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*Full Length Research Paper*

# Incidental findings of bacterial vaginosis and other infections in papanicolaou smears of human immunodeficiency virus (HIV)-infected and human immunodeficiency virus (HIV)-uninfected adolescent females in South Africa

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**Bacterial vaginosis (BV) is a widely prevalent infection that is associated with a range of adverse outcomes. We compared the rates of incidentally identified BV and other cervico-vaginal infections on Papanicolaou (Pap) smears of human immunodeficiency virus (HIV)-infected and HIV-uninfected adolescent females in South Africa. Cervical specimens from 50 HIV-uninfected and 32 HIV-infected sexually active South African adolescent females age 17 to 21 were collected and analyzed in accordance with the Bethesda system. We found a high overall prevalence of BV (54.9%) in our cohort. While previous research has found an increased prevalence of BV among HIV-infected women, the difference in the prevalence of BV between our HIV-infected group (62.5%) and HIV-uninfected group (50.0%) was not found to be statistically significant. The high rate of BV in both of these groups has significant implications for their risk of HIV acquisition and/or transmission in addition to other associated risks of BV.**

**Key words:** Bacterial vaginosis, human immunodeficiency virus (HIV), papanicolaou smear, adolescents, South Africa.

## INTRODUCTION

Bacterial vaginosis (BV) is the most common vaginal infection in women of childbearing age (Fethers et al., 2008; Morris et al., 2001). Globally, the prevalence of BV

varies widely. In the United States, the prevalence of BV is estimated to be 29.2% among women of ages 14 to 49 and 50.0% in African-American women, based on a

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sample of women who participated in the National Health and Nutrition Examination Survey (NHANES) (Koumans et al., 2007). Previous studies have estimated BV prevalence in South Africa ranging from 52.0 to 58.3% among sexually active women of all ages (Kenyon et al., 2013).

Bacterial vaginosis encompasses a complex change in the vaginal flora and is of increasing interest as laboratory developments, such as shotgun next generation sequencing (NGS) and/or 16S/ITS rDNA amplicon sequencing have allowed investigations into the vaginal microbiome and its impact on a wide range of reproductive health issues (Ameur et al., 2014). Bacterial vaginosis has been associated with a range of medical and gynecological adverse outcomes and an increased risk for HIV acquisition and transmission (Myer et al., 2005; Martin et al., 1999; Cohen et al., 2012). The role of sexual activity in the pathogenesis in BV is not completely understood. A systematic review and meta-analysis concluded that BV is significantly associated with sexual contact with new and multiple male and female partners, and decreasing the number of unprotected sexual encounters may reduce incident and recurrent BV infection (Fethers et al., 2008).

We compared the rates of BV and other incidentally identified cervico-vaginal infections on the Papanicolaou (Pap) smears of HIV-infected and HIV-uninfected adolescent females in South Africa. This study is novel in that it presents data from an unusually young sexually active cohort from an area with a very high density of HIV disease. Our results provide insight into the prevalence of BV among this high-risk population and underscore the multi-factorial nature of infectious reproductive health risks for sexually active adolescents with and without HIV co-infection.

## MATERIALS AND METHODS

Between October, 2012 and October, 2013 we conducted a cross-sectional prevalence study in which cervical specimens for Pap smear were collected from 50 HIV-uninfected and 32 HIV-infected sexually active South African adolescent females, age 17 to 21, who were participating in a longitudinal study of HPV infection and persistence. All HIV-uninfected and HIV-infected participants from this longitudinal study were included in this analysis of incidental findings on Pap smears. All study participants underwent HIV testing on the date of Pap smear testing to confirm HIV status.

Study participants were recruited from a youth community center in a Township community in Cape Town, South Africa. This youth center attracts youths from different schools and township communities and provides these youths with health education, nutrition services and recreation. Demographic and behavioral information from study participants were obtained by an interviewer. Pap smear results, including identification of BV, and infection with *Trichomonas*, *Candida* and genital herpes were reported in accordance with the Bethesda system. The Bethesda system includes, "*Trichomonas vaginalis*; fungal organisms consistent with

*Candida* species; shift in flora suggestive of bacterial vaginosis; bacteria morphologically consistent with *Actinomyces* species and cellular changes consistent with herpes simplex virus (Solomon et al., 2002). All positive conventional Pap smears that were identified by cytotechnologists were sent for review by a pathologist. Women with incidentally identified infections were referred for appropriate treatment according to Centers for Disease guidelines.

All participants signed informed consent (age 18 and older) or signed adolescent assent documents (age 17) to accompany parental consent forms in order to participate in the study. This study was approved by the Research Subjects Review Board at the University of Rochester Medical Center, US and the Research Ethics Committee of the University of Cape Town, South Africa. Continuous data are presented as means, standard deviations and inter-quartile ranges, and categorical data are presented as frequencies and percentages. Differences between HIV-infected and HIV-uninfected were examined using Pearson  $\chi^2$  analysis, and associations between participant demographics and vaginal infections were presented using Spearman correlations. All statistical analyses were performed using statistical package for social sciences (SPSS) 21.0.

## RESULTS

Eighty-two female adolescents participated in our study. The overall mean age of the participants was 19.0 years (standard deviation = 1.5), ranging from 17 to 21. There were 50 HIV-uninfected and 32 HIV-infected study participants (Table 1). HIV-infected participants were older than HIV-uninfected participants,  $t(80) = 5.07$ ,  $p < 0.001$ . The vast majority of participants reported between 2 and 5 lifetime sexual partners (83.0%), with smaller proportions reporting a single sexual partner (10.0%) or more than 5 partners (7.0%). Most participants reported having a single sexual partner in the past 6 months (94.0%). There were no differences in lifetime sexual partners,  $\chi^2_2 = 2.73$ ,  $p = 0.26$  and sexual partners in the past 6 months,  $\chi^2_1 = 0.00$ ,  $p = 0.96$ , across HIV infection status.

The overall prevalence of BV in our cohort was 54.9%. Although this prevalence was higher among HIV-infected participants (62.5%) than among HIV-uninfected participants (50.0%), this difference was not found to be statistically significant ( $\chi^2_1 = 1.23$ ,  $p = 0.27$ ). Table 2 outlines the incidental findings of bacterial vaginosis and other infections that were identified on the Papanicolaou smears. Additional incidental findings of other infections on the Pap smears included *Candida*, *Trichomonas* and genital herpes.

There was no significant difference in the prevalence of these other infections between the HIV-infected and HIV-uninfected groups ( $\chi^2_1$ 's  $\leq 0.65$ ,  $p$ 's  $> 0.10$ ). No incidental finding of *Actinomyces* was seen in our cohort sample. Bivariate Spearman correlations indicated that none of the investigated incidental findings were associated with participant age, number of lifetime sexual partners, and number of sexual partners in the past six months ( $p$ 's  $> 0.10$ ).

**Table 1.** Descriptive characteristics of HIV-infected and HIV-uninfected participants.

Parameter	HIV positive (n = 32)		HIV negative (n = 50)		P-value
	Mean (SD) Inter-quartile range	Frequency (Percentage)	Mean (SD) Inter-quartile range	Frequency (Percentage)	
<b>Age in years</b>	19.94 (1.13) 19 - 21		18.44 (1.40) 17 - 19.25	-	< 0.001
<b>Lifetime sexual partners</b>					
1	-	4 (12.5)	-	4 (8.0)	0.26
2-5	-	24 (75.0)	-	44 (88.0)	
5+	-	4 (12.5)	-	2 (4.0)	
<b>Sexual partners in past 6 months</b>					
1	-	30 (93.8)	-	47 (94.0)	0.96
2-5	-	2 (6.3)	-	3 (6.0)	

**Table 2.** Incidental findings of HIV-infected and HIV-uninfected participants.

Parameter	Overall frequency (Percentage)	HIV positive frequency (Percentage)	HIV negative frequency (Percentage)	p-value
<i>Bacterial vaginosis</i>	45 (54.9)	20 (62.5)	25 (50.0)	0.27
<i>Candida</i>	9 (11.0)	4 (12.5)	5 (10.0)	0.72
<i>Trichomonas</i>	5 (6.1)	2 (6.3)	3 (6.0)	0.96
Genital herpes	1 (1.2)	0 (0.0)	1 (2.0)	0.42
Multiple incidental findings	8 (9.8)	4 (12.5)	4 (8.0)	0.50
No incidental findings	31 (37.8)	10 (31.3)	21 (42.0)	0.33

## DISCUSSION

Bacterial vaginosis is associated with an array of adverse outcomes. A recent systematic review described the global epidemiology of bacterial vaginosis. The results showed that bacterial vaginosis covaries fairly closely with regional HIV prevalence. Sub-Saharan Africa was the region identified with the highest BV and HIV prevalence. Although BV prevalence tended to be highest in sub-Saharan Africa and lowest in Asia/Australia/Western Europe, there were populations with high and low prevalence in all of these regions (Kenyon et al., 2013). Our finding of a high prevalence of BV in our South African cohort is consistent with this review.

Our study did not identify a significant difference in the prevalence of BV between the HIV-infected and HIV-uninfected groups. These results are atypical compared to what has been previously reported. A prospective cohort study conducted over a five-year period found that bacterial vaginosis was both more prevalent (Odds ratio = 1.29; 95% CI 1.08, 1.55) and more persistent (Odds ratio

1.49; 95% CI = 1.18, 1.89) among HIV-infected women compared to those without HIV. In addition, the increased risk of prevalent and persistent BV was associated with lower CD4 cell count (Jamieson et al., 2001). Similarly, a study conducted in Zimbabwe assessing HIV seroprevalence and its association with other reproductive tract infections in asymptomatic women showed HIV infection to be positively associated with BV (Mbizvo et al., 2001). The limited power related to our small sample size may account for the lack of statistically significant difference in BV prevalence between the HIV-infected and HIV-uninfected groups.

The high rates of BV in both our HIV-infected (62.5%) and HIV-uninfected (50.0%) groups have important clinical implications. A meta-analysis looking at the role of BV in the spread of HIV estimated that 15.0% of HIV infections may be attributable to bacterial vaginosis (Atashili et al., 2008). This is especially important for the HIV-uninfected adolescent females who might be at a greater risk of acquiring HIV given the high prevalence of BV among them. There is also evidence that among HIV-infected women, those with BV shed more HIV particles



in their vaginal secretions (Mirmonsef et al., 2012). This is of particular importance given the high rates of HIV in sub-Saharan Africa and the imperative to control the spread of HIV infection. In addition, BV is associated with increased risk of HPV infection (Martin et al., 1999). Since HIV is a significant risk factor for cervical cancer (cervical cancer is an AIDS-defining illness (From the Centers for Disease Control and Prevention, 1993), BV plays a prominent role in promoting multiple factors that can lead to this disease.

About 50.0 to 75.0% of women with BV are asymptomatic and therefore, may not undergo specific testing. Those who are symptomatic generally present with vaginal discharge and/or vaginal odor. In clinical practice, the diagnosis of BV is usually based on the presence of at least three Amsel criteria (characteristic vaginal discharge, elevated pH, clue cells, fishy odor) if microscopy is available (Nugent et al., 1991). Although intended as a screening test for cervical cancer, the Pap smear has a high specificity (93.0%) for the diagnosis of bacterial vaginosis (Greene et al., 2000) and it may be an adequate diagnostic test when it is positive (Tokyol et al., 2004). In a study of over 400 women who underwent both vaginal smears for Gram staining and Pap smears, BV positive Gram stains were found in 93.0% of those with only coccobacilli on Pap smears. The most specific diagnosis of BV with pap smears requires coccobacilli only. Investigators concluded that the Bethesda system criteria for diagnosing BV was the most specific approach (Prey, 1999).

It has been reported that the Pap smear has a sensitivity of 43.1% to detect BV (Tokyol et al., 2004). This lower sensitivity is one of the limitations of this study. However, considering the modest sensitivity of detecting BV on Pap, the high prevalence of BV that we identified among our study population is likely to be an underestimate of the true prevalence. Similarly, in a recent review of over 1700 women who had incidental lower genital tract infections identified on Pap smear, Turkish researchers concluded that finding *Trichomonas vaginalis*, bacterial vaginosis, or *Actinomyces* infections on Pap smears could be considered an indication for treatment without performing other diagnostic tests since treatment of asymptomatic infections can prevent complications in some patients (Guducu et al., 2012).

## Conclusion

Our study found a high overall prevalence of BV among a unique adolescent South African cohort. We identified a non-statistically significant trend towards increased prevalence of BV among HIV-infected study participants. While the Pap smear is not intended as a test to diagnose cervico-vaginal infections, evidence suggests that it is specific for incidentally identified BV. Incidental

findings will ultimately arise in pap smears and placing them in a population context will be important for providers. Our results may be limited by sample size and our findings may not be generalizable to populations with a lower prevalence of BV and/or HIV. Additionally, another limitation of our study is the potential misreporting of self-reported sexual behaviors among our study participants. Given the associated risks of BV, especially with regards to HIV acquisition and transmission, a strong argument can be made in favor of treating BV that is incidentally identified on Pap smear among populations at high risk for HIV. Our cohort is being followed longitudinally and BV rates at follow up visits will be collected. Future studies will be needed assessing the prospective HIV risk after treatment for BV.

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## Conflict of interests

None of the authors have a conflict of interest to declare.

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