Supplemental Methods and Results

Supplemental Methods:

A) Detail on Treatment regimens:

Initial treatment regimens and outcomes with No DST:

When DST was not performed, all patients received the WHO recommended standard initial regimen (2HRZE/4HR). During initial treatment new cases can cure, die or fail. Cases that cure can subsequently relapse. Default is not explicitly included as a separate treatment category; however treatment success rates have been lowered to take default rates into account. For HIV negative cases, except for those with underlying MDR, the proportion of the hypothetical cohort that die during initial treatment is based on the most recent WHO global data (1). HIV uninfected MDR cases have the same spontaneous cure rate as untreated cases - 25% (2), and annual mortality of 33% (3), since they are effectively untreated. Failure and relapse rates vary based on underlying drug resistance, according to a recent systematic review and meta-analysis of published randomized trials (4;5). Cases with underlying non MDR INH resistance or MDR have an increased likelihood of failure, relapse, death and acquired drug resistance as shown in table S1a.

Table S1a. Treatment outcomes after standardized initial treatment by underlying drug resistance

Cure			Fail			Relapse after cure			Death during initial treatment (6 months)		
DS	Mono INH R	MDR	DS	Mono INHR	MDR	DS	Mono INHR	MDR	DS	Mono INHR	MDR
96.2%	93.4%	25%	0.3%	3.1%	58.5%	3.1%	6.6%	2.5%/yr	3.5%	3.5%	16.5%

Sources of data for Drug sensitive and Mono INH treatment outcomes:

- Failure and Relapse (4) (5)
- Death: Adapted from : WHO Global Report 2009: Figure 1.26: Treatment outcomes for HIV+ and HIV-ve patients
  - Cure - complementary value (meaning 100% - [Failure + Death])

Sources of data for MDR treatment outcomes:

- Fail- complementary value
- Relapse (2;6)
- Death- as if untreated (data from pre-antibiotic era) (3)

- Cure -equivalent to spontaneous resolution)(2)

Retreatment regimens and outcomes with No DST:

If DST was not performed for cases who are smear positive at 5 months or relapses, all failures or relapses after treatment completion (regardless of underlying drug resistance) received WHO standardized retreatment ("Category 2" which is 2SHRZE/1HRZE/5HRE). Retreatment outcomes varied according to underlying drug resistance as shown in table S1b. Cases with mono INH resistance or MDR had worse retreatment outcomes. Failures and relapses of standard retreatment were assumed to receive no further treatment.

Methods Table S1b. Treatment outcomes after retreatment by underlying drug resistance

Cure			Fail			Relapse after cure			Death during re-treatment (8 months)		
DS	Mono INH	MDR	DS	Mono INH	MDR	DS	Mono INH	MDR	DS	Mono INH	MDR
93.7 %	90.9%	0	0.3 %	3.1 %	78%	3.1%	6.6 %	2.5%/yr	6%	6%	22%

Sources of data: As per initial treatment

Initial and retreatment regimens and outcomes following DST:

If DST was performed, patients received an appropriate regimen once the DST results are available. Patients with drug sensitive (DS) TB continued the WHO recommended standard initial regimen. Patients with mono-INH resistant TB start (or restart-depending on the timing of DST) a 6 month regimen that was assumed to provide treatment outcomes equivalent to current standard therapy for drug sensitive cases. Patients with MDR received a standardized 24 month regimen (6 Amikacin-Cs-Eth-Lfx-PZA-EMB/ 18 Cs-Eth-Lfx-PZA-EMB). If DST was performed prior to or during initial treatment and mono INH is detected, then for those who relapse or fail after the regimen for INH resistant cases then they receive a standard retreatment regimen. Failures and relapses of standard retreatment were assumed to receive no further treatment. If MDR was previously detected and standardized MDR treatment given, patients will not have further treatment, even if they fail or relapse. The regimens given to different types of cases are summarized in table S2.

Methods Table S2: Summary of initial and retreatment regimens given to cases following DST

Initial Drug resistance	Initial regimen	Retreatment regimen
Drug sensitive	Standard WHO 6	WHO Cat II

	month initial regimen. 2HRZE/4HR	retreatment regimen 2SHRZE/1HRZE/5HRE
Detected Mono INH Resistant	Hypothetical regimen that would provide treatment outcomes equivalent to current standard therapy for drug sensitive cases	WHO Cat II retreatment regimen 2SHRZE/1HRZE/5HRE
Detected MDR	Standardized WHO MDR 24 month regimen. 6 Amikacin-Cs-Eth-Lfx-PZA-EMB/ 18 Cs-Eth-Lfx-PZA-EMB	No retreatment

Treatment outcomes for mono INH cases are assumed to be the same as those shown for drug sensitive cases given the WHO initial regimen (as per Table S1a). Retreatment outcomes are the same as those shown for mono-INH cases in table S1b. Treatment outcomes for MDR cases under appropriate therapy are summarized below in tables 3a.

Methods Table 3a. Treatment outcomes for detected MDR cases on standardized MDR treatment

Cure	Fail	Relapse after cure	Death during treatment
67%	20%	3%	13%

B) Detail on Acquisition of Drug Resistance:

Cases with undetected underlying drug resistance that are not treated appropriately can acquire additional drug resistance during each course of treatment (7). Data on rates of acquisition of drug resistance for cases undergoing initial or retreatment with different categories of underlying initial drug resistance are taken from recent systematic reviews (4;5;8). Tables S4 and S5 provide a summary of acquisition of drug resistance rates. Cases with undetected mono-INH resistance can acquire MDR during standardized initial and retreatment. If there is a delay in performing DST, or obtaining DST results, then cases can also acquire resistance during that interval while being treated with the standardized initial regimen, particularly if they have INH-mono-resistance. Other forms of drug

resistance are not considered, nor whether the resistance pattern of MDR-TB could be further worsened (amplified) by standardized initial and retreatment, since we are considering tests that detect INH and RIF only. These assumptions hold for all cases, regardless of HIV status.

Table S4 and S5: Rates of acquisition of drug resistance for cases undergoing initial or retreatment wiht different categories of underlying initial drug resistance.

Table S4a: Probability of *failures* acquiring drug resistance after a standardized 6 month regimen, by initial drug sensitivity were derived from published reviews(4;8) although the estimates in Table S4a come from additional secondary analysis that were not published.

Initial drug resistance category	Probability of drug resistance amongst failures after treatment		
	Sensitive (%)	Mono INH(%)	MDR (%)
Sensitive to all	38.5%	44.2%	17.3%
Mono INH	-	0%	100.0%

Table S4b: Probability of *relapses* having different types of drug resistance after a standardized 6 month regimen, by initial drug sensitivity - derived from published reviews(4;8), although these estimates come from additional secondary analysis that were not published.

Initial drug resistance category	Probability of drug resistance amongst relapses after treatment		
	Sensitive (%)	Mono INH(%)	MDR (%)
Sensitive to all	94.1%	3.7%	2.3%
Mono INH	-	100%	0%

Table S5a: Probability of *failures* with mono INH resistance (given regimen that provides treatment outcomes equivalent to current standard therapy for drug sensitive cases), or standard retreatment acquiring MDR (rates as per drug sensitive in table S4a)

Initial drug resistance category	Probability of drug resistance amongst failures after treatment	
	Mono INH(%)	MDR (%)
Mono INH (getting appropriate regimen	82.7%	17.3%

and standardized retreatment)		

Table S5b: Probability of *relapses* with mono INH resistance, (given regimen that provides treatment outcomes equivalent to current standard therapy for drug sensitive cases), or standard retreatment acquiring MDR (rates as per drug sensitive in table S4a)

Initial drug resistance category	Probability of drug resistance amongst relapses after treatment	
	Mono INH(%)	MDR (%)
Mono INH (getting appropriate regimen and standardized retreatment)	97.7%	2.3%

C) Additional Detail on Health System costs (See Table S6 below)

Table S6: Additional detail on drug regimens and associated treatment and health system costs*

Regimen	Duration of Regimen	Regimen cost**	Single visit to doctor (2007 USD)	# of visits to doctor per regimen (1 per month)	Single DOT cost* (2007 USD)	# of DOT visits per regimen	TOTAL health system cost
Initial standardized	6mth	2RHZE/4RH blisters = $16.62	$22.70	6	$7.52	=5 visit/wk for 8.7 wks =3 visit /wk for 17.3 wks Total=95 visits	$867
Retreatment standardized	8mth	2RHZES/1RHZE/5RHE blisters, water for inj, 2 syringes = $29.43	$22.70	8	$7.52	=5 vst/wk for 8.7 wks (injectable) *=44 injectable visits* =5 visit /wk for 4.3 wks =3 visit /wk for 21.7 wks *=87 non injectable visits* Total=131 visits	$1527
INH-R regimen	6mth	Initial regimen, with Levoquin (Lfx)† 2RLfxZE/4RLfx = $43.33	$22.70	6	$7.52	=5 visit /wk for 8.7 wks =3 visit /wk for 17.3 wks Total=95 visits	$894
Standardized MDR	24mths	6Cm/18CsLfxEthPAS no syringe, no water for inj = $2,118.79	$22.70	24	$7.52	=5 visit /wk for 26 wks (injectable) *=130 injectable visits* =5 visit /wk for 70 wks *=350 non injectable visits* Total=480 visits	$7250

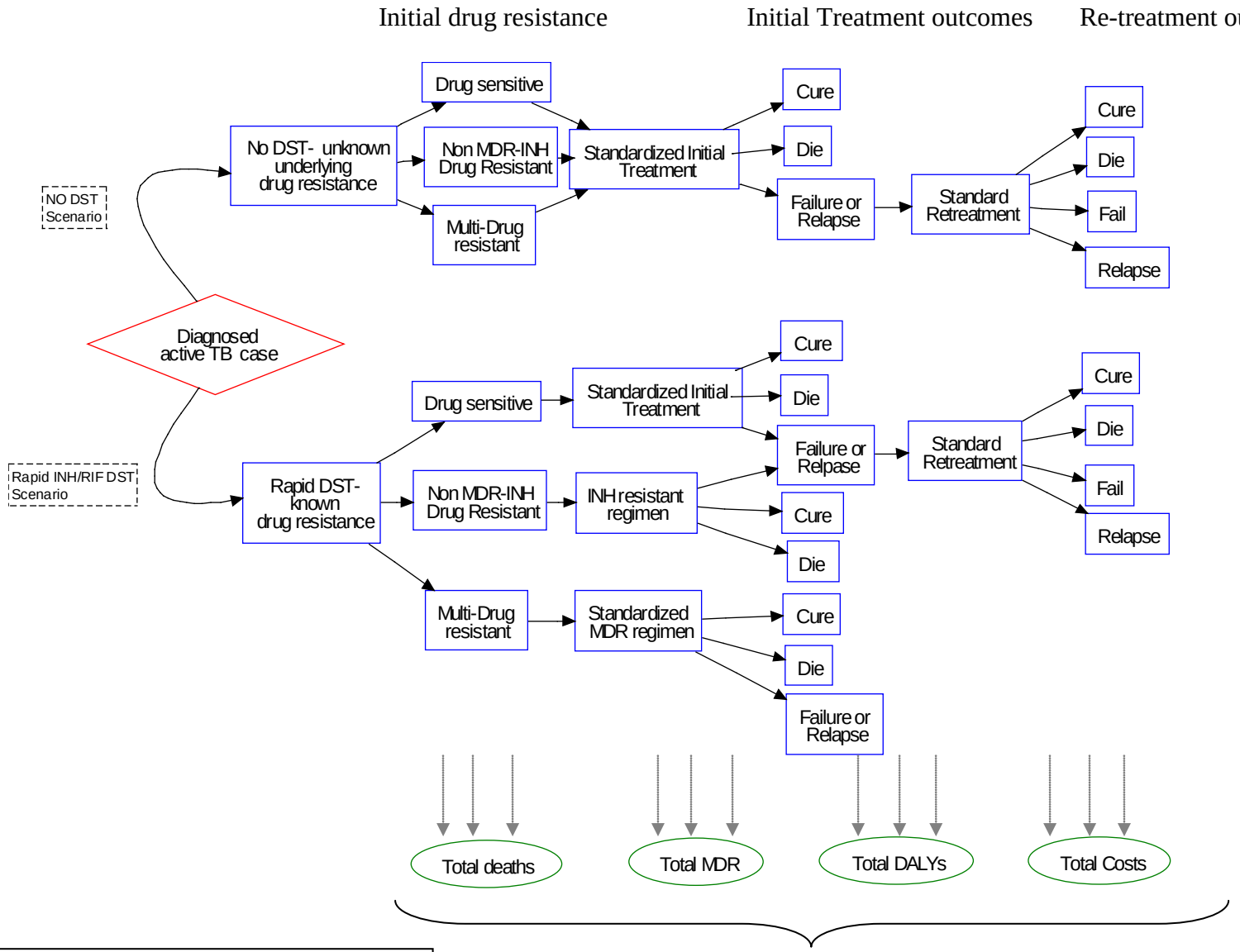
*Hospitalization costs excluded- ambulatory costs only

**Data obtained from survey of health system costs conducted in Rio De Janeiro, Brazil, 2007(9). Costs were originally obtained from direct surveys conducted in Brazil, but are assumed to be appropriate for South Africa, as the GDP per capita (PPP) for the two countries were almost identical in 2007 (10).

***Drug regimen costs estimated using data from Global Drug Facility (GDF) (www.stoptb.org/gdf/)

† In the absence of a known effective regimen for mono-INH resistant cases, for the purposes of costing, we assumed use of the regular standardized initial regimen, with a Quinolone (levofloxacin) replacement for isoniazid

Supplemental Figure S1: Illustration of progression through DST and treatment in model. Example of No DST strategy vs. Pre-treatment Rapid INH & RIF DST strategy



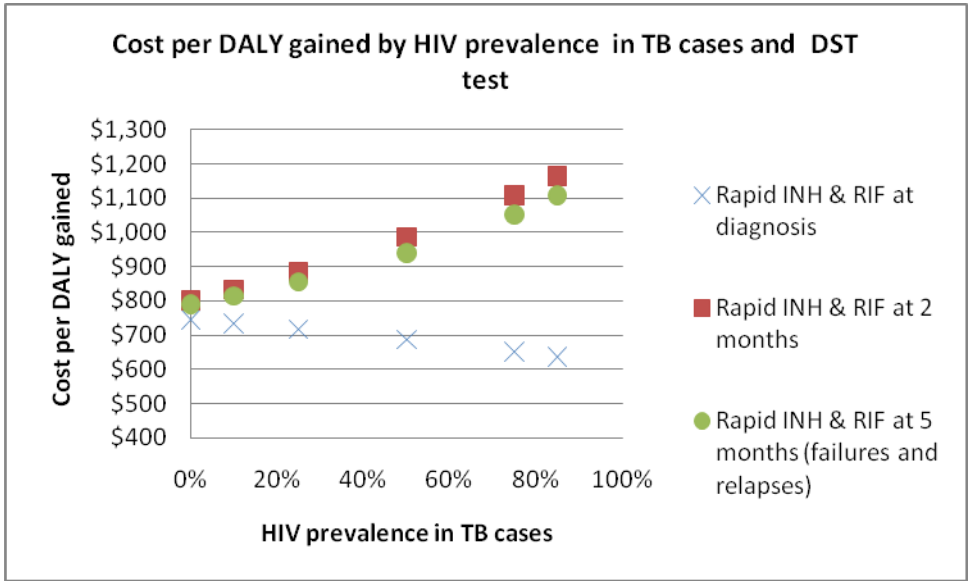
NOTE: Drug sensitive or non MDR- INH drug resistant may acquire drug resistance during initial and or retreatment.

Supplemental Results: Tables and Figures:

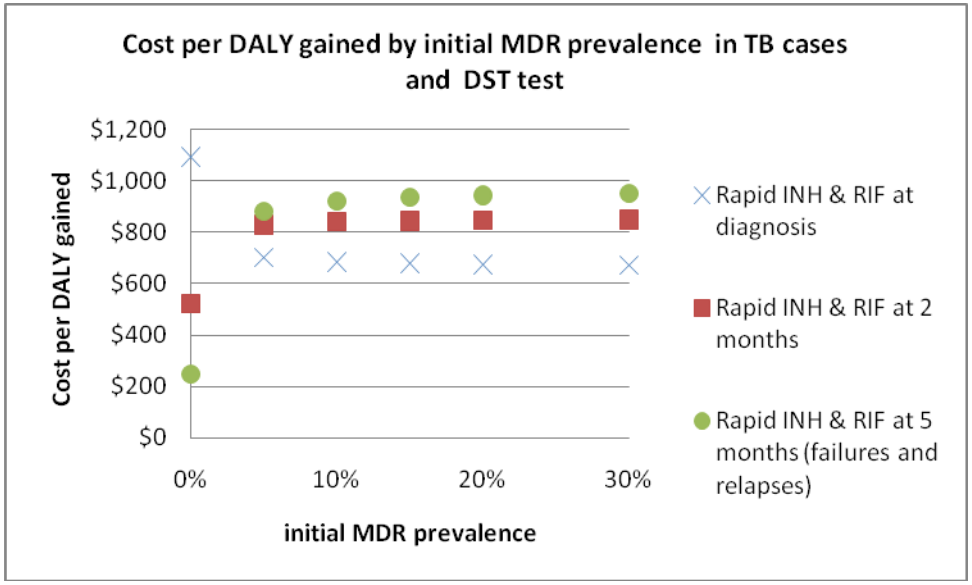
Supplemental Table S1. Sensitivity analysis- Cost of DST and drugs per 1000 new cases starting treatment: . Setting: (moderate drug resistance (non-MDR INH resistance of 5.8% and MDR of 2.1%)- no HIV)

	no DST	solid DST	rapid R	rapid HR	Rapid HR @ 2 months	Rapid HR @ 3 months	Rapid HR @ 5 mths fail only	Rapid HR @ 5 mths fail and relapse
Baseline total Cost per case	$919	$1,073	$1,058	$1,054	$1,048	$1,043	$1,037	$1,039
Cost per case- DST and drug cost only	$18	$80	$97	$99	$69	$64	$60	$63
% DST and drug only	1.9%	7.4%	9.2%	9.4%	6.6%	6.2%	5.8%	6.0%

Supplemental Figure S2: Sensitivity analysis- Prevalence of HIV in TB cases. Setting: Moderate DR, Low HIV

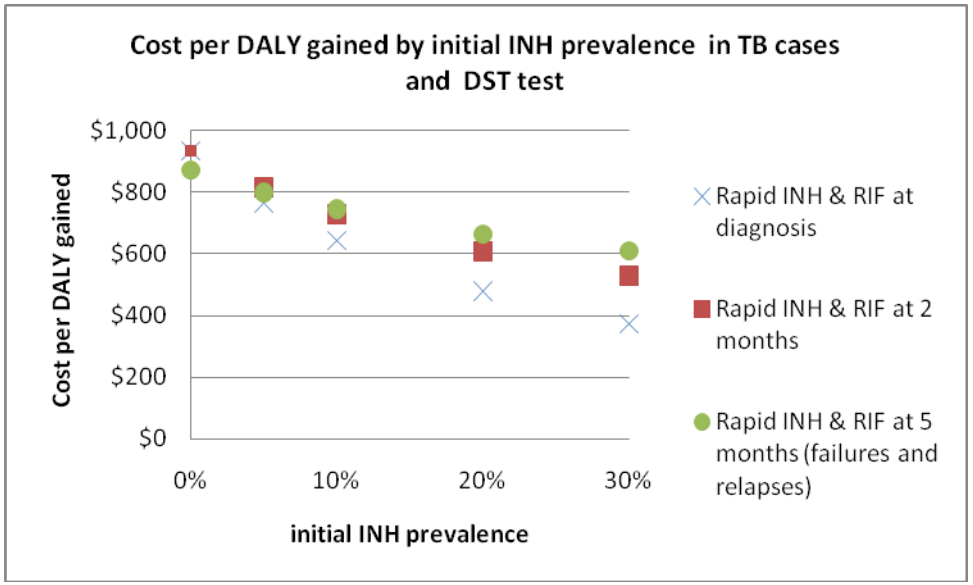


Supplemental Figure S3: Sensitivity analysis - Prevalence of initial MDR



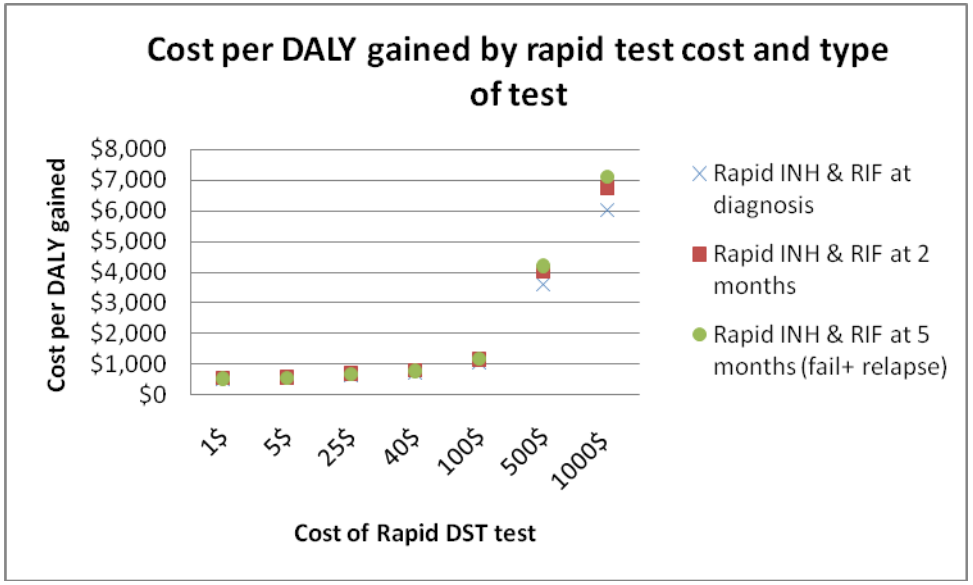
* When the prevalence of initial MDR changes, it is absorbed by drug sensitive cases (i.e. prevalence of mono INH always remains at the base line level (5.8%))

Supplemental Figure S4. Sensitivity analysis - Prevalence of initial mono INH. Setting: Moderate DR, Low HIV



** When the prevalence of initial INH changes, it is absorbed by drug sensitive cases (ie. prevalence of MDR remains at baseline level (2.1%))

Supplemental Figure S5. Sensitivity analysis - Cost of rapid test. Setting: Moderate DR, Low HIV



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