

Pharmacological treatment of multidrug-resistant tuberculosis (MDR-TB) in patients co-infected with HIV and its incidence in Federal District – Brazil

Tratamento farmacológico da tuberculose multirresistente (TBMR) em pacientes coinfectados com HIV e sua incidência no Distrito Federal – Brasil

Tratamiento farmacológico de la tuberculosis multidrogorresistente (MDR-TB) en pacientes coinfectados por el VIH y su incidencia en el Distrito Federal – Brasil

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Natália Rocha Almeida

ORCID: <https://orcid.org/0000-0002-6931-7204>

Universidade de Brasília, Brazil

E-mail: nataliaalmeidaba@gmail.com

Caio Azevedo Lima

ORCID: <https://orcid.org/0000-0001-8843-3684>

Universidade de Brasília, Brazil

E-mail: caiolima93@gmail.com

Natália Lopes de Freitas

ORCID: <https://orcid.org/0000-0002-4814-7736>

Universidade de Brasília, Brazil

E-mail: natalialopes.nlf@gmail.com

Fabiana Brandão

ORCID: <https://orcid.org/0000-0001-8358-8062>

Universidade de Brasília, Brazil

E-mail: fabianabrandao@unb.br

Abstract

People living with HIV (PLHIV) are at greater risk of infection and development of tuberculosis, caused by *Mycobacterium tuberculosis*. In Brazil, the high mortality rate is identified precisely on the occasion of coinfection and it can actively lead to severe complications. This study aimed to analyze the treatment of multidrug-resistant tuberculosis in patients co-infected with HIV and the incidence of this condition in the Federal District, Brazil. We reviewed the literature via the databases PubMed, Embase, and *Biblioteca Virtual em Saúde* between September and October of 2021, and selected 15 studies fitting the eligibility criteria. The unified health system provides the first-line treatment and recommends using the Directly Observed Treatment. However, when there is resistance or significant intolerance to first-line drugs, second-line drugs are needed. Drug repositioning may be a promising strategy to improve tuberculosis treatment through new therapeutic options and to overcome these problems. The risk of interactions and their complications in PLHIV in antiretroviral therapy and second-line treatment of tuberculosis is even more concerning, which can result in reduced efficacy or increased toxicity of both treatments. Nevertheless, children show better outcomes among patients in TB/HIV co-infection studies, even after second-line treatment fails. These results demonstrate the complexity and seriousness of co-infection epidemiology, treatment, follow-up, and margin of success. Aggravated by factors such as increasing resistance to *M. tuberculosis* in Brazil and the world, the challenge of monitoring patients' treatment and keeping their adherence, and the high rate of adverse effects caused by drugs.

Keywords: Brazil; Co-infection; Drug resistance; Epidemiology; Federal District; HIV; Multidrug-resistant tuberculosis.

Resumo

As pessoas vivendo com HIV (PVHIV) apresentam maior risco de infecção e desenvolvimento da tuberculose, causada pelo *Mycobacterium tuberculosis*. No Brasil, a alta taxa de mortalidade é identificada justamente na ocasião de uma coinfeção e pode levar ativamente a complicações graves. Este estudo teve como objetivo analisar o tratamento da tuberculose multirresistente em pacientes coinfectados pelo HIV e a incidência dessa condição no Distrito Federal, Brasil. Revisamos a literatura por meio das bases de dados *PubMed*, *Embase* e *Biblioteca Virtual em Saúde* entre setembro e outubro de 2021 e selecionamos 15 estudos que se enquadraram nos critérios de elegibilidade. O Sistema Unificado de Saúde oferece o tratamento de primeira linha e recomenda o uso do Tratamento Diretamente Observado. No entanto, quando há resistência ou intolerância significativa aos medicamentos de primeira linha, são necessários medicamentos de segunda linha. O reposicionamento de medicamentos pode ser uma estratégia promissora para

melhorar o tratamento da tuberculose por meio de novas opções terapêuticas e superar esses problemas. O risco de interações e suas complicações em PVHIV em terapia antirretroviral e tratamento de segunda linha da tuberculose é ainda mais preocupante, podendo resultar em redução da eficácia ou aumento da toxicidade de ambos os tratamentos. No entanto, as crianças apresentam melhores resultados entre os pacientes em estudos de coinfeção TB/HIV, mesmo após a falha do tratamento de segunda linha. Esses resultados demonstram a complexidade e a gravidade da epidemiologia, tratamento, acompanhamento e margem de sucesso da coinfeção. Agravado por fatores como o aumento da resistência à *M. tuberculosis* no Brasil e no mundo, o desafio de acompanhar o tratamento dos pacientes e manter sua adesão, e o alto índice de efeitos adversos causados pelos medicamentos.

Palavras-chave: Brasil; Coinfeção; Resistência a medicamentos; Epidemiologia; Distrito Federal; HIV; Tuberculose multirresistente.

Resumen

Las personas que viven con el VIH (PVVIH) tienen mayor riesgo de infección y desarrollo de tuberculosis, causada por *Mycobacterium tuberculosis*. En Brasil, la alta tasa de mortalidad se identifica precisamente con ocasión de una coinfección y puede conducir activamente a complicaciones graves. Este estudio tuvo como objetivo analizar el tratamiento de la tuberculosis multidrogoresistente en pacientes coinfectados por el VIH y la incidencia de esa condición en el Distrito Federal, Brasil. Revisamos la literatura a través de las bases de datos *PubMed*, *Embase* y *Biblioteca Virtual em Saúde* entre septiembre y octubre de 2021, y seleccionamos 15 estudios que cumplían con los criterios de elegibilidad. El sistema de salud unificado proporciona el tratamiento de primera línea y recomienda utilizar el Tratamiento Directamente Observado. Sin embargo, cuando hay resistencia o intolerancia significativa a los medicamentos de primera línea, se necesitan medicamentos de segunda línea. El reposicionamiento de fármacos puede ser una estrategia prometedora para mejorar el tratamiento de la tuberculosis a través de nuevas opciones terapéuticas y superar estos problemas. El riesgo de interacciones y sus complicaciones en PVVIH en terapia antirretroviral y tratamiento de segunda línea de la tuberculosis es aún más preocupantes, lo que puede resultar en una eficacia reducida o una mayor toxicidad de ambos tratamientos. Sin embargo, los niños muestran mejores resultados entre los pacientes en estudios de coinfección TB/VIH, incluso después de que falla el tratamiento de segunda línea. Estos resultados demuestran la complejidad y la gravedad de la epidemiología, el tratamiento, el seguimiento y el margen de éxito de la coinfección. Agravado por factores como el aumento de la resistencia de *M. tuberculosis* en Brasil y en el mundo, el desafío de monitorear el tratamiento de los pacientes y mantener su adherencia, y la alta tasa de efectos adversos causados por los medicamentos.

Palabras clave: Brasil; Coinfección; Farmacorresistencia; Epidemiología; Distrito Federal; VIH; Tuberculosis multirresistente.

1. Introduction

Around the 1980s, healthy homosexual men, injecting drugs users, hemophiliacs, and blood recipients showed signs and symptoms of pneumonia, later identified as caused by *Pneumocystis carinii* and Kaposi's sarcoma. The cause was then identified in the USA and in 1981 the world discovered the acquired immunodeficiency syndrome (AIDS) (Ribeiro et al., 2009). When infected with HIV, the patient may be asymptomatic for a period until the immune system deteriorates, presenting a decline of CD4 cells soon and, as a consequence, immunosuppression (Danwang et al., 2022). At this moment, the patient begins to present symptoms of AIDS - which, when untreated, progresses to death (Egger et al., 2002). Therefore, habits such as the use of protection in sexual relations, not sharing needles, and adherence to the available treatments protects the immune system, not only by reducing the chance of infections but also by increasing the quality of life and minimizing the adverse effects resulting from the infection (Castro et al., 1993).

Mycobacterium tuberculosis was first described in detail in 1882 by Robert Koch, a German bacteriologist, thus also being called Koch's bacillus (KB). *M. tuberculosis* is a strict aerobic intracellular pathogen bacillus, able to survive and multiply inside phagocytic cells, therefore, considered a facultative intracellular parasite, and it is responsible for causing tuberculosis (TB) (Campos, 2006). Tuberculosis is an opportunistic infection that stands out in HIV patients, as being infected with HIV increases the risk of individuals with latent TB developing the active form, and TB is the main cause of death from infectious diseases in people living with HIV (PLHIV) (Ministério da Saúde et al., 2018). The World Health Organization (WHO) declared, in 2016, that there were approximately 10.4 million new cases of TB and, in the same year, 1.3 million individuals not co-infected

with HIV and 374,000 individuals co-infected died from this condition (World Health Organization, 2016). Thus, TB is one of the ten leading causes of death worldwide, even ahead of HIV/AIDS as the cause of death from a single infectious agent (Carvalho et al., 2018). The challenges of treating both conditions include drug interactions, increased toxicity of medication, immune reconstitution inflammatory syndrome, and abandonment of treatment (Pimpin et al., 2011).

Surprisingly, many patients only discover HIV infection when they are in the investigative phase of the TB diagnosis, as described by Brazil's Ministry of Health (Ministério da Saúde, 2013). In Brazil, the state with the highest incidence of TB is Amazonas, with 68.4 new cases per 100,000 inhabitants, a position that once belonged to Rio de Janeiro (Magno et al., 2017). In a survey carried out using data from the Ministry of Health database Sistema de Informação de Agravos de Notificação (SINAN), from 2001 to 2012, in the State of Amazonas, the estimated prevalence of TB/HIV/AIDS co-infection was 7.7%, with this result still under the influence of an underreporting rate of 35% (Magno et al., 2017).

There are different resistance levels, with different nomenclatures, of *M. tuberculosis* to the drugs commonly used in its treatment. Drug-Resistant Tuberculosis (DR-TB) refers to strains resistant to one or more antibiotics. Multidrug-Resistant Tuberculosis (MDR-TB) refers to strains resistant to isoniazid and rifampicin, drugs used as first-line on TB treatment. Drug-Resistant Extensive Tuberculosis (XDR-TB) applies to strains resistant to isoniazid, rifampicin, fluoroquinolones, bedaquiline and/or linezolid (Schluger et al., 2021). Factors that influence the resistance development to conventional treatments are previous treatment, clinical or radiographic findings that indicate disease progression even with first-line treatment, living in or visiting a region with a high incidence of MDR-TB, or having contact with a person with suspicion or diagnosis of this condition (Schluger et al., 2021).

Although treatments for TB and HIV are well-defined, data on how much the population is still affected is alarming, particularly with the growth of cases of multiple resistance of *M. tuberculosis* to the recommended antibiotic therapy. This study aimed to analyze the treatment used in cases of MDR-TB in patients co-infected with HIV; as a secondary objective, discuss the treatment, drug interactions, adverse effects, treatment adherence and verify the incidence of this condition in the Federal District (DF), Brazil.

2. Methodology

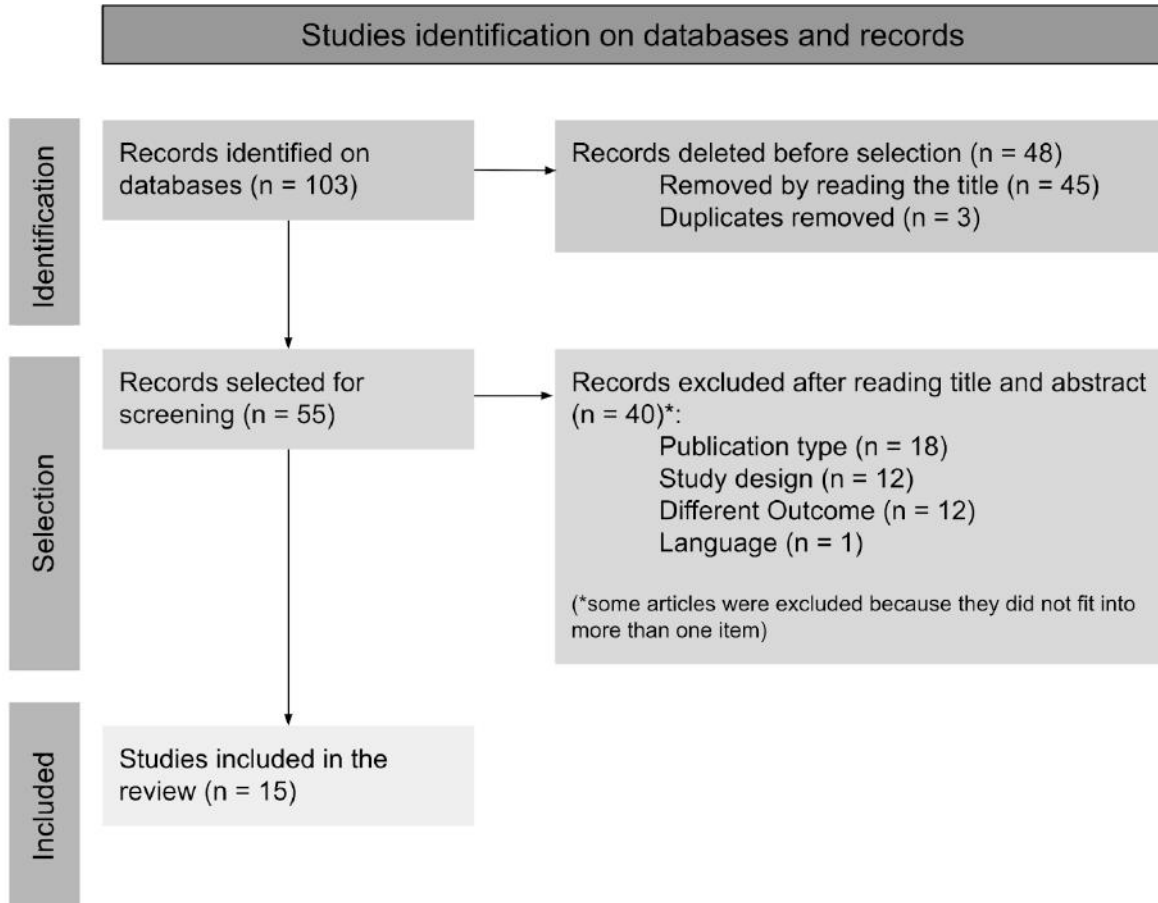
In this integrative literature review, based on the PRISMA model, we accessed the databases PubMed, Embase, and *Biblioteca Virtual em Saúde (BVS)* through *Portal de Periódicos da CAPES/MEC*. Searches were carried out between 25-29/09/2021, and additional searches were done between 16-26/10/2021. For the initial research, DeCS/MeSH terms and keywords, such as "acquired immunodeficiency syndrome", "human immunodeficiency virus infected patient", "aids related opportunistic infections", "multidrug resistant tuberculosis", "co-infection", "drug therapy", "antibiotic therapy", "clinical protocols" and their respective synonyms were used, according to each database. The articles identified were incorporated into Rayyan Systems Inc. application for organization purposes. As eligibility criteria, observational studies, systematic reviews, meta-analyses, retrospective cohort studies, case series reports - published in English or Portuguese - were chosen. We excluded publications such as expert opinions, narrative reviews, letters to the editor, and articles with outcomes or study designs not compatible with our objectives aforementioned. In order to comprehend the distribution of this condition in the Federal District, searches were carried out for epidemiological data in official publications of the Ministry of Health and the Health Department of the Federal District. Additionally, manual searches were performed to complement the theoretical framework of the article.

3. Results

Initially, 103 articles were identified on the databases. After excluding duplicates, the articles were filtered by title

reading - 45 were immediately eliminated for not being suited and 55 were selected for screening. Subsequently, title and abstract reading was performed to verify if the selected articles fulfilled the aforementioned eligibility criteria. Finally, 15 articles were included in the study, (Figure 1). Table 1 shows the selected articles and a briefing of each study (Table 1).

Figure 1. Flowchart of the studies selected for the review.



Source: Elaborated by the authors.

Table 1. Articles selected after analysis on databases (See Methodology).

Author/Date	Study type	Intervention/Objective	Results
Daftary et al. (2014)	Qualitative study with data collection through focus group discussions.	Patients who had started treatment for resistant TB were separated into small groups to openly discuss different views regarding treatment and adherence with a facilitator/moderator.	This methodology made it possible to identify and understand factors that lead to non-adherence to treatment for resistant tuberculosis in patients with HIV in a more comprehensive and in-depth way than traditional adherence studies.
de Kock et al. (2014)	Crossover, randomized study.	Characterize the pharmacokinetic effects of para-aminosalicylic acid in treatments on a sample of coinfecting patients undergoing antiretroviral treatment.	PAS concentrations are reduced in HIV-infected TB patients and that the concomitant administration of EFV probably plays a role in this deficiency. Efavirenz and PAS still need to be elucidated.
Dooley et al. (2021)	Open-label, phase 2, randomized, controlled clinical trial.	Characterize the influence of bedaquiline and/or delamanid on the QTc interval of patients with multidrug-resistant or rifampicin-resistant tuberculosis on multidrug treatment.	Results showed that the co-administration of bedaquiline with delamanid is safe from a cardiological point of view, in addition, the microbiological results of this association were promising.
Efsen et al., (2015)	Prospective, observational cohort study.	Analysis of the characteristics of TB/HIV patients in Eastern Europe compared to other regions of Europe and Latin America, identifying factors associated with MDR-TB and investigating empirical treatment activity.	Patients from Latin America had a lower incidence of multidrug-resistant tuberculosis when compared to patients from Western Europe, possibly because the therapeutic regimens were better defined.
Kvasnovsky et al. (2011)	Retrospective cohort study.	It evaluates the final clinical outcomes and adverse events (AEs) of patients with XDR-TB, most of them HIV+, receiving a treatment regimen containing bedaquiline.	The diagnosis of XDR-TB, even with HIV co-infection, can be successfully identified. Concomitant therapy with XDR-TB and HIV is feasible and effective in children, although more research is needed on potential overlapping toxicities.
Ndjeka et al. (2015)	Interim cohort analysis.	Monitor the use of bedaquiline for the treatment of XDR-TB, especially among HIV-infected patients on ART.	HIV status did not affect culture conversion time or risk of non-conversion, and QTc prolongation was little, suggesting that bedaquiline is effective and safe.
Ndjeka et al. (2018)	Prospective, observational study.	Select and enroll patients according to criteria selected in conjunction with the Government of South Africa for treatment with bedaquiline and observe the results.	The bedaquiline treatment showed to be promising among those who followed the treatment, especially in addition to DOT.
Padayatchi et al. (2014)	Retrospective cohort study.	Addition of 200 or 300 mg of clofazimine to therapeutic regimens defined by physicians.	Patients receiving clofazimine had <i>M. tuberculosis</i> 's culture conversion faster than those who did not.
Rose et al. (2012)	Retrospective review of case reports.	Verify the safety of linezolid treatment in children with resistant TB.	Linezolid may be effective in treating children with resistant tuberculosis even after second-line treatments have failed, but adverse effects and drug interactions should be monitored, especially in HIV+ children.
Salinas et al. (2017)	Multivariable Analysis of cases reports.	Analysis of data from TB cases in the United States reported during 1993-2013 to the National Tuberculosis Surveillance System (NTSS) at the Centers for Disease Control and Prevention.	All-cause mortality among MDR-TB patients declined significantly over this period in the United States. However, foreign-born patients living with HIV infection still have twice the risk of death compared to US-born patients living with HIV infection.
Schnippel et al. (2016)	Retrospective cohort study.	Report the occurrence of adverse events (AEs) during a MDR-TB treatment regimen in hospital patients in South Africa.	The incidence of serious adverse effects was higher in patients co-infected with HIV, increasing the risk of treatment abandonment and death.
Seung et al. (2009)	Retrospective cohort analysis.	Retrospective analysis of baseline results from the first cohort of patients enrolled in Lesotho's national MDR-TB program between 21 July 2007 and 21 April 2008.	There is strong evidence of the difficulty of treating MDR-TB in settings with high HIV prevalence in Lesotho. An innovative community-based treatment model that involved social and nutritional support, directly observed twice-daily treatment, and early empirical use of second-line TB drugs was successful in reducing the mortality of MDR-TB patients.
van der Laan et al. (2018)	Population pharmacokinetic model.	Characterize the effects of drugs used in the treatment of MDR-TB on the pharmacokinetics of lopinavir and ritonavir in HIV+ children.	No significant effect was found for the antituberculosis drugs tested on the pharmacokinetic parameters of the ARVs ritonavir and lopinavir.
Wang et al. (2021)	Population pharmacokinetic model.	To characterize the pharmacokinetics of delamanid when administered with different treatment regimens for MDR-TB and to identify factors that may influence these values.	The use of the ARV efavirenz increased delamanid clearance by 35% and decreased its Area Under the Curve (AUC ₀₋₂₄) by approximately 25%, but no dose adjustment was necessary.
Yuengling et al. (2018)	Prospective, observational study.	Follow adult patients with XDR-TB until the end of treatment, collect clinical data, questionnaires, adherence data and samples for whole genome sequencing in <i>Mycobacterium tuberculosis</i> isolates.	Despite improved HIV care, treatment outcomes and mortality were only modestly improved compared to previous South African XDR-TB/HIV treatment cohorts.

Source: Elaborated by the authors.

4. Discussion

4.1 First-line treatments

Drugs recommended as first-line in susceptible TB treatment are rifampicin, isoniazid, pyrazinamide, and ethambutol. In Brazil, this treatment scheme is provided by the unified health system (SUS), which recommends using the Directly Observed Treatment (DOT), consisting of a trained healthcare professional assisting the patient to take their medication, as a strategy for monitoring of pharmacotherapy and to guarantee treatment adherence (Seung et al., 2009). However, when resistance is suspected or confirmed, or when there is significant intolerance to first-line drugs, second-line drugs are preferable - such as amikacin, amoxicillin and clavulanate, bedaquiline, clofazimine, delamanid, pyrazinamide, among other antibiotics (Schluger, 2021). To successfully treat DR-TB, it is necessary to identify the susceptibility of the *M. tuberculosis* strain and use this laboratory diagnosis to choose the appropriate antibiotic therapy. If it is necessary to use empirical treatment, the drug choice should be based on epidemiological criteria. However, in cases of MDR-TB, there is still no consensus on the empirical treatment (Schluger et al., 2021).

Drug repositioning may be a promising strategy to improve TB treatment through new therapeutic options and to overcome the problem of resistance to drugs commonly used for this condition. In the case of XDR-TB, Padayatchi demonstrated that the addition of clofazimine - a drug used against *Mycobacterium leprae* - to different treatment regimens in patients co-infected with HIV had a positive impact on the outcome, as evidenced by the time of culture conversion - i.e., the time interval between the initiation of pharmacotherapy until the first negative result for *M. tuberculosis* culture - shorter than patients who received a drug regimen without clofazimine (Padayatchi et al., 2014). Nonetheless, HIV status, the use or not of Antiretroviral Therapy (ART), and CD4 cell count did not cause a significant difference in culture conversion, similar to results obtained in other studies. Furthermore, the researchers demonstrated that the majority of patients who experienced adverse effects to clofazimine were HIV-positive on ART, but there were no adverse effects of magnitude.

Some drugs used as a second-line in TB treatment, such as fluoroquinolones (Hooper, 2021) and clofazimine (Lexicomp, 2021), can increase the QTc interval. Therefore, Dooley et al. carried out a phase II clinical trial focusing on bedaquiline and delamanid - which are in phase II and phase III clinical trials, respectively - to assess the cardiac risk of their co-administration. For this, they verified whether patients with MDR-TB or Rifampicin-Resistant Tuberculosis (RR-TB) would increase the QTc interval as a consequence of the association of bedaquiline and delamanid, plus first-line drugs for TB treatment and dolutegravir, in the case of patients with HIV. Bedaquiline and delamanid caused a slight increase in the QTc interval, but the researchers found that they did not impair the patients' safety, including people living with HIV/AIDS (PLHIV). Although not confirmed, the microbiological results were promising, showing that this association improved culture conversion to TB (Dooley et al., 2021).

4.2 Drug interactions between ART and MDR-TB drugs

In Brazil, the treatment considered first-line for individuals co-infected with TB-HIV consists of tenofovir + lamivudine and efavirenz (EFV), however, EFV can be replaced by dolutegravir in the case of an alternative regimen (Ministério da Saúde, 2021a). Following the guidelines of the Ministry of Health of Brazil, all PLHIV who have an active TB infection should use ART. If the patient is not already on HIV therapy, it is recommended to start treatment for TB and start ART after 2-8 weeks, since it is not recommended to start treatment for both conditions simultaneously (Ministério da Saúde, 2013).

Nonetheless, there may be drug interactions between ART and drugs for MDR-TB, especially from a pharmacokinetic point of view. Interactions can result in reduced efficacy or increased toxicity of both treatments (Perini, 2017). In a study to verify the occurrence of drug interactions between ART in HIV co-infected children receiving treatment for MDR-TB, VAN

DER LAAN et al. found no significant effect of the antituberculosis drugs tested on the pharmacokinetic parameters of ritonavir and lopinavir. However, the study had limitations, such as a small number of participants, and it is still necessary to study the possibility of pharmacokinetic interactions between ART and antituberculosis drugs that were not evaluated in this study - such as levofloxacin, clofazimine, linezolid - and newer drugs - such as bedaquiline and delamanid (van der Laan et al., 2018).

In a recent study, Wang et. al used data from clinical trials with delamanid to create a population pharmacokinetic model of this drug in patients with MDR-TB. Factors such as age, sex, other anti-TB drugs or ART, and HIV status did not significantly affect delamanid exposure. However, EFV use resulted in a 35% increase in delamanid clearance and an approximately 25% decrease in its Area Under the Curve (AUC₀₋₂₄), a phenomenon not found in healthy patients. Despite this finding, there were no relevant influences on the treatment as a whole which indicated the need for dose adjustment (Wang et al., 2020).

Second-line TB treatment has its administration complications, with frequent adverse reactions and drug interactions, many with potential for serious reactions. The adverse effects add complexity to the treatment, nearly 60% for TB patients and up to 80% for RR-TB patients (Schnippel et al., 2016). Considering that the population in this review is infected with HIV, and therefore eligible for ART, the risk of interactions and their complications in these individuals is even more concerning.

MR-TB and XDR-TB led to the reintroduction of second-line TB drugs, including para-aminosalicylic acid (PAS), an antimycobacterial agent generally reserved for the treatment of XDR-TB. Most second-line drugs are notorious for toxic effects such as intolerances, gastrointestinal problems, including nausea, vomiting, abdominal cramps, and diarrhea, among others; nevertheless, their results are significant against DR-TB. However, its co-administration with ART becomes complex, especially with EFV. Kock et al. (2014) demonstrated a possible interference on the pharmacokinetics of PAS in HIV and MDR-TB infected patients, with an overall reduction of approximately 30% of exposure to PAS, in simultaneous treatment with EFV (de Kock et al., 2014).

Another reason why RR-TB treatments and ART have complications and increased AEs is the overlap of toxicities that can be aggravated by concomitant use. For example, both kanamycin and tenofovir can cause renal dysfunction, as reported by Schnippel et. al. (2016). The author also points out that these two drugs can overload the kidneys and considerably damage, even if the patient is under increased fluid consumption. AEs themselves can also result in hospitalization, permanent disability, or death. Furthermore, AEs can negatively impact the effectiveness of RR-TB treatments in many ways, directly or indirectly. Patients or physicians can reduce dosages or even interrupt treatment attempting to alleviate adverse effects, aggravating the risk of resistance to the drugs used and resulting in treatment failure or even leading the patient to death from TB (Schnippel et al., 2016).

4.3 Adverse effects

Due to high dropout rates recorded in South Africa, only 49% of the 2012 cohort of MDR-TB patients were cured or completed treatment with second-line TB drugs and ART, below the global average (50%) and the study's goal (75%). According to Schnippel et al. (2016), which analyzed 578 AEs reports, 204 patients (35.3%) had at least one severe AE (grade 3+). Patients who reported at least one AE experienced an average of three other AEs. Gastrointestinal effects were the most common, with 138 reports of vomiting, nausea, epigastric abdominal pain, abdominal discomfort, diarrhea, constipation, loss of appetite, and weight loss. The most common severe AE reported was hearing loss or ototoxicity, affecting 17.3% of patients. Kidney dysfunction or failure accounted for 10.3% of reported severe AEs. Even reports of psychosis were registered in 6.7% of cases, neuropathies in 6.1%, and hepatitis or liver dysfunction in 5.6% of cases; the latter was also among the most frequent severe AEs. Serious AEs considered rare include deep venous thrombosis (n = 2), sepsis (n = 1), suicidal thoughts (n = 1), spontaneous abortion (n = 1) and neuroleptic malignant syndrome (n = 1). Kanamycin was the suspected drug for causing a higher number of

AEs or severe AEs in 54.4% of patients who had at least one AE. Among the 309 cases of AEs that contained at least one drug suspected of causing them, kanamycin was listed 175 times. In a similar list of drugs suspected to cause at least one of the reported serious AEs, terizidone was listed in 25.4% of cases (Schnippel et al., 2016).

4.4 Treatment adherence

Not only is adherence to both ART and antituberculosis drugs crucial for a positive outcome in co-infected patients, but adherence to ART and antibiotic therapy must be proportional; otherwise, there is an increased risk of the mycobacteria developing antibiotic resistance (Daftary et al., 2014). However, the abandonment of antituberculosis treatment was a phenomenon that drew attention and, therefore, was addressed in this review; the main cause being treatment non-adherence due to adverse effects resulting from ART and anti-TB drugs co-administration in these patients. Dooley et al. mention as factors that make MDR-TB treatment particularly challenging in HIV patients: drug interactions, the large number of pills causing discomfort in the patient's dosage, and complications of the acquired immunodeficiency syndrome itself (Dooley et al., 2021).

Researchers followed patients admitted to a hospital in South Africa, monitored the intake of drugs used in MDR/XDR-TB treatment, and held discussion groups where patients could openly discuss with each other and with a moderator concerning the treatment and factors that hindered adherence to it. In addition to more subjective factors (such as social discomfort associated with this condition due to stigmas), these patients reported discomfort with the number of pills they needed to ingest daily. Moreover, a complaint repeated in several groups was the adverse effects (such as nausea, diarrhea, and mental confusion) caused by antituberculosis drugs, which were not present when patients were using only ART, making patients prefer to maintain ART and abandon antibiotic therapy against TB (Daftary et al., 2014).

4.5 Treatment of MDR-TB in HIV-positive children

As described in a retrospective review of patients, children show better outcomes among patients in TB/HIV co-infection studies. Linezolid-containing regimens may effectively treat children with DR-TB, even after second-line treatment fails. Adverse events (AE) should be monitored, especially when combining medications with similar adverse effects. In a series of case reports from South Africa, linezolid was well tolerated by HIV-uninfected children, none of whom experienced any adverse effects while on linezolid. Yet, all three HIV-infected children experienced AE, possibly due to linezolid, alone or in combination with drugs involved in ART (Rose et al., 2012). Comparatively, AEs associated with linezolid-containing regimens are usually reported in adult patients and are more common in cases of children receiving prolonged treatment with linezolid. Linezolid's adverse effects in children are similar to those previously described with second-line TB drugs: gastrointestinal complications, reversible myelosuppression, peripheral neuropathy (which may be irreversible), optic neuropathy, headache, skin rash, pancreatitis, and lactic acidosis (Rose et al., 2012).

In a retrospective case series, Thomas et al. (2010) characterized four HIV-positive children aged 6–8 years identified with XDR-TB, admitted to a hospital in a rural area of South Africa. Three of them received active ART before being diagnosed with XDR-TB; one started ART after completing six months of treatment for XDR-TB (Thomas et al., 2010). All four responded well clinically, even with suppressed viral loads. Two of them tolerated the co-treatment of XDR-TB and HIV well. Simultaneous XDR-TB and HIV therapy are feasible and effective in children, although more research is required on the potential overlapping toxicities. TB and HIV are some of the leading infectious causes of mortality worldwide. Among the estimated 9.4 million cases of active TB annually, children represent 11%. In sub-Saharan Africa, the burden of childhood TB is even more alarming, with up to 40% of all TB cases occurring among children (Thomas et al., 2010).

4.6 Aggravated mortality

The risk factors observed in HIV and TB-associated infections may present not very alarming data when correctly monitoring the treatment. However, the co-infection can actively lead to severe complications, even if the conditions are being treated. The situation is aggravated by the growing presence of DR-TB or MDR-TB cases to the once efficient standard treatments. According to Seung et al. (2009), in HIV-negative patients in South Africa, cure rates of MDR-TB treatment programs ranged from 61-77%, and their mortality rates ranged from 5–19%. Compared to early treatment outcomes in one of their communities in Lesotho, however, they indicate that treatment outcomes for MDR-TB in HIV-positive people tend to be significantly worse. The average duration of treatment time for TBMR/HIV co-infected was at least 18 months, which is three times the time of the 6-month regimen for drug-susceptible TB, which in itself can lead to treatment dropout or misapplication of it (Seung et al., 2009).

Globally, the mean rate of successful treatments for TB was 83% on a 2015 cohort; comparatively, the success rate for patients with RR/MDR-TB was 54%, and for patients with XDR-TB, only 30% on a 2014 cohort (Ndjeka et al., 2018). In 2014, again in South Africa, success rates were reported of 54% for patients with RR/MDR-TB and only 27% for patients with XDR-TB, in addition to 21.7% mortality from RR/MDR-TB patients and 42.5% of patients with XDR-TB died during treatment (Ndjeka et al., 2018).

Although PLHIV care has progressed, treatment outcomes and mortality have improved modestly compared to previous cohorts analyzing XDR-TB/HIV treatment. Despite current ART efficiency and satisfactory adherence to treatment, mortality from XDR-TB/HIV remains unacceptably high, especially before employing new antimycobacterial drugs - for example, bedaquiline and delamanid. Therefore, only improving HIV care and ARV may not be enough to ameliorate outcomes in the treatment of XDR-TB/HIV co-infected patients. In their studies, Yueling et al. (2018) registered a high percentage of patients with XDR-TB/HIV receiving ART at baseline, supplied with high rates of HIV testing before starting treatment for identified XDR-TB. Improving the immune response by suppressing the retrovirus viral load is understandable and logical. Despite this high ART coverage, mortality rates (68.8%) and treatment outcomes remained unfavorable, being the majority in the study population: 41% deaths most likely caused by complications due to XDR-TB co-infection (Yuengling et al., 2018).

4.7 Epidemiological data in the DF

Brazil remains among the 30 high-burden countries for TB and TB-HIV co-infection, as it represents one-third of all TB cases in the Americas (Ministério da Saúde, 2021b). Data from the Ministry of Health shows that the proportion of TB-HIV co-infection per Federated unit in 2020 averaged 8.5%, being led by the Distrito Federal, Rio Grande do Sul, Santa Catarina, and Amazonas, respectively - the first surpassing the national average for almost double its value (Ministério da Saúde, 2021b).

The Ministry of Health and the Department of Health of the Federal District recommend carrying out the HIV test as soon as the patient is identified with tuberculosis, as the early diagnosis of TB-HIV co-infection allows to reduce its morbidity and mortality (Secretaria de Saúde do Distrito Federal, 2021). Brazil has continuously dropped the number of HIV tests performed in cases of TB infection since 2018, but DF has the better number of tests performed, being 77.7% in 2017 (Ministério da Saúde, 2017).

In 2020, 291 new cases of tuberculosis were reported in the Federal District, resulting in an incidence of 9.5 cases per 100,000 inhabitants. From those cases, only 79.4% (n = 231) were tested for HIV, and 15.1% (n = 44) were co-infected. Moreover, only 68.2% (n = 30) were carrying out ART among new TB cases with co-infection (Ministério da Saúde, 2021b). In addition, it was possible to observe the predominance of TB-HIV of patients with 35 to 49 years and males, in DF (Alves et al., 2021). Furthermore, it was noted that in the cases recorded, about 20.6% of the cases, co-infection with HIV was ignored in the treatment

(Ministério da Saúde, 2021a).

5. Conclusion

In conclusion, it is relevant to address TB/HIV co-infection as the data demonstrates the complexity of its epidemiology, treatment, follow-up, and margin of success, differing from the isolated infections. The situation is aggravated by factors such as increasing resistance to *M. tuberculosis* in Brazil and the world, the challenge of monitoring patients' treatment and keeping their adherence, the high rate of adverse effects caused by ART alongside anti-TB drugs, the risk of microorganisms resistance, co-infected patients mortality. Directly Observed Treatment has proven to be effective, considering the challenges of this condition, thus demonstrating the importance of attention from a health professional in a successful treatment. The searches and methods used proved satisfactory, obtaining a significant number of pertinent and content-related studies. The Federal District presents distressing data related to the number of co-infected patients and non-adherence to joint treatment. The number of requests for tests performed and treatment adherence is also low, especially considering DF is the capital of Brazil. Moreover, all patients diagnosed with TB in DF must get tested for HIV and have access to preconized pharmacological treatment alongside DOT. Altogether, more research and clinical trials must be done to optimize second-line treatment, especially for patients co-infected with HIV, to reduce complications such as adverse effects and insufficient treatment adherence.

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