


# Growth Trajectories of HIV Exposed and HIV Unexposed Infants. A Prospective Study in Gweru, Zimbabwe

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## Abstract

**Background:** With the increasing HIV seroprevalence among women of childbearing age in sub-Saharan Africa, limited data on growth outcomes of HIV exposed infants under current policies of universal maternal antiretroviral therapy exist.

**Methods:** The longitudinal growth patterns of 114 HIV exposed and unexposed infants were assessed and compared. The prevalence and factors associated with malnutrition were established. Infants under prevention of mother to child transmission care were recruited at 6 weeks post-delivery as were their HIV unexposed counterparts. Weight and length measurements were recorded at birth, 6 and 16 weeks postpartum.

**Results:** HIV vertical transmission rate was 8.8%. HIV exposed infants had significantly lower mean birth weights compared to HIV unexposed infants ( $2.9 \pm 0.3$ ;  $3.2 \pm 0.5$ ;  $P < .001$ ) respectively. Mean weight/length-for-age z-scores for HIV exposed, uninfected (HEU) infants were significantly below those of the HIV unexposed infants during follow up. By 6 weeks of age, 28.5% of HEU infants were malnourished while no malnutrition was evident in HIV unexposed infants. A gestational age  $<37$  weeks (OR: 3.83; 95% CI: 1.03-14.30;  $P = .045$ ) and HIV exposure (OR: 1.62; 95% CI: 0.17-15.73;  $P = .017$ ) substantially increased the risk of stunting.

**Conclusion:** Growth deficits were witnessed in HIV exposed infants compared to HIV unexposed infants. There is need for early nutritional monitoring and support among HIV exposed infants.

## Keywords

antiretroviral therapy, HIV, infants, growth

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## Introduction

The total number of people living with HIV in Zimbabwe was estimated to be 1.33 million in 2017, 1.25 million being adults and children under 15 years of age accounted for 5.8% of all people living with HIV.<sup>1</sup> Globally, about 1.4 million HIV infected pregnant women give birth every year.<sup>2</sup> The increased coverage of antiretroviral therapy (ART) for pregnant and breastfeeding women through prevention of mother to child transmission (PMTCT) programme has caused significant reductions in perinatal and postnatal HIV transmission.<sup>3</sup> HIV exposed and uninfected (HEU) infants are a growing

subpopulation in sub-Saharan Africa, with increasing coverage of PMTCT regimens such as option B+ ART

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for all pregnant and breastfeeding women until cessation of breastfeeding or lifelong.<sup>4</sup>

However, evidence is accumulating that, despite being HIV uninfected, HEU infants experience greater infectious morbidity (hospitalization and poor nutrition) and mortality than HIV unexposed infants.<sup>5</sup> Children born to HIV infected mothers are more likely to be malnourished.<sup>6,7</sup> The mechanisms, however, are not fully understood. Recent research has also indicated that maternal ART during pregnancy may have independent negative effects on infant health and growth.<sup>8-10</sup> Children may additionally be exposed to ART through breast milk or directly as prophylaxis. However, very few studies have assessed the effect of HIV and ART exposure on long term health outcomes such as growth.<sup>11,12</sup>

Linear growth is an essential reflection of overall wellbeing in infants. Impaired growth and development have far reaching consequences across the life course of an individual, impacting academic outcomes, employment and risk of long term non-communicable diseases, as well as intergenerational effects on human capital and health.<sup>13</sup> In the largest cohort to date, of Zimbabwean HEU children in the pre-ART era, 23% more stunting was evident in exposed infants than HIV unexposed children from the same communities by 12 months of age.<sup>14</sup> Reducing antenatal HIV exposure through ART and control of maternal viraemia during pregnancy, reduces the risk of transmission and may have additional benefits for HIV exposed infants.<sup>15</sup> In a cohort study conducted in America, infants whose mothers were enrolled in a PMTCT program from pregnancy recorded very low birth weight and lengths below the mean. By 24 months postpartum, their mean weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WFL) *z*-scores had risen above average.<sup>16</sup> Conversely, the majority of Ugandan HEU childrens' weight and height measurements were significantly below the World Health Organisation (WHO) growth standards during the first 4 years of life.<sup>17</sup> In a longitudinal study conducted in Zambia, HEU infants had lower WAZ and LAZ *z*-scores compared to their HIV unexposed peers from infancy to school going age.<sup>18</sup>

In this study, we aimed to compare growth parameters between HIV exposed (HIV infected and uninfected) and HIV unexposed infants and to establish the prevalence of malnutrition among infants during the first 4 months of life in Gweru, Zimbabwe. We also aimed to determine demographic and socioeconomic factors associated with malnutrition.

## Methods

### Study Population

The study was conducted at Gweru district polyclinics (Mkoba, Mtapa and Senga) that offer maternal and child health services in the Midlands Province of Zimbabwe between June 2019 and February 2020. This was a prospective cohort study of HIV exposed and HIV unexposed infants. HIV exposed infants whose mothers had enrolled into a PMTCT programme during antenatal care receiving option B+ therapy were recruited at 6 weeks post-delivery and followed up to 6 months. HIV unexposed infants were recruited and followed up as part of the same protocol at the same sites. Eligible infants were those whose mothers had given written informed consent, at 6 weeks of age, born singleton, being breastfed exclusively for 6 months and visiting the same clinic with their mothers for post antenatal care.

At baseline, 160 mother-infant pairs were considered for the study. However, 32 infants were unavailable for the second study follow-up visit, 10 HIV exposed infants with missing baseline HIV DNA test results and 4 sets of twins were excluded from the study. Mothers enrolled in PMTCT programmes were subjected to HIV antibody testing using Determine test kits (Abbott Diagnostics, Abbott Park, Illinois, U.S.A.) to confirm infection status as per national testing algorithm. HIV negative mothers were retested after 6 weeks using the same protocol to detect possible seroconversion. All HIV exposed infants received nevirapine prophylaxis from birth to 6 weeks of age and were commenced on cotrimoxazole from 6 weeks post-delivery until cessation of breastfeeding.

### Sample Collection

Infant heel prick blood samples were collected at 6 weeks and 6 months of age for HIV DNA-polymerase chain reaction (PCR) testing. Maternal plasma was collected on recruitment from HIV infected mothers for determination of baseline HIV RNA viral load. All tests were conducted at Gweru Provincial Hospital Laboratory, Gweru, Zimbabwe.

### Data Collection

Information on mothers' HIV status, antiretroviral use, duration and regimen was obtained and recorded. Maternal anthropometric measurements including mid upper arm circumference, height and weight were recorded at enrolment. Maternal demographic and

**Table 1.** Baseline Infant Characteristics by Infant HIV Status.

Infant characteristics	CHE infants		HEU infants		HUU infants	
	n	%	n	%	n	%
Sex (n % Female)	30	(52.6)	27	(51.9)	29	(50.9)
HIV Status n %	5	(8.8)				
Birth Weight (kg)	mean (SD)	2.9 (0.3)	3	(0.4)	3.2	(0.5)
Birth weight (<2.5 kg)	n %	6 (10.5)	6	(11.5)	3	(5.3)
Birth length (cm)	mean (SD)	49.7 (1.8)	49.6	(1.9)	50.6	(1.7)
Head circumference, cm	mean (SD)	33.7 (1.7)	33.8	(1.7)	35.1	(2.5)
Gestational age (weeks)	mean (SD)	35.5 (1.3)	35.4	(1.4)	37.1	(1.2)
Preterm birth <37 weeks	n %	47 (82.5)	43	(82.7)	18	(31.6)

Abbreviations: CHE, combined HIV-exposed; HEU, HIV-exposed and uninfected; HUU, HIV-unexposed and uninfected; SD, standard deviation; P1, comparison of characteristics of CHE and HEU infants; P2, comparison of characteristics of CHE and HUU infants.

socioeconomic data, including marital status, monthly income, education, and employment, were also obtained.

For the infants; birth date, gender, gestational age, and anthropometry namely birth weight (kg), length (cm), and head circumference (cm) were accessed from the birth records. Thereafter, weight and length measurements were recorded at each visit; 6 and 16 weeks postpartum and an average of 2 readings was taken.

### Ethical Approval and Informed Consent

Ethical approval was granted by Joint Research Ethics Committee (JREC) for the University of Zimbabwe College of Health Sciences and Parirenyatwa Group of Hospitals (JREC 256/18) and also by the Medical Research Council of Zimbabwe (MRCZ/A/2466) before commencement of study.

### Power Calculation

The minimum sample size required to estimate the prevalence of malnutrition of infants was determined to be 114 mother-infant pairs under an assumption of statistical power of 80%, 22.5% stunting with a precision of 4.5%. Attrition rate was calculated at 5%.

### Statistical Analysis

Demographic variables were analyzed using descriptive statistics. Data was summarized by proportions (%), mean  $\pm$  standard deviation for normally distributed data and median interquartile range (IQR) for non-normal data. The Pearson's Chi square test was used to assess differences in categorical variables. Kruskal Wallis test was used to compare medians for non-parametric data. The Z-score for each anthropometric parameter, including WAZ, LAZ, WFL, and body mass index-for-age

(BMIAZ) was calculated using the WHO Child Growth Standards. All values were generated using WHO Anthro (version 3.2.2, January 2011) software (WHO, 2011). The Z-score results are reported as mean  $\pm$  SD at each age. Student's *t* test was used to compare WAZ, LAZ, and BMIAZ Z-mean score differences between HIV-exposed and infected (HEI), HEU, and HUU infant groups. Proportions of malnutrition indicators (stunting, wasting, and underweight) were compared between infant groups using Pearson's Chi-squared test. In order to identify factors associated with being underweight, stunting and wasting, logistic regression analysis was done using several maternal and infant covariates. Maternal and infant characteristics were reviewed and only those which may be potential confounders using clinical judgment and knowledge from literature were considered in the regression model. Univariate analysis was performed on each variable and those found to reach statistical significance ( $\alpha$  set at 0.05) were included in the multiple variable logistical regression model. In all such cases, odds ratios and their 95% confidence intervals were reported. Statistical analysis was performed using STATA version 14.2 software (Stata Corporation, College Station, Texas, USA). The level of significance was established at  $<0.05$ .

## Results

### Baseline Infant and Maternal Characteristics

The baseline maternal and infant characteristics are presented in Tables 1 and 2 respectively. A total of 114 mother-infant pairs were included in the study. Among 57 infants born from HIV infected mothers, 5 were HIV infected by 6 weeks of life, while 52 were HIV exposed but uninfected. On the other hand, 57 HUU were also included in the study. There were significant

**Table 2.** Baseline Maternal Characteristics by Infant HIV Status.

Characteristics		CHE infants	HEU infants	HUU infants	P1	P2
		n=57	n=52	n=57		
Age (years)	mean (SD)	30.6 (5.4)	30.6 (5.2)	26.5 (5.9)	.931	<.001
Marital status (n %)	Married	25 (43.9)	24 (46.1)	20 (35.1)	.410	.530
	Divorced	10 (17.5)	8 (15.4)	10 (17.5)		
	Single	16 (28.1)	15 (28.9)	23 (40.3)		
	Widowed	6 (10.5)	5 (9.7)	4 (7)		
Education (n %)	Primary	7 (12.3)	7 (13.5)	1 (1.8)	.157	.083
	Secondary	34 (59.7)	29 (55.8)	40 (70.2)		
	Tertiary	16 (28.1)	16 (30.8)	16 (28.1)		
Employment (n %)	Employed	15 (26.3)	15 (28.9)	14 (24.6)	.209	.835
	S-employed	25 (43.9)	23 (44.2)	23 (40.4)		
	Unemployed	17 (29.8)	14 (26.9)	20 (35.1)		
Viral Load copies/ml	median (IQR)	56 (0-215)	56 (0-215)			
Viral load > 1000	n %	6 (10.5)	2 (3.8)		<.001	
Duration of ART (months)	median (IQR)	48 (8-60)	48 (10-62)		.041	
Monthly Income (US\$)	median (IQR)	81 (69-98)	87 (69-98)	69 (58-87)	.091	.009
Income <\$50	n %	3 (5.3)	2 (3.9)	9 (15.8)	.122	.067
Gravidity	mean (SD)	2.9 (1.2)	3 (1.2)	2.6 (1.4)	.517	.240
Parity	mean (SD)	2.4 (1)	2.4 (1)	2.5 (1.2)	.714	.932
MUAC (cm)	mean (SD)	26.4 (3.4)	26.5 (3.4)	26.2 (3.6)	.284	.847
Height (cm)	mean (SD)	163.3 (5.8)	163 (5.6)	164.3 (95.9)	.187	.366
Weight (kg)	mean (SD)	64.2 (12.6)	64.8 (12.9)	63.4 (12)	.252	.728

Abbreviations: CHE, xombined HIV-exposed; HEU, HIV-exposed and uninfected; HUU, HIV-unexposed and uninfected; S-employed, self-employed; IQR, interquartile range; SD, standard deviation; US\$, United States dollar; ART, antiretroviral therapy; MUAC, mid upper arm circumference; P1, comparison of characteristics of CHE and HEU infants; P2, comparison of characteristics of CHE and HUU infants.

differences in mean birth weights between HIV exposed and HUU infants ( $2.9 \pm 0.3$ ;  $3.2 \pm 0.5$  respectively,  $P < .001$ ). The mean head circumference at birth was significantly lower for HIV exposed infants compared to their unexposed counterparts ( $33.7 \pm 1.7$ ;  $35.1 \pm 2.5$ ) respectively,  $P < .001$ ). A significantly higher proportion of HEU were born preterm before 37 weeks (82.7%) compared to the unexposed infants (31.6%),  $P < .001$  (Table 1).

The mean age of HIV infected mothers was significantly higher at  $30.6 \pm 5.4$  years compared to that of HIV negative mothers;  $26.5 \pm 5.9$  years ( $P < .001$ ). The majority of HIV infected mothers were married ( $n=25$ , 43.9%), while the majority of HIV negative mothers were single ( $n=23$ , 40.3%). There were no significant differences in education level or employment status between HIV infected and uninfected mothers. Mothers of combined HIV exposed infants (HIV infected and uninfected infants) had significantly high baseline HIV viral loads above 1000 c/ml ( $n=6$ , 10.5%) compared to the mothers of HIV exposed uninfected infants ( $n=2$ , 3.8%) ( $P \leq .001$ ). HIV infected mothers had significantly higher median monthly income compared to their HIV negative counterparts (\$81; \$69) respectively

( $P = .009$ ). The average gravidity, parity, height, weight, and mid upper arm circumference were not significantly different between the HIV infected and uninfected mothers (Table 2).

### Growth Comparison between HEU Infants and HUU Infants

**Weight-for-age/Length-for-age.** The mean WAZ and LAZ  $z$  scores for HEU infants were all significantly lower than those of the HUU infants from birth to 16 weeks of age ( $P < .05$  in all cases; Table 3).

**Weight-for-length.** The mean WFL  $z$  score of HEU was significantly higher than that of HUU from 6 weeks (1.937;  $-0.716$ ) to 16 weeks of age respectively (1.064; 0.246);  $P < .001$  (Table 3).

**Body mass index-for-age.** There were no significant differences in mean BMIAZ  $z$  scores between HEU and HUU infants at birth and 16 weeks postpartum. However, at 6 weeks of age mean BMIAZ  $z$  score for HEU was significantly higher than that of HUU ( $P < .001$ ; Table 3).

**Table 3.** Anthropometric Characteristics of Study Infants.

Age (Weeks)	CHE Infants		HEU Infants		HUU Infants		P1	P2
	(n = 57)		(n = 52)		(n = 57)			
	Mean	SD	Mean	SD	Mean	SD		
<b>Weight-for-age Z score</b>								
0	-0.716	0.87	-0.723	0.89	-2.884	1.000	.019	.016
6	-0.110	1.17	-0.419	1.13	0.706	0.72	***	***
16	-0.422	1.02	-0.335	1.00	0.855	0.64	***	***
<b>Length-for-age Z score</b>								
0	0.085	0.99	0.065	1.04	0.599	0.91	.005	.005
6	-1.491	0.98	-1.485	1.01	1.509	0.72	***	***
16	-1.516	1.42	-1.456	1.43	1.152	0.89	***	***
<b>Weight-for-length Z score</b>								
0	-1.349	1.61	-1.355	1.67	-1.174	1.48	.550	.547
6	1.839	1.92	1.937	1.85	-0.716	1.13	***	***
16	1.014	1.44	1.064	1.45	0.246	0.97	***	***
<b>BMI-for-age Z score</b>								
0	-1.188	1.42	-1.186	1.47	-0.935	1.36	.356	.334
6	1.055	1.73	1.152	1.66	-0.150	1.00	***	***
16	0.639	1.35	0.709	1.37	0.293	0.96	.067	.118

Abbreviations: P1, Z score comparison of HEU and HIV unexposed and uninfected (HUU); P2, Z score comparison of CHE and HUU; BMI, body mass index.

\*\*\* $P < .001$ .

### Growth Comparison between CHE Infants and HUU Infants

**Weight-for-age/Length-for-age.** There were significant differences in mean WAZ and LAZ z scores of CHE and HUU infants from birth up to 16 weeks of age ( $P < .05$ ).

**Weight-for-length.** At baseline no significant differences were observed in mean WFL z scores between the 2 infant groups. However, mean WFL z scores of CHE infants were significantly higher compared to those of HUU from 6 weeks (1.839; -0.716) to 16 weeks (1.014; 0.246);  $P < .001$  (Table 3).

**Body mass index-for-age.** Significant differences in terms of mean BMIAZ z scores were only observed at 6 weeks of age between the CHE (1.05) and HUU infants (-0.15);  $P < .001$  (Table 3).

### Prevalence of Malnutrition by Infant HIV Status and Age

**Comparison of HEU and HUU.** The levels of malnutrition between HEU and HUU infants were not significantly different at birth. However, there were statistically significant differences in proportions of infants that were stunted between HEU and HUU at 6 and 16 weeks of

age (28.85%; 0%;  $P < .001$ ) respectively. None of the HUU infants were either stunted or underweight at 6 and 16 weeks of age. There was a sharp decrease in the proportion of HEU and HUU infants that were wasted from birth up to 16 weeks (32.69-3.85%; 29.82-1.75%) respectively though this was not statistically significant (Table 4).

**Factors Associated with Malnutrition.** Factors associated with stunting, being underweight, and wasting are presented in Table 5. Generally no association was observed between maternal income, education level, viral load levels, duration of ART treatment and the measures of malnutrition in infants. The same observation was true in respect of infant sex, HIV status, and low birth weight. However, infants born from single (OR: 0.08; 95% CI: 0.01-0.54;  $P = .010$ ) and divorced (OR: 0.18; 95% CI: 0.01-0.85;  $P = .036$ ) mothers had a significantly lower risk of being wasted. A gestational age of below 37 weeks (OR: 3.83; 95% CI: 1.03-14.30;  $P = .045$ ) and HIV exposure (OR: 1.62; 95% CI: 0.17-15.73;  $P = .017$ ) substantially increased the risk of stunting (Table 5).

## Discussion

This study made important revelations with regards to growth of HIV exposed and unexposed infants. The

**Table 4.** Prevalence of Malnutrition by Infant HIV Status from Birth to 16 weeks.

Characteristic	Indicator	HEU	HUU	PI
		n=52	n=57	
		Frequency (n %)	Frequency (n %)	
	0 weeks			
Stunting	LAZ-Z score < -2	1 (1.92)	0 (0)	.293
Underweight	WAZ-Z score < -2	1 (1.92)	2 (3.51)	.613
Wasting	WFL-Z score < -2	17 (32.69)	17 (29.82)	.747
	6 weeks			
Stunting	LAZ-Z score < -2	15 (28.85)	0 (0)	***
Underweight	WAZ-Z score < -2	2 (3.85)	0 (0)	.135
Wasting	WFL-Z score < -2	2 (3.85)	6 (10.53)	.182
	16 weeks			
Stunting	LAZ-Z score < -2	15 (28.85)	0 (0)	***
Underweight	WAZ-Z score < -2	2 (3.85)	0 (0)	.135
Wasting	WFL-Z score < -2	2 (3.85)	1 (1.75)	.505

Abbreviations: PI, comparison of HEU and HIV unexposed and uninfected (HUU); LAZ, length-for-age; WAZ, weight-for-age; WFL, weight-for-length.

\*\*\* $p < .001$ .

**Table 5.** Factors Associated with Stunting, Underweight and Wasting.

Variable	Stunting LAZ < -2		Underweight WAZ < -2		Wasting WFL < -2	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Maternal characteristics						
Income < \$500	0.53 (0.62-4.47)	.556	–		7.8 (0.46-132.66)	.155
Primary education	1.44 (0.23-9.0)	.694	–		–	–
Single (Marital status)	0.42 (0.08-2.12)	.296	–		0.08 (0.01-0.54)	<b>.010</b>
Divorced	0.58 (0.10-3.32)	.544	0.47 (0.27-8.46)	.611	0.18 (0.01-0.85)	<b>.036</b>
Self-employed	1.28 (0.38-4.29)	.689			1.32 (0.29-5.91)	.718
Viral load > 1000 c/ml	–		4.9 (0.38-64.07)	.226	4.9 (0.38-64.07)	.226
cART > 12 months	1.92 (0.53-7.00)	.323	1.09 (0.09-12.77)	.948	0.25 (0.02-2.94)	.271
Infant characteristics						
Female	0.51 (0.17-1.51)	.224	0.46 (0.04-5.19)	.527	0.44 (0.10-1.84)	.206
Low birth weight < 2.5 kg	3.54 (0.79-15.90)	.100	–		–	–
Gestation age < 37 weeks	3.83 (1.03-14.30)	<b>.045</b>	1.52 (0.13-17.30)	.734	0.35 (0.08-1.46)	.149
HIV exposure	1.62 (0.17-15.73)	<b>.017</b>	0.16 (0.011-2.17)	.168	0.49 (0.434-5.42)	.557

A P-value < .05 was considered statistically significant; OR, odds ratio; 95%CI, 95% confidence interval; Viral load > 1000 c/ml, viral load > 1000 copies/ml; LAZ, length-for-age z score, WAZ, weight-for-age z score; WFL, weight-for-length z score; –, indicates none significant results; bold values indicate statistically significant values.

growth of HIV exposed infants was demonstrated to be inferior to that of HUU infants from birth to 16 weeks with regards to WAZ and LAZ z scores. However, WFL and BMIAZ z scores of HIV exposed infants were significantly higher compared to unexposed infants from 6 weeks onwards. Our findings are consistent with previous studies. A study conducted in Rwanda demonstrated low early WAZ and increased WFL z scores in HIV exposed infants compared to HUU infants in the

same setting.<sup>19</sup> However, this pattern was not witnessed in studies of infants born before the widespread availability of dual ART. In Ghana, HIV exposed infants born to HIV infected mothers and treated with nevirapine had persistently low WAZ z scores during the first 12 months of life compared to HUU counterparts and no differences in WFL z scores were evident by infant HIV status.<sup>20</sup> In Zimbabwe, before the availability of option B+ therapy and extended breastfeeding, HEU had

increased risk of stunting and wasting but LAZ and WFL *z* scores were not significantly different from those of HIV unexposed infants.<sup>14</sup> Therefore, in the present study, the increased WFL *z* scores among HEU infants could be attributed to exclusive breast feeding and reduced opportunistic infections in lactating mothers as a result of the dual ART under option B<sup>+</sup> therapy.

In the current study, a higher prevalence of stunting (28.85%) was evident in HEU infants from 6 to 16 weeks compared to HIV unexposed infants (0%). HEU infants also had lower mean birth weights and the majority of the infants were preterm compared to their unexposed counterparts. This is consistent with previous studies.<sup>21-23</sup> Findings from the current study indicate that growth impairment continues to be a major problem among HEU children in the current PMTCT era despite observed suppressed maternal viraemia (viral load median: 56 c/ml, IQR: 0-215 c/ml). Growth failure is a well-documented complication of HIV infection in children which can present as stunting, weight loss, failure to thrive and severe acute malnutrition.<sup>24-26</sup> Although the benefit of cART in reducing HIV transmission and improving maternal health is clear, there is potential for ART to have negative effects on the developing fetus, and separating the effects of HIV and ART exposure is challenging.<sup>27</sup> However, intrauterine growth restriction and preterm birth have been associated with certain cART combinations in some studies. Since mean LAZ in HIV exposed infants was already lower at birth, the fetal environment may have influenced infant growth. Infant growth restriction may be partly driven by maternal HIV infection and inflammation during pregnancy.<sup>28</sup>

A recent meta-analysis found that HIV infected women who conceived on ART had 41% greater risk of preterm delivery compared to HIV infected women who started ART during pregnancy.<sup>15</sup> In the current study the majority of the HIV infected mothers conceived while on ART with a median duration on ART treatment >12 months at the time of recruitment (median: 48, IQR: 1-62) which further increased the odds of stunting in infants (OR: 1.92, 95% CI: 0.53-7.00). In addition, HIV exposure and a gestational age below 37 weeks also significantly increased the risk of stunting. A study from Botswana showed a similar risk of preterm delivery between efavirenz and dolutegravir containing regimens. Recently, concerns have been raised over neural tube defects following dolutegravir exposure at conception.<sup>29</sup> Therefore, further data on the impact of drug regimens and the relationship between poor birth outcomes and timing of ART initiation are urgently needed.

In this study we examined social determinants of health that could possibly contribute to malnutrition in

infants. No association was observed between maternal income, education level, viral load levels, duration of ART treatment and the measures of infant malnutrition. However, maternal single and divorced status reduced the risk of wasting. In contrast, in a study conducted in India, low maternal education, being single, maternal advanced HIV disease state (based on CD4 count and viral load), low infant birth weight and morbidity were the key factors associated with poor infant growth outcome.<sup>30</sup> However, this was not the case in our study because the majority of HIV exposed mothers had reached at least secondary level of education and the widespread exposure to ART at preconception resulted in decreased maternal viraemia. Girma and co-workers identified poverty with low maternal education, unemployment and single motherhood as risk factors of malnutrition in Ethiopian children.<sup>31</sup> In a study conducted in western Kenya, female infants were less likely to be malnourished while being male, HIV positive, and attending an urban clinic significantly increased the risk of malnutrition.<sup>32</sup> Conversely, in reports from India and Pakistan, females were at greater risk for malnutrition than males.<sup>33</sup> Studies in developing countries have also established being preterm, low birth weight and small for gestational age as risk factors for stunting in infants. Children born with low birth weight succumb to neurological abnormalities which impair growth.<sup>34</sup>

Apart from socio-economic conditions, infant HIV exposure has been attributed to biological factors that might influence growth such as chronic immune activation<sup>35</sup> thymic dysfunction and lower levels of specific antibodies and CD4 cells.<sup>36</sup> Immune activation and inflammation demonstrated in HIV exposed fetuses and infants<sup>37</sup> may trigger release of cytokines, directly impacting cell migration and brain development.<sup>38-41</sup> It was also noted that the disruption of growth hormone axis in Zimbabwean HEU children was associated with systemic immune activation and cytomegalovirus (CMV) viral load.<sup>42</sup> Direct exposure of infants to opportunistic infections may also cause neurotoxicity and impair growth. CMV infection in early life has been reported to be very common in sub-Saharan Africa and the impact on growth and development may be even greater in HEU children.<sup>43</sup> Lastly poor maternal nutritional status as a result of HIV infection has been shown to be associated with adverse fetal and early infancy growth.<sup>44</sup> Food insecurity in pregnancy is a risk factor for adverse birth outcomes and has been associated with poor growth and neurodevelopment due to complex mechanisms including nutritional deficiencies and increased parental stress.<sup>45</sup>

Our study had some limitations. Firstly, adequate comparison of socio-demographic and clinical variables

between HIV infected infants and HEU/HUU infants was difficult due to the small sample size of HIV infected infants. The effectiveness of PMTCT programmes among women of childbearing ages has caused significant reductions in MTCT cases. In addition, the findings of the study which was conducted in the Midlands Province in Zimbabwe may not be applicable to other regions of the country where socioeconomic and demographic characteristics may differ. In addition, all PMTCT mothers enrolled in the study were already on ART and as such non-availability of ART naive breastfeeding maternal controls made it impossible to really separate the possible effects of HIV infection from those of ART on the growth of HIV exposed infants. Moreover, detailed feeding patterns of breastfeeding mothers were not available to account for different growth patterns observed in their infants. Important strengths of the study include its prospective nature and the longitudinal physical growth measurements obtained by trained clinical staff using calibrated measuring equipment.

## Conclusion

The continued global focus on reducing the burden of antenatal HIV infection is fundamental in eliminating HIV exposure in children. However, given the ever growing population of HEU children, significant efforts that focus on prevention and intervention strategies to reduce the burden of poor HEU child outcomes are needed. This study demonstrated poor growth among HIV exposed infants, including HIV infected and HEU infants, compared with their HUU counterparts. The growth deficits identified in this study emphasize the vulnerability of infants born to HIV infected Zimbabwean women, regardless of whether the infants become infected or not. Given that children are now more commonly exposed to ART in utero and postnatally, and more women are conceiving on ART, studies examining the contributions of HIV related pathways in the context of pregnant and breastfeeding mothers in the era of ART are needed. The results highlight the need for early nutritional monitoring and intervention, counseling, and long term follow up as well as support for HIV exposed infants and their families through policy making and community based health services.

## Author Contributions

LM, HTM, DMT, and CM: designed and planned the study. JM and LM: responsible for data collection. LM: primary statistical analysis and initial draft of the manuscript. All five authors made substantial contribution in data analysis and interpretation as well as critical revision of intellectual content and approval of final manuscript for publication.

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