Inequalities by educational level in response to combination antiretroviral treatment and survival in HIV-positive men and women in Europe (1996-2013): a collaborative cohort study

Del Amo, Julia

Journal Article Accepted Version
Originally published at: Del Amo, Julia (2017). Inequalities by educational level in response to combination antiretroviral treat-ment and survival in HIV-positive men and women in Europe (1996-2013): a collaborative cohort study. AIDS, 31(2):253-262.
DOI: https://doi.org/10.1097/QAD.0000000000001270

AIDS

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Inequalities by educational level in response to combination antiretroviral treatment and survival in HIV-positive men and women in Europe (1996-2013): a collaborative cohort study

Short title: Educational level and response to ART

Authors: The Socio-economic Inequalities and HIV Working Group for Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord

Corresponding author:

Julia del Amo,

National Center of Epidemiology, Instituto de Salud Carlos III,

C/ Sinesio Delgado 6 28029 Madrid, Spain.

e-mail: jdamo@isciii.es

Tel + 34 91 822 2142

Abstract word count: 250

Word count: 2872

Abstract

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 COHERE, 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 over-represented in lower educational strata. During 132,507 person-years of follow-up, 1,081 individuals died; cumulative mortality decreased with higher educational level ($p<0.001$). Over 122,765 person-years, new AIDS events or death occurred in 2,598 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-count at cART initiation and at each time after cART but rate of CD4-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.

Conclusions: 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.

Keywords: HIV; Mortality; Socioeconomic Factors; Inequality; Cohort Studies

INTRODUCTION

Even in settings with universal healthcare access, socioeconomic 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 (1-3). In HIV-positive persons, socioeconomic 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 socioeconomic status, in HIV testing rates and cART initiation in European countries. In these countries with universal access to health care, the study highlighted gender 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 socioeconomic variables were associated with mortality (5-6). Educational level predicts all-cause mortality in HIV-positive persons in countries with and without universal health care systems (7-11), although no clear association was evident in Switzerland (12-13).

Few of these studies compared the effects of socioeconomic variables for men and women separately. Indeed, since 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 gender 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 gender. 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 standardised 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 1st January, 1996 and 31st 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 count and one HIV-RNA measurement recorded in the six months before and the six 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 ≥3 drugs from ≥2 classes, or ≥3 nucleoside reverse-transcriptase inhibitors, at least one of which was tenofovir or abacavir. Death and date of death were ascertained by reviewing charts or crosschecking with mortality registers. Further information on COHERE is available at www.cohere.org.

In 2012, EuroCoord investigators standardised 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 i) death from any cause; ii) a new AIDS-defining event or death from any cause; iii) virological suppression, defined as the first

of two consecutive HIV-RNA measurements <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 (HRs) 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 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 (17). To test for differences in rate of CD4 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 (men having sex with men [MSM], heterosexual, injecting drug users [IDU], other/unknown); country of origin/country of birth (Europe, non-European, unknown); pre-cART HIV-RNA on the log10 scale; pre-cART AIDS diagnosis; and initial class type of regime (non-nucleoside

reverse transcriptase inhibitors [NNRTI], protease inhibitors PI], and others). We also adjusted models for clinical and virological response outcomes by pre-cART CD4 count category (<200, 200-349, 350, 499, ≥500 cells/mm^3). 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 analyzed, 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 i) primary education, ii) secondary education, or iii) tertiary education. Since younger individuals may not yet have finished their education, we restricted analyses to patients aged ≥25 years at cART initiation.

We used Stata statistical software, version 12 (StataCorp) 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). 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 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 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, Figure 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)). We found similar mortality gradients when we restricted analyses to those with CD4 >200 cells/mm^3 and no AIDS at cART initiation, and those with CD4>350 cells/mm^3 and no AIDS at cART initiation and age ≥25 years (Appendix Table 3). We found no evidence of interaction by sex (p=0.582) (Appendix Table 4). 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).

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; Figure 1b, Table 2b). We found no evidence of interaction by sex ($p=0.314$, data not shown).

Virological suppression

At one 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, Figure 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 count at cART initiation (Table 1) and at each point after cART initiation compared to patients with lower educational levels (Figure 2). However, there was no evidence that the rate of CD4 count recovery differed by educational level in the six months after cART initiation (Figure 2, Table 3).

DISCUSSION

HIV-positive patients on combination antiretroviral therapy 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 to those less educated. We observed such health differentials for an eighteen-year period in eight European countries where access to health care and cART is universal, and gradients in mortality were similar for men and women. Men dominated in the participating cohorts, but women were over-represented 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, since differences largely remained after we restricted analyses to those initiating cART with CD4 >350 cells/mm^3 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, 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 EU, and better educated people live longer (1-2). By reducing HIV-related mortality, cART makes pre-existing mortality differentials by gender (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 since this is unavailable in the dataset. In a systematic review of data published up to 2006, Falagas et al. reported that about one-third of studies identified significant associations between educational level and adherence (36). More recently, Sobrino et al. have reported that less educated individuals have poorer

short-term virological response to cART (9), and similar findings have been reported by Gueler et al. when socio-economic status is measured at the neighbourhood level (13). Immunological responses also have been reported to be less favourable in less educated persons (9,14) due to 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. have reported higher resistance to any class of drugs in less educated HIV-positive individuals, and attributed it to on-going HIV replication as a result of poor adherence (37). Since 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 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 gender differences may be a consequence of the relatively low number of

women and their over-presentation 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 gender differences. We found no effect of gender 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 (38), 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

The Socio-economic Inequalities and HIV Working Group for Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord: Julia del Amo, Sara Lodi, Rosemary Dray-Spira, Linda Wittkop, Susana Monge, Dominique Braun, Janne Vehreschild, Ramon Teira, Colin Campbell, Antonella d'Arminio Monforte, Robert Zangerle, Jade Ghosen, Sofia Koukounti, François Dabis, Catherine Leport, Laurence Meyer, Monique Termote, Ole Kirk, Kholoud Porter, Bruno Spire, Genevieve Chêne, Matthias Egger.

Steering Committee—Contributing Cohorts: Ali Judd (AALPHI), Robert Zangerle (AHIVCOS), Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Linda Wittkop (ANRS CO13 HEPAVIH), Peter Reiss (ATHENA), Ferdinand Wit (ATHENA), Maria Prins (CASCADE), Heiner Bucher (CASCADE), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne-Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Osamah Hamouda (German ClinSurv), Barbara Bartmeyer (German ClinSurv), Nikoloz Chkhartishvili (Georgian National HIV/AIDS), Antoni Noguera-Julian (CORISPE-cat), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), Luis Prieto (Madrid PMTCT Cohort), Pablo Rojo Conejo (CORISPES-Madrid), Antoni Soriano-Arandes (NENEXP), Manuel Battegay (SHCS), Roger Kouyos (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele),

Deborah_Konopnick (St. Pierre Cohort), Tessa Goetghebuer (St Pierre Paediatric Cohort), Anders Sönnerborg (Swedish InfCare), Carlo Torti (The Italian Master Cohort), Caroline Sabin (UK CHIC), Ramon Teira (VACH), Myriam Garrido (VACH). David Haerry (European AIDS Treatment Group)

Executive Committee: Stéphane de Wit (Chair, St. Pierre University Hospital), Jose Mª Miró (PISCIS), Dominique Costagliola (FHDH), Antonella d'Arminio-Monforte (ICONA), Antonella Castagna (San Raffaele), Julia del Amo (CoRIS), Amanda Mocroft (EuroSida), Dorthe Raben (Head, Copenhagen Regional Coordinating Centre), Geneviève Chêne (Head, Bordeaux Regional Coordinating Centre). Paediatric Cohort Representatives: Ali Judd, Pablo Rojo Conejo.

Regional Coordinating Centres: Bordeaux RCC: Diana Barger, Christine Schwimmer, Monique Termote, Linda Wittkop; Copenhagen RCC: Maria Campbell, Casper M. Frederiksen, Nina Friis-Møller, Jesper Kjaer, Dorthe Raben, Rikke Salbøl Brandt.

Project Leads and Statisticians: Juan Berenguer, Julia Bohlius, Vincent Bouteloup, Heiner Bucher, Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Mary-Anne Davies, Julia del Amo, Maria Dorrucci, David Dunn, Matthias Egger, Hansjakob Furrer, Marguerite Guiguet, Sophie Grabar, Ali Judd, Ole Kirk, Olivier Lambotte, Valériane Leroy, Sara Lodi, Sophie Matheron, Laurence Meyer, Jose Mª Miró, Amanda Mocroft, Susana Monge, Fumiyo Nakagawa, Roger Paredes, Andrew Phillips, Massimo Puoti, Michael Schomaker, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, , Marc van der Valk, Linda Wittkop, Natasha Wyss.

The authors gratefully acknowledge Christopher Ritter for language editing and commenting on the manuscript.

Funding: The COHERE study group has received unrestricted funding from Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, The Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694. The group has also received project specific funding from The European Union Seventh Framework Programme (FP7/2007-2013) under Marie Curie grant agreement n8 n 274817 FOR Sara Lodi. A list of the funders of the participating cohorts can be found at www.COHERE.org.

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Appendix Table 1. Characteristics of patients with known and unknown educational level

	Known	Unknown
N (%)	24069 (69%)	10994 (31%)
AIDS before cART	16%	15%
Median [IQR] age of cART, years	37 [31,44]	37 [30,44]
Median [IQR] year of cART	2007 [2002,2010]	2006 [2001,2010]
Median [IQR] CD4 count	263 [136,380]	260 [127,377]
Median [IQR] HIV RNA	4.8 [4.1,5.3]	4.8 [4.0,5.3]
Sex		
Female	21%	23%
Male	79%	77%
Transmission category		
Sex between men	46%	39%
Sex between men and women	37%	36%
Injecting drug use	12%	13%
Other/Unknown	5%	11%
Initial cART combination		
NNRTI	35%	37%
PI	49%	46%
Other	16%	18%
Geographical origin		
Europe	68%	71%
Other	10%	11%
Unknown	22%	18%

Number of CD4 count	12 [6,23]	11 [5,22]
Mean per patient CD4 count interval (months)	4 [3,5]	4 [3,5]
Time to last CD4 count (years)	4 [2,8]	4 [2,8]
Number of HIV RNA	11 [5,21]	11 [5,22]
Mean per patient HIV RNA interval (months)	4 [3,5]	4 [3,5]
Time to last HIV RNA (years)	4[2,7]	4 [2,8]

Appendix Table 2.

2 (a) Results from unadjusted and adjusted Cox model for time to death from any-cause after initiation of cAR

Characteristics at cART initiation	Bivariate analyses			Adjusted analyses		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Educational level						
Incompleted basic	2.54	(2.05,3.15)		1.93	(1.54,2.43)	
Basic	2.04	(1.62,2.56)		1.68	(1.32,2.12)	
Secondary	1.42	(1.15,1.75)		1.30	(1.05,1.60)	
Tertiary	1		<0.001	1		<0.001
Female		Xxx		0.78	(0.66,0.92)	0.003
Previous AIDS diagnosis				1.33	(1.16,1.54)	<0.001
Risk group						
Sex between men				1		<0.001
Injecting drug use				2.93	(2.44,3.51)	
Sex between men and women				1.14	(0.96,1.35)	
Other				1.34	(0.78,2.31)	
Unknown				1.49	(1.13,1.99)	
Age (10 years)				1.74	(1.65,1.84)	<0.001
Calendar year						
<2001				1		<0.001
2001-2004				0.95	(0.80,1.13)	
2005-2008				0.76	(0.62,0.93)	
2009-2013				0.60	(0.46,0.79)	
Geographical Origin						

European		1.06	(0.75,1.52)	0.696
Non European		1		
Unknown		0.71	(0.58,1.50)	
CD4 cell count, cells/mm^3				
<200		1		0.004
200-349		0.85	(0.73,0.99)	
350-499		0.67	(0.54,0.84)	
≥500		0.89	(0.71,1.12)	
Initial cART combination				
NNRTI based		1.15	(0.98,1.34)	0.001
PI based		1		
Other		1.39	(1.16,1.67)	
HIV-RNA (log10 scale)		1.04	(0.97,1.10)	0.273

2 (b) Results from unadjusted and adjusted Cox model for time to a new AIDS event or death from any-cause after initiation of cART.

Characteristics at cART initiation	Bivariate analyses			Adjusted analyses		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Educational level						
Incompleted basic	2.19	(1.91,2.50)		1.60	(1.39,1.85)	
Basic	2.04	(1.62,2.56)		1.51	(1.30,1.75)	
Secondary	1.35	(1.19,1.54)		1.21	(1.06,1.38)	
Tertiary	1		<0.001	1		<0.001
Female				0.9	(0.81,1.00)	0.052
Previous AIDS diagnosis				1.33	(1.22,1.46)	<0.001
Risk group						

Sex between men		1		<0.001
Injecting drug use		1.84	(1.63,2.07)	
Sex between men and women		1.12	(1.01,1.25)	
Other		1.20	(0.83,1.75)	
Unknown		1.29	(1.06,1.56)	
Age (10 years)		1.74	(1.65,1.84)	<0.001
Calendar year				
<2001		1		<0.001
2001-2004		0.85	(0.76,0.95)	
2005-2008		0.65	(0.58,0.74)	
2009-2013		0.57	(0.49,0.66)	
Geographical Origin				
European		0.89	(0.74,1.06)	0.058
Non European		1		
Unknown		0.72	(0.55,0.95)	
CD4 cell count, cells/mm3				
<200		1		<0.001
200-349		0.58	(0.53,0.65)	
350-499		0.47	(0.41,0.55)	
≥500		0.52	(0.44,0.61)	
Initial cART combination				
NNRTI based		1.12	(1.02,1.24)	<0.001
PI based		1		
Other		1.36	(1.21,1.52)	
HIV-RNA (log10 scale)		1.14	(1.09,1.19)	0.273

Appendix Table 3. Adjusted hazard ratios for sensitivity analyses restricting to patients with i) CD4>200 cells/mm3 and no AIDS at cART initiation, ii) with CD4>350 cells/mm3 and no AIDS at cART initiation and iii) age ≥25 years

Educational level	CD4>200 and no AIDS (N 14528)	CD4>350 and no AIDS (N 7028)	Age ≥ 25 (N=22922)
Incompleted basic	2.38 (1.63,3.50)	1.79 (1.00,3.17)	1.94 (1.54,2.44)
Basic	2.04 (1.39,3.00)	2.14 (1.23,3.71)	1.67 (1.31,2.12)
Secondary	1.70 (1.21,2.35)	1.36 (0.83,2.22)	1.29 (1.05,1.60)
Tertiary	1	1	1
	p<0.001	p 0.039	p<0.001

*Models adjusted for sex, risk group, previous AIDS diagnosis, calendar period, initial cART combination, geographical origin, CD4 count, age and HIV-RNA at cART initiation

Appendix Table 4. Assessing the role of gender as an effect modifier. Unadjusted and adjusted* time ratios of mortality for males and females and results from the likelihood ratio test to test the interaction by gender.

	Unadjusted		Adjusted	
Educational level	Male (N=18906)	Female (N=5163)	Male (N=18906)	Female (N=5163)
Incompleted basic	2.87 (2.27,3.62)	3.04 (1.55,5.94)	1.89 (1.47,2.43)	2.84 (1.43,5.66)
Basic	2.25 (1.75,2.89)	2.36 (1.18,4.70)	1.71 (1.32,2.21)	2.17 (1.07,4.38)
Secondary	1.40 (1.12,1.75)	2.02 (1.03,3.96)	1.27 (1.01,1.58)	1.91 (0.97,3.78)
Tertiary	1	1	1	1
Likelihood ratio test for interaction	p 0.352		p 0.566	

*Models adjusted for risk group, previous AIDS diagnosis, calendar period, initial cART combination, geographical origin, CD4 count, age and HIV-RNA at cART initiation and stratified by cohort.

Figure 1. Cumulative incidence of mortality (a), AIDS or mortality (b), and virological success (c) after initiation of combined antiretroviral therapy (cART) by educational level.

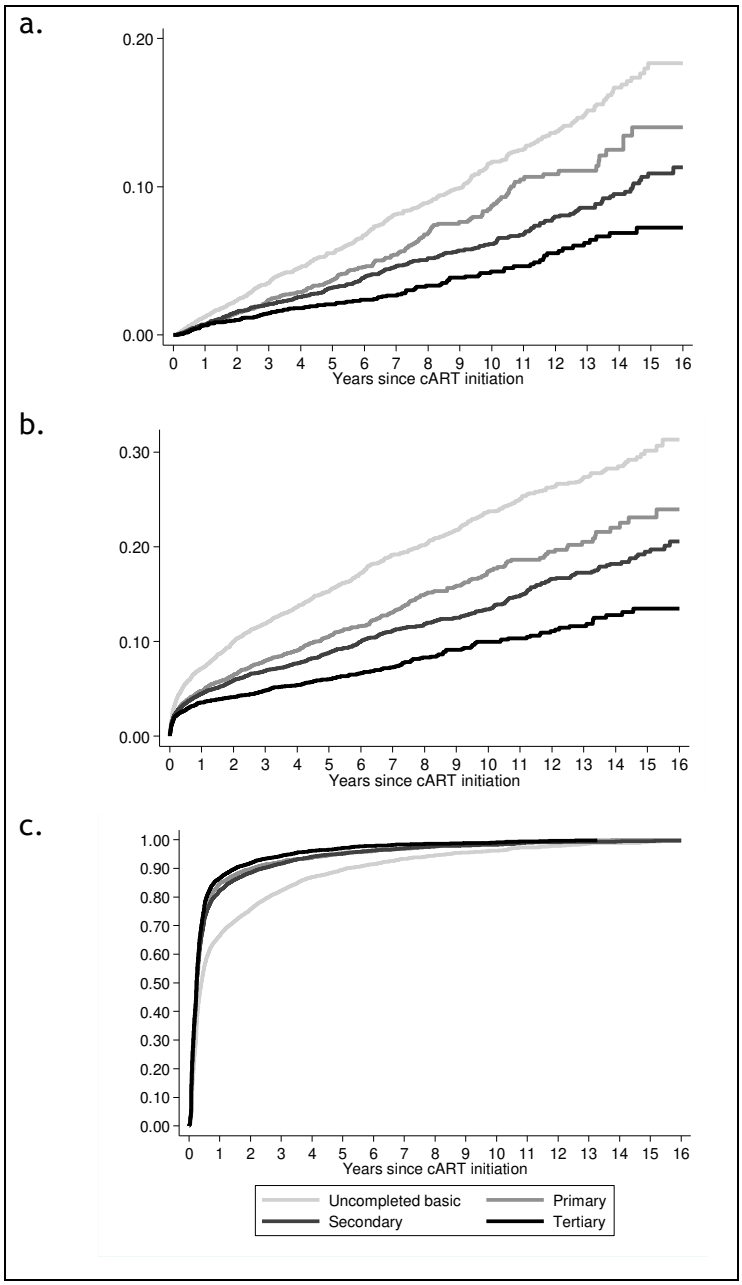

Figure 2. Estimated of in CD4 count after cART initation from a piecewise linear mixed model. Baseline individual: no AIDS, male, MSM, cART initiation <2001, European origin, NNRTI-based initial cART combination, age 37 years and viral load of 5.4 log copies/mL.

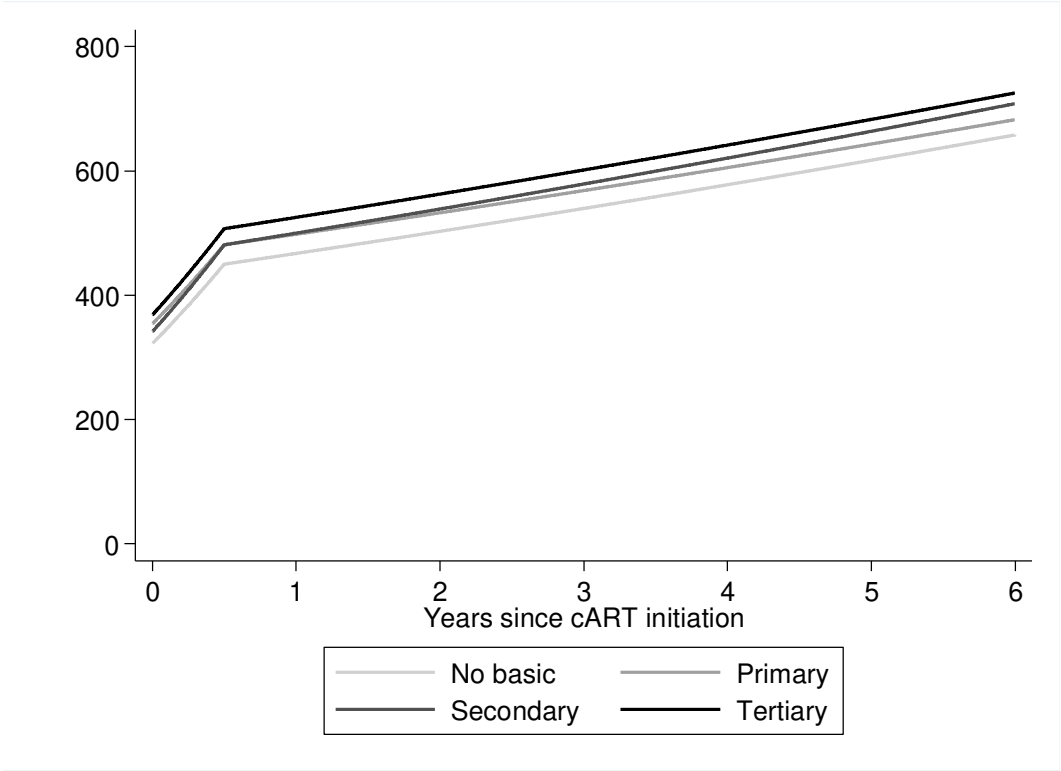

Table 1 Patient characteristics at cART initiation, overall, and by educational level

	Incompleted 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					
Sex between men	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%)
Injecting drug use	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 count	220 [90,343]	259 [136,375]	267 [140,382]	300 [189,411]	263 [136,380]
Number of CD4 count per patient	13 [6,24]	12 [6,22]	12 [6,23]	11 [5,21]	12 [6,22]
Mean CD4 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 [3,57]	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, 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%)

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

Educational level	a) Mortality	b) New AIDS event or mortality	c) Virological success
Incompleted 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

*Cox models adjusted for sex, risk group, previous AIDS diagnosis, calendar period, initial cART combination, geographical origin, CD4 count, age and HIV-RNA at cART initiation and stratified by cohort.

Table 3. Estimates of change in square root CD4 count after initiation of combined antiretroviral therapy (cART) from a piecewise linear mixed model.

	Estimate	(95% CI)		P
CD4 count at time 0 for baseline* patient with tertiary education	21.96	(21.49,	22.42)	<0.001
Incompleted 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
Incompleted 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
Incompleted 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
Pre-cART AIDS	-3.62	(-3.79,	-3.44)	<0.001
Sex				
Male	ref			
Female	0.39	(0.21,	0.57)	<0.001
Mode of exposure				
Sex between men	ref			<0.001
Injecting drug use	-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 (log10 scale)	-0.32	(-0.38,	-0.26)	<0.001