Part 0: Preamble

UNIVERSITY OF CAPE TOWN
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Prevalence of asymptomatic sexually transmitted infections: A retrospective review of screening data from Desmond Tutu HIV Centre clinical trial cohorts from 2012 to 2017, Cape Town.

Nomcebo Precious Garnett

NYWNOM001

Supervisor: Associate Professor Catherine Orrell

Desmond Tutu HIV Centre/ Institute of Infectious Disease and Molecular Medicine

University of Cape Town

DECLARATION

I, Nomcebo Precious Garnett, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signature: ..... Signed by candidate

Date: .....31 August 2019....

Dedication

This work is dedicated to our research participants that dedicate their lives and time in partnering with researchers to help find better solutions for our public health burdens.

I would like to extend my gratitude to my mentor and supervisor, Associate Professor Catherine Orrell, who's support, and guidance has been invaluable in this research process and in my overall work. Thank you for seeing the potential in me.

To my colleagues that became friends in this master's journey, Sheetal Kassim; Yashna Singh, Mary Chidanyika; this is to us!

To my family and friends that have been both supportive and understanding as they have travelled this journey towards my masters with me.

Last, but not least, to my son Matisse Garnett; my sister Qophelo Hlatshwayo; my partner Aurelien Taberner, you've been my rock and thank you for being patient with me. I hope to show you how where you come from does not have to define who you become and restrict your ability to dream for a better future.

Abstract

Background: The burden of Sexually transmitted infections (STIs) is high globally. The World Health Organisation (WHO) recommends syndromic management of these STIs, based on presentation with signs and symptoms, in resource-limited countries. Due to this syndromic approach, there is little current data on STI prevalence, including asymptomatic STIs, in high risk populations.

Methods: We reviewed secondary data collected as part of the screening procedures of 6 clinical trials between 2012 and 2017 in Cape Town, South Africa. These trials recruited populations of different sexual orientation and gender, mostly key populations at risk of HIV and STI acquisition. Routine screening for STI symptoms and testing for Chlamydia, Gonorrhoea, Trichomonas, Syphilis and HIV was performed for all of the studies at screening/enrolment.

Results: A total of 639 participants were screened; 411 (64.3%) self-identifying as female, 198 (31%) males, 29 (4.5%) transgender women and 01(0.2%) transvestite. Median age was 20 years (IQR: 18-24) and with the 15-24year age category contributing 77% to the cohort. 224(34.5%) were MSM, 12(1.9%) MSW, 128(19.7%) WSM, 03(0.5%) WSW, 282(43,5%) having not revealed their sexual orientation. 54(8.3%) of the participants had no sexual partner in the preceding 6 months, 284(43.8%) monogamous and 311(47.9%) in polygamous relationships.

There were 309 laboratory diagnosed STIs in 239 people (37.4%) Only 37 (15.5%) showed signs and symptoms. There were 156 Chlamydial infections (65.3% of overall STIs), a

population prevalence of 24.4%, with only 15 (11.2%, p<0.01) presenting with any symptoms and 6 (4.0%) presenting with Chlamydia-specific symptoms.

There were 85 Gonorrheal infections (35.6% of overall STIs), a population prevalence of 13.3%, with 14 (17.9%, p<0.001) eliciting any kind of symptoms and 7 (8%) presenting with symptoms commonly associated with Gonorrhea.

Trichomonal infection had a prevalence of 29 (12.1%) of overall diagnosed STIs, a population prevalence of 4.5%; with only two (8%, p-value-0.03) having symptoms commonly associated with Trichomoniasis infection.

While 39 (16.3%) Syphilis Infections were diagnosed in this cohort, a population prevalence of 6.1%, only 8 (20.5%, p-value-0.02) of these had any form of symptoms. Primary Syphilis typical symptoms were present in 1 (2.6%) of confirmed cases of Syphilis infection.

Conclusion: A vast majority of STIs in this high-risk population were asymptomatic. Laboratory testing of causal organism was more reliable in diagnosing STIs than the use of signs and/or symptoms as recommended by WHO.

Keywords: 'Sexually transmitted Infection', 'Prevalence', 'Asymptomatic STIs', 'syndromic management of STIs', 'STI testing'.

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Abbreviations

WHO- World Health Organization

CDC- Center of Disease Control

MSM- Men who have sex with men

WSM- Women who have sex with me

WSW- Women who have sex with women

MSW- Men who have sex with women

TGF- Transgender female

HIV- Human Immuno-deficiency Virus

STIs- Sexually Transmitted Infections

C.Trachomatis(CT)- Chlamydia Trachomatis

N. Gonorrhoea/Gonococcus/NG- Nesseira Gonorrhoea

T. Vaginalis/Trichomonas- Trichomonas Vaginalis

RPR- Rapid Plasms Reagin

VDRL- Veneral Disease Research Laboratory

PCR- Polymerase Chain Reaction

Contents

PART A: PROTOCOL

Title:	**Prevalence of asymptomatic sexually transmitted infections: retrospective review of screening data from Desmond Tutu HIV Centre clinical trial cohorts from 2012 to 2017, Cape Town.**
Collaborators:	Precious Garnett, Catherine Orrell, Katherine Gill, Linda-Gail Bekker, Keren Middlekoop, Karen Dominguez
Data collection:	Saori Iwase
Statistical analysis	Collaborative DTHC team

Background:

Sexually transmitted infections are one of the most common infections in Sub-Saharan Africa and globally(Global health sector, 2019; WHO 2019, UNAIDS, 2018). In 2012, the WHO recorded a worldwide estimate of 357 million new cases annually of four curable sexually transmitted infections among people aged 15–49 years. *Trichomonas vaginalis* at 142 million, *Chlamydia trachomatis* at 131 million, *Neisseria gonorrhoeae* at 78 million and *Syphilis* at 6 million. Viral infection also proving very prevalent, with approximately 291 million women infected with Human papilloma virus and 417 million of men and women infected with Herpes Simplex 2 virus(WHO, 2012).

The World Bank estimates further indicate that STIs, with HIV excluded, are the second leading cause of healthy life years lost by women aged between 15-44 years in the continent of Africa and this is responsible for an approximately 17% of the total burden of disease(*Mayaud et al, 2001)*

Sexually transmitted infections come with an increase in the morbidity and economic cost to the health systems as they have adverse effects on child, reproductive and sexual health. More significantly evident in the developing world (Ramjee et al, 2015).

Through the WHO's Global Strategy on Reproductive Health, emphasis has been placed on the control of STIs as a public health priority globally and made essential for achieving Millennium Development Goals: child health, maternal health, and HIV prevention(WHO, 2012; Reproductive health strategy, 2018).

The National Department of Health South Africa, has sexually transmitted infections management guidelines that are in line with the WHO recommendations that do not encourage routine testing for causative organisms whether symptomatic or not, but rather a syndromic/ empiric approach to STI management where there's standard treatment of one or more causative organisms that often occur at the same time. This is guided by the presenting symptom/s. These also emphasize the treatment of sexual partner/s of the symptomatic and treated partner, irrespective of their presence of symptoms(Department of health, 2019; STD Treatment Guidelines, 2015).

Contrary to the South African National Department of Health and WHO recommended management of STIs in resource-stricken health settings with syndromic management for the symptomatic and contact partners, other research studies have demonstrated that symptoms are a poor predictor of the presence of an STI or genital inflammation. Individuals with no symptoms of an STI go untreated, spreading the infections and thus compromising epidemic control(Johnson et al, 2005)

With growing concerns over emerging antibiotic resistance by common bacterial STIs; prevention, early identification through symptom recognition or testing and treatment of these STIs should be top of the priority list globally. This is even more urgent in countries with high incidence rates of HIV as a synergic relationship between the two infections is well documented in literature(WHO, 2019; Global health sector, 2019; WHO, 2012).

Hence availability of comprehensive data on the prevalence of STIs in South Africa is a step in the right direction(Johnson et al, 2005). This study seeks to fill this gap, by looking at people screened for STIs to see what the prevalence of asymptomatic STIs might be (across age, gender, sexual orientation and other socio-demographic characteristics).

HIV is known as an STI but for the purposes of this paper, HIV is viewed as another infection outside of STIs written about. As it is a big entity with many pathways and interactions that are beyond the scope of this analysis.

Hypothesis

The prevalence of asymptomatic STIs amongst the HIV negative population in the Cape Town area is higher than estimated.

Objectives

Primary Objective

To describe the prevalence of asymptomatic STIs amongst the HIV negative research participants in Cape Town.

Methodology

Study design

This study is a Retrospective Observational review of screening data from HIV-negative participants screened for HIV prevention studies completed at the Desmond Tutu HIV Centre research sites across Cape Town, South Africa.

Screening data will be reviewed, and the following variables collected: It will be looking at data collected at screening visits of HIV negative participants that have consented to be part of the various studies within the centre. This data will include: results from swabs and secretions (rectal, vaginal/ cervical), smears, urine testing, serum investigations that are collected as part of the different but individual research protocols the participants will have consented to participate on. No extra testing will be done as part of this study protocol, only

secondary data will be collated and analyzed looking at specific variables of interest in this study.

Characteristics of the study population: Eligibility criteria

Inclusion criteria:

1. Study:

HIV-Prevention study at the DTHF between 2012 and 2017 with STI testing for all participants at screening.

2. Participants:

HIV negative, consented and or assented to be part of an HIV-prevention studies at the Desmond Tutu HIV Centre between January 2012 to December 2017.

Key variables:

Baseline demographic variables to be explored include:

- Site/ area of study participation
- Age
- Self-identifying Gender
- Sexual orientation
- Number of Sexual partners in the last 6 months.

Clinical variables to be measured.

Any result of a mucosal swab collected, including:

- Vaginal/cervical, including pap smears
- Rectal

Any urine PCR results for Chlamydia and Gonorrhoea

Any serum results for infectious diseases:

- Serum RPR results and titres
- Serum VDRL results
- HIV results

Data Collection method

Data previously collected from different research studies, from different population groups, within the Desmond Tutu HIV Centre will be pulled out of the databases, collated and analyzed as part of this study.

No interaction with participant will occur.

Data Safety and Monitoring

All study data shall be accessed electronically and physically through folders, and will be kept in a secured hard drive/ database/cabinets. Only approved research staff will have access to the study materials and data.

After the study, the study files will be archived with Metro File company for a period of 10 years. After this time, they will be discretely and safely destroyed.

Participants are routinely allocated participant identities to allow for confidentiality and this will be upheld in the study.

All data entered will be quality checked by another member of the research team for accuracy and completeness.

Data Analysis

Descriptive and Exploratory analysis will be performed with this data.

Descriptive analysis will include socio-demographic characteristics of the cohort and crude relationships between different variables using appropriate statistical tests. Gender and Sexual orientation analysed as different terms, sexual orientation referring to 'the sex of those to whom one is sexually and romantically attracted' (American Psychology association 2012) while gender is 'describing one's persistent inner sense of belonging to either the male and female gender category'(Money, 1994).

Exploratory analysis will explore the presence of associations between the different variables, eg Chlamydia and Sexual orientation, while adjusting for any potential confounders or presence of interaction with other risk factors. This data will be synthesized and presented in shell tables as demonstrated below.

Table 1: Descriptive data- Socio-demographic characteristics of the cohort.

Variable	**Level**	**n**	**%**
Age	15-24 25-35 >35		
Gender	Male Female T/G Female* Transverstite		
Sexual Orientation	MSM** WSM*** WSW**** MSW*****		

	Not stated		
Number of Partners(total in past 6 months)	Single Monogamous Polygamous		
Site of study participation	GSH Masi		

*T/G Female- Transgender female. **MSM- men who have sex with men, also includes transgender female and transverstite **WSM- women who have sex with men ***WSW- women who have sex with women ****MSW- men who have sex with women.

Table 2: STI laboratory diagnoses versus STI symptoms, using chi-squared test.

Variable	**STI Symptoms**	**p-value**	**Interpretation: Asymptomatic Infections**
Chlamydia(n=)			
Gonorrhoea(n=)			
Trichomonas(n=)			
Syphilis(n=)			
**Overall STIs lab diagnosed(n=)			
HIV(n=)	**Any STI Lab Diagnosis**	**p-value**	

	STI Symptoms	**p-value**	

Table 3 for univariate and multi-variate relationship between socio-demographic data and STI symptoms.

Variable	**Crude Association**			**Adjusted Association**		
	Odds Ratio	**p-values**	**95% Confidence Interval**	**Odds Ratio**	**p-values**	**95% Confidence Interval**
Age: *Ref- 15-24* 25-35 >35						
Gender *Ref- Male* Female TGF* TransV**						

Sexual Orientation *Ref- MSM**** WSM**** WSW***** MSW******						
Number of Partners *Ref- Monogamous* No partner Polygamous						
Site(area) *Ref- GSH* Masi						

Table 4 to present relationship between socio-demographic characteristics and STI diagnosis.

Variable	**Crude Association**			**Adjusted Association**		
	Odds Ratio	**p-values**	**95% Confidence Interval**	**Odds Ratio**	**p-values**	**95% Confidence Interval**
Age:						

Ref- 15-24 25-35 >35						
Gender *Ref- Male* Female TGF* TransV**						
Sexual Orientation *Ref- MSM**** WSM**** WSW***** MSW******						
Number of Partners *Ref- Monogamous* No partner Polygamous						
Site(area) *Ref- GSH* Masi						

Table 5: STI diagnosis by STI symptoms, crude(univariate analysis) and adjusted for other risk factors(possible confounders-multi-variate analysis)

Variable	Crude Association			Adjusted Association		
	Odds Ratio	p-values	95% Confidence Interval	Odds Ratio	p-values	95% Confidence Interval
Any STI						
Chlamydia						
Gonorrhoea						
Trichomonas						
Syphilis						
HIV						

Ethical considerations

Description of Risks and Benefits: as this will be secondary data collections there should not be any added risk or benefit for the participants, from their already collected data being further explored and analysed in this study. Participant will not be at any point contacted as part of this study.

Informed Consent Process: As part of the ethical standards, all participants that participate in the DTHF studies go through a detailed informed consent process, where they give permission with full disclosure of information of the index study. But beyond that, they give

permission for the data collected during their index study to be possibly used in future studies if deemed appropriate by the local Ethics Committee.

Privacy and Confidentiality: privacy and confidentiality will be pre-study protected as the study team will only have access to the electronic data and folders, with minimal personal/ identifying information. The data will still be protected and kept private and confidential, as stated in the data safety section of this research proposal. Regulatory authorities/peers that may review or want to replicate the results may be granted access to the raw data, but such data will not be able to link the participant identity number to an actual participant in the community.

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PART B: LITERATURE REVIEW

Objectives of literature review.

1. To review currently available literature examining the burden of curable sexually transmitted infections (STIs) worldwide, whether symptomatic or asymptomatic, in HIV negative or status unknown persons.
2. To describe this burden of disease within different populations, including key populations as defined by the World Health Organization (WHO) as HIV at risk groups
3. To review the current approach to reducing the prevalence and incidence of curable STIs, specifically evaluating the effect of syndromic or empiric management of these curable STIs on STI incidence.
4. To review currently available STI testing technologies.
5. To explore unanswered questions within the STI field for future research.

Literature search strategy, Inclusion and Exclusion criteria.

Online platforms were used to search for articles and publications related to the above objectives.

Databases viewed and literature extracted from included PubMed, Google Scholar, Google search engine, CDC, WHO, HPTN (HIV Prevention Trials' Network) and AVERT.org platforms.

Search terms that were used were "Sexually transmitted infections", "Asymptomatic sexually transmitted infections, "asymptomatic STIs in Africa", "Low and middle income countries and STIs", "Global STI prevalence", "WHO STI statistics", "Chlamydia" " Chlamydia

Trichomoniasis", "Gonorrhoea", "Gonococcus", "Neisseria Gonorrhoea", "Sexually transmitted infections in MSM populations", "Sex workers and sexual transmitted infections", "Sexually transmitted infections in women", "STIs in pregnant women", "Sexually transmitted infections in heterosexual men", "Syndromic management of sexually transmitted infections evaluation", "Management and treatment of sexually transmitted infections/disease", "Testing in sexually transmitted infections", "Risk of HIV with sexually transmitted infections", "Strategies for sexually transmitted infection management", "Evaluation of syndromic management for STIs".

Inclusion criteria:

Any study noting:

- prevalence and / or incidence of sexually transmitted infections or disease
- symptomatic or asymptomatic STIs (including chlamydia, Gonorrhoea, syphilis, trichomoniasis and/or HIV)
- HIV negative or HIV status unknown individuals, population or not stated) from low and middle income countries
- No restriction to publication date.

Exclusion criteria:

- Publications presenting STI data only in HIV positive individuals.
- Full article not freely available or not accessible online.
- Publications only reporting on Hepatitis B and /or Hepatitis C.

Summary and interpretation of literature.

Types of Sexually transmitted Infections.

Over 30 different organisms (bacteria, parasites, viruses) are known to be sexually transmitted, of which eight cause the highest burden of disease in reproductive health (WHO.Int, 2019). Half are incurable. The currently incurable STIs are Hepatitis B, Herpes Simples virus (HSV), Human Immuno-deficiency virus (HIV) and Human Papilloma Virus (HPV). The curable STIs include Treponema Pallidum (TP), Chlamydia Trachomatis (C. Trachomatis), Neisseria Gonococcus(N. Gonorrhoea) and Trichomonas Vaginalis(T. Vaginalis) causing Syphilis, Chlamydia, Gonorrhoea and Trichomoniasis respectively(WHO.Int, 2019).

Addressing Objective 1: Burden of Sexually Transmitted Infections.

There is a high incidence of sexually transmitted infections globally (Davey et al, 2016). The World Health Organization (WHO) estimates up to 1 million new infections were acquired daily worldwide in 2016 (CROI conference, 2014; British Association for Sexual Health, 2019).

C. Trachomatis and T. Vaginalis infections are the most common curable STIs in Sub-Saharan Africa, accounting for up to 7,8% and 29% of incident STIs, respectively (Davey et al, 2016; Davey et al, 2019; Hussen et al, 2018; Torrone et al, 2018). The Eastern and Southern African regions have slightly higher prevalence (6.9% C. Trachomatis and 29.1% T. Vaginalis) than the West and Central countries of the Africa (6.1% C. Trachomatis and 17.8% T. Vaginalis (Chico et al, 2012).

Other infections, such as Syphilis and Gonorrhoea, are also common in these regions of Africa. A systematic review by Chico et al in pregnant women shows these infections

account for up to 4,5% and 3,7% of all STIs respectively, in East and Southern Africa (Chico et al, 2012).

The US Center for Disease Control (CDC) presents Syphilis prevalence by stage, with statistics dating back to 1941. This report demonstrates an alarming increase in rates of reported Syphilis cases over the past 80 years in the US. A 23.2% per 100 000 rise in incident cases of Syphilis of all stages was noted in 2015, 27.3% per 100 000 in 2016 and 31.4% per 100 000 population in 2017. (STD Facts, 2019).

Addressing Objective 2: STI burden.

Key populations.

While there is an overall high global STI prevalence, there is an increased burden of disease within certain population groups e.g. low and middle Income countries, key populations such as Men who have Sex with Men (MSM), adolescent girls and young women(AGYW), pregnant women and sex workers (Avert, 2019)

The WHO has identified key populations in relation to the risk of acquiring HIV and STIs. Key populations are specific populations that need to be targeted in order to reduce both HIV prevalence and incidence. These populations are: Men who have Sex with Men (MSM), sex workers and transgender women (TGW), people who inject drugs, and people in prisons and other closed settings (Avert, 2019). In sub-Saharan Africa adolescent girls and young women aged between 15-24 years are added as a high-risk group, while people who inject drugs are not at higher risk in this environment as is observed in regions of the US (Avert, 2019).

Adolescent girls and young women: South Africa has the highest number of new HIV infections every year, with the majority of these infections occurring in AGYW aged between

15 and 24 years (Marrazzo, 2019). Shisana et al, 2012, reported HIV prevalence amongst 15-24 years to be 2.9% in male and 11.4% in women. In 2016, new HIV infections among young women were 44% higher than men of similar age (Avert, 2019). In Eastern and Southern Africa, young women made up 26% of new HIV infections despite only accounting for 10% of the total population in 2017 (Shisana et al, 2012; Avert, 2019).

In the worst-affected countries, 80% of new HIV infections among adolescents are among girls, who are up to eight times more likely to be living with HIV than adolescent boys (Avert, 2019). Statistics have shown that some 7,000 young women across the world acquire HIV every week (Shisana et al, 2012). In terms of curable STIs in AGYW, a cohort of participants involved in HIV prevention studies in KwaZulu Natal reported an estimate of 13% of overall STIs in young women from rural and urban areas with a mean age of 28 years(Torrone et al, 2018).

This evidence necessitated the addition of young women to the WHO definition of a key population at risk of HIV(Avert, 2019).

Extensive research has identified contextual factors that are linked to this increased risk. These include: gender inequality, violence and sexual assault, poverty, food insecurity, lack of access to health care, poverty, obstacles to education in general, but more specifically lack of sex education in the home and at school as well as obstacles to sexual and reproductive health services (Lewis et al, 2016; CDC, 2013). In South Africa, this risk is further increased through transactional sex between young women and older men (the "sugar-daddy" culture). A research study in South Africa reviewing of age-disparate sex and HIV risk for young women between 2002 and 2012, estimated that 33% of sexually active adolescent girls will experience a relationship with a man at least five years older during

their adolescent years. It also describes a cycle of transmission, where the high HIV prevalence in young women was found to be driven by sex with older men (on average 8.7 years older), who themselves had female partners with HIV, acquired as young women (Avert, 2019).

P*regnant women:* Anonymous antenatal sero-prevalence studies have provided historical data to quantify the HIV burden in the early days of the epidemic (Davey et al, 2019). By virtue of being pregnant, having engaged in non-barrier protected vaginal receptive sexual intercourse; these women are at risk of acquiring HIV and other STIs too. A systematic review of published literature reviewing global prevalence of STIs in pregnant women in low- and middle-income countries between 2010 and 2015, noted the highest prevalence of STIs in Southern Africa compared to other regions of the world. Gonorrhoea prevalence in Latin America was 1,2% while 4.6% in Southern Africa and Syphilis prevalence was 1.1% in Asia, but 6.5% in Southern Africa. Trichomonas vaginalis was 3.9% in Latin America compared to 24.6% in Southern Africa (Davey et al, 2016).

A recent, July 2019, publication of a cross-sectional study done in Cape Town supports these high rates . Overall STI prevalence was noted to be 32%; Gonorrhoea accounting for 5.8% of the prevalence and Trichomonas vaginalis 15% in this Southern African city (Davey et al, 2019).

MSM: The high incidence of STIs in the MSM population is also multifactorial. Risks involve both individual behaviours and sexual network characteristics, including the number of lifetime or recent sex partners, concurrency of sex partners, rate of partner exchange, and frequency of condomless sex. Each influence an individual's probability of exposure to an STI (CDC, 2019; Mimiaga et al, 2009). There are also institutional factors that might decrease

the likelihood of diagnosis and treatment of STIs and therefore contribute to the spread of these infections. These include limited access to healthcare through experiences of stigma and negative attitudes encountered at the health care settings when this population seeks care. Societal factors that may be associated with increased sexual risk behaviour among MSM may include verbal harassment, discrimination and physical assault (CDC, 2019; Zou et al, 2012).

In 2017 Syphilis was the most prevalent STI amongst MSM (6.0%) in the US, accounting for 68.2% of all STIs, an 8.6% increase from 2016, with Gonorrhoeal and Chlamydial infections accounting for 38.5% and 10.7% respectively. Black and Hispanic MSM were disproportionately affected. 45.5% of these men were HIV co-infected (CDC,2019).

Also of note in this key population group, is the higher rate of extra-genital STIs, such us rectal and oro-pharyngeal STIs. In 2017, the CDC estimated 13,4% of MSM were treated for oropharyngeal Gonorrhoea (CDC, 2019).

Sex workers: The nature of sex work places these individuals at higher risk of HIV and STI acquisition. Risky sexual practices (sex without use of condoms, multiple partners), substance use, inaccessible health care facilities, population stigma, discrimination and mistrust, as well as fear of losing income if identified with HIV or STIs, all contribute to increased risk. There is very limited data available in this population, likely related to criminalization of sex work in many countries (Ramjee et al, 2005; Project T, 2019; ,CDC, 2019).

Correlation between HIV and other STIs.

Sexually transmitted infections have long been recognised as major modifiable risk factors for HIV infection (Kaida et al, 2018; Passmore et al, 2016; Wall et al, 2017; Ramjee et al, 2005; Thienkrua et al, 2016; Mlisana et al, 2012; Cohen, 2012). HIV prevention research studies often use STI incidence as a predictor or risk marker for subsequent HIV infection (Marrazzo, 2019).

Passmore and colleagues have shown a relationship between the increased inflammatory markers associated with STIs and susceptibility to HIV acquisition.

Inflammation in the female genital tract, regardless of the cause, has been shown to create an environment that promotes HIV replication and therefore establishment of a productive infection. Women with elevated concentrations of pro-inflammatory cytokines, such as MIP-1α, MIP-1β and IP-10, in their genital tracts were found to be at increased risk of HIV acquisition. IP-10, MIP-1α, and MIP-1β are chemotactic for HIV target cells, including T cells, macrophages and dendritic cells. Thus explaining the disporportional incidence of HIV in young women compared to men(heterosexual or MSM)of the same age, as mentioned earlier(Passmore et al, 2016).

Complications of STIs.

Just under 1 million pregnant women were infected with syphilis in 2016, as per WHO estimates, and this infection is known to result in many adverse outcomes for the new-born and the mother. Complications include preterm labour, stillbirth and mother to child transmission of the organism leading to disease in the new-born, low birth weight, premature rupture of membranes (Davey et al, 2019; Avert, 2019). A cohort study noted the

highest rate of adverse outcome in infants of women with co-infection of Chlamydia and Gonorrhoea (23/35, 65.7%) compared to Gonorrhoea alone (16/28, 57.1%), Chlamydia alone (84/214, 39.3%), and no STI (405/1096, 37%, p=0.001)(Adachi et al, 2016).

Other major complications resulting from sexually transmitted infections include pelvic inflammatory disease with resultant tubal infertility, risk of ectopic pregnancy, chronic pelvic pain, cervical and other genital tract tumours as well as psychosexual problems(Mullick, 2005; Badman et al, 2016; Romoren et al, 2007; Adachi et al, 2016).

The high burden of STIs may have negative financial consequences. In the U.S. alone, estimated annual costs of the 8 major STIs to be US$16 billion (Gaydos et al, 2014; Biggest Threats and Data, CDC, 2019).

Further negative effects resulting from the high incidence and prevalence of curable STIs is emerging drug resistance, which is largely influenced by the syndromic antibiotic management of bacterial sexually transmitted infections, especially Gonorrhoeal infections (Avert, 2019). This is emerging as a public health threat globally. In 2013 N. Gonorrhoea drug resistance, with 246 000 cases per year, was estimated to be up to 38.9% for standard doses of ciprofloxacin, 4.3% for azithromycin and fluctuating at about 0.2% for ceftriaxone(CDC, 2017; CDC (2019). The British Association for Sexual Health and HIV has recently updated their national guidelines for management of Neisseria Gonorrhoea to increase the dose of ceftriaxone from 250mg to 1g, in light of the increasing incidence of drug resistance of Gonorrhoea (British Association for Sexual Health, 2019).

Addressing Objective 3: Symptomatology of Sexually Transmitted Infections.

Literature has shown that clinical signs and symptoms of STIs can be non-specific. When they do occur, they may be attributed to a collective of STI causative organisms (Naidoo et al, 2014, Mimiaga, 2009). For example, a genito-urinary / genito-rectal lesion maybe caused by primary syphilis, herpes or HPV, and these are commonly termed ulcerative STIs. Clinical differentiation between these lesions based on the morphology of the lesion alone may be difficult (Sexually Transmitted Diseases Surveillance, 2019).

Chlamydia, Gonorrhoea and Trichomoniasis also have a similar and non-specific constellation of symptoms, including vaginal/penile/rectal discharge or bleeding/itching. These are often termed discharge causing STIs (Mlisana et al, 2012; Mohammed et al, 2016; Neisseria: Molecular Mechanisms, 2019; Sonkar et al, 2016; Zemouri et al, 2016; Vallely et al, 2017).

Other local non-specific symptoms (which may be caused by ulcerative-or discharge-causing organisms) include pain on micturition, lower abdominal pain, and rectal/ genito-urinary pain (WHO.int, 2019).

Syphilis is one of the more complex STIs due to the different stages of the disease process. Secondary Syphilis is the most distinct stage in terms of its presentation; characterized by a skin rash or mucous membranes abnormalities. If undiagnosed, the disease evolves to become tertiary syphilis which is largely asymptomatic. Symptoms only reappear once organs such as the central nervous system, eyes, ears etc. become involved in the final stages of disease (Sexually Transmitted Diseases Surveillance, 2019).

Other STIs may present extra-genitally with atypical symptomatology, such as pharyngeal chlamydia(CDC,2019).

However, the majority of STIs are asymptomatic and thus do not present with any signs and symptoms of ill-health. Some studies demonstrate rates of lack of symptoms in as many as 80% of people diagnosed with Chlamydial infection, and around 70% of those diagnosed with Gonorrhoea (Mlisana et al, 2012; Mohammed et al, 2016).

Evaluating syndromic management

Even though the gold standard for diagnosis and management of sexually transmitted infections is testing, the World Health Organization has long recommended syndromic management in low-and middle- income settings due to limitation in resources for testing (Sonkar et al, 2016; Zemouri et al, 2016; Vallely et al, 2017).

The syndromic management approach is based on the identification of consistent groups of clinical symptoms and easily recognized signs, and the provision of treatment that will deal with the majority or the most serious organisms responsible for producing a syndrome. WHO developed a simplified algorithm to guide health workers in the implementation of syndromic management of STIs and in 2003, the WHO guidelines were revised to focus exclusively on syndromic management (Garrett et al, 2018). Kenya, along with other countries, adapted these guidelines for the national program (Otieno et al, 2014).

Ideally, syndromic management is recommended to eliminate the need for laboratory testing and extra clinic visits for follow-up, which may potentially be associated with delays in accessing treatment, and to some extent the need for a physical examination. This approach is viewed as a practical strategy for use in resource-limited settings as it provides

an affordable, easy and quick access to treatment while helping to avoid potential loss to follow-up observed in STI management involving laboratory-based diagnosis (Vallely et al, 2017; Zemouri et al, 2016). Moreover, the practice may be necessary in cases where pathogen detection is difficult such as with upper genital tract infections (Otieno et al, 2014).

A few studies have been done globally evaluating the accuracy of using the signs and symptoms of STIs as per the syndromic management approach as a predictor of disease, compared to aetiological, laboratory testing. A study done in Sub-Saharan Africa in Kisumu, Kenya, screened participants for HIV prevention research, found an STI prevalence of 10.4% in clinician-based syndromic diagnosis compared to 32.2% in aetiological/laboratory STI diagnosis. The prevalence of STIs was greater among women than men for both the syndromic diagnosis, 17.2% vs. 3.6% (p <0.0001), and the aetiological diagnosis, 48.6% vs. 15.6% (p <0.0001) (Otieno et al, 2014).

Another study done amongst the Soweto and Durban youth concurs with the poor performance of syndromic management. It showed that the bulk of STIs are asymptomatic and the sensitivity of symptom-based diagnosis is 0% in males, and 14% amongst women (Kaida et al, 2018).

Mlisana and colleagues in 2012 further contributed to concerns about syndromic management, with results from a prospective cohort study done in South Africa, including 242 women at risk for HIV-1 infection. This study measured 4 parameters: presence or absence of a vaginal discharge; detection of ≥1 STI pathogens; vaginal cytokine concentrations; and HIV-1 acquisition (Mlisana et al, 2012). The results were consistent with the global concern of the asymptomatic nature of most of these infections (Badman et al,

2016; Mohammed et al, 2016; Cohen, 2012; Gaydos et al, 2014). Only 12.3% of women infected with a pathogen that might cause a vaginal discharge had signs or symptoms of infection. Women with STIs were >3-fold more likely to acquire HIV-1 than those who harboured no pathogens. Women with gonorhoeal infections, among the most inflammatory of the classical STI agents, had a 7-fold increased risk of HIV-1 acquisition. Surprisingly, inflammatory cytokines were not significantly different whether a woman had a symptomatic or an asymptomatic STI, compared with asymptomatic infections, although the inflammatory cytokines were still greater than in women with no STIs or women infected with bacterial vaginosis (Mlisana et al, 2012).

Across all population groups, sexually transmitted infections have shown to be largely asymptomatic. An MSM study done in Boston showed that 65% of MSM tested were asymptomatic with 7% of asymptomatic MSM testing positive for at least one STD. Among the 7% MSM that were asymptomatic and tested positive, 1.0% had urethral gonorrhea; 1.7% had pharyngeal gonorrhea; 5.6% had rectal gonorrhea; 2.2% had urethral chlamydia; and 4.3% were seroreactive for syphilis (Mimiaga, 2009). These are cases that would otherwise be missed without testing; and result in further spread of infection. This discrepancy has been repeatedly been demonstrated by other studies and evaluations (Badman et al, 2016; Sonkar et al, 2016; Zemouri et al, 2016; Vallely et al, 2017).

While the adoption of the syndromic approach initially showed some success, as time goes on using clinical signs and symptoms is proving to be a poor method of predicting the presence of sexually transmitted infections (Zemouri et al, 2016).

Addressing Objective 4: Testing technologies

Testing technologies such as urine Polymerase Chain Reaction (PCR), swabs of mucosal secretions and blood tests for organisms that cause STIs are available. However, largely due to lack of financial resources, personnel and access to health care, most low- and middle-income countries cannot afford their use (Kuupiel et al, 2017).

In order to assist in reducing the epidemic of undiagnosed STIs, testing needs to be available, cheap and ideally point of care (Toskin et al, 2017; Gaydos et al, 2014; Kuupiel et al, 2017). Point of care assays for Gonorrhoea and T. Vaginalis are available, but still perform inadequately (Toskin et al, 2017; Guy et al, 2017).

Other barriers to availability of ideal point of care tests include regulatory issues, information system integration, the physical and electronic environment (Gaydos et al, 2014; Kuupiel et al, 2017).

Other testing methodologies available for STIs include traditional ones such as Gram stain microscopy, wet preparation and direct fluorescent antibody. The utility of these tests is very limited outside of laboratory setting and many also have low sensitivity and specificity. Other options include immunological methodologies such as ELISA but these are no longer recommended by the CDC e.g. for C. Trachomatis, due to also lower sensitivity (Gaydos et al, 2014).

Nucleic acid amplifications tests (NAATs) are currently considered the gold standard assays for detection of C. Trachomatis and N. Gonorrhoea with several approved commercial assays available (Guy et al, 2017). These are recommended by the CDC, with high sensitivity, specificity and rapidity compared with culture techniques (hours instead of days) (CDC,

2014). Although NAATs solve the issue of low sensitivity and specificity, they are not universally practical due to their cost and time limitations. These assays are expensive and only accessible in more developed countries (Gaydos et al, 2014).

Newer PCR tests for C. Trachomatis and N. Gonorrhoea have been developed with high sensitivity (as high as 95-100%) and specificity (as high as 99-100%), with results available within 90 minutes and may be more easily transferred into a resource-limited setting (Gaydos et al, 2014). A recent study done in South Africa, the CAPRISA 083 prospective cohort study, compared lab assays versus point of care swab testing. Xpert C. Trachomatis/N. Gonorrhoea performed on the GeneXpert System (Cepheid, Sunnydale, California, US), a real-time PCR test for the rapid detection of C. Trachomatis and N. Gonorrhoea, showed that Xpert C. Trachomatis/N. Gonorrhoea from a swab was as highly accurate among young South African women and might prove a useful tool in this high HIV/STI burden setting. Results would be available within 2 hours (Garrett et al, 2019).

For current syphilis testing, guidelines recommend serological testing, using a non-treponemal test (Venereal Disease Research Laboratory-VDRL /Rapid Plasma Reagin-RPR) , and then a treponemal test (Treponemal Pallidum Hemagglutination-TPHA or Treponema Pallidum particle agglutination-TPPA antibody) for confirmation (Gaydos et al, 2014; Diagnostics direct, 2010). Newer rapid syphilis tests are available, some with results available within 15 minutes, but their specificity and sensitivity are still questionable. The only FDA approved 'Trinity Health Check' currently in use in the U.S has high specificity (90%) and sensitivity (95%) (Nakku-Joloba, 2016; Diagnostics Direct, 2010). A meta-analysis of literature between 1980-2012, however, identified 18 rapid point of care tests that

showed comparable sensitivities and specificities to laboratory based Treponema Pallidum tests(Jafari et al, 2013).

A systemic review done to review research on point of care tests identified 33 articles between 2010 and 2015. Of these only six publications presented tests that had >80% sensitivity and specificity, including at least one test for each of C. Trachomatis, N. Gonorrhoea, and T. vaginalis (Herbst de Cortina et al, 2016). This demonstrates the need for more research into the development of practical and functional STI testing techniques.

Addressing Objective 5: Identification of gaps or needs for further research.

As elicited above, most STIs are asymptomatic and therefore do not prompt diagnostic testing. Yet the associated inflammation that increases the acquisition of HIV is still operative (Marrazzo, 2019; Cohen, 2012; Gaydos et al, 2014).

Due to years of syndromic management in LMICs, estimates of the actual burden of disease are lacking. This data is critical if prevention and control of STIs is to be achieved, but might be difficult to generate without widespread low cost, accurate and rapid STI testing (Kaida et al, 2018). While some estimates of STI incidence and prevalence are available, much of this data stems from STI clinics that may not necessarily be representative of the general population, as these are dependent on access and self-selection. Moreover, data is needed in the key populations mostly affected by these infections and at the highest synergic risk of HIV.

This paper seeks to explore the prevalence of asymptomatic STIs in different key populations from the same sub-Saharan African setting – exploring differences between

individuals with different sexual preferences and different HIV/STI risk profiles in the same country that screen for HIV-related research studies.

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PART C: MANUSCRIPT

Prevalence of asymptomatic sexually transmitted infections: A retrospective review of screening data from Desmond Tutu HIV Centre clinical trial cohorts from 2012 to 2017, Cape Town.

Main Author: *Dr Nomcebo Precious Garnett*(Masters of Public Health candidate, University of Cape Town). Desmond Tutu HIV Centre, Groote Schuur Hospital CRS (senior research officer and Principal Investigator). Based in Cape Town, South Africa.

Co-authors:

Associate Professor Catherine Orrell(MBChB, MSc(Clin Pharmacol), MMed(CLin Pharmacol), PhD). Affiliated with Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine and Department of Medicine, Faculty of Health Sciences, University of Cape Town

Dr Katherine Gill(MBChB, Dip HIV Man, DA(SA), Dip pal med) Affiliated with Desmond Tutu HIV Centre, Faculty of Health Sciences, University of Cape Town

Dr Keren Middlekoop(MBChB, MPH, PhD) Affiliated with Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine and Department of Medicine, Faculty of Health Sciences, University of Cape Town

*Karen Dominguez(*MPH). Affiliated with Desmond Tutu HIV Centre, Faculty of Health Sciences, University of Cape Town

Professor Linda-Gail Bekker(MBChB, DCH, DTM&H, FCP (SA) PhD) Affiliated with Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Department of Medicine, Faculty of Health Sciences, University of Cape Town.

Corresponding Authour details

Dr Nomcebo Precious Garnett

Groote Schuur Clinical Research Site

J52 Old Main Building

Groote Schuur Hospital

Observatory

7925

Email address: precious.garnett@hiv-research.org.za

Telephone number: 021 650 6964

Fax number: 021 650 6963

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Short Summary of findings

This analysis found that most STIs are asymptomatic, up to 92% of STIs eliciting no symptoms. The understood relationship between STI symptoms and presence of STI infection is not strong.

Abstract

Background: The burden of Sexually transmitted infections (STIs) is high globally. The World Health Organisation (WHO) recommends syndromic management of these STIs, based on presentation with signs and symptoms, in resource-limited countries. Due to this syndromic approach, there is little current data on STI prevalence, including asymptomatic STIs, in high risk populations.

Methods: We reviewed secondary data collected as part of the screening procedures of 6 clinical trials between 2012 and 2017 in Cape Town, South Africa. These trials recruited populations of different sexual orientation and gender, mostly key populations at risk of HIV and STI acquisition. Routine screening for STI symptoms and testing for Chlamydia, Gonorrhoea, Trichomonas, Syphilis and HIV was performed for all of the studies at screening/enrollment.

Results: A total of 639 participants were screened; 411 (64.3%) self-identifying as female, 198 (31%) males, 29 (4.5%) transgender women and 01 (0.2%) transvestite. Median age was 20 years (IQR: 18-24), with the 15-24-year age category contributing 77% to the cohort.

Laboratory testing diagnosed 239 (37.4%) people with STI infections in this cohort; only 28 (11.7%) people were symptomatic. 119 (88.8%) of Chlamydial, 64 (82.1%) of Gonorrhoeal, 23 (92%) of Trichomonal and 31(79.5%) of Syphilis infections elicited no signs and/or symptoms.

Conclusion: A vast majority of STIs in this high-risk population were asymptomatic. Laboratory testing of causal organism was more reliable in diagnosing STIs than the use of signs and/or symptoms as recommended by WHO.

Keywords: 'Sexually transmitted Infection', 'Prevalence', 'Asymptomatic STIs', 'syndromic management of STIs', 'STI testing'.

Introduction

The World Health Organization (WHO) estimates up to 1 million new sexually transmitted infections (STIs) were acquired world-wide daily in 2016 (16). This burden is more pronounced in Low and Middle income countries, which are also resource-limited (WHO.Int, 2019)Surveillance and study data has defined groupings of people at the high risk of STIs, including HIV, termed 'key populations', including men who have sex with men and transgender women, sex workers, pregnant women, people who inject intravenous drugs and, in resource-limited settings, young heterosexual women(WHO, Int, 2019; AVERT, 2019).

Since the 1990's, due to the documented increase in these infections, and limited global resources, the WHO has recommended syndromic management of STIs. These recommendations were based on common clinical presentations (signs and symptoms) of people with STIs i.e. uro-genital discharge or ulceration, which would be treated with two to three antibiotics, to cover all likely organisms. This was coupled with partner treatment, whether symptomatic or not(Zemouri et al, 2016; Vallely et al, 2017).

This strategy limits expensive confirmatory testing, removes the need to wait for results, and ensures the majority of symptomatic people are treated, thus reducing further

transmission of disease. However, besides the over-use antibiotics and potential increase in drug resistance with syndromic management, there is emerging data to show that symptoms of STIs are not specific and are an unreliable method of diagnosis(Vallely et al, 2017; Zemouri et al, 2016). Not every STI will manifest in symptoms while other STIs may present extra-genitally with atypical symptomatology, such as pharyngeal chlamydia(CDC,2019)

High rates of undiagnosed STIs will drive both STI and HIV transmission. Few studies have examined the prevalence of asymptomatic STIs in Key Populations in resource-limited settings. The aim of this study was to investigate the frequency of both symptomatic and asymptomatic common curable STIs in MSM and young heterosexual women attending HIV-prevention clinical trial sites in Cape Town, South Africa.

Materials and Methods:

Study population

The participants included in this secondary analysis were people who had been screened for one of six different clinical research protocols at two different clinical trial sites, Masiphumele Clinical Research Site (Masi-CRS) in the Southern Peninsula of Cape Town and Groote Schuur Hospital Clinical Research Site (GSH-CRS) in the more central part of Cape Town. Both trial sites are within the Desmond Tutu HIV Centre (DTHC).

The profile of the population recruited in these studies varied. Three studies recruited young heterosexual women at high risk of HIV-infection, two recruited MSM and Transgender Women, and the last recruited populations at the low risk of HIV and STIs. STI data was collected at the study screening visits.

Eligibility criteria

***Inclusion criteria*:**

For studies to be included into the analysis, they had to be actively screening participants between January 2012 and December 2017, within the DTHC; the principal investigator and sponsor of the individual study had to have given permission for data being accessed and used for analysis. The studies had to recruit HIV-negative participants. Inclusion was regardless of type of population recruited, whether young women or high risk MSM or low risk participants.

For participant inclusion into this analysis: a signed consent or assent to be screened for one of the eligible studies was required. Inclusion age was 11 years and older (in sub-Saharan Africa, especially South Africa, high incidence of STI has been shown is this younger group).

The studies selected meeting these criteria were:

UChoose study (a contraceptive methods as proxy for HIV prevention methods using Injectable Nur-isterate, Intra-vaginal nuvaring and daily oral triphasil tablets in South African women aged 16-17 years of age); 3P study (a demonstration open label study to assess the acceptability, safety and use of truvada pre-exposure prophylaxis in healthy, HIV uninfected adolescents, 15-19 years of age); HPTN081/HVTN703 (a phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa); HVTN116 (a phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC01 and VRC01LS in the serum and mucosa of healthy, HIV-uninfected adult participants); HPTN075 (a multi-country prospective study that evaluated the feasibility of recruiting and retaining MSM for

HIV prevention studies in SSA conducted in Kenya, Malawi, and South Africa) and Sibanye (a pilot study of HIV prevention interventions for men who have sex with men in South Africa).

Exclusion criteria.

Excluded studies were those recruiting HIV-positive participants and studies that did not do routine STI testing as part of the screening process. Studies where principal investigators and/or sponsors were not agreeable to sharing the data were also excluded.

Participants excluded were participants that screen failed on the studies (thus no STI testing available).

Data Collection

Data was accessed study databases, participant folders and some requested and sent by the sponsor. Data was collated according to the variables to be explored in this analysis. Where the variable was not collected directly. E.g. one study did not request number of recent sexual partners at screening, data from future visits related to partnerships was collected.

Demographic data including age, gender (per participant identification) and self-identified sexual orientation, was available across all studies. Clinical variables were collected from clinician's history (symptoms of STIs) and examination (signs of STIs) of the participants; and laboratory results of mucosal swabs, blood and urine testing. All studies included urine PCR for Chlamydia and Gonorrhoea, serum RPR (for syphilis), and rapid HIV testing. Four protocols also included Trichomoniasis.

After collation, data was cleaned and analysed.

Ethics

All studies, including this one, were approved by the University of Cape Town Human Research Ethics Committee. All participants gave written informed consent to the parent studies. For this secondary analysis, no interaction with participant occurred, so no additional informed consent was required.

Data analysis

Data was captured in Excel and analyzed using a statistical software Stata version 15(Stata Corporation, College Station, Texas, USA). Numerical data, such as age, was analysed as continuous and categorical data, with categories determined by high risk age groupings used by the WHO when quantifying STI and HIV risk. This allowed for meaningful comparison to available statistics and literature.

Descriptive analysis was performed. Data was otherwise largely categorical, non-binary in nature. This prompted the use of chi squared as well as univariate and multivariate logistic regression modeling to analyze potential associations between variables, adjusted for socio-demographic characteristics and HIV infection. Lab testing results and STI symptoms were used as outcome variables: both as overall variables and recategorized as binary variable (negative or positive) to allow for more detailed analysis. Confounders adjusted for included HIV, age, sexual orientation, gender, number of partners and site of research study. Subgroup analysis was also performed to account for missing data. Participants with missing data were either excluded at data cleaning, or the data was denoted as ‘Not Stated’ or ‘Unknown’ depending on how much of the data was missing.

Results

Descriptive analysis: This cohort had a total of 639 participants from the six research studies. The majority of the cohort, 76.6% (n=489), was 15 to 24 years old. The minimum age was 15 years; with a median age of 20 years (IQR 18 - 23.6 years).

By self-identification; 411 (63.3%) of participants were female, 206 (31.7%) male, 31 (4.8%) Transgender female and 01 (0.2%) Transvestite. 352 (55.0%) people would be considered to fall into a WHO Key Population: 224 (34.5%) MSM and 128 (19.7%) WSM. 43,5% (n=282) did not revealed their sexual orientation. 54(8.3%) of the participants had had no sexual partner in the preceding 6 months, 284 (43.8%) were in monogamous and 311 (47.9%) were in polygamous relationships.

There were 309 lab diagnosed STIs in 239 people (37.4%) Only 37 (15.5%) showed signs and symptoms. There were 156 Chlamydial infections (65.3% of overall STIs), a population prevalence of 24.4%, with only 15 (11.2%, $p<0.01$) presenting with any symptoms and 6 (4.0%) presenting with Chlamydia-specific symptoms. There were 85 Gonorrheal infections (35.6% of overall STIs), a population prevalence of 13.3%, with 14 (17.9%, $p<0.001$) eliciting any kind of symptoms and 7 (8%) presenting with symptoms commonly associated with Gonorrhea. Trichomonal infection had a prevalence of 29 (12.1%) of overall diagnosed STIs, a population prevalence of 4.5%; with only two (8%, p-value-0.03) having symptoms commonly associated with Trichomoniasis infection.

While 39 (16.3%) Syphilis Infections were diagnosed in this cohort, a population prevalence of 6.1%, only 8 (20.5%, p-value-0.02) of these had any form of symptoms. Primary Syphilis typical symptoms were present in 1 (2.6%) of confirmed cases of Syphilis infection.

Of the 37 participants that experienced any signs and symptoms, 6 types of urogenital/rectal STI symptoms were reported; discharge 8 (21.6%), ulcer 3 (8.1%), warts 8 (21.6%), skin tags 9 (24.3%), itching 2 (5.4%) and pain on urination 2 (5.4%).

57 (9%) people were diagnosed with HIV Infection. 34 (59.6%) of these participants were STI co-infected. Of these 16 (28.1%) had any symptoms of an STI ($p<0.001$), i.e. 53% of STIs in HIV infected participants was asymptomatic.

Univariate and Multivariate Analysis: Multivariate logistic regression modelling to explore the odds of overall STI diagnosis showed a statistically significant association between number of sexual partners and STI diagnosis. People in polygamous relationships had increased odds of an STI diagnosis (OR = 1.8, 95% CI 1.01-3.2; $p<0.05$). Of interest, those with no reported sexual partners, also had increased odds of an STI diagnosis (OR = 3.9, 95% CI 1.24-12.47; $p= 0.02$). There was, however, no statistically significant association between overall STI diagnosis and age, gender, sexual orientation or site of the research study (Table 3).

There was an observed association between WSM and the odds of experiencing STI symptoms: WSM were less likely to experience STI symptoms than MSM (OR 0.3, 95% CI 0.13- 0.82; $p<0.02$). There were no observed associations between experiencing STI symptoms and age, gender or number of partners when adjusted for possible confounders (Table 4).

Participants experiencing STI symptoms were more likely to be diagnosed with either any STI (OR 5.1, 95% CI 2.26- 11.39; $p <0.001$) or Chlamydial (OR 3.3, 95% CI 1.51- 7.09 $p <0.001$) and Gonorrheal infections (Or 4.3, 95% CI 1.98- 9.37 $p <0.001$). No statistically significant

association was observed between Syphilis (p= 0.13), Trichomonas (p= 0.29) and STI symptoms when adjusted for other factors (Table 5).

Discussion

This analysis shows a high prevalence of asymptomatic STIs in young people, most at high risk of HIV infection, enrolling into HIV-prevention studies in Cape Town, South Africa. Of 639 people screening, 239 (37.4%) had a confirmed STI. This is similar to that in a recent local cross-sectional study, showing a 32% prevalence of STI in antenatal women. (Davey et al, 2019).

In our cohort, although symptoms of STIs were highly predictive of there being an STI present (OR 5.1, 95% CI 2.26-11.39), the majority of those with laboratory diagnosed STI were asymptomatic (82-92%). Other South African cohorts (Gauteng and KZN) have shown similar high prevalence of asymptomatic disease (Kaida et al 2018, Mlisana et al 2012, Mohammed et al, 2016). Age, gender and sexual orientation were not predictors of overall STI infection, but number of sexual partners was predictive. Having had two or more partners in the last 6 months, compared to someone in a monogamous relationship, had increased odds of infection (OR 1.8, 95% CI 1.01-3.2). This data is supported by the current literature, with increased risk of STI expected with higher number of partners. (Mimiaga et al, 2009)

Of interest, in our cohort, those who reported no sexual partners in the last six months had even greater odds of being diagnosed with an STI. We expect that this is contributed to by a number of factors: underreporting of sexual relationships, especially noted in younger women and adolescent girls, and STIs such as chlamydia and trichomonas remaining asymptomatic for longer than the reporting period. Underreporting of sexual partners is

supported by similar underreporting of sexual identity in young women as well (Schaefer et al, 2017).

Another key finding is that heterosexual women (WSM), seem to under-report or to not experience symptoms of STI (OR 0.3, 95% CI 0.13-0.82), making it more important to move away from syndromic management and toward laboratory-based diagnosis in this population.

A Cape Town study, by Davey et al, showed a Chlamydial and Gonorrhoeal prevalence of 15% and 5.8%, while this analysis shows higher prevalence's of 24.4% and 13.3%, respectively(Davey et al, 2019). There are, however, differences between these two analysis, this analysis is inclusive of the whole population (adolescent girls and young women, MSM, MSW, WSW) and includes a mostly young population with median age of 20 years while the Davey et al analysis was exclusively on pregnant women in Cape Town.

This analysis further shows a high prevalence of STIs in young women and MSM, which is consistent with current literature, but the prevalence in young women in Cape Town seems to be higher at 23% compared to currently available data in young women in KwaZulu Natal(13%)as published by Torrone et al (2018).

Overall Syphilis prevalence of 6.1% and 5.8% in MSM population concurs with available data from CDC, 2019 that estimates a 6.0% burden in this key population. Lower rates are observed in adolescent girls and young women, and heterosexual men.

In terms of HIV infections, this analysis shows MSM (98%) as the worse infected with HIV compared to adolescent girls and young women (2%). Which contradicts current data that suggests in worse-affected countries, 80% of new HIV infections among adolescents are among girls (Avert, 2019).

Moreover, this analysis shows a 14.2% in HIV/STI co-infection. STIs have long been recognized to increase risk of HIV (Kaida et al, 2018; Passmore et al, 2016; Wall et al, 2017) and this analysis concurs.

Study Limitations

Data analyzed came from different research studies with different rationale and objectives, therefore was not uniform. Some studies did not collect all the observations necessary for this analysis such as trichomonas testing in men and sexual behaviour variables.. However, for other variables collateral information could be still be collected to make a conclusion about the observation for this analysis .

Data that could not be obtained from other variables collected, was dropped from the exploratory analysis. Potentially negatively affecting the sample size in this analysis.

A specific type of participant that has interest in HIV related research might not be representative of the population. Moreover, most of these protocols recruited participants that were at high risk of HIV (part of the HIV prevention research trials) hence the chance that this population may not be representative of the general population of the region.

Moreover, by virtue of these studies recruiting HIV negative participants, the observed HIV prevalence may not be representative of the population prevalence as the participants would have been excluded at a pre-screening process.

However, the prevalence of these STIs and HIV in this analysis is comparable to currently available literature on similar groups.

Conclusion

This analysis adds to the current body of evidence that shows that most STIs are asymptomatic, the understood relationship between STI symptoms and presence of STI infection is not strong. This data supports calls for change in the current recommendations of the syndromic management of STIs that relies on these inconsistent symptoms, especially in resourced-limited but highly burdened countries. Investment in laboratory-based testing is essential both to reduce the epidemic of STI infection and to reduce HIV transmission, which goes hand in hand.

This study is limited by not being a representative sample of young people in Cape Town; and by being a retrospective analysis. However, this data on asymptomatic STIs is lacking from resource-limited settings and our data emphasises the need to explore this area of need in more depth.

Recommendation:

Guidelines need to shift away from syndromic STI management, particularly in high-risk Key Populations. Investment in low cost, rapid STI testing technologies is required, to allow laboratory-based STI testing in resource-limited settings.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5052075/ [Accessed 17 Aug. 2019]

PART D: APPENDICES

Appendix A: Data analysis Tables and Figures.

Table 1: Descriptive data- Socio-demographics of the cohort.

Variable	Category	N	%
Age (years)	15-24	489	76.5%
	25-35	106	16.6%
	>35	44	6.9%
Gender	Male	198	31.0%
	Female	411	64.3%
	T/G Female*	29	4.5%
	Transvestite	1.0	0.2%
Sexual Orientation	MSM**	214	33.5%
	WSM***	128	20.0%
	WSW****	3.0	0.5%
	MSW*****	12.0	1.9%
	Not stated	282	44.1%
Reported number of sexual partners	None	54.0	8.4%
	Monogamous	283	44.3%
	Polygamous	302	47.3%

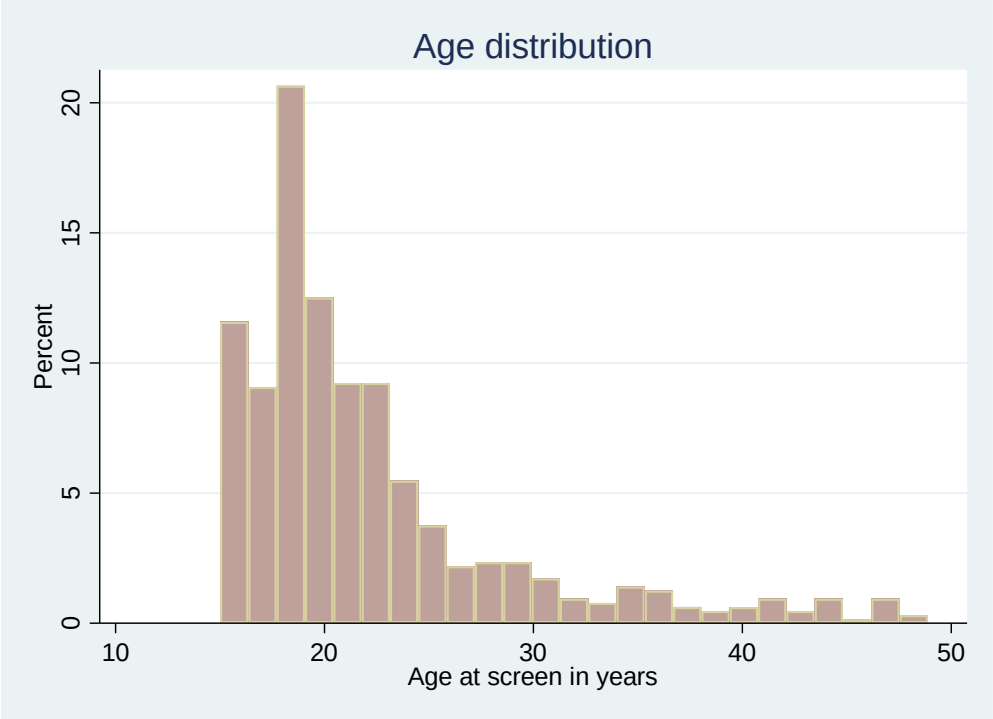
(total in past 6 months)			
Site of study participation	GSH-CRS Masi-CRS	357 282	55.9% 44.1%

*T/G Female- Transgender female. **MSM- men who have sex with men, also includes transgender female and transvestite ***WSM- women who have sex with men ****WSW- women who have sex with women *****MSW- men who have sex with women.

Table 2: *STI laboratory diagnoses versus STI symptoms, using chi-squared test.

Variable	**Number of diagnoses: n (%)**	**STI Symptoms**	**p-value**	**Interpretation: Asymptomatic Infections**
Chlamydia	134 (49.8)	15 (11.2%)	0.01	88.8%
Gonorrhoea	78 (29.0)	14 (17.9%)	<0.001	82.1%
Trichomonas	25 (9.3%)	2 (8%)	0.03	92%
Syphilis	39 (14.5%)	8 (20.5%)	0.02	79.5%
****Overall non-HIV STIs lab diagnosed**	**212 (78.8%)**	28 (13.2%)	<0.001	
HIV (n=57)	**57 (21.2%)**	**Any non-HIV STI Lab Diagnosis**	**p-value** <0.001	53%
		34 (59.6%)		
		STI Symptoms	**p-value**	
		16 (28.1%)	<0.001	

Figure 1: Age at screening Distribution by Histogram and summary statistics



Variable	p25	p50	p75	min	max
Age	18	20	23.59452	15	48.88493

Figure 2: Overall STI laboratory diagnosis by Sexual Orientation

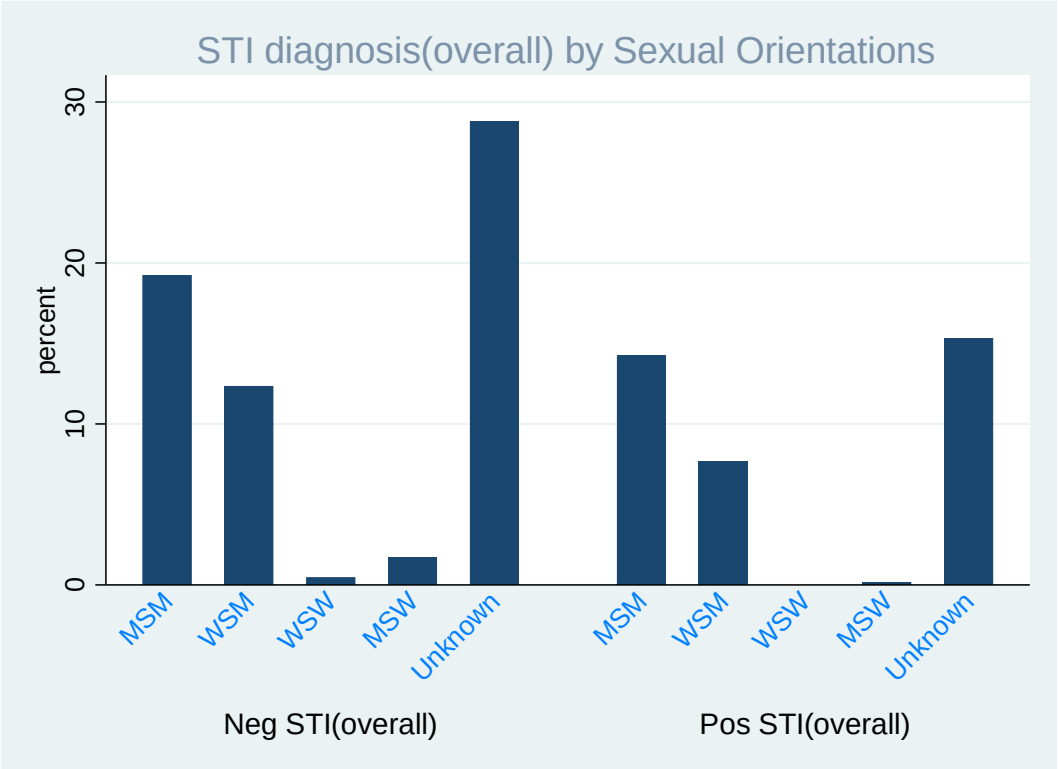


Figure 3: STI laboratory diagnosis by gender

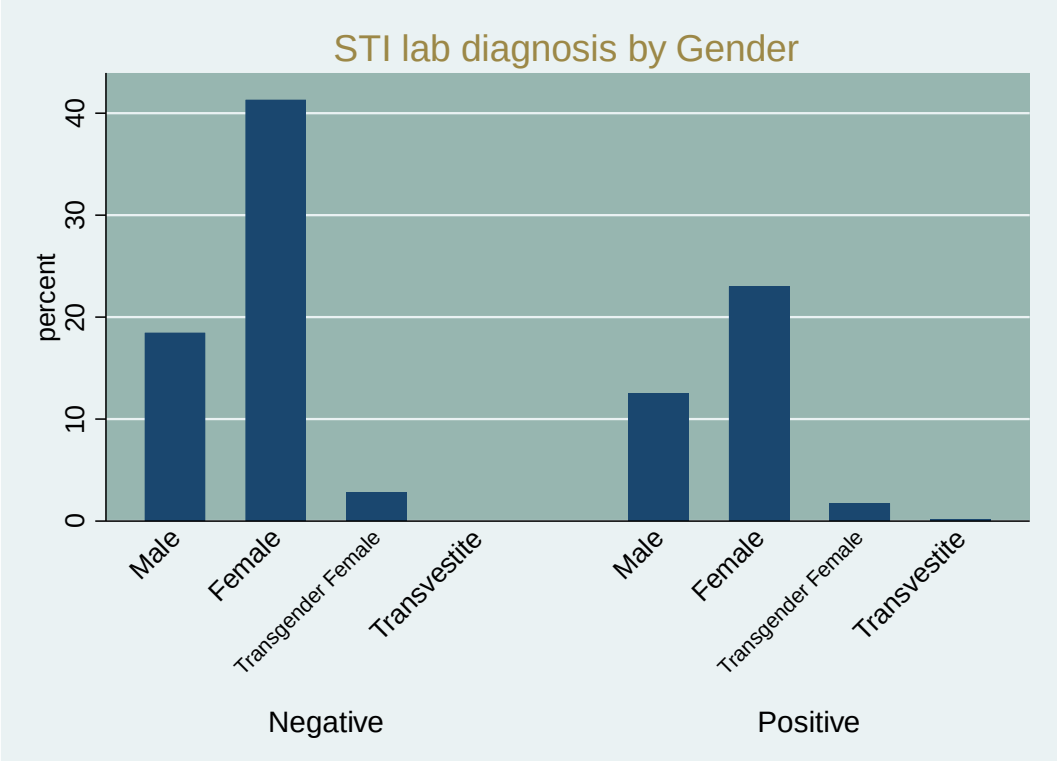


Table 3: Odds of overall STI diagnosis (logistic regression modelling) by laboratory.

Variable	**Crude Association**			**Adjusted Association**		
	Odds Ratio	**p-values**	**95% Confidence Interval**	**Odds Ratio**	**p-values**	**95% Confidence Interval**
Age (years)						
Ref- 15-24						
25-35	0.9	0.59	0.57 – 1.37	0.7	0.21	0.44 – 1.19
>35	0.6	0.14	0.3 – 1.18	0.6	0.13	
Gender						
Ref- Male						
Female	0.8	0.29	0.58 – 1.16	1.5	0.35	0.64 – 3.53
TGF*	0.9	0.8	0.4 – 2.01	0.8	0.5	0.33 – 1.71
TransV**	Few					
Sexual Orientation						
*Ref- MSM****						
WSM****	0.8	0.44	0.53 – 1.3	0.9	0.79	0.54 – 1.59
WSW*****	Few					
	0.1	0.05	0.02 – 0.97	0.2	0.16	0.03 – 1.84

MSW***** *						
Number of Partners *Ref-Monogamous* No partner Polygamous	 1.0 1.3	 0.9 0.11	 0.57 – 1.92 0.94 – 1.84	 3.9 1.8	 0.02 0.05	 1.24 – 12.47 1.01 – 3.2
Site (area) *Ref- GSH-CRS* Masi-CRS	 0.8	 0.22	 0.59 – 1.13			

*TGF- Transgender Female **TransV- Transverstite ***MSM- men who have sex with men

****WSM- women who have sex with men *****WSW- women who have sex with women

******MSW- men who have sex with women

Table 4: Odds of STI symptoms (Logistic regression)

Variable	**Crude Association**			**Adjusted Association**		
	Odds Ratio	**p-values**	**95% Confidence Interval**	**Odds Ratio**	**p-values**	**95% Confidence Interval**
Age: *Ref- 15-24*						
25-35	2.2	0.04	1.04 –	1.0	0.9	0.46 – 3.94
>35	2.5	0.08	4.780.88 – 6.90	1.4	0.6	0.19 – 1.12
Gender *Ref- Male*						
Female	0.2	<0.001	0.10 – 0.47	0.46	0.09	0.19 – 1.12
TGF*	2.1	0.15	0.76 – 5.65	2.1	0.15	0.76 – 5.68
TransV**	Few					
Sexual Orientation *Ref-*						
*MSM****	0.4	0.03	0.16 – 0.91	0.3	0.02	0.13 – 0.82
WSM****	Few					
WSW*****	Few					
MSW***** *						

Number of Partners *Ref-Monogamous*						
us	1.24	0.79	0.25 – 6.03	1.2	0.9	0.20 – 6.65
No partner	2.8	0.01	1.24 – 6.26	1.1	0.9	0.42 – 2.76
Polygamous						
Site (area) *Ref- GSH-CRS*						
	0.11	0.001	0.02 – 0.36			
Masi-CRS						

*TGF- Transgender Female **TransV- Transverstite ***MSM- men who have sex with men

****WSM- women who have sex with men *****WSW- women who have sex with women

******MSW- men who have sex with women

Table 5: Odds of any laboratory diagnosed STI with STI symptoms (logistic regression analysis)

Variable	Crude Association			Adjusted Association		
	Odds Ratio	**p-values**	**95% Confidence Interval**	**Odds Ratio**	**p-values**	**95% Confidence Interval**
Any STI	6.0	<0.001	(2.77 – 13.0)	5.1	<0.001	2.26 – 11.39
Chlamydia	2.4	0.01	1.21 – 4.77	3.3	0.003	1.51 – 7.09
Gonorrhoea	4.5	<0.001	2.21 – 9.20	4.3	<0.001	1.98 – 9.37
Trichomonas	5.4	0.05	0.99 – 29.23	3.6	0.29	0.34 – 37.37
Syphilis	2.8	0.02	1.16 – 6.65	2.0	0.13	0.82 – 4.97
HIV	9.2	<0.001	4.47 – 19.02	5.2	<0.001	2.31 – 11.7

APPENDIX B: ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 February 2018

HREC REF: 109/2018

Prof C Orrell
Desmond Tutu HIV Centre
N1.21.5 WBN
IDM-FHS

Dear Prof Orrell

PROJECT TITLE: RATES OF ASYMPTOMATIC SEXUALLY TRANSMITTED INFECTIONS: RETROSPECTIVE REVIEW OF SCREENING DATA FROM DESMOND TUTU HIV CENTRE CLINICAL TRIAL COHORTS FROM 2012-2017

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28 February 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

HREC:109/2018

Appendix C: SEXUALLY TRANSMITTED DISEASES JOURNAL INSTRUCTION TO AUTHORS.

Sexually Transmitted Diseases. Journal of the American Sexually transmitted diseases association.

Author Instructions

Home > **Submit a Manuscript**

Online Submission and Review System

Scope

SEXUALLY TRANSMITTED DISEASES (STD) is a peer-reviewed journal that welcomes the submission of papers on clinical, laboratory, immunological, epidemiological, behavioral, public health, and historical topics pertaining to *Sexually Transmitted Diseases* and related fields. The Journal publishes:

GENERAL INFORMATION All submissions to *STD* must be made electronically via Editorial Manager, our online submission and peer review system at the following URL: http://www.editorialmanager.com/std. (E-mailed submissions will not be accepted.)

Authors

Please click the log-in button from the menu at the top of the page and log in to the system as an Author. *STD* has a strict 15 author limit. A study group, surveillance team, working group, consortium, or the like (e.g., the Active Bacterial Core Surveillance Team) may be listed as a coauthor in the byline if its contributing members satisfy the requirements for authorship and accountability. The names (and institutional affiliations if desired) of the contributing members may be given in a footnote keyed to the study group name in the

byline or as a separate paragraph in Acknowledgments. Submit your manuscript according to the author instructions. You will be able to track the progress of your manuscript through the system. If you experience any problems, please contact Jeanne Moncada, Assistant Editor, STD@ucsf.edu, phone 415-824-5117, fax 415-821-8945. Requests for help and other questions will be addressed in the order received.

If you are a young investigator, defined as "Current graduate, medical or other professional student, current postdoctoral fellow including clinical fellows, or within two years of completing graduate school or postdoctoral training", please check the status box. Young investigators with articles accepted for publication will be entered into a "Best Paper Award."

Expectations to Review

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Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding:"

For example:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y and is on the speaker's bureau for Organization X - the CME organizers for Company A. For the remaining authors none were declared.

Patient Anonymity and Informed Consent

The author is responsible for ensuring that a patient's anonymity be carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. Photographs with bars placed over eyes of patients should NOT be used in publication. If these photos are used or other identifying details (race, sex, age, occupation, nationality, sexual orientation, etc) are included in the article, then the author must provide proof of informed consent that he/she obtained from the patient (signed permission form). The informed consent form

(http://edmgr.ovid.com/std/accounts/PatientConsentforPub_STD.docx) must be uploaded online at the time of submission.

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When reporting experiments involving human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. For research involving animals, authors should indicate whether the procedures followed were in accordance with the standards set forth in the Guide for the Care and Use of Laboratory Animals (published by the National Academy of Science, National Academy Press, Washington, D.C.)

Compliance with NIH and Other Research Funding Agency Accessibility Requirements

A number of research funding agencies require authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to

PubMed Central. The author must clearly indicate their funding source in the copyright/conflict of interest (COI) form to complete this process.

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All copyright/COI forms are signed electronically. During the submission process, you must list all coauthors and their e-mail addresses in the 'Add/Edit/Remove Authors' step. The form will be e-mailed to your coauthors for acknowledgment and completion. The corresponding author will submit their copyright/COI via Editorial Manager.

Acknowledgment Form

The corresponding author must electronically sign the Acknowledgment form at the time of submission. This form declares that all people involved in the study have been clearly identified and acknowledged in the article.

Cover Letter

A cover letter is required for most submissions. It should include: a very brief overview of the work submitted (1-2 sentences), why your article is appropriate for *STD* (1-2 sentences), a statement of authorship, notifications of conflicts of interest, and ethical adherence.

Organization and Format

General Requirements

For submissions, all text should be double-spaced. Font size should be no smaller than 12 pt. Left, and right margins should be set at 1 inch. Number all pages in sequence and insert continuous line numbers, starting on page 1.

Style

Sexually Transmitted Diseases is in accordance with the Uniform Requirements for

Manuscripts Submitted to Biomedical Journals (ICMJE). Pattern manuscript style after the *American Medical Association Manual of Style* (10th edition). *Stedman's Medical Dictionary* (28th edition) and *Merriam Webster's Collegiate Dictionary* (11th edition) should be used as standard references. Refer to drugs and therapeutic agents by their accepted generic or chemical names, and do not abbreviate them. The name should not be abbreviated. Use code numbers only when a generic name is not yet available. In that case, supply the chemical name and a figure.

Original Articles

Title Page

Must contain the following information (a) complete manuscript title; (b) authors' full names (limit of 12), highest academic degrees, and affiliations; (c) name and address of corresponding author, including fax number, telephone number, and e-mail address; (d) address for reprints if different from that of corresponding author; (e) word counts for the summary, abstract, and text; number of references, figures and tables; and (f) a statement disclosing whether or not any conflict of interest exists; and (g) all sources of support (ie. National Institutes of Health; Wellcome Trust; Howard Hughes Medical Institute); including pharmaceutical and industry support, that require acknowledgement.

Short Summary

A brief summary of your findings is needed for the Table of Contents. Limit the summary to a few sentences (<30 words).

For example: *A study of clients in an STD clinic in Malibu, California found that women with chlamydial infection were younger than women with gonorrhea and were less likely to have multiple partners.*

Abstract and Key Words

Limit the abstract to 250 words. Use the following subheads: Background, Methods, Results, and Conclusions. Do not cite references in the abstract. Limit the use of abbreviations and acronyms. List three to five key words. Choose these words carefully, as they are critical for accurate searches in PubMed and similar databases. We encourage use of at least one broad term and one specific term.

Text

Organize the manuscript into these main headings: Introduction, Materials and Methods, Results, and Discussion (3500-word limit). References, Tables, and Figures should follow. Generally, the introduction should be 2-4 paragraphs. The Editor discourages a limitations paragraph simply listing limitations. Instead, provide a full discussion of each limitation (typically one paragraph per key limitation) or incorporate the discussion of the limitations into the discussion of previous studies. Define abbreviations at first mention in text and in each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country).

Abbreviations

For a list of standard abbreviations, consult the Council of Biology Editors Style Guide (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

References

The authors are responsible for the accuracy of the references. There is a limit of 30 print references. Extra references may be included as Supplemental content and are submitted

as a separate file. These extra references should be numbered as 31s, 32s, 33s, etc. Key the references (double-spaced) at the end of the manuscript. Number the references in text in the order of appearance. To limit references, choose key citations for each point, rather than an exhaustive listing. Cite unpublished data-such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications-in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names at http://www.ncbi.nlm.nih.gov/nlmcatalog/journals.

Sample references are given below.

Journal article:

1. Golden MR, Barbee LA, Kerani R, et al. Potential Deleterious Effects of Promoting the Use of Ceftriaxone in the Treatment of *Neisseria gonorrhoeae*. Sex Transm Dis 2014; 41(10): 619-625.

Book chapter:

2. Elias J, Frosch M, Vogel U. *Neisseria*. In: Versalovic J, Carroll KC, Funke G, Jorgensen JH Landry ML, Warnock DW, eds. Manual of Clinical Microbiology. 10th ed. Washington, DC: American Society of Microbiology; 2011:559-603.

Entire book:

3. Sherman IW. The Power of Plagues. Washington, DC: ASM Press; 2006.

Software:

4. Epi Info [computer program]. Version 7.1.5. Atlanta, GA: Centers for Disease Control and Prevention; 2015.

Online journals:

5. Plecko V, Zele-Starcevic Li, Tripkovic V, et al. Unusually low prevalence of *Mycoplasma genitalium* in urine samples from infertile men and healthy controls: a prevalence study. BMJ Open (Online) August 2014; 4:8 e005372. Available from: http://bmjopen.bmj.com/ Accessed October 22, 2015.

Database:

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 2015. Updated July 17, 2015.

World Wide Web:

7. Keating N L and Pace LE. New Guidelines for Breast Cancer Screening in US Women (JAMA Web site). Available at: http://jama.jamanetwork.com/article.aspx?articleid=2463237. Accessed October19, 2015.

Paper Presented at a Conference:

8. Moncada J, Schachter J, Rauch L, et al. How many MSM with chlamydial and gonorhoeal infections are missed if only urine specimens are screened? Presented at: 6th European Chlamydia Meeting [P07]; 2008; Aarhus.

Photographs/Figures

Art should be created/scanned and saved and submitted as either a TIFF (tagged image file format), an EPS (encapsulated PostScript) file, or a PPT (PowerPoint) file. Line art must have a resolution of at least 1200 dpi (dots per inch), and electronic photographs- radiographs, CT scans, and so on-and scanned images must have a resolution of at least 300 dpi. If fonts are used in the artwork, they must be converted to paths or outlines or they must be embedded

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Create tables using the table-creating and editing feature of your word processing software (e.g., Word, GoogleDocs). Do not use Excel or comparable spreadsheet programs. Tables should generally be very neat and readable. For example, tables made with separate columns for each number type (e.g. N (%) requires two columns, N justified to the right, (%) justified to the left) are usually easier to read. Group all tables in a separate file. Cite tables consecutively in the text, and number them in that order. Each table should appear on a separate sheet and should include the table title, appropriate column heads, and

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