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EDITORIAL REVIEW

Vulvovaginal candidiasis: a comparison of HIV-positive and -negative women

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Summary: Although considerable information has accumulated in the last decade regarding rates of both vaginal colonization and vulvovaginal candidiasis (VVC) in HIV-positive women, gaps in our knowledge remain, particularly with regard to pathophysiology of clinical disease. Unfortunately, early and possibly premature conclusions were reached in the late 1980s which resulted in the widespread dissemination of information indicating that recurrent VVC (RVVC) was a manifestation of HIV infection and that women with RVVC should be tested for HIV. Unfortunately, subsequent data from cohort studies involving HIV-positive women failed to determine attack rates of symptomatic Candida vaginitis requiring therapy. Recent studies indicate that Candida vaginitis, even if more frequent in HIV infected women, is clinically similar to that experienced in HIV-negative women and does not appear to be of increased clinical severity. VVC in HIV-positive women can be treated by conventional methods including the use of maintenance suppressive antifungal therapy and most importantly RVVC in women is not in itself a sentinel of HIV infection. Ongoing concerns include vaginal acquisition of non-*albicans Candida* species and the development of antimycotic drug resistance in *C. albicans* vaginal isolates.

Keywords: vulvovaginal candidiasis, HIV seropositive, AIDS, candida vaginitis

INTRODUCTION

In the early 1980s, HIV infection and AIDS was rarely reported in women. Much of the focus was in reporting new clinical syndromes of unknown aetiology in homosexual men and intravenous drug abusers. In 1987, the first report of *Candida* vaginitis in HIV-positive women appeared. In this report, Rhodes *et al*. described vulvovaginal candidiasis (VVC) in HIV-positive women as more frequent and chronic, more persistent, and poorly responsive to anti-fungal therapy[1]. Accordingly, the authors recommended that HIV testing be performed in women who reported recurrent VVC. The initial report also suggested an increased risk of death in HIV-infected women with recurrent vulvovaginal candidiasis (RVVC). This article was soon followed by a second report by Imam *et al*., who similarly reported an increase in frequency of VVC in HIV-infected women[2]. On the basis of these two reports, the Centers for Disease Control (CDC), in 1992, classified VVC among Category B conditions and further endorsed the importance of HIV testing adult females with RVVC. The US Food and Drug Administration (FDA) also endorsed this concern and commercial topical anti-fungal agents were required to include a warning to women as to the need for HIV testing. The concern was also supported by the World Health Organization (WHO) concluding that VVC was associated with intermediate or moderate HIV disease. The implications of initial publications[1–3] and the subsequent actions taken by the aforementioned groups had an enormous impact on women throughout the developed world causing enormous personal and public anxiety and even on element of panic. The fundamental criticism of these actions is that they ignored the fact that VVC is common in healthy HIV-negative women, moreover many women carrying the label of RVVC, and assumed to have RVVC, have recurrent vulvovaginal symptoms due to causes other than yeast. These women are frequently symptomatic, but the diagnosis of Candida vaginitis is never substantiated by diagnostic tests. There is enormous over-diagnosis, including self-diagnosis of acute, sporadic and recurrent Candida vaginitis in healthy women[4–5]. Moreover, even when RVVC

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is confirmed microbiologically, this clinical syndrome is of multifactorial aetiology and idiopathic RVVC is a common entity in HIV-negative women at low risk of acquiring HIV disease. Hence, the likelihood of identifying HIV infection in a healthy adult woman on the basis of recurrent Candida vaginitis only, is remote.

Candida spp. differ from other traditional STD pathogens in several characteristics. Whether or not Candida can be considered part of the normal flora or not remains controversial; but point prevalence studies indicate that at any time, one may find 10–20% of healthy asymptomatic adult women colonized vaginally with *Candida* spp. If one performs longitudinal studies, the cumulative prevalence of Candida colonization is significantly higher, viz $>80\%$. Candida vaginitis is extremely common in all strata of society, including celibate, pre- and post-menopausal women. While there is some evidence that sexual transmission of Candida organisms does occur by both intercourse and oral sex, nevertheless, *Candida* spp. are not considered STD pathogens[5]. The epidemiology of Candida vaginitis lacks traditional markers of other sexually transmitted diseases and STD pathogens, i.e., no association with age of onset of sexual activity or number of lifetime sexual partners. Moreover, recurrence of symptomatic Candida vaginitis is common in healthy, immunocompetent women. Accordingly, VVC lacks the same public health implications as the various STDs and in no way indicates unsafe sexual behaviour. Finally, the incidence of VVC is unlikely to be affected by changes in behaviour within any given population. On this basis, the initial conclusions of the CDC, FDA and WHO have been widely criticized[6]. Regrettably, the original reports that formed the basis for these conclusions consisted of small studies without appropriate controls, particularly, a control population of HIV negative women with matched high-risk sexual behaviour. The controversial significance of VVC in HIV infected women has resulted in a variety of research questions. These are summarized in Table 1.

Table 1. Questions regarding vulvovaginal candidiasis (VVC) in HIV-infected women

1. Is vaginal colonization with *Candida* spp. more common in HIV positive women?
2. Is Candida vaginitis more severe or clinical presentation different?
3. Any difference in microbiology of VVC?
4. Is VVC more likely to be recurrent?
5. Any difference in response to therapy?
6. Can and should recurrent VVC be treated with maintenance suppressive azole drugs?
7. Is antifungal drug resistance an issue?
8. Are there differences in oropharyngeal candidiasis and VVC in infected women?
9. Is recurrent VVC a sentinel of HIV infection justifying serological testing?

IS VAGINAL COLONIZATION WITH *CANDIDA* SPP MORE COMMON IN HIV-INFECTED WOMEN?

The frequency of asymptomatic vaginal colonization varies in population groups studied in developed countries. Candida colonization occurs in 10–20% of HIV negative non-pregnant females. This frequency increases to 15–30% in pregnant women and declines significantly in post-menopausal women. Women in STD clinics tend to have a higher frequency of asymptomatic colonization. Several studies conducted in non-pregnant and pregnant HIV-positive women, which included both microscopy and culture, have indicated that vaginal colonization is significantly increased in HIV-infected women[7–12].

Factors predicting positive colonization in HIV positive women include pregnancy, diabetes and a history of previous symptomatic Candida vaginitis[7,11]. The highest colonization rates correlate with low CD4 counts and viral load[11]. The cause of the increased colonization has not yet been determined but appears to be related to loss of immunoprotective mechanisms in the vagina. It should be emphasized that in epidemiological studies in which a matched control group of HIV negative women was included, that higher than predicted vaginal colonization rates were also present in HIV-negative women with high-risk sexual behaviour[7,11]. This suggests a possible role of behavioural factors in influencing transmission of Candida microorganisms and hence vaginal colonization rates. Colonization is important in that it serves as a predisposing factor to subsequent transformation to symptomatic Candida vaginitis when the appropriate risk and contributing factors are present. Long-term longitudinal studies indicate that not only is vaginal colonization increased in HIV positive women, but colonization is more likely to be persistent with reduced likelihood of finding culture negative periods. On the other hand, reduced vaginal colonization has been associated with exposure to systemic antifungal agents[7,11].

CLINICAL PRESENTATION OF VVC

Little attention has been directed at the clinical presentation of Candida vaginitis in HIV-infected women. No evidence exists that the clinical spectrum of signs and symptoms vary in HIV-infected women. Moreover, unpublished data [HIV Epidemiology Research Study (HERS) cohort] indicate that severity of disease, as a function of the total numbers of signs and symptoms present, does not differ in HIV-positive and HIV-negative women.

MICROBIOLOGY OF VVC

There remains scant available information on the frequency of non-*albicans Candida* spp. as a cause of

vaginitis in HIV-infected women. *C. albicans* remains the dominant cause of both colonization and symptomatic vaginitis in HIV-infected women[7–12]. In HIV negative women, one can anticipate at least a 10% increase in the frequency of non-*albicans Candida* spp. as a cause of chronic and recurrent disease. Similarly, HIV-seropositive women followed for two years in the HERS, a progressive increase in non-*albicans Candida* spp. isolated from the vagina was documented, but at a very slow incremental rate[11]. The most common non-*albicans Candida* spp. isolated from the vagina was *Candida glabrata*. Overall, mixed vaginal infections consisting of more than one simultaneous *Candida* spp., occur rarely in HIV-negative women. However, an increase of co-colonization with two species has been reported in HIV-positive women[11].

IS VVC IN HIV-POSITIVE WOMEN MORE LIKELY TO BE RECURRENT?

This question emerged as the single dominant issue in discussions on the epidemiology of VVC in HIV-infected women and was the basis for recommendation for HIV testing described above. RVVC was also identified by a variety of women's groups, as being a major intractable problem in HIV-positive women. Unfortunately, the answer to this question remains incomplete since no prospective controlled studies have studied and measured the attack rate of Candida vaginitis in HIV-positive women. Based on the increased frequency of vaginal colonization, one might predict that the attack rate of Candida vaginitis would be significantly increased in women who are HIV-positive. However, in addition to colonization and exposure to anti-microbial agents, a variety of other factors contribute to the transformation from asymptomatic colonization to symptomatic Candida vaginitis. Foremost among these factors is sexual behaviour and many women with AIDS become less sexually active and acquire varying degrees of oestrogen deficiency that may well protect against episodes of Candida vaginitis. In limited studies that have been performed, incidental symptomatic Candida vaginitis was not measured but rather the presence of single signs or symptoms at the time of a routine scheduled visit. Using an epidemiological, but no clinical definition of VVC, the rate of VVC appears to be increased, but not nearly as frequent as predicted or as described for oropharyngeal candidiasis. In the absence of data reporting the true attack rate of symptomatic Candida vaginitis in HIV-infected women, and given the frequency of this entity in low-risk HIV-negative women, it appears unreasonable to have defined RVVC as a manifestation of HIV infection or as a justification for HIV testing in women with recurrent vaginal candidiasis[1–3].

THERAPY

No evidence from controlled studies exists that HIV-positive women with symptomatic episodes of Candida vaginitis respond less well, with regard to clinical or mycological outcome than HIV-seronegative women. Accordingly, therapy should be prescribed utilizing either topical or systemic anti-mycotic agents according to general principles applied in HIV-negative women. Women who are HIV-negative, with recurrent Candida vaginitis, benefit from long-term maintenance suppressive therapy, usually systemic oral anti-fungal therapy[5]. Both retrospective and prospective studies have indicated the benefit of such long-term maintenance therapy. In a study recently completed by Schuman *et al.*, the authors used a dose of fluconazole 200 mg once weekly, based upon the pharmacokinetics of fluconazole which provides therapeutic concentrations of fluconazole in the vagina for three to five days[13]. A significant protective effect with reduction in the attack rate of recurrent Candida vaginitis was achieved in HIV-positive women. The results were similar to that experience in HIV negative women. This does not imply that all women who are HIV positive should be given long-term suppressive anti-fungal therapy. Therapy should be selected only for those women who experience recurrent Candida vaginitis ($\geqslant 4$ episodes per year) in whom the morbidity and frequency of individual attacks justifies suppressive prophylactic therapy. As in HIV negative women, the protective effects of maintenance fluconazole are sustained in less than 50% of women when fluconazole therapy is discontinued after six months.

ANTIMYCOTIC DRUG RESISTANCE

The problem of azole resistance resulting in refractory, recurrent or chronic, oropharyngeal candidiasis is widely recognized and studies indicate that approximately 6–7% of adults with AIDS suffered from this problem in the pre-highly active antiretroviral therapy (HAART) era[14–16]. The problem retreated somewhat with the initial availability of anti-retroviral therapy, but has re-emerged as a major clinical challenge. The development of azole-resistance in *C. albicans* as well as the reduced therapeutic response in oropharyngeal candidiasis (OPC) caused by *C. glabrata*, is the basis for the chronic refractory oral disease[16,17]. Similar clinical evidence has not emerged with regard to RVVC in HIV positive women. Vaginal isolates of *C. albicans* resistant to azoles remain rare, although a recent study in the United States did observe a 3–4% presence of fluconazole resistant *C. albicans* in a large population of HIV negative women with complicated Candida vaginitis[18]. Similar data in women with recurrent Candida vaginitis does not exist. Nevertheless, to date, clinical experience indicates that vaginal *C. albicans* resistance to azoles is

Table 2. Comparison of oral and vaginal candidiasis

	Oropharynx	Vagina
Normally colonized by *Candida* spp.	Yes	Yes
Candidiasis in healthy women	Rare	50% to 75%
Candida albicans	90% to 95%	75% to 85%
Mixed fungal species	Common in AIDS	Rare
Percentages of colonization in healthy state	5 to 50% (mean 20%)	5 to 30% (mean 15%)
Increased colonization in diabetes	Yes	Yes
Increased colonization in pregnancy	+	++
Thrush following antibiotics	±	++
Thrush following corticosteroids	Yes	?
Thrush as oestrogen-dependent	?	+++
Thrush in chronic mucocutaneous candidiasis	Always	Less common
Thrush in AIDS	>90%	~50% (?)

not yet of clinical significance in HIV-negative and -positive women, however, additional information is clearly needed.

In HIV-negative women, the more relevant problem is azole refractory vaginitis caused by non-*albicans Candida* spp., particularly but by no means confined to, *C. glabrata*. Treatment response rates decrease by 50% in women infected with *C. glabrata* and recurrent colonization and symptomatic relapses are common[19]. At this stage, the problem of refractory vaginitis caused by non-*albicans Candida* is not a widespread problem but constant observation is needed. Non-*albicans Candida* spp. are more likely to be a cause of recurrent disease and any patient with recurrent Candida vaginitis, regardless of HIV serology should not only be cultured, but the *Candida* spp. identified. Only rarely are antifungal susceptibility tests necessary. Non-*albicans Candida* infections frequently will require the use of non-azole therapy, including topical therapy with boric acid, flucytosine or 3–4% amphotericin B[20]. The lack of fungicidal agents, both topical and systemic for eradication, as opposed to suppression of organisms, continues to be a major challenge in both HIV-positive and HIV-negative women.

COMPARISON OF ORAL AND VAGINAL CANDIDIASIS

A variety of striking differences have emerged between these two sites of mucosal Candida colonization and infection. Although both sites are frequently colonized in healthy women, colonization rates in the oropharynx tend to be two or three times higher than rates found in the vagina. Secondly, whereas vaginal candidiasis is common in healthy HIV-negative women, OPC is, in fact, rare. *C. albicans* is responsible for more than 95% of OPC episodes, but lower numbers are reported with vaginal candidiasis, particularly in women with recurrent disease. Mixed fungal infections with two or more concomitant *Candida* spp. tend to be more common in oropharyngeal disease. It is noteworthy that thrush following antibiotics is much more common in the vagina than in the oral cavity, in contrast to the use of corticosteroids. Moreover, VVC is a highly-oestrogen dependent syndrome. These differences can be summarized in Table 2. The implications for these profound differences indicate that differences in pathogenesis of disease are present at the two anatomical sites.

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