Validity of Chlamydia, Gonorrhea, and Syphilis Management in Men who have Sex with Men of Kisumu, Kenya

BY

NICHOLAS A. DAVIS
B.S., Auburn University 2013
B.A., Auburn University 2013

THESIS

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Defense Committee:

Robert C. Bailey, Chair and Advisor
Supriya Mehta, Epidemiology
Ronald Hershow, Epidemiology

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LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CT	*Chlamydia trachomatis*
CT/NG	*Chlamydia trachomatis* and *Neisseria gonorrhoeae*
GBMSM	Gay and Bisexual Men Who Have Sex with Men
HIV	Human Immunodeficiency Virus
MeSH	Medical Subject Headings
MSM	Men Who Have Sex with Men
NAAT	Nucleic Acid Amplification Test
NASCOP	National AIDS and STI Control Programme
NG	*Neisseria gonorrhoeae*
NPV	Negative Predictive Value
PID	Personal Identification Number
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RPR	Rapid Plasma Reagin
STI	Sexually Transmitted Infection
UTI	Urinary Tract Infection
WHO	World Health Organization
WoS	Web of Science

SUMMARY

This work presents a three-part analysis. First was an analysis of the sensitivity, specificity, positive predictive value, and negative predictive value of sexually transmitted infection syndromic management compared to laboratory diagnoses in men who have sex with men of Kisumu, Kenya. The analysis was performed on data collected through the Anza Mapema study, and included diagnoses of chlamydia, gonorrhea, and syphilis. Second was an analysis of the timeliness of treatment for participants who were positively diagnosed with chlamydia, gonorrhea, or syphilis through clinical examination and laboratory diagnosis. Third was an analysis of the failure-to-treat rate for participants who were diagnosed with chlamydia, gonorrhea, or syphilis.

Syndromic diagnosis of chlamydia, gonorrhea, and syphilis was limited to urethral infection and had very low sensitivity. The treatment of infections for men who received a syndromic diagnosis was generally given the same day, while those who received a laboratory diagnosis received treatment months after their initial visit. Failure-to-treat rates were very high for participants who received a laboratory diagnosis of their infection. Detailed documentation of the diagnosis to treatment of these sexually transmitted infections is needed to identify parts of the system that require improvement.

I. SYSEMATIC LITERSTURE REVIEW

A. BACKGROUND

1. Diagnosis and Management of Sexually Transmitted Infections

A systematic review was performed in order to describe the available research literature of curable, sexually transmitted infections among gay and bisexual men who have sex with men (GBMSM) in east and southeast Africa. This region was chosen to more accurately reflect the region of Kenya where subsequent research on sexually transmitted infections (STIs) would take place. While literature for the rest of sub-Saharan Africa exists, the quality and quantity of research focused in east and southeast Africa was determined sufficient to accurately evaluate the literature of STIs in the coastal region most geologically and culturally similar to Kenya. A common method of STI diagnosis and treatment is the identification of signs and symptoms followed by the treatment of a group of symptoms. This is referred to as syndromic management. The following research question was presented: How well does syndromic management identify curable, sexually transmitted infections among GBMSM in east and southern Africa? Curable, STIs were defined as *Chlamydia trachomatis* (CT), *Neisseria gonorrhea* (NG), and syphilis. These STIs were chosen because they are most commonly tested for and treated, and urethral infections are addressed by syndromic management guidelines. This research question can be summarized as one primary outcome: The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of syndromic management compared to diagnostic laboratory testing. Secondary outcomes were identified as: the surveillance (prevalence and incidence rates) of curable STIs, the rate of treatment for diagnosed individuals, and the timeliness of treatment for diagnosed individuals with a curable STI among MSM in East and southern Africa.

B. METHODS

1. Electronic Databases Searched

A review of the literature focused on chlamydia, gonorrhea, and syphilis of gay, bisexual MSM in east and southeast Africa. The following electronic databases were searched on September 16th, 2017: PubMed and Web of Science (WoS). The search methodology used is described in Appendix B. Searches were limited to English, and no year criteria were specified. All types of literature were included in the search of the two electronic databases, including review papers, conference reports, cohort studies, etc. This was an attempt to not exclude possibly relevant materials in the topic of interest. Including review papers and conference reports in the search may also help to reduce study or research bias.

2. Outcomes, Location, and Population of Interest

The primary outcome for the current review was the analysis of syndromic management of curable STIs which include CT, NG, and syphilis. Secondary outcomes of interest included timeliness of treatment, rates of treatment, and surveillance of the above STIs. The primary location of interest was East and southern Africa which included Burundi, Djibouti, Eritrea, Ethiopia, Kenya, Rwanda, Somalia, South Sudan, Sudan, Tanzania, Uganda, Mozambique, Malawi, South Africa, and Lesotho. The primary population of interest was the GBMSM group. The addition of GBMSM group was to help account for gender distinction along with the physical act of intercourse. Attempts were made to include as much of the literature possible that focused on the primary and secondary outcomes of interest in the specified population. Much of the literature focused on one or multiple outcomes of interest, and some of these outcomes were just reporting of statistical information in studies that focused on STIs as a risk

factor of HIV. This being said, studies and review papers of HIV were excluded, unless their main exposure or correlates were STIs in the specified population.

3. Keywords and Search Technique

The two electronic databases have varying search functions. All keywords were included in both searches. The application of the keywords varied slightly, however. The key terms were searched for as "TS" in the WoS database, which denotes the keyword as a topic search. The search in PubMed, however, utilized the title and abstract, text word, and mesh term functions. These functions are unique to PubMed, and are explained more in Appendix B. All specific search terms, the search sequence, and all recorded output can also be found in Appendix B.

4. Inclusion and Exclusion Criteria

Upon completion of a search of the included databases, inclusion and exclusion criteria were used to identify literature that would be relevant to the objective of this review. The inclusion and exclusion criteria were selected *a priori* to this step of the review process. Specific criteria for the inclusion and exclusion of literature can be found in Appendix C. The evaluation for eligibility and inclusion followed the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Group flowchart, which can be found in Appendix C. This summarizes that all literature from the search of databases follows the following procedure: Exclusion of duplicate material, screening of titles and abstracts for eligibility, inclusion and exclusion based on criteria, then evaluation of full-text literature.

C. RESULTS

1. Electronic Database Searches

Results from the searches were included in the review if they provided results in one of the primary or secondary outcomes of interest. These outcomes are parts of a proposed research topic involved with the testing, syndromic management, and treatment of STIs among gay, bisexual MSM in Kenya. Through the systematic approach described above, PubMed identified 225 articles while WoS identified 370 articles of possible interest. Among all of the articles, 511 were unique, providing evidence that there existed overlap between the two electronic databases which can be defined as 84 duplicate articles. From these 511 unique articles, titles and abstracts were scanned for the primary and secondary outcomes of interest, and 411 were excluded based upon the inclusion and exclusion criteria which left 100 articles. A second screening for eligibility occurred for the remaining 100 abstracts in which all abstracts were read in their entirety of inclusion of a full text review. After the second round of screening, there were 25 articles remaining in the systematic review process. The full texts of these 25 articles were reviewed for eligibility using the same inclusion and exclusion criteria, and it was decided that 21 were eligible to be included in the review. The results presented below are drawn from these 21 eligible articles. A diagrammed representation of searching, screening, and eligibility can be found in Appendix C. A description of the 75 articles excluded from the second round of review can be found in Appendix F, including reasons for their exclusion. A description of the 21 articles submitted through full-text evaluation can be found in Appendix G, with relevant information provided pertaining to the outcomes of interest for the 21 eligible, and reasons why the other 4 were deemed ineligible which can be found in

Appendix F. A bibliography of all articles included in and excluded from this review can be found in Appendix F.

2. Primary Outcome: Analysis of STI Syndromic Management

This review did not encounter any article that directly analyzed syndromic management of STIs among gay, bisexual MSM in east or southeast Africa. The articles discovered provided information on the rates of symptoms, rates of disease, and even discussed syndromic management, but did not exclusively provide insight into the sensitivity, specificity, positive predictive value, negative predictive value, nor accuracy of syndromic management compared to laboratory testing. One article by Sanders et al. involved a similar evaluating the WHO algorithm for the presumptive treatment of rectal gonorrhea and chlamydia (2014). The cross-sectional analysis of 244 MSM in coastal Kenya found the presumptive treatment of asymptomatic, rectal NG and CT to be 74.1% sensitive and 45.8% specific with a PPV of 23.5% and an NPV of 88.7% (Sanders et al., 2014). The self-collected samples were compared against samples collected by nurses at a clinic.

3. Secondary Outcome: Timeliness of Treatment

As with the primary outcome, no literature was found that identified the timeliness of STI treatment among gay, bisexual MSM in east or southeast Africa. Two articles, however, qualitatively discussed the possibility of prolonged time to treatment or even failure-to-treat because of stigma, social standards, and perception of sexual behavior (Sharma et al., 2008). The article was based upon the results and responses from an exploratory questionnaire given to 486 MSM in Nairobi, Kenya (Sharma et al., 2008). These findings discussed responses that MSM reported having or suspected having an STI, but delayed a visit to be treated in fear of the

perception of their sexual behavior and social stigma associated with rectal STIs (Sharma et al., 2008). While both of these articles included discussion about timeliness of treatment, neither one provided any analysis or specific rates of treatment.

4. Secondary Outcome: Rate of Treatment

Two manuscripts included in this review give specific results for the rates of treatment among the MSM population in east or southeast Africa (Bernstein, Marcus, Nieri, Philip, & Klausner, 2010; Lewis et al., 2013). A case study of two MSM in South Africa described the genetics and phenotypes of two confirmed cases of extended-spectrum cephalosporin resistant gonorrhea in South Africa (Lewis et al., 2013). These two cases were resultant for two MSM who had persistent urethral discharge, even after multiple rounds of treatment. The article includes that after the collection of specimens, neither of the men returned for a final treatment of their condition. This put the failure-to-treat rate of these two men at 100% (Lewis et al., 2013). The other article focused around a two year, retrospective cohort study of 541 HIV-negative MSM (Bernstein, Marcus, Nieri, Philip, & Klausner, 2010). The goal of this study was to analyze the number of rectal CT/NG cases in association with HIV seroconversion. Out of all 541 CT/NG positive MSM, 260 were treated for rectal CT/NG under the WHO guidelines for the presumptive treatment of rectal infection, and another 265 returned for treatment after positive laboratory results for rectal CT/NG. This left the failure-to-treat rate at 2.6% (Bernstein, Marcus, Nieri, Philip, & Klausner, 2010).

5. Secondary Outcome: Surveillance of STIs

Through this review, 15 articles (see Appendix G) were identified which reported on the surveillance of curable STIs among MSM in east or southeast Africa (Bernstein, Marcus, Nieri,

Philip, & Klausner, 2010; Kajubi et al., 2008; Kim et al., 2016; Mmbaga, Moen, Makyao, Mpembeni, & Leshabari, 2017; Muraguri et al., 2015; Otieno et al., 2015; Rebe et al., 2015; Rees et al., 2017; Ross et al., 2014; Ross, Larsson, Nyoni, & Agardh, 2017; Sanders et al., 2010; Sanders et al., 2014; Stahlman et al., 2015; Mohammed, Hughes, & Fenton, 2016; Ross, Larsson, Nyoni, & Agardh, 2017). Throughout the literature, the type of surveillance for STIs among this group ranged significantly from self-report of previous diagnosis to positive laboratory results. The surveillance, however, can be broken into two distinct categories. The first being surveillance of symptoms and syndrome and the second being surveillance of lab testing results.

Surveillance of curable STI symptoms and syndrome was reported in ten of the 15 articles. A cross-sectional analysis of 224 MSM in Kampala, Uganda reported that respondents self-reported ever having urethral discharge, anal discharge, genital sores, or anal sores at rates of 11%, 1%, 7%, and 2% respectively (Kajubi et al., 2008). Another cross-sectional analysis of 43 sex worker MSM in coastal Kenya asked men about STI symptoms upon entry for a larger study. At the time of questioning, 0% reported rectal or urethral discharge, 2.3% reported having urethral pain, and another 2.3% had rectal pain (Sanders et al., 2010). A cross-sectional evaluation of 244 HIV positive and negative MSM enrolled in a cohort study in coastal Kenya found that only 1.6% had any symptoms of CT or NG (Sanders et al., 2014). In 2015, a cross-sectional analysis of 200 random MSM attending a men's health clinic in Cape Town said that 29% self-reported symptoms of an STI, while 5% reported urethral discharge and 11% reported anal discharge in the previous 12 months (Rebe et al., 2015). A separate cross-sectional survey analysis of 295 MSM identified through respondent driven sampling in Kampala, Uganda found

that 47.3% reported an STI symptom in the past six months (Kim et al., 2016). Retrospective cohort analysis of 541 HIV-negative MSM in 2010 reported that 5.9% of the men had rectal symptoms through the two-year study period (Bernstein, Marcus, Nieri, Philip, & Klausner, 2010). In 2015, a cross-sectional analysis of self-reported responses generated through respondent driven sampling from 530 identified MSM in Lesotho found that 10% reported an STI diagnosis in the past 12 months (Stahlman et al., 2015). A separate retrospective cohort study of 7188 male STI episodes in Johannesburg looked at the rates of STIs across a two-year period. The authors reported that 16.9% of these episodes were MSM, from the sample of all men, 68.2% of the episodes were urethritis, 9.8% were genital ulcers, and only 1% were rectal. They also found that through two years of routine data collection, the rates of urethritis did not change while the rates of genital ulcers decreased overtime (Rees et al., 2017). The authors did not provide rates specifically for the MSM population.

The surveillance of laboratory reported diagnoses of STIs was reported in ten of the 15, previously mentioned articles. A cross-sectional evaluation of 43 MSM in coastal Kenya reported that 26% had CT, NG, or both infections. The authors also reported that 13.9% had a urethral infection with 11.6% being CT and the other 2.3% being NG. Of the same sample, 11.6% had rectal infection with 2.3% being CT, 4.7% being NG, and another 4.7% being both CT and NG (Sanders et al., 2010). Another cross-sectional evaluation in coastal Kenya found that of the 244 MSM included, 11.7% had either CT or NG (Sanders et al., 2014). Another article summarized the findings for two separate cross-sectional analyses in Tanga and Dar es Salaam with 100 and 200 MSM, respectively. The results were reported that 4.4% in Tanga and 23.7% in Dar es Salaam had a curable STI (Ross et al., 2014). The difference in STI burden between Dar

es Salaam and Tanga was briefly commented on, but no statistical testing of the difference was reported. According to Ross et al., the prevalence of STIs and HIV among MSM seems to be lower, yet still significantly high, in provincial cities compared to large cities with a population nearly ten times as large (2014). Authors of a paper that evaluated differences in STIs between MSM who sold sex and MSM who did not sell sex tested 563 MSM in Nairobi, Kenya. The authors found that MSM who had previously sold sex had rates of NG and CT at 8.8% and 7.7%. Among MSM who had never sold sex, the rates of NG and CT were 4.2% and 1.7% (Muraguri et al., 2015). The authors presented the difference of NG and CT prevalence between the two groups of MSM to not be statistically significant at an alpha of 0.05. The difference of CT prevalence between the two groups, however, had a p-value of 0.06 being just about the 0.05 cutoff (Muraguri et al., 2015).

Another cross-sectional analysis of 200 MSM attending a men's health clinic in Cape Town found that 24% had CT or NG, 16% had NG, and 12% had CT meaning that 4% of these men had CT and NG (Rebe et al., 2015). A cross-sectional study of 295 MSM identified through respondent driven sampling in Kampala, Uganda found that 9% had syphilis, 1.1% had rectal CT, 1.1% had urethral CT, 1.8% had rectal NG, and 1.4% had urethral NG. They reported that 13.5% had any curable STI, meaning at least one of the men had multiple STIs (Kim et al., 2016). The prevalence of syphilis in this study, 9%, is much higher than any other reported prevalence encountered in this review which ranged from 0.2% to 5%. It is the only study in the review that reports a syphilis prevalence higher than CT, NG, or CT and NG combined. The location of the study, Kampala, may inherently have higher rates of syphilis, but another possible cause is the use of respondent driven sampling. The identified individuals may reside in the same sexual

partner circle where a current outbreak of syphilis is passing through the group. A cross-sectional analysis of 200 MSM in Dar es Salaam found that 21.4% of the sample had urethral or rectal CT or NG (Ross, Larsson, Nyoni, & Agardh, 2017). In Dodoma, Tanzania, a cross-sectional analysis reported that of 409 MSM, only 0.2% tested positive for syphilis (Mmbaga, Moen, Makyao, Mpembeni, & Leshabari, 2017). In 2015, a cross-sectional analysis of 530 MSM in Lesotho found that 5% of the sample tested positive for syphilis (Stahlman et al., 2015). One article performed a cross-sectional analysis of 486 men and women in Kisumu, Kenya. Of all men in the analysis, the authors reported that 0% had NG, 2.8% had CT, and 0.7% had syphilis. It was also noted that 1.2% of the men had a co-infection of the previously mentioned STIs (Otieno et al., 2015). While these studies provided rates of infection for specific groups, they were each limited to a single clinic. This limitation takes away from generalizability and as seen the rates fluctuate drastically between studies. This can be seen where the prevalence of syphilis ranges between 0.2% to 5% and the range for CT or NG was anywhere from 2.8% to 21.4%.

D. DISCUSSION

1. Summary of Review

This review reveals that the literature of STIs among MSM in east and southeast Africa is lacking, especially when discussing the evaluation of syndromic management. There were no articles that included an evaluation of syndromic management; eight articles reported the symptoms of STIs in some way. The only study that was identified to resemble a sensitivity analysis of syndromic management was the evaluation of presumptive treatment of anorectal CT and NG (Sanders et al., 2014). This systematic review did not exclusively evaluate literature based around presumptive treatment, but the sensitivity and specificity calculations follow

similar methodology. The authors also provided information in one of the secondary outcomes as well, surveillance of STIs. The article even provided symptomatic and laboratory surveillance (Sanders et al., 2014). While the prevalence rates of urethral and rectal infection differ slightly between studies, the literature seems to be consistent in that rectal symptoms were less frequent than urethral symptoms. The combined prevalence of curable STIs (chlamydia, gonorrhea, and syphilis) also consistently remain about 10%, yet almost no data on treatment is provided. The gaps in the literature on sensitivity analysis of syndromic management, failure-to-treat rates, and time-to-treat estimations indicate that research should focus on these aspects of STI management in this key population given their fairly high rates of infection.

2. Limitations of Review

This review utilized two electronic databases, PubMed and WoS, for the identification of studies pertaining to the outcomes of interests. While these are large databases focused on biomedical research, it may have been limiting that only two databases were included in this systematic review. The addition of more databases would increase the generalizability of this review and likelihood that all relevant literature would be identified. Future reviews should utilize PubMed and WoS, but also include at least one or two more databases such as EMBASE, MEDLINE, or the National Library of Medicine. The specific search strategy may have also been limiting. While East Africa was included as a Medical Subject Heading (MeSH) term, and other specific countries were included in the search, many countries of the region may have been excluded. These were not necessarily excluded by design, but instead negligent author omission. They should, however, be covered by the region based MeSH term utilized in the search. Countries that may have been neglected are Zimbabwe, Zambia, Botswana, and

Swaziland. Another limitation of the search strategy was not utilizing secondary articles. An improvement would be to screen the references of all articles included in the review for potential studies that were missed during the search of electronic databases.

Another limitation is the physical number of individuals that were included in this systematic review. All criteria were created, searches were performed, articles were screened, and articles were deemed eligible by a single reviewer. The inclusion of more reviewers might allow a more accurate assessment of inclusion/exclusion criteria, the development of a more robust list of keywords for search criteria, and even improve the screening process by means of a unanimous agreement on the screening of articles. This addition of multiple independent reviewers would be important in the future of systematic reviews of this topic. A level of reviewer bias may be present, as all materials, selection criteria, and results were presented by a single reviewer.

The review was further limited by the large proportion of research studies included through the search and selection process. We see only two pieces of literature that presented a review of findings, which may impose a researcher bias. The inclusion of more reviews or meta-analyses may help to identify overarching themes from the current research. Inclusion of more conference summaries or review articles could improve the identification of more broad issues that are often overlooked by a researcher's focus on a goal. One review article provided results from multiple studies, while a conference presentation was also included. Further reviews should make an effort to include or even search specifically for conference summaries, meta-analyses, and literature reviews.

3. Strengths of Review

This review process provided the ability to systematically screen two large databases with a large variety of relevant search terms. The relevant list of search terms was extensive. It also utilized the standardized Mesh terms which allowed the searches to look at all relevant search terms included under the provided search term. For example, “Africa, Eastern Mesh” would automatically search for all standardized keywords provided under the eastern Africa category through the subject terms of each article. This created a very extensive search into the population (MSM), location (east Africa), and outcome of interest (STIs). These three Mesh terms combined with the search for 49 key terms allowed the reviewer to get a large range of literature for screening.

The narrow and specific focus of this review can be seen as a limitation, but it can also be seen as a strength. While much of the research of the primary outcome were missed due to the narrow scope of geographic location, the review gave insight into the stigmatized population in east and southeast Africa. It provided insight into STIs of the population, and the small amount of literature focused on the evaluation of syndromic management of MSM in east and southeast Africa. The review provided knowledge of the gaps in the current STI literature of specifically vulnerable populations. No articles either assessing the sensitivity of syndromic management or exploring the timeliness of treatment of the MSM population in east or southeast Africa were found.

II. ANALYSIS OF STI TREATMENT AT ANZA MAPEMA

A. BACKGROUND

Globally, chlamydia, gonorrhea, and syphilis are three of the most common curable STIs with an estimated 131 million, 78 million, and 6 million new cases in 2012, respectively (World Health Organization, 2016d). These STIs occur disproportionately by region, with more than 90% of curable STI diagnoses occurring in low- and middle-income level countries (Unemo et al., 2017). It is estimated that one fifth of all curable STIs occur on the African continent (Mohammed, Hughes, & Fenton, 2016). The burden of STIs also has higher incidence and prevalence among marginalized populations such as sex workers and men who have sex with men (MSM) (Unemo et al., 2017). National syphilis reporting for GBMSM is available for only five countries in Africa, with the country specific median prevalence being 5.1% (World Health Organization, 2015). Reporting by only five countries does not provide an accurate representation of the GBMSM population of Africa.

Creating standardized systems for the surveillance of curable STIs is difficult in many developing areas of the world. Much of the STI surveillance data in Africa is based upon cross-sectional surveys, and the methods of collection are variable across countries, as is the validity of diagnoses (Mohammed, Hughes, & Fenton, 2016). Surveillance data representative of highly vulnerable populations may not actually exist in areas of Africa, and the available data may not be sensitive enough to capture emerging or continuing epidemics within these communities. The inability to accurately capture these data is influenced by many challenges. Among them are conservative sexual values, strict criminal punishment for sex workers, and the difficulty of engaging MSM within homophobic societies which inhibit individuals from seeking treatment or

accurately reporting any risky behavior such as receptive anal intercourse (Mohammed, Hughes, & Fenton, 2016).

Lack of funding for STI surveillance is considered a barrier as well. Much of the developed world utilizes laboratory testing as a diagnostic method, and STIs are often infections that are mandated to be reported to public health institutes (Mohammed, Hughes, & Fenton, 2016). As a more accurate method of surveillance, developing regions could make routine screening through serology tests for syphilis and nucleic acid amplification tests (NAATs) for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG). While modern laboratory testing is very accurate and precise for the identification of CT, NG, and syphilis, it is expensive and largely unavailable for many regions of the world. According to the WHO, "In settings without available laboratory diagnostic support, diagnosis is often made clinically, based on the presence of symptoms" (2016). This method described by the WHO is referred to as syndromic management, which is defined as the diagnosis, treatment, and care of STIs determined by the presence of a group of symptoms that represent clinical infection. A group of symptoms is also known as a syndrome (Ghebremichael, 2014).

A study of chlamydia and gonorrhea in Zimbabwe, China, India, Peru, and Russia divides the difficulties of surveilling and screening for curable STIs into three main reasons (Detels et al., 2011). First, is the high stigma associated with having an STI. The authors report that 60% or more of individuals with symptomatic STIs feel reluctant to seek treatment from government clinics. Second, symptomatic individuals often go to traditional doctors and pharmacies where they often receive inadequate treatment with nearly zero reporting of the infections. Last, the authors identify that current strategies rely on the individuals seeking help or recognizing

symptoms (Detels et al., 2011). A study in Kenya found that only 4 of 41 MSM (13%) with positive chlamydia or gonorrhea laboratory results had symptoms at the time of visit (Sanders et al., 2014). Another challenge is the de-emphasis of addressing curable STIs among MSM as a byproduct of the view that HIV is much more serious (Zou, Fairley, Guy, & Chen, 2012).

According to McCall et al., intersectionality is, "the relationships among multiple dimensions and modalities of social relations and subject formations" (2005, p1771). The intersectionality of living in a developing area and being GBMSM creates a disparity in healthcare that is experienced by these men. In Kenya, punishment of unnatural acts including sodomy can result in up to 14 years imprisonment. Social stigma is also part of life for GBMSM; the public declaration of non-heteronormative sexual orientation is uncommon or even dangerous (Geibel, 2012). While this does sole cause of the high risk for STIs among GBMSM, it is likely a contributing factor. The identification and treatment of curable STIs that we will define as *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and syphilis may be affected by this intersectionality of GBMSM living in a developing region of Kenya. While intersectionality is not being directly studied in this research, it is important to recognize that these men systematically experience healthcare disparity.

Curable STIs are often found in different anatomical locations, such as vaginal, urethral, rectal, and oropharyngeal. A baseline analysis of a cohort study in Kenya found that of 244 MSM nearly 62% reported receptive anal intercourse in the past six months, putting them at risk for rectal infection (Sanders et al., 2014). Of these 147 MSM who reported anal intercourse in the past six months, 12% tested positive for anorectal CT or NG. Out of all 244 MSM, 6% tested positive for urethral Ct or Ng infection. Further, only four of the 244 men (1.6%)

presented with any urethral (one urethral discharge and one dysuria) or rectal (one rectal pain and one rectal discharge) symptoms of STIs (Sanders et al., 2014). These high rates of rectal infection with low rates of rectal symptoms, gives plausibility that many rectal infections of CT and NG are going undetected and untreated and could be a driving force of STI incidence among MSM in Kenya.

The literature puts an emphasis on improvement of the surveillance and monitoring of STIs due to problems with access, utilization, and sensitivity of STI reporting. This includes evaluating the effectiveness of activities aimed at identifying and treating curable STIs (Mohammed, Hughes, & Fenton, 2016). One of the major activities used for identification and treatment of STIs is syndromic management. It is often encouraged that an effective strategy for STI control would be syndromic management with periodic laboratory surveillance. This is pertinent for increasing the quality of STI surveillance, and the accuracy of surveillance data (Mohammed, Hughes, & Fenton, 2016). One systematic review highlights the need to identify clinical interventions that are successful at increasing the screening and treatment of curable STIs among MSM. The same review also points out that very few studies, out of the 1809 screened, evaluated the efficacy of attempts to improve clinical screening procedures for curable STIs among MSM. Just four clinic-based intervention studies were identified. The results showed that basic strategies to create routine STI testing for MSM decreased both the median time to treatment and the median time to STI retesting (Zou, Fairley, Guy, & Chen, 2012).

B. PURPOSE

This study's goal is to describe and analyze the diagnosis, testing, management, and treatment of STIs among gay and bisexual MSM (GBMSM) participating in a cohort study in

Kisumu, Kenya. The cohort study of these GBMSM is called Anza Mapema. A sensitivity and specificity analysis of the syndromic management of STIs in the Anza Mapema cohort study was be performed using diagnostic laboratory test results as a gold standard. Failing to treat vulnerable populations, such as MSM, may affect the overall population because many of MSM also have female sexual partners, making heterosexual transmission possible. MSM may act as a bridge between sub-populations, contributing to the overall spread of HIV in the general population (World Health Organization, 2015). The HIV subtypes of MSM in Africa resemble the strains that circulate among the general population, supporting the idea that HIV transmission among MSM is not confined within this group but rather transmitted between MSM and the general population (Smith, A. D. et al., 2009). This situation stresses the importance of treatment timeliness for individuals who are positive for STIs.

Laboratory diagnostic testing is the most accurate method for diagnosing STIs, but the results can take days or even weeks to receive from the laboratory and to subsequently reach the patient. This time delay could be due to many factors: time for culture, transportation time to and from external labs, insufficient laboratory resources (e.g., staff, test kits, equipment), lost results, or inability to contact individuals with positive results for treatment.

Syndromic management offers an opportunity to decrease the time from diagnosis to treatment and to decrease the failure-to-treat rate, which is defined as the percentage of diagnosed individuals who never receive treatment. Diagnosis by syndrome usually happens at an initial visit, and drugs can be administered immediately after diagnosis. One major issue with syndromic management is that it relies on infected individuals having and recognizing symptoms, then seeking help (Detels et al., 2011). For syndromic management to reliably

identify an STI, the patient must experience symptoms, recognize these symptoms, and then seek care for the recognized symptom. If a large majority of MSM with curable STIs are asymptomatic (i.e., do not experience symptoms), then the sensitivity of syndromic management is reduced. A study of 1,440 women in Moshi, Tanzania found that syndromic management, when analyzed against diagnostic laboratory test, had a sensitivity between 2%-17% while the specificity was between 85%-99% (Ghebremichael, 2014). Similar analyses of syndromic management for MSM in east and southeast Africa could not be found.

A potential major barrier to successful syndromic management of STIs is the lack of standardized syndromic management guidelines for rectal STIs. While the WHO provides guidelines for numerous anatomical sites, rectal infection is not included (World Health Organization, 2016). An evaluation of WHO STI syndromic management for men and women in El Salvador suggested that the inclusion of an anoscopy examination would be beneficial for STI identification among high risk groups (Shah et al., 2014). This could be extremely beneficial to gay and bisexual MSM who are at risk for rectal infection. For example, a study of 244 MSM in Kenya found that only two of 30 (6.7%) rectal STI infections presented with symptoms (Sanders et al., 2014). Specific treatments for rectal infections are iterated by the WHO, but disease identification is according to laboratory diagnosis. It is conceivable, however, that syndromic management of STIs can be combined with laboratory diagnostics and presumptive treatment of rectal infections based upon identifiable sexual behavior risks to control the STI epidemic seen in vulnerable populations. Some limitations of one method may be met by another. To determine effectiveness of syndromic management for curable STIs in the MSM population of

Kenya, this research evaluated the syndromic management of STIs at the Anza Mapema cohort study in Kisumu, Kenya.

A systematic review was performed that explored the following research question: How well does syndromic management identify curable, sexually transmitted infections (STIs) among gay and bisexual men who have sex with men (GBMSM) in East and southern Africa? The review described literature that focused on four main outcomes. First was the sensitivity, specificity, PPV, and NPV estimation of STI syndromic management in MSM of southern and East Africa. Second was the surveillance and prevalence of STIs in the same population. Third was the treatment rate for curable STIs in the MSM population of East and southern Africa. Fourth was the timeliness of treatment for STI positive MSM in the same region. The review of two major electronic databases (PubMed and Web of Science) found 21 articles relevant to the four main outcomes, and a majority of the literature focused on the surveillance of STIs along with distribution of anatomical location of infection along with prevalence of presented symptoms. No article reported a statistical analysis of STI syndromic management or timeliness of treatment. Two articles estimated the rate of treatment for their particular study populations. Specific details on these studies can be found in the results of the systematic review. This review informed the development of the Specific Aims and purpose of the following analyses. The literature of MSM in East and southern Africa does not provide sensitivity analyses of syndromic management of STIs nor the timeliness of treatment, while failure-to-treat rates are estimated by only two manuscripts. The systematic review suggests that surveillance of STIs and apparent symptoms among MSM in this region has been low in the past, but the literature identified from the past decade cites 10 studies that presented STI rates

based on laboratory results and 10 studies presenting rates of presented signs or symptoms. Not a single article was found through the systematic review that estimated the sensitivity, specificity, PPV, and NPV of syndromic management of STIs in MSM of East and southern Africa. The specific aims of this study will fill this gap by focusing on an analysis of sensitivity, specificity, PPV, and NPV of syndromic management of STIs, to estimate failure-to-treat rates, and to estimate time from visit to treatment of select STIs.

C. SPECIFIC AIMS

Aim 1: to calculate the sensitivity, specificity, positive predictive value, and negative predictive value of syndromic management of chlamydia, gonorrhea, and syphilis in gay and bisexual MSM (GBMSM) participating in the Anza Mapema study in Kisumu, Kenya.

Aim 2: to estimate the time between specimen collection and treatment of MSM with laboratory and clinically diagnosed sexually transmitted infections at Anza Mapema in Kisumu, Kenya.

Aim 3: to estimate the rate of men who test positive for a curable sexually transmitted infection, but have no documented treatment. The rate will be described as failure-to-treat.

D. ETHICAL CONSIDERATIONS

This study was approved by the Institutional Review Boards for Protection of Human Subjects in Research at Maseno University, University of Illinois at Chicago, and University of Washington.

E. STUDY DESIGN/METHODS

1. Methods: Anza Mapema Study

This study analyzes data from a cohort study called Anza Mapema which took place between 2015 and 2017. The cohort study was a behavioral, clinical, and laboratory-based evaluation of 711 GBMSM in Kisumu, Kenya who were aged 18 years or older, had reported oral or anal sex with another man in the past six months, and were not currently enrolled in ART or other HIV care in the three months prior to enrollment. For details regarding recruitment and enrollment of participants, see Kunzweiler et al., 2017. Each participant entered the study at a baseline visit (visit 0) as either HIV negative (Cohort 1) or HIV positive (Cohort 2) and was followed for 12 months. The participants' study data were also labeled with a six-digit Personal Identification number (PID) to protect their privacy and identification. Individuals in Cohort 1 were expected to have checkups at three months (visit 3), six months (visit 6), nine months (visit 9), and twelve months (visit 12). Individuals enrolled in Cohort 2 were expected to have monthly visits in which the visit number coordinated with the respective month. Study participants were required to come to Anza Mapema at their regularly scheduled visits, but were also allowed to come at any other time for medical attention. Syndromic diagnosis visits other than 0, 6, and 12 were not subject to specimen collection for laboratory testing. This lack of specimen collection limits the overall evaluation of syndromic management because part of the calculation is the true infection as defined by laboratory diagnosis. A separate variable for all visits between visit 0-visit 6 and visit 6-visit 12 was created to estimate the prevalence of syndromic STI treatment between visits with laboratory testing. Visits 0, 6, and 12 are more extensive for individuals in both cohorts. At these visits, clinicians routinely collected urine, blood, and rectal swab specimens to be sent to the Center for Disease Control

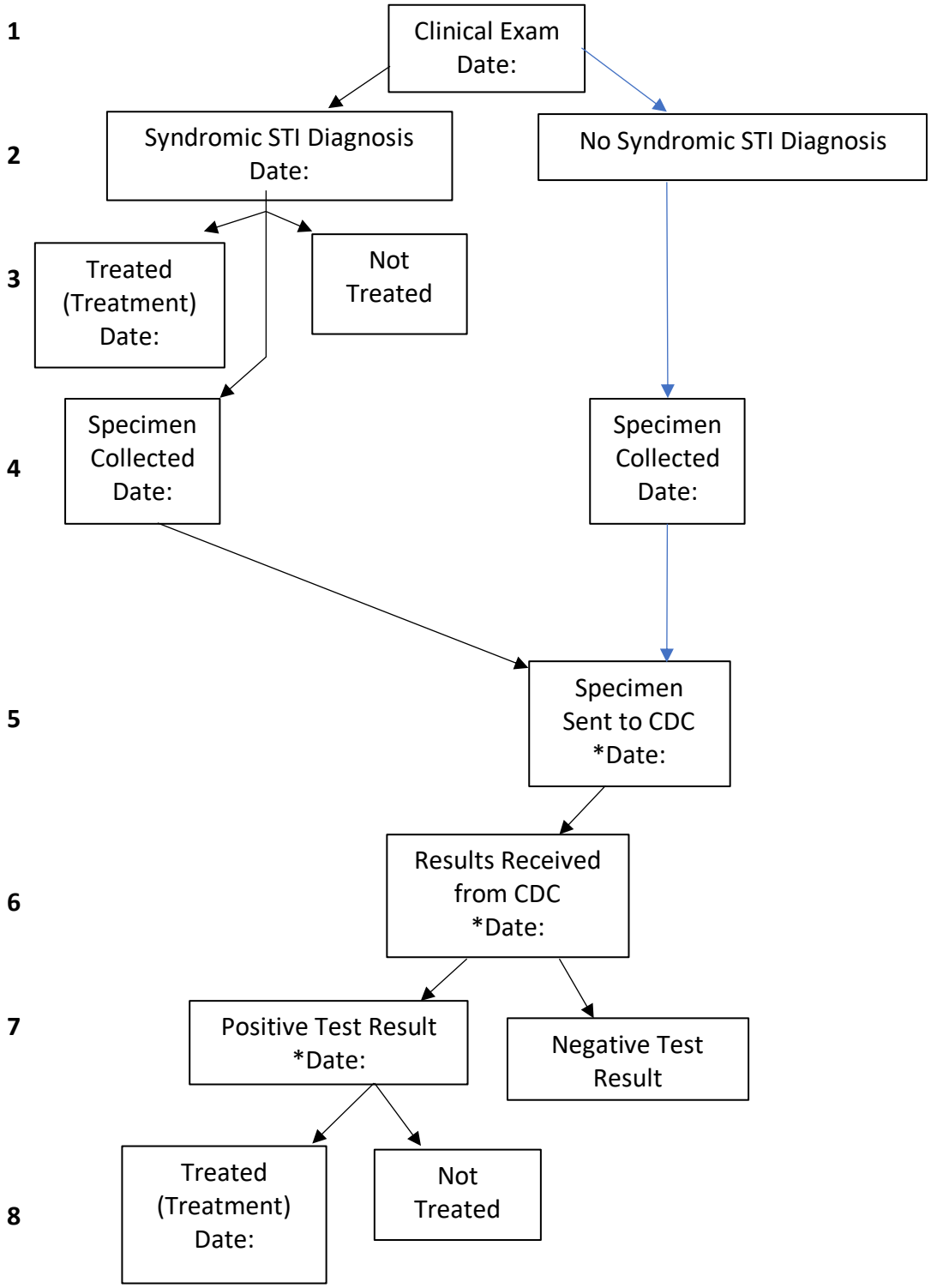
(CDC) and Kenya Medical Research Institute (KEMRI) laboratories in Kisumu, Kenya for STI diagnostic testing.

During the second half of the study, results were received from the laboratory by email, and dates can be traced through the receipt. During the first year of the study, however, the laboratory results were received by either phone call or hand delivered at the Anza Mapema clinic. No timestamps were recorded for these laboratory results, so there is no way of verifying the date for which results were received from the CDC laboratory. Clinicians were responsible for contacting the individuals with positive laboratory results and scheduling a time for them to come to receive treatment. Records of clinicians contacting individuals with positive tests were not available in the study files. The individual would either be treated or not treated for their STI. Figure 1, illustrates the points on the timeline where the Specific Aims apply (time points 1 through 8). Specific Aim 1 estimates the concordance of time 2 with time 7, where time 2 is actually defined by either being treated or not. Specific Aim 2 evaluates the period between time 1 and time 8. Specific Aim 3 estimates the number of men not treated at time 3 and time 8 out of those positive for an STI at 2 and 7.

2. Methods: Diagnostic Laboratory Tests

Laboratory testing for STIs was expected to be performed on all participants of Anza Mapema at visit 0, visit 6, and visit 12. The tests were diagnostic for chlamydia, gonorrhea, syphilis, and HSV-2. Urine, rectal swab, and blood specimens were collected from the patients at the visit, and stored in a cooler until the end of the day or next morning. These specimens were then

Figure 1: Flow Chart of STI Diagnosis, Treatment, and Testing with Specific Aims



Proposed Points/Measurements of Interest

- Specific Aim 1: Concordance of 2 with 7
- Specific Aim 2: Time from 1 to 8 and from 4 to 8
- Specific Aim 3: Negative Results from 3 and 8 out of positive results from 2 and 7

* Indicates data that were not recorded or unavailable

brought to the laboratory at CDC in Kisumu, Kenya within 24 hours of collection. The laboratory technicians then used Polymerase Chain Reaction (COBAS® AMPLICOR CT/NG) type NAATs with a sensitivity/specificity of 97.1%/98.1% for the detection of CT and NG (Roche Molecular Systems, 2004). The blood samples were tested for syphilis with a Rapid Plasma Reagin (RPR) test, which screens for antibodies the body uses in combatting syphilis. Reactive tests were confirmed with a solid phase immunochromatographic assay of blood serum (SD Bioline syphilis 3.0) for antibodies that are specific in combatting *Treponema* pallidum, the bacteria responsible for syphilis, with a sensitivity/specificity of 99.3%/99.5% (Alere, 2017). Figure 1 provides a visual on the succession of STI testing, diagnosis, and treatment at Anza Mapema. A participant with a specific PID number had a specific visit ID for each individual visit to Anza Mapema. Within that visit, clinicians evaluated symptoms of participants, and recorded any diagnosis of disease or infection with which the individual may present. The clinician collected urine, blood, and rectal swab specimens and stored them in a refrigerated box for transport to the CDC laboratory in Kisumu, which was approximately a ten-minute drive away. Any clinician-detected infection or STI diagnosis by syndrome would be treated as specified in the Anza Mapema protocol, which follows dual-therapy treatment regimens recommended by the National AIDS and STI Control Programme (NASCOP) of Kenya (National AIDS/STD Control Programme, 2015). On occasion, alternate single-therapy regimens were recorded, and these were defined as non-recommended therapy. The test results for every diagnostic laboratory test were recorded in a computer database.

These results were extracted to a Microsoft Excel spreadsheet. The dates of specimen collection, treatment results, specific treatment given, and the date of treatment were available in the study records on hand written clinical notes. This information was extracted from the study records and placed on the same spreadsheet as the diagnostic laboratory results. All records were extracted and identified by PID for the protection of identities.

3. Methods: Syndromic Diagnosis

Clinicians at Anza Mapema diagnosed STIs following a WHO adapted syndromic diagnosis flowchart (see Figure 2 and Figure 3). Recognition of signs, symptoms, diagnosis of an STI by syndrome, specific treatment received (if any), and date of treatment were recorded in handwritten chart notes within the Anza Mapema study records. Syndromic diagnosis of an STI was defined by the immediate treatment with a recommended dual- or single-therapy, while signs and symptoms were compared to the diagnoses. Dual-therapy is recommended for all syndromic diagnoses; therefore all results are based off of dual-therapy regimens. All available signs and symptoms were available in study databases while diagnoses, treatment, and dates of treatment variables were extracted by recording all chart notes into a Microsoft Excel spreadsheet separate from the laboratory diagnosis spreadsheet and can be found in Table I. The syndromic diagnosis data can occur at any point in the study, while the laboratory diagnosis occurs only at visits 0, 6, and 12. Due to the nature of a scheduled visit at Anza Mapema, STI signs may be detected by the clinician and treated even without participant recognition.

A number of signs of STIs were extracted from the medical records: genital ulcers, “STI”, urinary tract infection (UTI), anal abscess, balanitis, epididymitis, non-gonococcal urethritis, urethritis, and combinations of these. Non-gonococcal urethritis indicates an etiologic diagnosis

Figure 2: Urethral Discharge- Syndromic Management Algorithm Used at Anza Mapema
*National AIDS/STD Control Programme, 2015

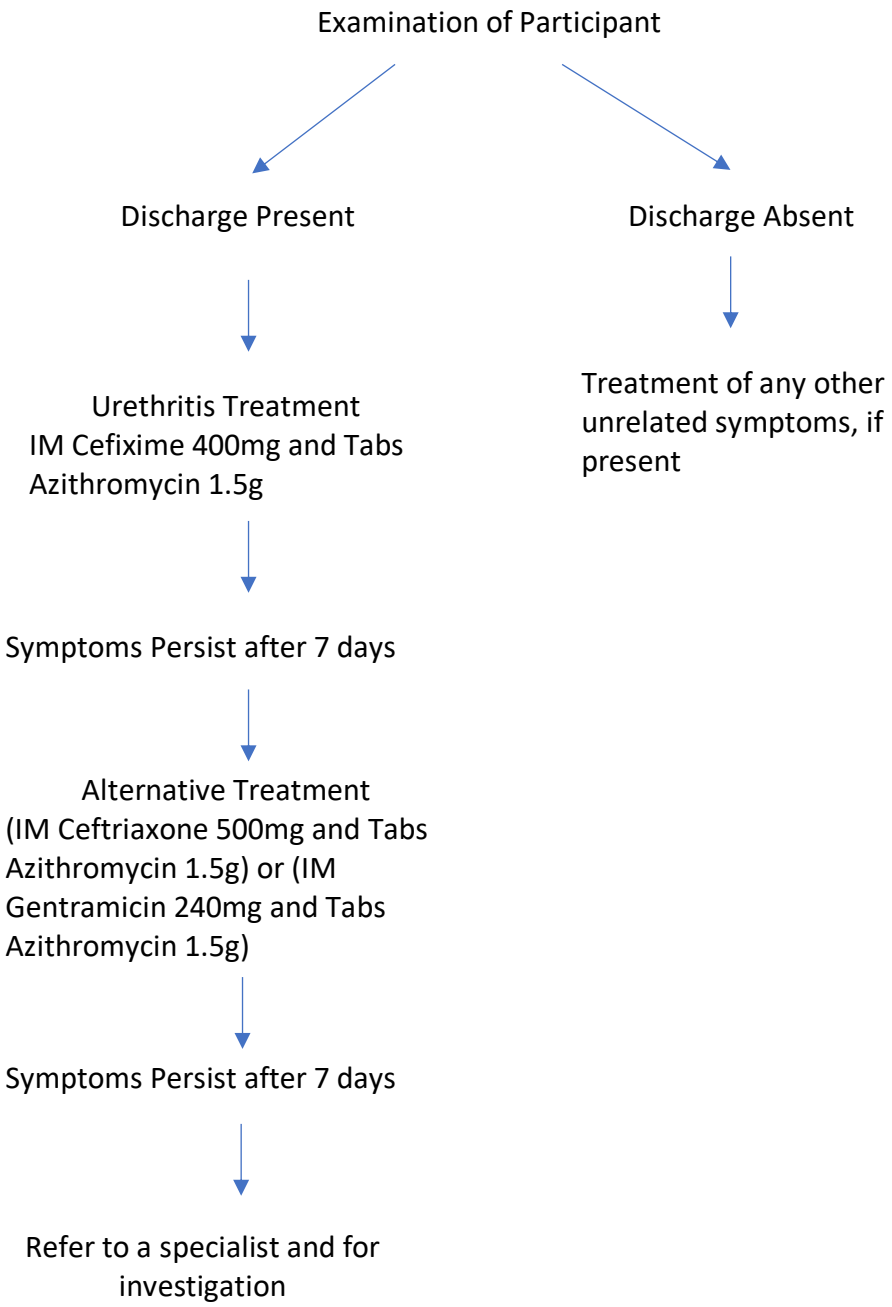
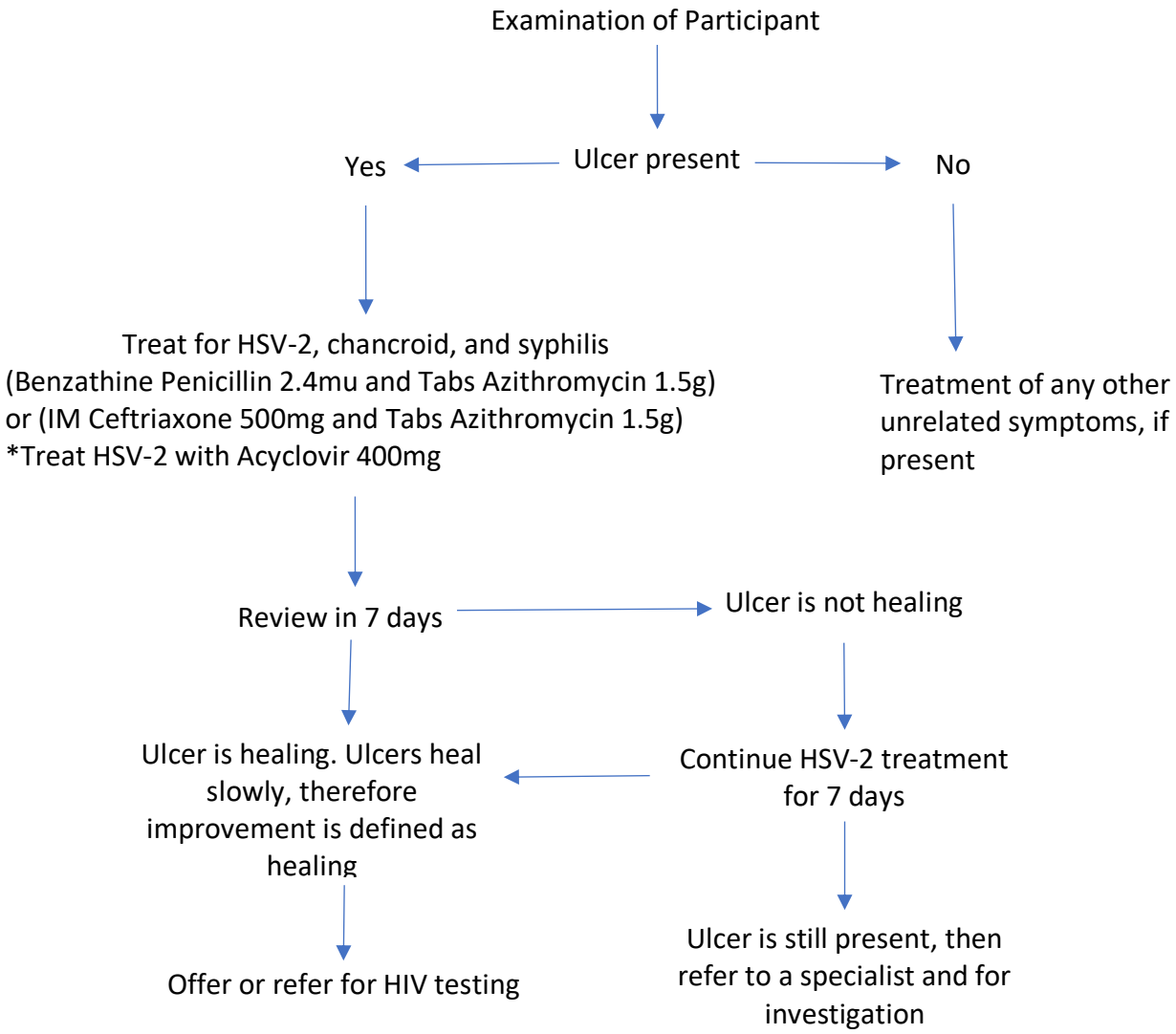


Figure 3: Genital Ulcers- Syndromic Management Algorithm used at Anza Mapema



but was included as it may indicate a misdiagnosis and improper treatment. Anal, urethral, and intra-penile warts were excluded since they are not a sign of CT, NG, or syphilis. The management of STI signs and symptoms were then divided into anal and urethral. Chlamydia and gonorrhea were also reported in the medical records but were not included as symptoms as these would indicate etiological diagnoses. Symptoms were reported as being experienced by the participant during the three months prior to the study visit. Signs – such as urethral discharge, epididymitis, genital ulcers, or testicular pain – were defined as detection by a clinician during the study visit. Syndromic diagnosis was labeled as positive or negative based on a treatment that resulted from the same visit. These diagnoses were then categorized as recommended dual-therapy or non-recommended therapy, which can be seen in Table VI. The signs and symptoms were categorized as symptoms of curable STIs or symptoms of non-curable STIs, which is depicted in Figure 4.

4. Methods: Correlates of Interest with Accuracy of Syndromic Management

The sensitivity, specificity, PPV, and NPV of syndromic management were estimated at each of the three scheduled visits. Demographic and behavioral variables may contribute to an increased prevalence of presented signs and symptoms among certain groups of men. A previous study that focused on the correlates of STIs among the general population in Kisumu, Kenya, found that laboratory diagnosed STIs were more prevalent in HIV positive individuals compared to HIV negative (Otieno et al., 2015). While no specific literature was identified to indicate HIV-status has an effect on the presented symptoms of other STIs, it is plausible that an alteration in the immune system may play a role in the presentation of STI symptoms. Separately, a cross-sectional study of MSM found that age was associated with HIV and STI

prevalence (Mmbaga, Moen, Makyao, Mpembeni, & Leshabari, 2017). A cohort study of individuals with high risk sexual activity in five developing countries suggests that the proportion of asymptomatic versus symptomatic gonorrhea was lower in higher age groups when evaluated from baseline to 12-month follow up where 18-24, 25-34, and 35+ year olds 88%, 86%, and 67% of infection being asymptomatic, respectively (Detels et al., 2011). Reporting the percent of asymptomatic from all chlamydia infections was similar at 91%, 86%, and 84% for the same age groups (Detels et al., 2011).

Increasing age may have an effect on the presentation of symptoms, just as with HIV, an altered immune system may change the rate in presentation of STI symptoms. Covariates indicative of risky sexual behavior were also chosen from the availability of risk behavior data collected as part of the Anza Mapema Study. We included preferred sex position (insertive, receptive, or versatile), age, HIV status, circumcision status, and condomless sex. Sexual position may have a different likelihood of presenting symptoms for different anatomic location of infection (i.e., urethral vs. rectal). Men who usually engage in insertive anal intercourse would be at greater risk for penile infection compared to versatile men who have receptive and insertive intercourse. The immune response to an infection of the anus may be different than the response in the penile tissue, which could even cause a different rate of symptom presentation. This may cause men with different preferred sexual positions to have different rates of STI symptoms. HIV was considered as a covariate since immunocompromised individuals, while being infected more often, may present symptoms less frequently due to a decrease in the number of inflammatory producing cells that could cause acute inflammation. As mentioned, increasing age is often associated with a decreased immune response to

infections. This may also act on the presentation of STI symptoms in a similar manner as HIV. The aging population may have a lower inflammatory response, thereby decreasing the chance of presenting symptoms. Circumcision may also cause a decrease in the symptom presentation of STIs as it causes a reduction in the inflammatory response in the penile area. Sex with a condom is not a complete protection to STIs as many individuals improperly use condoms, and there is always the risk for breaks. The use of condoms, however, may cause less irritation to tissues during sex, and produce fewer symptoms. Also, men who frequently use condoms may be more aware of the risk of sexual behavior. This would cause the men who use condoms to be more cognizant of STI symptoms, and plausibly more likely to recognize STI symptoms compared to men who do not use condoms This could increase or decrease the likelihood of symptom presentation based on infection with a higher inflammatory response from condomless sex.

5. Methods: Combination of Laboratory and Syndromic Data

Utilizing SAS University Edition, spreadsheets were imported, sorted, and merged together into a single dataset by matching each observation on two criteria: The PID number and the visit ID. Anza Mapema had enrolled 711 GBMSM. After withdrawn participants, and participants that did not show up to their scheduled visits, the dataset of laboratory and syndromic management results are from a sample at visit 0 of 701 GBMSM, at visit 6 from 553 GBMSM and at visit 12 from 575 GBMSM in the Anza Mapema cohort study.

6. Methods: Specific Aim 1 Variables

The syndromic diagnosis and positive urine laboratory results are the two main variables of interest. Syndromic diagnosis was defined as being given a recommended dual-therapy

regimen for the treatment of a documented STI sign or symptom. The recommended dual-therapy included combinations of: cefixime or ceftriaxone with azithromycin or gentamicin. The single-therapy treatment regimens for syndromic diagnosis included any of the above drugs not used in combination with each other but were then considered not-recommended therapy and not included as fully treated. Urine laboratory results were defined as either positive or negative based on the diagnostic testing for urethral CT, NG, and syphilis. Proper treatment for CT is azithromycin, while NG requires a dual-therapy regimen of either cefixime or ceftriaxone combined with azithromycin. Syphilis requires treatment by benzathine penicillin. A distribution of these two variables by scheduled visit number can be found in Table I, Appendix A. Treatments by a different regimen than specified were considered to be non-recommended therapy.

The data overlap between syndromic diagnosis and laboratory results only exists at scheduled visits 0, 6, and 12. Unscheduled visits could occur at any point between visits 0-6 and visits 6-12. Scheduled visits at month 3 and month 9 were also available, but just as with the unscheduled visits, there were no STI laboratory tests performed at these visits. Individuals at these unscheduled, month 3, and month 9 visits were examined syndromically for STIs, and these reported results can be found in Table II, Appendix A. Symptoms of an STI may be recognized by participants and reported as having been experienced in the previous 3-months. These symptoms included in the analysis were dysuria, penile ulcer, and urethral discharge. Signs of an STI are characteristics that are noticed by a clinician upon examination. These included urethritis, genital ulcers, and epididymitis. A distribution of recommended dual-therapy, non-recommended therapy, and no treatment by clinician recognized signs can be

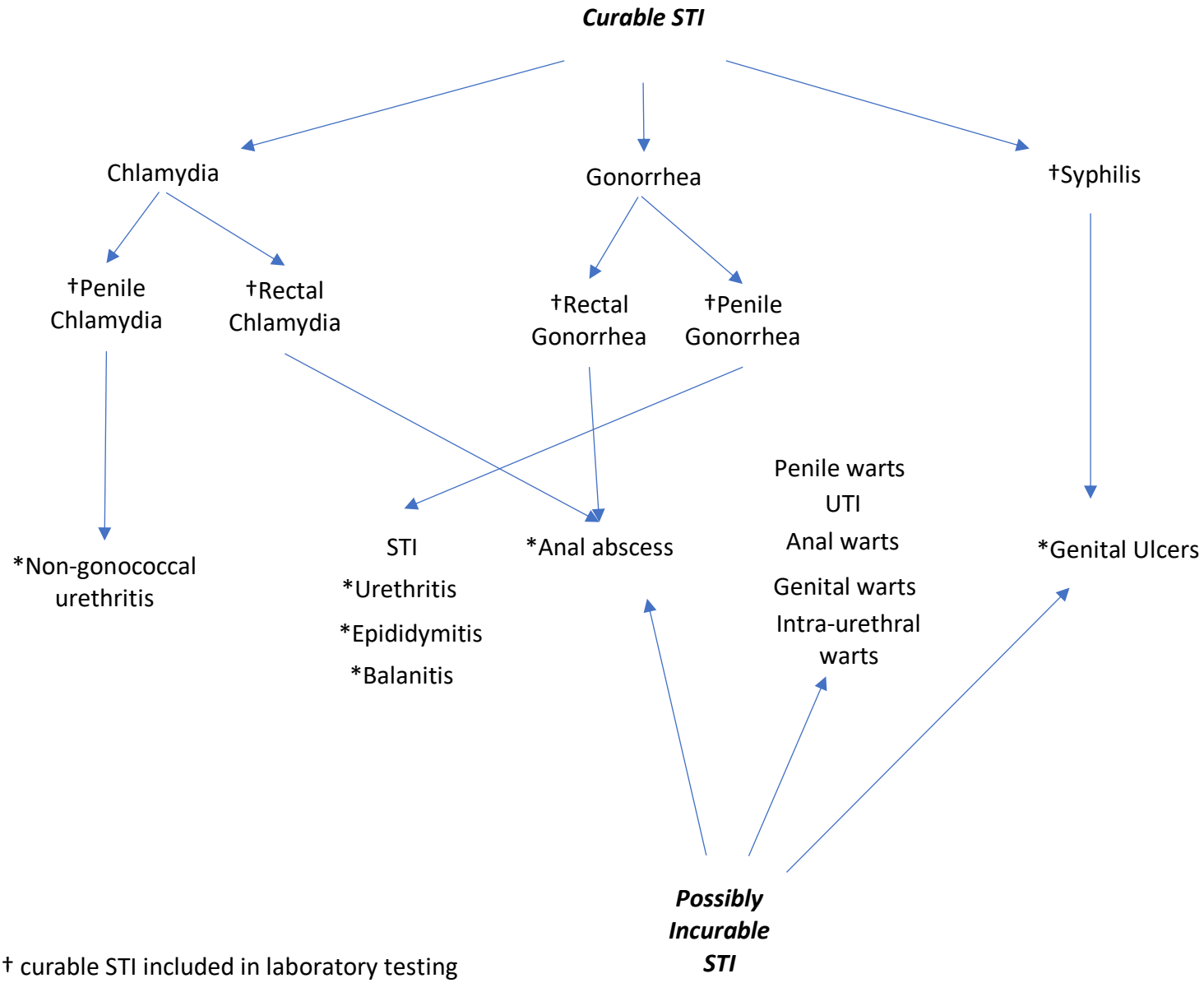
found in Table III. The table was divided into scheduled (months 0, 6, and 12) and unscheduled visits (any visit between months 0-6 and months 6-12)

All rectal diagnoses, signs, and symptoms were excluded for the following two reasons. First, clinicians recorded only two events during the Anza Mapema study in which a sign of rectal infection (one anal abscess and one anal discharge). Second, diagnosis did not distinguish whether treatment of an STI by syndrome was due to apparent urethral or rectal infection, though reporting of STI signs by the clinicians indicates that the treatments were likely for urethral infection (as noted above, there were only 2 cases with documented signs of rectal infection). Moreover, anoscopy was not uniformly conducted. The inclusion of genital ulcers was decided upon since an ulcer can be indicative of chlamydia, particularly Lymphogranuloma venereum (LGV), or syphilis. Typically, a distinction is made between painful ulcers and painless ulcers that can indicate syphilis or genital ulcer disease, but this distinction was not available. The treatment of genital ulcers with dual-therapy can be found in Figure 2. The diagnoses, signs, symptoms, and laboratory test results included can be found in Figure 4.

7. Methods: Specific Aim 1 Statistical Analysis

Frequencies and percentages of categorical variables along with medians and interquartile ranges (IQR) for continuous variables were estimated (Table I, Appendix A). The prevalence of urethral STI by laboratory diagnosis can be seen in Table I, Appendix A. Treatment by syndrome (recommended and non-recommended therapy combined) and all covariates were assessed for statistical difference between frequencies at 0, 6, and 12 months using a chi-

Figure 4: Signs and Symptoms of Curable and Incurable Sexually Transmitted Infections



† curable STI included in laboratory testing
*curable STI symptom recognized in syndromic management and included in our analysis

square test (Table I, Appendix A). A non-significant chi-square (alpha 0.05) would indicate no significant difference in distribution between the variable and visit number. No difference in the distibution of syndromic diagnosis by visit number would indicate that the data could be combined and analyzed as an overall. Analysis of variance (ANOVA) was used to test for statistical difference between the mean ages at visit 0, 6, and 12. A p-value of greater than 0.05 indicates that no significant difference in distribution exists between the mean age at the 3 scheduled visits. A significant difference in the distribution may indicate the need for a longitudinal analysis.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for any syndromic dual-therapy treatment using the laboratory diagnosis as a gold standard at each of the 3 scheduled visits. The calculation of sensitivity. Specificity, PPV, and NPV can be seen below using figure 5 for reference. Each of the estimates are provided with exact 95% confidence intervals, and results can be seen in Table IV, Appendix A.

$$\text{Sensitivity} = a/(a+c)$$
$$\text{Specificity} = d/(b+d)$$
$$\text{PPV} = a/(a+b)$$
$$\text{NPV} = d/(c+d)$$

Figure 5: Syndromic and Laboratory Diagnosis Contingency Table

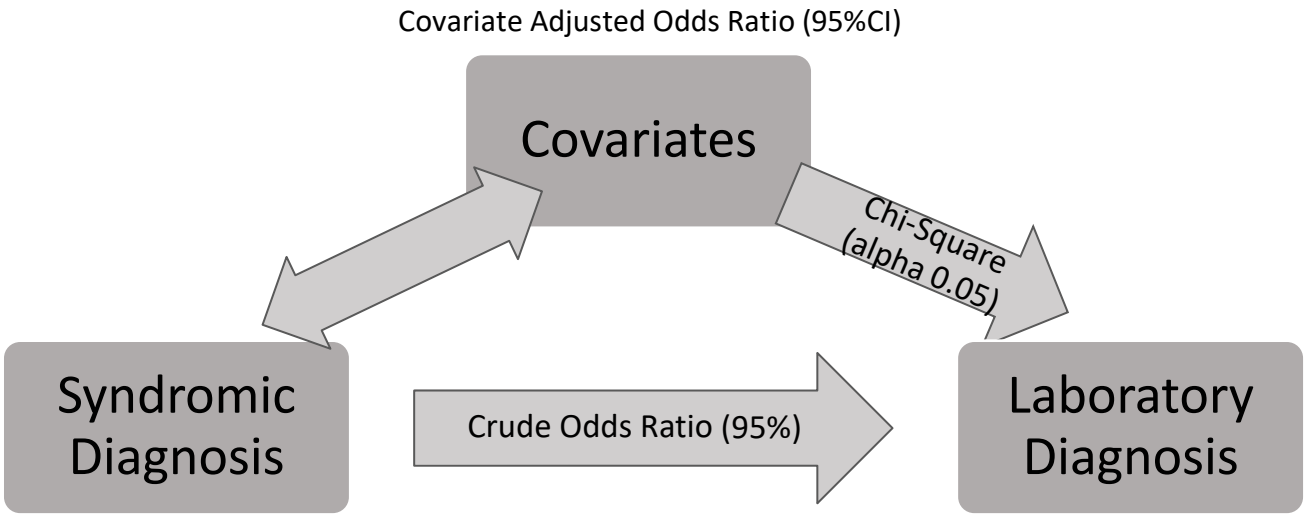
	Positive Laboratory Diagnosis	Negative Laboratory Diagnosis
Positive Syndromic Diagnosis	a	b
Negative Syndromic Diagnosis	c	d

The sensitivities of syndromic diagnosis were then compared between visits 0, 6, and 12 using an exact chi-square estimation to determine if an association exists between laboratory test results and positive syndromic treatment at visits 0, 6, and 12. A significant chi-square (alpha 0.05) indicates that the proportion of at least one of the sensitivities is different than the others. A non-significant chi-square, p-value greater than 0.05, would indicate that the three scheduled visits can be combined for the remainder of the analysis. The results of this chi-square analysis can be found in Table V, Appendix A.

A crude prevalence odds ratio was calculated to model the association between the odds of having a positive laboratory STI diagnosis when syndromically treated compared to having a positive laboratory STI diagnosis when not syndromically treated. A Mantel-Haenszel odds ratio was calculated after adjusting for the covariates found to have a significant chisquare p-value (alpha 0.05) with the overall laboratory results (Table VI, Appendix A). These odds ratios in Table VI, Appendix A are the odds of having positive urine laboratory tests when syndromically treated compared to no syndromic treatment after adjustment by each covariate. A difference greater than 10% between the crude odds ratio and the Mantel-Haenszel adjusted odds ratio indicates that the covariate is a possible confounder associated to the laboratory results and syndromic treatment. Logistic regression modeling was then used to estimate an adjusted odds ratio for having a positive laboratory diagnosis among those who were syndromically treated compared to those who were not syndromically treated. From these adjusted models, the sensitivity, specificity, PPV, and NPV were calculated with exact 95% confidence intervals. Based upon a difference between adjusted and crude odds ratios, if no confounding variables were found, then the crude odds ratio was reported and sensitivity,

specificity, PPV, and NPV required no adjustment. A conceptual model of the estimations used to assess for confounding can be seen in Figure 6.

Figure 6: Conceptual Model for Assessment of Confounding



8. Methods: Specific Aim 2 and Specific Aim 3 Variables

Timeliness of treatment was evaluated for all diagnoses of a curable STI, being CT, NG, and syphilis. These curable STIs included positive laboratory tests for syphilis, urethral CT/NG, and rectal CT/NG. The syndromic diagnosis of a curable STI was determined by identified signs of urethral or rectal infection by a clinician (i.e. urethritis, epididymitis, testicular pain, anal abscess, anal discharge, and genital ulcers). Self-reported symptoms of an STI in the previous 3-months (urethral discharge, dysuria, testicular pain) were not utilized in the syndromic

diagnosis for this study. Variables of interest are the date of diagnosis (for syndromic diagnoses), the date of specimen collection (for laboratory diagnoses), and the date of treatment. The date of treatment was reported in clinical notes and included both single- and dual-therapy regimens. The sample of this analysis was taken from all syndromic and laboratory diagnoses that were eventually treated, while the sample who was never treated falls into Specific Aim 3 as failure-to-treat. The variable known as time-to-treat was the number of days from date of specimen collection (laboratory diagnosis) or date of syndromic diagnosis subtracted from the date of prescribed treatment by a clinician and can be seen in Table VIII, Appendix A.

It is important to note that while Specific Aim 1 only used observations at the scheduled visits at Months 0, 6, and 12, this analysis utilized the three scheduled visits plus all visits at months 3 and 9, plus unscheduled visits. Results for time-to-treat and failure-to-treat rates were separately reported for all visits, and for visits 0, 6, and 12. Unlike in the analysis for Specific Aim 1, this analysis also does not ignore rectal infections diagnosed by laboratory tests, because to estimate "time-to-treat" does not require both a syndromic and laboratory diagnosis. Just as time-to-treat, the failure-to-treat analysis included both rectal and urethral CT and NG, along with syphilis. Failure-to-treat rate was estimated by STI diagnoses originating from syndromic management and laboratory diagnoses (Table IX, Appendix A).

9. Methods: Specific Aim 2 and Specific Aim 3 Statistical Analysis

The variable "time-to-treat" was divided into two categories according to the main method of diagnosis: syndromic diagnosis and laboratory diagnosis. Time to treat was calculated as a median time in days from date of infection diagnosis by syndromic management

and specimen collection for laboratory testing to date of treatment. Minimum and maximum time-to-treat was also reported for both syndromic and laboratory diagnoses. The syndromic and laboratory time-to-treat was calculated for recommended and non-recommended therapy as to provide a description of proper and improper treatment. Results can be seen in Table VIII, Appendix A. Failure to treat rates were estimated by dividing the number of untreated positive laboratory diagnosed STIs by the total number of positive diagnoses (i.e., treated plus untreated). Laboratory treatment was based upon the proper treatment depending on the laboratory diagnosis as mentioned in the *Methods: Specific Aims 2 and 3* section. In addition, rates of treatment were estimated based upon recommended therapy, non-recommended therapy. Results can be found in Table IX, Appendix A.

F. RESULTS

1. Results: Specific Aim 1

Among the 703 GBMSM with urine laboratory results at visit 0, the prevalence of urethral chlamydia and/or gonorrhea was found to be 12.5%. At visit 6, the prevalence was 7.5% among 536 participants, and at visit 12, the prevalence was 9.4% among 552 participants. The prevalence of infection by syndromic treatment as a proxy was 1.1% at visit 0, 2.0% at visit 6, and 1.6% at visit 12 with no significant difference in prevalence between visits (chi-square p=0.55). If including non-recommended single-therapy for syndromic treatment would increase each prevalence by 0.6%, 0.3%, and 0.0% for the respective time-points. The distribution of demographic and behavioral variables can be found in Table I, Appendix A. HIV prevalence was similar across the three visits at 10.5%, 11.0%, and 13.0% (chi-square p= 0.35). The prevalence of self-reported STI symptoms decreased from baseline to Visit 12. Dysuria decreased over time from 20.5% to 9.4%, penile ulcer from 10.6% to 4.4%, and urethral discharge from 17.1% to

6.3%, all decreases significant at p< 0.001. The behavioral variable “Ever Use a Condom” increased over time from 78.8% to 87.1% (chi-square p< 0.001).

From the 576 unscheduled and 3-month follow-up visits, of which 538 were 3-month follow-up visits, to Anza Mapema between visits 0 and 6, 28 (4.9%) of the men were treated with a dual-therapy regimen for STIs, while another 7 (1.2%) were treated with a non-recommended single therapy-regimen. Between visits 6 and 12, another 564 unscheduled and 9-month follow-up visits, of which 531 were 3-month follow-up visits, were recorded with 21 (3.7%) resulting in a dual-therapy STI treatment regimen and another 1 (0.2%) being treated with a non-recommended single-therapy regimen. These are about three times higher than the rates of STI syndromic treatment at scheduled visits but are the result of men seeking treatment for STI symptoms. The distribution of clinician recognized STI signs by treatment regimen can be found in Table III. During the scheduled visits, 26 (96.3%) of the urethritis diagnoses resulted in a correct dual-therapy treatment regimen while the other 1 (3.7%) did not have any recorded treatment. Of penile ulcer diagnoses, 5 (100%) resulted in a non-recommended single-therapy treatment regimen by antibiotics that are common for chlamydia or gonorrhea. From the unscheduled visits, 5 (41.7%) of the urethritis diagnoses were treated with dual-therapy, 4 (33.3%) were treated with single-therapy, and 3 (25%) had no recorded treatment. Penile ulcers received dual-therapy treatment for 37 (84.1%) of diagnoses, single-therapy for 2 (4.5%) of the diagnoses, and 5 (11.4%) of the diagnoses went untreated according to the recorded treatments. For scheduled visits and unscheduled visits, 3 (0.2%) and 9 (0.8%) of those that had no recorded sign of an STI received treatment by dual- or single-therapy regimens. This could indicate treatment for a separate condition, the diagnosis was not

properly recorded, or the patient reported symptoms but was showing no signs upon examination.

The sensitivity, specificity, PPV, and NPV are presented in Table IV, Appendix A. These were calculated using only recommended dual-therapy syndromic treatment. The sensitivity (95% CI) was consistently low across visits 0, 6, and 12 being 6.9% (2.6,14.6), 12.5% (4.2,26.8), and 7.7% (2.1,18.5) respectively. This sensitivity refers to the ability of syndromic management to correctly identify an STI. The specificity refers to syndromic management's ability to correctly identify an individual without an STI, and was estimated at 99.7% (98.8,99.9), 99.2% (97.9,99.8), and 99.0% (97.7,99.7) for visits 0, 6, and 12. In Table V, Appendix A, a chi-square test was performed to test for an association between the positive laboratory diagnosis and syndromic treatment results. The p-value of 0.568 indicates that there is no significant difference in the distribution of sensitivity of syndromic management by the scheduled visits. For this reason, the three visits were combined into single dataset of observations from scheduled visits. An overall sensitivity, specificity, PPV, and NPV were calculated with exact 95% confidence intervals (Table IV, Appendix A). The overall sensitivity of any syndromic management throughout the Anza Mapema study was 8.4% (4.8,13.5) meaning an estimated 91.6% of all urethral gonorrhea and chlamydia infections were missed by recommended, dual-therapy syndromic management. The overall specificity was estimated to be 99.3% (98.8,99.7) meaning 99.3% of all laboratory negative individuals were not treated by syndromic management. The PPV was 57.7% (36.9,76.7) which means of all those treated by syndromic management, 57.7% were truly positive by laboratory diagnosis while the NPV was estimated to be 90.7% (89.3,92.1) meaning

of all those who were not treated by syndromic management, 90.7% were negative by laboratory diagnosis.

An analysis of behavioral covariates against urine laboratory test results was done to determine which covariates were associated with a laboratory STI diagnosis and should be assessed for confounding through an analysis of adjusted odds ratios. Chi-square was used to estimate a statistical association between levels of covariates and the laboratory diagnosis. The test variable, syndromic treatment by dual-therapy was found to be associated with STI laboratory diagnosis (chi-square $p<0.001$). This would be expected as it is being used as a predictor for diagnosing an STI. Age was also associated with the laboratory STI diagnoses with a chi-square p-value of 0.008. The usual sexual position of the participant was also significantly associated with laboratory results (chi-square $p=0.013$). HIV status, circumcision status, and self-reported condom use were not found to have an association with urine laboratory STI results. Signs and symptoms of STIs were included in the assessment for confounding as they lie within the causal pathway of having an STI.

A crude prevalence odds ratio of having a positive urine laboratory result for syndromic treatment compared to no syndromic treatment was calculated to be 13.4 with 95% confidence interval of 6.0 to 29.6 (Table VII, Appendix A). This means that the odds of having a laboratory STI diagnosis is 13.4 times higher when syndromically treated compared to the odds of having a laboratory STI diagnosis when not being syndromically treated. This is expected, as the true positive between the two diagnoses should be higher than the false positive. The odds ratio after adjusting for age group was 13.9 (6.4,31.2). Adjustment for usual sexual position gave an OR between syndromic diagnosis and laboratory diagnosis of 13.4 (6.0,29.9). Neither the age

adjusted, nor the sexual position adjusted odds ratios provided a noticeable change from the crude odds ratio. While a 10% change was used to indicate a meaningful change in the odds ratio of association between syndromic diagnosis and laboratory diagnosis, it is important to note that this is not a statistical test. The lack of confounders provided evidence to report the crude measures of association.

2. Results: Specific Aim 2 and Specific Aim 3

Through the Anza Mapema study at visits 0, 6, and 12, a total of 46 participants had a recorded date of diagnosis and treatment by syndromic management, and another 67 had a recorded date of laboratory specimen collection and treatment. The 67 treatments based of laboratory diagnoses were then categorized as correct, recommended treatment (49) and incorrect, non-recommended treatment (18). Syndromic and laboratory based treatment may not be wholly independent as some syndromic treatment may have resulted in a treated laboratory diagnosis and vice versa. Of the 46 syndromic diagnoses and treatments, 45 of 46 (97.8%) were treated on the same day of diagnosis. One outlier was treated at 30 days, the only individual to not receive treatment on the same day of diagnosis. The 49 laboratory diagnoses based recommended treatments had a median time-to-treat of 130 days (IQR 92-173) with a minimum of 69 days to treat and a maximum of 306 days. The minimum time-to-treat of 69 days could be the result of lengthy time delays at multiple time points from specimen collection, time until the test is performed, communication of test results to the clinic, a clinician contacting the participant, and the participant returning for treatment. An additional 18 individuals were treated by a non-recommended treatment regimen with a median time-to-

treat of 126 days (IQR 1-5-181). These treatments are not considered to be correct therapy regimens and are thus included in the failure-to-treat rates.

Laboratory results in the failure-to-treat analysis included results of urine tests, rectal swabs, and syphilis serology. Of the 1,799 laboratory tests, 226 (12.6%) came back as positive for syphilis or a curable urethral or rectal STI. From these 226 positive tests, only 49 (21.7%) individuals received recommended therapy, 159 (70.3%) did not have documented treatment, and 18 (8.0%) received a non-recommended treatment regimen (Table IX, Appendix A). The failure-to-treat rate from laboratory diagnosis is the combination of no documented treatment and non-recommended treatment regiments, which is estimated at 78.3%. Of the 1,566 negative results, 0 (0.0%) were treated with either a single- or dual-therapy regimen. From the 1,840 clinic visits, 32 (1.7%) were diagnosed by a clinician recognizing an STI sign. Of these 32 visits that resulted in a syndromic STI diagnosis, only 1 (3.1%) was never treated, 5 (15.6%) were improperly treated with a non-recommended single-therapy regimen, and 26 (81.3%) were treated with the recommended dual-therapy regiment. This translates to a failure-to-treat rate of 18.7% for those diagnosed by syndromic management. From the 1,808 clinic visits that did not lead to a syndromic diagnosis, 3 (0.2%) were treated with either a single- or dual-therapy regimen. This may indicate that the participant may have had some other infection, the participant was treated based upon symptoms, or the treatment coincided with the treatment of a positive laboratory result, since the two are not independent.

G. DISCUSSION

To evaluate syndromic management of urethral STIs in the GBMSM population of Kisumu, Kenya, the sensitivity, specificity, PPV, and NPV were estimated using laboratory

diagnoses as a gold standard. The STI results from the Anza Mapema cohort study were used, and the sensitivity was found to be similar between three scheduled visits of baseline, month 6, and month 12. The similarity of syndromic diagnosis sensitivity across visits is logical as the diagnosis relies on a patient presenting signs or symptoms of an STI that can be noticed by a clinician. Each scheduled visit's sensitivity of syndromic management was consistently low with baseline being 6.9% (95%CI; 2.6,14.6), the 6-month visit being 12.5% (95%CI; 4.2,26.8) and the 12-month visit being 7.7% (95%CI; 2.1,18.5). The findings are slightly lower than the sensitivity of syndromic diagnosis of chlamydia and gonorrhea in a study of 503 MSM in El-Salvador, which was estimated to be 17% (Shah et al., 2014). The low sensitivity results in part from the necessary presentation of signs or symptoms for diagnosis. Asymptomatic infections would not be detected, and STIs have very high rates of asymptomatic infection as reported in the literature. For example, Sanders et al. found that only 4 of 41 (13%) of MSM in coastal Kenya that tested positive for an STI by laboratory diagnosis presented signs or symptoms at the time of visit (2014). Syndromic treatment of an STI occurred a total of 14 times, or 0.9% of the 1,611 negative laboratory tests between the three scheduled visits. This number may have been due to the presentation of signs or symptoms for an STI that were not included in the laboratory diagnostic testing such as *Trichomonas vaginalis* or *Mycoplasma genitalium*.

While the sensitivity was calculated at scheduled visits, the unscheduled visits between baseline and month 6 or between month 6 and month 12 did not include specimen collection for STI laboratory diagnosis. Due to the nature of a scheduled visit at Anza Mapema, many STI signs may be detected and treated even with the participant not recognizing the symptom. The nature of these scheduled visits, therefore, reduces the generalizability of results towards a

typical STI clinic or general practice. In the general population, an individual would need to recognize a symptom in order to seek care. The scheduled visits allow the identification of a clinical sign regardless of the participant's awareness. Due to this, the sensitivity of syndromic management in this study may be underestimated since the men were required to visit on these specified dates even if they were feeling healthy. Typically, an individual would not seek out care unless they recognized an ailment. An estimated 4.9% of unscheduled visits between baseline and month 6 and an estimated 3.7% of unscheduled visits between month 6 and month 12 resulted in recommended dual-therapy treatment by syndromic diagnosis. This may be more representative of the syndromic rates of diagnosis at a general STI clinic since it relied on the individual seeking care for a recognized symptom, but may still under represent the true rate of STIs as it only includes signs recognized by the physician and not reported symptoms.

Upon entry into the study, the prevalence of urethral STI was about 12.5%. This is double the 6% from a baseline evaluation of a cohort of 244 MSM in costal Kenya (Sanders et al., 2014). A study in Nairobi by Muraguri et al. of 290 MSM who had never sold sex and 273 MSM who had sold sex found the prevalence of genital chlamydia (0.7% to 3.3%) and genital gonorrhea (3.5% to 5.4%) where the lower prevalence rates refer to the MSM who had never sold sex (2015). Treatment and behavioral change may have impacted the baseline prevalence at Anza Mapema since the prevalence of urethral STIs at 12 months was 9.4%. The change in behavioral characteristics at Anza Mapema and reported STI symptoms from baseline to month 12 was observed for several variables. These results could indicate a successful STI treatment program, educational information provided by Anza Mapema, the reliable availability of free condoms, the possibility that the participants most likely to be retained through the entire

study are those with lower rates of symptoms, social desirability/response bias, or a combination of factors. The laboratory diagnosis by urine sample was positively associated with younger age groups and those who usual sexual position is insertive. Although associations were found between sexual position and laboratory diagnosis and between age group and laboratory diagnosis, the odds ratio of association between syndromic diagnosis and laboratory diagnosis was not different after adjusting for the age and sexual position. No confounding was found on the relationship between syndromic diagnosis and laboratory diagnosis by any of the measured covariates.

The sensitivity analysis only included penile and urethral infections since a large majority of rectal infections are asymptomatic and clinicians identified only two participants with signs of rectal infection. Thus, syndromic management of rectal STIs could not be analyzed. This is a large limitation in the diagnosis and treatment of STIs in the GBMSM community where nearly two fifths of the participants in the Anza Mapema cohort report receptive anal or versatile intercourse. Sanders et al. found that of 244 Kenyan MSM, 147 (62%) had participated in receptive anal intercourse in the past six months, with 30 of these individuals having a laboratory diagnosis of rectal chlamydia or gonorrhea infection (2014). Further evidence of high rates of receptive anal intercourse (70% in the past 12-months) can be found in a cross-sectional study of 200 MSM in Cape Town (Rebe et al., 2015). The study in Cape Town discussed the treatment of laboratory diagnosed infections but made no mention of syndromic treatment (Rebe et al., 2015). High rates of anal intercourse provides plausibility for significant rates of rectal infection and that laboratory based STI screening for GBMSM is needed.

Laboratory diagnostic testing is an accurate method for the identification of STIs. It is an important method for identification of asymptomatic infection, especially in a high-risk population where STI rates tend to be higher than the general population. The major barriers are often cost and access, as the diagnostic testing can be unaffordable in many settings. Syndromic management is often utilized for the identification and treatment of STIs, especially in resource limited settings. According to the results of this study, however, syndromic management missed 91.5% of urethral and penile STIs, and supplementation by regular laboratory diagnostic testing should occur. Rebe et al., estimated that of 32 MSM with gonococcal infection and of 23 MSM with chlamydial infection, 26 (67%) and 21 (91%) were asymptomatic meaning no syndromic diagnosis would be possible. Studies have even recommended combining syndromic management with presumptive treatment which dictates when to treat for an STI based upon a grouping of sexual behaviors that are identified as high-risk (Okuku et al. 2012). The benefit to syndromic management, is the resultant immediate treatment, where laboratory diagnosis in this study provides a delayed treatment through a lengthy process. This is apparent in our study in which 99% of all syndromic diagnosed cases were treated the same day, while laboratory diagnoses were not treated until a minimum of 69 days after specimen collection, with a median time-to-treat of 130 days. In resource limited settings, this time can be due to a lengthy process of transporting the specimen to an external laboratory, understaffed laboratories where the tests can take weeks to be processed, the process of communicating the results back to the clinic, the responsibility of the clinician to contact the patient, and the responsibility of the patient to return for treatment. At Anza Mapema, the majority of laboratory diagnoses STIs, 78.3%, did not have documented

treatment. This is compared to the failure-to-treat rate of syndromic diagnosis being only 18.7% who had no record of having received appropriate treatment. This failure-to-treat rate, however, may be overestimated as a number of treatments could have occurred that were never documented in clinical notes. No reports in the clinical notes were found that indicate a clinician's failed or successful attempt to contact an individual for treatment that had a positive laboratory diagnosis. Documentation of these contacts or attempted contacts could assist in the identification of where treatment by laboratory diagnosis was failing

The inability to include an analysis of rectal infections in the management of STIs was an important finding from this study. The proportion of asymptomatic versus symptomatic rectal infections was high, which may be affected by the fact that anoscopy was not routinely performed. The prevalence of laboratory diagnosed rectal infections ranged between 4% and 5% at visits 0, 6, and 12; no signs of these infections were detected by clinicians. At unscheduled visits, only 2 rectal infections were identified through clinician recognized signs. High rates of anal intercourse and high proportions of asymptomatic versus symptomatic rectal infection may result in a continued high STI rate in MSM due to the lack of rectal management. While laboratory diagnoses exist for the diagnosis of rectal STIs, syndromic management is limited in the identification of rectal infection without anoscopy.

Evaluation of the specific time points in which treatment was delayed is a necessary step towards improving the overall strength of a clinic that offers laboratory screening. Originally, the time-to-treat aim was to calculate time points between specimen collection and treatment of the diagnosed STI. External laboratories used for the testing may be an issue in terms of timely treatment as the specimens need to be delivered to the laboratory, processed

into the laboratory, tested, results must be recorded, and then sent back to the clinic of origin. Another section of concern in the timeline is between receipt of the laboratory test results and treatment. This timeframe includes a clinician contacting the STI positive individual, scheduling a time for treatment, and providing the treatment when the individual returns. Time may be lost in this procedure as many individuals in Kisumu have intermittent access to telephones, email, or other types of communication. When a known turnaround time is expected, it may be beneficial for a clinic to offer a token or card that can help a patient remember that they had testing performed. If they do not hear from their physician within the allotted time, they would be reminded to check in with the clinic. This may also increase accountability for the clinic staff to be proactive in assuring quick laboratory turn around through continued communication.

Syndromic management's strength is rapidly treating individuals for a urethral STI; however, only about 8.5% of infections were recognized in our study. Treating only 8.5% of the infected population is not sufficient for curtailing the STI epidemic. Laboratory diagnoses are the gold standard for surveillance and identification of STIs. In resource limited settings, however, the process of specimen collection, transportation to a laboratory, receipt of results, contact of infected individuals for treatment, and accurate treatment of the infection can possibly lead to delayed treatment. A properly run system for testing and treating is needed to make an impact on the STI epidemic in MSM.

H. LIMITATIONS

A limitation to this study is the inability to strongly generalize the sensitivity of syndromic management to a general STI clinic. This is because laboratory diagnosis of STIs was available only at scheduled visits and because testing and assessment of signs and symptoms

occurred for all men, rather than among men seeking care on the basis of signs or symptoms or known exposure. In resource limited settings, syndromic diagnosis is often heavily relied upon, where laboratory diagnosis may be forgone due to cost or lack of availability. Another limitation was the exclusion of rectal infections in the analysis of syndromic management. These infections were excluded due to small numbers of detected signs by a clinician. While these infections were included in the time-to-treat and failure-to-treat rates, they were excluded in the sensitivity analysis. This limitation by exclusion of rectal infections could be reduced if rectal syndromic management included an examination for signs of proctitis at every visit. Future studies may consider focusing on the rectal infections. This limits the sensitivity analyses of syndromic management to urethral infections. The sensitivity of syndromic management may differ depending on the type of signs or symptoms being reported, but small cell sizes prevented a stratified analysis by signs from being possible.

Given the prolonged time-to-treat laboratory diagnosed infections, another limitation is the inability to identify the specific time points where delay in treatment may be the longest. The original analysis was to look at the time between specimen collection to reception at the external laboratory, the time from reception to testing, the time from achieving the test result to reception of results by Anza Mapema, the time to contact the participant, and the time for the participant to return for treatment. This was reduced to the time from specimen collection to treatment because of a lack of recorded information. Dates were not available for the time points in between. Future studies may consider recording all dates, so an analysis of the time-to-treat can be more robust, especially in resource limited settings where understaffing is maybe problem, external laboratories are utilized, and communication challenges may exist.

I. CONCLUSIONS

The low sensitivity of syndromic chlamydia, gonorrhea, and syphilis diagnosis compared to laboratory diagnoses in MSM of Kisumu, Kenya is low but may be improved as other studies in other parts of the world have shown higher sensitivities. Rectal screening for STIs should begin to include more sensitive approaches such as presumptive treatment or definitive procedures such as anoscopy. Laboratory diagnoses of this study show a very high failure-to-treat rate and detailed documentation of specimen transport, laboratory testing, reception of results, and communication between patients and clinicians should be included in future studies as to identify where improvement can be made. This detailed documentation is also important for the timeliness of treatment as the median time-to-treat from specimen collection for laboratory diagnosed MSM in Kisumu, Kenya was more than four months. Continued education on the treatment of STIs with proper regimens is important as well, as many men may receive improper treatment and remain infected. Syndromic diagnosis of chlamydia, gonorrhea, and syphilis is not sufficient and laboratory testing in this study has shown a low rate of treatment. Improved systems or the addition of a separate method for treatment, such as presumptive treatment or rapid test kits should be considered in clinics that treat MSM in eastern Kenya.

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APPENDICES

Appendix A

Table I: Distribution of Demographic Variables, Laboratory STI Results, and Syndromic STI Results by Visit Number in the Anza Mapema Cohort Study				
	Visit 0	Visit 6	Visit 12	X^2/ANOVA p-value[1]
TOTAL SAMPLE SIZE = 1840	N=711	N=554	N=575	
Urethral Laboratory Results	**n=703**	**n=536**	**n=552**	0.0114
Positive	88 (12.5)	40 (7.5)	52 (9.4)	
Negative	615 (87.5)	496 (92.5)	500 (90.6)	
Syndromic Treatment	**n=703**	**n=554**	**n=575**	0.5513
Recommended Dual-Therapy	8 (1.1)	11 (2.0)	9 (1.6)	
Non-recommended Therapy	4 (0.6)	2 (0.3)	0 (0.0)	
None	689 (98.3)	540 (97.7)	566 (98.4)	
Rectal Laboratory Results	**n=702**	**n=537**	**n=555**	0.5427
Positive	36 (5.1)	22 (4.1)	22 (4.0)	
Negative	666 (94.9)	515 (95.9)	533 (96.0)	
Median Age (IQR)	24 (21-28)	24 (21-29)	24 (21-28)	
Age Group	**n=711**	**n=554**	**n=575**	0.9723
18-24	398 (56.0)	301 (54.3)	320 (55.6)	
25-34	252 (35.4)	202 (36.5)	207 (36.0)	
35+	61 (8.6)	51 (9.2)	48 (8.4)	
HIV Status	**n=711**	**n=547**	**n=568**	0.3515
Positive	75 (10.5)	60 (11.0)	74 (13.0)	
Negative	636 (89.5)	487 (89.0)	494 (87.0)	
Circumcision Status	**n=711**	**n=547**	**n=568**	0.4079
Yes	541 (76.1)	425 (77.7)	450 (79.2)	
No	170 (23.9)	122 (22.3)	118 (20.8)	
Ever Use a Condom	**n=711**	**n=549**	**n=573**	<0.0001
Yes	560 (78.8)	472 (86.0)	499 (87.1)	
No	151 (21.2)	77 (14.0)	74 (12.9)	
Typical Sexual Positioning	**n=698**	**n=541**	**n=565**	0.2091
Insertive	386 (55.3)	320 (59.1)	336 (59.5)	
Receptive	152 (21.8)	95 (17.6)	96 (17.0)	
Versatile	160 (22.9)	126 (23.3)	133 (23.5)	
STI Signs (Penile)	**n=711**	**n=554**	**n=575**	0.3394
Urethritis	7 (1.0)	11 (2.0)	9 (1.6)	
Genital Ulcers	3 (0.4)	2 (0.4)	0 (0.0)	
None	701 (98.6)	541 (97.7)	566 (98.4)	
STI Symptoms				
Dysuria	**n=706**	**n=549**	**n=572**	<0.0001
Yes	145 (20.5)	56 (10.2)	54 (9.4)	
No	561 (79.5)	493 (89.8)	518 (90.6)	
Penile Ulcer	**n=709**	**n=547**	**n=572**	<0.0001
Yes	75 (10.6)	33 (6.0)	25 (4.4)	
No	634 (89.4)	514 (94.0)	547 (95.6)	
Urethral Discharge	**n=709**	**n=548**	**n=572**	<0.0001
Yes	121 (17.1)	45 (8.2)	36 (6.3)	
No	588 (82.9)	503 (91.8)	536 (93.7)	

[1]Chi-square and ANOVA p-values <0.05 identify association between covariate levels and visits 0, 6, and 12

Appendix A (continued)

Table II. Recommended and Non-Recommended Syndromic Treatment by Visit without Laboratory Confirmatory Test for Urethral Infections		
	Unscheduled 0-6 N(%)	Unscheduled 6-12 N(%)
Sample Size	N=576	N=564
Recommended Dual-Therapy	28 (4.9)	21 (3.7)
Non-recommended Therapy	7 (1.2)	1 (0.2)
No Syndromic Treatment	541 (93.9)	542 (96.1)

*Unscheduled 0-6 and Unscheduled 6-12 include 3-month and 9-month scheduled follow-up

Table III. Distribution of Clinician Detected Urethritis and Penile Ulcer by Syndromic Diagnosis Treatment Regimens			
	Syndromic Diagnosis Treatment at Scheduled Visits		
	Dual-Therapy	Non-recommended Therapy	Not Treated
Urethritis N(%)	26 (96.3)	0 (0.0)	1 (3.7)
Penile Ulcer N(%)	0 (0.0)	5 (100.0)	0 (0.0)
None N(%)	1 (0.1)	2 (0.1)	1805 (99.8)
	Syndromic Diagnosis Treatment at Unscheduled Visits		
	Dual-Therapy	Non-recommended Therapy	Not Treated
Urethritis N(%)	5 (41.7)	4 (33.3)	3 (25)
Penile Ulcer N(%)	37 (84.1)	2 (4.5)	5 (11.4)
None N(%)	7 (0.6)	2 (0.2)	1073 (99.2)

Appendix A (continued)

Table IV. Sensitivity, Specificity, PPV, and NPV of Recommended Syndromic Dual-Therapy by Scheduled Visit with Laboratory Diagnostic Results as a Gold Standard						
	Visit 0		Visit 6		Visit 12	
	Laboratory Positive N(%)	Laboratory Negative N(%)	Laboratory Positive N(%)	Laboratory Negative N(%)	Laboratory Positive N(%)	Laboratory Negative N(%)
Recommended Dual-Therapy	6 (6.8)	4 (0.7)	5 (12.5)	4 (0.8)	4 (7.7)	5 (1.0)
Non-recommended Therapy	2 (2.3)	0 (0.0)	0 (0.0)	1 (90.2)	0 (0.0)	0 (0.0)
No Syndromic Treatment	80 (90.9)	611 (99.3)	35 (87.5)	491 (99.0)	48 (92.3)	495 (99.0)
Sensitivity (95%CI)	6.98 (2.6,14.6)		12.50 (4.2,26.8)		7.69 (2.1,18.5)	
Specificity (95%CI)	99.67 (98.8,99.9)		99.19 (97.9,99.8)		99.00 (97.7,99.7)	
PPV (95%CI)	75.00 (34.9,96.8)		55.56 (21.2,86.3)		44.44 (13.7,78.8)	
NPV (95%CI)	88.42 (85.8,90.7)		93.35 (90.9,95.3)		91.16 (88.5,93.4)	
Dual-Therapy Sensitivity% (95%CI)	8.43 (4.8,13.5)					
Dual-Therapy Specificity% (95%CI)	99.32 (98.8,99.7)					
Dual-Therapy PPV% (95%CI)	57.69 (36.9,76.7)					
Dual-Therapy NPV% (95%CI)	90.74 (89.3,92.1)					

Appendix A (continued)

Table V. Chi-Square Analysis of Positive Laboratory Results at Scheduled Visits Recommended Dual-Therapy Syndromic Treatment				
	Laboratory Results			
Any Syndromic Treatment	Visit 0	Visit 6	Visit 12	Chi-Square p-value
Positive	6	5	4	0.568
Negative	80	35	48	

Appendix A (continued)

Table VI. Distribution of Covariates by Laboratory Diagnostic Test Results at Scheduled Visits 0, 6, and 12			
	Laboratory Results		
	# Positive (%)	# Negative (%)	Chi-Square p-value
Syndromic Treatment			<0.001
Recommended Dual Therapy	15 (57.7)	11 (42.3)	
Non-recommended Therapy	2 (40.0)	3 (60.0)	
None	163 (9.3)	1597 (90.7)	
Age Group			<0.001
18-24	120 (12.1)	873 (87.9)	
25-34	55 (8.6)	585 (91.4)	
35+	5 (3.2)	53 (96.8)	
HIV Status			0.202
Positive	15 (7.5)	185 (92.5)	
Negative	165 (10.4)	1425 (89.6)	
Circumcision Status			0.774
Yes	141 (10.2)	1246 (89.8)	
No	39 (9.7)	364 (90.3)	
Ever Use a Condom			0.372
Yes	146 (9.8)	1347 (90.2)	
No	34 (11.5)	77 (88.5)	
Typical Sexual Position			0.013
Insertive	88 (8.7)	929 (91.7)	
Receptive	34 (10.2)	299 (89.8)	
Versatile	57 (13.9)	354 (86.1)	
STI Signs			
Urethral			<0.001
Urethritis	6 (85.7)	1 (14.3)	
Genital Ulcers	1 (33.3)	2 (66.7)	
None	76 (11.9)	560 (88.1)	
STI Symptoms			
Dysuria			<0.001
Yes	46 (18.3)	206 (81.8)	
No	134 (8.8)	1397 (91.2)	
Penile Ulcer			0.078
Yes	19 (14.4)	113 (85.6)	
No	159 (9.6)	1494 (90.4)	
Urethral Discharge			0.005
Yes	31 (15.7)	166 (84.3)	
No	149 (9.4)	1439 (90.6)	

Appendix A (continued)

Table VII. Odds Ratio of Positive Urine Laboratory Diagnoses with Syndromic Treatment Versus No Syndromic Treatment after Adjusting for Age and Typical Sexual Position		
	Adjusted OR (95%CI)	Confounder based on 10% Difference from Crude OR (Yes or No)
Crude OR	13.35 (6.0,29.6)	--
Age Group	13.92 (6.2,31.2)	No
Typical Sexual Position	13.44 (6.0,29.9)	No

Table VIII. Median Time-to-Treat measured in Days by Syndromic and Laboratory STI Diagnosis at Scheduled Visits			
	Syndromic	Laboratory (Recommended Treatment)	Laboratory (Non-Recommended Treatment)
N= 124	46	49	18
Median Time-to-treat (IQR)	0 (0-0)	130 (92-173)	126 (105-181)
Minimum Time-to-Treat	0	69	73
Maximum Time-to-Treat	30	306	224

Table IX. Rates of Treatment and Failure-to-Treat-Rate by Syndromic and Laboratory STI Diagnosis at Scheduled Visits (Penile and Rectal STIs)				
	Treatment Regimen			
Laboratory STI Diagnosis	**Recommended Therapy**	**Non-Recommended Therapy**	**None**	**Failure-to-Treat Rate**
# Positive (%)	49 (21.7)	18 (8.0)	159 (70.3)*	78.3%
# Negative (%)	0 (0.0)	0 (0.0)	1573 (100.0)	
Syndromic STI Diagnosis	**Recommended Dual-Therapy**	**Non-Recommended Therapy**	**None**	**Failure-to-Treat Rate**
# Positive (%)	26 (81.3)	5 (15.6)	1 (3.1)*	18.7%
# Negative (%)	2 (0.1)	1 (0.1)	1805 (99.8)	

*Unscheduled 0-6 and Unscheduled 6-12 include 3-month and 9-month scheduled follow-up

Appendix B

Search Terms and Search Results

The following searches were implemented in separate search steps in order to identify relevant materials for the scoping review.

In PubMed, three Medical Subject Heading (MeSH) terms were utilized as a way to identify literature in three key areas of the review: "Homosexuality, Male", "Sexually Transmitted Diseases, Bacterial", and "Eastern Africa". These MeSH terms are of a standardized vocabulary from the National Library of Medicine's controlled thesaurus, and help to identify the subjects of research literature in PubMed. These three MeSH terms created the first step of each individual search. Each search also included a string of relevant keywords that were searched for in the titles and abstracts of all literature. The keywords were followed by [tiab], which tells PubMed to look for the keywords in titles and abstracts. The "East African" keywords were followed by [tw] which tells PubMed to search the titles, abstracts, and keywords of publication authors. A list of the keywords, and under which MeSH term they belong can be seen below.

- "Homosexuality, Male"
    - "men who have sex with men"
    - bisexual
    - gay
    - homosexual
    - homosexuality
    - MSM
- "Sexually Transmitted Diseases, Bacterial"
    - diagnosis
    - treatment
    - treated
    - "time to treat"
    - surveillance
    - syndrome
    - "syndromic management"
    - syphilis
    - chlamydia
    - gonorrhea
    - gonorrhoea
    - anal
    - rectal
    - penile
    - proctitis
    - urethritis
    - epididymitis
    - "Sexually Transmitted Infections"
    - STI
    - STD
    -

Appendix B (continued)

    - Sensitivity
    - Specificity
    - "positive predictive value"
    - "negative predictive value"
- "Eastern Africa"
    - "East Africa"
    - "Eastern Africa"
    - Kenya
    - Kenyan
    - Tanzania
    - Tanzanian
    - Uganda
    - Ugandan
    - Mozambique
    - Mozambican
    - Malawi
    - Malawian
    - "South Africa"
    - "South African"
    - Nairobi
    - Kisumu
    - Mombasa
    - Kampala
    - "Dar Es Salaam"

Each of the searches were performed in PubMed separately using the Boolean "or", and then combined using the Boolean "and". The same search terms and combinations were used Web of Science, except the MeSH terms, [tw], and [tiab] features were not utilized. All relevant searches with number of results can be seen below in Appendix B and C.

Appendix C

Search results from PubMed database

History Download history Clear history

Search	Add to builder	Query	Items found	Time
#7	Add	Search ((((((**"Homosexuality, Male" [mesh] or homosexual [tiab] or homosexuality [tiab] or "men who have sex with men" [tiab] or bisexual [tiab] or gay [tiab] or MSM [tiab])))) AND ((((((("sexually transmitted diseases, bacterial" [mesh] or STI [tiab] or STD [tiab]or syphilis [tiab] or chlamydia [tiab] or gonorrhea [tiab] or treatment [tiab] or syndrome [tiab] or "syndromic management" [tiab] or "sexually transmitted infections" [tiab] or sensitivity [tiab] or "positive predictive value" [tiab] or anal [tiab] or rectal [tiab] or penile [tiab] or proctitis [tiab] or urethritis [tiab] or epididymitis [tiab] or "negative predictive value" [tiab] or specificity [tiab] or "time to treat" [tiab] or treated [tiab] or diagnosis [tiab] or gonorrhoea [tiab])))))))))) AND ((((((("Eastern Africa" [mesh] or Kenya [tw] or Tanzania [tw] or Uganda [tw] or Mozambique [tw] or Kenyan [tw] or Tanzanian [tw] or Ugandan [tw] or Mozambican [tw] or Nairobi [tw] or Kisumu [tw] or Mombasa [tw] or Kampala [tw] or "East Africa" [tw] or "Eastern Africa" [tw] or "South Africa" [tw] or "South African" [tw] or "Dar Es Salaam" [tw] or Malawi [tw] or Malawian [tw]**)	225	09:51:48
#5	Add	Search (((((("Eastern Africa" [mesh] or Kenya [tw] or Tanzania [tw] or Uganda [tw] or Mozambique [tw] or Kenyan [tw] or Tanzanian [tw] or Ugandan [tw] or Mozambican [tw] or Nairobi [tw] or Kisumu [tw] or Mombasa [tw] or Kampala [tw] or "East Africa" [tw] or "Eastern Africa" [tw] or "South Africa" [tw] or "South African" [tw] or "Dar Es Salaam" [tw] or Malawi [tw] or Malawian [tw])))))))**	101687	09:49:29
#2	Add	Search (((((("sexually transmitted diseases, bacterial" [mesh] or syphilis [tiab] or chlamydia [tiab] or gonorrhea [tiab] or treatment [tiab] or syndrome [tiab] or "syndromic management" [tiab] or "sexually transmitted infections" [tiab] or sensitivity [tiab] or "positive predictive value" [tiab] or anal [tiab] or rectal [tiab] or penile [tiab] or proctitis [tiab] or urethritis [tiab] or epididymitis [tiab] or "negative predictive value" [tiab] or specificity [tiab] or "time to treat" [tiab] or treated [tiab] or diagnosis [tiab] or gonorrhoea [tiab])))))))**	6482427	09:38:14
#1	Add	Search (("Homosexuality, Male" [mesh] or homosexual [tiab] or homosexuality [tiab] or "men who have sex with men" [tiab] or bisexual [tiab] or gay [tiab] or MSM [tiab]))	31487	09:37:42

Search results from Web of Science database

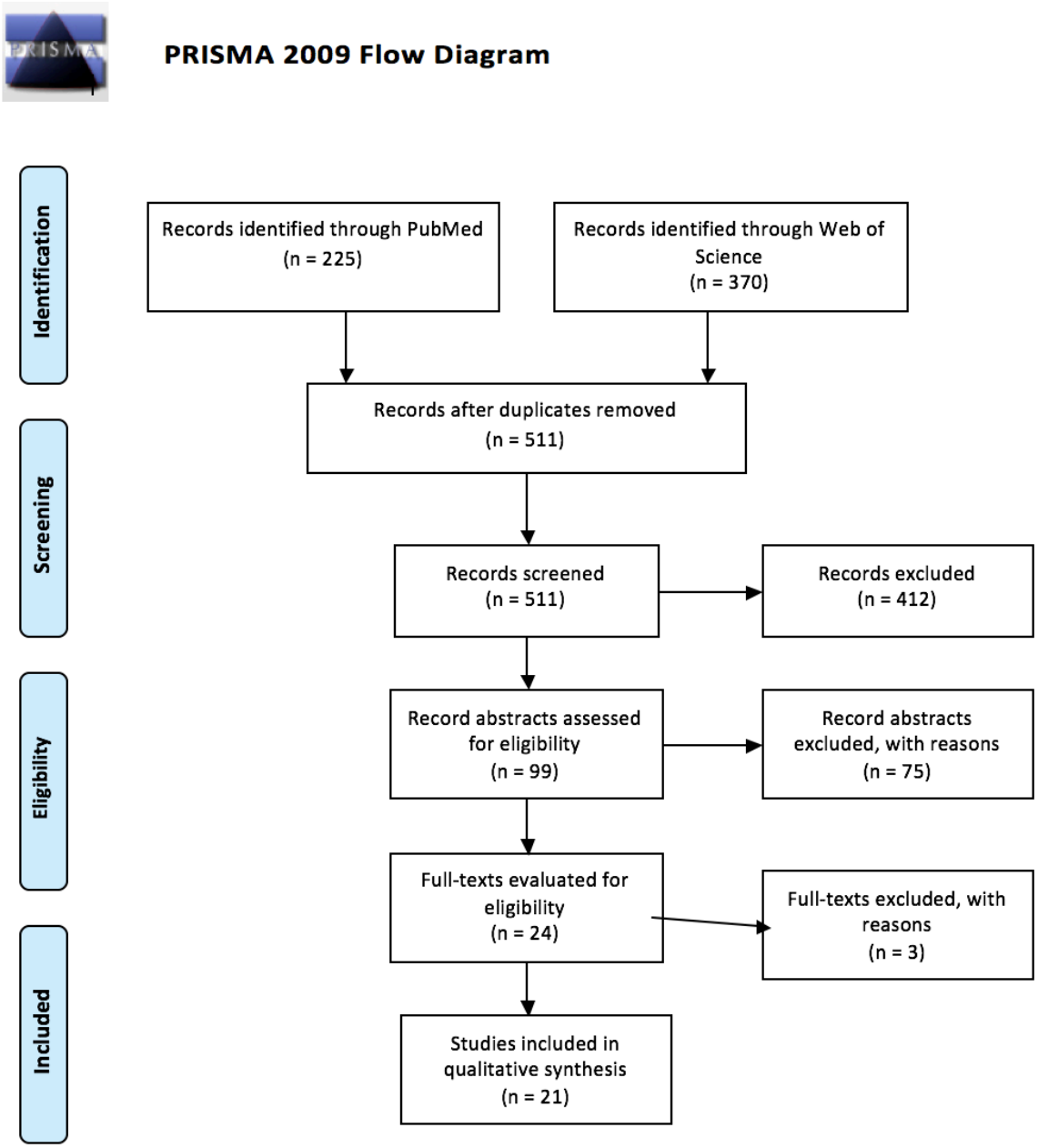
Search History:

Set	Results	Save History / Create Alert · Open Saved History	Edit Sets	Combine Sets (AND OR) Combine	Delete Sets Select All · Delete
# 4	370	#3 AND #2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	Edit		
# 3	198,688	TS = ("Eastern Africa" or Kenya or Tanzania or Uganda or Mozambique or Kenyan or Tanzanian or Ugandan or Mozambican or Nairobi or Kisumu or Mombasa or Kampala or "East Africa" or "Eastern Africa" or "South African" or "South Africa" or Malawi or Malawian or "Dar es Salaam") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	Edit		
# 2	7,129,931	TS = ("sexually transmitted diseases bacterial" or syphilis or chlamydia or gonorrhea or treatment or syndrome or "syndromic management" or "sexually transmitted infections" or sensitivity or "positive predictive value" or anal or rectal or penile or proctitis or urethritis or epididymitis or "negative predictive value" or specificity or "time to treat" or treated or diagnosis or gonorrhoea) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	Edit		
# 1	52,286	**TOPIC:** ("Homosexuality, Male" or homosexual or homosexuality or "men who have sex with men" or bisexual or gay or MSM) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	Edit		
				AND OR Combine	Select All · Delete

Appendix D

Table X. Screening and Eligibility Criteria for Systematic Review		
Criteria	**Exclusion- Record Excluded because**	**Inclusion- Record included because**
Main outcome	Presented an outcome that was either HIV, HPV, HSV-2, HCV, Drug Use, etc. without chlamydia, gonorrhea, or syphilis	Presented an outcome that was chlamydia, gonorrhea, or syphilis (could be combined with other diseases)
Location	Presented research or review in an area outside of eastern or southern Africa	Presented research or review in an area of eastern or southern Africa
Gender	Presented research or review exclusively on women	Presented research or review on men (could be combined with women)
Sexuality	Focused exclusively on heterosexual males	Focused on gay or bisexual men who have sex with men (could include other sexual groups)
Type	Text-book or qualitative review paper with no particular data reported	Abstract, fully published text of review papers, cohort studies, etc.

Appendix E



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Appendix F

Table XI. Results of Screening (N=99)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
Misser, F. (1986)	Trying to break the African connection	Exclude	Main Outcome
Piot, P. (1988)	AIDS: the impact of other sexually transmitted diseases	Exclude	Sexuality
Simonsen, J.N. et al. (1988)	Human immunodeficiency virus infection among men with sexually transmitted diseases. Experience from a center in Africa	Exclude	Sexuality/Main Outcome
World Aids (1989)	Can community carers cope?	Exclude	Main Outcome
Malu, F.S. (1990)	Inter-relationships between HIV infection and other sexually transmitted diseases	Exclude	Sexuality/Main Outcome
Tebere, R. (1991)	Uganda opens new fronts	Exclude	Main Outcome
Panos Institute (1991)	Unsung heroes in the South	Exclude	Main Outcome
Laga, M. (1992)	Interactions between STDs and HIV infection	Exclude	Gender/Sexuality
SAfAIDS news : Southern Africa AIDS Information Dissemination Service bulletin (1997)	Should condoms be available in prisons?	Exclude	Main Outcome
Zachariah, R. et al. (2002)	Sexually transmitted infections among prison inmates in a rural district of Malawi	Exclude	Sexuality/Main Outcome
Zenilman, J.M. (2005)	Behavioral interventions--rationale, measurement, and effectiveness	Include	All Criteria
Kajubi, P. et al. (2008)	Gay and bisexual men in Kampala, Uganda	Include	All Criteria
Sharma, A. et al. (2008)	Sexual identity and risk of HIV/STI among men who have sex with men in Nairobi	Include	All Criteria
Onyango-Ouma, W., Birungi, H., & Geibel, S (2009)	Engaging men who have sex with men in operations research in Kenya	Exclude	All Criteria

Appendix F (continued)

Table XI. Results of Screening (N=99) (continued)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
Raymond, F.H. et al. (2009)	Correlates of unprotected receptive anal intercourse among gay and bisexual men: Kampala, Uganda	Exclude	Main Outcome
Sanders, E.J. et al. (2010)	High prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae infections among HIV-1 negative men who have sex with men in coastal Kenya	Include	All Criteria
Knox, J. (2010)	The fallacy of intimacy: sexual risk behaviour and beliefs about trust and condom use among men who have sex with men in South Africa	Exclude	Main Outcome
Stephenson, R., de Voux, A., & Sullivan, P.S. (2011)	Intimate Partner Violence and Sexual Risk-taking among Men Who Have Sex with Men in South Africa	Exclude	Main Outcome
Moen, K. (2012)	Not at all so hard-to-reach: same-sex attracted men in Dar es Salaam	Exclude	Main Outcome
Obiero, J., Mwethera, P.G., & Wiysonge, C.S. (2012)	Topical microbicides for prevention of sexually transmitted infections	Exclude	Main Outcome
Arnold, M.P., et al. (2013)	Contextual correlates of per partner unprotected anal intercourse rates among MSM in Soweto, South Africa	Exclude	Main Outcome
Mannava, P., et al. (2013)	Male sex workers who sell sex to men also engage in anal intercourse with women: evidence from Mombasa, Kenya	Exclude	Main Outcome
Lewis, D.A. et al. (2013)	Phenotypic and genetic characterization of the first two cases of extended-spectrum-cephalosporin-resistant Neisseria gonorrhoeae infection in South Africa and association with cefixime treatment failure	Include	All Criteria
Eaton, L.A. et al. (2013)	Men who report recent male and female sex partners in Cape Town, South Africa: an understudied and underserved population	Exclude	Main Outcome
Okall, D.O. et al. (2013)	Men who have sex with men in Kisumu, Kenya: support group membership and knowledge of HIV-risk factors	Exclude	Main Outcome
Kaighobadi, F. et al. (2014)	Age and sexual risk among Black men who have sex with men in South Africa:	Exclude	Main Outcome

Appendix F (continued)

Table XI. Results of Screening (N=99) (continued)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
	the mediating role of attitudes toward condoms		
Tucker, A. et al. (2014)	Homophobic stigma, depression, self-efficacy and unprotected anal intercourse for peri-urban township men who have sex with men in Cape Town, South Africa: a cross-sectional association model	Exclude	Main Outcome
Sanders, E.J. et al. (2014)	Evaluation of WHO screening algorithm for the presumptive treatment of asymptomatic rectal gonorrhoea and chlamydia infections in at-risk MSM in Kenya	Include	All Criteria
Van der Elst, E.M. et al. (2013)	Experiences of Kenyan healthcare workers providing services to men who have sex with men: qualitative findings from a sensitivity training programme	Exclude	Main Outcome
Van der Elst, E.M. et al. (2013)	Men who have sex with men sensitivity training reduces homoprejudice and increases knowledge among Kenyan healthcare providers in coastal Kenya	Exclude	Main Outcome
Bui, T.C. et al. (2014)	Sexual motivation, sexual transactions and sexual risk behaviors in men who have sex with men in Dar es Salaam, Tanzania	Exclude	Main Outcome
Wirtz, A.L. et al. (2014)	A qualitative assessment of health seeking practices among and provision practices for men who have sex with men in Malawi	Exclude	Main Outcome
Ross, M.W. et al. (2014)	High HIV seroprevalence, rectal STIs and risky sexual behaviour in men who have sex with men in Dar es Salaam and Tanga, Tanzania	Include	All Criteria
Muraguri, N. et al. (2015)	HIV and STI prevalence and risk factors among male sex workers and other men who have sex with men in Nairobi, Kenya	Include	All Criteria
Dijkstra, M. et al. (2015)	Emerging themes for sensitivity training modules of African healthcare workers attending to men who have sex with men: a systematic review	Exclude	Main Outcome
Rebe, K. et al. (2015)	A Cross Sectional Analysis of Gonococcal and Chlamydial Infections among Men-Who-Have-Sex-with-Men in Cape Town, South Africa	Include	All Criteria

Appendix F (continued)

Table XI. Results of Screening (N=99) (continued)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
Stahlman, S. et al. (2016)	Respondent-driven sampling as a recruitment method for men who have sex with men in southern sub-Saharan Africa: a cross-sectional analysis by wave	Exclude	Main Outcome
Kim, E.J. et al. (2016)	Sexually transmitted infections associated with alcohol use and HIV infection among men who have sex with men in Kampala, Uganda	Include	All Criteria
Van der Elst, E.M. et al. (2015)	The green shoots of a novel training programme: progress and identified key actions to providing services to MSM at Kenyan health facilities	Exclude	Main Outcome
Romijinders, K.A. (2016)	Lubricant use and condom use during anal sex in men who have sex with men in Tanzania	Exclude	Main Outcome
Moller, L.M. et al. (2015)	Changes in sexual risk behavior among MSM participating in a research cohort in coastal Kenya	Exclude	Main Outcome
Smith, A.D. et al. (2015)	Heterosexual behaviours among men who sell sex to men in coastal Kenya	Include	All Criteria
Okal, J. et al. (2016)	Lessons learned from respondent-driven sampling recruitment in Nairobi: experiences from the field	Exclude	Main Outcome
Scheibe, A. et al. (2016)	Finding solid ground: law enforcement, key populations and their health and rights in South Africa	Exclude	Main Outcome
Hladik, W. et al (2017)	Men Who Have Sex with Men in Kampala, Uganda: Results from a Bio-Behavioral Respondent Driven Sampling Survey	Exclude	Main Outcome
Lee, M. et al. (2017)	Breakage is the norm: use of condoms and lubrication in anal sex among Black South African men who have sex with men	Exclude	Main Outcome
Larsson, M. et al. (2016)	Stretching the Boundaries: Tanzanian Pharmacy Workers' Views and Experiences of Providing STI Services for Men Who Have Sex with Men	Exclude	Main Outcome
Tucker, A. et al. (2016)	Efficacy of Tailored Clinic Trainings to Improve Knowledge of Men Who Have Sex with Men Health Needs and Reduce	Exclude	Main Outcome

Appendix F (continued)

Table XI. Results of Screening (N=99) (continued)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
	Homoprejudicial Attitudes in South Africa		
Ross, M.W. et al. (2017)	Prevalence of STI symptoms and high levels of stigma in STI healthcare among men who have sex with men in Dar es Salaam, Tanzania: a respondent-driven sampling study	Include	All Criteria
Cranston, R.D. et al. (2017)	MTN-017: A Rectal Phase 2 Extended Safety and Acceptability Study of Tenofovir Reduced-Glycerin 1% Gel	Exclude	Main Outcome
Khatib, A. et al. (2017)	Reproducibility of Respondent-Driven Sampling (RDS) in Repeat Surveys of Men Who have Sex with Men, Unguja, Zanzibar	Exclude	Main Outcome
Mmbaga, E.J. et al. (2017)	HIV and STI s among men who have sex with men in Dodoma municipality, Tanzania: a cross-sectional study	Include	All Criteria
Muller, A. (2017)	Scrambling for access: availability, accessibility, acceptability and quality of healthcare for lesbian, gay, bisexual and transgender people in South Africa	Exclude	Main Outcome
Larsson, M. et al. (2017)	Acting within an increasingly confined space: A qualitative study of sexual behaviours and healthcare needs among men who have sex with men in a provincial Tanzanian city	Exclude	Main Outcome
Ress, K. et al. (2017)	Utilization of Sexually Transmitted Infection Services at 2 Health Facilities Targeting Men Who Have Sex With Men in South Africa: A Retrospective Analysis of Operational Data	Include	All Criteria
Augenbraun, M.H. & McCormack, W.M. (1994)	SEXUALLY-TRANSMITTED DISEASES IN HIV-INFECTED PERSONS	Exclude	Type
Catchpole, M.A. (1996)	The role of epidemiology and surveillance systems in the control of sexually transmitted diseases	Exclude	Location
Fleming, D.T. & Wasserheit, J.N. (1999)	From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection	Exclude	Sexuality/Main Outcome

Appendix F (continued)

Table XI. Results of Screening (N=99) (continued)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
Goodman, R. (2001)	Beyond the enforcement principle: Sodomy laws, social norms, and social panoptics	Exclude	Main Outcome
Malta, M. et al. (2006)	Knowledge, perceived stigma, and care-seeking experiences for sexually transmitted infections: a qualitative study from the perspective of public clinic attendees in Rio de Janeiro, Brazil	Exclude	Location
Reproductive Health Matters (2007)	HIV/STI prevention for men who have sex with men, Kenya	Exclude	Type
Nel, J.A., Rich, E., & Joubert, K.D. (2007)	Lifting the veil: Experiences of gay men in a therapy group	Exclude	Main Outcome
O'Farrell, N., Morison, L., & Chung, C.K. (2007)	Low prevalence of penile wetness among male sexually transmitted infection clinic attendees in London	Exclude	Main Outcome
Gebel, S. et al. (2007)	`Are you on the market?': a capture-recapture enumeration of men who sell sex to men in and around Mombasa, Kenya	Exclude	Main Outcome
Grov, C. et al. (2007)	Barebacking, the Internet, and harm reduction: An intercept survey with gay and bisexual men in Los Angeles and New York City	Exclude	Location/Main Outcome
Wayal, S. et al. (2009)	Self-sampling for oropharyngeal and rectal specimens to screen for sexually transmitted infections: acceptability among men who have sex with men	Exclude	Location
Bernstein, K.T. et al. (2010)	Rectal Gonorrhea and Chlamydia Reinfection Is Associated With Increased Risk of HIV Seroconversion	Include	All Criteria
Grov, C., Parsons, J.T., & Bimbi, D.S. (2010)	Sexual Compulsivity and Sexual Risk in Gay and Bisexual Men	Exclude	Main Outcome
Jesus Martin, M., Manuel Martinez, J., & Rojas, D. (2011)	Theory of planned behavior and risky sexual behavior in homosexual men	Exclude	Main Outcome

Appendix F (continued)

Table XI. Results of Screening (N=99) (continued)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
Muraguri, N., Temmerman, M., & Geibel, S. (2012)	A decade of research involving men who have sex with men in sub-Saharan Africa: Current knowledge and future directions	Exclude	Main Outcome
Okuku, H.S. et al. (2012)	Evaluation of presumptive treatment recommendation for asymptomatic anorectal gonorrhoea and chlamydia infections in at-risk MSM in Kenya	Include	All Criteria
Awondo, P., Gescheire, P., & Reid, G. (2012)	Homophobic Africa? Toward A More Nuanced View	Exclude	Main Outcome
Hankins, C. (2013)	Overview of the Current State of the Epidemic	Exclude	Main Outcome
Lewis, D.A. (2013)	The role of core groups in the emergence and dissemination of antimicrobial-resistant N gonorrhoeae	Exclude	All Criteria
McNamara, T. (2014)	Not the Malawi of our Parents: Attitudes toward Homosexuality and Perceived Westernisation in Northern Malawi	Exclude	Main Outcome
Wirtz, A.L. et al. (2014)	A qualitative assessment of health seeking practices among and provision practices for men who have sex with men in Malawi	Exclude	Main Outcome
Tucker, A. et al. (2014)	Homophobic stigma, depression, self-efficacy and unprotected anal intercourse for peri-urban township men who have sex with men in Cape Town, South Africa: a cross-sectional association model	Exclude	Main Outcome
Muraguri, N. et al. (2015)	HIV and STI Prevalence and Risk Factors Among Male Sex Workers and Other Men Who Have Sex With Men in Nairobi, Kenya	Include	All Criteria
Ross, M.W. et al. (2015)	Health care in a homophobic climate: the SPEND model for providing sexual health services to men who have sex with men where their health and human rights are compromised	Include	All Criteria
Sega, L. et al. (2015)	The effect of risk-taking behaviour in epidemic models	Exclude	Main Outcome

Appendix F (continued)

Table XI. Results of Screening (N=99) (continued)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
Nyanzi, S. & Karamagi, A. (2015)	The social-political dynamics of the anti-homosexuality legislation in Uganda	Exclude	Main Outcome
Nala, R. et al. (2015)	Men Who Have Sex with Men in Mozambique: Identifying a Hidden Population at High-risk for HIV	Exclude	Main Outcome
Bekker, Linda-Gail (2015)	Building our youth for the future	Exclude	Main Outcome
Otieno, F.O. et al. (2015)	Correlates of prevalent sexually transmitted infections among participants screened for an HIV incidence cohort study in Kisumu, Kenya	Include	All Criteria
Muphey, D.A. (2015)	Processing, selecting and ritualizing: ambivalent relationships to semen	Exclude	Main Outcome
Dijkrsta, M. et al. (2015)	Emerging themes for sensitivity training modules of African healthcare workers attending to men who have sex with men: a systematic review	Exclude	Main Outcome
Musinguzi, G. et al. (2015)	Barriers to Condom Use among High Risk Men Who Have Sex with Men in Uganda: A Qualitative Study	Exclude	Main Outcome
Tontoyai, J. et al. (2015)	Prevalence and Correlates of Chlamydia trachomatis and Neisseria gonorrhoeae by Anatomic Site Among Urban Thai Men Who Have Sex With Men	Exclude	Location
Stahlman, S. et al. (2015)	Depression and Social Stigma Among MSM in Lesotho: Implications for HIV and Sexually Transmitted Infection Prevention	Include	All Criteria
Smith, A.D. et al. (2015)	Heterosexual behaviours among men who sell sex to men in coastal Kenya	Exclude	Main Outcome
Hove, M. (2016)	Local specificities, global resonances: contesting representations of violence in african films	Exclude	Main Outcome
Mohammed, H., Hughes, G., & Fenton, K.A. (2016)	Surveillance systems for sexually transmitted infections: a global review	Include	All Criteria
Kim, E.J. (2016)	Sexually transmitted infections associated with alcohol use and HIV infection among men who have sex with men in Kampala, Uganda	Exclude	Main Outcome

Appendix F (continued)

Table XI. Results of Screening (N=99) (continued)			
Author (year)	**Title**	**Include/Exclude**	**Criterial Reason**
Mehta, S. et al. (2016)	The Prevalence and Associated Factors of Self-reported Penile and Rectal Coital Injuries among Men who Have Sex with Men (MSM) in Kisumu, Kenya	Exclude	Type/Main Outcome
Ubrihien, A., Davies, S.C., & Driscoll, T. (2016)	Is cost a structural barrier preventing men who have sex with men accessing condoms? A systematic review	Exclude	Main Outcome
Scheibe, A.P. et al. (2017)	Attitude shifts and knowledge gains: Evaluating men who have sex with men sensitisation training for healthcare workers in the Western Cape, South Africa	Exclude	Main Outcome
Hladik, W. et al. (2017)	Men Who Have Sex with Men in Kampala, Uganda: Results from a Bio-Behavioral Respondent Driven Sampling Survey	Exclude	Main Outcome
Meer, T. & Muller, A. (2017)	``They treat us like we're not there'': Queer bodies and the social production of healthcare spaces	Exclude	Main Outcome
Velan, B. & Yadgar, Y. (2017)	On the implications of desexualizing vaccines against sexually transmitted diseases: health policy challenges in a multicultural society	Exclude	Main Outcome
Spencer, S., Meer, T., & Muller, A. (2017)	``The care is the best you can give at the time'' : Health care professionals' experiences in providing gender affirming care in South Africa	Exclude	Main Outcome

Appendix G

Table XII. Summary of Findings from Included Texts

Author (year)	Method	Sample Size	Location	STI prevalence	Analysis of syndromic management	Failure to treat	Time to treat
Zenilman, J.M. (2005)	Clinical Intervention Manuscript				Longitudinal analysis of behavioral interventions		
Kajubi, P. et al. (2008)	Cross-sectional survey	224 MSM	Kampala, Uganda		Ever had urethral discharge, anal discharge, genital sores, anal sores (11%, 1%, 7%, 2%)		
Sharma, A. et al. (2008)	Exploratory Questionnaire	486 MSM	Nairobi			Respondents discussed suspecting or being diagnosed with an STI but never going to receive treatment because of stigma of sexual behavior	
Sanders, E.J. et al. (2010)	Cross-sectional evaluation for entry to study	43 MSM	Coastal Kenya	26% had CT/NG or both. 13.9% urethral infection (11.6% CT and 2.3% NG). 11.6% rectal infection (2.3% CT, 4.7% NG, and 4.7% both)	0% rectal or urethral discharge. 2.3% urethral pain and 2.3% rectal pain		
Lewis, D.A. et al. (2013)	Case-study	2 MSM	South Africa		Discusses how WHO ignores anal infection	100%	
Sanders, E.J. et al. (2014)	Cross-sectional evaluation	244 MSM	Coastal Kenya	11.7% had CT/NG	Evaluated WHO PT of rectal infection. Sens/Spec/PPV/NPV (74.1%/45.8%/23.5%/88.7%) 1.6% had symptoms of CT/NG		
Ross, M.W. et al. (2014)	Two separate Cross-sectional surveys	100 and 200 MSM	Tanga and Dar es Salaam	4.4% and 23.7% for Curable STI			
Muraguri, N. et al. (2015)	Cross-sectional Survey	563 MSM	Nairobi	Those who did not sex sex-those who sell sex. 5.3-15% any STI. 4.2-8.8% for NG. 1.7-7.7% for CT			

Appendix G (continued)

Table XII. Summary of Findings from Included Texts (continued)

Author (year)	Method	Sample Size	Location	STI prevalence	Analysis of syndromic management	Failure to treat	Time to treat
Rebe, K. et al. (2015)	Cross-Sectional Analysis	200 MSM	Cape Town	24% for CT/NG. 16% for NG. 12% for CT	Self-report of symptoms. 29% reported clinical symptoms. 5% reported urethral discharge. 11% reported anal discharge		
Kim, E.J. et al. (2016)	Cross-sectional analysis from a bio behavioral survey	295 MSM	Kampala, Uganda	13.5% curable STI. Syphilis 9.0% Rectal CT (1.1%) Penile CT (1.2%) Rectal NG (1.8%) Penile NG (1.4%)	Self-report STI symptoms in the past 6 months. 47.3% reported any STI symptom		
Smith, A.D. et al. (2015)	Sexual Diary study for participants in 2 ongoing cohort studies	Excluded for main outcomes	Excluded for main outcomes	Excluded for main outcomes	Excluded for main outcomes	Excluded for main outcomes	
Ross, M.W. et al. (2017)	Cross-sectional Survey	200 MSM	Dar es Salaam	21.4% had penile/rectal CT/NG	Discusses prevalence of symptoms		
Mmbaga, E.J. et al. (2017)	Cross-sectional study	409 MSM	Dodoma, Tanzania	0.2% for Syphilis			
Ress, K. et al. (2017)	Retrospective analyzation of routine data for 2 years	7188 STI episodes (16.9% were MSM)	Johannesburg, South Africa		Urethritis did not change over time. GUD decreased over time (longitudinal). 68.2% of episodes were urethritis and 9.8% as GUD. Anal discharge 1% of episodes		
Bernstein, K.T. et al. (2010)	Retrospective cohort between 2 years. Rectal CT/NG on getting HIV	541 MSM			5.9% had rectal symptoms. 82.3% had no rectal infection diagnosis in previous 2 years, 15.3% had 1 and 2.4% had 2	2.6% 265 presumptive Rx and 260 returned for Rx	
Okuku, H.S. et al. (2012)	Cross-sectional study of a continuing cohort study	204 MSM	Mtwapa, Kenya	15% prevalence of CT/NG	Only 2% of MSM had symptomatic infection		
Ross, M.W. et al. (2015)	Review paper	MSM	Tanzania		1/5 to 1/6 of Tanzanian MSM go to receive treatment for STI symptoms. Many report receiving multivitamins.	Discussion of not giving Rx, wrong Rx, wrong dose	
Otieno, F.O. et al. (2015)	Cross-sectional analysis	486 men and women	Kisumu, Kenya	For men- 0% for NG. 2.8% for CT. 0.7% for syphilis. 1.2% for co-infection			
Stahlman, S. et al. (2015)	Cross-sectional data (self-report)	530 MSM	Lesotho	10% for STI (self-report) 5% test for syphilis			

Appendix G (continued)

Table XII. Summary of Findings from Included Texts (continued)

Author (year)	Method	Sample Size	Location	STI prevalence	Analysis of syndromic management	Failure to treat	Time to treat
Mohammed, H., Hughes, G., & Fenton, K.A. (2016)	Review paper		global		"There have been some reports to demonstrate the viability of syndromic surveillance in the West African countries of Burkina Faso and Cote D'Ivoire"		
Ross, M.W. et al (2017)	Cross-sectional analysis	200 MSM	Dar es Salaam		Ever had symptoms of an STI. 49% genital pain. 24.5% urethral discharge. 14% testicular pain. 10% anal discharge		

Appendix H

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VITA

Nicholas Andrew Davis

PROFESSIONAL INTERESTS

Nicholas has a strong interest in research-based health outreach, epidemiologic methods, and graphical representation of data in a healthcare setting.

EDUCATION

Aug 2018	M.S. in Epidemiology with a concentration in Global Health at the University of Illinois at Chicago.
May 2013	B.S. in Biomedical Sciences from Auburn University with a focus on Organic Chemistry research under Dr. Peter Livant.
May 2013	B.A. in Psychology with a focus in developmental neuroscience including a practicum under Dr. Steven Shapiro.

TEACHING EXPERIENCE

Aug 2017-May 2018	Peer support team quantitative specialist for the Office of Diversity and Inclusion at the University of Illinois at Chicago which focused on individual and group tutoring of biostatistics and epidemiology to undergraduate and graduate students.
Sept 2013-Nov 2015	High school physics, chemistry, and biology teacher with the Peace Corps Mozambique.