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# Tuberculosis and HIV infection in Brazil: magnitude of the problem and strategies for control

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## ABSTRACT

The aim of the article was to propose, based on an analysis of the current scenario and of the interaction between tuberculosis and AIDS, strategies to minimize the epidemiological impact of one disease over the other in Brazil. The manner by which health policies aimed at controlling the HIV/AIDS epidemic is analyzed – such as access to antiretroviral drugs and campaigns for the early detection of HIV infection and for encouraging adherence to treatment – and their impact on the achievement of goals related to controlling tuberculosis. The implementation of measures for preventing the onset of tuberculosis in HIV-infected individuals, early detection of tuberculosis disease, and ensuring treatment adherence, is discussed. It is commented upon the role that Brazil may assume in the global effort to develop a therapeutic arsenal and the need for integrated work between the fields of tuberculosis and HIV/AIDS.

**KEY WORDS:** Tuberculosis, epidemiology. Tuberculosis, prevention & control. Antibiotics, antitubercular, supply & distribution. Comorbidity. HIV infections, epidemiology. HIV Infections, prevention & control. Anti-HIV agents, supply & distribution. Brazil.

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## INTRODUCTION

The increase of coinfection rates by human immunodeficiency virus (HIV) and the tuberculosis (TB) bacillus has hindered attempts to reduce the incidence of both infections, posing challenges which have been well documented in the past few years. The increase in global prevalence of HIV has severely impacted tuberculosis control programs, especially in countries with high prevalence of the bacillus. HIV has not only contributed towards an increase in the number of cases of TB, but has also been one of the major factors behind the increased mortality seen among coinfecting patients.<sup>7</sup>

In Brazil, about 85 thousand cases of TB and 30 thousand cases of AIDS are registered per year.<sup>\*\*\*</sup> With the exception of oral candidiasis, TB is the opportunistic disease most frequently found among HIV-infected patients, and small-scale studies have shown that TB is also among the major causes of death in this population.<sup>8,9</sup> Whereas the probability of immunocompetent individuals infected with the TB bacillus developing the disease is around 10%

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\* Ministério da Saúde. Secretaria de Vigilância em Saúde. Manual Técnico para o Controle da Tuberculose. Cadernos de Atenção Básica. Brasília (DF); 2002.

\*\* Ministério da Saúde. Secretaria de Vigilância em Saúde. Dados Epidemiológicos -Aids. *Boletim Epidemiol Aids*. 2005; 1(1): p. 26. [Acesso em 6/7/2007] Disponível na URL: [www.aids.gov.br/documentos\\_e\\_publicacoes](http://www.aids.gov.br/documentos_e_publicacoes).

throughout the individual's lifetime, in those coinfecting with HIV and without therapeutic intervention, this probability rises to around 10% per year.<sup>1,4</sup> In 2000 and 2001, respectively, 8.1% and 7.8% of all the cases of TB notified in Brazil, were also infected with HIV. However, this percentage was much higher in states in which the incidence or number of cases of AIDS and/or TB was also higher.\*

In areas of high prevalence of HIV, TB cannot be prevented and effectively treated without the prevention and treatment of HIV/AIDS. Conversely, measures aimed at controlling TB are of fundamental importance to the effectiveness of HIV/AIDS programs.

The aim of the present article was to propose strategies to minimize the epidemiological impact of AIDS over TB in Brazil, based on an analysis of the current scenario and of the interaction between one disease over the other.

### Considerations on specificities in care for tuberculosis and HIV/AIDS

The public TB care network in Brazil was structured and decentralized in the course of the last few decades by means of a control policy firmly grounded on primary health care. On the other hand, the AIDS care network is relatively recent, and is controlled primarily at the secondary and tertiary levels.

Some aspects of the treatment of coinfecting individuals in the public health care network are worthy of note; these include the structure and the geographical location of care. As coinfecting individuals require integral and effective care, the fact of treating TB and HIV/AIDS patients in different locations renders the patient access to care more difficult and costly, thus contributing to lower treatment adherence.

Another aspect of this issue is the changes occurred in the national recommendations for treatment throughout the years, after the importance of the coinfection was set up. During the period in which these recommendations have been published, there has been a change in orientation regarding the priority of treatment. Early on, antiretroviral (ARV) treatment was dominant over TB treatment, that is, the TB treatment regimen was defined according to the antiretroviral regimen used by the patient at the time of TB diagnosis. In subsequent years, the TB regimen became the priority, with

antiretroviral treatment being adapted to it whenever possible.\*\*,\*\*\*

Coinfecting patients require multidisciplinary care, which must include medical and psychological care, social services, legal advice, referral to other specialists and support structures; many of these activities are often available in non-governmental organizations (NGO). In addition, treatment adherence must be stimulated among coinfecting patients; for this there must be a structure capable to rescuing patients from non-adherence or doing inadequate use of medication.

### Evaluation and monitoring strategies

Effective epidemiological surveillance of coinfection can provide important subsidies for its control. To achieve this, a number of programmatic strategies may be adopted.

Both programs work based on the strategy of priority municipalities. This involves the identification of municipalities with relevant prevalences of TB and HIV, which are prioritized with regard to treatment of coinfection. The definition of priority municipalities for TB/HIV coinfection would allow for the targeting and articulation of initiatives, and could prevent the lack or duplication of efforts, in addition to optimizing available resources.

In order to simultaneously evaluate the situation of both TB and HIV in these municipalities, it will be necessary to adopt a series of indicators that can allow one to monitor the current scenario in terms of both epidemiology and health care. We suggest the following indicators for such follow-up:

- percentage of notified TB cases that have been tested for anti-HIV, which is a measure of the concern with detecting coinfection;
- percentage of HIV-infected cases among notified TB cases, which allows one to identify coinfection and monitor its magnitude in these populations;
- percentage of TB cases confirmed by sputum culture among all notified TB cases in HIV/AIDS patients, as an indicator of the reliability of TB diagnosis. Since HIV-infected individuals are more likely to be infected with other mycobacteria than immunocompetent

\* Ministério da Saúde. Programa Nacional de Controle da Tuberculose. Epidemiologia da tuberculose no Brasil-2002.

\*\* Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa Nacional de DST/Aids. Recomendações para tratamento da co-infecção HIV-tuberculose em adultos e adolescentes – 1999; Atualização das Recomendações para Tratamento da Co-Infecção HIV-Tuberculose em adultos e adolescentes – 2000; Recomendações para terapia ARV em adultos e adolescentes – 2001; Recomendações para terapia ARV em adultos e adolescentes infectados pelo HIV-2004. [Acesso em 6/7/2007] Disponível em: [www.aids.gov.br](http://www.aids.gov.br) (área técnica>tratamento de HIV e aids>consensos de terapia>versões anteriores de consensos de tratamento)

\*\*\* Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa Nacional de DST/Aids. Recomendações para terapia anti-retroviral em adultos e adolescentes infectados pelo HIV – 2006. [Acesso em 6/7/2007] Disponível em: [www.aids.gov.br](http://www.aids.gov.br) (área técnica>tratamento de HIV e aids>consensos de terapia).

individuals, a confirmed TB diagnosis may indicate the need for change in ARV regimen;

- percentage of patients under treatment with ARV and rifampicin among all patients under ARV, as an indicator of cases requiring specific ARV for concomitant use with rifampicin, a drug included in the first-line regimen for TB treatment;
- percentage of HIV-infected patients with tuberculin test among the estimated total number of HIV-infected patients seen at the facility. This is an indicator of the quality of health care, given the possibility of prevention of TB in coinfecting patients
- percentage of HIV-infected patients receiving treatment for latent TB among all HIV-infected patients that need chemoprophylaxis.

### Impact of tuberculosis and AIDS on health indicators

Brazil has established as targets for TB control by 2010.\* increasing the detection rate to 90%, the cure rate to 85%, and reducing the treatment non-adherence to 5%.

However, the interaction between AIDS and TB, and the negative impact of one disease on the other may lead to Brazil falling far short of the established goals. In the case of TB, success will not be attained unless the burden and interference of HIV on TB incidence are considered, e.g., for the goal of 90% of case detection rate. TB is widely acknowledged to be more difficult to diagnose in HIV-infected individuals. A high percentage of cases show negative direct sputum bacilloscopy, which makes of routine sputum cultures for mycobacteria an absolute need for TB diagnosis in HIV patients.<sup>3</sup>

As to the remaining goals – increasing the cure rate to 85% and reducing nonadherence to 5% – if these are interdependent where TB prevalence is not influenced by HIV, such relationship is not as clear in regions where this influence is greater. The reasons for this are the high mortality rates among HIV infected people under treatment for TB, which exceed 25% in certain institutions,\*\* resulting in failure to achieve the cure rate goal.

In this scenario, the goal of 90% case detection rate becomes more directly related with the cure rate goal, since TB must be diagnosed in HIV-infected people

as quickly as possible. This is required to prevent dissemination of the disease and its evolution to more severe clinical forms and consequently death, which are responsible for the increase in the case fatality rate in patients under treatment. Ultimately, this would hamper the goal of curing 85% of detected cases.

Thus, in order to reach the defined goals, efforts must be focused on the following objectives: 1 – Preventing the development of TB disease in HIV-positive cases already infected with the TB bacillus (coinfecting individuals); 2 – Early detection of TB disease among HIV-infected cases; and 3 – Ensuring adherence to treatment.

### MEASURES NECESSARY FOR THE CONTROL

#### Prevention of the clinical form of tuberculosis in coinfecting individuals

Focusing efforts on controlling TB/HIV coinfection requires the implementation of measures across different areas, as health care, epidemiological surveillance, and the programmatic area.

Thus, in accordance to the first objective - preventing the appearance of TB disease in HIV-positive individuals already infected with the TB bacillus - two measures are of fundamental importance: the early initiation of ARV therapy and the diagnosis and treatment (chemoprophylaxis) of latent TB infection in HIV-infected individuals.

Initiating ARV treatment as soon as the HIV-positive individual fulfils the necessary criteria is an important action, since HIV is the strongest TB activator.<sup>6</sup> ARV therapy, on the other hand, is currently regarded as the most important protective factor against the development of TB disease in coinfecting cases.<sup>2,10</sup> Therefore, the early detection of HIV seropositivity is an important weapon against TB, allowing the HIV-infected patient to be provided with the necessary clinical and therapeutic care.

Treatment of latent TB infection in HIV-positive people is widely acknowledged to significantly prevent the development of TB.<sup>5</sup> Latent TB diagnosis through skin tests and its effective treatment have been part of the national recommendations on TB for several years.\*\*\* Health care services, however, face certain challenges to the effective implementation of this recommendation by physicians and patients. From the physician's

\* Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa de tuberculose. Diretrizes para o controle da tuberculose. Brasília (DF); 2007.

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perspective, there is the difficulty of incorporating skin tests and prophylactic TB treatment into clinical routine. On the other hand, patient adherence is complicated by a treatment regimen lasting six months and with a daily dose of three pills, which further increases the already enormous amount of medication that HIV patients take daily.

In order to deal with these challenges, it will be necessary first to ensure effective logistics for acquisition and administration of both tuberculin skin tests and isoniazid, thus creating objective conditions for their incorporation into routine care for HIV carriers. All efforts must be focused on patient adherence to the first TB treatment regimen, so as to avoid drug resistance. Analogously, the same recommendation in terms of quality and logistics should also be made for managers and technicians of all administrative spheres. The high level of credibility achieved after years of efforts to ensure that recommendations are followed, may be severely impaired by only a few months of recurrent disorganization. This may lead to the emergence of resistance among health care professionals to following these recommendations, a phenomenon which is already seen in clinical practice. In order to attain the best possible effects in daily practice, these recommendations may be made at the federal level, and, similarly to what has been done in the state of São Paulo, by means of a Ministry of Health decree, to be elaborated jointly by the two programs.

Second, the 300 mg isoniazid pill (INH) should be introduced as quickly as possible into the list of basic anti-TB drugs in order to facilitate adherence to preventive treatment.

Last but not least, we emphasize the importance of promoting research focused on determining the best moment for the introduction (or reintroduction) of chemoprophylaxis. This issue remains currently unresolved due to the lack of knowledge, to this date, about the length of protection provided by INH in an HIV-infected case. In this sense, it will be necessary to finance researches in order to prioritize this subject so as to produce answers based on solid evidences.

In parallel, the detection of HIV-infection in TB patients allows for the planning of a specific treatment and follow-up, with the inclusion of all items necessary for HIV/AIDS care. Moreover, the greater the number of HIV-infected people known in the population, the greater will be the likelihood of an intervention being effective in breaking its transmission chain. As a facilitating measure and similarly to what is already operating in the state of São Paulo state since 1998, offering anti-HIV testing to all patients with recent diagnosis of TB could be made mandatory by Ministry decree. In addition, since the offering and results delivery of anti-HIV testing should be done ideally by

a professional trained in pre- and post-test counseling, this procedure should be incorporated into the training already provided to TB care personnel. The lack of agile release of anti-HIV results in certain services is another problem that can be avoided by the use of rapid anti-HIV tests in TB outpatient services.

### **Early diagnosis of the clinical form of tuberculosis in coinfecting individuals**

The second objective – the early detection of TB-disease – is aimed at reducing the time of the bacillus replication, even when residing within a potentially debilitated organism. Early diagnosis and treatment reduce the risk of pulmonary cavitations, which are the most effective form of the bacillus dissemination and the most severe form of the disease. Early treatment of TB also represents, in the case of HIV infected people, a greater chance of survival. This can be achieved through the implementation of specific treatment prior to disease spreading, which associated with increased risk of death even during treatment with effective drugs. Failing to diagnose and treat active TB cases in a timely manner may ultimately lead to failure to reduce the number of cases and to achieve the expected increase in cure rates.

However, it is insufficient the number of public state laboratories with capacity on rapid detection of TB through methods such as automated culture, mycobacterial identification, and sensitivity testing. It will thus be necessary to identify facilities that may act as reference laboratories for carrying out differentiated diagnostic testing for TB. An example of such relationship is the laboratory network for carrying out CD4 and viral load testing for HIV-positive patients, created in order to ensure, both the technology and the logistics, to turn available the tests necessary to treat and follow up HIV/AIDS patients. In addition to centralized national and state laboratories, this network also relies on reference laboratories at the municipal level, or run by universities. The cost of automated TB diagnosis is higher than that of manual methods. However, the benefits of early diagnosis (13-15 days for the first method and 35-40 days for the second) are clear, especially for the HIV-infected population and for patients where therapeutic failure is suspected, or undergoing retreatment.<sup>3</sup> Similarly to what is done with CD4 and viral load tests in the HIV laboratory network, the on-line registration of all tests generated in laboratories included in this network may also provide an important source of information for both programs, and serve as a sentinel network for the development of drug resistant strains.

The set up of such network would evidently require infrastructure and financial support so that these tests can be performed. To this end, it is of great urgency to

establish means for financing TB diagnosis procedures, including manual BAAR culture, automatic mycobacterial culture, biochemical and molecular mycobacterial identification, and manual and automatic sensitivity tests for *M. tuberculosis*.

### **Treatment adherence**

As to our third objective – treatment adherence – there are many mechanisms capable of promoting the achievement of more satisfactory results. One of the key issues for achieving greater adherence is to establish mechanisms that facilitate patient access to the health care facility, and that encourage patients to do so. This may be either the facility directly responsible for treatment, or that responsible for supervising medication use in facilities in which oriented and supervised treatment has been adopted.

Another important aspect is to ensure that the patient receives high-quality care. This must include both the actions of health care professionals and administrative issues – including reception, ease and agility of treatment, respect to the patient's needs, privacy, and social assistance. Achieving this will lead patients to acknowledge both facility and health workers as partners in the process of recovering health. To this end, it will be necessary that all training programs conceived for the multiprofessional team responsible for care be guided by these fundamental directives.

In addition to the points mentioned above, it will also be necessary to stimulate the supply of new drugs presentations for treating TB in order to facilitate administration and increase the effectiveness of the recommended regimens. It will be of fundamental importance to be able to rely on novel formulations that combine fixed doses for treatment regimen (capsules containing the three drugs in scheme 1: rifampicin, isoniazid, and pyrazinamide) and retreatment regimen (supplemented scheme 1: rifampicin, isoniazid, pyrazinamide, and ethambutol). In addition to contributing towards an increase in treatment adherence, such combinations may also help reduce the emergence of resistant strains and facilitate the logistics (stock management and transportation).

### **Measure implementation**

Effective implementation within the scope of control programs of the measures listed above will require a series of initiatives aimed at generating the conditions required for this implementation.

As in all activities within the health care sector, the implementation of novel strategies requires training human resources, which are essential for delivering these interventions. Achieving this will require the provision of specific and periodic training in the management of

coinfection to all professionals working either directly or indirectly with TB patients, including those that provide care to HIV/AIDS patients.

Other important initiatives that can provide support and political legitimacy to the recommended measures are to encourage and to promote the participation of NGO to discuss the coinfection control, allowing them to participate in the processes that can support decision making.

In the scope of health care services, another key element for the proper functioning of control measures is the organization and maintenance of an agile and decisive surveillance and information system capable of providing essential data for designing preventive measures and for evaluating the current scenario and trends in terms of coinfection.

Finally, it will also be necessary to promote and finance basic and clinical-operational research projects designed and conducted with the goal of answering to the major technical-scientific needs mentioned above.

## **FINAL CONSIDERATIONS**

If, on one hand, the ability to better respond to public health issues is characteristic of developed countries, on the other, the greatest public health problems are found in either developing or poor countries with little capacity of a technologically-based response.

Brazil, with its high prevalence of TB and HIV/AIDS, is one of the few developing countries with sufficient technology and researchers capable enough to respond to the therapeutic challenge imposed by having to effectively treat a patient with both AIDS and TB. If ARV therapy is an important weapon against the development of TB in HIV-infected people, it is also of immense value to the survival of patients already affected by TB. Currently, there are only a few ARV that can be used concomitantly with rifampicin, the major drug used in the treatment of TB, which makes achieving better results for the patient much more difficult.

In this scenario, there is a huge interdependence of measures related to AIDS or TB, in both the technical and political spheres. Efforts in this sense must emanate not only from governmental and nongovernmental organizations linked to AIDS, but also from those involved with fighting TB. These may be directed towards detecting the greatest possible proportion of HIV-infected individuals, or to ensuring the sustainability of the policy of free and universal access to antiretroviral drugs and the availability of ARV manufactured in Brazil or purchased in the foreign market at accessible prices. On the other hand, given that TB is one of the major causes of death among AIDS patients, and that it is likely that human populations will have to live with

HIV for many decades, it is essential to focus efforts on reducing prevalence of *M. tuberculosis* infection, so as to reduce the burden of TB among the HIV-infected population. Thus, AIDS programs in all administrative spheres should include among their objectives efforts to detect cases of TB within the general population (e.g., through active search or by systematic contact screening), towards effective quality control for anti-TB medication (which would ensure cure among patients using these drugs, thus interfering in the transmission chain), to improve the quality of diagnosis, and to improve adherence to treatment. In parallel, it will be essential to promote articulation between the two programs for the development of preventive and/or curative vaccines for TB and HIV. Success in at least one of these initiatives will affect the incidence, prevalence, or even mortality rates of both diseases.

The close and strong interaction of these two diseases, demands an interaction between control measures developed by the TB and HIV/AIDS programs. Articulated efforts between these two fields will allow for better management of resources allocated to personnel training, diagnosis of both diseases/infections, and control of their respective treatments. It will also invest new strength into technical argumentation, so that may be considered at all levels of political decision-making. A response that is adequate and in accordance with the needs posed by all challenges involved must necessarily include the sustainability of any strategy adopted. In this sense, the planning of efforts must run in parallel to the incentive towards the development of new therapeutic and diagnostic technologies, as new antiretroviral drugs, TB medication, or vaccines.

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