Randomized, Controlled Clinical Trial of Zinc Supplementation to Prevent Immunological Failure in HIV-Infected Adults

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(See the editorial commentary by Mehta and Fawzi, on pages 1661–1663.)

Background. Adequate zinc is critical for immune function; however, zinc deficiency occurs in >50% of human immunodeficiency virus (HIV)–infected adults. We examined the safety and efficacy of long-term zinc supplementation in relation to HIV disease progression.

Methods. A prospective, randomized, controlled clinical trial was conducted involving 231 HIV-infected adults with low plasma zinc levels (<0.75 mg/L), who were randomly assigned to receive zinc (12 mg of elemental zinc for women and 15 mg for men) or placebo for 18 months. The primary end point was immunological failure. HIV viral load and CD4+ cell count were determined every 6 months. Questionnaires, pill counts, and plasma zinc and C-reactive protein levels were used to monitor adherence to study supplements and antiretroviral therapy. Intent-to-treat analysis used multiple-event analysis, treating CD4+ cell count <200 cells/mm^3 as a recurrent immunological failure event. Cox proportional hazard models and the general-linear model were used to analyze morbidity and mortality data.

Results. Zinc supplementation for 18 months reduced 4-fold the likelihood of immunological failure, controlling for age, sex, food insecurity, baseline CD4+ cell count, viral load, and antiretroviral therapy (relative rate, 0.24; 95% confidence interval, 0.10–0.56; P < .002). Viral load indicated poor control with antiretroviral therapy but was not affected by zinc supplementation. Zinc supplementation also reduced the rate of diarrhea by more than half (odds ratio, 0.4; 95% confidence interval, 0.183–0.981; P = .019), compared with placebo. There was no significant difference in mortality between the 2 groups.

Conclusions. This study demonstrated that long-term (18-month) zinc supplementation at nutritional levels delayed immunological failure and decreased diarrhea over time. This evidence supports the use of zinc supplementation as an adjunct therapy for HIV-infected adult cohorts with poor viral control.

Trial registration. ClinicalTrials.gov identifier: NCT00149552.

Adequate zinc status is critical for immune function [1]. Zinc deficiency reduces generation of T cells, depresses humoral and cell-mediated immunity, leads to lymphopenia and thymic atrophy [2], and increases the frequency and number of infections [2]. Low plasma zinc levels and inadequate zinc intake were found in up to 50% of participants in several cohorts of human immunodeficiency virus (HIV)–infected adults [3–5] and were independently associated with faster HIV disease progression [6, 7] and increased mortality [8], whereas increased plasma zinc levels were associated with improved relative risk of virological response [5] and slower HIV disease progression [9].

Zinc supplementation delayed HIV disease progression and decreased the rate of opportunistic infections with and without receipt of antiretroviral therapy (ART) [10], and zinc supplementation along with multivitamins and selenium supplements significantly reduced HIV-related mortality [11]. Nutritional doses of zinc for chi-
dren have shown beneficial effects on acute and persistent diarrhea, including lower stool and diarrheal frequency [12–15]. Zinc at doses higher than the US Food and Drug Administration Daily Values, however, may lead to faster HIV disease progression [16].

The effects of zinc deficiency and zinc supplementation on the development of immunological failure, morbidity, and mortality have not been adequately explored. For patients not receiving ART, a CD4+ cell count <200 cells/mm3 is considered immunological failure [17]. For those receiving ART, immunological failure has been defined as inadequate increase in CD4+ cell count above a certain threshold, although the specific definitions vary in the amount of the increase in CD4+ T cell counts expected [18]. Immunological failure is associated with twice the relative risk of clinical progression and with increased risk of mortality [19–21].

This study responded to a need created by convergence of the following factors: the role of zinc in maintaining the integrity of the immune system; the low zinc intake and inadequacy of zinc status among a large proportion of HIV-infected adults; the association between zinc deficiency, faster HIV disease progression, and HIV-related mortality; and the need to develop an optimal zinc therapy for HIV-infected adults. Therefore, we investigated the benefits and safety of zinc supplementation in nutritional doses to prevent immunological failure and to decrease morbidity and mortality among HIV-infected adults.

METHODS

Study design. A prospective, longitudinal, randomized, double-blind, placebo-controlled clinical trial consisting of a pre-treatment phase followed by an 18-month treatment protocol was conducted to test the safety and effectiveness of zinc supplementation. A cohort of 231 HIV-infected adults was recruited from March 2002 through December 2005. Participants were eligible for the study if HIV infection was documented, if they had low plasma zinc levels (<0.75 mg/L), if they were aged ≥18 years, and if they did not have history of endocrine or psychiatric disorders; premenopausal women were excluded if they were pregnant or had an intention to become pregnant. Participants with plasma zinc levels ≤0.35 mg/L at any time during the study were excluded for scientific and ethical reasons. HIV viral load, complete blood counts and chemistries, including parameters of renal and liver function were monitored at baseline and every 6 months, and any abnormal values were communicated to the primary care physician. The study protocol was approved by the Florida International University Institutional Review Board.

The prerandomization phase included 1 screening and 2 run-in visits that were used to obtain confirmation of eligibility and to identify potential noncompliant individuals who were no longer interested in participating. Participants were counseled on strategies to overcome problems with supplement adherence. Demographics, plasma zinc levels, and urine toxicology were determined at the initial screening visit. Participants who attended all 3 pretreatment visits within a 2-week time window, who returned the supplement bottles, and who used >80% of the pills were randomized in the study. In the last prerandomization visit, HIV viral load was obtained and was used as a stratification variable for randomization (<1000 copies/mL; 1000–99,999 copies/mL; 100,000–500,000 copies/mL; and >500,000 copies/mL). For the treatment protocol, participants were assigned randomly to receive zinc supplementation or placebo and were contacted monthly for 18 months for dispensation of the study supplement (12 mg of zinc for women and 15 mg for men or placebo). The pharmacist bottled 35 zinc or placebo pills, indistinguishable in shape, size, and color, for the entire study and coded the bottles with the participants’ identification number following the randomization code. Only the pharmacist and the statistician were aware of randomization assignments during the trial. The bottles were dispensed to each participant monthly, and the remaining pills were counted to assess adherence. A questionnaire was administered to collect data on acceptability of the supplement, adherence, adverse effects, and intercurrent morbidity. Clinical and study personnel and participants were blinded to the assignment groups. The Monarch Company prepared the pills but was not involved in the study design, implementation, analysis, or reporting of findings. The pill doses and randomization scheme were independently validated by the Oscar E. Olson Biochemistry Laboratory (Brookings, SD).

Assessments. At baseline and every 6 months, physical examination, medical history, and urine toxicology were performed by a nurse practitioner, and blood was drawn for assessment of CD4+ cell count, HIV viral load, high-sensitivity C-reactive protein (hsCRP) levels, plasma zinc levels, and blood chemistry. History of alcohol and drug use in the preceding 6 months was obtained. Medical history included currently prescribed medications, past and current use of ART, and adherence in the previous 6 months; a review of records was used to verify prescriptions and to determine changes in ART. Adherence to the study regimen was determined with questionnaires, pill counts, plasma zinc levels, and plasma hsCRP levels measured using frozen plasma samples (~80°C) after the study was completed and the assignment was unblinded. Morbidity information was collected by questionnaires at screening, at every monthly visit, and was confirmed by documentation in the medical chart. Cause of death was obtained through authorized contacts, medical records, and death certificates from Miami-Dade Health Department of Vital Statistics.
**Biochemical assays.** Lymphocyte phenotype was determined with a 4-color immunophenotyping panel of monoclonal antibodies. Differential counts were determined using a Coulter MaxM hematology instrument and were corroborated with cytocentrifuge smears. HIV viral loads were determined using an in vitro nucleic acid amplification test (Amplicor reagents and protocol; Roche-Diagnostics); hsCRP levels were determined using the CRP Ultra-Range Reagent Kit (Equal Diagnostics). Plasma zinc levels were measured by atomic-absorption spectrophotometry; quality assurance used standard reference material (National Institute of Standards and Technology).

**Statistical analysis.** The intent-to-treat principle was used for analyses. The primary end point of this trial was HIV disease progression, specifically immunological failure. Multiple event analysis was performed with the use of a marginal approach [22], in which confirmed CD4+ cell counts <200 cells/mm³ were treated as a recurrent immunological failure event. The Wei, Lin and Weissfeld model controlled for demographic factors, baseline CD4+ cell count, ART, and viral load. Differences in CD4+ cell count and viral load between treatment groups were estimated with generalized estimating equations models for repeated measurements [23]. Point estimates of postrandomization change in values and 95% confidence intervals (CIs) directly modeled the difference between repeated measures. P values were obtained through group analyses and were adjusted for baseline. Descriptive statistics were used to characterize the population. Continuous variables with non-normal distribution were analyzed using the Mann-Whitney U test, and those with normal distribution were analyzed using Student’s t test. All P values reported are 2-sided; statistical significance was defined as P<.05.

**Study outcomes and sample size.** A sample size of 210 participants (105 in each arm of the study) was proposed to examine the effect of zinc supplementation on immunological failure, defined as any CD4+ cell count <200 cells/mm³, which was the primary end point. HIV viral load, morbidity, and mortality were secondary end points. With a proposed sample size of ≥210, we had 91% power to detect a 20-cell/mm³ change in CD4+ cell count [24, 25]. With the permission of the Florida International University Institutional Review Board and the Data and Safety Monitoring Board, the sample size exceeded the proposed 210 (231 were recruited).

At study initiation and at 6-month intervals, the Data and Safety Monitoring Board reviewed the safety and efficacy of the

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**Figure 1.** Randomization flow chart. Flow chart depicts the study participant screening, randomization, and disposition and those included in the analyses.
Table 1. Baseline Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All participants (N = 231)</th>
<th>Zinc supplement group (n = 115)</th>
<th>Placebo group (n = 116)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD</td>
<td>42.7 ± 7.0</td>
<td>42.5 ± 7.1</td>
<td>42.8 ± 7.0</td>
<td>.73</td>
</tr>
<tr>
<td>Ethnicity, % of participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>77</td>
<td>78</td>
<td>76</td>
<td>.44</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Sex, % of participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73.2</td>
<td>72.2</td>
<td>74.1</td>
<td>.74</td>
</tr>
<tr>
<td>Female</td>
<td>26.8</td>
<td>27.8</td>
<td>25.9</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family monthly income</td>
<td>$326.4 ± $630.6</td>
<td>$402.8 ± $829.0</td>
<td>$249.3 ± $311.4</td>
<td>.066</td>
</tr>
<tr>
<td>Highest grade attained, years</td>
<td>11.1 ± 3.0</td>
<td>11.4 ± 2.7</td>
<td>10.8 ± 3.3</td>
<td>.092</td>
</tr>
<tr>
<td>HIV disease stage classification, % of participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>28.57</td>
<td>29.57</td>
<td>27.59</td>
<td>.87</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>37.66</td>
<td>36.52</td>
<td>38.79</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>33.77</td>
<td>33.91</td>
<td>33.62</td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count stratification, % of participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>33.8</td>
<td>33.9</td>
<td>33.6</td>
<td>.703</td>
</tr>
<tr>
<td>200–350 cells/mm³</td>
<td>21.6</td>
<td>19.1</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>&gt;350 cells/mm³</td>
<td>44.6</td>
<td>47</td>
<td>42.3</td>
<td></td>
</tr>
<tr>
<td>Time since HIV disease was diagnosed, mean years ± SD</td>
<td>10.1 ± 8.7</td>
<td>9.5 ± 6.0</td>
<td>10.8 ± 10.9</td>
<td>.30</td>
</tr>
<tr>
<td>Antiretroviral use, no. of participants (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiving ART</td>
<td>144 (62.3)</td>
<td>68 (59.1)</td>
<td>76 (65.5)</td>
<td>.104</td>
</tr>
<tr>
<td>Not receiving ART</td>
<td>87 (37.7)</td>
<td>47 (40.9)</td>
<td>40 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Receiving ART and with undetectable viral load, % of participants</td>
<td>29.9</td>
<td>32.4</td>
<td>27.6</td>
<td>.54</td>
</tr>
<tr>
<td>HCV seropositive, % of participants</td>
<td>25.1</td>
<td>21.7</td>
<td>28.5</td>
<td>.24</td>
</tr>
<tr>
<td>Total no. of changesa in ART during the study (%) with changes</td>
<td>181 (18.1)</td>
<td>97 (18.7)</td>
<td>84 (17.5)</td>
<td>.7</td>
</tr>
<tr>
<td>Cocaine use, abuse, or dependence, % of participants</td>
<td>29.9</td>
<td>28.7</td>
<td>31.0</td>
<td>.70</td>
</tr>
<tr>
<td>Other drug abuse, % of participants</td>
<td>69.7</td>
<td>69.6</td>
<td>69.8</td>
<td>.97</td>
</tr>
<tr>
<td>Alcohol use, % of participants</td>
<td>54.6</td>
<td>51.3</td>
<td>57.8</td>
<td>.33</td>
</tr>
<tr>
<td>Cigarette use, % of participants</td>
<td>82.6</td>
<td>80</td>
<td>85.2</td>
<td>.30</td>
</tr>
<tr>
<td>CD4+ cell count, mean cells/mm³ ± SD</td>
<td>373.1 ± 279.7</td>
<td>385.3 ± 285.1</td>
<td>360.9 ± 275.0</td>
<td>.51</td>
</tr>
<tr>
<td>HIV-1 viral load, mean log₁₀ copies/mL ± SD</td>
<td>4.0 ± 1.0</td>
<td>4.0 ± 1.0</td>
<td>4.0 ± 1.1</td>
<td>.83</td>
</tr>
<tr>
<td>Serum zinc level, mean mg/L ± SD</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>.61</td>
</tr>
</tbody>
</table>

NOTE. ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.
a Changes include initiation, discontinuation, intermittent use, and switches in antiretrovirals.

supplement. The Peto stopping boundary was used for early stopping, with nominal P = .001 for efficacy end points and P = .05 for safety end points [26].

RESULTS

**HIV disease progression (CD4+ cell count and viral load).** As shown in Figure 1, participants were randomized: 115 in the zinc supplementation group and 116 in the placebo group; 104 who received the zinc supplements and 96 who received placebo completed the 18-month trial. There were no significant differences in demographic or any other characteristics, including plasma zinc levels, disease stage, drug use, intermittent treatment, or adherence to ART at baseline, between the zinc supplementation and placebo groups.

Intervention with the study supplement did not result in any adverse effects. At the end of the trial, participants who received zinc supplements had significantly higher plasma zinc levels over time (β = 0.04; P = .047) than did those receiving placebo, after controlling for hsCRP at baseline and over time. The mean hsCRP level was 4.93 ± 1.97 mg/L and was used in the analyses to control for acute-phase reaction and to distinguish between those with low plasma zinc levels due to zinc deficiency and those with an acute-phase reaction due to infectious diseases and/or inflammation, as presented elsewhere.
TABLE 2. Results of the Multiple Event Analysis (Wei, Lin and Weissfeld Model) of Zinc Supplementation

<table>
<thead>
<tr>
<th>Measure</th>
<th>Multivariate RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in immunological events a</td>
<td>0.24 (0.10–0.56)</td>
<td>.002 a</td>
</tr>
</tbody>
</table>

**NOTE.** Relative rate (RR) is adjusted for age, sex, food insecurity, baseline CD4+ cell count, baseline HIV viral load (log scale), and antiretroviral therapy. CI, confidence interval.

a In the group receiving zinc supplements, compared with the placebo group.

b Significant at the level of P<.05.

[27]. The mean study pill return throughout the study was 3.65 ± 0.31 pills of a possible 4 pills monthly for those who came to their visits on time. A mean of 89.7% ± 4.17% came on time for each visit, with a dropout rate of 8% annually. These rates did not differ between the study groups. Despite the majority (62.3%) of this cohort reporting the use of antiretroviral medications, of those receiving ART, more than two-thirds (70.14%) had detectable viral load (>400 copies/mL) [28], and the rate was not different between the 2 study groups. Viral load indicated poor control with ART but was not affected by zinc supplementation.

Intent-to-treat analyses of the effect of zinc supplementation, compared with placebo, on HIV disease progression showed that zinc supplementation for 18 months prevented immunological failure, defined as a decrease of CD4+ cell count to <200 cells/mm³. Multiple event modeling analyses (the Wei, Lin and Weissfeld model) indicated that zinc supplementation for 18 months reduced 4 times the likelihood of immunological failure, compared with placebo, controlling for age, sex, food insecurity, baseline CD4+ cell count, viral load, and ART (relative rate, 0.24; 95% CI, 0.10–0.56; P<.002) (Table 2). This relationship remained significant after hsCRP level was included in the model.

**Morbidity.** At baseline, 32% of the participants reported history of diarrhea within the past year, with 11.6% reporting moderate or severe diarrhea. Although there was no difference in the prevalence of diarrhea between the groups at baseline, the intent-to-treat analysis showed that zinc supplementation significantly reduced the rate of diarrhea over time by more than half (odds ratio, 0.4; 95% CI, 0.183–0.981; P = .019), compared with placebo. This reduction was evident by 12 months and was maintained during the study period. Diarrhea was also significantly associated with lower mean plasma levels of zinc (0.59 ± 0.11 vs. 0.68 ± 0.21 mg/L; P<.001) and remained significant after controlling for ART, levels of hsCRP, CD4+ cell count, and viral load (P = .006). There were no significant differences among lower or upper respiratory disease or other health events between the groups. Changes in weight, wasting, or incidence of anemia also did not affect the findings.

No symptoms of zinc toxicity were detected with the level of supplementation given during the study.

**Mortality.** Using the Cox proportional hazards models, no significant difference in the rate of mortality was found between the arms of the study. Eleven participants died in the group receiving zinc supplements, and 8 participants died in the placebo group. Death certificates were obtained to verify time and cause of death and to determine whether the death was HIV related.

**Subset analyses.** Analyses were conducted involving participants who were receiving ART and had suppressed viral load (n = 40; 20 participants in each group); 7 were excluded from the Cox analyses because their CD4+ cell count was <200 cells/mm³ (ie, they had immune failure) at baseline. There were 4 new events of immune failure during the 18-month follow-up, all in the placebo group (χ² = 4.4; P = .043).

**DISCUSSION**

In this randomized, double-blind, placebo-controlled trial, nutritional levels of zinc supplementation given to HIV-infected adults resulted in a 4-fold decrease in the likelihood of immunological failure, defined as a decrease of CD4+ cell count to <200 cells/mm³, after 18 months of use, compared with placebo. Viral load indicated poor control with ART but was not affected by zinc supplementation. Zinc supplementation also significantly reduced diarrhea, compared with placebo. Respiratory diseases and HIV-related mortality were not affected by supplementation. There were no adverse effects associated with the dose of zinc supplementation used.

In this trial, we defined immunological failure as a decrease in CD4+ cell count to <200 cells/mm³ with or without ART, because this definition is predictive of HIV-related morbidity and mortality as well as non–AIDS-related morbidity [20, 29, 30]. Moreover, patients with CD4+ cell counts <200 cells/mm³ remain susceptible to opportunistic infections despite ART and have an increased risk of mortality [19–30]. Although this cohort was at risk for several factors associated with defective immune reconstitution [31], including poor access to therapy, previous therapeutic failure, intermittent duration, and low adherence to ART, a nutritional dose of zinc for 18 months prevented immunological failure, compared with placebo. In addition, zinc supplementation provided immunological and clinical benefits despite persisting detectable HIV viral load in the majority of the participants. Similar findings were reported by Grabar et al [32], who found that improvement in immunological response is associated with favorable clinical outcomes regardless of virologic response. The adherence to our study regimen was higher than to ART, most likely because of a low pill burden, lack of adverse effects, and active case management with the study supplement [28]. We used similar active
case management strategies to refer participants to treatment and to increase their adherence and compliance with ART [28]. Because zinc is also obtained from the diet, zinc therapy might not require adherence as strict as that needed to maintain the benefits of ART.

Because of early reports that intakes of zinc above nutritional levels were associated with disease progression [16], this study included only participants whose baseline plasma zinc levels were <0.75 mg/L, which has been recognized in the literature as low levels of zinc with clinical implications [8, 33]. The use of plasma zinc levels to detect true zinc deficiency has been controversial, because zinc is an acute-phase reactant [34]. To distinguish between true zinc deficiency and acute-phase reaction due to inflammation, hsCRP level was used to control for acute-phase reaction [35]. The cautious approach to zinc supplementation, by using nutritional levels of zinc to supplement HIV-seropositive individuals with low plasma zinc levels, might have produced the delayed (18-month) effect on prevention of immunological failure and morbidity observed in this study.

Zinc supplementation may prevent immunological failure through its action on thymic function, expression of interleukin 2, T cell proliferation, and potential reduction of mitochondrial toxicity and oxidative stress [36]. Thymulin, a thymic peptide important for the maturation and differentiation of immature thymocytes [37], is active only when bound to zinc, and its activity is reduced in immune-suppressed and zinc-deficient conditions [38]. Improved ability to reconstitute CD4⁺ cells, as shown in this clinical trial, may be related to the effects of supplementation on increasing the levels of the active zinc-bound thymulin, offering an additional mechanism for slowing HIV disease progression.

Zinc supplementation also affected morbidity in this population. Long-term zinc supplementation significantly decreased the rate and prevented new episodes of diarrhea over time, compared with placebo. Findings in the literature have been contradictory, mostly because of the use of variable doses of zinc, variable durations of therapy, and differences in whether zinc supplementation was used for prevention or treatment of diarrhea. High doses of zinc for short periods of time and during episodes of diarrhea have shown adverse outcomes or no effect [39, 40], whereas preventive zinc supplementation at low doses over long periods has had successful results [15]. An in vitro mechanism that supports these conclusions demonstrates that Tat (viral peptide essential for HIV replication) stimulates active fluid secretion from the serosal to the luminal side of enterocytes. Addition of zinc prevents the Tat-induced fluid secretion [41], which may explain the clinical benefits of zinc supplementation in preventing HIV-related diarrhea.

We did not observe significant differences in upper or lower respiratory infections or in mortality between the group receiving zinc supplements and the placebo group, although other studies have reported a reduction in rates of tuberculosis, pneumonia, and mortality among HIV-infected populations given zinc supplementation in developing countries [42, 43]. Our results may be limited by the small number of cases of pneumonia (n = 4) and tuberculosis (n = 1), and although we confirmed 19 HIV-related deaths, the lack of significant difference between study groups might be a result of the equal use of ART in both arms of the study.

Limitations. The study had a strong design, adequate power, and modest dropout rates. Our findings may be extended to other HIV-infected cohorts with high prevalences of zinc deficiency, such as men who have sex with men, children, and those in developing countries [5, 8, 15, 43]. However, because of the high prevalence of substance abuse and poor viral control with ART, these findings might not be generalizable to populations receiving ART with adequate viral control. Subset analyses of the participants receiving stable ART with controlled viral load (n = 40), however, indicate that those receiving zinc supplementation had no immunological failure, compared with 4 events in the placebo group. Although this subset analysis had a small sample size, it appears that it may broaden our findings to cohorts with adequate viral control. Further studies with adequate sample size and power are needed to confirm our findings in populations receiving stable ART with adequate viral control.

Conclusions. Nutritional levels of zinc supplementation given to HIV-infected adults resulted in a 4-fold decrease in the likelihood of immunological failure, defined as a decrease of CD4⁺ cell count to <200 cells/mm³, in this randomized, double-blind, placebo-controlled trial after 18 months of use, with no effect on viral load. Zinc supplementation also significantly reduced the morbidity associated with HIV-related diarrhea, compared with placebo. Respiratory diseases and mortality were not affected by zinc supplementation. Viral load indicated poor control with ART but was not affected by zinc supplementation. The results of this study can be generalized primarily to HIV-infected populations with prevalent zinc deficiency, such as drug users, children, men who have sex with men, and populations in developing countries [5, 8, 15, 43], as well as those with poor viral control while receiving ART.

This evidence supports the recommendation of zinc therapy as a safe, simple, and cost-effective tool to improve the immune response and to reduce morbidity and should be considered as an adjunct therapy for HIV infection.

Acknowledgments

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**References**


