

Factors Associated with Symptomatic Vulvovaginal Candidiasis: A Study among Women Attending a Primary Healthcare Clinic in Kwazulu-Natal, South Africa

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Abstract

Background: Symptomatic vulvovaginal candidiasis (VVC) is one of the most common problems leading women to seek advice in primary healthcare facilities. **Aim:** The aim of this study is to describe the associations between some hypothesized factors and the presence of symptomatic VVC. **Subjects and Methods:** An analytical cross-sectional study was conducted. A total of 90 women diagnosed with symptomatic VVC and 108 women without symptomatic VVC were recruited when attending Umlazi D clinic, a primary health clinic in KwaZulu-Natal, South Africa between June 2011 and December 2011. Confirmed symptomatic VVC was determined by Gram stain and microbiological culture of vaginal swabs. For human immunodeficiency virus (HIV)-infected women, HIV ribonucleic acid load in plasma and genital fluid was determined by real-time-polymerase chain reaction (BioMerieux, Lyon, France). CD4 counts were obtained from patients' medical records. Data were analyzed using the statistical package for the social sciences (SPSS) version 21.0 (SPSS Inc.; Chicago, IL, USA). Multiple logistic regression models were used to exclude univariate confounders. All tests were two-sided and a $P < 0.05$ was considered to be significant. **Results:** A total of 90% (81/90) of patients with symptomatic VVC complained of vulval itching, soreness and vaginal discharge when compared to 75.9% (82/108) of patients without symptomatic VVC ($P < 0.01$). Whilst pregnancy was independently associated with symptomatic VVC ($P < 0.01$), the latter was inversely related to Nugent's scores ($P < 0.01$). When compared with HIV negative women, the odds for symptomatic VVC increased among women with HIV-associated immunocompromise (CD4 counts < 200 cells/mm³, $P < 0.001$), significantly shedding HIV in their genital tracts ($P = 0.04$), with plasma HIV load > 1000 copies/mL ($P < 0.001$). There was a significant negative association between the use of highly active anti-retroviral therapy and the presence of symptomatic VVC in HIV-infected women ($P < 0.01$). **Conclusion:** Although symptomatic VVC is not classified as acquired immunodeficiency syndrome-related condition, HIV-related immune compromised women and particularly those who are anti-retroviral therapy-naïve are likely to develop symptomatic VVC.

Keywords: Human immunodeficiency virus-related immune suppression, Vulvovaginal candidiasis, Primary healthcare clinic

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Introduction

Vaginitis is one of the most common problems leading women to seek advice in gynecology and primary health clinics. Bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) are responsible for the vast majority of cases of infectious vaginitis.^[1] Almost 75% of healthy women develop VVC at least once during their reproductive age.^[1,2] It is estimated

that 5-10% of women develop recurrent VVC.^[2] The latter is defined as the occurrence of 4 or more episodes of VVC per year.^[3] Symptomatic VVC is characterized by an acute onset of vulvovaginal pruritis, irritation and/or soreness accompanied by the presence of vaginal erythema/edema, and/or discharge.^[4] *Candida albicans* has been reported as the cause of VVC in 85-95% of cases whilst *Candida glabrata* represents the most common cause of non-albicans candida vaginitis.^[1]

Although *C. albicans* often colonises the vagina without causing disease, it can cause VVC by responding to a variety of environmental signals— i.e., changes in vaginal pH (pH of 4-4.5) lead to a switch from *C. albicans* blastospore phenotype into a filamentous form (hyphae or pseudohyphae), increasing its ability to cause vaginitis. Numerous risk factors have been reported as being associated with VVC. Those risk factors for VVC include mainly pregnancy,^[1,5,6] use of broad spectrum antibiotics,^[7,8] uncontrolled diabetes mellitus,^[9,10] use of contraceptives and hormone replacement therapy,^[1,11,12] use of corticosteroids,^[1] cancer chemotherapy,^[13-15] organ transplantation,^[13-15] tight-fitting clothing,^[1,13-15] synthetic underwear,^[13-15] various dietary deficiencies or excesses,^[1,12-14] increase sexual activity,^[1,13-15] and vaginal douching.^[11,13-15] Existing data pertaining to some of these factors on the risk of developing VVC are conflicting.^[1,12]

Human immunodeficiency virus (HIV) infection has been also reported by others as a risk factor for developing VVC.^[16-18] Rates of vaginal colonization and symptomatic VVC were reported to increase with immune compromise, especially at CD4 counts below 200 cells/mm³.^[11,17,18] Some of the authors have suggested that women with low CD4 counts should be closely monitored for the development of symptomatic VVC.^[11,17,18] Although VVC is not known as an acquired immunodeficiency syndrome (AIDS)-defining condition, cases of VVC are often diagnosed among women with HIV-associated immunosuppression. The province of KwaZulu-Natal in South Africa where this study was conducted is an epicenter of HIV infection. There are anecdotal reports that HIV-infected women present in primary health-care facilities with frequent, severe and recurrent forms of VVC during advanced stages of HIV infection. We aimed to describe the associations between some hypothesized risk factors and the presence of symptomatic VVC among primary healthcare attendees in rural KwaZulu-Natal, South Africa.

Subjects and Methods

Study design and population

This is an analytical cross-sectional study. Study subjects were women who consecutively presented at Umlazi D clinic, a primary healthcare facility in KwaZulu-Natal, between June 2011 and December 2011 for signs and symptoms suggestive of lower genital tract infections (LGTIs), and were diagnosed or not with symptomatic VVC.

A standardized questionnaire was used to collect information regarding patients' demographics (age and race), presenting

symptoms, history of sexually transmitted infections (vaginal discharge syndrome, genital ulcer syndrome or mixed infections) within the past 3 months and selected risk factors for symptomatic VVC including prior knowledge of HIV sero-status. Known HIV positive women were further asked whether or not they were receiving highly active anti-retroviral therapy (HAART) while confirmation of the use of HAART and CD4⁺ T lymphocytes count values were obtained from patients' medical records. This study questionnaire has been used by the STI research group of the Department of Medical Microbiology, UKZN for the past many years and has been tested for validity and reliability. Validity was established using a panel of experts in the Department and a field test that determined whether the questionnaire measured what it intended to, does it represented the appropriate content, was it appropriate for the study population and was the questionnaire comprehensive enough to collect the needed information. Reliability was computed after a pilot field test to indicate the accuracy of the measuring questionnaire using the test-retest approach as numerous knowledge questions were part of the study questionnaire.

A physical examination was performed by the attending medical practitioner and signs of the genital tract infections were noted. Patients were recruited in the study only if they had signs and symptoms suggestive of non-ulcerative LGTIs/vaginal discharge syndrome whilst those with confirmed genital ulcer syndrome were excluded. All patients were treated using the standard of care treatment in South Africa for the presenting syndrome.

The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Ref. BE 224/11). Consent forms were signed by all participants and confidentiality was maintained throughout the study.

Specimen collection and process

Cervical and vaginal Probetec swabs (Becton Dickinson, Sparks, Maryland, USA) were obtained from patients with vaginal discharge syndrome. The first vaginal swab, which collected material from the posterior fornix, was used to make a smear onto a glass slide for Gram staining. The second vaginal swab (obtained from the anterior fornix) as well as the cervical swabs were stored in a dry container and kept in a cooler box with ice-pack awaiting transport to the laboratory.

A vaginal tampon (8 Ks, Tampax Regular® Compak) was inserted into the vagina, left *in situ* for 3 min. After removal, the tampon was immersed in 10 mL of phosphate buffered saline (PBS; Oxoid Limited Basingstoke, Hampshire, United Kingdom) (pH = 6.9) in a sterile container. All samples were immediately stored at 4°C prior to transport to the laboratory.

Blood samples were collected by venipuncture into sterile vacutainers (Becton Dickinson) containing

ethylenediaminetetraacetic acid for plasma samples and without anticoagulant (red cap tubes) for serum samples.

All specimens were transported within 4 h to the Infection Prevention and Control laboratory, Nelson R Mandela School of Medicine, UKZN.

Initial HIV test was performed in the clinic by a trained research nurse on blood using the HIV rapid test determine HIV-1/2/O (Abbott Laboratories, Abbott Park, IL, USA) following voluntary counseling and testing. The diagnosis of HIV negative with an appointment for another test 3 months later was given to the patient following a negative initial test. Positive samples were transported in the research laboratory and were subsequently retested by a medical technologist using a second HIV rapid test Smart Check test (World Diagnostics Inc. USA). A diagnosis of HIV infection was reported to the participants if both rapid tests were positive. Samples that showed discordant results were further evaluated with a third rapid test Uni-Gold™ Recombigen® HIV (Trinity Biotech PLC, USA) and only two positive test results were interpreted as a positive diagnosis for HIV.

As part of the routine management of the patients in the clinic, all HIV-infected patients benefited directly from CD4⁺ T cell count measurements and CD4⁺ T cell counts used in this study were obtained from patients' medical records. However, for the purpose of this research, HIV-1 ribonucleic acid was measured from the plasma and cell-free fraction of vaginal secretions using Nuclisens Easyq HIV-1 assay (Bio Merieux, Lyon, France) with a lowest detection limit of 20 copies/mL.

Vaginal fluid was expressed from vaginal tampon using an autoclaved wooden tongue depressor and filtered through a 0.22 µm Costar Spin-X cellulose acetate filter membranes (Sigma). The filtered soluble fraction was aliquoted (in 1 mL cryotubes) and stored at -70°C until use.

Vaginal swab taken from the anterior fornix was directly plated onto Sabouraud Dextrose agar with chloramphenicol (BBL™ Becton Dickinson) and incubated at 29°C, 48 h to estimate the relative vaginal fungal burden. The numbers of yeast colonies were recorded as the number of colonies per plate (evidence level III, recommendation grade B).^[11,19,20]

BV was diagnosed using the Nugent score, which ranges from 0 to 10. A score of 7-10 is consistent with BV.^[21] Microscopic slides for the diagnosis of BV were viewed consistently and independently by two different medical technologists, all blinded to the patients' clinical history. In the case of a discrepancy among the two readers, a third reader was assigned the task of viewing discrepant slides.

BD Probe Tec ET *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (CT/GC) amplified deoxyribonucleic acid (DNA)

assay (Becton Dickinson Probetec Assays, Sparks, Maryland, USA) using strand displacement amplification technology for the direct, qualitative detection of *C. trachomatis* and *N. gonorrhoeae* DNA in endocervical swabs was performed.

DNA product for the detection of *Mycoplasma genitalium*, *Trichomonas vaginalis* and herpes simplex virus type 2 was extracted from a volume of 200 µl of genital swab eluate using specific QIAamp DNA mini kits (Qiagen Ltd, Chastsworth, CA) according to the manufacturer's protocols as previously described.^[22] Amplification was performed by in-house polymerase chain reaction (PCR) under specific thermal cycling conditions using the Thermo Cycler instrument. The following DNA oligonucleotide primers (Roche Diagnostics, Basel, Switzerland) appropriate for PCR amplification were used – for *M. genitalium*: MgPa1 (5'-AGT TGA TGA AAC CTT AAC CCC TTG G-3') and MgPa3 (5'-CCG TTG AGG GGT TTT CCA TTT TTG C-3');^[23] for *T. vaginalis*: TVK3 (5'AT TGT CGA ACA TTG GTC TTA CCC TC3') and TVK7 (5' TCT GTG CCG TCT TCA AGT ATG C3');^[24] for herpes simplex virus type 2: KS30 (5'-TTC AAG GCC ACC ATG TAC TAC AAA GAC GT-3') and KS31 (5'-GCC GTA AAA CGG GGA CAT GTA CAC AAA GT-3').^[25] The amplified PCR product was analyzed by electrophoresis in 2% of agarose gels stained with ethidium bromide under ultra violet (UV) light (254-366 nm); and the gel image was recorded by taking a Polaroid™ photograph. Identification of the PCR product was based on the appearance of a DNA band of the expected length. Sizing of the DNA bands was achieved by running the PCR products next to DNA markers.

Diagnostic criteria of symptomatic VVC and vaginal candida colonization

The diagnosis of symptomatic VVC was based on a combination of clinical and laboratory criteria (evidence level III, recommendation grade B).^[11,19,20]

Symptoms suggestive of symptomatic VVC included vulval pruritus/itching, vulval soreness, superficial dyspareunia and/or non-offensive vaginal discharge. Signs included vulval erythema, vulval edema, fissures, excoriation, or thick curdy vaginal discharge.

In addition to the self-reported above symptoms and observation of signs suggestive of VVC in physical examination, cases of symptomatic VVC were confirmed if one of the following criteria was fulfilled (evidence level III, recommendation grade B):^[11,19,20] (i) A positive Gram-stain preparation with budding yeasts, pseudohyphae, and/or hyphal forms; (ii) positive culture with either moderate (10-99 colonies per plate) or heavy candida growth (>100 colonies per plate).

Participants without symptomatic VVC were defined as: (i) Patients whose genital specimens had a negative microscopy result for yeasts, pseudohyphae and/or hyphal forms of candida together with negative culture; (ii) patients whose

genital specimens had a negative microscopy result for yeasts, pseudohyphae, and/or hyphal forms of candida together with light candida growth (<10 colonies per plate). The latter was considered to indicate vaginal candida colonization rather than infection.

Statistical analyses

Data analysis was performed using the statistical package for the social sciences (SPSS)[®] statistical software version 21.0 (SPSS Inc; Chicago, IL, USA). Data were expressed as proportions (percentages) for the categorical variables. Student's *t*-test was performed to assess differences between two means and ANOVA between groups. Either Chi-square test with and without trend or Fischer's exact test was used to test the degree of association of categorical variables. Multiple logistic regression models were used to evaluate the prediction capacity of each independent variable in the occurrence of the expected condition. Unadjusted odds ratios (ORs) were initially calculated to screen for inclusion in multivariate models; variables that exhibited at least moderate association ($P < 0.20$) with the outcome were considered for inclusion in the final models. Multivariate ORs (95% CI) were computed after adjusting for confounding univariate factors. All tests were two-sided and a $P < 0.05$ was considered to be significant.

Results

Univariate associations of women with symptomatic VVC and those without symptomatic VVC with selected hypothesized factors are depicted in Table 1. A total of 90% (81/90) of patients diagnosed with symptomatic VVC complained of vulval itching, soreness and vaginal discharge when compared to 75.9% (82/108) of controls ($P < 0.01$). Pregnancy was significantly ($P = 0.01$) associated with symptomatic VVC. Although women with symptomatic VVC reported of using the contraceptive products more than women without VVC, this difference did not reach statistical significance ($P = 0.06$). Nugent score < 7 ($P < 0.01$), plasma HIV load > 1000 copies/mL ($P < 0.001$), genital HIV load > 1000 copies/mL ($P = 0.04$), CD4 count < 200 cells/mm³ ($P < 0.001$) and absence of anti-retroviral therapy ($P < 0.01$) among HIV positive women were significantly associated with symptomatic VVC.

When controlled for the confounding effects of contraceptive use and the presence of concurrent pathogens causing sexually transmitted infections, pregnancy was 5-fold ($P < 0.01$) as likely to be associated with symptomatic VVC in a logistic multivariate analysis [Table 2]. Symptomatic VVC remained inversely related to Nugent's scores as depicted in Table 2. The combination of vulval itching, soreness and vaginal discharge remained independently associated with symptomatic VVC ($P < 0.01$) as compared to other presenting symptoms.

When compared to HIV negative women, the risk of symptomatic VVC increased with HIV genital shedding among

HIV-infected women. The risk of symptomatic VVC was 2-fold ($P = 0.04$) and 4-fold ($P = 0.04$) higher when genital HIV load was respectively below and above 1000 copies/mL [Table 2]. In addition, as compared with HIV negative women, HIV-infected women with plasma HIV load above 1000 copies/mL were 8 times likely to develop symptomatic VVC ($P < 0.001$, OR = 7.6 [3.2-18.2]). Furthermore, HIV-infected women with CD4 count below 200 cells/mm³ had 8-fold higher risk for symptomatic VVC as compared with HIV negative women ($P < 0.001$, OR = 7.7 [3.2-18.4]). Finally, a logistic multivariate analysis showed that HIV positive women but anti-retroviral therapy (ART)-naïve had 5-fold ($P < 0.001$, OR = 4.5 [1.9-10.7]) higher risk for symptomatic VVC as compared to HIV negative women.

Discussion

Six factors clearly increased risk for symptomatic VVC in this study. Four factors were associated with HIV infection— increased HIV shedding in the vagina, plasma HIV load above 1000 copies/mL, CD4 count below 200 cells/mm³ and absence of HAART. Previous studies have reported on the association between low CD4 counts particularly < 200 cells/mm³ and symptomatic VVC.^[17,18] Although symptomatic VVC is not classified among AIDS-defining conditions, the present study provides an additional body of evidence that symptomatic VVC is frequent among HIV-infected women with CD4 counts < 200 cells/mm³. Data on the association between HIV loads and symptomatic VVC are very scanty. In 2003, Ohmit *et al.* found that odds of symptomatic VVC increased by > 2 -fold for women whose plasma HIV load was > 1000 copies/mL. The authors found an increase of 11-14% for every Log₁₀ increase in plasma HIV viral load.^[26] In addition, Sobel *et al.* (2000) reported that higher HIV loads rather than lower CD4⁺ T-lymphocyte counts were associated with statistically significant increased odds for both persistent candidal vaginal colonization and symptomatic VVC.^[27] However, the study by Sobel *et al.* (2000) only found an association between plasma HIV viral load and the proportion of *Candida* infections that were non-*C. albicans*, not the absolute prevalence of symptomatic VVC.^[27] The present study determined plasma HIV load > 1000 copies/mL and genital HIV shedding (below and above 1000 copies/mL) as independently associated with increased odds for symptomatic VVC. Plausible biological reasons why HIV viral loads can correlate with symptomatic VVC have not been clearly established.

We can hypothesize that during advanced HIV infection (as measured by systemic CD4⁺ T cell levels) with subsequently observed higher HIV viral loads in plasma and in the vagina, HIV particles might change the vaginal environment by downregulated the activation of mucosal CD4⁺ T cells and the recruitment of other immune cells into vaginal tissues, hence promoting virulence of *Candida species* by switching from its non-pathogenic form into a filamentous form that causes symptomatic VVC. We can further speculate that because

Table 1: Univariate associations of symptomatic vulvo-vaginal candidiasis and vaginal Candida colonization with selected host characteristics among 198 women attending a primary healthcare clinic between June - December 2011

Characteristics	Symptomatic vulvo-vaginal candidiasis n (%)	Vaginal Candida colonization n (%)	P value
Age categories (years)			0.99
18-24	47 (52.2)	56 (51.9)	
25-34	30 (33.3)	37 (34.3)	
≥35	13 (14.4)	15 (13.9)	
Presenting complains			<0.01
Group 1 :	81 (90)	82 (75.9)	
Vulval itching - vulval soreness- vaginal discharge			
Group 2 :	9 (10)	26 (24.1)	
Low abdominal pain - dysuria - dyspareunia			
Contraceptive use	77 (85.6)	82 (75.9)	0.06
Pregnancy	16 (17.8)	7 (6.5)	0.01
History of antibiotic use within the past 3 months	53 (58.9)	60 (55.6)	0.64
History of sexually transmitted infections (STIs)			
Within the past 3 months			0.49
Vaginal discharge syndrome	32 (35.6)	46 (42.6)	
Genital ulcer syndrome	11 (12.2)	9 (8.3)	
No defined sexually transmitted infections	47 (52.2)	53 (49.1)	
Concurrently isolated STI pathogens			0.33
<i>Trichomonas vaginalis</i>	10 (11.1)	21 (19.4)	
<i>Chlamydia trachomatis</i>	3 (3.3)	8 (7.4)	
<i>Neisseria gonorrhoeae</i>	5 (5.6)	6 (5.6)	
<i>Mycoplasma genitalium</i>	1 (1.1)	2 (1.9)	
Herpes simplex virus type 2	5 (5.6)	3 (2.8)	
Polymicrobial infection	12 (13.3)	18 (16.7)	
No STI pathogen identified	54 (60)	50 (46.3)	
Vaginal flora (Nugent scores)			<0.01
0 to 3	19 (21.1)	9 (8.3)	
4 to 6	11 (12.2)	8 (7.4)	
7 to 10	60 (66.7)	91 (84.3)	
Plasma HIV viral load (VL) categories			<0.001
HIV negative	38 (42.2)	63 (58.3)	
HIV positive with plasma VL less than 1000 copies/mL	22 (24.4)	34 (31.5)	
HIV positive with plasma VL more than 1000 copies/mL	30 (33.3)	11 (10.2)	
Genital HIV viral load (VL) categories			0.04
HIV negative	38 (42.2)	63 (58.3)	
HIV positive with genital VL less than 1000 copies/mL	44 (48.9)	41 (38)	
HIV positive with genital VL more than 1000 copies/mL	8 (8.9)	4 (3.7)	
CD4+T cell stages			<0.001
HIV negative	38 (42.2)	63 (58.3)	
HIV positive with CD4 count ≥ 350 cells/mm ³	5 (5.6)	19 (17.6)	
HIV positive with CD4 count: 200-349 cells/mm ³	17 (18.9)	15 (13.9)	
HIV positive with CD4 count less than 200 cells/mm ³	30 (33.3)	11 (10.2)	
Therapy groups			<0.01
HIV negative	38 (42.2)	63 (58.3)	
HIV positive anti-retroviral therapy (ART)-naïve	26 (28.9)	11 (10.2)	
HIV positive receiving highly active anti-retroviral therapy	26 (28.9)	34 (31.5)	

HIV: Human immunodeficiency virus, STIs: sexually transmitted infections, VL: Viral load, ART: anti-retroviral therapy

ART-naïve HIV-infected women had 5-fold higher risk of developing symptomatic VVC as compared to HIV negative women, controlling the replication of HIV by using HAART could possibly restore local mucosal immune functions in the vagina, suggesting that high level of HIV load could suppress

genital mucosal immune mechanisms independently of systemic cell-mediated immunity, leading to symptomatic VVC.

We found a significant negative association between the presence of BV and symptomatic VVC. The present study is

Table 2: Independent determinants of symptomatic vulvo-vaginal candidiasis among 198 women attending a primary healthcare clinic between June - December 2011

	B Coefficient	Standard error	Wald Chi-square	OR (95% CI)	P value
Independent variables					
Vaginal flora (Nugent scores)					
0 to 3	1.377	0.497	7.688	4 (1.5-10.5)	<0.01
4 to 6	1.287	0.574	5.029	3.6 (1.2-11.2)	0.03
7 to 10			Referent	1	
Genital HIV viral load (VL) categories					
HIV positive with genital VL more than 1000 copies/mL	1.318	0.672	3.843	3.7 (1.03-14)	0.04
HIV positive with genital VL less than 1000 copies/mL	0.696	0.34	4.183	2 (1.03-3.9)	0.04
HIV negative			Referent	1	
Pregnancy					
Yes	1.646	0.567	8.435	5.2 (1.7-15.7)	<0.01
No			Referent	1	
Presenting complains					
Group 1 :	1.622	0.512	10.029	5.1 (1.9-13.8)	<0.01
Vulval itching - vulval soreness- vaginal discharge					
Group 2: Others			Referent	1	
Constant	-2.436	0.54	20.391		<0.001

Adjusted for contraceptive use and concurrently isolated pathogens causing sexually transmitted infections, VL: Viral load, HIV: Human immunodeficiency virus

in support of a previous study from KwaZulu-Natal in South Africa that reported BV as a predominant cause of vaginitis among the clinic’s attendees. In 2002, Moodley *et al.*, during a study in northern KwaZuluNatal found the prevalence of BV to be 70% among their study population.^[28] We found that symptomatic VVC was significantly associated with Nugent’s score below 7. Symptomatic VVC has been reported as associated with normal vaginal pH (pH <4.5) while BV is established when pH of the vaginal fluid becomes >4.5. In addition, these findings are also in keeping with results from Moodley *et al.* (2002) who found out that yeast colonization and symptomatic VVC were inversely related to Nugent’s scores.^[28]

Another factor identified in this study as associated with symptomatic VVC was pregnancy. This finding was consistent with what has been published by others.^[1,29]

Other traditionally reported risk factors such as contraceptive use and use of antimicrobial agents were not shown by this study to be independently associated with symptomatic VVC. Reports from the literature have shown conflicting data regarding these two risk factors for VVC.^[1,12] In addition, we had a small sample size and relied on the history of antibiotic use to collect information that might not be totally accurate.

Conclusion

The study showed that HIV-related immune compromised women and particularly those who are ART-naïve are likely to develop symptomatic VVC. Limitation to this study is mainly its cross-sectional design and a small population size. Another study is required in the future in order to ascertain our conclusions after addressing the present limitations.

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