6-24-2020

Predictors of Persistent and Recurrent Bacterial Vaginosis (BV) among Young African American (AA) women in the United States

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PREDICTORS OF PERSISTENT AND RECURRENT BACTERIAL VAGINOSIS (BV) AMONG YOUNG AFRICAN AMERICAN (AA) WOMEN IN THE UNITED STATES (US)

A dissertation submitted in partial fulfillment of

the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PUBLIC HEALTH

by

Makella Shaniece Coudray

2020

To: Dean Tomás R. Guilarte
Robert Stempel College of Public Health and Social Work

This dissertation, written by Makella Shaniece Coudray, and entitled Predictors of Persistent and Recurrent Bacterial Vaginosis (BV) among Young African American (AA) Women in the United States (US), having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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Date of Defense: June 24, 2020

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DEDICATION

This dissertation is dedicated to my parents. Without their patience, understanding, support, and most of all love, the completion of this work would not have been possible. They are the pillars of my success.

ACKNOWLEDGMENTS

I wish to thank the members of my committee for their support and patience. Their knowledge and guidance have been most appreciated. Drs. Diana Sheehan and Tan Li were particularly helpful in guiding me through my methodology and statistical analyses. I remain forever grateful for their open doors and listening ears, even for the most trivial of questions. Dr. Giri Narasimhan's expertise allowed me to explore additional areas of my research. Finally, I would like to thank my major professor, Dr. Purnima Madhivanan. From the beginning, she had confidence in my abilities to not only complete my degree, but to complete it with excellence. Her continued and unwavering support has been instrumental in the completion of my dissertation.

I would also like to thank my family. Their silent prayers, well wishes and tremendous support have allowed me to successfully complete this work. I would be remiss to neglect the friends I acquired during this process who in turn provided me with balance and comfort in times of need. Their contribution to my success remains invaluable.

Finally, this work was supported by the National Institutes of Health grant (R15AI28714-01) and by the Division of Microbiology and Infectious Diseases of the NIAID (contract HHSN26620040073C). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ABSTRACT OF THE DISSERTATION

PREDICTORS OF PERSISTENT AND RECURRENT BACTERIAL VAGINOSIS (BV) AMONG YOUNG AFRICAN AMERICAN (AA) WOMEN IN THE UNITED STATES (US)

by

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Bacterial vaginosis (BV) is a common vaginal dysbiosis among women of reproductive age. Literature presents discordant findings with respect to the predictors of BV and there is a paucity of literature examining the mechanisms by which multiple episodes of BV occur. This dissertation summarized current literature on BV, identified BV incidence patterns over a twelve-month period, and estimated the risk of sexually transmitted infections (STI) among women with episodic and persistent BV. Previously collected randomized clinical trial data were analyzed, where oral metronidazole was the administered treatment. Latent class analysis (LCA) was used to assess BV incidence patterns. Multinomial Logistic Regression was used to estimate adjusted Odds Ratios (adjOR) associated with the predictors of BV incidence patterns. Binary Logistic Regression models were used to estimate adjOR associated with STI acquisition among women with persistent BV compared to episodic BV.

The results of the review identified conflicts in the literature further highlighted what little is known about the etiology and pathogenesis of BV, recurrent BV and

persistent BV. LCA illustrated three emergent patterns of multiple cases of BV: persistent (55.9%; 95 % Confidence Interval [CI]: 52.5%-59.3%), recurrent (30.5%; 95% CI: 27.5%-33.7%) and clearance (13.5%; 95% CI:1.3%-16.0%). Compared with belonging to the clearance group, women who had sex with women (WSW) had significantly lower odds of belonging to the persistent class (adjOR: 0.38; 95% CI: 0.22-0.68) and the recurrent class (adjOR: 0.43; 95% CI: 0.23-0.81) than women who did not. Those who were treated with metronidazole had significantly increased odds of being in the recurrent class (adjOR: 1.92; 95% CI: 1.22-3.03) than those who were not treated. Additionally, women with persistent and episodic BV were at increased risk (p= 0.02) of developing an STI. Women without BV did not acquire an STI.

Assessment of BV cases revealed distinct patterns of recurrence and persistence despite treatment with oral metronidazole. These preliminary findings suggest, Metronidazole may not be the most effective treatment to reduce the prevalence of recurrent and persistent cases of BV. More effective treatment of singular episodes of BV may reduce the adverse sequalae of incident STI, we reported associated with recurrent, episodic and persistent BV. The review identified gaps in the literature, which were addressed by the second and third aims.

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ABBREVIATIONS AND ACRONYMS

adjOR	Adjusted Odds Ratio
BV	Bacterial Vaginosis
CI	Confidence Interval
CT	*Chlamydia Trachomatis*
HR	Hazard Ratio
IUD	Intra-Uterine Device
LCA	Latent Class Analysis
NG	*Neisseria Gonorrhoeae*
NS	Nugent Score
OR	Odds Ratio
US	United States

INTRODUCTION

Bacterial Vaginosis (BV) is the most common cause of abnormal vaginal discharge.(Bradshaw et al., 2006; Koumans et al., 2007; Hay, 2014) BV is characterized by an imbalance in vaginal microflora where there is overgrowth of naturally occurring bacteria such as *Gardnerella vaginalis* and *Mycoplasma hominis* and a decrease in levels of *Lactobacilli*.(Bradshaw et al., 2006; Koumans et al., 2007; Hay, 2014; Lambert, John, Sobel, & Akins, 2013; J. Wilson, 2004) BV is the most common vaginal infection among women of reproductive age (Guédou et al., 2013) that affects approximately 29% of women in the United States (US) compared to 12% of Australian women and more than 50% of women in Eastern/Southern Africa.(Bradshaw & Sobel, 2016; Chen, Tian, & Beigi, 2009; Koumans et al., 2007; Jung, Ehlers, Lombaard, Redelinghuys, & Kock, 2017; Madden, Grentzer, Secura, Allsworth, & Peipert, 2012; J. Wilson, 2004) Approximately 50% of women with BV are asymptomatic.(Koumans et al., 2007; Hay, 2014) BV can increase the risk of contracting many sexually transmitted infections (STIs) (Muzny, Sunesara, Austin, Mena, & Schwebke, 2013) such as human immunodeficiency virus (HIV), *Neisseria gonorrhea* (NG), *Chlamydia trachomatis* (CT), *Trichomonas vaginalis* (TV) and Herpes simplex virus-2 (HSV-2).(Bradshaw & Sobel, 2016; Bradshaw et al., 2006; Chen et al., 2009; Koumans et al., 2007; Hay, 2014; Jung et al., 2017; Machado, Castro, Palmeira-de-Oliveira, Martinez-de-Oliveira, & Cerca, 2015; Madden et al., 2012; Payne, Cromer, Stanek, & Palmer, 2010; Sobel et al., 2006) HIV infected women with BV experience increased viral shedding.(Koumans et al., 2007; Madden et al., 2012) This may be a result of specific bacteria associated with BV that

induce viral replication and shedding. Increased viral shedding may lead to increased HIV transmission.(Wessman et al., 2017) Additionally, BV is associated with adverse reproductive health outcomes such as spontaneous abortion, low birth weight, pelvic inflammatory disease and gynecologic post-operative infections.(Bradshaw & Sobel, 2016; Chen et al., 2009; Machado et al., 2015; Madden et al., 2012; Payne et al., 2010; Sobel et al., 2006) BV associated sequelae also impact health care expenditure. For example, the population attributable risk of BV for preterm delivery in the US was previously estimated to be 30%, incurring a cost of approximately one billion US dollars annually. (Bradshaw & Sobel, 2016)

The etiology and pathogenesis of BV are still not completely clear leading to high recurrence rates despite treatment.(Bradshaw & Sobel, 2016; Bradshaw & Brotman, 2015; Cook, Redondo-Lopez, Schmitt, Meriwether, & Sobel, 1992; Guédou et al., 2013; Lambert et al., 2013; Machado et al., 2015; Madden et al., 2012; Marshall, 2015; Menard, 2011; Payne et al., 2010; Schwebke, Richey, & Weiss2, 1999; Sobel et al., 2006; J. D. Wilson et al., 2005) There is a 15-30% recurrence rate of BV within three months of completing treatment.(Bradshaw & Sobel, 2016; Bradshaw et al., 2006; Cook et al., 1992; J. Wilson, 2004) Recurrent BV can be described as women having three or more confirmed episodes of BV within twelve months.(J. Wilson, 2004) BV persists in instances where recommended treatment methods are not effective, or lactobacilli levels fail to recolonize to normal levels.(Bradshaw & Sobel, 2016) Long term cure rates, 6-12 months, of BV treatment are approximately 50%.(Bradshaw & Sobel, 2016) It is unclear whether these high failure rates are due to failure of the treatment to eradicate the causative agents or failure of the women to re-establish a Lactobacilli dominant vaginal

microbiota. Women with recurrent BV experience periods where they are completely cured of BV and are later diagnosed with BV, whereas women with persistent BV are not cured. Distinguishing between BV persistence and recurrence could help to determine the possible causes of high failure rates for BV treatment.

The overall objective of this dissertation was to examine the factors associated with recurrent and persistent BV among young African American women of reproductive age. The first study aimed to summarize current literature on the epidemiology of BV and highlight areas of deficiency in current clinical practice with respect to BV. The second study aimed to identified BV incidence patterns over a twelve-month period and evaluated the demographic and behavioral risk factors associated with these patterns. The third study examined whether women with persistent BV were more likely to acquire a CT/NG infection compared to women with episodic BV in a population of African American women.

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MANUSCRIPT 1

Coudray MS, Madhivanan P. Bacterial Vaginosis - A Brief Synopsis of the Literature. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020; 245:143-148.

Abstract

Background: Bacterial vaginosis (BV) affects women of reproductive age and can either be symptomatic or asymptomatic. Approximately 50% of women are symptomatic and experience vaginal malodor, discharge, itching and increased vaginal pH. BV can increase the risk of contracting many sexually transmitted infections (STIs) such as human immunodeficiency virus (HIV), Neisseria gonorrhea (NG), Chlamydia trachomatis (CT), Trichomonas vaginalis (TV) and herpes simplex virus-2 (HSV-2). Though effective treatment options do exist, metronidazole or clindamycin, these methods have proven not to be effective long term. **Objective:** The purpose of this review is to summarize current literature on the epidemiology of BV and highlight areas of deficiency in current clinical practice with respect to BV. **Results:** BV recurrence rates are high, approximately 80% three months after effective treatment. Furthermore, in some instances treatment is ineffective and BV persists. Literature also documents the relationship between BV and human papillomavirus (HPV). HPV is the most common sexually transmitted infection among young adult women while BV is the most common cause of vaginal symptoms among women of reproductive age. BV is associated with high levels of anaerobic organisms which can damage the vaginal epithelium and increase the risk of HPV infection. Recent research also highlights the role of the vaginal

microbiome in BV. **Conclusion:** The results of this review warrant further exploration into the etiology of BV as well as exploration of more long-term effective treatment and the investigation of prognostic indicators. Additionally, the need for a standard definition of recurrent and persistent BV is recognized.

Keywords: Bacterial vaginosis, treatment, vaginal microbiome, sexually transmitted infections

Introduction

Bacterial Vaginosis (BV) is a common vaginal dysbiosis among women of reproductive age.(Bautista, Wurapa, Sateren, et al., 2016; Morris, Rogers, & Kinghorn, 2001; Ranjit, Raghubanshi, Maskey, & Parajuli, 2018; Schwebke & R. Desmond, 2007a) Gardner and Dukes first described BV in 1955.(Bautista, Wurapa, Sateren, et al., 2016; Gardner & Dukes, 1955; Menard, 2011) The syndrome was initially termed "*Haemophilus vaginalis* vaginitis," based on the organism that was previously believed to be the etiologic agent, *H. vaginalis*.(Bautista, Wurapa, Sateren, et al., 2016; Gardner & Dukes, 1955; Morris et al., 2001) It was later discovered that *H. vaginalis* did not belong to the genus *Haemophilus* and the bacteria was renamed *Gardnerella vaginalis*.(Bautista, Wurapa, Sateren, et al., 2016) BV was also called nonspecific vaginitis and *Gardnerella vaginalis* vaginitis.(Gibbs, 2007; Hay, 2014; Holzman et al., 2001) Currently, the etiology of BV is unknown.(Bautista, Wurapa, Sateren, et al., 2016; Bautista, Wurapa, & Sanchez, 2016; Bradshaw et al., 2006; Fethers et al., 2009; Guedou et al., 2013; Hay, 2014; Joesoef & Schmid, 1995; Kenyon, Colebunders, & Crucitti, 2013; Klatt, Cole, Eastwood, & Barnabei, 2010; Lambert, John, Sobel, & Akins, 2013; Muzny, Sunesara, Austin, Mena, & Schwebke, 2013; Schwebke, 2000; J. R. Schwebke & R. Desmond,

2007a; Schwebke, Richey, & Weiss, 1999; Wilson, 2004) However, it has been determined that BV is characterized by overgrowth of opportunistic bacteria and a decrease in the levels of *Lactobacilli*.(Bradshaw et al., 2006; Bradshaw & Sobel, 2016; Hay, 2014; Holzman et al., 2001; Klatt et al., 2010; Madden, Grentzer, Secura, Allsworth, & Peipert, 2012; Muzny et al., 2013; Ranjit et al., 2018; Schwebke & Desmond, 2007b; Schwebke et al., 1999; Wilson, 2004) A healthy vaginal flora is dominated by *Lactobacilli*,(Bautista, Wurapa, Sateren, et al., 2016; Bautista, Wurapa, & Sanchez, 2016; Hay, 2014; Klatt et al., 2010; Lambert et al., 2013; Madden et al., 2012; Marshall, 2015; Schwebke et al., 1999) approximately 90-95% of total bacteria.(Bautista, Wurapa, Sateren, et al., 2016; Japanese Society of Chemotherapy Committee on guidelines for treatment of anaerobic & Japanese Association for Anaerobic Infection, 2011) However, research also indicates that some healthy women do not possess a Lactobacillus-dominated vaginal microbiota.(Ravel et al., 2011; Smith & Ravel, 2017; Zhou et al., 2004) In cases of BV, mainly anaerobic microorganisms such as gram-positive cocci and gram-negative bacilli dominate the vaginal flora.(Cook, Redondo-Lopez, Schmitt, Meriwether, & Sobel, 1992) Common opportunistic bacteria include *Prevotella* species, *Gardnerella vaginalis* and *Mobiluncus* species.(Bautista, Wurapa, Sateren, et al., 2016; Holzman et al., 2001; Joesoef & Schmid, 1995; Lambert et al., 2013; Madden et al., 2012; Marshall, 2015; Mohammadzadeh, Dolatian, Jorjani, & Alavi Majd, 2014; Muzny et al., 2013; Schwebke, 2000; Wilson, 2004)

BV is the most common cause of abnormal vaginal discharge.(Bautista, Wurapa, Sateren, et al., 2016; Bradshaw et al., 2006; Hay, 2014; Muzny et al., 2013) Symptomatic BV is also characterized by vaginal malodor, increased vaginal pH and vaginal

itching.(Bradshaw & Sobel, 2016; Hay, 2014; Joesoef & Schmid, 1995; Klatt et al., 2010; Menard, 2011; Schwebke, 2000; Schwebke & Desmond, 2007a) There has been approximately 65 years of research conducted on BV. After over six decades, researchers have still been unable to elucidate the causative agent of BV and issues of adverse BV-associated sequelae are very poorly understood, further emphasizing the clinical conundrum that is BV. This review presents a brief summary of the major research findings with respect to the epidemiology of BV, recurrence and persistence of BV, known correlates of BV and the effect of BV on the vaginal microbiota.

Epidemiology of BV

The prevalence of BV varies internationally and intranationally.(Bautista, Wurapa, Sateren, et al., 2016; Kenyon et al., 2013) The prevalence of BV can range from 20-60% from country to country.(Bautista, Wurapa, Sateren, et al., 2016) BV prevalence is highest in Sub-Saharan Africa.(Bautista, Wurapa, Sateren, et al., 2016; Kenyon et al., 2013) The prevalence of BV is higher in South East Africa when compared to West Africa.(Bautista, Wurapa, Sateren, et al., 2016; Kenyon et al., 2013) A study conducted by Myer *et al*. in South Africa reported that the prevalence of BV was 58.3% as of 2002.(Kenyon et al., 2013; Myer et al., 2005) Additionally, in the year 2000, reported BV prevalence in Zimbabwe was 30.3%.(Kenyon et al., 2013; Kurewa et al., 2010) This can be compared to Nigeria, where in 2005 the prevalence of BV was reported to be 14.2%.(Anukam, Osazuwa, Ahonkhai, & Reid, 2006; Kenyon et al., 2013) Prevalence of BV is moderate in regions such as South and Southeast Asia, Latin America and the Caribbean and the US.(Kenyon et al., 2013) In these regions the prevalence of BV was

determined to be 23.2% in Bangladesh as of 2002,(Kenyon et al., 2013; Rahman et al., 2008) 32% in Chile as of 2006(Kenyon et al., 2013; Villaseca et al., 2015) and 29.2% in the US as of 2004.(Kenyon et al., 2013; Koumans et al., 2007; Mohammadzadeh et al., 2014) Of note are regions such as Australia and New Zealand and Western Europe where BV prevalence is the lowest.(Kenyon et al., 2013) The prevalence of BV in Australia was determined to be 4.7% in 2008.(Fethers et al., 2009; Kenyon et al., 2013) Comparatively low BV prevalence was also reported in Finland for the year 2008 as 8.6%.(Eriksson, Adolfsson, Forsum, & Larsson, 2010; Gibbs, 2007; Kenyon et al., 2013) The aforementioned countries used Nugent Scoring to evaluate the presence of BV.(Kenyon et al., 2013)

Literature has not yet explored the predictors of intranational and international differences with respect to the prevalence of BV. Cultural factors may play a role in the in these observed differences. Additionally, there may be differences in surveillance techniques used and BV may not be a reportable disease in every country. Diagnostic techniques vary depending on the availability of resources. Approximately 50% of cases of BV are asymptomatic.(Hay, 2014) Due to variations in clinical guidelines, BV may not be screened for and the true prevalence of BV, within country, and reported prevalence would not be the same. The US Preventive Services Task Force does not currently recommend the screening of asymptomatic pregnant women for BV due to a lack of data supporting the benefits of screening.(Guise, Mahon, Aickin, & Helfand, 2001; U.S. Preventive Services Task Force, 2008) Furthermore, literature illustrates that there a lack of studies which compare a screened and non-screened population.(Guise, Mahon, Aickin, & Helfand, 2001; Guise, Mahon, Aickin, Helfand, et al., 2001) Similarly

Canadian clinical guidelines only recommend BV screening for asymptomatic pregnant women.(van Schalkwyk & Yudin, 2015) Our literature search did not highlight the screening practices of other countries. It remains unclear why such a large percentage of cases of BV are asymptomatic.(Schwebke, 2000) Longitudinal studies are needed to assess the effect of screening for asymptomatic BV among pregnant and non-pregnant women.

Diagnosis and Treatment of BV

BV is diagnosed using either Amsel's criteria or Nugent score.(Allsworth & Peipert, 2011; Hay, 2014; Madden et al., 2012; Marshall, 2015; Martin & Marrazzo, 2016; Menard, 2011; Mohammadzadeh et al., 2014; Schwebke, 2000) Amsel's criteria is more commonly used in clinical settings(Allsworth & Peipert, 2011; Rebecca M. Brotman, 2011; Madden et al., 2012; Martin & Marrazzo, 2016; Menard, 2011) since it is faster and more affordable than Nugent scoring.(Mohammadzadeh et al., 2014) Three of the following Amsel's criteria must be present to be diagnosed with BV; increased homogeneous thin vaginal discharge, pH of the secretion greater than 4.5, amine odor when potassium hydroxide 10% solution is added to a drop of vaginal secretions or presence of clue cells in wet mount preparations.(Allsworth & Peipert, 2011; Bautista, Wurapa, Sateren, et al., 2016; Klatt et al., 2010; Madden et al., 2012; Martin & Marrazzo, 2016; Menard, 2011; Mohammadzadeh et al., 2014) Gram stain techniques are utilized to diagnose BV by Nugent scoring.(Bautista, Wurapa, Sateren, et al., 2016; Martin & Marrazzo, 2016) Scoring is based upon the presence of different bacterial morphotypes where a score ≥ 7 indicates the presence of BV, 4-6 intermediate and 0-3

normal.(Bautista, Wurapa, Sateren, et al., 2016; Koumans et al., 2007; Madden et al., 2012; Martin & Marrazzo, 2016; Menard, 2011; Spiegel, Amsel, & Holmes, 1983) Due to the methodological differences between these two diagnostic techniques, this results in varying degrees of accuracy when these methods are compared. However, once BV is diagnosed it can be treated.

Treatment is only recommended for symptomatic women, according to the United States (US) Centers for Disease Control and Prevention (CDC) treatment guidelines, due to a lack of sufficient evidence to support treatment of asymptomatic women.(Koumans et al., 2007; Workowski & Berman, 2010) The guidelines further indicate that there are limited benefits of treatment in non-pregnant women and that treatment only provides relief of symptoms.(Mark, Jordan, Cruz, & Warren, 2012) Thus women with asymptomatic BV often experience high recurrence rates due to a lack of treatment. The recommended forms of treatment for BV include metronidazole and clindamycin.(Bradshaw et al., 2006; Bradshaw & Sobel, 2016; Cook et al., 1992; Guaschino et al., 2003; Hay, 2014; Joesoef & Schmid, 1995) The aforementioned antibiotics can be administered orally or intravaginally.(Chen, Tian, & Beigi, 2009; Joesoef & Schmid, 1995) These recommended regimens have similar efficacy.(Bradshaw & Sobel, 2016; Chen et al., 2009; Hay, 2014) Though treatment for BV is only recommended for symptomatic cases of the disease,(J. R. Schwebke & R. Desmond, 2007b) literature suggests that treatment of asymptomatic BV may reduce the risk of BV associated adverse sequelae.(Gibbs, 2007; Spiegel et al., 1983) Schwebke and Desmond determined that treatment with intravaginal metronidazole gel significantly reduced the risk of *Chlamydia trachomatis* (CT) infection.(J. R. Schwebke & R. Desmond, 2007b) In

light of the studies which suggest that treatment of asymptomatic BV may reduce the risk of acquisition of sexually transmitted infections (STIs) the current clinical guidelines should be revaluated and modified accordingly. Health care providers should institute screening for BV regularly, similar to screening for STIs, to potentially diagnose asymptomatic cases as well as reduce the risk of incident STIs. However, considering the findings of Ravel and others that indicate that there is a non-Lactobacillus dominant subgroup of healthy women,(Ravel et al., 2011; Smith & Ravel, 2017; Zhou et al., 2004) screening practices should implement tools such as molecular testing to discern true cases of BV.

BV treatment is usually effective. Studies have reported initial cure rates varying between 80-90% after one month.(Bradshaw et al., 2006; Joesoef & Schmid, 1995) However, there are high rates of recurrence of BV.(Bradshaw & Brotman, 2015; Bradshaw & Sobel, 2016; Brotman, 2011; Guedou et al., 2013; Lambert et al., 2013; Morris et al., 2001) Bradshaw *et al*. reported the recurrence rate of BV could be as high as 58% in the first year after treatment.(Bradshaw et al., 2006; Chen et al., 2009) Cook *et al*. determined that after the completion of treatment with metronidazole that 30-40% of women would experience another episode of BV within three months.(Cook et al., 1992) Comparatively, Wilson *et al*, reported recurrence rates between 15-30% after treatment.(Wilson, 2004) Additionally, BV recurrence rates of up to 60% have been reported within twelve months,(Marshall, 2015) whereas Hillier and Holmes reported recurrence rates up to 80% within 9 months.(Cook et al., 1992) It may be necessary for the scientific community to explore alternative methods of treatment for BV since the current treatment methods are highly ineffective.

Recurrent and Persistent BV

Recurrent BV, though recognized as a common problem associated with the treatment of BV,(Hay, 2014) has no universally accepted definition and therefore no means of definitive diagnosis.(Klatt et al., 2010; Marshall, 2015) However, it is accepted that the presence of repeated cases of BV after treatment is indicative of recurrent BV.(Klatt et al., 2010) In literature, recurrent BV is diagnosed in multiple ways. Klatt *et al*. defined recurrent BV as "*at least three clinic visits within the previous two years that results in an ICD-9 diagnosis code for BV*".(Klatt et al., 2010) Cook *et al*. defined recurrent BV as *three or more episodes of BV in the previous year*.(Cook et al., 1992) Chen *et al*. defined recurrent BV as *"filling a vaginal or oral prescription for BV therapy 4-28 weeks post index date"*.(Chen et al., 2009) Marshall also defines recurrent BV as BV cases that "*recur one or more times after the completion of an episodic regimen*".(Marshall, 2015) A standard definition of recurrent BV is required for effective and efficient diagnosis, treatment and surveillance of this irregular dysbiosis. Nocturnal application of topical metronidazole twice a week for six months is the only approved treatment for recurrent BV.(Marshall, 2015) Currently, the treatment of the partners of women with recurrent BV is not recommended.(Marshall, 2015) The etiology of recurrent BV is not known, however there are many theories as to why it may occur.

Available research suggests that recurrent BV may be caused by reinfection or relapse of infection.(Cook et al., 1992; Wilson, 2004) BV reinfection may occur by two mechanisms, either endogenously or via infection by a partner who has been colonized by BV associated microorganisms.(Cook et al., 1992) Literature supports the hypothesis that

recurrent BV occurs by reinfection through studies which indicate that recurrence rates are lower among women who abstain from sex or use condoms consistently after sex compared to women who have unprotected sex.(Hutchinson, Kip, & Ness, 2007) Conversely, Wilson suggests that the lack of evidence to support partner therapy as a means to reduce recurrent BV indicates that reinfection may not be the cause of recurrent BV.(Wilson, 2004) Fethers *et al*. also determined that partner therapy failed to reduce recurrent BV rates in women.(Fethers et al., 2009) For example, Hay determined, after reviewing four double blind placebo-controlled clinical trials that after treatment of male partners there was no difference in the rate of recurrence of BV.(Hay, 2014)

In 2012, Mehta reviewed six randomized clinical trials (RCTs) which assessed the treatment of male sexual partners for improved bacterial vaginosis outcomes.(Mehta, 2012) It was determined that though the RCTs concluded that male partner treatment did not provide beneficial effect on BV recurrence in women, that these RCTs were inherently flawed.(Mehta, 2012) For example, Vejtorp *et al.* determined that there was no significant difference in symptom improvement or cure between the intervention and control groups [RR=1.03, 95% CI:0.83-1.29],(Vejtorp et al., 1988) but their methods were subpar.(Mehta, 2012) Recruitment and screening methods were not reproducible; eligibility criteria for both men and women were not reproducible; sample size calculations were not appropriately addressed; blinding methods were not reported; adherence was not reported for both men or women; and harms of treatment were not reported in women or women.(Mehta, 2012) Furthermore it should be noted that many studies do not assess the treatment of male partners.

The theory of relapse versus reinfection may be more plausible.(Cook et al., 1992) Relapse may occur due the inability to reestablish a *Lactobacillus* dominant vaginal flora or ineffective treatment.(Cook et al., 1992) Clinical guidelines do not recommend routine test of cure after treatment of an initial BV infection.(Marshall, 2015) Relapse of BV infection could indicate persistent BV where positive BV diagnosis remains unchanged after treatment.(Cook et al., 1992) Thus it is important to consider prognostic indicators of BV. There is a lack of diagnostic tests which predict BV recurrence after treatment.(Sobel et al., 2019) Sobel *et al*. present novel findings where they illustrate the use of a quantitative PCR-based test in combination with Lactobacillus Relative Composition and Nugent scores to predict the likelihood of BV recurrence.(Sobel et al., 2019) They determined that the microbial composition of women with BV within seven days of completing standard metronidazole treatment determined the likelihood of BV recurrence.(Sobel et al., 2019) It is important to consider whether BV is an STI versus a sexually enhanced infection in order to further understand the etiology of BV and its risk factors and develop enhanced diagnostic and prognostic tests.

Predisposing Factors associated with BV

Numerous risk factors are associated with BV, such as sexual history, intravaginal practices, contraceptive use, antibiotic use, race, education, age and menstrual cycle.(Guedou et al., 2013; Ranjit et al., 2018; Schwebke et al., 1999) However data with respect to risk factors of recurrent BV are lacking.(Guedou et al., 2013) It is uncertain whether or not BV is an STI.(Guedou et al., 2013; Holzman et al., 2001; Koumans et al., 2007; Morris et al., 2001) The lack of a known etiologic agent makes it difficult to

classify BV as an STI.(Bautista, Wurapa, Sateren, et al., 2016; Fethers et al., 2009) However, current literature suggests that BV is related to sexual activity.(Fethers et al., 2009; Morris et al., 2001) Factors such as number of lifetime sex partners, women who have sex with women (WSW), use of a sex toy, early coitarche, frequency of vaginal intercourse, recent partner change, oral sex, anal sex and history of bacterial STIs, have been proven in the literature to increase the risk of BV.(Bautista, Wurapa, Sateren, et al., 2016; Rebecca M. Brotman, 2011; Fethers et al., 2009; Guedou et al., 2013; Hutchinson et al., 2007; Koumans et al., 2007; Menard, 2011; Morris et al., 2001; Muzny et al., 2013; Ranjit et al., 2018) Fethers and colleagues reported that BV did not occur in women without a history of sexual experience.(Fethers et al., 2009) Further to this, they also determined that there was a strong association between BV and penile-vaginal sex with multiple sex partners.(Fethers et al., 2009)

Additionally, Morris *et al*. determined that the diagnosis of BV was positively associated with a recent sex partner change, increasing number of lifetime sex partners, WSW and a history of bacterial STIs.(Morris et al., 2001) Furthermore, Madhivanan *et al*. presented findings that indicated that *Trichomonas vaginalis* (TV) was positively associated with BV.(Madhivanan et al., 2008) Few studies have reported the prevalence of BV among women who report never having sex.(Fethers et al., 2009) However, Koumans *et al*. determined that the prevalence of BV among women who never reported having had sex was 18.8.%.(Koumans et al., 2007) Papanikolaou *et al.*, assessed a serious case of recurrent BV in a 17 year old female adolescent.(Papanikolaou, Tsanadis, Dalkalitsis, & Lolis, 2002) Physical examination revealed an intact hymen and Amsel's criteria confirmed the presence of BV.(Papanikolaou et al., 2002) This may indicate that

other factors are necessary for BV infection,(Bautista, Wurapa, Sateren, et al., 2016; Koumans et al., 2007) and BV may be a sexually enhanced rather than sexually transmitted infection.(Bautista, Wurapa, Sateren, et al., 2016)

The association between BV and methods of birth control varies depending on which methods are used. Studies have shown that combined oral contraceptives, progestin only contraceptives and condom use,(Brotman, 2011) are protective against BV.(Bautista, Wurapa, Sateren, et al., 2016; Madden et al., 2012; Menard, 2011; Muzny et al., 2013; Ranjit et al., 2018) Ranjit *et al*. reported that the risk of BV increased among women that used contraceptives on anatomical sites compared to women that did not.(Ranjit et al., 2018) They postulated that the observed difference among women that used oral contraceptives compared to those that did not could have been attributed to the effect of increased levels of estrogen that could potentially support the growth of specific bacteria responsible for lowering the risk of BV.(Ranjit et al., 2018) Of note, Ranjit *et al*. reported that the risk of BV was higher among individuals who used condoms daily compared to those that used condoms sometimes, however this difference was not statistically significant. They also determined that oral contraceptives reduced the risk of BV.(Ranjit et al., 2018) Conversely, consistent condom use has been reported in other studies to significantly lower the risk of recurrent BV.(Bautista, Wurapa, Sateren, et al., 2016; Guedou et al., 2013; Hutchinson et al., 2007) The relationship between BV and intrauterine devices (IUDs) is unclear.(Madden et al., 2012) Some studies have determined that IUDs increase the risk of BV,(Kenyon et al., 2013) while others determined that there is a decreased risk.(Madden et al., 2012) Madden and colleagues did not find a statistically significant association between IUDs and BV.(Madden et al.,

2012) However, they determined that intravaginal bleeding during the first six months among IUD users resulted in a twofold increased risk of BV.(Madden et al., 2012) They further postulated that irregular bleeding may be on the causal pathway between IUD use and BV.(Madden et al., 2012) Conversely, Joesoef determined that BV was significantly associated with IUDs.(Joesoef et al., 2001) It is important to consider that there may be differences in the type of IUDs used in each study (hormone loaded versus copper IUDs). The aforementioned studies did not differentiate between the types of IUDs used.

Intravaginal practices such as douching, also known as vaginal cleansing or vaginal washing, have been determined to be associated with BV.(Baisley et al., 2009; Bautista et al., 2017; Rebecca M. Brotman, 2011; Guedou et al., 2013; Holzman et al., 2001; Hutchinson, Kip, Ness, & Gynecologic Infection Follow-Through, 2007; Kenyon et al., 2013; Menard, 2011; Morris et al., 2001; Muzny et al., 2013; Ranjit et al., 2018) Mixed conclusions about this relationship have been posed in current literature.(Guedou et al., 2013; Jespers et al., 2014) Some studies have determined that douching increased the risk of BV infection.(Bautista, Wurapa, Sateren, et al., 2016; Guedou et al., 2013; Koumans et al., 2007; Morris et al., 2001; Muzny et al., 2013; Ranjit et al., 2018) Ranjit and colleagues reported a statistically significant difference between women that douched daily compared to women that douched occasionally and BV.(Ranjit et al., 2018) Women who douched daily were more likely to have BV.(Ranjit et al., 2018) Additionally, Schwebke *et al*., determined that women who refrained from douching were more likely to be cured of BV.(Schwebke & Desmond, 2007) Conversely, Jespers *et al*., Demba *et al*. and Fethers *et al*. determined that douching was not associated with BV.(Demba et al., 2005; Fethers et al., 2009; Jespers et al., 2014) Few studies present findings related to

douching as a risk factor of recurrent BV. However, Guédou *et al*. determined that recent douching was positively associated with recurrent BV,(Guedou et al., 2013) whereas Klatt *et al*. determined that douching was not associated with recurrent BV.(Klatt et al., 2010) Discrepancies observed in the literature may be due to the varying cultural differences that influence vaginal practices and a lack of understanding of the causal relationship between BV and douching.(Guedou et al., 2013; Hutchinson et al., 2007) Hutchinson and colleagues determined that existing abnormal flora influenced the association between BV and douching.(Hutchinson et al., 2007) They determined that douching was associated with incident cases of BV among women with intermediate vaginal flora but not among women with normal vaginal flora.(Hutchinson et al., 2007) Literature further suggests that women douche following the development of BV to reduce the effect of the associated symptoms.(Hutchinson et al., 2007) Studies which assess the relationship between BV and douching using longitudinal versus cross sectional methods should be further explored.

The risk of BV also varies by race and ethnicity.(Fettweis et al., 2014; Holzman et al., 2001; Koumans et al., 2007; Menard, 2011; Morris et al., 2001; Muzny et al., 2013; Ness et al., 2003; Peipert et al., 2008; Ranjit et al., 2018) African American (AA) race is a risk factor for BV,(Gallo et al., 2012; Kenyon et al., 2013) however, the cause of this relationship remains unclear.(Holzman et al., 2001; Muzny et al., 2013) AA women are more likely to have BV compared to non-Hispanic white women.(Bautista et al., 2017; Ness et al., 2003) Fettweis and colleagues further suggest that AA women are more than twice as likely to develop BV compared to women of European ancestry (non-Hispanic Caucasians) and more than twice as likely to have a preterm delivery.(Fettweis et al.,

2014) AA race is also positively associated with recurrent BV.(Klatt et al., 2010) It is also important to consider the difference between AA women and women from continental Africa in terms of the prevalence and recurrence of BV. Torrone *et al.* determined that the prevalence of BV was 42.1%, 35.2% and 49.5% among 15-24 year olds in the Southern African, Sothern/Eastern African and Eastern African regions of continental Africa respectively.(Torrone et al., 2018) BV occurs in approximately 29% of US women and approximately 50% of these cases occur among AA women.(Alcendor, 2016) Rates of BV infection are higher among women from continental Africa compared to AA women.(Alcendor, 2016) Statistically significant differences are also observed among the vaginal microbiomes of women of different ethnic backgrounds.(Brotman, 2011) Education level is also associated with BV.(Holzman et al., 2001; Ranjit et al., 2018) Holzman *et al*. determined that lower education level was a significant predictor of BV.(Holzman et al., 2001) Ranjit *et al*. also came to a similar conclusion in their study where data indicated that BV was most prevalent among illiterate women.(Ranjit et al., 2018)

Current literature suggests that menstrual cycle is associated with BV.(Bautista, Wurapa, Sateren, et al., 2016; Hay, 2014; Holzman et al., 2001; Kenyon et al., 2013) Holzman *et al*. concluded that BV was more common during the first week of the menstrual cycle.(Holzman et al., 2001) Bautista and colleagues have also reported a positive association between BV and the menstrual cycle as well as vaginal hygiene.(Bautista, Wurapa, Sateren, et al., 2016) For example, the use of cloth or cotton for menstrual hygiene compared to sanitary pads was found to be a risk factor for BV.(Baisley et al., 2009; Dahal, Jhendi, Pun, & Maharjan, 2017) A history of pregnancy

also increases the risk of BV.(Bautista, Wurapa, Sateren, et al., 2016) Broad spectrum antibiotic use is also a risk factor for BV.(Dahal et al., 2017; Ranjit et al., 2018) Baeten and colleagues determined that recent antibiotic use was a risk factor for loss of *Lactobacilli* which is associated with BV.(Baeten et al., 2009)

The Vaginal Microbiota and BV

The vaginal microbiota is instrumental in female reproductive health.(Rebecca M. Brotman, 2011) Advancements in bioinformatics allow for the characterization of the changes in vaginal microbiota during BV through 16S RNA sequencing.(Vitali et al., 2015) Current literature indicates that there is a correlation between vaginal microbiota and BV.(Rebecca M. Brotman, 2011; Vitali et al., 2015) A healthy vaginal microbiota typically presents with a low pH and low levels of species diversity.(Deng et al., 2018) Community state types (CSTs) can be used to describe the variation in the vaginal microbiota by classifying them into dominant groups.(Deng et al., 2018; Ravel et al., 2011) CSTs are dominated by *Lactobacillus* such as *L. crispatus, L. iners, L. gasseri, L. jensenii* or a diverse community.(Deng et al., 2018; Ravel et al., 2011) Vitali and colleagues determined that *L. iners* was more common among women infected with BV compared to *L. crispatus* which is more common among women with a healthy vaginal microbiota.(Vitali et al., 2015) They further conclude that *Atopobium*, *Prevotella* and *M. hominis* were more prevalent among women with BV.(Vitali et al., 2015)
Deng *et al.* determined that G. vaginalis was the most abundant active species in BV.(Deng et al., 2018)

The vaginal metabolome also highlights characteristics of BV; however, few studies explore this relationship.(Srinivasan et al., 2015) Significant differences have been demonstrated between the metabolic profiles of women with and without BV.(Srinivasan et al., 2015) In cases of BV there is a general increase in amines such as tyramine, trimethylamine and cadaverine.(Srinivasan et al., 2015; Vitali et al., 2015) In addition to assessing the vaginal metabolome, the frequency and length of time of sampling needs to be explored. The vaginal microbiome is dynamic and findings from cross sectional versus longitudinal studies can vary. Literature suggests that there are high levels of species turnover in the vaginal microbiota.(Gajer et al., 2012) Lambert and colleagues determined from their longitudinal analysis of the vaginal microbiome of women with recurrent BV, levels of *Lactobacilli* decrease long before symptomatic BV presents.(Lambert et al., 2013) Ravel and colleagues determined through daily assessment of the vaginal microbiota that prior to symptomatic BV the vaginal microbiota mainly comprised of strict anaerobes like *Atopobium*, *Prevotella*, *Megasphera*, BV-associated bacterium 2 and *G. vaginalis*.

BV and Adverse Sequalae

The epidemiological profile of BV is similar to many common bacterial STIs.(Bautista, Wurapa, Sateren, et al., 2016) BV also increases the risk of acquiring many STIs such as human immunodeficiency virus (HIV),(Baisley et al., 2009; Bautista, Wurapa, Sateren, et al., 2016; Bautista, Wurapa, & Sanchez, 2016; Bautista et al., 2017; Bradshaw & Brotman, 2015; Gallo et al., 2012; Muzny et al., 2013) *Neisseria gonorrhoeae* (NG),(Bautista, Wurapa, Sateren, et al., 2016; Bautista, Wurapa, &

Sanchez, 2016; Bautista et al., 2017; Bradshaw & Brotman, 2015; Gallo et al., 2012) CT,(Bautista, Wurapa, Sateren, et al., 2016; Bautista, Wurapa, & Sanchez, 2016; Bautista et al., 2017; Bradshaw & Brotman, 2015; Gallo et al., 2012) TV and herpes simplex virus-2 (HSV-2)(Baisley et al., 2009; Bautista, Wurapa, & Sanchez, 2016; Bautista et al., 2017; Bradshaw & Brotman, 2015; Gallo et al., 2012).(Allsworth & Peipert, 2011; Kenyon et al., 2013; Koumans et al., 2007) Wiesenfeld *et al*. determined that the likelihood of positive NG/CT increased as the abnormality of vaginal flora increased and that BV was associated with a 4 and 3.4 times increased risk of testing positive for NG and CT respectively.(Wiesenfeld, Hillier, Krohn, Landers, & Sweet, 2003) Similarly, Baustista *et al* determined that there was a 1.5 and 2.4 times increased risk of CT and NG diagnosis respectively among women diagnosed with BV.(Bautista, Wurapa, & Sanchez, 2016; Bautista et al., 2017) Furthermore, *Lactobacillus* bacteria produce H_2O_2 which inhibits the growth of NG.(Gallo et al., 2012) In cases of BV where Lactobacillus decrease and the levels of H_2O_2 also decrease, there is increased risk of NG.(Gallo et al., 2012) Though research supports that BV increases the risk of STIs through biological mechanisms, BV can also be a consequence of STIs.(Gallo et al., 2012)

Studies have shown mixed results about the treatment of BV to prevent acquisition of STIs. Schwebke *et al* determined that treatment of BV resulted in significantly lower number of CT cases.(Schwebke & R. Desmond, 2007b) BV has been associated with concurrent infections of NG/CT, as well as longitudinal studies have shown that BV is associated with NG/CT bidirectionally.(Bautista, Wurapa, & Sanchez, 2016; Morris et al., 2001; Ness et al., 2005) In addition to BV increasing the risk of HIV,(Myer et al., 2005) BV also increases HIV viral shedding.(Baisley et al., 2009;

Koumans et al., 2007) Among women HIV seropositive women, BV increases the risk of transmission of HIV to male partners.(Bradshaw & Brotman, 2015) There is a twofold increased risk of HSV-2 among women with BV.(Koumans et al., 2007) Additionally, BV increases the risk of human papillomavirus (HPV).(Bautista, Wurapa, & Sanchez, 2016; Bautista et al., 2017; R. M. Brotman et al., 2014) Brotman et al. determined that women with a *L. gasseri* dominant vaginal microbiota were more likely to clear detectable HPV from the vaginal microbiota.(R. M. Brotman et al., 2014) Additionally, they concluded that BV associated vaginal microbiota, low levels of *Lactobacillus* spp or *L. iners* dominant, had the greatest relative proportion of HPV positive samples.(Brotman et al., 2014) BV is also associated with adverse reproductive outcomes, such as preterm delivery, intrauterine infection and pelvic inflammatory disease.(Baisley et al., 2009; Morris et al., 2001; Ness et al., 2003)

Conclusions and Implications for the Future

Conflicts in the literature further highlight what little is known about the etiology and pathogenesis of BV, recurrent BV and persistent BV. Though we have presented many known risk factors of BV in this narrative review no true causative agent has been identified. Further investigation is needed to determine potential predictors that may differentiate whether or not BV is a sexually transmitted or sexually enhanced disease. Enhanced analytical techniques such as structural equation modelling or multi-state Markov models should be implemented to better understand the relationship between sexual correlates and BV.

In addition to the current literature which examines the serious associated medical comorbidities, lack of known etiology and poor long-term treatment, future research should investigate the predictors and prognostic indicators of recurrent and persistent BV, differences in the vaginal microbiota of women with recurrent and persistent BV, the effect of recurrent and persistent BV on incident NG/CT and the effect of treatment of the aforementioned factors. Emphasis should be places on the novel findings of Sobel et al with respect to prognostic indicators and further explored. There is a noted lack of standard definitions of recurrent and persistent BV. This hinders the scientific community in making definitive conclusions with respect to treatment options of these very common conditions associated with BV cases. Additionally, the current screening and treatment guidelines should be reviewed.

Furthermore, the designs of studies to investigate BV need to be addressed. Many studies measure BV at long intervals or cross sectional. More emphasis should be placed on the daily assessment of BV. Additionally, studies which examine the vaginal microbiome of women with BV should place more emphasis on metabolomic assessments in order to assess the effects of metabolites on the vaginal microbiome.

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MANUSCRIPT 2

Factors Associated with the Recurrence, Persistence and Clearance of Bacterial Vaginosis among Young African American Women: A Latent Class Analysis

Abstract

Background: While risk factors of recurrent and persistent BV have been explored in the literature, the long-term incidence patterns of BV remain elusive. **Methods**: Previously concluded randomized clinical trial data were analyzed, where oral metronidazole was the administered treatment. Latent class analysis (LCA) techniques were used to assess the patterns of multiple episodes of BV over twelve months. Multinomial regression analysis was used to determine the predictors of class membership. The multivariable model included age, last BV treatment, douching frequency, birth control, sexual risk behavior and treatment with metronidazole. **Results**: A total of 858 African American women, asymptomatic for BV were included in the analysis. There were three emergent patterns of multiple cases of BV determined by LCA: persistent (55.9%), recurrent (3.5%) and clearance (13.5%). Participants who had douched at least once had significantly lower odds to be in the recurrent class (Adjusted Odds Ratio [adjOR]: 0.55; 95% Confidence Interval [CI]: 0.18-0.63) than participants who never douched. Women who had sex with women (WSW) had significantly lower odds of belonging to the persistent class (adjOR: 0.38; 95% CI: 0.22-0.68) and the recurrent class (adjOR: 0.43; 95% CI: 0.23-0.81) than women who did not. Those who were treated with metronidazole had significantly increased odds of being in the recurrent class (adjOR: 1.92; 95% CI: 1.22-3.03) than those who were not treated. **Conclusion**: Assessment of

BV cases revealed distinct patterns of recurrence and persistence of BV despite treatment, which were significantly associated with age and women having sex with women.

Keywords

bacterial vaginosis, latent class analysis, clearance, persistence, recurrence

Introduction

Bacterial vaginosis (BV) is a polymicrobial condition with vaginal dysbiosis that was first documented by Gardner and Dukes in 1955.(Bautista et al., 2016; Gardner & Dukes, 1955) BV is the most common cause of vaginal discharge,(Bradshaw et al., 2006; Falconi-McCahill, 2019; Muzny et al., 2019) and is associated with increased risk of preterm birth, pelvic inflammatory disease and sexually transmitted diseases.(Muzny et al., 2019) The current recommended forms of treatment include metronidazole or clindamycin.(Bradshaw et al., 2006; Bunge, Beigi, Meyn, & Hillier, 2009; Faught & Reyes, 2019) Though short term BV cure rates are high, approximately 80-90%, there are however high long term recurrence rates of BV post treatment.(Bradshaw et al., 2006) There is no universally accepted definition of recurrent BV and effective treatment for recurrent BV does not exist.(Faught & Reyes, 2019) Oral metronidazole is the recommended form of treatment for symptomatic BV, however, it may not be an effective treatment for women with recurrent BV who have failed metronidazole treatment in the past.(Bunge et al., 2009; Faught & Reyes, 2019) The effect of metronidazole on normalizing vaginal flora in women with asymptomatic BV is not known. It should be noted that approximately 25% of women with BV experience

spontaneous resolution of BV.(Bunge et al., 2009) Furthermore, in some cases, BV continues to persist. Thus, BV incurs alarmingly high treatment costs, estimated to be $4.8 billion annually, and the high prevalence of BV is of public health concern.(Falconi-McCahill, 2019)

The National Health and Nutrition Examination Survey (NHANES) data between 2001 and 2004 estimated the prevalence of BV in the United States (US) to be 29.2%.(Falconi-McCahill, 2019) The prevalence of BV varies by race and ethnicity with Black and Hispanic women having a higher prevalence of BV compared to White and Asian women.(Falconi-McCahill, 2019) Cultural backgrounds also influence the use of intravaginal practices such as vaginal douching which is associated with BV.(Aslan & Bechelaghem, 2018) Vaginal douching involves the use of cleansing solution in the vagina,(Yanikkerem & Yasayan, 2016) and the effects of this practice have been disputed as some literature has found varying effects of douching.(Gresenguet, Kreiss, Chapko, Hillier, & Weiss, 1997; Hutchinson, Kip, Ness, & Gynecologic Infection Follow-Through, 2007; Tevi-Benissan et al., 1997) Additionally, sexual activity increases the risk of incident and recurrent BV.(Falconi-McCahill, 2019; Ranjit, Raghubanshi, Maskey, & Parajuli, 2018) Women who have sex with women (WSW) and women who have sex with multiple male sex partners are at increased risk of BV.(Falconi-McCahill, 2019) Furthermore, women who remain with their male sex partner after treatment are at increased risk of recurrent BV.(Falconi-McCahill, 2019) Literature states that hormonal contraception and condom use are protective against BV.(Bautista et al., 2016; Falconi-McCahill, 2019; Ranjit et al., 2018) Though there are multiple known risk factors of BV, the etiology of BV continues to remain unknown.(Bautista et al., 2016) Novel approaches

are needed to further elucidate the etiology of BV. One such possible method is Latent Class Analysis (LCA).

LCA has been used in research to assign participants to discrete, mutually exclusive groups known as latent classes through a probabilistic approach.(Kongsted & Nielsen, 2017; Schreiber, 2017) Latent classes are determined based on selected observed categorical variables.(Lanza, Collins, Lemmon, & Schafer, 2007) LCA has been increasingly popular in behavioral science research to investigate latent risk factors.(Okeke, Clement, McKellar, & Stout, 2018) Okeke and colleagues have implemented LCA techniques to investigate health care utilization behaviors and disengagement from HIV care.(Okeke et al., 2018) LCA has also been used in BV research by Jespers *et al*.(Jespers et al., 2012) They identified two types of "normal flora" and one "BV type flora" with LCA, which were significantly associated with various *Lactobacillus* bacteria.(Jespers et al., 2012) Though their research used LCA to examine BV and its relationship with vaginal flora, to the best of our knowledge, LCA has not been used to examine demographic and behavioral characteristics of BV and BV incidence patterns after treatment. Our study aimed to identify BV incidence patterns over a twelve-month period and evaluate the demographic and behavioral risk factors associated with these patterns among women with BV at baseline. This is of public health importance due to the high rates of recurrence of BV.

Materials and Methods

Study Design

We conducted a retrospective analysis of data from African American women of

reproductive age who participated in a randomized clinical trial (RCT) which investigated home screening for BV to prevent sexually transmitted diseases (STDs). The RCT was conducted in six geographic locations (Baltimore, Maryland; Birmingham, Alabama; Durham and Raleigh, North Carolina; Pittsburgh, Pennsylvania; and San Francisco, California). The methodology used for the RCT has been previously described.(Schwebke et al., 2016) Here, we briefly summarize the key aspects of the study.

Women at increased risk for STDs who had asymptomatic BV were recruited from STD, family planning, obstetrics-gynecology and clinical research clinics.(Schwebke et al., 2016) Participants were eligible for the study if they had vaginal pH >4.5 and >20% clue cells on vaginal wet preparation microscopy and did not complain of abnormal vaginal discharge or odor. Women who exhibited BV symptoms, such as increased vaginal discharge and vaginal odor, were not included in the study. Eligible participants were randomized to treatment and control groups, and followed-up for a period of twelve months. Women randomized to the treatment group received 500mg of oral metronidazole for seven days upon enrollment. Participants received home testing kits every two months to collect vaginal samples for BV testing. Every four months an additional swab was collected to test for chlamydia and gonorrhea. Women in the treatment arm received 500mg of oral metronidazole for seven days after every positive BV result. Women in the control arm did not receive treatment for asymptomatic BV at any time during the study, in accordance with Centers for Disease Control and Prevention (CDC) guidelines.(Workowski & Berman, 2010) All women, irrespective of the arm they were randomized to, could receive treatment if they developed symptoms

during the follow-up period from their respective primary care physicians. Institutional Review Board (IRB) approvals were obtained by all participating sites prior to the conduct of the initial study. The current study was approved by the Florida International University IRB.

Measures

Participants were trained to obtain self-collected swabs. Swabs were rolled across a microscope slide and sent to a lab for evaluation. Nugent Scores (NS) of vaginal smears were used to assess the presence of BV every two months. The slides were gram-stained and assessed for BV using NS. NS between 0-3 are considered to not have BV, 4-6 intermediate flora and 7-10 BV. For this study, a NS between 0-6 was considered as 'no BV' and 7-10 indicated 'BV'.(Mohammadzadeh, Dolatian, Jorjani, & Alavi Majd, 2014) Baseline demographic, medical and sexual risk behavior characteristics were assessed using a self-administered questionnaire. Age, race, ethnicity and highest level of education were measured. Medical history assessed included prior antibiotic use (past 30 days), prior lifetime episodes of BV (never, once, 2-4 times, ≥ 5 times), prior lifetime treatment for BV (≤6 months, 7-12 months, ≥12 months ago), prior pregnancy (yes/no) and frequency of vaginal douching (ever/never). Types of birth control used in the past year were also assessed; birth control pills, birth control patch, Nuva-ring, condoms, spermicide cream, Depo-Provera shot, intra-uterine device (IUD) and other. Sexual risk behavior characteristics evaluated in the past year included; number of different sex partners, number of oral sex partners (receptive), number of unprotected anal sex partners, number of unprotected vaginal sex partners, women who have sex with women

and new sex partners. Randomization arms were also assessed; treatment with metronidazole and no treatment.

Statistical Analysis

There were 1,365 women enrolled in the original RCT and 1,160 agreed to the future use of the data for research. For this study, we only included women who self-identified as African American (n=977). African American women were selected due to their increased risk of BV and unique cultural attributes. For LCA of BV patterns over a twelve-month period, we used the BV results (yes/no) at months two, four, six, eight, ten and twelve. Baseline BV results were excluded since all women had BV at baseline and inclusion of these participants may bias the results. Participants with missing BV results for all timepoints were excluded from the analysis (119 women; 12.2%). Listwise deletion was selected since there was a large enough sample and BV results were missing completely at random. Consequently, 858 African American women were included in the analysis. There were no statistically significant differences with respect to age, education, ethnicity and race between women that were included compared to those who were excluded. Baseline participant characteristics were described using frequencies for categorical variables and means and standard deviations for continuous variables. Age was the only continuous variable and was categorized for easy comparison of groups. Chi-squared or Fisher exact tests for categorical variables were used as appropriate to assess differences by latent class.

Latent classes were modeled using PROC LCA in SAS.(Lanza et al., 2007) We assessed the model fit statistics of models which included two to five latent classes. The

maximum number of iterations for each model was 9000 and the seed was 1000. Bayesian information criterion (BIC), adjusted Bayesian information criterion (aBIC), Akaike information criterion (AIC) and entropy were used to identify the best model.(Lanza et al., 2007) Participants were assigned to latent classes based on the highest posterior probability of membership. We used multinomial logistic regression to examine the relationship between baseline demographic characteristics, medical history, sexual risk behavior in the past year and latent class membership. Baseline predictors evaluated behavior and characteristics among participants of the previous year. Variables with Chi-squared test p-values <0.2 were included in the multivariable multinomial logistic regression, as seen in literature.(Zellner, Keller, & Zellner, 2004) Age, frequency of douching, last BV treatment, prior pregnancy, birth control (Depo Provera shot), unprotected anal sex partners, sex with other women, new sex partners and treatment with metronidazole were included in the final model. SAS version 9.4 (SAS Institute Inc, Cary, NC) was used to clean and analyze all data and LCA was conducted using the SAS-based add on package PROC LCA, version 1.3.2 (University Park, PA).

Results

Participant Characteristics

The mean age of the sample was 21.25 (SD: ±2.12) years. Chi-squared test results showed significant associations between some baseline variables and latent classes. All women were African American and 3.85% of women also self-identified as Hispanic/Latino (p=0.45). Most women were educated, with 48.4% completing more than a high school diploma or GED (p=0.48). Participant responses indicated a lack of

prior antibiotic use in the past 30 days (0.1%; p=0.96), most women had never been diagnosed with BV (54.2%; p=0.25) and of those who reported prior episodes of BV, most (61.9%; p=0.04) were treated ≤6 months ago. Additionally, 57.0% of women reported a prior pregnancy (p=0.05) and 50.4% reported having douched at least once (p=0.02). Various forms of birth control were used by majority of women (93%) such as, birth control pills/patches (19.6%; p=0.98), Nuva Ring (4.2%; p=0.33), condoms (77.6%; p=0.69), Depo-Provera shot (15.7%; p=0.04), IUDs (9.8%; p=0.34) and spermicide (1.2%, p=0.42). All women engaged in sexual activity in the prior year. Most women had two or more sex partners (76.6%; p=0.75) as well as two or more oral sex partners (52.4%; p=0.39) in the prior year. There were 150 (17.5%; p=0.16) women that had engaged in unprotected anal sex, and 799 (93.1%; p=0.95) women that had engaged in unprotected vaginal sex. Moreover, 97 (11.3%; p=0.01) women reported having had sex with other women and 418 (48.7%; p<0.01) had new sex partners. Approximately half of the sample were assigned to the treatment arm (N=438; 51%; p<0.01). The aforementioned p-values were associated with the comparison between latent classes. Table one details the participant characteristics of the study sample stratified by latent class.

Latent Class Description

A three-class model was selected based on its optimal fit for the data. BIC, aBIC, AIC and entropy scores were used to compare a five-class (AIC-99.79, BIC-261.45, aBIC-153.47, Entropy-0.63), four-class (AIC-97.05, BIC-225.43, aBIC- 139.68, Entropy-0.58), three-class (AIC-102.90, BIC-197.99, aBIC-134.47, Entropy-0.61), and two-class

model (AIC-120.17, BIC-181.98, aBIC-140.69, Entropy-0.65). Classes were named based on item-response probabilities as follows: “persistent” (55.9%), “recurrent” (30.5%) and “clearance” (13.5%) (Table 2). The persistent class was characterized by high probability (>77%) of being positive for BV (NS:7-10) at each time point (months two, four, six, eight, ten and twelve). This class had the highest probability of BV at every timepoint, with the highest probability (87%) at month ten. Women in the recurrent class alternated between decreasing (as low as 13%) and increasing (as high as 31%) probabilities of having BV at each timepoint. The probability of BV in this class decreased between months two and six and then steadily increased until month twelve. Finally, women in the clearance class had a consistently decreasing probability of BV from 72% to 8% from months two to ten and increased to 19% at month twelve. This class had the lowest probability (8%; month ten) of BV of all three classes.

Factors associated with Latent Class Membership

Women >21 old years were significantly more likely to be in the persistent class (adjOR: 1.90; 95% CI: 1.23-2.95), or recurrent class (adjOR: 1.88; 95% CI: 1.17-3.00) than the clearance class. Women who had experienced a prior episode of BV and received treatment seven to twelve months ago had significantly lower odds of being in the persistent class compared to clearance class (adjOR: 0.34; 95% CI: 0.18-0.63) than women who did not have a prior episode of BV. Participants who douched at least once had significantly lower odds of being in the recurrent class compared to clearance class (adjOR: 0.55; 95% CI: 0.35-0.87) than participants who never douched. WSW also had significantly lower odds of being in the persistent class (adjOR: 0.38; 95% CI: 0.22-0.68)

or the recurrent class (adjOR: 0.43; 95% CI: 0.23-0.81) compared to clearance class than women who did not. Those who were randomized to the treatment arm were significantly more likely to be in the recurrent class versus the clearance class (adjOR: 1.92; 95% CI: 1.22-3.03) than those who did not.

Discussion

Our findings illustrate distinct patterns of multiple cases of BV over a twelve-month period. Through LCA, we were able to elucidate three distinct patterns; persistence, recurrence and clearance. Of these three groups, two groups (persistence and recurrence) were at significantly increased risk of multiple episodes of BV. Our evidence supports the hypothesis that older age, unprotected anal sex and treatment with metronidazole were associated with risk of recurrence and/or persistence of BV. We also determined that women who reported a history of douching, and women who have sex with women, had lower odds of being in either BV persistence or recurrence groups. Rates of BV recurrence have been evaluated in the literature; however, this is the first study to characterize BV patterns over a twelve-month period using LCA. The proportion of women assigned to the treatment arm classified as persistent was high, and highlights the poor efficacy of oral metronidazole to reduce the long-term occurrence of multiple cases of BV.

Although women who were assigned to the treatment arm were less likely to be classed as persistent, this observation was not statistically significant (adjOR: 0.79; 95% CI: 0.52-1.20). Conversely, women who were assigned to the treatment arm were significantly more likely to be classed in the recurrent compared to clearance class

(adjOR: 1.92; 95 % CI:1.22-3.02). Standard BV treatment includes a course of 500mg of oral metronidazole for seven days for symptomatic cases.(Faught & Reyes, 2019) Standard BV treatment was administered to all participants who tested positive for BV in the treatment arm; the follow-up questionnaire did not fully assess symptoms after baseline. It should be noted that clinical guidelines do not recommend the treatment of asymptomatic BV.(Guise et al., 2001) Furthermore, literature also does not support standard BV treatment for recurrent BV.(Faught & Reyes, 2019) If it is assumed that the mechanism of asymptomatic and symptomatic BV are the same, the increased likelihood of multiple episodes of BV may have been caused by ineffective treatment of those randomized to the treatment arm.(Faught & Reyes, 2019) Faught *et al.* present alternative treatment methods for recurrent BV such as metronidazole 750 mg/miconazole 200 mg for five nights each month for twelve months or metronidazole vaginal gel (0.75%) for three to six months.(Faught & Reyes, 2019) Furthermore, the mechanism for recurrent BV is unknown. It is hypothesized that recurrent BV may be caused by residual infection due to the persistence of *Gardnerella vaginalis,* which is resistant to metronidazole treatment.(Faught & Reyes, 2019) Women who received BV treatment 7-12 months ago were less likely to be classed as persistent (adjOR: 0.34; 95% CI: 0.18-0.63). This finding is unclear and may be an artefact due to the skewed distribution observed among the categories.

Though BV is not considered an STI, as there is no known pathogen, it is associated with sexual activity.(Falconi-McCahill, 2019; Faught & Reyes, 2019) Specifically, irregular condom use, multiple sex partners and having a consistent sex partner are associated with recurrent BV.(Falconi-McCahill, 2019; Faught & Reyes,

2019) We determined that the only significant associations between sexual activity and class membership occurred among WSW. WSW were less likely to be classed as persistent (adjOR: 0.38; 95% CI: 0.22-0.68) or recurrent class (adjOR: 0.43; 95% CI: 0.23-0.81). Our findings are similar to those of Muzny *et al.* who determined that WSW were less likely to be diagnosed with BV (adjOR: 0.08; 95% CI: 0.01-0.74).(Muzny, Sunesara, Austin, Mena, & Schwebke, 2013) Contrary to these findings, Falconi-McCahill *et al*. present data which concludes that there is an increased risk of BV among WSW.(Falconi-McCahill, 2019) The discrepancies observed may be due to varying practices among WSW such as vaginal lubricant use, oral-anal sex and improper cleaning of vaginal sex toys.(Muzny et al., 2013) Women engaging in unprotected anal sex with one partner versus none were more likely to be classed as persistent (adjOR: 2.45; 95% CI: 1.21-4.98). This is consistent with literature which suggests that unprotected anal sex increases the risk of BV.(Cherpes, Hillier, Meyn, Busch, & Krohn, 2008) Though women who had one unprotected anal sex partner were more than twice as likely to be in the persistent class compared to the clearance class, women with two or more sex partners did not have a significant association with class membership. Of note, though the confidence interval did not include one, the association between anal sex and latent class did not yield a significant p-value (type III). The lack of a significant relationship may be a result of the small number of women who had unprotected anal sex with two or more partners. The distribution did not allow for significant results and the confidence interval observed may have resulted from chance. This may be a spurious finding.

Intravaginal practices such as douching are also associated with the risk of BV.(Aslan & Bechelaghem, 2018; Brotman et al., 2008) However, the effects of

douching vary.(Aslan & Bechelaghem, 2018; Gresenguet et al., 1997; Hutchinson et al., 2007; Pavlova & Tao, 2000; Tevi-Benissan et al., 1997) Our results show that women who douched at least once were less likely to be classed as recurrent versus clearance (adjOR: 0.55; 95% CI: 0.35-0.87) as compared to women who had never douched. This association may be the result of the postulated beneficial effects of vaginal douching such as removal of semen after sex, and alleviation of vaginal irritation.(Aslan & Bechelaghem, 2018; Tevi-Benissan et al., 1997) The removal of semen decreases the load of sexually transmitted pathogens.(Tevi-Benissan et al., 1997) Furthermore, the temporal association between BV and vaginal douching is also disputed.(Hutchinson et al., 2007) It is possible that women douche to alleviate the symptoms of BV as well as that vaginal douching causes BV.(Hutchinson et al., 2007) Hutchinson *et al*. determined through prospective longitudinal analyses that douching was not associated with BV,(Hutchinson et al., 2007) however, cross-sectional studies have determined that douching was associated with BV.(Hutchinson et al., 2007; Ranjit et al., 2018) Our analysis was cross-sectional, thus the bidirectional nature of the association between BV and vaginal douching could not be assessed. There were no statistical differences in terms of douching between the persistent and clearance class. This may suggest that douching may only be beneficial for women with recurrent BV. There may be inherent differences in the vaginal microbiota of women classed as recurrent versus persistent which could account for this observation. Older women (>21 years) were more likely to be members of the persistent and recurrent classes compared to the clearance class, indicating that older women were more likely to experience multiple episodes of BV over a twelve-month period. BV is the most common vaginal dysbiosis among women of reproductive

age.(Ranjit et al., 2018) Our findings are consistent with those of Ranjit *et al*. who determined that BV was least prevalent among women <21 years.(Ranjit et al., 2018)

Though our study is novel in its approach, it is also subject to some limitations. There was no test of cure for BV done by the RCT from which data for this study was acquired. Therefore, it is possible that participants did not take the medication as prescribed. Furthermore, the treatment administered has been shown in literature to be ineffective. Additionally, all responses received on the baseline questionnaire were self-reported and subject to recall and social desirability bias. Consequently, sexual risk behavior may have been underreported. The analysis was further limited by the lack of inclusion of time varying predictors though the outcome is based on a twelve-month assessment. The presence or absence of BV symptoms were not assessed after baseline and therefore could not be accounted for in the analysis. There is also limited generalizability of results since only African American women were included in the analysis. For future research, Latent Transition Analysis could be explored to assess the risk factors associated with transitions between BV states at each time point and include time varying predictors. Our study also failed to incorporate the use of microbiota data. For future research, the use of metabolomics to examine the longitudinal changes in the vaginal microbiome should be conducted to assess the microbiological factors which contribute to the recurrence and persistence of BV. Additionally, the host immune response should be considered. Furthermore, LCA can be used to create classes which combine epidemiologic and microbiome data to comprehensively assess the multiple predictors of repeated cases of BV. Considering the lack of knowledge of the mechanisms of recurrent and persistent BV, novel analytical approaches are needed to

examine these phenomena. Examination of epidemiologic and microbiome data *in silo* is not sufficient.

Here we present novel findings that classify women based on BV persistence, recurrence and clearance over a twelve-month period. Our findings illustrate high incident cases of BV. Women aged 21 years and over, who douched at least once, who engaged in sexual activity with other women in the past year, and received metronidazole treatment were significantly more likely to be in the recurrent class compared to the clearance class. Similarly, women aged 21 years and over who had sex with other women were significantly more likely to have a persistent case of BV. Efforts should be made to evaluate alternative treatment for recurrent and persistent cases of asymptomatic BV.

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Tables

Table 1: Participant Characteristics stratified by Latent Class

Characteristics	**Categories**		**Latent Classes (N=858)**			**p value[a]**
	Levels	**Overall**	**Persistent (N=480; 55.9%)**	**Recurrent (N=262, 30.5%)**	**Clearance (N=116; 13.5%)**	
Demographic Variables						
Age, n (%)						***0.03***
	≤21 years	355 (41.4%)	184 (38.3%)	111 (42.4%)	60 (51.7%)	
	>21 years	503 (58.6%)	296 (61.7%)	151 (57.6%)	56 (48.3%)	
Education, n (%)						0.48
	No HS	151 (17.6%)	85 (17.7%)	46 (17.6%)	20 (17.2%)	
	HS	292 (34.0%)	173 (36.0%)	78 (29.8%)	41 (35.3%)	
	More than HS	415 (48.4%)	222 (46.3%)	138 (52.7%)	55 (47.4%)	
Ethnicity, n (%)						0.45
	Hispanic/Latino	33 (3.8%)	15 (3.1%)	12 (4.6%)	6 (5.2%)	
	Not Hispanic/Latino	825 (96.2%)	465 (96.9%)	250 (95.4%)	110 (94.8%)	
Medical History						
Prior Antibiotic Use[b], n (%)						0.96
	Yes	45 (5.2%)	26 (5.4%)	13 (5.0%)	6 (5.2%)	
	No[c]	813 (94.8%)	454 (94.6%)	249 (95.0%)	110 (94.8%)	
Prior Episodes of BV, n (%)						0.25
	Once	176 (20.5%)	93 (19.4%)	57 (21.8%)	26 (22.4%)	
	2-4 times	161 (18.8%)	83 (17.3%)	51 (19.5%)	27 (23.3%)	
	5 or more times	56 (6.5%)	26 (5.4%)	22 (8.4%)	8 (6.9%)	
	Never[d]	465 (54.2%)	278 (57.9%)	132 (50.4%)	55 (47.4%)	
Last BV treatment, n (%)						***0.04***

≤6 months ago	154 (18.0%)	83 (17.3%)	50 (19.1%)	21 (18.1%)	
7-12 months ago	92 (10.7%)	38 (7.9%)	34 (13.0%)	20 (17.2%)	
≥12 months ago	148 (17.3%)	81 (16.9%)	46 (17.6%)	21 (18.1%)	
Never[e]	464 (54.1%)	278 (57.9%)	132 (50.4%)	54 (46.6%)	
Prior Pregnancy, n (%)					0.05
Yes	493 (57.5%)	292 (60.8%)	135 (51.5%)	66 (56.9%)	
No	365 (42.5%)	188 (39.2%)	127 (48.4%)	50 (43.1%)	
Douching History, n (%)					***0.02***
At least once	432 (50.3%)	254 (52.9%)	113 (43.1%)	65 (56.0%)	
Never	426 (49.7%)	226 (47.1%)	149 (56.9%)	51 (44.0%)	
Birth Control Methods					
Pills/Patch, n (%)					0.98
Yes	168 (19.6%)	95 (19.8%)	51 (19.5%)	22 (19.0%)	
No	690 (80.4%)	385 (80.2%)	211 (80.5%)	94 (81.0%)	
Nuva Ring, n (%)					0.33
Yes	36 (4.2%)	17 (3.5%)	15 (5.7%)	4 (3.5%)	
No	822 (95.8%)	463 (96.5%)	247 (94.3%)	112 (96.5%)	
Condoms, n (%)					0.69
Yes	666 (77.6%)	377 (78.5%)	202 (77.1%)	87 (75.0%)	
No	192 (22.4%)	103 (21.5%)	60 (22.9%)	29 (25.0%)	
Depo-Provera Shot, n (%)					***0.04***
Yes	126 (14.7%)	58 (12.1%)	49 (18.7%)	19 (16.4%)	
No	732 (85.3%)	422 (87.9%)	213 (81.3%)	97 (83.6%)	
Intra-Uterine Device, n (%)					0.34
Yes	84 (9.8%)	50 (10.4%)	27 (10.3%)	7 (6.0%)	
No	774 (90.2%)	430 (89.6%)	235 (89.7%)	109 (94.0%)	
Spermicide, n (%)					0.42
Yes	10 (1.2%)	7 (1.5%)	3 (1.2%)	0 (0.0%)	
No	848 (98.8%)	473 (98.5%)	259 (98.8%)	116	

				(100.0%)	
No Birth Control, n (%)					0.42
	Yes	60 (7.0%)	36 (7.5%)	14 (5.3%)	10 (8.6%)
	No	798 (93.0%)	444 (92.5%)	248 (94.7%)	106 (91.4%)
Sexual Risk Behavior[f]					
Different Sex Partners, n (%)					0.75
	One	201 (23.4%)	115 (24.0%)	62 (23.7%)	24 (20.7%)
	Two or more	657 (76.6%)	365 (76.0%)	200 (76.3%)	92 (79.3%)
Oral Sex Partners[g], n (%)					0.39
	None	101 (11.8%)	56 (11.7%)	30 (11.5%)	15 (12.9%)
	One	307 (35.8%)	177 (36.9%)	83 (31.7%)	47 (40.5%)
	Two or more	450 (52.4%)	247 (51.5%)	149 (56.9%)	54 (46.6%)
Unprotected Anal Sex Partners, n (%)					0.16
	None	708 (82.5%)	384 (80.0%)	221 (84.4%)	103 (88.8%)
	One	129 (15.0%)	83 (17.3%)	36 (13.7%)	10 (8.6%)
	Two or More	21 (2.4%)	13 (2.7%)	5 (1.9%)	3 (2.6%)
Unprotected Vaginal Sex Partners, n (%)					0.95
	None	59 (6.9%)	32 (6.7%)	17 (6.5%)	10 (8.6%)
	One	424 (49.4%)	239 (49.8%)	128 (48.9%)	57 (49.1%)
	Two or more	375 (43.7%)	209 (43.5%)	117 (44.7%)	49 (42.2%)
Sexual Activity with Other Women, n (%)					***0.01***
	Yes	97 (11.3%)	48 (10.0%)	26 (9.9%)	23 (19.8%)
	No	761 (88.7%)	432 (90.0%)	236 (90.1%)	93 (80.2%)
New Sex Partners, n (%)					0.19
	Yes	418 (48.7%)	224 (46.7%)	129 (49.2%)	65 (56.0%)
	No	440 (51.3%)	256 (53.3%)	133 (50.8%)	51 (44.0%)
Treatment Arm, n (%)					**<0.01**
	Yes	438 (51.0%)	211 (44.0%)	170 (64.9%)	57 (49.1%)
	No	420 (49.0%)	269 (56.0%)	92 (35.1%)	59 (50.9%)

HS- High school
BV- Bacterial vaginosis

[a]p values compare latent classes
[b]Antibiotic use in the past 30 days
[c]No prior and unsure of antibiotic use in the past 30 days
[d]Never diagnosed and unsure if diagnosed
[e]Never treated and unsure of treatment
[f]In the past year
[g]Receptive oral sex

Table 2: Crude and Adjusted Odds Ratios for Risk Factors Associated with Latent Class by Multinomial Logistic Regression Analysis

Characteristics	Persistent vs Clearance		Recurrent vs Clearance	
	Crude OR (95% CI)	**Adjusted OR[a] (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR[a] (95% CI)**
Demographic Variables				
Age				
>21 years	*1.72 (1.15-2.59)*	*1.90 (1.23-2.95)*	1.46 (0.94-2.26)	*1.88 (1.17-3.00)*
≤21 years	-	-	-	-
Education				
HS	0.99 (0.55-1.80)	-	0.83 (0.43-1.58)	-
More than HS	0.95 (0.54-1.68)	-	1.09 (0.59-2.01)	-
No HS	-	-	-	-
Ethnicity				
Hispanic/Latino	0.59 (0.22-1.56)	-	0.88 (0.32-2.4)	-
Not Hispanic/Latino	-	-	-	-
Medical History				
Prior Antibiotic Use[b]				
Yes	1.05 (0.42-2.61)	-	0.96 (0.36-2.58)	-
No[c]	-	-	-	-
Prior Episodes of BV				
Once	0.71 (0.42-1.19)	-	0.91 (0.52-1.60)	-
2-4 times	0.61 (0.36-1.03)	-	0.79 (0.45-1.38)	-
≥5 times	0.64 (0.28-1.49)	-	1.15 (0.48-2.73)	-
Never[d]	-	-	-	-
Last BV treatment				

≤6 months ago	0.77 (0.44-1.35)	0.74 (0.42-1.32)	0.97 (0.54-1.78)	0.98 (0.53-1.82)
7-12 months ago	0.37 (0.20-0.68)	*0.34 (0.18-0.63)*	0.70 (0.37-1.31)	0.68 (0.35-1.30)
>12 months ago	0.75 (0.43-1.31)	0.68 (0.38-1.21)	0.90 (0.49-1.64)	0.90 (0.48-1.68)
Never[e]	-	-	-	-
Prior Pregnancy				
Yes	1.18 (0.78-1.77)	1.08 (0.69-1.67)	0.81 (0.52-1.25)	0.70 (0.44-1.13)
No	-	-	-	-
Douching History				
At least once	0.88 (0.59-1.33)	0.80 (0.53-1.22)	*0.60 (0.38-0.93)*	*0.55 (0.35-0.87)*
Never	-	-	-	-
Birth Control Methods				
Pills/Patch				
Yes	1.05 (0.63-1.77)	-	1.03 (0.59-1.80)	-
No	-	-	-	-
Nuva Ring				
Yes	1.03 (0.34-3.12)	-	1.70 (0.55-5.24)	-
No	-	-	-	-
Condoms				
Yes	1.22 (0.76-1.96)	-	1.12 (0.67-1.87)	-
No	-	-	-	-
Depo-Provera Shot				
Yes	0.70 (0.40-1.23)	0.67 (0.37-1.20)	1.17 (0.66-2.10)	1.26 (0.69-2.30)
No	-	-	-	-
Intra-Uterine Device				
Yes	1.81 (0.8-4.1)	-	1.79 (0.76-4.24)	-
No	-	-	-	-
None				
Yes	0.86 (0.41-1.79)	-	0.60 (0.26-1.39)	-
No	-	-	-	-

Sexual Risk Behavior[f]				
Different Sex Partners				
Two or More	0.83 (0.50-1.36)	-	0.84 (0.49-1.43)	-
One	-	-	-	-
Oral Sex Partners[g]				
One	1.01 (0.52-1.94)	-	0.88 (0.43-1.81)	-
Two or more	1.23 (0.65-2.33)	-	1.38 (0.69-2.76)	-
None	-	-	-	-
Unprotected Anal Sex Partners				
One	*2.23 (1.12-4.44)[h]*	*2.45 (1.21-4.96)[h]*	1.68 (0.80-3.51)	1.80 (0.85-3.82)
Two or More	1.16 (0.33-4.16)	1.54 (0.41-5.69)	0.78 (0.18-3.31)	1.06 (0.24-4.71)
None	-	-	-	-
Unprotected Vaginal Sex Partners				
One	1.31 (0.61-2.82)	-	1.32 (0.57-3.06)	-
Two or More	1.33 (0.61-2.89)	-	1.41 (0.60-3.29)	-
None	-	-	-	-
Sexual Activity with Other Women				
Yes	*0.45 (0.26-0.78)*	*0.38 (0.22-0.68)*	*0.45 (0.24-0.82)*	*0.43 (0.23-0.81)*
No	-	-	-	-
New Sex Partners				
Yes	0.69 (0.46-1.03)	0.71 (0.47-1.09)	0.76 (0.49-1.18)	0.76 (0.48-1.20)
No	-	-	-	-
Treatment Arm				
Yes	0.81 (0.54-1.22)	0.79 (0.52-1.20)	*1.91(1.23-2.98)*	*1.92 (1.22-3.02)*
No	-	-	-	-

HS- High school

[a]*The model was adjusted for age, last BV treatment, douching frequency, use of Depo-Provera shot, use of IUDs, women who have sex with women in the past year, unprotected anal sex in the past year, new sex partners in the past year and treatment.*

[b]Antibiotic use in the past 30 days

[c]No prior and unsure of antibiotic use in the past 30 days

[d]Never diagnosed and unsure if diagnosed

[e]Never treated and unsure of treatment

[f]In the past year
[g]Receptive oral sex
[h]p value >0.05

MANUSCRIPT 3

Risk of Chlamydia and Gonorrhea among young African American women with Persistent and Episodic Bacterial Vaginosis

Abstract

Background: The purpose of this study was to assess the influence of episodic and persistent bacterial vaginosis (BV) on incident *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infection among young African American women in the US. **Methods:** Data from 428 African American women who were previously enrolled in a randomized clinical trial to assess the efficacy of metronidazole treatment of asymptomatic BV to reduce incident CT and NG infection were included in this secondary data analysis. Persistent cases of BV were defined as being positive for BV at month two, four and six. Women who were negative for BV at month two, four and six were classified as no BV. All other cases were defined as episodic BV. Incident STI was defined as any new case of CT or NG at month eight. Factors associated with STI acquisition were determined using Binary Logistic Regression. **Results:** Most women were ≤21 years (55.8%) and completed some post high school/GED education (50.9%). There were 179 (41.8%; 95 % Confidence Interval [CI]: 37.1%-46.7%) women with persistent BV and 204 (47.7%; 95% CI: 42.8%-52.5%) women with episodic BV. About 8.6% (95% CI: 6.2%-11.7%) of women tested positive for CT and/or NG. Fisher's exact test demonstrated a significant association between BV status and STI acquisition. Women with high school or more than high school education (adjusted Odds Ratio (adjOR): 0.38; 95%CI: 0.15-0.92; and adjOR: 0.31; 95%CI: 0.13-0.73) had decreased

odds of developing an STI. Education was the only significant predictor in the final model. Women with no BV did not acquire an STI. **Conclusion:** Incident STIs were only observed among women with BV. Higher education was associated with lower odds of STI acquisition.

Keywords

bacterial vaginosis, chlamydia, gonorrhea

Introduction

Reproductive tract infections (RTIs) among women are of significant public health concern.(Diadhiou et al., 2019) Studies have shown that RTIs are one of the most significant causes of reproductive morbidity.(Diadhiou et al., 2019) Vaginal dysbiosis and sexually transmitted infections (STIs) are the two major causes of RTIs.(Diadhiou et al., 2019) These include infections such as bacterial vaginosis (BV), *Chlamydia trachomatis* (CT), and *Neisseria gonorrhoeae* (NG).(Diadhiou et al., 2019) BV is a polymicrobial vaginal dysbiosis characterized by a decrease in *Lactobacillus* bacteria and an increase in anaerobic organisms.(Ness et al., 2005) BV-associated microorganisms produce substances such as mucin-degrading enzymes, cytokines, and inflammatory mediators, which increase the susceptibility to STIs, specifically, CT and NG.(Allsworth, Lewis, & Peipert, 2008; Allsworth & Peipert, 2011) Numerous studies have found BV to be associated with CT and NG, however, the majority of these studies were cross sectional and could not adequately assess the temporality of the relationship between BV

and CT and/or NG.(Allsworth & Peipert, 2011; Bautista et al., 2017; Ness et al., 2005; Wiesenfeld, Hillier, Krohn, Landers, & Sweet, 2003)

Wiesenfeld and colleagues conducted a cross sectional study, which included predominantly African-American (59%) women, and concluded that women with BV had four times increased odds to test positive for NG infection and 3.4 times increased odds to test positive for CT than women without BV.(Wiesenfeld et al., 2003) They hypothesized that hydrogen peroxide (H_2O_2) -producing lactobacilli was an essential defense against CT/NG infection. Bautista *et al*. conducted a population based, nested case-control study among US army women and determined that antecedent BV was associated with an increased risk of NG (Adjusted incidence rate ratio: 2.42; 95% Confidence Interval [CI]: 2.27-2.57) and CT infections (Adjusted incidence rate ratio: 1.51; 95% CI: 1.47-1.55).(Bautista et al., 2017) They further concluded that there was a monotonic dose-response relationship between BV and CT and/or NG infections.(Bautista et al., 2017) Though the relationship between BV and CT and/or NG infections have been explored in the literature, many studies have not assessed the longitudinal effect of persistent and episodic BV on the acquisition of CT/NG infection.

Due to a lack of effective treatment, multiple episodes of BV are common in the same women over a period of time.(Brotman et al., 2007) Furthermore, the distinction between BV reinfection and relapse is unclear, since the etiopathogenesis of BV remains unknown.(Brotman et al., 2007) Episodic BV may be due to ineffective antibiotic treatment, which fails to resolve a persistent BV infection.(Bradshaw et al., 2006; Coudray & Madhivanan, 2020) Persistent BV is diagnosed among women with BV at consecutive visits.(Lennard et al., 2018) Persistent BV infection is associated with genital

inflammation and biofilm formation.(Lennard et al., 2018) These biofilms enhance microbial attachments to the genital epithelium and block antimicrobial action resulting in persistent BV.(Lennard et al., 2018) Though the literature has examined the association between BV and incident STIs, this has historically been assessed based on a singular episode of BV. In this study, we sought to determine whether women with persistent BV were more likely to acquire a CT/NG infection compared to women with episodic BV in a population of African American women.

Methods

Study Design

Our study was a secondary analysis of previously collected data from a randomized clinical trial (RCT). A detailed account of the RCT study procedures is described elsewhere.(Schwebke et al., 2016) Briefly, the RCT aimed to investigate the effect of home screening and treatment of asymptomatic BV to reduce the incidence of CT and NG infections. This US-based study recruited reproductive age women (15-25 years) with asymptomatic BV from clinical research sites, STI and obstetrics/gynecology clinics from five states (Maryland, North Carolina, Pennsylvania, California, and Alabama). Women were eligible for the RCT if they had asymptomatic BV and considered high-risk for STIs. Eligible women were randomized to a treatment or control arm. Women assigned to the treatment arm received oral metronidazole (500mg, twice a day for seven days) at enrollment. According to the Centers for Disease Control and Prevention (CDC) guidelines (standard of care), women in the control arm did not receive treatment for asymptomatic BV.(Workowski & Berman, 2010) All women could receive

treatment from healthcare providers, outside the parameters of the study, if necessary. Women received home testing kits every two months to self-collect vaginal swabs to test for BV. Every four months, additional swabs were included to test for CT and NG. For every BV positive home testing kit, only women assigned to the treatment arm received oral metronidazole (500mg, twice a day for seven days). The presence or absence of BV symptoms was not assessed after baseline. Participants were followed for 12 months. The current study only examined women assigned to the control arm. We aimed to compare the effect of persistent versus episodic cases of BV on STI acquisition.

Measures

BV was assessed microbiologically using NS at every time point. A NS of 0-3 was considered as 'no BV', 4-6 as 'intermediate flora', and 7-10 indicative of 'BV'.(Mohammadzadeh, Dolatian, Jorjani, & Alavi Majd, 2014) NS at two months, four months and six months were combined to classify women as persistent BV, episodic BV or no BV. Women with NS of 7-10 at months two, four and six were classified as persistent BV. Women with NS 0-6 at month two, four and six were defined as no BV. All other cases were classified as episodic BV. A BV status variable was created to include the following categories: persistent BV, episodic BV and no BV.

A baseline questionnaire was administered, which examined sociodemographic factors such as age, race, and the highest level of education. All women completed a self-administered questionnaire at each visit, which evaluated factors such as contraceptive methods and sexual risk behaviors. The use of birth control pills, birth control patch, Nuva-ring, condoms, spermicide cream, Depo-Provera shot, Intra-uterine device (IUD)

were assessed at each visit. These birth control methods were further categorized as barrier methods (yes/no) where the use of condoms was considered as a barrier method and all other forms of birth control were not. The number of different sex partners (any sexual encounter), number of oral sex partners (receptive), number of unprotected anal sex partners, number of unprotected vaginal sex partners, women who have sex with women and new sex partners (partners they did not have sex with previously) were evaluated. Sexual behavior was assessed as yes/no. Responses for all variables were assessed for month two, four and six. Outcomes were classified as 'yes' if participants responded yes at any time point (month two, four or six) and no if they responded 'no' at all timepoints (month two, four or six). Vaginal swabs were tested for chlamydia and gonorrhea by the BD ProbeTec Amplified DNA Assay™ (Becton-Dickson, Inc. Sparks, MD) according to manufacturer instruction.

Sample

There were 1,365 women included in the original RCT. A subset of 1,160 women agreed for their data to be used in future research. From this sample of 1,160 women, only African American women were included (N= 976, 84.1%) due to their increased risk of both BV and STIs as well as the need for further research among this population. Follow-up data were available for 872 (89.3%) of these women. Women in the treatment arm (N=444; 50.9%) were then excluded to remove the effect of treatment for BV. Consequently, 428 women (59.3%) were included in the final analysis.

Statistical Analysis

The absence or presence of CT/NG at month eight was categorized as a single outcome, "STI" (yes/no). Age was the only continuous variable assessed and then categorized for analysis into two levels (≤21 years and >21 years). Descriptive analyses were conducted using either Chi-Squared or Fisher's Exact Test, as appropriate, to compare women with and without any STIs. Differences among BV status groups were also determined.

The bivariate relationship between all demographic, contraceptive methods and sexual risk behavior variables and incident STI were examined using the Binary Logistic Regression Model. Variables with p-value <0.20 were included in the final model. Two-way interactions among BV status, contraceptive methods and sexual risk behavior were tested. The final Logistic Regression Model included age, education, women who have sex with women and BV status. None of the model assumptions were violated. Multicollinearity was assessed using Cramer's V and Phi Coefficient as appropriate. The R Project for Statistical Computing version 3.5.1 (Vienna, Austria) was used for the cleaning and analysis of data.

Results

Participant Characteristics

All women included in this study were African American. Of these, 239 women (55.8%) were ≤21 years. The mean age of the women was 21.3 (Standard Deviation (SD): ±2.1) years. Most women in the study completed more than a high school diploma or GED (50.9%). Additionally, 141 women (32.9%) completed up to high school and 69

women (16.1%) did not complete high school. Most women (82.2%) used barrier contraception methods (i.e., condoms) and engaged in sexual behavior that might put them at risk for STI: 402 (93.9%) women had one or more sex partners, 397 (92.8%) women had one or more oral sex partners (receptive), 267 (62.4%) women had unprotected anal sex, 400 (93.5%) women had unprotected vaginal sex with two or more partners, 203 (47.4%) women had sex with other women, and 238 (55.6%) women had new sex partners. There were 179 women (41.8%; 95% CI: 37.1%-46.7%) with persistent BV, 204 women (47.7%; 95% CI: 42.8%-52.5%) with episodic BV, and 45 women (10.5%; 95% CI: 7.8%-13.8%) with no BV after baseline. About 8.6% (95%CI: 6.2%-11.7%) of women were diagnosed with an incident case of STI, either CT or NG, within eight months. There were 28 (75.7%; 95% CI: 58.8%-88.2%) cases of CT only, 2 (5.4%; 95% CI: 0.6%-18.2%) cases of NG only, and 7 (18.9%; 95% CI: 7.9%-35.2%) women were coinfected with CT and NG. None of the exposure variables were significantly associated with BV status. Participant characteristics stratified by STI presence and BV status are detailed in tables one and two, respectively.

Factors Associated with STI Incidence

Descriptive analyses indicated that STI incidence after eight months was significantly associated with age ($p=0.04$), education ($p<0.01$), and BV status ($p=0.02$). These variables were then included in the final binary logistic regression model. Additionally, sexual activity with other women ($p=0.09$) was also included in the final model since the p-value was <0.20. There were no STIs diagnosed at eight months among women who had no BV. Thus, in the final model, women with persistent BV were

compared to women with episodic BV. The unadjusted logistic regression model indicated women older than 21 years (Crude Odds Ratio (OR): 0.44; 95%CI: 0.20-0.90), who had completed at least high school (OR: 0.36; 95%CI: 0.15-0.86) or more than high school (OR: 0.27; 95% CI: 0.12-0.63) had decreased odds of an incident STI. Additionally, when compared to women with episodic BV, women with persistent BV had decreased odds (OR: 0.59; 95% CI: 0.28-1.17) of acquiring an STI at eight months, although this was not statistically significant. Similarly, women who had sex with women had 1.93 increased (95% CI: 0.97-3.94) odds of developing an STI within eight months. The final logistic regression model after adjusting for age, education, sexual activity with other women and BV status, indicated that persistent BV was not associated with STI acquisition when compared to episodic BV. Furthermore, it should be noted there were no STIs among women classified as no BV. Additionally, women who had sex with women (adjOR: 1.98; 95% CI: 0.97-4.17) had increased odds of developing an STI compared to women who did not have sex with other women. This finding approached marginal significance (p=0.06). Education was also associated with decreasing the odds of STI acquisition, as women with high school education (adjOR: 0.38; 95% CI: 0.15-0.92) and more than high school education (adjOR: 0.31; 95% CI: 0.13-0.73) had lower odds of acquiring incident STI compared to women with less than high school education. Women aged 21 years and older had decreased odds of STI acquisition (adjOR: 0.47; 95% CI: 0.21-1.00). This finding approached marginal significance (p=0.06). Education was the only significant predictor of STI acquisition in the final model. All interaction terms were not statistically significant.

Discussion

We examined the relationship between episodic and persistent BV with the acquisition of CT/NG in a longitudinal study. BV status was associated with the acquisition of STIs ($p=0.02$) in the bivariate analysis using Fisher's Exact test. The association between BV and CT/NG infection has been adequately documented in the literature.(Bautista et al., 2016; Bautista et al., 2017; Ness et al., 2005) The findings of the logistic regression models revealed that women with persistent BV had decreased odds of acquiring CT and/or NG compared to women with episodic BV. We speculate that it is possible women with persistent BV would most likely exhibit symptoms associated with BV, such as vaginal discharge and foul odor. This may reduce the likelihood of these women engaging in unprotected sex, thus reducing their odds of acquiring an STI. However, we cannot confirm this hypothesis as the presence or absence of symptoms was not assessed after baseline in the parent study. We would further like to emphasize that this finding did not yield statistically significant results in the regression model, and the magnitude of the association between BV status and STI acquisition could not be determined.

Though the association between BV status and STI acquisition was not significant in the regression model, our descriptive analyses showed a significant association. Women without BV did not acquire CT and/or NG. Previous studies have suggested that the relationship between persistent and episodic cases of BV and STI acquisition may be due to the lack of the H_2O_2-producing lactobacilli bacteria, and the corresponding host defense effect, associated with BV.(Wiesenfeld et al., 2003) Additionally, it is possible that the production of mucin degrading enzymes may also contribute to STI

susceptibility.(Allsworth & Peipert, 2011) We postulate that this effect may be exaggerated in women who experience episodic or persistent BV further disrupting the vaginal ecosystem. Though the etiology for this phenomenon remains unclear, the clinical implications of these findings are still pertinent. Due to the high likelihood of episodic and persistent BV, the mechanism by which BV recurs or persists and subsequent STI infection needs to be further elucidated.

Women who had sex with women compared with women who did not have sex with women (adjOR: 1.98; 95%CI: 0.97-4.17; p=0.06) had increased odds of acquisition of CT and/or NG. This increased odds of STI acquisition may be due to vaginal sexual activity with fingers, hands, and shared sex toys common among women who have sex with women.(Singh, Fine, & Marrazzo, 2011) Additionally, it is possible that there was infrequent use of barrier methods among this group to prevent STI transmission as most women who report having sex with women do not believe that they are at increased risk of STIs from their female sex partners.(Marrazzo, Coffey, & Bingham, 2005; Singh et al., 2011) Furthermore, literature shows that women who have sex with women are more likely to select high-risk sex partners.(Koh, Gómez, Shade, & Rowley, 2005; Lemp et al., 1995) These women may also engage in unprotected sex with men.(Singh et al., 2011) We did not assess exclusive sexual activity with women and thus cannot confirm this hypothesis. Finally, we found that higher levels of education significantly decreased the risk of STIs. This finding was consistent with the published literature.(Annang, Walsemann, Maitra, & Kerr, 2010) Annang *et al*. determined that there was an inverse association between the level of education and STI diagnosis.(Annang et al., 2010) This

may be a result of increased awareness and reduced engagement in sexual behavior that might increase their risk for STI.

Despite our findings, our study was subject to a few limitations. First, our final models compared between women categorized as persistent and episodic BV. We could not include women without BV into the model since none acquired an STI. Additionally, though our sample was restricted to the control group, women could see their healthcare providers for any symptom development, but these data were not captured. Finally, we did not include partner testing for CT and NG; therefore, the effect of this on CT or NG acquisition could not be assessed. However, our study is inherently strengthened by its longitudinal assessment of STI acquisition. Furthermore, we implemented unique definitions of persistent and episodic BV. Finally, we explored the lesser examined area of research on BV and looked at the effect of multiple episodes of BV on STI acquisition.

Our study highlights the increased risk of STI acquisition among women with persistent and episodic BV as no women without BV acquired an STI. These findings demonstrate the serious effects associated with disruptions in the vaginal ecosystem caused by persistent and episodic BV. Maintenance of a *Lactobacillus* dominant, inflammation free vaginal ecosystem is essential to prevent the acquisition of STIs.

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Tables

Table 1: Characteristics associated with incident STI[a] Infection after eight months

Characteristics	**Categories**	**N (%)**	**Any STI[a] (N=428)**		**p-value**
			Yes (37; 8.6%)	**No (391; 91.4%)**	
Age					***0.04***
	≤21 years	239 (55.8%)	27 (73.0%)	212 (54.2%)	
	>21 years	189 (44.2%)	10 (27.0%)	179 (45.8%)	
Education					***<0.01***
	No HS	69 (16.1%)	13 (35.1%)	56 (14.3%)	
	HS	141 (32.9%)	11 (29.7%)	130 (33.2%)	
	More than HS	218 (50.9%)	13 (35.1%)	205 (52.4%)	
Barrier Methods[b]					0.68
	No	76 (17.8%)	8 (21.6%)	68 (17.4%)	
	Yes	352 (82.2%)	29 (78.4%)	323 (75.5%)	
Different Sex Partners[c]					0.27
	No	26 (6.1%)	4 (10.8%)	22 (5.6%)	
	Yes	402 (93.9%)	33 (89.2%)	369 (94.4%)	
Oral Sex Partners[c,d]					0.50
	No	31 (7.2%)	1 (2.7%)	30 (7.7%)	
	Yes	397 (92.8%)	36 (97.3%)	361 (92.3%)	
Unprotected Anal Sex Partners[c]					0.22
	No	161 (37.6%)	10 (37.0%)	151 (38.6%)	
	Yes	267 (62.4%)	27 (73.0%)	240 (61.4%)	

Unprotected Vaginal Sex Partners[c]					0.50
	No	28 (6.5%)	1 (2.7%)	27 (6.9%)	
	Yes	400 (93.5%)	36 (97.3%)	364 (93.1%)	
Sexual Activity with Other Women[c]					0.09
	No	225 (52.6%)	14 (37.8%)	211 (54.0%)	
	Yes	203 (47.4%)	23 (62.2%)	180 (46.0%)	
New Sex Partners[c,e]					0.75
	No	190 (44.4%)	15 (40.5%)	175 (44.8%)	
	Yes	238 (55.6%)	22 (59.5%)	216 (55.2%)	
BV Status[f]					***0.02***
	Persistent BV	179 (41.8%)	13 (35.1%)	166 (42.5%)	
	Episodic BV	204 (47.7%)	24 (64.9%)	180 (46.0%)	
	No BV	45 (10.5%	0 (0.0%)	45 (11.5%)	

[a]Incident Chlamydia trachomatis (CT) or Neisseria gonorrhoeae (NG) infection
[b]Used condoms at either month two, four or six
[c]Responded yes at either month two, four or six
[d]Receptive oral sex
[e]Partners they did not have sex with previously
[f]BV status- Women with NS:0-6 at baseline, two months and four months were classed as no BV. Women with NS:7-10 at baseline, two months and fourth months were classified as persistent BV. All other cases were defined as episodic BV.
HS- High school

Table 2: Factors Associated with BV Status (N=428)

Characteristics	Categories	N (%)	BV Status[a] (N=428)			p-value
			Persistent BV (179; 41.8%)	Episodic BV (204; 47.7%)	No BV (45; 10.5%)	
Age						0.49
	≤21 years	239 (55.8)	95 (53.1%)	120 (58.8%)	24 (53.3%)	
	>21 years	189 (44.2)	84 (46.9%)	84 (41.2%)	21 (46.7%)	
Education						0.69
	No HS	69 (16.1%)	31 (17.3%)	31 (15.2%)	7 (15.6%)	
	HS	141 (32.9%)	60 (33.5%)	70 (34.3%)	11 (24.4%)	
	More than HS	218 (50.9%)	88 (49.2%)	103 (50.5%)	27 (60.0%)	
Barrier Methods[b]						0.46
	No	76 (17.8%)	31 (17.3%)	34 (16.7%)	11 (24.4%)	
	Yes	352 (82.2%	148 (82.7%)	170 (83.3%)	34 (75.6%)	
Different Sex Partners[c]						0.41
	No	26 (6.1%)	8 (4.5%)	14 (6.9%)	4 (8.9%)	
	Yes	402 (93.9%)	171 (96.5%)	190 (93.1%)	41 (91.1%)	
Oral Sex Partners[c,d]						0.71
	No	31 (7.2%)	14 (7.8%)	13 (6.4%)	4 (8.9%)	
	Yes	397 (92.8%)	165 (92.2%)	191 (93.6%)	41 (91.1%)	
Unprotected Anal Sex Partners[c]						0.22
	No	161 (37.6%)	74 (41.3%)	68 (33.3%)	19 (42.2%)	
	Yes	267 (62.4%)	105 (58.7%)	136 (66.7%)	26 (57.8%)	
Unprotected Vaginal Sex Partners[c]						1.00

	No	28 (6.5%)	12 (6.7%)	12 (5.9%)	4 (8.9%)	
	Yes	400 (93.5%)	167 (93.3%)	192 (94.1)	41 (91.1%)	
Sexual Activity with Other Women[c,e]						0.10
	No	225 (52.6%)	105 (58.7%)	99 (48.5%)	21 (46.7%)	
	Yes	203 (47.4%)	74 (41.3%)	105 (51.5%)	24 (53.3%)	
New Sex Partners[c]						0.53
	No	190 (44.4%)	74 (41.3%)	94 (46.1%)	22 (48.9%)	
	Yes	238 (55.6%)	105 (58.7%)	110 (53.9%)	23 (51.1%)	

[a]BV status- Women with NS:0-6 at baseline, two months and four months were classed as no BV. Women with NS:7-10 at baseline, two months and fourth months were classified as persistent BV. All other cases were defined as episodic BV.
[b]Used condoms at either month two, four or six
[c]Responded yes at either month two, four or six
[d]Receptive oral sex
[e]Partner they did not have sex with previously
HS- High school

Table 3: Factors Associated with Sexually Transmitted Infection Diagnosis among Participants (N=383)

Characteristics	**Categories**	**Unadjusted**		**Adjusted**	
		Odds Ratio (95%CI)	**p-value**	**Odds Ratio (95%CI)**	**p-value**
Age					
	≤21 years	Ref		Ref	
	>21 years	0.44 (0.20-0.90)	***0.03***	0.47 (0.21-1.00)	0.06
Education					
	No HS	Ref		Ref	
	HS	0.36 (0.15-0.86)	***0.02***	0.38 (0.15-0.92)	***0.03***
	More than HS	0.27 (0.12-0.63)	***<0.01***	0.31 (0.13-0.73)	***0.01***
Sexual Activity with Other Women[a]					
	Yes	1.93 (0.97-3.94)	0.06	1.98 (0.97-4.17)	0.06
	No	Ref		Ref	
BV Status[b]					
	Persistent BV	0.59 (0.28-1.17)	0.14	0.62 (0.29-1.28)	0.21
	Episodic BV	Ref		Ref	

[a]Responded yes at either month two, four or six
[b]BV status- Women with NS:7-10 at baseline, two months and fourth months were classified as persistent BV. Women with a NS:7-10 at either month two, four or six were defined as episodic BV. Women with NS:0-6 at baseline, two months and four months were classed as no BV and were not included in the final logistic regression model.
HS- High school

CONCLUSIONS

Despite the many years of research on BV, the mechanisms by which BV recurs and persists remain unknown. Our literature search highlighted that though BV treatment is effective short term, the long-term recurrence rates are high. It further illustrated what little is known about the etiology of single cases of BV, recurrent BV and persistent BV. To our knowledge this is the first study to implement LCA techniques to examine the patterns of BV incidence over time. We concluded that over a twelve-month period most women were classed as persistent or recurrent BV despite treatment, further emphasizing the poor efficacy of metronidazole treatment. Treatment increased the odds of recurrent cases of BV.

Additionally, it is also the first study to compare the risk of STI acquisition among women with persistent and episodic BV. Women who had sex with women were more likely to have a recurrent or persistent case of BV. Our final study demonstrated that women without BV did not acquire an STI. Our findings suggest that multiple episodes of BV are common among women of reproductive age despite treatment with metronidazole. Additionally, women with multiple episodes of BV were more likely to acquire an STI in bivariate analyses.

Our findings collectively highlight the effects of poor BV treatment and the increased risk of adverse sequalae among women with multiple episodes of BV. Further research should examine the longitudinal microbial changes among women with persistent, recurrent and episodic BV. Transition models should be used to examine the risk factors of multiple cases of BV and the protective factors of women able to maintain a healthy vaginal microbiota. Additionally, the host immune response among women

with BV should be investigated to elucidate potential mechanisms by which the vaginal microenvironment could be normalized. These findings may lead to more effective treatment to reduce persistence and recurrence of BV.

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