ORIGINAL ARTICLE

Use of antiretroviral therapy in pregnancy and association with birth outcome among women living with HIV in Denmark: A nationwide, population-based cohort study

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Abstract

Objective: To describe antiretroviral therapy (ART) regimens during pregnancy among women living with HIV (WLWH) in Denmark and to examine the association between ART use in pregnancy and adverse birth outcomes.

Methods: A population-based cohort study including all pregnancies among WLWH in Denmark between 2000 and 2019. Data were collected through national registries. Temporal trends of ART use in pregnancy were evaluated. Logistic regression models were used to examine the association of ART use in pregnancy and other risk factors with adverse birth outcomes.

Results: In total, 589 pregnancies were included. Combination treatment with a nucleoside reverse transcriptase inhibitor (NRTI) and a protease inhibitor (PI) was the most common ART regimen (96%). ART regimen, PI use in pregnancy and timing of ART initiation were not significantly associated with increased odds of preterm birth, small for gestational age or low birth weight. First-trimester initiation of ART was significantly associated with increased odds of intrauterine growth restriction in the multivariate analysis [adjusted odds ratio (aOR) = 3.78, 95% confidence interval (CI): 1.23–11.59], while first trimester PI use was associated with increased odds of IUGR in the univariate analysis only [OR = 3.24, 95%

CI: 1.13–9.30]. Smoking, comorbidity, and maternal HIV RNA $\geq$ 50 copies/mL were independently associated with increased odds of adverse birth outcomes.

Conclusions: Pregnant WLWH living in Denmark are generally well treated with HIV RNA < 50 copies/mL at delivery and NRTI + PI as the most common ART regimen used in pregnancy. Initiation of ART in the first trimester may be associated with poor fetal growth. The association between ART use in pregnancy and adverse birth outcomes may partly be explained by maternal risk factors.

KEYWORDS

antiretroviral therapy, birth outcome, Danish HIV Birth Cohort, pregnancy

INTRODUCTION

Antiretroviral therapy (ART) is recommended worldwide for all people with HIV, including pregnant women [1]. As a result, an increasing number of women living with HIV (WLWH) will either conceive or start treatment during pregnancy. The success of ART in combination with changing recommendations has resulted in a decreased risk of perinatal transmission to < 1% in Denmark and other high-income countries [2,3], leading to a growing population of HIV-exposed, uninfected (HEU) children [4]. From a treatment perspective, pregnant women are a special population, largely because of the opportunity to prevent perinatal transmission of HIV and the need to consider the safety of the women themselves and their exposed foetuses and children [5].

No single antiretroviral (ARV) regimen has consistently been considered first-line for pregnant women, and recommended regimens and indications for some ARV drugs have changed over time as more potent and tolerable drugs have become available [6]. European guidelines currently recommend universal HIV testing of pregnant women, immediate initiation of treatment with a combination of three or more ARV drugs from at least two drug classes (combination ART), and continuation of treatment if the woman is already taking ART prior to pregnancy [7].

It has been widely debated whether *in utero* exposure to HIV and/or ARVs may be associated with an increased risk of adverse birth outcomes. Several studies have reported a higher risk of preterm birth (PTB) [8–10], low birth weight (LBW) [8,10,11], and small for gestational age (SGA) [11] among neonates born to WLWH compared with neonates born to women without HIV (WWOH). Other studies have not been able to confirm these findings [12–14]. The timing of ART seems to be important and several studies have reported an increased risk of adverse birth outcomes among WLWH with pre-conception ART compared with WLWH who started ART in pregnancy [8,11,15]. However, this risk may differ depending

on the specific ART regimen [16]. The use of protease inhibitors (PIs) during pregnancy has been associated with PTB [15,17], particularly regimens that include lopinavir/ritonavir [15,18].

Using data from the Danish HIV Birth Cohort (DHBC), we previously reported a higher prevalence of PTB, intrauterine growth restriction (IUGR) and LBW among children born to WLWH compared with children born to WWOH in Denmark [19–21]. In this nationwide, population-based cohort study, we aimed to describe ART regimens during pregnancy among WLWH in Denmark, including regimen changes during pregnancy, and to examine the association of ART use in pregnancy and other risk factors with different adverse birth outcomes.

METHODS

Setting

The Danish population consists of 5.85 million inhabitants, with an estimated adult HIV prevalence of 0.1% [22]. There are approximately 1600 WLWH in Denmark, the majority of whom are immigrants, mainly from sub-Saharan Africa [2,22]. The healthcare system in Denmark is tax-based and ensures universal access to medical healthcare [23]. Hence, ART is provided free of charge (to the individual) and people with HIV in Denmark are generally well treated, with life expectancies approaching those of the general population [24]. National antenatal screening of HIV, hepatitis, and syphilis for all pregnant women was implemented in the year 2010 as an opt-out programme [25]. Approximately 20% of WLWH were diagnosed during pregnancy between the years 2000 and 2018 [2]. Treatment with combination ART has been recommended for all pregnant WLWH in Denmark since the late 1990s and most women have an undetectable viral load at the time of delivery, defined as an HIV RNA < 50 copies/mL [2]. Vaginal delivery is recommended in

WLWH with an HIV RNA < 400 copies/mL. Neonatal post-exposure prophylaxis (neo-PEP) lasts for 4 weeks after birth and breastfeeding is not recommended [26].

Data sources

Data for the present study were collected between January 2000 and December 2019. We used the unique 10-digit personal identification number (PIN) assigned to all Danish residents at birth (or with approved immigration status) to identify and track the study participants in the following registries [27].

The Danish HIV Birth Cohort

The DHBC is a prospective, nationwide, population-based cohort study including all WLWH giving birth to one or more live-born children in Denmark after 31 December 1999, with consecutive ongoing enrolment [2]. Eligible women are identified and enrolled in the DHBC through the specialized clinical centres responsible for the treatment and care of pregnant WLWH in Denmark. The DHBC collects clinical and demographic data on both the mother and the child from the medical records. We used the DHBC to identify all WLWH giving birth during the study period and extracted the following data: maternal demographics, smoking, alcohol or illicit drug use during pregnancy, BMI, parity and perinatal transmission of HIV. Definitive exclusion of HIV infection of the child was based on two negative virological test results prior to or at 18 months of age.

The Danish HIV cohort

Information on ART use and HIV viral loads during pregnancy was collected from the Danish HIV Cohort Study (DHCS); a population-based prospective nationwide cohort study including all people with HIV, who have been treated at Danish HIV centers since 1 January 1995 [28]. Participants are consecutively enrolled in the DHCS and data are updated yearly and include demographics, date of HIV infection, mode of transmission, ART, CD4 +cell counts, and HIV RNA measurements.

The Medical Birth Registry

The Medical Birth Registry (MBR) contains complete information on all births in Denmark since 1973 [29]. The following data were extracted for the child: date of birth, gestational age, sex, birth weight and birth length.

The National Patient Registry

The National Patient Registry (NPR) contains information on all in- and outpatient hospital admissions in Denmark since 1977 [30]. The discharge diagnoses are classified according to the *International Classification of Diseases*, 10th revision (ICD-10 codes). Information on pre-existing and gestational comorbidities was obtained using the ICD-10 codes; diabetes (DO240-249), hypertension (DO100-169), depression (DO993), and anxiety (DF400-249). Information on IUGR or placenta insufficiency was obtained using the ICD-10 codes DO365A-D.

Statistics Denmark

From the registries at Statistics Denmark, we extracted data on the family's socioeconomic status defined by the adult with the highest income in the household, vital status of the child and migration.

Study population

Using the DHBC, we identified all WLWH with a delivery of a live-born infant between 1 January 2000 and 31 December 2019. Women and children were excluded if their PIN was invalid.

Statistical analysis

Maternal and child characteristics were summarized overall. In view of the changing guidelines, the women were divided into three time periods: 2000–2006, 2007–2014 and 2015–2019. Continuous variables were summarized as means with 95% confidence interval (CI) or medians with the 25th to 75th interquartile range (IQR). Categorical variables were presented as counts (%). Time of ART initiation was defined as prior to conception (ART initiated prior to the date of conception), first trimester (from date of conception to 90 days of gestation), second trimester (91–180 days of gestation), and third trimester (181 days to delivery).

Temporal trends of ART use in pregnancy were evaluated by calculating the proportion of women who used the different ARV drugs by calendar year. We classified the use of ART individually by (1) drug class: treatment with any nucleoside reverse transcriptase inhibitor (NRTI), treatment with any PI, treatment with any nonnucleoside reverse transcriptase inhibitor (NNRTI), and treatment with any integrase inhibitor (InSTI); (2) combination regimen categories at conception or initiation in pregnancy (no ART treatment, NRTI + PI, NRTI + NNRTI, three NRTIs, NRTI + InSTI and other regimens). We also calculated the proportion of individual drugs within the different drug classes (PI, NRTI, NNRTI and InSTI).

Univariate and multivariate logistic regression models were used to examine the association of ART use in pregnancy and other risk factors with different adverse birth

outcomes: PTB defined as gestational age < 37 weeks, SGA defined as birth weight < 10th percentile for gestational age by sex using the World Health Organization (WHO) foetal growth charts [31], IUGR defined by ICD-10 codes DO365A–D, and LBW defined as < 2500 g. Analysis was restricted to all singleton children born to women receiving ART during pregnancy ($n = 566$). The following covariables were included *a priori* in the multivariate models: maternal age at delivery (< 25 years, 25–35 years, > 35 years), maternal region of birth, year of birth (2000–2006, 2007–2014, 2015–2019), mode of delivery (vaginal/caesarean section), alcohol or illicit drug use in pregnancy, smoking in pregnancy, maternal comorbidity, and maternal CD4 cell count and HIV RNA at delivery. All models were also adjusted for intragroup correlations in children born to the same mother. Individuals with missing explanatory values were excluded from the multivariate analysis. The validity of the different models was tested using the Hosmer and Lemeshow goodness-of-fit test. Analyses were carried out using STATA 16 (Stata Corporation, College Station, TX, USA) and p-values < 0.05 were considered significant.

Ethical approval

The project was approved by the Danish Data Protection Agency (2012-58-0004; AHH-2017–027) and the Danish Medical Agency (3–3013-406/1/). Access to the different databases used in the study is granted by these regulatory agencies. According to Danish Law, approval from the National Committee on Health Research Ethics was not required as no biomedical intervention was performed.

RESULTS

Characteristics of the study population

In total, 606 children were born to 411 WLWH during the study period. Of these, 16 children and one mother had an unknown PIN and were thus excluded. Hence, 589 pregnancies were included in the study, including seven twin pregnancies. The characteristics of the cohort are presented in Table 1. The mean age at delivery was 32.7 years (95% CI: 32.2–33.1) and 154 women were included with more than one pregnancy during the study period. Most women were born abroad ($n = 457$; 78%), with more than half of the women originating from an African country (58%), and most were diagnosed with HIV prior to conception (81%). The proportion of women diagnosed after conception

TABLE 1 Maternal and child characteristics among 589 pregnancies with a live-born child born between 2000 and 2019

	Total (n = 589)
Maternal characteristics	
Maternal age at birth (years) [mean (95% CI)]	32.65 (32.22–33.09)
Married [n (%)]	248 (42)
Missing [n (%)]	148 (25)
Country of birth [n (%)]	
Denmark	132 (22)
African country	342 (58)
Asian country	69 (12)
Other	46 (8)
BMI [mean (95% CI)]	24.16 (23.72–24.60)
Missing [n (%)]	131 (22)
Family socioeconomic group[a] [n (%)]	
Working	229 (41)
Unemployed	8 (2)
Social benefits/disability	80 (14)
Other/missing	272 (46)
Smoking during pregnancy [n (%)]	69 (12)
Missing	41 (7)
Illicit drug or alcohol use [n (%)]	32 (5)
Missing	36 (6)
Comorbidity[b] [n (%)]	101 (17)
Time of maternal HIV diagnosis [n (%)][c]	
Before conception	475 (81)
First trimester	57 (10)
Second trimester	34 (6)
Third trimester	16 (3)
During or within < 30 days of delivery	7 (1)
Time since HIV diagnosis at delivery (years) (median [IQR])	5.29 (1.51–9.37)
Mode of HIV transmission [n (%)]	
Sexual	508 (86)
Injection drug use	22 (4)
Congenital	22 (4)
Other/missing	37 (6)
Time of ART initiation [n (%)][d]	
Before conception	385 (65)
First trimester	60 (10)
Second trimester	117 (20)
Third trimester	17 (3)
No treatment in pregnancy	9 (2)

TABLE 1 (Continued)

	Total (*n* = 589)
ART regimen at conception or initiation [*n* (%)]	
No treatment	9 (2)
NRTI + PI	369 (63)
NRTI + NNRTI	137 (23)
Three NRTIs	13 (2)
NRTI + InSTI	22 (14)
Other	39 (7)
ART at conception or initiation by class [*n* (%)]	
NRTI	564 (96)
NNRTI	54 (26)
PI	395 (67)
InSTI	33 (6)
Entry inhibitors	0
Intrapartum prophylaxis [*n* (%)]	324 (55)
Missing	44 (7)
CD4 cell count at delivery [*n* (%)]	
> 500 cells/µL	324 (55)
200–499 cells/µL	225 (38)
< 200 cells/µL	34 (6)
Unknown	6 (1)
HIV viral load at delivery [*n* (%)][e]	
< 50 copies/mL	509 (86)
≥ 50 copies/mL	76 (13)
Unknown	4 (1)
Nulliparous [*n* (%)]	230 (39)
Missing	35 (6)
Type of gestation [*n* (%)]	
Singleton	575 (98)
Twins	14 (2)
Child characteristics	
Year of birth [*n* (%)]	
2000–2006	157 (27)
2007–2014	280 (48)
2015–2019	152 (26)
Gestational age < 37 weeks [*n* (%)]	71 (12)
Missing	7 (1)
Delivered by Caesarean section [*n* (%)]	318 (54)
Missing	7 (1)
Birth weight (g) [mean (95% CI)]	3147.40 (3093.54–3201.25)
Missing [*n* (%)]	4 (1)
Birth length (cm) [mean (95% CI)]	49.32 (48.77–49.86)
Missing [*n* (%)]	9 (1)

(Continues)

TABLE 1 (Continued)

	Total (*n* = 589)
Male sex [*n* (%)]	289 (49)
Missing	28 (5)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; InSTI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor

[a]The employment status of the adult with the highest income in the household was used to indicate socioeconomic status.

[b]Comorbidity defined by pre-existing and gestational diabetes, hypertension, depression and anxiety.

[c]Proportion of women diagnosed prior to conception: 2000–2006, 77% (*n* = 121); 2007–2014, 81% (*n* = 226); 2015–2019, 85% (*n* = 128).

[d]Proportion of women initiating ART prior to conception: 2000–2006, 54% (*n* = 85); 2007–2014, 67% (*n* = 187); 2015–2019, 75% (*n* = 114).

[e]Proportion of women with an HIV RNA < 50 copies/mL at delivery: 2000–2006, 79% (*n* = 125); 2007–2014, 86% (*n* = 242); 2015–2019, 93% (*n* = 142).

decreased over time from 23% (*n* = 36) in the early study period to 15% (*n* = 24) in the late study period. Most women had an HIV RNA < 50 copies/mL at delivery (86%), which increased over time from 79% (*n* = 125) in the early study period to 93% in the late study period. Perinatal transmission of HIV occurred in four children, giving a perinatal transmission rate of 0.7%. In all these cases, the mother was diagnosed just prior to, during or shortly after delivery, and none of the four women received ART prior to delivery.

ART use in pregnancy

In total, 65% (*n* = 385) of the WLWH were on ART at conception, which increased over time from 54% (*n* = 54) in the early study period to 75% (*n* = 114) in the late study period. The trends of ARV use in pregnancy over time are presented in Figures 1 and 2. Nine women did not receive any treatment during pregnancy; no reason was provided for two of these women, while seven of the women were diagnosed with HIV during delivery or shortly thereafter. The most frequently used regimen throughout the study period was NRTI + PI. NRTIs were the most frequently used drug class (96%). In the early study period, mainly lamivudine (3TC) and zidovudine (ZDV) were used. After 2007, an increase in tenofovir/emitribine (TDF/FTC) or abacavir/lamivudine (ABC/3TC) was seen. PIs were the second most frequently used drug class (67%); nelfinavir (NFV) was the most frequent until 2005. By 2005, the use of NFV and ritonavir-boosted lopinavir (LPV/r) was almost equal. An increase in atazanavir/ritonavir (ATV/r) was seen from 2009, while the use of darunavir/ritonavir (DRV/r) increased in the later study period. Excluding entry inhibitors, which no women received, NNRTIs were
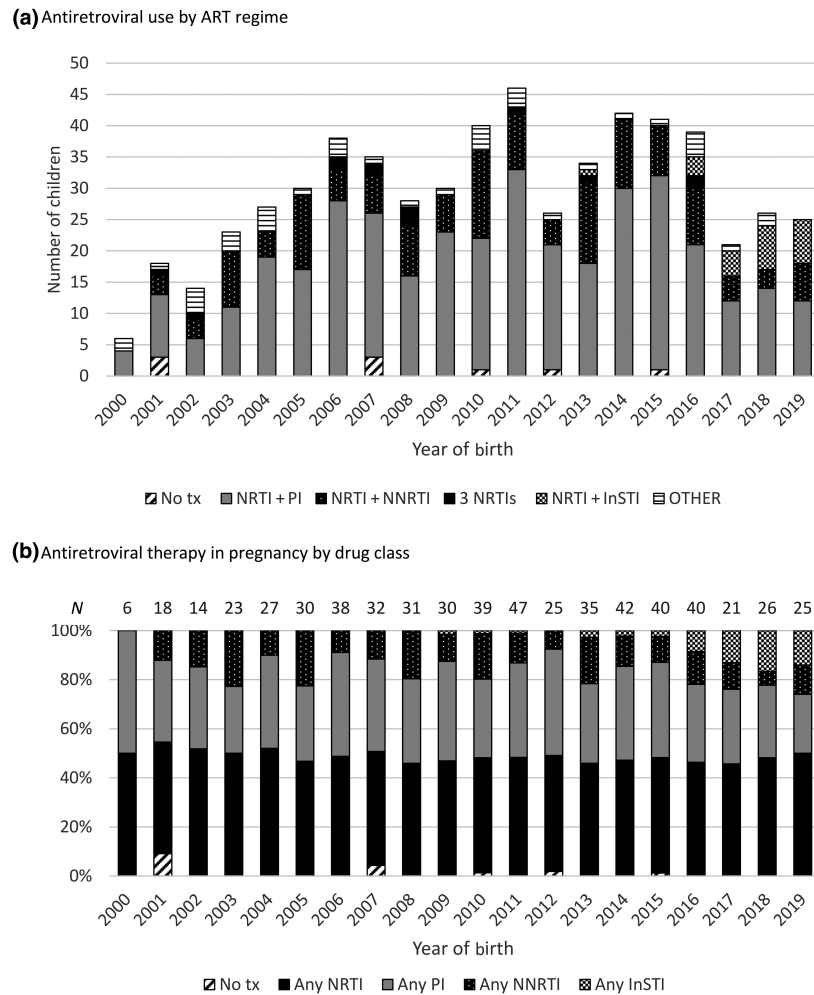
(a) Antiretroviral use by ART regime

(b) Antiretroviral therapy in pregnancy by drug class

FIGURE 1 (a) Antiretroviral use by antiretroviral therapy (ART) regime; (b) ART in pregnancy by drug class. *N*, number of live-born children; Tx, treatment; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; InSTI, integrase inhibitor

the least commonly used drug class (26%) together with InSTIs. The proportion of women receiving InSTIs after 2008, when raltegravir was licensed, was 9% (33/370). An increase in InSTI-based regimens in pregnancy, especially dolutegravir (DTG) use, is seen in recent years.

Change in ART regimen in pregnancy

In total, 118 (20%) women had a change in their ART regimen during pregnancy. Ninety-six (81%) women changed treatment regimen once during pregnancy, 17 (14%) changed treatment regimen twice during pregnancy, and five (4%) changed treatment regimen three times during pregnancy. Overall, 51 (41%) women changed their ART regimen in the first trimester, 40 (34%) in their second trimester, and 27 (23%) in their third trimester. Change was more common in women who were diagnosed with HIV prior to conception (*n* = 102, 86%) than among women diagnosed with HIV in pregnancy (*n* = 16, 14%). Twenty-one per cent of women

who conceived on efavirenz switched regimen during pregnancy (26/125), the majority of whom discontinued the drug (83%). All women receiving cobistat-boosted PI (*n* = 3) changed regimen early in pregnancy, while less than three women taking DTG experienced a change in regimen. The median viral load around the time of change was 20 (IQR: 19–40) among women who changed ART in the first trimester, 39 (IQR: 39–67) among women who changed ART in the second trimester, and 153 (IQR: 29–2213) among women who changed ART in the third trimester.

Birth outcome

The results of the regression analysis are presented in Tables 2 and S1. In total, 12% (*n* = 71) of the children were born preterm, 9% (*n* = 55) were born SGA, 6% (*n* = 37) had IUGR and 12% (*n* = 68) had LBW at delivery. Twelve of the 37 children with IUGR were born preterm. Antiretroviral regimen, PI use in pregnancy and timing of ART initiation
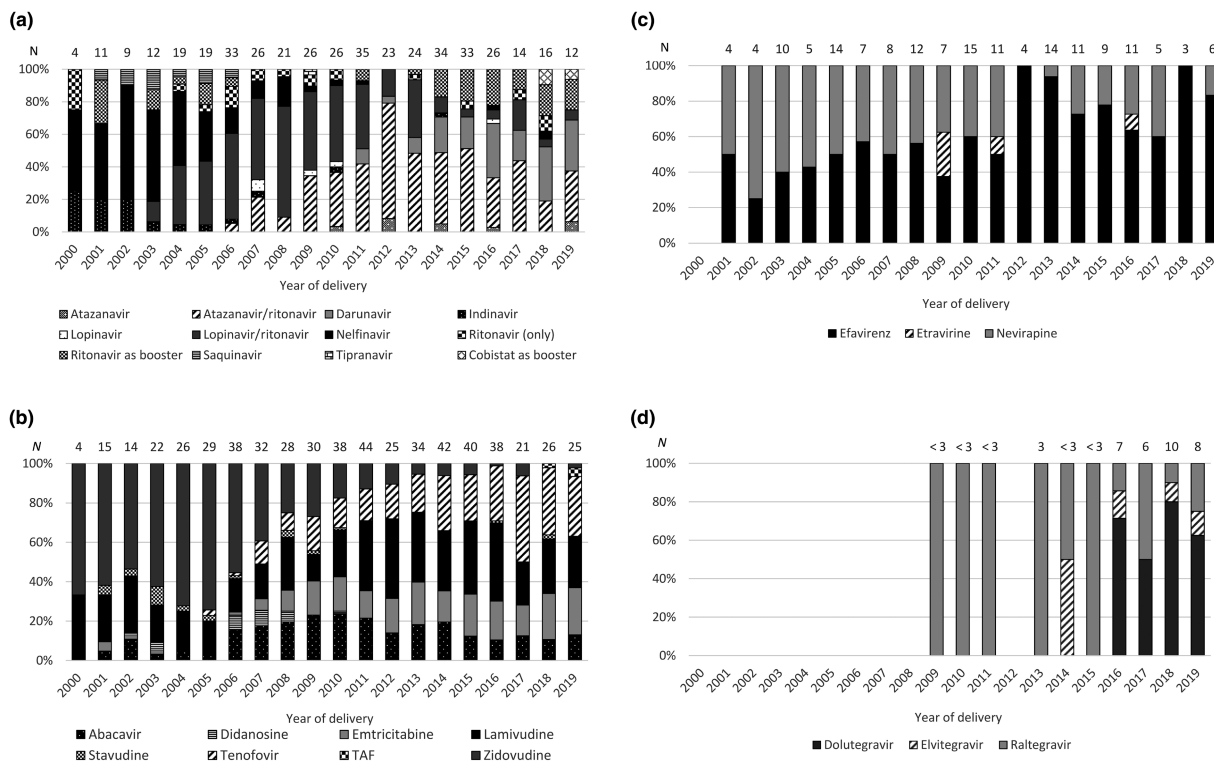
FIGURE 2 Antiretroviral use in pregnancy calculated as the proportion of individual drugs within the different drug classes. (a) Protease inhibitors; (b) Nucleoside reverse transcriptase inhibitors; (c) nonnucleoside reverse transcriptase inhibitors; (d) integrase inhibitors; raltegravir was licensed in Europe in 2008, elvitegravir in 2013, and dolutegravir in 2014. *N*, total number of women receiving the specific antiretroviral drug class per year; TAF, tenofovir alafenamide

in pregnancy were not significantly associated with increased odds of PTB, SGA or LBW. First-trimester initiation of ART was significantly associated with increased odds of IUGR in the multivariate analysis (adjusted OR (aOR) = 3.78, 95% CI: 1.23–11.59, *p* = 0.02), while PI use in the first trimester was associated with increased odds of IUGR in the univariate analysis only (OR = 3.24, 95% CI: 1.13–9.30, *p* = 0.03). Smoking in pregnancy was significantly associated with increased odds of SGA (aOR = 3.03, 95% CI: 1.03–8.91, *p* = 0.04) and LBW (aOR = 2.72, 95% CI: 1.06–6.98, *p* = 0.04). Maternal HIV RNA ≥ 50 copies/mL was associated with increased odds of PTB (aOR = 2.29, 95% CI: 1.03–5.12, *p* = 0.04) and SGA (aOR = 2.87, 95% CI: 1.20–6.86, *p* = 0.02), while maternal comorbidity was associated with increased odds of IUGR (aOR 2.95, 95% CI: 1.22–7.14, *p* = 0.02).

DISCUSSION

The results of this study provide an understanding of ART use in pregnancy over time and the association between different adverse birth outcomes and other risk factors among WLWH with free access to care. The proportion of WLWH on ART at conception increased over time. This is in line with

other studies [6,32]. However, a relatively high proportion of women were diagnosed during screening in early pregnancy [2,25], highlighting the importance of this screening practice.

The observed temporal trends in this study reflect the changes in the guidelines. An NRTI + PI regimen was most commonly used throughout the study period consistent with both Danish and European guidelines [7,26]. Among the NRTIs, we observed a steady decline in ZDV over time and an increase in TDF/FTC and ABC/3TC, which were the dual-NRTI regimen backbones recommended for pregnant women from 2006. Concerns have been raised regarding a possible increased risk of PTB with TDF [33]. However, several reviews have concluded that exposure to TDF in pregnancy is well tolerated in terms of birth outcomes [34,35]. Nevertheless, given the likely increase in children exposed to TDF *in utero*, more research is needed to clarify the risks and benefits of this exposure.

Among the PIs, we observed a transition from a NFV-based therapy to a LPV/r- or ATV/r-based therapy. Currently, DRV/r is recommended as the third agent in an NRTI + PI regimen [7,26], and an increase in DRV/r use in pregnancy was observed in recent years.

Contraindications for the use of nevirapine (NVP) and efavirenz (EFV) in pregnancy, especially in the early study period, may partly explain the limited use of NNRTIs. EFV

TABLE 2 Unadjusted and adjusted odds ratios (ORs) for preterm birth (PTB), small-for-gestational age (SGA), intrauterine growth restriction (IUGR) and low birth weight (LBW) by exposure to antiretroviral therapy (ART) regimes during pregnancy and other maternal and demographic factors among 566 mother–infant pairs

| | | PTB | | | | SGA | | |
| | | (*n* = 64) | | | | (*n* = 47) | | |
	n	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)[a]	*p*-value	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)[a]
Antiretroviral regime								
Combination with NNRTI	152	Ref		Ref		Ref		Ref
Combination with PI	364	0.75 (0.40–1.39)	0.36	0.76 (0.38–1.48)	0.41	0.59 (0.29–1.23)	0.17	0.53 (0.24–1.20)
Combination with three NRTIs	12	1.21 (0.24–6.06)	0.82	1.17 (0.25–5.47)	0.84	0.67 (0.08–5.69)	0.71	0.48 (0.07–3.04)
Combination with InSTI	38	0.61 (0.17–2.19)	0.45	0.53 (0.12–2.40)	0.41	1.02 (0.31–3.35)	0.98	0.67 (0.18–2.51)
PI use in pregnancy								
No PI use in pregnancy	154	Ref		Ref		Ref		Ref
Prior to conception	255	0.81 (0.41–1.59)	0.53	0.76 (0.37–1.59)	0.47	0.86 (0.42–1.76)	0.69	0.81 (0.38–1.75)
In first trimester	45	1.33 (0.49–3.59)	0.57	1.49 (0.49–4.52)	0.48	0.76 (0.20–2.83)	0.68	0.83 (0.21–3.23)
In second trimester	100	1.03 (0.42–2.51)	0.95	1.11 (0.41–2.99)	0.84	0.72 (0.24–2.23)	0.57	0.89 (0.25–3.19)
In third trimester	12	0.69 (0.41–1.59)	0.53	0.63 (0.07–5.84)	0.69	-		-
Time of ART initiation								
Before conception	385	Ref		Ref		Ref		Ref
First trimester	51	1.25 (0.49–3.17)	0.64	1.41 (0.48–4.13)	0.54	0.71 (0.21–2.46)	0.59	0.84 (0.24–2.98)
Second trimester	113	1.03 (0.47–2.24)	0.95	1.10 (0.48–2.55)	0.82	0.85 (0.34–2.15)	0.74	1.16 (0.39–3.51)
Third trimester	17	0.54 (0.07–4.21)	0.55	0.46 (0.05–4.28)	0.50	-		-
Drug/alcohol abuse in pregnancy								
No	501	Ref		Ref		Ref		Ref
Yes	32	2.69 (1.09–6.57)	**0.03**	2.31 (0.81–6.61)	0.12	1.25 (0.37–4.23)	0.36	0.83 (0.16–4.14)
Smoking in pregnancy								
No	465	Ref		Ref		Ref		Ref
Yes	64	2.51 (1.20–5.23)	**0.01**	1.98 (0.78–5.00)	0.15	2.45 (1.04–5.78)	**0.04**	3.03 (1.03–8.91)
Maternal comorbidity								
No	463	Ref		Ref		Ref		Ref
Yes	101	2.09 (1.12–3.89)	**0.02**	2.02 (0.96–4.24)	0.06	1.63 (0.73–3.62)	0.23	1.54 (0.62–3.84)
HIV RNA at delivery								
< 50 copies/mL	498	Ref		Ref		Ref		Ref
≥ 50 copies/mL	68	2.12 (1.02–4.34)	**0.04**	2.29 (1.03–5.12)	**0.04**	2.59 (1.19–5.68)	**0.02**	2.87 (1.20–6.86)

Note: Significant results are highlighted in bold.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; InSTI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor

[a]Adjusted for maternal age, country of birth, year of birth, mode of delivery, alcohol/drug abuse, smoking, maternal comorbidity, CD4 count at delivery and HIV RNA at delivery. The validity of the models were tested using the Hosmer–Lemeshow goodness-of-fit test.

was more commonly used after 2012 when there was substantial evidence that use of EFV in pregnancy was not associated with an increased risk of adverse birth outcomes [36].

Few women were treated with a regimen containing an InSTI. This could be related to concerns about teratogenicity, especially the risk of neural tube defects

p-value	IUGR				LBW			
	(n = 34)				(n = 56)			
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)[a]	p-value	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)[a]	p-value
	Ref		Ref		Ref		Ref	
0.13	0.75 (0.37–1.53)	0.43	0.89 (0.40–1.97)	0.77	0.60 (0.31–1.17)	0.14	0.54 (0.26–1.13)	0.10
0.44	-		-		0.55 (0.07–4.59)	0.58	0.40 (0.06–2.65)	0.34
0.55	-		-		0.83 (0.26–2.68)	0.76	0.58 (0.16–2.08)	0.41
	Ref		Ref		Ref		Ref	
0.60	0.73 (0.30–1.78)	0.49	0.63 (0.21–1.79)	0.38	0.89 (0.45–1.76)	0.75	0.83 (0.40–1.73)	0.62
0.79	3.24 (1.13–9.30)	**0.03**	2.95 (0.89–9.77)	0.08	0.65 (0.17–2.39)	0.52	0.64 (0.17–2.49)	0.52
0.86	1.17 (0.40–3.46)	0.77	1.29 (0.22–4.51)	0.70	0.86 (0.32–2.27)	0.75	1.01 (0.32–3.21)	0.98
	-				-		-	
	Ref		Ref		Ref		Ref	
0.79	3.39 (1.34–8.58)	**0.01**	3.78 (1.23–11.59)	**0.02**	0.59 (0.17–2.05)	0.42	0.64 (0.18–2.27)	0.49
0.79	1.56 (0.64–3.78)	0.32	2.00 (0.75–5.27)	0.16	0.94 (0.42–2.14)	0.89	1.23 (0.47–3.21)	0.67
	-		-		-			
	Ref		Ref		Ref		Ref	
0.82	2.39 (0.78–7.36)	0.13	1.40 (0.37–5.26	0.62	1.93(0.71–5.25)	0.20	1.24 (0.36–4.24)	0.74
	Ref		Ref		Ref		Ref	
0.04	2.68 (1.20–5.99)	**0.02**	2.29 (0.81–6.44)	0.12	2.54 (1.14–5.62)	**0.02**	2.72 (1.06–6.98)	**0.04**
	Ref		Ref		Ref		Ref	
0.35	3.31 (1.62–6.77)	**<0.01**	2.95 (1.22–7.14)	**0.02**	2.00 (0.99–4.05)	0.05	1.91 (0.84–4.35)	0.12
	Ref		Ref		Ref		Ref	
0.02	0.77 (0.23–2.56)	0.67	0.82 (0.20–3.29)	0.78	2.07 (0.98–4.38)	0.06	2.26 (0.96–5.30)	0.06

with DTG use in early pregnancy [37]. There is increasing evidence about the safety of DTG, and although the latest results from the Tsepamo study showed a small non-statistically significant increase in neural tube defects among women receiving DTG from conception [38], DTG is now recommended as a first-line

treatment with an NRTI backbone in both the European and Danish guidelines [7,26]. However, the use of DTG should be discussed with women who are considering pregnancy or if it is to be used in the first 6 weeks of pregnancy [7]. Even so, the use of DTG in pregnancy is likely to increase, as it is well tolerated with a high barrier to resistance and rapid virological control [39].

We did not collect information about the reasons for changes in ART regimen in pregnancy; however, most changes were likely due to concerns about teratogenicity or failure to achieve viral load suppression, especially among women changing ART in the third trimester. Guidelines currently recommend that women on ART prior to conception continue their regimen throughout pregnancy [7,26]. If a change in ARV regimen is warranted, this should be based on shared decision-making, taking into account the woman's willingness to switch and her history of treatment and adherence [7].

The association between ART use in pregnancy and risk of adverse birth outcome remains controversial [40]. We did not find an association between ART regimen or timing of ART initiation in pregnancy and risk of PTB, SGA or LBW. This is in line with a meta-analysis, where there was no significant association between timing of ART initiation and risk of PTB and LBW in a subgroup analysis of studies conducted in high-income countries [8]. However, we did find that first-trimester initiation of ART was significantly associated with an increased risk of IUGR, even after adjusting for maternal factors. It has been suggested that HIV *per se* can cause IUGR as viral infection of the placenta might lead to impaired maternal-foetal exchange or disrupt normal placental implantation and development [41]. Most women in our cohort had suppressed viral loads (i.e. HIV RNA < 50 copies/mL) at delivery, suggesting that ART it self may have a specific effect on fetal growth in the first trimester. One explanation could be that initation of ART may induce change the women's cytokine profile and this could potentially impact fetal growth [11]. More reseach is needed to elucidate a possible association between timing of ART and IUGR.

We also did not find an association between PI use in pregnancy and associated risk of PTB, SGA or LBW. This is in line with other studies conducted in high-income settings [14,42]. However, the association between use of PI in pregnancy and risk of adverse birth outcome remains controversial, and conflicting results have been reported in the literature [14,15,17]. Moreover, boosted PIs have been associated with an increased risk of adverse birth outcome compared with treatment with non-boosted PIs [15,43], and in our analysis boosted and non-boosted PIs were considered together. We found that first-trimester PI use was significantly associated with an increased risk of IUGR in the univariate analysis, but not in the multivariate analysis adjusting for maternal and demographic factors. Although the mechanisms of PI used in pregnancy are not fully understood, it has been suggested that PIs may reduce progesterone levels in pregnancy, leading to foetal growth restriction [44,45]. As IUGR is a major contributor to perinatal morbidity and mortality [46], more research is needed to elucidate possible associations between ART use and IUGR.

Known risk factors for adverse birth outcome among WLWH include smoking, comorbidity, and advanced maternal HIV [47,48]. Smoking causes vasoconstriction and placental insufficiency [49], and, as proposed by Westreich et al. [47], HIV and smoking may have a synergistic intrauterine effect, as both are associated with inflammation and immune activation. Variation in these factors and differences between periods concerning the population studied and drug regimens used could partly explain the discrepancy between findings in previous studies assessing the association between ART use in pregnancy and adverse birth outcome [40].

Strength and limitations

A strength of the current study is the use of a population-based approach, including a nationwide population of all pregnant WLWH giving birth during a study period of almost 20 years. Moreover, the use of registries ensures prospective data, uniformly and neutrally collected on an individual level, which restricts the methodological problems of loss to follow-up, selection bias and emigration. The relatively low number of WLWH is a limitation, and although the analysis was adjusted for several known confounders, residual confounding cannot be ruled out. Moreover, it was not possible to identify the PIN for 16 mother/infant pairs for whom information about treatment and birth outcome is therefore unknown.

CONCLUSIONS

Most WLWH living in Denmark have suppressed viral loads at delivery. Temporal trends of ART reflect the changing guidelines. ARV regimen, PI use in pregnancy and timing of ART initiation were not associated with risk of PTB, LBW or SGA. First-trimester initiation of ART was associated with an increased odds of IUGR in the adjusted analysis, while first trimester PI-use was associated with IUGR in the unadjusted analysis only. Smoking, comorbidity, and advanced maternal HIV were significantly associated with adverse birth outcome, suggesting that maternal risk factors could explain some of the effects of ART on adverse birth effects.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

EM and NW developed the original concept for the study. All authors contributed to the study design, data collection, data interpretation and writing of the report, and approved the final version. EM had full access to the data and carried out the statistical analysis.

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