ANALYSIS OF PROGESTIN-BASED INJECTABLE CONTRACEPTION AND THE RISK CURABLE SEXUALLY TRANSMITTED INFECTIONS IN A PROSPECTIVE COHORT OF ADOLESCENT GIRLS AND YOUNG WOMEN IN JOHANNESBURG, SOUTH AFRICA

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Declaration

I Juliet Vimbai Rundogo declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Public Health: Maternal and Child Health at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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__18th___day of__September__2024____in_Johannesburg, South Africa

Dedication

To my parents that have been incredibly supportive of every dream I have ever had.

Abstract

Introduction: Several studies have shown an increased risk for sexually transmitted infections (STIs) in women using hormonal contraception. We explored this association in a cohort of adolescent girls and young women (AGYW) in Johannesburg, South Africa.

Methods: CHOICES was a prospective observational study that investigated the association between progestin-based injectable contraception (IC) and *Neisseria gonorrhoea* (GC), *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG), and *Trichomonas vaginalis* (TV) in Human-Immuno-Deficiency Virus (HIV) uninfected AGYW aged 16-24 years. We used logistic regression to explore the associations between IC compared to non-HC use for each STI.

Results: Of 736 AGYW screened, 611(83%) were eligible, and 577 included in this analysis. Median age was 21 years (IQR 19-22 years). Overall, 183/577 (32%) had a curable STI, with 130/577 (23%) having CT, 37/577 (6%) MG, 24/577(4%) NG and 19/577 (3%) TV at baseline. In both bivariate and after adjusting for sexual behavioural factors, there were no statistically significant associations between IC use and having an STI.

Conclusion: Although there was a trend, there was no statistically significant association between IC and any STIs were observed in this cohort with a high STI burden.

Acknowledgements

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Nomenclature/List of Abbreviations and Symbols

Abbreviations

AIC	Akaike information criterion
aOR	Adjusted odds ratio
AMR	Ant-microbial resistance
AGYW	Adolescent Girls and Young Women
ART	Antiretroviral therapy
AYFS	Adolescent and youth-friendly health services
AYP	Adolescent and Young People
BIC	Bayesian information criterion
CASI	Computer Assisted Self-Interview
CCR5	C-C Chemokine Receptor 5
CDC	Centres for Disease Control and Prevention
CHW	Community health worker
COC	Combined Oral Contraceptives
COVID 19	Coronavirus Disease 2019
CRS	Clinical Research Site
CT	*Chlamydia trachomatis*
CXCR4	C-X-C Chemokine Receptor Type 4
CYPR	Couple Year Protection Rate
DMPA	Depot Medroxyprogesterone Acetate
DHB	District Health Barometer
DOE	Department of Education
DOH	Department of Health
Doxy-PEP	Doxycycline post exposure prophylaxis
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GC	*Neisseria gonorrhoea*
HIV	Human-Immuno-Deficiency Virus
HPTN	HIV Prevention Trials Network
HPV	Human Papilloma Virus
HR	Hazard Ratio
HSV	Herpes simplex virus
IC	Injectable Contraception

ISHP	Integrated school health program
IUCD	Intra-Uterine Contraceptive Device
IUD	Intra-uterine device
LH	Luteinizing Hormone
LMIC	Low- and Middle-Income Countries
MG	*Mycoplasma genitalium*
mHealth	Mobile health
NAAT	Nucleic Acid Amplification Tests
NAFCI	National Adolescent-Friendly Clinic Initiative
NET-EN	Norethisterone Enanthate
NH	Non-hormonal contraception
NICD	National Institute of Communicable Diseases
NGO	Non-governmental Organisations
OR	Odds ratio
PEP	Post exposure prophylaxis
PID	Pelvic inflammatory diseases
POC	Point-of-care
PrEP	Pre-exposure prophylaxis
PSI	Population Services International
QALY	Quality-adjusted life-years
SA	South Africa
SADHS	South African Demographic and Health Survey
SASSA	South African Social Security Agency
SBCC	Social And Behaviour Change Communication
STI	Sexually Transmitted Infection
STIs	Sexually Transmitted Infections
SOP	Standard Operating Procedures
SRH	Sexual and reproductive health
TV	*Trichomonas vaginalis*
UBIG	Universal basic income grant
UBPL	Upper-bound poverty line
USA	United States of America
VDS	Vaginal discharge syndrome
WBPHCOT	Ward-Based Primary Healthcare Outreach Teams

WHO	World Health Organisation
YFS	Youth Friendly Services
YZ	Youth Zones

Chapter 1 Introduction

1.1 Background

In 2022, there were an estimated 1,8 billion adolescents and young people (AYP) aged 10-24 years, with a substantial proportion (90%) living in Low-and Middle-Income Countries (LMICs) (1,2). These AYP are experiencing puberty and sexual debut at earlier ages than in previous decades (3) Risky sexual behaviours which include early sexual debut, having high-risk sexual partner/s, transactional sex, multiple sexual partners, condomless sex, unprotected mouth-to-genital contact, sexual activity under the influence of drugs and alcohol are frequent in AYP (4–8). For example, only 51% of 4399 adolescent girls and young women (AGYW) in 10 districts in South Africa between 2018 and 2019 reported condom use at last sex (6). Shayo et al reported close to 21% of 15 318 adolescent scholars had multiple sexual partners (two or more sexual partners) in five Sub-Saharan countries, namely Benin, Mozambique, Namibia, Seychelles and Tanzania (7) whilst other countries such as Sierra Leone have reported as many as 85.2% adolescent scholars aged 10-19 years had multiple sexual partners (8).

Risky sexual behaviours place AGYW at risk for adverse health effects such as unplanned pregnancies and sexually transmitted infections (STIs), including Human Immunodeficiency Virus (HIV). More than one million STIs are acquired daily globally (9). Women bear the brunt of these infections (10), for example, in 2019, it was estimated there were 53 371 000 cases (33 cases per 1 000 women) of CT, 33 822 000 cases (21 cases per 1 000 women) of GC, 66 807 000 cases (41 cases 1 000 women) of TV, 2 774 000 cases (2 cases per 1 000 women) of syphilis where in women aged 15-49 in LMIC (10,11). AYP contribute to 50% of the global STI burden (12) which translates to one in twenty AYP contracting an STI, including HIV, each year (5) and an estimated 4900 incident HIV infections occurred weekly in AGYW globally in 2022 (13).

Most STIs are asymptomatic or unrecognised. This has implications for the diagnosis and management of STIs, particularly in LMIC where syndromic management is the standard of care. For example, in *Chlamydia trachomatis* (CT) infections, only 6%–17% in women are symptomatic (14–16) and for *Neisseria gonorrhoea* (GC) infections only 14%–35% are symptomatic in women (14,15). AGYW bear a greater burden of negative health outcomes from untreated STIs (13). Some of the STI complications AGYW face are infertility, pregnancy complications, septic shock, endometritis, acute and chronic pain, pelvic inflammatory disease,

cervical cancer, anal cancers, lost quality-adjusted life-years (QALYs), high morbidity, high mortality (3,17–25)

May et al reported on the following equation: Ro = BxcxD as a formula to sexual transmitted infection reproduction in a population (26,27). It describes the reproduction rate of STIs (Ro) summarised by B, the transmission efficiency of the organism, c, the rate of sex partner change and D the duration of infection (26,27). We will explore the effect of progestin-based IC on the transmission efficacy of STI, thereby affecting "B". We will also explore partner numbers which affect "c" which is the rate of partner change in the equation mentioned above.

It remains unclear whether progestin-based contraceptives increase the risk for curable STIs including GC, CT, *Trichomonas vaginalis* (TV) and *Mycoplasma genitalium* (MG). In some trials the use of hormonal contraceptives was protective for STIs, whilst other trials reported increased susceptibility to curable STIs for hormonal contraceptive users (28–46). These observational studies were prone to several limitations such as, challenges in defining the exposure, i.e. contraception due to a substantial portion of the participants transitioning between different types of contraception during the trial, different age groups being evaluated, and different sexual risks being evaluated .(30,32,35,47) It is hypothesized that in the case of GC, the reduced menstrual blood flow associated with hormonal contraception use decreases the availability of iron, a crucial mineral for GC growth and pathogenicity (33,48–50). Additionally, injectable contraception may thicken cervical mucus, which could protect against GC by limiting its access to the cervical mucosa(33,50) For CT, the use of progestin-based injectable contraception is thought to induce a hypo-estrogenic state, leading to vaginal dysbiosis and increasing the risk of CT infection(33,41) Regarding TV, since TV requires estrogenic and androgen receptors, the high progestin content in progestin-based contraception may block androgen receptors, which are closely related to progestin receptors, thereby potentially preventing TV infection. (33,44,51).

Behavioural factors that put AGYW at risk for STI include early sexual debut (52–55), having multiple sexual partners (28,52–54,56,57), reporting a previous STI (53,58), age disparate relationships of five or more years (53,54,56), condomless sex (6,28,54,55,57,59) and high consumption of alcohol and drugs (54). Structural risk factors for acquiring STIs are experiencing forced sexual activity (60), transactional sex (55,56,60–62), low socio-economic status (56), food insecurity (56), low educational attainment (56), lack of parental/guardian support or supervision experience (8,63), interpersonal violence (56,60,64), gender

discrimination (52,56,64) and patriarchal societies (56,60,64). Being younger is also a risk factor for acquiring STIs (28) due to lower social power and agency to advocate for condom use as well as higher risk taking behaviours. These STI risks in AYP are exacerbated by disparities in access to health care in AYP compared to older peers (65) due to multiple barriers to health care access (66) that will be discussed in detail below.

1.2 Literature review

1.2.1 Sexually Transmitted Infections Prevalence

High STI prevalence remains a public health challenge. WHO estimates there were approximately 374 million incident infections of curable STIs (*CT, GC, TV* and syphilis*)* in 2021 for both men and women globally (10,67,68). This translates to more than 1 million curable STIs occur each day (10,67,68). Sub-Saharan Africa contributes significantly to the global burden of STIs, accounting for 40% of all cases (10). Women bear a disproportionate burden of STIs (10). In 2019, it was estimated there were 53 371 000 cases (33 cases per 1 000 women) of CT, 33 822 000 cases (21 cases per 1 000 women) of GC, 66 807 000 cases (41 cases 1 000 women) of TV, 2 774 000 cases (2 cases per 1 000 women) of syphilis in women aged 15-49 in LMIC (10,11). *Mycoplasma Genitalium* (MG) prevalence reporting has been on the rise for the last two decades with LMIC reporting higher prevalence of 3.9% compared to 1,3% reported in high income countries (11). Whilst this huge burden of STIs affects all ages, AYP are largely affected (5) .

In South Africa, in 2016, 12%% of women and 7% of men reported to have been treated for an STI or to have experienced STI symptoms in the last 12 months (69). STI symptoms were defined as genital ulcer and/or foul-smelling, abnormal vaginal/penile discharge. In 15–49-year-olds, 5% of women reported an STI in the last 12 months; 9% reported a foul smelling abnormal vaginal discharge and 4% reported genital ulcers, 4 % of men reported a foul smelling and abnormal penile discharge and 2% of men reported a genital sore or ulcer (69). As the SADHS is a self-reporting survey, the numbers reported may be underestimates of the true values. These could also be underestimates due to the asymptomatic nature of most STIs.

A 2018 South African Spectrum-STI estimation (using laboratory diagnosed GC and CT data) estimated GC prevalence rate of 6%, (95% CI, 3.8–10.8%) in women and 3.5% (95%CI, 1.7–6.1%) in men in 2017, which translate to 2.3 (95%CI, 1.1–5.0) million cases in women and 2.2 (95%CI, 1.1–3.8) million GC cases (i.e., episodes) in men (70). They also reported CT prevalence in women at 14.7% (95%CI, 9.9–21%) and in men at 6.0% (95%CI, 3.8–10,4%), which translates to 1.9 (95%CI, 1.1–3.8) million cases in women and 3.9 (95%CI, 2.2–6.3)

million cases in men (70). A meta-analysis in Sub-Saharan HIV prevention studies conducted 1993-2011 reported on STI prevalences such as 8% to 20.6% for CT in AGYW aged 15-24 year (71). CT prevalence was higher in women aged 15-24, compared to women aged 25-49 (71). The same meta-analysis reported GC prevalence from 1.4%-8.9% in 15-24 years old (71). Similar to CT, GC prevalence was higher in AGYW aged 15-24 compared to women aged 25-49 (71). A trend for higher STI prevalence in AGYW aged less than 25 years compared to women older than 25 years has been noted in other studies with younger AGYW twice as likely to have a STI (70–72). The aforementioned meta-analysis also noted that contracting one sexually transmitted infection (STI) heightened the risk of acquiring another. For instance, among individuals aged 15-24 years in South Africa, the prevalence of CT was 15.1% in those with a single infection, whereas it rose to 38.7% among women who were co-infected with GC (71).

Reported TV prevalence rates in South Africa have varied depending on the location and specific age group. In AGYW aged 15-24 years in rural KwaZulu Natal, South Africa, TV prevalence rate of 4.6% was reported (73). A study in Mopani District, South Africa reported TV prevalence rate of 20% in women aged 18-49 (74). In the ECHO study, which was a large randomised controlled trial of women in Eswatini, South Africa, Zambia and Kenya aged 16-35, women were randomised to either DMPA, intra-uterine copper device (IUCD) or levonorgestrel implant. Women were recruited from research sites that were stand alone, university affiliated or providing sexual reproductive health services. A high TV prevalence of 31% was reported for the eThekwini and Tshwane participants (South African participants) at baseline (75).

Regarding MG, Baumann et al reported prevalence to range from 1.3% to 3.9% in the general population from a meta-analysis that included six high income countries and five LMIC (Honduras, Vietnam, Kenya, Madagascar and Tanzania) (76). In South Africa MG prevalent rates reported in studies in different populations range from 5.9% to 24% (58,75,77,78). Pregnant women aged 18 years and older in KwaZulu- Natal, South Africa attending an antenatal clinic had MG prevalence of 5.9% (78). The ECHO study with 18–33-year-olds reported MG prevalence rate of 7% at baseline for the eThekwini and Tshwane participants (75). A prevalence of 7.4% was reported in women living with HIV in South Africa (79). In another study in pregnant women aged 18 and over in Cape Town, MG prevalence was 24% in HIV-infected women and 12% in HIV- uninfected women was reported (77). It is essential to

analyse the prevalence of MG in AGYW as it is an organism that is emerging as one of the major STIs.

1.2.2 Sexually Transmitted Infections Incidence

CT Incidence remains high globally and in Sub-Saharan Africa. The global incidence rate for CT is estimated to be 38 cases per 1 000 in women (19). In South Africa CT incidence rates have ranged from 27.8/100 person years to 42.4/100 person years (59,75,80,81). In women aged 18-40 years in Orange Farm, South Africa, Pettifor et al reported CT incidence rate of 28.2/100 person years (81). In the HIV Prevention Trials Network (HPTN) 082 trial which consisted of young women aged 16-25 years in South Africa and Zimbabwe, CT incidence rate of 27.8/ 100 person years was reported (59). In the ECHO study, women aged 18–33 years old, from eThekwini and Tshwane, South Africa, a CT incidence rate of 40.4/100 women years was reported (75). In the EVRI study of 16–24-year-old women, in the Western Cape, South Africa a higher CT incidence rate of 42.4 /100 person-years was reported (80).

GC incidence rates vary by region and population. Global estimate of GC incidence remains at a rate of 19 cases per 1 000 women (19). In South Africa, trials have reported GC incidence rate ranging from 7.7/100 women year to 20.8/100 women years (59,75,80). In women aged 18-40 in Orange Farm, South Africa, Pettifor et al reported GC incidence rate of 9.9 per 100 person years in an old trial that ran from 1991-2001 (81). In the ECHO study, women aged 18–33 years old, from eThekwini and Tshwane, South Africa, a GC incidence rate of 7.7/100 women years was reported (75). In the HPTN 082 trial, which consisted of young women aged 16-25 years in South Africa and Zimbabwe, a GC incidence rate of 11.4/ 100 person years was reported. (59). In the EVRI study, 16–24-year-old women, in the Western Cape, South Africa GC incidence rate was higher as 20.8 per 100 person-years(80). The ECHO trial (75), HPTN 082 (59)and EVRI trial (80) cover a period from 1999 to 2018.

Global estimates for TV incidence are 38 cases per 1 000 women (19). In Sub-Sharan Africa, TV incidence in women is reported to range from 2.4/100 person years to 43.7/100 person years (59,75,80–82). In the HPTN 082 trial which consisted of young women aged 16-25 years in South Africa and Zimbabwe, TV incidence rate was lower at 6.7/ 100 person years (59). In women aged 18-40 in Orange Farm, South Africa, Pettifor et al reported TV incidence rate of 10.2 per 100 person years (81). In the ECHO study, with women aged 18–33 years old, from eThekwini and Tshwane, South Africa TV incidence rate was as high as 43.7 /100 women (75).

In a metanalysis including women in high income countries, the incidence rate of MG was reported to be 1.07 per 100 person-years (83). In South Africa, the incidence rate in MG varied across different population groups. In South African pregnant women in KwaZulu-Natal, incidence rate was reported to be 3.7/100 person years (78). In the ECHO study, with women aged 18–33 years old, from eThekwini and Tshwane, South Africa MG incidence rate of 18 /100 women years was reported (75).

It is noteworthy that over the years, the incidence rate of STIs has been steadily increasing in each study. Moreover, studies involving younger women report higher STI incidence rates compared to the general population. These persistently high and rising rates among AGYW represent a significant public health concern. What is particularly troubling is that, despite offering women in these studies condoms, risk reduction counselling, treatment, and treatment for their sexual partners or partner notification and treatment slips, the incidence rates have remained high. This underscores the shortcomings of current STI management strategies for women. These findings highlight the urgent need for targeted interventions aimed at improving the diagnosis, prevention, and treatment of STIs in AGYW.

1.2.3 Risk factors for STIs

Most STIs are asymptomatic or unrecognised. This has implications for the diagnosis and management of STIs, particularly in LMIC where syndromic management is the standard of care. For example, in *Chlamydia trachomatis* (CT) infections, only 6%–17% in women are symptomatic (14–16) and for *Neisseria gonorrhoea* (GC) infections only 14%–35% are symptomatic in women (14,15). AGYW bear a greater burden of negative health outcomes from untreated STIs (13). Some of the STI complications AGYW face are infertility, pregnancy complications, septic shock, endometritis, acute and chronic pain, pelvic inflammatory disease, cervical cancer, anal cancers, lost quality-adjusted life-years (QALYs), high morbidity, high mortality (3,17–25).

May et al reported on Ro = BxcxD as a formula to measure sexually transmitted infection reproduction in a population (26,27). It describes the reproduction rate of STIs (Ro) summarised by B, the transmission efficiency of the organism, c, the rate of sex partner change and D the duration of infection(26,27). This gives a framework to look at transmission of STI and risk factors for STI epidemics. We will explore the effect of that progestin-based IC on the transmission efficacy of specific STIs, thereby affecting "B" in the equation above and consequently increasing Ro. We will also explore the effect of partner numbers which affects "c" in the equation mentioned above.

Compared to their older counterparts, AGYW, particularly in South Africa, are at a higher risk for acquiring STIs due to numerous biological, behavioural and structural factors (52–55,84–96). Biological risk factors for acquiring STIs include larger surface area to acquire infections (cervico-vaginal) in women, increased expression of inflammatory markers in immature immunological system, immature cervical-vaginal mucosa, and poor decision making due to prefrontal-cortex immaturity in biological development of AGYW (92,93,96). The use of hormonal contraception is also a potential biological risk for STI. The relationship between progestin-based contraceptives and the risk for curable STIs including GC, CT, TV, and MG remains unclear. In some studies the use of hormonal contraceptives was protective for STIs, whilst other studies reported increased susceptibility to curable STIs for hormonal contraceptive users (28,29,81,82,97–111). We will explore the effect of progestin-based IC on the transmission efficacy of STI (affecting "B" the transmission efficacy of the STIs) in the CHOICES cohort of AGYW in inner city Johannesburg, controlling for known risk factors. Behavioural risk factors to acquiring STIs include: early sexual debut (52–55), condomless sex (6,28,54,55,57,59), multiple sexual partners (28,52–56), high risk use of alcohol and drugs, previous STI (53,58), and age disparate relationships of five or more years (53,54,56). Structural risk factors for acquiring STI include experiencing forced sexual activity (60), transactional sex (55,56,61,94), low socio-economic status (56) food insecurity (56), low educational attainment (56), lack of parental/guardian support or supervision (63,112), interpersonal violence (55,56,64), gender discrimination (52,56,64) and patriarchal societies (57,64,113). Health system associated risk factors are mentioned under Syndromic STI management.

Syndromic STI Management

South Africa is one of the many countries in Sub-Saharan Africa that use syndromic management for treatment of STIs (114). Syndromic management of STIs is an approach of treating signs or symptoms that belong to a group of infections (a syndrome) rather than a specific infection (114). Syndromic management is used because it allows for management of STI in low resource settings where there might be lack of trained clinical and laboratory personnel for diagnosis as well as lack of laboratory equipment (115). Although syndromic management has advantages such as being cost-effective, a large proportion of individuals have no STI symptoms therefore they remain untreated due to low specificity and sensitivity of syndromic management (116). Syndromic management leads to overtreatment, inadequate treatment and missed opportunities for treatment as some syndromes such as vaginal discharge syndrome (VDS) have multiple causes (117). Untreated individuals also face risks and costs

associated with STI complications, adding to the negative effects of STIs in AGYW. The rising resistance to macrolides (for MG), fluoroquinolones (for MG) and cephalosporins (for GC) is also a major public health concern associated with syndromic management (118,119). Specifically for GC, this is a major problem as cephalosporins are first line management for GC (118).

Even if individuals that are symptomatic and recognise their symptoms, there may be further barriers to health care access. Newton-Levinson et al, published a systemic review of studies published between 2001 and 2014 on the barriers to accessing STI care for AYP in LMIC, where they reported on personal, family/community and health system factors (66). Countries that were included in the systemic review were, Nepal, Pakistan, Thailand, India, Vanuatu, Nigeria, Ghana, Ethiopia, Gambia, Uganda, Burkin Faso, Kenya, Malawi, Zimbabwe and South Africa (66). Personal factors include poor knowledge of sexual reproductive health, poor knowledge of STI services, and fear of seeking out health services (66). Family/community factors include overbearing parents/guardians, cultural beliefs, and gender and societal norms (66). Health system barriers included provider ignorance, provider beliefs and perceptions, provider attitude, intimidated providers who feel ill-equipped to provide care to AYP, staff shortages, stockout, inaccessible health care (due to cost of treatment, opening hours, waiting time, distance, cost of transport to health centre), lack of youth friendly services and lack of integration of health services (66).

1.2.4 Consequences of untreated STI

A considerable burden of health issues arises from both acute and untreated long-term sexually transmitted infections (STIs). This burden encompasses various health complications, including gynaecological issues such as abdominal pain, chronic pelvic pain, pelvic inflammatory disease (PID), infertility, and cervical cancer (5,120,121). Obstetric complications that can occur due to untreated STI include ectopic pregnancies, stillbirths, neonatal infections, neonatal deaths, low birth weight, preterm and premature deliveries (5,120,121). Additionally, there are psychological complications such as poor mental health, stigma, and discrimination(5,120,121). Morbidity and mortality stemming from these complications, along with an increased risk for HIV transmission, further compound the health burden (5,120,121).

Among AGYW aged 12–21 in USA, the direct cost associated with PID was reported to be US$3,025 in 2009 (122). The cost of treatment of STIs and their sequalae is a financial strain to countries in Sub-Saharan Africa that are burdened by multiple infectious disease. It is estimated that in 2019, it cost LMIC USD $2eroeg

million in direct costs and system costs for treatment of four STIs (syphilis, CT, NG, TV) in women aged 15-49 years (11). We found most studies on direct and indirect costs of STI and their complications to be from upper-middle income countries.

1.3 Contraception use

1.3.1 Global prevalence and importance of modern contraception

An increase in global use in contraception has been reported by the United Nations (UN) from 900 million users in 2000 to 1.1 billion users in 2020, which equates to an increase in contraceptive prevalence from 47,4 % to 49 % . (123)

Modern contraception use reduces the number of unintended and unplanned births. By reducing unintended and unplanned births, this also reduces a woman's risk for mortality and morbidity associated with pregnancy and labour (124). Among the 111 million unintended pregnancies in women in LMIC in 2019, 35 million underwent an unsafe abortion and 12 million resulted in miscarriage (11). Unsafe abortion and miscarriages are also risk factors for maternal mortality and morbidity (11). In 2019, 89 000 maternal deaths in LMIC were associated with unintended pregnancies (11).

Modern contraception use also reduces the number of high-risk pregnancies among high-risk populations, including AGYW (124). Countries in Asia and Africa account for 80% of all adolescent maternal mortality (124). Adolescent pregnancy has increased risk for mortality and morbidity due to increased risk for preterm delivery, unsafe abortion, eclampsia, systemic infections, endometritis and other labour complications (125). Modern contraception use remains especially important in ensuring healthy and long lives in AGYW.

The World Health Organisation (WHO) reports one in four pregnancies in women are unintended due to unmet needs for contraception (123). In AGYW, approximately 50% of all pregnancies are unintended, with 55% of unintended pregnancies ending in abortion (11,123). In AGYW in Sub-Saharan Africa, 30 % of pregnancies are unwanted and 24.88% are unintended (126,127). Unintended pregnancies in AGYW can lead to dropping out of school, lower educational attainment and lower economic contribution (128,129). Unintended pregnancies can also be associated with negative health outcomes and complications due to immature body physiology such as eclampsia, prolonged labour, puerperal endometritis, maternal morbidity and maternal mortality (25,128,129) Neonates born to AGYW are at greater risk of complications compared to neonates born to older women, with those born to adolescents aged 10-19 at higher risk compared to those born to young women aged 20-24

(25,130). Neonatal complications include, preterm birth, still births and neonatal deaths (25,128,129). As contraception use is important in AGYW, there is a public health need to better understand the association between contraception use and STIs.

1.3.2 Contraceptive use in Africa and South Africa

The use of contraception, particularly IC such as DMPA and NET-EN, is steadily increasing globally with a notable uptick observed in Sub-Saharan Africa (69,131) which is an area with a large burden of STIs (40% of the global distribution) (10).

Based on demographic health survey data from 1995 to 2020 in 37 countries of women aged 15-49 years using modern contraception, South Africa was ranked 4th highest user of modern contraception after Namibia, Lesotho and Zimbabwe in Sub Saharan Africa (132). Given South Africa's high rates of hormonal contraception usage (132), there exists a considerable number of women who may face heightened vulnerability to STIs if a link between hormonal contraception and STIs is established.

In 2016 as part of the SADHS, amongst women aged 15-49 years, 60% of sexually active women reported using a family planning method (69). Among them, 0.4% opted for traditional methods, while 57.9% employed modern methods (69). Modern contraception can be defined as any medicinal product or medical procedure that interferes with reproductive potential (133). Amongst all age groups in South Africa, the most popular contraceptive methods are injectables (25%), followed by male condoms (16%), oral pills (7%), and female sterilization (6%) (69). In South Africa, contraception can be obtained from the private sector at a cost to the individual or through health insurance, as well as from government facilities at no cost to the individual. In the private sector the following contraceptive methods are available: condoms (male and female), oral contraceptive tablets, contraceptive patches, injectable progestin-based contraceptives, subdermal implants, and intrauterine devices. In government facilities (clinics, adolescent clinics, hospitals, mobile clinics) the following methods are available: condoms (male and female), oral contraceptive tablets, injectable progestin-based contraceptives, subdermal implants, and intra-uterine devices. Oral contraceptive tablets and patches contain combined oestrogen and progestin hormones. Whilst injectables, implants and some IUD and some oral tablets are progestin only based contraceptives. In South Africa, two injectable contraceptives, NET-EN and DMPA, are available for administration via intramuscular injection in the arm or buttock. DMPA is prescribed at 12-14 weekly intervals whilst NET-EN is prescribed at eight weekly intervals (134,135). IC function by inhibiting ovulation, thickening the cervical mucus and making the endometrium unfavourable for implantation (135). IC is

also ideal for women and AGYW who cannot use oestrogen containing contraception, and for women with menstrual problems to reduce premenstrual syndrome symptoms, menstrual pain and flow, ovulation pain, pelvic pain, to reduce endometriosis-associated pain, and to reduce endometrial hyperplasia. Progestin-based contraceptives can also reduce menopausal symptoms, and the effects of haemoglobinopathies (134,135). As a large number of sexually active women and AGYW find IC to be favourable and are using IC in South Africa (69,132), it is important to study any risks that might be associated with the use of IC.

A decline in Couple Year Protection Rate (CYPR) was reported in the District Health Barometer (DHB) 2019/2020 from 60.7% in 2018/2019 to 54.5% in 2019/2020 (136). The years 2019/2020 was also affected by severe physical movement restrictions at the height of the Coronavirus Disease 2019 (COVID 19) pandemic which might have also affected DMPA usage. Significant stock outs of DMPA contributed to a decline by 10.2% in DMPA use in 2019/2020 from 6 206 245 injections to 5 574 653 injections. NET-EN use in contrast increased from 1 939 006 injections to 2 868 579 injections which was a 47% absolute increase. Potentially this could be due to users shifting between IC methods. This rise in the number of NET-EN injections is still lower than the number of NET-EN injections that was reported in 2017/2018, which was 3 720 442 injections (136). These numbers highlight an unmet need for contraception amongst women of reproductive potential in South Africa even though contraception use has been high. Additionally, the report highlighted a decrease in the distribution of female and male condoms by 6.2% and 11%, respectively (136), which is a concern as barrier protection remains essential for STI protection. The numbers above show a general high demand for IC in women of reproductive age in South Africa. With higher volumes of women on injectable contraception and lower numbers of condoms distributed, there is a larger population of women potentially vulnerable to STIs.

Contraception use in adolescents in South Africa continues to rise with the South African Demographic and Health Survey (SADHS) 2016 reporting 60% and 60.7% of AGYW aged 15-19 and 20-24 years respectively using modern contraceptive methods (137) . In adolescents aged 15-19, 16.1% are using Depot Medroxyprogesterone Acetate (DMPA) and 10.9% are using Norethisterone Enanthate (NET-EN) (137) . Of the young women aged 20-24 years, 19.6% are using DMPA and 12.5% are using NET-EN (137). These are significant statistics highlighting a substantial amount of AGYW use IC. Even in previous years, there was a similar high demand for IC in AGYW. For instance, in 2012, 40.6% of AGYW were using condoms, 34.8% were using injectables, 9.6% were using oral contraceptives, 6.3% were using the

withdrawal method, 3.3% were using the rhythm method, 2.3% were using intrauterine devices, 1% were using emergency contraception, and 1% were sterilized as reported in a nationally representative population-based survey of AGYW (138). In an implementation science study conducted in 2018-2020 on HIV pre-exposure prophylaxis (PrEP) provisions and use for AGYW, 61,9% of 3083 participants were using IC at baseline (139). Participants who were not using contraception at baseline were then offered contraception counselling and any contraceptive method of their choice after the counselling. Among these that were counselled and offered any contraceptive method of their choice, 42.7% chose injectables, indicating that IC remains one of the most favoured forms of contraception in AGYW (139). Health care providers in South Africa also contribute to the high demand for IC as they tend to advocate for IC more than other forms of contraception (140,141). This high demand for IC is also noted in AGYW who want a discrete and easy method of contraception with reduced interaction with a health facility (142,143). For IC, the AGYW would need to go to clinic every 2/3 months for injections whilst with oral contraceptives there is need to take a tablet consistently at the same time every day, which makes it burdensome. IUCD are discrete and reduce interaction with the health facility but are limited in use in AGYW due to the need higher skill levels for insertion which most local clinics do not have. To add on, health care providers have reservations s with IUD insertion in nulliparous patients

1.3.3 Contraception use and lower condom usage

Behaviourally, AYP do not frequently use condoms (144). Moreover AYP on hormonal contraception often discontinue their barrier contraception use thereby increasing their susceptibility to STIs (145,146). Condom use also varies amongst different types of contraception users: long-acting contraception users are 40-60 % less likely to use condoms compared to short and medium acting contraception in South African women aged 15-49 years (147). In AYP specifically, condom use is significantly lower in long-acting contraception users compared to short and medium acting contraception users [Odds ratio (OR 0.46, 95% CI 0.38-0.55] (147). In AGYW in South Africa, only 7% reported dual contraception use of condoms and hormonal contraception (148). Decreased condom use by contraceptive users in AGYW puts them at a significantly increased risk for STI.

1.4 Observational evidence for the association between Hormonal Contraception and Sexually Transmitted Infections

1.4.1 Hormonal contraception and STI association overview

The relationship between hormonal contraceptives and the risk for curable STIs including GC, CT, TV, and MG remains unclear. Some studies report hormonal contraceptives offer protection against STIs, whilst others report elevated risk of STIs in individuals using hormonal contraceptives (28,29,81,82,97–111).

Below are two figures extracted from Akter et al, who did a meta-analysis on the association between contraception and STI/BV prevalence and incidence in 37 studies published between 2005 and 2020 (33). The metanalysis' eligibility criteria was studies that had women aged 15–49, studies that reported prevalence, incidence and/or recurrence using laboratory diagnostic procedures, studies with use of any hormonal contraception versus a comparator/control group of individuals using no contraception or non-hormonal contraception, studies published between 2005 and 2020, studies with the following STIs and conditions as outcomes: GC, CT, TV, Herpes simplex virus (HSV), Syphilis, BV, PID, study designs that were descriptive or observational or randomised trials. Trials before 2005 and after 2020 were not included. HIV and Human Papilloma Virus (HPV) studies were also excluded. Studies that lacked laboratory diagnostic methods or that had no comparator groups were excluded. Review articles were also excluded. Trials that reported less than 20 STIs cases and trials that had less than 10% of the participants using HC were also excluded (33). **Figure 1.1** looks at the association between hormonal contraception and prevalent STI/BV, whilst **figure 1.2** represents the association between hormonal contraception and incident STI/BV. For GC, overall, the estimated random-effects [reES] did not show a significant reduction in prevalence (reES = 0.75; 95% CI 0.39–1.45) **(Figure 1.1.)** nor a significant increased risk for incidence (feES = 1.19; 95% CI 0.70–2.02) **(Figure 1.2)** in hormonal contraception users. For CT, the overall estimated random-effects [reES] showed a significant increase in risk of prevalence of CT in hormonal contraception users (reES = 1.58; 95% CI 1.19–2.08) **(Figure 1.1.)**, but the association was not significant for the risk of incident CT (reES = 1.25; 95% CI 0.86–1.82) (**Figure 1.2**) in hormonal contraception users. For TV, there was no significant reduction in prevalence in hormonal contraception users (feES = 0.76; 95% CI 0.58–1.00) (**Figure 1.1**) nor was a significantly reduced risk of incidence TV (feES = 0.53; 95% CI 0.35–0.810, **(Figure 1.2)** in hormonal contraception users observed. The figures also show associations between hormonal contraception and pelvic inflammatory disease, Herpes Simplex Virus and bacterial vaginosis which will not be discussed here.

Figure 1. 1 Studies and meta-analysis on association between contraception and STI/BV prevalence

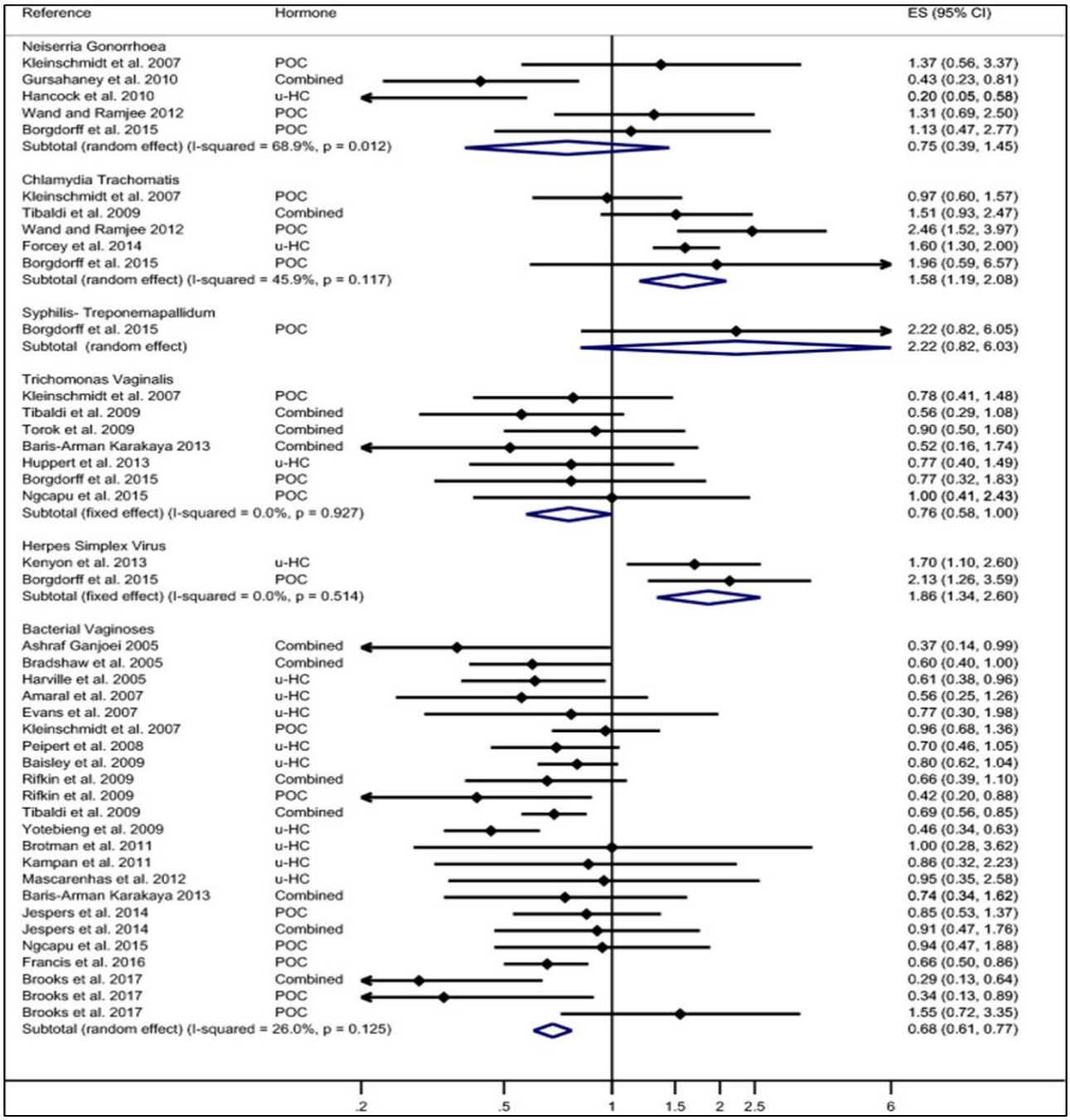


Figure 1.1 was extracted from a meta-analysis demonstrating the association of prevalent STI prevalence and hormonal contraceptives by Akter et al (33). *In the figure above HC stands for Hormonal Contraception. COC stands for Combined oestrogen-progesterone contraception. POC stands for Progesterone-only contraception (progesterone-releasing vaginal ring, progering, depot medroxyprogesterone acetate, intrauterine device, levonorgestrel), UHC stands for Unspecified hormonal contraception. The control group was the women who did not use any contraceptives or used non-HC. Point estimate of effect is represented by a diamond for each*

study, the 95%CI for each study is represented by the horizontal line. The larger blue diamond represents the group effect, with the width of the diamond representing the 95% CI.

Figure 1. 2 Studies and meta-analysis on association between contraception and STI/BV incidence

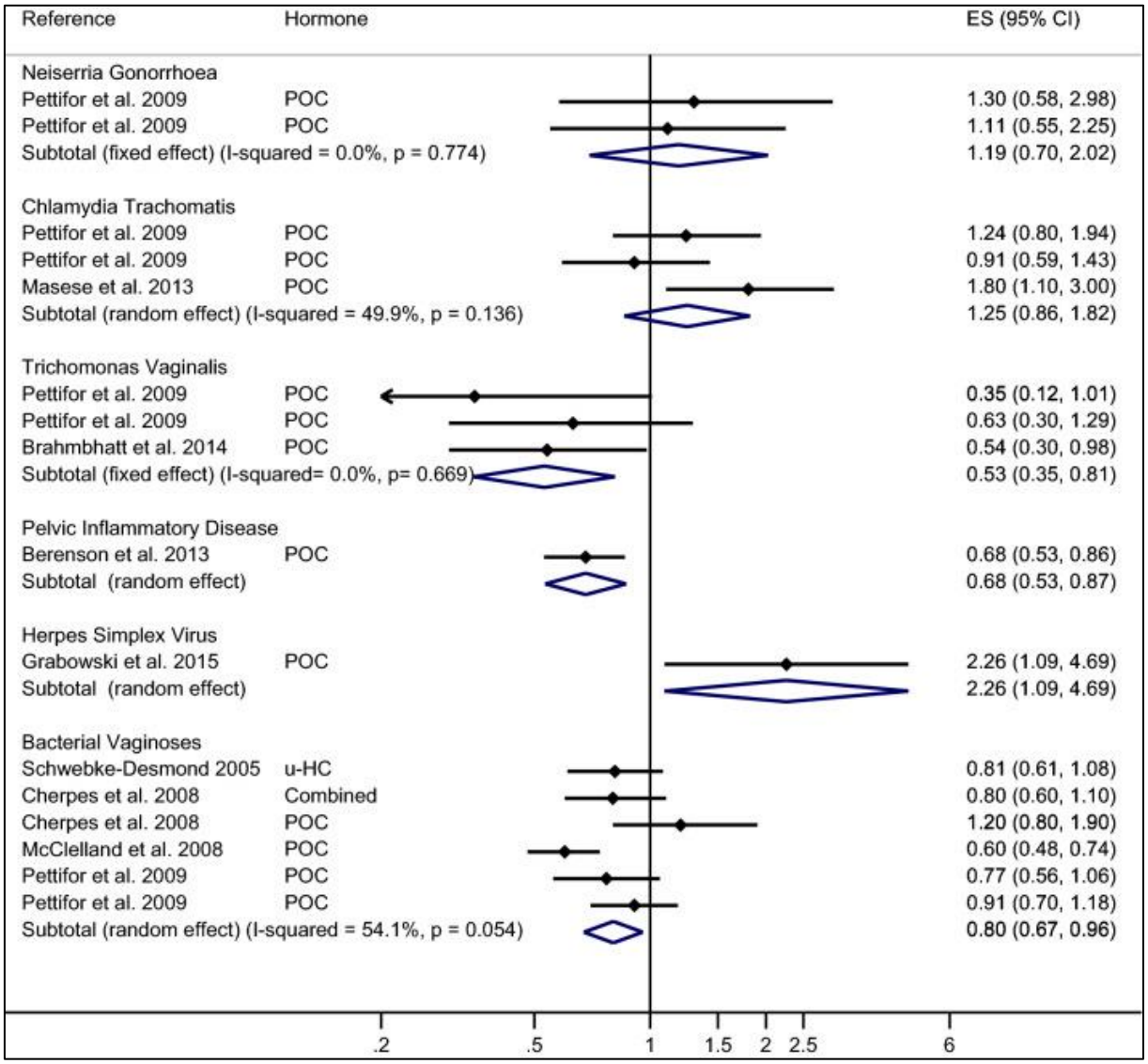


Figure 1.2 was extracted from the meta-analysis mentioned above demonstrating the association between incidence of STI and hormonal contraceptives by Akter et al (33). In the figure above HC stands for Hormonal Contraception. COC stands for Combined oestrogen-progesterone contraception. POC stands for Progesterone-only contraception (progesterone-releasing vaginal ring, proge-ring, depot medroxyprogesterone acetate, intrauterine device, levonorgestrel), UHC stands for Unspecified hormonal contraception. The control group was the women who did not use any contraceptives or used non-hormonal contraception. Point estimate of effect is represented by a diamond for each study, the 95% CI for each study is

represent by the horizontal. The larger blue diamond represents the group effect, with the width of the diamond representing the 95% CI.

1.4.2 *C. trachomatis*

Several studies have investigated the association between progestin-only contraceptives and risk for CT. Akter et al's metanalysis of studies published between 2005 and 2020 reported overall significant positive association between hormonal contraception and CT (reES 1.45, 95% CI, 1.14–1.84) . Figures 1.1 and 1.2 above were extracted from the meta-analysis mentioned above (33). Looking specifically at prevalence, a positive association was reported with any hormonal contraception (reES 1.58, 95% CI, 1.19–2.08) as well as a positive association for incidence (reES 1.25, 95% CI, 0.86–1.82) . Other studies not included in the meta-analysis above due to not meeting the inclusions and exclusion criteria mentioned earlier [time period (102–104) and study design reasons (28,97,99)] also reported significant positive associations (28,97,99,102–104). In women aged 15-45 a fourfold increased risk for CT was noted in DMPA [Hazard ratio (HR) 4.3, 95% CI, 1.7–11.1] compared to individuals using no contraception in Baltimore, USA (104). In women aged 15-35, in Pittsburgh and North Carolina, USA, there was an almost two-fold increased risk for CT incident infection in DMPA users compared to non-contraception users (HR, 1.80, 95% CI, 1.08–3.01]) (99). In Indianapolis, USA, 11-20-year-old AGYW on DMPA were five times more likely to have CT compared to non-hormonal contraception users (aOR 5.44 95% CI, 1.25-23.6) (103). Increased CT incidence was also reported in Kenyan women who sell sex on hormonal contraception (HR 1.6, 95% CI, 1.1- 2.4) (102).

There were two studies that reported a protective association that is not significant, that were not included in then meta-analysis by Akter et all mentioned above (28,97). Romer et al, in adolescents aged 14-17 reported reduced risk for CT incidence in DMPA [adjusted odds ratio (aOR) 0.76, 95 % CI, 0.45-1.31] (97). In HPTN 055, reduced risk for CT in DMPA users (OR 0.8, 95% CI, 0,4-1,2]) that was not significant was reported (28).

Some limitations that may have confounded results of studies mentioned above on the association between hormonal contraception and CT include diverse age groups, which make the studies unsuitable for comparison with AGYW (99) and participants recruited from STI clinics who were symptomatic or had symptomatic partner/s for STIs. Also, the population risk for STI is potentially different than the risk in AGYW and the general population for these

participants (99). One study focused on a high-risk population of women who sell sex, who do not adequately represent AGYW (111). Potential social desirability bias (110), small cross section cohorts (103), unclear definitions of outcome (combine CT and NG into one infection) (104) were other limitations of the studies mentioned above that affect their generalization to AGYW as well as potentially confounding the association between STI and hormonal contraception. Furthermore, one cannot totally exclude residual confounding associated with sexual behavioural practises in HC users as HC are less likely to use condoms.

1.4.3 *N. gonorrhoeae*

In a systematic review that included studies from 1966 to 2008 including 2 case control studies, 4 prospective cohorts and 13 cross sectional studies, the relationship between GC and contraception (oral contraceptive, DMPA, IUD) could not be concluded (107). Another systematic review of studies published between 2009 and 2017 reported no significant association between progestin only hormonal contraception (DMPA and NET-EN) and GC after analysing 5 prospective cohorts (109). Akter et al's meta-analysis showed an overall protective association between GC and any hormonal contraception (pooled effect size (reES 0.87, 95% CI, 0.55–1.38) that was not significant (33). Specifically, for prevalent GC, a reduced risk of infection was reported (reES 0.75, 95% CI, 0.39–1.45) whilst for incidence an increased risk (feES 1.19, 95% CI, 0.70–2.02) was reported, though not significant in both circumstances (33). Some studies not covered in the meta- analysis above [due to time-period (104) or study designs (28,97,107,109)]have reported an increased risk that was not significant (28,97,104,107,109). For the studies that reported an increased risk, Romer et al reported an increased risk for GC incidence in adolescents aged 14-17 using DMPA compared to non-contraception users (aOR1.19, 95%CI, 0.57—2.48) (97), and Kapiga et al also reported an increased risk for GC incidence (aOR 1.8, 95%CI, 1.0-3.3) that was not significant (28).

The limitation of the studies that looked at the association between GC and IC mentioned above include the following: older studies with different diagnostic approaches (45), definitions of outcomes are not always clear (combined CT and GC as one type of infection) (104), larger numbers of participants lost to follow up causing selection bias and potentially affecting the powering of studies (104), selection of women that don't represent all women based on geographical locations and sex work (28), switching between contraceptive methods confounding results (29) and long follow up in between visits potentially underestimating STIs and confounding the association between STI and hormonal method. (29). Also as mentioned

above, there is potential residual confounding associated with sexual behaviours as hormonal contraceptive users are less likely to use condoms.

1.4.4 *T. vaginalis*

A systematic review of studies published between 2009 and 2017 reported protective association that is not significant between IC and TV after analysing seven prospective cohorts (109). Akter et al's metanalysis reported significant protective association between hormonal contraception and TV (feES 0.75, 95%CI, 0.65–0.86) (33). This meta-analysis reported a significant reduction in incidence and a reduction in prevalent TV that was not statistically significant (33). For TV incidence a significant protective association was noted for DMPA users (feES 0.53, 95% CI, 0.35–0.81) and for TV prevalence the protective association was not significant (feES 0.76, 95% CI, 0.58–1.00). Other studies not included in the meta-analysis due to study design also reported a lower risk of infection that was not statically significant in DMPA users (28,97,109). Romer et al, also reported reduced TV incidence risk in 14–17-year-olds in USA attending an adolescent clinic that were DMPA users (aOR 0.66 95%CI 0.32—1.36) (97). In women who sell sex in Kenya, reduced risk for TV incident in DMPA user was also noted (HR 0.6; 95% CI 0.4-1.0) (102).

Some of the limitations in the studies mentioned above looking at the association between TV and IC are: switching between different types of contraception (IC, oral contraceptives, implants) which potentially leads to undermining of associations between hormonal contraception and TV infection (29), prolonged follow up periods that affect diagnosis and treatment of STI and potentially undermine the number of infections leading to underpowering of trials, sexual behaviour confounders as hormonal contraception users are less likely to use condoms (29,102) and very high risk participants such as women who sell sex whose risk profile might be different from that AGYW and whose sexual behaviours are different from AGYW (29,102).

1.4.5 *M. Genitalium*

We could not locate any studies that investigated the association between IC and MG.

1.5 Potential biological mechanisms by which progesterone only contraception may increase or decrease STI risk

Progestin in IC functions by suppressing ovulation, making the endometrium sub-optimal for implantation, altering the levels of *Luteinizing hormone (*LH) and Follicle-stimulating hormone (FSH), and increasing the thickness of cervical mucus (149). DMPA use leads to hypoestrogenic states which results in changes to vaginal flora, dysbiosis, thinning of vaginal

epithelium and vaginal inflammation (150,151). These effects are thought to increase susceptibility to STIs (109,152).

Lactobacillus species in healthy vaginal microbiota, produce hydrogen peroxide and lactic acid to maintain an acidic environment which is a barrier to STIs (153). However, the use of progestin IC typically leads to a hypoestrogenic state and vaginal dysbiosis. Vaginal dysbiosis is strongly associated with bacterial vaginosis and higher vaginal PH which in turn increases susceptibility to STIs (153).

Progesterone and progestin are believed to affect immunity in women due to identification of progesterone receptors on immune cells (dendritic cells, natural killer cells, T cells and macrophages) (154). Epithelial and endothelial sites have also been noted to have progesterone receptors suggesting progesterone and progestin can affect infection outcomes at mucosal sites (154). Moreover, humoral and cellular immune responses are influenced differently by different quantities of progesterone and progestin (155). Progesterone and progestins stimulate the production of anti-inflammatory cytokines, supress inflammatory cytokines and pathways (e.g. by binding to glucocorticoid receptors) (156), and increase the expression of virus entry co-receptors (C-C Chemokine Receptor 5 (CCR5) and C-X-C Chemokine Receptor Type 4 (CXCR4). These actions weaken the immune response and contribute to vulnerability towards STIs (155,157–161).

In some instances, the reduced risk of infection associated with hormonal contraception may be linked to decreased menstrual flow. Hormonal contraception can lead to lower menstrual flow, which in turn reduces iron availability. Since GC requires a high iron supply for growth, the decreased iron levels associated with hormonal contraception may inhibit GC growth, as iron is essential for its intracellular and extracellular development. (162). TV has both estrogenic and androgen receptors. The high content of progestin in DMPA could potentially block androgen receptors since androgen receptors are closely related to progestin receptors. By blocking androgen receptors DMPA could interfere with the ability of TV to infect host cells (82,163).

1.6 Problem Statement

AGYW in South Africa have substantial risk of acquiring STIs, and of developing complications from untreated STIs because of unrecognized or asymptomatic infections and poor access to healthcare. In South Africa 25% of sexually active women use injectable progestins for contraception (69). The SADHS reported for AGYW aged 15-24 years that close

to 18% were using DMPA and close to 12% were using NET-EN (69). AGYW may also be at increased risk for STIs because of elevated levels of injectable progestin contraceptive use. Observational evidence suggests that injectable progestin contraceptives may increase the risk for CT, decrease the risk for TV with mixed evidence of effect on GC. Observational evidence for the association between MG and IC is currently lacking. IC may alter STI risk through both behavioural means (lower condom use) and biological means (changes in immune responses, vaginal microbiome, and vaginal epithelium). Given the priority to reduce unintended pregnancies in adolescents, and the widespread use of IC for pregnancy prevention in this age group, it critical to understand this association between progestin IC and STI among AGYW in South Africa in order to recommend potential interventions to reduce STI acquisition.

1.7 Justification

This analysis will provide insights into observations concerning the association between STI and IC. We would like to see if observations noted in other settings and populations are also observed in AGYW in Johannesburg. Results from this analysis may inform recommendations for future STI prevention interventions as well as counselling for AGYW contraceptive users.

1.8 Research question, overall aim, specific objectives for the secondary data analysis

1.8.1 Research Question

Does injectable progestin contraceptive use alter the risk for CT, GC, TV, or MG in AGYW aged 16-24 years in Johannesburg, South Africa when compared to non-hormonal contraceptive users?

1.8.2 Aim

To investigate the risk of CT, NG, TV, or MG acquisition in cisgender women aged 16-24 years using progestin-based IC compared to individuals not using hormonal contraception in Johannesburg, South Africa.

1.8.3 Objectives

1. To estimate and compare baseline prevalence for each STI (CT, GC, TV, and MG) and overall curable STI prevalence (at least one STI) in a prospective cohort of AGYW.
2. To investigate the association between the use of progesterone based injectable contraception and the prevalence of STI in AGYW.
3. To measure and compare the incidence of four STIs (CT, GC, TV, and MG) and overall curable STI incidence in a prospective cohort of AGYW.

Chapter 2: Methodology

2.1 Description of the parent study

CHOICES was a prospective observational study on the association of injectable contraception, HIV and STIs among young women in South Africa. HIV negative AGYW aged 16-24 in Johannesburg South Africa were recruited. Hormonal contraception and non-hormonal contraception users who were not pregnant were eligible.

The objectives of the primary CHOICES primary study were:

- To examine the association between IC and the incidence of HIV and HSV-2 and the point prevalence of other common STIs in sexually active HIV negative adolescent girls and young women (AGYW) aged 16-24 years.
- To explore the association between contraceptive use and HIV-associated risk behaviours in young AGYW aged 16-24 years
- To examine the associations between IC use and genital tract immune markers and microbiota, among a subset of the cohort of young women (N=75).

These objectives of the primary study are different from the secondary analysis. This secondary data analysis explored the association between incidence and prevalence of four specific STIs: MG, TV, GC, CT and injectable contraception. This secondary data analysis excluded analysis of viral STIs of HPV, HIV, HSV (Herpes simplex virus).

2.2 Study design

This is a secondary analysis of data for the CHOICES prospective observational cohort study conducted from March 2016 to December 2019 in sexually active, HIV uninfected AGYW aged 16-24 years in Johannesburg, South Africa to investigate the association between IC (DMPA and NET-EN) and STIs (GC, CT, TV, MG).

2.3 Study setting

Participants were recruited from primary health care facilities and the surrounding community in inner city Johannesburg, South Africa through established community practices. Participants were recruited from health care facilities and surrounding community and invited to attend the study site for a visit and enrolment in the study if they consented and met the eligibility criteria . They attended scheduled study visits at the Wits RHI Ward 21 Clinical Research Site (CRS), Hillbrow, Johannesburg, South Africa. The study was conducted from March 2016 to December 2019. Recruitment began February 2016, with the first participant enrolled in March 2016. The last participant had their exit study visit (month 24 visit) in December 2018. Participants were followed up for up to 24 months or less for those who joined the trial later as the team stopped participant follow up after December 2018.

2.4 Study population

Participants were enrolled in the CHOICES study if they were sexually active (sexual intercourse at least once in the preceding 6 months), aged 16–24-years, HIV seronegative confirmed on HIV rapid test, not pregnant or breastfeeding, residing in Johannesburg and planning to stay in the study area for the duration of the follow up period, and willing to provide consent or assent with parental consent if < 18 years. Participants were included if they were using DMPA, NET-EN or progestin-implants for pregnancy prevention or non-hormonal methods for pregnancy prevention e.g. condoms, IUCD. Participants were excluded if they were enrolled in an HIV prevention trial using investigational products or if they had had genital tract surgery in the previous 3 months prior to screening.

For this secondary data analysis, AGYW that were enrolled into the CHOICES study using NET-EN, DMPA and non-hormonal contraception were included into the secondary data analysis. Non-hormonal contraception users were those who were using condoms or IUCD. In the initial ethics application, we had stated we would analyse all participants that where enrolled into the parent study. On receipt of the data, a decision was made after a step wise approach to determine differences between contraceptive methods to exclude implant users (due to implant duration of action being longer than IC as well different mechanism of action from IC). The stepwise approach investigated differences in sociodemographic features between the contraception users. At follow up time points month 12 and month 24, those that were pregnant or HIV positive were censored from analysis at those time points.

2.5 Study procedures

Participants we recruited through existing community engagement structures between Wits RHI and individuals residing and employed in the district of Johannesburg. Some of the participants were recruited from the Gauteng Department of Health Ward 21 Adolescent and Youth Friendly Services (AYFS) as well as other health facilities and structures in Johannesburg. This approach was ideal as it gave access to many AGYW who were aware of the services offered at Ward 21 AYFS. Participants they were recruited from health care facilities and surrounding community and invited to attend the study site for a visit and enrolment in the study if they consented and met the eligibility criteria.

Trained study staff recruited these AGYW and offered information sessions. Potential participants were also given written information during the information session to read at home and discuss with friends and family. At the information sessions those interested in the study

were requested to leave contact information (phone numbers), so the team could call them for screening if they were still interested to participate in the trial. Participants were followed up from March 2016 to December 2018 with data collection was from March 2016 to December 2018 during follow up visits that took place 2/3 monthly as stated in the protocol. For this specific analysis, the baseline assessment at enrolment and assessments at months 12 and 24 were the only 3 visits that were analysed.

At the screening visit, informed consent was administered. Following written informed consent, locator information was collected and validated. Participants were then checked for co-enrolment at this point and at all subsequent visits and assigned a participant identification numbers (PTID). A brief medical history, including contraceptive assessment were also performed. Contraception assessment was done through confirmation of contraceptive status from a clinic contraception card as well a counselling session on contraception. HIV pre-test counselling was then conducted, followed by collection of blood samples [HSV-2 serology, syphilis serology, HIV plasma RNA (in seroconversions, CD4+ (in HIV seroconversion)], plasma/serum (for archiving) dry blood spot (for archiving), urine pregnancy test samples were collected. HIV post-test and risk reduction counselling was then offered. Participants who reported STI symptoms were examined and treated syndromically in alignment with the standard of care at the time. Appropriate medical referrals were offered as needed. Once all results were received a final eligibility assessment was completed. Eligible participants were then invited to enrol.

At enrolment, data on socio-demographics, medical history (including reproductive history), contraception history, current contraception use, and mental health status was captured. Data on sexual behaviour, partner and relationship characteristics, and current genital symptoms was also collected. Computer-assisted-self-interviews (CASI) were utilised for socio-demographics, sexual behaviour questions, reproductive history, and mental health status questions. A clinician-administered questionnaire was utilised for medical history and contraception history. A physical examination, including a pelvic examination was performed and cervico-vaginal swabs and cervico-vaginal lavage (CVL) were collected. Testing for CT, GC, TV, and MG was conducted. Urine was also collected for pregnancy testing. Following pre-test counselling, blood samples were collected for syphilis and HIV serology. Risk reduction counselling was provided following HIV test results. Syndromic management of STI was offered if required for the symptomatic and for the asymptomatic who were laboratory diagnosed, treatment was offered.

Enrolled participants were followed for up to 24 months for a maximum of eight visits at intervals (enrolment, month 2/3, month 6, month 8/9. month 12, month 14/15, month 18, month 20/21, month 24). Not all participants completed 24 months of follow up. This was due to a cut off time in the follow up period. All participants exited the study prior to 31 December 2018. At each follow up visit, clinician-administered questionnaires and medical examinations took place. The clinician administered questionnaire, and medical examinations were for collection of the following information: current genito-urinary and rectal symptoms, sexual behaviour history, sexual partner/partners history, relevant medical conditions history, contraception use history, contraception complications history, and relationship characteristics. HIV counselling was conducted before an HIV rapid test and after an HIV rapid test. Counselling post a HIV rapid test included risk reduction counselling. Referrals to appropriate different levels of care were offered as seen necessary.

For participants on hormonal contraception, contraception counselling and provision was conducted every 2/3 months depending on contraceptive method. During contraception counselling, information on different contraceptive methods was offered. Participants were encouraged to raise concerns and fears concerning different contraceptive choices. Myths were debunked and information was offered. Participants were then supported in deciding on the contraceptive method they wanted to use based on their eligibility for that contraception. They were then offered the contraceptive method they would have chosen.

At all visits, urine pregnancy testing was conducted before contraception administration. Genital swabs and cervical-vaginal swabs were collected during physical examination which included a pelvic examination at enrolment, months 12 and 24 for CT/GC/TV/MG testing and cervical-vaginal swab archive. At visit month 2/3, month 8/9, month 14/15, 20/21, self-collected genital swabs were archived for future CT, MG, TV, and NG testing. At every visit, blood samples were collected for archiving of dried blood spots and plasma.

Symptomatic participants were managed syndromically based on the South African National Department of Health Guidelines (164), whilst asymptomatic participant who were laboratory diagnosed to have an STI were treated aetiologically at the follow up visit. For participants that tested positive for STIs, only those that were lost to follow up were not treated. Participants were considered cured if they received treatment in accordance with national guidelines. Of the participants that had consecutive infections, we believe based on evidence of treatment that these were re-infections rather than treatment failure. We treated each infection as a new event given that detected infections had been treated at interim visits. Those included in this

secondary data analysis were treated according to national guidelines for infection at baseline, as well as at months 12 and 24. No test of cure was conducted. Participants that tested positive for STIs that come to site for treatment, were provided with risk reduction counselling, condoms and partner/s notification slips to encourage treatment of partner/s.

2.6 Laboratory testing

CT/GC/TV/MG was tested at National Institute for Communicable Diseases Laboratory (NICD) using NICD in-house multiplex PCR testing. CT/GC/TV/MG PCR were performed at enrolment, and annually thereafter (M12, 24) and results provided to participants. Additional samples collected at additional time points were stored for future testing. STI treatment was administered for participants who have positive results for curable STIs.

2.7 Sample size considerations

Power calculations: The study was powered at over 80% to detect HR of 2.15 with 600 participants to detect HIV and HSV2 incidence in the control group at 9% per year, and incidence at 6% for HR 2.45 and a HR of 3.0 at 3% incidence per year. This was based on assumptions of equal sample sizes in the HC and non-hormonal contraception groups. They also assumed control group incidence rates of 3/100PY for HIV and 6 or 9/100PY for HSV2, With a total follow-up period of 24 months and a 10% per year loss to follow-up. .In this secondary data analysis, we conducted a power analysis to estimate prevalence drawing from existing literature and previous South African studies, a sample size of 600 is considered sufficiently powered (>80%) to detect absolute differences in the prevalences and incidence of curable STIs by different contraception methods with an OR of 2.15.Assuming STI prevalence of 14.7% for CT in the non-hormonal group and GC prevalence of 6% in the non-hormonal group based South African Spectrum-STI estimation (using laboratory diagnosed GC and CT data) by Kularante et al using data from 1990-2017 (165).

2.8 Data source

2.8.1 Grouping values:

A step wise analysis was done to decide on how to categorise variables for analysis.

Categorical Variables

Exposure: Contraception use was the exposure of interest. At enrolment, for the parent study the following contraception options were stated: DMPA, NET-EN, condoms, IUCD, and implant. No oral contraceptive users were enrolled into the study (even though later some participants changed to oral contraceptive methods).

For this secondary data analysis, contraception use of interest was DMPA, NET-EN, condoms and IUD. Implant users at baseline were excluded from this secondary data analysis. Implant users were excluded because the the original expectations were for their numbers to be large but they were small. Furthermore we studied DMPA and NET-EN separately it due to having different progestins, implant users would have been a different type of progestin as well and it would have led to bias if we had joined them any other progestin group, hence they were dropped.

Condom and IUD users were grouped to create the non-hormonal group The use of injectable contraception (DMPA and NET-EN) was abstracted from the contraception card.

DMPA and NET-EN were analysed as distinct categories due to their different progestin compositions and potential biological effects (166). Some participants switched contraceptive methods between visits. To calculate STI incidence, they were categorized based on their contraceptive method at the 12th and/or 24th month STI tests. However, the Kaplan-Meier analysis of STI failure rates stratified participants by their *baseline* (enrolment) contraceptive method. Individuals who switched to oral contraceptives or implants were excluded from the Kaplan-Meier analysis but were included in the swimmer's plot, which depicted contraceptive changes throughout the study.

Outcomes of interest where laboratory diagnosed CT, MG, TV, GC at baseline as well as incident infection diagnosed at month 12 and month 24. Any STI category includes participants that had one or more of the four infections (GC, CT, TV, and MG).

Other explanatory variables: The sociodemographic features were collected via CASI to adjust for confounding effects. Potential confounders identified for this analysis included age, age difference with main sexual partner, receiving financial and/or material support from main sex partner, AGYW having more than one sex partner in the past 3 months, number of sex partners other than main partner in the last 3 months, AGYW who were involved in transactional sex in the last 3 months.

There were four questions on having experienced some form of violence. The four questions covered physical, emotional, and sexual experiences. The physical question covered being punched, slapped, kicked, bit and any physical harm. Emotional violence covered being different forms which were being insulted, ignored, humiliated, yelled at, made to feel ashamed or bad. Sexual violence covered forced sex, sexual act, or touched inappropriately. Another question covered being made to feel afraid, feeling unsafe and in danger. All these questions

were about experiencing violence in the hands on ‘anyone’ which included partners, family members, friends, neighbours, clients, strangers, supervisors, colleagues, police officer, or other persons in the past year.

The Centre for Epidemiological Studies Depression 10 (CES-D 10) scale was utilised to assess risk for depression. This tool has been validated in South Africans (167).

Ever having used illicit substance in their entire life was stratified into ‘no’ and ‘yes.’ In the parent study AGYW selected the illicit substances they had ever used in non-medical use, these included: tobacco substances, amphetamine, alcoholic beverages, cannabis, cocaine, inhalants, sedatives, , and any other.

Transactional sex in the last 3 months, was defined as having sex with a man because he would provide with any one or more of the following: food or clothes, shoes, accessories, cosmetics, cell phone, transport, tickets or money for transport, school fees, residence fees, somewhere to stay, social status, cash, items for your children or family such as clothes.

For the following variables: level of education, food security, marital status, vaginal or anal sex in the last month, main sex partner having other sex partners, having more than one sex partner in the last 3 months, experienced forced sex or sexual act in the previous year, experienced some form of violence in ,the previous year, experienced anxiety symptoms in the last 30 days we did a sensitivity analyses through probabilistic model selection utilising Akaike information criterion (AIC) and Schwarz’s Bayesian Information Criterion (BIC) to ensure better model selection.

Age of the AGYW was stratified into 16-19 years and 20-24 years based on general age classification used in other studies as well as used by the WHO. Age of main sex partner was stratified into 17- 24 years, 25-34 years and greater than 34 years based on previous studies. Age disparate relationship was stratified into less than five years and five years and greater for age difference between the AGYW and their main sexual partner based on previous studies. Number of sex partners besides main sex partners in the last 3 month has been stratified into 0-1, 2 and greater based on previous studies.

Table 2. 1 Co variables analysed in this secondary data analysis

Variable	Definition	Categorisation
Age	Age of the AGYW was stratified based on general age classification used in other studies as well as used by the WHO.	1. 16-19 years 2. 20-24 years
Level of education	Level of completed education	Secondary and less Tertiary
Currently in school	AGYW that were in some sort of formal schooling system	Yes No
Food security	Whether the AGYW had in the last 4 weeks (1 month) been worried that they would not have enough food in their household?	Worried Not worried
Marital Status	Whether the AGYW was single (never married or divorced) or married	Single Married
Vaginal or anal sex in the last 3 months	Whether the AGYW had practised vaginal or anal sex on the last 3 months	Yes No
Had anal sex in the last 1 month	Whether the AGYW had practised anal sex on the last 1 months	Yes No
Currently have a main sex partner	Whether the AGYW had a main sexual partner	Yes No
Main sex partner age categories	The age of the main sexual partner	17-24 years 25-34 years >34 years
Age difference with main sexual partner (years)	The age difference between the AGYW and her main sexual partner.	<5 years =>5 years
Live with main sex partner	Whether the AGYW lived with the main sexual partner or not	Yes No
Receiving financial and/or material support from main sex partner	Whether the main sexual partner was providing for the AGYW financially	Yes No

Variable	Definition	Categorisation
Main sex partner has other sex partners	Whether the AGYW's main sexual partner had other partners	Yes No
AGYW had more than one sex partner in the past 3 months	Wheater the AGWY had more than one sex partner in the last 3 months	Yes No
Number of sex partners other than main partner in the last 3 months	Number of sex partners besides the main sex partner that the AGYW has had in the last 3 month.	0-1 =>2
Transactional sex in the last 3 months	Having sex with a man because he would provide with any one or more of the following: food or clothes, shoes, accessories, cosmetics, cell phone, transport, tickets or money for transport, school fees, residence fees, somewhere to stay, social status, cash, items for your children or family such as clothes in the last 3 months	Yes No
Condom use at last sex	Whether the AGYW or her partner had used a condom at last sex	Yes No
Experienced some form of violence in, the previous year	Violence covered physical, emotional, and sexual experiences. Physical violence included being punched, slapped, kicked, bit and any physical harm. Emotional violence covered being different forms which were being insulted, ignored, humiliated, yelled at, made to feel ashamed or bad. Sexual violence covered forced sex, sexual act, or touched inappropriately. Furthermore we covered being made to feel afraid, feeling unsafe and in	Yes No

Variable	Definition	Categorisation
	danger. All these questions were about experiencing violence in the hands on 'anyone' which included partners, family members, friends, neighbours, clients, strangers, supervisors, colleagues, police officer, or other persons in the past year	
Experienced forced sex or sexual act in the previous year	AGYW were asked whether the past one year they had experienced anyone forcing to have sex or perform any sexual act, or touching them sexually in any way they did not want	Yes No
Experienced anxiety symptoms in the last 30 days	AGYW were asked whether they experienced some anxiety symptoms or if they suddenly acted or felt like a stressful experience was happening again (like they were reliving it) and how much did they feel very upset when something reminded them of a stressful experience from the past	Yes No
CES -D scale in the last 30 days. Depressive symptoms?	The Centre for Epidemiological Studies Depression 10 (CES-D 10) scale was utilised to assess risk for depression.	=>10 Yes <10 No
Any suicidal symptoms in the past year	AGYW were asked on seriously thinking about attempting suicide, planning to attempt and attempting suicide in the past year	Yes No
Ever used illicit substances	In the parent study AGYW selected the illicit substances they had ever used in non-medical use, these included: tobacco substances, amphetamine, alcoholic beverages, cannabis, cocaine, inhalants, sedatives and any other.	Yes No

2.9 Missing data

Participants that had all baseline STI results missing were dropped from analysis. In the analysis, for each categorial variable we created a missing category so those missing values

would be cropped out for that categorical calculation only. When participants did not attend a specific follow up visit, for that follow up visit they were excluded from the point prevalence calculation and treated as a lost to follow up for that specific visit.

2.10 Managing bias

A CASI was utilised to collect sociodemographic information to mitigate social desirability and information bias. The study staff worked hard to encourage retention efforts to reduce selection bias based on some participants being lost to follow up. The did this through phone calls to participants that had missed visits. To mitigate mis-categorisation of exposure, contraceptive methods were categorized based on information from the contraception card at the time of STI testing. A quality check was conducted to verify that both baseline and 12-month incident infections had been treated, ensuring no untreated infections influenced the analysis.

2.11 Statistical Analysis

Statistical analysis was conducted using STATA 16 (168).

We took a stepwise approach to explore for any differences between different contraceptive groups utilising Pearson's CHI2, with p value of less than 0.05 as significant. We used this approach to look at factors associated with each contraceptive group to determine if we could combine specific groups together in either hormonal group or non-hormonal group. As the results were not significant, and led to similar results condom users and IUCD users were combined to create the non-hormonal contraception group. This approach has also been used in other studies

Descriptive statistics were used to summarize socio-demographic, partner, and risk characteristics. Socio-demographic factors were presented as frequencies and percentages. Bivariate association between sociodemographic features and contraceptive methods was assessed using Pearson's CHI2 for categorical values and Kruskal-Wallis for continuous values (age), with p value of 0.05 as significant.

To compare the association between contraceptive method used at baseline and baseline STI outcomes, multivariate logistic regression was used. Bivariate analysis with a significant p value of 0.10 were included in the adjusted multivariate model for each STI and composite variable any STI. Age category was an *a priori* adjustment. We conducted sensitivity checks through probabilistic model selection utilising AIC, BIC to ensure better model selection for some sociodemographic responses. We also conducted a sensitivity analysis by running a Poisson regression and Exact regression as some categories had small values. The results of those models were mostly similar to the logistic regression results we obtained.

Point prevalence was calculated at baseline, month 12 and at month 24 to allow for comparison of disease burden across three time points. Prevalences at baseline, 12 months and 24 months were calculated as frequencies and percentages. Prevalence was calculated by dividing number of laboratory-diagnosed infections over total number of participants that attended that specific visit. Participants whose follow up visits fell between the 9th and 15th month post enrolment were include in the prevalence for month 12. Those whose visits fell more than 15 months post enrolment were in the prevalence calculation for month 24.

For incidence calculations, total time contributed by individuals was based on the time they were enrolled to the time of event (they got censored) or to the time the completed month 24 or had an event at month 24 (if they hadn't had an event at month 12). STI Incidence rate was calculated per 100 person years. All individuals who had at least two time points, enrolment, and a follow up time point (either month 12, month 24, or both) were included. Incidence was calculated based on time to first event by considering only the first infection occurring after baseline as incident cases. Incidence was calculated by dividing the number of new STI events by total person-time of the AGYW. Follow up time for pregnant participants was censored. Follow up time was also censored for participants that tested HIV positive. For some participants, the exposure status changed between visits. The analysis was constrained to assess the association between incidence STI and contraception methods due to participants transitioning between different contraception methods during the follow-up period, as illustrated in Figure 3.2: A swimmer's plot to illustrate changes in contraceptive methods (located in Chapter3: Results). In this analysis, incident calculations were stratified based on the contraceptive methods at baseline in Kaplan Meier curves.

2.12 Ethical considerations

2.12.1 Consent and assent

Informed consent was provided for all study participants during the original study. When the CHOICES study was conducted, written consent from parents for those less than 18 years old was obtained. Written assent from the minor was also obtained. For participants that were older than 18 years old, written consent was obtained from them directly prior to conduct of any study procedures

2.12.2 Ethics review and approval

The CHOICES study was originally reviewed and approved by Wits HREC (reference numbers of M150139). This secondary data analysis obtained ethics approval from Wits HREC: Reference: M230304. Attached as appendix 1.

2.12.3 Reimbursement

Participants were reimbursed for every visit, R50 at screening and R150 at enrolment and follow up visits. A maximum of R1350 per participant was reimbursed over the 24 month follow up period for those who attended all scheduled visits.

2.13 Privacy and confidentiality

2.13.1 Data integrity

All data was treated as confidential. Hard copy data of the parent study was archived offsite at the end of the study as per Good Clinical Practise requirements. Hard copy data was not made available to the candidate. The candidate received an export of the de-identified participant database in excel format from the Principal Investigator of the CHOICES study, Professor Sinead Delany- Moretlwe, who is also one of the supervisors of this secondary data analysis. The export was saved on a password protected cloud server and was received after signing a data sharing agreement and after receiving ethics approval. Only the candidate had access to the electronic database. A codebook was provided for defining all analysis variables. Providing an export of the database was the approach taken in order to protect the original database.

2.13.2 Parent study privacy and confidentiality

Participants had to share identification data during the registration process. Identification data was needed to ensure consenting and assenting processes were conducted appropriately based on age. Efforts were made to ensure participant confidentiality. A unique participant study ID (PTID) was allocated to each participant at screening. The PTID was used through the study to identify participant records and samples associated with that participant. No names were used to identify the participant on the study records and on laboratory records. All records were locked in an access-controlled data storage room during the study. All documents that linked PTIDS to other identifying information were stored in a separate locked file, which was also access controlled. All electronic data was stored on a network system with password restricted access which was limited to the Principal Investigator and other named staff.

2.13.3 Secondary Data analysis privacy and confidentiality

All participants were identified by a unique code, no names were used in the database. Data confidentiality was maintained by using a database export which had de-identified information, using PTID and no names. Access to the database was limited to the candidate and supervisors only. Data security was ensured by restricting access to the password required to unlock the electronic database. Furthermore, the candidate stored the database on a cloud-based server with password protections in place.

Chapter 3 Results

3.1 Participant characteristics at baseline

Of 736 AGYW screened, 611 (83%) were eligible and enrolled into the CHOICES study. Participants who were not enrolled (n=125) into the parent study were excluded for: being unwilling to complete study procedures (73/125, 58%), HIV positive(23/125, 18%), pregnant (23/125, 18%), using an oral contraceptive (2/125, 2%), not age eligible (1/125, 1%), using post exposure prophylaxis for HIV (1/125, 1%), unsatisfactory assessment of understanding of the study (1/ 125, 1%), planning to get pregnant in the period the trial was supposed to run (1/125, 1%). (Figure 3.1)

For this analysis, 577 participants were included with two omitted due to missing baseline STI results (Figure 3.1). A decision was made to exclude implant users because the number enrolled was small (n=32) and because they could not be combined with IC users given a potential different mechanism of action. There were 42% (240/577) AGYW on non-hormonal contraception (NH). NH group comprised of 97% (234/240) condom users and 3% (6/240,) IUCD users. Among IC users, 34% (196/577) were using NET-EN, and 24% (141/577) DMPA. (Figure 3.1)

Figure 3. 1 Screening and Enrolment of participants

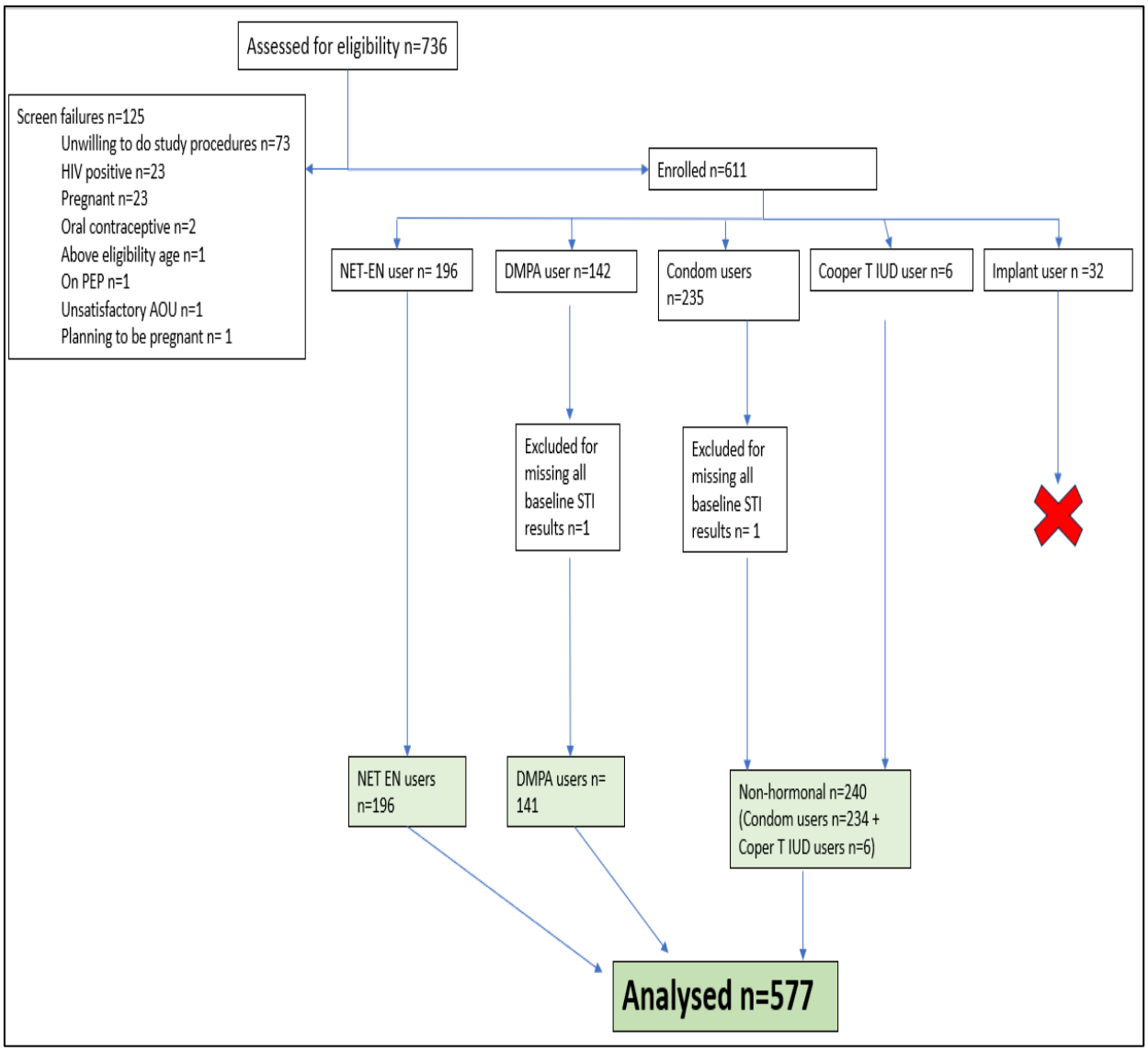


Table 1 represents participants sociodemographic characteristics per contraceptive method category. Most participants (394/577, 68%) were aged 20 to 24 years, with a median age at enrolment of 21 years (IQR 19-22 years). Most AGYW, (455/577, 79%) were attending high school or have completed high school as their highest level of schooling. A high proportion of AGYW reported main sexual partners that were five years and older (183/504, 37%). A considerable proportion of AGYW were receiving financial /or support from their main sex partner (276/505, 55%) and a large proportion of AGYW reported condom use at last sex (307/505, 61%). In the AGYW 10% (57/562) reported a forced sexual act in the past year. A high prevalence of mental health issues was identifiable in the cohort. Anxiety symptoms in the last 30 days, were experienced by 86% (499/577), those at risk for depression in the last 30 days based on CES-D 10 scale were 36% (208/577), suicidal symptoms in the last year were

experienced by 34% (196/577). Similarly, a high proportion, 63% (362/577) reported having experienced some form of violence in the past year.

A greater proportion of individuals using NH contraception and NET-EN were in school (p=<0.001). A greater proportion of individuals using NH had vaginal or anal sex in the past 3 months (p=0.046), had more than one sex partner in the last 3 months (p=0.043), used a condom at last sex (p=0.001) compared to NET-EN and DMPA. A greater proportion AGYW were using DMPA were married (p=0.047) and were not living with their main sex partner compared to (p=0.014). NET-EN had a greater proportion of the 16–19-year-olds (p=0.033) compared to DMPA (Table 3.1).

Table 3. 1Baseline Characteristics

Characteristics	**non-Hormonal contraception N=240**	**NET-EN N=196**	**DMPA N= 141**	**Total N=577**	**p value**
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Median age, years (IQR)	20 (19-22)	20 (19-22)	21 (20-22)	21 (19-22)	0.016
AGE, years					
16-19	78 (33)	72 (37)	33 (23)	183 (32)	0.033
20-24	162 (68)	124 (63)	108 (77)	394 (68)	
Highest level of education (n=562)					
Secondary and less	179 (75)	161 (82)	115 (82)	455 (79)	0.081
Tertiary	55 (23)	30 (15)	22 (16)	107 (19)	
Currently in school(n=562)	162 (68)	130 (68)	69 (49)	361 (63)	<0.001
Food security worry in last 4 week (n=562)					
Worried	135 (56)	125 (64)	90 (64)	350 (61)	0.166
Not worried	99 (41)	66 (34)	47(33)	212 (37)	
Current marital status(n=562)					
Single	231 (96)	185 (94)	129 (91)	545 (94)	0.047
Married	3 (1)	6 (3)	8 (6)	17 (3)	
Had vaginal or anal sex in the past 3 months (n=562)	169 (70)	126 (64)	82 (58)	377 (65)	0.046
Had anal sex in the last 1 month (n=505)					
Yes	47 (22)	54 (31)	35 (29)	136 (27)	0.151
No	162 (78)	120 (69)	87 (71)	369 (73)	
Currently have a main sex partner(n=562)					
Yes	209 (87)	174 (89)	122 (87)	505 (88)	0.780
No	25 (10)	17 (9)	15 (11)	57 (10)	
Main sex partner age categories (n=504)					
17-24 yrs.	119 (57)	99 (57)	54 (45)	272 (54)	0.160
25-34yrs	88 (42)	72 (41)	66(55)	226 (45)	
>34 yrs.	2(1)	3 (2)	1 (1)	6 (1)	
Age difference with main sexual partner, years (n=504)					

Characteristics	non-Hormonal contraception N=240	NET-EN N=196	DMPA N= 141	Total N=577	p value
<5 yrs.	139 (67)	110 (63)	71 (59)	320 (63)	0.362
>=5 yrs.	70 (33)	63 (37)	50 (41)	183 (37)	
Live with main sex partner (n=505)					
Yes	10 (5)	15 (9)	17 (14)	42 (8)	0.014
No	199 (95)	159 (91)	105 (86)	463 (92)	
Receiving financial and/or material support from main sex partner (n=505)					
Yes	107 (51)	98 (56)	71 (58)	276 (55)	0.402
No	102 (49)	76 (44)	51 (42)	229 (45)	
Main sex partner has other sex partners (n=505)					
Yes	7 (3)	7 (4)	7(6)	21 (4)	0.573
No	202 (97)	167 (96)	115 (94)	484 (96)	
AGYW had more than one sex partner in the past 3 months (n=505)					
Yes	46 (22)	23 (13)	17 (14)	86 (17)	0.043
No	163 (78)	151 (87)	105 (86)	419 (83)	
Number of sex partners other than main partner in the last 3 months (n=497)					
0-1	112 (54)	97 (56)	65 (55)	274 (55)	0.905
>=2	95 (46)	75 (44)	53 (45)	223 (45)	
Transactional sex in the last 3 months (n=496)					
Yes	8 (4)	12 (7)	10 (8)	30 (6)	0.202
No	199 (96)	158 (93)	109 (92)	466 (94)	
Condom use at last sex (n=505)					
Yes	148 (71)	92 (53)	67 (55)	307 (61)	0.001
No	61 (29)	82 (47)	55 (45)	198 (39)	
Experienced any form of Violence in the past year (n=562)					
Yes	152 (63)	117 (60)	93 (66)	362 (63)	0.454
No	82 (34)	74 (38)	44 (31)	200 (35)	
Forced sex or sexual act in the past year(n=562)					
Yes	25 (10)	15 (8)	17 (12)	57 (10)	0.378
No	209 (87)	176 (90)	120 (85)	505 (88)	
Experienced anxiety symptoms in the last 30 days (n=562)					
Yes	208 (87)	166 (85)	125 (89)	499 (86)	0.471
No	26 (11)	25 (13)	12 (9)	63 (11)	
CES -D scale in the last 30 days. Depressive symptoms? (n=562)					
(>=10) Yes	79 (33)	68 (35)	61 (43)	208 (36)	0.103
(<10) No	155 (65)	123 (63)	76 (54)	354 (61)	
Any suicidal symptoms in the past year (n=562)					
No	160 (67)	121 (62)	85 (60)	366 (63)	0.382
Yes	74 (31)	70 (36)	52 (37)	196 (34)	

Characteristics	non-Hormonal contraception N=240	NET-EN N=196	DMPA N= 141	Total N=577	p value
Ever used illicit substances (n=562)					
No	69 (29)	62 (32)	42 (30)	173 (30)	0.803
Yes	165 (69)	129 (66)	95 (67)	389 (67)	

In the table above CES-D 10 stands Centre for Epidemiologic Studies Depression Scale out of 10. N=505 is due to skip pattern excluding 72 participants without sexual partners for specific questions. N=562 is due to 15particpants who had missing enrolment CASI data. N=504 is due to skip pattern excluding 72 participants without sexual partners for specific questions and 1 participant with a missing response for that specific category. N=497 is due to 15 participants with missing enrolment CASI and 65 participants with missing responses for that category. N= 496 is due to 15 participants with missing enrolment CASI and 66 missing responses for that category.

Figure 3. 2 STI prevalence at enrolment, by contraceptive method

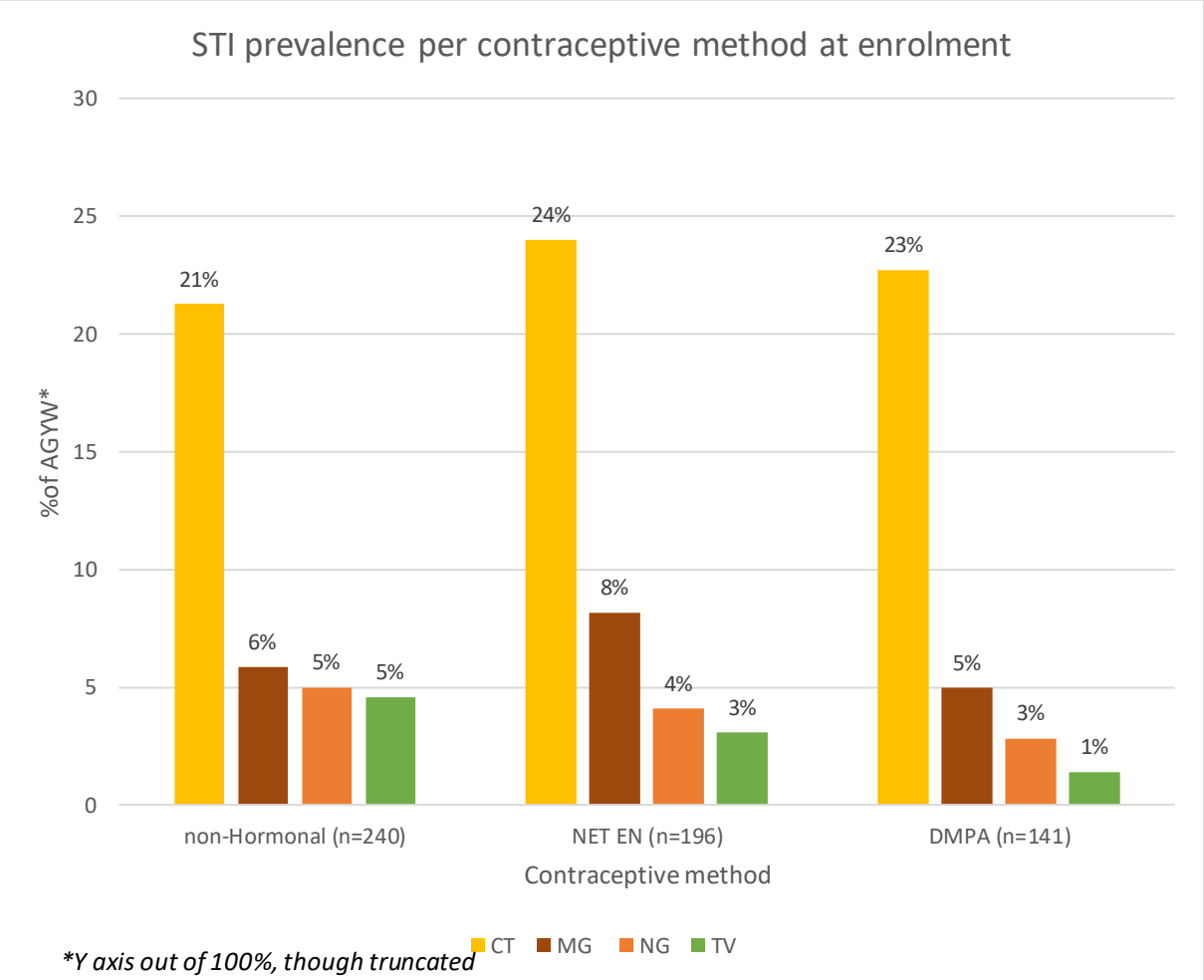


Figure 3.2 demonstrates baseline STI prevalence per contraceptive method. Overall, 23% (130/577) participants had CT, 6% (37/577) participants had MG, these were the two highest infections at enrolment. Enrolment GC prevalence was 4% (24/577) of participants and TV 3%

(19/577) of participants. This analysis of STI prevalence per contraceptive method suggests no significant differences in STI prevalence by different contraceptive methods. (Figure3.2)

3.2 Factors associated with STI at enrolment

In unadjusted analyses, neither NET-EN (OR 1.08, 95%CI, 0.66-1.79) nor DMPA (OR 1.16, 95% CI, 0.74-1.83) was significantly associated with CT infection at baseline, although a trend towards a positive association was observed. After adjusting for age group, financial and/or material support from partner, two or more sex partners other than main sex partner, the positive association between NET-EN and CT strengthened (aOR 1.16, 95% CI, 0.71-1.88) but was still not statistically significant, and the association with DMPA weakened (aOR 0.94, 95%CI, 0.54-1.64). Having two or more sex partners was independently associated with having a CT infection at enrolment (aOR1.71, 95% CI, 1.12-2.62) (Table 3.2).

In unadjusted analyses, neither NET-EN (OR 1.43, 95% CI, 0.68-3.02) nor DMPA (OR 0.84, 95% CI 0.34-2.14) was significantly associated with MG infection at baseline. After adjusting for age group, marital status, age disparate relationship, having more than one sexual partner in the last 3 months, transactional sex in the last 3 months and forced sex in the past year, the positive association strengthened between NET-EN and MG (aOR 1.95, 95 % CI, 0.83-4.57) but was not statistically significant, and the protective association between with DMPA and MG (aOR 0.77, 95% CI, 0.26-2.27) strengthened but was not statistically significant. Having more than one sex partner in the last 3 months (aOR 2.45, 95% CI, 1.07-5.65) and reporting transactional sex in the last 3 months (aOR 2.97, 95%CI, 1.04-8.45) was also independently associated with having MG at baseline. (Table 3.2)

In unadjusted analyses, there was a trend towards a negative association between both NET-EN (OR 0.81, 95%CI, 0.32-2.02) and DMPA (OR 0.55, 95% CI, 0.18-1.75) with GC infection at baseline, although it was not statistically significant. After adjusting for age group, living with main sexual partner, receiving financial and/or material support from partner, the negative association between NET-EN and GC did not change (aOR 0.82, 95% CI, 0.31-2.19), and the negative association with DMPA strengthened but did not achieve statistical significance (aOR 0.38, 95% CI, 0.10-1.46). Living with main sex partner (aOR 3.28, 95% CI, 1.08-10.05) and receiving financial and/or material support from main sex partner (aOR 3.18, 95%CI, 1.02-9.88) were independently associated with having GC at enrolment. (Table 3.2)

In unadjusted analyses, NET-EN (OR 0.66, 95% CI 0.24-1.81) and DMPA (OR 0.30, 95% CI, 0.07-1.37) were associated with a lower risk for TV infection at baseline, although this was not statistically significant. After adjusting for age group, food security, vaginal or anal sex in the

last 3 months, experiencing violence in the previous year, the negative association between NET-EN and TV strengthened (aOR 0.62, 95%CI, 0.21-1.81) as did the association with DMPA but this did not achieve statistical significance (aOR 0.26, 95% CI, 0.05-1.26). Having vaginal or anal sex in the last 3 months (aOR 0.19, 95% CI, 0.07-0.51) was independently associated with TV. (Table 3.2)

We conducted sensitivity checks through probabilistic model selection utilising AIC, BIC to ensure better model selection for some sociodemographic responses. We also conducted a sensitivity analysis by running a Poisson regression and exact regression as some categories had small values. The results of those models were mostly similar to the logistic regression results with the strengths of the associations very similar.

Table 3. 2 Factors associated with CT, MG, GC and TV at enrolment

Characteristic	**CT OR (95%CI)**	**CT aOR (95%CI)**	**MG OR (95%CI)**	**MG aOR (95%CI)**	**GC OR (95%CI)**	**GC aOR (95%CI)**	**TV OR (95%CI)**	**TV aOR (95%CI)**
Contraception								
Non-hormonal	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
NET-EN	1.08 (0.66-1.79)	1.16 (0.71-1.88)	1.43 (0.68-3.02)	1.95 (0.83-4.57)	0.81 (0.32-2.02)	0.82 (0.31-2.19)	0.66 (0.24-1.81)	0.62 (0.21-1.81)
DMPA	1.16 (0.74-1.83)	0.94 (0.54-1.64)	0.84 (0.34-2.14)	0.77 (0.26-2.27)	0.55 (0.18-1.75)	0.38 (0.10-1.46)	0.30 (0.07-1.37)	0.26 (0.05-1.26)
AGE, years								
16-19	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
20-24	1.21 (0.79-1.86)	1.11 (0.70-1.77)	2.07 (0.89-4.81) **	1.83 (0.74-4.50)	1.41 (0.55-3.62)	1.26 (0.44-3.63)	0.79 (0.31-2.04)	0.77 (0.28-2.09)
Currently in school (n=562)								
No	Ref		Ref		Ref		Ref	
Yes	1.07 (0.71-1.62)		0.67 (0.34-1.34)		0.65 (0.28-1.47)		0.87 (0.33-2.28)	
Highest level of education. (n=562)								
Secondary or less	Ref		Ref		Ref		Ref	
Tertiary	1.01 (0.62-1.67)		0.67 (0.25-1.77)		0.60 (0.17-2.04)		0.52 (0.12-2.31)	
Food security worry in the last 4 weeks (n=562)								
Not worried	Ref		Ref		Ref		Ref	
Worried	1.01 (0.67-1.51)		0.84 (0.42-1.66)		1.01 (0.43-235)		3.11 (0.89-10.90) **	2.85 (0.78-10.40)
Current marital status (n=562)								
Single	Ref		Ref		Ref		Ref	
Married	0.70 (0.20-2.49)		3.32 (0.91-12.15) **	2.99 (0.69-12.90)	3.17 (0.68-14.72)		empty	
Had vaginal or anal sex in the past 3 months (n=562)								

Characteristic	CT OR (95%CI)	CT aOR (95%CI)	MG OR (95%CI)	MG aOR (95%CI)	GC OR (95%CI)	GC aOR (95%CI)	TV OR (95%CI)	TV aOR (95%CI)
No	Ref		Ref		Ref		Ref	
Yes	0.91 (0.60-1.37)		1.78 (0.79-3.98)		0.68 (0.29-1.54)		0.23 (0.08-0.63) ***	0.19(0.07-0.51) ***
Had anal sex in the last 1 month (n=505)								
No	Ref		Ref		Ref		Ref	
Yes	1.29 (0.82-2.04)		1.07 (0.48-2.36)		1.71 (0.69-4.22)		1.84 (0.64-5.29)	
Currently have a main sex partner (n=562)								
No	Ref		Ref		Ref		Ref	
Yes	0.92 (0.49-1.74)		0.90 (0.31-2.63)		0.78 (0.23-2.70)		0.55 (0.15-1.96)	
Age difference with main sexual partner, years (n=504)								
<5 yrs.	Ref		Ref		Ref		Ref	
>=5 yrs.	0.93 (0.60-1.43)		2.06 (1.01-4.25) **	2.00 (0.94-4.25) **	0.40 (0.13-1.20)		1.54 (0.55-4.32)	
Live with main sex partner (n=562)								
No	Ref		Ref		Ref		Ref	
Yes	0.90 (0.42-1.95)		1.15 (0.34-3.95)		3.78 (1.31-10.88) **	3.28 (1.08-10.05) **	Omitted	
Receiving financial and/or material support from main sex partner (n=505)								
No	Ref		Ref		Ref		Ref	
Yes	3.69 (1.22-11.12) **	1.39 (0.90-2.15) **	1.22 (0.59-2.54)		3.69 (1.22-11.13) **	3.18 (1.02-9.88) **	0.54 (0.19-1.54)	
Main sex partner has other sex partners (n=505)								
No	Ref		Ref		Ref		Ref	

Characteristic	CT OR (95%CI)	CT aOR (95%CI)	MG OR (95%CI)	MG aOR (95%CI)	GC OR (95%CI)	GC aOR (95%CI)	TV OR (95%CI)	TV aOR (95%CI)
Yes	0.78 (0.26-2.36)		2.61 (073-9.39)		Empty		1.66 (0.21-13.40)	
AGYW had more than one sex partner in the past 3 months (n=505)								
No	Ref		Ref	Ref	Ref		Ref	
Yes	0.67 (0.40-1.14)		2.37 (1.08-5.21) **	2.45 (1.07-5.65) **	1.24 (0.36-4.31)		0.74(0.16-3.36)	
Number of sex partners other than main sex partner in the last 3 months (n=497)								
0/1	Ref		Ref		Ref		Ref	
>=2	1.72 (1.12-2.62) **	1.71 (1.12-2.62) **	0.83 (0.40-1.72)		1.01 (0.41-2.47)		1.08 (0.38- 3.02)	
Transactional sex in the last 3 months (n=496)								
No	Ref		Ref		Ref		Ref	
Yes	1.02(0.43-2.44)		4.23 (1.59-11.25) ***	2.97 (1.04-8.45) **	1.68 (0.37-7.58)		2.49 (0.54-11.57)	
Condom use at last sex (n=505)								
No	Ref		Ref		Ref		Ref	
Yes	1.23 (0.81-1.87)		0.93 (0.44-1.93)		0.95 (0.39-2.34)		0.55 (0.17-1.77)	
Experienced any form of Violence in the past year (n=562)								
No	Ref		Ref		Ref		Ref	
Yes	1.27 (0.83-1.92)		1.11 (0.54-2.28)		0.92 (0.39-2.14)		4.58 (1.04-20.11) **	4.00(0.87-18.30) **
Forced sex or sexual act in the last (n=562)								
No	Ref		Ref	Ref	Ref		Ref	

Characteristic	CT OR (95%CI)	CT aOR (95%CI)	MG OR (95%CI)	MG aOR (95%CI)	GC OR (95%CI)	GC aOR (95%CI)	TV OR (95%CI)	TV aOR (95%CI)
Yes	1.37 (0.74-2.54)		2.30 (0.96-5.51) **	2.31 (0.84-6.36)	1.28 (0.37-4.43)		1.11 (0.25-4.96)	
Anxiety symptoms in the last 30 days (n=562)								
No	Ref		Ref		Ref		Ref	
Yes	0.96 (0.52-1.78)		0.77 (0.29-2.05)		3.00 (0.40-22.57)		1.01 (0.23-4.50)	
CES-D scale in the last 30 days. Depressive symptoms? (n=562)								
(<10) No	Ref		Ref		Ref		Ref	
(>=10) Yes	0.84 (0.55-1.27)		1.57 (0.80-3.09)		1.02(0.42-2.38)		0.85(0.31-2.29)	
Any suicidal symptoms in the past year (n=562)								
No	Ref		Ref		Ref		Ref	
Yes	0.89 (0.59-1.33)		0.93 (0.45-1.90)		0.76 (0.31-1.87)		0.93(0.34-2.52)	
Ever used illicit substance (n=562)								
No	Ref		Ref		Ref		Ref	
Yes	0.90 (0.59-1.36)		0.88 (0.43-1.81)		0.73(0.31-1.70)		0.69(0.265-1.81)	

** p <0.10 *** p <0.010 ****p<0.001

In the table above OR stands Odds Ratio, aOR stands for adjusted Odds Ratio. CES-D 10 stands Centre for Epidemiologic Studies Depression Scale out of 10

N=505 is due to skip pattern excluding 72 participants without sexual partners for specific questions. N=562 is due to 15particpants who had missing enrolment CASI data. N=504 is due to skip pattern excluding 72 participants without sexual partners for specific questions and 1 participant with a missing response for that specific category. N=497 is due to 15 participants with missing enrolment CASI and 65 participants with missing responses for that category. N= 496 is due to 15 participants with missing enrolment CASI and 66 missing responses for that category.

Table 3.3 represents an exploratory analysis for risk factors for detection of any STI. In unadjusted analyses, reporting transactional sex in the last 3 months (OR 1.92, 95%CI, 0.91-4.03), having more than one sex partner in the past 3 months (OR 1.67 95%CI 1.39-2.70), having two or more other sex partners beside the main sex partner in the last 3 months (OR 1.54, 95%CI, 1.05-2.26), receiving financial support and/or material support from main sex partner (OR 1.42, 95%CI, 0.97-2.07), and experiencing any form of violence in the last year (OR1.37, 95%CI, 0.94-2.00) were positively associated with having at least one curable STI detected at baseline. After adjusting for each of the factors stated above, having more than one sex partner in the last 3 months (aOR 1.80, 95%CI, 1.09-2.97), receiving financial support and/or material support from main sex partner (aOR 1.67, 95%CI, 1.12-2.49), and having two or more sex partners other than main sex partner (aOR 1.59, 95%CI, 1.07-2.36) were independently associated with having a curable STI. These behavioural risk factors increased risk for any STI by 60-80% (Table 3.3)

Table 3. 3 Factors associated with having at least one curable STI detected at enrolment

Characteristic	**Any STI Odds Ratio (95%CI)**	**Any STI adjusted OR (95%CI)**
AGE, years		
16-19	Ref	
20-24	1.36 (0.92-1.99)	
Contraceptive method		
Non-hormonal	Ref	
NET-EN	1.10 (0.70-1.72)	
DMPA	0.81 (0.49-1.36)	
Currently in school (n=562)		
No	Ref	
Yes	0.87 (0.60-1.26)	
Highest level of education (n=562)		
Secondary or less	Ref	
Tertiary	0.87(0.55-1.39)	
Food security worry in the last 4 weeks (n=562)		
Not worried	Ref	
Worried	1.18 (0.81- 1.70)	
Current marital status (n=562)		
Single	Ref	
Married	1.14 (0.42-3.14)	
Had vaginal or anal sex in the past 3 months (n=562)		
No	Ref	
Yes	0.77 (0.53-1.12)	
Had anal sex in the last 1 month (n=505)		
No	Ref	

Characteristic	Any STI Odds Ratio (95%CI)	Any STI adjusted OR (95%CI)
Yes	1.39 (0.92-2.10)	
Currently have a main sex partner (n=562)		
No	Ref	
Yes	0.87 (0.49-1.55)	
Age difference with main sexual partner, years (n=504)		
<5 yrs**.**	Ref	
>=5 yrs**.**	0.99 (0.67-1.47)	
Live with main sex partner (n=562)		
No	Ref	
Yes	0.94(0.48-1.87)	
Receiving financial and/or material support from main sex partner (n=505)		
No	Ref	Ref
Yes	1.42 (0.97-2.07)	1.67 (1.12-2.49)
Main sex partner has other sex partners (n=505)		
No	Ref	
Yes	1.06 (0.42-2.68)	
AGYW had more than one sex partner in the past 3 months (n=505)		
No	Ref	Ref
Yes	1.67 (1.39-2.70)	1.80 (1.09-2.97)
Number of sex partners other than main sex partner in the last 3 months (n=497)		
0/1	Ref	Ref
>=2	1.54 (1.05-2.26)	1.59 (1.07-2.36)
Transactional sex in the last 3 months (n=496)		
No	Ref	Ref
Yes	1.92 (0.91-4.03)	1.81 (0.84-3.90)
Condom use at last sex (n=505)		
No	Ref	
Yes	1.06 (0.72-1.55)	
Experienced any form of Violence in the past year (n=562)		
No	Ref	Ref
Yes	1.37 (0.94-2.00)	1.25 (0.82-1.90)
Forced sex or sexual act in the last year (n=562)		
No	Ref	
Yes	1.47 (0.84-2.58)	
Anxiety symptoms in the last 30 days (n=562)		
No	Ref	
Yes	1.12 (0.64-1.99)	
CES -D scale in the last 30 days. Depressive symptoms? (n=562)		
(<10) No	Ref	

Characteristic	Any STI Odds Ratio (95%CI)	Any STI adjusted OR (95%CI)
(>=10) Yes	1.02 (0.71-1.47)	
Any suicidal symptoms in the past year (n=562)		
No	Ref	
Yes	0.94 (0.61-1.38)	
Ever used illicit substance (n=562)		
No	Ref	
Yes	1.00 (0.68- 1.46)	

CES-D 10 stands Centre for Epidemiologic Studies Depression Scale out of 10

N=505 is due to skip pattern excluding 72 participants without sexual partners for specific questions. N=562 is due to 15particpants who had missing enrolment CASI data. N=504 is due to skip pattern excluding 72 participants without sexual partners for specific questions and 1 participant with a missing response for that specific category. N=497 is due to 15 participants with missing enrolment CASI and 65 participants with missing responses for that category. N= 496 is due to 15 participants with missing enrolment CASI and 66 missing responses for that category.

3.3 STI trends over time

Off the 577 participants analysed, 135 (23.4%) had only an enrolment visit, 164 (28.4%) had at least one follow up visit at month 12 or month 24, 278 (48.2%) had two or more follow up study visits (month 12 and month 24).

Analysis of the sociodemographic features and their association with the number of follow up visits attended revealed a few significant differences between the groups. Participants who attended one follow up visit experienced more forced sex or sexual act in the previous year compared to those that only attended the enrolment visit (p=0.010). Participants who attended one follow up visit significantly experienced more suicidal symptoms compared to those that showed up for enrolment only (p=0.012). Participants that only attended the enrolment visit had significantly higher rates of ever having used illicit substance compared to those that attended one follow visit (p=0.039). Those that only attended enrolment visit and were lost to follow up where at a lower risk for forced sex, suicidal symptoms but at higher risk for substance use. The rest of the socio-demographic features were not associated with the number of visits the AGYW attended (Table 3.4). We ran a sensitivity analysis by combining those who had one follow up and two follow ups as one group. The results were similar for that bivariate analysis in described here and in table 3.4.

Table 3. 4 Participant characteristics, by number of follow up visits attended

Characteristic	Enrolment only (N=135)	One f/u (N=164)	Two f/u (N=278)	Total N=577	p value
	n (%)	n (%)	n (%)	n (%)	
Median age, years (IQR):	21 (19-22)	20 (19-22)	20 (19-22)	21 (19-22)	0.343
AGE, years					

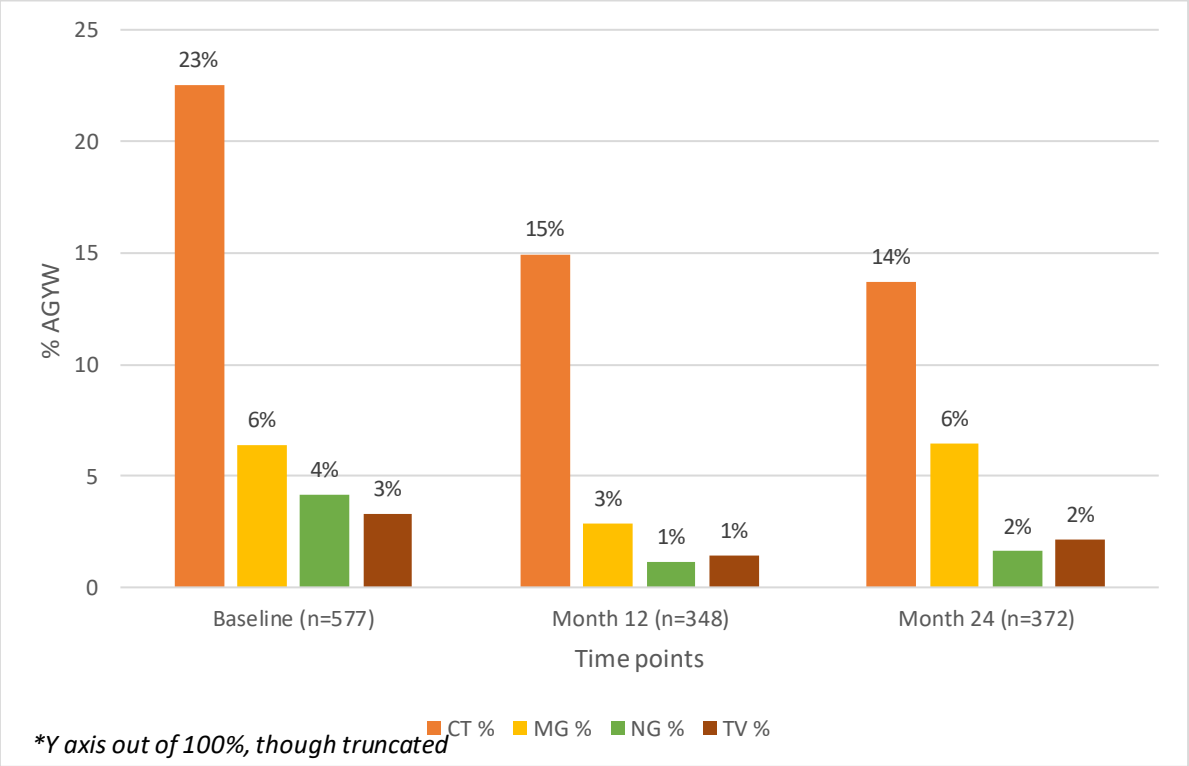
Characteristic	Enrolment only (N=135)	One f/u (N=164)	Two f/u (N=278)	Total N=577	p value
16-19	38 (29)	61 (37)	84 (30)	183 (32)	0.187
20-24	97 (72)	103 (63)	194 (70)	394 (68)	
Currently in school (n=562)					
No	52 (40)	63 (40)	86 (32)	201 (36)	0.138
Yes	80 (60)	95 (60)	186 (68)	361 (64)	
Level of education. (n=562)					
Secondary and less	108 (82)	127 (80)	220 (81)	455 (81)	0.952
Tertiary	24 (18)	31 (20)	52 (19)	107 (19)	
Food security worry in last 4 week (n=562)					
Not worried	54 (41)	60 (38)	98 (36)	212 (38)	0.635
Worried	78 (59)	98 (62)	174 (64)	350 (62)	
Current marital status (n=562)					
Single	127 (96)	153 (97)	265 (97)	545 (97)	0.794
Married	5 (4)	5 (3)	7 (3)	17 (3)	
Had vaginal or anal sex in the past 3 months (n=562)					
No	42 (32)	55 (34)	88 (32)	185 (33)	0.832
Yes	90 (68)	103 (66)	184 (68)	377 (67)	
Had anal sex in the last 1 month (n=505)					
No	89 (75)	93 (68)	187 (75)	369 (73)	0.276
Yes	30 (25)	44 (32)	62 (25)	136 (27)	
Currently have a main sex partner (n=562)					
No	13 (10)	21 (13)	23 (8)	57 (10)	0.275
Yes	119 (90)	137 (87)	249 (92)	505 (90)	
Main sex partner age year: Median age, years (IQR):	24 (23-27)	24 (22-26)	24 (23-26)	24 (23-26)	0.899
Main sex partner age categories (n=504)					
17-24 yrs.	66 (55)	73 (54)	133 (53)	272 (54)	0.616
25-34yrs	50 (42)	62 (45)	114 (45)	226 (45)	
>34 yrs.	3 (3)	1 (1)	2 (1)	6 (1)	
Age disparate relationships (n=504)					
<5 yrs.	72 (60)	89 (65)	159 (64)	320 (64)	0.698
>=5 yrs.	47 40)	47 (35)	89 (36)	183 (36)	
Live with main sex partner (n=505)					
No	107 (90)	129 (94)	227 (91)	463 (92)	0.432
Yes	12 (10)	8 (6)	22 (9)	42 8)	

Characteristic	Enrolment only (N=135)	One f/u (N=164)	Two f/u (N=278)	Total N=577	p value
Receiving financial and/or material support from main sex partner (n=505)					
No	53 (45)	56 (41)	120 (48)	229 (45)	0.377
Yes	66 (55)	81 (59)	129 (52)	276 (55)	
Main sex partner has other sex partners n= (505)					
No	112 (94)	131 (96)	241 (97)	484 (96)	0.481
Yes	7 (6)	6 (4)	8 (3)	21 (4)	
Had more than one sex partner in the past 3 months (n=505)					
No	101 (85)	109 (80)	209 (84)	419 (83)	0.450
Yes	18 (15)	28 (20)	40 (16)	86 (17)	
Number of sex partners other than main partner in the last 3 months (n=497)					
0-1	65 (56)	70 (51)	139 (57)	274 (55)	0.529
>=2	51 (44)	67 (49)	105 (43)	223 (45)	
Transactional sex in the last 3 months (n=496)					
No	108 (94)	126 (93)	232 (95)	466 (94)	0.724
Yes	7 (6)	10 (7)	13 (5)	30 (6)	
Condom use at last sex(n=505)					
No	50 (42)	48 (35)	100 (40)	198 (39)	0.475
Yes	69 (58)	89 (65)	149 (60)	307 (61)	
Experienced any form of Violence in the past year (n=562)					
No	53 (40)	50 (32)	97 (36)	200 (36)	0.321
Yes	79 (60)	108 (68)	175 (64)	362 (64)	
Forced sex or sexual in the past year (n=562)					
No	125 (95)	133 (84)	247 (91)	505 (90)	0.010
Yes	7 (5)	25 (16)	25 (9)	57 (10)	
Experienced anxiety symptoms in the last 30 days (n=562)					
Yes	117 (89)	138 (87)	245 (90)	499 (89)	0.565
No	15 (11)	21 (13)	27 (10)	63 (11)	
CES -D scale in the last 30 days. Depressive symptoms? (n=562)					
(>=10) Yes	53 (40)	62 (39)	93 (34)	208 (37)	0.402
(<10) No	79 (60)	96 (61)	174 (65)	354 (63)	

Characteristic	Enrolment only (N=135)	One f/u (N=164)	Two f/u (N=278)	Total N=577	p value
Any suicidal symptoms in the past year (n=562)					
No	98 (74)	91 (58)	177 (65)	366 (65)	0.012
Yes	34 (26)	67 (42)	95 (35)	196 (35)	
Ever used illicit substance (n=562)					
No	31 (23)	59 (37)	83 (31)	173 (31)	0.039
Yes	101 (76)	99 (63)	189 (69)	389 (69)	

Figure 3.3 represents STI point prevalence by time. CT point prevalence declined from 23% to 14%. Similar declining trends were noted for GC from 4% to 2%. By contrast MG point prevalence was unchanged at month 24 despite a lower point prevalence at month 12 (which were adequately treated), and TV also remained unchanged (also despite adequately treated infections at baseline and month 12). The prevalence of Any STI at enrolment was 183/577, 32% of the participants. At month 12 it was 63/348 (18%) of participants and it was 75/372 (20%) at month 24. Total number of participants per visit declined over time and so the absolute numbers of infections declined over time. (Figure 3.3)

Figure 3. 3 STI point prevalence by time



3.4 STI incidence over time

Table 3. 5 STI Incidence

STI INCIDENCE	CT	MG	GC	TV	Any STI
Events	88	32	9	12	118
Person years	699.83	719.40	725.03	721.86	685.22
event/ person years	0.1268	0.0445	0.01241	0.0166	0.1722
events per 100 person years	12.68	4.45	1.24	1.66	17.22
95% CI	10.29-15.63	3.14-6.29	0.65-2.39	0.94-2.92	14.38-20.63

Note: Five individuals were censored from the incidence analysis due to a positive pregnancy test (5 condom users) . Eleven participants were censored due to positive HIV testing (3 DMPA users, 2 NET-users, 3 condom users 3 IUD users). These participants had similar socio-behavuoral qualities across the different contraception use groups. These numbers are small in terms of overall numbers of participants and the potential effect they would have had on the analysis given group sizes at baseline is negligible.

For CT, 88 incident infections occurred over 699.83 person-years of follow up, with a calculated incidence rate of 12.68 per 100 person-years (95% CI 10.29–15.63). For MG, 32 incident infections occurred over 719.40 person-years for a calculated incidence rate of 4.45 per 100 person-years (95% CI 3.14–6.29). For GC, 9 incident infections occurred over 725.03 person-years with an estimated incidence rate of 1.24 per 100 person-years (95% CI 0.76–2.39). For TV, 12 incident infections occurred over 721.86 person-years giving an incidence rate of 1.66 per 100 person-years (95% CI 0.94–2.92). A total of 118 incident infections occurred over 685.22 person-years for any STI, giving an incidence rate of 17.22 per 100 person-years (95% CI 14.38–20.63). (Table 3.5)

Differences in STI incidence by baseline contraceptive method were assessed using survival analysis. Below are Kaplan Meier survival curves plotted for incident STI stratified by baseline contraception approach. This approach was taken due to multiple contraception changes in between visits by participants that will be discussed below. Each graph demonstrates the different rates of failure events (getting diagnosed with a specific STI or any STI) by the participants through the follow up time. For each STI there is a Figure and a paragraph after each figure to explain it

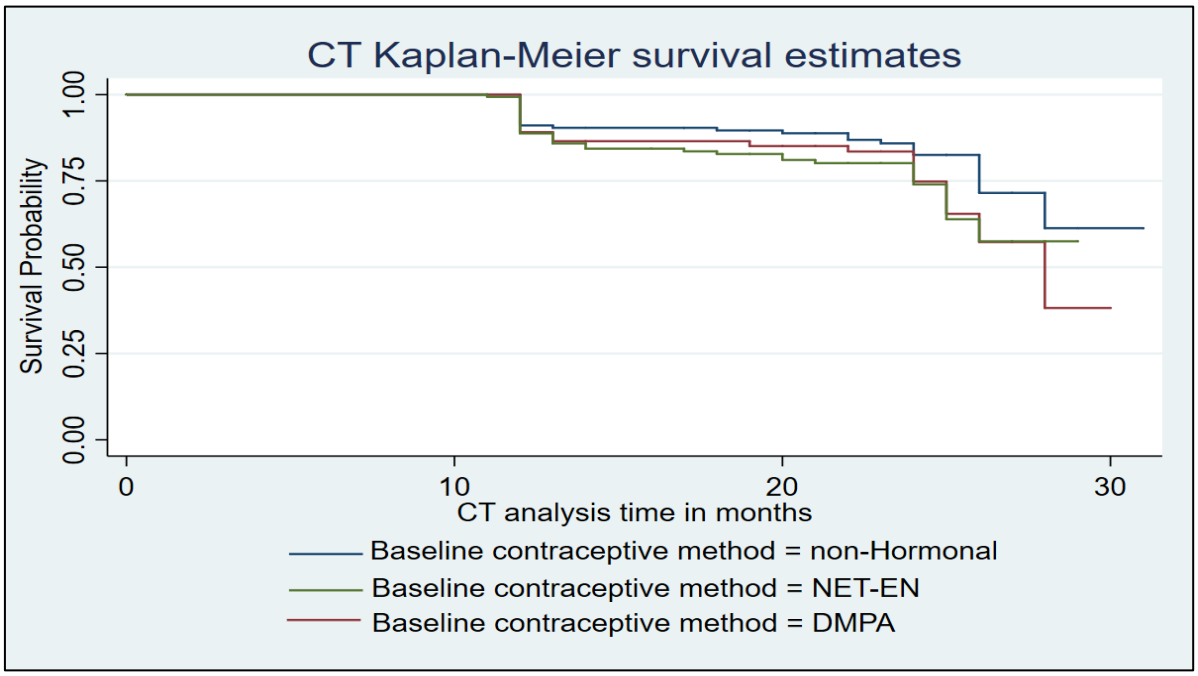
As stated in the methods section, visits for month 12 took place between 9 months and 15 months of follow up, which explains why survival curves mostly separate after or round 10 months. Five individuals were censored from the survival analysis due to a positive pregnancy test (5 condom users). Eleven participants were also censored due to positive HIV testing (3 DMPA users, 2 NET-users, 3 condom users, 3 IUD users). These participants had similar socio-

behavuoral qualities across the different contraception use groups. These numbers are small in terms of overall numbers of participants and the potential effect they would have had on the analysis given group sizes at baseline is negligible

Due to multiple changes in contraceptive methods, the graphs below were stratified by baseline contraceptive methods which is not an optimal approach.

Kaplan-Meier survival curves for incidence STI are shown in Figure 3.4-3.8

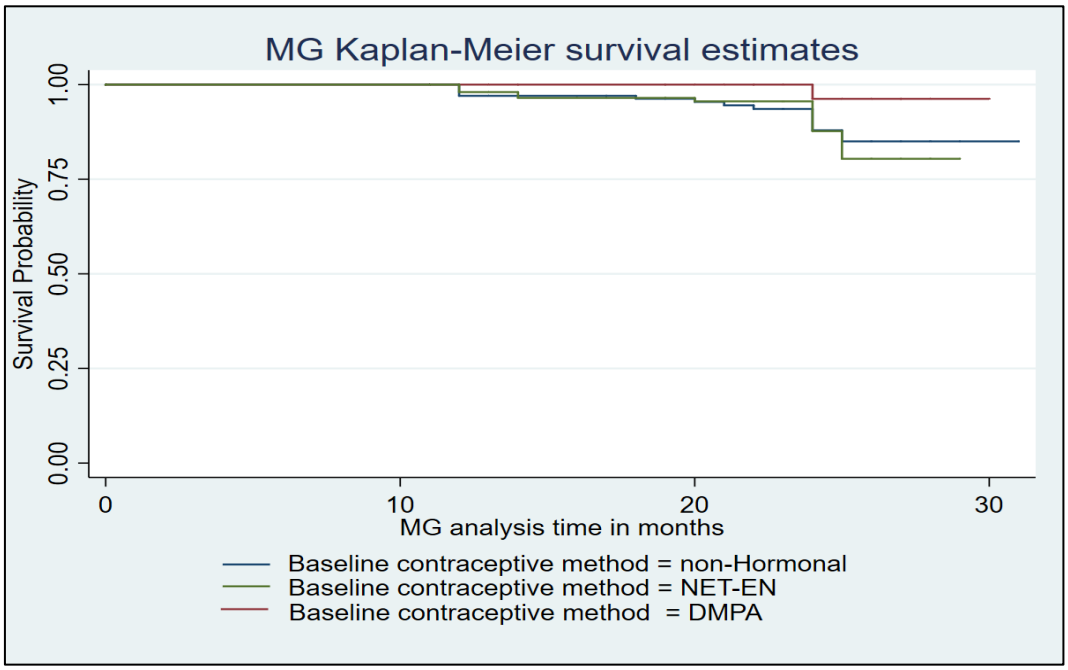
Figure 3. 4 CT Kaplan Meier Survival curve



CT Log rank test by baseline contraceptive method p= 0.50

For CT survival analysis, earlier failure of curves is noted compared to other STI curves. Hormonal contraception has more failure events than NH contraception. DMPA users had more failure events than NET-EN and NH contraception users, who had the least failure events. There was no significant difference in the survival curves between the different baseline contraceptive methods (p=0.50). (Figure 3.4)

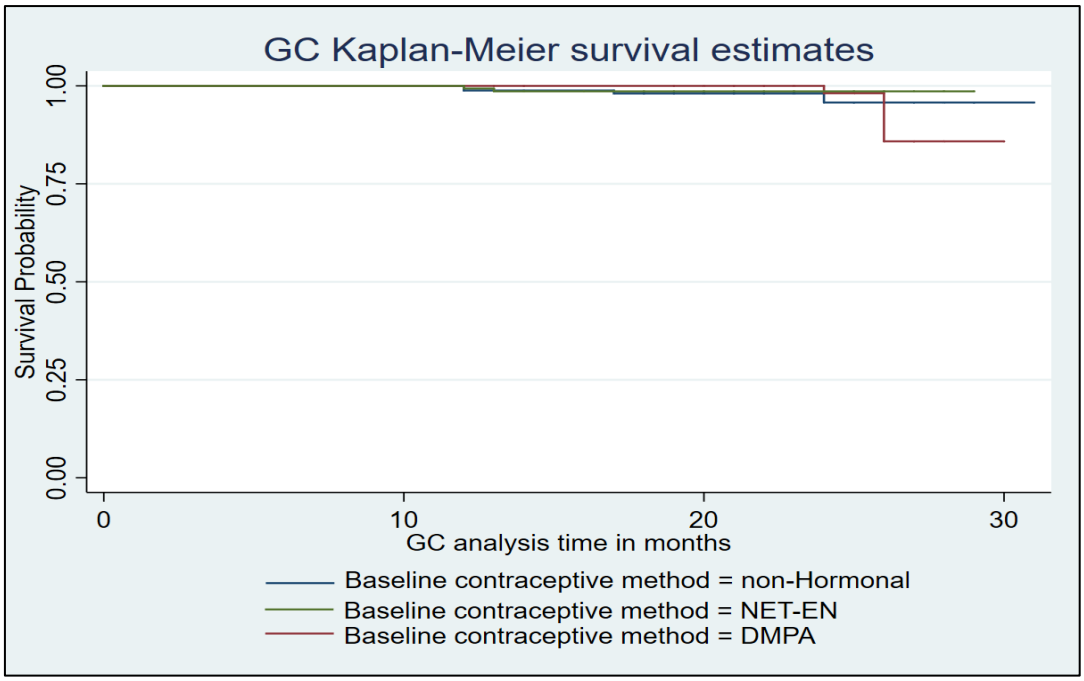
Figure 3. 5 MG Kaplan Meier Survival curve



MG Log rank test by baseline contraceptive method p= 0.11

For MG survival analysis, baseline NET-EN users had more failure events with baseline and DMPA users had the least failure events. There were no significant differences in the survival curves between the different baseline contraceptive methods (p=0.11). (Figure 3.5)

Figure 3. 6 GC Kaplan Meier Survival curve

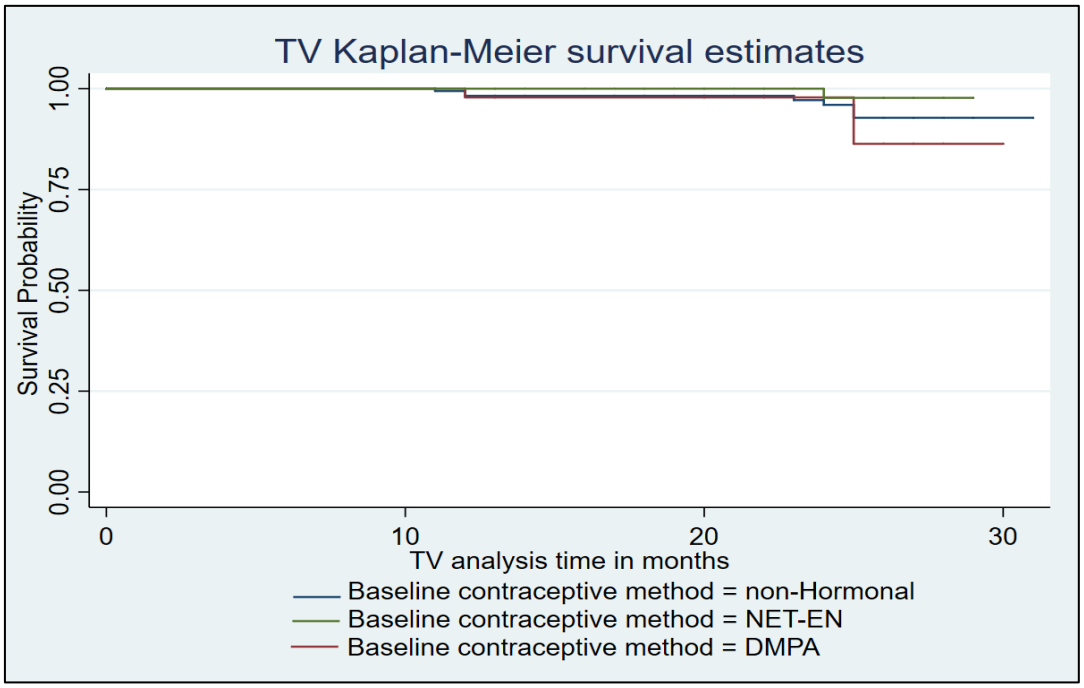


GC Log rank test by baseline contraceptive methods p= 0.61

For GC survival analysis, baseline DMPA users had more failure events than NET-EN and NH contraception users. NET-EN had the least failure events There was no significant differences

in the survival curve between the different baseline contraceptive methods (p=0.61). (Figure 3.6)

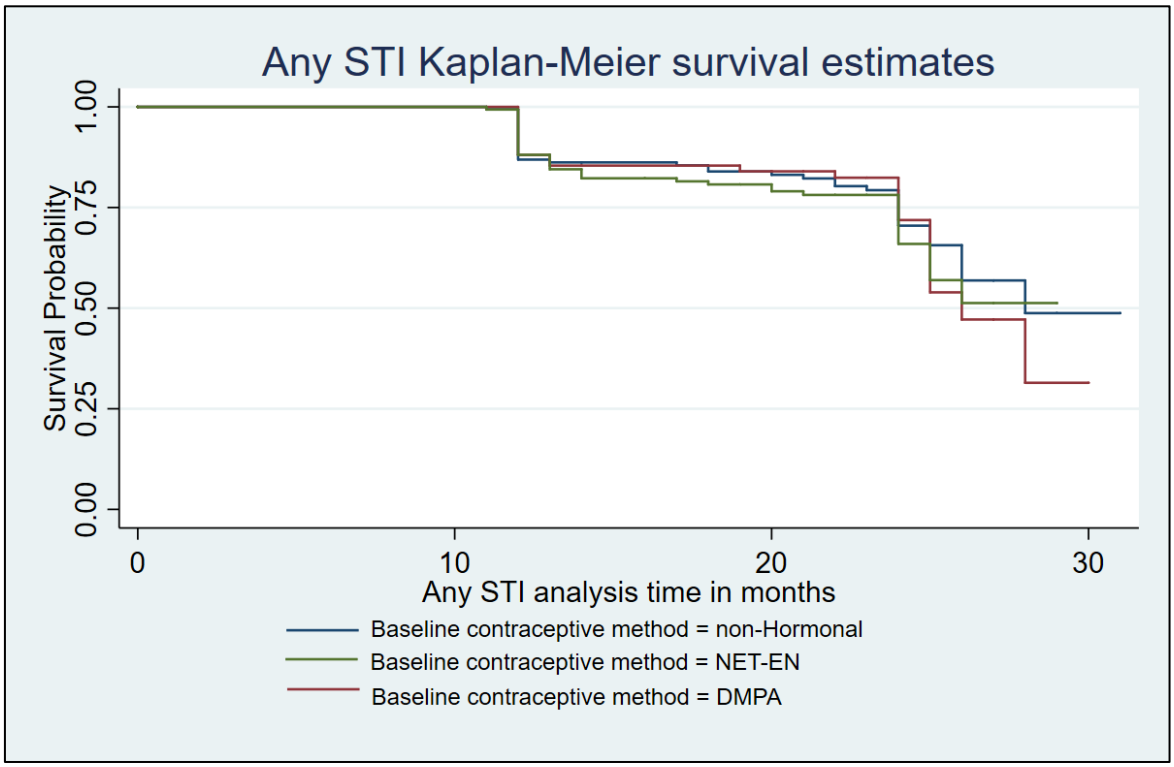
Figure 3. 7 TV Kaplan Meier survival curve



TV Log rank test by baseline contraceptive method p= 0.29

For TV survival analysis, baseline DMPA user had more failure events than NET-EN and NH contraception users. NET-EN had the least failure events There was no significant difference in the survival curves of between the different baseline contraceptive methods (p=0.29). (Figure 3.7)

Figure 3. 8 Any STI Kaplan Meier survival curve



Any STI Log rank test by baseline contraceptive method p= 0.48

For any STI survival analysis, baseline DMPA users had more failure events than NET-EN and NH contraception users. NET-EN had the least failure events There was no significant different in the survival curves between the different baseline contraceptive methods (p=0.48). (Figure 3.8)

Below is Figure 3.9 which is a swimmer plot illustrating changes in contraceptive method over time, highlighting these major limitations into the initial proposed analysis. Participants made changes between DMPA, NET-EN, NH and other methods (oral contraceptive or implant) in between visits. There were over 45 combinations of changes in contraception methods between the three study visits. Below is Figure 3.9 which is a swimmer plot illustrating changes in contraceptive method over time, highlighting major limitations into the initial proposed analysis These changes in contraception are highlighted in the swimmer's plot through colour changes. Those that were using DMPA are highlighted in orange, lime was for those that were using NET-EN, blue is for non-hormonal contraception users. Purple highlights a category we termed "other". These are the participants that changed to either oral contraceptive or who changed to the Implanon implant. Of the participants that attended enrolment visit, 135/577 (23%) did not attend both month 12 and month 24.

For non-hormonal contraception users, 52/240 (22%) only attended the enrolment visits and 52/240 (22%) used non-hormonal methods for all three visits (enrolment, month 12 and month 24). The following 18 contraception changes occurred in those that used non-hormonal methods at baseline: 8/240 (3%) used non-hormonal method at enrolment, NET-EN at month 12 and month 24, 16/240 (7%) used non-hormonal methods at enrolment, and DMPA at month 12 and month 24, 2/240 (1%) used non-hormonal method at enrolment, changed to NET-EN at month 12 then changed to DMPA at month 24, 1/240 (1%) used non-hormonal methods at enrolment, changed to DMPA at month 12 and changed to NET-EN at month 24, 4/240 (2%) used non-hormonal methods at enrolment and month 12 then changed to NET-EN at month 24, 1/240 (1%) used non-hormonal method at enrolment and month 12 then changed to DMPA at month 24, 1/240 (1%) used non-hormonal method at enrolment then changed to NET-EN at month 12 then changed to other at month 24, 11/240 (5%) used non-hormonal methods enrolment, changed to NET-EN at month 12, changed to back to non-hormonal method at month 24, 5/240 (2%) used non-hormonal method at enrolment then changed to other at month 12 then changed to non-hormonal method at month 24, 7/240 (3%) used non-hormonal method at enrolment and month 12 then changed to other at month 24 and 4/240 (2%) used non-hormonal methods at enrolment, changed to DMPA at month 12 then changed back to non-hormonal method at month 24. Participants also had missing visits e.g. some switched contraceptive method and missed month 24 including 27/240 (11%) used non-hormonal method at enrolment and month 12 then didn't attend month 24, 7/240(3%) used non-hormonal method at enrolment, changed to NET-EN at month 12 , but didn't attend month 24, 1/240 (1%) used non-hormonal methods at enrolment and changed to DMPA at month 12, then didn't attend month 24. Some participants missed an intervening visit at month 12 including 2/240 (1%) used non-hormonal method at enrolment, didn't attend month 12, then used DMPA at month 24, 3/240 (1%) used non-hormonal methods at enrolment, didn't attend moth 12 then changed to other (implant or oral contraceptives) at month 24, 27/240 (11%) used non-hormonal method at enrolment, didn't attend month 12 and used non-hormonal method at month 24, 9/240 (4%) used non-hormonal methods at enrolment, didn't attend month 12 then changed to NET-EN at month 24, These multiple changes are illustrated below in the swimmer's plot (Figure 3.9)

For NET-EN users, 39/196 (20%) only attend enrolment and 51/196 (26 %) used NET-EN through all three vests (enrolment, month 12 and month 24). The following 14 contraception changes occurred in those that were using NET-EN at baseline: 1/196 (1%) used NET-EN at enrolment and used DMPA at month 12 and month 24, 2/196 (1%) used NET-EN at enrolment

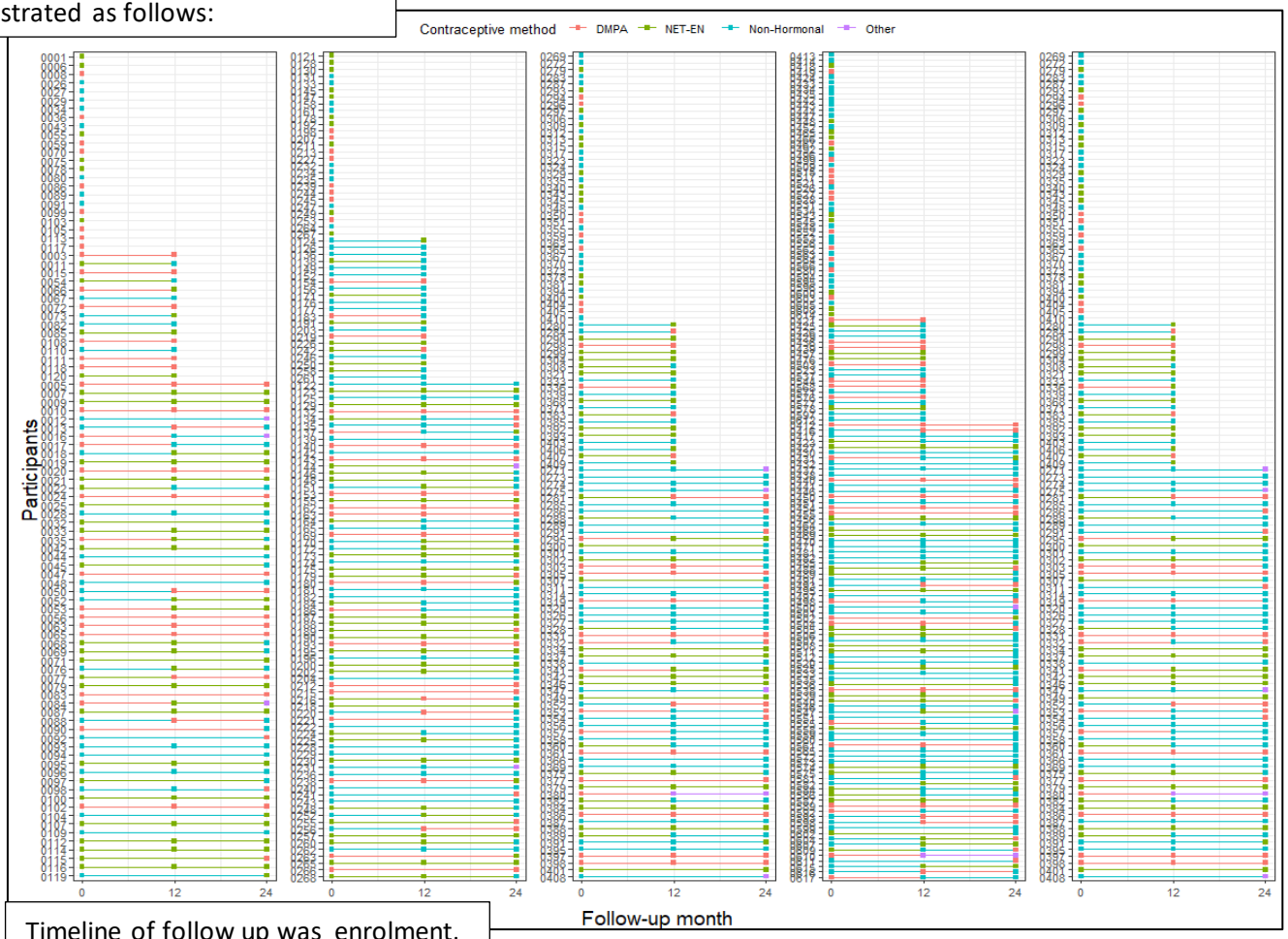
,changed to DMPA at month 12 then changed to non-hormonal contraception at month 24, 4/196 (2%) used NET-EN at enrolment, then changed to DMPA at month12 and didn't attend month 24, 2/196 (1%) used NET-EN at enrolment, changed to non-hormonal method at month 12 then changed back to NET-EN at month 24, 8/196 (4%) used NET-EN at enrolment and month 12 then changed to DMPA at month 24, 21/196 (11%) used NET-EN at enrolment and month 12 then changed to non-hormonal method at month 24, 14/196 (7%) used NET-EN at enrolment, then used non-hormonal method at month 12 and month 24, 16/196 (8%) used NET-EN at enrolment, didn't attend month 12 then used non-hormonal method at month 24, 5/196 (3%) used NET-EN at enrolment, missed month 12 visit then used NET-EN at month 24, 9/196 (5%) used NET-EN at enrolment then used non-hormonal method at month 12, then didn't attend month 24 visit, 4/196 (2%) used NET-EN at enrolment, didn't attend month12 then used DMPA at month 24, 16/196 (8%) used NET-EN at enrolment and month 12 then didn't attend month 24, 2/196 (1%) used NET-EN at enrolment, non-hormonal methods at month12 then DMPA at month 24, 2/196 (1%) used NET-EN at enrolment, then didn't attend month12 then changed to other at month 24. These multiple changes are illustrated below in the swimmer's plot (Figure 3.9)

For DMPA users 42/141(30%) only attended enrolment and didn't attend month 12 and month 24 and 32/141 (22%) used DMPA through all 3 visits(enrolment, month 12 and month 24). The following 18 contraception changes took place in those that were using DMPA at enrolment: 20/141 (14%) used DMPA at enrolment and month 12 and didn't attend month 24, 2/141 (1%) used DMPA at enrolment and month 12 then changed to NET-EN at month 24, 4/141 (3%) used DMPA at enrolment and month12 and changed to non-hormonal at month 24, 8/141 (6%) used DMPA at enrolment, didn't not attend moth 12, then used DMPA at month 24, 3/141(2%) used DMPA at enrolment, did not attend month 12 then changed to non-hormonal methods at month 24, 1/141(1%) used DMPA at enrolment, non-hormonal method at month 12, then changed to other (either oral contraceptives or implant) at month 24, 3/141(2%) used DMPA at enrolment, changed to non-hormonal methods at month 12 then changed to DMPA at month 24, 2/141 (1%) used DMPA at enrolment, changed to no-hormonal methods at month 12 , then didn't attend month 24, 7/141(5%) used DMPA at enrolment, then used non- hormonal methods at month 12 and month 24, 2/141(1%) used DMPA at enrolment, changed to NET-EN at month 12 and didn't attend month 24, 1/141(1%) used DMPA at enrolment, changed to NET-EN at month 12 then changed to other at month 24, 4/141(3%) used DMPA at enrolment and used NET-EN at month 12 and month 24, 2/141(1%) used DMPA at enrolment, changed to non-

hormonal at month 12 then used NET-EN at month 24, 1/141(1%) used DMPA at enrolment, NET-EN at month 12 then non-hormonal contraception at month 24, 2/141(1%) used DMPA at enrolment, didn't attend month 12 then used NET-EN at month 24, 2/141(1%) used DMPA at enrolment, changed to other at month 12, then changed to NET-EN at month 24, 1/141(1%) used DMPA at enrolment, didn't attend month 12 then changed to other at month 24, 2/141(1%) used DMPA at enrolment and used other at month 12 and month 24. These multiple changes are illustrated below in the swimmer's plot (Figure 3.9)

Figure 3. 9 A swimmer's plot illustrating changes contraceptive method at enrolment, month 12 and month 24. Participants were either using DMPA, NET, Non-hormonal or other (Other only exists at month 12 and month 24 as it represents participants that changed to either implant or oral contraceptives)

Different contraceptives were at use at different visits these are illustrated as follows:



Timeline of follow up was enrolment, month 12 and month 24

Chapter 4 Discussion, recommendations, conclusions

4.1 Discussion

4.1.1 Overall results

While we were not able to show a statistically significant increase in risk in any of the curable STIs (CT, GC, TV, MG) in AGYW aged 16-24 years in Johannesburg using progestin-based IC and NH contraception, we did show a trend to increased CT, possibly MG and decreased GC and TV, consistent with previously reported trends in other studies. These associations strengthened after adjusting for sexual behaviour. We attempted to explore the relationship with incident infection, but this proved challenging given frequent contraceptive switching.

We observed a high prevalence and incidence of curable STIs in this population of AGYW seeking contraceptive services. In our cohort, MG baseline prevalence was higher than GC and TV baseline prevalences, making MG a noteworthy infection that needs further investigation and management. Several factors other than IC were found to be associated with an increased risk for STIs that highlight the need for additional preventive interventions for STIs.

4.1.2 IC and STI

For CT our results follow the general trend of CT prevalence in women aged 15-49, in a recent metanalysis reporting on the association between STI and hormonal contraception (unspecified hormonal contraception, progesterone only and combined oral contraceptives) (reES 1.58, 95% CI, 1.19–2.08) (33). This metanalysis utilised three cross sectional studies and two prospective cohorts for CT prevalence calculation (33). Three of these contained association measures for IC specifically and CT at enrolment. These three reported: an increased risk for CT in South African women that was significant (aOR 2.46, 95%CI, 1.52– 3.97) (33,91), a decreased risk that is not significant in South African women (OR 0.97, 95% CI 0.60- 1.57) (169) and increased risk in Rwandan women who sell sex that is not significant (aOR 1.96, 95%CI 0.59-6.57). We potentially did not see the same significance as the metanalysis (33) due to not being inadequately powered for this analysis. The associations between infections and hormonal contraception did strengthen when we adjusted for sexual behavioural risks, but we could not eliminate all residual confounding associated with sexual behaviour.

For MG in NET-EN there was increased risk, whilst with DMPA there was decreased risk of infections. As an emerging important pathogen, we could not find any studies that look specifically at the association between MG and contraception. The use of progestin IC in women is normally associated with hypoestrogenic state, vaginal dysbiosis and bacterial vaginosis which increase the risk for MG (170). Based on these hypothetical reasons, the expectation was for an increased risk of infection for MG in both DMPA and NET-EN. Dabee

et al compared vaginal microbiota and genital cytokine changes using samples of 53 women from the ECHO trial (171) for DMPA use and 44 women from the UChoose trial (172) for NET-EN use. Although they did report more unstable vaginal microbiota and an increase in certain BV- associated microbiota in DMPA compared to NET-EN the differences were not significant (173). They also reported differences in cytokine changes that were non-significant even though there were trends of different specific cytokines being elevated or reduced between the two IC (173). Dabee et al was powered to detect a 2.45 fold or larger difference between the IC users, which may have missed smaller differences (173). Based on Dabee et al's analysis there is biological plausibility as to why we saw differences in associations between MG and NET -EN and MG and DMPA.

For GC both NET-EN and DMPA were associated with reduced risk of infections that was not significant. In contrast to our findings, Borgdorff et al in a cross sectional study of Rwandan women aged 18-49 that sell sex, reported increased prevalence risk (aOR 1.13, 95%CI, 0.47-2.77) in IC users, although not significant (29). The reduced risk we reported is similar to a metanalysis of women aged 15-49 that reported reduced GC prevalence for hormonal contraceptives (combined oral contraceptives, progesterone only and unspecified hormonal contraception) that was not significant compared to non-hormonal contraception (reES0.75; 95% CI 0.39–1.45) (33). This metanalysis utilised two prospective cohort studies, two cross sectional cohorts and one longitudinal cohort for GC prevalence calculation (33). Of the studies used by Akter et al (33), three had reported on associations between IC specifically and GC prevalence: Wand et al (91,174)reported increased risk for IC users (aOR 1.31, 95%CI 0.69-2.50), Borgdorff et al (29) reported increased risk as mentioned above, and Kleinschmidt et al (169) also reported increased risk in IC users (OR 1.37, 95%CI, 0.56-3.37). We presume we did not report significant results due to a smaller number of GC reported in this cohort, which may have affected the powering of the study. In a larger cohort we might potentially be able to detect significant results. For GC, use of hormonal contraception could lead to reduced risk of infection. This is because hormonal contraception use may lead to reduced menstrual flow. In turn reduced menstrual flow reduces sources for iron which is an essential component for GC growth intracellularly and extracellularly (162). Potentially this is why we were able to report a protective association with IC though it was not significant.

For TV, NET-EN and DMPA were associated with reduced risk of infection that was not significant. This cohort's results are also in support of a metanalyses in women aged 15-49 that reported non-significant reduction in prevalence of TV (feES = 0.76; 95% CI 0.58–1.00) (33).

This metanalysis included three cross-sectional studies, three prospective cohorts, and one case control study for TV prevalence analysis (33). Of these studies, three reported on the association between TV prevalence and IC specifically: Kleinschimdt et al (169) reported reduced risk for TV (OR 0.78, 95%CI 0.41-1.48) in South African women, Borgdorff et al (29)reported reduced risk as well that was not significant (aOR 0.77-0.32-1.83) in women in Rwanda who sell sex, Ngcapu (175) reported unchanged risk (OR 1.00, 95%CI, 0.41-2.43) in women in South Africa. As our data seems to follow the general trend of the metanalysis mentioned above yet the association remains insignificant, we believe this small number if TV may have affected the powering of the study in association with TV. A larger cohort may be essential in future trials. TV has estrogenic and androgen receptors. Potentially the high content of progestin in DMPA may block androgen receptors because androgen receptors are closely related to progestin receptors. This would prevent TV infection (82,163).

Using the equation Ro = BxcxD (26,27)we explored the effect of progestin-based IC on the transmission efficiency of STI, thereby affecting "B". "B" is the transmission efficiency of the organism. For CT, we did see an increase in transmission efficacy in both DMPA and NET-EN user, this increase was not statistically significant. For MG, we saw increased transmission efficiency in NET-EN users and a decrease in DMPA although these were not statistically significant. For both GC and TV we saw decreased transmission efficiency of GC and TV in both DMPA and NET-EN users. This reduced transmission efficiency was not significant.

4.1.3 Sexual behaviour and STI

As all four infections have different pathophysiology, for any STI we looked more at the sociodemographic features that would predict infection instead of an association with IC. Having more than one sex partner in the last 3 months, receiving financial support and/or material support from main sex partner, and having two or more sex partners other than main sex partner had increased risk for any STI by 60-80%. This is in line with other studies that have reported financial vulnerability and multiple sexual partners as risk factors for STI (58,176,177). This is also in line with the equation on STI transmission and epidemics: Ro = BxcxD (26,27) as a formula to sexual transmitted infection reproduction in a population (26,27) The reproduction rate of STIs (Ro) was increased by having more than one sexual partner in the last 3 months and by having multiple sexual partners (26,27). The number of sexual partners affect "c" in the equation (which is the rate of is sex partner change) as reported in this cohort, thereby increasing the rate in infections in the study. This also applies to CT, MG which are discussed below.

In the analysis for CT, having two or more sexual partners other than the main sexual partner in the last 3 months had an almost two-fold increased risk for CT in this cohort. Being younger: 18-25 years old, being single, previous CT, having two or sexual partners and earlier sexual debut have been associated with increased risk for CT in other studies (63,154,155). Armstrong-Mensah et al, also reported condomless sex, transactional sex and lower educational attainment as risk factors for CT in Sub-Saharan African women . These were not significantly associated with CT in this cohort. Other risk factors for CT that have been reported are sexual partners that have other sex partners, condomless sex in non-monogamous relationships, transactional sex (154). In our cohort these also were not significantly associated with CT.

For MG, having more than one sexual partner in the last 3 months had a twofold increased risk for MG and transactional sex had an almost three-fold increased odds for MG in our cohort. These factors are similar to those identified in other studies for MG which were, increased number of sex partners (156–158), and new sexual partners (157,158).

For GC, living with main sex partner was associated with a threefold increased risk for GC and receiving financial support from the main partner was associated with a threefold increased risk for GC in our cohort. Living with a sexual partner may heighten the susceptibility to infection, both through potential reinfection and heightened exposure resulting from unprotected intercourse. Receiving financial assistance was linked to an elevated risk, possibly stemming from financial vulnerability. Financial instability, limited income, low socioeconomic status, and poverty serve as factors predisposing individuals to engage in transactional sex, have multiple partners, and engage with high-risk partners (159,160). A model developed in the USA by Ibragimov et al, found a minimum wage increase of $1 would lead to a 7.5% reduction in GC infections in women (9.7 cases fewer per 100 000 women) (139). Other studies have reported alcohol use, a higher number of sex partners and younger women as risk factors for GC (63,161). These where not significantly associated with GC in this cohort.

Our analysis found that individuals who had engaged in vaginal or anal sex within the past three months were less likely to have TV. Looking at TV outcomes table, we didn't not see any behavioural differences between those that had TV and those that did not. This could be potentially these participants had TV infection that was cleared or treated elsewhere. In some cohorts it has been noted that some people have who have higher risk behaviours e.g. sex workers are known to share medication (186)and so potentially the AGYW could have illicit access antibiotics like metronidazole. We also speculate that this analysis may has have been affected by desirability bias when participants were reporting on sexual behaviours. The reason

for this protective effect we noted in this cohort is unclear and requires further investigation in a larger study specifically powered to detect prevalence and incidence for TV. We were not sufficiently powered for TV. Other risk factors that have been reported as risk factors for TV are co-infection with BV or other STI, drug use, lower education attainment, lower socio-economic status and condomless sex (85,153). In this cohort we did not analyse some of these factors (co infection with BV, lower socio-economic status) and some (lower educational attainment, condomless sex, drug use) were not significantly associated with TV.

As shown in Table 1, a higher proportion of individuals using NH reported using condoms during their last sexual encounter (p=0.001) compared to NET-EN and DMPA. This may have contributed to the lower STI prevalence observed in the NH group, despite having a higher number of sexual partners in the past three months (p=0.043). NET-EN users had a higher STI prevalence than non-hormonal users, potentially due to the younger age of NET-EN users (16-19 years old) compared to DMPA and non-hormonal users. Younger participants are often associated with riskier sexual behaviours and a higher likelihood of acquiring STIs.

4.1.4 STI point prevalence and incidence

A high baseline prevalence of STI was noted in this cohort. These baseline prevalence rates were similar to prevalence rates that was reported in AGYW in the Western Cape, South Africa, with CT prevalence rate at 33.7%, NG prevalence rate at 10.4% (80) and in 15-24 year olds in a Sub-Saharan metanalysis for STIs with CT prevalence of 15.1%, GC prevalence of 4.6% and TV prevalence of 7.9% (71).

The incidence rate of infections within our cohort was lower compared to rates reported in other studies conducted locally. Harryparsad et al. documented a higher incidence, reporting an STI incidence of 107.9 per 100 women per year for all women, and a CT incidence of 75.9 per 100 women per year for AGYW aged 18-21 years, along with an NG incidence of 8.4 per 100 women for all women in eThekwini and Tshwane, South Africa (75). The higher incidence of CT and NG reported in Harryparsad et al (75), could be due to contraceptive methods (injectable, intrauterine and implantable devices) that were under observation in that study. Users of long-acting contraception such as intrauterine and implantable device used in Harryparsad et al (75), tend to have higher rates of condomless sex, increasing the risk for acquiring STI, therefore increasing STI incidence. In 16-25year olds in Zimbabwe and South Africa in the HPTN 082 trial, higher incidence rates of STI were also reported (CT incidence was 27.8/100 person/year, GC incidence was 11.4/100 person/year, and TV incidence was

6.7/00 person/year) (59). Jongen et al also reported higher STI incidence in young women in the Western Cape South Africa, CT incidence of 42.4 per 100 person-years, NG incidence of 20.8 per 100 person-year (80). The low incidence rate we reported in our cohort could also be to the long follow up period between baseline testing and testing at month12 and month 24, we potentially underestimated the incidence of STI as AGYW could have been diagnosed and treated or treated without diagnosis due to the use of antibiotics for a different indication. Compared to services obtained in a local clinic, we believe participants received quality comprehensive sexual reproductive health services during the trial which could potentially have been another reason for reduced incidence. Although this may have reduced the incidence of STI, the risk reduction counselling offered did not totally eliminate the risk of reinfection.

We faced challenges in managing the high rates of contraception switching between visits which led to limitations in the analysis plan. The initial protocol plan had been to check for the association between IC and incident infections. The level of analysis that would be required due to the contraceptive switching, was beyond the scope of what could be included in this Master's report. However, this analysis is ongoing.

Visits attended and STI

We assessed the sociodemographic characteristics of AGYW who attended subsequent visits to assess if dropping out affected subsequent STI risk. Only three characteristics were statistically significant, which were: experienced forced sex or sexual act in the previous year, experienced more suicidal symptoms in the past year and ever having used ever having used illicit substance. AGYW who attended one follow up visit after the enrolment had significantly higher forced sex/ sexual act experiences in the past year than those that attended enrolment only. Forced sex directly or indirectly is associated with increased risk for STI (187,188). We had expected to see high prevalences at month 12 and month 24, but that is not what we observed. Our expectations were founded on a trial that reported that in AGYW aged 12-21-years, those who had a history of experiencing forced sex were associated with risky sexual behaviours (earlier sexual debut, use of drugs at their last sexual encounter, greater number of lifetime sexual partners) which increased the odds of STI (163). In these 12–21-year-olds, forced sex was also independently associated with increased odds for history of an STI (163).

Experiencing suicidal symptoms was significantly increased in participants that had one more follow up besides the enrolment visit compared to only those that attended the enrolment visit. Based on that observation, we had have expected to see high STI prevalence at month 12 and month 24 as suicidal symptoms have been demonstrated in AYP to be associated with risky

sexual behaviour such as increased sexual partners (164,165),and inconsistent condom use(165).

Ever having used illicit substance was significantly higher in the participants that attend the enrolment visit alone compared to one other follow up visit beside enrolment. This characteristic is possibly why we only saw a higher prevalence of STI at enrolment compared to month 12 and month 24. Illicit substance use has been associated with STI acquisition in AGYW (163,166).

The analysis in Table 3.4 indicates that the large number of participants who attended enrolment but were lost to follow-up may have influenced the observed STI incidence. While these participants reported lower rates of forced sex, sexual assault, and suicidal ideation (potential risk factors for STIs), they also had significantly higher rates of illicit substance use (another risk factor). It's uncertain whether the potential decrease in STI risk due to the lower rates of forced sex, assault, and suicidal ideation would have outweighed the potential increase in risk due to illicit substance use if these participants had completed follow-up visits. The rates of contraception change and discontinuation we witnessed was like other cohorts of adolescent contraceptive users (192) It is also important that this age group is a highly mobile population especially for school and tertiary education

Though incidence in this study is lower than other cohorts, the values still highlight the possibility of reinfection and lack of control on partner/s treatment. Different risk factors were independently associated with each infection which points strongly to partner factors being important for increased risk. Overall, having more than one sex partner in the last three months, receiving financial support and/or material support from main sex partner, and having two or more sex partners other than main sex partner increased risk for any STI by 60-80%. Current standard of care relies on the index participant notifying their partner/s of an STI diagnosis. Using partner notification as a public health measure to reduce STI incidence is not ideal as there are multiple barriers to notifying partners and barriers for partners accessing care. These barriers include opportunity costs to accessing care, stigma, shame and discrimination, fear of interpersonal violence, fear of infidelity accusations, poor mental health and health system barriers such as health worker attitudes, clinic hours etc (167–169). Furthermore, young people are known to less likely notify their partners compared to older individuals (195). As demonstrated in Durban and Soweto in a study on AYP partner notification during 2015-2016. Only 86,7% AGYW reported notifying their partners. Of these 86,7% only, 38% reported partner treatment (169).This study reported greatest attrition in the STI cascade (first step being

diagnoses and treatment 2nd step completing STI treatment, 3rd step notifying partner, 4 step reporting partner treatment) to be at partner notification and partner treatment (169). Partner notification and treatment approaches need to be prioritised in AGYW to reduce STI incidence

4.1.5 Limitations of the study

This study involved a secondary data analysis of an existing cohort, which imposed certain limitations on the available data. The reported incidence rates may have underestimated the true values due to longer intervals between follow-ups, particularly between months 12 and 24, during which participants may have experienced STI episodes and sought treatment. We only analyzed samples that were collected at 12 and 24 months but participants had attended the clinic more frequently than that and had received contraception at those visits. Shorter testing intervals would have been more ideal. A potential mitigation strategy could have involved testing archived vaginal swabs collected every 2-3 months, though this would have required additional funding.

Although adjustments were made for sexual behaviors, residual confounding still likely affected the association between IC use and STI prevalence. The analysis was also impacted by a significant number of participants being lost to follow-up or attending only one of the two time points, which potentially led to an underrepresentation of incident infections. Understanding the reasons for loss to follow-up, especially if related to contraception use or STI outcomes, would have been beneficial, this data we did have but didn't include in this analysis as we tried to stick to the objectives of this MPH

Frequent switching between contraception methods during the follow-up period complicated the analysis of the association between injectable contraception (IC) and sexually transmitted infections (STIs), making it beyond the scope of this report. Contraception status was derived from a contraception card, which limited our ability to capture recent switches between methods or the duration since those changes occurred. This lack of a "wash-out" period may have weakened the analysis. As we were able to document large numbers of switches, this a common challenge in contraceptive studies and sophisticated methods outside the scope of this Masters study like marginal structural models could have accounted for this in the analysis. Ideally, a sub-analysis could have been conducted among participants who did not switch methods or who switched to similar contraceptive methods (e.g., DMPA to NET-EN and vice versa), but these participants were few. Furthermore, the analysis we did that showed survival analysis curves for STI based on baseline contraception had limitations as at incident infections most participants had changed contraceptive method. The baseline status was not appropriate to use as a large proportion of participants switched contraceptive method at follow up. We could have

potentially accounted or that by doing an analysis that would censor the contraception switchers. But those the numbers of those participants were small.

While intrauterine contraceptive devices (IUCDs) and condoms are both non-hormonal methods, they have different mechanisms of action. Although combined into a single category for analysis due to no significant socio-demographic differences, this might have limited the interpretation of the findings. They both contain no hormones but users might have differed in their demographic or sexual behavior characteristics. We assessed this and did not observe significant differences. We combined these two based on the practice observed in other studies similar studies. At the time hormonal IUCD were not available in the public sector and were not observed. Nevertheless, it is possible that there were unmeasured factors that made this group heterogeneous thus undermining comparisons with the non-hormonal contraception group.

Given that this study was recruiting individuals based on their contraceptive exposure, it was appropriate to recruit them from health care facilities since the question of interest was the influence of contraceptive use on STIs. The participants in this study are individuals from the local community. They are generalizable insofar as they reflect young women attending primary health clinic services in South Africa using contraception but may not represent all AGYW including those that do not live in urban areas or that are not sexually active or use contraception. Nevertheless, they provide insight into the potential mechanisms or associations between contraceptive use and STI risk. Finally, there were differences in the characteristics of those who returned for follow-up visits, which were not differentiated by baseline exposure status, adding another layer of limitation to the analysis.

4.1.6 Future studies recommendations

A large prospective randomised controlled study would be essential to study the associations between STI and hormonal contraception with fewer limitations. The ECHO trial was a multicentre (eSwatini, South Africa, Zambia and Kenya), randomised open label trial that enrolled sexually active 16–35-year-old women, HIV negative, not pregnant women, seeking contraception which were randomised to either DMPA, or IUD, and levonorgestrel implant (170). The ECHO trial was primarily interested in the association between IC and HIV risk. However, a secondary analysis explored HSV, CT and NG outcomes (170,171). The ECHO trial reported significantly lower risk for final visit CT prevalence in DMPA continuous use compared to levonorgestrel implant group (PR 0.77, 95% CI, 0.66 -0.89). The reduced risk for final visit CT prevalence was not significant for DMPA continuous use versus IUCD use (PR

0.86, 95%CI, 0.74-1.01). For GC, there was also reduced final visit GC prevalence that was not significant in DMPA continuous use compared to levonorgestrel implant (PR 0.75, 95%CI 0.56-1.02), but significantly reduced risk was reported in final visit GC prevalence for DMPA continuous use compared to IUD (PR 0.67, 95%CI 0.49-0.90) (171). The strengths of the ECHO trial included randomisation to contraceptive method, and a large proportion of participants sticking to randomised contraceptive method (148,171). This study did not report the specific associations we wanted to establish as they looked at CT/GC prevalence associations at last study visit and not specifically looking into incidence of STIs (171).

To more comprehensively address the current study question, a similar large, prospective randomized controlled trial would be required. Participants would be randomised to a contraceptive method (non-hormonal group vs hormonal group). The non-hormonal group would be copper intra-uterine device and the hormonal group would be DMPA and NET-EN to reduce bias associated with contraceptive method choice. It would not be ethical to have participants assigned to no contraceptive method. Participants would be screened and counselled at enrolment to reduce the likelihood of contraceptive switching. Ideally the participants would use that contraceptive method for the period of the trial, as the switching between methods affects exposure classification and influences the physiology of the participants. Sample size will be calculated with assumption of 5-10% of participants per contraceptive method changing contraceptive during the follow up period. Participants selected for the trial should ideally all be of similar sexual behavioural characteristics i.e. recruiting high risk participants using a specific criterion [e.g. 1. multiple sexual partners 2. treated for STI in the past year (12 months), 3. new sexual partner in the past 3 months] to reduce confounding effects of different sexual behavioural characteristics.

4.2 Public Health Recommendations

4.2.1 Health systems interventions

Strengthening sexual and reproductive health services for adolescents

AGYW remain a vulnerable and high-risk group for STI acquisition globally and locally (5,71,75). It is important to note that AGYW that are seeking contraceptive services should be targeted for STI prevention, diagnosis, and treatment as they have already made an effort to seek out a health facility. Services offered to AGYW as part of the package in family planning should include risk reduction counselling and provision of condoms to facilitate dual protection. Modern contraception use should continue being advocated for and facilitated for in AGYW, as its use it associated with increased educational attainment, socio-economic achievement as well as reduction in mortality and morbidity (11,124,125). Long acting reversible contraception

(LARC) is especially important and should be advocated for in AGYW as LARC is discrete, cost effective, has few contraindications, needs few interactions with health facilities, has less opportunity costs of accessing care and there is a quick return to fertility when no longer in use (198,199).

Current efforts to manage STI in AGYW are hampered by the large proportion of infected individuals being asymptomatic, symptomatic ones facing barriers to accessing healthcare, poor sensitivity and specificity associated with syndromic management, rising antibiotic resistance, re-infection and lack of partner notification and treatment (14,16,70,116,118,119,200,201). There is need for a different approach to symptomatic and asymptomatic treatment of STI in AGYW. Symptomatic AGYW would need aetiological treatment whilst asymptomatic AGYW would need detection of the STI first before aetiological treatment. These are discussed in further detail below.

Introduction of STI testing into primary health care services

The American Academy of Paediatrics and the Centres for Disease Control and Prevention (CDC) recommend yearly STI diagnostic testing for sexually active AYP (176,177) to ensure early detection, early treatment and reduced transmission of STIs. One in five AGYW in the IC and NH groups had CT in our cohort at enrolment. Similar high rates of CT and other STI have been reported in other studies in AGYW in South Africa e.g. Cape Town (80) and in Sub-Saharan Africa (71) highlighting the need for a different approach to STI management in AGYW. We advocate for diagnostic testing in South Africa for every sexually active AGYW (at a frequency to be determined based on empiric data and modelling studies but potentially once a year), especially those seeking contraception, to tackle the high prevalence and incidence of STI reported in AGYW in South Africa. We are advocating for a change from syndromic management because syndromic management does not support antibiotic stewardship in an era of rising AMR (118,119), has poor specificity and sensitivity for STIs (116), leads to overtreatment, under treatment and missed treatment (117), excludes asymptomatic individuals which leads to health risks and costs associated with STI complications.

The current South African national strategy to diagnose and treat STIs is syndromic management (114). The best approach would be diagnostic laboratory testing of all sexually active AGYW and their partners. Symptomatic AGYW would get diagnostic testing at the time of symptoms, whilst sexually active AGYW that are not symptomatic would get diagnostic testing at a frequency to be determined based on empiric data and modelling studies (potentially once a year) (176,177). This would enable accurate diagnosis and treatment of both

asymptomatic and symptomatic individuals, reducing the duration of infections in the society and the transmission efficiency of STIs. Currently laboratory diagnosis of STI is not offered in standard of care due to

1. Increased laboratory cost (specialised testing equipment, laboratory facilities, trained technicians) (178).
2. Time associated factors (time to run the tests, time to receiving the test results, time associated opportunity costs for patients when they have to return for results and treatment (178).
3. A change from syndromic management to diagnostic approach would need revisions of polices and Standard Operating Procedures (SOPs) (178).

There would also be significant costs associated with implementation of laboratory diagnostic testing for STI. As resource limited countries are fighting multiple infectious disease epidemics and non-infectious disease epidemics, LMIC cannot afford setting up laboratory diagnosis approaches in their countries in an equitable way for the public health sector. There is therefore a need to overcome barriers associated with diagnostic testing as syndromic management will not ensure control of STIs in AYP. Laboratory diagnostic testing remains a priority as it identifies the specific organisms, identifies asymptomatic infections (especially for at risk population like individuals who sell sex, AYP, etc), allows for rational use of antibiotics, and also allows for easier national surveillance (179). Testing time can be reduced by employing newer technologies like Cepheid's 90-minute GeneXpert® Nucleic Acid Amplification Test (NAAT) for CT and NG (180), thereby expediting the testing process and enabling individuals to receive results on the same day at the clinic. This approach minimizes the necessity for result follow-ups and ensures prompt treatment administration on the same day. The requirement for complex laboratory equipment, infrastructure, and specialized personnel in this case is alleviated to some extent by this innovative testing technology which is characterized by high sensitivity and specificity. Other novel technologies with less infrastructure and human resources needs include fluorescence-based detection for GC (181), developed by FIND, and Cepheid's GeneXpert® NAAT testing for CT and NG (180). These novel technologies will still need to be assessed for cost-effectiveness. The need for prescribing etiological treatment can be addressed through policy and SOP changes. As it stands in South Africa, the needed antibiotics: doxycycline, azithromycin, ceftriaxone and metronidazole are included in the primary health care essential medicines list (182), there is no need for new polices and SOP to allow nurses to dispense antibiotics in the primary health facilities.

A viable alternative to optimise diagnostic testing that we are proposing is Point-of-care (POC) testing and treatment for all sexually active AGYW that encounter any health facility (local clinics, youth friendly clinics, hospitals, etc). A currently available test that could fulfil this purpose is Cepheid's 90 mins GeneXpert® Nucleic Acid Amplification Test (NAAT) for CT and NG using urine samples. It has proven to have more than 95% sensitivity and specificity for CT/NG testing using vaginal swabs, endocervical swabs and urine samples (180). For TV testing we propose implementation of Cepheid's 40 minutes GeneXpert® TV assay which has sensitivity and specificity of more than 95% (183) or OSOM Rapid POC TV Antigen Test with specificity more than 95% and sensitivity ranging 83%-90% (184). All these can be run in a clinic at a cheaper cost and do not need extensive elaborate laboratory infrastructure and personnel when compared to standard laboratory testing. There are other POC for STI covered in a metanalysis by de Cortina et al (185) and a review by Gaydos et al (184) , that we didn't not select due to pending approval from the Food and Drug administration. Cepheid's GeneXpert® test for CT/NG was successfully used in women aged 18-40 in KwaZulu-Natal, South Africa by a laboratory technologist at the clinic laboratory, who had experience in using the GeneXpert platform (186) and in 15–23-year-olds in Cape Town, South Africa, were clinical staff were was trained on operating the GeneXpert® platform (213). GeneXpert® TV assay was utilised in 430 pregnant women in Tshwane South Africa, where one study staff who had undergone a 7 hour training for the GeneXpert system on how to operate, maintain, and troubleshoot the system did the testing (188). OSOM Rapid test has also been evaluated in 18–40-year-olds in KwaZulu-Natal, with the testing conducted by a nurse (186). As AGYW remain the target group for our interventions, offering POC testing to AGYW who encounter health facilities seeking contraception (including once yearly for asymptomatic AGYW) would enable aetiological treatment and diagnosis of symptomatic and asymptomatic STIs. Offering POC will reduce transmission, incident infection in partners and STI sequalae. POC provides quick, same date testing and treatment, reducing the likelihood of undertreatment, miss-diagnosis, and the need for follow up for treatment. We found reviews on proving the cost effectiveness of STI POC in LMIC, in other populations that are not AGYW such as in pregnant women (215) , paediatrics populations (190) and general adult populations (191,192). POC testing and treating for CT and syphilis was demonstrated to be cost effective in a systematic review of STIs in LMIC pregnant women when compared to no screening of women, laboratory-based testing of women and/or syndromic management, with cost difference ranging between 19% - 170 % when POC was compared to the comparator (189). POC for STI in LMIC has also been proven to be cost effective in Paediatric HIV diagnosis (190),and in CD4

monitoring POC in adults (191,192). Even though there have been cost effectiveness studies done in other populations, POC have not been implemented in those populations potentially due to missing budget impact analyses which should happen alongside economic evaluations to ensure adoption of POCs. We believe POC testing and treatment for STI in AGYW could potentially be cost effective in LMIC. In a study conducted in Cape Town of 15–23-year-olds, the cost of syndromic management vs aetiological management with POC (Cepheid's 90 minutes GeneXpert® for CT/NG) at clinic site vs aetiological management with lab testing (Cepheid's 90 minutes GeneXpert® for CT/NG) was studied. Syndromic management cost USD $16 .01 per patient, whilst POC with aetiological treatment cost USD $ 55.70 at site and aetiological treatment with laboratory testing costing USD$ 28.84 (213). Although this study reported high cost of treatment for POC it is important to note that this is not a cost effectiveness study. We are aware there is need for cost-effective analysis and budget impact analysis for the POC tests we have proposed. We presume, POC will be cost effective and money efficient in South Africa once set up costs and training costs have been covered as predicted by modelling in high income countries (193,194). We are also aware of potential pitfalls that will be associated with POC implementation such as acquisition of laboratory equipment and human resources at primary health care facilities, changes in clinic flow and clinic logistics, ensuring quality control of testing processes to avoid contamination, linking POC tests to current national surveillance reporting, maintenance of cloud systems and electronic records associated with some testing machines (184). We also presume there may be other implementation pitfalls such as AGYW not willing to wait for 90 minutes or more, staff feeling overwhelmed and overworked, staff needing training, the need for new polices and SOPs and the need for piloting and funding on a strained health budget. Answers to these questions could be addressed through well-designed implementation studies.

Interventions to address barriers to health access by adolescents

One of the ways STI services are being offered to AGYW currently is through a limited number of youth friendly clinics. As nations moved towards establishing safe spaces for AYP in the form of youth friendly clinics, the South Africa government quickly established these clinics through the National Adolescent-Friendly Clinic Initiative (NAFCI) which was part of the national HIV prevention campaign (195–199). LoveLife, a non-governmental organisation (NGO) in collaboration with Department of Health (DOH) ran NAFCI services between 1999 and 2006 (197). In 2006 DOH took over running NAFCI, under the Youth Friendly Services (YFS) programme (197). DOH is still supported by loveLife and other NGOs in certain aspects of the YFS (197). These YFS clinics specifically cater for adolescent and young people as their

only clients. Although the number of YFS clinics and services offered by YFS has increased, these clinics and services are still lagging behind in certain DOH youth friendly services indicators (200). AYP report challenges with accessing care, staff shortage, staff beliefs and attitude, medication shortages, poor service, unfriendly staff, long waiting times, lack of privacy and confidentiality (197,198,201–205). Equitable coverage of YFS clinics remains unclear as it is not clear how many have been established within each province and district. These implementation and operation barriers hinder the purpose that YFS clinic were established for, which was easy access to healthcare and social support for AYP. YFS clinics are ideal for reaching AGYW and ensuring screening, testing and treatment for STIs. When functioning ideally, AYFS provide safe, stigma-free, friendly, accessible health care with short waiting time, reduced barriers to accessing care and youth friendly health care workers (195,205–207). To add on, when functioning well YFS clinics can also be the centre of sexual reproductive health literacy, STI and HIV testing, treatment, support groups etc (197,198,207). When functioning well, adequately trained youth friendly staff, can offer peer influencers support, mentoring and support peer led activities (207). Adequately trained staff can also support group activities such as support groups (207).

Another way that STI services are supposed to be offered to AYP currently is through Youth Zones (YZ). In clinics that are not in proximity with a YFS clinic, YZ were part of the National Department of Health youth policy to ensure there were still YFS available in those communities. YZ were created with the goal to increase access to sexual and reproductive health services as well other health needs for AYP (208). The extent of implementation of these youth zones in primary health facilities remains unclear. Lack of implementation of YZ in communities without YFS clinics is a missed opportunity to reach AGYW who need diagnosis, treatment, and peer support.

There is a need to reassess the functionality of YFS clinics and YZ to optimize these existing channels of health care to reach AGYW more frequently and constantly for the current services they are offering and for more in the form of sexual reproductive health services.

We propose optimisation of the AYFS to ensure more AGYW are reached for sexual and reproductive health (SRH) services. Other researchers such as Smith et al, advocate for physical YFS or creating of youth zones based on qualitative information provided by AYP stating the need for space dedicated to youth where they can receive services without shame and judgement (198,200). To increase access to YFS in Malawi, Population Services International (PSI) helped set up 69 physical clinics named Tunza Family Heath Network which led to a five year trend

rise in AGYW aged 15-24 who sought family planning in these clinics (209). In western Kenya in a bid to increase uptake of HIV testing and linkage to care in AYP, an intervention of extended YFS clinic hours, the use of adolescent friendly screening tools, monitoring and evaluation tools and healthcare worker training was implemented (210). Clinic hours were extended to 5pm-7pm on weekdays and opened on Saturdays and Saturdays. The intervention led to increased AYP accessing care and testing for HIV (almost triple the amount before the intervention with the greatest rise being among AGYW) and being linked to antiretroviral therapy (ART) treatment (210). In Malawi in a quasi-experimental trial of AGYW attending a clinic that had created YZ – like space and time as well as with an appropriately trained health worker, it was noticed the attendants of the clinic received more sexual reproductive health services compared to those that attended the standard of care clinic (211). These implementation projects demonstrate in increase in uptake and access of sexual reproductive health services by AYP and AGYW due to increased YZ and YFS clinics. We propose that at each of the 3 141 public primary health care facilities in South Africa (212), should have a functional YZ or YFS clinic using the above-mentioned suggestions to create space or time for it. We also propose YZ or YFS clinics should be affiliated with peer educators and influencers [such as "groundbreakers" from loveLife (213)] that can assist with coaching and mentoring of their peers as part of sexual behavioural interventions. In the Yathu-Yathu intervention for 15-24 AYP in Zambia Lusaka, the arm with peer educators attached to hubs where AYP could access comprehensive sexual health services saw increased health literacy in HIV and PrEP and increased HIV testing (214).

South Africa already has a framework for AYFS and has implemented portions of it, however there is still more work needed to ensure full implementation, monitoring and evaluation so as to optimise YFS to have a larger reach and to create youth friendly spaces that AGYW access willingly and as frequently as possible. In Kenya as part of monitoring and evaluation of two clinics that offered services in AYP, continuous quality improvement (CQI) intervention also led to an increase in health literacy about HIV for AYP and an increased intent to retest for HIV yearly in one of the clinics for AYP due to improved services offered by health care workers (215),

Once AGYW attend YFS for contraception and other services, they can be offered testing and diagnosis (comprehensive sexual reproductive health). Task shifting would need to be implemented between different calibres of nurses as well as the use of other healthcare calibres such as community health workers (CHW) to help support the nurses currently providing services in YZ and YFS clinics. All staff would also need to be fully trained, mentored, and

supported for capacity building in dealing AYP. As evidenced in Malawi, PSI trained health care workers and provided guidelines to assist in creating YFS services in the Tunza clinics, this led to an increase in AGYW attending Tunza clinics, the most increase in AGYW attending the clinic coincided a period of training or soon after training sessions (209), AYP mentioned staff at Tunza that had been trained where private and confidential, fast, respectful, which made services acceptable to the AYP (209). Optimised AYFS allow for easy access to healthcare, comprehensive sexual reproductive health and safe spaces for AYP.

Schools-based interventions to address barriers to health access

Besides universities and colleges, schools are another place that health care workers can reach a large number of AYP at any point in time. School health programmes have an opportunity to impact large numbers of AYP by offering comprehensive sexual education and comprehensive sexual reproductive health services.

In the Eastern Cape, in 6th graders, an intervention in 34 schools (17 school in the intervention arm and 17 schools as controls) was designed and delivered over two days where they were exposed to games, discussions, role playing, video watching, storylines and comic workbooks (216). These were aimed at HIV/STI risk reduction, increased decision making skills and self-efficacy, health promotion, healthier eating and exercising, habits reducing risky sexual behaviours (216). The intervention also included parent collaboration through discussions and homework (216). The students in the control schools received no intervention and attended school as normal on those two days. At 42 months post intervention there was a significant reduction in STI incidence for CT, GC,TV (OR 0.71, 95 % CI , 0.54–0.95) in intervention schools (216). Students in the intervention arm, 54 months post the intervention had managed to retain lower level of self-reported condomless sex, open conversations with parents and guardians on sexual reproductive health (216). Such interventions that are associated with increased healthier sexual behaviours must be implemented and supported.

In Zambia an intervention in 12 schools had 3 arms, the first arm AYP in schools had standard of care which teachers gave give comprehensive sexual education (243). The second arm AYP received comprehensive sexual education at school, referral information to nearest clinic and health affair days at school where sexual reproductive health services were offered on a weekend at school by health care workers (243). In the 3rd arm, comprehensive sexual education scholars was offered and referral to local clinics was then given to scholars by healthcare workers that work as those clinics, the same health care workers were trained and sensitised to provide YFS (243). The second arm and third arm saw increased utilisation of sexual

reproductive health services at the clinics and reduced AGYW pregnancies (243). Though this intervention aimed and reported on pregnancy reduction, it illustrates that:

1 Compressive sexual education can be offered at schools.

2. Once AYP are reached through schools it is important to ensure comprehensive services are offered either at the school or at the referral clinic/hospital.

3. It is important to ensure referral clinics/ hospital are welcoming, trained on AYS, and associated with the school health programmes as well. Collaboration or some sort of linkage from school healthcare and local clinics in important.

Ahmed et al piloted offering a school health programme in one district in Cape Town South Africa, which was terminated earlier than planned. During the time the intervention ran, a nurse visited the school every two weeks. A high demand for service was demonstrated by 55% of the scholars that were requesting sexual reproductive health services, 50% of scholars received a HIV test, and 9% needed further referral for genital symptoms(14).

The integrated school health programme (ISHP) introduced in 2012 is one of the strategic models of care that was introduced to reach scholars and part of the pillars of reforming primary healthcare (219). The initial plan was to have one professional nurse do health assessment in scholars: one nurse for every 2000 learners in a year (219). The same nurse was also to do the administrative and liaison duties associated with this role (219). Quantitative questionnaires conducted on 2015 and 2016 reported ISHP issues such as a lack of integration, incomplete referrals and poor collaboration with local health care facilities (220). Furthermore, effective implementation of ISHP was also reported to be hampered by poor collaboration between DOH, Department of Education (DOE), scholars, parents/guardians, and the private sector (220). The basic health services that are offered to scholars are different and inconsistent between districts and provinces. (220) Furthermore, these health services are not offered constantly and systematically (220). The true coverage of ISHP is unknown, but there have been reports of poor coverage of the ISHP with some children completing schooling without having seen a school health nurse all through their schooling years (220). In the City of Tshwane, 65% of schools, who were part of survey reported no collaboration with school health nurses (220). The ISHP currently offers preventive and curative health care in the form of checking for vision problems, hearing problems, physical, emotional and cognitive impartment and referring appropriately (220). These services are not enough for sexually active AYP and AGYW, there is need to offer comprehensive sexual education and sexual reproductive health services. The scope of services offered and the reach of ISHP reported above, reveal an under-optimised channel of health care that could be effectively utilised to offer sexual and reproductive health

service to AYP and AGYW. The Department of Basic Education (DBE) released a national policy in 2017 on HIV/STI and TB for scholars and educators (221). The policy details partnerships between DBE and ISHP to ensure structural, medical and behaviour interventions are offered The policy detailed plans for comprehensive sexual education to be offered to all scholars as age appropriate as a compulsory topic in the curriculum. Teachers would be trained on delivering age-appropriate comprehensive sexual education. The policy details all scholars would receive non-judgemental, non-biased information on HIV/STI, pregnancy prevention, etc for scholars aged 12 and older. The life-skills curriculum would include topics on pregnancy, HIV/STI and TB. The policy also details a plan to ensure male and female condoms are made available to scholars. The policy details ISHP utilising mobile clinics and local clinics to ensure sexual reproductive health services will be offered to scholars. The policy also details the ISHP being run by professional nurses and where professional nurses are not available scholars would be linked to the nearest local clinic.

We support the proposed increased reach, scope of practise and services to be offered through the ISHP. We propose that every scholar attending schools classified under quantile 1,2 and 3 (222) should be seen by a school health nurse at least once a year to ensure all health needs are meet including comprehensive sexual reproductive health services. There will be drawbacks such as the quantile system doesn't fully identify all vulnerable scholars and some scholars attend schools in a higher quantile compared to where they leave (223). This approach still allows ISHP to reach some of the most vulnerable scholars.

We support the plan for school health nurses offering both group and private health literacy counselling on sexual reproductive health. This will ensure demand creation for condom use; contraception use and health-seeking behaviours. We also support the training of teachers to ensure they are capacitated to offer comprehensive sexual education to scholars. DBE will face challenges in training teachers similar to the challenges DOH has faced with training health care workers in the acceptance of adolescent sexuality and the need for non-judgemental approach to sexual reproductive health issues for AYP.

School health nurses should also be able to provide screening, testing services, condoms, contraception, and dispensing medications such as antibiotics for diagnosed STI as proposed in the national policy.

We propose the use of enrolled nurses under professional nurse supervision which will allow for task shifting and an increase in staffing available, reducing infrequent visits to schools and poor coverage of learners in the ISHP.

We proposed as part of the social and behaviour change communication (SBCC) campaigns mentioned below, that parent/guardians should be part of the stakeholders that ISHP and DBE collaborate with to ensure successful delivery of sexual reproductive health service to scholars. Parents/ guardians need to be invited to health literacy discussions on YP health issues and on health services offered through ISHP.

As part of the DOH's plans for re-engineering PHC, there are three arms which are to deliver services to the community. The three arms are ward-based primary healthcare outreach teams (WBPHCOT), ISHP and district clinical specialist teams. Though designed to run separately, we propose the integration of the ISHP into WBPHCOTS. A report on the implementation of WBPHCOTS reported human resources limitation with a lack of professional nurses to support CHW, leading to the use of enrolled nurses as team leaders for some teams (224). To add on, as the health budget is limited, WBPHCOT are currently only being established and scaled up in communities with families whose household income falls below the poverty line (224). Scaling up of services will continue to other communities as resources increase (224). We propose ISHP should be integrated into WBPHCOTS as both arms are currently plagued by similar problems of funding and human resources. Above we proposed ISHP to be initially offered to quantile 1,2 and 3 schools. This was due to the limited human resources and funding that ISHP faces. Integrating ISHP and WBPHCOT then ensures schools in those poor communities that are below the poverty line will be serviced by the similar enrolled nurses/professional nurses that support CHW in those wards. Integrating both will ensure equitable provision of services to the most vulnerable communities and schools at the same time. Integrating the two allows the utilisation of already existing stakeholder relationship within WBPHCOTS and communities for ISHP as well. This integration would need to be piloted and evaluated before it can be implemented and scaled up. Besides integration costs between ISHP and WBPHCOT costs that arise from optimising ISHP could be managed through partnership with the private sector such as pharmaceutical companies whilst awaiting implementation of the National Health Insurance (NHI). Pharmaceutical companies are specially mentioned as sources for funds as they benefit from comprehensive sexual and reproductive health services being offered to scholars as DOH will be buying more stock from them. The 2017 national policy for DBE highlights potential increase in services offered through ISHP. We support the proposed changes and plans to offer comprehensive sexual education and comprehensive sexual reproductive health services to AYP through ISHP. Reaching AGYW through ISHP would remove barriers and opportunity costs associated with

accessing care, would reach the target population, would reduce durations of infection, and efficiency of STI organisms and incident rates.

Community based interventions to increase access to health services

Community based testing is ideal for those AGYW that would not have visited any health facility, have not encountered ISHP and have not done any self-testing during the year. Community based testing could reduce opportunity costs associated with healthcare access and reduce exposure to stigma and health system barriers. Community based testing can be facilitated and supported by CHW as part of WBPHCOT (225) or through mobile clinics, hubs and temporary structures. Healthcare workers would need to be trained on chain of custody and quality measures to ensure urine sample integrity at time arrive to health facilities. Logistics associated with samples transportation and linkage to care, or community delivered treatment would also need to be ironed out.

As we reported that one of every five AGYW had an STI, aside from symptomatic management and yearly asymptomatic diagnostic testing done in health facilities, for AGYW that do not access a health facility or health care worker traditionally in the year, we propose they should still be offered once yearly community-based testing. In Zambia community hubs named Yathu-Yathu were created where AYP aged 15-24 could access comprehensive sexual reproductive health services, AYP in the intervention arms using the hubs had increased health literacy on HIV testing, PrEP (214). In the CHIEDZA trial in Zimbabwe, 74% of 16–24-year-old AYP participants chose community-based, non-clinical setting as a preferred STI testing location compared to traditional clinic setting (65%) (226), illustrating how community-based testing is acceptable in AGYW in Southern Africa. In Cape Town Metropolitan area, a mobile clinic offering care (screening for pregnancy, STIs, HIV, TB, obesity, high blood and diabetes mellitus) to 12-24 AYP had more than 90% reporting services were quicker, acceptable, private and that they would reuse the services of the mobile clinic as well as tell other AYP of the services at the mobile clinic (227).

Home/self-testing

As the goal is to reach all sexually active AGYW, it is essential to offer multiple models of care that reach as many AGYW as possible. In the South African National Strategic Plan for HIV, TB and STIs 2023-2028, sub-objective 2.8.1 states AGYW as a target population for scale up of implementation of STI diagnostic testing to detect and treat asymptomatic infections (228). How this is to be done is not stated as this is a strategic plan. Self or home testing for specific STI such as CT and GC is another way to reach asymptomatic AGYW. Currently there is no Food and Drug Administration (FDA) approved self/home testing STI test that gives immediate

results except for the oral HIV test (229,230). For other STI, self/home testing is conducted by collection of samples (swabs or urine) at home that are then shipped to laboratory/healthcare centre for processing (229). Home-based self-testing is ideal as it offers privacy, convenience, reduced opportunity costs associated with accessing health care, avoids stigma and healthcare associated barriers and also reduces the burden of clinic visits on the health care system (231). Development of cheaper STI self-testing kit through repurposing of technology should also be a priority for LMIC. During the COVID 19 pandemic, we experienced different types of home/self-testing kits being produced and made available to the populations quickly due to political will and funding. Similarly, getting STI CT/NG swabs or urine containers for self-testing kits that are currently available approved and distributed in LMIC should be a priority. These swabs and urine containers could be given and collected from AGYW through existing channels of CHW assigned to WBPHCOT. For using self-testing kits, individuals are provided with instructions on the packaging or telephonically or internet-based videos demonstrating how to collect and ship samples. CHW can also share these instructions with AGYW in person. Results are shipped/made available in less than a week. The individual would still need to ensure they initiate contact with health care facility to obtain treatment, in some instances the results are also received by the individual's practitioner/ clinic to ensure follow up and treatment (232). There are some draw backs to home based self-testing which include, incorrect sample collection, needing telemedicine support for sample collection and sample dispatching to lab and results, needing linkage between laboratory and primary clinic/physician to ensure results are shared and treatment is offered if needed (233,234). Aside from these draw backs, some countries e.g. Sweden saw a rise of 115% in self/home collected samples from 2013 (n=33 119) up to 2017 (n=71 185) (235). Self-collected samples also comprised 20.3% of all CT cases in both men and women in Sweden (235). Though this success is from a high-income country, it is possible in South Africa to a similar high uptake of self/home testing for STI as this would allow testing of AGYW that do not visit a health facility during the year, especially if costs of obtaining the swabs/urine collection kit and transportation of samples to the clinic/ laboratory is covered by DOH. In the United States, the following self-testing kits are available, CT, HIV, hepatitis and syphilis (232). South Africa can start with self-testing of CT/NG as there is multiple literature on CT/NG self-testing in other countries (235,236) as well as here in South Africa (237). Between 2003 and 2004, women aged 14-25 in Gugulethu, Cape Town were randomised either to self-collection of samples in a clinic or at home based self-collection of samples for STI testing (CT/NG/TV) (237). The group that did home based self-collection was given a mailing bag with pre-paid postage to mail the two vaginal swab samples to the clinic,

87% women in this group did post the self-collected samples back to the clinic (262). It has been demonstrated that home/self-collected urine samples and swabs for NAAT testing in GC and CT are of similar quality to physician collected samples (114). AGYW in Zimbabwe demonstrated confidence and comfort in self-collection of swabs (115). Young women in the study mentioned above from Gugulethu, Cape Town also reported acceptability of self-sampling with 97% selecting home based self-sample collection compared to 57% selecting clinic based self-sample collection (237). Yearly home/self-testing remains a viable option for AGYW in South Africa to help in diagnoses of asymptomatic STI.

Scientific advancements in vaccine research

Expediting research and increasing funding in vaccine research for bacterial STI is crucial for primary prevention. Vaccines are crucial as there is a rise in antimicrobial resistance (118,119). Treatment of current STI does not offer protection from future infections, therefore vaccines remain an essential avenue of protection for AGYW. Vaccines offer primary prevention which is essential for preventing incident infections, complications and costs associated with infections. Currently approved vaccines are for viral STIs (Hepatitis A, Hepatitis B and Human Papilloma Virus) (238) which have significantly reduced risks of infections and complications. This is evidenced in HPV vaccination in AGYW were it leads to a 90% reduction in cervical cancer risk (239,240). Therefore, supporting the development of NG, CT, TV, MG vaccines will significantly affect the health of AGYW for the better. Early stage trials for vaccines against GC and CT have are in progress and show promise.

Doxycycline PEP

Doxycycline is a second generation tetracycline (241) which can be used for post exposure prophylaxis (PEP) for STI as a stat dose of 200mg up to 72 hours (maximum effectivity within 24 hours) of condomless sex (242,243). Success in the use of doxycycline for PEP has been demonstrated in randomised trials for MSM such as IPERGAY study which reported a 47% reduction in CT, GC and syphilis due to doxycycline PEP use (244) and Luetkemeyer et al in the Doxy-PEP trial also reported 55-87% decreased risk for GC,CT and syphilis due to doxycycline PEP (245). In cisgender woman in Kenya, doxycycline PEP showed a lower risk for CT that was not significant (246). Risks associated with doxycycline PEP include an increase in tetracycline-resistant GC. In the Doxy-PEP trial, GC cases resistant to tetracycline doubled from baseline to the follow up period. This public health concern is not much of a risk as South Africa currently uses cephalosporins as first line treatment for GC (247), however there is still a possibility for anti-microbial resistance (AMR) in respiratory and gastro-intestinal

pathogens(248). Further research is essential to investigate doxycycline PEP provision for prevention of CT in AGYW in South Africa, especially given high prevalence in women.

4.2.2 Structural interventions to reduce STIs

To reduce some of the risk factors mentioned above, there is a need to tackle poverty and the socioeconomic status of AGYW and their families. Factors such as transactional sex, the need for financial support, experiencing violence and having more than one sex partner are affected by socioeconomic status and poverty. Basic income and cash transfers, when introduced for AGYW and their immediate household reduce exposure to violence, reduce financial vulnerability, reduce the need for multiple sex partners, reduce transactional sex, reduce food insecurity, reduce age disparate relationships and increase women agency and the ability to stay in school longer (159,257–259). In Tanzania, an intervention managed to incentivise safer sex by a conditional cash transfer based on negative STI results for GC, CT, TV and MG tested quarterly. They reported significant decline in composite STI for those that were receiving USD $20 per quarter for negative STI results (risk ratio (RR 0.73, 95% CI, 0.47-0.99)(260). Conditional cash transfers been shown to reduce risk for HIV and STI incidence, especially in the form of cash transfers in low income households given as incentives for high school attendance (261). Condomless sex was reduced in a school attendance conditional cash transfer as an effort to reduce HIV incidence in 13-20 AGYW in rural Mpumalanga South Africa (262). In the Western Cape and Mpumalanga among 10-18 year AGYW whose household were receiving the South African child support grant, they had significantly reduced transactional sex (aOR 0.49, 0.26 to 0.93) and age disparate relationships (aOR 0.29, 95%CI, 0.13-0.67) (263). Receiving the child support grant was also associated with later sexual debut in AGYW in South Africa (264). In 2015, it was estimated that 49.2% of adult South Africans live below the upper-bound poverty line (UBPL), meaning they are living on less than R1417.00 per month (265,266).

Marcovitz et al, argue that South Africa can afford a universal basic income grant (UBIG) of R1400 for individuals below UBPL by increasing income tax to create R700 billion per year to cover the UBIG. (266). We argue this amount can be raised through sin tax (267). The World Bank recommends health taxes (sin tax) as way to increase revenue, reduce poverty and redistribute resources and wealth (268). The South African Constitution, section 27 (269) details an individual's right to social security, including social assistance if they cannot provide for themselves and their dependents. To try ensuring this constitutional right is observed, the Department of Social Development in South Africa offers a R510 South African Social Security Agency (SASSA) child support grant per month per child for single earner households earning

R61 200 or less a year (R5 100 a month) or combined household earning of R122 400 or less a year (R10 200 a month) (270). This grant is only offered until 18 years old (270). It is estimated that 65-70% of children (0-18 year) eligible for the child support grant receive it (263,271). This translate to 65-70 % children (0-18 years) who are receiving a small proportion of the money needed to reach UBIG. There is also 30 % of children in need of financial support that are not receiving any financial support. Furthermore, the child support grant does not cover the rest of the AGYW from 19 -24 who are financially vulnerable. A basic income grant is not just an intervention for STI, but it is a constitutional right for AGYW to living below the UBPL that would help curb poverty and socioeconomic difficulties that make AGYW vulnerable and lead to risky sexual behaviours.

4.3 Conclusion

We also found high baseline prevalence of STI. While we were not able to show a statistically significant increase in risk in any of the curable STIs [CT, GC, TV, MG] in IC users compared to non-users, we did show a trend to increased CT, possibly MG and decreased GC etc consistent with previously reported trends at the enrolment visit. These associations strengthened after adjusting for sexual behaviour. We also found high prevalence and incidence of STI in AGYW. To tackle this public health challenge in AGYW there is need for reduction of risky sexual behaviours, early diagnosis of infections, appropriate treatment of infections and primary prevention strategies such as vaccines. Current models of care and syndromic management of STI have limitations in managing STI in AGYW. There is a need to optimise existing health care models to reach all sexually active AGYW for STI diagnosis and management. Already established models of care such as ISHP, AYFS, YZ need to be optimised and supported to ensure greater reach of AGYW to offer STI diagnosis and management. Other models of care that have not yet been fully implemented such as community and home-based testing could potentially reach asymptomatic individuals thereby reducing transmission and incidence of STI. Sexual behaviours remain significant in acquisition STI in AGYW, therefore interventions that investigate sexual behavioural change should be prioritized and scaled up when found to be effective. Financial interventions to alleviate poverty and lack are important in reducing risky sexual behaviours. Technological advancement and scientific advancements can support intervention to ensure task shifting, provision of comprehensive services, monitoring and evaluation of comprehensive sexual reproductive services offered to AYP.

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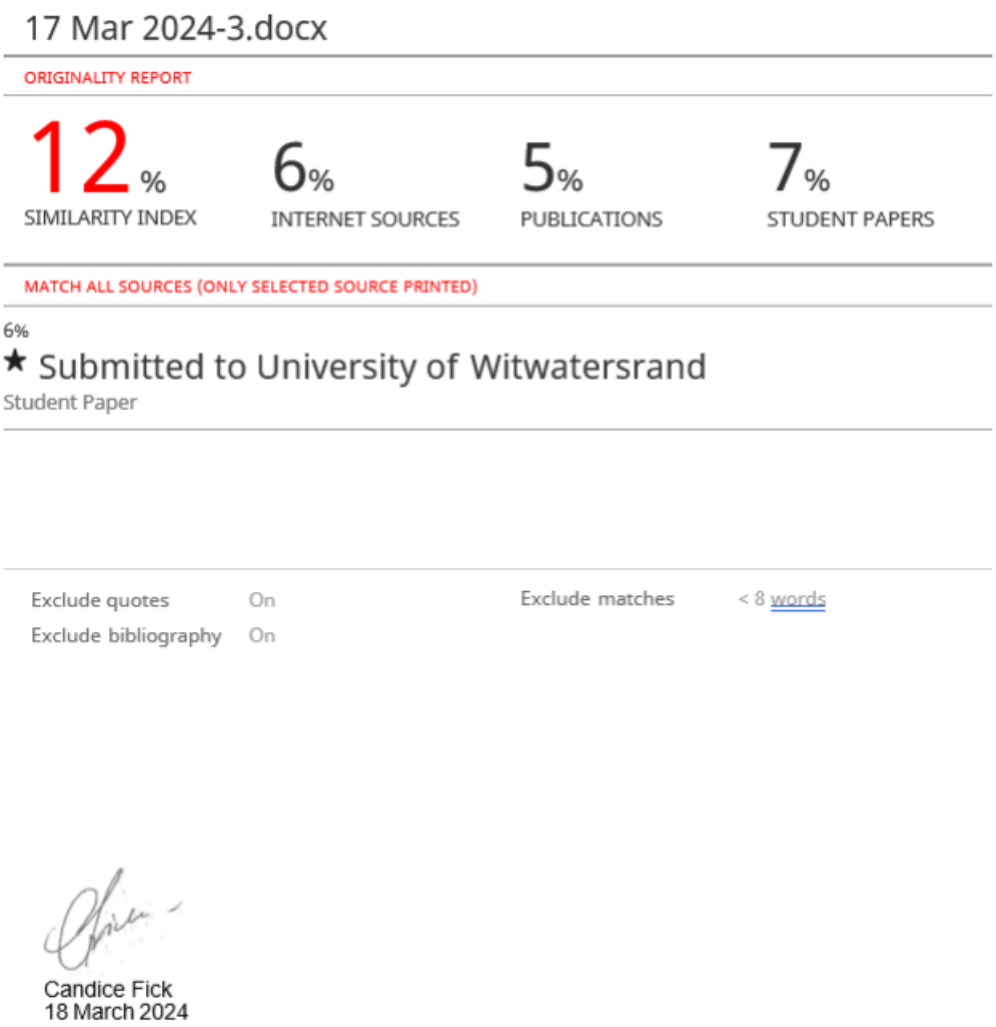
5.Appendices

5.1 Appendix 1: Turnitin cover page



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Candice Fick
18 March 2024

5.2 Appendix 2: Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr JV Rundogo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230304

NAME: (Principal Investigator)	Dr JV Rundogo
DEPARTMENT:	School of Public Health Medical School University
PROJECT TITLE:	*Analysis of progestin-based injectable contraception and the risk of curable sexually transmitted infections in a prospective cohort of adolescent girls and young women in Johannesburg, South Africa*
DATE CONSIDERED:	2023/03/31
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr C Fick and Professor S Delany-Moretlwe
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/07/07 **EXPIRY DATE:** 2028/07/06

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **March** and therefore reports and re-certification will be due in the month of **March** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

23 Jul 2023
Date

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr JV Rundogo
School of Public Health
Medical School
University

E-mail: julietrundogo@ymail.com

CC: Supervisor: Dr C Fick and Professor S Delany-Moretlwe
<cfick@wrhi.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2023/07/07

REF: R14/49

PROTOCOL NO: **M230304** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Analysis of progestin-based injectable contraception and the risk of curable sexually transmitted infections in a prospective cohort of adolescent girls and young women in Johannesburg, South Africa*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps