

SUPPLEMENTARY INFORMATION

Baseline Radiographic and Microbiologic Predictors of Treatment Outcomes in a Shortened All-Oral Regimen for MDR/RR-TB

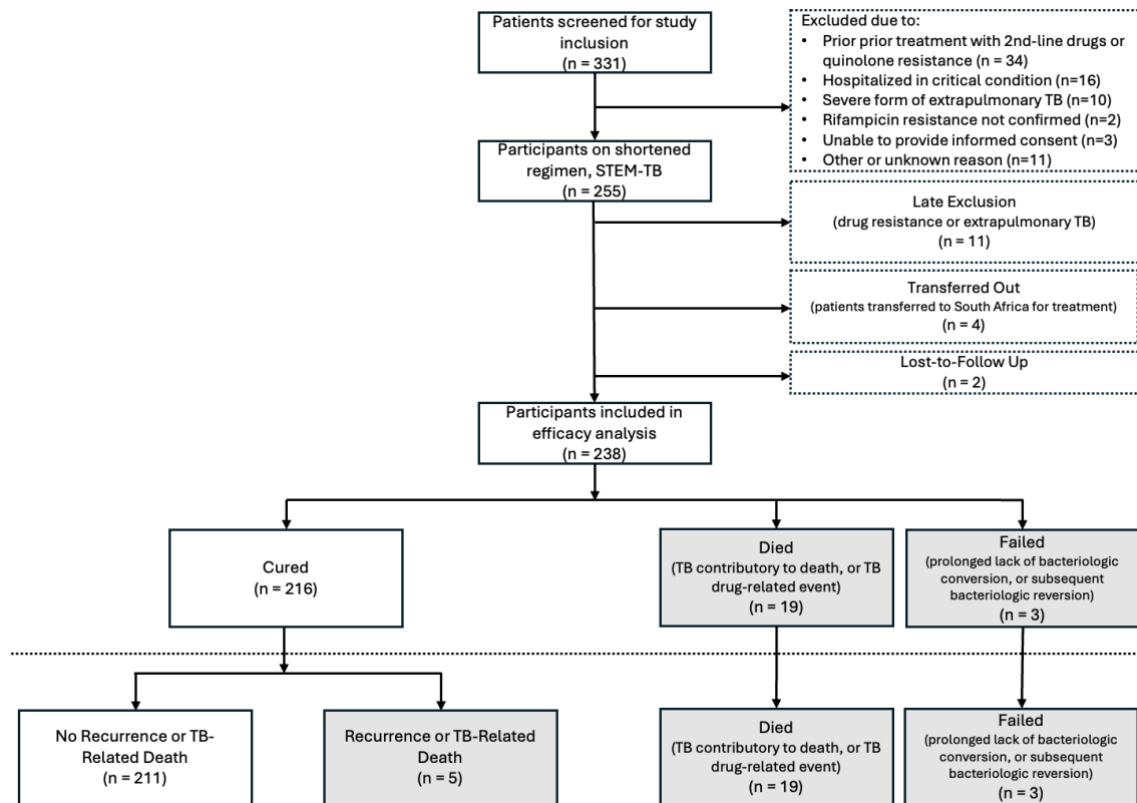
Appendix A. Exclusion Criteria for Initiation of a Shortened All-Oral Regimen, STEM-TB Lesotho Cohort

- Inability to take oral medications
- Baseline fluoroquinolone resistance
- Previous fluoroquinolone use longer than one month
- Known fluoroquinolone intolerance
- Baseline TB DST indicating a strain with evidence of resistance against at least two drugs in the all-oral regimen
- Previous exposure to at least two drugs in the all-oral regimen for more than one month
- Isolated extrapulmonary MDR/RR-TB without pulmonary involvement
- Baseline AST or ALT greater than 5 times the upper limit of normal
- Baseline corrected QT interval (per Fridericia's formula) ≥ 500 milliseconds;
- Known medical contra-indications or allergy to at least two drugs in the all-oral regimen

Data Management

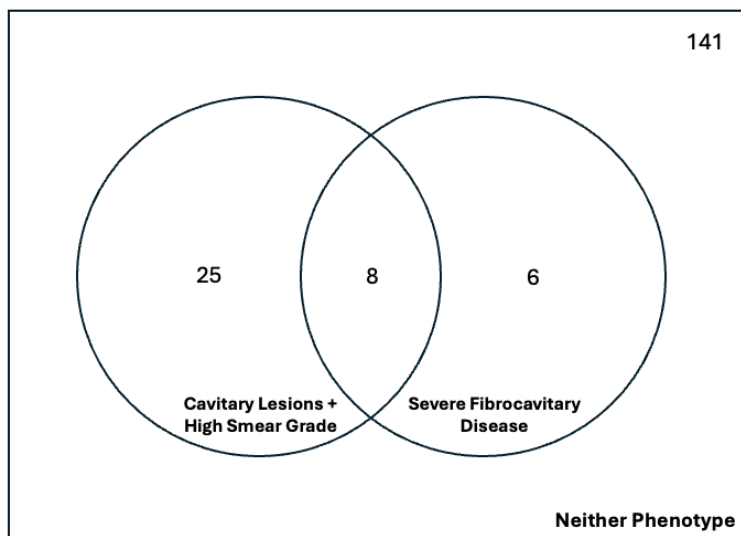
Data were entered into an electronic data system, which was based on the Bahmni open-source medical-record system (<https://www.bahmni.org>) and administered by Partners In Health. Data quality checks were performed on a bimonthly basis.

Supplementary Figure 1. Flow Diagram of Participant Inclusion in End-of-Treatment and Final Treatment Outcome Analyses, STEM-TB Lesotho Cohort



Four participants had post-treatment recurrence; one participant had death attributed to post-TB lung disease and was characterized as being TB-related for the purposes of this analysis.

Supplementary Figure 2. Venn Diagram of Clinical Phenotypes for Participants included in End of Treatment and Final Outcomes Analyses, STEM-TB Lesotho (N=180)¹



¹ One hundred and eighty participants had complete baseline smear and radiographic data such that they could be classified for both the 'cavitary and high smear grade' phenotype and the 'severe fibrocavitary disease' phenotype.

Supplementary Table 1. Baseline Characteristics of Participants Included in End-of-Treatment and Post-Treatment Outcomes Analyses, Stratified by Baseline Radiographic and Smear Features (N=238)

Characteristics	Cavitary Disease		Fibrosis		Bilateral Disease		High Smear Grade	
	Yes (N = 67)	No (N = 141)	Yes (N = 59)	No (N = 148)	Yes (N = 96)	No (N = 112)	Yes (N = 68)	No (N = 138)
Age (median, IQR)	43 (31-54)	40 (31-58)	43 (31-54)	38 (29-51.5)	43 (33-61.5)	38 (29-51)	40.5 (30.5-53.5)	42 (33-58)
Female	18 (26.9)	43 (30.5)	11 (18.6)	50 (33.8)	21 (21.9)	40 (35.7)	19 (27.9)	44 (31.9)
Unemployed	32 (47.8)	51 (36.1)	27 (45.8)	55 (37.2)	43 (44.8)	40 (35.7)	31 (45.6)	54 (39.1)
Alcohol Consumption ¹	35 (52.2)	74 (52.9)	30 (50.8)	79 (54.1)	52 (54.2)	57 (51.8)	41 (47.7)	22 (23.2)
Actively Smoking ¹	22 (33.3)	51 (26.1)	28 (48.3)	45 (30.4)	36 (37.9)	37 (33.0)	23 (34.3)	50 (36.2)
HIV Infection	43 (64.2)	84 (59.6)	32 (54.2)	94 (63.5)	56 (58.3)	71 (63.4)	42 (61.8)	84 (60.9)
Diabetes ¹	12 (8.6)	7 (10.6)	5 (8.5)	14 (9.6)	11 (11.5)	8 (7.3)	5 (7.4)	13 (9.6)
Low BMI (<18.5) ¹	30 (44.8)	50 (35.5)	32 (54.2)	48 (32.4)	49 (51.0)	31 (27.7)	35 (51.5)	42 (30.4)
Hospitalized at Treatment Initiation	23 (34.3)	31 (22.0)	21 (35.6)	32 (21.6)	32 (33.3)	22 (19.6)	19 (27.9)	31 (22.5)
Previous Use of First-Line TB Drugs	35 (52.2)	56 (39.7)	31 (52.5)	59 (39.9)	49 (51.0)	42 (37.5)	35 (51.5)	53 (38.4)

¹ Among participants included in end-of-treatment and post-treatment outcomes analyses, data on baseline alcohol consumption, smoking status, diabetes status, and low BMI were available for 236, 237, 235, and 237, respectively.

Supplementary Table 2. Univariable Analyses of Non-Radiographic Baseline Clinical Characteristics on Time-to-Culture-Conversion and Favorable End-of-Treatment Outcomes, STEM-TB Lesotho Cohort

Characteristics	Time-to-Culture-Conversion (N = 145)		Favorable End-of-Treatment Outcome (N = 238)	
	Hazard Ratio (95% Confidence Interval)	p-value	Odds Ratio (95% Confidence Interval)	p-value
Age (median, IQR)	1.00 (0.98-1.01)	0.46	0.98 (0.96-1.01)	0.25
Female	0.98 (0.68-1.40)	0.89	1.50 (0.53-4.23)	0.45
Unemployed	0.75 (0.53-1.06)	0.10	0.67 (0.28-1.62)	0.38
Alcohol Consumption ¹	0.82 (0.59-1.15)	0.25	0.75 (0.31-1.82)	0.52
Actively Smoking ²	0.86 (0.61-1.20)	0.37	1.96 (0.69-5.55)	0.21
HIV Infection	1.20 (0.85-1.70)	0.29	0.75 (0.29-1.91)	0.54
Diabetes ³	1.40 (0.77-2.55)	0.27	0.55 (0.15-2.05)	0.37
Low BMI (<18.5) ⁴	0.78 (0.55-1.10)	0.16	0.62 (0.25-1.53)	0.30
Hospitalized at Treatment Initiation	0.88 (0.59-1.30)	0.52	0.37 (0.15-0.91)	0.03
Previous Use of First-Line TB Drugs	0.82 (0.59-1.15)	0.25	0.80 (0.33-1.92)	0.62

¹ Data on alcohol consumption were available for 143 and 236 participants in culture conversion and end-of-treatment outcomes, respectively.

² Data on active smoking were available for 144 and 237 participants in culture conversion and end-of-treatment outcomes, respectively.

³ Data on diabetes status were available for 144 and 235 participants in culture conversion and end-of-treatment outcomes, respectively.

⁴ Data on baseline low BMI were available for 145 and 237 participants in culture conversion and end-of-treatment outcomes, respectively.

P-values are from two-sided Wald z-tests.

Supplementary Table 3. Analyses of Baseline Chest X-Ray Findings and Sputum Smear Grade on Primary Outcomes, with Additional Adjustment for Hospitalization at Treatment Initiation¹, STEM-TB Lesotho Cohort (N=238)

	Favorable End-of-Treatment Outcome	Favorable Post-Treatment Outcome
	Odds Ratio (95% Confidence Interval)	Odds Ratio (95% Confidence Interval)
Cavitary Disease	0.74 (0.25 - 2.21)	0.67 (0.25 – 1.81)
<i>P-value</i>	<i>0.59</i>	<i>0.43</i>
Fibrosis	0.48 (0.17 – 1.36)	0.56 (0.21 – 1.46)
<i>P-value</i>	<i>0.17</i>	<i>0.24</i>
Bilateral Disease	0.57 (0.18 - 1.78)	0.47 (0.16 – 1.35)
<i>P-value</i>	<i>0.33</i>	<i>0.16</i>
High Smear Grade	0.57 (0.20 – 1.67)	0.60 (0.22 - 1.61)
<i>P-value</i>	<i>0.31</i>	<i>0.31</i>

¹ Models of individual radiographic and smear features, adjusted for hospitalization at treatment initiation and for each other. Missing indicator method.

P-values are from two-sided Wald z-tests.

Supplementary Table 4. Analyses of Baseline Chest X-Ray Findings and Sputum Smear Grade on Time to Culture Conversion, Complete Case Analyses, STEM-TB Lesotho Cohort

	Univariable Hazard Ratio (95% Confidence Interval)						Multivariable Hazard Ratio (95% Confidence Interval)		
	Overall		No HIV		HIV		Overall	No HIV	HIV
	N	HR	N	HR	N	HR	(N = 125)	(N = 43)	(N = 82)
Cavitary Disease	133	0.74 (0.51 - 1.06)	46	0.51 (0.26 - 0.98)	87	0.87 (0.56 - 1.36)	0.98 (0.64 - 1.51)	0.69 (0.32 - 1.53)	1.20 (0.71 - 2.02)
<i>P-value</i>		0.10		0.04		0.54	0.93	0.36	0.50
Fibrosis	132	0.81 (0.55 - 1.19)	46	0.44 (0.23 - 0.84)	86	1.23 (0.75 - 2.02)	1.10 (0.71 - 1.71)	0.55 (0.25 - 1.24)	1.65 (0.92 - 2.93)
<i>P-value</i>		0.29		0.01		0.41	0.67	0.15	0.09
Bilateral Disease	133	0.51 (0.35 - 0.73)	46	0.61 (0.32 - 1.14)	87	0.43 (0.28 - 0.69)	0.56 (0.37 - 0.86)	0.93 (0.44 - 1.95)	0.47 (0.27 - 0.79)
<i>P-value</i>		<0.001		0.12		<0.01	<0.01	0.84	<0.01
High Smear Grade	141	0.58 (0.41 - 0.81)	49	0.46 (0.25 - 0.84)	91	0.64 (0.41 - 0.98)	0.69 (0.45 - 1.06)	0.82 (0.39 - 1.72)	0.65 (0.38 - 1.12)
<i>P-value</i>		<0.01		0.01		0.04	0.09	0.59	0.12

¹ Multivariable model contains all four features, adjusted for each other

P-values are from two-sided Wald z-tests.

Supplementary Table 5. Univariable Analyses of High-Risk Combinatory Chest X-Ray and Sputum Smear Grade Phenotypes on Primary Outcomes, Complete Case Analyses, STEM-TB Lesotho Cohort

	Time-to-Conversion		Favorable End-of-Treatment Outcome		Favorable Final Treatment Outcome	
Baseline Variable	N	HR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Both cavitary disease and high smear grade	126	0.54 (0.35 - 0.82)	181	0.34 (0.11 - 1.01)	181	0.29 (0.11 - 0.78)
<i>P-value</i>		<i><0.01</i>		<i>0.05</i>		<i>0.01</i>
Severe Fibrocavitary Disease ¹	132	0.48 (0.23 - 0.99)	207	0.20 (0.05 - 0.70)	207	0.19 (0.06 - 0.61)
<i>P-value</i>		<i>0.05</i>		<i>0.01</i>		<i><0.01</i>

¹ Participants with baseline radiographic evidence of both multi-lobar fibrosis and at least one cavity ≥5cm in diameter

P-values are from two-sided Wald z-tests.

Supplementary Table 6. Analyses of Baseline Chest X-Ray Findings and Sputum Smear Grade on Primary Outcomes, Complete Case Analyses, STEM-TB Lesotho Cohort

	Univariable Odds Ratio (95% Confidence Interval)						Multivariable ¹ Odds Ratio (95% Confidence Interval)		
	Overall		No HIV		HIV		Overall	No HIV	HIV
	N	OR	N	OR	N	OR	(N=180)	(N=71)	(N=109)
End-of-Treatment Outcome									
Cavitary Disease	208	0.39* (0.15 - 1.01)	81	0.28 (0.06 - 1.35)	127	0.47 (0.14 - 1.57)	0.62 (0.19 - 2.06)	0.35 (0.05 - 2.52)	0.86 (0.18 - 4.19)
<i>P-value</i>		0.05		0.11		0.22	0.43	0.29	0.85
Fibrosis	207	0.28 (0.11 - 0.75)	81	0.34 (0.07 - 1.64)	126	0.24 (0.07 - 0.86)	0.30 (0.09 - 0.96)	0.47 (0.06 - 3.33)	0.25 (0.06 - 1.12)
<i>P-value</i>		0.01		0.18		0.03	0.04	0.45	0.07
Bilateral Disease	208	0.36 (0.13 - 0.99)	81	0.14 (0.02 - 1.24)	127	0.53 (0.16 - 1.77)	0.71 (0.20 - 2.48)	0.32 (0.03 - 3.48)	0.96 (0.20 - 4.57)
<i>P-value</i>		0.05		0.08		0.30	0.59	0.35	0.96
High Smear Grade	206	0.40 (0.15 - 1.10)	80	0.45 (0.08 - 2.41)	126	0.38 (0.11 - 1.33)	0.97 (0.30 - 3.15)	0.95 (0.15 - 6.10)	1.02 (0.21 - 4.85)
<i>P-value</i>		0.08		0.35		0.13	0.96	0.95	0.98
Final Post-Treatment Outcome									
Cavitary Disease	208	0.35 (0.15 - 0.84)	81	0.29 (0.07 - 1.18)	127	0.40 (0.13 - 1.18)	0.51 (0.17 - 1.52)	0.34 (0.06 - 1.97)	0.60 (0.14 - 2.53)
<i>P-value</i>		0.02		0.08		0.10	0.23	0.23	0.49
Fibrosis	207	0.31 (0.13 - 0.76)	81	0.35 (0.09 - 1.44)	126	0.29 (0.09 - 0.90)	0.36 (0.13 - 1.02)	0.54 (0.10 - 3.04)	0.32 (0.08 - 1.23)
<i>P-value</i>		0.01		0.15		0.03	0.05	0.49	0.10
Bilateral Disease	208	0.31 (0.12 - 0.78)	81	0.10 (0.01 - 0.84)	127	0.48 (0.16 - 1.45)	0.47 (0.15 - 1.53)	0.16 (0.02 - 1.57)	0.79 (0.18 - 3.43)
<i>P-value</i>		0.01		0.03		0.19	0.21	0.12	0.76
High Smear Grade	206	0.41 (0.16 - 1.01)	80	0.78 (0.17 - 3.56)	126	0.27 (0.08 - 0.88)	1.04 (0.36 - 3.03)	1.92 (0.33 - 11.17)	0.69 (0.17 - 2.85)
<i>P-value</i>		0.05		0.75		0.03	0.94	0.47	0.61

¹ Multivariable models contain all four features, adjusted for each other

P-values are from two-sided Wald z-tests.

Supplementary Table 7. Analyses of High-Risk Combinatory Chest X-Ray and Sputum Smear Grade Phenotypes on Primary Outcomes, Lost to Follow-Up Sensitivity Analyses ¹, STEM-TB Lesotho Cohort (N = 240)

	Favorable End-of-Treatment Outcome	Favorable Final Treatment Outcome
Baseline Variable	Odds Ratio (95% Confidence Interval)	Odds Ratio (95% Confidence Interval)
Both cavitory disease and high smear grade	0.41 (0.14 - 1.18)	0.34 (0.13 - 0.88)
<i>P-value</i>	<i>0.10</i>	<i>0.03</i>
Severe Fibrocavitary Disease ²	0.24 (0.07 - 0.84)	0.22 (0.07 - 0.71)
<i>P-value</i>	<i>0.02</i>	<i>0.01</i>

¹ Two participants with outcomes of “lost to follow-up” included as having unfavorable end-of-treatment and final post-treatment outcomes.

² Participants with baseline radiographic evidence of both multi-lobar fibrosis and at least one cavity ≥5cm in diameter

P-values are from two-sided Wald z-tests.

Supplementary Table 8. Analyses of Baseline Chest X-Ray Findings and Sputum Smear Grade on Primary Outcomes, Lost to Follow-Up Sensitivity Analyses, STEM-TB Lesotho Cohort (N = 240)¹

	Univariable Odds Ratio (95% Confidence Interval)		Multivariable Odds Ratio (95% Confidence Interval)	
	Overall (N = 240)	HIV (N = 150)	Overall (N = 240)	HIV (N = 150)
Favorable End-of-Treatment Outcome				
Cavitary Disease	0.48 (0.19 - 1.18)	0.63 (0.21 - 1.96)	0.81 (0.29 - 2.27)	1.00 (0.28 - 3.59)
<i>P-value</i>	0.11	0.43	0.68	1.00
Fibrosis	0.39 (0.15 - 0.96)	0.39 (0.12 - 1.22)	0.52 (0.19 - 1.41)	0.48 (0.14 - 1.64)
<i>P-value</i>	0.04	0.11	0.20	0.24
Bilateral Disease	0.48 (0.19 - 1.22)	0.74 (0.24 - 2.26)	0.71 (0.25 - 2.01)	1.08 (0.30 - 3.85)
<i>P-value</i>	0.12	0.60	0.52	0.91
High Smear Grade	0.33 (0.13 - 0.86)	0.29 (0.09 - 0.93)	0.42 (0.15 - 1.17)	0.31 (0.09 - 1.11)
<i>P-value</i>	0.02	0.04	0.10	0.07
Favorable Final Treatment Outcome				
Cavitary Disease	0.42 (0.18 - 0.95)	0.51 (0.18 - 1.44)	0.71 (0.28 - 1.82)	0.84 (0.26 - 2.73)
<i>P-value</i>	0.04	0.20	0.48	0.77
Fibrosis	0.40 (0.17 - 0.93)	0.41 (0.14 - 1.19)	0.58 (0.23 - 1.45)	0.56 (0.18 - 1.75)
<i>P-value</i>	0.03	0.10	0.25	0.32
Bilateral Disease	0.40 (0.17 - 0.94)	0.64 (0.23 - 1.79)	0.57 (0.22 - 1.50)	0.97 (0.30 - 3.18)
<i>P-value</i>	0.04	0.40	0.25	0.96
High Smear Grade	0.34 (0.14 - 0.83)	0.22 (0.07 - 0.68)	0.47 (0.19 - 1.21)	0.25 (0.07 - 0.85)
<i>P-value</i>	0.02	<0.01	0.12	0.03

¹ Two participants with outcomes of “lost to follow-up” included as having unfavorable end-of-treatment and final post-treatment outcomes. Both participants who were lost to follow-up were living with HIV.

P-values are from two-sided Wald z-tests.