INT J TUBERC LUNG DIS 13(6):719–725

Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil

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SUMMARY

BACKGROUND: Although treatment of latent tuberculosis infection (LTBI) is an essential component of tuberculosis (TB) control in countries such as the United States, it is not widely practiced in most TB-endemic countries.

OBJECTIVE: To examine the practice of and adherence to LTBI treatment in a high-risk population in Brazil.

DESIGN: We followed household contacts (HHCs) of patients hospitalized with pulmonary TB in Salvador, Brazil, for 6 months after they initiated LTBI treatment with isoniazid (INH). HHCs were asked to return to the hospital once a month for 6 months for follow-up visits and INH refills.

RESULTS: Of 101 HHCs who initiated LTBI treatment, 54 (53.5%) completed the 6-month regimen. The risk of treatment non-completion was significantly higher in HHCs who reported side effects to INH (RR 2.69, 95%CI 1.3–5.8, $P = 0.01$), and in those who had to take two buses for a one-way trip to the hospital (RR 1.8, 95%CI 1.01–3.3, $P = 0.04$). Of the 101 HHCs, 29 (28.7%) did not return for any follow-up visits; these HHCs were significantly more likely to have a 2-bus commute to the hospital compared to HHCs who completed treatment (OR 20.69, 95%CI 2.1–208.4, $P = 0.01$).

CONCLUSION: Nearly 50% of HHCs at high risk for developing TB completed a 6-month course of LTBI treatment. Completion of LTBI treatment was most affected by medication intolerance and commuting difficulties for follow-up visits.

KEY WORDS: latent tuberculosis infection; isoniazid; adherence; household contacts

A HIGH PREVALENCE of latent tuberculosis infection (LTBI) occurs among close contacts of persons with pulmonary tuberculosis (TB).[1–3] Individuals infected with *Mycobacterium tuberculosis* are at an increased risk of developing active disease during the first years after new infection.[4–6] Treatment of LTBI is therefore a strategic component of TB control programs.[7,8]

Isoniazid (INH) significantly reduces the risk of progression from LTBI to active disease,[6,9] and is a mainstay of TB control in industrialized countries such as the United States. In most TB-endemic countries, contact investigation is accorded low priority, and formal LTBI treatment programs do not exist.[1] TB prevention relies mostly on bacille Calmette-Guérin (BCG) vaccination in these countries. The World Health Organization (WHO) currently recommends INH preventive treatment only for children aged <5 years who are contacts of infectious cases.[10,11] Despite the lack of specific recommendations for the broader population, WHO guidelines state that programs that provide screening and INH treatment to all household contacts (HHCs) of infectious cases—both children and adults—are desirable.[11] Reasons often cited for lack of LTBI treatment of the general population in developing countries include the lack of standardized diagnostic criteria for LTBI, the inability to distinguish the effect of BCG vaccination on tuberculin skin test (TST) results, the possibility of mistakenly treating those who may have active disease with INH alone, and the side effects of INH. Information related to the feasibility, adherence, and acceptability of LTBI treatment is thus limited in most TB-endemic countries.

The Brazilian National TB Control Program (NTP) recommends a 6-month LTBI treatment course of daily INH for children aged $\leqslant 15$ years who live in the same household as a sputum-positive case, who are not BCG-vaccinated, and who have a TST reaction $\geqslant 10$ mm, and for BCG-vaccinated children aged

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Article submitted 19 November 2008. Final version accepted 18 January 2009.

≤15 years who have a TST reaction ≥15 mm.[12] The Brazilian NTP guidelines also state that treatment for all HHCs of pulmonary TB cases with a TST reaction ≥10 mm should be considered.[12] However, these recommendations are not widely followed. In this study, we studied HHCs with documented LTBI exposed to hospitalized TB index cases in Salvador, Brazil, to observe what happens to this high-risk cohort in a TB-endemic setting when they are offered LTBI treatment.

METHODS

Setting

We prospectively enrolled study participants between November 2006 and February 2008 from Hospital Especializado Octávio Mangabeira (HEOM), a 217-bed public chest disease hospital in Salvador, Brazil. Salvador is the capital of Bahia state, with a population of 2 714 018 in 2006.[13] In 2005, it had a TB incidence of 88 per 100 000 population—one of the highest TB incidence rates in Brazil.[14] Salvador does not have an active TB contact investigation program.

Study participants

The study was approved by the respective human subjects committees of Oswaldo Cruz Foundation in Salvador, Brazil, and the University of California at Berkeley, USA. Informed consent was obtained from all subjects who agreed to participate in the study.

Index cases

Index cases were defined as hospitalized patients with symptoms consistent with TB and one or more of the following characteristics: 1) chest radiography suggestive of TB; 2) sputum samples that contained acid-fast bacilli on microscopy; 3) individuals who responded to anti-tuberculosis drugs. Sputum was analyzed with the Ziehl-Neelsen staining method and its burden was classified as negative, 1+, 2+ or 3+, as previously reported.[15] The characteristics of the index cases are described elsewhere.[16]

Household contacts

Contacts who spent at least 100 h with the index case during the latter's symptomatic period and who lived in the same residence were considered HHCs and were invited to participate in the study.[16,17]

Data collection

HHCs who were enrolled underwent TST and were interviewed by members of the study team (AM, KE, IT) when they returned for TST reading. A standardized questionnaire was used to collect the interview data. Study participants were asked about their current use of medications and diabetes status. They were not directly asked about their human immunodeficiency virus (HIV) status, nor were the data sought from clinic charts. Data were entered into a desktop computer maintained at Gonçalo Moniz Research Center with Epi Info Version 3.4.3 (Centers for Disease Prevention and Control, Atlanta, GA, USA, 2007).

Distance between the residence of the study participant and HEOM was calculated in km with Google maps.* We determined the number of buses necessary for each study participant to commute one way between their residence and the hospital by consulting the Salvador Transportation Agency.

Laboratory test

TST was performed by a trained nursing staff with 0.1 ml of purified protein derivative (PPD) RT23 (2 tuberculin units [TU], Statens Serum Institute, Copenhagen, Denmark). The reaction was read 72 h later by the chest physician on the study team (AM). The cut-off point for a positive reaction was an induration diameter of ≥10 mm, according to the Brazilian NTP guidelines.[12]

Treatment

Six months of daily INH treatment was offered to eligible HHCs with a positive TST result; this is the standard LTBI treatment regimen in Brazil.[12] INH was supplied to the study participants by the Brazilian Ministry of Health without charge. INH treatment was not offered to patients with a positive TST if they were pregnant or if they were diagnosed with active TB.

Following consent, participants received a 1-month supply of INH, 5 mg/kg of body weight (maximum 300 mg), and were asked to return every 30 days for refills. HHCs who completed LTBI treatment were defined as those who returned to HEOM every 30 days for 6 months and received six 30-day supplies of INH. HHCs who did not complete treatment were defined as those who missed at least one but not all of the follow-up visits and missed an INH refill. HHCs who were immediately lost to follow-up were defined as those who did not return to HEOM for a follow-up visit or any INH refills.

Participants were instructed to terminate therapy immediately upon onset of any adverse reactions (nausea, vomiting, jaundice, abdominal pain, headache, peripheral neuropathy, itching, rash). Blood tests to monitor liver toxicity were conducted for patients with major gastrointestinal symptoms. Payment or incentives were not offered.

Statistics

The database was created in Epi Info Version 3.4.3. Interview data were entered into Epi Info by members of the study team (KE, IT) and were analyzed using Stata 10.0 Intercooled (StataCorp, College Station, TX, USA). Patients who completed the 6-month treatment

* www.maps.google.com

were compared to patients who did not complete treatment. Relative risks (RRs) were calculated with a modified Poisson regression with a robust error variance.[18] Odds ratios (ORs) were calculated with single and multivariate logistic regression models. Adjustments were made for clustering by household.

RESULTS

Between 30 November 2006 and 15 February 2008, 301 HHCs of 76 patients hospitalized with pulmonary TB agreed to participate in the study and were administered TST; 261 (86.7%) returned to HEOM to have their TST result read. Of these 261, 145 (55.6%) had a positive TST result, of whom 101 (69.7%) initiated LTBI treatment. The 101 HHCs represented 39 distinct households in Salvador, with a median of two study participants per household. Of the 44 (30.3%) HHCs who did not initiate LTBI treatment, 10 (23%) did not meet the criteria for treatment and 34 (77%) refused treatment; interview data were not available for these 34 HHCs. Four HHCs reported diabetes. None of the study participants were on antiretroviral treatment, and none had been previously treated for TB or LTBI.

Of the 101 HHCs who initiated LTBI treatment, 29 (28.7%) were immediately lost to follow-up (Table 1). At the end of the 6-month follow-up, 54 (53.5%) of 101 HHCs had completed treatment and 47 (46.5%) had not (Table 1).

Adverse effects

Nine (13%) of the 72 HHCs who returned for one or more follow-up visits reported adverse effects; three (4%) reported major gastrointestinal symptoms (nausea, vomiting and abdominal pain). Blood tests for bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase and akaline phosphatase were performed on these patients; the results were all within normal range. The remaining six (8%) reported loss of appetite, acne and/or skin rash; these effects disappeared over the course of the treatment in all six. There were no cases of peripheral neuropathy or hepatotoxicity.

Risk for failure to complete LTBI treatment

Of the nine HHCs who reported any adverse effects, five (56%) did not complete treatment, while of 63 HHCs who did not report side effects, 13 (21%) did not complete treatment (RR 2.69, 95% confidence interval [CI] 1.3–5.8, $P = 0.01$; Table 2).

Of the 61 HHCs who took two buses to commute to HEOM, 32 (52%) did not complete LTBI treatment, while of 35 HHCs who took one bus in a one-way commute, 10 (29%) did not complete treatment (RR 1.84, 95%CI 1.0–3.3, $P = 0.04$; Table 2). After adjusting for the distance between their residence and HEOM, there was no association between the number of buses a study participant took and failure to complete LTBI treatment (adjusted RR 1.38, 95%CI 0.7–2.6, $P = 0.31$).

Of 38 HHCs who lived at a distance of >10 km from HEOM, eight (21%) did not complete treatment, while of 28 HHCs who lived within 5 km of HEOM, 15 (54%) did not complete treatment (RR 0.39, 95%CI 0.2–0.8, $P = 0.01$; Table 2). After adjusting for the number of buses a HHC took in a one-way commute between their home and HEOM, HHCs who lived at a distance of >10 km had a lower risk of treatment failure compared to those who lived within 5 km of HEOM (adjusted RR 0.40, 95%CI 0.2–0.8, $P = 0.01$).

Table 1 Characteristics of household contacts* who initiated LTBI treatment, $N = 101$

Characteristics	*n* (%)
Age, years	median 23
0–10	14
11–21	33
22–39	30
⩾40	24
Male sex	44 (44)
Ethnicity†	
Black	49 (52)
Multiracial	36 (38)
White	10 (10)
Presence of BCG scar	82 (81)
Current employment status‡	29 (48)
Family income, US$§	mean 525
210–420	35 (34.7)
630–840	39 (38.6)
Did not say	27 (26.7)
Distance from HEOM, km¶	
⩽5	28 (29)
5.1–10	29 (31)
>10	38 (40)
Number of buses required to commute to HEOM#	
One	35 (35)
Two	61 (64)
Relationship to index case	
Spouse/child/parent	42 (42)
Aunt/uncle/cousin/neighbor/grandparent/sibling	59 (58)
Time of exposure to index case	mean 2.7 months
⩾2.7 months	33 (33)
Number of 30-day INH refills received	
1	29 (29.7)
2	10 (9.9)
3	3 (3.0)
4	5 (5.0)
5	0
6	54 (53.5)

*Data were not available for the 34 HHCs who were eligible for the study but who refused to participate.
†Six individuals did not report their ethnicity.
‡Only the 61 HHCs aged ⩾18 years were asked for their employment status.
§Family income was approximated and categorized, and includes only the monthly income of household members aged ⩾18 years.
¶Data not available for six individuals.
#The number of buses a study participant must take in a one-way commute between their residence and the hospital; data not available for five individuals.
LTBI = latent tuberculosis infection; BCG = bacille Calmette-Guérin; HEOM = Hospital Especializado Octávio Mangabeira; INH = isoniazid; HHC = household contact.

Table 2 Risk for failure to complete 6 months of isoniazid treatment for latent tuberculosis infection among HHCs of index cases hospitalized with pulmonary tuberculosis*

	Treatment non-completion (n = 47) n (%)	Treatment complete (n = 54) n (%)	RR (95%CI)†	P value‡
Age, years	median 23	median 24		
0–10	7 (15)	7 (13)	0.0	
11–21	15 (32)	18 (33)	0.91 (0.5–1.7)	0.77
22–39	13 (28)	17 (31)	0.87 (0.4–1.7)	0.67
⩾40	12 (26)	12 (22)	1 (0.5–1.9)	1.0
Male sex	19 (40)	25 (46)	0.88 (0.57–1.35)	0.56
Relationship to index case				
Spouse, child, parent	22 (47)	20 (37)	1.24 (0.8–1.9)	0.32
Aunt, uncle/cousin/neighbor/ grandparent/sibling	25 (53)	34 (63)	0.0	
Report of adverse effects§	5 (28)	4 (7)	2.69 (1.3–5.8)	0.01
Monthly family income, US$				
210–420	12 (25)	23 (43)	0.64 (0.4–1.1)	0.11
630–840	21 (45)	18 (33)	0.0	
Did not say	14 (30)	13 (24)	—	—
Distance to HEOM, km¶				
0–5	15 (37)	13 (24)	0.0	—
5.1–10	18 (44)	11 (20)	1.16 (0.7–1.8)	0.52
>10	8 (20)	30 (56)	0.39 (0.2–0.8)	0.01
Number of buses required to commute to HEOM#				
One	10 (24)	25 (46)	0.0	
Two	32 (76)	29 (54)	1.84 (1.0–3.3)	0.04

* Generalized linear models were built in Stata.
† Based on robust standard errors that account for clustering by household.
‡ Fisher's exact P values.
§ Data only available for patients who returned at least once for a follow-up visit; reports of adverse effects are available for 18 HHCs who did not complete treatment.
¶ Data not available for six individuals who did not complete INH.
# Data not available for five individuals who did not complete INH.
HHC = household contact; RR = relative risk; CI = confidence interval; HEOM = Hospital Especializado Octávio Mangabeira.

Subgroup analysis of HHCs immediately lost to follow-up

Of the 53 HHCs who took two buses to commute to HEOM, 24 (45%) were immediately lost to follow-up, while of the 26 HHCs who took one bus, one (4%) was immediately lost to follow-up (OR = 20.69, 95%CI 2.1–208.4, P = 0.01; Table 3).

DISCUSSION

A recent systematic review of INH trials of ⩾6 months in non-HIV-infected persons from 1955 to 2003 found that among 11 relevant studies selected for review, only two were conducted among HHCs of index TB cases in TB-endemic countries—Kenya (1963) and the Philippines (1965).[19] All others were conducted in the United States and other industrialized countries, or in cohorts with underlying medical problems.[19] Today, neither Kenya nor the Philippines routinely conduct contact investigations to identify candidates for INH treatment. Our study, in a country that administers BCG to prevent TB, found that INH treatment, when offered, was well accepted (77%) and tolerated. Furthermore, we found that of the 101 HHCs who initiated LTBI treatment, slightly more than 50% completed the full 6-month course. This completion rate falls towards the higher end of completion rates reported in the United States for 6 months of LTBI treatment.[6,20] Our rate of treatment completion may be attributed to prospective study enrollment.[20] However, a prospective study that enrolled pediatric HHCs of pulmonary TB patients in Cape Town, South Africa, found that only 36/180 (20%) completed <5 months of INH treatment.[21]

There are no reported studies on factors associated with failure to complete INH treatment for LTBI in non-HIV-infected persons in countries that administer BCG to prevent TB. Two recent articles that examined time to treatment failure are from studies conducted in the United States.[22,23] A retrospective cohort study of LTBI patients at the Boston Medical Center TB clinic in 1998 found that over half of the patients who initiated LTBI treatment and did not complete it were lost to follow-up within the first month.[22] This study did not investigate risk factors for immediate loss to follow-up.

Of the 47 HHCs who did not complete 6 months of treatment, 42 (89%) did not return for INH refills after the third month of treatment, and nearly two thirds of non-completers were immediately lost to

Table 3 Risk factors for immediate loss to follow-up among HHCs of index cases hospitalized with pulmonary tuberculosis who initiated treatment for latent tuberculosis infection*

	Treatment stopped in first month (n = 29) n (%)	Treatment complete (n = 54) n (%)	OR (95%CI)†	P value‡
Age, years	median: 23	median: 24		
0–10	6 (21)	7 (13)	1.0	
11–21	8 (28)	18 (33)	0.52 (0.1–2.0)	0.35
22–39	6 (21)	17 (31)	0.23 (0.1–1.7)	0.23
⩾40	9 (31)	12 (22)	0.85 (0.2–3.5)	0.88
Male sex	11 (38)	25 (46)	0.71 (0.3–1.8)	0.46
Relationship to index case				
Spouse, child, parent	13 (45)	20 (37)	1.38 (0.4–5.0)	0.49
Aunt, uncle/cousin/ neighbor/ grandparent/sibling	16 (55)	34 (63)	1.0	
Monthly family income, US$				
210–420	5 (17)	23 (43)	0.21 (0.02–1.9)	0.17
630–840	19 (66)	18 (33)	1.0	
Did not say	5 (17)	13 (24)	—	—
Report of adverse effects§	n/a	4 (7)	—	—
Distance to HEOM, km¶				
0–5	8 (32)	13 (24)	1.0	
5.1–10	13 (52)	11 (20)	1.92 (0.2–22.2)	0.60
>10	4 (16)	30 (56)	0.22 (0.2–3.0)	0.25
Number of buses required to commute to HEOM#				
One	1 (4)	25 (46)	1.0	
Two	24 (96)	29 (54)	20.69 (2.1–208.4)	0.01

*Logistic regression models were built in Stata.
†Standard errors are adjusted to account for clustering by household for household level variables (monthly family income, distance to HEOM, time of exposure to index case, number of buses required to reach HEOM).
‡Fisher's exact P values.
§Data not available for study participants who did not return for any follow-up visits.
¶Data not available for six individuals, four of whom stopped treatment in the first month.
#Data not available for five individuals, four of whom stopped treatment in the first month.
HHC = household contact; OR = odds ratio; CI = confidence interval; HEOM = Hospital Especializado Octávio Mangabeira.

follow-up (Table 1). HHCs requiring a 2-bus commute to the hospital accounted for 96% of those immediately lost to follow-up (Table 3). The number of buses a study participant is required to take in a one-way commute between their residence and HEOM is not related to the distance the HHC lives from the hospital. Our findings suggest that the number of bus trips, and not distance, is the variable that best describes HHCs who did not complete treatment.

A significant proportion of the 47 HHCs who completed treatment lived at a distance of >10 km from HEOM (Table 2). There is no plausible explanation as to why living farther from the hospital would promote treatment completion; this is likely to be a spurious finding. When we adjusted for the distance between residence and HEOM, a 2-bus commute was not independently predictive of failure to complete INH treatment (Table 2). We believe that the true association between the number of bus trips and failure to complete INH treatment was blurred by the spurious association between the farthest distance category and treatment completion. Most of these 47 were immediately lost to follow-up. The sub-group analysis that excludes the eight HHCs who did not complete treatment but who were not immediately lost to follow-up eliminates the association between distance and completion of LTBI treatment (Table 3).

At the time of our study, the bus fare in Salvador was about US$1, and users must pay the full fare again when transferring to another bus. The median number of study participants per household was two; these households paid US$8 per month in bus fares to participate in the study if they had a two-bus round-trip commute. This is a considerable cost, given the mean monthly family income in our study population of US$525 (Table 1). Income itself was not associated with treatment completion because there was little variation in income distribution in our study population (income range US$210–$840; Table 1). Our findings suggest that subsidizing bus rides for patients would greatly improve the number of INH refills a patient receives and, ultimately, LTBI treatment completion.

This observation in Brazil suggests that a routine LTBI treatment program could be introduced in a high-risk population if it is coordinated by a team that reliably supplies INH and monitors for adverse

effects. We also found that if the patients returned for the first follow-up visit, LTBI treatment, with close monitoring and reassurance, was well accepted and tolerated. Most importantly, we identified factors that contribute to non-completion of the 6-month treatment course in an endemic setting. Treatment tolerability and the ease of monthly commute between the patient's residence and the hospitals using public transport are good predictors of whether an individual will complete treatment. In summary, an LTBI treatment program focused on HHCs in a country that administers BCG is feasible and should be considered as a major part of an NTP.

Acknowledgements

The authors thank the director of the HOEM and the clinical laboratory at the hospital. Financial support was provided by NIH Fogarty International Center 5U2RTW 006885.

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RÉSUMÉ

CADRE : Bien que le traitement de l'infection tuberculeuse latente (LTBI) soit une composante essentielle de la lutte antituberculeuse dans des pays comme les Etats-Unis, on n'y recourt pas fréquemment dans la plupart des pays où l'endémie tuberculeuse est importante.

OBJECTIF : Examiner la pratique et l'adhésion au traitement de la LTBI dans une population à haut risque au Brésil.

SCHÉMA : Nous avons suivi à Salvador, Brésil, pendant 6 mois après le début du traitement de la LTBI par l'isoniazide (INH), les contacts au sein du ménage (HHC) de patients hospitalisés pour une tuberculose (TB) pulmonaire. On a demandé aux HHC de revenir à l'hôpital une fois par mois pendant 6 mois pour les visites de suivi et pour obtenir leur réapprovisionnement d'INH.

RÉSULTATS : Le régime de 6 mois a été achevé chez 54 (53,5%) des 101 HHC qui ont commencé le traitement de la LTBI. Le risque de non-achèvement du traitement est significativement plus élevé chez les HHC qui ont signalé des effets indésirables de l'INH (RR 2,69 ;

IC95% 1,3–5,8 ; *P* = 0,01), ainsi que chez les HHC qui devaient prendre deux bus pour un voyage aller vers l'hôpital (RR 1,8 ; IC95% 1,01–3,3 ; *P* = 0,04). Sur les 101 HHC qui ont commencé le traitement de la LTBI, 29 (28,7%) ne sont revenus pour aucune visite de suivi ; ces HHC avaient des chances significativement plus élevées d'avoir à changer deux fois de bus pour aller à l'hôpital par comparaison avec ceux qui ont achevé leur traitement (OR 20,69 ; IC95% 2,1–208,4 ; *P* = 0,01).

CONCLUSION : Près de la moitié des HHC à haut risque de développement d'une TB ont achevé un traitement de 6 mois pour la LTBI. L'achèvement du traitement de la LTBI est le plus affecté par l'intolérance à l'égard des médicaments et les difficultés de correspondance des transports publics pour les visites de suivi.

RESUMEN

MARCA DE REFERENCIA : Si bien el tratamiento de la infección tuberculosa latente (LTBI) en países como los Estados Unidos constituye un componente esencial de la lucha contra la enfermedad, esta práctica no está muy difundida en la mayoría de los países endémicos.

OBJETIVO : Se evaluar la aplicación y el cumplimiento terapéutico del tratamiento de la LTBI en una población de alto riesgo del Brasil.

MÉTODO : Se practicó un seguimiento a los contactos domiciliarios (HHC) de pacientes hospitalizados por tuberculosis (TB) pulmonar durante 6 meses, desde que comenzaron el tratamiento preventivo con isoniazida (INH), en Salvador, Brasil. Se solicitó a los HHC que acudieran al hospital una vez por mes durante el seguimiento para control y suministro de las dosis del medicamento.

RESULTADOS : De los 101 HHC que iniciaron el tratamiento, 54 (53,5%) completaron la pauta de 6 meses. El riesgo de tratamiento incompleto fue significativamente más alto en los HHC que refirieron reacciones adversas a la INH (RR 2,69 ; IC95% 1,3–5,8 ; *P* = 0,01) y en quienes debían tomar dos buses en cada desplazamiento hacia el hospital (RR 1,8 ; IC95% 1,01–3,3 ; *P* = 0,04). De los 101 HHC que comenzaron el tratamiento preventivo, 29 (28,7%) no acudieron a ninguna cita de control ; en estos contactos, la probabilidad de tener un trayecto con dos buses para llegar al hospital fue significativamente más alta que en los contactos que completaron el tratamiento (OR 20,69 ; IC95% 2,1–208,4 ; *P* = 0,01).

CONCLUSIÓN : Cerca de la mitad de los HHC con alto riesgo de padecer TB activa completaron el tratamiento preventivo de 6 meses. Los principales factores que influyeron sobre la compleción del tratamiento de la LTBI fueron la intolerabilidad al medicamento y las dificultades con el transporte público para asistir a las consultas de control.