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Genital infections and syndromic diagnosis among HIV-infected women in HIV care programs in Kenya

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Abstract

Background—Control of genital infections remains challenging in most regions. Despite advocacy by the World Health Organization (WHO) for syndromic case management, there are limited data on the syndromic approach, especially in HIV care settings. This study compared the syndromic approach against laboratory diagnosis among women in HIV care in Kenya.

Methods—A mobile team visited 39 large HIV care programs in Kenya and enrolled participants using population-proportionate sampling. Participants provided behavioral and clinical data with genital and blood specimens for lab testing.

Results—Among 1,063 women, 68.4% had been on antiretroviral therapy >1 year; 58.9% were using cotrimoxazole prophylaxis; 51 % had CD4+T-lymphocytes < 350 cells/mL. Most women (63.1%) reported at least one genital symptom. Clinical signs were found in 63% of women; and 30.8% had an etiological diagnosis. Bacterial vaginosis (17.4%), vaginal candidiasis (10.6%) and trichomoniasis (10.5%) were the most common diagnoses. Using laboratory diagnoses as gold standard, sensitivity and positive predictive value of the syndromic diagnosis for vaginal discharge were 47.6% and 52.7%, respectively, indicating a substantial amount of overtreatment. A systematic physical examination increased by 9.3% the positive predictive value for genital ulcer disease.

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The authors state no conflicts of interest.

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Author contributions
GD, NB, BS, GJS conceptualized the present analysis. HG and ED conducted the data analysis. NB and GD obtained the funding. SH, JO, BS and GD designed study procedures and oversaw field implementation. GD, NB, GJS, and RSM contributed to the design, conduct and interpretation of study results.

Conclusions—Women attending HIV care programs in Kenya have high rates of vaginal infections. Syndromic diagnosis was a poor predictor of those infections.

Keywords

Genital infections; syndromic management; vaginal discharge; Kenya

Introduction

Each year an estimated 340 million new sexually transmitted infections (STIs) are diagnosed globally, with 75–85% in developing countries (1). STI control measures include the promotion of safe sexual behaviors, prompt STI diagnosis and systematic treatment and partner notification and treatment (2). Owing to a lack of equipment and trained laboratory staff in developing countries, and testing costs, the World Health Organization (WHO) recommends a syndromic approach to STI management (3). Syndromic approaches rely on uniform treatment strategies to cover all likely pathogens responsible for a variety of infections. These syndromes are defined by a combination of self-reported symptoms and signs detected on physical examination. The most common syndromes are urethral discharge (UD) in men, vaginal discharge (VD) and lower abdominal pain (LAP) in women and genital ulcer disease (GUD) in both sexes (3).

Because it is unknown whether syndromic management is an effective STI control intervention in African populations infected with HIV, we conducted a large study within HIV care and treatment programs in Kenya to: 1) quantify the prevalence of genital infections; 2) evaluate the performance of STI syndromic case management for VD and GUD in symptomatic women against laboratory diagnoses and; 3) weigh the utility of incorporating systematic clinical STI screening in these programs.

Methods

Patient sampling and procedures

Probability proportional to size (PPS) sampling was used to select a random sample of 1,063 women. Sampling and procedures for this study have been previously described by Singa et al. (4). Sociodemographic, sexual risk behaviors data and HIV/medical history were collected. Current STI symptoms were assessed and a genital examination with bimanual pelvic examination was performed. Blood, urine and genital specimens were systematically collected for laboratory testing. Participants diagnosed with a genital infection were provided immediate treatment. Asymptomatic patients diagnosed etiologically with laboratory confirmation were contacted to receive treatment. A referral card was provided for partner (s) to seek STI care and HIV testing. The study was approved by the institutional review boards of the U.S. Centers for Disease Control and Prevention, the University of Washington, and the Kenya Medical Research Institute.

Clinical definitions

A brief questionnaire on genital symptoms was administered and a physical examination was performed. The Kenyan syndromic diagnosis (KSD) was established on self-reported

symptoms and then genital examination. To assess whether systematic physical examination provided incremental STI diagnosis in the absence of symptoms, we defined the study clinician diagnosis (SCD) as any findings at systematic genital examination irrespective of symptom reporting. A VD syndrome was defined as self-reported vaginal discharge and the presence of profuse and/or mucopurulent or white, mucoid, yellowish-green vaginal discharge and/or the presence of discharge only at the time of examination. A GUD syndrome was defined as self-reported vesicles, ulcers and/or wounds in the genital, perineal and/or buttocks area and/or signs of genital ulcers at the time of examination.

Laboratory

Testing was performed for chlamydia, gonorrhea, trichomoniasis, syphilis, herpes simplex virus types 1 and 2 (HSV-1, HSV-2), bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC). Vaginal swabs were collected from women during pelvic exam; a genital ulcer specimen was collected using a Dacron swab for genital ulcers. All participants had blood drawn to measure CD4 T-cell counts and for syphilis serology. A urine sample was collected for pregnancy testing.

Vaginal swab specimens were tested for *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* by transcription-mediated amplification (TMA) using the Gen-Probe APTIMA Combo 2GC/CT system (Hologic Gen-Probe, Inc., San Diego, CA). A positive TMA test for *C. trachomatis*, *N. gonorrhoeae* or *T. vaginalis* defined chlamydial, gonorrheal, or trichomoniasis infection, respectively. Syphilis testing was performed using rapid plasma reagin (RPR) assays for screening and *Treponema pallidum* haemagglutination assays (TPHA) for confirmation. Participants with positive RPR and TPHA were reported as having latent syphilis, in the absence of signs suggestive of active syphilis (5). Microscopy was used to examine Gram stained vaginal smear slides for *Candida albicans* and to evaluate for BV using Nugent's scoring system (6). Scores of 0–3 represented normal vaginal flora, scores from 4–6 represented abnormal flora, and scores from 7–10 were classified as BV. Vulvovaginal candidiasis was defined as the presence of budding yeast or pseudohyphae on Gram stained vaginal swab smear along with self-reported genital itching and/or VD on exam. CD4 counts were assessed using FACSCalibur equipment (BD Biosciences, San Jose, CA). A real time multi-plex PCR test was used to detect HSV-1, HSV-2, *Hemophilus ducreyi* and *Treponema pallidum* from genital ulcers swabs.

Statistical analysis

Study enrollment site and sampling weight were included in the data analysis, which was conducted using SAS (Version 9.2, SAS Institute, Cary, NC, USA). Sampling weight was derived from the total number of patients on ART at each site, the number of patients sampled for recruitment at each site, and the number of patients ultimately enrolled. Tables and text present un-weighed sample size and weighed estimates with corresponding 95% confidence intervals (CIs).

The number of women who reported symptoms, who had at least one sign on physical examination, and who had asymptomatic genital infections were calculated separately. Asymptomatic infection was defined as women reporting no symptoms and had no signs on

physical examination, but had at least one positive laboratory result. Sensitivity, specificity, negative and positive predictive values and corresponding 95% CIs were calculated respectively for the KSD and the SCD. Microbiological diagnosis was used as gold standard in the above calculation for VD and GUD.

Results

One thousand and sixty-three women were enrolled. The median age was 36 years [range 18–70] (Table 1). Approximately 46.5% were married and 55.6% had a primary education level. More than a third (44.3%) had not been sexually active three months prior to enrollment, while 53.8% and 1.9% reported one sex partner and more than one sex partner, respectively. Overall, 64.4% of sexually active women reported condom use at last sex. Twenty-two percent had been diagnosed with HIV within the past year, 68.4% had been on ART for more than 12 months, and 58.9% were on cotrimoxazole prophylaxis for opportunistic infections during the study.

Symptoms and signs

Overall, 63.1% of women reported at least one STI symptom, with VD as the most common, and 36.9% of women did not complain of any symptoms. Signs on examination were observed in 63.0% of women. Vulvovaginal discharge was observed in 66.2% (95%CI; 57.6–74.8) of women reporting symptoms of VD (Table 2). Table 2 shows the most common diagnoses for women with signs of VD and GUD. All women presenting with signs at the physical examination were treated according to the syndromic management algorithms from the Kenyan ministry of health, regardless of the presence of symptoms.

Etiologic diagnosis and performance of syndromic management

Overall, 30.8% of women had a single diagnosis and 6.4% had mixed etiological diagnosis of genital infections. Bacterial infections such as gonorrhea and chlamydia accounted for 1.6% and 0.5% of all diagnoses, respectively, and were never found together. The most common diagnoses were vaginal infections, including BV (17.4%), VVC (10.6%), and trichomoniasis (10.5%). Diagnoses stratified by cotrimoxazole prophylaxis were not statistically different (OR=0.94; 95%CI 0.66–1.35).

Table 3 summarizes the sensitivity, specificity, and positive and negative predictive values of the KSD and SCD using laboratory diagnosis as the gold standard for symptomatic women with VD and GUD syndromes. The sensitivity and positive predictive value of KSD for VD were estimated at 31.5% and 47.6%, respectively. Among symptomatic women with a KSD, 47.6% also had a laboratory diagnosis. The specificity was 78.1%, showing that approximately 22% of infections were misclassified. SCD yielded a sensitivity and positive predictive value of 34.3% and 49.1% respectively.

For GUD, KSD and SCD had a sensitivity of 77.6% and 89.1%, respectively; and a positive predictive value of 55.4% and 64.7%, respectively. Both yielded a relatively high specificity, as well as negative predictive value estimated above 99%. In summary, KSD for VD showed that 52.4% of women with a syndromic diagnosis did not have a positive

laboratory result. A SCD of GUD was a better predictor, by 9.3%, of a positive laboratory result.

Discussion

This etiologic study described genital infections among women in HIV care in Kenya. Overall, most women reported symptoms consistent with vaginal infections. Approximately 17.4% of women had laboratory-confirmed BV, 10.5% candidiasis and 10.6% trichomoniasis. Because syndromic management relies on self-reported symptoms and clinical examination for visible signs, it is often unsuccessful at detecting asymptomatic infections. Fortunately, this study identified a low number of asymptomatic infections and none was primarily gonococcal or chlamydial infection, as usually reported (7).

Studies from sub-Saharan Africa indicate that VD syndrome is not helpful in the differential diagnosis of genital infections (8) and represents only a modest predictor of genital tract inflammation (9). Our stratification by cotrimoxazole prophylaxis use did not yield any difference in the prevalence of STIs or syndromes, especially VD. The study also suggests that syndromic management of genital infections in HIV care settings in Kenya would identify and treat around 47.6% and 55.4% of symptomatic, curable, episodes of VD and GUD, respectively, but would over treat an important number of women without indication for treatment.

The performance of KSD or SCD in predicting actual infections among symptomatic women was modest indicating that syndromic diagnosis may not be effective for screening genital infections in this population of HIV-infected women. An extensive review conducted by Pettifor et al. documented the ineffectiveness of syndromic management to treat genital infections in low-risk populations of women (10). Our findings are consistent with the review and highlight the urgent need for development of affordable and rapid diagnosis.

This study has some limitations. Because of the low number of bacterial infections such as gonorrhea and chlamydia, we were unable to assess co-factors associated with symptomatic, laboratory-confirmed genital infections. Because the gold standard for LAP diagnosis is not laboratory-centered, we were not able to validate the performance of syndromic diagnosis for LAP.

While annual laboratory-based screening for trichomoniasis among HIV-infected women has been recommended in a few studies (4, 11), aggressive partner notification and management should be equally sought. Growing evidence indicates genital microbiota is shared between sexual partners (12) and trichomoniasis prevalence may rise up to 73% among male partners of women diagnosed with vaginal trichomoniasis (13). Furthermore, up to 77% of trichomoniasis are asymptomatic in men (14) and may represent critical sources of infection and re-infections in women.

Given the relatively high study prevalence of vaginal infections such as BV, it is important to emphasize approaches to increase women's awareness of urogenital symptoms with health care providers' pro-active inquiry of genital symptoms and treatment (15). A recent study found an association between BV and increased risk of HIV-1 transmission to male

partners (15). Furthermore, BV recurs after treatment in 20%–30% of women within 3 months (16) and in 75% of women with symptomatic and asymptomatic BV within 2 months of treatment (17). Because of the high recurrence of BV and the potential ongoing risk of HIV transmission to male partners, approaches such as presumptive treatment may be warranted to promote healthy lactobacilli-dominant vaginal flora (18, 19) and to suppress inflammatory immune activation associated with the risk of HIV transmission and acquisition (20, 21). Research is needed to increase understanding of BV and to promote development of new therapies that maintain a sustained lactobacilli-dominant flora in the vagina. Because it is important to screen for STIs in HIV care programs, given the poor performance of syndromic management, it is essential develop better tools for laboratory diagnosis of STIs and genital infections in resource-constrained settings".

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Summary

Women attending HIV care programs in Kenya have high rates of vaginal infections. Syndromic diagnosis was a poor tool in predicting these infections.

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Table 1

Sociodemographic characteristics of 1063 HIV-positive women in HIV care clinics in Kenya.

Variable	**Number of HIV positive women (%), total=1063**	
Age in years (n=1060	Un-weighted sample size	Weighted percentages (95%CI)
18–24	67	6.5(4.8–8.2)
25–34	400	38.5(35.3–41.6)
35+	593	55.0(51.5–58.6)
Marital status (n= 1060)		
Single	180	17.8(13.2–22.4)
Married	483	46.5(41.7–51.3)
Widowed/divorced/separated	344	31.7(27.0–36.5)
Polygamous marriage	53	4.0(1.8–6.1)
Education (n=989)		
Primary school and below	556	55.6(49.8–61.5)
Vocational/secondary	357	36.3(32.8–39.9)
Post-secondary and above	76	8.1(5.1–10.9)
Partners in the past 3 months (n=1058)		
0	471	44.3(40.9–47.8)
1	568	53.8(50.6–57.0)
2+	19	1.9(1.1–2.7)
Condoms used at last sex (n=586)	377	64.4(59.3–69.4)
ART Use n (%)	773	74.9(70.9–78.9)
ART > 12 months, n (%)	404	68.4(63.4–73.5)
Cotrimoxazole n (%)	626	58.9(45.6–72.2)
CD4 Median (range)	344 (0–1383)	–
CD4<350	530	51.0(45.7–56.2)

Table 2

Prevalence of clinical signs and laboratory etiologies by self-reported symptoms among 1063 HIV-positive women attending HIV care clinics in Kenya.

Clinical assessment			Laboratory assessment N (weighted percentages) (95% CI)						
Self–reported symptoms (unweighted sample size)		**Clinical Signs N (weighed %) (95% CI)**	**NG**	**CT**	**TV**	**BV**	**VVC**	**Syphilis**	**Herpes**
Vaginal discharge	392	254(66.2) (57.6–74.8)	9 (2.4) (0.9–3.9)	***	54(14.6) (10.6–18.7)	73(18.4) (13.9–22.9)	58(15.2) (11.7–18.6)	***	16(4.2) (2.4–6.1)
Genital ulcer	139	32(24.3) (15.8–32.8)	***	***	***	29(21.4) (12.6–30.1)	18(12.4) (6.2–18.7)	***	27(20.8) (13.3–28.3)
Other*	432	**11(2.9) (1.2–4.5)	***	***	55(13.4) (8.3–18.4)	85(20.3) (15.3–25.4)	74(17.2) (13.8–20.6)	***	24(5.7) (3–8.5)
No Symptoms	392	Any sign 200 (52.4%)	***	***	18 (8.8) (3.8–13.8)	37(19.9) (13.5–26.3)	24(11.6) (5.7–17.4)	***	0(0.0%)
		No sign 19 (5.4%)	***	***	***	***	***	***	***

* Other includes redness and itching of the vulva or dyspareunia

** Includes genital warts

Laboratory assessment: NG= Neisseria gonorrhea; CT= Chlamydia trachomatis; TV=Trichomonas vaginalis; BV= Bacterial vaginosis; VVC: =vulvovaginal candidiasis).

*** Suppressed because relative standard error >25% and estimate not reliable.

Table 3

Performance of the syndromic management for the Kenya syndromic diagnosis (KSD) and the study clinician diagnosis (SCD), using laboratory results as gold standard among women in HIV care in Kenya.

Criteria	Syndrome	Number of patients (un-weighed sample size)	Sensitivity (%) (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)
KSD	VD	251	31.5 (26.9–36.1)	78.1 (73.2–82.9)	47.6 (40.1–55.0)	64.3 (59.6–69.1)
SCD* (KSD+physical exam)		263	34.3 (29.9–41.7)	77.5 (71.5–83.5)	49.1 (41.3–56.8)	65.1 (60.3–70)
Incremental SCD effect		-	2.8	0.6	1.5	0.8
KSD	GUD	49	77.6 (62.0–93.1)	98.8 (97.1–98.5)	55.4 (43.5–67.3)	99.2 (98.6–99.8)
SCD (KSD+physical exam)		47	89.1 (75.1–99.9)	98.3 (97.5–99.1)	64.7 (51.2–78.2)	99.6(99.1–100)
Incremental SCD effect		-	11.5	−0.5	9.3	0.4

*Study Clinician diagnosis includes KSD plus signs or signs only at physical examination, irrespective of symptoms.