

# Incidence of Tuberculosis in Latent TB Infected (LTBI) Patients Living with HIV under Antiretroviral Therapy in the Lomé Infectious Disease Department

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## Abstract

**Objective:** To determine the incidence of tuberculosis in person living with HIV infected by latent TB and under antiretroviral (ARV) therapy. **Method:** We studied prospectively for 36 months the occurrence of bacilliform pulmonary tuberculosis in patients infected with HIV, naive of BCG and receiving antiretroviral treatment. Each patient had an intradermal reaction (IDR) of 10 IU tuberculin Mérieux. The measurement of the nodule is made 72 hours later. During follow-up, patients were reviewed every six months for active tuberculosis. **Results:** A total of 212 out of 257 patients had an IDR greater than 5 mm, an ITL prevalence of 86.33%. Three patients were lost to follow-up during the study. The predominant female sex is 69.81%. The mean age was  $42.8 \pm 10.02$  years. A previous history of tuberculosis was found in 14.15% of patients and 208 patients (98.11%) had HIV1. In 39.15% of patients, patients had a CD4 count lower than 350 cells/mm<sup>3</sup> at baseline in the study. At the end of the three-year follow-up, among the 14 patients, 11 had failed ARV therapy and had developed TB, with an incidence of 2.20 cases per 100 patients. **Conclusion:** The incidence of active tuberculosis in LTBI was very high in HIV-positive patients with low CD4 count, hence the importance of reliable LTBI screening such as gamma interferon is better than patient follow-up.

## Keywords

LTBI, Incidence, Tuberculosis, HIV

## 1. Introduction

Latent tuberculosis infection (LTBI) is a persistent immune response to pre-

viously acquired mycobacterium tuberculosis antigens with no evidence of active tuberculosis. On the one-third (1/3) of the world's infected population [1], only 10% will develop active TB in their lifetime. The evolution of LTBI to tuberculosis disease depends on several factors, including HIV immunodeficiency, as evidenced by the high incidence of TB in HIV [2] [3]. In patients infected with HIV and the KOCH bacillus, the annual risk of progression to tuberculosis disease is 10% [4] [5]. Togo does not escape this reality where 23.7% of patients are co-infected TB/HIV [6] and 76% HIV infected under HAART are latent TB infected [7]. We therefore initiated this study to determine the incidence of tuberculosis disease among HIV infected patients who have never received tuberculosis vaccination, but under antiretroviral treatment, 3 years after, been detected latent TB infected at the Sylvanus Olympio hospital in Lomé.

## 2. Method

This is a prospective study that ran from 1 June 2013 to 31 May 2016 at the day hospital of the Infectious Diseases Service of the CHU-SO in Lomé (TOGO). All patients were infected with HIV and had no history of BCG vaccination. Measurement of CD4 counts has determined a group of patients with a major immunosuppression of CD4 < 350 cells per mm<sup>3</sup> and another group considered moderately immunosuppressed with CD4 > 350 cells/mm<sup>3</sup> in accordance with Togolese national guidelines in force up to 2014, inspired by the WHO's 2013 recommendations on AIDS. In all cases, all patients had CD4 < 500 cells per mm<sup>3</sup> and were therefore treated with ARVs. The recruitment was done on the ESSOP software which was set up for the follow-up of persons living with HIV as part of the collaboration with Gip Esther. An intradermal reaction (IDR) or tuberculin skin test of the Mérieux laboratory was performed in all patients. Thus, those with an induration greater than 5 millimeters were considered positive and included in the study like Latent TB Infected patients. Latent tuberculosis infection (LTBI) is a persistent immune response to previously acquired mycobacterium tuberculosis antigens with no evidence of active tuberculosis. A medical follow-up every six months for 3 years was carried out for the early detection of tuberculosis. The diagnosis of is done on a smear test, culture, Genexpert (real time PCR) within patients coughing more than 2 weeks. The immune status and the occurrence of smear-positive tuberculosis were the parameters studied.

The analysis of the data was based on the epi info 7.1.2.0 software and the tests of chi 2 and/or Fisher in case of necessity were used. A value of  $p < 5\%$  was significant.

## 3. Results

### 3.1. Epidemiological Characteristics

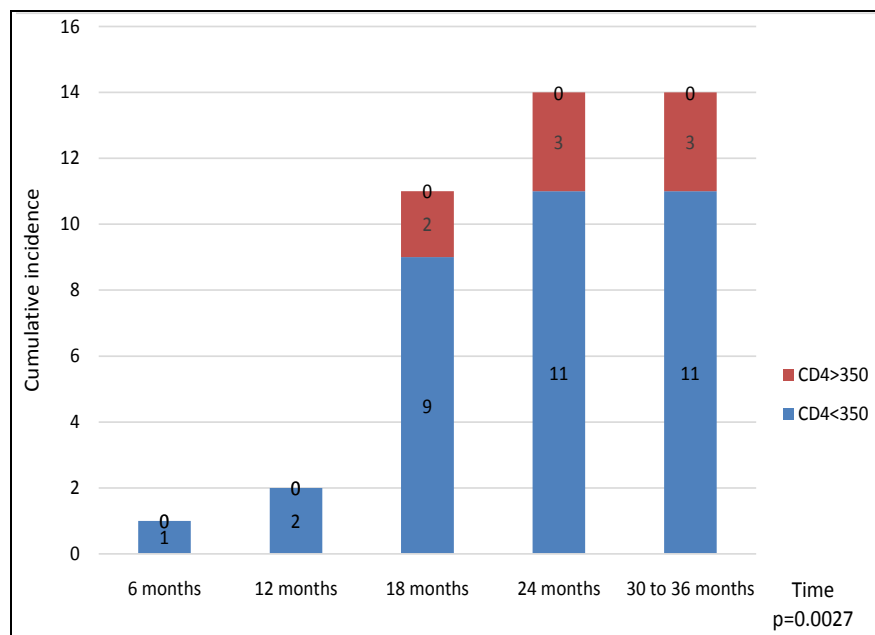
A total of 257 patients were collected. Among them, 212 (148 women and 64 men) who had an IDR skin test greater than 5 mm were included at 83.66%.

The female sex was predominant (69.8%) with a male/female ratio of 0.43. The mean age of patients was  $42.8 \pm 10$  years with extremes of 21 and 69 years. Those under 55 years old represent 85.38% of the population. A previous history of tuberculosis was observed in 14.15% of patients. All patients were infected with HIV. Among them, those HIV1 infected (208) are treated with tenofovir, lamivudine and efavirenz and 04 HIV-2 or dual HIV infected are receiving the tenofovir, lamivudine and lopinavir/r. according to the immune status, 83 patients were highly immune compromised with a CD4 cell count less than 350 cells/mm<sup>3</sup> of blood and 129 had moderate immune suppression with a CD4 cell count greater than 350 cells/mm<sup>3</sup> of blood (**Table 1**).

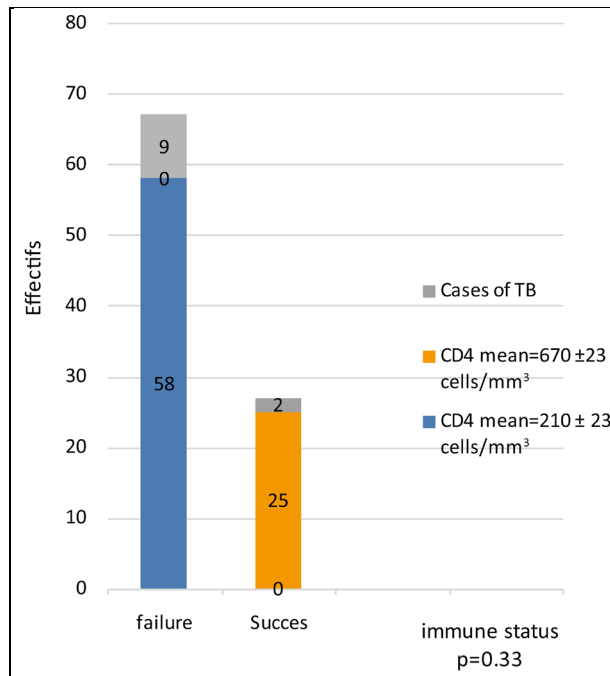
### 3.2. Evolution

Among 212 patients, 3 with CD4 counts above 350 were lost in the first six months. Within the 209 remaining, 14 developed tuberculosis during the 3 years of follow-up with a peak observed at 18 months (11 cases). The mean annual incidence was 2.20 per 100 patients. In addition, patients with CD4 < 350 (83/209) at initiation of treatment developed more cases of tuberculosis (11/14) than those with CD4 > 350 (126/209) with a significant difference,  $p = 0.0027$  (**Figure 1**).

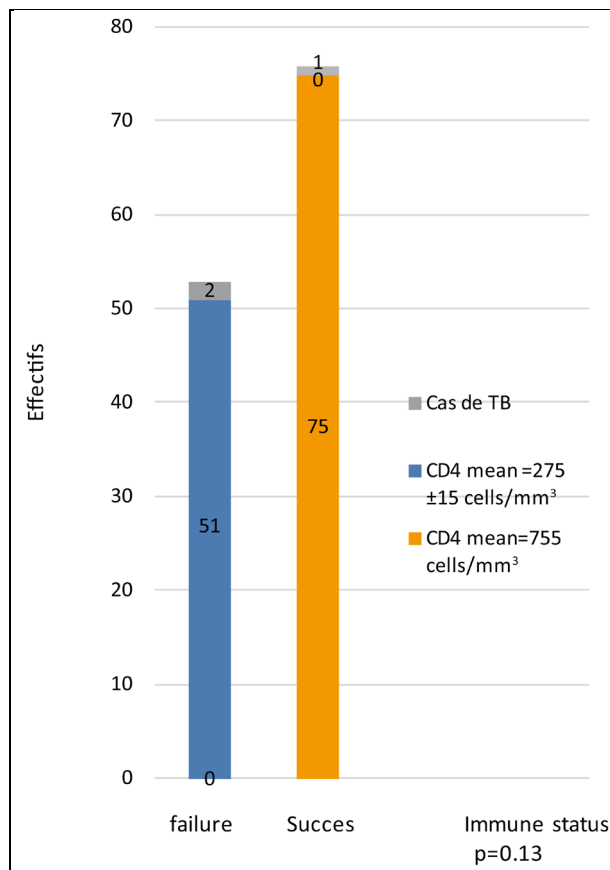
However, when comparing tuberculosis cases in the population according to immune status after 3 years of ARV treatment, no statistically significant difference was seen in **Figure 2** and **Figure 3** ( $p > 0.05$ ). The revival of tuberculosis does not seem to be influenced by the ARV treatment but rather by the latent TB infection preexisting before the initiation of the ARV treatment.



**Figure 1.** Cumulative incidence of TB cases according to initial immune status and time.



**Figure 2.** Occurrence of TB according to CD4 rate after 3 years of ART among patients with CD4 rate less than 350.



**Figure 3.** Occurrence of TB according to CD4 rate after 3 years of ART among patients with CD4 rate greater than 350.

**Table 1.** General characteristic of the population.

	Effectif (N)	Pourcentage (%)
<b>Age</b>		
<55	181	85.38
≥55	31	14.62
<b>Gender</b>		
Male	64	30.19
Female	148	69.81
<b>Contamination</b>		
Yes	30	14.15
No	182	85.85
<b>Type of HIV</b>		
HIV 1	208	98.11
HIV2 an/or dual	4	1.89
<b>Beginning CD4 rate</b>		
TCD4 < 350	83	39.15
TCD4 ≥ 350	129	60.85
<b>Total</b>	<b>212</b>	<b>100</b>

#### 4. Discussion

The risk to develop TB is increased in people infected with HIV. This risk appears very early in the progression of the HIV infection [8]. Its occurrence in latent tuberculosis patients requires a reliable diagnosis of LTBI, which nowadays use methods of gamma interferon release assay. Indeed, tuberculin skin test (TST) is not always synonymous TB infection but only attests to the existence of antibodies against the TB bacillus. This situation may occur during vaccination and in immunizations after contamination. While the gamma interferon release assay is a specific reaction of lymphocytes when they are infected by TB bacillus. This situation was reported in Poland where LTBI was found only in 8.9% of cases with interferon release assay versus 48.9% for TST [9]. Thus, the TST diagnoses in excess the cases of ITL. It is therefore more sensitive than specific. However, in developing countries, IDR may be an interesting diagnostic indicator for LTBI for epidemiological purposes for tuberculosis surveillance in HIV infected patients. In our case, tuberculin IDR skin test was the test available. This is also why the study only considered patients without a history of BCG and who had never done a tuberculin IDR in the aim to minimize the positive reactions of IDR secondary to vaccination To the BCG.

Thus, we obtained a 2.2% incidence of tuberculosis in patients with latent tuberculosis infection (LTBI), infected with HIV under antiretroviral therapy. The study also showed that the patients were adults with a female predominance and the majority of patients (98%) were infected with HIV1, compared with 0.2% for

HIV2, like the epidemiological data of HIV/AIDS in Togo [10] and in other countries of the West African sub-region where there is a tendency to feminize HIV infection. [11] [12]. Because of have living closely with TB infected patients, 30 patients (14.15%) were exposed to a risk of contamination at different periods before admission. Adjoh *et al.* found in a previous study a proportion of 7.14% of patients who had a notion of tuberculosis [8].

The evolution of patients was influenced by the immune status of the patients at inclusion. Thus, the majority of tuberculosis cases observed at the end of the study were found among patients with a CD4 cell count  $< 350$  cells/mm<sup>3</sup> at the initiation of the study with a significant difference,  $p = 0.0027$ . Indeed, the risk of contracting TB is higher in the AIDS phase of HIV, of which it remains one of the most frequent opportunistic infections affecting 1 out of 5 seropositive patients [13]. In our study, the occurrence of active tuberculosis in patients who started taking ARV with very low CD4 can be an immune reconstitution syndrome with ARV. Usually for tuberculosis, this syndrome is more precocious and is often seen in the first few months of the initiation of ARV therapy, especially when the immune restoration is rapid and cause the constitution of a tuberculous granuloma around the Bacillus, whose clinical manifestations evoke the awakening of a tuberculosis hitherto latent.

Our study also shows that the occurrence of active tuberculosis was not influenced by the antiretroviral treatment at the end of the three-year follow-up,  $p > 0.05$  (Figure 2 and Figure 3). ARV therapy probably have enough action on the Immune restoration to prevent the occurrence of opportunistic pathologies with low virulence, but insufficient for the most pathogenic ones, such as tuberculosis [14].

In our study, the majority of tuberculosis cases occurred in the 18th month (11 cases out of 14). This phenomenon is a failure which stems from the fact that the modest technical plateau in our condition does not always make it possible to demonstrate the viral failure which often precedes clinical failure.

## 5. Conclusion

This study found a high incidence of tuberculosis within a maximum of 18 months in latent tuberculosis-infected PHAs who started their late ARV treatment or do not restore their immunity under ARV. Similarly, the improvement in the diagnosis of LTBI by interferon-gamma release assays can make it possible to consider the administration of chemoprophylaxis with isoniazid in order to reduce the incidence of tuberculosis in this category of immune compromised patients.

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