

National HIV prevalence surveillance among TB patients through periodic surveys: experience in Cambodia

M. Tamura,^{**} K. K. Eam,[†] K. Kimura,[†] N. Yoshihara,^{**} T. Miura,^{*} H. Yanai,[†] N. Yamada,[†] P. Jayavanth,[§] P. van Maaren,[§] K. Okada,^{**} I. Onozaki,^{**} M. T. Eang[†]

^{*} National Centre for Tuberculosis and Leprosy Control (CENAT)/Japan International Cooperation Agency (JICA) National Tuberculosis Control Project, Phnom Penh, Cambodia; [†] Research Institute of Tuberculosis/Japan Anti-Tuberculosis Association, Tokyo, Japan; [‡] CENAT, Phnom Penh, Cambodia; [§] World Health Organization, Manila, Philippines

SUMMARY

SETTING: The National Tuberculosis Programme (NTP) in Cambodia, one of the countries most affected by tuberculosis (TB) and human immunodeficiency virus (HIV) infection in Asia.

OBJECTIVE: To conduct national HIV prevalence surveillance among TB patients, to estimate HIV prevalence among TB patients and to determine the potential of the NTP as a source for antiretroviral treatment (ART) scale-up.

DESIGN: Anonymous unlinked cross-sectional seroprevalence surveys including all TB patients registered by the NTP in January 2003 and January 2005.

RESULTS: HIV prevalence among all TB patients fell from 11.8% in 2003 to 9.9% in 2005 ($P < 0.05$). In

2003 and 2005, respectively 265 and 261 TB patients were identified as HIV-positive in a given month. Among new smear-positive pulmonary TB patients, the prevalence dropped from 8.2% to 5.2% ($P < 0.01$).

CONCLUSION: The two periodic surveys demonstrated a high prevalence of HIV among TB patients in Cambodia. However, the declining incidence of HIV from the late 1990s might now be reflected in the HIV prevalence among new smear-positive TB patients. The NTP is a potential source of ART if HIV counselling and testing are made more widely available to TB patients.

KEY WORDS: tuberculosis; TB-HIV; surveillance; Cambodia

WITH A POPULATION of 14 million, Cambodia is one of the countries most affected by tuberculosis (TB) and human immunodeficiency virus (HIV) infection in Asia. It ranks 22nd among high-burden countries for TB by the World Health Organization (WHO),¹ with an estimated incidence of 506 per 100 000 population for all forms of TB and 226/100 000 for new smear-positive pulmonary TB (PTB).¹ The national TB prevalence survey conducted in 2002 found the prevalence of smear-positive PTB to be 269/100 000.² The country attained good treatment outcomes, with a cure rate of new smear-positive PTB of 89%, exceeding the global target of 85%. Although the case detection rate of new smear-positive PTB was 60% in 2003,¹ according to the National TB Programme (NTP) it reached 70% in 2005 (National TB conference, Phnom Penh, Cambodia, March 2006).

The HIV epidemic in South-East Asia, which started in the late 1980s, reached Cambodia in the early 1990s.³ Among the population aged 15–49 years, estimated HIV prevalence rates peaked at 3.0% in 1997 and have remained at around 2% (Figure 1).⁴ In the late 1990s, the NTP noted an increase in the number

of deaths during TB treatment, as well as an increase in notifications of smear-negative PTB and extra-pulmonary TB (EPTB) cases in Phnom Penh, the capital. These phenomena were considered to be mostly due to the HIV epidemic. A rapid increase in HIV-related TB was observed in neighbouring countries in the 1990s.^{5,6}

Beginning in 1995, HIV sentinel surveillance included TB patients as one sentinel group.⁷ HIV prevalence among hospital-based samples of TB patients was 2.5% in 1995 and steadily increased to 8.4% in 2002 (Figure 1).⁷ Although the sentinel surveillance was adequate for assessing the overall trend of HIV prevalence, it was questionable whether the hospital-based sampling of TB patients was representative of TB patients after the change in official policy of the NTP in 2001, where, under decentralised DOTS, most TB patients detected by a primary health centre were treated there without visiting a hospital.

HIV care in Cambodia, including antiretroviral treatment (ART), has been changing rapidly with strong donor support. However, the availability of services for TB patients seeking HIV testing and counselling

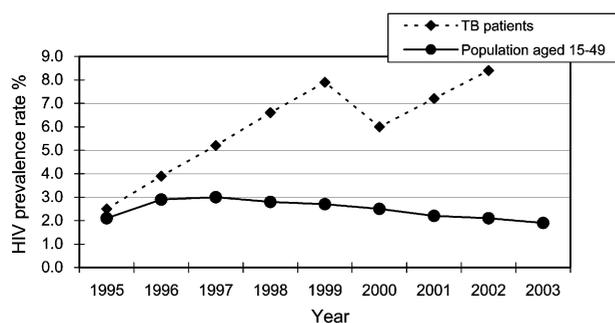


Figure 1 Estimated HIV prevalence rates among persons aged 15–49 years and among TB patients by HIV sentinel surveillance in Cambodia, 1995–2003. Source: National Centre for HIV/AIDS, Dermatology and STDs, Cambodia. Note: HIV sentinel surveillance in 2003 did not include TB patients, and was suspended in Cambodia after 2003.

and ART has been limited. Although most TB patients, especially smear-positive patients, are detected and treated by DOTS at primary care level, HIV counselling and testing are available only in Voluntary Counselling and Testing Centres (VCTC) in the district capitals. Moreover, provider-initiated testing is rarely practised or recommended in Cambodia.

To estimate HIV prevalence among TB patients and to determine the potential of the TB services as an entry point for ART, the first cross-sectional survey of HIV seroprevalence among TB patients was carried out in 2003. After the survey revealed high HIV prevalence, HIV counselling and testing began to be routinely offered to TB patients at the National Centre for Tuberculosis and Leprosy Control (CENAT) and some pilot districts; however, systematic methods of surveillance through the health information system were still lacking. Furthermore, periodic special surveys should be repeated every 2–3 years to collect corroborative surveillance information.⁸ The second national HIV seroprevalence survey among TB patients was therefore implemented in 2005 to monitor changes in HIV among TB patients.

METHODS

Study population

Both surveys were anonymous, unlinked cross-sectional surveys. All TB patients newly diagnosed and registered with the NTP in January 2003 and January 2005 were eligible for inclusion. All TB facilities under the NTP were involved in the study to avoid missing any extremely high prevalence areas due to cluster sampling. The surveys included patients with any type of TB in every treatment category except those who were transferred in. Patients whose serum samples could not be obtained or who did not meet the NTP definition of a TB patient (such as smear-negative PTB without chest radiography) were excluded from the analysis.

Sample size and sampling procedure

For the calculation of sample size in the 2003 survey, we assumed an estimated HIV prevalence of 10% among new smear-positive PTB patients. Allowing for a 2% difference as an acceptable error with a 95% confidence interval (CI), 864 samples were necessary.⁹ Assuming a refusal rate of 10% and misclassification rate of 20% (based on the experience of the NTP), $864/0.9/0.8 = 1200$ samples were required for the first survey. To obtain the required inclusion period to reach the sample size, we found that the number of registered new smear-positive PTB cases in the first quarter of 2002 was 3982. The required inclusion period was thus 0.9 months ($1200/[3987/3] = 0.9$). All consecutive eligible patients registered in one month across the country were therefore recruited.

To enhance comparability, the 2005 survey used the same sampling framework and took place in the same month as in 2003 (January).

Laboratory procedures

Blood samples were sent to the central NTP laboratory at CENAT. Particle agglutination assay (Serodia HIV1/2, Fujirebio, Tokyo, Japan) and immunochromatography (Determine HIV1/2, Abbott, Wiesbaden, Germany) were used simultaneously. Serum samples that reacted to both tests were considered positive. Those that reacted to only one test were further examined by ELISA (Genscreen Plus Ag-Ab, Bio-Rad, Hercules, CA, USA).

Data management and analysis

Basic demographic and TB case-related data were gathered on each patient and recorded anonymously on the data collection form to protect patient privacy. The form and the serum sample for each patient were labelled by a unique study number. Patient information was matched with HIV test results and handled only by responsible investigators at the central level. All data were entered into a computerised database and analysed using Stata8 (Stata Corp LP, College Station, TX, USA).

Ethical consideration

Anonymous unlinked HIV testing was applied and the surveys were carried out following Cambodian Ethical Guidelines for Health Research Involving Human Subjects. Informed consent for the survey was obtained from all participants who agreed to blood drawing. The protocol for both surveys was reviewed and accepted by the Institutional Review Board of the Cambodia Ministry of Health.

RESULTS

HIV prevalence

The total number of TB patients contacted was 2295 in 2003 and 2668 in 2005. Results were obtained from 97.8% in 2003 and 98.7% in 2005.

The overall HIV prevalence among TB patients was 11.8% in 2003 and 9.9% in 2005 (Table 1). Respectively 265 and 261 HIV-positive TB patients were identified for the month of January in 2003 and 2005. HIV prevalence for smear-positive PTB, smear-negative PTB and EPTB was respectively 8.5%, 21.9% and 19.7% in 2003, and 5.4%, 15.5% and 22.2% in 2005. HIV prevalence among males was higher than among females in the 2003 survey ($P < 0.01$); however, there was no difference in 2005. Higher HIV prevalence was seen among the sexually active age groups 25–34 and 35–44 years.

Although the survey was not designed to compare prevalence by province, large geographic differences were observed, ranging from 0% to >30%. The prevalence rate in Phnom Penh was as high as 26.0% in 2005, having declined from 34.3% in 2003. The Thai border area and coastal area were also sites with a high HIV-positive rate.

HIV prevalence among new smear-positive PTB cases declined from 8.2% (128/1558) in 2003 to 5.2% (87/1674) in 2005 (Figure 2). Although the decline in HIV prevalence was also observed in smear-negative PTB cases, from 21.9% to 15.5% ($P < 0.05$),

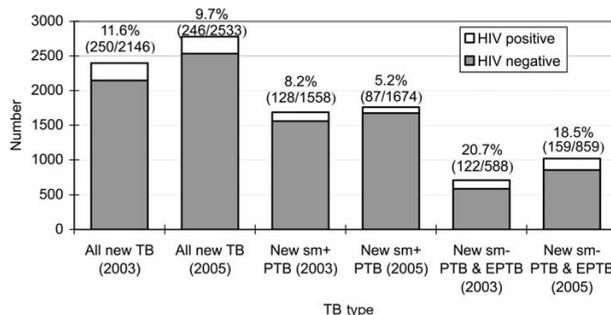


Figure 2 Comparison of HIV prevalence among new TB cases between the HIV seroprevalence surveys among TB patients in Cambodia (2003 vs. 2005). HIV = human immunodeficiency virus; TB = tuberculosis; sm+ = smear-positive; PTB = pulmonary TB; sm- = smear-negative; EPTB = extra-pulmonary TB.

the HIV prevalence increased slightly, from 19.7% to 22.2%, in EPTB patients.

HIV prevalence among males and females in each age group in 2005 was compared. In the sexually active age groups, the prevalence among females was higher than in males in younger adults (Table 2). The difference in HIV prevalence between males (2.6%)

Table 1 HIV seroprevalence among TB patients in Cambodia by patient characteristics, January 2003 and January 2005

	2003		2005		P value
	HIV-positive n/N (%)	95%CI	HIV-positive n/N (%)	95%CI	
New smear-positive PTB	128/1558 (8.2)	6.8–9.6	87/1674 (5.2)	4.1–6.3	0.001
All TB cases tested	265/2244 (11.8)	10.5–13.2	261/2632 (9.9)	8.8–11.1	0.034
Sex					
Male	161/1189 (13.5)	11.7–15.6	130/1302 (10.0)	8.4–11.6	0.006
Female	104/1055 (9.9)	8.2–11.9	131/1330 (9.8)	8.2–11.5	0.995
Age group, years					
0–14	9/60 (15.0)	7.1–26.6	4/52 (7.7)	0.4–14.9	0.229
15–24	21/216 (9.7)	6.1–14.5	14/226 (6.2)	3.1–9.3	0.170
25–34	94/346 (27.2)	22.6–32.2	104/420 (24.8)	20.6–28.9	0.449
35–44	85/503 (16.9)	13.8–20.5	103/587 (17.5)	14.5–20.6	0.778
45–54	25/438 (5.7)	3.8–8.4	26/498 (5.2)	3.3–7.2	0.743
55–64	19/402 (4.7)	2.9–7.4	8/468 (1.7)	0.5–2.9	0.011
≥65	12/279 (4.3)	2.2–7.4	2/381 (0.5)	0.0–1.3	0.001
TB type					
Smear-positive PTB	140/1644 (8.5)	7.2–10.0	95/1748 (5.4)	4.4–6.5	<0.001
Smear-negative PTB	67/306 (21.9)	17.5–27.0	68/440 (15.5)	12.1–18.8	0.025
EPTB	58/294 (19.7)	15.3–24.7	98/442 (22.2)	18.3–26.0	0.427
Category					
New	249/2146 (11.6)	10.3–13.1	246/2533 (9.7)	8.6–10.9	0.036
Relapse	13/83 (15.7)	8.6–25.3	9/68 (13.2)	5.2–21.3	0.674
Other retreatment	1/7 (14.3)	0.4–57.9	0/3 (0.0)	0	—
Unknown	2/8 (25.0)	3.2–65.1	0/4 (0.0)	0	—
Others	0	0	6/24 (25.0)	7.7–42.3	—
Province*					
Phnom Penh	99/289 (34.3)	28.8–40.0	61/235 (26.0)	20.4–31.6	0.040
Thai border area	57/445 (12.8)	9.7–15.9	85/568 (15.0)	12.0–17.9	0.327
Coastal area	22/134 (16.4)	10.1–22.7	21/154 (13.6)	8.2–19.1	0.509
North-east	3/58 (5.2)	0.0–10.9	3/68 (4.4)	0.0–9.3	0.842
Others	84/1318 (6.4)	5.1–7.7	91/1607 (5.7)	4.5–6.8	0.420

* Provinces are categorised into five areas according to geographical and socio-economic similarities, to highlight regional differences.

HIV = human immunodeficiency virus; TB = tuberculosis; CI = confidence interval; PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis.

Table 2 Comparison of HIV prevalence by sex in each age group among TB patients in the HIV seroprevalence survey in Cambodia in 2005

Age group, years	Total <i>n</i>	Male <i>n</i>	Female <i>n</i>	Male HIV patients %	Female HIV patients %	OR	<i>P</i> value*
0–14	52	26	26	11.5	3.8	3.26	0.61
15–24	225	114	111	2.6	9.9	0.25	0.03
25–34	420	203	217	23.6	25.8	0.89	0.65
35–44	587	301	286	19.3	15.7	1.28	0.28
45–54	498	215	283	6.5	4.2	1.57	0.31
55–64	468	241	227	1.2	2.2	0.56	0.49
≥65	381	202	179	0.5	0.6	0.89	1.00

* Statistically significant at the 5% level.

HIV = human immunodeficiency virus; TB = tuberculosis; OR = odds ratio.

and females (9.8%) was statistically significant in the 15–24 years age group ($P < 0.05$).

DISCUSSION

The study design, anonymous and unlinked surveys, might have contributed to the high participation rates. January, in the middle of the cool dry season, is also considered the best season for carrying out the survey: we may have captured more incident TB cases owing to the better accessibility of the health facilities. The high prevalence of HIV among TB patients was confirmed by the two surveys. However, there was a decline in PTB patients, especially in new smear-positive PTB, while HIV prevalence among EPTB patients remained high.

There are several possible reasons for this phenomenon. First, a major reason could be that the HIV epidemic in Cambodia has been declining for several years. In the early stages of HIV/AIDS, clinical features of TB are generally similar to those in HIV-negative cases, while TB in advanced AIDS is more likely to be smear-negative PTB or EPTB.¹⁰ HIV prevalence among smear-positive PTB cases might therefore reflect a more recent profile of the HIV epidemic, although HIV prevalence among EPTB cases might reflect HIV infection that occurred at the peak of the HIV epidemic in Cambodia in the 1990s.⁴ The HIV prevalence rate among antenatal clinic attendants in the HIV sentinel surveillance had a peak of 2.82% in 1997 and then

declined slowly to 1.9% in 2003.⁴ It is inferred that the decline of HIV prevalence among smear-positive PTB cases in 2005 reflected the recent downward trend in HIV in Cambodia. Second, improved case detection of smear-positive PTB owing to the expansion of DOTS to peripheral health centres between 2003 and 2005 (Table 3) might have affected the survey results. The NTP started ambulatory DOTS in 1999 and expanded the DOTS service rapidly from 2002 to cover all primary care health centres by the end of 2004.¹¹ Improved access to microscopy examination in rural villages where HIV prevalence is usually low possibly diluted the HIV prevalence in smear-positive PTB cases in 2005. Third, although the capacity to diagnose smear-negative PTB and EPTB is still limited in Cambodia,¹¹ recognition of a high incidence of TB among HIV-infected patients might change diagnostic practices to suspect and diagnose more TB among HIV-positive patients.

It seems reasonable that the age group 25–34 years showed the highest prevalence of HIV in both surveys. The higher prevalence among females than males aged 15–24 years might suggest that sexual activity begins earlier among females than among males and that the main route of HIV transmission in Cambodia is sexual.

There are two major limitations of this surveillance. One is the uncertain diagnosis of smear-negative PTB and EPTB. Smear-negative PTB is particularly likely to be diagnosed in hospitals without a radiologist or chest physician. Culture examinations to confirm diagnosis are available only in the National TB Centre and a few provinces with strong donor support. The other limitation is the very low involvement of child TB cases in the NTP, which may have led to the very strange observation in the 2005 survey where 11.5% of boys aged <15 years were HIV-positive.

From the NTP's point of view, not only the proportion but also the absolute number of HIV-positive cases underlines the importance of expanding TB-HIV collaborating activities, such as examinations for ART eligibility, screening for other opportunistic infection and cotrimoxazole preventive therapy (CPT). As the notification of all TB cases was 28 386 in 2003 and 36 123 in 2005, the expected numbers of HIV-positive TB patients in the NTP in 2003 and 2005 would be respectively 3350 (95%CI 2980–3747) and 3576

Table 3 Number of service facilities for TB and for HIV as of January 2000, 2003 and 2005

	DOTS treatment and sputum collection centres	TB microscopy centres	TB diagnostic centres with radiography	VCT sites for HIV testing	ART centres
January 2000	154	150	48	12	0
January 2003	531	169	63	36	5
January 2005	1042	180	63	74	17

Source: National Centre for Tuberculosis and Leprosy Control and National Centre for HIV/AIDS, Dermatology and STDs, Cambodia.

TB = tuberculosis; HIV = human immunodeficiency virus; VCT = voluntary counselling and testing; ART = antiretroviral treatment.

(95%CI 3178–4010), if we applied our study findings from nearly 100% sampling of TB patients across the country in a given month. The WHO estimated the number requiring ART to be 22 000, and Cambodia set itself a target to treat 10 000 patients through the 3 by 5 initiative.¹² With strong efforts made to expand the programme, the target was achieved: a total of 12 355 patients were receiving ART by the end of 2005.¹³ However, the number of people with HIV/AIDS in need of ART is increasing, even as the incidence of HIV infection among the general population is reported to be declining in Cambodia.¹³ The survey identified that the NTP is a potential source for detecting ART candidates if HIV counselling and testing is made more widely available to TB patients. Moreover, CPT prevents a significant portion of deaths during TB treatment.^{14,15} Considering the high proportion of HIV-positive patients among smear-negative PTB and EPTB cases, HIV testing should also be included in the TB diagnostic process, especially in provinces where TB-HIV prevalence is thought to be high.

A previous study indicated that the HIV epidemic has had a profound and prolonged impact on the TB burden for a decade after the peak of the HIV epidemic in a northern province in Thailand.¹⁶ Because Cambodia is adjacent to Thailand and the countries share geographic and cultural similarities, and also because of the similarities in the HIV epidemic trend between the two countries, it is estimated that the HIV epidemic will continue to have an effect on the TB epidemic for the next few years in Cambodia.

Our study revealed some high prevalence areas in the country: Phnom Penh, the Thai border area and the coastal area. This demonstrates the need for early implementation of TB-HIV services in these areas, which were designated as pilot sites for joint collaborative activities.^{17,18}

The surveillance method of conducting two periodic surveys within a 2-year interval was appropriate at this time in Cambodia, as HIV data from the routine TB service, as seen in Côte d'Ivoire,¹⁹ were not available. There was a large and growing disparity between the numbers of TB service centres and HIV testing centres during the two survey periods (Table 3). Health services for HIV/AIDS have been limited, and testing for HIV among TB patients was not as advanced as we had expected. These situations highlight the necessity to repeat periodic surveys.

Continuing this surveillance will provide a unique account of the TB and HIV epidemic from Asia in the era of ART, in contrast to the many reports about TB as it relates to the ART programmes in Africa^{20,21} and other continents.^{22,23} Because the HIV epidemic trends and cultures are different in Africa and Asia, our surveillance is useful for other Asian countries besides Cambodia, and there should be a great deal of interest in observing the impact of ART expansion through the next round of this periodic survey. Furthermore, as

HIV counselling and testing is rapidly expanding from province to district, a survey in which results can be provided to TB patients is anticipated in the next round.

CONCLUSION

Although a significant decline in HIV prevalence among new smear-positive and -negative PTB patients was observed, HIV seroprevalence among TB patients of all forms remains as high as 10%. More than 3500 HIV-positive TB cases a year could be diagnosed by the NTP in Cambodia, and the TB services could be a potential entry point for ART. Where a systematic method of surveillance of HIV among TB patients is underdeveloped, as in Cambodia, repeating periodic surveys, such as monitoring the dual TB-HIV epidemic, estimating its trend and future course and identifying the risk factors for HIV infection, provides useful information. As Cambodia is a resource-limited country where HIV prevalence among TB patients could remain high, a survey using the same method may need to be repeated until such a time as reliable HIV data from routine TB services become available.

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R É S U M É

CONTEXTE : Programme National de Tuberculose (PNT) au Cambodge, un des pays d'Asie les plus affectés par l'infection de la tuberculose (TB) et le virus de l'immunodéficience humaine (VIH).

OBJECTIF : Mener une surveillance nationale de la séroprévalence VIH chez les patients TB afin d'estimer la prévalence du VIH chez les patients TB et de déterminer les potentialités du PNT comme source d'expansion du traitement antirétroviral (ART).

SCHÉMA : Enquêtes anonymes transversales et non-liées impliquant tous les patients TB enregistrés par le PNT respectivement en janvier 2003 et janvier 2005.

RÉSULTATS : En 2005, la prévalence du VIH dans l'ensemble des patients TB a été de 9,9%, en décroissance depuis 11,8% en 2003 ($P < 0,05$). En 2003 et 2005, re-

spectivement 265 et 261 patients TB ont été identifiés comme séropositifs pour le VIH dans l'ensemble d'un mois. Parmi les nouveaux patients TB à bacilloscopie positive des crachats, la prévalence du VIH a baissé de 8,2% à 5,2% ($P < 0,01$).

CONCLUSION : Deux enquêtes périodiques ont démontré une haute prévalence du VIH chez les patients TB au Cambodge. Toutefois, la décroissance de l'incidence du VIH à partir de la fin des années 1990 pourrait se refléter maintenant dans la séroprévalence du VIH chez les nouveaux patients TB à bacilloscopie positive des crachats. Le PNT est une source potentielle d'ART si l'on veille à ce que l'accompagnement et les tests pour le VIH soient plus largement accessibles aux patients TB.

R E S U M E N

MARCO DE REFERENCIA : Programa Nacional de la Tuberculosis (PNT) en Camboya, uno de los países más afectados por la tuberculosis (TB) y la infección por el virus de la inmunodeficiencia humana (VIH) en Asia.

OBJETIVO : Realizar una vigilancia nacional de seroprevalencia del VIH en pacientes tuberculosos, a fin de estimar la prevalencia del VIH en los pacientes con TB y determinar el potencial del PNT como fuente de ampliación del tratamiento con antirretrovíricos (ART).

MÉTODOS : Se llevaron a cabo encuestas anónimas no vinculadas de todos los pacientes con TB registrados en el PNT en enero de 2003 y enero de 2005.

RESULTADOS : La prevalencia global de infección por el VIH en todos los pacientes tuberculosos fue 9,9% en 2005, una disminución con respecto al 11,8% en 2003

($P < 0,05$). En 2003, 265 pacientes tuberculosos presentaron serología positiva para el VIH y 261 en 2005 durante un lapso de un mes. En los casos nuevos de TB pulmonar con baciloscopia positiva la prevalencia de VIH disminuyó de 8,2% a 5,2% ($P < 0,01$).

CONCLUSIÓN : Dos encuestas periódicas pusieron en evidencia la alta prevalencia de infección por el VIH en los pacientes tuberculosos en Camboya. Sin embargo, la incidencia decreciente del VIH desde finales de la década de 1990 se podría reflejar ahora en la seroprevalencia de los casos nuevos de TB con baciloscopia positiva. El PNT es una fuente potencial de suministro de ART, siempre y cuando se amplíe el acceso a la orientación y prueba diagnóstica del VIH a los pacientes con TB.