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RESEARCH ARTICLE

Estimation of the duration between HIV seroconversion and HIV diagnosis in different population groups in French Guiana: Strategic information to reduce the proportion of undiagnosed infections

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Data Availability Statement: In France, all computer data (including databases, in particular patient data) are protected by the National Commission on Informatics and Liberty (CNIL), the national data protection authority for France. CNIL is an independent French administrative regulatory body whose mission is to ensure that data privacy law is applied to the collection, storage, and use of personal data. As the database of this study was authorized by the CNIL, we cannot make available

Abstract

Background

Given the great efforts put into the strategic objective of reducing the proportion of HIV-infected patients that are undiagnosed, the aim of the present study was to review the temporal trends between 1997 and 2016 for median estimates of infection duration and median CD4 count at diagnosis for the main patient origins in French Guiana.

Methods

CD4 cell count at HIV sero-conversion and square root of CD4 cell decline were obtained using the CD4 decline in a cohort of HIV-infected persons in the UK, fitting random effect (slope and intercept) multilevel linear regression models. Multivariate analysis used robust regression for modeling the delay between estimated HIV seroconversion and diagnosis and quantile regression for CD4 at HIV diagnosis.

Results

The median interval between the estimated HIV seroconversion and HIV diagnosis was 8 years for patients from Brazil, 4.5 years for those from Haiti, 6.6 years for those from Suriname, 3.3 years for patients from Guyana, and 3.1 years for French patients. A simple robust regression model with French patients as reference group adjusting for sex and age at the time of diagnosis showed that the interval was significantly longer for Brazilian

data without prior agreement of the CNIL. The data may be made available by the authors but according to French law, researchers wishing to obtain the data must obtain additional authorization with the CNIL. In practice, the first step for any researcher wishing to obtain the data should be to ask the Coordination Regionale de lutte contre le SIDA (corevih@ch-cayenne.fr) who will guide the researcher through the process with the CNIL. The COREVIH collects data for all of French Guiana and analyzes the data for the purposes of improving interventions. Interested researchers may also contact Mathieu Nacher, chair of the COREVIH and author, using the following email address: mathieu.nacher@ch-cayenne.fr.

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($\beta = +3.7$ years, $P = 0.001$), Surinamese ($\beta = +4.2$ years, $P < 0.0001$), Haitian origins ($\beta = +1.5$ years, $P = 0.049$) but not for those originating from Guyana ($\beta = -0.03$ years, $P = 0.9$); Men independently had a longer interval than women ($\beta = +3.5$ years, $P < 0.0001$).

Conclusions

Despite great efforts in French Guiana regarding HIV testing both in terms of diversification and intensification we still need to tailor the offer to better reach the communities in need. These results should help authorities scale up and optimize initiatives to reduce the proportion of patients who are unaware of their infection. They also raise the question of the role of stigma and discrimination as a barrier to HIV testing in small communities, and further emphasize the importance of reducing it.

Introduction

Since 1981 and the first description of AIDS, there has been dramatic progress in the development of antiretrovirals and treatment strategies. If all patients were effectively treated, the elimination of HIV would even be theoretically possible [1]. But in real life, undiagnosed HIV-infected patients contribute disproportionately to the epidemic. A major strategic goal is thus to continually reduce the proportion of undiagnosed HIV infections and to treat all diagnosed with HIV in order to reduce morbidity and transmission.

French Guiana is the French territory with the worst HIV epidemic [2]. Over 75% of patients are foreign born. The prevalence of HIV among pregnant women has been over 1% for 2 decades. AIDS incidence is ten times higher than the national average (21.6 per 100,000 vs. 2.1 per 100,000) [3,4]. The territory has access to all the newest antiretroviral drugs, PrEP, free universal health care for all HIV patients and residence permits for foreign patients. The suspected drivers of the epidemic are sex work, crack cocaine use, and multiple concurrent sexual partnerships [2].

Males, older age groups and foreign born patients were diagnosed later on average than other groups [5]. In the past 5 years, HIV testing strategies have been diversified with ELISA lab testing, testing in emergency services, mobile testing centers, rapid testing at private practices, community based testing, and self testing [6]. The number of tests performed in French Guiana is also very high, over twice of what is performed in Mainland France (205 tests per 1000 inhabitants versus 81 tests per 1 000 inhabitants, respectively). [7]

Methods based on CD4 count decline have been used to estimate the probable country of infection and they have allowed to estimate the duration between seroconversion and HIV diagnosis. [8] We recently estimated that in French Guiana 44–64% of foreign born patients were infected within French Guiana. [9]

Given the great efforts put into the strategic objective of reducing the proportion of HIV-infected patients that are undiagnosed, the aim of the present study was to review the temporal trends for median estimates of infection duration and median CD4 count at diagnosis for the main patient origins in French Guiana. The use of country of birth as a categorization category rests on the assumption that communities are often grouped and that community-based interventions would help in reducing the duration of the interval between seroconversion and HIV diagnosis and reducing the proportion of HIV patients unaware of their HIV infection thus slowing down transmission in these communities.

Methods

Study design

Setting and participants. Data on HIV patients has been available since 1989 in French Guiana. Clinical, biological and epidemiological data are collected by specific trained research technicians in the DMI2 government software until 2008, and then in eNADIS/DATAIDS [10].

Inclusion criteria. We included patients who were followed in Cayenne, Saint Laurent and Kourou between 1997 and 2016 for whom the initial CD4 count at the time of diagnosis was available.

Statistical methods

Time since seroconversion. The duration of infection was estimated for each patient. This estimation was based on the rate of CD4 decline, which depended on each person's age and ethnicity, between the CD4 count at the time of diagnosis and the estimated CD4 count at the time of HIV infection. CD4 cell count at HIV sero-conversion and square root of CD4 cell decline were obtained using the CD4 decline in a cohort of HIV-infected persons, fitting random effect (slope and intercept) multilevel linear regression models, as originally described in the UK. [8,11] This allowed to calculate CD4 counts at the time of infection and the slope in an age and ethnicity-dependent variable. [8,11] Most migrants French Guiana are from African American ancestry thus the median CD4 count and interquartile range, and the slope of CD4 (square root) decline used were those calculated for black populations (median 487 (IQR = 377–619)), and $0.2+0.02 \times \text{age}$ at diagnosis, respectively. [8,11] For persons from northern Brazil, who are very often of mixed Amerindian ethnicity median CD4 count and interquartile range were used, and the slope of CD4 (square root) for other ethnicities (median 538 (IQR = 403–701)), $0.55+0.02 \times \text{age}$ at diagnosis (S1 Table).

The time between seroconversion and time at diagnosis was estimated using the formula $[\text{square root}(\text{CD4 at seroconversion}) - \text{square root}(\text{CD4 at HIV diagnosis})] / \text{slope of CD4 decline}$. [8,11]

Statistical analysis. The statistical analysis was performed using Stata 13.0 (Stata Corp LP, College Station, TX, USA).

Descriptive statistics were computed. Mostly the estimation of time between seroconversion and HIV diagnosis was plotted per year of diagnosis to describe temporal trends. Median CD4 counts were also plotted to see if this objective measure was coherent with the estimated durations between infection and diagnosis. This was performed separately for patients originating from Brazil, France (French Guiana), Guyana, Haiti, and Suriname. The choice of these risk groups was based on the fact that most HIV-infected patients are of foreign origin and that in an operational perspective, identifying differences would help scale up HIV testing efforts. Comparisons used the ranksum test and the Kruskal Wallis test. Multivariate analysis used robust regression for modeling the delay between estimated HIV seroconversion and diagnosis and quantile regression for CD4 at HIV diagnosis.

Ethics and funding. Patients included in the FHDH give informed consent for using their case record data for research and publication of research results. Patient identity is encrypted before the data is sent to the Institut National de la Recherche Médicale (INSERM), which centralizes data from Regional Coordinations for the fight against HIV (COREVIH) throughout France. The cohort has been approved by the Commission Nationale Informatique et Libertés (CNIL) since Nov 27th 1991 and has led to many international scientific publications. No specific funding was obtained for this study.

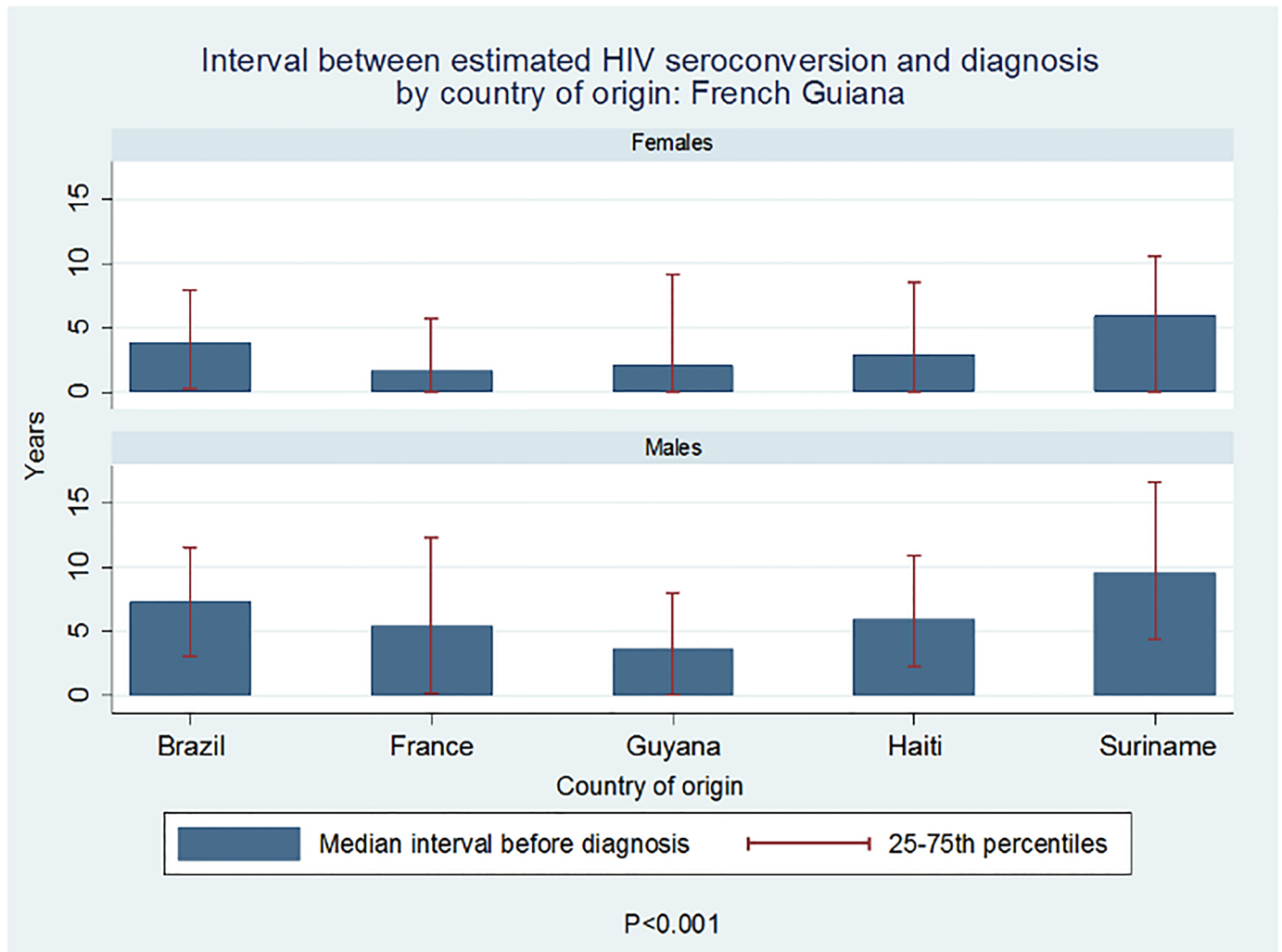


Fig 1. Median interval between the estimated HIV seroconversion and HIV diagnosis by country of origin.

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Results

Overall, in 2016, there were 1383 patients actively followed in the database of whom 279 were of French origin, 607 were of Haitian origin, 419 were of Surinamese origin, 173 were from Brazil and 173 from Guyana. The median interval between HIV seroconversion and HIV diagnosis was 3.5 years (Lower-Higher estimates = 0.5–6.7) in women and 6.4 years (IQR = 8–9.3) in men, $P < 0.001$.

The median interval between the estimated HIV seroconversion and HIV diagnosis was 5.1 years for patients from Brazil, 4.5 years for those from Haiti, 7.2 years for those from Suriname, 2.9 years for patients from Guyana, and 3.1 years for French patients (Fig 1).

These differences were statistically significant, $P < 0.0001$ (Kruskal Wallis). A simple quantile regression model with French patients as reference group adjusting for sex and age at the time of diagnosis showed that the interval was significantly longer for Surinamese patients ($\beta = +4.5$ years, $P < 0.0001$), but not for those originating from Brazil ($\beta = +1.6$ years, $P = 0.16$), Haiti ($\beta = +1.3$ years, $P = 0.13$) or Guyana ($\beta = -0.5$ years, $P = 0.6$); Men independently had a longer interval than women ($\beta = +3$ years, $P < 0.0001$). Some of the estimations were obviously

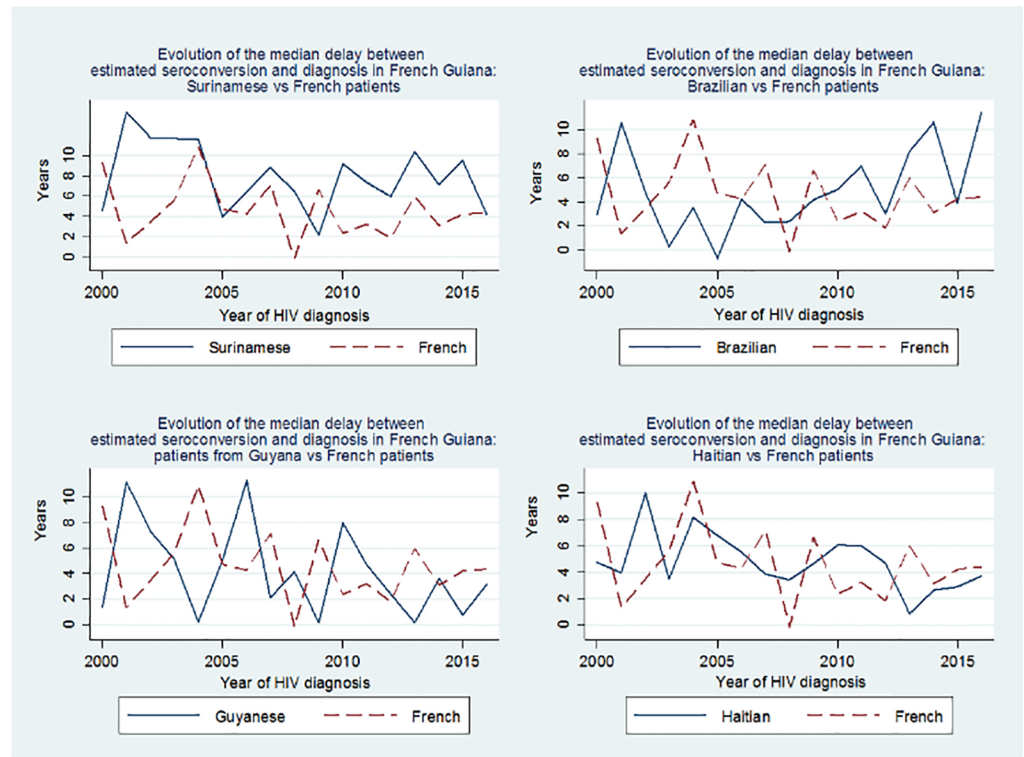


Fig 2. Temporal evolution of the median of the estimated delay between HIV seroconversion and diagnosis by country of origin.

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distorted, leading to estimated dates of seroconversion that would have taken place after the actual diagnosis. Therefore, the median estimate seemed the more prudent option.

Fig 2 shows the temporal evolution of the median of the estimated delay between HIV seroconversion and diagnosis for patients from Suriname, Brazil, Guyana, Haiti, relative to those from France (French Guiana). The data show that for Suriname and Brazil this delay was high, was stable for Suriname and seemed to increase for Brazil. For French citizens and for persons from Guyana the delay between seroconversion and diagnosis was shorter and seemed to decline. For patients from Haiti, this delay was intermediate and seemed on a downward trend (Spearman's $Rho = -0.06$, $p = 0.2$). These trends are also apparent when looking at the median CD4 count at the time of diagnosis with those from Brazil and Suriname having the lowest mean CD4 count at the time of diagnosis.

Fig 3 shows the CD4 count at diagnosis over time broken down by sex, which shows a regular difference with men testing later.

Quantile regression with CD4 count at diagnosis and country of origin with French patients as a reference group also found that patients from Suriname and Brazil had lower CD4 counts at the time of diagnosis. A quantile regression model with French patients as reference group adjusting for sex and age at the time of diagnosis showed that initial CD4 counts were significantly lower for patients from Brazil ($\beta = -108$ CD4 per mm^3 , $P = 0.006$) and Suriname ($\beta = -136$ CD4 per mm^3 , $P < 0.0001$), but not from Haiti ($\beta = -39$ CD4 per mm^3 , $P = 0.16$) or patients from Guyana ($\beta = +14$ CD4 per mm^3 , $P = 0.7$). Fig 2 shows the temporal evolution of initial CD4 count at diagnosis among the main migrant groups and among French patients. There was a significant worsening of the situation for patients from Brazil (Spearman's $Rho = -0.21$,

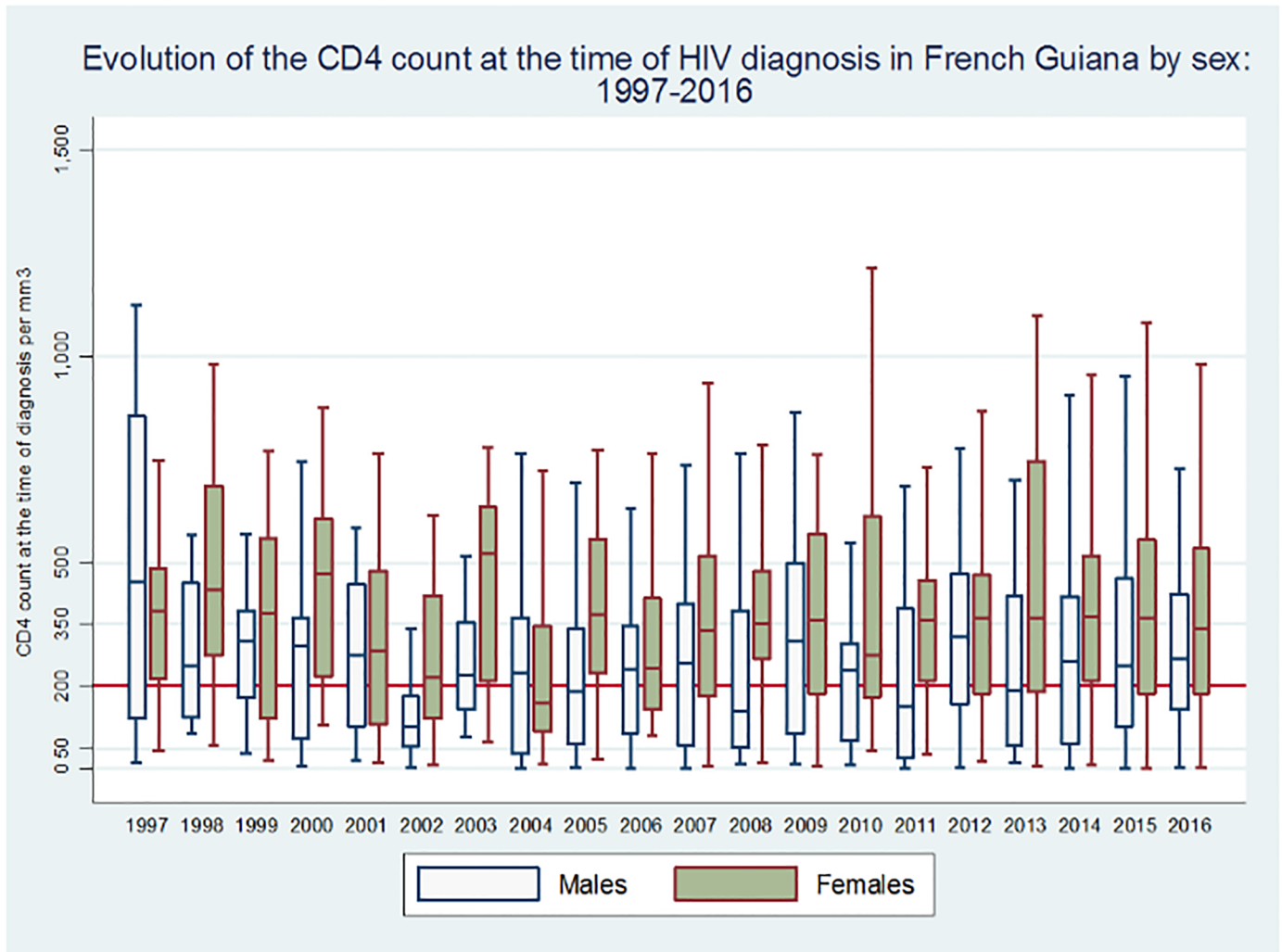


Fig 3. Temporal evolution of the CD4 count at diagnosis, by sex.

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$p = 0.046$), but not other countries of origin (France Spearman’s $Rho = -0.08$, $p = 0.27$; Haiti, Spearman’s $Rho = -0.07$, $p = 0.17$; Guyana, Spearman’s $Rho = 0.02$, $p = 0.8$; Suriname, Spearman’s $Rho = -0.08$, $p = 0.18$).

Discussion

Undiagnosed HIV infections are a major driver of the HIV epidemic and thus reducing the interval between seroconversion and diagnosis through the improvement of HIV testing is a crucial strategic objective [1]. CD4 counts at the time of diagnosis give crucial information about diagnostic delay. However, despite possible errors, transforming CD4 counts into a quantified estimation of the duration of the undiagnosed infection is not trivial because it frames the problem in a more meaningful way. The present results identify groups where HIV has a prolonged evolution before diagnosis. The results are also sobering because they show that improvement is at best slow. Furthermore, they suggest that among patients from Brazil, diagnosis is being performed later than before.

The fact that patients from neighboring Brazil and Suriname are tested so late, may reflect the fact that they are often persons living in remote areas in the interior, often patients living along the remote villages along the Surinamese side of the Maroni river, or more recently, Garimpeiros working in illegal goldmines.[12–14] They may be less informed about the benefits of HIV testing and perhaps less motivated than persons living in cities, and have fewer opportunities to get tested than urban populations. Stigma and discrimination in small communities may also be an important reason for not getting tested[15,16]. In these remote areas, scaling up of health education and testing efforts is recent and may still not be sufficient to impact the hidden infections' reservoir. Patients from Guyana more often live in the Cities, originate from Georgetown, and have more opportunities and perhaps interest to get tested for HIV. Patients from Haiti had intermediate results, with after adjustments for sex and age, shorter intervals (1.3years later than French) than those from Suriname (4.5years later than the French) or from Brazil (1.6 years later than the French) but longer than patients from France (French Guiana) or Guyana. With median estimates between seroconversion and diagnosis of 5.1years among patients from Brazil, 7.2 years among patients from Suriname, 4.5years among patients from Haiti, 2.9 years among patients from Guyana, and 3.1years among French patients there is still a prolonged window of opportunity for HIV transmission. For patients of foreign origin, one hypothesis underlying the diagnostic delay would be that those starting to have symptoms related to their immunosuppression seek care in French Guiana because the French Health system is attractive to them. Patients from Guyana seem to go against this reasoning but this hypothesis could mainly concern those living in neighboring countries like Suriname or Brazil. However, in a recent study in foreign patients from the Cayenne area it was estimated that 55% (Quartiles 45%–65%) of HIV-infected patients had acquired HIV in French Guiana (Manuscript in revision). This may go against the hypothesis of a special influx of the most immunosuppressed patients, and suggest that our interventions struggle to percolate through all population layers in French Guiana, especially the most in need.

The limitations of this study are that the estimation of the seroconversion date based on CD4 counts at diagnosis is an approximation. The calculations are based on ethnic groups, information that is not available in our data base and we made assumptions that may not always be right: all French patients are not of African descent but we used this hypothesis because creoles and maroons are the main population groups in French Guiana[17]. Although, the parameters in this method were calculated in the UK, populations from Latin America and the Caribbean were present and most of the viruses are also HIV1-B as in French Guiana. However, the slope parameters used and the estimations of median CD4 at diagnosis are susceptible to variation between ethnic groups and we cannot exclude distortions in our estimates.[18] Other authors have used methods relying on additional variables which may have been more precise[19–21], but because some of the information used was not available in our dataset, we used the above simpler method. Some of the computed infection dates were estimated to be after the diagnosis which is impossible. Thus calculated intervals should be taken with caution on an individual basis. However, at the population level, which was our frame of reference, central measures may be an acceptable approximation. The above estimates are computed from HIV individuals who are diagnosed with the underlying assumption of proportionality of undiagnosed individuals. Possible limitations could arise if the proportion of HIV infected persons who are diagnosed differed between groups.

UNAIDS 90x90x90 goal is within reach in French Guiana. Using the ECDC models, the estimated proportion of undiagnosed HIV-infections is *globally* estimated to be 15% in French Guiana, 91% of diagnosed patients in care are on antiretrovirals and 91% are virologically suppressed (Manuscript in review). The first part of the 90x90x90 objective still requires additional progress. There have been great efforts in French Guiana regarding HIV testing both in terms

of diversification of the offer, and intensification of the numbers of tests performed. Each year, there are 205 HIV tests per every 100 000 inhabitants, and increasing, versus 81 per 100 000 in mainland France.[22] We probably need to do even more in global quantity but also we need to tailor the offer to better reach the communities in need. We emphasize that looking at the country of origin is not aimed at stigmatizing foreigners, but at improving HIV diagnosis and care. These results should help authorities scale up and optimize initiatives to reduce the proportion of patients who are unaware of their diagnosis. They also raise the question of the role of stigma and discrimination as a barrier to HIV testing in small communities, and further emphasize the importance of reducing it[23]. Finally, all physicians should keep in mind that before HIV diagnosis, in most cases there are missed testing opportunities.[24] These long estimates of the undiagnosed period suggest that this is also very much the case in French Guiana, and that we should do even more.

In conclusion, the present analysis provides estimates for the duration between HIV infection and diagnosis in the attempt to gain additional insights to reduce late HIV diagnoses. Despite the potential limitations, the information is of public health interest. There have been many efforts to improve early diagnosis of HIV in French Guiana, but the results remain mostly humbling, with great differences between communities. The above results should incite the intensification of testing in the most vulnerable communities of French Guiana where the epidemic is presumably most active.

Supporting information

S1 Table. Parameters used to calculate the delay between HIV seroconversion and diagnosis for the main populations in French Guiana.

(DOCX)

Author Contributions

Conceptualization: Mathieu Nacher.

Data curation: Mathieu Nacher.

Formal analysis: Mathieu Nacher.

Methodology: Mathieu Nacher.

Validation: Antoine Adenis, Florence Huber, Edouard Hallet, Philippe Abboud, Emilie Mosnier, Bastien Bideau, Christian Marty, Aude Lucarelli, Vanessa Morel, François Lacapère, Loïc Epelboin, Pierre Couppié.

Writing – original draft: Mathieu Nacher.

Writing – review & editing: Mathieu Nacher, Antoine Adenis, Florence Huber, Edouard Hallet, Philippe Abboud, Emilie Mosnier, Bastien Bideau, Christian Marty, Aude Lucarelli, Vanessa Morel, François Lacapère, Loïc Epelboin, Pierre Couppié.

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