

RESEARCH NOTE

Tuberculosis and HIV: Renewed Challenge

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HIV infection is responsible for an increased incidence of pulmonary tuberculosis (TB) in several areas of the world (MC Raviglione et al. 1995 *JAMA* 276: 220-226). In general, active TB happens as a consequence of a recently acquired exogenous infection of *Mycobacterium tuberculosis* or of endogenous reactivation of old infection. In some regions, besides the increase of the incidence, an important change in the dynamics of the transmission of *M. tuberculosis* took place. This change was more evident in closed places (hospitals, prisons, housings) where the prevalence of inmates infected by HIV is high (D Alland et al. 1994 *N Engl J Med* 330: 1710-1716, PM Small et al. 1994 *N Engl J Med* 330: 15-21, TR Frieden et al. 1996 *JAMA* 276: 1229-1235). The infection by HIV also interferes with the diagnosis of TB, especially in patients in the advanced form of the HIV infection. In these cases, the clinical picture of TB is quite similar to other opportunistic infections (PC Hopewell et al. 1992 *Clin Infect Dis* 15: 540-547, RE Chaisson & CA Benson 1995 p. 1-125. In MD Rossman, RR MacGregor (eds), *Tuberculosis Clinical Management, and New Challenges*, AL Kritski et al. 1995 *Bol Ofic Sanit Pan-Amer* 118: 542-554). HIV seropositive patients tend to stay longer in hospitals, increasing the risk of transmission of TB or even of multidrug resistant TB (TB-MDR) to other patients, health care workers and students in teaching institutions (Alland et al. *loc.*

cit., Frieden et al. *loc. cit.*). The clinical evolution of co-infected patients is diverse from immuno-competent individuals, with higher rate of adverse drugs reaction and mortality (JH Perriens et al. 1995 *N Engl J Med* 332: 77, Kritski et al. *loc. cit.*). The emphasis given in the last decades to outpatient treatment of TB should be now revised in areas with high rate of TB and AIDS, especially in great urban centers. Hospital treatment of tuberculosis patients with co-morbidities, such as AIDS, is much more common now. Should be taken into account in the elaboration of public politics the occurrence of TB in general hospitals, above all in developing countries, such as Brazil.

According to the World Health Organization (WHO), in the year 2000, 14 million cases of tuberculosis will be notified, of which 3 to 4 million will die (WHO 1996 TB/96.197). Of these, about 1.5 million patients will die with HIV/AIDS. It is important to call attention to the fact that TB is an easily curable disease in 85-95% of HIV seronegative patients. In Brazil, up to 1990, the incidence of TB was falling 2 to 4% a year. In the last years, however, this rate decreased to 0.4% a year (Ministério da Saúde 1996 Boletim Epidemiológico No. 9, 12 pp). Brazil is a country of great dimensions, with many disparities. When we analyzed the data for the city of Rio de Janeiro, in the southeast region, we verified that while in 1986 the TB incidence rate was 80/100,000 inhabitants, in 1995 it reached 160/100,000, similar to some African countries (Coordenação de Pneumologia Sanitária, Secretaria Municipal de Saúde, Município do Rio de Janeiro 1997, unpublished data). Even in areas with good TB control programs, as in Malawi and Mozambique, the TB incidence increased 30 to 50% in the last years (Raviglione et al. *loc. cit.*).

In many countries, the TB control programs do not usually include the information on HIV when a case of TB is notified. Also, the AIDS control programs do not share its information related to the AIDS cases with notified TB. Therefore, there is a sub-notification and little reliability of the epidemiological indicators about the association of TB/HIV, mainly in developing countries. In 1991, seroprevalence studies in the city of Rio de Janeiro showed that, in the health posts, 4% of the patients notified as having TB were infected by HIV. In 1996, this rate reached 10%. In 1997, about 9,500 cases of tuberculosis were notified, 70% in health posts and 30% in hospitals (Coordenação de Pneumologia Sanitária, Secretaria Municipal de Saúde, Município do Rio de Janeiro 1997, unpublished data). The frequency of HIV/AIDS infection among tuberculosis patients was of 5-10% in health posts and of 15-35% in the hospitals. In the

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Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro (HUCFF), among 300 patients notified a year, the infection rate for HIV was 35% (Kritski et al. *loc. cit.*).

In 1995, patients with pulmonary TB and positive bacilloscopy in the sputum in health posts were 50% while in the hospitals were 56%. These data are alarming because these patients are assisted in hospitals without infection control measures, placing under risk health care professionals and other patients. In the city of Rio de Janeiro the culture for mycobacteria carried out in just 30% of the cases assisted in hospitals. A study accomplished in the HUCFF showed that introduction of the culture in the patients' investigation under suspicion of TB increased the diagnosis yield from 6% to 21% (MB Conde et al. 1998 pers. comm.).

Among the 72,209 cases of pulmonary TB notified to the state secretaries of health in Brazil in 1995, 38% were treated without bacteriological confirmation, 22% with negative acid fast bacilli of sputum and 16% without bacilloscopy (Ministério da Saúde *loc. cit.*). In Rio de Janeiro and São Paulo the proportion of patients treated empirically was even higher (43 to 45%), mainly in hospitals (FQ Mello et al. 1996 *Tuberc Lung Dis* 77: 95). This probably has an impact in patients co-infected by *M. tuberculosis* and HIV, because they tend to present smaller expectoration and/or larger frequency of negative smears.

A current subject of consideration is the relationship between infection by HIV and the risk of MDR-TB. In the United States of America (USA), from 1984 to 1992, the frequency of primary resistance to at least one of the anti-TB drugs increased from 10% to 23% (AB Bloch et al. 1994 *JAMA* 271: 665-671). In New York, where several outbreaks took place in hospitals and in prisons, the frequency of primary MDR (resistance to isoniazide and rifampin) in patients with HIV/AIDS was 20% (Frieden et al. *loc. cit.*). However, in Tanzania, differences were not observed in the frequency of primary resistance to anti-TB drugs among patients infected or not by HIV (HJ Chum et al. 1996 *AIDS* 10: 229-309). In this study most of the patients originated from health posts. In England, in a national study of resistance to anti-TB drugs performed in TB clinics and hospitals, the frequency of primary multi-drug resistance in HIV seropositive patients was 7% and in seronegative ones 1% (DE Bennet et al. 1996 *Tuberc Lung Dis* 77: 91). These data suggest that the primary MDR in patients infected by HIV increases in closed places such as hospitals, prisons and shelters. In New York, the "clusters" of strains associated with the occurrence of recent exogenous infection and followed by active TB happened

more frequently in patients born in the USA, in blacks, in patients with AIDS and in health care workers. However, this frequency was smaller among immigrants thus probably happened because these patients got sick due to endogenous reactivation of old infection acquired in their countries of origin (CR Friedman et al. 1995 *Am J Respir Crit Care Med* 152: 355-359). From 1992 through 1994, in New York, with the expansion of measures to prevent and control tuberculosis, a decrease in MDR-TB has been detected. But, among notified MDR-TB patients, the proportion of health care workers was 5% (6/109) in 1995 and 15% (13/84) in 1996 (TR Frieden et al. 1995 *N Engl J Med* 333: 229-233, B Nivin et al. 1997, p. 145, Infect Dis Soc America 35th Annual Meeting).

Among Latin American countries, Bolivia presents high primary resistance to streptomycin and isoniazide, while in Argentina it is elevated to isoniazide and rifampin (A Laszlo & I Kantor 1994 *Bull WHO* 72: 603-610). In Buenos Aires, several outbreaks were described in hospitals for MDR tuberculosis, similar to that observed in New York (V Ritacco et al. 1997 *J Infect Dis* 176: 637-639). In these studies, techniques of molecular biology such as the "fingerprint" were useful. Recently, an outbreak of tuberculosis in a rural community of 10,000 inhabitants was described, and when checked with epidemiological evaluation with molecular methods and studies in animals, the *M. tuberculosis* strain was found to be one of the most virulent identified up to this moment. Just after casual contacts, three patients infected 25% of the 337 appraised close contacts and 21 people got ill (L Valways et al. 1997, p. 137, Infect Dis Soc America 35th Annual Meeting).

The preliminary data of a national survey of resistance of 6,000 *M. tuberculosis* strains performed by the Ministry of the Health in Brazil in patients attended in health posts indicate a prevalence of primary MDR to isoniazide and rifampin of 1%. In this study the HIV infection rate was not evaluated. In the city of São Paulo, in the reference center for treatment of AIDS, the prevalence of primary MDR was of 11% while in two AIDS reference general hospitals in the city of Rio de Janeiro it was of 15% and 5%, respectively (W Pinto et al. 1995 *Tuberc Lung Dis* 76: 141, FCO Fandinho et al. 1995 *Tuberc Lung Dis* 76: 94). The evaluation of these data suggests that in some urban areas of Brazil primary MDR is happening mainly in closed places that assist patients infected by HIV.

AIDS has produced a great impact in the control of tuberculosis. TB now should be analyzed in a different way. Although maintaining the emphasis in primary ambulatory treatment, surveillance

should also increase on patients under risk of co-infection by HIV, mainly in those originating from closed environments such as hospitals, prisons, shelters, etc. In hospitals with high prevalence of TB and AIDS, specific measures should be implemented: (a) the notification of cases, (b) environmental control of the infection, and, (c) education of health care workers. Emphasis should also be given to shorten the time of diagnosis. In areas with a high frequency of treatment failure, some of the patients admitted to the hospitals can harbor a MDR strain. With the absence of rapid methods for diagnosis of tuberculosis in these places, it could take up to six days for the result of the bacilloscopy before treatment starts and/or the patient is isolated. As a consequence, some authors have proposed some rapid amplified direct tests to detect deletion or mutation of certain gen related to the resistance to anti-tuberculous drugs. In 1994, deletion or mutation of the catalase/peroxidase gen (Katgen) was analyzed by the technique of polymerase chain reaction (PCR) for the identification of resistant strains to isoniazide (INH). However, further studies performed in clinical samples with resistant strains showed low sensitivity of this technique (11 to 25%) (L Ferrazoli et al. 1995 *J Infect Dis* 171: 237-240). Other studies showed that the sensitivity of the technique increased when *M. tuberculosis* strains with high minimal inhibitory concentration of resistance to isoniazide (>50mg/ml), were evaluated while no association with virulence of the strains in guinea pigs was observed (AL Kristki et al. 1996 *Am J Respir Crit Care Med* 153: 806A).

More recently, it was observed that the rapid tests usually used to detect deletion and/or mutation of the gen *rpoB*, associated to the resistance to rifampin, detected just 89% of the resistant Brazilian strains in comparison to the French ones (100%). The analysis of the profile of the Brazilian strains should be emphasized to evaluate the true impact of the new methodologies of molecular biology diagnosis in the control of the tuberculosis (SS de Miranda et al. 1998 pers. comm.).

An excellent indicator for the evaluation of the hospital transmission of tuberculosis is the detection of PPD conversion rate among health professionals. In Brazil, the annual rate of infection for *M. tuberculosis* in the general population is estimated by the Ministry of Health to be 0.8%. In New York, hospitals, where outbreaks by resistant strains took place, the PPD conversion rate among health professionals varied from 20 to 50%. In hospitals without identified outbreaks, the PPD conversion rate varied from 2 to 10% (D Menzies et al. 1995 *N Engl J Med* 332: 92-98). In Rio de Janeiro, the HUCFF, an AIDS reference hospital, with 2,300 health professionals in clinical activi-

ties, the annual PPD conversion rate evaluated in 351 professionals was of 8%, nine times higher than the estimated for the general population. The PPD conversion happened more in the nursing personnel (12%), laboratory and radiology technicians (13%) and doctors (15%), being infrequent in the office employees group (0.9%) (GR Muzy de Souza et al. 1998 *Am J Respir Crit Care Med* 157: 415A). Hospitals do not have an internal system of infection control procedures, establishing the use of special masks, education of health professionals and the use of HEPA filters and/or exhausting systems. All these difficulties point to the need of hospital TB control programs. Thus, in the general AIDS reference hospitals of the great urban centers, the existence of a group of health professionals that act in the same way as the existent hospital infection committees is necessary. These professionals, among other activities, would make sure that the contagious patient is isolated just after admission, would verify if the bacilloscopy of sputum was promptly requested and if the laboratory results were released on time. The presence of a professional working in tuberculosis control has great impact in the decrease of *M. tuberculosis* risk transmission (K Sepkowitz 1995 *Clin Infect Dis* 20: 232-242, NP Wenger et al. 1995 *Lancet* 345: 235-240, JE McGowan 1995 *Clin Infect Dis* 21: 489-505).

In relation to tuberculosis treatment of patients with HIV infection, three aspects should be considered: (a) the higher frequency of adverse reactions, (b) the impact of the use of protease inhibitors and, (c) the higher occurrence of abandonment of the treatment followed by acquired resistance. In Brazil, the drugs used in the treatment of TB are rifampin, isoniazide and pyrazinamide for six months in the HIV seronegative patients and nine months in the HIV seropositive ones. In retreatment patients ethambutol is also indicated. For all HIV cases culture for *M. tuberculosis* should be requested, besides bacilloscopy. The susceptibility test is indicated for individuals in retreatment for patients in close contact with MDR-TB or in failure of the anti-tuberculosis treatment (Ministério da Saúde *loc. cit.*).

The literature shows that the frequency of adverse reactions varies from 20 to 30% in AIDS patients. In Brazil, the frequency of adverse reactions varies from 4 to 6% in patient in the initial phase of the HIV infection. In this phase, with CD4 lymphocyte count 300 to 400 cells/mm³, the cavities observed in the chest X ray were identified in 50%. However, in the advanced phase of HIV infection, the frequency of adverse reactions was higher (25%) with higher hepatitis occurrence and, with cavity observation in the chest X ray occur-

ring less than 10% (Kritski et al. *loc. cit.*). These adverse reactions happened more commonly in the first three months of treatment, and were related to the use of rifampin, followed by pyrazinamide, and isoniazide (A Toledo et al. 1995 *Tuber Lung Dis* 76: 138, NA Ackhah et al. 1995 *Lancet* 345: 607-610). The failure of the tuberculosis treatment in HIV seropositive patient varies of 0 to 6% and the relapse from 0 to 15% (A Castelo et al. 1995 *Pharmaco Economics* 8: 385-399). These data have been noted in Brazil and in most of the developed and developing countries. In Spain, higher relapse rates have been described (23%). In the studies in USA and in African countries with schemes that contain rifampin, the relapse occurrence did not differ much among the patients with positive and negative HIV. Other studies show that the relapse was larger among individuals in the more advanced stages of HIV infection (Castelo et al. *loc. cit.*). In Brazil, a study was accomplished by the National TB Program -Ministry of Health in 12 capitals. In HIV seropositive patients, the frequency of abandonment was 40%, while in HIV seronegative ones 28% (LS Diniz et al. 1995 *Bol Pneumol Sanit* 3: 6-18). These data suggest that HIV seropositive patients tend to abandon the treatment more frequently and therefore can produce more resistant strains of *M. tuberculosis*. Among HIV seropositive patients, recent studies identified some variables associated with higher mortality: (a) anergy to PPD, (b) the disseminated tuberculosis, (c) lymphopenia < 1000 cells for mm³, (d) the atypical image in the chest x ray, (e) oral candidiasis and, (f) previous condition associated with AIDS phase as citomegalovirus or *Pneumocystis carinii* pneumonia (C Whalen et al. 1996 *Am J Respir Crit Care Med* 153: 1977-1981, RW Shafer et al. 1996 *AIDS* 10: 269-272). Although the patients with higher CD4 counts have longer survival, they tend to have a higher rate of relapse and may continue or not disseminating the resistant bacillus to the community.

More recent data observed in USA show that the occurrence of acquired resistance to anti-TB drugs was associated with HIV seropositive patients in the AIDS phase, even among those that use the anti-TB drugs under supervision (CM Nolan et al. 1995 *Am J Respir Crit Care Med* 152: 1067-1071, WZ Bradford et al. 1996 *Lancet* 348: 928-931). The real impact in the community of the higher occurrence of acquired mycobacteria drug resistance rate among AIDS patients has to be evaluated.

Some authors have proposed that the active pulmonary tuberculosis enhances local HIV-1 replication *in vivo* (K Nakata et al. 1997 *Am J Respir Crit Care Med* 155: 1996-1999). More recently, in

Uganda, it was observed that even after the treatment adapted for tuberculosis, HIV seropositive patients continue with elevated viral replication in relation to the individuals that did not have tuberculosis. These patients, co-infected by HIV and *M. tuberculosis*, develop faster to AIDS and have a lower survival rate. Probably the survival rate will increase with the use of anti-retroviral drugs associated to anti-TB drugs. Rifampin cannot be used in concomitance with protease inhibitors due to the impact on the protease inhibitor's on rifampin's metabolism. Recently, in a Consensus Meeting organized by the Ministry of Health and the Brazilian Society of Pneumology, alternatives schemes were proposed regarding the use of anti-TB drugs in association with anti-retroviral treatment (I Consenso Brasileiro de Tuberculose 1997. *J Pneumol* 23: 279-346). When the patient is not using anti-retroviral and TB is diagnosed, he/she should use na anti-TB scheme with rifampin until the end of the treatment. Later on, protease inhibitors should be initiated. When he/she is already using protease inhibitors and TB is diagnosed, it is proposed not to suspend the use of the protease inhibitor. Rifampin use should be avoided. The alternative anti-TB scheme is ethambutol, isoniazide, pyrazinamide, streptomycin for three months followed by ethambutol and isoniazide for nine months.

Regarding the chemoprophylaxis of TB for HIV seropositive patients, the Brazilian Ministry of Health proposed that isoniazide use is indicated for: (a) asymptomatic with positive PPD skin reaction (induration > 5 mm) and normal chest X ray; (b) patient's close contact with smear positive pulmonary tuberculosis, with normal chest X ray and asymptomatic (PPD skin test here is not necessary). However, there is little information about the effectiveness of INH in these patients under field conditions in the TB control programs. In 1995, an operational study conducted by WHO demonstrated the difficulty in the use of INH for HIV seropositive individuals (T Aisu et al. 1995 *AIDS* 9: 267-273). WHO proposed that the developing countries prioritize tuberculosis treatment. In these countries, only when the TB control programs reach high levels of cure (> 85%) of the TB cases detected, they should start preventive anti-TB treatment for the individuals infected by HIV+. These activities should be discussed with the AIDS control programs mainly in countries of intermediary level of development, like Brazil. On one side, we should treat only active TB, reaching a frequency of high cure and of low abandonment (<5%). On the other hand, some experts propose to offer preventive anti-TB treatment for HIV se-

ropositive patients, in spite the the quality of TB control program. In these countries the AIDS and TB control programs should pursue: (a) to evaluate the implementation of the supervised treatment as proposed by WHO; (b) better performance of both programs, with crossing of the data, to define specific strategies; (c) to improve the traditional methods of TB diagnosis like the bacilloscopy, culture and susceptibility tests, and, (d) to evaluate the usefulness of new rapid diagnostic methods (D Chin et al. 1995 *Am J Respir Crit Care Med* 151: 1872-1877). The Food and Drugs Administration (FDA) approved the Genprobe and of Roche kits for the diagnosis of smear positive patients. The usefulness of those kits did not receive the fi-

nal approval among smear negative pulmonary TB patients, extra-pulmonary TB patients or among patients treated for TB in the past (AL Kritski et al. 1997 *J Pneumol* 23: 33-42). Some diagnostic kits for resistant TB have been proposed. Until now, there are few studies that evaluate its usefulness in clinical practice. In developing countries it is extremely important to evaluate its usefulness in the health posts and in hospitals. In places of cold climate, where there is no exhausting system of the air, nor ventilation, without infection control policy, probably the implementation of rapid diagnostic tests for tuberculosis can be useful. Isolation procedures can be improved and decreasing the nosocomial transmission of tuberculosis will occur.

