UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

# HORMONAL CONTRACEPTION USE AND HIV INFECTION IN MTHATHA

Eugene Jamot Ndebia

**A research report submitted to the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Masters of Science in Epidemiology (Epidemiology and Biostatistics)**

**November 2019**

**DECLARATION**

I, Eugene Jamot NDEBIA declare that this research report is my own work. It is being submitted for the degree of Master's in Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

28.10.2019

**DECLARATION: STUDENT'S CONTRIBUTION TO ARTICLE(S) AND AGREEMENT OF CO-AUTHOR(S)**

I, Eugene Jamot Ndebia, student number 1004262, declare that this Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Research Report.

Signature of Student  Date: 26/06/2019

Name of Primary Supervisor……Jabulani Ncayiyana……

Signature of Primary Supervisor  ……Date…01/07/2019……

**Agreement by co-authors**: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of his Research Report.

**Article title**: Hormonal contraception use and HIV infection in Mthatha

Journal name, volume, page number: _____

| **Authors** | **Name** | **Signature** | **Date** |
|---|---|---|---|
| 1st author | Eugene Jamot Ndebia |  | 26/06/2019 |
| 2nd author | Jabulani Ncayiyana | | 01/07/2019 |

## DEDICATION

I dedicate this work to God, through him everything is possible, to my spouse Caroline, and my children: Yanis, Yoanna, Yelena, Yadiel & Adam

## ABSTRACT

**Background:** Hormonal contraception (HC) is used by over 150 million women worldwide with 100 million using oral contraception and 40 million using injectable contraception. Hence, the choice of a contraceptive method with lower human immunodeficiency virus (HIV) acquisition risk is a problem of concern for women. Many studies have been reported to clarify the effect of HC on HIV acquisition risk, but the results are still very controversial, inconsistent with conflicting findings among them. The objective of this study is to evaluate the risk of HIV acquisition when using HC in a rural setting of Mthatha in South Africa.

**Methods:** This study was a cross-sectional study. HC and sexual behaviour risk information was obtained directly from participants by the administration of a structured questionnaire. Results of HIV testing was made available to the researcher after the counselling session. The prevalence of HIV was estimated using a single proportion method, the association between hormonal contraceptive use and HIV was assessed using logistic regression models. The presence of effect modification between covariates and HIV acquisition was measured by calculating the relative excess risk of interaction.

**Results:** 501 women aged 18-45 years agreed to participate in the study. Among them 159 were HIV positive representing a prevalence of 32% (95% CI: 28% - 36%). After adjusting for confounders, women who used HC had higher odds of HIV infection compared to women who did not use HC (OR: 1.87, 95% CI: 1.08-3.23). The effect of HC on HIV was modified by age and marital status with a coefficient for interaction of 1.39 (95% CI: 1.13-1.71) and 1.22 (95% CI: 1.10-1.41) respectively.

**Conclusion**: In summary, we found that HC was associated with the risk of HIV acquisition in women coming for voluntary HIV screening in the rural setting of Mthatha. While further research is required, it is advised that contraceptive counselling should be included in HIV screening and counselling for optimisation of women sexual reproductive health and HIV prevention.

**Keywords:** Hormonal contraception, HIV acquisition, injection contraceptive, Sexual behaviour, Women

**ACKNOWLEDGEMENTS**

My deepest appreciation to my supervisor Dr Jabulani Ncayiyana. Thank you for your guidance, encouragement and support.

To all the staff of the School of Public Health for their motivation and support.

To all my colleagues from Walter Sisulu University for their encouragement.

To the Staff of Stanford terrace CHC, Ngangelizwe CHC and Gateway CHC for their help in facilitating my access to participants.

To my closest friend Anne Melanie Toyem for all her support and guidance.

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## LIST OF ABBREVIATIONS

HC: Hormonal contraception

STI: Sexually transmitted disease

HSRC: Human Science Research Council

SABSSM: South African National HIV Prevalence, Incidence, Behaviour and Communication Survey:

OC: Oral contraception

WHO: World Health Organisation

COC: Combined oral contraception

DMPA: Depo-Medroxyprogesterone Acetate

POC: Progesterone only contraceptive

NET-EN: Description Norethisterone Enanthate

HSV2: Herpes simplex virus type 2

VCT: Voluntary Counselling and Testing

CHC: Combined Hormonal Contraception

MEC: Medical eligibility criteria

ART: Anti-retroviral treatment

DAG: Directed Acyclic Graphs

RERI: Relative excess risk due to interaction

# Chap 1: INTRODUCTION

## 1.1. Background

The prevalence of human immunodeficiency virus (HIV) in South Africa is still among the highest in the continent of Africa despite all the effort made to control the disease by the government. The most recent fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (SABSSM V) done in 2017 showed that 20.6 % of adults aged 15-49 years (7.9 million) are HIV positive (1). The overall results of the survey showed that women have an overall prevalence of 26.3 % against 14.8 % for men (1). The prevalence of HIV among women is maintained higher as compared to men throughout the reproductive age (15-49 years) (1). The number of new HIV infection in 2017 showed a higher incidence among female as compared to male throughout the different age group with the overall incidence of 0.93 for female and 0.69 for male (1). This disparity in HIV prevalence is higher among young adults (20 – 25 years) with the prevalence of 15.6 % among female which is three times higher than the prevalence of 4.8 % among male (1). Surprisingly, these alarming figures showed that female have a higher HIV incidence and prevalence than male during their reproductive age (15-49 years). From 15 years old or sometimes younger, female starts to use hormonal contraceptive to avoid unnecessary pregnancy when sexually active at an early age, with little information on sexually transmitted infections (STIs) transmission, placing them at potential risk of HIV infection.

Access to safe and effective contraceptive methods is one the leading concern in reproductive health. In the context where HIV is a worldwide pandemic, the choice of contraception method taking into consideration the risk of HIV acquisition is an important concern in women's health and a public health priority (2, 3). Hormonal contraception (HC) are among the best and the most used methods of pregnancy prevention (4), HC is used mainly for unwanted pregnancies and has an advantage which is to decrease maternal and infant mortality and morbidity (5). Also, HC decreases recourse to abortion and provides non-health related benefits such as increased education for women (6). Preventing unwanted pregnancies among HIV-positive women reduces HIV transmission from mother to child and increases the wellbeing of women, children and families (7).

HC is used by over 150 million women worldwide (3) with 100 million using oral contraception (OC) and 40 million using injectable contraception (3). In Africa, the use of contraceptive methods has increased exponentially during the last decade. The self-reported use of contraception has increased from 1% each year in 1999 to 17% in 2000 and 28% in 2015 in the continent (8). In sub-Saharan Africa, a region of higher prevalence and incidence of HIV, 60 % of woman use HC (8), therefore the choice of a contraceptive method with lower HIV acquisition risk is a problem of concern. In South Africa, the only available data on the prevalence of contraceptive use was the report of the latest South African Demographic and Health Survey (SADHS) in 2003, which reported that the contractive prevalence rate increased from 61 % in 1998 to 65 % in 2003 (9). The use of dual protection (condom and HC) has been emphasized by public services, one for unwanted pregnancy and the other one to prevent infections. Mechanical barriers such as condom have been the most used to prevent infection and HC for unwanted pregnancy making the two methods very popular among the majority of women worldwide. The magnitude of hormonal contraceptive use among women leads us to investigate its possible relationship with HIV acquisition.

### 1.2. Statement of the problem

There is still no agreed consensus on the effect of HC on HIV acquisition. Many studies have reported clarifying the effects of HC on HIV acquisition risk, but the results are still very controversial, inconsistent and with conflicting findings, partly because of the variable methodology and the diversity of the study population. Some studies found that HC increased the risk of HIV acquisition in both women and the men partner (10-13). Others did not find any association (4, 14). In Africa, studies have also been exploring this relationship between HC and HIV acquisition risk. A recent study involving seven African countries reported that women using injectable contraceptives had a 2.05 fold increased risk of HIV acquisition (15). In another study done by Balkus et al., 2016 (16) in the southern Africa region, they found that using injectable contraceptive was not associated with the increased risk of HIV confirming the results of previous studies done in the region (17). In South Africa, the relationship between HC and HIV acquisition has also been investigated by few studies and still the results are discordant. A 24-month cohort study done in an

African community of Khayelitsha in Cape Town showed that there was no association between HC and HIV acquisition (18). This finding is also supported by a 36 months cohort study involving many sites in South Africa, they found that HC did not significantly increase the risk of HIV acquisition (17). In another multicentre 24 months cohort study done in Durban and Johannesburg, authors have found that there is a slight increase in the risk of HIV acquisition in women using injectable contraception, even though it was not conclusive as they reported a large confidence interval (19). This latter finding is also supported by a most recent 30 months cohort study done in Umlazi, a Township in South Africa that showed a finding supporting that injection contraceptive significantly increase the risk of HIV acquisition (20). These conflicting findings led to the WHO call for further research on this topic (3). Also, most of these studies were done in an urban setting where accessibility to health facilities such as woman clinic, antenatal clinics are readily available. There is little available data in the rural setting where the underlying factors driving the choice of a contraceptive method could be different from an urban environment. Also, these studies focussed on the use of oral contraception and injection contraception, the remaining hormonal contraceptive categories such as implant and intrauterine devices were neglected. Most importantly, they did not highlight the relationship between HC and HIV according to age group knowing that younger females (15-24 years) are the most vulnerable to HIV infection mainly in the rural setting.

### 1.3. Justification

Understanding the relationship between HC and the risk of HIV acquisition is critical as most women around the world use this method for preventing pregnancy. The need to better understand the effect of HC on the risk of HIV acquisition in HIV-free women, HIV progression in HIV-confirmed women, and female-to-male HIV infection is one of the WHO priority. Although many studies were done to evaluate the relationship between HC and HIV risk acquisition, there is still for now no agreement on this issue. As a results, research on this problem is still on-going. In rural areas, there are more challenges to access primary health care services and the behavioural risk factors driving the use of HC may be completely different from urban settings. Little has been reported so far in the literature on the relationship between HC and HIV acquisition risk in younger female (15-24 years) as they are the most

vulnerable group at risk of HIV infection. Taking this into consideration, WHO has requested to develop more studies to assess the real effects of HC on HIV risk acquisition as this is of global public health importance (3).

### 1.4. Research Question

Is hormonal contraception associated with HIV infection in women attending HIV screening facilities in Mthatha selected health communities centre?

### 1.5. Aim

The aim of this study is to evaluate the association between hormonal contraception and HIV infection in Mthatha community's health centre.

### 1.6. Objectives

1. To estimate the prevalence of HIV infection among women in the selected Mthatha communities health centre.

2. To examine the association between hormonal contraception use and HIV prevalence.

## Chap 2: LITERATURE REVIEW

### 2.1. Overview of hormonal contraception

Contraception is a voluntary act to prevent pregnancy from sexual intercourse by using artificial methods which interfere with the normal process of ovulation, fertilization, and implantation. HC methods use hormone to prevent ovulation and/or implantation. They are two main classes of HC: combined contraceptives which contain both oestrogen and progesterone and a progesterone only contraceptive which contains only progesterone or a derivative (21).

#### 2.1.1. Combined contraceptives

Combined oral contraceptives (COCs) contain oestrogen and progestin, they are available in two formulations: the monophasic formulation in which each pill contain the same dosage of oestrogen and progestin and the multiphasic formulation containing different dosage. Combined contraceptives act in two ways: firstly, by preventing the female body from releasing the egg (ovulation) and secondly, by thickening the mucus in the entrance of the womb (cervical mucus), making it very challenging for the sperm to enter (22), and reducing the opportunity for the sperm to fertilize the ovum.

- **Pills:** These are the most popular form of HC, it is also called birth control pill, and it is suitable for most healthy women regardless of age and can be used long term (23). Over 100 million women worldwide rely on it for child birthcontrol (23). It is taken daily for 21 days followed by 7 days break. They also have other regiments in place. The primary action mechanism of pills is inhibition of the egg release, also it produces an endometrium that is not adequate for egg implantation and slow sperm movement by increasing the thickness of the cervical mucus.

- **Contraceptive patch:** This is a small, stick-on patch that can be applied to your stomach, tight, bottom or upper body. They discharge oestrogen and progesterone hormones through the skin. The patch prevents pregnancy by stopping the ovaries from releasing the egg. Its method of action is very

similar to pills as it may also make the cervical mucus thicker thus preventing sperm to get into the uterus (23). It is changed on the same day every week for 3 weeks and the last week is patch-free.

- **Vaginal ring:** It is a flexible and soft ring that measures 54 mm in diameter and is inserted inside the vagina. They discharge oestrogen and progesterone hormones through the vagina wall. It is used for 3 weeks, then remove for 1 week break for the period to occur. Following the break, a new ring is inserted. The mode of action is very similar to the pill, the patch prevent pregnancy by stopping the ovaries from releasing the egg. It's may also make the cervical mucus thicker thus preventing sperm to get into the uterus

### 2.1.2. Progesterone only

Progesterone only contraceptive prevents pregnancy by thickening the mucus at the entrance of the womb, making extremely difficult for the sperm to get through. It also changes the lining of the womb, making implantation difficult in the event of fecundation.

- **Mini-pills**: These are the most popular form of progesterone only contraception. They contain no oestrogen, thereby making it tolerable to women with oestrogen allergies. They are taken at the same time every day, with a delay which must not exceed 3 hours. There is no interruption, meaning pills are even taken during the menstruation.
- **Injections**: They are injected once a month or once every 3 months. Good choice for women having trouble with daily, weekly or monthly compliance. Also known as birth control, they are highly effective and reversible methods of contraception shot. The most popular injectable contraception is Depot Medroxy Progesterone Acetate, or Depo-Provera (DMPA), which is taken after 3 months (24). Suppression of ovulation is considered as the main action mechanism of DMPA, it also has an effect on the thickening of the womb (21). The DMPA does not interfere with sexual intercourse, also suitable during breastfeeding because it has no oestrogen, these advantages make injections the contraceptive method of choice of many South African women (25).

- **Contraceptives implants:** They are tiny flexible tubes filled with progesterone, which is inserted under the skin of the upper arm. They can give continuous protection for three to five years, depending on the number of tubes inserted.
- **Emergency contraceptive:** This can be used after unprotected intercourse or when the used contraceptive method fails. It is only used as a backup, therefore must not be regular. It is also called “morning after pill” and should be taken directly after intercourse or less than 12h.

### 2.1.3. Benefits and disadvantages of hormonal contraception use.

**- Combined oral contraceptives (COCs)**

The main advantages of COCs are effectiveness, safety, reversibility and they improve the quality of menstrual period with no pain, no cramps and decrease blood loss (26). The weaknesses of COCs are the price, the fact that it must be taken daily thus reduce the compliance, provide no protection against sexually transmitted infections including HIV, there is a possibility of side effect including nausea, vomiting, headache, depression and more (26).

**- Progesterone only contraceptive (POCs)**

The main benefit of POCs is the fact that they can be used by people who are unable to tolerate oestrogen. Also, it can be taken during lactation, had no effect on blood pressure or on coagulation. The disadvantages of POCs are the irregular menses, also the requirement of timing as it must be taken at the same time daily (26).

## 2.2. Factors associated with hormonal contraceptive

Hormonal contraceptive is widely used among women in sub-Saharan African, with the dominance of injectable and oral contraceptives (27). It is well known that acceptability, accessibility and affordability are among the most important determinants of hormonal contraceptive use (28). Women residing in rural areas have difficulties in using HC because of the shortages of family planning facilities and low socio-economic status (29). Women who are educated are likely to use

more easily HC as compared to their non-educated counterpart (30). Women in the middle who are in need of limiting their birth for a long period of time also use HC to achieve this goal (31).

The use of pills requires to be consistent for optimal efficacy. However, as many of 20% of woman have reported a falling consistency (32). Some women have also reported the fear of side effect for their unwillingness to use hormonal contraceptive (33), the fear was mainly about infertility, menstrual cycle disorders, cancer and weight gain or loss (34, 35). Misconceptions like using HC may cause disease such as anaemia and hypertension were also reported (36). A study by Tang (2016) in Malawi reported that among women HIV positive, younger age, not wanting children in the next 2years, being in a relationship more than 4 years , being independent in decision making were significantly associated with the use of hormonal contraction (37). Women who opted for skin patch and vaginal ring reported that their choices were determined by the small probability of omission and convenience (38). In contrast, these two methods were not well accepted by other women because of the suspicion of inconvenience, fear of foreign object in their body and vaginal insertion intimacy (38).

In a study by Kumar et al., (2018), it was found that husband's approval was the main factor associated with hormonal contraceptive use in India (39), while in South Africa these factors were not (40), showing more control of South African women in terms of their reproductive health. This later results are also confirmed in South Africa by Seutlwadi et al, 2012 , where husband approval were not significantly associated with Hormonal contraceptive use (40).

### 2.3. Hormonal contraception and HIV risk acquisition

HC is the contraceptive method of choice of most women around the world, therefore many studies have been carried out to investigate its possible relationship with HIV transmission. The obtained results are still controversial till date, where some studies suggested a positive association and other not.

A study done in Kenya among sex workers showed that both oral contraceptive pills and DMPA were highly associated with HIV infection with a Hazard ratio (HR) of 1.5

[1.0-2.1] and 1.8 [1.4-2.4] respectively (41). A meta-analysis conducted recently showed strong evidence that DMPA is associated with HIV acquisition (42) with an adjusted HR of 1.5[1.24-1.82]. The same study showed no evidence that combined oral contraceptive (COC) or norethisterone enanthate (NET-EN) is associated with HIV acquisition (42) with an adjusted HR 1.03[0.88-1.20] for COC and 1.24[0.84-1.82] for NET-EN. A study done in Zimbabwe and Uganda simultaneously among woman attending family planning clinic showed that no association between both oral contraceptive pills and DMPA with HIV acquisition, the obtained hazard ratio were 0.99[0.69-1.14] and 1.25[0.89-1.78] respectively (43).

These inconsistencies between results may be due to methodology divergence among studies that have interfered with the ability of comparing the data. As an example, some of the studies assessed both HC use and HIV acquisition infrequently and at the same time make it difficult to know whether HC were used at the time of HIV acquisition. Also, sexual behaviour differences between participants using and those not using HC particularly in cross-sectional studies may confound the results.

### 2.4. Biological changes related to hormonal contraception use

The physiological mechanism by which HC alter HIV acquisition has been investigated by few studies in order to clarify the effect at the biological level. Several biological mechanisms were suggested including structural changes in the genital tract, altering immune responses, changing the vaginal flora, and increased risk of sexually transmitted infections (44). They are summarised in figure 2.1.

#### 2.4.1. Changes in vaginal and cervical wall

Few studies have shown that the use of HC appears to be responsible for an increase level of HIV-1 DNA in the female genital tract, therefore increasing the risk of HIV infection (45, 46). Several other mechanisms by which HC will increase HIV acquisition was brought forward including change in the genital tract and change in the vaginal flora (figure 2.1).

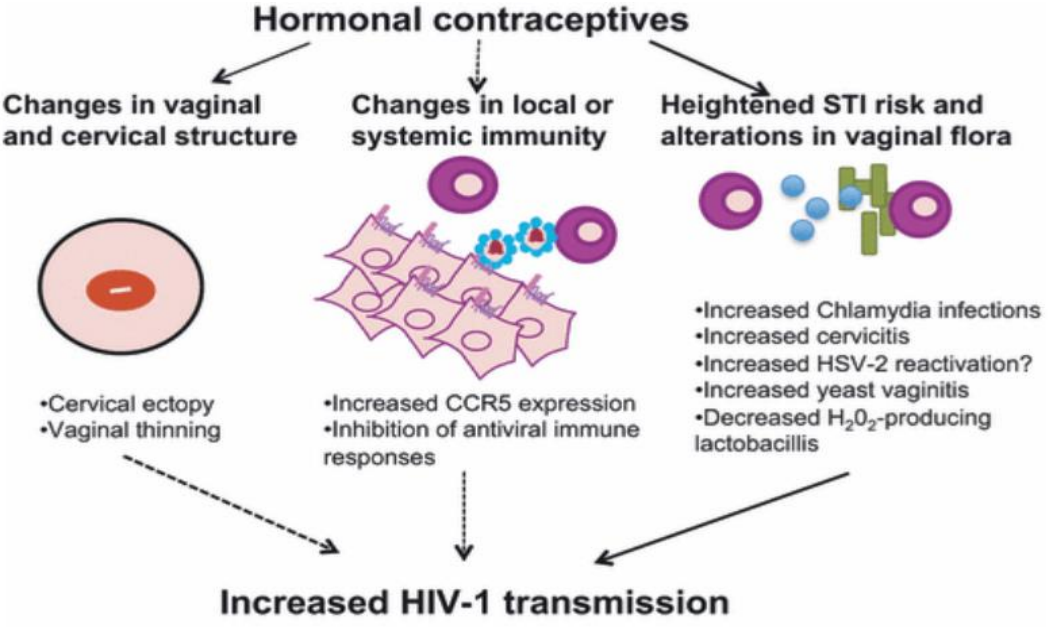


**Figure 2.1: Potential mechanisms by which hormonal contraceptives could influence HIV-1 transmission are summarized (Blish & Baeten, 2011)**

Changes in the vagina wall due to HC are showed to be a consequence of two majors structural changes which are cervical ectopy and genital tract alteration (44). Cervical ectopy is the extension of the endocervical columnar epithelium onto the exocervical face which in turn increase the susceptibility of HIV-1 transmission (47). Genital alteration is the tear of the virginal wall making it tinier due to the loss of epithelial cell, which in turn increase the susceptibility of HIV-1 transmission (48). Also, the variation of oestrogen and progesterone during the menstrual cycle influences the change to the epithelial lining of the vagina and cervix making it more susceptible to HIV penetration (49).

### 2.4.2. Changes in local or systemic immunity

The use of HC leads to the decrease of local systemic immunity as a consequence of increasing in the number expressing T-Cells leading to inflammation which in turn could increase the risk if HIV acquisition (50). The changes in the immune system during the menstrual cycle are making genital innate immune response weaker to HIV explaining the theory in which the HIV acquisition is higher during hormonal contraceptive use (51). Also, the increased risk of cervical sexually transmitted infections and inflammation mainly chlamydia are seeing when taking HC (52). Vaginal flora alteration is seeing when using HC, this includes an increase in yeast

vaginitis and a decrease of protective $H_2O_2$, which in turn could enhance HIV acquisition (53). A meta-analysis including 36 studies showed that both COC and DMPA use reduce bacterial vaginosis by 10-20 % and 18-30 % respectively (54), this could also be implicated in the increase of HIV infection.

### 2.5. Other risk factors and confounding effects

The risk of HIV acquisition in women in Africa rural setting is largely influenced by behavioural factors. Besides the debate around the role of HC and the risk of HIV acquisition, there are other factors which have been proven by previous studies to influence HIV infection in Southern African rural woman. These factors will be considered as confounding or effect modification in the relationship between HC and HIV acquisition in this population. Women with older partners who are more experienced are therefore more likely to be at greater risk of having HIV (55). Having being diagnosed with a previous STI is also well known to be associated with HIV infection among women. A meta-analysis study showed that HIV acquisition was three-fold associated with previous STI like HSV 2, Gonorrhoea, Syphilis and Chlamydia (56). The number of sex partners and the history of paid sex was also associated with increased HIV acquisition in women in previous studies (57). Also, some studies have shown that increase SES may decrease the risk of HIV in women (58). Hazardous alcohol consumption and age at first sex were also found to be associated with HIV acquisition in a rural setting (59, 60). In evaluating the real effect of HC on HIV acquisition, it is essential to control for confounders and interaction variables which may be related to the underlying risk of HIV acquisition (61). In addition, confounding and mediating factors that result from HC and that may be responsible for HIV acquisition can confuse the analysis and interpretation of the results.

## Chap 3: METHODOLOGY

### 3.1. Study design

This study was a cross-sectional study.

### 3.2 Study population

The study population were women coming for the VCT in one of the selected community health centres. Inclusion criteria included all women aged from 18-45 years coming for routine HIV screening test. Exclusion criteria included all women coming to the hospital for a reason other than routine HIV screening test, pregnant woman and mentally disabled women.

### 3.3. Participant selection

Participants were approached as they arrived to request the VCT. All participants who agreed to complete the questionnaire were recruited after signing the consent form. All consenting female participants aged 18-45 years coming for the VCT were recruited for the study from the 1st September 2017 till the 30th November 2017. They were invited to participate in the study without knowledge of their hormonal use exposure status and their HIV infection status. Participants who agreed to participate were enrolled in the study as they came for the VCT. Prior to enrolment, the purpose of the study was explained to them and they were asked to sign two consent forms on the agreement to be part of the study. The first consent form was the agreement to be part of the study and the second consent form was the authorisation given to the researcher to get access to the participants HIV status after the VCT session. Also, the authorisation to get access to the participant file for recording the HIV status was requested from the Hospital.

### 3.4. Procedure

Female volunteers were asked to fill in a structured questionnaire by the researcher just before VCT session. The questionnaire was done before the VCT session because of the higher risk of information bias due to the newly confirmed HIV status of the participant if this was done after the session. The VCT session was done by a

qualified nurse in a private environment, the researcher did not attend these sessions. The HIV test result of the participant was made available to the researcher and used only for research purpose.

### 3.5. Data collection

Enrolled women participated in a face-to-face structured Interview prior to undergoing the VCT. HC and sexual behaviours information were obtained directly from participants by the administration of a structured questionnaire after obtaining written informed consent. Information on demographic parameters, relationship and HIV testing pattern, pregnancy and contraceptive history and as well as a risk factor for contraceptive use were all recorded. The HIV test was done using the rapid screening test results. HIV screening test is a rapid test that is simplified version of antibody ELISA tests. It detects the presence of HIV antibody in the blood. All non-conclusive tests were repeated. The questionnaire was administered to all female volunteers coming for the VCT. Participants filled in the questionnaire with the help of the researcher just before they underwent the HIV screening test. A qualified nurse pricked the participant's finger with a small needle and took a drop of blood which was used for detecting the presence of HIV antibodies.

### 3.6. Study site

The selected community health centres (CHC) were the following: Stanford terrace CHC, Ngangelizwe CHC and Gateway CHC. These three CHC were selected purposively because they are among the largest CHC in Mthatha.

### 3.7. Data Processing

Data was entered into Epi-Info version 7 and was transferred to STATA 13. The Data was checked by two different researchers to reduce errors. Data was cleaned from implausible values and missing data. The final cleaner version of the data was safely stored in a password protected backup to a cloud and a hard copy filed for eventually later use. The final cleaner version of the data was transferred to Stata version 13 for statistical analysis.

### 3.8. Data analysis

Descriptive statistics including frequency tabulations, charts for categorical variables and summary statistics (mean, standard deviation and range) for quantitative variables was initially performed. Prevalence of HIV was estimated by dividing the number of women with HIV positive results by the total number of the study participants with HIV results. The 95% confidence interval of the prevalence was calculated from using single proportion method. The association between hormonal contraceptive use and HIV was assessed using logistic regression models. Unadjusted and adjusted odds ratio (PRs) and its 95 % confidence intervals (CI) for HIV with respect to hormonal contraceptive use were presented, taking into account plausible confounding variables which will be identified based on prior knowledge, causal diagram, and change-in-estimate strategies (62). The presence of effect modification between covariates and HIV acquisition was assessed from the fully adjusted model on the additive scale by calculating the relative excess risk due to interaction (RERI) (63) and on the multiplicative scale, by examining the statistical significance of the interaction coefficients. A p-value <0.05 was considered statistically significant.

### 3.9. Ethical considerations

The University of Witwatersrand Committee for Research on Human Subjects (medical) approved this study for the MSc project. Ethics approval number: M170427 (Appendix II). Participants were enrolled in the study as they come for the VCT. Prior to the enrolment, they were explained the purpose of the study and they were asked to sign two consent forms on agreement to be part of the study. The first consent form was the agreement to be part of the study and the second consent form was the authorisation given to the researcher to get access to the participants HIV status after the VCT session. Both consent forms were written in English and Xhosa which is the language spoken in the study area. Also, the authorisation to get access to the participant file for recording the HIV status was requested from the Hospital and from the Department of Health. Participants were asked to participate voluntarily in the study before they undergo the HIV voluntary screening test. Female volunteers were asked to fill in a structured questionnaire by the researcher just before they underwent the VCT session. The researcher assisted them in filling out

the questionnaire by giving them enough details to each question. The questionnaire was not done after the VCT because of the higher risk of information bias due to the new HIV status of the participant. The VCT session was done by a qualified nurse in a private environment, the researcher did not attend these sessions. The interview was carried out in the language of choice of the participant. They were free to participate and withdraw from the study at any moment and information obtained from this study was treated with confidentiality.

## Chap 4: PUBLISHABLE PAPER

# HORMONAL CONTRACEPTION USE AND HIV INFECTION IN MTHATHA

Eugene Jamot Ndebia[1&2] & Jabulani Ncayiyana[3]

1. Department of Human Biology, Faculty of Health Sciences, Walter Sisulu University, Mthatha, South Africa
2. Division of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
3. Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

## 4.1. Abstract

**Background:** Hormonal contraception (HC) is used by over 150 million women worldwide with 100 million using oral contraception and 40 million using injectable contraception. Hence, the choice of a contraceptive method with lower human immunodeficiency virus (HIV) acquisition risk is a problem of concern for women. Many studies have been reported to clarify the effect of HC on HIV acquisition risk, but the results are still very controversial, inconsistent with conflicting findings among them. The objective of this study is to evaluate the risk of HIV acquisition when using HC in a rural setting of Mthatha in South Africa.

**Methods:** This study was a cross-sectional study. HC and sexual behaviour risk information was obtained directly from participants by the administration of a structured questionnaire. Results of HIV testing was made available to the researcher after the counselling session. The prevalence of HIV was estimated using a single proportion method, the association between hormonal contraceptive use and HIV was assessed using logistic regression models. The presence of effect modification between covariates and HIV acquisition was measured by calculating the relative excess risk of interaction.

**Results:** 501 women aged 18-45 years agreed to participate in the study. Among them 159 were HIV positive representing a prevalence of 32% (95% CI: 28% - 36%). After adjusting for confounders, women who used HC had higher odds of HIV infection compared to women who did not use HC (OR: 1.87, 95% CI: 1.08-3.23).

The effect of HC on HIV was modified by age and marital status with a coefficient for interaction of 1.39 (95% CI: 1.13-1.71) and 1.22 (95% CI: 1.10-1.41) respectively.

**Conclusion**: In summary, we found that HC was associated with the risk of HIV acquisition in women coming for voluntary HIV screening in the rural setting of Mthatha. While further research is required, it is advised that contraceptive counselling should be included in HIV screening and counselling for optimisation of women sexual reproductive health and HIV prevention.

**Keywords:** Hormonal contraception, HIV acquisition, injection contraceptive, Sexual behaviour, Women

## 4.2. Introduction

Access to safe and effective contraceptive methods is one the leading concern in reproductive health. In the context where HIV is a worldwide pandemic, the choice of contraception method while taking into consideration the risk of HIV acquisition is an important concern in women's health and a public health priority (2, 3, 64, 65). Understanding the relationship between HC and the risk of HIV acquisition is critical as most women around the world use this method for preventing pregnancy. The need to better apprehend the effect of HC on the risk of HIV acquisition in HIV-free women, HIV progression in HIV-confirmed women, and female-to-male HIV infection is one of the WHO priority. Many studies have been reported to clarify the effect of HC on HIV acquisition risk, but the results are still very controversial, inconsistent with conflicting findings among them. Some studies found that HC increased the risk of HIV acquisition in both women and the men partner (10-13), others did not find any association (4, 14). These conflicting findings call for further research on this topic (3). In rural areas, there are more challenges to access primary health care services and the behavioural risk factors driving the use of HC may be completely different from urban settings. Little has been reported so far in the literature on the relationship between HC and HIV acquisition risk in younger women (15-24 years) as they are the most vulnerable group at risk of HIV infection. Taking this in consideration, WHO has published the Medical Eligibility Criteria for Contraceptive

Use (MEC) which is an evidence-based guideline document that characterizes the safety of contraceptive methods for women at high risk of HIV, living with HIV conditions or women using antiretroviral therapy (ART)(64). Furthermore, WHO has requested more studies to clarify the real effect of HC on HIV risk acquisition as this is of global public health importance (3). Therefore, this study aimed to evaluate the risk of HIV acquisition when using HC in a rural setting of Mthatha in South Africa.

### 4.3. Methods

This cross-sectional study was approved by both WITS University and Walter Sisulu University Faculty of Health Sciences human ethics committees. The study was done in Mthatha which is the main town of the King Sabata Dalindyebo Local Municipality in Eastern Cape Province of South Africa and the capital of OR Tambo District Municipality. The majority population of the municipality resides in rural areas, where they still practice cultural tradition (66). The study was conducted at Stanford terrace, Ngangelizwe and Gateway community health centres (CHCs) from the 1$^{st}$ September 2017 till the 30$^{th}$ November 2017. These CHCs are among the largest CHCs in Mthatha with an active HIV screening test Unit. Study participants were recruited by convenience from the general waiting rooms. Women were approached as they arrived to request the VCT. Those who were interested in the study were invited into a private room, where they would be screened for eligibility into the study. Selected women were asked to complete a structured questionnaire by the researcher prior to VCT session. The questionnaire was not done after the VCT session because of the higher risk of information bias due to the newly known HIV status of the participant. The VCT session was done by a qualified nurse in a private environment, the researcher did not attend these sessions. The interview was administered in the language of choice of the participant. The participant's HIV test result was made available only to the researcher post VCT session and used only for research purpose. HC and sexual behaviour risk history were obtained directly from participants during the administration of the structured questionnaire. Information on demographic parameters, relationship and HIV testing pattern, pregnancy and contraceptive history and as well as a risk factor for contraceptive use were all recorded. The HIV test was done using a rapid screening HIV test detecting the presence of HIV antibody in the blood. All non-conclusive tests were repeated.

### 4.4. Statistical Analysis

The data were analysed using Stata version13. Descriptive statistics including frequency tabulations, charts for categorical variables and summary statistics (mean, standard deviation and range) for quantitative variables was initially performed. Prevalence of HIV was estimated by dividing the number of women with HIV positive results by the total number of the study participants with HIV results. The 95% confidence interval of the prevalence was calculated from using single proportion method. The association between hormonal contraceptive use and HIV was assessed using logistic regression models. Directed Acyclic Graphs (DAGs) or causal diagrams were used to explain a theoretical causal structure of all the variables included in the analysis (67), to identify and minimize the effects of probable biases by adjustment for confounders. All variables selection included in the construction of the DAG for HIV acquisition were drawn from the literature and subject matters experts (Figure 4.1). We controlled for all variables selected for the minimal sufficient adjustment sets for estimating the total effect of HC on HIV acquisition in order to reduce or eliminate their confounding effect. Unadjusted and adjusted odds ratio (PRs) and its 95 % confidence intervals (CI) for HIV with respect to hormonal contraceptive use were presented, taking into account plausible confounding variables which will be identified based on prior knowledge, causal diagram, and change-in-estimate strategies (62).. The presence of effect modification between covariates and HIV acquisition was assessed from the fully adjusted model on the additive scale by calculating the relative excess risk due to interaction (RERI) (63) and on the multiplicative scale, by examining the statistical significance of the interaction coefficients. A p-value <0.05 was considered statistically significant.

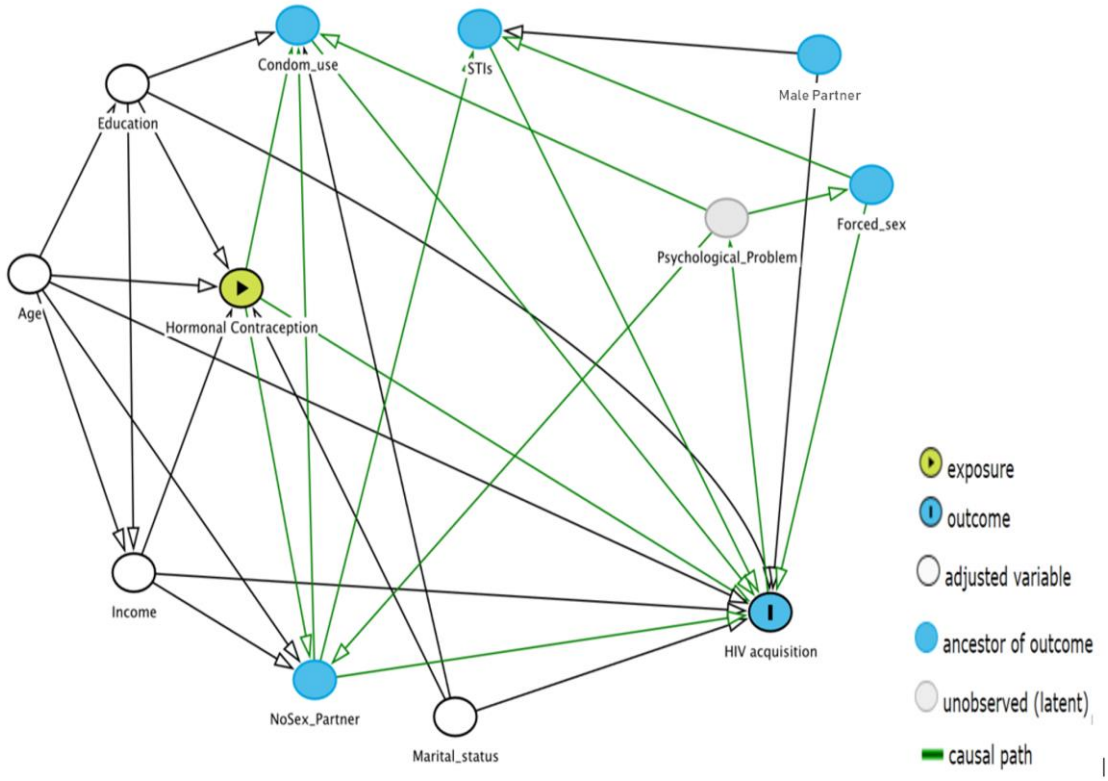


**Figure 4.1: Directed acyclic graph (DAG) for HIV acquisition among women using HC in Mthatha CHC. DAG helped in the selection of appropriate variables in which to condition on, to control for confounding of exposure variables on the outcome**

### 4.5. Results

A total of 501 women agreed to participate in the study. The overall prevalence of HIV acquisition in this study population was 32% (Table 4.1). The lowest HIV prevalence of 24 % HIV was observed in women with less than 20 years while the highest HIV prevalence of 42% was observed in more than 30 years. Participants with the level of education of high school showed an HIV prevalence of 32% as compared to university (30%) and Primary (29%). There was a high participation of women with a high school level of education as compared to primary or tertiary level. The prevalence of HIV was higher among women using HC (34%) as compared to women using other contraceptive methods (24%) (Table 4.1).

We had 32% of women aged more than 30 years, 64% with a salary less than R1000 per month (71 US dollar), 81% were single, 70% had a high school education (Table 4.2). Women who used injection were 51 % of the entire population, while

women who use pill and implant were both respectively 14 %. Only 2 % of women were using patch showing that this method of contraception is not well adopted by the population as compared to injection (Figure 4.2). Women who used HC showed a higher frequency of HIV acquisition (34 %) as compared to women who did not use HC (24%) (Figure 4.3). We also evaluated sexual behaviour risk among participants, the data showed that 68% of participants had sexual intercourse more than one time a month, 26 % had more than one partner and 85% came for HIV screening for health reasons (Table 4.2).

**Table 4.1: Characteristics of woman attending CHC in Mthatha**

| | | Number (%), N: 501 |
|---|---|---|
| Age (year) | < 20 | 67(13) |
| | 20-24 | 150(30) |
| | 25-29 | 126(25) |
| | >30 | 158(32) |
| Salary (Rand) | 0-999 | 319(64) |
| | 1000-4999 | 152(30) |
| | +5000 | 30(6) |
| Marital status | Single | 404(81) |
| | Married | 97(19) |
| Education | Primary | 35(7) |
| | High School | 348(70) |
| | University | 118(23) |
| Sex Frequency/Month | none | 63(13) |
| | 1-5 time | 340(68) |
| | +5 time | 98(20) |
| Number of Sex Partner in the past year | one | 371(74) |
| | 2 or more | 130(26) |
| Age at first sex (year) | 15 or less | 131(26) |
| | 16 - 17 | 168(34) |
| | 18 or more | 202(40) |
| Ever experienced forced sex | No | 446(89) |
| | Yes | 55(11) |
| Diagnose With STD in the past Year | No | 353(70 |
| | Yes | 148(30) |
| Reason of doing HIV test | Health issues | 425(85) |
| | Sex no Condom | 44(9) |
| | Sex HIV man | 32(6) |
| Exposure to family planning | No | 199(40) |
| | Yes | 302(60) |

**Table 4.2: HIV prevalence in woman attending CHC in Mthatha**

| | | HIV Prevalence [95% CI], N: 501 |
|---|---|---|
| Age (year) | < 20 | 0.24[0.15-0.36] |
| | 20-24 | 0.25[0.18-0.33] |
| | 25-29 | 0.32[0.24-0.40] |
| | >30 | 0.42[0.34-0.50] |
| Education | Primary | 0.29[0.16-0.46] |
| | High School | 0.32[0.28-0.36] |
| | University | 0.30[0.23-0.39] |
| Hormonal contraceptive use | Yes | 0.34[0.29-0.38] |
| | No | 0.24[0.16-0.34] |
| Overall | | 0.32[0.28-0.36] |

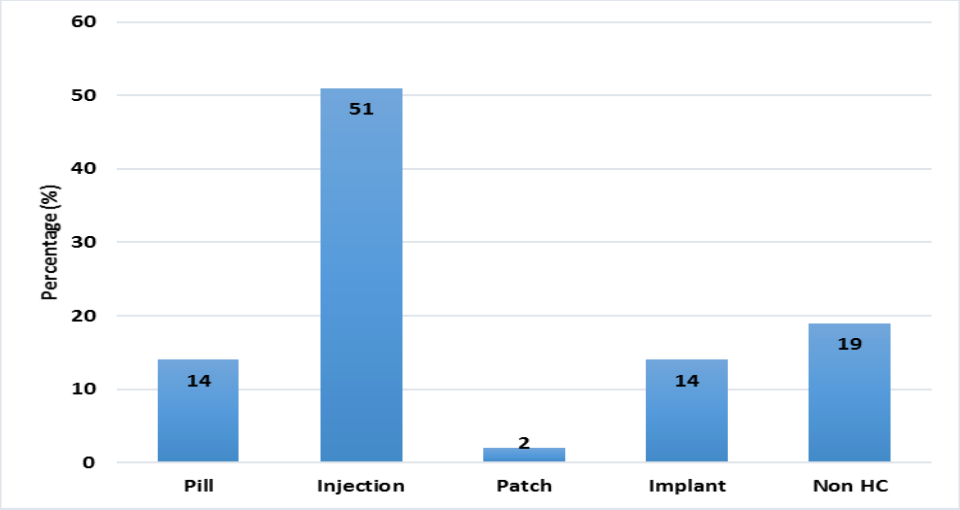


**Figure 4.2: Hormonal contraceptive use distribution in women attending HIV screening units in Mthatha (N:501)**

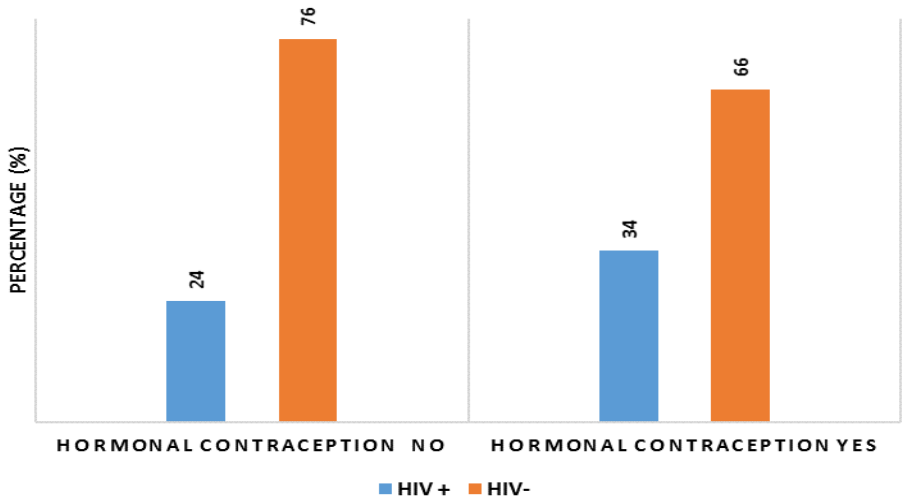


**Figure 4.3: HIV acquisition prevalence in woman attending CHC in Mthatha**

The adjusted and unadjusted odds ratio associated with a 95% confidence interval were obtained from univariate and multivariate logistic regressions by considering HIV acquisition as the outcome variable (Table 4.4). The unadjusted odds ratio showed that women who used hormonal contraception are 1.63 times as more likely to acquire HIV as women who did not use hormonal contraception (OR:1.63, 95%CI:0.97-2.74, P:0.065). When controlling recognisable risk factors of HIV acquisition identified by the use of DAG which are education, age, marital status and income, the adjusted odds ratio showed that women who used hormonal contraception are 1.87 times as more likely to acquire HIV as women who did not use hormonal contraception (OR:1.87, 95%CI:1.08-3.23, P:0.026). These results seem to confirm that HC may influence the risk of HIV acquisition in women attending CHC for HIV screening test in Mthatha.

**Table 4.3: Univariate & Multivariate analysis of the risk of HIV acquisition in relation to hormonal contraceptive.**

| | | Univariate (Unadjusted) | | Multivariate (Adjusted) | |
|---|---|---|---|---|---|
| | | OR (95%CI) | P | OR (95%CI) | P |
| Hormonal contraception use | No | 1 | | 1 | |
| | Yes | 1.63(0.97-2.74) | 0.065 | 1.87(1.08-3.23) | 0.026 |

Results were controlled for the following covariates: Education, Age, Marital status and Income

The test of effect modification between all controlled covariates and HIV acquisition is summarized in table 4.4, the result showed a significant interaction of Age and Marital status with the effect of HC on HIV acquisition on the additive scale (assessed using the RERI statistic) or multiplicative scale (assessed using the coefficient of the interaction term). This demonstrates that the interaction effect of these variables may alter the effect of HC on HIV acquisition (Table 4.4).

**Table 4.4: Test of interaction on the additive scale (RERI) and multiplicative scale (Beta) after adjusting for covariates.**

| | Test of effect modification | | | |
|---|---|---|---|---|
| | RERI[a] | P | Beta[b] | P |
| Age | 0.39 (-0.29,107) | 0.26 | 1.39 (1.13-1.71) | 0.02 |
| Education | 1.09 (-0.28, 2.5) | 0.12 | 0-1.90 (0.62.32) | 0.60 |
| Marital status | 0.43(0.11,0.74) | 0.07 | 1.22 (1.10-1.41) | 0.04 |
| Income | 0.31(-0.03,0.65) | 0.07 | 0.99 (0.71-1.40) | 0.62 |

The model is adjusted for age, education, marital status and income.
[a]Relative Excess Risk of Interaction (test of interaction on the additive scale); LB: Lower bound, UP: Upper bound
[b]Coefficient for the interaction dummy variable (test of interaction on the multiplicative scale).

Furthermore, to reinforce the later results on interaction, table 4.5 revealed that the prevalence of HIV acquisition gradually increased from younger women to older women and from married women to single women. Younger women showed an HIV prevalence of 11% while older women showed an HIV prevalence of 42% among all HIV newly diagnosed (Table 4.5). Additionally, married women showed an HIV prevalence of 24% while single women showed an HIV prevalence of 76 % among all HIV newly diagnosed (Table 4.5). Also, table 4.5 revealed that the prevalence of hormonal contraceptive use is evenly distributed among all age group in all women using hormonal contraceptive, and 82% of all women using HC were single (Table 4.5).

**Table 4.5: HIV Acquisition and hormonal contraceptive uses pattern by Age group and Marital status in woman attending CHC in Mthatha**

| | | Confirmed HIV positive (%) | Confirmed using hormonal contraception (%) |
|---|---|---|---|
| Age (year) | < 20 | 11 | 13 |
| | 20-24 | 23 | 31 |
| | 25-29 | 25 | 27 |
| | >30 | 42 | 28 |
| Marital status | Single | 76 | 82 |
| | Married | 24 | 18 |

## 4.6. Discussion

### 4.6.1. HIV prevalence

The study reported an HIV prevalence of 32%, which is comparatively higher than the national estimate for all age and gender at 14.0% in 2017 (68, 69). The overall

HIV prevalence was estimated at 15% for the province of Eastern Cape in 2017(69), this is still considerably lower than our recorded results. In addition, our participants were all female, it is well known that females have the higher HIV prevalence as compared to males (70, 71). The 2017 national HIV prevalence rate for female was estimated at 17% as compared to 11% for male, therefore confirming the higher prevalence rate found our study in females. All participants in this study were recruited in HIV screening unit for VCT, it is well known that the prevalence of HIV in screening facilities is positively correlated with sexual risk behaviour and health status (72). Our data recorded that 85% of women recruited for this study were coming to the voluntary screening facility with health problems as a motive. Furthermore, 15 % were found to have had sex without condoms and sex with an HIV positive man, hence making these women to be considered as high-risk population. Previous studies also done in South Africa reported that the prevalence of HIV is exponentially higher in high-risk population to such as sex workers, women having unprotected sex, women having multiple partners (73, 74). Subsequently, considering our participants as high-risk population will be the logical explanation of the higher recorded prevalence of HIV in our study.

### 4.6.2. Hormonal contraceptive and HIV acquisition association

The general finding of this study showed that HC usage is significantly associated with an increased risk of HIV acquisition in the present population. More precisely, our result showed that the risk of HIV acquisition is 1.87 time in women using HC as compared to woman who did not use (Table 4). Even, when we adjusted for multiples potential interaction factors, they were still no substantial variation in our results showing that confounding variables did not meaningfully alter the impact of HC in HIV acquisition in our study population. Our study reinforced the theory that the use of HC was significantly associated with the risk of HIV acquisition. These findings are similar to previous studies examining the role of HC on HIV acquisition (4, 42). A meta-analysis done by Polis in 2016 showed an estimated overall results that HIV acquisition is 1.2 and 1.7 in women using DMPA and COC respectively (75). Polis's analysis showed lower HIV acquisition risk as compared to our study partly because none of the studies used in his review recruited their participants in HIV screening facilities. In Africa, studies have also been also exploring the relationship between HC and HIV acquisition risk. A recent study involving seven

African countries reported that women using injectable contraceptives had a 2.05 fold increased risk of HIV acquisition (26). In South Africa, a multicentre 24 months cohort study done in Durban and Johannesburg, authors have found that there is a 34 % increase in the risk of HIV acquisition in women using injectable contraception, even though it was not conclusive as they reported a large confidence interval (19). In a more recent study done in Umlazi, a Township in South Africa, results showed that injection contraceptive significantly increases the risk of HIV acquisition by a hazard ratio of 2.4 (20). This later study location is closely similar to our study setting as it was also done in a rural area and more than half of our participants were similarly using injectable contraception, therefore supporting that the risk of HIV infection may be higher in women using injectable contraceptive as compared to other type HC (76).

### 4.6.3. Effect modification of the hormonal contraception and HIV acquisition

We conducted several analyses to consider possible effect modification on the effect of HC and HIV acquisition by age, education, marital status and Income. We found no indication of interaction between education and Income. However, there was a significant interaction between age and marital status on the effect of HC and HIV acquisition. A similar age interaction on the effect of HC on HIV acquisition was found in previous studies done in South Africa (77, 78). These previous studies did not explain the reason for the age interaction, suggesting that the mechanism is still unclear. We may suggest that physiological differences between younger and older women using HC may play a role in HIV acquisition. The difference in systemic immunity between younger and older woman could be altered leading to the observed results, it is well proven that HC affects immune function (79). Our study also confirmed the presence of interaction between marital status and the effect of HC and HIV acquisition. Previous studies have shown that the use of HC is higher in married women as compared to their counterpart single women (80, 81). Also, another study done in South Africa investigating the relationship between marital status and HIV acquisition clearly concluded that there is an association between marital status and HIV prevalence and incidence, they also found that the odds of being HIV-positive were lower among married individuals who lived with their spouses compared to all other marital status groups (82). Similarly to age, the

reasons behind the interaction of marital status on the effect of HC and HIV acquisition are still unclear.

### 4.6.4. Strength and Limitation

Our study is the first cross-sectional study evaluating the relationship between HC and HIV infection and also, one of the few studies to look at this relationship in a rural environment with limited health resources availability. Our findings deliver new data showing that contraception might increase a woman's risk of acquiring HIV, and they are consistent with results from longitudinal studies (20, 83). Previous studies were done in an urban setting where access to health facilities such as woman clinic, antenatal clinics are readily available. There is no available data on the effect of HC on HIV acquisition in the rural setting where the underlying factors driving the choice of a contraceptive method could be different from an urban environment. Also, previous studies were focused on the use of oral contraception and injection contraception, the remaining hormonal contraceptive categories such as implant and intrauterine devices were neglected. Most importantly, they did not highlight the relationship between HC and HIV according to age group knowing that younger women (15-24 years) are the most vulnerable to HIV infection mainly in the rural setting (82). Our investigation corrected these limitations by controlling for identifiable confounder variables and assessing the presence of effect modification. The shortcomings observed in our study were that HC use was evaluated using a self-report questionnaire and the data on HC adherence was not recorded. Measuring sexual behaviours in a cross-sectional study is difficult and barely relies on the participant's report. Other limitations are related to the study design itself, crossectionnal studies are not suitatble for determining causal relationship, therefore a cohort study would have been more appropriate. Lastly, the study was only conducted in Mthatha area making the conclusions not necessarily generalizable to other parts of South Africa.

## 4.7. Conclusions and recommendations

In summary, we found that HC was associated with the risk of HIV acquisition in women attending CHC in the rural setting of Mthatha. These results reinforce the theory of the contributing role of HC in the growing incidence of HIV as already suggested by prior studies. While further physiological and biochemical research is

required, it is advised that contraceptive counselling should be included in HIV screening and counselling for optimization of women sexual reproductive health and HIV prevention.

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## APPENDIX I


**PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS**

I *Eugene Jamot Ndebia* (Student number: 1004262) am a student registered for the degree of Masters of Science in Epidemiology (Epidemiology and Biostatistics) in the academic year 2019

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

- I have followed the required conventions in referencing the thoughts and ideas of others.

- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature: _____ Date: 26/06/2019

## APPENDIX II: Ethics clearance Certificate

R14/49 Dr Eugene Jamot Ndebia

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**

**CLEARANCE CERTIFICATE NO. M170427**

| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr Eugene Jamot Ndebia |
| **DEPARTMENT:** | School of Public Health<br>Community Health Centres in Mthatha:<br>Mhlakulo CHC, Stanford Terrace CHC,<br>Mbekweni CHC and Ngangelizwe CHC |
| **PROJECT TITLE:** | Hormonal Contraception Use and HIV Infection in Mthatha |
| **DATE CONSIDERED:** | 05/05/2017 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Dr Jabulani Ncayiyana |
| **APPROVED BY:** | Prof P Cleaton-Jones, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 10/07/2017 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**