TDF/FTC in Pregnancy Shows No Increase in Adverse Infant Birth Outcomes in US Cohorts

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BACKGROUND

- The IMPAACT PROMISE[1] trial allowed comparison of 2 maternal combination antiretroviral therapies:

TDF/FTC/LPV/r (tenofovir disoproxil fumarate, emtricitabine, and ritonavir-boosted lopinavir) vs. ZDV/3TC/LPV/r (zidovudine, lamivudine, and ritonavir-boosted lopinavir)

- Compared to ZDV/3TC/LPV/r, women randomized to TDF/FTC/LPV/r had infants with greater risk of death and twice the risk of being very premature (<34 weeks) or very low birth weight (<1,500g)
- Unclear whether risks are shared by all TDF/FTC-based regimens or how findings may generalize

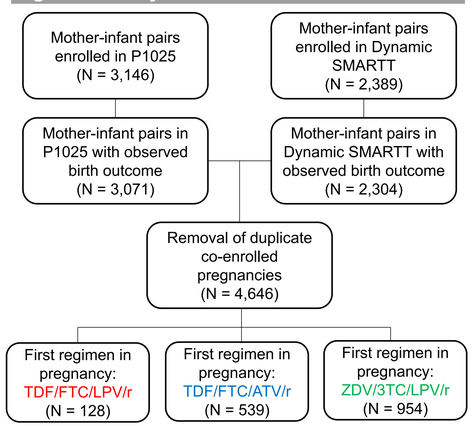
OBJECTIVE

Using data from two large US-based cohort studies, compare the risk of adverse birth outcomes for infants with *in utero* exposure to: TDF/FTC/LPV/r, TDF/FTC/ATV/r, and ZDV/3TC/LPV/r

METHODS

- We included 2 US-based perinatal cohort studies:
  - IMPAACT P1025
  - Dynamic cohort of PHACS SMARTT study
- Included all women with birth outcome information whose first antiretroviral regimen was: TDF/FTC/LPV/r, TDF/FTC/ATV/r, or ZDV/3TC/LPV/r
- Exposure classified by first regimen during pregnancy
- Infant birth outcomes:
  - Preterm (<37 weeks) & very preterm (<34 weeks)
  - Low (<2,500g) & very low (<1,500g) birth weight
  - Composite adverse & severe adverse outcomes (outcomes above plus fetal loss, infant mortality)
- Log binomial models fit for regimen comparisons
  - Adjusted for race/ethnicity, pre-gestational diabetes, sexually transmitted infections, smoking, and timing of regimen initiation

Figure 1. Study inclusion flowchart



RESULTS

Table 1. Maternal characteristics by initial regimen

	TDF/FTC/LPV/r n = 128		TDF/FTC/ATV/r n = 539		ZDV/3TC/LPV/r n = 954	
	n	(%)	n	(%)	n	(%)
Year of delivery						
2002-2004	0	(0.0)	0	(0.0)	29	(3.0)
2005-2008	38	(29.7)	92	(17.1)	260	(27.3)
2009-2012	76	(59.4)	290	(53.8)	554	(58.1)
2012-2016	14	(10.9)	157	(29.1)	111	(11.6)
Age at delivery						
24 years or less	50	(39.1)	136	(25.2)	355	(37.2)
25 to 34 years	67	(52.3)	293	(54.4)	473	(49.6)
35 years or more	11	(8.6)	109	(20.2)	125	(13.1)
Education						
Less than high school	34	(26.6)	188	(34.9)	331	(34.7)
High school diploma	61	(47.7)	240	(44.5)	427	(44.8)
College or more	33	(25.8)	109	(20.2)	194	(20.3)
Race/ethnicity						
Non-Hispanic White	15	(11.7)	44	(8.2)	68	(7.1)
Non-Hispanic Black	81	(63.3)	365	(67.7)	611	(64.0)
Hispanic	30	(23.4)	120	(22.3)	258	(27.0)
Other	1	(0.8)	9	(1.7)	11	(1.2)
First CD4 in pregnancy						
< 250 cells/mm^3	30	(23.4)	100	(18.6)	194	(20.3)
250 - 500 cells/mm^3	47	(36.7)	205	(38.0)	381	(39.9)
> 500 cells/mm^3	47	(36.7)	225	(41.7)	365	(38.3)
First HIV RNA in pregnancy						
< 400 copies/mL	61	(47.7)	277	(51.4)	281	(29.5)
400 - 10,000 copies/mL	33	(25.8)	137	(25.4)	361	(37.8)
> 10,000 copies/mL	33	(25.8)	122	(22.6)	305	(32.0)
Pre-pregnancy HIV diagnosis	107	(83.6)	470	(87.2)	673	(70.5)
Timing of regimen initiation						
Before pregnancy	58	(45.3)	265	(49.2)	111	(11.6)
Trimester 1	18	(14.1	82	(15.2)	115	(12.1)
Trimester 2 or 3	52	(40.6)	192	(35.6)	728	(76.3)
Alcohol use in pregnancy	25	(19.5)	92	(17.1)	182	(19.1)
Tobacco use in pregnancy	30	(23.4)	105	(19.5)	182	(19.1)
Illicit drug use in pregnancy	21	(16.4)	61	(11.3)	115	(12.1)
Pregestational diabetes	1	(0.8)	10	(1.9)	12	(1.3)
Hepatitis B/C in pregnancy	20	(15.6)	71	(13.2)	99	(10.4)
STI in pregnancy	36	(28.1)	208	(38.6)	373	(39.1)

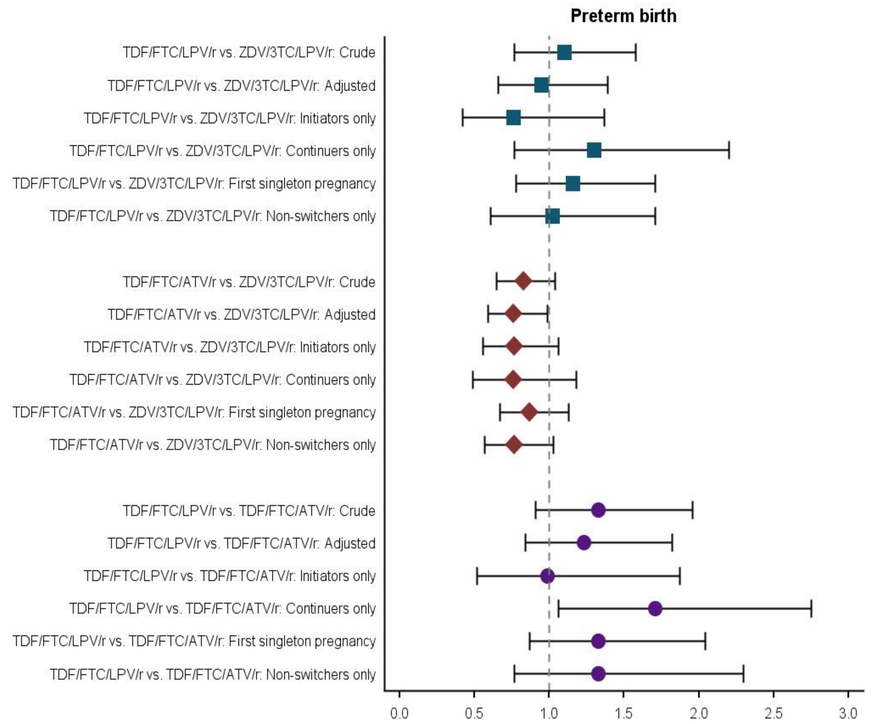
Table 2. Risk of outcomes by initial regimen

	Initial **antiretroviral** regimen during pregnancy					
	TDF/FTC/LPV/r		TDF/FTC/ATV/r		ZDV/3TC/LPV/r	
	n	Risk (%)	n	Risk (%)	n	Risk (%)
Preterm birth	27	(21.4)	86	(16.1)	184	(19.5)
Very preterm birth	5	(4.0)	26	(4.9)	44	(4.7)
Low birth weight	30	(23.8)	86	(16.2)	175	(18.8)
Very low birth weight	1	(0.8)	10	(1.9)	18	(1.9)
Adverse outcome	36	(28.1)	127	(23.7)	256	(27.2)
Severe adverse outcome	7	(5.5)	28	(5.2)	51	(5.4)

Table 3. Risk ratios and 95% confidence intervals for infant outcomes based on comparisons of initial antiretroviral regimen used during pregnancy

	TDF/FTC/LPV/r vs ZDV/3TC/LPV/r				TDF/FTC/ATV/r vs ZDV/3TC/LPV/r				TDF/FTC/LPV/r vs TDF/FTC/ATV/r			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Preterm birth	1.10	(0.77, 1.58)	0.95	(0.66, 1.39)	0.83	(0.65, 1.04)	0.76	(0.59, 0.99)	1.33	(0.91, 1.96)	1.23	(0.84, 1.82)
Very preterm birth	0.85	(0.19, 2.11)			1.04	(0.65, 1.68)			0.82	(0.32, 2.08)		
Low birth weight	1.27	(0.90, 1.78)	1.08	(0.76, 1.54)	0.86	(0.68, 1.09)	0.83	(0.64, 1.09)	1.47	(1.02, 2.13)	1.40	(0.97, 2.03)
Very low birth weight	0.41	(0.06, 3.06)			0.97	(0.45, 2.10)			0.42	(0.05, 3.27)		
Adverse outcome	1.03	(0.77, 1.39)	0.90	(0.66, 1.23)	0.87	(0.72, 1.05)	0.83	(0.67, 1.02)	1.18	(0.86, 1.62)	1.11	(0.81, 1.52)
Severe adverse outcome	1.01	(0.47, 2.17)			0.96	(0.61, 1.51)			1.04	(0.47, 2.34)		

Figure 2. Subgroup analyses (unadjusted) for comparison of initial antiretroviral regimen during pregnancy and risk of preterm birth: Risk ratios and 95% confidence intervals



LIMITATIONS

- Some analyses for severe adverse outcomes were underpowered due to a small number of events, especially for comparisons involving TDF/FTC/LPV/r
- Cohorts allowed enrollment late in pregnancy and shortly after delivery, meaning stillbirths and very preterm births may not be well captured
- High rate of switching off TDF/FTC/LPV/r before delivery, yet subgroup analyses restricted to non-switchers did not alter conclusions
- Lack of information on some outcome predictors (previous preterm delivery, hypertension, and parity) could lead to residual confounding
- Unclear how results will generalize outside the US

CONCLUSIONS

- TDF/FTC/LPV/r use in pregnancy was not associated with adverse birth outcomes when compared to ZDV/3TC/LPV/r or TDF/FTC/ATV/r, though we were underpowered to evaluate severe outcomes
  - Differences from PROMISE: dosing, lack of randomization, eligibility criteria, setting, standard of prenatal care
- TDF/FTC/LPV/r was rarely used by pregnant women in two large US-based cohorts
- Given the results of the PROMISE trial and treatment alternatives, it may be advisable to limit the use TDF/FTC/LPV/r in pregnancy
- Our findings support the use of TDF/FTC-based regimens with other protease inhibitors in pregnancy

ACKNOWLEDGMENTS

References

1. Fowler MG, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med 2016; 375:1726-37

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