Longitudinal interrelationship between HIV viral suppression, maternal weight change, breastfeeding, and length in HIV-exposed and uninfected infants participating in the Kabeho study in Kigali, Rwanda

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Purpose: The health of infants that are HIV exposed and uninfected (HEU) is a major public health concern as HIV becomes a chronic condition. We investigate the interrelationship between maternal viral suppression, maternal weight status, breastfeeding, and infants that are HEU.
Methods: The Kabeho study followed 502 HEU infants in Kigali, Rwanda, for 24 months from 2013 to 2014. We use a structural equation modeling approach to investigate the dynamic relationships between viral suppression, maternal weight change, breastfeeding, and infant length for age z score (LAZ) as defined by the WHO.
Results: Older mothers are more likely to be virally suppressed and to breastfeed. Viral suppression and the mother being on antiretroviral treatment for longer were related to lower infant LAZ at three months. A more positive maternal weight change was related to higher infant LAZ at the end of each period. At 12 months, a higher infant LAZ was related to increased probability of continued breastfeeding. At 18 months, continued breastfeeding was related to lower LAZ, and food shortages were related to higher LAZ.
Conclusion: There is a complex interrelationship between viral suppression, maternal weight change, breastfeeding, and infant LAZ. These relationships demonstrate the link between maternal and infant health in the context of HIV.

Introduction

Success in the management of HIV has significantly increased the lifespan of women with the disease and reduced vertical transmission, so more infants are born HEU (1). Therefore, the number of infants exposed to but uninfected by HIV is increasing worldwide (1,2). These infants continue to be at increased risk of early morbidity and mortality (1,3,4). Therefore, there is a growing public health focus on the health of infants born to mothers with HIV (1,5).

Linear growth is one aspect of infant health and wellbeing. Growth can be viewed as a determinant of future health or a marker of underlying processes, which also determine future outcomes (6,7). Infant growth is related to school attainment, productivity, cognitive development, wages, obesity, insulin resistance, blood pressure, and more (8).

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Maternal and infant health are inexorably linked, especially through early nutrition and breastfeeding (9,10). This link is particularly important in the context of HIV as the health of the mother and infant are fragile. In this context, maternal and infant health can be connected through several mechanisms, which we explore using a longitudinal, structural equation model (SEM, Fig. 1). Structural equation modeling is similar in theory to traditional linear regression. However, in an SEM diagram, the arrows represent a set of hypothetical relationships that can be tested. Instead of specifying and examining one relationship at a time, this approach allows for the simultaneous estimation of multiple relationships. By doing this, we are able to account for the inherent dependencies between the various factors examined here. The longitudinal, interdependent nature of this analysis is especially important as these factors feedback on one another.

1. We expect that viral suppression will reduce maternal weight loss. HIV progression and ART can induce weight loss through changes in diet, absorption, metabolism, and other factors (11,12). There is conflicting evidence regarding the presence of a relationship between weight loss among lactating women with HIV and disease progression (13–15). However, malnutrition is known to accelerate HIV progression (16,17); therefore, it is possible that weight loss could result in a loss of viral suppression status. Although there is no association between maternal body mass index (BMI) and disease progression in sub Saharan Africa (18), the effect of *changes* in weight remains unknown.
2. Similarly, we predict that viral suppression will be related to increased infant length. Maternal viral suppression will decrease infant exposure to HIV through breastmilk (19), thereby decreasing any negative biological effects of HIV exposure on infant growth. Viral suppression will also improve maternal health, decreasing the infant's exposure to other HIV related opportunistic infections, and improving the mother's ability to care for the infant. Measures of maternal viral load and CD4 + are related to infant growth and health outcomes (20–22).
3. We expect that breastfeeding will induce maternal weight loss; however, it is equally possible that women who are rapidly losing weight may choose to stop breastfeeding. It is as yet unclear if HIV increases the energetic demands of breastfeeding; however, breastfeeding requires about 500 kilocalories a day (23). Women may mobilize their fat stores to meet these demands (23). Or, women with significant weight loss may choose not to breastfeed to preserve their own nutritional resources. The association between breastfeeding and postpartum weight loss remains uncertain (24), with some studies showing no effect in women with HIV (14,15). Nonetheless, women in Malawi believe there is an interaction between nutrition, HIV disease progression, and the ability or choice to breastfeed, especially in resource restricted settings (25). This belief is likely to result in women adjusting their breastfeeding status in response to their weight status.

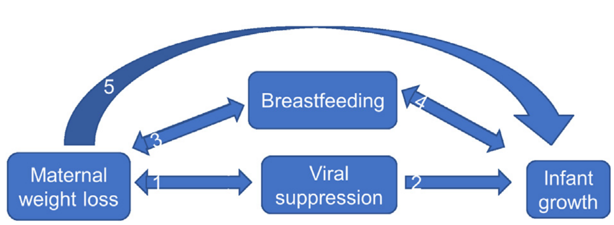

Fig. 1. Theoretical model examining the relationship between maternal nutritional status, viral load, and infant growth.

4. We anticipate that breastfed infants will be longer and, conversely, being longer may be related to the early cessation of breastfeeding. Breastfeeding supports infant growth, and rapidly growing infants may breastfeed more. Many studies have found relationships between breastfeeding and growth outcomes, but these relationships are not consistent, affecting some measures of weight and length and not others at various ages (26–30). A major limitation of these studies is the possibility of reverse causation. Women tend to adjust their breastfeeding status to cues from the infant and perceived infant health (31–34). As such, it is possible that breastfeeding may affect infant growth, and infant growth may affect breastfeeding decisions.
5. Rapid maternal weight loss may be harmful to infant growth independent of breastfeeding. Some maternal weight loss is expected in the first year after pregnancy, with the rate decreasing over time (35–37). However, among women with HIV in sub Saharan Africa, there is little change in BMI from six to 24 months postpartum (18). The effect of maternal weight status on infant growth after birth remains unclear, with some evidence indicating that low maternal weight may affect infant growth, especially in the context of HIV (38–40). Accelerated weight loss could reflect increasing HIV disease severity. Even mild weight loss is associated with an increased risk of death (41). As such, maternal weight loss could represent maternal depletion, increasing disease severity, or environmental hardships affecting both the mother and the infant.

Materials and methods

Cohort description

The Kabeho Study (Kigali Antiretroviral and Breastfeeding Assessment for the Elimination of HIV) enrolled 608 pregnant or postpartum women with HIV participating in the prevention of mother to child HIV transmission programs in selected high volume health facilities in Kigali, Rwanda from April 2013 to January 2014 (Fig. 2). All women were placed on lifelong antiretroviral therapy (Option B+). The majority of women received tenofovir, lamivudine, and efavirenz. In some cases of contraindications, zidovudine replaced tenofovir or nevirapine replaced efavirenz. Women were required to have documented HIV infection, plan to remain in the Kigali area after delivery, and provide consent. HIV testing of the infants was conducted according to standard national procedures for early infant diagnosis by HIV polymerase chain reaction (PCR) or rapid HIV testing at 6 weeks, 9 months, 18 months, and 24 months by the National Reference Laboratory using Roche COBAS AmpliPrep/TaqMan (V2.0).

Study visits were conducted at the health facilities within two weeks of birth; at six, 10, and 14 weeks; monthly from four to 18 months; and at 21 and 24 months. Attendants in the clinical settings measured birth weight where births took place. If recorded birth weight was not available, we used measurements taken at the Kabeho birth visit as a measure of neonatal weight. At each visit, trained nurses took duplicate measures of infant length to the nearest centimeter (cm) using Shorr boards, and weight to the nearest 10 grams using United Nations International Children's Relief Fund scales. Maternal weight was measured at six, 12, 18, and 24 months. Viral load was measured at birth, 18 months, and 24 months. Viral load testing was conducted using the Roche Cobas Ampli Prep/Cobas TaqMan HIV 1 quantitative test. The lower limit of detection for this test (10 copies/mL) was used to define viral suppression. At each visit, women were asked if they had experienced a food shortage in the last month, if they were currently

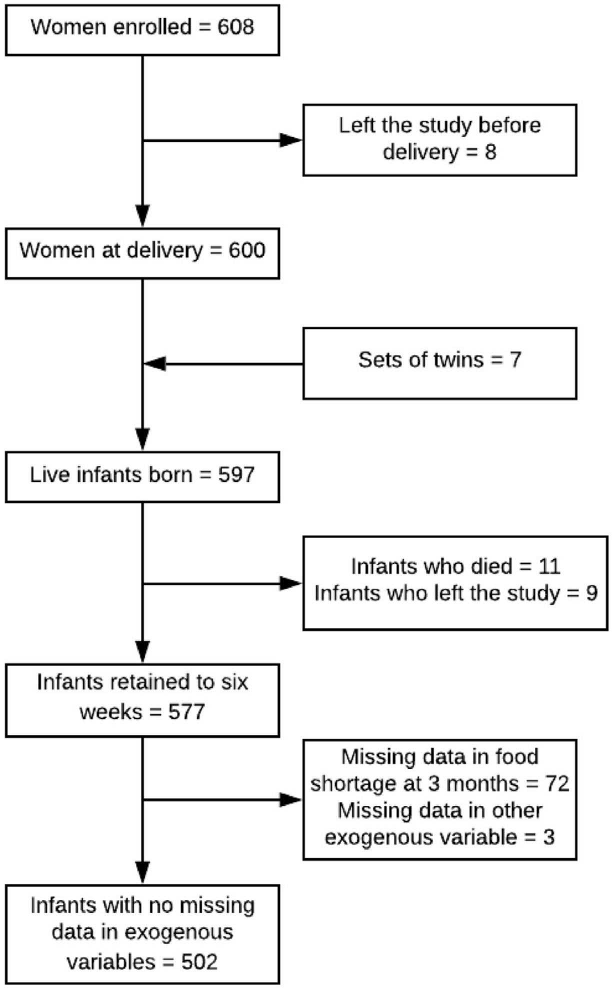

Fig. 2. Flow diagram indicating reflecting how the final analytical sample was arrived at.

breastfeeding, and if their infant had been sick since the last visit. Women were asked if they had a cesarean delivery, a predictor of breastfeeding initiation in Rwanda, and the date at which ART treatment was initiated.

Defining key variables

Maternal rate of weight change was calculated by subtracting the weight at the beginning of the period from the weight at the end and dividing by the number of months between measures. A factor score was developed for each facility that represented the level of training of staff in infant feeding counseling. This was a significant predictor of breastfeeding initiation in our previous work on the Kabeho sample (unpublished). Because this is a facility level variable, data were clustered at the facility level. Time since the start of antiretroviral therapy (ART) was defined by subtracting the date at which ART was started from the birth date. This results in most values being negative, reflecting starting ART before infant birth. The median time since the initiation of ART was 1.55 years. Infant z scores were calculated using the WHO igrowup macro parameters (42).

Building the structural equation model

The SEM was developed in MPLUS using full information maximum likelihood (FIML) (43). Continuous variables, other than LAZ, were standardized to have a mean of zero and a standard deviation of one. As such, path coefficients can be interpreted similarly to beta coefficients in linear regressions with standardized data.

Temporality was considered in the development of the models. Viral suppression measures can be viewed as reflecting a longer period of suppression, which started several weeks or months before the measure. If this approach is adopted, current viral suppression could have already affected the current infant length. Alternatively, viral suppression can be viewed as only reflecting current status, and therefore, only affecting future growth outcomes. Because 118 women (21%) initiated treatment within 3 months of birth, we consider the viral birth measure to reflect only the current status and affect only future growth. However, more than 80% of women showed concordance in their viral status at 18 and 24 months, so these are considered to reflect a chronic state and to have already acted on infant growth by the time of measurement. Maternal weight change is modeled as influencing infant growth by the end of the period. Because breastfeeding reflects a continuous caloric demand, breastfeeding status at the beginning of a period is assumed to affect weight change throughout the period. A reciprocal relationship between breastfeeding at the end of a period and weight change throughout the period is modeled as maternal depletion could cause breastfeeding cessation. All values are expected to influence their own subsequent values.

Maternal education, age, and height; time since the initiation of ART; staff trained in infant feeding; delivery method; neonatal WAZ; food shortages; and infant sex are included in the model to control for confounding and allow for model estimation. The model was originally estimated with size outcomes at three, 12, 18, 21, and 24 months. However, the 12 and 21 month time points were dropped due to a large amount of missingness, which severely reduced the available sample size. The ratio of children to adults in the household, dietary diversity, meal frequency, and illness episodes were included in the original model but removed due to poor model fit. Breastfeeding at 24 months was dropped from the model due to limited variation; 97% of infants were already weaned.

Results

A final sample of 502 infants had sufficient data to be included in the analysis (Table 1). Maternal weight change was unrelated to food security or viral suppression status. In univariate analysis, weight change from 6 to 12 and 18–24 months was inversely related to weight at the beginning of the period (p value <0.04). Maternal BMI was approximately 23 kg per m^2 at all time periods. Infants whose mothers reported a food shortage were more likely to be breastfed at 18 months (p value <0.001).

The final model estimated is illustrated in Figure 3 (Sup 1). The root mean square error of approximation (RMSEA) was 0.01. The standardized root mean square residual (SRMR) was 0.08. The comparative fit index (CFI) was 0.97. These values indicate adequate model fit.

Older mothers are more likely to be virally suppressed (ß 0.39) and to breastfeed (ß 0.17); although, the effect on breastfeeding diminishes with age (ß 0.32). Viral suppression and the mother being on ART for longer are related to lower infant LAZ at three months ($ß_{\text{viral suppression}}$ 0.16, $ß_{\text{time on ART}}$ 0.11). A more positive maternal weight change is related to higher infant LAZ at the end of each period ($ß_{6\ \ 12\text{mo}}$ 0.04, $ß_{12\ \ 18\text{mo}}$ 0.91, $ß_{18\ \ 24\text{mo}}$ 0.11). At 12 months, a higher infant LAZ is related to an increased probability of breastfeeding (ß 0.25). At 18 months, breastfeeding is related to lower LAZ (ß 0.23), and food

Table 1
Descriptive statistics of sample across time

	Baseline		12 mo		18 mo		21 mo		24 mo	
	n/mean	%/SD.	*n*/mean	%/SD.	*n*/mean	%/SD.	*n*/mean	%/SD.	*n*/mean	%/SD.
Total *n*[*]	502		409		431		219		355	
Female infant *n*[*]	289	52%	215	52%	224	52%	120	55%	185	52%
Neonatal WAZ[†]	0.00	1.00								
Maternal age (y)	29.52	6.03								
Maternal height (cm)	157.24	6.27								
Time since ART (months)	−39.54	66.40								
Mother completed primary school	225	45%								
Cesarean delivery	96	19%								
Staff trained in feeding counseling factor score	−0.6	0.79								
Virally suppressed (<10 copies/mL)	276	56%			306	78%			310	80%
LAZ[‡,§]	−0.81	1.09	−1.28	1.17	−1.52	1.12	−1.66	1.10	−1.55	1.03
Rate of maternal weight Change over preceding six mo. (kg)			0.02	0.89	0.00	0.96			0.00	0.99
Breastfed[§]	474	94%	277	64%	84	20%	18	5%	14	3%

[*] Number with LAZ measurements.
[†] Weight-for-age z-score.
[‡] Length-for-age z-score.
[§] Baseline is considered 3 mo.

shortages are related to higher LAZ (ß 0.12). Generally, values among repeated measures predicted subsequent values.

Discussion

Model fit indexes demonstrate that our structural equation model fits the data. There is persistence in viral suppression, food shortages, breastfeeding status, and infant LAZ; the values at one period are positively related to the values in the following period. Weight change at 12–18 months is related to the inverse change in the subsequent period, reflecting stable maternal weight. The re lationships of the repeated measures over time are both logical and intuitive, indicating that the model is well specified.

Maternal weight change was related to higher infant LAZ at the end of the period. A standard deviation (0.9 kg) increase in maternal weight change from six to 12 months was related to a 0.04 unit increase in infant LAZ, holding all other factors constant. However, the pathways between weight change and LAZ function independently of breastfeeding, thus it is unlikely that this rela tionship was the result of maternal depletion leading to the mother being unable to adequately care for her infant. At six and 18 months, 10–13 women had BMIs less than 18. There was no relationship between viral suppression and weight change; there fore, it is unlikely that weight change represents a measure of disease severity in our sample. Furthermore, because food security and maternal weight change were not related in univariate analysis or in this structural equation model, and maternal education does not affect infant LAZ, maternal weight change is unlikely to be acting as a measure of socioeconomic status. As such, maternal weight change must reflect some other environmental factor that supports infant and maternal wellbeing. Future research should attempt to identify this protective factor.

Older women were more likely to be virally suppressed and to breastfeed. There was little difference in mortality risk between individuals with HIV initiating treatment between the ages of 18–30 and 30–40 in South Africa, indicating little difference in disease progression (44). In the United States and Canada, older individuals were more likely to achieve viral suppression (45). This may be because older individuals have better adherence (46). We were unable to consider adherence because most of our

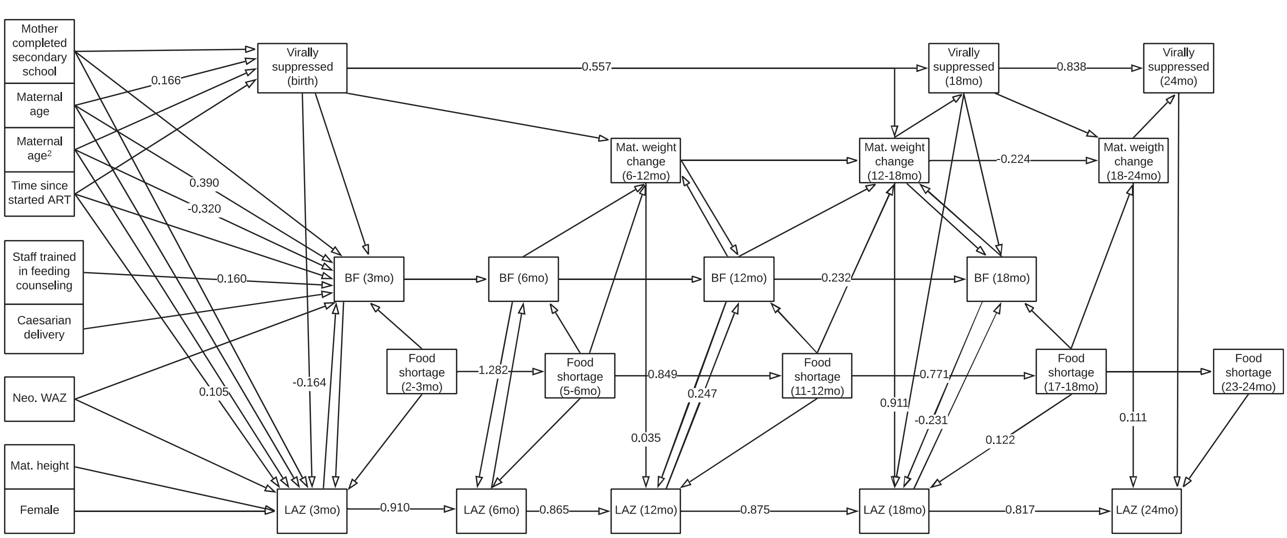

Fig. 3. Structural equation model of the relationship between viral suppression, maternal weight change, breastfeeding, and infant LAZ. All effects reported have *p*-values less than 0.05. Age^2 reflects and age squared term.

participants reported perfect adherence. The association between maternal age and breastfeeding is well established (47–51).

Women who initiated ART treatment with standard deviation (5.5 years) more recently have infants with 0.11 unit higher LAZ. This pathway functions independently viral suppression, indicating that it does not reflect the HIV disease state. The effect of exposure to ART on infant growth is unknown, but certain drugs have been associated with infant growth in utero (1,3,52,53). While the effects of ART exposure through breastmilk are less clear, the majority of women in this study received reverse transcriptase inhibitors, which are transferred through breastmilk and could have similar effects postnatally (54). Infants whose mothers started treatment more recently may have less exposure to ART and, therefore, better early growth. This could also explain the negative association between maternal viral suppression and early LAZ. Women with more medication in their bodies are more likely to be suppressed, their infants are exposed to more of the treatment, and the drug has a larger, negative effect on growth.

The hypothesized negative effect of ART on LAZ is supported by the lack of a relationship between viral suppression and growth at 18 and 24 months when infants were likely to have already been weaned, and therefore, would not be exposed to ART through breastmilk. However, at 18 months, breastfeeding was related to decreased linear growth, possibly because continued exposure to HIV and ART was harmful. Furthermore, infants who were still breastfed at this time may not receive sufficient complementary foods. These infants have lower dietary diversity and meal frequency.

In sub Saharan Africa, breastfed infants ages 12–18 months are shorter and lighter than their weaned counterparts (55). However, this analysis was unable to determine the direction of causation. At 12 months, taller infants were more likely to still be breastfed and, at 18 months, breastfed infants tended to be shorter. This indicates the possibility of a two way, time varying relationship that should be investigated further in future research.

The reason for a positive relationship between food shortages on LAZ at 18 months remains unclear. Although non significant in the model, infants who experienced food shortages at 18 months were more likely to be breastfed than those who do not. The same altered dietary pattern associated with continued breastfeeding was associated with food shortages. Food shortages were also associated with lower maternal height and education. Therefore, the relationship between food shortages and LAZ must be considered in the context of the complete model and other sources of variation. In univariate analysis, food shortages at 18 months were related to decreased LAZ (β 0.41, *p* value 0.003); however, in multivariate linear regressions, this relationship became non significantly positive. As such, the relationship between food security and LAZ at this age likely reflects an interaction between this variable and the others in the model.

This study has several limitations. First, structural equation modeling is often used as an explicitly causal framework. However, there no need to make causal claims because structural equation modeling is employed. Although we hypothesize about potential mechanisms, our analysis does not demonstrate causation. Second, our sample has some loss to follow up. The use of FIML allows infants to contribute partial data and only drops infants with missing data in the exogenous variables. The mechanisms reflected in our dataset should function similarly within the subgroup of infants who were lost to follow up. Finally, because we do not have a comparator with infants without HIV exposure, we are unable to determine if the pathways, which are not specific to HIV, such as maternal weight change, would act similarly in a population without HIV exposure.

Conclusions

We demonstrate the relationship between maternal and infant health in the context of HIV. Time on ART and viral suppression are both related to decreased early infant LAZ. Maternal weight change is correlated with infant LAZ. This supports the ongoing shift in the public health approach to postpartum care that prioritizes the wellbeing of the mother infant dyad rather than considering each separately. Additional work is needed to understand how the mother and infant influence one another, and their health responds to their shared environment.

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Appendix

Supplemental Table 1
Weights of all variables in the structural equation model

Acted upon variable	Acting variable	Coefficient	SE.	*p*-value
Virally suppressed at birth	Time since the initiation of ART (d)	0.123	0.063	.051
	Maternal age (y)	0.166	0.066	.012
	Maternal age^2 (y)	−0.032	0.066	.628
	Mother attended secondary school (binary)	0.01	0.145	.942
Breastfeeding at 3 mo.	Time since the initiation of ART (d)	0.045	0.052	.385
	Maternal age (y)	0.39	0.071	0
	Maternal age^2 (y)	−0.32	0.058	0
	Mother attended secondary school (binary)	−0.008	0.131	.949
	Neonatal WAZ	−0.011	0.062	.861
	Food shortage at 3 mo. (binary)	0.07	0.082	.391
	Virally suppressed at birth (binary)	0.079	0.09	.377
	LAZ at 3 mo.	0.202	0.412	.624
	Staff trained in infant feeding counseling (continuous factor)	0.16	0.081	.049
	Planned caesarian delivery (binary)	−0.076	0.118	.523
LAZ at 3 mo.	Time since the initiation of ART (d)	0.105	0.04	.009
	Maternal age (y)	0.119	0.16	.46
	Maternal age^2 (y)	0.005	0.127	.966
	Mother attended secondary school (binary)	0.075	0.076	.322
	Neonatal WAZ	−0.02	0.051	.697
	Food shortage at 3 mo. (binary)	−0.091	0.097	.35
	Virally suppressed at birth (binary)	−0.164	0.062	.008
	Maternal height (cm)	−0.032	0.05	.523
	Breastfeeding at 3 mo. (binary)	−0.524	0.591	.376
	Female infant (binary)	0.179	0.141	.203
Breastfeeding at 6 mo.	Breastfeeding at 3 mo. (binary)	3.674	4.356	.399
	LAZ at 6 mo.	0.495	0.61	.418
	Food shortage at 6 mo. (binary)	0.01	0.135	.939
LAZ at 6 mo.	LAZ at 3 mo.	0.91	0.036	0
	Breastfeeding at 6 mo. (binary)	−0.046	0.052	.369
	Food shortage at 12 mo. (binary)	−0.009	0.05	.861
Food shortage at 6 mo.	Food shortage at 3 mo. (binary)	1.282	0.072	0
Maternal weight change from 6 to 12 mo.	Virally suppressed at birth (binary)	−0.074	0.061	.226
	Breastfeeding at 6 mo. (binary)	0.06	0.12	.621
	Breastfeeding at 12 mo. (binary)	−0.336	0.337	.318
	Food shortage at 6 mo. (binary)	0.098	0.081	.228
Breastfeeding at 12 mo.	Breastfeeding at 6 mo.(binary)	0.379	0.409	.354
	LAZ at 12 mo.	0.247	0.064	0
	Food shortage at 12 mo. (binary)	0.11	0.065	.093
	Maternal weight change from 6 to 12 mo. (kg)	0.316	0.274	.248
LAZ at 12 mo.	LAZ at 6 mo.	0.865	0.038	0
	Breastfeeding at 6 mo.(binary)	0.002	0.036	.959
	Food shortage at 12 mo. (binary)	0.054	0.052	.3
	Maternal weight change from 6 to 12 mo. (kg)	0.098	0.046	.035
Food shortage at 12 mo.	Food shortage at 6 mo. (binary)	0.849	0.139	0
Maternal weight change from 12 to 18 mo.	Virally suppressed at birth (binary)	−0.125	0.132	.345
	Maternal weight change from 6 to 12 mo. (kg)	−0.656	0.41	.11
	Breastfeeding at 12 mo. (binary)	0.484	0.277	.08
	Breastfeeding at 18 mo. (binary)	−2.92	2.686	.277
	Food shortage at 12 mo. (binary)	0.189	0.168	.26
Breastfeeding at 18 mo.	Breastfeeding at 12 mo.	0.232	0.108	.031
	LAZ at 18 mo	−0.08	0.051	.112
	Food shortage at 18 mo.	0.031	0.056	.575
	Maternal weight change from 12 to 18 mo.	0.911	0.142	0
	Virally suppressed at 18 mo.	−0.046	0.109	.674
LAZ at 18 mo.	LAZ at 12 mo.	0.875	0.028	0
	Breastfeeding at 18 mo. (binary)	−0.231	0.11	.036
	Food shortage at 18 mo. (binary)	0.122	0.043	.004
	Maternal weight change from 12 to 18 mo. (kg)	−0.052	0.045	.251
	Virally suppressed at 18 mo. (binary)	−0.015	0.051	.765
Food shortage at 18 mo.	Food shortage at 12 mo. (binary)	0.771	0.124	0
Virally suppressed at 18 mo.	Virally suppressed at birth (binary)	0.557	0.166	.001
	Maternal weight change from 12 to 18 mo. (kg)	−0.106	0.13	.413
Maternal weight change from 18 to 24 mo.	Virally suppressed at 18 mo. (binary)	−0.036	0.068	.595
	Maternal weight change from 12 to 18 mo. (kg)	−0.224	0.048	0
	Food shortage at 18 mo. (binary)	0.015	0.04	.704
LAZ at 24 mo.	LAZ at 18 mo.	0.817	0.027	0
	Food shortage at 18 mo. (binary)	0.039	0.131	.767
	Maternal weight change from 18 to 24 mo. (kg)	0.111	0.034	.001
	Virally suppressed at 24 mo. (binary)	−0.032	0.038	.398
Virally suppressed at 24 mo.	Virally suppressed at 24 mo. (binary)	0.838	0.114	0
	Maternal weight change from 18 to 24 mo. (kg)	−0.111	0.088	.204
Food shortage at 24 mo.	Food shortage at 18 mo. (binary)	0.104	0.096	.275

Age^2 reflects and age squared term.