Supplementary Appendix

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

Supplement to: Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med 2012;366:2368-79.

Appendix- Table of Contents:

Table of Contents:	p. 1
Table 1 complete: Demographic and baseline characteristics by study treatment arm for infants and mothers	pp. 2-4
Table 3 complete: Relationship of intrapartum HIV-1 infection with maternal demographic and clinical characteristics	pp. 5-6
Appendix 1: Flow diagram of enrollments	pp. 7-8
Appendix 2: Mortality Table	pp. 9-11
Appendix 3: Grade 2 or higher laboratory abnormalities overall and by study arm	p. 12
Appendix 4: SAE by System Organ Class and Study Treatment Arm	pp.13-14
Acknowledgments:	p. 15

Table 1. Demographic and baseline characteristics by study treatment arm for infants and mothers.

	Overall (N=1684) n (%)	ZDV (N=566) n (%)	ZDV+NPV (N=562) n (%)	ZDV+3TC/NFV (N=556) n (%)	p value[1]
Study treatment arm [2]					
ZDV	566 (33.61)				
ZDV+NVP	562 (33.37)				
ZDV+3TC+NFV	556 (33.02)				
Median time of study ARV delivery[3] (Range)		29 hours (2- 48)	28 hours (3- 48)	29 hours (3- 48)	
Inadvertent enrollments					
Mother HIV- on confirmatory testing	51/1735 (2.9)	15/581 (2.6)	18/580 (3.1)	18/574 (3.1)	0.8346
Unknown HIV status (deceased or discontinued before primary endpoint)	97 (5.8)	31 (5.5)	33 (5.9)	33 (5.9)	0.9600
Maternal age (years)					
Median (min-max)	26 (13-47)	26 (13-43)	26 (14-47)	26 (14-45)	0.8570
13-24	658 (39.54)	218 (38.72)	207 (37.16)	233 (42.83)	0.1510
25-29	470 (28.25)	166 (29.48)	171 (30.70)	133 (24.45)	
30 and older	536 (32.21)	179 (31.79)	179 (32.14)	178 (32.72)	
Race/Ethnicity					
Black	819 (49.22)	273 (48.49)	283 (50.81)	263 (48.35)	0.4955
Mixed/Mulatto	451 (27.10)	145 (25.75)	147 (26.39)	159 (29.23)	
White/Others	394 (23.68)	145 (25.75)	127 (22.80)	122 (22.43)	
Alcohol use frequency					
≥1/week	279 (16.93)	93 (16.70)	94 (17.03)	92 (17.07)	0.0531
Never	1058 (64.20)	378 (67.86)	358 (64.86)	322 (59.74)	
≥5 alcoholic drinks/day	235 (14.33)	73 (13.11)	80 (14.57)	82 (15.36)	0.5588
Illegal Substance use in pregnancy					
Yes	147 (8.88)	43 (7.68)	62 (11.21)	42 (7.75)	0.0617
Tobacco use frequency					
>10 cig/day	167 (10.11)	58 (10.38)	57 (10.31)	52 (9.63)	0.0681
6-10 cig/day	129 (7.81)	30 (5.37)	57 (10.31)	42 (7.78)	
≤5 cig/day	237 (14.35)	79 (14.13)	86 (15.55)	72 (13.33)	
Never	1119 (67.74)	392 (70.13)	353 (63.83)	374 (69.26)	
Viral load (copies/mL)					
>100,000	226 (13.65)	71 (12.70)	82 (14.80)	73 (13.44)	0.4887

10,000-100,000	726 (43.84)	254 (45.44)	247 (44.58)	225 (41.44)	
≤10,000	704 (42.51)	234 (41.86)	225 (40.61)	245 (45.12)	
Log_{10} viral load[4] Median (min-max)	4.17 (1.65-6.78)	4.17 (1.65-6.78)	4.20 (1.84-6.36)	4.13 (1.86-6.49)	0.2936
CD4 counts (cells/mm^3)					
<200	191 (11.70)	67 (12.23)	55 (10.07)	69 (12.80)	0.3339
200 to 350	358 (21.92)	115 (20.99)	137 (25.09)	106 (19.67)	
351 to 500	358 (21.92)	115 (20.99)	120 (21.98)	123 (22.82)	
>500	726 (44.46)	251 (45.80)	234 (42.86)	241 (44.71)	
CD4 count Median (min-max)	459(12-2678)	471(31-1748)	447(12-2678)	458 (23-2556)	0.8327
Attended prenatal care	1038 (62.61)	343 (61.25)	341 (61.44)	354 (65.19)	0.3144
At least 3 prenatal care visits	790 (47.48)	263 (47.05)	251 (45.39)	276 (50.00)	0.2986
ZDV during labor	682 (40.99)	227 (40.32)	231 (41.47)	224 (41.18)	0.9204
Maternal Syphilis	151 (9.29)	49 (8.93)	56 (10.28)	46 (8.65)	0.6138
Timing of Maternal diagnosis					
Labor and delivery via HIV-1 rapid testing	1230 (73.04)	416 (33.82)	415 (33.74)	399 (32.44)	0.7028
Prior to labor with 2 + serology results	454 (26.96)	150 (33.04)	147 (32.28)	157 (34.58)	
Region					
Americas	1198 (72)	407 (72.29)	399 (71.63)	392 (72.06)	0.9696
South Africa	466 (28)	156 (27.71)	158 (28.37)	152 (27.94)	
Type of delivery					
Cesarean before rupture	395 (23.47)	132 (23.32)	131 (23.35)	132 (23.74)	0.9831
Vaginal + cesarean after rupture	1288 (76.53)	434 (76.68)	430 (76.65)	424 (76.26)	
Gestational age					
Median (min-max)	39 (32-42)	39 (32-42)	39 (32-42)	39 (32-42)	0.7630
37 or more	1509 (89.61)	510 (90.11)	509 (90.57)	490 (88.13)	0.3654
Breastfed at birth only					
Yes	155 (9.35)	47 (8.39)	54 (9.75)	54 (9.94)	
No	1502 (90.65)	513 (91.61)	500 (90.25)	489 (90.06)	0.6267
Breastfed at any visit					
Yes	178 (10.74)	54 (9.64)	64 (11.55)	60 (11.05)	

No	1479 (89.26)	506 (90.36)	490 (88.45)	483 (88.95)	0.5659
Apgar scores					
Median (min-max)	9 (1-10)	9 (1-10)	9 (1-10)	9 (6-10)	0.7311
7-10	1482 (88.00)	503 (88.87)	495 (88.08)	484 (87.05)	0.8716
Not done	191 (11.34)	59 (10.42)	63 (11.21)	69 (12.41)	
Median birth weight (gram) (min-max)	3000 (1510-4850)	3020.00 (1510-4385)	3000 (1595-4850)	2985 (1570-4300)	0.8058
Time of membrane rupture to infant delivery (hours)					
Median (min-max)	0.08 (1-114.92)	0.09 (0-60.57)	0.08 (0-114.92)	0.08 (0-105.42)	0.1421

[1] Pearson chi-square tests were used to calculate p-values.

[2] N=1684 is the total number of infants. Due to 20 pairs of twin babies, the total number of mothers was 1664.

[3]Non-study standard of care ZDV initiated before study regimen in 2/3 of subjects.

[4]Viral load $\leq$ 400 copies/mL was recoded as 400 over square root of two.

Table 3. Relationship of intrapartum HIV-1 infection with maternal demographic and clinical characteristics

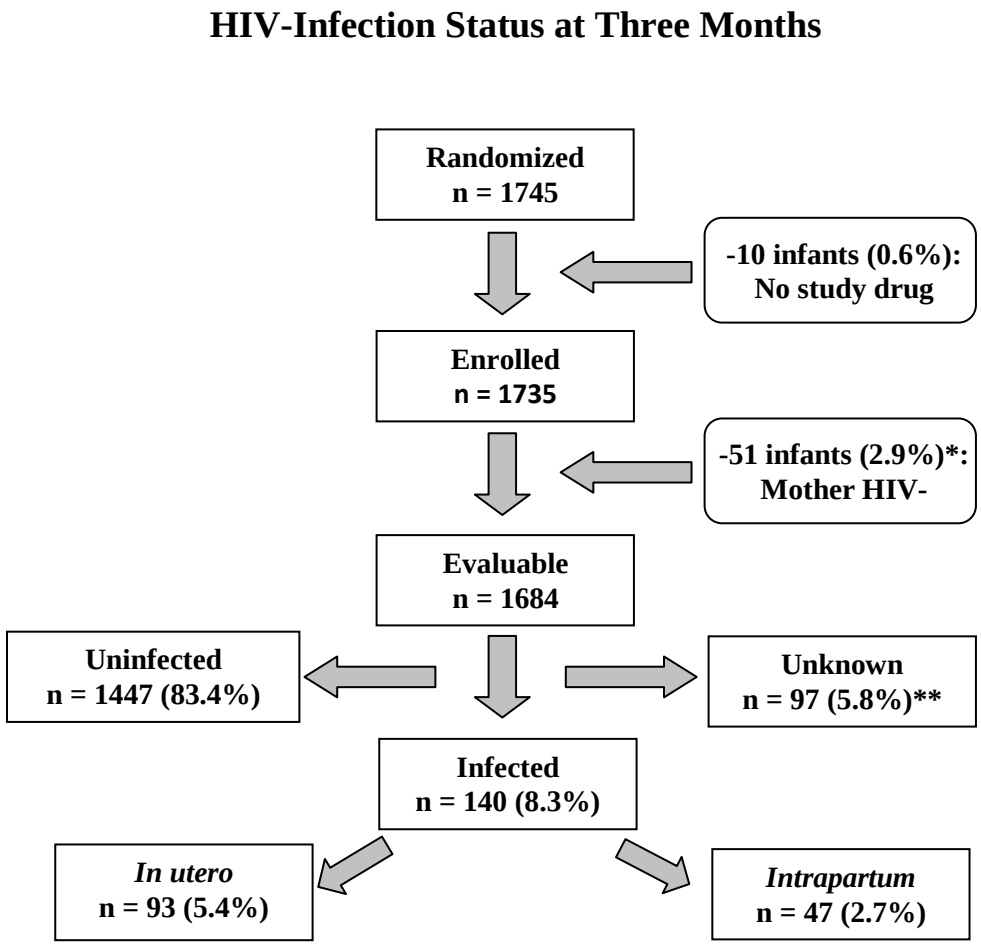
	Infected	Uninfected	Unadjusted		Adjusted [1]	
	n (%)	n (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Study Treatment Arm						
ZDV+3TC/NFV	12 (2.27)	516 (97.73)	0.49 (0.24 - 0.99)	0.0465	0.50 (0.24-1.01)	0.0539
ZDV+NVP	11 (2.06)	523 (97.94)	0.44 (0.21 - 0.91)	0.0273	0.39 (0.19-0.82)	0.0128
ZDV	24 (4.54)	505 (95.46)	1.00		1.00	
Age (years)						
13 to 24	20 (3.19)	607 (96.81)	0.85 (0.45 - 1.60)	0.6087		
25 to 29	8 (1.83)	429 (98.17)	0.48 (0.21 - 1.11)	0.0844		
30 and older	19 (3.75)	488 (96.25)	1.00			
Race/ethnicity						
Black	29 (3.74)	747 (96.26)	1.56 (0.73 - 3.32)	0.2524		
Mixed/mulatto	9 (2.12)	416 (97.88)	0.87 (0.34 - 2.21)	0.7662		
White and other	9 (2.43)	361 (97.57)	1.00			
Race/ethnicity						
Black/ Mixed/mulatto	38 (3.16)	1163 (96.84)	1.31 (0.63 - 2.74)	0.4717		
White and other	9 (2.43)	361 (97.57)	1.00			
Alcohol use frequency						
≥1/week	12 (4.62)	248 (95.38)	1.62 (0.82 - 3.23)	0.1669		
>1/month, <1/week	3 (2.70)	108 (97.30)	0.93 (0.28 - 3.11)	0.9088		
≤1/month	3 (1.63)	181 (98.37)	0.56 (0.17 - 1.84)	0.3376		
Never	29 (2.89)	973 (97.11)	1.00			
≥5 or more alcoholic drinks/day						
Yes	9 (4.05)	213 (95.95)	1.44 (0.69 - 3.02)	0.3368		
No	38 (2.85)	1293 (97.15)	1.00			
Illegal Substance use during pregnancy						
Yes	7 (5.11)	130 (94.89)	1.87 (0.82 - 4.25)	0.1374	2.51 (1.08-5.86)	0.0328
Tobacco use frequency						
>10 cig/day	5 (3.18)	152 (96.82)	1.16 (0.44 - 3.05)	0.7609		
6-10 cig/day	1 (0.82)	121 (99.18)	0.29 (0.04 - 2.16)	0.2280		
≤5 cig/day	12 (5.26)	216 (94.74)	1.96 (0.99 - 3.91)	0.0551		
Never	29 (2.75)	1024 (97.25)	1.00			
Viral load (copies/mL)						
Log_{10} Viral Load			2.16 (1.49 - 3.13)	< 0.0001	2.28 (1.56-3.35)	<0.0001
CD4+ count (cells/mm^3)			0.90 (0.81-1.01)	0.0768		

Prenatal care				
No	18 (3.04)	574 (96.96)	1.02 (0.56 - 1.86)	0.9433
Yes	29 (2.98)	945 (97.02)	1.00	
ZDV during labor				
No	29 (3.11)	902 (96.89)	1.11 (0.61 - 2.02)	0.7297
Yes	18 (2.81)	622 (97.19)	1.00	
Syphilis				
Yes	3 (2.24)	131 (97.76)	0.71 (0.22 - 2.31)	0.5662
No	44 (3.14)	1359 (96.86)	1.00	
Region				
Americas	30 (2.67)	1094 (97.33)	0.69 (0.38 - 1.27)	0.2362
South Africa	17 (3.80)	430 (96.20)	1.00	
Type of delivery				
Cesarean before rupture	7 (1.88)	366 (98.12)	0.56 (0.25 - 1.27)	0.1650
Vaginal/ Cesarean after rupture/timing unknown	40 (3.29)	1177 (96.71)	1.00	
Gestational age				
32-36 weeks	6 (3.64)	159 (96.36)	1.28 (0.53 - 3.05)	0.5851
37 weeks or more	41 (2.88)	1385 (97.12)	1.00	
Time of membrane rupture to infant delivery (hours) by strata				
<0.5	16 (2.03)	771 (97.97)	1.00	
0.5- <6	14 (3.51)	385 (96.49)	1.75 (0.85 - 3.63)	0.1308
6 - <12	4 (3.31)	117 (96.69)	1.65 (0.54 - 5.01)	0.3792
12-24	5 (5.88)	80 (94.12)	3.01 (1.07 - 8.44)	0.0360
>24	3 (7.14)	39 (92.86)	3.71 (1.04 - 13.3)	0.0439
Unknown	5 (3.18)	152 (96.82)	1.59 (0.57 - 4.39)	0.3757

1 All available demographic and clinical variables were tested for association with transmission rate. All variables that were significant at $p \leq 0.20$ we re included in the multivariable regression model. Variables that were not significant were then removed from the model. The backward elimination method was used to select the final model.

2 This model used maternal virus load and maternal CD4 cell counts as continuous variables in addition to study treatment arm and illegal substance use. CD4 count was eliminated from the final adjusted model.

Appendix 1: Flow diagram of enrollments



Randomized infants: Mothers signed consent form for study participation and infant received a study treatment assignment.

Enrolled infants: Received study drug

* There were 15/581 (2.6%) inadvertent enrollments in the ZDV group, 18/580 (3.1%) in the ZDV+NVP group, and 18/574 (3.1%) in the ZDV+3TC/NFV group. These rates were not significantly different (p = 0.8346, exact chi-square test).

** Ninety-seven infants (5.8%) had unknown HIV-1 status: 31 in the ZDV arm, 33 in the ZDV+NVP arm, 33 in the ZDV+NFV/3TC arm. Reasons for study discontinuation prior to endpoint determination included: death of infant (21), withdrawn consent (37), lost to follow-up (32), subject relocated (6), and other reasons (1). Two infants (1 in the ZDV arm, 1 in the ZDV+NVP arm) had a positive DNA test at birth but no subsequent specimens.

Appendix 2: Mortality Table

Treatment Arm	Observation No.	HIV Status	Age at Death (days)	[1]Cause of Death
ZDV	1	Infected - In Utero	123	Multi-Organ Failure
ZDV	2	Infected - In Utero	102	Pneumocystis Carinii Pneumonia
				Sepsis
ZDV	3	Infected - In Utero	145	Sepsis
ZDV	4	Infected - Intrapartum	106	Sepsis
ZDV	5	Uninfected	150	Bronchiolitis
				Encephalitis
				Pneumonia
ZDV	6	Unknown	81	Sepsis
ZDV	7	Unknown	76	Diarrhea
ZDV	8	Unknown	97	Gastroenteritis
ZDV	9	Unknown	34	Pneumonia Aspiration
ZDV	10	Unknown	15	Pneumonia Aspiration
ZDV	11	Unknown	26	Sudden Infant Death Syndrome
ZDV+NVP	1	Infected - In Utero	151	Pneumonia
ZDV+NVP	2	Infected - In Utero	44	Respiratory Failure
ZDV+NVP	3	Infected - In Utero	83	Respiratory Tract Infection
ZDV+NVP	4	Infected - In Utero	121	Sudden Infant Death Syndrome
ZDV+NVP	5	Infected - Intrapartum	152	Respiratory Distress

Treatment Arm	Observation No.	HIV Status	Age at Death (days)	[1]Cause of Death
ZDV+NVP	6	Uninfected	131	Sudden Infant Death Syndrome
ZDV+NVP	7	Uninfected	139	Gastroenteritis
ZDV+NVP	8	Uninfected	103	Vomiting
ZDV+NVP	9	Uninfected	196	Bronchopneumonia
ZDV+NVP	10	Unknown	53	Pneumonia Aspiration
ZDV+NVP	11	Unknown	12	Respiratory Failure
ZDV+NVP	12	Unknown	36	Septic Shock
ZDV+NVP	13	Unknown	9	Renal Failure
ZDV+NVP	14	Unknown	80	Pulmonary Tuberculosis
ZDV+NVP	15	Unknown	26	Respiratory Tract Infection
ZDV+NFV/3TC	1	Infected - In Utero	175	Anemia
				Pneumonia
				Sepsis
				Thrombocytopenia
ZDV+NFV/3TC	2	Infected - In Utero	95	Asphyxia
ZDV+NFV/3TC	3	Infected - In Utero	95	Pneumonia
ZDV+NFV/3TC	4	Infected - In Utero	141	Dyspnea
ZDV+NFV/3TC	5	Infected - In Utero	75	Sudden Infant Death Syndrome
ZDV+NFV/3TC	6	Infected - In Utero	60	Diarrhea
				Vomiting

Treatment Arm	Observation No.	HIV Status	Age at Death (days)	[1]Cause of Death
ZDV+NFV/3TC	7	Infected - In Utero	116	Diarrhea
ZDV+NFV/3TC	8	Uninfected	149	Pneumonia
ZDV+NFV/3TC	9	Unknown	23	Sepsis
ZDV+NFV/3TC	10	Unknown	6	Ileus
				Meningitis
				Sepsis Neonatal
ZDV+NFV/3TC	11	Unknown	48	Sudden Infant Death Syndrome
ZDV+NFV/3TC	12	Unknown	4	Hematochezia
ZDV+NFV/3TC	13	Unknown	10	Sudden Infant Death Syndrome
ZDV+NFV/3TC	14	Unknown	26	Sepsis
ZDV+NFV/3TC	15	Unknown	130	Sudden Infant Death Syndrome
ZDV+NFV/3TC	16	Unknown	1	Congenital Syphilis
ZDV+NFV/3TC	17	Unknown	81	Sudden Infant Death Syndrome

[1]Infants could have more than one cause of death.

Appendix 3: All Grade 2 or higher laboratory abnormalities overall and by study arm

	Overall N= 1684	ZDV N= 566	ZDV + NVP N= 562	ZDV + 3TC/NFV N= 556	*p-value*[2]
	No. Events (No. Subjects)	No. Events (No. Subjects)	No. Events (No. Subjects)	No. Events (No. Subjects)	
Neutropenia	407 (330)	116 (93)	109 (84)	182 (153)	< 0.0001
Alanine Aminotransferase (ALT) increase	40 (34)	15 (13)	16 (13)	9 (8)	0.49
Aspartate Aminotransferase (AST) increase	46 (43)	20 (18)	11 (11)	15 (14)	0.43
Anemia	822 (432)	294 (153)	237 (132)	291 (147)	0.35
Thrombocytopenia[1]	33 (26)	11 (9)	9 (7)	13 (10)	0.75
Total	1348 (865)	456 (286)	382 (247)	510 (332)	

[1] Thrombocytopenia values of 75,000 or less are included in the table.
[2]Chi square tests were used to calculate p-values.

Appendix 4: All SAE by System Organ Class and Study Treatment Arm

	Overall (infants enrolled=1684)		ZDV (infants enrolled=566)		ZDV + NVP (infants enrolled=562)		ZDV + 3TC + NFV (infants enrolled=556)		
Serious Adverse Event By System Organ Class	Infants[1]	Events	Infants[1]	Events	Infants[1]	Events	Infants[1]	Events	p-value[2]
Blood and lymphatic system disorders	255	310	86	95	59	76	110	139	0.0001
Cardiac disorders	10	11	2	2	4	5	4	4	0.6776
Congenital, familial and genetic disorders	167	177	53	56	62	65	52	56	0.5559
Eye disorders	1	1	0	0	1	1	0	0	0.6639
Gastrointestinal disorders	25	29	7	8	5	5	13	16	0.1126
General disorders and administration site conditions	22	22	8	8	8	8	6	6	0.8467
Hepatobiliary disorders	18	19	11	12	4	4	3	3	0.0440
Infections and infestations	257	356	82	120	88	122	87	114	0.8209
Injury, poisoning and procedural complications	6	6	0	0	3	3	3	3	0.2028
Investigations	46	73	20	31	12	19	14	23	0.3299
Metabolism and nutrition disorders	36	50	13	18	12	16	11	16	0.9343
Neoplasms benign, malignant and unspecified (includes cysts & polyps)	1	1	0	0	0	0	1	1	0.3302
Nervous system disorders	11	13	5	6	4	5	2	2	0.6462
Pregnancy, puerperium and perinatal conditions	52	55	18	18	10	12	24	25	0.0489
Renal and urinary disorders	3	3	1	1	1	1	1	1	1.0000
Respiratory, thoracic and mediastinal disorders	30	34	8	10	14	15	8	9	0.2969
Skin and subcutaneous tissue disorders	2	2	0	0	1	1	1	1	0.5535
Social circumstances	50	50	12	12	13	13	25	25	0.0341
Surgical and medical procedures	1	1	0	0	1	1	0	0	0.6639
Vascular disorders	3	3	1	1	0	0	2	2	0.3298

	Overall		ZDV		ZDV + NVP		ZDV + 3TC + NFV		
	(infants enrolled=1684)		(infants enrolled=566)		(infants enrolled=562)		(infants enrolled=556)		
Serious Adverse Event By System Organ Class	Infants[1]	Events	Infants[1]	Events	Infants[1]	Events	Infants[1]	Events	p-value[2]
Total	675 (40%)	1216	219 (38.7%)	398	208 (37.0%)	372	248 (44.6%)	446	

[1] For a specific system organ class, the 'infants' column gives the number of infants with SAEs corresponding to that term. In the 'total' row, the 'infants' column gives the number of infants with one or more SAEs of any type. Since an infant may have more than one type of SAE, the entries in the 'infants' column for the system organ classes do not sum to the number with one or more SAEs.

[2] P-value is from the Chi square test comparing the difference in number of subjects with at least one SAE among three treatment arms.

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