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Compliance with the treatment by patients with the co-infection HIV/tuberculosis: integrative literature review

ADESÃO AO TRATAMENTO POR INDIVÍDUOS COM A CO-INFECÇÃO HIV/TUBERCULOSE: REVISÃO INTEGRATIVA DA LITERATURA

ADHESIÓN AL TRATAMIENTO DE INDIVIDUOS CON LA CO-INFECCIÓN DE HIV/TUBERCULOSIS: REVISIÓN INTEGRADORA DE LA LITERATURA

Lis Aparecida de Souza Neves[1], Renata Karina Reis[2], Elucir Gir[3]

ABSTRACT

This is an integrative review whose objective was to evaluate the evidences available in the literature about the factors associated to the compliance with the treatment by patients with the co-infection HIV/TB. Articles published in the period from 2002 to 2008, in the databases LILACS and MEDLINE were analyzed. The material was categorized according to the year of publication, periodical, study location and factors related to the compliance. The final sample included eight articles. The factors found, associated to the compliance with the treatment of the co-infection HIV/TB, related to: the individual and his lifestyle (previous TB treatment, fear of stigma and discrimination, use of chemical substances, depression, social support); the disease and the medication (type of medication regime, use of other medication, adverse effects, difficulty to diagnose TB in these patients); and the health services (operational problems to follow up the treatment, training of the professionals, supervision, different locations to treat TB and HIV).

KEY WORDS
Acquired Immunodeficiency Syndrome.
HIV.
Tuberculosis.
Treatment refusal.
Patient dropouts

RESUMO

Trata-se de revisão integrativa cujo objetivo foi avaliar as evidências disponíveis na literatura sobre os fatores associados à adesão ao tratamento por pacientes com a co-infecção HIV/TB. Foram levantados artigos publicados no período de 2002 a 2008, nas bases de dados LILACS e MEDLINE. O material foi categorizado de acordo com ano de publicação, periódico, local do estudo e fatores relacionados à adesão. A amostra final foi composta por oito artigos. Os fatores encontrados, associados à adesão ao tratamento da co-infecção HIV/TB, relacionam-se: ao indivíduo e ao estilo de vida (tratamento prévio de TB, receio de estigma e discriminação, uso de substâncias químicas, depressão, suporte social), à doença e aos medicamentos (tipo de regime medicamentoso, uso de outros medicamentos, efeitos colaterais, dificuldade de diagnóstico de TB nestes pacientes), e aos serviços de saúde (problemas operacionais para acompanhar o tratamento, treinamento dos profissionais, supervisão, locais distintos para atendimento de TB e de HIV).

DESCRITORES
Síndrome de Imunodeficiência Adquirida.
HIV.
Tuberculose.
Recusa do paciente ao tratamento.
Pacientes desistentes do tratamento.

RESUMEN

Se trata de una revisión integradora cuyo objetivo fue evaluar las evidencias disponibles en la literatura sobre los factores asociados a la adhesión al tratamiento de pacientes con la coinfección HIV/TB. Fueron recopilados artículos publicados en el período de 2002 a 2008, en las bases de datos LILACS y MEDLINE, se categorizaron de acuerdo con el año de publicación, periódico, local del estudio y factores relacionados con la adhesión. La muestra final se compuso de ocho artículos. Los factores asociados con la adhesión al tratamiento de la coinfección HIV/TB encontrados fueron: relacionados al individuo y el estilo de vida (tratamiento previo de TB, recelo a estigma y discriminación, uso de sustancias químicas, depresión, soporte social); a la enfermedad y a los medicamentos (tipo de régimen medicamentoso, uso de otros medicamentos, efectos colaterales, dificultad de diagnóstico en estos pacientes) y a los servicios de salud (problemas operativos para seguimiento del tratamiento, entrenamiento de los profesionales, supervisión, locales distintos para la atención de TB y HIV).

DESCRIPTORES
Síndrome de Inmunodeficiencia Adquirida.
VIH.
Tuberculosis.
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INTRODUCTION

The Human Immunodeficiency Virus (HIV) was identified little more than two decades ago, but the number of infected and ill patients has steeply increased in this short period. HIV is a retrovirus that compromises cellular immunity, making the patient susceptible to the development of opportunistic infections[1].

Nowadays, tuberculosis (TB) has been considered one of the diseases most associated with HIV infection, as the latter is considered one of the main risk factors in the progression of latent infection by the TB bacillus to active disease[2].

HIV/aids patients' individual, social and program vulnerabilities negatively contribute to tuberculosis co-infection, as TB remains one of the main Public Health problems for developing countries[3]. TB is directly related to poverty, bad income distribution and accelerated urbanization[4], colliding with the HIV/aids epidemic, which is facing an increasing pauperization process.

According to the World Health Organization, Brazil ranks 14th among 23 countries responsible for 80% of all tuberculosis cases around the world[5], with an estimated prevalence of 58/100,000 cases/inhabitants and about 100,000 new cases per year. On the other hand, until June 2008, 506,499[6] cases of aids had been notified, with an estimated number of approximately 600,000 HIV-positive individuals.

According to the Ministry of Health[6], in 2006, 83,977 new TB cases were notified in Brazil, 7,557 of which co-infected with HIV (9%). The states with the highest percentages are Santa Catarina (20.25 %), Rio Grande do Sul (19.9 %) and São Paulo (15.6 %). It is estimated that 18% of HIV/aids patients in the country suffer from TB, which is one of three main causes of death by infectious disease in this group.

HIV/TB co-infection strongly affects both diseases' epidemics and is also responsible for the increase in mortality ratios, turning into a challenge for public health.

The main problem appointed to treat both illnesses is non-adherence[4], which entails increased incidence and mortality ratios.

The issue of aids treatment adherence gained relevance in 1996, when antiretroviral therapy (ARV) was introduced as a part of the Brazilian policy of universal and free access to health services and drugs. Factors jeopardizing the success of the universal and free medication distribution program include patients' adherence to antiretroviral therapy[7].

Non-adherence to the ARV medication regimen is considered one of the main dangers for individual treatment response[8], contributing to the increase in mortality and morbidity ratios. It is also directly related to therapeutic failure, facilitating the emergence of HIV strains resistant to existing drugs, implying the need to use combinations with other drugs, which can jeopardize treatment adherence even further.

With regard to TB, patients who abandon treatment become an important source of bacillus transmission, prolonging infectiousness, causing individual and public health damage, as this can lead to a rise in multiple drug resistance ratios.

Knowledge on factors associated with treatment adherence in co-infected patients is extremely important to redirect strategies that guide health actions aimed at enhancing cure and non-dissemination of TB, and also to improve the quality of life of HIV patients.

In the attempt to contribute and add up to efforts to achieve treatment excellence for co-infected patients, this research aimed to assess available evidence in literature on the factors associated with treatment adherence in HIV/TB co-infected patients.

OBJETIVE

To assess available evidence in literature on the factors associated with treatment adherence in HIV/TB co-infected patients.

The main problem appointed to treat both illnesses is non-adherence, which entails increased incidence and mortality ratios.

METHOD

An integrative literature review was carried out, which is a *way to investigate existing studies with a view to reaching conclusions on a particular topic*[9]. It is considered a strategy used to identify existing evidence, supporting health practice in different specialties.

The methodological procedures used to elaborate this integrative review were as follows[10]:

1. Formulation of question and review aims;

2. Establishment of article selection criteria;

3. Categorization of studies;

4. Assessment of studies included in the integrative review;

5. Data analysis and presentation of results.

The question that guided this review was: what factors are associated with treatment of HIV/TB co-infection?

To select the articles, two electronic databases were used to broaden the research context, minimizing possible bias in this process of the integrative review elaboration process, which were:

A) LILACS (Latin American and Caribbean Health Sciences Literature): is a directory, part of a set of instruments, which comprises the method created by BIREME/OMS/OPAS to construct a Latin American and Caribbean Health Sciences literature database. It has been available since 1983, is issued every four months and indexes publications in Portuguese and Spanish.

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B) MEDLINE (1997- 2008): is a database for health publications, offering summaries of international papers in English.

The following inclusion criteria were defined: journal articles published in Portuguese, English and Spanish, with abstracts available in the selected databases, covering the period from 2002 to 2008.

Initially, the papers were selected through their abstracts, after which the full versions were recovered and analyzed.

For the sake of analysis and further synthesis of the articles that complies with the inclusion criteria, a synoptic table was elaborated with the following aspects: year of publication, journal of publication, place of study and adherence-related factors mentioned in the paper.

In a first phase, the topic descriptors *AIDS* or *infecções oportunistas relacionadas com a aids* and *tuberculose* were used to survey the articles; next, these descriptors were combined with the word *adesão* or *adherence* with a view to final selection.

The search based on the descriptors alone produced a large number of articles related to other particularities of co-infection, mainly types of treatment, pathogenesis, case reports and prevalence studies. When refining the search through the word *adesão* or *adherence*, six papers were found in LILACS and twelve in MEDLINE. After eliminating repeated articles and reading the full versions, eight articles were selected, which discussed the theme and contained answers to the review question.

The study was carried out between October 2008 and January 2009.

Due to the type of research, the project did not need approval from a Research Ethics Committee.

RESULTS AND DISCUSSION

The eight articles were distributed as follows according to publication year: 02 (25%) articles published in 2002, 01 (12.5%) in 2003, 01 (12.5%) in 2004, 02 (25%) in 2005, 01 (12.5%) in 2007 and 01 (12.5%) in 2008, as presented in Table 1.

Table 1 - Distribution of articles according to publication year, database, language and research country - Brazil - 2002 to 2008

Nº	Publication Year	Database	Language	Research country
01	2002	Medline	English	Brazil
02	2002	Medline	English	Brazil
03	2003	Lilacs	Portuguese	Brazil
04	2004	Medline	English	USA
05	2005	Lilacs	Portuguese	Brazil
06	2005	Medline	English	France
07	2007	Lilacs	Portuguese	Brazil
08	2008	Medline	English	Peru

With regard to language, three (37.5%) articles were published in Portuguese and five (62.5%) in English, two of which were published in Brazilian journals; five studies (62.5%) were developed in Brazil, one in Peru, one in the United States and one in France.

In Brazil, independently of high co-infection ratios, the treatment adherence of aids patients has been a source of concern since the start of antiretroviral therapy, when free medication distribution started for all patients as part of the Unified Health System[7]. In the literature search, many studies on prevalence and co-infection treatment were found in African, Asian and Latin American countries, but available literature on these patients' adherence is practically inexistent, with Brazil at the frontline of articles published on this aspect.

Table 2 shows the seven journals where the papers were published, three of which are focused on infectious diseases, one pneumology, one tuberculosis, one public health and one nursing. This fact shows that publications on TB and aids are found not only in specialized infectology journals, but also in public health and nursing.

Table 2 - Distribution of selected articles according to journal of publication - Brazil - 2002 to 2008

Nº	Authors	Journal
01	Rabahi MF; Rodrigues AB; Queiroz de Mello F; Almeida Netto JC; Kritski AL	Brazilian Journal Infectious Diseases
02	Atomiya AN; Uip DE; Leite OH	Brazilian Journal Infectious Diseases
03	Lana FCF; Rodrigues FG; Diniz MB	REME - Revista Mineira de Enfermagem
04	Friedland G; Abdool Karim S; Abdool Karim Q; Lalloo U; Jack C; Gandhi N; El Sadr W	Clinical Infectious Diseases
05	Oliveira HB; Marin-León L; Gardinali J	Jornal Brasileiro de Pneumologia
06	Fujiwara PI; Clevenbergh P; Dlodlo RA	International Journal Tuberculosis Lung Disease
07	Jamal LF; Moherdaui F	Revista de Saúde Pública
08	Shin S; Muñoz M; Espiritu B; Zeladita J; Sanchez E; ; Rojas C; Arevalo J; Ying W; Caldas A; Sebastian JL	Journal International Association Physicians Aids Care

Some level of non-adherence universally occurs in any country, whether developed or underdeveloped, and even in diseases that involve potentially life risks. Studies carried out to analyze aids patients' adherence confirm that treatment adherence is a complex and multi-causal phenomenon[7,10].

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Although most papers presented broader aspects of HIV/TB co-infection, findings from each articles showed factors associated with treatment adherence as described in Table 3.

Table 3 - Factors associated with treatment adherence of co-infected patients according to article under analysis - Brazil - 2002 to 2008

Article No	Factors associated with adherence
01	Previous TB treatment; use of other drugs.
02	Medication regimen; lack of training for health professionals; Need for hospitalization.
03	Previous TB treatment abandonment; Operating problems to follow TB treatment.
04	Revelation of HIV diagnosis status, with fear of stigma and discrimination; Collateral and drug toxicity effects.
05	Lack of treatment surveillance; Low physician-patient interaction.
06	Patient's disbelief in treatment efficacy; treatment complexity; Inaccessibility and cost of drugs; fear of stigma in society; Physician-patient relationship.
07	Distinct places for TB and HIV care; Need for interprofessional care; TB diagnosis difficulties in AIDS patients.
08	Use of chemical substances; Depression; lack of social support.

After reading the findings, the factors associated with adherence were classified in three analytic categories, shown in Table 4.

Table 4 - Factors associated with treatment adherence of co-infected patients according to analytic category - Brazil - 2002 to 2008

Categories	Factors associated with adherence
Factors related to patient and lifestyle	- previous TB treatment; - patient's disbelief in treatment efficacy; - use of chemical substances; - depression; - revelation of HIV diagnosis status, fear of stigma and discrimination; - lack of social support.
Factors related to disease and treatment	- collateral and toxicity effects of drugs; - medication regimen / treatment complexity; - use of other drugs; - TB diagnosis difficulty in AIDS patients.
Factors related to health services	- operating problems to follow TB treatment; - patient-physician relationship; - drug inaccessibility and cost; - lack of treatment surveillance; - need for interprofessional care; - lack of training for health professionals; - distinct places for TB and HIV care.

Factors related to the patient and lifestyle

Factors related to people and their lifestyle correlate with the socioeconomic-cultural profile, age, depression, social isolation and use of chemical substances.

Previous TB treatment experience is a behavioral variable that can be determined by permanent or prompt contexts. The probability of a new interruption or unsatisfactory adherence is higher among people with a history of treatment abandonment[11]. Patients often perceive the collateral effects only, preferring to interrupt treatment as they do not believe it will offer benefits.

Adherence cannot be forecasted based on patients' behavior; it is a phenomenon related to their experience during the treatment and changes can occur in this period, according to the patients' difficulties and experiences, entailing moments of greater or lesser adherence[12].

Some drugs users' lifestyle can turns into a determining factor for non-adherence, instead of drugs use itself. The use of illegal substances is a factor significantly associated with low adherence[13] and health professionals frequently do not address usage patterns. The stereotypes associated with drugs use make it difficult to approach users in their singularity, preventing the health team from helping them with specific difficulties[12], besides the fact that, generally, these professionals lack specific training.

Depression, negative feelings and loss of hope can reduce motivation for patients to get treatment. For patients with HIV/aids, which remains a disease associated with death, one way to survive is to relegate the disease to the background, not allowing it to occupy a large space in their lives[14]. Thus, treatment is often left aside, as patients feel incapable of maintaining treatment due to the constant reminder of the disease.

HIV and TB patients often self-impose concerns with the revelation of being infected, out of fear that, when their diagnosis is known, they will be subject to prejudice, as both diseases are still a cause of stigma. At the start of the aids epidemic, reports of reduced civil rights were common, due to the HIV diagnosis getting publicly known.

Patients often decide to keep their diagnosis a secret, which can lead to distancing from people who could offer support. Many HIV/aids patients are obliged to pretend or lie on important aspects of their lives, facing constraining situations, such as lying to go to the doctor, hiding or covering up to take the medication, facing the fear of being identified as an HIV patient at the health service, generating a clandestinity that affects their lives in different aspects: affective, professional, social and even the way they conduct treatment itself[14].

The fear of being a victim of prejudice can cause social isolation and restrict interpersonal relations, with a negative impact on the social support network of people living with HIV/aids. Social support plays an important role by decreasing the negative consequences of stressful events, which insufficient support from people in the social, family or community environment seems to negatively influence adherence and can even lead to depression and despair[11].

Factors related to the disease and treatment

Studies show that the collateral effects of the drugs also influence adherence[15,16].

The treatment against TB uses several drugs, as the bacillus causing the disease routinely presents mutations. The initial scheme associates three drugs – rifampicin, hydrazide and pyrazinamide – for 2 months, followed by rifampicin and hydrazide between the third and sixth month[5]. In parallel, antiretroviral medication for continuing use show a large number of collateral effects, including nausea, vomiting, headache and diarrhea, among others; when associated with tuberculostatics, these effects can compromise patients' social life even further.

Other factors are also directly related with medication intake, such as dissolving or swallowing difficulties and intolerance to smell and taste[7].

The larger the number of pills and intakes per day, the more complex treatment adherence becomes[16]. Adequate adherence to concomitant anti-tuberculosis and ARV schemes represent a great challenge, due to the large number of pills to be taken every day. Therefore, whenever possible, delaying the start of ARV treatment is considered in co-infected patients, particularly in those with a less severe immunodeficiency condition from a clinical-laboratory perspective.

Some authors[17] suggest new forms of tuberculostatistics, reducing the number of daily pills, with a view to raising the efficacy of recommended medication scheme administration.

TB is knowingly harder to diagnose in HIV patients. IN this group, extra-pulmonary TB is more frequent, demanding more accurate professional investigation[12]. A large number of cases show negative direct sputum bacilloscopy results, making it fundamental to routinely perform microbacteria cultures for TB diagnosis in HIV patients[5], which is not always possible due to laboratory difficulties to establish this routine.

Factors related to health services

It should be taken into account that treatment adherence is not limited to the traditional clinic and is related not only to how the patient conceives the disease, but also to health service organization[16].

The characteristics of health services and the relation with the received care are appointed as one of the predictive factors of potential non-adherence[18]. A study at a Referral Center for AIDS treatment in São Paulo assesses that so-called *functional accessibility* that is, good bonding and the relation with health professionals, plays a preponderant role in service adherence in terms of *geographical accessibility*[18].

With regard to drug inaccessibility and cost, in Brazil, antituberculostatics and ARV are distributed freely and universally; in some places, however, barriers to start treatment persist due to delayed TB or HIV diagnosis.

The World Health Organization has recommended the strategy to supervise medication intake – DOTS (Directly

Observed Treatment Short-Term), also called Supervised Treatment (ST) since 1993. ST represents an important strategy in TB treatment, as it guarantees that the drugs are being taken correctly and for as long as appropriate; it also permits approximation with the patients' social context and continued monitoring, as a result of bonding between patients and health professionals[16]. It is especially recommended for patients with adherence difficulties, including HIV/TB co-infected patients.

Another important aspect is to guarantee that patients receive quality care in all care-related actions – welcoming, respect for their needs, privacy, social work, making patients acknowledge the service and its professionals as partners to recover their health[17]. In this sense, interprofessional teamwork (physician, nurse, pharmacist, social worker, psychologist) can favor and stimulate the patient's adherence.

TB is a disease that rests on misery and, therefore, is not solved by attacking the disease only, which demands a broader and humanized view from the health team. Specific and periodical training is needed on HIV/TB co-infection management, for all professionals working direct or indirectly in care delivery to TB patients and HIV-positive individuals.

This training should also be offered to hospital workers as, although TB treatment mainly occurs at outpatient level, patients have also been diagnosed in hospitals and are often discharged without proper orientation on treatment continuity.

The fact that, at some services, care is specific to treat only one of the diseases, obliging the patient to seek care at another place in case of co-infection, represents yet another obstacle to good adherence, increasing the frequency of consultations, with professionals who are not always *fine-tuned* on informing the patient.

The extent of tuberculosis and HIV/aids interactions demands articulation among the respective programs' actions, permitting better management of diagnosis, care and control resources for both infections[17].

FINAL CONSIDERATIONS

Scientific literature has not paid much attention yet to treatment adherence regarding HIV/TB co-infection, with Brazil leading these studies.

Multiple factors influence patients' adherence, which can be related to the individual, the disease or health services. Teams should be trained and pay more attention to the presence of living conditions or situations patients experience that can increase vulnerability to adherence interruption.

Technical actions are needed, such as the active search for both illnesses (offering anti-HIV tests and sputum collection with culture for bacilloscopy).

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Services should get structure to offer supervised treatment in the most comprehensive way possible, as it has shown to be an efficient strategy to improve adherence.

Managers from both programs should interact to make efforts aimed at increasing adherence levels and TB cure rates, and also at improving the quality of life of HIV/aids patients.

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