ISSN 2150-5349 (online)

World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2021 May 5; 12(3): 40-55

Published by Baishideng Publishing Group Inc

WJGPT

World Journal of Gastrointestinal Pharmacology and Therapeutics

Contents

Bimonthly Volume 12 Number 3 May 5, 2021

SYSTEMATIC REVIEWS

World Journal of Gastrointestinal Pharmacology and Therapeutics

Bimonthly Volume 12 Number 3 May 5, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Pharmacology and Therapeutics*, Mariusz Madalinski, FEBG, PhD, Doctor, Department of Gastroenterology, North Manchester general Hospital, Crumpsall M8 5RB, Manchester, United Kingdom. m.h.madalinski@pro.onet.pl

AIMS AND SCOPE

The primary aim of the *World Journal of Gastrointestinal Pharmacology and Therapeutics* (*WJGPT*, *World J Gastrointest Pharmacol Ther*) is to provide scholars and readers from various fields of gastrointestinal pharmacology and therapeutics with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGPT mainly publishes articles reporting research results obtained in the field of gastrointestinal pharmacology and therapeutics and covering a wide range of topics including acid-related disorders, functional gastrointestinal disorders, fundamentals of gastrointestinal pharmacology, *etc.*

INDEXING/ABSTRACTING

The *WJGPT* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN
ISSN 2150-5349 (online)

LAUNCH DATE
May 6, 2010

FREQUENCY
Bimonthly

PUBLICATION DATE
May 5, 2021

World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Pharmacol Ther 2021 May 5; 12(3): 40-55

DOI: 10.4292/wjgpt.v12.i3.40

ISSN 2150-5349 (online)

SYSTEMATIC REVIEWS

Overview of drug induced liver injury in Brazil: What is the role of public health policy on the evidence?

Matheus William Becker, Karin Hepp Schwambach, Michele Lunardelli, Carine Raquel Blatt

ORCID number: Matheus William Becker 0000-0002-0190-3688; Karin Hepp Schwambach 0000-0003-3271-2566; Michele Lunardelli 0000-0003-3093-7374; Carine Raquel Blatt 0000-0001-5935-1196.

Author contributions: Becker MW, Lunardelli M, and Blatt CR collected the data and wrote the paper; Becker MW, Schwambach KH, Blatt CR wrote and revised the paper.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

PRISMA 2009 Checklist statement: The guidelines of the PRISMA 2009 statement have been adopted.

Matheus William Becker, Karin Hepp Schwambach, Michele Lunardelli, Carine Raquel Blatt, Graduate Program in Medicine-Hepatology, Federal University of Health Sciences of Porto Alegre, Porto Alegre 90050-170, RS, Brazil

Carine Raquel Blatt, Pharmacoscience Department, Federal University of Health Sciences of Porto Alegre, Porto Alegre 90050-170, RS, Brazil

Corresponding author: Matheus William Becker, MSc, Pharmacist, Graduate Program in Medicine-Hepatology, Federal University of Health Sciences of Porto Alegre, Sarmento Leite, 245 Street, Porto Alegre 90050-170, RS, Brazil. matheuswbecker@gmail.com

Abstract

BACKGROUND

Adverse drug reactions are responsible for increased costs and morbidity in the health system. Hepatotoxicity can be induced both by non-prescription drugs and by those used for chronic diseases. It is the main cause of safety-related drug marketing withdrawals and could be responsible for irreversible and fatal injuries.

AIM

To identify and to summarize Brazilian studies reporting the drug-induced liver injury.

METHODS

A systematic review of Brazilian studies was carried out until June 2020. It was found 32 studies, being 10 retrospective cohorts, 12 prospective cohorts, 5 cross-sectional, 3 case-control, one case series and one randomized clinical trial. In most studies were investigated tuberculosis patients followed by other infectious conditions like human immunodeficiency virus (HIV) and hepatitis C virus. The hepatotoxicity ranged from one to 57%, led by isoniazid, rifampicin, and pyrazinamide. Few studies reported algorithm to assess causality. In most studies, there were moderate outcomes and it was necessary drug interruption. However, few severe outcomes, such as chronic liver damage and liver transplantation were reported.

RESULTS

Twenty-two different criteria for hepatotoxicity were found. The great heterogeneity did not allow a meta-analysis. Standardization of parameter of drug-induced liver injury and greater effort in pharmacovigilance could contribute to learn more about drug-induced liver injury (DILI)'s epidemiology in

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: November 25, 2020
Peer-review started: November 25, 2020
First decision: January 7, 2021
Revised: January 20, 2021
Accepted: April 25, 2021
Article in press: April 25, 2021
Published online: May 5, 2021

P-Reviewer: Di Pasqua LG, Pavlovic M, Volynets GV
S-Editor: Zhang L
L-Editor: A
P-Editor: Liu JH

Brazil.

CONCLUSION
The development of strategic public health policies seems to have an influence on the DILI scientific evidence in Brazil due to main studies are in HIV and tuberculosis line care, two strategic health policies in Brazil.

Key Words: Chemical and drug-induced liver injury; Pharmacovigilance; Pharmacoepidemiology; Adverse effects; Infectious disease medicine; Hepatotoxicity

Core Tip: Hepatotoxicity is the main cause of safety-related drug marketing withdrawals and could be responsible for irreversible and fatal injuries. A systematic review of Brazilian studies was found 32 studies and the hepatotoxicity ranged from one to 57%, led by isoniazid, rifampicin, and pyrazinamide. Few studies reported algorithm to assess causality and twenty-two different criteria for hepatotoxicity were found. Standardization of parameter of drug-induced liver injury and greater effort in pharmacovigilance could contribute to learn more about drug-induced liver injury's epidemiology in Brazil.

Citation: Becker MW, Schwambach KH, Lunardelli M, Blatt CR. Overview of drug induced liver injury in Brazil: What is the role of public health policy on the evidence? *World J Gastrointest Pharmacol Ther* 2021; 12(3): 40-55
URL: https://www.wjgnet.com/2150-5349/full/v12/i3/40.htm
DOI: https://dx.doi.org/10.4292/wjgpt.v12.i3.40

INTRODUCTION

Drug-induced liver injury, also known as drug-induced liver injury (DILI), is the main cause of discontinuation of new drug research and for their withdrawal from the market during the marketing period[1]. Some mechanisms have been described according to the drug, but these are not fully known yet[2]. Identification is a challenge due to the diversity of drugs with hepatotoxic potential, the lack of symptoms specificity, and the absence of specific biomarkers for DILI in the clinical practice[3]. In France and Iceland, incidences of 13.9/100000 and 19.1/100000 inhabitants/year were identified, respectively, in the general population[4,5]. DILI manifests itself through elevation of hepatic transaminases, in addition to alteration of hepatic function markers, and may vary from asymptomatic presentation to hepatic encephalopathy[6]. Detection is done by exclusion of other causes along with the use of a drug with hepatotoxic potential. The Russel Uclaf Causality Assessment Method (RUCAM) algorithm is the most accepted tool to aid in DILI detection[7]. Some risk factors have been described, such as gender, age, lifestyle, but the huge diversity of drugs hinders generalization; it is believed that individual characteristics, drug properties, and genetic, metabolic and immunological factors have an important impact on the development of idiosyncratic DILI[6].

Idiosyncratic reactions may occur at therapeutic doses with a latency of 5 to 90 d after the use of the drug. The drugs most commonly associated with this type of reaction are antimicrobials, with many cases for amoxicillin associated with clavulanate[5,8-10]. In prospective studies published in 2005 and 2013, the drugs most frequently related to DILI were erythromycin, sulfamethoxazole/trimethoprim, diclofenac, isoniazid, and ibuprofen[5,8,11]. When DILI is not detected early, it may progress to acute liver failure, rapidly leading to death. However, when well managed it evolves favorably with the suspension of medication and support measures for the symptoms[12]. Different treatment strategies are adopted, but with little evidence of efficacy. The use of corticosteroids has been the most frequent practice. In addition, N-acetylcysteine is used in cases of acute hepatic impairment induced by medication, but, except for paracetamol, it has limited efficacy[13]. In the presence of cholestasis, ursodeoxycholic acid and cholestyramine are reported in the management[14]. In

Japan, a compound consisting of L-cysteine, glycine and Glycyrrhiza glabra is routinely used in DILI intoxications[15]. Silymarin, used preventively along with tuberculostatics, has presented good results, but these are still preliminary[16,17]. In the most acute cases, plasma exchange, among other extracorporeal therapies, are alternatives to avoid transplantation[13,18].

The notification and diagnosis of the cases as well as the knowledge and involvement of health professionals regarding the hepatotoxicity of the drugs are of great importance for the early detection and reduction of damages to the patients affected by DILI[19-21]. In this context, this paper aims to identify Brazilian studies with data on drug-induced hepatotoxicity in order to know the profile of DILI in Brazil.

MATERIALS AND METHODS

A systematic review of published Brazilian studies of drug-induced liver injury was performed. The databases searched were PubMed, Scielo, Science Direct and the Brazilian thesis bank. The search strategy combined the descriptors for DILI with Brazil in Portuguese and English as follows: (Hepatotoxicity or drug-induced liver injury or liver injury or hepatotoxic adverse drug) and (Brasil or Brazil or Brazilian). There was no limitation by language, year of publication or study design. Other sources of access to the studies were used, such as contact with authors and references. The last search was performed in June 2020.

The eligibility of the studies was defined by the identification or suspicion of DILI due to drug or plant use and by being Brazilian studies. In order organize the results, case reports were excluded from this publication.

The selection of the studies was performed by two independent reviewers and in three sequential stages by reading the title, the abstract and the full text. A third reviewer resolved the disagreements. Data extraction are doing independently, the following variables were analyzed: Age; gender, comorbidities; local; and design; sample size; suspected drugs; HIV, tuberculosis (TB) or HCV infection; use of algorithm to support diagnosis; classification criteria for hepatotoxicity; outcomes related to DILI; frequency of DILI.

All Brazilian DILI cases reports are included. Risk of bias in individual studies aren't available and we didn't perform a summary of measures or a sensitivity or subgroup analyses.

RESULTS

Initially, 441 studies were found. After excluding case reports and duplicates and including gray literature, 32 studies were included as can be seen in Figure 1. The selected studies comprised 29 articles, 2 dissertations, and one monograph.

Table 1 presents some data from the studies included in this review. The publication date of the studies ranged from 1989 to 2015. Among the Brazilian states, Rio Grande do Sul, Rio de Janeiro and São Paulo accounted for 62% of the studies. Regarding the studied population, the average age was 37.9 years. In studies that DILI was analyzed by gender (n = 8), on average 55% of all patients who developed DILI were men.

Concerning the study design, we identified cohort studies (n = 22), 10 retrospective and 12 prospective, cross-sectional (n = 5), case-control (n = 3), case series (n = 1) studies and randomized clinical trial (n = 1). The studies were performed in outpatient (45%) and hospital settings (55%).

Analyzing the populations, 24 studies investigated patients under treatment for tuberculosis, 7 of them had patients co-infected with HIV, of which 5 had HIV and HCV. We identified studies with patients under treatment for acute myeloid leukemia (n = 2), metabolic syndrome (n = 1), colorectal cancer (n = 1), rheumatoid arthritis (n = 1), ulcerative colitis (= 1) and other unspecific severe disease (n = 1).

The main drugs associated with DILI were: Rifampicin, Isoniazid, and Pyrazinamide (RHZ), Nevirapine; Azathioprine; Fluorouracil; Methotrexate; Leflunomide; Tretinoin; Amphotericin B deoxycholate; and Propylthiouracil.

In four studies, causality algorithms were used to identify the drug responsible for hepatotoxicity. The Naranjo algorithm used generically for adverse drug reactions was used in one study[22-24]; RUCAM, used specifically in liver injury by drugs, was used in tree studies[25-27]. In addition, 22 different criteria for DILI determination were identified, categorized and summarized in Table 2.

Table 1 Summary of published Brazilian studies on drug-induced hepatotoxicity data

Ref.	Year	Place	State	Design	*n*	Class or medication	Use of algorithm	Frequency of DILI
Silva *et al*[22]	2019	Ho	BA	Cross-cut	306	MTX	No	2.0%
Alves *et al*[59]	2011	Ho	SC	Cross-cut	71	MTX/LEF	No	11.0%
Carvalho *et al*[74]	2014	A	RJ	Cross-cut	219	Azathioprine	No	2.7%
de-Medeiros *et al* [75]	1998	Ho	PR	RCT	37	Tretinoin	No	16.0%
Werner *et al*[61]	1989	Ho	SP	PC	389	Propylthiouracil	No	1.3%
Santos *et al*[63]	2013	Ho	RS	RC	185	5-Fluorouracil	No	57.8%
Uehara *et al*[76]	2005	Ho	SP	RC	12	Amphotericin B	No	30.0%
Magalhães[26]	2015	Ho	BA	Case series	31	Multiple	RUCAM	NA
Prado *et al*[27]	2019	A	BA	PC	149	Nimesulide, budesonide and valacyclovir	RUCAM	2.0%
Antonello *et al*[55]	2014	Ho	RS	PC	65	ARV	No	45.0%
Tovo *et al*[47]	2006	Ho	RS	PC	CI 385 MI 198	ARV	No	CI 57.8% MI 13.0%
Kondo *et al*[49]	2008	A	PR	RC	157	Nevirapine	No	4.0%
Gil *et al*[48]	2007	A	SP	Cross-cut	152	Tuberculostatic ARV and sulfonamides	No	19.7%
Tomich *et al*[77]	2015	Ho	SP	RC	149	Tuberculostatic, ARV among others[1]	No	22.1%
Santos *et al*[23]	2019	Ho	RJ	PC	45	Tuberculostatic	No	13.0%
Heinrich[24]	2014	A	MS	PC	100	Tuberculostatic	NARANJO	11.1%
Monteiro *et al*[25]	2012	A	RJ	PC	177	Tuberculostatic	RUCAM	33.3%
Gusmão Filho *et al* [43]	2001	Ho	PE	RC	52	RHZ/ RHE/	No	35.6%
Lima Mde *et al*[65]	2012	Ho	PE	Control case	156	RHZ and RHZE	No	26.9%
Zaverucha-do-Valle *et al*[41]	2014	A	RJ	RC	131	RHZ	No	26.7%
Coca *et al*[73]	2010	Ho	MG	Control case	162	RHZ	No	H^3 56.2% and H^4 10.4%
de Castro *et al*[44]	2010	A	RJ	PC	154	RHZ	No	19.5%
Nader *et al*[45]	2010	Ho	RS	RC	534	RHZ	No	8.8%
Vieira *et al*[78]	2008	A	SP	RC	297	RHZ	No	8.1%
de Souza *et al*[79]	1996	Ho	MG	PC	1096	RHZ	NI	6.0%
Fernandes *et al*[68]	2015	Ho	PA	PC	220	RHZ/RH	No	14.1%
Brito *et al*[64]	2014	A	RS	PC	245	RHZ/RH	No	6.1%
Schultz *et al*[46]	2014	Ho	RS	RC	69	Rifampicin	No	33.3%
Santos *et al*[53]	2013	A	PA	PC	270	Isoniazid	No	6.5%
Teixeira *et al*[52]	2011	A	RJ	Control case	167	Isoniazid	No	16.0%
Szklo *et al*[67]	2007	A	RJ	RC	40	SEO3[2]/EO9[2]	No	12.5%
Picon *et al*[66]	2002	A	RS	PC	78	SHE3[2]/HE3[2]/H3[2]	No	1.3%

[1]Sulfa drugs, statins, imidazole, anticonvulsant, nonsteroidal.
[2]Months.
H^3 transaminases > 1.25 to 2.5 × upper limits of normality.
H^4 transaminases > 2.6 to 5 × upper limits of normality. RUCAM: Causality algorithm; ARV: Antiretrovirals; MTX/LEF: Methotrexate/leflunomide; NA:

Not applicable; CI: Human immunodeficiency virus and hepatitis C coinfected; PC: Prospective cohort; RC: Retrospective cohort; MI: Monoinfected for human immunodeficiency virus; DILI: Drug-induced liver injury; RCT: Randomized clinical trial; R: Rifampicin; H: Isoniazid; Z: Pyrazinamide; S: Streptomycin; and ethambutol. O: Ofloxacin, Ho: Hospital; A: Ambulatory.

Table 2 Criteria used for the definition of liver injury

Criteria applied for liver injury definition	Ref.	Condition
Elevated ALT	Tovo *et al*[47], 2006	HIV/HCV
ALT > 2 × ULN	Monteiro *et al*[25], 2012	TB
ALT > 2.5 × ULN	Zaverucha-do-Valle *et al*[41], 2014; Kondo *et al*[49], 2008	TB/smoker; HIV
ALT > 3 × ULN	Fernandes *et al*[68], 2015; Santos *et al* [53] 2013;	TB; TB
ALT or AST > 2 × ULN	Alves *et al*[59], 2011; de Castro *et al* [44], 2010	AR; TB/HBV
ALT or AST > 3 × ULN	Heinrich[24], 2014; Vieira *et al*[78], 2008; Uehara *et al*[76] 2005	TB/ indigenous; TB; IMQ
ALT or AST > 3 × or BT > 1.5 ×	**Schultz *et al*[46]**, 2014	TB/TX
ALT > 3 × ULN; BT > 2 ×	Brito *et al*[64], 2014; Nader *et al*[45], 2010	TB/HCV
ALT or AST > 3 × ULN; BT > 2 ×	**Lima Mde *et al*[65]**, 2012; Picon *et al* [66], 2002	TB/HIV; TB
ALT ≥ 5 × LSN ou FA ≥ 2 × LSN ou ALT ≥ 3 × ULN e BT ≥ 2 × LSN	Prado *et al*[27], 2019	Gastro-hepatology conditions
(1) ALT > 3 × lower limit of normality; (2) ALT > 3 × ULN; (3) ALT > 3 × ULN and BT > 2 × ULN	Coca *et al*[73], 2010	TB/HIV
ALT or AST: (1) 1.25 a 2.5 × ULN; (2) 2.6 a 5 × ULN; (3) 5.1 a 10 × ULN; (4) > 10 × ULN	Antonello *et al*[55], 2014	HIV
ALT or AST: (1) 1.25 a 2.5 × ULN; (2) 2.6 a 5 × ULN; (3) 5.1 a 10 × ULN; (4) > 10 × ULN or BT – (1) 1.1 a 1.5 × ULN; (2) 1.6 a 2.5 × ULN; (3) 2.6 a 5.0 × ULN; (4) > 5.0 × ULN	Tomich *et al*[77], 2015	TB/HIV
Altered ALT or AST (hepatotoxicity) and ALT or AST > 5 × (hepatitis)	Gusmão Filho *et al*[43], 2001	TB/children
ALT or AST > 3 × ULN and hepatitis syndromes	Teixeira *et al*[52], 2011	TB
AST > 3 × ULN and hepatitis syndromes	Szklo *et al*[67], 2007	TB/previous liver injury
Altered ALT, AST, AP or BT	de Souza *et al*[79], 1996	TB
Increase in liver function tests	de-Medeiros *et al*[75], 1998	LMA
Histological assessments	Santos[63], 2013	QT/HPTC
AST or ALT: (1) 1.1-4.9 × ULN; (2) 5.0-9.9 × ULN; (3) 10.0-15.0 × ULN; (4) > 15.0 × ULN	Gil *et al*[48], 2007	HIV/child/adolescent
ALT > 2 times ULN or the ALT/AP ratio ≥ 5 or AP > 2 times ULN ALT/AP ratio ≤ 2 or ALT > 2 times ULN and ALT/AP ratio between 2 and 5	Magalhães[26], 2015	Several
ALT ou AST > 2 × LSN e BT > 1.3 mg/dL	Santos *et al*[23], 2019	TB
NI	Silva *et al*[22], 2019; Carvalho *et al*[74], 2014; Werner *et al*[61], 1989	IBD; Ulcerative colitis; Grave's disease

ALT: Alanine methyltransferase; ULN: Upper limits of normality; AST: Aspartate methyltransferase; BT: Total bilirubin; AP: Alkaline phosphatase; NI: Not identified; TB: Tuberculosis; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; HBV: Hepatitis B virus; IMQ: Immunosuppressed by chemotherapy; TX: Transplantation; QT: Chemotherapy; HPTC: Hepatectomy; IBD: Inflammatory bowel disease.

Concerning studies evaluating DILI-related outcomes (n = 16), only one did not require drug suspension or dose adjustment; one case progressed to chronic hepatitis and one reported the need for liver transplantation according to data presented in Table 3. A summary of the Brazilian studies and their findings is shown in Table 4.

Table 3 Main outcomes related to drug-induced liver injury in Brazilian studies

Ref.	DILI outcomes	Medications
Santos *et al*[23], 2019	6 Cases were resolved after the suspension of medications	Tuberculostatic
Magalhães[26], 2015	21 Cases were resolved after the suspension of the substance, but without the use of medications; 9 cases were resolved with the suspension of the substance associated with medications; 1 case with acute hepatic failure, requiring liver transplantation	Isoniazid, valproic acid, amitriptyline, cyclosporine, clozapine, dasatinib, imatinib, ACO, simvastatin, melphalan, and others
Antonello *et al* [55], 2014	There was no need to suspend or change the treatment	ARV
Kondo *et al* [49], 2008	7/157 Patients (4.4%) were hospitalized and, after discontinuation of Nevirapine, all presented clinical and laboratory improvement	Nevirapine
Brito *et al*[64], 2014	Changed therapeutic regimen in all who developed DILI 15/245 (6.1%)	RHZ
Lima Mde *et al* [65], 2012	Drug maintenance 26/156 (16.6%), temporary interruption 12/156 (7.7%), treatment change 11/156 (7%), suspension of medications TB 7/156 (4.5%)	RHZ, RHZE
Coca *et al*[73], 2010	Medication suspended in 7/30 (23.3%) HIV and 15/132 (11.4%) non-HIV	RHZ
Vieira *et al*[79], 2008	There was a need to modify the treatment regimen in 11/24 (45%) of the patients	RHZ
Picon *et al*[66], 2002	RHZ: 45 cases changed treatment; SHM: 1 case changed treatment	RHZ, SHM
Gusmão Filho *et al*[43], 2001	3/52 (5.76%) Required replacement of the medication. In 16/52 (30.7%) there was no need for intervention and in other 13/52 (25%) only the doses of Isoniazid and Rifampicin were changed	RHZ, RHE
de-Medeiros *et al*[75], 1998	Medication was suspended and 1/37 (2%) patient was excluded from the RCT	Tretinoin
Alves *et al*[59], 2011	Medication doses were temporarily reduced	MTX
Prado *et al*[27], 2019	The culprit drug was discontinued, and drug therapy was not necessary to resolve the problem in 3 patients	Nimesulide, budesonide, valacyclovir
Werner *et al* [61], 1989	There was clinical and laboratory Improvement with the suspension of the medication in 4/389 (1%) and 1/389 (0.25%) evolved to chronic hepatitis	Methimazole, Propylthiouracil

DILI: Drug-induced liver injury; R: Rifampicin H: Isoniazid; Z: Pyrazinamide; S: Streptomycin; and E: Ethambutol; RCT: Randomized clinical trial; MTX: Methotrexate; ARV: Antiretroviral; ACO: Oral contraceptives.

DISCUSSION

Some systematic reviews about DILI[28-31] can be found in the literature, but none in the Brazilian studies. The hepatotoxicity frequency ranged from one to 57%; however, as these studies investigate specific populations, these data do not allow to infer the frequency of DILI or to generalize the findings. The drugs with the highest number of reports were those with known hepatotoxic potential, such as isoniazid, pyrazinamide, and rifampicin, nevirapine[9].

The low incidence of DILI makes it difficult to develop prospective cohort studies, which would be more robust in verifying the causality between the drug and liver damage. In this review, one-third of the studies were prospective. The low frequency of clinical trials with hepatotoxicity data, attributed to the low number of clinical trials exclusively in the Brazilian population, is noteworthy. Clinical trials are not the best study design to assess drug safety, in addition to involving the potential of conflict of interests. Therefore, the cohort study is the ideal design for detecting ADRs, since it frequently reveals toxicities undetected in clinical trials.

Pharmacovigilance studies may be alternatives for better knowledge about DILI, but when coming from spontaneous reports they have the underreporting bias[32]. A Brazilian study found only ten cases of hepatotoxicity by herbal medicines from notification data of the regulatory agency, in a 10-year interval. Two cases developed acute liver failure and died, both of which reported the use of kava[33]. Liver transplantation was recently performed by kava in Brazil[34]. Through RUCAM it was considered probable, therefore it was possible to exclude extrinsic toxicity and contaminants after performing chemical analyses of the drug used. In this way, the

Table 4 Summarization of the Brazilian studies according to the drugs evaluated

Ref.	Drugs	Summary of Brazilian researches
Santos *et al*[23], 2019	Tuberculostatics	Patients with the *CYP2E1* variant genotype or Null GSTT1 showed higher risk of presenting DILI. Individuals with both genotypes had no increased risk compared to individuals with one genotype
Prado *et al*[27], 2019	Nimesulide, budesonide, valacyclovir	The present prospective study allowed reporting new cases of DILI in 2% outpatients. It also allowed estimating the incidence of hepatotoxicity induced by allopathic medicines, which are standardized by public healthcare authorities
Silva *et al*[22], 2019	MTX	The frequency of drug hepatotoxicity was about 2% of hepatobiliary disorders in inflammatory bowel disease patients
Fernandes *et al* [68], 2015	RHZ	An association founded between the 516 TT polymorphism and drug-induced hepatotoxicity
Tomich *et al*[77], 2015	Tuberculostatics ARV, sulfonamide drugs, statins, imidazoles anticonvulsants, non-steroidal anti-inflammatory	In HIV patients admitted to a tertiary hospital, it was found a high incidence (22.1%) of severe DILI. The use of anti-tuberculosis drugs and baseline liver injury were independent factors associated with severe DILI during a hospital stay
Magalhães[26], 2015	Various	Hepatotoxicity caused by a wide variety of medicines, plant supplies, and dietary supplements. Anti-infectives and chemotherapeutics were responsible for most reactions, in 41% and 19% of cases, respectively. There is a shortage of records in information records to evaluate the causality of reactions
Antonello *et al* [55], 2014	ARV	The coinfected patients are at an increased risk for developing hepatotoxicity, but the clinical and immunological benefits of highly active antiretroviral therapy are higher than the risk of hepatotoxicity and rarely justify discontinuation of therapy
Heinrich[24], 2014	Tuberculostatics	Age over 60 year old, the time after the start of treatment (15 d) and being indigenous (Brazilian native American) are risk factors for the development hepatotoxicity during treatment of TB
Zaverucha-do-Valle *et al*[41], 2014	RHZ	The anti-TB drugs interactions with smoking on hepatotoxicity, as well as the *NAT2* phenotype, may require adjusting therapeutic regimen dosages or alarm in case of adverse event developments
Schultz *et al*[46], 2014	Rifampin	The use of rifampin at daily doses of 600 mg or higher and lung transplantation founded to be an independent risk factor for liver toxicity in solid organ transplants recipients. Kidney transplantation appeared as a protective factor. Mortality was higher in the patients who had hepatotoxicity (43.5%), compared with those who did not
Brito *et al*[64], 2014	RHZ	Clinical (HIV, female and extrapulmonary TB) and genetic characteristics (*CYP2E1* without any mutations, having *NAT2* slow acetylator profile) are at higher risk of developing DILI in this population. Genotyping for glutathione S-transferase *GSTM1* and *GSTT1* showed no influence on drug response
Santos *et al*[53], 2013	5-fluorouracil	Patients exposed to chemotherapy have a 2.2-fold increase in the risk of developing hepatic steatosis
Santos *et al*[63], 2013	Isoniazid	Large-scale screening for *NAT2* and *CYP2E1* genotypes can prove useful in predicting the risk of adverse effects
Monteiro *et al* [25], 2012	Tuberculostatics	*GSTM1* and *GSTT1* null genotypes do not seem to play important roles in DILI in Brazilians. However, there was evidence that *GSTM1* polymorphisms were possibly related to the intensity of toxicity. Active HBV and initial high ALT could predict DILI
Lima Mde *et al* [65], 2012	RHZ, RHZE	The absence of hepatotoxicity was a protective factor against death. Coinfection with the B and C hepatitis virus and a T CD4+ cell count below 200 cells/mm^3 were independent risk factors for hepatotoxicity in these patients
Teixeira *et al* [52], 2011	Isoniazid	Slow acetylators had a higher incidence of hepatitis than intermediate/rapid acetylators. Slow acetylation status was the only independent risk factor for the occurrence of anti-TB drug-induced hepatitis during anti-TB treatment with INH-containing schemes in Brazilian individuals
Alves *et al*[59], 2011	MTX, Leflunomide	There was no difference between the elevation of aminotransferases in patients treated with MTX alone or with combined therapy
Coca *et al*[73], 2010	RHZ	Depending on the definition of drug-induced hepatitis, HIV infection may or may not be associated with hepatotoxicity. The impact that minor alterations in the definition had on the results was impressive. The emergence of new symptoms after initiating antituberculosis therapy could not be attributed to hepatotoxicity in over one-third of the cases
Nader *et al*[45], 2010	RHZ	The anti-HIV drugs and high doses of isoniazid were considered independent risk factors for hepatotoxicity due to RHZ regimen in this study. Though univariate analysis showed that anti-HCV drugs was associated with the outcome, it was not identified as an independent risk factor for hepatotoxicity related to the use of RHZ when the analysis controlled to HIV
de Castro *et al* [44], 2010	RHZ	Active HBV, indicated by the detection of surface antigen HBV, could predict hepatotoxicity, although with low precision

Vieira *et al*[78], 2008	RHZ	The frequency of adverse effects related to the treatment of tuberculosis with RHZ was 49.1% in this group of patients. However, in most cases, there was no need to modify the treatment regimen due to adverse effects
Kondo *et al*[49], 2008	Nevirapine	There was no correlation between high CD4 counts and adverse events when skin and hepatic reactions were analyzed together. However, hepatotoxicity occurred only in pregnant women with a CD4 count of ≥ 250 cells/μL
Szklo *et al*[67], 2007	SEO3/EO9	In this series of TB patients with serious liver injury, 3SEO/9EO was well tolerated, and it was effective in 85% of patients when used under routine clinical care conditions
Gil *et al*[48], 2007	tuberculostatics, ARV, sulfonamide drugs	One-fifth of patients experienced mild hepatotoxicity, attributed to antituberculosis agents and sulfonamides. Our results suggest that the ARV was well tolerated
Tovo *et al*[47], 2006	ARV	There was no difference between the groups concerning the type of ARV used, as well as cases of hepatotoxicity attributed to PI. There was no difference concerning tolerability to PI between the two groups
Picon *et al*[66], 2002	SHE3/HE3/H3	Streptomycin, isoniazid, and ethambutol regimen may be recommended as an alternative for the treatment of tuberculosis whenever the RHZ regimen cannot be indicated
de Souza *et al* [79], 1996	RHZ	Liver changes characterized as of small and medium intensity translated as pure cholestasis or hepatocanalicular hepatic reactions. Possibly Rifampicin was important in this evolution, acting as a potentiator of the actions triggered by isoniazid and pyrazinamide
Werner *et al*[61], 1989	Propylthiouracil	The adverse effects of thionamide drugs were similar in both high- and low-dose regimens. These undesirable effects demand a strict follow-up, as well as the high dose regimen for Graves' disease treatment particularly advised for patients with severe symptoms

TB: Tuberculosis; TBD: Tuberculostatic drugs HIV: Human immunodeficiency virus; DILI: Drug-induced liver injury; NAT2: N-acetyltransferase 2; MTX: Methotrexate; HCV: Hepatitis C virus; RHZ: Rifampicin, isoniazid and pyrazinamide; HBV: Hepatitis B virus; ARV: Antiretroviral; PI: Protease inhibitors; SEO3: Streptomycin, ethambutol and ofloxacin for 3 mo; SO9: Streptomycin and ofloxacin for 9 mo; SHE3: Streptomycin, isoniazid, and ethambutol for 3 mo; HE3: Isoniazid ethambutol for 3 mo; H3: Isoniazid for 3 mo.

pharmacovigilance studies associated with the appropriate technical support should be stimulated to facilitate the detection and elucidation of the cases.

The DILI studies were concentrated in the southern and southeastern regions of Brazil. In addition, most of the studies were conducted by research groups linked to academic centers. In Brazil, the continental dimension, the large population, and the great cultural diversity make it difficult to carry out a single representative study in the country. For this reason, it is important to encourage further regional studies.

Most Brazilian studies on drug-induced liver injury investigate population groups using drugs for the treatment of infection and chronic diseases–whose ambulatory therapy is provided by the Unified Health System–such as Tuberculosis, HIV, Rheumatoid Arthritis, Ulcerative Rectocolitis, and Acute Myeloid Leukemia. Public health policies like specialized care offered by these lines of care, and the clinical protocols and therapeutic guidelines are technologies that seem to be effective in the prevention and the management of these ADRs. Whereas the hepatotoxic potential is foreseen in the guidelines, a structured information technology and resources for monitoring pharmacotherapy are required for the operations of these services. The well-structured care line makes it possible to gather a large volume of data at the national level. Professional performance in the care lines also plays a role in training and research, enabling the formation of research groups. This impulse in scientific production seems to be able to influence the existing evidence at the national level.

Some risk factors were associated to DILI such as previous liver disease, immune dysfunction, diabetes, hypertension, alcohol consumption, gestation, female age, advanced age, polymedicine, dose and lipophilicity of the drug, among others[1,35,36]. The female gender was associated with the occurrence of hepatotoxicity with tuberculostatic drugs[10,37-39], but Brazilian studies, as well as in a Peruvian study[40], have shown a lower frequency of DILI in women. In the population with TB, unexpectedly, a higher prevalence of DILI was found in nonsmoking patients when compared to smokers; however, it was argued that the genetic profile of the sample could have influenced the result[41]. No further development of DILI in advanced age was found, unlike in international studies[5,10,42], but it is suggested that the specificity of the populations studied cannot be comparable. A differential factor in Brazilian studies is the frequent profile of infectious diseases. American and European studies generally present populations with chronic diseases. Therefore, the frequency of DILI related to certain drugs may change regionally according to the characteristics of the populations studied and the profile of drug use. Some authors have studied specific populations taking tuberculostatic drugs, such as Brazilian native Americans[24], children[43], hepatitis

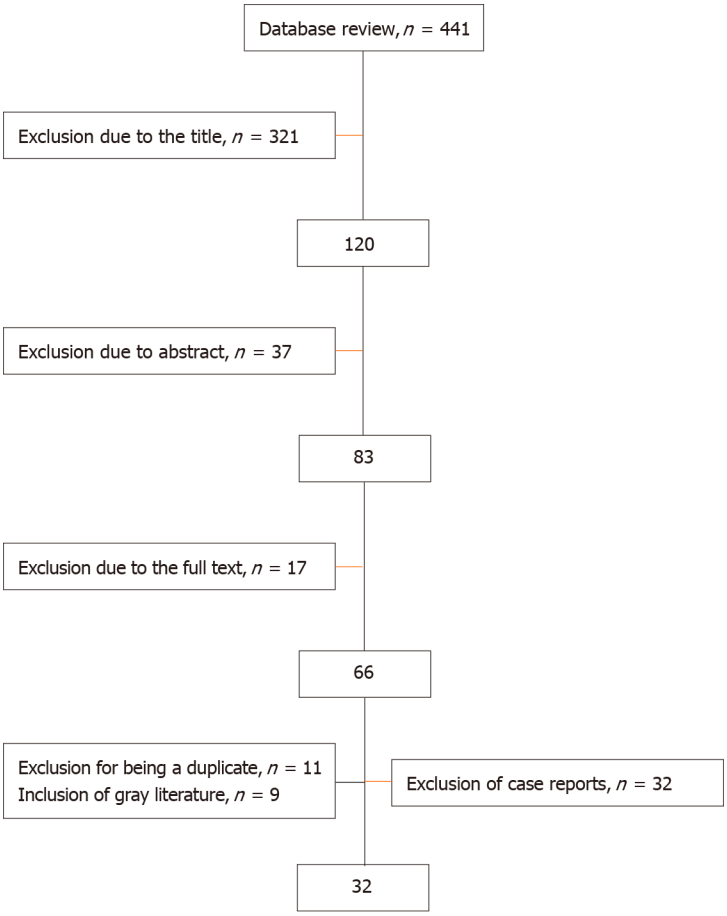

Figure 1 Flowchart of studies selection about drug-induced liver injury published in Brazil.

B[44], hepatitis C[45], solid organ transplanted patients[46], smokers[41], HCV/HIV coinfected[47], and antiretroviral (ARV) in children and adolescents[48] and nevirapine in pregnant women[49].

This review found that when patients using RHZ were analyzed the frequency ranged from 6% to 14%; however, some characteristics such as HIV infection, alcohol use, and polypharmacy were present and may have contributed to the frequency found. Some studies were developed from the analysis of drugs prescription. The DILI frequency by the drug was estimated. The number of prescriptions by a number of exposed users further the DILI frequency. In a study of hospitalized patients, the risk of developing DILI for erythromycin was 14 per 100000 prescriptions, penicillin had a risk of 10.9 per 10000 users of the drug[50]. Another study found DILI risk around 1 per 1000 users for chlorpromazine, azathioprine, and sulfasalazine[51]. Two Brazilian studies attributed RHZ hepatotoxicity more specifically to isoniazid[52,53]. In a United Kingdom study, Isoniazid, together with chlorpromazine, was associated with a DILI risk of 100/100000 users[54].

Considering the ARVs, nevirapine, abacavir, and ritonavir are the main hepatotoxic agents[47,55]. The information regarding the hepatotoxicity of ARVs is known and presented in the Brazilian clinical protocol for the management of HIV in adults. In addition, in the mentioned protocol there is a classification of the severity of hepatotoxicity according to the levels of transaminases[56,57]. In relation to TB treatment, the most reported was the basic regimen with RHZ for 2 mo, followed by Rifampicin and Isoniazid for 4 mo. Since 2009, ethambutol has been added to this treatment regimen. Known as a quadruple regimen, one tablet has all four drugs to facilitate adherence to treatment, but in the case of hepatotoxicity, there is no way to identify which drug is responsible[58]. In general, co-infection with HIV and TB seems to be one of the situations that draw the most attention to the monitoring of hepatotoxicity, since both treatments are complex and contain drugs with potential for hepatotoxicity. Both protocols emphasize the need for caution in the administration of the two concomitant therapies. Few serious outcomes were found in this review, perhaps because in most cases the suspension or change of the drug was clinically sufficient for regression of the injury. The structuring of specialized centers, the

development of clinical protocols and efficient pharmaceutical assistance seems to have been essential for the monitoring, knowledge, and management of adverse drug reactions in these patient groups.

Some studies compared different treatment regimens or combinations compared to monotherapy with drugs of known hepatotoxic potential, in order to establish a safety relation in its use. In one of the Brazilian studies of patients with rheumatoid arthritis, the use of methotrexate (MTX) or MTX associated with leflunomide had no significant difference in DILI[59]. An Argentine study in rheumatoid and psoriatic arthritis found a higher incidence of DILI in NSAIDs, whereas MTX was responsible for steatosis, but without the need to interrupt treatment[60]. Although MTX is a drug known to be hepatotoxic, it has been shown to be safe in association with leflunomide. However, monitoring of hepatic enzymes and liver function seems to be important in patients treated with other hepatotoxic drugs. In patients with Graves' disease treated in groups with propylthiouracil or methimazole at high or low doses, there was no difference in hepatotoxicity between the groups[61]. However, several cases have been reported, with the most serious cases being children and adolescents who show a frequency of acute liver failure of 1:2000 children[62]. In both studies, the safety profile for hepatotoxicity was evaluated, however, in the treatment of chronic diseases, safety should also be evaluated in the long term, in this case only cohorts with long follow-up, and pharmacovigilance studies can establish a long-term safety profile.

Amoxicillin with clavulanate leads the cases of DILI in the United States, Spain, France, and Iceland[4,5,8,42]. Drugs such as antimicrobials, non-steroidal anti-inflammatory, and other chronic medications have demonstrated a high DILI index in the world, but its prevalence of toxicity in the Brazilian population is not known[9]. However, in a case series study, anti-infective were the main hepatotoxic drugs, followed by chemotherapies[26]. Santos[63] described that patients with metastases in colorectal cancer, who underwent hepatectomy and underwent chemotherapy, had a 2.2-fold increased risk of hepatic steatosis. The most commonly reported antineoplastic drugs are immunobiological drugs, such as imatinib, and hormone antagonists, such as cyproterone and tamoxifen, but irinotecan also appears in the list of most commonly reported. However, it is hard to define the causality of antineoplastic agents when there is hepatic metastases[9].

In HIV-positive patients, HCV coinfection increased the risk of liver damage but did not justify the suspension of ARVs, as well as the use or not of protease inhibitors, which had no significant difference between monoinfected and coinfected[47,48,55,63]. In a study that evaluated the population using TBS, independent risk factors for the development of DILI were considered: age above 60 years, the first 15 d of treatment, extra pulmonary TB, HCV/HBV coinfection, CD4 count < 200 μL cells, being indigenous[28,64,65]. In a study with transplant patients, doses of rifampicin above 600 mg and lung transplantation were found to be risk factors for DILI, just as kidney transplantation seemed to act as a protective factor[46]. Two studies have demonstrated the safety of alternative TB regimens after the previous hepatotoxicity; the association of streptomycin, ofloxacin, and ethambutol for three months followed by another nine months with ofloxacin and ethambutol, and the association of streptomycin, ethambutol, and isoniazid for three months followed by ethambutol and isoniazid three months and isoniazid three months[66,67].

Some lines of Brazilian research have evaluated the genetic profile associated with the development of DILI with tuberculostatics. The *CYP2B6* gene had the 516 TT polymorphism associated with DILI[68]. Genotypes of *CYP2E1* and *CYP3A4* were not associated with hepatotoxicity; when different acetylators of NAT2 were analyzed, slow acetylators had an increased risk of DILI[41,52,64]. Another study defined the genetic profile of NAT2 and CYP2E1 as predictors of the development of adverse reactions with isoniazid[53,65]. In two studies, glutathione S transferase genotypes were not associated with the development of DILI[25,64]. Thus, it can be seen that the development of DILI has been investigated at the molecular genetics level, and Brazil has conducted important studies on the knowledge of the variants in its population.

The causality algorithms for the identification of adverse reactions are tools that help in the detection and classification of the suspicious factor probability. Only four studies reported using an algorithm. The Naranjo algorithm was one of the precursors, but its general character does not allow contemplating the specificity of DILI[69]. The RUCAM was the first and most widely used algorithm specific for DILI. Subsequently, others emerged, such as Maria and Vitorino, Drug-induced Liver Injury Network and Digestive Disease Week Japan Scale[8,51,70,71]. Algorithms are great tools for prospective data analysis. However, its validity for retrospective studies is questionable because registry biases may compromise the validity of the result[7]. The fact that there is low frequency use of these tools makes it possible to launch some

hypotheses. Are researcher's unfamiliarity regarding algorithms? Or do they think that it is hard applying them? This gap found in Brazilian studies cannot be easily answered. The use of algorithms in clinical practice is often unfeasible since they require considerable time for their application in addition to an excess of information or exams sometimes unavailable or considered unnecessary. However, in the field of research it would be very important that the algorithms were widely used tools to determine the causality of the liver injury. In addition to greater reliability of the results, would improve data quality, which would make possible to classify the liver injury and improve the knowledge of the outcomes.

Twenty-two different strategies in the definition of liver injury were found, and also made it difficult to compare the findings. HIV Research Groups consider the guideline of the AIDS Clinical Trials Group to grade the hepatic lesion according to the transaminase value range[56]. Studies with TB often follow the standards of the II Brazilian Consensus on Tuberculosis[72]. The RUCAM algorithm performs the best definition, which is the most internationally accepted standard in the determination of liver damage by drugs or plants[7].

However, in Brazil the divergences of the guidelines promoted by the public policies hinder the formation of a national database on hepatotoxicity. The concept of hepatic injury adopted is decisive in the study findings, as indicated in a study comparing three different DILI criteria in HIV patients; in these patients, DILI may be undetectable or may affect up to 77% depending on the criteria adopted[73]. This study reinforces the need for standardization of the definition of drug-induced liver injury in Brazil, also in national guideline with tools like RUCAM. The follow-up of patients undergoing treatment for chronic diseases should include the identification of adverse drug reactions and the reporting of adverse drug reactions when suspected. Monitoring of ADRs is essential to establish the safety profile of medicines during their marketing. Encouraging the use of this resource will be important to improve not only the criteria but also the definition of causality in cases of DILI[74-79].

This review had as a limitation the impossibility of inferring a frequency of DILI in Brazilian studies through meta-analysis since few of the studies found were performed aiming to determine liver injury as well as the high heterogeneity found. In this sense, all studies with hepatotoxicity data were included. The studies included with few or incomplete data could result in low quality of evidence, but due to the scarcity of Brazilian studies, we decided to maintain them. The quality of the studies included in the review was not evaluated. Due to the impossibility of performing a meta-analysis, this study aimed to have an exploratory and baseline character for future studies in the area. Retrospective studies are biased by the lack of available information, and some studies have not used criteria for the identification of drug-induced liver injury. Despite these limitations, the studies included in this review have contributed to learn more about achievements and challenges in Brazilian DILI's researches. The DILI's evidence in Brazil has been strongly influenced by public health policy. However, this relationship between health policies and evidence must be reversed with the evidence guiding public health policies.

CONCLUSION

The drugs associated with liver injury reported in the Brazilian studies were Isoniazid, Rifampicin and Pyrazinamide, Nevirapine, in addition to methotrexate, propylthiouracil, azathioprine; the Brazilian studies published on DILI investigate specific populations with chronic use of drugs, mainly tuberculostatic and antiretrovirals. These patients are included in priority health policies of care, which favors the detection of DILI and the proper management of the patient, reducing the frequency of more severe outcomes. The diversity of methods and criteria for the definition of hepatotoxicity did not allow obtaining frequency estimates. The standardization of criteria for identification of drug-induced liver injury and greater effort in pharmacovigilance could contribute to the knowledge on the injury as well as on the safety profile of drugs marketed in Brazil. This research is expected to broaden the debate to establish a solid pharmacovigilance policy and the creation of a wide national DILI monitoring network and his integration with other DILI networks. Finally, bringing together experiences and cases bringing doctors, pharmacists, industry and patients closer together.

ARTICLE HIGHLIGHTS

Research background

Drug-induced liver injury (DILI) is the main cause of safety-related drug marketing withdrawals and could increase costs and morbidity in the health system. DILI identification is a challenge due to the diversity of drugs with hepatotoxic potential, the lack of symptoms specificity, and the absence of specific biomarkers in the clinical practice.

Research motivation

Identify and summarize Brazilian studies reporting the drug-induced liver injury.

Research objectives

The aim of this study was to know the profile of DILI in Brazil. A systematic review of Brazilian DILI studies was carried out until June 2020. It was found 32 studies, being 10 retrospective cohorts, 12 prospective cohorts, 5 cross-sectional, 3 case-control, one case series and one randomized clinical trial. Tuberculosis, human immunodeficiency virus and hepatitis C virus patients were the mainly group investigated the hepatotoxicity rate ranged from one to 57%, led by isoniazid, rifampicin, and pyrazinamide. Few studies reported algorithm to assess causality Drug interruption and moderate outcomes are report in the most of studies. Severe outcomes, such as chronic liver damage and liver transplantation were reported in some studies.

Research methods

It was found 32 studies, being 10 retrospective cohorts, 12 prospective cohorts, 5 cross-sectional, 3 case-control, one case series and one randomized clinical trial. In most studies were investigated tuberculosis patients followed by other infectious conditions like human immunodeficiency virus (HIV) and hepatitis C virus. The hepatotoxicity ranged from one to 57%, led by isoniazid, rifampicin, and pyrazinamide. Few studies reported algorithm to assess causality. In most studies, there were moderate outcomes and it was necessary drug interruption. However, few severe outcomes, such as chronic liver damage and liver transplantation were reported.

Research results

DILI could be caused both by non-prescription drugs and by those used for chronic diseases. The diagnosis and notification of the DILI cases are of great importance for the early detection and reduction of damages to the patients.

Research conclusions

Twenty-two different criteria for hepatotoxicity were found. Standardization of parameter of drug-induced liver injury and greater effort in pharmacovigilance could contribute to learn more about DILI's epidemiology in Brazil.

Research perspectives

This research is expected to broaden the debate to establish a solid pharmacovigilance policy and the creation of a wide national DILI monitoring network and his integration with other DILI networks. Finally, bringing together experiences and cases bringing doctors, pharmacists, industry and patients closer together.

REFERENCES

1 **Stevens JL**, Baker TK. The future of drug safety testing: expanding the view and narrowing the focus. *Drug Discov Today* 2009; **14**: 162-167 [PMID: 19100337 DOI: 10.1016/j.drudis.2008.11.009]

2 **Zhang J**, Doshi U, Suzuki A, Chang CW, Borlak J, Li AP, Tong W. Evaluation of multiple mechanism-based toxicity endpoints in primary cultured human hepatocytes for the identification of drugs with clinical hepatotoxicity: Results from 152 marketed drugs with known liver injury profiles. *Chem Biol Interact* 2016; **255**: 3-11 [PMID: 26581450 DOI: 10.1016/j.cbi.2015.11.008]

3 **Robles-Díaz M**, Medina-Caliz I, Stephens C, Andrade RJ, Lucena MI. Biomarkers in DILI: One More Step Forward. *Front Pharmacol* 2016; **7**: 267 [PMID: 27597831 DOI: 10.3389/fphar.2016.00267]

4 **Sgro C**, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, Lenoir C, Lemoine A, Hillon P. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology* 2002; **36**: 451-455 [PMID: 12143055 DOI: 10.1053/jhep.2002.34857]

5 **Björnsson ES**, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; **144**: 1419-1425, 1425. quiz e19-20 [PMID: 23419359 DOI: 10.1053/j.gastro.2013.02.006]

6 **Ortega-Alonso A**, Stephens C, Lucena MI, Andrade RJ. Case Characterization, Clinical Features and Risk Factors in Drug-Induced Liver Injury. *Int J Mol Sci* 2016; **17** [PMID: 27187363 DOI: 10.3390/ijms17050714]

7 **Danan G**, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update. *Int J Mol Sci* 2015; **17** [PMID: 26712744 DOI: 10.3390/ijms17010014]

8 **Andrade RJ**, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, González-Grande R, Pizarro A, Durán JA, Jiménez M, Rodrigo L, Romero-Gomez M, Navarro JM, Planas R, Costa J, Borras A, Soler A, Salmerón J, Martin-Vivaldi R; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005; **129**: 512-521 [PMID: 16083708 DOI: 10.1016/j.gastro.2005.05.006]

9 **Björnsson ES**. Hepatotoxicity by Drugs: The Most Common Implicated Agents. *Int J Mol Sci* 2016; **17**: 224 [PMID: 26861310 DOI: 10.3390/ijms17020224]

10 **Lucena MI**, Andrade RJ, Kaplowitz N, García-Cortes M, Fernández MC, Romero-Gomez M, Bruguera M, Hallal H, Robles-Diaz M, Rodriguez-González JF, Navarro JM, Salmeron J, Martinez-Odriozola P, Pérez-Alvarez R, Borraz Y, Hidalgo R; Spanish Group for the Study of Drug-Induced Liver Disease. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. *Hepatology* 2009; **49**: 2001-2009 [PMID: 19475693 DOI: 10.1002/hep.22895]

11 **Chalasani N**, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; **135**: 1924-1934, 1934.e1-1934. e4 [PMID: 18955056 DOI: 10.1053/j.gastro.2008.09.011]

12 **Björnsson E**. Review article: drug-induced liver injury in clinical practice. *Aliment Pharmacol Ther* 2010; **32**: 3-13 [PMID: 20374223 DOI: 10.1111/j.1365-2036.2010.04320.x]

13 **Chughlay MF**, Kramer N, Spearman CW, Werfalli M, Cohen K. N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review. *Br J Clin Pharmacol* 2016; **81**: 1021-1029 [PMID: 26757427 DOI: 10.1111/bcp.12880]

14 **Stine JG**, Lewis JH. Current and future directions in the treatment and prevention of drug-induced liver injury: a systematic review. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 517-536 [PMID: 26633044 DOI: 10.1586/17474124.2016.1127756]

15 **Koga K**, Kawashima S, Shibata N, Takada K. [Novel formulations of a liver protection drug glycyrrhizin]. *Yakugaku Zasshi* 2007; **127**: 1103-1114 [PMID: 17603270 DOI: 10.1248/yakushi.127.1103]

16 **Gu J**, Tang SJ, Tan SY, Wu Q, Zhang X, Liu CX, Gao XS, Yuan BD, Han LJ, Gao AP, Wu MY, Huang LH, Ma J, Xiao HP. An open-label, randomized and multi-center clinical trial to evaluate the efficacy of Silibinin in preventing drug-induced liver injury. *Int J Clin Exp Med* 2015; **8**: 4320-4327 [PMID: 26064348]

17 **Luangchosiri C**, Thakkinstian A, Chitphuk S, Stitchantrakul W, Petraksa S, Sobhonslidsuk A. A double-blinded randomized controlled trial of silymarin for the prevention of antituberculosis drug-induced liver injury. *BMC Complement Altern Med* 2015; **15**: 334 [PMID: 26400476 DOI: 10.1186/s12906-015-0861-7]

18 **Larsen FS**, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, Triantafyllou E, Bernal W, Auzinger G, Shawcross D, Eefsen M, Bjerring PN, Clemmesen JO, Hockerstedt K, Frederiksen HJ, Hansen BA, Antoniades CG, Wendon J. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. *J Hepatol* 2016; **64**: 69-78 [PMID: 26325537 DOI: 10.1016/j.jhep.2015.08.018]

19 **Tajiri K**, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. *World J Gastroenterol* 2008; **14**: 6774-6785 [PMID: 19058303 DOI: 10.3748/wjg.14.6774]

20 **Verma S**, Kaplowitz N. Diagnosis, management and prevention of drug-induced liver injury. *Gut* 2009; **58**: 1555-1564 [PMID: 19834119 DOI: 10.1136/gut.2008.163675]

21 **Lunardelli MJM**, Becker MW, Blatt CR. Hepatite medicamentosa: qual o papel do farmacêutico clí nico? *Rev Bras Farm Hosp Serv Saúde* 2016; **4**: 31-35

22 **Silva J**, Brito BS, Silva INN, Nóbrega VG, da Silva MCSM, Gomes HDN, Fortes FM, Pimentel AM, Mota J, Almeida N, Surlo VC, Lyra A, Rocha R, Santana GO. Frequency of Hepatobiliary Manifestations and Concomitant Liver Disease in Inflammatory Bowel Disease Patients. *Biomed Res Int* 2019; **2019**: 7604939 [PMID: 30834274 DOI: 10.1155/2019/7604939]

23 **Santos EA**, Gonçalves JCS, Fleury MK, Kritski AL, Oliveira MM, Velasque LS, E Silva JRL, Estrela RCE. Relationship of anti-tuberculosis drug-induced liver injury and genetic polymorphisms in CYP2E1 and GST. *Braz J Infect Dis* 2019; **23**: 381-387 [PMID: 31697922 DOI: 10.1016/j.bjid.2019.09.003]

24 **Heinrich MM**. Fatores associados às reações adversas no tratamento da tuberculose no município de Dourados/MS. MsC. In: Escola Nacional de Saúde Pública Sergio Arouca 2014 [cited 20 March 2021]. Available from: https://www.arca.fiocruz.br/handle/icict/22853

25 **Monteiro TP**, El-Jaick KB, Jeovanio-Silva AL, Brasil PE, Costa MJ, Rolla VC, de Castro L. The roles of GSTM1 and GSTT1 null genotypes and other predictors in anti-tuberculosis drug-induced

liver injury. *J Clin Pharm Ther* 2012; **37**: 712-718 [PMID: 22845549 DOI: 10.1111/j.1365-2710.2012.01368.x]

26 **Magalhães MP**. Série de casos de hepatotoxicidade induzida por medicamentos, insumos vegetais e suplementos alimentares em pacientes de hospital universitário em Salvador – Bahia (Brasil). In: Universidade Federal da Bahia 2015 [cited 20 March 2021]. Available from: http://repositorio.ufba.br/ri/handle/ri/18587

27 **Prado NMBL**, Messias GC, Santos Junior GO, Nunes VS, Schinonni MI, Paraná R. Prospective monitoring of drug use: drug-induced liver injury in a primary healthcare center. *Arq Gastroenterol* 2019; **56**: 390-393 [PMID: 31721973 DOI: 10.1590/S0004-2803.201900000-73]

28 **Björnsson ES**. Epidemiology and risk factors for idiosyncratic drug-induced liver injury. *Semin Liver Dis* 2014; **34**: 115-122 [PMID: 24879977 DOI: 10.1055/s-0034-1375953]

29 **Fisher K**, Vuppalanchi R, Saxena R. Drug-Induced Liver Injury. *Arch Pathol Lab Med* 2015; **139**: 876-887 [PMID: 26125428 DOI: 10.5858/arpa.2014-0214-RA]

30 **Leise MD**, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. *Mayo Clin Proc* 2014; **89**: 95-106 [PMID: 24388027 DOI: 10.1016/j.mayocp.2013.09.016]

31 **Au JS**, Navarro VJ, Rossi S. Review article: Drug-induced liver injury--its pathophysiology and evolving diagnostic tools. *Aliment Pharmacol Ther* 2011; **34**: 11-20 [PMID: 21539586 DOI: 10.1111/j.1365-2036.2011.04674.x]

32 **Pillans PI**. Clinical perspectives in drug safety and adverse drug reactions. *Expert Rev Clin Pharmacol* 2008; **1**: 695-705 [PMID: 24422739 DOI: 10.1586/17512433.1.5.695]

33 **Balbino EE**, Dias MF. Farmacovigilância: um passo em direção ao uso racional de plantas medicinais e fitoterápicos. *Rev Bras Farmacogn* 2010; **20**: 992-1000 [DOI: 10.1590/S0102-695X2010005000031]

34 **Becker MW**, Lourençone EMS, De Mello AF, Branco A, Filho EMR, Blatt CR, Mallmann CA, Schneider M, Caregnato RCA. Liver transplantation and the use of KAVA: Case report. *Phytomedicine* 2019; **56**: 21-26 [PMID: 30668342 DOI: 10.1016/j.phymed.2018.08.011]

35 **Lu RJ**, Zhang Y, Tang FL, Zheng ZW, Fan ZD, Zhu SM, Qian XF, Liu NN. Clinical characteristics of drug-induced liver injury and related risk factors. *Exp Ther Med* 2016; **12**: 2606-2616 [PMID: 27703513 DOI: 10.3892/etm.2016.3627]

36 **Lammert C**, Bjornsson E, Niklasson A, Chalasani N. Oral medications with significant hepatic metabolism at higher risk for hepatic adverse events. *Hepatology* 2010; **51**: 615-620 [PMID: 19839004 DOI: 10.1002/hep.23317]

37 **Shu CC**, Lee CH, Lee MC, Wang JY, Yu CJ, Lee LN. Hepatotoxicity due to first-line anti-tuberculosis drugs: a five-year experience in a Taiwan medical centre. *Int J Tuberc Lung Dis* 2013; **17**: 934-939 [PMID: 23743313 DOI: 10.5588/ijtld.12.0782]

38 **Yee D**, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med* 2003; **167**: 1472-1477 [PMID: 12569078 DOI: 10.1164/rccm.200206-626OC]

39 **Marra F**, Marra CA, Bruchet N, Richardson K, Moadebi S, Elwood RK, Fitzgerald JM. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. *Int J Tuberc Lung Dis* 2007; **11**: 868-875 [PMID: 17705952]

40 **Chung-Delgado K**, Revilla-Montag A, Guillen-Bravo S, Velez-Segovia E, Soria-Montoya A, Nuñez-Garbin A, Silva-Caso W, Bernabe-Ortiz A. Factors associated with anti-tuberculosis medication adverse effects: a case-control study in Lima, Peru. *PLoS One* 2011; **6**: e27610 [PMID: 22110689 DOI: 10.1371/journal.pone.0027610]

41 **Zaverucha-do-Valle C**, Monteiro SP, El-Jaick KB, Rosadas LA, Costa MJ, Quintana MS, de Castro L. The role of cigarette smoking and liver enzymes polymorphisms in anti-tuberculosis drug-induced hepatotoxicity in Brazilian patients. *Tuberculosis (Edinb)* 2014; **94**: 299-305 [PMID: 24793319 DOI: 10.1016/j.tube.2014.03.006]

42 **Chalasani N**, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, Watkins PB, Navarro V, Barnhart H, Gu J, Serrano J; United States Drug Induced Liver Injury Network. Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study. *Gastroenterology* 2015; **148**: 1340-52. e7 [PMID: 25754159 DOI: 10.1053/j.gastro.2015.03.006]

43 **Gusmão Filho FA**, Marques-Dias MJ, Marques HH, Ramos SR. [Central nervous system tuberculosis in children: 2. Treatment and outcome]. *Arq Neuropsiquiatr* 2001; **59**: 77-82 [PMID: 11299436 DOI: 10.1590/s0004-282x2001000100016]

44 **de Castro L**, do Brasil PE, Monteiro TP, Rolla VC. Can hepatitis B virus infection predict tuberculosis treatment liver toxicity? *Int J Tuberc Lung Dis* 2010; **14**: 332-340 [PMID: 20132625]

45 **Nader LA**, de Mattos AA, Picon PD, Bassanesi SL, De Mattos AZ, Pineiro Rodriguez M. Hepatotoxicity due to rifampicin, isoniazid and pyrazinamide in patients with tuberculosis: is anti-HCV a risk factor? *Ann Hepatol* 2010; **9**: 70-74 [PMID: 20308724]

46 **Schultz V**, Marroni CA, Amorim CS, Baethgen LF, Pasqualotto AC. Risk factors for hepatotoxicity in solid organ transplants recipients being treated for tuberculosis. *Transplant Proc* 2014; **46**: 3606-3610 [PMID: 25498098 DOI: 10.1016/j.transproceed.2014.09.148]

47 **Tovo CV**, Souza ARd, Santos DEd, Mattos AZd, Mattos AAd, Santos BR. Avaliação da hepatotoxicidade dos anti-retrovirais na co-infecção VHC/HIV. *Rev Amrigs* 2006; **50**: 217-221

48 **Gil AC**, Lorenzetti R, Mendes GB, Morcillo AM, Toro AA, Silva MT, Vilela MM. Hepatotoxicity in HIV-infected children and adolescents on antiretroviral therapy. *Sao Paulo Med J* 2007; **125**: 205-209 [PMID: 17992389 DOI: 10.1590/s1516-31802007000400002]

49 **Kondo W**, Astori Ade A, Gomes Sel-K, Fernandes Rde B, Sasaki Md, Sbalqueiro RL. [Evaluation of the adverse effects of nevirapine in HIV-infected pregnant women in a South Brazilian University Hospital]. *Rev Bras Ginecol Obstet* 2008; **30**: 19-24 [PMID: 19142538 DOI: 10.1590/s0100-72032008000100004]

50 **Pérez Gutthann S**, García Rodríguez LA. The increased risk of hospitalizations for acute liver injury in a population with exposure to multiple drugs. *Epidemiology* 1993; **4**: 496-501 [PMID: 8268277]

51 **de Abajo FJ**, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Br J Clin Pharmacol* 2004; **58**: 71-80 [PMID: 15206996 DOI: 10.1111/j.1365-2125.2004.02133.x]

52 **Teixeira RL**, Morato RG, Cabello PH, Muniz LM, Moreira Ada S, Kritski AL, Mello FC, Suffys PN, Miranda AB, Santos AR. Genetic polymorphisms of NAT2, CYP2E1 and GST enzymes and the occurrence of antituberculosis drug-induced hepatitis in Brazilian TB patients. *Mem Inst Oswaldo Cruz* 2011; **106**: 716-724 [PMID: 22012226 DOI: 10.1590/s0074-02762011000600011]

53 **Santos NP**, Callegari-Jacques SM, Ribeiro Dos Santos AK, Silva CA, Vallinoto AC, Fernandes DC, de Carvalho DC, Santos SE, Hutz MH. N-acetyl transferase 2 and cytochrome P450 2E1 genes and isoniazid-induced hepatotoxicity in Brazilian patients. *Int J Tuberc Lung Dis* 2013; **17**: 499-504 [PMID: 23394127 DOI: 10.5588/ijtld.12.0645]

54 **García Rodríguez LA**, Ruigómez A, Jick H. A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom. *Pharmacotherapy* 1997; **17**: 721-728 [PMID: 9250549]

55 **Antonello VS**, Kliemann DA, Rigel Santos B, Tovo CV. HAART and liver: is it safe? *J Infect Dev Ctries* 2014; **8**: 1444-1450 [PMID: 25390056 DOI: 10.3855/jidc.5012]

56 **Sulkowski MS**, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* 2000; **283**: 74-80 [PMID: 10632283 DOI: 10.1001/jama.283.1.74]

57 **Brasil**. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em Adultos. In: Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância, Prevenção e Controle das Infecções Sexualmente Transmissíveis, do HIV/Aids e das Hepatites Virais. Brasília 2018 [cited 20 March 2021]. Available from: http://www.aids.gov.br/pt-br/pub/2013/protocolo-clinico-e-diretrizes-terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-adultos

58 **Brasil**. Manual de recomendações para o controle da tuberculose no Brasil. In: Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis. – Brasília: Ministério da Saúde, 2019 [cited 20 March 2021]. Available from: http://www.aids.gov.br/pt-br/pub/2019/manual-de-recomendacoes-para-o-controle-da-tuberculose-no-brasil

59 **Alves JANR**, Fialho SCdMS, Morato EF. Toxicidade hepática é rara em pacientes com artrite reumatoide usando terapia combinada de leflunomida e metotrexato. *Rev Bras Reumatol* 2011; **51**: 141-4 [DOI: 10.1590/S0482-50042011000200004]

60 **Santiago García D**, Saturansky E, Poncino D, Ortiz V, Martínez Artola Y, Rosenberg S, Abritta G, Palermo C, Enriquez N, Cravero A. [Liver diseases in rheumatoid and psoriatic arthritis]. *Acta Gastroenterol Latinoam* 2012; **42**: 112-119 [PMID: 22876713]

61 **Werner MC**, Romaldini JH, Bromberg N, Werner RS, Farah CS. Adverse effects related to thionamide drugs and their dose regimen. *Am J Med Sci* 1989; **297**: 216-219 [PMID: 2523194 DOI: 10.1097/00000441-198904000-00003]

62 Propylthiouracil 2012 [PMID: 31643306]

63 **Santos FAI**. Prevalência da Hepatotoxicidade por Quimioterapia Pré-operatória e Correlação com a Morbidade das Hepatectomias no Câncer Colorretal Metastático. Universidade Federal de Ciências da Saúde de Porto Alegre 2013 [cited 20 March 2021]. Available from: https://docplayer.com.br/6699757-Prevalencia-da-hepatotoxicidade-por-quimioterapia-pre-operatoria-e-correlacao-com-a-morbidade-das-hepatectomias-no-cancer-colorretal-metastatico.html

64 **Brito TC**, Possuelo LG, Valim ARM, Todendi PF, Ribeiro AW, Gregianini TS, Jarczewski CA, Hutz MH, Rossetti MLR, Zaha A. Polymorphisms in CYP2E1, GSTM1 and GSTT1 and anti-tuberculosis drug-induced hepatotoxicity. *An Acad Bras Cienc* 2014; **86**: 855-865 [PMID: 30514013]

65 **Lima Mde F**, Melo HR. Hepatotoxicity induced by antituberculosis drugs among patients coinfected with HIV and tuberculosis. *Cad Saude Publica* 2012; **28**: 698-708 [PMID: 22488315 DOI: 10.1590/s0102-311x2012000400009]

66 **Picon PD**, Della Giustina MdL, Rizzon CFC, Bassanesi Sl, Zanardo AP, Michalczuk MTea. Resultado do tratamento da tuberculose com estreptomicina, isoniazida e etambutol (esquema SHM). *J Pneumologia* 2002; **28**: 187-92 [DOI: 10.1590/S0102-35862002000400003]

67 **Szklo A**, Mello FC, Guerra RL, Dorman SE, Muzy-de-Souza GR, Conde MB. Alternative anti-tuberculosis regimen including ofloxacin for the treatment of patients with hepatic injury. *Int J Tuberc Lung Dis* 2007; **11**: 775-780 [PMID: 17609053]

68 **Fernandes DC**, Santos NP, Moraes MR, Braga AC, Silva CA, Ribeiro-dos-Santos A, Santos S. Association of the CYP2B6 gene with anti-tuberculosis drug-induced hepatotoxicity in a Brazilian Amazon population. *Int J Infect Dis* 2015; **33**: 28-31 [PMID: 25271170 DOI: 10.1016/j.ijid.2014.04.011]

69 **Naranjo CA**, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245 [PMID: 7249508 DOI: 10.1038/clpt.1981.154]

70 **Maria VA**, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997; **26**: 664-669 [PMID: 9303497 DOI: 10.1002/hep.510260319]

71 **Hanatani T**, Sai K, Tohkin M, Segawa K, Kimura M, Hori K, Kawakami J, Saito Y. A detection algorithm for drug-induced liver injury in medical information databases using the Japanese diagnostic scale and its comparison with the Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method scale. *Pharmacoepidemiol Drug Saf* 2014; **23**: 984-988 [PMID: 24596340 DOI: 10.1002/pds.3603]

72 **Castelo Filho A**, Kritski AL, Barreto ÂW, Lemos ACM, Netto AR, Guimarães CA. II Consenso Brasileiro de Tuberculose: Diretrizes Brasileiras para Tuberculose 2004. *J Bras Pneumol* 2004; **30**: S57-S86

73 **Coca NS**, Oliveira MS, Voieta I, Antunes CM, Lambertucci JR. Antituberculosis drug-induced hepatotoxicity: a comparison between patients with and without human immunodeficiency virus seropositivity. *Rev Soc Bras Med Trop* 2010; **43**: 624-628 [PMID: 21181011 DOI: 10.1590/s0037-86822010000600004]

74 **Carvalho AT**, Esberard BC, Fróes RS, Rapozo DC, Grinman AB, Simão TA, Santos JC, Carneiro AJ, Ribeiro-Pinto LF, de Souza HS. Thiopurine-methyltransferase variants in inflammatory bowel disease: prevalence and toxicity in Brazilian patients. *World J Gastroenterol* 2014; **20**: 3327-3334 [PMID: 24696613 DOI: 10.3748/wjg.v20.i12.3327]

75 **de-Medeiros BC**, Strapasson E, Pasquini R, de-Medeiros CR. Effect of all-trans retinoic acid on newly diagnosed acute promyelocytic leukemia patients: results of a Brazilian center. *Braz J Med Biol Res* 1998; **31**: 1537-1543 [PMID: 9951549 DOI: 10.1590/s0100-879x1998001200005]

76 **Uehara RP**, Sá VH, Koshimura ET, Prudente FV, Tucunduva LT, Gonçalves MS, Samano ES, del Giglio A. Continuous infusion of amphotericin B: preliminary experience at Faculdade de Medicina da Fundação ABC. *Sao Paulo Med J* 2005; **123**: 219-222 [PMID: 16358096 DOI: 10.1590/s1516-31802005000500004]

77 **Tomich LG**, Núñez M, Mendes-Correa MC. Drug-induced liver injury in hospitalized HIV patients: high incidence and association with drugs for tuberculosis. *Ann Hepatol* 2015; **14**: 888-894 [PMID: 26436361 DOI: 10.5604/16652681.1171778]

78 **Vieira DEO**, Gomes M. Efeitos adversos no tratamento da tuberculose: experiência em serviço ambulatorial de um hospital-escola na cidade de São Paulo. *J Bras Pneumol* 2008; **34**: 1049-55 [DOI: 10.1590/S1806-37132008001200010]

79 **de Souza AF**, de Oliveira e Silva A, Baldi J, de Souza TN, Rizzo PM. [Hepatic functional changes induced by the combined use of isoniazid, pyrazinamide and rifampicin in the treatment of pulmonary tuberculosis]. *Arq Gastroenterol* 1996; **33**: 194-200 [PMID: 9302332]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com