**Supplementary table 1: Detailed databases search history**

|  |  |  |  |
| --- | --- | --- | --- |
| **S.N.** |  | **Search terms** | **citations** |
| **PubMed** | | | |
| 1 |  | chemical and drug induced liver injury OR chemical and drug induced liver injury, chronic | [28220](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) |
| 2 |  | anti-tuberculous therapy induced liver injury OR anti-tuberculosis drug-induced liver injury OR att hepatotoxicity OR Hepatotoxicity OR Liver injury OR drug induced acute liver injury OR drug-induced liver injury OR drug-induced liver condition OR drug-induced liver disease OR drug induced liver disorders OR drug-induced liver failure OR drug-induced liver damage OR drug-induced hepatotoxicity OR drug-induced hepatic injury OR drug-induced hepatitis OR drug-induced cholestasis OR idiosyncratic liver condition OR idiosyncratic liver disease OR idiosyncratic liver disorder OR toxic hepatitis OR toxic liver condition OR toxic liver disease OR toxic liver disorders | [138545](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) |
| 3 |  | reintroduction of anti-tubercular drugs OR reintroduction of anti-tubercular therapy OR att reintroduction guidelines OR reintroduction of rifampicin OR reintroduction of isoniazid OR reintroduction of pyrazinamide | [298](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) |
| 4 | (1 OR 2) AND 3 |  | [19](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) |
| Embase | | | |
| 1 | 1 | ‘chemical and drug induced liver injury’ OR ‘chemical and drug induced liver injury, chronic’ | 8 |
| 2 | 2 | 'anti-tuberculous therapy induced liver injury' OR 'anti-tuberculosis drug-induced liver injury' OR 'att hepatotoxicity' OR hepatotoxicity OR 'liver injury' OR 'drug induced acute liver injury' OR 'drug-induced liver injury’ OR ‘drug-induced liver condition’ OR ‘drug-induced liver disease’ OR ‘drug induced liver disorders’ OR ‘drug-induced liver failure’ OR ‘drug-induced liver damage’ OR ‘drug-induced hepatotoxicity’ OR ‘drug-induced hepatic injury’ OR ‘drug-induced hepatitis’ OR ‘drug-induced cholestasis’ OR ‘idiosyncratic liver condition’ OR ‘idiosyncratic liver disease' OR 'idiosyncratic liver disorder' OR 'toxic hepatitis' OR 'toxic liver condition' OR 'toxic liver disease' OR 'toxic liver disorders' | 96886 |
| 3 |  | ‘reintroduction of anti-tubercular drugs’ OR ‘reintroduction of anti-tubercular therapy’ OR ‘att reintroduction guidelines’ OR ‘reintroduction of rifampicin’ OR ‘reintroduction of isoniazid’ OR ‘reintroduction of pyrazinamide’ |  |
| 4 | (1 OR 2) AND 3 |  | 5 |
| Scopus | | | |
| 1 | 1 | “chemical and drug induced liver injury” OR ”chemical and drug induced liver injury, chronic” | 2,519  2673 |
| 2 | 2 | “anti-tuberculous therapy induced liver injury” OR “anti-tuberculosis drug-induced liver injury” OR “att hepatotoxicity” OR hepatotoxicity OR “liver injury” OR “drug induced acute liver injury” OR “drug-induced liver injury” OR “drug-induced liver condition” OR “drug-induced liver disease” OR “drug induced liver disorders” OR “drug-induced liver failure” OR “drug-induced liver damage” OR “drug-induced hepatotoxicity” OR “drug-induced hepatic injury” OR “drug-induced hepatitis” OR “drug-induced cholestasis” OR “idiosyncratic liver condition” OR “idiosyncratic liver disease” OR “idiosyncratic liver disorder” OR “toxic hepatitis” | 219,356 |
| 3 | 3 | “toxic liver condition” OR “toxic liver disease” OR “toxic liver disorders” | 264 |
| 4 | 4 | “reintroduction of anti-tubercular drugs” OR “reintroduction of anti-tubercular therapy” OR “anti-tubercular therapy **reintroduction guidelines” OR “**reintroduction of rifampicin” OR “reintroduction of isoniazid” OR “reintroduction of pyrazinamide” | 22 |
| 5 | (1 OR 2 OR 3) AND 4 | ( "anti-tuberculous therapy induced liver injury"  OR  "anti-tuberculosis drug-induced liver injury"  OR  "att hepatotoxicity"  OR  hepatotoxicity  OR  "liver injury"  OR  "drug induced acute liver injury"  OR  "drug-induced liver injury" )  OR  ( "toxic liver condition"  OR  "toxic liver disease"  OR  "toxic liver disorders" ) OR   ( "chemical and drug induced liver injury"  OR  "chemical and drug induced liver injury, chronic" )  AND ( "reintroduction of anti-tubercular drugs"  OR  "reintroduction of anti-tubercular therapy"  OR  "anti-tubercular therapy reintroduction guidelines"  OR  "reintroduction of rifampicin"  OR  "reintroduction of isoniazid"  OR  "reintroduction of pyrazinamide" ) | 10 |
| Web of Science | | | |
| 1 | 1 | (‘chemical and drug induced liver injury’ OR ‘chemical and drug induced liver injury, chronic’)Timespan: All years. Databases:  WOS, KJD, RSCI, SCIELO.Search language=Auto | 27,769 |
| 2 | 2 | ('anti-tuberculous therapy induced liver injury' OR 'anti-tuberculosis drug-induced liver injury' OR 'att hepatotoxicity' OR hepatotoxicity OR 'liver injury' OR 'drug induced acute liver injury' OR 'drug-induced liver injury’ OR ‘drug-induced liver condition’ OR ‘drug-induced liver disease’ OR ‘drug induced liver disorders’ OR ‘drug-induced liver failure’ OR ‘drug-induced liver damage’ OR ‘drug-induced hepatotoxicity’ OR ‘drug-induced hepatic injury’ OR ‘drug-induced hepatitis’ OR ‘drug-induced cholestasis’ OR ‘idiosyncratic liver condition’ OR ‘idiosyncratic liver disease' OR 'idiosyncratic liver disorder' OR 'toxic hepatitis' OR 'toxic liver condition' OR 'toxic liver disease' OR 'toxic liver disorders')Timespan: All years. Databases:  WOS, KJD, RSCI, SCIELO.Search language=Auto | 184,913 |
| 3 | 3 | (‘reintroduction of anti-tubercular drugs’ OR ‘reintroduction of anti-tubercular therapy’ OR ‘att reintroduction guidelines’ OR ‘reintroduction of rifampicin’ OR ‘reintroduction of isoniazid’ OR ‘reintroduction of pyrazinamide’)Timespan: All years. Databases:  WOS, KJD, RSCI, SCIELO.Search language=Auto | 43 |
| 4 | (1 OR 2) AND 3 | #3 AND #4Timespan: All years. Databases:  WOS, KJD, RSCI, SCIELO.Search language=Auto | 20 |
| LILACS | | | |
| 1 | 1 | reintroduction of rifampicin OR reintroduction of isoniazid OR reintroduction of pyrazinamide | 15 |
| CENTRAL (Cochrane library) | | | |
| 1 | 1 | chemical and drug induced liver injury | 353 |
| 2 | 2 | antitubercular agents | 1522 |
| 3 | 1 AND 2 | 41 trials, 1 review | 42 |
| Clinical trial.gov | | | |
| 1 | 1 | reintroduction of anti-tubercular drugs | 2 |
| ScienceDirect | | | |
| 1 | 1 | reintroduction of anti-tubercular drugs | 30 |

**Supplementary table 2: Description of ATT reintroduction regime used in included studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID** | **Tahaoglu 2001** | **Sharma 2010** | **Zuberi 2014** | **Meena 2016** |
| Group: 1 **Sequential regimen** |  | Day 1- R (maximum dosage)    Day 8 - H (maximum dosage)    Day 15 - Z (maximum dosage) | Day 1- R (maximum dosage)    Day 8 - H (maximum dosage)  Day 15 - Z (maximum dosage) | **Group A:**  Day 1- R (maximum dosage)  Day 8- H (maximum dosage) |
| **Group B:**  Day 1- H (maximum dosage)  Day 8- R (maximum dosage) |
| Pyrazinamide was added if they tolerated the above regimen in 3 weeks |
| Number of patients with recurrence of ATT induced hepatitis after reintroduction of anti-TB drugs with total patients |  | 6/59 | 18/162 | 3/22 |
| Group: 2 **Incremental regimen** | Drug regimens not containing Z were started gradually as follows    Day 1, S 1000 mg/day and E 1500 mg/day  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, E1500 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 | Day 1 - H 100 mg/day, maximum dosage from day 4    Day 8 - R -150 mg/day, maximum dosage from day 11    Day 15 - Z 500 mg/day from, maximum dosage from day 18 | Day 1 - H=100 mg/day, maximum dose from day 4    Day 8 - R=150 mg/day, maximum from day 11    Day 15 - Z=500 mg/day, maximum from day 18 |  |
| Number of patients with recurrence of ATT induced hepatitis after reintroduction of anti-TB drugs with total patients | 0/20 | 5/58 | 16/163 |  |
| Group: 3 **Concomitant regimen** | Retreated with the same drug regimen as previously, i.e.,  H 300 mg/day,  R 600 mg/day,  Z 1500 mg/day  E 1500 mg/day | H, R, and Z at maximum dosages from day 1 |  | H and R at full dosages from day 1 |
| Number of patients with recurrence of ATT induced hepatitis after reintroduction of anti-TB drugs with total patients | 6/25 | 8/58 |  | 4/10 |

H: isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin

**Supplementary Table 3: Odd ratio of the** **direct and indirect comparisons**

|  |  |  |  |
| --- | --- | --- | --- |
| ATT regimens | Comparison | Odds ratio with 95% CrI | P value |
| Incremental vs Concomitant | Direct | 0.17 (0.0044, 2.2) | 0.979 |
| Indirect | 0.18 (0.00075, 41) |
| Sequential vs Concomitant | Direct | 0.45 (0.041, 3.8) | 0.018 |
| Indirect | 5.3×10-13 (4.4×10-41, 0.056) |
| Sequential vs Incremental | Direct | 1.2 (0.17, 8.7) | 0.031 |
| Indirect | 5.4×1010(2.8, 1.7×1036) |

**Supplementary Table 4: Critical interpretation of analyzed ATT regimens**

|  |  |  |  |
| --- | --- | --- | --- |
| Regimen | Risk of ATT Hepatitis | Delay in initiation of ATT | Recognition of Culprit agent |
| Concomitant | Highest risk | No delay | Not possible |
| Sequential | Low risk | Some delay | Possible |
| Incremental | Lowest risk | Maximum delay | Possible |

-: Least risk/chance

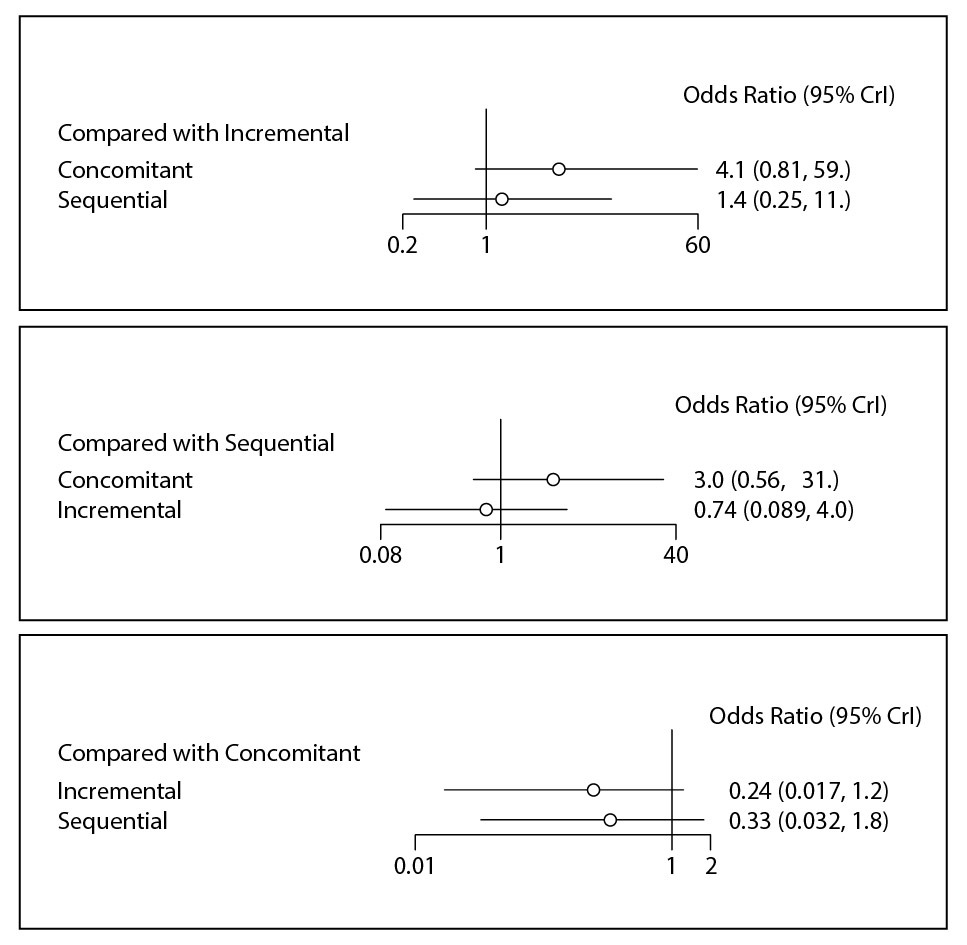
+ : Some risk

++: High risk

**Supplementary Figure 1: Direct comparisons between the various reintroduction regimens**

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**Supplementary Figure 2: Odd ratio of the direct comparisons with taking a regimen as standard**



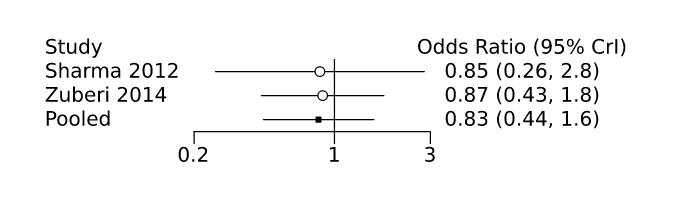
**Supplementary Figure 3: The Gelman Rubin Plot of the variation in the Shrink factor with modelling**

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**Supplementary Figure 4:** The SUCRA plot for all three reintroduction regimens

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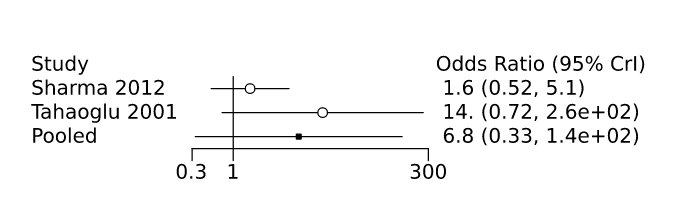
**Supplementary Figure 5:** Pairwise meta-analysis providing comparison between all three regimens in all possible combinations



Incremental vs Sequential



Concomitant vs Sequential



Concomitant vs Incremental

**Supplementary Figure 6:** Pairwise meta-analysis comparing staggered regimen with concomitant reintroduction; A: random effect model and B: Fixed effect model

