Growth Patterns and Clinical Outcomes in Association with Breastfeeding in HIV Exposed and Unexposed Infants in KwaZulu Natal, South Africa

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Research article

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Growth Patterns and Clinical Outcomes in Association with Breastfeeding in HIV Exposed and Unexposed Infants in KwaZulu Natal, South Africa

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Running title: Infant growth faltering breastfeeding HIV-exposed and unexposed infants

Keywords: HIV; Infants; Breastfeeding; Growth trajectories, Clinical outcomes

Abstract

Background: Exclusive breastfeeding for six months and breastfeeding with complementary feeds until 12 months for infants exposed to HIV (IEH) or 24 months for infants unexposed to HIV (IUH) is the current World Health Organisation (WHO) recommendation for LMICs to improve clinical outcomes and growth trajectories in infants. In a post hoc evaluation of IEH and IUH cohorts, we examine growth patterns and clinical outcomes in the first six months of infancy in association with breastfeeding duration.

Methods: Two non–contemporaneous cohorts of infants born to women living with HIV and women without HIV, from a low-socioeconomic township in South Africa, were evaluated from birth until nine months of age. Clinical, anthropometric and infant feeding data were analysed. Standard descriptive statistics and regression analysis were performed to determine the effect of HIV exposure and breastfeeding duration on growth and clinical outcomes.

Results: Included in this secondary analysis were 123 IEH, and 157 IUH infants breastfed for a median of 26 weeks and 14 weeks, respectively. Median WLZ score was consistently and significantly lower in IEH than IUH at 3, 6 and 9 months (-0.19 vs 2.09; -0.81 vs 0.28; 0.05 vs 0.97 respectively). In contrast, the median LAZ score was significantly lower among IUH at 3 and 6 (-1.63 vs 0.91; -0.37 vs 0.51). A significantly higher proportion of IUH was classified as stunted (LAZ<-2SD) at 3 and 6 months (3.9% vs 44.9%, 4.8% vs 20.9% respectively) and a higher proportion of IEH experienced one or more episodes of skin rash (44.5% vs 12.8%) and upper respiratory tract infection (30.1% vs 10.9%) ($p<0.0001$). In a multivariable analysis, the odds of occurrence of wasting, skin rash, URTI or any clinical adverse event in IEH were 2.86, 7.06, 3.01 and 8.89 times higher than IUH after adjusting for breastfeeding duration.

Conclusion: Our study has generated additional evidence that IEH is at substantial risk of infectious morbidity and decreased growth trajectories independent of breastfeeding duration. We further report shorter breastfeeding duration in infants not exposed to HIV and the higher prevalence of stunting in this cohort is also independent of breastfeeding duration.

Introduction

UNAIDS reports more than 60% decline in new perinatal HIV infections in 2018 associated with the universal coverage of antiretroviral treatment in antenatal clinics worldwide [1]. South Africa has an estimated 3.5 million HIV exposed uninfected (HEU) children, the highest recorded in the world [2]. This is attributed to one of the most successful Prevention of Mother-to-Child Transmission (PMTCT) programmes in Sub-Saharan Africa with universal combination antiretroviral treatment (cART) for all pregnant and breastfeeding women living with HIV, safe breastfeeding guidance for 12 months and repeat HIV testing during pregnancy and breastfeeding to identify new HIV infections and to allow for early commencement of cART [3,4].

Despite the reduction in perinatal HIV infections and HIV-associated morbidity and mortality in the current ART era, the persistently high rate of gastroenteritis, acute respiratory infections and malnutrition in children in general in Sub-Saharan Africa is of increasing concern [5-7]. The rates of stunting, severe acute malnutrition and moderate acute malnutrition remain high in hospital admissions of HIV infected and HIV unexposed children [8].

Breastfeeding has long been established as the best form of adequate nutrition in infants to reduce the risk of childhood morbidity and mortality [9,10]. The World Health Organisation (WHO) has made substantial investments towards promoting exclusive breastfeeding for six months and continued breastfeeding for up to two years [11]. Much attention, however, has been given to promoting and monitoring breastfeeding among women living with HIV (WLHIV). There is limited evidence of feeding practices and infant wellbeing among women not living with HIV (WNLHIV). In a pooled analysis of 21 clinical trials involving over 19 000 HEU infants in Sub-Saharan Africa and Asia, half of the infant deaths occurred before three months of age [12]. While mothers not receiving cART for life contributed to almost 50% of infant deaths, never breastfeeding contributed to 10.8% of infant deaths. Current WHO infant feeding recommendations for HIV exposed infants in low- and middle-income countries (LMIC) are exclusive breastfeeding for six months and continued breastfeeding with

complementary feeds until 12 months while mothers are virally suppressed on cART. For women not living with HIV (WNLHIV), it was recommended that infants be exclusively breastfed for six months but a longer duration of breastfeeding with complementary feeds thereafter until 24 months [11]. Two recent studies in South Africa reported short breastfeeding duration among women in general regardless of their HIV status [13,14].

With the high rates of HIV infection in childbearing women in SSA and SA, in particular, there has been widespread usage of antiretroviral treatment for both treatment, PMTCT and infant prophylaxis and the known effect of intrauterine exposure to antiretrovirals on infant growth, the opportunity to assess the growth of infants, rates of malnutrition and childhood infections in infants born to mothers not exposed to antiretroviral drugs is becoming rare [15,16].

Our study aimed at describing the growth patterns and clinical outcomes in two cohorts of infants born to WLHIV and WNLHIV and living in the same geographical and socioeconomic context. In a secondary analysis of data, we report the incidence of respiratory infections, rash or skin infections, diarrhoea, malnutrition and growth faltering in the first six to nine months of infancy in association with breastfeeding duration.

Patients and Methods

This is a secondary analysis of two cohorts of infants born to WLHIV and WNLHIV residing in Umlazi, a peri-urban low-socioeconomic township in South Africa. Between 2007 and 2009, infants exposed to HIV (IEH) were enrolled in a multi-centred randomised placebo-controlled trial (HPTN046) designed to investigate the efficacy of extended Nevirapine prophylaxis in preventing breastfeeding transmission of HIV-1 [17]. For the secondary analysis, we selected infants who were enrolled in Umlazi and who did not receive NVP prophylaxis, nor did their mothers receive cART during pregnancy and breastfeeding. Between 2017 and 2018, pregnant women without HIV were enrolled in an observational cohort study (CAP088) designed to determine the incidence of HIV during pregnancy and breastfeeding [18].

Infants in the HPTN046 study were enrolled within seven days of birth, had to test negative with HIV DNA PCR, birthweight at least 2000g and able to breastfeed. Gestational age was not determined. Clinical, anthropometric and infant feeding assessments were conducted by research nurses and clinicians at two, five, six and eight weeks and three, four, five, six, nine, 12 and 18 months. In the CAP088 study, clinical, anthropometric and infant feeding assessments were conducted and documented in the Road-to-Health Card by primary health care nurses as per the IMCI guidelines at three, six and nine months of age. A copy of the completed Road-to-Health Card was filed in the maternal folder.

For this study, the growth outcomes, length and weight measurements at birth, three, six and nine months were used to estimate the weight-for-age (WAZ), length-for-age (LAZ) and weight-for-length (WLZ) z-scores using the WHO growth standards [19]. Infants were classified as being underweight, having stunting or wasting based on WAZ, LAZ and WLZ <-2 respectively [20]. Clinical outcomes included having a minimum of one episode of rash or skin infection, fever, upper respiratory tract infection (URTI), acute gastroenteritis (AGE) and lower respiratory tract infection (LRTI) between birth and nine months. Hospitalisation during the first nine months of infancy was also included as a clinical outcome.

Breastfeeding practice was ascertained by a questionnaire and documented as a “Yes” or “No” at three, six and nine months and duration of breastfeeding were determined at nine months or the last clinic visit if infants were not seen at nine months. Infants in the HPTN046 study were tested for HIV at three, six and nine months using HIV DNA PCR assay. Mothers in the HPTN046 study had a CD4 count done at the time of infant enrolment.

Select data were extracted from the HPTN046 database and transferred to an excel spreadsheet. The substudy Investigator reviewed infant source documents from the CAP088 study and populated the excel spreadsheet with relevant data. The excel database was analysed using the SPSS version 24

statistical package. Descriptive statistics, such as frequencies and percentages, were used to summarise categorical data. We tested for normal data distribution using the Shapiro-Wilk test. With continuous variables that were not normally distributed, we report the median and IQR. Measures of central tendency mean and median and measures of dispersion such as standard deviation and interquartile range were calculated for numerical variables. Pearson chi-square test or Fisher's exact test was used to test if there is an association between clinical and growth outcomes and breastfeeding duration in the two cohorts. An alpha value of 0.05 was considered significant.

Results

Included in this secondary analysis were 123 infants born to women living with HIV (Infants exposed to HIV) and 157 infants born to women without HIV (Infants not exposed to HIV). Women living with HIV and not living with HIV were similar in age, with a median age of 25 vs 23 years, respectively (Table 1). Majority of the women living with HIV or without HIV were not married and not living with their partner (91.8% vs 84.7%). A significantly higher proportion of women without HIV were employed (23.6% vs 4.9%) when compared to women living with HIV ($p < 0.0001$). Women living with HIV were generally healthy with a median CD4 count of 529 (IQR 457; 612) cells/ml and infants exposed to HIV (IEH) or not exposed to HIV (IUH) were of similar birth weight (3200 g) ($p= 0.878$). The two groups of infants (IEH and IUH) differed significantly in the duration of breastfeeding, with a larger proportion of IUH breastfed for less than six months (52.9%) when compared to IEH (38.2%) ($p<0.05$) (Table 1). Overall, 70% of women who were employed versus 42% of unemployed breastfed for less than six months ($p=0.001$).

Table 1: A comparison of Maternal and Birth Characteristics for Cohorts 1 and II

Characteristics	Cohort I: Infants Exposed to HIV (n=123)	Cohort II: Infants Not Exposed to HIV (n=157)	P-Value
Study Period	2007-2008	2017-2018	
Residence	Umlazi, South Africa	Umlazi, South Africa	
Maternal age (median [IQR])	25 [21; 29]	23 [19; 28]	0.072
Relationship			
Married	1 (0.8)	6 (3.8)	0.132
Not Married, Living with Partner	9 (7.4)	18 (11.5)	
Not Married, Not Living with Partner	112 (91.8)	133 (84.7)	
Employed			
No	116 (95.1)	120 (76.4)	<0.0001
Yes	6 (4.9)	37 (23.6)	
Mode of Delivery [n (%)]			
Vaginal Delivery	87 (71.9)	126 (82.8)	0.039
Cesarean Section	34 (28.1)	26 (17.1)	
Maternal CD4 count, cells/mm^3 (median [IQR])	529 [457; 612]	856 [706; 1044]	<0.001
Birth weight, g [median IQR]	3200 [3000;3450]	3200 [2870; 3530]	0.373
Birth Weight Category [n (%)]			
<2500g	10 (7.6)	8 (5.4)	0.878
≥ 2500g	121 (92.4)	140 (94.6)	
Duration of Breastfeeding (weeks) Median (IQR)	26 (25 ; 38)	14 (14; 38)	0.003
Duration of breastfeeding Category [n (%)]			
< 6months	47 (38.2)	83 (52.9)	0.010
> 6months	76 (61.8)	74 (47.1)	

Overall median weight-for-length z scores were consistently and significantly lower in IEH than IUH at three, six and nine months (Table 2) (-0.19 vs 2.09; -0.81 vs 0.28; 0.05 vs 0.97 respectively). The median weight-for-age z score was significantly lower in IEH than IUH at nine months only (0.41 vs 0.85). In contrast, the median length-for-age z score was lower among IUH at three, six and nine months (-1.63 vs 0.91; -0.37 vs 0.51; 0.13 vs 0.77) reaching statistical significance at three and six months only. When compared to IEH, a significantly higher proportion of IUH were classified as underweight (WAZ<-2SD) at three months (1.6% vs 8.18%) and stunted (LAZ<-2SD) at three and six months (3.9% vs 44.9%, 4.8% vs 20.9% respectively).

Table 2: A comparison of Growth and Clinical Outcomes between Infants Exposed to and Not Exposed to HIV in the 1st nine months of life

Infant Growth and Clinical Outcomes	Infants Exposed to HIV (n=123)	Infants Not Exposed to HIV (n=157)	P-Value
Infant Growth, WHO Z scores (median [IQR])			
Age 3 months			
WAZ	0.27 (-0.41; 0.88)	0.03 (-0.69; 1.03)	0.360
LAZ	0.91 (-0.24; 1.72)	-1.63 (-3.60; -0.31)	<0.001
WLZ	-0.19 (-1.26; 0.76)	2.09 (0.16; 3.79)	<0.001
Age 6 months			
WAZ	0.31 (-0.38; 0.85)	0.54 (-0.40; 1.25)	0.115
LAZ	0.51 (-0.48; 1.47)	-0.37 (-1.59; 0.99)	0.001
WLZ	0.17 (-0.81; 0.79)	0.92 (0.28; 2.15)	<0.001
Age 9 months			
WAZ	0.41 (-0.39; 0.97)	0.85 (-0.03; 1.82)	0.007
LAZ	0.77 (-0.22; 1.93)	0.13 (-0.58; 1.37)	0.077
WLZ	0.05 (-0.67; 0.71)	0.97 (-0.21; 2.15)	<0.001
Growth Faltering n(%)			
Age 3 months			
Underweight	2 (1.6)	9 (8.18)	0.026
Stunting	5 (3.96)	48 (44.9)	<0.001
Wasting	11 (8.73)	6 (5.61)	0.452
Age 6 months			
Underweight	4 (3.23)	1 (1.49)	0.659
Stunting	6 (4.84)	14 (20.9)	<0.001
Wasting	9 (7.26)	3 (4.48)	0.545
Age 9 months			
Underweight	1 (0.82)	0	1.000
Stunting	7 (5.74)	1 (2.0)	0.440
Wasting	2 (1.64)	2 (4.0)	0.581
Infants with 1 or more episodes n(%)			
Rash/Skin Disease	59 (44.4)	20 (12.8)	<0.0001
Fever	1 (0.8)	6 (3.9)	0.129
URTI	40 (30.1)	17 (10.9)	<0.0001
Acute GE	7 (5.3)	5 (3.2)	0.395
LRTI	4 (3.0)	4 (2.6)	1.000

When compared to IUH a markedly higher proportion of IEH experienced one or more episodes of skin rash (12.8% vs 44.5%) and upper respiratory tract infection (10.9% vs 30.1%) (p<0.0001) (Table 2). When stratified by breastfeeding duration, the growth and clinical outcomes among IUH were not significantly different between infants breastfed for less than six months or six months or more (Table 3). In addition, the median LAZ score and the prevalence of stunting did not differ by breastfeeding duration among the IUH (Table 4).

Table 3: A comparison of Growth and Clinical Outcomes between LTBF and STBF in Infants Exposed to HIV

Infant Growth and Clinical Outcomes	Breastfed ≥ 6 months (LTBF)	Breastfed < 6 months (STBF)	P-Value
Infant Growth, WHO Z scores (median [IQR])			
Age 3 months			
WAZ	0.40 (-0.23; 1.03)	-0.80 (-0.65; 0.82)	0.051
LAZ	1.02 (-0.09; 1.96)	0.54 (-0.41; 1.49)	0.068
WLZ	-0.13 (-1.31; 0.58)	-0.43 (-1.22; 0.82)	0.975
Age 6 months			
WAZ	0.32 (-0.17; 1.11)	0.20 (-0.71; 0.53)	0.147
LAZ	0.61 (-0.64; 1.69)	0.46 (-0.33; 1.26)	0.878
WLZ	0.20 (-0.75; 1.06)	0.15 (-0.96; 0.62)	0.229
Age 9 months			
WAZ	0.47 (-0.35; 1.03)	0.29 (-0.62; 0.75)	0.488
LAZ	0.68 (-0.25; 1.45)	0.85 (-0.14; 1.98)	0.375
WLZ	0.11 (-0.51; 0.76)	0.09 (-1.08; 0.37)	0.117
Growth Faltering n(%)			
Age 3 months			
Underweight	1 (1.32)	1 (2.13)	0.620
Stunting	3 (3.95)	2 (4.26)	0.635
Wasting	6 (7.89)	5 (10.64)	0.416
Age 6 months			
Underweight	3 (3.95)	1 (2.17)	0.514
Stunting	3 (3.95)	2 (4.35)	0.626
Wasting	4 (5.26)	5 (10.87)	0.212
Age 9 months			
Underweight	1 (1.37)	0	0.624
Stunting	4 (5.48)	3 (6.82)	0.529
Wasting	1 (1.37)	1 (2.27)	0.613
Infants with 1 or more episodes n(%)			
Rash/Skin Disease	36 (47.37)	22 (46.81)	0.550
Fever	0	1 (2.13)	0.382
URTI	21 (27.63)	16 (34.04)	0.289
Acute GE	2 (2.63)	4 (8.51)	0.149
LRTI	1 (1.32)	2 (4.26)	0.325

Table 4: A comparison of Growth Outcomes between LTBF and STBF in Infants Not Exposed to HIV

Infant Growth and Clinical Outcomes	Breastfed ≥ 6 months (LTBF)	Breastfed < 6 months (STBF)	P-Value
Infant Growth, WHO Z scores (median [IQR])			
Age 3 months			
WAZ	0.17 (-0.31; 0.88)	-0.04 (-0.88; 1.13)	0.370
LAZ	-1.45 (-2.97; -0.31)	-1.77 (-3.69; -0.01)	0.698
WLZ	2.09 (0.19; 3.99)	2.13 (0.16; 3.72)	0.839
Age 6 months			
WAZ	0.43 (-0.57; 1.24)	0.72 (-0.10; 1.71)	0.453
LAZ	-0.36 (-1.54; 0.85)	-0.45 (-2.07; 1.04)	0.978
WLZ	0.86 (-0.06; 2.11)	1.56 (0.38); 2.75)	0.408
Age 9 months			
WAZ	0.81 (-0.02; 1.7)	1.22 (0.78; 2.14)	0.929
LAZ	-0.03 (-0.75)	0.36 (-0.23; 1.41)	0.280
WLZ	0.89 (0.13; 2.18)	1.31 (-0.63; 1.92)	0.812
Growth Faltering n(%)			
Age 3 months			
Underweight	0	8 (10.53)	0.058
Stunting	11 (37.93)	36 (48.0)	0.387
Wasting	1 (3.45)	5 (6.67)	0.463
Age 6 months			
Underweight	1 (2.08)	0	0.716
Stunting	9 (18.75)	5 (26.32)	0.353
Wasting	2 (4.17)	1 (5.26)	0.638
Age 9 months			
Underweight	0	0	0
Stunting	1 (2.78)	0	0.720
Wasting	1 (2.78)	1 (7.14)	0.485

In a multivariable analysis, the odds of occurrence of wasting, skin rash, URTI or any clinical adverse event in IEH were 2.86, 7.06, 3.01 and 8.89 times higher than IUH after adjusting for breastfeeding duration (Table 5).

Table 5: Multivariable Analysis of adverse growth outcomes and clinical adverse events in Infants Exposed to HIV relative to Infants Not Exposed to HIV adjusted for breastfeeding duration < 6 months

Infant Growth and Clinical Outcomes	Unadjusted OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Underweight at 3 or 6 months				
Infants exposed to HIV	0.55 (1.84-1.66)	0.292	0.44 (0.11-1.79)	0.254
Infants not exposed to HIV	Ref		Ref	
Stunting at 3 or 6 months				
Infants exposed to HIV	0.15 (0.07-0.30)	<0.001	0.15 (0.07-0.34)	<0.001
Infants not exposed to HIV	Ref		Ref	
Wasting at 3 or 6 months				
Infants exposed to HIV	2.65 (1.10-6.36)	0.030	2.86 (1.09-7.50)	0.033
Infants not exposed to HIV	Ref		Ref	
Rash/Skin Disease				
Infants Exposed to HIV	5.42 (3.03-9.69)	<0.001	7.06 (3.69-13.51)	<0.001
Infants not exposed to HIV	Ref		Ref	
Upper Respiratory Tract Infection				
Infants Exposed to HIV	3.52 (1.88-6.57)	<0.001	3.01 (1.50-6.03)	0.002
Infants not exposed to HIV	Ref		Ref	
Any Clinical Adverse Event				
HIV Exposed Uninfected	6.35 (3.78-10.68)	<0.001	8.89 (4.75-16.61)	<0.001
Breastfeeding<6 months	Ref		Ref	

Discussion

In this secondary analysis of growth, clinical and breastfeeding data collected for infants who were HIV exposed (IEH) and unexposed (IUH), we report a significantly shorter breastfeeding duration (median 14 weeks) and a higher occurrence of stunting (45% at 3 months and 21% at 6 months) among IUH in the first six months of life. The shorter duration of breastfeeding was not associated with stunting. We also report lower WLZ scores and higher frequency of rash/skin disease and URTI among the IEH independent of breastfeeding duration.

Breastfeeding has long been established as the best form of adequate nutrition in infants to reduce the risk of childhood morbidity and mortality [9,10]. The WHO has made large investments towards promoting exclusive breastfeeding for six months and continued breastfeeding up to two years [11]. In our study, the median duration of breastfeeding was 20 weeks among IUH and 26 weeks among IEH. Only 46% of IUH and 61% of IEH were breastfed for six months or more. Early cessation of

breastfeeding in the South African population has also been reported in other studies independent of HIV exposure [13,14]. In Horwood's study, mothers who were returning to work or school were less likely to breastfeed (AOR 3.76) [14]. This is consistent with our findings: 70% of women who were employed breastfed for <6 months versus 42% of unemployed breastfed <6 months.

In our study, a significantly higher proportion of IUH was underweight at three months (8.2% vs 1.6%) and stunted at three and six months (44.9% vs 3.96%; 20.9% vs 4.84%) when compared to their IEH counterparts. Other South African studies have also reported a high prevalence of stunting in children (28.5%) [21,22]. Although a larger proportion of the IUH were breastfed for less than six months, stunting and being underweight were independent of breastfeeding duration. The occurrence of stunting even among the longer breastfed infants is suggestive of other factors that could contribute to the high prevalence of stunting such as mixed feeding or poor quality of breastmilk as a result of poor nutrition in lactating mothers [23,24]. More recent studies have underscored the role of maternal nutrition among lactating mothers [25,26]. Maternal nutrition supplementation preconception or early pregnancy was shown to improve linear growth in infants in the first six months, suggesting that poor nutrition in lactating mothers could influence infant growth despite optimal breastfeeding practice [25,26].

We report significantly lower median WLZ scores among IEH at three, six and nine months and WAZ score at nine months in comparison to IUH and independent of breastfeeding duration. Poor growth has long been associated with HIV exposure; however, nutrition and socioeconomic status have also been considered as significant determinants. In a cross-sectional study in Botswana where IEH were more likely to have been formula-fed, a higher proportion of IEH between six and 24 months was underweight and stunted underscoring the benefits of breastfeeding [27]. However, even if breastfeeding is the norm, in the slums of Nairobi, Kenya stunting was the most common form of undernutrition among IEH infants when compared to their HU counterparts [28]. The authors concluded that high undernutrition among IEH was as a result of HIV exposure, the number of children in a household and the lack of food aid [28]. Here again, we raise the question of nutrition among lactating mothers. Consistent with our findings, a Ugandan study conducted in the pre-ART era also concluded that duration of breastfeeding

253 was not associated with adverse growth outcomes in IEH [29]. No matter how long women breastfed,
254 if nutritionally compromised themselves, they are more likely to provide inadequate nutrition to their
255 infants via breastfeeding [25,26].
256
257 After adjusting for breastfeeding duration, we have shown that IEH were 2.9, 7.1, 3.0 and 8.9 times at
258 risk of wasting, skin rash, URTI, or any clinical adverse event respectively when compared to their IUH
259 counterparts. Consistent with other studies in the pre-ART era, HIV exposure was independently
260 associated with a higher frequency of any clinical event in early infancy. The largest HIV-exposed,
261 uninfected cohort (ZVITAMBO), which prospectively followed up 14 110 infants in Zimbabwe before
262 the availability of ART, reported higher morbidity and three times higher mortality in IEH when
263 compared to IUH; this mortality risk was higher in the first year of life compared with the second [30].
264 A study in South Africa after universal ART became available, reported significantly more
265 hospitalisations, five times higher prevalence of lower respiratory tract infections and three times higher
266 diarrhoeal diseases in IEH compared to IUH (n=410) [31]. The higher incidence was attributed to
267 advanced maternal HIV disease and late ART initiation.
268
269 In conclusion, our study has generated additional evidence that infants exposed to HIV are at substantial
270 risk of infectious morbidity and decreased growth trajectories independent of breastfeeding duration.
271 We further report shorter breastfeeding duration in infants not exposed to HIV and the higher prevalence
272 of stunting in this cohort is also independent of breastfeeding duration.
273
274 Limitations
275 Our study is not without limitations. We accept that non-contemporaneous studies are not ideal, but this
276 was the only opportunity to disentangle the effect of ART from HIV on infant growth outcomes. To
277 reduce the selection bias, we selected the IEH cohort specifically enrolled from the same community as
278 the IUH cohort but only a few years apart.
279

The high attrition rate of IUH infants at three, six and nine months was not unusual at the primary health clinic. As a result, we acknowledge that our findings at nine months are not conclusive due to the small number of IUH assessed at this time point.

Another limitation to our study findings is the lack of breastfeeding quality data and maternal nutritional status.

Implications of our findings:

The findings presented in this study raise concerns on maternal nutrition irrespective of HIV exposure in SSA. The possible interplay of maternal nutrition, the role of maternal nutrition supplements preconception or in early pregnancy must be considered when developing breastfeeding policies for HIV unexposed, and HIV exposed mother-infant pairs.

DECLARATIONS

Ethics approval and consent to participate: The Institutional Review Board of University of KwaZulu-Natal approved the study (Ref BE 643/16 sub-study of BE 616/16). In this retrospective data analysis, participant consent was not obtained, and we used de-identified data.

Authors Contributions: LP conceptualised the study, collated the data, interpreted the statistical analysis and wrote the manuscript. DM and KN assisted with conceptualising the study, interpretation of statistical analysis and helped write the manuscript. LME assisted with data collation and reviewed the manuscript. NMN performed the statistical analysis and reviewed the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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