Aspects associated with drug resistance in people with tuberculosis/HIV: an integrative review

Aspectos associados à drogarresistência em pessoas com Tuberculose/HIV: revisão integrativa

Aspectos relacionados con la drogorresistencia en personas con tuberculosis/VIH: revisión integradora

Vanessa da Frota Santos[1] https://orcid.org/0000-0002-1198-6560
Ana Karoline Bastos Costa[1] https://orcid.org/0000-0002-5994-081X
Ivana Cristina Vieira de Lima[1] https://orcid.org/0000-0002-2698-9086
Marli Teresinha Gimeniz Galvão[1] https://orcid.org/0000-0003-3995-9107

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Corresponding author
Vanessa da Frota Santos
Email: doutorandavanessasantos@outlook.com

Abstract

Objective: To analyze scientific productions on aspects associated with drug resistance in people with tuberculosis (TB)/HIV coinfection.

Methods: Integrative literature review performed in the CINAHL, LILACS, SciELO, Web of Science, SCOPUS, MEDLINE and COCHRANE databases. The following descriptors were used in Portuguese, English and Spanish: HIV, Tuberculosis and Multidrug resistance. In total, 1,177 articles were found and 19 were selected; 1,158 were excluded, of which 41 were duplicates and 1,117 did not answer the research question and addressed other topics, namely: HIV and pneumonia coinfection; impact of multidrug resistance on the lives of people with coinfection, with emphasis on mortality; diagnostic tests for multidrug resistance; and association between HIV and meningeal tuberculosis.

Results: Data were organized into three thematic categories, as follows: Clinical aspects, highlighting: HIV infection, hypoalbuminemia, elevated bacillus load; drug-related aspects, including treatment abandonment, non-adherence to therapy, previous treatment for tuberculosis, drug malabsorption, adverse effects caused by antiretroviral therapy, interaction between treatments for both infections; and social aspects, including hospitalizations, living with other people with multidrug-resistant bacilli, deprivation of liberty, delayed diagnosis and late start of treatment.

Conclusion: The main aspects identified were abandonment of therapy, previous treatment for tuberculosis and inadequate intervention, and these results may also extend to people who do not have coinfection. This review is important to instigate new research, with emphasis on strategies focused on the early identification of people with multidrug resistance, prevention and encouragement of adherence to treatment.

Resumo

Objetivo: Analisar as produções científicas acerca dos aspectos associados à drogarresistência em pessoas com coinfecção Tuberculose/HIV.

Métodos: Revisão integrativa de literatura, realizada nas bases de dados CINAHL, LILACS, SciELO, *Web of Science,* SCOPUS, MEDLINE e COCHRANE. Utilizaram-se dos descritores HIV, Tuberculose e Resistência a múltiplos medicamentos, em português, inglês e espanhol. Encontraram-se 1.177 artigos e selecionaram-se 19, excluíram-se 1.158, 41 duplicados e 1.117, por não atenderem à pergunta de pesquisa e abordarem outras temáticas, como: coinfecção do HIV e pneumonia; impacto da multirresistência na vida de pessoas com coinfecção, destacando-se a mortalidade; testes diagnósticos de multirresistência aos fármacos; e associação entre HIV e tuberculose meníngea.

[1]Universidade Federal do Ceará, Fortaleza, Ceará, Brazil.
Conflicts of interest: none to declare.

Resultados: Os dados obtidos foram organizados em três categorias temáticas: Aspectos clínicos, destacando-se: infecção pelo HIV, hipoalbuminemia, carga elevada do bacilo; Aspectos relacionados aos fármacos, incluindo abandono do tratamento, não adesão à terapia, tratamento prévio para tuberculose, má absorção de medicamentos, efeitos adversos causados pela terapia antirretroviral, interação entre os tratamentos de ambas as infecções; e Aspectos sociais, sinalizando-se hospitalizações, convivência com outras pessoas com bacilos multirresistentes, privação de liberdade, atraso no diagnóstico e início tardio do tratamento.

Conclusão: Os principais aspectos identificados foram o abandono da terapêutica, tratamento prévio para tuberculose e intervenção inadequada, tais resultados, também, podem estender-se às pessoas que não apresentam coinfecção. Enfatiza-se a importância desta revisão para instigar novas pesquisas, com destaque para estratégias com foco na identificação precoce de pessoas com multirresistência, prevenção e incentivo à adesão ao tratamento.

Resumen

Objetivo: Analizar las producciones científicas sobre los aspectos relacionados con la drogorresistencia en personas con coinfección tuberculosis/VIH.

Métodos: Revisión integradora de literatura, realizada en las bases de datos CINAHL, LILACS, SciELO, *Web of Science,* SCOPUS, MEDLINE y COCHRANE. Se utilizaron los descriptores VIH, tuberculosis y resistencia a múltiples medicamentos, en portugués, inglés y español. Se encontraron 1.177 artículos, de los que se seleccionaron 19 y se excluyeron 1.158, 41 duplicados y 1.117 por no abordar la pregunta de la investigación y tratar otros temas, como: coinfección de VIH y neumonía; impacto de la multirresistencia en la vida de personas con coinfección, con énfasis en la mortalidad; pruebas diagnósticas de multirresistencia a los fármacos, y relación entre VIH y tuberculosis meníngea.

Resultados: Los datos obtenidos fueron organizados en tres categorías temáticas: aspectos clínicos, con énfasis en: infección por VIH, hipoalbuminemia, carga del bacilo elevada; aspectos relacionados con los fármacos, como abandono del tratamiento, no adherencia al tratamiento, tratamiento previo para tuberculosis, mala absorción de medicamentos, efectos adversos causados por el tratamiento antirretroviral, interacción entre los tratamientos de ambas infecciones; y aspectos sociales, con foco en internaciones, convivencia con otras personas con bacilos multirresistentes, privación de la libertad, retraso en el diagnóstico e inicio tardío del tratamiento.

Conclusión: Los principales aspectos identificados fueron el abandono del tratamiento, el tratamiento previo para tuberculosis y la intervención inadecuada. Estos resultados también pueden extenderse a las personas que no presentan coinfección. Se resalta la importancia de esta revisión para estimular nuevas investigaciones, con énfasis en estrategias centradas en la identificación temprana de personas con multirresistencia, prevención e incentivo para adherir al tratamiento.

Introduction

Tuberculosis (TB) is among the most frequent infections in people with Human Immunodeficiency Virus (HIV).[1] It is difficult to be diagnosed because the immunodeficiency itself leads to the possibility of modifying the radiological and clinical presentation, and the lower sensitivity to smear microscopy. Although HIV patients at different stages of the disease can be affected by TB, it is more prevalent in those with immune suppression, when it poses a greater risk of progressing to the final stage of the disease and death.[2]

Both infections share sociodemographic risk factors and have higher prevalence among people with less education and income. Furthermore, they are chronic conditions of difficult control and adherence to drugs given the complexity of treatment and side effects.[3]

It is estimated that 10 million people developed TB worldwide in 2017, with estimated 1.3 million deaths, out of which 300,000 associated with HIV. In that year, worldwide, of these 10 million people, 9% were coinfected with HIV.[4] In Brazil, of the 69,509 new TB cases reported in 2016, 6,501 tested positive for HIV, which represents 9.4% of TB/HIV coinfection.[5] The HIV/TB association has become a challenge for both diagnosis and treatment and led to a higher mortality, especially when associated with multidrug resistance.[6]

In 2016, 1,044 cases of resistance to TB drugs were diagnosed in Brazil, and 752 new cases of drug-resistant TB were inserted in the Special Tuberculosis Treatment Information System (Portuguese acronym: SITETB), of which 177 (23.5%) monoresistant, 330 (43.9%) resistant to rifampicin, 49 (6.5%) poly drug resistant, 193 (25.7%) multidrug resistant and three (0.3%) without information.[5]

There are two ways of developing drug-resistant TB. Primary resistance is acquired by people who were never treated for TB and get contaminated with previously resistant bacilli. Secondary resistance or acquired resistance is found in people with initially sensitive TB who become resistant after exposure to drugs. Several factors can cause such resistance, but the following stand out: treatment abandonment; inadequate schemes resulting in the selection of resistant and mutant strains; low adherence to therapy; wide range of systemic diseases and treatments with immunosuppressants.[7]

Some personal aspects are among the predictors for the development of drug-resistant TB, namely alcohol use and HIV infection itself. Multidrug resistance makes the control, prevention and treatment of disease difficult, which can worsen the person's clinical condition, thereby increasing the risks for morbidity and mortality.[1]

Therefore, the World Health Organization (WHO) launched the elimination of the TB endemic as a global objective, with reduction of the number of deaths by 90% and of incidence rates by 80% until year 2030, and disease eradication until 2050. In addition, were launched strategies aimed at supporting these goals, such as the End TB strategy.[2]

Understanding the main aspects that motivate multidrug resistance in people with TB/HIV coinfection is essential for the design of prevention and identification actions and adequate management of this condition, with a view to minimizing preventable deaths. Thus, the objective was to analyze scientific productions on aspects associated with drug resistance in people with TB/HIV coinfection.

Methods

This integrative literature review was developed from the following steps: formulation of the guiding question, definition of the inclusion and exclusion criteria of scientific productions, search in databases, analysis of study abstracts, selection of studies, careful evaluation of the selected studies, and analysis of data[8] and recommendations provided in the PRISMA Statement.[9]

We sought to answer the guiding question that was formulated based on the PICO strategy:[10] what are the aspects associated with drug resistance in people with TB/HIV coinfection? The inclusion criteria were complete articles available electronically in Portuguese, English and Spanish, with no time frame. The following were excluded: publications that did not answer the research question; studies with children and animals; and repeated publications, which were grouped in the database that contained more articles.

The electronic search was performed by two reviewers simultaneously during July and August 2018, in four databases, namely Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin American and Caribbean Literature in Health Sciences (LILACS/BIREME), Web of Science and SCOPUS; in the portal Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed); and in two libraries, Scientific Electronic Library Online (SciELO) and COCHRANE. The descriptors "HIV", "Tuberculosis" and "Multidrug resistance", available in the Medical Subject Headings (MeSH) and in the Health Sciences Descriptors (DeCS) were used in Portuguese, English and Spanish, together with the Boolean operator AND.

From the crossing, 1,177 publications were identified, 19 articles were selected, of which 17 were indexed in MEDLINE and two in SCOPUS. The total of 1,158 articles were eliminated, among which 41 were duplicated and 1,117 did not address the guiding question, but the following themes: HIV/pneumonia coinfection; impact of multidrug resistance on the lives of people with coinfection, with emphasis on mortality; diagnostic tests for multidrug resistance; HIV and TB meningitis associated.

Figure 1 shows the identification, screening and inclusion of articles in this review.

Data analysis was performed independently by two authors, who read and translated the articles in full. In case of doubts, there was a meeting between the reviewers for consensus. The information was transcribed and organized with use of a validated instrument[11] that investigated: authorship, year, country of publication, type of study, aspects associated with drug resistance in people with TB/HIV and the levels of evidence.

The levels of evidence were determined as follows: Level I - Evidence from systematic review or meta-analysis of multiple controlled and randomized clinical studies or from clinical guidelines, based on systematic reviews of controlled and randomized clinical trials; Level II - Evidence from individual controlled and randomized studies; Level III - Evidence from experimental studies without randomization; Level IV - Evidence from cohort or

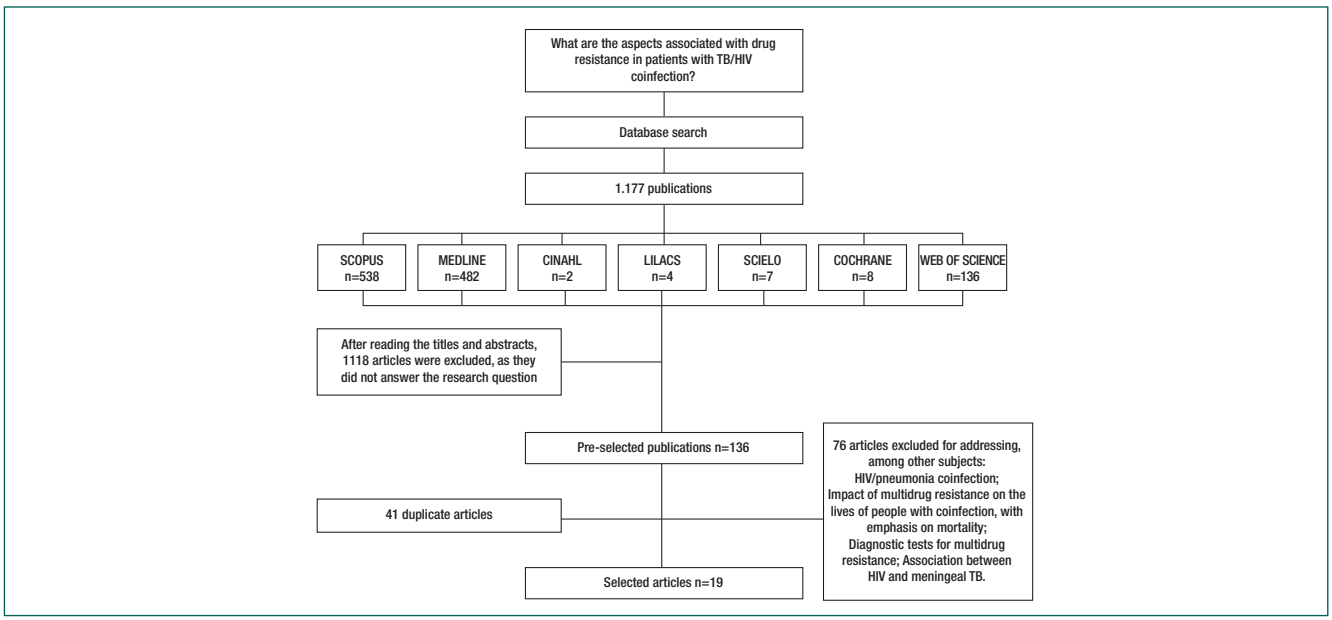

Figure 1. Flowchart of identification, screening and inclusion of studies

case-control studies; Level V - Evidence from systematic review of descriptive and qualitative studies; Level VI - Evidence originating from a descriptive or qualitative study; Level VII - Evidence obtained from opinions of authorities or reports from expert committees.[12]

After analysis, the aspects associated with drug resistance in people with TB/HIV coinfection were grouped into three categories delimited according to the findings of studies, as follows: 1. clinical aspects, 2. drug-related aspects and 3. social aspects. The findings were discussed based on the scientific literature. The integrity of articles and copyright were respected, and no changes to the content found were necessary for the benefit of this study.

Results

As for the characterization of studies, the year of publication ranged from 1992 to 2017, eight were published in European countries, ten in the United States and one in the African continent. The analysis of the levels of evidence showed the following distribution: one level II;[13] three articles classified as level IV;[14-16] five as level V;[17-21] and ten articles as level VI.[22-31] Descriptive and cross-sectional studies stood out (Chart 1).

Aspects related to drug resistance in people with TB/HIV coinfection were classified into one of three categories: a) clinical aspects, b) drug-related aspects, and c) social aspects. Category 1 addressed the clinical aspects that influence the higher drug resistance in people with TB/HIV coinfection. The HIV infection itself is emphasized, given its strong relation with the development of multi resistance to TB drugs in people with coinfection. Another related aspect was malnutrition-associated hypoalbuminemia, which may impair the host's immunity with *Mycobacterium tuberculosis*. The high bacillus load can be considered a cause of drug resistance, since the high bacterial load in the body may be related to the difficulty in treatment (Chart 1).

Category 2 referred to drug-related aspects, highlighting that abandonment of TB treatment is essential for developing drug resistance in people with TB/HIV coinfection, in addition to non-adherence to therapy, inadequate treatment and TB treatment failures. Prior treatment for TB was another factor, because of its direct relation to the development of multidrug resistance, as well as the malabsorption of medications and adverse effects caused by antiretroviral therapy. Another aspect identified was the interaction between treatments of both infections that results in a reduced concentration of antituberculosis drugs in the blood when associated with antiretroviral drugs (Chart 1).

Chart 1. Characterization of selected articles regarding authorship, year of publication, country of publication, type of study, aspects associated with drug resistance in people with TB/HIV coinfection and level of evidence

Author/ Year	Country of publication	Type of study	Aspects associated with drug resistance in people with TB/ HIV coinfection	Level of evidence*
Fischl et al., 1992[14]	United States	Case-control	HIV infection; Hospitalizations; Exposure to other people with multidrug-resistant TB.	IV
Sacks et al., 1999[22]	United States	Prospective descriptive	HIV infection; Previous treatment for TB.	VI
Campos et al., 2003[15]	United States	Case-control	Inadequate treatment; Low adherence to treatment; HIV infection.	VI
Aaron et al., 2004[17]	England	Literature review	HIV infection; Malabsorption of drugs; Treatment abandonment.	V
Drobniewski et al., 2005[25]	England	Cross-sectional	Inadequate treatment	VI
Kawai et al., 2006[30]	United States	Descriptive longitudinal	Previous treatment for TB; HIV infection; Non-availability of susceptibility tests for multidrug-resistant bacilli.	IV
Vermund; yamamoto, 2007[21]	Scotland	Literature review	Treatment abandonment; Inadequate treatment.	V
Kim et al., 2007[28]	United States	Cross-sectional	Hipoalbuminemia; Malnutrition.	VI
Bifani et al., 2008[23]	United States	Cross-sectional	HIV infection	VI
Chakraborty et al., 2010[24]	England	Cross-sectional	Excessive use of first-line drugs; Treatment abandonment.	VI
Hom et al., 2012[27]	United States	Cross-sectional	HIV infection	VI
Munawwar; singh, 2012[20]	Scotland	Systematic review	HIV-associated factors; Exposure to other people with TB; Increased adverse effects of ART; Poor absorption of drugs with poor pharmacokinetics; Malnutrition; Delay in diagnosis.	V
Janbaz et al., 2012[19]	England	Literature review	Treatment abandonment	V
Mclleron et al., 2012[29]	United States	Descriptive longitudinal	Inadequate treatment	VI
Berhan; berhan; yizengaw, 2013[18]	Ethiopia	Meta-analysis of longitudinal and cross-sectional studies	Previous treatment for TB	V
Kock et al., 2014[13]	United States	Randomized crossover clinical trial	Interaction between antituberculosis and antiretroviral drugs	II
Elmi et al., 2015[16]	Italy	Case-control	Low adherence to treatment; Treatment abandonment; HIV infection; Previous treatment for TB; High bacterial load; Exposure to other people with multidrug-resistant TB.	IV
Heysell et al., 2016[26]	France	Cross-sectional	Treatment abandonment	VI
Rockwood et al., 2017[31]	United States	Cross-sectional	Deprivation of liberty	VI

* Level I - Evidence from systematic review or meta-analysis of multiple controlled and randomized clinical studies or from clinical guidelines, based on systematic reviews of controlled and randomized clinical trials; Level II - Evidence from individual controlled and randomized studies; Level III - Evidence from experimental studies without randomization; Level IV - Evidence from cohort or case-control studies; Level V - Evidence from systematic review of descriptive and qualitative studies; Level VI - Evidence from a descriptive or qualitative study; Level VII - Evidence obtained from opinions of authorities or report from expert committees

With regard to category 3, the following stood out: hospitalizations in places with people with HIV living with others who had multidrug-resistant bacilli or active TB in hospital environments, and contact with these people in waiting rooms for consultations, which increases the risk for transmission of resistant strains; as well as the deprivation of liberty of these people and their permanence in prisons. In addition, the delay in diagnosis and the consequent late start of TB treatment were also considered predictive aspects of drug resistance (Chart 1).

Discussion

There is a strong relation between HIV infection and the development of multidrug resistance to TB treatment in people with coinfection, and immunosuppression stands out as a factor influencing this process.[23] Another related factor is malnutrition caused by low calorie intake, frequent nausea, vomiting and diarrhea, associated with ART.[20] This can impair the immunity of the host with *Mycobacterium tuberculosis* by decreasing the production of cytokines, including Interferon gamma,

or by reducing CD4+ T and CD8+ T cells, in addition to the relationship with failures in the treatment of people with TB/HIV coinfection.[28]

In addition, the high *Mycobacterium tuberculosis* load can be considered a cause of drug resistance. A high bacterial load in the organism may be related to treatment difficulties and lead to the permanence of bacterial positivity in the smear of Bacillus Alcohol-Acid Resistant (BAAR) and increased drug resistance. This relationship is much more potent in people with previous treatment for TB compared to people undergoing primary treatment.[16]

The abandonment of TB treatment is another fundamental factor for the development of drug resistance in people with coinfection. It can be a result of double treatment and lead to a greater propensity to abandon therapy, given the high drug load and toxicity or side effects of drugs.[26] A study conducted in Morocco found that among 2,532 people treated for TB, 10% had adverse reactions, of which gastrointestinal (7.4%) reactions prevailed, followed by cutaneous (3.7%), hepatic (2.0%), articular (1.14%), immunoallergic (1.07%), neuropsychiatric (0.7%) and to a lesser extent, ocular reactions (0.1%).[32]

Adverse drug reactions represent a potential obstacle to completing treatment and may negatively affect the expected result. Documentation, evaluation, management and immediate intervention on symptoms of adverse drug reactions is important to achieve better adherence to treatment and improve its results.[33]

In a meta-analysis, the success rate of TB treatment was significantly lower among people with HIV (67%) compared to those that did not have the virus (81%). In addition, for almost 50% of people in which antituberculosis treatment was not successful, death was the outcome.[34]

Thus, measures to reduce the treatment interruption rates should be developed through the provision of social and psychological support to the most vulnerable people, in addition to other strategies, such as travel allowance and food supplies, given the effects caused by pharmacological therapy.[26] Strengthening the care services for people with TB/HIV is also important through measures such as Directly Observed Treatment (DOT) by specialized professionals.[18]

Non-adherence to treatment was also cited as a cause of the development of resistance to antituberculosis drugs because of the infrequent and irregular medication intake.[16] In a study conducted in Ethiopia, the following factors resulted in treatment failures: living far from the capital, having low weight at the beginning of TB treatment, being bedridden and having experienced some side effect of antituberculosis medications.[6]

Another cause was inadequate treatment with fixed prescriptions of rifampicin, isoniazid, pyrazinamide and ethambutol (first-line drugs) according to the patient's weight, as recommended by the WHO. However, these concentrations were not evaluated in all weight ranges, which can cause underdosing, result in prolonged infection, treatment failures and multidrug resistance.[15,25,29] The administration of inadequate doses leads to a higher use of first line without initial and individual assessment of each patient regarding the ideal drug concentration, and causes higher chances of developing multidrug resistance.[24]

Furthermore, prior TB treatment is directly related to the development of multidrug resistance.[30] A worldwide survey conducted by the WHO in 2002-2007 showed a 60% prevalence of multidrug-resistant TB among previously treated cases.[18]

The malabsorption of medications and the consequent reduction of pharmacokinetic action associated with immunosuppression caused by HIV also stood out.[17,20] In addition, the adverse effects caused by antiretroviral therapy can cause multidrug resistance in TB treatment.[20]

Other factors include hospitalizations in places with people living with HIV[14] and contact with people with multidrug-resistant bacilli or active TB, which are predictors for the development of drug resistance. This can be justified by constant visits to care centers for people with TB/HIV coinfection and contact with these people in waiting rooms for consultations, which increases the risk of transmission of resistant strains.[14,20] In addition, the length of stay in institutions with deprivation of liberty increases the risk for developing resistance to antitu-

berculosis drugs in coinfected men. Health systems are precarious in these institutions and people live clustered in poorly ventilated environments. These aspects increase the risk for dissemination of the bacillus, prejudice and fear of disclosure of the diagnosis, and result in interruptions in the treatment of both TB and HIV during incarceration.[31]

The delayed diagnosis of drug-resistant TB and the consequent late start of treatment were also considered predictive factors of drug resistance. These can be caused by the lack of early testing for susceptibility to multidrug-resistant bacilli, which leads to the use of first-line drugs during the first six or nine months. Later, resistance is identified and appropriate therapy with second-line drugs, more toxic and costly, is initiated, thereby generating treatment failures and risks to the person's health, such as increased mortality and prolonged multidrug-resistant TB.[20]

To avoid such conduct, actions are necessary, such as: raising awareness and training the multidisciplinary team regarding diagnosis, treatment and adherence to therapy; testing for HIV serology in all people diagnosed with TB; notification and adequate feeding of information systems.[35] Finally, the importance of creating strategies and the political involvement of managers and health professionals are emphasized for a better quality of life and increased survival of this population.

Conclusion

Several aspects can be predictors for the development of resistance to antituberculosis drugs in people with TB/HIV coinfection, contemplating social and drug-related clinical aspects that damage the health of this population and change the course of the coinfection. Most aspects were drug related and the most common variables were abandonment of therapy, previous TB treatment and inadequate intervention. This review is important for identifying the main aspects associated with drug resistance in people with TB/HIV coinfection, can instigate new studies, particularly those focused on the need to investigate educational strategies directed to the early identification of people with multidrug resistance, prevention, and encouragement of adherence to treatment, with a view to reducing rates of therapy abandonment and mortality. Health professionals must be sensitized about the importance of adequate treatment prescription and the reduction of indiscriminate use of antituberculosis drugs in the search for health promotion and improvement of the clinical condition of these people, including comprehensive prevention strategies. Furthermore, professionals in health services serving this public should receive training on the proper conduct of each case and the importance of interdisciplinary and multidisciplinary work, seeking to promote the construction of comprehensive and articulated care involving programs of both infections.

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