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Randomized Controlled Trial of the Impact of Treating Moderately Malnourished Women in Pregnancy

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Abbreviations and Acronyms

ANOVA	analysis of variance
BMI	body mass index
cm	centimeter(s)
CSB+	fortified corn-soy blend
FH	fundal height
g	gram(s)
HCZ	head circumference-for-age z-score
HIV	human immunodeficiency virus
HSD	honest significance difference
IFA	iron and folic acid
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter(s)
LAZ	length-for-age z-score
LNS	lipid-based nutrient supplement(s)
µg	microgram(s)
mg	milligram(s)
mm	millimeter(s)
MUAC	mid-upper arm circumference
RA	research assistant
RDA	recommended dietary allowance
RR	relative risk
RUSF	ready-to-use supplementary food
SGA	small-for-gestational-age
WAZ	weight-for-age z-score
WFP	World Food Programme
WHO	World Health Organization
WLZ	weight-for-length z-score

Executive Summary

Background

Malnutrition during pregnancy among women in the developing world is often due, in part, to inadequate dietary intake in the face of increased nutrient requirements during pregnancy. The adverse consequences of malnutrition during pregnancy may have a lifelong impact on the developing fetus.

Methodology

A randomized controlled clinical trial (the Mamachiponde study) was conducted in rural Malawi with pregnant women who were moderately malnourished, defined as having a mid-upper arm circumference (MUAC) ≥20.6 cm and ≤23.0 cm. The trial was designed to determine whether a ready-to-use supplementary food (RUSF) or a fortified corn-soy blend (CSB+) along with a daily multiple micronutrient antenatal supplement (UNIMMAP) would improve maternal weight gain from the onset of supplemental feeding until the last clinic visit before delivery and would improve infant birth weight and length outcomes compared to the standard of care, CSB+ with a daily iron and folic acid (IFA) tablet.[1] A total of 1,828 pregnant women were recruited from 15 clinics in southern Malawi for the study. Study foods provided approximately 900 kcal and 35 g of protein daily. Women returned to clinic every 2 weeks for anthropometric measurements and health checks and received their 2-week supply of treatment food/supplements until recovery, which was defined as a MUAC ≥23.1 cm on two consecutive visits. After recovery, women returned to clinic every 4 weeks and were assessed for relapse. If relapse occurred, mothers went back onto their assigned treatment food/supplements. Anthropometric measurements of infants were taken at birth, at 6 weeks, and at 3 months.

Results

Overall, the results were similar when moderately malnourished pregnant women received supplemental food, whether it was RUSF, CSB+ with UNIMMAP, or CSB+ with IFA. Women were treated for an average of about 9.4 weeks, receiving 5.0 biweekly rations of food. Mothers in the RUSF group had the highest mean weight gain from the time they began treatment until their final weight measurement (3.4 kg, 3.2 kg, and 3.0 kg in RUSF, CSB+ with IFA, and CSB+ with UNIMMAP, respectively, P=0.03). Newborn birth weights and lengths were similar across intervention groups, but the incidence of newborns with birth weight <2.4 kg (weight-for-age z-score [WAZ] <−2) was lowest in the CSB+ with IFA group (17%, 18%, and 24% in CSB+ with IFA, RUSF, and CSB+ with UNIMMAP, P=0.02). The treatment regimen did not affect infant anthropometry measurements at 6 and 12 weeks after birth. A subgroup analysis of the 194 HIV-infected women showed no differences in response across intervention groups, but there were differences between HIV-infected and non-HIV-infected women. At birth, HIV-exposed newborns had a similar length and weight as newborns without HIV exposure, but head circumference was less (34.0 cm vs. 34.3 cm, P=0.02). At 3 months of age, HIV-exposed infants had smaller weights, lengths, and head and arm circumferences than infants without HIV exposure.

Conclusions

RUSF improved gestational weight gain during treatment for moderate malnutrition more than CSB+ with UNIMMAP. Mean infant weight, length, and head circumference was similar regardless of the intervention, but compared to those consuming CSB+ with UNIMMAP, birth weight <2.4 kg was less frequent in those consuming CSB+ with IFA.

[1] The CSB+ formulation was “super cereal: CSB with sugar” (17).

Introduction

Malnutrition during pregnancy is common among poor women in the developing world. Malnutrition during pregnancy is often due, at least in part, to inadequate dietary intake in the face of increased nutrient requirements. Malnutrition during pregnancy impacts the health of both the mother and the fetus. It is estimated that 5%–20% of African women of childbearing age have a body mass index (BMI) <18.5, meaning that many women enter pregnancy already in a malnourished state (1). In Malawi, 9.2% of women have a BMI <18.5 (2) and malnutrition is estimated to affect about 15% of pregnant women (3). The maternal mortality rate in Malawi is one of the highest in the world and low birth weight in the newborn is present in 14% of live births (4, 5). Malawi also has one of the highest rates of preterm births in the world at 181 per 1,000 live births (6). Malnourished pregnant women are at an increased risk for maternal mortality and disability and poor birth outcomes, yet the benefits of treating moderate malnutrition during pregnancy remain largely undocumented (7,8). Food supplements during pregnancy may lessen a woman's malnutrition and improve infant birth outcomes.

In Malawi, as elsewhere in the world, fortified corn-soy blend flour (CSB+) is recommended for adults with malnutrition (9). In regions with high rates of iron deficiency, an iron and folic acid supplement (IFA) is also frequently provided to pregnant women through antenatal clinics, generally in the second and third trimesters of pregnancy. Although food supplementation of pregnant women with moderate malnutrition is the prescribed standard of care in Malawi, it is commonly not given. Ready to use supplementary food (RUSF) has been added to the Integrated Management of Childhood Illness guidelines as the standard of care for young children with moderate or severe malnutrition (10); however, it is not commonly used in other populations with malnutrition. While use of lipid-based nutrient supplements (LNS) has been studied in pregnant women (11, 12), there is little published evidence about RUSF (a type of LNS) as treatment specifically for malnourished pregnant women.

Internationally, there is no agreement on the method of diagnosis or treatment of moderate or severe malnutrition during pregnancy (13), therefore the World Health Organization (WHO) currently does not have guidelines for diagnosis or nutritional treatment of malnutrition during pregnancy (14). For classification of moderate malnutrition in pregnancy, the World Food Programme (WFP) uses a cutoff of a mid-upper arm circumference (MUAC) ≤22.0 cm, which is consistent with Malawian guidelines for HIV nutrition intervention treatment, though there is no clear evidence for use of this criterion (15). Additionally, the Integrated Guidelines for the Clinical Management of HIV for Malawi state that, in pregnancy, women with a MUAC ≤22.0 cm should begin supplementary feeding, but does not define what the treatment should be (16).

The aim of this study was to determine whether RUSF designed specifically for pregnant women with malnutrition or CSB+ with a daily UNIMMAP multiple micronutrient antenatal supplement would improve maternal recovery from malnutrition and increase infant birth weight and length outcomes compared to the standard of care (CSB+ with daily IFA).

Methods, Participants, and Measurements

Methods

The Mamachiponde study was an assessor-blinded, randomized controlled clinical trial conducted in southern Malawi at government antenatal clinics. There were 15 study sites at mostly rural clinics in four districts: Blantyre, Chikhwawa, Mulanje, and Zomba. There were initially two additional urban sites, but recruitment attempts ended after several months with only 15 women identified as meeting the enrollment criteria for low MUAC. These 15 women completed the study and were included in the analysis. Primary outcomes originally defined for the study were maternal recovery from moderate malnutrition, defined as MUAC ≥23.1 cm on two consecutive visits; change in maternal MUAC; premature delivery (not defined); and newborn birth weight and length. Secondary outcomes were infant length-for-age z-score (LAZ) at birth; infant weight, length, and survival at 3 months; maternal skinfold thickness; duration of treatment; change in maternal hemoglobin concentration from onset of treatment until 10 weeks later; change in maternal weight from the onset of treatment until final weight measurement; and, among HIV-infected women, CD4 count.

A few months after initiating the study, three consistent observations were made that led to reassessment of the initial primary outcomes: 1) while women did gain weight, it was not reflected in a change in maternal MUAC[2]; 2) measurement of CD4 counts was sporadic and largely unavailable; and 3) while the researchers recognized that premature delivery was an important outcome, there was no reliable method of assessing gestational age in the study. As a result, primary outcomes were revised to include the following:

- Newborn birth weight and length (measures of in utero growth)
- Maternal weight gain from the onset of treatment until the last clinic visit before delivery (a measure of maternal nutritional status)

These were deemed to be the most reliable measures of treatment outcomes collected in the study and are presented in this report. For purposes of data analysis, women were not designated as recovered or graduated from their malnutrition.

Participants

Pregnant women with moderate malnutrition, defined as MUAC ≥20.6 cm and ≤23.0 cm, were recruited into the Mamachiponde study between March 2014 and December 2015. Maternal and infant follow-up continued until 3 months postpartum. Pregnant women attending an antenatal clinic and in catchment communities were screened for moderate malnutrition by local clinic and community health staff. Enrollment criteria were: having a fundal height (FH) of <35 cm, willingness to attend the antenatal clinic every 2 weeks during pregnancy, remaining in the area for delivery and until 3 months postpartum, and providing written and verbal consent. Women who had pregnancy complications, such as severe malnutrition (MUAC <20.6 cm), gestational diabetes, preeclampsia, hypertension, or severe anemia (blood hemoglobin level <70 g/L) at enrollment, were excluded from the study but were provided the standard of care nutritional treatment and were referred to a health facility clinician for medical management. Women who were participating in any other nutrition study or supplementary feeding program were also excluded from the study. Women who met the enrollment criteria were asked to undergo HIV testing, if they had not done so previously, as this is the standard of care in Malawi. If a

[2] The relationship between MUAC and weight, as observed in the Mamachiponde study, is plotted in **Figure 1**.

woman tested positive for HIV, the study nurse asked if she was taking antiretroviral treatment, and, if not, the mother was referred to the district clinic HIV counselors.

One enrollment criterion was modified during the course of the study. At the start of the Mamachiponde study, women below age 18 were excluded. This criterion was changed in November 2014 to include women 16 and 17 years of age due to the high rate of pregnant teenagers presenting to antenatal clinics who might benefit from the study. This change was reviewed by the Institutional Review Boards of the College of Medicine at the University of Malawi (Blantyre), Washington University (St. Louis), and California Polytechnic State University (San Luis Obispo), who all accepted the change and deemed that no changes in the consent content or consenting process were required.

Study Interventions

Two interventions, RUSF and CSB+ with UNIMMAP, were compared to the standard of care, which consisted of CSB+ with IFA. The food supplements were provided in biweekly rations of ten 250 g bottles of RUSF or 5 kg of CSB+. The RUSF provided 920 kcal/day, 36 g of protein/day, and approximately 200% of the recommended dietary allowance (RDA) for most micronutrients during pregnancy. The energy content of RUSF was designed to provide 450 kcal/day to support the increased energy needs during the third trimester of pregnancy plus an additional 470 kcal/day to support recovery from moderate malnutrition. The CSB+ with UNIMMAP treatment ration had fairly similar amounts of energy, protein, and micronutrients as the RUSF treatment (**Table 1**). The antenatal UNIMMAP micronutrient tablet contained 15 micronutrients (**Table 2**). The CSB+ with IFA treatment provided the same quantity of CSB+ as the CSB+ with UNIMMAP ration, but with a daily iron (60 mg) and folic acid (400 µg) tablet instead of a daily UNIMMAP tablet. The CSB+ formulation was "super cereal: CSB with sugar" (17).

Enrollment

Upon enrollment, the participant was interviewed. Demographic information was recorded, as was time of last menses and estimated date of delivery, which was established by the health clinic nurse at the first antenatal visit. Anemia was assessed by measuring hemoglobin; anthropometric measurements included current weight, height, MUAC, triceps skinfold thickness, and weight history (if available). BMI was calculated. If HIV testing results were available, the results were confirmed via medical records. For women not already tested for HIV, HIV status was determined after routine counseling by clinic voluntary counseling and testing counselors. Available medical records were reviewed, with attention to any current or previous pregnancy complications and medications.

Follow-Up

Enrolled women visited the clinic every 2 weeks for anthropometric measurements (weight, MUAC, and triceps skinfold thickness) and health checks (blood pressure, interim illness questions, FH measurement) and to receive their 2-week supply of treatment food/supplements. Women who achieved a MUAC ≥23.1 cm were considered "graduated." When MUAC remained ≥23.1 cm for two consecutive visits, the treatment food was no longer provided; however, women were given IFA supplements for the remainder of their pregnancy. After graduation, women were asked to visit the clinic every 4 weeks and were assessed for relapse. If relapse (MUAC ≥20.6 cm and ≤23.0 cm) occurred, mothers went back onto their assigned treatment regimen. If a woman did not recover prior to delivery, she was referred to Malawi's Health Sector Strategic Plan services after delivery. At each clinic visit, women were counseled not to share their food and advised to eat a balanced diet. Hemoglobin was measured at enrollment and

10 weeks later. Women who delivered before 10 weeks of treatment were not included in this analysis. Hemoglobin <110 g/L during pregnancy was considered anemic.

At the 6-week and 3-month postpartum visits, maternal weight and MUAC were measured and health checks were made on illnesses and medications taken. Infant weight, length, head circumference, and MUAC were also measured. In addition, at the 3-month visit, infant hemoglobin was measured.

Anthropometric Measurements

Anthropometric measurements were taken by trained study team members.

Adult weight was measured in kilograms, to the nearest 100 g, using a Detecto Slimpro scale (Webb City, MO, USA) or a Seca 803 Precision for Health scale (Hamburg, Germany); women removed their shoes and excess clothing, and wore only light clothing during weighing. Height was recorded in centimeters to the nearest tenth of a centimeter, using a Seca stadiometer (Birmingham, UK). MUAC was measured on the left arm in centimeters to the nearest tenth of a centimeter, twice, with a flexible measuring tape (TALC, Herts, UK), according to standard procedures; if the measurements differed by more than 1 mm, a third measurement was made and the two closest measurements were recorded and averaged.

For infants, recumbent length was measured (Seca 417 length board, Hamburg, Germany) to the nearest millimeter. Measurements were made in triplicate and averaged for analysis. Birth weight was made in duplicate (Adam Equipment digital scale, MTB20, CT, USA) to the nearest 10 g and averaged. If the two measurements differed by more than 10 g, a third was taken and the outlier eliminated. Head circumference was measured (Seca head circumference measuring band 212, Hamburg, Germany) to the nearest millimeter in duplicate and averaged. Efforts were made to minimize inter-observer bias by periodic inter-observer comparison and standardized training and technique.

FH was measured in the supine position with a non-elastic tape, measured to the nearest 0.5 cm as described by Westin (18). The number of centimeters measured was considered to be equivalent to gestational age in weeks. Malawian nurse-midwives were trained by a Malawian certified nurse trainer to measure FH and were inter-rater reliable to within 1.0 cm.

Hemoglobin Measurements

Hemoglobin levels were collected from the women at enrollment and after 10 weeks of treatment if the participant had not delivered. Hemoglobin was measured via finger stick using a portable photometer utilizing the cyanmethemoglobin method (Hemocue Hb 201+, Angelholm, Sweden). Hemoglobin levels of the infants were also measured at their 3-month follow-up. The infants were given heel pricks to collect blood for screening using the portable photometer.

Birth Measurements

A birth weight team was established, consisting of a research assistant (RA) for each clinic location, a birth weight coordinator, and the study team. When a woman enrolled in the study, the study team made a note in her maternal health passbook (a red “M”) to indicate that she was in the study. When she came to the clinic in labor and ready to deliver, the clinic nurse-midwife noted the red “M” in the passbook and identified the woman as a study participant. The nurse would then call the birth weight team to initiate arrangement for measurements. Study participants were continuously reminded at the health clinic about the importance of delivery at the health clinic with a trained professional. The participants were given mobile minutes if they presented at a clinic visit with a FH >26 cm and were urged to have someone call the birth weight team right away when they delivered. If a mother missed a clinic visit and had a FH >30

cm at the previous visit, the RA would go to the woman's home to see if she had delivered. If she had delivered, the RA requested the mother to return to the clinic for the infant to be measured. Only 7.4% of women delivered at home.

Sample Size, Randomization/Blinding

The sample size goal was estimated to be 1,800 mothers divided equally among the two treatment groups (RUSF and CSB+ with UNIMMAP) and the control group (CSB+ with IFA). This sample size allowed for 15% attrition, leaving a final sample size of 1,530 (510 per group) with a two-tailed significance of 0.05, power of 80%, with two group comparisons able to detect a difference of 50 g in birth weight between groups.

All participants were randomized to receive the RUSF, CSB+ with UNIMMAP, or CSB+ with IFA using a random number generator that prospectively assigned participant identification numbers to a treatment group in blocks of 60. Locally, since study participants like to have a choice in their treatment, the women were offered sealed envelopes to choose from; in each envelope, there was a pregnancy study number that was linked to the previously randomly assigned treatment. Because the RUSF was visually distinct from the CSB+, and the UNIMMAP tablets were visually distinct from the IFA tablets, neither the study subjects nor the research study team members working directly with participants were blinded. To minimize study personnel becoming aware of a participant's treatment, the study driver who dispensed the treatment food would look up each woman's study number to identify which treatment she would receive and placed it in a colored opaque bucket so that neither research team members nor other study participants could see which treatment group the woman was assigned to when she was in the clinic. Senior research team members and data entry and data analysis personnel were blinded to treatment group assignment.

Institutional Review Board Approvals and Ethics

Study team members attended each participating antenatal clinic site for subject recruitment on the designated antenatal clinic date each fortnight. All women attending the antenatal clinics were informed of the study and entry criteria in a group setting (after the morning song and education). Additionally, community health workers were trained in accurately measuring MUAC in adults and they screened pregnant women in their clinic catchment villages. If they identified a woman with a low MUAC, they provided her with a referral card with the next study clinic date. Women willing to be measured and potentially participate in the study were offered measurement of MUAC at the clinic by study staff. After determining eligibility by MUAC status, a woman was further screened for study eligibility. If the woman was determined to be eligible for the study, she was invited to participate in the study. A study nurse reviewed the study information with the woman, and, if the woman consented to participate, the subject either signed her name (if able to write) or placed her thumb on an inkpad and signed with a thumbprint.

Clinic site selection and permissions to conduct the study were obtained from each health district; quarterly reports were submitted and annual meetings were held to discuss study progress and any concerns. Approvals were also obtained from traditional authority leaders in each clinic region. The study team coordinated with the regional WFP personnel and provided quarterly reports to WFP on the number of women served at each clinic location. So that there would be no dual enrollment in both the WFP program and the research study, the study managed all supplementary feeding for pregnant women in study clinic locations.

The study was registered in ClinicalTrials.gov NCT02120599 and was approved by the Institutional Review Boards of Washington University (St. Louis), California Polytechnic State University (San Luis Obispo), and the College of Medicine at University of Malawi (Blantyre).

Data Analyses

Data were double entered and discrepancies resolved after examination of the data collection card. Data were analyzed using JMP Pro software (Version 12.1.0, SAS Institute, Cary, NC, USA). WHO's R macro (WHO Anthro version 3.2.2, January 2011; http://www.who.int/childgrowth/software/en/) was used to calculate children's anthropometric z-scores.

The participant flowchart is shown in **Figure 2**. Of the 2,284 pregnant women with MUAC ≤23.0 cm screened for the study, 456 were excluded. The most common reasons for study exclusion were being too young (under 16 years), suffering from severe acute malnutrition (MUAC <20.6 cm) or severe anemia (hemoglobin <70 g/L), and being too far along in the pregnancy (FH ≥35 cm). In addition, 19 women had multiple births. These women and their infants were excluded from all outcome analyses, but were included in the baseline analyses. An infant was considered to have died when his/her mother or health worker reported such.

An intention-to-treat analysis was used to compare all outcomes using analysis of variance (ANOVA) for continuous parameters and a chi-square test to compare categorical outcomes. Wilcoxon Rank Sum tests were performed if the normality requirement was not met and a Fisher's exact test was used if the expected cell count was less than five for categorical outcomes. For pairwise comparisons, connecting letters plots were created using Tukey-Kramer honest significance difference (HSD) tests.

Some women delivered before receiving their second treatment ration, raising the concern that they had not been treated long enough to observe a clinical effect. In a second analysis, the intention-to-treat analysis was repeated with these women excluded. Those women who delivered prior to receiving their second ration were also compared as a group to women who received two or more treatment rations.

In addition, a subgroup analysis was conducted among HIV-infected women and another analysis was conducted to compare HIV-infected women to women who were not HIV-infected.

A multiple linear regression was run to determine whether duration of treatment or treatment group had an effect on maternal weight gain up until final weight measurement. The equation for the regression line is as follows:

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 z + \beta_4 x_1 (z - \bar{z}) + \beta_5 x_2 (z - \bar{z})$$

where:

x_1 = 1 for RUSF, 0 for CSB+ with UNIMMAP, and −1 for CSB+ with IFA

x_2 = 0 for RUSF, 1 for CSB+ with UNIMMAP, and −1 for CSB+ with IFA

z = duration of treatment

We centered the numeric predictor, duration of treatment, to reduce collinearity in the model. A generalized linear model (binomial distribution with logit link, i.e., logistic regression) with the same predictor parameterization as shown above was used to determine whether duration of treatment or treatment group influenced the categorical response, stunting at birth. Partial F-tests or likelihood ratio tests (x^2) were first calculated to determine if treatment group or treatment duration had any association with the response variable through either the main effect or the interaction term. The null hypothesis used to test for the treatment group effect was H_0: $\beta_1 = \beta_2 = \beta_4 = \beta_5 = 0$ and for the duration of treatment

effect was $H_0: \beta_3 = \beta_4 = \beta_5 = 0$. $P<0.05$ was considered to be significant. If the treatment effect was found to be significant, tests to resolve the main effect of treatment and the treatment by duration of treatment interaction were each considered. For the main effect of treatment, the null hypothesis was $H_0: \beta_1 = \beta_2 = 0$ and for the interaction was $H_0: \beta_4 = \beta_5 = 0$. Similarly, if the duration of treatment effect was found to be significant, tests to resolve the main effect of duration of treatment and the treatment by duration of treatment interaction were each considered. For the main effect of duration of treatment, the null hypothesis was $H_0: \beta_3 = 0$ and for the interaction was $H_0: \beta_4 = \beta_5 = 0$ as above.

Results

Study Population

A total of 2,284 pregnant women with MUAC ≤23.0 cm were screened and evaluated for study enrollment, and 1,828 women met study inclusion criteria and were enrolled (**Figure 2**). The most common reasons for exclusion were being under 16 years of age, having severe acute malnutrition, having severe anemia, and being more than 35 weeks gestation. As is expected with randomization, maternal characteristics at enrollment were very similar across intervention groups (**Tables 3–5**).

On average at enrollment, the study women were 21.5 years of age (range 16–45 years) and for nearly half of the participants this was their first pregnancy. The majority of women completed 1–6 years of primary education, with 10% having no formal education. About 50% of the households had two or fewer adults and one or no child. Eighty-six percent of the mothers lived with the father of their infant (**Table 3**). In terms of household resources, thatch roofing and a borehole water source were most common. The majority of mothers did not have household livestock, radios, or bicycles. About 71% of the women were classified as severely food insecure. Only 2% of households had electricity (**Table 4**). None of these characteristics was different across intervention groups.

Women typically enrolled in the study toward the end of the second trimester, with an average FH of 22.6 cm (range 7.0–34.0 cm), BMI of 19.7 (range 15.24–24.05), and MUAC of 22.3 cm (range 20.6–23.0 cm) (**Table 5**). About 5% of women were of short stature, with a height of <145 cm. About 10% of women were HIV-infected. Twenty percent of women reported an unspecified illness in the previous 2 months; 25% reported taking medication currently, with antimalarial treatment being the most common. None of these characteristics was different across intervention groups at enrollment (**Table 5**).

Maternal Outcomes

On average, women received a total of 5.0 rations of the food intervention over a period of 11.4 weeks from enrollment until delivery. The weight gain analysis excluded 103 women who delivered before receiving their second treatment ration (n=1,646). Women in the RUSF group had the highest mean weight gain during treatment until final weight measurement (3.4 kg, 3.2 kg, 3.0 kg in the RUSF, CSB+ with IFA, and CSB+ with UNIMMAP groups, respectively, P=0.03) (**Table 6**). Of all participants who received their second treatment ration, 75% had low weekly weight gain during treatment until final weight measurement, defined as <454 g/week (19).

A multiple linear regression model was run to predict weight gain from the time treatment began until final weight measurement, using treatment group, duration of treatment (in weeks), and an interaction variable (treatment group * duration of treatment) as the independent variables in the model. The multiple linear regression model statistically significantly predicted gestational weight gain before delivery [F (5, 1633) =112.96, P<0.0001, adj. R^2=0.26. Partial F-tests for the treatment effect and duration of treatment were both significant [F (4, 1633) =2.53, P=0.0385 and F (3, 1633) =184.55, P<0.0001, respectively]. There was no significant evidence for a treatment by duration of treatment interaction [F (2, 1633) =0.06, P=0.9382]; however, the main effects for both treatment group and duration of treatment were significant [F (2, 1633) =5.01, P=0.0067 and F (1, 1633) =553.53, P<0.0001] (**Table 12**). The only statistically significant difference in mean weight gain was between the RUSF and CSB+ with UNIMMAP treatments. Women receiving the CSB+ with UNIMMAP treatment gained 0.41 fewer kg than those on RUSF, on average (95% CI: 0.10 to 0.70 kg). Regardless of treatment group, each additional week of treatment is associated with 0.21 additional kilogram of weight gain (95% CI: 0.20 to 0.23 kg).

Average final MUAC was 22.2 cm and was not different by treatment group (*P*=0.11). Change in MUAC was very close to 0 for all intervention groups and the variance was 4–10 times greater than the means (**Table 6**). The RUSF group had the greatest number of participants (35%) who attained MUAC >23.0 cm prior to delivery, followed by CSB+ with IFA (33%) and CSB+ with UNIMMAP (30%), but there were no differences between groups (*P*=0.14). Anemia was reduced 10 weeks after enrollment in all groups, from an average prevalence of 71% to 56% across the three intervention groups. Hemoglobin concentrations were not affected by the treatment type (**Table 6**).

Infant Outcomes

There were 1,467 live singleton births, 18 live twin pairs, and 1 live set of triplets. Among singleton births, 94% were measured within 24 hours and 98% were measured within 48 hours.

An estimate of extreme prematurity is delivery FH <28 cm (6). About 5% of deliveries occurred in women with FH <28 cm, and there were no differences by intervention group (**Table 6**).

On average, at birth, infants weighed 2.7 kg, with length of 47.1 cm, head circumference of 34.2 cm, and MUAC of 9.6 cm (**Table 7**). Almost 27% of all infants measured were born with birth weight <2.5 kg, with the RUSF and CSB+ with IFA groups having the lowest incidence of low birth weight (24% and 25%, respectively, compared to 32% in the CSB+ with UNIMMAP group; *P*=0.01). The CSB+ with IFA group had the lowest incidence of underweight (WAZ <−2 or birth weight <2.4 kg) infants at birth (17%, 18%, 24% in CSB+ with IFA, RUSF, and CSB+ with UNIMMAP, *P*=0.02) (**Table 8**). Infants in this study were small, with mean z-scores at birth near −1.3 for length-for-age and weight-for-age and −0.5 for weight-for-length (**Table 8**). There were 188 infants who had to be excluded from the weight-for-length analysis at birth because they were too short (<45.00 cm) for a WHO weight-for-length growth standard to be available. Although the linear and ponderal growth of infants born to women with moderate malnutrition during pregnancy were generally compromised, head circumference was not, with a mean z-score of 0.0 (**Table 8**).

A logistic regression was performed to ascertain the effects of the treatment regimen, the duration of treatment, and the interaction of treatment regimen and duration of treatment on the likelihood that a mother would not have an infant who was stunted at birth. The model was statistically significant, $X^2(5)=14.86$, *P*=0.01; however, results from likelihood ratio tests showed no evidence of a treatment effect [$X^2(4)=3.67$, *P*=0.3419]. There was evidence of a duration of treatment effect [$X^2(3)=12.37$, *P*=0.0062] through the main effect only [main effect $X^2(1)=11.18$, *P*=0.0008; interaction $X^2(2)=1.23$, *P*=0.5406]. The model showed that the odds of an infant not being stunted at birth increases 3.9% with each additional week the woman is on a treatment (95% CI: 1.59% to 6.34%) and that the odds of not having a stunted infant birth are three times greater among women who received the longest amount of treatment compared to those who had the shortest duration of treatment (95% CI: 1.6 to 5.8) (**Table 13**).

At 6 and 12 weeks after birth, no differences in infant anthropometry or hemoglobin were found among intervention groups (**Tables 10** and **11**).

Morbidity, Mortality, and Adverse Effects

There were no maternal deaths during the study. There were 71 infant deaths within the first 3 months of life, with no differences in mortality across treatment groups (*P*=0.71) (**Table 9**). About 2% of pregnancies were lost due to stillbirth or miscarriage. There were four stillbirths in both the RUSF and the CSB+ with IFA group, and 11 in the CSB+ with UNIMMAP group (*P*=0.07). The RUSF group was the only group in which there were intervention food intolerances, with six women reporting vomiting and

two women reporting diarrhea immediately after feeding; these women were transferred to non-study status and their data were not included in the analyses (**Figure 2**).

Analyses after Excluding Mothers Who Did Not Receive a Second Treatment Ration

There were 161 women who delivered before their return for their first follow-up visit or who received only one treatment ration. They were evenly distributed across the treatment groups. Such a short duration of treatment raised the concern that the intervention did not have the duration to affect the pregnancy outcomes. To address this concern, we carried out an analysis excluding these women (**Appendix A**). There were 103 women with one visit who had singleton births and were not lost to follow-up. The results for this subgroup analysis are remarkably similar to those in the intention-to-treat analyses and all differences identified in the intention-to-treat analyses remained. Among the subgroup analyses, only one additional difference between treatment groups was observed. The CSB+ with IFA group had fewer women with FH <28 cm within 14 days of delivery, 3% vs 6% for the CSB+ with UNIMMAP and RUSF groups (**Table 6A**, P=0.06); this finding was noted as a trend in the full sample analysis (**Table 6,** P=0.06).

An analysis comparing the 161 women who received fewer than 14 days of treatment with women who received at least 14 days of treatment was also completed (**Appendix B**). Women who did not receive a second treatment ration were less food insecure (**Table 4B**); had a higher BMI, FH, and hemoglobin level; and were less anemic at enrollment than women who received at least two treatment rations (**Table 5B**). The FH 14 days prior to delivery was less in women receiving one treatment ration (P<0.01), and a larger percent of the final FH of these women was <28 cm (P<0.01) (**Table 6B**). Infants born to these women had a lower birth weight by 100 g (P=0.02) and length by 0.4 cm (P=0.01) and were more likely to have a birth weight <2.5 kg (P=0.02) (**Table 7B**). The anthropometric z-scores of infants born to mothers receiving just one treatment ration also reflected that the infants were smaller (**Table 8B**). No differences were seen in maternal morbidity or lost pregnancies due to miscarriages or still births (**Table 9B**). The differences in weight and length seen at birth were also apparent at 3 months of life, but not at 6 weeks (**Tables 10B** and **11B**).

HIV-Infected Women

A subgroup analysis of the 194 HIV-infected women was also conducted (**Appendix C**). The number of HIV-infected participants in each treatment group was modest, but across the treatment groups, the HIV-infected women were similar in health and demographic characteristics upon enrollment to the study (**Tables 3C**, **4C**, and **5C**). Maternal outcomes were also similar between the treatment groups (**Table 6C**). Infant outcomes were also largely similar across treatment groups (**Tables 7C–11C**), with one exception: at 3 months, infants whose mothers received CSB+ with UNIMMAP had a larger MUAC compared to those whose mothers received RUSF (P=0.04) (**Table 11C**).

Results for HIV-infected and non-HIV-infected women were also compared (**Appendix D**). Those with HIV infection were, on average, 6 years older, lived in households with a greater number of individuals sleeping per room, and were less likely to be primagravid upon enrollment into the study (**Tables 3D** and **4D**). HIV-infected women also had, upon enrollment, a lower BMI, lower hemoglobin, and smaller triceps skinfold thickness and were more likely to be taking medications in the 14 days prior to enrollment (**Table 5D**). No significant differences between HIV-infected and non-HIV-infected participants were observed for weight gain from initiation of treatment until last clinic visit before delivery, final MUAC, or change in maternal MUAC from initiation of treatment to final MUAC;

however, HIV-infected women did have lower hemoglobin concentration than non-HIV-infected women ten weeks after enrollment ($P<0.01$, **Table 6D**). Birth weight and length were not affected by maternal HIV status, but head circumference at birth was smaller in HIV-exposed infants (**Tables 7D** and **8D**). At 6 weeks of life, HIV-exposed infants weighed less and had a smaller head circumference and a smaller MUAC (**Table 10D**). At 12 weeks, these differences persisted. In addition, HIV-exposed infants were shorter (**Table 11D**).

Discussion

In this randomized controlled supplementary feeding trial among pregnant women with moderate malnutrition in Malawi, women given RUSF gained more weight from initiation of treatment for moderate malnutrition until their final clinic visit than women given CSB+ with UNIMMAP, but there were no significant differences in weight gain between the standard of care (CSB+ with IFA) and the RUSF group or between the standard of care and the CSB+ with UNIMMAP group. In all groups, maternal rates of weight gain were very low: 75% of participants, who received a second treatment ration, had an average weight gain from the time of treatment initiation until final weight measurement of <454 g/week, which is considered abnormally low weight gain during pregnancy (19).

Mean birth weights and lengths were not affected by type of treatment provided to women during pregnancy, and mean LAZ at birth was −1.3, well below what might be expected in a well-nourished population. The duration of treatment was associated with a reduction in the likelihood a woman would have a stunted infant at birth. When comparing women who had the longest duration of treatment to those with the shortest duration of treatment, the odds for the women with the longest duration of treatment were three times greater for not having a stunted infant at birth. The duration of the treatment ranged from 1 week to 28.6 weeks, but was on average 9.4 weeks.

The study is limited in that no true control group was included; all women received some supplementary feeding. This was because the national guidelines in Malawi prescribe that moderately malnourished pregnant women receive supplemental food, although this is rarely done in practice. Thus, it would be unethical not to offer these women some supplementary food, and, therefore, these data do not inform us as to the birth outcomes in untreated moderately malnourished pregnant women. Additionally, data regarding gestational age could have been obtained if ultrasound technology had been employed to assess the subjects. Use of ultrasound is not routine in Malawi (or in most rural clinics in Africa). Our goal in this study was to work within the context of current antenatal care in rural Malawi; thus, we did not institute ultrasound evaluation.

Malawi is a low-income, food-insecure country with high rates of childhood stunting (42.4%) and maternal anemia (47.3%) and sub-clinical vitamin A deficiency (59.2%) (20). The study clinics were located mostly in areas where subsistence farming is the primary livelihood. There was a particularly poor farming production season during the study due to flooding and drought, which likely contributed to increased maternal malnutrition (20). Care should be exercised in generalizing our data to populations that live in dissimilar settings or consume diets other than one that is corn-based.

The 161 women who delivered prior to receiving their second treatment ration represent women who enrolled in the study later in their pregnancies, as well as women who delivered prematurely. The observed outcomes among these women were what might be expected, that is, their infants were smaller at birth than women who received more treatment rations, but infant weights and lengths at 3 months were similar to infants born to women who received more than one treatment ration. A small effect of 0.4 cm was observed for birth length when comparing those who received food for at least 14 days to those who were only on treatment fewer than 14 days; however, no effect between groups was observed when analyzed by treatment group.

Among HIV-infected women, there was no observed effect of any one of the treatment groups compared to another, but the sample size of 185 women is quite small to detect such differences. The HIV-infected study participants were clearly different from non-HIV-infected study participants. The HIV-infected women were more likely to be older and multiparous and to have more children in their household. The

HIV-infected women were also more likely to be in receipt of regular health care visits and on medication given their HIV status. Their malnutrition was probably due in large part to their chronic illness. The birth anthropometry of the infants born to women with HIV was similar to that of infants born to uninfected women; however, it was observed that the HIV-exposed infant did have a 0.3 cm smaller head circumference at birth. It is also notable that growth faltering was observed in HIV-exposed infants after birth.

In the past 50 years, both observational and experimental studies have been conducted assessing the effect of food supplementation or dietary intake on neonatal outcomes (21). Antenatal micronutrient and macronutrient supplementation have both been extensively studied as a means to improve pregnancy outcomes. Multiple micronutrient supplementation in pregnancy has been shown to decrease small-for-gestational-age (SGA) births by 11%–13% (22). In a pooled analysis of 15 trials, Kawai et al. (22) found that maternal multiple micronutrient supplementation increased birth weight (pooled mean difference: 44 g; 95% CI: 28–60) and reduced low birth weight infants (pooled relative risk [RR]: 0.86, 95% CI: 0.79–0.93) compared with IFA supplementation. Although multiple micronutrient supplementation led to larger babies, it showed no effect on preterm delivery (pooled RR: 0.99; 95% CI: 0.95–1.03) (22). A multiple micronutrient supplementation trial in rural Bangladesh, however, showed a significant reduction in risk for preterm birth (RR, 0.85; 95% CI, 0.80–0.91; P=0.001) and low birth weight (RR, 0.88; 95% CI, 0.85–0.91; $P < 0.001$) among babies born in the intervention group compared to the IFA control group, while detecting little difference in the risk for babies born SGA, accrediting observed gains in size to longer gestation (23). Alternately, in a large trial among rural Vietnamese women that involved pre-pregnancy provision of weekly IFA, provision of multiple micronutrient supplements or folic acid alone, and provision of IFA during pregnancy, no difference was observed between groups in birth weight, SGA, low birth weight, or preterm delivery (24).

Balanced protein-energy supplements have shown the most persuasive evidence for the prevention of adverse neonatal outcomes, reducing the rate of SGA births by 44% and the prevalence of low birth weight by 32% (25). The effects of balanced protein-energy supplements have been evaluated in a variety of reviews and meta-analyses. A recent review reported increased birth weight by about 75 g, comparable to findings reported by Imdad et al.(mean difference 73 g; 95% CI: 30–117) and in the LiST review (mean difference 59 g; 95% CI: 33–86) (25-27). Effects on birth length were less significant, with a reported average increase of about 0.16 cm.

This is the first study to the authors' knowledge to investigate the impact on birth outcomes of treating moderately malnourished pregnant women, defined as MUAC $\geq$20.6 cm and MUAC $\leq$23.0 cm, with different treatment regimens. However, studies have explored potential effect modifiers, such as the nutritional status of the mothers on the magnitude of the effect of supplementation during pregnancy. These findings on micronutrient and macronutrient supplementation show that the benefits are most pronounced in mothers who were malnourished or anemic and in younger and first-time mothers (25).

A randomized control trial in Burkina Faso showed a significant effect of a fortified food supplement plus multiple micronutrient supplementation on increased birth length with a small, insignificant effect on birth weight (28). In the sub-analysis of participants who were defined as nutritionally inadequate or underweight at enrollment, treatment was even more efficacious for birth length, and an insignificant increase in birth weight of 111 g compared to the control group was reported. The improved birth length was an unanticipated outcome, as previous studies, such as a clinical trial in the Gambia, revealed a significant positive effect on birth weight with nonsignificant effects on birth length (29). The investigators (Huybregts et al.) speculate on potential reasons for this discrepancy, suggestive of the higher energy content in the Gambia supplement that was established for the study's target of exclusively

undernourished mothers (28). The improved birth length could also possibly be attributed to the combination of a fortified food supplement with multiple micronutrient supplementation, as micronutrient supplementation alone has been found to reduce the incidence of SGA babies by 9% (30). A LNS trial in rural Bangladesh showed comparable birth weight effects to the Gambia study, finding a significant effect on mean birth weight (2,629 g compared with 2,588 g, *P*=0.006), also reporting a 25% reduction of newborn stunting, as well as trend in effect on low birth weight infants (36.0% compared with 39.5%) among women in the treatment group with LNS (118 kcal and 22 vitamins and minerals) versus the group that received IFA only (31). Unlike the study in Burkina Faso, the subgroup analysis of undernourished mothers (low BMI participants) for the trial in Bangladesh did not show improved efficacy with the treatment. The study in Bangladesh did, however, perform a subgroup analysis based on severity of household food insecurity and revealed that, for the participants determined to have levels of severe, moderate, or mild food insecurity, the treatment had a larger effect on mean birth length and decreased prevalence of stunting at birth than for the participants identified as food secure (31). A standardized criterion for defining undernourished women has not been consistently used in these previous studies; consequently, the mixed effects observed in the various interventions have poor transferability.

In the current study, in spite of receiving a generous ration of supplementary food for about 9.4 weeks, only about one-third of women increased their MUAC to >23.0 cm. Change in MUAC also did not correlate well with maternal weight gain. This indicates MUAC should not be used as a criterion upon which to stop feeding during the treatment of malnourished pregnant women.

Maternal undernutrition, especially during the second and third trimesters, is associated with reduced birth weight and length (21), and was observed in the present study. The mean birth weight and length was equivalent to being ≤15 percentile weight- and length-for-age on WHO growth curves, with 20%–23% of infants stunted or underweight at birth. Compared with national statistics of 47% stunting in under-5s (32), in this population of undernourished pregnant women, it appears that approximately 50% of stunting begins in utero and is evident at birth. Along with increased risks for intrauterine growth retardation, low birth weight babies, and preterm deliveries, the consequences of undernutrition during pregnancy (33) can have lifelong implications of poor cognition, academic performance, and professional achievement, and lower wages as adults (34) In addition, poor nutritional and socioeconomic status during pregnancy affects growth and development in subsequent generations (35,36).

Our study provided no evidence that the 79 mg of iron provided in the standard of care treatment (CSB+ with IFA supplement) resulted in higher hemoglobin and less anemia than a more physiologically appropriate iron dose of 45 g provided in the CSB+ with UNIMMAP supplement. Certainly among moderately malnourished pregnant women in the developing world, provision of some iron supplements prenatally is indicated.

Van den Broek reported 57% of 4,646 pregnant women in southern Malawi were anemic (3); the rate of anemia in this study population of pregnant women with moderate malnutrition was 14 percentage points higher. Along with a diet low in bioavailable iron sources and a physiological state that increases the iron requirement for increased red blood cell production; endemic malaria may be a contributing factor to the high levels of anemia. Anemia during pregnancy also contributes to low birth weight, intrauterine growth retardation, preterm deliveries (37), and infant mortality (38). Worldwide, iron deficiency is the most common nutrient deficiency among pregnant women (39); it accounts for about 50% of the cases of anemia globally (40). It is likely that the iron stores of these women were low before pregnancy and made worse with the additional demands during pregnancy. It is difficult to replete iron stores once pregnancy has begun (41), so that may be partly responsible for less than half of the women recovering from anemia during the study in spite of high iron doses.

In the current study, there was an increase in hemoglobin across all treatment groups from study entry until 10 weeks later. All treatment regimens in this study included generous amounts of iron. However, on average, across treatment groups, hemoglobin levels in the women who had not delivered were just 5 g/L higher 10 weeks after enrollment. If the anemia was primarily the result of iron deficiency, one might have expected larger increases, especially in the CSB+ with IFA group. At 3 months of age, infants had, on average, a hemoglobin of 99 g/L, about 15 g/L lower than North American children. Children born to mothers with inadequate iron stores are at increased risk for anemia and have a higher risk of lower cognitive, motor, and socioeconomic development skills since iron is necessary for neurodevelopment and transporting oxygen to the brain (42).

In this study, the size of the supplemental ration was substantial and there were no indications that compliance was poor; still, 22% of newborns were stunted. It seems clear that food and micronutrients alone were not enough in the rural Malawian context to affect better growth in utero. The relatively modest benefits seen from food and micronutrient supplementation prompt a renewed focus on the paradigm that a multitude of domains, such as diet, inflammation, gut health, and epigenetics, affect growth in utero (43). Research on some of these domains has been conducted on pregnant women, most notably, malaria and other interventions against infectious disease; while these studies have helped reduce the risk of prematurity, fetal growth stunting, and SGA birth, their impact has also been modest (44,45). Interventions that include a combination of both nutrition-specific and nutrition-sensitive interventions to affect multiple domains may be necessary to improve growth in utero. Trials exploring this issue should be given high priority in the future.

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Tables and Figures

Table 1. Nutrient content of supplementary foods

Nutrient	RUSF[1] Amount (% RDA)	CSB+ with UNIMMAP[2] Amount (% RDA)	CSB+ with IFA[3] Amount (% RDA)	Pregnancy, aged 19–30 years RDA	Pregnancy, aged 19–30 years Tolerable upper limit
energy, kcal	920	893	893		
protein, g	36	33	33		
α-linolenic, g (Omega 3)	2.3 (161)	0.0 (0)	0.0 (0)	1.4	
linoleic, g (Omega 6)	14.0 (107)	0.0 (0)	0.0 (0)	13	
Docosahexaenoic acid, g	211	0	0		
Eicosapentaenoic acid, g	43	0	0		
Vitamin A, ug	2628 (341)	3210 (417)	2410 (312)	770	3000
Vitamin B1 (thiamine), mg	3.2 (228)	1.7 (121.5)	0.3 (20)	1.4	
Vitamin B2 (riboflavin), mg	3.8 (270)	4.7 (335)	3.3 (235)	1.4	
Niacin (B3), mg	35.0 (194)	36.8 (204)	18.8 (104)	18	35
Vitamin B6, mg	4.0 (210)	5.9 (198)	4.0 (210)	1.9	100
Vitamin B12, ug	5.5 (262)	7.3 (253)	4.7 (181)	2.6	
Folic acid, ug	574 (143)	659 (165)	659 (163)	400	1000
Vitamin C, mg	170 (200)	281 (331)	211 (249)	85	2000
Vitamin D, ug	30 (200)	31 (206)	25 (169)	15	100
Vitamin E, mg	39 (261)	30 (197)	20 (130)	15	1000
Vitamin K, ug	192 (213)	71 (78)	71 (78)	90	
Iodine, ug	300 (136)	244 (170)	94 (43)	220	1100
Copper, mg	2.4 (240)	2 (200)	0 (0)	1.0	10.0
Iron, mg	45 (170)	45 (181)	79 (292)	27	45
Zinc, mg	24.6 (223)	26.8 (243)	11.8 (107)	11	40
Magnesium, mg	327 (93)	400 (114)	400 (114)	350	350
Calcium, mg	1830 (183)	851 (85)	851 (85)	1000	2500
Selenium, ug	123 (205)	65 (108)	0 (0)	60	400

[1] Assumes a daily portion of 175 g RUSF
[2] Assumes daily portion of 235 g CSB+/day with UNIMMAP.
[3] Assumes a daily portion of 235 g CSB+/day plus iron (60 mg) and folic acid (400 mcg).

Table 2. Content of UNU/UNICEF/WHO antenatal micronutrient supplement (UNIMMAP)

	UNIMMAP	RDA
Vitamin A, µg	800	770
Vitamin D, µg	5	15
Vitamin E, µg	10	15
Vitamin B1 (thiamine), mg	1.4	1.4
Vitamin B2 (riboflavin), mg	1.4	1.4
Vitamin B6, mg	1.9	1.9
Vitamin B12, µg	2.6	2.6
Folic acid, µg	400	400
Niacin, mg	18	18
Vitamin C	70	85
Iron, mg	30	27
Zinc, mg	15	11
Copper, mg	2	1
Selenium, µg	65	60
Iodine, µg	150	220

Figure 1. Change in MUAC by treatment group

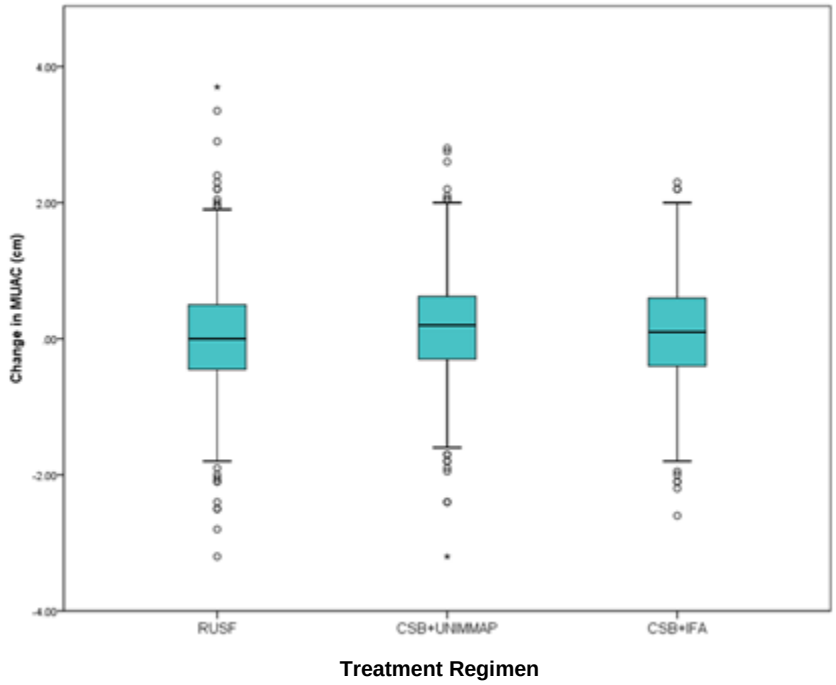
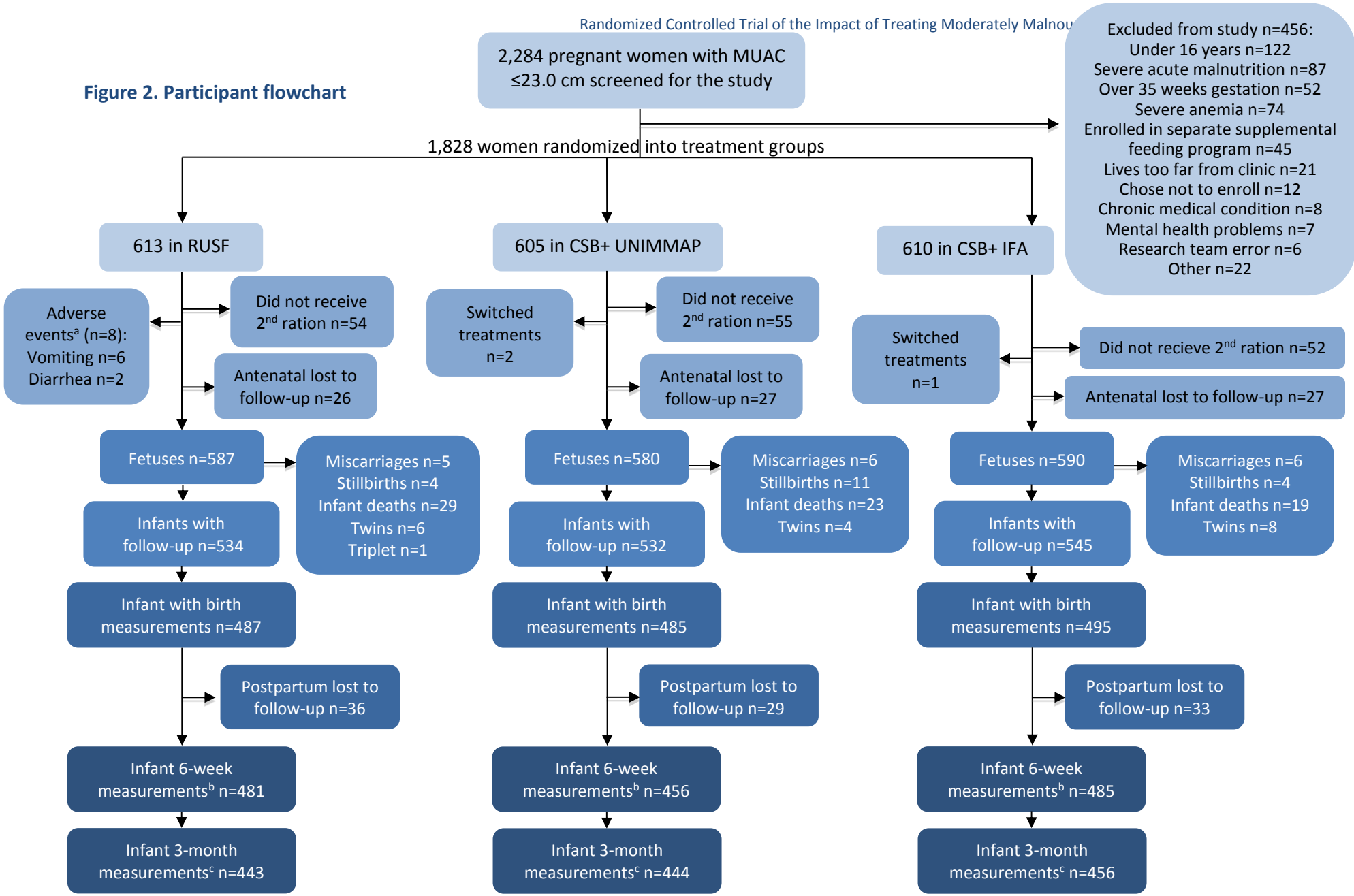


Figure 2. Participant flowchart



[a] Mothers in the RUSF treatment group experiencing adverse events were switched to non-study.

[b] Infant 6-week measurements include infants who were not included in birth measurements but came back for 6-week follow-up measurements.

[c] Infant 3-month measurements include infants who were not included in birth measurements and/or the 6-week measurements but who came back for the 3-month follow-up measurements.

Table 3. Demographic characteristics of study participants at enrollment, by treatment group

Characteristic	RUSF n=613	CSB+ with UNIMMAP n=605	CSB+ with IFA n=610	*P*-value
Age (years)	21.5 ± 5.4	21.3 ± 5.0	21.9 ± 5.5	0.21
First pregnancy	300 (49)	285 (47)	268 (44)	0.20
Education				0.89
None	64 (10)	61 (10)	71 (12)	
1–3	94 (15)	102 (17)	89 (15)	
4–6	224 (37)	218 (36)	231 (38)	
7–8	148 (24)	158 (26)	147 (24)	
Secondary	79 (13)	63 (10)	69 (11)	
Tertiary	4 (1)	3 (1)	2 (0.3)	
Adults in household	2.3 ± 0.9	2.3 ± 0.8	2.2 ± 0.8	0.55
Children in household	1.2 ± 1.5	1.2 ± 1.5	1.2 ± 1.5	0.39
Mother lives with infant's father	527 (86)	520 (86)	518 (85)	0.78

N=1,828 women.

Cells contain mean ± SD or n (%).

Table 4. Household resources of study participants at enrollment, by treatment group

Characteristic	RUSF n=613	CSB+ with UNIMMAP n=605	CSB+ with IFA n=610	*P*-value
Roof type				0.39
Thatch	495 (81)	468 (77)	499 (82)	
Metal	117 (19)	136 (23)	110 (18)	
Clean water source used				
Borehole	430 (70)	425 (70)	438 (72)	0.78
Tap	73 (12)	69 (11)	68 (11)	0.91
Animals kept in house				
Guinea fowl/chicken	152 (25)	178 (29)	180 (29)	0.12
Goat/pig	57 (9)	67 (11)	58 (10)	0.53
Home with radio	221 (36)	250 (41)	225 (37)	0.13
Home with bicycle	224 (36)	261 (43)	278 (46)	0.55
Home with electricity	17 (3)	13 (2)	15 (2)	0.78
Number of people sleeping in the same room as mother	2.3 ± 0.8	2.4 ± 0.8	2.4 ± 0.8	0.10
Household food insecurity				0.14
Secure	25 (4)	29 (5)	33 (5)	
Mild	23 (4)	25 (4)	29 (5)	
Moderate	115 (19)	123 (20)	132 (22)	
Severe	450 (73)	427 (71)	416 (68)	

N=1,828 women.

Cells contain mean ± SD or n (%).

Table 5. Clinical and nutritional status of study participants at enrollment, by treatment group

Characteristic	RUSF n=613	CSB+ with UNIMMAP n=605	CSB+ with IFA n=610	*P*-value
BMI	19.6 ± 1.4	19.8 ± 1.3	19.7 ± 1.3	0.35
MUAC (cm)	22.3 ± 0.6	22.3 ± 0.6	22.3 ± 0.6	0.56
Stature <145 cm	27 (4)	34 (6)	25 (4)	0.42
Hemoglobin (g/L)	102 ± 16	101 ± 15	100 ± 14	0.29
HIV-infected	64 (10)	60 (10)	70 (11)	0.67
Took medications in the 14 days prior to enrollment	149 (24)	149 (25)	156 (26)	0.87
Mother's report of any illness in previous 2 months	123 (20)	127 (21)	120 (20)	0.84
Triceps skinfold (mm)	9.3 ± 2.3	9.4 ± 2.3	9.2 ± 2.3	0.24
FH (cm)	22.3 ± 5.7	22.6 ± 5.3	22.8 ± 5.4	0.21

N=1,828 women.

Cells contain mean ± SD or n (%).

Table 6. Maternal outcomes of singleton pregnancies, by treatment group

Characteristic	RUSF n=579	CSB+ with UNIMMAP n=580	CSB+ with IFA n=590	*P*-value[2]
Weight gain from enrollment to final measurement (kg)[1]	3.4 ± 2.6[a]	3.0 ± 2.2[b]	3.2 ± 2.4[a,b]	0.03
Time from enrollment to delivery (weeks)	11.7 ± 6.6	11.1 ± 6.4	11.4 ± 6.3	0.26
Treatment rations received	4.9 ± 2.9	4.9 ± 2.8	5.0 ± 2.8	0.73
Delivery before receiving second treatment ration	32 (6)	40 (7)	31 (5)	0.53
Weight gain <454 g/week[1]	403 (74)	424 (79)	408 (73)	0.42
Change in MUAC	0.04 ± 0.9	0.2 ± 0.8	0.1 ± 0.8	0.11
Final MUAC (cm)	22.2 ± 1.0	22.1 ± 0.9	22.2 ± 0.9	0.11
Hemoglobin 10 weeks after enrollment (g/L)[3]	104 ± 15	108 ± 16	107 ± 15	0.07
Final FH (cm)	31.2 ± 2.6	31.0 ± 2.6	31.4 ± 2.2	0.12
Final FH <28 cm	33 (6)	39 (6)	20 (3)	0.06

N= 1,749 women.

Cells contain mean ± SD or n (%).

[1] Weight gain analysis includes only women on treatment for at least 14 days; 103 women with one visit who had singleton births and were not lost to follow-up were excluded from this analysis. RUSF n=547, CSB+ with UNIMMAP n=540, and CSB+ with IFA n=559.

[2] For *P*-values <0.05, values labeled with the same superscript are not significantly different; for example, values labeled “a” and “b” are different, but values labeled “a” and “a,b” are not.

[3] These measures were taken only in women whose pregnancy extended at least 10 weeks after enrollment; RUSF n=245, CSB+ with UNIMMAP n=206, CSB+ with IFA n=225, for a total of 676.

Table 7. Birth outcomes of singleton pregnancies, by treatment group

Characteristic	RUSF n=487	CSB+ with UNIMMAP n=485	CSB+ with IFA n=495	*P*-value
Birth length (cm)	47.1 ± 2.2	47.0 ± 2.3	47.1 ± 2.2	0.75
Birth weight (kg)	2.8 ± 0.4	2.7 ± 0.4	2.7 ± 0.4	0.86
Birth head circumference (cm)	34.3 ± 1.6	34.1 ± 1.5	34.3 ± 1.6	0.13
Birth MUAC (cm)	9.6 ± 0.9	9.5 ± 0.9	9.6 ± 0.8	0.12

N= 1,467 infants.

Cells contain mean ± SD or n (%).

Table 8. Birth z-scores of singleton pregnancies, by treatment group

Characteristic	RUSF n=487	CSB+ with UNIMMAP n=485	CSB+ with IFA n=495	*P*-value[1]
WAZ	−1.2 ± 1.0	−1.3 ± 1.0	−1.2 ± 0.9	0.29
LAZ	−1.3 ± 1.2	−1.3 ± 1.2	−1.3 ± 1.2	0.66
Weight-for-length z-score[2] (WLZ)	−0.4 ± 1.0	−0.5 ± 1.1	−0.5 ±1.0	0.33
Head circumference-for-age z-score (HCZ)	0.1 ± 1.3	−0.5 ± 1.2	−0.1 ± 1.3	0.10
Underweight (WAZ <−2)	89 (18)[a,b]	110 (24)[a]	81 (17)[b]	0.02
Stunted (LAZ <−2)	107 (22)	116 (24)	101 (20)	0.32
Wasted (WLZ <−2)[2]	18 (4)	25 (6)	23 (6)	0.46
Small HCZ (HCZ <−2)	27 (6)	18 (4)	16 (3)	0.19

N= 1,467 infants.

Cells contain mean ± SD or n (%).

[1] For *P*-values <0.05, values labeled with the same superscript are not significantly different; for example, values labeled “a” and “b” are different, but values labeled “a” and “a,b” are not.

[2] 188 infants were excluded from WLZ analysis because they were too short (<45.00 cm); RUSF n=424; CSB+ with UNIMMAP+ n=417; CSB+ with IFA n=438.

Table 9. Infant and maternal morbidity, mortality, and loss to follow-up, by treatment group

Characteristic	RUSF n=613 women n=587 infants	CSB+ with UNIMMAP n=605 women n=580 infants	CSB+ with IFA n=610 women n=590 infants	*P*-value
Infant death[1]	29 (5)	23 (4)	19 (3)	0.71
Lost pregnancy type				
Miscarriage	5 (0.8)	6 (1)	6 (1)	0.94
Stillbirth	4 (0.7)	11 (2)	4 (0.7)	0.07
Maternal antenatal lost to follow-up	26 (4)	27 (5)	27 (4)	0.99
Maternal postnatal lost to follow-up	36 (6)	29 (5)	33 (5)	0.71

N=1,828 women. N=1,757 infants.

Cells contain n (%).

[1] "Infant death" is defined as death reported by mother or local health workers before 12 weeks.

Table 10. Infant anthropometric outcomes at 6 weeks of age, by treatment group

Characteristic	RUSF n=481	CSB+ with UNIMMAP n=456	CSB+ with IFA n=485	*P*-value
Length (cm)	53.8 ± 2.3	53.6 ± 2.6	53.9 ± 2.4	0.13
Weight (kg)	4.4 ± 0.6	4.4 ± 0.7	4.4 ± 0.6	0.70
Head circumference (cm)	38.1 ± 1.4	38.0 ± 1.5	38.0 ± 1.4	0.60
MUAC (cm)	11.9 ± 1.0	11.8 ± 1.1	11.9 ± 1.1	0.67

N=1,422 infants.

Table 11. Infant anthropometric and clinical outcomes at 3 months of age, by treatment group

Characteristic	RUSF n=443	CSB+ with UNIMMAP n=444	CSB+ with IFA n=456	*P*-value
Length (cm)	58.2 ± 2.5	58.2 ± 2.6	54.4 ± 2.5	0.67
Weight (kg)	5.5 ± 0.7	5.6 ± 0.8	5.5 ± 0.8	0.62
Head circumference (cm)	40.4 ± 1.6	40.3 ± 1.4	40.3 ± 1.5	0.35
MUAC (cm)	13.0 ± 1.1	13.1 ± 1.1	13.0 ± 1.2	0.63
Hemoglobin (g/L)	99 ± 14	98 ± 16	100 ± 15	0.25

N=1,343 infants.

Cells contain mean ± SD.

Table 12. Summary of multiple regression analysis of treatment regimen and duration of treatment on maternal weight gain before delivery in moderately malnourished pregnant women[1]

Variable	B[2]	SE_B[3]	*P*-value
Intercept	1.00	0.10	<0.001
Treatment regimen (RUSF)	0.20	0.07	<0.01
Treatment regimen (CSB+ with UNIMMAP)	-0.21	0.07	<0.01
Treatment regimen (CSB+ with IFA)	*0.01*	*0.07*	*0.93*
Duration of treatment (in weeks)	0.21	0.00	<0.001
Treatment regimen (RUSF) * (Duration of treatment −9.44)[4]	0.00	0.01	0.98
Treatment regimen (CSB+ with UNIMMAP) *(Duration of treatment −9.44)[4]	-0.00	0.01	0.75
*Treatment regimen (CSB+ with IFA) * (Duration of treatment* −9.44)[4]	*0.00*	*0.01*	*0.77*

[1] Italicized rows are included for the reader's convenience as the parameter estimates are constrained by model parameterization (sum-to-zero coding). The italicized estimates are computed as minus the sum of the other estimates for the main effect and interaction, respectively.

[2] B = unstandardized regression coefficient. Using the sum-to-zero coding, these main effect values estimate and test effects relative to the overall mean weight gain at the mean duration of treatment. The interaction estimates compare treatment deviations from the overall linear relationship between duration of treatment and weight gain.

[3] SE_B = standard error of the coefficient.

[4] Duration was centered in the model for the treatment interactions; 9.44 weeks is the mean treatment duration.

Table 13. Logistic regression predicting likelihood of infant stunting at birth based on treatment regimen, duration of treatment, and treatment regimen * duration of treatment[1]

Variable	B[2]	SE_B[3]	Wald Chi-Square	*P*-value	Odds Ratio
Intercept	0.86	0.12	50.18	<0.001	
Treatment regimen (RUSF)	0.00	0.10	0.00	0.98	
Treatment regimen (CSB+ with UNIMMAP)	−0.12	0.10	1.65	0.20	
Treatment regimen (CSB+ with IFA)	*0.11*	*0.10*	*1.54*	*0.21*	
Duration of treatment (in weeks)	0.04	0.02	10.82	0.00	1.04
Treatment regimen (RUSF) *(Duration of treatment −9.44)	−0.02	0.02	0.91	0.34	
Treatment regimen (CSB+ with UNIMMAP) * (Duration of treatment −9.44)[4]	0.02	0.02	0.90	0.34	
*Treatment regimen (CSB+ with IFA) *(Duration of treatment* −9.44)[4]	*−0.00*	*0.02*	*0.00*	*0.99*	

[1] Italicized rows are included for the reader's convenience as the parameter estimates are constrained by model parameterization (sum-to-zero coding). The italicized estimates are computed as minus the sum of the other estimates for the main effect and interaction, respectively.

[2] B = unstandardized regression coefficient. Using the sum-to-zero coding, these main effect values estimate and test effects relative to the overall log-odds of stunting at the mean duration of treatment. The interaction estimates compare treatment deviations from the overall logistic relationship between duration of treatment and stunting.

[3] SE_B = standard error of the coefficient.

[4] Duration was centered in the model for the treatment interactions; 9.44 weeks is the mean treatment duration.

Appendix A. Analyses after Excluding Women Who Did Not Receive a Second Treatment Ration

Table 3A. Demographics characteristics for women treated at least 14 days, by treatment group

Characteristic	RUSF n=559	CSB+ with UNIMMAP n=550	CSB+ with IFA n=558	*P*-value
Age (years)	21.4 ± 5.2	21.3 ± 5.0	21.8 ± 5.5	0.18
First pregnancy	276 (49)	262 (48)	245 (44)	0.17
Education				0.83
None	57 (10)	53 (10)	66 (12)	
1–3	88 (16)	93 (17)	80 (14)	
4–6	201 (36)	206 (38)	213 (38)	
7–8	139 (25)	141 (26)	132 (24)	
Secondary	70 (12)	54 (10)	64 (11)	
Tertiary	4 (0.7)	3 (0.5)	2 (0.4)	
Adults in household	2.3 ± 0.9	2.3 ± 1.0	2.2 ± 0.8	0.62
Children in household	1.2 ± 1.5	1.2 ± 1.7	1.3 ± 1.5	0.32
Mother lives with infant's father	479 (86)	469 (85)	476 (85)	0.96

Table 4A. Household resources for women treated at least 14 days, by treatment group

Characteristic	RUSF n=559	CSB+ with UNIMMAP n=550	CSB+ with IFA n=558	*P*-value
Roof Type				0.53
Thatch	451 (81)	421 (77)	453 (81)	
Metal	107 (19)	128 (23)	104 (19)	
Clean water source used				
Borehole	395 (71)	388 (71)	401 (72)	0.87
Tap	66 (12)	60 (11)	64 (12)	0.89
Animals kept in house				
Guinea fowl/chicken	140 (25)	158 (29)	163 (29)	0.21
Goat/pig	54 (10)	58 (11)	51 (9)	0.73
Home with radio	200 (36)	225 (41)	210 (38)	0.21
Home with bicycle	236 (42)	230 (42)	260 (47)	0.20
Home with electricity	15 (3)	12 (2)	14 (3)	0.86
Number of people sleeping in the same room as mother	2.3 ± 0.7	2.4 ± 0.8	2.4 ± 0.8	0.15
Household food insecurity				0.25
Secure	23 (4)	27 (5)	27 (5)	
Mild	19 (3)	21 (4)	25 (5)	
Moderate	103 (18)	109 (20)	121 (22)	
Severe	414 (74)	392 (71)	385 (69)	

N=1,667 women.

Cells contain mean ± SD or n (%).

Table 5A. Clinical and nutritional status upon enrollment for women treated at least 14 days, by treatment group

Characteristic	RUSF n=559	CSB+ with UNIMMAP n=550	CSB+ with IFA n=558	*P*-value
BMI	19.6 ± 1.4	19.7 ± 1.3	19.6 ± 1.3	0.36
MUAC (cm)	22.3 ± 0.6	22.3 ± 0.6	22.3 ± 0.6	0.31
Stature <145 cm	27 (5)	30 (6)	25 (5)	0.37
Hemoglobin (g/L)	101 ± 15	101 ± 15	100 ± 14	0.25
HI- infected	60 (11)	56 (10)	65 (12)	0.73
Took medications in the 14 days prior to enrollment	136 (24)	135 (25)	138 (25)	0.99
Mother's report of any illness in previous 2 months	110 (20)	117 (21)	112 (20)	0.79
Triceps skinfold (mm)	9.3 ± 2.3	9.4 ± 2.3	9.2 ± 2.3	0.21
FH (cm)	21.6 ± 5.5	22.1 ± 5.1	22.3 ± 5.2	0.08

N=1,667 women.

Cells contain mean ± SD or n (%).

Table 6A. Maternal outcomes of singleton pregnancy women treated at least 14 days, by treatment group

Characteristic	RUSF n=547	CSB+ with UNIMMAP n=540	CSB+ with IFA n=559	*P*-value
Weight gain from enrollment to final measurement (kg)	3.4 ± 2.6[a]	3.0 ± 2.2[b]	3.2 ± 2.4[a,b]	0.03[1]
Time from enrollment to delivery (weeks)	12.4 ± 6.2	11.8 ± 6.0	12.0 ± 5.9	0.31
Treatment rations received	5.1 ± 2.8	5.2 ± 2.7	5.3 ± 2.7	0.79
Weight gain <454 g/week	403 (74)	424 (79)	408 (73)	0.42
Change in MUAC	.05 ± 0.9	0.2 ± 0.8	0.1 ± 0.8	0.09
MUAC (cm)	22.2 ± 1.0	22.1 ± 0.9	22.2 ± 0.9	0.12
Hemoglobin 10 weeks after enrollment (g/L)[2]	104 ± 15	108 ± 16	107 ± 15	0.07
Final FH (cm)	31.3 ± 2.6	31.2 ± 2.5	31.4 ± 2.1	0.26
Final FH <28 cm	30 (6)	31 (6)	15 (3)	0.06

N=1,646 women.

Cells contain mean ± SD or n (%).

[1] For *P*-values <0.05, values labeled with the same superscript are not significantly different; for example values labeled a and b are different, but values labeled a and a,b are not.

[2] These measures were taken only in women whose pregnancy extended at least 10 weeks after enrollment; RUSF n=245, CSB+ with UNIMMAP n=206, CSB+ with IFA n=225, for a total n=676.

Table 7A. Birth outcomes of singleton pregnancy women treated at least 14 days, by treatment group

Characteristic	RUSF n=458	CSB+ with UNIMMAP n=450	CSB+ with IFA n=468	*P*-value
Birth length (cm)	47.1 ± 2.3	47.1 ± 2.3	47.2 ± 2.2	0.90
Birth weight (kg)	2.8 ± 0.4	2.7 ± 0.4	2.8 ± 0.4	0.48
Birth head circumference (cm)	34.3 ± 1.6	34.1 ± 1.5	34.3 ± 1.6	0.24
Birth MUAC (cm)	9.6 ± 0.9	9.5 ± 0.8	9.6 ± 0.8	0.49

N=1,376 infants.

Cells contain mean ± SD or n (%).

Table 8A. Birth z-scores of singleton pregnancy women treated at least 14 days, by treatment group

Characteristic	RUSF n=458	CSB+ with UNIMMAP n=450	CSB+ with IFA n=468	*P*-value
WAZ	−1.2 ± 1.0	−1.3 ± 1.0	−1.2 ± 0.9	0.45
LAZ	−1.3 ± 1.2	−1.3 ± 1.2	−1.2 ± 1.2	0.81
WLZ[1]	−0.4 ± 1.0	−0.5 ± 1.1	−0.5 ± 1.0	0.35
HCZ	0.10 ± 1.3	−0.03 ± 1.2	0.12 ± 1.3	0.18
Underweight (WAZ <−2)	83 (19)	98 (23)	78 (17)	0.12
Stunted (LAZ <−2)	102 (22)	105 (23)	91 (19)	0.31
Wasted (WLZ <−2)[1]	18 (5)	22 (6)	20 (5)	0.71
Small head circumference (HCZ <−2)	25 (6)	16 (4)	16 (4)	0.21

N=1,376 infants.

Cells contain mean ± SD or n (%).

[1] 174 infants were excluded from the WLZ analysis because they were too short (<45.00 cm); RUSF n=398; CSB+ with UNIMMAP n=387; CSB+ with IFA n=417

Table 9A. Infant and maternal morbidity, mortality, and loss to follow-up for women treated at least 14 days, by treatment group

Characteristic	RUSF n=559 women n=539 infants	CSB+ with UNIMMAP n=550 women n=532 infants	CSB+ with IFA n=558 women n=547 infants	*P*-value
Infant death[1]	18 (3)	19 (4)	16 (3)	0.58
Lost pregnancy type				
Miscarriage	5 (0.9)	6 (1)	6 (1)	0.94
Stillbirth	3 (0.5)	10 (2)	4 (0.7)	0.07
Maternal antenatal lost to follow-up	20 (4)	18 (3)	11 (2)	0.23
Maternal postnatal lost to follow-up	35 (6)	29 (5)	28 (5)	0.58

N=1,667 women. N=1,618 infants.

Cells contain n (%).

[1] "Infant death" is defined as death reported by mother or local health workers before 12 weeks.

Table 10A. Infant anthropometric outcomes at week 6 for women treated at least 14 days, by treatment group

Characteristic	RUSF n=458	CSB+ with UNIMMAP n=433	CSB+ with IFA n=468	*P*-value
Length (cm)	53.7 ± 2.4	53.6 ± 2.6	53.9 ± 2.3	0.12
Weight (kg)	4.4 ± 0.6	4.4 ± 0.7	4.4 ± 0.6	0.64
Head circumference (cm)	38.1 ± 1.5	38.0 ± 1.5	38.1 ± 1.4	0.81
MUAC (cm)	11.9 ± 1.0	11.8 ± 1.1	11.9 ± 1.1	0.77

N=1,359 infants.

Cells contain mean ± SD.

Table 11A. Infant anthropometric and clinical outcomes at 3 months for women treated at least 14 days, by treatment group

Characteristic	RUSF n=417	CSB+ with UNIMMAP n=420	CSB+ with IFA n=436	*P*-value
Length (cm)	58.2 ± 2.5	58.3 ± 2.5	58.4 ± 2.5	0.39
Weight (kg)	5.5 ± 0.7	5.6 ± 0.8	5.6 ± 0.7	0.39
Head circumference (cm)	40.3 ± 1.6	40.3 ± 1.4	40.3 ± 1.5	0.18
MUAC (cm)	13.0 ± 1.1	13.2 ± 1.1	13.0 ± 1.2	0.95
Hemoglobin (g/L)	99 ± 14	98 ± 16	100 ± 15	0.25

N=1,273 infants.

Cells contain mean ± SD.

Appendix B. Subgroup Analysis Comparing Women Who Received fewer than 14 Days of Treatment with Women Who Received at least 14 Days of Treatment

Table 3B. Demographic characteristics comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristic	Received treatment at least 14 days n=1,667	Received treatment fewer than 14 days n=161	*P*-value
Age (years)	21.5 ± 5.3	22.1 ± 5.6	0.21
First pregnancy	783 (47)	70 (44)	0.39
Education			0.65
None	176 (11)	20 (12)	
1–3	261 (16)	24 (15)	
4–6	620 (37)	53 (33)	
7–8	412(25)	41 (26)	
Secondary	188 (11)	23 (26)	
Tertiary	9 (0.5)	0 (0)	
Adults in household (n)	2.3 ± 0.8	2.3 ± 0.9	0.55
Children in household	1.2 ± 1.5	1.3 ± 1.5	0.47
Mother lives with infant's father	1,424 (85)	141 (88)	0.36

N=1,828 women.

Cells contain mean ± SD or n (%).

Table 4B. Household resources comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristic	Received treatment at least 14 days n=1,667	Received treatment fewer than 14 days n=161	*P*-value
Roof type			0.22
Thatch	1,325 (80)	137 (85)	
Metal	339 (20)	24 (15)	
Water source			
Borehole	1,184 (71)	109 (68)	0.38
Tap	190 (11)	20 (12)	0.70
Animals in house			
Guinea fowl/chicken	461 (28)	49 (30)	0.53
Goat/pig	163 (10)	19 (12)	0.41
Radios in house	635 (38)	61 (38)	0.96
Bicycles in house	726 (44)	37 (23)	0.47
Electricity in house	41 (3)	4 (3)	0.98
Number of people sleeping in the same room	2.4 ± 0.8	2.4 ± 0.7	0.61
Household food insecurity			0.02
Secure	77 (5)	10 (6)	
Mild	65 (4)	12 (8)	
Moderate	333 (20)	37 (23)	
Severe	1,191 (71)	102 (63)	

N=1,828 women.

Cells contain mean ± SD or n (%).

Table 5B. Baseline health at enrollment comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristic	Received treatment at least 14 days n=1,667	Received treatment fewer than 14 days n=161	*P*-value
BMI	19.6 ± 1.4	20.4 ± 1.2	<0.01
MUAC (cm)	22.3 ± 0.6	22.3 ± 0.6	0.66
Stature <145 cm	82 (5)	4 (3)	0.23
HIV-infected	181 (11)	13 (8)	0.38
Hemoglobin (g/L)	101 ± 15	104 ± 17	0.02
Took medications in the 14 days prior to enrollment	409 (25)	45 (28)	0.35
Mother's report of any illness in previous 2 months	339 (20)	31 (19)	0.74
Triceps skinfold (mm)	9.3 ± 2.3	9.1 ± 2.4	0.37
FH (cm)	22.0 ± 5.3	28.2 ± 4.3	<0.01

N=1,828 women.

Cells contain mean ± SD or n (%).

ANOVA or chi-square tests were conducted. A Wilcoxon/Kruskal-Wallis test or Fisher's exact test was conducted if corresponding model requirements were not met.

Table 6B. Maternal outcomes comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristic	Received treatment at least 14 days n=1,646	Received treatment fewer than 14 days n=103	*P-value*
Treatment rations received	5.2 ± 2.7	1.0 ± 0.0	<0.01
Change in MUAC	0.1 ± 0.8	0.1 ± 0.5	0.99
Final MUAC (cm)	22.2 ± 0.9	22.3 ± 0.8	0.47
Final FH (cm)	31.3 ± 2.4	29.9 ± 2.5	<0.01
Final FH <28 cm	76 (5)	16 (16)	<0.01

N=1,749 women.

Cells contain mean ± SD or n (%).

ANOVA or chi-square tests were conducted. A Wilcoxin/Kruskal-Wallis test or Fisher's exact test was conducted if corresponding model requirements were not met.

Connecting letters plot created using Tukey-Kramer HSD tests.

Table 7B. Birth outcomes comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristic	**Received treatment at least 14 days** n=1,376	**Received treatment fewer than 14 days** n=91	*P*-value
Birth length (cm)	47.1 ± 2.2	46.7 ± 2.3	0.01
Birth weight (kg)	2.7 ± 0.4	2.6 ± 0.4	0.02
Birth weight <2.5 kg	359 (26)	33 (38)	0.02
Birth head circumference (cm)	34.2 ± 1.6	34.0 ± 1.5	0.18
Birth MUAC (cm)	9.6 ± 0.8	9.5 ± 0.9	0.29

N=1,467 infants.

Cells contain mean ± SD or n (%).

Table 8B. Birth z-scores comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristics	Received treatment at least 14 days n=1,376	Received treatment fewer than 14 days n=91	*P*-value
WAZ	−1.3 ± 1.0	−1.5 ± 1.1	0.02
LAZ	−1.3 ± 1.2	−1.5 ± 1.2	0.06
WLZ[1]	−0.5 ± 1.0	−0.5 ± 1.1	0.75
HCZ	0.1 ± 1.3	−0.2 ± 1.2	0.12
Underweight (WAZ <−2)	259 (19)	21 (23)	0.44
Stunted (LAZ <−2)	298 (23)	26 (34)	0.17
Wasted (WLZ <−2)[1]	60 (5)	6 (9)	0.24
Small head circumference(HCZ <−2)	57 (4)	4 (6)	0.67

N=1,467 infants.

[1] 188 infants were excluded from the WLZ analysis because they were too short (<45.00 cm). Received treatment at least 14 days n=1,202; received food fewer than 14 days n=77

Table 9B. Infant and maternal morbidity, mortality, and lost to follow-up comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristic	Received treatment at least 14 days n=1,667 women n=1,618 infants	Received treatment fewer than 14 days n=161 women n=139 infants	*P*-value
Infant death[1]	53 (3)	18 (13)	<0.01
Lost pregnancy type Miscarriage Stillbirth	 17 (1) 17 (1)	 0 (0) 2 (1)	 0.20 0.79
Maternal antenatal lost to follow-up	49 (3)	31 (22)	<0.01
Maternal postnatal lost to follow-up	92 (6)	6 (4)	0.98

N=1,828 women. N=1,757 infants.

Cells contain n (%).

[1] "Infant death" is defined as death reported by mother or local health workers before 12 weeks.

Table 10B. Infant anthropometric outcomes at week 6 comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristic	Received treatment at least 14 days n=1,359	Received treatment fewer than 14 days n=63	*P*-value
Length (cm)	53.8 ± 2.4	53.4 ± 2.9	0.21
Weight (kg)	4.4 ± 0.6	4.3 ± 0.7	0.21
Head circumference (cm)	38.0 ± 1.4	38.0 ± 1.7	0.83
MUAC (cm)	11.9 ± 1.1	11.7 ± 1.4	0.17

N=1,422 infants.

Cells contain mean ± SE (SD).

Table 11B. Infant anthropometric and clinical outcomes at 3 months comparing pooled treatment groups treated at least 14 days to pooled treatment groups treated fewer than 14 days

Characteristic	Received treatment at least 14 days n=1,273	Received treatment fewer than 14 days n=70	*P*-value
Length (cm)	58.3 ± 2.5	57.6 ± 2.8	0.03
Weight (kg)	5.6 ± 07	5.3 ± 0.8	0.01
Head circumference (cm)	40.3 ± 1.5	40.2 ± 1.6	0.10
MUAC (cm)	13.1 ± 1.1	12.8 ± 1.2	0.36
Hemoglobin (g/L)	99 ± 15	97 ± 11	0.41

N=1,343 infants.

Cells contain mean ± SE (SD).

Appendix C. Subgroup Analysis of HIV-Infected Women by Treatment Group

Table 3C. Demographics characteristics of HIV infected women, by treatment group

Characteristic	RUSF n=64	CSB+ with UNIMMAP n=60	CSB+ with IFA n=70	*P*-value
Age (years)	26.8 ± 6.9	27.5 ± 6.6	26.8 ± 6.2	0.81
First pregnancy	7 (11)	6 (10)	5 (7)	0.73
Education				0.29
None	13 (20)	9 (15)	12 (17)	
1–3	11 (17)	18 (30)	20 (29)	
4–6	23 (36)	20 (33)	22 (31)	
7–8	6 (9)	5 (8)	12 (17)	
Secondary	11 (17)	8 (13)	4 (6)	
Tertiary	0 (0)	0 (0)	0 (0)	
Adults in household	2.1 ± 0.4	2.2 ± 0.7	2.1 ± 0.8	0.72
Children in household	1.8 ± 1.4	2.0 ± 1.5	2.1 ± 1.3	0.48
Mother lives with infant's father	55 (86)	47 (78)	58 (83)	0.54

N=194 women.

Cells contain mean ± SD or n (%).

Table 4C. Household resources of participants of HIV-infected women, by treatment group

Characteristic	RUSF n=64	CSB+ with UNIMMAP n=60	CSB+ with IFA n=70	*P*-value
Roof Type				0.41
Thatch	52 (81)	42 (70)	54 (77)	
Metal	12 (19)	17 (28)	16 (22)	
Clean water source used				
Borehole	49 (77)	41 (68)	54 (77)	0.45
Tap	7 (11)	8 (13)	10 (10)	0.84
Animals kept in house				
Guinea fowl/chicken	20 (31)	17 (28)	20 (28)	0.92
Goat/pig	7 (11)	8 (13)	7 (10)	0.83
Home with radio	24 (38)	20 (33)	25 (36)	0.89
Home with bicycle	28 (44)	27 (45)	30 (43)	0.97
Home with electricity	2 (3)	1 (2)	3 (4)	0.69
Number of people sleeping in the same room as mother	2.4 ± 0.7	2.5 ± 1.0	2.7 ± 0.8	0.32
Household food insecurity				0.35
Secure	1 (2)	1(2)	3 (4)	
Mild	2 (3)	1(2)	0 (0)	
Moderate	14 (22)	10 (17)	20 (29)	
Severe	47 (73)	48 (80)	47 (67)	

N=194 women.

Cells contain mean ± SD or n (%).

Table 5C. Clinical and nutritional status upon enrollment of HIV-infected women, by treatment group

Characteristic	RUSF n=64	CSB+ with UNIMMAP n=60	CSB+ with IFA n=70	*P*-value
BMI	19.4 ± 1.3	19.5 ± 1.4	19.4 ± 1.3	0.84
MUAC (cm)	22.2 ± 0.6	22.2 ± 0.6	22.3 ± 0.6	0.59
Stature <145 cm	1 (3)	3 (5)	5 (7)	0.31
Hemoglobin (g/L)	98 ± 16	96 ± 15	99 ± 13	0.36
Took medications in the 14 days prior to enrollment	46 (72)	39 (65)	50 (71)	0.74
Mother's report of any illness in previous 2 months	10 (16)	18 (30)	14 (20)	0.14
Triceps skinfold (mm)	8.6 ± 2.4	8.5 ± 2.9	8.1 ± 2.1	0.44
FH (cm)	22.4 ± 5.1	22.9 ± 4.7	22.3 ± 5.9	0.78

N=194 women.

Cells contain mean ± SD or n (%).

Table 6C. Maternal outcomes of HIV-infected women, by treatment group

Characteristic	RUSF n=62	CSB+ with UNIMMAP n=59	CSB+ with IFA n=68	*P*-value
Weight gain from enrollment to final measurement (kg)[1]	3.1 ± 2.7	2.9 ± 2.3	3.1 ± 2.5	0.83
Time from enrollment to delivery (weeks)	11.0 ± 5.8	11.1 ± 6.0	11.6 ± 6.7	0.86
Treatment rations received	4.9 ± 2.8	5.2 ± 3.0	5.0 ± 2.7	0.81
Delivery before receiving second treatment ration	2 (3)	3 (5)	4 (6)	0.78
Weight gain <454 g/week[1]	41 (73)	42 (84)	50 (85)	0.23
Change in MUAC	0.02 ± 1.1	0.4 ± 0.9	0.1 ± 0.9	0.12
Final MUAC (cm)	22.2 ± 1.1	21.9 ± 0.9	22.3 ± 0.9	0.06
Hemoglobin 10 weeks after enrollment (g/L)[2]	96 ± 1.6	99 ± 16	104 ±15	0.18
Final FH (cm)	31.5 ± 2.1	31.3 ± 3.1	31.2 ± 2.2	0.81
Final FH <28 cm	1 (2)	4 (8)	3 (5)	0.39

N=189 women.

Cells contain mean ± SD or n (%).

[1] Weight gain analysis includes only women on treatment for at least 14 days; 9 women were excluded from this analysis. RUSF n=60, CSB+ with UNIMMAP n=56, and CSB+ with IFA n=64.

[2] These measures were taken only in women whose pregnancy extended at least 10 weeks after enrollment; RUSF n=25, CSB+ with UNIMMAP n=22, CSB+ with IFA n=28, for a total n=75.

Table 7C. Birth outcomes of HIV-infected women, by treatment group

Characteristic	RUSF n=52	CSB+ with UNIMMAP n=50	CSB+ with IFA n=62	*P*-value
Birth length (cm)	47.0 ± 2.2	46.4 ± 2.4	47.0 ± 1.9	0.21
Birth weight (kg)	2.8 ± 0.4	2.7 ± 0.5	2.7 ± 0.5	0.35
Birth head circumference (cm)	34.0 ± 1.2	33.9 ± 1.6	34.1 ± 1.8	0.72
Birth MUAC (cm)	9.5 ± 0.9	9.5 ± 0.8	9.6 ± 1.0	0.94

N=164 infants.

Cells contain mean ± SD or n (%).

Table 8C. Birth z-scores of HIV-infected women, by treatment group

Characteristic	RUSF n=52	CSB+ with UNIMMAP n=50	CSB+ with IFA n=62	*P*-value
WAZ	−1.2 ± 1.0	−1.4 ± 1.1	−1.3 ± 1.0	0.38
LAZ	−1.3 ± 1.1	−1.6 ± 1.3	−1.3 ± 1.0	0.24
WLZ[1]	−0.2 ± 1.2	−0.4 ± 1.2	−0.4 ± 1.2	0.73
HCZ	−0.1 ± 0.9	−0.2 ± 1.3	0.0 ± 1.4	0.71
Underweight (WAZ <−2)	6 (12)	15 (30)	12 (20)	0.07
Stunted (LAZ <−2)	8 (16)	17 (34)	12 (20)	0.08
Wasted (WLZ <−2)[1]	1 (2)	3 (8)	2 (4)	0.47
Small head circumference (HCZ <−2)	2 (4)	3 (6)	3 (5)	0.90

N=164 infants.

Cells contain mean ± SD or n (%).

[1] 24 infants were excluded from the WLZ analysis because they were too short (<45.00 cm); RUSF n=46; CSB+ with UNIMMAP n=39; CSB+ with IFA n=55.

Table 9C. Infant and maternal morbidity, mortality, and lost to follow-up among HIV-infected women, by treatment group

Characteristic	RUSF n=64 women n=62 infants	CSB+ with UNIMMAP n=60 women n=59 infants	CSB with IFA n=70 women n=68 infants	*P*-value
Infant death[1]	2 (3)	3 (5)	0 (0)	0.64
Lost pregnancy type				
Miscarriage	0 (0)	1 (2)	1 (1)	0.61
Stillbirth	1 (2)	1 (2)	1 (1)	0.99
Maternal antenatal lost to follow-up	2 (3)	1 (2)	1 (1)	0.76
Maternal postnatal lost to follow-up	3 (5)	0 (0)	2 (3)	0.64

N=194 women. N=189 infants.

Cells contain n (%).

[1] "Infant death" is defined as death reported by mother or local health workers before 12 weeks.

Table 10C. Infant anthropometric outcomes at 6 weeks of age of HIV-infected women, by treatment group

Characteristic	RUSF n=50	CSB+ with UNIMMAP n=48	CSB+ with IFA n=59	*P*-value
Length (cm)	53.7 ± 2.7	53.1 ± 2.5	53.6 ± 2.3	0.44
Weight (kg)	4.2 ± 0.7	4.3 ± 0.7	4.2 ± 0.5	0.95
Head circumference (cm)	37.6 ± 1.3	37.7 ± 1.3	37.7 ± 1.3	0.99
MUAC (cm)	11.5 ± 1.1	11.8 ± 1.2	11.6 ± 0.9	0.54

N=157 infants.

ANOVA was used to determine *P*-values.

Table 11C. Infant anthropometric and clinical outcomes at 3 months of age of HIV-infected women, by treatment group

Characteristic	RUSF n=51	CSB+ with UNIMMAP n=52	CSB+ with IFA n=62	*P*-value
Length (cm)	57.5 ± 3.1	57.4 ± 2.1	57.7 ± 2.2	0.76
Weight (kg)	5.2 ± 0.9	5.5 ± 0.8	5.3 ± 0.7	0.17
Head circumference (cm)	39.6 ± 1.6	40.0 ± 1.4	39.9 ± 1.4	0.47
MUAC (cm)	12.5 ± 1.5[a]	13.1 ± 1.2[b]	12.8 ± 1.1[a,b]	0.04[1]
Hemoglobin (g/L)	99 ± 13	96 ± 15	100 ± 12	0.35

N=165 infants.

Cells contain mean ± SD.

[1] For *P*-values <0.05, values labeled with the same superscript are not significantly different; for example, values labeled [a] and [b] are different, but values labeled [a] and [a,b] are not.

Appendix D. Subgroup Analysis of HIV-Infected and Non-HIV-Infected Women

Table 3D. Demographic characteristics comparing pooled treatment groups with HIV-infected to pooled treatment groups with non-HIV-infected women

Characteristic	HIV-infected n=194	Non-HIV-infected n=1,634	*P*-value
Age (years)	26.9 ± 6.6	20.9 ± 4.7	<0.01
First pregnancy	18 (9)	835 (51)	<0.01
Delivery before receiving the second treatment ration	11 (6)	118 (7)	0.40
Education			<0.01
None	34 (18)	162 (10)	
1–3	49 (25)	236 (14)	
4–6	65 (34)	608 (37)	
7–8	23 (12)	430 (26)	
Secondary	23 (12)	188 (12)	
Tertiary	0 (0)	9 (0.6)	
Adults in household	2.1 ± 0.6	2.3 ± 0.8	0.01
Children in household	2.0 ± 1.4	1.1 ± 1.5	<0.01
Mother lives with infant's father	160 (82)	1,405 (86)	0.17

N=1,828 women.

Cells contain mean ± SD or n (%).

Table 4D. Household resources comparing pooled treatment groups with HIV-infected women to pooled treatment groups with non-HIV-infected women

Characteristic	HIV-infected n=194	Non-HIV-infected n=1,634	*P*-value
Roof type			0.22
Thatch	148 (76)	1,314 (80)	
Metal	45(23)	318 (19)	
Water source			0.27
Borehole	144 (74)	1,149 (70)	0.49
Tap	25 (13)	185 (11)	
Animals in house			0.57
Guinea fowl/chicken	57 (29)	453 (28)	0.53
Goat/pig	22 (11)	160 (10)	
Radios in house	69 (36)	627 (38)	0.45
Bicycles in house	85 (44)	678 (41)	0.96
Electricity in house	6 (3)	39 (2)	0.57
Number of people sleeping in the same room	2.5 ± 0.8	2.1 ± 0.8	0.01
Household food insecurity			0.07
Secure	5 (3)	82 (5)	
Mild	3 (2)	74 (5)	
Moderate	44 (23)	326 (20)	
Severe	142 (73)	1,151 (70)	

N=1,828 women.

Cells contain mean ± SD or n (%).

ANOVA or chi-square tests were conducted. A Wilcoxon/Kruskal-Wallis test or Fisher's exact test was conducted if corresponding model requirements were not met.

Table 5D. Baseline health at enrollment comparing pooled treatment groups with HIV-infected women to pooled treatment groups with non-HIV-infected women

Characteristic	HIV-infected n=194	Non-HIV-infected n=1,634	*P*-value
BMI	19.4 ± 1.3	19.7 ± 1.4	<0.01
MUAC (cm)	22.2 ± 0.6	22.3 ± 0.6	0.29
Stature <145 cm	9 (5)	77 (5)	0.73
Hemoglobin (g/L)	97 ± 15	101 ± 15	<0.01
Took medications in the 14 days prior to enrollment	135 (70)	319 (20)	<0.01
Mother's report of any illness in previous 2 months	45 (23)	325 (20)	0.55
Triceps skinfold (mm)	8.4 ± 2.5	9.4 ± 2.2	<0.01
FH (cm)	22.5 ± 5.5	22.5 ± 5.5	1.00

N=1,828 women.

Cells contain mean ± SD or n (%).

ANOVA or chi-square tests were conducted. A Wilcoxon/Kruskal-Wallis test or Fisher's exact test was conducted if corresponding model requirements were not met.

Table 6D. Maternal outcomes comparing pooled treatment groups with HIV-infected women to pooled treatment groups with non-HIV-infected women

Characteristic	HIV-infected n=189	Non-HIV-infected n=1,560	*P-value*
Weight gain from enrollment to final measurement (kg)[1]	3.1 ± 2.0	3.0 ± 2.4	0.88
Time from enrollment to delivery (weeks)	11.2 ± 6.2	11.5 ± 6.4	0.64
Treatment rations received	5.0 ± 2.8	5.0 ± 2.8	0.87
Weight gain <454 g/week[1]	113 (81)	1,122 (72)	0.92
Change in MUAC	0.1 ± 0.9	0.1 ± 0.8	0.41
Final MUAC (cm)	22.1 ± 1.0	22.2 ± 0.9	0.27
Hemoglobin 10 weeks after enrollment[2] (g/L)	100 ± 16	107 ± 15	<0.01
Final FH (cm)	31.3 ± 2.5	31.2 ± 2.4	0.43
Final FH <28 cm	8 (5)	84 (5)	0.39

N=1,749 women.

Cells contain mean ± SD or n (%).

ANOVA or chi-square tests were conducted. A Wilcoxin/Kruskal-Wallis test or Fisher's exact test was conducted if corresponding model requirements were not met.

[1] Weight gain analysis includes only women on treatment for at least 14 days; 103 women were excluded from this analysis. HIV-infected n=180 and non-HIV-infected n=1,466

[2] These measures were taken only in women whose pregnancy extended at least 10 weeks after enrollment; HIV-infected n=75 and non-HIV-infected n=602.

Table 7D. Infant outcomes comparing pooled treatment groups for HIV-infected women to pooled treatment groups for non-HIV-infected women

Characteristic	Born to HIV-infected woman n=164	Born to non-HIV-infected woman n=1,303	*P*-value
Birth length (cm)	46.8 ± 2.2	47.1 ± 2.3	0.09
Birth weight (kg)	2.7 ± 0.4	2.7 ± 0.4	0.73
Birth head circumference (cm)	34.0 ± 1.5	34.3 ± 1.6	0.02
Birth MUAC (cm)	9.6 ± 0.9	9.6 ± 0.8	0.87

N=1,467 infants.

Cells contain mean ± SD or n (%).

ANOVA or chi-square tests were conducted. A Wilcoxon Rank Sum test was used when conditions for a parametric distribution were not met.

Table 8D. Birth z-scores comparing pooled treatment groups for infants born to HIV-infected women to pooled treatment groups for infants born to non HIV-infected women

Characteristic	Born to HIV infected woman n=164	Born to non- HIV infected woman n=1,303	*P*-value
WAZ	−1.3 ± 1.1	−1.3± 1.0	0.89
LAZ	−1.4 ± 1.2	−1.3± 1.2	0.22
WLZ[1]	−0.3 ± 1.2	−0.5 ± 1.0	0.07
HCZ	−0.08 ± 1.2	0.07 ± 1.3	0.14
Underweight (WAZ <−2)	33 (21)	247 (19)	0.78
Stunted (LAZ <−2)	37 (23)	287 (22)	0.99
Wasted (WLZ <−2)[1]	6 (4)	60 (5)	0.57
Small head circumference (HCZ <−2)	8 (5)	53 (4)	0.65

N=1,467 infants.

Cells contain mean ± SD or n (%).

[1] 188 infants were excluded from WLZ analysis because they were too short (<45.00 cm);

With HIV infection n=140 and without HIV infection n=1,139

Table 9D. Infant and maternal morbidity, mortality, and lost to follow-up comparing pooled treatment groups for HIV-infected women to pooled treatment groups for non-HIV-infected women

Characteristic	HIV-infected n=194 women n=189 infants	Non-HIV-infected n=1,634 women n=1,568 infants	*P*-value
Infant death[1]	5 (3)	66 (4)	0.43
Lost pregnancy type			
Miscarriage	2 (1)	15 (0.9)	0.82
Stillbirth	3 (2)	16 (1)	0.47
Maternal antenatal lost to follow-up	4 (2)	76 (5)	0.11
Maternal postnatal lost to follow-up	5 (3)	93 (6)	0.04

N=1,828 women. N=1,757 infants.

Cells contain n (%).

[1] "Infant death" is defined as death reported by mother or local health workers before 12 weeks.

Table 10D. Infant anthropometric outcomes at week 6 comparing pooled treatment groups for HIV-infected women to pooled treatment groups for non-HIV-infected women

Characteristic	HIV-infected n=165	Non-HIV-infected n=1,257	*P*-value
Length (cm)	53.5 ± 2.5	53.8 ± 2.4	0.13
Weight (kg)	4.2 ± 0.6	4.4 ± 0.6	<0.01
Head circumference (cm)	37.6 ± 1.3	38.1 ± 1.5	<0.01
MUAC (cm)	11.6 ± 1.0	11.9 ± 1.1	<0.01

N=1,422 infants.

Cells contain mean ± SE (SD).

Table 11D. Infant anthropometric and clinical outcomes at 3 months comparing pooled treatment groups for HIV-infected women to pooled treatment groups for non-HIV-infected women

Characteristic	HIV-infected n=157	Non-HIV-infected n=1,186	*P*-value
Length (cm)	57.6 ± 2.5	58.4 ± 2.5	<0.01
Weight (kg)	5.3 ± 0.8	5.6 ± 0.7	<0.01
Head circumference (cm)	39.8 ± 1.5	40.4 ± 1.5	<0.01
MUAC (cm)	12.8 ± 1.3	13.1 ± 1.1	<0.01
Hemoglobin (g/L)	98 ± 13	99 ± 15	0.43

N=1,343 infants

Cells contain mean ± SE (SD).