Supplementary File 4: Detailed drug and regimen information

Among individuals with a positive regimen-specific outcome

Detailed regimen duration information could only be analysed for patients with a positive treatment outcome, as only these individuals had full documentation of the use of each drug (and associated dates) across the entire treatment course. Individuals with other outcomes had regimens truncated to the date treatment stopped. Among the 408 individuals with a positive outcome, 374 (91.7%) had regimen data for the full duration of treatment. Thus the subsequent text describes the regimens used for these 374 patients.

The median overall treatment duration was 11.9 months and interquartile range (IQR) 9.3-12.1 months. This figure was slightly lower in the presence of Fqs (10.5 months), with a similar IQR (9.1-12.0). The median length of time on treatment before Hr was known was 1.8 months (IQR 1.1-2.2; eight individuals zero day delay) and after resistance was known 9.9 months (IQR 8.0-10.7).

372/374 individuals (99.5%) received R only, one Rb only, and one both drugs. (Across the entire cohort four patients were treated with Rb.) The median duration of Rf usage was 11.9 months (IQR 9.2 to 12.1). The median duration of E (371 individuals) was 11.8 months (9.1 to 12.1). These figures were 2.2 months (2.0 to 3.0; usually entirely in the initiation phase) for the 368 individuals given Z and 5.5 months (3.9 to 8.7) for the 151 given M. 400mg administered daily was the standard M dosage, with a few patients receiving 600mg. Six individuals received Fqs other than M (three ofloxacin, two Lfx, one ciprofloxacin), seven received group 4/5 drugs (five prothionamide, one prothionamide and cycloserine, one clarithromycin), and 11 injectables (eight S, three amikacin). Three of those receiving group 4/5 drugs and two receiving injectables had meningeal or spinal TB, or other CNS involvement. Five of the individuals receiving group 4/5 drugs and five receiving injectables had non-S additional drug resistance. Thirty five of the 374 individuals (9.4%) had their Rfs, E or Z dosed intermittently; this information was not known for seven patients. There was no evidence that any patients were given high dose H.

Thirteen detailed drug regimen categories were generated on the basis of the drugs within the regimen and Rf duration (Supplementary File 4 Table 1). The most common regimen categories were HRfZE (210/374, 56.1%) and HRfZE-M (119/374, 31.8%) (Supplementary File 4 Table 1). For these categories, the most common Rf duration was 9-12 months in both cases (116/210, 55.2% and 63/119, 52.9%, respectively).

369 of the 374 patients (98.7%) who completed treatment and had full regimen information had a documented date on which Hr was known. The most regimen initiated at this point (step-down regimen) was RfE (124/369, 33.6%), followed by RfZE (98, 26.6%) and RfZEM (77, 20.9%).

Table 1: Overall treatment regimens

Regimens used to treat Hr TB across the entire treatment course for the 374 patients who successfully completed treatment and had full regimen information available. Cat.- category, Col.- column, E- ethambutol, Fq- fluoroquinolone other than M, H- isoniazid, M-moxifloxacin, m- months, No.- number, Rf- rifamycin, +- plus additional drugs, (+)- with or without additional drugs

Regimen	No.	Col. %	Rifamycin duration	No.	Cat. %	Additional drugs	No.	Cat. %
HRfZE	210	56.1	≤6m	6	2.9			
			>6-≤9m	18	8.6			
			>9-≤12m	116	55.2			
			>12m	70	33.3			
HRfZE-M	119	31.8	≤6m	3	2.5			
			>6-≤9m	22	18.5			
			>9-≤12m	63	52.9			
			>12m	31	26.1			
HRfZE-M+	12	3.2				Injectables	6	50.0
						Injectables, group 4/5	2	16.7
						Fqs, group 4/5	2	16.7
						Group 4/5	2	16.7
HRfZE-Fq(+)	3	0.8				None	2	66.7
						Group 4/5	1	33.3
HRfZE+	2	0.5				Injectables	2	100.0
HRfZ-M	3	0.8						
HRfE-M	2	0.5						
HRfE	1	0.3						
RfZE-M	14	3.7						
RfZE(+)	5	1.3				None	4	80.0
						Injectables	1	20.0
RfE-M	1	0.3						
RfE-Fq	1	0.3						
RfE	1	0.3						
Total	**374**	**100.0**						

Use of fluoroquinolones

In order to ascertain whether the use of Fqs was unevenly distributed across key clinical and demographic groups, or whether different durations of Fqs were used in these groups, data were further tabulated. The inclusion, but not duration, of Fqs was associated within the presence of additional drug resistance and site of disease (Supplementary File 4 Tables 2 and 3). These two variables were thus included in sensitivity analyses (Supplementary File 8).

Supplementary File 4: continued

Table 2: The inclusion of fluoroquinolones in the treatment regimen, by important clinical and demographic characteristics

594 patients had at least some regimen data (Figure 1); 16 of these did not have information on the inclusion of fluoroquinolones in their regimen and thus 578 remain to examine the usage of this drug. CNS- central nervous system, Fq- fluoroquinolone other than M, M- moxifloxacin, TB- tuberculosis, *19 additional people were missing information on dosing frequency, ±- plus or minus, +ve- positive, -ve- negative

Exposure variables	Total	Fq/M included in regimen (row %)
Age (years)		
18-37	336	136 (40.5)
38-57	179	87 (48.6)
58-77	57	27 (47.4)
≥78	6	1 (16.7)
Site of disease		
Pulmonary ± extrapulmonary, smear +ve	176	90 (51.1)
Pulmonary ± extrapulmonary, smear –ve	147	61 (41.5)
Meningeal TB or other CNS involvement	21	14 (66.7)
Other extrapulmonary	234	86 (36.8)
Any additional drug resistance		
No	534	224 (42.0)
Yes	44	27 (61.4)
Thrice weekly dosing*		
More frequent	497	209 (42.1)
Thrice weekly	62	33 (53.2)
Adherence issues or treatment gaps		
No or unknown	451	187 (41.5)
Not severe or of unknown severity	69	33 (47.8)
Severe	58	31 (53.5)

Table 3: The overall duration of treatment, by important clinical and demographic characteristics

374 patients successfully completed treatment, had full regimen information available, and thus can have overall treatment duration calculated (Table 3). Durations quoted in months. CNS- central nervous system, IQR- inter-quartile range, TB- tuberculosis, *- seven additional people were missing information on dosing frequency, ±- plus or minus, +ve- positive, -ve- negative

Exposure variables	Total	Overall treatment duration (IQR)
Age (years)		
18-37	225	12.0 (9.3-12.2)
38-57	109	11.9 (9.2-12.0)
58-77	36	10.9 (9.2-12.1)
≥78	4	12.0 (11.8-12.2)
Site of disease		
Pulmonary ± extrapulmonary, smear +ve	108	12.0 (9.5-12.2)
Pulmonary ± extrapulmonary, smear –ve	97	11.9 (9.2-12.0)
Meningeal TB or other CNS involvement	8	12.3 (11.9-15.2)
Other extrapulmonary	161	11.8 (9.2-12.2)
Any additional drug resistance		
No	347	11.9 (9.3-12.1)
Yes	27	11.9 (9.2-13.0)
Thrice weekly dosing*		
More frequent	332	11.9 (9.3-12.1)
Thrice weekly	35	11.5 (9.2-12.2)
Adherence issues or treatment gaps		
No or unknown	306	11.9 (9.2-12.1)
Not severe or of unknown severity	37	12.0 (11.5-13.9)
Severe	31	10.6 (9.3-12.6)