BACKGROUND: Vaginal infections are common and have been associated with increased risk for acquisition of human immunodeficiency virus type 1 (HIV-1). METHODS: We conducted a randomized trial of directly observed oral treatment administered monthly to reduce vaginal infections among Kenyan women at risk for HIV-1 acquisition. A trial intervention of 2 g of metronidazole plus 150 mg of fluconazole was compared with metronidazole placebo plus fluconazole placebo. The primary end points were bacterial vaginosis (BV), vaginal candidiasis, trichomoniasis vaginalis (hereafter, "trichomoniasis"), and colonization with Lactobacillus organisms. RESULTS: Of 310 HIV-1-seronegative female sex workers enrolled (155 per arm), 303 were included in the primary end points analysis. A median of 12 follow-up visits per subject were recorded in both study arms (P = .8). Compared with control subjects, women receiving the intervention had fewer episodes of BV (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.49-0.63) and more frequent vaginal colonization with any Lactobacillus species (HR, 1.47; 95% CI, 1.19-1.80) and H(2)O(2)-producing Lactobacillus species (HR, 1.63; 95% CI, 1.16-2.27). The incidences of vaginal candidiasis (HR, 0.84; 95% CI, 0.67-1.04) and trichomoniasis (HR, 0.55; 95% CI, 0.27-1.12) among treated women were less than those among control subjects, but the differences were not statistically significant. CONCLUSIONS: Periodic presumptive treatment reduced the incidence of BV and promoted colonization with normal vaginal flora. Vaginal health interventions have the potential to provide simple, female-controlled approaches for reducing the risk of HIV-1 acquisition.