Effect of multivitamin and vitamin A supplements on weight gain during pregnancy among HIV-1-infected women

Eduardo Villamor, Gernard Msamanga, Donna Spiegelman, Gretchen Antelman, Karen E Peterson, David J Hunter, and Wafaie W Fawzi

ABSTRACT

Background: The pattern of weight gain during pregnancy among HIV-infected women is largely unknown. Multivitamin supplementation was shown to be effective in preventing adverse pregnancy outcomes among HIV-positive women. These protective effects could be mediated in part by an improvement in the pattern of gestational weight gain.

Objective: We examined the effects of multivitamin and vitamin A supplements on weight gain during the second and third trimesters of pregnancy among HIV-infected women.

Design: We enrolled 1075 pregnant, HIV-1-positive women from Dar es Salaam, Tanzania, in a randomized, placebo-controlled trial. Using a 2-by-2 factorial design, we assigned each woman to 1 of 4 regimens: multivitamins (thiamine, riboflavin, niacin, folic acid, and vitamins B-6, B-12, C, and E), vitamin A, multivitamins including vitamin A, or placebo. The women took these oral supplements daily and were weighed monthly until the end of pregnancy.

Results: The mean rate of weight gain was 306 g/wk during the second trimester and 247 g/wk during the third trimester. During the third trimester, average weight gain was significantly greater (by 304 g; 95% CI: 17, 590; P = 0.04) and the risk of low rate of weight gain (≤100 g/wk) was significantly lower (relative risk: 0.73; 95% CI: 0.58, 0.93) in women who received multivitamins than in women who did not. Multivitamins including vitamin A were protective against low weight gain during the second trimester compared with multivitamins alone.


KEY WORDS Weight gain, pregnancy, HIV infection, AIDS, multivitamins, vitamin A, sub-Saharan Africa, maternal health, prenatal nutrition

INTRODUCTION

Maternal nutritional status before and during gestation is one of the strongest determinants of pregnancy outcomes. Gestational weight gains below recommended amounts are common in developing countries (1–6) and account for a significant proportion of the risk of low birth weight (LBW) (7–9) and preterm delivery (10–12). Identifying potential interventions for improving gestational weight gain may be important in reducing the incidence of adverse pregnancy outcomes.

Maternal HIV infection also contributes to LBW resulting from preterm delivery and intrauterine growth retardation (IUGR) (13), particularly in sub-Saharan Africa, where > 13 million women of childbearing age are infected (14). Progression of HIV disease is usually accompanied by opportunistic infections (15), diminished dietary intake (16), nutrient malabsorption (17), and metabolic and hormonal alterations (18–21) that lead to depletion of both body fat and fat-free compartments (22–25), resulting in weight loss. A part of the adverse effect of HIV disease on pregnancy outcomes is most likely mediated through the changes in maternal body composition and the weight loss induced by the infection. However, the magnitude and determinants of these changes remain virtually unknown.

It was shown that daily consumption of multivitamin supplements by HIV-infected pregnant women resulted in significant reductions in the risk of LBW [relative risk (RR): 0.56; 95% CI: 0.38, 0.82], severe preterm birth (RR: 0.61; 95% CI: 0.38, 0.96), IUGR (RR: 0.57; 95% CI: 0.39, 0.82), and fetal loss (RR: 0.61; 95% CI: 0.39, 0.94) and also improved the immunologic profile of the mothers and increased their hemoglobin concentrations (26). In another study, vitamin A supplementation during pregnancy was found to reduce the risk of preterm delivery among HIV-infected women (27). If a positive effect of vitamin supplementation on gestational weight gain is also found, this could constitute a mechanistic explanation for the reduced risk of adverse pregnancy outcomes. We examined this question in the context of a randomized trial of multivitamin and vitamin A supplementation among HIV-infected pregnant women in Tanzania.

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VITAMINS AND PREGNANCY WEIGHT GAIN IN HIV INFECTION

SUBJECTS AND METHODS

Study design and population

Between April 1995 and July 1997, pregnant women who were receiving prenatal care and tested positive for HIV infection at 1 of 4 clinics in Tanzania were invited to participate in a randomized clinical trial. The study aim was to test the effect of micronutrient supplements on vertical transmission and various health and pregnancy outcomes. Detailed descriptions of the trial design were published previously (26, 28). In brief, women eligible for enrollment were between 12 and 27 wk gestation according to the date of the last menstrual period; they resided in Dar es Salaam and intended to stay in the city until delivery and for ≥ 1 y thereafter.

As part of the prenatal screening, consent was sought for HIV-1 testing. Pretest and posttest counseling sessions were provided. We tested HIV-1 serostatus by using an enzyme-linked immunosorbent assay (Wellecozyme; Murex Biotech Ltd, Dartford, United Kingdom) and confirmed positive results with Western blot (Bio-Rad Laboratories Ltd, Hertfordshire, United Kingdom). HIV-1-infected women who consented to participate in the trial were randomly assigned in a 2-by-2 factorial design to receive a daily oral dose of 1 of 4 regimens. The 4 regimens were as follows: multivitamins (20 mg thiamine, 20 mg riboflavin, 25 mg vitamin B-6, 100 mg niacin, 50 μg vitamin B-12, 500 mg vitamin C, 30 mg vitamin E, and 0.8 mg folic acid), vitamin A alone (30 mg β-carotene plus 5000 IU preformed vitamin A), multivitamins including vitamin A, and placebo. Subjects consumed the supplements or placebo from enrollment until the end of the study (after delivery). The supplement and placebo tablets were indistinguishable. In addition, all subjects received 120 mg ferrous iron and 5 mg folate daily. Weekly malaria prophylaxis was also provided in accordance with the standard of prenatal care in Tanzania. Prenatal care and counseling were provided throughout the study period. Antiretroviral medications were unavailable in this setting at the time of the study.

Information on subject age, education, socioeconomic and marital status, and obstetric history was obtained at the first study visit by trained personnel. Study physicians performed a complete medical examination and collected blood, urine, stool, and vaginal specimens. Height, weight, and midupper arm circumference were measured in light clothing by trained personnel using standardized methods and calibrated instruments (29). At every monthly visit after enrollment, study personnel conducted a physical examination and obtained anthropometric measurements.

Laboratory investigations

Baseline tests were carried out to obtain a complete blood profile and routine urine and stool examinations and to test for malaria and sexually transmitted diseases. Hemoglobin was measured by using the CBC5 Coulter Counter (Coulter Corporation, Miami) or the cyanmethemoglobin colorimetric method (Corning Inc, Corning, NY). Absolute counts of CD3+, CD4+, and CD8+ T lymphocyte subsets were obtained with the FACS count system (Becton Dickinson, San Jose, CA). Serum retinol and vitamin E concentrations were measured with HPLC, and serum selenium was measured with atomic absorption analysis. Active syphilis was diagnosed if the subject had positive results for sera antibodies on 2 tests: the VDRL (Murex Diagnostic, Dartford, United Kingdom) and Treponema Pallidum Hemagglutination (Fujirebio, Tokyo). Infections caused by Neisseria gonorrhoea, Candida albicans, and Trichomonas vaginalis were identified from vaginal and cervical swabs. The presence of malaria parasites was ascertained from giemsa-stained thick- and thin-smear blood films. Virtually all malaria infections were caused by Plasmodium falciparum. Parasite density per cubic millimeter was calculated from the number of malaria parasites identified per 200 leukocytes and each subject’s total leukocyte count/mm3 in peripheral blood. Stool specimens were examined for the presence of helminths (Ascaris lumbricoides, hookworm, Trichuris trichiura, Strongyloides stercoralis, and Schistosoma mansoni) and protozoans (Giardia lamblia, Entamoeba histolytica, and Cryptosporidium parvum). Samples were examined macroscopically for worms and microscopically for eggs, larvae, trophozoites, and cysts by using saline and iodine wet mount and the formalin-ether concentration technique. A urine sample was examined for the presence of Schistosoma haematobium.

Data analyses

Analyses of weight gain during pregnancy were limited to women who had: 1) a singleton pregnancy, 2) a known date of pregnancy outcome, and 3) ≥ 2 weight measurements between enrollment and the end of gestation. Data from women with adverse outcomes, such as abortion or stillbirth, were not excluded from the analyses.

The distribution of baseline characteristics was compared across treatment groups by using the Wilcoxon rank sum and Kruskal-Wallis tests for continuous variables and χ2 tests for proportions.

Intent-to-treat analyses were carried out to examine treatment effects on both continuous and categorical weight gain outcomes. We examined the overall effect of multivitamin supplements by comparing women who received multivitamins alone or in combination with vitamin A with women who did not receive multivitamins, ie, those who received only vitamin A or placebo. Similarly, to assess the overall effect of vitamin A supplements, we compared women who received vitamin A alone or in combination with multivitamins with women who did not receive vitamin A, ie, those who received only multivitamins or placebo. We assessed the joint effect of multivitamins and vitamin A according to the methods described below.

Continuous outcomes

The continuous outcomes included overall and trimester-specific total weight gain and the rate of weight gain at various points during pregnancy. We calculated overall total weight gain as the arithmetic difference between the last weight recorded before the end of pregnancy and weight at randomization. Trimester-specific total weight gain was estimated separately for the subset of women contributing ≥ 2 weight measurements between weeks 12 and 26 (second trimester) and for those with ≥ 2 weight measurements after week 26 (third trimester), as the difference between the last and first weight measurements available during the interval. The effect of the supplements was then calculated as the difference in average weight change between treatment arms, overall and by trimesters. The 95% CI for the treatment effect was estimated from a two-way analysis of variance model with robust estimators of variance (30).

We also examined the effect of the supplements on the weekly rate of weight gain by using a mixed-effects regression model for repeated measures (PROC MIXED; SAS Institute Inc, Cary, NC):

\[
WT_{ij} = (\beta_0 + b_{i0}) + \beta_1MV_{ij} + \beta_2VA_{ij} + (\beta_3 + b_{i3}) GA_{ij} + \\
(\beta_4GA^2_{ij} + \beta_5MV_{ij} \times GA_{ij} + \beta_6VA_{ij} \times GA_{ij} + \beta_7MV_{ij} \times GA^2_{ij} + \beta_8VA_{ij} \times GA^2_{ij}) + \beta_9MV_{ij} \times \\
VA_{ij} \times GA_{ij} + \beta_{10}MV_{ij} \times VA_{ij} \times GA^2_{ij} + e_{ij}
\]  

(1)
Mixed effects models allow the use of all available measurements during follow-up (\(j\)) for every subject (\(i\)), adjusting for the within-person correlation of measurements in the estimation of the variance (31). The effect of multivitamins (MV) at any given week of gestation (GA) was estimated as the difference (\(\beta_1 + \beta_2\)) in the rate of weight (WT) gain between women who received multivitamins and those who did not. The effect of vitamin A (VA) was estimated as (\(\beta_6 + \beta_8\)), whereas a potential joint effect of multivitamins and vitamin A was assessed from a three-way interaction term between multivitamins, vitamin A, and gestational age. A quadratic term for time (GA\(^2\)) has been found appropriate to describe nonlinear patterns of weight gain during pregnancy (32), and was statistically significant in this population. CIs for the treatment effect were computed by using robust estimates of variance. Average weight gain curves were fitted by using restricted cubic splines (33).

Categorical outcomes

We considered the effect of supplements on 1) the risk of low total weight gain, 2) the risk of low rate of weight gain, and 3) the risk of weight loss. Low total weight gain, overall and by trimesters, was defined as a weight difference between the last and first measurements that was below the 25th percentile of the distribution for total or trimester-specific weight gain, respectively. For the definitions of low rate of weight gain and weight loss as categorical outcomes, the rate of weight gain was estimated separately for the second and third trimesters as the regression slope of every individual’s set of weight measurements on week of gestation during the trimester-specific interval. Low rate of weight gain was defined as a regression slope below the 25th percentile of the trimester-specific distribution, and weight loss was defined as a slope \(\leq 0\). To test the effect of supplements on these categorical outcomes, we calculated RRs with 95% CIs from \(2 \times n\) tables, and we used the chi-square test.

We also assessed whether the effect of supplements was modified by baseline characteristics, including midupper arm circumference, CD4+ and CD8+ T cell counts, clinical stage of HIV disease according to World Health Organization criteria (34), hemoglobin concentration, malaria infection, intestinal parasites, sexually transmitted diseases, season at conception, and serum retinol, vitamin E, and selenium concentrations. The statistical significance of all interactions was tested with the likelihood ratio test. Analyses were carried out with Statistical Analyses System software, version 8 (SAS Institute Inc, Cary, NC).

The study protocol was approved by the Research and Publications Committee of Muhimbili University College of Health Sciences, the Ethical Committee of the National AIDS Control Program of the Tanzanian Ministry of Health, and the Institutional Review Board of the Harvard School of Public Health. All subjects gave their informed consent to participate in the study.

RESULTS

A total of 1075 HIV-infected, pregnant women were randomly assigned to a treatment group; 6 of the women died before delivery. Twin pregnancies (\(n = 24\)), women with unknown date of pregnancy outcome (\(n = 42\)), and mothers with <2 weight measurements during pregnancy (\(n = 46\)) were excluded from the analyses of weight gain; thus, results are shown for 957 women (Figure 1). The distribution of baseline covariates, including sociodemographic characteristics of the mother, indicators of...
nutritional and immunologic status, stage of HIV disease, and presence of selected infectious diseases did not differ significantly across treatment regimens (Table 1). For each treatment arm, mean gestational age at randomization was 20 wk, and the last visit occurred at week 36, on average. The mean number of weight measurements per woman was 4.7, independent of treatment assignment, and 94% of the mothers had 3 measurements. We reported previously that compliance with treatment during pregnancy was high, as assessed by pill count (median: 90% by the time of delivery) (26). In addition, in a subset of 125 women, evidence of high compliance was reported. In the group that received vitamin A, the plasma β-carotene concentration increased significantly from 0.23 μmol/L at baseline to 1.71 μmol/L at delivery, whereas the values were 0.22 μmol/L at baseline and 0.25 μmol/L at delivery in the group not given vitamin A (28).

Total weight gain from randomization to the last visit during pregnancy was 4.0 ± 3.2 kg. The estimated average rate of weight gain during the second trimester, 306 g/wk (95% CI: 283, 329), was significantly higher than that during the third trimester, 247 g/wk (95% CI: 230, 263). This indicates that the pattern of weight gain in this population did not follow a linear trend. The incidence of weight loss was 14.2% (n = 94) during the second trimester and 15.7% (n = 131) during the third trimester. The subsets of women with ≥2 weight measurements in the second and third trimesters were comparable to each other with respect to baseline characteristics.

Supplementation with multivitamins significantly increased weight gain during the third trimester (Table 2). The average total effect was 304 g (95% CI: 17, 590; P = 0.04). We also observed a positive effect on the rate of weight gain, particularly after week 26 of gestation (Figure 2A). By week 36, mothers receiving multivitamins were gaining an average of 39 g/wk more than women not receiving multivitamins. During the third trimester, multivitamin supplements resulted in significantly reduced risks of low total weight gain (RR: 0.70; 95% CI: 0.55, 0.90; P = 0.005), weight loss (RR: 0.69; 95% CI: 0.50, 0.95; P = 0.02), and low rate of weight gain (RR: 0.73; 95% CI: 0.58, 0.93; P = 0.01).

**Table 1** Maternal characteristics at baseline according to treatment assignment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 234)</th>
<th>Vitamin A only (n = 239)</th>
<th>Multivitamins only (n = 237)</th>
<th>Multivitamins and vitamin A (n = 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at recruitment (wk)</td>
<td>20.4 ± 3.4</td>
<td>20.4 ± 3.4</td>
<td>20.8 ± 3.1</td>
<td>20.4 ± 3.2</td>
</tr>
<tr>
<td>Age (y)</td>
<td>24.8 ± 4.8</td>
<td>24.6 ± 5.0</td>
<td>24.6 ± 4.7</td>
<td>24.9 ± 4.6</td>
</tr>
<tr>
<td>Completed primary school (%)</td>
<td>85.9 [201]</td>
<td>87.9 [210]</td>
<td>83.6 [198]</td>
<td>88.7 [219]</td>
</tr>
<tr>
<td>Lives with partner (%)</td>
<td>90.2 [211]</td>
<td>86.2 [206]</td>
<td>88.6 [210]</td>
<td>88.3 [218]</td>
</tr>
<tr>
<td>Contributes to household income (%)</td>
<td>25.4 [59]</td>
<td>25.2 [60]</td>
<td>26.6 [63]</td>
<td>24.1 [60]</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>30.6 [71]</td>
<td>37.2 [89]</td>
<td>36.0 [85]</td>
<td>31.3 [77]</td>
</tr>
<tr>
<td>Money spent on food (Tanzanian shillings)</td>
<td>517 ± 260</td>
<td>581 ± 324</td>
<td>495 ± 243</td>
<td>510 ± 250</td>
</tr>
<tr>
<td>Season at conception (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January–February (Dry)</td>
<td>9.4 [22]</td>
<td>13.0 [31]</td>
<td>13.5 [32]</td>
<td>13.8 [34]</td>
</tr>
<tr>
<td>March–May (Long rains)</td>
<td>20.5 [48]</td>
<td>16.7 [40]</td>
<td>16.0 [38]</td>
<td>17.4 [43]</td>
</tr>
<tr>
<td>June–October (Dry)</td>
<td>56.8 [133]</td>
<td>53.1 [127]</td>
<td>54.0 [128]</td>
<td>56.3 [139]</td>
</tr>
<tr>
<td>November–December (Short rains)</td>
<td>13.3 [31]</td>
<td>17.2 [41]</td>
<td>16.5 [39]</td>
<td>12.6 [31]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.4 ± 5.9</td>
<td>156.7 ± 6.2</td>
<td>156.8 ± 5.4</td>
<td>156.5 ± 5.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.3 ± 8.7</td>
<td>57.6 ± 9.7</td>
<td>58.2 ± 9.5</td>
<td>57.3 ± 8.4</td>
</tr>
<tr>
<td>Midupper arm circumference (cm)</td>
<td>25.4 ± 2.9</td>
<td>25.7 ± 3.0</td>
<td>25.8 ± 2.9</td>
<td>25.6 ± 2.7</td>
</tr>
<tr>
<td>Serum retinol (μmol/L)</td>
<td>0.90 ± 0.41</td>
<td>0.85 ± 0.33</td>
<td>0.84 ± 0.33</td>
<td>0.86 ± 0.29</td>
</tr>
<tr>
<td>Serum vitamin E (μmol/L)</td>
<td>9.8 ± 3.0</td>
<td>9.8 ± 3.2</td>
<td>9.7 ± 3.0</td>
<td>10.4 ± 3.2</td>
</tr>
<tr>
<td>Serum selenium (ppm)</td>
<td>0.130 ± 0.03</td>
<td>0.127 ± 0.02</td>
<td>0.125 ± 0.02</td>
<td>0.126 ± 0.02</td>
</tr>
<tr>
<td>CD4+ cell count (cells/mm³)</td>
<td>449 ± 263</td>
<td>440 ± 273</td>
<td>451 ± 255</td>
<td>438 ± 242</td>
</tr>
<tr>
<td>CD8+ cell count (cells/mm³)</td>
<td>767 ± 366</td>
<td>751 ± 343</td>
<td>723 ± 324</td>
<td>764 ± 330</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>97 ± 17</td>
<td>96 ± 18</td>
<td>95 ± 17</td>
<td>94 ± 17</td>
</tr>
<tr>
<td>Symptomatic HIV disease (%)</td>
<td>23.1 [54]</td>
<td>28.4 [68]</td>
<td>20.7 [49]</td>
<td>24.7 [61]</td>
</tr>
<tr>
<td>Infectious diseases (%)</td>
<td></td>
<td></td>
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<tr>
<td>Malaria</td>
<td>15.8 [37]</td>
<td>18.5 [44]</td>
<td>17.8 [42]</td>
<td>22.7 [56]</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>25.9 [60]</td>
<td>21.0 [50]</td>
<td>27.5 [65]</td>
<td>25.2 [62]</td>
</tr>
</tbody>
</table>

1 ± SD; n in brackets.
2 Completed ≥ 8 y of formal schooling.
3 Mothers who provided part or all of the household income; those who did not were solely supported by the partner or another person.
4 Average household income spent on food per person per day, estimated by dividing the total amount of money spent on food by the number of household members. The exchange rate for 500 shillings was =US$0.62 at the time of data collection. The difference in median household income spent on food per person per day between treatments was significant, P = 0.05 (Wilcoxon rank-sum test).
5 The month at conception was estimated from the reported date of the last menstrual period plus 14 d.
6 Women in stages 2 or 3 at recruitment according to the World Health Organization staging system of HIV disease.
TABLE 2
Effects of multivitamins and vitamin A supplements on gestational weight gain outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Vitamin A only</th>
<th>Multivitamins only</th>
<th>Multivitamins and vitamin A</th>
<th>Difference, MV vs no MV</th>
<th>Difference, VA vs no VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total weight gain (g)</td>
<td>3914 ± 3474</td>
<td>3962 ± 3134</td>
<td>4041 ± 2975</td>
<td>4048 ± 3221</td>
<td>107 (−299, 512)</td>
<td>28 (−434, 377)</td>
</tr>
<tr>
<td>Overall: from baseline to last visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Second trimester: weeks 12 to 26</td>
<td>1953 ± 1886</td>
<td>1793 ± 1766</td>
<td>1613 ± 1961</td>
<td>1802 ± 1697</td>
<td>−161 (−117, 438)</td>
<td>13 (−292, 266)</td>
</tr>
<tr>
<td>Third trimester: week 27 to delivery</td>
<td>1855 ± 2187</td>
<td>1939 ± 2021</td>
<td>2272 ± 1954</td>
<td>2131 ± 2302</td>
<td>304 (17, 590)</td>
<td>−31 (−256, 319)</td>
</tr>
<tr>
<td>Estimated rate of weight gain (g/wk)</td>
<td></td>
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<tr>
<td>Second trimester (week 17)</td>
<td>295 ± 31</td>
<td>320 ± 30</td>
<td>309 ± 30</td>
<td>283 ± 28</td>
<td>−13 (−71, 46)</td>
<td>3 (−62, 55)</td>
</tr>
<tr>
<td>Third trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 27</td>
<td>254 ± 14</td>
<td>260 ± 12</td>
<td>266 ± 12</td>
<td>262 ± 12</td>
<td>7 (−17, 32)</td>
<td>1 (25, −24)</td>
</tr>
<tr>
<td>Week 36</td>
<td>198 ± 21</td>
<td>216 ± 20</td>
<td>247 ± 19</td>
<td>245 ± 21</td>
<td>39 (−1, 79)</td>
<td>9 (49, −31)</td>
</tr>
<tr>
<td>Risk of low total weight gain (%)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall: from baseline to last visit (&lt; 1.8 kg)</td>
<td>28.6 [67]</td>
<td>25.1 [60]</td>
<td>22.8 [54]</td>
<td>25.9 [64]</td>
<td>0.91 (0.73, 1.13)</td>
<td>0.99 (0.80, 1.23)</td>
</tr>
<tr>
<td>Second trimester: weeks 12 to 26 (&lt; 0.7 kg)</td>
<td>20.9 [34]</td>
<td>26.1 [42]</td>
<td>29.6 [47]</td>
<td>21.1 [38]</td>
<td>1.07 (0.82, 1.40)</td>
<td>0.93 (0.71, 1.22)</td>
</tr>
<tr>
<td>Third trimester: week 27 to delivery (&lt; 0.7 kg)</td>
<td>29.2 [59]</td>
<td>28.5 [59]</td>
<td>18.9 [40]</td>
<td>21.8 [47]</td>
<td>0.70 (0.55, 0.90)</td>
<td>1.05 (0.83, 1.33)</td>
</tr>
<tr>
<td>Risk of weight loss (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>During second trimester</td>
<td>11.7 [19]</td>
<td>15.5 [25]</td>
<td>19.5 [31]</td>
<td>10.6 [19]</td>
<td>1.09 (0.75, 1.58)</td>
<td>0.83 (0.57, 1.21)</td>
</tr>
<tr>
<td>During third trimester</td>
<td>18.8 [38]</td>
<td>18.4 [38]</td>
<td>9.4 [20]</td>
<td>16.2 [35]</td>
<td>0.69 (0.50, 0.95)</td>
<td>1.23 (0.90, 1.69)</td>
</tr>
<tr>
<td>Risk of low rate of weight gain (%)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During second trimester (≤ 130 g/wk)</td>
<td>22.7 [37]</td>
<td>24.8 [40]</td>
<td>30.2 [48]</td>
<td>22.2 [40]</td>
<td>1.09 (0.84, 1.42)</td>
<td>0.89 (0.68, 1.16)</td>
</tr>
<tr>
<td>During third trimester (≤ 100 g/wk)</td>
<td>28.7 [58]</td>
<td>30.0 [62]</td>
<td>20.3 [43]</td>
<td>22.7 [49]</td>
<td>0.73 (0.58, 0.93)</td>
<td>1.08 (0.85, 1.36)</td>
</tr>
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1 Mean difference between women receiving multivitamins (MV; multivitamins only or multivitamins plus vitamin A) and women not receiving multivitamins (vitamin A only or placebo); 95% CI in parentheses.
2 Mean difference between women receiving vitamin A (VA; vitamin A only or multivitamins plus vitamin A) and women not receiving vitamin A (multivitamins only or placebo); 95% CI in parentheses.
3 ± SD.
4 From 20 to 36 wk of gestation, on average.
5 From a repeated-measures mixed-effects model that included weight as the dependent variable and time, treatment, and their interaction term as predictors. A quadratic term for week of gestation was included to account for the nonlinearity of the weight gain pattern.
6 Defined as below the 25th percentile of the weight change distribution.
7 n in brackets.
8 Subject-specific slope of the regression of weight on gestational age ≤ 0.
9 Subject-specific slope of the regression of weight on gestational age < 25th percentile of the trimester-specific distribution of slopes.

Vitamin A supplements did not have a significant effect on weight gain outcomes overall or during the third trimester (Figure 2B). However, there was a positive, significant interaction between vitamin A supplements and multivitamins during the second trimester (P = 0.04). Women receiving both vitamin A and multivitamins had a 29% lower risk of low total weight gain than did women who received multivitamins alone (RR: 0.71; 95% CI: 0.49, 1.03). There was no effect of vitamin A alone compared with placebo (RR: 1.25; 95% CI: 0.84, 1.86).

We also examined whether the protective effect of multivitamins during the third trimester differed between strata of certain baseline characteristics that were potential effect modifiers (e.g., stage of HIV disease; Table 3). The protective effect tended to be greater among women in stage 1 of HIV disease compared with women in stage 2 or higher (P for interaction = 0.12). The protective effect also tended to be greater when the approximate date of conception coincided with the first dry season of the year (P for interaction = 0.11). During the second trimester, vitamin A supplementation was associated with a significant reduction in the risk of low rate of weight gain among mothers with hemoglobin concentration ≥ 110 g/L (RR: 0.31; 95% CI: 0.14, 0.68) but not among mothers with hemoglobin < 110 g/L (RR: 1.08; 95% CI: 0.81, 1.45) (P for interaction = 0.001). There were no significant interactions between the treatments and other potential effect modifiers including the mother’s level of education, CD4+ or CD8+ cell counts, malaria infection, intestinal parasites, sexually transmitted diseases, and plasma concentrations of vitamin A, vitamin E, or selenium.

**DISCUSSION**

We described the pattern of weight gain during pregnancy among HIV-infected women in Tanzania within the context of a randomized clinical trial. Multivitamin supplementation resulted in a small increase in maternal weight gain during the third trimester of pregnancy (304 g; 95% CI: 17, 590). Multivitamins were also associated with a significant 30% reduction in the risk of weight loss or low weight gain after week 27 of gestation. It is not likely that these results are attributable to either chance or confounding, given the large sample size and the randomized nature of the trial, respectively. The distribution of baseline covariates in each trimester subset was homogeneous across treatment arms, implying an absence of selection bias.

Little information is available on the relation between the micronutrient status of the mother and weight gain during pregnancy, especially among HIV-infected women. Some evidence of a beneficial association has been reported from an observational study conducted in the United States (35) and from trials performed in Greece (36) and Chile (37), all presumably among HIV-negative women. In the US study of prenatal micronutrient supplements, the proportion of mothers with inadequate weight gain was significantly higher among women who did not take prenatal.
VITAMINS AND PREGNANCY WEIGHT GAIN IN HIV INFECTION

The trimester-specific rates of weight gain in this group of HIV-infected mothers were generally below the average reported in presumably HIV-negative populations in developed countries (8, 46, 47) but were comparable to those documented in undernourished women of undetermined HIV status in developing countries (5, 6). HIV infection may be related to poor patterns of nutrition in presumably HIV-negative populations of developed countries (8, 46, 47) but were comparable to those documented in undernourished women of undetermined HIV status in developing countries (5, 6). HIV infection may be related to poor patterns of nutrition in presumably HIV-negative populations of developed countries, including weight loss and very low weight gain. Some studies among presumably HIV-negative women have linked low weight gain or weight loss during the third trimester of pregnancy with adverse pregnancy outcomes that include low birth weight and premature birth. In the Dutch Famine Birth Cohort Study, low weight gain (<0.5 kg/wk) or weight loss during the third trimester were related to lower birth weight, length, and ponderal index (39). In women from rural Malawi, the rate of weight gain during late pregnancy (defined as after week 32) was more strongly predictive of birth weight and length than was the weight-gain rate during early to mid pregnancy (40). In the same population, lower birth weight and length were observed among the offspring of women exposed to seasonal nutritional stress during the third trimester, but not during the second trimester (41).

In a group of low-income women in the United States, the risk of preterm delivery was found to be higher in those with low weight gain during the third trimester (after week 27) but not during the first or second trimester (42).

The observed protective effect of multivitamins against low maternal weight gain in our study population could be a mechanistic explanation for a protective effect of multivitamins against adverse pregnancy outcomes reported previously in this same group of mothers (26). Also, an effect of vitamin supplements on weight gain during the second trimester of pregnancy cannot be ruled out. In our study, the limitation of the beneficial effect to the third trimester suggests that it may take weeks for the correction of baseline deficiencies and the activation of regulatory mechanisms to occur; therefore, supplementation should be implemented as early as possible during pregnancy. Improvement of second trimester weight gain could also have a positive effect on birth outcomes, as was shown in various cohorts in the United States (43–45).

Supplements (28.7%) than among those who did (22.0%) (35). The mean rate of weight gain increased monotonically and significantly according to the total amount of folate consumed during pregnancy (38). In a trial conducted in Greece, pregnant women assigned to receive biweekly counseling about selecting foods with high nutrient value and using techniques for reducing nutrient loss during preparation had higher total weight gain than did the control subjects (11.3 and 10.3 kg, respectively; P < 0.05) (36). This coincided with increases in serum β-carotene concentrations during late pregnancy and serum vitamin C during early and late pregnancy in the intervention group. In a supplementation trial conducted in Santiago, Chile, mothers were randomly assigned to receive a milk-based product fortified with thiamine, pyridoxine, niacin, folate, zinc, iron, copper, iodine, and vitamins A, C, E, and D or a nonfortified supplement of powdered milk (37). Total weight gain during pregnancy was significantly greater for mothers receiving the fortified product than for those receiving unfortified powdered milk (12.3 compared with 11.3 kg; P < 0.05). The authors suggested that this effect could be attributable to the micronutrients in the fortified product, because the total energy, fat, and protein contents were higher in the unfortified powered milk. However, none of these 3 studies were designed to specifically address the effect of micronutrient supplementation on weight gain. Regarding the trials, one cannot conclude that the vitamins definitely had a causal effect, and in the observational study, only unadjusted associations were presented, opening the possibility of confounding by intakes of other nutrients or total energy, socioeconomic status, or other variables.

In our study, the effect of multivitamins on maternal weight gain was limited to the third trimester and was relatively modest (300 g between week 27 and term). Although this overall effect may have limited clinical relevance, our data suggest that multivitamin supplements may be particularly efficacious in preventing severe impairments in the weight-gain patterns of HIV-infected women, including weight loss and very low weight gain.

FIGURE 2. Effect of multivitamin (A) and vitamin A (B) supplements on weight gain during the third trimester of pregnancy. The average trends of weight gain were estimated by using cubic splines (33). The multivitamin group (n = 473) included those subjects assigned to receive multivitamins only or multivitamins plus vitamin A. In this group, the rate of weight gain became progressively higher over time (P = 0.06 for the rate difference at week 36 according to the Wald test). The “no multivitamins” group included those subjects assigned to receive placebo or vitamin A only (n = 484). The vitamin A group (n = 471) included those subjects assigned to receive vitamin A only or vitamin A plus multivitamins. The “no vitamin A” group included those subjects assigned to receive placebo or multivitamins only (n = 486). No significant effect was observed.
than for HIV-negative women, but the slope of weight gain was not significantly different (48). In a study conducted in Italy, total weight gain among opiate addicts was slightly higher for HIV-positive women than for HIV-negative women, but among non-addicts, HIV-negative women gained significantly more weight than did HIV-positive women (49).

Poor gestational weight gain among HIV-infected women could be explained by an HIV-related impairment of fetal and placental growth (13, 50) or by an effect of the infection on maternal body composition (51). Multivitamin supplements could ameliorate these adverse effects through several mechanisms. Regular use of multivitamins or B vitamins and higher dietary intakes of riboflavin, thiamin, and niacin were linked to maternal body composition (51). Multivitamin supplements could be a useful method of ameliorating this effect and, consequently, improving pregnancy outcomes. Additional research is needed to investigate the effects that HIV-induced changes in body composition may have on fetal loss, prematurity, intrauterine growth retardation, vertical transmission, and infant and maternal mortality. Also, the ways that pregnancy and infant and maternal mortality. Also, the ways that pregnancy management might lessen the burden of this cascade by improving the immune response against opportunistic infections.

In conclusion, HIV infection is likely to impair the pattern of weight gain during pregnancy in women from sub-Saharan Africa. Multivitamin supplementation could be a useful method of ameliorating this effect and, consequently, improving pregnancy outcomes. Additional research is needed to investigate the effects that HIV-induced changes in body composition may have on fetal loss, prematurity, intrauterine growth retardation, vertical transmission, and infant and maternal mortality. Also, the ways that pregnancy management might lessen the burden of this cascade by improving the immune response against opportunistic infections.

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