# Poor Response to Tuberculosis Treatment With Regimens Without Rifampicin in Immunosuppressed AIDS Patients

**O'Donnel M.M., Souza Carvalho S., Gadelha A.J., Morgado M.G., Galhardo M.C.G., Lourenço M.C. and Rolla V.C.**

*Department of Infectology and Laboratory of Bacteriology, Evandro Chagas Institute; National School of Public Health; Laboratory of Immunology in HIV/AIDS, Oswaldo Cruz Institute; FIOCRUZ, Rio de Janeiro, RJ, Brazil*

**A prospective study was conducted on 79 advanced immunosuppressed AIDS patients from 1997 to 1999, during which nine cases of tuberculosis (TB) were diagnosed. The main clinical and laboratory characteristics and the response to TB treatment were reviewed. The clinical manifestations of TB were: pulmonary (six cases), extrapulmonary (two cases) and disseminated (one case). These patients were being treated with highly active antiretroviral treatment (HAART) and were not responding. In three cases an optional regimen without rifampicin (RMP) was indicated to maintain HAART during TB treatment. A clinical response to TB treatment (disappearance of fever) was observed in 6/9 patients during a mean of 73 days (SD = 96). The three unresponsive patients were those treated without RMP. A switch to TB regimens containing RMP was proposed and successful. In our study, though it was limited by a small sample size, the response to TB regimens without rifampin was poor in immunossupressed patients failing HAART.**
**Key Words: AIDS, immunosuppression, rifampicin, tuberculosis.**

Tuberculosis is one of the most frequent opportunistic diseases in Rio de Janeiro, Brazil, an area of high prevalence of HIV infection [1]. Among HIV-related opportunistic diseases, tuberculosis stands out as the most important cause of morbidity and mortality in most developing countries [2].

Until March 2000, the concomitant use of rifampicin and protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRT) was not recommended by any guidelines [3, 4], including the Brazilian Consensus [5]. In our country, immunosuppressed AIDS patients with tuberculosis (TB) were treated with regimens without rifampicin (replacing rifampicin with ethambutol and streptomycin) in order to maintain highly active antiretroviral treatment (HAART) for HIV treatment (rifabutin is not offered free of charge by the National AIDS program in Brazil and therefore is not an available option in clinical practice). A double antiretroviral therapy without PI was also indicated as another alternative during TB treatment for co-infected patients [5].

Although the concomitant use of PI (ritonavir/saquinavir) or an NNRT (efavirenz) and rifampicin have been accepted [1, 6], the role of second line regimens for tuberculosis remains an important unanswered question in clinical practice. Few data are available in the literature describing the efficacy of these optional regimens for severely immunosuppressed individuals [7].

## Objective

To describe clinical and laboratory characteristics of TB in immunosuppressed AIDS patients and the response to TB regimens with and without rifampicin.

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Address for correspondence: Dr. Valeria Rolla, Instituto de Pesquisa Clinica Evandro Chagas, FIOCRUZ. Av. Brasil 4365, Rio de Janeiro, Brazil, Zip code: 21045-900.
E-mail: valeria @cpqhec.fiocruz.br or rolla@unisys.com.br
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## Material and Methods

A prospective study was conducted at a hospital from September, 1997, to December, 1999, in order to evaluate mucosal colonization by mycobacteria and the incidence of disseminated mycobacterial disease in 79 immunosuppressed AIDS patients (a $CD_4$ count below 100 cell/$mm^3$ detected at least once) [8]. Sputum, stools and blood submitted to lysis centrifugation techniques were cultivated monthly in Lowënstein-Jansen media. During this study TB was diagnosed and treated in nine patients. All patients with a diagnosis of TB were included in our study and their main clinical and laboratory characteristics, including their response to TB regimens, were reviewed. A clinical response to specific TB treatment was defined as disappearance of fever and night sweats, and weight gain and/or negativity of previously positive cultures.

## Results

Eight males (homosexuals) and one female (heterosexual) were found to have TB. Mean age at TB diagnosis was 42 years (SD±7).

AIDS-defining diagnosis was based on opportunistic diseases (OD) in four cases and on CD4 counts < 200 cells/$mm^3$ in five cases. TB was the first opportunistic disease diagnosed in 7/9 cases.

All patients included in our study were severely immunosuppressed. AIDS was diagnosed a mean of 1,039 days (SD±471) before TB. Mean $CD_4$ counts close to TB diagnosis were 73 cell/$mm^3$ (SD±65) and mean viral load was log 4.9 (SD±1). All patients had already been treated with other antiretroviral regimens preceding TB treatment. Those regimens were triple in seven cases and double in two cases. The main clinical and laboratory characteristics of these patients was recorded (Table 1). TB diagnosis was established by visualization of acid-fast bacilli in only 2/9 cases and by positive cultures in 7/9 cases. The cases for which we did not achieve positive cultures were treated with rifampicin isoniazid and pyrazinamide (two cases). They responded to treatment.

The regimens used for TB treatment (dosages for a 60kg individual) were: 1) rifampicin (600mg) izoniazid (400mg) and pyrazinamide (2g) – RIP. 2) isoniazid (400mg), pyrazinamide (2g), ethambutol (1200mg) and streptomycin (1g) – IPEE. One patient died before TB treatment could be offered. Clinical and laboratory characteristics of the cohort, TB and HIV treatments were recorded (Table 1).

None of the patients treated with IPEE responded to treatment. Patients treated with the first line regimens had a good clinical response (mean period from treatment to improvement of clinical signs = 23 days) and negativity of positive cultures. All patients who did not respond to IPEE were switched to RIP (interrupting PI or NNRT) and a good clinical and bacteriological response was obtained.

## Discussion

Tuberculosis is a major health problem in Brazil that has increased in frequency and severity because of the AIDS epidemic. Until recently, national guidelines recommended double antiretroviral treatment (without protease inhibitors or non-nucleoside reverse transcriptase inhibitors) for patients treated with rifampicin [5]. Although rifabutin has fewer interactions with PI and NNRT, this drug is not part of the TB program in Brazil because of its cost and viral cross-resistance with rifampicin. In our country, patients who are unable to stop HAART are treated with an alternative TB regimen, replacing rifampicin with ethambutol and streptomycin [9]. Second-line regimens either have been shown to be less effective and more toxic than the first line treatments or have not been studied as extensively (Small and Fujiwara 2001).

Although this is a descriptive study, we found a remarkably poor response to regimens without rifampicin in advanced immunosuppressed patients failing HAART. However, these patients responded to TB therapy when switched to regimens containing rifampicin, even in double therapy for HIV.

**Table 1.** Main clinical and laboratory characteristics of nine immunosuppressed AIDS patients with tuberculosis (TB) in Rio de Janeiro from 1997 to 1999, Brazil

| Variable | Category | Frequency |
|---|---|---|
| Clinical forms of TB | extrapulmonary | 2 |
| | disseminated | 1 |
| | pulmonary | 6 |
| $CD_4^+$ at TB diagnosis | >100 cell/ $mm^3$ | 3 |
| | 50-100 cell/$mm^3$ | 2 |
| | <50 cell/$mm^3$ | 4 |
| VL (log) at TB diagnosis | >5.1 log | 5 |
| | 3–5 log | 3 |
| | <3 log | 1 |
| ARV before TB | double combination | 2 |
| | triple combination | 5 |
| | quadruple combination | 2 |
| ARV after TB diagnosis | double combination* | 2 |
| | HAART | 3 |
| Initial TB treatment | RIP | 6 |
| | IPSEt | 3 |

TB = tuberculosis. N = number of observations. $CD_4^+$ = $CD_4$ T cell counts. VL = viral load. log = logarithmic. ARV = antiretroviral. R = rifampicin. I = isoniazid. P = pyrazinamide. S = streptomycin. Et = ethambutol. C = ciprofloxacin.
* = without protease inhibitors or NNRT.

Given that the strategy of replacing rifampicin is still a common option for AIDS treatment in Brazil, we believe our results contribute to improved knowledge about this particular group of immunosuppressed patients.

No other study has been conducted in our country to clarify these issues. We should be given to TB treatment over AIDS treatment in patients with low $CD_4$ counts who have already been exposed to HAART.

## Conclusions

In patients with advanced immunosuppression, there was poor response to TB regimens without rifampicin. The subsequent response to rifampicin-containing regimens was good although immunosuppression persisted.

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