

Editorial

Tuberculosis/HIV co-infection

Co-infecção tuberculose/HIV

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Tuberculosis (TB) is responsible for 1.6 million deaths annually, and this is a scenario that has played out for centuries. Since the advent of HIV in the beginning of the 1980s, there has been a change in the clinical and epidemiological profile of TB. Co-infection with TB and HIV is responsible for the increase in the incidence and prevalence of TB, as well as in TB-related mortality, this being more pronounced on the continent of Africa, where one third of all cases of TB occur.⁽¹⁾

Until 1993, two clinical presentations of TB/HIV co-infection were recognized: TB in the HIV-seropositive patient without AIDS; and TB accompanied by AIDS.⁽²⁾ Subsequently, the World Health Organization classified TB as an AIDS-defining condition in HIV-infected patients.⁽³⁾ The CD4 lymphocyte count, which defines the degree of immunosuppression, is used to compare the clinical-radiological presentations.⁽⁴⁾ The CD4 lymphocyte count cut-off point has been defined as 200 cells/mm³. Studies have shown the following presentations on chest X-rays: findings consistent with progressive primary TB; findings consistent with post-primary TB; miliary TB; minimum alterations in up to 5% of the cases; and normal chest X-rays in up to 14% of the cases. The primary progressive form and normal chest X-ray predominates in patients with CD4 counts < 200 cells/mm³. The post-primary form is more common in patients with CD4 > 200 cells/mm³.⁽⁴⁾ More severe immunosuppression makes it more likely that chest X-ray presentations will be atypical and that there will be greater extrapulmonary involvement, as well as increasing the risk of mycobacteremia. Positive blood culture for *Mycobacterium tuberculosis* occurs in up to 49% of cases in which the CD4 count is < 100 cells/mm³.⁽⁵⁾

The co-infection is synergic, interactive and reciprocal with significant impact. In this situation, there is an increase in plasma viremia with worsening of the immunosuppression, and, conversely, there is an increase in the risk of developing active TB, which ranges from 37% to 167%, depending on the degree of immunosuppression,⁽²⁾ as well as accelerated progression of the disease, especially in the context of exposure to the multidrug-resistant (MDR) bacillus.⁽⁶⁾

In this context, the same diagnostic techniques that are normally used for the diagnosis of TB are employed: chest

X-ray, sputum smear microscopy and sputum culture. To those, culture for mycobacteria in blood and urine should be added. Invasive tests, such as fiberoptic bronchoscopy and pleural and ganglion biopsy, must be conducted when indicated. Tests to identify mycobacteria in liver aspirate, bone marrow and spinal fluid are reserved for specific conditions.

Nontuberculous mycobacteria, as well as the resistant and MDR bacilli, are more prevalent in HIV-seropositive patients, and there is a need to develop rapid diagnostic and drug sensitivity determination methods. In cases presenting positive sputum smear microscopy results, the amplification of nucleic acid, using polymerase chain reaction, is indicated for rapid confirmation of the diagnosis of TB or identification of other mycobacteria. A rapid test for the detection of the MDR-TB, using a method that evaluates, using a molecular probe, mutations in three genes, is already available. The *rpoB* gene is associated with resistance to rifampicin; the *kat G* and *inh A* genes are associated with resistance to isoniazid (INH). In a study conducted in Cape Town, South Africa, this rapid test was compared to the standard method and was found to have a sensitivity and specificity of 99%, with results obtained in two days.⁽⁷⁾ This could revolutionize the control of MDR-TB.

The treatment of TB in TB/HIV co-infection has peculiarities that deserve attention, specifically in the concomitant use of rifampicin and antiretroviral therapy, in which case, frequently, these drugs cannot be used jointly. Antiretroviral therapy increases the response to the purified protein derivative test, as well as reducing TB incidence and TB-related mortality. The CD4 counts obtained pre-treatment and at six months after the initiation of antiretroviral therapy are determining factors.⁽⁸⁾

Africa has 11% of the world population, but accounts for 29% of the cases of TB and 34% of the reported deaths due to TB worldwide. The incidence rate is on the rise, increasing from 145/100,000 inhabitants in 1990 to 342/100,000 inhabitants in 2005. In addition, Africa accounts for approximately 85% of all cases of TB/HIV co-infection. It is known that MDR-TB is a world problem, although its prevalence in Africa is lower than that observed in some countries, such as China, India and Russia. A six-

country study demonstrated that the incidence of MDR-TB ranges from 0.7% in Madagascar to 3.9% in Ruanda. In treatment-naïve patients in Botswana, the incidence of monoresistance was 10.4%, compared with 0.8% for MDR. In previously treated patients, these values were 22.8% and 10.4%, respectively.⁽⁹⁾ These rates are lower than those we observed in a study involving 217 patients hospitalized with TB in a referral hospital in Bahia, Brazil, 15 being HIV-infected and 202 being non-HIV-infected (7% of primary resistance, 43.1% of acquired resistance, 4.2% of primary MDR strains and 34.7% of acquired MDR).⁽¹⁰⁾ Extensively drug-resistant TB (XDR-TB) was evaluated in three countries in Africa, but was only identified in South Africa, where 5.6% of the MDR-TB cases were XDR-TB. In this context, the TB/HIV combination is fatal, as demonstrated in an outbreak in KwaZulu-Natal, South Africa.⁽⁶⁾

In this issue of the Brazilian Journal of Pulmonology, Nunes et al. analyzed 503 HIV-infected patients suspected of having TB/HIV co-infection in two hospitals in Maputo, Mozambique.⁽¹⁰⁾ Smear microscopy or sputum sample culture were conducted in 447 patients. Culture for mycobacteria was positive in 320 cases. In this group, smear microscopy was positive in 235. Although the species of mycobacteria was identified in only 277 cultures, there being loss of 43 cases, it was demonstrated that other mycobacteria were infrequently observed—only 3 cases, 2 cases being of *M. avium intracellulare* and one of *M. simiae*. These data reinforce what has been demonstrated in the medical literature and justify the initiation of the treatment in patients with positive sputum smear microscopy, even in the context of TB/HIV co-infection. The radiological classification in the cases presented a predominant model of primary progressive TB, with 67% of interstitial lesions, 18% miliary, 30% with mediastinal lymph nodes and only 12% with cavitations, which is justified by median CD4 count of 134 cells/mm³. The sensitivity test was conducted in 258 cases, there being loss of 62 cases. Primary monoresistance was 9% in patients without previous treatment, varying to 13% in those with previous treatment. Monoresistance was 6% and 10%, respectively, to INH and 25% and 1%, respectively, to rifampicin. The incidence of MDR-TB was 5% and 1%, respectively, in patients

with and without previous treatment. These resistance levels are consistent with those observed in other countries in Africa, although lower than those observed among patients hospitalized in Brazil. These data demonstrate a low incidence of MDR-TB in patients without previous treatment and perhaps justify the use of an initial treatment regimen consisting of four drugs, based on the 6% rate of primary resistance to INH. I believe that the authors contribute to better understanding of TB in Mozambique, where cases of TB are diagnosed in patients presenting advanced immunosuppression and where the incidence of primary resistance to INH is high. The authors conclude that the directly observed therapy, short-course strategy should be reinforced, and that chemoprophylaxis with INH should be used with caution in the context of TB/HIV co-infection.

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References

1. Chaisson RE, Martisson NA. Tuberculosis in Africa--combating an HIV-driven crisis. *N Engl J Med.* 2008; 358(11):1089-92.
2. Barnes PF, Bloch AB, Davidson PT, Snider DE Jr. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med.* 1991;324(23):1644-50.
3. Cantwell MF, Snider DE Jr, Cauthen GM, Onorato IM. Epidemiology of tuberculosis in the United States, 1985 through 1992. *JAMA.* 1994;272(7):535-9.
4. Greenberg SD, Frager D, Suster B, Walker S, Stavropoulos C, Rothpearl A. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology.* 1994;193(1):115-9.
5. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis.* 1993;148(5):1292-7.
6. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Laloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet.* 2006;368(9547):1575-80.
7. Barnard M, Albert H, Coetzee G, O'Brien R, Bosman ME. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. *Am J Respir Crit Care Med.* 2008;177(7):787-92. Epub 2008 Jan 17.

8. Lawn SD, Bekker LG, Wood R How effectively does HAART restore immune responses to Mycobacterium tuberculosis? Implications for tuberculosis control. *AIDS*. 2005;19(11):1113-24.
9. Nelson LJ, Talbot EA, Mwasekaga MJ, Ngirubiu PK, Mwansa RA, Notha M, et al. Antituberculosis drug resistance and anonymous HIV surveillance in tuberculosis patients in Botswana, 2002. *Lancet*. 2005;366(9484):488-90.
10. Matos ED, Lemos AC, Bittencourt C, Mesquita CL. Anti-tuberculosis drug resistance in strains of Mycobacterium tuberculosis isolated from patients in a tertiary hospital in Bahia. *Braz J Infect Dis*. 2007;11(3):331-8.
11. Nunes EA, de Capitani EM, Coelho E, Panunto AC, Joaquim OA, Ramos MC. Mycobacterium tuberculosis and nontuberculous mycobacterial isolates among patients recently infected with HIV in Mozambique. *J Bras Pneumol*. 2008;34(10):822-828.