IMPACT OF A PUBLIC ANTIRETROVIRAL PROGRAM ON TB/HIV MORTALITY: BANTEAY MEANCHEY, CAMBODIA

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Abstract. The WHO recommends antiretroviral therapy (ART) for most HIV-infected tuberculosis patients. To assess the impact of ART on tuberculosis case-fatality rates in Cambodia, we compared treatment outcomes of patients newly diagnosed with tuberculosis in 2004 (before implementation of ART clinics) with outcomes of patients diagnosed in 2005 (after these clinics opened). In 2004, 37% of HIV-infected tuberculosis patients died during TB treatment compared with 5% of HIV-uninfected tuberculosis patients. In 2005, 18% of HIV-infected tuberculosis patients died compared with 5% of HIV-uninfected tuberculosis patients. The case-fatality rate for HIV-associated tuberculosis decreased from 2004 to 2005, coincident with the introduction of ART.

INTRODUCTION

Tuberculosis (TB) is one of the most common causes of death in HIV-infected persons. The World Health Organization (WHO) recommends that antiretroviral therapy (ART) should be offered to all HIV-infected TB patients (except for those with a documented CD4>350) to improve survival during TB treatment (WHO, 2006). Observational studies have documented improved survival for HIV-infected TB patients but are subject to bias and do not quantify the impact of ART on TB programs (Mocroft *et al*, 2003; Dheda *et al*, 2004; Manosuthi *et al*, 2006; Akksilp *et al*, 2007). No published studies demonstrate the impact of ART on survival of HIV-infected TB patients in Cambodia, which has one of the highest HIV prevalence rates in Asia (0.9% among adults in 2006) and the highest TB incidence in Asia, (estimated 506 per 100,000 persons in 2005) (UNAIDS, 2006; WHO, 2007).

Banteay Meanchey is a province in northwestern Cambodia with an estimated population of 795,000. The HIV prevalence in 2006 was 2.2% among pregnant women tested as part of the Prevention of Mother-to-Child Transmission of HIV Program (unpublished data, Banteay Meanchey Provincial Health Department). Almost one-fourth of all HIV-infected persons had TB disease at the time of HIV diagnosis, and over one-fourth of HIV-infected TB patients died during TB treatment (Cain *et al*, 2007). In 2005, the first three public ART clinics opened in Banteay Meanchey, with the first patient commencing ART in January 2005. Our objective was to determine what impact the implementation of government-sponsored ART clinics in Banteay Meanchey had on the case-fatality rate of HIV-associated TB in this province.

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Table 1
Characteristics of TB patients, stratified by year of registration for treatment, 2004 and 2005.

Characteristic	2004 (*N*=582)	2005 (*N*=620)	*p*-value
Age in years, median (range)	43 (2-84)	40 (0-87)	<0.01
Female, *n* (%)	254 (44)	289 (47)	0.29
HIV status[a], *n* (%)			
Infected	102 (18)	237 (38)	<0.01
Uninfected	243 (42)	247 (40)	0.50
Unknown	237 (40)	134 (21)	<0.01
Smear-negative TB, *n* (%)	171 (29)	246 (40)	<0.01
Extrapulmonary TB, *n* (%)	96 (16)	122 (20)	0.15

[a]In 2005, 2 patients had a recorded HIV test result of "indeterminate".

MATERIALS AND METHODS

We conducted an ecological study of TB patients treated in the 11 TB clinics which had implemented TB/HIV collaborative activities (including HIV testing of TB patients and TB screening of HIV-infected persons) in 2004 and 2005 (Kanara *et al*, 2008). We analyzed data on all new TB patients who registered for treatment at these sites during these two years. We used standard WHO definitions for case registration and treatment outcomes (WHO, 2003). Patients with treatment outcomes of failure, default, or transfer out were excluded from the primary analysis. Because death may be misclassified as default, we also compared the combined rate of death and default in 2004 with that in 2005.

We compared death during TB treatment among patients treated in 2004, before initiation of government-sponsored ART clinics in the province, with death among those treated in 2005, after implementation of ART, stratified by HIV status. We compared proportions using chi-square, calculated relative risks for associations in bivariate analysis, and compared relative risks using the Breslow-Day statistic. Since ART may not decrease early mortality, we also compared rates of death between the two years after excluding patients with treatment outcomes ≤14 days after registration.

This study underwent ethical review and was determined by the CDC to not constitute research and thus not require full review by an institutional review board.

RESULTS

In 2004 and 2005, 1,399 patients were newly diagnosed with TB. Of these, 197 (14%) were excluded from the primary analysis because they had a treatment outcome other than cure, complete, or death (including 1 failure, 53 defaults, and 143 transferred out). Of the remaining 1,202 patients, 373 (27%) had an unknown HIV status, while 339 (28%) were HIV-infected and 490 (41%) were HIV-uninfected. The median age was 42 years (range 0 to 87); 45% were females. Overall, 135 (11%) TB patients died during treatment. When compared to patients treated in 2004, those treated in 2005 tended to be younger, were more commonly HIV-infected and less commonly had an unknown HIV status, and they were more often smear-negative (Table 1).

In 2004, 37% of HIV-infected TB patients died during TB treatment compared with 5% of HIV-uninfected TB patients [relative risk

Table 2
Case-fatality rates for TB patients registered for treatment in 2004 and 2005, stratified by year and by HIV status.

		No. died / Total (%) by year		
	HIV status[a]	2004	2005	*p*-value
All patients included	Infected	38/102 (37)	42/237 (18)	<0.01
	Uninfected	12/243 (5)	12/247 (5)	0.97
	Unknown	14/237 (6)	17/134 (13)	0.02
Patients with outcome ≤14 days after registration excluded	Infected	33/97 (34)	35/228 (15)	<0.01
	Uninfected	11/241 (5)	7/241 (3)	0.34
	Unknown	9/232 (4)	9/126 (7)	0.18

[a]In 2005, 2 patients had a recorded HIV test result of "indeterminate".

(RR) 7.5; 95% confidence interval (CI) 4.1-13.8]. In 2005, 18% of HIV-infected TB patients died, compared with 5% of HIV-uninfected TB patients (RR 3.6; CI 2.0-6.8) (p=0.04 for homogeneity of relative risks). From 2004 to 2005, mortality rates were unchanged for HIV-uninfected TB patients, but decreased from 37% to 18% (p<0.01) for HIV-infected TB patients. Mortality rates for HIV-unknown patients increased from 6% in 2004 to 13% in 2005 (p=0.02). When patients with a treatment outcome ≤14 days after registration were included, mortality rates still decreased by more than half among HIV-infected persons from 34% in 2004 to 15% in 2005, while rates for HIV-uninfected and HIV-unknown patients remained unchanged (Table 2).

In 2004, 45 (41%) of 109 HIV-infected TB patients died or defaulted compared with 52 (21%) of 247 in 2005 (p<0.001). Among HIV-uninfected patients, the combined rate of deaths or defaults remained constant at 9% in 2004 and 2005.

DISCUSSION

The case-fatality rate among HIV-infected TB patients decreased by over half from 2004 to 2005 and remained stable in HIV-uninfected TB patients, coincident with the introduction of public ART clinics in Banteay Meanchey Province.

Since this study is ecological, it is not possible to prove that ART was the only reason for improved survival. However, observational studies which collect individual data on ART use are inherently biased toward showing a benefit to ART use, since clinicians often do not initiate ART in patients who are the sickest and most likely to die. The findings of this study avoid that bias and support the benefit of improving ART access for HIV-infected TB patients. Since HIV testing and TB screening rates improved in 2005 (Kanara *et al*, 2008) it is possible the population of HIV-infected persons in 2005 was less ill compared to 2004 due to earlier diagnosis. While we cannot exclude this possibility, it is unlikely to be the sole contributor to decreased mortality rates given evidence from similar settings, such as Thailand, in which ART use was the primary determinant of survival in HIV-infected TB patients (Manosuthi *et al*, 2006; Akksilp *et al*, 2007). As these clinics provide both ART and Co-trimoxazole preventive therapy (CPT) to patients, it is possible the measured im-

provement in survival was due to both introduction of ART and expansion of CPT use.

This study supports observational data from other settings on the survival benefit of improving access to HIV care, including ART, in HIV-infected TB patients and supports the hypothesis that ART contributes substantially to improved TB program outcomes in Cambodia.

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REFERENCES

Akksilp S, Karnkawinpong O, Wattanaamornkiat W, *et al*. Antiretroviral therapy during tuberculosis treatment and marked reduction in death rate of HIV-infected patients, Thailand. *Emerg Infect Dis* 2007; 13: 1001-7.

Cain KP, Kanara K, Laserson F, *et al*. The epidemiology of HIV-associated tuberculosis in rural Cambodia. *Int J Tuberc Lung Dis* 2007; 11: 1008-13.

Dheda K, Lampe FC, Johnson MA, Lipman MC. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *J Infect Dis* 2004; 190: 1670-6.

Kanara N, Cain KP, Laserson KF, *et al*. Using a program evaluation to improve the performance of a TB/HIV project in Banteay Meanchey, Cambodia. *Int J Tuberc Lung Dis* 2008; 12 (3 suppl 1): 44-50.

Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. *J Acquir Immune Defic Syndr* 2006; 43: 42-6.

Mocroft A, Ledergerber B, Katlama C, *et al*. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003; 362: 22-9.

UNAIDS. AIDS epidemic update: special report on HIV/AIDS. 2006.

WHO. Treatment of tuberculosis: guidelines for national programmes. 3rd ed. *WHO/CDS/TB/2003.313*. 2003. [Cited 2008 Jun 23]. Available from: URL: http://www.who.int/tb/publications/cds_tb_2003_313/en/index.html

WHO. Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach. Geneva: WHO, 2006. [Cited 2008 Jun 23]. Available from: URL: http://www.who.int/hiv/pub/guidelines/adult/en/index.html

WHO. Global tuberculosis control: surveillance, planning, financing. WHO report 2007. *WHO/HTM/TB/2007.376. 2007*. [Cited 2008 Jun 22]. Available from: URL: http://www.who.int/tb/publications/global_report/2007/en/index.html