Shortened Tuberculosis Treatment for People with HIV in South Africa

A Model-based Evaluation and Cost-effectiveness Analysis

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Abstract

Rationale: Recent tuberculosis treatment trials failed to show that some 4-month (4m) regimens were noninferior to conventional 6-month (6m) regimens for a composite clinical outcome. Novel shortened regimens may still have important clinical and economic benefits in populations with high loss to follow-up (LTFU) and in subgroups such as people with human immunodeficiency virus.

Objectives: To identify scenarios in which a novel 4m regimen would be preferred to a conventional 6m regimen for treatment of drug-susceptible tuberculosis in people with human immunodeficiency virus in South Africa, in terms of short-term and long-term clinical and economic outcomes.

Methods: We used the Cost-Effectiveness of Preventing AIDS Complications-International microsimulation model to project outcomes modeled on participants in the OFLOTUB trial. For calibration purposes, we did a base case analysis by applying trial-informed parameters for the 4m/6m regimens, including monthly LTFU during treatment (0.68%/0.83%), average monthly tuberculosis recurrence (0.65%/0.31%), and monthly drug costs (U.S. dollars [USD]25.90/3.70). We then evaluated different scenarios and 4m regimen characteristics, varying key parameters, including LTFU (informed by observational cohort data), recurrence, and cost. We projected outcomes, including 2-year mortality and life expectancy. We conducted a cost-effectiveness

analysis, evaluating the incremental cost-effectiveness ratio of a 4m versus 6m regimen.

Results: In the base case model analysis, risk of the composite unfavorable outcome in the 4m/6m groups was 19.8%/15.9%, similar to the trial; projected life expectancies were 22.1/22.3 years. In analyses of alternative scenarios and 4m regimen characteristics, a 4m regimen yielded lower risk of the composite unfavorable outcome than the conventional 6m regimen if LTFU increased to greater than 3.5%/mo or if average recurrence after a 4m regimen decreased to less than 0.45%/mo, and it yielded higher life expectancy if LTFU was greater than 3.5%/mo or if recurrence was less than 0.5%/mo. A 4m regimen was not cost-effective in the base case but became cost-effective (incremental cost-effectiveness ratio <USD940/yr of life saved) in two-way sensitivity analysis; for example, if LTFU was greater than or equal to 5.3%/mo and either average recurrence was less than or equal to 0.5%/mo or drug cost was less than or equal to USD15/mo.

Conclusions: A novel shortened tuberculosis treatment regimen could improve outcomes such as survival despite conferring a higher recurrence risk, particularly in settings where LTFU is higher than that seen in recent trials.

Keywords: tuberculosis; treatment; human immunodeficiency virus; simulation; cost-effectiveness

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Tuberculosis is the leading killer of people with human immunodeficiency virus (PWH) worldwide (1). Though efficacious tuberculosis treatments exist, their real-world effectiveness is hindered by incomplete adherence to multidrug regimens for 6 months or more (2–4). Of all PWH with drug-susceptible tuberculosis in South Africa, only half successfully complete treatment (5). Shortened regimens could improve tuberculosis outcomes by improving treatment completion rates. Shorter-course regimens might also reduce healthcare system costs via fewer follow-up visits and less monitoring. These benefits are particularly important in settings where human immunodeficiency virus (HIV)/tuberculosis coinfection is common and where resources are especially limited.

Despite the anticipated benefits, the recent OFLOTUB (A Controlled Trial of a 4-Month Quinolone-Containing Regimen for the Treatment of Pulmonary Tuberculosis), REMoxTB (Controlled Comparison of Two Moxifloxacin Containing Treatment Shortening Regimens in Pulmonary Tuberculosis), and RIFAQUIN (An International Multicentre Controlled Clinical Trial to Evaluate High Dose Rifapentine and a Quinolone in the Treatment of Pulmonary Tuberculosis) trials failed to show that 4-month (4m) fluoroquinolone-containing regimens were noninferior to a conventional 6-month (6m) treatment regimen for drug-susceptible tuberculosis (6–8). These trials differed in their primary outcome, usually defined as a composite “unfavorable” outcome entailing some combination of loss to follow-up (LTFU) during treatment, treatment failure, death during treatment, or recurrence, each considered equally unfavorable. Although these trials generally found the shorter regimen associated with fewer losses to follow-up, fewer treatment failures, and fewer deaths, the shorter regimen resulted in more recurrences, and thus noninferiority was not demonstrated (6–8).

Nonetheless, there may still be a role for novel shortened tuberculosis treatment regimens, especially in settings where LTFU

from tuberculosis care is more common than that in clinical trials; LTFU was generally less than 1%/mo in the trials, whereas cohort studies report LTFU of 1.9–5.3%/mo (5–10). Moreover, prior studies were not focused on PWH, in whom the balance of risks and benefits from shortened tuberculosis regimens may differ from those of people without HIV, as suggested in subgroup analyses in the trials (6–8).

Our objective was to identify scenarios in which a novel 4m regimen would be preferred to a conventional 6m regimen for treatment of drug-susceptible tuberculosis in PWH, in terms of short-term and long-term clinical outcomes and cost-effectiveness. In this manner, our analysis could identify benchmarks for future trials of shortened tuberculosis regimens.

Methods

Analytical Framework

We expanded the Cost-Effectiveness of Preventing AIDS Complications-International model, a validated Monte Carlo microsimulation of HIV-related disease and treatment in low- and middle-income countries (11–13), with detailed structure and parameters around tuberculosis natural history, diagnosis, and treatment (see Table E1 and Figure E1 in the online supplement). Relevant to this analysis of PWH in South Africa, we modeled LTFU from tuberculosis care, success and failure of tuberculosis treatment, tuberculosis-related and other deaths, recurrent tuberculosis, and tuberculosis and HIV care costs. We compared a 4m regimen with a conventional 6m regimen for treatment of drug-susceptible pulmonary tuberculosis in PWH in South Africa.

We chose the OFLOTUB trial participants as the basis for our model analysis because, of the three trials published simultaneously (6–8), OFLOTUB had the largest number of subjects assigned to a fluoroquinolone- and isoniazid-containing 4m regimen or to a conventional 6m regimen. In addition, OFLOTUB reported

detailed baseline characteristics and outcome data necessary for a model-based analysis. For calibration purposes, the base case 4m regimen in the model consisted of isoniazid, rifampin, pyrazinamide, and gatifloxacin for 2 months, followed by isoniazid, rifampin, and gatifloxacin for 2 months, as in OFLOTUB (6). The 6m regimen consisted of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months. We modeled cohorts of 1 million PWH to attain stable per-person estimates, calibrating short-term model results to OFLOTUB trial results and then projecting longer-term clinical and economic outcomes (6). We then varied key parameters to identify the scenarios and regimen characteristics under which a novel 4m regimen would be preferred to the conventional 6m regimen in terms of various clinical and economic outcomes.

Like the OFLOTUB trial, our study projected the risk of a composite unfavorable outcome, consisting of LTFU during treatment, treatment failure (positive smear or culture despite completing a full [4m or 6m] treatment course), death during treatment, or tuberculosis recurrence within 2 years of completing treatment (6). Unlike the trials, the model tracks survival status for those lost to follow-up. To assess longer-term outcomes, we projected all-cause mortality at 2 years from treatment initiation and overall life expectancy.

We conducted a cost-effectiveness analysis from the health system perspective over a lifetime horizon, accounting for ongoing HIV care costs. The outcome measure was the incremental cost-effectiveness ratio (ICER), the difference in costs (in 2017 U.S. dollars [USD]) divided by the difference in life-years, between the 4m and 6m treatment strategies. We considered a 4m regimen to be cost-effective if its ICER was below USD940/yr of life saved (YLS), the ICER of South African guideline-recommended second-line antiretroviral therapy (ART) (see online supplement) (13, 14). We also evaluated alternative cost-effectiveness thresholds of

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USD500/YLS and USD2,000/YLS. We report undiscounted outcomes for clinical evaluations alone and outcomes discounted 3%/yr for clinical and economic outcomes in cost-effectiveness analysis (15).

Model Overview

For this analysis, a simulated person with HIV enters the model upon initiating 4m or 6m tuberculosis treatment and is tracked monthly until death. Individual characteristics, such as age, sex, and initial CD4 count, are randomly generated on the basis of user-defined distributions. The model tracks clinical outcomes and costs as an individual transitions monthly through states of disease progression and treatment related to tuberculosis and HIV (www.massgeneral.org/medicine/mppec/research/cpac-model; see online supplement) (11). Below are descriptions of key model components for this analysis.

Tuberculosis treatment. Each individual has a probability of treatment failure. In the base case, this is derived from OFLOTUB (6). Each month, an individual has a probability of being lost to follow-up wherein she or he stops tuberculosis treatment. On the basis of determination at the start of the simulation, those who would have achieved treatment success (negative smear/culture upon completing treatment) but are lost to follow-up have a reduced probability of success proportional to the duration of the treatment regimen completed (online supplement). While on treatment, individuals accumulate monthly costs of drugs, follow-up clinic visits, and laboratory monitoring (6). Because serious adverse events related to tuberculosis drugs were infrequent and their effect on other clinical outcomes unclear (6), we excluded adverse reactions to tuberculosis drugs.

Tuberculosis recurrence and diagnosis. In the model, tuberculosis recurrence can occur via reinfection and reactivation or via relapse. Relapse probability depends on time since completing treatment (16). In the base case, each simulated patient is screened for recurrent tuberculosis by sputum smear microscopy and culture every 2 or 3 months for 2 years after treatment completion, as in OFLOTUB (6). Those with a positive result initiate conventional 6m treatment, regardless of initial regimen.

ART and HIV care. All modeled individuals are ART-eligible, regardless of CD4 count and tuberculosis treatment (14).

Details about HIV natural history and care are provided in the online supplement and elsewhere (11).

Model Calibration and Validation

We calibrated base case model-generated results for LTFU, treatment failure, and recurrence within 2 years of treatment completion to OFLOTUB results in the modified intention-to-treat population (6). We assumed that our modeled cohort, of whom 100% were PWH, would have higher all-cause mortality than the trial population, of whom 18% were PWH, because of risks of nontuberculosis, HIV-related diseases. For longer-term projections, we also calibrated mortality by time period for external validation with 4-year mortality reported in a cohort of PWH in South Africa (online supplement) (17).

Input Parameters

Cohort characteristics. We used participant characteristics from OFLOTUB when available (Table 1) (6). In the modeled cohort, mean (standard deviation) age was 31.4 (8.7) years; 44% were women; and median (interquartile range) CD4 count was 355 (247–455)/ μ l.

Tuberculosis treatment. In the base case, tuberculosis treatment outcomes reflected OFLOTUB (Table 1) (6). Monthly probabilities of LTFU during 4m treatment (0.68%) and 6m treatment (0.83%) were derived from OFLOTUB-reported treatment default (6). Based on natural history studies, the probability of tuberculosis death was 8.6%/mo for those with untreated tuberculosis (12). Those lost to follow-up during tuberculosis treatment without attaining cure and those whose recurrent tuberculosis was not diagnosed were considered “untreated.”

Tuberculosis recurrence and diagnosis. We applied base case tuberculosis recurrence probabilities from OFLOTUB data at 2 years from treatment completion. We used an exponential decay function such that the recurrence probability was highest soon after completing treatment and then declined (16). Over 2 years, the average probability of recurrence was 0.65%/mo after 4m treatment and 0.31%/mo after 6m treatment. Performance characteristics of diagnostic tests, used in surveillance, were based on published data (Table E2).

Costs. Costs of drugs, follow-up visits, and laboratory monitoring came from the

South African National Health Laboratory Service and published studies (Tables 1 and E2). Tuberculosis drug costs were USD25.90/mo for the base case 4m regimen and USD3.70/mo for the 6m regimen.

Sensitivity Analyses: Alternative Scenarios and Regimen Characteristics

In sensitivity analyses, we systematically varied key input parameters to identify benchmarks for a novel 4m treatment regimen. We varied the probability of each parameter associated with the composite unfavorable outcome in OFLOTUB. These included LTFU during treatment, which we increased to levels reported in South African operational settings (1.9–5.3%/mo) (5, 9, 10, 18). We varied probabilities of treatment failure, death during treatment, and tuberculosis recurrence across values reported in other trials and across other plausible values (7, 8). We investigated the threshold values of each of the key parameters at which a novel 4m regimen would be favored over the 6m regimen in terms of the composite unfavorable outcome, 2-year mortality, or life expectancy. Additional one-way sensitivity analyses are described in the online supplement. In multiway deterministic and probabilistic sensitivity analyses for clinical and cost-effectiveness outcomes, we simultaneously varied LTFU probability, recurrence probability after a novel 4m regimen, and/or cost of a novel 4m regimen (online supplement).

Results

Validation

After calibration, our base case model-generated outcomes were similar to those in OFLOTUB. Slightly higher mortality reflected HIV-related mortality risks among the modeled patients (Table 2).

Base Case

The model-generated risk of the composite unfavorable outcome (any one of LTFU during treatment, treatment failure, death during treatment, or recurrent tuberculosis) was 19.8% with the 4m regimen and 15.9% with the 6m regimen (Table 2). The 4m group, compared with the 6m group, had higher projected 2-year mortality (12.5% vs. 12.2%) and lower life expectancy (22.1 yr vs. 22.3 yr). We also compared results when the

Table 1. Base case model input parameters

Parameter	Values (Range Examined)		References
Baseline cohort characteristics			
Age, yr, mean [SD]	31.4 [8.7]		(6)
Women/men, %	44/56		(6)
CD4 at start of TB treatment, cells/ μ l, median [IQR]	355 [247–455]		(8)
TB treatment parameters			
	4-mo regimen	6-mo regimen	
Loss to follow-up during TB treatment, monthly, %	0.68 (0.68–5.8)	0.83 (0.83–5.8)	(5, 6, 9, 10)
Probability of treatment failure (positive smear or culture upon completing treatment), %	1.7 (1.0–1.7)	2.4	(6)
Recurrent TB, monthly probability,* %	0.65 (0.31–0.75)	0.31	(6–8)
TB natural history parameters			
Mortality of untreated TB, monthly probability, %	8.6 (4.3–12.9)		(12)
Infection by <i>M. tuberculosis</i> , monthly probability, [†] %	0.36–0.80		(31)
Reactivation, monthly probability, [‡] %	0.052–0.69		(32)
HIV- and ART-related parameters			
Patients receiving ART at TB treatment initiation, %	100		Assumption (33, 34)
Mean ART efficacy, % virologic suppression at 48 wk	72		
Costs of drugs, USD/mo			
	4-mo regimen	6-mo regimen	
TB treatment	25.90 (7.50–60.00)	3.70	(6, 35)
First-line ART	7.50		(36)
Second-line ART	26.60		(36)

Definition of abbreviations: 4 mo = 4-month TB treatment regimen; 6 mo = 6-month TB treatment regimen; ART = antiretroviral therapy; HIV = human immunodeficiency virus; IQR = interquartile range; *M. tuberculosis* = *Mycobacterium tuberculosis*; SD = standard deviation; TB = tuberculosis; USD = 2017 U.S. dollars.

Range refers to values assessed in sensitivity analysis.

*Recurrence probability was modeled as an exponential decay function, such that the monthly probability declined over the 2-year period after TB treatment completion. Here, we provide the average monthly probability of recurrence over the 2-year period.

[†]Values differ by CD4 count and age.

[‡]Values differ by CD4 count.

composite unfavorable outcome was defined differently (online supplement text and Figure E2).

Sensitivity Analyses

Operational setting scenario: varying LTFU.

As LTFU increased to probabilities reported in operational settings, the composite unfavorable outcome risk increased more with the 6m regimen than with the 4m regimen. When LTFU was greater than 3.5%/mo, the value reported in a study of the South African tuberculosis care cascade (5), the composite unfavorable outcome risk was lower with the 4m regimen than with the 6m regimen (Table 2, Figure E3).

Two-year mortality was lower with the 4m regimen than with the 6m regimen when LTFU was greater than or equal to 1.9%/mo (Table 2). As monthly LTFU increased, the difference in mortality between the two groups widened, always favoring the 4m group (Figure E4).

Regimen characteristics. In one-way sensitivity analyses, we varied the probability of each of the other unfavorable outcomes for a novel 4m regimen (Table 2)

(6–8). We determined the thresholds at which a novel 4m regimen would result in fewer composite unfavorable outcomes, lower 2-year mortality, or higher life expectancy than the 6m regimen (Figure 1). For example, a novel 4m regimen was preferred to the 6m regimen in terms of composite unfavorable outcome risk, 2-year mortality, and life expectancy when average monthly recurrent tuberculosis probability after completing the 4m regimen was less than 0.45%, less than 0.6%, and less than 0.5%, respectively. Results of other one-way sensitivity analyses are provided in the online supplement text and Table E3. Overall, LTFU during treatment and recurrence were among the parameters that most influenced differences in 2-year mortality (Figure 2).

Two-way sensitivity analysis. In a two-way sensitivity analysis of 12 scenarios of LTFU and recurrent tuberculosis, we found that a novel 4m regimen would result in fewer composite unfavorable outcomes in nine scenarios; namely, when monthly LTFU probability was higher and when probability of recurrent tuberculosis after the 4m regimen was lower (Figure E5A). Two-year

mortality was lower with a novel 4m regimen than with the 6m regimen in each of the 12 scenarios except the base case (Figure E5B). Life expectancy was higher with a novel 4m regimen in 10 of the 12 scenarios, including all in which recurrence was less than or equal to 0.50%/mo (data not shown).

Cost-Effectiveness Analysis

In the base case, the 4m compared with the 6m regimen yielded lower life expectancy and higher costs and therefore was “dominated.” In one-way sensitivity analyses, a novel 4m regimen became cost-effective (ICER <USD940/YLS) compared with the 6m regimen when LTFU was greater than or equal to 5.8%/mo (Table E4) or when average probability of recurrent tuberculosis after the 4m regimen was less than or equal to 0.21%/mo (Table E5). In multiway sensitivity analyses, a novel 4m regimen became cost-effective compared with the 6m regimen when monthly LTFU was higher, recurrence probability after the 4m regimen was lower, and/or the 4m regimen cost was lower (Figure 3). Results when using alternative cost-effectiveness thresholds are provided in

Table 2. Trial-reported and model-generated clinical and economic outcomes comparing a shortened tuberculosis treatment regimen with a conventional regimen

	LTFU during TB Treatment, Cumulative (%)	Treatment Failure (%)	All-Cause Mortality during TB Treatment (%)	Recurrent TB within 2 yr of Treatment Completion (%)	Composite Unfavorable Outcome (%)	All-Cause Mortality within 2 yr of TB Treatment Initiation (%)	Life Expectancy, Undiscounted (yr)	Life Expectancy, Discounted (yr)	Cost, Discounted (USD)	ICER (USD/YLS)
Trial-reported outcomes										
6m	5.0	2.4	1.4	7.1	15.8	—	—	—	—	—
4m	2.7	1.7	0.7	14.6	19.7	—	—	—	—	—
Model-generated outcomes, base case										
6m	5.0	2.3	1.8	7.3	15.9	12.2	22.3	14.2	\$9,090	—
4m	2.7	1.7	1.0	14.8	19.8	12.5	22.1	14.0	\$9,120	Dominated
Model-generated outcomes, sensitivity analysis										
Key parameters equivalent between 6m and 4m strategies*										
6m	6.3	1.9	1.6	7.3	14.9	11.7	22.5	14.2	\$9,130	—
4m	4.7	1.9	1.1	14.7	20.4	12.8	22.1	14.0	\$9,090	No clinical benefit
LTFU, monthly, % (base case monthly LTFU, 6m, 0.83%; 4m, 0.68%)										
6m, 1.9	11.2	2.3	1.7	6.9	21.5	15.9	21.4	13.6	\$8,740	—
4m, 1.9	7.7	1.7	0.9	14.1	23.9	15.7	21.3	13.5	\$8,820	Dominated
6m, 3.5	19.4	2.3	1.6	6.3	28.7	20.6	20.3	12.9	\$8,300	—
4m, 3.5	13.5	1.7	0.9	13.4	28.7	19.4	20.4	13.0	\$8,470	1,530
6m, 5.3	28.5	2.3	1.5	5.8	36.9	26.0	18.9	12.0	\$7,800	—
4m, 5.3	20.2	1.7	0.9	12.5	34.2	23.7	19.4	12.3	\$8,060	960
Treatment failure, % with positive smear/culture upon completing TB treatment (base case, 6m, 2.4%; 4m, 1.7%)										
6m, 2.4	5.0	2.3	1.8	7.3	15.9	12.2	22.3	14.2	\$9,090	—
4m, 1.0	2.7	1.0	1.0	14.8	19.3	12.5	22.1	14.0	\$9,130	Dominated
All-cause mortality during TB treatment, % (base case, 6m, 1.8%; 4m, 1.0%)										
6m, 1.8	5.0	2.3	1.8	7.3	15.9	12.2	22.3	14.2	\$9,090	—
4m, 0.5	2.7	1.6	0.5	14.8	19.5	12.0	22.3	14.1	\$9,170	Dominated
6m, 1.8	5.0	2.3	1.8	7.3	15.9	12.2	22.3	14.2	\$9,090	—
4m, 1.3	2.7	1.6	1.3	14.7	20.1	12.9	22.0	14.0	\$9,090	No clinical benefit
Recurrent TB, %/mo[†] (base case: 6m, 0.31%; 4m, 0.65%)										
6m, 0.31	5.0	2.3	1.8	7.3	15.9	12.2	22.3	14.2	\$9,090	—
4m, 0.50	2.7	1.6	1.0	11.5	16.6	11.5	22.4	14.2	\$9,210	3,830
6m, 0.31	5.0	2.3	1.8	7.3	15.9	12.2	22.3	14.2	\$9,090	—
4m, 0.75	2.7	1.6	1.0	16.7	21.7	13.0	22.0	14.0	\$9,070	No clinical benefit

Definition of abbreviations: 4m = 4-month treatment strategy; 6m = 6-month treatment strategy; ICER = incremental cost-effectiveness ratio; LTFU = loss to follow-up; TB = tuberculosis; USD = 2017 U.S. dollars; YLS = years of life saved.

"Discounted" refers to discounted 3%/yr. "Dominated" refers to 4-month strategy resulting in lower life expectancy and higher cost than 6-month strategy. "No clinical benefit" refers to 4-month strategy resulting in lower life expectancy and lower cost than 6-month strategy. The bold numbers indicate the regimen (4-mo or 6-mo) that leads to preferred results in terms of the specified clinical outcome.

*The trial-derived probabilities of monthly LTFU, treatment failure, and monthly mortality during TB treatment differed slightly between the groups assigned to the 6-month and 4-month regimens. Here, we calculated the mean for each outcome probability and applied it equally to the 6-month and 4-month regimens. Cumulative LTFU and mortality were still higher for the 6-month regimen than for the 4-month regimen because of a longer at-risk period.

[†]Recurrence probability was modeled as an exponential decay function, such that the monthly probability declined over the 2-year period after TB treatment completion. Here, we show the average monthly probability of recurrence over the 2-year period.

Figure 1. One-way sensitivity analysis of key input parameters and outcomes. The figure shows the values, for monthly loss to follow-up (LTFU), mortality during the 4-month treatment regimen, and recurrent tuberculosis (TB) probability after the 4-month treatment regimen, at which the 4-month regimen is favored over the 6-month regimen in terms of composite unfavorable outcome (red small-dashed line), mortality at 2 years (purple dashed line), or life expectancy (blue large-dashed line). Threshold values for LTFU are rounded to the nearest 0.5%, for treatment failure to the nearest 0.1%, and for recurrence to the nearest 0.05%. The brown solid line represents the range of values reported in South African observational cohorts or registry studies (for LTFU) (5, 9, 10) or the range of values reported in clinical trials of shortened TB treatment regimens (for mortality during 4-mo treatment and for recurrent TB after 4-mo treatment) (6–8). The white X represents the value reported in the OFLOTUB trial (6), which was applied in the base case model analysis and which was notably different from the LTFU values in the cohort studies. The 4-month regimen resulted in a higher risk of the composite unfavorable outcome even when there were no deaths during the 4-month regimen; hence, no red dotted line is shown for that outcome. Recurrence probability was modeled as an exponential decay function, such that the monthly probability declined over the 2-year period after TB treatment completion. Here, we show the average monthly probability of recurrence over the 2-year period. 4m = 4-month treatment regimen; 6m = 6-month treatment regimen.

Figures E6 and E7. Cost-effectiveness acceptability curves from a probabilistic sensitivity analysis are shown in Figure E8.

Discussion

In this model-based analysis, we show that, despite trials failing to demonstrate noninferiority of some 4m regimens, there may be a role for novel shortened tuberculosis treatment regimens, particularly when LTFU during treatment is higher than that seen in trials or when a novel regimen results in fewer recurrences than the trials' fluoroquinolone-based regimens. Under such scenarios or regimen characteristics, a novel 4m regimen not only might be noninferior to the conventional 6m regimen in terms of a composite unfavorable outcome but also could reduce mortality and be cost-effective.

Assessing noninferiority of a novel tuberculosis regimen compared with the standard of care is not straightforward: Both the noninferiority margin and the outcome(s) of interest are debatable (19). Recent trials of shortened regimens used a 6-percentage-point noninferiority margin, based largely on historical data on the efficacy of specific drug components of the conventional 6m regimen (6–8). The

primary outcome of interest and time horizon were not consistent in the historical studies. The OFLOTUB trial used a composite unfavorable outcome, considering LTFU, treatment failure, death during treatment, and recurrence to be equally unfavorable. These outcomes, however, are not equal. Healthcare programs may be, and perhaps should be, willing to tolerate an increase in recurrences (especially if they can be detected and treated) if deaths are fewer.

The goal of our analysis was not to advocate for the OFLOTUB treatment regimen specifically, but rather 1) to highlight limitations of noninferiority trials that evaluate variable composite clinical outcomes (especially when each component of the composite outcome is considered equally unfavorable), 2) to demonstrate how important clinical outcomes such as mortality and life expectancy may show patterns different from shorter-term trial outcomes, and 3) to identify critical benchmarks for future novel shortened tuberculosis treatment regimens when considering both trial and operational settings.

We performed extensive one-way and multiway sensitivity analyses to evaluate uncertainty and to determine the thresholds at which a novel 4m regimen would result in

fewer composite unfavorable outcomes than the 6m regimen. We also found numerous scenarios within published data in which a 4m regimen could reduce 2-year mortality, increase life expectancy, and demonstrate cost-effectiveness. Prior model-based analyses found that a hypothetical shortened tuberculosis treatment regimen could be cost-effective in South Africa, but those studies were not focused on PWH; were not calibrated to results of the recent trials; and did not specifically account for relapse, an important outcome in the trials (20, 21).

LTFU probabilities had a substantial influence on model results. Notably, the LTFU probabilities at which a 4m regimen becomes clinically favorable are those reported in operational settings in South Africa, outside the trial settings where LTFU was extraordinarily low (6–8). Cost-effectiveness interpretations were also affected by LTFU: a 4m regimen became cost-effective compared with the conventional 6m regimen when LTFU was higher.

As shown in our multiway sensitivity analysis, for a novel 4m regimen to be clinically favorable while LTFU probability remained at the level reported in the trials, recurrence probability after a 4m regimen would have to decrease below that in the trials. In this case, novel shortened regimens

Figure 2. One-way sensitivity analysis of key input parameters and their effect on the difference between 4-month and 6-month tuberculosis treatment regimens in 2-year all-cause mortality. In this tornado diagram, the horizontal axis represents the difference in 2-year all-cause mortality between those treated with the 6-month tuberculosis regimen and those treated with the 4-month regimen (6-mo minus 4-mo); a negative difference means that the 6-month regimen resulted in lower mortality than the 4-month regimen. Each bar represents a single one-way sensitivity analysis in which we varied an input parameter. In the vertical axis labels, the value to the left of the colon represents the base case value. To the right of the colon is the range of values across which we varied each parameter, with the value resulting in the mortality difference least favorable for the 4-month regimen listed before the hyphen. The vertical solid line represents the base case scenario, in which 2-year mortality with the 6-month regimen was 0.3 percentage points lower than that with the 4-month regimen. The vertical dashed line represents no difference in 2-year mortality between the two regimens. Red shading indicates where the 6-month regimen results in lower 2-year mortality, and green shading indicates where the 4-month regimen results in lower 2-year mortality. 4m = 4-month treatment regimen; 6m = 6-month treatment regimen; LTFU = loss to follow-up; TB = tuberculosis. *Absolute difference in LTFU is the cumulative probability of LTFU during 6-month treatment minus the cumulative probability of LTFU during 4-month treatment. [†]This reflects the average monthly probability of TB recurrence within 2 years of completing the 4-month regimen. Recurrence followed an exponential decay function such that the risk was highest soon after completing treatment. [‡]This is the monthly probability of TB death for those undergoing treatment for recurrent TB. [§]This reflects the percentage difference between cumulative mortality (for those not lost to follow-up) during 6-month treatment minus the cumulative mortality during 4-month treatment. ^{||}This is the probability of returning to TB care for those lost to follow-up during TB treatment.

including higher-dose rifamycins or other drugs might prove noninferior to a 6m regimen (22–24). Our base case included scheduled surveillance for recurrent tuberculosis but did not include presentation for testing based on symptoms. We varied these assumptions in sensitivity analysis to better reflect nontrial scenarios in which scheduled surveillance (especially with culture) might not occur but symptomatic presentation among some would occur.

We focused exclusively on PWH, who comprised 18% of the study population in OFLOTUB and were a prespecified subgroup for analysis (6). In our analysis, PWH were ART-eligible, but in OFLOTUB, those receiving ART and/or with more

severe HIV disease were excluded (6). For PWH in OFLOTUB, the point estimate of the absolute difference in composite unfavorable outcome risk between the 4m and 6m groups was -4.0% (i.e., fewer unfavorable outcomes in the 4m group), but the upper limit of the 95% confidence interval (7.6%) crossed the 6% noninferiority margin, and thus noninferiority was not demonstrated. Among PWH in REMoxTB and RIFAQUIN, there were more unfavorable outcomes with the 4m regimen than with the 6m regimen, but in RIFAQUIN, the difference was less for PWH than for HIV-negative people (this interaction did not reach statistical significance) (7, 8).

A recent pooled analysis of OFLOTUB, REMoxTB, and RIFAQUIN reported that PWH may need longer tuberculosis treatment regimens (4), but this conclusion was based on the trials with very low LTFU and in which those receiving ART were generally excluded, different from the scenarios and population modeled in our analysis. Because clinical presentations of tuberculosis in PWH in the ART era may be more similar to those of HIV-negative patients (25), more PWH than anticipated might achieve a favorable outcome with a shortened regimen. Being engaged in an ART program could promote tuberculosis treatment adherence and retention in care, but it is unlikely that LTFU during treatment in an operational setting would be

Figure 3. Multiway sensitivity analysis comparing the incremental cost-effectiveness ratio (ICER) of a 4-month versus a 6-month tuberculosis (TB) treatment regimen in people with human immunodeficiency virus in South Africa, varying probability of recurrence after TB treatment, loss to follow-up (LTFU) during TB treatment, and drug cost. These heat maps represent the ICERs while simultaneously varying clinical and economic input parameters. The average monthly probabilities of recurrent TB within 2 years of completing the 4-month regimen reflect those of (A) the base case, the 4-month arm in the OFLOTUB trial (0.65%/mo) (6); (B) a 4-month regimen in the REMoxTB trial (0.50%/mo) (7); and (C) the 6-month arm in the OFLOTUB trial (0.31%/mo) (6). The average monthly probability of recurrent TB after the 6-month regimen is maintained at the base case value (0.31%/mo) throughout the sensitivity analyses. In all three panels, monthly LTFU during TB treatment is varied across the vertical axis, and drug cost of the 4-month TB treatment regimen is varied across the horizontal axis. The red boxes represent scenarios in which the 4-month regimen resulted in lower life expectancy than the 6-month regimen (no clinical benefit). The yellow boxes represent scenarios in which the 4-month regimen resulted in greater life expectancy and greater costs than the 6-month regimen, with an ICER greater than the cost-effectiveness threshold of USD940/yr of life saved (i.e., the 4-mo regimen was not cost-effective). The green boxes represent scenarios in which the 4-month regimen resulted in greater life expectancy and greater costs than the 6-month regimen, with an ICER lower than the cost-effectiveness threshold (i.e., the 4-mo regimen was cost-effective). 4m = 4-month treatment regimen; 6m = 6-month treatment regimen; USD = 2017 U.S. dollars. *This reflects the upper bound of the 95% confidence interval for LTFU reported by Claassens and colleagues (9). †This reflects LTFU reported by Naidoo and colleagues (5). ‡This reflects LTFU reported by Pepper and colleagues (10).

lower than the very low LTFU reported in the trials.

Our analysis focused on South Africa, though sensitivity analyses aimed to reflect a range of possible scenarios, tuberculosis clinical outcomes, and willingness-to-pay thresholds. Additional morbidity and mortality risks, costs, and cost-effectiveness interpretations may differ in other countries. There could be sex differences in 4m treatment effectiveness, as reported in a *post hoc* analysis of REMoxTB in which outcomes between 4m and 6m regimens

were similar in women but not in men (26). Body mass index, smear grade, and presence of cavitation may also influence the relative efficacy of a shortened regimen (4, 6).

A concern about shorter-duration treatment regimens is the risk of drug resistance in recurrent cases. Though OFLOTUB did not report drug resistance patterns of recurrent tuberculosis cases, REMoxTB and RIFAQUIN reported no increase in drug-resistant cases after the 4m regimen compared with the 6m regimen (7, 8). Therefore, we did not include a higher

risk of drug resistance after 4m regimens. If there were drug-resistant cases among those with recurrent tuberculosis and a higher risk of recurrence after a 4m regimen than after the 6m regimen, then the potential benefits of a 4m regimen would be attenuated.

Even without drug resistance, recurrent tuberculosis may be more difficult to treat than initial tuberculosis, as we assessed in a sensitivity analysis. A higher treatment failure probability for those with recurrent tuberculosis had little impact on 2-year mortality or life expectancy. Higher

mortality among recurrent tuberculosis cases, however, expectedly increased mortality to a greater extent for those treated with a 4m regimen than for those treated with the 6m regimen.

In the base case analysis, where the 4m regimen does not provide overall clinical benefit compared with the 6m regimen, cost-effectiveness analysis is not useful. However, in scenarios including those with lower recurrence probability after a novel 4m regimen and higher LTFU, a 4m regimen results in higher life expectancy than the 6m regimen. From these analyses, we demonstrate the scenarios in which a novel 4m regimen would also be cost-effective; notably, monthly drug costs generally would have to be lower than the USD25.90/mo cost of the base case OFLOTUB regimen.

Our results, as with any model-based analysis, should be interpreted in the context of limitations in model structure and input

parameters. We calibrated base case model outputs to OFLOTUB outcome data for all patients, not only PWH, because PWH-specific detailed outcomes were not reported from the trial. We conservatively assumed that monthly LTFU probability did not change by month of treatment; higher LTFU earlier in treatment compared with later would favor the 4m regimen compared with the 6m regimen because of a higher proportion of treatment completed with the 4m regimen. We did not specifically model tuberculosis transmissions between simulated individuals, though we included probabilities of reinfection and recurrence. Our cost-effectiveness analysis was done from the health system perspective and did not include costs or savings to patients. Lacking country-specific preference weights for all health states in our model, and because prior tuberculosis studies found that mortality was the major influence on

disability-adjusted life-years, we examined YLS rather than quality-adjusted life-years (27–30).

In conclusion, when accounting for LTFU probabilities commonly reported in operational settings and the associated mortality risks, novel shortened regimens for drug-susceptible tuberculosis could reduce mortality, increase life expectancy, and be cost-effective compared with the conventional 6m regimen. Our results help identify benchmarks for future trials of novel shortened tuberculosis regimens, which should consider various outcome measures when evaluating noninferiority. ■

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