# Hepatotoxicity induced by antituberculosis drugs among patients coinfected with HIV and tuberculosis

## Hepatotoxicidade das drogas antituberculose entre pacientes coinfectados HIV/tuberculose

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**Abstract**

*Hepatotoxicity due to antituberculosis drugs limits treatment in patients coinfected with HIV and tuberculosis. We conducted a case-control study to identify risk factors for hepatotoxicity among patients coinfected with tuberculosis and HIV in two hospitals in Recife, Pernambuco State, Brazil. The sample consisted of 57 patients (36.5% of the total) who developed hepatotoxicity and a control group of 99 patients (63.5% of the total), who did not present this effect. Hepatotoxicity consisted of jaundice or a high concentration of AST/ALT or total bilirubinemia. Multivariate logistic regression showed that a T CD4+ count of < 200cells/mm³ increased the risk of hepatotoxicity by a factor of 1.233 (p < 0.001) and that coinfection with hepatitis B or C virus increased this risk by a factor of 18.187 (p = 0.029). Discharge occurred among 66.1% of the case group (p = 0.026). The absence of hepatotoxicity was a protective factor against death (OR = 0.42; 95%CI: 0.20-0.91). Coinfection with the B and C hepatitis virus and a T CD4+ cell count below 200cells/mm³ were independent risk factors for hepatotoxicity in these patients*

*Drug Toxicity; Coinfection; Tuberculosis; HIV*

Tuberculosis (TB) continues to be a major public health challenge in Brazil and around the world [1]. Increased poverty, a progressive decline in investment in the healthcare sector and the HIV pandemic have contributed towards the reappearance and persistence of this disease to the present day [2].

World Health Organization (WHO) estimates indicate that around 100 million people worldwide are infected with tuberculosis and that almost 8.3 million new cases appear each year, resulting in 1.8 million deaths every year [3]. Ninety-five percent of tuberculosis cases and 98% of the deaths worldwide are concentrated in developing countries where 75% of the cases affect the economically active population [4].

Brazil is one of 22 countries prioritized by the WHO that together account for 80% of the world's TB cases. In 2007 Brazil notified 72,194 new cases, representing an incidence rate of 38/100,000 inhabitants. Of these, 41,117 were cases of bacilliferous tuberculosis (cases in which bacilloscopy was positive), representing a rate of 41/100,000 inhabitants [2]. These indicators put Brazil in 19th place in the world ranking of absolute numbers of tuberculosis cases and in 104th place in terms of incidence rate [5].

In parallel with this alarming context, HIV infection promotes the progression of tuberculosis. Asymptomatic HIV-infected individuals and those with AIDS are much more susceptible to infection with tuberculosis than those with-

out HIV infection [2,3,4,6,7]. Worldwide, nine percent of all new tuberculosis cases in adults in the age range 15-49 years are attributable to HIV infection [3].

The introduction of combined antiretroviral therapy has reduced deaths and opportunistic infections by between 60% and 90% [8]. However, the use of combined antiretroviral therapy in individuals undergoing treatment for tuberculosis may increase the risk of toxicity, drug interactions and other adverse effects [6].

Some important classes of drugs used in combined antiretroviral therapy, such as protease inhibitors, present significant drug interactions with rifampicin. This results in frequent changes in drug regimens in hospitalized patients coinfected with HIV and TB [9].

All tuberculostatics are potentially hepatotoxic, particularly rifampicin and isoniazid. Rifampicin rarely causes hepatic abnormalities if used alone innormal doses. However, when it does cause adverse effects, its clinical manifestation is intrahepatic cholestasis, caused by competition with glucuronyltransferase [10].

The most important adverse effects of isoniazid are hepatic toxicity and potentially fatal drug-induced hepatitis [11], especially when associated with rifampicin. This is a result of metabolic products of the liver, particularly monoacetylhydrazide, associated with the slow acetylator phenotype [12]. The relationship between genetic polymorphism and the toxicity of these drugs has also been investigated. This characteristic includes the cytochrome P 450 and glutathione S-transferase genes, together with genes of the major histocompatibility complex II associated with HLA-DQ alleles [13]. Hepatotoxicity due to hypersensitivity to antituberculosis drugs may occur in some cases, especially when clinical conditions such as skin rashes, fever, arthralgia or eosinophilia are concomitantly present in these patients. An abnormality in the antioxidant profile with increased peroxidation would suggest that hepatotoxicity induced by rifampicin and isoniazid is mediated by oxidative damage [14].

The frequency of occurrence of isoniazid-associated hepatitis depends on age. Although practically nonexistent among individuals under 20 years of age, it occurs in 0.3% of people aged between 20 and 34 years of age, in 1.2% of those aged between 35 and 49 years and in 2.3% of individuals aged 50 years and over [15].

Other factors linked to a predisposition to isoniazid-associated hepatotoxicity include alcohol abuse, use of illegal drugs and a previous history of liver disease. Asymptomatic elevations of hepatic transferases may occur in more than 20% of patients during the first two months of treatment, with a return to normal values as the therapy proceeds [9].

Among individuals coinfected with HIV and TB, adverse effects take on a much greater importance due to their potentially fatal nature and the frequent need to change therapeutic regimens [16].

The frequency of hepatoxicity caused by tuberculostatics varies in accordance with the type of definition used for this event, as observed by Coca et al. [17]. For hepatoxicity defined as an increase in ALT (alanine aminotransferase) levels of up to three times the lower normal limit, the frequency of hepatotoxicity was greater in the group of patients also infected with HIV [17].

Considering the specific characteristics of coinfected individuals and the side effects resulting from joint treatment with antituberculosis and antiretroviral drugs, we conducted the present study with the aim of identifying the risk factors associated with hepatotoxicity among patients hospitalized for treatment of tuberculosis patients coinfected with HIV.

## Patients and methods

A retrospective case-control study was conducted in the wards of two referral hospitals for infectious diseases in the city of Recife, Pernambuco State. Using data obtained from medical files,156 hospitalized patients were evaluated, of whom 50 (32.1%) were from the teaching hospital (Hospital das Clínicas) of the Pernambuco Federal University (Universidade Federal de Pernambuco – UFPE) and 106 (67.9%) from the Oswaldo Cruz University Hospital of UFPE. The data obtained from the patients' medical files were registered on a form designed for the present study.

The HIV-infected patients were aged between 17 and 65 years and were hospitalized at the above study locations between January 2004 and October 2007. They underwent tuberculosis treatment that had either started not more than 30 days before admission or during hospitalization. As additional inclusion criteria, the presence of the following information in the medical files was considered obligatory: results of tests for alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase or gamma-glutamyltransferase performed during the treatment; description of the therapeutic regimen ofthe tuberculosis treatment; the type of antiretroviral regimen; and starting dates. The pretreatment transaminases values of the cases and controls were evaluated and those already presenting levels higher than the upper normal limit prior to the start of treatment for tuberculosis were excluded.

The 156 patients were divided into two groups: the case group (group A), consisting of 57 patients (36.5%) who developed hepatotoxicity; and the control group (group B), consisting of 99 patients (63.5%) who did not present this adverse reaction. Following criteria adapted from a number of authors [18], hepatotoxicity was taken to be the presence of one or more of the following abnormalities between four and 90 days after the start of the tuberculosis treatment: (a) jaundice, whether associated or not with symptoms suggestive of hepatitis, including nausea, vomiting, anorexia, asthenia or pain in the upper right abdominal quadrant; (b) concentration of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper normal limit; (c) total levels of bilirubinemia greater than twice the upper normal limit.

The risk factors for hepatotoxicity were classified as follows: biological (gender, age group and self-reported skin color); behavioral (alcohol consumption, smoking and use of illegal drugs such as marijuana, crack, cocaine, solvents and others); laboratory data relating to HIV/AIDS infection (T CD4+ cell count, HIV viral load and concomitance of HIV and hepatitis B or C infection); data relating to antiretroviral treatment [antiretroviral therapy regimen comprising non-nucleoside reverse transcriptase inhibitors or protease inhibitors; period when antiretroviral therapy started (before, up to three months prior to the tuberculosis therapy, or after up to 30 days following the tuberculosis treatment); presence of opportunistic infections at the start of the therapy with antituberculosis drugs]; and factors relating to the tuberculosis disease and its treatment.

Tuberculosis was classified in the medical files in terms of its clinical form, namely pulmonary, extrapulmonary or disseminated. The latter form related to conditions involving bloodstream, bone marrow, liver or two or more non-contiguous sites [19].

Among the factors relating to the treatment of tuberculosis, the analysis considered previous history of liver disease diagnosed up to three months prior to the start of treatment with antituberculosis drugs and the number of other hepatotoxic drugs used during the tuberculosis treatment, such as fluconazole, ganciclovir, quinolone, benzodiazepines-hypnotics-antidepressives, sulfamethoxazole-trimethoprim, sulfadiazine and clindamycin.

The following approaches taken to combat adverse reactions to the tuberculosis treatment were analyzed: maintenance of the tuberculosis treatment regimen, discontinuation of the treatment, changing the treatment regimen or temporary interruption of the treatment with a return to the same regimen after normalization of the clinical condition. The outcomes ofthe cases were classified as discharge or death.

The dependent variable of interest in this study was the occurrence of hepatotoxicity categorized as hepatitis without jaundice, hepatitis with jaundice, fulminating hepatitis (time from developing jaundice to encephalopathy less than 14 days in the absence of previous liver disease) or decompensated liver disease (presence of jaundice, coagulopathy or encephalopathy in cases of previous history of cirrhosis of the liver) [18].

The timing of the onset of hepatotoxicity was taken as the period of time fromthe start of the tuberculosis treatment to the diagnosis of this adverse reaction by the alteration of aminotransferase levels or the day the appearance of symptoms were recorded on the patient's medical file. This period of time was categorized as follows: < 15 days, 15-29 days, 30-44 days, or > 45 days.

Data was organized using the Epi Info software, version 6.04d (Centers for Disease Control and Prevention, Atlanta, USA) and analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, USA) software, version 13.0. Descriptive statistics of frequency distributions, summary measurements and variability measurements were used. The association of each variable with the presence of hepatotoxicity was evaluated by means of the Mann-Whitney test at a significance level of 0.20 for rejection of the null hypothesis of absence of association between the variables. Multivariate analysis was performed using multiple logistic regression on the independent variables that presented associations with the outcome after bivariate analysis. The model was initially saturated by including all the variables. Stepwise removal of each variable from the proposed model was tested and its significance was expressed as a p-value using the maximum likelihood test. In analyses with two or more independent variables, those with more than three categories were grouped together to ensure greater statistical stability of results.

The research project was approved by the Ethics Committees for Research Involving Human Beings of the Health Sciences Center of UFPE (protocol nº. CEP/CCS/UFPE 370/07) and of the Oswaldo Cruz University Hospital of UFPE (protocol nº. CEP/HUOC 146/2007).

## Results

Of the 156 hospitalized patients that were analyzed, 57 (36.7%) developed hepatotoxicity. Of

this case group, 42 (73.7%) were diagnosed as presenting hepatotoxicity on the basis of laboratory criteria and 15 (26.3%) solely on the basis of clinical criteria. The laboratory parameters relating to means, medians and ranges of concentrations are shown in Table 1.

The most frequent manifestation of hepatotoxicity was toxic hepatitis with jaundice (31 cases or 56.4% of the total) of which 23 cases(63.9%) appeared more than 15 days after the start of the treatment of tuberculosis. The following approaches were taken after the diagnosis of hepatotoxicity: maintenance of the therapeutic regimen (26 or 46.4% of the patients); temporary interruption of treatment (12 or 21.5% of the patients); change in tuberculosis treatment (11 or 19.6% of the patients) (Table 2). The decision to maintain the treatment in the majority of cases differs slightly from what is advocated by the Brazilian Ministry of Health (Ministério da Saúde), which recommends the temporary interruption of the administration of drugs and the resumption of one drug after another following the normalization of the hepatic enzymes and disappearance of symptoms such as jaundice [1]. The adoption of this more conservative strategy may be due to the temporary rise in levels of aminotransferases that occurs in the vast majority of patients treated with tuberculosis drugs. Very often these levels spontaneously return to normal with the continuation of treatment [20,21].

The individuals were dominantly male (56.1% of group A and 77.6% of group B), brown skinned

Table 1

Laboratory parameters of 42 cases. Recife, Pernambuco State, Brazil, January 2004 to October 2007.

| Laboratory parameters | Alanine transaminase (UI/L) | Aspartate transaminase (UI/L) | Total bilirubin (mg/dL) |
|---|---|---|---|
| Number of patients | 16 | 39 | 25 |
| Average ± standard error of the mean | 277.7 ± 27.4 | 353.4 ± 56.9 | 5.56 ± 0.75 |
| Median | 229.0 | 202.0 | 4.73 |
| Minimum | 163.0 | 109.0 | 2.34 |
| Maximum | 522.0 | 1,771.0 | 20.62 |

Note: more than one of the patient's parameters could have been changed by the biochemist.

Table 2

Distribution of factors related to hepatotoxicity in 57 patients with HIV/AIDS and tuberculosis. Recife, Pernambuco State, Brazil, January 2004 to October 2007.

| Factors related to hepatotoxicity | n | % |
|---|---|---|
| Clinical presentation of hepatotoxicity | | |
| Toxic jaundice | 31 | 56.4 |
| Toxic without jaundice | 19 | 34.5 |
| Decompensation of pre existing liver disease | 5 | 9.1 |
| Emergence of hepatotoxicity after initiation of antituberculosis drug | | |
| Before 15 days | 23 | 63.9 |
| Between 15 and 29 days after | 8 | 22.2 |
| Between 30 and 44 days after | 3 | 8.3 |
| After 45 days or more | 2 | 5.6 |
| Decision of treatment after hepatotoxicity | | |
| Maintenance regimen for tuberculosis | 26 | 46.4 |
| Temporary interruption of the regimen for tuberculosis | 12 | 21.5 |
| Changing the treatment regimen for tuberculosis | 11 | 19.6 |
| Suspension of the regimen for tuberculosis | 7 | 12.5 |

Table 3

Distribution of factors related to hepatotoxicity in 156 patients with HIV/AIDS and tuberculosis (TB). Recife, Pernambuco State, Brazil, January 2004 to October 2007.

| Factors related to hepatotoxicity | Groups of patients | | | | OR | 95%CI | p-value * |
|---|---|---|---|---|---|---|---|
| | With hepatotoxicity | | Without hepatotoxicitity | | | | |
| | n | % | n | % | | | |
| Biological characteristics | | | | | | | |
| Age (years) | 57 | 100.0 | 99 | 100.0 | 0.63 ** | 0.22-1.83 | 0.783 |
| < 25 | 7 | 12.3 | 6 | 6.1 | | | |
| 25-49 | 43 | 75.4 | 85 | 85.8 | | | |
| 50-75 | 7 | 12.3 | 8 | 8.1 | | | |
| Gender | 57 | 100.0 | 99 | 100.0 | 0.61 | 0.31-1.20 | 0.151 |
| Male | 32 | 56.1 | 67 | 67.6 | | | |
| Female | 25 | 43.9 | 32 | 32.4 | | | |
| Skin color | 22 | 100.0 | 22 | 100.0 | 0.63 *** | 0.10-4.22 | 0.828 |
| White | 6 | 27.3 | 6 | 27.3 | | | |
| Black | 3 | 13.6 | 2 | 9.1 | | | |
| Brown | 13 | 59.1 | 14 | 63.6 | | | |
| Behavior characteristics | | | | | | | |
| Alcohol consumption | 36 | 100.0 | 64 | 100.0 | 0.96 | 0.42-2.20 | 0.861 |
| Yes | 21 | 58.3 | 38 | 59.4 | | | |
| No | 15 | 41.7 | 26 | 40.6 | | | |
| Smoking | 35 | 100.0 | 66 | 100.0 | 0.55 | 0.24-1.30 | 0.125 |
| Yes | 12 | 34.3 | 32 | 48.5 | | | |
| No | 23 | 65.7 | 34 | 51.5 | | | |
| Illegal drugs | 27 | 100.0 | 35 | 100.0 | 0.36 | 0.09-1.49 | 0.152 |
| Yes | 3 | 11.1 | 9 | 25.7 | | | |
| No | 24 | 88.9 | 26 | 74.3 | | | |
| HIV/AIDS infection | | | | | | | |
| T CD4+ count (cells/mm³) | 43 | 100.0 | 58 | 100.0 | 1.87 | 0.77-4.55 | 0.165 |
| < 200 | 33 | 76.7 | 37 | 63.8 | | | |
| ≥ 200 | 10 | 23.3 | 21 | 36.2 | | | |
| Viral load (copies/mm³) | 38 | 100.0 | 57 | 100.0 | 0.70 | 0.31-1.60 | 0.634 |
| < 100,000 | 18 | 47.4 | 32 | 56.1 | | | |
| ≥ 100,000 | 20 | 52.6 | 25 | 43.9 | | | |
| Antiretroviral therapy | 55 | 100.0 | 96 | 100.0 | 0.63 | 0.25-1.62 | 0.340 |
| No | 7 | 12.7 | 18 | 18.8 | | | |
| Yes | 48 | 87.3 | 78 | 81.2 | | | |
| Hepatitis B or C coinfection | 52 | 100.0 | 82 | 100.0 | 21.73 | 2.71-174.18 | < 0.001 |
| Yes | 11 | 21.2 | 1 | 1.2 | | | |
| No | 41 | 78.8 | 81 | 98.8 | | | |
| Start of antiretroviral therapy | 55 | 100.0 | 95 | 100.0 | 0.55 | 0.28-1.09 | 0.085 |
| Previous to TB treatment | 28 | 50.9 | 62 | 65.3 | | | |
| Simultaneous to TB treatment | 27 | 49.1 | 33 | 34.7 | | | |
| Antiretroviral therapy regimen | 48 | 100.0 | 78 | 100.0 | 0.91 | 0.44-1.88 | 0.623 |
| With non-nucleoside reverse transcriptase inhibitors | 26 | 54.2 | 44 | 56.4 | | | |
| With protease inhibitors | 22 | 45.8 | 34 | 43.6 | | | |
| Other opportunistic infection | 55 | 100.0 | 96 | 100.0 | 2.06 | 1.03-4.10 | 0.04 |
| Yes | 37 | 67.2 | 48 | 50.0 | | | |
| No | 18 | 32.8 | 48 | 50.0 | | | |

(continues)

Table 3 (continued)

| Factors related to hepatotoxicity | Groups of patients | | | | OR | 95%CI | p-value * |
|---|---|---|---|---|---|---|---|
| | With hepatotoxicity | | Without hepatotoxicitity | | | | |
| | n | % | n | % | | | |
| TB characteristics | | | | | | | |
| TB disease presentation | 57 | 100.0 | 99 | 100.0 | 1.42 | 0.74-2.75 | 0.380 |
| Pulmonary | 28 | 49.1 | 40 | 40.4 | | | |
| Extrapulmonary | 20 | 35.1 | 42 | 42.4 | | | |
| Pulmonary and extrapulmonary | 4 | 7.0 | 9 | 9.1 | | | |
| Disseminated | 5 | 8.8 | 8 | 8.1 | | | |
| TB treatment characteristics | | | | | | | |
| TB disease treatment regimen | 55 | 100.0 | 92 | 100.0 | 0.92 # | 0.37-2.29 | 0.674 |
| Isoniazid+rifampicin+pyrazinamide for 6 months (regimen I) | 39 | 70.9 | 70 | 76.1 | | | |
| Isoniazid+rifampicin+pyrazinamide for 9 months (regimen II) | 6 | 10.9 | 11 | 12.0 | | | |
| Regimen III | - | - | 3 | 3.2 | | | |
| Isoniazid+rifampicin+pyrazinamide+ethambutol (regimen IR) | 7 | 12.7 | 8 | 8.7 | | | |
| Izoniazid+streptomicin+ethambutol for 12 months (regimen for patients with hepatic diseases) | 3 | 5.5 | - | - | | | |
| Preexisting hepatic disease | 56 | 100.0 | 90 | 100.0 | 0.08 | 0.02-0.39 | < 0.001 |
| No | 44 | 78.6 | 88 | 97.8 | | | |
| Yes | 12 | 21.4 | 2 | 2.2 | | | |
| Other hepatotoxic drugs | 56 | 100.0 | 98 | 100.0 | - | - | 0.029 |
| No | 0 | - | 6 | 6.1 | | | |
| Yes | 56 | 100.0 | 92 | 93.9 | | | |
| Outcome | 56 | 100.0 | 95 | 100.0 | 0.42 | 0.20-0.91 | 0.026 |
| Discharge | 37 | 66.1 | 78 | 82.1 | | | |
| Death | 19 | 33.9 | 17 | 17.9 | | | |

OR: odds ratio; 95%CI: 95% confidence interval.

* p-value by Mann-Whitney test;

** OR considering < 25 to 49 years e ≥ 50 years;

*** OR considering self-reported skin color white+brown and black;

# OR considering TB regimen containing regimens I + IR and regimens II + III + regimens for hepatopathy.

(59.1% of group A and 63.6% of group B) and between 25 and 49 years of age (75.4% of group A and 85.8% of group B) (Table 3).

With regard to behavioral factors, alcohol consumption, smoking and use of illegal drugs, such as marijuana, crack, cocaine and solvents, was less frequent in group A than in group B: however, these differences were not significant. Regarding the factors relating to HIV/AIDS infection, lower T CD4+ lymphocyte counts, higher viral loads and histories of coinfection with the hepatitis B or C virus were observed with the cases as compared to the controls. The cases were also more likely to start their antiretroviral therapy before the tuberculosis treatment, with a slight predominance of non-nucleoside reverse transcriptase inhibitor regimens. In this respect, the cases showed a significantly higher frequency of coinfection with hepatitis B or C ($p < 0.001$), with an odds ratio of 21.73 (95%CI: 2.71-174.18) (Table 3).

Considering the factors relating to the tuberculosis disease and its treatment, there was seen to be a greater frequency of the pulmonary form of tuberculosis among the cases, although the difference was not significant ($p = 0.380$). However, the predominance of a previous history of liver disease, opportunistic infection and higher mortality as the outcome of the hospitalization were significantly greater among the cases.

The most frequently prescribed therapeutic regimen for tuberculosis was isoniazid + ri-

fampicin + pyrazinamide (IRZ) for a period of six months (regimen I) for both the cases and controls. In the case group, the second most frequent regimen was isoniazid + rifampicin + pyrazinamide + ethambutol (regimen IR), whereas in the control group it was IRZ for nine months (regimen II). The regimen for liver diseases izoniazid + streptomicin + ethambutol was instituted solely for patients in the case group. This variable was not subjected to statistical tests because of the small number of patients in each category (Table 3).

With regard to the treatment outcome, 66.1% of the patients who developed hepatotoxicity-were discharged compared to 82.1% of patients who did not present this adverse effect (p = 0.026). The absence of this side effect was shown to be a protective factor against death (OR = 0.42; 95%CI: 0.20-0.91) (Table 3).

The majority of the patients who developed hepatotoxicity continued the treatment, since temporary rises in aminotransferases may occur with the use of antituberculosis drugs, with levels very often returning to normal with the maintenance of the drugs in question. Another strategy used was the temporary discontinuation of treatment with the reintroduction of the drugs one after the other. Although this approach is recommended by certain authors [22], there is no consensus on the most effective way of reintroducing these drugs. The most common causes of death other than hepatotoxicity were infections, mainly pneumonia and sepsis, contracted during hospitalization.

In the multivariate logistic regression using the backwards method, the variables included were sex, T CD4+ count, coinfection with hepatitis B or C, start of antiretroviral therapy, presence of opportunistic infection, history of previous liver disease (esquistosomiasis, viral hepatitis, hepatic steatosis) and use of hepatotoxic drugs. These were included because they showedsignificance in the bivariate analyses at levels of less than or equal to 0.20. The variables smoking and use of illegal drugs were not included because they presented percentage losses of information greater than 30%. The variable outcome was also not included in the model because it was a consequence of hepatotoxicity.

From the multivariate logistic regression, it was shown that a T CD4+ count of lower than 200 cells/mm$^3$ increased the risk of hepatotoxicity by a factor of 1.233 ($p < 0.001$), while the presence of coinfection with the hepatitis B or C virus increased this risk by a factor of 18.187 (p = 0.029) among HIV-seropositive patients undergoing tuberculosis treatment. The other variables tested lost significance when analyzed together, thus constituting confounding factors for the risk of hepatotoxicity.

## Discussion

Isoniazid, rifampicin and pyrazinamide are the principal agents successfully used for treating tuberculosis, due to their therapeutic effectiveness and the good acceptance of these drugs among patients. However, a variety of adverse effects have been reported. Hepatic toxicity is one of the most common effects that lead to frequent interruptions of treatment [23].

In this study, 36.7% of the hospitalized coinfected patients who were undergoing tuberculosis treatment presented hepatotoxicity. This proportion is larger than that shown by other studies in which incidence rates ranged from 6% to 27.3% [24,25], and slightly larger than that seen in Japan (36%) and India (8% to 36%), as cited by Singlaet al. [26]. In other studies, the highest incidence rateshave been found in Asian countries, which may be indicative of ethnic susceptibility, peculiarities inherent in drug metabolism or the presence of various risk factors such as the hepatitis B virus or poor nutrition [15,25]. However, most of these studies were ofoutpatients and it should be emphasized that the percentages observed by the present study relate to hospitalized patients and that this fact may have contributed towards a higher incidence rate in the present study.

The relationship between age and the occurrence of hepatotoxicity was not found to be significant in the present study. This finding may have been due to the fact that more than 85% of the cases were individuals up to 50 years of age. A study conducted with the aim of comparing the incidence and severity of hepatotoxicity associated with antituberculosis drugs among patients with and without the hepatitis B virus revealed that this adverse event was more frequent among younger patients and among patients with hepatitis B [27]. A study of 346 patients undergoing tuberculosis treatment showed that age was an independent risk factor for the development of hepatotoxicity [28]. However, other studies have demonstrated an absence of correlation between age and the occurrence of hepatotoxicity [29,30,31].

With respect to gender, no significant difference was found between the cases and controls. This finding was also reported by a study conducted in India [28]. Furthermore, no association between self-reported skin color and hepatotoxicity was identified by the present study. Although this was one of the variables that presented the greatest loss of information, it should be noted that even if an association had been detected, it

would not have been possible to make comparisons with other studies in the literature because of difficulties categorizing ethnicity in Brazil [32].

Although alcohol consumption is a frequently mentioned risk factor associated with hepatotoxicity [28,29,33,34], no relationship was observed in the present study. This may have been because of the failure to record such information in the medical files or because little importance was given to this factor by individuals.

Previous history of liver disease and coinfection with hepatitis B or C were shown to be significant in the bivariate analyses, with p-values < 0.001. However, in the multivariate analysis, the only variables that showed any degree of significance were coinfection with hepatitis B or C and the T CD4+ lymphocyte counts. Ungo et al. [16] reported that chronic infection with the hepatitis C virus increased the risk of hepatotoxicity among patients treated for tuberculosis with isoniazid, pyrazinamide and rifampicin. Other studies have also corroborated this finding [35,36]. With regard to coinfection with the hepatitis B virus, similar findings were made in other studies, such as that of Wong et al. [27] who analyzed patients undergoing tuberculosis treatment and observed that the presence of the hepatitis B virus was a risk factor underboth univariate analysis (p = 0.011) and multiple logistic regression (p < 0.001).

However, certain studies disagree with this association, possibly because they were conducted with a small number of patients with the hepatitis B or C viruses [37,38,39,40].

A relationship between diminished immune status, as represented by the T CD4+ lymphocyte counts, and the occurrence of hepatotoxicity has been described in some studies. This might be explained in part by the occurrence of greater numbers of opportunistic infections and therefore by the consumption of a greater number of drugs [37,41,42,43]. Nevertheless, other studies, similarly to the present study, did not confirm the role of opportunistic diseases in the development of major hepatotoxicity, and attributed the risk to an unknown immunological factor that was thought to be present in individuals with low T CD4+ lymphocyte levels [34,39].

All the patients in group A and more than 90% of the patients in group B reported using hepatotoxic drugs. This may explain the absence of any effect relating to hepatotoxicity in the present study or any potential confounding factors, aswas demonstrated in the multivariate analysis. This lack of association was concordant with the studies of Yee et al. [33], Yimer et al. [37] and Koju et al. [44].

Concerning the clinical forms of tuberculosis, almost 50% of the cases presented the pulmonary form, compared with 40% of the controls, although this difference was not significant. Similarly, in 2007, Kwon et al. [36] found no difference between the clinical forms or in the relationship between the type of therapeutic regimen and the appearance of hepatotoxicity (p = 0.692).

It should be noted that no analysis was performed in relation to the variable viral load. The information loss relating to this variable corresponded to 39.1% of the patients in this study, thereby demonstrating that the medical files were inadequately kept.

In most cases, hepatotoxicity began within the first 15 days after the start of treatment with the antituberculosis drugs. In more than 80% of the cases, it started within the first 29 days of treatment. The predominant form of hepatotoxicity was jaundice (in 56.4% of the cases). This finding coincides with those of McNeill et al. [45] and Shakya et al. [46].

In more than 60% of the cases, the tuberculosis treatment was successfully maintained or temporarily interrupted and then gradually restarted (drug by drug) after the hepatotoxicity had been resolved. There is no consensus regarding the correct approach to treating hepatotoxicity resulting from the use of antituberculosis drugs administered to HIV/TB coinfected individuals. Changing regimen I (IRZ) is not a routine recommendation, since itis the most potentand shortest term regimen used in Brazil. Reintroduction drug-by-drug (new challenge) is a practice that has also been recommended by Kwon et al. [36] and Saukkonen et al. [47], and many patients will tolerate this regimen without any change in the medication. In the present study, the frequency of change in regimen of 17% is similar to that cited for individuals without HIV infection [48].

Mortality was greater among patients who developed hepatotoxicity than among those that did not present this effect. This gives rise to the supposition that the presence of this side effect may have contributed in some way to the negative outcome. Thus, it might be supposed that the options of maintaining and reintroducing the regimen could have proved harmful. On the other hand, it could be argued that the difficulties in making therapeutic choices in the light of the complications caused by the hepatotoxicity in patients with CD4+ lymphocyte counts lower than 200cells/mm$^3$ may have been the main factor responsible for greater mortality.

Drug-related hepatotoxicity may be fatal if detected at a late stage. Rapid recognition of the inherent conditions and risk factors is of great importance to ensure the best possible care for hospitalized patients who are undergoing tuberculosis treatment and are coinfected with HIV.

With regard to alcoholism, it can be seen from the present study that objective criteria need to be defined to characterize patients in relation to alcohol consumption. For example, the CAGE or AUDIT questionnaires can be used, or Widmark's method, which considers blood alcohol level calculated from the patient's alcohol intake [49].

The present study has several limitations inherent in retrospective analyses. For example, a lack of information in the medical files compromised some analyses important tothe study, such as the HIV viral load, body weight, ethnicity, smoking habits and use of illegal drugs. The lack of uniformity in the diagnosis of tuberculosis at the two different hospitals was also a limiting factor. Nevertheless, these limitations were of minimal significance because this was a uniform population receiving care at two university hospitals that have medical residence programs in infectology so ensuring better quality annotations in the medical files. The two institutions have similar facilities for diagnosis and treatment. However, the fact that the study was carried out with hospitalized patients, who are usually more serious cases, may have led to an increase in the prevalence of hepatotoxicity in the present study. The sample evaluated by this study was smaller than the optimal sample size calculated for a case control study of this nature, therefore conferring a low to moderate power to the present study.

Based on these results, it was concluded that there was a high incidence of hepatotoxicity, most frequently of the jaundice variety, and a high risk of death among the hospitalized patients coinfected with HIV and undergoing tuberculosis treatment. It was observed that coinfection with the hepatitis B or C virus and T CD4+ counts lower than 200cells/mm$^3$ in these patients acted as risk factors for hepatotoxicity caused by antituberculosis drugs.


## Resumo

*Hepatotoxicidade secundária às drogas antituberculose limita o tratamento em pacientes coinfectados com HIV e tuberculose. Conduzimos estudo caso-controle para identificar fatores de risco para hepatotoxicidade entre pacientes com tuberculose e infecção pelo HIV em dois hospitais de Recife, Pernambuco, Brasil. O grupo caso consistiu de 57 (36,5%) pacientes com hepatotoxicidade e o grupo controle, 99 (63,5%) pacientes que não a apresentaram. Hepatotoxicidade foi definida como icterícia ou alta concentração de ALT/AST ou de bilirrubinemia total. Regressão logística multivariada mostrou que a contagem de linfócitos T CD4+ < 200 células/mm$^3$ aumentou o risco de hepatotoxicidade em 1,233 vezes (p < 0,001), e coinfecção com vírus de hepatite B ou C aumentou o risco em 18,187 (p = 0,029). Alta hospitalar ocorreu em 66,1% dos pacientes do grupo caso (p = 0,026). Ausência de hepatotoxicidade foi fator de proteção para óbito (OR = 0,42; IC: 0,20-0,91). Coinfecção pelos vírus das hepatites B e C e linfócitos T CD4+ abaixo de 200 células/mm$^3$ foram fatores de risco independentes para a hepatotoxicidade nesses pacientes.*


*Toxicidade de Drogas; Coinfeccção; Tuberculose; HIV*

## Contributors

M. F. S. Lima made a substantial contribution to the conception and design of this study and data collection, analysis and interpretation. H. R. L. Melo contributed to drafting and reviewing the article for its technical content.

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