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Abstract

To develop new strategies aimed to reduce the delay in seeking HIV diagnosis, we proposed to identify correlates of late diagnosis of HIV infection in France. Late testing was studied among the 1077 patients diagnosed from 1996 and enrolled in the ANRS-EN12-VESPA, a representative sample of the French HIV-infected population. Patients were defined as "late testers" if they had presented either clinical AIDS events or CD4 cell count <200/mm3 at diagnosis. 33.1% were classified as late testers, among whom 42.6% had discovered their HIV infection at the time of AIDS events. This proportion increased with age and was higher for heterosexual men and migrants. Among the non migrants heterosexual population, late diagnosis was more frequent among people in longstanding couple, with children and conversely was less likely among individuals with large number of sexual partners. Being on welfare benefit before diagnosis was associated with a lower risk of late diagnosis. Among migrants, lack of recent steady partnership was associated with an increased risk, as being diagnosed during the first year of stay in France.

Our results showed low risk factors of infection were risk factors of late testing. Public communication should aimed at improving the awareness of HIV risk in longstanding couples with stable employment, both among homosexual and heterosexual populations. Among migrants, HIV testing with informed consent short after entry should be improved, especially towards individuals not in couple.

Introduction

Since its introduction in the mid-1990s, the benefits of Highly Active Antiretroviral Therapy (HAART) on AIDS incidence and mortality disease have been well established [1, 2] particularly when treatment is initiated before patients present with symptoms of AIDS [3] or before CD4 cell count reach 200 cells/mm^3 [2].

Delay in HIV diagnosis has been identified as the main determinant of late presentation to care [4] and has a major impact on subsequent morbidity and mortality [5]. Earlier HIV diagnosis and entry to care are associated with lower rates of disease progression [6]. Besides, early entry into medical care might reduce the likelihood of further spread of infection thanks to safer sexual behaviour [7].

Early access to HIV diagnosis is thus a major public health issue [8, 9] and is essential to HIV prevention care and control [10]. However, the late diagnosis of HIV infection remains common, could be in progression in the last years in Western European countries and United States [4, 9, 11, 12].

Thus, new strategies aiming at reducing delay in seeking HIV diagnosis and care are needed. To design such focused interventions, identifying individuals correlates of late diagnosis of HIV infection is needed. This is the purpose of this paper on the basis of a random sample of patients recruited in 2002-2003 in the ANRS-EN12-VESPA.

Methods

Sampling and recruitment

The ANRS-EN12-VESPA study is a large French cross-sectional survey aimed at describing the impact of HIV infection on the social situation of persons living with HIV-AIDS and its

determinants. As HIV infection is mostly managed through hospital outpatient clinics with universal free access (93% of HIV infected patients) [13], the study was carried out in outpatient hospital clinics. The sampling procedure aimed at constituting a representative sample of the whole population of patients followed at hospital nationally for HIV infection in order to reflect the diversity of the epidemics in terms both of individuals' characteristics and of disease management. The study design has been described in detail elsewhere [14]. The study was conducted between December 2002 and September 2003 among a random stratified sample of 4,963 HIV-infected patients recruited in a random sample of 102 hospital settings delivering HIV care. The stratification criteria were departments' geographic location and the size of their HIV caseload. Eligible patients were those diagnosed HIV1-infected for at least 6 months, aged 18 or older, and living in France for at least six months. Physicians invited a random sample of HIV-infected patients to participate in the study. Patients with very poor understanding of the French language were excluded (n=117). Patients who agreed to participate signed an informed consent and answered a face-to-face standardized questionnaire administered by a trained interviewer (median length: 40 minutes). Patients received a 15€ voucher. A medical questionnaire including information on HIV disease and health status characteristics was filled in by the medical staff. The study reached CNIL (Commission Nationale de l'Informatique et des Libertés) ethical requirements.

Data collected

Only patients diagnosed from 1996 onwards were considered in the analysis. The questionnaire covered the history of illness and a range of social issues both retrospectively at time of diagnosis and at time of data collection.

Status at diagnosis was defined according to CD4 count and clinical stage within the calendar year for diagnosis to take account of the usual delay between the diagnosis and the first contact

with hospital. Patients were defined as “late testers” if they had presented either symptoms of clinical AIDS or CD4 cell count <200/mm3 during this period, as non late testers if CD4 count was above 200 and as unknown if information regarding CD4 count at time of diagnosis was not documented.

Homo-bisexuals were men who self defined as homo/bisexuals or who declined to self identify and had had a male sexual partner during the year preceding the enrolment in the study.

Injecting drug users (IDU) were defined in three groups: never injected or used opiates, past IDU, active or substituted IDU.

Subjects born abroad with a non French nationality at birth were defined as “ migrants”. Time between immigration and HIV diagnosis was split in 4 categories (<0, 0, 1 year, >2 years).

Social characteristics were education (primary school or not at all, secondary, high school, university), employment status (employed, on unemployment benefit, inactivity), resources (on welfare benefit or not); accommodation (own accommodation or not); steady sexual partner combined with the length of the couple (no steady partner, couple <5 years, couple >5 years, 5 years being the median value; for homosexual the cut-off value was 3 since the media was lower); having children. Number of lifetime sexual partners was documented at the time of data collection (<5, 6-10, 11-20, >20 for heterosexual, <10, 11-20, 21-50, >50 for homosexuals) and was considered as a proxy of lifetime sexual lifestyles.

Statistical analysis

A global analysis compared the risk of late diagnosis across the whole sample of patients diagnosed from 1996 to 2003.

A sub-group study was carried out separately among homo/bisexual males (n=323), heterosexual French natives (n=288) and heterosexual migrants (n=274), because of different epidemiological patterns regarding estimated HIV prevalence, dynamics of the epidemics and HIV progression at

diagnosis according to national surveillance data [15] and because of different profiles regarding social and demographic characteristics and sexual lifestyles. IDU were not considered in the sub-group study because their number in the study sample was small (n=69).

Comparisons used χ^2 test for categorical variables and ANOVA for continuous variables. Multivariate analysis used logistic regression with a stepwise analysis in descending sequence (threshold: 0.05). Each variable statistically significant at the threshold of 0.2 in bivariate analysis was included into the model. Analyses were systematically adjusted on calendar period of HIV diagnosis divided in four two-year periods.

Comparisons and logistic modelling were made using weighted data (INSEE-CALMAR SAS macro program) [14]. Statistical analyses were performed using SAS (version 9.1; SAS Institute; Cary, North Carolina, USA).

Results

Study population

Among 4,963 eligible patients, 2,932 subjects (59%) were included in the ANRS-EN12-VESPA study. Two hundred and sixty four were not solicited because of major cognitive impairment or health problems and 1,767 patients declined participation. Non-respondents were more likely to have been infected through a way other than homo/bisexual contacts, and at time of the study, to be under 40 year of age, to be employed and to have CD4 cell count <200.

Among these 2932 participants, 1077 had been diagnosed HIV-infected from 1996 (table 1). The group was mainly male (67.9%), 34% were homo/bisexual males, 33.9% heterosexual males and 32.1% women, and 33.7% were migrants, mostly born in sub Saharan Africa (73.3%). Mean age at diagnosis was 37 ± 10.9 years, and was significantly lower for migrants compared to French-natives (35 vs. 39 years; p<0.0001).

Frequency of late diagnosis

In the study population, 33.1% were classified as late testers (among whom 42.6% had discovered their HIV infection at the time of clinically defined AIDS), 55.9% as non late testers, and 11% had an unknown testing status. Median time between HIV diagnosis and first measure of CD4 cell count was 30 days. Patients with an unknown testing status were more frequently diagnosed in 1996-97, past or current injecting drug users and migrants born in Europe.

Among late testers, HIV testing was performed more frequently because of symptoms (63.7% vs 33.5% among non late testers, $p<0.0001$) or at physician's request (52.7% vs 36.4% among non late testers, $p<0.0001$) and more often performed at hospital (64.1% vs 43% among non late testers, $p<0.0001$). Late testers stated more often that they were not aware of having been tested previously (17.4% vs 7.5% among non late testers, $p<0.0001$).

Characteristics of late testers

The proportion of late testers was significantly higher among heterosexual males, subjects over 30, migrants, former injecting drug users, and persons diagnosed between 1998 and 2001. In multivariate analysis heterosexual men had a significantly higher probability of late testing compared to homosexual males (adjusted odds-ratio [aOR]: 1.71, 95% confidence interval [CI]: 1.17-2.51), as did migrants compared to French natives (aOR: 1.84, 95% CI: 1.26-2.69) and those reporting a former IDU (aOR: 2.44, 95% CI: 1.29-4.62). The risk of late testing increased significantly with age and period at diagnosis.

Homo/bisexual males, non injecting drug users (n=323)

The proportion of late diagnosis (27.6%) increased with age and was less likely among men in steady partnership for <=3 years compared to men in longer partnership or without a steady partner (13.7vs. 34%, p=0.003 and 29.8%, p=0.01 respectively). Year of diagnosis, education,

employment, accommodation, resources, number of lifetime partners were not statistically associated with late diagnosis.

Heterosexual French natives, non injecting drug users (n=288)

The probability of late testing (36.2%) was significantly higher for men, subjects aged over 30, those diagnosed for HIV infection between 1998 and 2001 compared to those diagnosed in 1996-97 (table 3). Persons being in a couple for 5 years or more and persons with children were more likely to be late testers. Education, employment, and accommodation were not statistically associated with late diagnosis

In multivariate analysis (table 2), period of diagnosis between 1998 and 2001 remained significantly associated to the risk of late testing. The risk of late testing was higher among men (aOR: 5.18, 95% CI: 2.37-11.30), among subjects aged 30-39 compared to those under 30 (aOR: 3.56, 95% CI: 1.24-10.19), among those in couple for 5 years or more (aOR: 2.22, 95% CI: 1.09-4.52) and among those with children (aOR: 2.41, 95% CI: 1.14-5.09). Conversely risk of late testing was decreased among patients with more than 20 lifetime sexual partners (aOR: 0.24, 95% CI: 0.10-0.58), and for those being on welfare benefit before HIV diagnosis (aOR: 0.28, 95% IC: 0.10-0.84).

Heterosexual migrants, non injecting drug users (n=274)

No time trend was observed in the risk of late testing (table 3). The proportion of late testers (44.3%) was significantly higher among subjects aged over 25, among patients diagnosed within the very first year of their stay in France compared to patients with a 2 years or more stay, and among those without a steady partner compared to those in a recent steady partnership (less than 5 years). Gender, country of birth, education, employment, accommodation, number of lifetime partners were not statistically associated with late diagnosis.

In multivariate analysis, the risk of late diagnosis increased with age and during the first year of stay in France (aOR: 2.15, 95% IC: 1.04-4.47). Conversely, being in a recent steady partnership was associated with a reduced risk of late testing (aOR:0.34, 95% IC: 0.15-0.76).

Discussion

To our knowledge, for the first time, our study provides nationwide representative data on late HIV diagnosis in France from the beginning of the HAART era. Our results showed that late diagnosis of HIV infection is still frequent in France despite wide access to free Voluntary Counselling and Testing (VCT), and more frequent among specific subgroups of patients, i.e. heterosexual males and migrants. Among the heterosexual population, late diagnosis is more frequent among people with children in a longstanding steady partnership and conversely is less likely among individuals with a large number of sexual partners. Among migrants, no difference was found between men and women and lack of steady partnership is associated with an increased risk. As the HIV epidemic situation in France is similar to that one in the rest of western Europe in respect of the profile of the infected group and the proportion of migrants [10] our results could be of relevance to European countries.

This study has several limitations. Data was collected in hospital settings and non response reached 41% of the randomised patients, with higher rates of refusal among those employed, mostly attributable to a lack of time for answering the questionnaire. In France, antiretroviral drugs are provided exclusively through hospital physicians' prescription and management of HIV infection is mostly provided at hospital. Thus the hospital-based nature of the study allowed patients randomisation. Major socio-demographic and health-related characteristics of the non-respondents were collected, allowing for a weighting procedure accounting both for the unequal hazard of a patient to be randomised and for the participation bias. Thus, rate of late diagnosis

are likely to be extrapolated to the whole population of persons living with HIV/AIDS and followed at hospital in France in 2002-2003. However, because of the cross sectional design of the study, the rate of late diagnosis might be underestimated due to higher mortality rates among persons diagnosed with advanced HIV infection even though mortality has dramatically decreased since 1996.

For 11% of patients, CD4 count during the study period was not documented. The global analysis was repeated first by assuming unknown status cases to be late testers, then non late testers. The findings remained unaltered when unknown cases were considered as late testers. As non late testers, the only difference concerned the proportion of injecting drug users, that was similar between late and non late testers.

The proportion of late testers in our study (33%) is comparable to that reported in other studies focusing on the same calendar period [4, 16] and appears to increase with time, as reported in other studies [11, 12, 17].

High risk groups for late testing in our study were similar to those identified in the most recent studies conducted in European countries [4, 11, 16, 17] and in the United States [3]. Heterosexuals are at higher risk of late diagnosis than homosexual males who use VCT on a somewhat regular basis : in 2004, 87 % reported having ever been tested, 72 % in the two preceding years with an average of 2.8 tests [18]. Nevertheless late testing remains frequent in France among homosexuals: 27.6% in our study, as reported recently in England and Wales [19] or in Italy [20].

Women are less likely to be diagnosed at advanced stages of disease progression. This situation might be related to routine prenatal testing and gynaecological follow-up. However among migrants, women were not diagnosed earlier than men which might be accounted for by younger age at HIV contamination and for late arrival in France. Diagnosis took place mostly during the very first period after arrival, as in another French study [21]. Most infections might have taken

place in the country of origin as shown in English data [16]. Diagnosis concomitant with immigration supports the assumption of infection in the country of origin and either request or proposal of testing shortly after arrival.

Steady partnership appears to be determinant of testing behaviour. Among homosexual men, recent partnership appears as protective compared to longer duration of couple or absence of stable partner. This finding is supported by the ANRS-INVS Gay press study [18], in which men in new established partnership are more likely to have performed an HIV test in the preceding 12 months (75.4 % vs. 43.2 to 46.3%, Velter A, personal communication). French natives in longer partnership (>5 years) are exposed to an increased risk of late diagnosis. In the 2004 French general population KABP survey [22], individuals in shorter partnerships (<5 years) more often reported that they had ever thought they might have been infected and individuals in longer couples were less likely to report such a perception compared to singles. Individuals in longer partnerships (>5 years) were more likely to perceive they were at no risk than singles and individuals in recent couples (Beltzer N, personal communication).

In countries with concentrated epidemics, persons in steady partnership, with children are perceived to be at low risk and may not consider themselves at risk and thus do not seek voluntary counselling and testing (VCT). If infected, they are likely to be diagnosed with advanced HIV infection.Our findings suggest that promoting awareness of risk in longstanding couples and knowledge of one's HIV status regardless of sexual risk behaviour and routine proposed of testing might complement the current testing policy aimed at populations and persons at risk. The association between welfare benefit and lower risk of late testing is consistent with this result since a free check up including an HIV test is offered to the beneficiaries on a routine basis.

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Competing interest statement

None declared

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Table 1: Weighted frequency of socio-demographic characteristics at the time of HIV diagnosis of the 1077 patients of the study sample according to status regarding late testing,(weighted data). ANRS-EN12-VESPA study.

	Non late testers (N=570)	Late testers (N=384)	Unknown testing status (N=123)	Total sample (N=1077)
Period of HIV diagnosis				
1996-97	25.1	18.2	49.4	25.5
1998-99	28.4	33.6	33.0	30.6
2000-2001	27.6	33.5	16.2	28.3
2002-2003	18.9	14.7	1.4	15.6
Age at HIV diagnosis (years)				
<30	32.8	18.5	38.8	28.7
30-39	36.2	36.7	34.6	36.2
40-49	19.4	25.5	16.9	21.1
50-59	9.6	13.7	6.1	10.6
>=60	2.0	5.6	3.6	3.4
Sexual group				
Homosexual men	38.8	26.1	33.0	34.0
Heterosexual men	26.2	45.7	37.5	33.9
Heterosexual women	35.0	28.2	29.5	32.1
Injecting drug use				
No	95.0	90.0	85.3	92.3
In the past	2.7	7.9	9.2	5.7
Substituted or active	1.3	2.1	5.5	2.0
Country of origin				
France	70.5	60.6	62.4	66.3
Europe	2.9	3.9	7.1	3.7
North Africa	3.0	1.9	3.6	2.7
Sub-Saharan Africa	20.6	31.1	25.8	24.7
Others	3.0	2.5	1.1	2.6

Table 2: Factors associated with late testing, among French heterosexual group, in a logistic regression model. ANRS-EN12-VESPA study. N=288

	Observed number	OR (95% CI)*	aOR (95% CI)**
Years of diagnosis			
1996-97	76	1	1
1998-99	96	3.80 (1.84-7.85)†	5.73 (2.66-12.35)†
2000-2001	76	4.10 (1.97-8.51)†	5.28 (2.40-11.64)†
2002-2003	40	1.85 (0.76-4.55)	3.42 (1.15-10.15)†
Age at HIV diagnosis			
<30	54	1	1
30-39	73	5.65 (2.22-14.39)†	3.55 (1.24-10.19)†
40-49	74	5.05 (2.02-12.62)†	1.70 (0.56-5.15)
50-59	59	4.31 (1.62-11.50)†	1.24 (0.38-4.08)
>=60	28	17.16 (5.35-55.00)†	3.52 (0.86-14.43)
Gender			
Female	112	1	1
Male	176	4.29 (2.44-7.56)†	5.18 (2.37-11.30)†
On welfare benefit			
No	258	1	1
Yes	30	0.40 (0.16-0.97)†	0.28 (0.10-0.83)†
Length of relationship			
No partner	110	1	1
Partner since less than 5 years	73	0.54 (0.27-1.09)	0.65 (0.30-1.43)
Partner since more than 5 years	105	3.23 (1.82-5.75)†	2.22 (1.09-4.52)†
Having children			
No	123	1	1
Yes	165	2.07 (1.26-3.42)†	2.41 (1.14-5.08)†
Number of lifetime sexual partners			
<=5	109	1	1
6-10	66	0.58 (0.30-1.10)	0.58 (0.27-1.24)
11-20	49	1.33 (0.65-2.71)	1.03 (0.47-2.26)
>20	63	0.61 (0.31-1.20)	0.24 (0.10-0.58)†

Variables included in the model: year of diagnosis, age at HIV diagnosis, gender, level of education, employment, on welfare benefit, stay in jail, length of couple, having children, number of lifetime sexual partners
Data were not available for all patients in all categories; *weighted OR: Odds-ratio; CI: Confidence Interval; ** aOR: adjusted odds-ratio; †$p \leq 0.05$

Table 3: Factors associated with late testing, among migrants heterosexual group, in a logistic regression model. ANRS-EN12-VESPA study. N=274

	Observed number	OR (95% CI)*	aOR (95% CI) **
Years of diagnosis			
1996-97	30	1	1
1998-99	64	0.97 (0.38-2.45)	0.99 (0.33-2.95)
2000-2001	104	1.03 (0.41-2.57)	0.89 (0.30-2.63)
2002-2003	76	0.94 (0.38-2.29)	0.73 (0.24-2.26)
Age at HIV diagnosis			
<25	28	1	1
25-30	68	6.46 (1.81-23.03)†	6.59 (1.88-23.10)†
30-35	55	4.85 (1.31-17.97)†	4.03 (1.03-15.76)†
35-40	45	10.09 (2.57-39.57)†	9.49 (2.22-40.56)†
>=40	78	8.13 (2.30-28.78)†	5.59 (1.50-20.81)†
Length of relationship			
No partner	135	1	1
Partner since less than 5 years	64	0.31 (0.16-0.62)†	0.34 (0.15-0.76)†
Partner since more than 5 years	75	0.77 (0.42-1.39)	0.61 (0.30-1.24)
Time between immigration and HIV diagnosis			
<0	9	2.41 (0.55-10.62)	2.62 (0.58-11.92)
0	68	2.57 (1.33-4.95)†	2.15 (1.04-4.47) †
1	53	0.52 (0.25-1.12)	0.53 (0.23-1.22)
>1	112	1	1

Variables included in the model: year of diagnosis, age at HIV diagnosis, origin, length of couple, time between immigration and HIV diagnosis
Data were not available for all patients in all categories; *weighted OR: Odds-ratio; CI: Confidence Interval; ** aOR: adjusted odds-ratio; †$p \leq 0.05$