RESEARCH ARTICLE

Etiologies of genital inflammation and ulceration in symptomatic Rwandan men and women responding to radio promotions of free screening and treatment services

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Abstract

Introduction

The longstanding inadequacies of syndromic management for genital ulceration and inflammation are well-described. The Rwanda National Guidelines for sexually transmitted infection (STI) syndromic management are not yet informed by the local prevalence and correlates of STI etiologies, a component World Health Organization guidelines stress as critical to optimize locally relevant algorithms.

Methods

Radio announcements and pharmacists recruited symptomatic patients to seek free STI services in Kigali. Clients who sought services were asked to refer sexual partners and symptomatic friends. Demographic, behavioral risk factor, medical history, and symptom data were collected. Genital exams were performed by trained research nurses and physicians. We conducted phlebotomy for rapid HIV and rapid plasma reagin (RPR) serologies and vaginal pool swab for microscopy of wet preparation to diagnose Trichomonas vaginalis (TV), bacterial vaginosis (BV), and vaginal Candida albicans (VCA). GeneXpert testing for Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) were conducted. Here we assess factors associated with diagnosis of NG and CT in men and women. We also explore factors associated with TV, BV and VCA in women. Finally, we describe genital ulcer and RPR results by HIV status, gender, and circumcision in men.

Results

Among 974 men (with 1013 visits), 20% were positive for CT and 74% were positive for NG. Among 569 women (with 579 visits), 17% were positive for CT and 27% were positive for NG. In multivariate analyses, factors associated with CT in men included younger age,
responding to radio advertisements, <17 days since suspected exposure, and not having dysuria. Factors associated with NG in men included not having higher education or full-time employment, <17 days since suspected exposure, not reporting a genital ulcer, and having urethral discharge on physical exam. Factors associated with CT in women included younger age and ≤10 days with symptoms. Factors associated with NG in women included younger age, lower education and lack of full-time employment, sometimes using condoms vs. never, using hormonal vs. non-hormonal contraception, not having genital ulcer or itching, having symptoms ≤10 days, HIV+ status, having BV, endocervical discharge noted on speculum exam, and negative vaginal wet mount for VCA. In multivariate analyses, only reporting >1 partner was associated with BV; being single and RPR+ was associated with TV; and having ≤1 partner in the last month, being pregnant, genital itching, discharge, and being HIV and RPR negative were associated with VCA. Genital ulcers and positive RPR were associated with being HIV+ and lack of circumcision among men. HIV+ women were more likely to be RPR+. In HIV+ men and women, ulcers were more likely to be herpetic rather than syphilitic compared with their HIV-counterparts.

Conclusions
Syndromic management guidelines in Rwanda can be improved with consideration of the prevalence of confirmed infections from this study of symptomatic men and women representative of those who would seek care at government health centers. Inclusion of demographic and risk factor measures shown to be predictive of STI and non-STI dysbioses may also increase diagnostic accuracy.

Introduction
Globally, over 1 million new sexually transmitted infections (STI) occur each day [1]. The prevalence of STI increased an estimated 59% in sub Saharan Africa between 1999 and 2005 and has continued to rise [2]. The World Health Organization (WHO) 2016–2021 Global Health Sector Strategy on Sexually Transmitted Infections aims to reduce STI 90% by 2030 using “[epidemiologic] information for focused action” [3].

The association between genital ulceration and inflammation (GUI) due to STI and non-STI etiologies and heterosexual HIV transmission and acquisition has been extensively studied in Africa [4–12]. Broadly, in observational studies GUI is associated with both transmitting and acquiring HIV in both men and women, and with transmission of more than one virion, an otherwise rare event, in cohabiting heterosexual discordant couples which comprise one of the largest HIV risk groups [6, 13–17].

Ulcerative STI that may facilitate HIV transmission include syphilis (Treponema pallidum, TP), Herpes simplex virus (HSV), and chancroid (Haemophilus ducreyi, HD) [18–20]. Inflammatory STI that increase HIV transmission include gonorrhea (Neisseria gonorrhoeae, NG), chlamydia (Chlamydia trachomatis, CT), and Trichomonas vaginalis (TV) [21–24]. Common non-STI dysbioses associated with genital inflammation include bacterial vaginosis (BV) and vaginal Candida albicans (VCA) [25–29].

Untreated TP, HD, HSV, NG, CT and TV can cause severe morbidity and, along with BV and VCA (which are troublesome but non-invasive), can contribute to HIV transmission. In our studies in African HIV discordant heterosexual couples, GUI contribute a substantial population attributable fraction of HIV transmission in both donor and recipient [15].
The longstanding inadequacies of syndromic management for GUI are well-described [30–37] but this approach remains the default in many resource-limited settings in Africa due to the high cost of molecular and culture-based diagnostics. The Rwanda National Guidelines for HIV and STI syndromic management were last updated in 2019 but these guidelines are not yet informed by the local prevalence and correlates of STI etiologies, a component WHO guidelines stress as critical to optimize locally relevant algorithms. We have previously published results of a survey of GUI among Female Sex Workers (FSW) in Kigali, but that study lacked molecular diagnostics for NG and CT [38].

Here we contribute to the epidemiologic data needed to inform improved diagnostic and treatment algorithms in Rwanda by exploring demographic, behavioral, medical history, symptom, genital exam, and laboratory factors associated with molecular diagnosis of NG and CT in men and women. We also explore factors associated with vaginal pathogens TV, BV and VCA in women. Finally, we describe genital ulcer and rapid plasma reagin (RPR) results stratified by gender, HIV status, and among men, by male circumcision status.

**Methods**

**Ethics**

This program was approved as non-research by the Rwandan National Ethics Committee. This program was determined to be non-research by the Emory Institutional Review Board criteria. Diagnostic and treatment were provided anonymously as free services.

**Setting**

Kigali, the capital of Rwanda, has a population of over 1 million people and an adult HIV prevalence of 4.3% [39]. Between January 2016 and August 2019, The Center for Family Health Research (CFHR), a research site established in Kigali in 1986 and affiliated with Emory University in Atlanta, GA, USA, implemented a program for diagnosis and treatment of symptomatic GUI residents of Kigali. CFHR has worked closely with the Rwanda Ministry of Health (MoH) on research for improved HIV and reproductive health care in government-run health centers for many years [25, 40–43].

**Patient recruitment**

Patients were residents of Kigali, Rwanda and were recruited in three ways: radio announcements, partner/friend referral, and pharmacist referral. Radio announcements were made in Kinyarwanda, Rwanda’s vernacular, encouraging men and women with symptoms suggestive of GUI (e.g., genital discharge, discomfort, ulcer) to seek free services at CFHR clinic and were broadcast throughout Kigali. Clients who sought services were then asked to refer sexual partners and symptomatic friends. Local pharmacists were alerted to the program and asked to refer individuals seeking treatments for suggestive symptoms. There were no inclusion/exclusion criteria applied to participant recruitment. Participants are representative of residents of Kigali with genital symptoms who self-selected to receive care.

**Data collection and diagnostic procedures**

Demographics, behavioral risk factors, medical histories, and symptoms were collected using a standard instrument (S1 Fig). This information was obtained during interviews conducted by nurses who recorded data on paper and entered it into MS Access. Similarly, findings from genital exams performed by trained physicians and nurses were recorded on paper and entered into MS Access. Samples for laboratory testing were taken from all patients and included
phlebotomy for rapid HIV and RPR serologies and vaginal pool swab for microscopy of wet preparation to diagnose TV, BV and VCA. GeneXpert testing for NG and CT (Cepheid, Sunnyvale USA) was conducted for all patients using endocervical swabs obtained from women and either urethral swabs (when discharge was reported or noted on physical exam) or urine samples from men. In collaboration with the MoH, CFHR developed a uniform alphanumeric identifier to allow anonymous data recording.

Data analysis
Analyses were conducted with Statistical Analysis Software (SAS, Cary, NC). Frequencies of single and multiple infections were stratified by gender and HIV status. Demographic, behavioral, medical history, physical exam, microscopy and serology results were tabulated by gender and by NG and CT results. Bivariate and multivariate analyses of factors associated with NG or CT are presented in tables. Multivariable logistic regression models included variables associated with each outcome at $p<0.05$ in bivariate analysis and then backward selection was applied. Prevalence odds ratios (crude and adjusted, cPOR and aPOR, respectively) and 95% confidence intervals (CIs) and 2-sided p-values are presented. Variable multi-collinearity was assessed. Repeated visits by STI clients with new complaints were accounted for using the GENMOD procedure.

Bivariate and multivariate factors associated with vaginal pathogens TV, BV and VCA in women were analyzed in analogous fashion with results summarized in text. Demographic, behavioral, medical history, and HIV and RPR serology results were considered for model inclusion. Finally, genital ulcer and RPR results were described by gender, HIV status, and among men, by male circumcision status.

Results
Unless specified in text, p-values are <0.05 for comparisons with details presented in Tables.

Summary of GUI diagnosed in men and women (Table 1)
GeneXpert for NG and CT were provided to men during 1013 visits (974 unique men) between March 2017 and February 2019. Men tested HIV+ during 5% of these visits. Prevalence of NG was 74% and prevalence of CT was 20%, with no differences by HIV status. In the 975 visits with RPR results, TP prevalence was significantly higher among HIV+ (13%) compared with HIV- (5%) men. Nineteen percent of visits were negative for all pathogens, and 17% of visits had more than one infection identified.

GeneXpert for NG and CT were provided to women during 579 visits (569 unique women) between March 2017 and February 2019. Women tested HIV+ during 13% of these visits. Prevalence of NG was 26% and prevalence of CT was 17%, with higher prevalence of NG among HIV+ women. The prevalence of TV (overall 13%) was higher in HIV+ women, whereas the prevalence of VCA (overall 21%) was higher in HIV- women. In the 568 visits with RPR results, TP prevalence was significantly higher among HIV+ (22%) compared with HIV- (6%) women and having multiple pathogens identified was more prevalent among HIV+ (36%) compared with HIV- (24%) women’s visits. Conversely, having no pathogen identified was more prevalent in HIV- (31%) versus HIV+ (18%) women’s visits.

Demographics and factors associated with CT and NG in men (Tables 2 and 3)
Men averaged 30.8 years of age, 77% were single, 64% had at least a secondary education, 55% were employed full time, 22% reported more than one partner in the last 30 days and 57% reported never using condoms in the past three months. The most common symptoms
reported were urethral discharge (89%) and dysuria (80%). Physical findings included urethral discharge in 91% and genital ulcer in 5% of men (Table 2).

Multivariate analyses (Table 3) showed younger age, responding to radio advertisements, <17 days since suspected exposure, and not having dysuria as independent factors associated with CT.

Multivariate analyses (Table 3) showed not having higher education or full-time employment, <17 days since suspected exposure, not reporting a genital ulcer, and urethral discharge on physical exam as independent factors associated with NG.

HIV, RPR serologic results, and circumcision status were not associated with either CT or NG.

Demographics and factors associated with CT and NG in women (Tables 4 and 5)

The mean age women was 28.7, they had 1.3 children and desired 1.4 more on average, 54% were single, 53% had a secondary education or more, 34% had full-time employment, 83% reported < = 1 partner in the last 30 days and 63% reported never using condoms in the past three months. Vaginal discharge was the most common presenting symptom (82%) and endocervical inflammation or discharge was noted on 49% of speculum exams. (Table 4)

Multivariate analyses (Table 5) showed younger age and having symptoms < = 10 days as independent factors associated with CT.
Table 2. Factors associated with CT or NG infection in men in Kigali, Rwanda (N = 1013).

| Demographics                  | Total (N = 1013) | CT-infected (N = 204) | CT-uninfected (N = 809) | p-value | NG-infected (N = 751) | NG-uninfected (N = 262) | p-value |
|-------------------------------|-----------------|-----------------------|------------------------|---------|-----------------------|------------------------|---------|
|                              | n/mean | Col%/SD | n/mean | Row%/SD | n/mean | Row%/SD | n/mean | Row%/SD | n/mean | Row%/SD | n/mean | Row%/SD | n/mean | Row%/SD |
| Age, continuous (years)       | 30.8 7.1         | 29.4 5.6            | 31.1 7.4 | 0.001   | 30.5 7.0         | 31.6 7.3            | 0.029   |
| Referrer                      |                  |                      |                       |         |                      |                       |         |
| Radio Advert                  | 688 68%          | 151 22%             | 537 78% | 0.037   | 488 71%          | 200 29%             | 0.001   |
| Friends/Walk-in/Pharmacy/Contact Partner/Internet | 325 32%          | 53 16%              | 272 84% | 0.011   | 263 81%          | 62 19%              | 0.006   |
| Living and Marital Status     |                  |                      |                       |         |                      |                       |         |
| Married and Cohabitating      | 232 23%          | 33 14%              | 199 86% | 0.011   | 156 67%          | 76 33%              | 0.006   |
| Single or Divorced/Separated/Widow | 781 77% | 171 22% | 610 78% | 0.011 | 595 76% | 186 24% | 0.011 |
| Education Level               |                  |                      |                       |         |                      |                       |         |
| None                          | 25 2%            | 1 4%               | 24 96% | 0.095   | 16 64%           | 9 36%               | 0.001   |
| Primary                       | 339 34%          | 66 19%             | 273 81% | 0.095   | 267 79%          | 72 21%             | 0.001   |
| Secondary                     | 454 45%          | 89 20%             | 365 80% | 0.095   | 343 76%          | 111 24%            | 0.001   |
| Higher                        | 193 19%          | 47 24%             | 146 76% | 0.095   | 123 64%          | 70 36%             | 0.001   |
| Employment Status             |                  |                      |                       |         |                      |                       |         |
| Full-time employment          | 552 55%          | 122 22%            | 430 78% | 0.095   | 392 71%          | 160 29%            | 0.015   |
| Part-time/Student/Jobless      | 459 45%          | 82 18%             | 377 82% | 0.095   | 357 78%          | 102 22%            | 0.015   |
| Sexual behaviors              |                  |                      |                       |         |                      |                       |         |
| Number of partners in last 30 days | 704 78% | 138 20% | 566 80% | 0.422 | 518 74% | 186 26% | 0.051 |
| More than one partner         | 203 22%          | 45 22%             | 158 78% | 0.422   | 163 80%          | 40 20%             | 0.051   |
| Condom use during vaginal sex in the last three months | 27 3%            | 4 15%             | 23 85% | 0.555   | 14 52%           | 13 48%             | 0.015   |
| Sometimes                     | 363 40%          | 69 19%             | 294 81% | 0.555   | 279 77%          | 84 23%             | 0.015   |
| Never                         | 517 57%          | 110 21%            | 407 79% | 0.555   | 387 75%          | 130 25%            | 0.015   |
| Number of days since sexual contact you suspect STI was acquired from |                  |                      |                       |         |                      |                       |         |
| < 8                           | 331 35%          | 83 25%             | 248 75% | 0.010   | 292 88%          | 39 12%             | <0.0001 |
| 9–16                          | 288 31%          | 58 20%             | 230 80% | 0.010   | 235 82%          | 53 18%             | <0.0001 |
| > = 17                        | 323 34%          | 50 15%             | 273 85% | 0.010   | 177 55%          | 146 45%            | <0.0001 |
| Urethral discharge            |                  |                      |                       |         |                      |                       |         |
| Yes                           | 895 89%          | 188 21%            | 707 79% | 0.081   | 717 80%          | 178 20%            | <0.0001 |
| No                            | 114 11%          | 16 14%             | 98 86%  | 0.081   | 32 28%           | 82 72%             | <0.0001 |
| Dysuria                       |                  |                      |                       |         |                      |                       |         |
| Yes                           | 810 80%          | 153 19%            | 657 81% | 0.034   | 599 74%          | 211 26%            | 0.680   |
| No                            | 199 20%          | 51 26%             | 148 74% | 0.034   | 150 75%          | 49 25%             | 0.680   |
| Genital itching               |                  |                      |                       |         |                      |                       |         |
| Yes                           | 67 7%            | 14 21%             | 53 79%  | 0.864   | 39 58%           | 28 42%             | 0.001   |
| No                            | 854 93%          | 171 20%            | 683 80% | 0.864   | 649 76%          | 205 24%            | 0.001   |
| Genital ulcer                 |                  |                      |                       |         |                      |                       |         |
| Yes                           | 41 4%            | 6 15%              | 35 85%  | 0.336   | 13 32%           | 28 68%             | <0.0001 |
| No                            | 878 96%          | 183 21%            | 695 79% | 0.336   | 681 78%          | 197 22%            | <0.0001 |
| Number of days with symptoms  |                  |                      |                       |         |                      |                       |         |
| 1–5                           | 385 41%          | 100 26%            | 285 74% | 0.004   | 332 86%          | 53 14%             | <0.0001 |

(Continued)
Multivariate analyses (Table 5) showed younger age, lower education and lack of full-time employment, sometimes using condoms vs. never, using hormonal contraception vs. other or no contraception, not having a genital ulcer or itching, having symptoms for <10 days, HIV+ status, endocervical discharge noted on speculum exam, BV, and negative VCA as independent factors associated with NG.

Factors associated with of BV, TV and VCA in women (not tabled)

Only reporting >1 partner remained independently associated with BV in multivariate analyses (POR 2.21, p = 0.003). Factors associated with TV in multivariate analyses were being single and RPR+ (aPOR 2.05, p = 0.009 and aPOR 2.37, p = 0.023, respectively). Factors associated with VCA were having <1 partner in the last month (aPOR 4.26, p = 0.005), being pregnant (aPOR 3.05, p = 0.002), always using condoms or not having sex in the last three months vs. never using condoms (aPOR 2.42, p = 0.023), genital itching (aPOR 1.69, p = 0.034), genital discharge (aPOR 2.56, p = 0.011), and being HIV and RPR negative (aPOR 2.93, p = 0.025 and aPOR 4.94, p = 0.031, respectively).

Genital ulcers in men and women (not tabled)

Reported and/or observed genital ulcers were more common among HIV+ (20%) compared with HIV- (5%) men (p<0.001). Genital ulcers were noted during physical examination in

### Table 2. (Continued)

| Demographics | Total (N = 1013) | CT-infected (N = 204) | CT-uninfected (N = 809) | p-value | NG-infected (N = 751) | NG-uninfected (N = 262) | p-value |
|--------------|----------------|----------------------|------------------------|---------|----------------------|------------------------|---------|
| n / mean     | n / mean      | n / mean             | n / mean              |         | n / mean             | n / mean              |         |
| 6–10         | 254 27%       | 40 16%               | 214 84%               | 0.181   | 191 75%             | 63 25%               | 0.981   |
| 11–21        | 192 21%       | 33 17%               | 159 83%               | 0.354   | 43 83%              | 9 17%                | 0.136   |
| >21          | 105 11%       | 17 16%               | 88 84%                | 0.199   | 56 53%              | 49 47%               | <0.0001 |

Laboratory and physical exam

HIV Status

| Positive    | 54 5%          | 7 13%              | 47 87%               | 0.623   | 17 37%              | 29 63%               | <0.0001 |
| Negative    | 958 95%       | 196 20%           | 762 80%              |         | 711 74%           | 247 26%              |         |

RPR Result

| Positive    | 52 5%         | 13 25%           | 39 75%               | 0.196   | 41 82%              | 9 17%                | 0.136   |
| Negative    | 923 95%      | 182 20%          | 741 80%              |         | 677 73%            | 246 27%              |         |

Urethral discharge

| Yes         | 858 91%      | 178 21%          | 680 79%              | 0.058   | 416 79%            | 108 21%              | 0.192   |
| No          | 87 9%       | 13 15%           | 74 85%               |         | 15 17%              | 72 83%               |         |

Genital ulcer

| Yes         | 46 5%        | 8 17%            | 38 83%               | 0.623   | 17 37%              | 29 63%               | <0.0001 |
| No          | 898 95%      | 183 20%          | 715 80%              |         | 686 76%            | 212 24%              |         |

Circumcision status

| Circumcised | 524 67%      | 122 23%          | 402 77%              | 0.058   | 416 79%            | 108 21%              | 0.192   |
| Uncircumcised | 259 33%   | 45 17%           | 214 83%              |         | 195 75%            | 64 25%               |         |

Not significant not shown include: Self-reported symptoms dyspareunia, unpleasant odor, abdominal pain, anal discharge, anal ulcer, anal warts, and sore throat; genital exam results white accumulation, condyloma/warts, inguinal adenopathy >1 cm unilateral and bilateral, inflammation, and testicular mass/tenderness

RPR: Rapid plasma reagin; STI: Sexually transmitted disease; NG: Neisseria gonorrhoeae, CT: Chlamydia trachomatis

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### Table 3. Univariate and multivariate analysis of factors associated with CT or NG infection in men in Kigali, Rwanda (N = 1013).

| Demographics                          | CT infection | NG infection |
|---------------------------------------|--------------|--------------|
|                                       | cPOR  | 95% CI | p-value | aPOR  | 95% CI | p-value | aPOR  | 95% CI | p-value |
| Age (per year increase)               | 0.96  | 0.94  | 0.99   | 0.001 | 0.96  | 0.94  | 0.98   | 0.001 | 0.98  | 0.96  | 1.00 | 0.029 |
| Referrer                              |        |        |        |       |        |        |        |       |        |        |      |      |
| Radio Advert                          | 1.44  | 1.02  | 2.04   | 0.038 | 1.44  | 1.01  | 2.07   | 0.046 | ref   | ---   | ---  | ---  |      |
| Friends/Walk-in/Pharmacy/Contact      | ref   | ref   |        |       | 1.76  | 1.28  | 2.43   | 0.001 |       |       |      |      |
| Partner/Internet                      |        |        |        |       |       |       |        |       |       |       |      |      |
| Living and Marital Status             |        |        |        |       |       |       |        |       |       |       |      |      |
| Married and Cohabiting                | ref   | ref   |        |       |       |       |        |       |       |       |      |      |
| Single or Divorced/Separated/Widow    | 1.69  | 1.13  | 2.54   | 0.011 | 1.56  | 1.14  | 2.15   | 0.006 |       |       |      |      |
| Education Level                       |        |        |        |       |       |       |        |       |       |       |      |      |
| None/Primary/Secondary                | ref   | 1.84  | 1.32   | 2.58  | 0.000 | 1.57  | 3.63   | <0.0001 |       |       |      |      |
| Higher                                | 1.37  | 0.95  | 1.99   | 0.092 | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| Employment Status                     |        |        |        |       |       |       |        |       |       |       |      |      |
| Full-time employment                  | 1.30  | 0.96  | 1.78   | 0.094 | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| Part-time/Student/Jobless             | ref   | 1.45  | 1.09  | 1.92   | 0.011 | 1.51  | 1.05   | 2.17   | 0.028 |       |      |      |
| Sexual behaviors                      |        |        |        |       |       |       |        |       |       |       |      |      |
| Number of partners in last 30 days    |        |        |        |       |       |       |        |       |       |       |      |      |
| None or one partner                   | ref   | ref   |        |       |       |       |        |       |       |       |      |      |
| More than one partner                 | 1.17  | 0.80  | 1.71   | 0.424 | 1.5   | 1.02  | 2.2    | 0.040 |       |       |      |      |
| Condom use during vaginal sex in the last 3 months |       |       |        |       |       |       |        |       |       |       |      |      |
| No partners or always used condoms    | 0.64  | 0.22  | 1.90   | 0.426 | 0.37  | 0.17  | 0.8    | 0.012 |       |       |      |      |
| Sometimes                             | 0.87  | 0.62  | 1.21   | 0.411 | 1.13  | 0.83  | 1.54   | 0.450 |       |       |      |      |
| Never                                 | ref   | ref   |        |       |       |       |        |       |       |       |      |      |
| Number of days since sexual contact you suspect STI was acquired from |       |       |        |       |       |       |        |       |       |       |      |      |
| 0–16                                  | 1.61  | 1.13  | 2.30   | 0.009 | 1.64  | 1.15  | 2.35   | 0.007 | 4.68  | 3.43  | 3.37 | <0.0001 | 3.29  | 2.30  | 4.7   | <0.0001 |
| >= 17                                 | ref   | ref   |        |       | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| Self-reported symptoms                |        |        |        |       |       |       |        |       |       |       |      |      |
| Urethral discharge                    |        |        |        |       |       |       |        |       |       |       |      |      |
| Yes                                   | 1.63  | 0.94  | 2.83   | 0.084 | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| No                                    | ref   | ref   |        |       | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| Dysuria                               |        |        |        |       |       |       |        |       |       |       |      |      |
| Yes                                   | ref   | ref   |        |       | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| No                                    | 1.48  | 1.03  | 2.13   | 0.034 | 1.51  | 1.03  | 2.22   | 0.035 | 1.05  | 0.74  | 1.49 | 0.792 |       |       |      |      |
| Genital itching                       |        |        |        |       |       |       |        |       |       |       |      |      |
| Yes                                   | 1.05  | 0.57  | 1.93   | 0.872 | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| No                                    | ref   | ref   |        |       | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| Genital ulcer                         |        |        |        |       |       |       |        |       |       |       |      |      |
| Yes                                   | ref   | ref   |        |       | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| No                                    | 1.53  | 0.63  | 3.70   | 0.345 | 7.50  | 3.79  | 14.85  | <0.0001 | 4.50  | 2.22  | 9.13 | <0.0001 |       |       |      |      |
| Number of days with symptoms          |        |        |        |       |       |       |        |       |       |       |      |      |
| 1–10                                  | 1.39  | 0.97  | 1.98   | 0.075 | 3.06  | 2.26  | 4.15   | <0.0001 |       |       |      |      |
| > = 11                                | ref   | ref   |        |       | ref   | ---   | ---    | ---    | ref   | ---   | ---  | ---  |      |
| Laboratory and physical exam          |        |        |        |       |       |       |        |       |       |       |      |      |
| HIV Status                            |        |        |        |       |       |       |        |       |       |       |      |      |
| Positive                              | 0.58  | 0.26  | 1.31   | 0.189 | 0.99  | 0.53  | 1.86   | 0.980 |       |       |      |      |

(Continued)
19% of RPR+ and 4% of RPR- men and conversely 20% of men with ulcers were RPR+ compared to 4% of men without ulcers (p < 0.001). Among HIV+ men, none of the seven who were RPR+ had reported and/or observed ulcers while 23% of 43 HIV+ RPR- men had ulcers (p = 0.319). In contrast, among HIV- RPR+ men 21% had reported or observed ulcers compared to only 4% of HIV-RPR- men (p < 0.001). This suggests that ulcers among HIV+ men were more likely herpetic while among HIV- men at least one fifth were syphilitic.

Although HIV- men were more likely to be circumcised than HIV+ men (67% vs. 58%) in our program, this difference was not significant (p = 0.196). Among circumcised men, those who were HIV+ were more likely to have ulcers (13% vs. 4%, p = 0.074) and to be RPR+ (20% vs. 4%, p = 0.003). Among uncircumcised men, those who were HIV+ were also more likely to have ulcers (27% vs. 7%, p = 0.001) while the difference in RPR+ results was not significant (12% vs. 6%, p = 0.324).

Among women, the prevalence of reported or observed ulcers was not significantly different by HIV serostatus (20% in HIV+ vs. 14% p = 0.196). Genital ulcers were noted during physical examination for 28% of RPR+ women compared with 14% of RPR- women (p < 0.001). As with men, the association between RPR results and reported and/or observed ulcers differed in HIV+ and HIV- women: 25% of HIV+RPR+ vs. 20% of HIV+RPR- had ulcers, p = 0.729, compared with 37% of HIV-RPR+ vs. 13% of HIV-RPR- women having ulcers (p = 0.001).

### Discussion

We found a high prevalence of NG and CT among symptomatic men and women in Kigali. Among men, urethral discharge was strongly associated with a diagnosis of NG while dysuria was not associated with either infection. Specific symptoms were less helpful in identifying NG and CT among women. Physical exam findings, demographic variables and reported risk behaviors were independently predictive of NG and/or CT in both men and women, as were vaginal wet mount findings and HIV serologies among women. Among women, TV and BV were associated with sexual risk behaviors but not with symptoms while VCA was associated with vaginal itching and discharge and with low-risk profiles. There were complex inter-

### Table 3. (Continued)

| Demographics | CT infection | NG infection |
|--------------|-------------|--------------|
|              | cPOR | 95% CI | p-value | aPOR | 95% CI | p-value | cPOR | 95% CI | p-value | aPOR | 95% CI | p-value |
| Negative     | ref | ref | ref | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RPR Result   |     |     |     |     |     |     |     |     |     |     |     |     |
| Positive     | 1.30 | 0.68 | 2.52 | 0.429 | 1.65 | 0.82 | 3.3 | 0.158 |     |     |     |     |
| Negative     | ref | ref | ref | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Urethral discharge |     |     |     |     |     |     |     |     |     |     |     |     |
| Yes          | 1.49 | 0.81 | 2.75 | 0.204 | 19.94 | 11.12 | 35.76 | <0.0001 | 16.38 | 7.28 | 36.89 | <0.0001 |
| No           | ref | ref | ref | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Genital ulcer |     |     |     |     |     |     |     |     |     |     |     |     |
| Yes          | 0.82 | 0.38 | 1.80 | 0.626 | ref | --- | --- | --- | ref | --- | --- | --- |
| No           | ref | ref | ref | --- | --- | --- | --- | --- | --- | --- | --- | --- |

aPOR: Adjusted prevalence odds ratio; cPOR: Crude prevalence odds ratio; RPR: Rapid plasma reagin; CI: Confidence interval; STI: Sexually transmitted disease; NG: Neisseria gonorrhoeae, CT: Chlamydia trachomatis

Not significant not shown include: Self-reported symptoms dyspareunia, unpleasant odor, abdominal pain, anal discharge, anal ulcer, anal warts, and sore throat; genital exam results white accumulation, condyloma/warts, inguinal adenopathy >1cm

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| Demographics | Total (N = 579) | CT-infected (N = 98) | CT-uninfected (N = 481) | p-value | NG-infected (N = 152) | NG-uninfected (N = 427) | p-value |
|--------------|----------------|---------------------|------------------------|---------|----------------------|------------------------|---------|
| Age, continuous (years) | | 28.7 7.2 | 25.6 6.1 | 29.3 7.2 | <0.0001 | 26.8 6.3 | 29.4 7.4 | <0.0001 |
| Referrer | | | | | | | | |
| Radio Advert | 284 49% | 37 13% | 247 87% | 0.014 | 67 24% | 217 76% | 0.153 |
| Friends/Walk-in/Pharmacy/Contact Partner/Internet | 295 51% | 61 21% | 234 79% | 0.012 | 85 29% | 210 71% | |
| Living and Marital Status | | | | | | | | |
| Married and Cohabiting | 268 46% | 34 13% | 234 87% | 0.012 | 60 22% | 208 78% | 0.050 |
| Single or Divorced/Separated/Widow | 311 54% | 64 21% | 247 79% | 0.012 | 92 30% | 219 70% | |
| Education Level | | | | | | | | |
| None | 25 4% | 2 8% | 23 92% | 0.513 | 9 36% | 16 64% | 0.001 |
| Primary | 242 42% | 38 16% | 204 84% | 81 33% | 161 67% | |
| Secondary | 246 42% | 46 19% | 200 81% | 54 22% | 192 78% | |
| Higher | 66 11% | 12 18% | 54 82% | 8 12% | 58 88% | |
| Employment Status | | | | | | | | |
| Full-time employment | 199 34% | 30 15% | 169 85% | 0.012 | 39 20% | 160 80% | 0.008 |
| Part-time/Student/Jobless | 379 66% | 68 18% | 311 82% | 113 30% | 266 70% | |
| Sexual behaviors | | | | | | | | |
| Number of partners in last 30 days | | | | | | | | |
| None or one partner | 444 83% | 70 16% | 374 84% | 0.112 | 95 21% | 349 79% | <0.0001 |
| More than one partner | 88 17% | 20 23% | 68 77% | 43 49% | 45 51% | |
| Condom use during vaginal sex in the last 3 months | | | | | | | | |
| No partners or always used condoms | 35 7% | 6 17% | 29 83% | 0.259 | 4 11% | 31 89% | <0.0001 |
| Sometimes | 163 31% | 34 21% | 129 79% | 66 40% | 97 60% | |
| Never | 334 63% | 50 15% | 284 85% | 68 20% | 266 80% | |
| Number of days since sexual contact you suspect STI was acquired from | | | | | | | | |
| <= 8 | 46 9% | 8 17% | 38 83% | 0.066 | 15 33% | 31 67% | 0.003 |
| 9–16 | 78 15% | 20 26% | 58 74% | 31 40% | 47 60% | |
| > = 17 | 409 77% | 61 15% | 348 85% | 92 22% | 317 78% | |
| Number of children under 18, continuous | 1.3 1.3 | 1.0 1.1 | 1.1 1.3 | 1.3 1.3 | 0.026 | 1.2 1.1 | 1.3 1.3 | 0.600 |
| Number of additional children desired, continuous | 1.4 1.1 | 1.6 1.1 | 1.1 1.4 | 1.2 1.0 | 0.040 | 1.3 1.0 | 1.4 1.2 | 0.279 |
| Pregnant | | | | | | | | |
| Yes | 48 8% | 8 17% | 40 83% | 0.947 | 14 23% | 37 77% | 0.569 |
| No | 528 92% | 90 17% | 438 83% | 141 27% | 387 73% | |
| Want more children in next two years | | | | | | | | |
| Yes | 125 23% | 20 16% | 105 84% | 0.666 | 33 27% | 88 73% | 0.821 |
| No | 419 77% | 74 18% | 345 82% | 106 26% | 298 74% | |
| Family planning method among women not pregnant and do not want more children in next two years | | | | | | | | |
| Non-Hormonal Method (IUD/Condom/Tube Ligation/Natural Method) or No Method | 268 66% | 47 18% | 221 82% | 0.498 | 56 21% | 212 79% | 0.001 |
| Hormonal Implant | 50 12% | 9 18% | 41 82% | 24 48% | 26 52% | |
| Injectable | 48 12% | 5 10% | 43 90% | 16 33% | 32 67% | |

(Continued)
| Demographics                              | Total (N = 579) | CT-infected (N = 98) | CT-uninfected (N = 481) | p-value | NG-infected (N = 152) | NG-uninfected (N = 427) | p-value |
|------------------------------------------|-----------------|----------------------|-------------------------|---------|-----------------------|-------------------------|---------|
| **Pills**                                | n /mean         | Col %/SD             | n /mean                 | Row %/SD| n /mean               | Row %/SD               | n /mean | Row %/SD |
| 40                                       | 10%             | 9                    | 23%                     | 31      | 78%                   | 12                      | 30%     | 28       | 70%       |
| **Family planning method and pregnancy composite** |                 |                      |                         |         |                       |                         |         |          |
| Pregnant                                 | 48              | 8%                   | 8                       | 17%     | 40                    | 83%                     | 11      | 23%      | 37        | 77%       | 0.003     |
| Hormonal method (implant, injectable, pills) | 139            | 24%                  | 23                      | 17%     | 116                   | 83%                     | 52      | 37%      | 87        | 63%       |           |
| Non-Hormonal (IUD/Condom/ Tubal Ligation/ Natural Method) or No Method | 388            | 67%                  | 67                      | 17%     | 321                   | 83%                     | 89      | 23%      | 299       | 77%       |           |
| **Self-reported symptoms**               |                 |                      |                         |         |                       |                         |         |          |
| Vaginal discharge                        |                 |                      |                         |         |                       |                         |         |          |
| Yes                                      | 475             | 82%                  | 78                      | 16%     | 397                   | 84%                     | 123     | 26%      | 352       | 74%       | 0.704     |
| No                                       | 101             | 18%                  | 20                      | 20%     | 81                    | 80%                     | 28      | 28%      | 73        | 72%       |           |
| Genital itching                          |                 |                      |                         |         |                       |                         |         |          |
| Yes                                      | 320             | 56%                  | 52                      | 16%     | 268                   | 84%                     | 57      | 18%      | 263       | 82%       | <0.0001   |
| No                                       | 254             | 44%                  | 44                      | 17%     | 210                   | 83%                     | 92      | 36%      | 162       | 64%       |           |
| Dysuria                                  |                 |                      |                         |         |                       |                         |         |          |
| Yes                                      | 266             | 46%                  | 44                      | 17%     | 222                   | 83%                     | 73      | 28%      | 191       | 72%       | 0.306     |
| No                                       | 311             | 54%                  | 54                      | 17%     | 257                   | 83%                     | 76      | 24%      | 235       | 76%       |           |
| Genital ulcer                            |                 |                      |                         |         |                       |                         |         |          |
| Yes                                      | 64              | 11%                  | 9                       | 14%     | 55                    | 86%                     | 9       | 14%      | 55        | 86%       | 0.020     |
| No                                       | 508             | 89%                  | 89                      | 18%     | 419                   | 82%                     | 140     | 28%      | 368       | 72%       |           |
| Number of days with symptoms             |                 |                      |                         |         |                       |                         |         |          |
| 1–5                                      | 72              | 13%                  | 16                      | 22%     | 56                    | 78%                     | 24      | 33%      | 48        | 67%       | 0.003     |
| 6–10                                     | 77              | 14%                  | 17                      | 22%     | 60                    | 78%                     | 27      | 35%      | 50        | 65%       |           |
| 11–21                                    | 131             | 24%                  | 18                      | 14%     | 113                   | 86%                     | 40      | 31%      | 91        | 69%       |           |
| >21                                      | 257             | 48%                  | 37                      | 14%     | 220                   | 86%                     | 48      | 19%      | 209       | 81%       |           |
| **Laboratory and physical exam**         |                 |                      |                         |         |                       |                         |         |          |
| HIV Status                               |                 |                      |                         |         |                       |                         |         |          |
| Positive                                 | 75              | 13%                  | 8                       | 11%     | 67                    | 89%                     | 34      | 45%      | 41        | 55%       | <0.0001   |
| Negative                                 | 504             | 87%                  | 90                      | 18%     | 414                   | 82%                     | 118     | 23%      | 386       | 77%       |           |
| RPR Result                               |                 |                      |                         |         |                       |                         |         |          |
| Positive                                 | 46              | 8%                   | 10                      | 22%     | 36                    | 78%                     | 401     | 46%      | 25        | 54%       | 0.002     |
| Negative                                 | 522             | 92%                  | 88                      | 17%     | 434                   | 83%                     | 128     | 25%      | 394       | 75%       |           |
| Trichomonas                              |                 |                      |                         |         |                       |                         |         |          |
| Positive                                 | 72              | 13%                  | 18                      | 25%     | 54                    | 75%                     | 18      | 25%      | 54        | 75%       | 0.818     |
| Negative                                 | 491             | 87%                  | 75                      | 15%     | 416                   | 85%                     | 129     | 26%      | 362       | 74%       |           |
| Candida                                  |                 |                      |                         |         |                       |                         |         |          |
| Positive                                 | 118             | 21%                  | 12                      | 10%     | 106                   | 90%                     | 0.035   | 13%      | 110       | 89%       | <0.0001   |
| Negative                                 | 437             | 79%                  | 80                      | 18%     | 357                   | 82%                     | 132     | 30%      | 305       | 70%       |           |
| Bacterial vaginosis                      |                 |                      |                         |         |                       |                         |         |          |
| Positive                                 | 113             | 21%                  | 25                      | 22%     | 88                    | 78%                     | 0.062   | 47        | 42%       | 66        | 58%       | <0.0001   |
| Negative                                 | 438             | 79%                  | 65                      | 15%     | 373                   | 85%                     | 96      | 22%      | 342       | 78%       |           |
| Vaginal Inflammation or Discharge        |                 |                      |                         |         |                       |                         |         |          |
| Yes                                      | 469             | 87%                  | 75                      | 16%     | 394                   | 84%                     | 0.232   | 116       | 25%       | 353       | 75%       | 0.076     |
| No                                       | 69              | 13%                  | 15                      | 22%     | 54                    | 78%                     | 24      | 35%      | 45        | 65%       |           |
| Endocervical Inflammation or Discharge    |                 |                      |                         |         |                       |                         |         |          |

(Continued)
relationships between HIV and RPR serologies and genital ulcers, and these were further influenced by circumcision status among men. These findings exemplify the locally relevant data that can inform approaches to diagnosis and treatment in Rwanda as called for by WHO. Our models had good discrimination and use of these data may offer improvement over the current algorithm recommended by the Rwandan National Guidelines.

As in other studies, syndromic management may perform better among men compared to women due to the ease of detecting abnormalities on external genitalia and the high likelihood of NG among men reporting urethral discharge [44]. Surprisingly, dysuria was as common as discharge in men but contrary to conventional wisdom we did not find an association between dysuria and NG or CT [45].

The most common presenting symptom among women was vaginal discharge which was only associated with VCA and not with NG, CT, BV or TV. Genital itching was reported by over half of patients and was also predictive of VCA. Itching was also useful in pointing away from NG, as was reported ulcer. Gynecologic exam, specifically endocervical discharge, was helpful in the diagnosis of NG. Interestingly, wet mount results were predictive NG (BV+, VCA-), suggesting that these inexpensive and simple tests should be included in any workup of symptomatic women. Despite extensive laboratory testing, we failed to find an etiology for a substantial proportion of women seeking care. This may reflect poor sensitivity of microscopy as well as non-infectious causes of symptoms. As has been noted elsewhere, factors associated with NG were more useful in predicting infections than those for CT [46, 47].

For both men and women, younger age was predictive of both NG and CT and lower education level and jobless or part-time employment status were predictive of NG. Interestingly, number of partners was not independently associated with CT or NG. Most men and women reported never using condoms and very few reported always using condoms. Women who sometimes used condoms were at higher risk of NG than those who never used them. This may be due to increased condom use in women with higher risk partners.

Genital ulcers were not a common presenting symptom and were not associated with RPR results among HIV+ patients. RPR provided a diagnosis for 20% of ulcers among HIV- men and 15% among HIV- women. As others in Africa have reported, HSV is the most likely diagnosis for RPR- ulcers which was more common among HIV+ patients [48]. Non-circumcision among men is associated with HIV acquisition and with increased prevalence and incidence of ulcerative STI [49–52]. We have previously shown a relationship between ulcers, smegma and HIV acquisition in uncircumcised men [15]. Among HIV- men, those who were uncircumcised were not more likely to report ulcers or to be RPR+ than their circumcised counterparts.
Table 5. Univariate and multivariate analysis of factors associated with CT or NG infection in women in Kigali, Rwanda (N = 579).

| Demographics | CT infection | | NG infection | |
|--------------|--------------|------------------|------------------|------------------|
|              | cPOR | 95% CI | p-value | aPOR | 95% CI | p-value | cPOR | 95% CI | p-value | aPOR | 95% CI | p-value |
| Age (per year increase) | 0.91 | 0.88 | 0.95 | <0.0001 | 0.90 | 0.86 | 0.94 | <0.0001 | 0.95 | 0.92 | 0.97 | <.001 | 0.93 | 0.89 | 0.97 | <0.001 |
| Referrer | | | | | | | | | | | | |
| Radio Advert | ref | | | | | | | | | | | |
| Friends/Walk-in/Pharmacy/Contact Partner/Internet | 1.74 | 1.11 | 2.72 | 0.015 | 1.31 | 0.91 | 1.90 | 0.150 | | | | |
| Living and Marital Status | | | | | | | | | | | | |
| Married and Cohabitating | ref | | | | | | | | | | | |
| Other | 1.78 | 1.13 | 2.80 | 0.012 | 1.46 | 1.00 | 2.13 | 0.048 | | | | |
| Education Level | | | | | | | | | | | | |
| None/Primary | ref | | | | | | | | | | | |
| Secondary/Higher | 1.30 | 0.83 | 2.01 | 0.248 | ref | | | ref | | | |
| Employment Status | | | | | | | | | | | | |
| Full-time employment | ref | | | | | | | | | | | |
| Part-time/Student/Jobless | 1.23 | 0.77 | 1.96 | 0.383 | 1.76 | 1.16 | 2.66 | 0.008 | 1.95 | 1.12 | 3.39 | 0.019 | | | |
| Sexual behaviors | | | | | | | | | | | | |
| Number of partners in last 30 days | | | | | | | | | | | | |
| None or one partner | ref | | | | | | | | | | | |
| More than one partner | 1.56 | 0.89 | 2.75 | 0.119 | 3.53 | 2.19 | 5.69 | <0.0001 | | | | |
| Condom use during vaginal sex in the last 3 months | | | | | | | | | | | | |
| No partners or always used condoms | 1.17 | 0.46 | 2.97 | 0.741 | 0.48 | 0.15 | 1.50 | 0.207 | 0.74 | 0.22 | 2.41 | 0.611 | | | |
| Sometimes | 1.49 | 0.92 | 2.42 | 0.107 | 2.75 | 1.81 | 4.18 | <0.0001 | 1.79 | 1.07 | 2.98 | 0.025 | | | |
| Never | ref | | | | | | | | | | | |
| Number of days since sexual contact you suspect STI was acquired from | | | | | | | | | | | | |
| 0–8 | 1.20 | 0.53 | 2.69 | 0.666 | 1.66 | 0.87 | 3.16 | 0.126 | | | | |
| 9–16 | 1.96 | 1.1 | 3.49 | 0.022 | 2.29 | 1.36 | 3.87 | 0.002 | | | | |
| > = 17 | ref | | | | | | | | | | | |
| Number of children under 18 (per child increase) | 0.82 | 0.69 | 0.99 | 0.037 | 0.96 | 0.84 | 1.10 | 0.594 | | | | |
| Number of additional children desired per child increase | 1.22 | 1.02 | 1.45 | 0.027 | 0.92 | 0.79 | 1.07 | 0.274 | | | | |
| Family planning method and pregnancy composite | | | | | | | | | | | | |
| Pregnant | 0.96 | 0.43 | 2.14 | 0.915 | 1.00 | 0.49 | 2.03 | 0.999 | 1.30 | 0.57 | 2.99 | 0.532 | | | |
| Hormonal method (implant, injectable, pills) | 0.95 | 0.56 | 1.59 | 0.837 | 2.01 | 1.32 | 3.05 | 0.001 | 1.73 | 1.02 | 2.94 | 0.040 | | | |
| Non-Hormonal (IUD/Condom/Tubal Ligation/Natural Method) or No Method | ref | | | | | | | | | | | |
| Self-reported symptoms | | | | | | | | | | | | |
| Vaginal discharge | | | | | | | | | | | | |
| Yes | ref | | | | | | | | | | | |
| No | 1.26 | 0.73 | 2.18 | 0.408 | 1.10 | 0.68 | 1.78 | 0.692 | | | | |
| Genital itching | | | | | | | | | | | | |
| Yes | ref | | | | | | | | | | | |
| No | 1.08 | 0.69 | 1.68 | 0.738 | 2.62 | 1.79 | 3.84 | <0.0001 | 2.54 | 1.55 | 4.17 | 0.0002 | | | |

(Continued)
In contrast, among HIV+ men, those who were uncircumcised were more likely to have an ulcer and less likely to be RPR+ than circumcised men. Circumcision is widely promoted in Rwanda and available at no cost in most government health centers as part of HIV prevention services. Though the focus is on protecting HIV- men, our results here suggest that circumcision can benefit HIV+ men by reducing ulcer incidence [53].

It is likely that we missed other less common ulcer etiologies including HD, lymphogranuloma venereum (LGV), and granuloma inguinale (Klebsiella granulomatis) [54]. Our clinicians did suspect chancroid in a few cases, but the service program did not record detailed descriptions or photographs of ulcers and we lacked laboratory diagnostics. The most recent

| Table 5. | CT infection | NG infection |
|----------|--------------|--------------|
|          | cPOR         | 95% CI       | p-value | aPOR | 95% CI | p-value | aPOR | 95% CI | p-value |
| Yes      | ref          |              |         |      |        |         |      |        |         |
| No       | 1.06         | 0.68         | 1.64    | 0.796| 1.21   | 0.84    | 1.75  | 0.303  |
| Genital ulcer |             |              |         |      |        |         |      |        |         |
| Yes      | ref          |              |         |      |        |         |      |        |         |
| No       | 1.30         | 0.62         | 2.73    | 0.489| 2.33   | 1.12    | 4.84  | 0.024  | 2.52    | 1.09    | 5.80    | 0.030  |
| Number of days with symptoms |            |              |         |      |        |         |      |        |         |
| 1–10     | 1.72         | 1.06         | 2.78    | 0.027| 1.76   | 1.07    | 2.88  | 0.026  | 1.76   | 1.16    | 2.68    | 0.008  | 1.78   | 1.05    | 3.00    | 0.032  |
| 11 or more | ref          |              |         |      |        |         |      |        |         |
|          | ref          |              |         |      |        |         |      |        |         |
| Laboratory and physical exam |            |              |         |      |        |         |      |        |         |
| HIV Status |             |              |         |      |        |         |      |        |         |
| Positive | ref          |              |         |      |        |         |      |        |         |
| Negative | 1.83         | 0.85         | 3.96    | 0.124| 2.73   | 1.66    | 4.47  | <0.0001| 2.05   | 1.10    | 3.83    | 0.024  |
| RPR Result |             |              |         |      |        |         |      |        |         |
| Positive | 1.37         | 0.66         | 2.88    | 0.401| 2.58   | 1.41    | 4.7   | 0.002  |
| Negative | ref          |              |         |      |        |         |      |        |         |
| Trichomonas |            |              |         |      |        |         |      |        |         |
| Positive | 1.85         | 1.03         | 3.32    | 0.041| ref    |         |      |        |         |
| Negative | ref          |              |         |      |        |         |      |        |         |
| Candida |             |              |         |      |        |         |      |        |         |
| Positive | ref          |              |         |      |        |         |      |        |         |
| Negative | 1.98         | 1.04         | 3.77    | 0.038| 3.56   | 1.89    | 6.69  | <0.0001| 2.20   | 1.11    | 4.36    | 0.024  |
| Bacterial vaginosis |            |              |         |      |        |         |      |        |         |
| Positive | 1.63         | 0.98         | 2.72    | 0.063| 2.63   | 1.67    | 4.15  | <0.0001| 1.89   | 1.07    | 3.34    | 0.028  |
| Negative | ref          |              |         |      |        |         |      |        |         |
| Vaginal Inflammation OR Discharge |             |              |         |      |        |         |      |        |         |
| Yes      | ref          |              |         |      |        |         |      |        |         |
| No       | 1.47         | 0.79         | 2.75    | 0.2201| 1.67   | 0.97    | 2.86  | 0.063  |
| Endocervical Inflammation or Discharge |             |              |         |      |        |         |      |        |         |
| Yes      | 1.83         | 1.15         | 2.91    | 0.010| 2.17   | 1.46    | 3.23  | 0.000  | 1.80   | 1.11    | 2.93    | 0.018  |
| No       | ref          |              |         |      |        |         |      |        |         |
| Genital Ulcer |             |              |         |      |        |         |      |        |         |
| Yes      | 1.19         | 0.56         | 2.56    | 0.649| ref    |         |      |        |         |
| No       | ref          |              |         |      |        |         |      |        |         |

IUD: intrauterine device; aPOR: Adjusted prevalence odds ratio; cPOR: Crude prevalence odds ratio; RPR: Rapid plasma reagin; CI: Confidence interval; STI: Sexually transmitted disease; NG: Neisseria gonorrhoeae, CT: Chlamydia trachomatis

https://doi.org/10.1371/journal.pone.0250044.t005
publication presenting confirmed chancroid diagnoses in Rwanda was based on data collected in 1992, which found 27% of ulcers in men and 20% in women had culture-confirmed HD [55–59]. For many years the prevalence of HD had been decreasing in much of Africa [48, 54], but recent publications indicate HD may be staging a comeback [21]. More investigations are needed in Rwanda.

Physical exam findings made important contributions in our program. Examination of male genitalia does not require specialized equipment, but speculum exam requires a skilled clinician, a gynecologic exam table and light which are in limited supply in low resource settings. While genital exams would not be feasible for all symptomatic patients, targeted genital exams in specific circumstances would be feasible and potentially very useful. Distinguishing between vaginal and endocervical discharges would greatly improve diagnostic accuracy and bi-manual exam would identify pelvic inflammatory disease. Similarly, in our setting where less than one in five ulcer patients are RPR+, assessing ulcer characteristics may be worthwhile. Visual exam has traditionally been viewed as unreliable as many ulcers do not have a paradigmatic presentation (e.g. painless ‘clean’ TP ulcer, painful ‘dirty’ HD with inguinal adenopathy, multiple chronic or recurrent shallow vesicular HSV lesions). However, a recent study in Jamaica compared clinical diagnosis with M-PCR and found visual diagnoses of TP, HSV, and HD were 67.7%, 53.8%, and 75% sensitive and 91.2%, 83.6%, and 75.4% specific, respectively [60].

The advent of point-of-care diagnostics for NG and CT has transformed STI diagnosis, but given relatively expensive equipment and reagents, this remains out of reach in many low resource settings. We have used pooling to reduce the per-patient cost in Zambia and this could be explored in other settings [61]. GeneXpert kits are also available for TV and they are more sensitive than microscopy. The US CDC has in-house multiplex PCR (M-PCR) for ulcer etiologies including syphilis, HSV and chancroid. A focused study would provide prevalence information that could inform the next update of national guidelines.

Our program has several limitations. Social desirability bias may have led to under-reporting of risky sexual behaviors. We focused on symptomatic men and women and thus missed the many people who are asymptotically infected [62, 63]. We did not screen for active viral hepatitis as recent unpublished surveys have shown a low prevalence of both hepatitis B and C (4% and 3%, respectively reported nationally, 4% and 5% among female sex workers tested in our laboratory). We did not have funding or resources to perform any direct method of detection for TP using ulcer material, and thus may have misclassified some recently infected people who were negative by RPR test. While we did treat TV in male partners referred by TV + women, we did not systematically test for TV in men. Microscopy for TV detection in men is extremely insensitive, and we did not have resources to conduct GeneXpert testing for TV. TV could therefore be the reason for a portion of the symptomatic men with unknown etiology. We did not include HSV serologies because adult seroprevalence is high [64]. Assessment of cervical intraepithelial neoplasia requires more resources than would be achievable on a large scale in Rwandan health centers so we did not address this important problem. Fortunately, 93% of Rwandan girls now receive the human papillomavirus vaccine and future generations will be protected [65]. Lastly, we and others have published an association between female genital schistosomiasis and HIV [66, 67], but this is most commonly seen with S.Haematobium while only S.Mansoni is endemic in Rwanda, thus we did not screen for genital schistosomiasis [68].

Conclusions
Syndromic management guidelines in Rwanda can be improved with consideration of the prevalence of confirmed infections from this program offering services to symptomatic men
and women representative of those who would seek care at government health centers. Our findings indicate that syndromic management performs better among men but is poor among women. Inclusion of demographic and risk factor measures shown to be predictive of STI and non-STI dysbioses may also increase diagnostic accuracy. In symptomatic women, wet mount results for BV and VCA may help diagnose NG and are inexpensive and could be offered for management of women. Targeted genital exams for women in specific circumstances (e.g., in women without genital itching) may also be useful to diagnose NG. More data is needed on how often local prevalence and epidemiology should be reassessed to maintain improved syndromic management.

Supporting information
S1 Fig. STI baseline clinical form.

(DoCX)

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