

Supplementary Appendix

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

Supplement to: Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med* 2008;359:119-29. DOI: 10.1056/NEJMoa0801941.

WEB- ONLY SUPPLEMENT:

Extended Infant Antiretroviral Prophylaxis Reduces Breast Milk HIV-1 Transmission

Methods Section Additional Web-Only Information:

Randomization procedures employed permuted block algorithms of sizes 9 and 12, stratified by study clinic. A computer generated randomization list assigned infants to the appropriate treatment arms using a 1:1:1 allocation ratio.

Randomization numbers were placed in sequentially labeled and sealed envelopes.

Trained study staff completed structured case report forms at baseline (enrollment at delivery) and at each subsequent visit. Breastfeeding information was collected using structured questionnaires.

Physical examinations of the mother and infant were conducted at each visit. In addition to infant samples, maternal venous blood was collected for storage at all visits, and at birth, 14 weeks, 12 months, and 18 or 24 months for complete blood count (CBC) and CD4+ cell count. To monitor infant prophylaxis adherence, mothers were interviewed at each visit, and used bottles of NVP and ZDV syrup were collected.

HIV-1 testing was performed at the College of Medicine -Johns Hopkins University Research Laboratory in Blantyre, which participates in the Division of AIDS (DAIDS) Virology Quality Assurance Program.

Patient management was at the local level based on real-time HIV-1 test results. Infants with confirmed HIV-1 infection during the period of prophylaxis were taken off study drug, and continued to be followed off study drug for the duration of the study.

All Grade 3-4 toxicities, rashes Grade 2B or higher and ALT levels Grade 2 or higher were considered serious. Serious adverse events, including deaths and hospitalizations, were reported to the University of Malawi, Johns Hopkins University, and CDC Institutional Review Boards (IRBs). Abnormal clinical and laboratory findings were followed until resolution to Grade 2 or lower. Infants discontinued from study drug(s) were followed for the study duration.

Time to observed HIV-1 infection comparisons were repeated using: a) only infants with confirmed HIV-1 infection as an outcome; b) the mid-date between last negative and first positive HIV-1 test as the time of HIV-1 infection; and c) a discrete K-M method based on the visit of the first infant HIV-1-positive test result (data not shown). All analyses yielded comparable results. Two sided p-values not adjusted for multiple comparisons are reported in the paper

Web-only Supplementary Tables

Table 1: Cause-specific mortality ratio by study group*

Reported cause of death	Control Group [N (%)]	Extended- Nevirapine Group [N (%)]	Extended-Dual- Prophylaxis Group [N (%)]
Anaemia	1 (0.9)	1 (1.1)	5 (5.6)
Asphyxia	1 (0.9)	1 (1.1)	0 (0)
Gastroenteritis	32 (30.2)	23 (25.8)	27 (30)
Malaria	8 (7.5)	5 (5.6)	6 (6.7)
Malnutrition	5 (4.7)	5 (5.6)	7 (7.8)
Meningitis	4 (3.8)	2 (2.2)	3 (3.3)
Oral Thrush	1 (0.9)	1 (1.1)	1 (1.1)
Pneumonia	27 (25.5)	20 (22.5)	19 (21.1)
Sepsis	6 (5.7)	12 (13.5)	5 (5.6)
TB	0 (0)	0 (0)	2 (2.2)
Tetanus	0 (0)	0 (0)	1 (1.1)
Other	18 (17)	17 (19.1)	14 (15.6)
Unknown	3 (2.8)	2 (2.2)	0 (0)
Total	106 (100)	89 (100)	90 (100)

* Proportion of total number of deaths in each group.

Table 2: Proportion of type-specific serious adverse events (SAE) by study group*

SAE Type **	Control Group [N (%)]	Extended-Nevirapine Group [N (%)]	Extended-Dual-Prophylaxis Group [N (%)]	Total
C Respiratory	111 (33.7)	112 (34)	106 (32.2)	329
C Gastrointestinal	67 (29.5)	74 (32.6)	86 (37.9)	227
C Hematological	64 (33.5)	70 (36.6)	57 (29.8)	191
C Malnutrition	35 (32.7)	30 (28)	42 (39.3)	107
C Malaria	27 (26.2)	42 (40.8)	34 (33)	103
L Neutropenia	24 (25.5)	36 (38.3)	34 (36.2)	94
C Congenital	23 (30.7)	29 (38.7)	23 (30.7)	75
L Anemia	10 (28.6)	7 (20)	18 (51.4)	35
C Infections	9 (33.3)	7 (25.9)	11 (40.7)	27
C CNS	8 (34.7)	8 (34.7)	7 (30.4)	23
C Meningitis	9 (50)	2 (11.1)	7 (38.9)	18
C Unkwown Death	8 (44.4)	7 (38.9)	3 (16.7)	18
C Injuries	3 (42.9)	2 (28.6)	2 (28.6)	7
C Cutaneous Toxicity	0 (0)	1 (16.7)	5 (83.3)	6
C HIV	1 (20)	2 (40)	2 (40)	5
C Hepatotoxicity	1 (25)	1 (25)	2 (50)	4
L Hepatotoxicity	1 (25)	1 (25)	2 (50)	4

C SID	1 (33.3)	1 (33.3)	1 (33.3)	3
C Genito-urinary	1 (50)	1 (50)	0 (0)	2
C Visual	1 (50)	1 (50)	0 (0)	2
L Hematological	2 (100)	0 (0)	0 (0)	2
L Thrombocytopenia	1 (100)	0 (0)	0 (0)	1
Total	407 (31.7)	434 (33.8)	442 (34.5)	1283

* Proportion of total within each type

** C= Clinical adverse events; L= Laboratory adverse events.

Table 3: Cumulative HIV-1 infection rates by study group by infant age *

Estimate (%)	birth	1 wk	6 wks	9 wks	14 wks	6 mos	9 mos	12 mos	15 mos	18 mos	24 mos
Control Group	6.53	0.30	5.10	7.35	8.43	10.12	10.58	11.46	12.35	13.93	14.52
Extended-Nevirapine Group	7.10	0.10	1.67	2.55	2.79	4.00	5.19	6.95	7.82	10.08	11.20
Extended-Dual-Prophylaxis Group	7.07	0.20	1.58	2.37	2.84	5.19	6.37	8.05	8.68	10.18	12.25

* Obtained from Kaplan-Meier curves in Figure 2A.