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Cost-effectiveness of the *Three I's for HIV/TB* and ART to prevent TB among people living with HIV

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SUMMARY

OBJECTIVE—To evaluate the cost-effectiveness of *the Three I's for HW/TB* (human immunodeficiency virus/tuberculosis): antiretroviral therapy (ART), intensified TB case finding (ICF), isoniazid preventive treatment (IPT), and TB infection control (IC).

METHODS—Using a 3-year decision-analytic model, we estimated the cost-effectiveness of a base scenario (55% ART coverage at CD4 count ≤350 cells/mm^3) and 19 strategies that included one or more of the following: 1) 90% ART coverage, 2) IC and 3) ICF using four-symptom screening and 6- or 36-month IPT. The TB diagnostic algorithm included 1) sputum smear microscopy with chest X-ray, and 2) Xpert® MTB/RIF.

RESULTS—In resource-constrained settings with a high burden of HIV and TB, the most cost-effective strategies under both diagnostic algorithms included 1) 55% ART coverage and IC, 2) 55% ART coverage, IC and 36-month IPT, and 3) expanded ART at 90% coverage with IC and 36-month IPT. The latter averted more TB cases than other scenarios with increased ART coverage, IC, 6-month IPT and/or IPT for tuberculin skin test positive individuals. The cost-effectiveness results did not change significantly under the sensitivity analyses.

CONCLUSION—Expanded ART to 90% coverage, IC and a 36-month IPT strategy averted most TB cases and is among the cost-effective strategies.

RESUME

Nous évaluons le rapport coût-efficacité de l'approche des « 3 *I* » dans la lutte contre le virus de l'immunodéficience humaine (VIH) et la TB : traitement antirétroviral (ART) et intensification de la recherche de cas de TB (ICF), traitement préventif par isoniazide (IPT) et lutte contre l'infection tuberculeuse (IC).

Nous avons estimé, grâce à un modèle de décision analytique de 3 ans, le rapport coût-efficacité d'un scénario de base (55% de couverture du traitement ART quand la numération des CD4 est

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≤350 cellules/mm^3) et 19 stratégies qui incluaient une ou plusieurs des stratégies suivantes : 1) 90% de couverture par ART, 2) IC et 3) ICF grâce à un dépistage basé sur quatre symptômes et un IPT pendant 6 ou 36 mois. L'algorithme de diagnostic de la TB incluait 1) microscopie des frottis de crachats et radio pulmonaire et 2) Xpert® MTB/RIF.

Dans les contextes ressources limitées confrontés à un lourd fardeau de VIH et de TB, les stratégies les plus rentables en termes d'algorithmes de diagnostic incluaient 1) 55% de couverture par ART et IC; 2) 55 % de couverture par ART, IC et 36 mois d'IPT; et 3) expansion de l'ART à une couverture de 90% avec IC et IPT de 36 mois. Cette dernière stratégie a évité davantage de cas de TB que les autres scénarios avec augmentation de la couverture par ART, IC, 6 mois d'IPT et/ou IPT pour les cas positifs au test cutané tuberculinique. Les résultats en termes de coût-efficacité n'ont pas changé significativement avec les analyses de sensibilité.

La stratégie d'expansion de la couverture par ART à 90%, IC et 36 mois d'IPT a évité le plus de cas de TB et elle est parmi les stratégies les plus rentables.

RESUMEN

Se llevó a cabo una evaluación de la rentabilidad de las intervenciones de prevención de la tuberculosis (TB), el tratamiento antirretrovírico (ART) y la estrategia de las 'Tres íes' (que comporta la intensificación de la búsqueda de casos [ICF] de coinfección por el virus de la inmunodeficiencia humana [VIH] y TB, el tratamiento preventive con isoniazida [IPT] y el control de la infección [IC] tuberculosa).

Se construyó unmodelo analítico decisional destinado a evaluar en una población positiva frente al VIH durante un período de 3 años, la rentabilidad de la prevención de la TB en un contexto hipotético de base (cobertura del 55% con el ART en pacientes con recuentos de linfocitos CD4 ≤350 células/μl) y en 19 estrategias comparativas que comportaban una o varias de las siguientes condiciones: 1) una cobertura del 90% con el ART, 2) medidas de IC tuberculosa y 3) la ICF mediante un sistema de detección por cuatro síntomas y el IPT durante 6 meses o 36 meses en los casos negatives. Se compararon todas las estrategias al usar dos algoritmos diagnósticos diferentes: 1) la baciloscopia del esputo con radiografía de tórax y 2) la prueba Xpert® MTB/RIF.

En los entornos con recursos limitados y una alta carga de morbilidad por TB e infección por el VIH, las estrategias más rentables con ambos algoritmos diagnósticos fueron: 1) una cobertura del 55% con el ART y las medidas de IC tuberculosa; 2) una cobertura del 55% con el ART y 36 meses de IPT; y 3) la ampliación de la cobertura con el ART al 90%, con medidas de IC tuberculosa y 36 meses de IPT. Esta última estrategia evitó más casos de TB que otras dos hipótesis con ampliación de la cobertura a 90%, IC y 6 meses de IPT o con tratamiento preventive en los casos de reacción tuberculínica positiva. Los resultados de rentabilidad no se modificaron de manera significativa en los análisis de sensibilidad.

La estrategia que comporta la ampliación de la cobertura con el ART a 90%, las medidas de IC tuberculosa y el IPT durante 36 meses evitó el mayor número de casos de TB y es rentable.

Keywords

isoniazid; Xpert®; MTB/RIF; intensified TB case finding; economic analysis

The human immunodeficiency virus (HIV) infection and tuberculosis (TB) epidemics are major threats to global public health. About one third of the 35.3 million people living with HIV are latently infected with *Mycobacterium tuberculosis*, and are more likely to develop active TB disease than people who are not infected with HIV[1,2] The World Health Organization (WHO) recommends the *Three I's for HIV/TB* and early initiation of antiretroviral therapy (ART) to reduce the burden of TB in HIV-positive people.[3] They include 1) intensified TB case finding (ICF), 2) TB prevention with isoniazid preventive treatment (IPT) and early ART, and 3) TB infection control (IC) in health care facilities and congregate settings.

A recent systematic review confirmed that ART reduces the risk of developing TB by 65% across all CD4 count strata.[4] The expansion of ART coverage also reduces TB incidence at the community and population levels in settings with a large burden of HIV-associated TB.[5,6] The 2010 WHO ART guidelines recommend ART initiation at CD4 count ≤350 cells/mm^3 for all asymptomatic people living with HIV, and irrespective of CD4 cell count for those with active TB.[7] More recently, the WHO recognised the benefits of earlier treatment and recommended ART at CD4 count ≤500 cells/mm^3 and irrespective of CD4 count for serodiscordant couples, pregnant women, children aged <5 years and persons with TB or hepatitis B.[8] The 2011 WHO ICF/IPT guidelines recommend four-symptom screening (current cough, fever, weight loss or night sweats) to identify HIV-infected persons eligible for either IPT or further diagnostic work-up for TB and other conditions.[9] The tuberculin skin test (TST) is not a requirement for the administration of IPT, but may be used where feasible.[9] The 2009 WHO policy on IC proposes managerial, administrative and environmental controls and personal protection measures in health facilities to reduce the risk of nosocomial TB transmission.[10]

Most countries currently recommend and implement different TB prevention strategies to reduce morbidity and mortality among people living with HIV This study evaluates the cost-effectiveness of different TB prevention strategies in a setting with a generalised HIV epidemic and high TB burden among people living with HIV to determine the optimal mix of interventions that will maximise health benefits with the given resources.

METHODS

We developed a decision-analytic model (Appendix Figure A.1)* to estimate the cost-effectiveness of TB prevention strategies in a hypothetical cohort of 10 000 HIV-positive people with a prevalence of active TB of 5%. TB prevention interventions were provided at time zero, and the cohort was followed up for a period of 3 years. Ethical approval was not required for the study. The model for Year 1 was constructed using TreeAge 2012 (TreeAge Software, Inc, Williamstown, MA, USA). TB cases among people living with HIV and costs in subsequent years were calculated using Microsoft Excel 2011 (Microsoft, Redmond, WA, USA).

*The Appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2014/00000018/00000010/art00006.

The base scenario was defined as one with ART coverage at the 2011 global ART coverage rate of 55% (at CD4 count ≤350 cells/mm^3).[11] The TB symptom considered for screening was current cough. The 19 comparative strategies included one or more of the following TB prevention interventions: 1) ART coverage increased to 90% at CD4 count ≤350 cells/mm^3; 2) IC measures in health care facilities, which included administrative measures such as triage, personal protective measures such as respirators for nurses and surgical masks for patients with cough and natural ventilation through construction and maintenance of fans and windows; and 3) ICF using a four-symptom screening algorithm and 6-month or 36-month IPT (life-long IPT) for those screening negative (Table 1). The costs and number of TB cases were calculated for all strategies under two separate TB diagnostic algorithms: 1) sputum smear microscopy with chest X-ray (CXR); and 2) Xpert® MTB/RIF assay for diagnosis of *Mycobacterium tuberculosis* and resistance to rifampicin (Cepheid, Sunnyvale, CA, USA).

Model parameters and assumptions

The parameter values for TB prevalence, TB incidence, sensitivity and specificity of TB screening and diagnostic tests and the efficacy of the TB prevention interventions were derived from the published literature (Table 2).[11–24] Outcomes and costs related to drug-resistant TB were not considered in the analysis.

We chose a 3-year analytic horizon to be able to compare the preventive effect of long-term IPT use (i.e., 36 months) against the use of short-term IPT (i.e., 6 months). We assumed that the 6 months of IPT would be effective for a period of 1 year. We assumed that the effectiveness of the IC package was similar to that of a study investigating the effects of IC measures in the epidemic trajectory of a setting with high TB-HIV co-infection.[12]

Costs

The analysis took a health system perspective and considered health care utilisation costs from South Africa (Table 3).[9,25–30] Development and maintenance costs of diagnostic capacity, productivity loss and out-of-pocket costs incurred by individuals to seek care were not included. Costs for TB diagnostic tests and drugs were derived from published studies; in-patient and out-patient costs came from WHO-CHOICE (CHOosing Interventions that are Cost Effective).[28] Cost data for IC interventions were taken from a primary health care facility in South Africa, and building cost indices from the Bureau of Economic Research, Stellenbosch University, Cape Town, South Africa.

Using the South African consumer price index for medical goods and services from 2006 to 2012 (Statistics South Africa, South Africa Consumer Price Index, Pretoria, South Africa, http://www.statssa.gov.za), all the costs were converted into 2010 USD and adjusted for inflation for 2011 and 2012.

Cost-effectiveness analysis

The primary outcome of the analysis was cases of TB averted, calculated as the difference between the number of TB cases under two different strategies. The incremental cost-effectiveness ratio (ICER) was calculated as the ratio of the difference between total costs

under alternative TB prevention strategies to the TB cases averted. This ratio was expressed in terms of US dollars spent in health care costs per TB case averted. Strategies that prevented fewer TB cases and at greater cost compared to other strategies (i.e., strongly dominated), and strategies with higher ICER than the next most effective alternative (i.e., weakly dominated) were excluded from the incremental analysis.

Sensitivity analysis

For strategies under the two TB diagnostic algorithms, univariate sensitivity analyses were performed using TreeAge for Year 1 using calculations of net monetary benefit. For different willingness-to-pay (WTP) thresholds, we generated tornado diagrams for all parameters except for those that were common across all policy alternatives. The ranges for relative risk (RR) of TB from different interventions, and the sensitivity and specificity of TB screening and diagnostic tests came from the published literature. Cost inputs were varied by 50–200% of their base values. We considered two WTP thresholds: 1) US$1000 (approximate cost of diagnosis and treatment of active TB) and 2) US$35 000 (equivalent to highest ICER value generated when only TB prevention benefits of ART are taken into account). We further conducted threshold analysis for parameters with the greatest influence on outcomes to determine the value at which other alternatives become more effective. We also conducted Monte Carlo simulation probabilistic sensitivity analysis (PSA) and compared the two most comprehensive strategies: ‘ART IC ICF IPT 36′ and ‘ARTexp IC ICF IPT 36′ (Appendix Figure A.2).

RESULTS

TB diagnostic algorithm: sputum smear and chest radiography

Considering sputum smear and CXR as the diagnostic tool for TB, the ‘base scenario’ cost US$3.4M and resulted in 1289 TB cases per 10 000 HIV-positive people. The most cost-effective strategies included 1) 55% ART coverage and IC (‘ART IC’), 2) 55% ART coverage, IC and 36-month IPT (‘ART IC ICF IPT 36’) and 3) expanded ART coverage with IC and 36-month IPT (‘ARTexp IC ICF IPT 36’) (Appendix Figure A.3). Adding IC averted 99 TB cases at an additional cost of US$34 000 (ICER = US$342). Compared to the ‘ART IC ICF IPT 36′ scenario, the ‘ARTexp IC ICF IPT 36′ scenario averted 47 TB cases and cost an additional US$1.5M. This resulted in an ICER of US$31 463 (Appendix Table A.1). The ICER would likely be far less if it took into account the other benefits of ART beyond TB prevention.

Strategies with ICF using four-symptom screening and IPT for 6 or 36 months were weakly dominated when compared with corresponding strategies with IC, which prevented additional TB cases at a small net cost. Increasing the duration of IPT from 6 to 36 months prevented a substantial number of TB cases, such that the strategies with 6-month IPT were weakly dominated. Although TB incidence was not significantly lower in TST-negatives receiving IPT, strategies with IPT for all people living with HIV dominated the strategies that provided IPT to TST-positive people living with HIV.

TB diagnostic algorithm: Xpert MTB/RIF

The results remained consistent with Xpert as the TB diagnostic tool. The base scenario cost US$3.3M, and resulted in 1308 TB cases per 10 000 HIV-positive people (Appendix Figure A.4). The ‘ART IC’ scenario averted 101 TB cases at an additional cost of US$33 900 (ICER = US$336). The ‘ARTexp IC ICF IPT 36’ scenario prevented 51 additional TB cases over the ‘ART IC ICF IPT 36’ scenario at an incremental cost of US$1.5M, resulting in an ICER of US$28 936 (Appendix Table A.1). This ICER would likely be markedly lower if we consider the benefits of ART beyond TB prevention.

Sensitivity analysis

For both the diagnostic algorithms, six parameters accounted for variations in cost-effectiveness results at a WTP threshold of US$1000: ART coverage, sensitivity and specificity of TB screening with cough, the RR of TB from ART and from IC, and cost of IC. At the higher WTP threshold of US$35 000; the RR of TB from 1) continuous IPT vs. 6-month IPT, 2) 6-month IPT for TST-negative and 3) IC, and cost of 36-month IPT were responsible for maximum variation in the ICERs (Appendix Figures A.5 and A.6). Threshold analyses showed that for an RR of TB from IC of >0.985 (at WTP threshold of US$1000) and 0.994 (at WTP threshold of US$35 000), the alternatives without IC would be cost-effective compared to the corresponding scenarios with IC. At a high WTP for a TB case averted (US$35 000), PSA revealed that the ‘ARTexp IC ICF IPT 36′ strategy would be preferred to the ‘ART IC ICF IPT 36’ scenario 13% of the time (Appendix Figure A.2). However, the probability of choosing the expanded ART strategy would likely be much higher if we include benefits beyond preventing TB.

DISCUSSION

Effective anti-tuberculosis treatment remains a key strategy to reduce TB incidence, but this approach is unlikely to contain the rise in incidence resulting from HIV. In high HIV burden settings, the health systems need to be strengthened to provide the *Three I’s for HIV/TB*, including early ART for people living with HIV. We calculated the cost-effectiveness of these WHO-recommended TB prevention strategies using a decision-analytic model.

This is the first study to estimate the costs and benefits of the *Three I’s for HIV/TB* including ART together under different WHO-recommended TB diagnostic algorithms. Our findings suggest that in resource-constrained settings with a high burden of HIV and TB, a complete TB prevention package with 90% ART coverage at CD4 ≤350 cells/mm^3, IC interventions and IPT for 36 months averted more TB cases than other scenarios with increased ART coverage, IC, 6-month IPT and/or IPT for TST-positives. This scenario, along with the ‘ART IC and ‘ART IC ICF IPT 36’ scenarios, was among the most cost-effective strategies.

The health care utilisation costs from South Africa may be higher than in other countries. Our results were therefore probably an overestimation of the true cost of TB diagnosis and treatment in many TB-HIV-endemic countries. While the portability of health care costs may restrict the interpretation of the costs and cost-effectiveness ratios to countries with higher

costs, it does not change our conclusions about the effectiveness of the interventions evaluated in this study.

The figures for scenarios involving ART at 90% coverage need to be interpreted with caution, as we did not consider the impact of expanded access to ART on other HIV-related illnesses. Studies from similar settings have shown that increasing the provision of ART is highly cost-effective or cost saving for reducing the HIV- and TB-related burden (e.g., ICERs of US$530–590 per life-year saved in India and South Africa).[31,32] Thus, the scenario with 90% ART coverage, IC and 36-month IPT will likely be more cost-effective when prevention benefits of ART beyond TB are considered. We also did not explore the potential impact of using the WHO 2013 guidelines or the initiation of ART regardless of CD4 count on TB incidence. We assumed the ART eligibility criteria to be CD4 count ≤350 cells/mm^3, as recommended by the 2013 ART guidelines from South Africa. As ART prevents TB across all CD4 cell counts,[4] it is likely that the scenarios with ART at CD4 count ≤500 cell/mm^3 or regardless of CD4 count along with the *Three I's for HIV/TB* will be cost-effective. In addition, we did not consider the effects of expanded ART coverage on the prevention of HIV transmission to sexual partners and children, which could have a considerable impact on the TB burden.[33]

The effect of IC measures on nosocomial transmission of TB and the costs of these interventions are not well documented, and the assumption that a TB prevention package with respirators, surgical masks and natural ventilation will cost US$3.4 per person is an estimate. We kept our model simple by assuming that TB prevention interventions are independent of one another. We did not model long-term TB or HIV transmission dynamics, and estimated the costs and benefits of one-time TB screening over a period of 3 years. We did not consider the potential impact of Xpert on TB incidence by reducing the time between detection and initiation of appropriate treatment for TB.

Our study highlights the importance of the *Three I's for HIV/TB*, including expanded ART coverage to address TB, in communities with high HIV and TB prevalence. The availability of these interventions has significantly improved in sub-Saharan Africa. In 2012, according to the WHO 2010 guidelines, ART coverage was >80% in six countries.[2] An estimated 2.3 million people were screened for TB, a two-fold increase from 860 000 in 2009. IPT was initiated among 470 000 people newly registered in HIV care in 2012, compared to <50 000 people in 2009.[1]

However, despite this remarkable progress, the vast majority of people who could benefit from these interventions do not have access. Likewise, IC for TB is often not a priority for many HIV and TB programmes. Expanding access to HIV treatment remains a priority, as coverage of the 28.6 million people eligible for ART (per the WHO 2013 guidelines) is less than 40%. Our study highlighted the potential cost-effectiveness of the *Three Is for HIV/TB*, including early ART, in preventing TB from a health sector perspective. However, it is likely to be even more cost-effective to prevent both TB and HIV with these interventions if we take the significant societal and individual costs of these diseases into consideration. In addition to the health benefits for the individual and the community, national TB and HIV/AIDS (acquired immune-deficiency syndrome) programmes may benefit from considering

the economic implications of TB prevention as they develop an integrated approach to ensuring people living with HIV have access to high-quality HIV and TB prevention, care and treatment services.

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APPENDIX

Appendix Table A.1

Costs, outcomes and ICERs (in USD spent in health care costs/TB case averted)

A) TB diagnostic algorithm: sputum smear and chest radiography

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base *	1289	3 434 704			
ART IC *	1190	3 468 604	99	33 900	342
ARTexp	1180	4 941 979	10	1 473 375	147 338
ART ICF IPT 6 *	1168	4 502 542	12	−439437	(36 620)
ARTexp IC	1094	4 975 879	74	473 337	6 396
ART IC ICF IPT 6*	1084	4 485 802	10	−490 077	(49 008)
ARTexp ICF IPT 6	1076	5 954 018	8	1 468 216	183 527
ARTexp IC ICF IPT 6	1002	5 943 379	74	−10 639	(144)
ART ICF TST IPT 36 *	988	4 739 030	14	−1 204 349	(86 025)
ART ICF IPT 6 TST IPT 36	974	4 874 713	14	135 683	9 692
ART IC ICF TST IPT 36*	926	4 743 516	48	−131 197	(2 733)
ARTexp ICF TST IPT 36	919	6 212 020	7	1 468 504	209 786
ART IC ICF IPT 6 TST IPT 36 *	915	4 872 908	4	−1339 112	(334 778)
ARTexp ICF IPT 6 TST IPT 36	908	6 341 615	7	1 468 707	209815
ART ICF IPT 36*	888	5 097 662	20	−1 243 953	(62 198)
ARTexp IC ICF TST IPT 36	865	6 220 368	23	1 122 706	48813
ARTexp IC ICF IPT 6 TST IPT 36	856	6 344 626	9	124 258	13 806
ART IC ICF IPT 36*	838	5 101 438	18	−1243 188	(69 066)
ARTexp ICF IPT 36	833	6 571 933	**m**	1 470 495	294099
ARTexp IC ICF IPT 36*	791	6 580182	42	8 249	196

Ai) After removing the dominated strategies from incremental analysis:

A) TB diagnostic algorithm: sputum smear and chest radiography

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base *	1289	3 434 704			
ART IC *	1190	3 468 604	99	33 900	342
ART ICF IPT 6	1168	4 502 542	22	1 033 938	46 997
ART IC ICF IPT 6 *	1084	4485 802	84	−16 740	(199)
ART ICF TST IPT 36	988	4 739 030	96	253 228	2 638
ART IC ICF TST IPT 36 *	926	4 743 516	62	4 486	72
ART IC ICF IPT 6 TST IPT 36	915	4 872 908	11	129 392	11 763
ART ICF IPT 36	888	5 097 662	27	224754	8 324
ART IC ICF IPT 36 *	838	5 101 438	50	3 776	76
ARTexp IC ICF IPT 36 *	791	6 580182	47	1 478 744	31 463

Aii)

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base *	1289	3 434 704			
ART IC *	1190	3 468 604	99	33 900	342
ART IC ICF IPT 6	1084	4485 802	106	1 017198	9 596
ART IC ICF TST IPT 36 *	926	4 743 516	158	257714	1 631
ART IC ICF IPT 36 *	838	5 101 438	88	357 922	4 067
ARTexp IC ICF IPT 36 *	791	6580 182	47	1 478 744	31 463

Aiii)

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base *	1289	3 434 704			
ART IC *	1190	3 468 604	99	33 900	342
ART IC ICF TST IPT 36	926	4 743 516	264	1 274912	4 829
ART IC ICF IPT 36 *	838	5 101 438	88	357 922	4 067
ARTexp IC ICF IPT 36 *	791	6 580182	47	1 478 744	31463

B) Incremental cost-effectiveness ratios for the cost-effective strategies

A) TB diagnostic algorithm: sputum smear and chest radiography

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base *	1289	3 434 704			
ART IC *	1190	3 468 604	99	33 900	342
ART IC ICF IPT 36 *	838	5 101 438	352	1 632 834	4639
ARTexp IC ICF IPT 36 *	791	6 580182	47	1 478 744	31463

C) TB diagnostic algorithm: Xpert® MTB/RIF

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base *	1308	3 315 687			
ART ICF IPT 6	1221	4 207 407	87	891 720	10250
ART IC *	1207	3 349 587	14	−857 820	(61 273)
ARTexp	1197	4 822 962	10	1 473 375	147 338
ART IC ICF IPT 6 *	1129	4185 320	68	−637 642	(9 377)
ARTexp ICF IPT 6	1120	5 652 851	9	1 467 531	163 059
ARTexp IC *	1109	4 856 862	11	−795 989	(72 363)
ARTexp IC ICF IPT 6	1042	5 639 057	67	782 195	11 675
ART ICF TST IPT 36 *	1018	4490 753	24	−1 148 304	(47 846)
ART ICF IPT 6 TST IPT 36	1004	4 626 362	14	135 609	9 686
ART IC ICF TST IPT 36 *	954	4493 283	50	−133 079	(2 662)
ARTexp ICF TST IPT 36	944	5 960 442	10	1 467 1 59	146716
ART IC ICF IPT 6 TST IPT 36 *	942	4 622 591	2	—1 337 851	(668 926)
ARTexp ICF IPT 6 TST IPT 36	935	6 091 225	7	1 468 634	209 805
ART ICF IPT 36 *	919	4 849 293	16	—1 241 932	(77621)
ARTexp IC ICF TST IPT 36	889	5 967 624	30	1 118331	37278
ARTexp IC ICF IPT 6 TST IPT 36	880	6 091 822	9	124198	13 800
ART IC ICF IPT 36 *	866	4851 163	14	—1 240 659	(88 619)
ARTexp ICF IPT 36	859	6319731	7	1 468 568	209795

A) TB diagnostic algorithm: sputum smear and chest radiography

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
ARTexp IC ICF IPT 36*	815	6 326 899	44	7 168	163

Ci) After removing the dominated strategies from incremental analysis:

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base*	1308	3 315 687			
ART IC*	1207	3 349 587	101	33 900	336
ART IC ICF IPT 6*	1129	4185 320	78	835 733	10715
ARTexp IC	1109	4 856 862	20	671 542	33 577
ART ICF TST IPT 36*	1018	4490 753	91	−366109	(4 023)
ART IC ICF TST IPT 36*	954	4493 283	64	2 530	40
ART IC ICF IPT 6 TST IPT 36	942	4 622 591	12	129308	10 776
ART ICF IPT 36	919	4 849 293	23	226702	9 857
ART IC ICF IPT 36*	866	4851 163	53	1 870	35
ARTexp IC ICF IPT 36*	815	6 326 899	51	1 475 736	28 936

Cii) TB cases Total cost Incremental cases averted Incremental costs

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base*	1308	3 315 687			
ART IC*	1207	3 349 587	101	33 900	336
ART IC ICF IPT 6	1129	4185 320	78	835 733	10715
ART ICF TST IPT 36	1018	4490 753	111	305 433	2 752
ART IC ICF TST IPT 36*	954	4493 283	64	2 530	40
ART IC ICF IPT 36*	866	4851 163	88	357 880	4 067
ARTexp IC ICF IPT 36*	815	6 326 899	51	1 475 736	28936

Ciii)

Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base*	1308	3 315 687			
ART IC*	1207	3 349 587	101	33 900	336

A) TB diagnostic algorithm: sputum smear and chest radiography

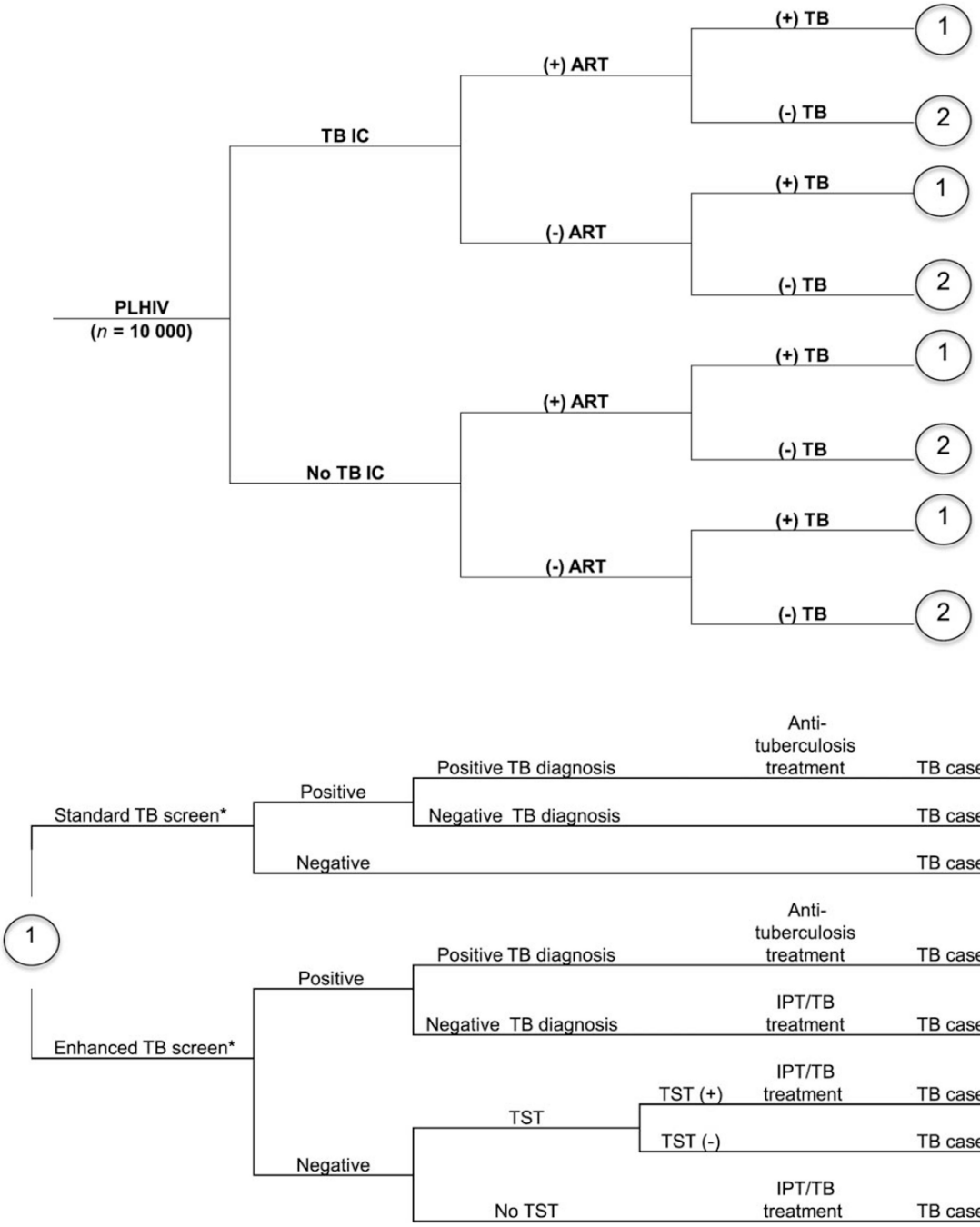
Strategy	TB cases *n*	Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
ART IC ICF TST IPT 36	954	4493 283	253	1 143 696	4 521
ART IC ICF IPT 36*	866	4851 163	88	357 880	4 067
ARTexp IC ICF IPT 36*	815	6 326 899	51	1 475 736	28936

D) Incremental cost-effectiveness ratios for the cost-effective strategies

Strategy	TB cases *n* Total cost USD	Incremental cases averted *n*	Incremental costs USD	ICER/case averted
Base*	1308 3 315 687			
ART IC*	1207 3 349 587	101	33 900	336
ART IC ICF IPT 36*	866 4851 163	341	1 501 576	4 403
ARTexp IC ICF IPT 36*	815 6 326 899	51	1 475 736	28936

*Non-dominated strategies (defined in the main paper)

ICER = incremental cost-effectiveness ratio; USD = US dollars; TB = tuberculosis; ART =antiretroviral therapy; IC = infection control; ARTexp = expanded ART (90% coverage); IPT = isoniazid preventive therapy; ICF = intensified TB case finding; TST = tuberculin skin test.



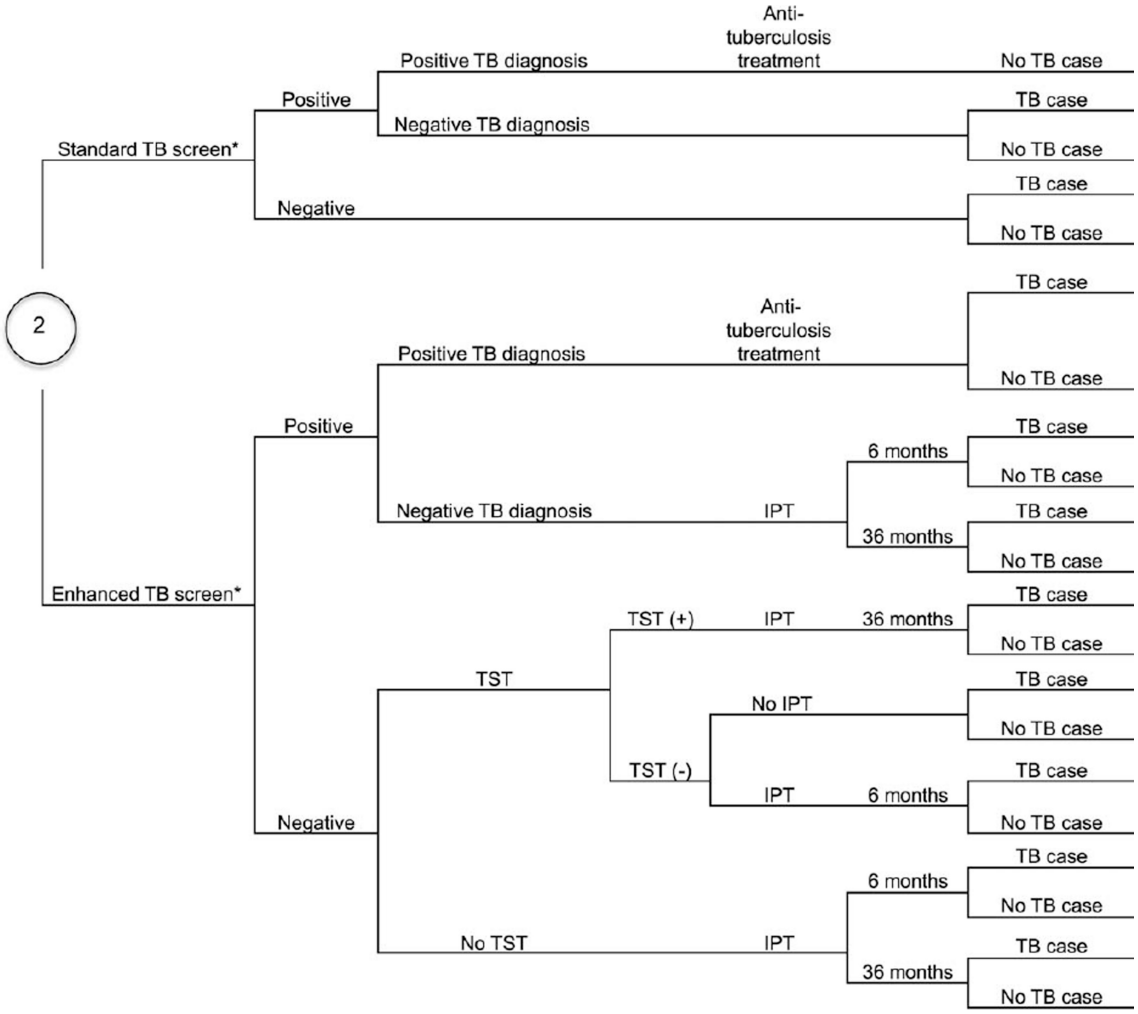


Figure A.1.

Decision tree. TB was diagnosed using sputum smear and chest radiography or Xpert® MTB/RIF. * Standard TB screening is using cough; enhanced TB screening refers to the WHO-recommended four-symptom screening algorithm. PLHIV = people living with HIV; TB = tuberculosis; IC = infection control;+= positive;-= negative; ART=antiretroviral therapy; TST = tuberculin skin test; IPT = isoniazid preventive therapy; WHO = World Health Organization.

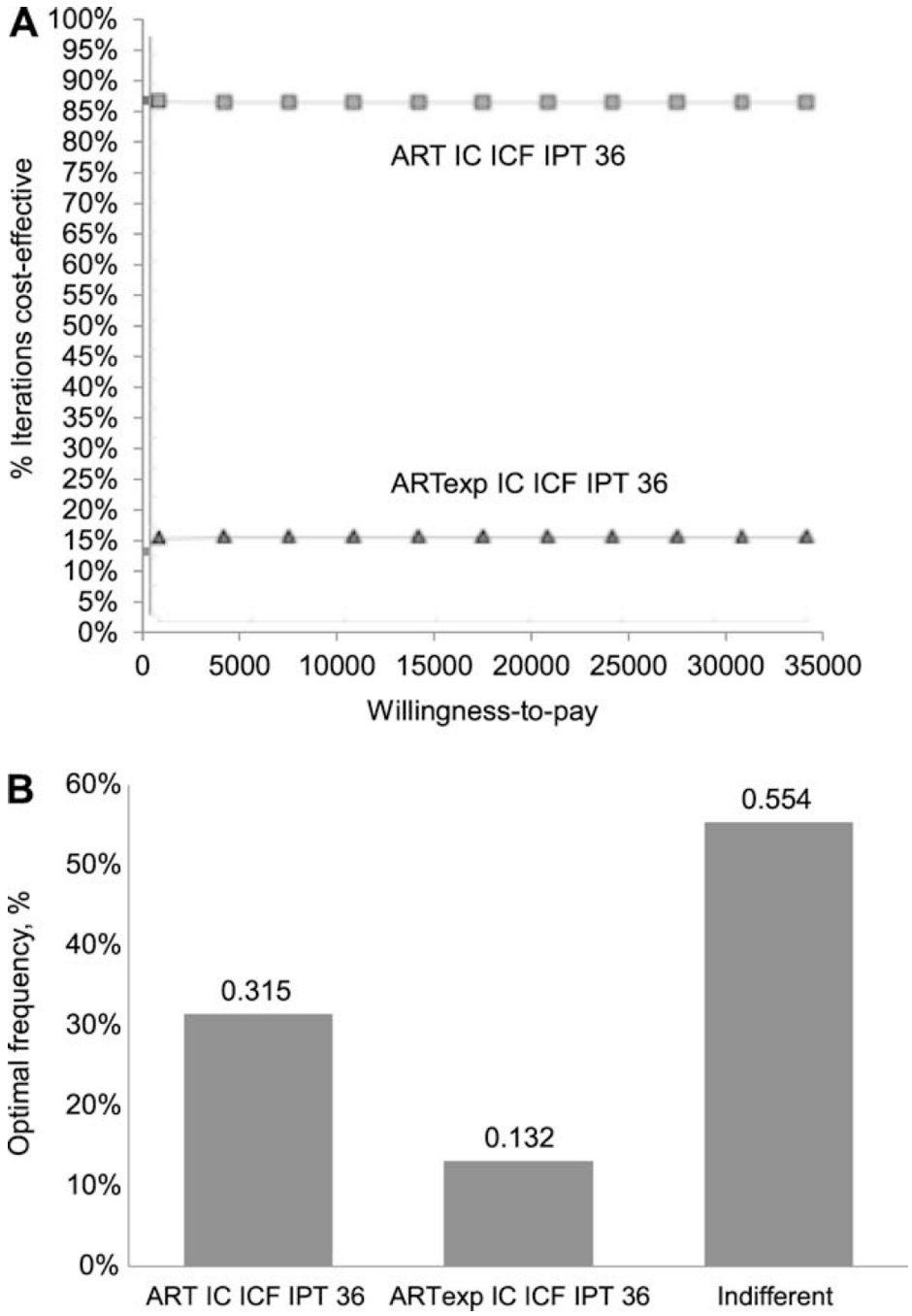


Figure A.2.

Probabilistic sensitivity analysis. **A)** Cost-effectiveness acceptability curve; **B)** strategy selection (willingness-to-pay/TB case averted = USD35 000). We ran 10 000 iterations of the model for Year 1 using Monte Carlo simulation probabilistic sensitivity analysis and compared the two most comprehensive strategies that were also among the cost-effective strategies (ART IC ICF IPT 36 and ARTexp IC ICF IPT 36, Xpert TB diagnostic algorithm). We set distribution for only those variables found to be influential in the oneway sensitivity analysis under the two willingness-to-pay thresholds of USD1000 and 35 000 (ART

coverage, relative risk of TB from ART and from IC, cost of IC interventions and cost of IPT). The result of the probabilistic sensitivity analysis using the willingness-to-pay threshold of USD35 000 indicated that we will choose the ART IC ICF IPT 36 strategy 32% of the time and we will be indifferent between both the strategies 55% of the time. We will choose the ARTexp IC ICF IPT 36 strategy 13% of the time. Note that strategy selection is based on costs and outcomes of the scenarios in Year 1. The probability of choosing ARTexp IC ICF IPT 36 strategy is likely to be higher over a 3-year period. Furthermore, the probability of choosing the expanded ART strategy would likely be much higher if we include benefits of ART beyond the prevention of TB. ART=antiretroviral therapy; IC = infection control; ICF = intensified case finding; PT = isoniazid preventive therapy; ARTexp = expanded ART (90% coverage); USD = US dollars.

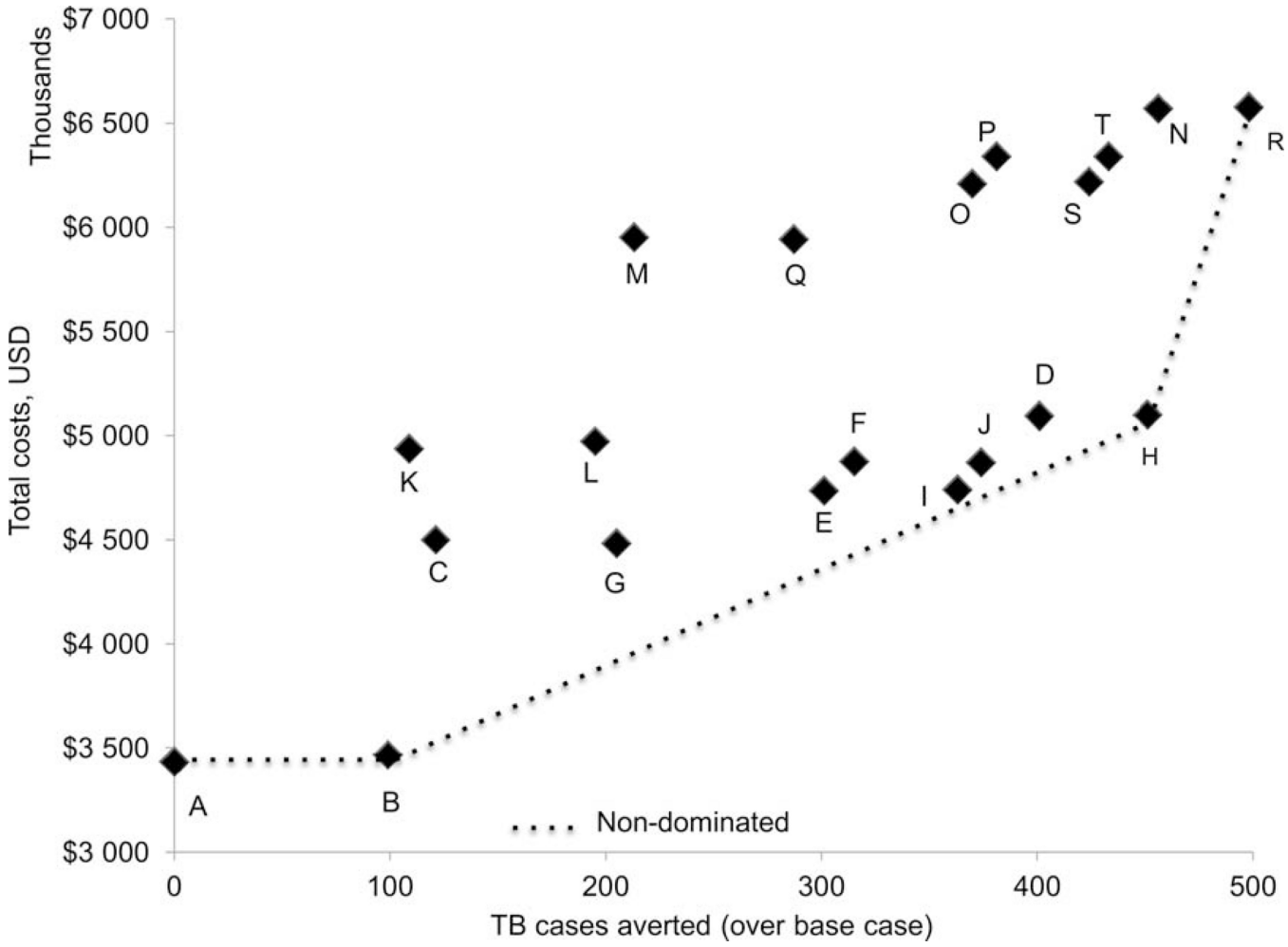


Figure A.3.

Expected costs and TB cases (TB diagnostic algorithm: sputum smear and chest radiography). Note: The description of the strategies (A to T) is given in Table 1. Base (A), ART IC (B), ART IC ICF IPT 36 (H) and ARTexp IC ICF IPT 36 (R) scenarios were most cost-effective. The total TB cases and total costs under each strategy are available in the Online Appendix. USD = US dollars; TB = tuberculosis; ART =antiretroviral therapy; IC =

infection control; ICF = intensified case finding; IPT = isoniazid preventive therapy; ARTexp = expanded ART (90% coverage).

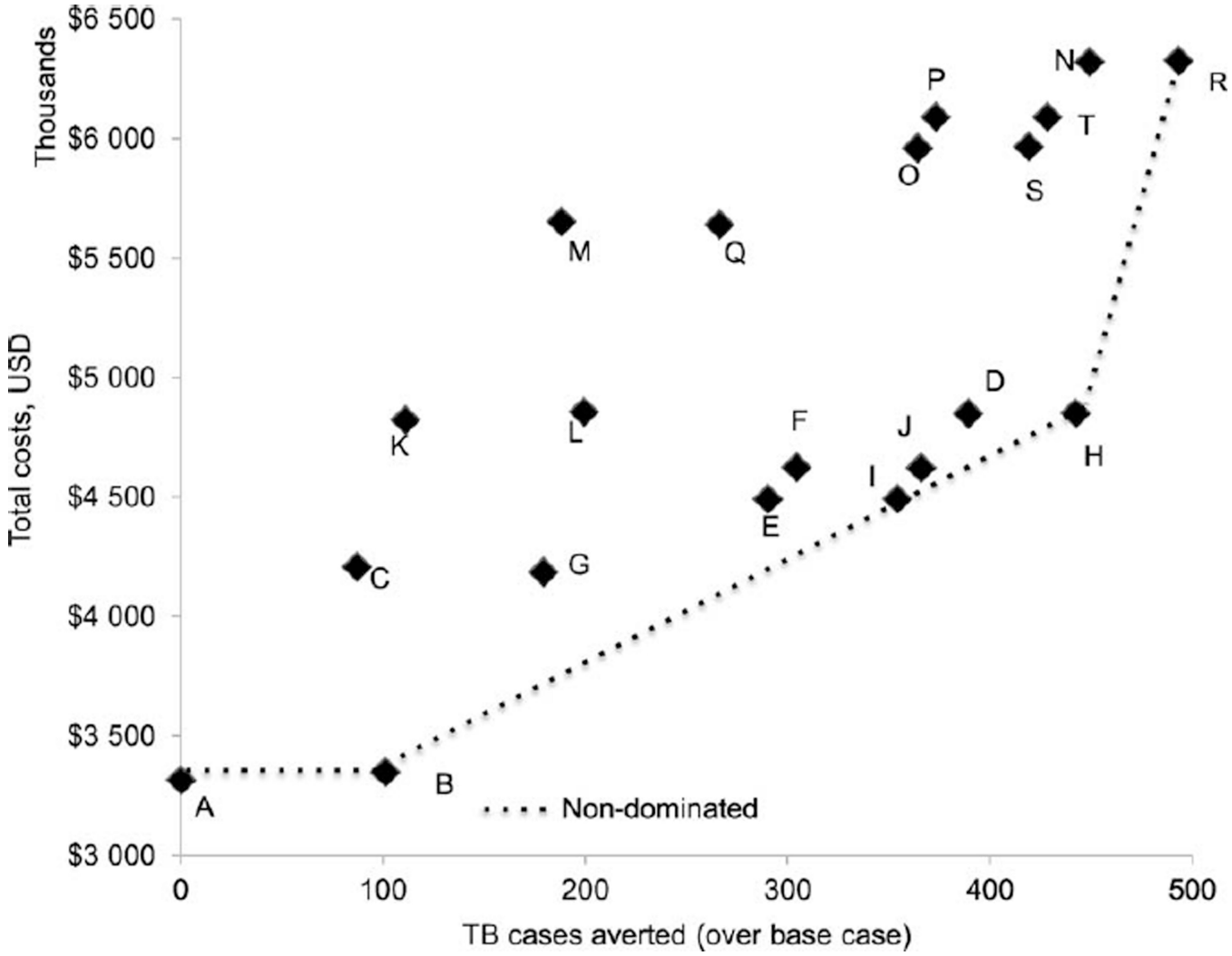


Figure A.4.

Expected costs and TB cases (TB diagnostic algorithm: Xpert® MTB/RIF assay). Note: The description of the strategies (A to T) is given in Table 1. Base (A), ART IC (B), ART IC ICF IPT 36 (H) and ARTexp IC ICF IPT 36 (R) scenarios were most cost-effective. The total TB cases and total costs under each strategy are available in the Online Appendix. USD = US dollars; TB = tuberculosis; ART=antiretroviral therapy; IC = infection control; ICF = intensified case finding; IPT= isoniazid preventive therapy; ARTexp = expanded ART (90% coverage).

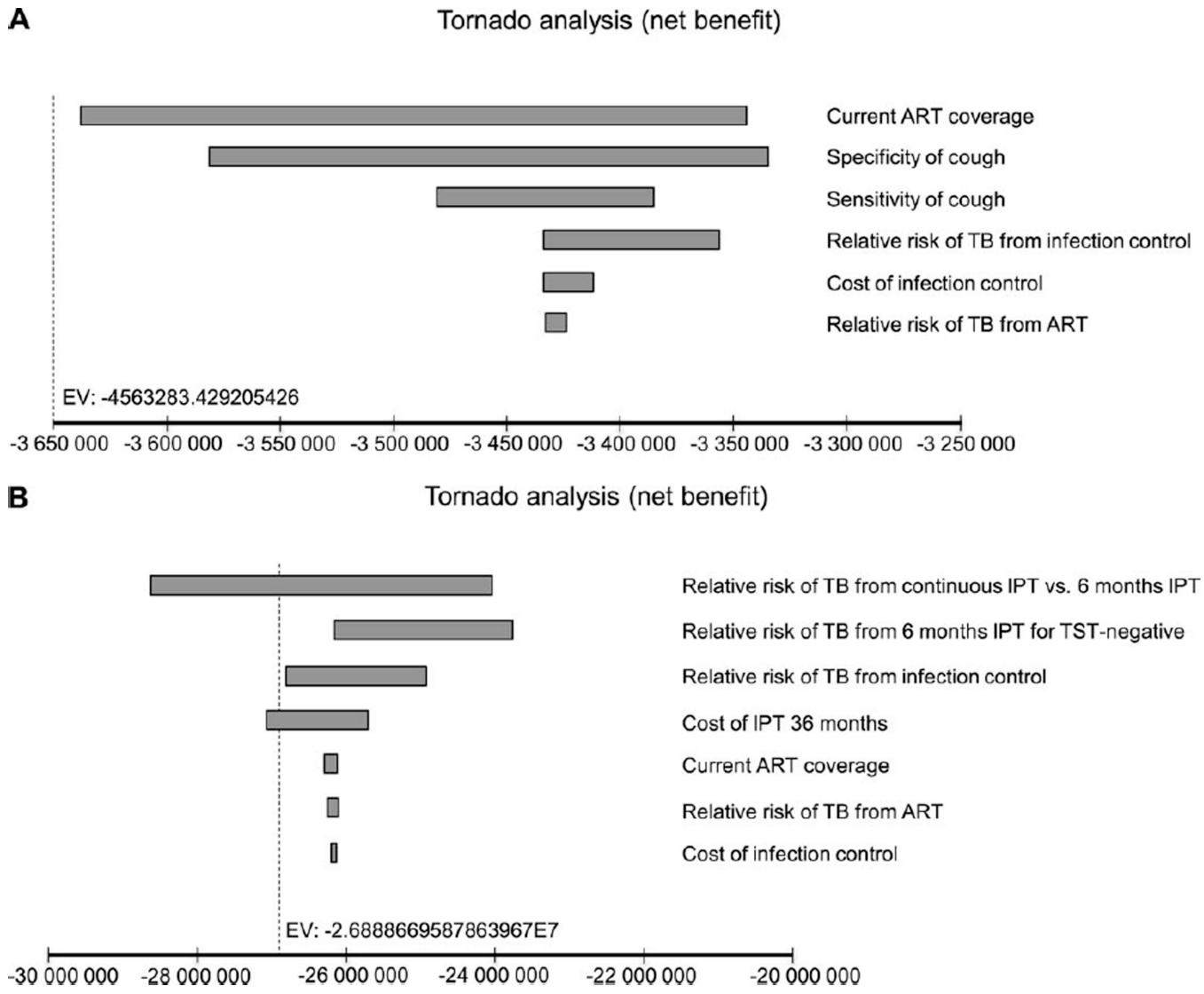


Figure A.5.

Tornado diagram of univariate analyses for strategies with sputum smear and chest radiography for TB diagnosis. **A)** Willingness-to-pay threshold of USD1000. Note: the diagram shows the degree to which uncertainty in current ART coverage, specificity and sensitivity of TB screening with cough, the RR of TB from IC and ART and cost of IC interventions accounted for 100% variation in cost-effectiveness results. Variations in other parameters (cost of TST, IPT and anti-tuberculosis treatment, sensitivity and specificity of four-symptom screening, the RR of TB from 6-month or 36-month IPT, proportion of people testing TST-positive of those with active TB and without active TB, and expanded ART coverage) had no effect on the results. **B)** Willingness-to-pay threshold of USD35 000. Note: this diagram shows the degree to which uncertainty in RR of TB from continuous IPT vs. 6-month IPT, 6-month IPT for TST-negatives and IC and cost of 36-month IPT accounted for nearly 100% variation in cost-effectiveness results. Variations in other parameters (cost of TST and anti-tuberculosis treatment, sensitivity and specificity of TB screening using cough or four-symptom screening, proportion of people testing TST-positive of those with active

TB and without active TB, and expanded ART coverage) had no effect on the results. ART = antiretroviral therapy; RR = relative risk; TB = tuberculosis; IC = infection control; IPT = isoniazid preventive therapy; TST = tuberculin skin test; USD = US dollars.

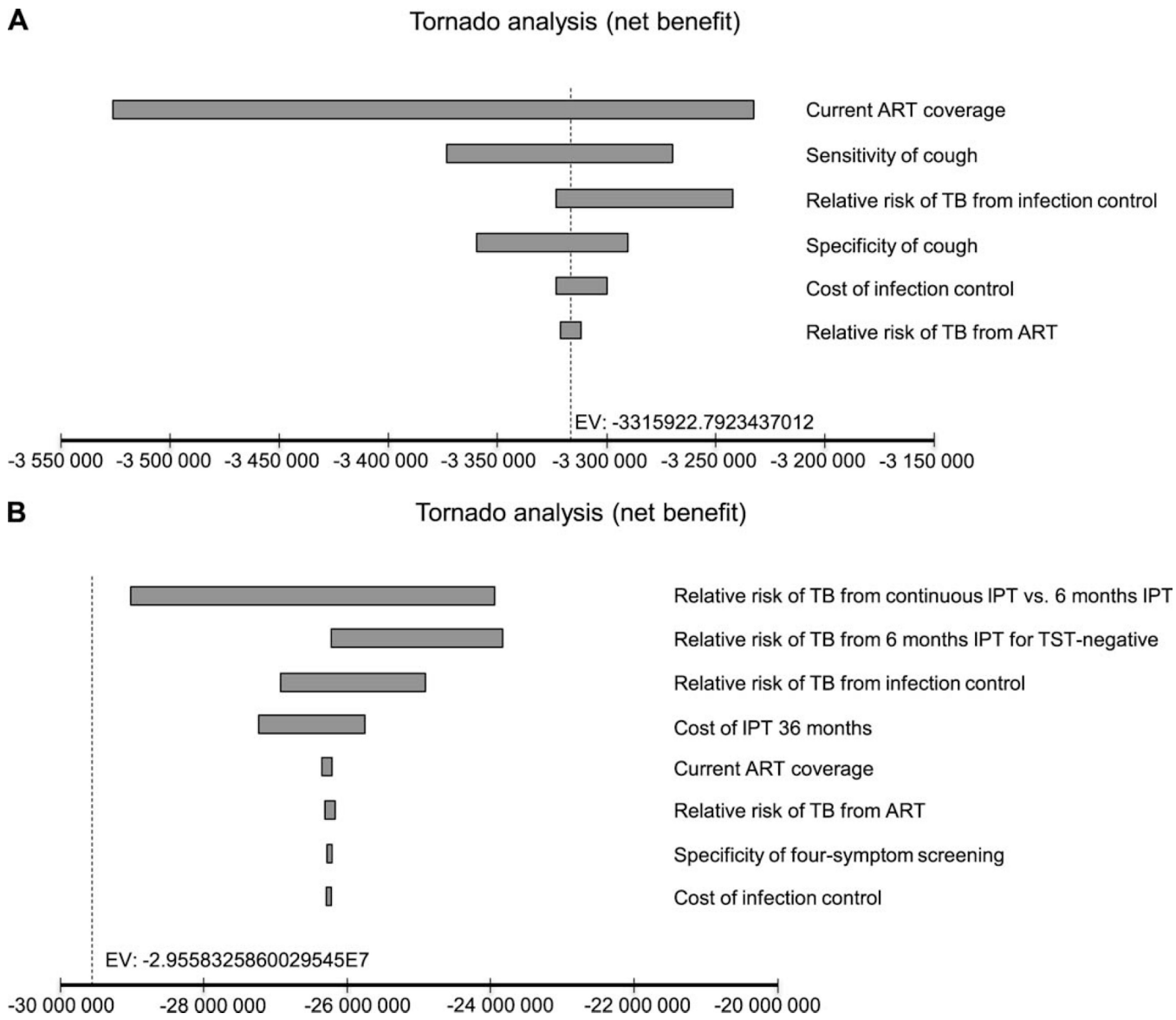


Figure A.6.

Tornado diagram of univariate analyses for strategies with Xpert® MTB/RIF for TB diagnosis. **A)** Willingness-to-pay threshold of USD1000. Note: the diagram shows the degree to which uncertainty in current ART coverage, specificity and sensitivity of TB screening with cough, RR of TB from IC and ART, and cost of IC interventions accounted for 100% variation in cost-effectiveness results. Variations in other parameters (cost of TST, IPT and anti-tuberculosis treatment; sensitivity and specificity of four-symptom screening; RR of TB from 6-month or 36-month IPT; proportion of people testing TST-positive of those with active TB and without active TB; and expanded ART coverage) had no effect on

the results. **B)** Willingness-to-pay threshold of USD35 000. Note: this diagram shows the degree to which uncertainty in RR of TB from continuous IPT vs. 6-month IPT, 6-month IPT for TST-negative, and IC and cost of 36-months IPT accounted for nearly 100% variation in cost-effectiveness results. Variations in other parameters (cost of TST and anti-tuberculosis treatment; sensitivity and specificity of TB screening using cough; sensitivity of four-symptom screening; proportion of people testing TST-positive of those with active TB and without active TB; and expanded ART coverage) had no effect on the results. ART =antiretroviral therapy; RR = relative risk; TB = tuberculosis; IC = infection control; IPT = isoniazid preventive therapy; TST = tuberculin skin test; USD = US dollars.

Table 1

Description of TB prevention interventions included in the 20 scenarios *

	Scenario	ART coverage %	TB screening	TST	Duration of IPT	IC
A	Base	55	Cough	No		No
B	ART IC	55	Cough	No		Yes
C	ART ICF IPT 6	55	Four symptom	No	6 months	No
D	ART ICF IPT 36	55	Four symptom	No	36 months	No
E	ART ICF TST IPT 36	55	Four symptom	Yes	36 months for TST+	No
F	ART ICF IPT 6 TST IPT 36	55	Four symptom	Yes	36 months for TST+; 6 months for TST+	No
G	ART IC ICF IPT 6	55	Four symptom	No	6 months	Yes
H	ART IC ICF IPT 36	55	Four symptom	No	36 months	Yes
	ART IC ICF TST IPT 36	55	Four symptom	Yes	36 months for TST+	Yes
J	ART IC ICF IPT 6 TST IPT 36	55	Four symptom	Yes	36 months for TST+; 6 months for TST-	Yes
K	ARTexp	90	Cough	No		No
L	ARTexp IC	90	Cough	No		Yes
M	ARTexp ICF IPT 6	90	Four symptom	No	6 months	No
N	ARTexp ICF IPT 36	90	Four symptom	No	36 months	No
0	ARTexp ICF TST IPT 36	90	Four symptom	Yes	36 months for TST+	No
P	ARTexp ICF IPT 6 TST IPT 36	90	Four symptom	Yes	36 months for TST+; 6 months for TST-	No
Q	ARTexp IC ICF IPT 6	90	Four symptom	No	6 months	Yes
R	ARTexp IC ICF IPT 36	90	Four symptom	No	36 months	Yes
S	ARTexp IC ICF TST IPT 36	90	Four symptom	Yes	36 months for TST+	Yes
T	ARTexp IC ICF IPT 6 TST IPT 36	90	Four symptom	Yes	36 months for TST+; 6 months for TST-	Yes

* TB cases and costs under all the strategies were calculated for two different TB diagnostic algorithms: 1) sputum smear microscopy and chest radiography; and 2) Xpert® MTB/RIF assay for *Mycobacterium tuberculosis* and resistance to rifampicin.

TB=tuberculosis; ART =antiretroviral therapy; TST=tuberculin skin test; IPT = isoniazid preventive therapy; IC = infection control; ICF = intensified case finding; += positive; — = negative; ARTexp = expanded ART (90% coverage).

Table 2

Model parameter inputs and their range

Variables	Base value	Range	Source (author, year, reference)
TB prevalence among HIV-positive people	0.05	0.004–0.26	Getahun, 2011[13]
Proportion of PLHIV eligible for ART at CD4 count ≤350 cells/mm^3, %	45	43–49	UNAIDS report, 2012[11]
ART coverage, %	55	53–60	
Expanded ART coverage, %	90	80–100	Assumption
Annual incidence of TB in PLHIV			
All	0.0395*	0.034–0.1	Shrestha, 2007[14]
TST-positive	0.047	0.034–0.1	
TST-negative	0.037	0.034–0.1	
Relative risk of TB			
ART	0.33	0.27–0.39	Lawn 2011[15]
6-month IPT	0.89†	0.84–0.96	Akolo 2010[16]
36-month IPT (all)	0.51	0.27–0.93	Samandari, 2011[17]
36-month IPT in TST-positive	0.21	0.04–0.75	
TB infection control	0.87	0.63–1.00	Harries, 2002[12, 18]
Sensitivity of screening and diagnostic test			
Cough	0.385	0.19–0.62	Getahun, 2011[13]
Four-symptom	0.789	0.58–0.91	
Sputum smear	0.36	0.09–0.50	Monkongdee, 2009[19]
Chest radiography	0.65	0.60–0.83	Cain, 2010[20]
Xpert	0.82	0.60–0.87	Lawn, 2011,[21] Boehme, 2011[22]
Specificity of screening and diagnostic test			
Cough	0.818	0.65–0.92	Getahun, 2011[13]
Four-symptom	0.496	0.29–0.70	
Sputum smear	0.99	0.98–1.00	Cain, 2010[20]
Chest radiography	0.85	0.35–1.00	Cain, 2010[20]
Xpert	0.99	0.98–1.00	Lawn, 2011,[21] Boehme, 2011[22]
Expected proportion of PLHIV testing			
TST-positive			
Active TB	0.65	0.50–0.74	Rangaka, 2007[23]
No active TB	0.26	0.19–0.35	Kerkhoff, 2012[24]

*Assuming 25% of HIV-positive people are TST-positive,[24] we calculated the annual incidence of TB in PLHIV

†Relative risk of TB from 6-month IPT is 0.67. Assuming 6-month IPT will only be effective in year 1, the average relative risk was calculated as 0.89.

TB = tuberculosis; HIV = human immunodeficiency virus; PLHIV = people living with HIV; ART=antiretroviral therapy; UNAIDS =Joint United Nations Programme on HIV/AIDS; TST = tuberculin skin test; IPT = isoniazid preventive therapy

Table 3

Cost inputs (in 2010 USD)

Parameter	Cost/unit USD	Units	Cost/patient USD	Source (author, year, reference)
Diagnostic				
Sputum smear	1.60	2 tests	3.20	Vassall, 2011[25]
Chest radiography	7.80	1 test	7.80	Fairall, 2010[26]
Tuberculin skin test	6.20	1 test	6.20	2011 WHO ICF/IPT Guidelines[9]
Xpert	22.00	1 test	22.00	Vassall, 2011[25]
Anti-tuberculosis treatment				
Drugs and DOT visits	437.20	DOTS course and DOTS visits	437.20	Dowdy, 2008[27]
TB hospitalisation	62	21 days average stay	1300.00	WHO-CHOICE[28]
TB infection control				
Respirator	0.60	1 per nurse per week *	0.29	Data from a primary hospital, and prices and building cost indices from the Bureau of Economic Research, Stellenbosch University, Cape Town, South Africa
Surgical masks	0.17	1 per patient with cough per visit †	2.50	
Windows: construction		3 years capital cost	0.35	
Windows: maintenance		3 years maintenance cost	0.12	
Fan		Cost of capital and maintenance for 3 years	0.13	
INH				
6-month course	0.92	One course of 300 mg INH daily	16.40	International drug price indicator§
36-month course		3-year cost	103.50	
INH-related hepatitis †				
LFT	4.50#	1 test		Arnold, 2011[29]
Out-patient cost		3 LFT and 3 clinical visits	50	WHO-CHOICE[28]
In-patient cost		1 LFT and 7 days hospital stay	438	
Antiretroviral therapy				
Antiretroviral drugs	274.50	3 years drug cost	867.20	Granich, 2012[30]
Monitoring visit (first)	34.30	1 visit	34.30	
Subsequent visits	25.70	2 visits (once every year)	55.50	

* Assuming 2 nurses per consulting room, the cost of respirators (life of 1 week) was calculated at US$2944 (in 2010 USD)

† The cost calculation assumed annual out-patient visit/patient/year to be approximately 2.5

‡ We assumed that 10% of hepatitis cases were hospitalised for an average of 7 days after an LFT; all other cases were managed on an out-patient basis requiring three clinic visits and three LFTs.[29]

§ http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=dmp&language=english

Using an exchange rate of US$1 = R8.8 and £1 = US$1.6.

USD = US dollars; WHO = World Health Organization; ICF = intensified case finding; IPT = INH preventive therapy; DOT = directly observed therapy; TB = tuberculosis; INH = isoniazid; LFT = liver function test; R = South African rand; £ = Great British pound.