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

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Abstract

Objectives: To describe cases of patients with tuberculosis (TB) and HIV / AIDS coinfection 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 na 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.

Gerenciamento da terapia medicamentosa em pacientes com tuberculose e HIV/aids: série de casos

Resumo

Objetivos: Descrever casos de pacientes com coinfecção 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 coinfectados 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 coinfectados 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 coinfectados. 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 considered 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.[8,9] 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.[10] 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 concomitantly with the HIV/AIDS diagnosis, aged 18 years old or more, and who accepted to participate in the study. The patients co-infected with TB and HIV/AIDS who met the following criteria were excluded: treatment abandonment, death, transfer prior to the approach, cognitive deficit, and change in diagnosis.

Initially, the patients were invited to participate in the study in a private room after medical consultation at the day care hospital or at the ward during hospitalization by signing the Informed Consent Form (ICF). Each case was monitored by the pharmacist until the end of the TB treatment, totaling a minimum of six meetings. The PW method proposed by Cipolle, Strand & Morley (2012) was used for MTM. The objective of this monitoring was to prevent, identify and solve DRPs. DRPs can be due to various reasons and are classified as follows: indication (DRP 1 – Unnecessary medication; DRP 2 – Need for additional medication), effectiveness (DRP 3 – Ineffective medication; DRP 4 – Low dose), 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).[2]

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 (*Comitê 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) presented hepatotoxicity with increase in transaminases and bilirubins. The course of action adopted was suspending the basic scheme and initiating the special one consisting of streptomycin, ofloxacin and ethambutol. The basic scheme was restarted, drug by drug, beginning with rifampicin and ethambutol, in order to minimize Adverse Drug Reactions (ADRs) and monitor liver function (Figure 1).

The patient in case 2 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.

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

Case, Age, Gender	TB schemes	HIV schemes	Viral load (Copies/mL)	CD4+ T lymphocytes (copies/µl)	Associated diseases	Drug-Related Problem[1]	Clinical and pharmacotherapeutic situation
1, 30, F	RMP+INH+PZA+ETH RMP+INH	AZT 3TC EFV TDF+3TC+EFV	Initial: 7,019 Final: 47	Initial: 178 Final: 281	Recurrent rhinosinusopathy and depression.	Untreated condition: 4 Non-adherence to the treatment: 11	Solved for TB, stable for HIV, no improvement for anxiety and depression, and solved for rhinosinusitis.
2, 38, M	RMP+INH+PZA+ETH Rifabutin+INH+PZA+ETH Rifabutin+INH +ETH	TDF+3TC+EFV TDF+ 3TC ATZ/r TDF 3TC RAL	Initial: 1,637,085 Final: <Detection Lim.	Initial: 25 Final: 207	Herpes zoster and Wallemberg's Syndrome	Untreated condition: 1 Most effective product available: 1 Undesirable effect: 2 Non-adherence to the treatment: 1	Solved for TB, stable for HIV and solved for herpes zoster.
3, 48, F	RMP+INH+PZA+ETH S+O+ETH RMP+ETH RMP+ETH+INH RMP+INH+PZA+ETH RMP+INH	TDF+3TC+EFV	Initial: 690,550 Final: <Detection Lim.	Initial: 101 Final: 554	Seizure and epilepsy	Untreated condition: 1 Undesirable effect: 1 Non-adherence to the treatment: 12	Solved for TB, stable for HIV, partially improved for seizure and epilepsy.
4, 34, M	RMP+INH+PZA+ETH S+O+ETH RMP+ETH RMP+ETH+INH RMP+INH+PZA+ETH RMP+INH	TDF+3TC+EFV ABC+3TC+ EFV	Initial: 39,220 Final: <Detection Lim.	Initial: 202 Final: 762	Osteomyelitis, prostatitis, Candida urethritis, pulmonary focus sepsis	Untreated condition: 2 Drug interaction: 1 Undesirable effect: 2 Non-adherence to the treatment: 13	Solved for TB, stable for HIV, and solved for prostatitis, osteomyelitis and Candida urethritis.
5, 19, F	RMP+INH+PZA+ETH S+O+ETH RMP+ETH RMP+ETH+INH RMP+INH+PZA+ETH RMP+INH +ETH	TDF+3TC+EFV TDF+ 3TC ATZ/r	Initial: 5,975,406 Final: 5,317	Initial: 84 Final: 485	Alopecia, hypothyroidism, and esophageal candidiasis	Untreated condition: 4 Dose too low: 1 Undesirable effect: 1 Medication not effective for the condition: 1	Solved for TB, stable for HIV, alopecia, and hypothyroidism.
6, 33, M	RMP+INH+PZA+ETH S+O+ETH RMP+ETH RMP+ETH+INH RMP+INH+PZA+ETH RMP+INH	TDF+3TC+EFV TDF+ 3TC ATZ/r	Initial: 13,222 Final: 181,052	Initial: 204 Final: 215	Candidiasis and oropharyngeal herpes	Untreated condition: 5 Undesirable effect: 1 Medication not effective for the condition: 1 Non-adherence to the treatment: 3	Solved for TB, solved for candidiasis, and stable for HIV.

3TC: lamivudine; ABC: abacavir; ATZ/r: atazanavir/ritonavir; AZT: zidovudine; EFV: efavirenz; ETH: ethambutol; INH: isoniazid; O: ofloxacin; PZA: pyrazinamide; RAL: raltegravir; RMP: rifampicin; S: streptomycin; TDF: tenofovir disoproxil fumarate; DRP: Drug-Related Problem; TB: Tuberculosis; HIV: Human Immunodeficiency Virus; < Detection Lim.: Below the detection limit. [1]DRPs 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. [9] 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.[12]

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.[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.[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.

References

1. Cipolle RJ, Strand LM, Morley PC. Pharmaceutical CarePractice: The patient-centered approach to medication management services. New York: McGraw-Hill; 2012.
2. Ramalho de Oliveira D. Atenção Farmacêutica: da filosofia ao gerenciamento da terapia medicamentosa. São Paulo: RCN Editora; 2011.
3. WHO - WORLD HEALTH ORGANIZATION, 2020. Global Tuberculosis Report. Available in: https://www.who.int/publications/i/item/9789240037021 Accessed on 29th Oct 2021.
4. Getahun H, Gunneberg C, Granich R *et al*. HIV infection–associated tuberculosis: the epidemiology and the response. Clin Infect Dis. 2010;50:S201–7. doi: 10.1086/651492.
5. Silva DR, Menegotto DM, Schulz LF *et al*. Características clínicas e evolução de pacientes imunocomprometidos não HIV com diagnóstico intra-hospitalar de tuberculose. J Bras Pneumol. 2010;36(4):475-484. DOI: 10.1590/S1806-37132010000400013.
6. Ford N, Matteelli A, Shubber Z et al. TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: a systematic review and meta-analysis. J Int AIDS Soc. 2016; 19:207-14. DOI: 10.7448/IAS.19.1.20714.
7. Lobo IS, Carvalho WS, Resende NH. Drug utilization research in coinfected patients with tuberculosis and HIV/AIDS. Rev Bras Farm Hosp Serv Saude. 2020;11(1):0420. DOI: 10.30968/rbfhss.2020.111.0420.
8. Resende NH, Miranda SS, Ceccato MGB, *et al*. Assessment of factors associated with potential drug-drug interactions in patients with tuberculosis and HIV/AIDS. Rev. Soc. Bras. Med. Trop. 2021; 54. DOI: 10.1590/0037-8682-0103-2021
9. Resende NH, Miranda SS, Ceccato MGB, *et al*. Problemas Relacionados ao uso de Medicamentos em pacientes com tuberculose e HIV/aids em hospital referência. einstein (São Paulo). 2019;17(4):eAO4696. DOI: 10.31744/einstein_journal/2019AO4696
10. EQUATOR Network. Enhancing the QUAlity and Transparency Of health Research. Available in: https://www.equator-network.org Accessed on 26th Nov 2021.
11. Rossetto M, Maffacciolli R, Rocha CMF, *et al*. Coinfecção tuberculose/HIV/aids em Porto Alegre, RS - invisibilidade e silenciamento dos grupos mais afetados. Rev Gaúcha Enferm. 2019;40:e20180033. doi: 10.1590/1983-1447.2019.20180033.
12. Ramalho DO, Brummel AR, Miller DB. Medication therapy management: 10 years of experience in a large integrated health care system. J Manag Care Pharm, 2010; 16(3):185-95. doi: 10.18553/jmcp.2010.16.3.185.
13. Ministério da Saúde (MS). Comissão Nacional de incorporação de tecnologias (Conitec). Dolutegravir para pacientes coinfectados com HIV e tuberculose. Brasília, 2019. Available in:http://conitec.gov.br/images/Consultas/Relatorios/2019/Relatorio_Dolutegravir_HIV_TB_CP_49_2019.pdf Accessed on 29th Oct 2021.
14. Ministério da Saúde (MS). Substituição do ofício circular nº 46/2019/CGAHV/DCCI/SVS/MS - Ampliação do uso de do-

lutegravir (DTG) 50mg 2X/dia para paciente com coinfecção tuberculose e HIV em uso de rifampicina. Brasília, 2019. Available in: https://siclom.aids.gov.br/informativo/Informe%20n%C2%BA%2001_20%20-%20Of%C3%ADcio%20circular%2047_19%20-%20DTG%20para%20coinfec%20TB.HIV.pdf Accessed on 29th Oct 2021.

15. Albrecht, J, A Meves, e M Bigby. Case reports and case series from Lancet had significant impact on medical literature. J Clin Epidemiol, 2005: 1227–1232. DOI: 10.1016/j.jclinepi.2005.04.003.