EACS European AIDS Clinical Society

15th EUROPEAN AIDS CONFERENCE
October 21–24, 2015
Barcelona, Spain

TDM Therapeutic Drug Monitoring

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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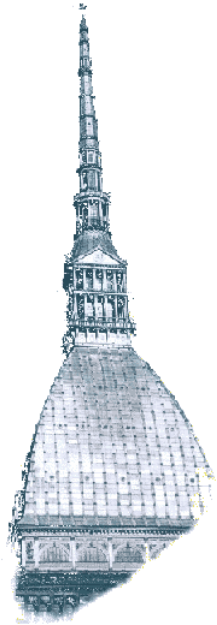
Ospedale Amedeo di Savoia



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

Plummer FA, et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. J Infect Dis 1991; 163: 233–39.

Oxford University Press

The Journal of Infectious Diseases

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

Author(s): Francis A. Plummer, J. Neil Simonsen, D. William Cameron, Jackoniah O. Ndinya-Achola, Joan K. Kreiss, Michale N. Gakinya, Peter Waiyaki, Mary Cheang, Peter Piot, Allan R. Ronald and Elizabeth N. Ngugi

Source: *The Journal of Infectious Diseases*, Vol. 163, No. 2 (Feb., 1991), pp. 233-239

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).

OR 3.1
95% CI 1.1 – 8.6, p < 0.03

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

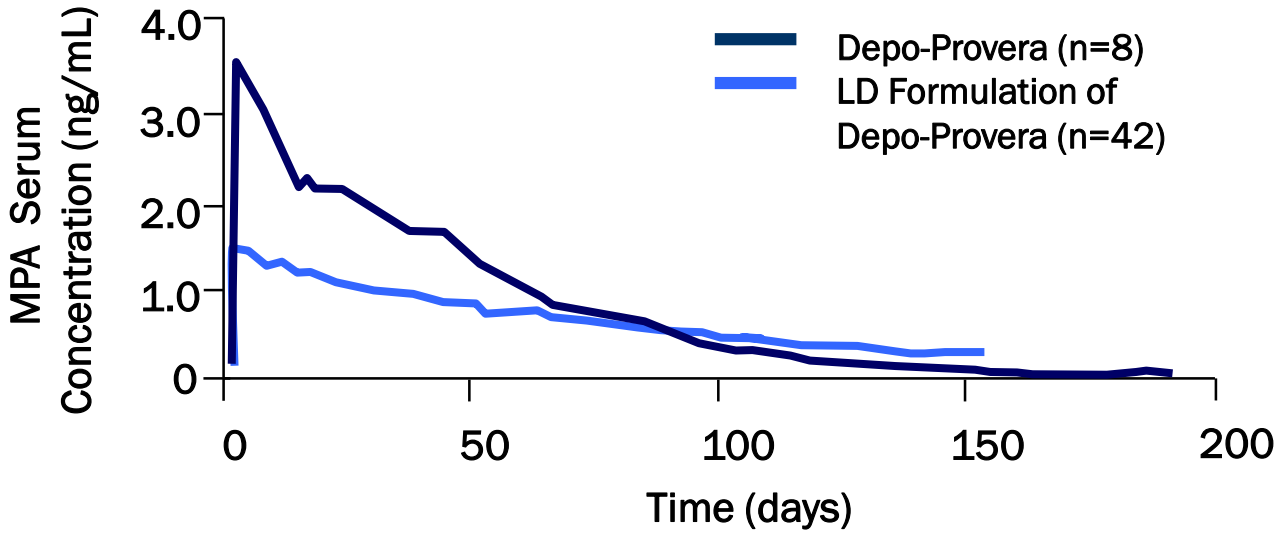
*** Major concerns are about the injectable drugs depot medroxyprogesterone acetate (DMPA)**

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.



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

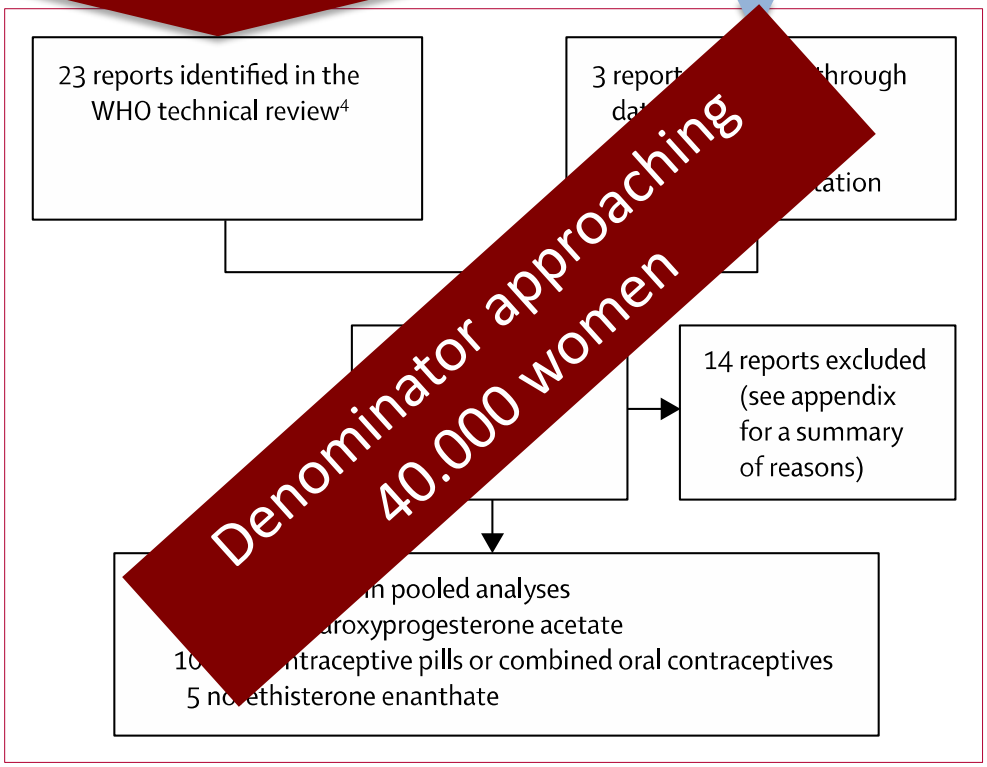
Lancet Infect Dis 2015; 15: 181–89

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

Polis CB, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. Contraception 2014;90: 360–90.

updated

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

DMPA
NET-EN

Combined oral
Progestin-only

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

Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies

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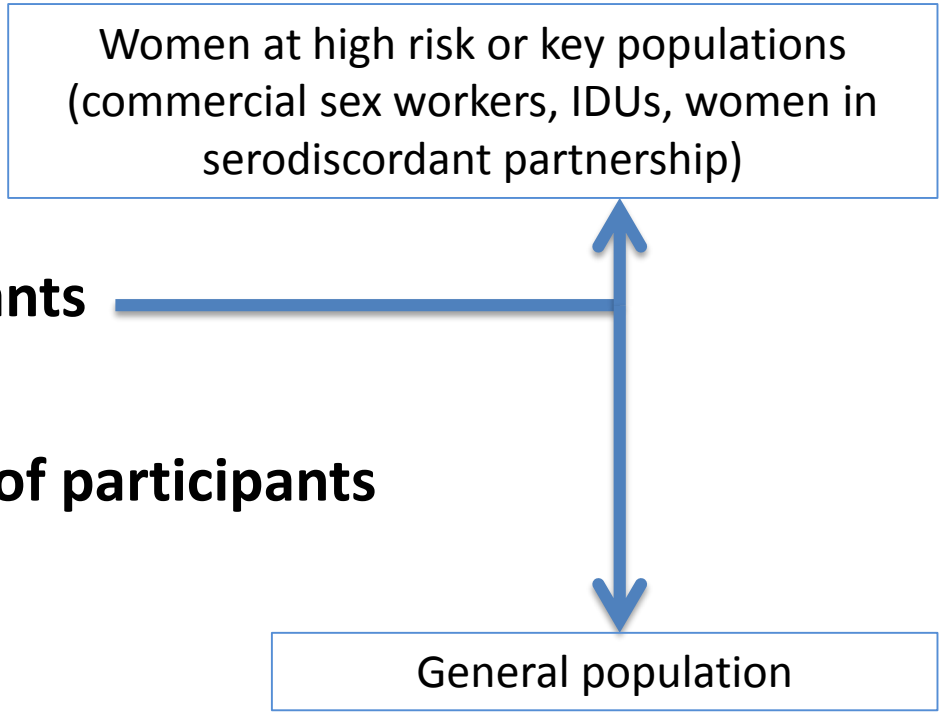
Lauren J Ralph, Sandra I McCoy, Karen Shiu, Nancy S Padian

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**



Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies

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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

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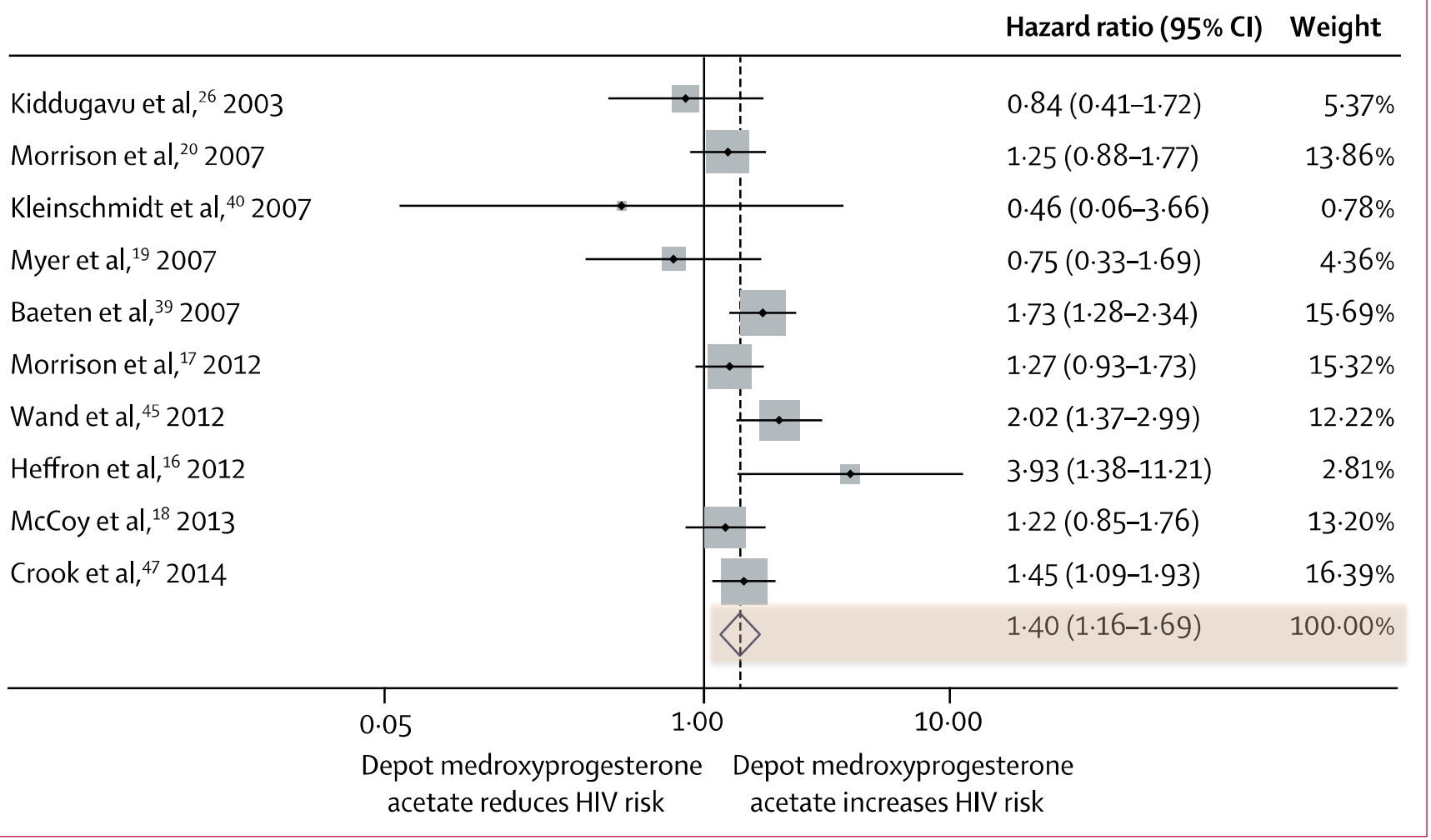

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Primary analysis, pooled studies:	**HR 1.40, 95% CI 1.16 – 1.69**
Pooled prospective cohorts:	HR 1.44, 95% CI 1.04 – 2.01
Pooled general population:	HR 1.31, 95% CI 1.10 – 1.57
Pooled Ref. group using condom	HR 1.44, 95% CI 1.20 – 1.73
Commercial sex workers	HR 1.73, 95% CI 1.28 – 2.34
Serodiscordant partnership	HR 3.93, 95% CI 1.37 – 11.2
Oral contraceptive	HR 1.00, 95% CI 0.86 – 1.16
Norethisterone enantate (NET – EN)	HR 1.10, 95% CI 0.88 – 1.37

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

PLOS | MEDICINE

Morrison CS, et al. PLOS Medicine | DOI:10.1371/journal.pmed.1001778 January 22, 2015

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.

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Study-level Variables:

a. Country
b. Study site
c. Study design (1ry & 2ry outcomes)
d. Population group(s)
e. Recruitment period
f. Study duration
g. Frequency of follow-up visits

Individual-level Variables:

a. Age
b. Education
c. Employment status
d. Religion
e. Socio-economic indicators
f. Parity
g. Marital status

Visit-level Variables:

a. Hormonal contraception use
b. Pregnancy status
c. Vaginal practices
d. N. and type of sexual partners
e. Coital frequency
f. Transactional sex
g. Condom use
h. Sexual partner risk
i. Other STIs

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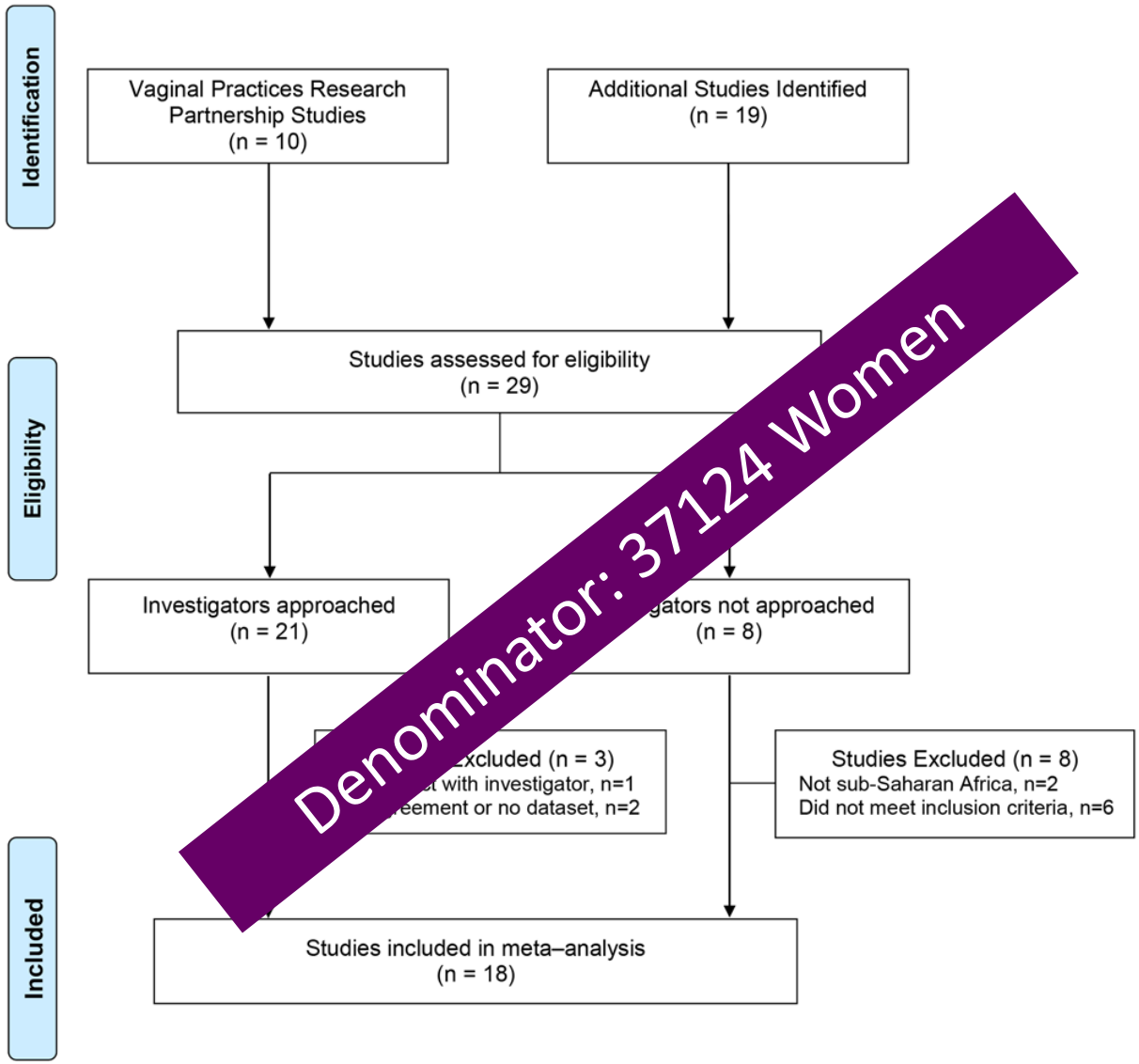

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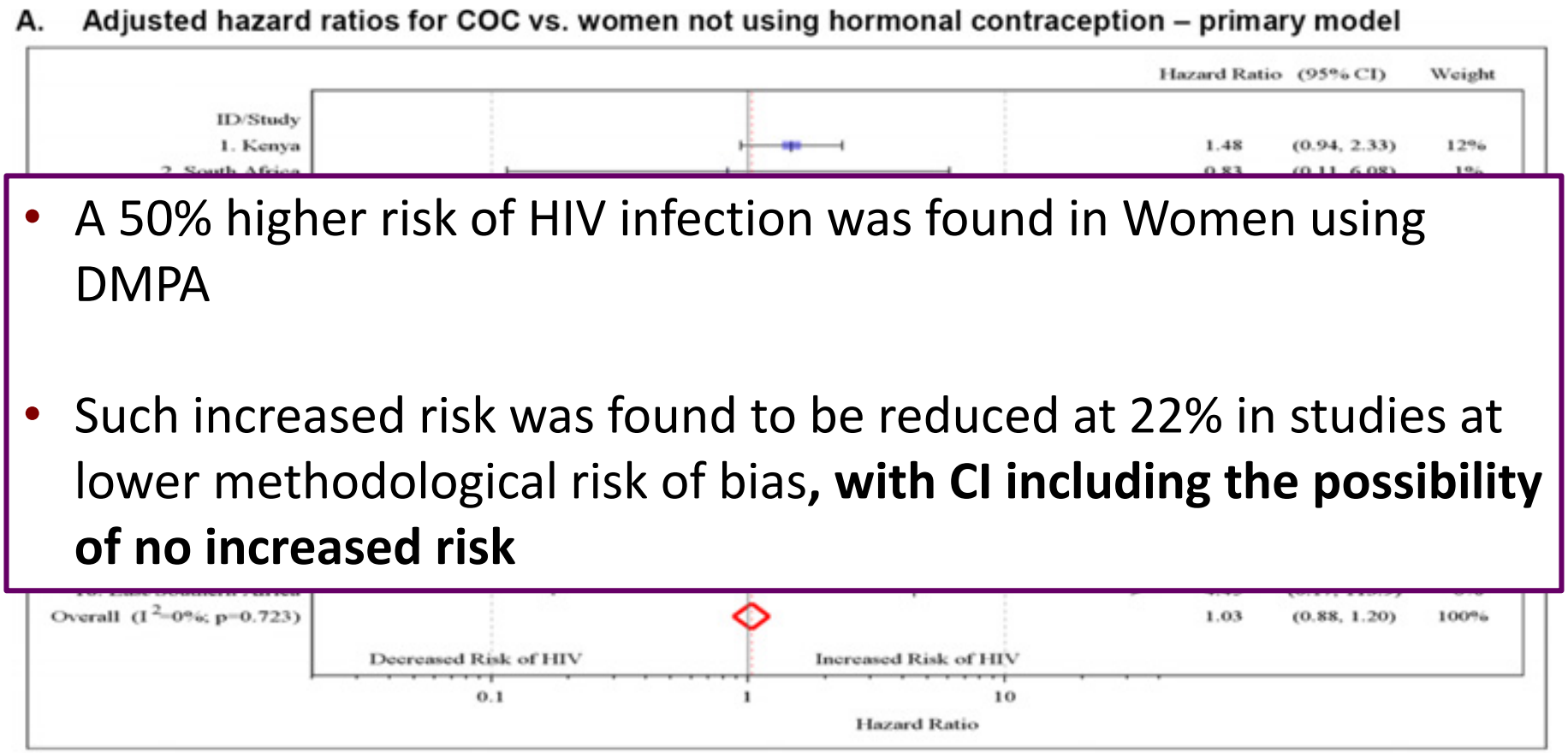
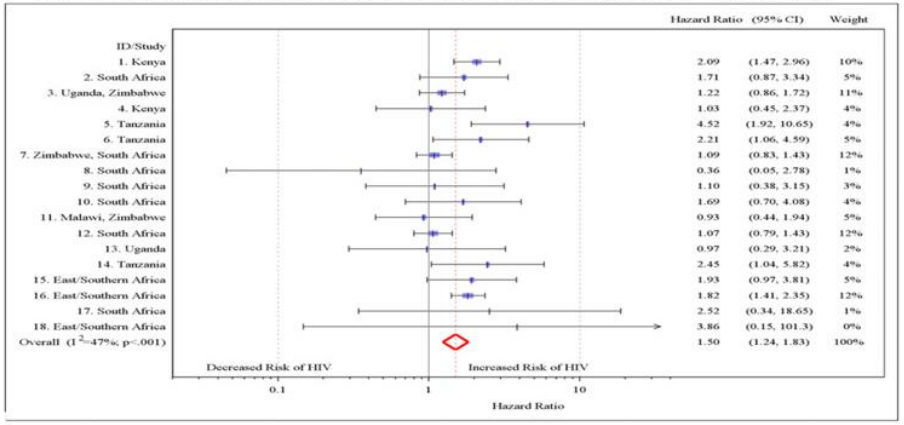


- A 50% higher risk of HIV infection was found in Women using DMPA
- Such increased risk was found to be reduced at 22% in studies at lower methodological risk of bias**, with CI including the possibility of no increased risk**

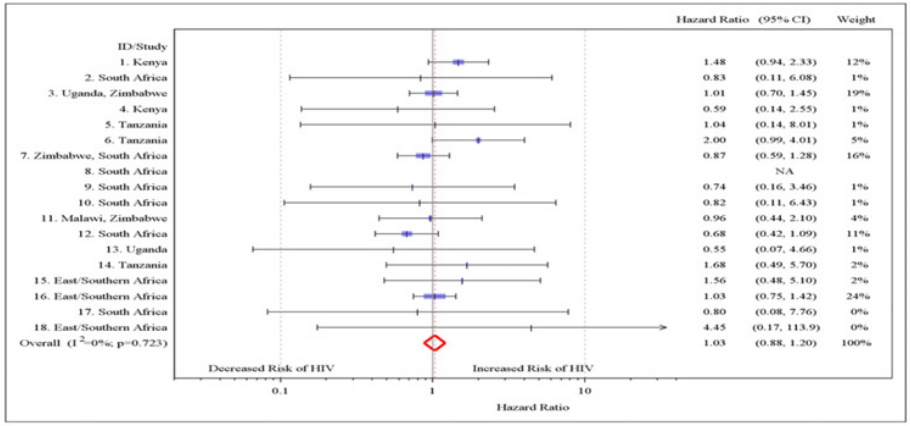
Hormonal Contraception and the Risk of HIV Acquisition: An Individual Participant Data Meta-analysis

Morrison CS, et al. PLOS Medicine | DOI:10.1371/journal.pmed.1001778 January 22, 2015

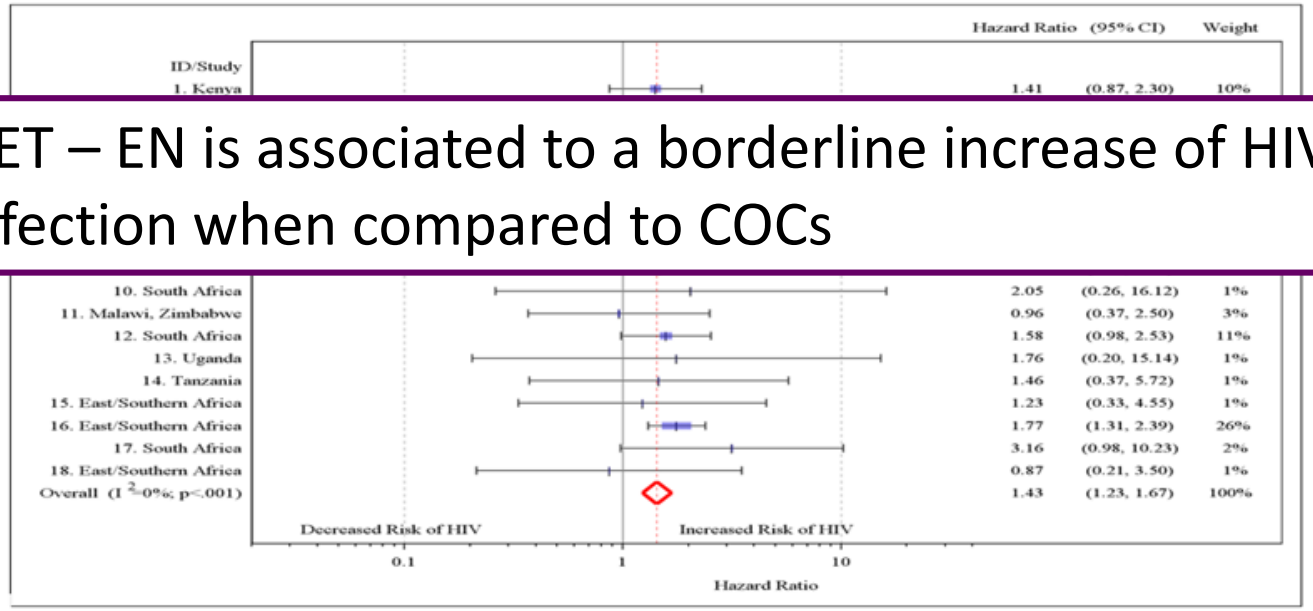
B. Adjusted hazard ratios for DMPA vs. women not using hormonal contraception – primary model



A. Adjusted hazard ratios for COC vs. women not using hormonal contraception – primary model



A. Adjusted hazard ratios for DMPA vs. COC – primary model



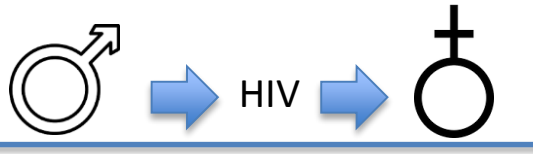
NET – EN is associated to a borderline increase of HIV infection when compared to COCs

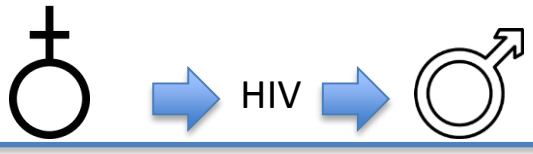
Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

Lancet Infect Dis 2012; 12: 19–26

*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**

	Hormonal contraception	No hormonal contraception
1314 serodiscordant couples (female HIV-1 negative)	6.61/100 person-years	3.78/100 person-years
	AHR 1.98, 95% CI 1.06 – 3.78 p = 0.03	
2476 serodiscordant couples (male HIV-1 negative)	2.61/100 person-years	1.51/100 person-years
	AHR 1.97, 95% CI 1.12 – 3.45 p = 0.02	





Contraceptive use (women)	Analysis of HIV-1 acquisition by women (N=1314 couples)	..	..	Analysis of HIV-1 transmission from women to men (N=2476 couples)
Any hormonal contraceptive use at enrolment	194 (14·8%)	..	..	430 (17·4%)
→ Any injectable use at enrolment	142 (10·8%)	..	..	→ 335 (13·5%)
Any oral use at enrolment	52 (4·0%)	..	..	95 (3·8%)
Any hormonal contraceptive use during follow up	275 (20·9%)	..	..	815 (32·9%)
→ Any injectable contraceptive use during follow up	208 (15·8%)	..	..	→ 656 (26·5%)
Any oral contraceptive use during follow up	87 (6·6%)	..	..	219 (8·8%)

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

*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**

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

*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**

Hormonal contraceptive use and female-to-male HIV transmission: a systematic review of the epidemiologic evidence. Polis CB, et al. AIDS. 2013 Feb 20;27(4):493-505

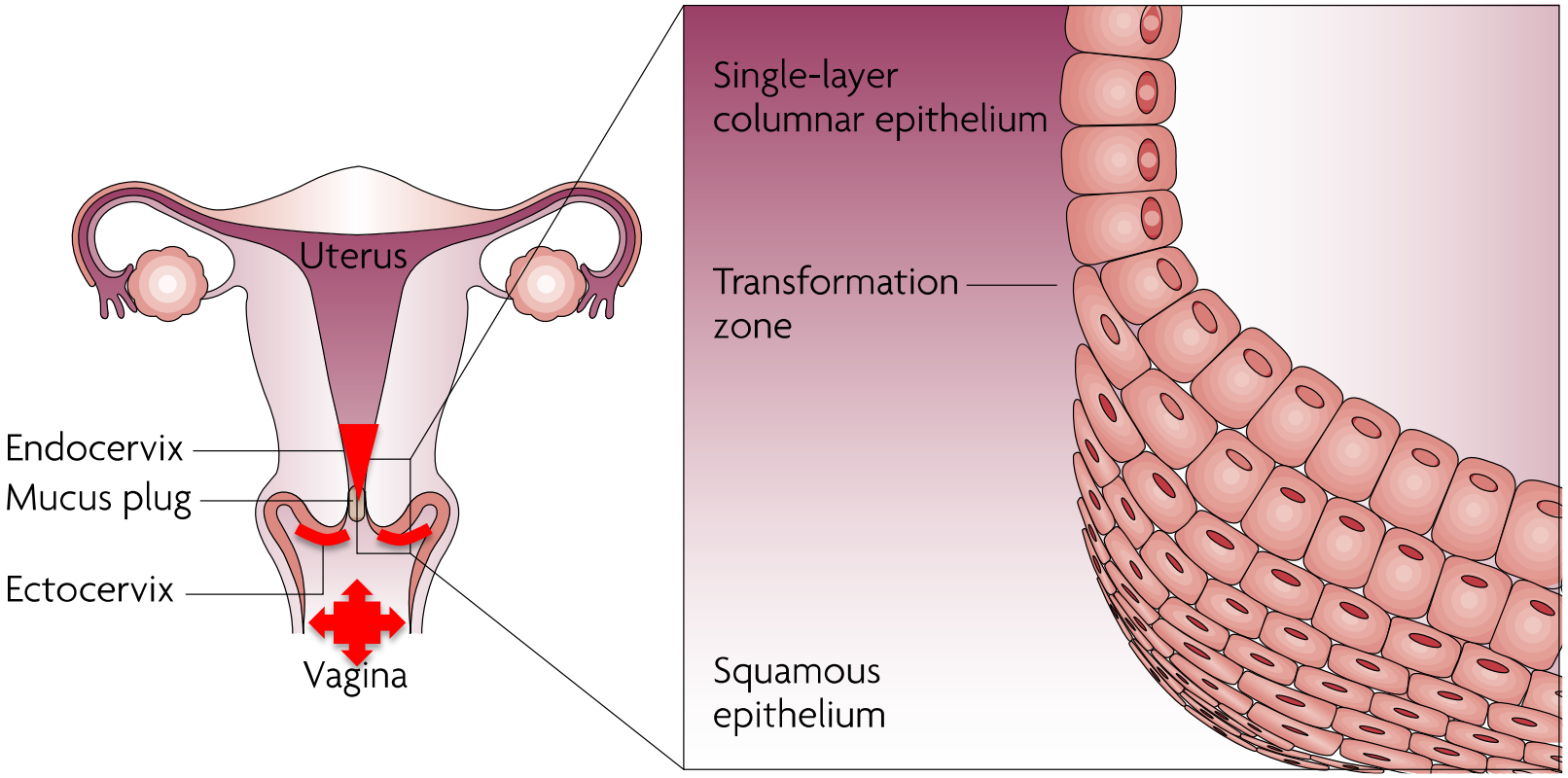
- Systematic review of epidemiologic evidence assessing whether hormonal contraception alters the risk of HIV transmission from an HIV-positive woman to an HIV-negative male partner.

- 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

Small changes in the genital tract epithelium observed after 6 months of DMPA use (numbers of epithelial cell layers and glycogen-positive thickness:

Miller I, et al. Depomedroxyprogesterone-induced hypoestrogenism and changes in vaginal flora and epithelium. Obstet Gynecol 2000; 96:431–439.

However, evidence for this mainly results from studies in NHP

Vishwanathan SA, et al. High susceptibility to repeated, low-dose, vaginal SHIV exposure late in the luteal phase of the menstrual cycle of pigtail macaques. J Acquir Immune Defic Syndr 2011; 57:261–264.

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:

Mauck CK, et al. The effect of one injection of Depo-Provera on the human vaginal epithelium and cervical ectopy. Contraception 1999; 60:15–24.

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

Bahamondes L, et al. The effect upon the human vaginal histology of the long-term use of the injectable contraceptive Depo-Provera. Contraception 2000; 62:23–27.

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

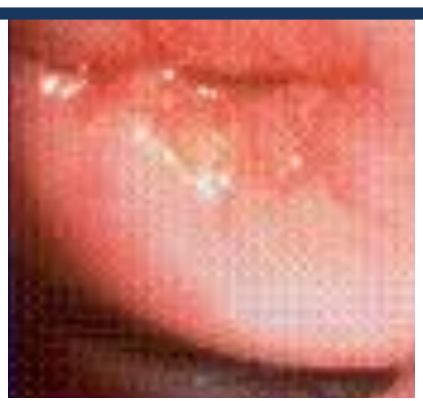
Moss GB, et al. JID 1991; 164: 588-591

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

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:

Mauck CK, et al. The effect of one injection of Depo-Provera on the human vaginal epithelium and cervical ectopy. Contraception 1999; 60:15–24.

Miller L, Patton DL, Meier A, Thwin SS, Hooton TM, et al. (2000) Depomedroxyprogesterone-induced hypoestrogenism and changes in vaginal flora and epithelium. Obstet Gynecol 96: 431–439.



Bahamondes L, Trevisan M, Andrade L, Marchi NM, Castro S, et al. (2000) The effect upon the human vaginal histology of the long-term use of the injectable contraceptive Depo-Provera. Contraception 62: 23–27.

The Journal of Infectious Diseases® 2015;211:1745–56

Medroxyprogesterone Acetate Regulates HIV-1

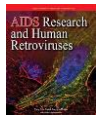
CCR5 Expression Levels in HIV-Uninfected Women Receiving Hormonal Contraception

Sciaranghella G, et al JID 2015; 212; 397-401

We determined peripheral CD4, CCR5, and CXCR4 expression levels in HIV-uninfected women who used depot medroxyprogesterone acetate (DMPA; n = 32), the levonorgestrel-releasing intrauterine device (LNG-IUD; n = 27), oral contraceptive pills (n = 32), or no hormonal contraception (n = 33).
The use of LNG-IUD increased the proportion of CD4+ and CD8+T cells that expressed CCR5; **increases in the magnitude of T-cell subset CCR5 expression were observed with DMPA and LNG-IUD use** (P < .01 for all comparisons).

Chandra N, et al. Depot medroxyprogesterone acetate increases immune cell numbers and activation markers in human vaginal mucosal tissues. AIDS Res Hum Retroviruses 2013; 29:592–601

15 women underwent vaginal biopsies in the follicular and luteal phase, 12 weeks following a single DMPA dose and increased CCR5 expression was found in vaginal tissues



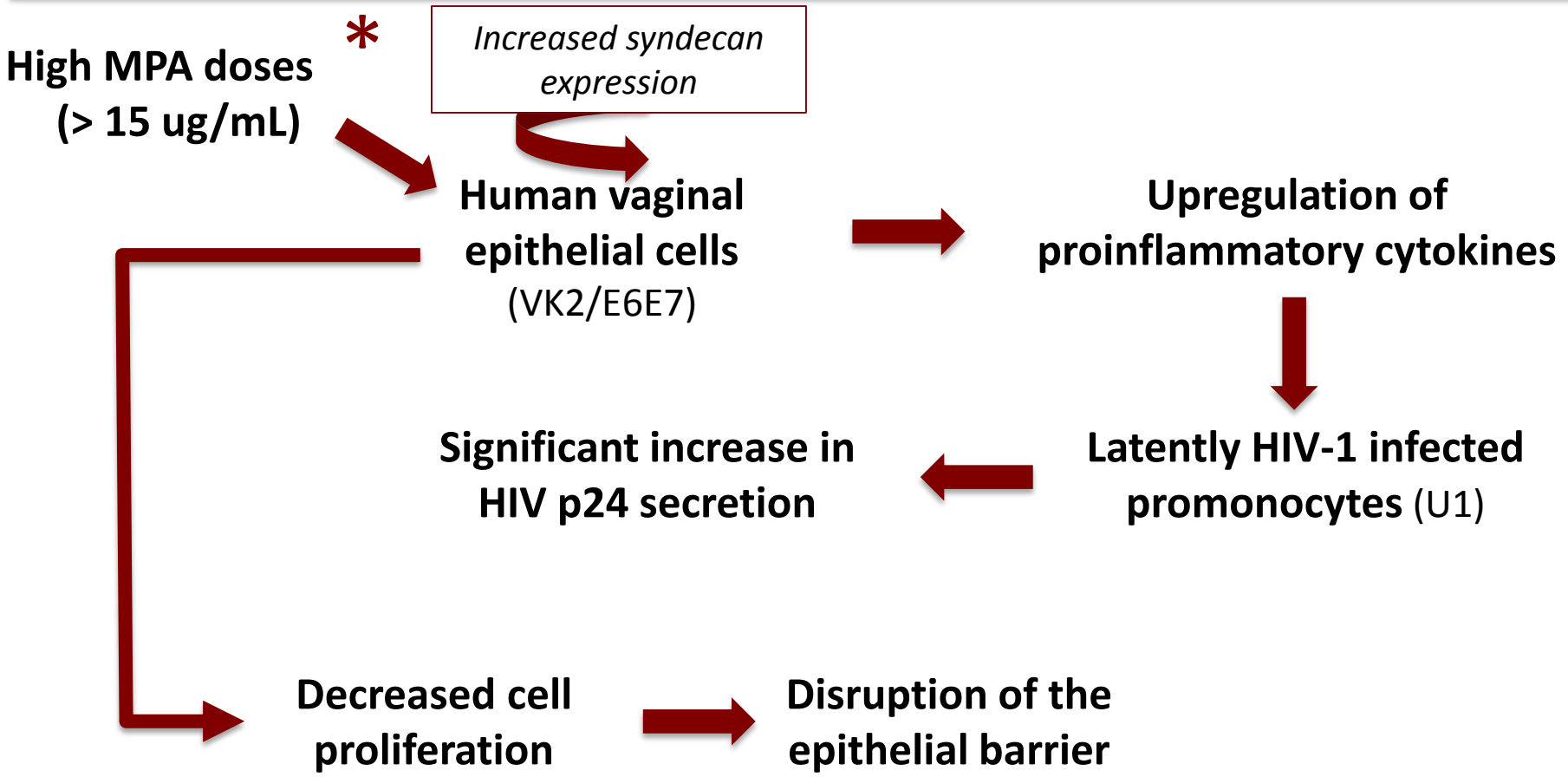
Africander D, et al. Differential regulation of endogenous pro-inflammatory cytokine genes by medroxyprogesterone acetate and norethisterone acetate in cell lines of the female genital tract. Contraception 2011; 84:423–435.

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.

Molecular Mechanisms Linking High Dose Medroxyprogesterone with HIV-1 Risk

Irvin SC, Herold BC.

PLOS ONE | DOI:10.1371/journal.pone.0121135 March 23, 2015



* 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

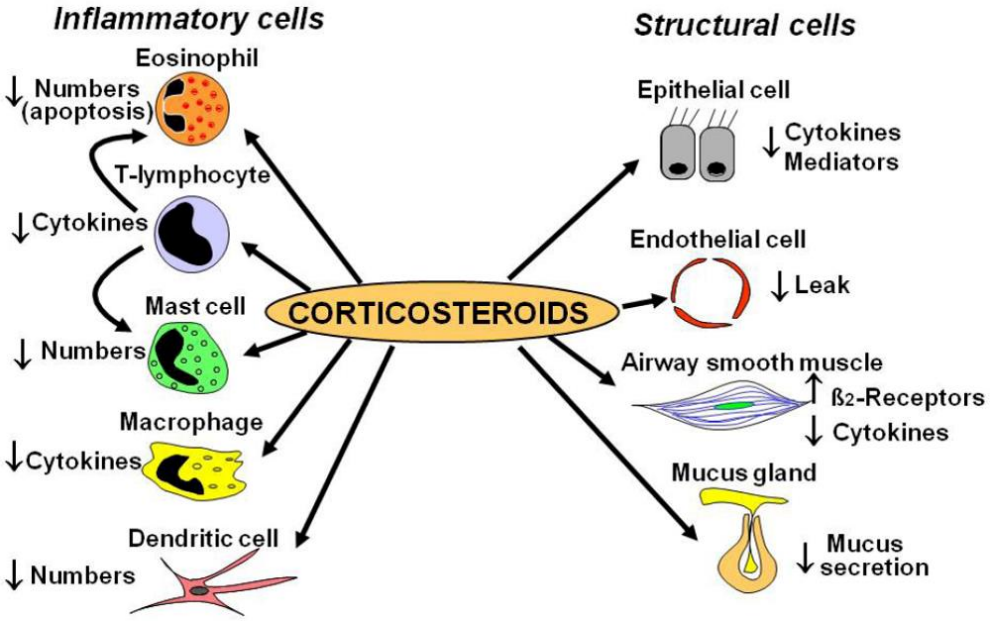
Glucocorticoid Receptor Mediates the Effect of Progesterone on Uterine Natural Killer Cells

AJRI American Journal of Reproductive Immunology

Wei Guo, et al. Am J Repr Immun 2012; 67: 463-73.

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



Schindler AE, et al. (2003) Classification and pharmacology of progestins. Maturitas 46 (Suppl 1): S7–S16.

Hapgood JP, Tomasicchio M (2010) Modulation of HIV-1 virulence via the host glucocorticoid receptor: towards further understanding the molecular mechanisms of HIV-1 pathogenesis. Arch Virol 155:1009–1019.

Huijbregts R, Michel K, Hel Z (2014) Effect of progestins on immunity: medroxyprogesterone but not norethisterone or levonorgestrel suppresses the function of T cells and pDCs. Contraception 90: 123–129.

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

Lancet Infect Dis 2012; 12: 19–26

*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**

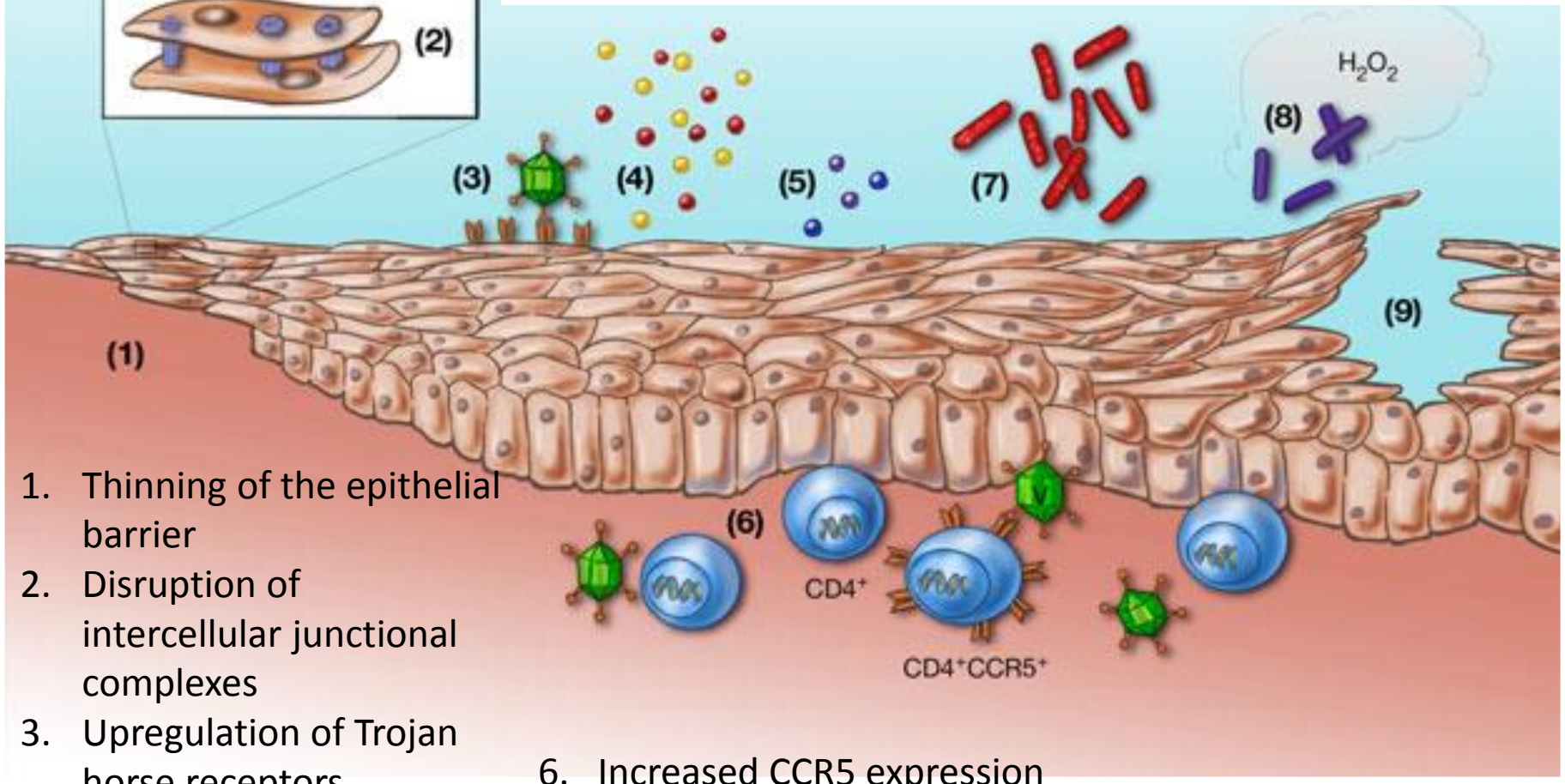
	Detection of any genital HIV-1 RNA				
	n/N (%)	Odds ratio (95% CI)	p value	Adjusted odds ratio* (95% CI)	p value
Overall	1011/1691 (59·9)	..	..	..	..
No hormonal contraception	782/1333 (58·7)	Reference	Reference	Reference	Reference
Any hormonal contraception	230/358 (64·3)	1·27 (0·99 to 1·61)	0·06	1·51 (1·13 to 2·01)	0·0054
→ Injectable	180/272 (66·2)	1·38 (1·05 to 1·81)	0·05	1·67 (1·21 to 2·31)	0·02
Oral	50/86 (58·1)	0·98 (0·63 to 1·52)	0·43	1·06 (0·62 to 1·84)	0·49

	Quantity of genital HIV-1 RNA detected (log_{10} copies/swab)				
	Median (IQR)	Regression coefficient* (95% CI)	p value	Adjusted regression coefficient† (95% CI)	p value
Overall	3·18 (2·08 to 3·85)	..	..	..	..
No hormonal contraception	3·14 (2·08 to 3·91)	Reference	Reference	Reference	Reference
Any hormonal contraception	3·29 (2·08 to 3·91)	0·10 (–0·01 to 0·21)	0·08	0·14 (0·04 to 0·23)	0·0055
→ Injectable	3·38 (2·08 to 4·02)	0·15 (0·03 to 0·28)	0·02	0·19 (0·08 to 0·30)	0·0005
Oral	2·96 (2·08 to 3·65)	–0·07 (–0·28 to 0·14)	0·53	–0·05 (–0·24 to 0·14)	0·60

Research Gaps in Defining the Biological Link between HIV Risk and Hormonal Contraception

Kerry Murphy*, Susan C. Irvin*, Betsy C. Herold

American Journal of Reproductive Immunology **72** (2014) 228–235

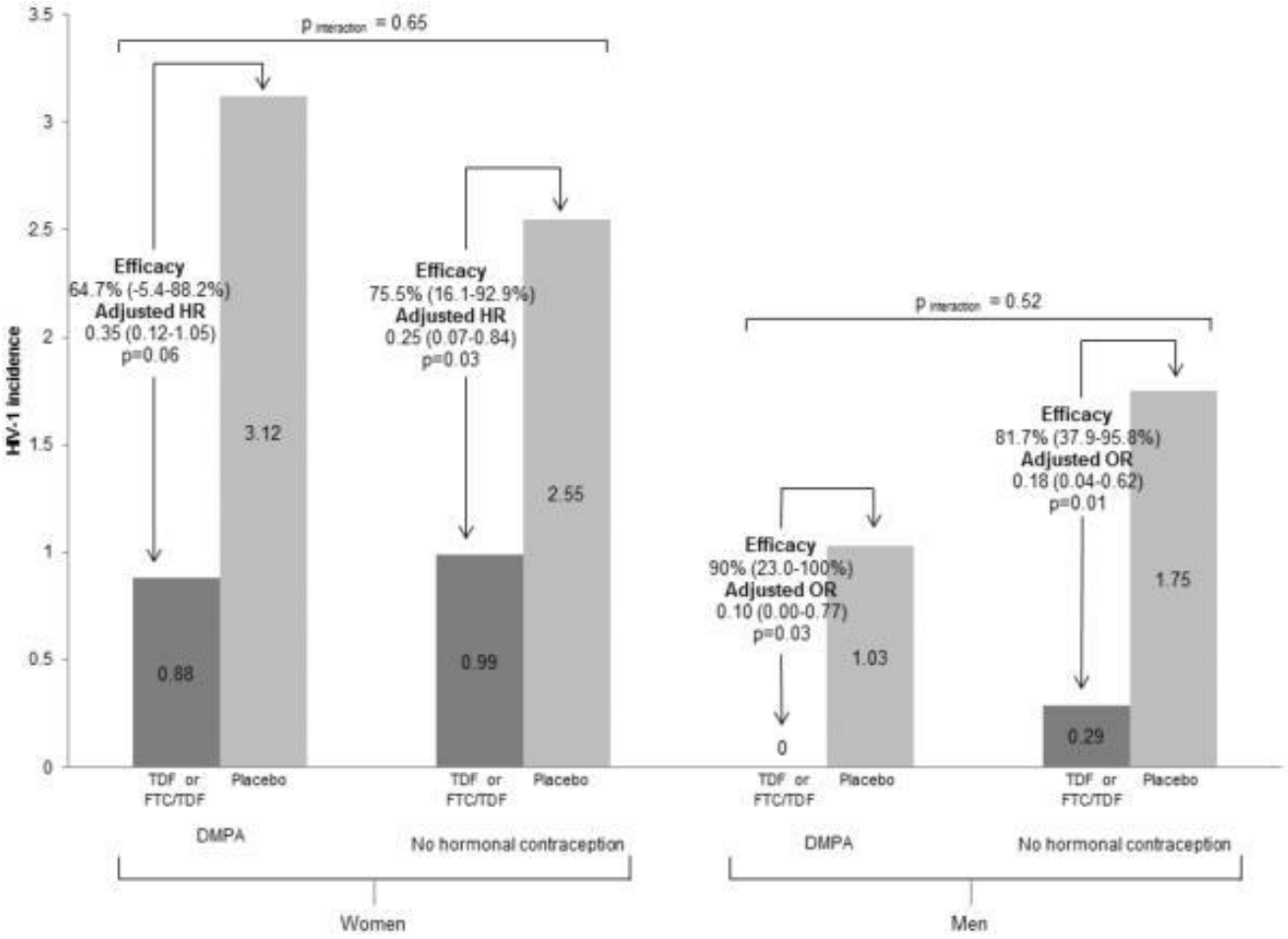


1. Thinning of the epithelial barrier
2. Disruption of intercellular junctional complexes
3. Upregulation of Trojan horse receptors
4. Increased secretion of inflammatory mediators recruiting target cells
5. Decreased secretion of antimicrobial peptides
6. Increased CCR5 expression
7. Increased BV-associated 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

Preexposure prophylaxis is efficacious for HIV-1 prevention among women using depot medroxyprogesterone acetate for contraception. Heffron R, et al. AIDS 2014; 28: 277-6



HIV-1 incidence among women and men exposure and unexposed to DMPA

Associations of hormonal contraceptive use with measures of HIV disease progression and antiretroviral therapy effectiveness.

an international reproductive health journal
Contraception

Whiteman MK, et al. Contraception. 2015 Jul 18. pii: S0010-7824(15)00476-X. doi: 10.1016/j.contraception.2015.07.003. [Epub ahead of print]

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 5233months follow-up among participants not using ART with enrollment CD4 ≥350cells/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.

Effect of hormonal contraceptive methods on HIV disease progression: a systematic review. Phillips SJ, et al. AIDS. 2013 Mar 13;27(5):787-94

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

Lancet Infect Dis 2015; 15: 181–89

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

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.

Oxford University Press

The Journal of Infectious Diseases

Cofactors in Male-Female Sexual Transmission of Human Immunodeficiency Virus Type 1
Author(s): Francis A. Plummer, J. Neil Simonsen, D. William Cameron, Jackoniah O. Ndinya-Achola, Joan K. Kreiss, Michale N. Gakinya, Peter Waiyaki, Mary Cheang, Peter Piot, Allan R. Ronald and Elizabeth N. Ngugi
Source: *The Journal of Infectious Diseases*, Vol. 163, No. 2 (Feb., 1991), pp. 233-239

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