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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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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?

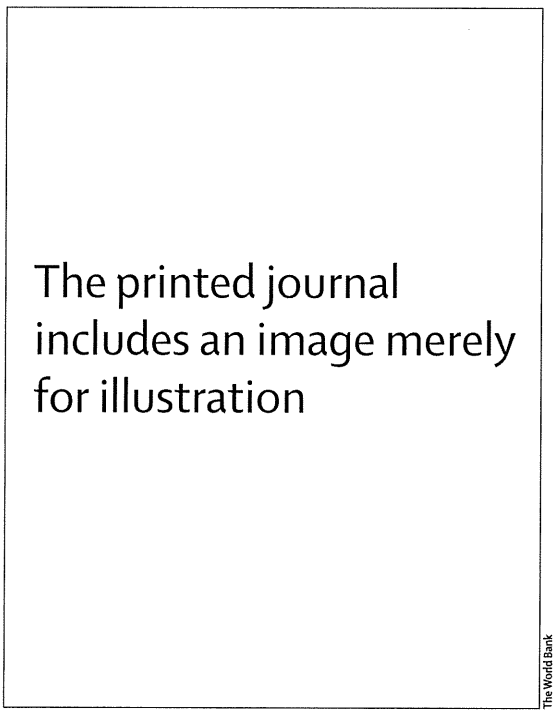
Despite the growing interest in the health of adults over the past two decades since the publication of the *World development report 1993: investing in health*,[1] a rigorous assessment of the levels and trends of adult mortality has been neglected, partly due to the huge measurement challenge (ie,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

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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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.

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.

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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.

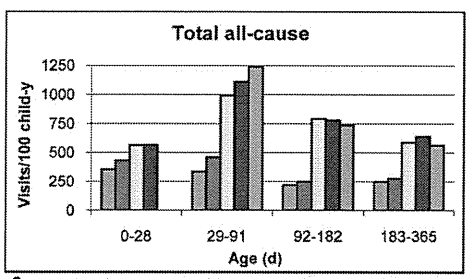
At baseline, HIV-positive mothers were more likely to be older, anemic, widowed or separated from their spouse, of higher parity and to have babies with lower birth weight and gestational age (Table 1).

Sick Clinic Visits

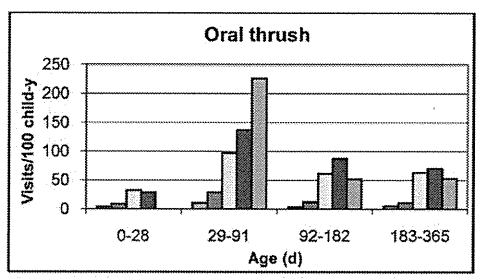
The infants in this analysis had a total of 35,108 sick clinic visits during the first year of life. Cause of visit was obtained from

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.

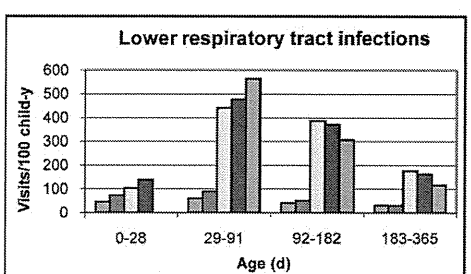
The all-cause sick clinic visit rate was significantly higher among HEU compared with not-exposed infants during all age periods (range of IRRs, 1.1–1.4; Fig. 1). The LRTI-associated visit rate was significantly higher (IRR = 1.3–1.6) during the first half of infancy for HEU compared with not-exposed 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



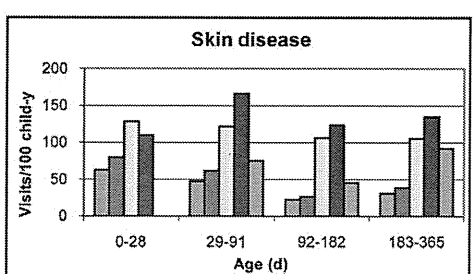
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	1.2 (1.1-1.4)	1.4 (1.3-1.5)	1.1 (1.1-1.2)	1.1 (1.1-1.2)
IU	1.6 (1.2-2.1)	3.0 (2.6-3.5)	4.2 (3.5-5.0)	2.5 (2.2-3.0)
IP	1.6 (1.3-2.0)	3.4 (3.0-3.8)	4.1 (3.5-4.7)	2.8 (2.5-3.1)
PN		3.7 (2.3-6.0)	3.3 (2.3-4.5)	2.2 (1.9-2.7)



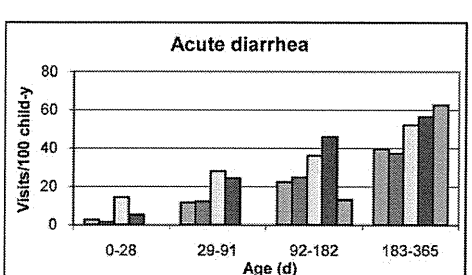
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	2.2 (1.0-4.8)	2.8 (2.1-3.8)	3.4 (2.2-5.3)	2.0 (1.5-2.8)
IU	7.8 (2.3-25.9)	9.6 (6.0-15.3)	18.8 (8.8-40.0)	12.4 (6.2-24.8)
IP	7.0 (2.4-20.5)	13.5 (9.1-19.8)	24.0 (13.3-43.1)	16.7 (9.9-28.3)
PN		20.6 (5.6-76.2)	13.6 (4.0-46.2)	9.7 (4.6-20.4)



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).

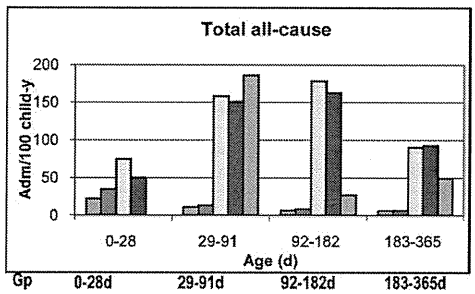
Hospitalizations

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.

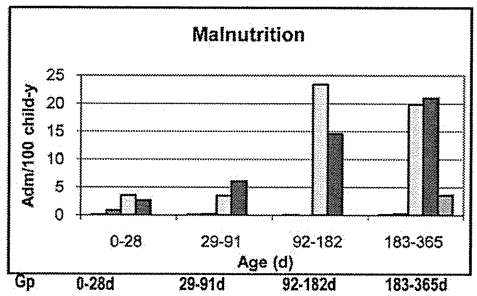
The neonatal period was the only time when hospitalization rates significantly differed between HEU and not-exposed (IRR = 1.5 [95% CI: 1.2–2.0] for all-cause and 2.7 [95% CI: 1.6–4.7] for LRTI hospitalizations) (Fig. 2). In sensitivity analyses including only infants who survived to the end of the interval, 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

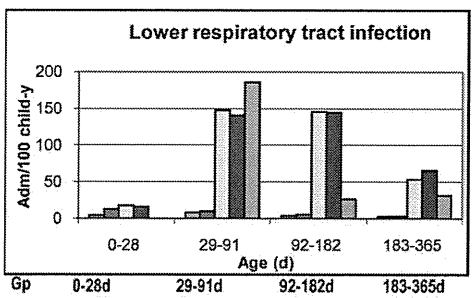
This analysis underlines the magnitude and severity of illness experienced by HIV-infected infants and the substantial burden to the health care system that results. HIV-infected infants in this cohort contributed only 6% of all the child-years of follow-up time but they accounted for 14% of the sick 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



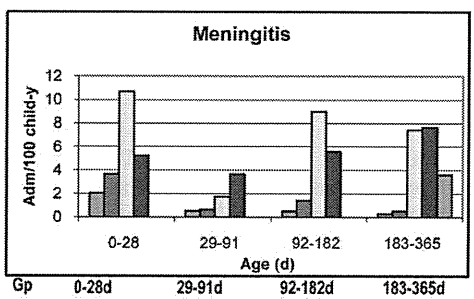
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	1.5 (1.2-2.0)	1.2 (0.9-1.6)	1.2 (0.9-1.7)	1.0 (0.8-1.3)
IU	3.3 (2.0-5.3)	14.3 (11.0-18.6)	26.0 (20.0-33.9)	13.9 (10.6-18.1)
IP	2.2 (1.3-3.6)	13.6 (10.7-17.3)	23.8 (18.8-30.1)	14.3 (11.5-17.7)
PN		17.0 (5.5-40.5)	5.7 (2.1-12.8)	10.1 (7.1-14.1)



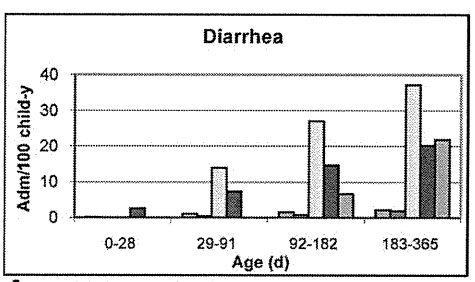
Gp	0-28d	29-91d	92-182d	183-365d
NE	1.0	1.0	1.0	1.0
HEU	6.3 (0.3-370.3)	1.6 (0.0-31.3)	NA	1.8 (0.3-8.5)
IU	24 (0.3-1916)	26 (2-364)	499 (75-21221)	136 (51-424)
IP	18 (0.2-1409)	46 (8-487)	311 (47-13222)	143 (59-421)
PN			NA	88 (27-308)



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)



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)



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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TABLE 1. NEW INFECTION RATES AND INCIDENCE DENSITY OF HIV AND SYPHILIS

	HIV		Syphilis[a]	
Type of recruited MSM cohorts	*Infection rate*	*Incidence density (95% CI)*	*Infection rate*	*Incidence density (95% CI)*
Recruited cohort in 2007	5.7 (3.1–9.5)%	4.7 (1.7–9.9)/100 PY	18.3 (13.5–24.0)%	21.6 (14.4–30.4)/100 PY
Recruited cohort in 2008	6.2 (4.4–8.4)%	6.1 (4.0–9.0)/100 PY	8.9 (6.7–11.4)%	26.0 (21.9–30.9)/100 PY
Recruited cohort in 2009	8.1 (5.8–11.0)%	10.2 (5.2–17.5)/100 PY	14.9 (11.8–18.6)%	29.8 (21.8–38.7)/100 PY

[a]The positive standard of syphilis was that both RPR and TPHA-ELISA were positive.

In 2007, 229 men who have sex with men (MSM) were recruited;13 persons were previously HIV positive; 128/100 PY were followed. The incidence density of HIV was 6/128 PY=4.7/100 PY; 19 persons were previously syphilis positive; 111/100 PY were followed. The incidence density of syphilis was 24/111 PY=21.6/100 PY.

In 2008, 598 MSM were recruited; 24 persons were previously HIV positive; 406/100 PY were followed. The incidence density of HIV was (10+15)/(238+336×0.5) PY=6.1/100 PY; 37 persons were previously syphilis positive; 393/100 PY were followed. The incidence density of syphilis was (33+70)/(225+336×0.5) PY=26.0/100 PY.

In 2009, 455 MSM were recruited; 26 persons were previously HIV positive; 108/100 PY were followed. The incidence density of HIV was 11/216 PY=10.2/100 PY; none was previously syphilis positive; 121/100 PY were followed. The incidence density of syphilis was 36/242×0.5 PY=29.8/100 PY.

In conclusion, we report a rapid increase in incidence of both HIV and syphilis among MSM living in Shenyang city based on three consecutive 12-month cohort studies. Without intervention, the prevalence of HIV and syphilis may continue to increase in coming years. To curb the rapid transmission of HIV through the MSM community, access to HIV screening strategies should be enhanced and promoted nationwide. A condom program targeting 100% participation should be promoted among the MSM population. Since infection with syphilis can increase the risk of acquiring HIV in MSM, syphilis screening and treatment programs should be adopted along with HIV prevention and treatment programs to decrease both the high incidence of syphilis and the rapidly growing trend of HIV.

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Author Disclosure Statement

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Predictive Value of Weight Loss on Mortality of HIV-Positive Mothers in a Prolonged Breastfeeding Setting

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Abstract

HIV-positive lactating women may be at high risk of weight loss due to increased caloric requirements and postpartum physiological weight loss. Ten percent weight loss is associated with a higher risk of mortality in HIV-positive patients and this alone is a criterion for highly active antiretroviral therapy (HAART) initiation where CD4 counts are not available. However, no study has investigated this association in lactating postpartum women. We investigated whether 10% weight loss predicts death in postpartum HIV-positive women. A total of 9207 HIV-negative and 4495 HIV-positive mothers were recruited at delivery. Women were weighed at 6 weeks, 3 months, and every 3 months thereafter for up to 24 months postpartum and data on mortality up to 2 years were collected. The median duration of breastfeeding was longer than 18 months. Among HIV-positive women, the independent predictors of ≥10% weight loss were CD4 cell count, body mass index, and household income. Mortality was up to 7.12 (95% CI 3.47–14.61) times higher in HIV-positive women with ≥10% weight loss than those without weight loss. Ten percent weight loss in postpartum lactating HIV-positive women was significantly predictive of death. Our findings suggest that 10% weight loss is an appropriate criterion for HAART initiation among postpartum breastfeeding women.

Introduction

WEIGHT LOSS IS A STRONG risk factor for death in HIV-positive people living in food-secure, industrialized country populations,[1–5] where it is usually due to increased basal metabolic rate,[6] the antitrophic effects associated with opportunistic infections,[7–9] malabsorption,[7] decreased dietary intake associated with anorexia,[10] and metabolic abnormalities.[11] Accordingly, the World Health Organization (WHO) guidelines for highly active antiretroviral therapy (HAART) state that when CD4 count is not available, ≥10% weight loss alone is a sufficient indication for treatment initiation. However, this recommendation is based on data from studies in developed countries while the majority of HIV-infected individuals (and nearly all those for whom CD4 is not available) live in developing countries, where many other factors besides HIV could contribute to weight loss and where less information on the association between weight loss and mortality is available.[12] Consequently, the weight loss indicator is not widely used in programs as a sole indicator for HAART initiation due to concern that it may be too sensitive in developing country settings[13] and lead to premature initiation of HAART, which is associated with a waste of resources, adverse events, pill fatigue, noncompliance, and the emergence of resistant virus strains.[14] There may be particular reluctance to rely on weight loss alone for postpartum lactating women in whom weight loss is expected due to physiological postpartum weight loss and the high energy demands of lactation[15] estimated to be 467–600 kcal/day between 0 and 23 months postpartum.[16–18] Among HIV-positive lactating mothers in Africa, longer breastfeeding duration was associated with less postpartum weight gain[19] and breastfeeding increased the risk of weight loss compared to formula feeding.[20] Furthermore, exclusive breastfeeding requires more caloric intake than partial breastfeeding,[16] but is the optimal feeding method for all babies during the first 6 months of life, including HIV-exposed infants.[21]

However, since weight loss can be identified without sophisticated diagnostic devices or a high level of training, it would be a highly valuable tool in identifying HAART eligibility in resource-limited settings if it is predictive of death. This analysis was conducted among HIV-negative and HIV-positive women enrolled in the ZVITAMBO trial in Harare, Zimbabwe. Mortality at 24 months was 2.3/1000

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person-years and 38.3/1000 person-years among HIV-negative and HIV-positive women, respectively.[22] The objective of the current article is to describe their weight loss pattern, identify risk factors for postpartum weight loss, and determine whether a ≥10% weight loss over this period was a significant predictor of mortality.

Materials and Methods

Details of the ZVITAMBO trial have been previously published.[22–24] Briefly, 14,110 mother–infant pairs were recruited within 96 h of delivery between November 1997 and January 2000 in Harare, Zimbabwe. Mothers and infants were included in the study if neither had an acutely life-threatening condition and the mother had planned to stay in Harare after recruitment. Written informed consent was obtained. Hospital records, questionnaires, and direct measurements were used to obtain baseline information. Follow-up was conducted at 6 weeks, 3 months, and then every 3 months up to 12 to 24 months. HIV-positive mothers and their infants were initially planned to be followed for 24 months. However, in June 2000, economic conditions necessitated discontinuing the second year of follow-up. Thus 24%, 48%, and 100% of the pairs were reassigned to 24 months, ≥18 months, and ≥12 months follow-up, respectively. Of the HIV-negative mothers, 4632 and 4930 were initially randomized to complete the study after 12 and 24 months of follow-up, respectively, and in June 2000, 24%, 48%, and 100% of the 4930 were reassigned to 24 months, ≥18 months, and ≥12 months follow-up, respectively. Antiretroviral drugs were not available in Harare during the study period. At baseline, women were tested for HIV by an algorithm incorporating two parallel ELISAs and Western blot.[24] Plasma CD4 cells were counted by FACScount (Becton Dickinson) and were available in 36% of the HIV-negative women and 87% of the HIV-positive women. Plasma viral load was measured in 36% of HIV-positive women (Roche Amplicor). Hemoglobin (Hb) was measured in women enrolled from October 1, 1998 to the end of the study (approximately 60% of the mothers) by HemoCue (Mission Viejo, CA). Height (Height-Rite statiometer, model 225, Seca, Hanover, MD) was measured at the first follow-up visit, and weight (balance beam scale model 700, Seca, Hanover, MD) at all follow-up visits but not at baseline. Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. Information on breastfeeding status and subsequent pregnancy was obtained by self-report at follow-up visits.

Statistical analysis

Statistical analysis was conducted using Stata Version 9.2 (StataCorp LP, Texas). Baseline characteristics were examined by chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables between HIV-negative and HIV-positive women. The rate of breastfeeding at 12, 18, and 24 months was calculated using the Kaplan–Meier (K-M) method. The women were censored on the date of weaning, if known, or at the last date in which they were known to be breastfeeding.

Postpartum weight change patterns between HIV-negative and HIV-positive women

To describe the postpartum weight change pattern as accurately as possible, we restricted the study population for this part of the analysis in three ways: (1) we included only mothers who had weight measured at 24 months to avoid follow-up bias; (2) we excluded women who became pregnant during follow-up to eliminate the effect of subsequent pregnancy on weight loss pattern; and (3) we included only weight measurements that were conducted within ±7 days of the scheduled date of follow-up to obtain an accurate estimate of weight and weight difference at each time point. Kruskal–Wallis tests were used to compare the median weight and median weight change from 6 weeks between HIV groups. Wilcoxon sign rank tests were used to test median weight change from 6 weeks within each HIV group against 0.

Cumulative risk of ≥10% weight loss relative to weight at 6 week postpartum in HIV-negative and HIV-positive women, and predictors of ≥10% weight loss in HIV-positive women

K-M methods were used to estimate the cumulative risk of ≥10% weight loss in HIV-negative and HIV-positive women between 6 weeks and 2 years postpartum. All women who had weight measured within ±7 days of the scheduled date at 6 weeks and at one or more subsequent time points were included in this analysis. This analysis was not restricted to those with weight measurement within ±7 days of the scheduled follow-up visit date after the 6-week visit. Women were censored at the date on which a ≥10% weight loss was detected or at the date of their last weight measurement. We compared the time to weight loss between HIV groups using the Cox regression model. Univariate Cox regression models were used to identify independent risk factors for experiencing a ≥10% weight loss in HIV-positive women. A multivariate Cox model was constructed by stepwise selection of variables (with entry and retention levels of $p = 0.10$ and 0.05, respectively) to identify influential covariates. The factors offered to the model were maternal BMI at 6 weeks, plasma CD4 cell count, plasma HIV-RNA, age, enrollment date, marital status, parity, hemoglobin, education, occupation, and household income.

Cumulative mortality risk by ≥10% weight loss in HIV-positive women

K-M methods were used to compare the cumulative maternal mortality risk for HIV-positive women who had and had not experienced a ≥10% weight loss during 10 different intervals (6 weeks and 3, 6, 9, 12 months; 3 months and 6, 9, 12 months; 6 months and 9 and 12 months; 9 months and 12 months). Only women who had weight measured at both time points within ±7 days of the scheduled follow-up date were included in these analyses. Mortality risk after the latter of the two weight measurements was calculated by a Cox proportional hazards model. Risk factors of mortality were identified by stepwise selection of variables with entry and retention levels of $p = 0.10$ and 0.05, respectively, in a Cox regression hazards model. Maternal BMI at 6 weeks, plasma CD4 cell count, plasma HIV-RNA, age, enrollment date, marital status, parity, hemoglobin, education, occupation, and household income and a binary variable of ever having ≥10% weight loss in respect to weight at 6 weeks (±7 days) were offered to the model.

TABLE 1. MATERNAL BASELINE CHARACTERISTICS BY MATERNAL HIV INFECTION STATUS

Characteristics	*Category*	*HIV−*	*%*	*HIV+*	*%*	*p-value*
Age (years)	<20	827	(20.3)	238	(10.7)	<0.001
	20–34	2883	(70.8)	1803	(80.9)	
	>34	362	(8.9)	188	(8.4)	
	Median (IQR)*	23.6	(20.5–27.8)	25.4	(22.2–29.3)	<0.001
Plasma CD4 (cells/μl)	<350	25	(7.9)	789	(40.5)	<0.001
	≥350	293	(92.1)	1157	(59.5)	
	Median (IQR)*	737	(529–961)	399	(251–559)	<0.001
Plasma HIV-1 RNA (copies/ml)	≤500	—	—	29	(3.4)	
	501–10,000	—	—	356	(41.1)	
	10,001–40,000	—	—	229	(26.4)	
	>40,000	—	—	252	(29.1)	
Hemoglobin (g/liter)	<70	39	(1.5)	40	(3.1)	<0.001
	70–120	1138	(44.8)	829	(63.3)	
	>120	1366	(53.7)	441	(33.7)	
BMI at 6 weeks (kg/m^2)	<18.5	179	(4.5)	118	(5.4)	0.001
	18.5–24.9	2684	(67.3)	1533	(70.6)	
	≥25.0	1127	(28.3)	521	(24.0)	
	Median (IQR)*	23.0	(20.9–22.6)	22.6	(20.7–24.9)	<0.001
Marital status	Married/stable	3857	(94.8)	2037	(91.7)	<0.001
	Separated/widowed	58	(1.4)	84	(3.8)	
	Single-never married	152	(3.7)	101	(4.6)	
Occupation	Unemployed	3322	(81.6)	1784	(80.1)	0.320
	Domestic worker	225	(5.5)	127	(5.7)	
	Other	525	(12.9)	316	(14.2)	
Household income per month (US$)[a]	<130	2374	(74.7)	1219	(75.1)	0.772
	≥130	803	(25.3)	404	(24.9)	
Parity	1	1647	(40.4)	570	(25.5)	<0.001
	2–4	2113	(51.8)	1513	(67.8)	
	≥5	320	(7.8)	150	(6.7)	
Education (years)	0–7	729	(17.9)	432	(19.4)	0.154
	8–13	3342	(82.1)	1799	(80.6)	
Enrollment date	16 Jul 1999–31 Jan 2000	1237	(30.3)	632	(28.3)	0.153
	1 Jan 1999–15 Jul 1999	965	(23.7)	507	(22.7)	
	16 Jun 1998–31 Dec 1998	988	(24.2)	580	(26.0)	
	25 Nov 1997–15 Jun 1998	890	(21.8)	514	(23.0)	
Breastfeeding status at 3 months (previous 7 days)	Exclusive	551	(10.3)	258	(10.2)	0.092
	Predominant	1892	(35.2)	833	(32.8)	
	Mixed	2929	(54.5)	1446	(57.0)	

Restricted to women who had weight measurement at 42 days (±7 days) and at least one subsequent weight measurement.
[a]Inflation adjusted.
IQR, interquartile range; *p*-value calculated by chi-square apart from values marked with an asterisk (*) that are tested by Kruskal–Wallis test; data, *n* (%) unless otherwise stated.

Ethical approval

Ethical approval was granted from the Medical Research Council of Zimbabwe, Medicines Control Authority of Zimbabwe, the Committee on Human Research of the Johns Hopkins University Bloomberg School of Public Health, and the Ethics Committee of the Research Institute of the McGill University Health Center.

Results

A total of 9207 women were HIV negative at baseline and never seroconverted and 4495 tested HIV positive at baseline. The rate of breastfeeding at 12, 18, and 24 months among HIV-negative women was 96.5%, 56.9%, and 16.5%, respectively, and among HIV-positive women was, respectively, 90.5%, 46.7%, and 13.0%. The age of weaning [median (IQR)] was 578 (515–661) and 548 (486–639) days for HIV-negative and HIV-positive women, respectively. The baseline characteristics of the HIV-negative and HIV-positive women who had weight measurement at 42 days (±7 days) and at least one subsequent weight measurement are illustrated in Table 1. In the HIV-positive population, the CD4 cell count [median (IQR)] was 399 (251–559). HIV-positive women were older with higher parity and more likely to be widowed or separated compared to HIV-negative women. Overweight was common where 28.3% and 24.0% of HIV-negative and HIV-positive women, respectively, had a BMI ≥25.

Postpartum weight change patterns between HIV-negative and HIV-positive women

A total of 625 HIV-negative and 561 HIV-positive women who were weighed within ±7 days of the scheduled date of follow-up at 24 months without subsequent pregnancy were included in the analysis. The [median (IQR)] weight was 60.0 (53.9–67.0) kg and 58.5 (52.8–65.5) kg for HIV-negative and HIV-positive women at 6 weeks postpartum, respectively (Fig. 1 and Table 2). After 6 weeks, median weight declined

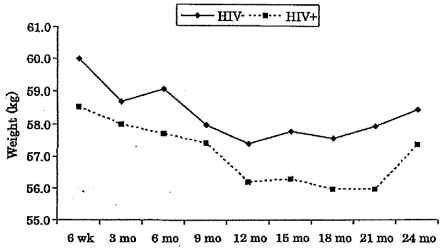

FIG. 1. Median weight at follow-up in HIV-negative and HIV-positive women. Only women who had weight measured at 24 months (within ±7 days of the scheduled visit) and did not become pregnant are included. Only weight measurements conducted within ±7 days of the scheduled follow-up date are included. Differences between HIV-negative and HIV-positive women are statistically significant at 6 weeks, 6 months, 15 months, 18 months, 21 months, and 24 months ($p < 0.05$, Kruskal–Wallis test).

among both HIV-negative and HIV-positive women reaching nadirs of 57.4 kg (IQR: 51.0–65.3) at 12 months and 56.0 kg (IQR: 51.0–62.5) at 18 months, respectively, before increasing to 58.5 kg (IQR: 53.0–65.9) and 57.4 kg (IQR: 51.4–63.8), respectively, at 24 months. The median weight of HIV-positive women was significantly lower than that of HIV-negative women at all time points except at 3 months, 9 months, and 12 months. The change in weight between 6 weeks and all subsequent time points was not significantly different between HIV groups for any of the intervals.

Cumulative risk of ≥10% weight loss relative to weight at 6 weeks postpartum in HIV-negative and HIV-positive women

A total of 4078 HIV-negative and 2233 HIV-positive women for whom weight was available at 6 weeks (±7 days) with at least one subsequent time point were included in the analysis. The cumulative risks (95% CI) of ≥10% weight loss relative to weight at 6 weeks among HIV-negative women were 15.5% (14.4–16.7%) and 34.1% (31.5–36.9%) at 365 and 730 days, respectively. The comparable values for HIV-positive women were 17.4% (15.8–19.2%) and 38.0% (35.3–40.9%). The cumulative probability of attaining ≥10% weight loss was 25% at 457 and 468 days for HIV-positive and HIV-negative women, respectively. Among women who experienced ≥10% weight loss between 6 weeks and 12 months, the median (IQR) weight loss for HIV-positive and HIV-negative women was 5.7 (3.1–8.3) kg and 6.3 (4.0–8.4) kg, respectively. The corresponding values for women who experienced ≥10% weight loss between 6 weeks and 24 months were 4.0 (3.0–7.0) kg and 3.7 (0.8–7.0) kg. HIV-positive women were 14% (HR 95% CI 1.02–1.27; $p = 0.018$) more likely to lose at least 10% of their body weight than HIV-negative women. After adjustment for BMI at 6 weeks, household income, age, and education, this association remained similar (data not shown).

Predictors of ≥10% weight loss in HIV-positive women

In univariate analyses, BMI <18.5 at 6 weeks, CD4 <350 cells/μl at delivery, monthly income <US$130, and schooling <7 years were significant predictors of subsequent ≥10% weight loss among HIV-positive women (Table 3). In the final Cox model, only CD4 at baseline, BMI at 6 weeks, and household income were retained. Lower household income was associated with a 55% higher risk of weight loss. Those with BMI <18.5 were 45% less likely to have weight loss but those with BMI ≥25 had a 26% higher risk of weight loss compared to those with BMI 18.5–24.9.

Cumulative maternal mortality risk among HIV-positive women with and without ≥10% weight loss

HIV-positive women who lost ≥10% of their body weight during any of the 10 intervals examined were at a 1.9–7.1 times higher risk of subsequent death compared to HIV-positive women who did not experience weight loss of this magnitude during the same interval (Table 4). This greater risk was statistically significant for 7 of the 10 times intervals. There were no distinct patterns in the risk of mortality associated with weight loss of an acute or chronic nature.

Baseline CD4, BMI, education, and ever having had ≥10% weight loss emerged as significant predictors of maternal mortality. After adjustment for CD4, education, and weight loss, BMI <18.5 was associated with a 3.24 (95% CI 1.62–6.48; $p = 0.001$) times higher risk of death compared to BMI 18.5–24.9, but BMI ≥25 conferred no significant protective effect compared to BMI 18.5–24.9 [HR 0.74 (95% CI 0.39–1.40; $p = 0.355$].

Discussion

In this study, 34.1% of HIV-negative and 38.0% of HIV-positive women lost at least 10% of their body weight between 6 weeks and 24 months postpartum. Yet despite this high background rate of weight loss, HIV-positive postpartum breastfeeding women who lost ≥10% of their body weight during any of the 10 time intervals between 6 weeks and 24 months postpartum were at substantially higher risk of death compared with similar women who did not experience this weight loss during the same time interval. Significant independent predictors of experiencing a ≥10% weight loss in HIV-positive women were BMI, CD4, and household income. Compared to women with a 6 week BMI 18.5–24.9, women with BMI ≥25 had a 26% higher risk of weight loss and women with BMI <18.5 had a 45% lower risk of a ≥10% weight loss. To investigate whether there was detection bias of weight loss in those with BMI <18.5 because they were too sick to have weight measured, sensitivity analysis was conducted by excluding women who died but results remained similar (data not shown). It has been reported that larger gestational weight gain is associated with more postpartum weight loss[25] and this result might be reflecting this phenomenon. Women whose household income was in the higher quartile were protected from weight loss. It might have been that poorer women had economic difficulties obtaining food that could fulfill the increased caloric demand of breastfeeding. Also, higher income women may have had more medical attention and access to drugs to control opportunistic infections that lead to weight loss, and/or more sedentary life styles with lower caloric requirements. The relationship between CD4 and weight loss is most likely mediated by the characteristics of advanced HIV infection such as higher risk of opportunistic infections,[7–9] malabsorption,[7] and abnormal metabolism,[11] which all contribute to weight loss.

TABLE 2. POSTPARTUM WEIGHT CHANGE IN HIV-NEGATIVE AND HIV-POSITIVE WOMEN

	6 weeks	*3 months*	*6 months*	*9 months*	*12 months*	*15 months*	*18 months*	*21 months*	*24 months*
HIV⁻									
Weight (kg)									
Median	60.0	58.7	59.1	58.0	57.4	57.8	57.6	58.0	58.5
(IQR)	(53.9–67.0)	(53.4–66.2)	(53.0–66.0)	(52.0–66.0)	(51.0–65.3)	(52.0–65.0)	(51.5–64.9)	(52.0–65.6)	(53.0–65.9)
N	419	519	548	538	588	595	549	568	625
Difference from 6 weeks (kg)									
Median		−0.2	−0.2	−1.3[a]	−1.3[a]	−1.4[a]	−1.2[a]	−1.5[a]	−1.0
(IQR)		(−1.5–1.0)	(−2.8–2.2)	(−3.6–1.5)	(−4.2–2.2)	(−4.0–2.2)	(−4.4–2.0)	(−4.0–1.6)	(−3.5–3.0)
N		334	319	301	320	327	303	301	327
HIV⁺									
Weight (kg)									
Median	58.5[b]	58.0	57.7[b]	57.4	56.2	56.3[b]	56.0[b]	56.0[b]	57.4[b]
(IQR)	(52.8–65.5)	(52.1–65.0)	(52.0–64.4)	(51.5–64.4)	(51.0–63.0)	(51.0–62.4)	(51.0–62.5)	(50.7–62.8)	(51.4–63.8)
N	448	505	497	527	529	546	526	520	561
Difference from 6 weeks (kg)									
Median		−0.5[a]	−0.5[a]	−0.9[a]	−1.6[a]	−2.0[a]	−1.5[a]	−1.6[a]	−1.0[a]
(IQR)		(−1.8–1.0)	(−2.9–1.6)	(−3.7–1.5)	(−4.4–1.1)	(−4.5–1.1)	(−4.7–1.8)	(−5.0–2.0)	(−4.0–2.8)
N		366	340	343	334	342	328	316	331

Only women who had weight measured at 24 months (within ±7 days of scheduled visit) and did not become pregnant again during follow-up are included. Only weight measurements conducted within ±7 days of scheduled follow-up date are included.
[a]Significantly different from 0 by the Wilcoxon sign rank test ($p < 0.05$).
[b]Median weight significantly different from HIV negative by the Kruskal–Wallis test ($p < 0.05$).
Weight difference from 6 weeks was not significantly different between HIV groups at any of the follow-ups by the Kruskal–Wallis test ($p \geq 0.05$).

TABLE 3. UNIVARIATE AND MULTIVARIATE COX PROPORTIONAL HAZARDS MODELS FOR ≥10% WEIGHT LOSS BETWEEN 6 WEEKS AND 24 MONTHS IN HIV-POSITIVE WOMEN

Baseline characteristic	*Category*	n	*HR*[a]	*95% CI*	*p-value*	*Adj HR*[b]	*95% CI*	*p-value*
Plasma CD4 count (cells/μl)	≥350	1157	1.00			1.00		
	<350	789	1.33	(1.12–1.59)	0.001	1.38	(1.16–1.65)	<0.001
Household income/month(US$)[c]	≥130	404	1.00			1.00		
	<130	1219	1.50	(1.17–1.91)	0.001	1.55	(1.21–1.97)	<0.001
BMI at 6 weeks postpartum[d]	18.5–24.9	1533	1.00			1.00		
	<18.5	118	0.57	(0.35–0.93)	0.024	0.55	(0.34–0.89)	0.016
	≥25.0	521	1.19	(0.99–1.44)	0.063	1.26	(1.04–1.52)	0.016
Plasma HIV-1 RNA (copies/ml)	≤500	29	1.00					
	501–10,000	356	1.73	(0.70–4.26)	0.232			
	10,001–40,000	229	1.47	(0.59–3.68)	0.405			
	>40,000	252	2.07	(0.84–5.12)	0.114			
Enrollment date	16 Jul 1999–31 Jan 2000	632	1.00					
	1 Jan 1999–15 Jul 1999	507	0.79	(0.60–1.03)	0.081			
	16 Jun 1998–31 Dec 1998	580	0.92	(0.72–1.18)	0.504			
	25 Nov 1997–15 Jun 1998	514	0.82	(0.64–1.06)	0.138			
Age (years)	20–34	1803	1.00					
	<20	238	0.77	(0.58–1.02)	0.070			
	>34	188	0.96	(0.72–1.28)	0.786			
Marital status	Married/stable	2037	1.00					
	Separated/widowed	84	0.83	(0.52–1.33)	0.440			
	Single-never married	101	0.88	(0.58–1.32)	0.525			
Parity	1	570	1.00					
	2–4	1513	0.97	(0.80–1.17)	0.767			
	≥5	150	1.09	(0.78–1.52)	0.606			
Hemoglobin (g/liter)	70–120	829	1.00					
	<70	40	1.08	(0.53–2.19)	0.841			
	>120	441	1.16	(0.90–1.49)	0.245			
Education (years)	>7	1799	1.00					
	≤7	432	1.24	(1.02–1.51)	0.034			
Occupation	Unemployed	1784	1.00					
	Domestic worker	127	1.03	(0.73–1.47)	0.851			
	Other	316	0.88	(0.69–1.12)	0.305			

[a]Univariate hazards ratio.
[b]Adjusted for baseline CD4 cell count, BMI at 6 weeks, and household income.
[c]Inflation adjusted.
[d]BMI (body mass index). Calculated as weight (kg)/[weight (m)]^2.

The observation that weight loss is associated with poor survival is in accordance with previous studies, which were all conducted in developed countries. First, in a group of mainly but not restricted to gay white men, ≥10% weight loss over a period of 4 months in HIV-positive individuals was associated with a 2.54 time higher risk of death when compared to those without this magnitude of weight loss.[3] Similarly, in another study, body weight of <90% of self-reported usual weight was associated with a 8.3 (95% CI 2.3–34.1) times higher risk of death.[1] Third, 10% weight loss from near the time of first AIDS diagnosis was associated with a 6.7 (95% CI 5.2–8.6) times higher mortality.[5] Finally, a weight loss of ≥4.5 kg between 3 and 9 months before development of AIDS was associated with a significantly shorter survival (median 1.06 vs. 1.45 years) compared to those without this magnitude of weight loss in gay men.[2]

Since weight loss is a simple measure that does not necessitate sophisticated diagnostic facilities or trained personnel, it may be a useful adjunct to CD4 or viral load estimations in assessing HAART eligibility in resource-limited settings. Although weight loss was a significant predictor of mortality in our study, it has been pointed out that weight loss alone may be too sensitive for HAART eligibility[13] and its utility as a HAART eligibility criterion must be assessed. The predictive value of weight loss on risk of disease progression or death must be compared to other conditions of HAART eligibility that can easily be identified in resource-limited settings. Furthermore, the inclusion of other conditions such as anemia, low BMI, presence of fever, diarrhea, or oral candidiasis with weight loss may further improve detection of those who are truly in need of HAART and this requires further investigation. Also, the WHO definition of 10% weight loss does not specify the timeframe in which weight loss occurs.[12] In our study, the highest hazard rate of death was observed in those who had weight loss over a short period of time (between 6 weeks and 3 months), but we could not detect a distinct pattern in the relationship between death and weight loss of an acute and chronic nature.

In this study, the peak weight loss was at 15 months (–2.0 kg) and 21 months (–1.5 kg) for HIV-positive and HIV-negative women, respectively. Two studies in Africa have reported postpartum weight change among lactating women. The first one from South Africa reported a 1.4 kg weight loss in HIV-positive women and a 0.4 kg weight gain in HIV-negative women between 8 and 24 weeks[26] and another study from Zambia reported a 1.1 kg weight gain between 4 and 24 months among HIV-positive women who breastfed for a median of 16 months.[19] Our results showed a median weight loss of 0.5 kg (HIV-positive women) and 0.2 kg (HIV-negative women) between 6 weeks and 6 months and no weight gain between 3 and 24 months among HIV-positive women. The reason why the weight change pattern between previous studies and ours differs is unclear, but the study from South Africa had a small sample size and thus this may be attributable to random variation.

We had three major limitations. First, the longest interval for weight measurement in our study was between 6 weeks and 12 months, so we were limited to weight loss that occurred within less than a year in our analyses. Future studies would be necessary to determine whether there is a difference in risk of death associated with acute and chronic weight loss with a longer follow-up period. Second, we did not have CD4 counts at follow-up. It would be important to investigate the correlation of weight loss with CD4 count (the gold standard for initiation of HAART) at the time of identification of a ≥10% weight loss. This is particularly important because nevirapine-based HAART, which is the most common regimen in developing countries, may be more likely to induce hepatotoxicity in those with high CD4 counts,[27] and thus evaluating the range of CD4 counts when a ≥10% weight loss is observed would be important. Finally, we did not have weight measurement before and during pregnancy. Since larger gestational weight gain has been reported to be associated with more postpartum weight loss,[25] the magnitude of the residual confounding effect of this factor remains unknown.

In conclusion, 10% weight loss after 6 weeks postpartum was predictive of death up to 24 months in HIV-positive women in a prolonged breastfeeding setting. Our findings support the WHO recommendation that HIV-positive people who experience a ≥10% weight loss should be initiated on HAART, and provide evidence that this recommendation is specifically applicable for HIV-positive lactating women in developing countries.

TABLE 4. MORTALITY IN HIV-POSITIVE WOMEN BY THE PRESENCE OF ≥10% WEIGHT LOSS

Mortality	*≥10% weight loss between*	*Total N*	*Median (IQR) weight change (kg)*	*%CD4 <350 cells/μl*[a]	*Number of deaths*	*HR*	*95% CI*	*p-value*
3–24 months	6 weeks and 3 months							
	No	1706	−0.5 (−1.8 to 0.9)	39.6	43	1.00		
	Yes	51	−9.5 (−12.8 to −6.7)	53.5	9	7.12	(3.47–14.61)	<0.001
6–24 months	6 weeks and 6 months							
	No	1446	−0.7 (−2.6 to 1.5)	38.5	23	1.00		
	Yes	114	−7.9 (−10.3 to −6.7)	41.4	9	5.03	(2.33–10.86)	<0.001
	3 months and 6 months							
	No	1631	−0.2 (−1.8 to 1.4)	38.2	26	1.00		
	Yes	55	−8.0 (−10.3 to −6.7)	46.0	4	4.84	(1.69–13.86)	0.003
9–24 months	6 weeks and 9 months							
	No	1340	−0.9 (−3.0 to 1.5)	38.4	21	1.00		
	Yes	146	−8.0 (−10.0 to −6.7)	47.7	7	3.18	(1.35–7.47)	0.008
	3 months and 9 months							
	No	1454	−0.6 (−2.5 to 1.5)	38.6	16	1.00		
	Yes	92	−7.9 (−9.8 to −6.8)	45.7	5	5.28	(1.93–14.42)	0.001
	6 months and 9 months							
	No	1615	−0.3 (−1.8 to 1.2)	39.4	25	1.00		
	Yes	43	−9.0 (−12.0 to −7.0)	51.4	1	1.91	(0.26–14.14)	0.526
12–24 months	6 weeks and 12 months							
	No	1255	−1.0 (−3.1 to 1.9)	39.6	13	1.00		
	Yes	196	−8.4 (−10.6 to −6.9)	38.6	5	2.27	(0.81–6.38)	0.119
	3 months and 12 months							
	No	1368	−0.8 (−2.9 to 1.6)	37.7	9	1.00		
	Yes	129	−7.7 (−10.0 to −6.7)	43.4	6	6.08	(2.16–17.09)	0.001
	6 months and 12 months							
	No	1440	−0.5 (−2.3 to 1.8)	38.8	12	1.00		
	Yes	100	−8.0 (−10.3 to −6.8)	52.9	3	3.44	(0.97–12.19)	0.056
	9 months and 12 months							
	No	1602	−0.2 (−1.8 to 1.3)	39.9	16	1.00		
	Yes	56	−8.5 (−10.0 to −6.9)	43.2	3	6.17	(1.80–21.19)	0.004

Only women who had weight measurements at both time points and within ±7 days of the scheduled visit date are included.
[a]CD4 cell count at baseline.
IQR, interquartile range.

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Hyponatremia, Hypochloremia, and Hypoalbuminemia Predict an Increased Risk of Mortality During the First Year of Antiretroviral Therapy Among HIV-Infected Zambian and Kenyan Women

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Abstract

Early mortality rates after initiating antiretroviral therapy (ART) are high in sub-Saharan Africa. We examined whether serum chemistries at ART initiation predicted mortality among HIV-infected women. From May 2005 to January 2007, we enrolled women initiating ART in a prospective cohort study in Zambia and Kenya. We used Cox proportional hazards models to identify risk factors associated with mortality. Among 661 HIV-infected women, 53 (8%) died during the first year of ART, and tuberculosis was the most common cause of death (32%). Women were more likely to die if they were both hyponatremic (sodium <135 mmol/liter) and hypochloremic (chloride <95 mmol/liter) (37% vs. 6%) or hypoalbuminemic (albumin <34 g/liter, 13% vs. 4%) when initiating ART. A body mass index <18 kg/m^2 [adjusted hazard ratio (aHR) 5.3, 95% confidence interval (CI) 2.6–10.6] and hyponatremia with hypochloremia (aHR 4.5, 95% CI 2.2–9.4) were associated with 1-year mortality after adjusting for country, CD4 cell count, WHO clinical stage, hemoglobin, and albumin. Among women with a CD4 cell count >50 cells/μl, hypoalbuminemia was also a significant predictor of mortality (aHR=3.7, 95% CI 1.4–9.8). Baseline hyponatremia with hypochloremia and hypoalbuminemia predicted mortality in the first year of initiating ART, and these abnormalities might reflect opportunistic infections (e.g., tuberculosis) or advanced HIV disease. Assessment of serum sodium, chloride, and albumin can identify HIV-infected patients at highest risk for mortality who may benefit from more intensive medical management during the first year of ART.

Introduction

Access to antiretroviral therapy (ART) in Africa has expanded rapidly, with an increase in the estimated number of people receiving treatment from 100,000 in 2003 to 2.9 million by December 2008.[1] Although increased ART coverage has led to substantial declines in mortality, mortality rates, especially during the first year after ART initiation, remain higher in African countries compared with higher-income countries.[2] Mortality rates of HIV-infected adults initiating ART in Africa have ranged from 8 to 16 deaths per 100 person-years.[3–7] Established predictors of mortality in low-income settings include indicators of advanced HIV infection (i.e., low CD4 cell count and WHO clinical stage 4 disease), low hemoglobin, low body mass index (BMI), and certain opportunistic infections (e.g., tuberculosis).[3,4,6–10] Several interventions have been proposed to reduce mortality in low-income settings, including promotion of earlier HIV diagnosis, treatment adherence support, and optimal prevention, screening, and management of opportunistic infections.[11]

Accurate identification of risk factors for mortality is a critical step toward reducing mortality in low-income settings. Ideally, we want to identify risk factors that (1)

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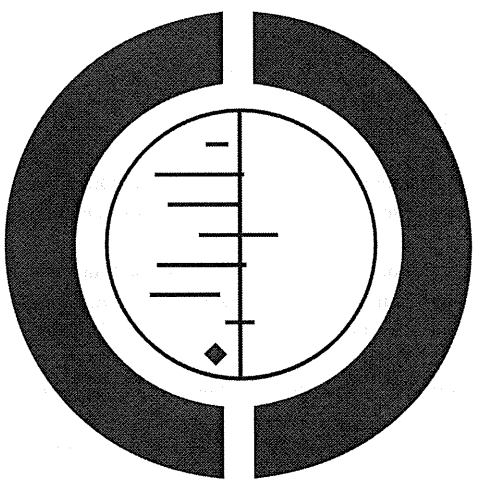
Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries (Review)

Ota E, Wariki WMV, Mori R, Hori N, Shibuya K



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[Intervention Review]

Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries

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ABSTRACT

Background

Interventions to change behaviour among sex workers and their clients have been identified as a strategy to reduce HIV transmission. However, there has been no systematic review that has examined and summarized their effects.

Objectives

To identify and evaluate the effects of the studies performed on behavioural interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries.

Search methods

Electronic searches were undertaken using MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and other databases between January 1980 and July 2010. Experts in the field were contacted to locate any other studies.

Selection criteria

Randomised controlled trials or specified quasi-experimental designs with comparison groups that examined the effects of behavioural interventions aimed at reducing the risk of HIV or sexually transmitted infections (STIs) transmission among sex workers in high-income countries. We reviewed studies for outcome relevance and methodological rigor.

Data collection and analysis

Two reviewers independently applied the inclusion criteria to potential studies, and any disagreements were resolved by discussion. Studies were assessed for completeness of reporting and extracted data.

Main results

A total of four studies were included, comprising two randomised controlled trials and two quasi-experimental pretest-posttest trials with control groups involving 1795 participants. No trials reported HIV prevalence/incidence as outcomes.

Overall, the effects of behavioural interventions for sex workers in high-income countries on STI incidence did not differ significantly among two studies using a random effects model (risk ratio (RR) 0.46, 95% confidence interval (CI) 0.11 to 1.98). Only one study found that the self-reported STI prevalence in clients of female sex workers was statistically significant (RR 0.09, 95%CI 0.01 to 0.72, P=0.02). There was no significant difference after behavioural intervention for condom use. Two studies demonstrated the effectiveness of intervention for knowledge of HIV transmission among sex workers (RR 1.82, 95%CI 1.55 to 2.14) and clients of sex workers (RR 1.93, 95%CI 1.46 to 2.55).

Authors' conclusions

There is limited evidence from randomised controlled trials for the effectiveness of behavioural interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries. Further randomised controlled trials are very likely to have important impacts on our confidence in the estimates of the effects, and are likely to change the estimates for effective interventions with outcomes of HIV incidence or prevalence and a variety of different settings among sex workers and their clients in high-income countries. Randomised controlled trials that test for the identification of effective interventions for HIV prevention with outcomes of biological endpoints, such as HIV incidence or prevalence, are needed for these neglected populations. More research is also needed for male or transgender sex workers and their clients in high-income countries.

PLAIN LANGUAGE SUMMARY

Behavioral interventions to reduce HIV transmission among sex workers and their clients in high-income countries

Behavioural interventions, such as individual counselling, voluntary counselling and testing, peer education, negotiation skills for using a condom with their clients, assertiveness and relationship support, discussing attitudes and beliefs, videos and role-playing, may reduce the prevalence of sexually transmitted infections (STI) and improve the knowledge of HIV transmission among sex workers and their clients.

Further randomised controlled trials that test for the identification of effective interventions for HIV prevention with outcomes of biological endpoints, such as HIV incidence or prevalence, are needed for these neglected populations. More research is also needed for male or transgender sex workers and their clients in high-income countries.