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ORIGINAL PAPER

Impact of Integrating HIV and TB Care and Treatment in a Regional Tuberculosis Hospital in Rural Guatemala

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Abstract Resource-limited settings have made slow progress in integrating TB and HIV care for co-infected patients. We examined the impact of integrated TB/HIV care on clinical and survival outcomes in rural western Guatemala. Prospective data from 254 newly diagnosed TB/HIV patients (99 enrolled in the pre-integrated program from August 2005 to July 2006, and 155 enrolled in the integrated program from February 2008 to January 2009) showed no significant baseline differences between clients in the two periods. They were principally male (65.5 %), Mayan (71 %), median age 33 years, and CD4 count averaged 111 cells/mm^3. TB/HIV co-infected patients were more likely to receive antiretroviral therapy in the integrated program than in the pre-integrated program (72 vs. 22 %, respectively) and had lower mortality (HR 0.22, 95 % CI 0.14–0.33). This study shows how using a TB setting as the entry point for integrated TB/HIV care can improve health outcomes for HIV-positive patients in rural Guatemala.

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Resumen Países en vía de desarrollo con recursos limitados han avanzado lentamente en la integración de los programas de TB y VIH para los pacientes co-infectados. Hemos examinado el impacto de la integración de la atención integral del TB/VIH sobre los resultados clínicos y de la sobrevivencia en área rural de Occidente de Guatemala. Datos prospectivos de 254 nuevos casos de infección de TB/VIH (99 reclutados entre agosto 2005 a julio 2006 en el programa pre-integrado y 155 reclutados entre febrero de 2008 a enero del 2009 en el programa integrado), no mostraron diferencias significativas en la línea basal entre los clientes de los programas en los dos periodos. Estos eran principalmente varones (65.5 %), maya (71 %), promedio de edad fue de 33 años, y el recuento de CD4 al inicio del estudio fue de 111 células/mm^3. Los pacientes en el programa TB/VIH integrado comparado a los pacientes en el programa pre-integrado eran más probables para recibir terapia antirretroviral (72 % vs. 22 %, respectivamente) y tuvieron menos riesgo de mortalidad (HR 0.22, 95 % CI 0.14–0.33). Este estudio mostró cómo la clínica de TB fue el punto de entrada para proporcionar un programa de atención integral de TB/VIH y ha logrado un mejor resultado de salud para pacientes con el VIH en el área rural de Guatemala.

Keywords HIV/AIDS · Tuberculosis · HIV and TB co-infection intervention · Guatemala

Introduction

Around 2 billion people worldwide are infected with Mycobacterium tuberculosis, the causative agent of tuberculosis (TB). Infection rates are especially high in resource-limited settings. The TB and human immunodeficiency virus (HIV) pandemics are closely intertwined [1, 2]. Since the

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late 1980s, countries with high HIV prevalence (i.e., more than 1 % of the general population infected with HIV) have experienced high mortality rates among individuals co-infected with TB and HIV [3]. Globally, a third of individuals with HIV are co-infected with TB, and in 2008 TB accounted for 26 % of AIDS-related deaths [2, 4].

Early recommendations for a long delay in initiating ART in TB patients to avoid immune reconstitution syndrome have proven largely unfounded, as research has demonstrated that early initiation of ART among co-infected patients reduces mortality [5–9]. This heightens the operational importance of integrated TB/HIV services. Integrated care was shown to increase ART initiation by 60 % among co-infected patients, reducing time to initiation by more than 2 months (72 days) on average [10]. Randomized trials have shown that early ART initiation (2 weeks after the onset of anti-TB treatment) vs later ART initiation (8 weeks after) reduces mortality among advanced immunodeficient ($\leq$50 CD4 cells/mm^3) HIV-positive patients who are smear positive for acid-fast bacilli [5, 6, 9]. Havlir et al. [7] showed in TB/HIV co-infected patients with low CD4 cell counts (<50 CD4 cells/mm^3) that earlier ART (within 2 weeks after TB treatment initiation) significantly reduced new AIDS-defining illnesses, such as extra-pulmonary tuberculosis, and death compared with late initiation (8–12 weeks after initiating TB treatment). A systematic review of integrated TB/HIV services in low- and middle-income countries has identified 5 types of TB/HIV service integration: TB services that refer a patient for HIV testing, TB services that test for HIV and refer for ART, facilities that test for and treat HIV and TB in one place, HIV services that refer for TB testing, and HIV services that screen for TB and refer for treatment [11]. Services based on referral may be easier to manage in resource-limited settings, but single-facility services that test for HIV and TB in one place are more likely to provide treatment for both diseases [11].

Tuberculosis continues to be a major infectious disease in Guatemala because many people are infected with latent TB. The estimated incidence rate of active TB is 61 (50–73) cases per 100,000 inhabitants [12]. The departments (a Guatemalan department is about the size of a large county in the USA) with the highest reported TB caseloads are Quetzaltenango (149 cases/100,000 inhabitants), San Marcos (31 cases/100,000 inhabitants), and Escuintla (88 cases/100,000 inhabitants) [13]. These same departments report caseloads above the national average (>226 cases/100,000 inhabitants) of HIV/AIDS [13, 14]. Overall HIV prevalence in the general population is estimated at 0.8 % [15]. WHO reported that 19 % of the TB incident population in Guatemala was also infected with HIV, and only 10.1 % of this population received treatments for both infections [16]. In 2008, the National Center for Epidemiology in Guatemala reported HIV seroprevalence of 17.3 % among TB patients.

Until now, most studies of HIV and TB treatment integration have been conducted in Africa, where the bulk of the TB/HIV co-infection burden exists [17–19]. No such studies have been published from the high-TB-burden countries in Central and South America. We therefore implemented and examined the impact of integrated TB/HIV treatment on mortality and other clinical outcomes among newly diagnosed, co-infected patients in rural western Guatemala.

Methods

Setting

The study took place at Hospital Dr. Rodolfo Robles (HRR), one of two regional TB hospitals in Guatemala, located in a rural setting in the highland region of Quetzaltenango. Patients are mostly Mayan and come to HRR from distant communities in western Guatemala and the southern part of Chiapas, Mexico. They have limited resources, minimal education, and are typically characterized as agricultural workers, housewives, house builders, teachers, or bus drivers. The region has experienced a growing HIV epidemic over the past 10 years. In 1991, HRR initiated HIV testing in its outpatient department. The number of HIV-positive patients among newly diagnosed TB patients has increased steadily, from 16 out of 379 (4 %) in 1995 to 172 out of 366 (47 %) in 2007 [20, 21].

Study Design

Newly diagnosed, TB/HIV co-infected patients were invited consecutively to participate in the study. A total of 254 co-infected individuals were eligible for inclusion: patients aged 15 years or older who had smear-positive or clinically diagnosed TB and had tested positive for HIV in the outpatient clinic of the regional TB hospital. Ninety-nine patients were enrolled from August 2005 to July 2006, before the integrated TB/HIV care and treatment intervention program (hereafter called "pre-integrated program"), and 155 were enrolled from February 2008 to January 2009, after the integrated TB/HIV intervention was installed (hereafter called "integrated program"). All patients provided consent to collect demographic information and use their clinical data for outcome evaluation of the programs. An ethics committee from the Autonomous University in Quetzaltenango, Guatemala, reviewed and approved the study protocol.

The study design was a quasi-experimental intervention with pre- and post-study evaluations. Practical and ethical

issues would have precluded assigning co-infected patients to a control group without access to ART and observing their survival rates in a randomized trial. Any patient who entered the study and subsequently discontinued contact for any reason, including withdrawal from the study or being unable to return to HRR due to illness or unascertained death, was considered a "loss to follow-up." "Referred out for ART treatment" is defined as a patient in the pre-integrated program who was given a written referral to receive HIV care and treatment at the integrated care clinic in Guatemala City.

Intervention Description

After the deaths of more than 250 TB/HIV co-infected patients—a significant proportion due to lack of ART access, presumably—a multisectorial consortium led by the national HIV program, a local NGO, an international organization, and HIV patient advocacy groups presented a model for integrated TB/HIV care and treatment to the HRR staff in late 2005. This plan was adopted by the hospital, and an integrated TB/HIV program was put in place that assured patients would receive quality care free of charge. Twenty TB health workers at HRR were trained in an HIV module that included HIV testing and counseling, differences between HIV and AIDS, challenges of TB diagnosis among HIV-positive patients, opportunistic-infections diagnosis and treatment, ART, and principles of integrated care for co-infected patients. Eight of these TB health workers received additional training in HIV integrated care through a national 8-month diploma program in Guatemala City.

TB care and treatment protocols were based on the national TB guidelines [22–25] and were similar for both the pre-integrated and integrated programs. All patients who reported fever, night sweats, and persistent coughing of more than 2 weeks' duration were provided with a physical examination, acid-fast bacilli (AFB) test on microscopic examination of sputum samples, and chest X-ray. Two sputum samples from each patient were used to identify AFB on microscopic examination. TB clinicians evaluated all test results, chest X-rays, and clinical symptoms. Patients who had a smear-positive sputum sample, had never received anti-TB treatment in the past, were clinically ill with TB, and were nonambulatory were admitted to the hospital. Patients who were ambulatory were referred to the health center nearest their residence to initiate short-course anti-TB direct observed treatment (DOTS) through a health worker (Table 1).

For smear-negative patients, TB diagnosis was based on clinical criteria. In 2007, HRR adopted the WHO recommendation to administer anti-TB treatment to smear-negative HIV-positive patients with clinical symptoms of TB. In the pre-integrated program, smear-negative co-infected patients with clinical symptoms of TB were not routinely given anti-TB treatment. In both the pre-integrated and integrated programs, all HIV-positive cases were confirmed by 3rd-generation HUMAN ELISA (Human Gesellschaft für Biochemica Diagnostica, Wiesbaden, Germany).

During the pre-integrated program, TB patients with positive confirmatory tests for HIV were referred for HIV care and treatment for 6 months at Roosevelt Hospital in the capital, which is 109 km or 5 h by bus from the study site, then transferred to the Coatepeque HIV clinic, which is 68.5 km or 2.5 h by bus from the study site. At Roosevelt Hospital, baseline CD4 count, viral load, complete blood count, hepatitis panel, and hepatic enzyme tests were administered. The patients received co-trimoxazole prophylaxis and treatment for opportunistic as well as sexually transmitted infections. This program also included access to diverse laboratory diagnoses for opportunistic infections,

Table 1 Differences between pre-integrated and integrated program among TB/HIV co-infected patients in rural Guatemala

Description	Pre-integrated	Integrated
TB treatment	Received treatment if smear-positive sputum sample	Received treatment if smear-positive sputum sample or clinical criteria for smear-negative samples, according to WHO recommendations
HIV care and treatment referral	Referred to outside service for HIV care and treatment	Received HIV care and treatment at the same facility as TB diagnosis
Clinic where ART was accessed	ART received at a distant referral site	ART clinic at the same facility as TB diagnosis
TB infection control at ART clinic	Forced-air ventilation system	Improved cross-air ventilation in waiting room, nurses' pre-exam room, psychology and adherence rooms. Exam rooms have air extraction systems, UVP filtration, and ultraviolet lighting

computer-assisted tomography (CT scanning), and magnetic resonance imaging.

During the integrated TB/HIV program, patients received HIV care and treatment within the same outpatient facility that managed their TB care. Patients in the integrated program received provider-initiated HIV counseling and testing in the outpatient clinic. All patients were given pre- and posttest counseling, and HIV-positive patients were referred to an onsite clinic for care and ART. Patients were tested for baseline CD4, viral load, complete blood count, hepatitis panel, and hepatic enzymes, and they were given co-trimoxazole prophylaxis and treatment for opportunistic and sexually transmitted infections. In addition to clinical tests and treatments, the integrated TB/HIV program offered CT scanning, magnetic resonance imaging, and lung and mass biopsies for HIV-positive patients, when requested by a physician.

Measurements

Two trained, professional nurses contracted by a local NGO collected case report forms (CRFs) at the initial TB/HIV testing and follow-up visits at the HRR TB outpatient clinic (every 3 months) and the ART clinic (every month) from August 2005 to January 2010. Pre-integrated program data were collected through July 31, 2007, allowing patients recruited during July 2006 to be followed for 50 weeks.

For the 45 days following tropical storm Stan on October 5, 2005, infrastructural damage and environmental hazards limited contact with many clinic patients. From March to October of 2007, the number of new patients who could initiate ART was limited by difficulty in securing funds from the Guatemalan Ministry of Health. We therefore waited until February 2008, when the situation was normalized, to initiate the evaluation of the intervention study. CRFs were entered into the computerized program INTEGRA in the integrated care clinic. INTEGRA was used to manage CRFs, CD4 count exams, laboratory reports, opportunistic-infection diagnoses, and women's health exams as well as ART medication, co-trimoxazole prophylaxis, and opportunistic-infection treatments given to patients.

HIV-unit nurses collected data on ART access and CD4 counts at baseline, 3, 6, 9 months, and 50 weeks. Physicians collected data monthly on opportunistic-infection treatment, STI diagnosis and treatment, and prophylaxis. Nurses and clerical personnel entered all information into the INTEGRA database. Treatment information was cross-checked by the pharmacy department. Administrative audits took place every 6 months to ensure that diagnoses corresponded to the medicines being given to each patient. The data were exported to STATA version 11.2 (Stata Corp, College Station, TX) for statistical analyses.

The main predictor variable was participation in the treatment program during the pre-integrated period vs during the integrated period. The primary outcome was mortality among co-infected patients (observed over approximately 50 weeks), and secondary outcomes included median CD4 cells/mm^3 at 50 weeks, TB treatment (yes/no), ART (yes/no), and co-trimoxazole prophylaxis for patients with fewer than 250 CD4 cells/mm^3 (yes/no).

Each CRF tracked baseline demographic information (sex, education level, linguistic group, and age), baseline TB symptoms, TB diagnosis and treatment completion, HIV care and treatment, and referral information. Linguistic group data were based on the patient's last name, which is usually easily distinguishable and considered a valid method for establishing linguistic group.

Statistical Analyses

Demographic characteristics and selected clinical data were summarized using descriptive statistics—including means, medians, and frequencies—for the pre-integrated and integrated programs. Differences between the two groups in clinical and other characteristics were assessed using the χ^2 test for categorical variables and the Wilcoxon test for continuous variables. Crude odds ratios were used to assess associations between intervention and mortality at 50 weeks and intervention and initiation of ART. Mortality outcomes were assessed using Kaplan–Meier (time to event) analyses. The Cox proportional hazards model was used to assess the effects of intervention (integration) on mortality, controlling for sex, ethnolinguistic group, and age. For patients who were still living at 50 weeks, data were censored at the last contact or when a follow-up period of 14 months was reached.

Results

A total of 254 TB/HIV co-infected clients were included in the study. Lost to follow-up were 4.3 % of patients from the pre-integrated program and 11.4 % from the integrated program. The age and sex distributions of those lost to follow-up were similar to the distributions of those who remained in the study. Among the pre-integrated patients, median age was 35 years [interquartile range (IQR) 29–46], while patients in the integrated program were slightly younger, with a median age of 32 years (IQR 27–44). Table 2 shows baseline demographic and clinical characteristics.

The majority of patients in both the pre-integrated and integrated programs were Mayan (73 and 70 %, respectively), which is one of the reasons why the study included Mayan linguistic subgroup as a potential confounding

Table 2 Demographic characteristics and clinical variables among TB/HIV co-infected clients in rural Guatemala ($N = 254$)

Demographic variable	Overall $N = 254$	Pre-integrated program $N = 99$	Integrated program $N = 155$	P value
Age				
Median years (IQR)	33 (28–44)	35 (29–46)	32 (27–44)	$P = 0.14$
15–29 years N (%)	85 (33.4)	26 (26.2)	59 (38.0)	$P = 0.11$
30–39 years N (%)	88 (34.7)	38 (38.4)	50 (32.3)	
40–49 years N (%)	32 (12.6)	17 (17.2)	15 (9.7)	
50 years and older N (%)	49 (19.3)	18 (18.2)	31 (20.0)	
Sex				
Female N (%)	86 (34.5)	29 (29.3)	58 (37.4)	$P = 0.18$
Ethnolinguistic groups	$N = 233$	$N = 85$	$N = 145$	
Mayan N (%)	166 (71.2)	65 (73.0)	101 (70.1)	$P = 0.63$
Occupation	$N = 213$	$N = 94$	$N = 119$	
Domestic worker N (%)	60 (28.2)	28 (29.7)	32 (26.9)	$P = 0.26$
Farmworker N (%)	101 (47.4)	51 (54.3)	50 (42.0)	
Other N (%)	52 (24.4)	15 (16.0)	37 (31.1)	
TB results among TB/HIV co-infected patients	$N = 254$	$N = 99$	$N = 155$	
Smear negative N (%)	189 (74.4)	78 (78.8)	111 (71.6)	$P = 0.20$
Smear positive N (%)	65 (25.6)	21 (21.2)	44 (28.4)	
Accessed anti-TB treatment		$N = 78$	$N = 111$	
Smear negative N (%)		30 (38.5)	64 (57.7)	$P = 0.01$
Accessed anti-TB treatment		$N = 21$	$N = 44$	
Smear positive N (%)		21 (100)	44 (100)	
Baseline CD4 count	$N = 175$	$N = 30$	$N = 145$	
Median cells/mm^3 (IQR)	111 (48–217)	126.5 (52–237)	108 (47–210)	$P = 0.43$
No CD4 available N (%)		69 (69.7)	10 (6.5)	

variable. The predominant occupations were farmworker and domestic worker. There were no significant differences between patients in the pre-integrated and integrated programs with respect to age, sex, linguistic group, occupation, and baseline CD4.

In the pre-integrated program, only 6 patients (6 %) received ART from the Roosevelt/Coatepeque clinics. Patients in the pre-integrated program had a median baseline CD4 count of 127 cells/mm^3 (IQR 52–237, $N = 30$), while patients in the integrated program had a median baseline CD4 count of 108 cells/mm^3 (IQR 47–210, $N = 145$). In the pre-integrated program, however, most patients did not have CD4 cell count results because they did not complete their referral to Roosevelt Hospital in Guatemala City or to the ART clinic in Coatepeque. Of these patients, 18 % survived and eventually received ART at the integrated TB/HIV care clinic when it opened in July 2006. All 155 patients in the integrated program received ART at the integrated care clinic of the regional HRR TB hospital.

As expected, due to changes in treatment protocol, there was a significant increase in the proportion of patients who received TB treatment during integrated care (95 % CI 58.6 vs. 100 %, $P < 0.0001$), as summarized in Table 3.

Substantially more patients received ART in the integrated program (95 % CI 72 vs. 22 %, $P < 0.001$). A significantly lower proportion of patients were deceased at 50 weeks in the post-integration period (95 % CI 27.1 vs. 77.5 %, $P < 0.001$). This difference persisted when examining only those who received TB treatment (95 % CI 27 vs. 71.9 %, $P < 0.001$). The proportion of patients who received co-trimoxazole prophylaxis was also higher in the integrated period (95 % CI 94 vs. 23 %, $P < .001$). Median CD4 cell count at 50 weeks was similar among individuals in the pre-integrated and integrated programs. It should be noted, however, that CD4 counts for pre-integrated patients were measured only among the minority who accessed HIV care. Analysis showed substantially improved survival rates in the integrated care period (Fig. 1). Being a patient in the integrated program was associated with lower rates of observed mortality at 50 weeks (OR 0.09, 95 % CI 0.04–0.17) and increased rates of ART initiation (OR 9.1, 95 % CI 4.8–17.4).

Table 3 Mortality and treatment outcomes among TB/HIV co-infected clients in rural Guatemala ($N = 254$)

Outcome	Pre-integrated program $N = 99$	Integrated program $N = 155$	P value
Anti-TB treatment			
N (%)	58 (58.6)	155 (100.0)	$P < 0.0001$
Co-trimoxazole prophylaxis for CD4 <250 cells/mm^3	$N = 94$	$N = 127$	
N (%)	22 (23.0)	119 (94.0)	$P < 0.0001$
Median CD4 cells/mm^3 (IQR) at 50 weeks	$N = 22$	$N = 108$	$P = 0.34$
	256 (145–414)	216 (120–345)	
Observed mortality at 50 weeks	$N = 98$	$N = 155$	
N (%)	76 (77.5)	42 (27.1)	$P < 0.0001$ odds ratio 0.09 (95 % CI 0.04–0.17)
Observed mortality at 50 weeks for only those who received TB treatment	$N = 57$	$N = 155$	
N (%)	41 (71.9)	42 (27.1)	$P < 0.0001$
Received ART	$N = 99$	$N = 155$	
N (%)	22 (22)	112 (72)	$P < 0.0001$ odds ratio 9.1 (95 % CI 4.8–17.4)

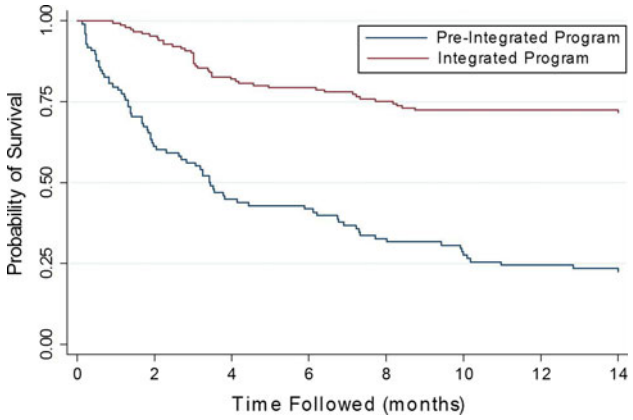

Fig. 1 Kaplan–Meir survival curve for pre-integrated and integrated programs

The adjusted hazard ratio for mortality in the Cox proportional hazards model was 0.22 (95 % CI 0.14–0.33) among patients who received integrated care, compared with patients in the pre-integrated program (Table 4). The adjusted hazard ratio is for comparing the two programs, the integrated one to the pre-integrated one.

Patients in the integrated program were significantly more likely to survive than patients in the pre-integrated program.

Table 4 Cox proportional hazards analysis for mortality among pre-integrated and integrated programs, adjusted for sex, ethnolinguistic group, and age ($N = 231$)

Description	Adjusted hazard ratio	95 % CI	P value
Integrated program vs pre-integrated program	0.22	(0.14–0.33)	$P = 0.001$
Sex (female)	0.48	(0.30–0.75)	$P = 0.001$
Ethnolinguistic groups (Mayan vs. other)	0.69	(0.43–1.11)	$P = 0.124$
Age (per year increase)	1.0	(0.99–1.02)	$P = 0.563$

Discussion

This study is among the first to describe the results of integrated TB/HIV care in Central America, demonstrating that the TB setting can be an effective entry point for treatment of TB/HIV co-infected patients in rural western Guatemala. Survival was significantly higher in the integrated TB/HIV program than in the pre-integrated program. While other factors may have contributed to this outcome, it seems to have been due mainly to the fact that a much higher proportion of patients in the later period received ART. Because more patients received HIV care, more patients received co-trimoxazole prophylaxis, an intervention proven effective for co-infected patients. During the pre-integrated program, HRR sometimes provided co-trimoxazole, but during the integrated program it was provided for all patients with CD4 counts below 250 cells/mm^3.

Our research is consistent with other studies of single-facility TB/HIV treatment integration. In Uganda, more patients were started on ART and TB treatment (94 vs. 78 %, $P < 0.001$), and deaths decreased from 33 to 25 % ($P < 0.001$) in an integrated TB/HIV care center separate from an ART facility [26]. There are no previously published studies from the medium- to high-TB-burden countries in Central and South America.

There were several limitations to this study. CD4 count ideally should have been measured for every patient in the pre-integrated program; instead, it was measured only if the patient reached an HIV care center. The national HIV program policy in 2005–2006 was that a newly detected HIV patient in the interior of the country had to travel to the capital city for initial CD4 and viral load exams as well as to initiate ART, and the majority of patients could not or did not do so. Another weakness was incomplete follow-up of some patients. Patient records at the regional hospital did not include a death date, so the last clinical visit was used for most patients. There was also a confounding variable of policy change during the two study periods. In 2007, there were changes in the minister of health and the HIV program director, which affected policies regarding HIV. Furthermore, WHO recommendations for the initiation of TB treatment based on clinical criteria (not just on smear positivity) in the integrated period probably had positive effects on survival not directly related to integration of care, even though a comparison excluding patients who did not receive TB treatment produced similar results.

In rural western Guatemala, single-facility integrated TB/HIV care seemed to overcome behavioral, structural, and medical obstacles to treatment for co-infected patients. However, more research is needed to find ways to further improve patient outcomes as well as how to extend and implement this model in other non-urban areas. Consideration should be given to intensifying TB case finding among HIV-positive patients, increasing the use of PCR diagnostic tools to determine whether a patient has TB, and assuring infection control for TB in the other 12 decentralized ART sites in Guatemala, thus leading to improvements in access to ART, effective TB diagnosis, and TB control for co-infected patients. Further studies should also examine which tools improve the diagnosis of TB among HIV-positive patients and help shorten the time to initiate ART among advanced immunodeficient ($\leq$50 CD4 cells/mm^3) patients according to international guidelines [27, 28].

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