Research article

Late presentation for HIV care across Europe: update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013

The late presenters working group in COHERE in EuroCoord [1]
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Late presentation (LP) for HIV care across Europe remains a significant issue. We provide a cross-European update from 34 countries on the prevalence and risk factors of LP for 2010–2013. People aged ≥16 presenting for HIV care (earliest of HIV-diagnosis, first clinic visit or cohort enrolment) after 1 January 2010 with available CD4 count within six months of presentation were included. LP was defined as presentation with a CD4 count <350/mm³ or an AIDS defining event (at any CD4), in the six months following HIV diagnosis. Logistic regression investigated changes in LP over time. A total of 30,454 people were included. The median CD4 count at presentation was 368/mm³ (interquartile range (IQR) 193–555/mm³), with no change over time (p=0.70). In 2010, 4,775/10,766 (47.5%) were LP whereas in 2013, 1,642/3,375 (48.7%) were LP (p=0.63). LP was most common in central Europe (4,791/9,625, 49.8%), followed by northern (5,704/11,692; 48.8%), southern (3,550/7,760; 45.8%) and eastern Europe (541/1,377; 38.3%; p<0.0001). There was a significant increase in LP in male and female people who inject drugs (PWID) (adjusted odds ratio (aOR)/year later 1.16; 95% confidence interval (CI): 1.02–1.32), and a significant decline in LP in northern Europe (aOR/year later 0.89; 95% CI: 0.85–0.94). Further improvements in effective HIV testing strategies, with a focus on vulnerable groups, are required across the European continent.

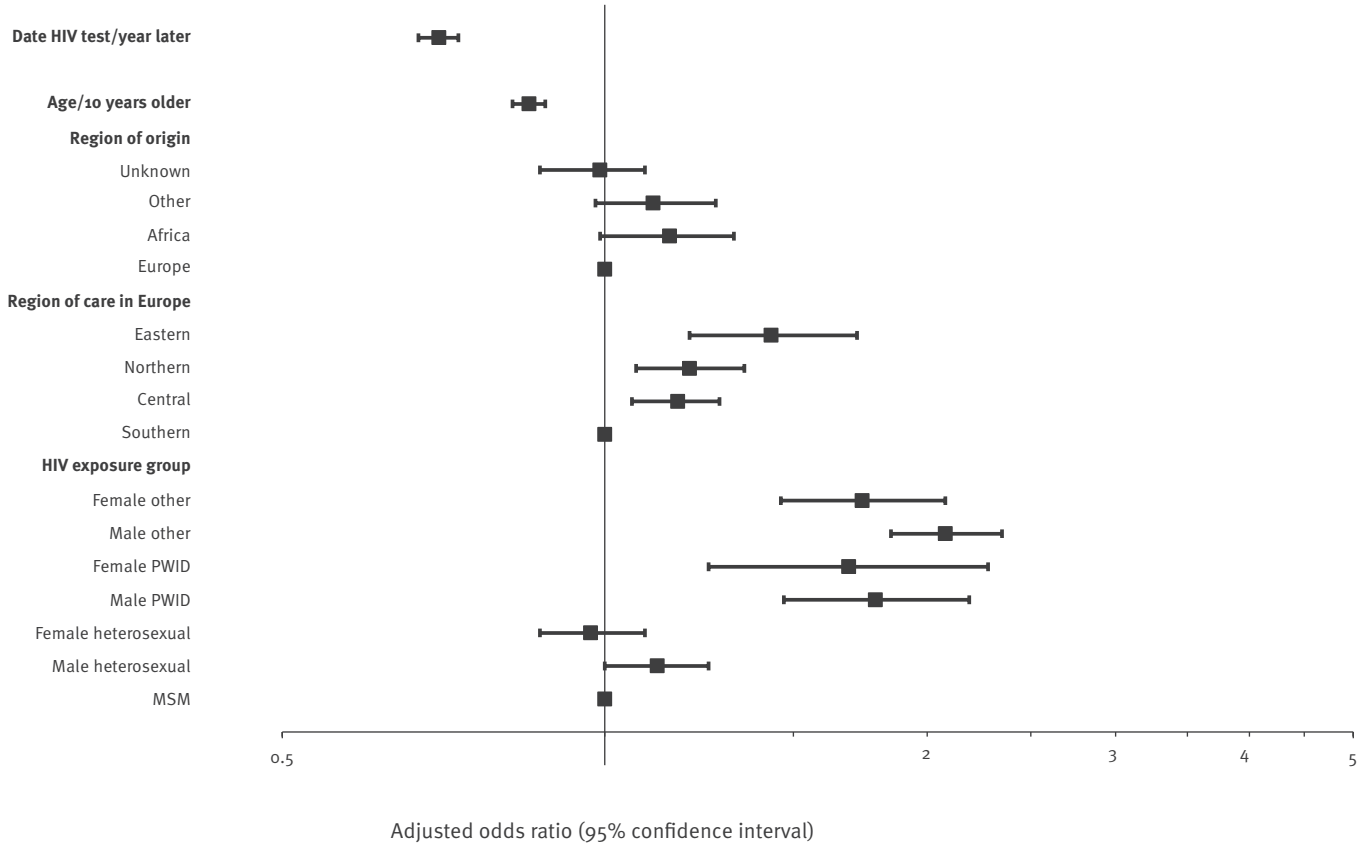
Introduction

The United Nations Programme on HIV/AIDS (UNAIDS) recently released an ambitious strategy that calls for 90% of HIV infections to be diagnosed by 2020 [1]. Many people however remain unaware of their HIV status and cascades for care for HIV vary widely from country to country within Europe, with 20–70% of people infected with HIV remaining undiagnosed [2-4]. These estimates rely on estimates of the population with HIV, which itself is estimated using a variety of different methods [5]. In addition, ca 40–60% of HIV-positive people are diagnosed with HIV at a late stage of infection [6,7], defined as people presenting for HIV care with a CD4 count of less than 350/mm³ or an AIDS defining illness [8]. Individuals at greatest risk of late diagnosis and/or late entry into care have poorer outcomes and higher resource use once diagnosed. Those who are unware of their HIV status are also less likely to take steps to prevent onward transmission to others [9-11]. However, many who present late, do so because they perceive their risk for HIV as low, as they have few sex partners for example.

The rates of late presentation (LP) among newly diagnosed HIV positive people in any setting serves as a proxy of effective HIV testing strategies. Such strategies should ensure people enter appropriate care to start antiretroviral therapy (ART) [12]. However, the extent to which these recommendations are implemented across Europe is variable [13]. Following the recent publication of findings from the Strategic Timing of Antiretroviral Treatment (START) [14], treatment is now recommended for all people infected with HIV [13]. The World Health Organization (WHO) recognises early HIV diagnosis as a crucial first step in the successful care of HIV [15]. There are a number of programmes and initiatives to increase HIV testing; these include indicator-condition-guided HIV testing and national HIV testing strategies, linkage and retention in care of those already diagnosed. Furthermore, there are initiatives specifically aimed at reducing HIV transmission, such as harm-reduction, condom use, initiation of antiretroviral therapy and pre-exposure prophylaxis [16-18].

Figure 1

Adjusted odds of having no CD4 count information within six months following HIV diagnosis, COHERE study, 2010–2013



COHERE: Collaboration of Observational HIV Epidemiological Research Europe; MSM: men who have sex with men; PWID: people who inject drugs.

Logarithmic scale.

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study provides a unique opportunity to describe the epidemiology of those diagnosed HIV-positive at a late stage of HIV infection compared with those diagnosed earlier, and to look at geographical differences within HIV exposure groups. COHERE is a collaboration of 39 cohorts across Europe and is part of the EuroCoord network (www.EuroCoord.net). COHERE was established in 2005 with the aim of conducting epidemiological research on the prognosis and outcome of HIV-positive people, which the individual contributing cohorts cannot address themselves because of insufficient sample size or heterogeneity of specific subgroups of HIV-positive people. Local ethics committee and/or other regulatory approvals were obtained as applicable according to local and/or national regulations in all participating cohorts unless no such requirement applied to observational studies. Each cohort submits data using the standardised HIV Collaboration Data Exchange Protocol (HICDEP) [19], including information on patient demographics, use of combination antiretroviral therapy (cART), CD4 counts, AIDS, and deaths. Further details can be found on EuroCoord website [20].

Previous work showed an overall 4% decrease in LP per year of late presentation between 2000 and 2010 across Europe, albeit with an increase over time in people who inject drugs (PWID) [7]. The aims of this update were to determine if the downward trend in LP observed between 2000 and 2010 continued, and whether there were any groups of individuals in which LP continues to increase.

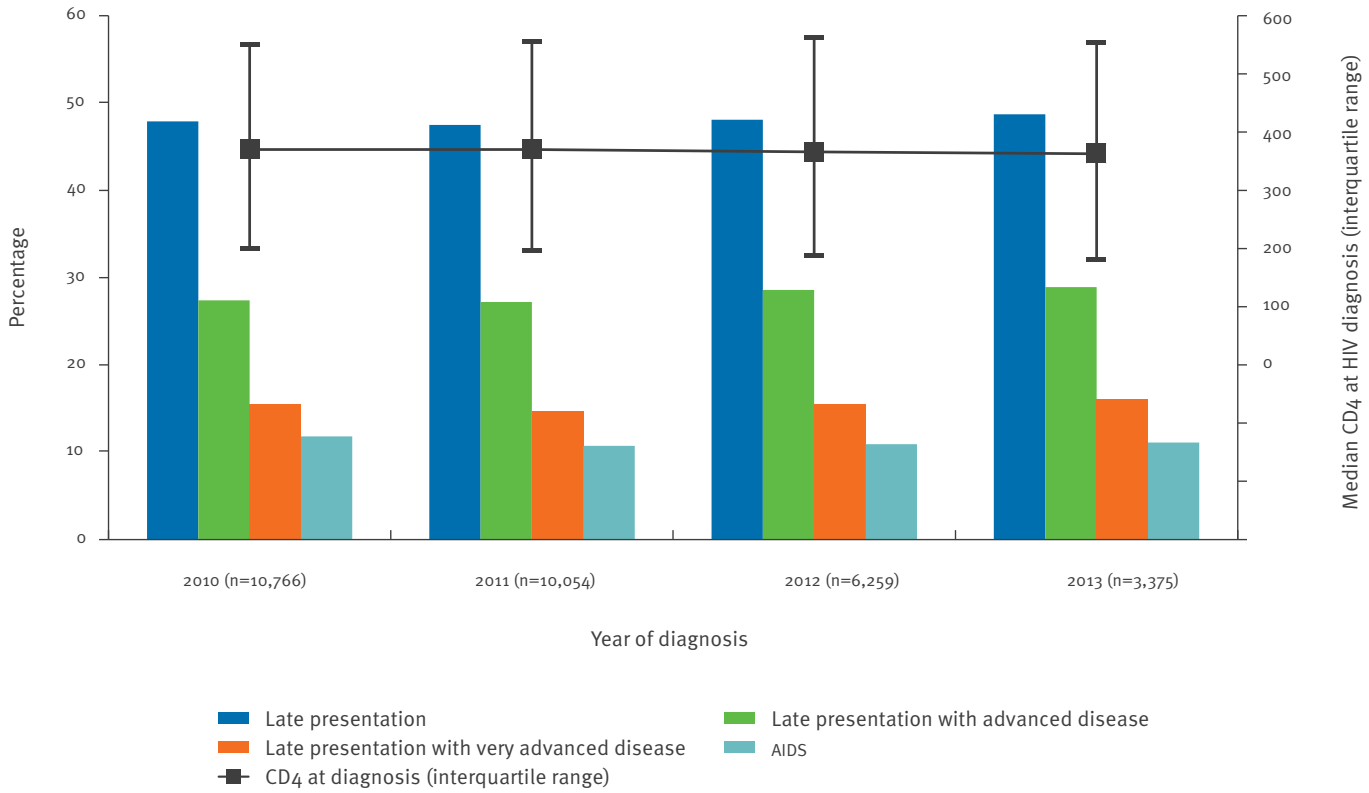
Methods

Patients

Twenty-four cohorts including data from 34 European countries provided data for the present analysis. All people aged ≥ 16 years, who presented for care (defined as earliest date of HIV diagnosis, first clinic visit, or enrolment into the participating cohort, referred to as 'baseline') for the first time after 1 January 2010 were included to provide an update to the report from 2013 which included people diagnosed to the end of 2010 [7]. People were excluded if information on sex or date of HIV diagnosis was missing, or where there was evidence of an earlier HIV diagnosis (CD4 count, AIDS diagnosis, or having started antiretroviral therapy

Figure 2

Changes over time in stages of late presentation and CD4 count at HIV diagnosis, COHERE study, 2010–2013 (N=30,454)



COHERE: Collaboration of Observational HIV Epidemiological Research Europe.

Late presentation: diagnosed with HIV with a CD4 count below 350/mm³ or an AIDS defining event regardless of the CD4 count, in the six months following HIV diagnosis.

Late presentation with advanced disease: diagnosed with HIV with a CD4 count below 200/mm³ or an AIDS defining event, regardless of CD4 cell count, in the six months following HIV diagnosis.

Late presentation with very advanced disease: diagnosed with HIV with a CD4 count below 50/mm³ or an AIDS defining event, regardless of CD4 cell count, in the six months following HIV diagnosis

(ART)) more than one month before first clinic visit, as were people from Argentinean centres in EuroSIDA [21]. People from the seroconverter cohorts in COHERE were also excluded, as in our previous work [7]. By definition, such people are diagnosed soon after HIV infection, even if they have a low CD4 count at HIV-1 diagnosis.

Definitions of late presentation

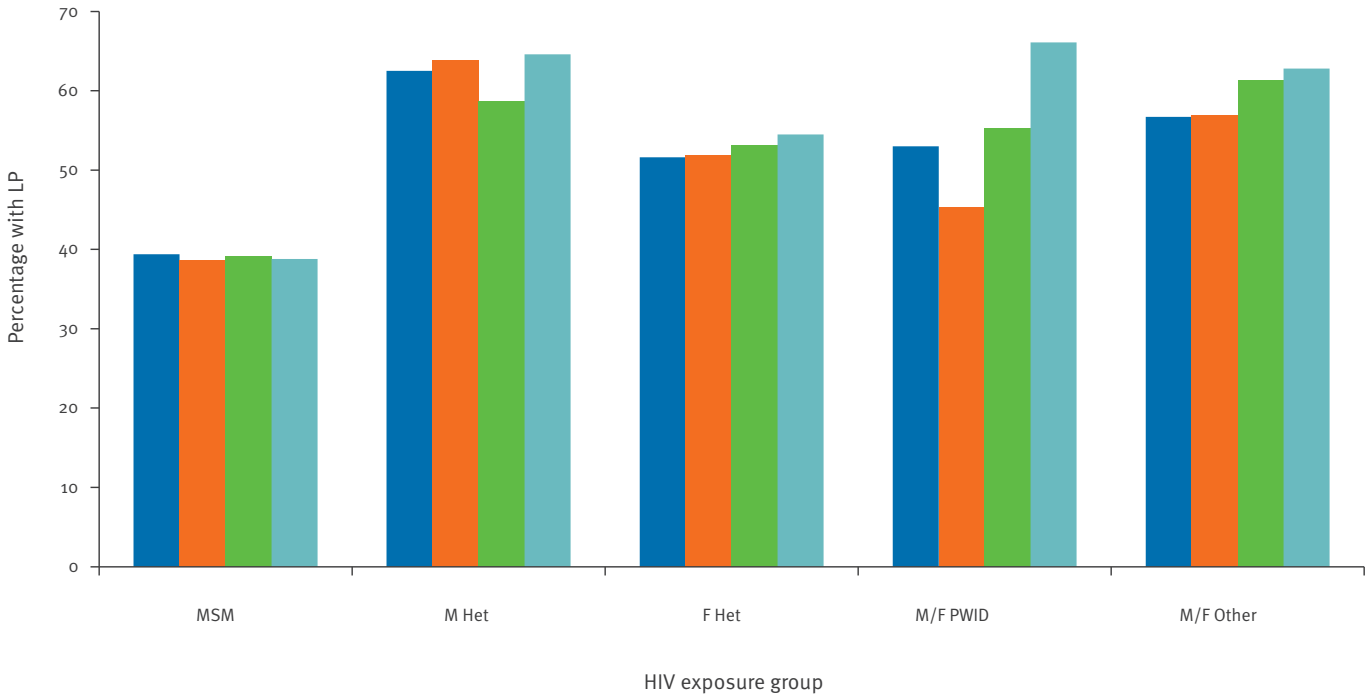
LP was defined as an individual diagnosed with HIV with a CD4 count below 350/mm³ or an AIDS-defining event regardless of the CD4 count, in the six months following HIV diagnosis. LP with advanced disease was defined as an individual diagnosed with HIV with a CD4 count below 200/mm³ or an AIDS defining event, regardless of CD4 cell count, in the six months following HIV diagnosis. LP with very advanced disease was defined as an individual diagnosed with HIV with a CD4 count below 50/mm³ or an AIDS defining event, regardless of CD4 cell count, in the six months following HIV diagnosis. The proportion presenting with AIDS, regardless of the CD4 count at which it occurred, was also presented. Delayed entry into care was defined as more than three months between HIV diagnosis and first clinic visit, in those where both dates were recorded. All people were required to have at least one CD4 count measured in the six months following diagnosis.

Statistical methods

Baseline characteristics of late presenters were compared with those of non-late presenters and logistic regression was used to identify factors associated with late presentation and late presentation with advanced disease. Factors investigated were age, HIV exposure group (men who have sex with men (MSM), heterosexual men, heterosexual female, male PWID, female PWID, other (including patients with unknown HIV exposure group)), continent of origin (Europe, Africa, other (including patients from Central/Southern

Figure 3

Changes over time in late presentation by HIV exposure groups, COHERE study, 2010–2013 (n=30,454)



Odds of late presentation: per year later of presentation.

Univariate	0.99 (0.96–1.03)	0.99 (0.93–1.05)	1.04 (0.98–1.09)	1.16 (1.03–1.31)	1.10 (1.02–1.17)
Multivariate[a]	0.98 (0.95 – 1.01)	0.97 (0.91 – 1.03)	0.99 (0.93 – 1.05)	1.16 (1.02 – 1.32)	1.08 (1.00 – 1.16)

2010 (n=10,766) 2011 (n=10,054) 2012 (n=6,259) 2013 (n=3,375)

COHERE: Collaboration of Observational HIV Epidemiological Research Europe; F: female; Het: heterosexual; LP: late presentation; M: male; MSM: men who have sex with men; PWID: people who inject drugs.

[a]Adjusted for age, region of care in Europe, continent of origin, delayed access to care.

Late presentation: diagnosed with HIV with a CD4 count below 350/mm^3 or an AIDS defining event regardless of the CD4 count, in the six months following HIV diagnosis.

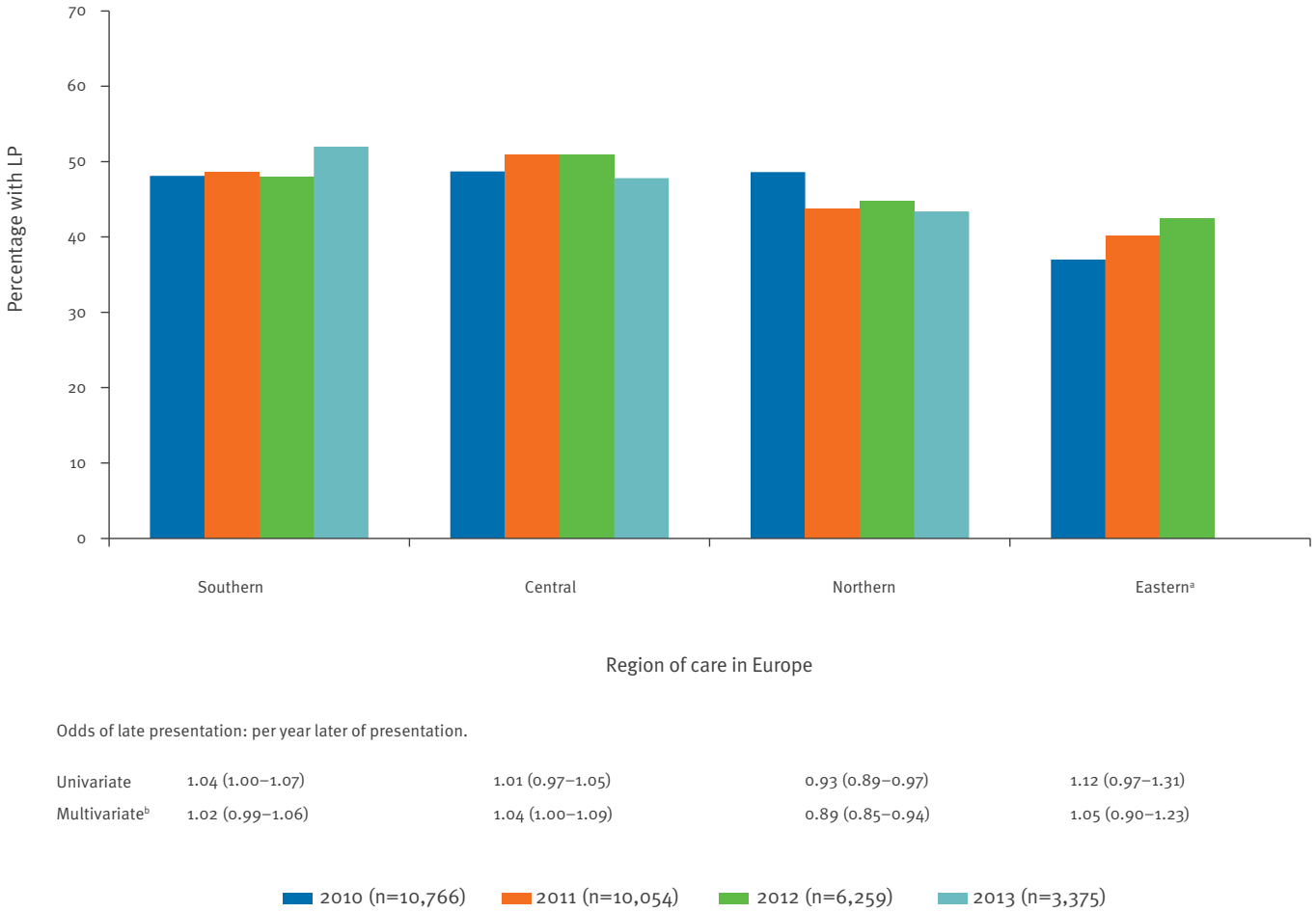
America and Asia), unknown), region of HIV diagnosis in Europe, based on the cohort location and defined similarly to the EuroSIDA study [22] (Table 1), calendar year of diagnosis, and delayed entry into care.

A priori, we were interested in comparing changes over time within region of HIV diagnosis in Europe and HIV exposure groups. Simple descriptive data were used to present the proportions of LP, advanced LP, very advanced LP and presentation with AIDS by country; countries were grouped into regions and anonymised, those countries with less than 50 people included were combined. Linear regression was used to assess change over time in CD4 counts overall and among LP, and Cox proportional hazards models were used to compare the risk of development of a new clinical event i.e. a new AIDS defining illness occurring more than one month after the first if the person had AIDS within six months of baseline or death), whether this has changed over time, and at a similar rate for LP and non-LP.

Descriptive analyses were used to investigate whether someone classified as a LP based on a CD4 count›350/mm^3 (but no AIDS diagnosis) would not be a LP if the next CD4 count was used (misclassification). This analysis was limited to the small subset with CD4 counts measured after HIV diagnosis and before starting ART. Logistic regression was used to determine whether potential misclassification of people as LP had changed over time, after adjusting for age, HIV exposure group, region of origin, region of HIV diagnosis in Europe,

Figure 4

Changes over time in late presentation by region of care in Europe, COHERE study, 2010–2013 (N=30,454)



COHERE: Collaboration of Observational HIV Epidemiological Research Europe; LP: late presentation.

[a]Adjusted for age, HIV exposure group, region of origin, delayed access to care.

[b]No data available for 2013.

Late presentation: diagnosed with HIV with a CD4 count below 350/mm^3 or an AIDS defining event regardless of the CD4 count, in the six months following HIV diagnosis.

calendar year of diagnosis, delayed entry into care, and CD4 count and HIV viral load at HIV diagnosis.

All analyses were performed using Statistical Analysis Software Version 9.3 (Statistical Analysis Software).

Results

Of 37,859 people with a HIV-1 test after 1 January 2010, 4,197 were excluded because they were aged‹16, from seroconverter cohorts, or where there was evidence that the person had started ART, had a CD4 count or an AIDS diagnosis more than 28 days before the first reported HIV-1 test. A further 3,208 of 33,662 (9.5%) were excluded due to missing CD4 counts, 9.6% from south Europe and 8.6%, 9.8% and 13.5% from central, northern and eastern Europe respectively. Compared with the 30,454 included, those excluded due to missing CD4 counts were more likely to be PWID, from other (including unknown) HIV exposure groups, and to be in care in northern, central or eastern Europe compared with southern Europe (Figure 1). Older people were less likely to be excluded, as were those with a more recent test for HIV.

Late presentation and changes over time

Table 2 summarises the characteristics of the 30,454 people included, stratified by LP status; 14,586 (47.9%) were LP, ranging from›60% of heterosexual men or people originating from Africa to ca 39% MSM and female PWID.

Table 1

Geographical categorisation of European countries to regions, COHERE study, 2010–2013[a]

Region in Europe	Countries included
Northern	Denmark, Finland, Ireland, the Netherlands, Norway, Sweden, United Kingdom
Southern	Greece, Israel, Italy, Portugal, Spain
Central	Austria, Belgium, France, Germany, Luxemburg, Switzerland
Eastern	Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, Ukraine

COHERE: Collaboration of Observational HIV Epidemiological Research Europe.

[a] Defined similarly to the EuroSIDA study [22].

Among people in whom both first visit and HIV test date were known, 1,247/27,818 (4.5%) had delayed entry into care. Figure 2 shows the annual proportion of people with LP, LP with advanced or very advanced disease, and with an AIDS diagnosis, regardless of the CD4 count at presentation.

In 2010 4,775/10,766 (47.5%) were LP, compared with 1,642/3,375 (48.7%) in 2013 or later (p = 0.63). The proportion of people with LP, advanced disease, very advanced disease, or AIDS did not change significantly over time (p = 0.63, 0.090, 0.16, and 0.075 respectively). The proportion of those presenting who would be eligible for starting cART with a CD4 count of ‹500/mm³ was 69.0% in 2010, 68.8% in 2011, 68.3% in 2012 and 69.0 in 2013 or later (p = 0.77).

In multivariate analyses, there was no evidence of a change over time in LP (adjusted odds ratio (aOR) 0.99/year later; 95% confidence interval (CI): 0.97–1.02; p = 0.60), or in LP with advanced disease (aOR 0.99/year later; 95% CI: 0.97–1.02; p = 0.65). This finding was consistent across a wide range of sensitivity analyses, such as including those with AIDS but without a CD4 count measured as LP, including deaths within the first six months as LP, when the window required for a CD4 count after HIV diagnosis to three months, and defining LP as a CD4 count ‹350/mm³ or an AIDS diagnosis within three months of HIV diagnosis. There was some evidence that presentation with very advanced disease had decreased over time by 3% per year later (aOR 0.97/year later; 95% CI: 0.93–1.00; p = 0.035), and that LP based on an AIDS diagnosis alone, regardless of the CD4 count at which it was diagnosed, had decreased by 7% per year (aOR 0.93; 95% CI: 0.89–0.96; p = 0.0001).

Changes in CD4 count at presentation

The median CD4 count at presentation was 368/mm³ (interquartile range (IQR) 193–555/mm³). There was no evidence of a change over time in the median CD4 count at presentation (p=0.70), suggesting that overall, the level of immunodeficiency at which HIV was diagnosed has not changed over time (adjusted change/year 1.2/mm³; 95% CI: -0.8 to 3.3/mm³; p = 0.89). Similar results were seen in an analysis limited to LP (adjusted change/year -1.1/mm³; 95% CI: -3.1 to 0.8/mm³, p = 0.31), demonstrating that LP are diagnosed with HIV at a similar level of immunodeficiency between 2010 and 2013.

Of 14,586 LP, 3,984 (27.3%) did not have AIDS as part of the LP definition and had at least one CD4 count during follow-up before starting ART. Among these, for 1,067 (26.8%) the next CD4 count was ›350/mm³, suggesting they may not be LP or they may be seroconverters; this proportion was highest for MSM (698/2,154; 32.4%), and was ca 20% in all other HIV exposure groups (p ‹ 0.0001). There was some evidence that the proportion that may be incorrectly classified as LP had increased over time (aOR 1.14/year later; 95% CI: 1.04–1.28; p = 0.0050). This proportion of potentially misclassified LP was lower using a confirmed CD4 count ›350/mm³ (317/1,279 (24.8%) with more than two CD4 counts after HIV diagnosis and before ART started).

Changes in late presentation in HIV exposure groups and regions of Europe

Figure 3 summarises the change over time in LP among HIV exposure groups. Male and female PWID were combined due to smaller numbers as were men and women belonging to the ‘other’ risk groups. There was strong evidence to suggest that the rate of change in LP differed between HIV exposure groups (p ‹ 0.0001, test for interaction). After adjustment, there was no change over time in LP among MSM, or male or female heterosexuals, but there was a significant increase in LP among PWID (both men and women combined) (aOR 1.16/year later; 95% CI: 1.02–1.32; p = 0.024) and in the other exposure groups (aOR 1.08/year later; 95% CI: 1.00– 1.16, p = 0.040).

LP was most common in central Europe (4,791/9,625, 49.8%), followed by northern (5,704/11,692; 48.8%), southern (3,550/7,760; 45.8%) and eastern Europe (541/1,377; 38.3%; p‹0.0001). There were considerable differences in LP in countries within regions of care in Europe (Table 3), particularly within eastern Europe. Figure 4 presents similar data to Table 3, stratified by region of care in Europe, with evidence to suggest the rate of change in LP differed between regions (p ‹ 0.0001; test for interaction). There was a marginally significant increase in LP over time in central Europe

Table 2

Characteristics of included patients, COHERE study, 2010–2013 (n=30,454)

Patients' characteristics		All		Late presenters	
		N	Percentage (%)[a]	N	Percentage of late presenters (%)[b]
All		30,454	100	14,586	47.9
Delayed entry to care[c]	No	26,751	95.5	12,818	47.9
	Yes	1,247	4.5	494	39.6
HIV exposure group	MSM	15,371	50.5	5,993	39.0
	Heterosexual men	4,826	15.8	3,011	62.4
	Heterosexual females	5,487	18.0	2,864	52.2
	PWID (male)	843	2.8	481	57.1
	PWID (female)	321	1.1	126	39.3
	Male other	2,551	8.8	1,495	58.6
	Female other	1,055	3.5	616	58.4
Region of care in Europe	Southern	11,692	38.4	5,704	48.8
	Central	9,625	31.6	4,791	49.8
	Northern	7,760	25.5	3,550	45.8
	Eastern	1,377	4.5	541	38.3
Continent of origin	Europe	20,701	68.0	9,495	45.9
	Africa	2,651	8.7	1,696	64.0
	Other	2,685	8.8	1,428	53.2
	Unknown	4,417	14.5	1,967	44.5
		Median	IQR	Median	IQR
Age	Years	36	29–45	39	31–48
CD4	/mm³	368	193–555	184	73–276
Baseline[d]	Month/year	6/2011	9/2010–4/2012	6/2011	9/2010–4/2012

COHERE: Collaboration of Observational HIV Epidemiological Research Europe; IQR: interquartile range; MSM: men who have sex with men; PWID: people who inject drugs.

[a]% represents percentage of total; for example, 15,371/30,454 (50.5%) of the population included were MSM.

[b] % represents the percentage of late presenters; for example, 5,993/15,371 (39.0%) of MSM were late presenters.

[c] Delayed entry into care was defined as more than three months between HIV diagnosis and first visit to clinic, in people with both dates recorded (n=27,998).

[d] Baseline was defined as the earliest of HIV test, first study visit or cohort enrolment.

Late presentation: diagnosed with HIV with a CD4 count below 350/mm³ or an AIDS defining event regardless of the CD4 count, in the six months following HIV-diagnosis [8].

(aOR 1.04/year later; 95% CI: 1.00–1.09, p=0.084), and a significant decrease in LP over time in northern Europe (aOR 0.89; 95% CI: 0.85–0.94; p<0.0001).

Clinical disease progression

During 39,790 person-years of follow-up (PYFU) 886 (2.9%) people developed a new AIDS defining illness or died, giving an incidence of clinical progression of 22.3/1,000 PYFU (95% CI: 20.8–23.7). A total of 409 disease progression events were death, 486 were a new AIDS event, and nine patients had both types of events on the same date. There were no differences in the proportion of events that were attributable to AIDS (63/125 (50.4%) vs 423/761 (55.6%); p=0.28), deaths (63/125 (50.4%) vs 346/761 (45.5%); p=0.31), or in the specific AIDS events diagnosed (p=0.053) comparing LP and non-LP. The incidence of clinical progression was 6.5-fold higher among LP (761 events, 39.6/1,000 PYFU; 95% CI: 36.8–42.4) compared with non-LP (125 events, 6.1/1,000 PYFU; 95% CI: 5.0–7.1).

There was no evidence of any change over time in the risk of developing a new AIDS event or death within the first six months of presentation or after this time (Table 4). For example, after adjustment, there was no change over time in the risk of developing a new clinical event per year later of presentation after six months of follow-up (adjusted hazard ratio (aHR) 1.04/year later; 95% CI: 0.91–1.19, p=0.40). There was no evidence that this relationship differed in LP vs non-LP (test for interaction>0.2), and the results are also shown in Table 4. These findings were also consistent for

Table 3

Late presentation, late presentation with advanced disease, late presentation with very advanced disease and presentation with an AIDS defining event at any CD4 count stratified by country, COHERE study, 2010–2013

			Late presentation		Late presentation with advanced disease		Late presentation with very advanced disease		AIDS	
Region of care in Europe	Country	N	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Southern	[a]	40	55.0	39.6–70.4	27.5	13.7–41.3	7.5	0.0–15.7	2.5	0.0–7.3
Southern	1	1,097	45.9	43.0–48.9	25.9	23.3–28.5	12.5	10.5–14.4	8.1	6.5–9.7
Southern	2	4,782	53.9	52.5–55.3	33.9	32.6–35.2	17.1	16.1–18.2	9.6	8.7–10.4
Southern	3	5,773	45.0	43.8–46.3	25.8	24.7–26.9	14.3	13.4–15.2	11.0	10.2–11.8
Central	[a]	19	31.6	10.7–52.5	15.8	0.0–32.2	10.5	0.0–24.3	5.3	0.0–15.3
Central	1	568	43.7	39.6–47.7	24.6	21.1–28.2	13.4	10.6–16.2	11.3	8.7–13.9
Central	2	778	47.6	44.0–51.1	27.9	24.7–31.0	17.4	14.7–20.0	14.1	11.7–16.6
Central	3	810	54.9	51.5–58.4	30.9	27.7–34.0	15.1	12.6–17.5	11.6	9.4–13.8
Central	4	2,675	56.2	54.3–58.1	37.2	35.3–39.0	24.6	23.0–26.2	20.0	18.5–21.6
Central	5	4,775	46.5	45.1–47.9	25.1	23.8–26.3	13.5	12.5–14.5	10.5	9.6–11.3
Northern	[a]	21	47.6	26.3–69.0	33.3	13.2–53.5	19.0	0.0–35.8	14.3	0.0–29.3
Northern	1	600	52.7	48.7–56.7	33.7	29.9–37.4	19.3	16.2–22.5	13.2	10.5–15.9
Northern	2	3,419	44.7	43.1–46.4	24.2	22.7–25.6	11.7	10.7–12.8	7.6	6.7–8.5
Northern	3	3,720	45.5	43.9–47.1	26.7	25.3–28.1	17.4	16.2–18.7	14.2	13.1–15.4
Eastern	1	74	63.5	52.5–74.5	18.9	10.0–27.8	8.1	1.9–14.3	6.8	1.0–12.5
Eastern	2	84	50.0	39.3–60.7	26.2	16.8–35.6	19.0	10.7–27.4	19.0	10.7–27.4
Eastern	[a]	98	58.2	48.4–67.9	39.8	30.1–49.5	24.5	16.0–33.0	19.4	11.6–27.2
Eastern	3	1,121	35.2	32.4–38.0	12.1	10.2–14.0	1.4	0.7–2.1	0.7	0.2–1.2

COHERE: Collaboration of Observational HIV Epidemiological Research Europe.

[a] Represents >1 country within specific regions where countries with <50 people have been combined.

Late presentation: diagnosed with HIV with a CD4 count below 350/mm3 or an AIDS defining event regardless of the CD4 count, in the six months following HIV diagnosis.

Late presentation with advanced disease: diagnosed with HIV with a CD4 count below 200/mm3 or an AIDS defining event, regardless of CD4 cell count, in the six months following HIV diagnosis.

Late presentation with very advanced disease: diagnosed with HIV with a CD4 count below 50/mm3 or an AIDS defining event, regardless of CD4 cell count, in the six months following HIV diagnosis.

AIDS: presentation with AIDS regardless of CD4 count.

different HIV exposure categories and across regions of care in Europe and when using death alone as the clinical endpoint.

Discussion

This study, which included more than 30,000 people from across 34 European countries, demonstrated no overall change in the proportion of LP across Europe since 2010. LP increased significantly in PWID as presumed HIV exposure. This lack of improvement in diagnosing HIV earlier was consistent across a wide range of analyses; there was no change over time in LP with advanced disease, in the average CD4 count at presentation, or in progression to a new AIDS event/death.

The proportion of LP decreased significantly across Europe between 2000 and 2010 [7], but despite numerous interventions and initiatives in recent years to optimise testing for HIV, we found no overall change between 2010 and 2013 in the proportion of LP across Europe. LP is impacted by the underlying incidence of HIV which itself is difficult to estimate [5]. If HIV incidence increases and HIV testing does not change, the proportion of LP will decline as more are diagnosed early. Conversely, if incidence is declining and HIV testing does not change, the proportion of LP increases. Assuming the overall incidence of HIV is not decreasing in Europe, as there appears to have been no decline in HIV diagnoses per 100,000 population over the last decade [4], our findings of no decrease in LP overall suggests there are areas for further interventions for reducing LP on a European level. A more detailed analysis by region showed a small decrease over time in LP from northern Europe, but not from other regions. Combining countries into these regions was decided a priori and used the stratification previously used by EuroSIDA [23]. Such a broad grouping may not be ideal for a number of reasons, including history, politics and economy and the rates of LP within regions varied considerably, reflecting this heterogeneity. HIV surveillance in Europe for the European Union (EU)/European Economic Area (EEA) is coordinated by the European

Table 4

Relative hazard of a new AIDS defining event or death following HIV diagnosis per year later of presentation, COHERE study, 2010–2013

		In first six months after presentation			More than six months after presentation		
		HR	95% CI	P	HR	95% CI	p
All	Univariate	1.02	0.92–1.11	0.83	1.01	0.89–1.15	0.87
	Multivariate [a]	0.98	0.89–1.08	0.73	1.04	0.91–1.19	0.40
Non-LP	Univariate	0.99	0.64–4.53	0.95	1.04	0.77–1.40	0.79
	Multivariate [a]	0.92	0.59–1.45	0.73	0.98	0.89–1.09	0.72
LP	Univariate	1.01	0.92–1.12	0.83	1.00	0.87–1.16	0.98
	Multivariate [a]	1.06	0.78–1.44	0.71	1.05	0.90–1.22	0.54

CI: confidence interval; COHERE: Collaboration of Observational HIV Epidemiological Research Europe; HR: hazard ratio; LP: late presentation.

[a] Multivariate models were adjusted for age, HIV exposure group, region of care in Europe, continent of origin, and whether an AIDS diagnosis was present at baseline. The model in all patients adjusts additionally for late presentation.

All HR are per year later of presenting for care.

Centre for Disease Prevention and Control (ECDC) in collaboration with the WHO Regional Office for Europe and the ECDC report displays LP in central-east and eastern Europe separately [4]; in this study, they were combined due to small numbers from the central-east region. Further, combining southern, central and northern Europe into one region in our study to compare to ECDC data may hide important findings within these regions. Despite these differences in classification, the proportion with LP in this study was very similar to that recently reported by the ECDC [4], who reported eight countries with›50% as LP, including Greece and Italy, both of which contributed significant numbers to our analyses.

Possible action points for increasing HIV awareness and HIV testing, and therefore minimising LP include a combination of both community-based and provider-initiated models for HIV testing, removal of stigmatisation, as well as working towards acceptance of verbal informed consent for testing [16,18,24,25]. Community-based testing should be a priority, as should targeting key populations.

Previous analyses from COHERE showed an increase in LP among PWID from southern and eastern Europe [7], a trend that continued in these analyses. It is worth noting again that these data are difficult to interpret; the number of new diagnoses of HIV is declining in PWID in Europe [4] and if HIV testing is stable this could lead to an increase in the proportion of PIWD presenting late. Although PWID account for a comparatively small proportion of new HIV infections in western Europe, this route of transmission is more common in eastern Europe [4,7], and issues continue to exist around needle exchange, opiate substitution therapy, as well as access to ART and retention in care once HIV has been diagnosed [26,27]. Recent data suggest that those in prison and migrants were among those least likely to be targeted for HIV testing; with challenges being providing HIV services and support, although the ECDC-funded report by Deblonde et al. acknowledges excellence in some countries [28]. Further, PWID are more likely to face greater barriers to accessing healthcare and to belong to lower socioeconomic groups and have lower levels of education, all factors known to be associated with poorer medical outcomes [29,30]. Thus while there is evidence for barriers for PWID to access care and be retained in care, there is much less evidence that HIV is not diagnosed, or that diagnosis of HIV or access to care is even worsening.

We found a small decline in the proportion of LP with very advanced disease or in the proportion presenting with AIDS over time. The fact that the CD4 count at presentation has remained stable over time may suggest that health systems are better able to recognise and capture people with symptomatic HIV disease occurring at higher CD4 counts and that asymptomatic patients are not routinely diagnosed with HIV, especially in groups at low risk of HIV infection. Evidence from other studies concerning changes over time in CD4 count at presentation in recent times have shown mixed results [31-34]; some have limited data from 2011 and others have not been able to adjust for confounding variables. Other studies have described a decrease in the proportion presenting with AIDS [35,36], although the extent to which this is due to the under-reporting of AIDS is unknown.

We found no evidence of a change over time in short-term clinical progression (within six months) or after that time in all people or in LP and non-LP considered separately, in different regions of Europe or HIV exposure categories, although median follow-up was limited by only including people diagnosed with HIV-1 since 2010. The greatest risk in clinical progression for LP has been observed in the years immediately following LP [7,10,37,38], and in this study, LP had approximately a six-fold higher incidence of clinical progression. A lack of change in clinical outcomes in LP over calendar time suggests that, once people have accessed care, treatment and outcomes are uniform across a variety of settings. Given the poor outcomes after LP, work is needed to reduce the proportion of those presenting

late to reduce morbidity and mortality associated with HIV, as well as to reduce the financial impact on health systems and onward transmission of HIV [9-11].

It is possible that some people presenting with symptomatic seroconversion for HIV are misclassified as LP due to the transient drop in CD4 count occurring at this time [39]. Misclassification of LP may be highest in MSM [40]. In our study, there was a small subset with CD4 counts after HIV diagnosis but before starting antiretroviral therapy. Approximately 20% did not have a CD4 count of ‹350/mm^3 at the next CD4 count, and this proportion was highest for MSM. This proportion was similar when using a confirmed CD4 count of ›350/mm^3, suggesting this is not largely due to laboratory variation, although it is worth noting that only a small subset of people had one or two CD4 counts after HIV diagnosis and before starting ART. In addition, only 5% had a CD4 count ›500/mm^3 at the second measurement, which is higher than the currently recommended threshold for initiation of antiretroviral therapy [12]. In addition, we found no changes over time in the proportion of LP, presentation with advanced or very advanced disease, suggesting that an increasing proportion of primary HIV infections is unlikely to explain the lack of change in LP in recent years.

There are a number of limitations which should be considered. We are likely underestimating LP as people who do not survive long enough to have a CD4 count measured were excluded [41]. Our data suggest this was more likely in PWID, other HIV exposure groups, those under care in northern and eastern Europe, and affected ca 10% of those in the COHERE cohorts. This is considerably lower than reported by surveillance studies [42], highlighting that cohort studies such as COHERE can supplement information available from the WHO or ECDC. Furthermore, cohorts participating in COHERE tend to be receiving healthcare at centres of excellence and clinic-based cohorts rather than non-clinic outpatient settings, where LP may be higher. We excluded seroconverter cohorts participating in COHERE as in our previous work, where inclusion of these cohorts did not alter our findings [7]. Even in a collaboration as large as COHERE we were not able to consider LP for male and female PWID separately, although it is worth noting that there was no statistically significant rise in LP in any one region, suggesting that the problem of LP in IDUs is not limited to one region of Europe, but a potential problem on a wider scale.

In conclusion, LP across Europe account for almost 50% of HIV diagnoses with no evidence of a change since 2010. Increased HIV testing, with a focus on vulnerable groups, will reduce the harm for the individual and it may as well reduce onward transmission. Earlier diagnosis for HIV is an important component of achieving the UNAIDS target of ending the AIDS epidemic by 2030 [1].

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Conflict of interest

None declared.

Authors' contributions

Amanda Mocroft, Ole Kirk and Jens Lundgren proposed and developed the project. Amanda Mocroft performed the analyses and wrote the first draft of the manuscript. All other authors contributed to discussions of results, interpretation of data and contributed to writing the manuscript.

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http://www.chip.dk/COHERE/Acknowledgements/tab-id/320/Default.aspx

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