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Article in *Frontiers in Medicine* · January 2022

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Specialty section:

This article was submitted to
Major Tropical Diseases,
a section of the journal
Frontiers in Tropical Diseases

Received: 27 July 2021

Accepted: 15 December 2021

Published: 19 January 2022

Citation:

Sant'Anna FM, Araújo-Pereira M,
Schmaltz CAS, Arriaga MB,
de Oliveira RVC, Andrade BB and
Rolla VC (2022) Adverse Drug
Reactions Related to Treatment of
Drug-Susceptible Tuberculosis in
Brazil: A Prospective Cohort Study.
Front. Trop. Dis. 2:748310.
doi: 10.3389/fitd.2021.748310

Adverse Drug Reactions Related to Treatment of Drug-Susceptible Tuberculosis in Brazil: A Prospective Cohort Study

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Standard anti-tuberculosis treatment is highly effective, but a great challenge is the management of adverse drug reactions (ADR). Our study aimed to characterize ADR according to type, severity and time of occurrence. A prospective tuberculosis (TB) cohort has been followed, from 2010 to 2016, at a reference center in Rio de Janeiro, Brazil. Clinical and laboratory tests information were collected in all visits. ADR were described according to the affected organ/system, classified as clinical and/or laboratory, early (first 2 months) or late. ADR's causality and intensity were assessed. In our study 552 patients were included, 78.8% presented at least one ADR, 34% were people living with HIV (PLHIV). Most ADR were clinical (53%), early (82.5%), mild/moderate (88.7%) events and of "metabolic annutritional disorders" category. There were no significant differences in type, severity or causality between "early" and "late" groups. However, "early" group presented a higher frequency of "metabolic and nutritional disorders" (27.8%) and "gastrointestinal system disorders" (23.5%), while "skin and appendages disorders" were more frequent in the "late" group. ADR are frequent and occur at any time during treatment, although the majority are early and grade and not severe.

Keywords: tuberculosis, adverse drug reaction, drug induced toxicity, anti-tuberculosis treatment, WHO-ART

INTRODUCTION

The World Health Organization (WHO) estimates that by 2019, 10 million people worldwide were infected with *Mycobacterium tuberculosis* and 1.4 million people died of tuberculosis (TB) (1). Early diagnosis and timely treatment of TB are essential for effective TB control (2). Standard anti-TB treatment (ATT) is highly effective and one of the great challenges for ATT success is management of TB drugs toxicity. This toxicity is manifested through adverse drug reactions (ADR) (3). ADR occurrence can lead to treatment interruption, decrease cure rates and an increase in multidrug resistance (MDR-TB). ADR can range from mild to severe (4), can occur early or late in the course of ATT and are associated with unfavorable TB outcomes; if not detected quickly may be associated with high morbidity (5). These events can result in treatment interruption, replacement of the associated drug and sometimes prolonged treatment length, hospitalization, low adherence and increased risk of resistance (6).

One of the strategies to approach this problem is to closely monitor patients undergoing treatment, so that an adverse reaction can be promptly detected, and appropriate therapeutic measures are provided by the health care team. Our study aimed to characterize adverse events according to type, severity, causality, and time of occurrence in a population prospectively followed at a reference center for tuberculosis in Rio de Janeiro, a region with high burden of TB in Brazil.

METHODS

Ethics Statement

The study was approved by the Institutional Review Board of the National Institute of Infectious Diseases Evandro Chagas (INI) (CAAE: 86215118.5.0000.5262). Written informed consent was obtained from all participants and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Study Design

A prospective cohort of TB patients has been followed at the Clinical Research Laboratory on *Mycobacteria* (LAPCLIN-TB) of the National Institute of Infectious diseases Evandro Chagas (INI), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil, since the year 2000. The present study is a prospective assessment performed from January 2010 to December 2016 of the ongoing cohort. Patients ≥ 18 years old, with pulmonary, extrapulmonary or disseminated TB were included. The exclusion criteria were death or treatment default within the first 15 days of ATT (early death or early default), not to compromise ADR detection, other diagnosis than TB after starting treatment and rifampicin and isoniazid resistance.

TB Diagnosis and Follow-Up Visits

TB diagnosis was clinical (symptoms and signs) and confirmed by laboratory exams (acid fast smears and/or culture and/or

histopathological findings) or clinical-radiological for those who started treatment and had a positive therapeutic response to TB drugs. Visits were done at baseline (TB diagnosis and treatment initiation), 15, 30, 60, 90, 120 and 180 days after ATT initiation. All visits were followed by physicians who are part of the same research group and were trained to follow the study procedures. Data were entered into an electronic medical record based on standardized information collected with a defined template in all visits.

During the baseline visit, information collected included demographic variables such as age, gender, race (self-reported), marital status, years of education, social behavior (alcohol, tobacco, illicit drugs use), clinical information such as clinical form of TB (pulmonary, extrapulmonary or disseminated), presence of comorbidities, and concomitant medications use. At baseline visits laboratory tests were requested: blood cell count, urea, creatinine, uric acid, Alanine (ALT) and Aspartate (AST) transferases, albumin, alkaline phosphatase, gamma glutamyl transferase (GGT), chest X-ray, hepatitis B, C and HIV serology. At subsequent visits, ADR were monitored with clinical information and laboratory evaluation [complete blood cell count and biochemical tests (urea, creatinine, total and direct bilirubin, albumin, alkaline phosphatase, ALT, AST, GGT and uric acid)].

Study Definitions

Anti-TB Treatment

Anti-TB treatment (ATT) followed the recommendations of the Tuberculosis Program of the Brazilian Ministry of Health (7). The first line ATT was the combination of rifampicin 600 mg, isoniazid 300 mg, pyrazinamide 1600 mg and ethambutol 1100 mg in fixed-dose combination, once a day, for two months, followed by four months of rifampicin 600 mg and isoniazid 300 mg once a day for patients weighing 50 Kg or more, except for central nervous system and bone TB. Doses were adjusted for patients with lower weight. In Brazil, the cutoffs used for doses are: 20 to 35 Kg (2 pills); 36 to 50 Kg (3 pills); above 50kg (4 pills). Some patients with disseminated TB and hepatic impairment initiated a regimen less likely to cause hepatitis (aminoglycosides, quinolones, and ethambutol) and first line therapy was gradually introduced according to their tolerance, based on attending physician's decision.

HIV Treatment

Antiretroviral therapy (ART) was prescribed for patients living with HIV (PLHIV), by each assistant physician, according to guidelines recommended by the Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis of the Brazilian Ministry of Health (8). The recommended ATT included a rifamycin, which was chosen according to ART used by the patient. Rifabutin 150mg/day was used when protease inhibitors were prescribed as part of ART (9). ART was introduced for naïve patients as soon as possible, which happened around the first month of ATT in the majority. For patients already on ART, those without resistance were treated with the same regimen without interruption, those who needed a

new regimen, the new one replaced the former treatment immediately. We always tried to keep rifamycins among the ATT.

Adverse Drug Reactions Related to ATT

Adverse drug reactions (ADR) were defined as “an unintended and harmful reaction to a medication, and which occurs at doses normally used in humans” (10). In this study ADR were described according to the affected organ or system, following the Adverse Reaction Terminology (10) and described in **Supplementary Methods**. The causality of ADR was assessed using the Naranjo Scale, as improbable, possible, probable, and definitely related (11).

We separated ADR in three groups: clinical, based on symptoms with no laboratory alteration, laboratory reactions based on laboratory alterations with no symptoms and clinical/laboratory based on both. The ADR's severity was classified according to the Division of AIDS table for grading the Severity of Adult and Pediatric Adverse Events (12): *Grade 1: mild event, Grade 2: moderate event, Grade 3: severe event, Grade 4: potentially life-threatening event, Grade 5: death*, details in **Supplementary Table 1**. According to the time of onset we classified ADR in early, if detected in the first two months of anti-TB treatment and late if it had started after two months of TB treatment initiation.

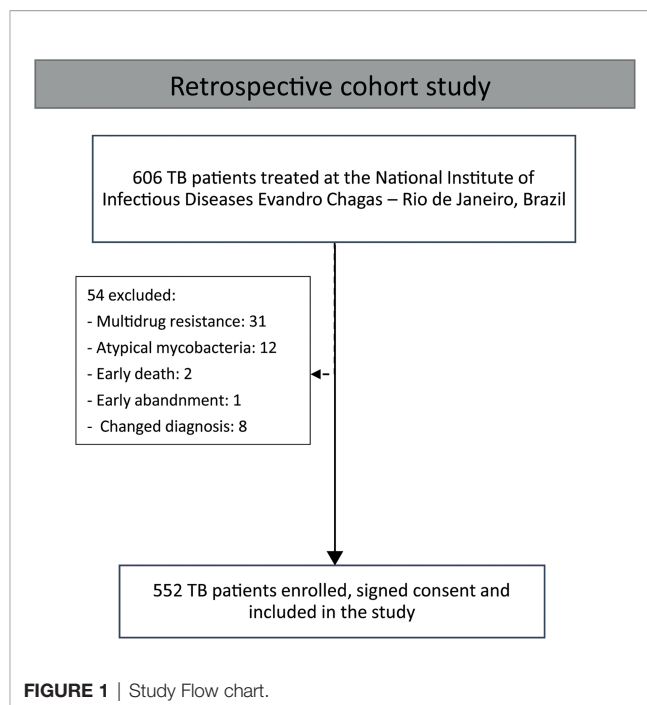
Data Analysis

Descriptive statistics was performed using the median values with interquartile ranges (IQR) as measures of central tendency and dispersion for continuous variables. Categorical variables were described using frequency (no.) and proportions (%). The Mann–Whitney *U* test (for two unmatched groups) was used to compare continuous variables and the Pearson chi-square test was used to compare categorical variables between study groups (with and without adverse reactions, as well as early and late onset). Kendall's τ was used to verify whether there was an association between adverse reaction occurrence and time in months after starting treatment.

All analyses were pre-specified. Differences with *p*-values below 0.05 after adjustment for multiple comparisons (Holm-Bonferroni) were considered statistically significant. The statistical analyses and data visualization were performed using *rstatix* (version 0.4.0), *stats* (version 3.6.2), and *ggplot2* (version 3.3.2) R packages.

RESULTS

From 2010 to 2016, 606 patients were enrolled for the study. Of these, fifty-four patients with exclusion criteria were ruled out (**Figure 1**). Thus, after selecting eligible patients, 552 were included, out of whom 435 (78.8%) presented at least one TB-related ADR, while 117 (21.2%) did not present any ADR during the entire treatment. The majority of study participants were male (59.4%), with a median age of 38.5 (IQR:29-49; *p*=0.063) years (**Table 1**). One hundred and six participants were less than



50kg at the start of ATT [20-35kg: 5 (71.4%); 36-50Kg: 101 (77.7%); >50kg 306 (79.8%) (*p*=0.699)]. Participants of the lower weight category did not present more ADR than those with higher weight. Patients that presented ADR were similar to participants that did not present with regard to sex, baseline weight, scholarship, social habits (smoking, alcohol and drug use), clinical form of TB and presence of comorbidities (**Table 1**). Clinical data showed that patients who experienced ADR were more self-declared white (54%, *p* = 0.023) and married (53%, *p*=0.036) (**Table 1**).

In our cohort, 191 (34.6%) patients were PLHIV, of which 139 (72.8%) developed ADR. Within each group (with and without ADR), the group without ADR had a higher frequency of PLHIV (*p*=0.034) (**Table 1**). In this subgroup, the vast majority (*n*=181, 94%) of PLHIV used ART during TB treatment (**Supplementary Figure 1A**) and 38.1% (*n*=69) of them were ART naïve at baseline (**Supplementary Figure 1B** and **Table 1**). PLHIV ART-naïve initiated ART after 15 days of TB treatment in most cases. Median time from TB treatment and ART initiation was 27 days (Interquartile Range: 14-32.25).

Adverse Drug Reactions According to the Time of Onset

In addition to the number of events, ADR were compared according to the time of onset during ATT. For this analysis, four patients were excluded due to the fact that the ADR they developed were not related with anti-TB drugs. All ADR not related to anti-TB drugs were excluded from the following analysis. Among the 431 patients who developed ADR events, 271 (62.9%) reported the occurrence of only one event, 115

TABLE 1 | Baseline clinical and sociodemographic characteristics of study population.

Characteristics	All (n=552)	Without adverse drug reaction (n=117)	With adverse drug reaction (n=435)	p-value
Age (years), median (IQR):	38.5 (29.0-49.0)	37.0 (28.0-46.0)	39.0 (29.5-50.0)	0.063
Gender, n (%):				0.996
Female	224 (40.6)	48 (41.0)	176 (40.5)	
Male	328 (59.4)	69 (59.0)	259 (59.5)	
Race, n (%):				0.023
White	283 (51.3)	48 (41.0)	235 (54.0)	
Black	165 (29.9)	46 (39.3)	119 (27.4)	
Pardo	104 (18.8)	23 (19.7)	81 (18.6)	
Initial weight (kg), median (IQR):	58.0 (50.6-67.6)	57.0 (50.3-66.8)	58.7 (50.7-68.0)	0.525
Married, n (%):	281 (50.9)	49 (41.9)	232 (53.3)	0.036
Scholarship, n (%):				0.056
Illiterate	22 (3.99)	2 (1.71)	20 (4.60)	
Elementary school	449 (81.3)	104 (88.9)	345 (79.3)	
Higher education	81 (14.7)	11 (9.40)	70 (16.1)	
Smoking habits, n (%):	191 (34.6)	44 (37.6)	147 (33.8)	0.564
Alcohol consumption, n (%):	210 (38.0)	49 (41.9)	161 (37.0)	0.520
Use of illicit drugs, n (%):	121 (21.9)	29 (24.8)	92 (21.1)	0.659
Type of TB, n (%):				0.369
Pulmonary	291 (52.7)	66 (56.4)	225 (51.7)	
Extrapulmonary	171 (31.0)	30 (25.6)	141 (32.4)	
Disseminated	90 (16.3)	21 (17.9)	69 (15.9)	
Changed treatment, n (%):	65 (11.8)	10 (8.55)	55 (12.6)	0.293
Reason for change treatment, n (%)				0.728
Adverse reaction	25 (40.3)	0 (0.00)	25 (43.9)	
Isoniazid resistance	8 (12.9)	2 (40.0)	6 (10.5)	
Rifampicin resistance	2 (3.23)	0 (0.00)	2 (3.5)	
Due to the use of ART	22 (35.5)	2 (40.0)	20 (35.1)	
Changed to RIPE ¹	5 (8.06)	1 (20.0)	4 (7.00)	
HIV+, n (%):	191 (34.6)	52 (44.4)	139 (32.0)	0.034
ART naive, n (%):	69(39.2)	7 (13.5)	62 (44.6)	<0.001
ART use, n (%):	181(94.8)	49 (94.2)	132 (95)	1
Diabetes Mellitus, n (%):	50 (9.06)	11 (9.40)	39 (8.97)	0.884
Hypertension, n (%):	80 (14.5)	11 (9.40)	69 (15.9)	0.106
COPD, n (%):	10 (1.81)	2 (1.71)	8 (1.84)	0.927
Hepatitis B or C, n (%):	28 (5.07)	5 (4.27)	23 (5.29)	0.837
Other comorbidities, n (%):	109 (19.7)	25 (21.4)	84 (19.3)	0.715
Concomitant medication², n (%):	422 (76.7)	81 (69.8)	341 (78.6)	0.063

Data are shown as median and interquartile (IQR) range or number and frequency (percentage). Data were compared between the clinical groups using the Mann-Whitney U test (continuous variables) or the Pearson's χ^2 tests (for data on frequency). Bold in p-value indicates $p < 0.05$.

¹Started with a different scheme due to hepatitis, and then went to RIPE.

²Excluding ART.

COPD, Chronic obstructive pulmonary disease; ART, Antiretroviral Therapy; HIV, Human immunodeficiency virus; Kg, kilograms; IQR, Interquartile Range; RIPE, rifampicin, Isoniazid, Pyrazinamide, Ethambutol; TB, tuberculosis.

(26.7%) reported the occurrence of two events and 45 (10.4%) reported 3 or more events (**Figure 2A**). Nearly 61.4% of ADR was possibly related to ATT, whereas 28.1% was probably related and a smaller fraction (10.5%) was diagnosed as certainly related to TB therapy (**Figure 2B**). Altogether, 759 ADR events were reported. According to the time of onset, 625 (82.5%) ADR events were observed in the first two months of anti-TB treatment (referred hereafter as "early ADR") and 134 (17.5%) were reported after two months of TB treatment initiation (referred hereafter as "late ADR") (**Figure 2C**). The number of ADR events detected decreased considerably over time (Kendall's τ p value < 0.001). During the study, 25 participants (40.3%) interrupted the ATT due to ADR (12 PLHIV and 14 HIV-seronegative patients). Among those patients, all had to replace at least one drug of the ATT and therefore ATT was changed. No deaths were associated with ADR.

For PLHIV (especially those previously treated with ART), 35% had to change ATT to include rifabutin and allow Protease Inhibitors to be used as part of the ART. While examining ADR according to the time of onset, we found that there were no significant differences in type of event, severity, or relation with TB drugs between early *versus* late ADR. Although, in general, both groups exhibited a high prevalence of severity between mild (grade 1) to moderate (grade 2), it is important to highlight that 10% of ADRs were severe (grade 3) and 1.3% were potentially lethal (grade 4). Of note, ADR median duration was 79 days (IQR: 4-146) (**Table 2**). By analyzing ADR in more detail, we observed that dyspepsia syndrome, arthralgia, peripheral neuropathy, and dermatological syndrome occurred more frequently during the early phase whereas cholestatic syndrome, vestibular syndrome and hepatitis were detected mainly in the first month of treatment (**Figure 3A**). Adverse

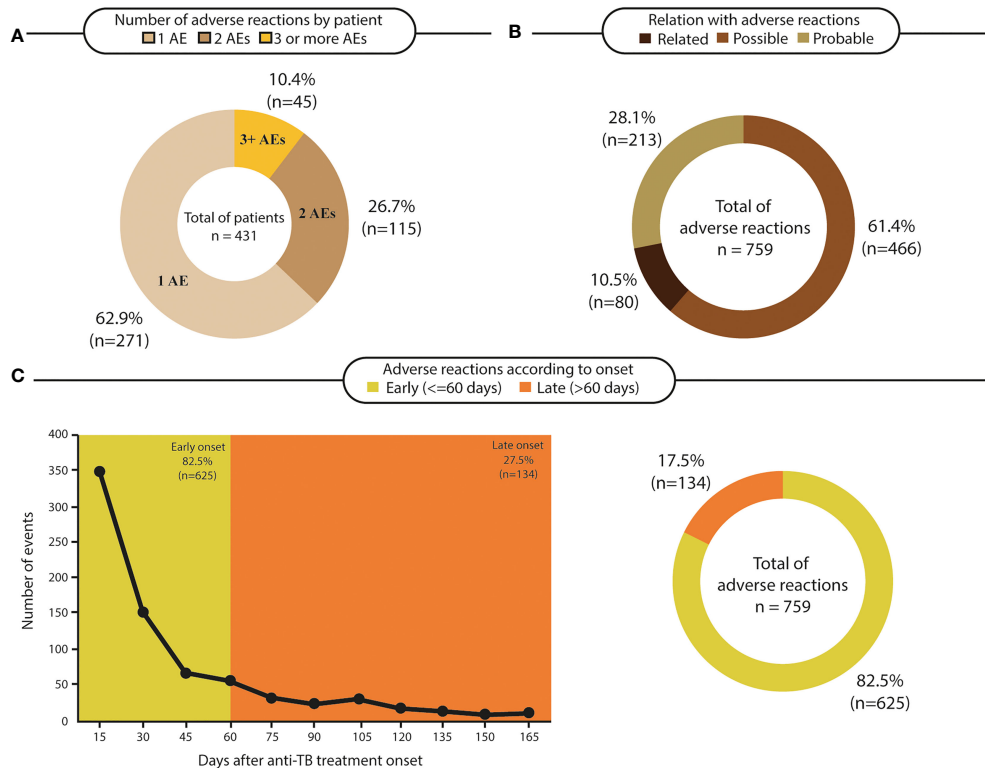


FIGURE 2 | Adverse reactions characteristics. **(A)** Number of adverse reactions by patient. **(B)** Relation of anti-TB treatment with adverse drug reactions. **(C)** Adverse drug reactions onset (days) after anti-TB treatment.

reactions are described in **Supplementary Table 2**. Overall, the most prevalent type of event was clinical ($n=402$; 53%), followed by laboratory ($n=259$; 34.1%) and both types clinical+laboratory ($n=98$; 12.9%) (**Figure 3B**). All types of adverse reaction had mainly an early onset (**Figure 3C**).

After grouping the ADR events according to the WHO-ART classification, it was possible to observe that the most frequent categories were “metabolic and nutritional disorders”, “gastro-intestinal system disorders” and “skin and appendages disorders”, all initiating throughout the early phase (**Figure 4A**). On the other hand, comparing ADR based on WHO-ART classification, significant differences were detected between groups as follows. The “early onset” ADR group presented a higher frequency of “metabolic and nutritional disorders” ($n=174$; 27.8%) and “gastrointestinal system disorders” ($n=147$; 23.5%), while “skin and appendages disorders” were more frequent in the “late onset” ADR group ($n=31$, 23.1%; $p<0.001$) (**Table 2**). Those that set the category “others” are described in **Supplementary Table 3**.

Using the WHO-ART classification, ADR were also analyzed for the severity of the reaction. All classifications had occurrences registered in a mild (grade 1) or moderate (grade 2), however some of them presented occurrences of severe (grade 3) or potentially lethal (grade 4) (**Figure 4B** and **Supplementary Table 4**). “White cell and Reticuloendothelial system (RES) and platelet disorders” and “Liver and biliary system disorders” stand

out in this analysis, respectively, with 29.2% and 28.2% of severe (grade 3); as well 3.1% and 5.1% of potentially lethal (grade 4). When comparing the severity of ADR in patients according to HIV co-infection, it was found that PLHIV experienced ADR with a more intense severity compared to patients without HIV co-infection ($p<0.001$, **Supplementary Figure 1C**).

DISCUSSION

Our data showed a high frequency of ADR during TB treatment, with 78.8% of patients having experienced at least one ADR. Other studies performed in Brazil have reported a wide range in incidence of ADR, between 23.6% (13) and 83.4% (14). In another study with 1011 participants, conducted in India, the authors found around 35% of ADR, but included different regimens in the analyses and laboratory tests were done just for patients who developed suggestive clinical signs and symptoms (15). In our analyses, we accounted for clinical and laboratory data (even for patients without symptoms), which may have contributed to the increased ADR detection. Thirty five percent of our cohort were PLHIV, and, in this group, the frequency of ADR was lower than in HIV-uninfected patients. However, PLHIV experienced more severe ADRs than the HIV-uninfected.

TABLE 2 | Adverse drug reaction characteristics according to onset.

Characteristics	ALL n=759	Early onset n=625	Late onset n=134	p-value
Relation with ATT, n (%):				0.683
Related	79 (10.4)	64 (10.2)	15 (11.5)	
Probable	199 (26.2)	165 (26.4)	34 (25.5)	
Possible	481 (63.4)	396 (63.4)	85 (63)	
Onset, n (%):				NA
month 1 ¹	508 (66.9)	508 (81.3)	0 (0.00)	
month 2	117 (15.4)	117 (18.7)	0 (0.00)	
month 3	55 (7.25)	0 (0.00)	55 (41.0)	
month 4	47 (6.19)	0 (0.00)	47 (35.1)	
month 5	22 (2.90)	0 (0.00)	22 (16.4)	
month 6	10 (1.32)	0 (0.00)	10 (7.46)	
Adverse reactions duration (days), median (IQR):	79 (4-146)	79 (40-148)	78 (42-123)	0.501
Type of event, n (%):				0.860
Laboratory	259 (34.1)	216 (34.6)	43 (32.1)	
Clinical	402 (53.0)	329 (52.6)	73 (54.5)	
Clinical + Laboratory	98 (12.9)	80 (12.8)	18 (13.4)	
Severity, n (%):				0.102
Grade 1	288 (38.0)	229 (36.6)	59 (44.4)	
Grade 2	384 (50.7)	318 (50.9)	66 (49.6)	
Grade 3	76 (10.0)	68 (10.9)	8 (6.02)	
Grade 4	10 (1.32)	10 (1.60)	0 (0.00)	
WHO-ART, n (%):				<0.001
Metabolic and nutritional disorders	195 (25.7)	174 (27.8)	21 (15.7)	
Gastro-intestinal system disorder	159 (20.9)	147 (23.5)	12 (8.96)	
Skin and appendages disorders	139 (18.3)	108 (17.3)	31 (23.1)	
Musculo-skeletal disorders	73 (9.62)	55 (8.80)	18 (13.4)	
Liver and biliary system disorders	65 (8.56)	53 (8.48)	12 (8.96)	
Central and peripheral nervous s. disorders	50 (6.59)	35 (5.60)	15 (11.2)	
White cell and RES and platelet disorders	40 (5.27)	24 (3.84)	16 (11.9)	
Other	38 (5.01)	29 (4.64)	9 (6.72)	

Data are shown as median and interquartile (IQR) range or number and frequency (percentage).

¹In the first day, 57 patients had presented some adverse drug reaction. Data were compared between the clinical groups using the Mann-Whitney U test (continuous variables) or the Pearson's χ^2 tests (for data on frequency). Bold in p value indicates $p < 0.05$. NA indicates not applicable.

ATT, anti-TB treatment; IQR, Interquartile Range.

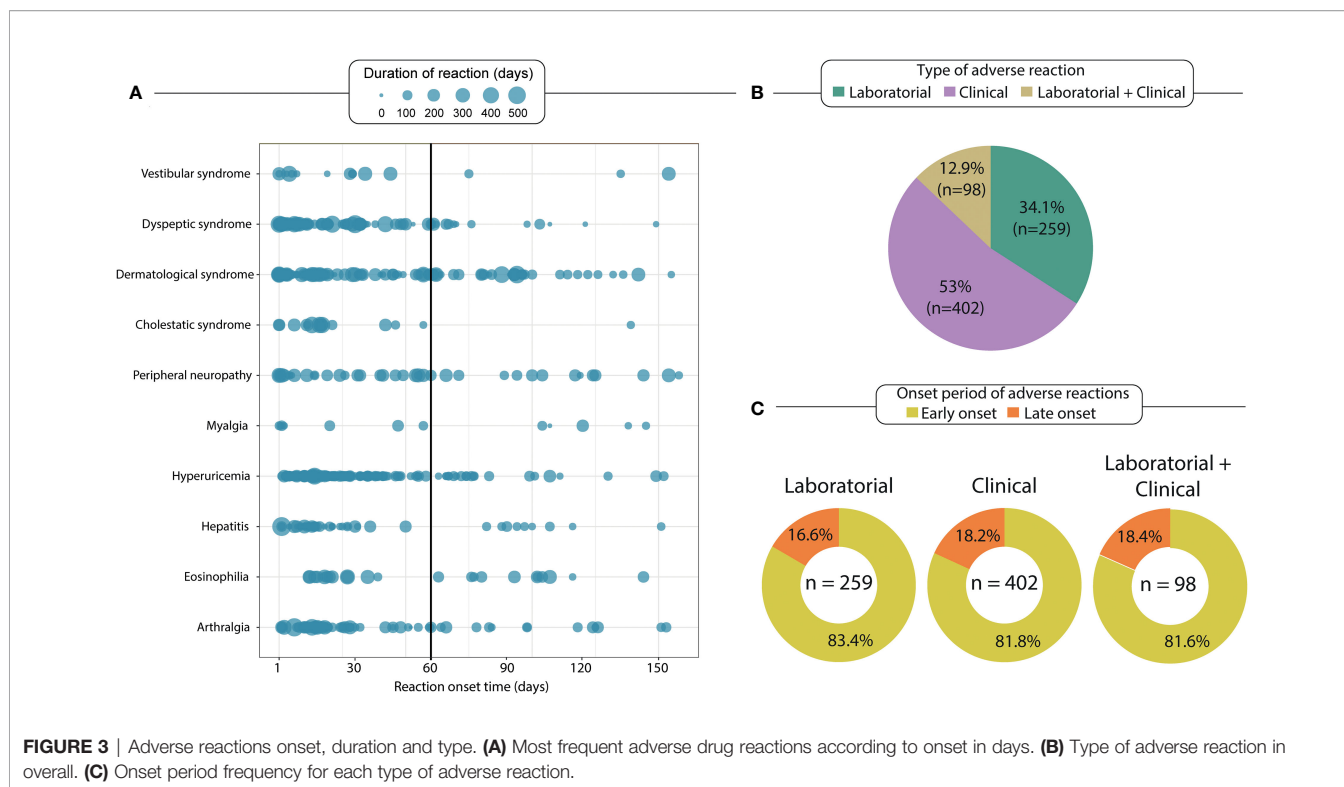
Our study shows that ADR were more prevalent in early stages of TB treatment, and after the second month the incidence significantly decreased. The frequency of late ADR was 17%, showing a decline, although still high. This finding is probably due to the intensive phase of TB treatment with 4 drugs including pyrazinamide and ethambutol that are not part of the continuation phase and therefore more drugs are used in the first part of therapy (16). ADRs were not associated with the dose of TB drugs and were not more frequent among patients with lower weight (below 50 kg).

When we look at clinical ADRs the most prevalent system affected was the digestive system, followed by skin. Gastrointestinal symptoms happened earlier than skin manifestations during ATT. Gastrointestinal disorders included nausea, vomiting, and sometimes were associated with liver and biliary system disorders. Gastrointestinal reactions are probably associated with a rifampicin serum peak and, later, when the rifampicin blood concentration decreases due to its auto metabolism (17) the symptoms generally disappear.

In our study "liver and biliary disorders" were identified in 65 (8.56%) patients, 53 of them in the early phase and 12 in the late phase. Other authors have also observed cases of hepatitis during TB treatment, however late hepatitis cases have not been actively screened in these studies (18, 19). No relationship with hepatitis

B or C in these "late" cases were observed in our study. Laboratory tests in these studies were done only during the first two months of therapy due to the high frequency of ADR in this early period (18, 19). In our study 25% of early hepatitis cases were grade 3. Patients on concurrent ART and ATT have high incidence of liver injury (20), therefore close monitoring of liver function in PLHIV is particularly important. In some cases, interruption of all drugs is necessary to overcome the ADR, especially when hepatobiliary toxicity is present and becomes severe. Drug to drug reintroduction is not infrequently necessary and, in some cases, hospitalization is needed (21). Some ADR occurred later, such as the case of isoniazid-induced gynecomastia and galactorrhea, which have been reported by a few cases. Although rare, these ADRs sometimes last a long time and cause a lot of inconvenience (22, 23) and thus should be monitored to avoid treatment dropout.

Skin symptoms are not rare and in most cases are associated with pyrazinamide or even with isoniazid, rifampicin, and ART in PLHIV (21). In our study, skin rash and pruritus were the most common early cutaneous ADR whereas acneiform lesions were observed later, after the intensive phase. One study conducted in Korea evaluated cutaneous ADR during TB treatment and skin rash was the most common presentation, followed by pruritus, and skin symptoms were accompanied by eosinophilia indicating a



hypersensitivity reaction (24). Skin rash can be mild, moderate and, more rarely, have a severe presentation, such as the Steven Johnson syndrome, presented just by one patient in our study. In this case, all drugs should be interrupted, and the suspected drug should not be reintroduced (21, 25).

Central and peripheral nervous system disorders are frequent in both treatment phases, mainly peripheral neuropathy, and were associated with isoniazid in our study. In Brazil, when isoniazid is prescribed, pyridoxine is also offered to prevent ADR. Isoniazid can cause toxicity in several ways: can lead to decreased synthesis of γ -aminobutyric acid (GABA), which is the main inhibitory neurotransmitter of the Central Nervous System. Other neuro-psychiatric disorders were described in our study, like headache, hallucination, agitation, insomnia and, despite being rare (11 cases), the events observed motivated drug replacement (21, 26, 27).

Another infrequent but equally important ADR identified was dizziness (vestibular disorders), which may lead to falls, especially in the elderly. Such ADR may be related with isoniazid and/or ethambutol but was not frequently reported by other researchers (27, 28). Other rare ADRs found in our study were gynecomastia and galactorrhea (one patient each), both late ADRs and possibly isoniazid related as described previously (22, 29).

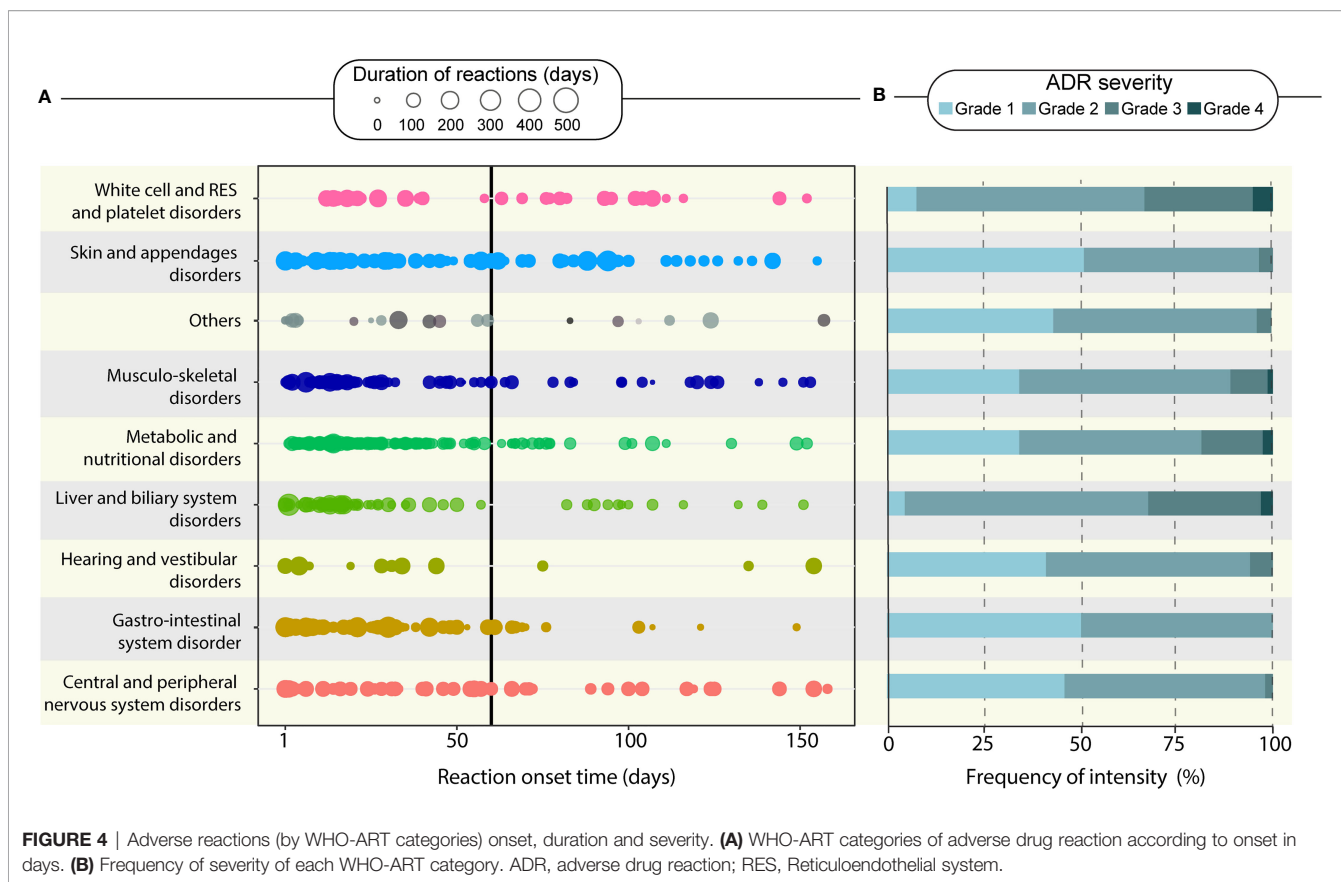
Visual toxicity was related to ethambutol in our cohort. Three of our patients reported this ADR and needed definitive discontinuation of the drug. This was an event reported by us and other researchers just in a few cases (30).

Leukopenia and thrombocytopenia may occur during TB treatment (31). In our data, we found a rate of 5,2%. Although leukopenia is not a reason for treatment discontinuation, when

leukopenia is detected, peripheral blood cell count must be checked regularly. TB treatment should be stopped if the leucocytes count progressively decreases, mainly if there is an important neutropenia. Generally, these hematological disorders occur in PLHIV due to the concomitant ART use or bone marrow impairment (31).

The most frequent laboratory related ADR observed was hyperuricemia (classified as metabolic and nutritional disorder). It is well known that TB treatment with pyrazinamide affects uric acid metabolism, increasing its circulating levels (4). However, most of the patients who had hyperuricemia were asymptomatic, not requiring treatment, but part of them had arthralgia, sometimes requiring nonsteroidal anti-inflammatory drugs to treat symptoms. Another study also found arthralgia as an ADR during TB treatment (15), however, in this study, tests were requested just for patients who had specific complains and not in a routine basis like in our study; such difference might explain the lower detection of hyperuricemia observed by Iman et al. (15).

In addition, most ADRs were mild (grade 1) to moderate in intensity (grade 2). When comparing this intensity in patients with and without HIV co-infection, it was observed that PLHIV more often experienced ADR with greater severity. A study of 103 TB patients treated at a tertiary hospital with first line ATT reported similar results. In this study, 92% of ADRs were mild-moderate, and HIV-TB patients had severe (grade 3) ADR (32). Another study, retrospective cross-sectional, with patients using first-line ATT, reported that 82.4% of related ADR were considered minor reactions (mild-moderate) and HIV coinfection was identified as a risk factor for ADR (33). Thus, PLHIV need to be better monitored for the appearance of ADR



because they seem to have a greater chance of experiencing severe reactions and, according to our study, even potentially lethal reactions (grade 4). In our study, potential risk groups such as alcohol consumption, diabetes, hepatitis B and C did not exhibit a higher frequency of ADR, different from what is described in the literature, probably due to a small number of patients in each specific group. On the other hand, patients of white race could potentially have more ADR due to genetic characteristics such as SNPs on drug metabolism not evaluated in this study. Married patients also had more ADR than the single participants and although this finding seems dubious, we hypothesized that married people have someone at home to check for treatment which potentially could improve adherence and therefore increase the chance to have ADR. In the literature we did not find this correlation, however we can speculate that the adherence could be improved by a spouse who cares and supervises de treatment.

Treatment interruption due to ADR occurred in 25 patients. All of these patients had to replace at least one drug of the ATT and therefore change TB treatment. When a change was necessary, the new therapy was introduced within an interval of up to 7 days. This is an important finding and highlights the new WHO definition for TB treatment outcomes that included discontinuation of ATT due to ADR and therefore the importance of clinical monitoring.

This study had several strengths such as the prospective design, a relatively large number of patients including PLHIV, active follow

up with clinical and laboratory characteristics. On the other hand, there were some limitations. Sometimes patients did not attend monthly visits and therefore laboratory and clinical evaluations of ADRs were missed. Especially in PLHIV, different regimens for both TB and HIV makes it difficult to identify the drug responsible for the ADR. Some patients used concomitant medications that could overlap with TB or ART drugs, which dampened our capacity to determine a relationship of adverse reactions to each drug separately. Regardless of such limitations, the present study adds to the current knowledge in the field by demonstrating a chronologic change in types of ADR upon TB treatment initiation and that HIV infection does not affect risk of ADR, but it does increase the odds of severe ADR once they occur.

The ATT was associated with a large number of ADR as we demonstrated in our study in the early and late phases. However, physicians or other health professionals treating TB must be aware of the specific moment of the therapy ADRs occurrence and follow up patients closely for any evidence of toxicity, as early identification and withdrawal of the causative drug can help to minimize risks. It is important to mention that laboratory tests for at least the first 2 months are desirable to avoid delays in drug interruption and replacement as well as observes that ADR in the late stages of therapy are more frequently clinical, but laboratory alteration of liver enzymes was detected as well.

In conclusion, ADR were frequent and were more prevalent in the intensive phase of TB therapy (early). The most important ADR

in this study was digestive and skin disorders. In the late phase, skin and appendages disorders were more frequent. Most ADR severity were grade 1 and 2. Liver and biliary disorders were grade 3 and were present in both treatment phases. The most frequent ADR, described as “metabolic disorders”, was hyperuricemia, usually related to pyrazinamide, therefore, limited to the intensive phase of treatment and without clinical importance. Although ADR were less frequent in PLHIV, they were more severe, showing that closer follow up of patients is quite important during all treatment. Our recommendation, based on our findings, is to perform safety tests for all TB patients during the first two months of therapy and keep the monthly visits until the end of the ATT asking actively for signs and symptoms and observe late ADR like galactorrhea and gynecomastia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the National Institute of Infectious Diseases Evandro Chagas. The patients/participants provided their written informed consent to participate in this study

AUTHOR CONTRIBUTIONS

FS, CS, and VR contributed to conception and design of the study. FS collected the data and organized the initial database.

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MA-P and MA performed the statistical analysis and data visualization. RO, VR, and BA supervised the project execution. All authors contributed to manuscript writing, revision, read, and approved the submitted version.

FUNDING

This work was supported by Brazilian Program of STD-AIDS and Viral Hepatitis, in partnership with the UNODC and the Clinical Research Laboratory on Mycobacteria of INI, FIOCRUZ, Edital modalidade pesquisas numero 01/2013. The study was partially supported by the Intramural Research Program of the Fundação Oswaldo Cruz. BA and VR. are senior scientists from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). M.B.A. received a scholarship from Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB). MA-P received a research fellowship from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, finance code: 001). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

The authors thank the study participants.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fitd.2021.748310/full#supplementary-material>

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