**Medication therapy management in patients with tuberculosis and HIV/AIDS: case series**

**Abstract**

**Objectives:** To describe cases of patients with tuberculosis (TB) and HIV/AIDS co-infection followed up at a Reference Hospital in infectious diseases. Identify, classify, and resolve the Drug Related Problems (DRP). And classify the clinical and pharmacotherapeutical situation.

**Methods:** For the identification, classification, and resolution of the DRP outcome as well as the clinical and pharmacotherapeutical situation, the Pharmacotherapy Workup methodology was used. This is a observational, descriptive, longitudinal, case series study carried out in a tertiary referral hospital in Belo Horizonte, following CARE guidelines endorsed by Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network. Patients coinfected with TB and HIV/AIDS, exposed to the treatment recommended by the Ministry of Health, aged 18 years or older, of both genders, followed for a minimum period of six months, were included.

**Results:** Six cases of patients co-infected with TB and HIV/AIDS were described. The average number of meetings with the pharmacist was 6.33 (standard deviation=0.82). A total of 69 DRPs were identified, of which 40/69 (58.0%) were related to adherence, 17/69 (24.6%) to the indication, 8/69 (11.6%) to safety and 4/69 (5.8%) to effectiveness. Of the total number of patients 4/6 (66.6%) had hepatotoxicity during follow-up. The clinical and pharmacotherapeutical situation was classified as positive for all patients.

**Conclusion:** There was a high number of adherence and indication DRP in coinfected patients. Monitoring the effectiveness and safety of treatments must be carried out, due to the greater susceptibility to adverse reactions, such as hepatotoxicity.

**Keywords:** medication therapy management; tuberculosis; HIV; effectiveness; medication adherence; drug related side effects and adverse reactions.

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**Resumo**

**Objetivos:** Descrever casos de pacientes com coinfeção tuberculose (TB) e HIV/aids acompanhados em um Hospital Referência em doenças infecciosas. Identificar, classificar e resolver os Problemas Relacionados ao uso de Medicamentos (PRM). E classificar a situação clínica e farmacoterapêutica. **Métodos:** Para a identificação, classificação e resolução do desfecho de PRM bem como a classificação da situação clínica e farmacoterapêutica, utilizou-se a metodologia Pharmacotherapy Workup. Trata-se um estudo observacional, descritivo, longitudinal, do tipo série de casos realizado em Hospital de Referência terciária em Belo Horizonte, seguindo as diretrizes CARE da Enhancing the QUALity and Transparency Of health Research (EQUATOR). Foram incluídos pacientes coinfetados com TB e HIV/aids, expostos ao tratamento preconizado pelo Ministério da Saúde, com 18 anos ou mais, de ambos os sexos, acompanhados por um período mínimo de seis meses. **Resultados:** Foram descritos seis casos de pacientes coinfetados com tuberculose e HIV/aids. A média de encontros com o farmacêutico foi de 6,33 (desvio padrão=0,82). Foram identificados 69 PRM, dos quais 40/69 (58,0%) relacionados à adesão, 17/69 (24,6%) à indicação, 8/69 (11,6%) à segurança e 4/69 (5,8%) à efetividade. Do total de pacientes 4/6 (66,6%) apresentaram hepatotoxicidade durante o acompanhamento. A situação clínica e farmacoterapêutica foi classificada como positiva para todos os pacientes. **Conclusão:** Houve alto número de PRM de adesão e indicação nos pacientes coinfetados. O monitoramento da efetividade e segurança dos tratamentos deve ser realizado, devido à maior susceptibilidade de reações adversas, como a hepatotoxicidade. **Palavras-chave:** conduta do tratamento medicamentoso; tuberculose; HIV; efetividade; adesão à medicação; efeitos colaterais e reações adversas relacionados a medicamentos.
**Introduction**

Medication use is one of the main options for the cure, treatment and prevention of countless diseases. However, the patients can present Drug-Related Problems (DRPs) that, if not identified, prevented and solved, may interfere with treatment effectiveness and safety.\(^1\)\(^2\)

Tuberculosis (TB) represents a major public health problem, aggravated by the presence of the Human Immunodeficiency Virus (HIV). In 2020, approximately 10 million people developed TB and it is estimated that 1.3 million died due to TB, in addition to 214,000 deaths among people living with HIV/AIDS.\(^3\)\(^4\) The presence of comorbidities, including HIV infection, and late treatment initiation have been identified as the causes of the high rates of both in- and out-of-hospital mortality.\(^3\)\(^5\)\(^6\)

Treatment of the co-infection reduces mortality, TB recurrence and transmission in the community. Pharmacotherapy is complex because it involves countless medications with clinically important and potential drug interactions, in addition to other associated diseases.\(^7\)\(^8\)

This case series is unique and, to our knowledge, it is the first study in which the researchers holistically monitored and assessed pharmacotherapy in patients co-infected with TB and HIV/AIDS. These patients present peculiar characteristics resulting from co-infection, as well as other clinical conditions that increase pharmacotherapy complexity and interfere with the treatment outcomes.

Monitoring centered on the patients’ pharmacotherapy needs is fundamental to optimize the outcomes. However, the number of published studies on pharmacotherapy monitoring in TB and HIV/AIDS co-infection is low.\(^9\)\(^10\) Medication Therapy Management (MTM) can reduce the impact of the TB and HIV/AIDS co-infection on public health, contributing to treatment effectiveness and safety. In this sense, this study aims at describing cases of co-infected patients exposed to the treatment recommended by the Ministry of Health for TB and HIV/AIDS and followed-up at a Reference Hospital in infectious diseases, in addition to identifying, classifying and solving the DRP outcomes, as well as the clinical and pharmacotherapeutic situation.

**Methods**

This is an observational, descriptive, longitudinal and case series study described according to the CARE guidelines endorsed by the Enhancing the QuAlity and Transparency Of health Research (EQUATOR) Network.\(^16\) Cases of patients co-infected with TB and HIV/AIDS and treated at a Reference Hospital in infectious diseases were reported. The study included patients diagnosed with TB and HIV/AIDS who initiated TB treatment after September 2015 and cases 3 and 5 underwent one hospitalization each.

Most of the patients (cases 3, 4, 5 and 6) presented hepatotoxicity caused by efavirenz and required changes in pharmacotherapy for TB and HIV/AIDS (Figure 1).

The mean number of meetings with the pharmacist was 6.33 (Standard Deviation=0.82). A total of 69 DRPs were identified, of which 40/69 (58.0%) were related to adherence, 17/69 (24.6%) to side effects (DRP 1 – Side effects), 16/69 (23.2%) to very expensive medication, 11/69 (16.5%) to safety (DRP 5 – Adverse drug reaction; DRP 6 – High dose), and convenience (DRP 7 – Medication not convenient).\(^1\)\(^2\)

The pharmacist assessed the patients’ actual results and determined their progress in relation to the therapeutic objectives. After identifying and documenting the DRPs, the status or situation of each health problem was classified as solved, stable, improved, partially improved, no improvement, deterioration, failure or death (Supplementary material 1).\(^1\)

The clinical and pharmacotherapeutic situation was considered positive when classified as solved, stable, improved or partially improved. It was considered negative when classified as with no improvement, deterioration, failure or death.\(^2\)

The study is part of the project entitled “Pharmaceutical care provided to patients living with tuberculosis and HIV/AIDS at a reference hospital, Belo Horizonte”, which was approved by the Research Ethics Committee (Comité de Ética em Pesquisa, COEP) of the Federal University of Minas Gerais (Universidade Federal de Minas Gerais, UFMG) (CAAE: 23692713.3.0000.5149) and of FHEMIG (CAAE:23692713.2.3001.5124) in 2014.

**Results**

Six co-infected patients were monitored, with a mean age of 37.5 years old (Standard Deviation=9.52) at treatment initiation. Three were male and three were female (Figure 1). All patients were diagnosed with pulmonary TB and were new cases, that is, had never undergone anti-TB treatments or had undergone it for up to 30 days. The patients reported in cases 4 and 6 also presented ganglionic TB. In cases 2 and 5, the TB diagnosis was of the probability type; the others had confirmed diagnoses and were treated. TB treatment length varied from six to seven months.

The HIV diagnoses occurred in the 2014-2016 period, except for the patient in case 1, who was diagnosed in 2007. Of the total patients, 4/6 (66.6%) required hospitalization during the monitoring period. The patients reported in cases 4 and 6 needed two hospitalizations, and cases 3 and 5 underwent one hospitalization each.

Most of the patients (cases 3, 4, 5 and 6) and cases 3 and 5 underwent one hospitalization each.

The patient in case 1 presented a severe adverse reaction of rash caused by efavirenz and required changes in pharmacotherapy for TB and HIV/AIDS (Figure 1).

The mean number of meetings with the pharmacist was 6.33 (Standard Deviation=0.82). A total of 69 DRPs were identified, of which 40/69 (58.0%) were related to adherence, 17/69 (24.6%) to indication, 8/69 (11.6%) to safety, and 4/69 (5.8%) to effectiveness. The causes for non-adherence were as follows: not understanding the instructions, 16/69 (23.2%); very expensive medication, 11/69 (15.9%); unavailable medication, 9/69 (13.1%); and preferring not to use the medications, 4/69 (5.8%).

Two patients presented virological failure due to viral resistance to efavirenz at the end of the TB treatment and needed to change the scheme to treat HIV.

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[2] Method proposed by Cipolle, Strand & Morley (2012) was used for MTM.

[3] It involves countless medications with clinically important and potential drug interactions, in addition to other associated diseases.

[4] This case series is unique and, to our knowledge, it is the first study in which the researchers holistically monitored and assessed pharmacotherapy in patients co-infected with TB and HIV/AIDS.

[5] Patients present peculiar characteristics resulting from co-infection, as well as other clinical conditions that increase pharmacotherapy complexity and interfere with the treatment outcomes.

[6] Monitoring centered on the patients’ pharmacotherapy needs is fundamental to optimize the outcomes.

[7] The number of published studies on pharmacotherapy monitoring in TB and HIV/AIDS co-infection is low.

[8] Medication Therapy Management (MTM) can reduce the impact of the TB and HIV/AIDS co-infection on public health, contributing to treatment effectiveness and safety.

[9] This study aims at describing cases of co-infected patients exposed to the treatment recommended by the Ministry of Health for TB and HIV/AIDS and followed-up at a Reference Hospital in infectious diseases.

[10] In addition to identifying, classifying and solving the DRP outcomes, as well as the clinical and pharmacotherapeutic situation.

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Figure 1. Characteristics of the patients included in the study (n=6). Belo Horizonte, Minas Gerais, Brazil, 2015-2016.

<table>
<thead>
<tr>
<th>Case, Age, Gender</th>
<th>TB schemes</th>
<th>HIV schemes</th>
<th>Viral load (Copies/mL)</th>
<th>CD4+ T cells (copies/μl)</th>
<th>Associated diseases</th>
<th>Drug-Related Problem</th>
<th>Clinical and pharmacotherapeutic situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5, 19, F</td>
<td>RMP+INH+PZA+ATZ/r +ETH + S+O+ETH</td>
<td>TDF+3TC+EFV</td>
<td>Initial: 5,975,406</td>
<td>Final: 5,317</td>
<td>Alopecia, hypothyroidism, and esophageal candidiasis</td>
<td>Untreated condition: 4</td>
<td>Dose too low: 1</td>
</tr>
<tr>
<td>6, 33, M</td>
<td>RMP+INH+PZA+ATZ/r +ETH + S+O+ETH</td>
<td>TDF+3TC+EFV</td>
<td>Initial: 13,222</td>
<td>Final: 181,052</td>
<td>Candidiasis and proprangypenal herpes</td>
<td>Untreated condition: 5</td>
<td>Undesirable effect: 1</td>
</tr>
</tbody>
</table>

3TC: lamivudine; ABC: abacavir; ATZ/r: atazanavir/ritonavir; AZT: zidovudine; EFV: efavirenz; ETH: ethambutol; INH: isoniazid; O: ofloxacin; PZA: pyrazinamide; RAL: raltegravir; S: streptomycin; TDF: tenofovir disoproxil fumarate; DRP: Drug-Related Problem; TB: Tuberculosis; HIV: Human Immunodeficiency Virus; < Detection Lim.: Below the detection limit. 1DRPs identified through the Pharmacotherapy Workup (PW) method.

Discussion

Based on this case series, many gaps were observed with regard to knowledge on the follow-up of patients with TB and HIV/AIDS co-infection, especially in the real world; in addition to the need to understand the experience with medication use, as the most frequent DRPs were related to adherence. Difficulties in monitoring were identified in a study conducted with co-infected individuals. Treatment was interrupted due to various reasons, such as death prior to the approach, transfer to another health service, and treatment abandonment. 11 In this case series, there were also return visits outside the scheduled date for two patients. This may interfere with care logistics, as well as with treatment effectiveness, as the individual spends days without using the medications, although they are available in the Unified Health System.

Despite being an ancient disease, TB is still underestimated, and HIV, despite being a more recent disease, carries with it a significant social stigma, especially when both diseases are associated. 11 Adherence is a complex network that involves costs regarding treatment, social services, social stigma of the disease itself, acceptance of the disease, individual’s socioeconomic level, low schooling and prejudice, 11 in addition to involving the entire patient’s experience with the medication. This can lead patients to change their own therapeutic regimen without medical indication, which directly interferes with treatment effectiveness. 11

The need for additional pharmacotherapy was also highly frequent in this study, which warns about the need to assess the presence of untreated clinical conditions during the entire follow-up. These conditions may be caused by the treatment itself or by prophylaxis and treatment requirements for concomitant acute (sinusitis, candidiasis, herpes) or chronic (depression, hypothyroidism, epilepsy) diseases, as well as to the need of intensive care, for being severe cases.

Described for most of the patients in this study, hepatotoxicity is very frequent, as the cure requires using medications that may potentially cause this ADR. There were also changes in the ART, and it is important to monitor the effectiveness of this treatment, as not all the patients achieve virological suppression of HIV after the end of the TB treatment.
The change in the HIV treatment scheme to atazanavir/ritonavir due to a severe adverse reaction of rash caused by efavirenz in the patient from case 2 led to the need to change the TB scheme to rifabutin. This drug is not available in a combined fixed dose, which led the patient to use more tablets. In the study period, raltegravir was used as a rescue medication. Recently, there has been a change in the clinical protocol of the HIV/AIDS treatment in patients co-infected with TB, with the inclusion of integrase inhibitors as an alternative to treatment with efavirenz. Such knowledge and the incorporation of these medications as therapeutic alternatives are important in patient-centered care. This alternative is paramount to prevent DRPs, to increase effectiveness and safety, and to promote rational use of medications.\textsuperscript{13,14} However, for being a new medication as a first choice, pharmacovigilance actions to monitor treatment effectiveness must be performed.

One of the study limitations is the absence of monitoring to assess the effectiveness of the antiretroviral therapy once TB was cured. The study design does not allow generalizing the data due to the number of cases. However, the population of co-infected patients requires individualized therapeutic care, considering the severity of the cases and the significant number of follow-up losses. Therefore, case reports and case series are important in the literature and in the clinical practice, due to their high sensitivity to detect unexpected news and to guide the development of other studies.\textsuperscript{15} After the development of this case series, new studies of this research group are in progress.

Conclusion
There was a high number of adherence and indication DRPs in the co-infected patients. Monitoring of treatment effectiveness and safety should be performed, due to the higher susceptibility to adverse reactions such as hepatotoxicity.

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Collaborators
NHR, WSC and JAS participated in the conception, design and planning of the study. UCM participated in data collection, discussion of the results and critical review of the article. WSC, AMR and SSM coordinated the project, participated in data analysis and discussion and critically reviewed the article. All the authors are responsible for the information presented in the paper and approved the final version of the manuscript.

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Conflict of interest statement
The authors declare that there is no conflict of interest in relation to this article.