1 Appendix D: Evidence tables – RQ HH & II - Diagnosis of active TB

Contents

RQ HH: According to their risk factors, which people with either latent TB infection or in close contact with people who have active TB should receive drug treatment to prevent the development of active TB?

Risk factors for benefit or harm from the treatment of latent tuberculosis

A.1.1 Radhakrishnan, S., & Subramani, R. (2011)

Bibliographic reference	**Radhakrishnan, S., & Subramani, R. (2011). Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases.*INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE*,*15*(6), 782-788.**
Study type	Cohort
Study quality	Population taken from a double-blind randomised control trial assessing the protective efficacy of BCG vaccination. Population does not exactly match population of interest as TST[1] negative participants are included; however subgroup analysis is possible. Baseline: Unclear if cohorts were matched for the amount that received BCG vaccination or placebo in the initial trial; however the primary paper found no difference in incidence of TB between these two populations. Analysis of variance was undertaken to balance the comparison groups for other potential confounding factors. Baseline: Cohort was significantly older in persons in households without a TB case. Isoniazid susceptible cohort had the lowest proportion of males. Isoniazid resistant cohort had the highest proportion of infected participants. Follow up: Planned follow up was 15 years however, in the primary study subjects with an initial induration of > 15 mm who were unlikely to benefit from BCG had follow up reduced to 7.5 years to reduce workload. Analysis was adjusted to allow for differences in length of follow up. In terms of person-years, follow up was similar in the three series in the first 5 years. An appropriate length of follow up was used.

Bibliographic reference	**Radhakrishnan, S., & Subramani, R. (2011). Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases.*INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE*,*15*(6), 782-788.**
	The study used a precise definition of outcome. A valid and reliable method was used to determine outcome. Investigators were blinded to important confounding and prognostic factors.
Number of patients	Total= 253,186 participants Isoniazid (INH) susceptible contacts= 5562 INH²-resistant contacts = 779 No household contact= 246845
Patient characteristics	Included Household contacts of TB patients Excluded Positive smear culture, abnormal radiograph or no radiograph available. Contacts of cases with no initial drug susceptibility testing Baseline characteristics

	INH² susceptible	INH² resistant	Control
Age at intake, years	876	129	35593
0-4	943	140	37063
5-9	932	136	34061

Bibliographic reference	**Radhakrishnan, S., & Subramani, R. (2011). Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases.*INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE*,*15*(6), 782-788.**			
	10-14	1056	134	39696
	15-24	688	113	36583
	25-34	462	49	27888
	35-44	348	43	19808
	45-54	257	35	16153
	≥55	5562	779	246845
	Total	19.8	19.0	22.7
	mean			
	Sex	2533 (45.5%)	383 (49.2%)	122581 (49.7%)
	Male	3029 (54.5%)	396 (50.8%)	124 264 (50.3%)
	Female			
	Infection status at intake	2444 (43.9%)	235 (30.2%)	132400 (53.6%)
	Not infected	3118 (56.1%)	544 (69.8%)	114445 (46.4%)
	Infected			
Intervention	Household contacts of isoniazid susceptible cases N= 5562 Household contacts of isoniazid resistant cases N= 779			

<table>
<tr><th>Bibliographic reference</th><th>Radhakrishnan, S., & Subramani, R. (2011). Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases.INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE,15(6), 782-788.</th></tr>
<tr><td>Comparison</td><td>Control group of participants without household contact of TB
N= 246845</td></tr>
<tr><td>Length of follow up</td><td>15 years</td></tr>
<tr><td>Location</td><td>India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Incidence of tuberculosis
<table>
<tr><th>Subgroup</th><th>Risk group</th><th>Population</th><th>Standardised incidence/100000</th><th>Hazard Ratio</th><th>95% confidence interval</th></tr>
<tr><td>Infected patients</td><td>No TB case at home</td><td>114445</td><td>314</td><td>1.0</td><td></td></tr>
<tr><td></td><td>INH²- susceptible contact</td><td>5835</td><td>530</td><td>1.8</td><td>1.4-2.2</td></tr>
<tr><td></td><td>INH²- resistant contact</td><td>728</td><td>436</td><td>2.2</td><td>1.5-3.3</td></tr>
<tr><td></td><td>Not infected female child</td><td>46303</td><td></td><td>1.0</td><td></td></tr>
</table>
Number of participants diagnosed with tuberculosis</td></tr>
</table>

Bibliographic reference	**Radhakrishnan, S., & Subramani, R. (2011). Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases.*INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE*,*15*(6), 782-788.**				
	Infected patients	Infected female child	8521	8.3	5.6-12.3
		Infected male child	9841	12.2	8.4-17.6
		Infected female adult	48132	15.8	11.0-22.7
		Infected male adult	54514	50.6	34.2-74.8
Source of funding	Unclear who provided funding for this project A trial from the Indian Council of Medical Research				
Comments	SUMMARY: The baseline prevalence of tuberculosis infection was substantially higher in contacts of INH-resistant than INH-susceptible patients, but the incidence of tuberculosis disease over a 15 year follow up was similar in the two series, and twice as high as in non-contacts.				
[1]TST- tuberculin skin test [2]INH- Isoniazid					

A.1.2 Casado JL, Moreno S et al (2002)

Bibliographic reference	**Casado, J. L., Moreno, S., Fortún, J., Antela, A., Quereda, C., Navas, E., ... & Dronda, F. (2002). Risk Factors for Development of Tuberculosis after Isoniazid Chemoprophylaxis in Human Immunodeficiency Virus—Infected Patients.*Clinical infectious diseases*, *34*(3), 386-389.**
Study type	Cohort
Study outline	Population matches the population of interest Question is relevant; discussing the risk factors for development of active tuberculosis. Unclear if all patients received the same level of care. Follow up: median follow up was 43 months (range 14-118 months). Adjustments were attempted to allow for differences. Length of follow up was appropriate. Patients included were comparable for intervention completion. Patients stopping treatment due to adverse events were excluded from the study. All patients received ≥ 9 months of isoniazid prophylaxis. Unclear if those stopping treatment were systematically different from those who remained in the study. Definition of outcome was unclear: persistence of predisposing conditions for TB infection was highlighted as the main risk factor with no attempt to break down the data any further. Unclear if a valid and reliable method was used to determine the outcome.
Number of patients	Population: 131
Patient characteristics	Included= 131 HIV infected patients under treatment for latent TB with isoniazid chemoprophylaxis. “Compliant” patients Received ≥9 months of isoniazid chemoprophylaxis Follow up lasting ≥1 year after isoniazid chemoprophylaxis, or until death Positive TST[1]

Bibliographic reference	**Casado, J. L., Moreno, S., Fortún, J., Antela, A., Quereda, C., Navas, E., ... & Dronda, F. (2002). Risk Factors for Development of Tuberculosis after Isoniazid Chemoprophylaxis in Human Immunodeficiency Virus—Infected Patients.*Clinical infectious diseases*, *34*(3), 386-389.**
	Excluded Receiving HAART[3] Baseline characteristics Mean age: 35 years (range, 21-58 years) Males/females: 102/29 patients Median CD4 cell count: 405 cells/ml Injection drug use: 82% Homosexuality: 8% Heterosexual intercourse with HIV infected partner 6% Unknown:4% Prior AIDS defining illness- 3% Drug addiction: 83% Prior imprisonment: 21% Close contact with recently diagnosed TB case: 10% Multiple factors for TB: 21%
Intervention	>9 months of isoniazid preventive therapy= 131
Length of follow up	Median follow up: 43 months
Location	Spain

Bibliographic reference	**Casado, J. L., Moreno, S., Fortún, J., Antela, A., Quereda, C., Navas, E., ... & Dronda, F. (2002). Risk Factors for Development of Tuberculosis after Isoniazid Chemoprophylaxis in Human Immunodeficiency Virus—Infected Patients.*Clinical infectious diseases*, *34*(3), 386-389.**
Outcomes measures and effect size	Risk of developing tuberculosis Multivariate model of risk factors: CD4 cell count (per each unit of increase): Relative hazard (95% CI²) 0.995 (0.992-1.003); P value 0.06 Persistence of predisposing factors for TB: Relative hazard (95% CI²) 3.17 (1.56-17); P value 0.0002 Unclear which predisposing factors proved the greater risk, or which were included in the multivariate model: Data initially collected included: demographic data, initial CD4 cell count, compliance, toxicity, predisposing factors for TB before and after isoniazid treatment, incidence of and time to development of TB, CD4 cell count at the time of disease and survival.
Source of funding	Unclear who provided funding for this project A trial from the Department of Infectious Diseases, Madrid
Comments	SUMMARY: Of all the factors investigated, only the persistence of predisposing conditions for TB infection, such as drug addiction or new prison admissions, was found to increase the risk of active TB. This suggests reinfection as the main cause of TB after isoniazid chemoprophylaxis. Most patients received isoniazid chemoprophylaxis early in the course of HIV infection and thus the effect of CD4 count drop on the rate of TB could not be estimated. All patients included were also compliant adherers to medication therefore the effect of non-compliance to treatment also could not be estimated.
Abbreviations: ¹TST- tuberculin skin test ²CI- confidence interval	

Bibliographic reference	**Casado, J. L., Moreno, S., Fortún, J., Antela, A., Quereda, C., Navas, E., ... & Dronda, F. (2002). Risk Factors for Development of Tuberculosis after Isoniazid Chemoprophylaxis in Human Immunodeficiency Virus—Infected Patients.*Clinical infectious diseases*, *34*(3), 386-389.**

[3]HAART- Highly active antiretroviral therapy

A.1.3 Tedla Z Nyrenda S et al (2010)

Bibliographic reference	**Tedla, Z., Nyirenda, S., Peeler, C., Agizew, T., Sibanda, T., Motsamai, O., ... & Samandari, T. (2010). Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. *American journal of respiratory and critical care medicine*, *182*(2), 278-285.**
Study type	Cohort
Study quality	Population does not exactly match population of interest as TST[1] negative participants were likely included in the population. Intervention matches intervention of interest Participants received the same isoniazid intervention under the Botswana national guidelines. Unclear if patients received the same care and support aside from this intervention at the different cities and health clinic settings in the study. Follow up: No follow up apparent beyond the 6 month treatment period. Groups were comparable for treatment completion and those who had completed less than 4 months of isoniazid treatment were excluded from the study. No attempt was made to examine those who dropped out for any important or systematic differences to the remaining participants. A precise definition of outcome was used and a valid and reliable method used to determine the outcome.
Number of patients	In total= 1,995 participants
Patient characteristics	1,995 HIV infected participants were enrolled at 8 different local health clinics in the cities of Gaborone and Francistown in Botswana. Included HIV infected Aged 18-70 years Free from cough, fever, clinical AIDS, respiratory illness or lymphadenopathy on examination Under isoniazid preventive therapy Excluded

Bibliographic reference	**Tedla, Z., Nyirenda, S., Peeler, C., Agizew, T., Sibanda, T., Motsamai, O., ... & Samandari, T. (2010). Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. *American journal of respiratory and critical care medicine*, *182*(2), 278-285.**
	Pregnant Serum aspartate aminotransferase > 85 international units (IU) Alanine aminotransferase > 103 IU/L (≥2.5 times upper limit of normal) Total Bilirubin greater than 39 µmol/L (≥1.5 times upper limit of normal) Baseline characteristics Male/Female: 28% / 72% Median age: 32 years (range 18-70 years) Underweight (BMI²): 18% Overweight (BMI²): 17% Obese (BMI²): 9% Tuberculin skin test positive: 24% CD4 count <200: 31% Undergoing antiretroviral therapy: 26%
Intervention	Isoniazid For body weight ranging 30-49 kg Isoniazid: 300mg daily, for 6 months Pyridoxine: 25mg daily, for 6 months Self-administered

Bibliographic reference	**Tedla, Z., Nyirenda, S., Peeler, C., Agizew, T., Sibanda, T., Motsamai, O., ... & Samandari, T. (2010). Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. *American journal of respiratory and critical care medicine*, *182*(2), 278-285.**
	For body weight ranging >50 kg Isoniazid: 400mg daily, for 6 months Pyridoxine: 25mg daily, for 6 months Self-administered
Length of follow up	No apparent follow up beyond treatment period
Location	Botswana
Outcomes measures and effect size	Risk factors associated with severe isoniazid-associated hepatitis during 6 months of isoniazid preventive therapy Relative risks:

	Fraction of participants with hepatitis	Relative risk (95% CI²)
Age	9/645	1.56 (0.64-3.82)
>35 y	10/1117	1.00
≤35 y		
Sex	13/1293	0.79 (0.30-2.06)
Female	6/469	1.00
Male		
Body mass index	2/304	0.63 (0.14-2.72)
Underweight	15/1426	1.00
Not underweight		

Bibliographic reference	**Tedla, Z., Nyirenda, S., Peeler, C., Agizew, T., Sibanda, T., Motsamai, O., ... & Samandari, T. (2010). Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. *American journal of respiratory and critical care medicine*, *182*(2), 278-285.**		
	CD4 lymphocyte count	10/501	2.80 (1.14-6.84)
	CD4 <200 cells/mm³	9/1261	1.00
	CD4 ≥200 cells/mm³		
	Anti-retroviral therapy (ART)	7/480	1.56 (0.62-3.93)
	Receipt of ART	12/1282	1.00
	No receipt of ART		
	Efavirenz	2/223	0.46 (0.09-2.35)
	Efavirenz based regimens	5/257	1.00
	ART not efavirenz		
	Efavirenz	2/223	0.96 (0.21-4.31)
	Efavirenz based regimens	12/1282	1.00
	Not ART		
	Nevirapine	5/256	2.19 (0.43-11.2)
	Niverapine therapy	2/224	1.00
	ART not using nevirapine		
	Nevirapine	5/256	2.09 (0.74-5.87)
	Niverapine therapy	12/1282	1.00
	Not ART		
	NNRTI[3]	7/479	-

Bibliographic reference	**Tedla, Z., Nyirenda, S., Peeler, C., Agizew, T., Sibanda, T., Motsamai, O., ... & Samandari, T. (2010). Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. *American journal of respiratory and critical care medicine*, *182*(2), 278-285.**		
	NNRTI[3]	0/1	-
	NO NNRTI[3]		
	Co-trimoxazole	4//245	1.65 (0.55-4.93)
	Co-trimoxazole use	12/1517	1.00
	No co-trimoxazole		
	Alcohol	8/597	1.42 (0.57-3.51)
	Drinks alcohol	11/1165	1.00
	No alcohol		
	Alcohol dependence	8/358	2.37 (0.96-5.84)
	CAGE ≤ 1	11/1165	1.00
	CAGE = 0		
Viral Hepatitis	Viral Hepatitis as a risk factor for isoniazid hepatotoxicity		
	Thirteen case subjects and 127 control subjects were tested for HBV and HCV.		

Hep B Viral Serological Pattern	Interpretation	Case Subjects	Control Subjects	Total
Hepatitis B core antibody: negative	Susceptible	4	51	55
Hepatitis B surface antibody: negative				
Hepatitis B surface				

Bibliographic reference	**Tedla, Z., Nyirenda, S., Peeler, C., Agizew, T., Sibanda, T., Motsamai, O., ... & Samandari, T. (2010). Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. *American journal of respiratory and critical care medicine*, *182*(2), 278-285.**				
	antigen: negative				
	Hepatitis B core antibody: positive	Natural infection that resolved	7	60	67
	Hepatitis B surface antibody: positive/negative				
	Hepatitis B surface antigen: negative				
	Hepatitis B core antibody: negative	Immune due to immunization	1	7	8
	Hepatitis B surface antibody: positive				
	Hepatitis B surface antigen: negative				
	Hepatitis B core antibody: positive	Chronic infection	0	8	8
	Hepatitis B surface antibody: negative				
	Hepatitis B surface antigen: positive				
	Incomplete serology	other	1	1	2
			13	127	140
	None of the cases of isoniazid hepatitis had chronic viral hepatitis B infection therefore no evidence of an association between the two was found.				

Bibliographic reference	**Tedla, Z., Nyirenda, S., Peeler, C., Agizew, T., Sibanda, T., Motsamai, O., ... & Samandari, T. (2010). Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. *American journal of respiratory and critical care medicine*, *182*(2), 278-285.**
Source of funding	Unclear who provided funding for this project One of the named researchers has full time employment under a pharmaceutical company
Comments	SUMMARY: Of all risk factors under study, only CD4 cell count <200 cells/mm³ was significantly related to a higher risk of isoniazid associated hepatitis after multivariate analysis. There was however a significant interaction term between this and antiretroviral therapy.
[1]TST- tuberculin skin test [2]BMI- Body Mass Index [3]NNRTI- Nonnucleoside reverse transcriptase inhibiter	

A.1.4 Mori MA, Leonardson G et al (1992)

Bibliographic reference	**Mori, M. A., Leonardson, G., & Welty, T. K. (1992). The benefits of isoniazid chemoprophylaxis and risk factors fo tuberculosis among Oglala Sioux Indians.*Archives of internal medicine*, *152*(3), 547-550.**
Study type	Case Control
Study quality	Population does not exactly match population of interest: Native American people were enrolled; this population has an incidence of TB two to three times that of the surrounding populations. Not all patients in the active tuberculosis group had a documented positive TST[1] test prior to TB diagnosis. 1 had a negative TST[1] and 8 had an unknown infection status. Outcome matches outcome of interest. The study does not ask a clearly focused question: It attempts to illicit the benefit of isoniazid preventive therapy in those that are tuberculin reactors however some non-reactors were also included in the analysis thereby confounding the study data. Also since documented TST[1] reactors are more likely to be offered chemoprophylaxis, the control group is likely to overestimate the proportion of latently infected people in the population who receive preventive therapy. The data on risk factors for developing tuberculosis is more useful but still confounded by the presence of non-TST[1] reactors in the case group. The cases and controls are taken from comparable populations, however, control patients were found to be more compliant to treatment when compared to tuberculosis cases. As mentioned, the same exclusion criteria were not used for both cases and controls in regard to previous positive TST[1] result. Participants and non-participants were not compared Cases are clearly defined and differentiated from controls. It is established that controls are not cases. No measures appear to have been taken to prevent knowledge of primary exposure(s) from influencing case ascertainment Exposure to diabetes may have not been measured in a standard and reliable fashion since patients with high random or fasting blood glucose recordings were listed as being diabetic, however British guidelines require more than just one isolated raised blood glucose level. Chart documentation supplied many of the other diagnoses such as notation of alcohol abuse or admissions related to alcoholism.

Bibliographic reference	**Mori, M. A., Leonardson, G., & Welty, T. K. (1992). The benefits of isoniazid chemoprophylaxis and risk factors fo tuberculosis among Oglala Sioux Indians.*Archives of internal medicine*, *152*(3), 547-550.**
	Multivariate analysis allows many of the main potential confounders to be taken into account Confidence intervals have been provided. As mentioned the fact that the control group were chosen on the basis of TST[1] reaction means that more of these participants were offered chemoprophylaxis than would have been in the general latently infected population. Therefore results would not be generalizable to this source population in regards to development of active tuberculosis. Comparisons are made for age, sex, chemoprophylaxis therapy, immunosuppression, alcohol abuse, diabetes, chronic renal failure and pulmonary scarring or nodules on x-ray. Unclear how long participant's histories were tracked for Unclear how this study was funded.
Number of patients	In total= 92 participants Active tuberculosis infected= 46 Tuberculin reactors without active disease= 46
Patient characteristics	Included Case group: every adult with active tuberculosis age > 18 years Control group: positive tuberculin test recorded in medical records before the median date of diagnosis of tuberculosis in the case group Excluded Case group: patients who had undergone reactivation of tuberculosis and had received chemotherapy

Bibliographic reference	**Mori, M. A., Leonardson, G., & Welty, T. K. (1992). The benefits of isoniazid chemoprophylaxis and risk factors fo tuberculosis among Oglala Sioux Indians.*Archives of internal medicine*, *152*(3), 547-550.**
	Baseline characteristics
	Cases n=46 / Controls n= 46
	Median age, y: 54.5 / 56.5
	Sex, %: 65.2 / 45.7
	M: 34.8 / 54.3
	F
	6+ months of isoniazid chemoprophylaxis: 1 / 24
	Immunosuppression: 3 / 1
	Alcohol abuse: 25 / 15
	Diabetes: 16 / 5
	M: 8 / 2
	F: 8 / 3
	Chronic renal Failure: 6 / 0
	Pulmonary scarring/nodules, among those with radiograms: 20 / 16
Intervention	Those who develop active tuberculosis
Comparison	Those who have latent tuberculosis but do not develop active disease
Length of follow up	Unclear

Bibliographic reference	**Mori, M. A., Leonardson, G., & Welty, T. K. (1992). The benefits of isoniazid chemoprophylaxis and risk factors for tuberculosis among Oglala Sioux Indians.*Archives of internal medicine*, *152*(3), 547-550.**					
Location	USA					
Outcomes measures and effect size	Risk factors for active tuberculosis After multivariate analysis					
		Cases n=46	Controls n=46	Crude odds ratio	95% confidence interval	Adjusted odds ratio	Adjusted 95% confidence interval
	6+ months chemoprophylaxis	1	24	0.02	0-0.15	0.02	0.002-0.16
	Alcohol abuse	25	15	2.5	0.97-6.3	3.8	1.15-12.3
	Diabetes	16	5	4.4	1.29-15.5	5.2	1.22-22.1
Source of funding	Unclear who provided funding for this project					
Comments	SUMMARY: After multivariate analysis: Diabetes, alcohol abuse and chronic renal failure were risk factors for active tuberculosis development after latent tuberculosis infection.					

[1]TST- tuberculin skin test

A.1.5 Fountain FF, Tolley E et al (2005)

Bibliographic reference	**Fountain, Francis F., Elizabeth Tolley, Cary R. Chrisman, and Timothy H. Self. "Isoniazid Hepatotoxicity Associated With Treatment of Latent Tuberculosis InfectionA 7-Year Evaluation From a Public Health Tuberculosis Clinic." *CHEST Journal* 128, no. 1 (2005): 116-123.**
Study type	Retrospective Cohort
Study outline	Population matches the population of interest Question is relevant; discussing the risk factors for development of isoniazid associated hepatotoxicity. Patients did not receive the same level of care as participants within the last three years of the study were given 9 months of isoniazid instead of 6 months, due to changes in American Thoracic Society Guidelines. Participants were treated from the same site. Follow up: testing for hepatotoxicity took place at 1 month, 3 months and 6 months. No further testing took place. Follow up was possibly not appropriate since patients may suffer hepatotoxicity following treatment or within the last 3 months of treatment. Treatment completion was poor across the board with only 43.13% of patients completing 3 months of therapy and 21.65% of patients completing 6 months of therapy. Attempts to find the systematic differences between those who did or did not complete treatment have been made. Those who completed treatment were more likely to be at least 50 years old. Those who did not complete treatment were associated with having hepatitis or being treated within the period that a longer regimen of isoniazid was recommended (9 months). Multivariate analysis was used. Unclear if multivariate analysis adjusted for varying compliance. Definition of outcome was clear A valid and reliable method was used to determine the outcome.
Number of patients	Population: 3,377
Patient characteristics	Included= 3,377 Receiving isoniazid chemoprophylaxis for latent tuberculosis Aged ≥25 years

Bibliographic reference	**Fountain, Francis F., Elizabeth Tolley, Cary R. Chrisman, and Timothy H. Self. "Isoniazid Hepatotoxicity Associated With Treatment of Latent Tuberculosis InfectionA 7-Year Evaluation From a Public Health Tuberculosis Clinic." *CHEST Journal* 128, no. 1 (2005): 116-123.**

Excluded

Pregnancy

3 months postpartum

Baseline AST[1] level more than 3 times the upper limit of normal

History of isoniazid allergy

Baseline characteristics

Characteristics	Number of participants	%
Year of treatment initiation	16	0.47
1996	276	8.17
1997	439	13.00
1998	484	14.33
1999	456	13.50
2000	553	16.38
2001	622	18.42
2002	531	15.72
2003		
Age, yr	1533	45.40
25-34	1409	41.72

Bibliographic reference	Fountain, Francis F., Elizabeth Tolley, Cary R. Chrisman, and Timothy H. Self. "Isoniazid Hepatotoxicity Associated With Treatment of Latent Tuberculosis InfectionA 7-Year Evaluation From a Public Health Tuberculosis Clinic." *CHEST Journal* 128, no. 1 (2005): 116-123.		
	35-49	435	12.88
	≥50		
	Gender	2075	61.45
	M	1302	38.55
	F		
	Race	2443	72.34
	African American	403	11.93
	White	285	8.44
	Hispanic	229	6.78
	Asian	17	0.50
	Unknown		
	Alcohol Consumption	2474	73.26
	None	665	19.69
	1-7	117	3.46
	8-14	121	3.58
	15+		
	History of liver disease	3220	95.35
	None	109	3.23
	Hepatitis A, B, or C	2	0.06

Bibliographic reference	**Fountain, Francis F., Elizabeth Tolley, Cary R. Chrisman, and Timothy H. Self. "Isoniazid Hepatotoxicity Associated With Treatment of Latent Tuberculosis InfectionA 7-Year Evaluation From a Public Health Tuberculosis Clinic." *CHEST Journal* 128, no. 1 (2005): 116-123.**		
	Cirrhosis	49	1.45
	Other		
Intervention	From 1996 to mid-1999 6 months of Isoniazid For patients ≥60 kg bodyweight: 300 mg, once a day. For patients <60 kg bodyweight: 5 mg/kg, once a day. From late 1999-2003 6 months of Isoniazid For patients ≥60 kg bodyweight: 300 mg, once a day. For patients <60 kg bodyweight: 5 mg/kg, once a day.		
Length of follow up	No follow up beyond treatment period, or within the last 3 months of treatment.		
Location	USA		
Outcomes measures and effect size	Risk of developing isoniazid associated hepatitis Multivariate logistic regression analysis of risk factors associated with elevation of transaminases by greater than five times the upper limit of normal. N= 2,182 (the number who completed at least one month of treatment)		
		Odds Ratio (95% confidence Interval)	P value
	Baseline AST[1] > upper limit of normal	5.398 (2.081-13.999)	0.0005
	Age ≥ 50 years	3.699 (1.428-9.584)	0.008

Bibliographic reference	**Fountain, Francis F., Elizabeth Tolley, Cary R. Chrisman, and Timothy H. Self. "Isoniazid Hepatotoxicity Associated With Treatment of Latent Tuberculosis InfectionA 7-Year Evaluation From a Public Health Tuberculosis Clinic." *CHEST Journal* 128, no. 1 (2005): 116-123.**
	Unclear if multivariate model included number compliant to treatment or year of treatment initiation. Results were adjusted for age, gender, race, alcohol consumption, history of liver disease and baseline transaminases.
Source of funding	Unclear who provided funding for this project Paper from College of Pharmacy, University of Tennessee
Comments	SUMMARY: Isoniazid hepatotoxicity is age related. Results suggest hepatotoxicity is also related to baseline AST[1] greater than the upper limit of normal. Moderate-to-severe hepatotoxicity frequently occurs without symptoms, suggesting the value of more widespread AST[1] monitoring.
Abbreviations: AST- aspartate aminotransferase	

A.1.6 LoBue, Philip A., and Kathleen S. Moser (2003)

Bibliographic reference	**LoBue, Philip A., and Kathleen S. Moser. "Use of isoniazid for latent tuberculosis infection in a public health clinic." *American Journal of Respiratory and Critical Care Medicine* 168, no. 4 (2003): 443-447.**
Study type	Retrospective Cohort
Study outline	Population matches the population of interest Question is relevant; discussing the risk factors for development of isoniazid associated hepatotoxicity and adverse effects. Patients did not receive the same level of care as rules regarding monitoring were altered during the study due to changes in American Thoracic Society Guidelines. Initially all patients over 35 were monitored with monthly transaminase levels as well as those at higher risk of hepatotoxicity; later this was changed to only those at higher risk. Participants were treated from the same site. Follow up: follow up did not appear to continue beyond treatment period (6-9 months of isoniazid therapy). This may not

Bibliographic reference	**LoBue, Philip A., and Kathleen S. Moser. "Use of isoniazid for latent tuberculosis infection in a public health clinic." *American Journal of Respiratory and Critical Care Medicine* 168, no. 4 (2003): 443-447.**
	have been appropriate. Treatment completion was poor with only 64% of patients completing 6 months of therapy. Attempts to find the systematic differences between those who did or did not complete treatment have been made. Those who completed treatment were more likely to be Hispanic. Those who did not complete treatment were associated homelessness and substance abuse. Multivariate analysis was used. Unclear if multivariate analysis adjusted for varying compliance. Definition of outcome was clear. A valid and reliable method was not necessarily used in all patients since those who were not deemed high risk were monitored using a symptoms checklist which would not catch subclinical presentations of hepatotoxicity. Unclear how cases of latent tuberculosis was diagnosed The paper does not provide the exact doses and lengths of regimens used
Number of patients	Population: 3,788
Patient characteristics	Included= 3,788 Included if treated with isoniazid for latent tuberculosis Baseline characteristics

Characteristics	Number of participants	%
Gender	1552	41
M	2229	58
F	7	0.2
unknown		
Age	1277	34
0-14	1939	51

Bibliographic reference	**LoBue, Philip A., and Kathleen S. Moser. "Use of isoniazid for latent tuberculosis infection in a public health clinic." *American Journal of Respiratory and Critical Care Medicine* 168, no. 4 (2003): 443-447.**		
	15-34	426	11
	35-49	95	2.5
	50-64	50	1.3
	65+		
	Race/ethnicity	3025	80
	White, Hispanic	170	4.4
	White, non-hispanic	117	3.1
	Black, non-hispanic	335	9
	Asian-pacific Islander	4	0.1
	Native American	13	0.3
	Other	124	3.3
	Unknown		
	Country of birth	782	21
	United States	2101	56
	Mexico	178	4.7
	Phillippines	62	1.6
	Vietnam	258	7
	Other	407	11
	Unknown		

Bibliographic reference	**LoBue, Philip A., and Kathleen S. Moser. "Use of isoniazid for latent tuberculosis infection in a public health clinic." *American Journal of Respiratory and Critical Care Medicine* 168, no. 4 (2003): 443-447.**
Intervention	Treatment followed American Thoracic Society treatment guidelines, specifics beyond this were unclear: ATS[1] recommends 9 months of isoniazid daily, or 6 months of therapy if deemed more cost-effective. Which was used is unclear.
Length of follow up	No follow up beyond treatment period apparent
Location	USA
Outcomes measures and effect size	Risk of developing isoniazid associated adverse events Occurrence of at least one adverse effect that had been reported as attributable to isoniazid, occurred following isoniazid treatment and for which no alternative cause was found. Multivariate analysis of factors associated with occurrence of at least one adverse effect.

Factor	N with at least one adverse effect	Odds Ratio (95% Confidence Interval)	P Value
Gender	217	Reference	<0.01
M	453	1.6 (1.4-2.0)	
F			
Age	177	Reference	0.04
0-14	360	1.3 (1.0-1.6)	<0.01
15-34	102	1.8 (1.3-2.5)	<0.01
35-49	25	2.2 (1.3-3.8)	0.38
50-64	8	1.5 (0.6-3.2)	
65+			
Race/ethnicity	530	1.3 (0.9-1.8)	0.19

Bibliographic reference	**LoBue, Philip A., and Kathleen S. Moser. "Use of isoniazid for latent tuberculosis infection in a public health clinic." *American Journal of Respiratory and Critical Care Medicine* 168, no. 4 (2003): 443-447.**			
	White, Hispanic	42	1.6 (0.9-2.6)	0.07
	White, non-hispanic	23	1.2 (0.7-2.2)	0.49
	Black, non-hispanic	57	Reference	
	Asian-pacific Islander			
	Country of birth	138	Reference	0.58
	United States	486	1.1 (0.8-1.4)	
	Other			
	Excess alcohol	670	Reference	0.52
	N	2	0.6 (0.1-2.8)	
	Y			
	Intravenous drug use	670	Reference	0.73
	N	2	1.3 (0.3-7.3)	
	Y			
	Homeless	654	Reference	0.02
	N	18	2.2 (1.2-4.2)	
	Y			
	Correctional Facility	645	Reference	<0.01
	N	27	2.6 (1.5-4.5)	
	Y			

Bibliographic reference	**LoBue, Philip A., and Kathleen S. Moser. "Use of isoniazid for latent tuberculosis infection in a public health clinic." *American Journal of Respiratory and Critical Care Medicine* 168, no. 4 (2003): 443-447.**
	Unclear if multivariate model included number compliant to treatment or year of treatment initiation. Results were adjusted for those variables that were associated with the outcome significantly (p=<0.05)
	Treatment Completion Multivariate Analysis of Factors Associated with Completion (number completing 6 months of therapy)

Factor	N completing	Odds Ratio (95% Confidence Interval)	P Value
Gender	961	Reference	0.03
M	1450	1.2 (1.0-1.4)	
F			
Age	943	4.1 (2.2-7.8)	<0.01
0-14	1173	2.1 (1.1-3.9)	0.02
15-34	223	1.8 (0.9-3.4)	0.07
35-49	54	1.9 (0.9- 4.1)	0.07
50-64	21	Reference	
65+			
Race/ethnicity	202	1.4 (0.9-2.3)	0.12
Asian-Pacific Islander	90	1.5 (0.9-2.5)	0.10
White, non-hispanic	1988	1.5 (1.0-2.3)	0.04
White, hispanic	49	Reference	

Bibliographic reference	**LoBue, Philip A., and Kathleen S. Moser. "Use of isoniazid for latent tuberculosis infection in a public health clinic." *American Journal of Respiratory and Critical Care Medicine* 168, no. 4 (2003): 443-447.**			
	Black, non-hispanic			
	Country of birth	471	Reference	<0.01
	United States	1679	1.4 (1.1-1.7)	
	Other			
	Excess alcohol	2412	Reference	<0.01
	N	2	0.1 (0.0-0.6)	
	Y			
	Intravenous drug use	2412	Reference	0.47
	N	2	0.5 (0.1-2.9)	
	Y			
	Homeless	2403	Reference	<0.01
	N	3	0.2 (0.1-0.5)	
	Y			
	Correctional Facility	2389	Reference	0.09
	N	25	0.6 (0.4-1.1)	
	Y			
	Hepatotoxicity	2411	Reference	0.24
	N	3	0.4 (0.1-1.8)	
	Y			

Bibliographic reference	**LoBue, Philip A., and Kathleen S. Moser. "Use of isoniazid for latent tuberculosis infection in a public health clinic." *American Journal of Respiratory and Critical Care Medicine* 168, no. 4 (2003): 443-447.**			
	Any other Adverse Event	2027	Reference	0.03
	N	387	0.8 (0.7-0.9)	
	Y			
Source of funding	Funding was provided by Centers for Disease Control and Prevention Tuberculosis Elimination Cooperative Agreement			
Comments	SUMMARY: A higher incidence of adverse effects was associated with increasing age, female sex, homelessness and having spent time in a correctional facility. The occurrence of hepatotoxicity was also associated with self-reported intravenous drug use. Higher completion rates were associated with female sex, younger age groups, white/Hispanic raceand non-USA country of birth. Lower completion rates were associated with self-reported excess alcohol use, homelessness and occurrence of at least one adverse event other than hepatotoxicity.			

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A.1.7 Fernández-Villar, A., Sopeña, B., et al (2003)

Bibliographic reference	**Fernández-Villar, A., Sopeña, B., Vázquez, R., Ulloa, F., Fluiters, E., Mosteiro, M., ... & Piñeiro, L. (2003). Isoniazid hepatotoxicity among drug users: the role of hepatitis C. *Clinical infectious diseases*, *36*(3), 293-298.**
Study type	Retrospective Cohort
Study outline	Population matches the population of interest Question is relevant; discussing the risk factors for development of isoniazid associated hepatotoxicity. Patients did not receive the same level of care as rules regarding monitoring adherence; some of the participants were enrolled in a methadone maintenance therapy programme where isoniazid was administered alongside. Others had their adherence monitored by means of pill count, urine samples and family supervision. Treatment duration ranged from 10-180 days, average duration of treatment was 154 days. Follow up: follow up did not appear to continue beyond treatment period (6 months of isoniazid therapy at most). This may not have been appropriate. Treatment completion was fairly low with 76.9% of patients completing 6 months of therapy. Attempts to find the systematic differences between those who did or did not complete treatment were not made. Multivariate analysis was used. Unclear if multivariate analysis adjusted for varying compliance. Definition of outcome was clear. A valid and reliable method was used. Unclear how cases of latent tuberculosis were diagnosed.
Number of patients	Population: 415
Patient characteristics	Included= 415 drug users in Spain Included: treated with isoniazid for latent tuberculosis Completed at least 7 days of therapy

Bibliographic reference	**Fernández-Villar, A., Sopeña, B., Vázquez, R., Ulloa, F., Fluiters, E., Mosteiro, M., ... & Piñeiro, L. (2003). Isoniazid hepatotoxicity among drug users: the role of hepatitis C. *Clinical infectious diseases*, *36*(3), 293-298.**
	Exclusion: HIV positivity Evidence of active tuberculosis History of isoniazid associated hepatotoxicity Previous “correct” treatment of latent tuberculosis or active tuberculosis Elevated aminotransferases greater 3 times the upper limit of normal. Baseline characteristics Average duration of treatment: 154.1 ± 51.4 days (range 10-180 days) Male: 363 patients (87.5%) Mean age 31.3 ± 5.5 years (range 17-49 years) Included in a methadone programme: 313 (75.4%) Included in a drug free programme: 74 (17.8%) HCV antibodies detected: 214 (51.6%) Hepatitis B surface antigen positive 8 (1.9%)
Intervention	6 months of isoniazid therapy Isoniazid: 300 mg, daily
Length of follow up	No follow up beyond treatment period apparent

Bibliographic reference	**Fernández-Villar, A., Sopeña, B., Vázquez, R., Ulloa, F., Fluiters, E., Mosteiro, M., ... & Piñeiro, L. (2003). Isoniazid hepatotoxicity among drug users: the role of hepatitis C. *Clinical infectious diseases*, *36*(3), 293-298.**
Location	Spain
Outcomes measures and effect size	Risk of developing isoniazid associated hepatotoxicity Symptoms of hepatitis with aminotransferase levels greater than 5 times upper limit of normal. Or aminotransferase levels greater than 5 times the upper limit of normal for two consecutive weeks. Or a unique elevation greater than 250 IU/L. Univariate analysis of associated factors.

Factor	N with hepatotoxicity	Odds Ratio (95% Confidence Interval)	P Value
Gender	19/361	2.9 (0.3-22)	0.23
M	1/54	1	
F			
Age	3/101	0.5 (0.1-1.8)	0.23
>35	17/314	1	
≤35			
Excessive alcohol consumption	3/73	4 (1.6-10.2)	0.04
Yes	11/330	1	
No			
Body mass index	3/26	2.4 (0.6-9.2)	0.17
≤20	12/236	1	

Bibliographic reference	**Fernández-Villar, A., Sopeña, B., Vázquez, R., Ulloa, F., Fluiters, E., Mosteiro, M., ... & Piñeiro, L. (2003). Isoniazid hepatotoxicity among drug users: the role of hepatitis C. *Clinical infectious diseases*, *36*(3), 293-298.**			
	>20			
	Receipt of methadone	17/313	1.8 (0.5-6.6)	0.22
	Yes	3/102	1	
	No			
	Anti-HCV antibodies	16/214	3.9 (1.3-12.1)	0.09
	Yes	4/201	1	
	No			
	Hepatitis B	0/8	0.98 (0.96-0.99)	0.6
	Yes	20/406	1	
	No			
	Baseline ALT	12/133	4.2 (1.6-10.9)	<0.01
	Abnormal	7/275	1	
	Normal			
	Multivariate analysis			
	Unclear if multivariate model included number compliant to treatment figures. Results were adjusted for those variables that were associated with the outcome significantly (p=<0.05)			
	Independent risk factors for the development of hepatotoxicity.	N with hepatotoxicity	Odds Ratio (95% Confidence Interval)	P Value
	Excessive alcohol consumption	3/73 11/330	4.2 (1.6-10.8)	0.002

Bibliographic reference	**Fernández-Villar, A., Sopeña, B., Vázquez, R., Ulloa, F., Fluiters, E., Mosteiro, M., ... & Piñeiro, L. (2003). Isoniazid hepatotoxicity among drug users: the role of hepatitis C. *Clinical infectious diseases*, *36*(3), 293-298.**			
	Yes			
	No			
	Baseline ALT	12/133	4.3 (1.6-11.4)	0.002
	Abnormal	7/275	1	
	Normal			
Source of funding	Funding was provided by Secretaria Xeral de Investigacion e Desenvolvemento da Xunta de Galicia, Spain			
Comments	SUMMARY: The only 2 factors independently associated with the development of isoniazid hepatotoxicity were excessive alcohol consumption and a high baseline alanine transferase level. Treatment with isoniazid in drug users appears to be safe and well tolerated, although frequent asymptomatic elevations in transaminase levels were observed.			

A.1.8 Nolan, C. M., Goldberg, S. V (1999)

Bibliographic reference	**Nolan, C. M., Goldberg, S. V., & Buskin, S. E. (1999). Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA 281*(11), 1014-1018.**
Study type	Cohort
Study outline	Unclear if population matches the population of interest. No general baseline characteristics were given making any population comparisons difficult. All patients receiving isoniazid preventive therapy were included, unclear if this includes high risk non-infected patients. Exclusion criteria not listed. Question is relevant; discussing the risk factors for development of isoniazid associated hepatotoxicity. Patients likely received the same standard of care at the same public health clinic. A comparison group received multidrug therapy for active tuberculosis, although this was mostly to compare incidence rates. Follow up: follow up did not appear to continue beyond treatment period. This may not have been appropriate. Treatment completion was fairly low with 64% of patients completing 6 months of therapy. Attempts to find the systematic differences between those who did or did not complete treatment were not made. 84% of patients on the multidrug therapy arm completed therapy. Dose and length of treatment was unclear and may vary. Multivariate analysis was used. Unclear if multivariate analysis adjusted for varying compliance. Definition of outcome was clear. However the method of diagnosis was based on the assumption that all hepatotoxic patients would be symptomatic. Non-symptomatic hepatotoxicity would have been missed. Unclear how cases of latent tuberculosis were diagnosed. The population is only compared for sex, age and race. This could be insufficient to cover all major confounding factors.
Number of patients	Population: 11,141
Patient characteristics	Included= 11,141 Included:

Bibliographic reference	**Nolan, C. M., Goldberg, S. V., & Buskin, S. E. (1999). Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA 281*(11), 1014-1018.**
	treated with isoniazid for latent preventive therapy Baseline characteristics Not listed
Intervention	Isoniazid preventative therapy, unclear duration and dose.
Length of follow up	No follow up beyond treatment period apparent
Location	USA
Outcomes measures and effect size	Risk of developing isoniazid associated hepatotoxicity Symptoms of hepatitis with aminotransferase levels greater than 5 times upper limit of normal. Symptoms and signs must resolve after the withdrawal of isoniazid therapy and a decision not to restart the therapy made. Case rates and multivariate analysis:

	Cases of Hepatotoxicity	Rate of hepatotoxicity (cases per 1000 persons starting therapy)	P value	Adjusted Odds Ratio (95% confidence interval)
Total Cohort	11	1.0	…	…
Sex	3	0.5	0.07	1.0 (reference)
M (n=6066)	8	1.6		3.30 (0.87-12.45)
F (n=5075)				
Age	0	…	0.02	…
0-14 (n=1468)	6	0.8		(reference)
15-34 (n=7449)	4	2.1		3.17 (0.94-10.70)

Bibliographic reference	**Nolan, C. M., Goldberg, S. V., & Buskin, S. E. (1999). Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA 281*(11), 1014-1018.**				
	35-64 (n=1865)	1	2.8		3.62 (0.43-30.42)
	≥65 (n=359)				
	Race	4	2.2	0.08	2.60 (0.75-8.95)
	White (n=1856)	7	0.8	…	1.0 (reference)
	Non-white (n=9285)	5	0.8	…	…
	Asian (n=5968)	2	1.2	…	…
	Black (n=1732)	0	…	…	…
	Hispanic (n=1050)	0	…	…	…
	Other (n=535)				
Source of funding	Unclear source of funding				
Comments	SUMMARY: The rate of hepatotoxicity in persons receiving preventive therapy increased with increasing age and there were trends towards increased rates in women and in those of white race. The rate of isoniazid hepatotoxicity during clinically monitored preventive therapy was lower than has been reported previously. Clinicians should have greater confidence in the safety of isoniazid preventive therapy.				

A.1.9 Dickinson, D. S., Bailey, W. C.,

Bibliographic reference	**Dickinson, D. S., Bailey, W. C., Hirschowitz, B. I., Soong, S. J., Eidus, L., & Hodgkin, M. M. (1981). Risk factors for isoniazid (INH)-induced liver dysfunction.*Journal of clinical gastroenterology*, *3*(3), 271-279.**
Study type	Cohort
Study outline	Population does not exactly match population of interest. Participants included 36 who were PPD[1] negative and therefore potentially not latently infected. Question is relevant; discussing the risk factors for development of isoniazid associated hepatotoxicity. Patients likely received the same standard of care as all were treated in the same health clinic. The patients who were persistently PPD[1] negative however received only 3 months of isoniazid whereas the other participants received a year. Follow up: follow up did not appear to continue beyond treatment period (1 year of isoniazid therapy at most). This may not have been appropriate. Treatment completion was low: 15 subjects dropped out before completing 8 weeks, 113 completed 2 months, 105 patients completed 3 months, 59 patients completed 5 months and 27 patients completed one year of therapy. Attempts to find the systematic differences between those who did or did not complete treatment were not made. Prognostic factors for hepatotoxicity included pre-existing liver dysfunction, acetylation phenotype, significant alcohol intake, age, concomitant drug therapy, sex and race. Hepatitis serology was also examined but no results reported. Definition of significant alcohol intake unclear. No baseline characteristics provided Multivariate analysis was used. Unclear if multivariate analysis adjusted for varying compliance or length of treatment. Definition of outcome was clear. A valid and reliable method was used however the definition differs from many used in other studies. Unclear how cases of latent tuberculosis were diagnosed.
Number of patients	Population: 113

Bibliographic reference	**Dickinson, D. S., Bailey, W. C., Hirschowitz, B. I., Soong, S. J., Eidus, L., & Hodgkin, M. M. (1981). Risk factors for isoniazid (INH)-induced liver dysfunction.*Journal of clinical gastroenterology*, *3*(3), 271-279.**
Patient characteristics	Included= 113 Included: Candidates for isoniazid therapy according to Center for Disease Control, U.S. Public Health Service recommendations Baseline characteristics: Not provided
Intervention	1 year of isoniazid therapy Isoniazid: 300 mg, daily Or 5 mg/kilogram bodyweight for children Or 3 months of Isoniazid therapy for persistent PPD[1] negative patients Isoniazid: 300 mg, daily Or 5 mg/kilogram bodyweight for children
Length of follow up	No follow up beyond treatment period apparent
Location	USA
Outcomes measures and effect size	Risk of developing isoniazid associated hepatotoxicity Symptoms of hepatitis with aspartate aminotransferase levels greater than 4 times mean baseline value on at least one occasion. Or significantly elevated more than 2 standard deviations above mean pretreatment control for this population. Multivariate analysis Unclear if multivariate model included number compliant to treatment figures. Results were adjusted for those variables

Bibliographic reference	**Dickinson, D. S., Bailey, W. C., Hirschowitz, B. I., Soong, S. J., Eidus, L., & Hodgkin, M. M. (1981). Risk factors for isoniazid (INH)-induced liver dysfunction.*Journal of clinical gastroenterology*, *3*(3), 271-279.**

that were associated with the outcome significantly (p=<0.05)

	No. Patients with Normal Baseline Lab	No. Developed Significant Liver Dysfunction	P value
Total No. of patients	101	19	
Acetylation phenotype	47	6	Not significant
Rapid	53	13	
Slow			
Age, y	54	6	0.034
<35	47	13	
≥35			
Sex	65	11	Not significant
F	36	8	
M			
Race	68	11	Not significant
Black	31	8	
White	2	0	
Oriental			

Source of funding	Funding was provided by University of Alabama Division of Gastroenterology and the Jefferson County Department of public health

Bibliographic reference	**Dickinson, D. S., Bailey, W. C., Hirschowitz, B. I., Soong, S. J., Eidus, L., & Hodgkin, M. M. (1981). Risk factors for isoniazid (INH)-induced liver dysfunction.*Journal of clinical gastroenterology*, *3*(3), 271-279.**
Comments	SUMMARY: Only age was found to be significantly correlated with liver dysfunction (p=0.034) after adjustment for all other factors.

Abbreviations:

[1]PPD purified protein derivative

A.1.10 Lee, A. M., Mennone, J. Z et al (2002)

Bibliographic reference	**Lee A M, Mennone, J Z., Jones, R. C., & Paul, W. S. (2002). Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *The International Journal of Tuberculosis and Lung Disease*, *6*(11), 995-1000.**
Study type	Retrospective Cohort
Study outline	Population matches population of interest. Question is relevant; discussing the risk factors for development of rifampicin and pyrazinamide associated hepatotoxicity. Patients did not receive the same standard of care as rifabutin was substituted for rifampicin in HIV positive patients on protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Doses of rifampicin and pyrazinamide initially followed guidelines established for HIV infected patients and those with active tuberculosis but dose of pyrazinamide was subsequently limited based on an expert opinion published in the American Thoracic Society guidelines. Follow up: follow up did not appear to continue beyond treatment period (2 months therapy maximum). This may not have been appropriate. Treatment completion was low: 57.4% of participants. Patients with presumed recent TB infection were less likely than others to discontinue therapy for reasons other than development of hepatotoxicity Patients reporting illicit drug use were more likely to discontinue therapy than those who did not and patients of White or Asian ethnicity were more likely to discontinue therapy than Hispanics. Prognostic factors for hepatotoxicity recorded included age, race, sex, weight, HIV status, reason for starting latent tuberculosis treatment, associated medical conditions, other medications, alcohol use, rifampicin dose, pyrazinamide dose, baseline AST[1] and ALT[2], peak AST[1], peak ALT[2], peak alkaline phosphate, peak bilirubin, onset of side effects or hepatotoxicity, presence or absence of symptoms associated with hepatotoxicity, outcome and hospitalization. Multivariate analysis was used. Unclear if multivariate analysis adjusted for all of the above factors. Definition of outcome was clear. Unclear how cases of latent tuberculosis were diagnosed.

Bibliographic reference	**Lee A M, Mennone, J Z., Jones, R. C., & Paul, W. S. (2002). Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *The International Journal of Tuberculosis and Lung Disease*, *6*(11), 995-1000.**
Number of patients	Population: 148
Patient characteristics	Included= 148 Included: Normal chest radiograph Indications for latent tuberculosis treatment under the ATS guidelines Baseline characteristics: Gender (m/f): 84/64 Age: median: 37 years. range: 18-84 years Recent infection (recent TST³ conversion or contact with an infectious case): 53 % Illicit drug use: 28 % Recent immigration from TB-endemic country: 11 % HIV infection: 6 %
Intervention	2 months of rifampicin and pyrazinamide Pyrazinamide: 15-20 mg daily, for 2 months Rifampicin: unclear dose, for 2 months
Length of follow up	No follow up beyond treatment period apparent
Location	USA
Outcomes measures and effect size	Risk of developing isoniazid associated hepatotoxicitySymptoms of hepatitis with aminotransferase levels greater than 5 times upper limit of normal (grade 3 or 4)

Bibliographic reference	**Lee A M, Mennone, J Z., Jones, R. C., & Paul, W. S. (2002). Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *The International Journal of Tuberculosis and Lung Disease*, *6*(11), 995-1000.**

Multivariate analysis

Unclear if multivariate model included number compliant to treatment figures. Results were adjusted for those variables that were associated with the outcome significantly (p=<0.05)

	n	Hepatotoxicity case n	Bivariate analysis. Risk ratio (95% confidence interval)	Multivariate analysis. Odds ratio (95% confidence interval)
Total patients	148	14		
Gender	64	10	3.3 (1.1-10.0)	4.1 (1.2-14.3)
Female	84	4	reference	reference
Male				
Race	48	8	6.5 (0.9-49.8)	
Hispanic	61	5	3.2 (0.4-26.3)	
Black	39	1	reference	
White or Asian				
Age, y	90	8	0.9 (0.3-2.4)	
≥35	58	6	reference	
<35				
Alcohol use	59	5	0.8 (0.3-2.4)	
Any	89	9	reference	
None				

Bibliographic reference	**Lee A M, Mennone, J Z., Jones, R. C., & Paul, W. S. (2002). Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *The International Journal of Tuberculosis and Lung Disease*, *6*(11), 995-1000.**				
	Illicit drug use	48	1	0.2 (0.0-1.2)	
	Any	100	13	reference	
	None				
	Pyrazinamide dose (mg/kg/day)	78	6	0.7 (0.3-1.8)	
	>20	70	8	reference	
	≤20				
	Presumed recent infection	79 (53.4)	13 (16.5)	11.4 (1.5- 84.6)	14.4 (1.8-115.3)
	Yes	69 (46.6)	1 (1.4)	reference	reference
	No				
Source of funding	Unclear source of funding				
Comments	SUMMARY: Hepatotoxicity occurred in a high proportion of patients prescribed pyrazinamide and was more common among females and those with recent infection. Caution is warranted in using rifampicin and pyrazinamide in populations where its safety has not been tested.				

Abbreviations:

[1]PPD purified protein derivative

[2]AST- aspartate aminotransferase

[3]ALT- alanine aminotransferase

A.1.11 Gilroy, S. A., Rogers, M. A.,

Bibliographic reference	**Gilroy, S. A., Rogers, M. A., & Blair, D. C. (2000). Treatment of latent tuberculosis infection in patients aged≥ 35 years. *Clinical infectious diseases*,*31*(3), 826-829.**
Study type	Retrospective Cohort
Study outline	Population matches population of interest. High risk groups were identified for treatment. Question is relevant; discussing the risk factors for not completing or adhering to therapy for latent tuberculosis. Patients received the same standard of care at the same health department. Follow up: follow up did not appear to continue beyond treatment period (6 months therapy maximum). This may not have been appropriate. Treatment completion was low: 76% of participants. Reasons for completion failure were recorded and characteristics compared between the groups. Comparisons were also made between those that accepted treatment and those that were lost to follow up for isoniazid preventive therapy. Differences were found in the mean age, sex, ethnicity, alcohol usage and medications taken between these groups. Prognostic factors for hepatotoxicity recorded included age, race sex, alcohol use, regular medication and baseline ALT levels Multivariate analysis was used Definition of risk factors was clear but unlikely to be valid or reliable since this was a retrospective study taken from patients charts. Alcohol use was defined as consuming >3 alcoholic beverages daily which is not a standardised measurement and susceptible to recall bias. Definition of treatment completion was unclear. A valid and reliable method of measurement was not used as patients were assumed to be compliant if they kept monthly appointments at the clinic.
Number of patients	Population: 335
Patient characteristics	Included= 335

Bibliographic reference	**Gilroy, S. A., Rogers, M. A., & Blair, D. C. (2000). Treatment of latent tuberculosis infection in patients aged≥ 35 years. *Clinical infectious diseases*,*31*(3), 826-829.**

Included:

Aged ≥35 years

Documented reaction to PPD[1] of >10 mm induration

Baseline characteristics:

If isoniazid was discontinued due to symptoms or isoniazid associated hepatotoxicity, patient was offered rifampicin therapy or chose to refuse treatment.

	Completed isoniazid n=253	Completed isoniazid and rifampicin n=26	Did not complete therapy n=56	P value
Gender	140	12	31	0.665
Male	113	14	25	
Female				
Ethnicity	108	17	31	0.062
White	81	6	18	
Black	64	3	7	
Other				
Alcohol	37	3	19	0.001
Male and used alcohol	103	9	12	0.390
Male and did not use	9	1	4	
Female and used alcohol	104	13	21	
Female and did not use				

Bibliographic reference	**Gilroy, S. A., Rogers, M. A., & Blair, D. C. (2000). Treatment of latent tuberculosis infection in patients aged≥ 35 years. *Clinical infectious diseases*,*31*(3), 826-829.**				
	Medication	85	7	19	0.205
	Male no medications	25	3	10	0.005
	Male 1 medication	29	2	2	
	Male ≥ 2 medications	56	3	4	
	Female no medications	32	5	5	
	Female 1 medication	25	6	12	
	Female ≥ 2 medications				
	ALT level	223	6	21	<0.001
	Normal	30	20	33	
	Abnormal				
Intervention	6 months of isoniazid Isoniazid: 300 mg daily, for 6 months Pyridoxine: 50 mg daily, for 6 months				
Length of follow up	No follow up beyond treatment period apparent				
Location	USA				
Outcomes measures and effect size	Risk of non-completion of therapy. Completion of 6 months of therapy Univariate analysis				
		Completed isoniazid n=253	Completed isoniazid and rifampicin n=26	Did not complete therapy n=56	P value

Bibliographic reference	Gilroy, S. A., Rogers, M. A., & Blair, D. C. (2000). Treatment of latent tuberculosis infection in patients aged≥ 35 years. *Clinical infectious diseases*,*31*(3), 826-829.				
	Gender	140	12	31	0.665
	Male	113	14	25	
	Female				
	Ethnicity	108	17	31	0.062
	White	81	6	18	
	Black	64	3	7	
	Other				
	Alcohol	37	3	19	0.001
	Male and used alcohol	103	9	12	0.390
	Male and did not use	9	1	4	
	Female and used alcohol	104	13	21	
	Female and did not use				
	Medication	85	7	19	0.205
	Male no medications	25	3	10	0.005
	Male 1 medication	29	2	2	
	Male ≥ 2 medications	56	3	4	
	Female no medications	32	5	5	
	Female 1 medication	25	6	12	
	Female ≥ 2 medications				

Bibliographic reference	**Gilroy, S. A., Rogers, M. A., & Blair, D. C. (2000). Treatment of latent tuberculosis infection in patients aged≥ 35 years. *Clinical infectious diseases*,*31*(3), 826-829.**				
	ALT level	223	6	21	<0.001
	Normal	30	20	33	
	Abnormal				
	Multivariate analysis				
	Only ALT level at baseline was statistically significant for non-completion after adjustment for the other variables.				
Source of funding	Unclear source of funding				
Comments	SUMMARY: Only ALT level at baseline was statistically significant for non-completion after adjustment for the other variables.				

Abbreviations:

[1]PPD purified protein derivative

A.1.12 Oni, T., Tsekela, R.,(2012)

Bibliographic reference	**Oni, T., Tsekela, R., Kwaza, B., Manjezi, L., Bangani, N., Wilkinson, K. A., ... & Wilkinson, R. J. (2012). A Recent HIV Diagnosis Is Associated with Non-Completion of Isoniazid Preventive Therapy in an HIV-Infected Cohort in Cape Town. *PloS one*, *7*(12), e52489.**
Study type	Cohort
Study outline	Population matches population of interest. Participants were taken from a HIV infected cohort. Question is relevant; discussing the risk factors for not completing or adhering to therapy for latent tuberculosis. Patients received the same standard of care at the same health department. Follow up: follow up did not appear to continue beyond treatment period (9 months maximum) Treatment completion was low: 69% of participants. Reasons for completion failure were not recorded. Comparisons were not made between those that accepted treatment and those who refused to be enrolled. No baseline characteristics were recorded other than those stated below. Risk factors for completion of therapy included: age, gender, employment status, alcohol consumption, smoking status, past TB history, recent TB contact, type of accommodation lived in, CD4 count, marital status, history of TB, BCG scar, time in Khayelitsha and date of HIV diagnosis. Multivariate analysis was used however the significant factor of smoking was not included in the multivariate analysis model as the alcohol variable provided a better fit of the model instead. It is unclear why all significant factors could not have been included. Definition of risk factors was clear but unlikely to be valid or reliable since alcohol use and smoking was self-reported, as were other important factors. Definition of treatment completion was clear. A valid and reliable method of measurement was not used as patients were assumed to be compliant if they kept monthly appointments at the clinic and self-reported adherence.
Number of patients	Population: 164
Patient characteristics	Included= 164

Bibliographic reference	**Oni, T., Tsekela, R., Kwaza, B., Manjezi, L., Bangani, N., Wilkinson, K. A., ... & Wilkinson, R. J. (2012). A Recent HIV Diagnosis Is Associated with Non-Completion of Isoniazid Preventive Therapy in an HIV-Infected Cohort in Cape Town. *PloS one*, *7*(12), e52489.**

Included:

Asymptomatic

TST[1] ≥5 mm induration

Enrolled from HIV Wellness Clinic, patients not suitable for antiretroviral therapy.

Baseline characteristics:

If isoniazid was discontinued due to symptoms or isoniazid associated hepatotoxicity, patient was offered rifampicin therapy or chose to refuse treatment.

	Completed isoniazid n=113	Did not complete therapy n=51	Univariable analysis OR (95% CI)
Gender (female)	96	39	2.34 (0.97-5.64)
Marital Status (married)	33	10	0.93 (0.40-2.14)
Smoker (yes)	11	11	3.59 (1.41-9.18)
Alcohol (yes)	16	19	4.66 (2.03-10.69)
TB contact (no, yes, don't know)	78, 30, 5	41, 10, 0	0.54 (0.23-1.26)
Previous TB (yes)	15	6	0.94 (0.32-2.79)
BCG scar (yes)	62	23	0.92 (0.44-1.94)
Self-reported BCG (no, yes, don't know)	19, 80, 14	11, 33, 7	1.13 (0.58-2.22)
Employed (yes)	41	17	0.85 (0.39-1.84)

Bibliographic reference	**Oni, T., Tsekela, R., Kwaza, B., Manjezi, L., Bangani, N., Wilkinson, K. A., ... & Wilkinson, R. J. (2012). A Recent HIV Diagnosis Is Associated with Non-Completion of Isoniazid Preventive Therapy in an HIV-Infected Cohort in Cape Town. *PloS one*, *7*(12), e52489.**			
	Accommodation (shack, house)	66, 47	21, 21	1.46 (0.69-3.06)
	Time in Khayelitsha (<1 year, ≥ 1 year)	6, 107	5, 37	0.39 (0.11-1.36)
	Age (years median)	32.7	29.8	0.99 (0.94-1.04)
	BMI, median	27.2	24.2	0.96 (0.90-1.02)
	Education (highest grade achieved median)	11	11	1.07 (0.90-1.29)
	Persons/bedroom, median	2.33	2	0.91 (0.68-1.20)
	CD4 count, median	360	363	1.00 (1.00-1.00)
	Years since HIV diagnosis, median	1.15	0.15	0.82 (0.67-0.99)
Intervention	6 months of isoniazid Dose unclear (followed South African national guidelines)			
Length of follow up	No follow up beyond treatment period apparent			
Location	South Africa			
Outcomes measures and effect size	Risk of non-completion of therapy. Completion of 6 months of therapy Univariate analysis			

Bibliographic reference	**Oni, T., Tsekela, R., Kwaza, B., Manjezi, L., Bangani, N., Wilkinson, K. A., ... & Wilkinson, R. J. (2012). A Recent HIV Diagnosis Is Associated with Non-Completion of Isoniazid Preventive Therapy in an HIV-Infected Cohort in Cape Town. *PloS one*, *7*(12), e52489.**
	See baseline characteristics Multivariate analysis The final logistic regression model included alcohol and time since HIV diagnosis variables only. Time since HIV diagnosis: There was a 19% decrease in odds of non-completion with every year after HIV-diagnosis (OR 0.81; 95% CI[2] 0.68-0.98; p=0.03). Non-completers were most likely to default therapy if initiated within 6 months of HIV diagnosis when compared to those initiated after at least 6 months after diagnosis of HIV. Alcohol drinkers: There was a four-fold increase in in odds of non-completion in drinkers compared to non-drinkers (OR 4.05; 95% CI[2] 1.89-9.06; p=0.001) There is univariate association between alcohol and smoking (p<0.001) and so the authors argue that both should be considered in the interpretation of these results. However smoking was not included in the multivariate model.
Source of funding	Funding by the Wellcome Trust, MRC and the European Union.
Comments	SUMMARY: Patients with a recent HIV diagnosis, in addition to self reported drinkers and smokers were higher risk of non-completion of isoniazid preventive therapy. The period of time since HIV diagnosis should therefore be taken into account when initiating therapy. Results suggest that smokers and alcohol drinkers should also be identified and targeted for adherence interventions.
Abbreviations: [1]TST- tuberculin skin test [2]CI- confidence interval	

A.1.13 Goswami, N. D., Gadkowski, L. B (2012)

Bibliographic reference	**Goswami, N. D., Gadkowski, L. B., Piedrahita, C., Bissette, D., Ahearn, M. A., Blain, M. L., ... & Stout, J. E. (2012). Predictors of latent tuberculosis treatment initiation and completion at a US public health clinic: a prospective cohort study. *BMC public health*, *12*(1), 468.**
Study type	Cohort
Study outline	Population matches population of interest. Question is relevant; discussing the risk factors for initiating or completing therapy for latent tuberculosis. Patients received the same standard of care at the same health department. Follow up: follow up did not appear to continue beyond treatment period (12 months maximum) Treatment initiation was low: 26% of participants. Treatment completion amongst those that initiated was also low: 53% o participants. Reasons for completion failure were recorded. Comparisons were made between those that accepted treatment and those who refused to be enrolled as well as completers and non-completers. Baseline characteristics were recorded. Risk factors for initiation/completion of therapy included: Length of time at current residence, planned future time at current residence, education level, co-habitance with any family members, pervious daily pill for at least 6 months, regula primary care, easy access to health departments, plan to tell family/friends about positive skin test, belief in getting sick from TB without medicine, fear of adverse effects from medicine, belief in medicine efficacy, belief in cure for TB, fear of phlebotomy, race ethnicity, gender, age, born in the United States, region of birth, reason for skin testing, mean distance from health department, neighbourhood poverty level, alcohol use, smoking, crack cocaine use, diabetes, ESRD, Gastrectomy, heroin use, homelessness, IV drug use, immunosuppressed, prior incarceration, long term care facility, evidence of old TB on radiography, history of organ or bone marrow transplantation, underweight, HIV. Multivariate analysis was used. Definition of risk factors was clear but unlikely to be valid or reliable since all risk factors were self-reported at baseline. Definition of treatment completion was clear. A valid and reliable method of measurement was not used as patients were assumed to be compliant if they picked up the required amount of medication.

Bibliographic reference	**Goswami, N. D., Gadkowski, L. B., Piedrahita, C., Bissette, D., Ahearn, M. A., Blain, M. L., ... & Stout, J. E. (2012). Predictors of latent tuberculosis treatment initiation and completion at a US public health clinic: a prospective cohort study. *BMC public health*, *12*(1), 468.**
	Unclear if the type of preventive therapy used was included in multivariate analysis. Some patients were taking 4 months of rifampicin, some were taking 9 months of isoniazid. Completion rate of isoniazid participants was 52%, completion rate in those treated with rifampicin was 61% (p=0.3). At least six months of isoniazid was completed by 63% of participants.
Number of patients	Population: 496
Patient characteristics	Included= 496 completed questionnaires, 26% of which initiated therapy. Included: Age: >17 years Meet CDC[1] guidelines for latent tuberculosis infection therapy Baseline characteristics: Of the 496 participants: 65% were predominantly foreign born, 87% were racial/ethnic minorities, mean age was 39.1± 12.3 years. Of those who were foreign born, 19% were from Africa and 20% from Latin America. 26% of participants initiated latent tuberculosis therapy, 70 % of these completed therapy. 61% of persons included in the study were referred after a tuberculin skin test (TST) was performed as part of employment screening and 19% received a TST as part of a contact investigation. 32% were former or current smokers, 9 % were drug users, 14% had a history of incarceration and 11% had a history of homelessness.
Intervention	9 months of isoniazid Dose unclear (followed CDC[1] guidelines) CDC guidance states a minimum of 270 mg of isoniazid daily for 9 months. OR 4 months of rifampicin Dose unclear (followed CDC[1] guidelines)

Bibliographic reference	**Goswami, N. D., Gadkowski, L. B., Piedrahita, C., Bissette, D., Ahearn, M. A., Blain, M. L., ... & Stout, J. E. (2012). Predictors of latent tuberculosis treatment initiation and completion at a US public health clinic: a prospective cohort study. *BMC public health*, *12*(1), 468.**
	CDC guidance states a minimum of 120 mg of rifampicin daily for 4 months.
Length of follow up	No follow up beyond treatment period apparent
Location	USA
Outcomes measures and effect size	Risk of non-completion of therapy, risk of non-initiation of therapy. Completion of 9 months of therapy of isoniazid, completion of 4 months of therapy of rifampicin. Multivariate analysis Backward elimination was used to arrive at a final log binomial model consisting of independent variables significantly associated with completion of latent tuberculosis therapy at p<0.10 by univariate analysis as well as any significant confounders.

Outcome	Factor	Relative Risk	95% Confidence Intervals
Treatment initiation	Close contact to a TB case	2.5	1.8-3.6
	Non-employment reason for screening	1.6	1.0-2.5
	Lower educational level	1.3	1.1-1.6
	Having a regular physician	1.4	1.0-2.0
	Fear of getting sick with TB without medicine	1.7	1.2-2.6
	Prior incarceration	1.7	1.1-2.8
Treatment completion	Plan to tell friends or family about latent tuberculosis diagnosis.	2.0	1.0-3.9

Bibliographic reference	**Goswami, N. D., Gadkowski, L. B., Piedrahita, C., Bissette, D., Ahearn, M. A., Blain, M. L., ... & Stout, J. E. (2012). Predictors of latent tuberculosis treatment initiation and completion at a US public health clinic: a prospective cohort study. *BMC public health*, *12*(1), 468.**
Source of funding	Unclear source of funding. Authors deny competing interests.
Comments	SUMMARY: Investment in social support and access to regular primary care may lead to increased latent tuberculosis therapy adherence in high-risk populations. After multivariate analysis factors independently associated with initiation of therapy included close contact with a TB case, non-employment reason for screening, lower educational level, having a regular physician, fear of getting sick with tuberculosis, and prior incarceration. After multivariate analysis factors independently associated with completion of therapy included planning to tell friends and family about their latent tuberculosis infection.
Abbreviations: [1]CDC- Centre for Communicable Disease Control	

A.1.14 Smith, B. M., Schwartzman, K., (2011)

Bibliographic reference	**Smith, B. M., Schwartzman, K., Bartlett, G., & Menzies, D. (2011). Adverse events associated with treatment of latent tuberculosis in the general population. *Canadian Medical Association Journal*, *183*(3), E173-E179.**
Study type	Retrospective Cohort
Study outline	Population may match population of interest. Participants were taken from an administrative healthcare database in Quebec. A historical cohort of all resident's therapy for latent tuberculosis between 1998 and 2003 was created. They took patients receiving the treatment for latent for tuberculosis as having had latent tuberculosis when this may not have been the case. This is an indirect definition of latent tuberculosis. Question is relevant; discussing the risk factors for hospitalisation for latent tuberculosis therapy-associated adverse events. Patients received three different kinds of care: isoniazid therapy, rifampicin therapy and no treatment. These were matched for different variables at baseline. Treatment completion was low: 54.1% of participants in the isoniazid group and 56.2% of participants in the rifampicin group. Rates of completion were similar between both groups. Comparisons were not made between those that accepted treatment and those who refused to be enrolled. Risk factors for hospitalization: a cohort received latent tuberculosis treatment split by rifampicin and isoniazid, this was further stratified by age, previous hospital admission and comorbidities. Multivariate analysis was used: Conditional logistic regression was used for comparisons between patients with latent tuberculosis and matched untreated cohorts. Variables included in the analysis were previous hospital admission, Charlson comorbidity score and cancer, diabetes, HIV infection, liver, renal and vascular disease. Definition of risk factors was clear but unlikely to be reliable since this was a retrospective study and data was retrieved from administrative health data. Definition of an adverse event outcome was clear but also reliant upon retrospective data. The study looked for five conditions possibility attributable to the treatment of latent tuberculosis however these could have causes other than the latent tuberculosis therapy. If the person was admitted to hospital for identical adverse events 6 months prior to treatment for latent tuberculosis, the event was not attributed to latent tuberculosis therapy. This system is clearly open to error however therefore the method is not reliable.

Bibliographic reference	**Smith, B. M., Schwartzman, K., Bartlett, G., & Menzies, D. (2011). Adverse events associated with treatment of latent tuberculosis in the general population. *Canadian Medical Association Journal*, *183*(3), E173-E179.**
	Unclear if participants received the same level of care apart from intervention studied, data was taken from the same provincial area but practice may vary between clinics. Attempts were made at baseline to balance the comparison groups for potential confounding factors by matching patients with controls and by multivariate statistical analysis. Neither participants nor clinicians were blinded to intervention allocation. Follow up: All groups were for a similar amount of time: from 6 months before to 12 months after initiation of therapy.
Number of patients	Population: 9145
Patient characteristics	Included= 9145 Included: Registered as beneficiaries of RAMQ health insurance (insurer for over 99% of permanent residents) Dispensed at least 30 days of treatment for latent tuberculosis infection between January and December of 2003 Taking isoniazid alone, rifampicin alone or sequential use of isoniazid and rifampicin Excluded: Patients dispensed rifampicin with an alternate indication Those dosed rifampicin and pyrazinamide simultaneously Baseline characteristics:

Characteristics	Total receiving treatment n= 9,145 (%)	Isoniazid n= 8,686 (%)	Rifampicin n=459 (%)	Untreated cohort n=18,290 (%)
Age, y	4523 (49.5)	4356 (50.1)	167 (36.4)	9046 (49.5)
≤ 35	2533 (27.7)	2408 (27.7)	125 (27.2)	5066 (27.7)

Bibliographic reference	**Smith, B. M., Schwartzman, K., Bartlett, G., & Menzies, D. (2011). Adverse events associated with treatment of latent tuberculosis in the general population. *Canadian Medical Association Journal*, *183*(3), E173-E179.**			
	36-50	1232 (13.5)	1,159 (13.3)	73 (15.9)	2464 (13.5)
	51-65	857 (9.4)	763 (8.9)	94 (20.5)	1714 (9.4)
	>65				
	Sex, female	5000 (54.7)	4784 (55.1)	216 (47.1)	10000 (54.7)
	Residence, urban	6216 (68.0)	5913 (68.1)	295 (64.3)	12 432 (68.0)
	≥ 1 hospital admissions in the previous 6 months	946 (10.3)	866 (10.0)	80 (17.4)	730 (4.0)
	Comorbid illness	54 (0.6)	45 (0.5)	9 (2.0)	17 (0.1)
	Liver disease	171 (1.9)	156 (1.8)	15 (3.3)	24 (0.1)
	Kidney disease	229 (2.5)	211 (2.4)	18 (3.9)	280 (1.5)
	Diabetes	50 (0.6)	48 (0.6)	2 (0.4)	8 (0.0)
	HIV infection or AIDS	287 (3.1)	267 (3.1)	20 (4.4)	221 (1.2)
	Malignancy	53 (0.6)	46 (0.5)	7 (1.5)	39 (0.2)
	Peptic ulcer disease	786 (8.6)	744 (8.7)	42 (9.2)	712 (3.9)
	Chronic pulmonary disease				
Intervention	6 months of isoniazid Dose unclear, daily (presumed to follow national guidelines for Canada) OR 4 months of rifampicin				

Bibliographic reference	**Smith, B. M., Schwartzman, K., Bartlett, G., & Menzies, D. (2011). Adverse events associated with treatment of latent tuberculosis in the general population. *Canadian Medical Association Journal*, *183*(3), E173-E179.**
	Dose unclear, daily (presumed to follow national guidelines for Canada)
Comparison	Control Group No treatment
Length of follow up	Observation period from 6 months prior to treatment to 12 months following treatment initiation
Location	Quebec, Canada
Outcomes measures and effect size	Results of multivariate analysis: Independent variables associated with subsequent hepatic events following treatment for latent tuberculosis infection include: Hospital admission Any physician visits for liver disease High Charlson comorbidity score during the 6 months before treatment initiation Age stratified adjusted odds ratios of hepatic events requiring hospital admission that were followed by premature cessation of isoniazid therapy:

Age group, y	Odds ratio adjusted for sex and prior liver disease (95% CI[1])	Odds ratio adjusted for sex and Charlson score (95% CI[1])
≤ 35	1.00 (reference)	1.00 (reference)
36-50	2.7 (0.5-16.0)	1.3 (0.2-10.0)
51-65	5.7 (1.0-33.7)	6.7 (1.2-39.2)

Bibliographic reference	**Smith, B. M., Schwartzman, K., Bartlett, G., & Menzies, D. (2011). Adverse events associated with treatment of latent tuberculosis in the general population. *Canadian Medical Association Journal*, *183*(3), E173-E179.**		
	>65	34.2 (7.6-153.8)	34.5 (7.0-170.2)
Source of funding	Funding from the Canadian Institutes of Health Research and the Fonds de la recherché en santé du Quebec		
Comments	SUMMARY: The risk of hospital admission due to adverse events is substantially increased in people over age 65.These estimates could be useful for a re-analysis of the risks and benefits of therapy for latent tuberculosis infection in the elderly, which could influence recommendations for therapy in this group. In the absence of such an analysis, this data suggests that the risks of therapy for latent tuberculosis are considerable amongst the elderly and should be considered very carefully before therapy is given. Hospital admission, any physician visits for liver disease or a higher Charlson comorbidity score during the six months before treatment initiation were associated with subsequent hepatic events in multivariate analysis.		
Abbreviations: [1]CI- confidence interval			

A.1.15 Anibarro, L., Casas, S.,(2010)

Bibliographic reference	**Anibarro, L., Casas, S., Paz-Esquete, J., Gonzalez, L., Pena, A., Guerra, M. R., ... & Santin, M. (2010). Treatment completion in latent tuberculosis infection at specialist tuberculosis units in Spain. *The International Journal of Tuberculosis and Lung Disease*, *14*(6), 701-707.**
Study type	Retrospective Cohort
Study outline	Population matches population of interest. Participants were taken from a healthcare database in Spain. A historical cohort of treatment completion and adherence for latent tuberculosis treatment was recorded in two different tertiary care sites. HIV infected patients were not included. Question is relevant; discussing the risk factors for non-completion of latent tuberculosis therapy. Patients received various different kinds of care: isoniazid therapy between 5-6 months; rifampicin therapy for 4 months; isoniazid and rifampicin for 3 months; isoniazid, rifampicin and pyrazinamide with or without ethambutol for 2 months followed by 2 months of isoniazid and rifampicin. Shorter regimens were grouped together in multivariate analysis despite obvious differences in side effect profile and length. Treatment completion was adequate: 79.2% of participants in the short regimens group and 81.0% of participants in the isoniazid group completed therapy satisfactorily. Rates of completion were similar between both groups. Comparisons were not made between those that accepted treatment and those who refused to be enrolled. Risk factors for treatment completion analysed included: age; sex; hospital site; health care worker; contact with a tuberculosis case; immigrant; episode of treatment; treatment duration; adverse events in the first month and social risk factors including illegal drug abuse, alcohol abuse, unemployment, or residence in a correctional facility). Multivariate analysis was used: logistic regression analysis was used to adjust for variables with a significance of $p<0.10$ Definition of risk factors was clear but unlikely to be reliable since this was a retrospective study and data was retrieved from administrative health data. Definition of treatment completion outcome was clear but also reliant upon retrospective data. Due to differences in the methods of evaluating adherence on the different hospital sites treatment completion was chosen as an endpoint instead. Participants did not receive the same level of care apart from intervention studied as different participants were taking different drugs in various combinations with different durations. Patients on one hospital site also received urine tests at every visit which may have improved adherence as patients knew they would be tested. Attempts were made at baseline to balance the comparison groups for potential confounding factors by multivariate

Bibliographic reference	**Anibarro, L., Casas, S., Paz-Esquete, J., Gonzalez, L., Pena, A., Guerra, M. R., ... & Santin, M. (2010). Treatment completion in latent tuberculosis infection at specialist tuberculosis units in Spain. *The International Journal of Tuberculosis and Lung Disease*, *14*(6), 701-707.**
	statistical analysis. Neither participants nor clinicians were blinded to intervention allocation. Follow up did not continue beyond treatment period
Number of patients	Population: 599
Patient characteristics	Included= 599 Included: “Adults” On preventive therapy for latent tuberculosis between January 2004 and march 2007 TST[1] positive Excluded: HIV infection Those told to stop therapy due to medical advice Baseline characteristics:

	Total n (%)	CHPo Hospital 1 n (%)	HUBell Hospital 2 n (%)	P value
Number	599	390	209	
Age, years, median [IQR[2]]	36 [28.0-50.2]	34.5 [26.9-49.8]	40.2 [30.5-50.7]	0.009
Male gender	310 (51.8)	206 (52.8)	104 (49.8)	0.48
Country of origin	508 (84.8)	361 (92.6)	147 (70.3)	<0.001

Bibliographic reference	**Anibarro, L., Casas, S., Paz-Esquete, J., Gonzalez, L., Pena, A., Guerra, M. R., ... & Santin, M. (2010). Treatment completion in latent tuberculosis infection at specialist tuberculosis units in Spain. *The International Journal of Tuberculosis and Lung Disease*, *14*(6), 701-707.**				
	Spain	91 (15.2)	29 (7.4)	62 (29.7)	
	Foreign				
	Recent immigrant	68 (11.4)	24 (6.2)	44 (21.1)	<0.001
	Health care worker	40 (6.7)	34 (8.7)	6 (2.9)	0.006
	Unemployed	14 (2.3)	5 (1.3)	9 (4.3)	0.03
	Alcohol abuse	26 (4.3)	20 (5.1)	6 (2.9)	0.30
	Residence in a correctional facility	4 (0.7)	3 (0.8)	1 (0.5)	0.68
	Drug abuse	19 (3.2)	16 (4.1)	3 (1.4)	0.09
	Presence of social risk factors	54 (9.0)	45 (11.5)	9 (4.3)	0.003
	Main characteristics and outcome of 599 courses of preventive treatment				
		Total n (%)	CHPo hospital 1 (%)	HUBell hospital 2 n (%)	P value
	Number	599	390	209	
	Indication for preventive treatment	496 (82.8)	289 (74.1)	207 (99.0)	<0.001
	Contact with TB case	103 (17.2)	101 (25.9)	2 (1.0)	
	Screening in high risk population				
	Treatment regimen	466 (77.8)	284 (72.8)	182 (87.1)	<0.001

Bibliographic reference	**Anibarro, L., Casas, S., Paz-Esquete, J., Gonzalez, L., Pena, A., Guerra, M. R., ... & Santin, M. (2010). Treatment completion in latent tuberculosis infection at specialist tuberculosis units in Spain. *The International Journal of Tuberculosis and Lung Disease*, *14*(6), 701-707.**				
	6 months isoniazid	80 (13.4)	60 (15.4)	20 (9.6)	
	9 months isoniazid	32 (5.3)	25 (6.4)	7 (3.3)	
	4 months rifampicin	21 (3.5)	21 (5.4)	0	
	other[a]				
	Adverse events in the first month	150 (25.0)	106 (27.2)	44 (21.1)	0.1
	Treatment outcome	484 (80.8)	310 (79.5)	174 (83.3)	0.29
	Completed	115 (19.2)	80 (20.5)	35 (16.7)	
	Not completed				
	[a]17 cases treated with 2 months of isoniazid rifampicin and pyrazinamide with or without ethambutol, 4 cases treated with 3 months of isoniazid and rifampicin				
Intervention	6 months of isoniazid Dose unclear, (presumed to follow national guidelines for Spain) OR 9 months of isoniazid Dose unclear, (presumed to follow national guidelines for Spain) OR 4 months of rifampicin Dose unclear, (presumed to follow national guidelines for Spain) OR				

Bibliographic reference	**Anibarro, L., Casas, S., Paz-Esquete, J., Gonzalez, L., Pena, A., Guerra, M. R., ... & Santin, M. (2010). Treatment completion in latent tuberculosis infection at specialist tuberculosis units in Spain. *The International Journal of Tuberculosis and Lung Disease*, *14*(6), 701-707.**
	3 months of isoniazid and rifampicin Dose unclear, (presumed to follow national guidelines for Spain) OR Isoniazid, rifampicin and pryrazinamide for 2 months followed by isoniazid and rifampicin for 2 months Dose unclear, (presumed to follow national guidelines for Spain)
Length of follow up	Follow up did not extend beyond treatment completion
Location	Spain
Outcomes measures and effect size	Results of multivariate analysis: logistic regression analysis was used to adjust for variables with a significance of p<0.10

Factors analysed	n	Treatment completion n	Adjusted odds ratio (95% CI²)	P value
Age, years	292	219	0.33 (0.30-0.76)	0.001
<36	307	263	1	
≥36				
Sex	310	235	0.58 (0.37-0.92)	0.02
Male	289	249	1	
Female				
Hospital	390	310		
CHPo	209	174		

Bibliographic reference	**Anibarro, L., Casas, S., Paz-Esquete, J., Gonzalez, L., Pena, A., Guerra, M. R., ... & Santin, M. (2010). Treatment completion in latent tuberculosis infection at specialist tuberculosis units in Spain. *The International Journal of Tuberculosis and Lung Disease*, *14*(6), 701-707.**				
	HUBell				
	Health care worker	559	449		
	No	40	35		
	Yes				
	Contact with a tuberculosis case	496	400		
	Yes	103	84		
	No				
	Immigrant (<5 years of residence)	68	36	0.21 (0.12-0.37)	<0.001
	Yes	531	448	1	
	No				
	Episode of treatment	562	459		
	Initial regimen	37	29		
	Alternative regimen				
	Treatment regimen	53	42		
	Short regimen	546	442		
	6-9 months isoniazid				
	Adverse events in the first month	449	353	0.59 (0.34-1.10)	0.07
		150	131	1	

Bibliographic reference	**Anibarro, L., Casas, S., Paz-Esquete, J., Gonzalez, L., Pena, A., Guerra, M. R., ... & Santin, M. (2010). Treatment completion in latent tuberculosis infection at specialist tuberculosis units in Spain. *The International Journal of Tuberculosis and Lung Disease*, *14*(6), 701-707.**				
	No				
	Yes				
	Social risk factors	54	30	0.21 (0.11-0.39)	<0.001
	Yes	545	454	1	
	No				
Source of funding	Funding from the Spanish Network for the Research in Infectious Diseases				
Comments	SUMMARY: Overall, completion rates of latent tuberculosis treatment in specialist TB units are good. Nevertheless, counselling should be strengthened and new strategies to enhance adherence should be sought for recent immigrants and for people in unfavourable social situations. People less than 35 years of age are also at an increased risk of defaulting treatment.				

Abbreviations:

[1]Tuberculin Skin Test

[2]CI- confidence interval

A.1.16 Li, J., Munsiff, S. S.(2010)

Bibliographic reference	**Li, J., Munsiff, S. S., Tarantino, T., & Dorsinville, M. (2010). Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *International Journal of Infectious Diseases*, *14*(4), e292-e297.**
Study type	Retrospective Cohort
Study outline	Population matches population of interest. Participants were taken from two healthcare databases in New York City. A historical cohort of treatment completion for latent tuberculosis treatment was recorded. Some subgroups such as the homeless and drug users were not examined in this analysis. Question is relevant; discussing the risk factors for non-adherence of latent tuberculosis therapy. Patients received different kinds of care: isoniazid therapy for 6-9 months (daily or twice weekly) or rifampicin based therapy for 4 months (daily). Data was split between those who took rifamycin and those who took isoniazid. There was no attempt to adjust for the differing types of dosing schedules in the isoniazid group, or for the patients taking rifabutin or rifampicin in the rifamycin group. Treatment completion was low: 45.2% of participants completed therapy satisfactorily. Comparisons were not made between those that accepted treatment and those who refused to be enrolled as this was data taken from a healthcare database. Data collected for the study included: age, sex, race and ethnicity, country of birth, length of time in the USA, borough of residence, date of first visit to a TB clinic, date treatment for latent tuberculosis started, regimen, length of latent TB treatment, and risk of TB disease. Multivariate analysis was performed using log-binomial regression. Multivariate analysis appears not to have been adjusted for gender, a major confounding factor. Definition of risk factors was clear but unlikely to be reliable since this was a retrospective study and data was retrieved from administrative health data. Definition of treatment completion outcome was clear but also reliant upon retrospective data. Different methods of evaluating adherence was used depending on the age and regimen of the participant: patients aged >18 years were considered to have completed treatment if they took 6-9 months of isoniazid daily or twice weekly within a 9-12 month period; or > 4 months of daily rifamycin doses within 6 months. Patients younger than 18 years were considered to have completed treatment if they had taken 9 or more months of daily or twice weekly isoniazid therapy within a 12 month

Bibliographic reference	**Li, J., Munsiff, S. S., Tarantino, T., & Dorsinville, M. (2010). Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *International Journal of Infectious Diseases*, *14*(4), e292-e297.**
	period, or 6 or more months of daily rifamycin therapy within 9 months. Outcome measure was not reliable as there was no guarantee that patients were taking their medication despite regular attendance at clinic to pick up their monthly supply of medications. Follow up did not continue beyond treatment period
Number of patients	Population: 15,035
Patient characteristics	Characteristic Isoniazid n % Rifampicin n % Total n % Included= 15 035 Inclusion criteria: All patients prescribed either isoniazid or rifamycin (rifampicin or rifabutin) for the treatment of latent tuberculosis Within any of 10 New York City Health Department Chest Clinics between January 2002 and August 2004 Screened and referred by non-health providers for evaluation of positive TST[1] Those screened at clinics who were eligible for and started treatment for latent tuberculosis. Excluded: Contacts of patients with multi-drug resistant forms of tuberculosis Not treated with an isoniazid or rifamycin containing regimen Baseline characteristics:

Bibliographic reference	Li, J., Munsiff, S. S., Tarantino, T., & Dorsinville, M. (2010). Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *International Journal of Infectious Diseases*, *14*(4), e292-e297.						
	Total	14030	44.1	1005	60.0	15,035	45.4
	Age, years	3928	40.3	191	52.4	4119	40.9
	<18	2539	39.9	146	61.6	2685	41.1
	18-24	3078	41.6	226	59.3	3304	42.8
	25-34	4485	51.5	442	63.1	4927	52.5
	≥35						
	Sex	6879	44.4	436	61.0	7315	45.4
	Male	7151	43.8	569	59.2	7720	45.0
	Female						
	Race/ethnicity	2245	48.8	162	67.9	2407	50.1
	Asian	4810	44.1	302	58.3	5112	44.9
	Non-Hispanic black	997	38.6	69	65.2	1066	40.3
		4728	44.2	385	58.7	5113	45.3
	Non-hispanic white	1250	39.5	87	52.9	1337	40.4
	Hispanic						
	Other/unknown						
	Country of birth	11821	44.3	862	60.4	12683	45.2
		2076	44.5	139	56.8	2215	45.3
	Non-US-born	133	27.8	4	75.0	137	29.2

Bibliographic reference	**Li, J., Munsiff, S. S., Tarantino, T., & Dorsinville, M. (2010). Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *International Journal of Infectious Diseases*, *14*(4), e292-e297.**					
	US-born					
	Unknown					
	Risk group	2344	55.7	388	67.8	2732	57.4
	Contact	1790	51.4	116	67.2	1906	52.4
	Medical Risk	8984	40.6	451	52.8	9435	41.1
	Population Risk	912	34.7	50	48.0	962	35.3
	Low risk					
	Ever on Directly observed preventive therapy	217	70.5	14	85.7	231	71.4
		13813	43.7	991	59.6	14804	44.7
	Yes					
	No					
	HIV serostatus	94	55.3	1	0.0	95	54.7
	Positive	3057	56.1	328	61.3	3385	56.6
	Negative	10879	40.6	676	59.5	11555	41.7
	Unknown					
Intervention	For adults:					
	6-9 months of isoniazid					

Bibliographic reference	**Li, J., Munsiff, S. S., Tarantino, T., & Dorsinville, M. (2010). Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *International Journal of Infectious Diseases*, *14*(4), e292-e297.**
	Dose unclear, (presumed to follow national guidelines for USA) Either daily or twice weekly OR 4 months of rifamycin Dose unclear, (presumed to follow national guidelines for USA) For those under the age of 18: 9 months of isoniazid Dose unclear, (presumed to follow national guidelines for USA) Either daily or twice weekly OR 6 months of rifampicin Dose unclear, (presumed to follow national guidelines for USA) Daily
Length of follow up	Follow up did not extend beyond treatment completion
Location	USA
Outcomes measures and effect size	Results of multivariate analysis: logistic regression analysis was used to adjust for all variables in the table:

Variable	% treatment of latent Tb completion	Crude risk ratio (95% CI²)	Adjusted risk ratio (95% CI²)
Age, years	40.9	0.95 (0.90–1.01)	0.99 (0.93–1.04)

Bibliographic reference	Li, J., Munsiff, S. S., Tarantino, T., & Dorsinville, M. (2010). Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *International Journal of Infectious Diseases*, *14*(4), e292-e297.			
	<18	41.1	0.96 (0.90–1.02)	0.97 (0.92–1.03)
	18-24	42.8	Referent	Referent
	25-35	52.5	1.23 (1.17–1.29)	1.16 (1.11–1.22)
	≥35			
	Race/ethnicity	50.1	1.24 (1.14–1.35)	1.20 (1.10–1.30)
	Asian	44.9	1.11 (1.03–1.21)	1.11 (1.02–1.19)
	Non-Hispanic black	40.3	Referent	Referent
	Non-Hispanic white	45.3	1.12 (1.04–1.22)	1.10 (1.02–1.19)
	Hispanic	40.4	1.00 (0.91–1.10)	1.01 (0.92–1.11)
	Other/unknown			
	Country of birth	45.3	1.00 (0.95–1.05)	1.08 (1.03–1.13)
	Non-US-born	45.2	Referent	Referent
	US-born			
	Risk group	57.4	1.62 (1.48–1.78)	1.51 (1.38–1.66)
	Contact	52.4	1.48 (1.35–1.63)	1.45 (1.32–1.60)
	Medical risk	41.1	1.16 (1.07–1.27)	1.16 (1.07–1.27)
	Population risk	35.3	Referent	Referent
	Low risk			
	Ever on directly observed preventive therapy	71.4	1.60 (1.47–1.74)	1.26 (1.18–1.34)

Bibliographic reference	**Li, J., Munsiff, S. S., Tarantino, T., & Dorsinville, M. (2010). Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *International Journal of Infectious Diseases*, *14*(4), e292-e297.**			
	Yes	44.7	Referent	Referent
	No			
	Treatment regimen	44.1	Referent	Referent
	Isoniazid alone	60.0	1.36 (1.29–1.44)	1.20 (1.14–1.26)
	Rifamycin alone			
Source of funding	Unclear source of funding			
Comments	SUMMARY: Shorter regimen and directly observed preventive therapy increase completion rates for latent tuberculosis. Though efforts to improve treatment of latent tuberculosis need to address all groups, greater focus is needed for persons who are contacts and HIV-infected, as they have a higher risk of developing tuberculosis. After multivariate analysis participants who were ≥35 years or older, Asian, non-hispanic black, Hispanic, non-US-born, contacts, at increased medical or population risk of TB, ever on directly observed preventive therapy or a regimen of rifamycin alone were significantly more likely to complete treatment of latent tuberculosis. The strongest factor was being a contact to a TB patient (adjusted relative risk was 1.5 (95% CI[2] 1.4–1.7)			
Abbreviations: [1]Tuberculin Skin Test [2]CI- confidence interval				

A.1.17 Machado Jr, A., Finkmoore, B (2009)

Bibliographic reference	**Machado Jr, A., Finkmoore, B., Emodi, K., Takenami, I., Barbosa, T., Tavares, M., ... & Riley, L. W. (2009). Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil. *The International journal of tuberculosis and lung Disease*, *13*(6), 719-725.**
Study type	Cohort
Study outline	Population matches population of interest. Participants were taken a sample of household contacts of pulmonary tuberculosis in Brazil. Data on HIV status, however, was not sought. Question is relevant; discussing the risk factors for non-completion of latent tuberculosis therapy. Patients received the same standard of care at the same public chest disease hospital: isoniazid therapy for 6 months. Treatment completion was low: 53.5% of participants who initiated latent tuberculosis therapy completed treatment satisfactorily. Comparisons were not made between those that accepted treatment and those who refused to be enrolled. Risk factors for treatment completion analysed included: age, gender, ethnicity, presence of BCG scar, current employment status, family income, distance from hospital, number of buses required to commute, relationship to index case, time of exposure to index case, number of 30 day isoniazid refills received. Multivariate analysis was used: poisson regression and logistic regression analysis was used to adjust for confounding variables. Definition of risk factors was clear but unlikely to be reliable since number of buses required to commute was discovered by asking the transportation agency rather than the patients themselves who may have another means of transport. Data was gathered by questionnaire. Definition of treatment completion outcome was clear but may be unreliable since the patient was judged to be adherent on the basis of attending monthly appointments and picking up pills; it is uncertain if patients were actually taking the pills Follow up did not continue beyond treatment period (6 months)
Number of patients	Population: 101
Patient characteristics	Included: Household contacts of hospitalized index pulmonary TB cases

Bibliographic reference	**Machado Jr, A., Finkmoore, B., Emodi, K., Takenami, I., Barbosa, T., Tavares, M., ... & Riley, L. W. (2009). Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil. *The International journal of tuberculosis and lung Disease*, *13*(6), 719-725.**
	Documented latent tuberculosis infection
	Spent at least 100 hours with the index case during the symptomatic period
	Living in the same residence
	TST[1] ≥10 mm induration
	Baseline characteristics:
	Characteristics — N (%)
	Age, years — Median 23
	0-10 — 14
	11-21 — 33
	22-39 — 30
	≥40 — 24
	Male sex — 44 (44)
	Ethnicity — 49 (52)
	Black — 36 (38)
	Multiracial — 10 (10)
	White
	Presence of a BCG scar — 82 (81)
	Current employment status — 29 (48)
	Family monthly income in US $ — Mean 525

Bibliographic reference	**Machado Jr, A., Finkmoore, B., Emodi, K., Takenami, I., Barbosa, T., Tavares, M., ... & Riley, L. W. (2009). Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil. *The International journal of tuberculosis and lung Disease*, *13*(6), 719-725.**	
	210-420	35 (34.7)
	630-840	39 (38.6)
	Did not say	27 (26.7)
	Distance from hospital, km	28 (29)
	≤5	29 (31)
	5.1-10	38 (40)
	>10	
	Number of buses required to commute	35 (35)
	1	61 (64)
	2	
	Relationship to index case	42 (42)
	Spouse/child/parent	59 (58)
	Aunt/uncle/cousin/neighbour/grandparent/sibling	
	Time of exposure to index case	33 (33)
	≥2.7 months	
	Number of 30 day isoniazid refills received	29 (29.7)
	1	10 (9.9)
	2	3 (3.0)
	3	5 (5.0)

Bibliographic reference	**Machado Jr, A., Finkmoore, B., Emodi, K., Takenami, I., Barbosa, T., Tavares, M., ... & Riley, L. W. (2009). Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil. *The International journal of tuberculosis and lung Disease*, *13*(6), 719-725.**
	4 0 5 54 (53.5) 6
Intervention	6 months of isoniazid Dose unclear, daily (presumed to follow national guidelines for Brazil)
Length of follow up	Follow up did not extend beyond treatment completion (6 months)
Location	Brazil
Outcomes measures and effect size	Results of multivariate analysis: logistic regression and poisson regression analysis was used to adjust for variables. Treatment completion defined as having picked up all 6 refills of isoniazid at monthly appointments, those who did not complete treatment were defined as those who missed at least one but not all of their appointments.

	Treatment non-completion n= 47	Treatment complete n=54	Relative risk (95% CI²)	P value
Age, years	Median 23	Median 24	0.0	0.77
0-10	7	7	0.91 (0.5-1.7)	0.67
11-21	15	18	0.87 (0.4-1.7)	1.0
22-39	13	17	1 (0.5-1.9)	
≥ 40	12	12		
Male sex	19	25	0.88 (0.57-1.35)	0.56
Relationship to index	22	20	1.24 (0.8-1.9)	0.32

Bibliographic reference	**Machado Jr, A., Finkmoore, B., Emodi, K., Takenami, I., Barbosa, T., Tavares, M., ... & Riley, L. W. (2009). Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil. *The International journal of tuberculosis and lung Disease*, *13*(6), 719-725.**				
	case				
	Spouse/child/parent				
	Aunt/uncle/cousin/neighbour/grandparent/sibling				
	Report of adverse effects	5	4	2.69 (1.3-5.8)	0.01
	Monthly family income, US $	12	23	0.64 (0.4-1.1)	0.11
	210-420	21	18	0.0	
	630-840	14	13		
	Did not say				
	Distance to health centre	15	13	0.0	0.52
	0-5	18	11	1.16 (0.7-1.8)	0.01
	5.1-10	8	30	0.39 (0.2-0.8)	
	>10				
	Number of buses required to commute	10 (24)	25 (46)	0.0	0.04
	1	32 (76)	29 (54)	1.84 (1.0-3.3)	
	2				
	Risk factors for immediate loss to follow up defined as enrolled study participants who did not return for any follow up				

Bibliographic reference	**Machado Jr, A., Finkmoore, B., Emodi, K., Takenami, I., Barbosa, T., Tavares, M., ... & Riley, L. W. (2009). Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil. *The International journal of tuberculosis and lung Disease*, *13*(6), 719-725.**			
	visits or receive any medication			
		Treatment non-completion n= 29	Treatment complete n=54	Relative risk (95% CI²)	P value
	Age, years	Median: 23	Median: 24	1.0	0.35
	0-10	6	7	0.52 (0.1-2.0)	0.23
	11-21	8	18	0.23 (0.1-1.7)	0.88
	22-39	6	17	0.85 (0.2-3.5)	
	≥ 40	9	12		
	Male sex	11	25	0.71 (0.3-1.8)	0.46
	Relationship to index case	13	20	1.38 (0.4-5.0)	0.49
	Spouse/child/parent	16	34	1.0	
	Aunt/uncle/cousin/neighbour/grandparent/sibling				
	Monthly family income, US $	5	23	0.21 (0.02-1.9)	0.17
	210-420	19	18	1.0	
	630-840	5	13		
	Did not say				
	Report of adverse effects	n/a	4		

Bibliographic reference	**Machado Jr, A., Finkmoore, B., Emodi, K., Takenami, I., Barbosa, T., Tavares, M., ... & Riley, L. W. (2009). Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil. *The International journal of tuberculosis and lung Disease*, *13*(6), 719-725.**				
	Distance to health centre	8	13	1.0	0.60
	0-5	13	11	1.92 (0.2-22.2)	0.25
	5.1-10	4	30	0.22 (0.2-3.0)	
	>10				
	Number of buses required to commute	1	25	1.0	0.01
	1	24	29	20.69 (2.1-208.4)	
	2				
Source of funding	Funding from the NIH Fogarty International Centre				
Comments	SUMMARY: Nearly 50% of household contacts at high risk for developing tuberculosis completed a 6 month course of isoniazid latent tuberculosis therapy. Completion of treatment was most effected by medication intolerance and commuting difficulties for follow up visits.				
Abbreviations: [1]Tuberculin Skin Test [2]CI- confidence interval					

A.1.18 Kwara A, Herold J S et al (2008)

Bibliographic reference	Kwara, A., Herold, J. S., Machan, J. T., & Carter, E. J. (2008). Factors associated with failure to complete isoniazid treatment for latent tuberculosis infection in Rhode Island. *CHEST Journal*, *133*(4), 862-868.
Study type	Retrospective Cohort
Study outline	Population matches population of interest. Participants were taken from a cohort of patients that began treatment for latent tuberculosis infection in Rhode Island, USA. Question is relevant; discussing the risk factors for non-completion of latent tuberculosis therapy. Patients did not necessarily receive the same standard of care due to increased clinical monitoring and blood tests in certain age groups of patients in accordance to guidelines. Treatment completion was low: 61.7% of participants who initiated latent tuberculosis therapy completed treatment satisfactorily. Comparisons were not made between those that accepted treatment and those who refused to initiate therapy. Risk factors for treatment completion analysed included: demographics, TB risk factors, birth country, duration of residence in the United States, reason for discontinuation of therapy and the nature of adverse events experienced. Multivariate analysis was used: logistic regression analysis was used to adjust for confounding variables. Definition of risk factors was mostly clear however the definition of “medical risk factor,” wasn’t. Data is unlikely to be reliable since it was obtained by looking retrospectively at medical records. Definition of treatment completion outcome was clear but may be unreliable since the patient was judged to be adherent on the basis of attending monthly appointments and picking up pills; it is uncertain if patients were actually taking the pills Data was also retrospective. Follow up did not continue beyond treatment period (9 months)
Number of patients	Population: 672
Patient characteristics	Included: Patients initiating isoniazid therapy for treatment of latent tuberculosis RISE TB clinic between January 2003 and December 2003

Bibliographic reference	Kwara, A., Herold, J. S., Machan, J. T., & Carter, E. J. (2008). Factors associated with failure to complete isoniazid treatment for latent tuberculosis infection in Rhode Island. *CHEST Journal*, *133*(4), 862-868.
	Positive tuberculin skin test Excluded Asymptomatic No chest radiographic findings Baseline characteristics: Of the 845 patients eligible to be candidates: 82.9% were foreign born, 17.1% were born in the United states, 54.8% were Hispanic, 19.7% were black or African American, 8.2% were white, 6.5% were Asian or Pacific Islanders and 1.5% were other. More baseline characteristics of the 672 patients included in the study can be found in the outcome measures and effects size section.
Intervention	9 months of isoniazid Dose unclear, daily (presumed to follow national guidelines for Brazil) Monitoring of patients: Age yr — Follow up and frequency of routine AST check <20 — Clinical monitoring only every 2 months 20-34 — AST at baseline and 2 months; clinical monitoring every 2 months 35-60 — AST at baseline, months 1 and 2, clinical monitoring at month 1 and then every 2 months. 61-80 — AST at baseline and months 1 through 5 with clinical monitoring, then clinical monitoring every 2 months >80 — AST at baseline and monthly with clinical monitoring for the entire course
Length of follow up	Follow up did not extend beyond treatment completion (9 months)
Location	Rhode Island, USA

Bibliographic reference	Kwara, A., Herold, J. S., Machan, J. T., & Carter, E. J. (2008). Factors associated with failure to complete isoniazid treatment for latent tuberculosis infection in Rhode Island. *CHEST Journal*, *133*(4), 862-868.
Outcomes measures and effect size	Results of multivariate analysis: Multiple logistic regression analysis was used to adjust for variables. Treatment completion defined as having picked up all 9 months of isoniazid pills. Those who did not constituted the treatment non-completion group. Multivariate analysis included age, gender, race, insurance, birthplace, duration in United States, pregnant, postpartum, illicit drug use, any alcohol, medical risk factors, HIV, TST[1] size of induration, history of BCG, known contact, chest radiograph, any reported side effects, skin rash, abnormal AST[2] level.

Variables	OR	95% Confidence Interval	P value
Age, yr	Reference	0.8-6.5	0.075
>50	2.3	0.6-1.5	0.874
<20	1.5	0.5-3.3	0.559
20-34	1.3		
35-50			
Medical Insurance	Reference	1.1-2.7	0.023
Yes	1.7		
No			
Reported side effect	Reference	2.2-6.2	<0.0001
No	3.6		
Yes			
Postpartum	Reference	0.9-12.6	0.064
No	3.4		

Bibliographic reference	Kwara, A., Herold, J. S., Machan, J. T., & Carter, E. J. (2008). Factors associated with failure to complete isoniazid treatment for latent tuberculosis infection in Rhode Island. *CHEST Journal*, *133*(4), 862-868.
	Yes
Source of funding	Unclear source of funding
Comments	SUMMARY: At multivariate analysis lack of medical insurance coverage and the occurrence of treatment side effects were the only factors that were simultaneously associated with the non-completion of INH therapy when all effects were eligible for inclusion in the model.
Abbreviations: [1]Tuberculin Skin Test [2]Aspartate aminotransferase	

A.1.19 Haley, C. A., Stephan, S. et al (2008)

Bibliographic reference	**Haley, C. A., Stephan, S., Vossel, L. F., Sherfy, E. A., Laserson, K. F., & Kainer, M. A. (2008). Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. *The international journal of tuberculosis and lung disease*, *12*(2), 160-167.**
Study type	Retrospective Cohort
Study outline	Population matches population of interest. Participants were taken from a cohort of patients that began treatment for latent tuberculosis infection in Tennessee, USA. However the sample included a large proportion of patients that were Hispanic or foreign born taking 4 months of rifampicin therapy, this may effect generalization to other populations on different therapy. Question is relevant; discussing the risk factors for non-completion of latent tuberculosis therapy and of adverse events. Patients generally received the same standard of care in various Tennessee Department of Health clinics. Rifampicin was given with directly observed therapy in 4 cases (0.5%). Treatment completion was adequate: 76% of participants who initiated latent tuberculosis therapy completed treatment satisfactorily. Comparisons were not made between those that accepted treatment and those who refused to initiate therapy. Risk factors for treatment completion analysed included: demographic, social and clinical characteristics, prior treatment of latent tuberculosis, daily rifampicin dose, number of bottles and dates dispensed, symptoms during treatment, laboratory values and, if applicable, reason for non-completion. Multivariate analysis was used: logistic regression analysis was performed using a manual forward stepwise method. Definition of risk factors was clear however data is unlikely to be reliable since it was obtained by looking retrospectively at medical records. Definition of treatment completion outcome was clear but may be unreliable since the patient was judged to be adherent on the basis of attending monthly appointments and picking up pills; it is uncertain if patients were actually taking the pills Data was also retrospective. Follow up did not continue beyond treatment period (4 months)
Number of patients	Population: 749
Patient characteristics	Included:

Bibliographic reference	**Haley, C. A., Stephan, S., Vossel, L. F., Sherfy, E. A., Laserson, K. F., & Kainer, M. A. (2008). Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. *The international journal of tuberculosis and lung disease*, *12*(2), 160-167.**

Patients initiating rifampicin therapy for treatment of latent tuberculosis

Treated between February 2000 and February 2004

Excluded

Aged <18 years

More than one antituberculosis drug at baseline

Prior completion of latent tuberculosis treatment

Elevated aminotransferase levels≥3 times the upper limit of normal at baseline

Explicitly stated that they had never taken any rifampicin

Refused treatment within 2 days for reasons other than adverse events

Baseline characteristics:

Patient characteristic	N (%) or median (range)	Patient characteristics	N (%) or median (range)
Median age, years	30 (18-84)	Diabetes	14 (1.9)
Male	531 (70.9)	End stage renal disease	1 (<1)
Ethnicity	623 (83.2)	Head and neck cancer	1 (<1)
White	94 (12.6)		
Black	32 (4.3)		
Asian	534 (71.3)		
Hispanic	598 (79.8)		

Bibliographic reference	**Haley, C. A., Stephan, S., Vossel, L. F., Sherfy, E. A., Laserson, K. F., & Kainer, M. A. (2008). Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. *The international journal of tuberculosis and lung disease*, *12*(2), 160-167.**			
	Foreign-born			
	Country of origin (n=597)	373 (62.4)	Weight loss of >10% body weight	6 (<1)
	Mexico	102 (17.1)		
	Guatemala	14 (2.3)		
	Honduras	10 (1.7)		
	El Salvador	9 (1.5)		
	Somalia	8 (1.3)		
	India	7 (1.2)		
	Sudan	7 (1.2)		
	Puerto Rico	6 (1.0)		
	Vietnam	63 (10.6)		
	37 other countries			
	Median length of US residence, months (n=594)	41.2 (0.2-432.0)	HIV status (n=737)	1 (<1)
	Recent immigrant within 5 years (n=594	385 (64.8)	HIV-infected	347 (47.1)
			HIV-negative	303 (41.1)
			Refused test	86 (11.7)
			Status unknown	
	Primary language other than English	599 (80.0)	TST[1] result, mm induration (n=744)	15 (0-60)

Bibliographic reference	**Haley, C. A., Stephan, S., Vossel, L. F., Sherfy, E. A., Laserson, K. F., & Kainer, M. A. (2008). Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. *The international journal of tuberculosis and lung disease*, *12*(2), 160-167.**			
	Travel to TB endemic area	159 (21.2)	Use of other medications reported at baseline	166 (22.2)
	Contact with an infectious case of TB	93 (12.4)	History of prior latent tuberculosis treatment	64 (8.5)
			Prior isoniazid	45 (6.0)
			Prior rifampicin	11 (1.5)
			Prior rifampicin and pyrazinamide	5 (<1)
			Other/unknown	3 (<1)
	Work or residence within a correctional facility in the past year	43 (5.7)	Average amount of alcohol reported at baseline (n=749)	492 (65.7)
			None	97 (13.0)
			≤1 drink/day	148 (19.8)
			>1 drink/day	6 (<1)
			Prior heavy use, none current	6 (<1)
			Consumers of unknown amount	
	Health care worker	26 (3.5)	Liver disease prior to treatment (n=748)	740 (98.9)
			None	2 (<1)
			Cirrhosis	5 (<1)
			Viral hepatitis	1 (<1)

Bibliographic reference	**Haley, C. A., Stephan, S., Vossel, L. F., Sherfy, E. A., Laserson, K. F., & Kainer, M. A. (2008). Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. *The international journal of tuberculosis and lung disease*, *12*(2), 160-167.**			
			Unknown	
	Homeless in past year	6 (<1)	Baseline category for aminotransferase values (n=725)	699 (96.4)
				20 (2.8)
			Both AST and ALT <80 U/L	4 (<1)
			AST <80, ALT 80-119	2 (<1)
			AST 80-119, ALT <80	
			Both AST and ALT 80-119	
	Work or residence in shelter in past year	9 (1.2)		
	Work or residence in other high-risk congregate setting in past year	19 (2.5)		
	Past or present injection drug use (n=584)	5 (<1)		
Intervention	4 months of rifampicin Rifampicin: 10 mg/kg, daily			
Length of follow up	Follow up did not extend beyond treatment completion (4 months)			
Location	Tennessee, USA			
Outcomes measures and effect size	Results of multivariate analysis: Treatment completion defined as having picked up all 4 months of rifampicin pills and a provider determination that treatment is complete. Below analysis shows risk factors for failure to complete rifampicin therapy among Hispanic and			

<table>
<tr><th>Bibliographic reference</th><th>Haley, C. A., Stephan, S., Vossel, L. F., Sherfy, E. A., Laserson, K. F., & Kainer, M. A. (2008). Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. The international journal of tuberculosis and lung disease, 12(2), 160-167.</th></tr>
<tr><td></td><td>non-hispanic subjects

Multivariate analysis included variables that were clinically relevant or had P value ≤ 0.2.

<table>
<tr><th>Risk factors</th><th>Adjusted odds ratio (95% Confidence interval)</th><th>P value</th></tr>
<tr><td>Hispanic subjects (n=534)</td><td>3.7 (1.8-7.4)</td><td><0.001</td></tr>
<tr><td>Contact with an infectious TB case</td><td>1.7 (1.1-2.8)</td><td>0.02</td></tr>
<tr><td>Alcohol use reported at baseline</td><td>2.2 (1.3-3.8)</td><td>0.01</td></tr>
<tr><td>Other medications reported at baseline</td><td>2.2 (0.8-5.7)</td><td>0.1</td></tr>
<tr><td>Work or residence in a correctional facility in past year</td><td></td><td></td></tr>
<tr><td>Non-Hispanic subjects (n=215)</td><td>2.6 (1.5-4.7)</td><td>0.001</td></tr>
<tr><td>Black race</td><td>0.97 (0.94-0.99)</td><td>0.03</td></tr>
<tr><td>Age</td><td>0.5 (0.2-0.9)</td><td>0.02</td></tr>
<tr><td>Foreign birth</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td></td><td>“Symptoms during treatment” was defined by the occurrence of any new symptom not present at baseline regardless of severity or relationship to rifampicin therapy.

Multivariate analysis included variables that were clinically relevant or had P value ≤ 0.2. Female sex and non-Hispanic ethnicity were independently associated with new symptoms during rifampicin therapy.</td></tr>
<tr><td>Source of funding</td><td>Unclear source of funding</td></tr>
<tr><td>Comments</td><td>SUMMARY: With high completion rates and minimal side effects, 4 months of rifampicin is a favourable treatment for latent tuberculosis in Hispanic and other foreign born populations. After multivariate analysis contact with a TB case and</td></tr>
</table>

Bibliographic reference	**Haley, C. A., Stephan, S., Vossel, L. F., Sherfy, E. A., Laserson, K. F., & Kainer, M. A. (2008). Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. *The international journal of tuberculosis and lung disease*, *12*(2), 160-167.**
	use of other medications or alcohol at baseline were significantly associated with non-completion among Hispanics. Among non-Hispanics, black race and younger age were independently associated with failure to complete 4 months of rifampicin. Female sex and non-Hispanic ethnicity were independently associated with new symptoms during rifampicin therapy.

Abbreviations:

[1]Tuberculin Skin Test

A.1.20 Leung, C. C., Yew, W. W et al (2007)

Bibliographic reference	**Leung, C. C., Yew, W. W., Law, W. S., Tam, C. M., Leung, M., Chung, Y. W., ... & Fu, F. (2007). Smoking and tuberculosis among silicotic patients.*European Respiratory Journal*, *29*(4), 745-750.**
Study type	Cohort
Study outline	Population mostly matches population of interest. Participants were taken from a cohort of male high risk silicotic patients in Hong Kong. The sample included those who had an induration less than 10 mm however tuberculin status was later adjusted for in multivariate analysis. The population is also highly specific which may effect generalization to other populations in different countries with different underlying conditions or risk factors. Question is relevant; discussing the risk factor of smoking for the development of active tuberculosis. Patients did not receive the same standard of care for latent TB as some were treated and others were not. Information on the number treated and on which treatment regimen is provided. Patients were also seen in differing clinics with potential for variance in standard of care. Adjustments for treatment of latent tuberculosis were attempted in multivariate analysis. A total of 435 male silicotic patients were recruited and data was available for all. It is possible that in prospective cohort analysis cases may have been missed although regular follow up of the cohort and screening of notification registry was put in place to minimise this risk. Follow up: unclear how regular follow up appointments were in the Pneumoconiosis Clinic or other chest clinics during the 7 year study period. Data analysed for risk of developing tuberculosis included: date of tuberculin testing; age; ethnicity; smoking history; alcohol use; BCG vaccination scar; coexisting medical conditions; occupation; duration of dust exposure; and disease indicies according to the International Labour Organisation classification (profusion/size/shape/ of lung nodules, progressive massive fibrosis). Multivariate analysis was used: logistic regression analysis was performed and Cox proportional hazards analysis. Definition of risk factors was clear although data was recorded by questionnaire which is vulnerable to recall bias. Definition of development of active tuberculosis was clear and a valid and reliable method was used to record outcome.
Number of patients	Population: 435
Patient characteristics	Included:

Bibliographic reference	**Leung, C. C., Yew, W. W., Law, W. S., Tam, C. M., Leung, M., Chung, Y. W., ... & Fu, F. (2007). Smoking and tuberculosis among silicotic patients.*European Respiratory Journal*, *29*(4), 745-750.**

All patients with silicosis

Excluded

Females (due to small numbers)

Previous history of tuberculin skin testing

Previous history of treatment for latent tuberculosis

Baseline characteristics:

Variable	Tuberculin reaction <10 mm	Tuberculin reaction ≥10 mm	Overall
Subjects n	118	317	435
Age years	58.4 ± 9.9	57.2 ± 9.9	57.6 ± 9.9
Smoking status	16.1	9.1	11.0
Never-smoked	44.9	36.9	39.1
Ex-smoker	39.0	53.9	49.9
Current smoker			
Current cigarette day	3.9 ± 8.3	4.6 ± 6.8	4.4 ± 7.3
Cigarette pack-years	24.0 ± 20.1	22.7 ± 21.5	23.1 ± 21.1
Regular alcohol use	5.1	13.6	11.3
BCG scar	1.7	3.8	3.2
BMI	23.1 ± 3.4	23.8 ± 3.3	23.6 ± 3.3
With other comorbidities	40.7	40.1	40.2

Bibliographic reference	**Leung, C. C., Yew, W. W., Law, W. S., Tam, C. M., Leung, M., Chung, Y. W., ... & Fu, F. (2007). Smoking and tuberculosis among silicotic patients.*European Respiratory Journal*, *29*(4), 745-750.**			
	Principle job	36.4	46.4	43.7
	Underground driller	31.4	32.2	32.0
	Surface driller	5.1	3.2	3.7
	Fine silica	27.1	18.3	20.7
	Other jobs			
	Exposure to dust years	24.2 ± 9.4	24.2 ± 8.3	24.2 ± 8.6
	Profusion of nodules	66.9	65.9	66.2
	Category 1	27.1	32.2	30.8
	Category 2	5.9	1.9	3.0
	Category 3			
	Size of nodules mm	28.0	32.2	31.0
	<1.5	61.0	57.4	58.4
	1.5-3	11.0	10.4	10.6
	3-10			
	Regular shape of nodules	81.4	82.3	82.1
	Progressive massive fibrosis	18.6	17.7	17.9
Intervention	For those identified as having latent tuberculosis n=317, only 101 (31.9%) accepted treatment for latent tuberculosis: 61 were administered 6 months of daily isoniazid and 40 were administered 2 months of daily rifampicin and pyrazinamide.			
Length of follow up	The mean duration of follow up from the day of enrolment to development of TB, death or the end of the study was 1,908 ± 847 days.			

Bibliographic reference	**Leung, C. C., Yew, W. W., Law, W. S., Tam, C. M., Leung, M., Chung, Y. W., ... & Fu, F. (2007). Smoking and tuberculosis among silicotic patients.*European Respiratory Journal*, *29*(4), 745-750.**
Location	Hong Kong
Outcomes measures and effect size	Results of multivariate analysis: Current smokers defined as an individual who had smoked ≥1 cigarette a day for ≥1 year and is still currently smoking within the previous 1 year. Multivariate analysis included the variables: age, past/current regular alcohol use, body mass index, presence of other co-morbidities, BCG scar, tuberculin status/treatment of latent tuberculosis infection, principle job type, duration of silica dust exposureprofusion, size and shape of lung nodules and progressive massive fibrosis. Adjusted hazard ratios (95% confidence interval) of active tuberculosis and culture confirmed TB with respect to smoking related variables:

Factors	Active TB	P value	Culture confirmed TB	P value
Current smokers versus other	1.96 (1.12-3.35)	0.015	2.13 (1.12-4.06)	0.021
Number currently smoked per day	1.00 (ref.)	0.011	1.00 (ref.)	0.002
<10	1.89 (1.04-3.43)		2.46 (1.19-5.05)	
10-<20	2.54 (1.28-5.03)		3.65 (1.63-8.16)	
≥ 20				
Cigarette pack-years	1.00 (ref.)	0.134	1.00 (ref.)	0.320
<20	1.29 (0.75-2.23)		1.19 (0.61-2.31)	
20-<40	1.96 (1.01-3.79)		1.83 (0.84-4.03)	
≥40				

Bibliographic reference	**Leung, C. C., Yew, W. W., Law, W. S., Tam, C. M., Leung, M., Chung, Y. W., ... & Fu, F. (2007). Smoking and tuberculosis among silicotic patients.*European Respiratory Journal*, *29*(4), 745-750.**
Source of funding	Unclear source of funding
Comments	SUMMARY: On Cox proportional hazard analysis, current smokers have a significantly higher risk of TB than other silicotic patients (adjusted hazard ratio (95% confidence interval): 1.96 (1.14-3.35) after controlling for age, alcohol use, tuberculin status, treatment for latent TB infection and other relevant background/disease factors. A significant dose-response relationship was also observed with daily number of cigarettes currently smoked. Snoking cessation may reduce 32.4% (95% confidence interval: 6.5-54.0) of the risk. Smoking increases the risk of both tuberculosis infection and subsequent development of disease among male silicotic patients.

A.1.21 Lobato MN, Reves RR et al (2005)

Bibliographic reference	**Lobato, M. N., Reves, R. R., Jasmer, R. M., Grabau, J. C., Bock, N. N., & Shang, N. (2005). Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *CHEST Journal*, *127*(4), 1296-1303.**
Study type	Cohort
Study outline	Population matches population of interest. Participants included two high risk groups for tuberculosis: homeless people and jail populations. Question is relevant; discussing the risk factors for non-completion and adverse events during treatment of latent tuberculosis therapy, specifically the regimen of rifampicin and pyrazinamide for 2 months. Patients mostly received the same standard of care as treatment was given via directly observed therapy in both groups with the exception that the homeless population were required to self-administer over weekends. One group was also treated in a jail setting where the care may have been different. During the study, due to the death of one of the participants from hepatotoxicity, the rate of laboratory testing was increased to every 2 weeks. AST[1] testing and ALT[2] testing was available for 97% and 56% of participants respectively. These factors may have led to missed cases of hepatotoxicity in some treated patients. Treatment completion was low but similar between groups: 43.6% of homeless participants and 47.5% of incarcerated participants who initiated latent tuberculosis therapy completed treatment satisfactorily. Comparisons were not made between those that accepted treatment and those who refused to initiate therapy. Risk factors for treatment completion and adverse events analysed included: demographics, risk factors for exposure to TB, symptoms of TB, and pertinent medical history including liver disease and current medications. Participants were offered HIV testing if not documented. Multivariate analysis was used: logistic regression analysis was performed using a backward stepwise selection procedure. Definition of risk factors was clear and the methods used to record the risk were generally reliable and valid although users of alcohol and intravenous drug use is likely to be under reported. Definition of treatment completion outcome was clear and mostly reliable and valid since treatment was directly observed. The ranges used for definition of hepatotoxicity (≥2.5 times the upper limit of normal) was slightly smaller than those used by other studies (≥3 times the upper limit of normal) which may lead to an overestimation of effect.

Bibliographic reference	**Lobato, M. N., Reves, R. R., Jasmer, R. M., Grabau, J. C., Bock, N. N., & Shang, N. (2005). Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *CHEST Journal*, *127*(4), 1296-1303.**
	There were clear differences in homeless and jail populations at baseline. Follow up did not continue beyond treatment period (3 months maximum). 34 inmates were transferred to another facility while receiving treatment and lost to follow up.
Number of patients	Population: 1,246
Patient characteristics	Included: Patients receiving pyrazinamide and rifampicin in jail and homeless populations Excluded Prefer treatment with another regimen Age <17 years Active tuberculosis Previous treatment for TB or latent TB Intolerance of treatment medication Pregnancy or attempting to become pregnant Serum concentration of AST[1] or ALT[2] greater than 5 times upper limit of normal at baseline. Baseline characteristics:

Characteristics	Jail inmates (n=844) (%)	Homeless (n=367) (%)	P value
Mean age, y	33.3	37.1	0.04
Male gender	758 (89.9)	334 (91.0)	0.59
Race/ethnicity	507 (60.1)	69 (18.8)	<0.001

Bibliographic reference	Lobato, M. N., Reves, R. R., Jasmer, R. M., Grabau, J. C., Bock, N. N., & Shang, N. (2005). Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *CHEST Journal*, *127*(4), 1296-1303.			
	Black, non–Hispanic	271 (32.1)	220 (59.9)	<0.001
	Hispanic	66 (7.8)	78 (21.3)	
	Other			
	US born	535 (63.4)	150 (40.9)	<0.001
	Drug use	44 (5.2)	17 (4.6)	0.78
	Injection	473 (56.0)	69 (18.8)	<0.001
	Non–injection			
	Excess alcohol use	225 (26.7)	101 (27.5)	0.81
	Unemployed past 24 months	163 (19.3)	112 (30.5)	<0.001
	Homeless in past 12 months	90 (10.7)	366 (99.7)	<0.001
	Prior jail incarceration	628 (74.4)	121 (33.0)	<0.001
	HIV serostatus	12 (1.4)	5 (1.4)	0.85
	Positive	474 (56.1)	210 (57.2)	0.78
	Negative	157 (18.6)	83 (22.6)	0.13
	Not tested	201 (32.8)	69 (18.8)	0.06
	Unknown			0.20
	Prior positive tuberculin skin test result	280 (33.2)	136 (37.1)	0.20

Bibliographic reference	**Lobato, M. N., Reves, R. R., Jasmer, R. M., Grabau, J. C., Bock, N. N., & Shang, N. (2005). Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *CHEST Journal*, *127*(4), 1296-1303.**
Intervention	2 months of rifampicin and pyrazinamide Rifampicin: 600 mg, daily Pyrazinamide: 15 to 20 mg/kg, daily (maximum, 2g) Treatment given via directly observed therapy, homeless population took medication self–administered on weekends.
Length of follow up	Follow up did not extend beyond treatment completion (3 months maximum)
Location	USA
Outcomes measures and effect size	Results of multivariate analysis: Treatment completion defined as 60 doses administered within 3 months.

Variables	Therapy not completed No./Total patients	Crude odds ratio	Adjusted odds ratio (95% confidence interval (CI))	P value
Age, y	NA	1.00	1.00 (0.99–1.01)	0.59
Female sex	88/119	0.38	0.35 (0.23–0.54)	<0.001
US born	342/685	1.45	1.19 (0.82–1.72)	0.37
Black, non–Hispanic	287/576	1.32	0.92 (0.65–1.30)	0.63
Hispanic	291/491	0.68	0.59 (0.46–0.75)	<0.001
Homeless	262/456	0.78	1.00 (0.77–1.31)	0.98
Unemployed	162/275	1.31	1.43 (1.07–1.90)	0.02
Prior positive tuberculin skin test	232/416	0.89	0.90 (0.70–1.15)	0.40

Bibliographic reference	**Lobato, M. N., Reves, R. R., Jasmer, R. M., Grabau, J. C., Bock, N. N., & Shang, N. (2005). Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *CHEST Journal*, *127*(4), 1296-1303.**

result

Previous incarceration	402/749	1.00	0.89 (0.69–1.15)	0.37
Injection drug use	40/61	0.60	0.54 (0.31–0.95)	0.03
Non–injection drug use	281/542	1.14	0.96 (0.75–1.23)	0.75
Excess alcohol	161/326	1.27	1.35 (1.04–1.76)	0.03
Elevated AST[1] before therapy	70/128	0.97	0.96 (0.77–1.20)	0.71

Multivariate analysis showed predictors for non–completion were female sex, Hispanic ethnicity, lack of employment, injection drug use within the past 12 months, or excessive use of alcohol.

Abnormal AST[1] was defined as developing a serum concentration of AST[1] ≥2.5 times the upper limits of normal during treatment with rifampicin and pyrazinamide.

Variables	Therapy not completed No./Total patients	Crude odds ratio	Adjusted odds ratio (95% confidence interval (CI))	P value
Age, y	NA	0.98	0.97 (0.95–0.99)	0.01
Female sex	8/51	0.95	0.97 (0.45–2.11)	0.95
US born	42/430	1.08	1.14 (0.70–1.85)	0.60
Black, non–Hispanic	34/335	0.98	0.96 (0.60–1.54)	0.86
Hispanic	33/257	0.94	0.89 (0.55–1.45)	0.65
Homeless	26/238	1.22	1.31 (0.77–2.24)	0.31

Bibliographic reference	**Lobato, M. N., Reves, R. R., Jasmer, R. M., Grabau, J. C., Bock, N. N., & Shang, N. (2005). Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *CHEST Journal*, *127*(4), 1296-1303.**				
	Unemployed	12/156	0.60	0.51 (0.27–0.97)	0.04
	Prior positive tuberculin skin test result	30/231	0.83	0.93 (0.57–1.52)	0.78
	Previous incarceration	50/467	0.90	1.29 (0.78–2.15)	0.32
	Injection drug use	2/30	2.09	2.57 (0.58–11.30)	0.21
	Non–injection drug use	30/333	1.32	1.18 (0.73–1.90)	0.50
	Excess alcohol	28/219	0.64	0.71 (0.43–1.17)	0.18
	Elevated AST[1] before therapy	17/1169	0.71	0.72 (0.54–0.95)	0.02
	Multivariate analysis found increasing age, an abnormal baseline AST[1] level, and unemployment within the past 24 months were independent risk factors for hepatotoxicity in this population of incarcerated and homeless individuals when treated with rifampicin and pyrazinamide.				
Source of funding	Unclear source of funding				
Comments	SUMMARY: This study detected the first treatment–associated fatality with the rifampicin and pyrazinamide regimen, prompting surveillance that detected unacceptable levels of hepatotoxicity and retraction of recommendations for its routine use. Completion rates for latent tuberculosis treatment using a short–course regimen exceeds historical rates using isoniazid. Efforts to identify an effective short–course treatment regimen for latent tuberculosis should be given high priority. Multivariate analysis showed predictors for non–completion were female sex, Hispanic ethnicity, lack of employment, injection drug use within the past 12 months, or excessive use of alcohol. Multivariate analysis found increasing age, an abnormal baseline AST[1] level, and unemployment within the past 24 months were independent risk factors for hepatotoxicity in this population of incarcerated and homeless individuals when treated with rifampicin and pyrazinamide.				

Bibliographic reference	**Lobato, M. N., Reves, R. R., Jasmer, R. M., Grabau, J. C., Bock, N. N., & Shang, N. (2005). Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *CHEST Journal*, *127*(4), 1296-1303.**
Abbreviations: [1]AST- aspartate aminotransferase [2]ALT- alanine aminotransferase	

A.1.22 Vinnard C, Gopal A (2013)

Bibliographic reference	Vinnard, C., Gopal, A., Linkin, D. R., & Maslow, J. (2013). Isoniazid Toxicity among an Older Veteran Population: A Retrospective Cohort Study.*Tuberculosis research and treatment*, *2013*.
Study type	Retrospective Cohort
Study outline	Population matches population of interest. Participants were a high risk group for isoniazid toxicity: the older veteran population. Question is relevant; discussing the risk factors stopping treatment due to adverse events during treatment of latent tuberculosis therapy, specifically during isoniazid therapy within 6 months of initiation. Patients appear to have received a great variety of different standards of care. Variability included testing for comorbidities, number of isoniazid tablets provided per prescription and frequency of follow up visits. The proportion of patients in the cohort without testing for important comorbidities was not determined. Women were under-represented in this study. Treatment completion was low: 46% of veterans who initiated latent tuberculosis therapy completed treatment satisfactorily. Comparisons were not made between those that accepted treatment and those who refused to initiate therapy. Data was not available for why 46% of patients discontinued treatment. Risk factors for treatment completion and adverse events gathered included: demographic and comorbidity data, including HIV infection, hepatitis C infection, past or current alcohol abuse, past or current intravenous drug use, baseline aminotransferase levels and peak levels during treatment. Uncertain how many of these variables were included in analysis. Cox regression analysis was performed however it is uncertain which variables were included in the analysis and whether certain significant variables were left out. Definition of risk factors was clear however data was gathered by retrospectively examining clinical charts which is unlikely to be reliable. Definition of treatment completion outcome was unclear and may be unreliable since data was gathered retrospectively. Also ALT[1] levels were available for only 84% of the participants at baseline and 71% of the participants during therapy which meant diagnosis of hepatotoxicity was reliant upon the clinician reporting this is both unclear and unreliable. Baseline characteristics were not provided for all patients. Follow up did not continue beyond treatment period (6 months maximum).

Bibliographic reference	**Vinnard, C., Gopal, A., Linkin, D. R., & Maslow, J. (2013). Isoniazid Toxicity among an Older Veteran Population: A Retrospective Cohort Study.*Tuberculosis research and treatment*, *2013*.**
Number of patients	Population: 219
Patient characteristics	Included: Patients receiving isoniazid alone for therapy of latent tuberculosis Single medical centre in Philadelphia Baseline characteristics: Not reported for all participants (for those who completed treatment and those who discontinued due to isoniazid hepatotoxicity see the outcomes measures and effect size section.
Intervention	Isoniazid alone Length of treatment and dose not recorded Type of care given varied with no data provided
Length of follow up	Follow up did not extend beyond treatment completion (6 months maximum)
Location	USA
Outcomes measures and effect size	Results of proportional hazards model: The relationship between hepatitis C infection and isoniazid discontinuation due to suspected hepatotoxicity remained significant even after adjusting for age and alcohol use (HR 3.03, 95% confidence interval 1.08–8.52). Age was not associated with treatment discontinuation due to suspected toxicity (HR 1.03, 95% confidence interval 0.99–1.07).
Source of funding	Funding provided in part by CDC Prevention Epicentres Programme
Comments	SUMMARY: The relationship between hepatitis C infection and isoniazid discontinuation due to suspected hepatotoxicity remained significant even after adjusting for age and alcohol use (HR 3.03, 95% confidence interval 1.08–8.52). Age was not associated with treatment discontinuation due to suspected toxicity (HR 1.03, 95% confidence interval 0.99–1.07).

Bibliographic reference	Vinnard, C., Gopal, A., Linkin, D. R., & Maslow, J. (2013). Isoniazid Toxicity among an Older Veteran Population: A Retrospective Cohort Study.*Tuberculosis research and treatment*, *2013*.

Abbreviations:

[1]ALT- alanine aminotransferase

A.1.23 Martinez-Pino I, Sambeat, MA et al (2013)

Bibliographic reference	**Martínez-Pino, I., Sambeat, M. A., Lacalle-Remigio, J. R., Domingo, P., & VACH Cohort Study Group. (2013). Incidence of tuberculosis in HIV-infected patients in Spain: the impact of treatment for LTBI. *The International Journal of Tuberculosis and Lung Disease*, *17*(12), 1545-1551.**
Study type	Cohort
Study outline	Population matches population of interest. Participants included HIV infected patients in 20 hospitals from the different regions in Spain. Data was drawn prospectively from an electronic case record shared between hospitals. As tuberculosis incidence was also estimated data included various patients who were not infected with latent tuberculosis, but this was separable from our population of interest. Question is relevant; discussing the risk factors for progression of latent tuberculosis to active tuberculosis. It is unclear if patients received the same standard of care since participants were spread over 20 different hospitals. All treated individuals received isoniazid 300mg, daily for 9 months. Treatment completion was low but similar between groups: 144 out of 270 receiving isoniazid completed therapy. Comparisons in baseline characteristics were not made between those that accepted treatment and those who refused to initiate therapy. Comparisons were made between those who had no information available on TST[1] results and those who did. Risk factors for development of active tuberculosis gathered included: age, gender, known date of HIV diagnosis, known start date of HAART[2], HAART[2] at TST[1], HAART[2] at TB diagnosis, ethnicity, education, socio-economic strata, previous incarceration, anti-HCV antibodies, HbsAg, CD4 cell count at enrolment, CD4 <200 cells/µl at enrolment, HIV viral load at enrolment, nadir CD4 cell count. Multivariate analysis was done using Cox's proportional hazards models. Unclear why CD4 count at registration<200 vs. ≥200 cells/µl was not included in final multivariate analysis when it was significant at the univariate level. Definition of risk factors was clear and the methods used to record the risk were generally reliable and valid although taken from a central electronic database. Definition of diagnosis of active and latent tuberculosis was well defined with a valid and reliable method used. However there was a large proportion of the population for whom There were clear differences in populations at baseline between those who had no TB, prevalent TB and incident TB. Information on TST[1] was not available for 4848 patients. Compared with patients with available TST[1] results, these

<table>
<tr><th>Bibliographic reference</th><td>Martínez-Pino, I., Sambeat, M. A., Lacalle-Remigio, J. R., Domingo, P., & VACH Cohort Study Group. (2013). Incidence of tuberculosis in HIV-infected patients in Spain: the impact of treatment for LTBI. The International Journal of Tuberculosis and Lung Disease, 17(12), 1545-1551.</td></tr>
<tr><td></td><td>patients were more likely to have had no education or only primary education (61.8% vs 49.1%), to be of lower socio-economic status (50.5% vs 40.2%) and to have a CD4 cell count of <200 cells/µl at enrolment (18.4% vs 14.3%, P=<0.001). No information on treatment adherence was provided either for those who received isoniazid or those who received HAART[2] therapy.

Follow up continued for a maximum of 5 years. Length of follow up was adjusted for in hazard ratios.</td></tr>
<tr><td>Number of patients</td><td>Population: 7902 (428 participants were TST[1] positive)</td></tr>
<tr><td>Patient characteristics</td><td>Included:

Participants entering the VACH Cohort after 1 January 2004

Patients without a history of TB at enrolment in the cohort who did not develop TB during follow up

Patients who developed TB during follow up after enrolment (incident cases)

Patients with a history of TB before enrolment in the cohort (prevalent cases).

Excluded

Patients with a history of tuberculosis before TST[1] and those with missing TB diagnosis dates were excluded from the analysis.

Baseline characteristics:
<table>
<tr><th></th><th>No TB (n=7220) n (%)</th><th>Prevalent TB (n=514) n (%)</th><th>Incident TB (n=168) n (%)</th><th>Total (n=7977) n (%)</th><th>P value</th></tr>
<tr><td>Age, years, median</td><td>37.4 [31.1–43.2]</td><td>39.8 [36.0–44.2]</td><td>37.0 [32.5–42.4]</td><td>37.7 [31.6–43.3]</td><td><0.001</td></tr>
<tr><td>Male sex</td><td>5404 (74.8)</td><td>422 (82.1)</td><td>122 (72.6)</td><td>6007 (75.3)</td><td>0.001</td></tr>
<tr><td>Known date of HIV diagnosis</td><td>5732 (79.4)</td><td>412 (80.2)</td><td>154 (91.7)</td><td>6368 (79.8)</td><td>–</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Martínez-Pino, I., Sambeat, M. A., Lacalle-Remigio, J. R., Domingo, P., & VACH Cohort Study Group. (2013). Incidence of tuberculosis in HIV-infected patients in Spain: the impact of treatment for LTBI. *The International Journal of Tuberculosis and Lung Disease*, *17*(12), 1545-1551.**					
	Known start date of HAART²	4710 (65.2)	402 (78.2)	138 (82.1)	5319 (66.7)	–
	HAART² at TST¹	592 (39.3)	3 (30.0)	12 (31.6)	644 (40.2)	NS
	HAART² at TB diagnosis	0	60 (57.7)	57 (54.3)	127 (57.2)	NS
	Ethnicity	3859 (81.9)	270 (81.8)	103 (77.4)	4286 (81.9)	0.001
	White	310 (6.6)	22 (6.7)	16 (12.0)	349 (6.7)	
	Black	289 (6.1)	8 (2.4)	5 (3.8)	305 (5.8)	
	Hispanic	251 (5.3)	30 (9.1)	9 (6.8)	293 (5.6)	
	Other					
	Education	74 (1.7)	13 (4.3)	5 (4.1)	94 (2.0)	<0.001
	Illiterate	267 (6.2)	27 (8.9)	11 (8.9)	309 (6.5)	
	No formal education	2135 (49.8)	204 (67.3)	75 (61.0)	2452 (51.3)	
	Primary	1205 (28.1)	53 (17.5)	28 (22.8)	1303 (27.3)	
	Secondary	610 (14.2)	6 (2.0)	4 (3.3)	620 (13.0)	
	University					
	Socio-economic strata	1949 (45.5)	220 (71.7)	83 (66.9)	2287 (47.9)	<0.001
		2141 (50.0)	85 (27.7)	41 (33.1)	2291 (48.0)	
	Low	190 (4.4)	2 (0.7)	0	193 (4.0)	
	Medium					

Bibliographic reference	**Martínez-Pino, I., Sambeat, M. A., Lacalle-Remigio, J. R., Domingo, P., & VACH Cohort Study Group. (2013). Incidence of tuberculosis in HIV-infected patients in Spain: the impact of treatment for LTBI. *The International Journal of Tuberculosis and Lung Disease*, *17*(12), 1545-1551.**					
	High					
	Previous incarceration	945 (23.1)	163 (57.6)	32 (27.8)	1162 (25.6)	<0.001
	Anti-HCV antibodies	1609 (22.3)	207 (40.3)	57 (33.9)	1906 (23.9)	<0.001
	HbsAg	264 (3.7)	19 (2.7)	9 (5.4)	293 (3.7)	<0.001
	CD4 cell count at enrolment, median [IQR][3]	427 [268–621]	300 [154–504]	272 [148–423]	415 [255–611]	<0.001
	CD4 cell count <200 cells/µl at enrolment	1101 (16.5)	165 (34.4)	53 (32.9)	1343 (18.2)	<0.001
	HIV viral load at enrolment, median [IQR[3]]	91 [49–16000]	50 [49–7101]	50 [49–44951]	80 [49–15988]	NS
	Nadir CD4 cell count, median [IQR[3]]	264 [134–431]	135 [51–259]	88 [30–212]	252 [118–418]	<0.001
	Patients with nadir CD4 count <200 cells/µl	2411 (36.1)	320 (66.8)	116 (72.0)	2893 (39.1)	<0.001
	Compared to TST[1] positive patients who received treatment, those who were TST[1] positive but did not receive treatment were (39.1 vs 36.8 years, P=0.007) and were less likely to have a history of incarceration (40.9% vs 53.6%, P=0.03).					
	Information on TST[1] was not available for 4848 patients. Compared with patients with available TST[1] results, these patients were more likely to have had no education or only primary education (61.8% vs 49.1%), to be of lower socio-economic status (50.5% vs 40.2%) and to have a CD4 cell count of <200 cells/µl at enrolment (18.4% vs 14.3%, P=<0.001).					

Bibliographic reference	**Martínez-Pino, I., Sambeat, M. A., Lacalle-Remigio, J. R., Domingo, P., & VACH Cohort Study Group. (2013). Incidence of tuberculosis in HIV-infected patients in Spain: the impact of treatment for LTBI. *The International Journal of Tuberculosis and Lung Disease*, *17*(12), 1545-1551.**
Intervention	Those who received treatment for latent tuberculosis = 229 Isoniazid: 300mg daily, for 9 months
Length of follow up	Follow up varied between participants but was adjusted for in analysis (10 889 person-years in total)
Location	USA
Outcomes measures and effect size	Results of multivariate analysis: Active TB was defined as microbiological confirmation of bacilli using culture or polymerase chain reaction. Below results are for patients treated for latent tuberculosis, n= 229.

	Univariate analysis Odds ratio (95% confidence interval)	P value	Multivariate analysis Hazard ratio (95% confidence interval)	P value
Age <35 vs. ≥35 years	4.6 (1.2–18.1)	0.031	6.1 (1.1–33.7)	0.037
Male sex	0.5 (0.1–1.9)	NS	0.6 (0.1–3.1)	NS
Ethnicity	Reference	–	Reference	NS
White	6.0 (1.4–26.0)	0.018	2.0 (0.4–10.7)	
Black				
CD4 at registration <200 vs. ≥200 cells/µl	5.4 (1.3–22.5)	0.021	–	–
Nadir CD4 <200 vs. ≥200 cells/µl	4.1 (1.1–15)	0.032	5.6 (1.3–23.7)	0.018

Variables that reached statistical significance at univariate level were included in multivariate analysis except for CD4 count at registration.

Bibliographic reference	**Martínez-Pino, I., Sambeat, M. A., Lacalle-Remigio, J. R., Domingo, P., & VACH Cohort Study Group. (2013). Incidence of tuberculosis in HIV-infected patients in Spain: the impact of treatment for LTBI. *The International Journal of Tuberculosis and Lung Disease*, *17*(12), 1545-1551.**
Source of funding	Supported by a grant from the foundation for AIDS research and Prevention in Spain, the Spanish Ministry of Health.
Comments	SUMMARY: Treatment of latent tuberculosis is effective in preventing the development of TB in HIV-infected patients, particularly in those who were TST[1] positive. Risk of development of active tuberculosis in those treated for latent tuberculosis was higher among cases aged <35 years (hazard ratio 6.14, 95% confidence interval 1.12–33.73) and in those with a nadir CD4 cell count of <200 cells/μl (hazard ratio 5.64, 95% confidence interval 1.34–23.70).
Abbreviations: [1]TST- tuberculin skin test [2]HAART- Highly active anti-retroviral therapy [3]IQR- Interquartile range	

A.1.24 Pettit AC, Bethel J et al (2013)

Bibliographic reference	**Pettit, A. C., Bethel, J., Hirsch-Moverman, Y., Colson, P. W., & Sterling, T. R. (2013). Female sex and discontinuation of isoniazid due to adverse effects during the treatment of latent tuberculosis. *Journal of Infection*, *67*(5), 424-432.**
Study type	Cohort
Study outline	Population matches population of interest. Participants were patients receiving isoniazid therapy for the treatment of latent tuberculosis as diagnosed by tuberculin skin test. Data was drawn prospectively from interviews with the patients and then later by reviewing the medical charts of the patients to check for outcomes. Question is relevant; discussing which factors make a person more at risk of stopping isoniazid therapy due to adverse events. Patients did not necessarily receive the same standard of care. The study was spread across 12 different sites in the USA and Canada, some patients received 9 months of isoniazid others received 6 months. Uncertain how patients were monitored or whether directly observed therapy was used in some cases and not others. Study site was adjusted for in multivariate analysis. There was little information provided on how adherence was recorded (e.g. pill count, urine sampling). Treatment completion was low: 47.2% of participants completed therapy. Comparisons in baseline characteristics were not made between those that accepted treatment and those who refused to initiate therapy. Risk factors for treatment completion and adverse events gathered included: demographics, socioeconomic status, cultural background, immigration status, health history, alcohol and substance abuse. The exit interview obtained information on treatment experiences including adverse events. Multivariate analysis was performed using forward stepwise regression. Adjusted relative risk was adjusted for study site, sex and current alcohol use. No other significant factors appear to have been adjusted for. Definition of risk factors was clear and the methods used to record the risk were generally reliable and valid although taken from in-person interviews which may have been subject to recall bias especially the factors of alcohol and substance use. Definition of diagnosis of a failure of treatment due to adverse events was well defined however reasons for treatment default were taken second hand from medical charts which may not have been reliable. Although data was gathered on the adverse events experienced by patients, this study provided no information of which specific adverse event led to discontinuation of isoniazid therapy.

Bibliographic reference	**Pettit, A. C., Bethel, J., Hirsch-Moverman, Y., Colson, P. W., & Sterling, T. R. (2013). Female sex and discontinuation of isoniazid due to adverse effects during the treatment of latent tuberculosis. *Journal of Infection*, *67*(5), 424-432.**
	Follow up did not appear to continue beyond length of treatment (maximum 12 months). 15% of participants were lost to follow up.
Number of patients	Population: 1323
Patient characteristics	Included: March 2007–September 2008 Adults initiating isoniazid for the treatment of latent tuberculosis ≥18 years of age Positive TST[1] Accepted self-administered isoniazid as treatment Excluded Incarcerated at the time treatment was offered Received directly observed therapy of latent tuberculosis Previously treated for latent tuberculosis or active tuberculosis Initiated a regimen other than isoniazid for latent tuberculosis Participated in other latent tuberculosis treatment studies Baseline characteristics:

Characteristic Total n= 1306	Isoniazid completed n=617 (%)	Isoniazid discontinued due to adverse effects n=196 (%)	P value	Isoniazid discontinued for other reasons n=493 (%)	P value

Bibliographic reference	**Pettit, A. C., Bethel, J., Hirsch-Moverman, Y., Colson, P. W., & Sterling, T. R. (2013). Female sex and discontinuation of isoniazid due to adverse effects during the treatment of latent tuberculosis. *Journal of Infection*, *67*(5), 424-432.**					
	Age in years–median (IQR²)	35 (28–46)	38 (27–49)	0.09	33 (25–45)	0.04
	Female sex	308 (49.9)	126 (64.3)	<0.001	272 (55.2)	0.09
	Race/ethnicity	57 (9.2)	36 (18.4)	<0.001	45 (9.3)	<0.001
	White, non-hispanic	142 (23.0)	28 (14.3)		151 (31.1)	
	Black, non-hispanic	215 (34.8)	68 (34.7		99 (20.4)	
	Asian	162 (26.3)	38 (19.4)		162 (33.3)	
	Hispanic	41 (6.6)	26 (13.3)		36 (7.3)	
	Other/unknown					
	US born	139 (22.5)	54 (27.5)	0.15	153 (31.0)	0.002
	High school or equivalent education	435 (70.5)	152 (77.5)	0.05	337 (68.4)	0.47
	Currently homeless	10 (1.6)	2 (1.0)	0.54	28 (5.7)	<0.001
	Employed	318 (51.5)	112 (57.1)	0.17	247 (50.1)	0.67
	Healthcare worker	39 (6.3)	16 (8.2)	0.37	33 (6.7)	0.81
	Household income <$20,000	235 (51.5)	112 (57.1)	0.17	247 (50.1)	0.67
	Jail >30 days in last 2 years	9 (1.5)	3 (1.5)	0.94	29 (5.9)	<0.001

Bibliographic reference	**Pettit, A. C., Bethel, J., Hirsch-Moverman, Y., Colson, P. W., & Sterling, T. R. (2013). Female sex and discontinuation of isoniazid due to adverse effects during the treatment of latent tuberculosis. *Journal of Infection*, *67*(5), 424-432.**					
	No health insurance	217 (35.5)	76 (39.4)	0.32	228 (47.0)	<0.001
	Current daily prescription medication	208 (33.8)	75 (38.3)	0.25	148 (30.2)	0.22
	Psychiatric hospitalization or prescription medication	46 (7.5)	21 (10.7)	0.16	45 (9.2)	0.38
	HIV infection	17 (2.8)	2 (1.0)	0.16	12 (2.5)	0.85
	Alcohol use	378 (61.3)	126 (64.3)	0.45	335 (67.9)	0.02
	Any ever	186 (30.1)	74 (37.8)	0.04	177 (35.9)	0.05
	Any current	20 (3.2)	6 (3.1)	0.90	34 (6.9)	0.007
	Problematic ever	8 (1.3)	3 (1.5)	0.80	14 (2.8)	0.08
	Problematic current	0 (0–2)	1 (0–4)	0.03	1 (0–3)	0.16
	Past 30 days–median (IQR[2])					
	Substance use	102 (16.5)	32 (16.3)	0.74	134 (27.2)	<0.001
	Any ever	19 (3.1)	12 (6.1)	0.05	53 (10.7)	<0.001
	Any current	22 (3.6)	10 (5.1)	0.33	65 (13.2)	<0.001
	Problematic ever	14 (2.3)	7 (3.6)	0.32	41 (8.3)	<0.001
	Problematic current					

Bibliographic reference	**Pettit, A. C., Bethel, J., Hirsch-Moverman, Y., Colson, P. W., & Sterling, T. R. (2013). Female sex and discontinuation of isoniazid due to adverse effects during the treatment of latent tuberculosis. *Journal of Infection*, *67*(5), 424-432.**
Intervention	Participants initiated an isoniazid course: Isoniazid: daily, for 9 months (96.4% of treatment completers) OR Isoniazid: daily, for 6 months (3.6% of treatment completers) 52 participants switched to a rifampicin-based regime due to adverse effects on isoniazid.
Length of follow up	Follow up did not extend beyond treatment period
Location	USA and Canada
Outcomes measures and effect size	Results of multivariate analysis: A participant was determined to have discontinued treatment due to adverse effects if the reason for stopping noted in the medical chart was due to adverse effects. Below is the relative risk of isoniazid discontinuation due to toxicity:

Characteristic n=813	Unadjusted relative risk	P value	Adjusted relative risk	P value
Age (in years)	1.01 (0.99–1.03)	0.40		
Female sex	1.57 (1.22–2.02)	<0.001	1.67 (1.32–2.10)	<0.001
White, non-Hispanic race	1.74 (1.14–2.64)	0.01		
US born	1.22 (1.06–1.41)	0.005		
High school education or equivalent	1.33 (1.02–1.73)	0.03		
Currently homeless	0.69 (0.17–2.77)	0.60		

Bibliographic reference	**Pettit, A. C., Bethel, J., Hirsch-Moverman, Y., Colson, P. W., & Sterling, T. R. (2013). Female sex and discontinuation of isoniazid due to adverse effects during the treatment of latent tuberculosis. *Journal of Infection*, *67*(5), 424-432.**				
	Employed	1.19 (1.00–1.42)	0.06		
	Healthcare worker	1.23 (1.02–1.47)	0.03		
	Household income <$20,000	0.80 (0.64–1.01)	0.06		
	Jail >30 days in the last 2 years	1.04 (0.32–3.40)	0.95		
	No health insurance	1.14 (0.78–1.65)	0.51		
	Current daily prescription medications	1.16 (0.87–1.54)	0.31		
	Psychiatric hospitalisation or prescription medication	1.33 (0.96–1.82)	0.08		
	HIV infection	0.43 (0.13–1.46)	0.17		
	Current alcohol use	1.29 (1.00–1.66)	0.05	1.41 (1.13–1.77)	0.003
	Current substance use	1.65 (0.93–2.90)	0.08		
	Adjusted relative risk is adjusted for study site, sex and current alcohol use. No other significant factors appear to have been adjusted for.				
Source of funding	Supported by the Tuberculosis Epidemiologic Studies Consortium and the Centers for Disease Control and Prevention.				
Comments	SUMMARY: In multivariate analysis, female sex (risk rate 1.67, 95% Confidence interval 1.32–2.10, p<0.001) and current alcohol use (risk rate 1.41, 95% confidence interval 1.13–1.77, p=0.003) were independently associated with isoniazid				

Bibliographic reference	**Pettit, A. C., Bethel, J., Hirsch-Moverman, Y., Colson, P. W., & Sterling, T. R. (2013). Female sex and discontinuation of isoniazid due to adverse effects during the treatment of latent tuberculosis. *Journal of Infection*, *67*(5), 424-432.**
	discontinuation due to adverse effects.

Abbreviations:

[1]TST- tuberculin skin test

[2]IQR- Interquartile range

A.1.25 DiPerri G, Micciolo R (1993)

Bibliographic reference	**Di Perri, G., Micciolo, R., Vento, S., Cruciani, M., Marocco, S., Carlotto, A., ... & Concia, E. (1993). Risk of reactivation of tuberculosis in the course of human immunodeficiency virus infection. *The European journal of medicine*, *2*(5), 264-268.**
Study type	Cohort
Study outline	Population matches population of interest. Participants were individuals infected with HIV and diagnosed by tuberculin skin test to have latent tuberculosis. The participants were seen at the same site in Verona, Italy. There was no indication that any of these participants were treated for latent infection of TB. 40 out of the 44 participants were IV drug users. Question is relevant; discussing which factors make a person more at risk of developing active tuberculosis following infection with HIV and latent infection of tuberculosis. However this paper seemed to focus upon immunological evaluation of patients with HIV rather than specific people groups. Participants received the same standard of care in regard to monitoring however immunological evaluation was performed at baseline and subsequently at 3-6 month intervals, leaving some uncertainty about consistency of monitoring tests. No other treatment appears to have been given however 10 patients were enrolled in a methadone maintenance programme during the study. Comparisons in baseline characteristics were not made between those that were enrolled in the study and those who refused. Risk factors for reactivation of tuberculosis gathered included: Total lymphocyte count, CD4 lymphocyte count and serum β-2 microglobulin levels. Multivariate analysis was performed using the Cox model. However the study has failed to adjust for external risk factors that may be relevant such as malnutrition, alcoholism, homelessness and drug dependence. Definition of risk factors was clear and the methods used to record the risk were valid and reliable. Definition of diagnosis of active and latent tuberculosis was clear and methods used for diagnosis were valid and reliable. Follow up was for 2 years. The study lost no subjects to follow up. The population studied was small: 44 participants were included for analysis.
Number of patients	Population: 44

Bibliographic reference	**Di Perri, G., Micciolo, R., Vento, S., Cruciani, M., Marocco, S., Carlotto, A., ... & Concia, E. (1993). Risk of reactivation of tuberculosis in the course of human immunodeficiency virus infection. *The European journal of medicine*, *2*(5), 264-268.**
Patient characteristics	Included: PPD[1] positive HIV infected Excluded Previous clinical episodes of tuberculosis BCG vaccination Clinical or instrumental evidence of active tuberculosis Baseline characteristics: Population consisted of: 37 males and 7 females; 40 IV drug abusers and 4 homosexuals; aged 19–46 years (mean 26); No signs of developing AIDS–related major pathologies; Oral candidiasis present in 5 subjects; seborrhoeic dermatitis present in 7 subjects; minor neurological abnormalities were recorded in 3 individuals; 10 subjects enrolled in a methadone maintenance programme and 40 drug abusers.
Intervention	No treatment administered for latent tuberculosis infection.
Length of follow up	Follow up was 2 years
Location	Italy
Outcomes measures and effect size	Results of multivariate analysis: A participant was determined to have developed active tuberculosis if microbiologically confirmed.

Variable	Estimation	Standard error	Z	P
Univariate analysis				
Total lymphocytes	-0.01507	0.000651	2.31	0.02

Bibliographic reference	**Di Perri, G., Micciolo, R., Vento, S., Cruciani, M., Marocco, S., Carlotto, A., ... & Concia, E. (1993). Risk of reactivation of tuberculosis in the course of human immunodeficiency virus infection. *The European journal of medicine*, *2*(5), 264-268.**

CD4 cell count	-0.004635	0.001416	3.27	0.001
β-2 microglobulin	0.006601	0.002032	3.25	0.001
Multivariate analysis				
CD4 cell count	-0.003686	0.001515	2043	<0.01
β-2 microglobulin	0.004974	0.002540	1.96	0.05

Analysis is adjusted for total lymphocytes, CD4 cell count and β-2 microglobulin. No other significant factors appear to have been adjusted for.

Source of funding	Unclear source of funding
Comments	SUMMARY: After multivariate analysis only CD4 cell count and β-2 microglobulin serum levels retained statistical significance in the prognosis of developing active tuberculosis. Tuberculosis in this setting most often reactivates only when immune surveillance has fallen to an identiable level. Starting prophylaxis in HIV-infected subjects only when CD4 cells have dropped below the value of 500/mm³ seems to be a more fruitfull option than the currently adopted strategy, which recommends time-limited (12 months) administration of daily isoniazid to all PPD[1] positive HIV infected subjects regardless of their immunological status.

Abbreviations:

[1]PPD- purified protein derivative

A.1.26 Antonucci G, Girardi E et al (1995)

Bibliographic reference	Antonucci, G., Girardi, E., Raviglione, M. C., Ippolito, G., Almi, P., Angarano, G., ... & Viale, P. (1995). Risk Factors for Tuberculosis in HIV-Infected Persons: A Prospective Cohort Study. *Jama*, *274*(2), 143-148.
Study type	Cohort
Study outline	Population does not exactly match population of interest. Participants were individuals infected with HIV and included those who were not tuberculin skin test positive or who were found to be anergic, however data for those with latent tuberculosis was separable. The participants were seen over 23 hospitals in Italy. None of these participants were treated for latent infection of TB in the past 18 months. Question is relevant; discussing which factors make a person more at risk of developing active tuberculosis following infection with HIV; this was separable for latent tuberculosis infected participants. This paper took into account both immunological evaluation of patients with HIV and clinical and demographic features of participants. The same standard of care in regard to monitoring was performed. Unclear if there were any further differences in care across the 23 hospital sites. During the study 104 subjects started preventive therapy for tuberculosis however this was only completed for 23 participants. Baseline characteristics were recorded. Comparisons in baseline characteristics were not made between those that were enrolled in the study and those who refused. Risk factors for development of active tuberculosis gathered included: age, sex, country of birth, place of residence, HIV transmission category, history of active tuberculosis, HIV clinical status and time of beginning preventive therapy for tuberculosis or antiretroviral therapy for HIV (if applicable), Medical history, physical examination, and CD4 count. Multivariate analysis was performed using the Cox proportional hazards model. All variables significantly associated with the development of tuberculosis in the univariate analysis were adjusted for. Definition of risk factors was clear and the methods used to record the risk were valid and reliable. Definition of diagnosis of active and latent tuberculosis was clear and methods used for diagnosis were valid and reliable. Follow up differed between participants over the study period (mean follow up 91 weeks). The study lost 27.4% of patients to follow up. Subjects who were unavailable for follow up had a significantly higher CD4 lymphocyte count than those who completed the study which could potentially lead to an overestimation of the risk of tuberculosis.
Number of patients	Population: 2695 (197 tuberculin skin test positive)

Bibliographic reference	**Antonucci, G., Girardi, E., Raviglione, M. C., Ippolito, G., Almi, P., Angarano, G., ... & Viale, P. (1995). Risk Factors for Tuberculosis in HIV-Infected Persons: A Prospective Cohort Study. *Jama*, *274*(2), 143-148.**
Patient characteristics	Included: ≥18 years of age HIV infected October 1, 1990–April 30, 1991 Excluded Episode of active tuberculosis in the previous 18 months Started a course of antituberculosis drugs in the previous 18 months Had completed a full course of isoniazid preventive therapy in the previous 18 months Died, lost to follow up or developed tuberculosis within the first 4 weeks of study Baseline characteristics:

	Subjects with feature, No. (%)	No. with tuberculosis	Incidence per 100 person-years (95% Confidence interval)	Crude rate ratio (95% Confidence interval)
Age, y	308 (11.4)	9	2.01 (0.91–3.80)	1.00
18–24	1133 (42.1)	33	2.08 (1.38–2.86)	1.04 (0.48–2.48)
25–29	747 (27.7)	25	2.46 (1.59–3.63)	1.23 (0.55–2.99)
30–34	507 (18.8)	16	2.51 (1.43–4.07)	1.25 (0.52–3.21)
≥35				
Sex	723 (26.8)	21	1.98 (1.22–3.02)	1.00
Female	1972 (73.2)	62	2.36 (1.81–3.03)	1.20 (0.72–2.07)

Bibliographic reference	Antonucci, G., Girardi, E., Raviglione, M. C., Ippolito, G., Almi, P., Angarano, G., ... & Viale, P. (1995). Risk Factors for Tuberculosis in HIV-Infected Persons: A Prospective Cohort Study. *Jama*, *274*(2), 143-148.				
	Male				
	HIV transmission category	1953 (72.5)	64	2.42 (1.87–3.10)	1.00
	Injecting drug users	366 (13.6)	10	1.81 (0.87–3.33)	0.75 (0.34–1.46)
	Heterosexual contacts	267 (9.9)	7	1.96 (0.79–4.04)	0.81 (0.31–1.76)
	Homosexual/bisexual	109 (4.0)	2	1.47 (0.18–5.31)	0.61 (0.07–2.28)
	Other/undefined				
	Place of residence in Italy	1103 (41.0)	34	2.25 (1.56–3.14)	1.00
	North	1098 (40.7)	30	2.01 (1.36–2.87)	0.89 (0.53–1.50)
	Center	494 (18.3)	19	2.79 (1.68–4.36)	1.24 (0.67–2.24)
	South				
	History of Tuberculosis	2663 (98.8)	79	2.16 (1.71–2.70)	1.00
	No	32 (1.2)	4	11.34 (3.09–29.03)	5.29 (1.41–14.09)
	Yes				
	Antiretroviral therapy	1475 (54.7)	37	1.90 (1.35–2.65)	1.00
	No	1220 (45.3)	46	2.61 (1.91–3.48)	1.36 (0.86–2.15)
	Yes				
	CDC clinical class	1570 (58.2)	33	1.36 (0.94–1.92)	1.00
	II–III	608 (22.6)	27	3.45 (2.27–5.01)	2.56 (1.12–6.04)

Bibliographic reference	**Antonucci, G., Girardi, E., Raviglione, M. C., Ippolito, G., Almi, P., Angarano, G., ... & Viale, P. (1995). Risk Factors for Tuberculosis in HIV-Infected Persons: A Prospective Cohort Study. *Jama*, *274*(2), 143-148.**				
	IV non–AIDS	517 (19.2)	23	4.71 (3.55–6.13)	6.73 (3.48–14.23)
	AIDS				
	CD4 lymphocytes, x 10^9/L	1025 (38.0)	11	0.70 (0.35–1.25)	1.00
	>0.35	634 (23.6)	17	1.79 (1.04–2.87)	2.56 (1.13–6.04)
	0.20–0.35	1036 (38.4)	55	4.71 (3.55–6.13)	6.73 (3.48–14.23)
	<0.20				
	Delayed-type hypersensitivity skin test status	849 (31.5)	6	0.45 (0.16–0.97)	1.00
	Tuberculin-negative nonanergic	1649 (61.2)	62	3.00 (2.30–3.85)	6.66 (2.92–18.99)
	Anergic	197 (7.3)	15	5.42 (3.04–8.95)	12.00 (4.46–38.22)
	Tuberculin-positive				
Intervention	During study period 104 subjects started preventive therapy for tuberculosis (34 were tuberculin-positive and 70 were anergic at baseline); only 29 subjects completed a 6–month course of preventive therapy. Otherwise unclear which drug regimen was prescribed.				
Length of follow up	Follow up differed between participants over the study period (mean follow up 91 weeks).				
Location	Italy				
Outcomes measures and effect size	Results of multivariate analysis: Below is the incidence of tuberculosis by baseline tuberculin skin test status and CD4 lymphocyte count (only separable data for latent tuberculosis)				

Bibliographic reference	**Antonucci, G., Girardi, E., Raviglione, M. C., Ippolito, G., Almi, P., Angarano, G., ... & Viale, P. (1995). Risk Factors for Tuberculosis in HIV-Infected Persons: A Prospective Cohort Study. *Jama*, *274*(2), 143-148.**			
		No. with tuberculosis/Total	Incidence per 100 person-years (95% Confidence interval)	Hazard ratio (95% Confidence interval)
	Tuberculin-positive			
	CD4 >0.35 x 10^9/L	4/109	2.59 (0.70–6.62)	5.49 (1.32–27.09)
	CD4 0.20–0.35 x 10^9/L	5/56	6.54 (2.12–15.25)	14.78 (3.49–62.63)
	CD4 <0.20 x 10^9/L	6/32	13.33 (4.89–29.01)	31.18 (7.62–127.50)
	Hazard ratio adjusted for tuberculin skin test status, CD4 lymphocyte count, history of tuberculosis, Centers for Disease Control clinical class, and the interaction term between tuberculin skin test status and CD4 lymphocyte count.			
Source of funding	Supported by Ministero della Sanita-Progetto AIDS grants.			
Comments	SUMMARY: Risk of tuberculosis can be more precisely quantified by jointly considering skin test reactivity and CD4 lymphocyte count. Incidence of active tuberculosis increased with decreasing levels of CD4 lymphocytes in the three groups of subjects with different skin test responsiveness; (including those who were tuberculin skin test positive at baseline).			
Abbreviations:				

A.1.27 Gessner BD, Weiss NS (1998)

Bibliographic reference	Gessner, B. D., Weiss, N. S., & Nolan, C. M. (1998). Risk factors for pediatric tuberculosis infection and disease after household exposure to adult index cases in Alaska. *The Journal of pediatrics*, *132*(3), 509-513.
Study type	Cohort
Study outline	Population does not exactly match population of interest. Participants were children with or without tuberculosis infection who were household contacts of an adult infected with tuberculosis, however data was separable for those children with latent infections. Question is mostly relevant; discussing which factors make a child higher risk of developing active tuberculosis after latent infection but also what factors make a child of higher risk of latent infection in the first place, data was separable for the former question of interest. It was stated that once diagnosed infected children were treated however it is unclear under what regimen they were treated for latent tuberculosis and whether all received the same standard of care. Unclear if the 30 villages in the area performed the same level of monitoring or care for the children and the infected adults. Few baseline characteristics are reported Risk factors for development of active tuberculosis gathered included: child's age, race, gender, adult's age and gender, number of children per household and exposure of the child to a parent with active disease. For the adult: level of sputum smear and culture positivity, presence of cavity chest lesion on x-ray, the location of the chest lesion (lobe), the presence of cough and a history of tuberculosis infection or active disease, and the season for which treatment began for the adult. Multivariate analysis was performed using backwards multiple regression models. Definition of risk factors was clear however the methods used to observe risk factors are unlikely to be reliable as data was recorded retrospectively. Definition of diagnosis of active and latent tuberculosis was not stated in full and the methods used to observe risk factors are unlikely to be reliable as data was recorded retrospectively. Observation period was for 7 years between 1987 and 1994. Unclear if length of observation was the same for all children (or if adjustments were made).
Number of patients	Population: 282
Patient characteristics	Included:

Bibliographic reference	**Gessner, B. D., Weiss, N. S., & Nolan, C. M. (1998). Risk factors for pediatric tuberculosis infection and disease after household exposure to adult index cases in Alaska. *The Journal of pediatrics*, *132*(3), 509-513.**
	Medical records from 1987–1994 Adult aged 15 years or older with sputum positive for mycobacterium tuberculosis living in a house with at least one person younger than 15 years. Excluded Adults without pulmonary tuberculosis No positive sputum culture in adults with tuberculosis Child aged ≥15 years No contact form available No tuberculin skin test recorded in child Positive result prior to the study documented Baseline characteristics: 25% of children younger than 15 years living in a house with an adult who had sputum positive for M. tuberculosis became infected. The age of infected children ranged from 1 month to 14 years (median 7.2 years). Resided in 30 villages located in 15 of the 27 census areas in the state. Tuberculin skin test reaction size varied from 0 (3 children) to 38mm (median, 15).
Intervention	It was stated that once diagnosed infected children were treated however it is unclear under what regimen they were treated for latent tuberculosis and whether all received the same standard of care.
Length of follow up	Observation period was for 7 years between 1987 and 1994. Unclear if length of observation was the same for all children (or if adjustments were made).
Location	Alaska
Outcomes measures and effect size	Results of multivariate analysis: Below is the risk factors for progression to active disease among infected childhood contacts of adults with active

Bibliographic reference	**Gessner, B. D., Weiss, N. S., & Nolan, C. M. (1998). Risk factors for pediatric tuberculosis infection and disease after household exposure to adult index cases in Alaska. *The Journal of pediatrics*, *132*(3), 509-513.**

pulmonary tuberculosis in Alaska, 1987–1994. Active and latent disease is diagnosed according to the American Thoracic Society standards of 1990.

Potential risk factor	Number with disease/number with risk factor (%)	Relative risk from univariate analysis (95% confidence interval)	Odds ratio from multivariate analysis (adjusted 95% confidence interval)
Left upper lobe lesion in adult	20/34 (59)	3.1 (1.5–6.4)	12 (2.2–65)
Alaska native child	25/55 (45)	3.6 (1.0–13.7)	8.9 (1.1–73)
Adult is parent of child	17/35 (49)	1.8 (0.9–3.3)	8.3 (1.6–44)
Age of child	Continuous	Continuous	1.5 (1.1–2.0)
3 or 4+ culture positive adults	22/46 (48)	2.3 (1.0–5.3)	–
3 or 4+ smear positive adults	19/36 (53)	2.2 (1.1–4.3)	–
Male adult	14/45 (31)	0.6 (0.4–1.1)	–

Variables examining risk factors for infection and for active disease significant at the 90% confidence level after initial regression analysis were entered into the final regression models.

Source of funding	Unclear source of funding
Comments	SUMMARY: Among the 71 children in whom infection developed, Alaska Natives and younger children were more likely to progress to active tuberculosis, as were children exposed to a parent who had active tuberculosis and children exposed to any adult who had a left upper lobe chest lesion.
Abbreviations:	

Bibliographic reference	**Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, Memish Z, Khan K, Gardam M, Hoeppner V, Benedetti A, Schwartzman K.2008 Nov 18;149(10):689-97. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial.**

A.2 RQ II: For people with latent TB infection, is a drug treatment regimen effective in preventing the development of active TB in comparison with placebo? If so, which regimen is the most effective in preventing the development of active TB?

A.2.1 Menzies D, Long R et al (2008)

Study type	RCT
Study quality	Population matches population of interest Intervention matches intervention of interest An appropriate method of randomisation and allocation concealment was used. Randomisation and allocation was controlled by a computer programme. Groups were comparable at the baseline Unclear if comparison groups received the same care apart from intervention studied since treatment was received at multiple sites in different countries. Blinding: This study was an open-label study, neither the clinicians nor patients were blinded: • A blinded independent panel reviewed all possible adverse events in an attempt to eliminate bias in attribution or grading of adverse events • Hepatic changes were diagnosed on the basis of laboratory results and were graded using a standardized classification. There was statistical difference in the number of participants that did not complete treatment within each group. Unclear if there were systematic differences between groups in terms of those for whom no outcome data was available. Groups were comparable for number for which no outcome data was available. Follow up beyond treatment period is not specified. Investigator blinding: once 75% of the planned total sample size had been randomly assigned, a planned interim analysis was performed revealing to the blinded data and safety monitoring board that the frequency of serious adverse events was significantly lower in one trial group. Once unblinded the board recommended discontinuation of enrolment earlier than planned. The study used a precise definition of outcome and a valid and reliable method was used to determine the outcome.
Number of patients	Randomised= 847 • 9 months of isoniazid: 427 patients • 4 months of rifampicin: 420 patients Outcome data for serious adverse events available for = 847 • 4 months of rifampicin group: 418 patients • 9 months of isoniazid: 421 patients Outcome data for completion of therapy was available for: • 4 months of rifampicin group: 420 patients • 9 months of isoniazid: 427 patients
Patient characteristics	Patients taken from sites in Canada, Brazil and Saudi Arabia Inclusion: Aged 18 or older, Documented tuberculin skin test (PPD) meeting criteria for a positive result.

<table>
<tr><td></td><td>Exclusion:
Contacts of rifampin or isoniazid resistant cases,
Allergic to either medication
Taking concomitant medications that could have significant potential drug interactions.
Baseline characteristics:
<table>
<tr><th>Characteristic</th><th>4 Months rifampicin (n=420), n (%)</th><th>9 Months isoniazid (n=427), n (%)</th></tr>
<tr><td>Age
18-34 y
≥35 y</td><td>229 (55)
191 (45)</td><td>242 (57)
185 (43)</td></tr>
<tr><td>Sex
Male
Female</td><td>218 (52)
201 (48)</td><td>228 (53)
199 (47)</td></tr>
<tr><td>TST size
5-9 mm
10-14 mm
≥15mm</td><td>23 (6)
150 (36)
247 (59)</td><td>20 (5)
132 (31)
275 (64)</td></tr>
<tr><td>History of BCG vaccination
Yes
No
Unknown</td><td>224 (54)
101 (24)
95 (33)</td><td>199 (47)
121 (28)
107 (25)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>9- month regimen of daily isoniazid
Dose: 5 mg/kg, up to 300 mg/d
All patients seen on an outpatient basis.</td></tr>
<tr><td>Comparison</td><td>4- month regimen of daily rifampicin
Dose: 10mg/kg, up to 600 mg/d
All patients seen on an outpatient basis.</td></tr>
<tr><td>Length of follow up</td><td>Could continue until a month after treatment regimen finishes</td></tr>
<tr><td>Location</td><td>Tuberculosis clinics located in university hospitals in Canada, Brazil and Saudi Arabia.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Adverse events: (Primary outcome: Grade 3/4 adverse events)
Number to experience hepatotoxicity, defined as liver aminotransferase levels that increased to 3/5 to 10 times the upper limit of normal in the presence of compatible symptoms (grade 3) or ≥10 time the upper limit of normal (grade 4): n(%)</td></tr>
</table>

	• 4- month rifampicin group = 3 of 420 (0.7) • 9- month isoniazid group = 16 of 427 (3.8) • Risk difference (95% CI) = -3 (-5 to -1) • i.e. statistically significant Number to experience rash (grade 1 or 2): n% Number to experience rash: n (%) • 4- month rifampin group = 9 of 420 (2.1) • 9- month isoniazid group = 5 of 427 (1.2) • Risk difference (95% CI) = 1 (-1 to 3) i.e. not statistically significant. • Gastro intestinal intolerance • 4- month rifampin group = 1 of 420 (0.2) • 9- month isoniazid group = 2 of 427 (0.5) Adherence: Number to complete therapy, defined as taking more than 80% of doses within a maximum of 150 days for 4 months of rifampicin or 301 days for 9 months of isoniazid. n (%) • 4- month rifampicin group = 328 of 420 (78) • 9- month isoniazid group = 255 of 427 (60) • Risk difference (95% CI) = 18 (12 to 24) • i.e. statistically significant.
Source of funding	The Canadian Institute of Health Research
Comments	

A.2.2 Samandari,T., Agizew,T.B., et al. (2011)

<table>
<tr><td>Bibliographic reference</td><td>Samandari,T., Agizew,T.B., et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet, 2011 377 (9777) 1588-98.</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Study quality</td><td>Population does not exactly match the population of interest:
• Tuberculin skin test negative patients were also enrolled however subgroup data is available.
Intervention matches the intervention of interest.
Appropriate method of randomisation included: computer generated randomisation list. Allocation concealed.
Double blind: clinicians and patients blinded; data and safety monitoring board, statistician and drug packaging company were unblinded. Investigators were blind to participant’s exposure. Unclear if investigators were blinded for other confounding factors.
Groups were comparable at baseline
Unclear if groups were comparable for treatment completion. Groups had a similar availability of outcome data.
Follow up: no follow up beyond treatment period (3 years)
A precise definition of outcome was used and a valid and reliable method employed to determine outcome.</td></tr>
<tr><td>Number of patients</td><td>Randomized 1,995.
• receiving 6 months Isoniazid- 989
• receiving 36 months of Isoniazid- 1,006</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Age ≥18 years
HIV infection
Attendance of one of eight government clinics in Botswana
Exclusion
Symptoms of: Cough, weight loss, night sweats
Other acute illness
Previous isoniazid preventive therapy
TB treatment within the past 3 years
Neutrophil count of fewer than 1.0 x 109 cells per L
Abnormal chest radiograph without antecedent tuberculosis or pneumonia.
Baseline characteristics
<table><tr><td></td><td>6 months isoniazid n (%)</td><td>36 months isoniazid. N (%)</td></tr></table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Samandari,T., Agizew,T.B., et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet, 2011 377 (9777) 1588-98.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Women/men</td><td>721/268 (73/27)</td><td>715/291 (72/28)</td></tr>
<tr><td>History of tuberculosis</td><td>31 (3)</td><td>43 (4)</td></tr>
<tr><td>BCG scar present</td><td>773 (78)</td><td>787 (78)</td></tr>
<tr><td>Tuberculin skin test
<5mm (negative)
≥5mm (positive)</td><td>729 (74)
216 (22)</td><td>722 (72)
252 (25)</td></tr>
<tr><td>Antiretroviral therapy
Before enrolment
By month 36</td><td>19 (2)
463 (47)</td><td>32 (3)
483 (48)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>For individuals weighing 30-49 kg:
• 300mg per day for 6 months
• Supplementation with 25 mg vitamin B6 for full treatment period
For individuals weighing ≥ 50kg
• 400mg per day for 6 months (this was later changed to 300mg)[1]
• Supplementation with 25mg vitamin B6 for full treatment period
Following the initial 6 months of open label isoniazid, these patients were switched to a placebo for the remaining 30 months period.</td></tr>
<tr><td>Comparison</td><td>For individuals weighing 30-49 kg:
• 300mg per day for 36 months
• Supplementation with 25 mg vitamin B6
For individuals weighing ≥ 50kg
• 400mg per day for 36 months (this was later changed to 300mg)[1]
• Supplementation with 25mg vitamin B6</td></tr>
<tr><td>Length of follow up</td><td>No follow up beyond treatment period (3 years)</td></tr>
<tr><td>Location</td><td>Government HIV care clinics in Botswana</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Incidence of active tuberculosis
Defined as clinical presentation consistent with tuberculosis and response to anti-tuberculosis therapy.
Incident disease was categorised as:</td></tr>
</table>

Bibliographic reference	**Samandari,T., Agizew,T.B., et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet, 2011 377 (9777) 1588-98.**
	• "definite" if one or more cultures were positive for tuberculosis and speciated as M. tuberculosis or if two or more sputum smears were positive for acid-fast bacilli. • "probable" if one sputum smear or one biopsy specimen was positive for acid fast bacilli. • "possible" if smears or cultures were negative or not done. In tuberculin skin test positive patients: Number of definite, probable and possible tuberculosis cases: (rate per 100 person years) • 6 month Isoniazid group: 13 (2.22) • 36 month isoniazid group: 4 (0.57) • Hazard ratio (95% CI): 0.26 (0.09-0.80) Number of definite and probable tuberculosis cases: (rate) • 6 month Isoniazid group: 12 of 216 (2.05) • 36 month isoniazid group: 4 of 252 (0.57) • Hazard ratio (95% CI): 0.28 (0.09-0.87) • In those who actually started the second masked phase of the trial (n=1655): Number of definite and probable tuberculosis cases: (rate) • 6 month Isoniazid group: 10 (2.30) • 36 month isoniazid group: 1 (0.19) • Hazard ratio (95% CI): 0.09 (0.01-0.67)
	Mortality Number of deaths: (rate per 100 person years) • 6 month isoniazid group: 13 of 216 (2.22) • 36 month isoniazid group: 5 of 252 (0.71) • Hazard ratio (95% CI): 0.32 (0.11-0.90) In those who actually started the masked phase of the trial (n=1655) Number of deaths: (rate) • 6 month isoniazid group: 9 (2.07) • 36 month isoniazid group: 3 (0.58) • Hazard ratio (95% CI): 0.28 (0.08-1.03)
	Hepatitis No subgroup data available for rates of hepatitis in patients that were TST positive.

Bibliographic reference	**Samandari,T., Agizew,T.B., et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet, 2011 377 (9777) 1588-98.**
Source of funding	US Centers for Disease Control and Prevention and US Agency for International Development
Comments	This publication provided data specifically for TST positive patients (with regards to the incidence of mortality and active tuberculosis however data was not split into subgroups for the incidence of hepatitis. Should indirect evidence be required this paper could provide a good source of additional data.
[1] All patients in both treatment arms ultimately received 300mg daily doses as a result of changes in national guidelines at the time of trial. Abbreviations: TST- tuberculin skin test	

A.2.3 Halsey,N.A., Coberly,J.S., (1998)

Bibliographic reference	**Halsey,N.A., Coberly,J.S., et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection Lancet 1998 351 (9105) 786-92.**
Study type	RCT
Study quality	This was a prospective, randomised, unblinded trial Randomisation: this was performed by the project coordinator using sealed sequentially numbered envelopes. Allocation: Sealed envelopes were possibly opaque but uncertain. Project coordinator organised the method; however, there was no certainty over whether this person had any other influence. Otherwise it is likely that allocation was adequately blinded. Blinding: trial was “unmasked” and neither patients nor physicians were blinded; investigators were kept blind to participant’s exposure to the intervention. Attrition: loss to follow up was similar in both treatment arms as were the amount for which no outcome data was available. There was no significant difference between participants lost to follow up between the two arms of study. Comparison groups were similar at baseline with respect to all important characteristics, except that more in the rifampicin and pyrazinamide group had “ever drunk alcohol.” Comparison groups received the same care apart from the intervention studied. Follow up was also similar between the two groups. Length of follow up was appropriate. • A valid and reliable method was used to determine primary outcome. Intervention matches the intervention of interest: Population matches the population of interest:
Number of patients	Randomised: 750 patients, • 370 received Isoniazid and pyridoxine • 380 received rifampicin and pyrazinamide
Patient characteristics	Inclusion Aged 16-77 years HIV-1 seropositive Positive PPD skin test of at least 5mm Normal chest radiograph No evidence of extrapulmonary TB Aspartate aminotransferase of less than 3 times upper normal limit Total bilirubin of less than 43 μmoles/L Serum creatinine of less than 221 μmoles/L

<table>
<tr><td>Bibliographic reference</td><td>Halsey,N.A., Coberly,J.S., et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection Lancet 1998 351 (9105) 786-92.</td></tr>
<tr><td></td><td>Platelet count of more than 100000/µL
White blood cell count of more than 4000/mL
Weight over 25kg
Informed consent
Exclusion
Pregnancy
Negative PPD test.
<table>
<tr><th>Characteristics</th><th>Isoniazid group (n=370)</th><th>Rifampicin and pyrazinamide (n=380)</th><th>P-value</th></tr>
<tr><td>Mean age</td><td>31</td><td>31</td><td>0.99</td></tr>
<tr><td>Male</td><td>108</td><td>129</td><td>0.18</td></tr>
<tr><td>Ever smoked</td><td>67</td><td>83</td><td>0.23</td></tr>
<tr><td>Ever drunk alcohol</td><td>9</td><td>26</td><td>0.005</td></tr>
<tr><td>Mean PPD size (mm)</td><td>11.7</td><td>11.7</td><td>0.75</td></tr>
<tr><td>Mean entry CD4/CD8</td><td>0.57</td><td>0.56</td><td>0.73</td></tr>
</table>
Baseline characteristics</td></tr>
<tr><td>Intervention</td><td>Isoniazid group:
For patients under 50kg:
• 600mg isoniazid and 25mg pyridoxine, twice weekly for 6 months
For patients over 50kg:
• 800mg Isoniazid and 25mg pyridoxine, twice weekly for 6 months
Participants were given two doses each week: the first given under direct supervision and the second to be taken at home three days later unsupervised.</td></tr>
<tr><td>Comparison</td><td>Rifampicin and Pyrazinamide group:
For patients under 40kg weight:
• 450 mg rifampicin and 1500mg pyrazinamide, twice weekly for 2 months
For patients over 40kg:
• 450mg rifampicin and 2000mg pyrazinamide, twice weekly for 2 months
Participants were given two doses each week: the first given under direct supervision and the second to be taken at home three days later unsupervised.</td></tr>
<tr><td>Length of follow up</td><td>Participants were followed up for up to 4 years.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Halsey,N.A., Coberly,J.S., et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection Lancet 1998 351 (9105) 786-92.</td></tr>
<tr><td></td><td>• median follow up was 2.5 years.</td></tr>
<tr><td>Location</td><td>Haiti</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Incidence of active tuberculosis
<table>
<tr><td></td><td>Isoniazid group (n=370)</td><td>Rifampicin and pyrazinamide group (n=380)</td><td>Total (n=750)</td><td>P</td></tr>
<tr><td>Culture confirmed</td><td>5</td><td>10</td><td>15</td><td></td></tr>
<tr><td>Sputum smear positive</td><td>2</td><td>5</td><td>7</td><td></td></tr>
<tr><td>Clinically compatible with response to TB</td><td>7</td><td>4</td><td>11</td><td></td></tr>
<tr><td>total</td><td>14 (3.8%)</td><td>19 (5.0%)</td><td>33</td><td>0.21</td></tr>
</table>
At 36 months:
• Hazard ratio for participants on rifampicin and pyrazinamide compared to those on isoniazid was 1.3 (95% CI 0.68-2.70).
• Annualised risk of developing TB= 1.8% for RIF/PYR and 1.7% for the isoniazid group.
• Cumulative risks 5.4% and 5.1% respectively (RR 1.1, p=0.90)
At 10 months
• The cumulative risk of tuberculosis was higher among those on RIF/PYR compared with those on ISO/PYR (3.7% vs 1.0%, Risk ratio 3.7, p=0.03)</td></tr>
<tr><td>Source of funding</td><td>Contract from the Division of Tuberculosis Elimination Branch of the Centers for Disease Control and Prevention</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">Abbreviations: PPD- Purified protein derivative (also known as the Mantoux test or TST test)</td></tr>
</table>

A.2.4 Pape,J.W., Jean,S.S., et al. (1993)

<table>
<tr><td>Bibliographic reference</td><td>Pape,J.W., Jean,S.S., et al. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 1993 342 (8866) 268-72.</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Study quality</td><td>Randomisation: appropriate method of computerised randomisation was used and there was adequate concealment of allocation.
Comparison: there were more PPD positive patients in the isoniazid group, which for the purposes of our study meant that there was more patients in total in the isoniazid group (38) than the no antituberculosis chemotherapy group (25). Otherwise patients were comparable at baseline.
Follow up in person–years was greater for the isoniazid group.
Blinding: neither the participants nor the clinicians were blinded; investigators were kept blind to the exposure of participants though it was unclear if they were kept blind to other important confounding factors
Loss to follow up: the groups were comparable in terms of numbers of those lost to follow up and for whom no outcome data was available
Length of follow up: appropriate
Outcome: There was a precise and definite definition and investigation of outcome.
Intervention matches the intervention of interest:
Population matches the population of interest:
Intention-to-treat principle was applied</td></tr>
<tr><td>Number of patients</td><td>Number of PPD positive patients randomised- 63,
• No antituberculosis chemotherapy group: 25
• isoniazid group: 38</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Symptom free, newly diagnosed HIV-infected individuals
Aged 18-65 years
Exclusion
History of tuberculosis
Abnormal Chest radiograph
Abnormal Liver Function tests
Baseline Characteristics
<table><tr><td>Characteristics</td><td>No antituberculosis chemotherapy</td><td>Isoniazid group (n=58)</td></tr></table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Pape,J.W., Jean,S.S., et al. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 1993 342 (8866) 268-72.</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><td></td><td>group (n=60)</td><td></td></tr>
<tr><td>Mean (SD) age</td><td>30.6 (7.6)</td><td>31.1 (6.6)</td></tr>
<tr><td>M/F</td><td>11/49</td><td>16/42</td></tr>
<tr><td>Months of follow up</td><td>33.5</td><td>39.1</td></tr>
<tr><td>PPD positive (%)</td><td>25 (42%)</td><td>38 (66%)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">12 months of
• daily isoniazid (300mg)
• vitamin B6 (50mg)
• Self-administered</td></tr>
<tr><td>Comparison</td><td colspan="3">No antituberculosis chemotherapy group
• 12 months of daily vitamin B6 (50mg)</td></tr>
<tr><td>Length of follow up</td><td colspan="3">Mean months of follow up (range)
• No antituberculosis chemotherapy group= 33.5 months (5.0-60.2)
• Isoniazid group= 39.1 (3.0-60.7)</td></tr>
<tr><td>Location</td><td colspan="3">Haiti- Institute National de Laboratoire et de Recherches in Port-au-Prince</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Incidence of active tuberculosis<table>
<tr><td>PPD positive</td><td>B6 Alone</td><td>Isoniazid + B6</td></tr>
<tr><td>N</td><td>25</td><td>38</td></tr>
<tr><td>No (%) of TB cases</td><td>6 (24)</td><td>2 (5)</td></tr>
<tr><td>Follow up time (person years)</td><td>61</td><td>118</td></tr>
<tr><td>Incidence (per 100 person-years)</td><td>5.7</td><td>3.2</td></tr>
<tr><td>RR for tuberculosis (95% CI)</td><td>1.8 (0.4-9.2)</td><td>1</td></tr>
</table></td></tr>
<tr><td></td><td colspan="3">Mortality<table>
<tr><td>PPD positive</td><td>B6 Alone</td><td>Isoniazid + B6</td></tr>
<tr><td>No (%) of deaths</td><td>7 (28)</td><td>3 (8)</td></tr>
<tr><td>Follow up time (person years)</td><td>61</td><td>118</td></tr>
<tr><td>RR for death (95% CI)</td><td>3.6 (1.0–12.4)</td><td>1</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td colspan="3">US Public Health Service</td></tr>
</table>

Bibliographic reference	**Pape,J.W., Jean,S.S., et al. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 1993 342 (8866) 268-72.**
Comments	Enrolment began in 1986. Enrolment was closed when isoniazid prophylaxis for PPD-positive HIV-infected patients was recommended in 1989. An interim analysis was done in January, 1990, and all subjects in the B6 group were offered isoniazid plus B6 for 12 months; 21 of 60 accepted. Intention-to-treat principle was applied.
Abbreviations:PPD- purified protein derivative	

A.2.5 Anon (1982)

Bibliographic reference	**Anon. Bulletin of the World Health Organization 1982 60 (4) 555-64. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis**
Study type	Randomised Controlled Trial
Study quality	Population: Participants match the population of interest: patients were required to have fibrotic lesions of probable tuberculosis origin that had been stable during the year prior to entry. As well as a positive PPD skin test. Intervention matches intervention of interest: Randomisation: An appropriate method of randomisation was used with patients assigned random ID numbers and a matching supply of pills. Allocation: Allocation concealment was applied Comparison Groups: All groups were comparable at baseline although the study merely stated the treatment arms were similar and did not provide a table. Populations were taken from 115 dispensaries in seven European countries: Czechoslovakia, Finland, Germany, Hungary, Poland, Romania and Yugoslavia; Comparison groups may not have received the same care apart from the intervention. Blinding: Both participants and clinicians were kept blind to treatment allocation. Follow up: Completion rates were inversely proportional to duration of treatment under study. Therefore loss to follow up was greater in the longer duration treatment arms. Follow up was of an appropriate duration Outcome: There was a precise definition and a valid reliable method used to determine the outcome. Investigators were kept blind to participant's exposure to intervention.
Number of patients	27,830 participants in total remained in the trial after exclusion. • 12 weeks of isoniazid: 6956 (25%) • 24 weeks of isoniazid: 6965 (25%) • 52 weeks of isoniazid: 6919 (24.9%) • 12 weeks of placebo: 2350 (8.4%) • 24 weeks of placebo: 2338 (8.4%) • 52 weeks of placebo: 2302 (8.3%)
Patient characteristics	Inclusion Fibrotic Lesions: • Well- delineated radiographic lesions • Of probably tuberculosis origin • Stable during the year prior to entry.

Bibliographic reference	**Anon. Bulletin of the World Health Organization 1982 60 (4) 555-64. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis**
	Greater than 5mm induration of Mantoux test (PPD positive) Persons 20-64 years of age (and “a few” who did not fit this category) Exclusion Less than 6mm induration to Mantoux test Radiographic lesions limited to solitary calcifications or thickening of apical or diaphragmatic pleura Previous treatment with antituberculosis drugs Previous record of positive bacteriological findings Baseline Characteristics Age: • Median age: 50 years. • Population skewed towards older age groups (38% between 55 and 65 years of age) Sex: • 53% Male • 47% female Median Induration size to tuberculin: • 15mm (range 6-90mm)
Intervention	300mg of Isoniazid, Daily for: • 12 weeks • 24 weeks • 52 weeks
Comparison	Placebo, Daily for • 12 weeks • 24 weeks • 52 weeks
Length of follow up	5 years
Location	Populations were taken from 115 dispensaries in seven European countries: Czechoslovakia, Finland, Germany, Hungary, Poland, Romania and Yugoslavia.

Bibliographic reference	**Anon. Bulletin of the World Health Organization 1982 60 (4) 555-64. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis**

Outcomes measures and effect size

Tuberculosis incidence:

Case rates of tuberculosis:

For all participants

Regimen	n of participants	Cumulative n of cases	5 year incidence (per 1000)	Risk Difference[a] (95% CI[1])	Relative risk[a] (95% CI[1])
Placebo	6990	97	14.3	0	1.00
12 weeks Isoniazid	6956	76	11.3	-0.003 (-0.005-0.000)	0.79 (0.58-1.06)
24 weeks Isoniazid	6965	34	5.0	-0.009 (-0.010- -0.007)	0.35 (0.24-0.52)
52 weeks Isoniazid	6919	24	3.6	-0.01 (-0.012- -0.009)	0.25 (0.16-0.39)

For Patients who completed treatment AND complied with 80% of daily doses.

Tuberculosis was considered to be confirmed only if tubercle bacilli were grown in culture.

Regimen	n of participants	Cumulative n of cases	5 year incidence (per 1000)	Percentage reduction	Relative risk
Placebo	5616	83	15.0	0	13.6
12 weeks Isoniazid	6039	61	10.4	31	9.4
24 weeks Isoniazid	5437	25	4.7	69	4.3
52 weeks Isoniazid	4543	5	1.1	93	1.0

Adherence

Compliance defined as 80% of pills taken daily

Completion defined as patients continuing to participate in the trial.

Percentage weeks completed (complied to therapy)

Duration	Product	12	24	36	52

Bibliographic reference	**Anon. Bulletin of the World Health Organization 1982 60 (4) 555-64. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis**

12 weeks	Isoniazid	95 (87)			
	Placebo	97 (91)			
24 weeks	Isoniazid	94 (84)	93 (78)		
	Placebo	96 (87)	95 (82)		
52 weeks	Isoniazid	93 (84)	91 (79)	89 (73)	88 (68)
	Placebo	95 (87)	93 (79)	91 (74)	90 (69)

Risk of Hepatitis

Risk of hepatitis by quarter (per 1000 persons)							
	Risk by quarter			Placebo Isoniazid Excess			
	Placebo	isoniazid	excess	placebo	isoniazid	excess	
Weeks	P	I	I-P	P	I	I-P	risk reduction, (cases prevented per 1000)
1-12	0.7	3.2	2.5	0.7	3.2	2.5	2.7
13-24	0.5	1.6	1.0	1.2	4.8	3.6	1.6
25-36	0.0	0.8	0.8	1.2	5.6	4.4	0.8
37-52	0.0	0.8	0.8	1.2	6.4	5.2	standard

Benefit to risk ratio by regimen and year

Year of follow- up	Regimen	Cumulative No. of tuberculosis cases prevented	Cumulative no. of hepatitis cases incurred	Benefit to risk ratio
First	12 weeks	2.6	2.5	1.0
	24 weeks	3.9	3.6	1.1
	52 weeks	3.6	5.2	0.7
Second	12 weeks	2.9	2.5	1.2
	24 weeks	5.5	3.6	1.5
	52 weeks	5.3	5.2	1.0
Third	12 weeks	3.6	2.5	1.4

Bibliographic reference	**Anon. Bulletin of the World Health Organization 1982 60 (4) 555-64. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis**

	24 weeks 52 weeks	7.6 8.0	3.6 5.2	2.1 1.5
Fourth	12 weeks 24 weeks 52 weeks	3.9 8.8 9.3	2.5 3.6 5.2	1.6 2.4 1.8
fifth	12 weeks 24 weeks 52 weeks	3.0 9.3 10.7	2.5 3.6 5.2	1.2 2.6 2.1

Definition of Hepatitis was unclear.

Source of funding	Scientific Committee on Prophylaxis of the International Union Against Tuberculosis “conception and support of the trial”
Comments	[a]Data calculated by technical analyst.

[1]CI- Confidence interval

A.2.6 Schechter,M., Zajdenverg,R., et al. (2006)

Bibliographic reference	**Schechter,M., Zajdenverg,R., et al. American Journal of Respiratory & Critical Care Medicine 2006 173 (8) 922-26.Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts**
Study type	RCT
Study quality	Population matches population of interest Intervention matches intervention of interest Randomisation: Participants were block randomised by households, methods described. Allocation: Allocation was concealed. Blinding: neither the participants nor the clinicians were blinded. Comparison: • The groups were comparable at baseline • Groups did not receive exactly the same care apart from the intervention, participants in the pyrazinamide/rifampicin group had to take their medication daily and mostly unsupervised. Patients in the rifapentine/Isoniazid group were directly observed for every dose given. • The pyrazinamide/rifampicin group were seen once more in follow up. Attrition: Groups were similar in regard to length of follow up and loss to follow up. Attrition was similar between the two arms of study. Unclear definition of outcome in regard to diagnosis of tuberculosis Unclear if investigators were kept blind to treatment arms or confounding factors (unlikely)
Number of patients	N= 399 • Rifampicin and pyrazinamide= 193 • Rifapentine and isoniazid= 206 Data available after treatment completion and follow up • Rifampicin and pyrazinamide= 193 • Rifapentine and isoniazid= 206 Loss to follow up • Rifampicin and pyrazinamide= 5 • Rifapentine and isoniazid= 3
Patient characteristics	Inclusion criteria Household contacts of patients with newly diagnosed pulmonary TB at public clinics in Rio de Janeiro who slept 2 nights or more per week in the same dwelling as the index case [1]TST positive- induration ≥ 5 mm

<table>
<tr><th>Bibliographic reference</th><th>Schechter,M., Zajdenverg,R., et al. American Journal of Respiratory & Critical Care Medicine 2006 173 (8) 922-26.Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts</th></tr>
<tr><td></td><td>No TB symptoms
Chest radiograph without evidence of active TB
Exclusion criteria
Evidence of liver or renal dysfunction
Evidence of anaemia
Received TB drugs for more than 1 month
Baseline characteristics
<table>
<tr><th>Variable</th><th>Rifapentine and isoniazid group</th><th>Rifampicin and pyrazinamide</th></tr>
<tr><td>N of subjects</td><td>206</td><td>193</td></tr>
<tr><td>Mean age (y)</td><td>37.7</td><td>37.0</td></tr>
<tr><td>Sex m/f (%)</td><td>37/63</td><td>44/56</td></tr>
<tr><td>HIV (%)</td><td>0.5</td><td>0</td></tr>
<tr><td>BCG vaccination (%)</td><td>65</td><td>66</td></tr>
<tr><td>Smoker (%)</td><td>22</td><td>25</td></tr>
<tr><td>Alcohol (%)</td><td>34.5</td><td>38</td></tr>
<tr><td>Injection drug use (%)</td><td>0</td><td>0.5</td></tr>
<tr><td>Ever in prison (%)</td><td>0</td><td>0</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Rifapentine and isoniazid
• rifapentine 900 mg once weekly for 12 weeks
• isoniazid 900 mg once weekly for 12 weeks
Directly observed in the clinic</td></tr>
<tr><td>Comparison</td><td>Rifampicin and pyrazinamide
For weight < 50 kg
• rifampicin 450 mg once daily for 8 weeks
• pyrazinamide 750 mg once daily for 8 weeks
For weight ≥ 50 kg
• rifampicin 600 mg once daily for 8 weeks
• pyrazinamide 1500 mg once daily for 8 weeks
• One dose directly observed, the rest self administered</td></tr>
</table>

Bibliographic reference	**Schechter,M., Zajdenverg,R., et al. American Journal of Respiratory & Critical Care Medicine 2006 173 (8) 922-26.Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts**
Length of follow up	Follow up for at least 2 years.
Location	Rio de Janeiro, Brazil
Outcomes measures and effect size	Incidence of tuberculosis TB evaluated with chest xray and sputum examination for smear and culture. Confirmed by reviewing medical records. Rifapentine and isoniazid group: • 3 cases in 564 person years of follow up (0.5/100 person-years) Rifampicin and pyrazinamide group: • 1 case in 522 person- years of follow up (0.2/100 person-years) • Relative risk, 2.8; 95% CI, 0.3-26.8; p=0.66 • i.e. non significant
	Mortality Number of cases of death during follow up • Rifapentine and isoniazid group= 1 of 206 • Rifampicin and pyrazinamide group= 3 of 193
	Incidence of hepatotoxicity Hepatotoxicity: Grade 3 defined as aspartate aminotransferase or alanine aminotransferase 5-10 times upper limit of normal. Grade 4 defined as aspartate aminotransferase or alanine aminotransferase > 10 times upper limit of normal. Number of cases of grade 3 hepatotoxicity during follow up • Rifapentine and isoniazid group= 2 of 206 • Rifampicin and pyrazinamide group= 14 of 193 Number of cases of grade 4 hepatotoxicity during follow up • Rifapentine and isoniazid group= 0 of 206 • Rifampicin and pyrazinamide group= 11 of 193 Number of cases of grade 3 or 4 hepatotoxicity during follow up • Rifapentine and isoniazid group= 2 of 206 • Rifampicin and pyrazinamide group= 20 of 193
Source of funding	Supported by National Institutes of Health grants, and TW 05574, and Conselho Nacionde Desenvolvimento Cientifico e Tecnologico

Bibliographic reference	**Schechter,M., Zajdenverg,R., et al. American Journal of Respiratory & Critical Care Medicine 2006 173 (8) 922-26.Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts**
Comments	Trial was prematurely terminated because of unexpectedly high rates of hepatotoxicity in the rifampicin and pyrazinamide arm.
Abbreviations: [1]TST- Tuberculin Skin Test	

A.2.7 Mwinga,A., Hosp,M., et al. (1998)

A.2.8 Quigley,M.A., Mwinga,A., et al (2001)

Bibliographic reference	**Mwinga,A., Hosp,M., et al.** **AIDS. 1998 12 (18) 2447-57.Twice weekly tuberculosis preventive therapy in HIV infection in Zambia** **Quigley,M.A., Mwinga,A., et al.AIDS. 2001 15 (2) 215-22.Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults.**
Study type	RCT
Study quality	Population does not exactly match population of interest: • Patients without a positive TST[1] were included in the study (subgroup data available) Intervention matches the intervention of interest Randomisation: an appropriate method was used; computerised block randomisation. Allocation was most likely adequately concealed providing sealed enveloped were opaque (unclear) Baseline characteristics were similar with respect to all characteristics, any differences reported were non-significant. Comparison groups received the same care apart from the interventions studied. Blinding: Participants and clinicians were kept blind to treatment allocation. Investigators were blind to treatment groups however blinding to other confounding factors was unclear. The groups were comparable for treatment completion in each group. However the amount for which no outcome data was available was greater in the rifampicin and pyrazinamide treatment arm. The study uses a precise definition of outcome, however a valid and reliable method was not always used to determine the outcome: for example the diagnosis of TB may be made on the basis of a positive response to TB treatment following the failure of antibiotic treatment. This is unlikely to be highly specific.
Number of patients	Subgroup (TST[1] ≥ 5 mm) = 161 Placebo group = 60 Isoniazid group = 52 Rifampicin and Pyrazinamide group = 49 From the total number enrolled in the study (n= 1080) The following did not complete treatment: Placebo group = 10 Isoniazid group = 8 Rifampicin and Pyrazinamide group = 9 The following had no outcome data available:

<table>
<tr><td>Bibliographic reference</td><td>Mwinga,A., Hosp,M., et al.
AIDS. 1998 12 (18) 2447-57.Twice weekly tuberculosis preventive therapy in HIV infection in Zambia
Quigley,M.A., Mwinga,A., et al.AIDS. 2001 15 (2) 215-22.Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults.</td></tr>
<tr><td></td><td>Placebo group = 38
Isoniazid group = 34
Rifampicin and Pyrazinamide group = 55</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
HIV positive
Over 15 years old
Excluded
Previous history of treatment for TB
Abnormal liver function tests
Evidence of TB (pulmonary or extra-pulmonary)
Pregnant
Unable to attend study clinic
Baseline characteristics
<table>
<tr><td></td><td>Placebo no. (%)</td><td>Isoniazid no. (%)</td><td>Rifampicin and Pyrazinamide no. (%)</td></tr>
<tr><td>Sex m/f</td><td>194/156</td><td>194/158</td><td>208/143</td></tr>
<tr><td>Age mean (SD)</td><td>30 (8.0)</td><td>30 (7.9)</td><td>31 (8.6)</td></tr>
<tr><td>Tuberculin skin test ≥ 5 mm</td><td>60 (27)</td><td>52 (23)</td><td>49 (22)</td></tr>
<tr><td>Visible BCG scar</td><td>281 (81)</td><td>278 (80)</td><td>268 (77)</td></tr>
<tr><td>Lymphocyte count (x109/l) <2</td><td>100 (36)</td><td>116 (39)</td><td>120 (42)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Patients = 101
• 3 months of rifampicin 600 mg, twice a week
• And 3 months of pyrazinamide 3500 mg, twice a week =49
Or
• 6 months of isoniazid 900 mg twice a week = 52
All regimens self-administered</td></tr>
</table>

Bibliographic reference	**Mwinga,A., Hosp,M., et al.** **AIDS. 1998 12 (18) 2447-57.Twice weekly tuberculosis preventive therapy in HIV infection in Zambia** **Quigley,M.A., Mwinga,A., et al.AIDS. 2001 15 (2) 215-22.Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults.**
Comparison	Patients = 60 • 3 months of twice weekly placebo to match the rifampicin group or 6 months of a twice weekly placebo to match the isoniazid group = 60
Length of follow up	Median follow up 1.8 years, maximum follow up 7 years.
Location	Zambia
Outcomes measures and effect size	Incidence of TB number of cases; total person years (rate per 100 person-years) • Placebo group: 9 of 98 (9.18) • Isoniazid group: 2 of 88 (2.27) • Rifampicin and pyrazinamide: 2 of 74 (2.70) Mortality: cases; total person years (rate per 100 person-years) • Placebo group: 4 of 114 (3.51) • Isoniazid group: 7 of 93 (7.53) • Rifampicin and pyrazinamide: 9 of 78 (11.54)
Source of funding	Supported by the World Health Organisation and the UK Department for International Development with additional support from the Beit Memorial Trust.
Comments	
Abbreviations: [1]TST: Tuberculin Skin Test	

A.2.9 Gupta,D.K., Kumar,R., Nath,N. (1993)

Bibliographic reference	**Gupta,D.K., Kumar,R., Nath,N. (1993) Chemoprophylaxis in high risk children-analysis of 8 years' follow up: Preliminary report Indian Journal of Tuberculosis. 40 (3) 125-27.**
Study type	RCT
Study quality	Population matches the population of interest Intervention matches the intervention of interest; control group was not given placebo however the other treatment arms can provide comparison. Unclear if an appropriate method of randomisation was used Unclear if there was adequate concealment of allocation Groups were comparable at baseline in regard to age, socio-economic status and sex. Comparison group received the same care apart from the intervention studied Blinding: neither participants nor clinicians were kept blind to treatment allocation. Investigators were neither blinded to the treatment allocation of the patient or to any potential confounding factors. Unclear if groups were followed up for an equal length of time. It was presumed that loss to follow up and poor adherence would affect each group equally and therefore no adjustments for these important factors were made. Unclear if groups were comparable for treatment completion, or the number that did not complete treatment. Unclear if groups were comparable for availability of outcome data, or the number for which there was no outcome data available. The study had an appropriate length of follow up. Unclear if the study had a precise definition of outcome or whether a valid and reliable method was used to measure outcome.
Number of patients	Enrolled= 415 children • “control” group= 85 • isoniazid group = 82 • rifampicin and isoniazid, one month group = 83 • rifampicin and isoniazid, three months group = 85 • isoniazid, rifampicin and pyrazinamide group = 80
Patient characteristics	Inclusion Age 5-15 years TST positive (≥ 10 mm) Exclusion Children with BCG scar Lymphadenopathy Prolonged respiratory problems

<table>
<tr><td>Bibliographic reference</td><td>Gupta,D.K., Kumar,R., Nath,N. (1993) Chemoprophylaxis in high risk children-analysis of 8 years' follow up: Preliminary report Indian Journal of Tuberculosis. 40 (3) 125-27.</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><th></th><th>No treatment group</th><th>Isoniazid group</th><th>Isoniazid and rifampicin group, 1 month</th><th>Isoniazid group and rifampicin group, 3 months</th><th>Isoniazid, rifampicin and pyrazinamide group</th></tr>
<tr><td>Sex m/f</td><td>46/39</td><td>42/40</td><td>42/41</td><td>43/42</td><td>42/38</td></tr>
<tr><td>Age 5-10</td><td>42</td><td>40</td><td>41</td><td>42</td><td>40</td></tr>
<tr><td>Age 11-15</td><td>43</td><td>42</td><td>42</td><td>43</td><td>40</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Isoniazid = 82
• Daily 15 mg/kg bodyweight to a maximum of 300 mg daily, for 3 months
Rifampicin and isoniazid = 83
• Daily isoniazid 15 mg/kg bodyweight to a maximum of 300 mg daily, for 1 month
• Daily rifampicin 10 mg/kg bodyweight, for 1 month
Rifampicin and isoniazid = 85
• Daily isoniazid 15 mg/kg bodyweight to a maximum of 300 mg daily, for 3 months
• Daily rifampicin 10 mg/kg bodyweight, for 3 months
Rifampicin, pyrazinamide and isoniazid = 80
• Daily isoniazid 15 mg/kg bodyweight to a maximum of 300 mg daily, for 1 month
• Daily rifampicin 10 mg/kg bodyweight, for 1 month
• Daily pyrazinamide 30 mg/kg bodyweight for 1 month</td></tr>
<tr><td>Comparison</td><td>“Control” group= 85
• not given any treatment</td></tr>
<tr><td>Length of follow up</td><td>8 years follow up</td></tr>
<tr><td>Location</td><td>India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Incidence of active TB (cases)
• Group receiving no treatment= 17 of 85
• Group receiving isoniazid alone= 10 of 82
• Group receiving isoniazid and rifampicin for 1 month = 9 of 83</td></tr>
</table>

Bibliographic reference	**Gupta,D.K., Kumar,R., Nath,N. (1993) Chemoprophylaxis in high risk children-analysis of 8 years' follow up: Preliminary report Indian Journal of Tuberculosis. 40 (3) 125-27.**
	• Group receiving isoniazid and rifampicin for 3 months = 4 of 85 • Group receiving isoniazid, pyrazinamide and rifampicin for 1 month = 0 of 80
Source of funding	Unclear
Comments	This paper was a preliminary report, unable to find full paper if one exists.

A.2.10 Hawken M.P., Meme H.K., et al. (1997)

Bibliographic reference	Hawken,M.P., Meme,H.K., et al. 1997. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. AIDS. 11 (7) 875-82.
Study type	RCT
Study quality	Population matches population of interest • TST negative patients were included in the study however subgroup analysis was possible Intervention matches intervention of interest Randomisation: an appropriate method of randomisation was used; computerised block randomisation. Allocation was adequately concealed. Groups were not comparable at baseline; there were differences in sex, generalized lymphadenopathy and history of herpes zoster infection. All other characteristics were similar. Groups were recruited at three different clinical sites where care may have differed. Blinding: participants and clinicians were kept blind to treatment allocation. Investigators were blind to treatment allocation although it is unclear if they were blinded to other confounding factors. Follow up was analysed to adjust for differences between lengths of follow up between patients. Unclear how many participants did not complete treatment in each treatment group Unclear how many participants there were in each group for which no outcome data was available The study had an appropriate length of follow up There was a precise definition of outcome and a valid and reliable method was used to determine the outcome.
Number of patients	Randomized = 684 participants • Isoniazid group = 342 • Placebo group = 342 Subgroup (TST[1] positive) • Isoniazid group = 67 • Placebo group = 69
Patient characteristics	Inclusion HIV-1 positive Age 14-65 years Resident in Nairobi Exclusion Past history of TB

<table>
<tr><td></td><td>Suspicion of current TB (symptomatic)
Adenopathy greater than 2cm in diameter
Abnormal liver enzymes
Life-threatening intercurrent illness
Pregnant
Baseline Characteristics
<table>
<tr><td></td><td>Isoniazid (n= 342)</td><td>Placebo (n= 342)</td></tr>
<tr><td>Mean age (years)</td><td>31.1</td><td>31.1</td></tr>
<tr><td>Female</td><td>217</td><td>196</td></tr>
<tr><td>Study Clinic
Group 1
Group 2
Group 3</td><td>78
159
114</td><td>77
149
116</td></tr>
<tr><td>BCG scar visible</td><td>256</td><td>248</td></tr>
<tr><td>Generalised lymphadenopathy</td><td>40</td><td>26</td></tr>
<tr><td>Herpes zoster</td><td>103</td><td>80</td></tr>
<tr><td>TST[1] positive (≥ 5 mm)</td><td>67</td><td>69</td></tr>
<tr><td>Total lymphocyte count (x109/l)</td><td>5.5 (2.7-10.8)</td><td>5.5 (2.6-17.4)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Isoniazid group = 342 participants
• 300 mg daily, for 6 months

Self-administered</td></tr>
<tr><td>Comparison</td><td>Placebo group = 342 participants
• Placebo, for 6 months

Self-administered</td></tr>
<tr><td>Length of follow up</td><td>Median length of follow up: (range)
• isoniazid group: 1.83 (0-3.41)
• placebo group:1.82 (0-3.37)</td></tr>
<tr><td>Location</td><td>Nairobi, Kenya</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Incidence of active tuberculosis:
In TST[1] positive subgroup, given per 100 person years of observation (95 % confidence interval)</td></tr>
</table>

	• Isoniazid Group: 5.59 (2.25-11.51) • Placebo group: 8.03 (3.85-14.77) • Adjusted risk ratio was 0.60 (95% CI, 0.23-1.60) • i.e. not significant
	Mortality In TST[1] positive subgroup, given as adjusted mortality risk ratio for Isoniazid versus placebo (95 % confidence interval) • Risk ratio was 0.33 (95% CI, 0.09-1.23) • i.e. not significant
Source of funding	The British Medical Research Council and the Overseas Development Administration
Comments	
[1]TST- tuberculin Skin Test	

A.2.11 Gordin,F., Chaisson,R.E., et al. (2000)

Bibliographic reference	**Gordin,F., Chaisson,R.E., et al. (2000). Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health. JAMA 283 (11) 1445-50.**
Study type	RCT
Study qualty	Population matches the population of interest • A “historic” positive PPD[1] test was also included Intervention matches the intervention of interest Unclear if an appropriate method of randomization was used Unclear if adequate concealment of allocation took place Groups were comparable at baseline Comparison groups did not always receive the same care apart from the intervention under study. Length of drug regimen could vary depending on whether the patient was perceived to take their drug continuously or not. Patients were taken from different sites in different countries however analysis was stratified by geography. Blinding: Neither patients nor participants were blinded to treatment allocation. Investigators were not blinded to allocation and any possible confounding factors. Follow up: groups were followed up for a similar length of time and analysis was adjusted to allow for any differences. Significantly more patients in the isoniazid group completed treatment than in the rifampicin and pyrazinamide group Outcome data was available for all patients taking part, including those that did not complete therapy. The study had an appropriate length of follow up; loss to follow up was similar in both treatment groups. A precise definition of outcome was stated and a valid and reliable method was used to determine the outcome. Treatment was usually self-administered
Number of patients	1583 patients randomized • Rifampicin and pyrazinamide group = 791 • Isoniazid group = 792
Patient characteristics	Included Aged 13 years or older Diagnosed with HIV infection PPD[1] positive (≥ 5 mm) Haemoglobin > 80 g/L Neutrophil count > 0.75 x 109/L Platelet count > 50 x 109/L Total bilirubin of 42.7 µmol/L or less

<table>
<tr><td>Bibliographic reference</td><td>Gordin,F., Chaisson,R.E., et al. (2000). Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health. JAMA 283 (11) 1445-50.</td></tr>
<tr><td></td><td>Aspartate aminotransferase and alkaline phosphatase levels < 5 times normal
Excluded
Clinical or radiological evidence of active TB
Current treatment with fluroquinolones or other active agents against TB
History of more than 2 months of continuous treatment against TB
Intolerance to medications
Acute hepatitis or peripheral neuropathy
Pregnancy
Baseline characteristics
<table>
<tr><td></td><td>Rifampicin and pyrazinamide</td><td>Isoniazid</td></tr>
<tr><td>Women (%)</td><td>29.2</td><td>27.8</td></tr>
<tr><td>Mean age, y</td><td>36.9</td><td>37.7</td></tr>
<tr><td>History of injection drug use</td><td>33.2</td><td>37.6</td></tr>
<tr><td>Median cell count CD4 (x 109/L)</td><td>454</td><td>427</td></tr>
<tr><td>PPD induration
5-9 mm
≥ 10 mm
Historical positive</td><td>11.8
45.0
43.2</td><td>10.7
46.0
43.3</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Rifampicin and pyrazinamide group
Bodyweight < 50 kg
• Rifampicin: 450 mg, daily for 2 months
• Pyrazinamide: 20 mg/kg, daily for 2 months
Bodyweight ≥ 50 kg
• Rifampicin 600 mg, daily for 2 months
• Pyrazinamide: 20 mg/kg, daily for 2 months
Patients who did not receive the drugs continuously were encouraged to complete a 60 day course.
Treatment was usually self-administered</td></tr>
<tr><td>Comparison</td><td>Isoniazid group
• Isoniazid 300 mg, daily for 12 months
• Pyridoxine hydrochloride 50 mg, daily for 12 months</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Gordin,F., Chaisson,R.E., et al. (2000). Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health. JAMA 283 (11) 1445-50.</td></tr>
<tr><td></td><td>Treatment was usually self-administered</td></tr>
<tr><td>Length of follow up</td><td>Rifampicin and pyrazinamide group: mean duration 37.2 months, maximum 5 years
Isoniazid group: mean duration 36.8 months, maximum 5 years</td></tr>
<tr><td>Location</td><td>United States, Mexico, Haiti, Brazil, Zambia</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Incidence of tuberculosis
Confirmed tuberculosis defined as a positive M tuberculosis culture from any source. Probable: Clinical evidence based diagnosis.
<table>
<tr><td></td><td>Rifampicin and pyrazinamide (cases)</td><td>Rate per 100 person-years</td><td>Isoniazid (cases)</td><td>Rate per 100 person-years</td><td>Unadjusted RR (95% CI²)</td><td>P value</td><td>Adjusted RR (95% CI²)</td><td>P value</td></tr>
<tr><td>TB confirmed</td><td>19</td><td>0.8</td><td>26</td><td>1.1</td><td>0.72 (0.40-1.31)</td><td>0.28</td><td>0.67 (0.36-1.24)</td><td>0.20</td></tr>
<tr><td>TB confirmed or probable</td><td>28</td><td>1.2</td><td>29</td><td>1.2</td><td>0.96 (0.57-1.61)</td><td>0.87</td><td>0.95 (0.56-1.61)</td><td>0.83</td></tr>
</table></td></tr>
<tr><td></td><td>Mortality
Incidence of death
<table>
<tr><td></td><td>Rifampicin and pyrazinamide (cases)</td><td>Rate per 100 person-years</td><td>Isoniazid (cases)</td><td>Rate per 100 person-years</td><td>Unadjusted RR (95% CI²)</td><td>P value</td><td>Adjusted RR (95% CI²)</td><td>P value</td></tr>
<tr><td>Death</td><td>139</td><td>5.7</td><td>159</td><td>6.5</td><td>0.87 (0.69-1.09)</td><td>0.23</td><td>0.87 (0.69-1.11)</td><td>0.27</td></tr>
</table></td></tr>
<tr><td></td><td>Adverse events
Adverse events were considered reportable if they were classified as at least grade 4 (potentially life threatening) or above on a scale of 1–5 (with grade 5 denoting death) and not considered due to progression of HIV disease, or if they led to discontinuation of the study drug regardless of severity level.
<table>
<tr><td>Adverse Event</td><td>Rifampicin and Pyrazinamide (n=791) (%)</td><td>Isoniazid (n=792) (%)</td><td>P value</td></tr>
<tr><td>≥1 adverse event</td><td>12.3</td><td>10.5</td><td>0.27</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Gordin,F., Chaisson,R.E., et al. (2000). Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health. JAMA 283 (11) 1445-50.**			
	≥1 adverse event grade 4 or higher	5.6	7.3	0.18
	Study drug permanently discontinued	9.5	6.1	0.01
	Abnormal liver function tests	1.4	3.3	0.02
	Hepatitis	0.8	0.4	0.34
	Peripheral neuropathy	0.1	0.5	0.37
	Skin rash	1.4	0.6	0.14
	Neutropenia	0.8	0.4	0.34
	Nausea and/or vomiting	1.9	0.1	<0.001
	Narcotic withdrawal	1.5	0.0	<0.001
Source of funding	National Institute of Allergy and Infectious Diseases and Centers for Disease Control and Prevention			
Comments				

[1]PPD- Purified Protein Derivative
[2]CI- Confidence Interval

A.2.12 Chan,P.C., Yang,C.H., et al. (2012)

Bibliographic reference	**Chan,P.C., Yang,C.H., et al. Latent tuberculosis infection treatment for prison inmates: a randomised controlled trial International Journal of Tuberculosis & Lung Disease. 2012 16 (5) 633-38.**
Study type	RCT
Study quality	Population matches population of interest Intervention matches intervention of interest Randomisation: an appropriate method of randomisation was used, computerised randomisation sequence used. Allocation: Unclear if there was concealment of allocation Groups were comparable at baseline Groups received the same care apart from the intervention studied Blinding: Neither participants nor clinicians were kept blind to treatment allocation. Investigators were not kept blind to participant's treatment allocation or other confounding factors. Follow up: all groups were followed up for an equal length of time, loss to follow up was similar. Data was available for all participants enrolled. The length of follow up was appropriate for the outcome under study (adverse events). Outcome: the study used a precise definition of outcome and a valid and reliable method was used to determine outcome.
Number of patients	373 participants Rifampicin group = 190 Insoniazid group= 183
Patient characteristics	Inclusion TST[1] positive (≥ 10 mm) IGRA[2] positive Prison population, Taiwan Exclusion Active TB Concomitant medications likely to cause potential drug interactions Elevated glutamic pyruvic transaminase levels ≥ 3 times normal values Bilirubin levels ≥ 2 times the upper limit of normal Platelet count < 150 k/mm^3 at baseline Prison term < 6 months

<table>
<tr><td>Bibliographic reference</td><td>Chan,P.C., Yang,C.H., et al. Latent tuberculosis infection treatment for prison inmates: a randomised controlled trial International Journal of Tuberculosis & Lung Disease. 2012 16 (5) 633-38.</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><td></td><td>Rifampicin n= 190</td><td>Isoniazid, n= 183</td></tr>
<tr><td>Age, years
18-24
25-34
35-44
45-64
≥65</td><td>4
42
73
64
7</td><td>10
47
59
60
7</td></tr>
<tr><td>Prison term, years
<13
≥ 13</td><td>107
83</td><td>114
69</td></tr>
<tr><td>TST[1] size, mm
10-14
15-19
≥20</td><td>60
98
32</td><td>55
102
26</td></tr>
<tr><td>Chronic hepatitis infection
HBsAg positive
Anti-HCV positive</td><td>28
42</td><td>24
38</td></tr>
<tr><td>Taking other medications</td><td>35</td><td>40</td></tr>
<tr><td>Diabetes mellitus</td><td>4</td><td>7</td></tr>
<tr><td>Medical problems other than diabetes</td><td>39</td><td>44</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Rifampicin group= 190 participants
• Rifampicin: 10 mg/kg (up to 600 mg/d), for 4 months
Treatment administered via directly observed therapy (DOT)</td></tr>
<tr><td>Comparison</td><td>Isoniazid group = 183 participants
• Isoniazid: 5 mg/kg (up to 300 mg/d), for 6 months
Treatment administered via directly observed therapy (DOT)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Chan,P.C., Yang,C.H., et al. Latent tuberculosis infection treatment for prison inmates: a randomised controlled trial International Journal of Tuberculosis & Lung Disease. 2012 16 (5) 633-38.</td></tr>
<tr><td>Length of follow up</td><td>1 month following treatment</td></tr>
<tr><td>Location</td><td>Prison near Taipei, Taiwan</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Incidence of adverse events
Primary outcome defined here as any adverse event that led to permanent discontinuation of treatment, as per pre specified criteria. Secondary outcome defined as any cause that led to permanent discontinuation of treatment.
Odds ratio was adjusted for the effects of HBsAg, anti-HCV, age ≥ 35 years and prison term > 2 years using logistic regression models.
<table>
<tr><td>Outcome</td><td>Rifampicin group n (%)</td><td>Isoniazid group N (%)</td><td>P value</td><td>Unadjusted odds ratio (CI[3] 95%)</td><td>Adjusted odds ratio (CI[3] 95%)</td></tr>
<tr><td>Primary outcome</td><td>4 (2)</td><td>22 (12)</td><td>< 0.001</td><td>0.16 (0.05-0.47)</td><td>0.15 (0.05- 0.46)</td></tr>
<tr><td>Secondary outcome</td><td>27 (14)</td><td>41 (22)</td><td>0.041</td><td>0.57 (0.34-0.98)</td><td>0.56 (0.32-0.97)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Taiwan CDC Grant DOH97-DC-1502</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">[1]TST- tuberculin skin test
[2]IGRA- Interferon gamma release assays
[3]CI- Confidence interval</td></tr>
</table>

A.2.13 Leung,C.C., Law,W.S., et al. (2003)

Bibliographic reference	**Leung,C.C., Law,W.S., et al. (2003) Initial experience on rifampin and pyrazinamide vs isoniazid in the treatment of latent tuberculosis infection among patients with silicosis in Hong Kong. Chest 124 (6) 2112-18.**
Study type	RCT
Study quality	Population matches population of interest Intervention matches intervention of interest Randomisation: An appropriate method of randomisation was used, using a random number table. Allocation: Unclear whether allocation was concealed. Groups were comparable at baseline Groups received the same care apart from the intervention under study. Blinding: neither participants nor clinicians were kept blind to treatment allocation. Investigators were not kept blind to patients treatment allocation or any other major confounding factors. Attrition: more participants did not complete treatment in the rifampicin and pyrazinamide group. The groups were comparable in respect to availability of outcome data. Treatment completion rates were relatively low in both study arms. There was a low degree of acceptance on to the RCT by the eligible participants identified. Unclear if there were significant differences between the characteristics of those that accepted and those that didn't. The study had an appropriate length of follow up. Unclear if differences of loss to follow up between groups, no adjustments made. There was a precise definition of outcome and a valid and reliable method was used to determine the outcome.
Number of patients	Randomized = 77 participants Rifampicin and pyrazinamide group = 40 Isoniazid group = 37
Patient characteristics	Inclusion Patients with silicosis PPD[1] positive (≥ 8 mm) Radiographic profusion of small opacities of category ≥ 1 (International Labor Office) Exclusion History of TB Suspicion of current TB History of having received >2 months of TB treatment Intolerance to study medications Poor general condition Gouty arthritis Cirrhosis

<table>
<tr><td>Bibliographic reference</td><td>Leung,C.C., Law,W.S., et al. (2003) Initial experience on rifampin and pyrazinamide vs isoniazid in the treatment of latent tuberculosis infection among patients with silicosis in Hong Kong. Chest 124 (6) 2112-18.</td></tr>
<tr><td></td><td>Symptomatic hepatitis
Liver dysfunction ALT² levels > 1.5 times upper limit of normal
Baseline characteristics

<table>
<tr><td></td><td>Rifampicin and pyrazinamide
N = 40</td><td>Isoniazid
N = 36</td><td></td></tr>
<tr><td>Age, y</td><td>61.6</td><td>57.6</td><td>0.06</td></tr>
<tr><td>Male</td><td>100 %</td><td>97 %</td><td>0.46</td></tr>
<tr><td>Progressive massive fibrosis</td><td>27.5 %</td><td>19.4 %</td><td>0.41</td></tr>
<tr><td>History of BCG vaccine</td><td>5.0 %</td><td>13.9 %</td><td>0.25</td></tr>
<tr><td>Tuberculin test, mm</td><td>16.7</td><td>15.4</td><td>0.14</td></tr>
<tr><td>Habitual alcohol drinker</td><td>17.5 %</td><td>11.1 %</td><td>0.52</td></tr>
<tr><td>HBsAg carrier</td><td>12.5 %</td><td>27.8 %</td><td>0.15</td></tr>
<tr><td>Significant comorbidity</td><td>5.0 %</td><td>19.4 %</td><td>0.08</td></tr>
<tr><td>Other medications</td><td>12.5 %</td><td>30.6 %</td><td>0.09</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Rifampicin and pyrazinamide group:
For those weighing < 50 kg
• Rifampicin: 450 mg daily, for 2 months
• Pyrazinamide: 1000 mg daily, for 2 months
For those weighing ≥ 50 kg
• Rifampicin: 600 mg daily, for 2 months
• Pyrazinamide: 1500 mg daily, for 2 months
Treatment as an outpatient, first dose in clinic</td></tr>
<tr><td>Comparison</td><td>Isoniazid group:
• Isoniazid: 300 mg daily, for 6 months
Treatment as an outpatient, first dose in clinic</td></tr>
<tr><td>Length of follow up</td><td>Up to 10 years</td></tr>
</table>

Bibliographic reference	**Leung,C.C., Law,W.S., et al. (2003) Initial experience on rifampin and pyrazinamide vs isoniazid in the treatment of latent tuberculosis infection among patients with silicosis in Hong Kong. Chest 124 (6) 2112-18.**
Location	Hong Kong, China
Outcomes measures and effect size	Significant hepatitis: defined by peak ALT² levels > 5 x the upper limit of normal. • rifampicin and pyrazinamide group: 14 of 40 participants • isoniazid group: 1 of 36 participants • p value = 0.00 • i.e. significant difference
	Skin rash: • rifampicin and pyrazinamide group: 4 of 40 participants • isoniazid group: 2 of 36 participants • p value = 0.67 • i.e. not significant difference
	Itchiness: • rifampicin and pyrazinamide group: 13 of 40 participants • isoniazid group: 6 of 36 participants • p value = 0.18 • i.e. not significant difference
	GI upset • rifampicin and pyrazinamide group: 8 of 40 participants • isoniazid group: 6 of 36 participants • p value = 0.78 • i.e. not significant difference
	Joint Pain • rifampicin and pyrazinamide group: 0 of 40 participants • isoniazid group: 1 of 36 participants • p value = 0.47 • i.e. not significant difference
	Treatment completion: • rifampicin and pyrazinamide group: 55 % of participants • isoniazid group: 63.9 % of participants

Bibliographic reference	**Leung,C.C., Law,W.S., et al. (2003) Initial experience on rifampin and pyrazinamide vs isoniazid in the treatment of latent tuberculosis infection among patients with silicosis in Hong Kong. Chest 124 (6) 2112-18.**
	• p value = 0.43 • i.e. not significant difference
	Adherence: defined as the percentage of actually received among the expected number of administered doses: • rifampicin and pyrazinamide group: 72 % of participants • isoniazid group: 72.9 % of participants • p value = 0.92 • i.e. not significant difference
Source of funding	Unclear
Comments	Data reporting was not very clear regarding outcome of hepatitis. Results were reported in percentages and only for one of the definitions (ALT[2] levels > 5 x upper limit of normal). The other definition of significant hepatitis was raised ALT levels with symptoms of hepatitis, data was only provided for the rifampicin and pyrazinamide group in regard to this definition. I used the definition from which a head to head comparison could be achieved. All other adverse effects data was presented as percentages from which I calculated the actual number of cases.
[1]PPD- purified protein positive [2]ALT- alanine transaminase	

A.2.14 Martinson,N.A., Barnes,G.L., et al.(2011)

Bibliographic reference	**Martinson,N.A., Barnes,G.L., et al. (2011) New regimens to prevent tuberculosis in adults with HIV infection. New England Journal of Medicine. 365 (1) 11-20.**
Study type	RCT
Study quality	The population matches the population of interest The intervention matches the intervention of interest Randomization: An appropriate method of computerised randomization was used. Allocation was adequately concealed. Groups were comparable at baseline. Comparison groups did not receive the same care apart from intervention under study. Treatment in the rifampicin and isoniazid group and the rifapentine and isoniazid group were directly observed in clinic. Treatment in the 6 month isoniazid group and continuous isoniazid group was self-administered. Scheduled visits occurred once weekly for the rifapentine and isoniazid group, twice weekly for the rifampicin and isoniazid group and every 2 weeks for the first 6 months of the isoniazid alone groups followed by every 6 months for the continuous isoniazid group. Blinding: neither participants nor clinicians were kept blind to treatment allocation. Investigators were not blinded to either treatment allocation or any confounding factors. Follow up: was an appropriate length and all groups were followed up for an equal length of time and analysis was adjusted to allow for differences. The groups were comparable for treatment completion and with respect to the availability of outcome data. A precise definition of outcome was used and a valid and reliable method of determining the outcome was used. The continuous isoniazid group had half as many participants as the other groups.
Number of patients	1150 randomized • rifapentine and isoniazid group = 329 • rifampicin and isoniazid group = 329 • isoniazid for 6 months = 328 • continuous isoniazid = 164
Patient characteristics	Included HIV infected TST[1] positive (≥ 5 mm) Age 18 or older Excluded Pregnant or breast feeding Active tuberculosis

<table>
<tr><td>Bibliographic reference</td><td>Martinson,N.A., Barnes,G.L., et al. (2011) New regimens to prevent tuberculosis in adults with HIV infection. New England Journal of Medicine. 365 (1) 11-20.</td></tr>
<tr><td></td><td>Ever received treatment for TB > 2 months
Receiving antiretroviral therapy
CD4 cell count < 200 per mm³
Baseline characteristics
<table>
<tr><th></th><th>Rifapentine with isoniazid, 12 weeks n= 328</th><th>Rifampicin with isoniazid twice weekly, 12 weeks n= 329</th><th>Isoniazid daily for ≤ 6 years n= 164</th><th>Isoniazid daily for 6 months n = 327</th></tr>
<tr><td>Female (%)</td><td>277</td><td>267</td><td>139</td><td>273</td></tr>
<tr><td>Age yr, median</td><td>30.3</td><td>30.5</td><td>30.2</td><td>30.4</td></tr>
<tr><td>TST¹ induration, (mm), median</td><td>14.5</td><td>15.0</td><td>15.0</td><td>15.0</td></tr>
<tr><td>CD4 count, cells/mm³, median</td><td>471</td><td>498</td><td>476</td><td>490</td></tr>
<tr><td>Viral load-log10copies/ml, median</td><td>4.3</td><td>4.0</td><td>4.2</td><td>4.2</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Rifapentine and isoniazid group
• rifapentine: 900 mg weekly, for 12 weeks
• isoniazid: 900 mg weekly, for 12 weeks
• pyridoxine: 25 mg weekly, for 12 weeks
• Treatment was directly observed
Rifampicin and isoniazid group
• rifampicin: 600 mg twice weekly, for 12 weeks
• isoniazid: 900 mg, twice weekly, for 12 weeks
• pyridoxine: 25 mg twice weekly, for 12 weeks
• Treatment was directly observed
Isoniazid, continuous group
• isoniazid: 300 mg daily for the duration of the study (≤6 years)
• pyridoxine: 25 mg daily, for the duration of the study
• Treatment was self-administered</td></tr>
</table>

Bibliographic reference	**Martinson,N.A., Barnes,G.L., et al. (2011) New regimens to prevent tuberculosis in adults with HIV infection. New England Journal of Medicine. 365 (1) 11-20.**
Comparison	Isoniazid, 6 month group • isoniazid: 300mg daily, for 6 months • pyridoxine: 25 mg daily, for 6 months • Treatment was self-administered
Length of follow up	Minimum of 3 years, 6 years maximum
Location	Soweto, South Africa
Outcomes measures and effect size	Incidence of tuberculosis Defined as clinical presentation consistent with tuberculosis and response to anti-tuberculosis therapy. Incident disease was categorised as: • “confirmed” if one or more cultures were positive for tuberculosis and clinical signs and symptoms. • “probable” if one sputum smear or one biopsy specimen was positive for acid fast bacilli and clinical signs and symptoms. • “possible” clinical signs and symptoms with response to TB treatment. All cases: • rifapentine and isoniazid group = 24 of 328 • rifampicin and isoniazid group = 24 of 329 • continuous isoniazid = 8 of 164 • isoniazid for 6 months = 22 of 327 Culture confirmed cases • rifapentine and isoniazid group = 21 of 328 • rifampicin and isoniazid group = 18 of 329 • continuous isoniazid = 5 of 164 • isoniazid for 6 months = 18 of 327 Incidence rate of all cases per 100 person-years • rifapentine and isoniazid group = 1.4 • rifampicin and isoniazid group = 1.3 • continuous isoniazid = 1.4 • isoniazid for 6 months = 1.9

Bibliographic reference	**Martinson,N.A., Barnes,G.L., et al. (2011) New regimens to prevent tuberculosis in adults with HIV infection. New England Journal of Medicine. 365 (1) 11-20.**
	Crude incidence-rate ration (95% CI) • rifapentine and isoniazid group = 1.05 (0.56-1.97), p value = 0.87 • i.e. not significant • rifampicin and isoniazid group = 1.02 (0.55- 1.91), p value = 0.94 • i.e. not significant • continuous isoniazid = 0.74 (0.29-1.73), p value = 0.48 • i.e. not significant • isoniazid for 6 months = reference 1.0
	Mortality Number of deaths (cases) • rifapentine and isoniazid group = 17 of 328 • rifampicin and isoniazid group = 16 of 329 • continuous isoniazid = 8 of 164 • isoniazid for 6 months = 25 of 327 Incidence rate per 100 person-year • rifapentine and isoniazid group = 1.4 • rifampicin and isoniazid group = 1.3 • continuous isoniazid = 1.4 • isoniazid for 6 months = 2.1 Crude incidence-rate ratio (95% CI) • rifapentine and isoniazid group = 0.66 (0.33-1.26), p value 0.18 • i.e. not significant • rifampicin and isoniazid group = 0.59 (0.30-1.16), p value 0.10 • i.e. not significant • continuous isoniazid = 0.66 (0.26-1.50), p value 0.31 • i.e. not significant • isoniazid for 6 months = reference 1.0

Bibliographic reference	**Martinson,N.A., Barnes,G.L., et al. (2011) New regimens to prevent tuberculosis in adults with HIV infection. New England Journal of Medicine. 365 (1) 11-20.**
	Adverse events Defined as Grade 3 or 4 according to the Division of AIDS, toxicity table. Grade 3 toxic effect • rifapentine and isoniazid group = 17 of 328 • rifampicin and isoniazid group = 15 of 329 • continuous isoniazid = 35 of 164 • isoniazid for 6 months = 17 of 327 Grade 4 toxic effect • rifapentine and isoniazid group = 4 of 328 • rifampicin and isoniazid group = 9 of 329 • continuous isoniazid = 18 of 164 • isoniazid for 6 months = 14 of 327 Hepatoxicity • rifapentine and isoniazid group = 1.5 % • rifampicin and isoniazid group = 2.4 % • continuous isoniazid = 28.0 % • P value <0.001 • i.e.significant • isoniazid for 6 months = 5.5 %
Source of funding	National Institue of Allergy and Infectious Diseases, National Institues of Health Fogarty International Center, US Agency for International Development Dr Martinson reports receiving lecture fees from Alere, no other potential conflict of interest.
Comments	
[1]TST- tuberculin Skin Test	

A.2.15 Matteelli,A., Olliaro,P., et al. (1999)

Bibliographic reference	**Matteelli,A., Olliaro,P., et al. (1999). Tolerability of twice-weekly rifabutin-isoniazid combinations versus daily isoniazid for latent tuberculosis in HIV-infected subjects: a pilot study. International Journal of Tuberculosis & Lung Disease. 3 (11) 1043-46.**
Study type	RCT
Study quality	Intervention matches intervention of interest Population matches population of interest Randomisation: Unclear if an appropriate method of randomisation was used. Unclear if there was adequate concealment of allocation. Unclear if groups were comparable at baseline in regard to ALT values Groups received the same care apart from the intervention studied. Blinding: neither participants nor clinicians were blinded to the treatment allocations. Investigators were not blinded to treatment allocation or confounding factors Follow up: Groups were not followed up for the same length of time, length of follow up was appropriate. Unclear if groups were comparable with regard to systematic differences to those that did not complete treatment. Outcome data was available for all participants. There was not a precise definition of outcome for adverse events however adherence was defined. Unclear if a valid and reliable method was used to determine the outcome. This study was terminated early by its pharmaceutical sponsor prior to reaching the planned number of eligible subjects.
Number of patients	Randomized 44 participants • rifabutin 300 mg and isoniazid = 16 • rifabutin 600 mg and isoniazid = 14 • Isoniazid 300 mg alone = 14
Patient characteristics	Inclusion HIV infected Age 18 or older PPD skin test positive (≥5 mm) Exclusion Pregnant Suspected active tuberculosis CD4 cell count < 200/mm³ Haemoglobin < 9 g/dl Platelets < 75000/mm³

Bibliographic reference	**Matteelli,A., Olliaro,P., et al. (1999). Tolerability of twice-weekly rifabutin-isoniazid combinations versus daily isoniazid for latent tuberculosis in HIV-infected subjects: a pilot study. International Journal of Tuberculosis & Lung Disease. 3 (11) 1043-46.**
	Neutrophil counts <1000/mm³ Serum creatinine > 1.5 g/dl Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper normal value Baseline characteristics Mean age = 31.5 years in the rifabutin groups and 34 years in the isoniazid alone group Mean weight ranged from 70.8 in group C to 72.1 in group A CD cell counts averaged 500/mm³ in each group ALT values at baseline were abnormal in 50%, 29% and 43% of the subjects in the three groups respectively.
Intervention	Rifabutin 300 mg and isoniazid • rifabutin 300 mg twice weekly, for 3 months • isoniazid 750 mg twice weekly, for 3 months Rifabutin 600 mg and isoniazid • rifabutin 600 mg twice weekly, for 3 months • isoniazid 750 mg twice weekly, for 3 months
Comparison	Isoniazid alone • isoniazid 300 mg twice weekly, for 6 months
Length of follow up	Average follow up length (mean) Rifabutin 300 mg and isoniazid = 18 months Rifabutin 600 mg and isoniazid = 19 months Isoniazid alone = 17 months
Location	Italy
Outcomes measures and effect size	Treatment completion ≥ 80 % of the prescribed drug total amount taken • Rifabutin 300 mg and isoniazid = 13 of 16 • Rifabutin 600 mg and isoniazid = 13 of 14 • Isoniazid alone = 10 of 14

Bibliographic reference	**Matteelli,A., Olliaro,P., et al. (1999). Tolerability of twice-weekly rifabutin-isoniazid combinations versus daily isoniazid for latent tuberculosis in HIV-infected subjects: a pilot study. International Journal of Tuberculosis & Lung Disease. 3 (11) 1043-46.**
Source of funding	Farmitalia-Carlo Erba (Pharmacia-Upjohn)
Comments	
PPD[1]- Purified protein derivative	

A.2.16 Jimenez-Fuentes,M.A., de Souza-Galvao,M.L., et al. (2013)

Bibliographic reference	**Jimenez-Fuentes,M.A., de Souza-Galvao,M.L., et al. (2013) Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population.International Journal of Tuberculosis & Lung Disease 17 (3) 326-32.**
Study type	RCT
Study quality	Population matches population of interest. Intervention matches intervention of interest Randomisation: an appropriate method of randomisation was used and allocation was adequately concealed. Groups were not comparable at baseline in regard to sex and illegal immigrant distribution Groups received same care apart from the intervention studied Blinding: neither participants nor clinicians were kept blind to treatment allocation. Investigators were not kept blind to allocation or confounding factors. Follow up: all groups were followed up for an equal length of time. Loss to follow up was significant, only 64.4 % of population available for evaluation at 5 years. Length of follow up was appropriate. Groups were not comparable for treatment completion; almost twice as many patients in the isoniazid group did not complete treatment. Outcome data was available for all randomised participants A precise definition of outcome was available for adherence study and hepatotoxicity there was no real definition of outcome for TB outcome. Unclear if valid and reliable methods were used to determine onset of active TB.
Number of patients	590 participants randomized • 6 months of isoniazid = 294 • 3 months of rifampicin and isoniazid = 296
Patient characteristics	Inclusion TST[1] positive (>5 mm in contacts, > 15 mm in other cases) Immigrants from countries with a TB incidence of > 40 cases per 100000 Less than 5 years in Catalunya Aged 12-40 years Exclusion No evidence of active TB (on chest Xray) History of TB Known TST[1] positivity Pregnancy or lactation Hepatopathy

<table>
<tr><td>Bibliographic reference</td><td>Jimenez-Fuentes,M.A., de Souza-Galvao,M.L., et al. (2013) Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population.International Journal of Tuberculosis & Lung Disease 17 (3) 326-32.</td></tr>
<tr><td></td><td>HIV
Baseline characteristics
<table>
<tr><td></td><td>6H² n = 294</td><td>3RH³ n = 296</td><td>Total n = 590</td><td>P value</td></tr>
<tr><td>Age, years, “average”</td><td>26.5</td><td>25.7</td><td>26.1</td><td>0.06</td></tr>
<tr><td>Sex m/f</td><td>180/114</td><td>220/76</td><td>400/190</td><td>0.006</td></tr>
<tr><td>Geographic origin
Eastern Europe
South and Central America
Africa
Asia</td><td>15
150
57
72</td><td>16
138
84
58</td><td>31
288
141
130</td><td>0.06</td></tr>
<tr><td>Administrative status
legal immigration
illegal immigration</td><td>141
153</td><td>106
190</td><td>247
343</td><td>0.001</td></tr>
<tr><td>Smoking</td><td>68</td><td>92</td><td>160</td><td>0.06</td></tr>
<tr><td>Alcohol >40 g/day</td><td>15</td><td>21</td><td>36</td><td>0.16</td></tr>
<tr><td>Illegal drug use</td><td>18</td><td>20</td><td>38</td><td>0.3</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>3 months of rifampicin and isoniazid = 296 participants
• Isoniazid: 5 mg/kg/day, for 3 months
• Rifampicin: 10 mg/kg/day (maximum 600 mg/day)
Treatment was self-administered in a daily oral dose.</td></tr>
<tr><td>Comparison</td><td>6 months of isoniazid = 294 participants
• Isoniazid: 5 mg/kg/day, for 6 months
Treatment was self-administered in a daily oral dose.</td></tr>
<tr><td>Length of follow up</td><td>5 years</td></tr>
<tr><td>Location</td><td>Barcelona, Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Adherence
Defined as taking 80 % of the prescribed dose (confirmed by urine testing)</td></tr>
</table>

Bibliographic reference	**Jimenez-Fuentes,M.A., de Souza-Galvao,M.L., et al. (2013) Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population.International Journal of Tuberculosis & Lung Disease 17 (3) 326-32.**
	• 6 months of isoniazid = 154 of 294 • 3 months of rifampicin and isoniazid = 213 of 296 Data was calculated using percentages stated in the study.
	Incidence of active tuberculosis: Assessed on the basis of a telephone interview, or checking case records for diagnosis of tuberculosis: Amongst treatment adherent patients: • 6 months of isoniazid = 0 of 213 • 3 months of rifampicin and isoniazid = 0 of 154 • Amongst treatment non-adherent patients: • 6 months of isoniazid = 1 of 83 • 3 months of rifampicin and isoniazid = 1 of 140
	Hepatotoxicity Slight defined as liver enzymes < 3 times the normal level Moderate defined as 3-5 times the normal level Severe defined as > 5 times the normal level • 6 months of isoniazid = 27 of 294 cases • slight = 17 • moderate = 9 • severe = 1 • 3 months of rifampicin and isoniazid = 20 of 296 • slight = 16 • moderate = 4 • severe = 0 • P value • slight = 0.8 • moderate = 0.1 • severe = 0.3 • i.e. not significant

Bibliographic reference	**Jimenez-Fuentes,M.A., de Souza-Galvao,M.L., et al. (2013) Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population.International Journal of Tuberculosis & Lung Disease 17 (3) 326-32.**
	Gastrointestinal Nausea or vomiting without hepatotoxicity • 6 months of isoniazid = 24 of 294 • 3 months of rifampicin and isoniazid = 23 of 296 • P value = 0.8 • i.e. not significant
	Cutaneous toxicity Rash, pruritis, photosensitivity • 6 months of isoniazid = 5 of 294 • 3 months of rifampicin and isoniazid = 8 of 296 • P value = 0.4 • i.e. not significant
	Headache • 6 months of isoniazid = 8 of 294 • 3 months of rifampicin and isoniazid = 5 of 296 • P value = 0.4 • i.e. not significant
Source of funding	Grant from Spanish Society of Pneumology and Thoracic Surgery
Comments	
[1]TST- tuberculin skin test [2]6H – isoniazid 6 months [3]3RH – 3 months of rifampicin and isoniazid	

A.2.17 White,M.C., Tulsky,J.P., et al. (2012)

Bibliographic reference	**White,M.C., Tulsky,J.P., et al. (2012). Isoniazid vs. rifampin for latent tuberculosis infection in jail inmates: toxicity and adherence. Journal of Correctional Health Care, 18 (2) 131-42.**
Study type	RCT
Study quality	Population matches population of interest Intervention matches intervention of interest Randomisation: unclear if an appropriate method of randomization was used, unclear if treatment group allocation was concealed. Groups were comparable at baseline Groups received the same care apart from intervention studied Blinding: Neither participants nor clinicians were kept blind to treatment allocation. Investigators were not blinded to either treatment allocation or other confounding factors. Follow up: unclear if groups were followed up following treatment course. Groups were comparable for treatment completion and availability of outcome data. Number that did not complete regimen was high in both groups. The study used a precise definition of outcome and a valid and reliable method.
Number of patients	Randomized = 362 • Isoniazid group = 184 • Rifampicin group = 180
Patient characteristics	Inclusion Inmates in San Francisco City and County Jail Diagnosed with LTBI Exclusion History of drug intolerance Pregnancy or breast feeding Aminotransferases > 3 times upper limit of normal Bilirubin > 2 times upper limit of normal Platelets < 150 k/mm³ Taking protease inhibitors or nonnucleoside reverse transcriptase inhibiters Not English or Spanish speaking Not in routine level of jail security Known transfer or immenent deportation Baseline characteristics

<table>
<tr><td>Bibliographic reference</td><td>White,M.C., Tulsky,J.P., et al. (2012). Isoniazid vs. rifampin for latent tuberculosis infection in jail inmates: toxicity and adherence. Journal of Correctional Health Care, 18 (2) 131-42.
<table>
<tr><td></td><td>INH²</td><td>RIF³</td><td>P value</td></tr>
<tr><td>Gender m/f</td><td>173/11</td><td>166/14</td><td>0.5</td></tr>
<tr><td>Age
<35
≥35</td><td>138
46</td><td>120
60</td><td>0.08</td></tr>
<tr><td>Drug Alcohol Problem
Yes
no</td><td>100
84</td><td>86
94</td><td>0.21</td></tr>
<tr><td>On INH² before
Yes
No</td><td>23
161</td><td>28
152</td><td>0.40</td></tr>
<tr><td>Health status
Poor
Fair
Good
Very good
excellent</td><td>15
45
63
38
23</td><td>17
52
54
37
20</td><td>0.83</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Rifampicin group = 180
• Rifampicin: 600 mg daily, for 4 months

Treatment was given by directly observed therapy both in jail and in the community.</td></tr>
<tr><td>Comparison</td><td>Isoniazid group = 184
• Isoniazid: 900 mg twice weekly, for 9 months

Treatment was given by directly observed therapy both in jail and in the community.</td></tr>
<tr><td>Length of follow up</td><td>3 months following treatment</td></tr>
<tr><td>Location</td><td>San Francisco City and County Jail, USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Elevated LFTs

From any baseline to aminotransferases > 3 times upper limit of normal</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>White,M.C., Tulsky,J.P., et al. (2012). Isoniazid vs. rifampin for latent tuberculosis infection in jail inmates: toxicity and adherence. Journal of Correctional Health Care, 18 (2) 131-42.</td></tr>
<tr><td></td><td>• Isoniazid group = 21 of 184
• Rifampicin group = 8 of 180
<table>
<tr><th></th><th>2 weeks % (N tested)</th><th>4 weeks % (N tested)</th><th>8 weeks % (N tested)</th><th>12 weeks % (N tested)</th><th>16 weeks % (N tested)</th><th>32 weeks % (N tested)</th></tr>
<tr><td>INH in jail</td><td>-</td><td>1 (107)</td><td>1 (82)</td><td>3 (73)</td><td>4 (50)</td><td>9 (22)</td></tr>
<tr><td>INH in community</td><td>-</td><td>5 (20)</td><td>5 (20)</td><td>0 (19)</td><td>0 (25)</td><td>4 (27)</td></tr>
<tr><td>RIF in jail</td><td>1 (131)</td><td>0 (82)</td><td>0 (60)</td><td>3 (40)</td><td>0 (33)</td><td>-</td></tr>
<tr><td>RIF in community</td><td>0 (14)</td><td>0 (22)</td><td>0 (23)</td><td>0 (26)</td><td>0 (25)</td><td>-</td></tr>
</table></td></tr>
<tr><td></td><td>Gastrointestinal symptoms
• Isoniazid group = 19 of 184
• Rifampicin group = 16 of 180</td></tr>
<tr><td></td><td>Rash/pruritis
• Isoniazid group = 12 of184
• Rifampicin group = 16 of 180</td></tr>
<tr><td></td><td>Central nervous system (unclear definition)
• Isoniazid group = 20 of 184
• Rifampicin group = 6 of 180</td></tr>
<tr><td></td><td>Allergy (rash, shortness of breath, oxygen saturations)
• Isoniazid group = 0 of 184
• Rifampicin group = 1 of 180</td></tr>
<tr><td>Source of funding</td><td>Award from National Institue of Allergy and Infectious Diseases</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">[1]TST- tuberculin skin test
[2]INH- isoniazid
[3]RIF- rifampicin</td></tr>
</table>

A.2.18 Whalen,C.C., Johnson,J.L., et al.(1997)

Bibliographic reference	**Whalen,C.C., Johnson,J.L., et al. (1997). A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. New England Journal of Medicine, 337 (12) 801-08.**
Study type	RCT
Study quality	Population matches population of interest Intervention matches intervention of interest Randomisation: an appropriate system of randomisation was used using a sequential list of random numbers. Allocation was most likely adequately concealed although sealed envelopes were not explicitly stated as opaque. Groups were comparable at baseline Groups received the same care apart from intervention under study Blinding: neither participants nor clinicians were blinded to treatment allocation. Investigators were blinded to treatment allocation for the most part although blinding was made difficult by the discolouration of bodily fluids in the rifampicin treatment groups. Follow up: all groups were followed up for an adequate length of time and analysis was adjusted to allow for any differences between groups. Groups were comparable for treatment completion and availability of outcome data. The study used a precise definition of outcome and a valid and reliable method was used to determine the outcome
Number of patients	2736 individuals randomized • Placebo group = 464 • Isoniazid group = 536 • Isoniazid and rifampicin group = 556 • Isoniazid, rifampicin and pyrazinamide = 462
Patient characteristics	Included Aged 18 or above HIV type 1 PPD[1] positive ≥ 5 mm (although anergy cohort was run alongside) Karnofsky performance score of > 50 Exclusion Active tuberculosis Previous treatment for TB Antiretroviral drugs use

White cell count < 3000 per mm³
Haemoglobin level < 80 g/L
Aspartate aminotransferase level > 90 U per litre
Serum creatinine level over 1.8 mg per decilitre
Positive pregnancy test
Residence more than 20 miles from a project clinic
Advanced HIV disease
Major underlying medical illness
Baseline characteristics

	Placebo n=464	Isoniazid n=536	Isoniazid-rifampicin n=556	Isoniazid-rifampicin-pyrazinamide n=462
Male (%)	31	31	29	34
Mean age yr	30	29	29	29
Karnofsky performance score	91	91	91	91
Person years of observation	616	645	680	577
PPD skin test mm	14	14	13	14
Completion of trial (%)	89	88	86	80

Intervention

Isoniazid group = 536
- isoniazid: 300 mg daily, for 6 months

Isoniazid and rifampicin group = 556
- isoniazid: 300 mg daily, for 3 months
- rifampicin: 600 mg daily, for 3 months

Isoniazid, rifampicin and pyrazinamide = 462
- isoniazid: 300 mg daily, for 3 months
- rifampicin: 600 mg daily, for 3 months
- pyrazinamide: 2000 mg daily, for 3 months
- All treatments were self-administered

<table>
<tr><td>Comparison</td><td>Placebo= 464
• ascorbic acid: 250 mg daily, for 6 months</td></tr>
<tr><td>Length of follow up</td><td>2 years</td></tr>
<tr><td>Location</td><td>Uganda</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Definite or probable tuberculosis
Culture-confirmed case = definite
Clinical illness consistent with TB: radiography consistent with pulmonary TB, smear positive for acid fast bacilli, response to anti tuberculosis therapy.= probable
<table>
<tr><th></th><th>No of cases</th><th>Rate (cases per 100 person-years)</th><th>Crude RR[2] (95% CI)</th><th>P value</th><th>Adjusted RR[2]</th></tr>
<tr><td>Placebo</td><td>21</td><td>3.41</td><td>1.0</td><td></td><td>1.0</td></tr>
<tr><td>Isoniazid</td><td>7</td><td>1.08</td><td>0.33 (0.14-0.77)</td><td>0.01</td><td>0.32 (0.14-0.76)</td></tr>
<tr><td>Isoniazid, rifampicin</td><td>9</td><td>1.32</td><td>0.40 (0.18- 0.86)</td><td>0.02</td><td>0.41 (0.19-0.89)</td></tr>
<tr><td>Isoniazid, rifampicin, pyrazinamide</td><td>10</td><td>1.73</td><td>0.51 (0.24-1.08)</td><td>0.08</td><td>0.43 (0.20-0.92)</td></tr>
</table>
Adjusted for age, sex, white cell count, haemoglobin level, karnofsky score, body mass index, history of HIV related infection and presence of chronic diarrhoea.</td></tr>
<tr><td></td><td>Mortality
Number of deaths
<table>
<tr><th></th><th>Deaths</th><th>Rate</th><th>RR[2] (95% CI[3])</th><th>P value</th></tr>
<tr><td>Placebo</td><td>64</td><td>10.2</td><td>1.0</td><td></td></tr>
<tr><td>Isoniazid</td><td>58</td><td>8.9</td><td>0.9 (0.6-1.2)</td><td>0.44</td></tr>
<tr><td>Isoniazid, rifampicin</td><td>57</td><td>8.3</td><td>0.8 (0.5-1.2)</td><td>0.25</td></tr>
<tr><td>Isoniazid, rifampicin,</td><td>58</td><td>9.8</td><td>0.96 (0.7-1.4)</td><td>0.83</td></tr>
</table></td></tr>
</table>

	pyrazinamide
	Adverse events Incidence of reported adverse events and the number for which it was the cause of discontinuation of therapy

	Cumulative incidence of reported adverse events (%)	Mild reaction	Moderate reaction	Severe reaction	Discontinuation of therapy
Placebo	23 (5.0)	23 (5.0)	0	0	1 (0.2)
Isoniazid	60 (11.2)	56 (10.4)	4 (0.7)	0	3 (0.6)
Isoniazid, rifampicin	54 (9.7)	48 (8.6)	6 (1.1)	0	13 (2.3)
Isoniazid, rifampicin, pyrazinamide	114 (24.7)	101 (21.9)	12 (2.6)	1 (0.2)	26 (5.6)

Source of funding	Grant from Fogarty International Center at the National Institues of Health
Comments	

[1]PPD- purified protein derivative

[2]RR- risk ratio

[3]CI- confidence interval

A.2.19 Swaminathan,S., Menon,P.A., et al. (2012)

Bibliographic reference	**Swaminathan,S., Menon,P.A., et al. (2012) Efficacy of a six-month versus a 36-month regimen for prevention of tuberculosis in HIV-infected persons in India: a randomized clinical trial. PLoS ONE [Electronic Resource] 7 (12) e47400.**
Study type	RCT
Study quality	Population does not match population of interest, however subgroup analysis is possible for patients > 5 mm TST[3] positive. Intervention matches intervention of interest An appropriate method of computerised block randomisation was used. Allocation was concealed in sequentially numbered opaque envelopes. Groups were comparable at baseline. Groups received the same care apart from the intervention studied. Blinding: neither participants nor clinicians were kept blind to treatment allocation. Investigators were blinded to treatment allocation however unclear if blinded to all confounding factors. All groups were followed up for an equal amount of time, groups were comparable for numbers who did not complete treatment and for whom there was no outcome data. Unclear if there were systematic differences between groups for these participants. An appropriate length of follow up was used. Intention to treat analysis was used A precise definition of outcome was used and a valid and reliable method used to determine the outcome.
Number of patients	Randomised = 712 • Ethambutol and isoniazid = 357 • 36 months, isoniazid = 355
Patient characteristics	Inclusion HIV infected Age > 18 years Normal chest radiograph Haemoglobin ≥ 70 g/L Granulocyte count ≥1.1 x 109/L Platelet count ≥100 x 109/L Serum alanine amino transferase ≤2.5 times upper limit of normal Serum creatinine concentration < 1.1 mg% Random plasma sugar < 140 mg% Exclusion Past or current evidence of TB disease

<table>
<tr><td>Bibliographic reference</td><td>Swaminathan,S., Menon,P.A., et al. (2012) Efficacy of a six-month versus a 36-month regimen for prevention of tuberculosis in HIV-infected persons in India: a randomized clinical trial. PLoS ONE [Electronic Resource] 7 (12) e47400.</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><td></td><td colspan="2">6 months of ethambutol and isoniazid n=344</td><td colspan="2">36 months of isoniazid n=339</td></tr>
<tr><td>Age (mean±SD[1]), years</td><td colspan="2">29.9±7</td><td colspan="2">30.2±7</td></tr>
<tr><td>Weight (mean±SD[1]) kgs</td><td colspan="2">51±10</td><td colspan="2">50±10</td></tr>
<tr><td>Females n (%)</td><td colspan="2">218 (63)</td><td colspan="2">212 (63)</td></tr>
<tr><td>Age distribution
<25 years
25-40 years
>40 years</td><td>N
106
208
30</td><td>%
30
61
9</td><td>N
97
216
26</td><td>%
29
64
7</td></tr>
<tr><td>TST Induration (mean), mm</td><td colspan="2">7.6</td><td colspan="2">7.2</td></tr>
<tr><td>CD4 count, median, cells/mm³</td><td colspan="2">326</td><td colspan="2">324</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Isoniazid and ethambutol
• isoniazid: 300 mg daily, for 6 months
• ethambutol: 800 mg daily, for 6 months
• pyridoxine:10 mg daily, for 6 months
• co-trimoxazole DS: one tablet daily for 6 months if CD4 count <250 cells/mm³
Self administration</td></tr>
<tr><td>Comparison</td><td>Isoniazid alone
• isoniazid: 300 mg daily, for 36 months
• pyridoxine:10 mg daily, for 6 months
• co-trimoxazole DS: one tablet daily for 6 months if CD4 count <250 cells/mm³
Self administration</td></tr>
<tr><td>Length of follow up</td><td>None beyond treatment period</td></tr>
<tr><td>Location</td><td>India</td></tr>
<tr><td>Outcomes measures and</td><td>Incidence of TB</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Swaminathan,S., Menon,P.A., et al. (2012) Efficacy of a six-month versus a 36-month regimen for prevention of tuberculosis in HIV-infected persons in India: a randomized clinical trial. PLoS ONE [Electronic Resource] 7 (12) e47400.</td></tr>
<tr><td>effect size</td><td>Definite: positive mycobacterial culture
Probable: clinical, radiographic, histopathological or biochemical features based on review by blinded panel.
Primary analysis was a modified intent to treat analysis
<table>
<tr><td></td><td>6 months, isoniazid and ethambutol n=141</td><td>36 months isoniazid, n=132</td></tr>
<tr><td>TB incidence/100 personyears (95% CI²)</td><td>3.18 (1.38-4.97)</td><td>1.81 (0.69-3.04)</td></tr>
<tr><td>Adjusted incidence rate ratio (95% CI²)</td><td>1.48 (0.55, 3.96)</td><td>reference</td></tr>
<tr><td>TB incidence/100 personyears (95% CI²) per protocol analysis</td><td>2.80 (1.06-4.70)</td><td>1.84 (0.37-3.32)</td></tr>
<tr><td>Adjusted incidence rate ratio (95% CI²), per protocol analysis</td><td>1.57 (0.50, 4.9)</td><td>reference</td></tr>
</table></td></tr>
<tr><td></td><td>Mortality
Incidence per 100 person years
Primary analysis was a modified intent to treat analysis
<table>
<tr><td></td><td>6 months, isoniazid and ethambutol n=141</td><td>36 months isoniazid, n=132</td></tr>
<tr><td>Mortality/100 personyears (95% CI²)</td><td>2.91 (1.19-4.63)</td><td>2.53 (1.21-3.85)</td></tr>
<tr><td>Adjusted incidence rate ratio (95% CI²)</td><td>1.51 (0.56, 4.02)</td><td>reference</td></tr>
<tr><td>Mortality/100 personyears (95% CI²) per protocol analysis</td><td>3.08 (1.26-4.89)</td><td>2.15 (0.56-3.74)</td></tr>
<tr><td>Adjusted incidence rate ratio (95% CI²), per protocol analysis</td><td>1.43 (0.53, 3.8)</td><td>reference</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>World Health Organisation, United States Agency for International Development</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">¹SD- standard deviation
²CI- confidence interval
³TST- tuberculin skin test</td></tr>
</table>

A.2.20 Sterling,T.R., Villarino,M.E., et al. (2011)

Bibliographic reference	**Sterling,T.R., Villarino,M.E., et al.(2011). Three months of rifapentine and isoniazid for latent tuberculosis infection New England Journal of Medicine 365 (23) 2155-66.**
Study type	RCT
Study quality	Unclear if population matches population of interest, some uncertainty around whether TST[1] negative participants were included in the analysis. No subgroup data available. Intervention matches intervention of interest An appropriate method of randomisation was used, randomising treatment by household (cluster). Unclear whether treatment allocation was adequately concealed Groups were not comparable at baseline in regard to numbers of participants who were homeless or native American. Groups did not receive the same standard of care aside from intervention studied. Combination therapy was given directly observed, isoniazid was self-administered. Blinding: neither participants nor clinicians were blinded to treatment allocation. Investigators were not blinded to treatment allocation or other confounding factors. Follow up: groups were followed up for an equal length of time. Unclear how many participants did not complete treatment within each group. Groups were comparable for number for which there is no outcome data available. Length of follow up was appropriate. Intention to treat principle was followed A precise definition of outcome was used. Valid and reliable method was used to determine outcome.
Number of patients	7731 participants • Isoniazid only= 3745 • Isoniazid and rifapentine= 3986
Patient characteristics	Inclusion Aged ≥12 years of age Close contact of a patient with culture confirmed TB Positive TST[1] HIV infection with positive TST[1] result Fibrotic changes on chest radiography with TST positive test Criteria expanded to also include: Children between the ages of 2 to 4 years with positive TST and close contact Exclusion Confirmed or expected tuberculosis

Bibliographic reference	**Sterling,T.R., Villarino,M.E., et al.(2011). Three months of rifapentine and isoniazid for latent tuberculosis infection New England Journal of Medicine 365 (23) 2155-66.**

Resistance to isoniazid
Received treatment with rifamycin or isoniazid within the past 2 years
Previous treatment for tuberculosis
Serum aspartate aminotransferase > 5 times the upper limit of normal
Pregnancy or lactation
HIV therapy within 90 days after enrolment
Weight of less than 10 kg
Baseline characteristics

	Isoniazid only n=3745	Combination therapy n=3986
Indication for treatment Close contact with a patient with tuberculosis Recent conversion to a positive TST HIV infection Fibrosis on chest radiograph	2609 972 74 90	2857 953 87 89
Age- yr Median Interquartile range	35 25-46	36 25-47
Male sex	2004	2210
HIV infection	100	105
Race or ethnicity White Black Asian Native American Multiracial	2160 947 490 33 115	2296 978 494 84 134
Risk factors History of incarceration Unemployed History of alcohol use History of injection drug use	175 390 1888 136 220	221 424 1929 149 293

Bibliographic reference	**Sterling,T.R., Villarino,M.E., et al.(2011). Three months of rifapentine and isoniazid for latent tuberculosis infection New England Journal of Medicine 365 (23) 2155-66.**
	Homelessness Current smoker: 1034 / 1112 Liver disease: 97 / 99 Hepatitis C: 60 / 42 Hepatitis B
Intervention	Rifapentine and isoniazid • rifapentine: 900 mg once weekly, for 3 months • incremental adjustment for subjects weighing ≤50 kg • isoniazid 15-25 mg per kg of body weight rounded up to nearest 50 mg (maximum 900 mg) • once weekly, for 3 months Doses given under directly observed therapy.
Comparison	Isoniazid alone • isoniazid: 5 to 15 mg per kilogram, rounded up to the nearest 50 mg, maximum dose 300 mg • daily, for 9 months Self administered
Length of follow up	33 months
Location	United States, Canada, Brazil, Spain

Bibliographic reference	**Sterling,T.R., Villarino,M.E., et al.(2011). Three months of rifapentine and isoniazid for latent tuberculosis infection New England Journal of Medicine 365 (23) 2155-66.**
Outcomes measures and effect size	Incidence of Tuberculosis Incidence of TB and Event rates

	No. of subjects	No. with tuberculosis	No. per patient year	Cumulative rate	Difference in cumulative rate	Upper limit of 95% CI for difference
Modified Intention to treat analysis						
Isoniazid only	3745	15	0.16	0.43	-0.24	0.01
Combination therapy	3986	7	0.07	0.19		
Per protocol analysis						
Isoniazid only	2585	8	0.11	0.32	-0.19	0.06
Combination therapy	3273	4	0.05	0.13		

Permanent drug discontinuation
Number who discontinued treatment:
For any reason
- Isoniazid alone group = 1160 of 3745 (who received at least one dose of study drug)
- Rifapentine and isoniazid group = 713 of 3986
- P-value = <0.001

Because of an adverse event
- Isoniazid alone group = 139 of 3745
- Rifapentine and isoniazid group = 196 of 3986
- P-value = 0.009

Mortality

Number of deaths
- Isoniazid alone group = 39 of 3745
- Rifapentine and isoniazid group = 31 of 3986

Bibliographic reference	**Sterling,T.R., Villarino,M.E., et al.(2011). Three months of rifapentine and isoniazid for latent tuberculosis infection New England Journal of Medicine 365 (23) 2155-66.**
	• P-value = 0.22
	Hepatotoxicity Unclear definition • Isoniazid alone group = 103 of 3759 • Rifapentine and isoniazid group = 18 of 4040 • P-value = <0.001
	Rash Unclear definition • Isoniazid alone group = 21 of 3759 • Rifapentine and isoniazid group = 31 of 4040 • P-value = 0.26
	Hypersensitivity Possible hypersensitivity • Isoniazid alone group = 17 of 3759 • Rifapentine and isoniazid group = 152 of 4040 • P-value = <0.001
	Severity of adverse event Grade1 or 2 • Isoniazid alone group = 341 of 3759 • Rifapentine and isoniazid group = 310 of 4040 • P-value = 0.03 Grade 3 • Isoniazid alone group = 202 of 3759 • Rifapentine and isoniazid group = 193 of 4040 • P-value = 0.24

Bibliographic reference	**Sterling,T.R., Villarino,M.E., et al.(2011). Three months of rifapentine and isoniazid for latent tuberculosis infection New England Journal of Medicine 365 (23) 2155-66.**
	Grade 4 • Isoniazid alone group = 42 of 3759 • Rifapentine and isoniazid group = 36 of 4040 • P-value = 0.32
Source of funding	Centers for Disease Control and Prevention
Comments	Dr Sterling reports receiving research grant funding from Bristol-Myers Squibb and Pfizer for HIV observational studies, Dr Hamilton, being employed by Family Health International; Dr Weiner, receiving research grant funding from Sanofi-Aventis; Dr Hordburgh, receiving payments from Otuska America Pharmaceutical for scientific reviews of study protocols.
[1]TST- tuberculin Skin Test	

A.2.21 Spyridis,N.P., Spyridis,P.G., et al. (2007)

Bibliographic reference	**Spyridis,N.P., Spyridis,P.G., et al. (2007) The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clinical Infectious Diseases, 45 (6) 715-22.**
Study type	RCT
Study quality	Population matches population of interest Intervention matches intervention of interest Unclear if an appropriate method of randomisation was used Unclear if there was adequate concealment of allocation Groups were not comparable at baseline since randomisation occurred in two periods and the population examined was different during the second period with an increased number of immigrants. The comparison groups received the same care apart from the intervention studied Blinding: neither participants nor clinicians were kept blind to treatment allocation. Investigators reviewing radiographs were kept blind to patient's treatment allocation and other confounding factors. Follow up: varied in length between treatment groups: patients in study group A and B were followed up for longer than those in groups C and D. Groups were not comparable for treatment completion: participants in the isoniazid alone group had a lower rate of completion. Length of follow up was appropriate. Unclear if groups were comparable for the availability of outcome data. Definition of outcome was unclear, for example parents were instructions regarding the recognition of symptoms that may suggest drug related adverse events. A valid and reliable method to determine outcomes was not used, for example parents were responsible for performing urine tests to record adherence and blood tests to detect liver toxicity were not performed routinely. Study was performed in two periods with separate randomisation meaning that some comparisons were indirect between study groups.
Number of patients	Randomised= 926 isoniazid, 9 months= 232 isoniazid and rifampicin, 4 months, period 1= 238 isoniazid and rifampicin, 4 months, period 2= 236 isoniazid and rifampicin, 3 months = 220
Patient characteristics	Inclusion Children aged < 15 years Asymptomatic with positive TST[1] results Normal chest radiograph findings, or inactive fibrotic or calcified parenchymal and/or lymph node lesions

Bibliographic reference	**Spyridis,N.P., Spyridis,P.G., et al. (2007) The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clinical Infectious Diseases, 45 (6) 715-22.**
	Exclusion History of positive BCG vaccination Known immunodeficiency or other chronic conditions that may influence TST[1] result

Baseline characteristics

	Period 1			Period 2		
	isoniazid, 9 months. N=232	Isoniazid and rifampicin, 4 months. N=238	P value	Isoniazid and rifampicin, 4 months. N= 236	Isoniazid and rifampicin, 3 months. N = 220	P value
Male sex	120	114	0.39	136	106	0.043
Age mean years ±SD[2]	9.1± 3.7	9.2±3.3		8.4 ± 3.4	7.9 ± 3.6	
Greek nationality	142	149	0.751	90	87	0.839
Immigrant	90	89	0.991	146	133	0.902

Intervention	isoniazid and rifampicin, 4 months, period 1= 238 • Isoniazid: 10 mg/kg daily, maximum 300 mg, for 4 months • Rifampicin: 600 mg daily, for 4 months isoniazid and rifampicin, 4 months, period 2= 236 • Isoniazid: 10 mg/kg daily, maximum 300 mg, for 4 months • Rifampicin: 600 mg daily, for 4 months isoniazid and rifampicin, 3 months = 220 • Isoniazid: 10 mg/kg daily, maximum 300 mg, for 3 months • Rifampicin: 600 mg daily, for 3 months Doses were given by parents at home
Comparison	isoniazid, 9 months= 232 • Isoniazid: 10 mg/kg daily, maximum 300 mg, for 9 months

<table>
<tr><td>Bibliographic reference</td><td>Spyridis,N.P., Spyridis,P.G., et al. (2007) The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clinical Infectious Diseases, 45 (6) 715-22.</td></tr>
<tr><td></td><td>Doses were given by parents at home</td></tr>
<tr><td>Length of follow up</td><td>isoniazid, 9 months= 7-11 years
isoniazid and rifampicin, 4 months, period 1= 7-11 years
isoniazid and rifampicin, 4 months, period 2= 3-7 years
isoniazid and rifampicin, 3 months = 3-7 years

Participants were followed up for at least 3 years</td></tr>
<tr><td>Location</td><td>Athens, Greece</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Tuberculosis incidence
New radiographic findings indicating “possible active disease.”
No cases of clinical TB were documented at the end of therapy and during follow up in any of the study groups.

<table>
<tr><td></td><td colspan="2">Period 1</td><td></td><td colspan="2">Period 2</td><td></td></tr>
<tr><td>Fibrosis or calcification</td><td>isoniazid, 9 months. N=232</td><td>Isoniazid and rifampicin, 4 months. N=238</td><td>P value</td><td>Isoniazid and rifampicin, 4 months. N= 236</td><td>Isoniazid and rifampicin, 3 months. N = 220</td><td>P value</td></tr>
<tr><td>Lung parenchyma</td><td>12</td><td>10</td><td>NS</td><td>8</td><td>7</td><td>NS</td></tr>
<tr><td>Lymph nodes</td><td>63</td><td>62</td><td>NS</td><td>75</td><td>73</td><td>NS</td></tr>
<tr><td>Lung parenchyma and lymph nodes</td><td>42</td><td>55</td><td>NS</td><td>68</td><td>60</td><td>NS</td></tr>
<tr><td>Normal</td><td>115</td><td>111</td><td>NS</td><td>85</td><td>80</td><td>NS</td></tr>
</table></td></tr>
<tr><td></td><td>Adherence
Excellent if patients sent positive urine strips and followed appointments without delay
Moderate if patients had to be reminded with telephone contact by the study nurse to send urine strips or to return for follow up visits
Poor if no medication was detected in > two urine strips in the 9 month isoniazid group and ≥1 times in the 3-4 month treatment</td></tr>
</table>

Bibliographic reference	**Spyridis,N.P., Spyridis,P.G., et al. (2007) The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clinical Infectious Diseases, 45 (6) 715-22.**
	protocols or if patients did not return for follow up visits, despite having received reminder phone calls, or if they were lost to follow up.

	Period 1			Period 2		
Adherence to treatment	isoniazid, 9 months. N=232	Isoniazid and rifampicin, 4 months. N=238	P value	Isoniazid and rifampicin, 4 months. N= 236	Isoniazid and rifampicin, 3 months. N = 220	P value
Compliance Excellent Moderate Poor	152 48 32	185 35 18	0.11	203 18 15	197 12 11	0.533
Refusal to take medication	21	3	0.005	5	2	NS
Nausea/epigastric pain	13	7	NS	2	2	NS
Discontinuation by family physician	5	18	0.005	9	5	NS
Poor understanding of instruction	9	7	NS	2	3	NS

Source of funding	Second Department of Pediatrics of Athens University
Comments	

TST[1]- tuberculin skin test

A.2.22 Byrd,R.B., Horn,B.R., Griggs,G.A..(1997)

Bibliographic reference	**Byrd,R.B., Horn,B.R., Griggs,G.A..(1977). Isoniazid chemoprophylaxis. Association with detection and incidence of liver toxicity. Archives of Internal Medicine. 137 (9) 1130-33.**
Study type	RCT
Study quality	Population matches population of interest Intervention matches intervention of interest Randomisation: An appropriate method of randomisation was used; random number table with allocation concealment. Groups were comparable at baseline Comparison groups received the same care apart from the intervention studied Blinding: participants and clinicians were blinded to treatment allocation. Investigators were blinded to allocation but unclear if blinded to other confounding factors. Follow up: Unclear if groups were followed up beyond the 3 month treatment period. Unclear if groups were followed up for an equal amount of time; the placebo group were crossed over to treatment group following 3 months and were followed up for a further 3 months. Unclear if follow up length was adequate. The study used a precise definition of outcome and a valid and reliable method was used to determine outcome. As mentioned, this trial incorporated a cross over element to the placebo group. The crossed over participants went on to add to the data collected on the treatment arm of the study but it is unclear to what extent this effected the data as results are reported in percentages and numbers cannot be separated.
Number of patients	Randomised = 120 • Isoniazid group= 60 • Placebo group= 60
Patient characteristics	Inclusion Aged > 17 years Latent TB criteria as advocated by the American Thoracic Society of 1974 Exclusion Evidence of clinical liver disease Baseline SGOT[1] test of greater than 20 IU Presence of co-existing non tuberculosis disease likely to result in death within a short period of time Individuals who believed they would be transferred to other areas within six months Baseline characteristics

	Isoniazid group= 60	Placebo group= 60
Age <30	19 23	22 25

<table>
<tr><td>Bibliographic reference</td><td>Byrd,R.B., Horn,B.R., Griggs,G.A..(1977). Isoniazid chemoprophylaxis. Association with detection and incidence of liver toxicity. Archives of Internal Medicine. 137 (9) 1130-33.</td></tr>
<tr><td></td><td>
<table>
<tr><td>30-39
>40</td><td>18</td><td>13</td></tr>
<tr><td>Sex
Male
Female</td><td>44
16</td><td>44
16</td></tr>
<tr><td>Race
White
Black
Other
Unknown</td><td>46
11
1
2</td><td>38
12
3
7</td></tr>
<tr><td>Alcohol taken
None or 1 oz a day
>1 oz a day</td><td>43
17</td><td>40
20</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Isoniazid
• Isoniazid: 300mg daily, for 9 months
• Results taken from first 3 months of treatment</td></tr>
<tr><td>Comparison</td><td>Placebo
• Placebo tablet: daily, for 3 months
• Results taken from first 3 months of treatment, then an additional three months follow up in the treatment group.</td></tr>
<tr><td>Length of follow up</td><td>Results taken from 3 months into the trial</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Hepatotoxicity
<table>
<tr><td></td><td colspan="2">Percent abnormal</td><td></td></tr>
<tr><td>Month of therapy</td><td>Isoniazid</td><td>Placebo</td><td>P value</td></tr>
<tr><td>1</td><td>5.0</td><td>3.3</td><td>NS</td></tr>
<tr><td>2</td><td>14.0</td><td>3.4</td><td><0.05</td></tr>
<tr><td>3</td><td>14.0</td><td>1.7</td><td><0.025</td></tr>
</table>
Defined by a raised SGOT[1]</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Byrd,R.B., Horn,B.R., Griggs,G.A..(1977). Isoniazid chemoprophylaxis. Association with detection and incidence of liver toxicity. Archives of Internal Medicine. 137 (9) 1130-33.</td></tr>
<tr><td></td><td>Clinical symptoms of hepatotoxicity
<table>
<tr><td></td><td colspan="2">Number of participants (percentage) during non cross over portion of trial.</td></tr>
<tr><td></td><td>Isoniazid</td><td>Placebo</td></tr>
<tr><td>Muscle aching</td><td>18 (30.0)</td><td>17 (28.3)</td></tr>
<tr><td>Joint aching</td><td>14 (23.3)</td><td>11 (18.3)</td></tr>
<tr><td>Flu-like symptoms</td><td>8 (13.3)</td><td>10 (16.7)</td></tr>
<tr><td>Fever</td><td>10 (16.7)</td><td>4 (6.7)</td></tr>
<tr><td>Chills</td><td>9 (15.0)</td><td>5 (8.3)</td></tr>
<tr><td>Skin rash</td><td>7 (11.7)</td><td>6 (10.0)</td></tr>
<tr><td>Clay colored stools</td><td>6 (10.0)</td><td>3 (5.0)</td></tr>
<tr><td>Dark urine</td><td>6 (10.0)</td><td>0 (0.0)</td></tr>
<tr><td>Anorexia</td><td>5 (8.3)</td><td>5 (8.3)</td></tr>
<tr><td>Nausea</td><td>2 (3.3)</td><td>1 (1.7)</td></tr>
<tr><td>Yellow cast to sclera</td><td>1 (1.7)</td><td>1 (1.7)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Unclear</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">SGOT[1]- better known as serum aspartate aminotransferase</td></tr>
</table>

A.2.23 Ferebee SH., Mount FW., Murray FJ.(1963)

Bibliographic reference	**Ferebee,S.H., Mount,F.W., Murray,F.J.(1963) A controlled trial of isoniazid prophylaxis in mental institutions. American Review of Respiratory Disease. 88 161-75.**
Study type	RCT
Study quality	Intervention matches intervention of interest Population does not match population of interest. TST[1] negative patients were included however subgroup analysis was possible Unclear if appropriate method of randomisation was used. Unclear if treatment allocation was concealed. Groups were not comparable at baseline in terms of mortality, weight and abnormal x-rays prior to enrolment. Groups received the same care apart from the intervention under study Blinding: both participants and clinicians were blinded to treatment allocation. Investigators were blinded to treatment allocation unclear if blinded to confounding factors. Follow up: groups were followed up for an equal length of time. Unclear if groups were comparable for treatment completion, unclear if groups were comparable for availability of outcome data. Follow up doesn't extend beyond treatment period. Study used a precise definition of outcome, however unclear how reliable diagnosis of active tuberculosis was; decision was made using a blinded review team looking at the patient history and available chest x-rays.
Number of patients	Randomised= 25210 • Placebo group= 12,326 • Isoniazid group= 12,884
Patient characteristics	Inclusion Patients admitted to psychiatric institutions Present on the wards before the end of the first month of the programme who took pills at any time during the year Exclusion Patients on the wards who did not take any of the medication Baseline characteristics

	Placebo n=12,326		Isoniazid n=12,884	
	number	percent	number	percent
Sex Male Female	5704 6613	46.4 53.6	6276 6599	48.8 51.2
Race White	10,916 11,187	88.6 11.4	11,187 1688	86.9 13.1

Bibliographic reference	**Ferebee,S.H., Mount,F.W., Murray,F.J.(1963) A controlled trial of isoniazid prophylaxis in mental institutions. American Review of Respiratory Disease. 88 161-75.**

Black					
Present Hospitalisation	1398	11.3	1766	13.7
< 2 years	1699	13.8	2049	15.9
2-4 years	2332	18.9	2602	20.2
5-9 years	1762	14.3	1744	13.5
10-14 years	5110	41.5	4686	36.4
>15 years	25	0.2	37	0.3
Not available				
Infection status	1071	8.7	1216	9.5
Abnormal chest x ray	6484	52.6	6403	49.7
TST[1] positive	3954	32.1	4333	33.6
TST[1] negative	817	6.6	932	7.2
Not known				

Intervention

Isoniazid group

In patients 15 years old or more:

- Isoniazid: 300mg daily, for one year

Children, younger than 15 years:

- Isoniazid: proportionally smaller doses, unclear exact dosing, for one year
- Average daily dose was 4.3 mg/kg of body weight for those receiving 100 mg a day; 5.0 mg/kg for 200 mg a day; 4.6 mg/kg for 300 mg a day.

Comparison

Placebo:

- Matching pills daily, for one year

Length of follow up

None beyond treatment period

Location

Psychiatric institutions in Wisconsin, Georgia, Michigan, and Massachusetts

Outcomes measures and effect size

Incidence of TB

Number of cases of active tuberculosis developing during medication year

	Placebo group = 6,484	Isoniazid group= 6,403

<table>
<tr><td>Bibliographic reference</td><td>Ferebee,S.H., Mount,F.W., Murray,F.J.(1963) A controlled trial of isoniazid prophylaxis in mental institutions. American Review of Respiratory Disease. 88 161-75.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Cases</td><td>7</td><td>0</td></tr>
<tr><td>Rate per 1000</td><td>1.1</td><td>0.0</td></tr>
</table>
Number of cases developing after medication year
Length of observation varied among institutes and the total of cases is not separated by time
<table>
<tr><td></td><td>Placebo group = 6,484</td><td>Isoniazid group= 6,403</td></tr>
<tr><td>Cases</td><td>17</td><td>5</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>National Tuberculosis Association</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">[1]TST- tuberculin skin test</td></tr>
</table>

A.2.24 Debre,R., Perdrizet,S., et al.(1973)

Bibliographic reference	**Debre,R., Perdrizet,S., et al. (1973) Isoniazid chemoprophylaxis of latent primary tuberculosis: in five trial centres in France from 1959 to 1969. International Journal of Epidemiology. 2 (2) 153-60.**
Study type	RCT
Study quality	Intervention matches intervention of interest Population matches population of interest Randomisation: Method was poor, involving separating participants by date of birth. Unclear if allocation was concealed Groups were not comparable at baseline for all major confounding factors, participants in the treatment group were younger. Comparison groups received the same care apart from the intervention studied. The treatment groups received “at least 5 months” to “over a year” of isoniazid; some variability within this group can be assumed. Blinding: Neither participants nor clinicians were blinded to treatment group. No placebo was offered to the control group. Investigators were neither blinded to participant’s treatment allocation or to other confounding factors. Follow up: all groups were followed up for an equal length of time. Unclear if groups were comparable for loss to follow up. Groups were not comparable for number of patients for whom outcome data was not available. Follow up was for an appropriate length of time. 29% of those initially enrolled were later eliminated from the trial because of an altered treatment plan breaking the protocol. This lead to subsequent differences between study groups such as lower socio-economic status, greater contact with other family members with TB and poorer housing conditions in the isoniazid group. The study used a precise definition of outcome. A valid and reliable method was used to determine outcome based on clinical and radiological findings, however only a small proportion were biologically tested.
Number of patients	Participants= 2970 • Isoniazid group= 1519 • Control group = 1451
Patient characteristics	Inclusion Aged 5 - 24 years Recent positive TST[1] Exclusion Clinical or radiological signs of TB Previous BCG vaccination Baseline characteristics

		5 to 9 years	10 to 14 years	15 to 24 years	Total number
	Control Group	31.6	42.3	26.1	1451
	Isoniazid Group	38.8	42.4	18.8	1519
		Male (%)	Female (%)		
	Control Group, n= 1451	814 (56%)	637 (44%)		
	Isoniazid Group, n= 1519	807 (53%)	712 (47%)		
Intervention	Isoniazid group= 1519 • Isoniazid: between 5-15 mg per kg according to age of subject. Majority between 5-9 months of therapy				
Comparison	Control group = 1451 • No treatment				
Length of follow up	Up to 10 years				
Location	France				
Outcomes measures and effect size	Incidence of tuberculosis Number of cases diagnosed bacteriologically or by radiological findings with clinical symptoms:				
		Observation Period	TB cases	Missing cases	Number under observation
	Control Group	First 6 months	6	1	1451
		Second 6 months	1	6	1444
		2nd year	4	3	1437
		3rd year	2	4	1428
		4th year	3	11	1344
		5th year	1	10	1226
		6th year	1	6	1063
		7th year	2	8	910
		8th year	2	7	762
		9th year	1	5	588
		10th year	1		336
		Total	24	61	

Isoniazid Group	First 6 months	2		1519
	Second 6 months	1	2	1517
	2nd year	1	6	1514
	3rd year	2	6	1506
	4th year	2	4	1423
	5th year		3	1309
	6th year	1	10	1148
	7th year		7	964
	8th year		7	796
	9th year	1	3	582
	10th year			332
	Total	10	48	

“Missing” cases is not a term that is properly explained, it could be that these patients fit the criteria for exclusion.

Mortality

Number of Deaths

	Observation Period	Deaths	Number under observation
Control Group	First 6 months		1451
	Second 6 months		1444
	2nd year	2	1437
	3rd year	1	1428
	4th year		1344
	5th year		1226
	6th year	1	1063
	7th year		910
	8th year	1	762
	9th year	1	588
	10th year	1	336
	Total	7	

	Isoniazid Group	First 6 months		1519
		Second 6 months		1517
		2nd year	1	1514
		3rd year	2	1506
		4th year		1423
		5th year		1309
		6th year	1	1148
		7th year	1	964
		8th year	1	796
		9th year		582
		10th year	1	332
		Total	7	
Source of funding	Supported by I.N.S.E.R.M. and Social Security Department			
Comments				
[1]TST- Tuberculin Skin Test				