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The cost of intensified case finding and isoniazid preventive therapy for HIV-infected patients in Battambang, Cambodia

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SUMMARY

SETTING: The current study evaluates one of four pilot sites initiated in Cambodia to establish feasible and effective ways to manage patients with human immunodeficiency virus (HIV) infection and tuberculosis (TB).

OBJECTIVE: To measure the costs of intensified case finding (ICF) and isoniazid preventive therapy (IPT) services for HIV-infected patients in Battambang Province, Cambodia.

DESIGN: We analyzed cost data retrospectively from September 2003 to February 2006 using a microcosting or ingredients-based approach and interviewed clinic personnel to determine the cost of ICF and IPT per person.

RESULTS: Adherence to IPT at Battambang IPT clinic was high (86%) relative to other reported studies of IPT among HIV patients in developing countries. The estimated cost per TB case averted through ICF was US$363, while the estimated cost per TB case averted through IPT was US$955.

CONCLUSION: Economic evaluations of TB-HIV integrated services are necessary as countries move to establish or scale-up these services. Based upon the estimated effectiveness of ICF and IPT used by other studies examining the provision of integrated HIV-TB services, the cost per TB case prevented by ICF and IPT in Battambang, Cambodia, is less than the reported cost of treating a new smear-positive TB case.

KEY WORDS: cost-effectiveness; human immunodeficiency virus; isoniazid preventive therapy; intensified case finding; tuberculosis

GIVEN THAT 8% of the globally estimated new tuberculosis (TB) cases and 14.5% of reported TB deaths occur among human immunodeficiency virus (HIV) infected individuals, addressing TB-HIV co-infection is at the forefront of government health programs for both diseases, especially in settings where the overlap in epidemics is pronounced.[1,2] Cambodia is among the 22 high-burden TB countries. In 2004, the number of TB cases, all forms, was estimated at 70 370 (510 per 100 000 population), including 36 606 smear-positive cases (226/100 000). With an estimated 64% of the population infected with *Mycobacterium tuberculosis* and 130 000 persons living with HIV/ AIDS (acquired immune-deficiency syndrome) as of December 2006, the numbers of active cases and latent TB infections are expected to rise.[3,4] HIV prevalence among TB patients has already increased nationally, from 2.5% in 1995 to 13% in 2004.[5,6]

Government, technical and donor agencies are jointly prioritizing TB-HIV integrated services.[6–9] Four pilot sites were therefore started in 2003 under the National AIDS Program's (NAP's) Continuum of Care (COC) package to establish feasible and effective ways to manage co-infected patients. The current study evaluates one such pilot site, initiated in Battambang Province, as a collaboration between the NAP, the National Tuberculosis Program (NTP), Family Health International (FHI) and the Gorgas Tuberculosis Initiative of the University of Alabama at Birmingham (GTI/UAB). This project was approved by the Ethics Committee of the Ministry of Health of Cambodia and UAB. Informed consent was obtained from all participants.

The project focuses on linking TB and HIV services utilizing voluntary counseling and testing as an entry point for TB screening among HIV-infected patients. The specific aim of this assessment is to determine the costs of implementing TB intensive case finding (ICF), linked to an isoniazid preventive therapy (IPT) service for HIV-infected patients in Battambang. As countries move to establish or scale up integrated services, this information is essential for health planning and informing regional and national health policies.[2,10,11]

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METHODS

During the study period from October 2003 to February 2006, we examined cost data retrospectively and interviewed clinic personnel. We adopted a microcosting or ingredients-based approach from the perspective of a third-party payer, where each component of resource utilization is assigned an estimated unit cost.[12,13] These expenditure data were used to derive patient level costs (Table 1).

Both financial costs, representing actual monetary expenditures, and economic costs, which may or may not involve a monetary expenditure, were included.[14] Economic costs are based upon the value given up by not using a resource in its next best alternative use. These costs include resources consumed in the provision of ICF and IPT clinic services for which no actual expenditure or budgetary line item exists, including capital costs and recurrent costs such as buildings, transportation, furniture, equipment, and training.[15]

In consultation with administrative personnel, capital outlays were annualized over the useful life of the asset to calculate an equivalent annual cost.[12] Training costs were included in capital costs, as the anticipated benefits of these activities were expected to exceed 1 year. Training and continuing education activities were carefully reviewed to include only those training-related activities deemed essential for the initiation and sustainability of the program beyond the initial study period.[16]

Several capital assets, including the Battambang hospital building, office equipment, transportation vehicles and X-ray machines, were jointly shared between the Battambang hospital and the HIV clinic where IPT is delivered. For the allocation of these jointly shared or overhead expenses, a direct allocation method was employed. The direct allocation method is a method for the allocation of overhead costs among cost centers.[12,17] An estimated annual equivalent cost for these capital assets was determined, then this amount was multiplied by the proportion of time the asset was used for IPT clinic-related services.[12,18] All capital costs were annuitized at 3%.[12,15]

Cambodian government personnel (i.e., physicians and nurses) were also jointly shared between the HIV clinic and the Battambang hospital. To determine labor costs that could be apportioned to the provision of IPT clinic services, the amount of time required to conduct patient screening, treatment and follow-up monitoring was determined by interviews with clinic staff. Remuneration paid to clinic personnel from this study was solely for the provision of IPT clinic-related services and not for other services provided at Battambang hospital.

Original outcomes focused on determining effective ways to manage co-infected patients, and did not directly measure the cost-effectiveness of ICF or IPT. In this analysis, we estimate effectiveness in terms of the number of TB cases prevented by ICF and IPT from previously published studies. In estimating the effectiveness of ICF, we assumed that ICF can potentially prevent 25 per 100 TB cases detected by reducing the infectious period in HIV-positive people by 30%.[8,19] To estimate the effectiveness of the IPT, we used results from a meta-analysis of randomized controlled trials comparing IPT among HIV-infected patients to placebo or no prophylaxis. It provides estimates of relative risk for all patients, tuberculin skin test (TST) positive patients, and TST-negative patients.[20] We assumed that IPT reduces TB incidence by 60% for 2 years, assuming an adherence rate of 60–80%.[20] Estimates of annual TB incidence in TST-positive individuals range from 4% to 8%. We estimate that TB incidence in TST-positive individuals is closer to 8% at Battambang due to a higher incidence among the Cambodian population. As a conservative estimate, considering that adherence rates reported in the meta-analysis are lower than those observed in the Battambang IPT clinic, we assume that 17 of every 100 patients completing IPT (95% confidence interval [CI] 11–24) could be TB cases prevented.

Of the 2326 patients for whom information on TB status was available, 642 had active TB and 1482 were ruled ineligible for IPT (Figure). Patients were

Table 1 Cost figures used in the cost analysis of intensified case finding and IPT for HIV-infected patients in Battambang, Cambodia*

Description	Reference case value US$	Lower bound US$	Upper bound US$
Clinic personnel†	2.55	1.28	3.83
Doctors	0.50		
Nurses	0.40		
X-ray technician	0.40		
Medical assistant	0.50		
Laboratory staff	0.37		
Laboratory and supplies			
Sputum smear	12.00	6.00	18.00
Culture	4.64	2.32	6.96
Identification	4.32		
X-ray solutions	0.43		
X-ray films	0.98		
INH (300 mg/day)‡	4.05	2.03	6.08
Vitamin B6 (25 mg/day)‡	1.62		
Transportation			
Transportation of specimens	1.86	0.93	2.79
Patient screening transportation	0.25		
Patient IPT transportation	1.50		
Capital cost§			
Building/furniture/office equipment	0.03		
X-ray machine	0.69	0.35	1.04
Transportation vehicles	0.19		
Personnel training	0.41		

* Costs were allocated per HIV-infected patient.
† Personnel costs are salaries paid solely for the provision of IPT clinic services.
‡ Cost of a 9-month supply for an individual patient of INH or vitamin B6.
§ Equivalent annual cost allocation for IPT clinic divided by the number of patients during the study period.
IPT = isoniazid preventive therapy; HIV = human immunodeficiency virus; INH = isoniazid.

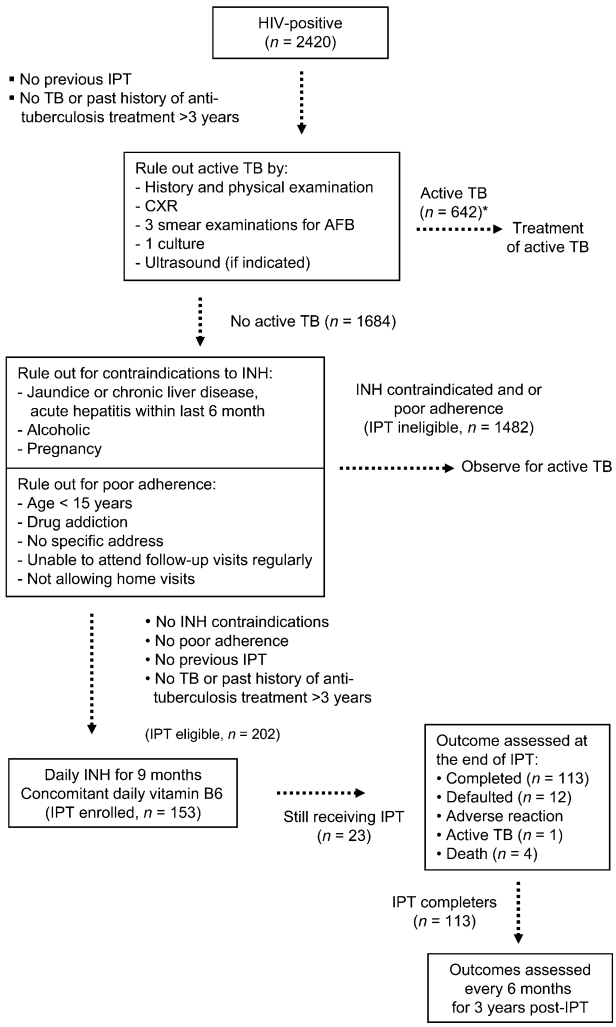

Figure Algorithm for ICF and IPT for HIV-positive patients at Battambang Hospital. *Unknown TB status (n = 94). HIV = human immunodeficiency virus; IPT = isoniazid preventive therapy; TB = tuberculosis; CXR = chest X-ray; AFB = acid-fast bacilli; INH = isoniazid.

ineligible for IPT if INH was contraindicated (jaundice, chronic liver disease, acute hepatitis within last 6 months, alcoholism, pregnancy) or there was a potential for poor adherence (<15 years of age, drug addiction, home visits not allowed, inability to attend regular follow-up visits, no specific address) (Figure).

Of the 202 patients eligible for IPT, 49 (24%) did not register, leaving 153 patients who started prophylaxis. Each patient receiving IPT attended once monthly to receive medication, for a total of 1377 possible patient visits to the clinic. The actual number of patient visits was 1181, for an adherence rate of approximately 86%. At the end of the study period, 23 patients were still receiving IPT.

To examine the effect of uncertainty on select cost data and effectiveness estimates, we conducted a sensitivity analysis to determine the impact on the cost-effectiveness of ICF and IPT. Cost data for personnel, drugs, diagnostic tests and transportation were allowed to vary to examine the impact on the cost per TB case detected through ICF, the cost per TB case prevented through ICF, and the cost per TB case prevented through IPT. To examine variation in the composition of a patient cohort with respect to TST results, we allowed the number of cases prevented to vary, to reflect a larger or smaller number of patients in a potential cohort who may be TST-positive. Similarly, variation in the number of TB cases detected by ICF and the number of cases prevented by ICF was allowed to examine changes in the cost per TB cases detected or prevented through this intervention.

RESULTS

Estimated program effectiveness and cost-effectiveness results are presented in Table 2. Based on previous studies examining the mean duration of infectiousness and incidence of TB in HIV-positive and HIV-negative individuals, we assumed that ICF would lead to a 30% reduction in the duration of infectiousness among HIV-positive individuals.[8] Previous estimates of the effectiveness of ICF suggest that the number of cases prevented by ICF is 25% of the number of TB cases detected by ICF.[19] Under these assumptions, the cost of ICF per case prevented was US$363 (Table 2).

Because the TST was not performed at this clinic, the prevalence of TST-positive or TST-negative patients is unknown. Using assumptions from previously published cost-effectiveness studies on the impact of IPT in averting TB cases, we assumed that TB incidence in TST-positive patients is 8% and that each HIV-positive case causes one additional case.[19] The observed

Table 2 Outcomes, cost ($US) and cost-effectiveness indicators for the Continuum of Care at Battambang IPT clinic

HIV-infected patients screened during study period	2420
Active TB cases at initial screening	642
Exclusions for contra-indications or poor adherence	1482
Patients enrolling in IPT	153
Patients completing 9 months of IPT by end of the study period	113
Patients still receiving IPT at end of the study period	23
Estimated effectiveness of ICF*[8,19]	25
Estimated effectiveness of 9 months of IPT†[20]	17
Cost of ICF per person‡	$24.08
Cost per person to starting IPT§	$105.35
Cost per person to complete 9 months of IPT#	$25.16
Cost per TB case detected through ICF**	$90.77
Cost per TB case prevented through ICF††	$363.06
Cost per TB case prevented through IPT‡‡	$955.33

* Number of cases of TB prevented per 100 TB cases detected by ICF.
† Number of cases of TB prevented per 100 patients completing IPT.
‡ Cost of ICF divided by the number of patients screened.
§ Cost of IPT divided by the number of patients enrolling in IPT.
# Cost of IPT divided by the number of patients completing 9 months of IPT (does not include the cost of determining eligibility for IPT).
** Cost of ICF divided by the number of active TB cases.
†† Cost of ICF divided by the number of estimated cases prevented by ICF.
‡‡ Cost of IPT divided by the number of estimated TB cases prevented by IPT (includes the cost of identifying patients eligible for IPT).
IPT = isoniazid preventive therapy; HIV = human immunodeficiency virus; TB = tuberculosis; ICF = intensified case finding.

Table 3 Results of the sensitivity analysis from changes in reference case values for selected cost data and estimated effectiveness indicators

Description	Sensitivity range	Sensitivity value	Cost per TB case, $US		
			Detected through ICF	Prevented through ICF	Prevented through IPT
Sputum smear cost	Low	6.00	68.15	272.6	732.03
	High	18.00	113.38	453.53	1178.63
Culture cost	Low	2.32	82.02	328.08	868.99
	High	6.96	99.51	398.04	1041.67
TB cases detected by ICF*	Low	20	121.02		
	High	34	72.61		
TB cases prevented by ICF†	Low	19		484.08	
	High	31		290.33	
TB cases prevented by IPT‡	Low	13			1273.78
	High	21			764.27

* Active TB cases detected per 100 patients through ICF.
† TB cases prevented per 100 patients receiving ICF.
‡ TB cases prevented per 100 patients receiving IPT (includes the costs of determining eligibility for IPT).
TB = tuberculosis; ICF = intensified case finding; IPT = isoniazid preventive therapy.

adherence from our study was higher than the reported range of adherence rates (60–80%) reported in studies estimating the effectiveness of IPT. As a conservative estimate of the effectiveness of IPT, we chose the midpoint of the 95%CI reporting the number of TB cases prevented per 100 patients completing IPT.[20] Assuming this level of estimated effectiveness, the cost per TB case prevented by IPT is US$955.

During the study, 642 active TB cases were identified and treated under the COC ICF screening protocol. The cost per active TB case detected was approximately US$91. During this same period, 113 of 153 patients enrolling in IPT completed the 9-month course. The annual cost of IPT was US$1540 and included a 9-month supply of isoniazid and vitamin B6, and transportation of patients for 9 monthly visits. At the observed adherence rate of 86%, the cost per person completing IPT was US$25. The average cost of determining patient eligibility for IPT under the exclusion criteria and completing 9 months of IPT was US$105. The cost of screening was US$24 per patient.

Sensitivity analysis was performed to examine the impact of changes in cost and program effectiveness on our cost-effectiveness indicators.[21–23] The cost of ICF per TB case detected, the cost of ICF per TB prevented and the cost of IPT per TB case prevented were robust to changes in personnel cost, drug costs, capital costs, and transportation costs. These cost-effectiveness measures were sensitive to changes in the cost of diagnostic tests and estimated program effectiveness (Table 3).

When the number of cases of TB prevented by ICF is allowed to vary around the reference of 25 cases prevented per 100 cases of TB detected by ICF, the cost per case prevented by ICF varies inversely with effectiveness. When the number of cases prevented by ICF falls to 19 per 100 cases detected by ICF, the cost per case prevented by ICF rises to US$484. If the effectiveness of ICF is increased to 31 per 100 cases detected by ICF, the cost per case prevented by ICF falls to US$290. Similarly, when the number of cases prevented by IPT falls from the reference of 17 per 100 persons completing IPT to 13 per 100 persons completing IPT, the cost of IPT per case prevented rises to US$1274. When the number of TB cases is set to 21 cases prevented per 100 people completing IPT, the cost of IPT per TB case prevented falls to US$764.

DISCUSSION

A total of 113 patients completed 9 months of IPT, and 23 patients were still taking IPT at the end of the study period. Non-adherence was minimized due to the restrictive selection criteria which led to a relatively small patient volume over the study period. The extent to which intensified training of health staff and patient monitoring may have impacted adherence rates with IPT was not evaluated in this study. However, adherence to IPT was high relative to other reported studies of IPT among HIV patients in developing countries. The cost per person completing IPT (excluding the cost of determining eligibility for IPT) of US$25 in Battambang is lower than other figures reported by a study of the cost-effectiveness of a collaborative TB-HIV intervention in South Africa, called ProTEST: the cost per person completing IPT in 2002 for the ProTEST intervention in Cape Town, South Africa was US$85.[19] Other reported figures from Africa range from US$24 in Uganda in 1992[24] to US$42 in Zambia in 1991.[25] Bell et al. report an average cost for a simulated cohort of HIV-infected patients from sub-Saharan Africa at US$38 for 6 months of IPT.[26] The cost per person starting IPT in Battambang, which includes the cost of determining eligibility for IPT, is US$105. More recent results from the AIDS Information Center in Uganda report a per

patient cost of 9 months of IPT, in 2003 US dollars (including program costs), of US$82.[27,28] The results from Battambang fall within the reported range of IPT costs per patient reported from the Ugandan study of US$57 to $139.

One area of uncertainty involves the number of TB cases prevented per 100 persons completing IPT.[22] Making assumptions similar to those in the ProTEST study in South Africa (19 cases prevented per 100 patients completing IPT), our cost per TB case prevented through IPT was US$855. The reported cost per TB case prevented through IPT for ProTEST in South Africa ranges from US$486 to $962 across clinics in Cape Town. If these figures are adjusted for inflation to 2006 US dollars, the costs range from US$593 to $1173.[29] The reported cost of treating a new smear-positive TB case in Cape Town ranges from US$726 to $1201.[30] When these figures are adjusted for inflation, the cost of treating a new case of TB becomes US$907 to $1501.

Several limitations of our study should be noted. As the TST was not performed at the Battambang IPT clinic, the prevalence of TST-positive or TST-negative patients is unknown. Care should be taken in comparing our results to those of other studies on the cost of ICF or IPT among HIV-infected patients in developing countries using this test. Our results were sensitive to assumptions about the effectiveness of ICF and IPT. Variation in adherence rates across countries and regions will lead to variation in the cost per TB case prevented through IPT. Variation in screening protocols used in ICF limit the comparability of our cost and cost-effectiveness results to those studies with similar referral and screening among HIV-infected patients in developing countries and programs attempting to integrate collaborative TB-HIV preventive treatment programs.

CONCLUSION

Our study addresses the need for cost and cost-effectiveness data on components of a comprehensive package of HIV care in developing countries. Based upon the estimated effectiveness of ICF and IPT used by other studies examining the provision of integrated TB-HIV services, the cost per TB case prevented by ICF and IPT is less than the reported cost of treating a new smear-positive TB case. When assessing the relative efficiency and affordability of components of comprehensive HIV care, program managers should consider the higher rates of adherence to IPT observed in Battambang, Cambodia. Our estimates of the cost of IPT per TB case prevented are based upon a meta-analysis of the effectiveness of IPT among studies reporting adherence rates from 60% to 80%. Based upon our adherence rate of 86%, our results are likely a conservative estimate of the actual cost per TB case prevented. A scaling up of integrated TB-HIV services requires that the average cost of ICF and IPT be combined with the number of projected patients based upon recent prevalence data and observed adherence rates.

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RÉSUMÉ

CONTEXTE : La présente étude évalue un des quatre sites-pilote établis au Cambodge afin de déterminer comment assurer de manière réalisable et efficiente la prise en charge des patients atteints d'infection par le virus de l'immunodéficience humaine (VIH) et de tuberculose (TB).
OBJECTIF : Mesurer les coûts d'un dépistage intensif des cas (ICF) ainsi que ceux des services de traitement préventif à l'isoniazide (IPT) chez les patients infectés par le VIH dans la Province de Battambang au Cambodge.
SCHÉMA : Nous avons analysé les données de coût respectivement entre septembre 2003 et février 2006 en utilisant une approche « micro-coût » ou basée sur les composantes. Nous avons interviewé le personnel clinique pour déterminer le coût par personne de l'ICF et de l'IPT.
RÉSULTATS : L'adhésion au traitement préventif au dispensaire de l'IPT à Battambang est élevée (86%) par comparaison avec les données d'autres études publiées au sujet de l'IPT chez les patients infectés par le VIH dans les pays en développement. Le coût estimé par cas de TB évité grâce à l'ICF a été de 363 US$, alors que le coût estimé par cas de TB évité grâce à l'IPT a été de 955 US$.
CONCLUSION : Les évaluations économiques des services intégrés TB-VIH sont nécessaires au fur et à mesure de la mise en route ou de l'extension de ces services dans les pays. En se basant sur une efficience estimée de l'ICF et de l'IPT utilisés par d'autres études examinant la mise à disposition de services intégrés TB-VIH, le coût par cas de TB évité par l'ICF et l'IPT à Battambang, Cambodge, est plus faible que le coût du traitement rapporté dans la littérature d'un nouveau cas de TB à bacilloscopie positive.

RESUMEN

MARCO DE REFERENCIA : El presente estudio evalúa uno de los cuatro centros pilotos instaurados en Camboya con el fin de establecer medios factibles y eficaces de tratar a los pacientes con infección por el virus de la inmunodeficiencia humana (VIH) y con tuberculosis (TB).
OBJETIVO : Determinar los costos de los servicios de búsqueda intensiva de casos (ICF) y tratamiento preventivo con isoniazida (IPT) en pacientes infectados por el VIH en la provincia Battambang en Camboya.
MÉTODOS : Se analizaron en forma retrospectiva los datos de costos entre septiembre de 2003 y febrero de 2006 mediante una estrategia de microcostos o basada en cada ingrediente y se entrevistó al personal médico a fin de determinar el costo por persona de la ICF y del IPT.
RESULTADOS : El cumplimiento terapéutico en el consultorio del IPT en la provincia de Battambang fue alto (86%), comparado con el observado en otros estudios equivalentes en países en desarrollo. El costo calculado por cada caso de TB prevenido mediante la ICF fue 363 dólares (USD) y mediante el IPT fue 955 dólares.
CONCLUSIÓN : A medida que los países establecen o amplían sus servicios integrados de TB-VIH, se hace necesaria una evaluación económica. Con base en la eficacia calculada de la ICF y el IPT, aplicada en otros estudios de evaluación de estos servicios, el costo por caso prevenido de TB mediante estas estrategias en Battambang, Camboya, es inferior al costo del tratamiento de un caso nuevo de TB con baciloscopia positiva.