Iron Status and the Severity of HIV Infection in Pregnant Women

Str—Emerging data suggest that the iron status of patients with HIV infection has an important effect on the development of opportunistic infection and the progression of HIV disease [1–7]. Few data are currently available on whether HIV infection or AIDS affects the iron balance of pregnant women differently than it affects that of nonpregnant women, men, and children. However, this is an important area of research because, in several sub-Saharan African nations, often 10%–25% of pregnant women are infected with HIV, and daily oral iron supplementation is routinely provided during antenatal care [8].

Thus, the recent report of Semba et al. [9] is of great interest. The authors performed a cross-sectional study among 483 HIV-infected women in Malawi and failed to find any correlation between serum ferritin levels (and other iron status markers) and HIV load and CD4⁺ lymphocyte count (markers of the severity of HIV disease) [9]. However, we question whether their methods affected the validity of their conclusions.

First, no adjustment was made for the fluctuation of ferritin as a positive acute-phase reactant, which can be a major confounding variable in subjects with multiple inflammatory stresses (e.g., malaria and HIV infection) [10]. Second, we question whether the statistical method used to analyze the ferritin concentrations (i.e., analysis of variance, which assumes normally distributed because some SD values are nearly twice as great as the mean values). No Spearman correlation coefficients were presented for the soluble transferrin receptor-log ferritin index and HIV severity markers; these analyses, perhaps, would be the most informative. In addition, the prevalence and range of iron depletion are not noted; if the study population had a very narrow range of iron status, then any effect of iron status upon HIV severity might not be detectable.

In contrast, significant associations between iron status and the severity of HIV infection were recently found in a cross-sectional study in a nonmalarial area in Zimbabwe, in which care was taken to control for potential confounding variables [8; H.F., unpublished data]. The study included 1669 pregnant women, of whom 526 were infected with HIV type 1 (HIV-1), and assessed serum concentrations of ferritin, folate, and the acute-phase protein α1-antichymotrypsin, as well as haptoglobin phenotype and HIV-1 load ([8], H.F., unpublished data). Of importance, the serum α1-antichymotrypsin concentration was included in the multivariate analyses to control for the potential misclassification of iron status due to the effect of the acute-phase response on serum ferritin concentrations. In addition, subjects had a broader range of iron deficiency and sufficiency than did the subjects in the study of Semba et al. [9].

Pregnant women with HIV infection had lower serum concentrations of folate, ferritin, and hemoglobin than did pregnant women without HIV infection, but the effects of HIV infection on hemoglobin concentration were strongest for those women with nondepleted iron stores (serum ferritin level, ≥12 μg/L) [8]. Further analysis showed that women with haptoglobin phenotype 2-2 had plasma HIV-1 RNA levels that were 2-fold greater than those of women with haptoglobin phenotype 1-1 (H.F., unpublished data); these data are in accord with data for a predominantly male population [7]. Finally, plasma HIV-1 loads in infected pregnant women with nondepleted iron stores (serum ferritin level, ≥24 μg/L) were 2-fold greater than those in infected pregnant women with iron depletion (serum ferritin level, <6 μg/L; H.F., unpublished data).

In view of the complexity and importance of these epidemiologic observations, we agree with Semba and colleagues that randomized, double-blind, controlled clinical trials of the effects of iron supplementation on HIV infection are needed [3, 9]. Design of such trials may be logistically and ethically difficult, however, because women with known

References


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iron deficiency during pregnancy should be treated (and, therefore, not randomized to a group that will not receive iron supplementation); conversely, administering an excessive amount of iron can be hazardous.

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Reply

Str—We have followed the helpful suggestions of Weinberg et al. [1] and have further analyzed the data from our study in Malawi [2]. We adjusted for the skewed distribution of ferritin concentrations and also for the presence of an acute-phase response, as indicated by elevated acute-phase proteins, such as C-reactive protein and α1-acid glycoprotein. When these data are reanalyzed (as in table 1 of the original paper [2]) according to plasma HIV load, by quartile, the mean (±SD) log_{10} ferritin concentrations (μg/L) are as follows (from lowest to highest quartile): 1.19 ± 0.52, 1.29 ± 0.49, 1.19 ± 0.48, and 1.23 ± 0.54 (P = .39). If subjects with C-reactive protein concentrations of >5 mg/L are excluded, the mean (±SD) log_{10} ferritin concentrations are as follows (from lowest to highest quartile): 1.17 ± 0.45, 1.20 ± 0.48, 1.07 ± 0.54, and 1.24 ± 0.53 (P = .37). If subjects with an α1-acid glycoprotein concentrations of >1 g/L are excluded, the mean log_{10} ferritin concentrations are as follows (from lowest to highest quartile): 1.11 ± 0.46, 1.22 ± 0.44, 1.13 ± 0.47, 1.18 ± 0.55, respectively (P = .32). These data show that there is no significant relationship between iron status and CD4+ lymphocyte count (by quartile).

The Spearman correlation between transferrin receptor-ferritin index and HIV load is r = −0.041 (P = .47), and the Spearman correlation between transferrin receptor-ferritin index and CD4+ lymphocyte count is r = 0.054 (P = .25). These data show that there is no significant correlation between the transferrin receptor-ferritin index and indicators of HIV disease severity. Moreover, for HIV-infected women with a serum ferritin level of ≥24 μg/L, the mean (±SD) log_{10} plasma HIV load (copies/mL) is 4.38 ± 0.80; the mean value (±SD) is 4.28 ± 0.85 for women with a serum ferritin level of <6 μg/L (P = .34; Student’s t test). Of the women in our study, 34.6% had plasma ferritin concentrations of <12 μg/ L, consistent with iron deficiency, and this prevalence of iron deficiency is similar to that described for pregnant women elsewhere in sub-Saharan Africa.

We thank Weinberg and colleagues for their suggestions to control for potential confounding variables [1]. These additional analyses further strengthen our conclusion that iron status is not related to indicators of severity of HIV disease among HIV-positive pregnant women in Malawi.

The data from our large study of HIV-positive women in Africa do not contraindicate iron supplementation, which is the current practice in developing countries in which there is a high prevalence of both HIV infection and iron defi-