# Trends of Mortality and Causes of Death among HIV-infected Persons in Guadeloupe: 1988-2009

N Elenga[1], MT Ggeorger-sow[2], T Messiaen[3], I lamaury[3], I Favre[3], M Nacher[4, 5], G Beaucaire[3]

ABSTRACT

The aim of this study was to investigate the mortality rate, risk factors and causes of death among HIV-infected patients in Guadeloupe from 1988 to 2009. We used Kaplan-Meier analysis to describe the survival trends and the Cox proportional hazard model to identify predictors of deaths in HIV-infected patients. Mortality rate and causes of death were compared among patients whose HIV diagnosis was made in two different study periods. There were 672 deaths recorded. The exact cause of death was clearly identified for 202 patients (35%). There were 165 AIDS defining events and 37 non-AIDS defining events. The most frequent causes of death reported were HIV encephalopathy (n=54), cerebral toxoplasmosis (n=39), HIV-wasting syndrome (n=37), malignancies (n=13), cytomegalovirus pneumopathy (n=10). The crude incidence rate for patients on HAART was between 2.2 and 3.1 per 100 person-years, whereas it was 17.2 for those not on HAART. The variables in the Cox model that were significantly associated with death were addiction, depression, low CD4 count and high viral load levels in baseline. These results suggested that increased screening efforts, particularly in marginalised populations could help with early diagnosis and better follow-up in order to reduce mortality among HIV-infected patients.

**Keywords:** HIV-infected patients, mortality, causes, risk factors, Guadeloupe

From: [1]Service de Pédiatrie, Centre hospitalier de Cayenne « Andrée Rosemon », Rue des Flamboyants, BP 6006-97306 Cayenne Cedex, Guyane Française, [2]Coordination Régionale VIH (COREVIH) Guadeloupe CHU de Pointe-à-Pitre / Abymes Bâtiment B Ancien Hôpital Ricou 2ème étage BP 465 97159 Pointe-à-Pitre Cedex, [3]Messiaen Thierry MD Service des maladies infectieuses, Guadeloupe CHU de Pointe-à-Pitre / Abymes Bâtiment B Ancien Hôpital Ricou 2ème étage BP465 97159 Pointe-à-Pitre Cedex, [3]Service des maladies infectieuses, Guadeloupe CHU de Pointe-à-Pitre / Abymes Bâtiment B Ancien Hôpital Ricou 2ème étage BP465 97159 Pointe-à-Pitre Cedex, [4,5]Coordination Régionale VIH (COREVIH) Centre hospitalier de Cayenne « Andrée Rosemon », Centre d'Investigation Clinique Epédémiologie Clinique CIC EC Antilles Guyane CIE 802, Centre hospitalier de Cayenne « Andrée Rosemon », Rue des Flamboyants, BP 6006-97306 Cayenne Cedex, Guyane française.

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Correspondence; Dr N Elenga, Service de Pédiatrie, Centre hospitalier de Cayenne « Andrée Rosemon », Rue des Flamboyants, BP 6006-97306. Fax: +594 594 394 819, e-mail: elengafr@yahoo.fr

## INTRODUCTION

By the end of 2009, approximately 1572 people were living with HIV and AIDS in Guadeloupe (1). Since the introduction of highly active antiretroviral therapy (HAART) in developed countries, the incidence of death in HIV-infected patients has dramatically decreased, and has changed the consideration of HIV infection from a rapidly fatal to a chronic manageable disease (2-5). Although access to antiretroviral (ARV) therapy has improved in the Caribbean, mortality rates were similar to those reported elsewhere for resource-limited settings (6). Health in Guadeloupe is different from other Caribbean countries; the standards of healthcare are closer to those of mainland France. All HIV-infected patients receive free antiretroviral treatment (including the most recent drugs) regardless of their origin or socioeconomic status. Viral loads, CD4 counts, genotyping and antiretroviral concentration measurements are available in routine care. HIV-infected patients in Guadeloupe are often diagnosed at more advanced stages of infection (7). In France, by the end of 2009, the incidence rate of deaths was 0.8 per 100 person-years. However, there was a decrease of AIDS-related deaths and malignancies were the most frequent causes of mortality (8, 9). In French Guiana, the incidence rate for patients on HAART was 1.6 per 100 person-years, whereas it was 6.1 for those not on HAART (10). Continued mortality surveillance of HIV/AIDS and the specific causes of death is imperative to follow the epidemic changes.

Although an increase in survival has been documented, there are no published data comparing specific causes of death between the pre-HAART and HAART eras in Guadeloupe. The

objective of this study was to assess the trends in mortality rate and cause of deaths over time among HIV-infected patients in Guadeloupe between the pre-HAART and HAART eras.

## METHODS

### Background

Even though it is located in the Region of the Americas, Guadeloupe is given special protection and granted structural funds from Europe devoted to assisting developing European regions. Population estimates in 2009 were 404,394 inhabitants, with the population below 25 years representing 35.8% of the total. In 2009, life expectancy in Guadeloupe was 83.4 years for women and 75.6 for men (11). Immigration from neighbouring developing countries accounted for part of the growth population; Guadeloupe, being a free port with a thriving tourism industry, has had a four-fold increase in the number of inhabitants in the past eight years; half of the population is currently foreign.

*Data sources*

The HIV-positive patients followed in Guadeloupe from January 1$^{st}$ 1988 and St Martin Hospital from January 1$^{st}$ 1992 until 31 December 2009 were enrolled in the French Hospital Database for HIV (GFHDH) as described elsewhere (12). Time-independent variables such as sex, nationality and mode of transmission, and time-dependent variables such as age, CD4 counts, HIV-1 viral loads, treatments, and clinical events were routinely entered in the database by trained Clinical Studies Technicians. The enrolment criteria were documented HIV-1 or HIV-2 infection and written informed consent. Trained research assistants used French Ministry of Health DMI2 software to collect and record, on standardised forms, clinical and biological data at the time of study inclusion and at each visit or hospital

admission for a HIV-related clinical event or a new treatment prescription or at least every 6 months. Diagnoses were coded by physicians, according to the 10th International Classification of Diseases (13). Patients included in the GFHDH gave informed consent for the use of their data. Their identity was encrypted before the data were sent to the Ministry of Health and the Institut National de la Recherche Médicale (INSERM) which centralises data from Centres for Information and Care of HIV (CISIH) throughout France. This data collection was approved by the Commission Nationale Informatique et Libertés (CNIL), which is a national committee that oversees research data. The origin date was the date of enrolment. Patients were censored at the date of death or date of last visit in cases lost to follow-up.

*Definitions*

The underlying cause of death was determined according to the International Classification of Diseases, 10th revision (ICD-10) rules: the underlying cause of death was disease or injury, which initiated the train of morbid events leading to death (13). Cause of death was defined as the main condition that initiated the sequence of events resulting in death. Cause of death was determined by the infectious disease specialist who had taken care of the patient if the patient died in the study hospital. If the patient died in another hospital, the first author determined the cause of death by reviewing medical records. If the hospital records were unavailable or the patient did not die in a hospital, the cause of death was determined from death certificates.

*Eligibility criteria*

Patients were eligible for the study if they were aged ≥ 18 years, and had started care in one of the study centres between 1988 and 2009.

*Variables*

The failure event was death. The main explanatory variables were age (≤40 years or >40 years), gender, nationality (French citizens or non-French citizens), CD4 count at enrolment (categorised as 0–199, 200–499 and ≥500 cells/mL), viral load count, CDC categories, mode of acquisition of the virus, availability of antiretroviral treatment (ART) and history of psychiatric problems during follow-up and treatment. Three study periods were defined; pre-HAART period (1988-1996), early-HAART period (1997-2004), and late-HAART period (2005-2009). The proportionality of the hazard functions was determined graphically by plotting hazard curves for each variable. Age, CD4 count category, viral load at the time of HIV diagnosis, and follow-up duration were transformed into dummy variables to compare different groups with a reference group.

*Statistical analysis*

We calculated the incidence rate of specific causes of death in the HIV-infected individuals that were followed-up in clinical centers in Guadeloupe between 1988 and 2009, using survival times (st) functions in Stata. A single failure Cox proportional hazards model was used with death as the failure variable. We evaluated the adjusted association between failure and explanatory variables. For all tests performed, a p value of 0.05 or less was considered statistically significant. The data were analysed with STATA 10.0 (Stata Corp LP, College Station, TX, USA)

## RESULTS

### Baseline characteristics of our study population

A total of 3368 subjects with 72,656 observations were included in the analysis, representing a total of 7204 person-years of follow-up. The median follow-up time was 1.9 years. Participants had a mean age of 36.9 ± 13 years. There were 1429 females (43%) and 1939 males (57%). Among these patients, 4% (n=115) reported addictions. Thirty-nine per cent of the patients had initial CD4 counts <200 cells/mL. Overall, 53% of the patients had a viral load >4.00 log (median 3.88 log, IQR 2.21–5.55 log).

*Incidence rates and Causes of death*

Table 1 shows the incidence rates of death and the adjusted hazard ratios for various factors. The crude incidence rate for patients on HAART was between 2.2 and 3.1 per 100 person-years, whereas it was 17.2 for those not on HAART. The variables in the Cox model (Table 1) significantly associated with death were addiction, depression, low CD4 count and high viral load levels in baseline.

There were 672 deaths recorded. Figure 1 shows Kaplan–Meier survival curves. The exact causes of death were clearly identified for 450 patients (67%).

There were 184 AIDS defining events and 266 non-AIDS defining events. The most frequently reported causes of death (Fig 2) were HIV encephalopathy (n=54), malignancies (n=51), cerebral toxoplasmosis (n=39), HIV-wasting syndrome (n=37), septicaemia (n=36), pneumocystis (n=16), cytomegalovirus pneumopathy (n=10), pneumonia (n=10), oesophageal candidiasis (n=6) stroke (n=6), neuro-meningeal cryptococcosis (n=5), pulmonary embolism (n=5), chronic herpes simplex infection (n=5), disseminated histoplasmosis (n=3), cerebral oedema (n=3), meningeal tuberculosis (n=1), multiple diseases (n=162), indeterminate cause (n=76) and unknown cause (n=157).

Table 2 shows the demographic and clinical characteristics of 672 HIV-infected patients who died in the period 1988-2009. A total of 77% of patients presented in the pre-HAART period, and 55% of them had a CD4 cell counts <200 cells/µL at first presentation for HIV care. The proportion of patients at C-stage (CDC) at the initial presentation was 32, 34 and 33% respectively, in the three periods.

Figure 3, which represents the causes of death according to the ART period, shows the increase of malignancies in the post-HAART period.

## DISCUSSION

In this study, we had a longitudinal follow-up over 21 years to monitor the changes in survival and causes of death among HIV-infected patients in Guadeloupe. This study showed that the survival of patients presenting to the hospital for HIV care in the HAART era significantly improved compared with those who presented in the pre-HAART era. These findings are generally consistent with findings of other studies conducted in Guadeloupe (14) and developed countries (2, 3, 5, 15-20). In our study, even during the HAART period, the survival of patients presenting in the late-HAART period improved compared to that of the patients presenting in the early-HAART period. However, as shown in Figure 1, despite of survival improvement in the HAART era, the early mortality was still substantial in the late-HAART period. This is presumably due to the high proportion of patients presenting late into care. More than 75% of the patients had presented in the pre-HAART period; furthermore, more than 50% of patients in this group who died had a CD4 cell count <200 cells/µL at first presentation for HIV care. The proportion of patients at C-stage (CDC) at the initial presentation remained stable during the three periods. However there was many changes in the causes of mortality during the different periods. In the pre-HAART period, the main

causes were HIV-encephalopathy, HIV-wasting syndrome and cerebral toxoplasmosis. In the HAART period, the tree first causes were septicaemia, HIV-encephalopathy and cerebral toxoplasmosis while in the late HAART period the main causes were malignancies, cerebral toxoplasmosis and HIV-encephalopathy.

However, there was a trend toward an increasing number of PCP and decreasing frequency of tuberculosis as the cause of death over time. These findings seem to be a result of the increase in the proportion of late presenters to care in early and late-HAART periods. Here, we provide evidence that AIDS-defining conditions remain a frequent cause of death. AIDS opportunistic infections have been reported to be the most frequent cause of death in the early ART era (20); this trend could be explained by two reasons: the young age of our population, a late presentation for care in immigrants who frequently live in precarious socio-economic conditions. Despite free access to care in France, poor socioeconomic conditions are associated with higher mortality among HIV-infected patients as well as the general population (21, 22); the standards of care are similar to those in mainland France. The main identified causes of non-AIDS-related deaths were cancer (11%), stroke (1%) and pulmonary embolism (1%). In our population, the mortality rate in the current HAART period is one-sixth the rate in the pre-HAART period. Our results could also be compared with data from France. In the study mortality 2010: the main underlying causes of death were AIDS related: 47 % in 2000, 36 % in 2005 and 25 % in 2010. Neoplasia accounted for a third of the causes of all deaths (9).

This study has several limitations. First, although all data were collected prospectively, the study was designed after data collection had ended. However, deaths were classified retrospectively without complete clinical histories. Also, in several patients (33%), the cause of death could not be determined. This study allowed us to monitor long-term trends of mortality and causes of death; however, we were not able to perform a more detailed analysis

of the causal role of the specific risk factors related to death, such as underlying conditions, the rate of loss to follow-up, the effectiveness of prophylaxis and HAART, or the effect of the immune reconstitutional inflammatory syndrome. Second, because our study was based on the population presented to the hospital for HIV care, AIDS-related deaths might have been overestimated.

In summary, our results are in agreement with the significant decline in the mortality of HIV-infected patients in the HAART era. Despite the survival improvement in the HAART era, early mortality was still substantial in late-HAART period mainly due to late HIV diagnosis and late presentation to care. Since AIDS-related death still remains the leading cause of death, these results suggest that increased screening efforts, particularly in marginalised populations, could help with the early diagnosis and better follow-up in order to reduce mortality among HIV-infected patients.

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**AUTHORS' NOTE**

NE has analysed, interpreted the data of this study and wrote the first draft of the manuscript. MT GS, TM, IL, IF, GB have contributed to acquisition of data, read and approved the final manuscript. MN has corrected and approved the final manuscript.

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