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► To cite this version:

A. Bosch, F. Valour, O. Dumitrescu, J. Dumortier, S. Radenne, et al.. A practical approach to tuberculosis diagnosis and treatment in liver transplant recipients in a low-prevalence area. *Médecine et Maladies Infectieuses*, 2019, 49, pp.231 - 240. 10.1016/j.medmal.2018.11.013 . hal-03485091

HAL Id: hal-03485091

<https://hal.science/hal-03485091>

Submitted on 21 Dec 2021

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A practical approach to tuberculosis diagnosis and treatment in liver transplant recipients in a low-prevalence area

Approche pratique de la prise en charge diagnostique et thérapeutique de la tuberculose chez les patients transplantés hépatiques en zone de faible prévalence

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[§] Members of the Lyon TB study group are listed in the acknowledgement section.

Keywords: *Mycobacterium tuberculosis*; liver transplantation

Mots clés : *Mycobacterium tuberculosis* ; transplantation hépatique

Abstract

Solid-organ transplant candidates/recipients are at risk of mycobacterial infections. Although guidelines on the management of latent tuberculosis infection and active tuberculosis are available for solid organ transplant recipients, limited guidance focuses on end-stage liver disease or liver transplant recipients who require management in a referral center. Therapeutic challenges arise from direct antituberculosis drug-related hepatotoxicity, and substantial metabolic interactions between immunosuppressive and antituberculosis drugs. Another issue is the optimal timing of therapy with regards to the time of transplantation. This review focuses on the importance of tuberculosis screening with immunological tests, challenges in the diagnosis, management, and treatment of latent tuberculosis infection and active tuberculosis, as well as risk assessment for active tuberculosis in the critical peri-liver transplantation period. We detail therapeutic adjustments required for the management of antituberculosis drugs in latent tuberculosis infection and active tuberculosis, particularly when concomitantly using rifampicin and immunosuppressive drugs.

Résumé

Les patients receveurs ou en attente d'une greffe d'organe solide ont un risque accru d'infection mycobactérienne. Les recommandations sur la gestion de l'infection tuberculeuse latente et de la tuberculose maladie chez les transplantés d'organe solide ne tiennent pas compte des particularités des patients en attente de transplantation porteurs d'une hépatopathie chronique évoluée ou transplantés hépatiques. Ces patients nécessitent une approche diagnostique spécifique, une stratégie thérapeutique combinant le timing du traitement par rapport à la transplantation et la gestion du risque de toxicité hépatique cumulée des antituberculeux et des immunosuppresseurs. Le dépistage de la tuberculose latente par tests immunologiques et les défis de la prise en charge diagnostique et thérapeutique de la tuberculose dans la période critique encadrant la transplantation hépatique sont les points importants. La surveillance pharmacologique et les ajustements nécessaires vis-à-vis des antituberculeux du fait de l'hépatopathie sous-jacente et des interactions avec les immunosuppresseurs sont proposés.

1. Introduction

Solid organ transplant recipients have a 20- to 75-fold increased risk of developing active tuberculosis compared with the general population [1]. Factors involved in the rate of post-transplant tuberculosis are recipient- and donor population-based prevalence (low- and high-endemicity area), the type of organ transplanted, pre-transplant latent tuberculosis infection screening, and a history of antituberculosis therapy [1,2]. Post-transplant active tuberculosis is also associated with an increased risk of graft loss and with a four-fold increase in lethal outcome after solid organ transplantation compared with the general population [3,4].

The diagnosis of active tuberculosis is challenging after solid organ transplantation because the percentage of recipients who develop extra-pulmonary or disseminated tuberculosis is higher than in the general population, and transplant-related conditions – particularly allograft organ rejection – can mimic tuberculosis presentation. In the specific setting of liver transplantation, further difficulties are associated with tuberculosis treatment: as most antituberculosis drugs require fully functional liver capacity, the risk of drug-induced adverse events is higher for liver transplant recipients, whether considering the intrinsic hepatotoxic effect of each drug (e.g., isoniazid and pyrazinamide) or the drug-drug interactions (e.g., rifampicin with immunosuppressive drugs and corticosteroids).

This review addresses specific challenges related to mycobacterial infections in case of liver transplantation. We intended to provide comprehensive guidance for the management of mycobacterial infections in case of liver transplantation focusing on prevention, clinical presentation, diagnostic assessment, and treatment optimization.

2. Epidemiology

2.1. Incidence and prevalence

The prevalence of tuberculosis reported among solid organ transplant recipients is 0.5-6.4% and 15.2% in low- and high-endemicity areas, respectively [2,5]. The prevalence of active tuberculosis was assessed at 1.3% (n=104/8,296) in a systematic review performed between 1963 and 2007, including liver transplant recipients [4]. The peak of tuberculosis incidence occurs during the first year after liver transplantation, matching the highest level of immunosuppression with a median onset between 6 and 16 months [1,6,7]. The pre-cited review reported a mean time of 1.1 month (range, 0-3.2) from symptom onset to tuberculosis diagnosis [4].

2.2. Risk factors

Risk factors for active tuberculosis after liver transplantation are listed in Table 1. A study matching liver transplant recipients with 10 randomly selected non-liver transplanted individuals by age, sex, and presence of comorbidities reported that age ≥ 50 years and mTOR inhibitors (i.e., everolimus and sirolimus) were significant risk factors for tuberculosis [6].

2.3. Outcome

Active tuberculosis-related case fatality among liver transplant recipients ranges from 30% to 40% in historic series [2,14,15]. Recently, the case fatality among a cohort of 49 patients presenting with active tuberculosis after liver transplantation was reported to be 26% [6]. The

attributable case fatality was 18% in a review [4] of 104 liver transplant recipients. Early disease onset (i.e., within five months after liver transplantation) is associated with a higher case fatality (36% vs. 17%, $p=0.04$) [4]. mTOR inhibitors were reported as independent risk factor for mortality [6]. Tuberculosis-associated immune reconstitution syndrome was assessed in 64 consecutive solid organ transplant recipients with a 12-month tuberculosis follow-up [16]. An immune reconstitution syndrome developed in 14% of patients (median of 47 days after antituberculosis therapy initiation). Liver transplantation, cytomegalovirus infection, and rifampicin use were identified as risk factors for the development of immune reconstitution syndrome.

3. Screening and treatment of latent tuberculosis infection

An executive summary is provided in Table 2 and Figure 1.

3.1. Screening for latent tuberculosis infection

Latent tuberculosis infection is a concern both in the pre- and post-transplantation period as recipients experience lifelong immunosuppression with a permanent risk of reactivation. Current guidelines recommend screening all living donor and recipient candidates for latent tuberculosis infection [8,12,17]. Although immunosuppressive drugs should in theory equally hamper T-cell reactivity in tuberculin skin test (TST) and in interferon gamma release assays (IGRAs), evidence indicates that IGRAs are less affected in patients with immunosuppression [18]. The performance of IGRAs seems to be further hampered among liver transplant candidates compared with non-liver transplant candidates, proportionally to end-stage liver

disease progression [19]. When immunological tests are negative in candidates with risk factors (Table 1), latent tuberculosis infection requires further assessment. The CT scan is the most accurate method to detect latent tuberculosis infection before liver transplantation [20], and several authors argue for a systematic lung CT scan in solid organ transplant candidates [10]. Practices at our facility have evolved to include an exploratory chest-abdomen-pelvic CT scan in case of positive screening for latent tuberculosis infection. When morphological findings suggestive of active or latent tuberculosis are observed (for instance reticular or nodular lung infiltrates), endobronchial aspirates must be collected through pre-transplant endoscopy. In this setting, an ^{18}F FDG PET/CT can also help to evaluate the infectious activity of the lesions [21], and therefore supports the decision to treat as a latent infection or an active disease.

3.2. Management of latent tuberculosis infection

If one or both immunological test result(s) is/are positive, latent tuberculosis infection treatment must be initiated after having excluded an active disease. Isoniazid is the drug of choice for latent tuberculosis infection in solid organ transplant patients over a 6- to 9-month period [8,12,17]. The alternative regimen is an isoniazid/rifampicin combination for 3 to 4 months, but their cumulative hepatotoxicity enhances the risk of fulminant hepatitis [22]. A recent network meta-analysis provided new insights into the benefits and hepatotoxicity risk of the various treatment options for latent tuberculosis infection [23]. Results suggest that rifampicin alone for 3-4 months is at least as effective as the 6- to 9-month single isoniazid treatment and has been associated with lower rates of hepatotoxicity. This shorter therapy duration may also improve treatment compliance and thus treatment completion. The 3- to

4-month single treatment with rifampicin could be considered as the first-line choice for latent tuberculosis infection treatment in the pre-transplantation period only as rifampicin-induced drug interactions limit its use after liver transplantation. The appropriate timing for latent tuberculosis infection treatment is unknown. Patients should theoretically be treated before liver transplantation. However, various specificities of the pre-transplantation period likely influence the decision making: *(i)* the timing of transplantation cannot be predicted, except for living donor transplantation; *(ii)* isoniazid use can induce acute liver failure (evaluated at 6% of treated patients) and precipitate liver transplantation procedure [22]; *(iii)* to avoid drug-induced toxicity on the implanted graft, we suggest discontinuing the latent tuberculosis infection treatment at the start of the transplantation process. A study reported a median time of five days (range, 3-12 days) to obtain graft stabilization, which is considered a reasonable minimal time before re-initiating isoniazid [7]. Antituberculosis therapeutic drug monitoring is also strongly suggested in the pre- and post-transplantation period due to metabolic changes induced by hepatic replacement. For cases detected at an advanced end-stage liver disease, the favored option is to wait for the liver transplantation and to initiate isoniazid upon graft stabilization [11].

Future research should focus on finding a safe alternative to isoniazid or rifampicin for latent tuberculosis infection in liver transplant recipients. A multicenter randomized safety trial reported a high incidence (18.2%) of severe tenosynovitis when using levofloxacin prophylaxis in liver transplant candidates [24]. Another monocenter retrospective experience of latent tuberculosis infection treatment with fluoroquinolones in 25 liver transplant candidates (17 on levofloxacin and eight on moxifloxacin) reported a much lower incidence (4%) of fluoroquinolone-related adverse events [25]. Among new antituberculosis drugs, bedaquiline has been approved as part of the combination therapy of multidrug-resistant (MDR)

pulmonary tuberculosis only, although active on drug-susceptible tuberculosis. Bedaquiline is metabolized by cytochrome P450 isoenzyme 3A4 to a less active metabolite, implying that the most frequent drug-drug interactions with immunosuppressive drugs are predictable [26]. Delamanid, a new nitroimidazole compound active against MDR tuberculosis, has few interactions with drugs metabolized by the cytochrome P450 enzyme (including CYP3A4) and fewer hepatotoxic effects [27]. The positioning of these two drugs in tuberculosis treatment strategies among solid organ transplant recipients and more restrictively liver transplant candidates/recipients, remains to be determined.

4. Mechanisms of transmission

A schematic representation of the mechanisms of transmission is provided in Figure 2. Endogenous reactivated latent tuberculosis infection accounts for most post-liver transplant cases of active tuberculosis, and usually occurs within the year after transplantation (Figure 2A) [12]. However, donor-derived tuberculosis transmission accounted for 3.6% of cases in a systematic review of 139 recipients [4] and may result from the transplantation of an organ from a donor with unrecognized active tuberculosis or graft-containing latent tuberculosis infection (Figure 2B) [28]. Consequently, living donors should be systematically screened before proceeding with liver transplantation (Table 2). Histological analysis of the graft may also help in detecting donor-derived transmission but has not been evaluated. The rate of *de novo* infection is likely to be higher in high- vs. low-endemicity area, although difficult to document. Liver transplant recipients who are exposed to and become infected with *M. tuberculosis* also have an increased risk of immediate progression to active tuberculosis (Figure 2C).

5. Diagnostic assessment of active tuberculosis

An executive summary is provided in Table 3.

5.1. Clinical features

Fever is more frequent in solid organ transplant recipients than in the general population [29]. Cryptic fever can be the only manifestation for weeks. Other hallmark symptoms such as night sweats and weight loss occur less frequently in solid organ transplant recipients [29]. Disseminated or extra-pulmonary presentations are more common after liver transplantation, accounting for up to 67% of cases compared with 15% of cases in standard patients [1–3,30]. These atypical clinical presentations postpone treatment initiation, with a mean time to treatment after symptom onset of 4.7 months (range, 1-16) [29].

5.2. Morphological evaluation

A wide range of radiographic manifestations can be observed in patients presenting with pulmonary tuberculosis (Figure 3), including focal infiltrate, miliary pattern, nodules (Figure 3B and 2C), pleural effusions (Figure 3C), and/or diffuse interstitial infiltrates (Figure 3C). However, tuberculosis with cavitation is less common as impaired T-cells fail to clear lung granuloma [29,31]. A normal chest X-ray is observed in up to 30% of solid organ transplant recipients presenting with active tuberculosis [29]. A chest-abdomen-pelvic CT scan is strongly recommended as extra-pulmonary presentations are more common (Figure 3A). Finally, ¹⁸FDG

PET/CT has demonstrated good sensitivity in standard tuberculosis but remains to be evaluated in solid organ transplant recipients [21,32].

5.3. Histopathological findings

The presence of granulomas on the explanted liver at the time of transplantation and in the absence of alternative etiological cause is a risk factor for post-transplantation tuberculosis [33].

Considering the atypical clinical presentation and frequent negativity of mycobacterial investigations, the diagnosis of post-transplantation tuberculosis often relies on pathological findings. However, in immunosuppressed hosts, tuberculosis is frequently associated with non-specific non-necrotic tissular granuloma, making the differential diagnosis between tuberculosis and acute cellular rejection challenging. The presence of liver graft granuloma is indeed not uncommon (up to 7.5% of patients) and is mostly related to acute cellular rejection and primary biliary cirrhosis relapse [34].

5.4. Bacteriological assessment

Tuberculosis diagnosis in solid organ transplant recipients can only be confirmed by *Mycobacterium tuberculosis* cultures or by identifying specific nucleic acid sequences in clinical specimens. The diagnostic approach aims at obtaining direct sampling from the involved sites: e.g., liver or lymph node biopsies, ascites aspiration [35]. Specimens should be sent for smear and culture for acid-fast bacilli detection, alongside with an histopathological evaluation. Culture remains the most sensitive detection method when using a combination

of liquid and solid mycobacterial culture specific media. Besides diagnostic assessment, growth allows species identification and full drug susceptibility testing. In case of fever of unknown origin raising suspicion of a disseminated disease, mycobacterial blood cultures should be obtained [36]. Amplification tests performed on extra-pulmonary specimens may confirm the clinical diagnosis, but do not rule it out. Xpert MTB/RIF (Cepheid, Sunnyvale, USA), an automated molecular test for *M. tuberculosis* and resistance to rifampicin detection, was recently shown to decrease time to diagnosis. However, such tests may be falsely negative when low levels of mycobacteria are present, such as in solid organ transplant recipients. Caution should be exercised when interpreting negative results, as the sensitivity in case of tissue specimens does not exceed 69% compared with culture results [37].

6. Treatment of active tuberculosis with a focus on pharmacological adjustments

An executive summary is provided in Table 4.

No general guidelines are available on the best drug combination and therapy duration for liver transplant recipients presenting with active tuberculosis. Antituberculosis drugs should be chosen on a case-by-case basis, taking into account the liver function, the individual risk and consequence of hepatotoxicity, the graft rejection risk, the risk of drug-drug interactions with immunosuppressive drugs and corticosteroids, and most importantly the clinical presentation and severity of tuberculosis [4]. Rifampicin and pyrazinamide are the most sterilizing drugs with the best probability of successful outcome for standard tuberculosis therapy. They are also the least appropriate in liver transplant patients because of major drug interactions with immunosuppressive drugs induced by rifampicin and intrinsic hepatotoxicity for pyrazinamide [51,57,62]. It has been estimated that 35% of liver transplant recipients

presenting with active tuberculosis experience treatment discontinuation because of hepatotoxicity (73%) and/or drug interactions (30%) [4]. A literature-based comprehensive approach of tuberculosis treatment in that setting features the following points (Table 4): (i) the induction phase should include at least three drugs with a proven antituberculosis activity; (ii) in patients presenting with severe or disseminated tuberculosis, the optimal induction regimen should include a rifamycin drug (rifampicin or rifabutin) and pyrazinamide; (iii) in patients presenting with localized or non-severe tuberculosis or with significant residual liver disease, pyrazinamide may not be used for safety reason; (iv) in case of rifamycin use (rifampicin or rifabutin), concentrations of immunosuppressive drugs should be monitored at least once a week and the dose should be increased as necessary to reach therapeutic levels. Accordingly, similar close monitoring of immunosuppressive drug concentrations is required after rifamycin discontinuation to guide the gradual dose decrease and to avoid an excessive exposure; (v) rifabutin should be considered for use in place of rifampicin (reduced induction potency) in case of a high risk of rejection and/or inability to maintain therapeutic concentrations of immunosuppressive drugs; (vi) genotype or phenotype-based dosing of isoniazid should be considered whenever possible, to optimize early response and safety. Therapeutic drug monitoring of isoniazid, pyrazinamide, and rifamycins should be performed, at least initially, to ensure achievement of target exposure. Therapeutic drug monitoring should be repeated every week or every other week for rifamycins during the induction phase because of potentially decreased concentrations due to auto-induction [38,47,48]; (vii) fluoroquinolones, ethambutol, cycloserine, or aminoglycosides may be used in case of hepatotoxicity with first-line agents; (viii) maintenance tuberculosis therapy should include isoniazid and a rifamycin as long as tolerability permits; (ix) the optimal duration is not determined and should be considered on a case-by-case basis. An initial induction/intensive

phase of two months is advisable with at least three active antituberculosis drugs [8,9,36]. The duration of maintenance therapy also depends on the use of rifamycins and on the presentation as localized non-cavitary disease, which allows for a standard total duration of 6 to 9 months [9,36]. Otherwise, rifamycin-free regimens, and/or cryptic tuberculosis localizations (central nervous system, bone and joints), and/or disseminated tuberculosis require a prolonged treatment of up to 12-18 months [8].

7. Conclusion

The risk of active tuberculosis after liver transplantation implies a systematic screening of latent tuberculosis infection prior to transplantation. However, the risk of post liver transplantation tuberculosis cannot be completely ruled out due to the poor accuracy of immunological tests and the risk of *de novo* infection or donor-related reactivation. The diagnosis of post-transplantation tuberculosis is challenging, with a high frequency of nonspecific symptoms, non-necrotic granuloma, and negative mycobacterial identification. Treatment must be initiated as soon as the diagnosis is clinically suspected. Monitoring of antituberculosis drugs, as well as immunosuppressive drugs is highly recommended in liver transplant recipients.

Acknowledgements

The authors gratefully acknowledge Pr. Fabien Zoulim and Pr. Jean-Yves Mabrut for their assistance with this work.

Lyon TB study group members: Ader F, Benech N, Biron F, Boibieux A, Bouaziz A, Braun E, Catho G, Chidiac C, Chumbi-Flores W, Conrad A, Couraud S, Devouassoux G, Dumitrescu O, Ferry T, Freymond N, Gerbier-Colomban S, Gillet Y, Goutelle S, Grard S, Grima R, Hees L, Hodille E, Kiakouama-Maleka L, Lina G, Maury JM, Miallhes P, Perpoint T, Perrot E, Provoost J, Reix P, Ronaux-Baron AS, Roux S, Saison J, Sénéchal A, Souquet PJ, Tronc F, Valour F, Vanhems P.

Funding

This review was carried out as part of our routine work.

Contribution of authors

AB performed the literature analysis and wrote the first draft of the article, with the help of OD for bacteriological aspects; JD, SR, and MPE for liver disease and transplantation aspects; FV, CC, TF, TP, AC, PM, and FA for infectious disease aspects; and SG for pharmacological aspects.

All authors reviewed the article and approved its final version.

FV and FA are the project initiators and coordinated it until the submission of the article.

Declaration of interests

The authors declare no competing interests.

References

- [1] Subramanian A, Dorman S, AST Infectious Diseases Community of Practice. Mycobacterium tuberculosis in solid organ transplant recipients. *Am J Transplant*. 2009;9 Suppl 4:S57–62.
- [2] Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis*. 1998;27:1266–77.
- [3] Aguado JM, Herrero JA, Gavalda J, Torre-Cisneros J, Blanes M, Rufi G, et al. Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. *Transplantation*. 1997;63:1278–86.
- [4] Holty J-EC, Gould MK, Meinke L, Keefe EB, Ruoss SJ. Tuberculosis in liver transplant recipients: a systematic review and meta-analysis of individual patient data. *Liver Transplant*. 2009;15:894–906.
- [5] Currie AC, Knight SR, Morris PJ. Tuberculosis in renal transplant recipients: the evidence for prophylaxis. *Transplantation*. 2010;90:695–704.
- [6] Chen C-Y, Liu C-J, Feng J-Y, Loong C-C, Liu C, Hsia C-Y, et al. Incidence and Risk Factors for Tuberculosis After Liver Transplantation in an Endemic Area: A Nationwide Population-Based Matched Cohort Study. *Am J Transplant*. 2015;15:2180–7.
- [7] Fábrega E, Sampedro B, Cabezas J, Casafont F, Mieses MÁ, Moraleja I, et al. Chemoprophylaxis with isoniazid in liver transplant recipients. *Liver Transplant*. 2012;18:1110–7.

- [8] Subramanian AK, Morris MI, AST Infectious Diseases Community of Practice. Mycobacterium tuberculosis infections in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:68–76.
- [9] Bumbacea D, Arend SM, Eyuboglu F, Fishman JA, Goletti D, Ison MG, et al. The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement. *Eur Respir J*. 2012;40:990–1013.
- [10] Horne DJ, Narita M, Spitters CL, Parimi S, Dodson S, Limaye AP. Challenging issues in tuberculosis in solid organ transplantation. *Clin Infect Dis*. 2013;57:1473–82.
- [11] Aguado JM, Torre-Cisneros J, Fortún J, Benito N, Meije Y, Doblas A, et al. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. *Clin Infect Dis*. 2009;48:1276–84.
- [12] Torre-Cisneros J, Doblas A, Aguado JM, San Juan R, Blanes M, Montejo M, et al. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. *Clin Infect Dis*. 2009;48:1657–65.
- [13] Canet E, Dantal J, Blancho G, Hourmant M, Coupel S. Tuberculosis following kidney transplantation: clinical features and outcome. A French multicentre experience in the last 20 years. *Nephrol Dial Transplant*. 2011;26:3773–8.
- [14] Meyers BR, Halpern M, Sheiner P, Mendelson MH, Neibart E, Miller C. Tuberculosis in liver transplant patients. *Transplantation*. 1994;58:301–6.
- [15] Meyers BR, Papanicolaou GA, Sheiner P, Emre S, Miller C. Tuberculosis in orthotopic liver transplant patients: increased toxicity of recommended agents; cure of disseminated infection with nonconventional regimens. *Transplantation*. 2000;69:64–9.

- [16] Sun H-Y, Munoz P, Torre-Cisneros J, Aguado JM, Lattes R, Montejo M, et al. Mycobacterium tuberculosis-associated immune reconstitution syndrome in solid-organ transplant recipients. *Transplantation*. 2013;95:1173–81.
- [17] Morris MI, Daly JS, Blumberg E, Kumar D, Sester M, Schluger N, et al. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. *Am J Transplant*. 2012;12:2288–300.
- [18] Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR*. 2010;59:1–25.
- [19] Theodoropoulos N, Lanternier F, Rassiwalla J, McNatt G, Preczewski L, DeMayo E, et al. Use of the QuantiFERON-TB Gold interferon-gamma release assay for screening transplant candidates: a single-center retrospective study. *Transpl Infect Dis*. 2012;14:1–8.
- [20] Lyu J, Lee S-G, Hwang S, Lee S-O, Cho O-H, Chae EJ, et al. Chest computed tomography is more likely to show latent tuberculosis foci than simple chest radiography in liver transplant candidates. *Liver Transplant*. 2011;17:963–8.
- [21] Kim IJ, Lee JS, Kim SJ, Kim YK, Jeong YJ, Jun S, et al. Double-phase 18F-FDG PET-CT for determination of pulmonary tuberculoma activity. *Eur J Nucl Med Mol Imaging*. 2008;35:808-14.
- [22] Li X, Liu Y, Zhang E, He Q, Tang Y-B. Liver Transplantation in Antituberculosis Drugs-Induced Fulminant Hepatic Failure: A Case Report and Review of the Literature. *Medicine (Baltimore)*. 2015;94:e1665.
- [23] Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. *Ann Intern Med*. 2014;161:419–28.

- [24] Torre-Cisneros J, San-Juan R, Rosso-Fernández CM, Silva JT, Muñoz-Sanz A, Muñoz P, et al. Tuberculosis prophylaxis with levofloxacin in liver transplant patients is associated with a high incidence of tenosynovitis: safety analysis of a multicenter randomized trial. *Clin Infect Dis*. 2015;60:1642–9.
- [25] Tien V, Robilotti E, Callister D, Subramanian A, Lutchman G, Ho DY. Tolerability of fluoroquinolones in management of latent tuberculosis in liver transplant candidates. *Clin Infect Dis*. 2015;61:1631–2.
- [26] van Heeswijk RPG, Dannemann B, Hoetelmans RMW. Bedaquiline: a review of human pharmacokinetics and drug-drug interactions. *J Antimicrob Chemother*. 2014;69:2310–8.
- [27] Shimokawa Y, Sasahara K, Yoda N, Mizuno K, Umehara K. Delamanid does not inhibit or induce cytochrome p450 enzymes in vitro. *Biol Pharm Bull*. 2014;37:1727–35.
- [28] Rose G. The risk of tuberculosis transmission in solid organ transplantation: Is it more than a theoretical concern? *Can J Infect Dis Med Microbiol*. 2005;16:304–8.
- [29] Benito N, García-Vázquez E, Horcajada JP, González J, Oppenheimer F, Cofán F, et al. Clinical features and outcomes of tuberculosis in transplant recipients as compared with the general population: a retrospective matched cohort study. *Clin Microbiol Infect*. 2015;21:651–8.
- [30] Centers for Disease Control and Prevention (CDC). Transplantation-transmitted tuberculosis--Oklahoma and Texas, 2007. *MMWR*. 2008;57:333–6.
- [31] Bodro M, Sabé N, Santín M, Cruzado JM, Lladó L, González-Costello J, et al. Clinical features and outcomes of tuberculosis in solid organ transplant recipients. *Transplant Proc*. 2012;44:2686–9.

- [32] Ankrah AO, van der Werf TS, de Vries EFJ, Dierckx RAJO, Sathekge MM, Glaudemans AWJM. PET/CT imaging of Mycobacterium tuberculosis infection. Clin Transl Imaging. 2016;4:131–44.
- [33] Olithselvan A, Rajagopala S, Vij M, Shanmugam V, Shanmugam N, Rela M. Tuberculosis in liver transplant recipients: experience of a South Indian liver transplant center. Liver Transplant. 2014;20:960–6.
- [34] Ferrell LD, Lee R, Brixko C, Bass NM, Lake JR, Roberts JP, et al. Hepatic granulomas following liver transplantation. Clinicopathologic features in 42 patients. Transplantation. 1995;60:926–33.
- [35] National Collaborating Centre for Chronic Conditions (UK), Centre for Clinical Practice at NICE (UK). Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for Its Prevention and Control. London: National Institute for Health and Clinical Excellence (UK); 2011.
- [36] Meije Y, Piersimoni C, Torre-Cisneros J, Dilektasli AG, Aguado JM, ESCMID Study Group of Infection in Compromised Hosts. Mycobacterial infections in solid organ transplant recipients. Clin Microbiol Infect. 2014;20 Suppl 7:89–101.
- [37] Hillemann D, Rüscher-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. J Clin Microbiol. 2011;49:1202–5.
- [38] Acocella G, Bonollo L, Garimoldi M, Mainardi M, Tenconi LT, Nicolis FB. Kinetics of rifampicin and isoniazid administered alone and in combination to normal subjects and patients with liver disease. Gut. 1972;13:47–53.

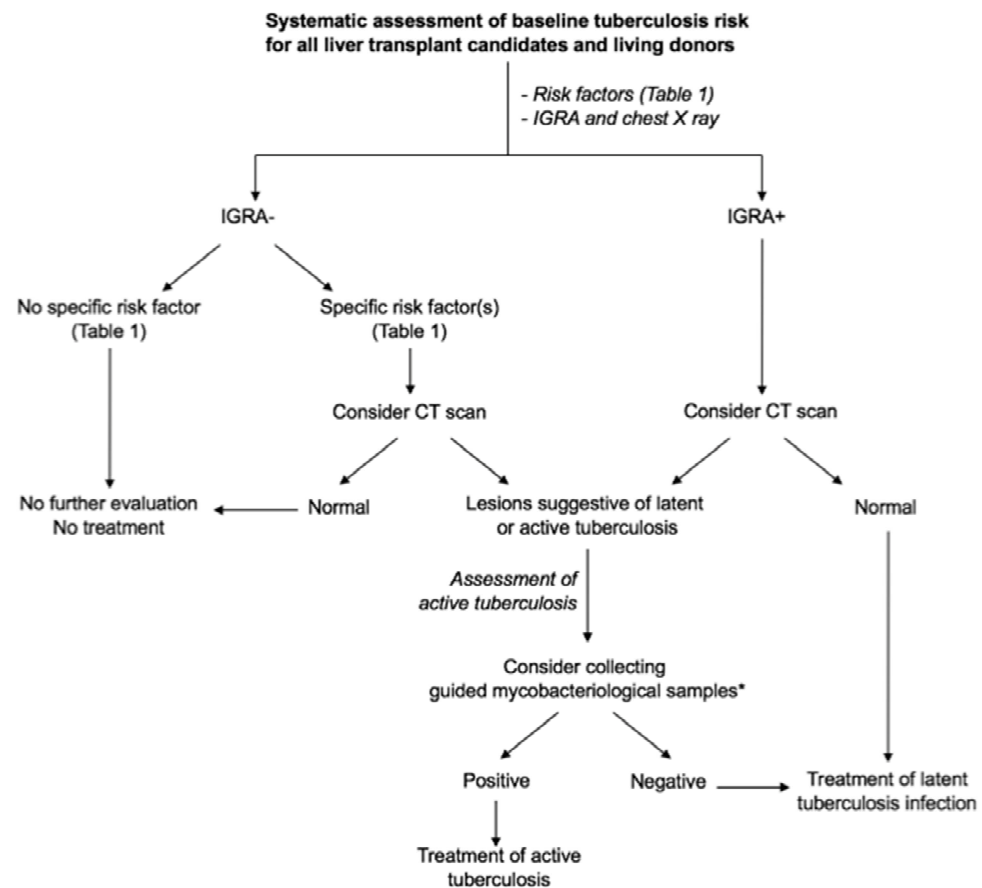
- [39] Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174:935–52.
- [40] Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest*. 1991;99:465–71.
- [41] Ohno M, Yamaguchi I, Yamamoto I, Fukuda T, Yokota S, Maekura R, et al. Slow N-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity. *Int J Tuberc Lung Dis*. 2000;4:256–61.
- [42] Huang Y-S, Chern H-D, Su W-J, Wu J-C, Lai S-L, Yang S-Y, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatol Baltim Md*. 2002;35:883–9.
- [43] Azuma J, Ohno M, Kubota R, Yokota S, Nagai T, Tsuyuguchi K, et al. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy. *Eur J Clin Pharmacol*. 2013;69:1091–101.
- [44] Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. *Drug Saf*. 2002;25:111–33.
- [45] Sarma GR, Kailasam S, Nair NG, Narayana AS, Tripathy SP. Effect of prednisolone and rifampin on isoniazid metabolism in slow and rapid inactivators of isoniazid. *Antimicrob Agents Chemother*. 1980;18:661–6.
- [46] Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs*. 2014;74:839–54.
- [47] Capelle P, Dhumeaux D, Mora M, Feldmann G, Berthelot P. Effect of rifampicin on liver function in man. *Gut*. 1972;13:366–71.

- [48] Curci G, Claar E, Bergamini N, Ninni A, Claar GM, Ascione A, et al. Studies on blood serum levels of rifampicin in patients with normal and impaired liver function. *Chemotherapy*. 1973;19:197–205.
- [49] Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interactions with rifampicin : clinical relevance. *Clin Pharmacokinet*. 2003;42:819–50.
- [50] Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin, rifabutin, and rifapentine drug interactions. *Curr Med Res Opin*. 2013;29:1–12.
- [51] Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. *J Infect Dis*. 2013;208:1464–73.
- [52] Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. *Clin Infect Dis*. 1996;22 Suppl 1:S15–21; discussion S21–2.
- [53] Thomas LD, Miller GG, AST Infectious Diseases Community of Practice. Interactions between antiinfective agents and immunosuppressants. *Am J Transplant*. 2009;9 Suppl 4:S263–6.
- [54] Crabol Y, Catherinot E, Veziris N, Jullien V, Lortholary O. Rifabutin: where do we stand in 2016? *J Antimicrob Chemother*. 2016;71:1759–71.
- [55] Weiner M, Benator D, Burman W, Peloquin CA, Khan A, Vernon A, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis*. 2005;40:1481–91.
- [56] Lacroix C, Tranvouez JL, Phan Hoang T, Duwoos H, Lafont O. Pharmacokinetics of pyrazinamide and its metabolites in patients with hepatic cirrhotic insufficiency. *Arzneimittelforschung*. 1990;40:76–9.

- [57] Chideya S, Winston CA, Peloquin CA, Bradford WZ, Hopewell PC, Wells CD, et al. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana. *Clin Infect Dis*. 2009;48:1685–94.
- [58] Donald PR, Maher D, Maritz JS, Qazi S. Ethambutol dosage for the treatment of children: literature review and recommendations. *Int J Tuberc Lung Dis*. 2006;10:1318–30.
- [59] Aminimanizani A, Beringer P, Jelliffe R. Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet*. 2001;40:169–87.
- [60] Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clin Pharmacokinet*. 2007;46:13–58.
- [61] Schenker S, Martin RR, Hoyumpa AM. Antecedent liver disease and drug toxicity. *J Hepatol*. 1999;31:1098–05.
- [62] Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis. *Int J Tuberc Lung Dis*. 2000;4:796–806.

Figure 1. Proposal for a practical risk assessment of latent tuberculosis in liver transplant candidates and living donors.

Figure 1. Proposition d'évaluation pratique du risque de tuberculose latente chez les candidats à la transplantation hépatique et les donneurs vivants.



* In this setting, a PET-CT can be useful to assess disease activity in center with easy access.

Figure 2. Mechanisms of transmission of tuberculosis in liver transplant recipients.

Figure 2. Mécanismes de transmission de la tuberculose chez les transplantés hépatiques.

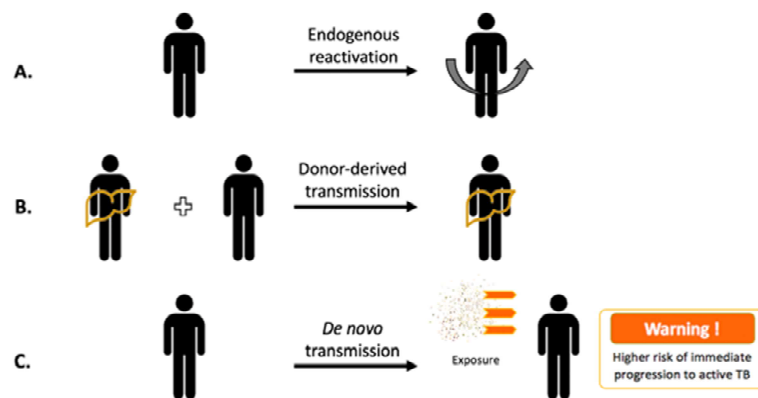


Figure 3. Examples of computed tomography imaging in three patients presenting with active tuberculosis after liver transplantation.

A) Abdominal CT scan showing diffuse ascites (asterisk) and mesenteric lymphadenopathies (arrows).

B) Chest CT scan showing pulmonary nodules (arrows).

C) Chest CT scan showing pulmonary nodules (arrow), diffuse interstitial infiltrates (arrow heads) associated with pleural (empty arrow heads) and circumferential pericardial (asterisk) effusions.

Figure 3. Exemples de présentation tomodensitométrique de tuberculose maladie chez trois patients receveurs de transplantation hépatique.

A) Scanner abdominal, ascite diffuse (astérisque) et adénopathies mésentériques (flèches)

B) Scanner thoracique, nodules pulmonaires (flèches)

C) Scanner thoracique, nodule pulmonaire (flèche), infiltrat interstitiel diffus (têtes de flèche) et épanchements pleural (têtes de flèches vides) et péricardique circonférentiel (astérisque).

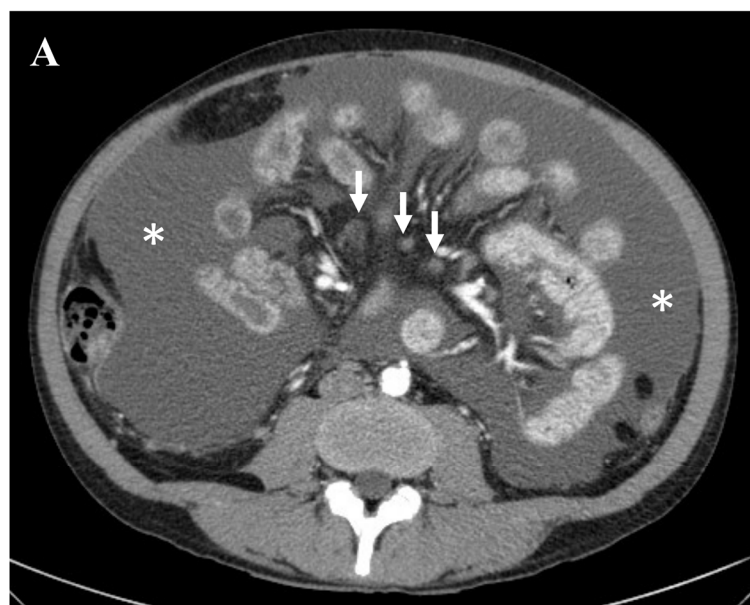


Table 1. Risk factors for active tuberculosis after liver transplantation.

Tableau 1. Facteurs de risque de tuberculose maladie après transplantation hépatique.

Risk factors	Characteristics	References
Native country prevalence	Low- <i>versus</i> high-endemicity area for tuberculosis	[6,8,9]
Age at transplantation	≥50 years	[6]
Social factors	Homelessness Incarceration	[9,10]
Known tuberculosis history	Personal or family history of untreated or treated tuberculosis	[4,8,10]
Underlying conditions	Diabetes mellitus Malnutrition Chronic HIV infection High MELD score (end-stage liver disease)	[4,9–13]
Chest imaging	Chest radiography or CT scan showing abnormalities	[6,8,10]
Immunosuppressive drugs	Intensification of immunosuppression for acute allograft rejection mTOR inhibitors: everolimus, sirolimus T-cell depleting antibodies (antithymocyte immunoglobulins)	[4] [6] [10]

Table 2. Screening and treatment of latent tuberculosis infection in liver transplant candidates.

Tableau 2. Dépistage et traitement de l'infection tuberculeuse latente dans le contexte de la transplantation hépatique.

Executive summary

- 1 Every liver transplant candidate should be screened for latent tuberculosis infection using at least one immunological test and a chest radiograph [8,12,17].
 - 2 Immunological tests include TST and IGRAs. IGRAs should be the standard tests in liver transplantation. They do not cross-react with BCG nor NTM [18, 19].
 - 3 If one or both immunological test(s) is/are negative (end-organ liver disease), risk assessment is still required to evaluate the relevance of latent tuberculosis infection treatment according to currently known risk factors (Table 1) and results of a chest CT scan [10,20].
 - 4 If one or both immunological test(s) is/are positive, latent tuberculosis infection treatment should be initiated after having ruled out an active tuberculosis disease [8,12,17].
 - 5 18-FDG PET/CT scan may help differentiate latent tuberculosis infection from active tuberculosis disease [10,20,21].
 - 6 In case of living-donor liver transplantation, the donor should be screened for latent tuberculosis infection using at least one immunological method and a chest radiograph.
 - 7 Isoniazid is the antituberculosis drug of choice and must be used at the dose of 2.5 to 5 mg/kg/day, without exceeding 300 mg/day, and with
-

pyridoxine (vitamin B6, 25-50 mg/day) supplementation to decrease neurotoxicity [8,12,17].

- 8 Latent tuberculosis infection treatment duration is 6 to 9 months (9 months is the favored option) [8,12,17].
 - 9 Alternative options are: 3 to 4-month treatment with rifampicin alone; isoniazid and rifampicin for 3 to 4 months (increased risk of acute liver failure) [22,23]. These rifampicin-based therapies are not recommended after liver transplantation due to the risk of drug interactions with immunosuppressive drugs.
 - 10 In liver transplant candidates or recipients or living-donor candidates on isoniazid, the acetylator status should be checked at treatment initiation and close monitoring of the liver function should be implemented (at least once a week), particularly in patients presenting with end-stage liver disease [38,47,48].
 - 11 Ideally, latent tuberculosis infection treatment is completed before liver transplantation, but can cover pre- and post-liver transplantation phases with a 3- to 12-day break after liver transplantation, upon stabilization of the liver function [7]. Alternatively, latent tuberculosis infection treatment can be carried out after liver transplantation upon liver function stabilization, ideally before the fifth month post-transplantation and without rifampicin [11].
 - 12 After liver transplantation, recipients should be screened for latent tuberculosis infection in case of:
 - (i) exposure to an active tuberculosis patient,
 - (ii) intensification of immunosuppressive regimen in case of allograft rejection.
-

TST: tuberculin skin test; IGRA: interferon gamma release assays; BCG: Bacillus Calmette–Guérin vaccine; NTM: nontuberculous mycobacteria

Table 3. Diagnosis of active tuberculosis in liver transplant recipients.

Tableau 3. Diagnostic de la tuberculose maladie chez les receveurs de transplantation hépatique.

Executive summary

- 1 Hallmark tuberculosis symptoms occur less frequently after liver transplantation and may be limited to a prolonged fever of unknown origin [29].
 - 2 Disseminated disease is more frequent than in the general population, accounting for two thirds of patients, justifying an initial body CT scan assessment in all patients [1-3,30].
 - 3 Pulmonary disease can be pleomorphic, but cavitary disease is rare due to the impaired T-cell function [29,31].
 - 4 Pathological examination of tissue biopsies usually reveals non-specific non-necrotic tissular granuloma, making the differential diagnosis with acute graft rejection difficult [33,34].
 - 6 Culture of samples obtained from the involved sites (including specific blood cultures in case of fever of unknown origin) remains the most sensitive detection method when using a combination of liquid and solid mycobacterial culture specific media [35, 36]. However, the low mycobacterial inoculum frequently leads to microbiological confirmation failure in solid organ transplant patients and should not delay treatment initiation in case of strong clinical and/or radiological suspicion.
 - 7 Amplification tests, including specific PCR and automated molecular test for tuberculosis and resistance to rifampicin detection, may help to
-

confirm diagnosis, although their sensitivity remains lower than culture especially in case of low inoculum [37].

PCR: polymerase chain reaction

Table 4. Pharmacological considerations in the use and monitoring of tuberculosis drugs in liver transplant recipients.

Tableau 4. Prescriptions et suivis pharmacologiques des antituberculeux chez les receveurs de transplantation hépatique.

Drug	Effect of liver disease on PK	Hepatotoxicity risk	Intervention for hepatotoxicity	Interactions with immunosuppressive drugs	Suggested initial dosage	Concentration targets for therapeutic drug monitoring
ISONIAZID	Increased serum concentrations and half-life. Drug accumulation in slow acetylators [38].	Clinically significant. Increased in combination with RMP and PZA, and in slow acetylators [39–43].	Stop INH in case of ALT x5-ULN or ALT x3-ULN with symptoms ^a . Treat at a lower dose (3 mg/kg/day) after ALT return to baseline and after safe reintroduction of RMP [39].	None with clinical significance [44,45].	Dosing adjustments based on the acetylator status (slow/rapid), if possible: 2.5-5 mg/kg in slow acetylators; 7.5 mg/kg in rapid acetylators [50,52,53]. Standard dose otherwise: 4-5 mg/kg/day.	C _{max} , 3-6 mg/L [46]
RIFAMPICIN	Increased serum concentrations and half-life. Reduced auto-	Clinically significant. Increased in combination	Stop RMP in case of ALT x5-ULN or ALT x3-ULN with symptoms ^a .	<u>RMP can greatly reduce concentrations of CS and</u>	Standard dose: 10 mg/kg/day Caution above	C _{max} , 8-24 mg/L AUC ₀₋₂₄ >13 mg.h/L [46,51]

	induction after repeated doses [38,47,48].	with INH and PZA.	Treat after ALT return to baseline [39].	<u>immunosuppressive drugs.</u> A 2-3-fold increase in the dosage of oral CS should be implemented at RMP initiation. Monitor immunosuppressive drug concentrations and implement a 2-5-fold increase in dosage, as necessary at RMP initiation. Consider switching for rifabutin in case of high rejection risk or failure to maintain therapeutic concentrations of immunosuppressive drugs [44,49,50].	600 mg/day	
RIFABUTIN	Increase in rifabutin exposure only in patients with	Uncommon [39]	Not determined. The same interventions as those suggested	Interactions similar to that of rifampicin, but of lower magnitude.	Standard dose 300 mg/day	C_{max} , 0.45-0.90 mg/L AUC_{0-24} >4.5 mg.h/L ^b

	severe liver disease (Child Pugh score ≥ 10) [52]		for rifampicin are advisable.	Monitor immunosuppressive drug concentrations and increase dosage as necessary [50,53,54].		[46,55]
PYRAZINAMIDE	Increased exposure and half-life [55]	Clinically significant. Increased in combination with INH and RMP [39]	Stop PZA in case of ALT x5-ULN or ALT x3-ULN with symptoms ^a No re-treatment [39]	None of clinical significance [56]	Standard dose: 20-30 mg/kg/day	$C_{\max} > 35$ mg/L $AUC_{0-24} > 363$ mg.h/L [46,51,57]
ETHAMBUTOL	Unknown but probably not significant (mostly excreted non-metabolized in urine) [58]	Not significant [39]	None [39]	None [39]	Standard dose: 15-20 mg/kg/day	C_{\max} , 2-6 mg/L [46]
FLUOROQUINOLONES (OFL, LVX, MXF)	Limited increase in drug concentrations, if any [59]	Clinically significant [39]	Not determined. Interventions indicated for first-line agents are advisable	Moderate increase in ciclosporin and tacrolimus with OFL. Putative risk of reduction in case of mycophenolic acid exposure (based on observations with norfloxacin and	Usual adult dose if the renal function is normal LVX, 500-1,000 mg/day MXF, 400 mg/day	LVX C_{\max} , 8-13 mg/L MXF C_{\max} , 3-5 mg/L [46]

ciprofloxacin)
[53,60]

AUC, area under the curve; C_{max} , maximum serum concentration; LVX, levofloxacin; OFL, ofloxacin; MXF, moxifloxacin; PK, pharmacokinetics;

ULN, upper limit of normal, PZA: pyrazinamide, INH: isoniazid; RMP: rifampicin, CS: corticosteroids.

^aWhen the baseline ALT level is already elevated, ALT increase of 50-100 IU/L from baseline may be considered as a toxicity threshold instead
[61]

^bValue based on observations in HIV-infected patients treated twice weekly