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 at 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 TB 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 much 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.

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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 admitted to 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 DM12 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 Veille Sanitaire (INVS) [9].

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).

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 2005-2009. In Figure 1, 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).

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Figure 1: Kaplan-Meier estimates representing the survival function with tuberculosis as failure event, over time*1988-2009 hospital cohort in Guadeloupe (n=2739).
CI=0.34-0.62; P=0.000) were associated with a low risk of tuberculosis. CI=0.30-0.84; P=0.009) and the antiretroviral therapy (HR=0.45; 95% CI=62.80-304.90; P=0.000) were at an increased risk of tuberculosis. On the other hand, low CD4 count at enrolment (HR=0.50; 95% CI=1.50-13.60; P=0.007) and patients with C CDC category (HR=138.30; 95% CI=1.50-13.60; P=0.000) were at an increased risk of tuberculosis. The patients who 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 a low risk of tuberculosis.

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]. In our study, patients with CD4 count <200/mm³ were usually put under ART in order to improve their immune status and to prevent tuberculosis and other opportunistic infection in these patients. That is why they were in low risk of tuberculosis. However, TB occurred in young patients (mean age 35.6 ± 0.4 years), which is similar to results found by other studies [2,12]. A higher proportion of our patients with TB had median baseline CD4+ T-lymphocyte counts <200 cells/mm³ [13] compared to patients without TB (62.9% vs. 39.9%, respectively, X²; p= 0.000). This suggests that those who developed TB may have been more immunocompromised at baseline than patients remaining TB free. TB-induced immunosuppression is a well-studied area: an investigation of T cell cytokine responses in HIV-negative pulmonary TB patients showed a persistent depressed tuberculin-induced IFN-γ response up to 18 months despite successful treatment, suggesting a long-lasting depletion or primary dysfunction of antigen-responsive T cells from the peripheral blood due to active TB [9].

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

| Variables           | Time at risk (years) | Tuberculosis ( n) | Crude incidence rate per 100 py | Adjusted hazard ratio* (95% CI) | P     |
|---------------------|----------------------|-------------------|-------------------------------|--------------------------------|-------|
| Age                 |                      |                   |                               |                                 |       |
| ≤40                 | 6050.14              | 136               | 1.9                           | 0.45(0.34-0.62)                 | 0.000 |
| >40                 | 2858.89              | 99                | 4.2                           | -                              | -     |
| Gender              |                      |                   |                               |                                 |       |
| Female              | 3676.3               | 77                | 1.9                           | 0.45(0.34-0.62)                 | 0.000 |
| Male                | 5032.7               | 158               | 3.1                           | -                              | -     |
| HIV diagnosis period|                      |                   |                               |                                 |       |
| 2005-2009           | 481.6                | 21                | 4.4                           | 0.50(0.30-0.84)                 | 0.009 |
| 2001-2004           | 1790.8               | 25                | 1.4                           | -                              | -     |
| 1997-2000           | 3077.8               | 74                | 2.4                           | 0.46(0.20-1.05)                 | 0.065 |
| 1988-1996           | 3558.8               | 115               | 3.2                           | 0.80(0.37-1.73)                 | 0.57  |
| CD4 cell count      |                      |                   |                               |                                 |       |
| > 500               | 2323.9               | 19                | 0.8                           | 1                              |       |
| 200-500             | 2887.4               | 64                | 2.2                           | 0.80(0.48-1.34)                 | 0.40  |
| <200                | 2122.8               | 109               | 5.1                           | 0.50(0.30-0.84)                 | 0.000 |
| CDC categories      |                      |                   |                               |                                 |       |
| A                   | 5113.7               | 47                | 0.9                           | 1                              |       |
| B                   | 1754.8               | 29                | 1.7                           | 4.50(1.50-13.60)                | 0.007 |
| C                   | 2040.6               | 159               | 7.8                           | 138.30(62.80-304.90)            | 0.000 |
| ARTherapy           |                      |                   |                               |                                 |       |
| No                  | 4399.40              | 132               | 3.1                           | 1                              |       |
| Yes                 | 4509.04              | 103               | 2.4                           | 0.45(0.34-0.62)                 | 0.000 |

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

CI: confidence interval; py: person-years.
“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 Guadeloupean 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.

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