Type and Timing of Antiretroviral Therapy During Pregnancy: Impact on Risk of Preterm Delivery and Small-for-Gestational-Age in Canada, A Retrospective Cohort Study

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No conflicts of interest to disclose.

BACKGROUND

- Previous studies have reported an increase risk (1.5-2.5 times higher) of preterm delivery (PTD) in pregnant people living with HIV despite antiretroviral therapy (ART)

Arch Gynecol Obstet. 2017 Mar;295(3):599-606.

- Published data remains controversial within and among countries on whether adverse pregnancy outcomes, especially PTD and small for gestational age (SGA), are linked to type and timing of ART

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OBJECTIVE

- To evaluate the impact of ART regimen type and exposure duration on the risk of preterm delivery and small-for-gestational-age births among pregnant people living with HIV in Canada

METHODS

Data:

- Retrospective cohort study
- Canadian Perinatal HIV Surveillance Program (CPHSP) 1990-2020

Participants:

- Pregnant people living with HIV who gave birth to live infants between 22-42 weeks
- Excluded: non-singleton pregnancies and vertical transmission cases

Methods:

- Comparison of characteristics of pregnancies based on mixed effects logistic regression with subject-specific random to account for dependence between multiple pregnancies of same person
- Time-dependent Cox proportional hazard model to assess the effect of ART regimen type and exposure duration on risk of PTD

RESULTS

- Total number of 5438 pregnancies, of which 4379 pregnancies included in the PTD cohort and 3947 pregnancies included in the SGA cohort
- Overall, 14.9% (654/4379) cases of PTD and 18.5% (732/3947) cases of SGA

Table 1.Comparison of pregnancy cases during first 37 weeks, by preterm delivery and small-for-gestational-age births

Variable	PTD (<37 weeks)			SGA (<10 percentile)		
	No (n=3725)	Yes (n=654)	p	No (n=3215)	Yes (n=732)	p
ART regimen type			<0.001			0.437
No treatment	275 (7.4)	85 (13.1)		223 (7.0)	57 (7.9)	
Mono- or bi-therapy	314 (8.5)	38 (5.9)		204 (6.4)	36 (5.0)	
NRTI + NNRTI	468 (12.7)	70 (10.8)		412 (12.9)	78 (10.8)	
NRTI + unboosted PI	554 (15.0)	75 (11.6)		444 (13.9)	105 (14.5)	
NRTI + boosted PI	1432 (38.8)	285 (44.0)		1341 (42.0)	307 (42.5)	
NRTI + INSTI	377 (10.2)	41 (6.3)		333 (10.4)	76 (10.5)	
Other ART regimen	274 (7.4)	54 (8.3)		237 (7.4)	64 (8.9)	
Start time of ART			<0.001			0.024
Unknown	221	36		125	37	
No treatment	275 (7.8)	85 (13.8)		223 (7.2)	57 (8.2)	
Before conception	1738 (49.6)	270 (43.7)		1599 (51.7)	315 (45.3)	
1-14 weeks	424 (12.1)	66 (10.7)		349 (11.3)	84 (12.1)	
>14 weeks	1067 (30.5)	197 (31.9)		919 (29.7)	239 (34.4)	

Abbreviations: ART, antiretroviral therapy; SGA, small for gestational age; NRTI, Nucleoside reverse transcriptase inhibitor; NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; PTD, preterm delivery; INSTI, Integrase strand transfer inhibitor.

Table 2. Association between ART regimen type and start time during first 37 weeks with preterm delivery and small-for-gestational-age births

Variable	PTD (n=2805)		SGA (n=2699)	
	HR (95% CI)	aHR (95% CI)*	OR (95% CI)	aOR (95% CI)*
ART regimen type				
No treatment	2.00 (1.36, 2.94)	0.89 (0.50, 1.56)	1.12 (0.75, 1.67)	1.02 (0.45, 2.29)
Mono- or bi-therapy	1.29 (0.82, 2.05)	1.44 (0.69, 2.99)	0.77 (0.49, 1.21)	0.59 (0.24, 1.45)
NRTI + NNRTI	1.41 (0.94, 2.10)	**1.73 (1.10, 2.73)**	0.83 (0.58, 1.19)	0.90 (0.59, 1.38)
NRTI + unboosted PI	1.31 (0.89, 1.94)	1.36 (0.82, 2.25)	1.04 (0.74, 1.47)	0.77 (0.47, 1.25)
NRTI + boosted PI	1.72 (1.22, 2.42)	**1.68 (1.15, 2.45)**	1.00 (0.75, 1.34)	0.99 (0.72, 1.37)
NRTI + INSTI	1	1	1	1
Other ART regimen	1.73 (1.13, 2.64)	1.61 (1.00, 2.60)	1.18 (0.80, 1.75)	1.23 (0.78, 1.94)
Start time of ART				
Before conception	1	1	1	1
1-14 weeks	0.99 (0.76, 1.30)	1.05 (0.78, 1.43)	1.22 (0.92, 1.61)	**1.45 (1.05, 2.00)**
>14 weeks	1.15 (0.96, 1.38)	0.93 (0.74, 1.17)	1.33 (1.10, 1.62)	**1.44 (1.11, 1.86)**

*Adjusted for viral load closest to delivery, ethnicity, risk factor for HIV infection, region, ART regimen type, and start time of ART.
Abbreviations: ART, antiretroviral therapy; SGA, small for gestational age; NRTI, Nucleoside reverse transcriptase inhibitor; NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; PTD, preterm delivery; INSTI, Integrase strand transfer inhibitor.

CONCLUSION

- INSTI-based ART regimens were associated with lower risk of PTD compared to NNRTI-based and boosted PI-based regimens
- ART initiation before conception compared to after was associated with a lower risk of SGA

IMPACT

- ART regimen type and exposure duration influence perinatal complications among pregnant people living with HIV in Canada
- Healthcare providers should consider these factors, along with overall safety data, when providing pregnancy planning counselling to patients living with HIV

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