WEIGHING 17 YEARS OF EVIDENCE: DOES HORMONAL CONTRACEPTION INCREASE HIV ACQUISITION RISK AMONG ZAMBIAN WOMEN IN DISCORDANT COUPLES?

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CONFLICT OF INTEREST DISCLOSURE

- The authors have no conflicts of interest due to financial or personal relationships that might be perceived to cause bias.

BACKGROUND

Hormonal contraception

- Prevents unintended pregnancy[1]
  - Prong 2 PMTCT for HIV+ women[1]
- Is widely used in high HIV prevalence areas[2]

Use among married women in Zambia[3]:

11% OCP

9% Injectable

0.4% Implant

Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence☆

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STUDY POPULATION

Discordant couples identified from couples' voluntary HIV counseling and testing services in Lusaka from 1994-2012

Eligibility

- M+F- couples with follow-up
- Male partner was not on ART

Followed 3-monthly at the research site

- Contraception methods provided/assessed
- HIV testing of negative partners

CONTRACEPTIVE EXPOSURES

Hormonal methods:

- Implant (Norplant, Jadelle)
- Injectable (150 mg IM DMPA)
- Oral contraceptive pills (OCPs)

Non-hormonal method control:

- Condoms
- Copper intrauterine device (IUD)
- Permanent methods

HIV INFECTION OUTCOMES AMONG WOMEN

- **Time to any HIV infection**
  - Genetically **linked or unlinked** to the study partner
- **Time to genetically linked HIV infections**

ANALYSES

Multivariate Cox models

- Potential effect-measure modifiers: genital ulceration, genital inflammation, viral load of HIV+ partner, fertility intentions, age

Sensitivity analyses explored effects of:

- Method exposure/control categories/definitions
- Misclassification of unprotected sex
- Time-dependent confounding (marginal structural models)

SEROCONVERSION RATES AMONG WOMEN (N = 1,393 COUPLES)

METHOD	# infections	CY	Incidence /100 CY	95%CI	
TOTAL	252	2839	8.9	7.8	10.0
Non-hormonal methods	152	1898	8.0	6.8	9.4
OCPs	49	425	11.5	8.6	15.1
Injectables	42	392	10.7	7.8	14.3
Implant	9	124	7.3	3.6	13.4

MULTIVARIATE MODEL: TIME TO ANY HIV SEROCONVERSION

METHOD	aHR*	95%CI		p-value (2-tail)
Non-hormonal methods				ref
OCPs	1.3	0.9	1.9	0.14
Injectables	1.2	0.8	1.8	0.32
Implant	0.9	0.4	2.0	0.86

***Controlling for woman's:**

- Age (per year increase)
- Literacy in Nyanja
- Sperm present on a wet prep
- Genital ulceration and inflammation

Conclusions remained the same when controlling for pregnancy and/or fertility intentions

MODELING RESULTS

Similarly, the results of:

- Multivariate models of **linked** infections only
  - **Controlling for:** woman's age, literacy, sperm present on a wet prep, couples' unprotected sex in past 3 months, genital ulceration/ inflammation of female and male partner in past 3 months, man's viral load at baseline
- All sensitivity analyses

did not indicate any significant increase in HIV risk for hormonal contraception users.

MEASURES OF UNPROTECTED SEX BY METHOD OF CONTRACEPTION

	Non-hormonal %	OCPs %	Injectable %	Implant %	p-value (2-tailed)
Incident pregnancy	3%	5%	1%	0%	^
Self-reported unprotected sex	29%	37%	34%	18%	^
Sperm on wet prep	6%	8%	6%	2%	^

^ <0.05: OCP vs. non-hormonal methods

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<0.001: injectables vs. non-hormonal methods

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Sperm on wet prep	6%	8%	6%	2%	&

& <0.001: implant vs. non-hormonal methods

STUDY DESIGN STRENGTHS

- **HIV-discordant couple population**
  - More homogenous HIV risk, more efficient study
  - Ethical study design: HIV testing partners together
- **Methods provided <u>at study site</u>**
  - More accurate exposure assessment
- **Method use assessed at <u>3-month intervals</u>**
  - Important for capturing high rates of method stopping/switching
- **Several time-varying measures of unprotected sex**
  - Sperm on a wet prep, self-report, incident STIs, incident pregnancy

CONCLUSIONS & RECOMMENDATIONS

After controlling for sexual behavior and other confounders in this large cohort study, we found no association between hormonal contraception and HIV acquisition risk in women.

- **Condom use and reinforced condom counseling should always be recommended for women at-risk of HIV.**
  - In our study, women at increased risk for unprotected sex were OCP and injectable users.
  - HIV testing of sex partners together is critical to establish HIV risk, ascertain couple fertility intentions, and counsel appropriately.
- **We support LARC method promotion and efforts to increase method mix, proven strategies to decrease unintended pregnancy, along with condoms for HIV prevention.**

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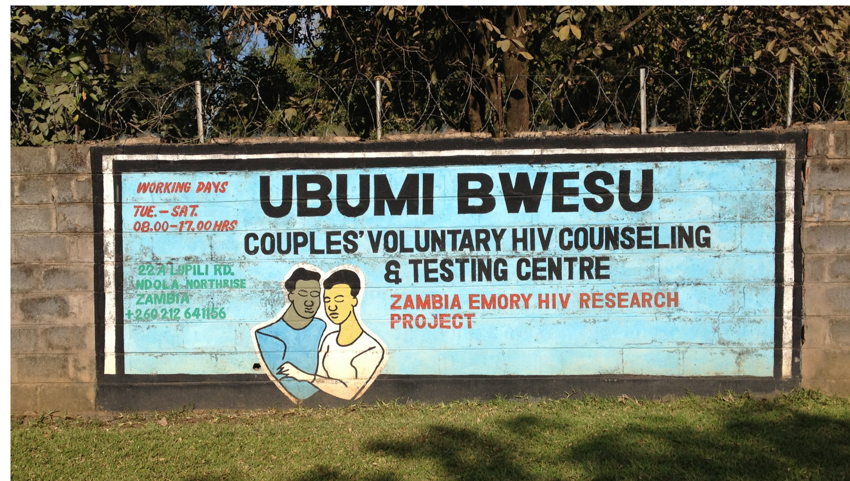

Study Participants & Clinic Staff

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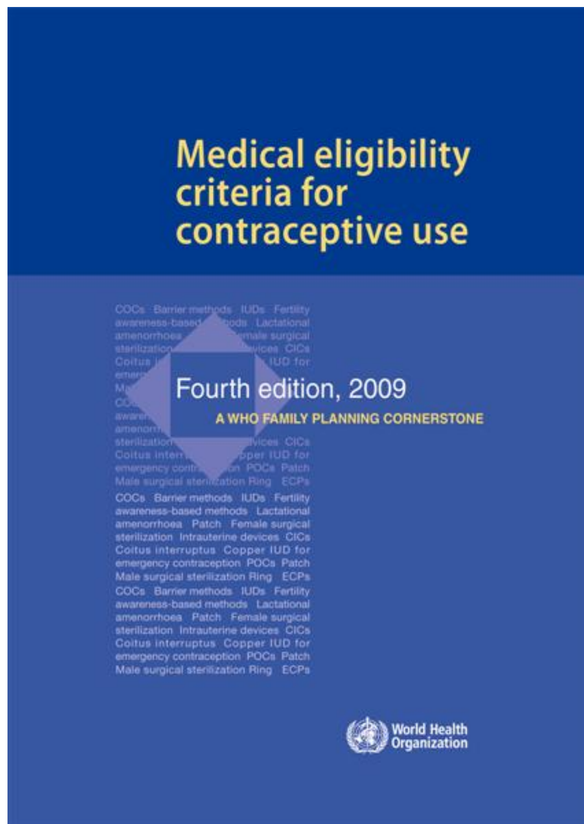
HIV and contraception – complex issues for safe choice: the latest recommendations from the World Health Organization (WHO)

Mary Lyn Gaffield, Sharon Phillips, Rachel Baggaley, Petrus Steyn, and Marleen Temmerman

UNDP · UNFPA · UNICEF · WHO · World Bank
Special Programme of Research, Development and Research Training in Human Reproduction

Medical eligibility criteria for contraceptive use (MEC)



1996, 2000, 2004, 2009

Purpose: Who can safely use contraceptive methods?

- Offers ≈ 1800 recommendations for 19 methods
- Women at high risk of HIV
- Women living with HIV
  - asymptomatic or mild HIV clinical disease
  - severe or advanced HIV clinical disease
- Women living with HIV and using antiretroviral therapy

MEC Categories

1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used

Where warranted, recommendations will differ if a woman is starting a method (I = initiation) or continuing a method (C = continuation)

CATEGORY	WITH CLINICAL JUDGEMENT	WITH LIMITED CLINICAL JUDGEMENT
1	Use method in any circumstances	**Yes** (Use the method)
2	Generally use the method	
3	Use of method not usually recommended unless other more appropriate methods are not available or not acceptable	**No** (Do not use the method)
4	Method not to be used	

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Methods

- Followed WHO requirements for guideline development
- 4 systematic reviews of epidemiological and pharmacological evidence
  - Does the use of hormonal contraception (HC) increase the risk of HIV acquisition ?
  - Does the use of HC accelerate HIV disease progression ?
  - Does the use of HC increase the risk of female-to-male HIV sexual transmission ?
  - Are there any possible interactions between HC and ARV medications?
- GRADE evidence profiles to assess quality of evidence

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Recommendations: High risk of HIV

CONDITION	CATEGORY							
	Combined oral pills	Patch, Vaginal ring	Combined injectable	Progestogen-only pills	DMPA	NET-EN	LNG/ETG implants	LNG-IUD
HIGH RISK OF HIV	1	1	1	1	1[a]	1[a]	1	2

[a] Available studies on the association between progestogen-only injectable contraception and HIV acquisition have important methodological limitations hindering their interpretation. Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition; other studies have not found this association. The public health impact of any such association would depend upon the local context, including rates of injectable contraceptive use, maternal mortality, and HIV prevalence. This must be considered when adapting guidelines to local contexts. WHO expert groups continue to actively monitor any emerging evidence. At the meeting in 2014, as at the 2012 technical consultation, it was agreed that the epidemiological data did not warrant a change to the MEC. Given the importance of this issue, women at high risk of HIV infection should be informed that progestogen-only injectables may or may not increase their risk of HIV acquisition. Women and couples at high risk of HIV acquisition considering progestogen-only injectables should also be informed about and have access to HIV preventive measures, including male and female condoms.

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Recomendations: Living with HIV

HIV-infected → Asymptomatic or mild HIV clinical disease (WHO Stage 1 or 2)

AIDS → Severe or advanced HIV clinical disease (WHO Stage 3 or 4)

CONDITION	CATEGORY I = initiation, C = continuation								
	Combined oral pill	Patch, Vaginal ring	Combined injectable	Progestogen - only pills	DMPA	NET-EN	LNG/ETG Implants	LNG-IUD	
								I	C
ASYMPTOMATIC OR MILD HIV CLINICAL DISEASE (WHO STAGE 1 OR 2)	1[b]	1[b]	1[b]	1[b]	1[b]	1[b]	1[b]	2	2
SEVERE OR ADVANCED HIV CLINICAL DISEASE (WHO STAGE 3 OR 4)	1[b]	1[b]	1[b]	1[b]	1[b]	1[b]	1[b]	3	2

[b] Because there may be drug interactions between hormonal contraceptives and ARV therapy, refer to the section on drug interactions.

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Recommendations: living with HIV using antiretroviral therapy

ANTI-RETROVIRAL DRUGS	CATEGORY I = initiation, C = continuation							
	COC	Patch, ring	CIC	POP	DMPA	NET-EN	LNG/ETG Implants	LNG-IUD	
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)								I	C
ABC, TDF, AZT, 3TC, DDI, FTC, D4T	1	1	1	1	1	1	1	2/3[c]	2[c]
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)								I	C
EFAVIRENZ (EFV) AND NEVIRAPINE (NVP)	2 [d]	2 [d]	2 [d]	2 [d]	1	2 [d]	2 [d]	2/3[c]	2[c]
ETRAVIRINE (ETR) AND RILPIVIRINE (RPV)	1	1	1	1	1	1	1	2/3[c]	2[c]
PROTEASE INHIBITORS (PIs)								I	C
ATV/r, LPV/r, DRV/r, RTV	2 [d]	2 [d]	2 [d]	2 [d]	1	2 [d]	2 [d]	2/3[c]	2[c]
INTEGRASE INHIBITORS								I	C
RALTEGRAVIR (RAL)	1	1	1	1	1	1	1	2/3 [c]	2 [c]

[d] Antiretroviral drugs have the potential to either decrease or increase the levels of steroid hormones in women using hormonal contraceptives. Pharmacokinetic data suggest potential drug interactions between some antiretroviral drugs (particularly some NNRTIs and ritonavir-boosted protease inhibitors) and some hormonal contraceptives. These interactions may reduce the effectiveness of the hormonal contraceptive.

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Conclusion

- For women at high risk of HIV or living with HIV, WHO recommends ***no restrictions*** for:
  - Combined hormonal contraceptives or progestogen-only contraceptives
  - Women and couples at high risk of HIV infection & using POIs should be informed about (and have access to) HIV preventative measures, including male and female condoms.
  - LNG –IUDs ***can generally be used***; however, initiation should be generally avoided if advanced/severe disease
- For women taking ART, WHO recommends they ***are generally eligible*** to use hormonal contraception:
  - Special consideration for efavirenz or neviripine & some protease inhibitors may be warranted.
- Consistent and correct use of condoms, male or female, is critical to protect against STIs/HIV and for prevention of HIV transmission

WHO’s commitment

- To continually review MEC recommendations
- Strongly supports the need for further research to identify definitive answers that address concerns around increased biological vulnerability to HIV and understanding of possible drug interactions

www.who.int/reproductivehealth/topics/family _planning