How does Contraceptive Use increase the Risk of HIV acquisition?

Emerging issues in contraception including but not limited to drug interactions and address Depo-Provera and HIV transmission issues

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Ospedale Amedeo di Savoia
1. Contraceptives play a life-saving role in preventing maternal and neonatal mortality from undesired pregnancies.

2. Birth control is estimated to reduce maternal deaths by 44% (272,000 deaths averted in 2008).

3. Additional 29% of maternal deaths could be prevented if the full demand of contraception was met.

4. Hormonal contraception, unlike barrier methods, does not protect against sexually-transmitted infections (STIs).

5. A debate is ongoing since the 1990s as to whether hormonal contraception may increase the risk of acquiring HIV infection.

of sexual activity were similar in the two groups — importantly, no woman reported any sexual practice other than genital-genital intercourse. Oral contraceptive use during the study period was associated with acquisition of HIV-1 infection. Of 39 reporting any oral contraceptive use, 32 seroconverted (OR, 3.1; 95% confidence interval [CI], 1.1–8.6; P < .03). Five women reported use of an IUD (intrauterine device), and one used a Depo progestational agent. Condoms were not used as methods of contraception but rather as methods of preventing STD and HIV-1 infection (see below).

To examine the relation between oral contraceptive use and acquisition in oral contraceptive users. However, stratifying the analysis for pregnancy did not affect the association. Thus, the potential influence of each of these is reduced or eliminated by the nature of the study population, the method of analysis, or both. It remains possible that the association is

* Major concerns are about the injectable drugs depot medroxyprogesterone acetate (DMPA)
Depo-Provera is a well-known brand name for medroxyprogesterone, a contraceptive injection for women that contains the hormone progestin.

Depo-Provera (150 mg) is given as an injection once every three months.

Depo-Provera typically suppresses ovulation, keeping your ovaries from releasing an egg. Depo-Provera also thickens cervical mucus to keep sperm from reaching the egg.

Medroxyprogesterone acetate is also available in a lower dosage. This version is called Depo-SubQ Provera 104 (104 mg). While Depo-Provera is injected deep into the muscle, Depo-SubQ Provera 104 is injected just beneath the skin.

![Graph showing MPA Serum Concentration (ng/mL) over time (days). The graph compares Depo-Provera (n=8) and LD Formulation of Depo-Provera (n=42).]
DMPA and the risk of acquiring HIV infection

- The available evidence
- The possible biological mechanisms
- The current translation into practice
Hormonal contraceptive use and women’s risk of HIV acquisition: a meta-analysis of observational studies

Lauren J Ralph, Sandra I McCoy, Karen Shiu, Nancy S Padian


Abstracts presented at the 2011–14 International AIDS Society and Conference on Retroviruses and Opportunistic Infections and followed up with authors to ascertain if their analyses had been published.

Inclusion criteria:
- Assessment horm. contr. exposure
- Prospective design
- HIV+ Women excluded
- Exposure assessment before incidental HIV infection

Analytic approach to minimize confounding and selection bias at least for:
- Age, condom use, loss to follow-up (<30%)
- Published in a PR journal by May 2014

Denominator approaching 40,000 women

23 reports identified in the WHO technical review

3 reports dated through publication

14 reports excluded (see appendix for a summary of reasons)

In pooled analyses
- DMPA
- Drospirenone
- Diene being yprogesterone acetate
- 10 oral contraceptive pills or combined oral contraceptives
- 5 medroxyprogesterone enanthate

updated
Information was extracted about features that might affect internal or external validity of the study or explain heterogeneity:

- **Study retention rates**
- **Intersurvey intervals**
- **Risk profile of study participants**
- **Study design**
- **Demographic characteristics of participants**
- **Recruitment sites**
- **Study duration**
- **Exclusion criteria**

Women at high risk or key populations (commercial sex workers, IDUs, women in serodiscordant partnership)

General population
The strength and heterogeneity of findings were further assessed by several a-priori secondary analyses:

• Whether any study alone disproportionately affected the results;

• Meta analyses stratified according to the risk profile of the study population (high risk vs general population);

• Whether the results were sensitive to the exclusion of condom users from the comparison group

• Influence of studies with intersurvey intervals longer than the duration of the contraceptive methods used (1 – 3 months)
Hormonal contraceptive use and women’s risk of HIV acquisition: a meta-analysis of observational studies

Lauren J Ralph, Sandra I McCoy, Karen Shiu, Nancy S Padian

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Hazard ratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiddugavu et al,⁵⁶ 2003</td>
<td></td>
<td>0.84 (0.41–1.72)</td>
<td>5.37%</td>
</tr>
<tr>
<td>Morrison et al,²⁰ 2007</td>
<td></td>
<td>1.25 (0.88–1.77)</td>
<td>13.86%</td>
</tr>
<tr>
<td>Kleinschmidt et al,⁴⁰ 2007</td>
<td></td>
<td>0.46 (0.06–3.66)</td>
<td>0.78%</td>
</tr>
<tr>
<td>Myer et al,¹⁹ 2007</td>
<td></td>
<td>0.75 (0.33–1.69)</td>
<td>4.36%</td>
</tr>
<tr>
<td>Baeten et al,³⁹ 2007</td>
<td></td>
<td>1.73 (1.28–2.34)</td>
<td>15.69%</td>
</tr>
<tr>
<td>Morrison et al,¹⁷ 2012</td>
<td></td>
<td>1.27 (0.93–1.73)</td>
<td>15.32%</td>
</tr>
<tr>
<td>Wand et al,⁴⁵ 2012</td>
<td></td>
<td>2.02 (1.37–2.99)</td>
<td>12.22%</td>
</tr>
<tr>
<td>Heffron et al,¹⁶ 2012</td>
<td></td>
<td>3.93 (1.38–11.21)</td>
<td>2.81%</td>
</tr>
<tr>
<td>McCoy et al,¹⁸ 2013</td>
<td></td>
<td>1.22 (0.85–1.76)</td>
<td>13.20%</td>
</tr>
<tr>
<td>Crook et al,⁴⁷ 2014</td>
<td></td>
<td>1.45 (1.09–1.93)</td>
<td>16.39%</td>
</tr>
<tr>
<td><strong>Depot medroxyprogesterone acetate reduces HIV risk</strong></td>
<td></td>
<td>1.40 (1.16–1.69)</td>
<td>100.00%</td>
</tr>
<tr>
<td><strong>Depot medroxyprogesterone acetate increases HIV risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hormonal contraceptive use and women’s risk of HIV acquisition: a meta-analysis of observational studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Hazard Ratio (HR)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis, pooled studies:</td>
<td>HR 1.40</td>
<td>1.16 – 1.69</td>
</tr>
<tr>
<td>Pooled prospective cohorts:</td>
<td>HR 1.44</td>
<td>1.04 – 2.01</td>
</tr>
<tr>
<td>Pooled general population:</td>
<td>HR 1.31</td>
<td>1.10 – 1.57</td>
</tr>
<tr>
<td>Pooled Ref. group using condom</td>
<td>HR 1.44</td>
<td>1.20 – 1.73</td>
</tr>
<tr>
<td>Commercial sex workers</td>
<td>HR 1.73</td>
<td>1.28 – 2.34</td>
</tr>
<tr>
<td>Serodiscordant partnership</td>
<td>HR 3.93</td>
<td>1.37 – 11.2</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>HR 1.00</td>
<td>0.86 – 1.16</td>
</tr>
<tr>
<td>Norethisterone enantate (NET – EN)</td>
<td>HR 1.10</td>
<td>0.88 – 1.37</td>
</tr>
</tbody>
</table>
**Source of information:** cohort studies that prospectively collected data on both hormonal contraceptive use (combined oral contraceptives – COC, DMPA, NET – EN) and incident HIV infections in women aged 15-49 from Sub-Saharan Africa:

1. Database containing Individual Participant Data (IPD) from 10 studies that contributed to an IPD meta-analysis of the effects of vaginal practices on the risk of HIV infection among women, gathered by the Vaginal Practices Research Partnership (VPRP);
2. Additional datasets from prospective cohort studies and RCTs completed by Sept 2012, by asking collaborators and investigators of HIV prevention trials;
3. Bibliography of two systematic reviews for studies published by Dec 2011 and bibliography to Jan 2014.
<table>
<thead>
<tr>
<th>Study-level Variables:</th>
<th>Individual-level Variables:</th>
<th>Visit-level Variables:</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Study site</td>
<td>b. Education</td>
<td>b. Pregnancy status</td>
</tr>
<tr>
<td>c. Study design (1ry &amp; 2ry outcomes)</td>
<td>c. Employment status</td>
<td>c. Vaginal practices</td>
</tr>
<tr>
<td>d. Population group(s)</td>
<td>d. Religion</td>
<td>d. N. and type of sexual partners</td>
</tr>
<tr>
<td>e. Recruitment period</td>
<td>e. Socio-economic indicators</td>
<td>e. Coital frequency</td>
</tr>
<tr>
<td>f. Study duration</td>
<td>f. Parity</td>
<td>f. Transactional sex</td>
</tr>
<tr>
<td>g. Frequency of follow-up visits</td>
<td>g. Marital status</td>
<td>g. Condom use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>h. Sexual partner risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i. Other STIs</td>
</tr>
</tbody>
</table>
Hormonal Contraception and the Risk of HIV Acquisition: An Individual Participant Data Meta-analysis

Morrison CS, et al.

PLOS Medicine | DOI:10.1371/journal.pmed.1001778  January 22, 2015

Denominator: 37124 Women
• A 50% higher risk of HIV infection was found in Women using DMPA

• Such increased risk was found to be reduced at 22% in studies at lower methodological risk of bias, with CI including the possibility of no increased risk
NET – EN is associated to a borderline increase of HIV infection when compared to COCs.
Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Nelly Mugo, Edwin Were, Guy de Bruyn, Edith Nakku-Joloba, Kenneth Ngure, James Kiarie, Robert W Coombs, Jared M Baeten, for the Partners in Prevention HSV/HIV Transmission Study Team*

<table>
<thead>
<tr>
<th>Contraceptive use (women)</th>
<th>Analysis of HIV-1 acquisition by women (N=1314 couples)</th>
<th>Analysis of HIV-1 transmission from women to men (N=2476 couples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any hormonal contraceptive use at enrolment</td>
<td>194 (14.8%)</td>
<td>...</td>
</tr>
<tr>
<td>Any injectable use at enrolment</td>
<td>142 (10.8%)</td>
<td>...</td>
</tr>
<tr>
<td>Any oral use at enrolment</td>
<td>52 (4.0%)</td>
<td>...</td>
</tr>
<tr>
<td>Any hormonal contraceptive use during follow up</td>
<td>275 (20.9%)</td>
<td>...</td>
</tr>
<tr>
<td>Any injectable contraceptive use during follow up</td>
<td>208 (15.8%)</td>
<td>...</td>
</tr>
<tr>
<td>Any oral contraceptive use during follow up</td>
<td>87 (6.6%)</td>
<td>...</td>
</tr>
</tbody>
</table>

1314 serodiscordant couples (female HIV-1 negative)

Hormonal contraception: 6.61/100 person-years
No hormonal contraception: 3.78/100 person-years

AHR 1.98, 95% CI 1.06 – 3.78
p = 0.03

2476 serodiscordant couples (male HIV-1 negative)

Hormonal contraception: 2.61/100 person-years
No hormonal contraception: 1.51/100 person-years

AHR 1.97, 95% CI 1.12 – 3.45
p = 0.02
Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Nelly Mugo, Edwin Were, Guy de Bruyn, Edith Nakku-Joloba, Kenneth Njuru, James Kiari, Robert W Coombs, Jared M Baeten, for the Partners in Prevention HSV/HIV Transmission Study Team*

<table>
<thead>
<tr>
<th>HIV</th>
<th>Number of HIV-1 seroconversions/person-years</th>
<th>Incidence per 100 person-years</th>
<th>Unadjusted Cox proportional hazards regression analysis</th>
<th>Adjusted Cox proportional hazards regression analysis*</th>
<th>Adjusted marginal structural models analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hazard ratio (95% CI) p value</td>
<td>Hazard ratio (95% CI) p value</td>
<td>Odds ratio (95% CI) p value</td>
</tr>
<tr>
<td>All women</td>
<td>73·0/1782·8</td>
<td>4·09</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>60·0/1586·2</td>
<td>3·78</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>13·0/196·6</td>
<td>6·61</td>
<td>1·73 (0·95–3·15) 0·07</td>
<td>1·98 (1·06–3·68) 0·03</td>
<td>1·84 (0·98–3·47) 0·06</td>
</tr>
<tr>
<td>Injectable</td>
<td>10·0/146·1</td>
<td>6·85</td>
<td>1·80 (0·92–3·52) 0·08</td>
<td>2·05 (1·04–4·04) 0·04</td>
<td>2·19 (1·01–4·74) 0·05</td>
</tr>
<tr>
<td>Oral</td>
<td>3·0/50·5</td>
<td>5·94</td>
<td>1·53 (0·48–4·90) 0·47</td>
<td>1·80 (0·55–5·82) 0·33</td>
<td>1·63 (0·47–5·66) 0·44</td>
</tr>
</tbody>
</table>

*Multivariate Cox proportional hazard regression model, adjusted for age, concentrations of plasma HIV-1 in the HIV-1-infected partners, and time varying unprotected sex and pregnancy. Further adjustment for additional factors did not substantially change the findings. †Weighted marginal structural model is adjusted for age, region, number of children, concentration of plasma HIV-1 RNA in the HIV-1-infected partner, and month of visit (5-knot cubic spline with knots at the 5th, 25th, 50th, 75th, and 95th percentiles) and contraceptive history; weights are truncated at the 1st and 99th percentiles.

Table 3: Hormonal contraceptive use and risk of HIV-1 acquisition by women

<table>
<thead>
<tr>
<th>HIV</th>
<th>Number of genetically linked HIV-1 seroconversions/person-years</th>
<th>Incidence per 100 person-years</th>
<th>Unadjusted Cox proportional hazards regression analysis</th>
<th>Adjusted Cox proportional hazards regression analysis*</th>
<th>Adjusted marginal structural model analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hazard ratio (95% CI) p value</td>
<td>Hazard ratio (95% CI) p value</td>
<td>Odds ratio (95% CI) p value</td>
</tr>
<tr>
<td>All men</td>
<td>59·0/3375·1</td>
<td>1·75</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>40·0/2647·9</td>
<td>1·51</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>19·0/727·2</td>
<td>2·61</td>
<td>1·76 (1·02–3·05) 0·04</td>
<td>1·97 (1·12–3·45) 0·02</td>
<td>2·05 (1·12–3·74) 0·02</td>
</tr>
<tr>
<td>Injectable</td>
<td>15·0/567·3</td>
<td>2·64</td>
<td>1·79 (0·99–3·22) 0·05</td>
<td>1·95 (1·06–3·58) 0·03</td>
<td>3·01 (1·47–6·16) 0·003</td>
</tr>
<tr>
<td>Oral</td>
<td>4·0/159·9</td>
<td>2·50</td>
<td>1·70 (0·60–4·81) 0·31</td>
<td>2·09 (0·75–5·84) 0·16</td>
<td>2·35 (0·79–6·95) 0·12</td>
</tr>
</tbody>
</table>

*Multivariate Cox proportional hazard regression model, adjusted for age, plasma HIV-1 levels in the HIV-1 infected partner, and time varying unprotected sex and pregnancy. Further adjustment for additional factors did not substantially change the findings. †Weighted marginal structural model is adjusted for age, region, number of children, plasma HIV-1 RNA concentration in the HIV-1 infected partner, and visit month (5-knot cubic spline with knots at the 5th, 25th, 50th, 75th and 95th percentiles) and contraceptive history; weights are truncated at the 1st and 99th percentiles.

Table 4: Hormonal contraceptive use and risk of HIV-1 transmission from women to men

- Systematic review of epidemiologic evidence assessing whether hormonal contraception alters the risk of HIV transmission from an HIV-positive woman to an HIV-negative male partner.

- We included articles published or in press through December 15, 2011. We assessed studies with direct evidence on hormonal contraception use and HIV transmission, and summarized studies with indirect evidence related to genital or plasma viral load.

- The **only direct study** on OCPs or injectable contraception and female-to-male HIV transmission suggests **increased risk with the use of injectables**. Given the potential for confounding in observational data, the paucity of direct evidence on this subject, and mixed indirect evidence, additional evidence is needed.
DMPA and the risk of acquiring HIV infection

- The available evidence
- The possible biological mechanisms
- The current translation into practice
In women viral invasion occurs mostly through the non-keratinized squamous epithelium of the vagina and ectocervix, as well as through the single-layer columnar epithelium of the endocervix. The endocervical canal is filled with mucus, providing a barrier against the ascent of pathogens.

Hladik F, McElrath MJ. Nat Rev Imm 2008; 8: 447-457
Thickness of the vaginal epithelium (dark purple) varies during the menstrual cycle. It is thickest during the first half of the cycle (top), when oestrogen is dominant, and thins out during the second half (bottom) of the cycle, when progesterone is dominant.


**However, evidence for this mainly results from studies in NHP**


In another study, Mauck and coll found no significant decrease in **vaginal epithelial thickness** in biopsies taken 1 and 3 months following administration of DMPA as compared to biopsies taken at baseline:


No differences in vaginal epithelial thickness in women using DMPA compared to women on no HC:

To identify risk factors involved in heterosexual transmission of human immunodeficiency virus (HIV), a cross-sectional study of HIV-seropositive men and their spouses was conducted in Nairobi, Kenya. Of 70 spouses, 40 (57%) were seropositive and 30 (43%) were seronegative for HIV. In univariate analysis, the presence of cervical ectopy (odds ratio, 4.7; P = .006) was the only statistically significant variable associated with HIV infection in women. After controlling for possible confounding variables using multivariate logistic regression analysis, the presence of cervical ectopy (odds ratio, 5.0; P = .007) remained the only independent predictor of HIV seropositivity. These findings suggest that cervical ectopy may be a newly identified risk factor for heterosexual transmission of HIV.

Association of Cervical Ectopy with Heterosexual Transmission of Human Immunodeficiency Virus: Results of a Study of Couples in Nairobi, Kenya


In another study, Mauck and coll found no significant decrease in vaginal epithelial thickness or increase in **cervical ectopy** (columnar epithelium in the vaginal portion of the cervix) in biopsies taken 1 and 3 months following administration of DMPA as compared to biopsies taken at baseline:


Endometrial
Endocervical
Exposed to HIV

P24 Ag measured following exposure to HIV and:
• No hormone (NH)
• Estradiol (E2)
• Progesterone (P4)
• Medroxyprogesterone acetate (MPA)


An increase in IL-8 and decrease in RANTES were seen in immortalized cervical cells treated with MPA and TNF.
RANTES decrease was blocked following addiction an androgen receptor antagonist.
High MPA doses (> 15 ug/mL)

* Increased syndecan expression

Human vaginal epithelial cells (VK2/E6E7)

Significant increase in HIV p24 secretion

Decreased cell proliferation

Disruption of the epithelial barrier

Upregulation of proinflammatory cytokines

Latently HIV-1 infected promonocytes (U1)

* However, this response was only observed when U1 cells were incubated with culture supernatants harvested from epithelial cells treated with doses of MPA that far exceeded the plasma concentration of 1-7 ng/mL observed in women treated with DMPA
Glucocorticoid Receptor Mediates the Effect of Progesterone on Uterine Natural Killer Cells


DMPA has a higher affinity for binding to the Glucocorticoid Receptor than either norethindrone/norethisterone enanthate and levonorgestrel (progestin used in NET – EN and most COCs)

Activation of the Glucocorticoid Receptor → Suppressed Local immunity

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Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

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<table>
<thead>
<tr>
<th>Detection of any genital HIV-1 RNA</th>
<th>n/N (%)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
<th>Adjusted odds ratio* (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1011/1691 (59.9)</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>782/1333 (58.7)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>230/358 (64.3)</td>
<td>1.27 (0.99 to 1.61)</td>
<td>0.06</td>
<td>1.51 (1.13 to 2.01)</td>
<td>0.0054</td>
</tr>
<tr>
<td>Injectable</td>
<td>180/272 (66.2)</td>
<td>1.38 (1.05 to 1.81)</td>
<td>0.05</td>
<td>1.67 (1.21 to 2.31)</td>
<td>0.02</td>
</tr>
<tr>
<td>Oral</td>
<td>50/86 (58.1)</td>
<td>0.98 (0.63 to 1.52)</td>
<td>0.43</td>
<td>1.06 (0.62 to 1.84)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantity of genital HIV-1 RNA detected (log_{10} copies/swab)</th>
<th>Median (IQR)</th>
<th>Regression coefficient* (95% CI)</th>
<th>p value</th>
<th>Adjusted regression coefficient† (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.18 (2.08 to 3.85)</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>3.14 (2.08 to 3.91)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>3.29 (2.08 to 3.91)</td>
<td>0.10 (-0.01 to 0.21)</td>
<td>0.08</td>
<td>0.14 (0.04 to 0.23)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Injectable</td>
<td>3.38 (2.08 to 4.02)</td>
<td>-0.15 (0.03 to 0.28)</td>
<td>0.02</td>
<td>0.19 (0.08 to 0.30)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Oral</td>
<td>2.96 (2.08 to 3.65)</td>
<td>-0.07 (-0.28 to 0.14)</td>
<td>0.53</td>
<td>-0.05 (-0.24 to 0.14)</td>
<td>0.60</td>
</tr>
</tbody>
</table>
1. Thinning of the epithelial barrier
2. Disruption of intercellular junctional complexes
3. Upregulation of Trojan horse receptors
4. Increased secretion of inflammatory mediators recruiting target cells
5. Decreased secretion of antimicrobial peptides
6. Increased CCR5 expression
7. Increased BV-associated bacteria
8. Decreased hydrogen peroxide producing lactobacilli
9. Increased genital herpes shedding
DMPA and the risk of acquiring HIV infection

- The available evidence
- The possible biological mechanisms
- The current translation into practice
Associations of hormonal contraceptive use with measures of HIV disease progression and antiretroviral therapy effectiveness.


A prospective cohort study of women with prevalent HIV infection in St. Petersburg, Russia

participants chose to use:

a) combined oral contraceptives (COCs),  
b) depot-medroxyprogesterone acetate (DMPA),  
c) a copper intrauterine device (IUD),  
d) male condoms for pregnancy prevention

During a total of 5233 months follow-up among participants not using ART with enrollment CD4 ≥350 cells/mm3 (n=315), 97 experienced disease progression. Neither current use of COCs [adjusted hazard ratio (aHR) 0.91, 95% confidence interval (CI) 0.56-1.48] nor DMPA (aHR 1.28, 95% CI 0.71-2.31) was associated with a statistically significant increased risk for disease progression compared with use of nonhormonal methods (IUD or condoms).

Among participants using ART at enrollment (n=77), we found no statistically significant differences in the predicted mean changes in CD4 cell count comparing current use of COCs (p=.1) or DMPA (p=.3) with nonhormonal methods.
Systematic assessment from the literature to see whether women living with HIV who use hormonal contraception are at increased risk of HIV-disease progression compared with those who do not use hormonal contraception.

Twelve reports of 11 studies met inclusion criteria.

The preponderance of evidence indicates that HIV-positive women can use hormonal contraceptive methods without concerns related to HIV-disease progression.

Cohort studies consistently found no association between hormonal contraceptive use and HIV-disease progression compared with nonuse of hormonal contraceptives.
The translation into practice

1. The limitations of the available studies refrain from a straightforward application of the results into clinical practice:

   The results of observational studies are prone to bias, e.g.:

   • DMPA recipients might have more frequent sexual intercourses....

   • DMPA recipients might be less likely to use condoms......

2. A Randomized Clinical Trial (RCT) has been planned by the ECHO Consortium:

   • Ethical issue: the primary outcome is harm (HIV acquisition)

   • Methodology: blinding unfeasible

3. Should a RCT confirm a higher risk of HIV infection among DMPA intakers, would this lead to a change in practice?

   • Even by doubling the HIV infection risk, the DMPA-associated benefits might actually outweigh the increased number of new HIV infections in terms of maternal and child mortality.....
Hormonal contraceptive use and women’s risk of HIV acquisition: a meta-analysis of observational studies

Lauren J Ralph, Sandra I McCoy, Karen Shiu, Nancy S Padian


Imperative for public health is the continued need to promote a wide array of existing methods and develop and promote long-term options for reversible contraceptives for women worldwide.

Condom use....

Hormonal Contraception and the Risk of HIV Acquisition: An Individual Participant Data Meta-analysis

Morrison CS, et al.

PLOS Medicine | DOI:10.1371/journal.pmed.1001778 January 22, 2015

This IPD meta-analysis found no evidence that COC or NET-EN use increases women’s risk of HIV but adds to the evidence that DMPA may increase HIV risk, underscoring the need for additional safe and effective contraceptive options for women at high HIV risk.

Cofactors in Male-Female Sexual Transmission of Human Immunodeficiency Virus Type 1

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