

# Sustained Effect of a Community-based Behavioral and Nutrition Intervention on HIV-related Outcomes Among Women Living With HIV in Rural India: A Quasi-experimental Trial

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**Background:** Women living with HIV (WLH) in rural communities face challenges to obtaining treatment and accurate disease-related information. Nutritional deficits exacerbate disease progression.

**Setting:** WLH were recruited from primary health centers in rural India.

**Method:** A quasi-experimental trial of a comprehensive Accredited Social Health Activist (Asha)-supported intervention compared 4 distinct Asha-based programs [(1) standard education (SE) alone; (2) nutrition education (+NE); (3) nutrition supplements (+NS); or (4) nutrition education and nutrition supplements (+NENS)] on key disease and nutrition-related outcomes [CD4 count, body mass index (BMI), serum albumin, and hemoglobin]. Assessments occurred at

baseline, and months 6 (immediately after intervention), 12, and 18. Multilevel modeling examined effects of program (group) over time.

**Findings:** Among 600 WLH enrolled (n = 150 per arm), mean age, CD4 count, and BMI (kg/m<sup>2</sup>) were 34.31, 447.42, and 20.09, respectively, at baseline. At 18-month follow-up, program 4 (+NENS) experienced greatest improvements in CD4 counts compared with program 1 (+SE) [adjusted difference = 223.81, 95% confidence interval (CI): 170.29 to 277.32]. For BMI, programs 3 (+NS; adjusted difference = 2.33, 95% CI: 1.39 to 3.26) and 4 (+NENS; adjusted difference = 2.14, 95% CI: 1.17 to 3.12) exhibited greater gains compared with program 1 (+SE). Programs 3 and 4 were not significantly different from each other (adjusted difference = -0.18, 95% CI: -1.12 to 0.76). Hemoglobin and serum albumin also improved over time; program 4 (+NENS) exhibited the greatest gains.

**Conclusions:** A low-cost Asha-supported behavioral and nutritional intervention improved outcomes for WLH. Gains were sustained at 18-month follow-up. Similar approaches may help improve HIV and other infectious disease-related outcomes in vulnerable populations.

**Key Words:** infectious diseases/HIV-AIDS, clinical trial, nutrition, nursing, health education, community health workers, behavioral medicine, CD4 lymphocyte count, body mass index

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## INTRODUCTION

There is a reciprocal relationship between adequate nutrition and effective immune functioning, a critical factor for managing HIV. Undertreated HIV increases metabolic demands among people living with HIV,<sup>1</sup> suggesting that interventions that incorporate nutritional components may promote better outcomes, particularly in food-insecure settings.<sup>2</sup> Meta-analytic findings demonstrate that food insecure individuals with HIV have, on average lower CD4 counts,<sup>3</sup> a critical marker of HIV disease progression and mortality.<sup>4</sup> High body mass index (BMI) tends to be protective against disease progression, highlighting the important role of overall adequate caloric intake for those with HIV.<sup>5</sup>

In resource-limited settings, such as India, poor nutrition may be related to limited access to nutritious food and low levels of nutritional knowledge, exhibited in low

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A.M.N. conceived the idea for the study, and M.L.E. and S.S. added critical details to the design. All 3 developed the metrics, secured funding, and oversaw all aspects of the study procedures and data interpretation. A.M.N. took the lead on the introduction, methods, and discussion of this manuscript. C.L.C. developed the nutrition intervention and contributed to the final review of the manuscript. M.L.E. contributed to the final editing and review of the manuscript. D.R.G. conducted the data analysis and literature review and contributed to the introduction, methods, results, and discussion sections. P.R.K. was actively involved in data collection in India and reviewed the final manuscript. K.Y. led study conduct, data collection, and data management and contributed to the methods and measures. S.S.S. contributed to the data analysis and the final editing of the manuscript. S.S. oversaw study procedures and protocol adherence in India and contributed to the final editing and review of the manuscript.

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macronutrient and micronutrient intake.<sup>6</sup> Micronutrient deficits, including iron deficiency, are exacerbated among people living with HIV because of malabsorption.<sup>7</sup> In fact, hemoglobin (a marker of anemia) is an independent risk factor of AIDS and death.<sup>8</sup> Low serum albumin has also been linked with these poor outcomes<sup>8–10</sup> by promoting inflammatory processes that limit nutrient effectiveness including lowering protein-intake effectiveness.<sup>11</sup> Serum albumin may also be a particularly useful marker of disease progression in resource-limited settings because it is a moderately inexpensive metric to analyze in a laboratory.<sup>10,12</sup>

Despite the robust findings between nutrition-linked indicators and key markers of HIV disease progression, previous research has not consistently found micronutrient supplements (eg, single or multiple formulations of vitamins and trace elements) to be effective in improving clinically relevant outcomes (CD4 count, viral load, nutritional status, hospital admissions, and mortality).<sup>13</sup> Such findings suggest the need for a more comprehensive approach that involves improvements to diet and nutrient intake through nutritious food, targeting a wider range of nutritional deficiencies (including protein deficiency) and accounting for the interconnected and complex systems that comprise nutrition processes. Improving nutrition through diet may also help address the nutritional and overall health needs of people living with HIV as a component of integrated care.

The Comprehensive Health Seeking and Coping Paradigm<sup>14</sup> provides a guiding framework for designing and implementing community-based interventions in vulnerable populations. Originating from a stress and coping<sup>15</sup> and health-seeking perspective,<sup>16</sup> the framework provides a biopsychosocial view of factors impacting health. For food-insecure women in India, pre-existing factors include socio-demographic risk factors (eg, sex and income), health history [HIV status and opportunistic infections (OIs)], and nutritional parameters (eg, poor nutrition and anemia). Barriers to improved immune status include stigma, low social support, and lack of HIV/AIDS knowledge; barriers to nutritional adequacy include inadequate knowledge and nutrition/food insecurity. To address these challenges, we implemented the Comprehensive Health Seeking and Coping Paradigm and the Accredited Social Health Activist (Asha)-based model of support to design, along with community members, a comprehensive, community-based intervention that incorporated psychosocial support and life skills training (based on the targeted needs of the community)<sup>17</sup> with nutrition education and nutrition supplements. Asha are members of the community with little or no formal training in health care and who are trained to assist doctors, nurses, and other health professionals, expanding existing structures in resource-limited settings. Importantly, the Asha-based model seeks to instill in women living with HIV (WLH) the knowledge (eg, importance of antiretroviral therapy (ART) regimens and healthy eating) and skills (eg, job skills and healthy cooking) to sustain positive change in their own lives after participation in intervention procedures. We have previously shown that Asha-supported nutritional interventions were effective in improving CD4 counts, BMI, and other health outcomes among WLH at the end of the 6-month intervention.<sup>18</sup>

This study investigated whether the effects of this Asha-supported behavioral and nutrition intervention were sustained 1 year (12 months) after completion of all intervention procedures (18 months after baseline assessments). We hypothesized that food supplements and nutrition training added to an Asha-supported intervention would each significantly improve key outcomes, and that combining supplements and nutrition education would produce greater improvements in key outcomes, with gains that would be sustained over time.

## METHODS

### Study Design

We conducted a prospective, quasi-experimental study among WLH in rural Andhra Pradesh (AP), India to evaluate the effects of an Asha-supported behavioral and nutrition intervention on critical HIV-related outcomes of disease progression and nutrition. Asha are lay community health care workers trained to facilitate participant's understanding of and adherence to health care regimens. The Asha in our study were hired and trained specifically for our study; the training and financial compensation were comparable with that received by government-supported Asha, and thus, the Asha would be qualified to work for government-based jobs after completion of the study.

We implemented a 2 × 2 factorial design with assessments taken at baseline, 6 months (immediately after completion of intervention procedures), and at 12 and 18 months. The intervention sought to improve physiological outcomes by improving nutrition and bolstering access to existing health care resources. Participants were allocated 1:1:1:1 into the 4 study arms: (1) standard education (SE) (including Asha support) alone; (2) SE plus enhanced nutrition education (+NE); (3) SE plus nutrition supplements (+NS); and (4) SE plus the combination of enhanced nutrition education and nutrition supplements (+NENS). The food supplements were selected from locally consumed food [urad dal (black gram) and tur dal (pigeon peas)] consisting of high protein legumes and high polyunsaturated vegetable oils at 500 K per adult and 250 K per child in the entire household.

SE (a component of every arm) included individual 1:1 weekly Asha support, 6 group sessions covering the content in modules 1–3 (Table 1), and referral to life skills classes. Life skills classes were designed to provide economic resources and sustainable jobs to the women in the program (eg, selling fruit and vegetables, sewing and embroidery, and computer skills). The entire program was designed in a culturally relevant manner with data derived from focus groups held with WLH in India.<sup>17</sup> An important component of the intervention design was imparting skills and knowledge to WLH that would allow for positive change to occur even after intervention procedures were terminated. For example, women learned health care skills (how to ask doctors questions, the importance of refilling and taking ART medications), job skills (to continue to generate income), and nutrition skills (eg, where to buy healthy food and how to cook culturally desirable healthy food).

**TABLE 1.** Overview of the Asha-Based Behavioral and Nutrition Intervention Components

Module 1A and 1B: keeping healthy	<ol style="list-style-type: none"> <li>1. Getting support; talking to my Asha and my doctor/nurse; learning about HIV/AIDS</li> <li>2. Learning about and taking ART recognizing an opportunistic infection; healthy eating</li> <li>3. Keeping with healthy routines</li> <li>4. Deciding with whom to share health problems</li> </ol>
Module 2A and 2B: care-giving	<ol style="list-style-type: none"> <li>1. Breastfeeding safely or learning to sterilize the formula</li> <li>2. Promoting care-giving for family while caring for my own mental and physical well-being</li> <li>3. Engaging in life skill education</li> <li>4. Staying in sync with my children; identifying their needs</li> </ol>
Module 3A and 3B: staying upbeat	<ol style="list-style-type: none"> <li>1. Finding the joys in life; creating a social network for myself</li> <li>2. Dealing well with problems; keeping positive relations with family</li> <li>3. Taking active steps to improve my life every day</li> <li>4. Getting psychological assistance</li> </ol>
Module 4A and 4B: healthy eating for self and family (nutrition education) (only programs 2 and 4 complete)	<ol style="list-style-type: none"> <li>1. Learning about low-cost foods that are nutritious</li> <li>2. Where to purchase food</li> <li>3. Learning how to monitor food intake</li> <li>4. Considering ways to eat healthy</li> <li>5. Participating in a cooking class</li> </ol>
Nutrition supplements (only for programs 3 and 4)	<ol style="list-style-type: none"> <li>1. Consists of high protein foods with minimal saturated fat, fiber, and cholesterol</li> <li>2. Food choices evaluated using India National Guidelines and our team's nutrition experts</li> <li>3. Food supplements consist of high protein legumes and high polyunsaturated vegetable oils at 500 K per adult and 250 K per child in household (Food given to entire household to ensure that the women would consume the supplements rather than giving it away to family members)</li> <li>4. Foods provided were popular in the region [eg, urad dal (black gram) or tur dal (pigeon peas)]</li> </ol>

The study was approved by University Human Subjects Protection Committees in the United States and the All India Institute of Medical Sciences and the Ministry of Health in India.

**Sample and Setting**

WLH between ages of 18–50 years with a verified HIV-positive diagnosis, ART prescription for the last 3 months,

and who were currently receiving care in one of the 16 Primary Health Centers (PHCs) located in Nellore and Prakasam districts of AP were recruited for participation. The PHCs were grouped into 4 regional clusters; the clusters were created so that they contained villages that were close to each other and yet distant from villages contained in other clusters. This design was implemented rather than randomizing each of the individual 16 PHCs into 1 of the 4 arms to increase feasibility and promote intervention fidelity by reducing cross-contamination. Additional inclusion criteria included having a child aged 3–8 years (separate analyses not relevant to the data presented herein focused on child outcomes). As part of enrollment criteria, all women were receiving HIV treatment.

Exclusionary factors included CD4 T-cell levels <100 cells/mm<sup>3</sup>, participation in previous Asha-interventions (used as pilot data) by our team, or currently pregnant. (No women became pregnant over the course of the study). Baseline data collection began April 30, 2014. Enrollment was staggered to best implement the group-based intervention every 6 months over a 2-year period; 4 cohorts were enrolled with 100 participants in each (25 per arm, per cohort). Cohorts were enrolled in equal proportions across sites concurrently.

**Procedures**

Flyers were posted in selected PHCs. Interested women met with a trained research staff who was blinded to the program hypotheses in a private location to receive study information and complete the eligibility screener. Verified diagnosis of HIV was assessed by showing government hospital-generated ART card. CD4<sup>+</sup> T-cell count was also measured during screening. WLH received cash compensation for each study procedure, including initial screening, 4 blood draws, thirteen 24-hour diet recalls that included 9 BMIs and urine collections, 4 interviews, and 6–8 group sessions depending on program assignment, totaling USD \$172–\$182 (9036–9562 INR) over the course of the 18-month study. Participants were also reimbursed for transportation costs and provided childcare as needed. All WLH interested in participating provided informed consent. A second informed consent was completed by all eligible participants based on the results of eligibility screening.

**Asha Selection and Training**

Asha were recruited from villages similar to the participants and ranged in age between 19 and 50 years, attained an education of eighth grade or higher, and were interested in caring for women and children with HIV. Some had received previous Asha training by the Indian government; training by our team was provided to those who had not.

Sixteen Asha were rigorously trained by the key investigators and Project Director; all received training by our team to ensure comparability of treatment. The focus was on the study protocol, needs of WLH, including emotional and social support, basics of HIV disease progression, importance of adherence to ART, strategies to assist coping

with illness, and maintaining participant confidentiality. Four Asha were assigned to each of the 4 programs and received training specific to that program design. Quality assurance assessments were performed quarterly. Nursing guidance and research staff were led by PIs, physicians, and nurses in the community. The Asha were employed full time by our team for study duration.

### Primary Outcomes

CD4<sup>+</sup> T cells were measured through blood samples collected at screening and at 6-, 12- and 18-month follow-ups. CD4<sup>+</sup> T-cell testing was performed at the Nellore District Hospital diagnostic laboratory using the Act Diff Coulter Analyzer (Beckman Coulter; Brea, CA). Laboratory personnel were blinded to the intervention group of the participants.

### Body Mass Index

Height and weight were measured at baseline, then monthly for 6 months, and then at 12- and 18-month follow-ups. Trained research staff used a calibrated scale to weigh WLH while barefoot and took heights using a stadiometer with BMI calculated by dividing weight in kilograms by height in meters squared.

### Secondary Outcomes

Hemoglobin was assessed in grams/liter (g/L) in the blood; anemia was defined according to WHO guidelines<sup>19</sup> for severe (<80 g/L), moderate (80–109 g/L), mild (110–119 g/L), or no anemia ( $\geq 120$  g/L) hemoglobin levels. Serum albumin concentration was evaluated as g/L concentration in the blood and analyzed as a continuous variable (Note: these were added post hoc from initial ClinicalTrials.gov submission).

### Key Covariates

Demographic data were collected at baseline. In addition, data were collected for the following risk factors for HIV-related outcomes. Percent past month ART adherence was represented by a self-reported measure that assessed adherence to ART through a visual analogue scale ranging from 0 to 100, with the number representing percent of pills taken in past month,<sup>20,21</sup> previously used in India and correlated with viral load.<sup>21</sup> Physical activity was evaluated with the International Physical Activity Questionnaire, which was summarized into metabolic equivalents of energy expenditure (MET) minutes per week.<sup>22</sup> Quality of life (QOL) was assessed by the internationally validated QOL Enjoyment and Satisfaction Questionnaire.<sup>23</sup> Food insecurity by The Household Food Insecurity Access Scale,<sup>24</sup> a widely used measure previously implemented in India with a similar population.<sup>25</sup> Depression was assessed by the Center for Epidemiological Studies Depression Scale, short version,<sup>26</sup> a 10-item scale with well-established reliability and validity including in India.<sup>27</sup> Internalized stigma was represented with a 10-item scale, previously used in India, that measured the extent respondents believed they deserved to be shunned (5 items, eg, should avoid social interactions) or blamed/shamed because of HIV (5 items, eg, shamed the family, feel guilty).<sup>28</sup> Social support was derived from the Medical

Outcomes Study (MOS) Social Support Survey<sup>29</sup> as both a composite scale and an assessment of number of friends one could turn to in the past month (composite scale was used in inferential statistics). OIs were assessed by using a list of 8 common OIs endorsed by our collaborating physicians that included tuberculosis, pneumocystis carinii, herpes simplex virus/varicella zoster, *Candida*, fungal dermatoses, diarrhea, febrile illness, or other. Participants indicated whether they had experienced any of these OIs in the previous 6 months, with a summation of endorsed OIs into one index measure.

### Statistical Analysis

Sample size was estimated based on effect sizes drawn from pilot study results of a behavioral intervention for WLH in India.<sup>30–32</sup> Alpha was set to 0.01 to mitigate for multiple dependent variables. We estimated an intraclass correlation of 0.05 and a design effect of 2.45 (to account for potential PHC clustering effects) and a 90% attrition rate after 18 months. For each main effect of parent study, we estimated differences of about half a SD in size ( $d = 0.48$ , medium effect size) between the outcome means of nutrition and supplement groups compared with the SE arm. Based on these parameters, the overall sample size of 600 (150 per group) provided 80% power for detecting the differences in outcomes across intervention groups.

All analyses were conducted using STATA 15 (Stata-Corp, College Station, TX). Although an intention-to-treat analysis was planned for the primary analysis, all participants provided complete data at all time points, and no attrition or mortality over time occurred; thus, analyses did not account for missingness. Significance tests were 2-sided and  $\alpha = 0.05$ .

Primary analyses examined between- and within-group differences over time between baseline and follow-ups (6, 12, and 18 months) for the 4 programs. Given the random allocation was by cluster and not individually based, equivalent distributions of covariates according to group membership were not expected; between-group differences at baseline were tested in bivariate models and covariates significantly different by group included in subsequent analyses. A multilevel, random-intercept mixed model was constructed, nested within participants to allow for clustering of data within each individual. This model included fixed effects for group (program), time, group (program)  $\times$  time, and covariates that explained between-group differences at baseline or were clinically relevant. Random slope models were also tested to allow slopes between groups to vary. Random-intercept only models exhibited best model fit based on likelihood ratio  $\chi^2$  tests. An independent covariance pattern was specified as our final models were random-intercept only (participant); results are presented using restricted maximum likelihood for optimal control of type 1 error.<sup>33</sup> In addition to models that separately compared programs 2–4 with the reference group (program 1), factorial models (which use an interaction term for program 4, defined by participation in both nutrition education and nutrition supplements, rather than creating a dummy coded variable for each of the 4 groups) were also constructed. Finally, recovery from anemia

**TABLE 2.** Description of the Sample on Key Variables at Baseline, N = 600

	<b>Total Sample (N = 600)</b>	<b>Program 1: Standard Education (n = 150)</b>	<b>Program 2: + Nutrition Education (n = 150)</b>	<b>Program 3: + Nutrition Supplements (n = 150)</b>	<b>Program 4: + Nutrition Education &amp; Supplements (n = 150)</b>	<b>Test of Between Group Differences*</b>
<b>Demographics</b>						
Age (Mean, SD)	34.31 (6.96)	36.05 (6.96)	34.66 (6.90)	33.61 (6.41)	32.91 (7.17)	F(3, 596) = 5.92, P < 0.001
No. of children (Mean, SD)	1.86 (0.80)	1.83 (0.73)	1.78 (0.78)	1.91 (0.93)	1.92 (0.76)	F(3, 596) = 1.05, P = 0.369
Monthly income (rupees) (Mean, SD)	2113.5 (678.68)	2110 (758.91)	2158.67 (611.98)	2137.33 (626.97)	2048 (707.93)	F(3, 596) = 0.75, P = 0.523
<b>Marital status, n (%)</b>						
Married	238 (39.67)	51 (34.0)	67 (44.67)	53 (35.33)	67 (44.67)	$\chi^2(6) = 8.72,$ P = 0.190
Widowed	308 (51.50)	87 (58.0)	68 (45.33)	85 (56.67)	68 (45.33)	
Divorced/separated	54 (9.00)	12 (8.0)	15 (10.00)	12 (8.00)	15 (10.00)	
<b>Disease-related variables (Mean, SD)</b>						
Percent past month ART adherence	30.37 (13.23)	30.37 (12.75)	32.0 (14.35)	28.6 (12.99)	30.5 (12.69)	F(3, 596) = 1.66, P = 0.174
No. of OIs past 6-mo	4.58 (1.20)	4.61 (1.35)	4.52 (1.35)	4.58 (0.96)	4.63 (1.13)	F(3, 596) = 0.22, P = 0.883
CD4+ T count	447.42 (273.60)	442.57 (272.66)	459.61 (284.48)	426.19 (275.34)	461.29 (262.75)	F(3, 596) = 0.54, P = 0.653
<b>Nutrition-related variables (Mean, SD)</b>						
Total MET min/wk	4608.57 (1663.57)	4957.09 (1873.23)	4569.73 (1416.82)	4691.85 (1718.60)	4215.60 (1539.27)	F(3, 596) = 5.25, P = 0.001
Body mass index	20.09 (4.16)	19.75 (3.77)	20.20 (3.97)	20.55 (4.67)	19.86 (4.16)	F(3, 596) = 1.15, P = 0.329
Weight (kgs)	46.22 (10.37)	45.17 (9.65)	46.42 (9.65)	47.43 (11.22)	45.84 (10.86)	F(3, 596) = 1.28, P = 0.283
Height (cm)	151.52 (5.98)	151.06 (5.81)	151.57 (6.06)	151.85 (5.80)	151.62 (6.27)	F(3, 596) = 0.46, P = 0.710
Food insecurity	21.15 (3.44)	20.27 (4.29)	21.63 (2.58)	20.76 (3.45)	21.94 (2.98)	F(3, 596) = 7.78, P < 0.001
Hemoglobin (g/L)	71.62 (12.87)	71.36 (11.34)	72.59 (11.38)	72.37 (14.57)	70.19 (13.83)	F(3, 596) = 1.08 P = 0.358
<b>Anemia n (%)†</b>						
Severe (hemoglobin < 80)	436 (72.67)	113 (75.33)	107 (71.33)	103 (68.67)	113 (75.33)	$\chi^2(3) = 2.42,$ P = 0.491
Moderate (hemoglobin 80–109)	164 (27.33)	37 (24.67)	43 (28.67)	47 (31.33)	37 (24.67)	
Mild (hemoglobin 110–119)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Not anemic (hemoglobin ≥ 120)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
<b>Psychological Variables (Mean, SD)</b>						
Quality of life	0.30 (0.29)	0.26 (0.33)	0.34 (0.25)	0.27 (0.33)	0.34 (0.25)	F(3, 596) = 2.92, P = 0.034
Internalized stigma	2.30 (0.25)	2.24 (0.41)	2.30 (0.16)	2.33 (0.19)	2.33 (0.15)	F(3, 596) = 3.54, P = 0.015
Summary CESD depression	9.18 (3.08)	9.12 (3.11)	9.09 (3.06)	9.16 (3.13)	9.35 (3.04)	F(3, 596) = 0.22, P = 0.879

(continued on next page)

**TABLE 2.** (Continued) Description of the Sample on Key Variables at Baseline, N = 600

	Total Sample (N = 600)	Program 1: Standard Education (n = 150)	Program 2: + Nutrition Education (n = 150)	Program 3: + Nutrition Supplements (n = 150)	Program 4: + Nutrition Education & Supplements (n = 150)	Test of Between Group Differences*
Social support (scale)	1.08 (0.22)	1.13 (0.41)	1.06 (0.12)	1.05 (0.08)	1.06 (0.08)	F(3, 596) = 4.52, P = 0.004
Number of friends	0.37 (0.65)	0.50 (0.93)	0.27 (0.49)	0.35 (0.53)	0.35 (0.55)	F(3, 596) = 3.24, P = 0.022

\*ANOVA for continuous outcomes; chi square for categorical outcomes.  
†Defined according to World Health Organization guidelines for anemia.  
CESD, Center for Epidemiologic Studies Depression Scale.

(defined as hemoglobin  $\geq 120$ ) at 18 months was examined using logistic regression (1 = anemia recovery; 0 = anemic).

## RESULTS

Beginning in April 2014, 972 women were screened, of whom, 600 (61.73%) were eligible (see Figure 1, Supplemental Digital Content, <http://links.lww.com/QAI/B309>). Of the eligible participants, 100% agreed to participate in the study, resulting in 600 women enrolled from the 4 intervention clusters (150 from each cluster). Table 2 presents descriptive statistics for total sample and each of the 4 arms as well as between-group differences between arms at baseline. As detailed in Table 2, arms differed on the following variables at baseline: age, QOL, MET, internalized stigma, food insecurity, social support, and education. Baseline ART adherence did not differ between arms but was included as a covariate in subsequent analyses given its critical importance in understanding HIV-related outcomes over time.<sup>21</sup>

### Primary Outcomes

Tables 3 and 4 present results from mixed-effects models examining effects of group by assessment time point for primary (CD4 count and BMI) and secondary (hemoglobin and serum albumin) outcomes, respectively, adjusted for key covariates and baseline ART adherence. CD4 count: Fixed effects for time indicated that, overall, groups improved CD4 count over assessments (baseline and 6-, 12-, and 18-month follow-ups). Group by assessment time point effects were significant, demonstrating that the 3 programs containing a nutrition component (+NE, +NS, and +NENS) experienced greater increases in CD4 count from baseline compared with the control (SE); Figure 1A. Analyses of the separate factorial model indicated a statistically significant interaction term for program 4 [18 months compared with baseline:  $b = 52.51$ , 95% confidence interval (CI): 24.19 to 80.82,  $P < 0.001$ ], suggesting a synergistic effect of nutrition education and supplements on CD4 counts. BMI: Fixed effects for time indicated that overall BMI increased over assessments (baseline and 6-, 12-, and 18-month follow-ups). From baseline, BMI

increased significantly more among participants in the 3 programs that contained a nutrition component (+NE, +NS, and +NENS) compared with the BMI among program 1 (SE) participants. Factorial effects signifying participation in program 4 (+NENS) were not statistically significant (18 months compared with baseline:  $b = 0.14$ , 95% CI:  $-0.01$  to  $0.30$ ,  $P = 0.074$ ). See Figure 1B. Model-estimated marginal (adjusted) means and contrasts for the 4 programs over time are presented in Tables S1 and S2, Supplemental Digital Contents, <http://links.lww.com/QAI/B309>.

### Secondary Outcomes

At baseline, 100% of the women in the sample were anemic, with the majority meeting WHO guidelines for severe anemia ( $n = 436$ , 72%, Table 2); at 18-month follow-up, none of the women in any of the 4 arms were severely anemic, and 19.67% of the total sample had normal hemoglobin levels ( $n = 118$ ;  $n = 15$  in +SE,  $n = 23$  in +NE,  $n = 26$  in +NS, and  $n = 54$  in +NENS). Results of logistic regression analyses found that, controlling for covariates, participants in each of the 3 programs with a nutrition component (+NE, +NS, and +NENS) were more likely to recover from anemia compared with the control (program 1, SE), who received SE (+NE: OR = 2.55, 95% CI: 1.2 to 5.36,  $P < 0.014$ ; +NS: OR = 2.21, 95% CI: 1.08 to 4.52,  $P = 0.030$ ; +NENS: OR = 9.59, 95% CI: 4.67 to 19.70,  $P < 0.001$ ). The interaction term signifying synergistic effect of the 2 nutrition interventions was not significant (OR = 1.70, 95% CI: 0.67 to 4.30,  $P = 0.261$ ). Mixed models examining hemoglobin levels as a continuous indicator over time demonstrated a similar pattern of results (Table 4 and Figure 1C), except that the interaction term at 18-month follow-up was statistically significant ( $b = 4.47$ , 95% CI: 1.31 to 7.63,  $P = 0.006$ ), suggesting synergistic effects for combining nutrition supplements and education on hemoglobin as a continuous variable.

Table 4 and Figure 1D present mixed models of serum albumin levels over time. All groups improved over time; with the greatest gains exhibited in the nutrition supplements and education group (program 4, +NENS; Table 4). The interaction term (signifying participation in program 4, +NENS) was not significant ( $b = -1.03$ , 95% CI:  $-2.51$  to  $0.44$ ,  $P = 0.169$ ).

**TABLE 3 . Mixed Effects\* for Primary Outcomes, N = 600**

	Primary Outcomes					
	CD4 count			BMI		
	b	95% CI	P	b	95% CI	P
Fixed effects						
Group†						
Standard education (+SE)‡						
+ nutrition education (+NE)	-39.94	-91.79 to 11.90	0.131	0.53	-0.41 to 1.48	0.271
+ nutrition supplements (+NS)	-11.63	-63.00 to 39.73	0.657	0.94	-0.01 to 1.88	0.048
+ nutrition education and supplements (+NENS)	-26.68	-80.19 to 26.84	0.329	0.20	-0.77 to 1.18	0.682
Time						
Baseline§						
6 mo	343.97	329.82 to 358.13	<0.001	1.01	0.94 to 1.09	<0.001
12 mo	441.19	427.08 to 455.35	<0.001	1.47	1.39 to 1.55	<0.001
18 mo	529.62	515.46 to 543.78	<0.001	1.97	1.90 to 2.05	<0.001
Group × time						
6 mo × (+NE)	12.17	-7.85 to 32.19	0.233	0.26	0.15 to 0.37	<0.001
12 mo × (+NE)	40.68	20.66 to 60.70	<0.001	0.40	0.29 to 0.51	<0.001
18 mo × (+NE)	54.94	34.92 to 74.96	<0.001	0.42	0.30 to 0.53	<0.001
6 mo × (+NS)	125.69	105.67 to 145.71	<0.001	1.36	1.25 to 1.47	<0.001
12 mo × (+NS)	137.71	117.69 to 157.73	<0.001	1.41	1.30 to 1.52	<0.001
18 mo × (+NS)	143.04	123.02 to 163.06	<0.001	1.38	1.27 to 1.49	<0.001
6 mo × (+NENS)¶	186.85	166.82 to 206.87	<0.001	1.71	1.60 to 1.82	<0.001
12 mo × (+NENS)¶	238.43	218.41 to 258.44	<0.001	1.90	1.79 to 2.01	<0.001
18 mo × (+NENS)¶	250.49	230.47 to 270.51	<0.001	1.94	1.83 to 2.05	<0.001

	CD4 count		BMI	
	Estimate (95% CI)		Estimate (95% CI)	
Random effects				
Constant	45,213.71 (40,221.93 to 50,825.00)		16.17 (14.42 to 18.14)	
Residual	3912.42 (3664.18 to 4177.47)		0.12 (0.11 to 0.13)	
Model statistics	Wald $\chi^2$ (24) = 38,216.79, $P < 0.001$		Wald $\chi^2$ (24) = 26,509.52 $P < 0.001$	

\*Multilevel model fixed effects: group (Asha + =reference group), time (baseline = reference group), group X time, % ART adherence and covariates explaining group differences at baseline (age, quality of life, total MET, internalized stigma, social support, food insecurity, and education).

†SE = program 1 (Standard Education); +NE = program 2 (Nutrition Education); +NS = program 3 (Nutrition Supplements); +NENS = program 4 (Nutrition Education and Nutrition Supplements).

‡SE (program 1) = reference group.

§Baseline (Month 0) is the reference group.

||Baseline and SE (program 1) are the reference groups.

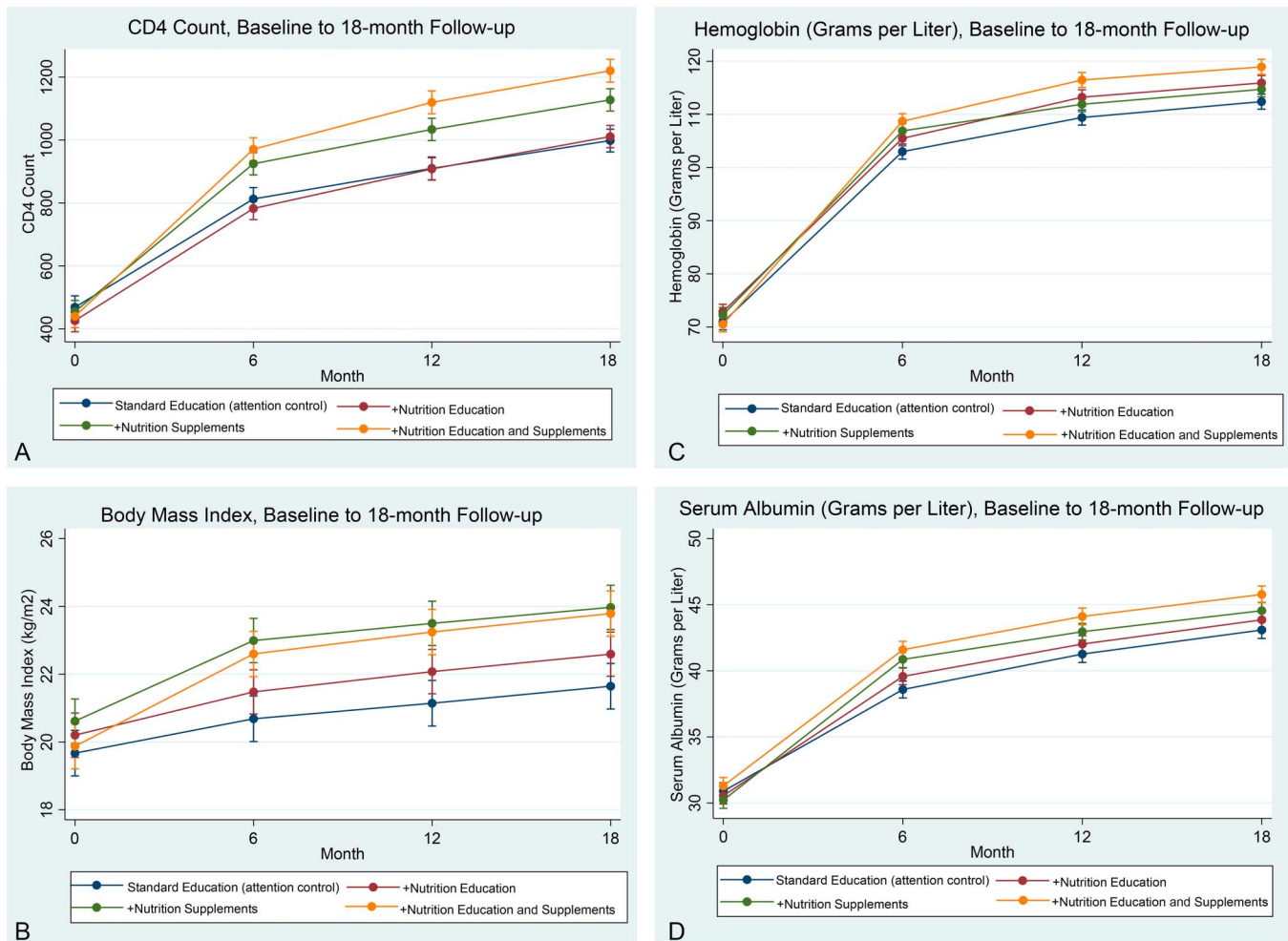
¶Additive effects are presented, rather than the interaction term.

## DISCUSSION

This study is, to the best of our knowledge, the most comprehensive clinical trial of a behavioral- and nutrition-based intervention for WLH. We evaluated a number of key primary and secondary outcomes at baseline, 6-month (immediately after termination of intervention activities) and 12- and 18-month longitudinal follow-up. We found that participating in any of the Asha-enhanced programs resulted in improved physiological and nutritional outcomes during follow-up, but gains were most dramatic in the most comprehensive program (program 4, +NENS). Gains were evident at 6 months and were retained over the year after termination of intervention procedures. This may be due to the focus on teaching skills and habits that can be maintained after intervention procedures are terminated. Psychosocial

problems (eg, depression and stigma) were also addressed as part of the care delivered in all 4 arms; previous analyses by our team demonstrate that key psychological variables improved over time in all groups; key psychosocial variables (eg, depression and stigma) were not different between groups after intervention.<sup>34</sup>

Importantly, we were able to see dramatic gains compared with previous work on nutrition supplementation in HIV populations, which found relatively small effects on improving HIV-related outcomes.<sup>13</sup> This may be because of our intervention's unique focus on food and nutrition training involving food, as opposed to vitamins or similar supplements. BMI, which is correlated with a number of salutary outcomes relevant for those with HIV (eg, higher CD4 count and decreased risk of AIDS-defining conditions),<sup>5</sup> also



**FIGURE 1.** Primary and secondary outcomes over 18 months; linear predictions. A, CD4 Count, B, BMI, C, Hemoglobin, and D, Serum Albumin.

improved in all groups with highest gains in programs that included supplements in addition to education and support. This suggests that reducing food insecurity through increased caloric intake should be a key goal in treating HIV in disadvantaged communities.

A study conducted in India demonstrated that anemia is more common in women who are HIV positive, with low iron levels correlated with low CD4 levels.<sup>35</sup> Serum albumin has been linked to mortality among malnourished individuals with HIV from developing countries.<sup>36</sup> Therefore, our findings on these secondary outcomes suggest that nutrition education and food supplements have the potential to improve critical disease-related outcomes, improving QOL and decreasing mortality in this population.

### Limitations and Future Directions

We note several limitations. Randomization occurred at the cluster level among 4 clusters, which resulted in between-group differences at baseline. Although we controlled for baseline differences in subsequent analyses, we cannot rule out the possibility of residual confounds leading to the

observed differences by group. In addition, as in any clinical or behavioral study, a degree of self-selection likely occurred; those who chose to participate may have been healthier or more motivated to seek care than WLH who did not. However, interest in participating in the study was very high across the PHCs, and bias is likely to be very minimal. Viral load was cost-prohibited to collect on all women at the time of study implementation. Future research with an Asha-based model should test for viral load as a primary outcome.

Increased dietary diversity in addition to caloric intake may have helped improved outcomes: our team intends to present more in-depth analyses of the nutrition intake data in a follow-up to the findings presented herein. Although our team has maintained close relationships with our community partners and continues to work with public health officials in India to disseminate findings, the long-term sustainability of this community-run approach outside of a research setting is unknown.

Findings demonstrate the capacity of integrated, comprehensive behavioral and nutritional interventions to improve a number of immune and nutrition-related outcomes in resource-limited settings. An Asha-supported approach



**TABLE 4 . Mixed Effects\* for Secondary Outcomes, N = 600**

	Secondary Outcomes					
	Hemoglobin			Serum Albumin		
	b	95% CI	P	b	95% CI	P
Fixed effects						
Group†						
Standard education (+SE)‡						
+ Nutrition education (+NE)	1.99	−0.02 to 3.99	0.052	−0.37	−1.27 to 0.52	0.413
+ Nutrition supplements (+NS)	1.39	−0.61 to 3.39	0.172	−0.70	−1.59 to 0.19	0.125
+ Nutrition education and supplements (+NENS)	−0.37	−2.42 to 1.67	0.721	0.38	−0.54 to 1.29	0.419
Time						
Baseline§						
6 mo	32.13	30.55 to 33.71	<0.001	7.69	6.95 to 8.42	<0.001
12 mo	38.54	36.96 to 40.12	<0.001	10.37	9.64 to 11.11	<0.001
18 mo	41.53	39.95 to 43.11	<0.001	12.19	11.46 to 12.93	<0.001
Group × time						
6-mo × (+NE)	0.50	−1.74 to 2.73	0.663	1.35	0.31 to 2.39	0.011
12-mo × (+NE)	1.83	−0.40 to 4.07	0.108	1.11	0.07 to 2.15	0.037
18-mo × (+NE)	1.53	−0.71 to 3.76	0.181	1.12	0.08 to 2.16	0.035
6-mo × (+NS)	2.51	0.28 to 4.75	0.028	2.96	1.92 to 4.00	<0.001
12-mo × (+NS)	1.10	−1.13 to 3.33	0.335	2.37	1.33 to 3.41	<0.001
18-mo × (+NS)	0.92	−1.31 to 3.15	0.420	2.14	1.10 to 3.18	<0.001
6-mo × (+NENS)¶	6.09	3.86 to 8.33	<0.001	2.61	1.57 to 3.65	<0.001
12-mo × (+NENS)¶	7.44	5.21 to 9.67	<0.001	2.45	1.41 to 3.49	<0.001
18-mo × (+NENS)¶	6.91	4.68 to 9.15	<0.001	2.29	1.25 to 3.33	<0.001

	Hemoglobin		Serum Albumin	
	Estimate (95% CI)		Estimate (95% CI)	
	Random effects			
Constant	27.13 (22.92 to 32.11)		4.67 (3.88 to 5.61)	
Residual	48.74 (45.65 to 52.04)		10.56 (9.91 to 11.30)	
Model statistics	Wald $\chi^2$ (24) = 15,385.32, $P < 0.001$		Wald $\chi^2$ (24) = 6381.54, $P < 0.001$	

\*Multilevel model fixed effects: group (Asha + = reference group), time (baseline = reference group), group X time, % ART adherence, and covariates explaining group differences at baseline (age, quality of life, total MET, internalized stigma, social support, food insecurity, and education).

†SE = program 1 (Standard Education); +NE = program 2 (Nutrition Education); +NS = program 3 (Nutrition Supplements); +NENS = program 4 (Nutrition Education and Nutrition Supplements).

‡SE (program 1) = reference group.

§Baseline (Month 0) is the reference group.

||Baseline and SE (program 1) are the reference groups.

¶Additive effects are presented, rather than the interaction term.

may be broadly applicable to treating HIV and other public health crises around the world.

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