

Delays in HIV and TB diagnosis and treatment initiation in co-infected patients in Colombia

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Abstract

We investigated the delays in the diagnosis of tuberculosis and/or HIV, their treatment initiation, and factors associated with each delay. All drug-susceptible tuberculosis cases diagnosed in 2014 and 2015 in Colombia, with a confirmed diagnosis of HIV were included. A total of 1909 patients were registered with tuberculosis/HIV co-infection. Seventy-nine percent of patients were men, 50% had sputum smear-negative tuberculosis, culture was done in 50% of cases, 68.5% had <200 CD4 cell count at diagnosis, and 35% had concurrent tuberculosis/HIV diagnosis. Delays in the tuberculosis diagnosis were identified in 54.8% of the patients, and delays in tuberculosis and HIV treatment initiation in 41.8% and 27.4%, respectively. The risk factors associated with delay in tuberculosis diagnosis were age between 15–34 and ≥ 45 years, and those patients who received tuberculin skin test. The risk factor associated with antiretroviral therapy initiation delay was previously-treated tuberculosis patients after failure. It is necessary to implement strategies for early detection and treatment initiation of HIV and to use rapid test for tuberculosis diagnosis in this population.

Keywords

Tuberculosis, HIV, antituberculosis treatment, antiretroviral therapy, delay

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Introduction

Delay in tuberculosis (TB) diagnosis has been associated with TB treatment failure and death (unfavorable outcome) (adjusted odds ratio [AOR]: 2.33; 95% confidence interval [CI] 1.04–5.26), and HIV-positive TB patients were more likely to experience unfavorable outcome than HIV-negative TB patients (AOR: 8.46; 95%CI: 3.14–22.79).¹ Risk factors that have been reported as associated with prolonged delay (>35 days from onset of symptoms to receipt of TB treatment) in TB diagnosis in patients co-infected with HIV are unemployment, alcohol consumption, crowding index, seeking prior treatment, cotrimoxazole treatment, and World Health Organization (WHO) stage 4 disease.²

In addition, HIV-positive TB patients have higher risk for delay in TB treatment compared to HIV-negative TB patients,³ and for delay in HIV treatment initiation due to lower baseline CD4 cell count, TB drug intolerance, nondisclosure of HIV infection,⁴

immune reconstitution inflammatory syndrome,^{5,6} and drug interactions of concomitant use of TB and HIV treatment.

Starting antiretroviral therapy (ART) before or during TB treatment has shown to reduce mortality rates between 44% and 71% (relative risk [RR]=

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0.42, 95% CI: 0.29–0.56).^{7–10} The guidelines for TB treatment from WHO in 2017 and ATS/CDC/IDSA in 2016 recommend that ART should be initiated within the first 2 weeks of TB treatment for patients with CD4 cell count <50 cells/ μ L, and by 8–12 weeks of TB treatment initiation for patients with CD4 cell count \geq 50 cells/ μ L.^{11,12}

Although prompt ART and TB treatment initiation during TB/HIV co-infection is the most relevant goal of TB/HIV collaborative activities in Colombia, the ART only reached 54.7% in 2014 and 60.6% in 2015 in this group (data from the National TB and Control Program reports, unpublished). This could contribute to the high mortality in the country in TB/HIV co-infected individuals (24% in 2014 and 27.2% in 2015) (data from the National TB and Control Program, unpublished).

Within all possible explanations for the high mortality, our aims were to identify the percentage of delays in the diagnosis of TB and/or HIV and their treatments initiation, and the risk factors associated with each delay in 2014 and 2015 in Colombia.

Materials and methods

Study design

This is an operational research (research based on routine reports to answer programmatic questions for decision making^{13,14}) that conducted a retrospective cross-sectional study based on all national reports of TB and HIV co-infected individuals, diagnosed with susceptible TB in 2014 and 2015, notified to the Ministry of Health and Social Protection in Colombia.

Inclusion criteria

All drug-susceptible TB cases diagnosed in the country in 2014 and 2015, with a confirmed diagnosis of HIV.

Exclusion criteria

All types of TB drug resistance (mono-resistance, poly-resistance, multidrug resistance, extensive drug resistance, and rifampicin resistance); no information of HIV status when patients did not accept the HIV test, or did not receive the HIV screening test; and duplicate records. In addition, records that in the National Public Health Surveillance System (SIVIGILA) database were reported as co-infection TB/HIV, but in the high-cost account database, the HIV diagnosis was ruled out.

Data collection

We used two national databases: (1) SIVIGILA: it contains the mandatory reporting of diseases and conditions for national public health surveillance, including all forms of TB cases. (2) High-cost account: this database has all records of people living with HIV, who belong to the contributive or the subsidized system, including the follow-up data.

We searched for all TB cases in both databases, and then, were linked with the “identity document number,” which is unique for each patient. Names and surnames of the patients were also used to validate each record. After the databases were merged, we deleted all names and IDs to keep the confidentiality of the patients.

Variables

Demographic and TB-related variables were taken from SIVIGILA and HIV-related variables from the high-cost account database.

The delays were estimated as follows:

1. *Delay in TB diagnosis:* Time from onset of TB symptoms to the TB case notification (as a proxy variable for TB diagnosis date), classified as “timely” (when it was up to 30 days) and “delayed” (when it was higher than 30 days).
2. *Delay in TB treatment initiation due to the system:* Time from TB case notification date to TB treatment initiation, classified as “timely” (if it started up to two days) and “delayed” (if it was higher than two days).
3. *Delay in HIV diagnosis in TB patients:* Time from HIV diagnosis to notification of the TB case, classified as “a previous diagnosis of HIV” (if the HIV diagnosis was made up to 61 days before the TB diagnosis), “concurrent” (if the HIV diagnosis was made within 60 days before or after the TB diagnosis), and “after the TB diagnosis” (if the HIV diagnosis was made after 61 days or more of the TB diagnosis).

In addition, we analyzed “timely HIV diagnosis” as follow: “early” when CD4+ T-cell count was \geq 500 cells/ mm^3 or a clinical stage of HIV infection was A1 or B1, and “late” with CD4 < 500 cells/ mm^3 or all the remaining clinical stages.

4. *Delay in HIV treatment initiation:* Time from TB treatment initiation to ART initiation, classified in three groups: “ART initiated prior to TB treatment” (if the patient was taking ART before the TB treatment initiation), “timely” (ART initiated within the

first 8 weeks of TB treatment), and “delayed” (ART initiated after 8 weeks of TB treatment).

TB-related variables: History of previous TB treatment (new, previously treated after lost to follow-up or failure and relapse), clinical form (pulmonary or extrapulmonary TB), sputum smear status (negative, 1+ to 3+), culture test result, other auxiliary test for TB diagnosis (clinical, x-ray abnormalities, epidemiological link, tuberculin skin test [TST], and adenosine deaminase).

HIV-related variables: CD4 T-cell count, cotrimoxazole prophylaxis and latent TB infection treatment in those with a previous diagnosis of HIV, and ART.

The other variables evaluated were as follows: gender, age, ethnicity, vulnerable population group (homeless, prisoners, immigrants, displaced, victims of violence, with disability, pregnant women, children abused or neglected under protection of a national agency, former illegal armed people, and mental illness), healthcare worker, living in capitals of the states, and health insurance (“Contributive” meaning those who have work or have the payment capacity to contribute with a percentage of their monthly wage to healthcare access, or have special systems of health like teachers or military forces; “Subsidized” for people that do not have the payment capacity and are subsidized both from the government as well as from resources from the contributive system; and “Not insured”, those that do not belong to any of the previous systems and need to pay with their own resources most of their health care).

Data analysis

We did a descriptive analysis for the variables included in the study and three multivariate analyses. For delays in the TB and HIV diagnosis, and TB and HIV treatment initiation, we estimated the percentages according to each delay and their 95% CI. Then, we estimated the crude and adjusted prevalence ratio (PR) associated with delays in the TB and HIV diagnosis, and TB and HIV treatment initiation. Three multivariate analyses using Poisson regressions were done to identify the risk factors associated with delay in TB diagnosis (model 1), delay in TB treatment initiation (model 2), and delay in HIV treatment initiation (model 3). Variables included in each model were as follows: gender, age, health insurance, classification based on history of previous TB treatment, pulmonary or extrapulmonary TB, and sputum smear status at diagnosis. The adjusted PRs and their 95% CI were reported.

Results

Among 26,459 TB cases reported in Colombia between 2014 and 2015, there were 13,125 TB cases in both databases. We excluded 10,524 TB cases that were HIV-negative, 178 that had TB drug resistance, 483 without information of HIV status, and 31 duplicated records. At the end, there were 1,909 TB/HIV co-infected patients with diagnosis of TB (954 in 2014 and 955 in 2015).

TB/HIV co-infection was higher in men than in women (ratio of 3.9 to 1). The age groups with the highest proportion were 25–34 years (35.6%) and 35–44 years (27.6%). In the vulnerable population groups, 3.4% were homeless people, and 3.3% were prisoners (Table 1).

Of the total cases, 10.8% were previously treated after lost to follow-up (5.4%) or after relapse (5.4%), and 66.3% had pulmonary TB. Sputum smear was carried out in 73.7% of patients (76.4% in patients with pulmonary TB and 23.6% in those with extrapulmonary TB), and 50% of them had a positive result. Culture was done in 42.9% of patients (130/642 = 20.2% in extrapulmonary TB cases), and only half of them had a reported result. Among those with available result, 67.7% were positive.

Half of patients had delays in TB diagnosis (54.8%) and 41.8% in TB treatment initiation. About 68.5% of cases had less than 200 CD4 cell count at diagnosis of HIV (Table 2).

There were no differences in the delays of TB diagnosis and TB treatment initiation by age, ethnicity, and people living in capitals of the states. Patients who received TST had higher percentage (13%) of delays in TB diagnosis than those without TST (8%) (Table 3).

There were no differences in HIV treatment initiation by age, ethnicity, or people living in capitals of states. The delays in ART initiation were higher in victims of violence (PR: 1.16; 95% CI: 1.14–1.18) compared to those who were not, and previously treated patients after failure compared to new TB cases (PR: 1.17; 95% CI: 1.15–1.19) (Table 4).

In the multivariate analysis, the risk factors associated with delay in TB diagnosis were age between 15 to 34 and ≥ 45 years, and those patients who received TST. The risk factor associated with delay in ART initiation was previously treated TB patients after failure (Table 5).

Discussion

The main findings of our study were as follows: (1) low percentage of sputum smear-positive and very low use of culture test in HIV-positive TB patients, (2) the

Table 1. Demographic characteristics of TB/HIV co-infected patients in Colombia, 2014–2015.

Variables	N = 1909	%	95% Confidence interval
Male gender	1516	79.4	77.5–81.1
Age in years			
≤14	17	0.9	0.5–1.3
15–24	174	9.1	7.8–10.4
25–34	680	35.6	33.5–37.8
35–44	526	27.6	25.5–29.5
45–54	333	17.4	15.7–19.1
≥55	179	9.4	8.1–10.8
Ethnicity			
Mestizo and white	1778	93.1	91.9–94.2
Black	94	4.9	4.0–5.9
Indigenous	26	1.4	0.9–1.9
Gypsy	7	0.4	0.1–0.7
Raizal	4	0.2	0.06–0.5
Population group ^a			
Homeless	65	3.4	2.6–4.2
Prisoners	63	3.3	2.5–4.1
Immigrants	20	1.0	0.6–1.5
Displaced	14	0.7	0.4–1.1
Victims of violence	9	0.5	0.2–0.8
Disability	7	0.4	0.1–0.7
Pregnant women	1	0.1	0.002–0.2
Children abused or neglected under protection of a national agency	1	0.1	0.002–0.2
Former illegal armed people	3	0.2	0.04–0.4
Mental illness	4	0.2	0.06–0.5
Nonvulnerable groups	1793	93.9	92.7–94.9
Healthcare workers	35	1.8	1.3–2.5
Living in capital of the states	1245	65.2	63.0–67.3
Health insurance ^b			
Subsidized	1055	55.3	53.0–57.4
Contributive	761	39.8	37.6–42.0
Without insurance	93	4.9	3.9–5.9

^aPeople could be part of two or more groups.

^b“Subsidized” are people that do not have the payment capacity and are subsidized by the government. “Contributive” means those who have work or have the payment capacity contribute with a percentage of their monthly wage to healthcare access.

advanced stage of HIV disease in these patients (68.5% had <200 CD4 cell count at diagnosis and 30% had concurrent TB/HIV diagnosis), and (3) high proportion of patients with delays in TB diagnosis (54.8%), TB treatment initiation (41.8%), and HIV treatment initiation (27.4%).

In 2010, Cain et al.¹⁵ reported the low sensitivity (33%) of traditional definition of cough lasting more than 15 days for TB screening in people with HIV and proposed a new algorithm for TB screening and diagnosis in this population: cough or fever of any duration, night sweats of ≥3 weeks within the last 4 weeks, or loss of appetite. This algorithm has a sensitivity of 93% and a negative predictive value of 97%. It is important to mention that a meta-analysis of observational studies conducted by Getahun et al.¹⁶ in 2011 reported that the algorithm (cough, fever, night

sweats, or weight loss of any duration) had a sensitivity of 78.9%, and a negative predictive value of 97.7%. This finding can be explained by the fact that the original paper of Cain et al.¹⁵ was conducted under ideal conditions, and when the algorithm was implemented in programmatic conditions, there are many factors (barriers) that may contribute to a lower sensitivity.

WHO recommended, in 2011, this rule in their guidelines for intensified TB case finding and isoniazid preventive therapy for people living with HIV in resource constrained settings¹⁷ and kept the recommendation in its latent tuberculosis infection guidelines 2018,¹⁸ based on a systematic review done to assess the performance of this symptom-based screening. In this review, a pooled sensitivity of this algorithm was found at 51% when applied to people living with HIV on ART, but 89.3% when applied to people living with

Table 2. Frequencies of delays in TB/HIV co-infected people in Colombia, 2014–2015.

Outcome	n/data available	%	95% Confidence interval
Delay in TB diagnosis	1043/1902	54.8	52.6–57.1
Delay in TB treatment initiation	715/1710	41.8	39.5–44.1
Delay in HIV diagnosis			
A previous diagnosis of HIV	1206/1906	63.3	61.1–65.4
Concurrent	668/1906	35.0	32.9–37.2
After the TB diagnosis	32/1906	1.7	1.1–2.3
Timely HIV diagnosis			
Early ^a	186/1812	10.3	8.9–11.7
Late ^b	1626/1812	89.7	88.2–91.1
CD4 T-cell count at HIV diagnosis, cells/mm ³			
<200	690/1007	68.5	65.6–71.3
200–350	177/1007	17.6	15.3–20.0
351–500	69/1007	6.9	5.4–8.5
>500	71/1007	7.0	5.6–8.8
Delay in HIV treatment initiation			
ART initiated prior to TB treatment	644/1550	41.5	39.1–44.0
Timely	482/1550	31.1	28.8–33.4
Delayed	424/1550	27.4	25.1–29.6

^aEarly when CD4+ T-cell count where ≥ 500 cells/mm³ or a clinical stage of A1 or B1.

^bLate with CD4 < 500 cells/mm³ or all the remaining clinical stages.

HIV not receiving ART. Specificity was 70.7% in the first group and 27.2% in the second group and a negative predictive value of 99.3% at a TB prevalence of 1% among people living with HIV. Under this screening, patients with cough, fever, weight loss, or night sweats, should be investigated for TB and other diseases. If there are no symptoms or TB is ruled out, patients should receive isoniazid preventive therapy. Despite that these recommendations were adopted in the country beginning 2015, their implementation is still far from optimal.

In addition, in Colombia it is mandatory to use culture for TB diagnosis in all TB/HIV co-infected patients,¹⁹ however, only 42.9% had it, of which 49.5% had available results. In addition, only 20.2% of patients with extrapulmonary TB had available culture test results. In a study conducted in Ethiopia, Balcha et al.²⁰ found that among 137 TB/HIV patients, 22.6% were smear-positive, 70.1% were Xpert-positive, and 89.8% were liquid culture-positive. In addition, they found that Xpert[®] MTB/RIF had a sensitivity to detect TB of 46.7% in patients with CD4 cell count >200 cells/mm³ and increased to 82.9% in those with CD4 cell count ≤ 100 cells/mm³. Compared to our study, TB diagnosis in Colombia could be underestimated due to the low use of culture and incipient use of Xpert[®] MTB/RIF. Those findings highlight the importance of the scale up of rapid tests like Xpert[®] MTB/RIF and liquid culture for TB diagnosis, following the 2013 WHO policy update for the use of Xpert[®] MTB/RIF and reinforced in the 2016 WHO consolidated ARV

guidelines which recommend to offer sputum Xpert[®] MTB/RIF as the first test for TB diagnosis among symptomatic people with any CD4 cell count.²¹

In our study, half of patients had delay in TB diagnosis, and the risk factors associated with the delay were age between 15 to 34 and ≥ 45 years, and those patients who received TST. A study conducted in eight cities in Colombia, that included newly smear-positive pulmonary TB cases found higher delay (72% had >30 days from onset of symptoms to TB treatment initiation).²² In this last study, the risk factors associated with delay were being without healthcare insurance and unknown HIV status. Coming from a neighborhood with a community health worker employed by the national TB program was a protective factor.

Other factors have been described as associated with delay in TB diagnosis in the general population such as self-medication, monetary concerns, smoking and alcohol use, stigma,²³ HIV, coexistence of chronic cough and/or other lung diseases, negative sputum smear, extrapulmonary TB, rural residence, old age, poverty, female gender, low educational level, and/or low awareness and knowledge about TB.²⁴ Healthcare assistance has also been associated with delays in the way of use of traditional healers, limited accessibility of healthcare facilities, initial consultation with government healthcare providers compared with private providers,²³ or with low-level healthcare facilities, and initial visit to unqualified practitioners.²⁵ Those factors could be similar in people living with HIV.

Table 3. Characteristics associated with delays in the TB diagnosis and TB treatment initiation in patients co-infected with HIV in Colombia, 2014–2015.

Characteristics	Delay in TB diagnosis			Delay in TB treatment initiation		
	Yes = 1043 <i>n</i>	% ^a	PR (95% CI)	Yes = 715 <i>n</i>	% ^a	PR (95% CI)
Female	222	56.6	1.0	163	46.0	1.0
Male	821	54.4	0.96 (0.87–1.05)	552	40.7	0.88 (0.77–1.00)
Age in years						
≤14	6	35.3	1.0	9	56.3	1.0
15–24	94	54.0	1.53 (0.79–2.95)	66	44.4	0.78 (0.49–1.25)
25–34	380	56.1	1.59 (0.83–3.03)	239	39.0	0.69 (0.44–1.07)
35–44	266	50.7	1.43 (0.75–2.74)	207	43.6	0.77 (0.49–1.20)
45–54	191	57.7	1.63 (0.85–3.13)	131	44.6	0.79 (0.50–1.24)
≥55	106	59.6	1.68 (0.87–3.24)	63	38.7	0.68 (0.42–1.10)
Health Insurance ^b						
Contributive	436	57.4	1.0	263	38.0	1.0
Without insurance	42	45.2	0.78 (0.62–0.99)	31	37.8	1.18 (1.05–1.33)
Subsidized	565	53.9	0.93 (0.86–1.02)	421	45.0	0.99 (0.74–1.33)
Healthcare worker	23	65.7	1.20 (0.94–1.53)	9	26.5	0.62 (0.35–1.10)
Classification of the TB case						
New	895	54.1	1.0	602	40.5	1.0
Relapse	64	62.7	1.15 (0.99–1.35)	42	45.7	1.12 (0.89–1.41)
Previously treated after failure	9	60.0	1.10 (0.73–1.67)	9	75.0	1.85 (1.32–2.57)
Previously treated after lost to follow-up	60	58.3	1.07 (0.90–1.27)	48	51.6	1.27 (1.03–1.56)
Other previously treated	14	51.9	0.95 (0.66–1.38)	12	46.2	1.13 (0.74–1.73)
Type of TB						
Pulmonary TB	680	53.9	1.0	474	41.3	1.0
Extrapulmonary TB	362	56.7	1.05 (0.96–1.14)	239	42.6	1.03 (0.91–1.16)
Sputum smear status at diagnosis						
Negative	398	57.6	1.0	248	40.1	1.0
Smear 1+	168	50.1	0.87 (0.76–0.98)	134	43.1	1.07 (0.91–1.25)
Smear 2+	119	57.2	0.99 (0.86–1.13)	90	49.2	1.22 (1.02–1.46)
Smear 3+	85	58.2	1.01 (0.86–1.17)	45	33.3	0.83 (0.64–1.07)
Culture negative	73	56.2	1.19 (1.00–1.41)	47	39.8	1.18 (0.91–1.53)
Other diagnosis test ^c						
Clinical	955	54.8	1.02 (0.87–1.17)	644	41.0	0.81 (0.68–0.98)
X-rays	647	55.6	0.97 (0.89–1.05)	427	40.2	0.91 (0.81–1.01)
Tuberculin skin test	135	66.2	0.81 (0.72–0.90)	79	43.4	0.96 (0.80–1.14)

^aPercentage by row.

Other possible explanations for delay in TB diagnosis could be the physician's perception of the patient's health state and health awareness of people living with HIV.²⁴ Mueller-Using et al.²⁴ reported that factors that have negative impact for TB screening were unavailability of an HIV test, no information about acute fever, high CD4 cell count and high hemoglobin.

In future studies in Colombia, it is important to evaluate the clinicians' and patients' perceptions about the reasons for the delay in TB diagnosis that may be very useful to design effective strategies to educate healthcare workers and to improve the awareness of the community.

Recently, Heuvelings et al.²⁶ reported that some strategies that were effective to identify and manage TB in low- and middle-income countries were mobile chest X-ray, active referral to a TB clinic, monetary incentives among drug users and homeless people.²⁶ This study shows some ideas for national and local TB programs to improve the TB diagnosis and outcomes in hard-to-reach populations.

On the other hand, early ART initiation has been demonstrated to decrease mortality in HIV-positive TB patients,^{7–10} and in general, in all HIV patients. In 2015, INSIGHT START study was published²⁷ that compared death from AIDS or any AIDS-defining event between the immediate ART initiation in

Table 4. Characteristics associated with delay in the HIV treatment initiation in patients co-infected with HIV in Colombia, 2014–2015.

Characteristics	HIV treatment initiation N = 1550						Prevalence ratio (95% CI)
	Delayed N = 424		Timely N = 482		ART initiated prior to TB treatment N = 644		
	n	%	n	%	n	%	
Female	67	27.7	92	29.3	135	43.0	
Male	337	27.3	390	31.6	509	41.2	1.02 (0.97–1.06)
Prisoners	15	29.4	17	33.3	19	37.3	0.98 (0.88–1.08)
Homeless	18	35.3	7	13.7	26	51.0	1.00 (0.92–1.09)
Former illegal armed people	2	100.0	0	0.0	0	0.0	—
Victims of violence	6	75.0	0	0.0	2	25.0	1.16 (1.14–1.18)
Health Insurance ^a							
Contributive	170	26.8	221	34.8	244	38.4	1.0
Subsidized	220	26.1	239	28.3	385	45.6	1.02 (0.99–1.05)
Without insurance	34	47.9	22	31.0	15	21.1	1.05 (0.99–1.12)
Classification of the TB case							
New	369	27.4	462	34.2	517	38.4	1.0
Relapse	20	22.7	9	10.3	59	67.0	1.02 (0.96–1.09)
Previously treated after failure	3	33.3	3	33.4	3	33.3	1.17 (1.15–1.19)
Previously treated after lost to follow-up	22	27.2	6	7.4	53	65.4	1.02 (0.96–1.09)
Other previously treated	9	40.9	2	9.1	11	50.0	0.99 (0.86–1.13)
Type of TB							
Pulmonary TB	292	28.0	308	29.6	441	42.4	1.0
Extrapulmonary TB	131	25.8	174	34.3	202	39.8	0.99 (0.96–1.03)
Sputum smear status at diagnosis							
Negative	142	24.8	202	35.3	228	39.9	1.0
Smear 1+	81	29.3	84	30.4	111	40.2	0.97 (0.92–1.01)
Smear 2+	51	31.3	49	30.1	63	38.7	0.99 (0.95–1.05)
Smear 3+	34	27.6	32	26.0	57	46.3	0.97 (0.91–1.04)
Culture negative ^b	35	32.4	36	33.3	37	34.3	1.03 (0.95–1.11)
Other diagnosis test							
Clinical	392	27.5	452	31.7	584	40.9	1.02 (0.96–1.09)
X-rays	267	27.6	322	33.3	377	39.0	1.01 (0.98–1.04)
Tuberculin skin test	41	25.2	55	33.7	67	41.1	0.90 (0.84–0.96)

^bAvailable results according to HIV treatment initiation: 331.

HIV-positive adults with CD4 cell count >500 cells/mm³ versus deferred ART initiation until CD4 cell count decreased to 350 cells/mm³ or the development of AIDS, or any other indication for ART, and found a hazard ratio of 0.28 (95% CI: 0.15–0.50). In addition, they found a hazard ratio for TB of 0.29 (95% CI: 0.12–0.73) between those groups, showing the significant reduction of TB presentation in those patients that received immediate ART initiation compared to deferred ART treatment initiation. In 2016, WHO guidelines recommend rapid ART initiation to all people living with HIV (defined as within seven days from the day of HIV diagnosis) following a confirmed HIV diagnosis and clinical assessment.²¹ In addition to mortality and AIDS-related events, immediate

initiation of ART improved self-perceived quality of life in early asymptomatic HIV infection.²⁸

It is important to bear in mind that rapid ART HIV initiation needs a strong follow-up due to the high mortality that have been reported within the first year after starting ART. In our study, 68.5% of people had CD4 cell count <200 cells/mm³ at HIV diagnosis and 11.7% died.

A study conducted in Uganda and Zimbabwe found that mortality risk was higher in those individuals with lower CD4 cell count and within the first three months after ART initiation with no difference between children and adults.²⁹ WHO recommends closer follow-up during the initial period of receiving ART in patients with advanced HIV¹⁷ to evaluate treatment response

Table 5. Risk factors associated with delays in the TB diagnosis and TB and HIV treatment initiation in patients co-infected with HIV in Colombia, 2014–2015.

Characteristics	Delays in TB diagnosis aPR (95% CI)	Delays in TB treatment initiation aPR (95% CI)	HIV treatment initiation aPR (95% CI)
Male gender	0.96 (0.86–1.08)	0.93 (0.80–1.09)	1.03 (0.98–1.08)
Age in years			
≤14	1.0	1.0	1.0
15–24	3.97 (1.08–14.5)	0.84 (0.51–1.38)	0.79 (0.72–0.87)
25–34	3.86 (1.06–14.0)	0.67 (0.42–1.07)	0.87 (0.82–0.92)
35–44	3.48 (0.95–12.6)	0.71 (0.44–1.13)	0.86 (0.81–0.92)
45–54	4.17 (1.14–15.1)	0.80 (0.50–1.28)	0.83 (0.77–0.89)
≥55	4.14 (1.13–15.1)	0.73 (0.44–1.22)	0.85 (0.79–0.92)
Insurance health ^a			
Contributive	1.0	1.0	1.0
Without insurance	0.91 (0.72–1.16)	1.00 (0.70–1.42)	1.05 (0.98–1.12)
Subsidized	0.90 (0.82–1.00)	1.25 (1.08–1.45)	1.00 (0.96–1.04)
Classification of the TB case			
New	1.0	1.0	1.0
Relapse	1.15 (0.95–1.40)	1.14 (0.87–1.50)	1.01 (0.94–1.09)
Previously treated after failure	0.84 (0.40–1.78)	1.36 (0.72–2.59)	1.09 (1.06–1.13)
Previously treated after lost to follow-up	1.05 (0.84–1.31)	1.07 (0.80–1.42)	1.00 (0.92–1.08)
Other previously treated	0.90 (0.60–1.37)	1.20 (0.76–1.90)	1.00 (0.85–1.16)
Type of TB			
Pulmonary TB	1.0	1.0	1.0
Extrapulmonary TB	1.03 (0.92–1.15)	0.97 (0.82–1.16)	0.99 (0.95–1.04)
Sputum smear status at diagnosis			
Negative	1.0	1.0	1.0
Smear 1+	0.89 (0.79–1.02)	1.04 (0.88–1.24)	0.96 (0.91–1.00)
Smear 2+	1.02 (0.89–1.17)	1.19 (0.99–1.44)	0.98 (0.93–1.04)
Smear 3+	1.03 (0.88–1.20)	0.81 (0.62–1.04)	0.97 (0.91–1.03)
Tuberculin skin test	1.31 (1.16–1.47)	1.06 (0.85–1.32)	0.89 (0.82–0.97)

^aPR: adjusted prevalence ratio.

and adverse events related to it because of the high mortality during the first six months after starting ART (8.9% to 12.2% within the first 24 weeks, and 11% to 14.4% at 48 weeks).³⁰

As limitations, we highlight that this is a retrospective study conducted with routine databases, and because of missing data, there were variables that we could not use. Since the high cost account does not collect information from patients without health insurance, that group of patients may have higher delays in TB and HIV diagnosis and treatment initiation, and even worse outcomes than this study population. On the other hand, the data analyzed correspond to 2014 and 2015, and since there were changes in the national and international guidelines for the management of HIV²¹ and TB,^{11,12} it is possible that delays in TB diagnosis and ART initiation could be currently less than what we found.

Taking into account that we used two national databases, our results reflect the reality in the country; therefore, policymakers now have evidence-based results that provide a baseline about the situation of

HIV-positive TB patients to design and plan strategies to improve TB/HIV screening and testing and prompt access to TB and HIV treatment.

In conclusion, with surveillance data, we found a high proportion of TB/HIV patients with delays in TB and HIV diagnosis, and the initiation of their treatments. Strengthening TB/HIV collaboration activities should be a priority for local governments to change this scenario, including the three I's for TB/HIV recommended by WHO: intensified case-finding including molecular tests for TB diagnosis in people living with HIV, isoniazid preventive therapy, and TB infection control in healthcare and congregated settings, in addition to early HIV detection and rapid HIV ART initiation.

Authors' contribution

Substantial contributions to the conception or design of the work: CR, DMP, ZVR. Acquisition of data: CR, MR, ML, RL. Analysis and interpretation of data for the work: LL, ZVR. Drafting the work: CR, ZVR. Revising it critically for

important intellectual content: MR, ML, AP, RL, DMP, LL. Final approval of the version to be published: CR, MR, ML, AP, RL, DMP, LL, ZVR. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CR, MR, ML, AP, RL, DMP, LL, ZVR.

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This study was approved by the Ethics Committee of the Universidad Pontificia Bolivariana (approval number: 5–2017), and the Ethics Committee of the Pan American Health Organization. In addition, the Ministry of Health and Social Protection of Colombia approved the study.

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References

1. Gebreegziabher SB, Bjune GA and Yimer SA. Total delay is associated with unfavorable treatment outcome among pulmonary tuberculosis patients in West Gojjam Zone, Northwest Ethiopia: a prospective cohort study. *PLoS One* 2016; 11: e0159579.
2. Otwombe KN, Variava E, Holmes CB, et al. Predictors of delay in the diagnosis and treatment of suspected tuberculosis in HIV co-infected patients in South Africa. *Int J Tuberc Lung Dis* 2013; 17: 1199–1205.
3. Ilangovan K, Nagaraja SB, Ananthkrishnan R, et al. TB treatment delays in Odisha, India: is it expected even after these many years of RNTCP implementation? *PLoS One* 2015; 10: e0125465.
4. Patel MR, Nana M, Yotebieng M, et al. Delayed antiretroviral therapy despite integrated treatment for tuberculosis and HIV infection. *Int J Tuberc Lung Dis* 2014; 18: 694–699.
5. da Silva TP, Giacoia-Gripp CBW, Schmaltz CA, et al. Risk factors for increased immune reconstitution in response to Mycobacterium tuberculosis antigens in tuberculosis HIV-infected, antiretroviral-naïve patients. *BMC Infect Dis* 2017; 17: 606.
6. Vignesh R, Swathirajan CR, Solomon SS, et al. Risk factors and frequency of tuberculosis-associated immune reconstitution inflammatory syndrome among HIV/Tuberculosis co-infected patients in Southern India. *Indian J Med Microbiol* 2017; 35: 279.
7. Odone A, Amadasi S, White RG, et al. The impact of antiretroviral therapy on mortality in HIV positive people during tuberculosis treatment: a systematic review and meta-analysis. *Plos One* 2014; 129: e112017.

8. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011; 365: 1482–1491.
9. Blanc F-X, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011; 365: 1471–1481.
10. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med* 2011; 365: 1492–1501.
11. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis* 2016; 63: e147–e195.
12. World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update [Internet]. WHO. 2017 [cited 21 December 2017]. <http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf?ua=1>
13. Zachariah R, Harries AD, Ishikawa N, et al. Operational research in low-income countries: what, why, and how? *Lancet Infect Dis* 2009; 19: 711–717.
14. Zachariah R, Ford N, Draguez B, et al. Conducting operational research within a non governmental organization: the example of Médecins Sans Frontières. *Int Health* 2010; 12: 1–8.
15. Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med*. 2010; 362: 707–716.
16. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLOS Med* 2011; 8: e1000391.
17. WHO | Intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings [Internet]. WHO. [cited 9 August 2019]. <http://www.who.int/hiv/pub/tb/9789241500708/en/>
18. WHO | Latent TB infection : Updated and consolidated guidelines for programmatic management [Internet]. WHO. [cited 9 August 2019]. <http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/>
19. Ministerio de Salud y Protección Social, Fondo de Población de las Naciones Unidas. Guía de práctica clínica (GPC) basada en la evidencia científica para la atención de la infección por VIH/Sida en adolescentes (con 13 años de edad o más) y adultos. [Internet]. Ministerio de Salud y Protección Social. 2014 [cited 21 December 2017]. http://gpc.minsalud.gov.co/gpc_sites/Repositorio/Otros_conv/GPC_VIH_adolescentes/GPC_Comple_VIHADULTOS_web.pdf
20. Balcha TT, Sturegård E, Winqvist N, et al. Intensified tuberculosis case-finding in HIV-positive adults managed at Ethiopian health centers: diagnostic yield of Xpert MTB/RIF compared with smear microscopy and liquid culture. *PLoS One* 2014; 9: e85478.
21. WHO | Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy [Internet]. WHO. [cited 26 December 2017]. <http://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/>
22. Rodríguez DA, Verdonck K, Bissell K, et al. Monitoring delays in diagnosis of pulmonary tuberculosis in eight cities in Colombia. *Rev Panam Salud Publica* 2016; 39: 12–18.
23. Sreeramareddy CT, Qin ZZ, Satyanarayana S, et al. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *Int J Tuberc Lung Dis* 2014; 118: 255–266.
24. Mueller-Using S, Feldt T, Sarfo FS, et al. Factors associated with performing tuberculosis screening of HIV-positive patients in Ghana: LASSO-based predictor selection in a large public health data set. *BMC Public Health [Internet]*. 2016; 16 [cited 26 December 2017]. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944423/>
25. Storla DG, Yimer S and Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 2008; 8: 15.
26. Heuvelings CC, de Vries SG, Greve PF, et al. Effectiveness of interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review. *Lancet Infect Dis* 2017; 117: e144–e158.
27. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; 373: 795–807.
28. Lifson AR, Grund B, Gardner EM, et al. Improved quality of life with immediate versus deferred initiation of antiretroviral therapy in early asymptomatic HIV infection. *AIDS* 2017; 31: 953–963.
29. Walker AS, Prendergast AJ, Mugenyi P, et al. Mortality in the year following antiretroviral therapy initiation in HIV-infected adults and children in Uganda and Zimbabwe. *Clin Infect Dis* 2012; 55: 1707–1718.
30. Hakim J, Musiime V, Szubert AJ, et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. *N Engl J Med*. 2017; 377: 233–245.