1 Appendix D: Evidence tables – Management of treatment interruptions RQ Z

A.1.1 Sharma, 2010

Bibliographic reference	**Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S (2010) Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clinical Infectious Diseases 50(6): 833-9**
Study type	Randomised controlled trial
Study quality	*Study limitations* Appropriate method of randomisation? *yes – computer-generated random numbers* Adequate allocation concealment? *yes – computer-generated random numbers were kept in sealed opaque envelopes; the envelopes were in the possession of an individual who was not involved in the conduct of study* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *unclear* Precise definition of outcome? *yes* Valid and reliable method of outcome measurement? *yes* Intent-to-treat principle adhered to? *yes* *Inconsistency* Groups comparable at baseline? *yes* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *unclear* Groups equivalent for intervention completion? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes, although initial antituberculosis regimen not explicitly stated (appeared to include some or all of isoniazid, rifampicin, and pyrazinamide)* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Recruited = 237 Exclusions: • 4 died • 11 alcoholics

Bibliographic reference	**Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S (2010) Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clinical Infectious Diseases 50(6): 833-9**
	• 5 receiving hepatotoxic drugs • 27 HIV-infected Randomised = 175 • sequential reintroduction R→H→Z = 59 • sequential reintroduction H→R→Z = 58 • simultaneous reintroduction = 58
Patient characteristics	*Inclusion* Patients with a diagnosis of antituberculosis drug-induced hepatotoxicity, as defined by the following criteria: 1) an increase ≥5 times the upper limit of the normal levels (50 IU/l) of serum AST and/or ALT on 1 occasion, or >3 times the upper limit of normal (>150 IU/l) on 3 consecutive occasions; 2) an increase in serum total bilirubin >1.5 mg/dl; 3) any increase in serum AST and or ALT level above pretreatment values together with anorexia, nausea, vomiting, and jaundice; 4) absence of serological evidence of infection with hepatitis A, B, C, or E virus; and 5) improvement in liver function test results (serum bilirubin level <1 mg/dl; AST and ALT level <100 IU/l) after withdrawal of antituberculosis drugs Drug-induced hepatotoxicity was diagnosed if criteria 1, 2, or 3 were present in combination with criteria 4 and 5 Patients of either sex Patients who were 16-65 years of age Initial antituberculosis regimen: not explicitly stated, but appeared to include some or all of isoniazid, rifampicin, and pyrazinamide *Exclusion* Serological evidence of acute viral hepatitis Ultrasonographic evidence of chronic liver disease HIV infection Long-term alcoholism, defined as consumption of >48g of alcohol per day for at least 1 year Concomitant consumption of other potentially hepatotoxic drugs (e.g. methotrexate, phenytoin, valproate, and fluconazole Pregnancy

Bibliographic reference	**Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S (2010) Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clinical Infectious Diseases 50(6): 833-9**
	Baseline characteristics

Parameter	Arm I (*n* = 58)	Arm II (*n* = 59)	Arm III (*n* = 58)	*P*
Age, years	37.36 ± 12.75	33.68 ± 12.73	34.29 ± 13.19	.26
Female sex, %	41.38	57.63	55.17	.17
History of TB, %	12.07	15.25	6.90	.38
History of jaundice, %	5.17	6.78	0	.16
BMI	19.55 ± 3.29	19.28 ± 3.01	19.28 ± 3.06	.87
MAC, cm	21.93 ± 3.85	22.12 ± 3.58	21.29 ± 2.66	.39
Distribution of DIH cases with respect to site of TB, %				
Pulmonary TB	29.3	22.0	25.9	
Extrapulmonary TB	56.9	55.9	53.5	
Miliary/disseminated TB	13.8	22.0	20.7	.96
Moderately/far advanced TB on chest radiograph, %	29.3	25.4	27.5	.76
Serum bilirubin level, mg/dL	0.65 ± 0.12	0.69 ± 0.16	0.65 ± 0.14	.13
Serum protein level, g/dL	7.76 ± 0.60	7.57 ± 0.77	7.43 ± 0.64	.03
Serum albumin level, g/dL	4.03 ± 0.66	3.77 ± 0.60	3.75 ± 0.59	.03
AST level, IU/L	36.5 ± 10.14	35.6 ± 13.21	36.4 ± 10.78	.90
ALT level, IU/L	35.7 ± 12.01	32.4 ± 12.96	36.2 ± 12.73	.21
ALP level, IU/L	201.0 ± 103.8	178.1 ± 71.8	170.9 ± 50.3	.11

NOTE. Data are mean value (± standard deviation), unless otherwise indicated. Arms I, II, and III are defined in Table 1. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index, calculated as weight in kilograms divided by the square of the height in meters; MAC, mid-arm circumference; TB, tuberculosis.

Interventions	*Sequential reintroduction R→H→Z (arm II)* Treatment with the hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) was immediately stopped Patients were administered a modified antituberculosis drug regimen consisting of ethambutol, streptomycin and 1 of the flouroquinolones Patients were subsequently followed up at weekly intervals until clinical and biochemical parameters of acute liver injury stabilized (i.e. absence of vomiting and abdominal pain, both AST and ALT levels <100 IU/l, and serum bilirubin level <1.0 mg/dl) After stabilization of liver functions, drugs were administered in a manner similar to that recommended in the American Thoracic Society guidelines for reintroduction: • rifampicin at a maximum dosage from day 1 • isoniazid at a maximum dosage from day 8 • pyrazinamide at a maximum dosage from day 15 Maximum dosage was determined according to body weight, as follows: H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg

Bibliographic reference	**Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S (2010) Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clinical Infectious Diseases 50(6): 833-9**
	Sequential reintroduction H→R→Z (arm III) Treatment with the hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) was immediately stopped Patients were administered a modified antituberculosis drug regimen consisting of ethambutol, streptomycin and 1 of the flouroquinolones Patients were subsequently followed up at weekly intervals until clinical and biochemical parameters of acute liver injury stabilized (i.e. absence of vomiting and abdominal pain, both AST and ALT levels <100 IU/l, and serum bilirubin level <1.0 mg/dl) After stabilization of liver functions, drugs were administered in accordance with British Thoracic Society guidelines: • isoniazid at a dosage of 100 mg/day from day 1, maximum dosage from day 4 • rifampicin at a dosage of 150 mg/day from day 8, maximum dosage from day 11 • pyrazinamide at a dosage of 500 mg/day from day 15, maximum dosage from day 18 Maximum dosage was determined according to body weight, as follows: H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg
Comparator	*Simultaneous reintroduction (arm I)* Treatment with the hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) was immediately stopped Patients were administered a modified antituberculosis drug regimen consisting of ethambutol, streptomycin and 1 of the flouroquinolones Patients were subsequently followed up at weekly intervals until clinical and biochemical parameters of acute liver injury stabilized (i.e. absence of vomiting and abdominal pain, both AST and ALT levels <100 IU/l, and serum bilirubin level <1.0 mg/dl) After stabilization of liver functions, isoniazid, rifampicin, and pyrazinamide simultaneously at full dosage from day 1 Maximum dosage was determined according to body weight, as follows: H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg
Length of follow up	
Location	New Delhi and Tirupati, India
Outcomes measures and effect size	*Adverse events – recurrence of hepatitis* Number of patients to experience hepatitis during retreatment • sequential reintroduction R→H→Z = 6 of 59 • sequential reintroduction H→R→Z = 5 of 58 • simultaneous reintroduction = 8 of 58 *Sequential vs simultaneous reintroduction* • sequential reintroduction = 11 of 117

Bibliographic reference	**Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S (2010) Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clinical Infectious Diseases 50(6): 833-9**
	• simultaneous reintroduction = 8 of 58 • OR (95% CI)[1] = 0.65 (0.25 to 1.71) *Sequential reintroduction R→H→Z vs simultaneous reintroduction* • sequential reintroduction R→H→Z = 6 of 59 • simultaneous reintroduction = 4 of 29 • OR (95% CI)[1] = 0.71 (0.18 to 2.73) *Sequential reintroduction H→R→Z vs simultaneous reintroduction* • sequential reintroduction H→R→Z = 5 of 58 • simultaneous reintroduction = 4 of 29 • OR (95% CI)[1] = 0.59 (0.15 to 2.39)
Source of funding	No details given
Comments	
[1] Odds ratio and confidence interval calculated by reviewer Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; Z, pyrazinamide	

A.1.2 Tahaoğlu, 2001

Bibliographic reference	**Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, Gemci I, Ongel A, Kapakli N and Aksoy E (2001) The management of anti-tuberculosis drug-induced hepatotoxicity. International Journal of Tuberculosis and Lung Disease 5(1): 65-9**
Study type	Randomised controlled trial
Study quality	*Study limitations* Appropriate method of randomisation? *unclear* Adequate allocation concealment? *unclear* Participants blinded? *unclear* Individuals administering care blinded? *unclear*

Bibliographic reference	**Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, Gemci I, Ongel A, Kapakli N and Aksoy E (2001) The management of anti-tuberculosis drug-induced hepatotoxicity. International Journal of Tuberculosis and Lung Disease 5(1): 65-9**
	Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *yes* Valid and reliable method of outcome measurement? *yes* Intent-to-treat principle adhered to? *yes* *Inconsistency* Groups comparable at baseline? *risk factors for hepatotoxicity (age, sex, alcohol consumption, hepatitis markers, radiological extension of the disease in the lungs, pretreatment serum albumin level, diabetes mellitus, additional hepatotoxic drug use, body weight and body mass index) were compared statistically to ensure that there was no increased susceptibility to hepatotoxicity in either group; however, reintroduction without Z group had more individuals with extensive disease (P = 0.001) and more individuals with hypoalbuminemia (P = 0.053)* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups equivalent for intervention completion? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	n = 45 • sequential reintroduction without Z = 20 • simultaneous reintroduction of standard regimen = 25
Patient characteristics	Individuals with pulmonary tuberculosis or tuberculous pleurisy who had experienced drug-induced hepatotoxicity whilst receiving antituberculosis chemotherapy For the diagnosis of pulmonary tuberculosis at least two positive sputum specimens for acid-fast bacilli by microscopy and/or culture positivity for *Mycobacterium tuberculosis* were required Tuberculous pleurisy was diagnosed by detection of caseating granulomas in histopathological examination of tissue specimens taken by parietal pleural needle biopsy

Bibliographic reference	**Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, Gemci I, Ongel A, Kapakli N and Aksoy E (2001) The management of anti-tuberculosis drug-induced hepatotoxicity. International Journal of Tuberculosis and Lung Disease 5(1): 65-9**
	Initial antituberculosis regimen: • initial phase of 2 months consisting of HRZ and E (or S), followed by a continuation phase of 7 months consisting of HR • treatment was given daily • drug dosages: H: 300 mg/day; R: 600 mg/day; Z: 1500 mg/day; E: 1500 mg/day; S: 1000 mg/day Drug-induced hepatotoxicity was defined as normalisation of liver functions after withdrawal of all antituberculosis drugs, and at least one of the following criteria: • a rise to five times the normal levels (40 U/L) of serum AST and/or ALT • a rise in the level of serum total bilirubin over 1.5 mg/dl • any increase in AST and/or ALT above pretreatment levels, together with anorexia, nausea, vomiting and jaundice *Baseline characteristics* Risk factors / Group I ($n = 20$) n (%) / Group II ($n = 25$) n (%) / P Age >50: 7 (35) / 6 (24) / 0.418 Female sex: 3 (15) / 11 (44) / 0.036 Alcohol use: 3 (15) / 1 (4) / 0.223 Extensive disease: 9 (45) / 0 / 0.001 Hypoalbuminemia: 13 (65) / 9 (36) / 0.053 Diabetes mellitus: 2 (1) / 1 (4) / 0.415 Low body weight: 11 (55) / 13 (52) / 0.841 Low BMI: 7 (35) / 8 (32) / 0.832 Additional hepatotoxic drugs: 2 (1) / 3 (12) / 0.608 Paracetamol: 1 / 2 Chloropropamide: 1 / 1 All patients were HIV-negative
Intervention	*Sequential reintroduction without Z* When drug-induced hepatotoxicity was detected, all antituberculosis drugs were withdrawn After hepatotoxicity-related symptoms had disappeared and laboratory findings had returned to normal levels, antituberculosis treatment was reintroduced as follows: • day 1, S 1000 mg/day and E 1500 mg/day

Bibliographic reference	**Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, Gemci I, Ongel A, Kapakli N and Aksoy E (2001) The management of anti-tuberculosis drug-induced hepatotoxicity. International Journal of Tuberculosis and Lung Disease 5(1): 65-9**
	• day 3, S 1000 mg/day, E 1500 mg/day and H 100 mg/day • day 6, S 1000 mg/day, E 1500 mg/ day and H 200 mg/day • day 9, S 1000 mg/day, E 1500 mg/day and H 300 mg/day • day 12: S 1000 mg/day, E 1500 mg/day, H 300 mg/day and R 150 mg/day; day 15, S 1000 mg/day, E 1500 mg/day, H 300 mg/day and R 300 mg/day • day 18, S 1000 mg/day, E 1500 mg/day, H 300 mg/day and R 450 mg/day All of the patients were hospitalised for at least the first 2 months for retreatment
Comparison	*Simultaneous reintroduction of standard regimen* When drug-induced hepatotoxicity was detected, all antituberculosis drugs were withdrawn After hepatotoxicity-related symptoms had disappeared and laboratory findings had returned to normal levels, antituberculosis treatment was reintroduced with the same drug regimen as previously: H 300 mg/day, R 600 mg/day, Z 1500 mg/day and E 1500 mg/day, with no change All of the patients were hospitalised for at least the first 2 months for retreatment
Length of follow up	For the duration of retreatment
Location	Istanbul, Turkey
Outcomes measures and effect size	*Adverse events – recurrence of hepatitis* Number of patients to experience hepatitis during retreatment • sequential reintroduction without Z = 0 of 20 • simultaneous reintroduction of standard regimen = 6 of 25 • OR (95% CI)[1] = 0.07 (0.00 to 1.39)
	Cure Number of patients to be cured, defined as a sputum smear-positive patient who is smear-negative at completion of treatment • sequential reintroduction without Z = 20 of 20 • simultaneous reintroduction of standard regimen = 20 of 25 • OR (95% CI)[1] = 1.24 (0.02 to 65.4)
Source of funding	No details given
Comments	

[1] Odds ratio and confidence interval calculated by reviewer

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R,

Bibliographic reference	Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, Gemci I, Ongel A, Kapakli N and Aksoy E (2001) The management of anti-tuberculosis drug-induced hepatotoxicity. International Journal of Tuberculosis and Lung Disease 5(1): 65-9
rifampicin; S, streptomycin; Z, pyrazinamide	