10 Years of Innovation in the treatment of latent tuberculosis infection: A comparison between standard and short course therapies in directly observed therapy[1]

G López*, M Wood**, FJ Ayesta***

*Penitentiary Facility of Bilbao; **Penitentiary Facility El Dueso;
***Pharmacology Department of the University Universidad de Cantabria

ABSTRACT

Objectives: The main aim of the study is to compare the acceptance, adherence, tolerance and safety of short course therapies in comparison to a standard 9 month treatment for latent tuberculosis infection (LTBI) in directly observed therapy (DOT) and contrast this with previous results from a standard therapy in patient self-administered treatment.

Materials and methods: Retrospective longitudinal study carried out at a medium sized prison. Period of inclusion covers 10 years, from January 2000 to December 2009. The *Centers for Disease Control and Prevention* (CDC) inclusion and exclusion criteria were used, as well as the ones included in the Program for Tuberculosis Prevention and Control in the Prison Environment. 4 LTBI therapies according to the preference of the patient and possible interactions with other treatments were utilised. Therapy I consisted of isoniazid (H) in doses of 300 mg/day for 9 months (9H), therapy II with rifampicin for 2 months, twice a week, ($2R_2Z_2$) therapy III with rifampicin and isoniazid for 3 months (3RH) and therapy IV with rifampicin for four months (4R). Treatment was administered under strict DOT conditions by nursing staff.

Results: 902 patients were included, of which 810 accepted the treatment (89.90%), distributed as follows: 400 in the 9H therapy, and 410 with short course therapies (316 in the $2R_2Z_2$, 82 in the 3RH therapy and 12 in the 4R therapy). 92 patients (10.20%) did not accept LTBI therapy, 271 patients (67.75%) concluded the LTBI treatment with 9H, and 314 (76.60%) with short courses. 232 patients (73.42%) concluded the $2R_2Z_2$, 85.40% with the 3RH 70 therapy and 12 (100%) with the 4R treatment.

129 patients (32.25%) did not complete the LTBI 9H therapy (63 due to voluntary withdrawal, 35 due to adverse reactions, 26 for release or transfer, 2 for unknown reasons, 1 due to tuberculosis in a HIV- patient and 1 due to suicide). 96 patients (23.41%) did not conclude the short course therapies (36 due to voluntary withdrawal, 54 due to adverse reactions, 1 due to release or transfer, 3 for unknown reasons, 1 due to a psychotic episode, and 1 due to hepatitis of unknown aetiology).

Significant differences could be discerned in the LTBI therapy conclusion rates when comparing the standard 9H and short course therapies. A greater, statistically significant, probability is observed with the short course therapies: p: 0.006; Odds Ration: 1.56 (LC95%: 1.14-2.12).

This difference is a result of the 9H therapy presenting a greater number of voluntary withdrawals for no apparent reason (p: 0.002; OR: 2.03 [1.30-3.15]) and a greater number of withdrawals as a result of transfers to another prison or release (p<0.0001; OR 30.22 [4.07-224.29]), with no significant differences being found in withdrawals for adverse reactions between the 9H therapy and the short course treatments as a whole.

The $2R_2Z_2$ therapy shows a higher probability of withdrawals for adverse reactions (p: 0.006; OR: 1.87 [(1.21-2.88]) than the other therapies.

Conclusion: Greater acceptance of initiating therapy was observed in all the DOT therapies. The 3RH, $2R_2Z_2$ and 4R short course therapies favoured better adherence, with significantly lower ratios of withdrawal than the 9H therapy for the treatment of latent tuberculosis infection. Tolerance and safety of the short course therapies was very similar to the standard 9H treatment, with a significantly higher percentage of adverse reactions in the $2R_2Z_2$ therapy in comparison to others.

Our data backs up the safety and adherence of a short course 3RH therapy in DOT for treating latent tuberculosis infection and its preferential use in the prison environment in comparison to isoniazid due to the greater number of patients concluding treatment.

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The administration of LBTI therapy in DOT achieves a high percentage of acceptance and conclusion of treatments in prison, significantly improving on the previous results in a cross-sectional study of the prison environment and others obtained at our centre in self-administered treatment.

Key words: latent tuberculosis; tuberculin test; directly observed therapy; medication adherence; permissiveness; safety; prisons; Spain.

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INTRODUCTION

Tuberculosis is a preventable and curable disease. The Program for Tuberculosis Prevention and Control in the Prison Environment of the Spanish Prison Department [1] has achieved to give priority to early detection of TB cases, decrease its numbers and reach high recovery rates, and so the following strategy must be directed at the treatment of latent tuberculosis infection. A person infected by tuberculosis is the one who hosts a latent infection by Mycobacterium tuberculosis. A special feature of Tuberculosis (TB) is that before its development, there can be a variable period of latent infection (which can last for several weeks or as long as a lifetime), during which bacilli do not reproduce, the person is not ill and does not transmit the disease. The treatment of latent tuberculosis infection (LTBI) is fundamentally aimed at preventing the development of TB disease in someone who is already infected.

Spain and its prisons present one of Europe's highest HIV infection rates and is the country most affected by AIDS. Different studies have determined the annual incidence of TB in patients coinfected by HIV and M. tuberculosis and lacking treatment of latent tuberculosis infection, and results ranged between 3% and 16% [2, 3]. In the same way, other risk factors such as contacts of TB patients, convertors, diabetes, malnutrition, alcoholism, the prevalence of injecting drug users, etc. favor the development of tuberculosis disease, especially in a risky environment such as the prison.

The effectiveness of the treatment for LTBI is determined by several factors among which pharmacological effectiveness of the regimen chosen, the probability of suffering TB within the involved community, and adherence [5] are highlighted. Depending on these three factors, the effectiveness varies extraordinarily, so that in some cases treatment is justified and in others it is not. Therefore, if the risk of suffering tuberculosis within the infected patients is low (5%) and the adherence to LTBI treatment is also low (30%), even if the effectiveness of the pharmacological regimen is high (80%), operational effectiveness will be low on the whole and in order to prevent one case of TB, LTBI treatment will have to be administered to 100 infected patients. This would be the case of communities with a low risk for developing TB. On the other hand, in infected groups with a high risk for developing TB (30%), if we manage a slightly higher adherence (50%) and we use the same effectiveness in the pharmacological regimen (80%), operational effectiveness is boosted and it will only be necessary to administer LTBI treatment to a few patients (about 8) in order to prevent one case of TB among them. Finally, if we take a population with the same risk for developing TB (30%) with the same pharmacological effectiveness (80%) and we increase the adherence (80%), it would only be necessary to treat very few patients (5) to avoid one case of Tuberculosis.

In summary, the treatment for LTBI depends on three factors, of which the first –the pharmacological regimen- stays regular and the second –the risk of developing TB- can be estimated among the differently risky communities, so that at least intervention on the high risk groups should be carried out. Nevertheless, adherence to treatment is the feature subject to more intervention to improve the operational effectiveness of LTBI treatment.

Even though the extraordinary importance of the adherence to LTBI treatment has been proved, very few DOT [6] experiences have been reported, because traditionally, it has been done in a self-administered way both within the prison environment and outside. Consequently, this has entailed low adherence to normally used regimens due to the poor perception of the disease by the infected patients, the long duration of the treatment and the profile of inmates in the prison environment.

The social profile of Spanish inmate in 2000 was a young person, with a history of drug consumption in over half of the cases, frequent infectious diseases,

psychiatric disorders, social uprootedness, and numerous refusals to treatments with poor adherence to them. Throughout recent years, this profile is changing, and so a fewer incidence of injecting drug users is being observed. Moreover, within this environment, discontinuation of treatment is not uncommon due to conduction of transfers between facilities and due to release, something which frequently entails treatment withdrawal before its completion due to poor coordination with the community's health services.

According to the conclusions achieved by the Cross-Sectional Study on Prison Health [7] carried out by the General Deputy Direction of Prison Health in 1998, LTBI treatment is initiated by 54.7% of the inmates under indication, and 48.6% of them conclude it. Our prison reported information on LTBI treatment between 1990 and 1998 reaching acceptance rates to initiate LTBI therapy of 73% (23% refused to do so) and conclusion of the treatment of 40% of those who firstly commenced. The treatment was carried out with isoniazid for 6 months (6H) in a weekly self-administered regimen. This data is accordance with other studies [8, 9, 10], which included high percentages of IDUs and were carried out outside the prison environment, with high withdrawal rates.

The major problem to complete LTBI therapy has been the limited alternatives to the long-term 6-9-12 month regimen with isoniazid (H). Another study [11], concluded that in comparison to the isoniazid 6-9-12 month regimen, a combined regimen with rifampicin and pyrazinamide was as effective as the first one, with similar toxicity and mortality rates, but the description of severe cases of hepatitis in patients not infected by HIV who received 2RZ and a higher incidence of hepatotoxicity within the group of patients who received 2RZ compared to those who received 6H [12], entailed the recommendation of not using 2RZ in patients who were not infected by HIV and doubts concerning its recommendation for HIV infected patients. Different studies [13, 14] have proven that other short course therapies can be used with similar effectiveness and safety degree as those observed in the standard therapy. These short course therapies consist of the administration of Rifampicin and isoniazid during three months (3RH) or Rifampicin during four months (4R).

Short course regimens have the advantage of their briefness, so that they are almost always chosen by patients. The disadvantages are, in some cases, the high number of pills taken at a time, the interactions of Rifampicin with ART and methadone and the fact that poor adherence can lead to failure of the preventive activity so that it is considered that short course therapy must be administered within the prison environment in DOT.

By using short course therapies with a similar effect as far as the prevention of tuberculosis is concerned, an increase of adherence is expected and therefore, of the effectiveness of the treatment for LTBI itself. This study pretends to analyze the degree of acceptance of these therapies, their tolerance, safety, effectiveness in comparison to the 9H regimen and whether the results previous to the completion of LTBI treatment in the prison environment can be improved by means of DOT.

MATERIALS AND METHODS

This study was designed as a retrospective longitudinal, observational, descriptive and analytical study in an imprisonment facility with an average population of 516 inmates. A total period of 10 years was analyzed, between January 1st 2000 and December 2009. The Access data base of the prison was studied as well as medical reports of all inmates imprisoned during those 10 years. 902 patients with an indication for LTBI treatment or primary chemoprophylaxis were included. A tuberculin test was carries out with Mantoux technique, with 0.1 ml of tuberculin (2 IU of PPD RT-23). The following were considered as positivity criteria for the Mantoux test:

- PPD values ≥5 mm, regardless of the vaccination status.

  The following were considered conversion criteria:
- An increase of PPD of >5 mm for contacts of an infectious case and for all those inmates with a risk factor for developing TB.

  The Booster Effect was researched for all those patients with an initially negative reaction to PPD.

  Regimens were offered according to priority criteria, establishing the following categories:
- High priority: Contacts of a smear-positive case with high risk for transmission and HIV+ patients.
- Average priority: People with risk factors for TB, recent convertors, patients with fibrotic lesions and contacts with previous PPD+ and no risk factors.
- Low priority: People with none of the aforementioned factors, under 35 years and with no risk factors for hepatic toxicity.

Exclusion factors were the following:

- Having undergone TB treatment previously.
- Having completed previous LTBI treatment, except for HIV+ patients, children or if intense exposure had taken place.
- The presence of signs or symptoms suggesting TB.
- A history of hypersensitivity to the drugs used.
- Transaminases concentrations 5 times higher than normal values.

INTERVENTIONS

The administration of drugs was carried out in agreement with the patient, after ensuring a correct understanding of the information concerning potential risks and benefits, as well as the clinical manifestations which should be known and immediately reported to health care staff, being able to choose one of the following regimens:

- 9H: Isoniazid (H): 5mg/kg/d up to 300 mg/d during 9 months (270 doses), completing the number of doses in a maximum of 12 months.
- $2R_2Z_2$: 2 months with a total of 16 doses, 2 days per week of Rifampicin (R) 10 mg/kg/d up to a maximum of 600 mg and Pyrazinamide (Z) 40 mg/kg/d, up o a maximum of 2.5 g. All the 16 doses were completed in a maximum period of 3 months. In was contraindicated and not administered from 2004.
- 3HR: 3 months of Isoniazid (H) 5mg/kg/d, maximum 300 mg/d, and Rifampicin 10 mg/kg/d, up to 600 mg, completing all of the doses in a maximum period of 4 months.
- 4R: the regimen includes Rifampicin 10 mg/kg/d, maximum 600 mg, during 4 months, being able to complete all of the 120 doses in 6 months.

In all cases, administration was oral.

Between 2000 and 2004, patients were able to choose between the 9H therapy (Isoniazid) and the $2R_2Z_2$ one (Rifampicin and Pyrazinamide) in 16 doses. The $2R_2Z_2$ regimen was generally discarded in the case of HIV+ patients under ART and/or methadone therapy, especially due to potential interactions entailing the patients' discomfort and therefore leading to poorer adherence. This could affect not only the patients themselves but also future patients which could have heard about these secondary effects by means of other patients and this could mean the failure of short therapies within the penitentiary environment. Since 2003 and due to the CDC recommendations, the $2R_2Z_2$ therapy was considered contraindicated and consequently only the 9H therapy was offered. Since 2008 the 3HR and 4R therapies were also offered.

Before initiating LTBI treatment, an individualized clinical assessment was carried out in order to rule out the existence of TB by means of clinical and epidemiological history, chest X-rays, blood tests, complete blood count and biochemical analysis, as well as urine test strip to rule out urinary tract TB and in HIV+ patients, sputum specimens analysis, CD4 count and viral load. Eventually, follow-up was carried out in order to exclude active disease, assess adverse reactions, promote the adherence and controls were set up in weeks 2, 4, 8, and 12 in short course therapies and every month in the long ones.

LTBI treatment is withdrawn whenever clinical manifestations suggesting acute hepatitis or a significant increase in transaminases takes place (>5 times the normal values). Minor and asymptomatic elevations do not entail the withdrawal of therapy. LTBI treatment is also withdrawn if other diseases recommending its discontinuation, are diagnosed, TB disease is developed or due to passing, as well as to adverse reactions attributable to the drugs in study. Amongst these, the following were considered: nausea and persisting vomiting for more than 3 days, skin rash, opiate withdrawal syndrome in those patients under R and methadone maintenance, hyperuricemia, acute hepatopathy, renal failure, optic neuritis, peripheral neuropathy, thrombocytopenia, psychiatric disorders (anxiety, depression, etc.) and others.

The adherence to LTBI therapy was assessed by nursing staff, which carried out strict directly observed therapy in all cases. An appropriate compliance was defined as the administration of 100% of the dosage. Nursing staff observed the administration of therapy and ensured drug intake, carried out definite reports, provided health education and healthcare support for the patient, carried out the previously established controls, and reported to physicians on any problems detected. In the case of patients under the Methadone Maintenance Program, methadone intake is used for administering LTBI therapy too. For R regimens, the methadone dose was readjusted.

In order to improve previously achieved results, an ambitious health education campaign was launched, aimed at all inmates and officers, by means of the provision of documentation, the preparation

of materials with basic rules (such as pens, diaries, notebooks, folders, calendars, leaflets, etc.), the publication of different articles in the prison's Journal, videos about the adherence of LTBI therapy, healthcare workshops, training of health agents, smoking assessment and education studies, the assignment of cells for non-smokers, conferences on the HIV infection and TB, training lectures on TB aimed at inmates and staff, training for healthcare staff on TB and coordination tasks with outside prison healthcare services. Since 2005, health agents provide lectures on TB to all new inmates.

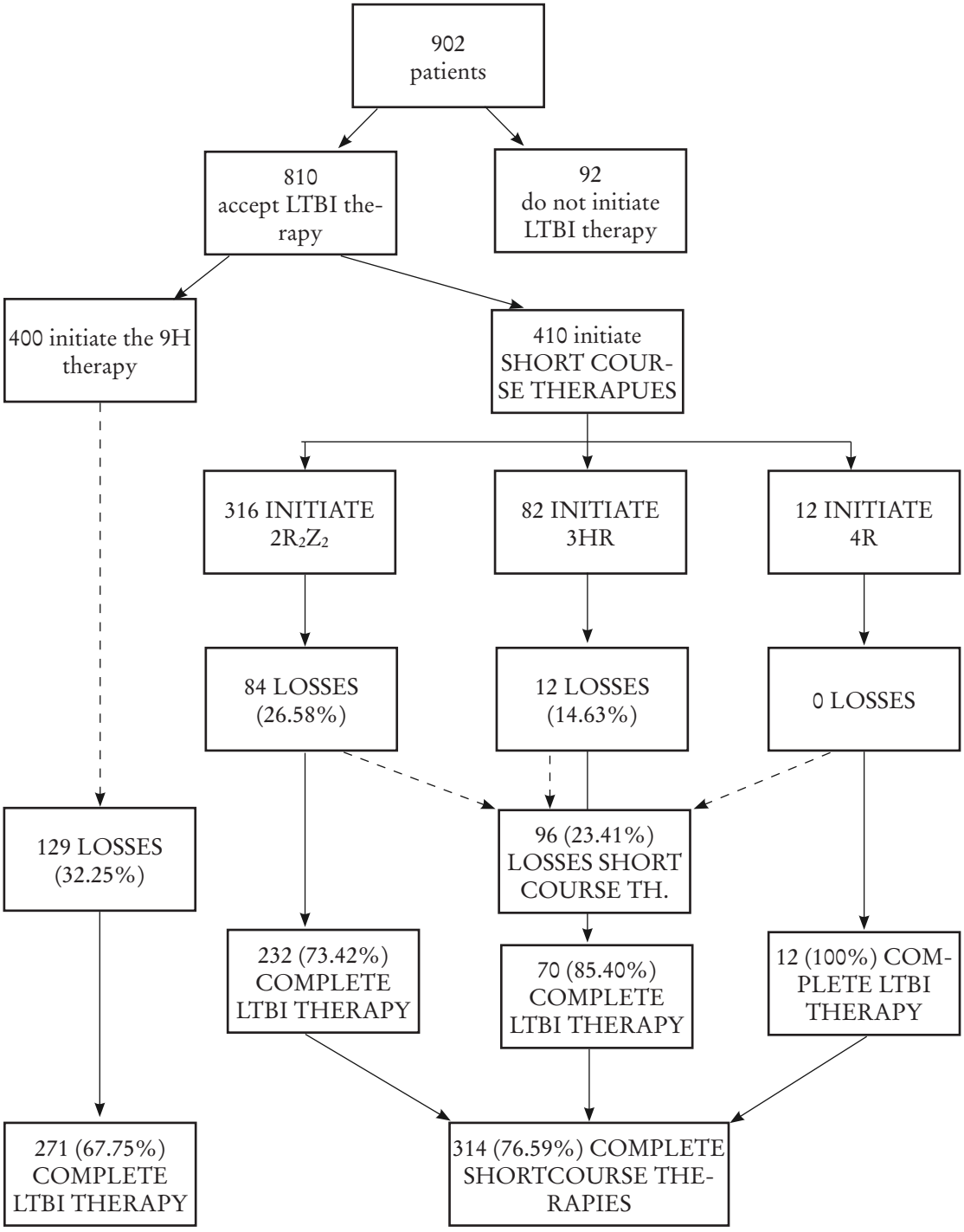

Figure 1. Development of the study.

ASSESSMENT AND FOLLOW-UP VARIABLES

The main assessment variables considered in the study were the adherence to each of the regimens, the cause of treatment withdrawal (voluntary withdrawal and adverse effects) and secondarily, the development of tuberculosis. Confirmed tuberculosis was defined as the isolation of *M. tuberculosis* in any of the samples. Once the therapy was completed, appropriate follow-up was not possible due to an average imprisonment time of less than 19 months.

SAMPLE SIZE AND STATISTICAL ANNALYSIS

The study included 902 patients, of whom 810 accepted the treatment: 400 in the 9H therapy and 410 in the short course therapies: 316 in the $2R_2Z_2$ therapy, 82 in the 3HR therapy and 12 in the 4R therapy.

The analysis of qualitative variables was carried out by means of the chi-square test ($\chi 2$). The analysis of continuous variables was carried out by means of Student's t-test.

The incidence rate of tuberculosis /100 people/ year was calculated by dividing the number of cases by the addition of the follow-up periods of each patient.

RESULTS

In the aforementioned period, 902 patients with inclusion criteria for LTBI treatment were studied, 810 of them accepted the treatment (89.80%), of which 697 were HIV- and 123 HIV+. For 40 patients (28 HIV+ and 12 HIV-) treatment was indicated as primary chemoprophylaxis (PPD-) due to contact with an index case; 29 accepted the treatment.

General Characteristics (see Table I)

Table I depicts basal differences among patients within the different treatment regimens. Statistically significant differences are observed as far as: 1) positive serology to HIV; 2) positive serology to HBV and HCV; 3) number of drug users, both injecting and non-injecting drugs; 4) number of convertors. Some of these differences are due to the fact that HIV+ patients and patients under MMP are systematically

BASAL CHARACTERISTICS AND RISK FACTORS OF PATIENTS INITITIATING LTBI TREATMENT	9H 400 PATIENTS	SHORT COURSE THERAPIES 410 PATIENTS	P	OR	CI95%
AGE	39,2	39,5	n.s.		
INDEX CASE CONTACTS WITH PPD-	19	10	0,090		
CONVERTORS	170	137	0,009	1,47	1,11-1,96
POSITIVE HIV SEROLOGY	114	9	<0,0001	17,76	8,86-35,60
POSITIVE HBV AND/OR HCV SEROLOGY	203	143	<0,0001	1,92	1,45-2,55
INJECTING DRUG USERS	101	50	<0,0001	2,43	1,68-3,53
NON-INJECTING DRUG USERS	172	137	0,006	1,50	1,13-2,00
EXCESSIVE ALCOHOL CONSUMPTION	60	64	n.s.		
DIABETES	14	9	n.s.		

Table I. Population features in each therapy

administered the 9H therapy in order to avoid the interactions between the antiretroviral treatment and Rifampicin.

92 patients (10.20%) do not initiate the treatment due to the following: 66 HIV- patients (64 refusals, 2 previous hepatopathy) and 26 HIV+ (18 refusals, 3 previous hepatopathy, 2 unknown causes and 3 pending initiation).

400 patients begin the 9H therapy: 286 HIV- patients and 114 HIV+; completing it 271 patients (67.75%): 207 HIV- and 64 HIV+ patients.

A total of 410 patients begin short course therapies, distributed as follows: 316 in the $2R_2Z_2$ therapy (309 HIV- and 7 HIV+ patients), 82 in the 3HR therapy (80 HIV- and 2 HIV+ patients) and 12 in the 4R therapy (12 HIV- patients) and finally 314 complete it (76.60%): 308 HIV- and 6 HIV+ patients.

The completion of treatment within the different short course therapies was distributed as follows: 232 patients complete the $2R_2Z_2$ therapy (73.42%) out of the 316 who initially began (228 HIV- and 4 HIV+); 70 complete the 3RH therapy (85.40%) out of the 82 initial patients (68 HIV- and 2 HIV+) and all the 12 initial 4R patients complete the therapy (100%), (12 HIV-).

Withdrawal Ratio (see Figure 1 and Table 2)

129 9H patients do not complete LTBI treatment (32.25%) (63 due to voluntary withdrawal, 35 due to adverse reactions, 26 due to release or transfer, 2 due to unknown causes, 1 due to TB development in an HIV- patients and 1 due to suicide).

96 patients of the short course therapies group do not complete LTBI treatment (23.41%) (36 due to voluntary withdrawal, 54 due to adverse reactions, 1 due to release of transfer, 3 due to unknown causes, 1 due to psychotic break in a psychiatric patient and 1 due to idiopathic acute hepatitis).

Statistically significant differences are observed as far as withdrawal before LTBI treatment completion, when comparing the 9H standard therapy and short course therapies. A significantly higher probability of withdrawal is observed in the 9H therapy (p: 0.006; Odds Ratio: 1.56 [CI95%: 1.14-2.12]).

Whenever comparing withdrawal before completion in the $2R_2Z_2$ and 3RH therapies, a significantly higher probability of withdrawal is observed in the $2R_2Z_2$ therapy (p: 0.029, OR: 2.11 [1.09-4.09]).

Significant differences are observed between voluntary withdrawals for no apparent reason with a superior number in the 9H therapy group in comparison to short course therapies (p: 0.002; OR: 2.03 [1.30-3.15]).

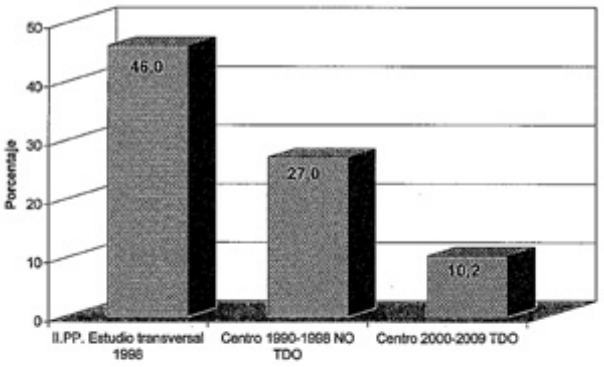

Figure 2. Comparison of refusal rates at the beginning of LTBI Treatment.

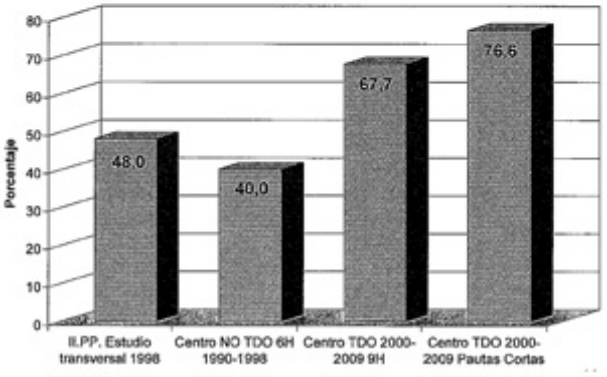

Figure 3. Comparison of LTBI Treatment completion rates.

Significant differences are also observed concerning withdrawal to transfer or release with a higher number in the 9H therapy group in comparison to short course therapies (p<0.0001; OR: 30.22 [4.07-224.29]).

NO significant differences are observed as far as withdrawal due to adverse reactions between the 9H therapy and short course therapies. When comparing all therapies as a whole, it is observed that the $2R_2Z_2$ therapy presents a higher probability of withdrawal due to adverse reactions (P: 0.006; OR: 1.87 [1.21-2.88]), without significant differences between the 9H and 3RH therapies.

Nevertheless, significant differences are observed in withdrawal due to hepatotoxicity (defined as transaminases increased over 5 times normal values), this being higher in the 9H therapy than in short course therapies (p. 0.037; OR: 2.94 [1.05-8.24]).

Higher withdrawal rates are also observed due to skin rash in the $2R_2Z_2$ group in comparison to the rest of the regimens: both in the 9H therapy (p<0.0001; OR: 70.07), and the 3RH therapy (p: 0.024; OR: 6.96).

If voluntary withdrawal and withdrawal due to transfer and/ or release are excluded, it is observed

that withdrawal ratios are similar when comparing the standard regimen and short course therapies.

LTBI THERAPY	9H	$2R_2Z_2$	3RH	4R
NUMBER OF PATIENTS	400	316	82	0
TOTAL ADVERSE EVENTS	37	49	7	
RASH		25	1	
GASTRIC INTOLERANCE	9	11	3	
MALAISE	8	5	2	
INCREASED TRANSAMINASES	14	4	1	
UNSPECIFIC DISCOMFORT	2			
STROKE+JAUNDICE	1			
PSYCHOTIC BREAK	1	1		
HIVES		2		
HEPATITIS		1		
SUICIDE	1			
TUBERCULOSIS	1			
UNKNOWN	3	3		
VOLONTARY WITHDRAWAL FOR NO APPARENT REASON	63	31	5	
TRANSFER OR RELEASE	26	1		

Table II. Adverse reactions and LTBI treatment withdrawal causes

When comparing withdrawal ratios between HIV+ and HIV- patients, it is proven that these are higher amongst HIV+ patients; p: 0.002; OR: 2.11 (1.34-3.33) and in the 9H therapy, which includes most of the HIV+ patients.

Only one patient in the 9H therapy develops tuberculosis (incidence rate 0.08), with no significant differences between different therapies.

DISCUSSION

The prevention of the TB infection within the prison environment entails a series of specific difficulties, mostly related to the inmates' behavior and lifestyle, derived from their poor awareness on the risk of becoming ill or being infected, the lack of information they have on TB and poor adherence to treatment programs. All this has lead to the revision of currently implemented strategies on the prevention and control of TB aimed at inmates, drug users and /or patients with poor treatment adherence. For them, directly observed therapy programs have been submitted for LTBI specifically or jointly with methadone maintenance programs. It has been proven in our country that including IDUs in a joint program significantly improves the compliance of LTBI treatment when administering under strict supervision both methadone and anti-TB drugs [15].

Over ten years ago, short course therapies proved to be effective and were included in international guidelines, as the Program for Tuberculosis Prevention and Control in the Prison Environment portrays. A study presented at the 5th Conference on Retroviruses and Opportunistic Infections in 2000 provided evidence on a similar effectiveness and safety between the short course therapy with R+Z and the 12H therapy for the prevention of TB [11]. Nevertheless, it must be taken into account that the short course therapy showed some cost-effectiveness advantages [16]. The 2RZ regimen was considered elective since Gordin [11] et al verified the results of a previous study on its safety and effectiveness and proved that not only was it as effective as the standard therapy, but it also improved therapy compliance. This therapy was disapproved in 2003 after 21 cases of severe or fatal hepatitis in HIV-patients under this treatment were reported to the CDC. The 9H therapy has proven able to reduce the risk of TB reactivation [17, 18] and the 3RH [1, 14, 19] therapy provides a similar protection level to the 12H regimen and has allowed cutting down by 60% the risk of developing TB in comparison to placebo in a wide population of patients with LTBI. The 3RH therapy in DOT is the option recommended in the Consensus Document on Tuberculosis Control in Spanish Prisons (Fernando Ruiz et al) [20], due to its briefness and the existence of commercial preparations including both drugs, which improve adherence. It is considered that the 4R [13] therapy might possibly be as effective as the 9H therapy with a BII evidence in HIV-patients, and a BIII evidence in HIV+ patients, and it is especially indicated in case of H intolerance or if contact with a H-resistant/R-sensitive TB case has taken place.

In our facility, we intended to improve the adherence by means of DOT (specifically for LTBI therapy or jointly with MMP) and short course therapies. Initial acceptance of LTBI treatment was 89.90%, analogous to other authors: 91% and 83% [21, 22], but higher than other groups which included IDU, 37% [6]. Acceptance was notably higher if compared to data included in the cross-sectional study carried out in the prison environment in 1998 (54%) or the one reported in our facility between 1990 and 1998 (73%). It has been considered that this improvement is due

Ltbi Therapy	Hiv-			Hiv+		
	Initiate LTBI T	Complete LTBI T	With-Draw LTBI T	Initiate LTBI T	Complete LTBI T	With-Draw **Ltbi T**
9H	274	200	74	114	64	50
$2R_2z_2$	309	228	81	7	4	3
3Rh	80	68	12	2	2	0
4R	12	12	0	0	0	0

Table III. LTBI Treatment comparison according to HIV serology.

to the wide offer or health education provided in the facility since 2000.

The completion of treatment was 72.22% in all of the therapies as a whole; it was higher (76.59%) in the short course therapies: $2R_2Z_2$ (73.42%) and 3RH (85.40%), than in the 9H long course therapy (67.75%), with similar results as those concluded in studies such as Rivero et al and better than those of Portilla et al with IDUs. Completion was notably improved in comparison to the information available on the prison environment of 1998 (48%) and data from our facility between 1990 and 1998 (40%). Both considered self-administered therapy and not DOT, therefore concluding the main role the nursing staff has played in achieving these results.

Voluntary withdrawal for no apparent reason was 16% in the 9H group in contrast to 8.80% in the short course therapies (10.13% in the $2R_2Z_2$ group and 4.90% in the 3RH one), considered this due to a greater weariness of patients concerning the number of months of LTBI therapy in the long course regimen. The number of patients which discontinues treatment due to release or transfer is higher in the long-course therapy than in the short-course ones (6.5% in contrast to 0.25%), even though this facility has an average imprisonment period of 19 months and a low inmates rotation degree. Therefore, withdrawal rates would be higher in those imprisonment facilities with a superior rotation degree.

As far as tolerance is concerned, adverse reactions took place in 11.48% as a whole, with similar results between the 9H therapy and short-course therapies. A significantly higher percentage of withdrawal due to adverse reactions was observed in the $2R_2Z_2$ group (15.5%) in contrast to the 9H one (9.25%), this being similar to the 3RH therapy (8.53%). In the 4R group no withdrawals due to adverse reactions took place (0%) but this was not considered significant due to the low number of patients enrolled in this group. Although higher hepatic toxicity was expected in the 3HR group in contrast to 9H, as observed in a previous meta-analysis[16]: 2.73% in contrast to 0.5%, this has not been proven in our study nor by Gordin et al [11], and actually a significantly higher hepatotoxicity has been observed in the 9H regimen (14 patients presented an elevation of transaminases 5 times higher basal values). Probably this is due to a higher number of HIV+ patients under LTBI treatment with that regimen, attributable to a higher frequency of interactions between ART and methadone, as well as due to a larger percentage of patients with positive serology for hepatic viruses. In the $2R_2Z_2$ group, 5 patients had to discontinue treatment (4 due to an elevation of transaminases 5 times higher than normal values and 1 due to idiopathic symptomatic hepatitis and release in an active IDU). In the 3RH regimen, 1 patient discontinued therapy due to an elevation of transaminases 3 times higher than basal values. In the $2R_2Z_2$ group, a significant number of adverse reactions consisting of rash were observed (25 patients).

The 4R regimen did not present adverse reactions leading to therapy discontinuation. This is not considered significant due to the number of patients enrolled in this group.

It is also observed in our study that a lower number of HIV+ patients complete therapy in comparison to HIV- patients, this mainly explained by the fact that rotation between facilities with regimental problems takes place, adverse effects derived from their treatments (antiretroviral, methadone, etc.) and voluntary withdrawal after weariness for long course therapies with 9H, as well as possible neurocognitive disorders in a large number of patients All this lead us to offer in the first place, short course LTBI therapies to HIV+ patients who were not under antiretroviral treatment, to better select those patients with ART who could take the 3RH therapy and recently, to create a self-help group for HIV+ patients, which lays emphasis

on self-care and the improvement of treatment adherence. We expect to assess in the future whether these strategies entail an improvement of adherence in this priority group.

Although one case on TB was observed within the 9H group, the relative risk of developing TB was not significantly higher in contrast with the other two therapies due to the low incidence of TB throughout the study.

Although DOT entails a series of controversial aspects such as the passive role of patients as receivers of medication or the implication of a larger number of resources, our experience has been very positive and DOT has not entailed many implementation problems. It would possibly be less effective if we only administrated the drugs and carried out clinical controls, since we believe it is necessary to implement healthcare closely connected to education, so that patients assume a better understanding of the disease, the reasons for treatment, its advantages and shortcomings and therefore become co-responsible for their recovery. In order to achieve this, a broad and continuous health education program that allows a positive influence as far as habits and health related values are concerned, is necessary.

In summary, it is observed that an improved acceptance for initiating treatment has been achieved, probably due to a larger awareness and knowledge derived from extensive health education programs implemented in our facility. It has also been observed that short-course therapies in DOT improve the adherence with inferior withdrawal rates than the 9H therapy.

Our data supports the safety and adherence of the 3RH short-course therapy in DOT and its predilection in contrast to the 9H regimen, as it improves previously achieved results, with a similar toxicity as that observed in the standard regimen and a higher completion rate which also improves significantly the operational effectiveness of the LTBI treatment. It is also verified that the 3RH therapy improves previously achieved results with a low voluntary withdrawal rate and due to transfer or release, so that it is considered the elective option for the treatment of LTBI within the penitentiary context. It entails a special benefit for those centers with preventive inmates and / or a high rotation as it allows that a large number of inmates with risk factors for developing TB to complete a preventive treatment which has proven effective.

In the same way, it is verified that the administration of LTBI treatment in DOT significantly improves the results previously achieved in a cross-sectional study of the prison environment and in our facility without DOT, as it reaches high acceptation and treatment completion rates.

In summary, the combination of short-course therapies, DOT and healthcare education together with the implementation and the development of programs coordinating inside and outside prison environments [16], can extraordinarily improve the acceptation and compliance of LTBI treatment with a significant improvement of its effectiveness in a population at risk of developing TB.

CORRESPONDECE

Dr. Gerardo López Palacio
Centro Penitenciario de Bilbao
gerardo_lopez@wanadoo.es

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