**Women need better guidance and more action on progestin-only injectable contraceptives**

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**Introduction**

The World Health Organization (WHO) released updated guidelines in February 2017 for use of progestin-only injectable contraceptives, including intramuscular depo medroxyprogesterone acetate (DMPA-IM), or Depo-Provera, by women at high risk of HIV1. The medical eligibility criteria (MEC) classification of DMPA-IM for women at high risk of HIV was category 1, indicating “no restriction for use”, and is now category 2, indicating that, “advantages generally outweigh the theoretical or proven risks”2. Additionally, the WHO noted continued uncertainty in the relationship between progestin-only injectable contraception and HIV acquisition and called for ensuring women are informed of this potential risk during contraceptive counseling. The WHO action followed biennial expert consultations in 2012, 2014, and 2016. At the December 2016 meeting, data from 31 observational studies and several systematic reviews were available.3-5 In the most recent review, estimates from the 12 studies deemed to be of highest quality were pooled, indicating an increased risk of HIV acquisition of approximately 40-50% with DMPA-IM use compared to non-hormonal contraceptive use3. Still, concerns remainabout insufficient adjustment for confounding by sexual activity and condom usage and the validity of hormonal injectable exposure measures, given that the vast majority of studies rely on self-reported use6. Meanwhile, a considerable literature of biological evidence has accrued on plausible mechanisms whereby HIV vulnerability could be increased with this compound—immunological, cellular, and microbiological5,7;these studies have raised strong hypotheses, however further research is required to draw firm conclusions about the exact biological mechanism(s). In September 2017, the new WHO recommendations were also adopted by the United States Centers for Disease Control and Prevention (CDC)8. While we applaud the higher MEC category recommended by WHO and CDC for DMPA-IM for those at high risk of HIV, we highlight several problems in the guidance documents, and recommend that DMPA-IM be differentiated from other progestin-based injectables and designated at an MEC category 3, as existing data suggest it is a higher risk method than the other progestin-based injectable, norethisterone enanthate (NET-EN). We address these issues in turn below.

**Different risk profiles of progestin-only injectables**

The first problem in the WHO and CDC advisories is internal inconsistency, whereby now *all* progestin-only injectables are considered to have the same risk profile for individuals at high risk of HIV, that of MEC category 2. To have DMPA-IM and NET-EN, a popular alternative injectable in South Africa, in the same category is not evidence-based. The recent systematic review and meta-analysis of epidemiological studies by Polis et al., for example, indicates a statistically significant *lower* risk of HIV with NET-EN use compared with DMPA-IM; specifically, the estimated DMPA-IM to NET-EN hazard ratios, after adjusting for confounding, ranged from 1.3-1.4, or a potential 30-40% increase in HIV risk with DMPA-IM use for the two studies that included a head-to-head comparison. There was no statistically significant elevation in HIV risk for NET-EN when compared to non-hormonal method users in the six studies with estimates3. Addressing biological mechanisms, Hapgood et al.7 recently published a comprehensive review of clinical, animal and ex-vivo data comparing medroxyprogesterone acetate (MPA, the active pharmaceutical ingredient in DMPA-IM injections) with other progestins. The review concludes that MPA exhibits cortisol-like immunosuppressive effects by binding strongly to the glucocorticoid-receptor, but this is not the case for other progestins such as NET-EN or natural progesterone7. Further, the evidence reviewed demonstrates an effect of DMPA-IM, but not NET-EN, on several other mechanisms that could increase HIV susceptibility: increasing permeability of the female genital tract by inducing hypoestrogenism, increasing the number of target cells for HIV, and increasing the levels of CCR5 co-receptors on those target cells7. Hapgood et al. conclude: “Together the data provide a compelling case against the continuous use of DMPA in areas of high HIV-1 prevalence provided other forms of safe, affordable, non-hormonal or hormonal contraceptive methods are readily available.” Further to Hapgood et al.’s review, a new study involving whole genome transcriptome profiling of human ectocervical tissues provides additional support for impaired mucosal integrity as a mechanism for increased risk of HIV infection9.

For the subcutaneous (SC) and lower dose DMPA preparations, Depo-subQ Provera 104 and Sayana Press (the latter is the same compound and dose as the former but administered via the single-use, “Uniject” system rather than syringe) there are no extant epidemiological data on HIV risk to date10. The limited biologic and pharmacokinetic data available suggest that DMPA-SC has similar effects as DMPA-IM7, but more research is needed. None of these distinctions are clear when NET-EN, DMPA-SC and DMPA-IM are aggregated under the same risk category, as they are in the 2017 WHO guidance.

**WHO should clearly signal DMPA-IM risks to stimulate real expansion of contraceptive alternatives**

At a minimum, the distinction between doses and modes of administration (IM versus SC) and progestin compound (DMPA vs. NET-EN) should be addressed in other parts of the WHO Guidance, specifically in the “Summary of the Evidence,” and in the section on “Knowledge Gaps and Areas of Active Research.” Not addressing these distinctions may act as a disincentive for further research and scale-up of existing and alternative injectable contraceptives, thereby decreasing women’s contraceptive options when we urgently need to expand access to alternatives safer than DMPA-IM.

In addition to the association with increased susceptibility to HIV and other sexually transmitted infections3,5, DMPA-IM is associated with a number of negative side effects including loss of bone mineral density (BMD), and slow return to fertility 11,12. NET-EN appears to pose no risk of significant BMD loss, though data are more limited13,14. Return to ovulation appears to be more rapid with NET-EN in limited data15; return to fertility may not differ across the two compounds but comparative data across the same population are scant. Furthermore, combined hormonal injectable contraceptives (such as Mesignya, which combines 50 mg of NET-EN and 5 mg of estradiol valerate) have lower discontinuation rates from irregular bleeding patterns than DMPA-IM16. One longstanding argument made in favor of DMPA-IM use is that infrequent provider contact is needed because of the 3-monthly spacing of injections—thus increasing the reach of family planning due to provider shortages, and logistical difficulties for women traveling long distances to access care. Yet, while current combined injectable contraceptives (administered monthly) and NET-EN (administered bimonthly for the first 6 months; then at 3 month intervals), require more provider contact compared to DMPA-IM and DMPA-SC (both administered from the start at 3 month intervals), the expansion of self-injection technologies and service provision by lay health workers could reduce barriers caused by more frequent injections.

These are important variables to consider in a cost-benefit analysis of the scope of methods to make available in a given setting, especially if other formulations of injectable contraceptives have better overall safety profiles (of course, those that include an estrogen need to consider cardiovascular risks). Indeed, published risk-benefit analyses (eg., Butler et al., 201317, Rodriguez et al., 201718) have examined the impact on maternal and HIV-related mortality of removal of DMPA-IM, with the worst case scenario presented as no replacement among DMPA users with other contraceptive methods. Not surprisingly, these studies find that DMPA-IM would have to be replaced with other effective contraceptive methods in order to have a net benefit on mortality. We question the premise of these analyses, as it is doubtful that anyone would recommend removing DMPA-IM from the method mix without well-planned and resourced, vigorous scale-up of replacement contraceptive methods. In sub-Saharan Africa where women’s risk of HIV is high, the fact that DMPA-IM is the most widely used contraceptive method19 is not acceptable – we urgently need to ensure access to the safest forms of contraceptives available in these settings, while recognizing that side effect profiles will vary for all contraceptive methods and these profiles are likely to influence contraceptive uptake and continuation. Experience has shown that increasing options and providing quality counseling will both enable women to make truly informed choices, as well as ensure better population-level contraceptive uptake among women seeking to prevent or space pregnancies.

Concerning the designated higher risk category announced in the WHO and CDC guidances, we agree that for NET-EN, MEC category 2 is appropriate, and consistent with available data. Available data, however, support placing DMPA-IM at an even higher level of risk for those at high risk of HIV—MEC category 3, indicating that “the theoretical or proven risks usually outweigh the advantages”. Per WHO, “provision of a method to a woman with a condition classified as Category 3 requires careful clinical judgment and access to clinical services; for such a woman, the severity of the condition and the availability, practicality and acceptability of alternative methods should be taken into account”2. Animal model data and biological data all support what is found in observational studies showing an increased risk of HIV acquisition from DMPA-IM7. In considering the MEC classification for DMPA-SC, we find there continues to be sufficient uncertainty to guide an evidence-based recommendation; more data are urgently needed. Indeed, we are concerned that, even in the absence of such data, DMPA-SC was introduced in Burkina Faso, Niger, Senegal and Uganda in 201420 and is being made available at low cost (US$0.85 per dose) in 69 resource poor countries, primarily in sub-Saharan Africa and Asia, through the Family Planning 2020 project21. The rationale for upgrading to an MEC 3 category clearly lies in the biological and pharmacokinetic data detailed above. Thus, the precautionary principle would dictate that DMPA-SC be designated at MEC 3 for individuals at high risk of HIV, with regular reviews of new data going forward, and a potential “downgrade” to an MEC category 2 if evidence builds to support a safer profile. On the other hand, retaining DMPA-SC at an MEC category 2 would acknowledge the need for epidemiologic data on that particular formulation of MPA supporting a higher risk level than NET-EN, before designating DMPA-SC at MEC 3. Such a position would need to be coupled with a serious commitment to frequent, ongoing, review of new data and later elevation to MEC category 3 should the evidence warrant it. With a serious scale-up of safer contraceptive alternatives in high-HIV prevalence settings, we find a move to designate DMPA-SC at MEC 3 sooner rather than later to be the better-justified choice.

A key concern (see, eg. Han et al., 201722) regarding a regulatory move that would limit access to DMPA-IM is that it would place the method out of reach for some women who do not have access to alternatives, which brings us back to the central question of why progress to expand contraceptive choice to women in sub-Saharan Africa has been so slow, and so inadequate in scale—especially considering the high and rising prevalence of DMPA-IM use. Epidemiologic and biologic data on the potential harm with DMPA-IM have accumulated over the last twenty years, when initial concerns were raised in 1996 from findings that progestin exposure increased HIV transmission in simian models23. Since that time, newer safer contraceptive technologies have become available.

The 2014 South Africa program to launch the hormonal subdermal implant (Implanon) demonstrates the urgency and intensity of the challenges ahead in expanding contraceptive services24,25. Importantly, the program paid careful attention to monitoring and evaluating both user and provider perspectives on the counseling and uptake process. A main problem identified in the program’s evaluation was the tendency for providers to promote the method to women as “first-line”—emphasizing effectiveness over all other attributes such as side effects (especially bleeding irregularities). This type of directive counseling has accompanied other LARC-promoting initiatives but clearly violates the principles of client-centeredness that honor a woman’s individual values on contraceptive risks and benefits and her right to make a free, informed choice26,27 In South Africa, the consequences of counseling heavily slanted toward the technological advance of implants, coupled with lack of trained providers for implant removal, was a wave of negative attention and press toward the method and a high discontinuation rate, often due to side effects that were inadequately addressed in counseling24,25. Thus, although the South Africa 2016 DHS report28 estimated implant use at 8%, an analysis of contraceptive methods dispensed over 2013-2016 showed a large reduction in implants dispensed over the time period; the analysis also showed a slight decrease in dispensed units of NET-EN, and stable distribution of DMPA-IM24. Likewise, the South Africa DHS data28 confirm that DMPA-IM remains far and away the most widely used method with a user prevalence at nearly 20% of all sexually active women, ranging up to nearly 25% among married women aged 20-29 years. Although the implant launch denotes a step toward a better contraceptive method mix, the results demonstrate anew that achieving real change in assuring safer options for women will take time and effort. In our view, compensatory resources must quickly be made available to deploy existing safer alternatives to DMPA-IM, to make up for the time lost in action.

**Resources for action to increase contraceptive choice have been diverted**

Indeed, considerable resources that might have supported programs to expand the method mix have been channeled into the “ECHO” (Evidence for Contraceptive Options and HIV Outcomes) study. This sub-Saharan African-based trial randomizes women at high HIV risk to DMPA-IM use, or two other highly effective methods that lack available data on HIV risk: the copper IUD, and progestin implant, Jadelle, with the aim of comparing HIV acquisition across the methods. The trial--for which WHO is a study consortium member6--was highlighted toward the end of the WHO 2017 guidance1, under “Knowledge Gaps” (noted above to be an incomplete section), where the agency called for more randomized clinical trials. WHO, by highlighting the need for ECHO trial results as a priority next step, appears to advocate for holding up decisive action on DMPA-IM until additional, more conclusive data are available on *other* methods; this position compromises women’s health. Urgent efforts to expand contraceptive choice and scale down DMPA-IM use should neither be stalled nor slowed as we attend results of the ongoing randomized trial, which, due to well-documented challenges29-31, including adequate study power to detect small effects, potential selection bias, limited external validity, and potentially uncontrolled confounding (as the trial is open label), is unlikely to provide a definitive answer on whether DMPA-IM use increases HIV acquisition outside the study setting. In addition, the ECHO trial will also be completely uninformative regarding the relative HIV acquisition risks of different injectable formulations (for example, DMPA-SC, NET-EN), which are not part of the trial.

**Conclusion**

In summary, we urge the WHO to formally and publicly clarify that available data suggest that DMPA-IM and NET-EN have different risk profiles for HIV-acquisition. Further, the agency should make more explicit its support and participation in research activities to maximize the deployment of alternative, available contraceptive methods especially in sub-Saharan Africa – with a vigor equal to or exceeding that demonstrated by the agency for the ECHO trial. WHO should raise the MEC classification of DMPA-IM for women at high risk of HIV to 3, which will also provide a much needed incentive to step up the pace and scope of these activities; and ensure adequate counseling about the potential risks and benefits of its use. This would have less of an impact in settings with low HIV-prevalence, as this categorization is only for women at high risk of HIV. Finally, studies are urgently needed to assess the HIV risk profile of DMPA-SC (including Sayana Press) prior to even wider-scale rollout of this product; study of NET-EN is also needed, in view of the small number of studies presently available. Combined injectable methods should also be explored, as should the combined etonogestrel/ethinyl estradiol hormonal ring (NuvaRing)32, and newly-approved segesterone acetate and ethinyl estradiol ring (Annovera)33, methods that do not require provider contact for discontinuation.

It is estimated that every minute one young woman is infected with HIV34. Women account for 67% of new HIV infections worldwide35.At the same time, women do not have access to the full range of contraceptive options they need to make informed choices in many high HIV prevalence settings. These choices do exist in more resourced contexts but have not been expanded in countries where DMPA-IM has a large market. The impact of these policy decisions is to raise the stakes for women by creating a contrived environment of low choice, limiting our ability as public health actors to respond appropriately on a body of risk data for any given method (here, DMPA-IM). Leadership to expand safe contraceptive options for women and to ensure appropriate counseling for women to make informed decisions is the type of action that is needed; the lives and safety of millions of women worldwide are at stake.

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