

1 **Forgiveness is the attribute of the strong: non-adherence and**
2 **regimen-shortening in drug-sensitive TB**

3

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66 Scientific Knowledge on the Subject

67 Non-adherence to tuberculosis (TB) treatment is known to be associated with a

68 greater likelihood of a negative outcome. It is possible that the robustness

69 ('forgiveness') of shorter treatment regimens for missing even a single dose will be

70 reduced versus longer regimens, as there are fewer doses within the regimen.

71 Additionally, regimens may be differentially robust towards missing doses during the

72 intensive phase versus the continuation phase of treatment.

73

74 What This Study Adds to the Field

75 Reassuringly, we did not find a difference in the robustness of the four- versus six-

76 month regimens included in this study to missing even small numbers of doses. The
77 intensive phase was not found to be less robust than the continuation phase to non-
78 adherence, despite the higher bacterial load expected in the former. The detrimental
79 impact of missing doses during the intensive phase may be partly explained because
80 these patients go on to miss doses during the continuation phase. Indeed, there will
81 common causes of missing doses in both periods that we could not adjust for in our
82 modelling. Critically, the continuation phase of treatment should not be neglected
83 when it comes to providing adherence-promoting support to patients.

84

85 This article has an online data supplement, which is accessible from this issue's
86 table of content online at www.atsjournals.org

87 **Abstract**

88 **Rationale**

89 'Forgiveness' charts the ability of a drug or regimen to withstand non-adherence
90 without negative clinical consequences.

91

92 **Objectives**

93 We aimed to determine the influence of regimen length, regimen drugs and dosing,
94 and when during treatment non-adherence occurs on the forgiveness of anti-
95 tuberculosis regimens.

96

97 **Methods**

98 Using data from three randomised controlled trials comparing experimental four-
99 month regimens for drug-sensitive tuberculosis with the standard six-month regimen,
100 we used generalised linear models to examine how the risk of a negative composite
101 outcome changed as dose-taking decreased. The percentage of doses taken and
102 absolute number of doses missed were calculated, during the intensive and
103 continuation phases of treatment, and overall. A mediation analysis was undertaken
104 to determine how much of the association between intensive phase dose-taking and
105 the negative composite outcome was mediated through continuation phase dose-
106 taking.

107

108 **Measurements and Main Results**

109 Forgiveness of the four-month and six-month regimens did not differ for any
110 treatment period. Importantly, four-month regimens were no less forgiving of small
111 numbers of absolute missed doses than the six-month regimen (e.g. for 3-7 missed

112 doses versus no missed doses (baseline), six-month regimen adjusted risk ratio 1.65
113 (95% confidence interval 0.80-3.41) and four-month regimens 1.80 (1.33-2.45)). No
114 four-month regimen was conclusively more forgiving than another. We found
115 evidence of mediation by continuation phase dose-taking on the intensive phase
116 dose-taking and negative composite outcome relationship.

117

118 **Conclusions**

119 With the current appetite for, and progress towards, shorter drug-sensitive
120 tuberculosis regimens worldwide, we offer reassurance that shorter regimens are not
121 necessarily less forgiving of non-adherence. Given the importance of continuation
122 phase adherence, patient support during this period should not be neglected.

123

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126

127 **Introduction**

128 Progress in reducing the length of treatment for drug-sensitive tuberculosis (TB)
129 during the 20th century culminated in the observation that use of rifampicin (R) and
130 pyrazinamide (Z) could reduce duration to six months.(1) Since the mid-1980s,
131 further reductions have been elusive. Various approaches have been taken,
132 particularly the inclusion of fluoroquinolones in the regimen or increasing the dose of
133 a rifamycin.(2) Until the landmark results from Study 31/A5349 (which used both
134 strategies),(3) no four-month regimen had demonstrated non-inferiority.

135

136 A frequently-used argument in favour of shortening treatment is that this will
137 decrease the medication burden and thus the likelihood of non-adherence.(4) This is
138 for two reasons- firstly, shorter regimens mean that the potential for early
139 discontinuation is reduced (i.e. stoppage of medication earlier than initially
140 prescribed) and secondly, a shorter duration of treatment means that there is less
141 time during which doses can be skipped.(5) Conversely, shortening treatment may
142 increase the relative importance of each dose and thus missing even a single dose
143 may be problematic.(6)

144

145 A drug can be 'forgiving' of missed doses if its duration of action extends from one
146 dosing interval into the next.(7) For example, if a drug is dosed daily and a dose is
147 taken on day one but missed on day two, a drug in which the duration of action is
148 longer than 24 hours will be able to withstand this gap in dosing without negative
149 clinical consequences. The drug composition of regimens, as well as dosing, can
150 therefore alter forgiveness for regimens of different lengths.(6) Improving regimen
151 forgiveness is a complementary measure to adherence-promoting interventions to

152 combat non-adherence.

153

154 Although non-adherence has been found to be strongly associated with negative
155 outcomes from treatment for both four- and six-month anti-TB regimens,(8) there has
156 been limited research directly comparing the forgiveness of the six-month and
157 different four-month regimens.

158

159 The phase of treatment in which non-adherence occurs may also be influential.
160 Given the step-down in the number of drugs that participants take between the
161 intensive and continuation phases and expected reduction in bacterial load, both
162 adherence behaviours and forgiveness may alter as participants progress through
163 treatment.

164

165 In our study, we investigated three research gaps- the influence of 1) regimen length,
166 2) regimen drugs and dosing, and 3) treatment period on forgiveness for non-
167 adherence- as follows:

168 1) By comparing the risk of a negative composite outcome (treatment failure,
169 death and recurrence/reinfection) when different a) percentages of doses are
170 taken or b) absolute numbers of doses were missed of i) four- versus ii) six-
171 month regimens,

172 2) By comparing the risk of a negative composite outcome when different
173 percentages of doses are taken in different four-month regimens,

174 3) By comparing the risk of a negative composite outcome when different
175 percentages of doses are taken during the i) intensive versus ii) continuation
176 phases of treatment.

177 We used secondary data from three randomised controlled trials (RCTs) of treatment
178 shortening for drug-sensitive TB, which provided high-quality, contemporary, data for
179 analysis from both four- and six-month treatment regimens. Some of the results of
180 this study have been previously reported in the form of an abstract.(9)

181

182

183 **Methods**

184 **Parent studies and population for analysis**

185 Data for this study were obtained from the OFLOTUB, REMox, and RIFAQUIN RCTs
186 of four-month fluoroquinolone-containing regimens versus six-month regimens for
187 drug-sensitive, newly diagnosed, smear positive pulmonary TB (Online Data
188 Supplement Table E1).(10-12) The fluoroquinolones used were either moxifloxacin
189 (M) or gatifloxacin (G). All studies used the standard short-course regimen of two
190 months of isoniazid (H), R, Z and ethambutol (E) followed by four months of HR
191 (2HRZE/4HR) as the control regimen against which non-inferiority of the four-month
192 regimens was assessed. We excluded the experimental six-month regimen from
193 RIFAQUIN and participants with an unknown regimen.

194

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196 Drug Regimens (CPTR) Database. The CPTR initiative is a public-private
197 partnership launched in March 2010 by Critical Path Institute (C-Path), the Bill &
198 Melinda Gates Foundation (BMGF) and the Global Alliance for TB Drug
199 Development (TB Alliance).

200

201

202 **Measuring and defining non-adherence to treatment**

203 Non-adherence to treatment for TB was captured by direct observation/supervision
204 of doses in all three RCTs (Online Data Supplement Table E1). In the available
205 datasets, the greatest frequency at which dose-taking was reported was weekly
206 (number of doses taken in seven days) and the lowest frequently was dose-taking in
207 the intensive or continuation phases (number of doses taken in each phase). Data
208 on dose-taking by phase was thus common to all studies.

209

210 The percentage of doses taken was calculated across three 'periods'- the intensive
211 phase, continuation phase, and overall (the sum of the two phases). These
212 calculations took into account the frequency of dosing (Online Data Supplement
213 Table E1) i.e.

214

215
$$\text{Percentage of doses taken for a given treatment period} = \frac{t}{p}$$

216 *t*= number of doses taken across the given treatment period

217 *p*= number of doses prescribed across the given treatment period, a function of
218 dosing frequency and regimen length

219

220 The absolute number of missed doses was also calculated for each of the three
221 periods:

222
$$\text{Absolute number of missed doses for a given treatment period} = p - t$$

223

224 Specific data cleaning per trial is documented in Online Data Supplement Text E1.

225

226

227 **Negative composite outcome**

228 Broadly (Online Data Supplement Table E2), our definition of a negative composite
229 outcome arising during or after treatment was taken from the primary efficacy
230 analyses of the original RCTs i.e. included treatment failed,
231 relapse/recurrence/retreatment of TB, death during or after treatment, adverse
232 events and lost to follow-up.

233

234 Additionally, as patients who died during treatment, were lost to follow-up and had
235 their regimen changed due to adverse events would have taken fewer doses of their
236 treatment because dose-taking was not possible from the date of this event onwards,
237 we also created a restricted negative composite outcome for sensitivity analyses. A
238 negative outcome for this variable consisted of treatment failure (which was
239 assessed at the end of treatment), post-treatment relapse/recurrence/retreatment of
240 TB, and death due to TB after treatment.

241

242 **Other variables**

243 See Online Data Supplement Text E1.

244

245 **Statistical methods**

246 Data cleaning and analyses were undertaken in Stata 15.1 and Stata 17. Online
247 Data Supplement Table E3 documents all the models used.

248

249 ***Forgiveness of the four- versus six-month regimens (objective 1)***

250 Objective 1 sought to compare the forgiveness of the four- versus six-month
251 regimens for non-adherence measured as either a) percentage of doses taken

252 (strictly, a measure of adherence rather than non-adherence) or b) absolute number
253 of doses missed.

254

255 Generalised linear models with a log link, Gaussian distribution and robust variance
256 estimator were used to calculate risk ratios (RRs) at different levels of non-
257 adherence (percentages of doses taken, baseline 100%) for the negative composite
258 outcome for both four- and six-month regimens.(13) This method was chosen
259 because of convergence issues using a binomial distribution; the robust variance
260 estimator corrects the resulting standard errors. Marginal probabilities were used to
261 calculate risks. Risk differences (RDs; identity link) were also determined. Risks,
262 RRs, and RDs were all calculated from both 'unadjusted' and 'adjusted' models.

263

264 In addition to the exposure and outcome, unadjusted models included a three-level
265 fixed-effect for trial- as this presented a potential source of clustering- and the four-
266 versus six-month regimen variable. Causal frameworks determined *a priori* the
267 additional covariates for adjusted models- age, sex, ethnicity, HIV status and CD4
268 count, smear status and cavitation at baseline. The most severe grouping of smear
269 status was used as the default.

270

271 *a) Percentage of doses taken*

272 Percentage dose-taking was modelled using fractional polynomials to allow for a
273 non-linear effect (Online Data Supplement Text E1).

274

275 Within both unadjusted and adjusted multiplicative (RR) and additive (RD) models,
276 the presence of an interaction between percentage dose-taking and the four- versus

277 six-month regimen variable was assessed (Wald test).

278

279 Models were run separately for the exposures of percentage dose-taking overall,
280 during the intensive phase, and during the continuation phase.

281

282 The following sensitivity analyses for the multiplicative models were undertaken for
283 each period: given that pill burden was greater among those of higher weight,
284 participant weight at screening/baseline was adjusted for. An alternative coding of
285 smear status at baseline (least severe grouping) was used. The impact of an
286 alternative coding of OFLOTUB percentage dose-taking was also assessed (Online
287 Data Supplement Text E1). Finally, models were re-run using the restricted negative
288 composite outcome.

289

290 *b) Absolute number of doses missed*

291 These analyses used the absolute number of pills missed (categorical variable) as
292 the exposure. Adjusted and unadjusted, multiplicative and additive, models were run
293 for the absolute number of doses missed overall, during the intensive phase, and
294 during the continuation phase. The presence of an interaction between the absolute
295 number of doses missed and the four- versus six-month regimen variable was
296 assessed.

297

298 In sensitivity analyses, these models were re-run using the restricted negative
299 composite outcome.

300

301

302 ***Forgiveness of different four-month regimens (objective 2)***

303 Next, we sought to examine the combined impact of drugs and dosing on the
304 forgiveness of the different four-month regimens. Percentage dose-taking was used
305 as the non-adherence measure. Adjusted and unadjusted, multiplicative and
306 additive, models were run separately for the exposures percentage dose-taking
307 overall, during the intensive phase, and during the continuation phase. The presence
308 of an interaction between percentage dose-taking and the different regimens was
309 assessed.

310

311 In sensitivity analyses, these models were re-run using the restricted negative
312 composite outcome.

313

314 ***Forgiveness during each treatment phase (objective 3)***

315 Here, we sought to examine the relative forgiveness of the intensive and
316 continuation phases of treatment. Separately for the four- and six-month regimens,
317 RRs for the negative composite outcome were calculated comparing >95-100%
318 (baseline) versus 0-95% dose-taking.

319

320 There is a known association between non-adherence during the intensive and
321 continuation phases of treatment- i.e. individuals who adhere less well during the
322 intensive phase are more likely to adhere less well during the continuation phase-
323 (14) and it seemed likely that non-adherence in both phases would separately
324 influence the likelihood of the negative composite outcome. We hypothesised that
325 the total effect c of percentage dose-taking during the intensive phase of treatment
326 on the risk of the negative composite outcome (as calculated above) is composed of

327 both a direct effect (purely as a result of intensive phase percentage dose-taking; c')
328 and an indirect effect (intensive phase percentage dose-taking influencing
329 continuation phase percentage dose-taking; a product of a and b) (Figure 1). This is
330 called mediation.

331

332 To examine the hypothesis that continuation phase percentage dose-taking is a
333 mediator of the intensive phase percentage dose-taking \rightarrow negative composite
334 outcome relationship, we used two approaches- a 'traditional' approach comparing
335 regression models with and without conditioning on the mediator and the medeff
336 package in Stata (Online Data Supplement Text E1).(15-17) For both methods, we
337 grouped dose-taking as a binary variable.

338

339 Within the traditional approach, we approximated the direct effect c' of intensive
340 phase percentage dose-taking on the composite outcome by adjusting for
341 continuation phase percentage dose-taking. We examined the association between
342 intensive phase percentage dose-taking and continuation phase percentage dose-
343 taking (path a) using a multiplicative model with continuation phase percentage
344 dose-taking as the outcome and intensive phase dose-taking as the exposure. Path
345 b was approximated by the RR for continuation phase percentage dose-taking on the
346 composite outcome, including adjusting for intensive phase percentage dose-taking
347 and/or culture status at two months. Models were run separately for the six- and
348 four-month regimens. In sensitivity analyses, these models were re-run using the
349 restricted negative composite outcome.

350

351 Use of medeff extended this analysis by including an interaction term between the

352 two phases of percentage dose-taking, and calculated the proportion of the total
353 effect of intensive phase percentage dose-taking mediated through continuation
354 phase percentage dose-taking (Online Data Supplement Text E1). In sensitivity
355 analyses, these models were re-run using the restricted negative composite
356 outcome.

357

358 **Results**

359 ***Characteristics of the study population***

360 3,686 participants were available from the three RCTs and met the inclusion criteria
361 for this study (Online Data Supplement Figure E1). 1,565 received six months of
362 treatment with 2HRZE/4HR, and 2,121 four months' of treatment with one of several
363 regimens. 1,491 (95.3%) participants who received six months' of treatment had
364 non-adherence and outcome data and 2,045 (96.4%) who received four months' of
365 treatment.

366

367 The characteristics of the study cohort are given in Table 1. 2,473/3,536 of included
368 study participants (69.9%) were male. The median age was 29 years (interquartile
369 range 24-38). 3,026/3,536 (85.6%) were HIV negative. Participants overwhelmingly
370 had smear positive disease and 2,153/3,418 (60.9%) had cavitation. Percentage
371 dose-taking was very high for both four- and six-month regimens (median 100%,
372 lowest decile 95%; median 100%, lowest decile 92%; respectively) and across all
373 treatment periods (Table 1 and Online Data Supplement Figure E2). Within the
374 cohort, 678/3,536 (19.2%) participants had the negative composite outcome (Table
375 1).

376

377 ***Forgiveness of the four- versus six-month regimens (objective 1)***

378 *Percentage of doses taken*

379 For all three periods of treatment (overall, intensive, and continuation) and in both
380 unadjusted and adjusted models, RRs (baseline 100% of doses taken) showed that
381 the risk of a negative composite outcome increased steeply with reducing
382 percentage dose-taking for both four- and six-month regimens (Online Data
383 Supplement Table E4; Figure 2b, e, h). Comparing the RRs, four-month regimens
384 seemed more robust to missed doses than the six-month regimen (Wald p-values for
385 test for interaction between regimens grouped by length and percentage of doses
386 taken all $p < 0.0001$). Examination of the marginal risks, however, demonstrated that
387 even at 100% dose-taking the four-month regimens had a greater risk of a negative
388 composite outcome than the six-month regimen (Figure 2a, d, g). As dose-taking
389 reduced, the risk curves for the four- and six-month regimens started to converge
390 thus, in fact, the four-month regimens were not more robust. RDs were similar for the
391 four- and six-month regimens (Figure 2c, f, i; Wald p-values for test for interaction
392 overall- 0.06, intensive phase- 0.06, continuation phase- 0.07).

393

394 Sensitivity analyses (weight, smear status, alternative coding of percentage dose-
395 taking) gave similar results (Online Data Supplement Table E5-7). Use of the
396 restricted negative composite outcome reduced the number of negative outcomes to
397 399; there were too few to fit fractional polynomials. Instead, percentage dose-taking
398 was grouped in 5% categories and used as the (linear) exposure. As expected, the
399 effect estimates were reduced in these models. These results also suggested that
400 the four-month regimens were no more or less robust to lower levels of dose-taking
401 than the six-month regimen (Online Data Supplement Table E8).

402

403 *Absolute number of doses missed*

404 The four-month regimens appeared no less robust to small absolute numbers of
405 missed doses than the six-month regimen across any period of treatment (Online
406 Data Supplement Table E9). This also held true in the sensitivity analysis using the
407 restricted negative composite outcome (Online Data Supplement Table E10).

408

409 ***Forgiveness of different four-month regimens (objective 2)***

410 The M and rifapentine (P) regimen dosed twice-weekly during the second half of
411 treatment (2MRZE/2P₂M₂) appeared potentially more forgiving than other four month
412 regimens on the multiplicative scale in the continuation phase (Wald p-value for
413 interaction 0.004), but had a greater marginal risk of a negative composite outcome
414 even at 100% dose-taking than the other regimens (Figure 3, Online Data
415 Supplement Table E11, Online Data Supplement Figure E3). The larger marginal
416 risk for 2MRZE/2P₂M₂ was also seen for the overall and intensive phase models, but
417 there was no evidence of differing effects of dose-taking by different regimens on the
418 additive or multiplicative scale for these periods.

419

420 In the sensitivity analysis using the restricted negative composite outcome
421 differences between regimens were not detected; data were sparse (Online Data
422 Supplement Table E12).

423

424 ***Forgiveness during each treatment phase (objective 3)***

425 In models unadjusted for percentage dose-taking in the other phase of treatment, the
426 association between percentage dose-taking (grouped as 0-95% versus >95-100%,

427 latter baseline) and the risk of a negative composite outcome for the six-month
428 regimen was: intensive phase adjusted risk ratio (aRR) 5.75 (95% CI 4.13-8.00),
429 continuation phase aRR 10.23 (95% CI 7.70-13.59) (Figure 4a). The marginal risks
430 at >95-100% dose-taking were 0.10 (0.08-0.12) and 0.06 (0.05-0.08), respectively.
431 For the four-month regimens, estimates were intensive phase aRR 3.06 (95% CI
432 2.57-3.63); continuation phase aRR 3.59 (95% CI 3.07-4.19) (Figure 4b). The
433 marginal risks at >95-100% dose-taking were 0.19 (0.17-0.21) and 0.18 (0.16-0.20)
434 respectively.

435

436 Adjustment of the intensive phase models for percentage dose-taking during the
437 continuation phase (an estimate of the direct effect, c') resulted in all aRRs being
438 attenuated towards one- a 74% reduction for the six-month regimen (5.75 to 1.52)
439 and a 44% reduction for the four-month regimens (3.06 to 1.71). Adjustment of the
440 continuation phase models for percentage dose-taking during the intensive phase
441 and/or culture status at two months (indicated by ** and ^ in Figure 4) made a
442 relatively minimal difference to the effect estimates.

443

444 Further, a strong association was detected between dose-taking in the intensive
445 phase and continuation phase for both regimen lengths. These data suggested that
446 continuation phase percentage dose-taking was a mediator of the intensive phase
447 percentage dose-taking-negative composite outcome association.

448

449 In the sensitivity analysis using the restricted negative composite outcome, for the
450 six-month regimen the estimates for the association between dose-taking and the
451 negative composite outcome were more similar between the intensive and

452 continuation phases than previously (Online Data Supplement Figure E4). For the
453 four-month regimen, the estimates were very similar.

454

455 Allowing for a potential interaction between percentage dose-taking in the two
456 phases using medeff, the direct effects (c') indicated a small remaining increase in
457 the odds of a negative composite outcome if intensive phase dose-taking changed
458 from >95-100% to 0-95% but continuation phase dose-taking was fixed (Table 2),
459 which was in line with the traditional analysis results (Figure 4). Also in line with the
460 analyses above, for the six-month regimen 64% (95% CI 49-90%) of the total effect
461 of intensive phase dose-taking was due to the impact dose-taking during this phase
462 had on dose-taking during the continuation phase. These figures were 51% (42-
463 66%) for the four-month regimens.

464

465 In the sensitivity analysis for the medeff analyses using the restricted composite
466 negative outcome, the percentage of the total effect of intensive phase dose-taking
467 due to the impact dose-taking during this phase had on dose-taking during the
468 continuation phase was reduced to 11% (5-73%) for the six-month regimen and to
469 1% (1-8%) for the four-month regimens (Online Data Supplement Table E13).

470

471 **Discussion**

472 In this study of non-adherence data from three RCTs, we did not find a difference in
473 the forgiveness of (i.e. robustness of) the included four-month regimens versus the
474 six-month regimen 2HRZE/4HR to different levels of percentage dose-taking across
475 any period of treatment, or to lower numbers of absolute missed doses (objective 1).
476 Even at 100% dose-taking, the four-month regimens had a higher risk of a negative

477 composite outcome. Among the four-month regimens, none convincingly appeared
478 differentially forgiving of lower levels of percentage dose-taking (objective 2). The
479 intensive phase of treatment may be more robust to different levels of percentage
480 dose-taking than the continuation phase for the six-month regimen (although we note
481 the limitations of comparing non-nested models), and more than 50% of the intensive
482 phase dose-taking effect on the risk of a negative composite outcome was found to
483 be mediated through continuation phase dose-taking (objective 3). In sensitivity
484 analyses restricting the definition of a negative composite outcome in order to avoid
485 over-emphasising the dose-taking and negative composite outcomes relationship,
486 we observed greater similarity between the two phases and less mediation than
487 before. We note that this restricted definition, although useful, is not the complete
488 picture of the dose-taking and negative composite outcomes relationship as, for
489 example, it does not account for the impact of dose-taking on the likelihood of death
490 during treatment.

491

492 Our objective 3 findings have interesting implications for adherence support during
493 the treatment course for TB participants. Importantly, stepping down non-adherence
494 monitoring and promotion efforts during the continuation phase would likely be
495 detrimental, even if the patient has done well to date. Indeed, close healthcare
496 worker engagement across the full treatment period is important given how (often
497 fluctuating) life events can derail treatment.⁽¹⁸⁾ As levels of non-adherence can be
498 linked between the two phases of treatment, it will be important to establish good
499 and lasting habits and relationships between participants and healthcare workers
500 early on.⁽¹⁹⁾ Previous pharmacokinetics-pharmacodynamics simulations have
501 highlighted the importance of good adherence during the intensive phase of

502 treatment;(20) moving forwards, understanding how such models translate to
503 population level effects and the common causes of non-adherence and negative
504 treatment outcomes will be critical.

505

506 Within objectives 1 and 2, we found that the different regimens were no more or less
507 forgiving than each other; this was particularly encouraging for the four-month
508 regimens when the absolute number of doses missed was analysed. Within the
509 recently published Study 31/A5349, exclusion of participants with at least 5% or 25%
510 non-adherence shifted the effect estimates in favour of the six-month regimen
511 2HRZE/4HR;(3) future work to examine the relative forgiveness of 2HPZM/2PHM
512 versus 2HRZE/4HR would be pertinent.

513

514 This is the first study of its kind to examine in depth the relationship between non-
515 adherence and outcomes in TB. A major strength was the availability of large
516 datasets of non-adherence and outcomes data from three RCTs that tested different
517 treatment regimens. Our analyses could have been improved by the availability of
518 daily non-adherence data to allow assessment of the implications of different non-
519 adherence patterns.(6, 21) Dose-taking within these trials was very high, so relatively
520 few data points were available to fit the fractional polynomials at low dose-taking
521 levels, resulting in lower statistical certainty. As the four-month regimens were
522 specific to each trial (although REMox had two), these regimens may be acting as a
523 proxy for trial in the analyses. Outcomes were measured from the time of
524 randomisation, which may have disadvantaged the four-month regimens, as they
525 had greater post-treatment time during which relapse could occur.

526

527 We were unable to adjust for post-randomisation risk factors for non-adherence.(22)
528 Incomplete adjustment for the propensity of participants to adhere to treatment-
529 known to be influenced by a complex dynamic of economic, structural, patient-
530 related, regimen, health provider, and healthcare delivery factors-(23) could be
531 influencing both the regression and mediation analyses. For the latter, this would
532 overestimate the association between non-adherence in the intensive and
533 continuation phases, leading to the level of mediation being overemphasized. We
534 note that the large number of factors influencing propensity to adhere means
535 confounding has rarely fully been adjusted for in observational studies in this
536 area.(24)

537

538 There is substantial interest globally in shortening treatment for drug-sensitive TB
539 from six months to four as this may decrease levels of non-adherence. Critically, our
540 study suggests that even four-month regimens previously found to be inferior to
541 2HRZE/4HR (at least in specific population groups)(8) are no more susceptible to
542 absolute small numbers of missed doses than the standard six-month regimen. Work
543 to better understand: a) the most important non-adherence patterns for the risk of
544 negative outcomes, b) how common these patterns are and where/in whom they
545 occur, and c) if some regimens are more forgiving of important and common non-
546 adherence patterns, may aid decisions about how to deploy different regimens
547 globally. (Indeed, the importance of documenting and analysing different non-
548 adherence patterns is part of the World Health Organization's position statement on
549 innovative trial design.)(25) Such studies can also inform discussions about relative
550 investment in interventions to prevent non-adherence versus regimens that are
551 forgiving of non-adherence.

552

553 In conclusion, with the current appetite for, and progress towards, shorter drug-
554 sensitive tuberculosis regimens worldwide, we offer reassurance that shorter
555 regimens do not necessarily equate to higher vulnerability to non-adherence. The
556 importance of continuation phase adherence should not be under-estimated, of
557 which clinical and public health programmes should be mindful. As new regimens for
558 drug-sensitive TB- and indeed, drug resistant TB- are formulated and trialled,
559 detailed consideration of forgiveness and its interplay with pharmacokinetics will be
560 important to maximise operational efficacy.

561

562

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568

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576

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665

666

667 **Figure 1. Hypothesised mediation model**

668 The total effect c of the exposure E (intensive phase percentage dose-taking) on the outcome O (negative
669 composite outcome) is composed of direct and indirect effects. The direct effect c' measures the extent to which
670 the risk of the negative composite outcome changes when intensive phase percentage dose-taking alters by one
671 unit but the mediator variable M (continuation phase percentage dose-taking) is fixed. The indirect effect, a
672 combination of a and b , measures the extent to which the risk of the negative composite outcome changes when
673 intensive phase percentage dose-taking is fixed and continuation phase percentage dose-taking changes by the
674 amount it would have changed had intensive phase percentage dose-taking alters by one unit.

675

676 **Figure 2. Forgiveness of the four- versus six-month regimens**

677 Adjusted marginal risks (a, d, g), risk ratios (b, e, h), and risk differences (c, f, i) for the negative composite
678 outcome by percentage of doses taken (modelled as fractional polynomials of the functional form x^3) across the
679 entire treatment period (overall, a-c), intensive phase (d-f) and continuation phase (g-i), presented stratified by
680 regimens grouped by length. One model per period of treatment, four- and six-month regimens in the same
681 model. Baseline for the multiplicative and additive models 100% of doses taken. For the multiplicative models,
682 Wald p-values for an interaction between regimens grouped by length and percentage of doses taken all
683 $p < 0.0001$; horizontal dotted line charts a risk ratio of 1. For the additive models, Wald p-values for an interaction
684 between regimens grouped by length and percentage of doses taken 0.06 (overall), 0.06 (intensive phase), 0.07
685 (continuation phase); horizontal dotted line charts a risk difference of 0. All models adjusted for sex, age (fitted
686 using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation
687 at baseline and a three-level fixed-effect for trial. All models contain data for 3,180 participants. Data presented
688 for 80-100% of doses taken due to data sparsity at lower levels, but the full range of values were included in the
689 statistical models. Panels a, b from model 3; c from model 4; d, e from model 7; f model 8; g, h from model 11; i
690 model 12. aRD- adjusted risk difference, aRisk- adjusted risk, aRR- adjusted risk ratio, CI- confidence interval.

691

692 **Figure 3. Forgiveness of different four-month regimens**

693 Adjusted risks (a, c, e, g, i, k, m, o, q, s, u, w) and risk ratios (b, d, f, h, j, l, n, p, r, t, v, x) for the negative
694 composite outcome by the percentage of doses taken (modelled as fractional polynomials of the functional form
695 x^3) across the entire treatment period (a-h), intensive phase (i-p) and continuation phase (q-x), stratified by four-
696 month regimen. Baseline for multiplicative and additive models 100% dose-taking. One model per period of
697 treatment, all four-month regimens in same model. For the multiplicative models, Wald p-values for an interaction
698 between regimens grouped by length and percentage of doses taken 0.10 (overall), 0.76 (intensive phase), 0.004

699 (continuation phase); horizontal dotted line charts a risk ratio of 1. For the additive models, Wald p-values for an
700 interaction between regimens grouped by length and percentage of doses taken 0.84 (overall), 0.50 (intensive
701 phase), 0.004 (continuation phase); horizontal dotted line charts a risk difference of 0. Models adjusted for sex,
702 age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe),
703 cavitation at baseline. No adjustment for study due to collinearity with regimen. Models contain data for 1,837
704 participants. Data presented for 80-100% of doses taken due to data sparsity at lower levels, but the full range of
705 values were included in the statistical models. Overall treatment from model 34; intensive phase from model 37;
706 continuation phase from model 40. Z- twice weekly dosing, aRisk- adjusted risk, aRR- adjusted risk ratio, CI-
707 confidence interval, E- ethambutol, G- gatifloxacin, H- isoniazid, M- moxifloxacin, P- rifapentine, R- rifampicin, Z-
708 pyrazinamide.

709

710 **Figure 4. Forgiveness during each treatment phase**

711 To compare forgiveness during the two treatment phases, intensive phase and continuation phase percentage
712 dose-taking were categorised into 0-95% versus >95-100% (baseline) and adjusted risk ratios calculated for a)
713 the six-month regimen and b) the four-month regimens, as follows:

714 (i) intensive phase dose-taking was the exposure and continuation phase dose-taking the outcome (models 51,
715 52);

716 (ii) continuation phase dose-taking was the exposure and the negative composite outcome the outcome (models
717 53, 55, 57, 59, 61, 63, 65, 67); and

718 (iii) intensive phase dose-taking was the exposure and negative composite outcome the outcome (models 43, 45,
719 47, 49).

720 Results from models (ii) and (iii) are presented without (*) and with (**) adjustment for dose-taking during the
721 other treatment phase, assuming no interaction. For model (ii) results are also presented with (^) adjustment for
722 culture status at two months. Models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV
723 and CD4 status, smear status at baseline (most severe), cavitation at baseline and a three-level fixed-effect for
724 trial. aRR- adjusted risk ratio, CI- confidence interval.

725
726

727

728

729 **Table 1. Characteristics of the study population, excluding participants**
730 **missing outcome or non-adherence data**

Exposure variables	Overall cohort		Negative outcome	
	No.	Col. %	No.	Row %
Overall	3,536	100.0	678	19.2
Overall percentage of doses taken				
100%	2,642	74.7	339	12.8
>95-<100%	479	13.5	78	16.3
>90-95%	139	3.9	40	28.8
>85-90%	31	0.9	7	22.6
>80-85%	24	0.7	10	41.7
>60-80%	59	1.7	43	72.9
0-60%	162	4.6	161	99.4
Intensive phase percentage of doses taken				
100%	3,015	85.3	464	15.4
>95-<100%	267	7.6	59	22.1
>90-95%	76	2.1	20	26.3
>85-90%	48	1.4	18	37.5
>80-85%	11	0.3	4	36.4
>60-80%	32	0.9	28	87.5
0-60%	87	2.5	85	97.7
Continuation phase percentage of doses taken				
100%	2,903	82.1	392	13.5
>95-<100%	222	6.3	32	14.4
>90-95%	64	1.8	13	20.3
>85-90%	85	2.4	20	23.5
>80-85%	14	0.4	5	35.7
>60-80%	45	1.3	22	48.9
0-60%	203	5.7	194	95.6
Length of treatment (months)				
6	1,491	42.2	216	14.5
4	2,045	57.8	462	22.6
Sex				
Male	2,473	69.9	514	20.8
Female	1,063	30.1	164	15.4
Age (years)				
Median (IQR)		29 (24-38)		32 (25-41)
16-<26	1,204	34.0	187	15.5%
26-<36	1,241	35.1	223	18.0
36-<46	644	18.2	157	24.4
46-<56	332	9.4	83	25.0
56-<66	86	2.4	20	23.3
66+	25	0.7	6	24.0
Missing	4	0.1	2	50.0
Ethnicity*				
Black	2,534	71.7	461	18.2
Asian	527	14.9	123	23.3
Other	475	13.4	94	19.8
HIV status / CD4 count (cells/mm ³)				
HIV negative	3,026	85.6	538	17.8
HIV positive, CD4 count <200	55	1.6	11	20.0

Exposure variables	Overall cohort		Negative outcome	
	No.	Col. %	No.	Row %
HIV positive, CD4 count 200-<500	274	7.7	75	27.4
HIV positive, CD4 count >=500	86	2.4	24	27.9
Missing	95	2.7	30	31.6
Smear status- most severe [†]				
Negative	47	1.3	18	38.3
1+	490	13.9	82	16.7
2+	798	22.6	113	14.2
3+ or more	2,157	61.0	453	21.0
Missing	44	1.2	12	27.3
Smear status- least severe [†]				
Negative	234	6.6	59	25.2
1+	786	22.2	122	15.5
2+	785	22.2	106	13.5
3+ or more	1,687	47.7	379	22.5
Missing	44	1.2	12	27.3
Cavitation				
Yes	2,153	60.9	422	19.6
No	1,161	32.8	202	17.4
Missing	222	6.3	54	24.3
Weight (kg)				
≤45	711	20.1	161	22.6
>45-≤50	728	20.6	141	19.4
>50-≤55	808	22.9	155	19.2
>55-≤70	1,168	33.0	197	16.9
>70	121	3.4	24	19.8
Culture status at two months				
Negative	2,618	74.0	376	14.4
Positive	625	17.7	159	25.4
Missing	293	8.3	143	48.8

731 Demographic and clinical characteristics of the study population at baseline (unless otherwise indicated) and
732 non-adherence data, excluding individuals missing outcome or non-adherence data. Both smear and cavitation
733 status recorded at baseline. [†]Ethnicity imputed for OFLOTUB. ^{*}Two alternative groupings of smear status, one
734 taking the most severe result recorded and one the least. CI- confidence interval, Col- column, IQR- inter-quartile
735 range, N/A- not applicable.

736

737

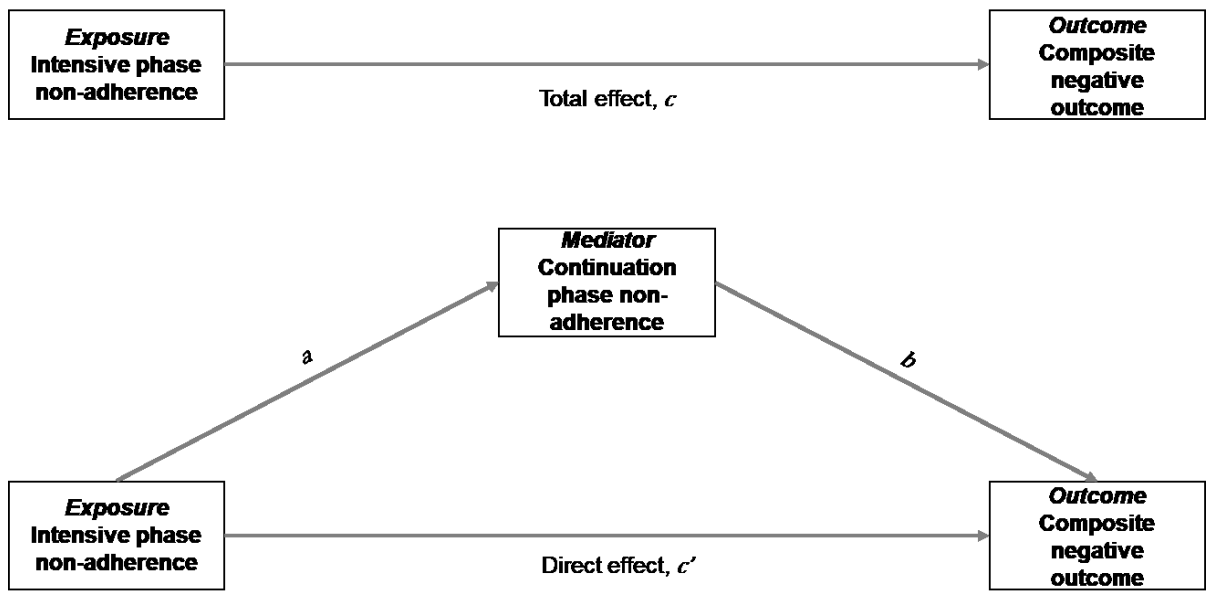
738 **Table 2. Forgiveness during each treatment phase: mediation analysis**

Regimens grouped by length	Direct effect 0	Indirect effect 1	Direct effect 1	Indirect effect 0	Proportion of total effect mediated
6-month	1.12 (1.01-1.32)	1.34 (1.19-1.50)	1.20 (1.07-1.34)	1.25 (1.17-1.34)	0.64 (0.49-0.90)
4-month	1.15 (1.04-1.27)	1.30 (1.21-1.40)	1.29 (1.18-1.41)	1.16 (1.10-1.23)	0.51 (0.42-0.66)

739 Direct effects and indirect effects expressed as odds ratios and (95% confidence intervals). 0-95% versus >95-
740 100% (baseline) dose-taking compared. Direct effect 0- how much the risk of the negative composite outcome
741 would change if intensive phase dose-taking changed from >95-100% to 0-95% but, for each individual,
742 continuation phase dose-taking was fixed at the level it would have taken, for that individual, when intensive
743 phase dose-taking was >95-100%. Direct effect 1- as per direct effect 0, but when continuation phase dose-
744 taking is fixed at the level it would have taken, for that individual, when intensive phase dose-taking (exposure)
745 was ≤95%. Indirect effect 0- how much the outcome would change, on average, if intensive phase dose-taking
746 was fixed at >95-100% but continuation phase dose-taking changed from the level it would take if intensive
747 phase dose-taking was >95-100% to if intensive phase dose-taking was ≤95%. Indirect effect 1- as per indirect
748 effect 0, but when intensive phase dose-taking fixed at ≤95%. Models adjusted for sex, age (fitted using a
749 fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at
750 baseline and a three-level fixed-effect for trial.

751

752 **Figure 1.**

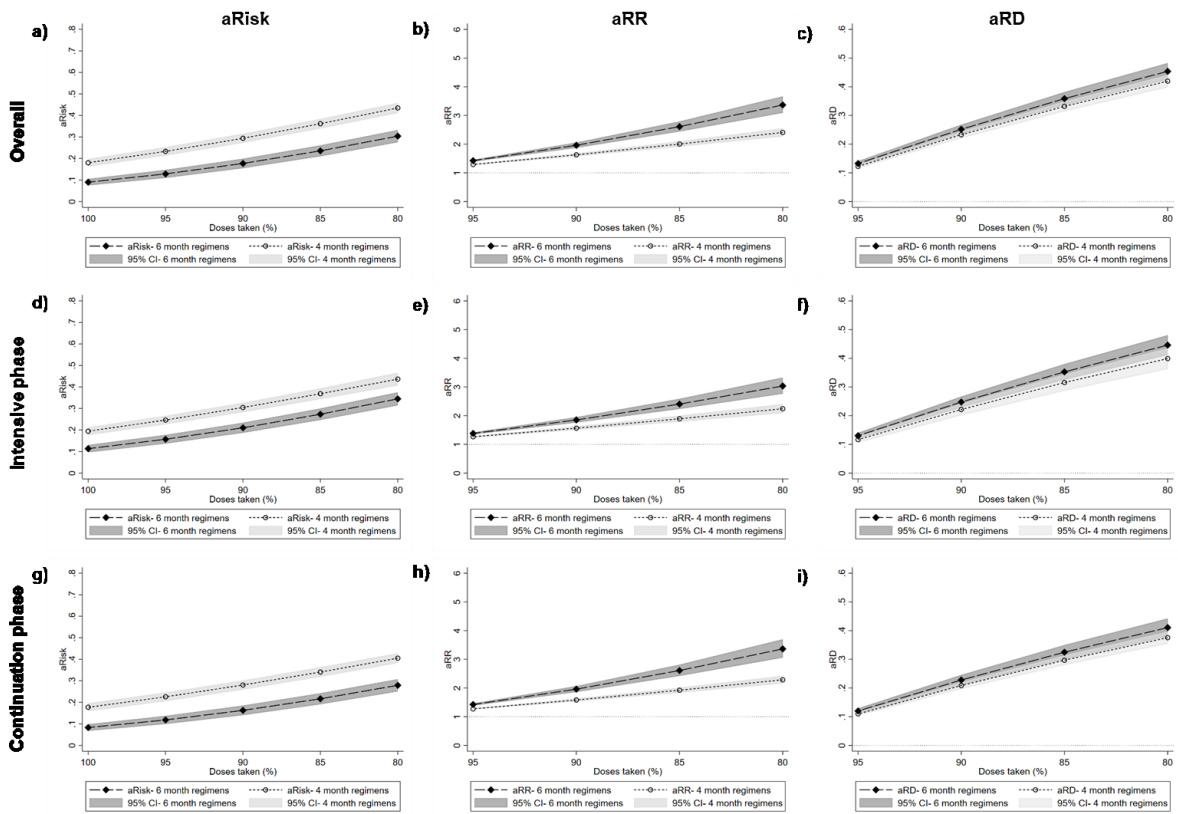


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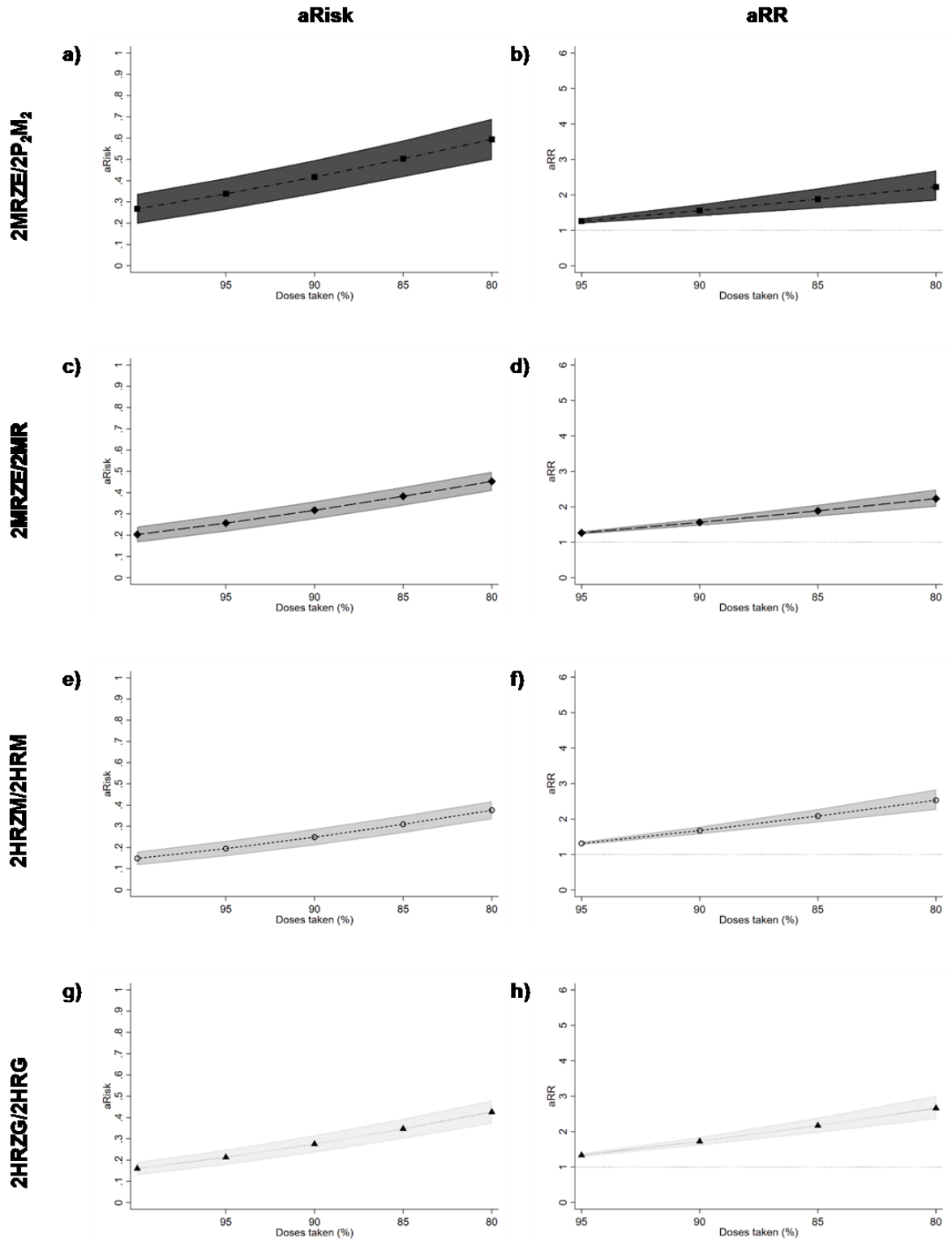
756 **Figure 2.**



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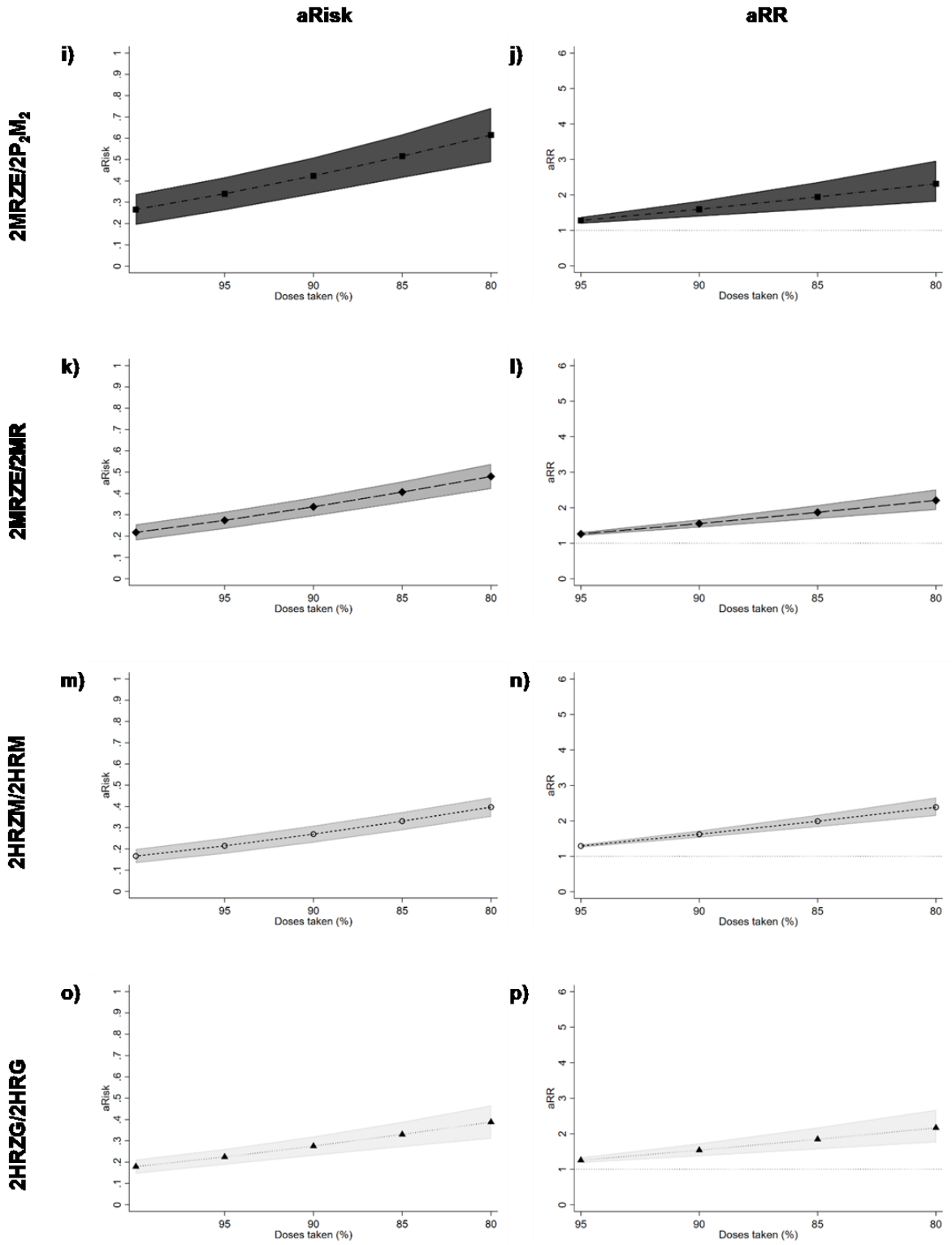
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760 **Figure 3.**
Overall treatment



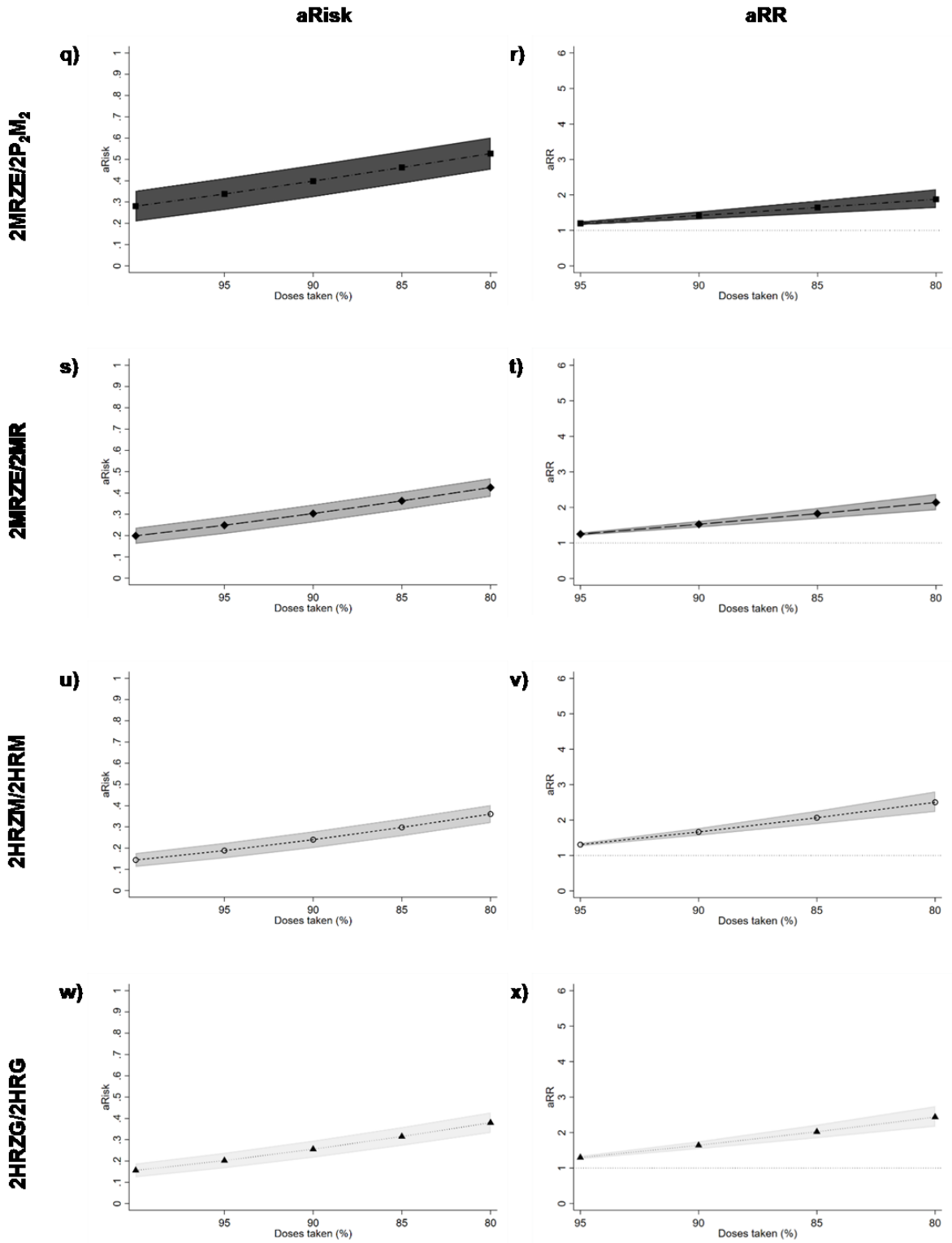
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Intensive phase



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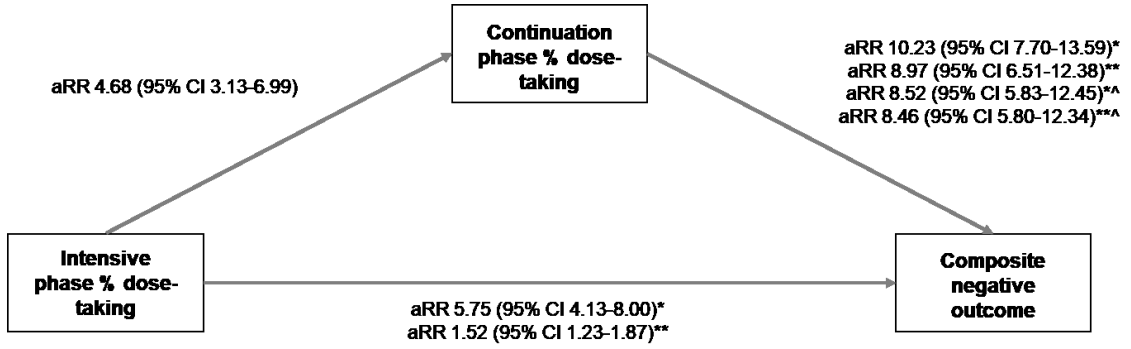
Continuation phase



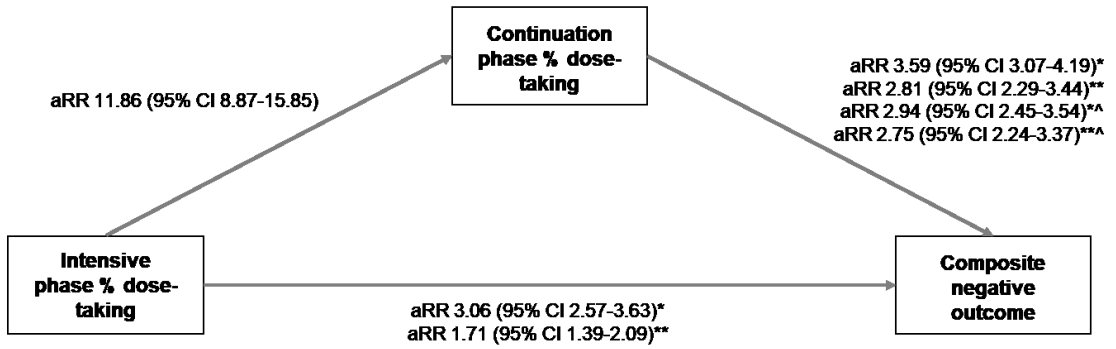
765
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768 **Figure 4.**

a)



b)



769
770

771 **Online Data Supplement**

772

773 **Forgiveness is the attribute of the strong: non-adherence and**
774 **regimen-shortening in drug-sensitive TB (a secondary analysis of**
775 **clinical trial data)**

776

777 Helen R Stagg; Jennifer A Thompson; Marc CI Lipman; Derek J Sloan; Mary Flook;

778 Katherine L Fielding; for the Critical Path to TB Drug Regimens

779

780

781 **Online Data Supplement Text E1- Methods**

782 ***Measuring and defining non-adherence to treatment***

783 In addition to the cleaning of the non-adherence data described in the methods, the
784 following was conducted within specific trials:

785

786 *OFLOTUB*

787 This randomised controlled trial (RCT) reported the number of doses taken of HRZE
788 (isoniazid, rifampicin, pyrazinamide, ethambutol - combined pill), HRZ (isoniazid,
789 rifampicin, pyrazinamide - combined pill), HR (isoniazid, rifampicin- combined pill) or
790 G (gatifloxacin) pills per week. For this study, data for the combined pills were used
791 for non-adherence calculations. Where non-adherence was documented for the
792 incorrect combined pill for the regimen received (e.g. HRZE when participants
793 actually received the four-month regimen), data for this combined pill were assumed
794 to actually document non-adherence to the correct combined pill.

795

796 For the four-month regimens, if data were missing for one pill type, but not the other,
797 it was assumed that the non-missing data were accurate for both pill types. Weekly
798 data were summed as appropriate to generate data for the two phases of treatment.
799 For some participants, non-adherence data for a given study visit (encompassing
800 four weeks of non-adherence data) were missing. For the main analyses, missing
801 was assumed to mean no doses taken, but non-adherence was also coded to the
802 opposite extreme (i.e. all doses taken) for a sensitivity analysis.

803

804 *REMox*

805 The total number of doses taken across the overall treatment period, intensive

806 phase, and two halves of the continuation phase (each of 2 months' duration) were
807 reported from the drug record. An overall continuation phase non-adherence variable
808 was then calculated, excluding non-adherence to the placebo during the second
809 continuation phase for the four-month regimens.

810

811 *Rifampin*

812 The total doses taken during the intensive and continuation phases were reported
813 and used to generate the total doses taken across the entire treatment period.

814

815

816 Where present, greater than 100% dose-taking was capped at 100%. Throughout
817 these analyses, non-adherence levels represent actual dose-taking/doses missed,
818 rather than whether a patient achieved or did not achieve a particular threshold of
819 doses taken.

820

821 ***Other variables***

822 Data on other variables was utilised from that recorded by the original RCTs:

- 823 • Sex- retained as originally coded;
- 824 • Age in years- grouped in 10 year categories and later fitted using fractional
825 polynomials (see statistical analysis section);
- 826 • Ethnicity- recoded as 'Black', 'Asian' and 'Other'. Ethnicity was not recorded
827 by OFLOTUB, but given the location of all study sites this was imputed to
828 Black for all participants, in line with Imperial *et al.*(8);
- 829 • HIV status and CD4 count- in OFLOTUB, participants with WHO HIV stage 3
830 disease (unless loss of >10% of body weight was the only criterion met) or

831 stage 4 disease were not eligible for the study.(12) In REMox, participants
832 who were co-infected with HIV were eligible to participate in the study if the
833 CD4 count was ≥ 250 cells/mm³ and they were not already receiving
834 antiretroviral therapy (ART).(10) In RIFAQUIN, participants co-infected with
835 HIV who required ART at diagnosis were initially ineligible.(11) Later in the
836 trial, participants starting ART at screening were deemed eligible. Participants
837 with a CD4 cell count < 200 cells/mm³ were initially ineligible, but this was
838 subsequently changed to < 150 cells/mm³. Within this study, HIV status and
839 CD4 count were combined into a single variable of 'HIV negative', 'HIV
840 positive, CD4 count < 200 cells/mm³', 'HIV positive, CD4 count 200- < 500
841 cells/mm³', 'HIV positive, CD4 count ≥ 500 cells/mm³', or 'missing' if HIV
842 status, or CD4 count among those HIV positive, was absent;

843 • Smear status at baseline- given the multiple smear results per patient at
844 baseline, which were not always concordant, these data were coded into two
845 variables (most and least severe). The former was used in the main analysis
846 and the latter in the sensitivity analyses. Smear grading varied by study,(8)
847 and was recoded as 'Negative', 'Scanty', '1+' (a category that included generic
848 smear positives), '2+', or '3+ or more'. For studies that included 'positive' and
849 'scanty' results, when compiling the least severe smear status these results
850 could be over-written with more precise, albeit more extreme, results, in the
851 absence of an additional negative result;

852 • Cavitation at baseline- retained as originally coded;

853 • Weight at screening/baseline- coded into categories ≤ 45 kg, $> 45 - \leq 50$ kg, $> 50 -$
854 ≤ 55 kg, $> 55 - \leq 70$ kg, > 70 kg, roughly in line with the key weights that resulted in
855 a change in the dose of drug prescribed (and thus pill numbers) across the

856 three trials;

- 857 • Regimen- retained as originally coded.

858

859 ***Forgiveness of the four- versus six-month regimens (objective 1)- non-***
860 ***adherence fractional polynomials***

861 To fully characterise the risk of the outcome associated with changes in non-
862 adherence (percentage dose-taking) as a continuous variable, without categorising
863 non-adherence and thus losing information, fractional polynomials were fitted. This
864 was done separately for regimens grouped by length and for overall, intensive phase
865 and continuation phase percentage dose-taking. Whilst fitting these models, robust
866 variance estimators were not used as these invalidate Stata's deviance difference
867 test. For continuation phase data, models were set to treat non-positive values as
868 zero when fractional polynomials were transformed. To determine the best fitting
869 fractional polynomial, a combination of p-value thresholds (0.05) from a partial F-test,
870 visual inspection, and biological plausibility was used. When running the regression
871 models using these fractional polynomials, complete dose-taking (i.e. 100%) was set
872 as the baseline.

873

874 Examining the p-values alone, the best fitting fractional polynomial for the
875 relationship between percentage dose-taking and the negative composite outcome
876 was found to be the degree-2 model $x^3x^3\ln(x)$ for the overall treatment period across
877 both four- and six-month regimens (Online Data Supplement Text E1 Figures E1a-
878 b), for the four-month regimen intensive phase data (Online Data Supplement Text
879 E1 Figure E1f) and for the six-month regimen continuation phase data (Online Data
880 Supplement Text E1 Figure E1i). The resulting curves demonstrated a slight

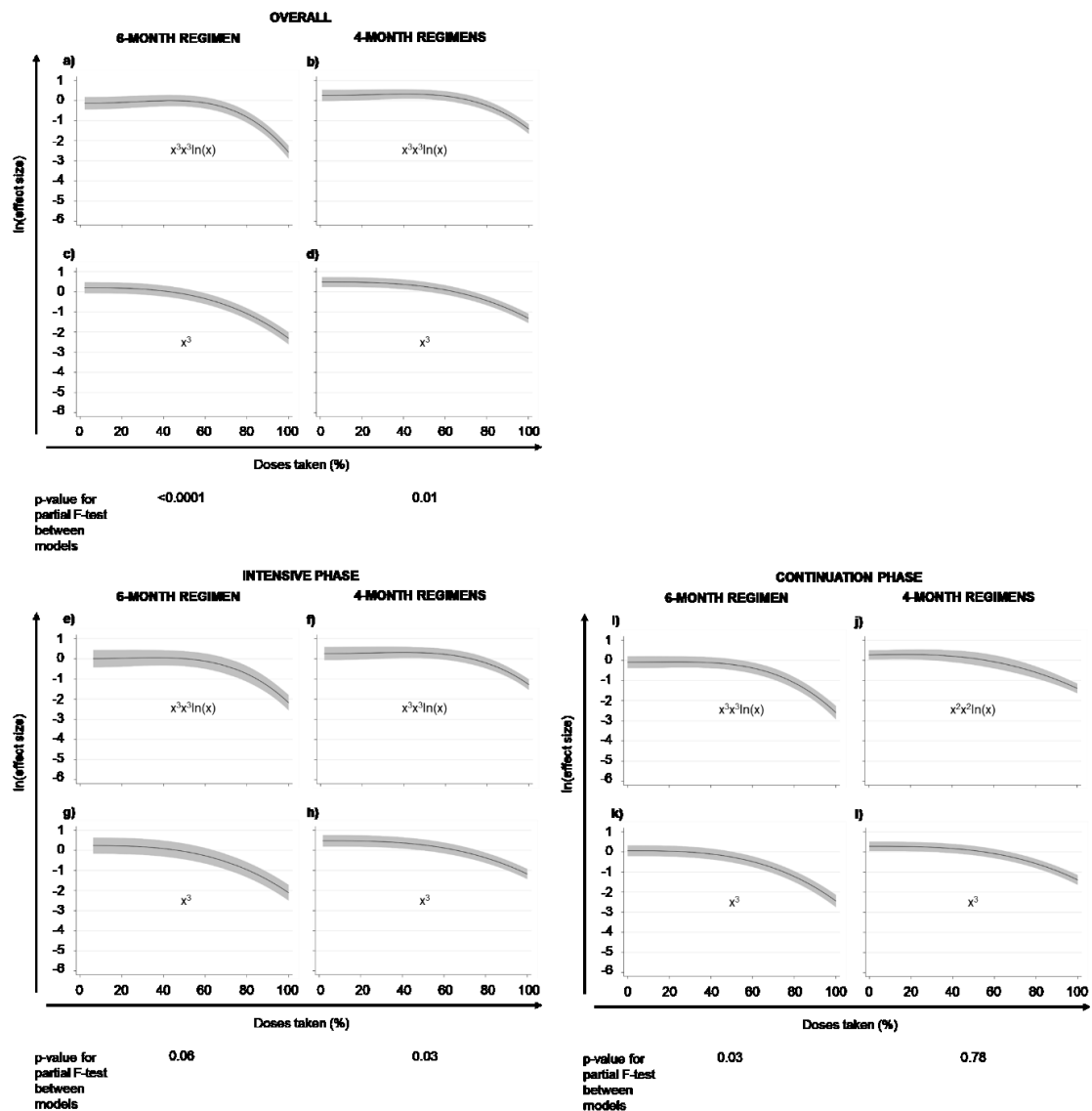
881 increase in the risk of a negative outcome at 60% of doses taken, before the
882 likelihood began to reduce. This could be for a series of reasons- over-fitting to the
883 dataset (a known issue with fractional polynomials), exposure to drugs becoming
884 sufficient to generate drug resistance,(26) or in order to generate a steep enough
885 slope as dose-taking increased from this point. Due to the small amount of data once
886 fewer than 90% of doses were taken and concerns about the biological plausibility of
887 a more complex relationship, we selected the second best model- the degree-1
888 model x^3 - for all periods of treatment (Online Data Supplement Text E1 Figures E1c-
889 d, h, k).

890

891

892 **Online Data Supplement Text E1 Figure E1. Fractional polynomials of the**
 893 **relationship between non-adherence and the negative composite outcome at**
 894 **different time points**

895 Natural log of the risk of the negative composite outcome for different percentages of doses taken
 896 overall (a-d), during the intensive phase (e-h), and during the continuation phase (i-l). Panels a, c, e,
 897 g, i, k) six-month regimen, panels b, d, f, h, j, l) four-month regimens. Top row of each set of graphs
 898 degree-2 fractional polynomials (panels a, b, e, f, i, j), bottom row degree-1 (panels c, d, g, h, k, l).
 899 Fractional polynomials fitted in a model adjusted for age, sex, ethnicity, HIV status and CD4 count,
 900 smear status at baseline (most severe), cavitation at baseline, regimens grouped by length of
 901 treatment, and a three-level fixed effect for trial. Six-month regimen models contain data for 1,343 and
 902 four-month regimens models contain data for 1,837.



903

904

905 For the intensive phase six-month regimen model the partial F-test gave a p-value of
906 0.06 between the degree-2 ($x^3x^3\ln(x)$) and degree-1 models (x^3). The degree-1
907 model was thus chosen (Online Data Supplement Text E1 Figures E1e, g).

908

909 For the continuation phase four-month regimens model, $x^2x^2\ln(x)$ and x^3 were not
910 statistically different and thus x^3 was chosen (Online Data Supplement Text E1
911 Figure E1j-l).

912

913 These polynomials were fitted in models adjusting for sex, age, ethnicity, HIV and
914 CD4 status, smear status at baseline (most severe), cavitation at baseline and a
915 three-level fixed effect for trial; inclusion of these variables was determined using a
916 causal framework.

917

918 After fitting the fractional polynomials on percentage dose-taking, further fractional
919 polynomials were fitted on age in the adjusted models. P-values indicated that age
920 could be omitted from models, but given that age had been defined as an *a priori*
921 confounder, it was retained in the adjusted model as a linear covariate.

922

923 ***Forgiveness during each treatment phase (objective 3)- additional statistical***
924 ***details***

925 We used medeff in Stata to estimate direct and indirect effects and the proportion of
926 the total effect due to mediation in models that included an interaction term between
927 intensive and continuation phase percentage dose-taking. Binary dummy variables
928 were created to adjust for confounding. Given the high proportion of participants with

929 a negative composite outcome, probit and logit were compared for both the
930 exposure-outcome and exposure-mediator models; as they produced similar results,
931 logit was chosen. Models were run with 1,000 simulations.

932

933 Two direct effects c' are outputted by medeff models. Direct effect 0 measured how
934 much the risk of the outcome would change if intensive phase dose-taking
935 (exposure) changed from >95-100% to 0-95% but, for each individual, continuation
936 phase dose-taking (mediator) was fixed at the level it would have taken, for that
937 individual, when intensive phase dose-taking (exposure) was >95-100%. Direct
938 effect 1 reported the same thing, but this time continuation phase dose-taking
939 (mediator) was fixed at the level it would have taken, for that individual, when
940 intensive phase dose-taking (exposure) was 0-95%.

941

942 Two indirect effects b are also outputted. Indirect effect 0 measured how much the
943 outcome would change, on average, if intensive phase dose-taking (exposure) was
944 fixed at >95-100% but continuation phase dose-taking (mediator) changed from the
945 level it would take if intensive phase dose-taking (exposure) was >95-100% to if it
946 was 0-95%. Indirect effect 1 measured the same thing, but this time intensive phase
947 dose-taking (exposure) was fixed at 0-95%.

948

949 Due to the use of both a binary mediator and outcome, sensitivity analyses to
950 examine the degree of sequential ignorability assumption violation could not be
951 performed.

952

953 **Online Data Supplement Table E1. Characteristics of the included randomised controlled trials, including regimens used**
 954 **and dosing frequency**

Trial	Population	Participants	Control regimen	Intervention regimen(s)	Method of observing adherence
OFLOTUB(12, 27)	Participants aged 18-65 years with R-sensitive, smear-positive pulmonary TB that was newly diagnosed. Benin, Guinea, Kenya, Senegal, South Africa. Enrolment 2005-09.	1,836 randomised and received medication on at least one occasion	Two months of HRZE, followed by four months of HR (2HRZE/4HR) Dosing six days per week	Two months of HRZG, followed by two months of HRG (2HRZG/2HRG) Dosing six days per week (Combined pills for all drugs aside from G)	Direct observation of each dose
REMOx(10)	Participants aged 18 years or over with R- and fluoroquinolone-susceptible, smear positive, pulmonary TB that was newly diagnosed. China, India, Kenya, Malaysia, Mexico, South Africa, Tanzania, Thailand, Zambia. Enrolment 2008-12	1,931 randomised	Two months of HRZE, followed by four months of HR (2HRZE/4HR) Daily dosing	Two months of HRZM, followed by two months of HRM, followed by two months of placebo (2HRZM/2HRM) Daily dosing OR Two months of MRZE, followed by two months of MR, followed by two months of placebo (2MRZE/2MR) Daily dosing (Single drug pills for both regimens)	Direct observation of each dose and pill counts
RIFAQUIN(11)	Participants aged 18 years and over with H-, R-, and M-sensitive, smear-positive, pulmonary TB that was newly diagnosed. Botswana, South Africa, Zambia, Zimbabwe. Enrolment 2008-11.	550 randomised to regimens included in this analysis	Two months of HRZE, followed by four months of HR (2HRZE/4HR) Daily dosing	Two months of MRZE, followed by two months of PM (2MRZE/2P ₂ M ₂) Daily dosing first two months, twice weekly (as indicated by the 2) second two months (Single drug pills)	Direct observation of each dose

955 The secondary data used for this study were derived from the OFLOTUB, REMox and RIFAQUIN randomised controlled trials. All pills were to be taken together once a day. E-

956 ethambutol, G- gatifloxacin, H- isoniazid, M- moxifloxacin, P- rifapentine, R- rifampicin, TB- tuberculosis, Z- pyrazinamide.

957 **Online Data Supplement Table E2. Re-coded outcomes from the TB PACTS-**
 958 **provided datasets**

959

Trial	Trial outcome	Classification
OFLOTUB*	Favourable modified intention to treat outcome	Positive
	Unfavourable modified intention to treat outcome	Negative
	MGIT invalid, contaminated, or borderline MDR or R resistant	Excluded
REMox†	Favourable with imputing of last observation for missing outcomes	Positive
	Unfavourable with imputing of last observation for missing outcomes	Negative
	Late screening failure: MDR	Excluded
	Late screening failure: protocol violation	
	Late screening failure: not TB	
	Mexico	
	Pregnancy	
	Exogenous reinfection	
	Withdrew consent	
	Death (non-TB)	
Lost to follow-up/moved away before 18 months (but not during treatment)		
Redacted		
Rifaquin	Culture negative at last culture at end of study	Positive
	In treatment, treatment failure	Negative
	In treatment, death during treatment	
	In treatment, adverse event during treatment	
	In treatment, lost to follow-up	
	In treatment, inadequate treatment	
	In treatment, withdrawal for pregnancy	
	In treatment, other retreatment during	
	Lost to follow-up	
	Died from non-TB causes	
	Withdrawn for pregnancy	
	Reinfection	
	Post-treatment, relapse during follow-up	
	Post-treatment, TB death during follow-up	
	Post-treatment, culture positive at last culture	
	Late screening failure: previous TB treatment	Excluded
	Initial H/R/M resistance	
Not culture positive in first two weeks		
Culture taken too early		
Missing culture result		
Contaminated culture		
Not produced sputum		

960 Outcomes used for this study, as recoded from the TB PACTS dataset. Broadly, our definition of a negative

961 composite outcome arising during or after treatment was taken from the original RCTs i.e. treatment failed, death,

962 or relapse/recurrence of disease. Participants with a composite positive outcome had a negative culture at the
963 end of follow-up and had not already had an outcome classified as negative. Outcomes for all studies taken at 18
964 months post-randomisation. *Unfavourable outcome defined within the original trial as treatment failure (at either
965 four-months or six-months after randomisation, depending on the treatment group), recurrence (relapse or
966 reinfection), and death or withdrawal from the study during the treatment period.(12) †Unfavourable outcome
967 defined within the original trial as bacteriologically or clinically defined failure or relapse.(10) H - isoniazid, M-
968 moxifloxacin, MDR- multidrug resistant, R- rifampicin, TB- tuberculosis.

969 **Online Data Supplement Table E3. List of regression models**

#	Comparing forgiveness of (objective)	Exposure	Outcome measure	Statistical measure	Unadjusted or adjusted	Period in which exposure measured	Regimens included	Sensitivity analysis?
1	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs, risks	Unadjusted	Overall	All	No
2	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RDs	Unadjusted	Overall	All	No
3	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs, risks	Adjusted	Overall	All	No
4	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RDs	Adjusted	Overall	All	No
5	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs, risks	Unadjusted	Intensive phase	All	No
6	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RDs	Unadjusted	Intensive phase	All	No
7	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs, risks	Adjusted	Intensive phase	All	No
8	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RDs	Adjusted	Intensive phase	All	No
9	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs, risks	Unadjusted	Continuation phase	All	No
10	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RDs	Unadjusted	Continuation phase	All	No
11	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs, risks	Adjusted	Continuation phase	All	No
12	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RDs	Adjusted	Continuation phase	All	No

#	Comparing forgiveness of (objective)	Exposure	Outcome measure	Statistical measure	Unadjusted or adjusted	Period in which exposure measured	Regimens included	Sensitivity analysis?
13	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Overall	All	Patient weight adjustment
14	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Overall	All	Alternative coding of smear status
15	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Overall	All	Alternative coding of OFLOTUB percentage dose-taking
16	4- vs. 6-month regimens (1)	Percentage of doses taken	Restricted negative composite outcome	RRs	Adjusted	Overall	All	Restricted negative composite outcome
17	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Intensive phase	All	Patient weight adjustment
18	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Intensive phase	All	Alternative coding of smear status
19	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Intensive phase	All	Alternative coding of OFLOTUB percentage dose-taking
20	4- vs. 6-month regimens (1)	Percentage of doses taken	Restricted negative composite outcome	RRs	Adjusted	Intensive phase	All	Restricted negative composite outcome
21	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Continuation phase	All	Patient weight adjustment
22	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Continuation phase	All	Alternative coding of smear status
23	4- vs. 6-month regimens (1)	Percentage of doses taken	Negative composite outcome	RRs	Adjusted	Continuation phase	All	Alternative coding of OFLOTUB percentage dose-taking
24	4- vs. 6-month regimens (1)	Percentage of doses taken	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	All	Restricted negative composite outcome

#	Comparing forgiveness of (objective)	Exposure	Outcome measure	Statistical measure	Unadjusted or adjusted	Period in which exposure measured	Regimens included	Sensitivity analysis?
25	4- vs. 6-month regimens (1)	Absolute number of doses missed	Negative composite outcome	RRs, risks	Adjusted	Overall	All	No
26	4- vs. 6-month regimens (1)	Absolute number of doses missed	Negative composite outcome	RDs	Adjusted	Overall	All	No
27	4- vs. 6-month regimens (1)	Absolute number of doses missed	Restricted negative composite outcome	RRs	Adjusted	Overall	All	Restricted negative composite outcome
28	4- vs. 6-month regimens (1)	Absolute number of doses missed	Negative composite outcome	RRs, risks	Adjusted	Intensive phase	All	No
29	4- vs. 6-month regimens (1)	Absolute number of doses missed	Negative composite outcome	RDs	Adjusted	Intensive phase	All	No
30	4- vs. 6-month regimens (1)	Absolute number of doses missed	Restricted negative composite outcome	RRs	Adjusted	Intensive phase	All	Restricted negative composite outcome
31	4- vs. 6-month regimens (1)	Absolute number of doses missed	Negative composite outcome	RRs, risks	Adjusted	Continuation phase	All	No
32	4- vs. 6-month regimens (1)	Absolute number of doses missed	Negative composite outcome	RDs	Adjusted	Continuation phase	All	No
33	4- vs. 6-month regimens (1)	Absolute number of doses missed	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	All	Restricted negative composite outcome
34	Different 4-month regimens (2)	Percentage of doses taken	Negative composite outcome	RRs, risks	Adjusted	Overall	4-month regimens	No
35	Different 4-month regimens (2)	Percentage of doses taken	Negative composite outcome	RDs	Adjusted	Overall	4-month regimens	No
36	Different 4-month regimens (2)	Percentage of doses taken	Restricted negative composite	RRs	Adjusted	Overall	4-month regimens	Restricted negative composite outcome

#	Comparing forgiveness of (objective)	Exposure	Outcome measure	Statistical measure	Unadjusted or adjusted	Period in which exposure measured	Regimens included	Sensitivity analysis?
			outcome					
37	Different 4-month regimens (2)	Percentage of doses taken	Negative composite outcome	RRs, risks	Adjusted	Intensive phase	4-month regimens	No
38	Different 4-month regimens (2)	Percentage of doses taken	Negative composite outcome	RDs	Adjusted	Intensive phase	4-month regimens	No
39	Different 4-month regimens (2)	Percentage of doses taken	Restricted negative composite outcome	RRs	Adjusted	Intensive phase	4-month regimens	Restricted negative composite outcome
40	Different 4-month regimens (2)	Percentage of doses taken	Negative composite outcome	RRs, risks	Adjusted	Continuation phase	4-month regimens	No
41	Different 4-month regimens (2)	Percentage of doses taken	Negative composite outcome	RDs	Adjusted	Continuation phase	4-month regimens	No
42	Different 4-month regimens (2)	Percentage of doses taken	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	Restricted negative composite outcome
43	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Intensive phase	6-month regimen	No
44	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Intensive phase	6-month regimen	Restricted negative composite outcome
45	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Intensive phase	4-month regimens	No
46	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Intensive phase	4-month regimens	Restricted negative composite outcome
47	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Intensive phase	6-month regimen	Continuation phase dose-taking adjustment

#	Comparing forgiveness of (objective)	Exposure	Outcome measure	Statistical measure	Unadjusted or adjusted	Period in which exposure measured	Regimens included	Sensitivity analysis?
48	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Intensive phase	6-month regimen	Continuation phase dose-taking adjustment. Restricted negative composite outcome
49	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Intensive phase	4-month regimens	Continuation phase dose-taking adjustment
50	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Intensive phase	4-month regimens	Continuation phase dose-taking adjustment. Restricted negative composite outcome
51	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Continuation phase dose-taking	RRs	Adjusted	Intensive phase	6-month regimen	No
52	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Continuation phase dose-taking	RRs	Adjusted	Intensive phase	4-month regimens	No
53	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Continuation phase	6-month regimen	No
54	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	6-month regimen	Restricted negative composite outcome
55	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	No
56	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	Restricted negative composite outcome
57	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Continuation phase	6-month regimen	Intensive phase dose-taking adjustment
58	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	6-month regimen	Intensive phase dose-taking adjustment. Restricted negative composite outcome

#	Comparing forgiveness of (objective)	Exposure	Outcome measure	Statistical measure	Unadjusted or adjusted	Period in which exposure measured	Regimens included	Sensitivity analysis?
59	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	Intensive phase dose-taking adjustment
60	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	Intensive phase dose-taking adjustment. Restricted negative composite outcome
61	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Continuation phase	6-month regimen	Culture status at 2 months adjustment
62	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	6-month regimen	Culture status at 2 months adjustment. Restricted negative composite outcome
63	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	Culture status at 2 months adjustment
64	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	Culture status at 2 months adjustment. Restricted negative composite outcome
65	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Continuation phase	6-month regimen	Intensive phase, culture status at 2 months adjustment
66	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	6-month regimen	Intensive phase, culture status at 2 months adjustment. Restricted negative composite outcome
67	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	Intensive phase, culture status at 2 months adjustment
68	Intensive vs. continuation phases (3)	Percentage of doses taken, categorised	Restricted negative composite outcome	RRs	Adjusted	Continuation phase	4-month regimens	Intensive phase, culture status at 2 months adjustment. Restricted negative composite outcome

970

RD- risk difference, RR- risk ratio

971 **Online Data Supplement Table E4. Forgiveness of the four- versus six-month regimens: unadjusted and adjusted models**

Doses taken (%)		Risk (95% CI)	RR (95% CI)	RD (95% CI)	aRisk (95% CI)	aRR (95% CI)	aRD (95% CI)
OVERALL							
6-month regimen	100%	0.09 (0.07-0.10)	baseline	baseline	0.09 (0.08-0.11)	baseline	baseline
	95%	0.13 (0.11-0.14)	1.44 (1.40-1.47)	0.13 (0.12-0.14)	0.13 (0.11-0.15)	1.43 (1.39-1.46)	0.13 (0.12-0.14)
	90%	0.17 (0.15-0.20)	2.00 (1.91-2.09)	0.25 (0.24-0.27)	0.18 (0.16-0.20)	1.96 (1.87-2.06)	0.25 (0.24-0.27)
	85%	0.23 (0.21-0.26)	2.68 (2.51-2.86)	0.36 (0.34-0.38)	0.24 (0.21-0.26)	2.61 (2.44-2.79)	0.36 (0.34-0.38)
	80%	0.30 (0.28-0.33)	3.48 (3.20-3.78)	0.45 (0.43-0.48)	0.30 (0.28-0.33)	3.37 (3.09-3.67)	0.45 (0.42-0.48)
4-month regimens	100%	0.18 (0.16-0.19)	baseline	baseline	0.18 (0.16-0.20)	baseline	baseline
	95%	0.23 (0.21-0.25)	1.30 (1.28-1.32)	0.12 (0.12-0.13)	0.23 (0.21-0.25)	1.29 (1.27-1.32)	0.12 (0.12-0.13)
	90%	0.29 (0.27-0.31)	1.64 (1.60-1.69)	0.23 (0.22-0.25)	0.29 (0.27-0.32)	1.63 (1.58-1.68)	0.23 (0.22-0.24)
	85%	0.36 (0.34-0.38)	2.03 (1.95-2.11)	0.33 (0.32-0.35)	0.36 (0.34-0.38)	2.00 (1.91-2.10)	0.33 (0.31-0.35)
	80%	0.43 (0.41-0.46)	2.45 (2.32-2.58)	0.42 (0.40-0.44)	0.43 (0.41-0.46)	2.41 (2.27-2.56)	0.42 (0.40-0.44)
INTENSIVE PHASE							
6-month regimen	100%	0.11 (0.09-0.13)	baseline	baseline	0.11 (0.10-0.13)	baseline	baseline
	95%	0.15 (0.13-0.18)	1.40 (1.36-1.43)	0.13 (0.12-0.14)	0.16 (0.14-0.18)	1.38 (1.35-1.42)	0.13 (0.12-0.14)
	90%	0.21 (0.19-0.23)	1.89 (1.81-1.98)	0.25 (0.23-0.27)	0.21 (0.19-0.23)	1.85 (1.76-1.95)	0.25 (0.23-0.27)
	85%	0.27 (0.25-0.30)	2.48 (2.32-2.64)	0.36 (0.33-0.38)	0.27 (0.25-0.30)	2.41 (2.23-2.59)	0.35 (0.33-0.38)
	80%	0.35 (0.32-0.38)	3.15 (2.90-3.42)	0.45 (0.41-0.48)	0.35 (0.31-0.38)	3.03 (2.76-3.33)	0.45 (0.41-0.48)
4-month regimens	100%	0.19 (0.17-0.21)	baseline	baseline	0.19 (0.18-0.21)	baseline	baseline
	95%	0.24 (0.22-0.26)	1.28 (1.26-1.30)	0.12 (0.11-0.13)	0.25 (0.23-0.27)	1.27 (1.24-1.29)	0.12 (0.11-0.13)
	90%	0.30 (0.28-0.33)	1.60 (1.55-1.65)	0.22 (0.20-0.24)	0.30 (0.28-0.33)	1.57 (1.51-1.63)	0.22 (0.20-0.24)
	85%	0.37 (0.35-0.40)	1.95 (1.87-2.04)	0.32 (0.29-0.35)	0.37 (0.34-0.39)	1.89 (1.79-2.00)	0.32 (0.29-0.34)
	80%	0.44 (0.42-0.47)	2.33 (2.20-2.47)	0.40 (0.37-0.44)	0.44 (0.41-0.47)	2.24 (2.09-2.41)	0.40 (0.36-0.44)
CONTINUATION PHASE							
6-month regimen	100%	0.08 (0.06-0.09)	baseline	baseline	0.08 (0.07-0.10)	baseline	baseline
	95%	0.11 (0.10-0.13)	1.44 (1.40-1.48)	0.12 (0.11-0.13)	0.12 (0.10-0.14)	1.43 (1.39-1.47)	0.12 (0.11-0.13)
	90%	0.16 (0.14-0.18)	2.00 (1.90-2.11)	0.23 (0.21-0.25)	0.16 (0.14-0.19)	1.96 (1.86-2.07)	0.23 (0.21-0.25)
	85%	0.21 (0.19-0.24)	2.68 (2.49-2.89)	0.32 (0.30-0.35)	0.22 (0.19-0.24)	2.61 (2.42-2.81)	0.32 (0.30-0.35)
	80%	0.28 (0.25-0.30)	3.49 (3.18-3.82)	0.41 (0.38-0.44)	0.28 (0.25-0.31)	3.36 (3.06-3.70)	0.41 (0.38-0.44)
4-month regimens	100%	0.17 (0.15-0.19)	baseline	baseline	0.18 (0.16-0.20)	baseline	baseline
	95%	0.22 (0.20-0.24)	1.28 (1.26-1.30)	0.11 (0.10-0.12)	0.23 (0.21-0.25)	1.27 (1.25-1.30)	0.11 (0.10-0.12)
	90%	0.28 (0.25-0.30)	1.60 (1.55-1.65)	0.21 (0.20-0.22)	0.28 (0.26-0.30)	1.58 (1.53-1.63)	0.21 (0.20-0.22)
	85%	0.34 (0.31-0.36)	1.95 (1.87-2.04)	0.30 (0.28-0.32)	0.34 (0.32-0.36)	1.92 (1.84-2.01)	0.30 (0.28-0.31)
	80%	0.40 (0.38-0.43)	2.33 (2.21-2.47)	0.38 (0.36-0.40)	0.41 (0.38-0.43)	2.29 (2.16-2.42)	0.38 (0.35-0.40)

972 Unadjusted and adjusted marginal risks, risk ratios, and risk differences for the negative composite outcome by percentage of doses taken (modelled as fractional polynomials)

973 of the functional form x^3) across the entire treatment period (overall), intensive phase and continuation phase, presented stratified by regimens grouped by length. One model
974 per period of treatment, four- and six-month regimens in the same model. For the unadjusted and adjusted multiplicative models, Wald p-values for an interaction between
975 regimens grouped by length and percentage of doses taken all $p < 0.0001$. For the unadjusted additive models, Wald p-values for an interaction between regimens grouped by
976 length and percentage of doses taken 0.08 (overall), 0.06 (intensive phase), 0.10 (continuation phase). For the adjusted additive models, Wald p-values for an interaction
977 between regimens grouped by length and percentage of doses taken 0.06 (overall), 0.06 (intensive phase), 0.07 (continuation phase). Unadjusted models adjusted with a
978 three-level fixed effect for trial and regimens grouped by length. Adjusted models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status,
979 smear status at baseline (most severe), cavitation at baseline and a three-level fixed effect for trial. All models contain data for 3,180 participants. Data presented for 80-100%
980 of doses taken due to data sparsity at lower levels, but the full range of values were included in the statistical models. Overall unadjusted risks and risk ratios from model 1;
981 intensive phase unadjusted risks and risk ratios from model 5; continuation phase unadjusted risks and risk ratios from model 9. Overall unadjusted risk differences from model
982 2; intensive phase unadjusted risk differences from model 6; continuation phase unadjusted risk differences from model 10. Overall adjusted risks and risk ratios from model 3;
983 intensive phase adjusted risks and risk ratios from model 7; continuation phase adjusted risks and risk ratios from model 11. Overall adjusted risk differences from model 4;
984 intensive phase adjusted risk differences from model 8; continuation phase adjusted risk differences from model 12. aRD- adjusted risk difference, aRisk- adjusted risk, aRR-
985 adjusted risk ratio, CI- confidence interval, RD- unadjusted risk difference, Risk- unadjusted risk, RR- unadjusted risk ratio.

986 **Online Data Supplement Table E5. Forgiveness of the four- versus six-month**
 987 **regimens: sensitivity analysis adjustment for weight**

Doses taken (%)	aRR (95% CI)	
	6-month regimen	4-month regimens
OVERALL		
100%	baseline	baseline
95%	1.42 (1.39-1.46)	1.29 (1.27-1.31)
90%	1.95 (1.86-2.05)	1.63 (1.57-1.68)
85%	2.59 (2.42-2.78)	2.00 (1.90-2.10)
80%	3.34 (3.06-3.64)	2.40 (2.26-2.55)
INTENSIVE PHASE		
100%	baseline	baseline
95%	1.38 (1.34-1.42)	1.26 (1.24-1.29)
90%	1.84 (1.74-1.94)	1.56 (1.50-1.63)
85%	2.39 (2.21-2.58)	1.88 (1.78-2.00)
80%	3.00 (2.73-3.31)	2.23 (2.07-2.40)
CONTINUATION PHASE		
100%	baseline	baseline
95%	1.42 (1.38-1.46)	1.27 (1.25-1.29)
90%	1.95 (1.85-2.06)	1.58 (1.53-1.63)
85%	2.60 (2.40-2.80)	1.92 (1.83-2.01)
80%	3.34 (3.03-3.68)	2.28 (2.15-2.42)

988 Adjusted risk ratios for the negative composite outcome by percentage of doses taken (modelled as fractional
 989 polynomials of the functional form x^3) versus a baseline of 100% across overall, during the intensive phase and
 990 continuation phase, presented stratified by regimens grouped by length. One model per period of treatment, four-
 991 and six-month regimens in the same model. Models adjusted for sex, age (fitted using a fractional polynomial),
 992 ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at baseline, a three-level fixed
 993 effect for trial and weight. All models contain data for 3,180 participants. Data presented for 80-100% of doses
 994 taken due to data sparsity at lower levels, but the full range of values were included in the statistical models.
 995 Overall from model 13; intensive phase from model 17; continuation phase from model 21. aRR- adjusted risk
 996 ratio, CI- confidence interval.
 997

998 **Online Data Supplement Table E6. Forgiveness of the four- versus six-month**
999 **regimens: sensitivity analysis alternative coding of smear status**

Doses taken (%)	aRR (95% CI)	
	6-month regimen	4-month regimens
OVERALL		
100%	baseline	baseline
95%	1.42 (1.39-1.46)	1.29 (1.27-1.32)
90%	1.95 (1.86-2.05)	1.63 (1.58-1.69)
85%	2.60 (2.42-2.78)	2.01 (1.92-2.11)
80%	3.34 (3.06-3.64)	2.42 (2.28-2.57)
INTENSIVE PHASE		
100%	baseline	baseline
95%	1.38 (1.34-1.42)	1.27 (1.24-1.30)
90%	1.84 (1.75-1.94)	1.57 (1.51-1.64)
85%	2.38 (2.21-2.56)	1.91 (1.80-2.02)
80%	3.00 (2.73-3.29)	2.26 (2.11-2.43)
CONTINUATION PHASE		
100%	baseline	baseline
95%	1.42 (1.38-1.46)	1.27 (1.25-1.30)
90%	1.95 (1.85-2.06)	1.59 (1.54-1.64)
85%	2.59 (2.40-2.80)	1.93 (1.84-2.02)
80%	3.33 (3.03-3.67)	2.30 (2.17-2.43)

1000 Adjusted risk ratios for the negative composite outcome by percentage of doses taken (modelled as fractional
1001 polynomials of the functional form x^3) versus a baseline of 100% across overall, during the intensive phase and
1002 continuation phase, presented stratified by regimens grouped by length. One model per period of treatment, four-
1003 and six-month regimens in the same model. Sensitivity analysis based on an alternative coding of baseline smear
1004 status (least severe). Models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV and CD4
1005 status, smear status at baseline (least severe), cavitation at baseline, a three-level fixed effect for trial. All models
1006 contain data for 3,180 participants. Data presented for 80-100% of doses taken due to data sparsity at lower
1007 levels, but the full range of values were included in the statistical models. Overall from model 14; intensive phase
1008 from model 18; continuation phase from model 22. aRR- adjusted risk ratio, CI- confidence interval.
1009

1010 **Online Data Supplement Table E7. Forgiveness of the four- versus six-month**
 1011 **regimens: sensitivity analysis alternative coding of the percentage dose-taking**
 1012 **data**

Doses taken (%)		aRR (95% CI)	
		6-month regimen	4-month regimens
OVERALL			
	100%	baseline	baseline
	95%	1.40 (1.36-1.43)	1.29 (1.26-1.32)
	90%	1.88 (1.79-1.98)	1.63 (1.56-1.69)
	85%	2.46 (2.29-2.65)	2.00 (1.89-2.12)
	80%	3.13 (2.85-3.43)	2.40 (2.23-2.58)
INTENSIVE PHASE			
	100%	baseline	baseline
	95%	1.38 (1.34-1.42)	1.27 (1.24-1.30)
	90%	1.83 (1.73-1.94)	1.58 (1.51-1.65)
	85%	2.37 (2.19-2.57)	1.92 (1.80-2.03)
	80%	2.98 (2.69-3.30)	2.28 (2.11-2.46)
CONTINUATION PHASE			
	100%	baseline	baseline
	95%	1.38 (1.34-1.42)	1.27 (1.24-1.29)
	90%	1.84 (1.75-1.95)	1.57 (1.51-1.62)
	85%	2.39 (2.21-2.58)	1.89 (1.80-1.99)
	80%	3.01 (2.73-3.32)	2.24 (2.10-2.39)

1013 Adjusted risk ratios for the negative composite outcome by percentage of doses taken (modelled as fractional
 1014 polynomials of the functional form x^3) versus a baseline of 100% overall, during the intensive phase and
 1015 continuation phase, presented stratified by regimens grouped by length. One model per period of treatment, four-
 1016 and six-month regimens in the same model. Sensitivity analysis based on an alternative coding of the OFLOTUB
 1017 percentage dose-taking, where missing data were not assumed to equate to no doses taken, but rather missing
 1018 data were coded to the opposite extreme (i.e. all doses taken). Models adjusted for sex, age (fitted using a
 1019 fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at
 1020 baseline, a three-level fixed effect for trial. All models contain data for 3,180 participants. Data presented for 80-
 1021 100% of doses taken due to data sparsity at lower levels, but the full range of values were included in the
 1022 statistical models. Overall from model 15; intensive phase from model 19; continuation phase from model 23.
 1023 aRR- adjusted risk ratio, CI- confidence interval.

1024

1025

1026 **Online Data Supplement Table E8. Forgiveness of the four- versus six-month**
 1027 **regimens: sensitivity analysis using the restricted negative composite**
 1028 **outcome**

Doses taken (%)		aRR (95% CI)	
		6-month regimen	4-month regimens
OVERALL			
	95-100%	baseline	baseline
	90-<95%	1.19 (1.15-1.23)	1.27 (1.17-1.38)
	85-<90%	1.41 (1.32-1.51)	1.61 (1.36-1.89)
	80-<85%	1.68 (1.52-1.86)	2.03 (1.59-2.61)
INTENSIVE PHASE			
	95-100%	baseline	baseline
	90-<95%	1.24 (1.19-1.29)	1.08 (0.95-1.23)
	85-<90%	1.54 (1.42-1.67)	1.17 (0.90-1.51)
	80-<85%	1.91 (1.70-2.15)	1.27 (0.86-1.86)
CONTINUATION PHASE			
	95-100%	baseline	baseline
	90-<95%	1.17 (1.13-1.21)	1.13 (1.10-1.17)
	85-<90%	1.37 (1.28-1.46)	1.29 (1.20-1.38)
	80-<85%	1.60 (1.46-1.76)	1.46 (1.32-1.61)

1029 Adjusted risk ratios for the restricted negative composite outcome by percentage of doses taken. Percentage
 1030 doses taken grouped into 5% categories and modelled as a linear variable; baseline of 95-100%. Doses taken
 1031 examined overall, during the intensive phase and continuation phase. Results presented stratified by regimens
 1032 grouped by length. One model per period of treatment, four- and six-month regimens in the same model.
 1033 Sensitivity analysis based on a restricted definition of the negative composite outcome. Models adjusted for sex,
 1034 age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe),
 1035 cavitation at baseline, a three-level fixed effect for trial. All models contain data for 2,952 participants. Data
 1036 presented for 80-100% of doses taken due to data sparsity at lower levels, but the full range of values were
 1037 included in the statistical models. Overall from model 16; intensive phase from model 20; continuation phase from
 1038 model 24. aRR- adjusted risk ratio, CI- confidence interval.

1039

1040 **Online Data Supplement Table E9. Forgiveness of the four- versus six-month**
 1041 **regimens: non-adherence measured by absolute number of missed doses**

Absolute number of missed doses		aRisk (95% CI)	aRR (95% CI)	aRD (95% CI)
OVERALL				
6-month regimen	No missed doses	0.07 (0.06-0.09)	baseline	baseline
	1-2	0.14 (0.07-0.21)	1.87 (1.08-3.26)	0.07 (-0.01-0.14)
	3-7	0.12 (0.04-0.21)	1.65 (0.80-3.41)	0.03 (-0.05-0.10)
	8-28	0.27 (0.17-0.38)	3.68 (2.33-5.81)	0.19 (0.09-0.29)
	29+	0.85 (0.77-0.93)	11.45 (8.90-14.74)	0.79 (0.71-0.87)
4-month regimens	No missed doses	0.17 (0.15-0.19)	baseline	baseline
	1-2	0.17 (0.12-0.23)	0.99 (0.70-1.40)	-0.01 (-0.07-0.04)
	3-7	0.31 (0.22-0.40)	1.80 (1.33-2.45)	0.13 (0.04-0.22)
	8-28	0.42 (0.29-0.56)	2.45 (1.74-3.46)	0.25 (0.12-0.38)
	29+	0.94 (0.90-0.99)	5.46 (4.79-6.22)	0.82 (0.79-0.84)
INTENSIVE PHASE				
6-month regimen	No missed doses	0.10 (0.09-0.12)	baseline	baseline
	1-2	0.19 (0.09-0.28)	1.81 (1.04-3.14)	0.11 (0.01-0.21)
	3-7	0.18 (0.05-0.31)	1.71 (0.81-3.62)	0.03 (-0.08-0.14)
	8-28	0.78 (0.64-0.93)	7.51 (5.76-9.79)	0.69 (0.53-0.85)
	29+	0.94 (0.83-1.05)	9.02 (7.28-11.18)	0.89 (0.85-0.92)
4-month regimens	No missed doses	0.19 (0.17-0.21)	baseline	baseline
	1-2	0.22 (0.16-0.29)	1.18 (0.86-1.64)	0.02 (-0.04-0.09)
	3-7	0.36 (0.25-0.47)	1.92 (1.39-2.67)	0.17 (0.06-0.29)
	8-28	0.68 (0.56-0.81)	3.63 (2.93-4.49)	0.51 (0.37-0.65)
	29+	0.91 (0.81-1.01)	4.83 (4.15-5.62)	0.80 (0.77-0.84)
CONTINUATION PHASE				
6-month regimen	No missed doses	0.08 (0.06-0.10)	baseline	baseline
	1-2	0.14 (0.06-0.22)	1.72 (0.91-3.25)	0.05 (-0.03-0.13)
	3-7	0.10 (0.01-0.18)	1.19 (0.49-2.91)	0.02 (-0.07-0.11)
	8-28	0.27 (0.16-0.38)	3.39 (2.10-5.46)	0.20 (0.09-0.30)
	29+	0.84 (0.76-0.92)	10.49 (8.22-13.38)	0.78 (0.70-0.86)
4-month regimens	No missed doses	0.18 (0.16-0.20)	baseline	baseline
	1-2	0.18 (0.10-0.27)	1.00 (0.62-1.63)	0.01 (-0.08-0.10)
	3-7	0.23 (0.10-0.37)	1.29 (0.73-2.29)	0.04 (-0.08-0.16)
	8-28	0.61 (0.47-0.75)	3.37 (2.60-4.36)	0.43 (0.27-0.58)
	29+	0.96 (0.90-1.02)	5.30 (4.69-5.99)	0.82 (0.79-0.84)

1042 Adjusted risks, risk ratios and risk differences for the negative composite outcome by numbers of missed doses
 1043 overall, during the intensive phase and continuation phase, presented stratified by regimens grouped by length.
 1044 Baseline for multiplicative and additive models zero missed doses. One model per period of treatment, four- and
 1045 six-month regimens in the same model. For the multiplicative models, Wald p-values for an interaction between
 1046 regimens grouped by length and percentage dose-taking were <0.001 for all periods. For the additive models,
 1047 Wald p-values for an interaction between regimens grouped by length and percentage dose-taking 0.12 (overall),
 1048 <0.001 (intensive phase), 0.11 (continuation phase). Models adjusted for sex, age (fitted using a fractional
 1049 polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at baseline and a
 1050 three-level fixed effect for trial. All models contain data for 3,180 participants. Overall risk differences from model
 1051 26; intensive phase risk differences from model 29; continuation phase risk differences from model 32. Overall
 1052 risks and risk ratios from model 25; intensive phase risks and risk ratios from model 28; continuation phase risks
 1053 and risk ratios from model 31. aRD- adjusted risk difference, aRisk- adjusted risk, aRR- adjusted risk ratio, CI-
 1054 confidence interval.

1055 **Online Data Supplement Table E10. Forgiveness of the four- versus six-month**
1056 **regimens: non-adherence measured by absolute number of missed doses,**
1057 **sensitivity analysis using the restricted negative composite outcome**

Absolute number of missed doses		aRR (95% CI)	
		6-month regimen	4-month regimens
OVERALL			
	No missed doses	baseline	baseline
	1-2	1.89 (0.94-3.79)	0.93 (0.60-1.45)
	3-7	1.40 (0.37-5.27)	1.64 (1.10-2.43)
	8-28	2.20 (0.89-5.46)	1.21 (0.54-2.71)
	29+	5.49 (1.90-15.85)	5.44 (4.29-6.91)
INTENSIVE PHASE			
	No missed doses	baseline	baseline
	1-2	1.62 (0.65-4.00)	0.97 (0.60-1.58)
	3-7	2.39 (0.76-7.54)	1.54 (0.89-2.64)
	8-28	6.25 (2.19-17.85)	1.20 (0.30-4.88)
	29+	21.39 (12.43-36.81)	-*
CONTINUATION PHASE			
	No missed doses	baseline	baseline
	1-2	1.96 (0.90-4.22)	1.12 (0.67-1.89)
	3-7	0.25 (0.03-2.01)	1.42 (0.75-2.67)
	8-28	1.75 (0.64-4.76)	1.10 (0.35-3.49)
	29+	5.13 (1.75-15.09)	5.24 (4.17-6.59)

1058 Adjusted risk ratios for the restricted negative composite outcome by numbers of missed doses overall, during
1059 the intensive phase and continuation phase, presented stratified by regimens grouped by length. Baseline zero
1060 missed doses. One model per period of treatment, four- and six-month regimens in the same model. Sensitivity
1061 analysis based on a restricted definition of the negative composite outcome. Models adjusted for sex, age (fitted
1062 using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation
1063 at baseline and a three-level fixed effect for trial. All models contain data for 2,952 participants. Overall from
1064 model 27; intensive phase from model 30; continuation phase from model 33. *- data too sparse to estimate,
1065 aRR- adjusted risk ratio, CI- confidence interval.

1066

1067 **Online Data Supplement Table E11. Forgiveness of different four-month**

1068 **regimens**

Doses taken (%)		aRisk (95% CI)	aRR (95% CI)	aRD (95% CI)
OVERALL				
2MRZE/2P ₂ M ₂	100%	0.27 (0.20-0.34)	baseline	baseline
	95%	0.34 (0.26-0.41)	1.26 (1.19-1.33)	0.13 (0.10-0.16)
	90%	0.42 (0.34-0.50)	1.56 (1.40-1.73)	0.24 (0.18-0.31)
	85%	0.50 (0.42-0.59)	1.88 (1.62-2.18)	0.35 (0.26-0.44)
	80%	0.59 (0.50-0.69)	2.22 (1.84-2.68)	0.44 (0.33-0.56)
2MRZE/2MR	100%	0.20 (0.17-0.24)	baseline	baseline
	95%	0.26 (0.22-0.30)	1.26 (1.22-1.30)	0.12 (0.11-0.13)
	90%	0.32 (0.28-0.36)	1.56 (1.47-1.66)	0.23 (0.21-0.25)
	85%	0.38 (0.34-0.43)	1.89 (1.73-2.05)	0.33 (0.30-0.36)
	80%	0.45 (0.41-0.50)	2.23 (2.00-2.49)	0.41 (0.38-0.45)
2HRZM/2HRM	100%	0.15 (0.12-0.18)	baseline	baseline
	95%	0.19 (0.16-0.23)	1.31 (1.27-1.36)	0.13 (0.12-0.13)
	90%	0.25 (0.21-0.29)	1.67 (1.57-1.78)	0.24 (0.23-0.25)
	85%	0.31 (0.27-0.35)	2.08 (1.90-2.28)	0.34 (0.32-0.36)
	80%	0.38 (0.33-0.42)	2.53 (2.26-2.83)	0.43 (0.41-0.45)
2HRZG/2HRG	100%	0.16 (0.13-0.19)	baseline	baseline
	95%	0.21 (0.18-0.25)	1.33 (1.28-1.38)	0.12 (0.10-0.14)
	90%	0.28 (0.24-0.32)	1.72 (1.61-1.84)	0.23 (0.19-0.27)
	85%	0.35 (0.30-0.39)	2.17 (1.97-2.39)	0.33 (0.27-0.38)
	80%	0.43 (0.37-0.48)	2.66 (2.35-3.01)	0.41 (0.34-0.48)
INTENSIVE PHASE				
2MRZE/2P ₂ M ₂	100%	0.27 (0.19-0.34)	baseline	baseline
	95%	0.34 (0.26-0.42)	1.28 (1.19-1.37)	0.12 (0.07-0.17)
	90%	0.42 (0.34-0.51)	1.59 (1.39-1.83)	0.23 (0.14-0.33)
	85%	0.52 (0.41-0.62)	1.94 (1.60-2.36)	0.33 (0.19-0.47)
	80%	0.62 (0.49-0.74)	2.31 (1.81-2.96)	0.42 (0.25-0.60)
2MRZE/2MR	100%	0.22 (0.18-0.25)	baseline	baseline
	95%	0.27 (0.23-0.31)	1.26 (1.21-1.31)	0.12 (0.10-0.14)
	90%	0.34 (0.29-0.38)	1.55 (1.44-1.67)	0.23 (0.19-0.27)
	85%	0.41 (0.36-0.46)	1.87 (1.69-2.07)	0.33 (0.27-0.38)
	80%	0.48 (0.42-0.54)	2.21 (1.94-2.51)	0.42 (0.35-0.49)
2HRZM/2HRM	100%	0.17 (0.13-0.20)	baseline	baseline
	95%	0.21 (0.18-0.25)	1.29 (1.25-1.33)	0.12 (0.12-0.13)
	90%	0.27 (0.23-0.31)	1.62 (1.53-1.72)	0.24 (0.22-0.26)
	85%	0.33 (0.29-0.37)	1.99 (1.82-2.16)	0.34 (0.31-0.36)
	80%	0.40 (0.35-0.44)	2.38 (2.14-2.66)	0.43 (0.39-0.46)
2HRZG/2HRG	100%	0.18 (0.15-0.21)	baseline	baseline
	95%	0.22 (0.19-0.26)	1.25 (1.18-1.33)	0.09 (0.05-0.13)
	90%	0.28 (0.23-0.32)	1.54 (1.37-1.73)	0.17 (0.09-0.25)
	85%	0.33 (0.27-0.39)	1.84 (1.56-2.17)	0.24 (0.13-0.36)
	80%	0.39 (0.31-0.47)	2.17 (1.76-2.67)	0.31 (0.16-0.46)
CONTINUATION PHASE				
2MRZE/2P ₂ M ₂	100%	0.28 (0.21-0.35)	baseline	baseline
	95%	0.34 (0.26-0.41)	1.20 (1.15-1.25)	0.10 (0.08-0.11)
	90%	0.40 (0.32-0.47)	1.42 (1.31-1.53)	0.19 (0.15-0.22)
	85%	0.46 (0.39-0.54)	1.65 (1.47-1.84)	0.26 (0.22-0.31)
	80%	0.53 (0.45-0.60)	1.88 (1.63-2.16)	0.33 (0.27-0.39)
2MRZE/2MR	100%	0.20 (0.16-0.24)	baseline	baseline
	95%	0.25 (0.21-0.29)	1.25 (1.21-1.29)	0.11 (0.10-0.12)
	90%	0.30 (0.26-0.35)	1.53 (1.44-1.62)	0.21 (0.19-0.23)
	85%	0.36 (0.32-0.41)	1.82 (1.68-1.98)	0.29 (0.26-0.32)
	80%	0.43 (0.38-0.47)	2.14 (1.92-2.38)	0.37 (0.33-0.41)
2HRZM/2HRM	100%	0.14 (0.11-0.18)	baseline	baseline

Doses taken (%)		aRisk (95% CI)	aRR (95% CI)	aRD (95% CI)
	95%	0.19 (0.15-0.22)	1.31 (1.26-1.35)	0.12 (0.12-0.13)
	90%	0.24 (0.20-0.28)	1.66 (1.56-1.77)	0.23 (0.22-0.24)
	85%	0.30 (0.26-0.34)	2.07 (1.89-2.26)	0.33 (0.31-0.35)
	80%	0.36 (0.32-0.40)	2.50 (2.23-2.80)	0.42 (0.40-0.44)
2HRZG/2HRG	100%	0.16 (0.12-0.19)	baseline	baseline
	95%	0.20 (0.17-0.24)	1.30 (1.25-1.34)	0.10 (0.08-0.12)
	90%	0.26 (0.22-0.30)	1.64 (1.54-1.75)	0.19 (0.15-0.22)
	85%	0.32 (0.27-0.36)	2.02 (1.84-2.22)	0.27 (0.22-0.32)
	80%	0.38 (0.33-0.43)	2.44 (2.17-2.74)	0.34 (0.28-0.40)

1069 Adjusted risks, risk ratios and risk differences for the negative composite outcome by percentage of doses taken
1070 (modelled as fractional polynomials of the functional form x^3) overall, during the intensive phase and continuation
1071 phase, stratified by four-month regimen. Baseline for multiplicative and additive models 100% dose-taking. One
1072 model per period of treatment, all four-month regimens in same model. For the multiplicative models, Wald p-
1073 values for an interaction between regimens grouped by length and percentage dose-taking 0.10 (overall), 0.76
1074 (intensive phase), 0.004 (continuation phase). For the additive models, Wald p-values for an interaction between
1075 regimens grouped by length and percentage dose-taking 0.84 (overall), 0.50 (intensive phase), 0.004
1076 (continuation phase). Models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV and CD4
1077 status, smear status at baseline (most severe), cavitation at baseline. No adjustment for study due to collinearity
1078 with regimen. Models contain data for 1,837 participants. Data presented for 80-100% of doses taken due to data
1079 sparsity at lower levels, but the full range of values were included in the statistical models. Overall risk differences
1080 from model 35; intensive phase risk differences from model 38; continuation phase risk differences from model
1081 41. Overall risks and risk ratios from model 34; intensive phase risks and risk ratios from model 37; continuation
1082 phase risks and risk ratios from model 40. 2- twice weekly dosing, aRD- adjusted risk difference, aRisk- adjusted
1083 risk, aRR- adjusted risk ratio, CI- confidence interval, E- ethambutol, G- gatifloxacin, H- isoniazid, M-
1084 moxifloxacin, P- rifapentine, R- rifampicin, Z- pyrazinamide.

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1086 **Online Data Supplement Table E12. Forgiveness of different four-month**
1087 **regimens, sensitivity analysis using the restricted negative composite**
1088 **outcome**

Doses taken (%)	aRR (95% CI)			
	2MRZE/2P ₂ M ₂	2MRZE/2MR	2HRZM/2HRM	2HRZG/2HRG
OVERALL				
95-100%	baseline	baseline	baseline	baseline
90-<95%	1.59 (1.37-1.85)	1.28 (1.18-1.39)	1.66 (0.61-4.49)	0.75 (0.47-1.21)
85-<90%	2.54 (1.88-3.43)	1.63 (1.38-1.93)	2.76 (0.38-20.17)	0.57 (0.22-1.47)
80-<85%	4.05 (2.58-6.35)	2.09 (1.62-2.69)	4.58 (0.23-90.57)	0.43 (0.10-1.79)
INTENSIVE PHASE				
95-100%	baseline	baseline	baseline	baseline
90-<95%	1.46 (0.93-2.32)	1.13 (0.77-1.65)	0.00 (0.00-0.13)	1.01 (0.89-1.16)
85-<90%	2.15 (0.86-5.36)	1.28 (0.60-2.72)	0.00 (0.00-0.02)	1.03 (0.79-1.35)
80-<85%	3.14 (0.80-12.42)	1.44 (0.46-4.48)	0.00 (0.00-0.00)	1.04 (0.70-1.56)
CONTINUATION PHASE				
95-100%	baseline	baseline	baseline	baseline
90-<95%	1.14 (1.09-1.19)	1.14 (1.10-1.18)	1.53 (0.96-2.44)	0.67 (0.34-1.32)
85-<90%	1.31 (1.20-1.43)	1.30 (1.21-1.39)	2.35 (0.93-5.95)	0.45 (0.11-1.73)
80-<85%	1.49 (1.31-1.70)	1.48 (1.33-1.64)	3.61 (0.90-14.50)	0.30 (0.04-2.29)

1089 Adjusted risk ratios for the restricted negative composite outcome by percentage of doses taken. Percentage
1090 doses taken grouped into 5% categories and modelled as a linear variable; baseline 95-100%. Doses taken
1091 examined overall, during the intensive phase and continuation phase. Results presented stratified by regimen.
1092 One model per period of treatment, all four-month regimens in same model. Sensitivity analysis based on a
1093 restricted definition of the negative composite outcome. Models adjusted for sex, age (fitted using a fractional
1094 polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at baseline. No
1095 adjustment for study due to collinearity with regimen. Models contain data for 1,707 participants. Data presented
1096 for 80-100% of doses taken due to data sparsity at lower levels, but the full range of values were included in the
1097 statistical models. Overall from model 36; intensive phase from model 39; continuation phase from model 42. z-
1098 twice weekly dosing, aRR- adjusted risk ratio, CI- confidence interval, E- ethambutol, G- gatifloxacin, H- isoniazid,
1099 M- moxifloxacin, P- rifapentine, R- rifampicin, Z- pyrazinamide.

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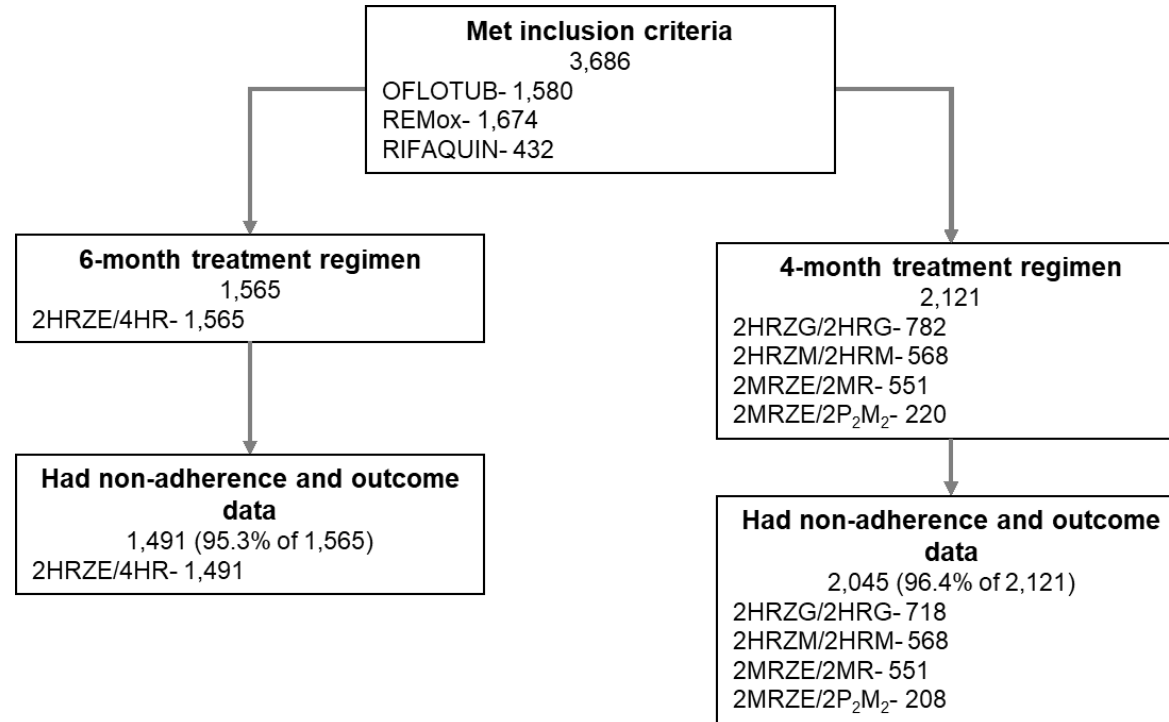
1102 **Online Data Supplement Table E13. Forgiveness during each treatment phase:**
 1103 **mediation analysis, sensitivity analysis using the restricted negative outcome**

Regimens grouped by length	Direct effect 0	Indirect effect 1	Direct effect 1	Indirect effect 0	Proportion of total effect mediated
6-month	1.13 (1.01-1.33)	1.01 (0.98-1.07)	1.13 (1.00-1.32)	1.02 (1.00-1.04)	0.11 (0.05-0.73)
4-month	1.11 (1.01-1.24)	1.00 (0.97-1.03)	1.11 (1.01-1.23)	1.00 (1.00-1.02)	0.01 (0.01-0.08)

1104 Direct effects and indirect effects expressed as odds ratios and (95% confidence intervals). 0-95% versus >95-
 1105 100% (baseline) dose-taking compared. Direct effect 0- how much the risk of the restricted negative composite
 1106 outcome would change if intensive phase dose-taking changed from >95-100% to 0-95% but, for each individual,
 1107 continuation phase dose-taking was fixed at the level it would have taken, for that individual, when intensive
 1108 phase dose-taking was >95-100%. Direct effect 1- as per direct effect 0, but when continuation phase dose-
 1109 taking is fixed at the level it would have taken, for that individual, when intensive phase dose-taking (exposure)
 1110 was ≤95%. Indirect effect 0- how much the restricted negative composite outcome would change, on average, if
 1111 intensive phase dose-taking was fixed at >95-100% but continuation phase dose-taking changed from the level it
 1112 would take if intensive phase dose-taking was >95-100% to if intensive phase dose-taking was ≤95%. Indirect
 1113 effect 1- as per indirect effect 0, but when intensive phase dose-taking fixed at ≤95%. Models adjusted for sex,
 1114 age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status (data were too sparse to adjust for one
 1115 binary dummy variable), smear status at baseline (most severe), cavitation at baseline and a three-level fixed-
 1116 effect for trial.
 1117

1118 **Online Data Supplement Figure E1. Flow chart of study participants**

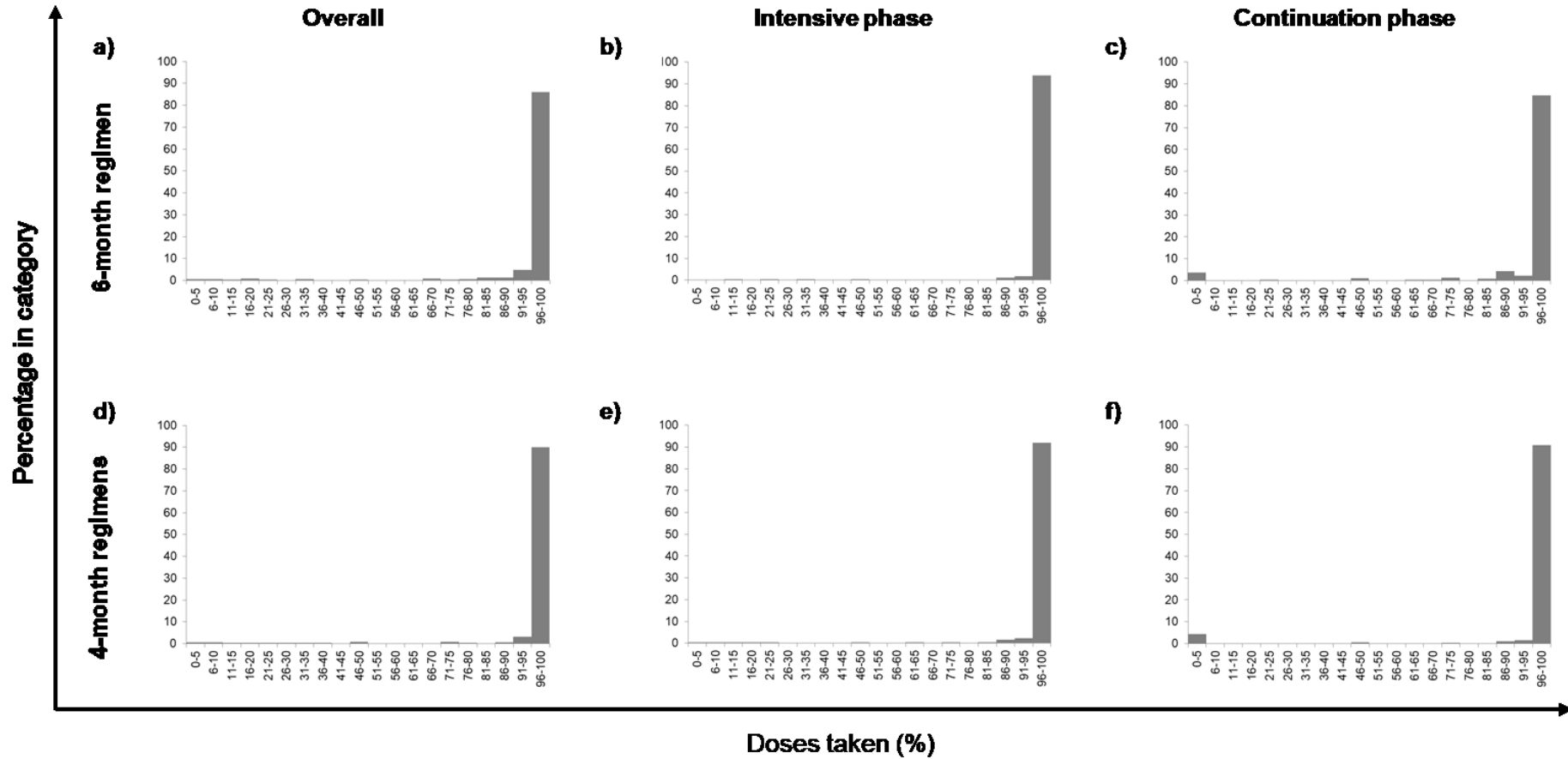
1119 For OFLOTUB and REMox, numbers meeting the inclusion criteria reflect the modified intention to treat analysis of the original trial and exclude individuals on an unknown
1120 treatment regimen. For RIFAQUIN, numbers match the modified intention to treat analysis of the original trial, but additionally contain participants lost to follow-up, who had
1121 confirmed reinfection, and who died from non-tuberculosis causes. E- ethambutol, G- gatifloxacin, H- isoniazid, M- moxifloxacin, P- rifapentine, R- rifampicin, Z- pyrazinamide



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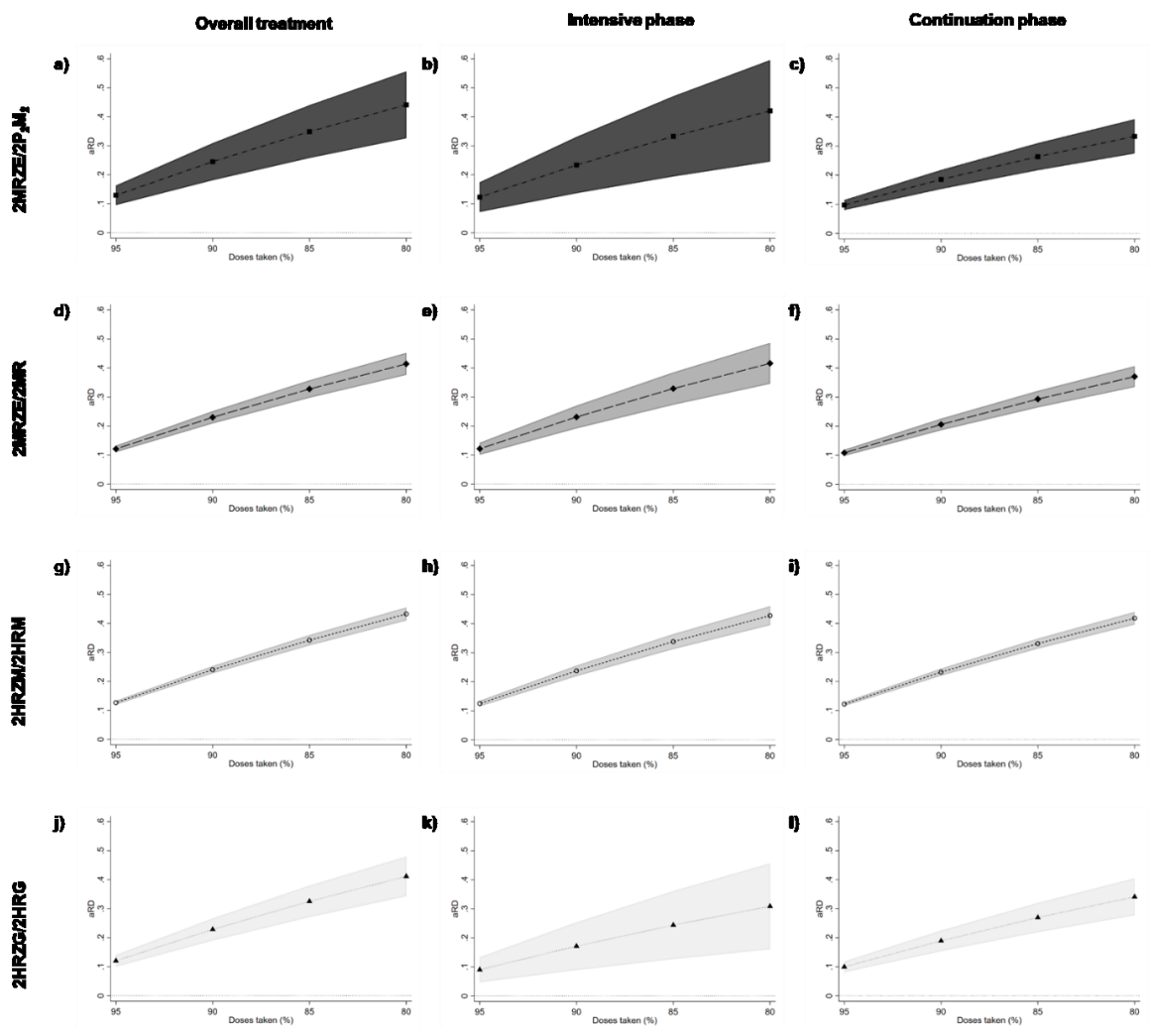
Online Data Supplement Figure E2. Histograms of percentage of doses taken

Distribution of percentage of doses taken overall (a, d), in the intensive phase (b, e), and continuation phase (c, f) for the six-month regimen (a-c) and four-month regimens (d-f).



Online Data Supplement Figure E3. Forgiveness of different four-month regimens- risk differences

Adjusted risk differences for the negative composite outcome by the percentage of doses taken (modelled as fractional polynomials of the functional form x^3) across the entire treatment period (a, d, g, j), intensive phase (b, e, h, k) and continuation phase c, f, i, l), stratified by four-month regimen. Baseline 100% dose-taking. One model per period of treatment, all four-month regimens in same model. Wald p-values for an interaction between regimens grouped by length and percentage of doses taken 0.84 (overall), 0.50 (intensive phase), 0.004 (continuation phase); horizontal dotted line charts a risk difference of 0. Models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at baseline. No adjustment for study due to collinearity with regimen. Models contain data for 1,837 participants. Data presented for 80-100% of doses taken due to data sparsity at lower levels, but the full range of values were included in the statistical models. Overall treatment from model 34; intensive phase from model 37; continuation phase from model 40. 2- twice weekly dosing, CI- confidence interval, E- ethambutol, G- gatifloxacin, H- isoniazid, M- moxifloxacin, P- rifapentine, R- rifampicin, Z- pyrazinamide.



Online Data Supplement Figure E4. Forgiveness during each treatment phase, sensitivity analysis using the restricted negative composite outcome

To compare forgiveness during the two treatment phases, intensive phase and continuation phase percentage dose-taking were categorised into 0-95% versus >95-100% (baseline) and adjusted risk ratios calculated for a) the six-month regimen and b) the four-month regimens, as follows:

- (i) intensive phase dose-taking was the exposure and continuation phase dose-taking the outcome (models 51, 52);
- (ii) continuation phase dose-taking was the exposure and the restricted negative composite outcome the outcome (models 54, 56, 58, 60, 62, 64, 66, 68); and
- (iii) intensive phase dose-taking was the exposure and the restricted negative composite outcome the outcome (44, 46, 48, 50).

Results from models (ii) and (iii) are presented without (*) and with (**) adjustment for dose-taking during the other treatment phase, assuming no interaction. For model (ii) results are also presented with (^) adjustment for culture status at two months. Models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at baseline and a three-level fixed-effect for trial. †- convergence not achieved, aRR- adjusted risk ratio, CI- confidence interval.

