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Factors associated with treatment adherence in a randomised trial of latent tuberculosis infection treatment

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SUMMARY

SETTING: Randomised controlled trial of latent tuberculosis infection (LTBI) treatment in 10 clinics in Canada, Saudi Arabia and Brazil.

OBJECTIVE: To identify early predictors of LTBI treatment adherence, including pre-treatment characteristics.

DESIGN: Patients randomised to 4 months of rifampicin (RMP; $n = 420$) or 9 months of isoniazid ($n = 427$) were monitored for adherence using an electronic device. Outcomes were 1) treatment completion, defined as intake of ⩾80% of the prescribed doses, and further categorised as completed within the allotted time or not; and 2) treatment regularity, measured by the time interval between doses. Relative risk (RR) and adjusted odds ratios (aOR) of patients' pre-treatment characteristics and adherence at first follow-up visit were calculated.

RESULTS: Completion of treatment was higher with RMP (aOR 4.3, 95%CI 2.7–6.8). Early predictors (first follow-up visit) of non-adherence were late first visit attendance (RR for completion in time 0.9, 95%CI 0.8–0.98), >20% of missed doses (RR 0.4, 95%CI 0.3–0.6) and greater variation of hours between doses (0.209 vs. 0.131, $P < 0.001$). Serious adverse events were not associated with irregularity of treatment.

CONCLUSION: The shorter RMP regimen was associated with better adherence. Patients with poor adherence could be identified at the first follow-up visit from their punctuality in follow-up, missed doses and variability of pill-taking.

KEY WORDS: adherence; compliance; isoniazid; rifampicin; tuberculosis

TREATMENT for latent TB infection (LTBI), an important strategy if tuberculosis (TB) is to be eradicated by 2050,[1] usually consists of 6 to 12 months of isoniazid (INH).[1] The effectiveness of LTBI treatment depends largely on adherence, which ranges from as low as 25% to 90%.[2–5] INH is known to cause drug-induced hepatitis, peripheral neuritis, skin rashes and other significant side effects.[6] Even when side effects are not present, completion rates of INH treatment are low, often less than 50%.[7–10] Although baseline factors such as alcoholism, homelessness, psychiatric disorders and drug addiction have been associated with TB treatment default,[11] few studies have addressed the predictors of non-adherence to LTBI treatment. Reasons for low adherence to preventive INH treatment, other than side effects, have been analysed in many, mostly retrospective, studies, and include patient preference for shorter regimens,[12] fear of stigma,[13] disbelief in INH safety,[14] and pharmacy shortage of INH supply,[14] among others.

Shorter regimens have been proposed, such as rifampicin (RMP) and pyrazinamide (PZA) for 2 months, which was widely used when recommended in 2000, but was abandoned due to unacceptable rates of adverse events.[15,16] One currently recommended alternative to INH treatment is RMP for 4 months.[8,17]

In the present prospective study, we aimed to identify early predictors of adherence to LTBI treatment, including pre-treatment clinical characteristics. We also aimed to analyse the association of side effects with irregularity of treatment.

METHODS

The study was conducted in 10 health care facilities in Canada, Brazil and Saudi Arabia, and was approved by the institutional review boards at each site. All patients gave written informed consent to participate.

The trial design and methods have been described elsewhere.[18] Briefly, adults aged ⩾18 years whose primary treating physician had recommended treatment for LTBI were randomised to take either one 300 mg tablet of INH daily for 9 months (9INH) or two 300 mg capsules of RMP daily for 4 months (4RMP).

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All doses were self-administered and patients were instructed to take doses at the same time every 24 h, at the time they found most convenient. A total of 847 patients were randomised and followed monthly for 4 months and thereafter, at the treating physician's discretion. No incentives for treatment adherence or clinic attendance were offered. Adverse events were reviewed by a panel of three external experts who judged the type and severity of adverse events and whether they were drug-related, without knowledge of the study drug or the opinions of the treating physicians or other panel members. Complete blood counts and liver transaminases (alanine aminotransferase/aspartate aminotransferase) were obtained before treatment (pre-treatment blood tests), after 1 and 2 months of treatment, and thereafter at the treating physician's discretion.

At each follow-up visit, the patients were assessed by their primary treating physician and nurse, who evaluated their punctuality with clinic appointments, self-reported pill-taking behaviour and any symptoms.

Measurement of adherence

Adherence to treatment was measured according to three different criteria: the number of doses taken (treatment completion), the allotted time to complete treatment (see definition of outcomes below) and the time interval between doses (regularity). Adherence was monitored by an electronic device in the pill bottle cap that recorded the date and time the bottle was opened (micro-electro-mechanical system [MEMS] device, Aprex Corporation, Fremont, CA, USA),[19] and by pill count by the attending physician or nurse. Whenever results were discordant, doses taken were based on MEMS recordings, given the published evidence of their better correlation with treatment outcomes.[20]

Data analysis

Definition of outcomes

Based on previous reports on INH treatment efficacy,[21] treatment completion was defined as the intake of at least 80% of prescribed doses. This represented 96 doses for patients taking 4RMP and 216 doses for patients taking 9INH. The time allotted to treatment completion was 150 days for 4RMP patients and 301 days for 9INH patients.[18] Treatment completion was classified as 1) completed within the allotted time, 2) completed in extended time (>150 days for RMP and >301 days for INH) or 3) not completed.

Regularity of treatment was measured by the variance of time interval between doses. Ideally, the interval between doses should have been 24 h. Pills taken more than 36 h after the previous dose were considered as a missed dose. Calculation of the variance of the dose-to-dose interval excluded intervals that contained missed doses. Adherence measures at the first follow-up visit included 1) the number and percentage of missed doses, 2) the variance of the time interval between doses (as defined below) and 3) punctuality in the first scheduled follow-up visit.

Methods of analysis

Associations between treatment outcomes and patient pre-treatment and first month characteristics were estimated with relative risks (RRs) and 95% confidence intervals (95%CIs). Variables associated with outcomes in the univariate analysis with $P < 0.10$ were included in a multivariate logistic regression analysis to calculate adjusted odds ratios (aORs).

The variance of the interval (in hours) between doses was calculated by dividing the standard deviation by the mean interval. The Kruskal-Wallis test was used to compare median variance among groups. $P < 0.05$ was considered statistically significant.

RESULTS

Between 27 April 2004 and 31 January 2007, 847 patients with a median age of 33 years (range 18–84) were included in the study. Among these, 427 patients were randomised to the 9INH arm and 420 to the 4RMP arm. Four patients were excluded from further analysis due to pregnancy and one due to death unrelated to the study drug.

The Figure shows the number of subjects included in each analysis. Forty patients were excluded from completion analysis as their treatment was interrupted by their treating physician: 23 developed severe (Grade 3–4) adverse events, and 17 developed Grade 1–2 adverse events,* but treatment discontinuation was considered justified by the independent review panel. Among 802 patients analysed for treatment completion (Table 1A), 583 (73%) completed treatment and were further analysed for time to completion (Table 1B). Among these, 494 completed treatment within the allotted time, representing 62% of all randomised patients.

As seen in Table 1A, pre-treatment factors associated with higher completion rates were the 4RMP treatment and study site. Because country of birth and site of recruitment were highly correlated, only study site was included in the multivariate analysis.

Among those who completed treatment, completion within the allotted time (Table 1B) was associated with 4RMP treatment, obtaining the pre-treatment blood tests and having an abnormal chest radiograph. On the other hand, smokers and close contacts presented lower rates of completion within the allotted time.

Irregularity of treatment, estimated from the variance of time interval between doses, was associated

*Adverse events were graded as recommended by the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0 (1999; http://ctep.info.nih.gov/reporting/ctc.html). Accessed December 2008.

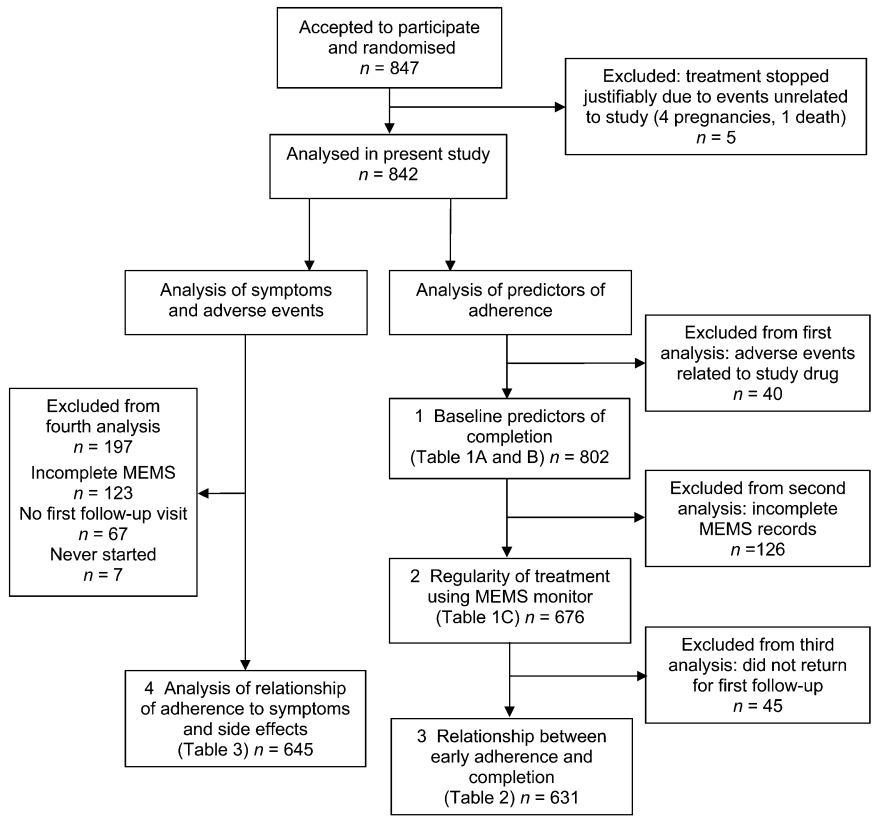

Figure Number of study subjects included in analyses. MEMS = micro-electro-mechanical system.

with 9INH treatment, study site, Canadian aboriginal ethnic origin, high incidence of TB in country of origin (including foreign and Canadian sites), recent immigration to Canada, being a contact and missing pre-treatment blood tests (Table 1C).

Measures of adherence at the first follow-up visit (1 month) that were associated with treatment completion included lower variance of interval between doses, return to first follow-up visit at scheduled time, and taking more than 80% of doses during the first month (Table 2). Reporting symptoms (any symptom) at the first follow-up visit was not associated with failure to complete treatment (Table 3). At the first month, 13% of patients on INH and 6% of patients on RMP had missed over 20% of doses (RR 2.3, 95%CI 1.4–3.8, $P = 0.001$).

Predictors of final completion of therapy, based on the first month follow-up visit, included all measures of adherence (Table 4). The highest variability in dose intervals and the highest percentage of missed doses were observed among patients who defaulted from treatment but did not report any symptoms at the 1-month follow-up visit.

DISCUSSION

Early recognition of patients at risk for sub-optimal adherence could help health care providers target strategies for these individuals. In the present study, a shorter regimen with 4 months of RMP was the factor most strongly associated with adherence, regardless of adverse events or symptoms and despite the higher number of pills to be taken daily. The odds of completing treatment within the allotted time were four-fold higher if the patient was assigned to 4RMP than if assigned to 9INH, and completion within the allotted time was 2.5 fold higher. In addition, regularity of drug intake was also higher with the 4RMP regimen.

The present study was not designed to evaluate if our findings were attributable to a shorter regimen or to the specific 4RMP regimen. Increased adherence to shorter regimens with drugs other than INH have been suggested in retrospective studies,[22,23] a review study[10] and small randomised clinical studies.[24] On the other hand, adherence to 2 months of RMP+PZA was often not better than to 6–12 months of INH,[25] which likely reflected poor tolerance, a factor not always accounted for. In a previous prospective study, Rennie et al. reported that another short regimen, 3 months of RMP+INH, had better completion rates than 6INH.[12] In that study, offering the choice of regimen to patients doubled the likelihood of completion, indicating the potential importance of patient preference. Adherence failure rates were greatest at the start of treatment for both regimens, despite a similar proportion of drug reactions. Moreover, clinic attendance before starting LTBI treatment was an early predictor

Table 1 Completion of latent tuberculosis treatment according to baseline characteristics

	A Numbers completing among 802 patients*				**B** Time to completion of 583 patients†				**C** Regularity of treatment among 676 patients‡	
	Completed (n = 583) n (%)	Did not complete (n = 219) n (%)	Relative risk for completion		Within time (n = 494) n (%)	In extended time (n = 89) n (%)	Relative risk for completion within allotted time		Median variance of interval between doses, hours [IQR]#	P value**
			Crude (95%CI)	Adjusted (95%CI)§			Crude (95%CI)	Adjusted (95%CI)¶		
Age, years										
18–34	322 (72)	126 (28)	0.98 (0.9–1.1)	0.9 (0.5–1.4)	271 (84)	51 (16)	0.99 (0.9–1.1)	0.7 (0.4–1.2)	0.159 [0.113–0.221]	0.096
⩾35	260 (74)	93 (26)	1.0 (reference)	1.0 (reference)	223 (85)	38 (15)	1.0 (reference)	1.0 (reference)	0.152 [0.098–0.210]	
Sex										
Male	324 (76)	102 (24)	1.1 (1.0–1.2)	1.1 (0.7–1.7)	283 (87)	41 (13)	1.1 (1.0–1.2)	1.5 (0.9–2.6)	0.154 [0.110–0.219]	0.830
Female	259 (69)	117 (31)	1.0 (reference)	1.0 (reference)	211 (81)	48 (19)	1.0 (reference)	1.0 (reference)	0.158 [0.108–0.213]	
Treatment arm										
4RMP	328 (81)	75 (19)	1.3 (1.2–1.4)	4.3 (2.7–6.8)	289 (88)	39 (12)	1.8 (1.1–2.9)	2.5 (1.5–4.1)	0.145 [0.092–0.198]	<0.001
9INH	255 (64)	144 (36)	1.0 (reference)	1.0 (reference)	205 (80)	50 (19)	1.0 (reference)	1.0 (reference)	0.173 [0.126–0.225]	
Country of birth										
Canada	91 (70)	39 (30)	—		74 (81)	17 (19)	—	—		
Aboriginal	19 (59)	13 (41)	0.8 (0.6–1.1)	—	14 (74)	5 (26)	0.9 (0.7–1.2)		0.152 [0.089–0.182]	0.029
Non-aboriginal	72 (73)	26 (27)	1.0 (reference)		60 (83)	12 (17)	1.0 (reference)		0.126 [0.125–0.198]	
Brazil	62 (53)	55 (47)	0.7 (0.6–0.9)		34 (55)	28 (45)	0.7 (0.5–0.8)		0.159 [0.108–0.243]	
Saudi Arabia	27 (64)	15 (36)	0.9 (0.7–1.1)		25 (93)	2 (7)	1.1 (0.96–1.3)		0.207 [0.163–0.249]	
Born elsewhere (Canadian centres)										<0.001
Low TB incidence	18 (75)	6 (25)	1.0 (0.8–1.3)	—	18 (100)	0	1.1 (0.99–1.3)††		0.119 [0.068–0.202]	
Intermediate TB incidence	42 (79)	11 (21)	1.1 (0.9–1.3)		35 (83)	7 (17)	1.0 (0.8–1.2)		0.147 [0.087–0.195]	
High TB incidence	343 (79)	93 (21)	1.1 (0.9–1.2)		308 (90)	35 (10)	1.1 (0.97–1.2)		0.159 [0.111–0.217]	
Reason for treatment[17]										
TB contact	167 (64)	92 (36)	0.9 (0.8–1.0)	—	121 (72)	46 (28)	0.3 (0.2–0.6)	0.5 (0.3–0.9)	0.167 [0.117–0.225]	
TST conversion	40 (74)	14 (26)	1.0 (0.9–1.2)		35 (88)	5 (13)	0.98 (0.9–1.1)		0.157 [0.099–0.216]	
Abnormal CXR	181 (85)	31 (15)	1.2 (1.1–1.3)		163 (90)	18 (10)	1.0 (0.94–1.1)	1.1 (0.6–1.9)	0.141 [0.096–0.191]	0.003
HIV infection	11 (92)	1 (8)	1.3 (1.1–1.6)		10 (91)	1 (9)	1.0 (0.8–1.2)		0.119 [0.096–0.184]	
Recent immigrant	31 (61)	20 (39)	0.9 (0.7–1.1)		28 (90)	3 (10)	1.0 (0.9–1.2)		0.164 [0.130–0.210]	
Other risk factors	153 (72)	61 (29)	1.0 (reference)		137 (90)	16 (10)	1.0 (reference)		0.165 [0.111–0.234]	
Recruitment centre										
1	263 (79)	69 (21)	1.0 (reference)	1.0 (reference)	239 (91)	24 (9)	1.0 (reference)		0.146 [0.101–0.210]	
2	104 (83)	22 (17)	1.0 (1.0–1.2)	1.0 (0.5–2.0)	91 (88)	13 (13)	0.96 (0.9–1.1)	0.8 (0.4–1.8)	0.163 [0.115–0.202]	
3	48 (76)	15 (24)	1.0 (0.8–1.1)	1.4 (0.5–3.7)	38 (79)	10 (21)	0.9 (0.8–1.0)	0.5 (0.2–1.2)	0.180 [0.140–0.263]	
4	18 (67)	9 (33)	0.8 (0.6–1.1)	0.5 (0.2–1.4)	17 (94)	1 (6)	1.0 (0.9–1.2)	2.5 (0.3–20.5)	0.198 [0.127–0.240]	
5	6 (46)	7 (54)	0.6 (0.3–1.0)	0.3 (0.2–1.1)	3 (50)	3 (50)	0.6 (0.3–1.2)	0.1 (0.0–0.4)	0.142 [0.090–0.201]	<0.001
6	20 (64)	11 (36)	1.7 (1.0–2.9)	0.8 (0.2–2.6)	17 (85)	3 (15)	0.9 (0.8–1.1)	0.6 (0.2–2.3)	0.153 [0.111–0.250]	
7	14 (74)	5 (26)	1.3 (0.6–2.8)	1.1 (0.2–5.5)	13 (93)	1 (7)	1.0 (0.9–1.2)	1.8 (0.2–15.2)	0.117 [0.063–0.168]	
8	21 (66)	11 (34)	0.8 (0.6–1.1)	0.5 (0.2–1.5)	17 (81)	4 (19)	0.9 (0.7–1.1)	0.3 (0.1–1.3)	0.143 [0.083–0.182]	
9	62 (53)	55 (47)	0.7 (0.6–0.8)	0.2 (0.1–0.4)	34 (55)	28 (45)	0.6 (0.5–0.8)	0.2 (0.1–0.6)	0.159 [0.108–0.243]	
10	27 (64)	15 (36)	0.8 (0.6–1.0)	0.5 (0.2–1.4)	25 (93)	2 (7)	1.0 (0.9–1.1)	1.1 (0.2–4.9)	0.207 [0.163–0.249]	
TST size, mm										
5–9	32 (70)	14 (30)	1.0 (reference)	—	28 (88)	4 (13)	1.0 (reference)	—	0.153 [0.090–0.195]	
10–14	180 (70)	78 (30)	1.0 (0.8–1.2)		142 (79)	38 (21)	0.9 (0.8–1.1)		0.159 [0.109–0.211]	0.453
⩾15	371 (75)	127 (26)	1.1 (0.9–1.3)		324 (87)	47 (13)	1.0 (0.9–1.1)		0.158 [0.110–0.221]	

History of BCG vaccination										
Yes	284 (70)	122 (30)	0.9 (0.8–1.0)	—	236 (83)	48 (17)	0.95 (0.9–1.0)	—	0.154 [0.101–0.215]	
No	153 (75)	51 (25)	1.0 (reference)		134 (88)	19 (13)	1.0 (reference)		0.156 [0.110–0.199]	0.845
Unknown	146 (76)	46 (24)	1.0 (0.9–1.1)		124 (85)	22 (15)	0.97 (0.9–1.1)		0.159 [0.114–0.235]	
Other medical problems										
Any	138 (72)	153 (28)	0.7 (0.6–0.7)	0.95 (0.6–1.6)	117 (85)	21 (15)	1.0 (0.9–1.1)	—	0.292 [0.110–0.217]	0.449
No	445 (73)	166 (27)	1.0 (reference)	1.0 (reference)	377 (85)	68 (15)	1.0 (reference)		0.300 [0.108–0.215]	
Use of hormonal contraception										
Yes	26 (67)	13 (33)	0.96 (0.8–1.2)	—	18 (69)	8 (31)	0.8 (0.6–1.1)	—	0.165 [0.111–0.245]	0.497
No	233 (69)	104 (31)	1.0 (reference)		194 (83)	39 (17)	1.0 (reference)		0.155 [0.107–0.212]	
Use of other medications										
Yes	135 (75)	44 (25)	1.1 (0.95–1.2)	—	113 (84)	22 (16)	0.98 (0.9–1.1)	—	0.155 [0.111–0.206]	0.739
No	448 (72)	175 (28)	1.0 (reference)		381 (85)	67 (15)	1.0 (reference)		0.157 [0.106–0.220]	
History of allergies										
Yes	43 (81)	10 (19)	1.1 (0.98–1.3)	—	36 (84)	7 (16)	0.99 (0.9–1.1)	—	0. 143 [0.115–0.169]	0.113
No	540 (72)	209 (28)	1.0 (reference)		458 (85)	82 (15)	1.0 (reference)		0.159 [0.108–0.219]	
Injecting drug use										
Yes	4 (57)	3 (43)	0.8 (0.4–1.5)	—	3 (75)	1 (25)	0.9 (0.5–1.6)	—	0.123 [0.067–0.185]	0.676
No	579 (73)	216 (27)	1.0 (reference)		491 (85)	88 (15)	1.0 (reference)		0.157 [0.109–0.217]	
Alcohol use										
Heavy (daily)	27 (64)	15 (36)	1.4 (0.9–2.1)	—	20 (74)	7 (26)	0.9 (0.7–1.1)	—	0.162 [0.118–0.230]	
Slight–moderate	186 (71)	76 (29)	1.1 (0.9–1.4)		155 (83)	31 (17)	0.97 (0.9–1.0)		0.161 [0.109–0.215]	0.913
None/never	370 (74)	128 (26)	1.0 (reference)		319 (86)	51 (14)	1.0 (reference)		0.155 [0.107–0.215]	
Cigarette smoking										
Currently	101 (64)	57 (36)	0.9 (0.8–0.98)	0.7 (0.4–1.3)	85 (84)	16 (16)	0.98 (0.9–1.1)	0.3 (0.1–0.9)	0.154 [0.111–0.209]	
Ex-smoker	46 (82)	10 (18)	0.9 (0.8–1.0)	1.5 (0.6–3.8)	34 (74)	12 (26)	0.9 (0.7–1.0)	0.9 (0.5–1.8)	0.140 [0.104–0.205]	0.547
Never	436 (74)	152 (26)	1.0 (reference)	1.0 (reference)	375 (86)	61 (14)	1.0 (reference)		0.159 [0.109–0.219]	
Baseline CXR[17]										
Abnormal	218 (81)	50 (19)	1.2 (1.1–1.3)	1.5 (0.9–2.5)	194 (89)	24 (11)	1.1 (1.01–1.2)	1.1 (0.6–1.9)	0.144 [0.099–0.198]	0.003
Normal	365 (68)	169 (32)	1.0 (reference)	1.0 (reference)	300 (82)	65 (18)	1.0 (reference)		0.164 [0.099–0.198]	
Baseline transaminases										
Normal	522 (75)	170 (25)	1.0 (reference)		451 (86)	71 (14)	1.0 (reference)		0.155 [0.109–0.215]	
Above normal limits	42 (67)	21 (33)	0.9 (0.7–1.1)		36 (86)	6 (14)	0.99 (0.9–1.1)		0.152 [0.100–0.218]	0.013
Missing	19 (40)	28 (60)	0.5 (0.4–0.8)	0.7 (0.3–2.0)‡‡	7 (37)	12 (63)	0.4 (0.2–0.8)	0.2 (0.1–0.6)	0.204 [0.150–0.275]	

*45 patients stopped treatment for reasons considered justified by an independent review panel (1 death, 4 pregnancies, 40 adverse events) and were excluded from these analysis (Figure).
†264 patients excluded from this analysis: 1 death, 4 pregnancies, 40 adverse events related to study drug and 219 who did not complete treatment (Figure).
‡171 patients excluded: 1 death, 4 pregnancies, 40 adverse effects related to study drug, 126 incomplete or unreliable MEMS records. Reasons included loss or destruction of bottles, problems with the electronic device and obvious repetitive opening of bottle without pill withdrawal (Figure).
§Relative risk adjusted for treatment arm and recruitment centre.
¶Adjusted for treatment arm, recruitment centre, cigarette smoking and missing baseline transminases.
#Intervals of >36 h were considered missed doses and are excluded from analysis of variance of interval between doses.
**Kruskal-Wallis test.
††1 added to each cell to allow calculation of relative risk.
‡‡Reference was blood test performed (regardless of normal or abnormal result).
CI = confidence interval; IQR = interquartile range; RMP = rifampicin; INH = isoniazid; TB = tuberculosis; TST = tuberculin skin test; CXR = chest radiograph; HIV = human immunodeficiency virus; BCG = bacille Calmette-Guérin.

Table 2 Relationship between evaluation at first follow-up visit and final latent tuberculosis treatment outcomes among 631 patients*

Data from first follow-up visit	Completed within allotted time (n = 470)	Completed in extended time (n = 67)	Did not complete (n = 94)	P value†
Time from start of treatment, days, median [IQR]	28 [25–32]	28 [27–35]	28 [26–35]	0.061
Visit >35 days after start of treatment, n (%)				
Yes	66 (14)	19 (28)	24 (26)	—
No	404 (86)	48 (72)	70 (74)	
RR (95%CI)‡	1.0 (reference)	0.9 (0.8–0.98)	0.9 (0.8–0.98)	
Variance between doses, hours, median [IQR]§	0.131 [0.064–0.213]	0.159 [0.092–0.283]	0.209 [0.137–0.311]	<0.001
Number of missed doses, median [IQR]	0 [0–1]	2 [0–5]	2 [0–6]	<0.001
Proportion of doses taken, n (%)				
≤80%	17 (4)	14 (21)	29 (31)	—
>80%	453 (96)	53 (79)	65 (69)	
RR (95%CI)	1.0 (reference)	0.6 (0.4–0.8)	0.4 (0.3–0.6)	

*216 patients excluded: 1 death, 4 pregnancies, 40 adverse effects related to study drug, 126 incomplete MEMS records and 45 who did not return for first follow-up visit (Figure).
†Kruskal-Wallis test.
‡RR for completion in time without symptoms.
§Intervals of >36 h were considered missed doses and are excluded from the analysis of variance of interval between doses.
IQR = interquartile range; RR = relative risk; CI = confidence interval; MEMS = micro-electro-mechanical system.

Table 3 Relationship between symptoms at first follow-up visit and final latent tuberculosis treatment outcomes among 707 patients*

	Completed within allotted time (n = 494) n (%)	Completed in extended time (n = 89) n (%)	Did not complete (n = 124) n (%)	P value†
Presence of any symptom				
Yes	134 (27)	29 (33)	44 (35)	
No	360 (73)	60 (67)	80 (65)	0.051
RR (95%CI)‡	1.0 (reference)	1.0 (0.9–1.0)	0.9 (0.8–1.0)	
Presence of CNS symptoms				
Yes	20 (4)	3 (3)	9 (7)	
No	474 (96)	86 (97)	115 (93)	0.180
RR (95%CI)	1.0 (reference)	1.0 (0.9–1.2)	0.9 (0.7–1.1)	
Presence of skin symptoms				
Yes	16 (3)	2 (2)	5 (4)	
No	478 (97)	87 (98)	119 (96)	0.777
RR (95%CI)	1.0 (reference)	1.1 (0.9–1.2)	1.0 (0.8–1.2)	
Presence of fatigue				
Yes	61 (12)	10 (11)	17 (14)	
No	433 (88)	79 (89)	107 (86)	0.763
RR (95%CI)	1.0 (reference)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	
Presence of peripheral neuritis				
Yes	7 (1)	2 (2)	3 (2)	
No	487 (99)	87 (98)	121 (98)	0.392
RR (95%CI)	1.0 (reference)	0.9 (0.7–1.3)	0.9 (0.6–1.3)	
Presence of gastrointestinal symptoms				
Yes	59 (12)	17 (19)	31 (25)	
No	435 (88)	72 (81)	93 (75)	<0.001
RR (95%CI)	1.0 (reference)	0.9 (0.8–1.03)	0.8 (0.7–0.9)	
Presence of non-specific symptoms				
Yes	28 (6)	6 (7)	15 (12)	
No	466 (94)	83 (93)	109 (88)	0.016
RR (95%CI)	1.0 (reference)	1.0 (0.8–1.1)	0.8 (0.6–1.0)	

*138 patients excluded: 1 death, 4 pregnancies, 40 adverse effects related to study drug, 93 who did not return for first follow-up visit (Figure).
†χ^2 for trend.
‡RR for completion in time without symptoms.
RR = relative risk; CI = confidence interval; CNS = central nervous system.

Table 4 Relationship of adherence in the first month of therapy to symptoms, adverse events and completion of latent tuberculosis treatment among 645 patients*

	Did not complete treatment			Completed treatment			
	Adverse events related to drug according to DMSB/MD decision to stop (n = 22)	Drop-out with symptoms (n = 44)	Drop-out without symptoms (n = 42)	Completed in extended time (n = 67)	Completed in time with symptoms (n = 131)	Completed in time without symptoms (n = 339)	P value†
Variance between doses in first month, hours, median [IQR]	0.193 [0.111–0.242]	0.177 [0.102–0.292]	0.236 [0.145–0.335]	0.159 [0.092–0.283]	0.131 [0.059–0.228]	0.133 [0.065–0.211]	<0.001
Number of missed doses in first month, median [IQR]	0 [0–1.5]	1.5 [0–5]	5 [0–14.5]	2 [0–5]	0 [0–1]	0 [0–1]	<0.001
Percentage of missed doses in first month, median [IQR]	0 [0–8.6]	6.1 [0–18.2]	16.6 [0–36.5]	5.9 [0–17.8]	0 [0–3.2]	0 [0–3.6]	<0.001
Proportion of doses taken at first follow-up, n (%)							
⩽80%	2 (9)	9 (20)	19 (45)	14 (21)	5 (4)	12 (4)	—
>80%	20 (91)	35 (80)	23 (55)	53 (79)	126 (96)	327 (96)	
RR (95%CI)‡	0.9 (0.7–1.1)	0.6 (0.4–0.9)	0.4 (0.3–0.7)	0.5 (0.4–0.8)	0.98 (0.7–1.3)	1.0 (reference)	

* 202 patients excluded: 1 death, 4 pregnancies, 7 who never started, 67 who did not return for first follow-up visit, and 123 incomplete MEMS records (Figure).
† Kruskal-Wallis test.
‡ RR for completion in time without symptoms.
DMSB = Drug Monitoring Safety Board; MD = medical doctor; IQR = interquartile range; RR = relative risk; CI = confidence interval; MEMS = micro-electro-mechanical system.

of adherence in that study, a finding that corroborates our results.

In a large retrospective study, Page et al. evaluated 2149 patients on LTBI treatment under routine programme conditions.[22] As in our study, treatment completion was higher (2.9 fold) among 4RMP-treated patients. Unlike Rennie et al.'s and our own findings, differences in adherence were not observed early on, and the authors attributed the higher completion rate to treatment duration. In Page et al.'s study, the best completion rate was observed among those aged <18 years, an age group not included in our study. Their completion rate was worse among those with side effects.[22]

For programmatic purposes, a significant finding was that early adherence, measured by regularity of treatment and percentage of doses taken, was predictive of final completion of treatment. This has been reported previously.[7,12] In a prospective study of 471 patients taking 4RMP, their odds of completing LTBI treatment were significantly higher than those of a historic control group who had taken 9INH.[10] Default at first month was nearly three times more frequent among 9INH- than among 4RMP-treated patients.[10] Interestingly, in our study, at early follow-up, completers in extended time, who represented 15% of completers, presented non-adherence characteristics such as frequent missed doses and irregularity of treatment. This means that patients presenting at early follow-up with non-adherence characteristics should be counselled for reinforcement to complete treatment, as a significant proportion may finally complete treatment. Indeed, based on the Bethel Isoniazid Studies, Comstock concluded that protection against TB is related to the number of doses taken, regardless of time to treatment completion.[26,27]

Patients in Brazil had consistently poorer adherence in our study, which is unexplained. The relationship between overall adherence and early pill-taking behaviour (percentage of doses taken or variability when they were taken) was not different in this site compared to others. To explore this finding, studies on health beliefs and cultural and socio-economic factors that might influence acceptance and adherence to LTBI treatment are ongoing in Brazil. It is noteworthy that the overall rate of treatment completion (73%) was higher than that reported under field conditions, regardless of the regimen, a finding already reported in other research randomised trials.[28,29] Interventions such as monetary or nutritional incentives, reminders, education, counselling and supervised treatment by health care workers have been applied to enhance adherence with LTBI treatment, but no single intervention has shown consistent effectiveness.[5] Identifying and understanding barriers to treatment adherence could facilitate the development of more effective and specific targeted interventions. Beliefs and attitudes may be more important than side

effects in predicting adherence and influencing health behaviour.[12,30,31]

The electronic device was helpful to measure irregularity of treatment, an early predictor of defaulting. Although electronic devices cannot attest that the drug was ingested, they have clear advantages over self-reported assessment and drug-level measurements, such as objectivity and long-term adherence evaluation. Nevertheless, around 15% of patients did not return the bottles or opened the bottle repeatedly, making the device records unreliable, which may have led to some bias in regularity analyses. We suggest that adherence should be measured by more than one method, when available.

It has been suggested that irregularity in treatment (erratic timing) may lead to varying levels of drug availability, with shorter intervals between doses resulting in the occurrence of more frequent side effects due to drug peaks.[32] In addition, irregular pill-taking has been associated with increased occurrence of acute immunologically mediated renal failure and hypersensitivity reactions to RMP.[33,34] In our study, however, irregularity of drug intake use was not related to adverse events.

In summary, completion of LTBI treatment can be predicted at the start of treatment based on certain health behaviours and can be more precisely predicted at the time of the first follow-up visit based on a careful assessment of early adherence. After initiating LTBI treatment, patients should be seen within the first month, at which time their adherence should be carefully assessed. Those with sub-optimal adherence must be targeted to enhance adherence, although the efficacy of such interventions remains to be proven.

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RÉSUMÉ

CONTEXTE : Essai contrôlé randomisé du traitement de la tuberculose latente (LTBI) dans 10 polycliniques au Canada, en Arabie Saoudite et au Brésil.

OBJECTIF : Identifier des facteurs prédictifs précoces de l'adhésion au traitement de la LTBI, y compris les caractéristiques préalables au traitement.

SCHÉMA : On a suivi grâce à un système électronique les patients randomisés vers un traitement de 4 mois à la rifampicine (RMP ; $n = 420$) ou vers 9 mois à l'isoniazide ($n = 427$) en ce qui concerne leur adhésion thérapeutique. Les résultats ont été 1) l'achèvement du traitement, défini comme la prise de 80% ou davantage des doses prescrites et ont été classés ultérieurement comme achèvement ou non au cours de la période permise ; et 2) la régularité du traitement mesurée par l'intervalle de temps entre les doses. On a calculé le risque relatif (RR) et le rapport des cotes ajusté (aOR) des caractéristiques du patient avant traitement et l'adhésion lors de la première visite de suivi.

RÉSULTATS : L'achèvement du traitement est plus fréquent lors du traitement à la RMP (aOR 4,3 ; IC95% 2,7–6,8). Les facteurs prédictifs précoces (lors de la première visite de suivi) de non-adhésion sont une présentation tardive lors de la première visite (RR pour achèvement à temps 0,9 ; IC95% 0,8–0,98), la non-utilisation de >20% des doses (RR 0,4 ; IC95% 0,3–0,6) et une plus grande variation du nombre d'heures séparant les doses (0,209 vs. 0,131 ; $P < 0,001$). Les effets indésirables graves ne sont pas en association avec l'irrégularité du traitement.

CONCLUSION : Le régime plus court avec RMP est en association avec une meilleure adhésion. Les patients dont l'adhésion est médiocre pourraient être identifiés lors de la première visite de suivi en fonction de leur ponctualité en matière de suivi, et en fonction des doses oubliées et de la variabilité dans la prise des médicaments.

RESUMEN

MARCO DE REFERENCIA: Un estudio comparativo aleatorizado del tratamiento de la infección tuberculosa latente (LTBI) en 10 consultorios en Canadá, Arabia Saudita y Brasil.

OBJETIVO: Detectar los factores pronósticos precoces de cumplimiento con el tratamiento de la LTBI, teniendo en cuenta las características previas al tratamiento.

MÉTODOS: Los pacientes se distribuyeron aleatoriamente en dos grupos que recibirían 4 meses de rifampicina (RMP; $n = 420$) o 9 meses de isoniazida ($n = 427$); se supervisó el cumplimiento terapéutico mediante un dispositivo electrónico. Las variables de evaluación fueron: 1) la compleción del tratamiento, definido como la toma como mínimo de 80% de las dosis recetadas, que luego se clasificó como en finalizado en el tiempo previsto o fuera de él; y 2) la regularidad del tratamiento evaluada mediante el intervalo entre las dosis. Se calcularon el riesgo relativo (RR) y el cociente de posibilidades ajustado (ORa) de las características analíticas de los pacientes antes del tratamiento y en la primera consulta de seguimiento.

RESULTADOS: La compleción del tratamiento en el grupo que recibió RMP fue más alta (ORa 4,3; IC95% 2,7–6,8). Los factores pronósticos tempranos de incumplimiento (en la primera cita de seguimiento) fueron una primera cita de seguimiento tardía (RR para el cumplimiento oportuno 0,9; IC95% 0,8–0,98), >20% de dosis no recibidas (RR 0,4; IC95% 0,3–0,6) y una variabilidad más grande en el horario de la toma de las dosis (0,209 contra 0,131; $P < 0,001$). Las reacciones adversas graves no se relacionaron con la irregularidad del tratamiento.

CONCLUSIÓN: El tratamiento más corto de 4 meses con RMP se asoció con un mejor cumplimiento. Los pacientes con cumplimiento precario se podrían detectar en la primera cita de seguimiento, en función de su puntualidad al control, las dosis perdidas y la variabilidad en la toma de los comprimidos.