

**Supplementary Table S1.** Sociodemographic and clinical characteristics of participants with WGS available (N = 344) according to SNP differences to the closest other study participant.

Characteristic	Total (N = 344) N (%)	0-2 SNPs (N = 95) N (%)	3-5 SNPs (N = 97) N (%)	6-10 SNPs (N = 67) N (%)	> 10 SNPs (N = 85) N (%)	p-value <sup>a</sup>
Female sex	202 (59)	52 (55)	66 (68)	39 (58)	45 (53)	0.15
Age (median, IQR)	34 (28-43)	35 (29-43)	34 (26-47)	35 (30-45)	32 (28-39)	0.20
Monthly household income ≤ 2500 ZAR <sup>b</sup>	273 (79)	72 (76)	85 (88)	54 (81)	62 (73)	0.07
Ever smoker	35 (10)	11 (12)	9 (9)	4 (6)	11 (13)	0.51
Healthcare worker	24 (7)	8 (8)	3 (3)	8 (12)	5 (6)	0.15
Mine worker	5 (1)	1 (1)	0 (0)	3 (4)	1 (1)	0.12
Diabetes	22 (6)	3 (3)	6 (6)	10 (15)	3 (4)	<b>0.01</b>
HIV-positive	266 (77)	76 (80)	74 (76)	55 (82)	61 (72)	0.42
Median CD4 cell count (IQR) (cells/mm <sup>3</sup> )	240 (111-420)	212 (87-375)	296 (120-461)	194 (97-327)	311 (167-434)	<b>0.03</b>
Viral load undetectable	133 (50)	37 (49)	38 (51)	27 (49)	31 (51)	0.99
Receiving ART at study enrollment <sup>c</sup>	153 (74)	44 (76)	35 (65)	30 (71)	44 (85)	0.13
Cough	284 (83)	83 (87)	78 (80)	57 (85)	66 (78)	0.31
Median duration – weeks (IQR)	8 (4-12)	8 (4-12)	8 (4-12)	10 (5-12)	9 (4-12)	0.75
Cavitation on CXR	60 (17)	22 (23)	15 (15)	6 (9)	17 (20)	0.10
Acid-fast bacilli (AFB) smear positive	235 (70)	62 (67)	65 (69)	47 (73)	61 (73)	0.81
Any previous TB treatment	247 (72)	72 (76)	63 (65)	44 (66)	68 (80)	0.07
Prior drug-susceptible TB treatment	219 (64)	64 (67)	54 (56)	41 (61)	60 (71)	0.16
Median duration treatment – months (IQR)	6 (6-12)	7 (6-12)	7 (6-13)	6 (6-10)	6 (6-12)	0.79
Prior multidrug-resistant TB	105 (31)	32 (34)	23(24)	10 (15)	40 (47)	<b>&lt; 0.0001</b>

treatment						
Median duration treatment – months (IQR)	6 (4-14)	6 (5-14)	10 (6-15)	3.5 (3-4)	6.5 (4-9)	0.26
Prior cure or treatment completed <sup>d</sup>	7 (7)	3 (10)	2 (8)	0 (0)	2 (7)	0.22
Prior treatment failure <sup>d</sup>	80 (82)	23 (79)	21 (91)	10 (100)	21 (70)	
Prior lost to follow-up or transferred <sup>d</sup>	11 (11)	3 (10)	1 (4)	0 (0)	7 (23)	

<sup>a</sup> P-values are chi-square, Fisher's exact or Kruskal-Wallis.

<sup>b</sup> Currency conversion during study period approximately 1 U.S. Dollar (USD) = 8.4 South African Rand (ZAR); 2500 ZAR = \$298 US.

<sup>c</sup> ART start date available for 206 (77%) of participants.

<sup>d</sup> Treatment outcome available for 98 (93%) of the 105 who reported prior MDR TB treatment.

**Supplementary Table S2.** Pairwise SNP distances between isolates within the same RLFP group (AH-W) and within the same cluster group (1001-2300). Cluster groups containing fewer than three isolates are excluded. Median pairwise distance is shown for the closest participant within a cluster and for the overall cluster.

Cluster	# Isolates	# WGS	Lineage	Family	SNP distance	
					Median closest	Median overall
<b>10(AH)</b>	<b>15</b>	<b>8</b>	<b>4</b>	<b>X</b>		<b>14</b>
1003	10	6			6	11.5
<b>11(BF)</b>	<b>3</b>	<b>1</b>	<b>4</b>	<b>T</b>	.	.
<b>12(BH)</b>	<b>6</b>	<b>4</b>	<b>4</b>	<b>S</b>		<b>13</b>
<b>13(BM)</b>	<b>2</b>	<b>1</b>	<b>4</b>	<b>S</b>	.	.
<b>14(BW)</b>	<b>9</b>	<b>5</b>	<b>4</b>	<b>Harlem</b>		<b>18.5</b>
1401	6	3			6	24
<b>15(CC)</b>	<b>7</b>	<b>4</b>	<b>4</b>	<b>LAM</b>		<b>6.5</b>
<b>16(GD)</b>	<b>2</b>	<b>0</b>	<b>3</b>	<b>CAS</b>	.	.
<b>17(GY)</b>	<b>15</b>	<b>11</b>	<b>4</b>	<b>T</b>		<b>20</b>
1701	4	3			10	20
1702	4	4			9	16
<b>18(HP)</b>	<b>285</b>	<b>230</b>	<b>4</b>	<b>LAM</b>		<b>18</b>
1801	4	4			7	23
1802	3	3			23	23
1805	4	4			19.5	23.5
1810	14	13			8	21.5

1817	5	5			10	15.5
1818	208	163			5	16
1823	8	8			10.5	17.5

<b>19(KO)</b>	<b>1</b>	<b>1</b>	<b>4</b>	<b>S</b>	<b>.</b>	<b>.</b>
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<b>20(KR)</b>	<b>1</b>	<b>1</b>	<b>4</b>	<b>T</b>	<b>.</b>	<b>.</b>
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<b>21(M)</b>	<b>1</b>	<b>1</b>	<b>4</b>	<b>T</b>	<b>.</b>	<b>.</b>
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<b>22(MH)</b>	<b>28</b>	<b>20</b>	<b>2</b>	<b>Beijing</b>		<b>18</b>
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2201	5	3			14	21
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2207	4	3			6	10
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<b>23(W)</b>	<b>7</b>	<b>4</b>	<b>2</b>	<b>Beijing</b>		<b>211.5</b>
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WGS: Whole genome sequencing

**Supplementary Table S3.** SNP differences by epidemiologic link and history of prior MDR TB for participants with available WGS and matching RFLP pattern.

	<b>Person-to-person links (N = 29)</b>		<b>Hospital-based links (N = 37)</b>		<b>Unlinked (N = 240)</b>	
	Prior MDR	No MDR	Prior MDR	No MDR	Prior MDR	No MDR
<b>N (%)</b>	4 (14)	25 (86)	19 (54)	16 (46)	68 (28)	172 (72)
<b>SNPs (median [IQR])</b>	44 (31-50)	10 (6-19)	18 (15-27)	12 (9-18)	5 (2-14)	5 (3-8)