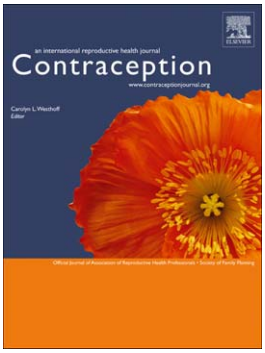

Hormonal contraceptive methods and HIV: research gaps and programmatic priorities

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Background:

Access to safe and effective contraception supports the autonomy of women worldwide and is key for promoting individual and public health [1]. When selecting contraceptive methods, women and their providers must weigh the risks and benefits of all available options. Access to the best available evidence on contraceptive safety supports the provision of high-quality family planning care. To assist providers and policymakers with decision-making, the World Health Organization (WHO) publishes the Medical Eligibility Criteria for Contraceptive Use (MEC), an evidence-based guideline document that characterizes the safety of contraceptive methods for women with various medical conditions or personal characteristics [2].

Providing clarity about the safety of hormonal contraceptive (HC) methods for women at risk of HIV and for women living with HIV is a public health priority. The MEC, which is informed by continuous review of relevant evidence, includes recommendations for use of various contraceptive methods by women at high risk of HIV, women living with HIV, and women using antiretroviral therapy (ART) [2-4]. Over the past few years, new evidence relevant to intersections between HC and various HIV-related risks prompted WHO to commission updates of two systematic reviews: one on HC method use and HIV acquisition in women [5], and another on potential drug interactions between HC methods and antiretrovirals (ARVs) [6].

In December 2016, WHO convened an expert review of available data on HC method use and risk of HIV acquisition in women. At this meeting, the guideline development group reached consensus, and the MEC recommendation for progestogen-only injectable use among women at high risk of HIV changed from a category 1 (meaning that the method can be used without restriction) with a clarification (stating that women should be informed that progestogen-only injectables may or may not increase risk of HIV acquisition) to a category 2 (meaning that advantages of using the method generally outweigh potential risks) with an updated clarification.

The clarification[1] highlights that women interested in, or using, these methods should be advised of the concern regarding a link between use of these methods and potential increased risk of HIV, about the uncertainty over whether the link is causal, and about how to minimize HIV risk [4]. It is also noted that, provided with full informed consent, women at high risk of HIV infection who still wish to use injectable contraceptives should not be denied access to them.

Since 2015, WHO has convened two other consultations with global stakeholders to discuss the emerging evidence and its implications for research, programmes, and policy – one in December 2015, prior to the MEC update, and another in April 2017, to review the implications of the updated guidance. Research and programmatic priorities that emerged from the 2015 consultation, which were shared with country partners and other key stakeholders in 2017, are described in this paper. These research gaps and programmatic priorities remain highly pertinent in light of continued uncertainty regarding progestogen-only injectable contraceptive use and risk of HIV acquisition in women.

Context:

In December 2015, WHO brought together 55 experts in family planning and HIV from nine countries, including clinicians, epidemiologists, researchers, program managers, policy-makers, communications specialists, implementation scientists, reproductive biologists, pharmacologists, HIV advocates, women's health advocates, and staff from the Joint United Nations Program on HIV/AIDS (UNAIDS), United Nations Population Fund (UNFPA), and

[1]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 these concerns, about the uncertainty over whether there is a causal relationship, and about how to minimize their risk of acquiring HIV.

WHO. This meeting was not a formal priority-setting meeting. Instead, the consultation brought together multidisciplinary stakeholders to discuss the implications of emerging research findings, highlight research gaps, and consider programmatic approaches to providing family planning and HIV services that support the health of women living with, or at risk of, HIV. Using presentations, panels, and working groups, we explored the following topics: epidemiological data on specific HC methods and risk of HIV acquisition; data on biological and immunological mechanisms by which HC method use may impact HIV acquisition risk; epidemiological, pharmacokinetic (PK), and pharmacodynamic (PD) data on potential drug interactions between HC methods and ARVs; ongoing relevant research studies related to the aforementioned topics plus related implementation and communication science research; modeling studies exploring the possible impact of methodological biases in observational analyses of HC methods and HIV.

In April 2017, 60 stakeholders met to review the implications of the updated MEC guidance. Representatives from ministries of health in countries with high HIV prevalence joined WHO staff, staff from other UN agencies, scientists, civil society representatives, and funding agency representatives. Many of the topics covered at the 2015 meeting were reviewed, including the research and programmatic priorities outlined in this manuscript. Additionally, working groups and panels focused on how to interpret and communicate new WHO guidance, adapting the guidance to country-specific contexts, and dissemination and implementation strategies. Importantly, ministry of health representatives discussed development of national responses to account for country-level contextual factors such as HIV prevalence, current contraceptive method mix, and current national family planning programmes.

The major themes that emerged from the 2015 meeting, which were shared and reaffirmed in 2017, will be of interest to researchers seeking to move the body of evidence

forward, to programme planners invested in providing high quality comprehensive sexual and reproductive health (SRH) services for women, and to individuals and groups advocating for SRH rights.

Major themes:

A. Areas for improvement in research methodology and measurement to strengthen future research

A1. Increased inter-disciplinary collaboration and dialogue between basic, clinical, and epidemiological scientists

Several possible biological mechanisms could potentially link use of depot medroxyprogesterone acetate (DMPA) to increased risk of HIV acquisition in women or transmission to men. These include: DMPA influenced structural changes in the female genital epithelium [7-12], alterations in cellular targets for infection [8, 13-15], alteration of innate and adaptive immune responses [13, 16-20], and changes to the female genital tract microbiome [21, 22]. Knowledge and perspective gaps were noted between basic scientists, epidemiologists and clinical scientists. Understanding the complex relationship between HC and HIV will likely require increased collaboration and cross-disciplinary dialogue between these different perspectives.

A2. Enhanced understanding of biological predictors of HIV acquisition:

The lack of identified biological predictors of HIV acquisition is a vital knowledge gap. In order to fully understand findings from clinical and epidemiological studies examining the relationship between HC and HIV acquisition, more knowledge is needed regarding which changes are clinically significant biomarkers of future HIV acquisition. If one or several strong biological predictors of HIV acquisition could be identified, epidemiologic and clinical studies

could examine biological changes rather relying on HIV seroconversion as the outcome. Participants noted that achieving adequate sample size using HIV seroconversion as an endpoint in clinical trials could become infeasible with introduction of PrEP as a standard of care. In this case, biological predictors will be valuable for evaluating HIV acquisition risk associated with new and existing contraceptive methods.

A3. Enhanced understanding of pharmacokinetic findings and potential drug interactions of clinical importance

We identified a lack of data on HC-ART interactions, as well as gaps in translating PK/PD data into clinically useful guidance. Further research is needed to understand how the full range of HC methods interact with a range of ARV regimens [6]. In particular, more research is needed on PK/PD data related to the concurrent use of certain HC methods, including norethisterone enanthate (NET-EN) and long-acting reversible contraceptives (LARCs), with newer ARVs, including integrase inhibitors. Second, it is vital to develop a greater understanding of how outcomes from PK and PD studies (such as changes in exposure to either contraceptive hormones or ARVs due to drug-drug interactions) translate into clinically relevant outcomes for contraceptive effectiveness and ARV safety [6]. Investing in PK/PD studies that follow participants to clinically relevant endpoints may help the research community gain clarity on the meaning of observed PK/PD changes, resulting in individual and public health benefits.

A4. Objective measures of progestin concentrations in blood and relevant tissues, where possible, will improve upon self-reported contraceptive use to inform data

Many studies investigating the relationship between HC method use and HIV have relied on self-reported data collection about HC use, which can introduce misclassification of exposure [23, 24]. Better understandings of systemic and local tissue concentrations of contraceptive

hormones associated with typical method use could permit investigators to more accurately categorize contraceptive exposure. Objective measures of progestin levels in blood and relevant tissues (e.g. cervical epithelium) could help avoid exposure misclassification, assist in characterizing differences between progestins, and enhance understanding of how progestin levels in blood and tissues may impact HIV risk.

A5. Ensuring that future studies appropriately categorize distinct contraceptive formulations, including disaggregating different progestins

Many studies have grouped HC methods together by route of administration, rather than by specific progestin-type; for example, grouping DMPA users with NET-EN users [5]. These progestin-only injectable contraceptive methods are also grouped together in the updated MEC guidance [4]. However, these DMPA and NET-EN are distinct progestins that could differentially impact the risk of HIV acquisition and thus may represent very different exposures [21, 25]. There is a need to characterize differential biological effects on genital epithelium and mucosal immunity, and ultimately, HIV acquisition risk, of the full complement of progestins.

A6. Increased understanding of barriers to diversifying the available contraceptive method mix

Despite the concerns of a potential causal association with increased risk of HIV acquisition in women who use DMPA [4, 5], this progestin is the most commonly used contraceptive method in many countries with high HIV prevalence [26]. The high prevalence of injectable use in these settings is likely due to a range of structural and systems issues and not to user preference alone [27]. The need to understand why DMPA is so widely used, and how to enhance acceptability and availability of other highly effective contraceptive methods in these settings, was identified as a critical research need. For decades, governments and non-

governmental organizations have made efforts to expand access to a range of contraceptive methods in sub-Saharan Africa [28-32]. Continuing to expand contraceptive method mix was noted as a key priority, both in 2015 and in 2017. Social science and health services research methods are key for understanding why the method mix in many countries with high HIV prevalence often shows a substantial proportion of DMPA use, and for determining which factors (e.g., provider attitudes, user preferences, government and funder investments, characteristics of health care delivery supply chains) may contribute to high rates of DMPA use in such settings.

A.7. Anticipated advantages and limitations of forthcoming randomized trial results

Observational data, including all currently available studies on HC and HIV acquisition, are vulnerable to bias by confounding. Randomized trials can reduce the possibility of confounding at baseline, although post-randomization behaviors may still differ by assignment arm. In 2015 and again in 2017, the stakeholder groups discussed the potential impact of data from a randomized trial, focusing on the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, a multi-center, open-label, randomized trial comparing the relative incidence of HIV acquisition and pregnancy rates in women using DMPA, levonorgestrel implants, and copper intrauterine devices (IUDs) [33]. Recruitment began in December 2015, and several key ECHO investigators, including WHO-affiliated investigators, participated in the 2015 and 2017 meetings. WHO serves as a coordinating partner on the ECHO study [33]. Some meeting participants and researchers have expressed concern both about whether the trial will provide clear answers to the question of whether DMPA increases women's risk of HIV, and about the ethics of randomizing women to DMPA [34-38]. ECHO investigators and other meeting participants, including members of the study's global community advisory boards (who were present at the 2017 meeting), cited that the unresolved relationship between DMPA and HIV

underscores the importance of obtaining randomized trial data to provide clarity on this relationship [39]. It was acknowledged that other questions will remain unanswered, given the limited range of contraceptive options included. Importantly, at the 2017 meeting, country partners were encouraged not to wait for ECHO results to begin implementing country-appropriate policies and programmes in response to the updated MEC guidance on progestogen-only injectables.

B. Programmatic recommendations to ensure high-quality provision of HIV and family planning care

B1. Detailed consideration of the SRH needs of women when developing ART and pre-exposure prophylaxis PrEP guidelines

Potential drug-drug interactions between ART and HC are important to consider in the development of HIV guidance, particularly when recommending first- and second-line ART regimens for use by women, many of whom also use HC. Data on potential drug-interactions between HC methods and ARVs should play a role in developing guidance for women exposed to both. The available data on drug interactions should also inform the guidance provided for women using HC methods and PrEP to prevent pregnancy and HIV, respectively.

B2. Integration of woman-centered family planning and HIV services

Findings from implementation research projects that have studied the impact of integrating HIV and family planning services were presented [40, 41]. Integrating HIV and family planning services is a key step that can allow for the provision of high-quality, woman-centered contraceptive services to women living with, and at risk of, HIV. If global use of PrEP expands among women of reproductive age, family planning service provision may be the best setting to reach women seeking PrEP. In 2015, the group also noted the changing demographics

of typical ARV users, who are generally healthier, since treatment is started earlier. PrEP roll out for HIV-negative women is beginning to scale up; as it expands, it will be critical to explore the opportunities for offering PrEP in SRH programs and integrating SRH services into PrEP programs. This changing picture demands consideration of a wider range of SRH needs at different stages in women's lives.

With the updated MEC guidance, conversations in 2017 centered on the importance of informed contraceptive choice for women at high risk of HIV, with particular attention on concerns related to use of progestogen-only injectable contraception. Working groups discussed adaptations to the WHO global handbook for family planning providers [42]. An updated job tool is in development to reflect messages that family planning providers can share with women during contraceptive counseling in light of uncertainty about HIV acquisition risk associated with injectable contraceptives. Country partners also reaffirmed the importance of promoting dual protection, as no hormonal contraceptive method protects against HIV acquisition.

Conclusions and next steps:

WHO and leaders in the research community will continue to monitor the evolving literature and will communicate evidence clearly to stakeholders, advocates, and the public. We hope that the suggested research and programmatic foci presented here will spark conversation and action, to move toward the best ways to collect quality data on the relationship between HIV and HC methods and the best ways to provide high quality, appropriate services for women and men, living with HIV and at risk of HIV acquisition.

Disclaimer: The authors alone are responsible for the views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. The authors of this summary have attempted to accurately reflect the discussions held during the meeting, but take full responsibility for any misinterpretations or errors in reflecting those conversations. J.K. and P.S. are current members of the ECHO trial consortium.

Acknowledgments and Conflicts of Interest:

P.S., J.K., and H.R. contributed to organizing the December 2015 meeting on which the manuscript is based. S.A., E.B., A.G., C.P., J.K., H.R., P.S. attended and contributed to the December 2015 meeting.

H.R. wrote the first draft of the manuscript and S.A., E.B., A.G., C.P., J.K., and P.S. provided substantive comments and feedback on manuscript drafts and final manuscript.

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