RESEARCH ARTICLE

Treatment outcomes in people with diabetes and multidrug-resistant tuberculosis (MDR TB) enrolled in the STREAM clinical trial
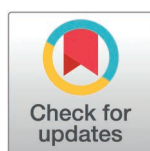
Meera Gurumurthy[1]*, **Narendran Gopalan**[2ʘ], **Leena Patel**[3ʘ], **Andrew Davis**[4],
Vignes Anand Srinivasalu[2], **Shakira Rajaram**[5], **Ruth Goodall**[4], **Gay Bronson**[3],
STREAM Trial Collaboration[¶]

1 Vital Strategies, Singapore, Singapore, **2** Indian Council of Medical Research – National Institute
for Research in Tuberculosis, Chennai, India, **3** Vital Strategies, New York, New York, United States
of America, **4** MRC Clinical Trials Unit at UCL, London, United Kingdom, **5** Wits Health Consortium,
Johannesburg, South Africa

¶ Membership of STREAM Trial Collaboration is provided in the Acknowledgments section
ʘ These two authors contributed equally
* mgurumurthy@vitalstrategies.org

Abstract

There is limited evidence on the effect of DM co-morbidity in those undergoing treatment
for MDR-TB. We report post-hoc analyses of participants from the STREAM Clinical Trial
(Stage 1 and 2 combined). Participants who self-reported diabetes, had random blood glu-
cose ≥200mg/dl at baseline, or reported taking concomitant medication for diabetes were
classified as the DM group. In total, 896 (n=84 DM, n=812 non-DM) and 976 (n=87 DM,
n=889 non-DM) participants were included respectively in the efficacy and safety analyses
reported here. Summary statistics for efficacy and safety outcomes were calculated. Haz-
ard ratios (HR) for time-to-event outcomes were estimated using Cox-proportional hazard
models. Compared to the non-DM group, the DM group were significantly older, more
likely to be male and had a higher BMI. The DM group experienced a significantly higher
proportion of serious adverse events (SAEs) (41% vs. 22%, p<0.001) but was comparable
to the non-DM group on all other safety (grade 3-5 adverse events, deaths, unscheduled
visits) as well as all efficacy parameters (proportion with unfavourable outcome, proportion
FoR, time to FoR and culture conversion) assessed. The STREAM clinical trial experience
indicated that it is possible to achieve similar treatment outcomes in people with MDR-TB
who have a DM co-morbidity. However, this sub-population experienced more SAEs,
underscoring the importance of close monitoring to manage their impact and improve
MDR-TB treatment outcomes.

Introduction

The dual burden of tuberculosis (TB) and diabetes mellitus (DM) is a global public health
concern. Globally, over 1.5 million deaths occurred due to TB in 2020 [1] and DM caused
an estimated 11.3% of total deaths in 2019 [2]. Both TB and DM are reported among the
top 10 causes of death worldwide. [1,3] Further, DM is a known risk-factor for developing

TB [4,5] with higher risks in those with poor glycaemic control. [5] DM results in poorer outcomes such as increased TB treatment failure, delayed culture conversion, higher TB recurrence [6,7] and has also been reported as an independent risk factor of multi-drug resistant TB. [7–9]

Multi-drug resistant TB (MDR-TB), defined as TB resistant to the first-line drugs isoniazid and rifampicin, is a serious threat to public health and has complicated the efforts of TB control programs worldwide. Historically, treatment for MDR-TB have been long-drawn out regimens comprising of less potent and tolerable drugs, resulting in lower rates of treatment success. Several of the top ten countries predicted to have the highest number of cases of DM by 2030 are also among those estimated to have highest MDR-TB prevalence.[1,2] DM therefore poses a significant challenge and evidence-based management of MDR-TB and DM is a public health imperative. The effect of DM on MDR-TB has been reported only in a small number of characterised cohorts [10–12] and treatment for MDR-TB is not optimized for various sub-groups or co-morbidities, including DM.[13] Understanding DM as a co-morbidity in MDR-TB has therefore been identified as a priority area of research. [14,15]

Further, there have been reports of poorer treatment outcomes in those with uncontrolled diabetes [16,17] and suggestions that achieving better glucose control may improve outcomes. [18,19] While several studies report the effect of glycaemic control on treatment outcomes in drug-susceptible TB [17,20–26], there have been none to our knowledge in MDR-TB.

Post-hoc analyses of data from STREAM, a phase 3 randomised control trial that evaluated shorter regimens for MDR-TB [27,28] presented an opportunity to evaluate treatment outcomes in a well-characterized cohort of people with MDR-TB and DM. Further, longitudinal glucose measures available from Stage 2 of STREAM allowed us to perform some preliminary evaluation on factors associated with glucose control in people with MDR-TB. We believe that the results reported, and insights offered here can inform better clinical management of MDR-TB and DM comorbidity.

Methods

Analysis population

Modified intention to treat (mITT) and safety populations of STREAM Stage 1 (ISRCTN78372190) and Stage 2 (ISRCTN18148631) were included in the post-hoc analyses reported here. mITT population included all participants who were randomized and had a culture that was positive for *M. tuberculosis* at baseline, excluding those in whom baseline isolates were subsequently found to be susceptible to rifampicin or resistant to both fluoroquinolones and aminoglycosides on phenotypic drug-susceptibility testing. Safety population included all who received at least one dose of trial medication.

STREAM Stage 1 randomized 424 adult participants with smear positive pulmonary TB, with evidence of resistance to rifampicin and sensitivity to fluoroquinolones and aminoglycosides, to "Long" and "Short" regimens in a 1:2 ratio from July 2012 through June 2015.[27] The long regimen (approximately 20 months) consisted of medications used in and provided by the National Tuberculosis Programs of the respective countries, based on the 2011 World Health Organization (WHO) guidelines and the short regimen consisted of moxifloxacin, clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, supplemented by kanamycin, isoniazid, and prothionamide in the first 16 weeks[1]. Participants had scheduled weekly visits during the first 4 weeks and thereafter were clinically evaluated at 4-week intervals through week 132; sputum samples for smear and culture were obtained at baseline and at every visit starting from the week 4 visit.

STREAM Stage 2 randomized 588 participants in a 1:2:2:2 ratio to the Stage 1 "Long" regimen (terminated early due to near universal adoption of the shorter regimen by TB programs), 9-month control regimen (Stage 1 "Short" regimen), 9-month "Oral" regimen with bedaquiline, or "Six-month" regimen with bedaquiline and 8 weeks of second-line injectable (also terminated early because of universal adoption of all-oral regimens and recommendations against use of injectables) between March 28, 2016 and Jan 28, 2020. [28] In terms of follow-up, participants were assessed weekly for the first month, then 4-weekly until week 52, 8-weekly until week 84, and 12-weekly thereafter until end of trial follow-up at week 132. Sputum samples for smear and culture were obtained at baseline and at every visit starting from the week 4 visit at least until week 96. Complete blood count and serum chemistry (including blood glucose) were performed at baseline and at every scheduled visit starting at week 4 visit at least until the week 76 visit (primary endpoint). Further details of trial regimens and trial design, including modifications during implementation are described earlier. [28,29]

Study exposure

Participants who self-reported DM status at enrolment, had random blood glucose ≥200mg/dl at baseline, or reported taking concomitant medication for diabetes were classified as the DM group. Participants whose DM status could not be determined were excluded from the analyses.

Study outcomes

We report efficacy outcomes as follows: proportions of participants with "unfavourable" and "favourable" status, proportions with Probable or Definite Failure or Recurrence at the time of primary outcome (FoR), and hazard ratios for times to FoR and culture conversion. And "unfavourable" outcome was defined as death, bacteriological failure or recurrence, and major TB treatment change for any reason. "Favourable" outcome was achieved for any participant with a negative culture for Mycobacterium tuberculosis (without a preceding unfavourable outcome) at week 132 for Stage 1, and at week 76 for Stage 2.[27,28]

A "Definite FoR" event required clear bacteriological evidence of failure or relapse (excluding a proven reinfection with exogenous strain of Mycobacterium tuberculosis), and a "Probable FoR" event required some evidence for failure or relapse in the absence of clear bacteriology.[28,30] We also report safety outcomes as follows: proportions of participants with grade 3-5 adverse events (AEs), serious adverse events (SAEs), treatment-related SAEs, deaths as well as proportions of participants with unscheduled visits, total and related to grade 3/4 AEs. In the STREAM trial, AEs were graded according to the Division of AIDS, National Institute of Allergy, and Infectious Diseases criteria.

Statistical analyses

Participants' demographic and clinical data at baseline were analyzed to assess association with DM status, using Chi-squared/Fisher's exact test for proportions or two-sample z-test/t-tests for continuous variables based on their distribution. The proportion of participants with favourable/unfavourable status, FoR event, SAE, death, AE, or unscheduled visits were calculated by DM status and compared between DM and non-DM groups using Chi-squared or Fisher's exact tests where appropriate. Regimen-wise comparison of outcomes by DM status was done if there were at least 20 events. Time-to-event endpoints (FoR and culture conversion) were analysed using Cox proportional hazard regression model (stratified by trial stage and regimen, if appropriate) to estimate hazard ratio between the DM and non-DM groups. All baseline factors considered potentially related to outcome as well as

a-priori variables were included in a multivariable model and the best model selected using Akaike Information Criterion (AIC). The proportional-hazards assumption was tested using Schoenfeld residuals and found to hold for all analyses. All analyses, except for proportion with favourable/unfavourable status are reported on a pooled basis, for Stage 1 and 2 participants combined. Proportions of participants with favourable/unfavourable status are reported separately for each trial stage because of differing primary endpoints (week 132 for stage 1 and week 76 for stage 2). All reported tests are two-sided, and analyses were conducted using STATA version 17.0.

Determinants of glucose control

Using longitudinal glucose measures for Stage 2 participants, we performed additional analyses, logistical as well as longitudinal modelling, to evaluate determinants of glucose control. Here we did not evaluate whether poor glycemic control was associated with poor treatment outcomes. Stage 1 participants were not included in this analysis because they had a single blood glucose measurement, taken at baseline. Glucose level was considered controlled if random glucose level was <140 mg/dl. Two analyses were considered – one at 8 weeks post-randomization and the other at 16 weeks post-randomization – to cover the end of intensive phase treatment for the different regimens. At each time-point, participants were categorized as controlled/not controlled.

A logistic model to identify factors associated with glucose control was fitted using demographic, baseline clinical characteristics, and other treatment factors. In addition, longitudinal glucose measures were summarized by visit and DM status and modelled using a linear mixed model by DM status, as glycaemic control appeared to be different in the two groups. Multiple functional forms for time were considered. The best fitting model was a piecewise exponential model with knot at 20 weeks; 20 weeks was chosen as this was the best fit based on a simple plot of mean glucose level over time and made clinical sense since this coincided with the end of intensive phase of treatment. Tests of interaction between demographic and baseline clinical characteristics with time were conducted to determine variables associated with glucose control.

Ethics Statement

The Union Ethics Advisory Group (EAG) approved (i) the use of deidentified data from the STREAM trials for this post-hoc secondary analysis, and (ii) the waiver of requirement for additional consent from participants (EAG 53/19).

Results

Efficacy Analysis population characteristics

Of the 1012 participants enrolled to the STREAM trial, a total of 896 participants were included in the efficacy analyses described here [116 were excluded either because they were not in the mITT populations (n=86), or their DM status could not be determined because of missing baseline glucose values]. Of these, majority were from Stage 2 (60%), male (62%), < 35 years (57%), self-reported as never having smoked (64%), and presented chest cavitation (76%) (Table 1).

A total of 84 (9.4%) participants had DM (per definition earlier). The mean random blood glucose (SD) at baseline was 263.2 (114.0) mg/dL in the DM group and 95.5 (19.1) mg/dl in the non-DM group (p<0.001). The proportion of the population from the two trial stages and various treatment regimens was similar in both the DM group and the non-DM group. There

Table 1. Demographics, Baseline characteristics between DM and non-DM in efficacy analysis.

	Total N=896	Non-DM N=812	DM N=84	P-value
Glucose (mg/DL), mean (SD)		95.5 (19.1)	263.2 (114.0)	<0.001
Stage of Trial, no. (%)				
Stage 1	357 (40)	322 (40)	35 (42)	0.93
Stage 2	539 (60)	490 (60)	49 (58)	
Regimens, no. (%)				
Long	147 (16)	132 (16)	15 (18)	0.99
Short	422 (47)	382 (47)	40 (48)	
Oral	195 (22)	179 (22)	16 (19)	
Six-month	132 (15)	119 (15)	13 (15)	
Country, no. (%)				
Ethiopia	176 (20)	168 (21)	8 (10)	<0.001
Georgia	32 (4)	30 (4)	2 (2)	
India	138 (15)	99 (12)	39 (46)	
Moldova	59 (7)	59 (7)	0	
Mongolia	151 (17)	141 (17)	10 (12)	
South Africa	192 (21)	184 (23)	8 (10)	
Uganda	54 (6)	54 (7)	0	
Vietnam	94 (10)	77 (9)	17 (20)	
Male, no. (%)	551 (62)	491 (60)	60 (71)	0.049
Age (years), no. (%)				
15 – 24	193 (21)	191 (24)	2 (2)	<0.001
25 – 34	321 (36)	314 (39)	7 (8)	
35 – 44	203 (23)	170 (21)	33 (39)	
45 +	179 (20)	137 (17)	42 (50)	
BMI Category (kg/m2), no. (%)				
Severely underweight (< 16)	117 (13)	116 (14)	1 (1)	<0.001
Underweight (16 – 18.49)	267 (30)	252 (31)	15 (18)	
Normal (18.5 – 24.99)	448 (50)	391 (48)	57 (68)	
Overweight (≥ 25)	64 (7)	53 (7)	11 (13)	
HIV+, no. (%)	191 (21)	185 (23)	6 (7)	0.001
Smoking status, no. (%)				
Never smoked	570 (64)	515 (63)	55 (65)	0.01
Current smoker	153 (17)	147 (18)	6 (7)	
Ex-smoker	173 (19)	150 (18)	23 (27)	
*Extent of opacities, no./total (%)				
None	1/844 (0)	1/764 (0)	0/80 (0)	0.48
Minimal	90/844 (11)	85/764 (11)	5/80 (6)	
Moderate	469/844 (55)	418/764 (55)	51/80 (64)	
Advanced	284/844 (34)	260/764 (34)	24/80 (30)	
*Number of cavities, no./total (%)				
None	206/844 (24)	188/764 (25)	18/80 (23)	0.31
Single	140/844 (17)	121/764 (16)	19/80 (24)	
Multiple	498/844 (59)	455/764 (60)	43/80 (54)	

*Variables with participants missing data at baseline. 52 participants were missing baseline chest X rays and therefore data for extent of opacity and number of cavities.

was an association between DM status and country (p<.001); India and Vietnam, combined, accounted for a majority of the participants in the DM group (66%).

Participants in the DM group were more likely to be older (p<0.001); the DM group had 2-3 times the proportion of participants in the 25-34 and 35-44 age groups, respectively, compared to the non-DM group. The DM group also had a higher BMI on average compared to non-DM participants (p<0.001) and had nearly double the proportion of participants in the 'Overweight' (>25) category compared to the non-DM group. There was also borderline significant evidence (p=0.049) of an association between sex and DM status; men were more likely to have diabetes compared to women. There was an association between DM status and HIV status (p=0.001), with DM participants less likely to be HIV+ compared to non-DM; possibly explained by varying prevalence of HIV and DM between countries. There was no association between DM status and smoking history, or extent of baseline disease as determined by the radiographic extent of cavitation and lung opacities.

Efficacy outcomes

Efficacy outcomes in the DM and non-DM groups are presented in Table 2.

The proportion of participants with an unfavourable trial outcome in the DM group was comparable to the non-DM group in both Stage 1 (unadjusted difference -6.0%, 95% CI: -21.1 to 9.2, p=0.41) and Stage 2 participants (unadjusted difference 3.9%, 95% CI: -7.1 to 14.8, p=0.52). Since this trial primary outcome was a composite endpoint that also included treatment changes, a more clinical/TB-related outcome (FoR) was also assessed. The proportion of participants who experienced definite/probable Failure or Recurrence (FoR) events were also comparable between the DM (8.3%) and the non-DM groups (5.9%); adjusted HR 1.38, 95% CI: 0.51, 3.73). Likewise, the time to culture conversion was also similar in both groups

Table 2. Efficacy outcomes in DM and non-DM participants.

	Non-DM N=812	DM N=84	P-value
Favourable/Unfavourable status, no. (%)			
Stage 1 – status at Week 132	*N=322*	*N=35*	
Favourable	248 (77)	26 (74)	0.34
Unfavourable	61 (19)	9 (26)	
Non-assessable	13 (4)	0	
Stage 2 – status at Week 76	*N=490*	*N=49*	
Favourable	391 (80)	41 (84)	0.52
Unfavourable	99 (20)	8 (16)	
Failure or Recurrence (FoR)			
FoR events (definite/probable), no. (%)	48 (5.9)	7 (8.3)	0.38
Time to FoR, unadjusted HR (95% CI)	1.00	1.40 (0.63, 3.09)	0.41
Time to FoR, stratified* HR (95% CI)	1.00	1.11 (0.48, 2.58)	0.80
Time to FoR, adjusted** HR (95% CI)	1.00	1.38 (0.51, 3.73)	0.53
Culture conversion			
Time to culture conversion, unadjusted HR (95% CI)	1.00	0.94 (0.74, 1.18)	0.57
Time to culture conversion, stratified* HR (95% CI)	1.00	0.87 (0.68, 1.11)	0.28
Time to FoR, adjusted** HR (95% CI)	1.00	0.90 (0.69, 1.18)	0.45

*Stratified by country and trial stage.

**Adjusted for treatment regimen, sex, age, HIV status, BMI category and stratified by country and trial stage.

https://doi.org/10.1371/journal.pgph.0004259.t002

(adjusted HR 0.90, 95% CI: 0.69, 1.18). None of the differences were statistically significant indicating similar efficacy outcomes in both the groups.

Safety outcomes

A total of 976 participants were included in the safety analysis reported here (Table 3).

A significantly higher proportion of participants in the DM group experienced SAEs, excluding deaths, than in the non-DM group (41% vs. 22%, p<0.001). One-fifth of the SAEs (20.6%) in the DM group were classified as surgical/medical procedures (12.7%) or as endocrine issues (7.9%) in comparison to less than 3% in the non-DM group (S4 Table) There was also a suggestion of regimen-based differences in SAEs; proportion of SAEs in the DM and non-DM groups were comparable in the 'Long' regimen (32% DM vs. 31% non-DM) but were higher in the DM group in the 'Six-month' (62% DM vs. 17% non-DM, p<0.001), 'Oral' (29% DM vs. 15% non-DM group, p=0.123), and 'Short' (44% DM vs. 23% non-DM, p=0.002) regimens (S4 Table).

Nevertheless, the proportion of participants in the DM vs. non-DM group who died (7% vs. 5%), experienced grade 3–5 AEs (63% vs. 54%) or and had unscheduled clinic visits (68% vs. 65%), including visits reported as related to grade 3/4 AEs (14% vs. 10%) were all comparable (Table 3).

Determinants of glucose control

Longitudinal glucose measures from 539 Stage 2 participants (490 non-DM and 49 DM) were analysed to determine determinants of glycaemic control in this population. We do not report effect of glycemic control on treatment outcomes.

Over two-thirds of DM participants (73%) were on medication for diabetes; over half (59%) on metformin and one-third on insulin (33%). In both DM and non-DM participants, blood glucose levels decrease in the first few months before plateauing (S1 Fig). Demographic characteristics of participants included in this glycemic control analysis were similar to the overall efficacy analysis population described earlier (S1 Table). There was an association between DM status and country (p <0.001), age category (p<0.001), and BMI (p<0.001). The majority of DM participants in this analysis were from India and Mongolia combined (96%), and none of them were HIV positive.

At 8 weeks post randomization, nearly all participants in the non-DM group (463/478, 97%) experienced glycaemic control (defined as glucose level <140 mg/dl). The odds of poor glycaemic control were higher in males (OR 4.55; 95% CI 1.01, 20.00) and in older

Table 3. Safety outcomes in DM and non-DM participants.

	Non-DM N=889	DM N=87	p-value
SAEs, excluding deaths No. participants experiencing event (%)	193 (22)	36 (41)	<0.001
Deaths No. participants (%)	43 (5)	6 (7)	0.40
Grade 3-5 AEs No. participants experiencing event (%)	481 (54)	55 (63)	0.10
Unscheduled visits – total No. participants experiencing event (%)	579 (65)	59 (68)	0.62
Unscheduled visits related to AEs No. participants experiencing event (%)	90 (10)	12 (14)	0.29

https://doi.org/10.1371/journal.pgph.0004259.t003

Table 4. Odds ratio estimates for association with poor glycaemic control from univariable logistic models (Stage 2 population only).

	8 weeks post randomisation				16 weeks post randomisation			
	Non-DM (n=478)		DM (n=46)		Non-DM (n=466)		DM (n=45)	
	OR estimate (95% CI)	P-value	OR estimate (95% CI)	P-value	OR estimate (95% CI)	P-value	OR estimate (95% CI)	P-value
Treatment regimen								
Long	1.84 (0.20, 17.22)	0.59	*	–	*	–	*	–
Short	1	–	1	–	1	–	1	–
Oral	2.26 (0.68, 7.50)	0.18	4.00 (0.39, 40.79)	0.24	1.98 (0.36, 10.94)	0.44	0.24 (0.04, 1.51)	0.13
Six-month	0.34 (0.04, 3.11)	0.34	0.49 (0.10, 2.40)	0.38	0.70 (0.06, 7.83)	0.77	0.13 (0.02, 0.86)	0.034
Male	4.55 (1.01, 20)	0.049	1.11 (0.24, 5.26)	0.89	1.69 (0.33, 9.09)	0.53	1.37 (0.36, 5.26)	0.64
Age (years)								
15 – 24	0.57 (0.06, 5.57)	0.63	–	–	*	–	–	–
25 – 34	1	–	1	–	1	–	1	–
35 – 44	4.07 (0.99, 16.62)	0.05	1.67 (0.13, 22.00)	0.70	2.98 (0.49, 18.17)	0.24	0.52 (0.05, 6.09)	0.61
45 +	4.16 (0.97, 17.83)	0.06	1.00 (0.09, 11.52)	1.00	2.41 (0.33, 17.41)	0.38	0.76 (0.07, 8.66)	0.83
BMI Category (kg/m²)								
Severely underweight (<16)	0.67 (0.14, 3.15)	0.62	*	–	*	–	*	–
Underweight (16–18.49)	0.33 (0.07, 1.52)	0.15	0.58 (0.09, 3.88)	0.58	0.28 (0.03, 2.33)	0.24	2.32 (0.23, 23.42)	0.48
Normal (18.5–24.99)	1	–	1	–	1	–	1	–
Overweight (>25)	0.71 (0.09, 5.70)	0.74	2.04 (0.21, 19.53)	0.54	*	–	1.16 (0.24, 5.58)	0.86
HIV+	0.80 (0.18, 3.60)	0.77	–	–	*	–	–	–
Smoking status								
Never smoked	1	–	1	–	1	–	1	–
Current smoker	1.36 (0.40, 4.62)	0.62	*	–	1.33 (0.24, 7.38)	0.74	*	–
Ex-smoker	1.71 (0.44, 6.63)	0.44	0.21 (0.04, 1.07)	0.06	1.14 (0.44, 1.29)	0.91	0.73 (0.14, 3.80)	0.71
Smear								
No AFB Seen/ Rare AFB	*	–	*	–	*	–	0.44 (0.02, 9.03)	0.60
1+	1	–	1	–	1	–	1	–
2+	1.31 (0.31, 8.02)	0.77	2.60 (0.39, 17.16)	0.32	*	–	1.33 (0.26, 6.83)	0.73
3+	2.43 (0.52, 11.34)	0.26	1.10 (0.22, 5.61)	0.91	0.60 (0.13, 2.74)	0.51	0.59 (0.12, 2.89)	0.52
Number of cavities								
None	*	–	0.67 (0.04, 12.27)	0.79	*	–	1.0 (0.16, 6.25)	1.00
Single	1	–	1	–	1	–	1	–
Multiple	3.85 (0.49, 30.10)	0.20	0.14 (0.01, 1.25)	0.08	0.78 (0.15, 4.11)	0.77	1.00 (0.22, 4.50)	1.00

- No participants in this group, OR not estimated.

*Perfectly predicts outcome, small numbers of participants.

https://doi.org/10.1371/journal.pgph.0004259.t004

participants (OR 4.07; 95% CI 0.99, 16.62 in 35-44 years & OR 4.16; 95% CI 0.97, 17.83 in 45+ years) (Table 4). At 8 weeks, only one-fifth of participants in the DM group (10/46, 22%) experienced glycemic control and there was no evidence of association with any baseline factor.

At 16 weeks post randomization, the proportion of participants in the DM group with glycaemic control increased (15/45, 33%) with the odds of poor glycaemic control being lower in the "Six-month" regimen (OR 0.13; 95% CI 0.02, 0.86) and the "Oral" regimen (OR 0.24; 95% CI 0.04, 1.51) compared to the "Short" regimen in this group (Table 4).

In a (piecewise) longitudinal model of glucose control over time, associations found were similar to the Week 8 analysis reported above for the non-DM population – glucose control over time was worse in older (p=0.04) and male (p=0.09) participants (S2 Table & S2 Fig). No such associations were found in the DM population (S3 Table & S3 Fig).

Discussion

There is incomplete and mixed evidence about the impact of DM on treatment and safety outcomes in TB. Several studies in people with drug-sensitive TB report poorer outcomes such as lower rates of treatment success,[21,23] culture conversion,[23] long-term survival[7,17,23] and higher rates of relapse[6,7,21], death and adverse events[7,23] in those with DM compared to those without. Studies in MDR-TB are limited but in general point to poorer outcomes in people with DM co-morbidity such as more adverse events[12], and lower rates of treatment success[10], culture conversion[11] or long-term survival[10].

The results of our study, however, provide evidence that it may be possible to achieve similar treatment outcomes in people with MDR-TB and DM co-morbidity, as those without DM. It is likely that better clinical oversight may have contributed to comparable TB outcomes between DM and non-DM in this clinical trial cohort. STREAM participants had clinic visits weekly for the first month, and then monthly for up to at least a year. Frequency of these visits likely resulted in better monitoring of participants' blood glucose which may in turn have contributed to better DM management and TB outcomes. This is consistent with some studies in drug-sensitive TB where close monitoring and good glucose control resulted in similar TB outcomes in DM and non-DM groups. In a well-resourced setting where glucose levels were closely monitored, DM was not an independent predictor of unfavorable outcomes[31]; diabetics with optimal levels of HbA1c (<7%) were more likely to have better microbiological outcomes[17]. There are several strengths to the analyses presented here from a randomised controlled trial. The study population was clearly defined with minimal loss to follow-up, data analysed was prospectively collected through standardized assessments, and confounding factors could be identified and adjusted for in the time-to-event analyses.

Nevertheless, the results presented here should be interpreted cautiously as the small sample size (84 and 87 DM participants in efficacy and safety respectively) may not have allowed detection of differences. Further, the exposure (DM status) was determined based on single random glucose measurements. A proportion of these glucose elevations may be a result of temporary dysglycaemia, commonly associated with TB disease, that auto-resolves with immune recovery following TB treatment. [2]Profile plots from the Stage 2 repeated measures analyses (S1 Fig) point to transient hyperglycaemia in all participants (DM and non-DM) early on with a decrease and plateauing of glucose levels following TB treatment and resolution of disease. In these plots, however, there is a clear distinction in glucose levels between the two groups suggesting limited misclassification using this surrogate marker for determining diabetes in this population.

Our analyses with longitudinal glucose measures also offer some valuable insights into glucose control in the Stage 2 population. While only 22% in the DM group experienced glycemic control (defined as RBG <140 mg/dl) at 8 weeks, as many as 30% and 54% had RBG levels below 154mg/dl and 200mg/dL respectively (corresponding to HBA1c levels of <7% and 9%). By 16 weeks, this increased to nearly half (42%) with optimal RBG levels (<154mg/dl), and to nearly three-fourths (71%) with RBG levels below threshold for being categorized as DM (<200mg/dl). The extent of glycemic control achieved in the DM population under this trial's setting probably explains the outcomes reported.

Responding to previous recommendations to study glycemic trajectories in MDR-TB cohorts, our analyses elucidate factors associated with glycemic control in the STREAM population [20]. Older males had worse glycemic control than their younger female counterparts in the non-DM group; this can be useful in designing clinical monitoring and management strategies.

However, given the limited number of participants in the DM group, we were not able to draw meaningful conclusions regarding factors associated with glycemic control in the DM group which needs to be further explored. Additionally, we did not evaluate whether poor glycemic control was associated with poor treatment outcomes. However, we do report better glycemic control in the DM population randomised to the "Six-month" and "Oral" regimens; intervention regimens for which superior efficacy outcomes have been reported. [28] Future studies with larger MDR-TB and DM cohorts may be able to generate further evidence around this by modelling the effect of glycemic trajectories on treatment outcomes.

Although improved treatment options for MDR-TB are now available, they are not tested or optimised for people with MDR-TB and co-morbidities such as DM. Treatment guidance and management of MDR-TB in people with and without DM co-morbidity remain the same despite several reports of poorer outcomes in those with uncontrolled diabetes [18,19]. Few trials of new drugs/regimens enrol people with diabetes and report treatment outcomes in this sub-population. Evidence needs to be generated on the efficacy of newer regimens in people with MDR-TB and DM that further informs their clinical management [13].

Our results add to the evidence on treatment outcomes using new regimens in people with MDR-TB/DM co-morbidity and support previous recommendation of use of closer monitoring and oversight to improve outcomes [32]. They also offer a promising insight that proper management of both diseases could possibly obviate the need for additional drugs or a different treatment regimen for this sub-population. While the DM group experienced more SAEs, this may be attributed to higher number of hospitalizations (S4 Table), regardless of severeness or relatedness either to TB or Diabetes, as per its definition in the conduct of clinical trials.

It would be important to evaluate the recommendations on monitoring and oversight presented here in more pragmatic settings and assess effectiveness of newer MDR-TB regimens in people with diabetes. Future research can be designed using more reliable glucose measures and advanced statistical methods/modelling techniques to describe glycemic trajectories, and to evaluate their effect on outcomes, including assessing the role of treatments for both MDR-TB and DM. Together, these can further the development of guidelines for the specific management of DM and MDR-TB co-morbidities.

Supporting information

S1 Fig. Glucose-level profile in glycemic control analysis population.
(TIF)

S1 Table. Baseline characteristics of glycemic control analysis population.
(DOCX)

S2 Table. Final piecewise longitudinal model for glucose levels (non-DM group).
(DOCX)

S2 Fig. Final piecewise longitudinal model for glucose levels (non-DM group).
(TIF)

S3 Table. Final piecewise longitudinal model for glucose levels (DM group).
(DOCX)

S3 Fig. Final piecewise longitudinal model for glucose levels (DM group).
(TIF)

S4 Table. Serious adverse events profiles.
(DOCX)

Acknowledgements

Author contributions

References

1. World Health Organization W. Global tuberculosis report 2021. 2021.

2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843. https://doi.org/10.1016/j.diabres.2019.107843 PMID: 31518657

3. WHO. Global Tuberculosis Report. 2023.

4. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008;5(7):e152. https://doi.org/10.1371/journal.pmed.0050152 PMID: 18630984

5. Hayashi S, Chandramohan D. Risk of active tuberculosis among people with diabetes mellitus: systematic review and meta-analysis. Trop Med Int Health. 2018;23(10):1058–70. https://doi.org/10.1111/tmi.13133 PMID: 30062731

6. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med. 2011;9:81. https://doi.org/10.1186/1741-7015-9-81 PMID: 21722362

7. Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis. Int J Tuberc Lung Dis. 2019;23(7):783–96. https://doi.org/10.5588/ijtld.18.0433 PMID: 31439109

8. Liu Q, Li W, Xue M, Chen Y, Du X, Wang C, et al. Diabetes mellitus and the risk of multidrug resistant tuberculosis: a meta-analysis. Sci Rep. 2017;7(1):1090. https://doi.org/10.1038/s41598-017-01213-5 PMID: 28439071

9. Tegegne BS, Mengesha MM, Teferra AA, Awoke MA, Habtewold TD. Association between diabetes mellitus and multi-drug-resistant tuberculosis: evidence from a systematic review and meta-analysis. Syst Rev. 2018;7(1):161. https://doi.org/10.1186/s13643-018-0828-0 PMID: 30322409

10. Kang YA, Kim SY, Jo K-W, Kim HJ, Park S-K, Kim T-H, et al. Impact of diabetes on treatment outcomes and long-term survival in multidrug-resistant tuberculosis. Respiration. 2013;86(6):472–8. https://doi.org/10.1159/000348374 PMID: 23689646

11. Salindri AD, Kipiani M, Kempker RR, Gandhi NR, Darchia L, Tukvadze N, et al. Diabetes reduces the rate of sputum culture conversion in patients with newly diagnosed multidrug-resistant tuberculosis. Open Forum Infect Dis. 2016;3(3):ofw126. https://doi.org/10.1093/ofid/ofw126 PMID: 27419188

12. Muñoz-Torrico M, Caminero-Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Diabetes is associated with severe adverse events in multidrug-resistant tuberculosis. Archivos de Bronconeumología (English Edition). 2017;53(5):245–50. https://doi.org/10.1016/j.arbr.2016.10.003

13. Esmail A, Sabur NF, Okpechi I, Dheda K. Management of drug-resistant tuberculosis in special sub-populations including those with HIV co-infection, pregnancy, diabetes, organ-specific dysfunction, and in the critically ill. J Thorac Dis. 2018;10(5):3102–18. https://doi.org/10.21037/jtd.2018.05.11 PMID: 29997980

14. Critchley JA, Restrepo BI, Ronacher K, Kapur A, Bremer AA, Schlesinger LS, et al. Defining a research agenda to address the converging epidemics of tuberculosis and diabetes: part 1: epidemiology and clinical management. Chest. 2017;152(1):165–73. https://doi.org/10.1016/j.chest.2017.04.155 PMID: 28434936

15. van Crevel R, Critchley JA. The interaction of diabetes and tuberculosis: translating research to policy and practice. Trop Med Infect Dis. 2021;6(1):8. https://doi.org/10.3390/tropicalmed6010008 PMID: 33435609

16. Ruslami R, Aarnoutse RE, Alisjahbana B, van der Ven AJAM, van Crevel R. Implications of the global increase of diabetes for tuberculosis control and patient care. Trop Med Int Health. 2010;15(11):1289–99. https://doi.org/10.1111/j.1365-3156.2010.02625.x PMID: 20955495

17. Chiang CY, Bai KJ, Lin HH, Chien ST, Lee JJ, Enarson DA, et al. The influence of diabetes, glycemic control, and diabetes-related comorbidities on pulmonary tuberculosis. PLoS One. 2015;10(3):e0121698. https://doi.org/10.1371/journal.pone.0121698 PMID: 25822974

18. Niazi AK, Kalra S. Diabetes and tuberculosis: a review of the role of optimal glycemic control. J Diabetes Metab Disord. 2012;11(1):28. https://doi.org/10.1186/2251-6581-11-28 PMID: 23497638

19. Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B, van de Vijver S, Panduru NM, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrinol. 2014;2(9):740–53. https://doi.org/10.1016/S2213-8587(14)70110-X PMID: 25194887

20. Shewade HD, Jeyashree K, Mahajan P, Shah AN, Kirubakaran R, Rao R, et al. Effect of glycemic control and type of diabetes treatment on unsuccessful TB treatment outcomes among people with TB-Diabetes: A systematic review. PLoS One. 2017;12(10):e0186697. https://doi.org/10.1371/journal.pone.0186697 PMID: 29059214

21. Mahishale V, Avuthu S, Patil B, Lolly M, Eti A, Khan S. Effect of poor glycemic control in newly diagnosed patients with smear-positive pulmonary tuberculosis and type-2 diabetes mellitus. Iran J Med Sci. 2017;42(2):144–51. PMID: 28360440

22. Magee MJ, Kempker RR, Kipiani M, Gandhi NR, Darchia L, Tukvadze N, et al. Diabetes mellitus is associated with cavities, smear grade, and multidrug-resistant tuberculosis in Georgia. Int J Tuberc Lung Dis. 2015;19(6):685–92. https://doi.org/10.5588/ijtld.14.0811 PMID: 25946360

23. Yoon YS, Jung J-W, Jeon EJ, Seo H, Ryu YJ, Yim J-J, et al. The effect of diabetes control status on treatment response in pulmonary tuberculosis: a prospective study. Thorax. 2017;72(3):263–70. https://doi.org/10.1136/thoraxjnl-2015-207686 PMID: 27553224

24. Liu Q, You N, Pan H, Shen Y, Lu P, Wang J, et al. Glycemic trajectories and treatment outcomes of patients with newly diagnosed tuberculosis: a Prospective Study in Eastern China. Am J Respir Crit Care Med. 2021;204(3):347–56. https://doi.org/10.1164/rccm.202007-2634OC PMID: 33705666

25. Calderon RI, Arriaga MB, Aliaga JG, Barreda NN, Sanabria OM, Barreto-Duarte B, et al. Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru. Int J Infect Dis. 2022;116:293–301. https://doi.org/10.1016/j.ijid.2022.01.012 PMID: 35033658

26. Mahato RK, Laohasiriwong W, Koju R. The role of Diabetes mellitus comorbidity on Tuberculosis treatment outcomes in Nepal: A prospective cohort study. SEEJPH. 2023. https://doi.org/10.56801/seejph.vi.260

27. Nunn AJ, Phillips PPJ, Meredith SK, Chiang C-Y, Conradie F, Dalai D, et al. A Trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med. 2019;380(13):1201–13. https://doi.org/10.1056/NEJMoa1811867 PMID: 30865791

28. Goodall RL, Meredith SK, Nunn AJ, Bayissa A, Bhatnagar AK, Bronson G, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. Lancet. 2022;400(10366):1858–68. https://doi.org/10.1016/S0140-6736(22)02078-5 PMID: 36368336

29. Goodall RL, Sanders K, Bronson G, Gurumurthy M, Torrea G, Meredith S, et al. Keeping up with the guidelines: design changes to the STREAM stage 2 randomised controlled non-inferiority trial for rifampicin-resistant tuberculosis. Trials. 2022;23(1):474. https://doi.org/10.1186/s13063-022-06397-4 PMID: 35672833

30. Phillips PPJ, Van Deun A, Ahmed S, Goodall RL, Meredith SK, Conradie F, et al. Investigation of the efficacy of the short regimen for rifampicin-resistant TB from the STREAM trial. BMC Med. 2020;18(1):314. https://doi.org/10.1186/s12916-020-01770-z PMID: 33143704

31. Baltas I, Sturdy A, Kavallieros K, McGregor A, Corrah T, John L, et al. Diabetes mellitus is not a predictor of poor TB treatment outcomes. Int J Tuberc Lung Dis. 2023;27(2):140–5. https://doi.org/10.5588/ijtld.22.0470 PMID: 36853108

32. Restrepo BI, Schlesinger LS. Impact of diabetes on the natural history of tuberculosis. Diabetes Res Clin Pract. 2014;106(2):191–9. https://doi.org/10.1016/j.diabres.2014.06.011 PMID: 25082309