Inequalities by educational level in response to combination antiretroviral treatment and survival in HIV-positive men and women in Europe

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Background: Socioeconomic inequality challenges population-level implementation of health interventions. We investigated differences by educational level in clinical, virological, and immunological responses to combined antiretroviral treatment (cART) in HIV-positive men and women in Collaboration of Observational HIV Epidemiological Research in Europe, a European collaboration.

Methods: Data were pooled from 15 cohorts in eight countries of patients initiating cART in 1996–2013 with data on educational level categorized in UNESCO/ISCED classifications. Kaplan–Meier curves, Cox and piecewise linear mixed models were used.

Results: Of 24 069 HIV-positive patients, 9% had not completed primary education, 32% had completed primary, 44% secondary, and 15% tertiary education. Overall, 21% were women, who were overrepresented in lower educational strata. During 132 507 person-years of follow-up, 1081 individuals died; cumulative mortality decreased with higher educational level ($P < 0.001$). Over 122 765 person-years, new AIDS events or death occurred in 2598 individuals; differences by education were more marked than for death alone ($P < 0.001$). Virological response was achieved by 67% of patients without completed basic education, 85% with completed primary education, 82% with secondary, and 87% with tertiary ($P < 0.001$). Patients with higher education had higher CD4$^+$ cell count at cART initiation and at each time after cART but rate of CD4$^+$ cell count recovery did not differ. Differences in mortality and clinical responses were similar for men and women and were not entirely explained by delayed HIV diagnosis and late cART initiation.

Conclusion: HIV-positive patients with lower educational level had worse responses to cART and survival in European countries with universal healthcare. To maximize the population impact of cART, Europe needs to decrease the socioeconomic divide.

Introduction

Even in settings with universal healthcare access, socio-economic inequality poses a challenge for implementing healthcare interventions at the population level. Socioeconomic gradients in morbidity and mortality in men and women are well described in the general population [13]. In HIV-positive persons, socioeconomic

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inequalities have been associated with poorer short-term immunological and virological response to combined antiretroviral treatment (cART) as well as worse clinical outcomes [4–15].

A large collaboration of HIV cohort studies, the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE), has recently reported inequalities by educational level; a proxy for socio-economic status, in HIV testing rates and cART initiation in European countries. In these countries with universal access to healthcare, the study highlighted sex differences [15]. Individuals with lower educational level, particularly men, were more likely to present late, with advanced HIV disease, and subsequently were more likely to initiate cART at later stages [15]. In cohort studies in France, educational level, employment status, and other socio-economic variables were associated with mortality [5–6]. Educational level predicts all-cause mortality in HIV-positive persons in countries with and without universal healthcare systems [7–11], although no clear association was evident in Switzerland [12–13].

Few of these studies compared the effects of socio-economic variables for men and women separately. Indeed, as socioeconomic position may be a poorer predictor of health outcomes in women than in men [16], and the number of women in HIV cohort studies is often lower, potential sex differences are often overlooked. In this study, we build on our previous findings [15], and hypothesize that inequalities by educational level persist among patients after treatment initiation, and that impaired response to cART also varies by sex. Our objectives were thus to investigate differences by educational level in virological and immunological response to cART, as well as incidence of all-cause mortality and new AIDS-defining events in HIV-positive men and women in COHERE data from 1996 to 2013.

Methods

Study design, setting and participants
COHERE (www.cohere.org) is a collaboration of 40 observational cohorts of HIV-positive persons from 32 European countries within the EuroCoord Network of Excellence (www.eurocoord.net). In our analyses, we included data from the 15 cohorts in eight European countries (Austria, France, Germany, Greece, Italy, Spain, Switzerland, and the Netherlands) that collect information on the educational level of HIV-positive patients.

Each cohort submitted data in a standardized format (the HIV Collaboration Data Exchange Protocol, http://www.hicdep.org) to coordinating centres at the Copenhagen HIV Program, Denmark, or the Institut de Santé Publique, d'Epidémiologie et de Développement (Bordeaux School of Public Health), Bordeaux, France.

The Regional Coordinating Centres ensured that strict quality assurance guidelines were adhered to, checked the plausibility of data, and removed duplicate records. Data were pooled in the COHERE in EuroCoord 2014 merger, completed in September 2014. One of the cohorts included in the analysis did not submit to the 2014 merger (ANRS CO3-Aquitaine); its submission from the previous year (2013) was used in the 2014 merger.

Patients recruited between 1 January 1996 and 31 December 2013 were included if they were 18 years or older and belonged to cohorts that systematically collected data on educational level, initiated cART while antiretroviral naïve, and had at least one CD4+ cell count and one HIV-RNA measurement recorded in the 6 months before and the 6 months after starting cART. Patients were followed in each cohort according to routine clinical practice.

Variables and definitions
Data included age, sex, geographical origin, HIV-1 transmission category, use of cART (type of regime and start and stop dates), CD4+ cell counts, and plasma HIV RNA over time with dates of measurements, prevalent and incident AIDS-defining conditions, dates of diagnoses, and vital status. cART was defined as a combination of either at least three drugs from at least two classes, or at least three nucleoside reverse-transcriptase inhibitors, at least one of which was tenofovir or abacavir. Death and date of death were ascertained by reviewing charts or cross-checking with mortality registers. Further information on COHERE [17] is available at www.cohere.org.

In 2012, EuroCoord investigators standardized data on educational level across cohorts. Maximum attained level of education was defined and classified according to the UNESCO/ISCED standard as no or incomplete primary (ISCED 0), primary (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 (eacea.ec.europa.eu/education/eurydice/eurypedia_en.php).

Outcomes
Outcomes were time from cART initiation to death from any cause; a new AIDS-defining event or death from any cause; virological suppression, defined as the first of two consecutive HIV-RNA measurements less than 400 copies/ml, and an increase in CD4+ cell count in the first 6 years of cART.

Statistical analyses
For mortality, clinical, and virological outcomes, we explored differences by educational level using Kaplan–Meier curves and log-rank tests. Hazard ratios for the

outcomes of interest were estimated using Cox proportional hazards models stratified by cohort.

Follow-up began at the start of cART and ended at the date the patient was last known to be alive, death, or the date of administrative censoring, whichever occurred first. We assumed that patients remained on therapy once cART was initiated, ignoring subsequent treatment changes or interruptions.

We used piecewise linear mixed models with a change in slope at 6 months after cART to compare trajectories of $CD4^+$ cell counts on the square root scale between educational groups over the first 6 years of cART. We determined the change point based on exploratory analyses using nonlinear models. To test for differences in rate of $CD4^+$ cell count recovery after cART, we included an interaction term between educational level and slope before and after the change point.

We chose, a priori, to adjust all models for the following potential confounding variables: sex; age at cART initiation; calendar period of cART initiation (<2001, 2001−2004 and 2005−2008, 2009−2013); transmission category (MSM, heterosexual, IDU, other/unknown); country of origin/country of birth (Europe, non-European, unknown); pre-cART HIV RNA on the log_{10} scale; pre-cART AIDS diagnosis; and initial class type of regime (nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and others). We also adjusted models for clinical and virological response outcomes by pre-cART $CD4^+$ cell count category (<200, 200−349, 350, 499, ≥500 cells/μl). Moreover, we described differences by broad cohort geographical areas defined as Western and Northern Europe (Austria, France, Germany, the Netherlands, and Switzerland), and Southern Europe (Greece, Italy, and Spain). These analyses were descriptive and not adjusted for potential confounders. Finally, we described differences by educational level in the proportion of patients lost to follow-up. This was defined as the proportion of living individuals who had no medical encounter in the 18 months prior to the median last clinical encounter date for the corresponding cohort.

Sensitivity analyses

The main analyses excluded patients whose educational level was unknown. In sensitivity analyses we imputed missing data on education by multiple imputation using chained equations, assuming the data were missing at random [18]. Twenty imputed data sets were generated, separately analysed, and combined using Rubin's rule. We also used an extreme scenario analysis and assumed that data from patients with unknown educational level were not missing at random and corresponded to primary education, secondary education, or tertiary education. As younger individuals may not yet have finished their education, we restricted analyses to patients aged at least 25 years at cART initiation.

We used Stata statistical software, version 12 (StataCorp, College Station, Texas, USA) for all analyses.

Ethics

All cohorts participating in COHERE adhere to local ethical standards, which extend to this study.

Results

A total of 35 063 individuals met eligibility criteria. The main analyses were based on the 24 069 individuals with data on educational level (69%). The characteristics of patients with and without educational level data were similar (Appendix Table 1, http://links.lww.com/QAD/A987). Individuals with secondary and tertiary education were more likely to be male, to have been infected through male-to-male sex, and less likely to have been infected using injectable drugs, or to have recently initiated cART (Table 1). There were marked differences in the pre-cART $CD4^+$ cell counts, which were highest for those with higher levels of education. The prevalence of AIDS at the start of cART was also lower for those with higher education. The number and frequency of $CD4^+$ cell count and HIV RNA measurements was similar across educational levels. The proportion of patients without completed primary education was considerably higher in Southern Europe than in other regions. Loss to follow-up was more common among patients with lower educational level.

Mortality

Over 132 507 person-years of follow-up, 1081 individuals died. Cumulative mortality decreased as educational level increased ($P < 0.001$ log-rank test, Fig. 1a). Differences in time to death persisted in the confounder-adjusted models; individuals without completed primary, primary, and secondary education had higher risks of death than those with tertiary education (Table 2a and Appendix Table 2 (a) and 2 (b), http://links.lww.com/QAD/A987). We found similar mortality gradients when we restricted analyses to those with $CD4^+$ cell count more than 200 cells/μl and no AIDS at cART initiation, and those with $CD4^+$ cell count more than 350 cells/μl and no AIDS at cART initiation and age at least 25 years (Appendix Table 3, http://links.lww.com/QAD/A987). We found no evidence of interaction by sex ($P = 0.582$; Appendix Table 4, http://links.lww.com/QAD/A987). Our conclusions were robust to the sensitivity analyses for missing educational level, except for the very implausible scenario in which it was assumed that all individuals with missing educational level had tertiary education (data not shown).

Table 1. Patient characteristics at cART initiation, overall, and by educational level.

	Incomplete primary	Primary	Secondary	Tertiary	Overall
N (%)	5719 (9%)	4999 (32%)	7945 (44%)	5406 (15%)	24069 (100%)
Sex					
Female	1851 (32%)	1307 (26%)	1462 (18%)	543 (10%)	5163 (21%)
Male	3868 (68%)	3692 (74%)	6483 (82%)	4863 (90%)	18906 (79%)
Transmission category					
MSM	1057 (18%)	1800 (36%)	4275 (54%)	3919 (73%)	11051 (46%)
Sex between men and women	2938 (51%)	2242 (45%)	2674 (37%)	1123 (21%)	8977 (37%)
IDU	1413 (25%)	729 (15%)	647 (8%)	118 (2%)	2907 (12%)
Other/Unknown	311 (5%)	228 (5%)	349 (4%)	246 (5%)	1134 (5%)
Median [IQR] age of cART (years)	37 [31,45]	37 [31,45]	37 [31,44]	37 [31,43]	37 [31,44]
Median [IQR] year of cART	2005 [2001, 2009]	2007 [2003,2010]	2007 [2003,2010]	2008 [2004,2011]	2007 [2002,2010]
Geographical origin					
Europe	4466 (78%)	3384 (68%)	5132 (65%)	3419 (63%)	16401 (68%)
Other	514 (9%)	667 (13%)	694 (9%)	517 (10%)	2392 (10%)
Unknown	739 (13%)	948 (19%)	2119 (27%)	1470 (27%)	5276 (22%)
AIDS before cART	1235 (22%)	746 (15%)	1153 (15%)	600 (11%)	3734 (16%)
Median [IQR] CD4$^+$ cell count	220 [90,343]	259 [136,375]	267 [140,382]	300 [189,411]	263 [136,380]
Number of CD4$^+$ cell count per patient	13 [6,24]	12 [6,22]	12 [6,23]	11 [5,21]	12 [6,22]
Mean CD4$^+$ cell count interval per patient (months)	4 [3,6]	4 [3,5]	4 [3,5]	4 (3,5)	4 [3,5]
Median [IQR] HIV RNA	4.9[4.2,5,4]	4.8 [4.1,5.3]	4.8 [4.2,5.3]	4.8 [4.2,5.3]	4.8 [4.2,5.3]
Number of HIV RNA	12 [6,23]	11 [6,20]	11 [5,21]	10 [5,19]	11 [6,21]
Mean per patient HIV RNA interval (months)	4 [3,6]	4 [3,5]	4 [3,5]	4 [3,5]	4 [3,5]
Initial cART combination					
NNRTI	2096 (37%)	1853 (37%)	2744 (35%)	1735 (32%)	8428 (35%)
PI	2768 (48%)	2218 (44%)	3960 (50%)	2763 (51%)	11709 (49%)
Other	855 (15%)	928 (19%)	1241 (16%)	908 (17%)	3932 (16%)
Cohort geographical area					
Greece, Italy, Spain	4748 (83%)	2855 (57%)	5574 (70%)	3373 (62%)	16550 (69%)
Austria, Germany, the Netherlands, Switzerland	971 (17%)	2144 (43%)	2371 (30%)	2033 (38%)	7519 (31%)
Median follow-up (years)	5.2	4.1	4.4	3.8	4.4
Proportion lost to follow-up	1486 (28%)	1006 (20%)	1427 (18%)	893 (17%)	4812 (21%)

cART, combined antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitors.
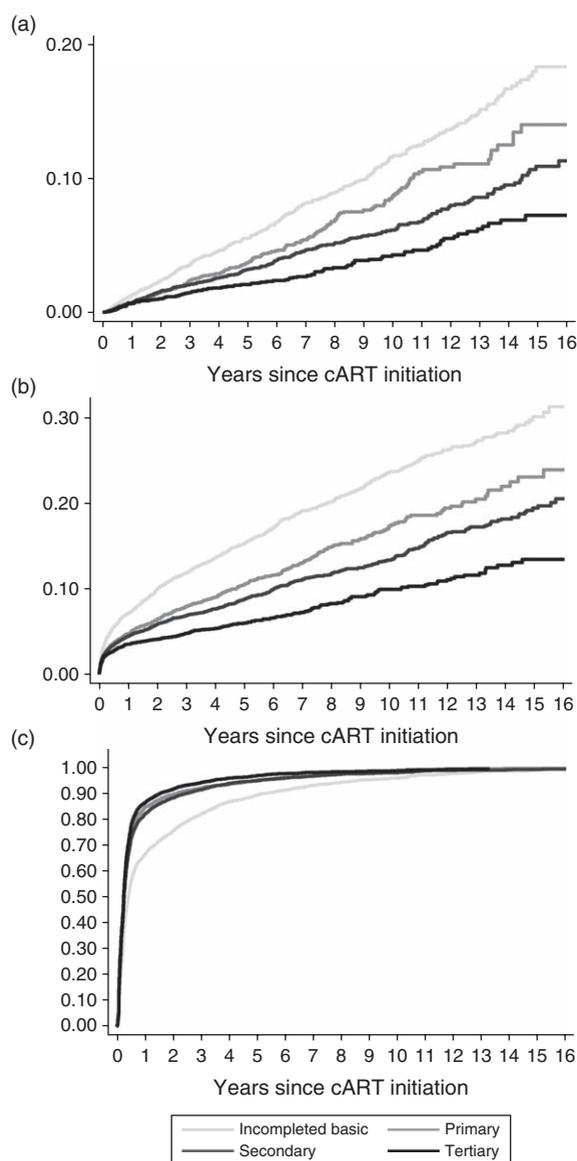
Fig. 1. Cumulative incidence of mortality (a), new AIDS events or mortality (b), and virological success (c) after initiation of cART by educational level. cART, combined antiretroviral therapy.

Incidence of AIDS or death

Over 122 765 person-years of follow-up, a new AIDS event or death occurred in 2598 individuals. Differences in the cumulative incidence of AIDS or death by educational level were more marked than for death alone ($P < 0.001$ log-rank test; Fig. 1b, Table 2b). We found no evidence of interaction by sex ($P = 0.314$, data not shown).

Virological suppression

At 1 year after initiating cART, 18 468 individuals (77%) had achieved virological suppression. Virological suppression was achieved by 85% of patients with primary

education, 82% with secondary, and 87% with tertiary education, and by 67% of patients with incomplete primary education ($P < 0.001$ log-rank test, Fig. 1c). The difference between groups became smaller over time, and was no longer evident from 10 years onwards. When we adjusted for potential confounders (particularly for transmission category), those with incomplete primary education and primary education had 20 and 7% lower risks, respectively, of achieving virological success than those with tertiary education (Table 2c).

Immunological response

The higher the educational level attained, the higher the $CD4^+$ cell count at cART initiation (Table 1) and at each point after cART initiation compared with patients with lower educational levels (Fig. 2). However, there was no evidence that the rate of $CD4^+$ cell count recovery differed by educational level in the 6 months after cART initiation (Fig. 2, Table 3).

Discussion

HIV-positive patients on cART who had less education had higher mortality, higher rates of new AIDS events, and worse virological responses than patients under care who had more education. Patients with higher educational attainment also had higher $CD4^+$ cell counts at cART initiation and maintained higher $CD4^+$ cell counts over time compared with those less educated. We observed such health differentials for an 18-year period in eight European countries where access to healthcare and cART is universal, and gradients in mortality were similar for men and women. Men dominated in the participating cohorts, but women were overrepresented in the lower educational strata. The present results build on our previous findings showing inequalities in HIV diagnosis and cART initiation by educational level in Western Europe [15]. The striking differences in mortality and clinical responses to cART could not be explained entirely by delayed HIV diagnosis and late cART initiation, as differences largely remained after we restricted analyses to those initiating cART with $CD4^+$ cell count more than 350 cells/µl and without previous AIDS diagnoses.

The associations we found between educational level and clinical outcomes are probably mediated by material and psychosocial paths already conceptualized by various investigators [4–14,19–21], and by the Socioeconomic Inequalities and HIV Working Group of COHERE [15]. Higher educational level is positively associated with choice of employment, higher salaries, and thus greater financial security, though the benefits of education on social outcomes persist after adjusting for income [4,19–21]. Educational achievement is also linked to health literacy and the ability to adhere to medication, as well as to healthier lifestyles (no smoking, good nutrition,

Table 2. Differences in mortality, new AIDS event/death, and virological suppression from cART initiation according to educational level.

Educational level	(a) Mortality	(b) New AIDS event or mortality	(c) Virological success
Incomplete primary	1.93 (1.54,2.43)	1.60 (1.39, 1.85)	0.80 (0.76,0.84)
Primary	1.68 (1.32, 2.12)	1.51 (1.30, 1.75)	0.93 (0.89,0.97)
Secondary	1.30 (1.05,1.60)	1.21 (1.06, 1.38)	0.97 (0.94,1.01)
Tertiary	1	1	1
	$P < 0.001$	$P < 0.001$	$P < 0.001$

cART, combined antiretroviral therapy. Cox models adjusted for sex, risk group, previous AIDS diagnosis, calendar period, initial cART combination, geographical origin, $CD4^+$ cell count, age and HIV RNA at cART initiation and stratified by cohort.

and exercise) [22−29]. Psychosocial factors such as enhanced cognitive, social, and emotional skills and resources that help people cope with stressful life situations are also associated with educational accomplishment [27−29]. Further, differentials by educational level are likely to be linked to causes that predate HIV infection and cART initiation. Indeed, excess mortality in disadvantaged populations has been widely reported in the European Union, and better educated people live longer [1−2]. By reducing HIV-related mortality, cART makes pre-existing mortality differentials by sex [4,30−31], ethnicity, and migrant status more visible [4,32,33]. A recent Danish study reported that elevated mortality observed in HIV-positive persons with low education was caused by non-AIDS-defining lifestyle factors (smoking and alcohol use) [26]. The increasing importance of non-AIDS morbidity and mortality in HIV-positive populations, secondary to smoking [25−28], and other risk-taking behaviours, will increase these socioeconomic gradients if no appropriate actions are taken. Finally, physicians may not prescribe optimum treatments to patients with lower educational attainment because inadvertently they may believe that they are too complex or difficult or to follow for less educated patients.

Poorer virological and immune response in less educated persons probably results from poorer adherence to cART, which relies heavily on psychosocial factors, including social support and health literacy, which in turn are closely associated with educational attainment [34−36]. Our results contribute to the body of evidence relating socioeconomic status and adherence to HIV medication, albeit through an indirect measure of treatment adherence as this is unavailable in the dataset. In a systematic review of data published up to 2006, Falagas et al. [36] reported that about one-third of studies identified significant associations between educational level and adherence. More recently, Sobrino et al. [9] have reported that less educated individuals have poorer short-term virological response to cART, and similar findings have been reported by Gueler et al. [13] when socioeconomic status is measured at the neighbourhood level. Immunological responses also have been reported to be less favourable in less educated persons [9,14], because of incomplete HIV viral suppression. We did not find differential immunological recovery rates by educational level, though patients with more education maintained higher $CD4^+$ cell counts throughout follow-up. Monge et al. [37] have reported higher resistance to any class of drugs in less educated HIV-positive individuals, and attributed it to ongoing HIV replication as a result of poor adherence. As the efficacy of life-long medication is grounded on adherence, interventions that target disadvantaged populations are key to controlling HIV. This could benefit from bringing in successful experiences from low-income countries, including clinic-linked community-based adherence support interventions, which have proven successful in South Africa [38].

A limitation of this study is that it was derived from the selection of patients recruited in cohorts who systematically collected information on educational status within the COHERE Collaboration. Additionally, as highlighted in previous work by the Socioeconomic Inequalities and HIV Working Group for COHERE, educational level is insufficient to fully capture socioeconomic status [15]. Including other variables such as income and occupation may allow us to dissect these complex relationships [4,19−20]. Analyses of a number of
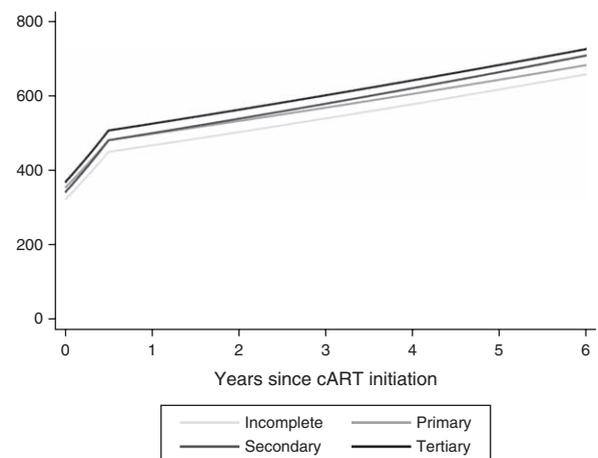

Fig. 2. Estimated of in $CD4^+$ cell count after cART initiation from a piecewise linear mixed model. Baseline individual: no AIDS, male, MSM, cART initiation less than 2001, European origin, NNRTI-based initial cART combination, age 37 years and viral load of 5.4 log copies/ml. cART, combined antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor.

Table 3. Estimates of change in square root CD4$^+$ cell count after initiation of combined antiretroviral therapy from a piecewise linear mixed model.

	Estimate	(95% CI)	P
CD4$^+$ cell count at time 0 for baseline patient with tertiary education*	21.96	(21.49,22.42)	<0.001
Incomplete primary	−1.24	(−1.50,−0.97)	
Primary	−0.38	(−0.63,−0.12)	
Secondary	−0.71	(−0.94,−0.48)	
Tertiary	Ref		<0.001
Annual rate of increase in the first 6 months for baseline patient with tertiary education	6.67	(6.37,6.96)	<0.001
Incomplete primary	−0.14	(−0.57,0.30)	
Primary	−0.41	(−0.83,0.02)	
Secondary	0.25	(−0.13,0.64)	
Tertiary	Ref		0.111
Annual rate of increase after 6 months for tertiary education	0.80	(0.76,0.85)	<0.001
Incomplete primary	0.00	(−0.05,0.06)	
Primary	−0.04	(−0.10,0.02)	
Secondary	0.05	(−0.01,0.10)	
Tertiary	Ref		0.115
PrecART AIDS	−3.62	(−3.79,−3.44)	<0.001
Sex			
Male	Ref		
Female	0.39	(0.21,0.57)	<0.001
Mode of exposure			
MSM	Ref		<0.001
IDU	−2.76	(−2.99,−2.54)	
Sex between men and women	−1.43	(−1.60,−1.26)	
Other	−1.16	(−1.82,−0.50)	
Unknown	−1.29	(−1.63,−0.96)	
Age at cART, 10 year	−0.56	(−0.62,−0.50)	<0.001
Year at cART initiation			
<2001	−1.58	(−1.79,−1.38)	<0.001
2001–2004	−2.16	(−2.36,−1.97)	
2005–2008	−1.58	(−1.74,−1.42)	
2009–2013	Ref		
Geographical origin			
European	Ref		<0.001
Non-European	−1.03	(−1.25,−0.81)	
Other	−0.63	(−0.79,−0.47)	
Initial cART combination			
NNRTI	Ref		0.024
PI	−0.21	(−0.36,−0.06)	
Other	−0.05	(−0.23,0.13)	
Viral load (log$_{10}$ scale)	−0.32	(−0.38,−0.26)	<0.001

cART, combined antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitors.

variables that may mediate the effect of educational level on outcomes such as smoking, lifestyle, and health-seeking behaviours are also lacking. Indeed, understanding the causal relationship between educational level and these factors was beyond the scope of our work. Further, the fact that we did not detect significant sex

differences may be a consequence of the relatively low number of women and their overpresentation in the lower educational strata. We hope our findings will encourage other researchers to collect information on socioeconomic status. Our findings are robust to the various sensitivity analyses based on different assumptions about missing data patterns.

Our analyses are based on the largest cohort collaboration of HIV-positive patients within Europe, which allows systematic exploration of sex differences. We found no effect of sex on the associations between educational status, and mortality and new AIDS events. However, given the relatively lower number of women in HIV cohort studies eliciting relevant outcomes by sex is of great interest. In these eight European countries, the effect of educational level on HIV diagnosis and cART initiation persists after HIV-positive patients are in care and have started on potent and efficacious treatments. Educational disadvantage compromises cART effectiveness [15].

Our results have implications for policy intervention and program design at multiple levels. They support the argument for sustained educational efforts at the European level to improve active citizenship, social cohesion, and health impacting on the macro-level determinants. They also reinforce the need for proximal down-stream interventions on clinical and preventive care among less educated HIV-positive patients once they are linked to care to address inequities. If these needs are met in accordance with the equity policy framework for Europe Health 2020 [39], the most vulnerable groups directly targeted by these interventions will benefit. As Scott-Samuel and Smith argue, though, it is unrealistic to expect inequalities to be substantially reduced without intensification of upstream policies challenging the wealth and power status quo of neoliberalism [40].

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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