

Prevalence and outcomes of pregnancies in women living with HIV over a 20-year period: The EuroSIDA study, 1996 to 2015

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Abstract

Objective:

To evaluate time trends in pregnancies and pregnancy outcomes among women living with HIV in Europe.

Design:

European multicentre prospective cohort study.

Methods:

EuroSIDA has collected annual cross-sectional audits of pregnancies between 1996 and 2015. Pregnancy data were extracted and described. Odds of pregnancy were modelled, adjusting for potential confounders using logistic regression with generalised estimating equations.

Results:

Of 5535 women aged 16 to <50 years, 4217 (76.2%) had pregnancy information available, and 912 (21.6%) reported 1315 pregnancies. The proportions with at least one pregnancy were 28.1% (321/1143) in East, 24.5% (146/596) in North, 19.8% (140/706) in West/Central, 19.3% (110/569) in Central East and 16.2% (195/1203) in South Europe. Overall 319 pregnancies (24.3%) occurred in 1996-2002, 576 (43.8%) in 2003-2009 and 420 (31.9%) in 2010-2015. After adjustment, the odds of pregnancy were lower in 1996-2002, in South, Central East and East compared to West/Central Europe, in older women, those with low CD4 counts or with prior AIDS, and higher in those with a previous pregnancy or who were HCV positive.

Outcomes were reported for 999 pregnancies in 1996-2014, with 690 live births (69.1%), seven stillbirths (0.7%), 103 spontaneous (10.3%) and 199 medical abortions (19.9%).

Conclusions:

Around 20% of women in EuroSIDA reported a pregnancy, with most pregnancies after 2002, when more effective antiretroviral therapy became available. Substantial differences were seen between European regions. Further surveillance of pregnancies and outcomes among women living with HIV is warranted to ensure equal access to care.

Key words: Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome, anti-retroviral therapy, pregnancy, birth outcome.

Introduction

Women contribute half of the persons living with HIV worldwide [1,2] and around 30% of those in Europe, where >1/3 of new diagnoses are now among women [3]. The majority of women living with HIV (WLWH) are of childbearing potential [3]. Nonetheless, gender disparities remain in access to treatment, adherence, virological suppression and retention in care, with impacts on perceived stigma and quality of life [4,5].

Although the introduction of antiretroviral therapy (ART) has significantly reduced mother-to-child transmission of HIV in Europe [6], guidelines still recommend avoiding certain antiretrovirals in women of reproductive age [7,8], which may limit access to certain modern ART components in some regions [9-11], resulting in reduced adherence and poorer virologic outcomes. There is a need to integrate HIV treatment with sexual and reproductive health to take account personal fertility and procreational plans [12-14].

There is little epidemiological information on the overall trends in pregnancies among WLWH and factors that impact on the probability of pregnancy. Here we aimed to evaluate trends and outcomes of pregnancies among WLWH in the European region to inform health interventions and ascertain equal access to family planning.

Methods

EuroSIDA is a multinational prospective observational cohort study that has systematically collected data for >23,000 HIV-positive individuals in 35 European countries, Israel and Argentina since 1994 (<https://www.chip.dk/Studies/EuroSIDA>, [15]). All individuals gave informed consent at enrolment.

Data on pregnancies in women of reproductive age (≥ 16 and < 50 years old) were collected between 1996 and 2015 as annual audits, with women asked whether they had been pregnant in the previous year and the outcome of the pregnancy (as birth of a HIV-negative child, HIV-positive child, or child with unknown HIV status, stillbirth, spontaneous abortion, medical abortion, still pregnant, or unknown). As no dates of conception or delivery were available, incidence rates for pregnancies could not be calculated. Pregnancy information was

extracted in each study year, with the baseline date for each record set to 01 January of the year. For outcomes reported as 'still pregnant', records were updated with outcome information in the following year, else the outcome was recorded as unknown. The collection of pregnancy data ended in 2015, with no outcome information available for pregnancies in 2015.

Trends in pregnancies were summarised for each woman, stratified by time period (TP1, 1996-2002; TP2, 2003-2009 and TP3, 2010-2015), with variables as on 1st January of the year when pregnancy information was first available for each participant. Descriptive tabulations show proportions of individuals, or medians and inter-quartile range (IQR). Confidence intervals (CI) are 95%, and P-values two-sided, with $P < 0.05$ considered significant.

To investigate factors associated with pregnancy, each record of pregnancy information was treated as a separate data item. Odds of pregnancy were modelled using logistic regression with generalised estimating equations (GEE) to account for repeated pregnancy information within women. An unknown category was used to account for missing data for categorical variables. Multivariable models included all factors with type-3 P-values < 0.1 in univariable analysis that were not considered collinear.

Analyses were conducted using Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Of 5535 women of reproductive age enrolled in EuroSIDA between 1996 and 2015, 4217 (76.2%) reported pregnancy information (pregnant in the previous year, yes/no) in at least one year. Overall, 23,380 annual entries of pregnancy information were collected (median of 4, IQR 2-7 audits/woman), with altogether 1315 pregnancies; 912/4217 women (21.6%) reported at least one pregnancy.

Trends in the reporting of pregnancy information and pregnancies are summarized in **Figure 1**. The proportion of women who reported ≥ 1 pregnancy increased from 15.3% (CI 13.6-17.2%) in TP1 to 17.3% (15.9-18.8%) in TP2, and declined to 12.6% (11.4-13.9%) in TP3 (**Figure 1a**), but this varied for different regions of Europe (**Figure 1b**). The highest proportions of women with pregnancy information were in Central East (87.9%) and East Europe (81.8%) and the lowest in West/Central Europe (62.2%). Of the women who reported a pregnancy, most resided in East Europe (321, 35.2%) and in the South (195, 21.4%). **Figure 1c** summarises of the numbers of women with at least one pregnancy, by time period and region of Europe. As EuroSIDA did not enrol participants in Central East Europe until 1999 and in East Europe until 2001, there were few women from East Europe under follow-up in TP1, but almost half of those (18/38, 47%) reported a pregnancy.

Characteristics of women under follow-up in the three time periods are shown in **Supplementary Table S1**. The median age of women when they first reported pregnancy information was 33 (IQR 29-39) years, and in all three time periods women who reported ≥ 1 pregnancy were younger than those who did not. Most women were of white ethnicity, 62% had acquired HIV heterosexually and 30% were injection drug users (IDUs). Pregnancies were more frequent in women with higher baseline or nadir CD4 counts. The proportion of women on any ART increased with time, but women with ≥ 1 pregnancy had lower rates of ART use than those who were not pregnant. Those with ≥ 1 pregnancy were also less likely to have a previous AIDS diagnosis than those without.

Of the 1315 pregnancies, 319 (24.3%) were reported in 1996-2002, 576 (43.8%) in 2003-2009 and 420 (31.9%) in 2010-2015. Factors associated with the odds of pregnancy are summarised in **Figure 2** (see also **Supplementary Table S2**). After multivariable adjustment, the odds of pregnancy were lower in TP1 vs TP2 (adjusted odds ratio (aOR) 0.74; CI 0.62-0.89, $P=0.0015$). The odds of pregnancy also decreased with older age (aOR 0.53; CI 0.50-0.56 per 5 years older, $P < 0.0001$). Higher odds of pregnancy were seen in those with a previous pregnancy reported in EuroSIDA (aOR 1.89; CI 1.59-2.24, $P < 0.0001$). After adjustment, the odds of pregnancy were similar in

West/Central and North Europe, and significantly lower in South, Central East and East Europe. The odds of pregnancy were higher in women diagnosed with HIV <2 years previously and in HCV co-infected women, while a prior AIDS-defining illness reduced the odds of pregnancy by around 40% (aOR 0.58; 0.47-0.71, P = <0.0001). There was no evidence that the change in pregnancies over time differed according to region of Europe (P for interaction = 0.94). Sensitivity analyses excluding Argentina as part of region South showed consistent results. Of 1217 pregnancies between 1996-2014, outcomes were reported for 999 (82.2%). There were 690 live births (69.1%, of which 342 (49.6%) were HIV-negative, 23 (3.3%) HIV-positive and 325 (47.1%) of unknown HIV status), seven stillbirths (0.7%), 103 (10.3%) spontaneous and 199 (19.9%) medical abortions (**Supplementary Figure S1**). The proportion of live births was lowest in TP1. The proportion of pregnancies ending in spontaneous or medical abortions decreased between TP1 and TP2, and for medical abortions also in TP3. The lowest proportion of live births was in South (49.6%) and North Europe (51.1%), where women also had lower odds of live birth (**Supplementary Table S3** and **Supplementary Figure S1c**).

Discussion

We investigated trends in pregnancies in >4200 WLWH in Europe over a 20-year period. Around 22% of women reported at least one pregnancy. Most pregnancies occurred in 2003-2009, with a decline in recent years. The highest number of pregnancies were reported in East Europe, where 28% of women had ≥ 1 pregnancy, and the lowest in the South (16.2%). The odds of pregnancy were higher in younger women and those with a previous pregnancy, and lower in those with baseline or nadir CD4 counts <200 cells/ μ L, or with prior AIDS.

The increase in pregnancies in EuroSIDA after 2002 may also be related to more effective and less toxic forms of ART [16], with decreased morbidity and improved quality of life. In many clinics across Europe reproductive counselling is now integrated into HIV care [17] and WLWH are encouraged to make long-term family plans and conceive safely [18,19]. The later decline in pregnancies in TP3 reflects trends in the general population. In the European Union, birth rates were relatively constant between 1996 and 2018, apart from a modest increase in 2008-2010 [20]; fertility rates in women <30 years have fallen since 2001, but increased in women aged 30-34,

and the number of children per woman has declined [20]. We also observed an increase in age at pregnancy in WLWH, but women in East Europe were younger than elsewhere [15]. A recent increase in maternal age was also noted by other HIV cohorts in Europe [21,22].

Of the 1217 pregnancies reported to 2014, outcomes were reported for 999 (82.2%). Almost 70% of pregnancies resulted in a live birth, but 20% were reported as medical abortion, though the proportion of medical abortions decreased over the three time periods. Other studies also indicate termination rates may be high in WLWH [23], but data are scarce in Europe. Published research generally assumes HIV status is the only reason for ending a pregnancy [24,25]. As abortions can follow unintended pregnancies, it is important to ensure access to contraceptive counselling and modern contraception methods for WLWH in Europe. Furthermore, drug-drug interactions with antiretrovirals may reduce contraceptive effectiveness (see <https://www.hiv-druginteractions.org/>). A better knowledge of the factors that influence reproductive decision-making is necessary to improve services and policies to meet the needs and rights of WLWH in Europe.

This study is, to our knowledge, the first report of cross-sectional audits of pregnancies among WLWH across Europe. A strength of the study is that the audits were performed uniformly over almost 20 years and data collected with consistency and regular validation. There are also limitations. No pregnancy information was available for around 25% of the women of reproductive age, though a comparison of women with and without pregnancy information suggests that those who reported pregnancy information were broadly representative of the women in the cohort. We considered many potential confounders in our model, but there may be unmeasured or unknown confounders. Eastern Europe only joined EuroSIDA in 2001, with little data in TP1, and results should therefore be interpreted with caution [26]. HCV testing was targeted to IDU women, hence the HCV status was not known for many women. The pattern of baseline characteristics and missing data suggests that in East Europe many HIV diagnoses were during antenatal care, reflecting care delivery in this region [27]. Some women were still pregnant when audit data were collected, and outcome information was not available for some of these pregnancies. Finally, the study was not powered to investigate the impact of individual anti-retrovirals, although this remains a key question for pregnant WLWH.

In conclusion, our analysis revealed heterogeneity in pregnancies and outcomes among WLWH in Europe. These differences highlight distinct approaches to the management of family planning and fertility needs among

WLWH across the European region. Further surveillance of the incidence and outcomes of pregnancies among

WLWH is warranted to ensure equal access to sexual and reproductive health counselling and antenatal care.

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List of Supplementary materials:

Supplementary Table S1. Characteristics of women of reproductive age under follow-up in the three time periods, stratified by whether they reported ≥ 1 pregnancy in the time period

Supplementary Table S2. Characteristics of women with a pregnancy compared to those who did not report a pregnancy in the year, based on the annual pregnancy audits 1996 to 2015.

Supplementary Table S3. Characteristics of women with live births vs. spontaneous abortions or stillbirths between 1996 and 2014.

Supplementary Figure S1. Analysis of pregnancy outcomes.

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Figure Captions:**Figure 1. Trends in pregnancies in Europe between 1996 and 2015.**

Proportions of women of reproductive age (≥ 16 and < 50 years old, light grey bars), women with pregnancy information available (medium grey bars) and who reported at least one pregnancy (dark grey bars), by time period (TP1, 1996-2002; TP2, 2003-2009; TP3, 2010-2015) **(a)** or by region of Europe **(b)**. The proportion of women who reported ≥ 1 pregnancy, stratified by time period and region, is shown in **(c)**.

Note that women could contribute data to more than one time period.

Bars indicate 95% confidence intervals for the proportions.

Regions of Europe were defined as described [15] and include: South and Argentina: Argentina, Greece, Israel, Italy, Portugal and Spain; West/Central Europe: Austria, Belgium, France, Germany, Luxembourg and Switzerland; North Europe: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom; Central East Europe: Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia; and East Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and the Ukraine.

Figure 2. Factors associated with the odds of pregnancy (vs. no pregnancy).

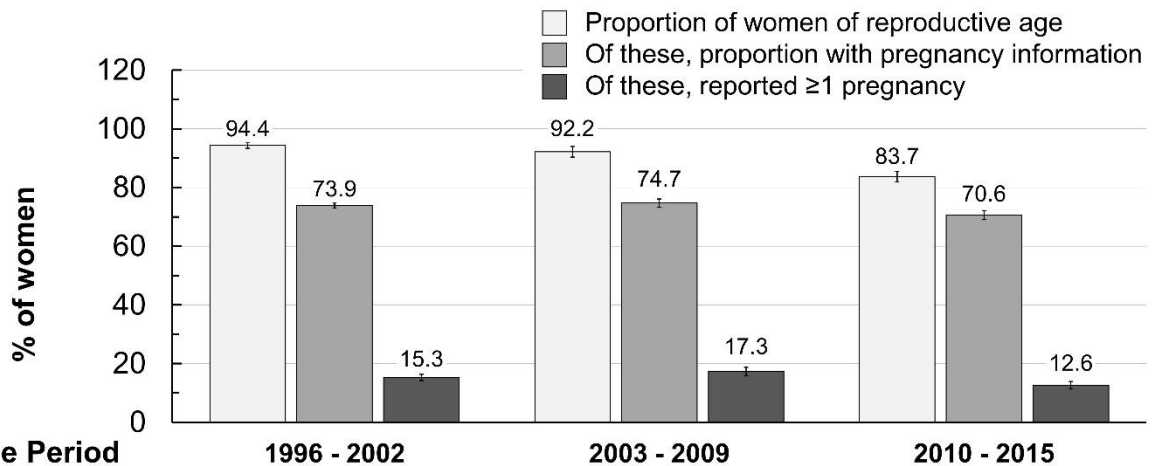
Adjusted odds ratios (aOR) of pregnancy are presented after adjusting for time period, age (as a continuous variable), smoking status, body mass index, previous pregnancy reported in EuroSIDA, region of Europe, baseline CD4 counts and viral load, time since HIV diagnosis, prior use of ART, hepatitis B (HBV) and hepatitis C (HCV) coinfection and prior AIDS.

Regions of Europe were defined as described in Figure 1.

Abbreviations: ART, anti-retroviral therapy; HBV, Hepatitis B virus; HCV, Hepatitis C virus; TP, time period; VL, viral load.

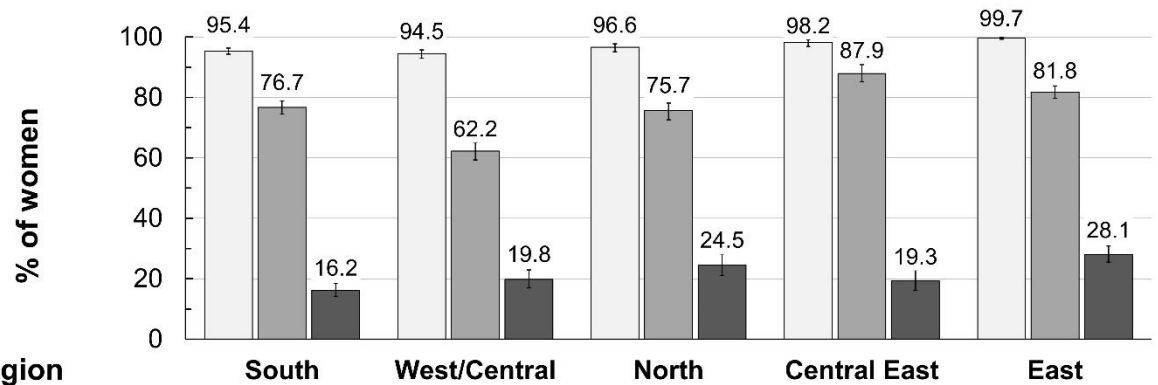
Figure 1.

(a)



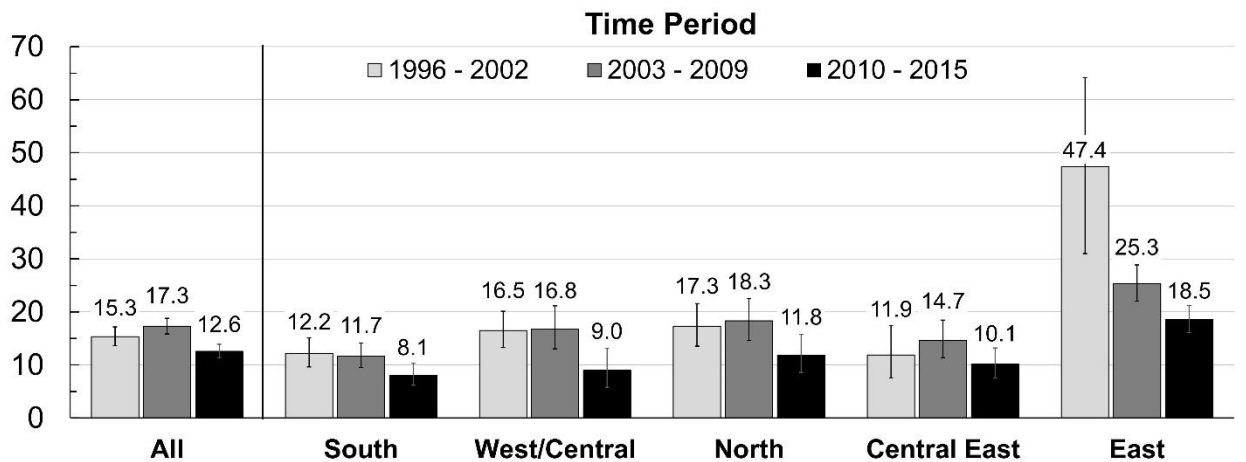
Time Period	1996 - 2002	2003 - 2009	2010 - 2015
Total number of women included	2375	3772	4584
Number of reproductive age	2241	3476	3835
With pregnancy information available	1655	2595	2708
Reported ≥1 pregnancy	254	449	341

(b)



Region	South	West/Central	North	Central East	East
Total number of women included	1643	1201	815	659	1402
Number of reproductive age	1568	1135	787	647	1398
With pregnancy information	1203	706	596	569	1143
Reported ≥1 pregnancy	195	140	146	110	321

(c)



Category	1996 - 2002	2003 - 2009	2010 - 2015
With ≥1 Pregnancy	254	449	341
N Total	1655	2595	2708
South	71	92	57
West/Central	80	59	23
North	63	72	40
Central East	22	60	48
East	18	166	173
N Total	38	655	933

Figure 1. Trends in pregnancies in Europe between 1996 and 2015.

Proportions of women of reproductive age (≥ 16 and < 50 years old, light grey bars), women with pregnancy information available (medium grey bars) and who reported at least one pregnancy (dark grey bars), by time period (TP1, 1996-2002; TP2, 2003-2009; TP3, 2010-2015) **(a)** or by region of Europe **(b)**. The proportion of women who reported ≥ 1 pregnancy, stratified by time period and region, is shown in **(c)**.

Note that women could contribute data to more than one time period.

Bars indicate 95% confidence intervals for the proportions.

Regions of Europe were defined as described [15] and include: South and Argentina: Argentina, Greece, Israel, Italy, Portugal and Spain; West/Central Europe: Austria, Belgium, France, Germany, Luxembourg and Switzerland; North Europe: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom; Central East Europe: Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia; and East Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and the Ukraine.

Figure 2

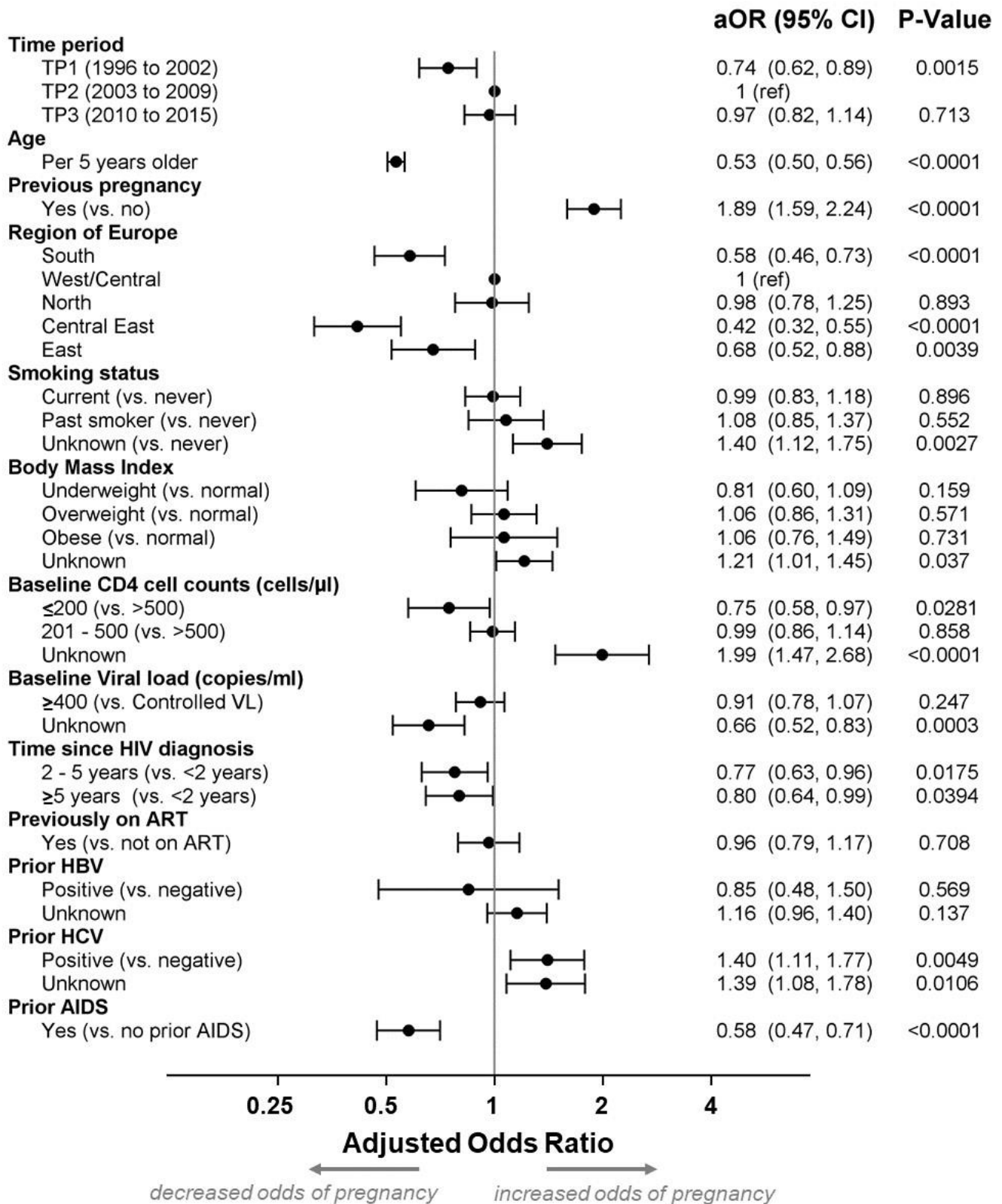


Figure 2. Factors associated with the odds of pregnancy (vs. no pregnancy).

Adjusted odds ratios (aOR) of pregnancy are presented after adjusting for time period, age (as a continuous variable), smoking status, body mass index, previous pregnancy reported in EuroSIDA, region of Europe, baseline

CD4 counts and viral load, time since HIV diagnosis, prior use of ART, hepatitis B (HBV) and hepatitis C (HCV) coinfection and prior AIDS.

Regions of Europe were defined as described in Figure 1.

Abbreviations: ART, anti-retroviral therapy; HBV, Hepatitis B virus; HCV, Hepatitis C virus; TP, time period; VL, viral load.

Supplementary Table S1. Characteristics of women of reproductive age under follow-up in the three time periods, stratified by whether they reported ≥ 1 pregnancy in the time period.

	Time Period 1 (1996-2002)			Time Period 2 (2003-2009)			Time Period 3 (2010-2015)		
	Pregnant in Time Period	Not Pregnant	P-value ^b	Pregnant in Time Period	Not Pregnant	P-value	Pregnant in Time Period	Not Pregnant	P-value
	N (%) ^a	N (%)		N (%)	N (%)		N (%)	N (%)	
Number under follow-up	254	1401		449	2146		341	2367	
Age (Years)									
Median (IQR)	30 (26, 33)	34 (30, 38)	<0.0001	30 (25, 34)	36 (30, 41)	<0.0001	31 (27, 35)	39 (33, 44)	<0.0001
Age group									
<30 years	131 (51.6)	361 (25.8)	<0.0001	234 (52.1)	533 (24.8)	<0.0001	150 (44.0)	389 (16.4)	<0.0001
30 to <40 years	118 (46.5)	775 (55.3)		198 (44.1)	963 (44.9)		171 (50.1)	880 (37.2)	
40 to <50 years	5 (2.0)	265 (18.9)		17 (3.8)	650 (30.3)		20 (5.9)	1098 (46.4)	
Ethnic group									
White/Caucasian	175 (68.9)	1073 (76.6)	0.0088	372 (82.9)	1803 (84.0)	0.5418	302 (88.6)	2045 (86.4)	0.2711
Other/unknown	79 (31.1)	328 (23.4)		77 (17.1)	343 (16.0)		39 (11.4)	322 (13.6)	
Risk group									
IDU	70 (27.6)	480 (34.3)	0.0813	128 (28.5)	605 (28.2)	0.4533	72 (21.1)	659 (27.8)	0.0014
Heterosexual	163 (64.2)	796 (56.8)		293 (65.3)	1370 (63.8)		252 (73.9)	1517 (64.1)	
Other/unknown	21 (8.3)	125 (8.9)		28 (6.2)	171 (8.0)		17 (5.0)	191 (8.1)	
Region of Europe^c									
South	71 (28.0)	512 (36.5)	<0.0001	92 (20.5)	695 (32.4)	<0.0001	57 (16.7)	650 (27.5)	<0.0001
West/Central	80 (31.5)	405 (28.9)		59 (13.1)	292 (13.6)		23 (6.7)	233 (9.8)	
North	63 (24.8)	301 (21.5)		72 (16.0)	321 (15.0)		40 (11.7)	298 (12.6)	
Central East	22 (8.7)	163 (11.6)		60 (13.4)	349 (16.3)		48 (14.1)	426 (18.0)	
East	18 (7.1)	20 (1.4)		166 (37.0)	489 (22.8)		173 (50.7)	760 (32.1)	
Smoking Status									
Never smoked	16 (6.3)	130 (9.3)	0.0012	100 (22.3)	522 (24.3)	0.2108	107 (31.4)	773 (32.7)	<0.0001
Current smoker	49 (19.3)	409 (29.2)		140 (31.2)	736 (34.3)		82 (24.0)	800 (33.8)	
Past smoker	1 (0.4)	2 (0.1)		31 (6.9)	148 (6.9)		40 (11.7)	316 (13.4)	
Unknown	188 (74.0)	860 (61.4)		178 (39.6)	740 (34.5)		112 (32.8)	478 (20.2)	
BMI									
Underweight	3 (1.2)	69 (4.9)	0.0094	17 (3.8)	115 (5.4)	0.1099	14 (4.1)	132 (5.6)	0.0001
Normal	55 (21.7)	393 (28.1)		183 (40.8)	938 (43.7)		136 (39.9)	1072 (45.3)	
Overweight	16 (6.3)	76 (5.4)		36 (8.0)	212 (9.9)		35 (10.3)	324 (13.7)	
Obese	3 (1.2)	15 (1.1)		12 (2.7)	53 (2.5)		9 (2.6)	114 (4.8)	

	Time Period 1 (1996-2002)			Time Period 2 (2003-2009)			Time Period 3 (2010-2015)		
	Pregnant in Time Period	Not Pregnant	P-value ^b	Pregnant in Time Period	Not Pregnant	P-value	Pregnant in Time Period	Not Pregnant	P-value
	N (%) ^a	N (%)		N (%)	N (%)		N (%)	N (%)	
Number under follow-up	254	1401		449	2146		341	2367	
Unknown	177 (69.7)	848 (60.5)		201 (44.8)	828 (38.6)		147 (43.1)	725 (30.6)	
Baseline CD4 cell count (cells/μl)									
Median (IQR)	337 (190, 441)	260 (145, 400)	0.0003	481 (342, 630)	440 (290, 626)	0.0167	455 (335, 633)	510 (336, 703)	0.0261
≤200	60 (23.6)	500 (35.7)	<0.0001	29 (6.5)	228 (10.6)	0.0001	20 (5.9)	206 (8.7)	<0.0001
201 to 350	60 (23.6)	362 (25.8)		73 (16.3)	440 (20.5)		63 (18.5)	404 (17.1)	
351 to 500	56 (22.0)	260 (18.6)		101 (22.5)	484 (22.6)		86 (25.2)	472 (19.9)	
>500	41 (16.1)	176 (12.6)		165 (36.7)	778 (36.3)		137 (40.2)	1167 (49.3)	
Unknown	37 (14.6)	103 (7.4)		81 (18.0)	216 (10.1)		35 (10.3)	118 (5.0)	
Nadir CD4 cell count (cells/μl)									
Median (IQR)	270 (146, 385)	190 (96, 300)	<0.0001	289 (170, 462)	234 (120, 371)	<0.0001	260 (160, 382)	234 (128, 367)	0.0183
≤200	85 (33.5)	695 (49.6)	<0.0001	112 (24.9)	831 (38.7)	<0.0001	100 (29.3)	950 (40.1)	<0.0001
>200	132 (52.0)	603 (43.0)		256 (57)	1099 (51.2)		206 (60.4)	1299 (54.9)	
Baseline viral load									
Controlled (<400 cp/ml)	38 (15.0)	234 (16.7)	0.1684	177 (39.4)	1038 (48.4)	<0.0001	182 (53.4)	1593 (67.3)	<0.0001
≥400 copies/ml	73 (28.7)	468 (33.4)		135 (30.1)	704 (32.8)		109 (32.0)	553 (23.4)	
Unknown	143 (56.3)	699 (49.9)		137 (30.5)	404 (18.8)		50 (14.7)	221 (9.3)	
Time since HIV diagnosis (years)									
Median (IQR)	3.5 (1.3, 6)	5.0 (2.4, 8.5)	<0.0001	3.1 (0.8, 8.3)	6.4 (1.8, 11.4)	<0.0001	5.6 (2.5, 8.9)	9.5 (4.6, 16.0)	<0.0001
< 2 years	78 (30.7)	295 (21.1)	<0.0001	179 (39.9)	564 (26.3)	<0.0001	74 (21.7)	279 (11.8)	<0.0001
2 - <5 years	87 (34.3)	407 (29.1)		89 (19.8)	369 (17.2)		77 (22.6)	371 (15.7)	
≥5 years	89 (35.0)	699 (49.9)		181 (40.3)	1213 (56.5)		190 (55.7)	1717 (72.5)	
Ever Exposed to any ART									
Yes	160 (63.0)	1127 (80.4)	<0.0001	285 (63.5)	1637 (76.3)	<0.0001	266 (78.0)	2058 (86.9)	<0.0001
Ever Exposed to any cART (≥3 ARVs from any class)									
Yes	83 (32.7)	493 (35.2)	0.4394	250 (55.7)	1500 (69.9)	<0.0001	257 (75.4)	2014 (85.1)	<0.0001
Prior HBV^d									
Yes	2 (0.8)	19 (1.4)	0.4394	3 (0.7)	24 (1.1)	<0.0001	1 (0.3)	37 (1.6)	<0.0001
Unknown	199 (78.3)	1037 (74)		361 (80.4)	1482 (69.1)		255 (74.8)	1315 (55.6)	
Prior HCV^e									
Yes	58 (22.8)	409 (29.2)	0.001	138 (30.7)	696 (32.4)	0.001	117 (34.3)	1042 (44.0)	<0.0001
Unknown	181 (71.3)	834 (59.5)		268 (59.7)	1101 (51.3)		180 (52.8)	856 (36.2)	

	Time Period 1 (1996-2002)			Time Period 2 (2003-2009)			Time Period 3 (2010-2015)		
	Pregnant in Time Period	Not Pregnant	P-value ^b	Pregnant in Time Period	Not Pregnant	P-value	Pregnant in Time Period	Not Pregnant	P-value
	N (%) ^a	N (%)		N (%)	N (%)		N (%)	N (%)	
Number under follow-up	254	1401		449	2146		341	2367	
Prior AIDS^f									
No	221 (87.0)	1077 (76.9)	0.0034	400 (89.1)	1660 (77.4)	<0.0001	306 (89.7)	1812 (76.6)	<0.0001
Mild	22 (8.7)	208 (14.8)		35 (7.8)	321 (15.0)		26 (7.6)	383 (16.2)	
Moderate	11 (4.3)	107 (7.6)		14 (3.1)	146 (6.8)		8 (2.3)	152 (6.4)	
Severe	0 (0)	9 (0.6)		0 (0)	19 (0.9)		1 (0.3)	20 (0.8)	

Footnotes: Values were calculated relative to January 1st of the first year when pregnancy information was available for each woman.

^a Column percentages.

^b Chi-squared P-values for proportions, or Wilcoxon signed rank test P-values for the continuous variables.

^c Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal and Spain; West/Central Europe: Austria, Belgium, France, Germany, Luxembourg and Switzerland; North Europe: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom; Central East Europe: Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia; and East Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and the Ukraine.

^d HBV positive if ever HBV surface antigen (HBsAg) positive prior to the analysis date.

^e HCV positive if ever had a positive HCV antibody test, HCV RNA test, an HCV genotype assay or received HCV treatment.

^f Prior AIDS-defining-diseases were classified as mild: candidiasis (oesophageal, bronchi, trachea, or lungs), mycobacterial infections, tuberculosis, cytomegalovirus infections, cryptosporidiosis, herpes simplex virus disease, Kaposi sarcoma, Pneumocystis jiroveci pneumonia and HIV wasting syndrome; moderate: bacterial pneumonia, coccidioidomycosis, cryptococcosis, invasive cervical cancer, AIDS dementia complex, focal brain lesions, histoplasmosis, isosporiasis, Mycobacterium avium complex, salmonella and toxoplasmosis; and severe: Progressive multifocal leukoencephalopathy and non-Hodgkin lymphoma (see [28]).

Abbreviations: BMI, body mass index; cART, combination antiretroviral therapy; HBV, Hepatitis B virus; HCV, Hepatitis C virus; IDU, intravenous drug user; IQR, inter-quartile range.

Supplementary Table S2. Characteristics of women with a pregnancy compared to those who did not report a pregnancy in the year, based on the annual pregnancy audits 1996 to 2015.

	Pregnancy reported N (%) ^a	Not pregnant N (%) ^a	Unadjusted Odds Ratio	P-value
Number of pregnancy information audit items available	1315	22065		
Time period				
TP1 - 1996 to 2002	319 (24.3)	5642 (25.6)	0.91 (0.79, 1.04)	0.16
TP2 - 2003 to 2009	576 (43.8)	8391 (38.0)	Ref	
TP3 - 2010 to 2015	420 (31.9)	8032 (36.4)	0.68 (0.60, 0.78)	<0.0001
Age group (years)				
<30	565 (43.0)	3462 (15.7)	Ref	
30 to <40	663 (50.4)	10102 (45.8)	0.41 (0.36, 0.47)	<0.0001
40 to <50	87 (6.6)	8501 (38.5)	0.07 (0.06, 0.09)	<0.0001
Previous pregnancy in EuroSIDA				
Yes	403 (30.6)	3420 (15.5)	0.77 (0.59, 1.00)	0.052
Ethnic group				
White/Caucasian	1067 (81.1)	18208 (82.5)	Ref	
Other/unknown	248 (18.9)	3857 (17.5)	1.04 (0.87, 1.25)	0.64
Risk group				
IDU	339 (25.8)	6073 (27.5)	0.92 (0.78, 1.08)	0.29
Heterosexual	888 (67.5)	14301 (64.8)	Ref	
Other/unknown	88 (6.7)	1691 (7.7)	0.79 (0.60, 1.05)	0.10
Region of Europe				
South	277 (21.1)	7504 (34.0)	0.57 (0.45, 0.72)	<0.0001
West/Central	204 (15.5)	3509 (15.9)	Ref	
North	234 (17.8)	3736 (16.9)	0.99 (0.77, 1.28)	0.90
Central East	162 (12.3)	3506 (15.9)	0.76 (0.58, 0.99)	0.045
East	438 (33.3)	3810 (17.3)	1.88 (1.51, 2.33)	<0.0001
Smoking status				
Never smoked	406 (30.9)	7367 (33.4)	Ref	
Current smoker	422 (32.1)	9067 (41.1)	0.91 (0.77, 1.08)	0.27
Past smoker	135 (10.3)	2539 (11.5)	0.91 (0.71, 1.15)	0.43
Unknown	352 (26.8)	3092 (14.0)	2.11 (1.79, 2.48)	<0.0001
BMI (kg/m²)				
Underweight (<18.5)	63 (4.8)	1561 (7.1)	0.85 (0.64, 1.12)	0.2397
Normal (18.5-24.9)	598 (45.5)	12017 (54.5)	Ref	
Overweight (25-29.9)	164 (12.5)	3132 (14.2)	0.95 (0.77, 1.18)	0.65
Obese (>30)	52 (4.0)	992 (4.5)	0.90 (0.62, 1.33)	0.61
Unknown	438 (33.3)	4363 (19.8)	1.98 (1.72, 2.27)	<0.0001
Baseline CD4 cell counts (cells/μL)				
≤200	104 (7.9)	2727 (12.4)	0.72 (0.57, 0.90)	0.0042
201 to ≤500	560 (42.6)	9463 (42.9)	1.05 (0.92, 1.20)	0.44
>500	529 (40.2)	9383 (42.5)	Ref	
Unknown	122 (9.3)	492 (2.2)	4.09 (3.29, 5.09)	<0.0001
Nadir CD4 cell counts (cells/μL)				
≤200	428 (32.5)	10883 (49.3)	0.53 (0.46, 0.62)	<0.0001
>200	765 (58.2)	10690 (48.4)	Ref	
Unknown	122 (9.3)	492 (2.2)	3.20 (2.59, 3.96)	<0.0001
Baseline viral load (copies/mL)				
<400	636 (48.4)	13496 (61.2)	Ref	
≥400	440 (33.5)	6053 (29.5)	1.41 (1.24, 1.60)	<0.0001
Unknown	239 (18.2)	2066 (9.4)	2.32 (1.99, 2.72)	<0.0001
Time since HIV diagnosis (years)				
< 2	281 (21.4)	1776 (8.0)	Ref	
2 to <5	291 (22.1)	3607 (16.3)	0.52 (0.43, 0.62)	<0.0001
≥5	743 (56.5)	16682 (75.6)	0.30 (0.25, 0.35)	<0.0001
Ever exposed to any ART				
Yes	1020 (77.6)	19846 (89.9)	0.39 (0.34, 0.46)	<0.0001
Prior HBV^b				
Yes	15 (1.1)	283 (1.3)	0.99 (0.51, 1.89)	0.97
Unknown	950 (72.2)	13627 (61.8)	1.78 (1.54, 2.06)	<0.0001

	Pregnancy reported N (%) ^a	Not pregnant N (%) ^a	Unadjusted Odds Ratio	P-value
Number of pregnancy information audit items available	1315	22065		
Prior HCV^c				
Yes	424 (32.2)	7860 (35.6)	1.49 (1.20, 1.85)	0.0003
Unknown	724 (55.1)	9929 (45.0)	2.05 (1.68, 2.50)	<0.0001
Prior AIDS				
no	1154 (87.8)	16481 (74.7)	Ref	
yes	161 (12.2)	5582 (25.3)	0.39 (0.32, 0.48)	<0.0001

Data for 4217 women, of whom 912 were ever pregnant, with overall 1315 pregnancies between 1996 and 2015 (1217 between 1996 and 2014). The 4127 women reported altogether 23,380 items of pregnancy information between 1996 and 2015; women provided a median of 4 (IQR 2, 7; range 1-20) items of pregnancy information per person.

Variables were calculated relative to January 1st of the year in which the pregnancy information was reported.

Footnotes:

^a Column percentages.

^b HBV positive if ever HBV surface antigen (HBsAg) positive prior to the analysis date.

^c HCV positive if ever had a positive HCV antibody test, HCV RNA test, an HCV genotype assay or received HCV treatment.

Abbreviations: HBV, Hepatitis B virus; HCV, Hepatitis C virus; IDU, intravenous drug user.

Supplementary Table S3. Characteristics of women with live births vs. spontaneous abortions or stillbirths between 1996 and 2014.

	Live Birth	Stillborn or medical abortion	Total	P-value
Number under FU	N (%) ^a	N (%) ^a	N (%) ^a	
	690	110	800	
Time period				
TP1 (1996 to 2002)	153 (22.2)	35 (31.8)	188 (23.5)	0.075
TP2 (2003 to 2009)	347 (50.3)	46 (41.8)	393 (49.1)	
TP3 (2010 to 2014)	190 (27.5)	29 (26.4)	219 (27.4)	
Previous pregnancy in EuroSIDA				
Yes	224 (32.5)	28 (25.5)	252 (31.5)	0.14
Age group				
<30 years	325 (47.1)	35 (31.8)	360 (45.0)	0.0046
30 to <40 years	329 (47.7)	64 (58.2)	393 (49.1)	
40 to <50 years	36 (5.2)	11 (10.0)	47 (5.9)	
Ethnic group				
White/Caucasian	562 (81.4)	89 (80.9)	651 (81.4)	0.89
Other/unknown	128 (18.6)	21 (19.1)	149 (18.6)	
Risk group				
IDU	171 (24.8)	28 (25.5)	199 (24.9)	0.81
Heterosexual	479 (69.4)	74 (67.3)	553 (69.1)	
Other/unknown	40 (5.8)	8 (7.3)	48 (6.0)	
Region of Europe^b				
South	133 (19.3)	27 (24.5)	160 (20.0)	0.043
West/Central	124 (18.0)	18 (16.4)	142 (17.8)	
North	112 (16.2)	28 (25.5)	140 (17.5)	
Central East	81 (11.7)	11 (10.0)	92 (11.5)	
East	240 (34.8)	26 (23.6)	266 (33.3)	
Smoking Status				
Never smoked	216 (31.3)	30 (27.3)	246 (30.8)	0.031
Current smoker	187 (27.1)	44 (40.0)	231 (28.9)	
Past smoker	78 (11.3)	13 (11.8)	91 (11.4)	
Unknown	209 (30.3)	23 (20.9)	232 (29.0)	
BMI (kg/m²)				
Underweight (<18.5)	24 (3.5)	2 (1.8)	26 (3.3)	0.013
Normal (18.5-24.9)	296 (42.9)	59 (53.6)	355 (44.4)	
Overweight (25-29.9)	68 (9.9)	18 (16.4)	86 (10.8)	
Obese (>30)	34 (4.9)	3 (2.7)	37 (4.6)	
Unknown	268 (38.8)	28 (25.5)	296 (37.0)	
Baseline CD4 (cells/μL)				
≤200	49 (7.1)	10 (9.1)	59 (7.4)	0.31
201 - 500	289 (41.9)	48 (43.6)	337 (42.1)	
≥500	267 (38.7)	45 (40.9)	312 (39.0)	
Unknown	85 (12.3)	7 (6.4)	92 (11.5)	
CD4 Nadir (cells/μL)				
≤200	221 (32.0)	37 (33.6)	258 (32.3)	0.19
>200	384 (55.7)	66 (60.0)	450 (56.3)	
Unknown	85 (12.3)	7 (6.4)	92 (11.5)	
Baseline VL (copies/mL)				
<400	317 (45.9)	57 (51.8)	374 (46.8)	0.042
≥400	219 (31.7)	40 (36.4)	259 (32.4)	
Unknown	154 (22.3)	13 (11.8)	167 (20.9)	
Time since HIV diagnosis (categories)				
< 2 years	181 (26.2)	16 (14.5)	197 (24.6)	0.029
2 - <5 years	138 (20.0)	24 (21.8)	162 (20.3)	
≥5 years	371 (53.8)	70 (63.6)	441 (55.1)	
Ever Exposed to any ART				
Yes	510 (73.9)	90 (81.8)	600 (75.0)	0.075
Ever Exposed to any cART (≥3 ARVs from any class)				
Yes	445 (64.5)	80 (72.7)	525 (65.6)	0.091

Number under FU	Live Birth	Stillborn or medical abortion	Total	P-value
	N (%) ^a	N (%) ^a	N (%) ^a	
	690	110	800	
Prior HBV ^c				
Yes	6 (0.9)	0 (0)	6 (0.8)	0.32
Unknown	506 (73.3)	87 (79.1)	593 (74.1)	
Prior HCV ^d				
Yes	214 (31.0)	34 (30.9)	248 (31.0)	0.08
Unknown	389 (56.4)	70 (63.6)	459 (57.4)	
Prior AIDS ^e				
No	616 (89.3)	98 (89.1)	714 (89.3)	0.43
Mild	51 (7.4)	6 (5.5)	57 (7.1)	
Moderate	23 (3.3)	6 (5.5)	29 (3.6)	
Severe	0 (0)	0 (0)	0 (0)	

Variables were calculated relative to January 1st of the year in which the pregnancy was reported.

Footnotes:

^a Column percentages.

^b Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal and Spain; West/Central Europe: Austria, Belgium, France, Germany, Luxembourg and Switzerland; North Europe: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom; Central East Europe: Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia; and East Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and the Ukraine.

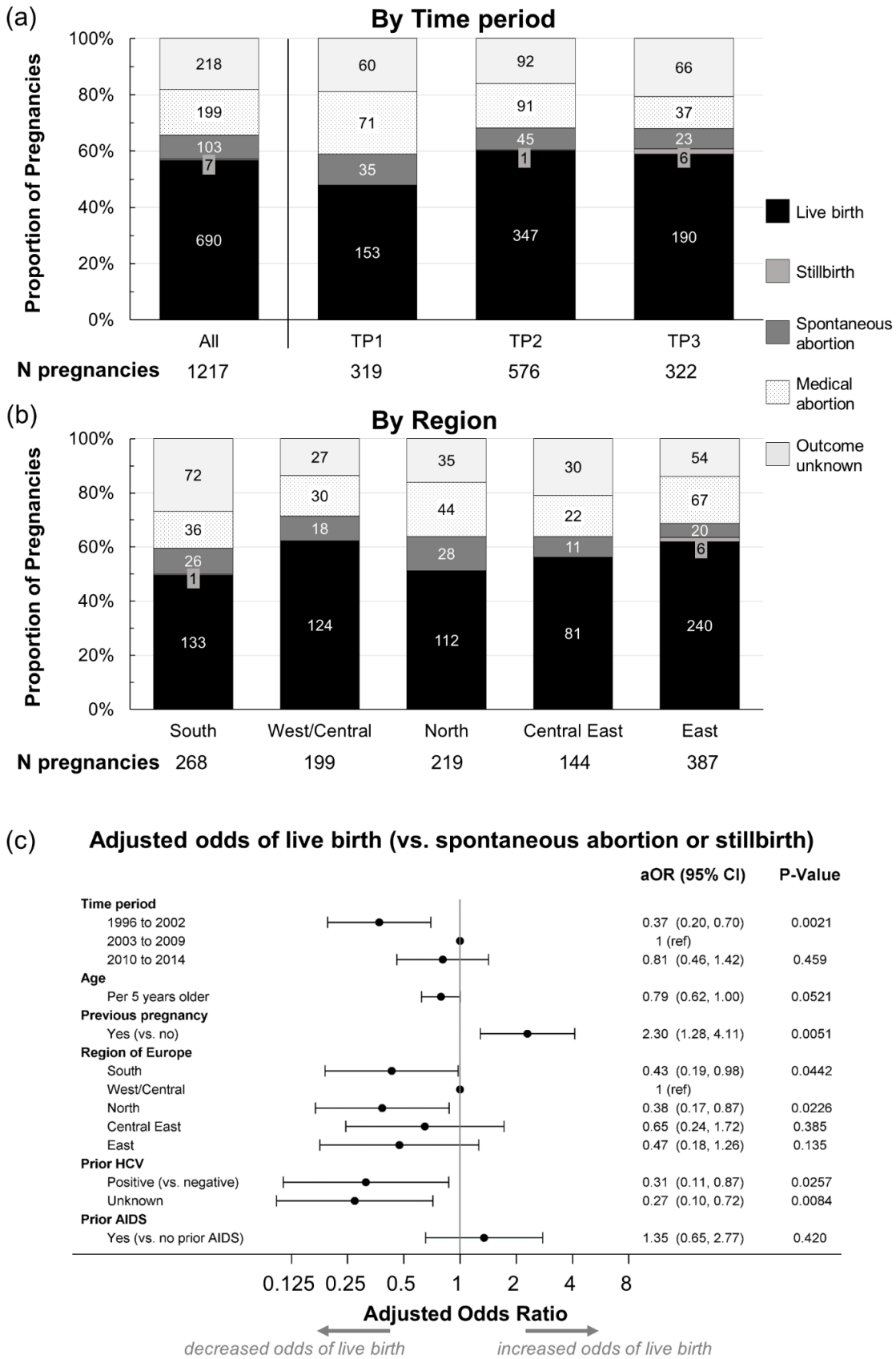
^c HBV positive if ever HBV surface antigen (HBsAg) positive prior to the analysis date.

^d HCV positive if ever had a positive HCV antibody test, HCV RNA test, an HCV genotype assay or received HCV treatment.

^e Prior AIDS-defining-diseases were classified as mild: candidiasis (oesophageal, bronchi, trachea, or lungs), mycobacterial infections, tuberculosis, cytomegalovirus infections, cryptosporidiosis, herpes simplex virus disease, Kaposi sarcoma, Pneumocystis jiroveci pneumonia and HIV wasting syndrome; moderate: bacterial pneumonia, coccidioidomycosis, cryptococcosis, invasive cervical cancer, AIDS dementia complex, focal brain lesions, histoplasmosis, isosporiasis, Mycobacterium avium complex, salmonella and toxoplasmosis; and severe: Progressive multifocal leukoencephalopathy and non-Hodgkin lymphoma.

Abbreviations: cART, combination antiretroviral therapy; HBV, Hepatitis B virus; HCV, Hepatitis C virus; IDU, intravenous drug user.

Supplementary Figure S1



Supplementary Figure S1. Analysis of pregnancy outcomes.

Outcomes of 1217 pregnancies reported between 1996 and 2014 by time period (TP1, 1996-2002; TP2, 2003-2009; TP3, 2010-2015) **(a)** or by region of Europe **(b)**. Factors associated with the odds of a live birth (n=690)

compared to spontaneous abortions or stillbirths (n=110) **(c)**, adjusting for all variables shown and in addition for smoking status, BMI, baseline CD4 counts, baseline viral load, time since HIV diagnosis and prior use of ART.

Abbreviations: ART, anti-retroviral therapy; BMI, body mass index; HCV, Hepatitis C virus; TP, time period.