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Delayed HIV diagnosis and initiation of antiretroviral therapy: inequalities by educational level, Cohere in EuroCoord

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Introduction

Socioeconomic status is inversely associated with access to and use of health services by the general population and, in Europe and elsewhere, health inequalities in the general and in sub-populations such as HIV-positive people are a growing concern[1-3]. Members of disadvantaged socio-economic groups face barriers to health services[2, 4], even in European countries with universal and public health insurance[5]. In spite of the existence of universal access to confidential HIV testing, HIV care and combination antiretroviral therapy (cART) in most European countries[6], a patient's socio-economic status may influence the ease or difficulty of access. Since the HIV epidemic is entrenched among the socially vulnerable, including homosexual men, injecting drug users and migrants,[7, 8] with access to health care increasingly limited for undocumented migrants[9, 10], questions about the effect of socio-economic status on the diagnosis and treatment of HIV-positive persons are pressing.

Timely diagnosis of HIV infection is the first step in the HIV treatment cascade, but the COHERE collaboration of HIV cohorts of routine clinical practice in Europe recently reported that there is a very high rate of late presentation [11]. Those who do not know they have an HIV infection are less likely to take steps to prevent its transmission. Late diagnoses delay cART initiation and raise the rates of hospitalisation, morbidity and mortality[12, 13]. Universal access does not, alone, ensure that health services will be utilized. Measuring socioeconomic status is difficult. In adults educational level is widely used as a proxy given that is fairly stable beyond early adulthood and is therefore less likely to be affected by reverse causation[14-17], ie if the association between socioeconomic status exists because better health status allows to achieve a better socioeconomic status. Previous studies on the association between educational level, the timing of HIV diagnosis and initiation of cART lack a pan-European perspective to present a clear picture of the problem[18-20]. These studies have been conducted in single countries, each applying a different classification of educational level. Without a clear understanding of the role that socio-economic inequality plays in access to HIV diagnosis and treatment, we cannot formulate effective policy and programs, or efficiently allocate resources, particularly at times of economic crisis [21].

We investigated the association between socio-economic status and delayed HIV diagnosis and initiation of cART in COHERE, a large European collaboration of HIV cohort studies. We chose educational level as a proxy for socio-economic position and harmonised data on education across cohorts. Our working hypothesis was that lower educational level is linked to higher risk of delayed diagnosis and cART initiation. Because of the widespread practice of antenatal testing in the study setting and the different testing strategies for the different HIV transmission categories, our secondary aims were to examine whether the association varied by sex and transmission category.

Methods

Patients

COHERE in EuroCoord is a collaboration of 35 observational cohorts covering 32 European countries, within the framework of the EuroCoord network of excellence (http://www.eurocoord.net). Each cohort submits data in a standardised format (the HIV Collaboration Data Exchange Protocol, http://www.hicdep.org) to co-ordinating centres at the Copenhagen HIV Program , Denmark, or the Institut de Sante Publique d'Epidémiologie et de Développement (Bordeaux School of Public Health), Bordeaux, France. The Regional Coordinating Centres ensure adherence to strict quality assurance guidelines and perform data checks, including the removal of duplicate records. Data include information on patients' characteristics (age, sex, geographical origin, and transmission category), use of cART (type of regimes and dates of start and discontinuation), CD4 counts and plasma HIV-RNA over time and their dates, AIDS defining conditions and deaths. Further information is available at www. cohere.org.

In 2012, EuroCoord defined socio-economic variables with the intent of standardising and harmonising collection of socio-economic data across cohorts in European countries. Educational level was the only available socio-economic variable whose harmonization across European countries could be performed retrospectively. The definition of the variable *maximum attained level of education* was based on the UNESCO/ISCED standard classification, and was classified as *uncompleted basic* (ISCED 0), *basic* (ISCED 1 and 2), *secondary* (ISCED 3 and 4) and *tertiary* (ISCED 5 and 6), based on data on education systems and reforms available from the European Encyclopaedia on National Education Systems (http://eacea.ec.europa.eu/education/eurydice/eurypedia_en.php).

These analyses included data from nine cohorts in six European countries (Austria, France, Greece, Italy, Spain and Switzerland) that collected data on maximum attained educational level. Patients were included if they were diagnosed with HIV between January 1st, 1996 and December 31st 2011, were aged ≥16 years, enrolled within six months of HIV diagnosis, had at least one measured CD4 count within six months of their HIV diagnosis while cART-naïve and the level of education was known[11]. Patients from COHERE's three seroconverter cohorts were excluded; by definition, they could not qualify as late presenters. Ethics approval was granted by the ethic committees of each of the participating cohorts according to country regulations. Signed informed consent was obtained from all patients.

Data were pooled in September 2011 within COHERE in EuroCoord (www.cohere.org and www.EuroCoord.net) and additional data on educational level data were received from the cohorts in 2012.

Statistical analyses

Delayed HIV presentation

We defined delayed HIV presentation based on definitions proposed by the European Late Presenter Consensus Working group: i) presentation with advanced HIV disease (AHD) as CD4 count below 200 cells/mm^3 or an AIDS defining event in the six months following presentation; and, ii) presentation with late HIV disease (LHD) as CD4 count below 350 cells/mm^3 or an AIDS defining event in the six months following diagnosis [22].

We used logistic regression models to explore the association between educational level with AHD and LHD, adjusting for the following potential confounders, chosen a priori: calendar period of HIV diagnosis (<2001 versus ≥2001, to reflect the introduction of optimal cART regimen, including boosted protease inhibitors and non-nucleoside reverse transcriptase inhibitors); transmission category (men who have sex with men [MSM], heterosexuals, injecting drug users [IDU], other/unknown); geographical origin (Europe, non-European, unknown); age at HIV diagnosis (<35 vs ≥ 35 years, median age of the dataset); sex; and cohort. Likelihood ratio tests were used to determine if sex and transmission category were effect modifiers for the association between educational level and delayed HIV diagnosis. We also refit the models treating age at HIV diagnosis as a continuous variable (linear and fractional polynomial [23]) and, since the younger patients might have not completed education yet, restricting to individuals with age>25 years. Finally, we described differences by broad cohort geographical areas defined *a priori* as i) Austria, France and Switzerland, and ii) Greece, Italy and Spain. These analyses were descriptive and not adjusted for potential confounders. We present detailed results for the AHD analyses and a summary of LHD analyses.

Because the analyses excluded patients with unknown educational level and complete case analyses may be biased if data on educational level are not missing completely at random (MCAR) we used the following sensitivity analyses. First, we used multiple imputation to impute educational level[24] assuming data are missing at random. After inspecting the characteristics of the individuals with available and with missing data on level of education, we decided to include in the imputation model CD4 count at HIV diagnosis in addition to all variables used in the analysis models. While age and CD4 count were treated as continuous variables, all other variables were treated as categorical. Twenty imputed data sets were generated, analysed separately and then combined using Rubin's rule [25]. Second, we imputed missing data on

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educational level under the assumption of data missing not at random and we assigned all patients with unknown educational level to i) basic education, ii) secondary education and iii) tertiary education in separate analyses. These extreme case scenarios are unrealistic in practice, but provide an illustration of how sensitive the analyses may be to assumptions regarding missing data. Since we excluded patients without CD4 count measured within six months of HIV, we also ran analyses in which we assumed these patients were i) all AHD and ii) none AHD. Finally, we reanalysed the data including patients who were enrolled and had >1 CD4 count within i) 3 months and ii) 12 months of HIV diagnosed rather than 6 months of HIV diagnosis as in the main analysis.

CD4 count at initiation of antiretroviral therapy

We explored patterns of delayed cART initiation among patients included in the analyses of delayed HIV diagnosis. We further restricted the analysis to individuals who initiated cART while cART-naïve and who had their CD4 cell count measured at least once, between six months before and one week after cART was initiated. Tests for trend and multiple median regression models estimated the association between level of education and CD4 count at cART initiation i) overall and ii) when restricted to individuals who did not present with AHD. All models were adjusted for sex, calendar year of cART initiation, transmission category, geographical origin, age at cART initiation, and cohort. Since there is no formal definition of late cART initiation, and national and international recommendations changed significantly across the study period, we decided that analyses of the distribution of CD4 count at cART initiation with median regression would return more interpretable and robust results. As a sensitivity analysis, we defined late cART initiation as individuals with a CD4 cell count <350 cells/mm^3 prior to initiation, and used logistic regression models adjusting for the same covariates above.

Analyses were performed using Stata version 11.0 (Stata Corp., College Station, Texas, USA).

Results

Of the 37,438 patients diagnosed with HIV 1996-2011, 22,024 were excluded (12,656 enrolled >6 months of HIV diagnosis; 2459 had no CD4 count measurements while cART-naïve within 6 months of HIV diagnosis; 6909 had unknown level of education). Of the remaining 15,414 patients 9%, 28%, 47% and 15% had uncompleted basic, basic, secondary and tertiary education. Compared to the excluded individuals these were more likely to be of European geographical origin, infected through sex between men and diagnosed with HIV after 2000. Median [IQR] CD4 cell count and age at HIV diagnosis were 304 [125-503] cells/mm^3 and 35 [29-43] years; 76% were men, and 83% acquired HIV through heterosexual or MSM contact.

Proportions with uncompleted basic, basic, secondary and tertiary education were 17%, 39%, 39% and 6% for women and 7%, 25%, 50% and 18% for men.

Delayed diagnosis

A total of 6,129 (40%) patients presented with AHD, of which 5,725 had CD4<200 cells/mm^3, 404 had an AIDS defining event, and 2,522 had both. The proportion of AHD decreased with educational level; 52%, 45%, 37%, and 31% for uncompleted basic, basic, secondary and tertiary education (p for trend <0.001). Although the proportion of patients presenting with AHD did not differ for men and women (39% and 41%, respectively), the proportion of AHD for uncompleted basic and tertiary education varied more for men (54% to 30%) than for women (49% to 41%) (p<0.001 for interaction test). The gradient was more pronounced after 2001 (p<0.001 test for interaction); the proportion of AHD with uncompleted basic and tertiary education was 55% and 43% before 2001 and 50% and 28% from 2001 onwards (Table 1). The gradient by educational level was more pronounced for MSM compared to other groups; the proportion of AHD ranged between 45% and 26% for patients with uncompleted basic and tertiary education (Table 1). Gradients by educational level varied by cohort, but were consistently observed when data were grouped by broad geographical regions, although more noticeable in Greece, Italy and Spain (Table 1).

The gradient by educational level was maintained in multivariate analyses; compared to tertiary education, the adjusted ORs (aORs) for AHD were 1.72 (95% confidence interval 1.48-2.00), 1.39 (1.24-1.56) and 1.20 (1.08-1.34) in patients with uncompleted basic, basic and secondary completed education. In the adjusted logistic model, male sex, calendar period of diagnosis 1996-2000, non-European geographical origin, membership in the heterosexual and injecting drug use transmission groups, and age>35 years at HIV diagnosis were significant predictors of presenting with AHD (data not shown).

Figure 1 shows the aOR for presentation with AHD and sex-stratified educational level. The gradient by level of education was more prominent in males (p-value for interaction 0.082). For instance, the aOR for uncompleted basic education versus tertiary education was 1.70 (1.41-2.04) in males and 1.31 (0.96-1.82) in females. The trend by educational level was maintained restricting our analysis to MSM; aORs were 1.88 (1.35-2.61), 1.67 (1.40-1.99), and 1.27 (1.10-1.46) compared to patients with tertiary education (Table 2) (p 0.225 for interaction test).

There were 9,486 (62%) individuals with LHD at presentation. Among patients with uncompleted basic, basic, secondary and tertiary educational level, the proportions of LHD were 73%, 65%, 59% and 55%. Trends in proportion of LHD and adjusted OR by level of education were similar to the AHD analysis (Appendix 1).

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Sensitivity analyses

Individuals with unknown level of education had similar demographic characteristics and similar proportions of AHD and LHD, but were more likely to have an unknown transmission mode and geographical origin (Appendix 2). Results were consistent in all sensitivity analyses (Appendix 3 and 4).

Delayed initiation of antiretroviral therapy

Of the 15,414 individuals included in the previous analysis, 72% (11,035) initiated cART. These patients were mostly men (78%), MSM, had initiated cART after a median [IQR] of 2 [1-7] months after HIV diagnosis with a median [IQR] CD4 cell count of 218 [90-331] cells/mm^3 and age 36 [31-42] years. Overall, results from the median regression analyses indicate a strong association between CD4 count distribution at cART initiation and educational level (p <0.001 heterogeneity test). Notably, patients with uncompleted basic, basic and secondary education had estimated median CD4 cell counts of 49, 27 and 19 cells/mm^3 lower than patients with tertiary education at time of cART initiation (Table 3). When the analyses were limited to the 5,906 individuals who did not present with AHD, we found a trend of lower CD4 count with lower educational level, but it was not statistically significant (Table 4). The logistic regression analysis for late cART initiation, defined as CD4<350 cells/mm^3, showed a statistically significant association between CD4 count distribution at cART initiation and educational level.

Discussion

We found that in Europe in the cART era, individuals with lower educational level were substantially more likely to present with AHD and LHD, even after taking into account individual characteristics that are traditionally associated with delayed HIV diagnosis. This gradient was more marked for men than for women. Among patients who initiated cART, lower level of education was independently associated with lower median CD4 cell count at cART initiation.

The mechanisms underlying the observed associations are likely to implicate a number of material and psychosocial pathways through which education influences attitudes toward HIV testing and cART initiation. As a surrogate of socio-economic status, individuals with higher education have better material resources such as employment and higher-paying occupations [26] which imply easier access to health care facilities. People with higher education are more likely to practice health-promoting behaviours, including timely health care check-ups and screenings [27] and therefore, might be more likely to test for HIV when they perceive themselves at increased risk. Higher education increases people's health literacy and cognitive skills, enabling them to make better informed health-related choices [4, 27], including the importance of appropriate HIV testing and timely initiation of cART with better access to websites and community resources. Finally, education in linked with social and psychological factors, including sense of control, social standing and social support [26] and individuals with higher education may face fewer barriers to access HIV care and be more resilient to stigma[28].

Interestingly, the association between lower education and lower CD4 count at cART initiation was substantially reduced though did not disappear, when the analyses were restricted to individuals with timely HIV diagnosis. Therefore, the observed association between delayed cART initiation and lower educational level could be largely, but not solely, attributed to patterns of delayed HIV diagnosis by educational level. This highlights the existence of additional socio-economic barriers that deter access to cART after HIV diagnosis. .

The observed differences concord with previous evidence from Spain and Italy indicating a higher frequency of delayed HIV diagnosis and cART initiation among individuals of lower educational level[19, 20], and build on previous work conducted within COHERE showing very high levels of delayed HIV diagnoses in Europe[11]. We show in this study that not only presentation with AHD and LHD is common across all educational level groups, but that it exhibits an increasing trend with decreasing educational levels. The gradient of the association between level of education and delayed diagnosis is more remarkable for AHD than for LHD. Thus, socio-economic inequalities are particularly visible in patients with very low CD4 count levels, usually associated with high risk of AIDS and mortality[29]. These results are compatible with inequity in access to HIV testing and are worrisome considering that the study was conducted in six European countries with universal public health systems.

This study shows that the association of delayed HIV diagnosis with educational level differed between men and women in absolute and relative terms. The milder gradient in AHD by educational level observed in women might be explained by universal HIV testing offered to all pregnant women in European countries for prevention of mother-to-child HIV transmission[30]. These findings, however, need to be put in the context of the literature that underlies that economic position may be a poorer predictor for a number of health outcomes in women[31]. The proportions of AHD for women from all four educational levels are lower than those of the heterosexual men but, compared to MSM, women with secondary and tertiary education exhibit higher levels of AHD. MSM, one of the key target groups for HIV screening in most European countries[6], still had a steep decline in AHD by educational level. These results indicate that universal HIV screening approaches such as those aiming at all pregnant women, as an alternative to targeted HIV testing policies based on HIV risk perception such as those

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aimed at MSM could have the additional benefit to decrease socio-economic inequities in accessing HIV testing. Whereas the former approach would offer a voluntary HIV test to all pregnant women, for MSM to be offered an HIV test, disclosure of unprotected sex with other men and/or gay identity becomes a prerequisite which is likely to be influenced by socio-economic position[28, 32].

For a long time, the interest to collect patient's socio-economic information in HIV cohorts has been rather limited, though some groups have strongly promoted it[33] . The advantages of this study which harmonized socio-economic variables across several cohorts in European countries are its large sample size, allowing exploring interactions by sex and transmission group, the inclusion of patients under routine care and its standardised definition of the exposure variable across European countries. The pan-European perspective of the study suggests that the observed gradient of increased risk of late HIV diagnosis and late cART initiation with lower educational level is present across European countries with different HIV health care and education systems. The study also has some limitations. Not all cohorts in COHERE collect data on educational level, so this study was based on data from only six European countries. Results thus might not be generalizable to settings with different social systems such as those from Northern and Eastern Europe. Some bias may have been introduced through misclassification since an individual's educational level might not always reflect their socio-economic status and whether this error is different for men and women. In smaller size cohort studies, combined indicators such as living on welfare, unstable housing and unemployment were found to be associated with non-adherence, while no association could be found with each component alone[34]. Protopopescu et al have recently described how an indicator combining low educational level and unemployment was found associated with higher rates of mortality in the APROCO cohort while none of each separate variable had a significant effect[35]. However, educational level was the only variable collected by the six participating cohorts and it is important to note that education is one of the most used measures of socio-economic status in healthcare research because of its influence on future occupational opportunities and earning potential[14]. Foreigners unfamiliar with the educational system of the host country may have misreported their educational level. However, these forms of misclassification are likely to be non-differential, resulting in an underestimate of the relationship between socio-economic status and delayed HIV diagnosis and cART initiation. Despite this potential bias, we found significant trends and a clear gradient by educational level, and we believe this strengthens, rather than weakens our conclusions about the existence of socio-economic inequalities. Finally, a number of individuals were excluded from the analyses because their educational level was unknown or no CD4 count measurement was available at the time of HIV diagnosis. Our estimates might be biased if the included and excluded patients had a different distribution of educational level and CD4 count at HIV diagnosis. Our conclusions were, however, robust to a set of sensitivity analyses exploring different scenarios of missing data mechanisms.

In conclusion, this study shows that inequalities by educational level, a proxy of a socio-economic status, in HIV testing and initiation of cART are present in European countries with universal health care systems and thus, individuals with lower educational level will not equally benefit from the effectiveness of cART. Policies and interventions that target socio-economic determinants leading to delays in HIV diagnosis and cART initiation are needed. Whether the observed inequalities are all avoidable, and thus amendable, is a discussion to be urgently advanced within the equity policy framework for Europe Health 2020[36] and more deeply taken into account in clinical and epidemiological research.

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The EuroCoord acknowledgment appendix may be found at

http://www.cphiv.dk/portals/0/files/EuroCoord_appendix_December2012.pdf

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Tables and Figures

Table 1. Patient characteristics at HIV diagnosis and proportion who presented with advanced HIV disease (AHD) by baseline characteristics, overall and stratified by completed level of education. COHERE in EuroCoord, 1996-2011.

Characteristics at HIV diagnosis	N	N with AHD	%	Proportion with AHD by completed level of education: Uncompleted basic	Basic	Secondary	Tertiary
Overall	15414	6129	40%	753 (52%)	1972 (45%)	2667 (37%)	737 (31%)
Sex							
Male	11667	4591	39%	444 (54%)	1392 (48%)	2106 (36%)	649 (30%)
Female	3737	1538	41%	309 (49%)	580 (40%)	561 (39%)	88 (41%)
Calendar year							
<2001	4763	2130	45%	321 (55%)	614 (43%)	998 (43%)	197 (44%)
≥2001	10651	3999	38%	432 (50%)	1358 (46%)	1669 (34%)	540 (28%)
Age (years)							
>35	7436	3665	49%	392 (59%)	1142 (56%)	1674 (47%)	457 (40%)
≤35	7978	2464	31%	361 (46%)	830 (36%)	993 (27%)	280 (23%)
Geographical origin							
European	11960	4691	39%	422 (52%)	1474 (46%)	2218 (37%)	577 (31%)
Non European	2484	1093	44%	292 (52%)	349 (45%)	341 (41%)	111 (34%)
Unknown	970	345	35%	39 (43%)	149 (41%)	108 (32%)	49 (27%)
Transmission mode							
MSM	6427	1995	31%	84 (45%)	394 (39%)	1090 (31%)	427 (26%)
Heterosexual – male	3313	1675	51%	221 (57%)	624 (55%)	682 (47%)	148 (46%)
Heterosexual- female	3070	1259	41%	252 (49%)	469 (40%)	465 (39%)	73 (39%)
IDU – male	1299	584	45%	86 (54%)	274 (45%)	204 (42%)	20 (49%)
IDU – female	423	165	39%	22 (34%)	79 (40%)	61 (39%)	3 (75%)
Other/unknown – male	638	337	53%	53 (62%)	100 (62%)	130 (48%)	54 (45%)
Other/unknown – female	244	114	47%	35 (67%)	32 (41%)	35 (38%)	12 (55%)
European region of the cohort							
Austria, France and Switzerland	3930	1384	35%	133 (45%)	287 (41%)	836 (34%)	128 (28%)
Greece, Italy and Spain	8508	3449	41%	445 (54%)	1443 (47%)	1079 (36%)	482 (30%)

MSM: males who have sex with males, IDU: Injecting drug users. Advanced HIV disease: a CD4 count below 200 cells/mm^3 or an AIDS defining event in the six months following HIV diagnosis.

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Figure. Multivariate analyses of presentation with advanced HIV disease (AHD) by sex. Estimates from multivariable logistic models adjusted by transmission mode, geographical origin, age at HIV diagnosis, calendar period and cohort. Test for interaction: p 0.082. COHERE in EuroCoord, 1996-2011.

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Table 2. Multivariate analyses of presentation with advanced HIV disease (AHD) by transmission category. Estimates from multivariable logistic models adjusted by sex, geographical origin, age at HIV diagnosis, calendar period and cohort. Test for interaction: p 0.225. COHERE in EuroCoord, 1996-2011.

	MSM	***IDU***	***Heterosexual***	***Other/Unknown***
Level of education	N 6427	N 1722	N 6383	N 881
Uncompleted basic	1.88 (1.35,2.61)	1.20 (0.61,2.34)	1.39 (1.11,1.74)	1.64 (0.97,2.81)
Basic	1.67 (1.40, 1.99)	0.93 (0.50,1.74)	1.13 (0.92, 1.38)	1.02 (0.64,1.63)
Secondary	1.27 (1.10,1.46)	0.99 (0.52,1.87)	1.24 (1.10,1.39)	0.89 (0.58,1.36)
Tertiary	1	1	1	1
	p <0.001	p 0.472	p 0.003	p 0.073

MSM: males who have sex with males, IDU: injecting drug users.

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Table 3. Distribution of CD4 at cART initiation and multivariable analyses. Estimates from multivariable median regression and logistic regression models adjusted by calendar period, sex, transmission mode, geographical origin, age at cART initiation and cohort. COHERE in EuroCoord, 1996-2011.

				Multivariable analysis			
				Median regression		**Logistic regression**	
	N	**Median [IQR] CD4 count at cART initiation**	**Proportion with CD4<350 at cART**	**Median CD4 count (95% CI)**	**P**	**Odds ratios for CD4<350 at cART (95% CI)**	**P**
Overall	11035	218 [90,331]	78%	Baseline 231 (216,248)			
Level of education					<0.001		<0.001
No basic	1036	173 [55,294]	86%	-49 (-67,-30)		1.71 (1.36 ,2.14)	
Basic	3288	198 [70,316]	82%	-27 (-41,-12)		1.23 (1.05,1.45)	
Secondary	5117	238 [101,342]	77%	-19 (-32,-6)		1.07 (0,93,1.24)	
Tertiary	1594	251[126,345]	77%	-		1	

IQR: Interquantile range; cART: combination antiretroviral therapy.

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Table 4. Distribution of CD4 at cART initiation and multivariable analyses restricting to individuals who did not present with advanced HIV diagnosis. Estimates from multivariable median regression and logistic regression models adjusted by calendar period, sex, transmission mode, geographical origin, age at cART initiation and cohort. COHERE in EuroCoord, 1996-2011.

				Multivariable analysis			
				Median regression		**Logistic regression**	
	N	**Median [IQR] CD4 count at cART initiation**	**Proportion with CD4<350 at cART**	**Median CD4 count (95% CI)**	**P**	**Odds ratios for CD4<350 at cART (95% CI)**	**P**
Overall	5906	314 [250,410]	62%	Baseline 312 (297,326)			
Level of education					0.132		0.006
No basic	441	305 [245,399]	42%	-18 (-34,-2)		1.44 (1.11 ,1.88)	
Basic	1517	310 [246,419]	36%	-9 (-21,3)		1.12 (0.93,1.35)	
Secondary	2923	319 [250,430]	38%	-4 (-14,6)		0.99 (0.84,1.16)	
Tertiary	965	315 [256,408]	37%	-		1	

IQR: Interquantile range; cART: combination antiretroviral therapy.

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Appendix

Appendix 1 . Adjusted odds ratios of late HIV diagnosis (LHD) by level of education and sex. Estimates from multivariable logistic models adjusted by transmission mode, geographical origin, age at HIV diagnosis, calendar period and cohort. COHERE in EuroCoord, 1996-2011.

	Male	*Female*
Level of education	N 11661	N 1366
No basic	1.56 (1.28,1.89)	1.46 (1.05,2.03)
Basic	1.22 (1.07, 1.39)	1.09 (0.80,1.48)
Secondary	1.05 (0.94,1.71)	1.08 (0.80,1.46)
Tertiary	1	1
	p <0.001	p 0.023

Appendix 2. Characteristics of 15414 and 6909 (31%) patients with known and unknown level of education

	Level of education	
	Known (N 15414)	*Unknown (N 6909)*
Presentation with advanced HIV disease	40%	44%
Presentation with late HIV disease	62%	65%
Median [IQR] first CD4 count	304 [125,504]	275[99,481]
AIDS within 6 months	3%	3%
Age in years at HIV diagnosis, median [IQR]	35 [29,43]	36 [29,43]
Female	24%	23%
Transmission mode		
MSM	42%	37%
IDU	11%	12%
Heterosexual	41%	40%
Other	1%	1%
Unknown	5%	10%
Geographical origin		
European	78%	55%
Non European	16%	11%
Unknown/other	7%	34%
Calendar period of HIV diagnosis		
<2001	31%	38%
Cohorts		
AHIVCOS	4%	3%
AMACS	6%	13%
Co-RIS	10%	11%
ICONA	11%	12%
PISCIS	11%	29%
SHCS	39%	<1%
VACH	17%	14%
Aquitaine	2%	17%
Copilote	<1%	<1%

MSM: males who have sex with males, IDU: Injecting drug users.

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Appendix 3. Sensitivity analyses for missing data on level of education and baseline CD4 count. Estimates from multivariable logistic models adjusted by calendar period, sex, transmission mode, geographical origin, age at HIV diagnosis and cohort.

		Including a category for unknown education	*Assume patients with unknown educational level had:*			*Multiple imputation of level of education*	Assume patients with no CD4 < 6 months after diagnosis		*Patients aged >24 years*
Level of education	Main analysis		Basic education	Secondary education	Tertiary education		were AHD	were not AHD	
No basic	1.72 (1.48,2.00)	1.71 (1.47,1.98)	1.71 (1.48,1.98)	1.70 (1.47,1.97)	1.34 (1.19,1.52)	1.63 (1.43,1.86)	1.43 (1.24,1.65)	1.67 (1.45,1.94)	1.56 (1.32,1.84
Basic	1.39 (1.24,1.56)	1.40 (1.25,1.57)	1.40 (1.26,1.56)	1.40 (1.24,1.56)	1.11 (1.02,1.21)	1.31 (1.17,1.46)	1.25 (1.12, 1.39)	1.38 (1.23, 1.55)	1.22 (1.08,1.37)
Secondary	1.20 (1.08,1.34)	1.22 (1.10,1.36)	1.22 (1.00,1.36)	1.29 (1.17,1.43)	0.99 (0.91,1.07)	1.15 (1.05,1.27)	1.11 (1.00,1.22)	1.21 (1.09,1.35)	1.09 (0.98,1.21)
Tertiary	1	1	1	1	1	1	1	1	1
Unknown		1.41 (1.26,1.57)							

AHD: Advanced HIV diagnosis.

Appendix 4. Sensitivity analyses for the time window of inclusion. Estimates from multivariable logistic models adjusted by calendar period, sex, transmission mode, geographical origin, age at HIV diagnosis and cohort.

		Proportion presenting with AHD				Adjusted odds ratio for presenting with AHD			
Inclusion criterion	N included	Uncompleted basic	Basic	Secondary	Tertiary	Uncompleted basic	Basic	Secondary	Tertiary
3 months	13200	52%	46%	38%	32%	1.57 (1.34,1.85)	1.32 (1.16,1.49)	1.17 (1.05,1.31)	1
6 months (main analysis)	15414	52%	45%	37%	31%	1.72 (1.48,2.00)	1.39 (1.24,1.56)	1.20 (1.08,1.34)	1
12 months	17497	51%	44%	36%	30%	1.68 (1.46,1.93)	1.42 (1.27,1.58)	1.21 (1.10,1.34)	1

AHD. Advanced HIV disease.

Appendix 5. Characteristics of 22323 and 2459 patients with and without CD4 count measurement in the first 6 months of at HIV diagnosis while cART naive

	CD4 count available (N 22323)	*CD4 not available (N 2459)*
Educational level		
Uncompleted basic	7%	4%
Basic	20%	13%
Secondary	32%	18%
Tertiary	11%	10%
Unknown	31%	55%
Age in years at HIV diagnosis, median [IQR]	35 [29,43]	34 [29,41]
Female	24%	23%
Transmission mode		
MSM	40%	37%
IDU	11%	19%
Heterosexual	41%	33%
Other	1%	1%
Unknown	6%	10%
Geographical origin		
European	78%	55%
Non European	16%	11%
Unknown/other	7%	34%
Calendar year of HIV diagnosis, median [IQR]	2003 [1999,2006]	2003 [2000,2006]
Cohorts		
AHIVCOS	4%	1%
AMACS	8%	9%
Co-RIS	10%	10%
ICONA	11%	4%
PISCIS	12%	58%
SHCS	27%	10%
VACH	16%	5%
Aquitaine	5%	1%
Copilote	1%	<1%

MSM: males who have sex with males, IDU: injecting drug users.