Incidence, Predictive Factors and Prognosis of Tuberculosis among Patients with HIV Infection in Guadeloupe 1988-2009

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Abstract

Objective: To determine the incidence, risk factors and prognosis for incident tuberculosis during the follow-up of HIV-infected patients in Guadeloupe.

Methods: We conducted a retrospective cohort study using STATA version IC 10.0 (College Station, Texas, USA).

Results: A single failure Cox proportional hazards model showed that patients with B CDC category (HR=4.50; 95%CI=1.50-13.60; P=0.007) and patients with C CDC category (HR=138.30; 95%CI=62.80-304.90; P=0.000) were associated with an increased risk of tuberculosis, whereas patients with low median CD4 count at enrolment (HR=0.50; 95%CI=0.30-0.84; P=0.009) and patients treated by ART (HR=0.45; 95%CI=0.34-0.62; P=0.000) were associated with a low risk of tuberculosis.

Conclusion: Our data showed a high incidence of tuberculosis and no socio-economic factors related to tuberculosis among HIV-infected patients. These findings help to effectively guide public health interventions.

Keywords: HIV-infected patients; Tuberculosis; Incidence; Predictive factors; Prognosis; Guadeloupe

Introduction

Tuberculosis (TB) continues to be an important global public health problem, intensified by the human immunodeficiency virus (HIV) epidemic. In 2010, there were 8.8 million (range, 8.5-9.2 million) incident cases of tuberculosis, 1.1 million (range, 0.9-1.2 million) deaths from TB among HIV-negative people and an additional 0.35 million (range, 0.32-0.39 million) deaths from HIV-associated TB [1]. The HIV/AIDS pandemic is responsible for the resurgence of tuberculosis worldwide, resulting in increased morbidity and mortality. HIV and Mycobacterium tuberculosis have a synergistic interaction; each propagates progression of the other.

In Guadeloupe, tuberculosis affecting the migrant population was characterised by the young age of the patients and a significant proportion of co-infection by the human immunodeficiency virus. However, HIV infection increased the risk of developing severe tuberculosis [2].

These French overseas territories are characterized by an important immigration from countries with high TB incidence and high HIV prevalence [3,4]. French Guiana and Guadeloupe have significant immigration from Haiti where TB is prevalent [5], and TB incidence in the island of Guadeloupe is much lower than in continental French Guiana or even in metropolitan France. Genotyping studies [6] in the overseas French territories have calculated that recent infections are more frequent in French Guiana (49.3%) than in Guadeloupe (27.2%) and that TB cases in foreign patients were of diverse South American sources in French Guiana whereas they mostly were from Haiti in Guadeloupe [6]. Although there are a lot of migrations in the Caribbean, and tuberculosis is frequent in Caribbean countries, tuberculosis was the 5th cause of AIDS in Guadeloupe, the 4th in French Guiana, whereas it was the number 1 cause of AIDS in metropolitan France. The more rural setting in the overseas French territories and the importance of migrations from sub-Saharan Africa in metropolitan France may explain this difference [7].

The study objective was to determine the incidence, risk factors and prognosis for incident TB during the follow-up of HIV-infected patients in Guadeloupe.

Background

Guadeloupe (French West Indies) is an overseas French department, which has a large number of persons living with HIV/AIDS. A large part of these are foreign females, mainly native to Haiti. The standards of healthcare in Guadeloupe are similar to those of metropolitan France. All human immunodeficiency virus (HIV) patients receive free antiretroviral treatments (including the most recent drugs) regardless of their origin or socioeconomic level. Radiology, viral loads, CD4 counts and genotyping, and antiretroviral concentration measurements are available for routine care. There is a reference university hospital with laboratories that specialise in parasitology, mycology and bacteriology.
as well as the Pasteur Institute for the diagnosis of tuberculosis (Pasteur Institute of Guadeloupe and Pasteur Institute of French Guiana).

Patients and Methods

Study population and sources of information

The HIV-positive patients followed in the University hospital of Pointe-à-Pitre, and Basse Terre hospital since January 1st 1988 and St Martin Hospital since January 1st 1992 until 31 December 2009 were enrolled in the Guadeloupe section of French Hospital Database for HIV (GFHDH). The French Hospital Database for HIV (FHDH) is a large prospective cohort study of HIV-infected patients who are aged >15 years and have been treated in a network of 68 French university hospitals. The enrollment criteria are documented HIV-1 or HIV-2 infection and written informed consent. Trained research assistants use French Ministry of Health DMI2 software to collect and record, on standardized forms, clinical and biological data at the time of study inclusion and at each visit or hospital admission for an HIV-related clinical event or a new treatment prescription or at least every 6 months. Diagnoses are coded according to the 10th International Classification of Diseases [8]. All patients (newly diagnosed and known HIV patients) followed between 1997 and 2009 were included.

Time-independent variables such as sex, nationality and transmission routes, and time-dependent variables such as age, weight, clinical events and therapeutic data, HIV-1 viral loads, CD4 and CD8 counts are routinely entered in the database by trained Clinical Studies Technicians. Patients included in the GFHDH have given informed consent to the use of their data. Their identity is encrypted before the data are sent to the Ministry of Health and the Institut National de la Recherche Médicale (INSERM) which centralize data from Regional Coordination of the Fight against HIV (COREVIH) throughout France. This data collection is approved by the Commission Nationale Informatique et Libertés (CNIL), a national committee that oversees research data, in order to protect patients personal data. The data were analysed with STATA 10.0 (Stata Corp LP, College Station, TX, USA).

In addition, general characteristics of AIDS patients in Guadeloupe, Metropolitan France and French Guiana were compared using data from the mandatory AIDS reporting system available on the Institut National de Veille Sanitaire (INVS) [9].

The patient characteristics in the Guadeloupe FHDH at the time of inclusion and at each visit or hospital admission for an HIV-related clinical event or a new treatment prescription or at least every 6 months, were compared to data from French Hospital Database on HIV infection in the study period, 235 cases of tuberculosis (77 females and 158 males) were noted (8.6%), including 21% of patients with AIDS. Overall, 4% of patients were reinfected and the mean number of new cases was 9.4 per 1000 person years (95% CI 8.3-10.4).

In the following, we will focus on data from patients living in Guadeloupe.

Results

Among the 2,739 patients enrolled in the Guadeloupe section of the French Hospital Database on HIV infection in the study period, 235 cases of tuberculosis (77 females and 158 males) were noted (8.6%), with a total of 8909 person-years of follow-up. The global incidence rate of tuberculosis was 2.8 per 100 person-years (CI 95% 2.4-3.1/py). This incidence decreased from the period 1988-1996 to the period 1997-2009 (3.2 per 100 person-years CI 95% 2.6-3.8/py). Among all patients, 60% (81/135) were antiretroviral naive at the time of TB diagnosis.

Definition of tuberculosis cases

All TB events (pulmonary or extra-pulmonary) were reported in the database.

A confirmed pulmonary TB case had to include two of the following three criteria

- Fever, dyspnoea, cough, weight loss or fatigue,
- Abnormal chest X-ray,
- Acid-fast bacillus (AFB) seen in sputum or lavage or lung tissue but not grown in culture,
- Response to anti-tuberculous treatment.

A confirmed case of extra-pulmonary TB was defined by both of the following criteria:

- Compatible symptoms,
- Culture or PCR from blood or affected tissue.

A probable case of extra-pulmonary TB was defined as:

- Compatible symptoms, plus either,
- AFB seen in affected tissue or blood,
- Concurrent diagnosis of pulmonary TB,
- or responds to treatment.

Statistical methods

TB incidence rates were calculated per 100 person years at risk (py). Patients were censored at the time of TB diagnosis or at the date of death or date of last visit in cases lost to follow-up. The factors associated with tuberculosis were analysed using a Cox model. Bivariate analysis first studied covariates and their relation to the outcome measure using a crude hazard ratio (HR) and its confidence interval. The covariates that were associated with the outcome (p<0.2) were then included in a multivariate Cox model yielding adjusted hazard ratios. For all tests performed, a p value of 0.05 or less was considered as statistically significant. The selection of the most parsimonious model was performed using the Akaike information criteria (AIC) by keeping the model with the lowest AIC value. The data were analysed with STATA 10.0 (Stata Corp LP, College Station, TX, USA).

Figure 1: Kaplan-Meier estimates representing the survival function with tuberculosis as failure event, over time*1988-2009 hospital cohort in Guadeloupe (n=2739)*.
The Kaplan-Meier estimates representing the survival function with tuberculosis as failure event, over time. Of the tuberculosis cases, 109 patients had a CD4 cell count below 200/mm³. Median age was 35.6 ± 0.4 years. There were 6 deaths recorded (2.6%): 4 pulmonary tuberculosis with cavity in Chest x-ray and 2 disseminated tuberculosis. Table 1 shows the incidence rates of tuberculosis and the adjusted hazard ratios for various factors. A single failure Cox proportional hazards model showed that patients, with B CDC category (HR=4.50; 95% CI=1.50-13.60; P=0.007) and patients with C CDC category (HR=138.30; 95% CI=62.80-304.90; P=0.000) were at an increased risk of tuberculosis. The patients who developed TB disease in our study had similar risk factors for TB in the Guadeloupian general population. However, patients with advanced CDC category were at increased risk of tuberculosis. The patients who recently started highly active antiretroviral treatment (HAART). Indeed, many recent studies have reported an increased incidence of TB-associated IRIS [19-30]. According to the International Network for the Study of HIV-Associated IRIS (INSHI), ART-associated TB refers to all TB diagnosed during ART, while the subset of patients who develop rapidly progressive signs and symptoms of TB, with exuberant inflammatory features, after the initiation of ART are called TB-associated IRIS [19-30]. According to the International Network for the Study of HIV-Associated IRIS (INSHI), ART-associated TB refers to all TB diagnosed during ART, while the subset of patients who develop rapidly progressive signs and symptoms of TB, with exuberant inflammatory features, after the initiation of ART are called TB-associated IRIS [19-30].

**Table 1:** Predictive factors of tuberculosis among patients with HIV infection in Guadeloupe: 1988-2009.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time at risk (years)</th>
<th>Tuberculosis (n)</th>
<th>Crude incidence rate per 100 py</th>
<th>Adjusted hazard ratio* (95% CI)</th>
<th>P</th>
</tr>
</thead>
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<td><strong>Age</strong></td>
<td></td>
<td></td>
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<tr>
<td>≤40</td>
<td>6050.14</td>
<td>136</td>
<td>1.9</td>
<td>0.80(0.37-1.73)</td>
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<td>&gt;40</td>
<td>2858.89</td>
<td>99</td>
<td>4.2</td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>3676.3</td>
<td>77</td>
<td>1.9</td>
<td>1</td>
<td>0.009</td>
</tr>
<tr>
<td>Male</td>
<td>5032.7</td>
<td>158</td>
<td>3.1</td>
<td>1</td>
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<tr>
<td>2005-2009</td>
<td>481.6</td>
<td>21</td>
<td>4.4</td>
<td>1</td>
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<td>2001-2004</td>
<td>1790.8</td>
<td>25</td>
<td>1.4</td>
<td>1</td>
<td>0.009</td>
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<td>1997-2000</td>
<td>3077.8</td>
<td>74</td>
<td>2.4</td>
<td>0.48(0.20-1.05)</td>
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<td>1988-1996</td>
<td>3558.8</td>
<td>115</td>
<td>3.2</td>
<td>0.80(0.37-1.73)</td>
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<td><strong>CD4 cell count</strong></td>
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<td>&gt; 500</td>
<td>2323.9</td>
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<td>0.8</td>
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<td>200-500</td>
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<td>2.2</td>
<td>0.80(0.48-1.34)</td>
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<td>&lt;200</td>
<td>2122.8</td>
<td>109</td>
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<td>A</td>
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<tr>
<td>B</td>
<td>1754.8</td>
<td>29</td>
<td>1.7</td>
<td>4.50(1.50-13.60)</td>
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<td>C</td>
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<td>103</td>
<td>2.4</td>
<td>0.45(0.34-0.62)</td>
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</tr>
</tbody>
</table>

*Obtained using a Cox proportional hazard model including all the above variables and tuberculosis as the failure event.

CI: confidence interval; py: person-years.

**Discussion**

In this population-based retrospective cohort analysis of adult HIV-infected patients, we observed a high incidence of TB. The high incidence of TB in our cohort patients suggests the importance of the early initiation of ART. Indeed, antiretroviral therapy (ART) has beneficial effects on mortality and lowers the risk of developing TB by 70-90% [8-11]. Our study had several limitations. First, although most of our results are consistent with previous studies, some potential risk factors, such as education, HIV knowledge and awareness, religion affiliations, and employment status, were not recorded. Due to the retrospective and observational design of this study, we were also unable to study the risk factors of TB-associated “immune reconstitution inflammatory syndrome” (IRIS), which occurs in HIV/AIDS patients who recently started highly active antiretroviral treatment (HAART). Indeed, many recent studies have reported an increased incidence of TB-associated IRIS [19-30]. According to the International Network for the Study of HIV-Associated IRIS (INSHI), ART-associated TB refers to all TB diagnosed during ART, while the subset of patients who develop rapidly progressive signs and symptoms of TB, with exuberant inflammatory features, after the initiation of ART are called TB-associated IRIS [19-30].
“unmasking TB-associated IRIS” [30]. The increased incidence of TB in the period 2005-2009 could be due to the increased number of cases of TB-IRIS. Clinicians should remain highly vigilant in HIV patients who develop TB after starting ART, as they can have much more severe disease, can deteriorate rapidly due to immune reconstitution, and may even require hospitalisation. Early ART initiation and intensified TB screening upon ART initiation are crucial to reduce incident TB.

In the present study, no statistically significant influence of age, gender or HIV diagnosis period was found, in contrast to the findings of previous studies [15,17-19].

Despite the limitations of the study, the high incidence of tuberculosis, its prognosis and its predictors in the Guadeloupian HIV-patients cohort helps to better understand the HIV/AIDS epidemic and effectively guide public health interventions. Our findings, however, are applicable to patients from other Overseas French Departments and the Caribbean areas.

Conclusion

TB incidence rates during the period 2001-2004 remained substantially lower than rates in the period 2005-2009. The duration of the disease, its advanced stage with profound immunosuppression, and the late initiation of ART are the predictive factors of tuberculosis in HIV-infected patients. Early ART initiation and intensified TB screening at ART initiation are crucial to reduce incident TB.

References
