オバンク・ジャパン
http://www.biobankjp.org/ と類似した、タイ・バイオバンクとして発展させている。バイオバンク・ジャパンは東京大学や理化学研究所に拠点を置き、公益財団法人結核予防会複十字病院等の協力医療機関の参加の基に運営されている。日タイ双方のフィールド・検体を使う連携研究の進展が期待される。バイオバンク・ジャパンの規定に類似して、検体バンクは、よりオープンにして国立感染症研究所、東京大学や他機関の研究者も参画を促し共同研究を推進する。

将来的に、本フィールドを国際的なネットワーク（INDEPTHネットワーク：An International network of HDSS sites involved in demographic and health research in developing countries）に参画することで、研究レベルの向上に寄与すると考えられる。さらに、タイ国保健省・医科学局衛生研究所(Thai NIH: National Institute of Health, Ministry of Public Health, Thailand)はは東南アジア地域のネットワークのハブとして活動しており、同様の機能を持つベトナム保健省NIHE(National Institute of Hygiene and Epidemiology)との連携発展が期待される。

E．結論

HIVと結核対策プログラム介入効果評価の為の研究フィールドと保健情報システム整備を初年度に実施した。

G．研究発表

1．論文発表

小柳

原著論文による発表

欧文

Koyanagi A, Humphrey JH, Ntozini R, Nathoo K, Moulton LH, Iliff P, Mutasa K, Ruff A, Ward B and the ZVITAMBO Study Group. Morbidity among HIV-exposed but uninfected (HEU), HIV-infected, and HIV-unexposed infants in Zimbabwe prior to availability of HAART. *Pediatr Infect Dis J* 2011 Jan;30(1):45-51.

Koyanagi A, Ruff AJ, Moulton LH, Ntozini R, Mutasa K, Iliff P, Humphrey JH; ZVITAMBO Study Group. Postpartum plasma CD4 change in HIV-positive women: implications for timing of HAART initiation. AIDS Res Hum Retroviruses. 2010; 26(5):547-52.

Koyanagi A,Shibuya K. What do we really know about adult mortality worldwide? Lancet 2010；375(9727):1668-70.

Koyanagi A, Humphrey JH, Moulton LH, et al. Effect of early exclusive breastfeeding on morbidity among infants born to HIV-negative mothers in Zimbabwe. Am J Clin Nutr. 2009; 89(5):1375-82.

Koyanagi A, Humphrey JH, Moulton LH, Ntozini R, Mutasa K, Iliff P, Ruff AJ and the Zvitambo Study Group. Predictive value of weight loss on mortality of HIV-positive mothers in a prolonged breastfeeding setting AIDS Research and Human Retroviruses. 2011 Feb 16. [Epub ahead of print].

2. 学会発表

野内英樹、山田紀男、吉山崇　結核患者における医療従事者主導のHIV検査(PITC：Provider Initiative Testing and Couseling)によるHIVの一次予防と二次予防、第85回日本結核病学会総会、京都、2010年5月

野内英樹、出井禎　タイと日本における菌体と人検体の長期縦断的検体バンクによる結核の発症と難治化に関する要因研究　第57回日本臨床検査医学会学術集会(一般口頭演題、微生物検査(2)演題番号10145)、東京、2010年9月

H. 知的財産権の出願・登録状況

1. 特許取得
2. 実用新案登録

3. その他

該当なし。

Table 1.1: ART regimen change rate within first year of HAART initiation by category of patients' characteristic (2006-2008), Chiang Rai, Thailand

Characteristic N= 4981	Regimen change rate (%)	Change /total number	*P* value
Overall	15.4%	765/4981	
Age (years)			
>50	19.4%	49/253	0.07
15-50	15.1%	716/4728	
Base line CD4 (cells/ul)			
>50	15.6%	665/4260	0.54
0-50	16.7%	70/418	
Missing	9.9%	30/303	
Gender			
Male	12.9%	308/2389	<0.001
Female	17.6%	457/2592	
ART regimen			
NVP based	14.9%	662/4445	<0.01
EFV based	20.3%	95/469	
PI based	11.9%	8/67	
NRTI Backbone			
D4T+3TC	15.9%	652/4095	0.02
AZT+3TC	12.8%	113/886	
Presence of OI at the start			
Yes	16.3%	17/104	0.82
No	15.5%	748/4820	
Missing	0.0%	0/57	
Type of hospital			
Provincial	19.1%	174/913	<0.01
District	14.5%	591/4068	
Year of starting treatment			
2006	11.0%	24/218	<0.01
2007	14.7%	539/3659	
2008	18.3%	202/1104	

Table 1.2: Cox proportional hazards model analysis for Predictors of ART regimen changes within one year of starting treatment

Characteristic N=4981	Unadjusted Hazards ratio (95%CI)	Adjusted Hazards ratio (95%CI)	*P*
Age (years)			
>50	1	1	
15-50	1.35 (1.01-1.8)	1.28 (0.96-1.71)	0.10
Base line CD4 (cells/ul)			
>50	1		
0-50	1.2 (0.94-1.54)		
Gender			
Male	1	1	
Female	1.4 (1.22-1.62)	1.48 (1.28-1.72)	<0.001
ART regimen			
NVP based	1	1	
EFV based	1.4 (1.13-1.74)	1.48 (1.19-1.84)	<0.001
PI based	0.79 (0.4-1.59)	0.77 (0.38-1.55)	0.46
NRTI Backbone			
AZT+3TC	1	1	
D4T+3TC	1.29 (1.06-1.58)	1.44 (1.17-1.77)	<0.01
Presence of OI at the start			
Yes	1		
No	1.18 (0.73-1.91)		
Type of hospital			
Provincial	1	1	
District	0.74 (0.63-0.88)	0.71 (0.6-0.84)	<0.001
Year of starting treatment			
2006	1	1	
2007	1.44 (0.96-2.17)	1.72 (1.14-2.6)	0.01
2008	1.96 (1.28-2.99)	2.28 (1.49-3.49)	<0.001

Table 2.1. Prevalence of HIV by motivation for HIV-testing and sex

Reason for HIV testing	N	Age (years) Median (IQR)	HIV-positive n (%)	Sex	N	HIV-positive n (%)
Visit to area with commercial sex	112	31 (41-48)	32 (28.6)	Male	107	32 (29.9)
				Female	5	0 (0.0)
Commercial sex worker	21	33 (27-39)	12 (57.1)	Male	7	3 (42.9)
				Female	14	9 (64.3)
Homosexual	118	37 (31-45)	20 (16.9)	Male	83	15 (18.1)
				Female	35	5 (14.3)
Intravenous drug use	9	37 (34-42)	3 (33.3)	Male	8	2 (25.0)
				Female	1	1 (100.0)
Multiple partners	78	31 (23-42)	20 (25.6)	Male	54	11 (20.4)
				Female	24	9 (37.5)
Partner engaged in risky behavior	812	38 (32-46)	202 (24.9)	Male	262	80 (30.5)
				Female	550	122 (22.2)
Partner is HIV-positive	373	38 (32-44)	176 (47.2)	Male	162	73 (45.1)
				Female	211	103 (48.8)
Antenatal care screening	1985	25 (20-30)	11 (0.6)	Male	NA	NA
				Female	1985	11 (0.6)
Husband of pregnant woman	134	30 (26-35)	1 (0.8)	Male	134	1 (0.8)
				Female	NA	NA
Mother is HIV-positive	161	7 (2-10)	42 (26.1)	Male	76	19 (25.0)
				Female	85	23 (27.1)
No condom	743	39 (31-48)	187 (25.2)	Male	520	119 (22.9)
				Female	223	26 (11.7)
Tuberculosis	128	47 (36-58)	18 (14.1)	Male	94	11 (11.7)
				Female	34	7 (20.6)
Symptoms suggestive of HIV (other than TB)	172	40 (27-51)	17 (9.9)	Male	110	12 (10.9)
				Female	62	5 (8.1)
Rape	12	13 (11-14)	1 (8.3)	Male	1	0 (0.0)
				Female	11	1 (9.1)
Exposure to blood	42	29 (24-37)	0 (0.0)	Male	19	0 (0.0)
				Female	23	0 (0.0)
Screening for medical procedure	165	49 (37-55)	0 (0.0)	Male	59	0 (0.0)
				Female	106	0 (0.0)
Premarital testing	92	31 (25-40)	3 (3.2)	Male	48	1 (2.1)
				Female	44	2 (4.6)
Health certificate for job	755	38 (30-46)	5 (0.7)	Male	402	3 (0.8)
				Female	353	2 (0.6)
Other	2182	39 (31-47)	15 (0.7)	Male	1062	9 (0.9)
				Female	1120	6 (0.5)

IQR Inter-quartile range

Table 2.2. Multivariate analysis of risk of HIV-seropositivity

Characteristic	Category	N	HIV-positive n (%)	Adjusted OR*	P-value
Risk behavior	No risk	3393	8 (0.2)	1.00	
	Visit to area with commercial sex worker	242	64 (26.5)	121.84 (57.16-259.71)	<0.001
	Prostitute	31	18 (58.1)	612.42 (221.23-1695.33)	<0.001
	Homosexual	164	54 (32.9)	167.88 (77.55-363.43)	<0.001
	IDU	12	4 (33.3)	159.70 (38.77-657.76)	<0.001
	No condom	3660	461 (12.6)	62.31 (30.90-125.66)	<0.001
Age (years)	15-20	799	10 (1.3)	1.00	
	21-30	2106	132 (6.3)	4.82 (2.41-9.63)	<0.001
	31-40	2264	332 (14.7)	11.40 (5.78-22.47)	<0.001
	41-50	1672	158 (9.5)	7.10 (3.56-14.18)	<0.001
	51-60	772	38 (4.9)	3.15 (1.47-6.77)	0.003
	>60	186	11 (5.9)	3.19 (1.24-8.22)	0.017
Sex	Female	4891	334 (6.8)	1.00	
	Male	3210	391 (12.2)	1.75 (1.45-2.11)	<0.001

IDU Intravenous drug use

*Adjusted for all covariates in the model

資料 1

Koyanagi A, Humphrey JH, Ntozini R, Nathoo K, Moulton LH, Iliff P, Mutasa K, Ruff A, Ward B and the ZVITAMBO Study Group. Morbidity among HIV-exposed but uninfected (HEU), HIV-infected, and HIV-unexposed infants in Zimbabwe prior to availability of HAART. *Pediatr Infect Dis J* 2011 Jan;30(1):45-51.

Koyanagi A,Shibuya K. What do we really know about adult mortality worldwide? Lancet 2010 ; 375(9727):1668-70.

Koyanagi A, Humphrey JH, Moulton LH, et al. Effect of early exclusive breastfeeding on morbidity among infants born to HIV-negative mothers in Zimbabwe. Am J Clin Nutr. 2009; 89(5):1375-82.

Koyanagi A, Humphrey JH, Moulton LH, Ntozini R, Mutasa K, Iliff P, Ruff AJ and the Zvitambo Study Group. Predictive value of weight loss on mortality of HIV-positive mothers in a prolonged breastfeeding setting AIDS Research and Human Retroviruses. 2011 Feb 16. [Epub ahead of print].

Morbidity Among Human Immunodeficiency Virus-exposed But Uninfected, Human Immunodeficiency Virus-infected, and Human Immunodeficiency Virus-unexposed Infants in Zimbabwe Before Availability of Highly Active Antiretroviral Therapy

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Background: Human immunodeficiency virus (HIV) remains a major cause of pediatric morbidity in Africa. In addition, HIV-exposed, but uninfected (HEU) infants can comprise a substantial proportion of all infants born in high prevalence countries and may also be a vulnerable group with special health problems.

Methods: A total of 14,110 infants were recruited within 96 hours of birth between November 1996 and January 2000. Rates and causes of sick clinic visits and hospitalizations during infancy were investigated according to infant HIV infection group: infected-intrauterine, infected-intrapartum, postnatally-infected, HEU, and not-exposed (born to HIV-negative mother).

Results: A total of 382 infected-intrauterine, 499 infected-intrapartum, 188 postnatally-infected, 2849 HEU, and 9207 not-exposed infants were included in the analysis. Compared with not-exposed infants, HIV-infected infants made 2.8 times more all-cause sick clinic visits and required 13.3 times more hospitalizations; they had 7.2 times more clinic visits and 23.5 times more hospitalizations for lower respiratory tract infection after the neonatal period and were 159.9 times more likely to be hospitalized for malnutrition during the second half of infancy. Compared with not-exposed infants, sick clinic visits were 1.2 times more common among HEU infants, were inversely associated with maternal CD4 cell count, and were significantly higher for all HEU infants except those whose mothers had a CD4 count ≥800 cells/μL, which was the mean value of HIV-negative women enrolled in the trial.

Conclusions: Morbidity is extremely high among HIV-infected infants. Compared with not-exposed infants, morbidity is higher among HEU infants and increases with severity of maternal disease, but is significantly higher for all mothers with CD4 cell count <800 cells/μL.

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A.K. analyzed the data and wrote the manuscript. J.H.H. designed the study and contributed to writing the manuscript. R.N. and L.H.M. provided statistical advice. K.M. conducted the laboratory work. P.I., A.R., K.N., and B.W. contributed in writing the manuscript.

None of the authors have a commercial or any other association that might pose a conflict of interest with the results presented in this paper.

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(*Pediatr Infect Dis J* 2011;30: 45–51)

In 2008, 2.1 million children were living with human immunodeficiency virus (HIV) most of whom had acquired the infection via mother-to-child-transmission (MTCT).[1] Globally, the number of pregnant HIV-positive women continues to increase because of an ongoing high incidence in many countries combined with the life-prolonging impact of highly active antiretroviral therapy.[1] In 2008, an estimated 1.5 million HIV-positive women delivered infants.[2] Fortunately, a steadily increasing proportion of infected women have received antiretrovirals to prevent MTCT such that the number of children newly infected each year has declined since 2004.[1] As prevention of MTCT programs further expand and deliver newer more efficacious regimens, the number of newly infected children will fall whereas the number of HIV-exposed, but uninfected (HEU) children will grow.[3] Thus, especially in Africa, where three-quarters of all HIV-positive women live, morbidity and mortality resulting from pediatric HIV remains a substantial problem, and addressing the special needs of HEU infants is receiving increasing attention.[4]

We have previously reported the rates and causes of mortality among 14,110 children enrolled in the ZVITAMBO trial in Harare Zimbabwe.[5] Two-year mortality was 67.5%, 65.1%, and 33.2% among those infected intrauterine, intrapartum, and postnatally compared with 9.2% among uninfected children of HIV-positive mothers and 2.9% among infants born to HIV-negative mothers.

In this article, we present the rates of total and cause-specific sick clinic visits and hospitalizations according to these HIV infection groups. The contributions offered by this analysis include a large sample of HIV-infected children with defined timing of infection, and concurrent cohorts of HEU children and infants born to HIV-negative women.

METHODS

Study Design

Details of the ZVITAMBO trial have been previously published.[5–7] In brief, 14,110 mother infant pairs were enrolled within 96 hours of delivery between November 1997 and January 2000. Mothers and infants were eligible if neither had an acutely life-threatening condition (eg, unconscious, receiving intensive care, or physician-ordered NPO), the infant was a singleton with birth weight ≥1500 g, and the mother planned to stay in Harare after delivery. Written informed consent was obtained. Baseline data were collected by questionnaire, transcription from hospital records, or direct measurement. Follow-up was conducted at 6

weeks, 3 months, and then every 3 months for 12 to 24 months. Medical care and counseling[8] were offered throughout the trial. The trial preceded availability of HIV testing and ARV prophylaxis for antenatal women in Harare public sector facilities and publication of the World Health Organization recommendations for cotrimoxazole prophylaxis of HIV-exposed infants.[9] Although women enrolled in ZVITAMBO were encouraged to learn their HIV test results, they were not required to do so and only 15% opted for post-test counseling. Through implementation of an infant feeding education and counseling program within the study, HIV-positive women who chose to breast-feed, HIV-negative women, and women who chose not to learn their HIV status were all advised to practice exclusive breast-feeding from birth to 6 months.

Morbidity Information

At each visit, mothers were asked if their infant had been hospitalized or visited a clinic for treatment of an illness since their previous visit. The causes and dates of these visits, and duration for hospitalizations, were determined from medical records (if available) or by maternal history. For hospitalizations, information was also sought by study nurses who regularly visited the major hospitals in Greater Harare to identify ZVITAMBO participants.

Laboratory Tests

At baseline, mothers were tested for HIV following an algorithm including parallel ELISA tests and Western blot, as previously described.[6] Baseline positivity was confirmed by testing the next available blood sample and baseline negative mothers were retested at all subsequent blood draws. Hemoglobin was measured at baseline in women enrolled from October 1998 through the end of recruitment (approximately 60% of the mothers) by HemoCue (Mission Viejo, CA). Among baseline HIV-positive mothers, CD4 cells were counted by FACScount (Becton Dickinson) among baseline HIV-positive mothers and a random subgroup of HIV-negative mothers. Viral load was measured (Roche Amplicor HIV-1 Monitor test version 1.5; Roche Diagnostics) on a random subgroup of HIV-positive mothers. From all HIV-exposed infants, cell pellets (Roche Diagnostics Systems, Alameda, CA) and plasma were prepared from whole blood collected at baseline and all follow-up visits, and archived at −70 °C. When patient contact was completed, the last specimen collected from each infant was tested for HIV by enzyme-linked immunosorbent assay (GeneScreen for samples collected at ≥18 months [plasma]) and Roche Amplicor (version 1.5 qualitative polymerase chain reaction (PCR) assay [Roche Diagnostic Systems]) for samples collected before 18 months (cell pellets). If the last specimen was negative, the child was considered to be uninfected until the end of follow-up; if positive, earlier specimens were tested to determine timing of infection.

Statistical Analysis

Children were classified into the following 1 of 6 HIV-exposure groups:

- Not-exposed—Mothers tested HIV-negative at baseline and never seroconverted during follow-up.
- HEU (HIV-exposed but uninfected)—Mother was HIV-positive at baseline and infant was PCR-negative at 6 weeks. The infant was censored at the time of their last negative test.
- Infected-intrauterine—Infant tested PCR-positive at baseline.
- Infected-intrapartum—Infant tested PCR-negative at baseline and PCR-positive at 6 weeks.
- Postnatally-infected—Infant tested PCR-negative at 6 weeks and became positive at any point thereafter.
- Infected with uncertain timing—Infant tested PCR-positive at 6 weeks but was missing a baseline test; OR infant tested PCR-negative at baseline, was missing a 6-week PCR test, and was then subsequently HIV-positive; OR infant was missing PCR test at baseline, and 6 weeks, and subsequently positive.

Statistical analysis was conducted using Stata Version 9.2 (StataCorp LP, TX). Baseline characteristics of the HIV exposure groups were compared by pairwise χ^2 tests for categorical variables and Mann-Whitney U tests for continuous variables. Incidence rates (IR) for all-cause and disease-specific (lower respiratory tract infection [LRTI], acute diarrhea, oral thrush, skin disease) sick clinic visits were calculated for each HIV-exposure group during each of 4 age periods (0–28, 29–91, 92–182, and 183–365 days) by dividing the number of clinic visits made during that interval by the child-years of observation in the interval. Incident rate ratios (IRR) were calculated using the negative binomial regression to correct for overdispersion and to compare the IR of sick clinic visits with the not-exposed group as the reference. Similarly, IRs for all-cause and LRTI, diarrhea, meningitis, and malnutrition-specific hospitalizations were calculated for each HIV-exposure group during the same 4 age intervals; a Poisson regression was used for estimating hospitalization rates because only minimal overdispersion was observed. For all analyses, infants were censored at death or loss to follow-up and, in addition, HEU infants were censored at their last negative PCR result. For postnatally infected infants, only health care visits occurring after the midpoint date of the last negative and first positive PCR test (when these infants were defined) were included in the analysis. No visits were attributed to the postnatally infected group during the 0 to 28 days interval because postnatal infections were defined only among infants testing PCR-negative at 6 weeks.

More detailed analyses were conducted to further elucidate the morbidity risk of HEU infants. First, because the differences in both sick clinic visits and hospitalization rates were relatively smaller between not-exposed and HEU than between not-exposed and all infected infants, we conducted 2 sensitivity analyses to investigate whether these differences may have been due to bias or misclassification: (1) To exclude potentially misclassified infants who had become infected but were within the window period of the test and so falsely tested PCR-negative, we repeated the analyses censoring HEU infants 42 days before their last HIV-1 PCR result.[10] (2) To investigate whether censoring HEU infants at their last negative PCR test result while retaining not-exposed infants until death or last follow-up date had biased our findings, we repeated the analyses but for each age interval, included only infants who survived to the end of that interval and only HEU infants whose last negative PCR test result was on or after the last day of the interval. (3) To investigate whether differences in morbidity risk between the HEU infants and the not-exposed infants changed after adjusting for other baseline factors, we conducted stepwise regression to identify influential covariates for all-cause and cause-specific clinic visits.

Second, to investigate whether severity of maternal HIV disease influenced morbidity among their HEU infants, we estimated the IRR of all-cause and cause-specific sick clinic visits among these infants, stratified by maternal CD4 cell count (<200, 200–499, 500–799, ≥800 cells/μL), compared with not-exposed infants using a multivariate negative binomial regression model. We repeated the analysis adjusting for maternal death, age, and parity since these factors were all inversely related to CD4 count.

RESULTS

A total of 14,110 mother infant pairs were recruited. At baseline, 4495 mothers tested HIV-positive and 9207 tested HIV-negative and never seroconverted during follow-up. Of the remaining mothers, 355 seroconverted during the study period and 53 had indeterminate results. During the 2-year follow-up, 1330 infants

TABLE 1. Baseline Characteristics According to Maternal and Infant HIV Status and Timing of Infant Infection

Baseline Characteristic	HIV-infected Mothers				
	HIV-infected Infants			Exposed-not-infected† (n = 2661)	HIV-negative Mothers (Not-exposed Infants) (n = 9207)
	Infected-intrauterine (n = 382)	Infected-intrapartum (n = 499)	Postnatally-infected* (n = 188)		
Infant					
Male sex	154 (40.31)	243 (48.70)‡	96 (51.06)‡	1362 (51.22)‡	4772 (51.85)‡
Birth weight <2500 g	91 (23.88)	108 (21.69)	30 (15.96)‡	358 (13.56)‡§	1108 (12.06)‡§¶
Mean (SD), g	2792 (471)	2876 (492)‡	2945 (453)‡	2964 (467)‡§	3000 (477)‡§¶‖
Gestational age <37 wk**	47 (12.40)	62 (12.65)	16 (8.51)	222 (8.45)‡§	579 (6.35)‡§¶
Maternal					
Hemoglobin, mean (SD; n) (g/dL)††	10.9 (2.1; 216)	10.7 (2.0; 276)	10.7 (1.9; 102)	11.3 (1.9; 1457)‡§‖	12.0 (1.9; 5204)‡§¶‖
Marital status					
Married/stable	346 (91.05)	453 (91.89)	173 (92.51)	2447 (92.34)	8677 (94.58)‡§¶‖
Separated/widowed	14 (3.68)	21 (4.26)	6 (3.21)	82 (3.09)	112 (1.22)
Single-never married	20 (5.26)	19 (3.85)	8 (4.28)	121 (4.57)	385 (4.20)
Age, mean (SD) (yr)††	24.8 (4.60)	26.3 (5.50)‡	26.9 (5.4)	25.6 (4.9)‡§‖	24.1 (5.40)‡§¶
Education <8 yr	58 (15.18)	119 (23.85)‡	32 (17.02)‡	507 (19.09)§	1581 (17.20)§¶‖
MUAC‡‡ <23 cm	49 (12.93)	62 (12.53)	28 (14.89)	310 (11.74)	1018 (11.12)
Parity					
1	144 (37.70)	128 (25.65)‡	40 (21.28)‡	777 (29.20)‡§‖	4520 (49.09)‡§¶‖
2–4	220 (57.59)	330 (66.13)	129 (68.09)	1748 (65.69)	4122 (44.77)
≥5	18 (4.71)	41 (8.22)	19 (10.11)	136 (5.11)	565 (6.14)
Plasma CD4 (cells/μL)					
<200	55 (16.72)	119 (27.74)‡	54 (32.93)‡	256 (10.98)‡§‖	5 (0.72)‡§¶‖
200–499	172 (52.28)	207 (48.25)	82 (50.00)	1196 (51.31)	120 (17.37)
≥500	102 (31.00)	103 (24.01)	28 (17.07)	879 (37.71)	566 (81.91)
Mean (SD; n)††	418 (225; 329)	365 (237; 429)‡	315 (210; 164)‡§	468 (250; 2331)‡	780 (315; 691)‡§¶‖
Plasma HIV RNA, mean (SD; n) (log_{10}copies/mL)††	4.5 (0.8; 52)	4.2 (0.8; 72)‡	4.4 (0.7; 31)	3.9 (0.8; 377)‡§‖	NA
Breastfeeding status at 3 mo§§					
Exclusive	15 (7.11)	23 (6.48)	4 (9.30)	221 (10.48)§	614 (9.27)
Predominant	67 (31.75)	126 (35.49)	14 (32.56)	645 (30.58)	2111 (31.85)
Mixed	129 (61.14)	206 (58.03)	25 (58.14)	1243 (58.94)	3902 (58.88)
Household income¶¶, median (IQR; n) US$/mo	87 (41–133; 286)	82 (48–130; 359)	77 (47–147; 140)	77 (48–139; 1952)	81 (53–139; 7105)
Enrollment date					
25 November 1997–15 June 1998	113 (29.58)	144 (28.86)	51 (27.13)	708 (26.61)‡	2516 (27.33)¶
16 June 1998–31 December 1998	84 (21.99)	115 (23.05)	50 (26.60)	717 (26.94)	2182 (23.70)
1 January 1999–15 July 1999	84 (21.99)	118 (23.65)	36 (19.15)	575 (21.61)	1948 (21.16)
16 July 1999–31 January 2000	101 (26.44)	122 (24.45)	51 (27.13)	661 (24.84)	2561 (27.82)

Data are n (%) unless otherwise stated.

<2% of data is missing for all characteristics except for CD4 count, viral load, hemoglobin, and household income and breastfeeding status at 3 months.

*Postnatally-infected group consists of infants whose midpoint of last negative HIV-1 PCR and first positive HIV-1 PCR was in first year of life.

†Exposed-not-infected group consists of infants who were PCR-negative at 6 weeks and never tested PCR-positive thereafter.

$P < 0.05$ by pairwise comparison between that group and ‡infected-intrauterine, §infected-intrapartum, ¶exposed-not-infected, and ‖postnatally-infected.

**Calculated by Capurro method.[30]

††P value calculated by Mann-Whitney U test; all other P values calculated by χ^2.

‡‡Mid-upper arm circumference; method described by Gibson.[31]

§§Exposed-not-infected group consists only of infants who were HIV-PCR-negative at 3 mo; Postnatally-infected groups consists only of infants whose midpoint between the last negative HIV- PCR and first positive HIV- PCR was before the 3-month-visit. Feeding defined according to the previous 7-day intake.

¶¶Inflation adjusted.

IQR indicates interquartile range.

became infected (382 infected-intrauterine, 499 infected-intrapartum, 252 postnatally-infected, 197 infected with uncertain timing). The HEU group initially consisted of 2849 infants who tested PCR-negative at 6 weeks; of these, 188 became postnatally infected during the first year and are included in this analysis (46 between 42 days and 183 days, 142 between 183 days and 365 days); these infants contributed child-time to the HEU analyses until their last negative PCR result. The 197 infants infected with uncertain timing, and 235 not-exposed and 13 infected-intrauterine infants with no follow-up after recruitment were excluded from the analyses. Results of the 355 infants whose mothers seroconverted postnatally are being reported in a separate article.

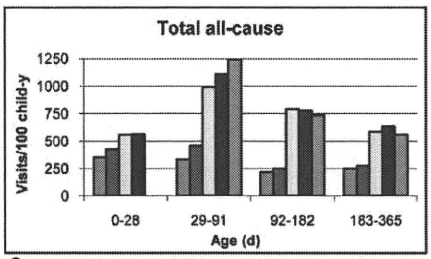
At baseline, HIV-positive mothers were more likely to be older, anemic, widowed or separated from their spouse, of higher parity and to have babies with lower birth weight and gestational age (Table 1).

Sick Clinic Visits

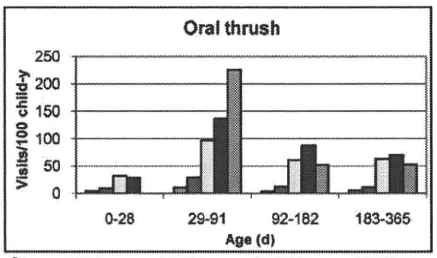
The infants in this analysis had a total of 35,108 sick clinic visits during the first year of life. Cause of visit was obtained from

medical records for about half of these visits; the remainder was by maternal report. The crude IR of all-cause sick clinic visits for HIV-infected infants (infected-intrauterine and infected-intrapartum during neonatal period; infected-intrauterine + infected-intrapartum + postnatally infected during postneonatal periods) increased from ~600/100 child-years during the first month of life to ~1000/100 child-years during the second and third month of life, and then declined to ~600/100 child-years during the second half of infancy (Fig. 1). This pattern of clinic visits peaking midinfancy was largely due to LRTI and oral thrush-specific visits. Among not-exposed infants, the crude IR for all sick clinic visits was highest during the neonatal period at approximately 350/100 child-years before, declining to 250/100 by the second half of infancy.

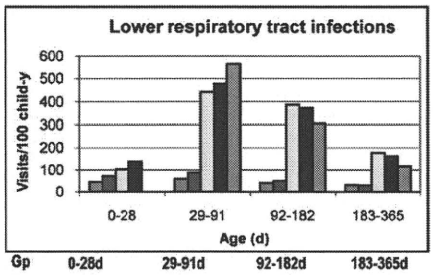
The all-cause sick clinic visit rate was significantly higher among HEU compared with not-exposed infants during all age periods (range of IRRs, 1.1–1.4; Fig. 1). The LRTI-associated visit rate was significantly higher (IRR = 1.3–1.6) during the first half of infancy for HEU compared with not-exposed infants, but did not differ between these 2 groups after 180 days. HEU infants were 2.0 to 3.4 times more likely to seek treatment for oral thrush during infancy



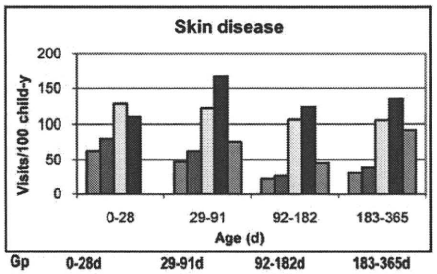
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	1.2 (1.1-1.4)	1.4 (1.3-1.5)	1.1 (1.1-1.2)	1.1 (1.1-1.2)
IU	1.6 (1.2-2.1)	3.0 (2.6-3.5)	4.2 (3.5-5.0)	2.5 (2.2-3.0)
IP	1.6 (1.3-2.0)	3.4 (3.0-3.8)	4.1 (3.5-4.7)	2.8 (2.5-3.1)
PN		3.7 (2.3-6.0)	3.3 (2.3-4.5)	2.2 (1.9-2.7)



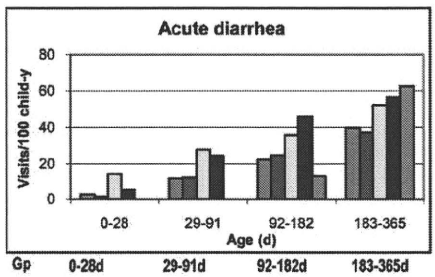
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	2.2 (1.0-4.8)	2.8 (2.1-3.8)	3.4 (2.2-5.3)	2.0 (1.5-2.8)
IU	7.8 (2.3-25.9)	9.6 (6.0-15.3)	18.8 (8.8-40.0)	12.4 (6.2-24.8)
IP	7.0 (2.4-20.5)	13.5 (9.1-19.8)	24.0 (13.3-43.1)	16.7 (9.9-28.3)
PN		20.6 (5.6-76.2)	13.6 (4.0-46.2)	9.7 (4.6-20.4)



Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	1.6 (1.1-2.3)	1.5 (1.2-1.8)	1.3 (1.0-1.6)	1.0 (0.8-1.2)
IU	2.2 (1.0-5.2)	7.4 (5.2-10.6)	13.5 (8.6-21.0)	7.6 (4.6-12.4)
IP	3.0 (1.5-6.1)	8.4 (6.2-11.3)	13.8 (9.6-20.0)	7.7 (5.3-11.2)
PN		10.0 (3.6-28.3)	6.8 (3.1-15.0)	3.6 (2.3-6.0)



Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	1.3 (1.0-1.7)	1.3 (1.1-1.6)	1.2 (0.9-1.5)	1.3 (1.1-1.5)
IU	2.0 (1.1-3.7)	2.5 (1.8-3.6)	4.4 (2.7-7.2)	3.4 (2.4-4.9)
IP	1.8 (1.0-3.0)	3.5 (2.7-4.6)	6.7 (4.4-10.0)	4.3 (3.4-5.6)
PN		1.5 (0.3-7.3)	1.8 (0.6-5.3)	3.0 (2.0-4.6)



Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	0.5 (0.1-1.9)	1.1 (0.7-1.6)	1.1 (0.9-1.4)	0.9 (0.8-1.1)
IU	5.4 (1.3-23.1)	2.5 (1.1-5.8)	1.7 (0.9-3.3)	1.4 (0.9-2.1)
IP	2.0 (0.4-10.7)	2.2 (1.1-4.5)	2.1 (1.3-3.4)	1.5 (1.1-2.0)
PN		NA	0.6 (0.1-3.0)	1.7 (1.1-2.7)

FIGURE 1. IRs and IRRs (95% CI) of sick clinic visits per 100 child-years by infection status group (Gp) and age (0–28, 29–91, 92–182, and 183–365 days). Child-years of follow-up for the 4 respective age intervals are 685, 1518, 2134, and 4109 for not exposed (Blue indicates NE); 218, 466, 626, and 1136 for HIV-exposed but uninfected (Red, HEU), 28, 58, 56, and 81 for infected intrauterine (Yellow, IU); 38, 81, 89, and 143 for infected intrapartum (Purple, IP); and 0, 3, 15, and 62 for the infected postnatally (Green, PN).

TABLE 2. Incident Rate and Incident Rate Ratio of All-cause and Cause-specific Sick Clinic Visits in Exposed-not-infected Infants Stratified by Maternal CD4 Count Compared to Not-exposed Infants During the First Year of Life*

Cause of Visit	Not-exposed Infants (n = 8972)		Exposed-not-infected Infants Stratified by Maternal CD4 Count (cells/uL)*							
			>800 (n = 227)		500–799 (n = 668)		200–499 (n = 1262)		<200 (n = 284)	
	IR†	IRR‡	IR	IRR	IR	IRR	IR	IRR	IR	IRR
All-cause	265.8	1.00	268.1	1.02§ (0.89–1.16)	314.7	1.11 (1.08–1.27)	323.7	1.24¶ (1.17–1.32)	337.8	1.33¶ (1.17–1.50)
LRTI	40.5	1.00	36.9	0.91 (0.63–1.33)	50.4	1.20 (0.97–1.49)	52.5	1.29 (1.09–1.52)	47.9	1.22 (0.87–1.71)
Acute diarrhea	27.3	1.00	21.6	0.79 (0.54–1.16)	26.9	0.97 (0.78–1.21)	26.2	0.94 (0.79–1.11)	27.5	1.00 (0.71–1.41)
Oral thrush	5.7	1.00	11.0	1.91 (1.02–3.58)	14.2	2.44 (1.69–3.53)	13.8	2.45 (1.69–3.53)	20.9	3.91¶‖ (2.29–6.66)
Skin disease	34.5	1.00	33.1	0.98 (0.70–1.37)	44.4	1.26 (1.04–1.52)	44.5	1.29 (1.11–1.49)	52.8	1.49¶ (1.12–1.98)

*Exposed-not-infected infants censored at last negative PCR test.
†Incidence rate per 100 child-years.
‡Incidence rate ratio (95% CI).
§Significant trend test ($P = 0.001$) within exposed-not-infected group.
¶Significantly different ($P < 0.05$) between that group and CD4 ≥800.
‖Significantly different ($P < 0.05$) between that group and CD4 200 to 499.
IR indicates incidence rates; IRR, incident rate ratios; LRTI, lower respiratory tract infection.

compared with not-exposed infants. Diarrhea-associated visits did not significantly differ between HEU and not-exposed infants during any age period. The IRRs of all-cause and cause-specific clinic visit rates for HEU compared with not-exposed infants were similar in all 3 sensitivity analyses (data not presented).

Within HEU infants, the all-cause sick clinic rate was inversely associated with maternal CD4 cell count (*P* value for trend test = 0.001: Table 2). Compared with not-exposed infants, the total sick clinic visit rate was significantly higher for HEU infants across the entire range of maternal CD4 cell count, except for the small proportion (9.3%) whose mothers had a CD4 count ≥800 cells/μL—comparable to the mean CD4 count among HIV-negative women (Table 1). These patterns did not change appreciably when adjusted for maternal death, parity, or age and were similar for LRTI, oral thrush, and skin disease-specific visits (data not shown).

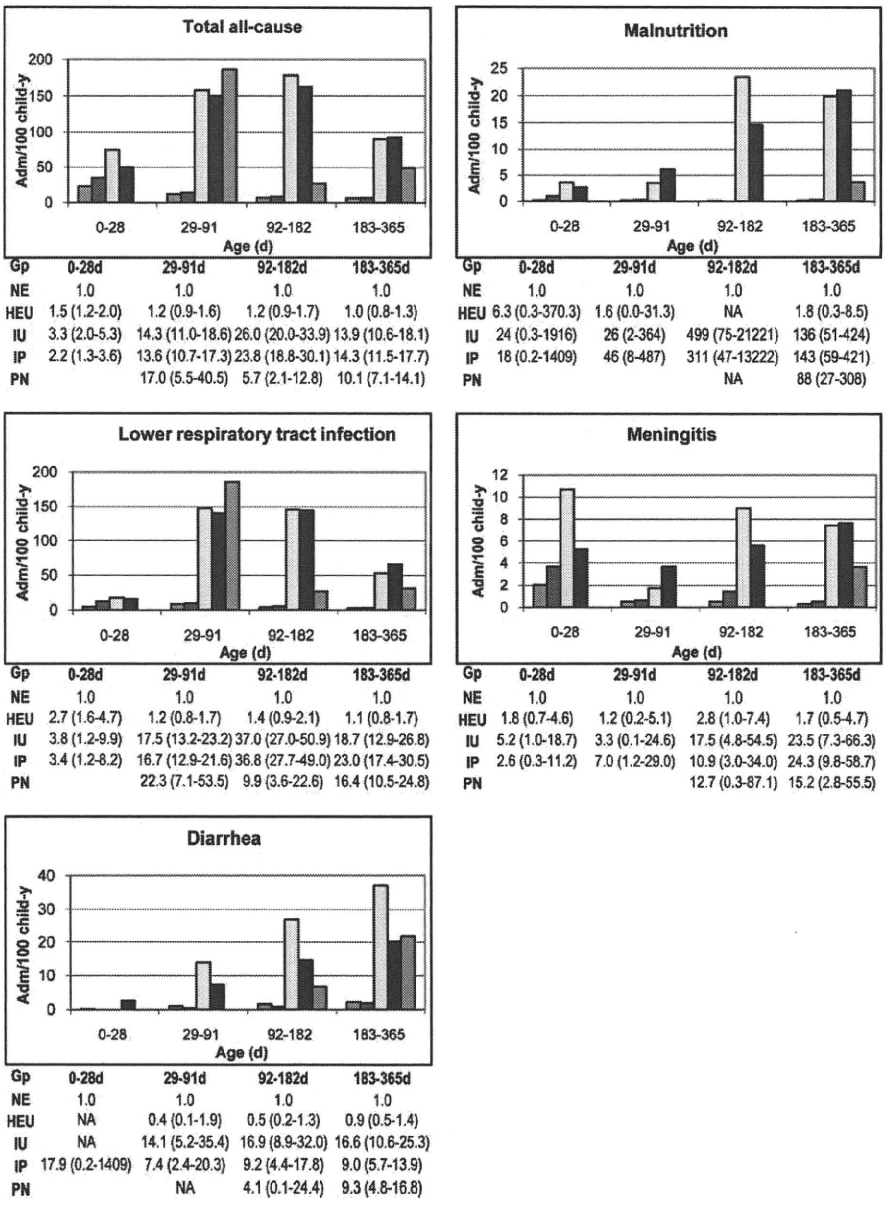
Hospitalizations

There were 1756 infant hospitalizations during the first year of life. Cause of hospitalization was extracted from medical records for 69% of these episodes, and the remainder from maternal report. Among not-exposed infants, the all-cause hospitalization rate was highest during the neonatal period, and decreased thereafter. However, among HIV-infected infants the all-cause hospitalization rate was lowest during the neonatal period, increased steeply between 3 and 6 months and then fell after 6 months; this peak was due to LRTI (93.4%, 93.5%, and 100% of the hospitalizations were due to LRTI in the 29 to 91 days age group in infected-intrauterine + infected-intrapartum + postnatally-infected infants, respectively). Diarrhea-specific hospitalization increased in a linear manner over the first year of life among all HIV-exposure groups, but was most dramatic for infected-intrauterine and infected-intrapartum infants who also experienced a concurrent increase in hospitalizations for malnutrition: compared with not-exposed infants, malnutrition-associated hospitalizations were 136 (95% CI: 51–424), 143 (95% CI: 59–421), and 88 (95% CI: 27–308) times higher for infected-intrauterine, infected-intrapartum, and postnatally-infected infants, respectively, in the second half of infancy.

The neonatal period was the only time when hospitalization rates significantly differed between HEU and not-exposed (IRR = 1.5 [95% CI: 1.2–2.0] for all-cause and 2.7 [95% CI: 1.6–4.7] for LRTI hospitalizations) (Fig. 2). In sensitivity analyses including only infants who survived to the end of the interval, these IRRs were greater compared with the primary analysis (1.9 [95% CI: 1.4–2.5] for all-cause hospitalizations and 3.4 [95% CI: 1.9–6.0] for LRTI hospitalizations) for the neonatal period and also became significant for the 92- to 182-day interval (1.4 [95% CI: 1.0–2.0] and 1.7 [95% CI: 1.1–2.5]) for all-cause and LRTI-specific hospitalizations, respectively. This suggests that the primary analysis may have underestimated the excess risk of hospitalization experienced by HEU compared with not-exposed infants as HEU infants were censored at the last negative PCR date and so were less likely to be followed till death, whereas not-exposed infants were retained until death.

DISCUSSION

This analysis underlines the magnitude and severity of illness experienced by HIV-infected infants and the substantial burden to the health care system that results. HIV-infected infants in this cohort contributed only 6% of all the child-years of follow-up time but they accounted for 14% of the sick clinic visits and 43% of the hospitalizations. HIV infection also changes the pattern of illness during infancy. Among not-exposed infants, health care visit rates were highest in the neonatal period. However, among HIV-infected infants, sick clinic visit and hospitalization rates peaked between 29 days and 182 days at approximately 1000/100 child-years and over 150/100 child-years, respectively, and most of these were for respiratory infections. This is consistent with the extremely high mortality among these infants between 8 weeks and 6 months previously reported (45% of infected-intrauterine infants and 33% of infected-intrapartum infants died before 6 months of age and more than 80% of these deaths were associated with acute respiratory infection).[5] These illnesses and deaths were most likely due to *Pneumocystis jiroveci,* the cause of *Pneumocystis* pneumonia.[11–14] This extremely high rate of illness, death, and health care burden emphasizes the importance of cotrimoxazole prophylaxis for all HIV-exposed infants from 4 to 6 weeks of age until HIV infection has been excluded as now recommended by World Health Organization[9] and also suggests that programs consider the targeting of HIV-exposed infants from the end of the neonatal period to 6 months, as has been proposed.[15] This analysis also underlines the deleterious effects of maternal HIV infection on infant health and survival—even for those infants who escape HIV infection (ie, HEU infants). HEU infants made an average of 30% more sick clinic visits and had an average of 20% more hospitalizations than not-exposed infants, consistent with the previously reported 4-fold higher infant mortality rate among exposed-not-infected compared



Total all-cause				
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	1.5 (1.2-2.0)	1.2 (0.9-1.6)	1.2 (0.9-1.7)	1.0 (0.8-1.3)
IU	3.3 (2.0-5.3)	14.3 (11.0-18.6)	26.0 (20.0-33.9)	13.9 (10.6-18.1)
IP	2.2 (1.3-3.6)	13.6 (10.7-17.3)	23.8 (18.8-30.1)	14.3 (11.5-17.7)
PN		17.0 (5.5-40.5)	5.7 (2.1-12.8)	10.1 (7.1-14.1)

Malnutrition				
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	6.3 (0.3-370.3)	1.6 (0.0-31.3)	NA	1.8 (0.3-8.5)
IU	24 (0.3-1916)	26 (2-364)	499 (75-21221)	136 (51-424)
IP	18 (0.2-1409)	46 (8-487)	311 (47-13222)	143 (59-421)
PN			NA	88 (27-308)

Lower respiratory tract infection				
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	2.7 (1.6-4.7)	1.2 (0.8-1.7)	1.4 (0.9-2.1)	1.1 (0.8-1.7)
IU	3.8 (1.2-9.9)	17.5 (13.2-23.2)	37.0 (27.0-50.9)	18.7 (12.9-26.8)
IP	3.4 (1.2-8.2)	16.7 (12.9-21.6)	36.8 (27.7-49.0)	23.0 (17.4-30.5)
PN		22.3 (7.1-53.5)	9.9 (3.6-22.6)	16.4 (10.5-24.8)

Meningitis				
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	1.8 (0.7-4.6)	1.2 (0.2-5.1)	2.8 (1.0-7.4)	1.7 (0.5-4.7)
IU	5.2 (1.0-18.7)	3.3 (0.1-24.6)	17.5 (4.8-54.5)	23.5 (7.3-66.3)
IP	2.6 (0.3-11.2)	7.0 (1.2-29.0)	10.9 (3.0-34.0)	24.3 (9.8-58.7)
PN			12.7 (0.3-87.1)	15.2 (2.8-55.5)

Diarrhea				
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	NA	0.4 (0.1-1.9)	0.5 (0.2-1.3)	0.9 (0.5-1.4)
IU	NA	14.1 (5.2-35.4)	16.9 (8.9-32.0)	16.6 (10.6-25.3)
IP	17.9 (0.2-1409)	7.4 (2.4-20.3)	9.2 (4.4-17.8)	9.0 (5.7-13.9)
PN		NA	4.1 (0.1-24.4)	9.3 (4.8-16.8)

FIGURE 2. IR and IRRs (95% CI) of hospitalizations per 100 child-years by infection status group (Gp) and age (0–28, 29–91, 92–182, and 183–365 days). Child-years of follow-up for the 4 respective age intervals are 685, 1518, 2134, and 4109 for not exposed (Blue indicates NE); 218, 466, 626, and 1136 for HIV-exposed but uninfected (Red, HEU), 28, 58, 56, and 81 for infected intrauterine (Yellow, IU); 38, 81, 89, and 143 for infected intrapartum (Purple, IP); and 0, 3, 15, and 62 for the infected postnatally (Green, PN).

with not-exposed infants (78/1000 child-years compared with 20/1000 child-years).[5] Our findings differ from those of 2 previous smaller studies in Africa that found little or no difference in mortality and morbidity rates between HEU and not-exposed infants,[16,17] but confirm and extend findings from Zambia[18] where HEU infants of mothers with more severe HIV disease and immune dysfunction had higher morbidity and mortality compared with HEU infants with healthier mothers. The Zambian study did not include a concurrent cohort of infants born to HIV-negative mothers. Our findings demonstrate that the excess morbidity attributable to maternal HIV infection is not limited to infants whose mothers have acquired immunodeficiency syndrome or severe disease: of the HEU infants in our study, all those whose mothers had <800 CD4 cell counts (90% of the HEU infants) had a significantly higher all-cause sick clinic visit rate compared with the not-exposed infants in the same cohort.

The underlying mechanism resulting in greater illness among HEU infants is likely to be multifactorial. First, infants who are born to HIV-positive mothers may have greater exposure to pathogens such as *Mycobacterium tuberculosis* or other common

pathogens. For example, HIV-positive women are more likely to have vaginal candidiasis than HIV-negative women[19] and among HIV-positive women, those who have lower CD4 counts are at higher risk of vaginal[19–21] and oral candidiasis.[22] Also, HIV-exposed infants may have more congenital or acquired infections with tuberculosis[23] or cytomegalovirus.[24] Second, many immunologic abnormalities have been identified in HEU infants, including changes in T-cell populations, cytokine production, and response to immunizations.[4,25–28] Finally, poor maternal psychologic and physical health may have lead to poor child care.[29] In ZVITAMBO, household income was lower for infected compared with uninfected women, and was significantly associated with mortality among HIV-exposed-uninfected infants but not with HIV-unexposed infants.[5] This suggests that household resources may have not only be more limited, but also shifted from child care into medical care of sick parents. An additional factor that may be important in some settings is reduced breast-feeding.[4] This was not likely a factor in our study because few women elected to learn their HIV status (since the study was conducted when antiretroviral prophylaxis and treatment were not yet available), and breast-feeding was prolonged among HIV-positive women with 99%, 94%, and 59% still breast-feeding at 6, 12, and 18 months.[7]

Elucidating these underlying mechanisms is crucial in designing interventions to improve the health of exposed-not-infected infants. For example, if tuberculosis is the cause of higher LRTI morbidity, it would be imperative to detect and treat the mother or father, not only for their own health but for the health of their uninfected infants; if antibody transfer across the placenta is lower among HIV-positive women, maternal highly active antiretroviral therapy or infant immunization may be an effective counteractive measure. Effective interventions targeting exposed-not-infected infants are a high priority now, and will become even more important as the efficacy and coverage of prevention of MTCT regimens increases.

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in 100% of patients, rather than in 40% of patients for intravenous alteplase. Indeed, for successfully recanalised endovascular-treated patients, data suggest the general upper limit for reperfusion to exert broad benefit for large artery ischaemic stroke patients is 6–7 h.[10]

An even more important message from today's pooled data lies at the other end of the time range, early after symptom onset. Although the investigators conservatively imposed a linear relation on the interaction between onset to start of treatment and good outcome, their tabular data suggest the relation is probably more an exponential decay (figure). Although odds ratios might overestimate effect size (compared with relative risk) when outcomes are common, the odds of favourable outcome seem to drop more precipitously in the first 90-min window (36%), moderately in the second (18%), and mildly in the third (9%)—essentially dropping off by a factor of two in each 90-min period.

These findings mandate a renewed commitment by clinicians and policy makers to foster very early intervention.[11,12] We need to increase the proportion of patients arriving at hospital in the first, golden hour after ischaemia onset by better educating the public to recognise stroke warning signs and activate the emergency medical system at the first sign of potential stroke, training prehospital personnel to scoop and go, having field personnel provide prearrival notification to receiving centres, and by routing ambulances carrying possible stroke patients directly to designated stroke centres. Moreover, stroke centres should target the improvement of hospital-response systems to achieve door-to-needle times of less than 60 min in the great majority of patients treated with intravenous alteplase. In thrombolytic stroke therapy, sooner is better than later, much better.

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JLS is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to Concentric Medical, Talecris, and Ev3; has received lecture honoraria from Boehringer Ingelheim; has been a site investigator in multicentre trials sponsored by Vernalis, Paion, Lundbeck, and Neurobiological Technologies, for which the University of California Regents received payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH IRIS, CLEAR, IMS 3, SAMMPRIS, and VERITAS multicentre clinical trials, for which the University of California Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; is a lead investigator in the NIH MR RESCUE multicentre trial; and is funded by NIH-NINDS Awards P50 NS044378 and U01 NS 44364. SRL has been an investigator for an NIH-funded trial of tenecteplase, manufactured by Genentec; has received an honorarium from the National Stroke Association for a webcast; and is funded by NIH-NINDS Awards R01 NS052417, R01 HL096944, U01 NS044364, and T32 NS051147. He is the independent medical monitor for NIH clinical trials IMS 3, CLEAR-ER, FAST-MAG, and INSTINCT.

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What do we really know about adult mortality worldwide?

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As child mortality continues to decline globally, more children survive to adulthood, and it is imperative to prevent premature deaths in adults. But what do we really know about how many adults aged between 15 and 60 years—the most healthy and productive age group in our society—are dying today?

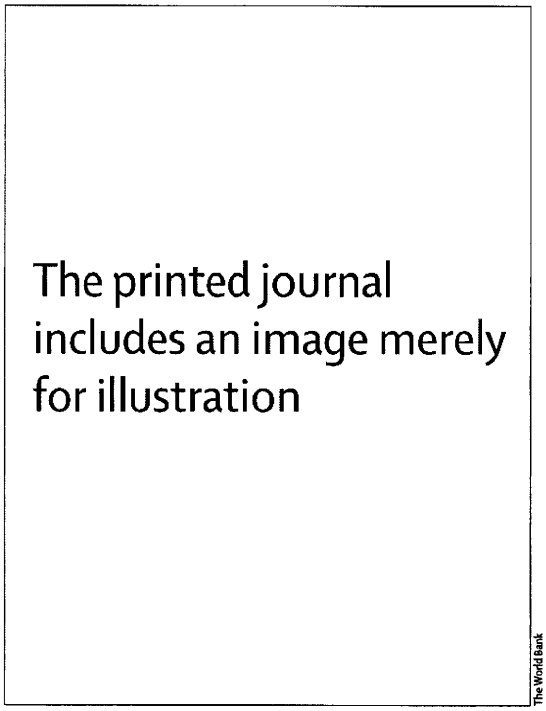
Despite the growing interest in the health of adults over the past two decades since the publication of the *World development report 1993: investing in health*,[1] a rigorous assessment of the levels and trends of adult mortality has been neglected, partly due to the huge measurement challenge (ie, adult deaths are rare events

compared with deaths in children) and the preference of donors to focus on disease-specific adult mortality estimates which cannot be consistent without all-cause adult mortality. With only 5 years left to achieve the Millennium Development Goals (MDGs), which include a subset of adult mortality, the global health community is in dire need of data to monitor progress in health-related MDGs and evaluate the impact of global health initiatives.

So what do we have? An abundance of incomplete data on adult mortality—only 26% of the world's population lives in countries with a complete civil registration system.[2] This incompleteness has rendered the modelling of adult mortality painstakingly difficult. To date, UN agencies, such as the UN Population Division and WHO, have relied on existing models which extrapolate adult mortality from child mortality[3,4] and which suffer from well known weaknesses especially in the era of HIV/AIDS. Furthermore, ambiguity remains in the source of data and underlying methods that yielded the estimates, thereby impeding replication of results.[3,4]

In *The Lancet* today, Julie Rajaratnam and colleagues[5] have tackled the difficulties of estimating adult mortality and provide detailed assessment of the levels and trends of adult mortality for the past four decades. At least three major breakthroughs should be noted in this landmark study. First, the investigators substantially improved the existing method of adult mortality estimation.[6,7] They made optimum use of available data, including incomplete or indirect empirical data on adult mortality, thereby allowing inclusion of a fairly large amount of new information in their estimation that was not included in previous UN assessments. Second, they used a method that generates the most likely substitute for missing data. In particular, they developed a new approach with high predictive validity to incorporate variation over time and across countries when estimating trends. Third, and perhaps most importantly, their approach is more transparent and replicable than previously published UN estimates on adult mortality.

Rajaratnam and colleagues comprehensively showed the diverse patterns of adult mortality across countries and changing trends. Because much of the variation in adult mortality cannot be explained by the combination of economic development, the HIV epidemic, and child mortality, the new analysis challenges the common theories behind health transition,[8] which will stimulate debates on alternative theories and the roles of social determinants, health systems, and medical technologies.



The method developed by Rajaratnam and colleagues is promising but is not our final goal. Without empirical measurements, knowledge on the levels and trends of adult mortality will still be haunted by ambiguity and uncertainty. For the past few years, the large discrepancy between the estimates published by UN agencies, notably WHO and UNICEF, and third parties in MDG 4 (child mortality) and 5 (maternal mortality) has been puzzling and frustrating the global health community,[9,10] which is now likely to spread to adult mortality. The impact of the global initiative to achieve MDG 6 relies heavily on cause-specific mortality data from major diseases such as HIV/AIDS and tuberculosis, but contradicting estimates will have a profound negative effect on the global health community, including beneficiaries of health programmes, countries, and policy makers.

This new modelling method by Rajaratnam and colleagues is a powerful monitoring tool for adult mortality with incomplete data while countries progress towards establishment of a sustainable civil-registration system.[6] All-cause adult mortality and causes of death are a must. The combination of these two will be invaluable in health-policy decision making irrespective of the

country's economic situation. Even in the most resource-limited setting, information on levels and causes of death can be obtained by standardised household surveys with modules on sibling survival and verbal autopsy.[7,11] In view of the multitude of existing household surveys in developing countries and a potential way of joint funding by the GAVI Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the World Bank in monitoring and evaluation at country level,[12] empirical data collection is now feasible, for which the UN agencies could play a crucial role through the UN's convening power and standard-setting roles. Only with a strong leadership, together with technical integrity among those involved in the process of scientific debates, will the global health community become confident with what works and what does not in achieving the health-related MDGs.

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AK declares that she has no conflicts of interest. KS has worked at WHO and is collaborating with the Institute for Health Metrics and Evaluation in the Global Burden of Disease 2005 study.

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Light-chain MGUS: implications for clinical practice

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Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition defined by the presence of a serum monoclonal protein (M-protein) of less than 3 g/dL with less than 10% monoclonal plasma cells in bone marrow in the absence of hypercalcaemia, renal insufficiency, anaemia, or skeletal lytic lesions.[1] Prevalence was 3·2% in a population-based survey of 21 000 residents aged 50 years or older in Olmsted County, Minnesota, USA.[2] Prevalence increased with age and reached 7·5% in individuals aged 85 years or older. Examination of the discharge records of 142 Veteran Affairs hospitals between 1980 and 1996 revealed that MGUS was three times more common in African-Americans than in white veterans.[3] Several studies have shown that the rate of progression of MGUS to multiple myeloma or related disorders is about 1% per year and remains constant over time.[4]

A nationwide cancer screening study prospectively enrolled nearly 77 500 healthy adults aged 55–74 years, of whom 71 developed multiple myeloma.[5] Analysis of stored blood samples dating back 2–8 years before the diagnosis of multiple myeloma revealed the presence of an M-protein in all patients, which suggests that multiple myeloma invariably evolves from MGUS. However, it cannot be excluded that some patients might have had undiagnosed multiple myeloma. In a second study of stored samples from the US Department of Defense Serum Repository, M-protein was detected before diagnosis of multiple myeloma in 27 of 30 patients, which lends further support to the hypothesis that an MGUS state precedes overt multiple myeloma.[6] Both studies found a small number of patients in whom light chains only were detected without a corresponding immunoglobulin heavy protein by serum assay of free light chain. The existence of light-chain MGUS was suspected from as early as 1982 with the description of idiopathic Bence-Jones proteinuria, a disease entity that might represent a more advanced stage of light-chain MGUS.[7] Further, with the advent of the highly sensitive free-light-chain assay, light-chain MGUS has been seen occasionally in every major referral centre for multiple myeloma.

See corresponding editorial on page 1281.

Effect of early exclusive breastfeeding on morbidity among infants born to HIV-negative mothers in Zimbabwe[1–3]

Ai Koyanagi, Jean H Humphrey, Lawrence H Moulton, Robert Ntozini, Kuda Mutasa, Peter Iliff, Robert E Black, and the ZVITAMBO Study Group

ABSTRACT

Background: Early exclusive breastfeeding (EBF) is recommended by the World Health Organization, but EBF rates remain low throughout the world. For infants born to breastfeeding HIV-positive mothers, early EBF is associated with a lower risk of postnatal transmission than is feeding breast milk together with other liquids or foods. No studies conducted in Africa have reported any benefits of EBF for infants born to HIV-negative women.

Objective: The objective was to compare the rate of sick clinic visits by infants aged 43–182 d according to breastfeeding exclusivity [EBF, predominant breastfeeding (PBF), and mixed breastfeeding (MBF)].

Design: We compared rates of all-cause clinic visits and clinic visits related to diarrhea and lower respiratory tract infection (LRTI) among a cohort of 9207 infants of HIV-negative mothers during 2 age intervals: 43–91 and 92–182 d according to exclusivity of breastfeeding. Breastfeeding exclusivity was defined in 2 ways ("ever since birth" and "previous 7 d") and was assessed at 43 and 91 d.

Results: EBF between birth and 3 mo was significantly protective against diarrhea between 3 and 6 mo of age with the "ever since birth" definition [incidence rate ratios (IRRs) of 8.83 (95% CI: 1.07, 65.53) and 8.76 (95% CI: 1.13, 68.09) for PBF and MBF, respectively] and with the "previous 7 d" definition [2.04 (95% CI: 1.11, 3.77) and 2.05 (95% CI: 1.13, 3.72) for PBF and MBF, respectively]. The adverse effect of MBF on LRTI visits was weaker, reaching borderline significance only by the "ever since birth" definition during the 43–91-d interval (IRR: 1.91; 95% CI: 0.99, 3.67).

Conclusion: Early EBF is associated with a significant reduction in sick clinic visits, especially those due to diarrhea. *Am J Clin Nutr* 2009;89:1375–82.

INTRODUCTION

The 2003 *Lancet* series on child survival identified the promotion of exclusive breastfeeding (EBF) during the first 6 mo of life and continued breastfeeding to 12 mo as the single most effective preventive public health intervention for reducing mortality among children aged <5 y (1). More recently, the 2008 *Lancet* series on maternal and child undernutrition estimated that 1.06 million child deaths (10% of all mortality in children aged <5 y) are attributable to nonexclusive breastfeeding in the first 6 mo of life (2). Most of the data supporting these analyses came from studies conducted in Asia and Latin America (3–6). In Africa, where >40% of the world's deaths of children aged <5 y occur each year, breastfeeding is nearly universal and prolonged, but EBF is rare (7). Over the past 8 y, accumulating evidence that early EBF substantially lowers the risk of breastfeeding-associated HIV transmission more than does predominant breastfeeding (PBF) or mixed breastfeeding (MBF) (8–10) has led to renewed enthusiasm for EBF promotion in sub-Saharan Africa, at least for HIV-infected mothers. Two studies in Ghana have examined EBF-associated health benefits for infants born to HIV-negative mothers. The first study observed higher neonatal mortality among MBF and PBF infants than among EBF infants, although the risk associated with PBF was not statistically significant. The second study (a multisite study in which 31% of the infants were Ghanaian) found no difference in mortality risk between EBF and PBF infants and no difference in hospitalization rates between EBF and either PBF or MBF infants (11). The authors of that study concluded that efforts should focus on sustaining high rates of PBF rather than encouraging mothers to practice strict EBF.

The ZVITAMBO (Zimbabwe Vitamin A for Mothers and Babies) trial enrolled 14,110 mother-infant pairs and assessed early infant feeding practices. Among the 4495 mothers who were HIV-positive at delivery, 2060 of their infants were HIV-negative (by polymerase chain reaction) at 6 wk and continued to be breastfed. Compared with early EBF, PBF and MBF infants before 3 mo of age had, respectively, 2.6 and 4.0 times greater risks of breastfeeding-associated HIV transmission by 6 mo and 1.6 and 2.6 times greater risks of transmission by 18 mo (9).

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[2] The ZVITAMBO project was supported by the Canadian International Development Agency (R/C Project 690/M3688), US Agency for International Development (cooperative agreement number HRN-A-00-97-00015-00 between Johns Hopkins University and the Office of Health and Nutrition–USAID), and a grant from the Bill and Melinda Gates Foundation, Seattle, WA. Additional funding was received from the Rockefeller Foundation (New York, NY) and BASF (Ludwigshafen, Germany).

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These findings indicated that early introduction of solid foods and nonhuman milk (MBF) conveys an especially high risk of HIV transmission, but that feeding even nonmilk fluids (PBF) increases transmission risk. In the present study, we investigated whether EBF is also associated with lower morbidity among infants in the same study population whose mothers tested HIV-negative at delivery and remained HIV-negative throughout the breastfeeding period. The results of this study would help clarify whether universal promotion of early EBF would benefit all infants, whether HIV-exposed or not.

SUBJECTS AND METHODS

The design of the ZVITAMBO trial was described elsewhere (9, 12). In brief, 14,110 mother-infant pairs were recruited within 96 h of delivery at 14 hospitals and clinics in greater Harare between November 1997 and January 2000. The vast majority of Harare residents had tap water and sanitation facilities at the time of the study. Mother-infant pairs were eligible if neither had an acutely life-threatening condition, the infant was a singleton with a birth weight $\geq$1500 g, and the mother planned to stay in Harare after delivery. Written informed consent was obtained. Information on baseline characteristics was obtained by questionnaire or transcription from medical records. Gestational age was estimated (13). Infant birth weight (model 727; Seca Hanover, MD) and maternal midupper arm circumference (MUAC) were measured (14). Household income was adjusted for inflation and converted to US dollars.

At enrollment, women were tested for HIV by an algorithm incorporating 2 enzyme-linked immunosorbent assays and Western blot as previously described (12). Women who tested negative at baseline were retested at every subsequent blood draw to identify those who seroconverted postpartum. Hemoglobin was measured in women enrolled from October 1998 to the end of the study ($\approx$60% of the total sample) by using a hemoglobinometer (HemoCue, Mission Viejo, CA).

Follow-up visits were conducted at 6 wk, 3 mo, and every 3 mo thereafter up to 24 mo. At each scheduled visit, mothers were asked if, since the previous visit, their infant had been taken to a health care provider for treatment of an illness. The date and reason for each visit were determined from records completed by the health care provider who attended the infant, or, when these records were not available, by maternal report. If a child was sick when making a scheduled study visit, or if a sick child presented to the research clinic between scheduled visits, free treatment was provided by the study. Public sector health care was free of charge for children aged <5 y when recruitment for the trial began. However, as economic conditions declined during the period of the study, fees were sometimes charged and medicines were occasionally out of stock. The Medical Research Council of Zimbabwe, Medicines Control Authority of Zimbabwe, Johns Hopkins Bloomberg School of Public Health Committee on Human Research and Montreal General Hospital Ethics Committee approved the ZVITAMBO trial protocol.

Definition of breastfeeding

Detailed infant feeding information was collected at baseline, 6 wk (28–56 d), and 3 mo (77–105 d). At each of these 3 visits, the mothers were asked whether any of 22 items had ever been given to the infant since birth. These included nonmilk liquids (eg, plain water, sugar water, and juice), nonhuman milks (eg, infant formula and cow milk), solid foods (eg, porridge, fruit, vegetables, and eggs), and medicines (eg, gripe water, traditional, and prescribed Western oral medicines). Because enrollment occurred anytime between birth and 96 h, to avoid misclassification due to age at baseline, at 6 wk, mothers were also asked how the infant was fed during the entire first 96 h; this information was considered together with the data collected at baseline in classifying baseline feeding practice. At 6 wk and 3 mo, the mother was also asked whether any of the 22 foods had been given to the infant within the previous 7 d.

The World Health Organization definitions for EBF, PBF, and MBF were used (15). EBF was defined as breast milk and Western oral medications only, PBF was defined as breast milk and nonmilk liquids including oral rehydration solution (ORS), and MBF was defined as breast milk and nonhuman milk or solid food. For each infant, the breastfeeding pattern for 2 intervals (birth to 6 wk and birth to 3 mo) was defined in 2 ways:

1) "Ever since birth" definition: data collected at 2 time points (baseline and 6 wk) were used for the 6-wk definition, and data collected at 3 time points (baseline, 6 wk, and 3 mo) were used for the 3-mo definition. This definition was applied only among infants who were breastfeeding and provided complete dietary data. (EBF infants: only received breast milk and Western medicine at all time points; PBF infants: received nonmilk liquid at at least one time point but never received nonhuman milk or solid food; MBF infants: received nonhuman milk or solid food at at least one time point.)
2) "Previous 7 d" definition: infants were classified into EBF, PBF, or MBF categories based on one 7-d diet history at 6 wk and 3 mo.

Statistical analysis

Statistical analysis was conducted by using Stata version 9.2 (StataCorp LP, College Station, TX). Baseline characteristics were compared between EBF, PBF, and MBF infants defined by the 7-d history at 3 mo. Between-group differences were tested by using chi-square and Kruskal-Wallis tests for categorical and continuous variables, respectively.

Preliminary analyses showed that a significantly greater proportion of MBF infants than EBF infants at baseline had an APGAR score <8, had a birth weight <2500 g, had a gestational age <37 wk, and had been delivered by a mode other than normal vaginal delivery. For nearly all (642/645) of these MBF infants at baseline, the food that resulted in their being classified as MBF was commercial infant formula. Because this formula feeding was most likely part of clinical care required by their vulnerable medical condition, we reasoned that subsequent morbidity more likely reflected poor health at birth rather than MBF at birth. To avoid this reverse causality, we excluded these 645 infants from the "ever since birth" definition in order to not overestimate the deleterious effects of MBF.

When the trial began, little information was available on breastfeeding-associated HIV transmission. When the United Nations Program on HIV/AIDS produced new guidelines in June 1998, we conducted formative research to inform an intervention to educate and counsel mothers about infant feeding and HIV. This intervention (16) promoted EBF to 6 mo for all HIV-negative mothers and HIV-positive mothers who chose to

breastfeed and was, respectively, partially and fully implemented by September and November 1999. Thus, EBF rates were higher among infants enrolled later; therefore, all regression analyses were adjusted for enrollment date.

Child-years of observation were calculated for 2 time periods: 43 through 91 d and 92 through 182 d of age; infants were censored on the date of loss to follow-up or death. We used these periods for the primary analyses to avoid reverse causality resulting from overlapping exposure and outcome periods. The number of total sick clinic visits and cause-specific visits for lower respiratory tract infection (LRTI) and diarrhea were summed for each child during each time interval. The incidence of total and cause-specific clinic visits was calculated for the 43–91 d-interval stratified by breastfeeding practice (EBF, PBF, and MBF) at 6 wk, as defined by each definition ("ever since birth" and "previous 7 d"). These calculations were repeated for the 92–182-d interval stratified by breastfeeding practice at 3 mo. Incidence rate ratios (IRRs) were calculated with EBF as the reference group by using negative binomial regression to adjust for overdispersion.

Important covariates were identified by stepwise selection of variables (with entry and retention levels of $P = 0.20$ and 0.10, respectively) in a negative binomial regression in which feeding group was forced into the model. In addition, baseline characteristics that were unevenly distributed among the breastfeeding groups were assessed for their confounding effect. Because of the small number of events in the cause-specific models, only the strongest covariates were retained. To address the possibility of breastfeeding status changing as a result of illness, a sensitivity analysis that excludes all sick clinic visits occurring within 7 d of breastfeeding status assessment was conducted.

We also hypothesized that if the breastfeeding mode changed because of infant disease or vulnerability and because infants who were sick in the past also tend to be sick subsequently, PBF and MBF in the past may be a marker of vulnerability. For example, provision of liquid or solid food because of loss of appetite due to disease or mixing of bitter medicine into sweet liquids or provision of ORS all shift children into PBF or MBF because of disease. To address this issue, we conducted a sensitivity analysis where we added a binary variable that was "ever having had sick clinic visit due to diarrhea or LRTI in last 42 or 91 d" as adjustment covariate to cause-specific regression analyses. A P value < 0.05 was considered to be significant.

RESULTS

Of the 14,110 mothers enrolled in the ZVITAMBO trial, 9207 tested HIV-negative at baseline and did not seroconvert during follow-up. Infant feeding data were provided by 6665 and 6878 HIV-negative mothers at 6 wk and 3 mo, respectively. After the exclusion of baseline MBF infants and mother-infant pairs who came for their visit more than ± 14 d from the scheduled visit date, 4965 and 4425 mothers were classified by the "ever since birth" definition at 6 wk and 3 mo, respectively (**Table 1**). A total of 5470 and 5398 mothers provided a 7-d feeding history within 14 d of the scheduled visit date at 6 wk and 3 mo, respectively (Table 1). Mothers who were primiparous and younger and those with a male infant were less likely to exclusively breastfeed; other baseline characteristics did not differ across the 3 feeding groups (**Table 2**). Baseline characteristics were similarly distributed across feeding groups when defined by the "ever since birth" definition at 3 mo or when defined by either definition at 6 wk (data not shown). The background mortality rate was low; 99.6% of the 5398 infants who provided "previous 7 d" breastfeeding status at 3 mo were alive at 6 mo.

TABLE 1
Breastfeeding exclusivity rates at 6 wk and 3 mo of age according to 2 definitions[1]

	"Ever since birth"			
"Previous 7 d"	EBF[2]	PBF[2]	MBF[2]	Total
6 wk [*n* (%)]				
EBF	403 (61.4/100.0)	237 (36.1/7.4)	16 (2.5/1.2)	656
PBF	0	2949 (93.2/92.6)	214 (6.8/15.6)	3163
MBF	0	0	1146 (100.0/83.3)	1146
Total	403	3186	1376	4965
3 mo [*n* (%)]				
EBF	147 (30.8/100)	296 (62.1/19.5)	34 (7.1/1.2)	477
PBF	0	1225 (78.0/80.5)	346 (22.0/12.5)	1571
MBF	0	0	2377 (100.0/86.2)	2377
Total	147	1521	2757	4425

[1] EBF, exclusive breastfeeding; PBF, predominant breastfeeding; MBF, mixed breastfeeding. "Previous 7 d" refers to breastfeeding practice during the previous 7 d, and "ever since birth" refers to breastfeeding practice since birth.

[2] The first value in parentheses corresponds to the proportion of infants classified as EBF, PBF, or MBF by the "previous 7 d" definition at 6 wk and 3 mo; the second value in parentheses corresponds to the proportion of infants classified as EBF, PBF, or MBF by the "ever since birth" definition at 6 wk and 3 mo.

Breastfeeding practice, household income, and sick clinic visit rates were all strongly associated with date of enrollment into the trial. The EBF rate (during both time intervals defined by either definition) was highest among infants enrolled in the last quartile, reflecting introduction of the EBF promotion intervention (**Table 3**). Median household income fell and the proportion of families living on <$1/d rose over the recruitment period. Rates of sick clinic visits fell, for both total and cause-specific visits and for the first and second 3-mo age intervals. This may reflect the declining economy because the proportion of sick clinic visits conducted at the study clinic (where treatment was free and transport costs were reimbursed) rose over the recruitment period.

Food items consumed by >1% of the PBF and MBF infants with the "previous 7 d" definition at 3 mo are illustrated in **Figure 1**. Water, cooking oil, juice, traditional medicine, and gripe water were the most common liquids that shifted infants from EBF to PBF. Porridge was the most common food item that shifted infants from PBF to MBF; however, most MBF infants also consumed water, cooking oil, and juice.

Between 43 and 182 d, the infants included in the "ever since birth" and "previous 7 d" definitions made a total of 4951 and 5690 sick clinic visits, respectively; the all-cause sick clinic rate was similar by the 2 definitions (282.3 visits/100 child-years and 276.1 visits/100 child-years, respectively). In addition, with the use of either definition, the all-cause visit rate was higher during the 43–91-d interval than during the 92–182-d interval (**Table 4**). Upper respiratory infection and skin disease were the most common causes of sick clinic visits, accounting for 45.5% and 12.6% respectively, of the total visits among children included in the "previous 7 d" definition at 3 mo. Because breastfeeding practice was not significantly associated with sick clinic visits