Supplementary Appendix

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

Supplement to: Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. N Engl J Med 2010;362:2271-81.

Supplementary Appendix

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

Maternal Antiretrovirals or Infant Nevirapine to Reduce HIV-1 Transmission

Methods Section:

The Malawi Global Fund Program did not implement antenatal zidovudine in women with CD4 lymphocyte counts > 250 cells per cubic millimeter until after our study enrollment had ceased in January 2008 (and then at only one site). Women were counseled on the benefits and risks of breastfeeding, and each received a family maize supplement (2 kg/week). Both women and infants received recommended vaccines and treatment for intercurrent infections. Beginning December 1, 2005, trimethoprim-sulfamethoxazole was given as prophylaxis to all mothers after the first trimester with CD4 <500 cells per cubic millimeter (480 mg twice daily), and to all infants older than 6 weeks (240 mg once daily). Mothers who developed AIDS-defining conditions or CD4 <250 cells per cubic millimeter were immediately referred for treatment. Mother-infant pairs lost to follow-up prior to 28 weeks were traced by a team of community nurses to determine vital and HIV status. Enrollment began in April 2004, and the last 28-week visit was in September 2009.

Both labs (the University of North Carolina at Chapel Hill Retrovirology Laboratory and the UNC Project Laboratory in Lilongwe, Malawi) are certified as proficient in HIV DNA and RNA testing by the NIH Division of AIDS Virus Quality Assurance Lab.

In the mothers on antiretrovirals, stavudine was substituted for zidovudine for hematologic toxicity, and nevirapine was substituted for nelfinavir for severe rash or hepatitis. In infants receiving nevirapine prophylaxis who developed a rash and eosinophilia, lamivudine was substituted. To ensure that there were no late complications of the interventions, we

monitored toxicities for 8 weeks after the intervention was discontinued or 36 weeks postpartum.

The trial was monitored by the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB). When the DSMB recommended stopping enrollment in the control arm in March 2008, all participants in the control arm were offered the choice to receive maternal antiretrovirals, infant nevirapine, or to remain in the control arm.

Although the maternal antiretroviral regimen changed twice during the trial, this was a strategy trial examining two different types of antiretroviral prophylaxis, maternal and infant, as opposed to testing specific antiretroviral regimens. As the medications used in the maternal-regimen group changed over the course of the study from a nevirapine-based, to nelfinavir-based, to lopinavir/ritonavir-based regimen, we examined the effect on transmission and HIV-free survival by type of maternal antiretroviral regimen. As the third component of the antiretroviral regimen, 27 women received nevirapine alone, 141 women received nelfinavir alone, 662 women received lopinavir/ritonavir alone, and 19 women switched antiretroviral regimens during study participation. Additional analyses were conducted using a Cox proportional hazards model with maternal antiretroviral regimen as a time varying covariate allowing for women to switch regimens during the study. Among all infants in the maternal-regimen group, no difference was found in the risk of infant HIV-1 transmission for the different regimens ($p=0.37$).

Table 1: Medication substitution table for toxicities in mothers

Toxicity	Original Study Drug	Substitution
Grade 3 or 4 Anemia, neutropenia, thrombocytopenia	Zidovudine (ZDV) as part of Combivir (ZDV/3TC) one twice daily	Stavudine (d4T) 40 mg if body weight ≥ 60 kg and 30 mg if < 60 kg plus lamivudine (3TC) 150 mg twice daily
Grade 2B, 3, 4 Rash and grade 2, 3, or 4 ALT or clinical hepatitis Grade 2A rash with HSR	Nevirapine (NVP) 200 mg twice daily	Nelfinavir (NFV) 1250 mg twice daily

Table 2: Medication substitution table for toxicities in infants

	Infant on Nevirapine		Mother on Nevirapine	
Toxicity	**Original Drug**	**Substitution**	**Original Drug**	**Substitution**
Grade 3 or 4 Anemia, neutropenia, thrombocytopenia	NVP	3TC	ZDV/3TC/NVP	d4T/3TC/NVP
Grade 2B, 3, 4 Rash Grade 2A rash with HSR Clinical Hepatitis or Grade 2, 3, or 4 ALT	NVP	3TC	ZDV/3TC/NVP	ZDV/3TC/Nelfinavir

Table 3. Percentage reported type of breast feeding by visit

	Infant Nevirapine			Maternal Regimen			Control			P-value*
	EBF†	MBF	NBF	EBF	MBF	NBF	EBF	MBF	NBF	
12-18 wks	98.3	1.2	0.5	97.6	1.9	0.5	98.1	1.3	0.6	0.83
18-21 wks	97.3	2.1	0.6	96.1	2.1	1.8	95.8	3.3	0.9	0.20
21-24 wks	90.4	5.0	4.6	88.9	6.0	5.1	87.8	7.6	4.6	0.51
24-28 wks	9.0	23.6	67.4	7.3	24.8	67.8	5.5	27.2	67.3	0.23

* A Fisher's exact test p-value is given at each visit, indicating whether there is a difference in the probability of reporting no breastfeeding between each of the two different antiretroviral arms and the control arm.

† EBF=Exclusive breastfeeding, MBF=Mixed breastfeeding, NBF=No breastfeeding

Table 4. Serious adverse events (SAEs) other than deaths in mothers by intervention.

	Treatment								P-value	
	Maternal Regimen [n=849]		Infant Nevirapine [n=852]		Control [n=668]		Total [n=2369]		Maternal vs. Control	Infant vs. Control
SAE	N*	% of mothers with ≥ 1 SAE	N*	% mothers with ≥ 1 SAE	N*	% mothers with ≥ 1 SAE	N*	% mothers with ≥ 1 SAE		
Puerperal Sepsis	11	1.30	3	0.35	4	0.60	18	0.76	0.201	0.706
Pneumonia	6	0.71	3	0.35	4	0.60	13	0.55	1.000	0.706
Serious febrile illness	7	0.71	4	0.47	3	0.45	14	0.55	1.000	1.000
Tuberculosis	3	0.35	2	0.23	3	0.45	8	0.34	1.000	0.659
Diarrhea	4	0.35	0	0	0	0	4	0.13	0.507	-
Hepatitis, clinical	2	0.24	0	0	0	0	2	0.08	0.507	-
Rash* **	1	0.12	0	0	1	0.15	2	0.08	1.000	0.440
Malaria	2	0.24	4	0.47	0	0	6	0.25	0.507	0.136
NVP hypersensitivity	6	0.71	0	0	0	0	6	0.25	**0.038**	-
Vomiting	2	0.24	0	0	0	0	2	0.08	0.507	-
Pelvic inflammatory disease	0	0	0	0	1	0.15	1	0.04	0.440	0.440
Syphilis	1	0.12	0	0	0	0	1	0.04	1.000	-
Other**	0	0	1	0.12	2	0.30	3	0.13	-	1.000
Total	45	4.59	17	1.64	18	2.69	80	3.00	0.052	0.406

* Count may include more than one SAE per mother.

** Bleeding arterio-venous fistula, cellulitis/abscess, jaundice.

*** Non-nevirapine related.

Table 5. Serious adverse events (SAEs) in infants other than deaths by intervention

	Treatment								P-value	
	Maternal Regimen [n=849]		Infant Nevirapine [n=852]		Control [n=668]		Total [n=2369]		Maternal vs. Control	Infant vs. Control
SAE	N*	% of infants with ≥ 1 SAE	N*	% of infants with ≥ 1 SAE	N*	% of infants with ≥ 1 SAE	N*	% of infants with ≥ 1 SAE		
Serious febrile illness	61	7.18	63	7.28	36	5.39	160	6.71	0.170	0.185
Pneumonia	36	4.12	36	3.99	32	4.79	104	4.26	0.605	0.366
Diarrhea	11	1.30	8	0.94	7	1.05	26	1.10	0.812	1.000
Malaria	8	0.94	15	1.41	9	1.20	32	1.18	0.778	0.743
Meningitis	7	0.82	11	1.29	6	0.90	24	1.01	1.000	0.625
NVP hypersensitivity	1	0.12	16	1.88	0	0	17	0.72	1.000	**<0.001**
Growth faltering	3	0.35	4	0.23	0	0	7	0.21	0.260	1.000
Rash* **	2	0.24	3	0.35	1	0.15	6	0.25	1.000	0.635
Vomiting	1	0.12	1	0.12	1	0.15	3	0.13	1.000	1.000
Tuberculosis	0	0	0	0	1	0.15	1	0.04	0.440	0.440
Other**	1	0.12	2	0.23	2	0.30	5	0.21	1.000	1.000
Total	131	14.02	159	15.73	95	12.57	385	14.23	0.588	0.145

* Count may include more than one SAE per infant.

** distended abdomen; spontaneous resolution, nasal congestion; hospitalized, croup, seizures

*** Non-nevirapine related

Table 6. Infant Cause of Death Line Listing

Treatment Arm	Age at Death (days)	HIV Status	Cause of death from death review
Maternal Regimen	2	Negative	Neonatal sepsis
Maternal Regimen	11	Negative	Pneumonia
Maternal Regimen	19	Negative	Pneumonia
Maternal Regimen	22	Negative	Unknown
Maternal Regimen	48	Negative	Pneumonia and staph aureus bacteremia
Maternal Regimen	61	Negative	Pneumonia
Maternal Regimen	61	Negative	Diarrhea; failure to thrive
Maternal Regimen	65	Negative	Meningitis
Maternal Regimen	76	Negative	Pneumonia
Maternal Regimen	92	Negative	Unknown
Maternal Regimen	173	Negative	Sepsis
Maternal Regimen	87	Positive	Pneumonia
Infant Nevirapine	8	Negative	Neonatal sepsis
Infant Nevirapine	13	Negative	Neonatal sepsis
Infant Nevirapine	43	Negative	Meningitis
Infant Nevirapine	57	Negative	Meningitis
Infant Nevirapine	95	Negative	Pneumonia
Infant Nevirapine	99	Negative	Drowning
Infant Nevirapine	154	Negative	Unknown
Infant Nevirapine	176	Negative	Sepsis
Infant Nevirapine	187	Negative	Sepsis
Infant Nevirapine	16	Positive	Pneumonia
Infant Nevirapine	110	Positive	Severe malaria
Control	7	Negative	Unknown
Control	7	Negative	Neonatal sepsis
Control	14	Negative	Neonatal sepsis
Control	15	Negative	Diabetes insipidus
Control	81	Negative	Diarrhea
Control	105	Negative	Pneumonia
Control	113	Negative	Severe symptomatic anemia possibly due to trimethoprim-sulfamethoxazole
Control	168	Negative	Unknown
Control	192	Negative	Seizures, probable organophosphate poisoning

Control	12	Positive	Neonatal sepsis
Control	129	Positive	Pneumonia, possibly Pneumocystis jiroveci
Control	131	Positive	Pneumonia, possibly Pneumocystis jiroveci
Control	138	Positive	Pneumonia
Control	169	Positive	Unknown