ORIGINAL PAPERS

A randomized trial of three regimens to prevent tuberculosis in HIV-infected patients with anergy

Antonio Rivero[a], Luis López-Cortés[b], Rafael Castillo[c], Fernando Lozano[d], Miguel Ángel García[e], Felipe Díez[f], José Carlos Escribano[g], Jesús Canueto[h], Juan Pasquau[i], Juan José Hernández[j], Rosa Polo[k], Francisco Javier Martínez-Marcos[b], José María Kindelán[l], Rafael Rey[k] and Grupo Andaluz para el estudio de las Enfermedades Infecciosas (GAEI)

Servicios de Enfermedades Infecciosas. Hospitales [a]Virgen de la Victoria (Málaga), [b]Virgen del Rocío (Sevilla), [c]Clínico Universitario San Cecilio (Granada), [d]Nuestra Señora de Valme (Sevilla), [e]Carlos Haya (Málaga), [f]Torrecárdenas (Almería), [g]Puerta del Mar (Cádiz), [h]Punta Europa de Algeciras (Cádiz), [i]Virgen de las Nieves (Granada), [j]Ciudad de Jaén (Jaén), [k]Instituto Nacional Carlos III (Madrid), [l]Universitario Reina Sofía (Córdoba). Spain.

INTRODUCTION. To evaluate the efficacy of three regimens of prophylactic therapy for tuberculosis in HIV-infected patients with anergy.

METHODS. Prospective, multi-center, randomized, comparative, and open clinical trial. Anergy was defined as absence of induration in response to three antigens (PPD, Candida albicans and parotiditis antigen) applied by the Mantoux method. Patients were randomized into one of the following prophylactic treatment groups: isoniazid for six months (6H), rifampin plus isoniazid for three months (3RH), rifampin plus pyrazinamide for two months (2RZ) or no treatment (NT). After completion of treatment, patients were followed up for two years.

RESULTS. A total of 319 patients were included in the study, 83 in the 6H regimen, 82 in 3RH, 77 in 2RZ and 77 in NT. The observation period following treatment was 88, 96, 81 and 126 person-years, respectively, for 6H, 3RH, 2RZ and NT. There were 11 cases of tuberculosis during the follow-up period. The tuberculosis rates (cases per 100 person-years) were 3.4, 3.1, 1.2 and 3.1 for 6H, 3RH, 2RZ and NT respectively, with relative risks in regimens 6H, 3RH and 2RZ with respect to NT of 1.07 (0.24-4.80), 0.98 (0.22-4.4) and 0.39 (0.04-3.48), all statistically non-significant. Twenty-nine patients died during the follow-up period, none due to tuberculosis, and no appreciable differences were found among the groups.

CONCLUSIONS. The results showed no significant decrease in the risk of developing tuberculosis with any of the evaluated regimens and, therefore, do not support the use of antituberculosis chemoprophylaxis in anergic HIV-infected patients.

Key words: HIV. Anergy. Chemoprophylaxis. Tuberculosis.

Ensayo clínico aleatorizado de tres pautas de quimioprofilaxis para prevenir la tuberculosis en pacientes infectados por el VIH con anergia cutánea

INTRODUCCIÓN. Evaluar la eficacia de tres pautas de quimioprofilaxis antituberculosa en pacientes infectados por el virus de la inmunodeficiencia humana (VIH) con anergia cutánea.

MÉTODOS. Ensayo clínico prospectivo, multicéntrico, aleatorizado, comparativo y abierto. La anergia cutánea se definió por la ausencia de reactividad a 3 antígenos aplicados por la técnica de Mantoux (PPD, candidina y parotiditis). Los pacientes se distribuyeron de forma aleatoria a uno de los siguientes grupos de tratamiento: isoniacida durante 6 meses (6H), rifampicina más isoniacida, 3 meses (3RH), rifampicina más piracinamida, 2 meses (2RZ) o sin tratamiento (NT). Tras finalizar la quimioprofilaxis los pacientes fueron seguidos 2 años.

RESULTADOS. Se incluyeron en el estudio 319 pacientes, 83 en la pauta 6H, 82 en 3RH, 77 en 2RZ y 77 en NT. El período de observación tras el tratamiento fue de 88, 96, 81 y 126 personas años, respectivamente para 6H, 3RH, 2RZ y NT. Se produjeron 11 casos de tuberculosis durante el seguimiento. Las tasas de tuberculosis (casos por 100 personas/año) fueron respectivamente de 3,4, 3,1, 1,2 y 3,1 para 6H, 3RH, 2RZ y NT, con un riesgo relativo en las pautas 6H, 3RH y 2RZ respecto a NT de 1,07 (0,24-4,80), 0,98 (0,22-4,4) y 0,39 (0,04-3,48), estadísticamente no significativo. Durante el seguimiento fallecieron 29 pacientes, ninguno de ellos por tuberculosis, sin que se apreciaran diferencias entre grupos.

CONCLUSIONES. Nuestro estudio no demuestra una reducción significativa del riesgo de tuberculosis en ninguna de las 3 pautas evaluadas y, por tanto, no apoya el empleo de quimioprofilaxis antituberculosa en pacientes con anergia cutánea.

Palabras clave: VIH. Tuberculosis. Quimioprofilaxis. Anergia.

Introduction

A number of studies have indicated that anergic HIV-infected patients have a high risk for developing tuberculosis (TB)[1,2], but diverse clinical assays have not conclusively demonstrated the advantages of establishing antituberculosis chemoprophylaxis in this patient population[3-4]. Thus, the initial recommendation to establish anti-tubercular chemoprophylaxis in HIV-infected patients with anergy[5] was later rejected[6] and, at present, neither delayed hypersensitivity skin tests[7] nor chemoprophylaxis is carried out on these patients[8].

Nevertheless, there is evidence that certain groups of anergic HIV-infected patients, such as prisoners, drug users and the homeless, can have a high risk of tuber culosis[1,2,8,9]. One observational study even demonstrated a reduction in the risk of TB when isoniazid chemoprophylaxis was used over a twelve-month period in HIV-infected patients with anergy[10].

We present the results of a prospective clinical study. The main objective of this study was to determine the tolerance to, and efficacy for TB prevention of three chemoprophylactic regimens in HIV-infected patients with anergy.

Methods

Design and study population

This study is a controlled, open, randomized, multi-center clinical assay, undertaken between 1 June 1994 and 31 December 1998 in twelve public hospitals, one located in Madrid and the remaining eleven in Andalusia. The study was authorized by the Clinical Research Ethics Committee of all participating centers and informed written consent was obtained from all the patients included. The criteria for enrollment in the study were as follows: 1) HIV infection confirmed by ELISA and Western blot; 2) age between 18 and 65 years; 3) life expectancy greater than two years; 4) cutaneous anergy defined by the absence of a reaction (0 mm) to skin reactivity tests with tuberculin, *Candida albicans,* and parotiditis antigens 72 hours after inoculation.

Testing for delayed cutaneous hypersensitivity was carried out on the inside of the lower left arm with the Mantoux method using: 0.1 ml of tuberculin (2 UI of PPD RT-23), 0.1 ml of *Candida albicans* antigen at a concentration of 1:10, and 0.1 ml of parotiditis antigen at a concentration of 1:10.000.

The exclusion criteria were as follows: 1) presence of active tuberculosis; 2) background of previous antituberculosis therapy or chemoprophylaxis; 3) presence of symptoms or signs suggesting pulmonary or extra-pulmonary tuberculosis; 4) history of hypersensitivity to the drugs used in the study (isoniazid, rifampin or pyrazinamide); 5) aspartate-aminotransferase and/or alanine-aminotransferase plasma concentrations more than or equal to four times their normal values, total bilirubin more than 2 mg/ml, and/or creatinine more than 2 mg/ml; 6) pregnancy; and 7) undergoing treatment incompatible with any of the drugs used in the study.

Randomization and interventions

The patients were randomly placed into one of the following four groups: isoniazid for 6 months (6H), rifampin plus isoniazid for 3 months (3RH), rifampin plus pyrazinamide for 2 months (2RZ) or no treatment (NT). The pharmaceuticals were administered daily by the patients themselves. The oral doses were as follows: isoniazid - 5 mg/kg/day (maximum 300 mg/day); rifampin - 10 mg/kg/day (maximum 600 mg/day); pyrazinamide - 1500 mg/day for patients weighing under 50 kg, 2000 mg/day for those weighing between 50 and 70 kg, and 2500 mg/day for those weighing more than 70 kg.

All of the participating subjects underwent a basal study that included clinical and epidemiological history, chest x-ray, hemogram, analysis of serum creatinine concentrations, BUN, uric acid, AST, ALT, alkaline phosphatase, and total bilirubin, as well as a CD4+ T-lymphocyte count.

During prophylactic treatment, patients were evaluated every 15 days for the first two months and monthly thereafter. At each check-up it was determined whether or not the patient was following the treatment properly and whether there were any adverse effects. A blood count and a biochemical study of hepatic and renal functions were also carried out at these visits.

The doctor in charge of each patient determined compliance to treatment by an oral interview. Therapeutic completion was defined as taking at least 80% of the total prescribed dosages. Prophylaxis was discontinued whenever a patient requested to do so or for any of the following reasons: appearance of Grade 3 or 4 side effects that could be attributed to the drugs used in the study; increases in AST and/or ALT values of three times or more their basal values; development of TB; or diagnosis of any disease that made interruption of the treatment advisable.

Evaluation and follow-up variables

The main variable of the study was development of TB. Confirmed TB was defined as isolation of *Mycobacterium tuberculosis* in any sample, probable TB as the presence of acid alcohol-resistant bacilli in any sample without confirmation or posterior identification in the cultures, and possible TB as clinically consistent disease that responded to treatment for tuberculosis. The other variables studied included suspension of prophylaxis (due to adverse effects, interactions between medications, or voluntary withdrawal) and mortality. Once prophylaxis was completed, clinical follow-up of the patients was performed for a two-year period, carrying out a study identical to the basal study every six months. In patients in whom TB was suspected, we performed the clinical tests required for its diagnosis, always including Ziehl-Neelsen staining and cultures in Lowenstein-Jensen media of fluids or tissue samples. If the latter were found to be positive, the procedure was to systematically identify the mycobacterium and perform sensitivity tests.

Sample size

The study was designed to have a sample size of 332 patients (83 patients per treatment group). The sample size was calculated assuming a confidence level of 95%, a power of 80%, an incidence of tuberculosis in the anergic patients not receiving treatment of 12.5% and an incidence of tuberculosis in the groups receiving treatment of 2%.

Statistical analysis

The analysis of continuous variables was carried out using the Student's t or the Mann-Whitney U tests. Chi-square or Fisher tests were used for the analysis of qualitative variables. The rate of TB per 100 person-years was calculated by dividing the number of cases of tuberculosis by the follow-up time of each subject. The relative risk of developing TB according to the chemoprophylaxis regimen was determined by calculating the reason for risk with a proportional risk regression or Cox regression method.

TABLE 1. **Basal characteristics of the patients**

	Total	6H	3HR	2RZ	NT	*P*
N	319	83	82	77	77	
Mean age	32.7	32	33	32	32	0.85
Sex (%male)	72	78	73	68	67	0.41
Lymphocytes CD4+/µL						
Median	230	193	271	232	215	0.79
Range	0-1495	3-974	0-883	5-858	2-1495	
AIDS (%)	15.0	16.8	18.2	10.3	14.2	0.52
Risk behavior						
IDU	58.9	63.8	59.7	54.5	57.1	0.66
HMX/BX	16.6	13.2	14.6	16.8	19.4	0.68
HTX	22.6	18.0	24.3	23.3	22.0	0.77
Hemoderivates	2.3	3.6	0	3.9	1.3	0.26
Others/unknown	1	1.2	1.2	1.3	0	0.80

6H: 6 months of isoniazid. 3HR: 3 months of isoniazid plus rifampin; 2RZ: 2 months of rifampin plus pyrazinamide. NT: no treatment. IDU: intravenous drug use. HMX/BX: Homosexual/bisexual relations. HTX: Heterosexual relations.

Results

The study included 319 patients whose basal characteristics, described in Table 1, were comparable among the study groups. Following randomization, 10 patients did not begin chemoprophylaxis for the following reasons: diagnosis of active tuberculosis in 2 patients, *Pneumocystis carinii* pneumonia in 2, *Mycobacterium avium intracellulare* in 1, visceral leishmaniasis in 1, metrorrhagia in 1, pregnancy in 1, previous *M. tuberculosis* treatment in 1 and hyperbilirubinemia in 1. There were no differences among the groups regarding withdrawal during prophylaxis or follow-up (Table 2). Two patients undergoing methadone treatment who were assigned regimens containing rifampin voluntarily withdrew from the study so as to avoid adjusting the methadone dosage.

Eleven cases of TB occurred during follow-up, 3 in the 6H group, 3 in the 3RH group, 1 in the 2RZ group, and 4 in the NT group (p= 0.65); all were bacteriologically confirmed. Tuberculosis occurred on average at 14.5 months of follow-up (range 4-24 months; median 13 months), with no statistically significant differences among the groups. Follow-up was 88 (6H), 96 (3RH), 81 (2RZ) and 126 (NT) person-years of observation, respectively. The following rates of TB were found: 3.4 cases per 100 person-years in the 6H group, 3.1 cases per 100 person-years in the 3RH, 1.2 cases per 100 person-years in the 2RZ and 3.1 cases per 100 person-years in the NT (p= 0.64). The number of patients who developed TB, according to the prophylactic regimen and the relative risk with the confidence interval are shown in Table 3. The clinical and diagnostic characteristics of the patients with TB are shown in Table 4. Thirty-four patients experienced side effects that led to withdrawal of the medication, but there were no significant differences in this aspect among the treatment groups (Table 5). Of the 9 patients with hepatotoxicity, only one was removed from treatment (6H) due to symptomatic hepatitis. The remaining 8 were removed because of an asymptomatic increase in transaminases, defined as a level at least 3-fold higher than the basal value in the absence of hepatitis symptoms.

TABLE 2. **Development of the study: Withdrawals and deaths**

	6H	3HR	2RZ	NT	*P*
Randomized	83	82	77	77	
Began CP	82	80	72		
Withdrawn during CP	17	11	10		
Completed prophylaxis	65	69	62		
Withdrawn during follow-up	5	3	3	6	0.62
Deaths					
During CP	1	0	0		
During follow-up	8	4	5	11	0.18

6H: 6 months of isoniazid. 3HR: 3 months of isoniazid plus rifampin. 2RZ: 2 months of rifampin plus pyrazinamide. NT: no treatment CP: chemoprophylaxis.

TABLE 3. **Cases of tuberculosis. Relative risk by treatment group**

	6H	3HR	2RZ	NT	*P*
Observation (person-years)	88	96	81	126	
Cases of tuberculosis					
Confirmed	3	3	1	4	0.65
Probable/Possible	0	0	0	0	–
Totals	3	3	1	4	0.65
Rate (100 person/years)	3.4	3.1	1.2	3.1	0.64

	Relative Risk	*P*
6H vs.3HR	1.09 (0.22-5.41)	1
6H vs. 2RZ	2.76(0.29-26)	0.62
6H vs. NT	1.07 (0.24-4.80)	1
3HR vs. 2RZ	2.53 (0.26-24)	0.63
3HR vs. NT	0.98 (0.22-4.4)	1
2RZ vs. NT	0.39 (0.04-3.48)	0.65

6H: 6 months of isoniazid. 3HR: 3 months of isoniazid plus rifampin. 2RZ: 2 months of rifampin plus pyrazinamide. NT: no treatment.

TABLE 4. **Description of the cases of tuberculosis**

	6H	3HR	2ZR	NT
TB Confirmed:				
Disseminated	1[A]	1	1[B]	0
Pulmonary	2[C]	2[A]	0	4[D]

6H: 6 month regimen with isoniazid. 3HR: 3 month regimen with isoniazid plus rifampin; 2RZ:2 month regimen with rifampin plus pyrazinamide. NT: no treatment.
[A] *M. bovis* multiresistant, [B] *M. tuberculosis* resistant to isoniazid and rifampin; [C] *M. tuberculosis* resistant to isoniazid, [D] *M. tuberculosis* resistant to isoniazid and streptomycin.

TABLE 5. **Adverse effects requiring withdrawal of treatment**

	6H	3HR	2RZ	*P*
Digestive intolerance	1	5	2	0.60
Exanthema	1	7	6	0.08
Hepatotoxicity	4	1	4	0.92
Fever	0	2	1	0.44

6H: 6-month regimen with isoniazid. 3HR: 3-month regimen with isoniazide plus rifampin. 2RZ: 2-month regimen with rifampin plus pyrazinamide.

Twenty-nine patients died during the follow-up period from causes unrelated to TB. These included 6 cytomegalovirus, 4 terminal HIV disease, 3 sepsis, 2 cerebral toxoplasmosis, 2 progressive multifocal leukencephalopathy, 2 *Pneumocystis carinii* pneumonia, 2 heroine overdose, 2 lymphomas, 1 bacterial meningitis, 1 meningeal cryptococcosis, 1 respiratory insufficiency, 2 cerebral abscess, 1 Kaposi's sarcoma and 2 undetermined causes. Mortality was 14.3% in the group of patients not receiving treatment and 7.7% (18/234) in the treated group (p=0.08).

Discussion

HIV infection produces a significant defect in cell-mediated immunity that is evidenced in the inability to develop a delayed cutaneous hypersensitivity response to one or more antigens[11]. Because of this fact, the ability to diagnose latent infection by *M. tuberculosis* is diminished in many HIV-infected patients and there is a possibility that coinfection with *M. tuberculosis* may go undetected.

Study of cutaneous anergy is a simple and inexpensive way to evaluate immune function in HIV-infected patients[12,13]. One important aspect when assessing anergy is the criteria used to define it. We required an absence of reactivity to three antigens (PPD, *C. albicans* and parotiditis antigen) applied by the Mantoux method to define anergy. These criteria, recommended by international organizations[14,15], have proven to be the most effective for defining cutaneous anergy in HIV-infected patients[16].

Chemprophylaxis is highly effective for reducing tuberculosis in patients co-infected by HIV and *M. tuberculosis*[4,17-19]. A number of studies have demonstrated that the risk for developing tuberculosis in anergic HIV-infected patients is higher than in non-anergic patients who do not react to tuberculin[20-23]. One retrospective study carried out in Spain demonstrated that the risk might be even higher than in tuberculin-reactive HIV-infected patients who do not receive chemoprophylaxis[2].

In the design of the present study carried out in the years 1993-1994, highly active antiretroviral treatment (HAART) was not taken into account. Therefore, the use of HAART during the follow-up period was not prospectively recorded and it was not possible to evaluate its effect on the incidence of tuberculosis. This is an important limitation of the study.

The incidence of tuberculosis in our group of anergic patients without chemoprophylaxis was 3.1 cases per 100 patient-years. The incidence of tuberculosis recorded in anergic HIV-infected patients depends on various factors, including the prevalence of TB in the area, the criteria used to define anergy, whether the study is prospective or retrospective, the degree of patient immunosuppression and the diagnostic criteria used to define tuberculosis. Our study found an incidence similar to that of other prospective studies carried out in areas with a high prevalence of tuberculosis, such as the one by Whalen et al[4] carried out in Uganda (3.1 cases per 100 patient-years), and the one by Guelar et al[20] carried out in Spain (2.6 cases per 100 patient-years). In contrast, our incidence is higher than that reported in studies from areas with a low rate of tuberculosis, such as the one by Gordin et al[3] carried out in the USA (0.9 cases per 100 patient-years). The high incidence of tuberculosis in anergic patients with tuberculosis (12.4 cases per 100 patient-years) obtained by Moreno et al[2] in a retrospective study carried out in Spain is striking. The incidence was even higher than that of tuberculin-reactive patients who were not receiving chemoprophylaxis in the same study. The fact that the study was retrospective and included a higher percentage of parenteral drug users (80%) and immunosuppressed patients (mean CD4+ lymphocyte count: 135/mm^3), could explain the difference with respect to our results.

The main goal of our study was to evaluate the efficacy of three regimens of chemoprophylaxis for decreasing the incidence of tuberculosis in anergic HIV-infected patients. The first of the three regimens evaluated was 6H. In tuberculin-reactive subjects without HIV infection, this regimen reduced the incidence of tuberculosis by 69%[24]. In tuberculin-reactive patients with HIV infection, reported results are discrepant; Whalen et al[4] demonstrated a 68% decrease in the incidence of tuberculosis with 6H, whereas Hawken et al[19] found no differences with respect to the placebo. In anergic HIV-infected patients receiving 6H, two randomized clinical trials were unable to demonstrate a significant decrease in the risk of acquiring tuberculosis with respect to the placebo[3,4], although in one of these studies tuberculosis risk decreased by 56%[3]. In the present study, the incidence of tuberculosis in patients receiving 6H was not lower than the incidence of tuberculosis in the non-treated group of patients.

The second of the evaluated regimens, 3RH, reduced the risk of tuberculosis in tuberculin-reactive HIV-infected patients by 60%[4]. However, this regimen has not been extensively evaluated in anergic patients. In one study conducted in Spain, 3RH showed an efficacy similar to 12H, but tuberculin-reactive patients as well as anergic patients were included, and equivalence between the two regimens was not demonstrated[25]. In our study, 3RH did not reduce the risk of tuberculosis with respect to the group of untreated patients.

The last of the regimens evaluated, 2RZ, has been considered one of the two regimens of choice for

antituberculosis chemoprophylaxis in tuberculin-reactive HIV-infected patients[9], since Gordin et al[26] confirmed the results from a previous study[27], showing that it was as efficient as the 12H regimen. In the present study, 2RZ reduced the risk of TB by 62%, but differences in risk with respect to the untreated group were not statistically significant. Cases of severe or fatal hepatitis have been reported in HIV-negative subjects receiving 2RZ as antituberculosis prophylaxis, making it unadvisable to treat such patients with this option[28]. In our study, as well as in other clinical trials[26], the incidence of hepatoxicity among patients receiving 2RZ was not found to be higher. None of the patients participating in our study died due to toxic hepatitis, no significant differences in hepatoxicity were found among the three regimens of treatment, and the four patients treated with 2RZ who were withdrawn from the study because of hepatoxicity showed asymptomatic elevation of transaminases.

Development of exanthema is a well-known side effect of rifampin treatment that can lead to withdrawal of the drug[29]. In our study, exanthema was more frequent in patients receiving one of the two regimens containing rifampin, although differences were not statistically significant.

Mortality among the non-treated patients (14.3%) was higher than in the combination of the treated patients groups (7.7%). We have no explanation for this difference, even though it is slightly above the limit for statistical significance (p=0.08) and, therefore, worthy of mention. The reason why prophylaxis decreases mortality in a given population is because it decreases the mortality provoked by the infection toward which it is directed. However, this was not verified in our study, since none of patients without prophylaxis died from tuberculosis.

In summary, although a 62% reduction in the incidence of tuberculosis was found in the 2RZ group with respect to untreated patients in our study, there was no significant reduction in the risk of tuberculosis with any of the three regimens evaluated. Therefore, our results do not support the use of chemoprophylaxis against tuberculosis in patients with skin anergy. However, the unexpectedly low rate of tuberculosis found in untreated anergic patients and the 62% reduction in TB incidence among patients treated with 2RZ when compared to the untreated patients despite this low rate, make it impossible to completely disregard the benefits of this strategy. In any case, the recommendations for avoiding tuberculosis in anergic HIV-infected patients should continue to be avoidance of exposure and, in the event that exposure should occur, initiation of appropriate chemoprophylaxis as soon as possible.

References

1. Selwyn PA, Sckell BM, Alcabes P, Friedland GH, Klein RS, Schoenbaum EE. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. JAMA 1992;268:504-9.
2. Moreno S, Baraia-Etxaburu J, Bouza E, Parras F, Pérez-Tascón M, Miralles P, et al. Risk for developing tuberculosis among anergic patients infected with HIV. Ann Intern Med 1993;119:194-8.
3. Gordin FM, Matts JP, Miller C, Brown LS, Hafner R, John SL, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. N Engl J Med 1997;337: 315-20.
4. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. N Engl J Med 1997; 337:801-8.
5. Centers for Disease Control. PPD-tuberculin anergy in persons with HIV infection. Guidelines for anergy testing and management of anergic persons at risk of tuberculous infection. MMWR 1991;40(RR-5):27-33.
6. Centers for Disease Control. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR 1997;46(RR-12):10-2.
7. Centers for Disease Control Anergy skin testing and preventive therapy for HIV-infected persons: Revised recommendations. MMWR 1997;46(RR-15):1-10. [Erratum, MMWR 1997;46:800].
8. Girardi E, Antonucci G, Armignacco O, Salmasso S, Ippolito G, the Italian Group for the Study of Tuberculosis and AIDS (GISTA). Tuberculosis and AIDS: a retrospective, longitudinal, multicentre study of Italian AIDS patients. J Infect 1994;28:261-9.
9. Centers for Disease Control. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR 1998;47(RR-20):1-58.
10. Gourevitch MN, Hartel D, Selwyn PA, Schoenbaum EE, Klein RS. Effectiveness of isoniazid chemoprophylaxis for HIV-infected drug users at high risk for active tuberculosis. AIDS 1999;13:2069-74.
11. Colebunders RL, Lebughe I, Nzila N, Kalunga D, Francis H, Ryder R, et al. Cutaneous delayed-type hypersensitivity in patients with human immunodeficiency virus infection in Zaire. J Acquir Immune Defic Syndr 1989;2:576-8.
12. Hegde HR. Anergy, AIDS and tuberculosis. Med Hypotheses 1995;45:433-40.
13. Miller WC, Thielman NM, Swai N, Cegielski JP, Shao J, Ting D, et al. Delayed type hypersensitivity testing in Tanzanian adults with HIV infection. J Acquir Immune Defic Syndr 1996;12:303-8.
14. Centers for Disease Control and Prevention. Purified protein derivative (PPD)-tuberculin anergy and HIV infection: Guidelines for anergy testing and management of anergic persons at risk of tuberculosis. MMWR 1991; 40(RR-5):27-33.
15. Centers for Disease Control and Prevention. Anergy skin testing and preventive therapy for HIV-infected persons: revised recommendations. MMWR 1997;46(RR-15):1-10.
16. Martínez-Marcos FJ, López-Cortés LF, Pachón J, Alarcón A, Cordero E, Viciana P. Comparison of two methods for the assessment of delayed-type hypersensitivity skin responses in patients with human immunodeficiency virus infection. Clin Infect Dis 1998; 26:1330-4.
17. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression on HIV infection. Lancet 1993;342:268-72.
18. Mwinga AG, Hosp M, Godfrey-Faussett P, Quigley M, Mwaba P, Mugala BN, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. AIDS 1998;12:2447-57.
19. Hawken MP, Meme HK, Elliot LC, Chakaya JM, Morris JS, Githui WA, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. AIDS 1997;11:875-82.
20. Guelar A, Gatell JM, Verdejo J, Podzamczer D, Lozano L, Aznar E, et al. A prospective study of the risk of tuberculosis among HIV-infected patients. AIDS 1993;7:1345-9.
21. Graham NM, Nelson KE, Solomon L, Bonds M, Rizzo RT, Scavotto J, et al. Prevalence of tuberculin positivity and skin test anergy in HIV-1 seropositive and seronegative intravenous drug users. JAMA 1992;267:369-73.
22. Antonucci G, Girardi E, Raviglione M, Ippolito G. Risk factors for tuberculosis in HIV-infected persons. JAMA 1995;274:143-8.
23. Markowitz N, Hansen NI, Hopewell PC, Glassroth J, Kvale PA, Mangura BT, et al. Incidence of tuberculosis in the United States among HIV-infected persons. Ann Intern Med 1997;126:123-32.
24. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull WHO 1982; 60:555-64.

25. Martínez E, Cuadra F, Solera J, Maciá MA, Geijo P, Sánchez PA, et al. Evaluación de dos pautas de quimioprofilaxis tuberculosa en pacientes infectados por el virus de la inmunodeficiencia humana. Med Clin (Barc) 2000;115: 161-5.
26. Gordin F, Chaisson RE, Miller C, Garcia ML, Hafner R, Valdespino JL, et al. Rifampin and Pyrazinamide versus Isoniazid for prevention of tuberculosis in HIV-infected persons. An international randomized trial. JAMA 2000;283: 1445-50.
27. Halsey NA, Coberly JS, Desormeaux J, Losikoff P, Atkinson J, Moulton LH, et al. Randomized trial of isoniazid versus rifampicin and pyrazynamide for prevention of tuberculosis in HIV infection. Lancet 1998;351: 786-92.
28. CDC. Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC Recomendations. United States, 2001. MMWR 2001; 50: 733-5.
29. Cook SV, Fujiwara PI, Frieden TR. Rates and risk factors for discontinuation of rifampicin. Int J Tuberc Lung Dis 2000;4:118-22.