

Study (Year)	Study location	Population	For those assigned to receive the WHO standard regimen (2HRZE/4HR)							
			Number treated per-protocol	HIV prevalence	Directly observed treatment	Treatment frequency	Follow-up duration	MIRU-VNTR confirmed relapse	Total relapsed	Risk of relapse (%)
Sharifi-Mood <i>et al.</i> (2006) ¹	Iran	HIV-negative adults with non cavitary, microbiologically confirmed, pulmonary tuberculosis	67	0 (0%)	Yes	Daily	60 months	Unclear	6	8.9
Blanc <i>et al.</i> (2011) ²	Multicentre	Adults not previously exposed to antiretroviral drugs with new diagnosed TB and a CD4 count <200 per cubic millimetre	484	484 (100%)	No	Daily	25 months (median)	No	22	4.5
Jawahar <i>et al.</i> (2013) ³	South India	HIV-negative adults with newly diagnosed, microbiologically confirmed, pulmonary tuberculosis	152	0 (0%)	Yes	3 times/ week	24 months	No	8	5.3
Jindani <i>et al.</i> (2004) ⁴	Multicentre	Adults with newly diagnosed, microbiologically confirmed, pulmonary tuberculosis	347	37 (9.7%)	Yes	Daily	30 months	Unclear	17	4.9
Johnson <i>et al.</i> (2009) ⁵	Multicentre	HIV-negative adults with non cavitary, microbiologically confirmed, pulmonary tuberculosis	185	0 (0%)	Yes	Daily	30 months	Yes	3	1.6
Lienhardt <i>et al.</i> (2011) ⁶	Multicentre	Adults with newly diagnosed, microbiologically confirmed, pulmonary tuberculosis	1170	77 (6.5%)	Yes	Daily intensive phase, 3 times/ week continuation	30 months	Yes	42	3.6
Mfinanga <i>et al.</i> (2014) ⁷	Multicentre	HIV-positive adults with culture-confirmed tuberculosis	1532	1532 (100%)	Unclear	Unclear	24 months	No	30	2.0
Nanteza <i>et al.</i> (2011) ⁸	Uganda	HIV-positive adults with microbiologically confirmed tuberculosis	214	214 (100%)	Yes	Unclear	23 months (mean)	Unclear	7	3.3
Swaminathan <i>et al.</i> (2010) ⁹	South India	HIV-positive adults with microbiologically confirmed tuberculosis	167	167 (100%)	Yes	3 times/ week	36 months	Yes	19	11.4

Table S1: Characteristics of excluded studies

Model	Predictors	Mixed Effect AUC	Fixed Effect AUC	Optimism corrected AUC for fixed effect ^a	N bootstrap replications
1	Reference Model [age + sex + HIV status]	0.66	0.67	0.64	200
2	Reference Model + cavitary disease	0.66	0.66	0.64	200
3	Reference Model + positive smear at 2 months treatment	0.67	0.67	0.65	200
4	Reference Model + positive culture at 2 months treatment	0.68	0.69	0.66	200
5	Reference Model + baseline cavitary disease plus positive smear at 2 months treatment	0.68	0.69	0.65	200
6	Reference Model + baseline cavitary disease plus positive culture at 2 months treatment	0.69	0.69	0.67	200

^a Optimism corrected AUC calculated for models where study was set as a fixed effect using rms (Version: 5.1.0) in RStudio (Version 1.0.44)

Table S2: Optimism corrected AUC

Model	1	2	3	4	5	6
Predictors	Reference Model [age + sex + HIV status]	Reference Model + cavitary disease	Reference Model + positive smear at 2 months treatment	Reference Model + positive culture at 2 months treatment	Reference Model + baseline cavitary disease plus positive smear at 2 months treatment	Reference Model + baseline cavitary disease plus positive culture at 2 months treatment
Participants who experienced relapse, n (% relapse within predicted probability category)						
< 5% predicted probability of relapse	19 (3.4)	15 (3.2)	15 (2.8)	15 (2.9)	15 (3.0)	13 (2.8)
5 - 15% predicted probability of relapse	38 (6.5)	40 (7.0)	42 (7.3)	43 (7.6)	36 (6.9)	41 (7.4)
> 15% predicted probability of relapse	10 (25.6)	10 (23.3)	9 (22.5)	7 (23.3)	14 (25.5)	10 (25.0)
Total	67	65	66	65	65	64
Participants who did not experience relapse, n (% who did not relapse within predicted probability category)						
< 5% predicted probability of relapse	545 (96.6)	447 (96.8)	506 (97.2)	504 (97.1)	484 (97.0)	451 (97.2)
5 - 15% predicted probability of relapse	545 (93.5)	533 (93.0)	535 (92.7)	524 (92.4)	488 (93.1)	511 (92.6)
> 15% predicted probability of relapse	29 (74.4)	33 (76.7)	31 (77.5)	23 (76.7)	41 (74.5)	30 (75.0)
Total	1119	1013	1072	1051	1013	992
NRI		0.02	0.11	0.17	0.23	0.15
95% CI	<i>Reference</i>	0.00-0.26	0.00-0.34	0.00-0.41	0.00-0.47	0.00 – 0.38
P Value		0.84	0.33	0.16	0.06	0.19
NRI = Net reclassification index						
Table S3: Reclassification among participants who did and did not experience relapse						

	Total number of patients	Total number of patients who relapsed (Risk of relapse, %)	Crude OR (95% CI)	Multi-predictor OR (95% CI) ^a
Age (years)				
Mean (SD)	31.4 (10.2)	33.8 (9.7)	1.0 (1.0-1.1)	1.0 (1.0-1.1)
Sex				
Female	370	13 (3.5)	<i>Reference</i>	<i>Reference</i>
Male	847	58 (6.8)	2.0 (1.1-3.6)	2.23 (1.17 - 4.24)
HIV co-infection				
Negative	1033	52 (5.0)	<i>Reference</i>	<i>Reference</i>
Positive	181	19 (10.5)	2.2 (1.2 - 3.8)	2.6 (1.4 - 4.6)
Weight (Kg)				
Mean (SD)	53.1 (9.0)	53.4 (8.0)	1.0 (0.9 - 1.0)	1.0 (0.9-1.0)
Cavitory disease at baseline				
No	409	24 (5.9)	<i>Reference</i>	<i>Reference</i>
Yes	697	44 (6.3)	1.2 (0.7-2.0)	1.2 (0.7 - 2.0)
Smear status at 2 months				
Negative	957	52 (5.4)	<i>Reference</i>	<i>Reference</i>
Positive	211	18 (8.5)	1.9 (1.1 - 3.3)	1.8 (1.0 - 3.2)
Culture status at 2 months				
Negative	902	47 (5.2)	<i>Reference</i>	<i>Reference</i>
Positive	244	22 (9.0)	2.0 (1.2 - 3.4)	1.8 (1.0 - 3.0)
Presence of baseline cavitory disease and positive smear at month 2				
No	946	53 (5.6)	<i>Reference</i>	<i>Reference</i>
Yes	160	16 (10.0)	2.2 (1.2 - 4.0)	2.1 (1.2 - 4.0)
Presence of baseline cavitory disease and positive culture at month 2				
No	906	50 (5.5)	<i>Reference</i>	<i>Reference</i>
Yes	178	18 (10.1)	2.2 (1.2 - 3.8)	2.0 (1.1 - 3.4)
^a Covariates included age, sex and HIV status at baseline.				
Table S4: Summary of association of patient level factors with treatment relapse for the modified intention to treat analysis set				

	Total number of patients	Total number of patients who relapsed (Risk of relapse, %)	Crude OR (95% CI)	Multi-predictor OR (95% CI) ^a
Age (years)				
Mean (SD)	31.4 (10.2)	35.0 (10.2)	1.0 (1.0 - 1.1)	1.0 (1.0 - 1.1)
Sex				
Female	392	12 (3.1)	<i>Reference</i>	<i>Reference</i>
Male	872	40 (4.6)	1.5 (0.8 - 2.9)	1.7 (0.9 - 3.4)
HIV co-infection				
Negative	1071	36 (3.4)	<i>Reference</i>	<i>Reference</i>
Positive	190	16 (8.4)	2.6 (1.4 - 4.9)	3.0 (1.6 - 5.6)
Weight (Kg)				
Mean (SD)	53.2 (9.0)	53.2 (8.7)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Cavitory disease at baseline				
No	425	15 (3.5)	<i>Reference</i>	<i>Reference</i>
Yes	730	35 (4.8)	1.4 (0.7 - 2.6)	1.4 (0.7 - 2.6)
Smear status at 2 months				
Negative	997	36 (3.6)	<i>Reference</i>	<i>Reference</i>
Positive	218	15 (6.9)	2.1 (1.1 - 3.7)	2.0 (1.1 - 3.8)
Culture status at 2 months				
Negative	936	34 (3.6)	<i>Reference</i>	<i>Reference</i>
Positive	255	17 (6.7)	1.9 (1.0 - 3.5)	1.7 (0.9 - 3.2)
Presence of baseline cavitory disease and positive smear at month 2				
No	989	36 (3.6)	<i>Reference</i>	<i>Reference</i>
Yes	166	14 (8.4)	2.4 (1.3 - 4.6)	2.5 (1.3 - 4.8)
Presence of baseline cavitory disease and positive culture at month 2				
No	943	35 (3.7)	<i>Reference</i>	<i>Reference</i>
Yes	188	15 (8.0)	2.2 (1.2 - 4.2)	2.1 (1.1 - 4.0)
^a Covariates included age, sex and HIV status at baseline.				
Table S5: Summary of association of patient level factors with treatment relapse determined at 12 months post-treatment completion				

	Total number of patients	Total number of patients who relapsed (Risk of relapse, %)	Crude OR (95% CI)	Multi-predictor OR (95% CI) ^a
Age (years)				
Mean (SD)	31.5 (10.3)	34.6 (9.9)	1.0 (1.0 - 1.1)	1.0 (1.0 - 1.1)
Sex				
Female	367	14 (3.8)	<i>Reference</i>	<i>Reference</i>
Male	832	63 (7.6)	2.1 (1.1 - 3.7)	2.2 (1.2 - 4.0)
HIV co-infection				
Negative	1020	59 (5.8)	<i>Reference</i>	<i>Reference</i>
Positive	177	18 (10.2)	1.9 (1.1 - 3.3)	2.2 (1.2 - 4.0)
Weight (Kg)				
Mean (SD)	53.0 (9.1)	52.5 (8.2)	1.0 (0.9 - 1.1)	1.0 (0.9 - 1.1)
Cavitory disease at baseline				
No	393	24 (6.1)	<i>Reference</i>	<i>Reference</i>
Yes	697	50 (7.1)	1.2 (0.7 - 2.0)	1.2 (0.7 - 2.1)
Smear status at 2 months				
Negative	943	56 (5.9)	<i>Reference</i>	<i>Reference</i>
Positive	207	19 (9.2)	1.7 (1.0 - 2.9)	1.6 (0.9 - 2.9)
Culture status at 2 months				
Negative	883	48 (5.4)	<i>Reference</i>	<i>Reference</i>
Positive	245	26 (10.6)	2.1 (1.3 - 3.5)	1.9 (1.2 - 3.2)
Presence of baseline cavitory disease and positive smear at month 2				
No	930	56 (6.0)	<i>Reference</i>	<i>Reference</i>
Yes	160	18 (11.3)	2.0 (1.1 - 3.6)	2.0 (1.1 - 3.6)
Presence of baseline cavitory disease and positive culture at month 2				
No	886	51	<i>Reference</i>	<i>Reference</i>
Yes	182	22	2.3 (1.3 - 3.9)	2.2 (1.3 - 3.7)
^a Covariates included age, sex and HIV status at baseline.				
Table S6: Summary of association of patient level factors with the combined outcome of relapse and reinfection for all studies				

Predictor	Model					
	1	2	3	4	5	6
HIV status at baseline	+	+	+	+	+	+
Cavitory disease at baseline		+				
Positive smear after 2 months of treatment			+			
Positive culture after 2 months of treatment				+		
Presence of both baseline cavitation and positive smear after 2 months of treatment					+	
Presence of both baseline cavitation and positive culture after 2 months of treatment						+
Total observations (N)	1187	1079	1139	1117	1079	1057
Total relapse (n)	67	65	66	65	65	64
AUC	0.62	0.62	0.63	0.65	0.64	0.66
95% CI^a	0.54-0.68	0.55-0.69	0.60-0.74	0.58-0.72	0.57-0.71	0.59-0.73
DeLong p-value	<i>Reference</i>	0.16	0.35	0.18	0.29	0.13

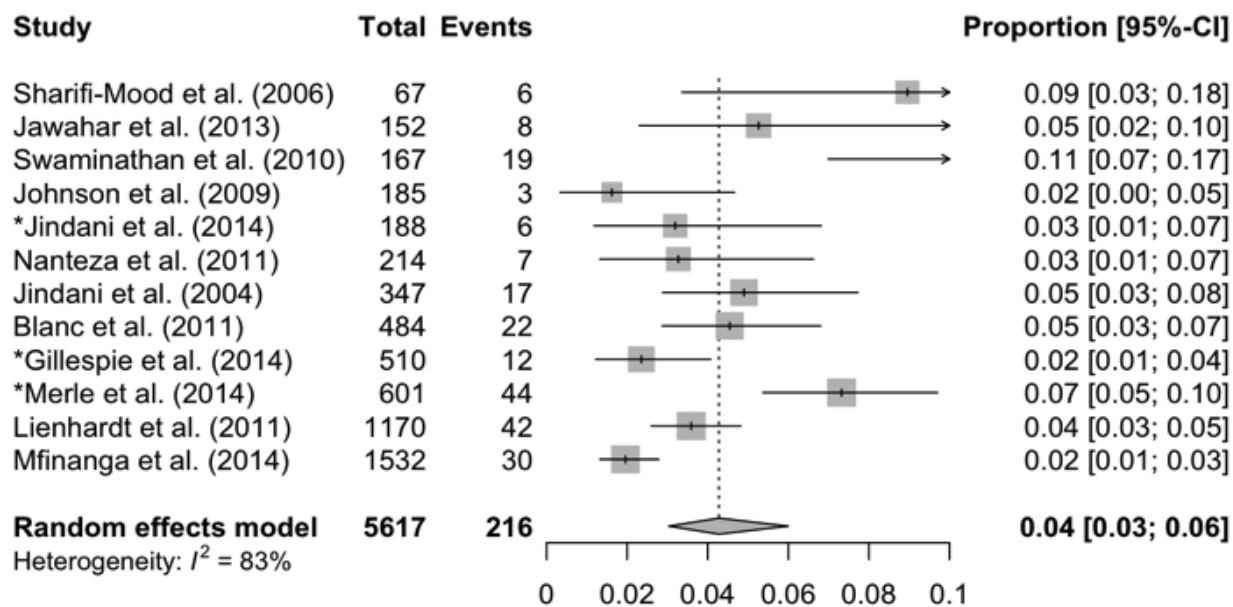
Variables included in the model are indicated by “+”

^a Bootstrap resampling (2000 resamples)

AUC = area under the ROC curve, ROC = receiver operating characteristic

Table S7: Summary of alternative multi-predictor models and ROC curves, without age or sex as a predictor.

Figure S1: Meta-analysis of relapse proportions from all published data (0.04 = 4% relapse rate). Studies included in the individual patient meta-analysis marked with an asterisk.



*Included in the IPD

References:

- 1 Sharifi-Mood B, Metanat M, Alavi-Naini R, *et al.* The comparison of six-month and four-month regimens of chemotherapy in the treatment of smear positive pulmonary tuberculosis. *J Med Sci* 2006; **6**: 108–111.
- 2 Blanc F-X, Sok T, Laureillard D, *et al.* Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011; **365**: 1471–1481.
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- 4 Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *The Lancet* 2004; **364**: 1244–1251.
- 5 Johnson JL, Hadad DJ, Dietze R, *et al.* Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. *Am J Respir Crit Care Med* 2009; **180**: 558–563.
- 6 Lienhardt C, Cook SV, Burgos M, *et al.* Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial. *Jama* 2011; **305**: 1415–1423.
- 7 Mfinanga SG, Kirenga BJ, Chanda DM, *et al.* Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. *Lancet Infect Dis* 2014; **14**: 563–571.
- 8 Nanteza MW, Mayanja-Kizza H, Charlebois E, *et al.* A randomized trial of punctuated antiretroviral therapy in Ugandan HIV-seropositive adults with pulmonary tuberculosis and CD4+ T-Cell Counts of \geq 350 cells/ μ L. *J Infect Dis* 2011; **204**: 884–892.
- 9 Swaminathan S, Narendran G, Venkatesan P, *et al.* Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. *Am J Respir Crit Care Med* 2010; **181**: 743–751.