Short-Term Micronutrient Supplementation Reduces the Duration of Pneumonia and Diarrheal Episodes in HIV-Infected Children\(^1\)\(^–\)\(^3\)

Siyazi Mda,\(^4,6\)* Joop M. A. van Raaij,\(^6\) François P. R. de Villiers,\(^4\) Una E. MacIntyre,\(^4,5\) and Frans J. Kok\(^6\)

\(^4\)Department of Paediatrics and Child Health, and \(^5\)Institute for Human Nutrition, University of Limpopo, Medunsa Campus, Pretoria 0204, South Africa; and \(^6\)Division of Human Nutrition, Wageningen University and Research Centre, 6700 EV Wageningen, The Netherlands

Abstract

The duration of pneumonia and of diarrhea is reported to be longer in HIV-infected than in uninfected children. We assessed the effect of a multi-micronutrient supplement on the duration of hospitalization in HIV-infected children. In a double-blind, randomized trial, HIV-infected children (4–24 mo) who were hospitalized with diarrhea or pneumonia were enrolled (\(n=118\)) and given a daily dose of a multi-micronutrient supplement (containing vitamins A, B complex, C, D, E, and folic acid, as well as copper, iron, and zinc at levels based on recommended daily allowances) or a placebo until discharge from the hospital. Children’s weights and heights were measured after enrollment and micronutrient concentrations were measured before discharge. On recovery from diarrhea or pneumonia, the children were discharged and the duration of hospitalization was noted. Anthropometric indices and micronutrient concentrations did not differ between children who received supplements and those who received placebos. Overall, the duration of hospitalization was shorter (\(P<0.05\)) among children who were receiving supplements (7.3 ± 3.9 d) (mean ± SD) than in children who were receiving placebos (9.0 ± 4.9); this was independent of admission diagnosis. In children admitted with diarrhea, the duration of hospitalization was 1.6 d (19%) shorter among children receiving supplements than in those receiving placebos, and hospitalization for pneumonia was 1.9 d (20%) shorter among children receiving supplements. Short-term multi-micronutrient supplementation significantly reduced the duration of pneumonia or diarrhea in HIV-infected children who were not yet receiving antiretroviral therapy and who remained alive during hospitalization. J. Nutr. doi: 10.3945/jn.109.110312.

Introduction

There were ~2.5 million children living with HIV worldwide in 2007 and 90% of them were in sub-Saharan Africa (1). In South Africa, there are ~300,000 children up to the age of 14 y infected with HIV (2). In sub-Saharan Africa, the HIV epidemic has resulted in a marked increase in childhood respiratory and diarrheal disease-related morbidity and mortality (3–5). In a South African academic hospital, the most common admission diagnosis among HIV-infected children was pneumonia, followed by diarrhea; these diseases were also noted to be more common in HIV-infected children than in uninfected children (6).

A survey in the US showed that the duration of hospital stays was longer in HIV-infected children than in uninfected children (7). HIV-infected South African children hospitalized with diarrhea or pneumonia also need longer periods of hospitalization (8,9,6,10). In a cross-sectional study at our hospital in Pretoria, we detected that duration of hospitalization was significantly longer (2.5 d) and that the micronutrient status was significantly poorer (our unpublished data). Micronutrient deficiencies are indeed known to be common in HIV-infected children (11,12). The severity of the micronutrient deficiencies may be partly related to the stage of the HIV disease (13) and to the severity of the pneumonia and/or diarrheal illness (14).

Studies assessing the effect of micronutrient supplementation on the duration of episodes of diarrhea or pneumonia reveal conflicting results. Zinc supplementation was shown to be beneficial in reducing the duration of diarrhea in South Asian children (15–18) but not in Bangladeshi male infants aged 1–6 mo (19). Analyses of pooled data from trials of acute diarrhea have concluded that zinc therapy is beneficial in the treatment of acute diarrhea (20,21). Although it has been found that zinc supplementation may reduce the duration of pneumonia (22), other studies failed to confirm this effect (23,24). The addition of vitamin A to the zinc supplement may have a synergistic effect on reducing diarrhea (25), partly due to the fact that zinc is essential for both intra- and intercellular transport of vitamin A (26,27). However, other studies do not show this effect (18,16). Vitamin A supplementation was shown to significantly reduce...
the duration of hospitalization among Mozambican children who were admitted with non-measles acute lower respiratory infections (28). Nonetheless, a metaanalysis revealed that there is no evidence that high-dose vitamin A improves recovery from pneumonia in developing countries (29).

Given that micronutrient supplements might be more effective in children who are malnourished (15,30,31), supplementation might be beneficial in children who are HIV-infected. However, studies on the effects of micronutrient supplementation on the duration of hospitalization of HIV-infected children are scarce.

Because micronutrient deficiencies rarely occur as single nutrient problems but rather as simultaneous deficiencies of more micronutrients, it is considered that the deficiencies should be addressed concurrently (32,33). The proportion of HIV-infected South African children receiving antiretroviral therapy (ART) in 2007 was estimated to be 10% according to UNAIDS (1). We therefore performed a randomized controlled trial to test our hypothesis that a multi-micronutrient supplement would significantly reduce the duration of hospitalization in HIV-infected children admitted with acute diarrhea and pneumonia who are not yet receiving ART.

Participants and Methods

Participants and study area

The participants were HIV-infected children aged between 4 mo and 2 y (overall number of children assessed for eligibility = 389; number of enrolled children = 118). These children had been admitted with diarrhea or pneumonia to the pediatric wards of Dr. George Mukhari hospital, the academic hospital for the Medunsa campus of the University of Limpopo. This public hospital is the second largest in the republic of South Africa with ~1800 beds. It is located ~35 km northwest of Pretoria, the capital city of South Africa. All the children were from the townships surrounding the hospital. The study was conducted between November 2005 and May 2007.

Diarrhea was defined as the passing of ≥3 loose stools/d in the previous 24 h as reported by the parent or guardian. Pneumonia was defined as an illness during which a child is reported to have a cough, has a temperature of 38°C or more, and has an elevated respiratory rate above the age-specific value on a minute estimation (30 breaths/min) (34). Because we intended to assess the effects of supplements on acute diarrhea, it was decided that children whose diarrheal episode was already longer than 72 h on admission should be excluded. Children admitted with pneumonia complicated by respiratory failure, i.e. hypoxia (saturation <90% on optimum amount of supplemental oxygen) and/or hypercarbia (PCO₂ >50 mm Hg), were also not included, because these children were eligible for transfer to the intensive care unit. To assess the effects of the supplements as such, children who were on ART or those who had received vitamin or micronutrient supplementation in the previous 2 mo were considered not eligible for inclusion. The proportion of HIV-infected South African children (<14 y) receiving ART in 2007 was estimated to be 10% according to UNAIDS (1). The proportion of HIV-infected children aged 4–24 mo who were on ART is not known, but it was probably below 10% (Dr. M.C. Moshe, personal communication).

Children who had a chronic illness unrelated to HIV were also excluded (total number excluded = 271; 258 because of not meeting inclusion criteria and 13 because of refusing to participate).

The Medunsa Research Ethics and Publications Committee approved the study; the permission of the GaRankuwa (now Dr. George Mukhari) hospital authorities was obtained. The parents or guardians of all participants provided signed informed consent prior to commencing the study.

Study design

A randomized, double-blind, placebo-controlled study was performed. A simple randomization schedule (computer-generated random numbers) was used to assign the children to 1 of 2 groups to receive a multi-micronutrient supplement or a placebo, stratified by admission diagnosis (pneumonia or diarrhea).

The HIV status of the children was confirmed by laboratory analysis. HIV-infected children whose parents agreed to participate in the study were enrolled within 24 h after admission. The assessment for eligibility (including obtaining consent for participation in the study) was conducted in the pediatric admission ward of the hospital in the morning (around breakfast time); this process lasted ~2 h. The supplement was then given to children who met the inclusion criteria and were willing to participate. The timing of the subsequent daily dose of supplement or placebo was standardized and was scheduled to be given at breakfast. Thus, the administration of supplement or placebo started on the morning of enrolment. The body weights and lengths of the children were measured when the child was fully rehydrated, usually within 24 h of enrolment.

The principal investigator monitored the progress of the children in the ward and when the attending physicians were of the opinion that the child was likely to be discharged (in line with discharge criteria) within 1 or 2 d, then blood samples were taken from fasting children for serum zinc, serum retinol, iron, and ferritin, plasma C-reactive protein (CRP), and hemoglobin (Hb) analyses. On the day of discharge, the duration of hospitalization was noted. Blood samples were also taken for CD4 and CD8 counts (within 24 h of admission) and these were used to classify the severity of HIV according to the CDC classification (35).

Treatment

The supplements and placebos used were crushable tablets provided by the pharmaceutical company Admnicile Trading. The multi-micronutrient supplements contained 300 μg retinol, 0.6 mg thiamin, 0.6 mg riboflavin, 8 mg niacin, 0.6 mg pyridoxine, 1 μg cobalamin, 70 μg folate, 25 μg ascorbic acid, 5 μg 1,25-dihydrocholecalciferol, 7 mg dl-α-tocopherol, 700 μg copper, 8 mg iron, 30 μg selenium, and 8 mg zinc at amounts based on recommended dietary allowances for a 1-y-old child (36). The amounts in the supplement were independently confirmed and certified by the Medicines Control Council of South Africa. The placebo and supplement tablets were identical in appearance and taste; the containers were also identical and were labeled only by study serial number. The supplements or placebos were crushed using a pill crusher and mixed with water and were administered by the nurse in the ward.

Methods

Clinical evaluation

The children were all examined by the principal investigator for any chronic illnesses. All the children were treated according to standard hospital protocols for diarrhea and pneumonia. The children with pneumonia were all given first-line antibiotics for community-acquired pneumonia. The children were ready for discharge when they passed 2 consecutive formed stools or no stools passed in the previous 24 h, as reported by the nurses in the hospital records. A child was considered to have recovered from pneumonia when the temperature and respiratory rate had been normal for at least 24 h, when there was no intercostal or sternal recession, and the child was able to drink and eat. The attending physicians discussed with the principal investigator prior to discharge to ensure adherence to the discharge criteria.

HIV tests. HIV-1 and HIV-2 serostatus was ascertained using 2 ELISA tests (Abbot Diagnostics) in children older than 15 mo (37). In children younger than 15 mo, a PCR test was performed in addition to the 2 ELISA (37). The PCR test (Gene Amp 2400, Applied Biosystems) was performed in the Virology laboratory of the National Health Laboratory Services (NHLS) at the Medunsa campus of the University of Limpopo.

Anthropometry. The ages of the children were calculated in months using the dates of birth, as given by the mothers. The weight was
measured to the nearest 0.1 kg without shoes and with the child wearing only light clothing using a single beam balance scale. The scale was calibrated before each measurement session using a standard weight of 10 kg. The children were not clinically dehydrated at the time of the weight measurements. The length was measured in the recumbent position to 0.1 cm, on a baby board, by the investigator with the help of an assistant. One examiner held the child’s head (with the chin in the neutral position) in contact with the fixed part of the board while the other examiner stretched the child to maximum length and then brought the movable part of the board into contact with the heels. Z-scores for weight-for-age (WAZ), length-for-age (HAZ), and weight-for-length (WHZ) were calculated based on the National Centre for Health Statistics reference values by means of the Epi-Info software version 3.2.2 (38).

Blood sampling and analysis. Blood samples were collected by venipuncture (puncture site cleaned with trace element-free alcohol). The samples for zinc were collected in trace element-free tubes, with removable lids.

All blood samples were collected after an overnight fast and were sent to the laboratory immediately after collection, protected from light, and stored at −20°C after centrifugation, until analysis. All the blood samples were stored at the Medunsa branch of the NHLS.

The serum zinc, serum iron, and ferritin measurements were performed at the Medunsa branch of the NHLS, while the retinol samples were batched and sent frozen to the main branch of the NHLS in Johannesburg and were analyzed within 10 d of sampling. Serum zinc was measured by atomic absorption spectrometry (Perkin Elmer ICP/330) (39), serum retinol by a fluorometric method (40), serum iron by rate spectrophotometry (39) (SynchronCX System, Beckman Coulter), and serum ferritin by using commercial ELISA kits (Beckman Access 2, Beckman Coulter) (41). Quality control for serum zinc, iron, and ferritin was assessed by repeat analysis of standard reference material for low, normal, and high values. The source of the reference material was BioRad Laboratories for serum zinc and iron and the material for the serum ferritin was obtained from Beckman Coulter. The intra-assay and inter-assay CV for serum zinc, retinol, iron, and ferritin were all <5%.

The Hb concentration was analyzed spectrophotometrically in whole blood (ABX Pentra DX 120, Horiba ABX Diagnostics). It was measured to test for anemia, defined as Hb <110 g/L (42).

Plasma concentrations of CRP were measured by nephelometry using an international reference standard for plasma proteins. CRP levels >10 mg/L were considered to be high and indicative of inflammation. The CD4 lymphocyte counts were measured using a Coulter flow cytometer (Coulter Epics XL-MCL, Beckman Coulter) to assess the immunological stage of HIV infection. The CD4 were reported as CD4 T-cell percentage (percent of total T-lymphocyte that is of the CD4 lineage) rather than absolute CD4 counts, because the CD4 percentages are commonly used in clinical pediatric practice and have less age-related variability (43).

Statistical analysis

Anthropometric Z-scores were calculated with Epi-Info software (version 3.2.2). Data elaboration and analysis was performed using SPSS 13.0 for Windows. Statistical analyses were 2-tailed where appropriate and significance was set at 5%.

The sample size calculation was based on a cross-sectional study conducted at the same hospital (our unpublished data) that revealed a mean duration of hospitalization of 5.9 ± 1.9 and 9.0 ± 2.5 d for HIV-infected children admitted with diarrhea and pneumonia, respectively. The calculations were based on a 5% level of significance and 80% power for a 2-tailed test, designed to be able to detect 1.5 d in the duration of diarrhea and of pneumonia. The required sample sizes per treatment group were 26 and 29 for diarrhea and pneumonia, respectively (44). In the present study, we ended up with slightly lower numbers than were calculated, but these lower numbers hardly affected the power of the tests. However, the power of the tests was strongly influenced by the much larger actual between-child duration of hospitalization (twice as much as we used in our a priori power calculations). Therefore, the actual power with which a relevant difference of 1.5 d in duration of hospitalization could be tested between treatment and placebo groups for all children was only 40%. Nevertheless, we did observe a significant treatment effect. However, in future studies, power calculations should be based on larger between-child variation in duration of hospitalization.

Analyses were conducted using coded treatment groups with the analysts unaware of the actual treatment.

Data were assessed for normality by visual examination of distribution plots followed by normality tests and were normalized where appropriate by log transformation.

Anthropometric measurements, serum zinc, retinol iron, ferritin, and CD4 lymphocyte percentages and Hb concentrations were compared using ANOVA with treatment group and gender as between-subject factors. The proportion of children with anemia and with CRP levels >10 mg/L was compared between the 2 groups by the chi-square test.

The differences in the duration of hospitalization of the 2 treatment groups were also contrasted by means of ANOVA, with admission diagnosis as a cofactor and age and gender as covariates. The effect of a covariate on the dependent variable was used to assess the interaction effect. ANOVA with or without the inclusion of data of children who died (i.e. intention to treat analysis) did not differ significantly from each other.

Results

A total of 389 children were screened, of whom 118 children were enrolled. Of the 118 enrolled children, 50 were admitted with diarrhea and 68 with pneumonia (Supplemental Fig. 1). In total, 12 (10%) children died during the period of hospitalization: 4 from the diarrhea group and 8 from with pneumonia group. In relation to treatment, 7 of the 12 children who died were from the placebo group and 5 were from the supplement group. The children who died were slightly younger and had lower weights and lengths than those who completed the study, but the WAZ, HAZ, and WHZ did not differ (Supplemental Table 1).

The serum zinc, vitamin A, iron, and ferritin concentrations in the 2 treatment groups and did not differ by diagnosis at admission (Supplemental Table 2). With respect to Hb levels, we found a significant interaction between admission diagnosis and the age of the children, but there was no treatment effect. The mean Hb levels were lower in the group of children admitted with pneumonia (89 ± 18 g/L) than those in children admitted with diarrhea (100 ± 15 g/L) (P < 0.05) (Supplemental Table 2). The number of children with inflammation (CRP >10 mg/L) was similar among children who received placebos (32) and supplements (28) (Supplemental Table 2). The proportion of children admitted with diarrhea exhibiting inflammation was 43% less than the proportion of those admitted with pneumonia with inflammation (73%) (P < 0.05).

The duration of hospitalization was shorter in children who were receiving supplements than in those who were receiving placebos (P < 0.05) (Table 2). When the data of the children who died were included (intention to treat analysis), the duration of hospitalization was also shorter among children who received the supplement (7.0 ± 3.8 d) than in those taking the placebo (8.6 ± 4.8 d) (P < 0.05). This reduction in the
period of hospitalization was independent of the children’s ages. There was no significant interaction between admission diagnosis and treatment group with respect to duration of hospitalization. The duration of hospitalization among children admitted with diarrhea was 1.6 d (19%) shorter in the supplement group. Similarly, among children admitted with pneumonia, the duration of hospital stay was 1.9 d (20%) shorter in the group of children receiving supplements.

Discussion

Our main objective in this study was to assess the effect of a commercially available multi-micronutrient supplement on the duration of acute diarrhea and of pneumonia in HIV-infected children who were not yet receiving ART. Duration of hospital stay was used as a measurement of the duration of acute diarrhea and of pneumonia. Supplementation indeed reduced the length of hospitalization significantly by ~20% (1.5 d), independent of admission diagnosis, a reduction that might be considered as clinically meaningful.

The nutritional status of the study children as measured by anthropometry and micronutrient status was poor. Mean values for WHZ indicate that a large portion of the children should be classified as wasted and mean values for HAZ demonstrate that most of the children were stunted (Table 1). Growth failure is common among HIV-infected children. The WAZ were significantly lower in HIV-infected children admitted with diarrhea to a South African academic hospital than in the uninfected control group (8). Stunting is said to be the growth problem most common among HIV-infected children. The WAZ were significantly lower in HIV-infected children admitted with diarrhea to a South African academic hospital than in the uninfected control group (8).

As mentioned before, the duration of hospitalization (only during hospitalization) was too short, but we did not collect serum samples before commencing treatment. The absence of such baseline serum concentrations hampers a valid interpretation of the lack of difference in micronutrient concentrations between the 2 treatment groups just before discharge. Anemia and low serum concentrations of micronutrients have been shown to be common among HIV-infected children (11,12).

The percentage of children with anemia was significantly higher among children admitted with pneumonia than among children admitted with diarrhea. This is consistent with our observation that the proportion of children with inflammation (CRP >10 mg/L) was significantly higher among children admitted with pneumonia. Systemic infectious diseases (with resultant inflammation) are known to cause acute hemolytic anemia (47) and elevated CRP levels have been shown to be highly correlated with anemia (48).

The proportion of children who died during hospitalization was 8% in the group of children admitted with diarrhea, whereas among those admitted with pneumonia it was 12%. This mortality rate of ~10% is similar to that observed among HIV-infected children in the general wards of our hospital. The anthropometry data suggest that the children who died were more stunted and underweight than the children who completed the study.

Despite a careful randomization, the children who were hospitalized with pneumonia and received the placebo treatment were 3.5 mo younger than those who received the supplement. However, ANOVA revealed that age was not significantly associated with duration of hospitalization. Therefore, it is unlikely that the difference in ages between the treatment groups might have confounded the treatment effect on the duration of hospitalization.

As mentioned before, the duration of hospitalization was ~20% shorter in the treatment group and this was independent

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### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected children with diarrhea</th>
<th>HIV-infected children with pneumonia</th>
<th>All children who completed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Supplement</td>
<td>Placebo</td>
</tr>
<tr>
<td>n</td>
<td>24</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Male/female, n/n</td>
<td>11/13</td>
<td>11/11</td>
<td>14/14</td>
</tr>
<tr>
<td>Age, mo</td>
<td>12.4 ± 5.3</td>
<td>14.2 ± 6.7</td>
<td>9.0 ± 3.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>6.6 ± 1.4</td>
<td>6.8 ± 1.7</td>
<td>5.8 ± 1.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>68.2 ± 7.1</td>
<td>69.5 ± 7.4</td>
<td>64.4 ± 7.1</td>
</tr>
<tr>
<td>WAZ</td>
<td>−2.71 ± 1.31</td>
<td>−2.83 ± 1.16</td>
<td>−2.83 ± 1.24</td>
</tr>
<tr>
<td>HAZ</td>
<td>−2.34 ± 1.59</td>
<td>−2.42 ± 1.72</td>
<td>−2.31 ± 1.62</td>
</tr>
<tr>
<td>WHZ</td>
<td>−1.63 ± 1.41</td>
<td>−1.73 ± 1.36</td>
<td>−1.45 ± 1.21</td>
</tr>
</tbody>
</table>

Values are the mean ± SD. Different from placebo group, P < 0.05.

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### TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected children with diarrhea</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
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<td>Placebo</td>
</tr>
<tr>
<td>n</td>
<td>24</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Hospitalization duration, d</td>
<td>8.6 ± 5.0</td>
<td>7.0 ± 4.5</td>
<td>9.4 ± 4.9</td>
</tr>
</tbody>
</table>

Values are the mean ± SD. Different from placebo group, P < 0.05.

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of the admission diagnosis. Unfortunately, there are hardly any studies that assess the effect of micronutrients in hospitalized HIV-infected children. Therefore, comparisons can only be made with studies in hospitalized children from developing countries where the nutritional status of the children might be similar to that found in HIV-infected children. Zinc supplements (combined with vitamin B complex) significantly reduced the stool output and duration of diarrhea in hospitalized Indian children compared with children given B complex vitamins only (49). Supplementation with a combination of zinc and copper to Indian children admitted with diarrhea did not significantly reduce the duration of hospitalization (50). Evidence suggests that zinc supplements have a beneficial effect on the duration of diarrhea, but the evidence for other micronutrients is equivocal. Analysis of pooled data indicated that zinc supplementation significantly reduces the duration of acute diarrhea (20). It is possible that the effects of the multi-micronutrient supplement (on the duration of diarrhea) that were observed in the current study are partly related to the zinc component. Nonetheless, the use of a multi-micronutrient supplement is likely to improve the overall micronutrient status of the children and may thus have greater benefits.

Among children admitted with pneumonia in the current study, those who received the supplement had a 20% shorter duration of hospitalization. In a group of children from India who were hospitalized with severe acute lower respiratory infection, supplementation with zinc reduced the duration of symptoms of severity, but this effect was noted only in boys; vitamin A on the other had no effect on the symptoms (23). Some studies have shown no effect on the duration of hospitalization among children who were given zinc and/or vitamin A supplements (51) or only zinc supplements (24). A metaanalysis revealed that there is no evidence that high-dose vitamin A improves recovery from pneumonia in developing countries (29). Studies on the efficacy of zinc supplements in reducing the duration of pneumonia have shown conflicting results and as far as we know, no metaanalysis has been conducted on the effect of zinc on acute pneumonia. The use of the antioxidant vitamins E and C as adjunct therapy in children with severe ALRI has also been shown to have no benefit (52). While the benefits of a single micronutrient may be equivocal, a multi-micronutrient supplement as used in the current study may be more beneficial in HIV-infected children.

We consider the reduction in duration of hospitalization of 1.5 d as clinically meaningful. A longer duration of hospitalization has an impact on hospital bed occupancy and the risks of acquiring a nosocomial infection are also increased with longer hospitalization. Apart from the clinical importance there is also the health care relevance. In an academic hospital in South Africa, the total daily cost to the hospital of caring for an inpatient HIV-infected child in 2005 was estimated at $1007 (calculated by using mid-2005 South African Rand to US dollars exchange rates) (53) and the costs of the multi-micronutrient supplement are around $0.10/d. We surmise that a reduction of 1.5 d in the duration of hospitalization would result in significant cost savings per patient.

The major finding of our study is that short-term multi-micronutrient supplementation will significantly reduce the duration of hospitalization in HIV-infected children admitted with diarrhea or with pneumonia who are not yet treated with ART and who do not die during hospitalization. Whether supplementation with the multi-micronutrient for a longer period may also reduce the number of episodes of diarrhea and of pneumonia in HIV-infected children should be investigated.

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Literature Cited


