in the absence of deep organ involvement—perhaps because drug penetration into infected organs is poorer, and drug concentration levels fall below those that are required to kill Candida species.

To address the issue of homogeneity of the study population, analyses were also performed on subpopulations with candidemia or with positive cultures of specimens from deep, normally sterile sites—populations from which patients with symptomatic candiduria were excluded [2]. These analyses showed highly statistically significant differences by day 10 in overall response (80% vs. 40%; \( P < .001 \)), clinical response (82% vs. 45%; \( P < .001 \)), mycological response (86% vs. 47%; \( P < .001 \)), Candida-attributable mortality rates by day 33 (5% vs. 21%; \( P = .033 \)), and the rate of culture-confirmed clearance of the infection, which remained more than twice as fast among those receiving combination therapy, compared with those receiving monotherapy (hazard ratio, 2.4; \( P = .011 \)).

The 2 deaths on day 1 referred to by Herbrecht et al. [1] resulted, respectively, from a tension pneumothorax (a complication of mechanical ventilation) and a discontinuation of life-support systems at the request of the family because of the patient’s irremediable underlying pathologies. Therefore, these deaths contributed to the overall mortality rate but not the Candida-attributable mortality rate.

It is usual practice in antifungal trials to base efficacy assessments on a modified intent-to-treat population, as we described [2]. By applying the primary efficacy variable to an intent-to-treat population composed of all patients who received at least 1 dose of study drug and by taking a conservative approach to the analysis of patients with no post-treatment disease assessment—such patients (including the 3 referred to in [1]) being classified as experiencing treatment failure—we showed an overall response by day 10 in 51% of the placebo group (35 of 69 patients) and 79% of the Mycograb group (54 of 68 patients)—a highly statistically significant difference (\( P < .001 \)).

All patients had culture-positive candidiasis before starting therapy. This was a prerequisite for study entry. Because it takes several days for Candida to grow on culture, there was inevitably a lag between the time the culture was performed, the positive culture result, obtaining patient consent, and the day of study entry. The protocol allowed 3 days for this process, and samples were not recultured on day 0 for all patients. The protocol required all patients to have clinical sepsis at the time of study entry. If a patient has culture-confirmed candidiasis within 3 days of study entry and active sepsis on the day of study entry, it is reasonable to assume the patient’s candidiasis is ongoing. The overall mortality rate at day 33 is given in our article, together with figures showing a breakdown with respect to cause and APACHE II score [2].

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Osteopenia in Patients with HIV Infection Is Not Associated with Elevated sTNFR2 Levels

To the Editor—We were interested in the study by Arnsten et al. [1] and the accompanying editorial by Yin and Glesby [2] addressing bone mineral density (BMD) in HIV-infected women. The authors cite the potential role of proinflammatory cytokines, such as TNF, in bone resorption and osteoporosis [3, 4]. Elevated TNF levels have been reported in HIV-infected individuals [5, 6], and several studies have examined BMD among this population [7]; however, to our knowledge, none has analyzed TNF levels in relation to BMD. We report the results of a case-control study that investigates relationships between soluble TNF receptor 2 (sTNFR2) levels and BMD in an HIV-infected cohort.

We reviewed the charts in our AIDS Treatment Center (Stony Brook, NY) of 46 HIV-infected patients for whom whole-body dual-energy X-ray absorptiometry (DEXA) was performed, and identified 7 with osteopenia (for whom the z score was between −1 and −2.5). To eliminate possible confounding variables, patients were matched for age, sex, race, CD4+ cell count, and body mass index (calculated as weight in kilograms divided by the square of height in meters) with 7 individuals...
from the same cohort who did not have osteopenia. Baseline characteristics and \( P \) values are shown in Table 1. We compared sTNFR2 levels in case patients and control subjects. We used \( \chi^2 \) and Fisher’s exact tests to compare categorical variables, and Student’s t test and Pearson’s correlation were used for analysis of continuous variables.

sTNFR2 levels were nearly identical in the 2 groups (mean level \( \pm \) SEM, 0.5 \( \pm \) 0.05 ng/mL among case patients and 5.2 \( \pm \) 0.8 ng/mL among control subjects; \( P = .85 \)). No correlation between sTNFR2 levels and osteopenia was identified, although levels were significantly elevated in the case patient group, compared with HIV-negative subjects (5.1 \( \pm \) 0.5 ng/mL vs. 3.1 \( \pm \) 0.3 ng/mL; \( P = .003 \)). When \( t \) score and total BMD were analyzed for the 2 groups, we encountered similar results. We found no associations between antiretroviral medications and osteopenia, including nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitors.

The number of patients studied was small; however, 15% of this predominantly male, young, overweight cohort with mean CD4\(^+\) cell counts >350 cells/\( \mu \)L, were osteopenic, by total \( z \) score. Elevated levels of proinflammatory cytokines have been classically demonstrated in patients with poorly controlled HIV infection or as a consequence of HAART. Before the advent of HAART, low BMD was rarely observed; however, studies performed since 1996 have demonstrated an association between osteopenia and HIV infection [3,7].

Given these observations, and as suggested by Arnsten et al. [1], HIV-infected patients with osteopenia would be expected to have higher circulating levels of TNF; however, we found that not to be the case. It may be that serum sTNFR2 is not a sensitive marker, because levels may vary in response to extraneous sources of inflammation. Cytokine levels in other tissues, such as adipocytes or osteocytes, might be more indicative. Alternatively, other cytokines may be more helpful in answering this question. Based on our findings, sTNFR2 is not associated with osteopenia.

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**References**


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**Antibiotic Pricing: When Cheaper May Not Be Better**

To the Editor—Antibiotics in India have always been cheaper in absolute terms thanks to weak patent laws that have been