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Impact of late presentation of HIV infection on short-, mid- and long-term mortality and causes of death in a multicenter national cohort: 2004—2013

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Keywords
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Summary *Objectives:* To analyze the impact of late presentation (LP) on overall mortality and causes of death and describe LP trends and risk factors (2004—2013).
Methods: Cox models and logistic regression were used to analyze data from a nation-wide cohort in Spain. LP is defined as being diagnosed when CD4 $<$ 350 cells/ml or AIDS.
Results: Of 7165 new HIV diagnoses, 46.9% ($CI_{95\%}$:45.7—48.0) were LP, 240 patients died.

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Cohort study

First-year mortality was the highest ($aHR_{LP.vs.nLP}$ = 10.3[$CI_{95\%}$:5.5−19.3]); between 1 and 4 years post-diagnosis, $aHR_{LP.vs.nLP}$ = 1.9(1.2−3.0); and >4 years, $aHR_{LP.vs.nLP}$ = 1.5(0.7−3.1).

First-year's main cause of death was HIV/AIDS (73%); and malignancies among those surviving >4 years (32%). HIV/AIDS-related deaths were more likely in LP (59.2% vs. 25.0%; $p < 0.001$). LP declined from 55.9% (2004−05) to 39.4% (2012−13), and reduced in 46.1% in men who have sex with men (MSM) and 37.6% in heterosexual men, but increased in 22.6% in heterosexual women.

Factors associated with LP: sex ($OR_{MEN.vs.WOMEN}$ = 1.4[1.2−1.7]); age ($OR_{31-40.vs.<30}$ = 1.6 [1.4−1.8], $OR_{41-50.vs.<30}$ = 2.2[1.8−2.6], $OR_{>50.vs.<30}$ = 3.6[2.9−4.4]); behavior ($OR_{InjectedDrugUse.vs.MSM}$ = 2.8[2.0−3.8]; $OR_{Heterosexual.vs.MSM}$ = 2.2[1.7−3.0]); education ($OR_{PrimaryEducation.vs.University}$ = 1.5[1.1−2.0], $OR_{LowerSecondary.vs.University}$ = 1.3[1.1−1.5]); and geographical origin ($OR_{Sub-Saharan.vs.Spain}$ = 1.6[1.3−2.0], $OR_{Latin-American.vs.Spain}$ = 1.4[1.2 −1.8]).

Conclusions: LP is associated with higher mortality, especially short-term- and HIV/AIDS-related mortality. Mid-term-, but not long-term mortality, remained also higher in LP than nLP. LP decreased in MSM and heterosexual men, not in heterosexual women. The groups most affected by LP are low educated, non-Spanish and heterosexual women.

Introduction

In Europe and other high-income settings, a high proportion of HIV diagnoses are made late.[1,2] Late diagnosis of HIV infection is widely acknowledged as a major public health issue strongly related to increased morbidity and mortality.[2−13] Not only is late presentation (LP) the main reason for delayed antiretroviral treatment (ART) leading to poorer patient immune and viral response, but it has been identified as a key factor in HIV transmission.[14] Finally, LP has been linked to more intense use of healthcare resources with the corresponding higher costs.[15]

Several studies have examined the impact of late HIV diagnosis on mortality[3,4,7,9−11,13]; however, most have assessed the effect on short-term mortality[3,4,13] or the cumulative effect over a period of time.[7,11] In fact, to our knowledge, there is no previous research on the impact of LP and clinical stage at diagnosis on short-, mid-, and long-term mortality. There is also a lack of studies on how LP relates to different causes of death.

The aim of this work is two-fold. First, we examine the impact of LP on short-, mid-, and long-term mortality including cause-specific mortality. Second, we describe temporal trends of late diagnosis and related risk factors.

Methods

We analyzed data from individuals newly-diagnosed with HIV between 2004 and 2013. Data came from CoRIS (Spanish acronym for the AIDS Research Network Cohort). CoRIS is an open, prospective, multicentre cohort of adult HIV-positive patients who are ART-naïve at study entry. Patients were followed-up in any of the participating sites after January 2004. Cohort participants were recruited in 33 public healthcare centres, 32 hospitals, and one HIV/STD clinic. Sites are distributed across 13 of the 17 regions in Spain. A detailed description of the cohort's methodology has been published elsewhere.[16]

This study was approved by each of the participating centres' research ethics committee (see addendum for a list of participating healthcare sites). Patients signed written informed consent forms before study entry. The cohort study meets all the requirements of the latest legislation (RD1617/11) as a data node of the Spanish HIV Biobank.

Study population

The study population includes all individuals newly-diagnosed with HIV with available CD4 cell count within 6 months of diagnosis and who were recruited up to the 31st of May of 2013 (administrative censoring date). We defined a newly-diagnosed individual as a patient diagnosed with HIV up to six months before study entry. To ensure that only newly-diagnosed patients were included, those presenting an AIDS-defining illness more than 6 months prior to the HIV diagnosis were excluded.

Based on consensus definitions,[17] we defined patients with **late presentation** (LP) as those presenting for care with a CD4 cell count below 350 cells/ml or with an AIDS-defining event (ADE), and patients with **late presentation with advanced HIV disease** (LPAD) as those presenting for care with a CD4 cell count below 200 cells/ml or with an ADE. Since our study population is comprised of newly-diagnosed individuals, in our case LP and late diagnosis are equivalent. In addition to the aforementioned consensus definition, we used the variable **clinical status at HIV diagnosis**. This variable determines four mutually exclusive patient groups which are classified according to the following order of priority: AIDS present at time of HIV diagnosis; CD4 cell count <200 cells/ml and AIDS-free; CD4 cell count ≥200 but <350 cells/ml and AIDS-free, and CD4 cell count ≥350 cells/ml and AIDS-free. The first two categories coincide with LPAD and the first three categories correspond to LP.

Statistical analyses

We compared sociodemographic characteristics among LP and non-LP (nLP) patients and used multiple logistic regression models to assess if factors such as sex, age at HIV diagnosis, transmission category, region of origin, and educational level were independently associated with LP (likewise for LPAD). We tested for potential interactions. The method of multiple imputation by chained equations (MICE) was used to handle missing values assuming a missing at random (MAR) pattern.[18] An imputation model was developed for each sex. An ordinal model was used for educational level and multinomial logistic models for the rest of the variables. Models included all variables under analysis plus the response variable. Twenty replicates were generated, and the final results were calculated according to the method described by Little and Rubin.[19] Sensitivity analyses were conducted comparing results from MICE with complete case analyses as well as with those obtained using an indicator category in variables with missing values. We described the proportion of LP (and LPAD) patients by year of HIV diagnosis, testing for trend. Annual declines were assessed with multiple logistic regression models adjusted for potential confounding variables and tested for potential interactions. Results from these analyses were interpreted based on adjusted Odds Ratios (aOR) and the corresponding 95% confidence intervals (95%CI).

We assessed how clinical status at HIV diagnosis, LP, or LPAD impacted survival using multivariate Cox regression models allowing for a time lag between HIV diagnosis and study entry. However, because Schoenfeld residuals tests indicated that the proportional hazards assumption was not confirmed, an interaction with follow-up time was included so that the hazards were proportional within each period of analyses, i.e., <1 year, 1—4 years, and >4 years. In addition to previously described potential confounders, year of inclusion in the cohort and ART initiation (defined as a time-varying variable) were modeled into the analyses. Crude Hazard Ratios (HR) and adjusted Hazard Ratios (aHR) with 95%CIs were calculated.

To evaluate the effect of patients lost to follow-up on mortality estimates, sensitivity analyses were performed using the Fine and Gray model, where lost to follow-up were considered as a competing event.[20] Causes of death were coded using a modified cause of death coding protocol for HIV which is based on the CoDe protocol developed by the Copenhagen HIV Program (www.cphiv.dk).[21]

Finally, we estimated confidence intervals using robust methods that assumed correlations among participants recruited at each site and independence among participants recruited at different sites.[22]

Analyses were conducted using Stata (V.13, Stata Corporation, College Station, Texas, USA).

Results

Of the 9667 patients enrolled in project CoRIS until the 31st of May of 2013, 7528 (77.8%) were diagnosed with HIV infection in the 6 months prior to inclusion in the cohort. Of those, 342 were excluded due to absence of CD4 cell counts measured within the first six months post-diagnosis. An additional 21 individuals with an AIDS-defining event over 6 months before HIV diagnosis were excluded as well. Finally, a total of 7165 participants were included; most were men (83.2%), median age was 34 years; 57.9% were men who have sex with men (MSM) and 32.3% were heterosexually infected; 38.5% had reached lower secondary education and 28.6% had university studies; 30.6% were not native to Spain, of whom 59.3% were from Latin America (LA) and 17.5% from Sub-Saharan Africa (SSA); 10.1% had a positive serology for hepatitis C virus (HCV) (Table 1).

Late presentation and presentation with advanced HIV disease: magnitude, trends and risk factors

A total of 3359 subjects (46.9%) were LP patients, of which 2047 (28.6%) were LPAD patients, and 1011 (14.1%) had an AIDS-defining event at time of HIV diagnosis. The remaining 3806 subjects were nLP, our reference category. During the follow-up, 90.4% of LP patients started ART, with a median time from HIV diagnosis to ART initiation of 55 days (IQR: 26—112).

Table 1 shows the percentage of LP and LPAD patients according to their characteristics as well as the results of multivariate analysis obtained after MICE. Risk factors for LP were: being male (aOR 1.38 [95%CI: 1.15—1.65]); being over 30 years of age (aOR_{31-40} 1.59 [95%CI: 1.39—1.82], aOR_{41-50} 2.18 [95%CI: 1.83—2.60], $aOR_{>50}$ 3.60 [95%CI: 2.92—4.44]); to be an injection drug user (IDU) (aOR 2.78 [95%CI: 2.01—3.84]) or heterosexually infected (aOR 2.21 [95%CI: 1.65—2.95]), versus MSM; lower educational achievement such as primary school or less (aOR 1.47 [95%CI: 1.12—1.94]) or lower secondary school (aOR 1.29 [95%CI: 1.09—1.52]) versus a university-level education. Finally, place of origin was also a risk factor. Participants from SSA (aOR 1.62 [95%CI: 1.32—1.99]) or LA (aOR 1.44 [95%CI: 1.15—1.81]) were at higher risk for LP than Spaniards. Risk factors for LPAD were very similar to the ones just described above.

In the period between 2004—05 and 2012—13 the percentage of LP decreased from 55.9% to 39.4%. However, the improvement was not homogeneous across transmission categories and sex (Fig. 1). Adjusted results for age at diagnosis, educational level, and region of origin confirm that LP annual decline was statistically significant among MSM (aOR 0.94 [95%CI: 0.88—0.99]) and heterosexual men (aOR 0.94 [95%CI: 0.89—0.99]), but not among heterosexual women (aOR 1.02 [95%CI: 0.97—1.08]) mainly among non-Spaniards. Specifically, in this period, the percentages of LP in MSM and heterosexual men declined 46.1% and 37.6%, respectively, whereas LP in heterosexual women increased by 22.6%.

Between the years 2004—05 and 2012—13, the proportion of LPAD also saw a reduction from 37.6% down to 21.9%. Regarding changes by transmission risk categories, LPAD followed the same patterns as described above for LP. Annual changes in MSM and heterosexual men were significant (aOR 0.90 [95%CI: 0.83—0.98] and aOR 0.94 [95%CI: 0.88—0.99], respectively). The number of LPAD among heterosexual women did not vary during the period under study (aOR 1.00 [95%CI: 0.93—1.07]).

Table 1 Sociodemographic and epidemiological characteristics of study patients and the association with late presentation (LP) and late presentation with advanced disease (LPAD).

	n (%)	Late presentation (LP)		LP with advanced HIV disease (LPAD)	
		n (%)	aOR (CI 95%)	n (%)	aOR (CI 95%)
Total	7165	46.9		28.6	
Sex					
Men	5959 (83.2)	2693 (45.2)	1.38 (1.15–1.65)	1606 (27.0)	1.39 (1.15–1.68)
Women	1206 (16.8)	666 (55.2)	1	441 (36.6)	1
Age at HIV diagnosis					
≤30 years	2448 (34.2)	854 (34.9)	1	395 (16.1)	1
31–40 years	2652 (37.0)	1245 (46.9)	1.59 (1.39–1.82)	747 (28.2)	1.96 (1.60–2.40)
41–50 years	1390 (19.4)	793 (57.1)	2.18 (1.83–2.60)	568 (40.9)	3.15 (2.52–3.96)
>50 years	675 (9.4)	467 (69.2)	3.60 (2.92–4.44)	337 (49.9)	4.35 (3.49–5.43)
Category of transmission					
Men who have sex with men	4151 (57.9)	1525 (36.7)	1	768 (18.5)	1
Injecting drug users	470 (6.6)	305 (64.9)	2.78 (2.01–3.84)	209 (44.5)	2.78 (1.93–4.00)
Heterosexuals	2315 (32.3)	1373 (59.3)	2.21 (1.65–2.95)	955 (41.3)	2.56 (1.88–3.48)
Others	80 (1.1)	54 (67.5)	2.97 (1.72–5.12)	42 (52.5)	3.87 (2.40–6.25)
Unknown	149 (2.1)	102 (68.5)	–	73 (49.0)	–
Education[a]					
Primary school or less	497 (8.3)	307 (61.8)	1.47 (1.12–1.94)	207 (41.6)	1.69 (1.33–2.13)
Lower secondary	1797 (30.2)	994 (55.3)	1.29 (1.09–1.52)	666 (37.1)	1.55 (1.30–1.85)
Upper secondary	1956 (32.9)	824 (42.1)	1.02 (0.89–1.17)	490 (25.1)	1.21 (1.06–1.37)
University	1703 (28.6)	644 (37.8)	1	312 (18.3)	1
Unknown	1212	590 (48.7)	–	372 (30.7)	–
Origin					
Spain	4967 (69.4)	2235 (45.0)	1	1336 (26.9)	1
Western Europe	198 (2.8)	79 (39.9)	0.84 (0.68–1.02)	48 (24.2)	0.93 (0.68–1.27)
Eastern Europe	168 (2.3)	77 (45.8)	1.02 (0.72–1.44)	47 (28.0)	1.13 (0.79–1.62)
Sub-Saharan Africa	384 (5.4)	245 (63.8)	1.62 (1.32–1.99)	170 (44.3)	1.61 (1.31–1.99)
Latin America	1302 (18.2)	642 (49.3)	1.44 (1.15–1.81)	394 (30.3)	1.54 (1.27–1.86)
Others	142 (2.0)	79 (55.6)	1.33 (0.90–1.96)	51 (35.9)	1.32 (0.90–1.94)
Unknown	4	2 (50.0)	–	1 (25.0)	–

aOR (CI 95%): adjusted Odds Ratio and confidence intervals 95%.
[a] Lower secondary: ISCED97-2; Upper secondary: ISCED97 3-4; ISCED97 refers to the 1997 International Standard Classification of Education (http://www.unesco.org/education/information/nfsunesco/doc/isced_1997.htm).

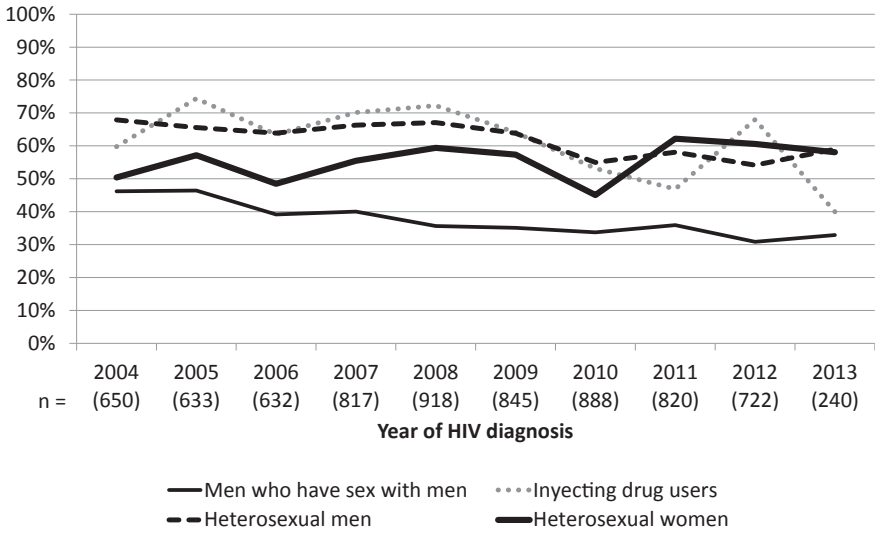

Figure 1 Progression of late presentation prevalence by category of transmission.

Impact of LP on mortality: short-, mid- and long-term effects

Of the 7165 participants completing the baseline, we collected at least some follow-up data for 6956 (97.1%), the equivalent of 23,820 person-years (py) observation. The median follow-up was 3.1 years (IQR: 1.2—5.3). There were 240 deaths, with a death rate of 1.01 (95%CI: 0.89—1.14) per 100 py. This rate increased as clinical status worsened and it was substantially and significantly higher in LP patients (1.71 vs. 0.31 per 100 py; $p < 0.001$) (Table 2).

Fig. 2 shows the survival curves by clinical status at HIV diagnosis. Table 2 illustrates the impact of LP and clinical status at HIV diagnosis on all-cause mortality. Using nLP as reference group our results show that during the first year post-HIV diagnosis LP is associated with a high risk of early death. The risk increases as clinical status worsens ($aHR_{200 \leq CD4 < 350}$ 2.8 [95%CI: 1.5—5.4]; $aHR_{CD4 \leq 200}$ 5.6 [95%CI: 2.7—11.9]; and aHR_{AIDS} 22.6 [95%CI: 11.5—44.6]). The prognostic effect of LP and clinical status at HIV diagnosis in the mid-term persists but is significantly lessened ($aHR_{200 \leq CD4 < 350}$ 1.4 [95%CI: 0.7—2.8]; $aHR_{CD4 < 200}$ 1.5 [95%CI: 0.9—2.4]; aHR_{AIDS} 3.0 [95%CI: 1.8—5.0]).

Among participants followed for over 4 years post-diagnosis, LP and LPAD increase mortality risk (aHR 1.5 [95%CI: 0.7—3.1] and 1.7 [95%CI: 0.8—3.8], respectively) although these effects fail to reach statistical significance (Table 2).

LP and causes of death

We have information on cause of death for 207 out of 240 deceased. There were 123 deaths during the first year post-diagnosis, 73.2% of them were HIV/AIDS-related, 8.9% were liver-disease related, 7.3% were malignancy-related, and 5.7% were due to other infectious diseases. Among participants with LP, HIV/AIDS-related causes represented 74.6% of all deaths, but only 40.0% of deaths among those with nLP ($p < 0.013$) (Fig. 3). Liver- and malignancy-related deaths were more frequent among nLP than LP (Liver-related: 40.0% nLP vs.7.6% LP; malignancy-related: 20.0% nLP vs.6.8% LP).

We recorded 59 deaths during the period between the end of the first year and the fourth year post-HIV diagnosis. About one third (32.2%) were HIV/AIDS-related (34.9% LP vs. 25.0% nLP); 25.4% were due to malignancies (27.9% LP vs. 18.8% nLP); 15.3% were due to other infectious diseases (11.6% LP vs. 25.0% nLP), and 5.1% were liver-related deaths (7.0% LP vs. 0% nLP).

Finally, malignancies were the most common cause of death among the 25 patients who passed away over 4 years post-HIV diagnosis (32.0% overall; 38.9% LP vs. 14.3% nLP). Liver-related deaths were the second most common cause (20.0% overall; 22.2% LP vs. 14.3% nLP), followed by HIV/AIDS-related conditions (16.0% overall; 16.7% LP vs. 14.3% nLP) and other infectious diseases (16.0% overall; 11.1% LP vs. 28.6% nLP).

Sensitivity analyses

We conducted sensitivity analyses to assess the missing data imputation method used to estimate factors associated with LP or LPAD and to estimate the effects of lost-to-follow up in mortality analyses. Results were similar to those reported here (data not shown).

Discussion

Compared to other HIV patients, the mortality risk of individuals with a late HIV diagnosis is 10-fold during the first year after diagnosis and two-fold between the first and fourth year post-diagnosis. Early mortality among patients with late diagnosis tends to be HIV/AIDS-related whereas for those with timely diagnoses liver- and malignancy-related deaths are more likely causes. In our cohort, almost half of the individuals newly-diagnosed with HIV between 2004 and 2013 were patients with late presentation and almost one third were exhibited late presentation with advanced disease. Although the proportion of LP has declined in men sexually-infected (MSM and heterosexual), LP could be increasing among heterosexual women.

The mortality rate in our cohort is comparable to that observed in other European studies[2,11,23,24] but much lower than in non-European countries.[5] As mentioned earlier, delayed HIV diagnosis is a major prognostic factor.[4,5,10,11,13] This is especially true regarding premature and HIV/AIDS-related mortality, as shown here. In our cohort, 71% of deaths of patients with late presentation and who died within one year of diagnosis were due to HIV/AIDS. Causes of death among those with LP who survived more than 4 years post-diagnosis were more likely to be liver-related and non-AIDS defining malignancies; thus resembling causes of death in individuals with timely diagnoses, those in other cohorts with long follow-up times,[24] or in patients undergoing ART treatment.[25] For patients presenting with an AIDS diagnosis, the likelihood of an early death is especially high as their mortality risk is 20 times greater during the first year post-diagnosis and 3 times greater between the first and fourth year post-diagnosis compared to their timely-diagnosed counterparts. Given that the death rate of patients with timely HIV diagnosis was 0.31 per 100 py, had all our participants been diagnosed sooner, 74 deaths would have been avoided and mortality would have been reduced by 69%.

Although the majority of patients with LP began ART immediately after HIV diagnosis, ART is not effective enough to eliminate the excess mortality related to LP, at least not during the first year post-diagnosis. However, we believe that ART is responsible for significantly attenuating the impact of LP on mortality overtime.[25,26] Among those LP patients that did not start ART, 10% died in the first three months after the diagnosis. The reason for them not starting ART could be they were considered too sick to benefit from it. One out of four patients who did not start ART, their follow-up was lower than a month since diagnosis.

The prevalence of LP and LPAD in our cohort is very similar to that reported by the Spanish National Surveillance System of New HIV Diagnoses (SINIVIH for its Spanish acronym),[27,28] and other European studies which report a LP prevalence between 45% and 63%.[6,10,23,29—32] In our cohort, and throughout the period under study, the percentages of LP by transmission category have evolved differently. LP has experienced substantial declines

Table 2 Impact of late presentation and clinical status at HIV diagnosis on mortality. Overall mortality rates. Results of survival analysis and Cox regression model for follow-up periods.

	Overall results			Results for follow-up periods								
				First year since diagnosis			1–4 years Since diagnosis			>4 years since diagnosis		
	Deaths	p-y	Rate (95%CI)	N at risk	Deaths	aHR(*) (95%CI)	N at risk	Deaths	aHR(*) (95CI%)	N at risk	Deaths	aHR(*) (95CI%)
Total	240	23,820	1.01 (0.89–1.14)	6956	132		5511	72		2840	36	
Late presentation												
nLP	37	11,921	0.31 (0.22–0.43)	3666	8	1	2923	19	1	1378	10	1
LP	203	11,900	1.71 (1.49–1.96)	3290	124	10.3 (5.5–19.3)	2588	53	1.9 (1.2–3.0)	1462	26	1.5 (0.7–3.1)
LPAD	176	7564	2.33 (2.00–2.70)	2010	114	14.5 (**) (7.4–28.3)	1578	41	2.2 (**) (1.4–3.5)	952	21	1.7 (**) (0.8–3.8)
Clinical status at HIV diagnosis												
AIDS	132	3817	3.46 (2.92–4.10)	999	94	22.6 (11.5–44.6)	769	28	3.0 (1.8–5.0)	476	10	1.5 (0.5–4.4)
CD4 $<$ 200 − AIDS-free	44	3747	1.17 (0.87–1.58)	1011	20	5.6 (2.7–11.9)	809	13	1.5 (0.9–2.4)	476	11	1.9 (0.9–4.0)
200 $\leq$ CD4 $<$ 350 − AIDS-free	27	4335	0.62 (0.43–0.91)	1280	10	2.8 (1.5–5.4)	1010	12	1.4 (0.7–2.8)	510	5	1.1 (0.4–2.7)
CD4 $\geq$ 350 − AIDS-free	37	11,921	0.31 (0.22–0.43)	3666	8	1	2923	19	1	1378	10	1

(*) aHR (CI 95%): adjusted Hazard Ratios by category of transmission-sex and age at HIV diagnosis and confidence intervals 95%.
(**) Reference category: Subjects not LPAD (CD4 $\geq$ 200 and AIDS-free).

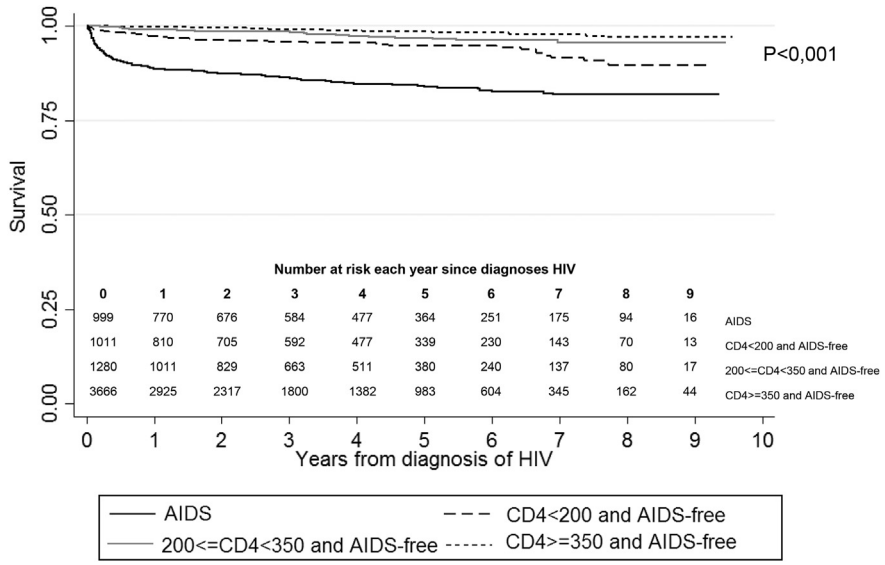

Figure 2 Kaplan Meier survival analysis according to clinical status at the time of HIV diagnosis.

among MSM and heterosexual men, 50% and 40% respectively. However, heterosexual women have not benefitted from this improvement, if fact, we observed a slight increase (23%), although it did not reach statistical significance. However, this upward tendency is consistent with increasing rates of LP among other South European women.[2] In general, women tend to be underrepresented in clinical trials and epidemiological studies on HIV except those concerning vertical transmission prevention. Thus, there is a substantial gap of knowledge when it comes to issues related to HIV diagnosis in women.[33]

Our current results regarding LP are consistent with previous work published by our group based on this same cohort,[13] and by other authors.[2,6,10,29–32,34,35] Finally, our analyses by region of origin determined that LP was more prevalent among patients from Sub-Saharan Africa and Latin America than among Spaniards, confirming the well-documented excess prevalence of delayed HIV diagnoses among migrant populations in Spain and other European countries.[2,6,10,29,30,32]

The nation-wide evidence presented in this work strengthens and adds support for further intensifying HIV testing efforts in Spain and covering larger segments of the population by facilitating access to the test. Our data provide strong backing to the Ministry of Health's recommendation to offer HIV testing in primary care as a strategy to reduce the burden of LP,[36] especially in heterosexual women. Similarly, granting undocumented migrants access to primary care is highly likely to make a dent in the high rates of delayed diagnoses among populations from other countries.

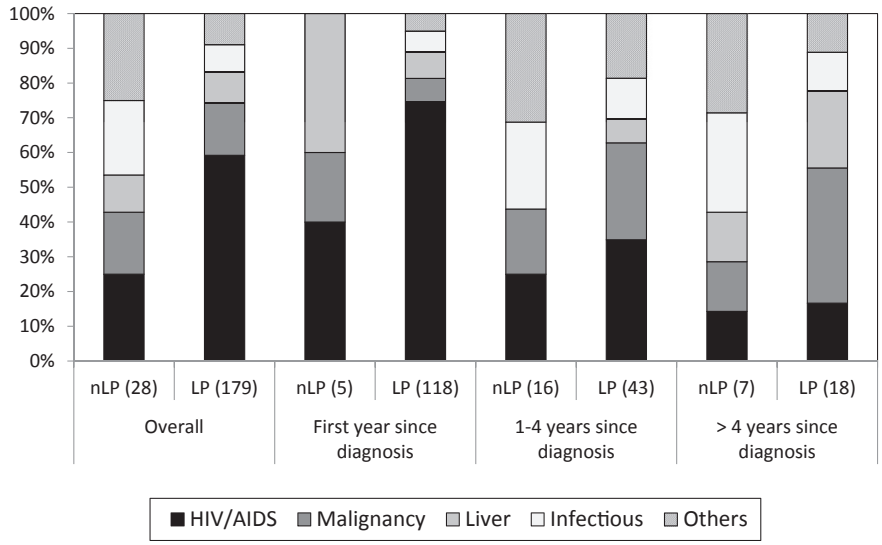

Figure 3 Causes of death distribution according to late presenters (LP) or not late presenters (nLP) and time elapsed since HIV diagnosis.

One of the strengths of the study is being based on CoRIS, a large national cohort representative of the epidemiological situation of HIV-infected individuals in Spain.

Our results should be interpreted in the context of the study's limitations. First, we were not able to include all new HIV diagnoses in our analysis because 4.6% of cases lack the CD4 cell count information at time of diagnosis. Missing data were less likely among MSM and among individuals with higher education. Another potential bias affecting mortality results is introduced by patients lost to follow-up. However, there are three indications that our results may not have been affected significantly by these biases. First, the favorable results from our sensitivity analyses; second, patients lost to follow-up had better clinical characteristics at study entry[16] than the rest; and, finally, the percentages of lost to follow-up were similar across LP groups. In addition, the project has a protocol in place to facilitate the inclusion of patients dying shortly after their first arrival to the hospital and before having a chance to sign the study's informed consent form. In these cases of early death, we collect basic anonymized data. Unfortunately, the unreliable implementation of this particular protocol may have led us to underestimate early mortality among late presenters.

In conclusion, individuals with a late HIV diagnosis experience higher mortality, especially within the first year post-diagnosis and mostly due to HIV/AIDS-related causes. Non-HIV/AIDS-related causes of death, such as liver- and malignancy-related disease, reach substantial percentages only among individuals who were diagnosed with HIV in a timely fashion.

The proportion of patients with late HIV diagnosis remains unacceptably high in a European country with a large public healthcare system. And further, despite the decline in LP among most groups, heterosexual women have not benefitted from this improvement which requires further investigation.

Conflict of interest

Authors have no conflicts of interest.

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