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Serological Markers for Syphilis Among Persons Presenting With Syndromes Associated With Sexually Transmitted Infections: Results From the Zimbabwe STI Etiology Study

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Abstract

Background: Syphilis prevalence in sub-Saharan Africa appears to be stable or declining but is still the highest globally. Ongoing sentinel surveillance in high-risk populations is necessary to inform management and detect changes in syphilis trends. We assessed serological syphilis markers among persons with sexually transmitted infections in Zimbabwe.

Methods: We studied a predominantly urban, regionally diverse group of women and men presenting with genital ulcer disease (GUD), women with vaginal discharge and men with urethral

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discharge at clinics in Zimbabwe. Syphilis tests included rapid plasma reagin and the *Treponema pallidum* hemagglutination assay.

Results: Among 436 evaluable study participants, 36 (8.3%) tested positive for both rapid plasma reagin and *Treponema pallidum* hemagglutination assay: women with GUD: 19.2%, men with GUD: 12.6%, women with vaginal discharge: 5.7% and men with urethral discharge: 1.5% ($P < 0.0001$).

Conclusions: Syphilis rates in Zimbabwe are high in sentinel populations, especially men and women with GUD.

Syphilis continues to be a major global public health problem. According to the World Health Organization syphilis prevalence and incidence rates are highest in the Africa region. Of the estimated 5.6 million incident syphilis cases that occurred worldwide in 2012, 32% were in Sub-Saharan Africa.[1] In that same year, an estimated 930,000 maternal syphilis infections caused 350,000 adverse pregnancy outcomes, including 143,000 early fetal deaths and stillbirths, 62,000 neonatal deaths, 44,000 preterm or low weight births, and 102,000 infected infants worldwide.[2] However, contemporary studies suggest that syphilis prevalence may be declining in southern Africa.

In Zimbabwe, a recent modeling study based on antenatal surveys and annual program data estimated that national syphilis prevalence among men and women declined from 1.9% in 2000 to 1.5% in 2016, although this decrease was not statistically signficant.[3] A household-based national survey conducted in Zimbabwe in 2015 to 2016 estimated the prevalence of active syphilis at 0.8%, whereas 2.7% had ever experienced infection.[4] Despite the possible decline in prevalence, these rates are 10 times higher than the global average[1] and also do not necessarily represent trends in high-risk populations, including persons presenting with sexually transmitted infection (STI)-related syndromes.

Studies from sentinel sites frequented by populations at high risk for STIs are important to inform epidemiologic trends. Thus, in a recent study conducted in six STI clinics in Zimbabwe, we found that 16% of genital ulcer disease (GUD) presentations among men and women was caused by *Treponema pallidum*, as evidenced through use of a multiplex polymerase chain reaction (m-PCR) assay of lesion specimens.[5] These rates were similar to those from a recently completed study in neighboring Zambia,[6] but substantially higher than rates from studies conducted more than 10 years ago in comparable populations in Botswana (5.1%),[7] Malawi (6%),[8] Mozambique (0%),[9] and South Africa (4.9%).[10] Furthermore, in our study, an additional 8% of GUD patients had negative m-PCR results, but both positive *T. pallidum* hemagglutination assay (TPHA) and positive rapid plasma reagin (RPR) test results, suggesting that up to 24% of GUD cases may have been associated with *T. pallidum* infection.[5]

The primary objective of this study was to further evaluate syphilis prevalence among persons presenting with STIs in Zimbabwe by assessing syphilis serological markers among all patients included in our study, thus including men presenting with urethral discharge and women presenting with vaginal discharge.

METHODS

The Zimbabwe STI Etiology Study was conducted in six primarily urban, regionally diverse STI clinics in Zimbabwe in 2014 to 2015. The study involved the enrollment of 600 participants; 200 women presenting with vaginal discharge, 200 men with urethral discharge, and 100 women and 100 men presenting with GUD. Based on statistical considerations detailed in the study protocol available online[11] and the limited resources available to the study, we felt that these sample sizes would strike an acceptable balance between available study resources and the need for precision.

Study methods are detailed in the study protocol and an article describing the study design, methods and population, both available online.[11,12] In addition, study outcome data have recently been published, including the etiology of GUD,[5] the etiologies of male urethral discharge[13] and vaginal discharge in women,[14] and a manuscript detailing the prevalence of human immunodeficiency virus (HIV) infection in this population.[15]

Although syphilis results among patients presenting with GUD in this study have been reported previously[5] we have included some of these data in this article to allow for comparisons with the other diagnostic groups.

The following methodological details are pertinent to this study.

Participant Recruitment and Specimen Collection

A team of three nurses was trained in study procedures and deployed sequentially for a period of 10 to 17 weeks to each of the six study sites, starting in two Harare clinics (Mbare and Budiriro), then moving to two clinics in Bulawayo (Khami Road and Nkulumane) and finally to clinics in Beitbridge (Dulibadzimu) and Gutu (Gutu Rural Hospital). These clinics were selected based on regional diversity and high rates of reported STI syndromes, including vaginal discharge in women, urethral discharge in men and GUD in women and men. The start of enrollment at each site was preceded by at least two site visits involving the study leadership of the team lead, the lead consultant, and senior officials representing the Zimbabwe Ministry of Health and Child Care.

Consecutive patients presenting with urethral discharge (men), vaginal discharge (women) and GUD (women and men) were enrolled in the study after obtaining informed consent. A paper-copy questionnaire was administered and completed by the study nurse. Information captured included demographic information, sexual history covering the previous 3 months (number of sex partners, condom use, sex work and sex with a sex worker) description of symptoms, history of STI/HIV, and current use of antimicrobials. GUD patients had swab specimens taken from the ulcer bases. Vaginal swabs for women and urine samples for men were obtained for chlamydia and gonorrhea testing. Blood specimens were collected from patients for syphilis serology and HIV testing. A separate consent for HIV testing was obtained. Declining a blood draw was not a reason for exclusion from the study. HIV results for this study have been published elsewhere.[15]

Patients who reported to have taken antimicrobial medication in the past 4 weeks, who were unable to provide consent, or who had been enrolled in the study previously were not eligible for study enrollment.

All patients were treated for their presenting STI syndrome according to the 2013 Zimbabwe STI syndromic management guidelines (see Box).[16]

Laboratory Procedures

All specimens were kept refrigerated after collection and shipped in a cooler box with cooling packs by overnight courier to the study laboratory at Wilkins Hospital in Harare, where they were kept refrigerated until further processing. All syphilis tests were conducted at the study laboratory. Syphilis serology included both treponemal and nontreponemal tests, TPHA and RPR, respectively (both SPINREACT, Girona, Spain). The RPR-positive samples were subsequently titrated up to 1:32 dilution for quantitative analysis.

All tests were performed according to test package inserts.

Ulcer samples were stored at −70°C and batched for shipment to the STI reference laboratory at the Centre for HIV and STIs of the National Institute of Communicable Diseases in Johannesburg, South Africa. Using m-PCR on a RotorGene platform(Corbett Research, Sydney Australia), samples were tested for the presence of *Treponema pallidum, Haemophilus ducreyi*, herpes simplex virus, and *Chlamydia trachomatis* strains associated with lymphogranuloma venereum.

We defined potentially “active” syphilis as reactivity on both treponemal (TPHA) and nontreponemal (RPR) tests with titers of 1:8 or greater, or an m-PCR test positive for *T. pallidum* regardless of serological test results among patients with GUD.

Vaginal and urine samples were shipped to two local laboratories and tested for *N. gonorrhoeae* and *C. trachomatis* by nucleic acid amplification testing using Becton Dickenson ProbeTec (BD Molecular Diagnostics, Franklin Lakes, NJ) at the University of Zimbabwe/ University of California San Francisco laboratory in the Obstetrics and Gynecology Department of the University of Zimbabwe School of Medicine and using GeneXpert (Cepheid, Sunnyvale, CA) at the Flowcytometry Laboratory in Harare. All testings were done according to test package inserts under standard operating procedures. All urine and vaginal specimens were tested on both platforms with greater than 95% concordance of test results.[17] For the purposes of this study, we considered a chlamydia or gonorrhea test result to be positive when it was positive on either platform.

Human immunodeficiency virus testing followed the algorithm promoted by the Zimbabwe Ministry of Health and Child Care and routinely employed nationwide: an initial test by First Response HIV1–2-O (Premier Medical Corporation, Daman, India); if positive, a confirmatory Alere Determine HIV1/2 test (Alere Inc. Waltham, MA); and, in case of discrepancy between these results, an INSTI HIV1/HIV2 test (bioLytical Laboratories Inc. Richmond, BC, Canada) as tie breaker.

More detail on laboratory procedures can be found in the online supplement.[12]

Data Management and Statistical Methods

After completion of the visit, questionnaire data were reviewed by the lead study nurse and then transcribed into a computer-based data system on handheld devices. Data were uploaded daily from study sites to an online secure central database.

Data were analyzed using SAS software (Cary, NC). Tests for statistical significance included the χ^2 test for categorical variables and Student *t* test for continuous variables with *P* values of 0.05 or less, indicating statistical significance.

Given the purposive and selective rather than random nature of sampling in our study, the provision of 95% confidence intervals would convey a level of precision to the study data that is not supported by the study methods, and we have therefore omitted them from the results.

Institutional Review

The protocol, including consent forms and questionnaires, was reviewed and approved by the Joint Research and Ethics Committee of Parirenyatwa Central Hospital, the Zimbabwe Medical Research Council and the US Centers for Disease Control and Prevention.

RESULTS

Of the 600women andmen enrolled in the study,494 (82.3%) agreed to submit a blood sample for syphilis testing. Women and men with GUD were more likely to submit blood samples for testing (90.5%) than women and men with vaginal and urethral discharge respectively (78.3%, $P < 0.001$) and participants recruited at the Dulibadzimu (66.7%) and Budiriro (80.0%) sites were less likely to submit a sample than other clinics ($P < 0.0001$).

Samples of 436 participants were successfully tested by both TPHA and RPR, including 138 women with vaginal discharge, 133 men with urethral discharge, and 78 women and 87 men with GUD, respectively. The remainder of the report is limited to this group.

Treponemal and Nontreponemal Test Results

TPHA and RPR results are summarized in Table 1. Thirtysix (8.3%) patients tested positive on both tests. In addition, 35 (8.0%) were positive on TPHA and negative on RPR, whereas 14 (3.2%) were positive on RPR, but negative on TPHA. Both tests were negative for 351 (80.5%) patients. Among patients with combined TPHA/RPR-positive results, 29 (80.6%) of 36 patients had RPR titers of 1:8 or greater.

Women and men with GUD had the highest prevalence of dual positive results (respectively, 19.2% and 12.6%, *P*=NS). Combined, men and women with GUD had significantly higher dual TPHA/RPR positivity than the combination of men with urethral discharge and women with vaginal discharge (15.8% vs. 3.7%, $P < 0.0001$). Women with vaginal discharge had higher combined positivity than men with urethral discharge (5.7% vs. 1.5%, $P = 0.06$, Table 1).

We did not find any associations between combined TPHA/ RPR positivity and demographic (gender, ethnicity, age) or behavioral risk factors, including number of sex partners, being or having sex with a sex worker, or condom use (data not shown). In addition, the prevalence of combined TPHA/RPR positivity was similar among those with (17 [10.8%] of 158) or without (19 [6.8%] of 278) gonorrhea ($P = 0.1$) and with (6 [6.9%] of 87) or without (30 [8.6%] of 349) chlamydia infections ($P = 0.6$). However, persons testing positive for HIV had a higher TPHA/RPR positivity prevalence (23 [12.7%] of 181) than those testing negative for HIV (13 [5.2%] of 250, $P < 0.01$).

Among the women and men with GUD, 27 (16.4%) of 165 had an m-PCR result positive for *T. pallidum*. Of these 15 (55.6%) tested positive for both TPHA and RPR, and all of these had an RPR titer of 1:8 or greater. In addition, 6 (22.2%), tested positive for TPHA but negative for RPR, and 4 (14.8%) tested positive for RPR but negative for TPHA (all ≥1:8), whereas another 2 (7.4%) tested negative for both. Among 138 persons with GUD testing negative for *T. pallidum* on m-PCR, TPHA was positive for 21 (15.2%) and a combined TPHA/RPR positivity was higher (8.0%)in this group compared with women with vaginal discharge or men with urethral discharge (3.7%, $P < 0.06$).

Five of 8 patients with a history of syphilis had a positive TPHA, of which two also had a positive RPR. Conversely, among patients with both positive TPHA and RPR, only 2 of 36 had a history of syphilis of which one had an RPR titer of 1:8 or greater. No records were available to verify previous syphilis history.

DISCUSSION

In our study of 436 patients presenting with various STI syndromes to six, primarily urban, STI clinics in Zimbabwe, we found evidence of current or past syphilis among 77 (17.7%), including 36 with TPHA/RPR dual positivity, 35 positive on TPHA and negative on RPR, and 6 with evidence of syphilis by m-PCR who were TPHA negative.

As expected, men and women with GUD had the highest syphilis prevalence with 48 (29.1%) of 165 showing evidence of the infection, including 27 with primary syphilis diagnosed by PCR and 21 negative on PCR, but positive on TPHA. In our view, these findings support the continued use of syndromic management for patients with GUD in Zimbabwe (see Box), in the absence of more widespread syphilis testing.

The combined TPHA and RPR positivity rates among women with vaginal discharge (5.7%) and men with urethral discharge (1.5%) may not warrant a change in the syndromic management of men and women with genital discharge syndromes to treat them presumptively for syphilis. Moreover, the antimicrobial components of syndromic management for these conditions may have some effect on (incubating) syphilis. However, these rates are high enough to continue to emphasize syphilis testing in these populations, especially among women given potential risk for pregnancy and vertical transmission.

In the presence of a positive treponemal test, RPR titers of ≥1:8 are often considered to be indicative of active, recently acquired syphilis, where lower titers or negative nontreponemal test results are thought to represent longer standing or treated infections.[18] However, as our

data show, such a distinction is arbitrary and of dubious clinical benefit, especially among patients with GUD. Of patients with PCR-proven (primary) syphilis, only 15 (55.6%) of 27 had RPR titers ≥1:8 in addition to a positive TPHA. By contrast, among 21 TPHA positive GUD patients with low-titer or negative RPR, six (28.6%) had PCR-proven primary syphilis (all RPR negative) and only two gave a history of syphilis.

A positive RPR in the absence of a positive TPHA or other treponemal test is typically interpreted as a biological false positive result. However, 4 (14.8%) of 27 patients with PCR-proven primary syphilis had RPR titers ≥1:8 but negative TPHA.

Thus, assessment of infection on the basis of serological interpretation is problematic and any person with positive treponemal and nontreponemal test results, regardless of titer, should be subject to careful history taking, clinical assessment and further diagnostic testing to determine syphilis stage and treatment duration.[19]

The most important limitation of this study is that it was based on a purposive sample of clinics in three urban regions in Zimbabwe and the results cannot be generalized to other regions inside and outside the country.

In addition, test performance may have been a limiting factor. In our study, tests were conducted by an experienced laboratorian who over the years had been the laboratory lead for a number of HIV prevention studies that involved collection and testing of a variety of STI tests, including RPR and TPHA testing. Nonetheless, possible laboratory errors cannot be ruled out, especially for tests that require subjective interpretation from a laboratorian. In a recent study, for example, Hamill et al. reported considerable variability in the interpretation of RPR results among four laboratories in Uganda.[20]

Traditional syphilis testing based on RPR screening followed by TPHA or other treponemal test confirmation has important limitations beyond potentially missed infections, especially loss to follow-up and treatment. In recent years, rapid point of care treponemal tests have become increasingly available in sub-Saharan Africa,[21] and, despite some performance limitations can potentially reduce the time from diagnosis to treatment.[22]

Whether the high rates of positive syphilis tests, especially among men and women with GUD in our study represent an increase in syphilis rates in Zimbabwe is unclear. The previously cited[3] study by Korenromp et al. suggests a decreasing incidence of syphilis in Zimbabwe and other studies have shown similar stable or decreasing rates in Zimbabwe[4] and other parts of southern Africa.[23] However, these estimates largely rely on studies among pregnant women accessing antenatal care or population-based studies that have been performed several years ago, and may lag increases in sentinel populations like those recruited in our study. In the United States, for example, increasing syphilis rates among men who have sex with men were reported for selected, high-risk populations over 15 years ago,[24,25] but the general population effects, including increases among heterosexual men and women and subsequent rises in congenital syphilis cases were only recently realized.[26]

With these considerations in mind, the prevalence of TPHA and RPR positivity among the three sentinel populations in this study warrants ongoing vigilance to the potential of a

syphilis resurgence in Zimbabwe and other sub-Saharan countries and supports efforts to continue strengthening programs for syphilis surveillance, prevention and clinical management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STI Syndromic Management in Zimbabwe (as used in this study)

Women with Vaginal Discharge

Kanamycin 2 g intramuscularly single dose – plus:

Doxycycline 100 mg orally twice daily for 7 days – plus:

Metronidazole 500 mg orally three times daily for 7 days

Men with Urethral Discharge

Kanamycin 2 g intramuscularly single dose – plus:

Doxycycline 100 mg orally twice daily for 7 days

Women and Men with GUD

Benzathine Penicillin G 2.4 Million Units intramuscularly single dose – plus:

Erythromycin 500 mg orally four times a day for 7 days – plus:

Acyclovir 200 mg orally five times a day for 7 days.

TABLE 1.

Treponemal and Nontreponemal Test Results

	GUD-F (%)	GUD-M (%)	Discharge-F (%)	Discharge-M (%)	Total (%)
TPHA+/RPR ≥ 1:8	12 (15.4)	9 (10.3)	6 (4.3)	2 (1.5)	29 (6.7)*
TPHA+/RPR <1:8	3 (3.8)	2 (2.3)	2 (1.4)	0 (0)	7 (1.6)
TPHA+/RPR−	10 (12.8)	6 (6.9)	11 (8.0)	8 (6.0)	35 (8.0)
TPHA−/RPR+	2 (2.6)	9 (10.3)	1 (0.7)	2 (1.5)	14 (3.2)
TPHA−/RPR−	51 (65.4)	61 (70.2)	118 (85.6)	121 (91.0)	351 (80.5)
Total	78 (100)	87 (100)	138 (100)	133 (100)	436 (100)

Discharge-F indicates vaginal discharge/female; discharge-M, urethral discharge/male; GUD, genital ulcer disease; GUD-F, GUD/female; GUD-M, GUD/male; RPR, rapid plasma regain; TPHA, *T. pallidum* hemagglutination assay.

Overall $P = <0.0001$; for comparisons between individual STIs—see text.