

**EVALUATION OF AN INFANT FEEDING SUPPORT STRATEGY  
AMONG HIV-EXPOSED INFANTS IN URBAN HAITI**

A Dissertation

Presented to the Faculty of the Graduate School

of Cornell University

in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

by

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August 2011

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# **Evaluation of an Infant Feeding Support Strategy among HIV-exposed Infants in Urban Haiti**

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Cornell University 2011

Nutrition support is essential to improve health outcomes among HIV-exposed children.

However, there are few evidence-based models for effective integration of nutrition support within clinical Prevention-of-Mother-to-Child-Transmission (PMTCT) services. To address this gap, we aimed: 1) to describe the problem of growth faltering among HIV-exposed uninfected infants at GHESKIO clinic in Port-au-Prince, Haiti, 2) to design an age- and context-appropriate infant feeding support intervention for this population and 3) to evaluate the effectiveness of the intervention in improving growth outcomes.

Medical record data from 360 HIV-exposed uninfected children seen at GHESKIO between July 2007 and October 2009 were used to describe the growth pattern from birth to 23 mo (Aim 1).

They were compared to the WHO 2006 Growth Standard and a nationally-representative sample of same-age Haitian children (n=1190). GHESKIO children were born proportionally stunted and improved in weight-for-age and length-for-age across the first 6 mo of life.

Faltering in weight and length began at 7 mo. Length faltering continued until 24 mo.

Outcomes in GHESKIO children were significantly better than the nationally-representative sample at age 24 mo.

As part of the intervention-design process (Aim 2), we identified contextual factors that influenced intervention implementation. The support of higher-level stakeholders was a key

facilitator. Factors related to the chaotic environment of urban poor HIV-infected mothers were the primary barriers. The caregivers club model provides a promising foundation for integration of nutrition support and PMTCT services at GHESKIO.

To assess the impact of the intervention on growth outcomes among a cohort of 6-12 month old HIV-exposed, uninfected children (Aim 3), outcomes in intervention participations (n=72) were compared to a historical control group of children in the GHESKIO PMTCT program in the previous year (n= 294). Participation in the 24-week intervention was associated with a 67.3% decrease in underweight ( $p=.007$ ) and 54.7% decrease in stunting ( $p=.029$ ) around age 12 mo. The magnitude of the benefit on prevalence of growth faltering was large compared to other infant feeding interventions. Further implementation research is needed to make the intervention sustainable in the GHESKIO context and to apply the model to similar contexts outside GHESKIO.

## BIOGRAPHICAL SKETCH

Rebecca Heidkamp was born and raised in the suburbs of Chicago, Illinois, USA. She graduated *summa cum laude* from Wheaton College (Illinois) in 2000 with a Bachelors of Science in Biology. Rebecca was introduced to the field of public health through Wheaton College's Human Needs and Global Resources (HNGR) certificate program. Her first experience living and working outside of the United States was a 6-month internship with a community-based child survival program in rural Honduras. After graduating from Wheaton, Rebecca spent one summer as the "nature lady" at a camp for youth from inner-city Detroit where she discovered that a career in environmental education required frequently touching snakes and frogs. She decided she preferred mothers and babies and so she joined World Relief, an international NGO. Rebecca spent 5 years with World Relief supporting community-based child survival and HIV prevention and care programs in East Africa (Kenya, Rwanda, Mozambique, South Sudan) and Haiti. Rebecca joined the Cornell University Program in International Nutrition in August 2005.

## DEDICATION

To my parents, whose deep and constant love continues to nurture, sustain and inspire me.

To Marie-Jean Mona Maitre – a nurse, educator, advocate, mentor and friend -  
who embodies the spirit of community health

In memory of Mona's beloved daughter, Laurie, and the countless others  
we lost on 12 January 2010 *Nap sonje nou anpil.*

## ACKNOWLEDGMENTS

This dissertation reflects the support of countless individuals and institutions – many of whom I will not be able to include here by name but for whom I am very grateful for.

### *At Cornell University*

My advisor, Dr. Rebecca Stoltzfus, for continually demonstrating that kindness and compassion can come hand in hand with high intellectual standards.

My dissertation committee members: Dr. Jean-Pierre Habicht, Dr. Kathleen Rasmussen, and Dr. Patsy Brannon who each encouraged my development as a practitioner-scholar.

My friends and colleagues in the Stoltzfus research group: Sunny Kim, Keriann Paul, Erica Phillips, Jackie Kung'u, Helena Pachon, Scott Ickes, Amanda Zongrone, Francis Ngure, Barnabas Natamba, Cynthia Ntare, Laura Smith, Rahul Rawat, Avril Armstrong

My CU friends and community beyond the Stoltzfus research group: Jeanne Moseley, Althea Sircar, Eva Monterrosa, Jim Goetz, Christine Dieterich, Emily Bielecki, Andrew Jones, Gabby Voeller, Stephanie Ghering, Renee Hill, Emily Leavitt, Sera Young, Mduzi Mbuya, Purnima Menon, Kate Dickin, Jason Slinker, Lacey Wrubel, the Sandersons, the Wests, and the Vineyard families

CU undergraduate research assistants: Choumika Simonis, Reginald Severe, Annie Symonds, Lauren Webster, Juhi Purshwani

The faculty, staff and students of the Cornell University Division of Nutritional Sciences

### *At GHESKIO / Weil-Cornell Medical College*

GHESKIO founder and director Dr. Jean William Pape - a truly great man who I am privileged to count as a mentor.

Drs. Warren Johnson and Daniel Fitzgerald in the WCMC Center for Global Health and the GHESKIO senior leadership team for embracing me as one of you own.

The GHESKIO Nutrition team – Marie Jean Mona Maitre, Ghisaline Saint Louis, Adeline Bernard, Suzette Fleury and Elizabeth Fox. *Yon bon ekip*. I cannot thank you enough.

All my GHESKIO colleagues and friends including Vanessa Rouzier, Sandra Camille, Lilian Fortilus, Rebecca Dillingham, Francine Noel, Janet Nicotera, and Serena Koenig.

WCMC research assistants (and friends) Kristin Gilbert and Cora Walsh

“Our “moms and babies with whom we shared much laughter and some tears.

#### *And Beyond*

My professional mentors past and present including Deborah Dortzbach, Dr. W. Meredith Long, Dr. Lilian Wambua, and Laura Van Vuuren

Many dear friends including my community in Haiti (A+B, CL, KA, AI, VR, EF, SC, EP, MS, SK, KB, HS, M+J, M+E, KH, DG, CL, MC, LW, MG, BF, JR,...), my Wheaton College family (R+G, S+J, M+J, SM, NH, SA, KO, AC....), Baltimore family/friends (GD, KB, W+G,MM, ML, J+C, M+H,...), Chicagoland (CS, JP, S+P, MW,...) and those special others who have shown up in between (ZA, RK, JWK...)

My large and loving biological family, the Heidkamps and Mikes, who never seem quite sure where I am or what I do but continually encourage me with their words and prayers.

My parents, Joy and Emil Heidkamp. I don't have words to express just how precious your love and support are to me. This success is as much yours as it is mine.

#### *Funding support*

A number of institutions provided funding support for my training and research including the Cornell University Division of Nutritional Sciences, Mario Einaudi Center at Cornell University, Weil-Cornell Center for Global Health, US National Institutes for Health, The President's Emergency Plan for AIDS Relief and United States Agency for International Development in Haiti



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## LIST OF ABBREVIATIONS

AI	Adequate Intake
ARV	Antiretroviral drug
DHS	Demographic and Household Survey
EBF	Exclusive Breastfeeding
FM	Fortified Manba
GHESKIO	Groupe Haïtien d' E'tudes du Sarcome de Kaposi et des Infections Opportunistes
HAART	Highly Active Antiretroviral Therapy
IFSS	Infant Feeding Support Strategy
IRB	Institutional Review Board
IUGR	Intrauterine Growth Restriction
IYCF	Infant and Young Child Feeding
LAZ	Length-for-Age Z-Score
LTF	Lost to follow-up
MCHN	Maternal and Child Health and Nutrition
NGO	Non-Governmental Organization
ORS	Oral Rehydration Solution
OVC	Orphans and Vulnerable Children
PCR	Polymerase Chain Reaction
PEPFAR	President's Emergency Plan for AIDS Relief
PMTCT	Prevention-of-Mother-to-Child Transmission (of HIV)
RUTF	Ready-to-use Therapeutic Foods
SAM	Severe Acute Malnutrition
SD	Standard Deviation
USG	United States Government
WAZ	Weight-for-Age Z-Score
WLZ	Weight-for-Length Z-Score

## **CHAPTER 1**

### **BACKGROUND**

This dissertation describes the design, implementation and evaluation of an intervention to improve growth outcomes among HIV-exposed Haitian children in late infancy. The research was conducted between June 2007 and January 2010 at the Groupe Haïtien d'Études du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) Centers, an HIV/AIDS and infectious disease clinic in Port-au-Prince, Haiti.

This research stands at the intersection of two high priority and rapidly advancing fields of public health practice: improving infant and young child feeding (IYCF) to prevent child undernutrition and the prevention of mother-to-child transmission (PMTCT) of HIV in resource-poor contexts. The research is timely given a) the magnitude of the global HIV/AIDS epidemic and the global burden of childhood undernutrition, b) emerging evidence from ongoing research in PMTCT and early childhood undernutrition showing the longer-term implications of not intervening in affected populations, and c) the current availability of resources to address these problems. Both PMTCT and childhood undernutrition are priority issues on the global health policy agenda.

Chapter 1 provides an overview of relevant literature on IYCF in the context of HIV/AIDS, the Haitian context, and policy-oriented evaluation research. Overall research objectives of the dissertation and specific research questions are identified at the end of this chapter.

## **INFANT AND YOUNG CHILD FEEDING IN THE CONTEXT OF HIV/AIDS**

In this section I will present relevant on IYCF and then PMTCT, concluding with their intersection in HIV and infant feeding.

### **Infant and Young Child Feeding**

Undernutrition is the underlying cause of 35% of young child deaths globally [2]. In addition, protein-energy and micronutrient deficiencies in early childhood can have significant long term negative effects on growth, immune function, neurobehavioral development and risk of chronic disease [2-4]. Malnutrition potentiates the progression of infectious disease [5, 6] .

#### *Assessment of child growth*

Growth is the primary outcome and indicator of nutritional status used in this research.

Growth is a composite indicator of the health status of a young child. It reflects the combined effects of past and present nutritional status as well as disease, injuries, and other non-nutritional factors. Weight and length<sup>1</sup> are relatively simple measures to obtain at the clinic or community level and the preferred measures for monitoring and evaluation of child health interventions in less developed countries [7, 8].

Weight-for-age, length-for-age and weight-for-length are the three most commonly used anthropometric indices for nutritional assessment in young children. Calculation of these indices depends on the growth curve of a reference population. They are most clearly

---

<sup>1</sup> Length is a recumbent measure of linear growth used for children under 2 years old. Height is a standing measure of linear growth used in children age 2 and older. Children under 2 are the focus of this research and therefore the term “length” will be used exclusively to refer to the measure of linear growth.

expressed as z-scores reflecting the number of standard deviations above or below the reference mean or median. Undernutrition is categorized as underweight (WAZ<-2 SD), stunting (LAZ<-2 SD) and wasting (WLZ<-2 SD). Growth z-scores between -2 to -3 SD are classified as moderate undernutrition and z-scores less than -3 SD are considered severe undernutrition [8].

The three indicators (WAZ, LAZ, WLZ) share common determinants but they each reflect “ a different combination of biological processes” [8] related to growth. For all three indices, overall risk of death increases with declining z-score and is significantly elevated below –3 SD [2].

Length-for-age is a measure of linear growth that reflects the cumulative effects of malnutrition and poor health over a longer period [8]. Early childhood stunting is associated with long-term consequences, including reduced adult height, poor intellectual development, lower adult economic productivity and lower birth weight in offspring [9]. While very young children can recover from stunting through catch-up growth, stunting is not typically reversible after 24-36 months of age [10]. Length-for-age is an important outcome for interventions looking to prevent the long-term effects of undernutrition and is included as a primary outcome in our research.

Weight-for-length is a measure of thinness that is independent of child age. Changes in WLZ can reflect acute changes in weight relative to length. Severe wasting is commonly termed severe acute malnutrition (SAM) and is associated with 5-20 times higher risk of mortality compared to well-nourished children [11]. Given their different etiologies, stunting and severe



wasting may not be found in the same children. In analysis of growth data from 19 Demographic and Health Surveys (DHS) in poor countries, severe wasting was not accompanied by stunting in 80-100% of younger children surveyed [2]. Therefore interventions targeting populations at risk of one outcome may or may not affect the other.

Weight-for-age is a composite marker of nutritional status that can reflect acute or longer term undernutrition. It is commonly used as an indicator of global undernutrition at the population level and is not a specific indicator of the cause of undernutrition in an individual child [8].

In April 2006 the World Health Organization (WHO) released new Child Growth Standards for assessment of growth and development outcomes in children age 0 to 5 years [12]. The new standards are based on data from the six-country WHO Multicentre Growth Reference Study that followed children from higher socioeconomic status households who were fed according to WHO breastfeeding recommendations longitudinally across the first 2 years of life. Using the WHO 2006 Growth Standard, a consistently well-nourished child will track steadily near the “0” z-score level across early childhood.

Introduction of the new standard has important implications for population-level assessment of malnutrition and targeting of public health interventions [13]. In particular, the proportion of children identified with severe wasting is 1.5- 8 times higher using the WHO 2006 Standard compared to the previously used National Center for Health Statistics/WHO international growth reference [14, 15].

Overall patterns of growth faltering based on the WHO 2006 Standards are consistent across low-income countries [16]. Mean WAZ and LAZ decline steadily from near birth across the first

two years of life. LAZ levels out around -2 SD after 24 months of age. WLZ declines from 2-9 months but improves and levels out near the mean by 24 months of age [16]. These patterns suggest that children under age two are the most vulnerable to growth faltering and the most likely to benefit from intervention [10, 17-19]. Therefore children in this age group are the focus of this research.

### *Determinants of child growth*

Growth across early childhood is determined by a number of factors beginning in the prenatal period. The UNICEF framework of childhood malnutrition [20] describes the underlying and immediate causes of childhood malnutrition as being related to access to “food, health and care” which in turn contribute to adequate dietary intake and risk of infectious disease.

Several of the key determinants of growth relevant to the dissertation research are discussed in greater detail here.

*Size at birth:* Size at birth is associated with postnatal growth outcomes. Low birth weight (LBW) (birth weight less than 2500 g) is associated with increased risk of early mortality [2]. The determinants of postnatal growth patterns among LBW infants are not well understood [21, 22]. It is important to distinguish infants who are born small because they are preterm (born at <37 weeks gestation) and full term infants who are small for gestational age (SGA) due to *in utero* growth restriction (IUGR). It is possible that an infant is both preterm and IUGR.

Preterm infants generally demonstrate early postnatal growth failure followed by catch-up growth over a 2-3 year period. Most do not reach the size of their full-term peers [21]. Among IUGR infants, infants who are born disproportionally growth restricted (low ponderal index

(kg/m<sup>3</sup>) or “skinny”) demonstrate early catch-up growth while proportionally growth restricted infants with normal ponderal index generally do not [23, 24]. Very little data are available about the postnatal growth patterns of infants classified as preterm versus IUGR in low income countries. LBW infants in Malawi did not reach the same size as their normal weight peers at 12 months of age [25]. Although the etiologies of preterm and IUGR remain poorly understood, the presence of either is a sign of an *in utero* environment that is not favorable to healthy fetal development.

*Dietary intake:* A child’s diet must provide adequate quantities of macro- and micronutrients to support healthy growth and development. Infants and young children have high nutrient needs relative to their body size but limited gastric capacity [26]. To achieve adequate intakes, WHO guidelines recommend exclusive breastfeeding (EBF) for the first 6 months of life followed by the gradual introduction of adequate quantities of energy-dense complementary foods with continued breastfeeding until at least age 2 years [27]. Increased frequency of feeding and diversity of food groups in the complementary diet are associated with improved nutrient intakes [26]. Fortified foods or micronutrient supplements are recommended for populations with low intakes of animal source foods [28]. Caregivers may not have knowledge of appropriate foods for children and/or household food insecurity and other structural barriers can limit caregiver access to appropriate foods for IYCF and in turn impact growth [29, 30].

*Infection:* Infection acts synergistically with undernutrition in a vicious cycle that contributes to poor growth. Infections contribute to undernutrition through decreased nutrient absorption, anorexia and other metabolic effects. Undernutrition in turn can lower immune function and

increase susceptibility to infection [31]. A higher incidence and duration of diarrheal episodes in infancy is associated with increased risk of stunting at 24 months [2]. In a pooled analysis of longitudinal data from 9 low income countries, 25% of all stunting at age 24 months was attributed to having 5 or more diarrheal episodes before age 24 months [32]. Other sources estimate the contribution of diarrheal illness to risk of stunting to be much lower [2].

Environmental enteropathy is emerging as potentially important determinant of growth faltering in early childhood. There is substantial evidence that sub-clinical enteric infections contribute to atrophy of the intestinal villi and inflammation which cause increased intestinal impermeability, reduced nutrient absorption and diversion of nutrients to activation of a immune response [33, 34]. In both the clinical diarrhea and environmental enteropathy pathways, improved sanitation and hygiene are needed to reduce risk of exposure to fecal bacteria and other environmental pathogens.

*Care:* Dietary intake and disease outcomes are influenced by caregiver behaviors [20]. The Guiding Principles for Complementary Feeding the Breastfed Child [35] and The Guiding Principles for Feeding Non-breastfed Children 6 to 24 months of age [28] describe ideal caregiver practices based on current knowledge related to IYCF. For non-breastfed children the principles include 1) providing appropriate amount of food to meet nutrient demands, 2) providing food with a developmentally-appropriate consistency, 3) providing meals at appropriate intervals based on overall energy density of available foods, 4) ensuring adequate micronutrient content of foods, 5) use of vitamin-mineral supplements or fortified products in diets lacking animal source foods, 6) meeting fluid intake needs without breast milk, 7) safe

preparation and storage of foods to prevent food-borne illness, 8) practicing responsive feeding to encourage adequate intake by children, and 9) feeding during and after illness [28].

### *Interventions to Improve Child Growth*

The 2008 *Lancet Series on Maternal and Child Undernutrition* identified a number of effective interventions for improving health and nutrition outcomes in young children. In food insecure environments, provision of behavior change education around IYCF with a food supplement was recommended to reduce risk of stunting and the burden of disease in children 6-24 months of age [19].

Preventive approaches are more effective than recuperative approaches. A study in rural Haiti showed that providing food rations and IYCF counseling to mothers of all children ages 6-24 months in the target population was more effective in reducing prevalence of stunting, underweight and wasting compared to targeting the intervention only to underweight children under age 5 [36].

The magnitude of effect that can be expected from preventative IYCF interventions is highly variable. Caulfield et al. [37] reviewed complementary feeding interventions from the 1970's to 1997. In 5 efficacy trials from breastfeeding populations with low HIV prevalence, improving the intake of complementary foods in 6 to 12 month-old infants by 65-302 kcal per day resulted in measurable improvements in growth by 0.04-0.46 SD [37]. When the outcomes of 16 community programs in 14 developing countries were included, achieved improvements in child growth translated into reductions in prevalence of malnutrition (<-2 SD) at 12 months by

1-19% and malnutrition-related deaths by 2-13% depending on the baseline prevalence of malnutrition [37].

Dewey and Adu-Afarwuah [38] reviewed 42 complementary feeding interventions published between 1998 and 2007, subsequent to the Caulfield et al. review. They classified intervention approaches as using education only, food supplementation with or without education, food fortification, and other techniques to increase energy density. The authors concluded that overall the interventions had a “modest” effect on growth outcomes with “no single universal best package of components” given the need for interventions to reflect local contexts. Eight studies included in the review involved food supplementation with education. Mean effect sizes for these studies were 0.35 (0.18, 0.66) WAZ and 0.17 (0,0.32) LAZ [38].

The impact of interventions to improve IYCF depends on the baseline health and nutritional status of the target population, age of initiation and duration of intervention [26, 37-39]. High quality intervention design and delivery increase the potential impact [38].

In addition to increasing the energy density and micronutrient quality of the infant’s diet, effective complementary feeding interventions promote positive maternal feeding practices (e.g. frequent feedings, responsive feeding, feeding during illness), food safety (e.g. clean water, proper food storage) and hygiene [26, 37, 40].

#### *Lipid-based nutrient supplements*

This research includes use of a lipid-based nutrient supplement (LNS). LNS are energy-dense pastes typically composed of peanuts or other legumes, dry milk powder, sugar, oil and

micronutrient premix. They are shelf stable products with low risk of contamination and no cooking requirements. Peanut-based LNS have been locally produced to international quality standards in Haiti, Malawi and other under-resourced contexts [41].

LNS were first used in public health practice in the early 2000's. LNS formulations known as ready-to-use therapeutic foods (RUTF) are promoted for the rehabilitation of children with SAM in a community setting [42, 43]. Clinical and community trials of RUTF products in Senegal and Malawi [44] have demonstrated successful rehabilitation of malnourished children including HIV-infected children, at rates equal or faster to standard inpatient rehabilitation programs using specially formulated therapeutic milks (F-75/100) or corn-soy blend [44]. Community-based Management of Acute Malnutrition using RUTF is now the global recommendation for treatment of SAM [11].

There has been growing interest in the use of LNS for prevention of malnutrition. A range of strategies are being tried including using small amounts of LNS as a vehicle to deliver micronutrients [45], use of LNS as a fortified complementary food for children 6-24 months of age [46-49] and large-scale blanket distribution of supplementary LNS rations to populations at acute risk of food insecurity [50-52]. Despite their popularity, studies thus far have demonstrated only a small relative improvement in growth outcomes when LNS-based preventative approaches are compared to the existing standards of care including multivitamins or micronutrient powders for micronutrient supplementation [45] and cereal-based fortified complementary foods [53].

There are potential advantages to using LNS compared to non-lipid based food supplements in populations with low intake of dietary fats [54]. Diets of children in low-income countries are often deficient in n-3 fatty acids [55]. Preliminary evidence suggests that improved intakes of polyunsaturated fatty acids in deficient populations are associated with improved growth, immune and development outcomes [56]. However consumption of LNS produced solely with seed plant-oil sources that are very low in linolenic acid could exacerbate the suboptimal balance of n-6 versus n-3 fatty acids and cause visual, cognitive or behavioral deficits [57]. LNS that use dried milk powder are very costly to produce but may be more effective than versions that use soy or other plant-based protein sources [58, 59].

Since 2009 there has been large-scale donor investment in research around LNS use and production [60]. An ongoing debate around international patent protection of the basic LNS formulation has affected the roll out of local LNS production in some countries [61]. Local production is seen as way to promote economic development by supporting the national agricultural sector and local food industry. It also has potential to reduce financial and logistical barriers associated with foreign imports such as tariffs and transport delays.

#### *IYCF policy environment*

The 2008 Lancet Series estimates that implementation of existing nutrition interventions of known effectiveness could reduce burden of early childhood stunting by one-third and mortality by one-quarter [19]. Over the last 5 years there has been a coordinated call to action [62] and response by policy makers in UN agencies, the World Bank [63], country governments [64] and major donors [65, 66] towards prioritizing interventions and policies that target



improved nutrition outcomes. The prenatal period through the first 2 years of life, sometimes referred to as “the first thousand days of life or “the window of opportunity,” is the priority period for intervention. While the role of agriculture and food production is increasingly recognized, models for the effective integration of nutrition-focused activities into existing health and agriculture sector initiatives are not yet well developed or documented [63, 67]. This research aims to build upon current knowledge related to effective IYCF interventions to help fill this gap.

### **Prevention of Mother-to-Child Transmission of HIV**

Each year, an estimated 1.4 million HIV-infected pregnant women living in low and middle income countries give birth [68-72]. An HIV-infected mother can transmit the virus to her child *in utero*, at the time of delivery or in through breast milk. Since 1999, advances in PMTCT programs have reduced mother-to-child HIV transmission rates in less-developed countries from 15-35% without intervention [73] to 2-5% with an intervention package that includes treatment with highly active antiretroviral therapy (HAART) for pregnant women with advanced HIV disease, short-course antiretroviral (ARV) prophylaxis for less advanced maternal cases, and support for safer infant feeding [74-76].

However, global coverage of PMTCT interventions remains inadequate. The universal coverage goal is 80% of HIV-infected pregnant women having access to PMTCT drug prophylaxis [77]. In 2009, just over half (53%) of HIV-infected pregnant women living in low and middle income countries received any form of ARV [78].

With or without intervention, the vast majority of the children born to HIV-infected mothers will not become HIV-infected through vertical transmission [73], however all children of HIV-infected mothers face substantial risks to their growth, development and survival [79].

All HIV-exposed children are born small compared to unexposed peers [80]. HIV is associated with elevated risk of preterm birth and LBW [81]. Exposure to certain HAART regimens *in utero* has been associated with even higher rates of LBW, IUGR and/or preterm delivery [82, 83]. The mechanisms by which exposure to HIV *in utero* with or without ARVs impacts fetal growth are not understood.

HIV-infected children are at high risk of early postnatal growth faltering. They experience higher rates of stunting and underweight compared to HIV-exposed uninfected children in the same populations [80, 84]. Pediatric HAART is associated with improved growth outcomes [85, 86].

The postnatal growth pattern of HIV-exposed uninfected children from less-developed countries has not been well characterized [80]. Most published studies of growth outcomes in this group were conducted before the year 2000 – when PMTCT and HAART for mothers with advanced disease were not yet available.

Perinatally HIV-infected children are at extremely high risk of early death [87]. Advances in the availability of Early Infant HIV Diagnosis using PCR methods and pediatric HAART have improved survival outcomes in these children in more resourced settings [88].

High rates of mortality among HIV-exposed uninfected infants have been seen in African contexts. In rural Uganda, cumulative 2-year mortality rates among uninfected infants born to

HIV-infected mothers (165.5/1000 live births) without treatment intervention was significantly higher than in uninfected infants born to HIV-negative mothers (128.1/1000 live births) [89].

The causes of increased mortality among HIV-exposed uninfected children can be difficult to discern in contexts with high intrinsic rates of infant and child mortality. Poor infant feeding practices including suboptimal breastfeeding and replacement feeding are associated with increased mortality outside the context of HIV [90, 91]. Poor maternal health, economic vulnerability and food insecurity in HIV-affected households may increase child malnutrition and decrease access to medical care [92, 93]. High rates of bacterial sepsis (e.g. *Staphylococcus aureus*) [94] and parasite infection (e.g. cryptosporidiosis) [20] contribute to the growth deficiencies and the disease burden.

WHO protocols from 2000 and 2006 recommended providing all HIV-exposed infants with the antibiotic cotrimoxazole from 4-6 weeks of age until the child's HIV status is confirmed and there is no longer risk of HIV transmission through breastfeeding [95]. In HIV-infected children, cotrimoxazole prophylaxis is associated with reduced morbidity and mortality primarily related to pneumonia [96, 97], and improved growth and anemia outcomes [98]. In HIV-exposed uninfected infants, cotrimoxazole prophylaxis reduces colonization with pneumonia-causing bacteria [99], and prevents malaria [100] but the benefit on overall morbidity, mortality and growth outcomes is not known [98, 101]. Concerns about increased risk of diarrhea [96], drug side effects and development of antibiotic resistance in HIV-exposed uninfected children have led some people to question the current recommendation for routine prophylaxis of all HIV-exposed children [101].

## **Infant feeding and HIV**

Breastfeeding is a cornerstone of strategies to promote child survival, but for infants of HIV-infected mothers, breastfeeding carries the risk of HIV transmission. Transmission risk depends on a number of factors including breastfeeding frequency, duration and pattern (e.g. EBF or mixed feeding), stage of maternal infection, disease progression and use of ARVs in mother and/or child [77]. Kourtis et al. [102] estimated that without other intervention, ~6% of HIV-exposed children who are uninfected at birth would become infected through EBF until age 6 months, eleven percent would become infected if they were mixed fed for 6 months and then weaned at 1 year, and 15% of infants would become infected if breastfeeding continued until age 2.

Global recommendations around breastfeeding by HIV-infected women in less-developed countries have changed considerably over the last decade due to expanded access to ARVs and emerging evidence about transmission and mortality endpoints associated with different feeding patterns [77, 103-106]. The 2006 WHO guidelines [105] were in place during most of the dissertation research period and will be discussed in greater detail. I will follow with a brief review of changes introduced in the more recent WHO 2010 guidelines [103].

WHO 2006 guidelines for infant feeding by HIV-infected mothers recommended the proper use of replacement feeding methods (e.g. infant formula with clean water, other animal milks, expressed and heat treated breast milk) when feasible, or EBF from birth with early cessation of all breastfeeding as soon as an alternative was available [105, 106]. WHO guidelines stressed the need for counseling that helped individual mothers assess whether replacement feedings

options were “AFASS” (acceptable, feasible, affordable, sustainable, safe) given her individual circumstances. In practice, HIV-infected women choosing to breastfeed were encouraged to wean children between 4-6 months of age [107, 108]. Therefore under the standard of care at the time, breastfeeding was not likely to continue past 4-6 months of age.

WHO guidelines for feeding the non-breastfed child between 6 to 24 months of age, stress the importance of providing other milks (e.g. animal milks, treated breast milk) or infant formula to meet the energy density and fluid intake needs normally provided by breast milk during this period (Table 1) [28]. In Haiti, as in many other AIDS-affected contexts, a month’s supply of formula costs about US\$ 40-70, far beyond the economic means of the population. In populations with limited access to animal source-foods, WHO guidelines recommend feeding children micronutrient-fortified products [28].

**Table 1.1:** Average breast milk contribution to total energy intake from 0-23 mo [26]

Age	Total daily energy requirement	Breast milk contribution
birth to 5 mo	-	100%
6 to 8 mo	682 kcal	60.5%
9 to 11 mo	830 kcal	45.7%
12 to 23 mo	1,092 kcal	31.6%

At the time of this research, babies of HIV-infected mothers in resource-poor contexts were frequently forced to make a rapid transition from a milk diet (i.e. EBF or infant formula) to a diet without either of those forms of milk. Availability of published data documenting HIV and

infant feeding practices after age 6 months is limited. One such study from the Ivory Coast followed a cohort of 262 HIV-exposed infants who were weaned from EBF at 4 months and found an association between inadequate complementary feeding practices at 6 months and a 37% increased risk of stunting at 12 months. This was in spite of the fact that infant formula was provided at no cost between age 4-9 months in the study population [109]. Studies among HIV-infected mothers in Malawi [110] and Zimbabwe [110] who practiced early weaning also showed that the post-weaning replacement diets were grossly inadequate in both energy and micronutrients.

Multiple studies conducted in sub-Saharan Africa that were published between 2008-2010 demonstrated an increased risk of growth faltering, morbidity and/or mortality among HIV-exposed replacement-fed children and HIV-exposed children who were weaned before 4-6 months compared to HIV-exposed children who continued breastfeeding [111-113]. In several studies, there was no difference between groups in “HIV-free survival,” a combined endpoint that reflects HIV transmissions and/or death [114-116]. HIV infections prevented by replacement feeding were fully offset by diarrhea and malnutrition related deaths caused by replacement feeding.

In light of these results and also new evidence about the protective effect of HAART on transmission during breastfeeding [76, 117], the WHO 2010 guidelines recommend breastfeeding through 12 months of age accompanied by maternal HAART for all women with CD4 < 350 cells/ $\mu$ l. In cases where the mother does not qualify for HAART, extended ARV prophylaxis is recommended for the mother or infant until 1 week post weaning. The AFSS

criteria for replacement feeding are more thoroughly defined under the 2010 guidelines.

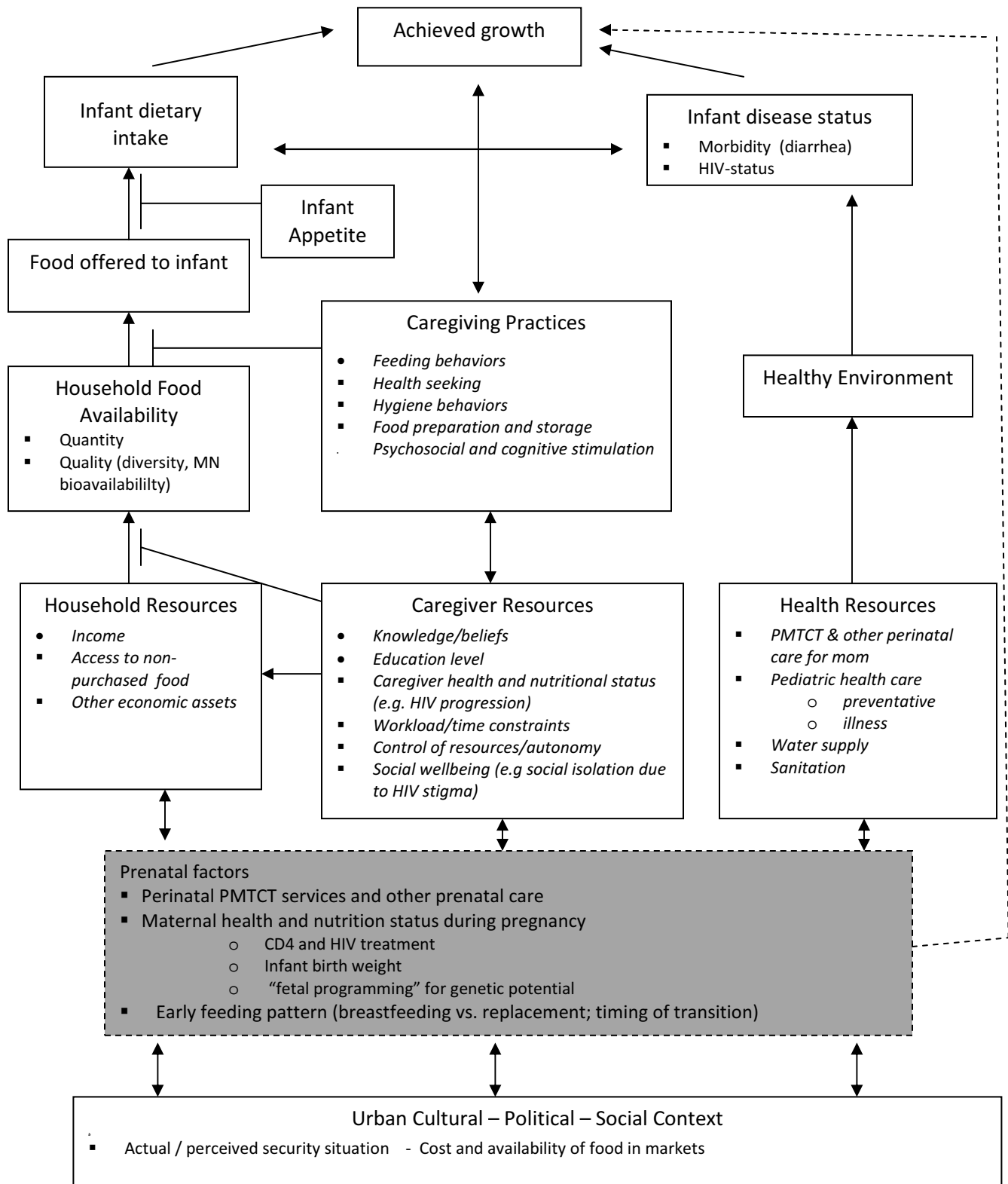
Instead of emphasizing individualized decision making by the HIV-infected mother, the 2010 guidelines recommend that national-level policy makers decide which infant feeding approach will be the primary strategy promoted among HIV-infected women in their context [103].

### **Conceptual framework**

To summarize the relationships between infant feeding and child growth in the context of HIV described above, Figure 1 identifies the underlying causes of poor postnatal growth in HIV-exposed infants. The figure is based on the expanded version of the 1990 UNICEF framework published by Engle et al. [20] which makes an explicit distinction between the resources needed for caregiving and the actual practice of caregiving (e.g. suggesting that resources are necessary but not sufficient for practice). This distinction is particularly useful in guiding evaluation design as indicators of resource availability and use should be considered separately [118, 119].

The grey box reflects prenatal factors that are hypothesized to impact growth outcomes at 12 months of age. These include factors that act as an underlying cause. (e.g. access to prenatal PMTCT is associated with risk of pediatric HIV infection which in turn directly impacts growth between 6-12 months) or that influence growth potential more directly (e.g. through “fetal programming”).

**Figure 1.1** Underlying causes of growth among urban poor HIV-exposed infants





## THE HAITIAN CONTEXT

The dissertation research was conducted in Port-au-Prince, Haiti. Haiti is the poorest country in the Latin American and Caribbean region and ranks 145 of 169 countries on the UNDP Human Development Index [120]. Eighty percent of the national population lives on less than US \$2 per day [121]. Fifty-six percent of the urban population lives on less than US \$1 per day [122]. In urban areas, 71% of the population has access to clean water and 24% to improved sanitation facilities [123]. These figures are substantially lower in rural areas.

Years of poor governance, internal conflict and natural disasters have resulted in economic devastation, loss of human capital, depletion of natural resources, and weakened institutions in Haiti. Recent years (2003-present) have been marked by waves of violence and insecurity centered in Port-au-Prince's slum communities. A United Nations peacekeeping force has been actively patrolling urban centers and some rural Haitian provinces since 2004. Compared to rural residents, urban residents have higher material living conditions but live in much greater fear of crime and violence [122]. Despite security concerns, rural to urban migration continues at a rapid rate [122].

The year 2008 was particularly challenging year, with food riots in April, a change in government that left the prime minister position unfilled for six months and four consecutive hurricanes in August and September that caused deadly flooding [124]. The year 2009 was notable for relative stability. In January 2010, at the end of the research period, Port-au-Prince was devastated by an earthquake of 6.9 magnitude on the richter scale that was estimated to have killed 230,000 people and displaced more than 1.7 million people [125].

Food insecurity is high in both urban and rural Haiti. Fifty-eight percent of the population has a caloric intake is below the minimum dietary energy requirement [126]. National agricultural production is not sufficient to meet national need and households depend on purchase of imported products which are subject to global price fluctuations. The combined index for flour, oil and rice prices in Port-au-Prince increased 35% between January 2005 and December 2007, vastly exceeding general inflation [127]

*Child health:* Haiti has high rates of childhood malnutrition. Table 1.2 compares national underweight (WAZ < -2 SD), stunting (HAZ < -2 SD), and wasting (WHZ < -2 SD), among children under 5 in metropolitan Port-au-Prince to rural and national data. The rural-urban gap may be partly explained by the greater range in socioeconomic status in urban populations and does not necessarily reflect better health among the poorest urban children compared to their rural peers [128].

**Table 1.2** Percent of Haitian children under 5 yr old with WAZ HAZ, < -2 SD using by region, WHO/NCHS Reference [1]

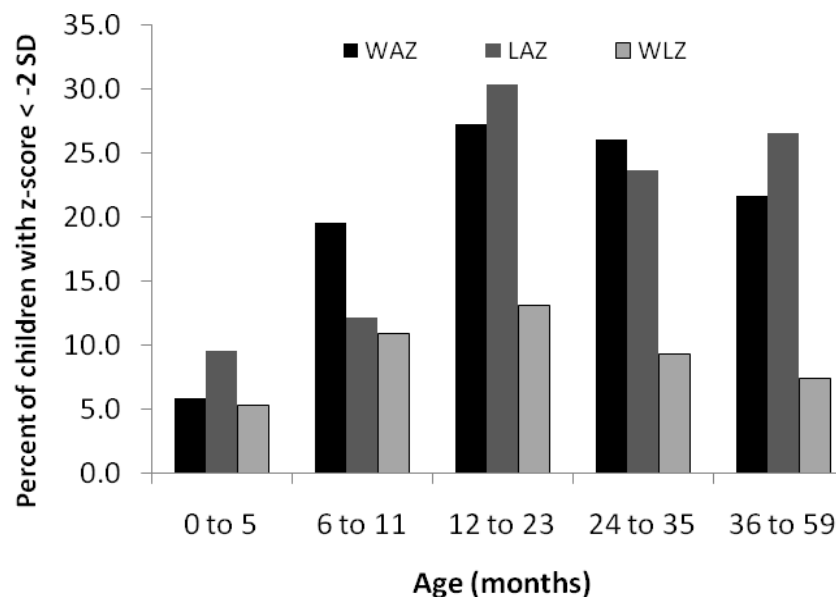
Region	n	WAZ	HAZ	WHZ
National <sup>1</sup>	2904	18.9	29.7	10.3
Rural (all zones)	1938	21.2	34.6	11.4
Port-au-Prince Metro	945	12.1	21.7	7.9

NOTES: <sup>1</sup> Using WHO 2006 Growth Standard: WAZ<-2 SD 19.21%, HAZ<-2 SD 30.13%, WHZ <-2 SD 10.34% [129]

Consistent with global patterns, national data suggests that most stunting occurs between 6 and 24 months of age after which stunting prevalence levels off (Figure 1.2). The trend in

underweight mirrors stunting through early childhood. Wasting is less prevalent and declines from the second year of life.

**Figure 1.2** Percent of Haitian children under 5 years with LAZ, WLZ, and WAZ < -2 SD by age group, National Data, WHO/NCHS Reference [1]



Comparison of DHS findings from 2005-2006 [130] to similar surveys in 2000 [131] and 1995 [132] show that after a 8.9 % fall in stunting between 1995 and 2000, rates of malnutrition increased slightly between 2000 and 2005-06. However, the 2005-6 survey was conducted during peak years of political violence and insecurity [130].

Among children under age 2 years, prevalence of diarrhea reported by caregiver in the previous 2 weeks was highest in the 6-11 month age group (40.9%) compared to 0-6 (22.2%) and 12-23 months (37.7%) [130].

*Infant and Young Child Feeding:* Almost all Haitian mothers breastfeed but few do so exclusively. In the 2005-2006 DHS, median duration of any breastfeeding in metropolitan Port-

au-Prince was 14.5 months compared to 19.2 nationally. Median duration of EBF was a very short 0.5 months in Port-au-Prince and 1.5 months nationally. However, breastfeeding initiation rates are high. Only 2.2.% of mothers nationally reported not breastfeeding their child during the first 2 months of life [130]

In the 2005-2006 DHS, 23.3% of mothers of infants less than 6 months old reported feeding non-liquid foods to their infants [130]. The cereal-based porridges commonly prepared as weaning foods in both urban and rural Haiti are generally energy sufficient but lack essential micronutrients including vitamin A, iron and zinc [133]. Frequency of feeding episodes is low, with many mothers stopping feeding solid and semi-solid foods by the early afternoon [133].

Haitian infants in low income households have little to no access to animal-source foods. Even in rural farming communities, milk is a rare commodity and not commonly fed to breastfeeding children [133]. Boxed ultra-heat-treated milk, canned evaporated milk and dried milk powder are readily available in urban markets, but are expensive.

*HIV/AIDS:* In the 1980s and 1990s, Haiti faced the most rapidly growing HIV/AIDS epidemic in the Western Hemisphere. Through a coordinated national response that included early recognition of the epidemic by the Haitian medical community [134], efforts by the Haitian government and Red Cross to ensure safety of the blood supply [135] and scale-up of prevention and treatment services led by two large national Non-Governmental Organizations (NGO), HIV prevalence rates among pregnant women in Haiti fell from 9.4 % in 1993 to 3.7 % in 2003. In 2007 prevalence in Haiti was 4.4% among pregnant women and 2.2 % among all adults

age 15-49 years [136]. As of 2008, the estimated number of persons living with HIV in Haiti was 115,000 [136]. Two-thirds of HIV-infected individuals live in Port-au-Prince.

### **Pediatric care at the GHESKIO Centers**

Founded in 1982, the GHESKIO Centers is a private Haitian institution dedicated to clinical care, research and training in HIV/AIDS and related diseases. GHESKIO's primary site is located in the center of Haiti's capital city, Port-au-Prince, immediately adjacent to the city's largest slum communities. It draws clients from across the greater Port-au-Prince area. Free services provided to this predominantly urban poor population include HIV voluntary counseling and testing (VCT), adult and pediatric HIV care, tuberculosis screening and treatment, sexually transmitted disease diagnosis and treatment, and PMTCT of HIV and syphilis. The number of people seeking HIV testing at GHESKIO has increased nearly 7-fold from 3,450 to 23,313 over the past decade, with 72% of those clients self-referred in 2004.

GHESKIO provides a unique research-oriented environment where high-quality clinical HIV care is delivered to a population affected by generalized poverty and insecurity. GHESKIO is led by an outstanding Haitian physician, Dr. Jean William Pape, and despite health workers shortages nationwide, maintains a staff of highly qualified physicians and nurses. GHESKIO's HIV care is primarily supported by PEPFAR, the Global Fund for AIDS, Tuberculosis and Malaria, the US National Institutes for Health and the Rodolphe Mérieux Foundation. It has strong academic ties with Cornell and Vanderbilt Universities. Treatment outcomes for GHESKIO's adult patients on HAART are comparable to those of patients treated in HIV clinics in the best academic medical centers in the United States [137].

*Pediatric clinical services:* GHESKIO's pediatric clinic provides comprehensive care for children ages 0-10 years old. It is staffed by a highly qualified team of three Haitian physicians, two nurses and two field workers. Care for HIV-infected pregnant women and adolescents (11-21 years old) is provided by separate units within GHESKIO. Three populations of children under age 2 are seen by the pediatric unit: a) children born to HIV-infected mothers enrolled in GHESKIO's PMTCT program (referred to here as "PMTCT children") b) children born to HIV-infected mothers who did not receive PMTCT services at GHESKIO but may or may not have received services elsewhere (referred to here as "non-PMTCT children") and c) children born to HIV-negative mothers. PMTCT children represent more than 75% of all infants seen at the GHESKIO pediatric unit. Table 1.3 summarizes clinical services provided to each of these populations.

**Table 1.3** GHESKIO Pediatric services by sub-population

Service	Description	HIV-positive mother		HIV-Negative mother
		PMTCT	Non-PMTCT	
<b>Routine physician visits*</b>	0-3 month olds	Every 2 wks	Every 2 wks	Every 2 wks
	4-6 month olds	Monthly	Monthly	Monthly
	7-9 month olds	Every 3 mo	Monthly	Monthly
	12-24 month olds	Every 3 mo	N/A	N/A
<b>Sick child visits</b>	<i>Walk-in visit due to sick child (e.g. diarrhea, fever)</i>	All	All	All
<b>HIV testing</b>	<i>RNA test – confirm status by 4 mo. Antibody test – require 2 negative tests to confirm sero-evert before 12-18 mo</i>	RNA test at 0 and 4 mo; or antibody	Antibody tests every 3 mo	Antibody at enrollment
<b>Vaccination*</b>	<i>Ministry of Health (MOH) series : BCG, Polio, DPT, Measles Expanded pkg: Hep B, HIB, Pneumovax</i>	MOH+ Expanded	MOH	MOH
<b>Vitamin A</b>	High dose of Vit A every 4-6 mo starting at age 6mo	All	All	All
<b>Pediatric HAART</b>	For infant confirmed positive	All*	All*	N/A
<b>No-cost infant formula</b>	Free Enfamil offered from 0-6 mo <sup>¥</sup>	All <sup>¥</sup>	special cases only	None
<b>Cotrimoxazole prophylaxis</b>	Cotrimoxazole given from birth until HIV-negative status confirmed	All	All	None
<b>Multivitamin syrup</b>	Prescription for pick up at GHESKIO pharmacy – stock out common	All	All	All
<b>Fortified cereals</b>	Limited supply of fortified infant cereal in transition period (4-7 mo)	Select cases	Special cases only	Rarely

NOTES: \* ALL infants who are confirmed to be HIV-positive are monitored monthly by physicians, started on ART and offered the expanded vaccine package. However, HIV-positive infants under age 2 are not common at GHESKIO due to availability of PMTCT services. <sup>¥</sup> PMTCT infants enrolled in 5207 study receive formula for 1 year per AIDS Clinical Trial Group Protocol 5207. N/A = not applicable.

*Outcomes in GHESKIO PMTCT children:* GHESKIO's PMTCT program started in 1999 using nevirapine monotherapy for perinatal ARV prophylaxis. In 2003, HAART became available for HIV-infected mothers with CD4 < 250 cells/ $\mu$ l and all HIV-infected infants. In 2006, GHESKIO and the Haitian Ministry of Health and Population revised ARV prophylaxis protocols to require consideration for the stage of pregnancy at PMTCT program enrollment and maternal health status in determining which combination of drugs (e.g. AZT, nevirapine, 3TC) are given to mother and infant and for what duration. All pregnant women at GHESKIO are counseled about infant feeding options and associated risks. Infant formula was provided free from birth to age 6 months to mothers who chose to replacement feed. After birth, mothers and infants have regularly scheduled follow-up visits at the PMTCT clinic and pediatric clinics respectively.

Mother-to-child HIV transmission and survival outcomes from 0 to 15 months were published for a cohort of 551 children born to GHESKIO PTMCT mothers between 1999 and 2005 [75]. The follow-up period allowed for comparison of outcomes pre-HAART availability versus post-HAART availability. Twenty percent of infants were LBW. Eighty-five percent were formula fed from birth. Overall MTCT rate across the period was 10.2%; but it was only 1.9% among the 52 infants whose mothers were on HAART during pregnancy for at least 60 days prior to delivery. Overall infant mortality rate was 15.2 per 100 births. The mortality rate pre-HAART was 0.23 per child-year followed compared to 0.12 per child-year followed post-HAART ( $p < 0.0001$ ). In multivariate models, LBW and infant HIV-status were predictive of mortality risk [75].



## EVALUATION RESEARCH

As described above, there is a substantial knowledge and experience gap around the translation of PMTCT and IYCF recommendations into feasible interventions that improve infant growth outcomes in the context of HIV. The dissertation research aimed to contribute towards filling that gap by conducting a scientifically rigorous evaluation of an intervention designed based on current PMTCT and IYCF recommendations. In order to be useful for public health decision making, the evaluation needed to meet the needs of policy and program delivery stakeholders.

Public health policy makers aim to identify effective intervention models that can be scaled and replicated across contexts. Results from impact evaluations are an important tool used by policy makers, program planners and implementers for decision making. However, evaluations often fail to assess *how* a program achieved its impact including the various contextual and delivery-related factors that may have contributed to the program outcomes [138, 139]. As a result, we often do not understand why interventions with proven efficacy or effectiveness in one context may fail to produce the same impact when they are implemented in a different context.

Delivery contexts for IYCF interventions are often complicated. Many efficacy-oriented evaluation approaches attempt to “control” for contextual factors and minimize bias from these factors via randomization. However it is these very factors that influence whether or not interventions will be effectively integrated into routine service delivery [139]. Implementation research approaches that aim to understand contextual factors and delivery processes have been underdeveloped in the field of public health [139] but are increasingly being utilized [140,

141]. As a result of constraints in publication formats, published studies involving complex interventions often lack the level of detail needed to fully understand intervention inputs, delivery process and context [142].

The dissertation research used an evaluation approach guided by program theory in order to answer the “how” and other contextual questions. A program theory is an explicit model of the pathways, including intermediates and mechanisms, that link program inputs to outcomes [118, 138]. Program theory helps to distinguish different ways inputs might contribute (or fail to contribute) to intended outcomes. Evaluations guided by program theory can help account for interventions that do not achieve their intended outcomes due to poor implementation, contextual issues or having an incorrect model to start with [118].

In several regards, the current environment around HIV and infant feeding policy and programming provides an ideal context for applying evaluation approaches guided by program theory. Interventions to improve IYCF are very context specific. PEPFAR, Global Fund and other donors are making large-scale investments in delivery of integrated PMTCT and MCHN services but lack evidence around effective models at the service delivery level [140, 143]. Several IYCF intervention studies outside the context of HIV/AIDS have used program-theory guided approaches to understand the implementation-related factors contributing to intervention impact [36, 144-148]. While randomization to treatment groups is considered by some in the global health policy community to be the gold standard approach for evaluation research, randomization to “no treatment” is often not ethical in infant feeding interventions in vulnerable populations [149]. A program-theory based analysis can strengthen causality

arguments in non-randomized designs and also be incorporated into a randomized controlled design in order to better answer the “how” questions that affect adaptation and scale-up to other contexts [149].

## **OVERALL RESEARCH OBJECTIVE OF THE DISSERTATION**

The overall objective of this research was to design a contextually appropriate Infant Feeding Support Strategy (IFSS) for GHESKO infants age 6-12 months and to evaluate whether the IFSS was effective in improving growth outcomes.

Chapter 2 describes the multiple levels of context that influenced the design and implementation of the IFSS. Key lessons learned about integration of programs at the service delivery level are identified. Chapter 3 presents results from an analysis of the pre-intervention growth status of the GHESKIO population under 24 months of age and provides the rationale for intervening in this population during late infancy. Chapter 4 presents the results of the impact evaluation and supporting program-theory-based analysis. A discussion of the overall findings, their implications and recommendations for future research is found in Chapter 5.

The full program theory model for the intervention evaluated in this dissertation is included in an appendix.

### *Specific research questions for Chapter 2*

- 1) What is the average growth trajectory from birth to 23 months of age among HIV-exposed uninfected children under the GHESKIO standard of care?

- 2) What are the predictors of growth faltering in this population?
- 3) How does the growth pattern of GHESKIO children compare to their peers in the general Haitian population?

*Specific research questions for Chapter 3*

- 1) What is the problem that led to the development of a new IFSS at GHESKIO?
- 2) What were the contextual factors that influenced the IFSS design?
- 3) What were the key lessons learned from the design, implementation and evaluation experience that can be applied to development of future integrated PMTCT and maternal child health and nutrition delivery strategies?

*Specific research questions for Chapter 4*

- 1) What was the magnitude of effect on growth associated with participation in the IFSS?
- 2) Were growth effects associated with the intervention sustained 6 months post-intervention?
- 3) Is it plausible to attribute the observed growth effects to participation in the intervention?

The answers to these research questions have important implications for addressing the gap in knowledge around the effective delivery of integrated PMTCT and children health and nutrition interventions.

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## **CHAPTER 2**

### **LESSONS LEARNED FROM THE INTEGRATION OF AN INFANT FEEDING SUPPORT STRATEGY INTO A CLINICAL PMTCT PROGRAM IN URBAN HAITI**

#### **ABSTRACT**

The President's Emergency Plan for AIDS Relief program guidance calls for the integration of Prevention of Mother to Child Transmission, pediatric HIV care and maternal newborn and child health services including nutrition support provided to HIV-affected populations. There is limited information available to guide the development of integrated interventions appropriate for local service delivery contexts. In 2007-2009 the GHESKIO Centers in Port-au-Prince, Haiti implemented a new Infant Feeding Support Strategy for HIV-exposed infants age 6-12 months. The strategy was developed to address the increased risk in growth faltering observed in GHESKIO infants after six months of age – an age group that GHESKIO's existing infant feeding support protocols did not cover. We identified six key contextual elements that facilitated or restricted the overall intervention design including institutional support, donor mandate, learning from existing program models outside the context of HIV, limited availability of appropriate supplements, the chaotic lives of poor urban mothers, and GHESKIO's existing model of care. Five "lessons learned" that can be applied to development of new integrated programs are 1) integration at service delivery level must be driven by the needs of the end users, 2) group-based strategies provide a channel for delivery of integrated services with



added benefit of social support, 3) delivery of integrated services among chaotic populations requires a skilled, motivated and flexible staff team, 4) delivery of integrated programs requires compromise by internal and external stakeholders, and 5) integrated programs require evaluation designs that can assess the contribution of various components to overall outcome. Implications of these lessons for GHESKIO's expanded intervention model for integrated Prevention of Mother to Child Transmission and maternal child health and nutrition care are considered.

## **INTRODUCTION**

In 2003, the United States Government (USG) launched the President's Emergency Plan for AIDS Relief (PEPFAR) a five-year initiative aimed at rapidly improving access to HIV prevention, care and treatment services in low-income countries with high prevalence of HIV/AIDS. Haiti is one of 15 focus countries that received substantial PEPFAR investment. With the renewal of PEPFAR in 2008, the initiative has transitioned from an "emergency response" focused on rapidly scaling up antiretroviral (ARV) drugs for HIV treatment and Prevention-of-Mother-to-Child Transmission (PMTCT) programs to helping countries develop more comprehensive packages of health services for HIV-affected individuals and their communities [1].

PEPFAR guidance from January 2011 calls for integration of PMTCT, pediatric HIV care and maternal newborn and child health services provided to HIV-affected populations [2]. PEPFAR defines integration as "the organization, coordination and management of multiple activities and resources to ensure the delivery of more efficient and coherent services in relation to cost, output, impact and use (acceptability)." Models for effective integration of maternal and child

health and nutrition (MCHN) services exist outside the context of HIV (e.g. Integrated Management of Childhood Illness) but “the science and evidence behind integration of PMTCT and MNCH services is still emerging” [2].

Moving from global policy guidance to actual delivery of integrated care is a complex process. There are few published examples of programmatic approaches that effectively integrate PMTCT and MNCH. Even less information is available to guide the process of designing such integrated programs at the service delivery level [3, 4].

From 2007-2009, the GHESKIO Centers in Port-au-Prince, Haiti developed and implemented a pilot Infant Feeding Support Strategy (IFSS) among HIV-positive women and their children age 6-12 months (Box 1). The GHESKIO team is continuing to build on the pilot IFSS experience to develop a more fully integrated PMTCT and MCHN strategy that serves HIV-affected women and their children from antenatal care through the first 2 years of life.

The objective of this paper is to share GHESKIO’s experience with development of an integrated PMTCT and MCHN strategy. The aims of this paper are: 1) to define the problem that led to the development of the new IFSS, 2) to describe key contextual factors that influenced the IFSS design and how we attempted to address contextual barriers and 3) to identify key lessons learned from the pilot implementation and evaluation experience that can be applied to development of future integrated delivery strategies. Implications for the next phase of PMTCT and MCHN integration at GHESKIO are discussed.

**Box 1: GHESKIO's Infant Feeding Support Strategy**

The intervention was structured around delivery of age-targeted infant and young child feeding (IYCF) education through a “caregiver club” approach. At enrollment, 6-month-old HIV-exposed infants were assigned to a caregiver club that included 8-12 infants within one month in age and their caregivers. Caregivers and infants came to the clinic every two weeks across the 24-week intervention period. Visits alternated between caregiver club meetings and individual appointments with a counselor. Key messages from club sessions were reinforced at the individualized growth monitoring and counseling visits. Participants were given a daily ration of fortified lipid-based nutrient supplement (LNS) that provided 50% of dietary energy and a daily allowance of key micronutrients for the 6-12 month age group. The IFSS promoted access to existing but underutilized GHESKIO clinic services including ORS, vaccinations, Vitamin A and household food rations [5]. The intervention pathways to impact growth outcomes are summarized in Figure 1.

An evaluation of the IFSS among a pilot cohort of 72 HIV-exposed uninfected children was conducted from July 2008-August 2009. Participation in the intervention was associated with a 67.3% reduction in the prevalence of underweight and 54.7% reduction in the prevalence of stunting at age 12 months compared to same-age HIV-exposed children seen at GHESKIO in the previous year [5]. Growth effects of the intervention were not sustained 6-months post intervention. By age 18 months, the prevalence of underweight and stunting were the same in the intervention and historical control groups.

## DEFINING THE PROBLEM

Poverty is an underlying problem that impacts every aspect of life in urban Haiti.

Unemployment is 40.6% and two-thirds of Haitians do not have formal jobs. Eighty percent of the population lives on less than US\$ 2 per day [6]. Food insecurity is considered widespread [7]. Local agricultural production is not sufficient to meet national demand and urban households depend on purchase of imported products subject to global price fluctuations [8]. The combined index for flour, oil and rice prices in Port-au-Prince increased 35% between January 2005 and December 2007, vastly exceeding general inflation [9].

Haiti has the highest rates of infant, under-five and maternal mortality in the Western Hemisphere [10]. Among children under 5, the prevalence of underweight in Haiti is 19.2 %, stunting 30.1% and wasting 10.3% (WHO 2006 Growth Standards) [11]. Almost all Haitian mothers breastfeed but few do so exclusively. Median duration of any breastfeeding in metropolitan Port-au-Prince is 14.5 months but median duration of exclusive breastfeeding is only 0.5 months [12]. Nearly 40% of Haitians have no access to primary health care [13].

In the 1980s and 1990s, Haiti faced the most rapidly growing HIV/AIDS epidemic in the Western Hemisphere. Through a coordinated national response that included early recognition of the epidemic by the Haitian medical community [14], efforts by the Haitian government and Red Cross to ensure safety of the blood supply [15] and scale-up of prevention and treatment services led by two large national Non-Governmental Organizations (NGO), HIV prevalence rates among pregnant women in Haiti fell from 9.4 % in 1993 to 3.7 % in 2003. In 2007

prevalence in Haiti was 4.4% among pregnant women and 2.2 % among all adults age 15-29 years old [16].

Founded in 1982, at the start of the AIDS epidemic, the GHESKIO Centers is a Haitian non-governmental organization dedicated to clinical care, research and training in HIV/AIDS and related infectious diseases. GHESKIO's primary outpatient clinical site is located in the center of Haiti's capital city, Port-au-Prince, immediately adjacent to several of the city's largest slum areas. The majority of clients come from urban poor communities in the greater Port-au-Prince metro area.

GHESKIO is uniquely positioned in the Haitian health system. It works in close partnership with the Ministry of Health and Population to develop evidence-based standards of clinical care for HIV, tuberculosis and other infectious diseases. GHESKIO has received ongoing recognition for its contributions to national and global HIV policy [17]. In addition to two GHESKIO-run clinical sites in greater Port-au-Prince, GHESKIO provides training and supervision to a network of more than 20 partner clinics around the country. Models of service delivery developed at the GHESKIO-run sites are adapted and scaled up to these national partners.

In 2007, 2087 pregnant women were tested for HIV at GHESKIO's downtown Port-au-Prince site. Two hundred ninety (13.9%) of these women tested HIV-positive and were eligible for enrollment in the PMTCT program. The GHESKIO PMTCT program provided a comprehensive package of medical services to HIV-infected women and their HIV-exposed children up to 24 month of age. In addition to routine pediatric clinic visits and childhood vaccinations, postnatal interventions included short-course ARV prophylaxis for mother and infant, HAART for women

with advanced HIV disease and all HIV-infected infants, early infant HIV diagnosis using PCR methods and antibiotic prophylaxis with cotrimoxazole for all HIV-exposed infants until HIV status was confirmed. During pregnancy, PMTCT participants were counseled by nurses, social workers and physicians about options for feeding their children from 0-6 months including replacement feeding from birth with breast milk substitutes and exclusive breastfeeding with early weaning by 4-6 months of age to avoid mixed feeding.

Driven by the desire to eliminate risk of MTCT through breastfeeding, GHESKIO leadership was committed to providing PMTCT mothers with the option of replacement feeding. Powdered infant formula was provided at no cost from birth to age 6 months to the more than 85% of PMTCT mothers who chose the replacement option [18] with no comparable support offered to breastfeeding mothers. The GHESKIO support strategy for mothers choosing replacement feeding included appropriate quantities of infant formula, reinforced counseling about safe preparation, and access to pediatric clinical services. GHESKIO strategy was based on the 2006 WHO Consensus Statement on HIV and Infant Feeding which stressed the importance of infant feeding counseling support based on the individual mother's situation and called for avoidance of any breastfeeding by HIV-infected women when replacement feeding was "acceptable, feasible, affordable, sustainable and safe (AFASS)" [19].

By 2008, MTCT at GHESKIO had reached the low rate of 5% at 18 months of age. Mean weight-for-age (WAZ) and length for age (LAZ) of HIV-exposed uninfected GHESKIO children improved steadily across the first 6 months of life suggesting the feeding strategy was adequate to support catch-up growth [5].

In contrast to the approach in place at GHESKIO for early infancy (0-6 months), there were no established protocols for infant feeding counseling or support for caregivers of HIV-exposed infants older than 6 months. Because of financial constraints, it was not possible to continue provision of infant formula. Available growth data suggested that GHESKIO infants were not making a healthy transition from infant formula to household-available foods. WAZ and WLZ declined rapidly from 6-10 months, while LAZ faltering continued across the first 23 months of life. Prevalence of underweight increased from 9.2% at 6 months to 17.1% at 12 months. Stunting increased from 13% at 6 months to 20.1% at 12 months [5]. Pediatricians described high rates of diarrhea across the 6-23 month period. Ninety-five percent of GHESKIO HIV-exposed infants were not HIV-infected themselves and all children had access to high quality medical care, pointing to a primary problem of inadequate diet exacerbated by diarrhea and other common infections.

The fundamental problem driving the IFSS design was the need to provide GHESKIO infants “a nutritionally adequate and safe diet without breast milk” [19] during late infancy. WHO guidelines for feeding the Non-Breastfed Child between 6 to 24 Months of Age [20], stress the importance of providing other milks (e.g. animal milks, treated breast milk) or infant formula to meet the energy density and fluid intake needs normally provided by breast milk during this period. Typically, children in developing countries obtain 65% of their calories from breast milk at 6-8 months of age, and 45% of calories at 9-11 months [21] – creating a large dietary energy gap if breast milk is not fed.

In the context of GHESKIO's PMTCT program, infants of HIV-infected mothers were frequently forced to make a rapid transition from a milk diet (e.g. infant formula or EBF) to a diet with little to no animal milk. In in-depth interviews with 11 PMTCT mothers, most reported having no consistent source of milk after the donated GHESKIO infant formula supply ended at 6 months. Many mothers were able to semi-regularly purchase a small quantity of tinned cow's milk but infant formula was prohibitively expensive for all mothers. In Haiti, as in many other HIV-affected contexts, a month's supply of formula costs about \$40-70, far beyond the economic means of the population [22].

## **IDENTIFICATION OF CONTEXTUAL FACTORS**

Not only did the IFSS need to meet dietary needs of non-breastfed children, but it had to be designed and delivered in the context of available resources, existing delivery structures and population-level factors. Some of the contextual elements were supportive but others created barriers to design and delivery which we tried to address as possible.

### *1. Strong institutional commitment at GHESKIO to addressing nutrition care issues*

In mid-2007, GHESKIO partnered with the Division of Nutritional Sciences at Cornell University (Ithaca, NY, USA) to develop a strategy for nutrition care at GHESKIO. The Cornell-GHESKIO team identified the gap in infant feeding support in late infancy as a priority action. GHESKIO provided full support to IFSS design and implementation process. The intervention design team was led by a doctoral candidate from the Cornell University Program in International Nutrition who had a background in community-based child survival programming.



## *2. PEPFAR mandate to integrate nutrition care*

GHESKIO's PMTCT program was funded through PEPFAR. PEPFAR issued a series of PTMCT, Orphans and Vulnerable Children (OVC), and nutrition-related guidance documents between 2006-2007 that identified HIV-exposed children less than 2 years of age as a high priority group for targeted nutrition support [23-25]. The guidance called for integration of nutrition support into existing PTMCT and OVC interventions and linkages to broader maternal child health programs [23-25]. Haiti was one of several PEPFAR target countries identified for priority roll-out of nutrition activities. PEPFAR funds previously received by GHESKIO for OVC and PMTCT activities were immediately available to implement the IFSS.

## *3. Growing body of evidence for IYCF intervention approaches outside the context of HIV*

The 2008 Lancet Series on Maternal and Child Undernutrition [26] identified a number of effective interventions for improving child health and nutrition outcomes. In food-insecure environments, provision of behavior change communication with a food supplement was a recommended approach to reduce risk of stunting and the burden of disease in children 6-24 months of age [26]. Factors influencing the impact of IYCF interventions include the baseline health and nutritional status of the target population, timing of initiation and duration of intervention [27-30]. In their 2008 review of complementary feeding interventions in developing countries, Dewey and Adu-Afarwuah examined a range of program models targeting 6-24 month olds and characterized the overall effect size for such interventions on growth as "modest" but noted that "optimally designed and implemented" programs had greater potential for impact [30].

The 2005 WHO Guiding Principles for Feeding Non-Breastfed Children age 6-24 Months [20] provided guidelines for key messages of IYCF interventions in non-breastfed population. In addition to increasing the energy density and micronutrient quality of the infant's diet, effective complementary feeding interventions promote positive maternal feeding practices (e.g. frequent feedings, responsive feeding, feeding during illness) and food safety (e.g. hand washing, clean water, proper food storage) [27, 28].

The IFSS design team visited several community-based health programs in rural Haiti that used participatory group-based approaches for IYCF education [31-34]. Published descriptions of clinic-based programs were available from Brazil [35] and Peru [36, 37].

#### *4. Commitment to local foods but limited quality options available*

GHEKIO was committed to using a locally-produced and procured supplementary food that met several key criteria related to the target population. The supplement needed to a) be energy dense and appropriate for child's small gastric capacity and developmental stage, b) be micronutrient fortified due to lack of animal source foods in diet, c) require little to no cooking due to shortages of cooking fuel and caregiver time, and d) meet food safety standards without refrigeration.

PEPFAR guidance [38] allowed for purchase of supplementary foods for HIV-exposed children with PEPFAR funds when other donor sources (e.g. World Food Program) were not available. The challenge in designing the IFSS was choosing a supplement option that met both the intervention needs and expectations of PEPFAR.

In 2007-2008 there were several locally produced flours cereal products commonly used for infant feeding in Haiti including a) flours made from local tubers/root vegetables (e.g. plantain flour, manioc flour), b) Akamil, a flour composed of mixed grains and legumes, developed in rural Haiti in the mid-1970s for treatment of malnourished children and c) Nourisoy, a fortified soy flour produced by a local pharmaceutical firm that was marketed for feeding children. None of these flour-based options was appropriately fortified, all required addition of milk to reach energy density targets, and all required between 20-60 minutes of cooking time. The only locally available product that met GHESKIO's requirements was "Medika Manba," an energy-dense fortified lipid-based nutrient spread (LNS) produced in Haiti by a local NGO. The NGO was able to produce a version with micronutrient fortification levels that matched the IFSS requirements.

However, the LNS did not initially meet PEPFAR's expectations. The PEPFAR "Food by Prescription" policy developed in Kenya promoted the use of cereal-based supplementary food products only for prevention programs and reserved LNS (e.g. Plumpynut) for treatment of severe malnutrition [39]. After several months of effort that contributed to a delay in IFSS implementation, GHESKIO was able to negotiate with USAID Haiti for the use of the LNS in the pilot implementation. PEPFAR funds were used to purchase the LNS product.

##### *5. Participants' chaotic life circumstances*

Urban poor HIV-infected Haitian mothers faced a unique combination of circumstances that create barriers to caring for their children effectively and to accessing available support services. Provision of the LNS as part of the IFSS addressed some of the food-access related

barriers associated with poverty and household food insecurity. The greater challenge to IFSS design was working within the chaotic contexts created by the caregivers' personal and household situations.

*Stigma around HIV/AIDS remains high.* Due to stigma, mothers sought to maintain secrecy around their HIV status secret. In our pilot cohort, only 40% of mothers said that another person in their household was aware of their HIV status. Mothers often felt the need to lie to their partners and other household members about the source of the IFSS supplement. To address this barrier, no IFSS-related supplies given to the caregivers (e.g. child growth card, supplement) had any GHESKIO-related identifiers or markings. Several mothers had highly supportive partners, family members or friends who would accompany them to their visits and provide child care. Even with these individuals, GHESKIO staff did not assume they knew about the mother's HIV status and would tailor their interactions with the mothers accordingly.

*Mothers were frequently not the primary caregiver of their children.* Among the 30.1% of women in the pilot cohort who had paid employment in the previous year, most worked as market vendors or live-in housekeepers for higher-income households. In Haiti children are not brought with mothers who work in these settings. Day-to-day caregiving responsibilities often fall to adult relatives, neighbors, older siblings or hired help. Often, these individuals are not aware of the mothers' HIV status making it difficult to target them as part of a PMTCT program. Custody disputes related to the breakdown of informal partnerships were another reason why mothers were not the primary caregivers of their children. Three of the 82 women in the pilot intervention cohort lost custody of their children for different durations of time because of the

breakdown of their informal partnerships. The IFSS addressed these situations on a case-to-case basis to the extent feasible. In one example, the GHESKIO counselor advised a mother who usually sold goods in the market to instead sell from the street in front of her own home so she would be available to care for her child. The strategy worked for that particular mother. Other working mothers were encouraged to bring the child's primary caregiver to the club or individual sessions if it did not risk disclosure of the mother's status. In two of the cases with estranged partners, the GHESKIO counselor was involved in facilitating discussions between the parents and was able to negotiate return of the children to the mothers' care.

*Mothers experienced social isolation.* With the trend towards urban migration, many GHESKIO caregivers lived long distances from extended family who are still in distant rural areas.

Caregivers would often send their children to family in rural areas while they stayed in the city. Again the IFSS team dealt with these situations on a case-by-case basis. Mothers were allowed to come to a visit without the child occasionally and still participate in club sessions. Mothers were encouraged to keep children with them to the extent possible.

*Volatile socio-political situation lead to public unrest and some violence.* Poor governance and economic hardship have contributed to elevated levels of violence in urban areas. A United Nations Stabilization Force has been present in Port-au-Prince and surrounding provinces since 2004. According to a 2006 World Bank report, 58% of residents in metropolitan areas felt unsafe in their own homes "often or most of the time" compared to 15% in rural areas [13]. An estimated 35% of women over the age of 15 in Haiti have been victims of physical violence [13]. The first half of the intervention period was notable for widespread protests related to

increasing food prices in April 2008, some of which were violent. Caregivers would miss IFSS visits if general insecurity levels were high because public transport was usually unavailable and people were afraid to be the streets. The IFSS program had to accommodate these circumstances by allowing individuals to join other clubs or make up visits on a case-by-case basis. Fortunately such periods rarely lasted more than 1 to 2 days at a time.

*Variable access to services outside of GHESKIO.* It is difficult to assess what health services or social programs GHESKIO-enrolled caregivers received outside of GHESKIO. Government-led social aid programs were not generally available but there are a number of local and international NGOs implementing health and development programs in and around Port-au-Prince. Only six caregivers participating in the pilot intervention reported receiving food support (including infant formula) from a source outside GHESKIO. GHESKIO does not limit participation based on access to other services so it is possible that some participants were receiving duplicate care. Although children with complicated cases of severe acute malnutrition were referred to the government or NGO-run hospitals for inpatient care, it was not possible to depend on availability of other external referral services in the IFSS design.

#### 6. *Delivery context at GHESKIO*

In 2007-2008 pediatric clinical care at the GHESKIO Centers was considered part of the “GHESKIO Integrated Model of Care” that used HIV counseling and testing as a gateway to connect clients to other on-site services including treatment of HIV and other sexually transmitted infections, tuberculosis diagnosis and treatment, reproductive health and family planning services, psychosocial support and a microcredit program. At the time, the model was

“integrated” in the sense of identifying needs for multiple services in an individual client and then delivering services through visits to separate units within GHESKIO (e.g. pediatrics clinic, family planning clinic, sexually transmitted infection clinic, etc). An HIV-infected woman might have to return to the GHESKIO site several times over multiple days in order to receive all the “integrated” services for her and her child.

GHESKIO faced a shortage of health workers common in many less-developed countries [40]. In 2007-2008, the GHESKIO pediatrics clinic faced a period of higher than usual staff turnover and several periods of understaffing. Given this situation, it was not possible to add IFSS responsibilities to those of existing staff members.

Prior to the launch of the IFSS, GHESKIO had little experience with the community-based models for delivering preventative health care services that are fairly common in parts of rural Haiti (e.g. “rally posts” for growth monitoring and counseling, use of community health agents) [31, 32, 41]. As a referral site focused on HIV-care, GHESKIO draws clients from across a relatively wide-spread metropolitan area. Because of security concerns and logistical constraints, all intervention delivery activities had to take place on the GHESKIO site rather than in the household. Part of the motivation for using the caregiver-club model was to bring some of the positive elements of these generally community-based approaches into the clinical context.

Despite operating in an extremely unstable context, GHESKIO had never suspended HIV-treatment services. This required constant contingency planning to ensure continuity of care and an extremely dedicated staff team to flexibly implement those plans. GHESKIO was also fundamentally committed to providing all services at no cost to clients. Any intervention

needed to be fully supported through resources from donors like PEPFAR or other implementing partners.

## **LESSONS LEARNED**

### *1. Integration at service delivery level must be driven by the needs of the end users*

As PEPFAR 2011 guidance notes, “Integration is not an end or objective but a means to achieve more effective and efficient service delivery” [2]. For integrated programs to be successful, the full package of services should reach the end users. Services must be structured to reflect their reality. As highlighted above, it should not be assumed that poor mothers do not have competing priorities for their time and resources.

The IFSS was “integrated” in terms of combining education and supplementation activities into a single intervention, but in the pilot phase, intervention delivery was, similar to the broader GHESKIO model, *in addition* to routine pediatric clinic visits. Participation in the IFSS pilot cohort added 1-2 additional visits to the GHESKIO site per month for each caregiver. For working caregivers or caregivers who lived a significant distance from the clinic, the opportunity cost of additional visits to the GHESKIO site was very high. Although not formally measured, it was clear to the IFSS team that some participants missed scheduled visits to the pediatric or PMTCT clinics to attend the IFSS visits.

Delivery of some services including distribution of oral rehydration solution (ORS) and Vitamin A through the IFSS team resulted in improved overall coverage rates for these services.

However, lack of full integration created further inefficiencies in service delivery. For example,



the IFSS team had to refer children missing vaccinations back to the pediatrics clinic where they would not necessarily receive the vaccine post referral.

*Looking ahead:* For the next phase of implementation, GHESKIO has modified both pediatric clinical protocols and the IFSS caregiver club model to achieve more complete integration of service delivery. It was not possible to integrate one service fully into the other – both needed to change. In the more fully integrated model, caregivers and infants will receive all preventive health services (e.g. growth monitoring, infant feeding counseling, vaccinations, vitamin A, distribution of food supplements, family planning services, etc) through monthly (age 0-12 months) or bimonthly (age 11-24 months) caregiver club meetings. Children will no longer have routine visits with the pediatricians or regularly scheduled individual visits with the IFSS team. Clinical triage will be done by a nurse practitioner during caregiver club meetings and complicated cases will be referred to pediatricians only as necessary. Eventually the model will be scaled up to include HIV-positive pregnant women.

*2. Group-based strategies provide a channel for delivery of integrated services with added benefit of social support*

In many ways, a more individualized service delivery model would have been easier to coordinate in the GHSEKIO population. Development of the caregiver club strategy required significant investments of staff time to set up meeting schedules and initial enrollment protocols. It was a challenge to make adjustments around holidays and unscheduled interruptions due to civic unrest and natural disasters. The caregiver club model required a meeting space that was large enough to hold a group of a group 15 adults and their children

with some degree of privacy. Space at GHESKIO was at a premium and the room used for IFSS was not ideal. The space was very small and connected to the administrative sector of the GHESKIO site rather than near the pediatric and PMTCT clinics. However both IFSS staff and participants were accommodating of these limitations.

Investments were worth the effort as the caregiver club strategy allowed for efficient delivery of participatory education and distribution of commodities. Furthermore, the caregivers club approach generated social support by fostering friendships between HIV-infected women facing similar circumstances. These friendships extended beyond the caregivers club meetings. Mothers reported communicating with one another outside of the clinic and arranging other GHESKIO visits at similar times. During exit interviews from the pilot cohort, all mothers expressed preference for the group sessions over individual counseling sessions (Box 2).

**BOX 2:** Illustrative quotes from exit interviews with participating caregivers (n= 72)

- Caregivers prefer group sessions – mothers clubs are a source of social support

*“We have become friends with one another”*

*“I can share my experiences with them”*

*“We sit and talk together”*

*“I would rather come with other mothers, it’s more interesting”*

- Program participation can impact the caregiver’s personal wellbeing.

*“When I first came I was very discouraged, now I have hope”*

*We love our children more now than we did before”*

- Positive relationship between caregivers and staff team

*“They always have a smile. They joke with me.”*

*“When they do not see me, they ask for me.”*

*“They love children.”*

*“They do not judge people by appearances. All people are people.”*

*Looking ahead:* The caregiver club model is the backbone of the expanded PMTCT and MCHN strategy that will include all children 0-24 months and eventually, pregnant women. As the number of participants increases, it will be essential to maintain a manageable group size that can continue to foster interpersonal relationships. Implementation models such as the “Care Group” approach used in community-based child survival programming [42, 43] combine small-group and peer educator methods with group-based training and supervision and effectively leverage a small number of paid staff. This may work for the GHESKIO program as it grows.

3. *Delivery of integrated services among chaotic populations requires a skilled, motivated and flexible staff team*

The four staff members who formed the IFSS pilot implementation team, a lead nurse-counselor, an auxiliary nurse-counselor and two program assistants, were experienced and motivated individuals. They had a genuine concern for and connection to the caregivers and infants in the program. The lead nurse would regularly drive to and from work along a route where she knew a homeless mother in the pilot cohort tended to stay in order to stay aware of the vulnerable mother's situation. The nutrition counselor traveled an hour to and from her home on her weekend time off in order to find a mother who missed her visit because her husband had been incarcerated. These qualities are not as exceptional as one might think – commitment to healing, professional satisfaction, positive interpersonal work environments, and non-financial recognition for accomplishments are often stronger motivators than financial incentives among health workers in both high and low income countries [40, 44].

The IFSS team was intentional about “staff care” – fostering an environment where staff felt encouraged and empowered as they worked with a very challenging population. Team members were expected to put in full 8-hour work days but were not required to work overtime. The team held regular formal and informal meetings during which team members were encouraged to talk about the situations they encountered and suggest modifications to improve IFSS delivery.

The caregiver club model allowed staff to engage with participants on a more personal level but that in turn, added an element of stress for the staff. It was challenging for them to confront

participant needs continually and have relatively limited tangible goods and services to offer them. In response, core IFSS protocols were clearly defined and club sessions were highly structured but staff were encouraged to identify individual participants who required additional investment and adapt a follow-up plan for them. Staff were given flexibility to offer small incentives (e.g. additional ORS packets, transport fees) to special needs caregivers based on their own discernment.

*Looking ahead* – The further integration of MCHN and PMTCT services will require GHESKIO staff to play expanded roles. Mothers will no longer be referred to a family planning counselor for family planning commodities or to the pediatric nurse for vaccinations. All of these functions will be completed by a small team of staff who are each able to carry out a number of these functions. In urban Haiti, unlike some other contexts, it is not so difficult to find individuals with the necessary skills. However, in an environment where people have previously defined their roles by a more narrow set of tasks it can generate tensions as one group “steps into” another’s “territory.” Continuing education and social support for the staff members will be important to maintain motivation.

#### *4. Delivery of integrated programs requires compromise by internal and external stakeholders*

Compromise is essential in the development of an integrated service delivery model. Practitioners from different disciplines often have different values and priorities. In 2007, when the GHESKIO IFSS model was first being developed, the team from Cornell’s Division of Nutritional Sciences had to respect the fundamental value placed on supporting a replacement

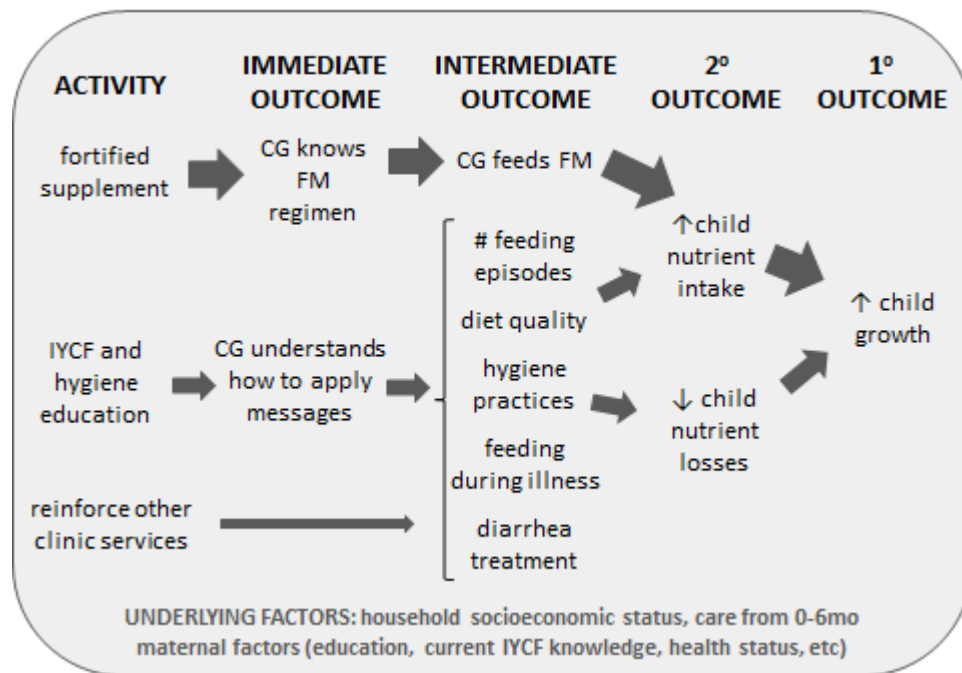
feeding option by GHESKIO leadership. The decision to use a locally-produced LNS was a compromise with PEPFAR policy based on GHESKIO's fundamental commitment to supporting local production. Delivery of integrated programs is more likely to require inputs from several different donor sources. PEPFAR promotes use of their funds for "wrap-around" programs that supplement activities supported by other donors [23-25]. Donors will not necessarily share the same goals and objectives. They often have different timeline and reporting requirements. There needs to be compromise on both the level of the donor and the implementer to enable integrated programs to move forward.

*Looking ahead:* Development of the new strategy will require ongoing compromise on multiple levels. For example, in the pilot GHESKIO IFSS model, physicians continued to conduct all well-baby visits. In the new model these tasks will be carried out by an advanced practice nurse. For the new model to succeed physicians must be willing to relinquish some of their established role.

*5. Integrated programs require evaluation designs that can assess the contribution of various components to overall outcome*

A challenge in the evaluation of integrated strategies is to identify which elements of the intervention have contributed to the overall impact. In the pilot evaluation of the IFSS we used a program-theory guided approach (Figure 1) [45, 46]. The non-randomized design included measures of compliance and changes in IYCF knowledge and reported caregiver behaviors. Our evaluation design was not intended to assess the relative contribution of each pathway but provided reasonable evidence that the intervention did follow the postulated pathways [46]. The evaluation included exit interviews with participants that helped identify unintended

consequences of the intervention- both positive (e.g. social support aspect of caregiver club) and negative (e.g. mothers missing their own clinic visits to attend IFSS visits) [45].



**FIGURE 2.1** The pathway between infant feeding support strategy activities and improved growth outcomes among intervention participants. Width of arrow reflects the assumed relative contribution of the activity to improved growth outcome compared to the other intervention activities. (IYCF = infant and young child feeding, CG=caregiver, FM = fortified manba supplement)

*Looking ahead:* GHESKIO will continue to integrate program-theory guided evaluation strategies in the more integrated PMTCT and MCHN strategy. Cost effectiveness is another important consideration to address in evaluation of the expanded model.

## **CONCLUSION**

Many of the contextual factors influencing the development and implementation of an integrated PMTCT and MCHN program at GHESKIO are shared by PMTCT programs in sub-Saharan Africa and other developing country contexts. Lessons learned from the GHESKIO experience can be applied and evaluated in these contexts in order to further our global understanding of how to achieve effective integration at the service delivery level. The learning is ongoing at GHESKIO where the delivery context continues to evolve in response to the devastating January 2010 earthquake and a gradual shift in GHESKIO infant feeding policy to support breastfeeding by HIV-positive mothers on ARV [47].



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## CHAPTER 3

### GROWTH OF HIV-EXPOSED UNINFECTED CHILDREN IN URBAN HAITI

#### ABSTRACT

Little is known about the postnatal growth patterns of HIV-exposed uninfected children in low-income countries who receive PTMCT interventions. We describe the growth pattern of 360 HIV-exposed, uninfected children under age 23 months who received PTMCT care at the GHESKIO Centers in Port-au-Prince, Haiti between July 2007 and October 2009. Longitudinal data on weight, height and other exposures were collected from GHESKIO medical records and growth indices were calculated using the WHO 2006 Growth Standards. Growth outcomes in HIV-exposed uninfected GHESKIO children were compared to a nationally-representative cross-sectional sample of 1190 children age 0-23 months from the 2005-2006 Haiti Demographic Health Survey.

GHESKIO infants were born at very low mean LAZ ( $-1.31 \pm 1.67$  SD) but normal WLZ ( $0.21 \pm 1.47$  SD). Prevalence of LBW (14.6%) and stunting at birth (40.0%) were high. Although smaller at birth, mean WAZ ( $-0.35 \pm 1.19$  SD) and LAZ ( $-0.56 \pm 1.41$  SD) at age 6 months in GHESKIO infants were not different from the DHS sample. LAZ and WAZ declined in both populations from 7 to 23 months, but were significantly higher in GHESKIO infants at 23 months. There was no difference in mean WLZ or prevalence of wasting between the two groups at any age. Within GHESKIO children, variables related to *in utero* HIV exposure and access to clinical care were significantly associated with birth size and growth outcomes in the 0-6 and 7-23 month periods.

Findings suggest that HIV-exposed uninfected infants receiving PMTCT services were born very stunted and demonstrated catch-up growth from birth to 6 months of age. Additional research is needed to understand the causes of *in utero* stunting and subsequent growth pattern in early infancy. GHESKIO children had better WAZ and LAZ outcomes in late infancy compared to the general Haitian population. This may reflect a disparity in medical services related to the intensive targeting of funding and services to HIV-affected populations compared to the general population in Haiti.

## **INTRODUCTION**

Over the last decade, there has been a dramatic increase in funding for interventions targeting the 1.4 million HIV-infected pregnant women living in low- and middle-income countries [1-5]. Since the early 2000s, advances in prevention-of-mother-to-child transmission (PMTCT) programs have reduced HIV transmission rates from 15-35% without intervention [6] to 2-5% with an intervention package that includes treatment with highly active antiretroviral therapy (HAART) for pregnant women with advanced HIV disease, short-course antiretroviral (ARV) prophylaxis for HIV-exposed infants and less advanced maternal cases, and support for safer infant feeding [7-9].

Growth is a composite indicator of the health status of a young child. It reflects the combined effects of genetic potential, *in utero* conditions, dietary intake, illness, access to care and other environmental exposures [10]. Regardless of the HIV-status of the mother, infants and young children in low income countries are at risk of poor growth [11, 12] and survival outcomes [13, 14]. Undernutrition is the underlying cause of 35% of deaths in children under 5 [11].

Intrauterine growth retardation (IUGR) or stunting in the first two years of life is associated with



negative health and economic consequences in infancy and continuing into adulthood [15]. For these reasons, prevention of early childhood malnutrition is a high priority for child survival and global development.

To date, evaluations of PTMCT interventions in low-income countries have focused on infant HIV transmission, morbidity and survival outcomes. Much less is known about the postnatal growth patterns of infants who receive the current standards of PMTCT care [16, 17]. In a 2009 review, Insanaka et al [17] concluded that there is “little evidence” that the postnatal growth of HIV-exposed uninfected infants is different from unexposed controls. The review included 15 longitudinal studies conducted among children under 23 months old from developing countries. However, only one of the fifteen studies involved a population recruited after 1999, the year when PMTCT interventions first became available [17]. Potential pathways by which PMTCT interventions could impact the postnatal growth of HIV-exposed uninfected children include *in utero* exposure to ARVs, postnatal exposure to cotrimoxazole prophylaxis, HAART-related changes in caregiver health and wellbeing, altered infant feeding practices (e.g. formula, heat-treated breast milk, early weaning), and access to other preventative health services offered in conjunction with PMTCT.

Four published studies conducted after the year 2000 report longitudinal growth outcomes for HIV-exposed uninfected children in sub-Saharan Africa [18-21]. All four studies included short-course ARV prophylaxis for the mother. Results are difficult to compare among studies due to differences in the overall clinical standard of care (e.g. access to HAART, cotrimoxazole prophylaxis), duration of follow-up, and reported growth outcomes (e.g. different reference

populations were used to standardize growth measurements). Authors of one of the two studies that compared HIV-exposed uninfected infants to unexposed infants concluded that early WAZ and LAZ growth patterns were different in the two groups [21]. The other concluded there was no difference in WAZ between HIV-exposed uninfected and unexposed children from 0-24 months [19].

Most published studies from low-income countries that compare early postnatal growth in HIV-exposed uninfected versus unexposed children involve prospective cohorts in which both HIV-exposed and unexposed infants received higher quality medical care than what is likely available to the general public [19, 21-26]. For policy purposes, it can be useful to include a comparison group who receive the locally-available standard of care. In 84 countries worldwide, nationally representative, cross-sectional growth data for children under 23 months are collected as part of the Demographic Health Survey (DHS), a household survey focused on maternal child health outcomes. Data are available for public use [27].

The primary aims of this study were to 1) describe average growth patterns from birth to age 23 months of HIV-exposed, uninfected children who received a package of PMTCT interventions and infant feeding support as part of routine care at Groupe Haïtien d'Études du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) in Port-au-Prince, Haiti and 2) identify factors associated with the observed growth outcomes. The secondary aim is to compare growth in GHESKIO children to the nationally representative 2005-2006 Haiti DHS.

## METHODS

### *GHESKIO Participants*

Primary study data were collected from outpatient medical records at GHESKIO, a Haitian non-governmental institution dedicated to clinical care, research and training in HIV/AIDS and related infectious diseases. GHESKIO's primary site for HIV voluntary counseling and testing and clinical care is located in downtown Port-au-Prince adjacent to several of the city's largest slum communities.

We included available growth data for all confirmed HIV-exposed, uninfected children age 0-23 months seen in the GHESKIO pediatric clinic between 1 July 2007 and 15 October 2009. A child was classified as HIV-exposed if the child's enrollment record was linked to a PMTCT-enrolled mother. Children without PMTCT-linked records were classified as HIV-exposed if they had a positive HIV antibody test result prior to age four months when maternal HIV antibodies are still detectable in HIV-exposed offspring. A child was classified as HIV-infected if there were two positive PCR or P-24 antibody test results for the child [28].

### *GHESKIO standard of care*

GHESKIO's PMTCT program was launched in 1999 to reduce the risk of HIV transmission and decrease mortality in infants born to HIV-infected mothers [8, 29]. The rate of mother to child HIV transmission at the time of the study was estimated to be less than 5% [8].

Starting in 2006, GHESKIO used the Haitian Ministry of Health and Population's (MOHP) multi-tiered PMTCT ARV prophylaxis protocols based on stage of maternal disease and timing of

presentation to prenatal clinical care. HAART was provided to all HIV-infected pregnant women with advanced disease ( $CD4 < 250 \text{ cells}/\mu\text{l}$  or WHO stage IV). Short-course perinatal monotherapy with zidovudine (AZT) starting at 28 weeks of gestation was provided to pregnant women who did not meet WHO eligibility criteria for HAART. Lamivudine (3TC) was added to the regimen of mothers presenting after 36 weeks gestation. Starting within 72 hours after delivery, infants were given AZT for 1 or 6 weeks with or without one-week of 3TC depending on maternal regimen.

HIV-positive women who enrolled in the PMTCT program during pregnancy were counseled about options for infant feeding. At the time of the study, these included replacement feeding from birth with artificial milk or exclusive breastfeeding with early weaning encouraged by 4-6 months of age. PMTCT-enrolled mothers who chose replacement feeding received powdered infant formula at no cost for the first 6 months of infancy. At the time of this study, 85-90% of all HIV-exposed infants at GHESKIO were replacement fed from birth [8, 29].

A team of GHESKIO clinicians provided well-baby and sick-child care to all HIV-exposed children under 23 months of age including children who enrolled at GHESKIO after delivery and did not participate in the GHESKIO ARV prophylaxis intervention. Children received the MOHP vaccination package (BCG, polio, DPT, measles) and high-dose vitamin A supplementation. Measles vaccine was given at 12 months of age. All HIV-exposed infants received cotrimoxazole from birth until HIV-negative status was confirmed. Pediatric HAART was provided to all confirmed HIV-infected infants [30].

A small number of children during the study period participated in a pediatric research trial (AIDS Clinical Trials Group Protocol 5207) that randomized HIV-infected pregnant women at delivery to a one-week or three-week regimen for postnatal ARV prophylaxis. Children of the 5207 trial participants received more intensive clinical follow-up in the second half of infancy than other GHESKIO infants and no-cost infant formula until 12 months of age.

#### *GHESKIO data collection*

All data were collected through a structured chart review of GHESKIO's electronic and paper medical records. Available variables were limited to those routinely collected at initial GHESKIO enrollment and pediatric clinic visits.

*Demographic variables.* The GHESKIO enrollment database included basic demographic data for all participating infants including enrollment date, gender, birth date and HIV-status. Maternal education level was available for all infants whose records included their mother's GHESKIO enrollment identification number.

*Birth weight.* First available weight within 7 days of birth was extracted from the paper chart or when available, the referral form from the hospital where infant was delivered. First available weight was captured regardless of whether the visit was before or after 1 July 2007.

*Postnatal growth.* All available growth data for each child up to age 24 months collected after 1 July 2007 were captured. Research-quality digital infant scales (Tanita 1583, Tokyo, Japan) and infantometers (Easy-Glide Bearing Infantometer, Perspective Enterprises, Portage, MI) were introduced to the pediatric clinics as of July 2007 along with staff training in anthropometric

measurement. Child growth (length and weight) were measured by pediatric nursing staff at every clinic visit and recorded in paper medical chart. Length was measured in recumbent position to the nearest 0.1 cm and weight was measured to 0.01 kg. Clinic staff received routine refresher training on measurement techniques.

*In utero environment.* *In utero* exposures were assessed using indicators of maternal HIV progression (CD4 cell count), treatment access (HAART) during pregnancy and birth weight. We collected the maternal CD4 count result during pregnancy that was closest to the child's delivery date from the PTMCT clinic records of all identifiable mothers. Data of initiation of HAART treatment in HAART eligible mothers was also extracted.

*Access to care.* We considered timely completion of short-course perinatal ARV prophylaxis and scheduled infant vaccinations as indicators of access to clinical care. Completion of ARV prophylaxis was available in the clinical record of all infants whose mothers enrolled in the GHESKIO PMTCT program during pregnancy. We extracted the data on vaccine and vitamin A supplementation recorded by pediatric nurses in child's paper chart for all children eligible to receive the vaccine. Children were considered eligible if they had 1) a vaccine chart in their paper medical record and 2) at least one documented clinic visit after the age scheduled to receive the vaccine (BCG at birth, DPT3 at 6 weeks, measles at 12 months, vitamin A starting at 6 months). As described previously, participants in the 5207 trials had access to an augmented package of clinical care and infant feeding support. Data on 5207 trial participation was collected from the GHESKIO enrollment database.

The study protocol was approved by IRBs at GHESKIO (Port-au-Prince, Haiti), Cornell University (Ithaca, NY, USA) and Weil Cornell Medical College (New York, NY, USA). All personal identifiers were removed from data before analysis.

#### *DHS data*

The 2005-2006 Haiti DHS Survey IV [31] included women of reproductive age 15-49 years and children under 5 years from 9998 households selected in a 2-stage stratified cluster sampling design from the 10 administrative departments and the metropolitan area of Port-au-Prince. Weight and length measurements were collected for all children 23 months and younger in participating households [32]. Data about HIV-exposure was not available for children in this analysis, however HIV prevalence was estimated at 2.2% nationally. Permission to use the DHS dataset was obtained from MACRO International (Calverton, MD, USA).

#### *Statistical analysis*

To describe the average growth pattern from birth to age 23 months of HIV-exposed uninfected children at GHESKIO, birth weight data were analyzed separately from data on subsequent postnatal growth. Mean growth outcomes by age group were calculated in two ways. First we used a cross-sectional approach and then we developed models to identify variables associated with growth across the study period that accounted for repeated measures on individual children.

*Size at birth.* Mean birth weight and prevalence of low birth weight (LBW) (birth weight < 2500 g) were calculated using earliest available weight from the first 7 days of life. It was not possible to calculate a birth weight z-score given the lack of complete data on gestational age

[33]. The association between birth weight and infant and maternal characteristics was assessed using a Generalized Linear Model (GLM) with birth weight in kilograms as the outcome. Variables significant at  $p < 0.2$  in the single variable GLM were included in the multivariable GLM. Although the total number of children with available data on gestational age at birth was quite small, we chose to run multivariable GLM with and without available preterm data given the strong correlation between preterm delivery and birth weight.

*Postnatal growth.* Weight-for-age (WAZ), length-for-age (LAZ) and weight-for-length (WLZ) z-scores were calculated using the WHO 2006 Child Growth Standards [34]. Individual z-scores were calculated using age in days and grouped by completed month  $\pm 15$  days. If more than one z-score was available for a child during the one-month period, the mean of all available z-scores was used. Cross sectional mean WAZ, LAZ, and WLZ by month of age were then calculated for the entire sample.

Infant and maternal determinants of growth from 0-23 months were assessed by fitting multi-level models for change controlling for child age at visit. The SPSS 19 MIXED procedure with random intercept and random slopes accounts for repeated measures on individuals and allows for irregularly spaced measurements and missing values across individuals. It includes estimates of the within and between individual error terms. Separate models were fitted by period (0-23 months, 0-6 months, 7-23 months) using each growth variable (WAZ, LAZ, WLZ) as the outcome. Single variable models were developed to test the association between each infant or maternal variable and the outcome while controlling for the effect of child age. All



variables with p-value <0.1 in single variable models were then included in a multivariable model to test their combined effects on the designated outcome.

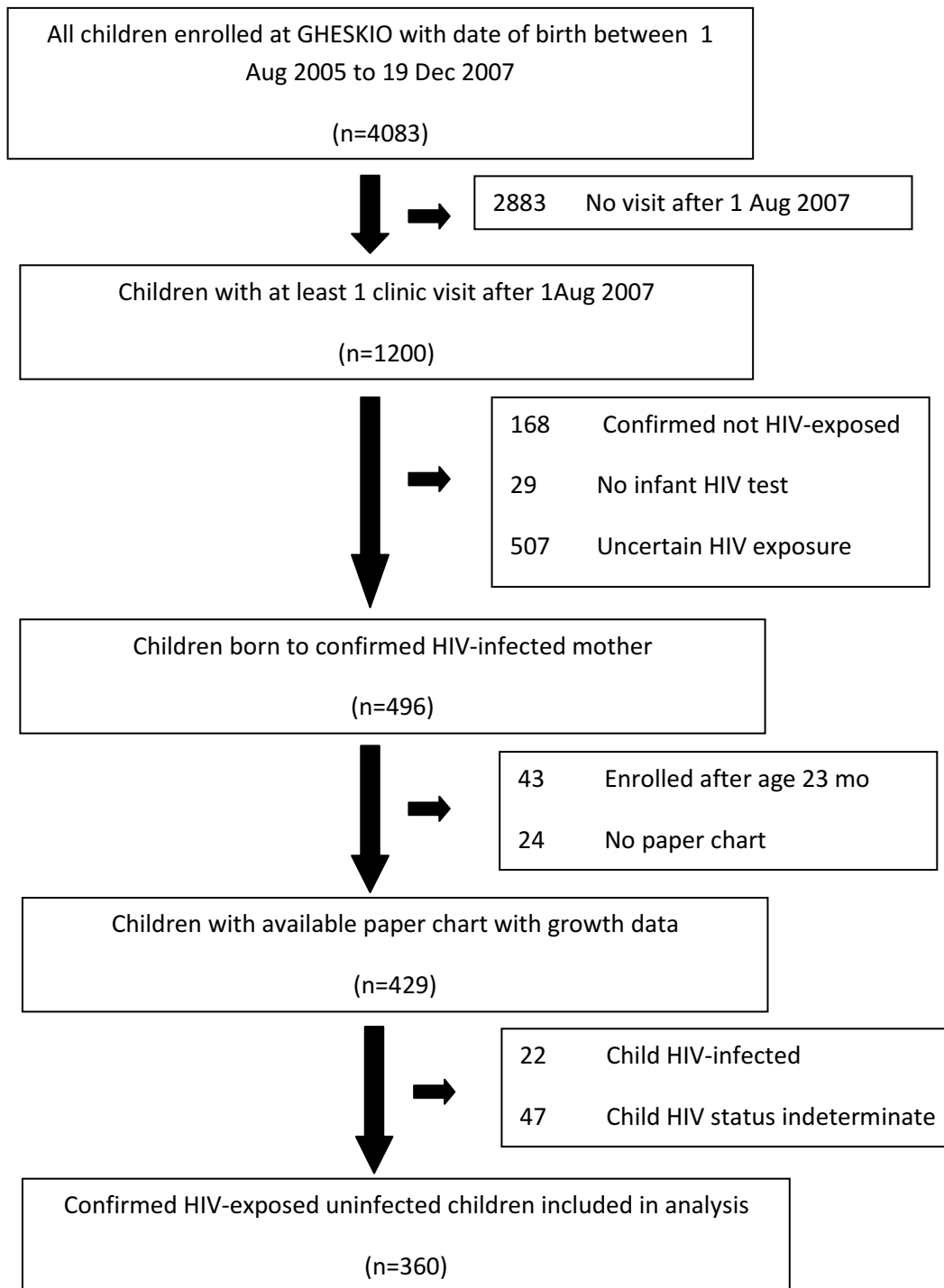
The same approach described above for GHESKIO data was used to calculate WAZ, LAZ, WLZ by age category in the DHS sample. Independent sample *t*-tests were used to compare mean growth outcomes for each age category in GHESKIO children compared to DHS children.

Prevalence of growth faltering by age group was compared between groups using Chi-Square analysis.

All statistical analyses were performed using SPSS Version 19 (SPSS Inc., Chicago, IL)

## **RESULTS**

Four hundred ninety six GHESKIO children met the criteria for confirmed HIV exposure. Children were excluded if they did not have a paper medical chart containing growth data from at least one clinic visit before age 2 years (n=67) (Figure 3.1). Children with positive or indeterminate HIV test results were excluded (n= 69). A total of 3700 observations from 360 GHESKIO children were included in the analysis. There was a large amount of variability in the timing and total number of visits completed by each child [median (IQR) visits per child = 10 (4.25, 14)].



**Figure 3.1** Flow chart describing the process of identifying GHESKIO child records for inclusion in chart review

Table 3.1 describes demographic and health characteristics of the GHESKIO population. Data on preterm delivery and early infant feeding method were incomplete in the clinical medical records and are therefore not reported. However we know that the vast majority (>95%) were predominantly formula fed.

**Table 3.1** Characteristics of HIV-exposed uninfected GHESKIO children included in the analysis (n=360)

	N*	%
<b>Infant characteristics</b>		
Female gender	360	49.2
Live in province / rural community	360	5.6
Median age GHESKIO enrollment (IQR) - days	360	19 (55)
PMTCT participant	360	84.4
Enrolled in 5207 protocol	360	5.6
Completed PMTCT prophylaxis regimen	302	76.5
Vaccine chart available	360	93.9
Received BCG	338 <sup>‡</sup>	93.2
Received DPT 3rd Dose	330 <sup>‡</sup>	86.7
Received Measles	307 <sup>‡</sup>	77.5
Received Vitamin A (≥1 dose)	319 <sup>‡</sup>	30.1
<b>Maternal characteristics</b>		
Median maternal age at delivery (IQR) - years	325	29.4 (24.4-34.2)
Education ≥ any secondary school	324	50
Median pregnancy CD4 closest to delivery (IQR) - cells/ul <sup>3</sup>	299	428 (293-578)
<200 cells/ul	299	10.4
200-349 cells/ul	299	24.7
350+ cells/ul	299	64.9
On HAART during pregnancy	312	25

NOTES: \* N identifies the total number of participants with available information for each characteristic. <sup>‡</sup>Total number of children eligible to receive vaccine per GHESKIO vaccine schedule.

### Size at birth

Birth weight data were available for 280 infants in the GHESKIO sample. Mean birth weight was  $2.99 \pm 0.50$  kg. Prevalence of LBW was 14.6%. In multivariable models with or without preterm delivery as a covariate, participation in the 5207 study, completion of infant ARV prophylaxis, maternal CD4 <200 and receipt of BCG vaccine in the first 7 days of life were significantly associated ( $p < 0.05$ ) with birth weight (Table 3.2).

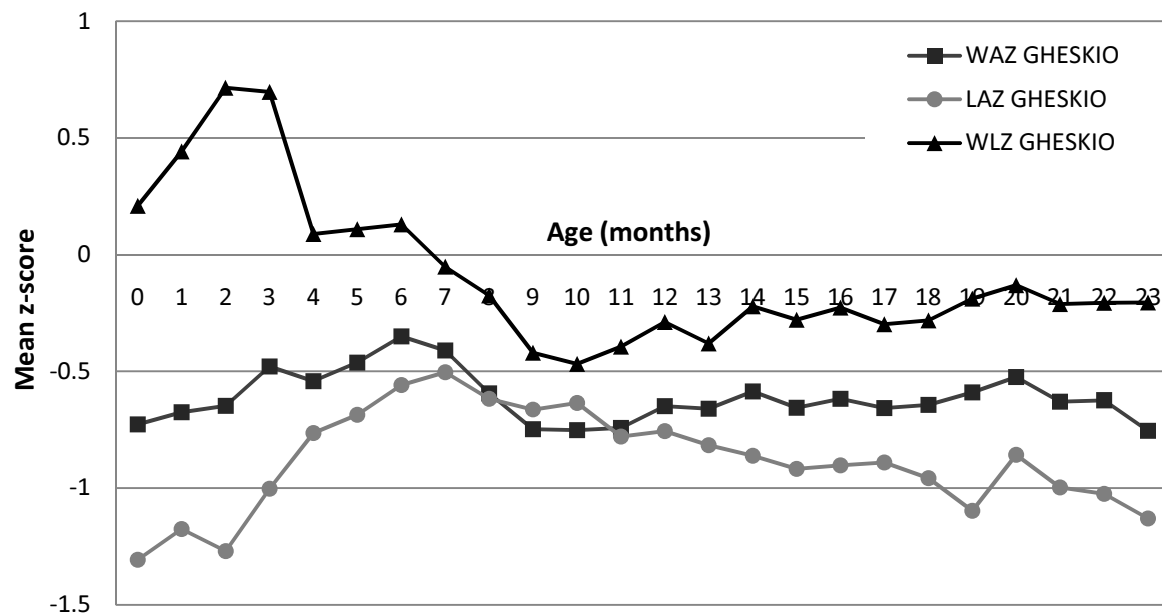
**Table 3.2** Generalized Linear Model for birth weight (BW)(kg) including all children with BW (n=237) and only children with available gestational age data (n=170)

	Multivariate Models					
	<i>All children with BW (n=237)</i>			<i>With BW + gestational age (n=170)</i>		
	B	SE	Sig	B	SE	Sig
Intercept	3.5600	0.1562	0.000 <sup>‡</sup>	3.5916	0.1760	0.000 <sup>‡</sup>
Pre-term birth (<37 weeks)		N/A		-0.5113	0.1750	0.004 <sup>‡</sup>
Maternal CD4 nearest delivery						
<200 cells/ $\mu$ l	-0.2900	0.1144	0.011 <sup>‡</sup>	-0.3030	0.1382	0.028 <sup>‡</sup>
200-349 cells/ $\mu$ l	-0.1070	0.0764	0.162	-0.1180	0.0937	0.206
> 350 cells/ $\mu$ l <sup>1</sup>	.	.	.	.	.	.
No HAART in pregnancy	-0.0100	0.0851	0.941	-0.0002	0.1040	0.998
Infant ARV prophylaxis, none or incomplete	-0.1220	0.0755	0.107	-0.1110	0.0932	0.235
No BCG in first 7days	-0.1990	0.0761	0.009 <sup>‡</sup>	-0.2090	0.0924	0.024 <sup>‡</sup>
5207 protocol, not enrolled	-0.3480	0.1162	0.003 <sup>‡</sup>	-0.3780	0.1191	0.002 <sup>‡</sup>

NOTES: <sup>1</sup>Reference category <sup>‡</sup> $p < 0.05$

### Postnatal growth

Figure 3.2 describes the overall growth pattern of GHESKIO children from 0-23 months. At month 0 (0-15 days post-delivery) mean WAZ was low ( $-0.73 \pm 1.27$  SD) and mean LAZ very low ( $-1.31 \pm 1.67$  SD) compared to the WHO 2006 Growth Standard (Table 3.3). Forty percent of infants were stunted (LAZ < -2 SD) (Table 3.4). Infants were proportionally sized at birth with mean WLZ above than the WHO Growth Standard Median (WLZ at month 0 =  $0.21 \pm 1.27$  SD).



**Figure 3.2** Unadjusted mean z-score by age category for HIV-exposed uninfected GHESKIO children. Number of children included ranges from 71 to 161 per age category.

**Table 3.3** Mean z-scores (WAZ, LAZ, WLZ) at 0, 6, 9, 12, 18, 23 months in GHESKIO children compared to national Haitian data from DHS 2005-6

		WAZ			LAZ			WLZ		
		N	Mean $\pm$ SD	p-value	N	Mean $\pm$ SD	p-value	N	Mean $\pm$ SD	p-value
0 mo	GHESKIO	91	-0.73 $\pm$ 1.27	0.061	85	-1.31 $\pm$ 1.66	0.047 <sup>‡</sup>	75	0.21 $\pm$ 1.47	0.78
	DHS 2005-6	22	-0.13 $\pm$ 1.51			-0.52 $\pm$ 1.45		22	0.10 $\pm$ 1.94	
6 mo	GHESKIO	130	-0.35 $\pm$ 1.19	0.66	123	-0.56 $\pm$ 1.41	0.80	124	0.13 $\pm$ 1.33	0.35
	DHS 2005-6	56	-0.44 $\pm$ 1.39		56	-0.50 $\pm$ 1.24		56	-0.08 $\pm$ 1.57	
9 mo	GHESKIO	161	-0.75 $\pm$ 1.43	0.10	157	-0.66 $\pm$ 1.46	0.11	158	-0.42 $\pm$ 1.26	0.38
	DHS 2005-6	48	-0.37 $\pm$ 1.24		48	-0.29 $\pm$ 1.22		48	-0.23 $\pm$ 1.41	
12 mo	GHESKIO	164	-0.65 $\pm$ 1.41	0.22	149	-0.76 $\pm$ 1.46	0.11	150	-0.29 $\pm$ 1.26	0.36
	DHS 2005-6	50	-0.93 $\pm$ 1.37		50	-1.14 $\pm$ 1.35		50	-0.49 $\pm$ 1.46	
18 mo	GHESKIO	140	-0.64 $\pm$ 1.30	0.005 <sup>‡</sup>	134	-0.96 $\pm$ 1.34	0.006 <sup>‡</sup>	133	-0.28 $\pm$ 1.21	0.064
	DHS 2005-6	54	-1.25 $\pm$ 1.36		54	-1.58 $\pm$ 1.50		54	-0.66 $\pm$ 1.35	
23 mo	GHESKIO	99	-0.75 $\pm$ 1.22	0.066	87	-1.13 $\pm$ 1.26	0.000 <sup>‡</sup>	87	-0.20 $\pm$ 1.17	0.73
	DHS 2005-6	44	-1.15 $\pm$ 1.12		44	-2.07 $\pm$ 1.02		44	-0.13 $\pm$ 1.25	

NOTES: <sup>‡</sup>p<0.05

**Table 3.4** Prevalence of growth faltering (%WAZ<-2SD, %LAZ<-2SD, %WLZ<-2SD) at 0, 6, 9, 12, 18, 23 months in GHESKIO children compared to national Haitian data from DHS 2005-6

		Underweight			Stunting			Wasting		
		% WAZ <-2 SD			% LAZ <-2 SD			% WLZ <-2 SD		
		N	%	p-value	N	%	p-value	N	%	p-value
0 mo	GHESKIO	91	15.4	0.84	85	40.0	0.006 <sup>‡</sup>	75	6.7	0.70
	DHS 2005-6	22	13.6		22	9.1		22	9.1	
6 mo	GHESKIO	130	9.2	0.18	123	13.0	0.25	124	8.1	0.35
	DHS 2005-6	56	16.1		56	7.1		56	12.5	
9 mo	GHESKIO	161	19.9	0.026 <sup>‡</sup>	157	16.6	0.029 <sup>‡</sup>	158	8.9	0.57
	DHS 2005-6	48	6.3		48	4.2		48	6.3	
12 mo	GHESKIO	164	17.1	0.64	149	20.1	0.78	150	8.0	0.21
	DHS 2005-6	50	20.0		50	22.0		50	14.0	
18 mo	GHESKIO	140	15.7	0.10	134	19.4	0.005 <sup>‡</sup>	133	8.3	0.092
	DHS 2005-6	54	25.9		54	38.9		54	16.7	
23 mo	GHESKIO	99	12.1	0.34	87	21.8	0.000 <sup>‡</sup>	87	8.0	0.53
	DHS 2005-6	44	18.2		44	59.1		44	11.4	

NOTES: <sup>‡</sup>p<0.05

Mean WAZ improved steadily by 0.38 SD over the first 6 months of life then declined by 0.40 SD between 6 to 9 months after which it improved slightly. LAZ increased by 0.81 SD by age 7 months then declined by 0.63 SD across the 7-23 month period. Mean WLZ remained above - 0.50 SD across the first 23 months of life (Figure 3.2).

Mixed-effects models with random intercepts and random slopes were fit for each outcome (WAZ, LAZ WLZ) using all available data from 0-23 months of age. The models included the fixed effects of age at visit and the interaction between age at visit and period (0-6 months vs. 7-23 months). The interaction term was significant for LAZ (p=0.000) and WAZ (p=0.000).



Therefore in subsequent analyses, the 0-6 month (Table 3.5) and 7-23 month (Table 3.6) periods were modeled independently.

**Table 3.5** Multilevel models for change predicting 0-6 month growth outcome (WAZ, LAZ, WLZ) at time of visit

Variable	Growth Outcome								
	WAZ			LAZ			WLZ		
	$\beta$	SE	p-value	$\beta$	SE	p-value	$\beta$	SE	p-value
Intercept	-4.9321	0.5573	0.000 <sup>‡</sup>	-5.5832	0.6694	0.000 <sup>‡</sup>	-0.1326	0.7690	0.863
Infant age	0.0211	0.0234	0.37	0.0668	0.0290	0.023 <sup>‡</sup>	0.1857	0.0823	0.025 <sup>‡</sup>
Infant age*Infant age							-0.0335	0.0121	0.006 <sup>‡</sup>
Infant, female gender				0.5360	0.1802	0.004 <sup>‡</sup>			
Maternal education < secondary							-0.4061	0.2010	0.046 <sup>‡</sup>
Birthweight (continuous)	1.4870	0.1441	0.000 <sup>‡</sup>	1.5080	0.1757	0.000 <sup>‡</sup>			
Maternal CD4 closest to delivery									
<200 cells/ $\mu$ l	0.1938	0.3028	0.52				-0.7071	0.3988	0.079
200-349 cells/ $\mu$ l	-0.1746	0.2082	0.40				0.0268	0.2841	0.925
> 350 cells/ $\mu$ l <sup>1</sup>	.	.	.				.	.	.
Not on HAART in 0-24 mo	0.2248	0.2143	0.30				0.2540	0.2815	0.369
Infant perinatal ARV prophylaxis, not given or incomplete	-0.4957	0.2036	0.017 <sup>‡</sup>	-0.3558	0.2374	0.137			
No DPT3	-0.3753	0.1774	0.038 <sup>‡</sup>	-0.4956	0.2081	0.019 <sup>‡</sup>			
PMTCT, not enrolled							-1.3821	1.1547	0.234
5207 protocol, not enrolled	-0.0307	0.2401	0.90	-0.0468	0.2820	0.869	-0.0717	0.3182	0.822

NOTES: Gray shading indicates that variable was not significant predictor ( $p < 0.1$ ) of outcome in single variable analysis and therefore not included in the multivariable model. Maternal age at delivery was not a significant predictor for any outcome in single variable models. <sup>1</sup>Reference category <sup>‡</sup> $p < 0.05$

**Table 3.6** Multilevel models for change predicting 7-23 month growth outcome (WAZ, LAZ, WLZ) at time of visit

Variable	Growth Outcome								
	WAZ			LAZ			WLZ		
	$\beta$	SE	p-value	$\beta$	SE	p-value	$\beta$	SE	p-value
Intercept	-3.3301	0.6687	0.000 <sup>‡</sup>	-2.6240	0.6894	.000 <sup>‡</sup>	-1.8542	0.6043	0.002 <sup>‡</sup>
Infant age	-0.0353	0.0163	0.030 <sup>‡</sup>	-0.1576	0.0224	.000 <sup>‡</sup>	-0.0242	0.0232	0.296
Infant age*Infant age	0.0011	0.0005	0.032 <sup>‡</sup>	0.0039	0.0007	.000 <sup>‡</sup>	0.0012	0.0007	0.101
Maternal education < secondary	-0.5674	0.1474	0.000 <sup>‡</sup>	-0.5184	0.1642	.002 <sup>‡</sup>	-0.3487	0.1313	0.008 <sup>‡</sup>
Birthweight (continuous)	1.2172	0.1595	0.000 <sup>‡</sup>	1.3007	0.1727	.000 <sup>‡</sup>	0.6886	0.1400	0.000 <sup>‡</sup>
Maternal CD4 closest to delivery									
<200 cells/ul	-0.0225	0.2915	0.938				0.1726	0.2650	0.516
200-349 cells/ul	0.0262	0.1954	0.894				0.1666	0.1776	0.349
> 350 cells/ $\mu$ l <sup>1</sup>	.	.	.				.	.	.
Not on HAART in 0-24 mo	0.2472	0.2080	0.236				0.3027	0.1901	0.113
Infant perinatal ARV prophylaxis, not given or incomplete	-0.1328	0.1956	0.498	-0.3743	0.2154	.084			
No measles vaccine	-0.3413	0.1780	0.057	-0.4939	0.1982	.013 <sup>‡</sup>			
5207 protocol, not enrolled	-0.5881	0.2976	0.050	-0.3500	0.3241	.281	-0.5807	0.2658	0.030 <sup>‡</sup>

NOTES: Gray shading indicates that variable was not significant predictor ( $p < 0.1$ ) of outcome in single variable analysis and therefore not included in the multivariable model. Infant sex, maternal age at delivery, receiving PMTCT services at GHESKIO were not significant predictors for any outcome in single variable models. <sup>1</sup>Reference category. <sup>‡</sup> $p < 0.05$

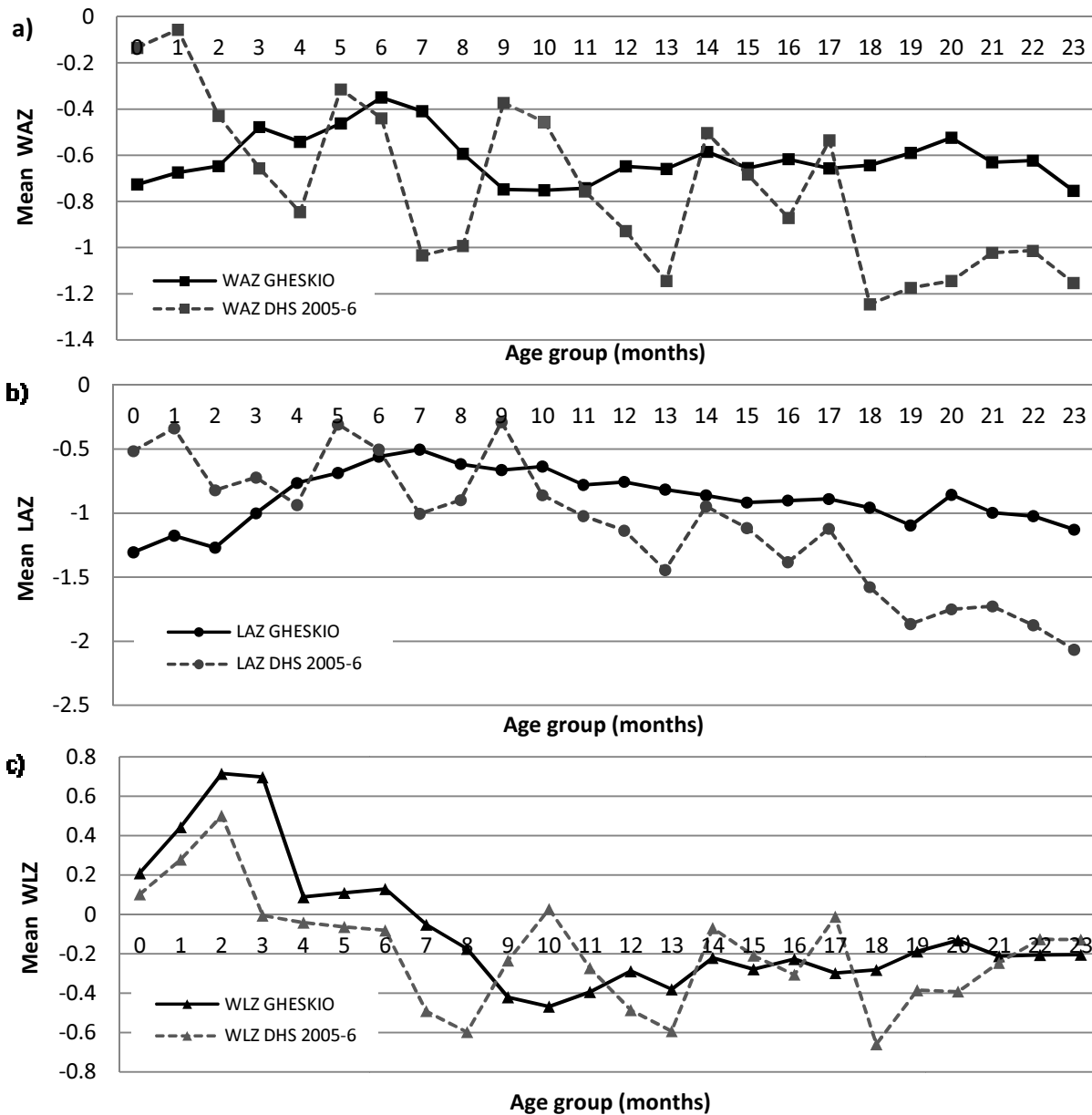
*Demographic variables.* Mother's education level was associated with all three outcomes from 7-23 months but only WLZ from 0-6 months. Female gender was associated with improved LAZ outcomes from 0-6 months of age.

*In utero environment variables.* Birth weight was strongly associated with all growth outcomes in 0 to 6 and 7 to 23 month periods except WLZ in the 0 to 6 month model. Neither low maternal CD4 nor HAART were significant in multivariable models for any of the 3 outcomes in either period.

*Access to care variables.* Infant completion of the ARV prophylaxis regimen was associated with improved WAZ from 0-6 months. Receiving the vaccine scheduled for the period being modeled (DPT3 at 6 weeks for 0-6 month, measles at 12 months for 7-24 months) was associated with improved LAZ and WAZ outcomes but not WLZ. Participation in 5207 was associated with WAZ and WLZ outcomes in late infancy but no outcomes during the 0-6 month period.

#### *Comparison to DHS data*

The 2005-2006 Haiti DHS dataset included cross-sectional growth outcomes on 1190 children aged 0-23 months. The smaller sample size in each age category is reflected in the higher standard deviations around estimates for the DHS children compared to GHESKIO (Table 3.3).



**Figure 3.3a-c** Unadjusted mean a) WAZ b) LAZ and c) WLZ by age for HIV-exposed uninfected GHESKIO children compared to nationally representative sample from Haiti 2005-6 DHS

At month 0, GHESKIO infants were significantly shorter (difference in LAZ = -0.83  $p=.047$ ) (Figure 3.3 and Table 3.3) and had a higher prevalence of stunting compared to the Haiti DHS group (LAZ < -2 SD 40.0% vs 9.1%  $p=0.006$ ) (Table 3.4). Mean WAZ was 0.60 z-score lower in the GHESKIO children at month 0 but this difference was not statistically significant (Table 3.3). The GHESKIO population improved in WAZ and LAZ over the first half of infancy (see above) while mean WAZ and LAZ decreased from 0 to 6 months in 2005-6 Haiti DHS. At 6 months of age there was no difference in mean z-score for any of the growth outcomes (Tables 3.3 and 3.4). Both populations demonstrated declining WAZ and LAZ scores over the 7-23 month period. However, by 23 months, growth outcomes were strikingly better in the GHESKIO population (mean LAZ  $-1.13 \pm 1.26$ SD, mean WAZ =  $-0.75 \pm 1.22$  SD) compared to the DHS (mean LAZ  $-2.07 \pm 1.02$  SD, mean WAZ =  $-1.15 \pm 1.12$  SD, LAZ  $p=0.000$ , WAZ  $p=0.066$ ). There was no difference in mean WLZ or prevalence of wasting (WLZ < -2 SD) between the two groups at any age (Table 3.3 and 3.4).

## DISCUSSION

Growth patterns of HIV-exposed uninfected children at GHESKIO were distinctive in three ways: 1) infants were born at very low LAZ and WAZ but normal WLZ, 2) WAZ and LAZ improved across the first 6 months of life, and 3) the decline in z-scores from 7-23 months was not as dramatic as seen in similarly impoverished populations [12]. Each of these findings is discussed in sequence.

*Size at birth:* LBW prevalence in the GHESKIO population (14.6%) was slightly higher than the 7-9% reported in HAART-naïve, HIV-exposed uninfected PMTCT cohorts from the early 2000s

[20]. It was not possible to assess preterm rates in the GHESKIO population but it was likely similar to the 25-42% reported in HAART-naïve, PTMCT populations in Sub-Saharan Africa [18, 19] given that maternal HAART treatment has been associated with increased rates of LBW and preterm [35]. Mothers receiving HAART for longer duration (e.g. starting pre-conception) are at higher risk of preterm and LBW than those starting later in pregnancy [36].

Such high rates of LBW and preterm suggest an *in utero* environment that is not favorable to fetal development. The association between LBW and advanced maternal HIV disease during pregnancy (CD4<200) in the GHESKIO infants was consistent with other HIV-exposed populations [17-19]. However the mechanism by which *in utero* exposure to HIV virus and/or HAART contribute to LBW and/or preterm is not well understood.

The most striking feature of the GHESKIO infants' birth size is that the infants were extremely short but proportional in WLZ, suggesting that it is a high prevalence of stunting (40%) rather than wasting that is driving the LBW. Although there is often concern about measurement error in length measurements on newborn infants [37], the steady gain in LAZ across 0-6 month period seen in the GHESKIO infants (as opposed to a more abrupt increase between 0-1 or 2 months) increases confidence in the precision of our measurements. Investigators in Zambia reported a similarly low LAZ at birth in HIV-exposed uninfected infants who received PMTCT intervention with ARV prophylaxis but no maternal HAART [20].

Improved birth weight outcomes associated with participation in 5207 trial and receiving BCG in the first 7 days of life likely reflect the effects of higher quality medical care during pregnancy and around delivery.

*0-6 month period:* WAZ and LAZ scores in the GHESKIO population improved dramatically and unexpectedly over the first six months of life. HIV-exposed uninfected PMTCT study participants in Zambia [20] and South Africa [18] also demonstrated improving LAZ across early infancy. This pattern of improving LAZ is noteworthy given that GHESKIO infants are proportionally sized at birth. Studies in IUGR populations consistently show that proportionally small-for-gestational age infants do not demonstrate catch-up growth while infants with low ponderal index do [38, 39]. With the assumed high prevalence of preterm in the GHESKIO population, the pattern may be at least partly attributed to accelerated postnatal growth rates observed in more mature preterm infants (gestational age >29 weeks ) [40].

The period of improving WAZ and LAZ scores in the GHESKIO population corresponded to the period when infant formula was provided to the majority of HIV-exposed infants at no cost. Data from higher-resource contexts show that growth patterns for artificially fed infants generally diverge from those of breastfed infants around 3 months of age with artificially fed children gaining up to 600-650 g more from 4-12 months than breastfed infants [41]. However differences in length gain are not usually as pronounced between feeding approaches [41]. This study did not include measures of morbidity including diarrhea – a major contributor to growth faltering in low income populations [42] and very common in children who are artificially fed [43]. The catch-up growth we observed in these formula-fed infants occurred in spite of diarrhea risks.

A possible explanation for this is that GHESKIO children were all receiving cotrimoxazole prophylaxis during early infancy [8, 44-48] – some children received the antibiotic daily for

more than 12 months before their HIV-status was confirmed. While cotrimoxazole has been shown to reduce morbidity risk in HIV-infected infants [49], it is not known whether cotrimoxazole would protect HIV-exposed uninfected infants against the morbidity-related growth deficits we might expect in a population exposed to artificial feeding and poor hygienic conditions. Further research on the potential growth-promoting effects of cotrimoxazole is needed.

It is plausible that differences in fetal and early postnatal growth patterns can be attributed more directly to *in utero* exposure to HIV infection and/or HAART. As mentioned previously, there is evidence for increased risk of preterm and LBW with or without HAART exposure during pregnancy. There is also evidence for altered postnatal immune system function in HIV-exposed uninfected infants with and without *in utero* exposure to HAART [50-52]. Changes in immune function may contribute to growth outcomes as alterations in pro-inflammatory cytokine proliferation can either restrict or accelerate bone formation in young children [53]. This presents a potential biological pathway for altered *in utero* and early postnatal growth in HIV-exposed uninfected infants compared to unexposed infants.

*7-23 month period:* Growth indicators of GHESKIO infants declined from 7-23 months, the period during which nutrition support was no longer provided by the clinic. However, this decline was not dramatic when compared to the decreased in LAZ described by Victora et al [12] when they applied the WHO 2006 Growth Standard to pooled results from nationally representative cross-sectional anthropometric surveys from in 54 low and middle income countries. Mean LAZ at age 24 months in the Victora et al analysis was below -1.75 SD [12].



Mean WAZ at 24 months for the GHESKIO children was above -1 SD and mean LAZ was just below -1 SD suggesting that many GHESKIO children were within the normal range on the WHO 2006 Growth Standard.

*Comparison to the DHS:* Our findings suggest that HIV-exposed uninfected infants at GHESKIO did not follow the same growth pattern as their unexposed peers in the general Haitian population. Although they were born at much lower LAZ, HIV-exposed uninfected infants at GHESKIO reached the same mean WAZ and LAZ as the general Haitian population by six months of age. The GHSEKIO children had better growth outcomes in the 7-23 month period compared to the DHS population. Marazzi et al [54] reported a similar finding in PMTCT cohorts in Malawi and Mozambique. With the dramatic scale-up of PTMCT and other interventions targeted specifically to HIV-affected populations in low-income populations, it is likely that HIV-exposed infants are receiving better medical care and support than the general population. This improved-access-to-care hypothesis is supported by findings within the GHESKIO cohort.

Improved growth outcomes in each age period (birth, 0-6 and 7-23) were associated with receiving the age-appropriate vaccine for that period. Participation in the 5207 protocol predicted improved growth outcomes from 7-24 months but not 0-6 months. The majority of GHESKIO infants received no-cost infant formula from 0-6 months but only 5207 protocol participants continued receiving infant formula during the 7-12 month period.

Maternal education level also predicted of growth in GHESKIO infants from 7-24 months but not 0-6. Assuming that higher education level reflects higher socioeconomic status and somewhat greater capacity to utilize available resources effectively, these characteristics may

have been more important during the period when most infants no longer received infant formula and caregivers had to access an adequate food supply on their own.

*Limitations:* Some limitations in our medical chart review study design and analysis approach must be taken in consideration when interpreting our findings. In particular, the lack of data on gestational age, infant feeding practices and morbidity as well as maternal height and economic status limit interpretation of multivariate models. Subjects from the DHS data were the most feasible comparison group available for a policy-relevant analysis but an adequately sized sample of unexposed children from the same urban/peri-urban Haitian environment would provide stronger verification of the the observed differences in growth patterns between GHESKIO infants and their urban peers.

## **CONCLUSIONS**

In the current era of advancing PMTCT interventions and HAART, findings from this descriptive comparative study highlight the need for studies that are designed to examine *in utero* development and subsequent growth across the first two years of life. Findings of improved outcomes in HIV-exposed infants in later infancy compared to the general population raise important policy-related questions about equity in targeting services to HIV-exposed children when the general population is also at risk of poor health outcomes.

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## CHAPTER 4

### **DOES PARTICIPATION IN AN INFANT FEEDING SUPPORT STRATEGY FROM 6-12 MONTHS OF AGE IMPROVE GROWTH OUTCOMES AMONG HIV-EXPOSED INFANTS IN URBAN HAITI?**

#### **ABSTRACT**

Nutrition support for non-breastfed babies of HIV-infected mothers is a recognized need, however there is a weak evidence base for effective programmatic solutions. The objective of our study was to implement and evaluate a new Infant Feeding Support Strategy (IFSS) for HIV-exposed infants 6-12 months of age attending the GHESKIO pediatric clinic. We compared growth outcomes in IFSS participants (n=73) at baseline, end of intervention and 6-months post intervention to a historical control group of same-age HIV-exposed uninfected infants seen at GHESKIO in the year before the intervention (n=294). The plausibility of attributing growth differences to participation in the intervention was assessed using multiple approaches.

The intervention and historical control groups did not differ significantly at baseline except that the intervention group had a lower proportion of children who had completed short-course perinatal ARV prophylaxis. At the end of the intervention period, the intervention group had a significantly lower prevalence of underweight (WAZ<-2 SD, 6.8%) and stunting (LAZ<-2 SD, 9.6%) than the historical control group (WAZ<-2 SD, 20.8%, p=0.007; LAZ<-2 SD, 21.2%, p=0.029). Wasting was lower in the intervention group (WLZ<-2 SD, 2.9%) than the historical control (WLZ<-2 SD, 8.9%) but the difference was not statistically significant. There were no differences between groups in mean WAZ, LAZ, WLZ at any time during the intervention or post-intervention period, nor in the prevalence of growth faltering between groups 6-months



post intervention. The additional analyses supports the conclusion that improvements in growth outcomes can be attributed to participation in the IFSS. The IFSS is a promising program model that can be adapted and scaled-up to other HIV-care contexts.

## **INTRODUCTION**

The need for better nutrition during infancy to improve growth and child survival outcomes is well recognized [1-5] and is especially acute in the context of maternal human immunodeficiency virus (HIV) infection. WHO Guidelines on Infant Feeding and HIV call for support of HIV-infected caregivers during infant feeding transitions across the first year of life [6].

In 2007, more than 85% of HIV-exposed infants at the GHESKIO centers in Port-au-Prince, Haiti, were replacement-fed from birth [7]. The clinic provided a six-month supply of no-cost infant formula to HIV-infected caregivers who chose to replacement feed and were enrolled in the Prevention of Mother to Child Transmission (PMTCT) program. A review of pediatric clinic medical records showed that risk of growth faltering in HIV-exposed uninfected infants increased from age 6 months onwards [8]. No infant feeding support existed at GHESKIO for infants for this age group.

Growth faltering is common globally, and food supplementation combined with behavior change education about infant and young child feeding (IYCF) practices is a recommended approach for reducing the risk of stunting and the burden of disease in children 6-24 months of age [9, 10]. The impact of IYCF interventions depends on the baseline health and nutritional status of the target population, timing of initiation and duration of intervention as well as a

range of other factors related to context, quality of program design and program delivery [11-13]. In addition to increasing the nutrient quality of the infant's diet, effective complementary feeding interventions promote responsive feeding practices and promote food safety and hygiene [11, 12].

The objective of our study was to implement and evaluate a new infant feeding support strategy (IFSS) at GHESKIO targeting HIV-exposed non-breastfed infants between 6-12 months of age. The evaluation had three aims: 1) to estimate the magnitude of effect on growth associated with participation in the IFSS 2) to determine whether growth effects were sustained 6 months post-intervention, and 3) to examine the plausibility of attributing the observed growth effects to participation in the intervention [14].

Due to ethical concerns and logistical constraints, it was not feasible to randomize treatment or follow a concurrent control group. For Aims 1 and 2 we compared growth outcomes in intervention participants to children of the same age who were seen at GHESKIO in the year prior to the intervention (referred to as the historical control). Available outcomes for the historical control were limited to data collected in routine clinic visits. For Aim 3, we examined indicators of comparability between groups, intervention utilization and a number of pre-post intermediate outcomes within the intervention group.

## **SUBJECTS AND METHODS**

*Study population.* The intervention study was conducted from July 2008 to February 2010 at the GHESKIO Centers, a Haitian NGO dedicated to clinical care, research and training in HIV/AIDS and related infectious diseases. GHESKIO provides free medical care to HIV-affected clients

from across the Port-au-Prince metro region, most of whom are poor. The study clinic is located immediately adjacent to some of the city's largest slum communities.

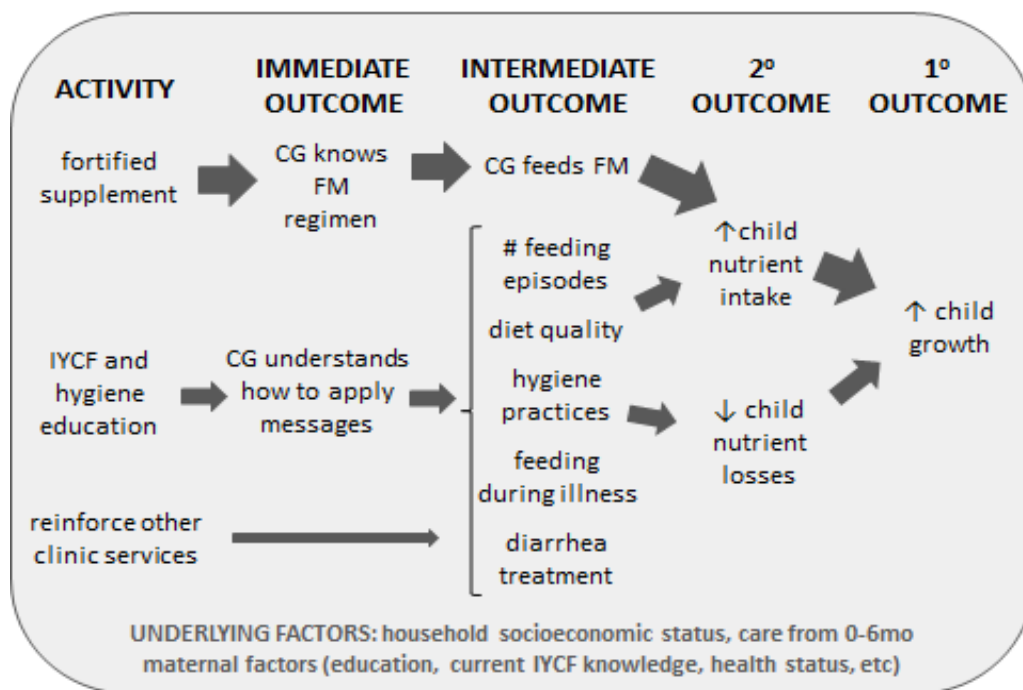
GHESKIO provided pediatric clinical care to all HIV-exposed children for the first 23 months of life. All HIV-exposed infants received cotrimoxazole prophylaxis from their first clinic visit until negative HIV status was confirmed. Pediatric HAART was provided to all confirmed HIV-infected infants. HIV-infected women who received prenatal care at GHESKIO as part of the PMTCT program were given perinatal ARV prophylaxis per Ministry of Health and Population guidelines and counseled about options for feeding during early infancy. At the time of this study, 85-90% of all HIV-exposed infants at GHESKIO were replacement fed from birth [7].

HIV-exposed children age 5.5-6.5 months without severe malnutrition ( $WLZ > -3$  SD) and no known allergy to peanuts who visited the pediatric clinic between 15 June 2008 and 5 January 2009 were eligible for recruitment into the intervention group. Potential participants were identified by pediatric clinic staff from the daily clinic visit registry. Infants were screened for enrollment based on birth date and maternal HIV test result as recorded in the GHESKIO enrollment database. Oral and written informed consent was obtained from caregivers of all infants prior to study enrollment.

The historical control group used medical records from all HIV-exposed uninfected children age 5.5-19.0 months who were born between 1 November 2005 and 15 December 2006, had a least one clinic visit after July 2007 and were not enrolled in a small pediatric study protocol conducted at GHESKIO during part of that period.

The study was approved by the GHESKIO Centers Institutional Review Board in Port au Prince, Haiti, the Cornell University Committee on Human Subjects in Ithaca, NY and the Weil-Cornell Medical College Institutional Review Board in New York, NY.

*Study design.* This was a quasi-experimental study of the effectiveness of a 24-week intervention for the prevention of growth faltering in HIV-exposed children. The IFSS was designed to increase infant nutrient intake through provision of a fortified-food supplement. Behavior change education about IYCF, hygiene and diarrhea treatment was a secondary pathway to improve overall dietary nutrient intake and decrease nutrient losses due to diarrheal illness (Figure 1). The evaluation was not designed to distinguish the relative contribution of the supplement versus the behavior change education components to growth outcomes.



**FIGURE 4.1** The postulated pathway between infant feeding support strategy activities and improved growth outcomes among intervention participants. *Width of arrow reflects the assumed relative contribution of the activity to improved growth outcome compared to the other intervention activities.* Figure legend: Infant and Young Child Feeding (IYCF), Fortified Manba supplement (FM), caregiver (CG)

*Intervention.* The IFSS included 3 activities 1) provision of a daily ration of lipid-based supplement that provided 50% of daily energy needs and the RDA or Adequate Intake (AI) of key micronutrients for the target age group 2) IYCF education delivered through biweekly group or individualized counseling sessions and 3) promotion of underutilized clinical services including immunizations, high-dose vitamin A supplementation, chlorine water purification solution and household food rations. Participants continued pediatric clinical visits according to the established schedule.

Caregivers and infants came to the clinic every two weeks across the 24-week intervention period. Children were enrolled in the intervention at age 5.5-6.5 months and were 11.0-12.35 months of age at intervention end. All participants were assigned to a “caregiver club” that included 8-12 infants born within 4 weeks of one another and their caregivers. Children were followed for 26 weeks post-intervention with visits scheduled every 4 weeks for data collection purposes only.

A team of two IFSS counselors and two study assistants delivered all intervention activities at the GHESKIO site. Each visit included a brief interview about illness and supplement use since last visit, IYCF education, and distribution of supplement. For the education component, visits alternated between one-on-one visits with a study counselor for growth monitoring and individualized counseling and “caregiver club” visits for interactive group-based IYCF education.

To help ensure delivery of the supplement, missed visits were followed up by study staff through phone calls and/or home visits as feasible. Educational messages from missed group lessons were reviewed in subsequent individual visits.

*Education sessions.* Topics for individual counseling and group education were based on key practices identified in the WHO Guiding Principles for Feeding non-Breastfed Children from 6-24 months of age [15]. Based on formative interviews with HIV-infected mothers of children in the targeted age range, we developed context-specific messages about food choice, quantity and frequency of feeding, responsive feeding behaviors, hygiene, and diarrhea care. Each 45-60 minute caregiver club session was delivered by a staff counselor who followed a structured

curriculum outlined in Table 4.1. Messages from club sessions were reinforced during the individual visits.

**TABLE 4.1** Topics for caregiver club IYCF education by intervention week and age

VISIT	APPROXIMATE INFANT AGE (MONTHS)	TOPIC
Week 0	6	How to use Fortified Manba supplement
Week 4	7	Hygiene and prevention and treatment of diarrhea
Week 8	8	Learning to eat: feeding children before 12 months
Week 12	9	Quantity and quality of food for children 9-12 months
Week 16	10	Responsive feeding
Week 20	11	Feeding children after 12 months of age

*Supplementary food.* Given that this was a non-breastfeeding population with limited access to breast milk replacements, we aimed to have the daily supplement ration provide about 50% of daily energy needs, approximating the usual energy intake from breast milk in fully breastfed children in this age group [12, 15]. Other criteria for the supplement were that it be developmentally appropriate for the infants' motor skills and small gastric capacity, required minimal cooking and preparation time, met food safety standards, was locally produced and was acceptable to the population.

The lipid-based nutrient supplement (LNS) used in the study was produced by Meds and Foods for Kids (Cap Haitien, Haiti). The ingredient composition by weight was 25% peanuts, 30% milk powder, 28% sugar, 15% oil, and 14% micronutrient pre-mix. The targeted daily ration of 65g

(approximately 4 tablespoons) provided 345 kcal and an RDA/AI of problem micronutrients for children age 6-12 months (Table 4.2).

**TABLE 4.2** Energy and micronutrient content of the supplement

Nutrient	Per 100g	Per 65g ration	Units	DRI <sup>1</sup> 6-8 mo	DRI <sup>1</sup> 9-11mo
Energy	529	344	kcal	769	858
Protein	15.9	10.3	g	11	11
Fat	33.5	21.8	g	30	30
Calcium	415	270	mg	260	260
Iron	17	11	mg	11	11
Zinc	7.7	5.0 <sup>2</sup>	mg	3	3
Iodine	200	130	mcg	130	130
Folate	123	80	DFE	80	80
Vitamin A	693	500	mcg RAE	500	500

NOTES: <sup>1</sup> Dietary Reference Intakes from the Institute of Medicine, National Academies. Energy and protein intakes are RDA. All other values are Adequate Intakes. <sup>2</sup> Zinc fortification levels were based on recommendations from the International Zinc Nutrition Consultative Group <http://www.izincg.org/>

The supplement was packaged in plastic 500-gram containers with screw caps. Each caregiver was given two jars per biweekly visit and a separate small glass jar for measuring purposes.

Caregivers returned containers with any unused supplement at the following visit.

Key supplement feeding messages were to mix the supplement into first portion of porridge or other soft food or to feed directly from a spoon as a snack. A one-week, home-based pilot trial



of supplement use conducted prior to the intervention launch confirmed that the supplement and delivery approach were acceptable to caregivers and infants in the target age group.

*Measurement of outcomes.* The primary outcomes were mean weight-for-age, length-for-age, and weight-for-length after 24 weeks of intervention. These were analyzed as both mean z-scores based on the WHO 2006 Growth Standard and prevalence of underweight (% of children with WAZ <-2 SD below median), stunting (% of children with LAZ <-2 SD below median), and wasting (% of children with WLZ <-2 SD below median).

Length and weight of intervention participants were measured every 4 weeks. Length was measured in the recumbent position using an infantometer (Easy-Glide Bearing Infantometer, Perspective Enterprises, Portage, MI) to the nearest 0.1 cm and weight was measured on a research-quality digital scale (Tanita Model 1583, Tokyo, Japan) to 0.01kg. Clinic staff received routine refresher training on anthropometric measurement techniques. Growth data for the historical control group was collected using the same equipment and staff protocols as the intervention period. Due to the use of medical record data there was variability in number and timing of visits available per child in the historical control.

Supplement disappearance was assessed every 2 weeks in the intervention group by weighing all jars delivered to and returned by caregivers. Caregivers were asked directly about supplement consumption by the child since the previous distribution. Supplement use was also assessed using 24-hour dietary recalls at weeks 12, and 24. Attendance at all visits was documented including portion of club session attended.

Data on diarrheal morbidity were collected by the study counselor at each visit. Caregivers were asked whether child had diarrhea in the previous 7 days. Follow-up questions included duration of illness, frequency of watery stools, and any treatment by the caregiver. A diarrhea episode was defined as 3 or more loose stools in a single day.

IYCF, hygiene and diarrhea-related knowledge and practices were assessed in the intervention group using a survey at weeks 0 and 24.

HIV status, immunization and vitamin A records, and a limited number of demographic variables were collected for all study children from their GHESKIO clinical records. Additional data on socioeconomic status and access to GHESKIO services were collected in the intervention group using a survey.

*Sample size.* A sample size of 82 intervention group children was estimated to be sufficient to detect a 0.5 LAZ difference between the intervention and historical control groups with 95% sensitivity and 80% power. This was calculated based on effect sizes observed in moderately malnourished Malawian children receiving a lower dosage of a similar LNS without education targeted to the mother [16]. Our sample size calculation assumed that 10% of the intervention children would not complete the 24-week intervention, 10% might be excluded due to HIV-infection, and up to 25% might be excluded if the mother did not receive prenatal care at GHESKIO.

*Statistical Analysis.* Data management was completed using Microsoft Access version 2000 and all statistical analyses were performed using SPSS software version 19 (Chicago, IL: SPSS Inc).

Growth z-scores were calculated based on the WHO 2006 Child Growth Standards using the WHO Anthro macro for SPSS (Geneva: WHO).

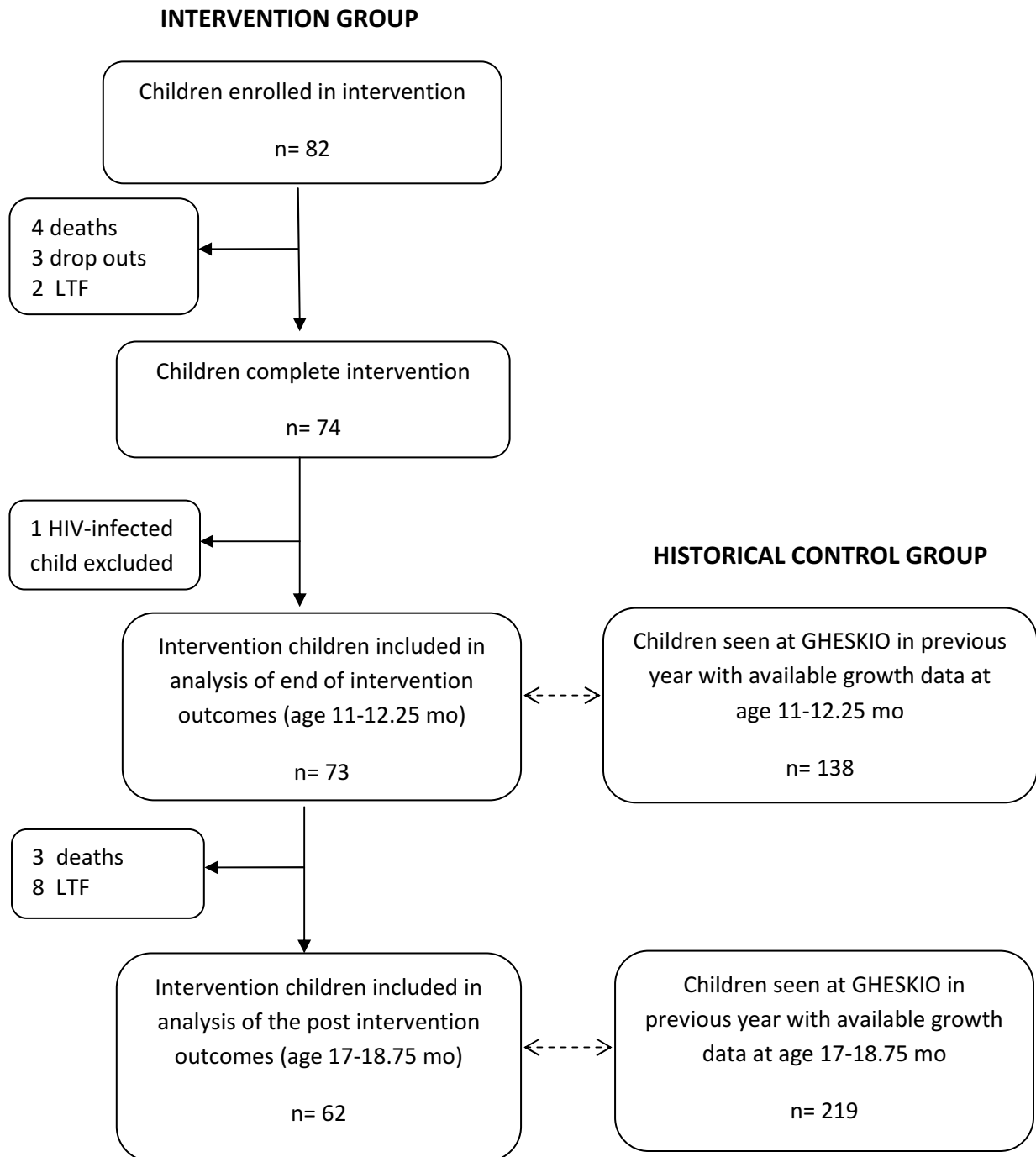
To assess cross-sectional growth outcomes at intervention start (week 0), end of intervention (week 24) and six-months post intervention (week 50), mean WAZ, LAZ, and WLZ were compared between intervention and historical control group using a *t* test and prevalence of underweight, stunting, and wasting were compared by Pearson's Chi-square or Fisher's Exact test. Multilevel models for change controlling for group and child age at visit were used to test for a treatment effect on the slopes of growth trajectories across the 0-24 week and 24-50 week periods. The SPSS 19 MIXED procedure with random intercept and random slopes accounts for repeated measures on individuals and allows for irregularly spaced measurements and missing values across individuals. The adjusted models included infant birth weight and maternal education as covariates.

For all other variables, means were assessed by *t* test and categorical variables by Pearson's Chi-square or Fisher's Exact test. Statistical significance was accepted at a 0.05 level and all tests were two-sided.

## **RESULTS**

Eighty-two children were enrolled in the intervention group (Figure 4.2). One HIV-infected child was excluded from analysis due to the known association between HIV infection and poor growth. Seventy-three HIV-negative infants completed the intervention and were included in the analyses of 24-week outcomes. The post-intervention follow-up period was interrupted by a highly destructive earthquake in January 2010. Sixty-two HIV-negative children completed a

post-intervention follow up visit at approximately 50 weeks (17-18 months of age) and were included in analysis. There was a total of 294 HIV-negative children included in the historical control group contributing 944 observations between 5.5 and 12.5 months of age and 844 observations between 12.5-19.0 months of age (Figure 4.2).



**FIGURE 4.2** Flow chart detailing the inclusion of children in analysis of growth outcomes at the end of intervention (week 24) and six months post-intervention (week 50). There was a total of N=294 children in the historical control with medical record data on growth available to be a comparison group at appropriate age for end of intervention and/or post intervention. LTF = lost-to-follow up .

The baseline characteristics of the intervention and historical control groups are presented in Table 4.3. There were no differences between intervention and historical control groups in gender, proportion enrollment in the GHESKIO PMTCT program, BCG vaccine coverage or other maternal variables. Although not statistically significant, mean birth weight was slightly lower and prevalence of low birth weight higher in the intervention group compared to historical control. Fewer infants in the intervention group completed the perinatal ARV prophylaxis regimen compared to the historical control ( $p=0.016$ ).

**TABLE 4.3** Baseline characteristics of intervention and historical control children from GHESKIO clinic records

Characteristic	Intervention		Historical Control		p-value
	N <sup>1</sup>	Statistic	N <sup>1</sup>	Statistic	
Infant characteristics					
Female gender (%)	73	49.3	294	49.0	0.96
PMTCT participant (%)	73	89.0	294	85.0	0.36
Mean birth weight (kg)	62	2.82 ± 0.55	231	2.95 ± 0.49	0.073
Birth weight < 2500g (%)	62	22.6	231	15.6	0.19
Completed short course ARV prophylaxis (%)	63	60.3	250	76.4	0.016*
Received BCG vaccine (%)	72	91.7	275	93.8	0.43
Ever breastfed before age 6 mo (%)	73	12.3		NA	
Still breastfed at age 6 mo (%)	73	0.0		NA	
Received free Enfamil before age 6 mo (%)	73	90.4		NA	
Started semi-solids before age 6 mo (%)	73	79.5		NA	
Maternal characteristics					
Education ≥ any secondary school (%)	67	50.7	269	50.6	0.98
On HAART during 0-24 month period (%)	64	37.5	258	31.8	0.38
Employed in previous 12 months (%)	73	30.1		NA	
Household characteristics					
Mean Household Asset Index <sup>2</sup>	73	10.15 ±2.58		NA	
Has a water source in home (%)	73	49.3		NA	
Has an improved latrine or toilet (%)	73	64.4		NA	

NOTES: <sup>1</sup> Total number of children with available data in GHESKIO record for characteristic. Overall N= 73 in the intervention group; N= 294 in historical control. <sup>2</sup> Asset Index is measure of how many total assets owned by participant's household out of a list of 16 items appropriate to the urban Haiti context. \* Statistically significant at p <.05 level, NA = Not available for historical control group

*Impact on growth.* In the cross-sectional analysis, there were no differences in mean z-scores between groups at any time across the intervention or post-intervention follow-up periods (Table 4.4).

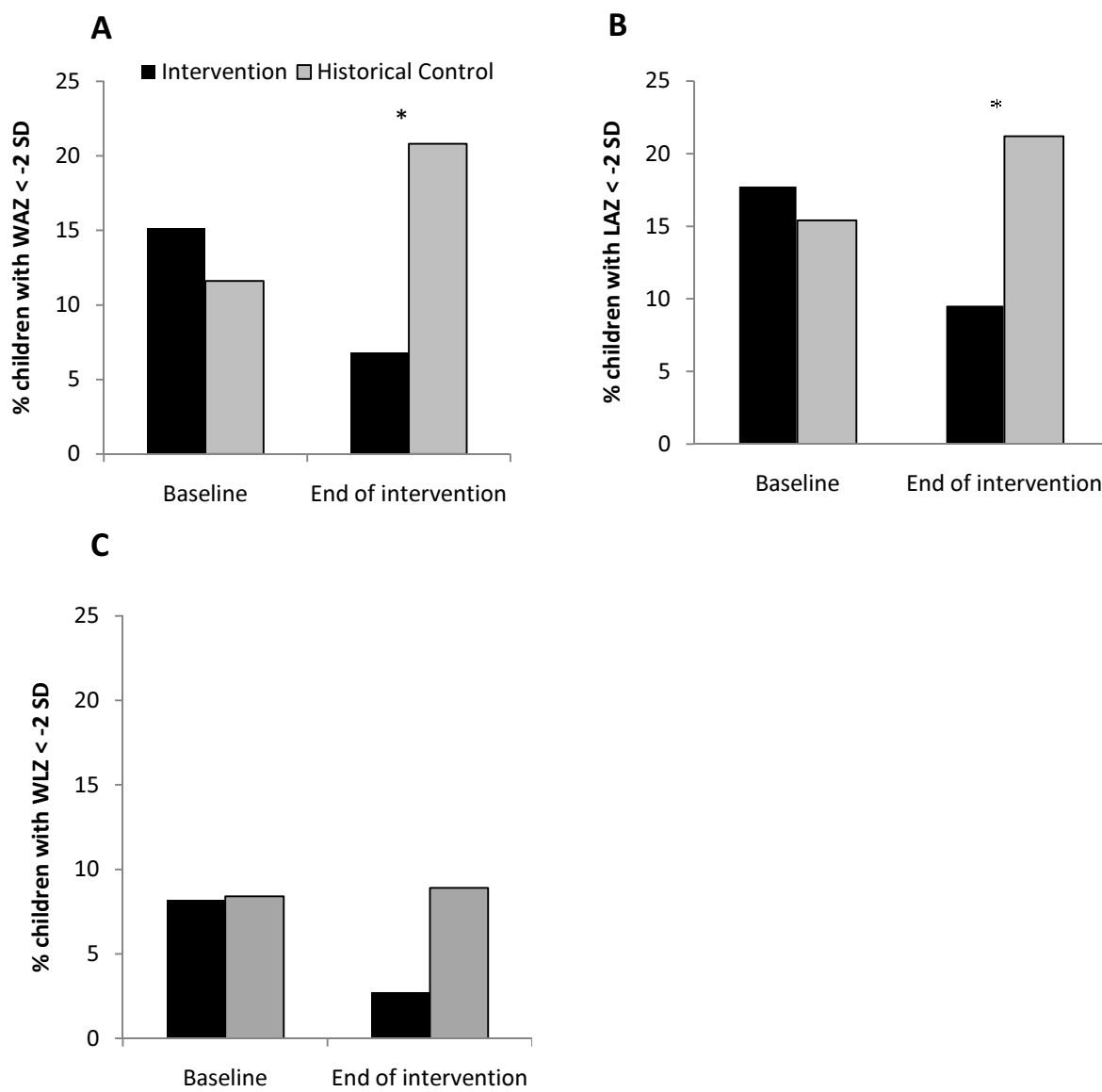
**TABLE 4.4** Cross-sectional mean WAZ, LAZ, and WLZ at baseline (week 0), end of intervention (week 24) and 6-months post intervention (50 weeks)

Anthropometric Outcome		Baseline			End of intervention			6-months post intervention		
		N	Mean $\pm$ SD	p-value	N	Mean $\pm$ SD	p-value	N	Mean $\pm$ SD	p-value
Weight-for-age (WAZ)	I	73	-0.69 $\pm$ 1.09	0.22	73	-0.58 $\pm$ 0.97	0.22	62	-0.70 $\pm$ 1.07	0.54
	HC	138	-0.49 $\pm$ 1.19		192	-0.77 $\pm$ 1.39		219	-0.60 $\pm$ 1.25	
Length-for-age (LAZ)	I	73	-0.78 $\pm$ 1.31	0.50	73	-0.74 $\pm$ 1.20	0.76	61	-1.07 $\pm$ 1.16	0.53
	HC	130	-0.64 $\pm$ 1.40		179	-0.79 $\pm$ 1.41		206	-0.95 $\pm$ 1.37	
Weight-for-length (WLZ)	I	73	-0.16 $\pm$ 1.19	0.34	73	-0.28 $\pm$ 0.98	0.31	61	-0.29 $\pm$ 1.09	0.84
	HC	131	0.01 $\pm$ 1.32		180	-0.43 $\pm$ 1.21		203	-0.25 $\pm$ 1.15	

NOTES: Age of intervention (I) and historical control (HC) children at 0 weeks was 5.5-6.76 months, 24 weeks was 11.0-12.25 months, 50 weeks was 17.0-18.75

Prevalence of all three indicators of growth faltering were slightly higher in the intervention group compared to historical control at week 0 (*n.s*) but thereafter growth faltering was much less prevalent in the intervention group. At week 24, the prevalence of underweight was 67.3 % lower ( $p=0.007$ ) and stunting 54.7% lower ( $p=0.029$ ) in the intervention compared to historical control. There was a 69.7% lower prevalence of wasting at 24 weeks in the intervention but this was not statistically significant (Figure 4.3).





**Figure 4.3** Prevalence of underweight (A), stunting (B) and wasting (C) in intervention and historical control groups at baseline (week 0) and end of intervention (week 24).

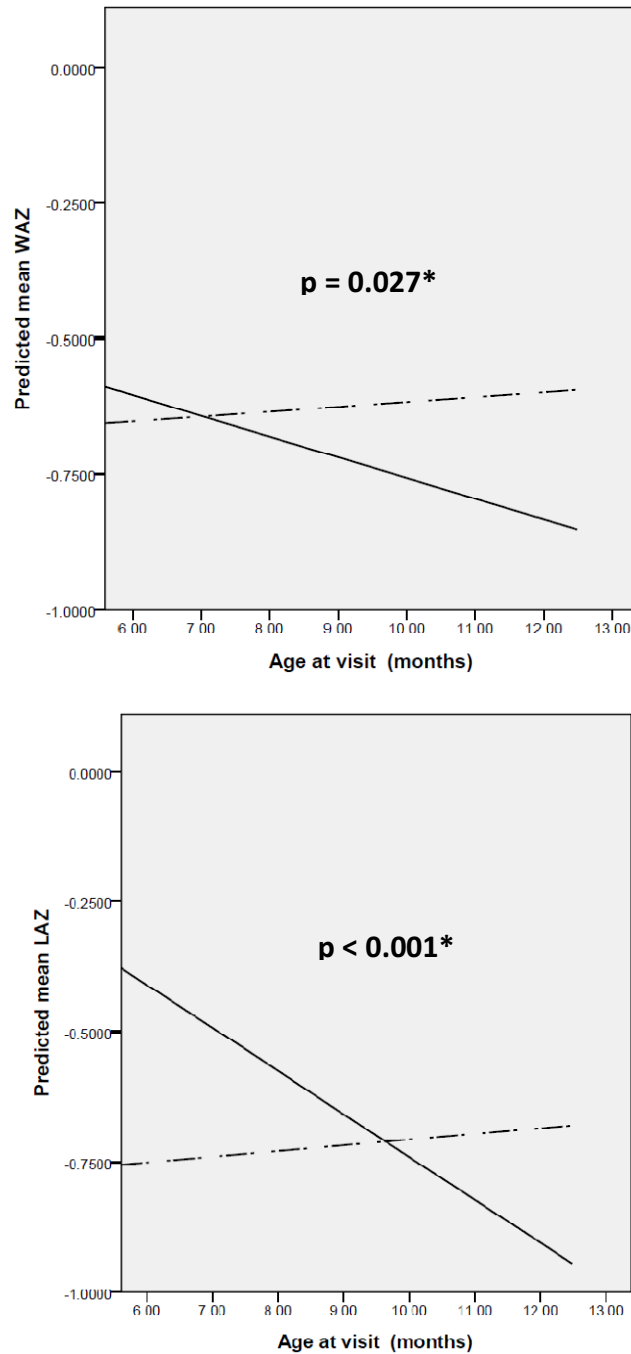
*73 children in intervention group at baseline and end of intervention, 138 children in historical control at baseline and 219 at end of intervention. Age range of children at 0 weeks was 5.5-6.76 months, 24 weeks was 11.0-12.25 months, \*statistically significant at  $p < 0.05$  level*

In further analysis using multilevel models for change to describe growth trajectories from age 6-12 months, there was a significant group\*age treatment effect in the WAZ and LAZ unadjusted and adjusted models but not the WLZ models (Table 4.5). This treatment effect is modeled for WAZ and LAZ in Figure 4.4. Across the 6 to 12 month age period, anthropometric indicators improved slightly in the intervention group while they decreased dramatically in the control group.

**TABLE 4.5** Multilevel models for change that assessed the interaction between group and child age at visit (months) on growth outcomes in intervention and historical control groups across the 0 to 24 week intervention period

	Weight-for-Age Z Score						Length-for-Age Z Score						Weight-for-Length Z Score					
	Unadjusted			Adjusted <sup>1</sup>			Unadjusted			Adjusted <sup>1</sup>			Unadjusted			Adjusted <sup>1</sup>		
	$\beta$	SE	p-value	$\beta$	SE	p-value	$\beta$	SE	p-value	$\beta$	SE	p-value	$\beta$	SE	p-value	$\beta$	SE	p-value
<b>Fixed Effects</b>																		
Intercept	-0.705	0.208	0.001	-3.425	0.435	0.000	-0.806	0.246	0.001	-3.508	0.506	0.000	0.120	0.250	0.63	-1.327	0.478	0.006
Age, mo	0.009	0.017	0.61	-0.005	0.017	0.79	0.010	0.021	0.63	0.004	0.024	0.87	0.041	0.024	0.08	-0.051	0.024	0.038
Group																		
historical control	0.333	0.248	0.18	0.131	0.235	0.58	0.890	0.299	0.003	0.716	0.322	0.028	0.181	0.305	0.55	-0.264	0.332	0.43
intervention <sup>2</sup>	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group*Age	-0.047	0.021	0.027	-0.050	0.021	0.020	-0.092	0.026	0.000	-0.096	0.030	0.001	0.004	0.029	0.90	-0.002	0.030	0.95
Birth weight, kg				1.129	0.136	0.000				1.070	0.152	0.000				0.637	0.138	0.000
Mother's level of education																		
< secondary school				-0.503	0.139	0.000				-0.373	0.153	0.016				-0.381	0.141	0.007
≥ secondary school <sup>2</sup>				-	-	-				-	-	-				-	-	-
<b>Random Effects</b>																		
Residual (within-child)	0.132	0.006		0.131	0.007		0.034	0.017		0.341	0.019		0.356	0.017		0.355	0.019	
Variance in initial status between children	2.710	0.317		1.821	0.258		3.252	0.483		2.949	0.516		3.342	0.471		3.197	0.508	
Variance in rate of change between children	0.017	0.002		0.013	0.002		0.018	0.004		0.019	0.004		0.025	0.004		0.021	0.004	
Co-variance	-0.144	0.025		-0.096	0.021		-0.176	0.039		-0.180	0.043		-0.237	0.042		-0.209	0.044	

NOTES: <sup>1</sup> Adjusted for birth weight and level of maternal education <sup>2</sup> Reference category \*Statistically significant at p<0.05



**Figure 4.4** (A) mean WAZ and (B) mean LAZ by age in months in intervention (---) and historical control (—) groups predicted using unadjusted multilevel models for change with random intercepts and slopes. p-value is reported for Group\*Age interaction. \* Statistically significant at  $p < .05$  level

There was no difference in mean z-scores (Table 4.4) or prevalence of growth faltering between the intervention and the historical control groups six-months post intervention. Stunting prevalence was 20% and wasting was 7-8% in both groups. The group\*age term was not significant for WAZ, LAZ or WLZ models for the 24-50 month period (not shown) suggesting that growth effects were not sustained post intervention.

*Provision and utilization of intervention.* There were no documented interruptions in provision of the intervention by the GHESKIO staff team. Mean disappearance of supplement across the 24-week intervention period was  $97.0\% \pm 3.51$  based on weighing of jars. 96.4% of participants used at least 90% of all supplement provided. There was good agreement between caregiver responses to direct questions about whether supplement was fed to the child in the previous day (80% at week 12, 73.6% at week 24) compared to supplement use in the previous day reported in the 24-hour recall (80.8% at week 12, 63.0% at week 24).

Mean attendance on caregiver club visit days was  $87.4\% \pm 15.7$ . Using a stricter measure requiring the caregiver to be present for at least 50% of the club teaching time, average attendance rate at caregivers clubs was  $73.3\% \pm 22.2$ .

Participation in the intervention was associated with increased utilization of other clinical services. 97.3% of the intervention group received at least one dose of vitamin A compared to 28.7% of the historical control. Within the intervention group, 95.9% reported ever receiving a household food ration from GHESKIO at week 24 compared to 52.1% at week 0.

*Caregiver knowledge.* Overall, the percentage of caregivers who identified positive IYCF and hygiene practices increased from baseline (week 0) to end of intervention (week 24) (Table 4.6).

This confirms that new IYCF knowledge was received and understood by the participating caregivers.

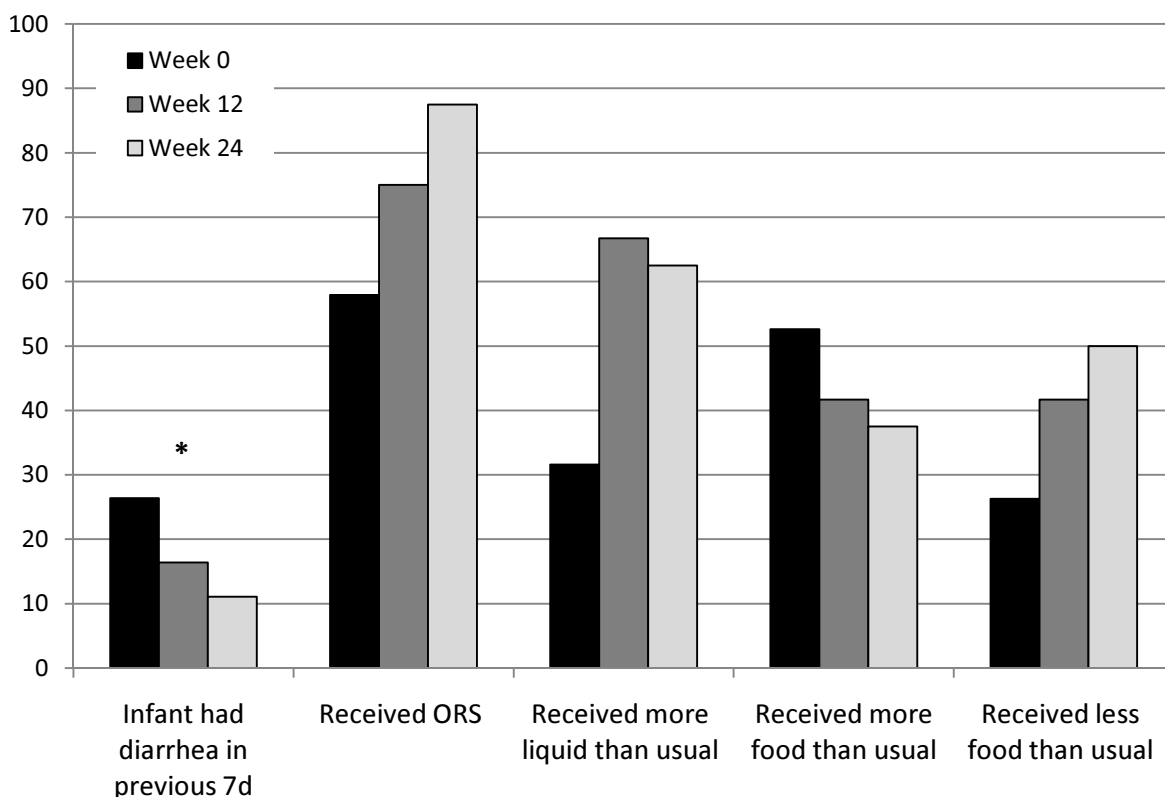
**TABLE 4.6** Changes in caregiver knowledge related to IYCF, diarrhea treatment and hygiene practices from baseline (week 0) to end of intervention (week 24)

	Baseline		End of intervention		p- value
	N <sup>1</sup>	% response	N <sup>1</sup>	% response	
<i>How can you encourage a child who does not want to eat?</i>					
Feed with patience	73	17.8	72	51.4	0.000*
Talk to child	73	13.7	72	55.6	0.000*
<i>How can you treat diarrhea?</i>					
Give ORS / home fluids	73	100	72	98.6	0.50
Give child same or more food during diarrhea	73	17.8	72	36.1	0.02*
Give child more liquid during diarrhea	73	6.8	72	45.8	0.000*
Give child an extra plate of food per day after diarrhea has finished <sup>3</sup>	72	76.4	72	95.8	0.001* <sup>2</sup>
<i>How can you protect your child from germs?</i>					
Wash hands	70	15.7	72	47.2	0.000*
Put pants on child	70	7.1	72	23.6	0.007*
Wash fruits and vegetables	70	1.4	72	16.7	0.001* <sup>2</sup>
Treat water	70	4.3	72	8.3	0.49

NOTES: <sup>1</sup> Total number of respondents for question. <sup>2</sup> Analysis by Fischer's Exact Test due to cell with count < 5. <sup>3</sup> Mothers were questioned directly about feeding after diarrhea ( e.g. Should you feed an extra plate her day?) Responses to other questions were not individually prompted by interviewer. All responses given by a mother to the question were noted. \* Statistically significant at p <.05 level

*Diarrheal morbidity.* There was a high prevalence of diarrhea in the intervention group. Mean prevalence of diarrhea (at least 3 stools) in previous 7 days across the 24-week intervention period was 20.2% ± 15.4. In our study, 69.9% of participating caregivers reported that the

infant had diarrhea in previous 7 days at 10% or more of their biweekly visits. Cross-sectional prevalence of diarrhea in the previous 7 days declined in the intervention group from baseline (26.4%) to end of intervention (11.11%) ( $p=0.019$ ) (Figure 4.5). Use of positive treatment practices among those with diarrhea, including use of oral rehydration solution (ORS) and increasing intake of liquids, increased across the intervention period while food-related positive behaviors declined. Changes in treatment behaviors were not statistically significant, possibly due to the small total number of children with diarrhea at any single visit (Figure 4.5).



**Figure 4.5** Diarrhea prevalence and caregiver treatment behaviors at baseline (week 0), mid-intervention (week 12) and end of intervention (week 24). Nine children had diarrhea at 6 weeks, 12 at 12 weeks, and 8 at 24 weeks. \*Decrease in prevalence of diarrhea from week 0 to 24 is statistically significant ( $p=0.019$ )

## DISCUSSION

HIV-exposed, replacement-fed GHESKIO infants who participated in the IFSS had lower rates of underweight and stunting at the end of the intervention period compared to HIV-exposed, replacement-fed children of the same age who were seen at GHESKIO during the year prior to the intervention. The pattern of reduced prevalence of growth faltering without a difference between groups in mean growth z-scores has been shown previously [9]. It suggests that children who were smaller at enrollment (e.g. in the left tail end of the z-score distribution) had greater potential to benefit from the intervention than children who started the intervention at a higher z-score.

Based on findings of a sustained post-intervention reduction in severe stunting among Malawian children of similar age who received LNS for 12 months [17], we hypothesized that exposure to the IFSS educational elements would contribute to sustained improvements in growth outcomes during the post-intervention period. However, growth effects in our study were not sustained at 6-months post intervention. Cross-sectional prevalence of growth faltering at week 50 was equally high in the intervention and historical control groups and suggests the need to extend the intervention period into the second year of life. This is consistent with data from populations across the developing world where children are at high risk of stunting until 24 months of age or beyond [18].

Given the non-randomized design, to assess the plausibility of attributing the growth impact observed in our study at end of intervention to the IFSS rather than external factors, we needed to answer three questions [14, 19]: 1) Were the intervention and historical groups comparable at the age of enrollment? 2) Was the intervention actually delivered to and utilized by



participants? 3) Was the direction and magnitude of changes in intermediate outcomes along the causal pathway from intervention inputs to growth outcomes in the expected direction?

*Comparability at baseline.* Mean WAZ, LAZ, and WLZ were slightly lower in the intervention group at week 0 compared to the historical control and prevalence of growth faltering was slightly higher. These differences were not statistically significant. Looking at available birth weight data, the intervention children had a slightly lower mean birth weight and higher rates of LBW than the historical control. This suggests that the differences in size and prevalence of growth faltering between the two groups were present since birth and not likely the result of postnatal divergence in the slope of their growth trajectories.

Comparison of other available baseline characteristics in the two groups showed that the intervention and historical control groups were similar in all characteristics except completion of perinatal ARV prophylaxis regimen. A previous study in the GHESKIO population showed no association between completion of ARV prophylaxis and growth in late infancy [20].

*Delivery and utilization.* Overall delivery and utilization of the intervention was high. Although it was not possible to measure supplement consumption by the individual children directly, measures of supplement disappearance using the weighing approach and caregivers' reported feeding practices were consistent and suggest that overall supplement consumption was high. We did not explicitly question caregivers about the degree of sharing of the supplement with other children or adults in the household at each visit. Based on qualitative interviews conducted at the end of intervention, mothers who were questioned about sharing behaviors

generally reported that sharing was limited. Mothers with fewer economic resources and larger family size were more likely to report sharing.

Caregivers were present for about three-quarters of the group teaching times. If a caregiver missed the teaching time for a particular club session they were likely to be exposed to the key messages from that lesson in subsequent group sessions and individual counseling sessions.

The increases in Vitamin A coverage and receipt of household food rations suggest that the intervention increased access to other services. It was not possible to assess what contribution access to these inputs made to growth effect but we think it was small. Previous studies of household food rations suggest they do not make a direct impact on child growth. Consistent use of chlorine water treatment can decrease exposure to pathogens and diarrhea risk, that in turn may impact growth. However the GHESKIO product was not distributed with extensive counseling. Vitamin A supplementation protects children from morbidity but is not associated with growth outcomes in non-deficient children.

*Intermediates along causal pathway.* The intervention was designed to impact growth outcomes through two causal pathways based on known determinants of child growth [21]—increased nutrient intakes through supplement use and IYCF education and decreased nutrient losses related to diarrheal illness through education about hygiene and diarrhea treatment.

Immediate outputs reflected caregiver knowledge that was gained or reinforced during the caregiver club and individual counseling visits. The changes in knowledge from baseline to the end of intervention about responsive feeding practices, diarrhea treatment and hygiene were statistically significant. This suggests that implementation of the intervention did follow

proposed pathway. Mothers did receive and understand the messages being delivered.

However with the exception of ORS use and feeding after diarrhea, at the end of intervention 50% or less of participants identified any particular behavior which suggests that there is room for improvement in delivery of IYCF education.

Intermediate outcomes were actual caregiver practices that would contribute to increased nutrient intakes or decreased nutrient losses. Caregiver education included messages about improving dietary diversity [15, 22, 23] and frequency of feeding [12, 15] to increase nutrient intakes. There was a slight decrease in the percentage of caregivers reporting feeding more food during diarrhea from 0 to 24 weeks and a slightly higher percentage of caregivers reported feeding less food at 24 weeks. The small numbers of children with diarrhea at any given time limit interpretation of these findings. Re-feeding after illness, an important behavior for growth [15] was not measured beyond the knowledge level.

The intervention pathway assumes that child intake of the supplement will increase overall nutrient intake. It is likely that there is some displacement of other foods in the diet because of supplement use but overall dietary intake data were not available to confirm this. It was also not possible to directly measure nutrient losses related to diarrhea. The frequency of diarrheal episodes over time is associated with risk of stunting [24]. Diarrhea rates in the intervention group are comparable to national data from the 2006-5 DHS that showed 40.9% prevalence of diarrhea in the previous *two weeks* in the 6-11 month old age group [25]. Prevalence of diarrhea in the intervention group decreased across the intervention period, but without a

concurrent comparison group it is not possible to attribute this reduction to participation in the intervention.

Overall, the findings related to comparability of groups at baseline, utilization of the intervention and analysis of the intervention pathway do support that the observed growth impact is attributable to participation in the IFSS.

It is difficult to compare the relative impact of IYCF interventions with different strategies, types of supplementary foods, timing and delivery contexts. Dewey and Adu-Afarwuah [9] reviewed 2 efficacy trials and 6 program evaluations of IYCF interventions that provided infants age 6-24 months a supplementary food along with another strategy, usually education, for at least four months. Reductions in the prevalence of growth faltering ranged from +1.3 to -9.4 percentage points in underweight and +2.9 to -6.8 percentage points in stunting. In our trial, the differences between intervention and historical control in prevalence of underweight (-14.0 percentage points) and stunting (-11.6 percentage points) were much larger.

There is an emerging body of literature around interventions that use energy-dense LNS for supplementary or complementary feeding in children under 24 months of age. In rural Malawi, 125 children fed 200 kcal (6-9 months) to 300 kcal (after 9 months) of LNS per day without education targeted at the mother gained an average of  $1110 \pm 440$  g in weight and  $6.6 \pm 1.4$  cm in length from 6 to 12 months of age [26]. In our trial, the intervention group gained an average of  $1552 \pm 588$  g in weight and  $7.5 \pm 2.12$  cm in length over the same age range. Results from a cluster-randomized study in Honduras that provided a LNS ration of 247 kcal/day to 6-12 month olds and 373 kcal/day to 13-30 months olds along with IYCF education and household

food vouchers for a total duration of 6-12 month showed no impact on growth outcomes compared to children who received education and food vouchers only. However supplement adherence was only 23-38% [27].

*Study limitations.* The lack of randomization to treatment or a concurrent control group increased the likelihood of confounding in the observed association between IFSS participation and growth outcomes. The plausibility-analysis design allowed us to develop a reasonable case for attributing the observed effect to the intervention. Aspects of the intervention design were highly contextualized to the high rates of replacement feeding at GHESKIO during the study period. Since the supplement was intended to compensate for lack of breast milk intake, the 65-gram dose was higher than other contexts that have used 47-55 grams of LNS in the 6-12 month age group [26].

## **CONCLUSION**

The findings of our study demonstrate that implementation of a clinic-based infant feeding support strategy that combines a supplement and infant feeding education is associated with reduced risk of growth faltering in HIV-exposed uninfected children from 6-12 months of age. Further research is needed to refine the duration of intervention, supplement dosing and education strategy to reflect the shift in HIV and infant feeding policies towards continued breastfeeding through at least the first year of life [6]. Implementation of the IFSS is ongoing at the GHESKIO Centers and the model is being refined and adapted with the aim of scaling-up throughout the country.

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## CHAPTER 5

### CONCLUSIONS

This dissertation attempts to answer the questions of *why* and *how* to intervene to improve growth outcomes of HIV-exposed children in urban Haiti. It describes the design, implementation and evaluation of a new Infant Feeding Support Strategy (IFSS) at the GHESKIO Centers. The problem of growth faltering in late infancy was identified in chapters 1 and 2. The context for intervention design and implementation was described in chapter 3. The evaluation of intervention outcomes was presented in chapter 4. In chapter 5, I will present key findings and their implications as well as recommendations for future research.

### KEY FINDINGS AND IMPLICATIONS

#### *Growth of HIV-exposed uninfected children at GHESKIO*

Analysis of cross-sectional and longitudinal growth outcomes among HIV-exposed uninfected children from 0-23 months of age showed that prevalence of stunting was extremely high (40%) at birth. Size at birth was predictive of WAZ and LAZ across the first two years of life. Mean growth indicators of GHESKIO children improved across the first six months of life, the period during which the majority of children received no-cost infant formula. By 6 months of age they reached the same mean WAZ and LAZ as children in the general Haitian population. Growth faltering in WAZ and LAZ started in late infancy and for LAZ, continued to age two years.

To our knowledge this is the first research describing the growth outcomes of HIV-exposed uninfected children in a less-developed country who received a clinical (e.g. *not* research) standard of care that included replacement feeding, maternal HAART and cotrimoxazole prophylaxis. Previous studies have reported that HIV-exposed uninfected infants are at higher risk of LBW. None, however, has reported both LAZ and WLZ near birth and considered the implications of proportional growth restriction on subsequent postnatal growth pattern.

Observed growth patterns suggest two problematic periods during which GHESKIO children have higher potential to benefit from a new intervention. High rates of early stunting and the association between birth weight and subsequent postnatal growth outcomes, suggest the need for a prenatal intervention. However so little is known about the etiology of poor growth *in utero* in this population that we have little evidence to support a particular intervention approach. After age 6 months is the other intervention period suggested by our findings. The relatively small overall decline in mean LAZ in the GHESKIO children across the 6-12 month period suggests there was less potential to benefit than we had originally anticipated.

#### *Context and intervention design*

A number of contextual factors shaped the way we went about designing the IFSS so that it would be integrated into the local service-delivery context. The facilitating factors were predominantly related to having the support and mandate of higher-level stakeholders including PEPFAR and GHESKIO leadership. The barriers were fundamentally related to the realities of working in a politically and socially chaotic environment with high rates of poverty.

Five “lessons learned” from the GHESEKIO IFSS are applicable to the development of integrated PMTCT and MCHN interventions at the clinical service delivery level. In particular, effective integration of nutrition care into existing PTMCT and child health services requires that both the nutrition strategy and the existing services be adapted to fit together and that they reflect the realities of the end beneficiaries. The caregivers club approach provides a promising foundation for integration of services at GHESKIO. Moving forward, GHESKIO will continue to adapt the IFSS model to reflect lessons learned in the pilot phase, respond to ongoing changes in the delivery context and better integrate PMTCT and MCHN services.

#### *Impact of the IFSS on growth of GHESKIO children*

Our findings suggest that it is possible to design and implement an effective clinic-based intervention to reduce the risk of growth faltering among HIV-exposed uninfected children. Unique relative to other published IYCF intervention studies, it involved a non-breastfed urban population and combined clinical and community-based delivery models.

Participation in the IFSS was associated with a significant reduction in the prevalence of underweight and stunting among IFSS participants compared to historical controls. The decline in growth faltering was a much higher magnitude than that seen in other IYCF interventions using education and supplementation approaches. The lack of impact on mean growth indicators suggests that it was children who started at the lower end of the weight and length for age distributions who benefited more from the intervention.

High compliance with supplement use and attendance at the educational sessions as well as reported changes in IYCF knowledge and practices suggest that the intervention did proceed

according to the postulated intervention pathways. Due to the small sample size and non-randomized design, it is not possible to attribute the relative growth effect to the primary (supplement) compared to secondary (education) pathways. However, the program-theory based evaluation design allowed us to identify potential weaknesses in the IFSS strategy. For example, the changes in IYCF knowledge were relatively small – suggesting that there is need for improvement in the design and delivery of the education aspect of the program.

#### *Lipid-based nutrient supplements*

The immediate problem driving the need for a new IFSS among HIV-exposed infants at GHESKIO was the increased risk of growth faltering in late infancy which we assumed was primarily caused by inadequate dietary intake. Provision of an energy-dense lipid-based nutrient supplement (LNS) was a feasible way to close the postulated nutrient gap in the diets of non-breastfed children. The study contributes to a growing body of literature around the use of LNS as a supplementary food. However, it does not address the more fundamental question of whether similar results could be obtained with a less-expensive supplement option such as a fortified cereal.

#### *Implications for scale-up of similar interventions*

Given the reach of PEPFAR's global programs and the explicit mandate from PEPFAR for implementation of integrated PTMCT and MCHN services at the service delivery level, the lessons learned from our experience have the potential to be used and applied by a wide range of policy makers, program planners and implementers in the near future. Our findings raise important questions regarding equity of service delivery in contexts with high rates of

malnutrition and poor child health outcomes in the general population. In using the nationally representative DHS children as a comparison group, we provide evidence for the inequity that can result from targeting services to HIV-exposed children in a context with widespread malnutrition. The magnitude of decline in LAZ from 7-24 months among HIV-exposed uninfected GHESKIO children was much less than that seen in the general Haitian population. Contrary to general assumption that HIV-affected children are at higher risk of poor health outcomes, the targeting of services to HIV-affected children only may be exacerbating an inequity rather than resolving one.

Building on the discussion of context started above, the GHESKIO IFSS experience contributes to a growing body of literature in implementation science that examines the processes and contexts underlying intervention choice, design, delivery, adaptation and scale-up [1, 2]. Policy makers and program planners should be cautioned against taking the exact approach used in the IFSS pilot study and applying it to other sites. As discussed throughout the dissertation, interventions must be adapted to delivery contexts.

## **RECOMENDATIONS FOR FUTURE RESEARCH**

### *Growth of HIV-exposed uninfected children*

There is an urgent need for research about *in utero* growth and development of HIV-exposed children in under-resourced contexts. Our findings suggest that prenatal factors are associated with growth outcomes across the first two years of life. At this stage, a longitudinal cohort study that follows HIV-infected women from early pregnancy through delivery and then follows their children through the first two years of life would help us better understand the

determinants of the high rates of *in utero* stunting and the early “catch-up” pattern observed in our population. Maternal weight gain, fetal skeletal growth, growth hormones (i.e. IGF-1, IGF-2), ARV drug activity, micronutrient status, and dietary intake are among the variables to collect during the prenatal period. For the postnatal period, measures of cotrimoxazole exposure and variables related to “environmental enteropathy” should be collected in addition to growth, morbidity, micronutrient status, and dietary intake. Specific research questions that could be addressed through a longitudinal cohort include:

- What are the determinants of *in utero* growth outcomes among HIV-exposed children?
- What *in utero* exposures and outcomes are associated with growth pattern in the postnatal period? More specifically, what factors are associated with improving z-scores observed across the 0-6 month period?
- What is the postnatal growth pattern under revised breastfeeding and ARV protocols?
- What is the association between cotrimoxazole prophylaxis and growth in HIV-exposed uninfected children exposed to poor hygienic environments?

*Pathways of intervention impact: assessment of immediate determinants of growth outcomes*

Dietary intake data collected through 24-hour recalls and stool pathogen analysis by PCR methods are available for the intervention group and a small comparison group of 9-month old controls. Using these data we can conduct a follow-up analysis to look at the two proximal determinants of growth – dietary intake and infection. Dietary intake data will address the question of whether supplement use actually increased overall nutrient intake. Depending on sample size and variability in outcomes, we might be able test whether specific dietary intake

factors or enteric pathogen types or loads were associated with relative benefit among intervention participants.

*Adaptation, integration and scale-up of IYCF interventions in the context of HIV/AIDS*

Implementation science-related research questions are only recently being addressed in the field of public health [1]. The roll-out of the GHESKIO integrated PMTCT and MCHN strategy provides the opportunity to address a wide-range of relevant questions including:

- How did the lessons learned from the IFSS experience actually get applied to the design and implementation of the expanded program at GHESKIO?
- How has the implementation context at GHESKIO changed post the 12 January 2010 earthquake and with the introduction of breastfeeding + ARV protocols?

Smaller-scale formative research about alternate supplement options and the delivery of IYCF education are needed to adapt the overall strategy to the changing contexts around infant and young feeding within GHESKIO and in other HIV-affected populations globally. Based on our findings, future evaluations of similar interventions should include measures of social support and caregiver capacity as well as address additional aspects of the intervention delivery process including cost-effectiveness, staff motivation, and time burden for staff and participants.

GHESKIO is limited by the relatively small size of its PMTCT program – so duration of such a study may need to be extended and/or additional sites recruited. HIV-affected populations in sub-Saharan Africa where the overall proportion of the population affected is much higher may



be more suitable for studies that compare different integrated PMTCT and MCHN delivery approaches.

## **CONCLUSION**

The dissertation research has contributed to the knowledge and experience gap around the translation of PMTCT and IYCF recommendations into feasible interventions that improve infant growth outcomes in the context of HIV.

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## **APPENDIX**

### **PROGRAM THEORY MODEL FOR INFANT FEEDING SUPPORT STRATEGY**

Program activity	Description	Target Pop.	Output	Intermediate Outcomes	Distal Outcome	Assumptions / potential barriers
<b>Delivery of core IYCF messages (0-6 mo) through group education sessions</b>	<p>Specific messages on IYCF behaviors are delivered to mothers by a trained GHESKIO nurse/counselor during monthly small group education sessions.</p> <ul style="list-style-type: none"> <li>▪ Apply adult learning principles</li> <li>▪ Core messages repeated monthly</li> <li>▪ See Table for targeted behaviors / specific messages</li> </ul>	Mother	Mother gains new and/or reinforces existing knowledge needed to implement or sustain a specific recommended behavior change.	<p>Mother practices recommended behavior.</p> <p>Infant responds to practice as intended.</p>	<p>↑ Energy intake</p> <p>↓ illness</p>	<p>Resources mother needs to implement knowledge/ behaviors are available to them (e.g. supplies to treat water)</p> <p>Mothers understand messages as delivered.</p> <p>Adequate space and time available in clinic to hold group session.</p>
<b>Provision of daily ration of 65g fortified manba (FM) for infant</b>	<p>Two 500g jars of FM are given to mothers on a bi-weekly basis. Mothers receive additional small jar to use to measure daily ration.</p>	Mother	Mother receives two jars of fortified manba at meeting.	FM manba available at household level.	↑ Energy intake	Present diet of infant is deficient in Energy and MN
	<p>Nurse/counselor gives instructions about how to feed FM during initial group session. Instructions are repeated at monthly group sessions and bi weekly individual meeting..</p> <ul style="list-style-type: none"> <li>▪ How to measure daily dose of 65g</li> <li>▪ feed alone as snack or mix in first small portion of other food</li> <li>▪ offer baby clean water after</li> <li>▪ special food for infant; not to share</li> </ul>		Mother has knowledge of how to feed FM correctly	<p>Mother offers correct quantity of FM daily.</p> <p>Infant consumes daily ration.</p>		<p>Replacement of existing diet with FM is minimal – most of FM nutrients are functioning as supplement.</p> <p>No interruptions in the supply chain – e.g. stock outs at clinics or mother selling product before reaching household.</p>
	GHESKIO staff monitors disappearance of FM from containers by weighing the contents in jars returned by mothers (biweekly visit).		<p>If under/over consumption staff provide individual counseling/follow-up.</p> <p>As needed, mother receives individualized messages to reinforce correct use FM.</p>	<p>Mother changes feeding practices to offer correctly.</p> <p>Infant consumes daily ration.</p>		<p>No interruptions in the supply chain – e.g. stock outs at clinics or mother selling product before reaching household.</p> <p>Manba is not shared in household.</p>

Program activity	Description	Target Pop.	Output	Intermediate Outcomes	Distal Outcome	Assumptions / potential barriers
<b>Growth monitoring with individualized counseling</b>	Staff member weighs and measures infant with assistance of mother and plots weight on ministry of health card in front of mother.	Staff Mother	Staff uses GM information to formulate and deliver counseling message.	Mother receives and understands message.	↑ Energy intake  AND/OR  ↓ illness	
	Staff reviews trend in weight and other current health indicators in infant's record file in order to formulate specific message for mother. Message/advice noted in written record.	Staff		Mother motivated/able to change behavior  Mother changes feeding and or care practices  Infant responds as intended to changed behavior.		
<b>Give caregiver access to monthly World Food Program food ration being distributed form GHESKIO and other commodities given at the clinic including immunizations, vitamin A, ORS, chlorine water solution.</b>	Caregiver attending group education sessions receive referral from nurse/counselor to allow access to GHESKIO WFP staple food ration distribution if caregiver chooses to pick it up. Intended to serve as an incentive to participate in group education (NOTE: Some families may already be accessing WFP ration at GHESKIO and will not receive additional through nutrition program.	Mother	Mother receives referral card from nurse/counselor or nutrition field worker.	Mother motivated to participate and attend education session.  Mother receives knowledge and puts into practice.  Infant responds as intended.	↑ Energy intake  ↓ illness	Assumes WFP ration size is not sufficient enough to significantly influence infant dietary intake through direct infant consumption and/or conversion to cash.  Assumes rations will continue despite rising commodity prices and size will be large enough to motivate mother behavior

## APPENDIX

### ABOUT THE MANBA FOTIFYE SUPPLEMENT

Medika Mamba (a Haitian Creole name that means *peanut butter medicine*) is a peanut-based energy-dense micronutrient fortified food produced locally in Haiti by Meds and Food for Kids (MFK), a nongovernmental organization ([www.medsandfoodforkids.org](http://www.medsandfoodforkids.org)). MFK established a factory to produce Medika Mamba in Cap Haitien (a major Haitian city on the north coast) for use in local programs to treat severe and acutely malnourished children.

The formulation of Medika Mamba was patterned after the similar product called PlumpyNut, produced by Nutriset (Lyon, France). Dr. Patricia Wolff, associate professor of pediatrics at the Washington University School of Medicine and executive director of MFK, has developed Medika Mamba and the MFK nutritional rehabilitation program in close consultation with Nutriset and with Dr. Mark Manary, also of Washington University, who is implementing similar work in Malawi and Sierra Leone [1]. MFK is in the midst of a UNICEF certification process for producers of Ready-to-Use Therapeutic Foods (RUTF) UNICEF has been charged with setting global quality standards for RUTF products.

Although Medika Mamba was designed for therapeutic feeding of acutely malnourished children, we propose using a reformulated version (referred to here as *fortified manba* (FM)) as a daily 65g ration (approximately 6 teaspoons) to prevent malnutrition. Based on independent commercial nutrient analyses made in preparation for this proposal, FM provides per 100 g: 531kcal, 36.6 g fat, 15.3 g protein. Thus 65 g of FM would provide 50% of calories (equivalent to breast milk intake) and 90% of protein needs for a 6-8 month baby. The micronutrient premix

for the FM will be formulated to provide approximately 1 RDA/AI of micronutrients for an infant 6-11 months old. Zinc fortificant levels are based on the IZINCG estimate for high-phytate cereal based diets (5mg) [2]. By providing high nutrient value in relatively small volume, supplement is in accordance with relatively small gastric capacity of infants [3].

It also allows for ongoing consumption of traditional Haitian weaning foods (see table 1) as the FM can be added to these porridges or consumed separately as a snack to meet overall daily nutrient targets.

**Table A.1: Sample infant diet incorporating FM supplement with traditional Haitian infants foods compared to the recommended nutrient intake levels**

	Medika Manba (65 g)	Wheat flour gruel (250 g)	Bread Gruel (125 g)	Total nutrients consumed	Recommended Intakes (DRI)	
					6-8 mo	9-11 mo
Energy (kcal)	345	277	109	731.4	769	858
Protein (g)	9.9	4.4	1.7	16.0	11	11
VA (µg)	300	0	0	300	500	500
Fe (mg)		10.0	1.1	0.8	11.9	11
Zn (mg)		5.0	0.4	0.05	5.4	3

*Cost and availability:* Compared to other imported micronutrient-fortified infant foods available in Haiti, FM is the most economical when considering cost per kcal (see Table 1). There are a number of locally produced flours marketed for infant feeding (e.g. plantain flour, manioc flour) however none of these products are micronutrient fortified and all require extended cooking times. Akamil, a flour composed of mixed grains and legumes, was developed in rural Haiti in the mid-1970s and the high-protein formula was targeted at malnourished children. However, Akamil is not micronutrient fortified, requires one hour cooking time (which

increases costs through fuel usage), and the high-protein formulation is no longer considered medically necessary, particularly in the treatment or prevention of mild to moderate malnutrition.

**Table A.2: Micronutrient-fortified infant foods currently available in Haiti**

	FM (1000g)	Nutribien Infant cereal Supermarket <sup>2</sup> (400 g)	Infamil Lipil Powder GHESKIO (12.9 oz)	Infamil Lipil Powder Supermarket <sup>2</sup> (12.9 oz)
Calories per unit (kcal)	5300	1770	1880	1880
Cost per unit (USD)	6.00	4.08	7.60	12.50
Cost per 100 kcal	0.11	0.23	0.42	0.66
Monthly cost per child <sup>1</sup>	11.39	23.80	43.47	68.31

NOTES: <sup>1</sup> Monthly cost per child is calculated as the cost to provide a daily ration of 345 kcals for 30 days. <sup>2</sup> Supermarket costs are the posted prices for products at the Caribbean Supermarket in Delmas, Haiti on 3 August 2007. Exchange rate: 1 USD = 7 Haitian dollars = 35 Haitian Gourdes

*Food safety:* Cornell University faculty member Dr. Dan Brown has been working with MFK to assure safe levels of aflatoxin in the product by applying low technology sorting procedures.

These procedures have been shown to remove 99.6% of the aflatoxins present in freshly harvested raw peanuts, with an average of only 0.2 parts per billion remaining, and often below the limits of detection. MFK tests batches with a one-step lateral flow immunochromatographic assay to ensure the sorting methods are effective. Periodic samples are also sent to Dr. Brown's lab for backup quantitative analyses by immunoaffinity/fluorometry and HPLC methods.

Risk of peanut allergy is assumed to be very low in the Haitian population compared to the United States or other industrialized contexts [4]. However, protocols are in place for



counseling about allergy risk during the informed consent process and for ongoing supervision by clinical staff to ensure mothers are prepared to respond immediately in case of adverse reaction.

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