

# 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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## Background

No single ART regimen has consistently been considered first-line for pregnant women living with HIV (WLWH). Exposure to HIV and/or different ART drugs during pregnancy may be associated with an increased risk of adverse birth outcomes.

## Objectives

- To describe ART regimens during pregnancy among women living with HIV in Denmark, including regimen changes during pregnancy.
- To examine the association between ART use in pregnancy and other risk factors, and different adverse birth outcomes.

## Methods

- A Danish population-based cohort study including all pregnancies among WLWH in Denmark between 2000 - 2019.
- Data was collected through national registries.
- Temporal trends of ART use in pregnancy were evaluated.
- Logistic regression models were used to examine the association between ART use in pregnancy (regimen, PI-use, and time of ART initiation in pregnancy) and other risk factors, and different adverse birth outcomes (preterm birth (PTB), small for gestational age (SGA), intrauterine growth restriction (IUGR), and low birth weight (LBW)).

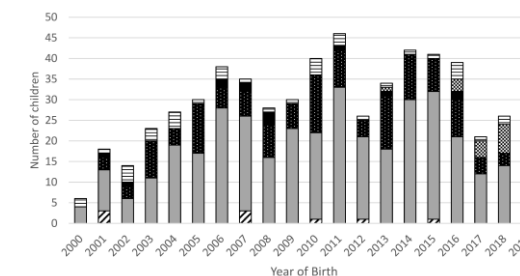
## Results

In total, 589 pregnancies were included (Table 1).

- 67% were on ART at conception, which increased over time from 33% (n=3) in year 2000 to 88% (n=22) in 2019.
- Combination treatment with a Nucleoside Reverse Transcriptase Inhibitor (NRTI) and a Protease Inhibitor (PI) was the most common regimen (96%). (Figure 1)
- 20% changed their ART regimen during pregnancy. 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%)).

- ART regimen, PI use in pregnancy, or timing of ART initiation in pregnancy was not significantly associated with increased odds of PTB, SGA, or LBW (Table 2).
- Initiation of ART in the first trimester and PI use in the first trimester were significantly associated with an increased odds of IUGR in the univariate analysis, but not in the multivariate analysis adjusting for maternal factors (Table 2).
- Smoking and maternal HIV RNA $\geq$ 50 copies/mL were independently associated with an increased odds of adverse birth outcome (Table 2).

Figure 1: Antiretroviral use in pregnancy by regime



Tx: Treatment, NRTI: Nucleoside Reverse Transcriptase Inhibitor, PI: Protease Inhibitor, NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor, InSTI: Integrase Inhibitor

Table 1: Maternal and child characteristics among 589 pregnancies with a liveborn child born between 2000-2019

Characteristic	Value (95% CI)
Maternal age at birth (mean)	32.65 (32.22 - 33.09)
Country of birth (n (%))	
Denmark	132 (23)
African country	342 (58)
Asian country	69 (12)
Other	46 (8)
Smoking during pregnancy (n (%))	
Missing	69 (12)
Missing	41 (7)
Time of maternal HIV diagnosis (n (%))	
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 of ART initiation (n (%))	
Before conception	385 (65)
First trimester	60 (10)
Second trimester	117 (20)
Third trimester	17 (3)
No treatment in pregnancy	9 (2)
ART regimen at conception or initiation (n (%))	
NRTI + PI	369 (63)
NRTI + NNRTI	137 (23)
3 NRTIs	13 (2)
NRTI + InSTI	22 (4)
Other	39 (7)
HIV viral load at delivery (n (%))	
<50 copies/mL	509 (86)
$\geq$ 50 copies/mL	76 (13)
Unknown	4 (1)
Gestational age <37 weeks (n (%))	
Missing	71 (12)
Missing	7 (1)
Delivered by cesarean section (n (%))	
Missing	318 (54)
Missing	7 (1)

Table 2: Unadjusted and adjusted Odds Ratios (ORs) for preterm birth (PTB), small-for-gestational age (SGA), interuterine growth restriction (IUGR) and low birth weight (LBW) by exposure to antiretroviral therapy regimens during pregnancy and other maternal and demographic factors among 566 mother-infant pairs

Characteristic	PTB (n=64)		SGA (n=47)		IUGR (n=34)		LBW (n=56)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
ARV regime								
Combination with NNRTI	152 Ref	Ref	Ref	Ref	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) 0.13	0.75 (0.37; 1.53) 0.43	0.88 (0.40; 1.97) 0.77	0.60 (0.31; 1.17) 0.14	0.54 (0.26; 1.13) 0.10
Combination with 3 NRTI	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) 0.44	-	-	0.55 (0.07; 4.59) 0.58	0.40 (0.06; 2.65) 0.34
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) 0.55	-	-	0.83 (0.26; 2.68) 0.76	0.58 (0.16; 2.08) 0.41
PI use in pregnancy								
No PI use in pregnancy	154 Ref	Ref	Ref	Ref	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) 0.60	0.73 (0.30; 1.78) 0.49	0.83 (0.40; 1.73) 0.62	0.89 (0.45; 1.76) 0.75	0.83 (0.40; 1.73) 0.62
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) 0.79	<b>3.24 (1.13; 9.30) 0.03</b>	0.64 (0.17; 2.49) 0.52	0.65 (0.17; 2.39) 0.52	0.64 (0.17; 2.49) 0.52
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) 0.86	1.17 (0.40; 3.46) 0.77	1.01 (0.32; 3.21) 0.98	0.86 (0.32; 2.27) 0.75	1.01 (0.32; 3.21) 0.98
In third trimester	12 0.69 (0.41; 1.15) 0.53	0.63 (0.07; 5.84) 0.69	-	-	-	-	-	-
Time of ART initiation								
Before conception	385 Ref	Ref	Ref	Ref	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) 0.21	0.84 (0.24; 2.98) 0.79	<b>3.39 (1.34; 8.58) 0.01</b>	0.64 (0.18; 2.27) 0.49	0.59 (0.17; 2.05) 0.42	0.64 (0.18; 2.27) 0.49
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) 0.79	1.56 (0.64; 3.78) 0.32	1.23 (0.47; 3.21) 0.67	0.94 (0.42; 2.14) 0.89	1.23 (0.47; 3.21) 0.67
Third trimester	17 0.54 (0.07; 4.21) 0.55	0.46 (0.05; 4.28) 0.50	-	-	-	-	-	-
Smoking in pregnancy								
No	465 Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	64 2.51 (1.20; 5.23) 0.01	1.98 (0.78; 5.00) 0.15	<b>2.45 (1.04; 5.78) 0.04</b>	<b>3.03 (1.03; 8.91) 0.04</b>	<b>2.68 (1.20; 5.99) 0.02</b>	<b>2.72 (1.06; 6.98) 0.04</b>	<b>2.54 (1.14; 5.62) 0.02</b>	<b>2.72 (1.06; 6.98) 0.04</b>
HIV RNA at delivery								
<50 copies/mL	498 Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
$\geq$ 50 copies/mL	68 <b>2.12 (1.02; 4.34) 0.04</b>	<b>2.29 (1.03; 5.12) 0.04</b>	<b>2.59 (1.19; 5.68) 0.02</b>	<b>2.87 (1.20; 6.86) 0.02</b>	0.77 (0.23; 2.56) 0.67	2.26 (0.96; 5.29) 0.06	2.07 (0.98; 4.38) 0.06	2.26 (0.96; 5.30) 0.06

\*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 and Lemeshow goodness-of-fit test. Significant results are highlighted in bold.

## Conclusion

WLWH living in Denmark are generally well-treated during pregnancy with NRTI+PI as the most common ART regimen used in pregnancy. The association between ART use in pregnancy and adverse birth outcomes may be explained by maternal risk factors.