

The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy in South Africa: a model-based analysis

**Technical Appendix  
for**

**The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy in South Africa: a model-based analysis**

### **Common Abbreviations**

DS	drug susceptible
MDR	multidrug resistant
XDR	extensive drug resistant
DST	drug susceptibility testing
FLD	first-line drugs
SLD	second-line drugs

### **Model Overview**

The model utilized for this analysis built upon the underlying structure of the Cost Effectiveness of Preventing AIDS Complications (CEPAC) International Model, a detailed description of which has been published elsewhere [1]. In brief, CEPAC International is a state-transition, Monte Carlo simulation model of HIV natural history and treatment in resource-limited settings. This model has previously been used to address policy questions pertaining to HIV testing and treatment in South Africa, Côte d'Ivoire and India [1–7]. A simulated cohort of 1,000,000 individuals enter the model one at a time and their clinical course is recorded from the time of entry until death. Probabilities of clinical events, such as the occurrence of opportunistic infections or default from antiretroviral therapy, are pre-specified and may be stratified by CD4 cell count, viral load, and other relevant variables. Use of random number generation with comparison to state-transition probabilities dictates the individual's course of disease, treatment and associated costs. The life expectancy and costs are reported by the model for a given set of simulations. Strategies are compared by changing the relevant parameters and comparing simulation results.

## **Tuberculosis Model**

We developed a tuberculosis natural history and treatment model that was layered upon the existing CEPAC International model structure. Individuals may enter the model with no history of tuberculosis infection, latent tuberculosis infection, active tuberculosis, or a history of active tuberculosis. The infecting strain may be drug susceptible, multidrug resistant (MDR), or extensive drug-resistant (XDR). Individuals with latent infection can reactivate to active disease; the risk of reactivation is strongly correlated to CD4 cell count and receipt of antiretroviral therapy [8–10]. Individuals with active tuberculosis have a delay to initiation of tuberculosis treatment that can be specified according to the diagnostic process being simulated.

Four lines of treatment are available: first-line therapy, standardized retreatment, second-line drugs, and third-line drugs (second-line drugs tailored to highly or extensive drug-resistant tuberculosis), each of which has associated duration, toxicities, and costs. A cure probability must be assigned for each combination of drug-resistance profile and treatment regimen. Individuals with active tuberculosis face a monthly probability of tuberculosis-associated mortality when not receiving treatment or when receiving a failing regimen. The probability of mortality was reduced by use of antiretroviral therapy. Upon failure of a regimen, the next regimen used is dictated according to pre-specified criteria. For the current analysis, we specified that individuals receiving first-line drugs or retreatment regimens who were smear-positive at two months of therapy would have a culture and drug-susceptibility performed; if the individuals had MDR tuberculosis, they would be started on second-line drugs upon receipt of the results (1 month delay). Individuals who completed first-line drugs and failed therapy would

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have drug susceptibility testing performed; those who were found to have MDR TB would receive SLD, while those without MDR TB would receive a standardized retreatment regimen. During treatment, individuals have a monthly probability of default from treatment. Upon cure, individuals have an increased risk of relapse to active tuberculosis, which is reduced by use of antiretroviral therapy.

We did not incorporate acquisition of drug resistance through failed treatment or amplification of drug resistance, as these events are relatively uncommon and were unlikely to substantially impact the model results. As incorporating these events would increase the utility of Xpert MTB/RIF (hereinafter abbreviated ‘Xpert’) and culture with drug-susceptibility testing, our model was conservative with respect to acquisition of drug resistance.

### **Tuberculosis Diagnostics Models**

We compared eight diagnostic strategies and a reference case of no active screening for tuberculosis. This consisted of four laboratory test strategies--sputum smear microscopy, sputum microscopy and culture, sputum Xpert MTB/RIF (1 sample), and sputum Xpert MTB/RIF (2 samples)—performed in all patients or symptomatic patients only.

### ***Smear Strategies***

Individuals with a positive test result are initiated on tuberculosis treatment. In the case of smear, individuals are initiated on first-line drugs (if they have no history of tuberculosis treatment) or a standardized retreatment regimen (if they have a history of tuberculosis treatment). If they have a negative smear, they are not treated initially and are diagnosed after a

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period of time, see **Figure A1**. Asymptomatic individuals who are not screened similarly have a diagnostic delay of 2 months.

Two months after initiation of tuberculosis treatment, sputum microscopy is repeated. For individuals with a positive sputum smear at 2 months, culture is obtained, and drug susceptibility testing is performed on positive culture specimens. For those found to have MDR TB, second-line drugs are initiated. There is assumed to be a one month delay between the time of obtaining a culture and the receipt of results (and initiation of second-line drugs). If individuals have a negative sputum smear at 2 months, they continue on their current regimen (first-line drugs or standardized retreatment). We assumed that all HIV co-infected individuals with MDR TB failed their first-line or retreatment therapy, consistent with recent data.<sup>[11]</sup> We assumed that culture and drug susceptibility testing was obtained at the end of the failed regimen, and that individuals were then started on second-line drugs upon receipt of the results. This pathway for a patient with MDR TB is shown below (**Figure A2**).

### ***Culture Strategies***

For the culture strategies, we assumed that individuals have both smear and culture performed; smear results are available immediately, while culture results are delayed by one month. If individuals are smear-positive, they start first-line drugs or retreatment according to their treatment history. Those that have MDR TB are switched after one month (upon receipt of DST results) to SLD, while those with DS TB continue on their present regimens. Individuals that are smear-negative are not started on treatment until one month later, when the results

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return. At that time, if they have DS TB, they are started on FLD; if they have MDR TB, they are started immediately on SLD. This treatment algorithm is displayed below (**Figure A3**).

### *Xpert Strategies*

Xpert is a rapid, PCR-based diagnostic for tuberculosis and rifampin resistance and is recommended by the World Health Organization. Though rapid, it still requires trained laboratory personnel as well as ongoing technical support and validation [12]. The South African Department has plans to roll out Xpert to all National Health Laboratory Service labs, ultimately replacing smear microscopy for tuberculosis screening [13]. In the Xpert strategy, we assumed that individuals did not have smear performed in addition to Xpert. Individuals with TB can be diagnosed by Xpert or missed by the test (false negative), according to Xpert's sensitivity. Individuals with a false negative Xpert are assumed to be diagnosed after a period of time, as in the case of patients with negative sputum smears (see above). Individuals with a positive Xpert can have either DS or MDR TB. Xpert screens for the most common mutations conferring rifampin resistance. Among individuals with DS TB, the false positive rate of this test is  $1 - \text{specificity}$ . Among individuals with MDR TB, the false negative rate is  $1 - \text{sensitivity}$ . We assumed that individuals with an Xpert result indicating rifampin resistance would have culture and DST performed to confirm the result and screen for SLD resistance. In the interim, we assumed that they would start on SLD, and would switch back to first-line drugs if found to be DS by conventional DST. Individuals with true positive rifampin screening tests continued on SLD. Among individuals with MDR TB and a false negative test for rifampin resistance, we assumed that they started on FLD or retreatment regimens and could switch to SLD if they were

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smear-positive at 2 months or failed their regimen at the end of treatment. This is comparable to individuals with MDR TB screened by smear (**Figure A2**). The diagnostic-treatment algorithm for the Xpert strategies are shown below (**Figure A4**).

### ***False Positive Screening Tests***

By any diagnostic modality, individuals could have a false positive test and be treated unnecessarily. The probability of a false positive result among individuals without tuberculosis is 1-specificity of the test. Treatment of individuals without tuberculosis was assumed to eradicate latent infection, but also carried costs and risk of drug toxicity.

### **Antiretroviral Therapy**

We simulated a cohort of individuals referred for initiation of antiretroviral therapy. We assumed that antiretroviral therapy was initiated one month after entry into the model. In patients in whom tuberculosis was diagnosed, initiation of antiretroviral therapy at one month is consistent with current guidelines. Recent studies have shown no significant differences in outcomes among individuals with tuberculosis and  $CD4 > 50/\mu l$  when starting ART within 2 weeks compared with starting at 8-12 weeks. For individuals with a  $CD4 < 50/\mu l$ , mortality has been shown to be higher with the deferred strategy [14,15].

We assumed that individuals were eligible for antiretroviral therapy if they had a  $CD4$  cell count of  $< 350/\mu l$  or had a WHO Stage IV diagnosis. We simulated two lines of therapy; the first-line consisted of tenofovir DF, emtricitabine and efavirenz [16]; individuals failing first-line therapy could receive lopinavir/ritonavir with zidovudine and lamivudine [17]. The

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modeling of efficacy, toxicities, clinical and laboratory monitoring, and indications for switching therapy have been previously described in detail [1].

## **Data**

The process of data review and selection for model parameterization for the CEPAC International model has been previously described [1]. Here, we discuss the key data sources for these input parameters.

### ***HIV Natural History***

CD4-stratified monthly probabilities of opportunistic infections, death due to opportunistic infections, and chronic AIDS-related deaths were obtained from the Cape Town AIDS Cohort [8]. CD4 count decline, stratified by baseline HIV RNA level, was obtained from the Multicenter AIDS Cohort Study [18]. All patients in the model are provided co-trimoxazole prophylaxis, which reduces the risk of *Pneumocystis*, bacterial infections, toxoplasmosis and other opportunistic diseases [19].

### ***Cohort Characteristics***

We took base-line demographic and clinical characteristics of the cohort from a prospective screening study of individuals initiating ART at this site [20]. Age, sex, mean CD4 cell count and TB history are shown in Table 1, main text. The prevalence of undiagnosed, culture-confirmed TB among individuals referred to ART clinics in South Africa has been reported to be 17-31% [20–22]; we used 22% as the base case by taking a weighted average



from the two studies where this analysis was focused [20,22]. The prevalence of MDR TB among new (3.3%) and retreatment patients (7.7%) was from a recent survey conducted in Khayelitsha, a township outside of Cape Town [23]. We did not include extensively drug-resistant (XDR) tuberculosis, as the prevalence is less than 0.5%, and few data are available to characterize treatment outcomes at this time.

### ***Tuberculosis Natural History***

Key parameter values and associated references are in Table 1 (main text). Individuals entering the model (i.e. presenting for evaluation for initiation of ART) with TB had a probability of dying in the absence of diagnosis and treatment. The monthly probability of mortality from untreated TB was from a prospective study of patients presenting for ART initiation at a clinic in peri-urban Cape Town [22]. All patients had smear, radiography and sputum cultures obtained. Among the individuals who were smear-negative (undiagnosed at time of screening), a proportion had culture-positive tuberculosis. We obtained the monthly probability of death prior to initiation of treatment by assessing the number of deaths before treatment divided by the exposure period (the time until TB treatment or death) (Table A1).

The small number of outcomes precluded stratification by CD4 cell count or other clinical factors. Of note, most deaths occurred prior to initiation of ART; in the model, ART further reduces the probability of mortality due to tuberculosis, consistent with multiple studies [24–28].

There is a dearth of literature estimates of the mortality of untreated TB in the setting of HIV co-infection. Studies published in the pre-ART therapy era yielded variable estimates of

TB mortality, all of which were higher than the value obtained above [29–35]. However, unlike the cohort examined above, which was an unselected cohort of individuals initiating ART, patients from these reports were typically presenting with an illness that was being evaluated and may have had higher mortality as a result. Another potential estimate for the mortality of untreated TB could be obtained from studies of XDR TB treated with first-line drugs, given the lack of efficacy. Monthly mortality was considerably higher in these cohorts [36–39]. Such high mortality rates were also seen in MDR TB and HIV co-infection in the 1990s [40–43]. However, these cohorts similarly were very symptomatic, many having been treated for TB in the preceding two years [44]. Nevertheless, the value used in our analysis was likely a conservative estimate for TB mortality, which results in conservative estimates for the benefit of screening and early detection.

### ***Tuberculosis Diagnosis***

The sensitivity of smear in screening individuals initiating ART was taken from two studies in which all individuals initiating antiretroviral therapy were screened for TB (Table A2). The sensitivity of sputum smear microscopy is much lower in this unselected population due to immunosuppression and lower bacillary load than is seen in symptomatic individuals who present to clinics and are considered ‘tuberculosis suspects’. The higher sensitivity seen in the second study [20] may be in part due to the sample processing and microscopy having been performed in a world class research laboratory.

The sensitivity of Xpert was obtained from a prospective study screening individuals initiating ART [20]. Of note, the sensitivity was considerably lower than that reported in the

initial multicenter evaluation studies [45,46]; however, these studies were done among mostly HIV-negative TB suspects with two weeks cough, who are likely to have a higher bacillary load in sputum. Among HIV co-infected individuals, the sensitivity of Xpert is lower [47].

The time to diagnosis of individuals who have only sputum microscopy performed and are smear-negative is an important model parameter. We used a time period of one month, consistent with several studies [46,48,49].

### ***Loss to follow up***

We modeled loss to follow up between TB screening and TB treatment among individuals in the culture (and smear strategy) strategy; we applied pre-treatment loss to follow up only on smear-negative individuals, as we assumed smear-positive individuals were referred for treatment on the same day. Utilizing the aforementioned database of individuals initiating ART who were screened for TB, we assessed loss to follow up among smear-negative, culture positive individuals prior initiation of TB treatment. Among 49 individuals, 8 (16%) were lost to follow-up. In the base case of the Xpert strategy, we assumed results were available on the same day and patients with positive were immediately referred for TB treatment. In sensitivity analysis, we modeled up to 20% loss to follow up between Xpert screening and treatment.

### ***Tuberculosis Treatment***

Treatment efficacy differed for each combination of drug resistance category and treatment regimen. For individuals receiving first-line drug (FLD) tuberculosis therapy with drug susceptible tuberculosis, we utilized national data on the successful treatment probability,

which is a slight underestimate given the presence—albeit low—of MDR and XDR TB among new cases [50]. This is consistent with HIV-associated TB outcomes from cohort studies [51,52]. We assumed that individuals with drug susceptible TB receiving a retreatment regimen would have comparable probability of cure, assuming similar history of tuberculosis. This is supported by a recent study of retreatment regimens that yielded data stratified by HIV status and drug-resistance of TB strain [11].

Among individuals with MDR, first-line drug cure probability was assumed to be nil in the setting of HIV co-infection, consistent with a recent study from Uganda [11]. Second-line drug efficacy has been highly variable between studies. Cure rates of HIV-associated MDR TB were much lower in studies in the 1990s [35,42,53,54], which may be due to a combination of fewer data on effective regimens as well as the absence of combination antiretroviral therapy. Recent studies from South Africa and Lesotho have found higher rates of culture conversion and cure, particularly when treatment is initiated early or empirically in the setting of high suspicion [55–58]. History of failed treatments has been associated with poor outcomes in almost all studies of MDR TB treatment [55,58,59]. We assumed a higher probability of cure in individuals who were treated initially with SLD than in those who received FLD or a retreatment regimen before starting SLD (Table 1).

### ***Treatment Toxicities***

In the model, individuals receiving TB treatment had probabilities of toxicities according to their regimen. We reviewed literature on major and minor TB drug toxicities among individuals with HIV. Toxicities were associated with costs but not probability of

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mortality in this model, given the rarity of toxicity associated mortality reported. For first-line drugs, we assumed that the probabilities of a minor and major toxicity were 30% and 5%, respectively, based on previous reports [60–63]. For second-line drugs, serious toxicities occur in 30-50% of HIV co-infected patients [38,57,58,64,65]. We used data on hospitalization duration to incorporate costs of toxicities [58].

### Costs

A discussion of the modeling of costs of ART, clinic visits and laboratory monitoring in the CEPAC International model has been previously published [1]. We used a unit-costing approach where data was available, with data from the Cape Town AIDS Cohort for HIV care costs [8].

Costs of TB drugs were derived from reported costs at King George V Hospital [66]. Monthly drug costs were weighted according to the intensive and continuation phases. For first-line drugs, we assumed a two-month intensive phase (\$9.10 per month) and four-month continuation phase (\$5.70 per month). For second-line drugs, we assumed a six-month intensive phase (\$164.40 per month) and eighteen-month continuation phase (\$131.80 per month).

First-line drug therapy included non-drug costs from previous reports in South Africa [67,68]. For second-line drugs, non-drug costs were analyzed according to the total number of inpatient hospital days (25), monitoring visits (21), daily DOTS visits, and x-rays [58]. Unit costs for inpatient hospital days (\$160 per day), monitoring visits (\$18.60), DOTS visits (\$7.70) and X-rays were derived from previously published papers [67,68].

Consistent with the recommendations of the Panel on Cost-Effectiveness in Health and Medicine, costs and life expectancy were discounted on a monthly basis with a 3% annualized discount rate [69].

### **Sensitivity Analysis**

We performed one-way sensitivity analysis to assess the impact of key model parameters on the incremental cost-effectiveness ratio for the Xpert-2-all strategy. We varied parameters over a broad range of plausible values. Parameters assessed in one-way sensitivity analysis were: prevalence of undiagnosed TB, prevalence of MDR TB among TB patients, mortality of untreated TB, sensitivity and specificity of Xpert for Rifampin resistance, sensitivity of Xpert in smear-negative disease, specificity of Xpert for TB, sensitivity of smear, cost of Xpert cartridges, probability of cure of MDR TB with second-line drugs, probability of cure of drug-susceptible TB with first-line drugs, probability of cure of MDR TB with first-line drugs and loss to follow up after Xpert screening. We depict the most influential parameters in the tornado diagram shown in Figure 2 (main text). We also depict the relationship between the two most influential variables (TB prevalence, untreated TB mortality), separately, on the incremental cost-effectiveness ratio (Figure 3, main results; Figure A7).

We evaluated a hypothetical diagnostic with increased sensitivity and cost, to determine the threshold sensitivity and cost at which that diagnostic would be very cost-effective (Figure A6). We performed two-way sensitivity analysis on the sensitivities of smear and Xpert in order to evaluate threshold areas for the optimal diagnostic strategy at a willingness to pay of \$7,100

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(Figure A8). In all scenarios where the prevalence of TB is greater than 7%, Xpert-2-all is preferred to smear.

**Table A1.** Descriptive data from a screening study of patients initiating ART.

Patients Screened	Culture Positive	Smear Negative*	Deaths	Exposure Days	Monthly Mortality
241	59	49	5	1754	0.086

\*Denotes smear-negative, culture positive individuals.

**Table A2.** Sensitivity in two studies of sputum smear microscopy among individuals with culture-positive TB initiating ART in South Africa. N: number of individuals with culture-positive TB.

Reference	N	Smear-positive	Sensitivity
[22]	59	10	16.9%
[20]	75	21	28.0%
<b>Total</b>	<b>134</b>	<b>31</b>	<b>23.1%</b>



### Additional Figures

**Figure A1.** Diagnostic pathway for individuals diagnosed based upon sputum microscopy.

Individuals without TB are not shown.

**Figure A2.** Treatment algorithm in patients diagnosed by sputum smear (in whom culture or Xpert MTB/RIF are not performed as initial screening). DS: drug susceptible; MDR: multidrug-resistant; FLD: first-line drugs; SLD: second-line drugs. DST: drug susceptible testing.

**Figure A3.** Treatment algorithm for individuals under the culture strategy. FLD or retreatment is given as dictated by TB history. Individuals without TB are not shown, though they incur costs and toxicities of TB treatment if they have a false positive test.

**Figure A4.** Diagnostic and treatment algorithm for patients receiving Xpert MTB/RIF.

Individuals without tuberculosis are not shown here.

**Figure A5.** Life expectancy and costs according to diagnostic strategy. The dotted line indicates the ‘efficiency frontier’, connecting all non-dominated strategies. Open shapes indicate screening strategies among symptomatic patients only; filled shapes indicate screening strategies among all patients. Strategies that fall below the dotted line are considered dominated (see Methods for details).

**Figure A6.** Preferred strategy, comparing Xpert-2-all and a theoretical diagnostic with greater sensitivity at additional cost, at a willingness-to-pay of \$7,100/YLS. For combinations of

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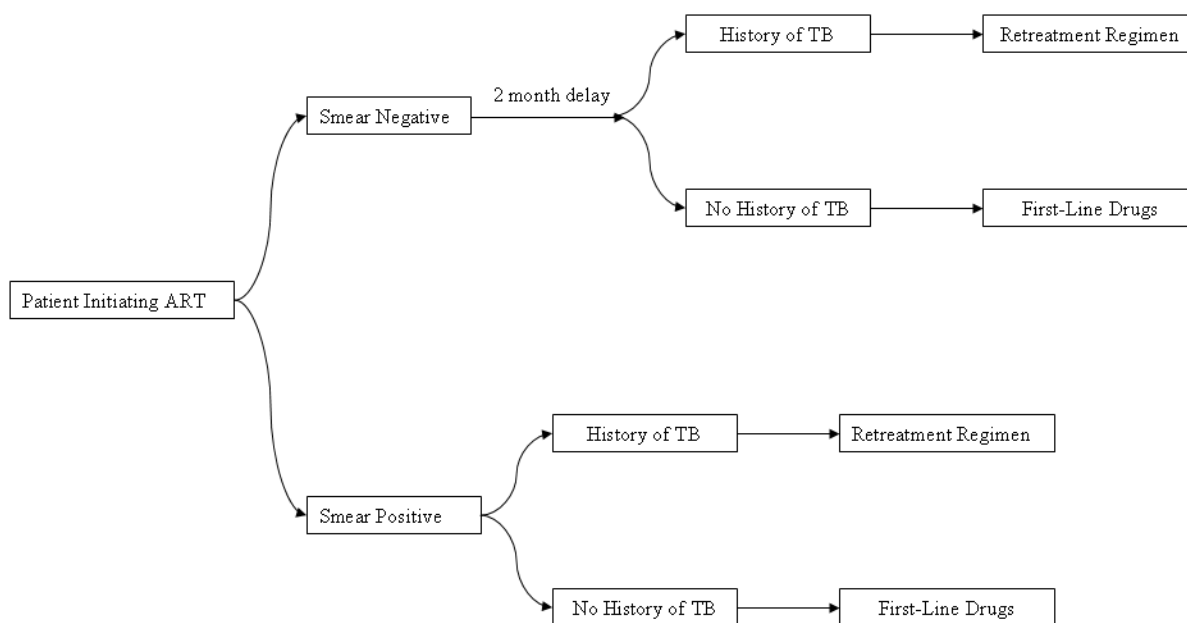
sensitivity and cost falling below the diagonal line, the theoretical diagnostic was very cost-effective.

**Figure A7.** One-way sensitivity analysis of mortality rate of untreated TB on incremental cost-effectiveness ratio of Xpert-2-All. The horizontal line indicates the very cost-effective threshold of \$7,100 per year of life saved.

**Figure A8.** Two-way sensitivity analysis of TB prevalence and sensitivity of smear microscopy on optimal strategy at a willingness to pay threshold of \$7,100 per year of life saved. At very low TB prevalence, smear is preferred, and as the sensitivity of smear microscopy increases, it is increasingly favored. Above a TB prevalence of 6%, Xpert-2-All is preferred to smear.

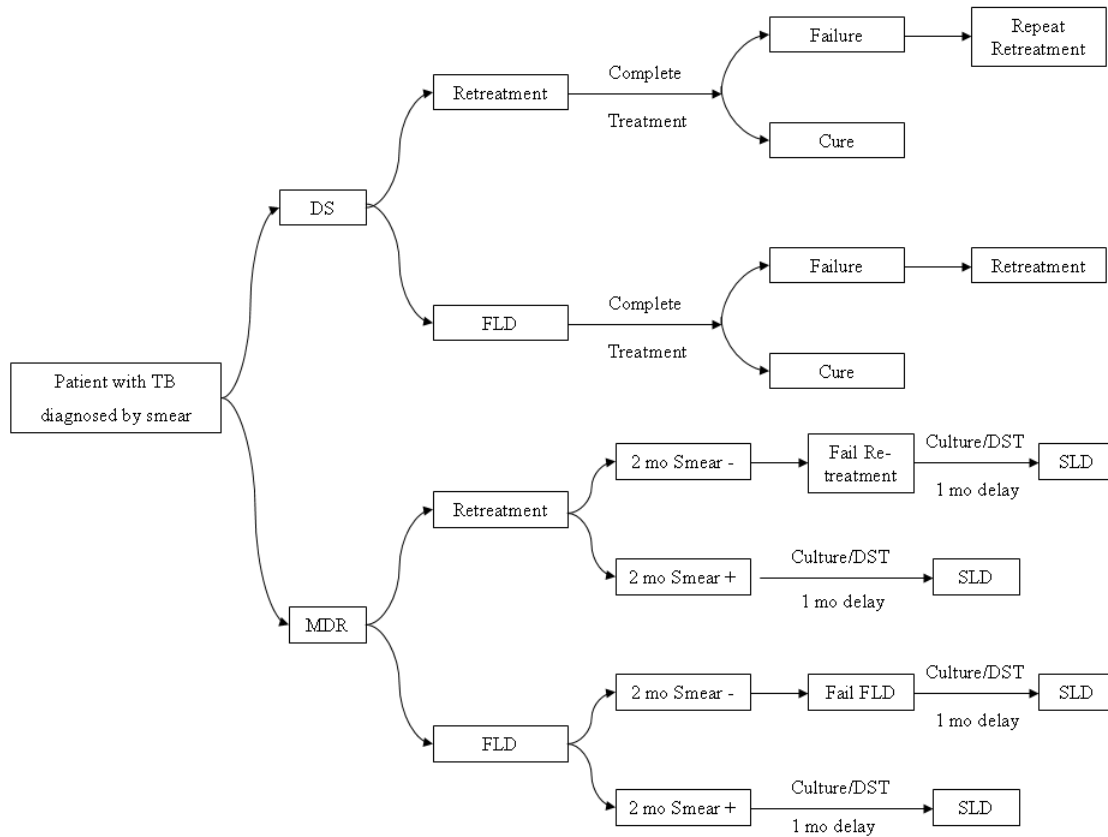
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Figure A1.



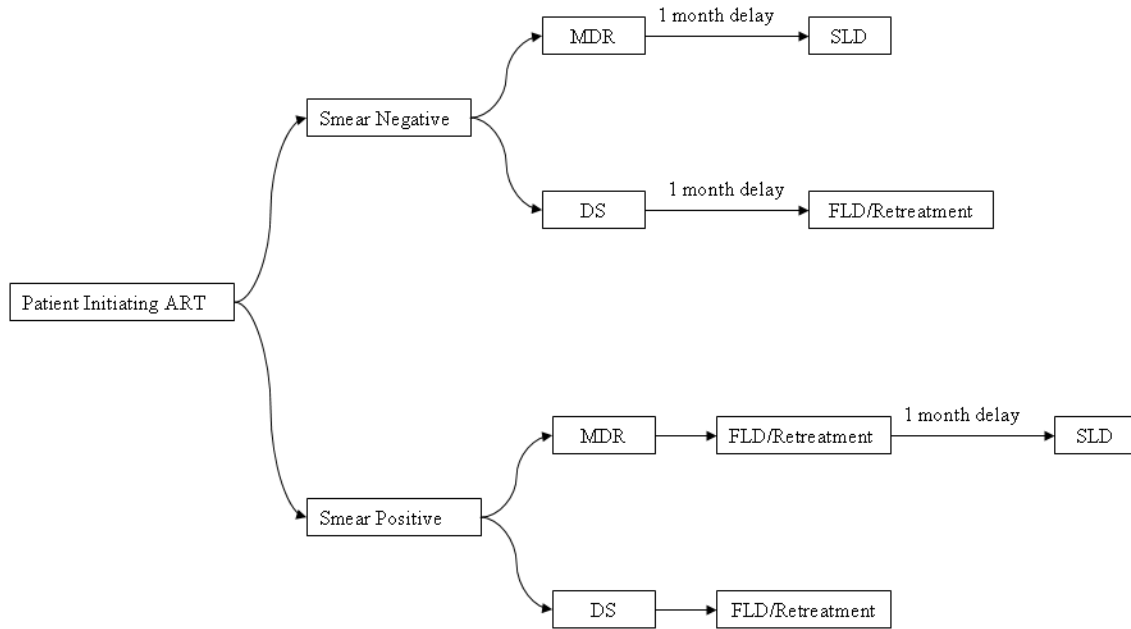
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Figure A2.



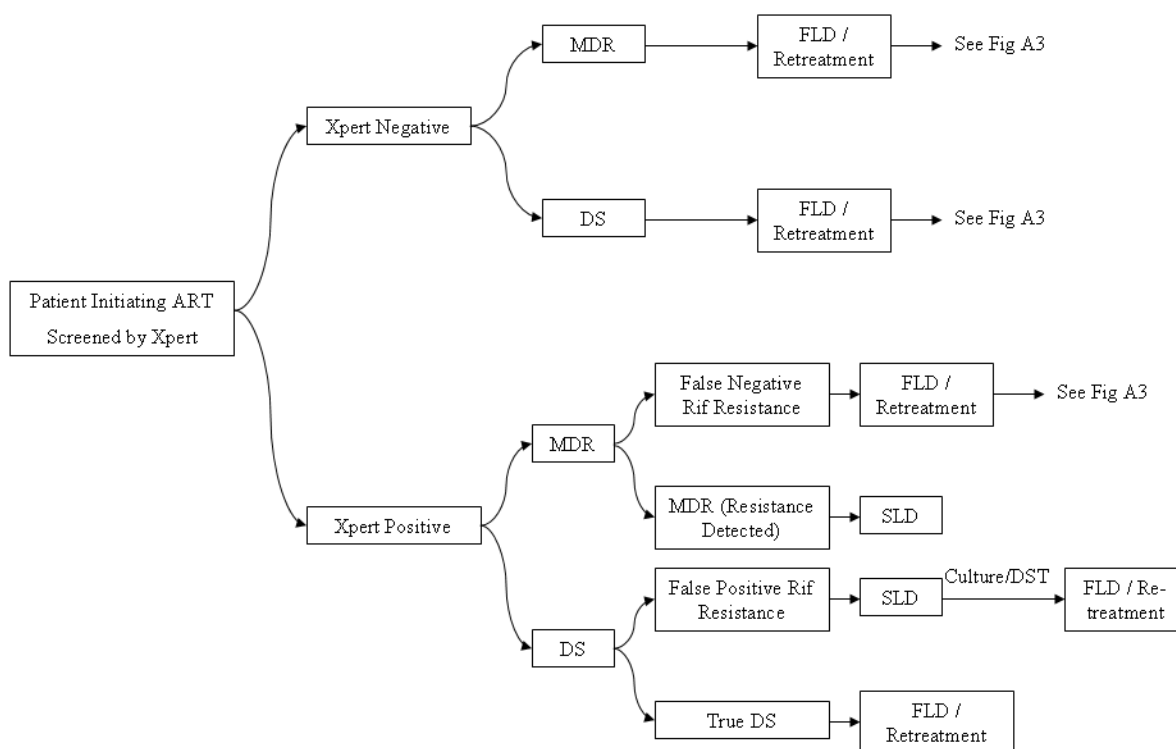
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Figure A3.



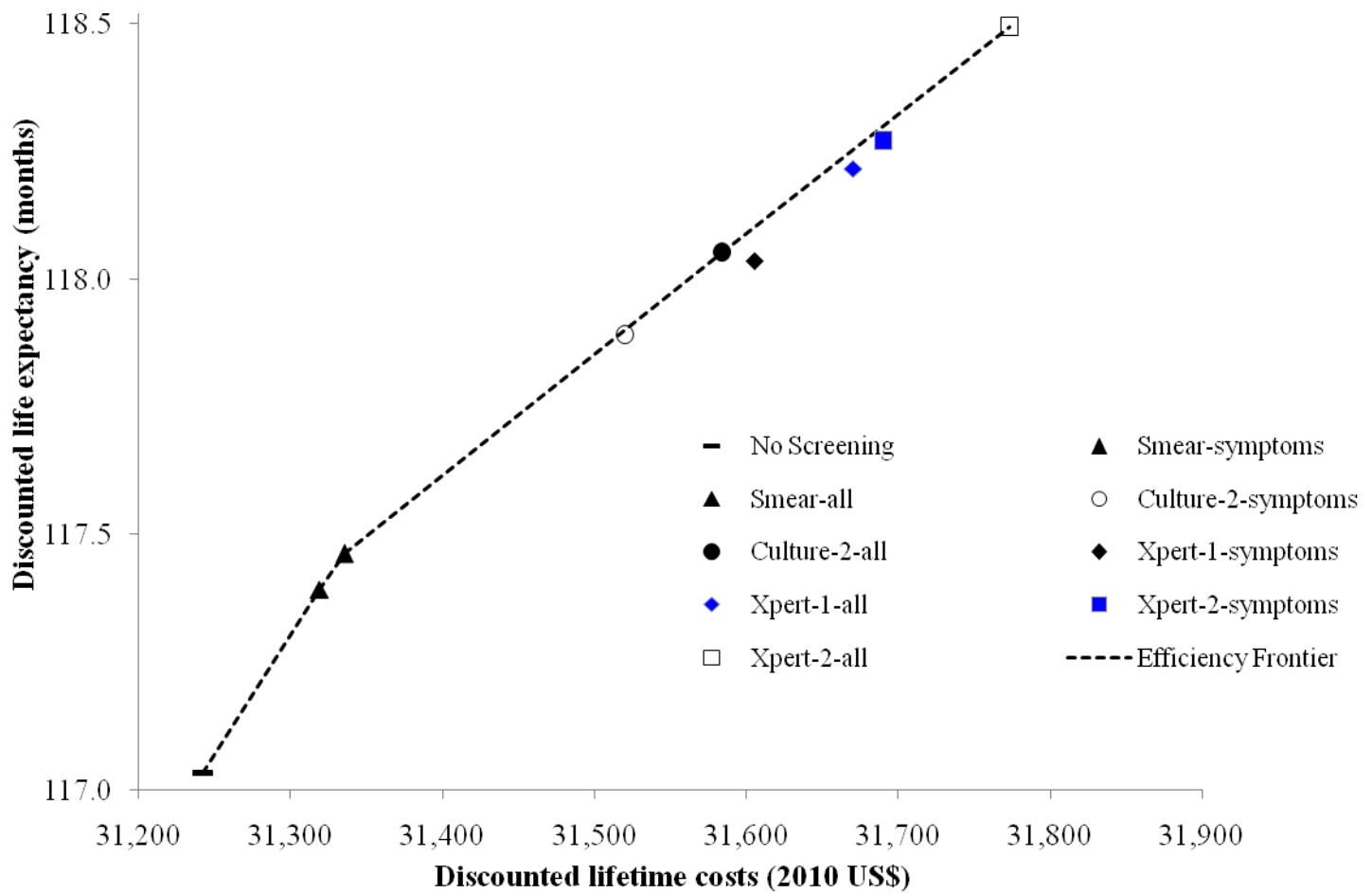
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Figure A4.



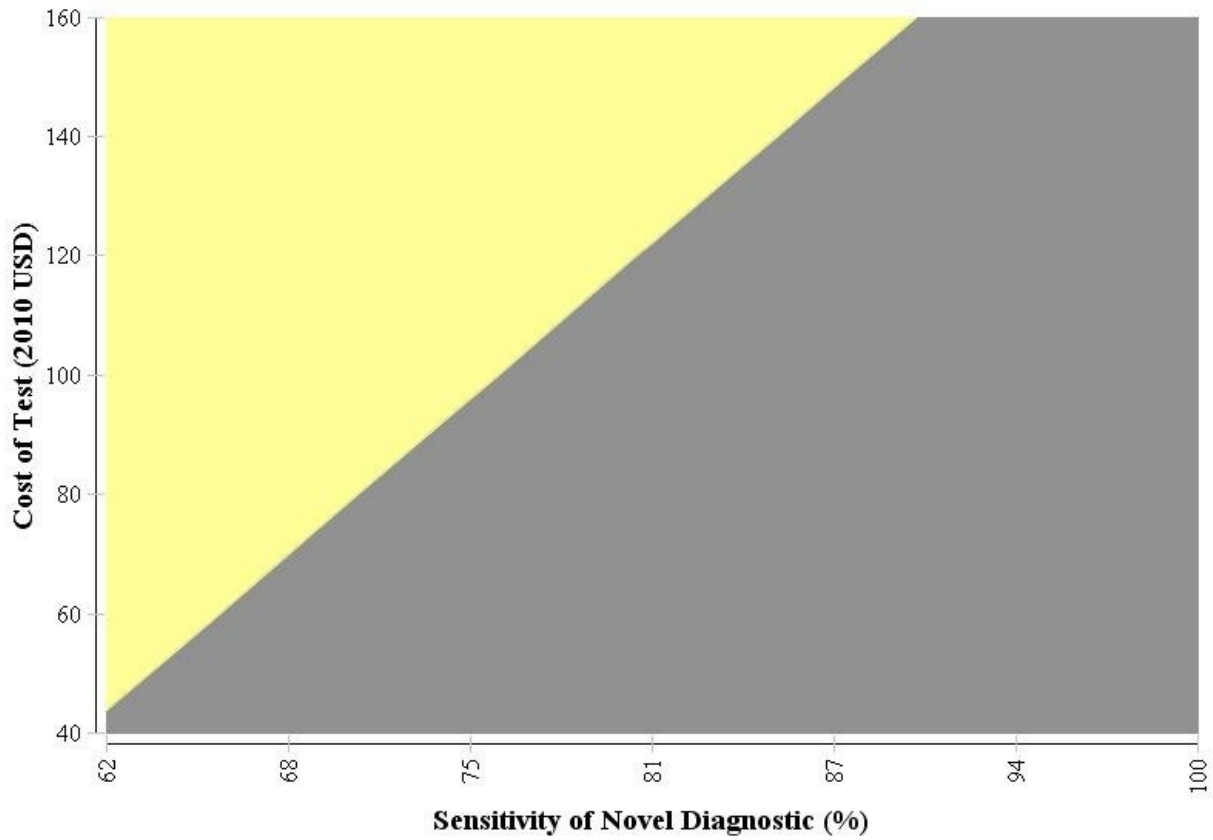
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Figure A5.



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Figure A6





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Figure A7.

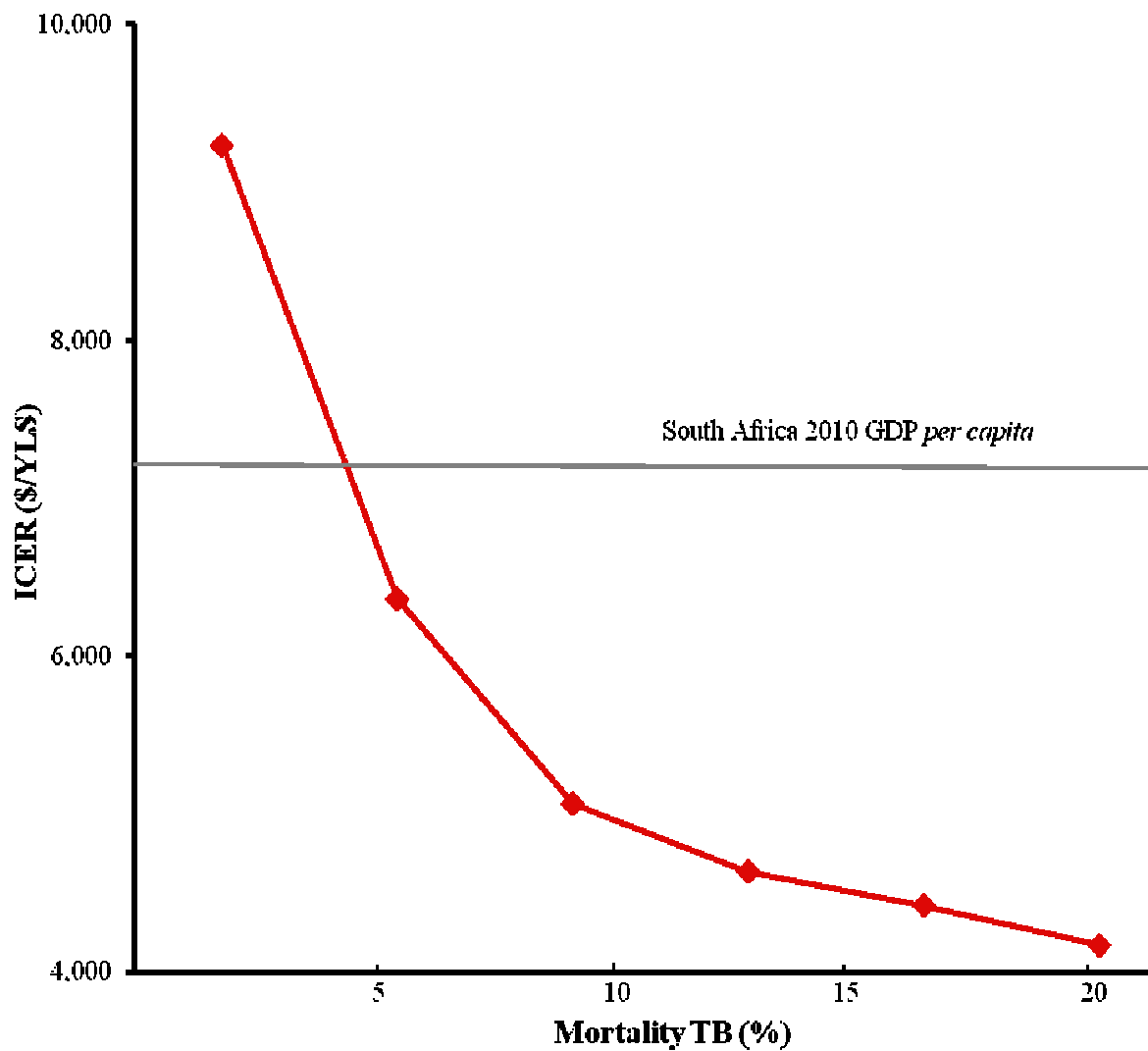
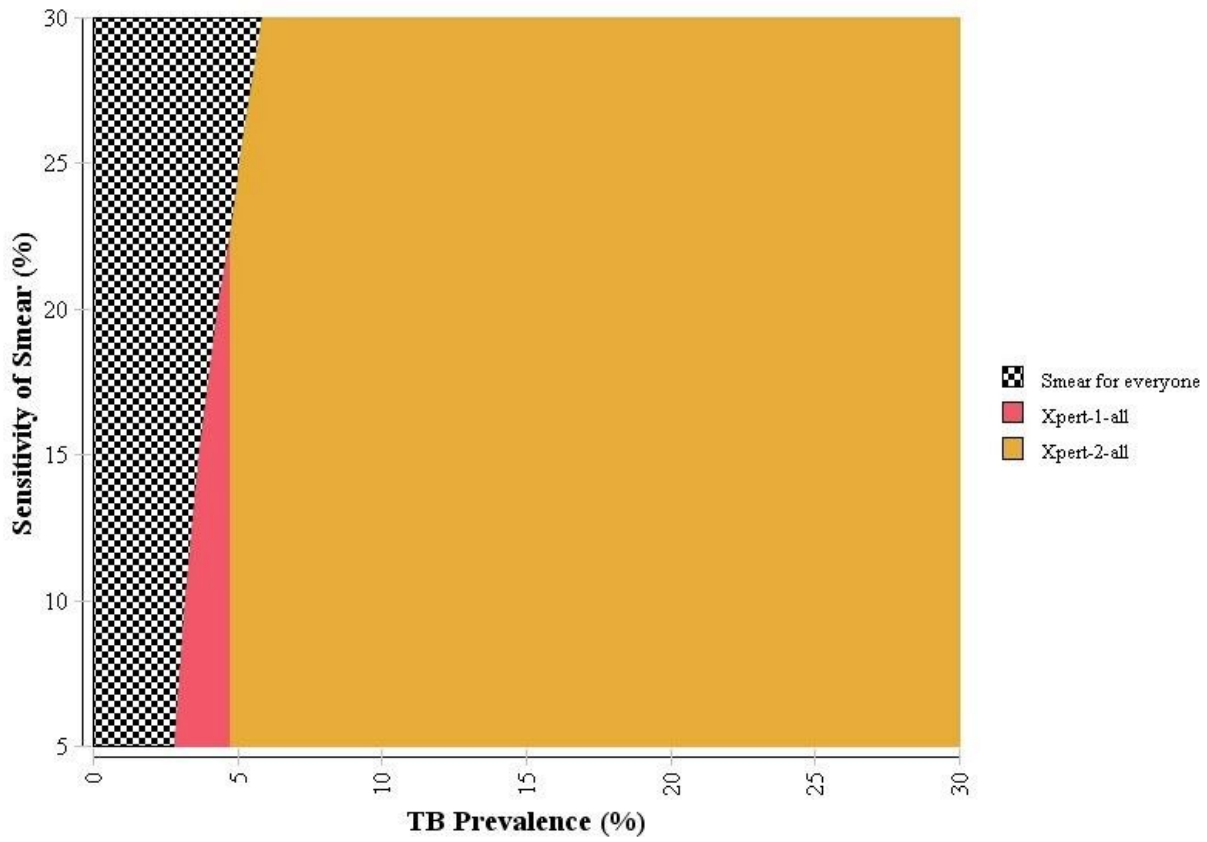


Figure A8.



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