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▶ **To cite this version:**

Elise Gouhier, Emilie Gaubert-Maréchal, Philippe Abboud, Pierre Couppié, Mathieu Nacher. Predictive factors of HTLV1-HIV coinfections in French Guiana.. American Journal of Tropical Medicine and Hygiene, 2013, 89 (3), pp.549-53. 10.4269/ajtmh.12-0769 . inserm-00913990

HAL Id: inserm-00913990

https://inserm.hal.science/inserm-00913990

Submitted on 12 Aug 2014

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Predictive factors of HTLV1-HIV coinfections in French Guiana

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French Guiana, the French territory most affected by HIV (1,3% of pregnant women), is also endemic for HTLV1. Those two retroviruses, targeting the same cells, T CD4+ lymphocytes, are known to have mutual interactions

The objective of this study was to determine if the HTLV1/HIV coinfected patients had particular characteristics. All the patients followed for an HIV infection in French Guiana and having a computerized medical file containing an HTLV1serology, were included : there were 1333 HIV monoinfections and 76 HTLV1/VIH coinfections.

The prevalence of HTLV1/HIV coinfections was 5,39%. This study showed that women (OR=1,91[1,13-3,24]), subjects aged more than 40 years and patients of Surinamese origin (OR=2,65 [1,25_5,61]) were overrepresented among coinfected. CD4 count at the time of diagnosis and that the viral load was higher among coinfected patients. The clinical stage was not significantly different between the two groups. The number of CD4 cells was not higher among coinfected, unlike most reports from the literature. Prevalence of HTLV1 among HIV infected patients is high in French Guiana, physicians seem to omit the prescription of serology for this potentially serious coinfection.

Introduction

Located in South America between Brazil and Suriname, French Guiana is the French territory with the worst HIV epidemic. With 1,3 % of infected pregnant women (1), the

epidemic is generalized according to UNAIDS criteria. But actually, 64 % of new patients are migrants and sex work and crack use are suspected drivers of the epidemic (2). The predominant mode of infection is heterosexual sex (3).

French Guiana is also an area where the human T lymphotropic virus 1 (HTLV1) is endemic, concentrated in descendants of African Slaves (notably Maroons) (4). This retrovirus is responsible for, in about 5% of infected persons, adult T cell lymphoma/leukemia, HTLV1-associated spastic tropical paraparesis/myelopathy, other autoimmune manifestations or certains opportunistic infections (5). It shares almost the same transmission routes as HIV: blood, sexual (mostly from men to women) and vertical transmission mostly through maternal breastmilk (5). In French Guiana, HTLV1 is mostly transmitted through breastfeeding and sexual relations(6). HTLV1-HIV coinfections are frequent in endemic regions for these two retroviruses.

Although they presented different viral cycles, the two viruses have the same cellular tropism : CD4 lymphocytes. In vitro, it was shown that HTLV1 provoked an upregulation of HIV(7), and conversely(8). In clinical studies, there is a frequent description of an increased CD4 count in coinfected patients, without any corresponding immunological benefit. However, given the number of discordant results(9), it was not conclusively demonstrated that HTLV1 coinfection accelerated the evolution of HIV infection.

The only study performed on HTLV1/HIV in French Guiana showed lower survival in coinfected patients (10), but the number of patients was small (151 persons, of which only 18 coinfected) and only looked at survival.

In the present study, the HIV parameters of two populations, coinfected and HIV-infected without HTLV1 were compared.

Methods

A retrospective comparative study was performed using a data base collecting the eNADIS electronic patient file, an HIV-specific tool devised to the care of HIV patients and viral hepatitis patients. The data base collected information on patients seen between january first 2000 and january 23rd 2012.

Since a large number of HTLV1 serology results were missing in the patient file, a preliminary stage was to collect the missing data from the main laboratories in French Guiana performing this serology. The missing data was then entered into eNADIS to complete the database.

Inclusion criteria were : patient followed for an HIV infection in one of the 3 main hospitals of French Guiana (Centre Hospitalier Andrée Rosemon de Cayenne, Centre Médico-Chirurgical de Kourou et Centre Hospitalier de l'Ouest Guyanais de Saint Laurent du Maroni), using the eNADIS file, with a result for HTLV1 serology.

The exclusion criterion was the absence of an HTLV1 serology after attempting to recover the results in the laboratories.

The eNADIS database and patient file system are in agreement with the French Law « Informatique et Libertés » and are declared at the Commission Nationale Informatique et Liberté. All data were anonymized and all patients gave written informed consent before the creation of the computerized patient file, which entails retrospective use of the data.

The data analysis was performed using Stata 8 (® College Station, Texas, USA).

A bivariate analysis was first performed comparing different variables between the HIV-HTLV1 coinfected patients and the HIV without HTLV1 infection. Student's t-test was used for Gaussian quantitative variables and Mann Whitney's test for non-gaussian variables. The Chi2 test, or Fisher's exact test were used for qualitative variables. For ordinal variables the linear trend Chi2 test was used. For binary variables odds ratios and their confidence intervals were calculated.

Finally, a multivariate analysis was performed to obtain adjusted odds ratios for age, gender, country of residence, clinical stage, antiretroviral treatment. Covariates were retained from the saturated model using the likelyhood ratio test to obtain the most parsimonious model.

Results

1333 patients HIV+/HTLV1 – were included in the single infection group and 79 patients HIV+/HTLV1+ were included in the coinfected group.

In this population, the proportion of coinfected patients was 5.4%, the sex ratio was 0.9, the mean age was 44.5 years(Standard Deviation (SD) 13.2). The most frequent nationalities were Haitians (29.4%) , French (25.8%) and Surinamese (15.5%). The main contamination mode was sexual transmission (90.1%). The median duration of infection was 7 years (interquartile range=8 years), 55.2% of patients were asymptomatic (CDC stage A), 31.3% had AIDS (CDC stage C), and 80,4% were on antiretrovirals.

Bivariate analysis showed no significant difference regarding gender, nationality, HIV infection duration, contamination mode, clinical stage, antiretroviral treatment, virologic and immunologic and coinfections with hepatitis B, hepatitis C, syphilis, toxoplasmosis. In the HTLV1-HIV coinfected group, age was significantly higher (an average of 7 years older, $p<0.0001$) and the odds ratio for diabetes was 2.2 (95CI=1.0-4.34), $p=0.02$. For other comorbidities (renal failure, malignancy, etc…), for CD4 count, nadir CD4, maximum viral load, viral load before treatment, CD4 count before treatment, Alanine amino transferase, there were no significant differences. In the HTLV1-HIV coinfected group, the viral load on treatment was higher (median

HTLV1+= 47copies/mL, interquartile range=7580, medianHTLV1-= 30 copies/mL, interquartile range= 208, p=0.02), the CD4 count at the time of diagnosis was higher (medianHTLV1+=376 CD4/mm3, interquartile range=363, medianHTLV1-= 316,interquartile range=365, p=0.02) and ASAT were higher (medianHTLV1+=27 UI/L, interquartile range=12, medianHTLV1-=23, interquartile range=13, p=0.02).

Multivariate analysis adjusting for age showed that diabetes was not more frequent among coinfected patients than in HIV patients without HTLV1. In the final model women (OR=1.9, 95CI=1.13-3.24, p=0.02), surinamese nationals, and older patients (starting 41 years old) were overrepresented in the coinfected group (Table1). Similarly, CD4 counts>500/mm3 at the time of diagnosis (OR=2.3, 95CI=1.04-5.25,p=0.04). And viral load >1000 copies were more frequent in the coinfected group than in HIV patients without HTLV1.

Discussion

The prevalence of HTLV1/HIV coinfections in this study was 5.39% which is higher than the prevalence observed in Martinique (3.36 %) (11). The eNadis data base in French Guiana included 1326 patients without HTLV1 serology, which is 48.48 % of all patients, despite considerable efforts to collect results of serologies, whereas the data base in Martinique only had 3.58% of missing results (11). This probably leads to a selection bias, which could have inflated the proportion of positive HTLV1 tests (symptomatic patients with HTLV1 or belonging to a high risk group being more likely to be tested, and positive results are more likely to be entered in the database than the default: negative).

As in most studies on HTLV1 here we observed that women and older persons were more at risk of HTLV1 (5,10,12). Surinamese nationals appeared more infected with HTLV1. This is explained by the epidemiology of HTLV1 in French Guiana where the maroon populations are most affected with this infection (6,13), living mostly on the Maroni river which marks the border with Suriname. It is noteworthy that Haitian nationals, or other nationalities from the Caribbean were not more at risk, although HTLV1 prevalence is high in these countries (12).

There was no difference regarding some risk factors described in other studies such as IV drug use (14,15). But in, contrast with the countries were those studies took place (Brazil, USA) (14), French Guiana transmission is essentially sexual or maternofoetal, and IV drug use is marginal (13,16).

The clinical stage was not significantly different between the 2 groups. In the literature, there are conflicting data with some reporting more advanced disease whereas other studies did not find any difference. (9,15).

The HIV infection duration and the proportion on antiretroviral treatment, which could have been confounders were equivalent in both groups. .

Other coinfections (hepatitis B, hepatitis C, syphilis, toxoplasmosis) were not more frequent in the HTLV1-HIVcoinfections. A previous study found increased hepatitis C prevalence in HTLV1-HIV coinfected patients (14) but then again this study took place in a north American population where intraveinous drug use is more frequent than in French Guiana.

After adjusting for age there were no more comorbidities such as diabetes, cardiopathies, or renal failure in the HTLV1-HIV coinfected patients than in the HIV patients without HTLV1.

Malignancies were not more frequent in the HTLV1 coinfected group but this may be due to a lack of statistical power.

It was surprising to find no difference in CD4 counts between groups because it is a finding that is often reported elsewhere (10,14,15,17-21). Only the CD4 count at the time of diagnosis was significantly higher in the HTLV1-HIV coinfected patients, this after adjusting for gender, a potential confounder.

The viral load was significantly higher in coinfected patients. Conflicting results are found in the literature regarding this variable (9,22) but certain authors have suggested looking at this variable rather than CD4 counts to reflect the activity of the HIV infection (17).

In the present study, the ASAT level was higher in HTLV1-HIV coinfected patients. There were no more hepatitis, or antiretroviral treatments in this group. In addition, a study showed that liver enzymes were higher in patients with HCV/HTLV1 coinfections than single HCV infections (23). However, the difference observed has no clinical significance (4 units) and both medians are well below the upper limit of the normal range. During multivariate analysis, using a cutoff of 50 units no difference was observed between HTLV1-HIV coinfections and HIV. It is thus plausible that the statistical difference observed during bivariate analysis for liver enzymes is purely due to chance.

The main limitation of this study is its retrospective design, leading to numerous missing variables. Indeed, the thoroughness of data entry varies between physicians. We also regret the absence of data on opportunistic infections (due to HIV or HTLV1) , haemoglobin, CD8 counts, and CD4 percentages which could have given additional informations on the interactions between HTLV1 and HIV. Finally in the absence of longitudinal data, no data on survival was available.

Despite these drawbacks, this study is interesting because it includes a large number of patients (76 coinfections, 1333 HIV without HTLV1). Moreover, it shows a high prevalence of HTLV1 in HIV patients in French Guiana, a reminder that this serology should be part of the normal initial investigations in an HIV patients. A longitudinal

study on HTLV1-HIV coinfections in French Guiana, and possibly other regional centers would be useful to complete the present results.

	HTLV1 – (N=1333)	HTLV1 + (N=76)	p
Age in years : mean (standard deviation)	44.05 (12.99)	51.87 (14.29)	p<0.0001*
Viral load with treatment in copies/mL : median (interquartile range)	30 (208)	47 (7580)	p=0.0178**
CD4 count at the time of the diagnosis in number/mm3 : median (interquartile range)	316(364.7)	376(363.2)	p=0.02**
Nadir CD4 in number/mm3 : médiane (interquartile range)	159.7(236)	196.6(237.7)	p=0.15**
ASAT in IU/L : median (interquartile range)	23(13)	27(12)	p=0.02**

Table 1 Distribution of age, viral load, CD4 count at the time of diagnosis, nadir CD4 and ASAT in a population of HIV+ French Guyanese patients

* Student's t test

** Mann Whitney's test

Variable	HTLV1 + N(%)	HTLV1- N(%)	Odds Ratio (95% confidence interval)	p
Antiretroviral Treatment			1.61(0.36-1.1)	0.069
Yes	55(72.37)	1078(80.87)		
No	21(27.63)	255(19.13)		
Diabetes			2.18 (1-4.34)	0.02
Yes	11(14.47)	96(7.2)		
No	65(85.53)	1237(92.80)		
Cardiopathies			2.84 (0.53-9.97)	0.08
Yes	3(3.95)	19(1.43)		
No	73(96.05)	1314(98.57)		

Table 2 Odds Ratio for antiretroviral treatment, diabetes et cardiopathies in a population of HIV + French Guyanese patients

Variable	HTlV1 + N (%)	HTLV1 - N (%)	Ajusted Odds Ratio* (95% confidence interval)	p
Sex				
Male	28(36.84)	638(47.86)	1	
Female	***48(63.16)***	***695(52.14)***	***1.91 (1.13-3.24)***	***0.02***
Age				
<31 years	6(7.89)	191(14.33)	1	
31-40 years	9(11.84)	383(28.73)	0.96 (0.33-2.80)	0.944
41-50 years	***23(30.26)***	***347(26.03)***	***3.64 (1.41-9.40)***	***0.008***
51-60 years	***16(21.05)***	***273(20.48)***	***4.88 (1.74-13.67)***	***0.003***
>60 years	***22(28.95)***	***139(10.43)***	***14.83 (5.30-41.5)***	***<0.001***
Nationality				
French	17(22.37)	346(25.96)	1	
Brazilian	2(2.63)	83(6.23)	0.47 (0.1-2.14)	0.326
Guyanian	7(9.21)	123(9.23)	1.48 (0.58-3.82)	0.415
Haitian	17(22.37)	397(29.78)	0.69 (0.33-1.42)	0.311
Caribbean but Haitian	3(3.95)	23(1.73)	1.94 (0.47-7.99)	0.356
Others	2(2.63)	23(1.73)	2.12 (0.42-10.62)	0.360
Surinamese	***19(25)***	***199(14.93)***	***2.65 (1.25-5.61)***	***0.011***
Unknown	9(11.84)	139(10.43)	1.21 (0.47-2.7)	0.798
Viral Load				
>30000 copies/mL	***12(15.79)***	***152(11.4)***	***2.56 (1.20-5.45)***	***0.015***
10000-30000	***8(10.53)***	***46(3.45)***	***5.68 (2.22-14.55)***	***<0.001***
1000-9999	***11(14.47)***	***100(7.5)***	***3.27 (1.48-7.24)***	***0.003***
400-999	2(2.63)	53(3.98)	1.05 (0.23-4.74)	0.946
50-399	8(10.53)	179(13.43)	1.17 (0.51-2.69)	0.718
<50	28(36.84)	640(48.01)	1	
Unknown	7(9.21)	163(12.23)	1.62 (0.67-3.95)	0.284
CD4 count at the time of diagnosis				
<200 CD4/mm3	21(27.63)	230(17.25)	1	
200-349	15(19.74)	196(14.7)	2.5 (0.98-5.18)	0.057
350-499	7(9.21)	181(13.58)	0.92 (0.33-2.56)	0.871
>500	***11(14.47)***	***295(22.13)***	***2.34 (1.04-5.25)***	***0.040***
Unkown	22(28.95)	431(32.33)	1.58 (0.72-3.45)	0.253

Table 2 Ajusted Odds Ratio* in a population of HIV + French Guyanese patients

* Adjusted using a logistic regression model. The saturated model included sex, age, nationality, viral load, CD4 count at the time of diagnosis, treatment, cardiopathies, diabetes, nadir CD4 and ASAT as explanatory variables, the most parsimonious model was obtained using the Likelyhood ratio test

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