Guidance on hormonal contraceptive eligibility for women at high risk of HIV infection: An update of WHO recommendations

James Kiarie
Medical eligibility criteria for contraceptive use (MEC)

- Provides recommendations (> 2000) on eligibility for 25 methods of contraception
- Conditions include:
  - A physiological status (e.g. parity, breastfeeding),
  - A group with special needs (adolescents, perimenopausal women)
  - A health problem (e.g. headache, irregular bleeding)
  - A known pre-existing medical condition (e.g. hypertension, STI, diabetes)
  - **High risk of HIV infection**
MEC Categories

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

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>WITH CLINICAL JUDGEMENT</th>
<th>WITH LIMITED CLINICAL JUDGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Use method in any circumstances</td>
<td>Yes (Use the method)</td>
</tr>
<tr>
<td>2</td>
<td>Generally use the method</td>
<td>No (Do not use the method)</td>
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<tr>
<td>3</td>
<td>Use of method not usually recommended unless other more appropriate methods are not available or not acceptable</td>
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<tr>
<td>4</td>
<td>Method not to be used</td>
<td></td>
</tr>
</tbody>
</table>
Current WHO recommendations for hormonal contraception and high risk of HIV

<table>
<thead>
<tr>
<th>Condition</th>
<th>COC/P/CVR</th>
<th>CIC</th>
<th>POP</th>
<th>DMPA/NET-EN</th>
<th>LNG/ETG Implants</th>
<th>LNG-IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>COC</td>
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<tr>
<td>CVR</td>
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<tr>
<td>P</td>
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<tr>
<td>CIC</td>
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<tr>
<td>POP</td>
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<tr>
<td>LNG/ETG</td>
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<td>1*</td>
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<tr>
<td>Implants</td>
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<tr>
<td>LNG-IUD</td>
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<td></td>
<td>2</td>
</tr>
</tbody>
</table>

COC = combined hormonal contraceptive  
P = combined contraceptive patch  
CVR = combined contraceptive vaginal ring  
CIC = combined injectable contraceptive  
POP = progestogen-only pill  
LNG/ETG = levonorgestrel and etonogestrel (implants)  
DMPA = depot medroxyprogesterone acetate (injectable)  
NET-EN = norethisterone enanthate (injectable)

**CLARIFICATION:** Women at high risk of HIV who are using progestogen-only injectables should be informed that available studies on the association between progestogen-only injectable contraception and HIV acquisition have important methodological limitations hindering 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.
Rationale for reviewing WHO guidance

- Updated synthesis of articles published through 15 January 2016 commissioned by WHO

- 10 new studies identified
  - Data from 5 new studies considered informative but with important limitations
  - Meta analysis of higher quality studies: DMPA hazard ratio 1.4 (1.2-1.7)

- Consideration of current DMPA recommendations in light of the updated review’s findings suggested
Process

- Presentations providing context
  - Decision analysis modelling competing risks of unintended pregnancy, maternal mortality and HIV acquisition risk
  - Survey of programme interpretation of WHO recommendations
  - Perspectives of programme managers/directors

- Summary of the systematic review findings

- Review of biological plausibility and potential mechanisms linking hormonal contraception and HIV acquisition

- Formulated recommendations, through consensus, considering:
  - Quality of the evidence (GRADE table)
  - Values and preferences of users and providers
  - Balance of benefits and harms of contraceptive use
  - Contraceptive choice
  - Equity and human rights
  - Acceptability
  - Feasibility
## Recommendations (combined methods)

<table>
<thead>
<tr>
<th>Condition</th>
<th>COC</th>
<th>P</th>
<th>CVR</th>
<th>CIC</th>
<th>Clarification/evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>COC = combined hormonal contraceptive</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>EVIDENCE: Eleven studies, deemed ‘informative but with important limitations’, assessed the use of oral contraceptives (OCs). Ten of these studies found no statistically significant association between use of OCs and HIV acquisition, while one study reported a marginally significant increased risk. No studies of P, CVR, or CIC were identified.</td>
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<tr>
<td>CVR = combined contraceptive vaginal ring</td>
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</tbody>
</table>

P = combined contraceptive patch
CIC = combined injectable contraceptive
PROGESTOGEN-ONLY CONTRACEPTIVES
# GRADE table for implants

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Indirectness</th>
<th>Overall quality</th>
<th>Estimate of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Implant use versus non-use</strong></td>
<td></td>
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</tr>
<tr>
<td>HIV acquisition</td>
<td>2 cohort studies* (2 665)^</td>
<td>Serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious imprecision</td>
<td>No indirectness</td>
<td>Very low</td>
<td>Adjusted HR 0.96 (0.29-3.14) and 1.6 (0.5-5.7)</td>
</tr>
</tbody>
</table>

*Restricted to studies classified as “informative with but with important limitations”

^Sample size is for the entire study population
# GRADE table for progestogen-only injectables

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Indirectness</th>
<th>Overall quality</th>
<th>Estimate of effect</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DMPA versus non-hormonal contraception</strong></td>
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</tr>
<tr>
<td>HIV acquisition</td>
<td>9 cohort studies plus 1 individual patient data meta-analysis of 7 studies* (39 562)^</td>
<td>Some limitations**</td>
<td>No serious inconsistency</td>
<td>No serious imprecision</td>
<td>No indirectness</td>
<td>Low-moderate ^^^</td>
<td>Adjusted HR: 0.46 to 2.04, 8 studies increased risk (HR: 1.25 to 2.04), 3 studies statistically significant; 2 studies trend towards decreased (HR 0.46 and 0.75 wide CIs). <strong>Pooled adjusted HR 1.40 (1.23-1.59), I^2=0%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>NET-EN versus non-hormonal contraception</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HIV acquisition</td>
<td>5 cohort studies, 1 individual patient data meta-analysis of 7 studies* (29 248)^</td>
<td>Some limitations**</td>
<td>No serious inconsistency</td>
<td>Some imprecision**</td>
<td>No indirectness</td>
<td>Low</td>
<td>Adjusted HR: 0.87 to 1.76, 5 studies increased risk (HR: 1.20 to 1.76), none statistically significant; 1 study no effect (HR 0.87, 95% CI 0.60 to 1.25). <strong>Pooled adjusted HR 1.15 (0.93-1.42), I^2=0%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>DMPA versus NET-EN</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HIV acquisition</td>
<td>1 cohort study and 1 individual patient data meta-analysis of 17 studies* (41 608)^</td>
<td>Some limitations**</td>
<td>No serious inconsistency</td>
<td>No serious imprecision</td>
<td>No indirectness</td>
<td>Low-moderate ^^^</td>
<td>Adjusted HR 1.32 (1.08-1.61) in cohort study and 1.41 (1.06-1.89) in IPD meta-analysis of 17 studies (I^2=0%)</td>
<td></td>
</tr>
</tbody>
</table>

*Studies included in meta-analysis

^CIs

**Some limitations

^^Adjusted HR

I^2=0%
## Evidence to decision table for DMPA/NET-EN injectables

<table>
<thead>
<tr>
<th>Factor</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>Low to low-moderate</td>
</tr>
<tr>
<td>Benefits &amp; harms</td>
<td>Benefits outweigh harms</td>
</tr>
<tr>
<td>Values &amp; preferences</td>
<td>Support for optimizing informed contraceptive choice and the availability of a wide range of contraceptive options</td>
</tr>
<tr>
<td>Priority of the problem</td>
<td>Hormonal contraception and HIV is a public health priority</td>
</tr>
<tr>
<td>Equity and human rights</td>
<td>Recommendations within WHO’s human rights guidance for contraception are paramount principles for decision-making on this topic</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Clear guidance essential for implementation</td>
</tr>
<tr>
<td>Resource implications</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
## Recommendations for progestogen-only contraceptives

<table>
<thead>
<tr>
<th>Condition</th>
<th>POP</th>
<th>DMPA/NET-EN</th>
<th>LNG/ETG</th>
<th>Clarifications/evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of HIV</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>CLARIFICATION: There continues to be evidence of a possible increased risk of acquiring HIV among progestogen-only injectable users. Uncertainty exists about whether this is due to methodological issues with the evidence or a real biological effect. In many settings, unintended pregnancies and/or pregnancy-related morbidity and mortality are common, and progestogen-only injectables are among the few types of methods widely available. Women should not be denied the use of progestogen-only injectables because of concerns about the possible increased risk. Women considering progestogen-only injectables should be advised about this possible increased risk, about the uncertainty about whether there is a causal association, and how to minimise their risk of acquiring HIV.</td>
</tr>
</tbody>
</table>

EVIDENCE: Evidence from 13 observational studies of DMPA, NET-EN, or non-specified progestogen-only injectables, which were considered to be “informative but with important limitations”, continues to show some association between use of progestogen-only injectables and risk of HIV acquisition, but it remains unclear whether this results from a causal association or methodologic limitations. Two small studies assessing levonorgestrel implants, which were considered to be “informative but with important limitations”, did not suggest an elevated risk, although the risk estimates were imprecise. One study reported no association between use of progestogen-only pills and HIV acquisition.

POP = progestogen-only pill  
DMPA = depot medroxyprogesterone acetate (injectable)  
NET-EN = norethisterone enanthate (injectable)  
LNG/ETG = levonorgestrel and etonogestrel (implants)
Conclusion

- For women at high risk of HIV, WHO recommends no restrictions for:
  - Combined hormonal contraceptives, progestogen-only pills or progestogen-only implants

- Women at high risk of HIV infection can use DMPA (IM or SC) and NET-EN
  - DMPA and NET-EN injectables are now MEC category 2
    - Optimise the rights of women and girls for contraceptive choice & informed decision-making
    - Clearer communication of the imperative for fully informed counselling; earlier recommendation had not lead to this intended goal

- Women should not be denied the use of progestogen-only injectables

- Women should be advised about the possible increased risk of HIV infection and about the uncertainty of whether there is a causal association

- Consistent and correct use of condoms, male or female, is critical to protect against STIs/HIV and prevention of HIV transmission
Implications for policies, programmes and providers

- Programmes can continue to offer all methods of contraception to women at high risk of HIV infection
- WHO resources available to complement and support these recommendations
- Comprehensive contraceptive and HIV information, counselling services must be available equally to everyone
- Contraceptive counselling is a core component for supporting informed choice and decision-making
- Integration of high quality family planning and HIV services is an essential strategy to optimize reproductive health for all individuals
- National programmes are urged to expand upon the range of available family planning/contraceptive method options
WHO’s commitment

- To continually review it recommendations on contraceptive eligibility
- Strongly supports the need for further research to address the twin epidemics of HIV and unintended pregnancy
## WHO follow up activities

- Pre launch webinar
- Frequently asked questions
- Web story
- Press brief
- Country follow up
  - HC HIV stakeholders meeting Johannesburg 10-13 April
  - Supporting in country consultations
- Implementing partners webinar
Stakeholder Reactions

- Dissemination: To regional, national and subnational implementers
- Research: informed consent forms and information sheets revised
- Guidance: Derivative technical briefs and medical and Service Delivery Guidelines
- Service delivery: development of message, particularly targeting low-literacy, most vulnerable and marginalized populations
- IEC: Update of IEC including Cue cards and other training, counseling and mentorship tools
- New tools: HIV risk assessment tools and new counseling tools that will better explain the possible increase in HIV risk
- Integration into national guidance: several countries
WHO and Partners Stakeholders' Meeting on Hormonal contraception and HIV:

- 3 day meeting in two parts
- Participants
  - WHO and MoH participants from 12 of 14 African countries with HIV prevalence > 5%
  - ECHO consortium members
  - Donors
  - Civil society and Advocates
- Outcomes
  - New WHO guidance on POI for women at high risk of HIV acquisition disseminated
  - Importance of continuing research in this area emphasized with stronger collaboration between basic scientists, epidemiologic and health systems researchers
  - Countries to host stakeholder consultations to ensure that the guidance is implemented
Next Steps

- On going support for in country consultations
- Monitoring implementation and impact
- Sharing lessons and documentation
- Continued dissemination
  - Franco phone webinar 1st week of May
- Global Handbook for Providers
- Collaboration with partners who supporting implementation activities
  - HC3’s Strategic Communication Framework for Hormonal Contraceptive Methods and Potential HIV-Related Risks
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