MSc Project Report
2012-2013

Literature review: Effect of hormonal contraceptive use on acquisition of HIV and other sexually transmitted infections

Supervisor: Prof. Dr. David Mabey

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RESEARCH PROJECT APPROVAL PAGE

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MEHMET TALHA KUTLU
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PROF.DR. DAVID MABEY

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
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I. **LIST OF ABBREVIATIONS**

- **WHO** World Health Organization
- **STI** Sexually Transmitted Infection
- **STD** Sexually Transmitted Disease
- **OC** Oral Contraceptive
- **HC** Hormonal Contraceptive
- **HIV** Human Immunodeficiency Virus
- **AIDS** Acquired Immunodeficiency Syndrome
- **COC** Combined Oral Contraceptive
- **POP** Progestin Only Pill
- **DMPA** Depot Medroxyprogesterone Acetate
- **MPA** Medroxyprogesterone Acetate
- **Net-En** Norethisterone Enanthate
- **CI** Confidence Interval
- **RCT** Randomized Controlled Trial
- **BV** Bacterial Vaginosis
- **RR** Rate Ratio
II. LIST OF FIGURES AND TABLES

**Figure 1** Prospective studies on HIV acquisition and oral contraceptive use

**Figure 2** Prospective studies on cervical chlamydial infection and oral contraceptive use

**Figure 3** Prospective studies on HIV acquisition and injectable hormonal contraceptive, DMPA, use

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**Table 1** Prospective studies on HIV acquisition and oral contraceptive use

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**Table 4** Prospective studies on cervical chlamydial infection and injectable hormonal contraceptive, DMPA, use
III. ACKNOWLEDGEMENTS

I am very grateful for the support I have received for this project, and indeed for the entire MSc, from my personal tutor and my project supervisor Dr. David Mabey. I would like to thank David, for his availability thought the year as my tutor, for advices and drinks during the course and I want to thank David again for helpful discussions and suggestions for the project report as my supervisor.

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At the end I would like to thank my scholarship programme, thank you very much “Jean Monnet Scholarship Programme” and thank you all of the support team and advisors. If you did not fund me, I even would not imagine to study in this programme whatsoever.
IV. ÖZET

Giriş: Kondom kullanımının istikrarsız olması birbirinden farklı iki sağlık olayının temel sorunusudur: istenmeyen gebelik ve cinsel yolla bulaşan enfeksiyonlar. Hormonal kontraseptif yöntemler istenmeyen gebeliklerin önlenmesinde çok etkin yöntemlerdir ancak cinsel yolla bulaşan enfeksiyonlar ile hormonal kontraseptif yöntemler arasındaki ilişkiye dair endişeler mevcuttur. Bu proje hormonal kontraseptif yöntemler ile HIV’yi de içeren cinsel yolla bulaşan enfeksiyonlar arasındaki ilişkiyi ve hormonal kontraseptif kullanımın cinsel yolla bulaşan enfeksiyonlara yakalanma üzerinde etkisini incelemeyi amaçlamaktadır.


V. ABSTRACT

**Background:** Inconsistent use of condoms is the main responsible of two different health related incidents: unplanned pregnancy and sexually transmitted infections. Hormonal contraceptive methods are highly effective for preventing pregnancy however there are concerns about the association between sexually transmitted infections and hormonal contraception. This project aims to review the relation between hormonal contraception and sexually transmitted infections including HIV and to evaluate the effect of hormonal contraceptive use on acquisition of sexually transmitted infections including HIV in women.

**Methods:** PubMed and Embase databases were searched for all articles published in English through June 2013. 79 articles were used to review the association.

**Results:** Association between oral/injectable hormonal contraception and STIs including chlamydia, trichomonas, gonorrhoea and HIV infection were reviewed. Studies on bacterial vaginosis were also included due to the relation between HIV and BV. There was no RCT conducted to answer if hormonal contraception causes an increased risk of STI or not. Results of the prospective cohort studies were the most important evidence in the absence of RCTs.

**Conclusions:** Both types of hormonal contraception were likely to be protective against bacterial vaginosis and trichomonas vaginalis. Evidence on association between hormonal contraception and gonorrhoea and chlamydia infections were not conclusive. Studies on HIV were concluded that there was no increased risk of HIV with oral contraceptive use however the link between injectable contraception and increased risk of HIV is likely to be causal. Condoms are the only contraceptive method to reduce risk of STI. All women must be encouraged to consistent use of condoms in any sexual contact. No matter if hormonal contraception increases the risk of HIV or not, it is known that hormonal contraception is not protective for HIV and women must avoid sexual contact without condom.
1. INTRODUCTION

1.1 Background

According to WHO estimates, 499 million new cases of STIs including 105.7 million chlamydial infections, 276 million cases of trichomonas vaginalis and 106 million gonorrhea occurred in 2008[1]. Between 1999 and 2008, total number of STIs increased dramatically from 340 million to 499 million[1]. In the meanwhile, hormonal contraception use increased around the world. In 2000, there were 75 million women using oral contraceptives and in 2009 it increased to more than 103 million[2]. Use of injectable contraception increased from 27 million to 40 million[2].

Possible association between hormonal contraceptives and sexually transmitted infections may have a bigger role on community health than it is expected because use of hormonal contraceptives is not equally distributed in the world. Less developed regions with high prevalence of STIs and HIV are the regions where hormonal contraceptives, especially injectables, are widely being used[2]. To give an example, in South Africa, 28.4% of sexually active women aged between 15 and 49 were using injectable hormonal contraception which was eight times higher than world average[2].

Inconsistent use of condoms is the main responsible of two different health related incidents: unplanned pregnancy and sexually transmitted infections[3]. Male condoms are the most widely used condom type yet women cannot control use of male condoms at all times. Hormonal contraceptive methods which can be controlled purely by women are highly effective for preventing pregnancy however there are concerns about the association between sexually transmitted infections and hormonal contraception [3-7]. According to WHO’s report, available studies are not satisfactory enough to say whether hormonal contraception causes an increased risk of HIV acquisition or not[7]. Besides, hormonal contraception is crucial to reduce vertical transmission of HIV infection and improving maternal health[7]. Due to the fact that hormonal contraception is important for family planning, it is substantial to answer the question if they cause an increased risk of any STIs or not.
1.2 Aims and objectives

This project aims to review the relation between hormonal contraception and sexually transmitted infections including HIV and to evaluate the effect of hormonal contraceptive use on acquisition of sexually transmitted infections including HIV in women. Due to limited time and space, only studies on chlamydia, trichomonas, gonorrhoea and HIV were reviewed. Although it is not an STI, studies on bacterial vaginosis were also reviewed because of the strong association between bacterial vaginosis and hormonal contraception and HIV.

2. METHODS

2.1 Literature search

PubMed and Embase databases were searched for all articles published in English through June 2013 using the following search terms: (("hormonal contraception" OR "hormonal contraceptive") OR ("ethinyl estradiol" OR "ethynodiol diacetate" OR "progestin only" OR "oral contraceptive" OR "oral contraception" OR etonogestrel OR dmpa OR levonorgestrel OR "depot medroxyprogesterone acetate" OR "depot medroxyprogesterone acetate" OR norethindrone OR desogestrel OR drospirenone OR norgestrel OR norgestimate OR mifepristone OR ulipristal)) and (STI OR "sexually transmitted infection" OR "sexually transmitted disease" OR STD OR HIV OR "human immunodeficiency virus OR Syphilis OR Gonorrhoea OR trachomatis OR Chlamydia OR "C.trachomatis" OR chancroid OR hepatitis OR trichomonas OR T.vaginalis OR herpes OR gonorrhoea). These two databases were selected because it is known that Embase is more European focused and PubMed -an interface of the US National Library of Medicine, which has access to Medline-, is more North America-centric. These two databases complete each other although it increases work load due to duplicates. Search terms include 2 parts: the first group is for “hormonal contraception” and the second is for “sexually transmitted infections”. These searches yielded 3603 articles (828 in PubMed and 2775 in Embase) including duplicates (n=268).
2.2 Selection of studies

The title and abstract of 3335 articles were read and 137 articles were gained recognition. 3198 subjects were eliminated because either they did not address the research question or they were not original studies (commentaries, letters and news). 8 of these 137 articles could not be accessed as a full text yet seven of eight articles were cross sectional studies and almost all of them were published before 1995. After reading the full text of remaining 129 articles, a further 50 were rejected because they did not address the research question. Remaining 79 articles, including 6 systematic reviews, were used in this literature review to discuss the research question.

2.3 Assessment of the study quality

A scoring system were set up by the help of previous studies before reading the articles and each article was scored according to this system[4, 5]. The scoring system works as follows:

- The study is prospective: 2 point
- The measure of effect was adjusted for the potential confounders: 1 point
- The switches between contraceptive groups were taken into account: 1 point
- The study did not target the symptomatic women nor sex workers: 1 point
- The control group did not include any pregnant women: 1 point
- The exposure group consisted of only one hormonal method: 1point

Scoring all articles from 0 to 7 allowed ordering the studies. If the studies had the same score, they were ordered from largest to smallest sample size. Due to nature of the research question, it is important to pay regard to the results of prospective cohort studies are much more valuable than the results of the cross sectional studies. Since it is aimed to identify whether an aetiological association exists or not, prospective studies were investigated more detailed. In the cross sectional studies, the temporal sequence of contraceptive exposure and disease outcome cannot be determined. This is the reason why these two types of studies were reported separately in results section.

Prospective studies were conducted with different populations, different countries, different risk and age groups. Because of the fact that heterogeneity of studies, I preferred to prepare a literature review rather than meta-analysis.
3. RESULTS

3.1 Oral Contraceptives

Many studies did not indicate if “oral contraceptive users” group include “progestin only pill” users or not. However, it is known that in most countries, COCs are used more widely than POPs, this is the reason why COCs and OCs studies were reported together.

3.1.1 HIV

Prospective studies

Evidence on whether oral contraceptives alter a women’s risk of HIV acquisition is mixed. 20 prospective studies including two case-control studies, one historical cohort and 17 prospective cohort studies that examined association between oral contraceptive use and HIV acquisition were identified (Figure1 & Table1) [8-27]. 6 studies were conducted among sex workers, one study had discordant couples, women who have HIV (+) partners and two studies recruited only HSV positive women[9, 10, 19, 21, 23, 25, 27] [16, 26]. Remaining studies were community based, mostly with women recruited from HIV prevention trials. There is only one recent study had different exposure group for POP users [11]. Two studies did not differentiate different types of hormonal contraceptives in the exposure group and they reported results for hormonal contraceptives[17, 26].

Only two of the 20 prospective studies found significantly increased risk of HIV associated with OC use[9, 23]. These studies had the quality score of 3 and 6 respectively. Both studies were conducted among Kenyan sex workers. In Plummer’s study, only 39 OC users were recruited and this relatively small number of population caused a wide confidence interval OR: 4.5 [1.4-13.8][23]. This study has been assessed as a poor quality study with score of 3. Lavreys et al. found weaker association but it is still statistically significant OR: 1.5 [1.0-2.1] in a better quality study with score of 6[9]. Of the 4 studies among sex workers with non-significant results, one reported estimates for the effect of OC use on HIV acquisition of at least 1.8, trend towards harmful, while one other reported estimates for OC use of 0.5 or lower, trend towards protective[21, 25].

None of six studies with a maximum quality score has a statistically significant result[8, 11-14, 19]. Only one study reported a trend towards harmful with OR of 1.8[19]. Other 5
studies did not find any increased or decreased risk, their OR were between 0.84-1.20, very close to 1.0[11-14]. Two of these articles were same study with different methods of data analysis. Morrison et al. used “cox proportional hazard regression models” in 2007 and then they thought “marginal structural modelling” could better explain their results regarding adjustment for confounders and they re-analysed their results in 2010. After re-analysis, the risk ratio for the association between OC use and HIV increased to 1.19 from 0.99[12, 13]. This cohort also had the largest number of OC users among all studies, 1542 women recruited for OC users arm[13]. So the insignificant results of other community based studies may be due to lower number of women recruited in the study. In a case control study, they reported odds ratio of 3.5[0.8-21.5] but it was a pilot study and the study population was less than 100 people[24].

**Cross-sectional studies**

11 cross sectional studies were identified to assess OC-HIV association [25, 28-37]. Five of these studies found statistically significant association between OC use and HIV acquisition however the results were controversial. Two studies reported negative association between HIV and OC use while 3 studies found a positive association[34] [29, 35, 36]. Lecrec et al. reported their results separately for different countries they conducted the study. They reported significantly less HIV infection in OC users for women in Zimbabwe but not for women in Malawi, Kenya and Lesotho[32]. One of the studies had different exposure groups for different duration of OC use and they showed that with the increased duration of OC use, HIV was increased[35].
Figure 1: Prospective studies on HIV acquisition and oral contraceptive use
<table>
<thead>
<tr>
<th>Year &amp; first author</th>
<th>Country</th>
<th>Study design &amp; population</th>
<th>Comparison group</th>
<th>Incident infections</th>
<th>Results adjusted for</th>
<th>Rate ratio [95% CI]</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCoy, 2013</td>
<td>South Africa &amp; Zimbabwe</td>
<td>Prospective study of 4913 non-pregnant sexually active women participating a phase III HIV prevention trial.</td>
<td>No hormonal methods</td>
<td>283</td>
<td>Site, Age, marital status, parity, sexual behaviours, living with partner, condom use</td>
<td>0.84 [0.57-1.22]</td>
<td>7</td>
</tr>
<tr>
<td>Morrison, 2012</td>
<td>South Africa</td>
<td>Prospective study of 5567 sexually active non-pregnant women aged 16–49 years participating in a HIV prevention Trial.</td>
<td>No hormonal methods</td>
<td>270</td>
<td>Site, Age, marital status, parity, sexual behaviours, living with partner, condom use</td>
<td>0.84 [0.51-1.39]</td>
<td>7</td>
</tr>
<tr>
<td>Morrison, 2010</td>
<td></td>
<td>Re-analyse of 2007, Morrison et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morrison, 2007</td>
<td>Uganda &amp; Zimbabwe</td>
<td>Prospective study of 4439 non-pregnant women aged 18–35 years, from family planning clinics.</td>
<td>No hormonal methods</td>
<td>213</td>
<td>Condom use, sexual behaviours, partner risk, number of sexual events, age, site, living with partner</td>
<td>1.19 [0.80-1.76]</td>
<td>7</td>
</tr>
<tr>
<td>Kiddugavu, 2003</td>
<td>Uganda</td>
<td>Prospective study of 5117 sexually active HIV-negative women selected from community for AIDS prevention trial.</td>
<td>No hormonal methods &amp; non condom users</td>
<td>202</td>
<td>Age, marital disruption, number of sex partners, genital ulcer diseases.</td>
<td>1.12 [0.48-2.56]</td>
<td>7</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Methodology</td>
<td>Age, pregnancy, unprotected sex, plasma HIV-1 levels of partners.</td>
<td>Reference</td>
<td>n</td>
<td>p-value</td>
</tr>
<tr>
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<td>------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Heffron, 2012</td>
<td>Uganda South Africa Botswana Zambia Tanzania Kenya &amp; Rwanda</td>
<td>Prospective study of 1314 heterosexual HIV-1 serodiscordant couples in which the HIV seronegative partner was female</td>
<td>No hormonal methods</td>
<td>73</td>
<td>1.80 [0.55-5.82]</td>
<td>[5]</td>
<td></td>
</tr>
<tr>
<td>Lavreys, 2004</td>
<td>Kenya</td>
<td>Prospective study of 1272 HIV negative female sex workers attending a municipal clinic for regular STI check.</td>
<td>None/tubal ligation</td>
<td>248</td>
<td>1.5 [1.0-2.1]</td>
<td>[6]</td>
<td></td>
</tr>
<tr>
<td>Wand, 2012</td>
<td>South Africa</td>
<td>Prospective study of 2 236 HIV-negative women who were screened in a biomedical intervention trial.</td>
<td>None and Condom users and other methods</td>
<td>227</td>
<td>0.95 [0.62-1.46]</td>
<td>[5]</td>
<td></td>
</tr>
<tr>
<td>Myer, 2007</td>
<td>South Africa</td>
<td>Prospective study of 4200 HIV-negative women aged 35–49 years enrolled into a cervical cancer screening trial from community.</td>
<td>No hormonal methods</td>
<td>111</td>
<td>0.65 [0.16-2.66]</td>
<td>[5]</td>
<td></td>
</tr>
<tr>
<td>Martin, 1998</td>
<td>Kenya</td>
<td>Prospective study of 779 HIV negative female sex workers attending a municipal clinic for regular STI check.</td>
<td>None/tubal ligation</td>
<td>111</td>
<td>1.3 [0.8-2.2]</td>
<td>[5]</td>
<td></td>
</tr>
<tr>
<td>Country, Year</td>
<td>Location</td>
<td>Study Type</td>
<td>Eligibility Criteria</td>
<td>Contraception Status</td>
<td>Variables Assessed</td>
<td>Odds Ratio (95% CI)</td>
<td>p-value</td>
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<tr>
<td>Reid, 2010</td>
<td>South Africa Zambia &amp; Zimbabwe</td>
<td>Prospective study of 1358 HIV negative, HSV-2 seropositive women who were attending family planning clinic and recruited for antiviral trial.</td>
<td>No contraception</td>
<td>Demographics, Site, Sexual behaviours</td>
<td>0.91 [0.45-1.83]</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Bulterys, 1994</td>
<td>Rwanda</td>
<td>Prospective study of 1150 HIV seronegative women aged 16-30 and who were pregnant 2 years before the study and recruited from a prenatal clinics.</td>
<td>No contraception</td>
<td>Age, marital status, history of STI, sexual relations with other partners</td>
<td>1.9 [0.8-4.6]</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Kilmarx, 1998</td>
<td>Thailand</td>
<td>Prospective study of 285 HIV seronegative female sex workers.</td>
<td>No OC</td>
<td>Age, chlamydial infection, oral sex, genital ulcer disease, vaginal sex during menses, years in sex work</td>
<td>1.8 [0.8-4.0]</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Feldblum, 2010</td>
<td>Nigeria Ghana Benin Uganda India &amp; South Africa</td>
<td>Historic cohort of 7364 non-pregnant, HIV negative women who were participating four different HIV prevention trials.</td>
<td>No contraception</td>
<td>Age, education Association is not statistically significant.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapiga, 1998</td>
<td>Tanzania</td>
<td>Prospective study of 1370 HIV negative women recruited from three family planning clinics.</td>
<td>No OC</td>
<td>Numbers of sex partner, alcohol consumption, having an uncircumcised husband, gonorrhoea and candidiasis at baseline</td>
<td>1.01 [0.45-2.28]</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Study Description</td>
<td>Methodology</td>
<td>Age (Odds Ratio)</td>
<td>Demographics, duration in sex work, syphilis (Odds Ratio)</td>
<td>Sexual behaviour, condom use, marital status (Odds Ratio)</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
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<td>-----------------------------------------</td>
<td>------------------</td>
<td>----------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Watson-Jones, 2009</td>
<td>Tanzania</td>
<td>Prospective study of 821 HSV-2 seropositive, HIV seronegative women aged 16-35.</td>
<td>No hormonal methods</td>
<td>63</td>
<td>1.60 [0.93-2.76]</td>
<td>0.22 [0.03-1.87]</td>
<td></td>
</tr>
<tr>
<td>Ungchusak, 1996</td>
<td>Thailand</td>
<td>Prospective study of 240 female sex workers working in illegal brothels.</td>
<td>No contraception</td>
<td>15</td>
<td>0.22 [0.03-1.87]</td>
<td>3.5 [0.8-21.5] (Odds Ratio)</td>
<td></td>
</tr>
<tr>
<td>Sinei, 1996</td>
<td>Kenya</td>
<td>Prospective study of 1030 seronegative women attending a family planning clinic. Afterwards, it was conducted a nested case control study with 17 cases and 51 controls from the same cohort.</td>
<td>Mainly IUD and some other nonhormonal methods</td>
<td>14</td>
<td>3.5 [0.8-21.5] (Odds Ratio)</td>
<td>(Odds Ratio)</td>
<td></td>
</tr>
<tr>
<td>Plummer, 1991</td>
<td>Kenya</td>
<td>Prospective study of 124 female sex workers who were recruited for an STI project.</td>
<td>No OC</td>
<td>83</td>
<td>4.5 [1.4-13.8]</td>
<td>0.9 [0-13.5] (Odds Ratio)</td>
<td></td>
</tr>
<tr>
<td>Laga, 1993</td>
<td>Zaire</td>
<td>Prospective study of 431 HIV negative female sex workers followed for two years and created a nested case control study with 68 cases and 126 controls.</td>
<td>No OC</td>
<td>68</td>
<td>4.5 [1.4-13.8]</td>
<td>0.9 [0-13.5] (Odds Ratio)</td>
<td></td>
</tr>
</tbody>
</table>
3.1.2 Chlamydia

*Prospective studies*

Nine prospective cohort studies have examined OC use and acquisition of Chlamydia trachomatis infection (Figure 2 & Table 2) [15, 18, 38-44]. Unlike HIV studies, not all of the chlamydia studies conducted in Africa, there is one cohort from Belgium, one from USA and one from Sweden. Four of nine studies included only high-risk populations like sex workers or women work at bars.

Two studies found statistically significant positive association between OC use and acquiring chlamydial infection [38, 39]. However Avontos et al. did not adjust the results for any possible confounders and there were only 10 incident infections in this study. The other study with significant result was conducted in Kenyan sex workers cohort, it had relatively larger sample with 147 OC users and 175 incident infections [38, 39].

Of the seven studies without significant results, one reported decreased risk with OR of 0.2, this is the only study showed decreased risk although its CI includes 1.0 [41]. It is important to indicate that median age of this sex workers cohort was 35, greater than all other studies [41]. There is another cohort of HIV (+) Kenyan sex workers and they reported statistically non significant increased risk, RR: 2.2 [0.7-7.3] [44]. It is worth to note that although these two cohorts had very similar baseline characteristics beside the median age of the cohort, they reported controversial results [41, 44].

*Cross-sectional studies*

Nine cross sectional studies were identified to discuss chalmydia and OC association [45-53]. Statistically significant results of five studies were consistent; they found positive association between OC use and chlamydial infection. However like most of the cross sectional studies, three of these five studies failed to adjust their results for possible confounders [45, 48, 50, 53]. Madger et al. reported separate results for women over and under 20 year old. They found positive association between OC use and Chlamydia for only women aged 20 or younger and they found an estimated protective effect of OC use against Chlamydia for women over 20 year old OR: 0.59 p=0.09 [50]. One of the biggest studies was conducted among randomly selected 70000 women from Nordic countries, Sweden, Norway, Denmark and Iceland showed positive association between chlamydial
infection and ever use of hormonal contraception, pills or injectables. Association was consistent after results were adjusted for age, education, lifetime number of partners and history of other STIs[47].
Figure 2: Prospective studies on cervical chlamydial infection and oral contraceptive use
<table>
<thead>
<tr>
<th>Year and first author</th>
<th>Country</th>
<th>Study design &amp; population</th>
<th>Comparison group</th>
<th>Incident infections</th>
<th>Results adjusted for</th>
<th>Rate ratio [95% CI]</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baeten, 2001</td>
<td>Kenya</td>
<td>Prospective cohort included 948 female sex workers participating a HIV prevention trial.</td>
<td>None/tubal ligation</td>
<td>175</td>
<td>Age, education, years of prostitution, parity, work place, number of sexual partners per week, number of sexual events per week, condom use</td>
<td>1.8 [1.1-2.9]</td>
<td>6</td>
</tr>
<tr>
<td>Morrison, 2004</td>
<td>USA</td>
<td>Prospective study of 819 women seeking gynaecologic care</td>
<td>No hormonal methods</td>
<td>37</td>
<td>Age, ethnicity, having multiple sex partners</td>
<td>1.5 [0.6-3.5]</td>
<td>6</td>
</tr>
<tr>
<td>Masese, 2013</td>
<td>Kenya</td>
<td>Prospective study of 865 female sex workers aged 18-50.</td>
<td>No hormonal methods</td>
<td>101</td>
<td>No adjustment</td>
<td>0.2 [0.0-1.7]</td>
<td>5</td>
</tr>
<tr>
<td>Lavreys, 2004</td>
<td>Kenya</td>
<td>A prospective cohort study of 242 HIV seropositive female sex workers followed by another cohort study.</td>
<td>None/tubal ligation</td>
<td>26</td>
<td>Demographics and sexual behaviour</td>
<td>2.2 [0.7-7.3]</td>
<td>5</td>
</tr>
<tr>
<td>Wand, 2012</td>
<td>South Africa</td>
<td>Prospective study of 2 236 HIV-negative women who were screened in a biomedical intervention trial.</td>
<td>None and Condom users and other methods</td>
<td>NA</td>
<td>Age, number of sexual partners, pregnancy, number of sexual events, condom used in last sexual act.</td>
<td>1.74 [0.93-3.25]</td>
<td>5</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Description</td>
<td>Contraception</td>
<td>Age, number of sex partners, sexual behaviour</td>
<td>Association</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
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<td>------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Feldblum, 2010</td>
<td>Nigeria, Benin, Uganda, India &amp; South Africa</td>
<td>Historic cohort of 7364 non-pregnant, HIV negative women who were participating four different HIV prevention trials.</td>
<td>No contraception</td>
<td>126 Age, education</td>
<td>Association is not statistically significant.</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Rahm, 1991</td>
<td>Sweden</td>
<td>Prospective study of 301 sexually active teenage girls attending an adolescence clinic.</td>
<td>No OC</td>
<td>51 No adjustment</td>
<td>0.67 [0.27-1.68]</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Avonts, 1990</td>
<td>Belgium</td>
<td>Prospective study of 164 women recruited in one family practice.</td>
<td>IUD</td>
<td>10 No adjustment</td>
<td>8.8 [1.3-59.0]</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Kapiga, 2009</td>
<td>South Africa, Tanzania, Zambia</td>
<td>Prospective study of 958 women at risk of STIs recruited from general population and family planning clinics.</td>
<td>No hormonal methods</td>
<td>NA Age, number of sex partners, sexual behaviour</td>
<td>1.4 [0.7-3.1]</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kapiga et al reported results separately for different countries.</td>
<td>No hormonal methods</td>
<td>NA Age, number of sex partners, sexual behaviour</td>
<td>0.9 [0.3-2.6]</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
3.1.3 Gonorrhea

**Prospective studies**

4 prospective and one historical cohort studies have examined OC use and acquisition of Neisseria gonorrhoea[15, 18, 39, 40, 44]. One of the studies conducted among HIV (+) sex workers and two of them among HIV(-) sex workers. There are two community based studies. None of these studies reported an increased risk of gonorrhea with OC use before or after adjustment for possible confounders like number of sexual partners, number of sexual events.

**Cross-sectional studies**

Among five cross-sectional studies, three of them found statistically significant results after adjustment[47, 48, 54-56]. One study among 98 females reporting sexual contact to a male partner diagnosed with N. gonorrhoea found a negative association between OC use and acquisition of gonorrhoea OR=0.42[0.22-0.78]. Since diagnosis of male partner were based on self reporting of women, it may not reflect the true association[56]. Another USA based cross sectional study showed increased risk of gonorrhea among OC users when it is compared to women not using any contraception however this study failed to adjust this result[54]. Additionally, one study from Tanzania found increased risk of gonorrhea among OC users comparing to non users[55]. The results were consistent even after adjusting for condom use and number of sexual partners but this study did not describe the comparison group well enough, it is not clear if the comparison group consisting women who use injectable hormonal contraception or not[55].

3.1.4 Trichomonas

**Prospective studies**

Four prospective studies have assessed the effect of OCs on risk of incident Trichomonas vaginalis infection[38-40, 57]. Of the four prospective studies on OC and risk of trichomonas, one study conducted among high risk groups found statistically significant protective effect, OR=0.6 [0.3-1.0][40]. However, Kenyan sex workers cohort, comparing OC users and none contraceptive users, did not find any effect of OC use on trichomonas infection[39]. There was only one community based prospective study, it compared IUD users to OC users and there were only ten incident cases of trichomonas infection, it estimates for the protective effect of OC use on trichomonas acquisition for 0.25[0.07-
In one case control study with 539 cases, it is found that oral contraceptive use was protective against trichomonas, however, after adjusting for demographics and condom use this association was not statistically significant[57].

**Cross-sectional studies**

Cross sectional studies suggest a decrease in risk of trichomonas infection associated with OC use. Six cross sectional studies evaluated the association between trichomonas and OC use, five reported statistically significant evidence of protective association[48, 52, 55, 58, 59]. One remaining study among women in four Nordic countries, reported no association between OC use and trichomonas. It is important to note that this is the largest cross-sectional study with 70000 women[47].

### 3.1.5 Bacterial vaginosis

**Prospective studies**

Five prospective and one historical cohort have evaluated association between OCs and BV [38, 39, 60-63]. 4 studies reported statistically significant protective effects against BV with OC use[38, 39, 61, 62]. The historical cohort had different exposure groups for POP users and COC users and it compared pill users and women not using a contraceptive method. According to this study while POP use was protective against BV, COC not [61]. Two large studies with 5198 and 2984 incident BV cases both reported protective effect of OC use against BV although one of them was conducted among Kenyan sex workers and the other one was US community based[39, 62]. These two studies adjusted the results for possible confounders like sexual behaviours and demographics. Last prospective cohort was conducted among Belgian women in 1990 found statistically significant protective effect however the results weren’t adjusted and only crude OR was available [38].

**Cross-sectional studies**

Results of five cross-sectional studies were consistent with prospective studies. Two studies had exposure group for only OC users and they showed protective effect of OCs against BV[52, 64]. Tibaldi et al. conducted a large study with more than 20000 women and 11838 incident BV cases. Although the association between OC use and BV was not significant in univariate analysis, it became significant after adjusting for age, marital status, sexual behaviour and pregnancy[52]. Three studies included injectable users in the
exposure group with OC users[49, 65, 66]. Of the three studies included injectable users in exposure group, one found statistically significant protective effect while two others reported no association.

3.2 Injectable contraception

Injectable contraception refers to DMPA in many studies yet there are some studies created a different exposure group for Net-En users, and there are some studies did not indicate the type or name of the injectable contraceptive. They all were aggregated under “injectable contraceptives” title in this project. If the authors reported different results for different Net-En users, it was indicated as well.

3.2.1 HIV

Prospective studies

20 prospective studies, including a nested case control study, one historical and 18 prospective cohort studies, have examined the relationship between injectable contraceptives and HIV acquisition in women(Figure3 & Table3) [8-22, 25, 26, 67-69]. Three studies included other hormonal contraceptive methods like OCs in the exposure group but none of them have a statistically significant results[17, 18, 26]. Only one of these three, reported raised but non-significant, relative risk[17]. 17 studies reported results for DMPA and four of them reported separate results for Net-En users, in addition to DMPA results[11, 14, 22, 69].

Eight studies found statistically significant increased risk of HIV associated with DMPA[9, 10, 12, 15, 19, 25, 67, 68]. Two studies reported non-significant protective effects for DMPA on HIV risk[20, 69]. Seven studies did not find any association between DMPA and HIV acquisition, risk ratios vary between 0.80-1.25[8, 11, 13, 14, 16, 21, 22].

Prospective studies among high risk groups, sex workers & serodiscordant couples

Of the eight studies found statistically significant result, two were Kenyan sex workers cohort [9, 10]. It was a dynamic cohort, new sex workers were recruited during years and due to loss to follow ups, cohort would renew in every 6-8 years. It is same design, same
study with different sex workers population. These two studies found risk of HIV acquisition in DMPA users increased two fold, results were significant even after adjustment for condom use, genital ulcer diseases and number of sex partners. However, these two studies don’t have the maximum quality score, they are mid-quality studies.

In 1996, Ungchusak et al. found statistically significant association between DMPA use and HIV in a Thai sex workers cohort, however cohort was followed for a year and there were only 15 incident cases. Result was adjusted for sexual behaviour however it was not clear if it is adjusted for barrier method use or not. This study has the poorest quality score among prospective studies[25]. On the other hand, in 1998, another Thai sex workers cohort, Kilmarx et al. did not find an increased risk for HIV in DMPA users when it is compared to non-users. There were 30 incident infection in this cohort and OR was 1.5[0.6-4.0] but this study failed to adjust crude odds ratios and OC users were included to comparison group of DMPA users[21].

One recent study among 1314 serodiscordant couples found the risk of HIV acquisition for DMPA users increased two fold[19]. This study used marginal structural modelling to adjust for time dependent confounding but results were statistically significant before and after this adjustment. This is one of the studies with maximum quality score of seven.

Community based prospective studies
There were four community based cohort studies with maximum quality score of seven. [8, 11, 13, 14]. All of four cohorts had more than 200 incident infections and study populations were about two thousand women to be able to reach statistically significant results. Only the most recent study was mainly designed to identify association between OC and HIV and it had only 59 injectable hormonal contraception users, which may not be enough to conclude significant results[11]. None of these studies have statistically significant results however Morrison et al. Reanalyse the cohort data with different modelling technique in 2010 and they found a statistically significant increased risk of HIV for DMPA users[12]. Re-analysis of the cohort showed that while DMPA use among young women was associated with increased risk of HIV acquisition, DMPA use in older women was not. Similar effect modification was also reported for HSV status of women. It is reported that DMPA increased the HIV risk in HSV positive women but not in HSV
negatives [12, 13]. However, this is the only study to be able to found age and HSV status as effect modifiers, some other studies have contradictive results[70].

There was only one study had quality score of six over seven. It was relatively small cohort with 23 incident infections and it found non-significant protective effect of DMPA on HIV acquisition OR: 0.46[0.06-3.79][69]. It is important to note that same study found non-significant increased risk of HIV for Net-En users[69].

There were six studies which have relatively low quality scores of four and five[15, 16, 18, 20, 22, 67, 68]. Only two cohorts found statistically significant association between DMPA use and HIV acquisition[15, 68]. Kumwenda et al. conducted a cohort in Malawi, among 787 family planning clinic attendees. There were 31 incident HIV case in this cohort and they also conducted a nested-case control study via matching each HIV (+) cases to two seronegative women having same number of sexual partners. They found statistically significant increased risk in DMPA users in both types of studies, odds ratios were 2.84[1.07-7.55] and 10.42[1.19-90.93] respectively[67, 68]. The other study with significant results found two fold increased risk for DMPA users however they included condom users in the comparison group[15].One study found statistically non-significant protective effect of DMPA use on HIV acquisition like Kleinschmidt et al. however loss to follow up was 44.5% in this study and the results might have been biased due to high number of loss to follow up[20, 69].
Figure 3: Prospective studies on HIV acquisition and injectable hormonal contraception, DMPA, use

Community based studies

Studies on high risk groups

Rate Ratios & 95% Confidence Intervals
<table>
<thead>
<tr>
<th>Year &amp; first author</th>
<th>Country</th>
<th>Study design &amp; population</th>
<th>Comparison group</th>
<th>Incident infections</th>
<th>Results adjusted for</th>
<th>Rate ratio [95% CI]</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCoy, 2013</td>
<td>South Africa &amp; Zimbabwe</td>
<td>Prospective study of 4913 non-pregnant sexually active women participating a phase III HIV prevention trial.</td>
<td>No hormonal methods</td>
<td>283</td>
<td>Site, Age, marital status, parity, sexual behaviours, living with partner, condom use</td>
<td>1.22 [0.84-1.74]</td>
<td>7</td>
</tr>
<tr>
<td>Morrison, 2012</td>
<td>South Africa</td>
<td>Prospective study of 5567 sexually active non-pregnant women aged 16–49 years participating in a HIV prevention Trial.</td>
<td>No hormonal methods</td>
<td>270</td>
<td>Site, Age, marital status, parity, sexual behaviours, living with partner, condom use</td>
<td>1.28 [0.92-1.78]</td>
<td>7</td>
</tr>
<tr>
<td>Morrison, 2010</td>
<td>Re-analyse of 2007, Morrison et al.</td>
<td></td>
<td></td>
<td></td>
<td>Condom use, sexual behaviours, partner risk, number of sexual events, age, site, living with partner</td>
<td>1.48 [1.02-2.15]</td>
<td>7</td>
</tr>
<tr>
<td>Morrison, 2007</td>
<td>Uganda &amp; Zimbabwe</td>
<td>Prospective study of 4439 non-pregnant women aged 18–35 years, from family planning clinics.</td>
<td>No hormonal methods</td>
<td>213</td>
<td>Site, living with partner, age, behavioural risk, number of sexual events.</td>
<td>1.25 [0.89-1.78]</td>
<td>7</td>
</tr>
<tr>
<td>Kiddugavu, 2003</td>
<td>Uganda</td>
<td>Prospective study of 5117 sexually active HIV-negative women selected from community for AIDS prevention trial.</td>
<td>No hormonal methods &amp; non condom users</td>
<td>202</td>
<td>Age, marital disruption, number of sex partners, genital ulcer diseases.</td>
<td>0.84 [0.41-1.72]</td>
<td>7</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Exclusion Criteria</td>
<td>n</td>
<td>Primary Outcomes</td>
<td>Odds Ratio [CI]</td>
<td>Studies</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>------------------------------------------------------------------------------</td>
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<td>-----------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Heffron, 2012</td>
<td>Uganda, South Africa, Botswana, Zambia, Tanzania, Kenya &amp; Rwanda</td>
<td>Prospective study of 1314 heterosexual HIV-1 serodiscordant couples in which the HIV seronegative partner was female</td>
<td>No hormonal methods</td>
<td>73</td>
<td>Age, pregnancy, unprotected sex, plasma HIV-1 levels of partners.</td>
<td>2.05 [1.04-4.04]</td>
<td>South Africa, Botswana, Tanzania, Kenya &amp; Rwanda</td>
</tr>
<tr>
<td>Kleinschmidt, 2007</td>
<td>South Africa</td>
<td>Prospective study of 551 HIV-negative women recruited from a family planning clinic</td>
<td>No hormonal methods</td>
<td>23</td>
<td>Condom use, partners, age, gonorrhoea, BV and trichomonas</td>
<td>0.46 [0.06-3.79]</td>
<td>South Africa</td>
</tr>
<tr>
<td>Lavreys, 2004</td>
<td>Kenya</td>
<td>Prospective study of 1272 HIV negative female sex workers attending a municipal clinic for regular STI check.</td>
<td>None/tubal ligation</td>
<td>248</td>
<td>Age, duration of prostitution, parity, work place, number of sex partners, condom use, vaginal douching with soap products, presence of STI</td>
<td>1.8 [1.4-2.4]</td>
<td>Kenya</td>
</tr>
<tr>
<td>Wand, 2012</td>
<td>South Africa</td>
<td>Prospective study of 2 236 HIV-negative women who were screened in a biomedical intervention trial.</td>
<td>None and Condom users and other methods</td>
<td>227</td>
<td>Age, number of sexual partners, pregnancy, number of sexual events, condom used in last sexual act.</td>
<td>2.02 [1.37-3.00]</td>
<td>South Africa</td>
</tr>
<tr>
<td>Myer, 2007</td>
<td>South Africa</td>
<td>Prospective study of 4200 HIV-negative women aged 35–49 years enrolled into a cervical cancer screening trial from community.</td>
<td>No hormonal methods</td>
<td>111</td>
<td>Marital status, housing type, alcohol consumption, condom use, previous treatment for a sexually transmitted infection, multiple sexual partners, baseline sexually transmitted infections</td>
<td>0.96 [0.58-1.59]</td>
<td>South Africa</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Country</td>
<td>Study Description</td>
<td>None/tubal ligation</td>
<td>Place of work, number of sex partners, condom use, parity, vulvitis, genital ulcer diseases, BV, candidiasis, gonorrhoea, vaginal discharge</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>Study Size</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Martin, 1998</td>
<td>Kenya</td>
<td>Prospective study of 779 HIV negative female sex workers attending a municipal clinic for regular STI check.</td>
<td>None/tubal ligation</td>
<td>111 Place of work, number of sex partners, condom use, parity, vulvitis, genital ulcer diseases, BV, candidiasis, gonorrhoea, vaginal discharge</td>
<td>2.0 [1.3-3.1]</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Reid, 2010</td>
<td>South Africa, Zambia &amp; Zimbabwe</td>
<td>Prospective study of 1358 HIV negative, HSV-2 seropositive women who were attending family planning clinic and recruited for antiviral trial.</td>
<td>No contraception</td>
<td>72 Demographics, Site, Sexual behaviours</td>
<td>0.94 [0.46-1.92]</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Bultery, 1994</td>
<td>Rwanda</td>
<td>Prospective study of 1150 HIV seronegative women aged 16-30 and who were pregnant 2 years before the study and recruited from a prenatal clinics.</td>
<td>No contraception</td>
<td>31 Age, marital status, history of STI, sexual relations with other partners</td>
<td>1.9 [0.8-4.6]</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Kilmarx, 1998</td>
<td>Thailand</td>
<td>Prospective study of 285 HIV seronegative female sex workers.</td>
<td>No OC</td>
<td>30 Age, chlamydial infection, oral sex, genital ulcer disease, vaginal sex during menses, years in sex work</td>
<td>1.5 [0.6-4.0]</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Feldblum, 2010</td>
<td>Nigeria, Ghana, Benin, Uganda, India &amp; South Africa</td>
<td>Historic cohort of 7364 non-pregnant, HIV negative women who were participating four different HIV prevention trials.</td>
<td>No contraception</td>
<td>114 Age, education</td>
<td>Association is not statistically significant.</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Description</td>
<td>Method of Contraception</td>
<td>Number</td>
<td>Outcome Measures</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>-------</td>
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<td>------------</td>
</tr>
<tr>
<td>Kapiga, 1998</td>
<td>Tanzania</td>
<td>Prospective study</td>
<td>1370 HIV negative women recruited from three family planning clinics.</td>
<td>No OC</td>
<td>75</td>
<td>Numbers of sex partner, alcohol consumption, having an uncircumcised husband, gonorrhoea and candidiasis at baseline</td>
<td>0.30</td>
</tr>
<tr>
<td>Watson-Jones, 2009</td>
<td>Tanzania</td>
<td>Prospective study</td>
<td>821 HSV-2 seropositive, HIV seronegative women aged 16-35.</td>
<td>No hormonal methods</td>
<td>63</td>
<td>Age</td>
<td>1.60</td>
</tr>
<tr>
<td>Kumwenda, 2008</td>
<td>Malawi</td>
<td>Prospective study</td>
<td>842 HIV seronegative women attending postpartum and family-planning clinics.</td>
<td>No injectable</td>
<td>31</td>
<td>Results were adjusted but it is not clear what it was adjusted for.</td>
<td>2.84</td>
</tr>
<tr>
<td>Kumwenda, 2008</td>
<td>Malawi</td>
<td>Nested case control study</td>
<td>27 cases picked up from previous prospective study.</td>
<td>No injectable</td>
<td>27</td>
<td>Age, number of sex partners, BV</td>
<td>10.42</td>
</tr>
<tr>
<td>Ungchusak, 1996</td>
<td>Thailand</td>
<td>Prospective study</td>
<td>240 female sex workers working in illegal brothels.</td>
<td>No contraception</td>
<td>15</td>
<td>Demographics, duration in sex work, syphilis</td>
<td>3.83</td>
</tr>
</tbody>
</table>
**Net-En specific prospective studies**

Four studies reported results for Net-En users alone but none of them was statistically significant[11, 14, 22, 69]. Kleinschmidt et al. reported non significant increased risk and other studies found odds ratios between 0.79-1.15[11, 14, 22, 69]. None of these studies reported an increased risk for DMPA either.

**Cross-sectional studies**

There are four studies identified to examine association between injectable hormonal contraceptive use and HIV acquisition[25, 31, 32, 37]. Only one study found statistically significant association between HIV acquisition and DMPA use[32]. This study was conducted in four different countries and although overall results showed significant association, in three out of four countries including the country had most incident infections, there was no association. They found association only in Malawi and since this association was big, statistically significant association was found in pooled analysis as well[32]. Other studies could not conclude a statistically significant result and failed to adjust results for possible confounders[25, 31, 37].

3.2.2 Chlamydia

**Prospective studies**

Eight prospective and four retrospective cohort studies were examined to investigate association between chlamydial infections and injectable hormonal contraception (Figure 4 & Table 4) [18, 39-42, 44, 71-73]. Two cohorts had the top score and they did not find a statistically significant association between chlamydial infection and neither DMPA nor Net-En[74, 75]. These studies were community based but one of these two conducted among adolescents only, median age of the cohort was 16. Although 157 incident chlamydial infections were observed in this adolescent cohort, there was no association between hormonal contraceptive use and chlamydia[74, 75].

Two well designed studies, got seven points, found statistically significant increased chlamydia risk among sex workers and women seeking gynaecological care using DMPA after adjustment for number of sexual partners, condom use, age, education and parity[39, 42].
Five of nine studies with moderate-low quality scores (4 or 5) found statistically significant association between injectable hormonal use and chlamydial infection[15, 40, 41, 44, 71]. One study compared DMPA users with IUD users in a retrospective cohort and reported that DMPA users were under 7.36 times more risk of Chlamydia infection than IUD users[71]. One community based prospective study found 2.5 times increased risk of chlamydial infection among DMPA users however since DMPA was compared to condom use in this study, it reported protective effect of condoms rather than increased risk with DMPA[15]. Three of four studies conducted among high risk populations like sex workers, HIV (+) women or HIV (+) sex workers, found strong association between DMPA use and chlamydial infection, odds ratios vary between 1.8 and 3.1[40, 41, 44]. None of the community based studies found statistically significant association between chlamydial infection and injectable contraceptive use when it is compared to non-hormonal method users besides Morrison et al[18, 42, 72, 74, 75].

One study among HIV (+) women did not report any significant result however HIV (+) women were different than general population, external validity of this study was low[73].

One US based case control study found statistically significant protective effect of DMPA use on chlamydial infection when it is compared to women don’t use any contraception[72]. It is important to mention that this study concluded that barrier methods were not protective against Chlamydia but hormonal methods were protective. This conclusion conflicted with general knowledge about protective effect of barrier methods like condoms[72].

**Cross-sectional studies**

There was no cross-sectional study examined association between hormonal contraception alone and chlamydial infection in this literature review. There were two studies had all types of hormonal contraception as one exposure group[47, 49]. As it was mentioned in oral contraceptives section, one study was conducted among randomly selected 70000 women from Nordic countries, showed positive association between chlamydial infection and ever use of hormonal contraception, pills or injectables[47]. Other Vietnam based study did not find any significant association between hormonal contraception and chlamydial infection[49].
Figure 4: Prospective studies on cervical chlamydial infection and injectable hormonal contraceptive, DMPA, use
<table>
<thead>
<tr>
<th>Year &amp; first author</th>
<th>Country</th>
<th>Study design &amp; population</th>
<th>Comparison group</th>
<th>Incident infections</th>
<th>Results adjusted for</th>
<th>Rate ratio [95% CI]</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romer, 2013</td>
<td>USA</td>
<td>Prospective study of 342 adolescent women aged 14–17 year recruited from three adolescent medicine clinics.</td>
<td>No hormonal methods</td>
<td>157</td>
<td>Age, presence of positive STI test at start of a diary period, number of lifetime sexual partners, number of sexual partners in the period, number of sexual events, number of unprotected sexual events.</td>
<td>1.17 [0.69-1.96]</td>
<td>7</td>
</tr>
<tr>
<td>Pettifor, 2009</td>
<td>South Africa</td>
<td>Prospective study of 643 HIV-1 negative, sexually active women aged 18-40 were recruited from family planning clinics.</td>
<td>No hormonal methods</td>
<td>119</td>
<td>Age, Education, Condom use consistency</td>
<td>1.24 [0.8-1.94]</td>
<td>7</td>
</tr>
<tr>
<td>Baeten, 2001</td>
<td>Kenya</td>
<td>Prospective cohort included 948 female sex workers participating a HIV prevention trial.</td>
<td>None/tubal ligation</td>
<td>175</td>
<td>Age, education, years of prostitution, parity, work place, number of sexual partners per week, number of sexual events per week, condom use</td>
<td>1.6 [1.1-2.4]</td>
<td>6</td>
</tr>
<tr>
<td>Morrison, 2004</td>
<td>USA</td>
<td>Prospective study of 819 women seeking gynaecologic care</td>
<td>No hormonal methods</td>
<td>37</td>
<td>Age, ethnicity, having multiple sex partners</td>
<td>3.6 [1.6-8.5]</td>
<td>6</td>
</tr>
<tr>
<td>Masese, 2013</td>
<td>Kenya</td>
<td>Prospective study of 865 female sex workers aged 18-50.</td>
<td>No hormonal methods</td>
<td>101</td>
<td>No adjustment</td>
<td>1.8 [1.1-3.0]</td>
<td>5</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample Description</td>
<td>Contraception Used</td>
<td>Follow-Up</td>
<td>Outcome Measures</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Wand, 2012</td>
<td>South Africa</td>
<td>Prospective study</td>
<td>Prospective study of 2 236 HIV-negative women who were screened in a biomedical intervention trial.</td>
<td>None and Condom users and other methods</td>
<td>NA</td>
<td>Age, number of sexual partners, pregnancy, number of sexual events, condom used in last sexual act.</td>
<td>2.46</td>
</tr>
<tr>
<td>Neu, 1998</td>
<td>USA</td>
<td>Retrospective case control study</td>
<td>Retrospective case control study of 843 women, 200 cases and 643 controls, attended a family planning or a young adult clinic.</td>
<td>No contraception</td>
<td>200</td>
<td>No adjustment</td>
<td>0.36</td>
</tr>
<tr>
<td>Feldblum, 2010</td>
<td>Nigeria, Benin, Uganda, India &amp; South Africa</td>
<td>Historic cohort</td>
<td>Historic cohort of 7364 non-pregnant, HIV negative women who were participating four different HIV prevention trials.</td>
<td>No contraception</td>
<td>126</td>
<td>Age, education</td>
<td>Association is not statistically significant.</td>
</tr>
<tr>
<td>Cropsey, 2010</td>
<td>USA</td>
<td>Retrospective chart review study</td>
<td>Retrospective chart review study of 385 women seeking contraception</td>
<td>IUD</td>
<td>67</td>
<td>No adjustment</td>
<td>7.36 [p&lt;0.001]</td>
</tr>
<tr>
<td>Overton, 2008</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>Retrospective cohort study among 304 HIV-infected women</td>
<td>No DMPA</td>
<td>33</td>
<td>No adjustment</td>
<td>1.19 [0.7-1.9]</td>
</tr>
<tr>
<td>Kapiga, 2009</td>
<td>South Africa, Tanzania, Zambia</td>
<td>Prospective study</td>
<td>Prospective study of 958 women at risk of STIs recruited from general population and family planning clinics.</td>
<td>No hormonal methods</td>
<td>NA</td>
<td>Age, number of sex partners, sexual behaviour</td>
<td>1.8 [1.0-3.3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kapiga et al reported results separately for different countries.</td>
<td>No hormonal methods</td>
<td>NA</td>
<td>Age, number of sex partners, sexual behaviour</td>
<td>1.9 [0.8-4.4]</td>
</tr>
</tbody>
</table>
2.2.3 Gonorrhea

**Prospective studies**

Six prospective and two historical cohort studies assessed injectable hormonal contraceptive use and gonorrhea found no association between gonorrhea and injectable hormonal contraceptives[15, 18, 39, 40, 44, 73-75]. There was only one study found positive association between DMPA and gonorrhea however this study compared DMPA and IUD instead of DMPA and non-hormonal users. Moreover there is no adjustment for possible confounders in this study and quality score of the study is lower comparing the other studies about gonorrhoea[71].

There is one study also created a Net-En exposure group and the result for Net-En users were similar to DMPA, there is no increased risk of gonorrhoeal infection for Net-En users[74].

**Cross-sectional studies**

One cross-sectional study among women reporting sexual contact to a male partner diagnosed with gonorrhoea reported negative association between DMPA use and gonorrhea however the number of women using DMPA were only nine in this study and it is not easy to generalize results to general population[56]. Another cross-sectional study among Nordic countries found no association between hormonal contraceptive use and gonorrhea infection[47].

2.2.4 Trichomonas

**Prospective studies**

Two of six studies including a case-control study and a historical cohort, found statistically significant decreased risk of trichomoniasis in DMPA users comparing non-hormonal contraceptive users [39, 40]. These two studies were conducted among high risk populations with high incidence of trichomonas infection. One community based study in South Africa reported statistically non-significant protective effect of DMPA on trichomonas OR: 0.35[0.12-1.01][74]. One recent prospective cohort, one historical cohort study among HIV (+) women and one hospital based case control study did not report any significant effect of DMPA on trichomonas[57, 73]. Overton et al. estimates a non-significant increased risk of trichomonas in DMPA users however this study failed to
adjust the results for condom use and condom use among two groups, DMPA users and non-hormonal contraceptive users were significantly different at the beginning of the study[73].

There was no cross sectional study identified to contribute prospective studies about association of DMPA with trichomonas.

2.2.5 Bacterial vaginosis

*Prospective studies*

Prospective studies suggest a protective effect against bacterial vaginosis with DMPA use. Five prospective studies evaluated the association between DMPA use and bacterial vaginosis and three reported statistically significant evidence of protective effect [39, 60, 62]. Two remaining studies reported non-significant protective effect[63, 74].

There was no specific cross sectional study examined to identify association between bacterial vaginosis and DMPA.

4. DISCUSSION

4.1 Causality

Quality and conclusiveness of the studies on hormonal contraception and risk of STIs are not same for different infections. It was better to discuss infections one by one regarding causation between hormonal contraceptive use and STIs. According to levelling system in evidence based medicine, systematic reviews with homogeneity in studies and randomised controlled trials are the best study types to demonstrate causation. Well designed RCTs could be enough to establish a causative bridge between two factors as well[76]. However it is known that there is no RCT conducted, due to ethical concerns, to answer if hormonal contraception causes an increased risk of STI or not. It cannot be approved ethically to randomize women to different contraceptive methods. Results of the prospective cohort studies are the most important evidence in the absence of RCTs.

For *bacterial vaginosis*, it can be concluded as both types of hormonal contraception are protective, in other saying, HC use decreases the risk of bacterial vaginosis. This
conclusion is consistent with a recent review focused mainly on bacterial vaginosis and candidiasis[5]. Bacterial vaginosis itself is not an STI however it is an internal condition related to STIs. According to recent studies, BV is a significant risk factor for HIV infection[77-80]. On the other hand effect of hormonal contraception on HIV acquisition is not clear. Even if hormonal contraception increased the risk of HIV, the reason wouldn’t be the vaginal floral changes like BV because hormonal contraception decreases BV incidence and prevalence as it was concluded in this review. The relation between HC and HIV did not seem to be mediated by bacterial vaginosis.

**Gonorrhoeal infection** does not appear to be associated with HC use. Although the number of prospective studies is not so many, none of them found an association between gonorrhoea and OC or hormonal contraception.

Not all the studies for *Trichomonas vaginalis* infection found significant association however existing studies seem enough to make a decision in favour of protective effect of both types of hormonal contraception against trichomonas.

Studies for *chlamydial infection* do not seem to be enough to conclude a harmful effect of either OCs or injectable contraceptives. Studies in high risk groups like sex workers suggest an increased risk of chlamydial infection however community based studies failed to support this results. Past two reviews on hormonal contraception and risk of Chlamydia concluded that there is an increase in risk of chlamydial infection associated with both OC and DMPA use[3, 4]. Two high quality community based prospective studies were conducted after these reviews and they found no association between DMPA use and chlamydial infection[74, 75]. According to quality system in this literature review, it is not possible to say that either DMPA or OCs increases the risk of chlamydial infection in general population.

The main focus of this literature review is *HIV infection*. Evaluating the relation between HIV and HC is not as simple as other infections. There are many prospective studies conducted from different populations, different countries, different risk and age groups. Heterogeneity of HIV studies precluded to conduct a meta-analysis. Lack of RCTs is another factor making decision process harder. I decided to use “Bradford Hill’s criteria” to investigate the causative association of hormonal contraceptive use and increased risk.
of HIV infection, in other words, does hormonal contraception cause an increased risk of HIV infection?[81]. Austin Bradford Hill set up nine guidelines to help evaluating whether an observed association between an exposure and an outcome is likely to be causal[81]. From time to time researchers modified the original Hill’s criteria to make them practical to use. One of the revised versions of guidelines were used and explained one by one for HIV-HC relationship[76]. Howick et al. omitted a guideline named “specificity” and merged two of the guidelines “experiment” and “strength” into one. The association between HC and HIV infection was investigated for remaining seven guidelines: temporality, coherence, biological plausibility, biological gradient, analogy, consistency and strength.

**Temporality**
Temporality means that exposure must precede the outcome[76, 81]. Since main focus is on the prospective studies, they all met temporality guideline. In all studies, only seronegative women were recruited and they excluded if seroconversion occurred in the beginning of studies. There is no room for thinking that HIV infection was established earlier and it made people use HC.

**Coherence**
Coherence is about not to be contraindicating with general knowledge and biology of the disease[82]. Association between HC and increased risk of HIV is still a discussion subject in current science. If it was found that HC caused increased risk of HIV infection, it would not conflict with current knowledge.

**Biological plausibility**
Is there a plausible mechanism supporting the causal chain between hormonal contraceptive use and increased risk of HIV? According to laboratory studies in animals, progesterone only hormonal contraceptives make vaginal epithelium thinner and getting thin may cause increased risk of HIV infection because the number of susceptible cells in genital tract increases with vaginal epithelial thinning[10, 83]. In additionally, progesterone only contraceptives, like depot injectables, may decrease the number of hydrogen peroxide-producing lactobacilli in vagina and causes decreased protective effect of the lactobacillus[83]. Moreover, hormonal contraceptives may suppress the local cell-mediated immunity and women using HC may be prone to HIV infection[84, 85]. In
laboratory conditions, it was reported that oestrogen treated vaginal macrophages were less susceptible to HIV infection however there is no hormonal contraception containing estradiol alone[86]. To conclude, there is plausible mechanism of action for progestin only hormonal contraceptives. There is not for combined hormonal contraceptives.

**Biological gradient**
Biological gradient refers to dose-response relationship. In HC case, it implies to either dose of the HC used by women or the duration of HC use. Injectable hormonal contraception has only one dose and it is not possible to compare women using different doses. Since none of the prospective studies had different study groups for increased or decreased amount of exposure, it is not possible to evaluate this guideline. There is only one cross sectional study found that association between HIV infection and oral contraceptive use is getting stronger with the years women used OCs[35]. Women using OCs for more than two years had more HIV than women using OCs for 1 year or less. However this study was cross-sectional and results were not adjusted for any possible confounders[35]. To conclude, in this conditions it is impossible to assess biological gradient.

**Analogy**
Analogy refers to other similar demonstrated associations. However there is no increased risk for other viral infections was identified among HC users. There were many studies to investigate if HC use increases the risk of HPV or HSV infections however these studies are not conclusive.

**Consistency**
If same association is observed in different studies, in different populations, in different designs and settings, it can be said that association is consistent. Studies for injectable hormonal contraceptives are consistent because there are studies found significant association in sex workers, in serodiscordant couples or in general population. There are also studies, with different age groups, found association between injectable contraception use and increased risk of HIV. On the other hand, there are only two studies found statistically significant association between OC use and HIV risk and these studies were conducted among sex workers [9, 23]. Results of community based studies are not consistent with sex worker studies[11, 12, 14, 22].
**Strength**

Strength in the guidelines refers to size of effect, how big is the measure of effect like odds ratios, risk ratios or rate ratios[81, 82]. Strength of the association must be greater than the cumulative effect of all possible confounders[76]. Although most of the prospective studies reported measure of effects after stratifying or adjusting for confounders, it is impossible to avoid effect of confounders completely. Unmeasured confounding, in other words residual confounding may be responsible from small effects reported by prospective studies. Moreover, sexual behaviour and condom use were the common confounders reported by all studies and there is no way to collect data about sexual behaviour or condom use besides self-reporting. Self-reporting may cause misinterpretation of data. Since studies are neither randomized nor blinded, they may suffer from selection bias in addition to residual confounding. In the studies had statistically significant results, measure of effects for the association between injectable hormonal contraceptive users and HIV infection vary between 1.48-3.83 and there are five different studies found two times higher risk of HIV infection in injectable contraceptive users. Studies among OC users did not report a big effect. There was only one study found risk ratio of 4.5[23]. To conclude, strength of association between injectable contraceptives and HIV risk may not be enough to overcome plausible confounders however it is still much bigger than the association between OCs and HIV infection. It will be useful to argue that there are some studies evaluated risk of HIV infection for OC users and injectable users in the same study. While these studies reported statistically significant increased risk for injectable users, they did not find any significant association between OC use and HIV infection[10, 12, 15, 19, 25]. In one study, number of OC users was very small and it may result the non-significant result however other studies had almost equal numbers for both study arms[19]. Results of these studies are important regarding strength of association and confounding factors. As it was indicated in many studies, major confounders in these designs were sexual behaviours and condom use and these confounders had an effect on both OC and injectable users. Although these two groups were under the effect of common confounders, strength of association for injectables was much larger than the association between OC use and HIV. On the other hand, it is important to bear in mind that women using injectables may differ from OC users regarding sexual behaviour and condom use however it is expected them to be more similar than nonhormonal method users or barrier method users.
To summarize, regarding causality and revised Bradford Hill’s guidelines, association between injectable contraceptive users and increased risk of HIV met five out of seven guidelines, temporality, coherence, biological plausibility, strength and consistency, two guidelines are not tested, analogy and biological gradient. In other respects, association between OC use and increased risk of HIV met only two guidelines, temporality and coherence, remaining five guidelines is either not relevant to be tested or not satisfied. Although there is no randomised controlled trial to evaluate if injectable hormonal contraceptives increase the acquisition of HIV infection, their association is likely to be causal according to Bradford Hill’s guidelines.

4.2 Behavioural and social aspect

WHO strongly advised to consistent use of condom for the women using progestin-only injectable contraception[7]. Most of the education and behavioural change campaigns target to increase consistent condom use in the high risk population because condom use is the most effective protective measure against STIs. If an intervention decreases the condom use dramatically, it will definitely increase the new infections. There are some studies conducted to understand condom use patterns of hormonal contraceptive users and they reported decreased consistent use of condom among women who started using hormonal contraceptive methods[87-90]. No matter if the association between HC use and HIV infection is causal or not, HC use will cause the more HIV infection as long as HC users stop consistent condom use. On the other hand, hormonal contraception, both OCs and injectables, are highly effective to prevent pregnancy and a decrease in HC use may result more unintended pregnancies and more vertical transmission of HIV infection. Before making any intervention or policy arrangements for HC use, the tradeoffs between HC and condom have to be analyzed deeply in the context of target country. Most effort must be made to increase condom use among HC users, especially in the countries with high HIV prevalence.

5. RECOMMENDATIONS

Taking into consideration that limitations in prospective cohort studies such as self reporting and residual confounding, better designed cohort studies or even randomised controlled trials are necessary to make the decision process more clear. For an ideal RCT,
groups must be same regarding all other factors but HC use. Ideally, groups must be exposed to infections equally to investigate the effect of hormonal contraception on infection. Although there are many criticisms on sero-discordant couple studies, exposure to infection is more balanced among groups in sero-discordant couple when it is compared to community based studies. Sero-discordant couples might be the best population to design an RCT answering the association between increased HIV risk and hormonal contraception.

If there is a plan to design a new community based prospective cohort study, this study must be conducted with a large group of participants; otherwise, it is easy to say by looking at previous studies, new study will not have the power to report statistically significant results. Additionally, there are not enough studies about newer modern contraceptive methods like patches, rings, or an injectable contraception, Net-En. Some studies must be conducted for these new contraceptives.

Condoms are the only contraceptive method to reduce risk of STI. All women must be encouraged to consistent use of condoms in any sexual contact. No matter if hormonal contraception increases the risk of HIV or not, it is known that hormonal contraception is not protective for HIV and women must avoid sexual contact without condom.

6. REFERENCES


