

Maternal HIV infection and other factors associated with growth outcomes of HIV-uninfected infants in Entebbe, Uganda

Lawrence Muhangi^{1,*}, Swaib A Lule¹, Harriet Mpairwe¹, Juliet Ndibazza¹, Moses Kizza¹, Margaret Nampijja¹, Esther Nakazibwe¹, Macklyn Kihembo¹, Alison M Elliott^{1,2} and Emily L Webb²

¹Medical Research Council/Uganda Virus Research Institute (MRC/UVRI) Uganda Research Unit on AIDS, PO Box 49, Plot 51–59 Nakiwogo Road, Entebbe, Uganda: ²London School of Hygiene and Tropical Medicine, London, UK

Submitted 20 October 2011: Final revision received 12 November 2012: Accepted 23 January 2013: First published online 18 March 2013

Abstract

Objective: To assess the associations between maternal HIV infection and growth outcomes of HIV-exposed but uninfected infants and to identify other predictors for poor growth among this population.

Design: Within a trial of de-worming during pregnancy, the cohort of offspring was followed from birth. HIV status of the mothers and their children was investigated and growth data for children were obtained at age 1 year. Length-for-age, weight-for-age and weight-for-length Z-scores were calculated for each child; Z-scores <−2 were defined as stunting, underweight and wasting, respectively.

Setting: The study was conducted in Entebbe municipality and Katabi sub-county, Uganda.

Subjects: The sample consisted of 1502 children aged 1 year: HIV-unexposed (*n* 1380) and HIV-exposed not infected (*n* 122).

Results: Prevalence of stunting, underweight and wasting was 14·2%, 8·0% and 3·9%, respectively. There was evidence for an association between maternal HIV infection and odds of being underweight (adjusted OR = 2·32; 95% CI 1·32, 4·09; *P* = 0·006) but no evidence for an association with stunting or with wasting. Young maternal age, low maternal education, low birth weight, early weaning and experiencing a higher number of episodes of malaria during infancy were independent predictors for stunting and underweight. A higher number of living children in the family was associated with wasting.

Conclusions: Maternal HIV infection was associated with being underweight in HIV-exposed uninfected infants. The success of programmes for prevention of mother-to-child HIV transmission means that an increasing number of infants will be born to HIV-infected women without acquiring HIV. Therefore, viable nutritional interventions need to be identified for this population.

Keywords
HIV exposure
Poor growth
Infancy
Uganda

Growth failure in children is a global health problem in developing countries. Data on predictors of growth failure in infants born to women infected with HIV are limited in this setting⁽¹⁾. In vertically HIV-infected children, poor growth may be an early marker of infection or progression to disease⁽²⁾. HIV-infected children normally grow considerably more slowly than their HIV-exposed, uninfected counterparts, and the gap between the two groups tends to widen with age. Children born to HIV-positive women are particularly susceptible to malnutrition. Growth failure is frequently found in this population, especially in areas where a high prevalence of HIV/AIDS coexists with high rates of food insecurity^(2,3).

HIV exposure *in utero* without subsequent infection may affect growth in infancy and early childhood⁽²⁾. Newborns whose mothers are infected with HIV may have higher rates of fetal malnutrition than newborns of HIV-seronegative mothers⁽⁴⁾, and this disadvantage is likely to extend beyond infancy. A study in Zambia found that HIV-exposed, uninfected infants had poorer growth than their HIV-unexposed counterparts⁽⁵⁾. According to a WHO working group, uninfected infants born to HIV-positive mothers grow in an unfavourable intra-uterine environment where, depending upon the setting, they may suffer from greater exposure to maternal infection and maternal malnutrition, or to drug addiction, smoking

*Corresponding author: Email Lawrence.Muhangi@mrcuganda.org

© The Authors 2013. The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution-NonCommercial-ShareAlike licence <<http://creativecommons.org/licenses/by-nc-sa/3.0/>>. The written permission of Cambridge University Press must be obtained for commercial re-use.

and poor social conditions⁽⁶⁾. Furthermore, maternal HIV severity is associated with higher morbidity and mortality, and lower weight at age 4 months, among HIV-exposed but uninfected children⁽⁷⁾. More studies have been recommended to elucidate the relationship between maternal immune status markers including viral load and CD4 cell count and child growth⁽⁸⁾.

Many other determinants of nutritional status of children have been reported. Parental education, particularly mother's education, is reported to have a strong influence on the nutritional status of the child^(9–11). Household socio-economic status and access to clean water may also have a significant impact on children's nutritional status^(11,12). Some studies have found that rural children are more likely to be stunted, wasted or underweight than those living in urban settings^(9,13). Maternal health is also important, for example maternal depression may interfere with the quality of care given to the infant⁽¹⁴⁾. In addition birth order of the child has been associated with poor growth; the higher the birth order, the higher the risk of malnutrition⁽¹⁵⁾.

The main aims of the present analysis were to: (i) assess the associations between maternal HIV infection and growth outcomes of HIV-exposed but uninfected infants; and (ii) identify other potential determinants for poor growth among infants in Entebbe municipality and Katabi sub-county of Uganda.

Materials and methods

Study area and participants

The study was conducted in Entebbe municipality and Katabi sub-county as previously described⁽¹⁶⁾. It was a randomized, double-blind, placebo-controlled trial of anthelmintics in pregnancy, using albendazole *v.* placebo and praziquantel *v.* placebo in a 2 × 2 factorial design. The study was originally designed to examine effects of anthelmintic treatment during pregnancy on infant responses to immunization and infectious disease incidence. Results of the trial have been reported elsewhere and no effect of the trial intervention on growth parameters was observed^(17,18). The study results reported herein represent a retrospective observational analysis of differences in growth at 1 year of age between HIV-exposed but uninfected infants and infants born to women who were HIV-negative. Socio-economic, maternal and infant characteristics were also evaluated for associations with growth outcomes at 1 year of age.

Women were recruited at the antenatal clinic at Entebbe Hospital between April 2003 and November 2005. They were eligible if they were well, resident in the study area, planning to deliver their baby at the hospital, willing to participate and willing to know their HIV status; and excluded if they had Hb <8 g/dl, clinically apparent severe liver disease, diarrhoea with blood in the stool, abnormal pregnancy, history of adverse reaction to anthelmintic drugs or had participated in the study during an earlier pregnancy.

Following delivery, children were followed up according to the study protocol. Morbidity data were collected prospectively at the research clinic. Malaria was diagnosed as fever ($\geq 37.5^\circ\text{C}$) with *Plasmodium falciparum* parasitaemia. Data on asymptomatic parasitaemia were collected annually. Study nurses were trained on how to take and record the anthropometric measurements. Weight measurements for 1-year-olds were taken using CMS Weighing Equipment, model MP25 (Chasmors Ltd, London, UK). The children were lightly dressed wearing undergarments only, and wore a measuring trouser which was then suspended on a weighing scale. Measurement of recumbent length at age 1 year was done using an adjustable child-length measuring board (Seca; Vogel & Halke, Hamburg, Germany).

In 2002, prior to the start of the study, the research team in collaboration with Entebbe Hospital established a programme for prevention of mother-to-child HIV transmission at the hospital. In accordance with guidelines current at the time⁽¹⁹⁾, women identified as HIV-positive were offered a single dose of nevirapine for themselves and their infants, to be taken during labour and after delivery, respectively. HIV-positive women were provided with cotrimoxazole daily for prophylaxis of opportunistic infections; HIV-exposed infants were provided with cotrimoxazole syrup from age 6 weeks until their HIV status was assessed at age 18 months; at this time, cotrimoxazole was discontinued for HIV-negative children. HIV-positive infants were referred for care at nearby specialist centres. Highly active antiretroviral therapy (HAART) for treatment was not widely available in Uganda at the time when women were recruited to the study; however, five HIV-positive women were recorded as taking HAART during pregnancy.

HIV diagnosis

Mothers' HIV status was assessed by a rapid test algorithm before delivery as previously described⁽²⁰⁾. Vertical HIV transmission was diagnosed by RNA and DNA PCR at age 6 weeks as previously described⁽¹⁸⁾ and by rapid test at age 18 months. Infants were regarded as being HIV-positive if the 6-week sample had a positive DNA PCR for any of the viral regions examined and a viral load of 1000 copies per millilitre or more, or if the rapid test at 18 months of age was positive.

Blood samples were obtained from HIV-infected pregnant women. CD4 cell counts were ordered as part of the baseline measurement and done using a BD FACScount™ flow cytometer (Becton Dickinson, San Jose, CA, USA). Maternal immunological status was dichotomized based upon results of CD4 testing performed at enrolment, with women having a CD4 count of ≤ 350 cells/mm³ being categorized as having poor immunological status.

Outcome measures

The outcome variables for the present study were the three continuous anthropometric measures, length-for-age Z-score (LAZ), weight-for-age Z-score (WAZ) and weight-for-length

Z-score (WLZ), derived by importing growth parameters into WHO Anthro software version 3 (April 2009). The continuous value of each of the three anthropometric measures was also used to derive three binary variables reflecting the presence or absence of a Z-score < -2 , i.e. stunting (LAZ < -2), underweight (WAZ < -2) and wasting (WLZ < -2), which were then also used as dependent variables for the study objectives.

Statistical methods

Data management was done using the Microsoft® Access database designed for the anthelmintic trial. Statistical analyses were performed using the STATA statistical software package version 10. The second⁽¹⁷⁾ or third infant⁽¹⁾ in a twin or triplet pregnancy was excluded from the analysis but five women on HAART were retained.

In order to evaluate the associations between HIV exposure, other factors and growth outcomes, we used as response variables the continuous Z-scores and the binary variables for stunting, underweight and wasting defined above.

Univariable analysis was first performed. For the continuous outcomes linear regression was used to investigate whether HIV exposure and other risk factors were associated with the mean Z-score; mean differences in Z-score and 95% confidence intervals were used to quantify the association between each risk factor and growth. For the binary outcomes, logistic regression was used to investigate whether HIV exposure and other risk factors were associated with the prevalence of stunting, underweight and wasting; odds ratios were used to quantify the association between each risk factor and poor growth. Multivariable analyses were then conducted investigating factors considered likely to be potential confounders, including maternal age, maternal education, maternal income, household socio-economic status (a score based on building materials, number of rooms and items owned) and episodes of malaria during infancy; variables assumed to be potential confounders and variables that presented a *P* value of < 0.05 in the univariable analysis were included in multivariable regression models. Significance levels in the final model were determined using likelihood ratio tests. A similar approach was used to investigate other risk factors for stunting, underweight and wasting in this population. The following factors were considered: sex of the child, low birth weight, low maternal CD4 cell count, number of living children in the family and early weaning (defined as introducing cow's milk at or before the age of 6 weeks).

Results

There were 2507 mothers enrolled and 2345 live births, with 2092 children under follow-up throughout the first year of life⁽¹⁸⁾; 1701 children were seen at age 1 year, of whom 1554 had data on HIV exposure status and growth

parameters. Retaining only one infant from twin or triplet pregnancies reduced this number to 1536. Mothers of children who did not have growth data available were, on average, younger than mothers whose children did have growth data ($P < 0.001$), more likely to be single mothers ($P = 0.001$), more likely to be HIV-positive ($P < 0.001$) and more likely to have malaria at enrolment ($P < 0.001$). There were no other differences between mothers whose children provided growth data at 1 year and mothers whose children did not contribute to growth data (data not shown).

Of the 1536 children, 1380 (89.8%) were not exposed to HIV, 122 (8.0%) were exposed but not infected, nineteen (1.2%) were exposed and infected, fifteen (1.0%) were exposed but their HIV infection status was not available. Of the nineteen exposed and infected, twelve infants tested positive for HIV at 6 weeks and at 18 months, five infants tested negative at 6 weeks but were HIV-positive at 18 months, two infants did not have a 6-week test result but tested positive for HIV at 18 months. The infected children (nineteen) and those whose status was not available (fifteen) were excluded, leaving a total of 1502 children for the present analysis.

Characteristics of the study participants, stratified by HIV exposure status, are shown in Table 1. HIV-positive mothers were more likely to be older, to have primary or no formal education, to be widowed/divorced/separated and to have had five or more pregnancies than HIV-negative mothers in this population. The CD4 count at enrolment ranged from 19 to 1473 cells/mm³, with a median of 538 (interquartile range 345–710) cells/mm³. HIV-exposed uninfected children had a significantly lower mean birth weight than unexposed children ($P = 0.028$).

Associations between maternal HIV and growth outcomes

The overall mean LAZ was -0.82 , WAZ was -0.31 and WLZ was 0.12 . Prevalence of stunting, underweight and wasting was 14.2%, 8.0% and 3.9%, respectively. At age 1 year, HIV-exposed uninfected babies had a lower mean LAZ (adjusted mean difference -0.16 ; 95% CI $-0.39, 0.06$; $P = 0.16$; Table 2) and a somewhat lower mean WAZ than HIV-unexposed babies (adjusted mean difference -0.13 ; 95% CI $-0.35, 0.09$; $P = 0.23$; Table 3). There was also little difference between mean WLZ in the two groups (adjusted mean difference -0.04 ; 95% CI $-0.27, 0.19$; $P = 0.74$; Table 4). Analysis of the binary variables showed that HIV exposure was significantly associated with underweight ($P = 0.006$; Table 3), but not with stunting or wasting. In other words, HIV-exposed but uninfected children tended to be shorter than HIV-unexposed infants, but their weight was proportionate to their length.

Associations between other factors and growth outcomes

Young maternal age, low maternal education, low birth weight, male sex and repeated episodes of malaria in

Table 1 Maternal and child characteristics for HIV-unexposed and HIV-exposed but uninfected infants, Entebbe municipality and Katabi sub-county, Uganda, 2003–2005

Characteristic	HIV-unexposed children (n 1380)		HIV-exposed, uninfected (n 122)		P value (χ^2 test)
	Mean, n or median	SD, % or IQR	Mean, n or median	SD, % or IQR	
Maternal characteristics					
Mother's age (years)*	23.78	5.36	26.35	5.43	<0.001
Maternal age group (years)†					
14–19	327	24	12	10	<0.001
20–24	526	38	36	30	
25–29	314	23	42	34	
30–34	148	11	21	17	
≥35	65	5	11	9	
Mother's education‡					
Primary or none	715	52	83	68	0.001
Secondary or tertiary	661	48	39	32	
Marital status (1 MV)†					
Single	161	12	11	9	<0.001
Married	1190	86	100	82	
Widowed/divorced/separated	28	2	11	9	
Number of pregnancies‡					
1	362	26	18	15	0.003
2–4	802	58	74	61	
≥5	216	16	30	24	
CD4 count at delivery (cells/mm ³)‡	–	–	538	345–710	
Child characteristics					
Child's sex†					
Male	709	51	57	47	0.324
Female	671	49	65	53	
Birth weight (kg)*	3.41	0.92	3.22	0.72	0.028
Birth weight category (12 MV)†					
Normal, ≥2.5 kg	1290	94	109	90	0.068
Low, <2.5 kg	79	6	12	10	

MV, missing values.

*Values are presented as mean and standard deviation.

†Values are presented as number and percentage.

‡Values are presented as median and interquartile range (IQR).

infancy were associated with an increased odds of stunting (Table 2), while being a male child, low birth weight, early weaning and having malaria during infancy were associated with being underweight (Table 3). Higher number of living children in the family, low birth weight and low maternal income were associated with wasting (Table 4). Maternal helminth infection was not associated with poor growth in this population (data not shown); as previously reported, anthelmintic treatment showed no effect on growth during infancy⁽¹⁸⁾.

Associations between growth outcomes and maternal CD4 cell count were explored among infants of HIV-positive mothers by categorizing enrolment CD4 count into two categories: ≤ 350 cells/mm³ and > 350 cells/mm³ (Tables 2, 3 and 4). Low maternal CD4 cell count increased the odds of both stunting and underweight but the association was not significant (Tables 2 and 3). The average breast-feeding duration for HIV-unexposed infants (mean 16.73 (SD 5.48) months) was significantly longer than that for HIV-exposed uninfected infants (mean 7.80 (SD 6.07) months; $P < 0.001$). Results from subgroup analysis showed that breast-feeding duration was not associated with growth outcomes.

Discussion

We have observed that maternal HIV infection is strongly associated with increased odds of being underweight, but not with stunting or wasting, among HIV-exposed uninfected infants in this population. The underlying mechanism is not fully understood and may be multifactorial. The association with underweight but not stunting or wasting indicates chronic nutritional deficiency, as opposed to a sudden effect of acute illness or deprivation. Our study finding that HIV exposure is associated with underweight among HIV-exposed uninfected children corroborates the findings of other studies from Sub-Saharan Africa⁽⁵⁾.

Growth faltering among HIV-exposed but uninfected infants could be caused indirectly by HIV-related symptoms in the mother: HIV may incapacitate the mother and this might translate into less provision of care to her child. HIV-positive women with low CD4 cell counts may be at greater risk of postnatal depression^(21,22), and this could also influence the care that they are able to provide for their children at a critical stage in their development. Our analysis on measures of maternal immune status showed

Table 2 Association of HIV exposure and other factors with stunting* in 1-year-olds, Entebbe municipality and Katabi sub-county, Uganda, 2003–2005

Risk factor	n	LAZ		Difference in LAZ		P value (trend)	Stunted		Odds for stunting				P value (trend)	
		Mean	SD	Adjusted difference†	95% CI		n/N	%	Unadjusted OR	95% CI	Adjusted OR†	95% CI		
HIV exposure														
HIV-unexposed	1362	-0.81	1.19	–	–		187/1356	13.8	1.00	–	1.00	–		
HIV-exposed	121	-0.94	1.30	-0.16	-0.39, 0.06	0.157	23/121	19.0	1.47	0.91, 2.37	1.55	0.92, 2.61	0.107	
Sex of child														
Male	754	-0.99	1.24	–	–		147/753	19.5	1.00	–	1.00	–		
Female	729	-0.65	1.13	0.33	0.22, 0.46	<0.001	63/724	8.7	0.39	0.29, 0.54	0.37	0.26, 0.51	<0.001	
Mother's age group (years)														
14–19	335	-1.08	1.23	–	–	<0.001	66/331	19.9	1.00	–	1.00	–	0.002	
20–24	555	-0.84	1.18	0.26	-0.10, 0.43	<0.001	84/554	14.8	0.70	0.49, 0.99	0.69	0.48, 1.01	0.001	
25–29	350	-0.65	1.05	0.41	0.22, 0.59		30/350	8.6	0.38	0.24, 0.60	0.38	0.23, 0.63		
30–34	167	-0.69	1.36	0.44	0.21, 0.67		22/167	13.2	0.61	0.36, 1.03	0.53	0.29, 0.96		
≥35	76	-0.67	1.26	0.46	0.16, 0.77		10/75	13.3	0.62	0.30, 1.27	0.54	0.24, 1.21		
Mother's education														
Secondary/tertiary	695	-0.64	1.22	–	–		80/691	11.6	1.00	–	1.00	–		
Primary/none	784	-0.98	1.16	-0.28	-0.41, -0.15	<0.001	129/782	16.5	1.51	1.12, 2.04	1.39	1.00, 1.93	0.048	
Mother's income (Ush)														
>60 000	102	-0.36	1.13	–	–		7/102	6.9	1.00	–	1.00	–		
≤60 000	1341	-0.86	1.19	-0.25	-0.50, -0.01	0.058	196/1335	14.7	2.34	1.07, 5.11	1.79	0.69, 4.59	0.197	
Birth weight														
Normal, ≥2.5 kg	1382	-0.77	1.19	–	–		180/1377	13.1	1.00	–	1.00	–		
Low, <2.5 kg	89	-1.55	1.19	-0.74	-0.99, -0.48	<0.001	29/88	33.0	3.27	2.04, 5.24	3.14	1.86, 5.29	<0.001	
Early weaning‡														
No	1123	-0.79	1.22	–	–		152/1117	13.6	1.00	–	1.00	–		
Yes	349	-0.95	1.13	-0.12	-0.27, 0.02	0.099	58/349	16.6	1.27	0.91, 1.76	1.20	0.84, 1.72	0.314	
Household socio-economic index§														
1 (low)	77	-0.92	1.05	–	–	0.019	11/76	14.5	1.00	–	1.00	–	0.408	
2	122	-1.13	1.06	-0.23	-0.57, 0.11	0.060	21/122	17.2	1.23	0.56, 2.72	1.45	0.63, 3.35		
3	451	-0.92	1.24	0.02	-0.26, 0.31		79/451	17.5	1.25	0.63, 2.49	1.23	0.59, 2.56		
4	408	-0.85	1.23	-0.04	-0.33, 0.25		60/407	14.7	1.02	0.51, 2.05	1.26	0.60, 2.65		
5	312	-0.52	1.18	0.20	-0.10, 0.50		26/310	8.4	0.54	0.25, 1.15	0.80	0.36, 1.78		
6 (high)	83	-0.81	1.02	-0.05	-0.43, 0.33		8/81	9.9	0.65	0.25, 1.71	0.99	0.36, 2.76		
Asymptomatic malaria at age 1 year														
No	1401	-0.79	1.19	–	–		190/1397	13.6	1.00	–	1.00	–		
Yes	76	-1.40	1.17	-0.35	-0.63, -0.07	0.014	19/74	25.7	2.19	1.27, 3.78	1.50	0.83, 2.70	0.191	
Episodes of malaria during infancy														
None	1025	-0.73	1.19	–	–	<0.001	127/1021	12.4	1.00	–	1.00	–	0.004	
One	256	-0.95	1.20	-0.18	-0.34, -0.01	0.001	41/255	16.1	1.35	0.92, 1.98	1.31	0.88, 1.94	0.001	
Two or more	172	-1.23	1.20	-0.48	-0.67, -0.28		39/171	22.8	2.08	1.39, 3.11	2.12	1.38, 3.27		
Maternal CD4 cell count														
>350 cells/mm ³	60	-1.04	1.37	–	–		12/60	20.0	1.00	–	1.00	–		
≤350 cells/mm ³	21	-0.93	1.28	0.00	-0.00, 0.00	0.261	4/21	19.1	0.94	0.27, 3.32	4.09	0.64, 25.9	0.126	

LAZ, length-for-age Z-score; Ush, Uganda shillings.

*Stunting: a chronic restriction of growth in length/height indicated by a low length-for-age (LAZ < -2).

†Adjusted differences and odds ratios estimated from multivariate linear and logistic regression models that included maternal age, maternal education, income, household socio-economic status, episodes of malaria and HIV exposure.

‡Early weaning: introducing cow's milk at or before the age of 6 weeks.

§Household socio-economic status is a score based on building materials, number of rooms and items owned ('1' representing lowest and '6' representing highest status).

Table 3 Association of HIV exposure and other factors with underweight* in 1-year olds, Entebbe municipality and Katabi sub-county, Uganda, 2003–2005

Risk factor	n	WAZ		Difference in WAZ		P value (trend)	Underweight		Odds for underweight				P value (trend)
		Mean	SD	Adjusted difference†	95% CI		n/N	%	Unadjusted OR	95% CI	Adjusted OR†	95% CI	
HIV exposure													
HIV-unexposed	1376	-0.30	1.16	–	–		102/1375	7.4	1.00	–	1.00	–	
HIV-exposed	122	-0.45	1.28	-0.13	-0.35, 0.09	0.229	18/122	14.8	2.16	1.26, 3.70	2.32	1.32, 4.09	0.006
Sex of child													
Male	763	-0.41	1.24	–	–		76/763	10.0	1.00	–	1.00	–	
Female	735	-0.20	1.13	0.22	0.10, 0.34	<0.001	44/734	6.0	0.58	0.39, 0.85	0.57	0.38, 0.85	0.006
Mother's age group (years)													
14–19	338	-0.48	1.13	–	–	0.052	34/338	10.1	1.00	–	1.00	–	0.609
20–24	562	-0.32	1.15	0.17	0.01, 0.33	0.009	41/561	7.3	0.70	0.44, 1.13	0.70	0.42, 1.14	
25–29	353	-0.21	1.13	0.22	0.04, 0.40		24/353	6.8	0.65	0.38, 1.13	0.67	0.37, 1.19	
30–34	169	-0.24	1.23	0.18	-0.04, 0.41		15/169	8.9	0.87	0.46, 1.65	0.80	0.39, 1.62	
≥35	76	-0.07	1.36	0.38	0.08, 0.67		6/76	7.9	0.77	0.31, 1.90	0.67	0.24, 1.82	
Mother's education													
Secondary/tertiary	699	-0.14	1.15	–	–		45/699	6.4	1.00	–	1.00	–	
Primary/none	795	-0.46	1.16	-0.21	-0.34, -0.09	0.001	74/794	9.3	1.49	1.02, 2.20	1.33	0.88, 2.02	0.173
Mother's income (Ush)													
>60 000	101	0.33	1.22	–	–		3/101	3.0	1.00	–	1.00	–	
≤60 000	1357	-0.36	1.14	-0.44	-0.69, -0.19	0.001	113/1356	8.3	2.97	0.93, 9.52	1.99	0.60, 6.64	0.222
Birth weight													
Normal, ≥ 2.5 kg	1397	-0.26	1.15	–	–		100/1396	7.2	1.00	–	1.00	–	
Low, <2.5 kg	89	-0.99	1.16	-0.73	-0.98, -0.48	<0.001	18/89	20.2	3.29	1.88, 5.73	3.00	1.62, 5.53	0.001
Early weaning‡													
No	1134	-0.26	1.15	–	–		77/1134	6.8	1.00	–	1.00	–	
Yes	353	-0.47	1.20	-0.17	-0.31, -0.03	0.020	43/352	12.2	1.91	1.29, 2.83	1.77	1.16, 2.71	0.010
Household socio-economic index§													
1 (low)	80	-0.37	1.02	–	–	0.011	3/80	3.8	1.00	–	1.00	–	0.128
2	122	-0.58	1.15	-0.20	-0.52, 0.13	0.012	12/122	9.8	2.80	0.76, 10.26	2.87	0.77, 10.74	
3	459	-0.45	1.20	-0.06	-0.34, 0.21		48/458	10.5	3.00	0.91, 9.89	3.00	0.90, 9.99	
4	411	-0.32	1.15	-0.04	-0.32, 0.24		33/411	8.0	2.24	0.67, 7.49	2.50	0.74, 8.49	
5	312	0.00	1.07	0.21	-0.08, 0.50		14/312	4.5	1.21	0.34, 4.30	1.59	0.44, 5.76	
6 (high)	84	-0.81	1.02	0.01	-0.36, 0.37		8/84	9.5	2.70	0.69, 10.57	3.69	0.92, 14.76	
Asymptomatic malaria at age 1 year													
No	1416	-0.29	1.16	–	–		109/1415	7.7	1.00	–	1.00	–	
Yes	76	-0.66	1.19	-0.14	-0.42, 0.13	0.311	10/76	13.2	1.82	0.91, 3.63	1.28	0.60, 2.73	0.538
Episodes of malaria during pregnancy													
None	1034	-0.24	1.15	–	–	0.008	75/1033	7.3	1.00	–	1.00	–	0.0894
One	258	-0.40	1.13	-0.13	-0.28, 0.03	0.002	20/258	7.8	1.07	0.64, 1.79	1.03	0.61, 1.74	0.052
Two or more	176	-0.58	1.27	-0.28	-0.47, -0.09		24/176	13.6	2.02	1.23, 3.29	1.85	1.09, 3.14	
Maternal CD4 cell count													
>350 cells/mm ³	61	-0.56	1.27	–	–		9/61	14.8	1.00	–	1.00	–	
≤350 cells/mm ³	21	-0.41	1.27	0.00	-0.00, 0.00	0.110	5/21	23.8	1.81	0.53, 6.17	3.13	0.61, 16.12	0.169

WAZ, weight-for-age Z-score; Ush, Uganda shillings.

*Underweight: a reflection of low weight-for-age (WAZ < -2).

†Adjusted differences and odds ratios estimated from multivariate linear and logistic regression models that included maternal age, maternal education, income, household socio-economic status, episodes of malaria and HIV exposure.

‡Early weaning: introducing cow's milk at or before the age of 6 weeks.

§Household socio-economic status is a score based on building materials, number of rooms and items owned ('1' representing lowest and '6' representing highest status).

Table 4 Association of HIV exposure and other factors with wasting* in 1-year olds, Entebbe municipality and Katabi sub-county, Uganda, 2003–2005

Risk factor	n	WLZ		Difference in WLZ		P value (trend)	Wasting		Odds for wasting				P value (trend)
		Mean	SD	Adjusted difference†	95% CI		n/N	%	Unadjusted OR	95% CI	Adjusted OR†	95% CI	
HIV exposure													
HIV-unexposed	1361	0.13	1.17	–	–		52/1361	3.8	1.00	–	1.00	–	
HIV-exposed	121	0.03	1.21	–0.04	–0.27, 0.19	0.741	5/121	4.1	1.09	0.43, 2.77	0.97	0.37, 2.52	0.947
Number of living children													
One	409	0.15	1.12	–	–		9/409	2.2	1.00	–	1.00	–	
Two	263	–0.01	1.17	–0.19	–0.39, 0.01	0.132	11/263	4.2	1.94	0.79, 4.75	2.38	0.92, 6.15	0.019
Three	167	0.16	1.25	–0.04	–0.29, 0.21		8/167	4.8	2.24	0.85, 5.90	2.34	0.73, 7.50	
Four or more	203	0.06	1.33	–0.25	–0.53, 0.03		17/203	8.4	4.06	1.78, 9.28	6.26	1.92, 20.45	
Mother's income													
>60 000	101	0.66	1.26	–	–		1/101	1.0	1.00	–	1.00	–	
≤60 000	1341	0.08	1.16	–0.42	–0.68, –0.16	0.002	55/1341	4.0	4.28	0.59, 31.23	4.41	0.58, 33.57	0.074
Birth weight													
Normal, ≥2.5 kg	1382	0.15	1.18	–	–		50/1382	3.6	1.00	–	1.00	–	
Low, <2.5 kg	88	–0.32	1.09	–0.52	–0.78, –0.26	<0.001	6/88	6.8	1.95	0.81, 4.68	2.31	0.93, 5.71	0.097
Early weaning‡													
No	1122	0.17	1.18	–	–		38/1122	3.4	1.00	–	1.00	–	
Yes	349	–0.03	1.18	–0.16	–0.31, –0.01	0.032	19/349	5.4	1.64	0.93, 2.89	1.35	0.73, 2.50	0.352
Maternal CD4 cell count													
>350 cells/mm ³	60	–0.02	1.15	–	–		2/88	2.3					
≤350 cells/mm ³	21	0.06	1.31	0.00	–0.00, 0.00	0.154	0/21	0					

WLZ, weight-for-length Z-score.

*Wasting: an acute weight loss indicated by a low weight-for-length (WLZ <–2).

†Adjusted differences and odds ratios estimated from multivariate linear and logistic regression models that included maternal age, maternal education, income, household socio-economic status, episodes of malaria and HIV exposure.

‡Early weaning: introducing cow's milk at or before the age of 6 weeks.

that 28% of HIV-positive mothers had a CD4 count of ≤ 350 cells/mm³, representing a category of mothers who qualify for antiretroviral therapy (ART) according to the most recent recommendations⁽²³⁾; low maternal CD4 cell count increased the odds of both stunting and being underweight (although weakly), but was not associated with wasting.

It has been suggested that infections may be more common among HIV-exposed uninfected children; if so, such infections could contribute to poor growth⁽²⁴⁾, but this was not the case in our study. The study clinic provided cotrimoxazole prophylaxis to all HIV-exposed uninfected infants and this could have helped to diminish infection risks. In multivariable models, following our modelling strategy we chose to adjust for malaria episodes in infancy as it was strongly associated with growth outcomes and hence may have improved the precision of estimates from linear regression. It is also likely to be a proxy for maternal malaria (which we considered likely to be a confounder of the association between HIV exposure and growth outcomes). Theoretically it is possible that malaria in infancy could be on the causal pathway between HIV exposure and growth outcomes, but this was not the case in our study due to the provision of cotrimoxazole for all HIV-exposed infants, so that HIV exposure was not in fact associated with infant malaria. Therefore inclusion of malaria episodes in infancy in the multivariable model had little impact on the adjusted associations between HIV exposure and growth outcomes.

Contrary to some of our study findings, researchers in Europe⁽²⁾ reported that exposure to maternal HIV infection is not associated with child's poor growth. This difference could be due to the fact that in Europe the HIV-infected population is more like the general population and less socio-economically disadvantaged than that in Uganda. This suggests that the associations that we and researchers in Zambia⁽⁵⁾ have observed in HIV-exposed but uninfected children may not be due to the infection itself, but rather to concomitant social or behavioural factors. It is also possible that the association we have observed between HIV exposure and underweight is a chance finding; this possibility is supported by the fact that analysis of the corresponding continuous WHZ outcome did not show an association with HIV exposure.

Uninfected children born to HIV-infected women are exposed antenatally to ART and this might affect their growth in early life. A study conducted in Thailand found that, although neither the total duration of exposure to zidovudine nor the duration of postnatal exposure was associated with infant growth from 6 weeks to 18 months, a longer *in utero* exposure to zidovudine had a negative impact on birth weight⁽²⁵⁾. A study in Europe found a minimal effect of combination ART on growth up to 18 months of age⁽²⁶⁾. Other findings in Europe showed that ART exposure was not significantly associated with prevalence of congenital abnormalities or low birth weight⁽²⁷⁾.

But ART exposure was associated with anaemia in infants, with Hb levels reverting to normal by 3 months of age⁽²⁷⁾. However, in our setting, single-dose nevirapine for mother and child was standard of care at the time of the study and prolonged exposure of the HIV-exposed but uninfected infants to ART in infancy or *in utero* was rare.

Strengths of the study are its large sample size and cohort design, meaning that data on exposures of interest and potential confounders were collected prospectively. Possible limitations of our study include the fact that the mothers and infants included in the present analysis were not representative of the study population, with children of HIV-infected women being less likely to provide growth data than children of HIV-uninfected women. Moreover, since HAART regimens were not standard of care during pregnancy in the study setting at the time, we are unable to comment on the impact of triple HAART regimens on infant growth.

On the other hand, in our study (as recommended in this setting), HIV-exposed but uninfected infants routinely received cotrimoxazole from 6 weeks to 18 months of age: a folate antagonist which can cause anaemia and might possibly interfere directly with growth. We found that HIV-exposed uninfected babies were more anaemic than HIV-unexposed, but the difference was not significant (data not shown).

As regards determinants of stunting or underweight other than HIV exposure, our results complement findings of previous studies^(13,28) that being a male child is associated with a higher risk of both stunting and underweight. Other studies have also found that young maternal age is a strong predictor for stunting and being underweight⁽²⁹⁾ although results are not consistent⁽¹³⁾. Low maternal education, low birth weight and early weaning were associated with increased odds of stunting and underweight in our study, consistent with findings of earlier studies^(9,30,31). As expected, the odds of stunting and being underweight increased significantly with the number of malaria episodes in infancy. This is in agreement with earlier reports that episodes of illness are associated with appetite loss, vomiting and poor nutrient utilization, which exacerbates malnutrition and perpetuates the cycle⁽³²⁾. Number of living children was not associated with stunting or underweight but significantly increased the odds of wasting, consistent with the hypothesis that the oldest child is likely to be the least malnourished and that subsequent children are increasingly poorly provided for.

Conclusions

Maternal HIV infection was associated with being underweight in HIV-uninfected infants in this population. The underlying mechanism is not fully understood and may be multifactorial. Additional independent predictors of stunting or underweight in this population included

young maternal age, low maternal education, low birth weight and malaria in infancy. In addition to effective interventions for prevention of mother-to-child HIV transmission, children born to HIV-infected mothers also require special care to ensure that their growth and development are not impaired. Prevention and treatment of undernutrition in children remain critical interventions in settings with high HIV prevalence.

Acknowledgements

Sources of funding: The study was funded by the Wellcome Trust (grant number 064693). *Conflicts of interest:* The authors have no conflict of interest to declare. *Ethics:* Ethical approval for the Entebbe trial of de-worming during pregnancy was given by the Science and Ethics Committee, Uganda Virus Research Institute; the Uganda National Council for Science and Technology; and the London School of Hygiene & Tropical Medicine. *Authors' contributions:* S.A.L., H.M., J.N. and M.N. carried out the interviews, collected the data and contributed to revising the paper. M. Kizza and E.N. facilitated data collection and supported the fieldwork. M. Kihembo supported laboratory work especially the measurement of maternal CD4 cell counts. L.M. planned and undertook the analysis, undertook the interpretation of the data and drafted the manuscript. E.L.W. contributed to analysis, interpretation of data and revising the paper. A.M.E. designed the study, provided overall research supervision, and contributed to analysis, interpretation of data and revising the paper. *Acknowledgements:* The authors thank the study participants, the fieldwork team, Entebbe Hospital and the MRC/UVRI Uganda Research Unit on AIDS for their support. They also thank Professor Jonathan Levin who gave useful technical comments and advice.

References

1. Webb AL, Manji K, Fawzi WW *et al.* (2009) Time-independent maternal and infant factors and time-dependent infant morbidities including HIV infection, contribute to infant growth faltering during the first 2 years of life. *J Trop Pediatr* **55**, 83–90.
2. Newell ML, Borja MC & Peckham C (2003) Height, weight and growth in children born to mothers with HIV-1 infection in Europe. *Pediatrics* **111**, e52–e60.
3. Arpadi S, Fawzy A, Aldrovandi GM *et al.* (2009) Growth faltering due to breastfeeding cessation in uninfected children born to HIV-infected mothers in Zambia. *Am J Clin Nutr* **90**, 344–353.
4. Gangar J (2009) Nutritional assessment of newborns of HIV-infected mothers. *Indian Pediatr* **46**, 339–341.
5. Makasa M, Kasonka L, Chisenga M *et al.* (2007) Early growth of infants of HIV-infected and uninfected Zambian women. *Trop Med Int Health* **12**, 594–602.
6. Agostoni C, Zuccotti GV, Giovannini M *et al.* (1998) Growth in the first two years of uninfected children born to HIV-1 seropositive mothers. *Arch Dis Child* **79**, 175–178.
7. Kuhn L, Kasonde P, Sinkala M *et al.* (2005) Does severity of HIV disease in HIV-infected mothers affect mortality and morbidity among their uninfected infants? *Clin Infect Dis* **41**, 1654–1661.
8. Ezeaka VC, Iroha EO, Akinsulie AO *et al.* (2009) Anthropometric indices of infants born to HIV-1-infected mothers: a prospective cohort study in Lagos, Nigeria. *Int J STD AIDS* **20**, 545–548.
9. Cattaneo A, Timmer A, Bomestar T *et al.* (2008) Child nutrition in countries of the Commonwealth of Independent States: time to redirect strategies? *Public Health Nutr* **11**, 1209–1219.
10. de Villiers A & Senekal M (2002) Determinants of growth failure in 12–24-month-old children in a high-density urban slum community in East London, South Africa. *Eur J Clin Nutr* **56**, 1231–1241.
11. Hong R & Mishra V (2006) Effect of wealth inequality on chronic under-nutrition in Cambodian children. *J Health Popul Nutr* **24**, 89–99.
12. Kikafunda JK, Walker AF, Collett D *et al.* (1998) Risk factors for early childhood malnutrition in Uganda. *Pediatrics* **102**, E45.
13. Hien NN & Hoa NN (2009) Nutritional status and determinants of malnutrition in children under three years of age in Nghean, Vietnam. *Pakistan J Nutr* **8**, 958–964.
14. Patel V, Rahman A, Jacob KS *et al.* (2004) Effect of maternal mental health on infant growth in low income countries: new evidence from South Asia. *BMJ* **328**, 820–823.
15. Kikafunda KK, Namusoke HK (2006) Nutritional status of HIV/AIDS orphaned children in households headed by the elderly in Rakai District, South Western, Uganda. *Afr J Food Agric Nutr Dev* **6**, issue 1; available at <http://www.ajol.info/index.php/ajfand/article/download/19169/62500>
16. Elliott AM, Kizza M, Quigley MA *et al.* (2007) The impact of helminths on the response to immunization and on the incidence of infection and disease in childhood in Uganda: design of a randomized, double-blind, placebo-controlled, factorial trial of deworming interventions delivered in pregnancy and early childhood [ISRCTN32849447]. *Clin Trials* **4**, 42–57.
17. Ndirizza J, Muhangi L, Akishule D *et al.* (2010) Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda: a randomized controlled trial. *Clin Infect Dis* **15**, 531–540.
18. Webb EL, Mawa PA, Ndirizza J *et al.* (2011) Effect of single-dose anthelmintic treatment during pregnancy on an infant's response to immunisation and on susceptibility to infectious diseases in infancy: a randomised, double-blind, placebo-controlled trial. *Lancet* **377**, 52–62.
19. Guay LA, Musoke P, Fleming T *et al.* (1999) Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* **354**, 795–802.
20. Muhangi L, Woodburn P, Omara M *et al.* (2007) Associations between mild-to-moderate anaemia in pregnancy and helminth, malaria and HIV infection in Entebbe, Uganda. *Trans R Soc Trop Med Hyg* **101**, 899–907.
21. Kapetanovic S, Christensen S, Karim R *et al.* (2009) Correlates of perinatal depression in HIV-infected women. *AIDS Patient Care STDS* **23**, 101–108.
22. Stewart RC (2007) Maternal depression and infant growth: a review of recent evidence. *Matern Child Nutr* **3**, 94–107.
23. World Health Organization (2010) Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach, 2010 revision. http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf (accessed May 2012).
24. Filteau S (2009) The HIV-exposed, uninfected African child. *Trop Med Int Health* **14**, 276–287.

25. Briand N, Le Coeur S, Traisathit P *et al.* (2006) Growth of human immunodeficiency virus-uninfected children exposed to perinatal zidovudine for the prevention of mother-to-child human immunodeficiency virus transmission. *Pediatr Infect Dis J* **25**, 325–332.
26. Hankin C, Thorne C, Newell ML *et al.* (2005) Does exposure to antiretroviral therapy affect growth in the first 18 months of life in uninfected children born to HIV-infected women? *Acquir Immune Defic Syndr* **40**, 364–370.
27. European Collaborative Study (2003) Exposure to antiretroviral therapy *in utero* or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr* **32**, 380–387.
28. Kabubo-Mariara J, Ndenge GK & Mwabu DK (2008) Determinants of children's nutritional status in Kenya: evidence from demographic and health surveys. *J Afr Econ* **18**, 363–387.
29. Linnemayr S, Alderman H & Ka A (2008) Determinants of malnutrition in Senegal: individual, household, community variables, and their interaction. *Econ Hum Biol* **6**, 252–263.
30. Bloss E, Wainaina F & Bailey RC (2004) Prevalence and predictors of underweight, stunting, and wasting among children aged 5 and under in western Kenya. *J Trop Pediatr* **50**, 260–270.
31. Mamiro PS, Kolsteren P, Roberfroid D *et al.* (2005) Feeding practices and factors contributing to wasting, stunting, and iron-deficiency anaemia among 3–23-month old children in Kilosa district, rural Tanzania. *J Health Popul Nutr* **23**, 222–230.
32. Devereux S, Baulch B, Phiri A *et al.* (2006) Vulnerability to Chronic Poverty and Malnutrition in Malawi. A report for DFID Malawi. http://www.ids.ac.uk/files/MalawiVulnerabilityReport_Final.pdf (accessed May 2012).