Factors associated with repeat genital symptoms among sexually transmitted infection service attendees in South Africa, 2015 - 2016

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Background. South African guidelines recommend a syndromic approach for the management of sexually transmitted infections (STIs), based on the presence of genital symptoms. However, the guidelines do not prescribe specific indications for microbiology testing for patients presenting with or without repeat genital symptoms.
Objectives. To describe the prevalence of and factors associated with repeat genital symptoms among STI service attendees at primary care facilities.
Methods. This was a cross-sectional study at 7 STI primary care facilities participating in the aetiological surveillance of STIs between January 2015 and December 2016. Demographic and clinical information and appropriate genital specimens were collected from participants presenting with vaginal discharge syndrome (VDS), male urethral syndrome (MUS) and/or genital ulcer syndrome (GUS). Repeat genital symptoms were defined as self-reported history of the same STI-related genital symptoms in the preceding 12 months. Multivariable logistic regression identified factors associated with repeat genital symptoms.
Results. Of 1 822 eligible participants, 480 (30%) had repeat genital symptoms (25% and 75% in the preceding 3 months and 12 months, respectively). Of those with repeat genital symptoms, the median age was 28 (interquartile range (IQR) 24 - 32) years, and 54% were females. The most common aetiological agents among participants with VDS, MUS and GUS were bacterial vaginosis (*n*=132; 55%), *Neisseria gonorrhoeae* (*n*=172; 81%) and ulcers (*n*=67; 63%), respectively. One hundred and seven (20%) participants had no detectable common STI aetiology. In the multivariable analysis, repeat genital symptoms were associated with HIV co-infection (adjusted odds ratio (aOR) 1.43; 95% confidence interval (CI) 1.14 - 1.78), VDS diagnosis (aOR 1.39; 95% CI 1.10 - 1.76), self-reported condom use (aOR 1.56; 95% CI 1.20 - 2.03) and age 25 - 34 years (aOR 1.33; 95% CI 1.03 - 1.71).
Conclusions. Our study found a high prevalence of repeat genital symptoms – a significant proportion without STI aetiology. Identified factors of repeat genital symptoms highlight the need for improved integration of HIV and STI prevention and management. Further research is needed to determine the aetiology of repeat genital symptoms and the contribution of non-STI causes.

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In South Africa (SA), as in most African countries, sexually transmitted infections (STIs) are managed using the syndromic approach.[1] This approach was adapted from the World Health Organization (WHO) guidelines as a core intervention for STI management. It is based on treating multiple causes or aetiological factors associated with common genital symptoms, rather than a specific laboratory-confirmed causative pathogen.[2] It allows for treatment to be prescribed on the same day without waiting for confirmatory laboratory results.[3] It also includes some general measures to reduce the risk of STI, such as risk-reduction counselling, partner notification, HIV counselling and testing, and condom and circumcision promotion.[3] The main limitation of this approach is that the treatment algorithms have poor specificity for STI pathogens, leading to inappropriate use of antimicrobials, particularly for non-STI repeat genital symptoms.[4-7] The consequences are persistence or non-resolution of genital symptoms, leading to repeat clinic visits for the same symptoms.

In SA, the National Institute for Communicable Diseases (NICD), through the Group for Enteric Respiratory and Meningeal disease Surveillance in South Africa (GERMS-SA), has since 2005 conducted microbiological surveillance of STIs at selected sentinel sites, in line with WHO recommendations. The microbiological surveillance programme monitors the prevalence of pathogens associated with the three main STI syndromes, i.e. vaginal discharge syndrome (VDS), male urethral syndrome (MUS) and genital ulcer syndrome (GUS). The programme also monitors *Neisseria gonorrhoeae* antimicrobial drug-resistance profiles over time. These data are used to validate and update the syndromic management guidelines used at primary healthcare facilities across the country.

The current primary healthcare standard treatment guidelines for STI management in SA do not prescribe specific indications for microbiological testing for patients with or without repeat STI symptoms.[3] Consequently, there is a lack of impetus among clinicians to conduct laboratory tests to identify specific pathogens.

Furthermore, there is a paucity of literature on the most common aetiological agents of genital symptoms to inform evidence-based decisions for healthcare workers, e.g. nurses in primary care clinics. The management of STIs is further complicated by the lack of a sufficient number of clinicians who are specifically trained for this role.[8] This predominantly affects the success of the syndromic approach, as healthcare workers need to have knowledge of the aetiology, epidemiology and antimicrobial susceptibility patterns of STIs.[9]

Objectives

The objective of this study was to determine the prevalence of repeat genital symptoms, and to identify associated pathogens and related factors among STI service attendees enrolled at primary care clinic sentinel surveillance sites in 5 provinces of SA.

Methods

Study design

We conducted a cross-sectional study using secondary data collected from STI microbiological sentinel surveillance sites from January 2015 to December 2016.

Study population and setting

From January 2015 to December 2016, the STI microbiological surveillance programme conducted sentinel surveillance at 7 sites in 5 provinces, including Gauteng (1 site), Mpumalanga (2 sites), KwaZulu-Natal (2 sites), Eastern Cape (1 site) and North West (1 site). Six of the 7 sentinel sites were primary healthcare clinics located in urban areas, and 1 primary healthcare facility in Mpumalanga was in a rural area. The surveillance enrolled participants aged ≥18 years, who presented with symptoms consistent with ≥1 of the 3 main STI syndromes, including VDS, MUS and/or GUS, from January 2015 to December 2016. The sites were chosen by purposive sampling of facilities that met predetermined criteria, including high caseload of MUS in the preceding year, willingness of province and district offices to grant approval, availability of resources, such as treatment, office space for surveillance nurses and willingness of local staff to participate in surveillance activities.

Data collection

Consecutive participants presenting with symptoms consistent with MUS, VDS or GUS at the sentinel sites were invited to participate in the survey conducted by trained professional nurses. The surveillance nurses assessed eligibility of each individual and thereafter obtained written informed consent. Information obtained from the survey included demographic data, as well as clinical and sexual history. Personal identifiers were not collected. The information included: (*i*) individual demographic characteristics (age, gender, ethnic group, self-reported sexual orientation); (*ii*) clinical information (diagnosis of VDS, MUS and/or GUS on the day of enrolment, past history of treatment for the same STI syndrome in the past 3 months, past history of treatment for the same or different STI syndrome in the past 12 months); and (*iii*) sexual behavioural history (condom use with last sexual encounter, age at sexual debut, sexual intercourse with someone living in another province and/or someone living outside SA in the preceding 3 months). The completed case investigation forms were couriered to the Centre for HIV and STI (CHIVSTI), National Institute for Communicable Diseases (NICD), and captured into a password-protected database that is stored on a server.

Specimen collection

For men with MUS, an endo-urethral swab was taken from each individual, placed in a plastic tube for multiplex polymerase chain reaction (M-PCR) testing at the CHIVSTI at NICD. For women with VDS, a swab was collected from the lateral vaginal wall and posterior fornix, followed by a smear made on a glass microscope slide. An endocervical swab was subsequently taken for M-PCR testing and handled similarly to the M-PCR swab from MUS participants. Men and women with genital ulceration had 2 swabs taken from the lesion. The first ulcer swab was smeared on a microscope slide and the second was placed in a plastic tube for subsequent M-PCR testing. Lastly, 10 mL of blood was drawn from consenting participants for HIV testing.

Laboratory testing

All specimens collected at sentinel sites were transported to the CHIVSTI reference laboratory for processing and storage. A Gram stain was used to detect bacterial vaginosis and candidiasis on vaginal smears. An in-house real-time M-PCR assay for STI discharge pathogens was used for the detection of *N. gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Trichomonas vaginalis*. M-PCR was also used to detect *Haemophilus ducreyi, Treponema pallidum, C. trachomatis* and herpes simplex virus (HSV) in DNA extracted from the ulcer swabs. If *C. trachomatis* was detected, an additional real-time in-house PCR assay was used to determine the presence of serovars L1 - L3, which cause lymphogranuloma venereum (LGV), with associated genital ulceration. If HSV was detected, a commercial PCR assay (Sacace Biotechnologies, Italy) was done to further categorise samples into subtypes HSV-1 and HSV-2. Serum specimens were screened for HIV using two rapid immunochromatographic assays to confirm the first positive results (Unigold, Ireland; Determine, Japan).

Case definition

For the purpose of this study, we defined repeat genital symptoms as the self-reported history of treatment for the same genital symptoms in the preceding 12 months.

Data management and statistical analysis

Demographic, clinical and laboratory data stored on the database were exported into Stata 14 (Stata Corp., USA) for all statistical analyses. Descriptive statistics were used to report characteristics of STI service attendees. Proportions were compared between participants with repeat genital symptoms and those without using the χ^2 or Fisher's exact test, where appropriate. The prevalence was calculated by dividing the number of all participants who met the criteria for repeat genital symptoms by the total number of all STI service attendees enrolled, and corresponding 95% confidence intervals (CIs) were calculated. Multivariable logistic regression was used to identify factors associated with repeat genital symptoms. A manual forward stepwise approach was used to identify statistically significant factors. A cut-off *p*-value of 0.2 in the bivariate analyses was used to include variables in the multivariable model. A *p*-value of ≤0.05 in the multivariable model was considered statistically significant. Multicollinearity tests were performed before entering variables in the multivariable model to ensure that only non-collinear variables were included.

Ethical approval

Ethical approval for ongoing activity of GERMS-SA surveillance was received from the Human Research Ethics Committee (Medical), University of the Witwatersrand, Johannesburg (ref. no. M081117). Ethical clearance and approval for this study was further obtained from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria (ref. no. 388/2016), and from the CHIVSTI at the NICD.

Results

Description of patients enrolled

A total of 1 824 participants were enrolled during the study period. Of these, 1 822 (99%) participants were included in the analysis. Two participants who were <18 years old were excluded. Of the 1 822 eligible participants, the prevalence of repeat genital symptoms was 30.0% (*n*=546) (95% CI 27.9 - 32.1). Among these, 138 (24.5%) and 408 (74.7%) reported repeat genital symptoms in the preceding 3 and 12 months prior to enrolment, respectively.

Demographic and clinical characteristics of patients with repeat genital symptoms

Of the 546 participants with repeat genital symptoms, the median age was 28 (interquartile range (IQR) 24 - 32) years, with the majority (57.6%) in the age group 25 - 34 years (Table 1). Most participants (*n*=173; 31.7%) were enrolled at KwaZulu-Natal sentinel sites, followed by participants at the Gauteng site (*n*=158; 28.9%). The Eastern Cape site had the lowest number of participants (*n*=39; 7.1%). Participants with repeat genital symptoms were more likely to be HIV co-infected (46.9% v. 35.0%; *p*=0.002), and diagnosed with VDS (44.5% v. 35.3%; *p*=0.001).

Prevalence of sexually transmitted infection aetiology in participants with repeat genital symptoms

Among participants with repeat genital symptoms and VDS, bacterial vaginosis (*n*=132; 55%) was the most common aetiology identified, followed by Candida infection (*n*=55; 23%). *M. genitalium* infection (*n*=21; 9%) was the least common aetiological agent detected (Fig. 1). Aetiological agents (>1) were detected in 36 (14%) participants, while none was detected in 53 (20%) participants.

Among participants with repeat genital symptoms and MUS, *N. gonorrhoeae* (*n*=172; 81%) and *C. trachomatis* infections (*n*=54; 25%) were the most common aetiological agents. *M. genitalium* (*n*=11; 5%) and *T. vaginalis* (*n*=8; 4%) were the least common aetiological agents (Fig. 1). Furthermore, aetiological agents (>1) were detected in 51 (24%) participants, while none was detected in 21 (10%) participants.

Among 107 participants with repeat genital symptoms and GUS, 67 (63%) had ulcers associated with HSV-2, and 8 (7%) with *T. pallidum* (Fig. 1). Donovanosis, lymphogranuloma venereum and *H. ducreyi* were not detected. The most common aetiological agent was HSV-2 and the least common cause was HSV-1 (Fig. 1). Mixed aetiological agents were identified in 2 (2%) and none was identified in 33 (31%) participants. Overall, there were no significant differences in the relative prevalence of aetiological pathogens in the three syndromes (VDS, MUS and GUS).

Factors associated with repeat genital symptoms

In the univariable analysis, repeat genital symptoms were associated with age (25 - 34 years) (odds ratio (OR) 1.34; 95% CI 1.05 - 1.71), enrolment at the KwaZulu-Natal (OR 2.62; 95% CI 2.02 - 3.43), Eastern Cape (OR 2.75; 95% CI 1.73 - 4.33) and North West (OR 1.44; 95% CI 1.02 - 2.03) sites, HIV co-infection (OR 1.64; 95% CI 1.34 -

Table 1. Description of participants with/without repeat genital symptoms in 5 provinces, South Africa, January 2015 - December 2016

Characteristics	Total (*N*=1 822), *n* (%)	With repeat genital symptoms (*n*=546), *n* (%)	Without repeat genital symptoms (*n*=1 276), *n* (%)	*p*-value
Age, years				
18 - 24	491 (27.2)	128 (23.6)	363 (28.7)	
25 - 34	977 (54.1)	314 (57.9)	663 (52.5)	0.116
35 - 44	259 (14.3)	80 (14.8)	179 (14.2)	
45 - 54	57 (3.2)	16 (3.0)	41 (3.2)	
≥55	22 (1.2)	4 (0.7)	18 (1.4)	
Gender				
Female	961 (52.7)	295 (54.0)	566 (44.4)	<0.001
Male	861 (47.3)	251 (46.0)	710 (55.6)	
Province				
Mpumalanga	414 (22.7)	112 (20.5)	302 (23.7)	
KwaZulu-Natal	400 (22.0)	173 (31.7)	227 (17.8)	<0.001
Gauteng	703 (38.6)	158 (28.9)	545 (42.7)	
Eastern Cape	88 (4.8)	39 (7.2)	49 (3.8)	
North West	217 (11.9)	64 (11.7)	153 (12.0)	
Ethnicity				
Black African	1 811 (99.4)	540 (98.9)	1 271 (99.6)	0.122
Other	9 (0.6)	6 (1.1)	5 (0.4)	
Sexual orientation				
Heterosexual	1 801 (98.9)	540 (98.9)	1 261 (98.8)	0.837
Homosexual	21 (1.1)	6 (1.1)	15 (1.2)	
Clinical syndrome at enrolment				
VDS	694 (38.1)	243 (44.5)	451 (35.3)	0.001
MUS	762 (41.8)	196 (35.9)	566 (44.4)	
GUS	366 (20.1)	107 (19.6)	259 (20.3)	
HIV status				
Positive	703 (38.6)	256 (46.9)	447 (35.0)	0.002

VDS = vaginal discharge syndrome; MUS = male urethral syndrome; GUS = genital ulcer syndrome.

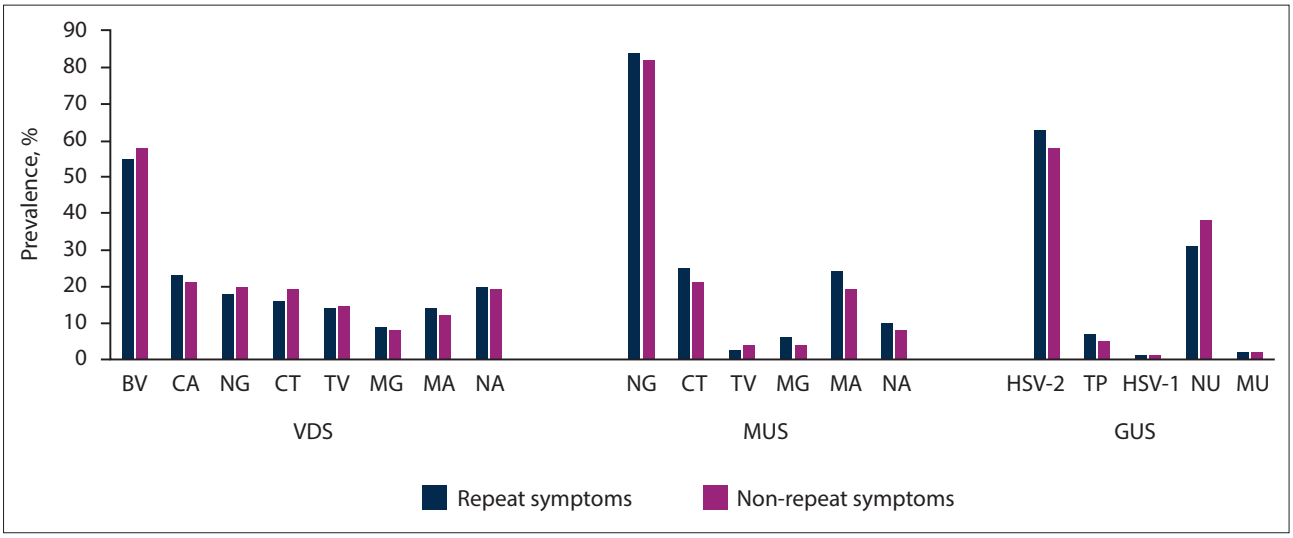

Fig. 1. Comparison of prevalence of sexually transmitted infection (STI) syndrome aetiological agents in recurrent and non-recurrent cases in South Africa (microbiological STI surveillance system, 2015 - 2016). (BV = bacterial vaginosis; CA = candidiasis; NG = Neisseria gonorrhoeae*; CT =* Chlamydia trachomatis*; TV =* Trichomonas vaginalis*; MG =* Mycoplasma genitalium*; MA = multiple aetiologies; NA = no aetiologies; HSV-2 = herpes simplex virus type 2; TP =* Treponema pallidum*; HSV-1= herpes simplex virus type 1; NU = no ulceration; MU = mixed ulcerations; VDS = vaginal discharge syndrome; MUS = male urethral syndrome; GUS = genital ulcer syndrome.)*

2.01), self-reported condom use during the last sexual encounter (OR 1.52; 95% CI 1.18 - 1.96) and VDS diagnosis (OR 1.48; 95% CI 1.19 - 1.85) (Table 2). Participants with a sexual partner in another country had decreased odds of repeat genital symptoms (OR 0.70; 95% CI 0.50 - 0.98).

In the multivariable analysis, repeat genital symptoms were independently associated with self-reported condom use at last sexual encounter (adjusted odds ratio (aOR) 1.56; 95% CI 1.20 - 2.02; p=0.001), HIV co-infection (aOR 1.42; 95% CI 1.14 - 1.78; p=0.002), age 25 - 34 years (aOR 1.33; 95% CI 1.03 - 1.71; p=0.028) and VDS diagnosis (aOR 1.39; 95% CI 1.10 - 1.76; p=0.006) (Table 2). Compared with those in Gauteng, participants from KwaZulu-Natal (aOR 2.38; 95% CI 1.79 - 3.16; p<0.001) and the Eastern Cape (aOR 2.96; 95% CI 1.85 - 4.75; p<0.001) were more likely to have repeat genital symptoms. Because most women had VDS, and MUS cases are generally males, we did not include gender in the model to avoid collinearity, as these variables are correlated.

Discussion

Our study found a high prevalence of repeat genital symptoms among participants presenting for STI services at primary care facilities, with a significant proportion having no detectable STI aetiology. The most prevalent STI aetiological agents were bacterial vaginosis, *N. gonorrhoeae* and HSV-2 among participants with VDS, MUS and GUS, respectively. Repeat genital symptoms were independently associated with a diagnosis of VDS at enrolment, HIV co-infection, self-reported condom use at last sexual encounter and age between 25 and 34 years.

The burden of repeat genital symptoms was significantly higher than the 12% reported in a study among Kenyan patients attending an STI clinic.[10] This difference between the two studies was probably due to the differences in the definition of repeat genital symptoms or the population under surveillance. We found that, although the prevalence of repeat genital symptoms was high, a significant proportion of participants had no detectable STI aetiology. Moreover, a study done in our STI microbiological surveillance on resistance of STI pathogens showed no evidence of *N. gonorrhoeae* resistance to the currently used dual treatment regimen.[11] Therefore, it is unlikely that the repeat genital symptoms in our study were due to treatment failure because of antibiotic resistance. The similar distribution of aetiological agents among those with repeat genital symptoms suggests that re-infection, persistent or recurrent infection due to suboptimal treatment, or non-STI causes that remain untreated after initial presentation, could have been important factors in our population. Further research studies are required to properly determine the aetiology of repeat genital symptoms and the contribution of non-STI causes.

Understanding the factors that predispose participants to repeat genital symptoms is necessary to improve the management of STIs. We identified a number of factors that place participants at increased risk of repeat genital symptoms, including VDS diagnosis. Women may be more vulnerable to repeat genital symptoms from STI infections due to their anatomical and physiological structure (genitalia), which is more susceptible to infection than that of men.[6,7,12] Furthermore, women may have less power to negotiate safer sex, and as a result they are more likely to be re-infected.[6,7,13] Studies also suggest that women with STI symptoms are more likely to seek medical treatment than their male counterparts.[13] Therefore, it is less probable that partners are treated, thereby resulting in repeat infections. Although partner notification and treatment are components of STI management in our standard treatment guidelines, it is poorly implemented in SA.[14]

Another concern in our study was the association of HIV with repeat genital symptoms, the relatively high HIV seropositivity rate of 47% among participants who reported repeat genital symptoms, as well as the high overall HIV seropositivity rate in the entire study population (~39%). These findings may be biologically plausible, given that the presence of STIs increases the likelihood of HIV acquisition and transmission.[6,7,12,15,16] Furthermore, STIs that cause ulcers or inflammation significantly increase vulnerability to HIV infection.[12,16,17] It is also known that HIV can modify the clinical progression of some STIs, especially among immunosuppressed participants.[17,18] This probably explains why there was also a high HIV prevalence in participants with repeat genital symptoms.

Table 2. Factors associated with repeat genital symptoms in microbiological sentinel sites, South Africa, January 2015 - December 2016

Characteristics	Total, *n*	Repeat genital symptoms, *n* (%)	Univariable analysis, crude OR (95% CI)	*p*-value	Multivariable analysis, adjusted OR (95% CI)	*p*-value
Age, years						
18 - 24	491	128 (26.1)	Reference			
25 - 34	977	314 (32.1)	1.34 (1.05 - 0.71)	0.017	1.33 (1.03 - 1.71)	0.028
35 - 44	259	80 (30.9)	1.27 (0.91 - 1.77)	0.265	1.13 (0.80 - 1.60)	0.487
45 - 54	57	16 (28.1)	1.11 (0.60 - 2.04)	0.745	0.82 (0.44 - 1.56)	0.552
≥55	22	4 (18.2)	0.63 (0.21 - 1.90)	0.412	0.55 (0.180 - 1.70)	0.300
Province						
Gauteng	703	58 (22.5)	Reference			
KwaZulu-Natal	400	173 (43.3)	2.63 (2.02 - 3.43)	<0.001	2.96 (1.79 - 3.16)	<0.001
Mpumalanga	414	112 (27.1)	1.28 (0.97 - 1.69)	0.085	1.23 (0.92 - 1.64)	0.154
Eastern Cape	88	39 (44.3)	2.75 (1.73 - 4.33)	<0.001	2.96 (1.85 - 4.75)	<0.001
North West	217	64 (29.5)	1.44 (1.03 - 2.03)	0.035	1.34 (0.94 - 1.91)	0.110
Having a sexual partner in another province						
No	1 530	465 (30.4)	Reference			
Yes	292	81 (27.7)	0.87 (0.67 - 1.16)	0.365		
Having a sexual partner outside SA						
No	1 608	495 (30.8)	Reference			
Yes	214	51 (23.8)	0.70 (0.50 - 0.98)	0.038	0.92 (0.64 - 0.30)	0.624
Age at first sex debut, years						
<17	652	198 (30.4)	Reference			
≥17	1 079	321 (29.8)	0.97 (0.79 - 1.20)	0.786		
HIV status						
Negative	1 119	290 (25.9)	Reference			
Positive	703	256 (36.4)	1.64 (1.34 - 2.01)	<0.001	1.43 (1.14 - 1.78)	0.002
Self-reported condom use						
No	1 500	425 (28.3)	Reference			
Yes	322	121 (37.6)	1.52 (1.18 - 1.96)	0.001	1.56 (1.20 - 2.03)	0.001
STI syndrome diagnosis						
MUS	762	196 (35.9)	Reference			
VDS	694	243 (44.5)	1.48 (1.19 - 1.85)	<0.001	1.39 (1.10 - 1.76)	0.006
GUS	366	107 (19.6)	1.14 (0.85 - 1.52)	0.380	1.16 (0.85 - 1.58)	0.353

OR = odds ratio; CI = confidence interval; SA = South Africa; STI = sexually transmitted infection; MUS = male urethral syndrome; VDS = vaginal discharge syndrome; GUS = genital urethral syndrome.

Of note was the association of repeat genital symptoms in the age category 25 - 34 years and self-reported condom use at last sexual encounter. The association of repeat genital symptoms between 25 and 34 years of age was not unexpected. The HIV prevalence is similarly high in this age group, which suggests unsafe sexual practices that may predispose to repeat genital symptoms. The self-reported recent condom use in our study may be an individual's response to the presence of genital symptoms and taking precautionary measures to prevent potential spread to a sexual partner. Other studies found that participants who perceived themselves to be at high risk of STIs were more likely to use condoms than those with a perceived low risk of STIs.[18-20] Repeat infection may be due to other STI causes, which condom use may not fully prevent, such as herpes and syphilis.[21] Unfortunately, our data did not permit us to evaluate the extent of or consistency in condom use during last sexual encounter.

Study limitations

This study had some limitations. Our study population comprised patients enrolled for microbiological surveillance; therefore, our findings may not be generalisable to the wider population of SA. Moreover, the data did not incorporate other potentially explanatory factors, such as number of sexual partners, partner notification, treatment history, knowledge of HIV status or antiretroviral treatment use, and frequency or duration of previous or current genital symptoms. The associations between repeat genital symptoms and some factors, e.g. HIV infection, could not be assessed conclusively because of the cross-sectional nature of the study. Information bias may have been introduced by the subjective ascertainment of using self-reported data of repeat genital symptoms and sexual behaviour. Therefore, the information may be subject to bias and/or misclassification.

Conclusions

Despite these limitations, our study found a high prevalence of repeat genital symptoms – a significant proportion without STIs, which are commonly identified as aetiological agents. The association of HIV infection with repeat genital symptoms highlights the need for improved integration of HIV and STI prevention and management. Further research studies are needed to properly determine the aetiology of repeat genital symptoms and the contribution of non-STI causes.

Declaration. None.

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Author contributions. RCM, TK and LRK were involved in the conception and design of the study, data analysis and manuscript development; AM reviewed the statistical analysis and interpretation of the results; RK and VM were involved with the interpretation of the data and critical review of the manuscript; and all authors critically revised the manuscript and approved the final version.

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Conflicts of interest. None.

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