Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Rough K, Seage GR III, Williams PL, et al. Birth outcomes for pregnant women with HIV using tenofovir–emtricitabine. N Engl J Med 2018;378:1593-603. DOI: 10.1056/NEJMoa1701666

Supplemental Materials:
Birth outcomes for pregnant women using tenofovir/emtricitabine in the US

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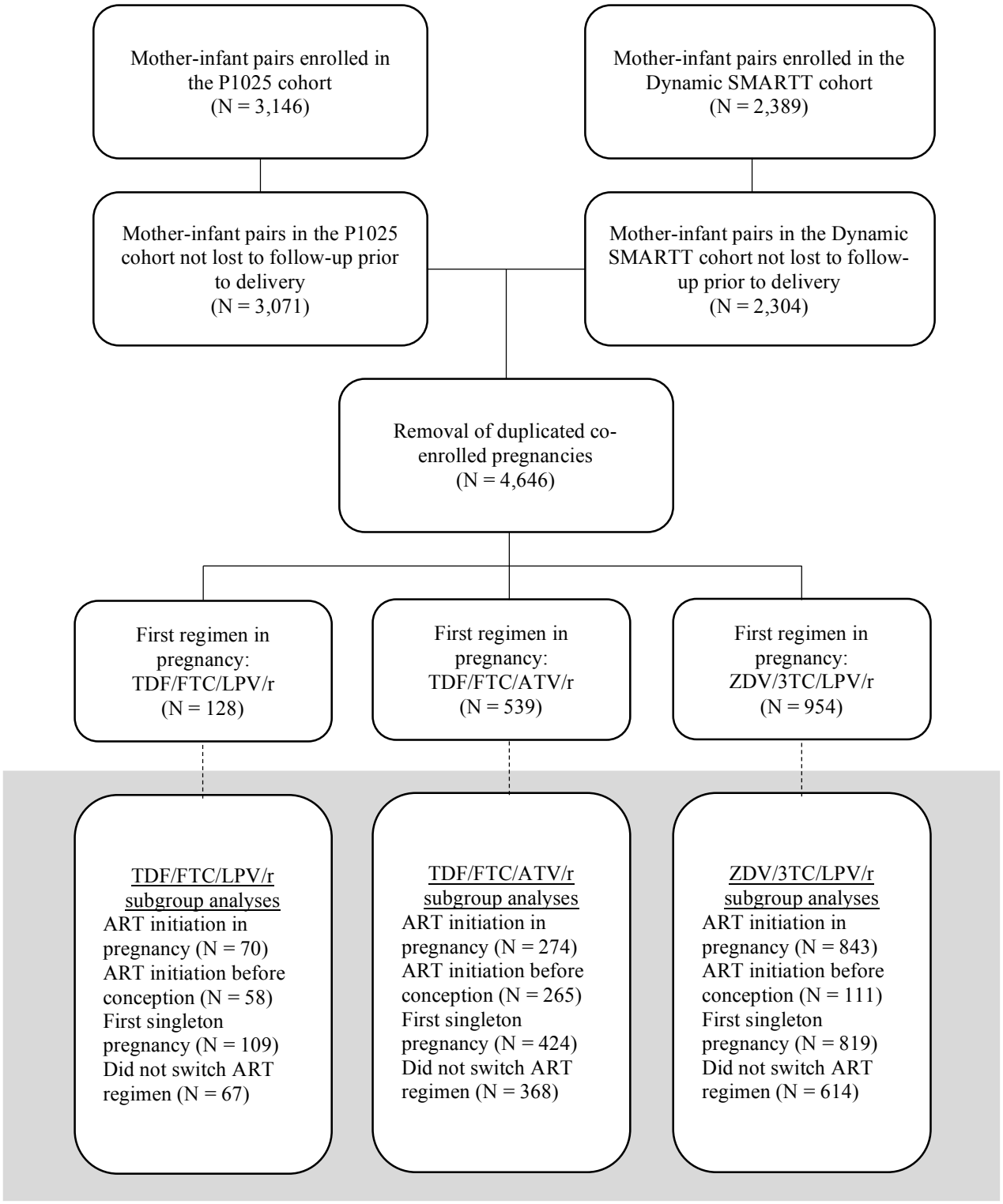
TABLE OF CONTENTS

Supplemental Figure S1. Flowchart of study pooling and inclusion criteria[1]



[1] Mothers may not be unique. Some women had multiple pregnancies under study observation. The unit of analysis in this figure is mother-infant pairs.

Supplemental Table S1. Full maternal characteristics[1] by initial antiretroviral regimen during pregnancy

	Initial regimen during pregnancy					
	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						
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
Missing	*0*	*0.0*	*1*	*0.2*	*1*	*0.1*
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
Missing	*0*	*0.0*	*2*	*0.4*	*2*	*0.2*
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
Missing	*1*	*0.8*	*1*	*0.2*	*6*	*0.6*
First CD4 in pregnancy						
Less than 250 cells/mm^3	30	23.4	100	18.6	194	20.3
250 to 500 cells/mm^3	47	36.7	205	38.0	381	39.9
More than 500 cells/mm^3	47	36.7	225	41.7	365	38.3
Missing	*4*	*3.1*	*9*	*1.7*	*14*	*1.5*
First viral RNA in pregnancy						
Less than 400 copies/mL	61	47.7	277	51.4	281	29.5
400 to 10,000 copies/mL	33	25.8	137	25.4	361	37.8
More than 10,000 copies/mL	33	25.8	122	22.6	305	32.0
Missing	*1*	*0.8*	*3*	*0.6*	*7*	*0.7*
Timing of HIV diagnosis						
Before pregnancy	107	83.6	470	87.2	673	70.5
During pregnancy	21	16.4	69	12.8	278	29.1
Missing	*0*	*0.0*	*0*	*0.0*	*3*	*0.3*
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 during pregnancy						
Yes	25	19.5	92	17.1	182	19.1

	Initial regimen during pregnancy					
	TDF/FTC/LPV/r n = 128		TDF/FTC/ATV/r n = 539		ZDV/3TC/LPV/r n = 954	
	n	%	n	%	n	%
No	91	71.1	432	80.1	705	73.9
Missing	*12*	*9.4*	*15*	*2.8*	*67*	*7.0*
Tobacco use during pregnancy						
Yes	30	23.4	105	19.5	182	19.1
No	77	60.2	387	71.8	628	65.8
Missing	*21*	*16.4*	*47*	*8.7*	*144*	*15.1*
Illicit drug use during pregnancy						
Yes	21	16.4	61	11.3	115	12.1
No	85	66.4	427	79.2	687	72.0
Missing	*22*	*17.2*	*51*	*9.5*	*152*	*15.9*
Pregestational diabetes						
Yes	1	0.8	10	1.9	12	1.3
No	126	98.4	527	97.8	939	98.4
Missing	*1*	*0.8*	*2*	*0.4*	*3*	*0.3*
Hepatitis B or C during pregnancy						
Yes	20	15.6	71	13.2	99	10.4
No	108	84.4	468	86.8	855	89.6
Sexually transmitted infection[2] during pregnancy						
Yes	36	28.1	208	38.6	373	39.1
No	78	60.9	297	55.1	513	53.8
Missing	*14*	*10.9*	*34*	6.3	*68*	*7.1*

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; ATV/r, ritonavir-boosted atazanavir; ZDV, zidovudine; 3TC, lamivudine

[1] Mothers may not be unique. Some women had multiple pregnancies under study observation. The unit of analysis is the mother-infant pair. Women are classified according to the initial antiretroviral therapy (ART) regimen received during pregnancy.

[2]Sexually transmitted infections include syphilis, gonorrhea, chlamydia, genital herpes, or "other" sexually transmitted infections noted in the medical chart.

Supplemental Table S2. Maternal characteristics[1] by initial antiretroviral regimen during pregnancy: TDF/FTC/Any PI versus ZDV/3TC/Any PI

	Initial regimen during pregnancy			
	TDF/FTC/Any PI n = 960		ZDV/3TC/Any PI n = 1, 593	
	n	%	n	%
Birth year				
2002-2004	0	0.0	138	8.7
2005-2008	178	18.5	610	38.3
2009-2012	514	53.5	693	43.5
2012-2016	268	27.9	152	9.5
Age				
24 years or less	254	26.5	592	37.2
25 to 34 years	533	55.5	785	49.3
35 years or more	170	17.7	214	13.4
Missing	*3*	*0.3*	*2*	*0.1*
Education				
Less than HS	313	32.6	570	35.8
HS diploma	434	45.2	690	43.3
College or more	209	21.8	327	20.5
Missing	*4*	*0.4*	*6*	*0.4*
Race/ethnicity				
Non-Hispanic White	81	8.4	113	7.1
Non-Hispanic Black	629	65.5	966	60.6
Hispanic	233	24.3	484	30.4
Other	15	1.6	19	1.2
Missing	*2*	*0.2*	*11*	*0.7*
First CD4 in pregnancy				
Less than 250 cells/mm^3	187	19.5	293	18.4
250 to 500 cells/mm^3	374	39.0	676	42.4
More than 500 cells/mm^3	379	39.5	591	37.1
Missing	*20*	*2.1*	*33*	*2.1*
First viral RNA in pregnancy				
Less than 400 copies/mL	503	52.4	469	29.4
400 to 10,000 copies/mL	224	23.3	601	37.7
More than 10,000 copies/mL	223	23.2	500	31.4
Missing	*10*	*1.0*	*23*	*1.4*
Diagnosed before pregnancy				
Yes	834	86.9	1,112	69.8
No	124	12.9	478	30.0
Missing	2	*0.2*	*3*	*0.2*
Timing of regimen initiation				
Before pregnancy	490	51.0	240	15.1
Trimester 1	135	14.1	177	11.1
Trimester 2/3	335	34.9	1,176	73.8
Alcohol use				
Yes	156	16.3	298	18.7
No	767	79.9	1,166	73.2

	Initial regimen during pregnancy			
	TDF/FTC/Any PI n = 960		ZDV/3TC/Any PI n = 1, 593	
	n	%	n	%
Missing	*37*	*3.9*	*129*	*8.1*
Tobacco use				
Yes	188	19.6	295	18.5
No	676	70.4	997	62.6
Missing	*96*	*10.0*	*301*	*18.9*
Illicit drug use				
Yes	115	12.0	191	12.0
No	741	77.2	1,079	67.7
Missing	*104*	*10.8*	*323*	*20.3*
Pregestational diabetes				
Yes	15	1.6	24	1.5
No	939	97.8	1,564	98.2
Missing	*6*	*0.6*	*5*	*0.3*
Hepatitis				
Yes	135	14.1	153	9.6
No	825	85.9	1,440	90.4
Sexually transmitted infection[2] during pregnancy				
Yes	338	35.2	586	36.8
No	553	57.6	849	53.3
Missing	*69*	*7.2*	*158*	*9.9*
Protease inhibitors				
+ LPV/r	128	13.3	954	59.9
+ ATV/r	539	56.1	47	3.0
+ DRV/r	164	17.1	48	3.0
+ NFV	13	1.4	497	31.2
+ Other PI	116	12.1	47	3.0

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PI, protease inhibitor; ZDV, zidovudine; 3TC, lamivudine; LPV, lopinavir; ATV, atazanavir; DRV, darunavir; NFV, nelfinavir

[1]Mothers may not be unique. Some women had multiple pregnancies under study observation.

[2]Sexually transmitted infections include syphilis, gonorrhea, chlamydia, genital herpes, or "other" sexually transmitted infections noted in the medical chart.

Supplemental Table S3. Risk of infant outcomes by initial antiretroviral regimen during pregnancy: TDF/FTC/Any PI versus ZDV/3TC/Any PI

	Initial antiretroviral regimen during pregnancy					
	TDF/FTC/Any PI			ZDV/3TC/Any PI		
Outcome	n	Risk (%)	95% CI	n	Risk (%)	95% CI
Preterm birth[1]	170	17.9	(15.4, 20.3)	311	19.7	(17.8, 21.7)
Very preterm birth[2]	47	4.9	(3.6, 6.3)	67	4.3	(3.3, 5.3)
Low birth weight[3]	167	17.7	(15.2, 20.1)	275	17.8	(15.9, 19.7)
Very low birth weight[4]	17	1.8	(1.0, 2.6)	32	2.1	(1.4, 2.8)
Adverse outcome[5]	237	24.9	(22.2, 27.7)	426	27.3	(25.1, 29.5)
Severe adverse outome[6]	51	5.4	(3.9, 6.8)	83	5.3	(4.2, 6.5)

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PI, protease inhibitor; ZDV, zidovudine; 3TC, lamivudine; CI, confidence interval

[1]Preterm birth defined as <37 weeks gestational age

[2]Very preterm birth defined as <34 weeks gestational age

[3]Low birth weight defined as <2,500g

[4]Very low birth weight defined as <1,500g

[5]Adverse outcome defined as preterm birth, low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

[6]Serious adverse outcome defined as very preterm birth, very low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

Supplemental Table S4. Risk ratios for infant outcomes: TDF/FTC/Any PI versus ZDV/3TC/Any PI

	Crude		Adjusted[1]	
	RR	95% CI	RR	95% CI
Preterm birth[2]	0.90	(0.76, 1.07)	0.77	(0.62, 0.96)
Very preterm birth[3]	1.16	(0.81, 1.67)	0.99	(0.66, 1.48)
Low birth weight[4]	0.86	(0.68, 1.09)	0.90	(0.73, 1.11)
Very low birth weight[5]	0.87	(0.49, 1.56)	0.69	(0.36, 1.31)
Adverse outcome[6]	0.87	(0.72, 1.05)	0.84	(0.71, 1.00)
Severe adverse outcome[7]	1.01	(0.72, 1.41)	0.90	(0.62, 1.31)

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PI, protease inhibitor; ZDV, zidovudine; 3TC, lamivudine; RR, risk ratio; CI, confidence interval

[1]Modified Poisson models adjusted for race/ethnicity, smoking, diabetes, sexually transmitted infection, and timing of antiretroviral therapy initiation

[2]Preterm birth defined as <37 weeks gestational age

[3]Very preterm birth defined as <34 weeks gestational age

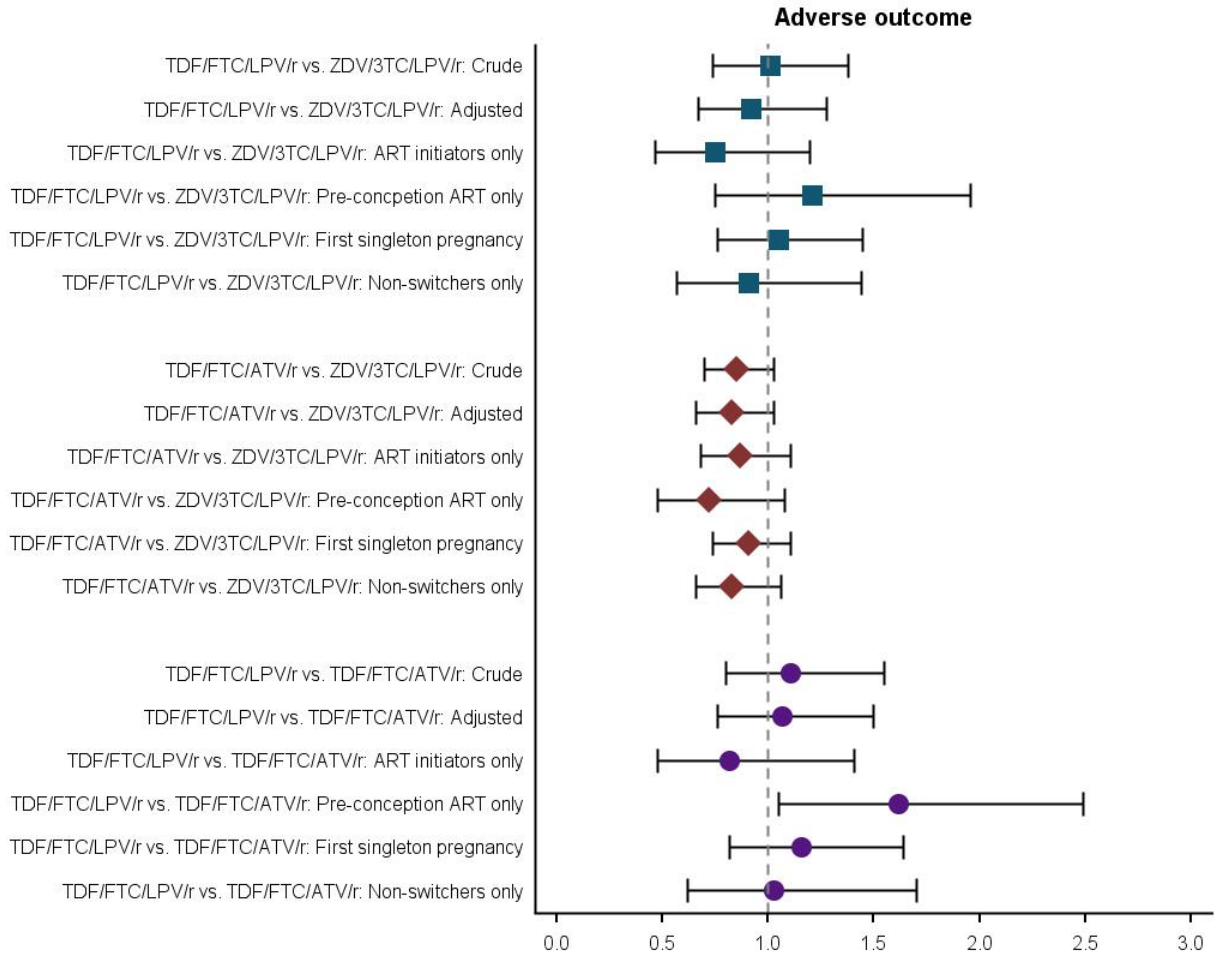
[4]Low birth weight defined as <2,500g

[5]Very low birth weight defined as <1,500g

[6]Adverse outcome defined as preterm birth, low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

[7]Serious adverse outcome defined as very preterm birth, very low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

Supplemental Figure S2. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of any adverse outcome[1]: Risk ratios and corresponding 95% confidence intervals

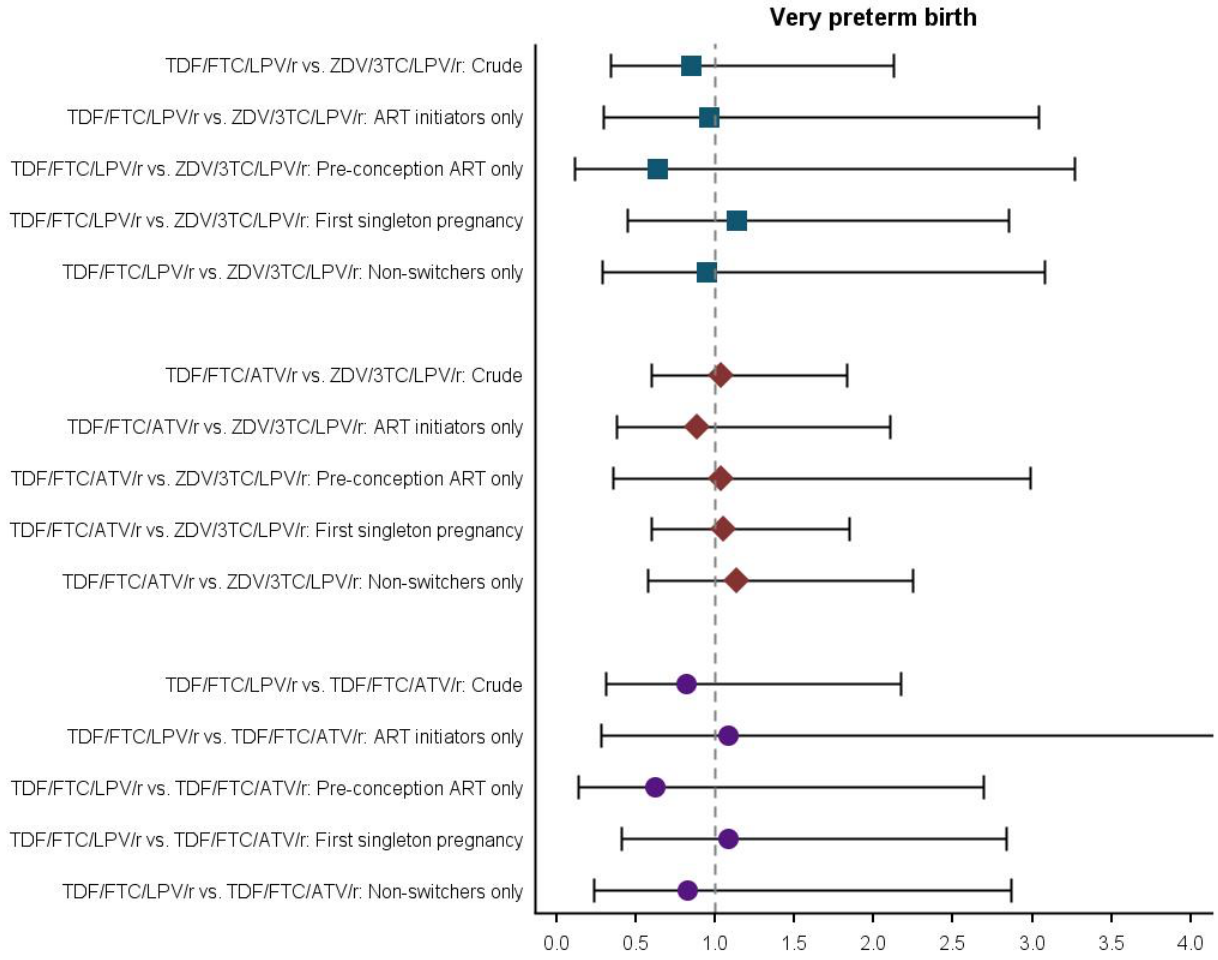


Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir

Note: "Adjusted" risk ratios obtained from log-binomial models adjusted for race/ethnicity, smoking, diabetes, sexually transmitted infection, and timing of antiretroviral therapy initiation

[1]Adverse outcome defined as preterm birth, low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

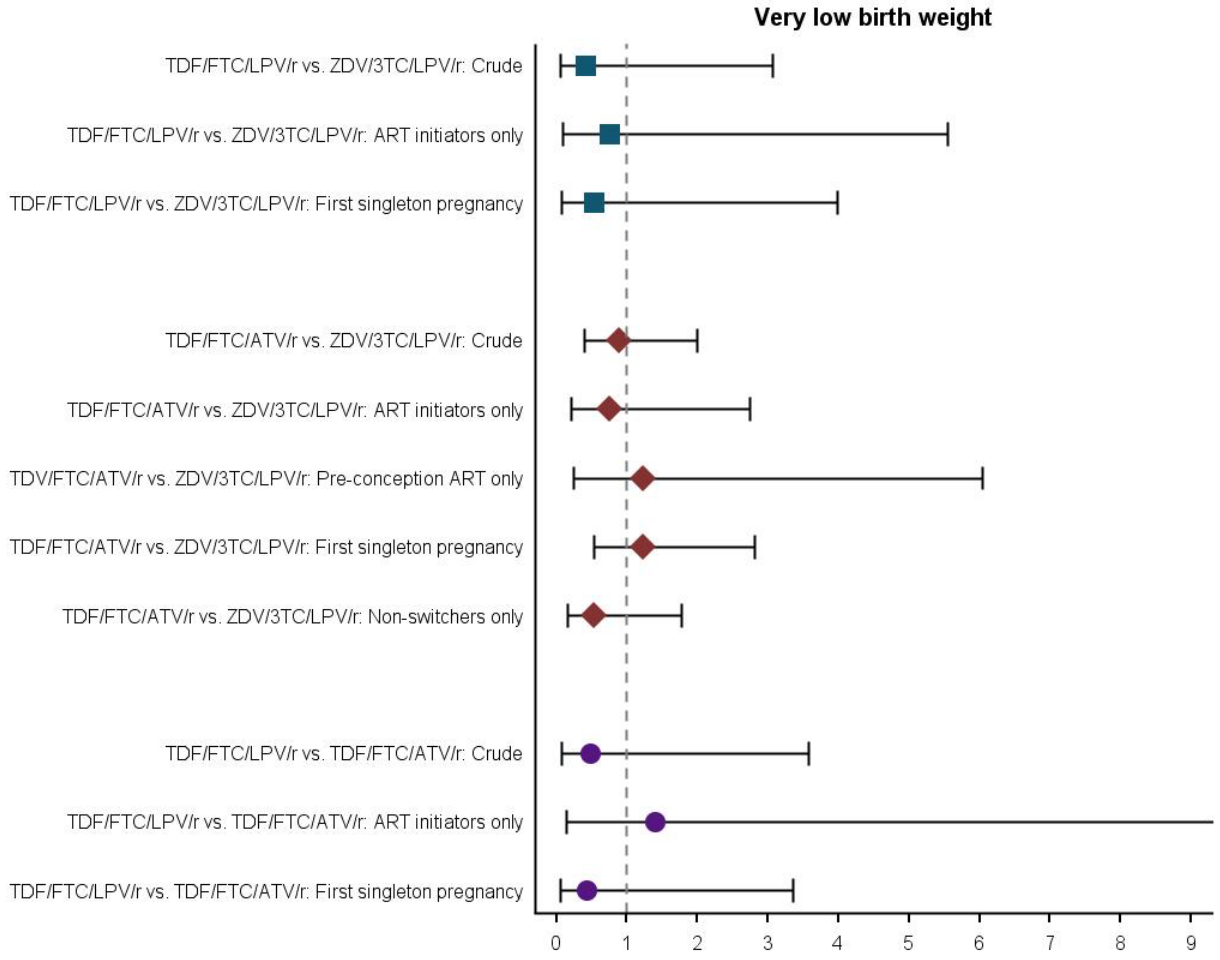
Supplemental Figure S3. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of very preterm birth[1]: Risk ratios and corresponding 95% confidence intervals



Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir

[1]Very preterm birth defined as <34 weeks gestational age

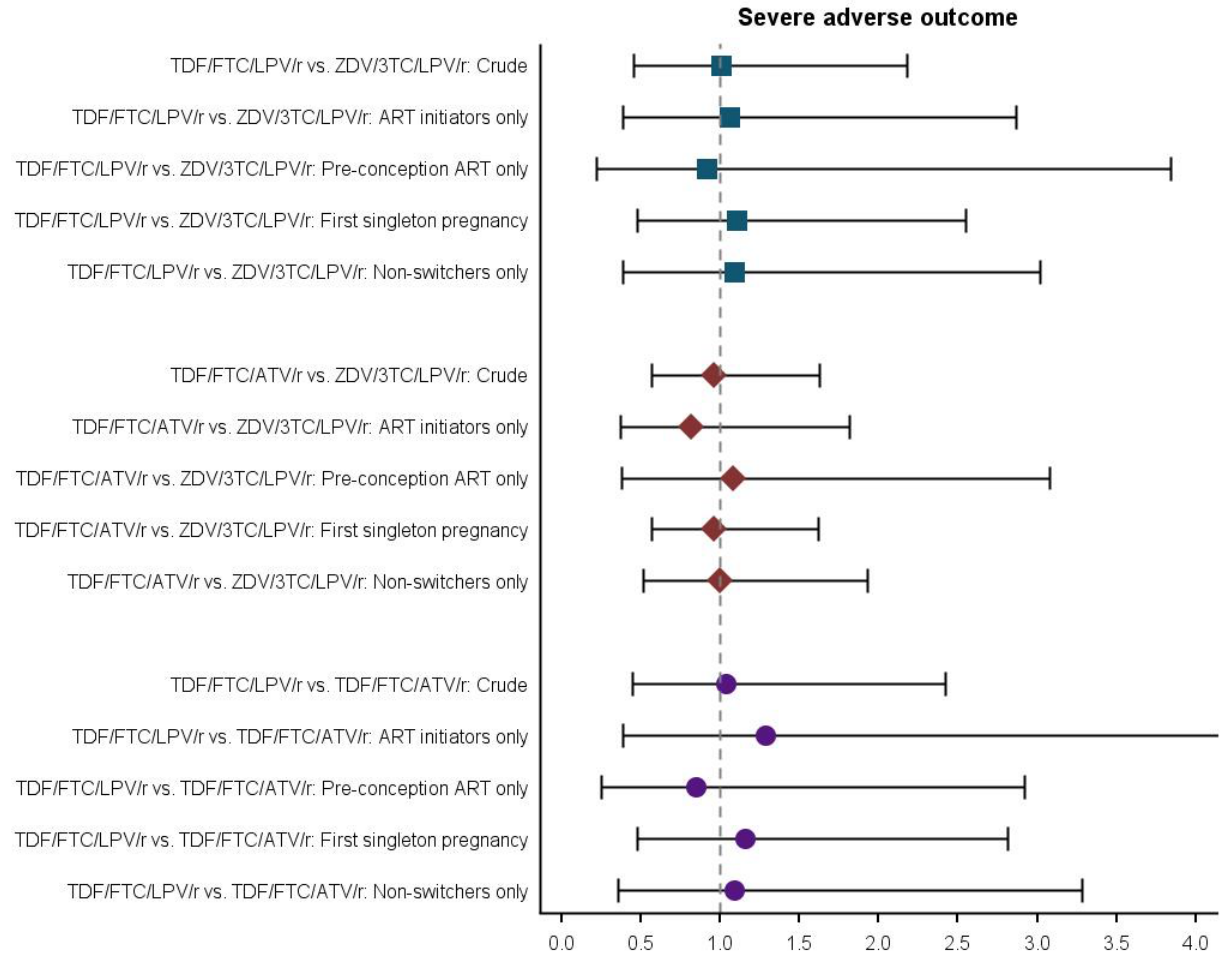
Supplemental Figure S4. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of very low birth weight[1]: Risk ratios and corresponding 95% confidence intervals



Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopanivir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir

[1]Very low birth weight defined as <1,500g

Supplemental Figure S5. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of serious adverse outcome[1]: Risk ratios and corresponding 95% confidence intervals



Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir

[1]Serious adverse outcome defined as very preterm birth, very low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

Supplemental Table S5. Regimens switched to after initial regimen of TDF/FTC/LPV/r

	n	%
TDF/FTC/LPV/r to TDF/FTC/ATV/r	2	3.3
TDF/FTC/LPV/r to TDF/FTC + other drug(s)	17	27.9
TDF/FTC/LPV/r to ZDV/3TC/LPV/r	20	32.8
TDF/FTC/LPV/r to ZDV/3TC + other drug(s)	3	4.9
TDF/FTC/LPV/r to other cART regimen	12	19.7
TDF/FTC/LPV/r to mono- or dual-therapy	7	11.5

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; ATV/r, ritonavir-boosted atazanavir; ZDV, zidovudine; 3TC, lamivudine; cART, combination antiretroviral therapy

Supplemental Table S6. Regimens switched to after initial regimen of TDF/FTC/ATV/r

	n	%
TDF/FTC/ATV/r to TDF/FTC/LPV/r	1	0.6
TDF/FTC/ATV/r to TDF/FTC + other drug(s)	104	60.8
TDF/FTC/ATV/r to ZDV/3TC/LPV/r	14	8.2
TDF/FTC/ATV/r to ZDV/3TC + other drug(s)	12	7.0
TDF/FTC/ATV/r to other cART regimen	36	21.1
TDF/FTC/ATV/r to mono- or dual-therapy	4	2.3

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; ATV/r, ritonavir-boosted atazanavir; ZDV, zidovudine; 3TC, lamivudine; cART, combination antiretroviral therapy

Supplemental Table S7. Regimens switched to after initial regimen of ZDV/3TC/LPV/r

	n	%
ZDV/3TC/LPV/r to TDF/FTC/LPV/r	34	10.0
ZDV/3TC/LPV/r to TDF/FTC/ATV/r	45	13.2
ZDV/3TC/LPV/r to TDF/FTC + other drug(s)	63	18.5
ZDV/3TC/LPV/r to ZDV/3TC + other drug(s)	142	41.8
ZDV/3TC/LPV/r to other cART regimen	27	7.9
ZDV/3TC/LPV/r to mono- or dual-therapy	29	8.5

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; ATV/r, ritonavir-boosted atazanavir; ZDV, zidovudine; 3TC, lamivudine; cART, combination antiretroviral therapy

Quantification of potential selection bias from loss to follow-up

Background:
There were 160 women who enrolled in either SMARTT or P1025 during their pregnancy who were lost to follow-up before delivering. Their birth outcome information is unknown. The exposure classification for many of these women is also unclear because the estimated date of conception was not recorded, making it difficult to determine the first regimen taken during pregnancy.

Methods:
If the loss to follow-up in our study is related to both antiretroviral regimens received and the pregnancy outcome, there is a potential for selection bias. We used methods described by Greenland [1] and Lash, Fink, and Fox [2] to quantify the potential impact of selection bias caused by the 160 women lost to follow-up. This sensitivity analysis was modeled after one by Huybrechts et al [3] that examined the potential impact of selective terminations on their study of first-trimester SSRI exposure and risk of cardiac malformations.

Below, we present the sensitivity analysis for the comparison of TDF/FTC/LPV/r to ZDV/3TC/LPV/r for the outcome of any adverse event.

To perform the sensitivity analyses, we examine how a range of plausible values for selection probabilities (i.e., the probability of not being lost to follow-up) would impact our estimates.

Observed

	Any adverse event	No adverse event
TDF/FTC/LPV/r	A	B
ZDV/3TC/LPV/r	C	D

Corrected

	Any adverse event	No adverse event
TDF/FTC/LPV/r	$A_{correct} = A/S_{11}$	$B_{correct} = B/S_{10}$
ZDV/3TC/LPV/r	$C_{correct} = C/S_{01}$	$D_{correct} = D/S_{00}$

A is the observed number of deliveries with adverse events among women receiving TDF/FTC/LPV/r.
B is the observed number of deliveries without adverse events among women receiving TDF/FTC/LPV/r.
C is the observed number of deliveries with adverse events among women receiving ZDV/3TC/LPV/r.
D is the observed number of deliveries without adverse events among women receiving ZDV/3TC/LPV/r.

S_{00} is the probability of not being lost to follow-up for women in the ZDV/3TC/LPV/r exposure group who did not have an adverse event.
S_{01} is the probability of not being lost to follow-up for women in the ZDV/3TC/LPV/r exposure group who had an adverse event.
S_{10} is the probability of not being lost to follow-up for women in the TDF/FTC/LPV/r exposure group who did not have an adverse event.
S_{11} is the probability of not being lost to follow-up for women in the TDF/FTC/LPV/r exposure group who had an adverse event.

$A_{correct}$ is the corrected number of deliveries with adverse events among women receiving TDF/FTC/LPV/r.
$B_{correct}$ is the corrected number of deliveries without adverse events among women receiving TDF/FTC/LPV/r.
$C_{correct}$ is the corrected number of deliveries with adverse events among women receiving ZDV/3TC/LPV/r.
$D_{correct}$ is the corrected number of deliveries without adverse events among women receiving ZDV/3TC/LPV/r.

RR_{obs} is the observed risk ratio.
$RR_{correct}$ is the corrected risk ratio.

$RR_{obs} = [A/(A+B)] / [C/(C+D)]$
$RR_{correct} = [(A_{correct} /(A_{correct} + B_{correct})] / [C_{correct} /(C_{correct} + D_{correct})]$

Selection probabilities:

Below is the observed contingency table for the comparison of TDF/FTC/LPV/r to ZDV/3TC/LPV/r for the outcome of any adverse event:

Observed

	Adverse event	No adverse event
TDF/FTC/LPV/r	A = 36	B = 92
ZDV/3TC/LPV/r	C = 256	D = 684

Because there were substantially fewer women in the TDF/FTC/LPV/r group compared to the ZDV/3TC/LPV/r group, it has greater potential to be influenced by the 160 women who were lost to follow-up. Therefore, to be more conservative in our conclusions about the sensitivity of our findings to selection bias, we focused the impact of differential loss to follow-up on the TDF/FTC/LPV/r exposure group.

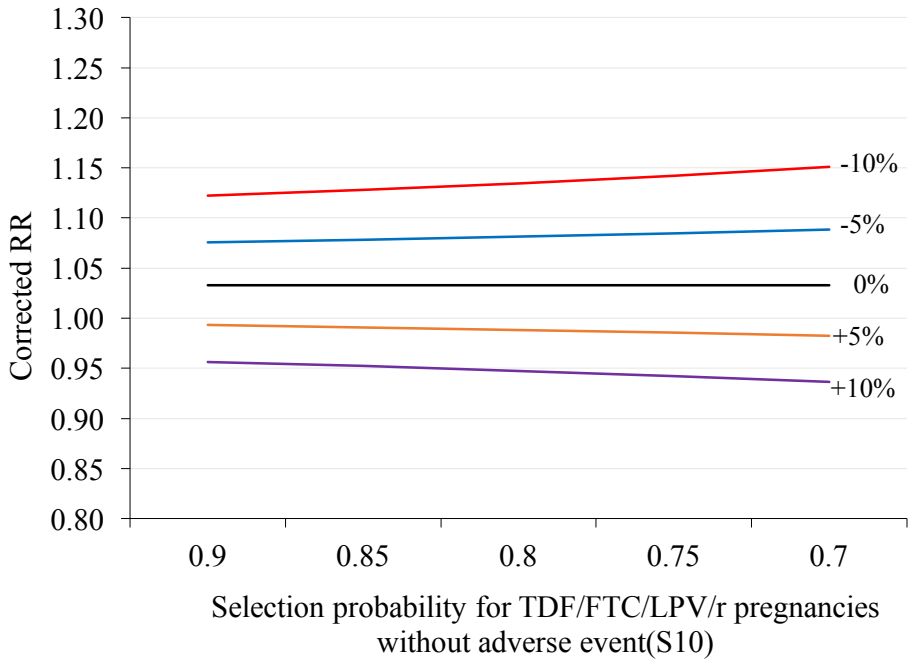
In our study, we found that 3% of pregnancies were lost to follow-up before delivery. For these sensitivity analyses, we assumed that this average probability of being lost to follow up applied to women with ZDV/3TC/LPV/r exposure, whether or not they had an adverse event (S_{00} = 0.97 [21.2 additional pregnancies]; S_{01} = 0.97 [7.9 additional pregnancies]).

The S_{10} and S_{11} were tested across a range of values, taking care to ensure that the number of additional cases implied by the selection probabilities never exceeded the 160 participants actually lost to follow-up. The scenarios examined are summarized in the table below:

TDF/FTC/LPV/r		ZDV/3TC/LPV/r	
No adverse event (S_{10})	Adverse event (S_{11})	No adverse event (S_{00})	Adverse event (S_{01})
70% - 90%	S_{10} + 10% S_{10} + 5% S_{10} + 0% S_{10} - 5% S_{10} - 10%	97%	97%

Results:

The figure below displays the corrected risk ratios for the scenarios described above. Even under the most extreme scenarios, the risk ratio never exceeds 1.2 or drops below 0.9.



It should be noted that some of the selection probabilities examined are improbably extreme. For instance, the scenario where S_{10} = 70% and S_{11} = 60% implies that approximately 63 of the 160 women lost to follow-up (40%) would have been in the TDF/FTC/LPV/r exposure group, despite a 2.8% prevalence of TDF/FTC/LPV/r in the primary analysis.

While the results displayed here pertain to the comparison of TDF/FTC/LPV/r and ZDV/3TC/LPV/r for the outcome of adverse events, sensitivity analyses for other outcomes and exposure comparisons yielded similar results.

Conclusions:
We find that the exclusion of the 160 women lost to follow-up prior to delivery in our primary analyses is unlikely to result in large selection bias in either direction. Even under rather extreme scenarios, our findings appear to be robust to bias from this source.

Works cited:
[1] Greenland S. Basic methods for sensitivity analysis of bias. *Int J Epidemiol*. 1996;25(6):1107-16.
[2] Lash TL, Fink AK, Fox MP. Selection bias. In: *Applying Quantitative Bias Analysis to Epidemiologic Data*. New York: Springer; 2009.
[3] Huybrechts KF, Palmsten K, Avorn J et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014;370:2397-407.