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

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At-a-glance commentary:

Scientific Knowledge on the Subject

Non-adherence to tuberculosis (TB) treatment is known to be associated with a greater likelihood of a negative outcome. It is possible that the robustness ('forgiveness') of shorter treatment regimens for missing even a single dose will be reduced versus longer regimens, as there are fewer doses within the regimen. Additionally, regimens may be differentially robust towards missing doses during the intensive phase versus the continuation phase of treatment.

What This Study Adds to the Field

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

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

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

Abstract

Rationale

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

Objectives

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

Methods

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

Measurements and Main Results

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

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

Conclusions

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

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Key words: tuberculosis, forgiveness, adherence, non-adherence, treatment, short

Introduction

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

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

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

combat non-adherence.

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

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

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

1) By comparing the risk of a negative composite outcome (treatment failure, death and recurrence/reinfection) when different a) percentages of doses are taken or b) absolute numbers of doses were missed of i) four- versus ii) six-month regimens,
2) By comparing the risk of a negative composite outcome when different percentages of doses are taken in different four-month regimens,
3) By comparing the risk of a negative composite outcome when different percentages of doses are taken during the i) intensive versus ii) continuation phases of treatment.

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

Methods

Parent studies and population for analysis

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

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Measuring and defining non-adherence to treatment

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

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

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

t= number of doses taken across the given treatment period

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

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

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

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

Negative composite outcome

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

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

Other variables

See Online Data Supplement Text E1.

Statistical methods

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

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

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

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

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

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

a) Percentage of doses taken

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

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

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

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

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

b) Absolute number of doses missed

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

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

Forgiveness of different four-month regimens (objective 2)

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

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

Forgiveness during each treatment phase (objective 3)

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

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

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

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

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

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

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

Results

Characteristics of the study population

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

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

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

Percentage of doses taken

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

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

Absolute number of doses missed

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

Forgiveness of different four-month regimens (objective 2)

The M and rifapentine (P) regimen dosed twice-weekly during the second half of treatment ($2MRZE/2P_2M_2$) appeared potentially more forgiving than other four month regimens on the multiplicative scale in the continuation phase (Wald p-value for interaction 0.004), but had a greater marginal risk of a negative composite outcome even at 100% dose-taking than the other regimens (Figure 3, Online Data Supplement Table E11, Online Data Supplement Figure E3). The larger marginal risk for $2MRZE/2P_2M_2$ was also seen for the overall and intensive phase models, but there was no evidence of differing effects of dose-taking by different regimens on the additive or multiplicative scale for these periods.

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

Forgiveness during each treatment phase (objective 3)

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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Figure 1. Hypothesised mediation model

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

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

Adjusted marginal risks (a, d, g), risk ratios (b, e, h), and risk differences (c, f, i) for the negative composite outcome by percentage of doses taken (modelled as fractional polynomials of the functional form x^3) across the entire treatment period (overall, a-c), intensive phase (d-f) and continuation phase (g-i), presented stratified by regimens grouped by length. One model per period of treatment, four- and six-month regimens in the same model. Baseline for the multiplicative and additive models 100% of doses taken. For the multiplicative models, Wald p-values for an interaction between regimens grouped by length and percentage of doses taken all p<0.0001; horizontal dotted line charts a risk ratio of 1. For the additive models, Wald p-values for an interaction between regimens grouped by length and percentage of doses taken 0.06 (overall), 0.06 (intensive phase), 0.07 (continuation phase); horizontal dotted line charts a risk difference of 0. All 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. All models contain data for 3,180 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. Panels a, b from model 3; c from model 4; d, e from model 7; f model 8; g, h from model 11; i model 12. aRD- adjusted risk difference, aRisk- adjusted risk, aRR- adjusted risk ratio, CI- confidence interval.

Figure 3. Forgiveness of different four-month regimens

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 composite outcome by the percentage of doses taken (modelled as fractional polynomials of the functional form x^3) across the entire treatment period (a-h), intensive phase (i-p) and continuation phase (q-x), stratified by four-month regimen. Baseline for multiplicative and additive models 100% dose-taking. One model per period of treatment, all four-month regimens in same model. For the multiplicative models, Wald p-values for an interaction between regimens grouped by length and percentage of doses taken 0.10 (overall), 0.76 (intensive phase), 0.004

(continuation phase); horizontal dotted line charts a risk ratio of 1. For the additive models, 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, aRisk- adjusted risk, aRR- adjusted risk ratio, CI- confidence interval, E- ethambutol, G- gatifloxacin, H- isoniazid, M- moxifloxacin, P- rifapentine, R- rifampicin, Z- pyrazinamide.

Figure 4. Forgiveness during each treatment phase

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 negative composite outcome the outcome (models 53, 55, 57, 59, 61, 63, 65, 67); and

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

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. aRR- adjusted risk ratio, CI- confidence interval.

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[ǂ]					
	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[ǂ]					
	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. ǂTwo 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.

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737

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)

Direct effects and indirect effects expressed as odds ratios and (95% confidence intervals). 0-95% versus >95-100% (baseline) dose-taking compared. Direct effect 0- how much the risk of the negative composite outcome would change if intensive phase dose-taking changed from >95-100% to 0-95% but, for each individual, continuation phase dose-taking was fixed at the level it would have taken, for that individual, when intensive phase dose-taking was >95-100%. Direct effect 1- as per direct effect 0, but when continuation phase dose-taking is fixed at the level it would have taken, for that individual, when intensive phase dose-taking (exposure) was ≤95%. Indirect effect 0- how much the outcome would change, on average, if intensive phase dose-taking was fixed at >95-100% but continuation phase dose-taking changed from the level it would take if intensive phase dose-taking was >95-100% to if intensive phase dose-taking was ≤95%. Indirect effect 1- as per indirect effect 0, but when intensive phase dose-taking fixed at ≤95%. 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.

752 **Figure 1.**

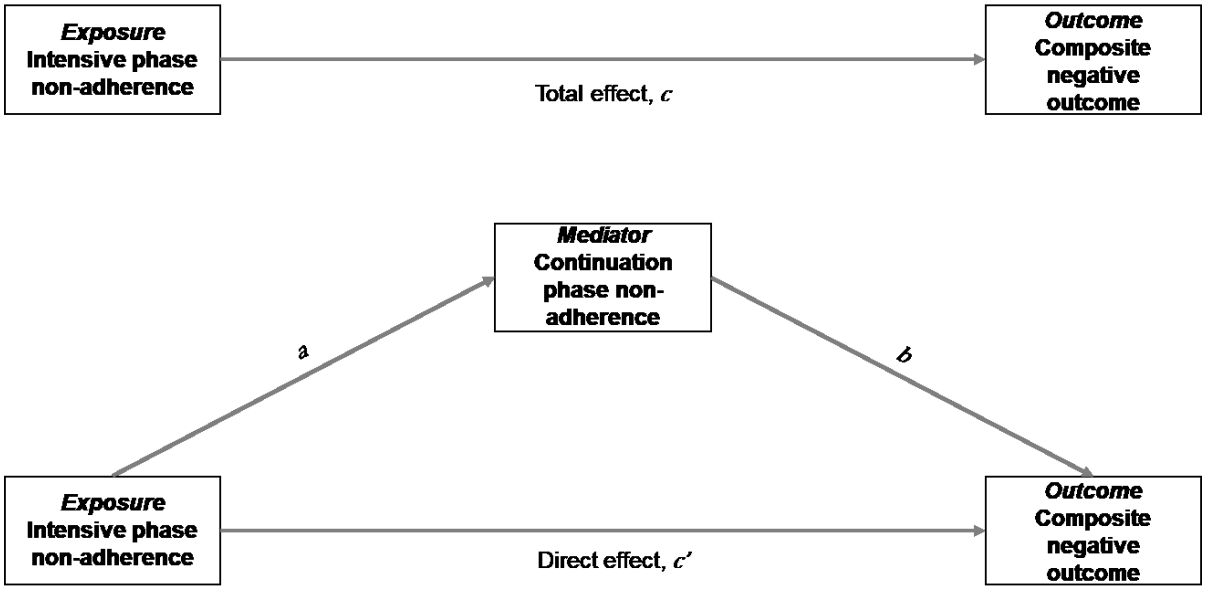

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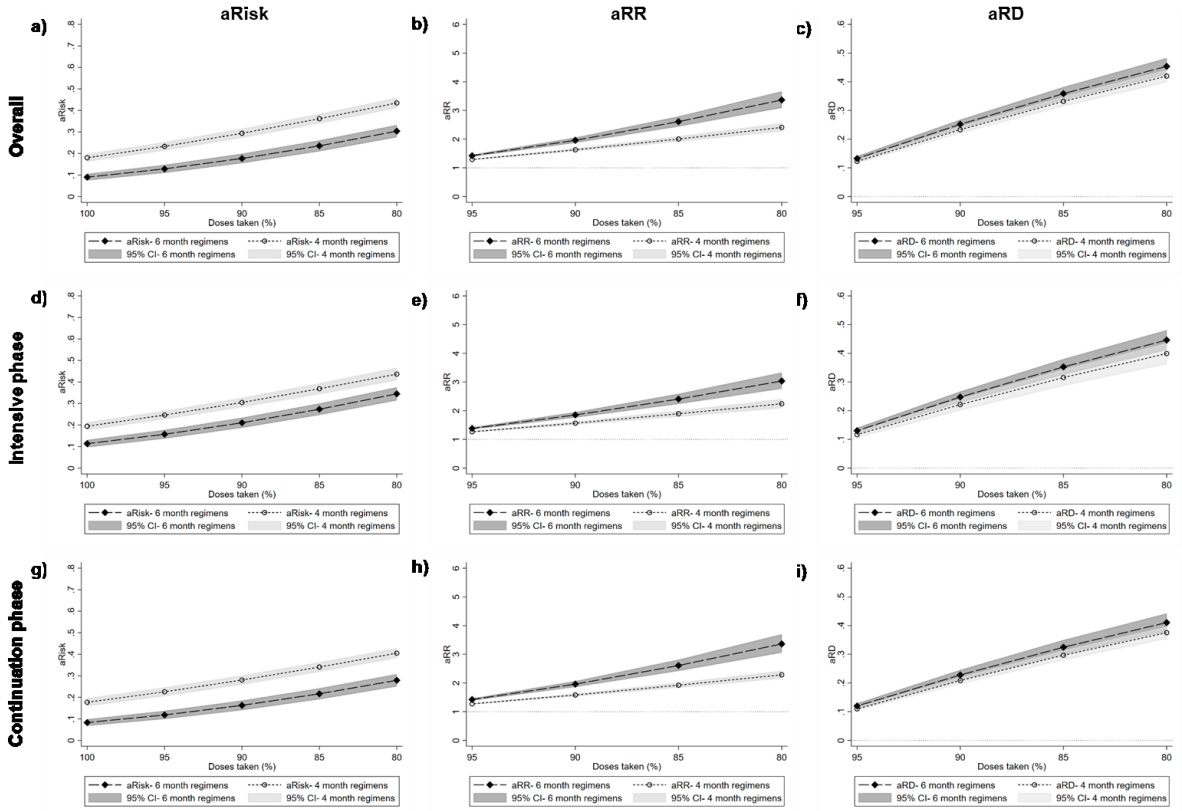
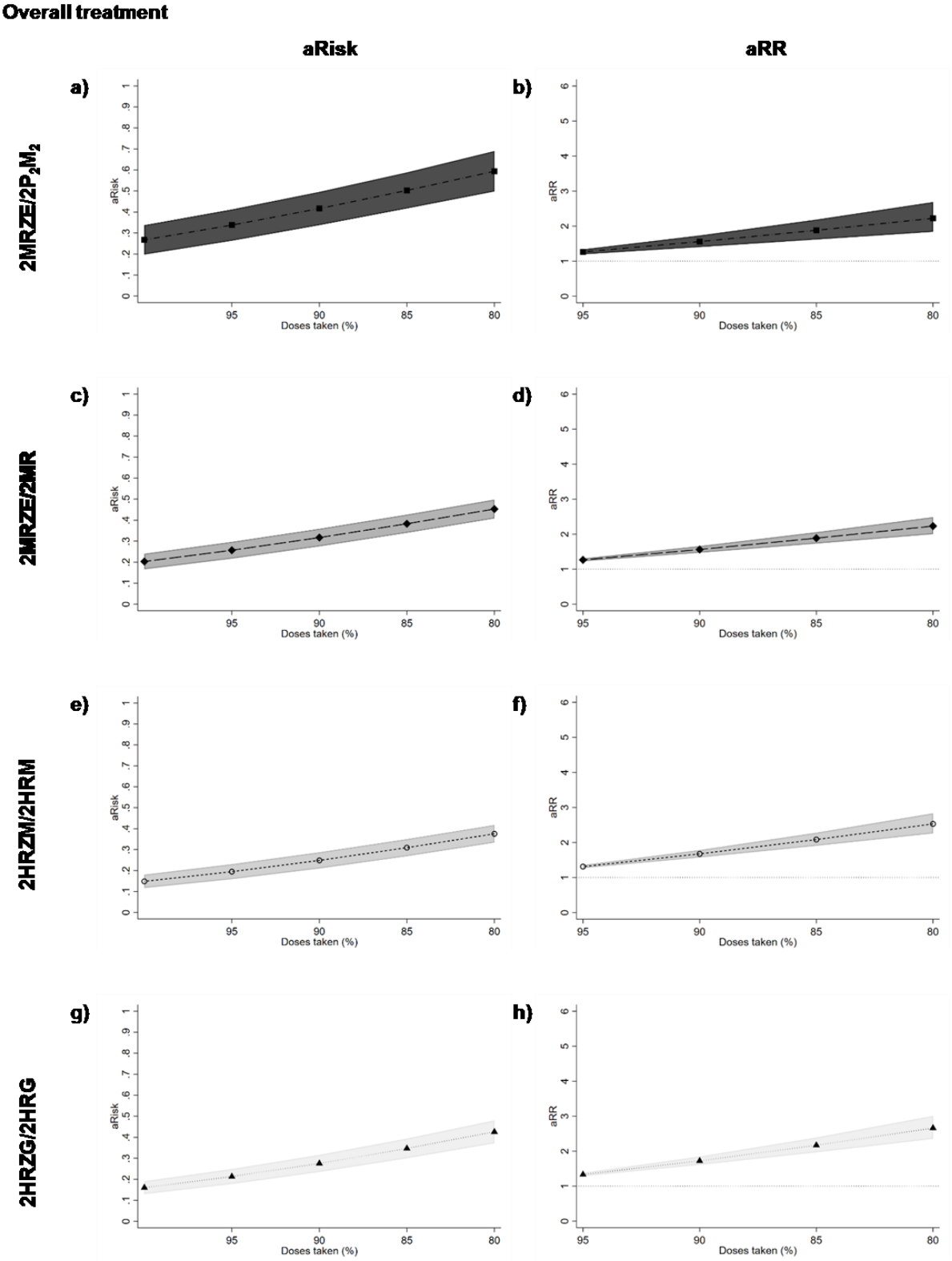
Figure 2.


aRisk
aRR
aRD
a)
b)
c)
d)
e)
f)
g)
h)
i)
Overall
Intenelve phase
Continuation phase
Doses taken (%)
aRisk- 6 month regimens
aRisk- 4 month regimens
aRR- 6 month regimens
aRR- 4 month regimens
aRD- 6 month regimens
aRD- 4 month regimens
95% CI- 6 month regimens
95% CI- 4 month regimens

760 **Figure 3.**



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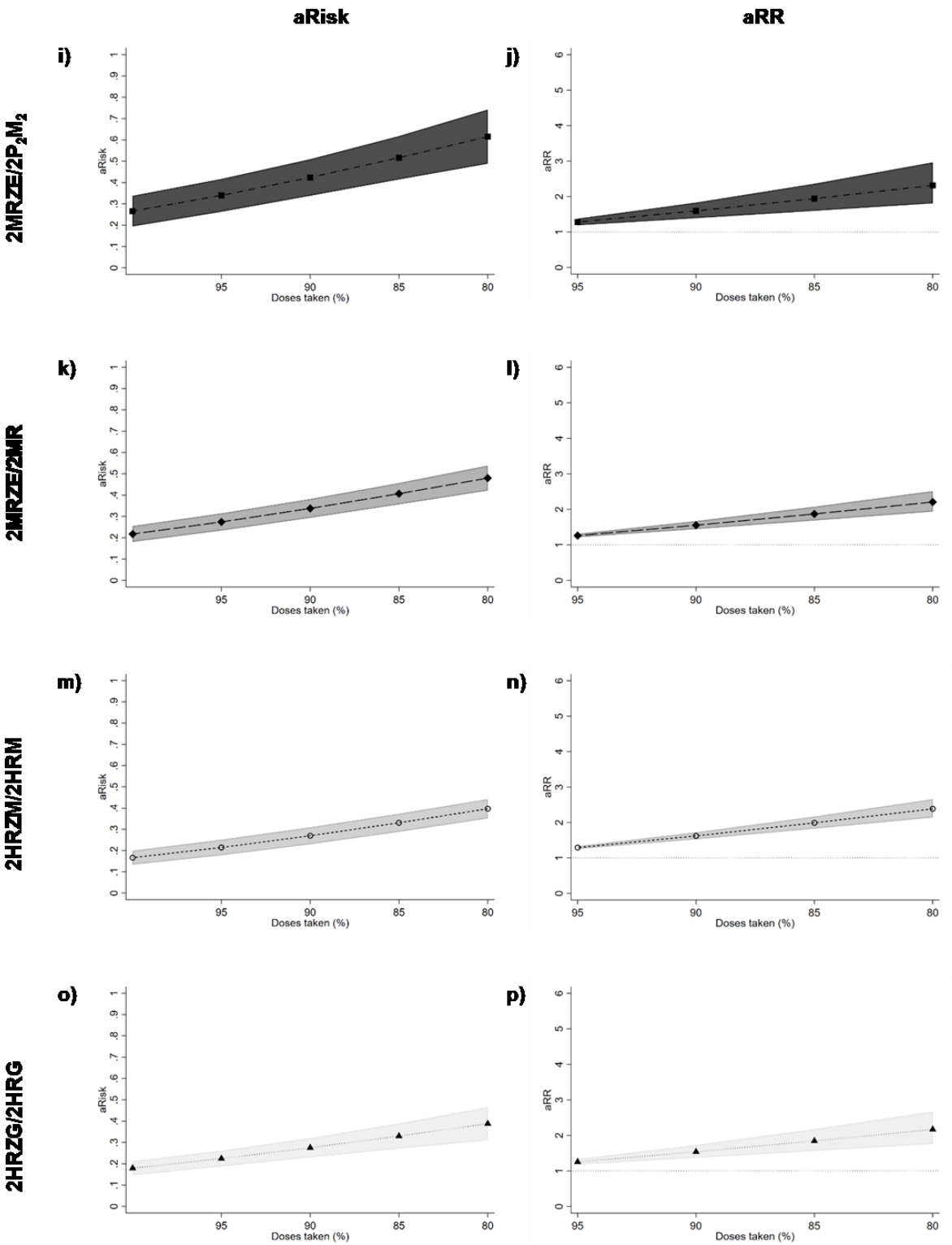
Intensive phase



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Continuation phase

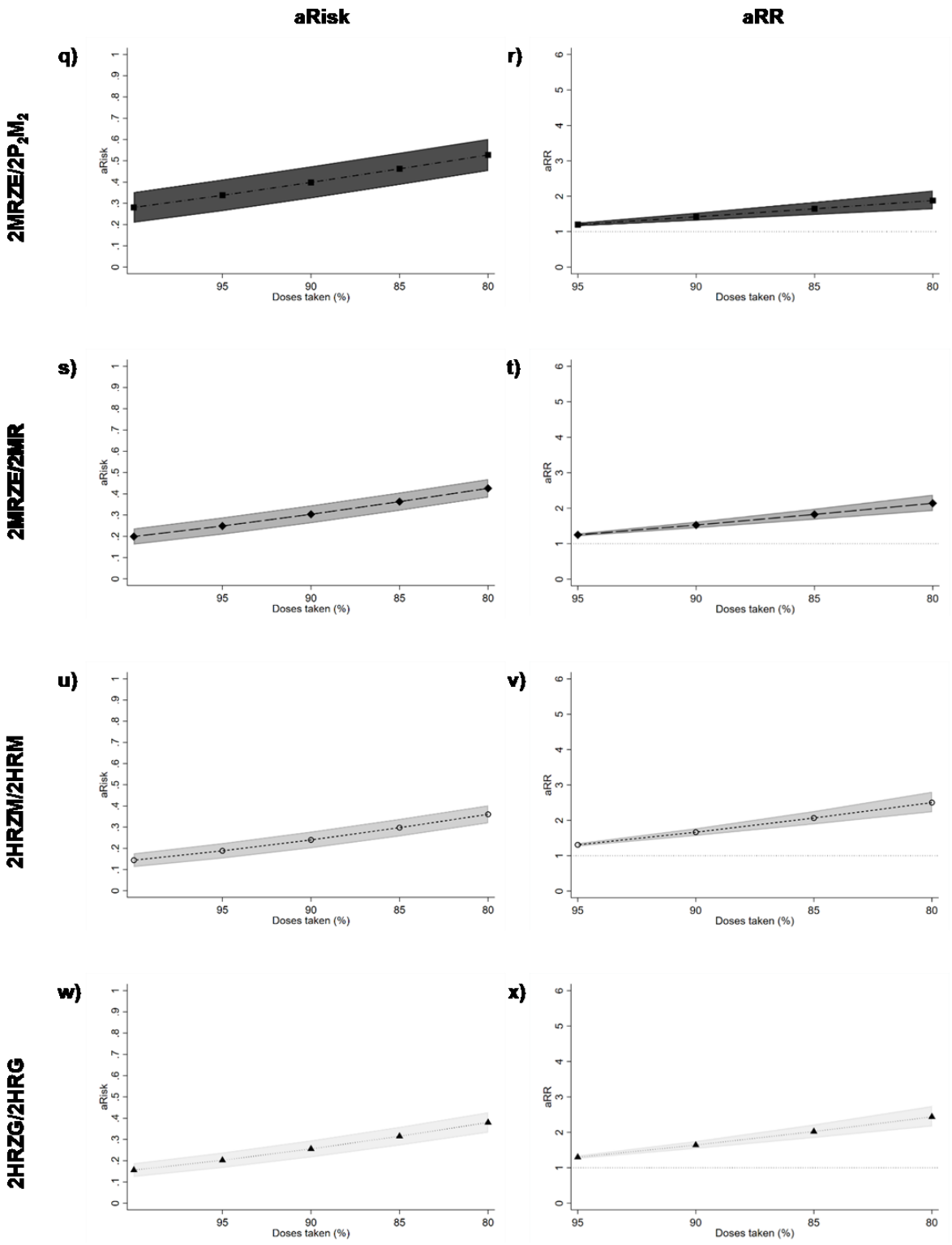

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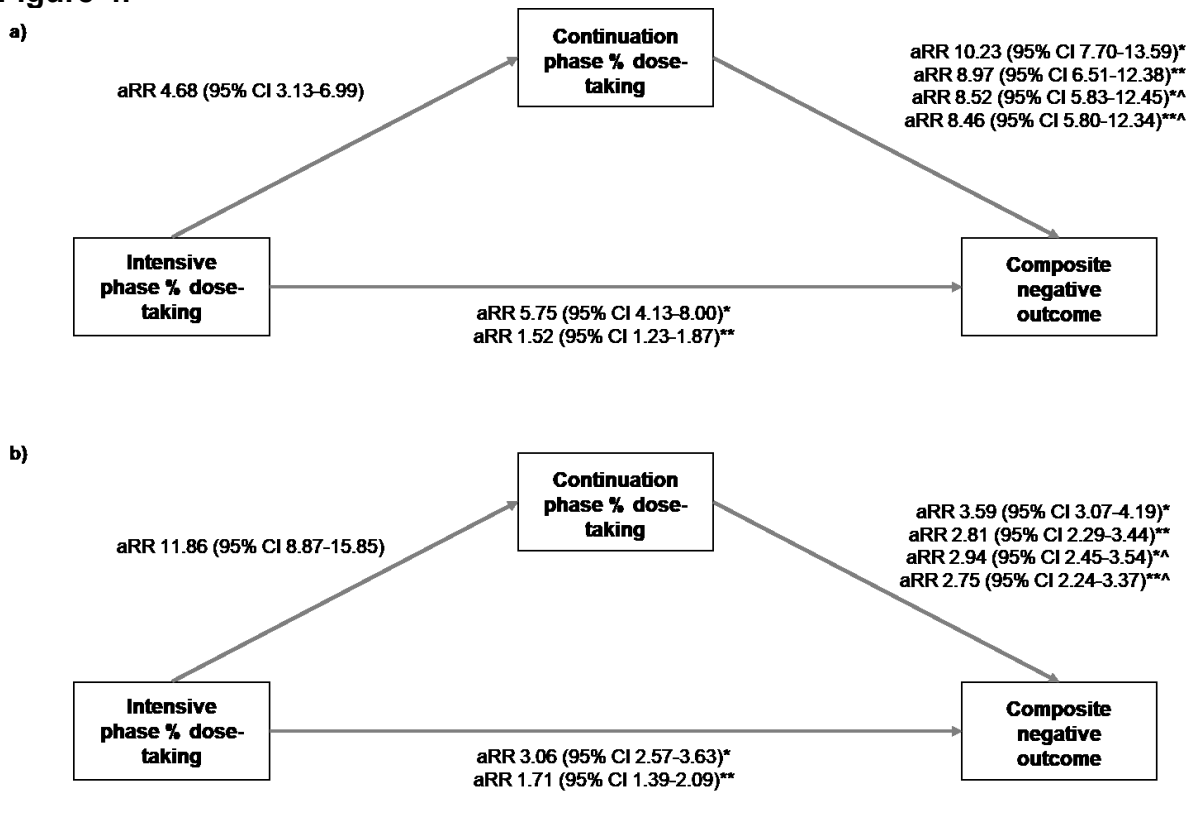
Figure 4.


a)
Continuation phase % dose-taking
aRR 4.68 (95% CI 3.13-6.99)
aRR 10.23 (95% CI 7.70-13.59)*
aRR 8.97 (95% CI 6.51-12.38)**
aRR 8.52 (95% CI 5.83-12.45)*^
aRR 8.46 (95% CI 5.80-12.34)**^
Intensive phase % dose-taking
Composite negative outcome
aRR 5.75 (95% CI 4.13-8.00)*
aRR 1.52 (95% CI 1.23-1.87)**
b)
Continuation phase % dose-taking
aRR 11.86 (95% CI 8.87-15.85)
aRR 3.59 (95% CI 3.07-4.19)*
aRR 2.81 (95% CI 2.29-3.44)**
aRR 2.94 (95% CI 2.45-3.54)*^
aRR 2.75 (95% CI 2.24-3.37)**^
Intensive phase % dose-taking
Composite negative outcome
aRR 3.06 (95% CI 2.57-3.63)*
aRR 1.71 (95% CI 1.39-2.09)**

Online Data Supplement

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

Helen R Stagg; Jennifer A Thompson; Marc CI Lipman; Derek J Sloan; Mary Flook; Katherine L Fielding; for the Critical Path to TB Drug Regimens

Online Data Supplement Text E1- Methods

Measuring and defining non-adherence to treatment

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

OFLOTUB

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

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

REMox

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

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

Rifaquin

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

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

Other variables

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

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

stage 4 disease were not eligible for the study.(12) In REMox, participants who were co-infected with HIV were eligible to participate in the study if the CD4 count was ≥250 cells/mm^3 and they were not already receiving antiretroviral therapy (ART).(10) In RIFAQUIN, participants co-infected with HIV who required ART at diagnosis were initially ineligible.(11) Later in the trial, participants starting ART at screening were deemed eligible. Participants with a CD4 cell count <200 cells/mm^3 were initially ineligible, but this was subsequently changed to <150 cells/mm^3. Within this study, HIV status and CD4 count were combined into a single variable of 'HIV negative', 'HIV positive, CD4 count <200 cells/mm^3', 'HIV positive, CD4 count 200-<500 cells/mm^3', 'HIV positive, CD4 count >=500 cells/mm^3', or 'missing' if HIV status, or CD4 count among those HIV positive, was absent;

- Smear status at baseline- given the multiple smear results per patient at baseline, which were not always concordant, these data were coded into two variables (most and least severe). The former was used in the main analysis and the latter in the sensitivity analyses. Smear grading varied by study,(8) and was recoded as 'Negative', 'Scanty', '1+' (a category that included generic smear positives), '2+', or '3+ or more'. For studies that included 'positive' and 'scanty' results, when compiling the least severe smear status these results could be over-written with more precise, albeit more extreme, results, in the absence of an additional negative result;
- Cavitation at baseline- retained as originally coded;
- Weight at screening/baseline- coded into categories ≤45kg, >45-≤50kg, >50-≤55kg, >55-≤70kg, >70kg, roughly in line with the key weights that resulted in a change in the dose of drug prescribed (and thus pill numbers) across the

three trials;

- Regimen- retained as originally coded.

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

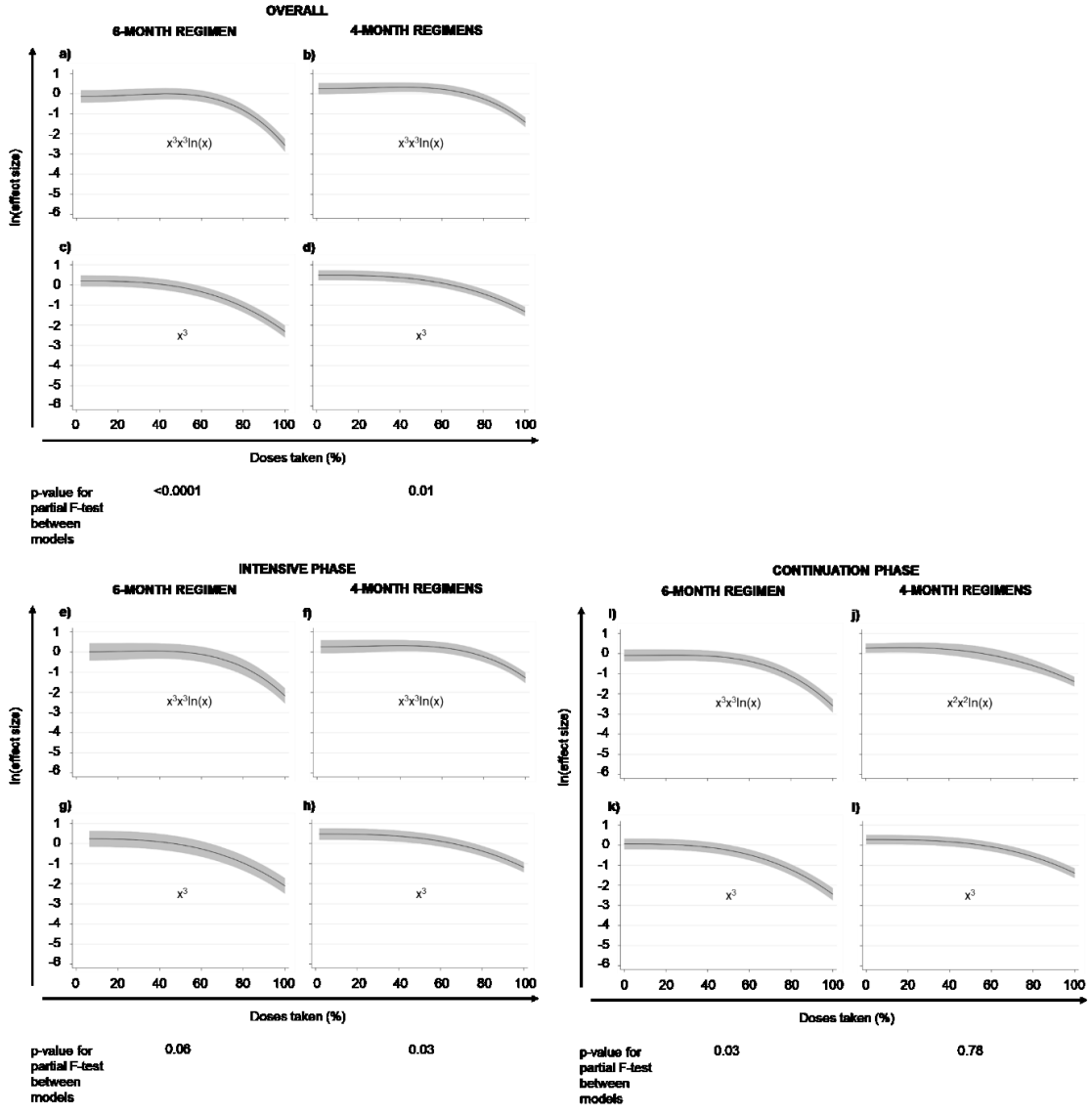
To fully characterise the risk of the outcome associated with changes in non-adherence (percentage dose-taking) as a continuous variable, without categorising non-adherence and thus losing information, fractional polynomials were fitted. This was done separately for regimens grouped by length and for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

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

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

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



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

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

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

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

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

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

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

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

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

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

Online Data Supplement Table E1. Characteristics of the included randomised controlled trials, including regimens used 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 ($2MRZE/2P_2M_2$) Daily dosing first two months, twice weekly (as indicated by the $_2$) second two months (Single drug pills)	Direct observation of each dose

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

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

Trial	Trial outcome	Classification
OFLOTUB*	Favourable modified intention to treat outcome	Positive
	Unfavourable modified intention to treat outcome	Negative
	MGIT invalid, contaminated, or borderline	Excluded
	MDR or R resistant	
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	

Outcomes used for this study, as recoded from the TB PACTS dataset. Broadly, our definition of a negative composite outcome arising during or after treatment was taken from the original RCTs i.e. treatment failed, death,

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

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

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)

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

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 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 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 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 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 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, 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% 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; 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 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; 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; intensive phase adjusted risk differences from model 8; continuation phase adjusted risk differences from model 12. aRD- adjusted risk difference, aRisk- adjusted risk, aRR- adjusted risk ratio, CI- confidence interval, RD- unadjusted risk difference, Risk- unadjusted risk, RR- unadjusted risk ratio.

Online Data Supplement Table E5. Forgiveness of the four- versus six-month 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)

Adjusted risk ratios for the negative composite outcome by percentage of doses taken (modelled as fractional polynomials of the functional form x^3) versus a baseline of 100% across overall, during the intensive phase and continuation phase, presented stratified by regimens grouped by length. One model per period of treatment, four- and six-month regimens in the same model. Models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at baseline, a three-level fixed effect for trial and weight. All models contain data for 3,180 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 from model 13; intensive phase from model 17; continuation phase from model 21. aRR- adjusted risk ratio, CI- confidence interval.

Online Data Supplement Table E6. Forgiveness of the four- versus six-month 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)

Adjusted risk ratios for the negative composite outcome by percentage of doses taken (modelled as fractional polynomials of the functional form x^3) versus a baseline of 100% across overall, during the intensive phase and continuation phase, presented stratified by regimens grouped by length. One model per period of treatment, four- and six-month regimens in the same model. Sensitivity analysis based on an alternative coding of baseline smear status (least severe). Models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (least severe), cavitation at baseline, a three-level fixed effect for trial. All models contain data for 3,180 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 from model 14; intensive phase from model 18; continuation phase from model 22. aRR- adjusted risk ratio, CI- confidence interval.

Online Data Supplement Table E7. Forgiveness of the four- versus six-month regimens: sensitivity analysis alternative coding of the percentage dose-taking 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)

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

Online Data Supplement Table E8. Forgiveness of the four- versus six-month regimens: sensitivity analysis using the restricted negative composite 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)

Adjusted risk ratios for the restricted negative composite outcome by percentage of doses taken. Percentage doses taken grouped into 5% categories and modelled as a linear variable; baseline of 95-100%. Doses taken examined overall, during the intensive phase and continuation phase. Results presented stratified by regimens grouped by length. One model per period of treatment, four- and six-month regimens in the same model. Sensitivity analysis based on a restricted definition of the negative composite outcome. Models adjusted for sex, age (fitted using a fractional polynomial), ethnicity, HIV and CD4 status, smear status at baseline (most severe), cavitation at baseline, a three-level fixed effect for trial. All models contain data for 2,952 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 from model 16; intensive phase from model 20; continuation phase from model 24. aRR- adjusted risk ratio, CI- confidence interval.

Online Data Supplement Table E9. Forgiveness of the four- versus six-month 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)

Adjusted risks, risk ratios and risk differences for the negative composite outcome by numbers of missed doses overall, during the intensive phase and continuation phase, presented stratified by regimens grouped by length. Baseline for multiplicative and additive models zero missed doses. One model per period of treatment, four- and six-month regimens in the same model. For the multiplicative models, Wald p-values for an interaction between regimens grouped by length and percentage dose-taking were <0.001 for all periods. For the additive models, Wald p-values for an interaction between regimens grouped by length and percentage dose-taking 0.12 (overall), <0.001 (intensive phase), 0.11 (continuation phase). 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. All models contain data for 3,180 participants. Overall risk differences from model 26; intensive phase risk differences from model 29; continuation phase risk differences from model 32. Overall risks and risk ratios from model 25; intensive phase risks and risk ratios from model 28; continuation phase risks and risk ratios from model 31. aRD- adjusted risk difference, aRisk- adjusted risk, aRR- adjusted risk ratio, CI- confidence interval.

Online Data Supplement Table E10. Forgiveness of the four- versus six-month regimens: non-adherence measured by absolute number of missed doses, 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)

Adjusted risk ratios for the restricted negative composite outcome by numbers of missed doses overall, during the intensive phase and continuation phase, presented stratified by regimens grouped by length. Baseline zero missed doses. One model per period of treatment, four- and six-month regimens in the same model. Sensitivity analysis based on a restricted definition of the negative composite outcome. 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. All models contain data for 2,952 participants. Overall from model 27; intensive phase from model 30; continuation phase from model 33. *- data too sparse to estimate, aRR- adjusted risk ratio, CI- confidence interval.

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

Doses taken (%)		aRisk (95% CI)	aRR (95% CI)	aRD (95% CI)
OVERALL				
2MRZE/2P_2M_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_2M_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_2M_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)

Adjusted risks, risk ratios and risk differences for the negative composite outcome by percentage of doses taken (modelled as fractional polynomials of the functional form x^3) overall, during the intensive phase and continuation phase, stratified by four-month regimen. Baseline for multiplicative and additive models 100% dose-taking. One model per period of treatment, all four-month regimens in same model. For the multiplicative models, Wald p-values for an interaction between regimens grouped by length and percentage dose-taking 0.10 (overall), 0.76 (intensive phase), 0.004 (continuation phase). For the additive models, Wald p-values for an interaction between regimens grouped by length and percentage dose-taking 0.84 (overall), 0.50 (intensive phase), 0.004 (continuation phase). 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 risk differences from model 35; intensive phase risk differences from model 38; continuation phase risk differences from model 41. Overall risks and risk ratios from model 34; intensive phase risks and risk ratios from model 37; continuation phase risks and risk ratios from model 40. $_2$- twice weekly dosing, aRD- adjusted risk difference, aRisk- adjusted risk, aRR- adjusted risk ratio, CI- confidence interval, E- ethambutol, G- gatifloxacin, H- isoniazid, M-moxifloxacin, P- rifapentine, R- rifampicin, Z- pyrazinamide.

Online Data Supplement Table E12. Forgiveness of different four-month regimens, sensitivity analysis using the restricted negative composite 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)

Adjusted risk ratios for the restricted negative composite outcome by percentage of doses taken. Percentage doses taken grouped into 5% categories and modelled as a linear variable; baseline 95-100%. Doses taken examined overall, during the intensive phase and continuation phase. Results presented stratified by regimen. One model per period of treatment, all four-month regimens in same model. Sensitivity analysis based on a restricted definition of the negative composite outcome. 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 1,707 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 from model 36; intensive phase from model 39; continuation phase from model 42. $_2$- twice weekly dosing, aRR- adjusted risk ratio, CI- confidence interval, E- ethambutol, G- gatifloxacin, H- isoniazid, M- moxifloxacin, P- rifapentine, R- rifampicin, Z- pyrazinamide.

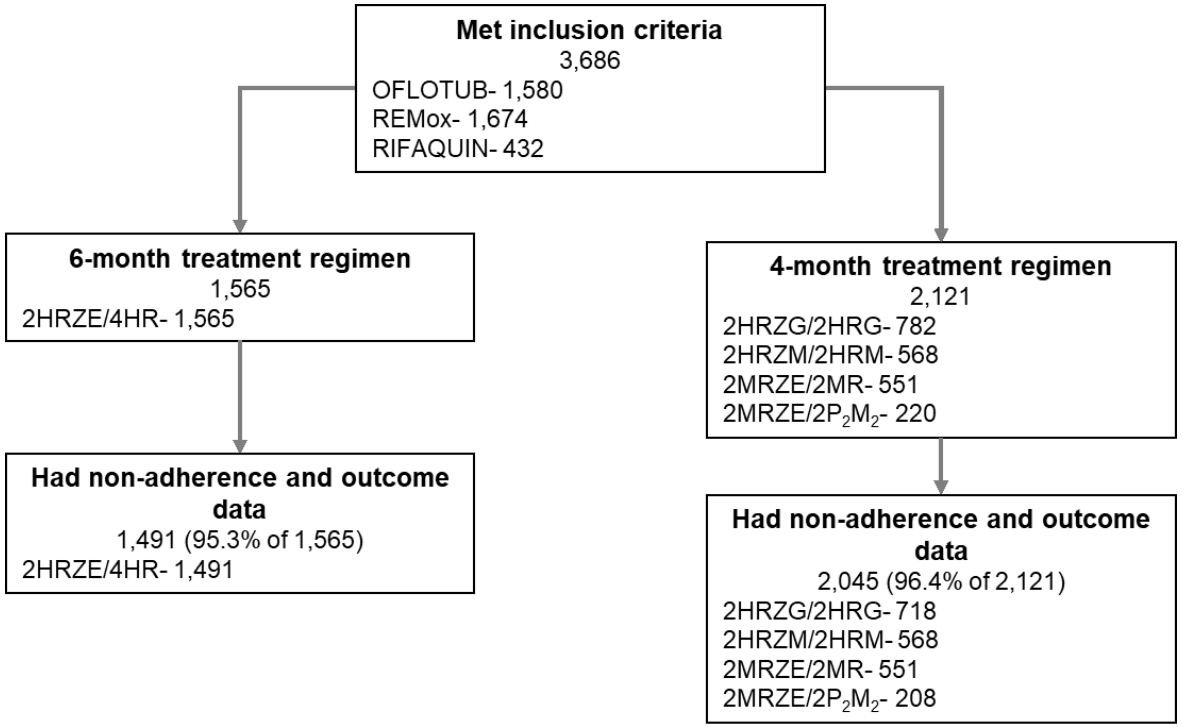
Online Data Supplement Table E13. Forgiveness during each treatment phase: mediation analysis, sensitivity analysis using the restricted negative outcome

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)

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

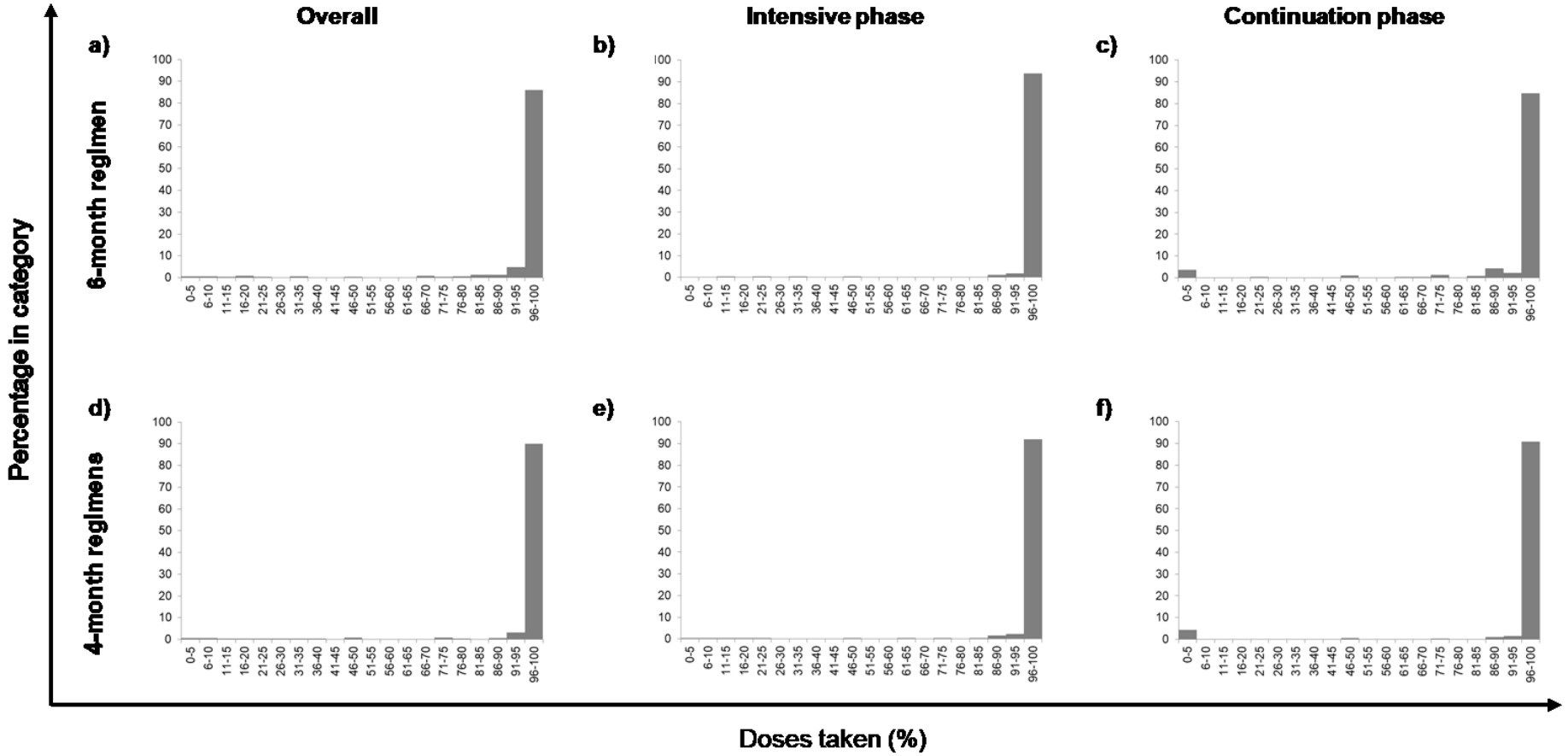
Online Data Supplement Figure E1. Flow chart of study participants

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 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 confirmed reinfection, and who died from non-tuberculosis causes. E- ethambutol, G- gatifloxacin, H- isoniazid, M- moxifloxacin, P- rifapentine, R- rifampicin, Z- pyrazinamide



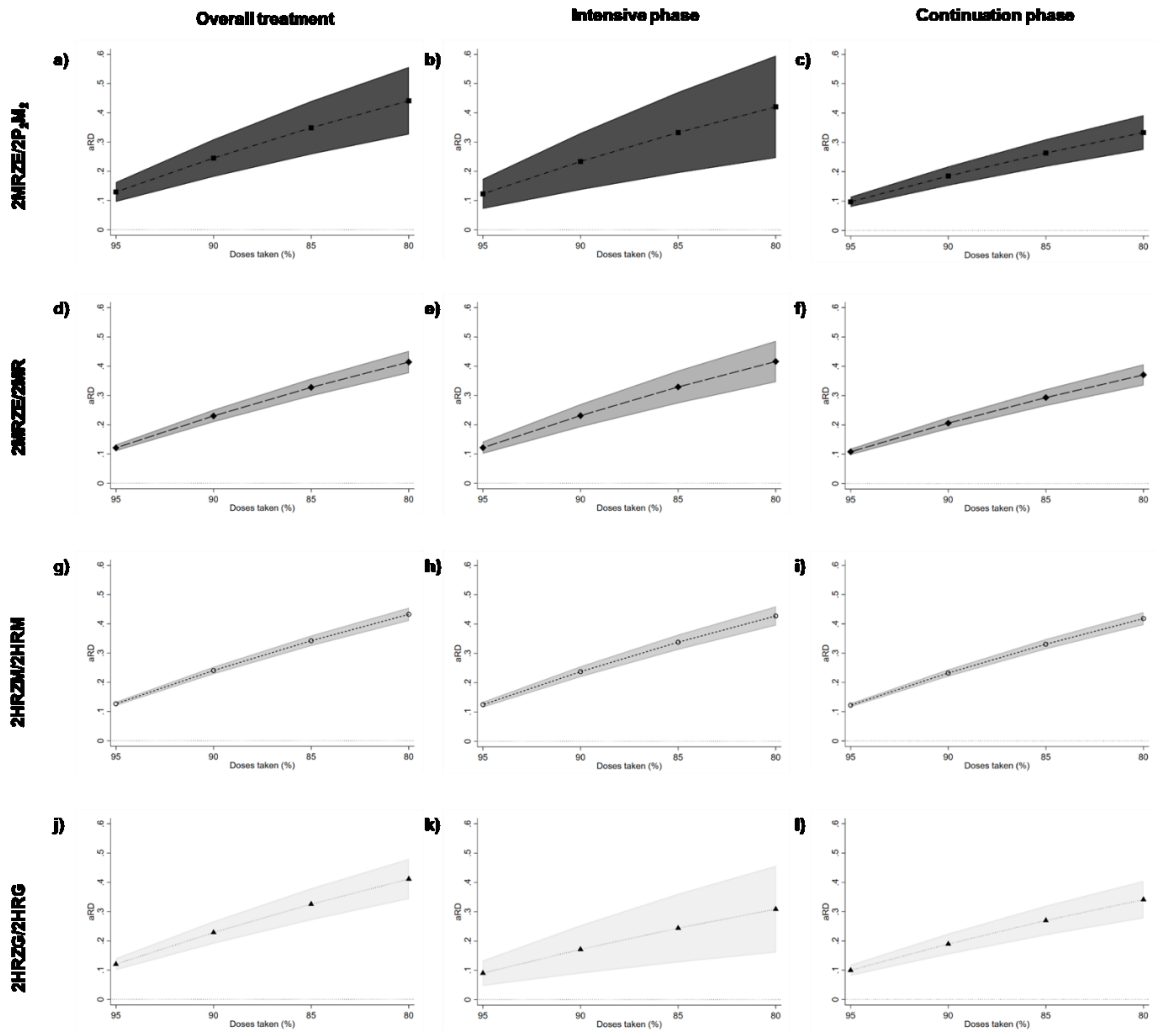
Online Data Supplement Figure E2. Histograms of percentage of doses taken

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.