
Evaluation of Two Self-Care Treatments for Prevention of Vaginal Candidiasis in Women With HIV

Ann B. Williams, RN, EdD, Chang Yu, PhD, Karen Tashima, MD
Jane Burgess, ACRN, and Karina Danvers

Vaginal candidiasis (VC) is a common concern for women living with HIV infection. The authors evaluated the effectiveness of two self-care approaches to prophylaxis of VC among HIV-infected women, weekly intravaginal application of Lactobacillus acidophilus or weekly intravaginal application of clotrimazole tablets, in a randomized, double-blind, placebo-controlled trial. VC was defined as a vaginal swab positive for Candida species in the presence of signs/symptoms of vaginitis and the absence of a diagnosis of Trichomonas vaginalis or bacterial vaginosis. Thirty-four episodes of VC occurred among 164 women followed for a median of 21 months. The relative risk of experiencing an episode of VC was 0.4 (95% CI = 0.2, 0.9) in the clotrimazole arm and 0.5 (95% CI = 0.2, 1.1) in the Lactobacillus acidophilus arm. The estimated median time to first episode VC was longer for clotrimazole ($p = .03$, log rank test) and Lactobacillus acidophilus ($p = .09$, log rank test) compared with placebo. Vaginal yeast infections can be prevented with local therapy. Education about self-care for prophylaxis of VC should be offered to HIV-infected women.

Key words: clotrimazole, Lactobacillus acidophilus, alternative therapy

Although AIDS incidence in U.S. women has declined modestly in recent years, HIV incidence continues to rise (Centers for Disease Control and Prevention, 1999). In addition, the recent, rapid expansion of the number of antiretroviral agents available for treatment of HIV has extended quality and quantity of life

for HIV-infected women. As a result, more women are living longer with chronic HIV infection. Among the gynecologic conditions experienced by women with chronic HIV infection, vaginal candidiasis (VC) has been studied frequently, with reported prevalences ranging from 10% to 62% (Burns et al., 1997; Carpenter et al., 1991; Duerr et al., 1997; Greenblatt et al., 1997; Imam et al., 1990; Leroy et al., 1995; Rhoads, Wright, Redfield, & Burke, 1987; Spinillo et al., 1994; Williams, Andrews, Tashima, Mezger, & Yu, 1998). Because VC is also common among the general population of women of childbearing age, it has been difficult to ascertain with certainty that HIV-infected women experience more frequent or more severe episodes of VC. There are, unfortunately, no solid longitudinal studies describing incidence rates of demonstrated VC in this group. Nevertheless, nurses caring for HIV-infected women and the women themselves have identified VC as a source of persistent discomfort and distress, significantly affecting their quality of life.

Candida species are commensal fungal organisms that can be isolated from the mucosal surfaces of the mouth, gastrointestinal tract, and vagina of 80% of

Ann B. Williams, RN, EdD, is a professor at the Yale University School of Nursing. Chang Yu, PhD, was a biostatistical consultant at Yale University School of Nursing at the time of the study. Karen Tashima, MD, is an assistant professor at the Brown University Department of Biomedicine. Jane Burgess, ACRN, is the director of the CT AIDS Education and Training Center. Karina Danvers is a senior peer educator at the Yale University School of Nursing.

individuals, where they cause no symptoms in the normal host (Vartivarian & Smith, 1993). *Candida* is present in the genital tract of 10% to 55% of asymptomatic women of childbearing age (Sobel, 1993). The opportunistic qualities of *Candida* organisms are well recognized. In the vagina, transformation from asymptomatic *Candida* colonization into clinical disease (VC) is precipitated by an alteration in host factors, which include the microflora in the local environment and other poorly described host immune factors (Vartivarian & Smith, 1993). The precise relationship between immune status and VC remains unclear, with no association reported in some cohorts (Greenblatt et al., 1997; Imam et al., 1990; Schuman et al., 1998), whereas an increased risk for VC is associated with lower CD4 counts in others (Burns et al., 1997; Duerr et al., 1997; Spinillo et al., 1994; Williams et al., 1998).

Predisposing factors for VC, in addition to HIV-associated immune suppression, include pregnancy, uncontrolled diabetes mellitus, corticosteroid use, and topical and systemic antibiotics (Abularach & Anderson, 2000). Women with one or more of these conditions may wish to initiate steps to prevent the development of VC, particularly if there is a history of recurrent vaginitis. The options for prophylaxis include pharmacologic and nonpharmacologic strategies.

Systemic antifungals such as ketoconazole and fluconazole represent the pharmacologic approach to prophylaxis of VC. In a study of 323 HIV-infected women with CD4 counts < 300 cells/mm³, 200 mg of fluconazole orally per week effectively prevented VC (relative risk 0.64, $p = .05$) (Schuman et al., 1997). However, concern about the potential emergence of resistant *Candida* species, drug interactions, and cost limit the usefulness of a systemic pharmacologic strategy. In the current era of potent HIV therapy, HIV-infected women can anticipate living for many years while taking an ever increasing variety of antiretroviral agents. Concerns about the long-term effects of additional medications and potential drug-drug interactions contribute to the potential benefit offered by alternative, nonsystemic strategies for VC prophylaxis.

Nonpharmacologic approaches to prophylaxis of VC, such as eliminating tight-fitting clothing and

synthetic underwear, douching with vinegar, and frequent ingestion of yogurt are commonly recommended (Nokes, 1995), although there is limited evidence that these interventions are effective for most women (Sobel, 1992). In contrast, topical application of antifungals has shown some effectiveness in reducing the frequency of symptomatic episodes of VC. Monthly use of 500 mg of clotrimazole in a vaginal suppository was more effective than placebo in one study (Sobel, Schmitt, & Meriwether, 1989), whereas others have suggested that the same dose applied weekly is as effective as daily oral ketoconazole therapy (Sobel, 1992).

Lactobacillus species are considered part of the normal vaginal flora, and some species are thought to protect against vaginal infections through the production of hydrogen peroxide (Eschenbach et al., 1989). *Lactobacillus* inhibition of *Candida* species may be the result of competition for nutrients, interference with *Candida* adherence to epithelial cells, or the production of bacteriocins (Sobel, 1993). Women interested in self-care and alternative therapy sometimes use nonprescription products containing *Lactobacillus*, such as yogurt, acidophilus milk products, and capsules containing *Lactobacillus* powder, as douches or suppositories for treatment or prevention of vaginitis. Daily oral ingestion of yogurt containing *Lactobacillus* or vaginal application of yogurt tablets has been recommended (Nokes, 1995).

The benefits of a topical approach to prevention of *Candida* vaginitis among HIV-infected women include reduced pill burden, reduced risk for drug-drug interactions, reduction in drug-associated toxicities, and a potential reduction in the development of antifungal resistant *Candida* species. No information is available on the effectiveness of topical antifungals among HIV-infected women, nor are data available comparing the effectiveness of antifungals to *Lactobacillus* for prophylaxis of VC. Therefore, to evaluate the effectiveness of self-administered topical therapy for prophylaxis of VC in HIV-infected women, we conducted a randomized, double-blind, clinical trial comparing weekly vaginal insertion of capsules containing clotrimazole 100 mg or *Lactobacillus acidophilus* with placebo.

Method

Study Patients

Women were eligible for enrollment in the study if they were HIV seropositive, more than 18 years of age, not currently receiving systemic antifungal medication, not pregnant, and had no evidence of VC on exam. Patients were recruited from a university affiliated HIV/AIDS clinic and two community-based primary care clinics serving women receiving substance abuse treatment. The study was approved by the institutional review board or ethics committee at each recruitment site and at the Yale School of Nursing. Informed consent was obtained.

Study Procedures and Data Collection

This was a randomized, double-blind, placebo-controlled trial. Subjects were stratified by CD4 count at enrollment (0 to 100, 101 to 300, 301 to 500, and 500 or more cells/mm³) and randomly assigned to receive capsules containing clotrimazole powder 100 mg, *Lactobacillus acidophilus* (Gynatren, Natren Inc., Westlake Village, CA), or placebo. The clotrimazole dose of 100 mg was selected because it is the dose available over the counter and thus available to women practicing self-care. Because the *Lactobacillus acidophilus* required refrigeration, subjects on all treatment arms were asked to keep their capsules refrigerated. The women received instruction about correct insertion of the capsules and were given a variety of reminder devices to enhance adherence to the once-a-week regimen.

At 6-month intervals, demographic and behavioral information, medical history, all prescribed medications, and current gynecologic symptoms were elicited in a structured interview. All subjects underwent a complete pelvic examination, including collection of vaginal samples for microscopic examination and vaginal swabs for culture for *Candida* species, at baseline and every 6 months thereafter. Subjects were contacted in person or by telephone every 3 months to ascertain adherence with the treatment regimen.

Women who were diagnosed with any vaginitis in the course of a study visit received therapy according to the examining clinician's clinical judgment. Subjects diagnosed with VC at the baseline visit received therapy and were not randomized into the prospective trial until they were symptom free. Subjects diagnosed with VC on subsequent study visits were treated and exited from the study until they were symptom free and a vaginal swab was culture negative for *Candida* species. They were then permitted to reenter the trial on their original treatment arm. Subjects who became pregnant in the course of the study were exited from the study until the pregnancy was completed. They then reentered the trial on their original treatment arm.

Women participating in the trial were encouraged to contact study staff if vaginal symptoms developed between study visits; if they did so, they were scheduled for an interim study visit and the findings from that visit were recorded in the database. However, because some women also sought care at other sites where VC may have been diagnosed, this analysis is restricted to data from the regularly scheduled 6-month study interviews and examinations.

Clinical and Microbiological Evaluation

Each clinical examination included collection of specimens for microscopic examination and culture for *Candida* species. The presence or absence of spores or hyphae was sought in KOH and saline preparations by an experienced nurse midwife or physician examiner at the time of the pelvic examination. Swabs from the vaginal fornix were sent to the clinical microbiology laboratory at Yale-New Haven Hospital to be cultured for *Candida* species.

Case Definition

The primary study outcome was the relative risk for experiencing an episode of VC while on treatment. An episode of VC required all of the following characteristics: vaginal pruritis or discharge, microscopic observation of spores or hyphae, a vaginal swab culture positive for *Candida* species, and the absence of a concurrent diagnosis of bacterial vaginosis or trichomoniasis.

Statistical Analysis

Analyses were conducted to compare baseline characteristics between groups and to compare treatment outcomes. Differences in categorical variables were assessed using Fisher's exact test. Normally distributed continuous variables were compared using *t* test between groups, and skewed variables were compared with the Wilcoxon rank-sum test. The incidence of VC was calculated per woman-year of follow-up and the relative risk determined for each of the treatment groups relative to placebo. Survival time, defined as the time from enrollment to the first episode of VC, was determined for each participant. The treatment groups were compared with placebo using the log rank test.

Results

Study Sample

Between April 1995 and March 1998, 164 women enrolled in the study and returned for at least one 6-month follow-up visit. Of the women, 50 were randomized to receive clotrimazole capsules, 58 to *Lactobacillus acidophilus*, and 56 to placebo. The mean age of the sample was 40 years (range = 25 to 59 years). Of the sample, 47% (*n* = 78) were African American, 15% (*n* = 24) were Hispanic, and 38% (*n* = 62) were European American. CD4 counts ranged from 10 to 1,160 cells/mm³. Subjects randomized to the three treatment arms did not differ in regard to age, race, CD4 count, antibiotic use, amenorrhea, self-reported sexual activity, or illicit drug use. At enrollment, antiretroviral therapy (ART) was uncommon in this cohort. During the course of the study, self-reported ART increased but did not differ between the study arms.

At the time of randomization, all women were free of vaginal symptoms and thus, by definition, free of VC. At the baseline visit, vaginal swabs were cultured for the presence of *Candida* species. The presence of asymptomatic *Candida* infection did not differ between the study arms. Prevalence of culture-proven *Candida* colonization was 32% in the placebo arm (18 of 56 women), 34% in the *Lactobacillus acidophilus*

Table 1. Women With at Least One Episode of *Candida* Vaginitis by Treatment Group

Treatment Group	Number of Episodes		
	0	1	2
<i>Lactobacillus acidophilus</i>	49	9	0
Clotrimazole	43	7	0
Placebo	40	14	2
Total	132	30	2

Table 2. Rates of *Candida* Vaginitis by Treatment Group

Treatment	Number of Cases	Rate per Woman-Year	<i>p</i> Value (vs. placebo)
<i>Lactobacillus acidophilus</i> (<i>n</i> = 58)	9	0.10	.09
Clotrimazole (<i>n</i> = 50)	7	0.08	.03
Placebo (<i>n</i> = 56)	18	0.19	

arm (20 of 58 women), and 26% (13 of 50 women) in the clotrimazole arm.

Incidence of VC

Time on study ranged from 6 to 34 months. Mean follow-up was 19 months for the *Lactobacillus acidophilus* arm, 22 months for the clotrimazole arm, and 20 months for placebo. Thirty-four cases of VC occurred—9 in the *Lactobacillus acidophilus* group, 7 in the clotrimazole group, and 18 of the women on placebo. Two women in the placebo arm had two episodes each; there were no recurrent episodes in either of the other treatment arms (see Table 1).

Treatment Effect

The rate of VC in each of the treatment groups was approximately half that of the placebo arm (see Table 2). The relative risk of experiencing an episode of VC was 0.4 (95% CI = 0.2, 0.9) among the women who received clotrimazole and 0.5 (95% CI = 0.2, 1.1) for those who received *Lactobacillus acidophilus*. The time to the first episode of VC (see Figure 1) was significantly different for the clotrimazole group (*p* = .03, log rank test) compared with placebo. Time to first

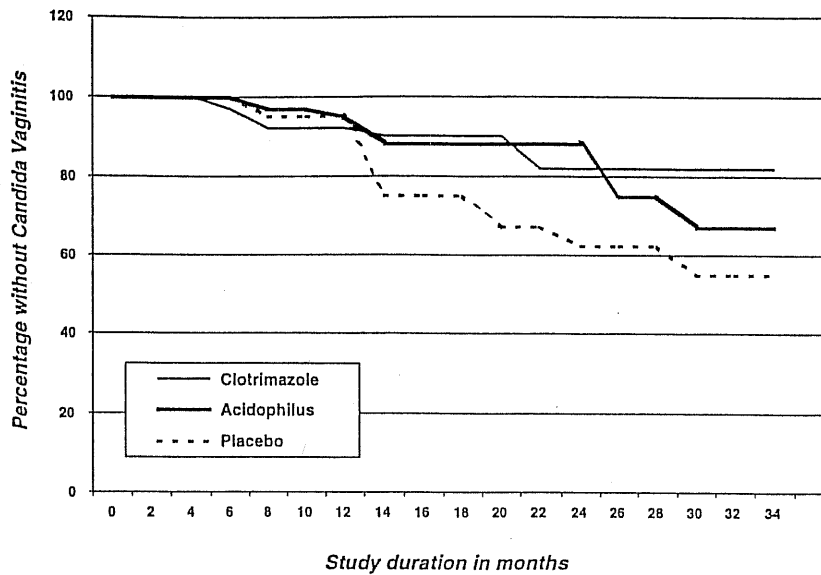


Figure 1. Survival Curve Representing the Time to First Episode of *Candida* Vaginitis for HIV-Infected Women Who Received Intravaginal Clotrimazole 100 mg, Intravaginal *Lactobacillus acidophilus*, or Placebo Weekly

episode was also longer for the *Lactobacillus acidophilus* group, although the difference was not statistically significant ($p = .09$, log rank test). There was no relationship between age, race, CD4 count, antibiotic use, amenorrhea, self-reported sexual activity, or illicit drug use at enrollment and subsequent development of VC.

Nursing Implications

VC is commonly experienced by HIV-infected women. Although prophylaxis of this problem has not received as much attention as other, more immediately life-threatening infections, for women living with HIV, prevention of VC may be an important quality-of-life goal. The recent rapid expansion of the number of antiretroviral agents available for treatment of HIV and the concomitant potential for drug interactions make topical strategies for prophylaxis appealing. It is therefore reassuring that this study confirms the effectiveness of two such approaches that can be recommended by nurses to their clients.

This study compared two topical therapies for VC prophylaxis to placebo. Both clotrimazole 100 mg and *Lactobacillus acidophilus* were effective when used intravaginally once a week. Both agents reduced the

relative risk for an episode of VC by about 50%. Clotrimazole was slightly more effective than *Lactobacillus acidophilus*; in comparison with placebo, the reduction in risk was statistically significant for clotrimazole but not for *Lactobacillus acidophilus*. The study employed a very restrictive case definition for VC by requiring visualization of spores or hyphae on microscopic examination and by requiring the absence of a concurrent diagnosis of bacterial vaginosis or trichomoniasis. A less restrictive case definition might well have resulted in a greater number of cases and a stronger treatment effect.

Although some cross-sectional studies suggest an increased risk for VC among HIV-infected women with lower CD4 counts (Burns et al., 1997; Duerr et al., 1997; Spinillo et al., 1994; Williams et al., 1998), such an association was not evident in this prospectively followed cohort. This analysis was restricted to CD4 count at study enrollment as a predictor of subsequent VC. It is possible that a lower CD4 count at the time of subsequent exams was associated with VC; we did not examine that question. It is also likely that the small proportion of women with very low CD4 counts at enrollment reduced the number of cases of VC and thus minimized the impact of the interventions under study. In view of previous data indicating that lower

CD4 counts are associated with increased risk, it is reasonable to consider women with severely compromised immune systems at risk for VC and offer education regarding self-care and prophylaxis.

Because both of these agents are easily available without a prescription, these interventions can be initiated by women as part of a gynecologic self-care program. Clotrimazole 100 mg tablets are available in many drugstores. *Lactobacillus acidophilus* is somewhat more problematic. The concentration and viability of *Lactobacillus* species in nonprescription products are not necessarily guaranteed. Previously, *Lactobacillus acidophilus*, the predominant species in the normal vagina, was found in only 4 of 16 commercially prepared nonprescription products (Hughes & Hillier, 1990). In this study, viability was guaranteed by the manufacturer (Natren, Inc., Westlake Village, CA) if the product was refrigerated; we did not confirm the presence of viable *Lactobacillus acidophilus* in the vaginas of women on the *Lactobacillus* treatment arm. More frequent use of the vaginal suppositories may have provided additional protection. Daily use of the *Lactobacillus acidophilus* product for 14 days is recommended by the manufacturer for treatment of VC. We chose a weekly schedule for this prevention trial as a practical matter to facilitate adherence over the long term.

Patient education about gynecologic health is an important aspect of the care of HIV-infected women. Information regarding signs and symptoms of vaginal infections and an emphasis on the importance of clinical examination and diagnosis may decrease the proportion of women with untreated or inappropriately treated infections. In addition, there are a number of other strategies women can use to prevent VC, including avoiding tight-fitting underwear and nylon stockings, avoiding chemical douches, and possibly reducing the amount of sugars in the diet.

This study confirms that alternatives to long-term systemic therapy with broad spectrum antifungal drugs offer effective prophylaxis for one troublesome complication of HIV infection. Nurses who care for HIV-infected women can also contribute to their gynecologic well-being by inquiring about vaginal symptoms, conducting regular pelvic examinations, and recommending prophylaxis for women who are

concerned, especially those with lower CD4 cell counts.

Acknowledgments

This work was supported by grant number NR03791 from the National Institute of Nursing Research and the General Clinical Research Center of Yale School of Medicine. As this article reports results of a study involving human experimentation, please note that informed consent was obtained from the patients or their parents or guardians and guidelines for human experimentation of the U.S. Department of Health and Human Services and/or those of the authors' institution(s) were followed in the conduct of clinical research.

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