Abnormal Vaginal Flora as a Biological Risk Factor for Acquisition of HIV Infection and Sexually Transmitted Diseases

Jane R. Schwebke
STD Program, Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham

(See the article by Myer et al., on pages 1372–80.)

The role that the vaginal flora plays in protecting the host from sexually transmitted infections (STIs), including HIV infection, is becoming increasingly appreciated. Significant alterations in the microbiological environment of the vaginal ecosystem, such as those that occur in bacterial vaginosis (BV), appear to be a biological risk factor for the acquisition and transmission of STIs/HIV, and, therefore, BV has tremendous public health implications.

BV occurs in 20%–25% of women in the general population and in 40%–50% of women attending STI clinics [1, 2]. An estimated 3 million symptomatic cases of BV, as well as an equal number of asymptomatic cases, occur in the United States annually [3]. BV is characterized by dramatic changes in the vaginal flora, from an environment in which lactobacilli are predominant to one in which there is a marked decrease in the number of lactobacilli, particularly those that produce H₂O₂ [4–6]. In BV, there are large numbers of anaerobic and facultative anaerobic organisms, the majority of which are normally found in the vagina in small amounts [6]. Changes in the vaginal flora are not all or none but comprise a spectrum of patterns [7]. Therefore, we are presently unable to attribute BV to a single pathogenic organism, and this limitation greatly hampers our diagnostic and treatment strategies.

Lactobacilli become the predominant inhabitant of the vagina at the time of puberty and are believed to be the key defense of the vaginal flora [8]. In vitro, lactobacilli produce various potential microbial toxins, including H₂O₂ and more poorly defined bacteriocins [8, 9]. Lactobacilli that produce H₂O₂ have been shown in vitro to inhibit various microorganisms, including Gardnerella vaginalis, anaerobes, Neisseria gonorrhoeae, and HIV [10–14]. Other means by which lactobacilli may play a protective role within the vaginal ecosystem include competition for epithelial cell attachment sites and stimulation of the local immune system [15, 16]. Additionally, lactobacilli maintain the acidity of the vagina through the production of lactic acid as a metabolic by-product. The acidic pH, normally <4.5, is inhospitable to many bacteria. The pH of the vagina becomes more alkaline as the flora shifts toward the population present in BV [17].

The pathogenesis of BV is poorly understood. Epidemiological correlates of BV include a history of STIs, increased numbers of sex partners, a new sex partner within the month preceding symptom onset, and douching [1, 18–21]. Epidemiologic data strongly suggest that BV is sexually transmitted, but the agent or agents that may be transmitted are unknown. Data are emerging on the effectiveness of condoms in preventing BV [22, 23].

BV is frequently present as a coinfection with STIs. Women with lactobacilli that produce H₂O₂ in vitro have been shown to be less likely than women without such lactobacilli to have BV as well as STI pathogens such as N. gonorrhoeae, Chlamydia trachomatis, and Trichomonas vaginalis [10, 24–26]. In addition, incident herpes simplex virus type 2 and human papillomavirus infections have both been associated with abnormal vaginal flora [27, 28]. The leading hypothesis to explain the coexistence of BV and STIs is that the absence of protective lactobacilli found in patients with BV precedes and facilitates the acquisition of an STI.

One of the first clinical studies to suggest an association between BV and HIV...
infection was reported from Thailand. In this cross-sectional study of female commercial sex workers, HIV seropositivity was significantly correlated with BV, independently of other behavioral variables [29]. Similar findings were documented in a study of women in Uganda [30]. Interestingly, in this latter study, the highest HIV seropositivity rates were found in those women with the most severe changes in their vaginal flora, as documented by Gram staining. Similar findings were observed in a study of pregnant women in North Carolina, a cohort with a relatively low HIV seroprevalence. The seroprevalence of HIV increased as the Gram stain score for the vaginal flora increased, independently of other demographic and behavioral variables [31].

A few prospective studies have been conducted that confirmed the earlier findings of the cross-sectional research. In a cohort of pregnant women in Malawi, HIV seroconversion was significantly associated with alterations in the vaginal flora [32]. There was a significant linear association with an increasing score for abnormal vaginal flora determined on the basis of Amsel clinical criteria (pH, whiff test, microscopy) [32]. A prospective study conducted in Kenya followed a population of commercial sex workers for HIV seroconversion and obtained samples of vaginal secretions for Gram staining as well as culturing for lactobacilli. Abnormal vaginal flora detected by Gram staining was significantly associated with HIV seroconversion as well as the acquisition of gonorrhea [33]. Transmission of HIV may also be enhanced by coinfection with the organisms responsible for BV [34].

In this issue of the Journal of Infectious Diseases, Myer et al. present additional data on the association between abnormal vaginal flora and HIV seroconversion [35]. The study followed a group of women enrolled in a cervical cancer screening trial near Cape Town, South Africa. Women were tested for the presence of HIV RNA at enrollment and were followed prospectively. Using a case-control study design, the authors compared women who underwent HIV seroconversion during the course of the study with those who remained seronegative. In a multivariate analysis adjusting for demographic characteristics, sexual behaviors, and STIs, women who had a diagnosis of BV by Nugent criteria were significantly more likely to seroconvert than were women with normal vaginal flora (adjusted odds ratio, 2.01 [95% confidence interval, 1.12–3.62]). The prevalence of BV in this population was 62% in control subjects and 74% in case patients.

Although production of H₂O₂ by lactobacilli is the leading explanation for the association seen between abnormal vaginal flora and HIV seroconversion, other mechanisms may play a role. For example, it has been hypothesized that the level of acidity within the vagina may affect CD4 lymphocyte activation. The more alkaline the environment, the more likely it is that CD4 lymphocytes will be activated and thus act as suitable target cells for HIV [36]. Tumor necrosis factor-α and interleukin-1β are found in high levels in cervical secretions from women with BV, and it has been suggested that these cytokines could up-regulate HIV replication in the vagina [37]. In vitro, certain anaerobic bacteria (Peptostreptococcus asaccharolyticus and Prevotella bivia) that are associated with BV appear to stimulate HIV expression in monocytoid cells and T cells [38].

STIs are also known to be important biological risk factors for the acquisition and transmission of HIV infection [39]. Rates of BV, however, are significantly higher than rates of STIs worldwide. Thus, the attributable risk of BV with regard to HIV transmission is high [40]. In the Myer et al. study, it is estimated that nearly one-third of all new HIV cases in this South African population might be prevented if all cases of BV could be cured [35]. Widespread control of BV has been suggested as a possible means for decreasing the incidence of HIV infection in the developing world. However, present achievable BV cure rates, combined with high recurrence rates, make this solution impractical. The recommended therapies for BV have cure rates of 70%–80%, and recurrence rates are high [41, 42]. Thus, in many women, it is difficult to achieve and maintain normal vaginal flora. For example, in a study of the control of STIs for the prevention of HIV infection in Uganda, therapy for BV was unable to significantly reduce the rates of BV in the treatment communities, compared with those in the control communities. This study also failed to show a difference between the groups in their rates of acquisition of HIV infection [43].

As a greater understanding of BV unfolds—including additional insights into pathogenesis, diagnosis, and therapy—there will be more opportunities to consider control efforts as a means to decrease acquisition and transmission of HIV infection. The high prevalence of BV and the emerging prospective data on its association with HIV infection mandate that research efforts be directed at the pathogenesis, diagnosis, and treatment of BV. Until efficacious therapy, as well as an understanding of prevention methods, for BV is available, it will not be feasible to go forward with studies aimed at preventing the complications of this common vaginal infection.

References

5. Eschenbach DA, Davick PR, Williams BL, et al. Prevalence of hydrogen peroxide-producing Lactobacillus species in normal women and