Lienhardt C, Nunn A J. Keeping phase III tuberculosis trials relevant: Adapting to a rapidly changing landscape. PLoS Med 2019; 16(3): e1002767.

9 Conwell D S, Mosher A, Khan A, et al. Factors associated with loss to follow-up in a large tuberculosis treatment trial (TBTC Study 22). Contemp Clin Trials 2007; 28(3): 288–294.

10 Moro R N, Sterling T R, Saukkonen J, et al. Factors associated with non-completion of follow-up: 33-month latent tuberculous infection treatment trial. Int J Tuberc Lung Dis 2017; 21(3): 286–296.

11 Padayatchi N, Mac Kenzie W R, Hirsch-Moverman Y, et al. Lessons from a randomised clinical trial for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2012; 16(12): 1582–1587.

12 Purchase S, Batist E, Mmile N, et al. Challenges in recruiting children to a multidrug-resistant TB prevention trial. Int J Tuberc Lung Dis 2021; 25(10): 814–822.

13 Sully B G O, Julious S A, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. Trials 2013; 14: 166.

14 Bouton T C, Phillips P P J, Mitnick C D, et al. An optimized background regimen design to evaluate the contribution of levofloxacin to multidrug-resistant tuberculosis treatment regimens: study protocol for a randomized controlled trial. Trials 2017; 18(1): 563.

15 Karnofsky D A, Abelmann W H, Craver L F, Burchenal J H. The use of the nitrogen mustards in the palliative treatment of carcinoma.With particular reference to bronchogenic carcinoma. Cancer 1948; 1(4): 634–656.

16 WHO. Global Tuberculosis Report 2020. Geneva: World Health Organization, 2020.

17 Espinal M A, Laserson K, Camacho M, et al. Determinants of drug-resistant tuberculosis: analysis of 11 countries. Int J Tuberc Lung Dis 2001; 5(10): 887–893.

18 Faustini A, Hall A J, Perucci C A. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. Thorax 2006; 61(2): 158–163.

19 Zhang C, Wang Y, Shi G, et al. Determinants of multidrug-resistant tuberculosis in Henan province in China: a case control study. BMC Public Health 2016; 16: 42.

20 Siwendu S, Mitchell M, Diacon A H, von Groote-Bidlingmaier F. Recruitment challenges for clinical trials with novel regimens for drug-resistant tuberculosis. Eur Respir J 2016; 47(2): 670–672.

21 Gul R B, Ali P A. Clinical trials: the challenge of recruitment and retention of participants. J Clin Nurs 2010; 19(1–2): 227–233.

Table 1. Demographic characteristics of screened patients.

Variable (n = 255)	**n (%)**
Screened and enrolled	111 (43.5)
Screened: TBTC Site 33, Cape Town, South Africa (% of total screened)	111 (43.5)
Enrolled (% of screened at site)	48 (43.2)
Screened: TBTC Site 38, Lima, Peru (% of total screened)	56 (21.9)
Enrolled (% of screened at site)	24 (42.9)
Screened: TBTC Site 99, Lima, Peru (% of total screened)	88 (34.5)
Enrolled (% of screened at site)	39 (44.3)
Country: Peru	144 (56.5)
Male sex	164 (63.9)
Age, years, median (IQR)	31 (22-43)
History of previous TB	104 (40.8)
No history of TB	151 (59.2)
Cure/completion	72 (28.2)
Negative previous treatment outcome	32 (12.6)
Treatment failure	4 (1.6)
Failed to adhere	17 (6.6)
Other	11 (4.3)
BMI, kg/m^2, median (IQR)	20.6 (18.5-23.3)
Karnofsky score ≤ 80	106 (41.6)
Homelessness	7 (2.8)
Unemployment	92 (36.4)
Non-IV drug use	29 (11.5)
IV drug use	0
Smoker	114 (45.1)
Diabetes	12 (4.7)
HIV	60 (23.8)
CD4 count among HIV positive, $cells/mm^3$, median (IQR)	196 (92-366)

Values are n (%) unless noted otherwise. Missing data: Homelessness (n=2), unemployment (n=2), non-IV drug use (n=2), IV drug use (n=2), smoker (n=2), HIV (n=3). TB: Tuberculosis; BMI: Body mass index; IV: Intravenous; HIV: Human immunodeficiency virus.

Table 2. Bivariable and multivariable analyses of factors associated with screening failure.

Variable	Enrolled (n = 111)	Screening failure (n = 144)	cPR (95%CI)	P value	aPR (95%CI)*	P value
Male sex	68 (61.3)	95 (66.0)	1.09 (0.87-1.38)	0.446		
Country: Peru	63 (56.8)	81 (56.3)	0.99 (0.79-1.23)	0.936		
Age ≥ median (31 years)	46 (41.4)	82 (56.9)	1.31 (1.05-1.64)	0.016	1.18 (0.91-1.52)	0.206
History of TB	36 (32.4)	68 (47.2)	1.29 (1.05-1.61)	0.015	1.22 (0.98-1.53)	0.075
No history of TB	75 (67.6)	76 (52.8)	-	-	-	-
Prior cure/completion	23 (20.7)	49 (34.0)	1.35 (1.08-1.69)	0.008	1.25 (0.99-1.59)	0.065
Prior negative treatment outcome	13 (11.7)	19 (13.2)	1.18 (0.85-1.64)	0.324	1.16 (0.83-1.63)	0.384
Karnofsky score ≤ 80	40 (36.0)	66 (45.8)	1.19 (0.96-1.47)	0.111	1.17 (0.94-1.45)	0.164
Homelessness	4 (3.6)	3 (2.1)	0.76 (0.32-1.79)	0.531		
Unemployment	35 (31.5)	57 (40.1)	1.17 (0.94-1.46)	0.149	1.09 (0.87-1.36)	0.462
Non-IV drug use	16 (14.4)	13 (9.2)	0.78 (0.51-1.18)	0.242		
Smoker	54 (48.7)	60 (42.3)	0.89 (0.71-1.12)	0.316		
Diabetes	2 (1.8)	10 (6.9)	1.51 (1.14-1.99)	0.004	1.41 (0.99-2.01)	0.054
HIV	22 (19.8)	38 (26.9)	1.18 (0.93-1.49)	0.164	1.03 (0.79-1.34)	0.814

Values are n (%) unless noted otherwise. Missing data: Homelessness (n=2), unemployment (n=2), non-IV drug use (n=2), smoker (n=2), HIV (n=3). Negative treatment outcome: treatment failure, non-completion, resistance or other. TB: Tuberculosis; IV: Intravenous; HIV: Human immunodeficiency virus.

*Multivariable model includes history of TB, age, Karnofsky score, unemployment, diabetes, and HIV

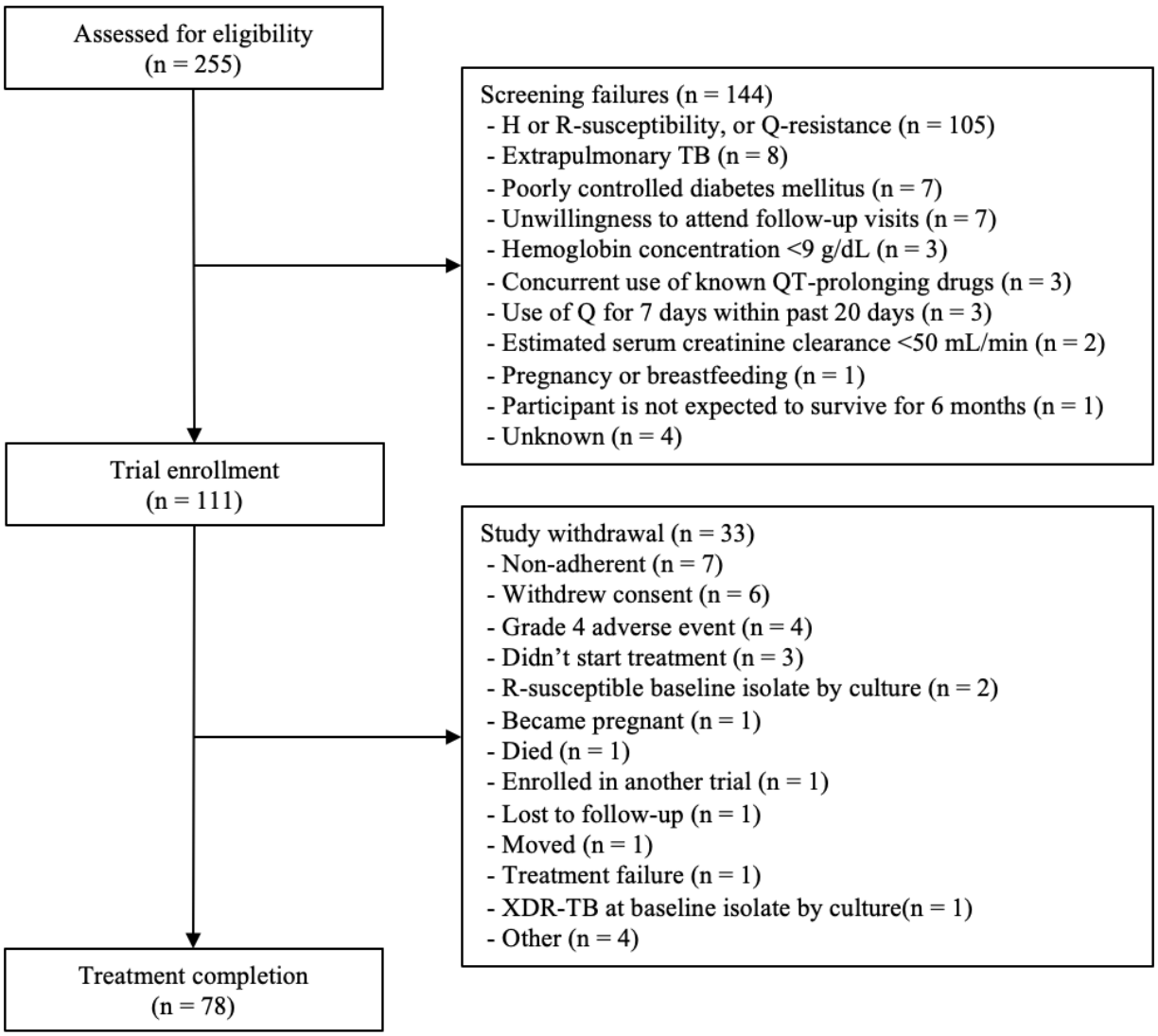
Table 3. Bivariable and multivariable analyses of factors associated with study withdrawal.

Variable	Treatment completion (n = 78)	Study withdrawal (n = 33)	cHR (95%CI)	P value	aHR (95%CI)*	P value
Male sex	44 (56.4)	24 (72.7)	1.76 (0.82-3.78)	0.150	1.61 (0.69-3.74)	0.265
Age ≥ median (31 years)	33 (42.3)	13 (39.4)	0.85 (0.42-1.71)	0.650		
Country: Peru	48 (61.5)	15 (45.5)	0.69 (0.35-1.36)	0.280		
History of TB	25 (32.1)	11 (33.3)	1.02 (0.49-2.11)	0.952	0.92 (0.44-1.91)	0.822
No history of TB	53 (67.9)	22 (66.7)	-	-	-	-
Prior cure/completion	19 (24.4)	4 (12.1)	0.58 (0.19-1.67)	0.309	0.50 (0.17-1.48)	0.212
Prior negative treatment outcome	6 (7.7)	7 (21.2)	1.84 (0.78-4.30)	0.161	1.72 (0.72-4.10)	0.224
Karnofsky score ≤ 80	30 (38.5)	10 (30.3)	0.84 (0.39-1.77)	0.646		
Homelessness	3 (3.9)	1 (3.0)	0.83 (0.11-6.05)	0.851		
Unemployment	21 (26.9)	14 (42.4)	1.58 (0.78-3.15)	0.198	1.96 (0.95-4.06)	0.070
Non-IV drug use	7 (8.9)	9 (27.3)	2.53 (1.17-5.46)	0.018	2.00 (0.88-4.54)	0.098
Smoker	38 (48.7)	16 (48.5)	0.89 (0.45-1.78)	0.762		
Diabetes	2 (2.6)	0	-	-		
HIV	13 (16.7)	9 (27.3)	1.50 (0.69-3.23)	0.299		

Values are n (%). Negative treatment outcome: treatment failure, non-completion, resistance or other. TB: Tuberculosis; IV: Intravenous; HIV: Human immunodeficiency virus.

*Multivariable model includes history of TB, sex, unemployment, and non-IV drug use

Figure 1. Opti-Q study flow diagram of screening failures and study withdrawal.



H: Isoniazid; R: Rifampicin; Q: Quinolones; TB: Tuberculosis; XDR: Extensively drug-resistant.