



HHS Public Access

Author manuscript

Contraception. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Contraception. 2018 March ; 97(3): 191–197. doi:10.1016/j.contraception.2017.12.003.

Is a lower-dose, subcutaneous contraceptive injectable containing depot medroxyprogesterone acetate likely to impact women's risk of HIV?

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INTRODUCTION

Injectable contraceptives are the most widely used method of contraception in sub-Saharan Africa among married or in-union women aged 15–44 [1]. Injectable contraceptive use grew more quickly than use of any other contraceptive method between 1994 and 2015: from 2% to 7% of the share of all contraceptive use (among married or in-union women) worldwide, and from 17% to 38% of the share of all contraceptive use in sub-Saharan Africa [1]. Injectables are quick to administer, highly effective, do not require daily user action, and can be used clandestinely [2]. Like all contraceptive methods, injectables can empower women and couples to achieve their reproductive goals, reduce unintended pregnancy, and prevent maternal morbidity and mortality [3].

Concerning observational data suggest that women who use the most common type of injectable contraception, depot medroxyprogesterone acetate (DMPA), may be at increased risk of HIV acquisition compared to women not using hormonal contraception [4]. In March 2017, the World Health Organization modified the Medical Eligibility Criteria for Contraceptive Use to indicate that women at high risk of HIV acquisition may use progestin-

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ROLE OF AUTHORS

CBP conceived of the idea for this manuscript, drafted the outline, and managed the overall writing process. All authors contributed equally to the writing and endorsed the final version.

CONFLICTS OF INTEREST

CBP, SLA, ZH, and JPH have no conflicts of interest to report.

only contraceptive injectables (including intramuscular or subcutaneous DMPA, and norethisterone enanthate [NET-EN]), and should be advised about concerns that these methods may increase risk of HIV acquisition, the uncertainty over whether there is a causal relationship, and how to minimize the risk of acquiring HIV [5].

DMPA is most commonly administered intramuscularly at a dose of 150 mg every three months (hereafter, DMPA-IM). A subcutaneous formulation containing 31% less hormone (104 mg; hereafter DMPA-SC) and offering similar efficacy has more recently been developed [6–9]. While some side effects may depend on differences in dose and route of administration [10], whether these differences would have any impact on HIV-1 acquisition risk relative to DMPA-IM is unknown. A key question is whether the risk of HIV acquisition associated with DMPA-SC is likely to be lower compared to that associated with DMPA-IM. An ongoing trial (NCT02550067) assessing HIV acquisition in women randomized to DMPA-IM, copper IUD, and levonorgestrel sub-dermal implants will not evaluate DMPA-SC. Therefore, understanding the risk of HIV acquisition in DMPA-IM users relative to DMPA-SC users is critical, particularly as access to DMPA-SC is set to expand, given the recent rollout of Sayana® Press, a convenient DMPA-SC product which offers the potential for self-administration.

WHAT IS SAYANA® PRESS?

Sayana® Press is DMPA-SC packaged in a pre-filled, single-dose, non-reusable subcutaneous injection system called Uniject™. Uniject simplifies injection provision and requires minimal training, expanding possibilities for community-based distribution and self-injection. Thus, Sayana® Press could increase contraceptive access, including for underserved populations in hard-to-reach areas, and has been referred to as a potential “game-changer” in reducing unmet need for modern contraception [11].

The product has regulatory approval in the European Union and over 25 countries worldwide, and is currently available in over 15 countries. Between 2014 and 2016, PATH coordinated a pilot introduction initiative in Burkina Faso, Niger, Senegal, and Uganda [12]. They administered nearly 500,000 doses, 44% of which went to women under age 25 [12]. Women [13, 14] and health workers [15] have expressed preferences for DMPA-SC over DMPA-IM. Studies have documented interest in self-injection [16, 17] and feasibility has been assessed in Senegal, Uganda, Malawi, and elsewhere [12, 18–23]. Sayana® Press has been approved for self-injection in several countries [12].

DMPA-IM AND HIV RISK IN WOMEN

No epidemiological studies have assessed DMPA-SC with respect to risk of HIV acquisition. In contrast, 25 observational epidemiological studies provided information relevant to DMPA-IM (or non-disaggregated injectables) and risk of HIV acquisition in women, 13 of which were considered to be of higher quality [4]. The quality of observational studies on this issue has improved over time [4, 24]. Though inferring causality from observational data is challenging, a recent systematic review of available observational data concluded that new data amplifies existing concerns of a potential causal link between DMPA-IM use and

increased HIV acquisition risk in women. Meta-analyses suggest that the hazard ratio would most likely be around 1.4, though such estimates should be interpreted with caution, given the potential for confounding in observational data [4, 25, 26].

Several biological mechanisms may underlie an association between DMPA and increased risk of HIV acquisition in women, including: structural changes and alterations in the permeability of the female genital tract, alterations of the frequency and activity of cellular targets for infection, modulation of levels of soluble mediators and defense molecules in the genital tract, alteration of innate and adaptive immune responses, and changes in the female genital tract microbiome [27, 28]. Research in this area has been stymied by lack of identified biomarkers that would predict significant risk of future HIV acquisition. Such biomarkers, if identified, could be used to link findings from biological and epidemiological studies on the issue of DMPA use and HIV risk. As discussed below, mounting evidence from human, animal, and *ex vivo* studies suggests that medroxyprogesterone acetate (MPA), at concentrations within the range of systemic MPA concentrations detected in DMPA-IM users, affects various biological mechanisms that may be integral to HIV acquisition risk, yet the clinical relevance remains unclear. Since epidemiological data directly comparing DMPA-IM and DMPA-SC for HIV outcomes are unavailable, below we explore the known similarities and differences between the two formulations to address potential differences in their impact on the acquisition of HIV.

DMPA-SC VS. DMPA-IM: SIMILAR OR DIFFERENT HIV ACQUISITION RISKS?

DMPA-IM and DMPA-SC contain the same progestogen but differ in dose and route of administration

Both DMPA-IM and DMPA-SC contain MPA as the active progestogenic contraceptive compound. Since MPA is virtually insoluble in water, both DMPA-IM and DMPA-SC are formulated as sterile aqueous suspensions of 150 mg/mL and 104 mg/0.65 mL, respectively [29]. Similar excipients, such as amino acids, salts, and agents to enhance viscosity are included in both formulations, although the quantities may differ [29].

Does administration of DMPA-IM vs. DMPA-SC result in a different systemic concentration of MPA?

Whether differences in dose and route of administration result in different systemic MPA concentrations (pharmacokinetics) and effects (pharmacodynamics) is likely relevant to possible effects on HIV acquisition. MPA concentrations above approximately 0.2 ng/mL are needed for high contraceptive efficacy and are maintained over at least 3 months for both regimens [30, 31]. Based on the 31% difference in MPA dose between formulations, an approximately 31% difference in systemic concentration might be assumed. Differences in serum concentrations could be due to different pharmacokinetic properties, metabolism, intrinsic individual factors, or different sites of injection (subcutaneous tissue of upper arm, thigh, or abdomen for DMPA-SC vs. muscle tissue of upper arm, hip, or buttock for DMPA-IM). DMPA-SC may have a lower peak serum concentration (C_{max}) and a slower rate of absorption than DMPA-IM [10, 31]. To date, only one head-to-head study comparing

women using DMPA-IM versus DMPA-SC has been published and identified no significant differences between the mean serum MPA trough levels (C_{min}) [8]. Notably, this study collected limited pharmacokinetic data, with no C_{max} data, and reported only serum C_{min} concentrations of MPA 6, 12 and 24 months after initiating use.

Whether a true C_{max} difference exists between DMPA-IM and DMPA-SC remains to be determined. Neither C_{max} nor other pharmacokinetic properties of single or multi-dose studies have been reported for head-to-head evaluations. When evaluated separately (non-comparative studies), the reported C_{max} values differ greatly between DMPA-SC and DMPA-IM. Three published primary studies evaluated pharmacokinetic parameters following a single injection of DMPA-SC with reported mean C_{max} values of 1.56 ng/mL (4.0 nM) [31], 1.3 ng/mL (3.4 nM) [32] and 0.95 ng/mL (2.5 nM) [33], and all report peak serum MPA concentration occurring by median day 8–13. C_{max} values reported for DMPA-IM from multiple studies are more variable, with average C_{max} values ranging from 2.2–24 ng/mL (5.8–62 nM)^a [29, 34–46] occurring 2–14 days post injection. Both large inter-individual and inter-study variations in C_{max} concentrations have been reported for DMPA-IM [10, 47, 48], whereas reported C_{max} values for DMPA-SC are less variable, though fewer studies exist.

Based on a comparison of non-parallel studies, the initial MPA serum concentration decline following administration of DMPA-IM appears steeper than that following DMPA-SC, particularly in the first month [10, 29, 31]. Thirty days after injection, serum MPA concentration has been reported to be 1 ng/mL for DMPA-IM [34, 49–51] and 0.8 ng/mL for DMPA-SC [31, 32]. Concentrations of about 0.4–1.2 ng/mL MPA measured at 90 days after administration do not appear to differ for DMPA-IM and DMPA-SC [8, 29, 31, 51]. Thus, serum concentrations of MPA from days 30 to 90 post administration may be similar between DMPA-SC and DMPA-IM. Although it appears likely that DMPA-SC and DMPA-IM have different C_{max} and pharmacokinetic properties, differences from non-parallel studies may be confounded by differences in methodology, numbers of women investigated, and variations in individual intrinsic factors. Based on these non-parallel studies, DMPA-SC may have up to 85% lower C_{max} as compared with DMPA-IM. To what extent such differences would exert an effect on MPA levels and pharmacokinetic parameters for DMPA-IM vs. DMPA-SC remains unclear [29, 30, 33]. Appropriately powered parallel studies of single and multi-dose regimens, randomized to minimize potential confounding by ethnicity, race, body mass index, weight, and other factors, are needed to address these questions.

How might different serum concentrations affect biological responses potentially relevant to HIV acquisition?

The intracellular mechanisms whereby MPA could influence biological effects are likely to involve the glucocorticoid receptor (GR) and/or the progesterone receptor (PR). MPA likely

^aThese values are from all 14 published studies describing C_{max} for DMPA IM and span ~40 years.[29, 34–46] Given that the study methods differ considerably, including times of measurement post injection, volume of injection, formulation, number and characteristics of participants, number of injections, and techniques used to measure MPA, all published studies have been included and contribute to this range in values. Reported C_{max} values likely reflect the heterogeneity of the studies and there is no apparent trend in C_{max} value that correlates with age of studies.

exerts contraceptive efficacy through high-affinity binding to and activation of the PR. However, MPA may act quite differently from other contraceptive progestins since MPA also exhibits significant binding to the GR [52–54]. The GR is ubiquitously expressed, regulates multiple biological processes, and is a well-established modulator of soluble mediators and innate and adaptive immune responses. Like all steroid receptors, the GR alters transcriptional activity in the cell and drives changes in expression levels of target genes once activated by steroid. Since steroid hormones regulate hundreds of genes and control multiple physiological functions, it is plausible that MPA may affect multiple biological processes, including those that are related to HIV acquisition.

Currently, limited and inconsistent data are available about how biological responses change with exposure to MPA in clinical studies, and no clinical data relate biological change to varying doses of MPA. DMPA-IM has been shown in some clinical studies to increase surface levels of CCR5 on peripheral and female genital tract (FGT) target T cells [55, 56], increase the frequency of CCR5⁺ T cells in the FGT mucosa [56], decrease the production of several immune modulators by immune cells [57, 58], increase FGT mucosal permeability and expression of barrier function proteins [59] and alter cervicovaginal levels of select secreted immunomodulators [57, 60–66]. Several of these studies are consistent with results from animal studies where MPA serum concentrations are similar to those of human DMPA-IM users [59, 67–71]. For example, in mice MPA at 4–7 nM decreases genital tract barrier function with an increased susceptibility to HSV-2 viral infection [59]. *Ex vivo* data are broadly consistent with results from animal studies; MPA appears to increase HIV-1 proliferation in human immune cells at about 0.1 nM [72], dampen the function of immune cells at 0.3 nM [73], increase transcytosis of HIV-1 across the FGT epithelial cells at 1 nM [74], and decrease expression of select immunomodulators by FGT epithelial cells at 1–20 nM [74, 75]. The relative roles of the GR and PR in these mechanisms is not established, although MPA has been shown *in vitro* to regulate expression of immunomodulators and the function of immune cells via the GR [54, 75–79].

A key pertinent question is: would a 31–85% reduction in the systemic concentration of MPA significantly affect biological processes critical for HIV susceptibility? As background, the dose-dependency for steroid responses varies depending on the specific response and cell-type, and cannot necessarily be predicted from the steroid affinity for a particular receptor. Further complicating this question is the presence of endogenous steroid hormones (progesterone and estradiol) in women using contraceptive progestins and their contributions to competitive target receptor binding and downstream impacts of receptor-mediated gene regulation. Many of these factors are also influenced by metabolic state, immune environment, and other physiological conditions. Thus, biological responses may be differentially affected by varying the progestin dose.

Plotting biological response (% response) versus steroid concentration (log₁₀) typically results in a sigmoidal curve as hypothetically illustrated in Figure 1 [52, 54, 76, 78, 80–84]. The 50% effective concentration (EC₅₀), or potency, is defined as the steroid concentration that imparts a response halfway between no response and the maximum possible response (Figure 1). The slope of the curve is steepest around the EC₅₀; this is where a change of concentration causes the largest change in biological response. Consistent with published *in*

vitro dose-response data for many steroid receptors [54, 76, 84, 85], lowering the systemic concentration of MPA by X% at concentrations around the EC50 would result in a <X% decrease in biological response (Figure 1). Dose-response curves reflecting *in vivo* data may differ in shape and/or slope and the actual impact on biological outcomes may be greater or less than those predicted here. Further studies are needed to examine both the true serum concentration differences between DMPA-IM and DMPA-SC and subsequent effects on individual biological responses.

CONCLUSIONS

Based on the available (notably, non-parallel) data, we hypothesize that DMPA-IM and DMPA-SC will not substantially differ in their effects on biological responses 30–90 days following injection since serum concentrations during this time are reportedly similar. Whether C_{max} values actually differ remains to be determined and C_{max} values in the first 30 days following DMPA administration may be substantially different and may exert differences on some biological responses. Clinically, the two regimens show therapeutic equivalence and similar effects on weight gain, bone mineral density, bleeding patterns, and frequency of serious adverse effects, which suggests limited differences, if any, in biological responses, despite the 31% dose difference [9]. Furthermore, both DMPA-IM and DMPA-SC result in similar degrees of hypoestrogenism, characterized by systemic estrogen concentrations of 10–100 pg/mL [31, 32, 56]. It is possible that within the initial 30 days following administration of DMPA-IM versus DMPA-SC, with notably different resulting serum concentrations of MPA, some biological responses critical to HIV susceptibility may be differentially impacted. This may occur despite no apparent effect on other side-effects, if these biological responses are more sensitive to changing serum concentrations of MPA (different EC50 values). Importantly, possible reduction of MPA C_{max} concentrations for DMPA-SC versus DMPA-IM is not likely to ameliorate the impact of MPA on biological responses with EC50 values below 1 nM [66–68].

Given growing concerns about HIV acquisition risk with DMPA-IM use, and given the broad introduction of DMPA-SC in sub-Saharan Africa, direct parallel comparisons of DMPA-IM and DMPA-SC are critical, particularly since such comparisons will not be evaluated in the currently ongoing trial assessing HIV acquisition risk in women randomized to DMPA-IM, copper IUD, and levonorgestrel sub-dermal implants. Similarly, comparative data for injectable progestin contraceptives, including DMPA-IM and DMPA-SC, on putative biological markers of HIV acquisition are needed urgently to evaluate whether these methods are likely to have a differential impact on HIV acquisition risk. In order to effectively evaluate biomarker data, researchers will need to identify appropriate biomarkers that correlate with HIV acquisition risk, and align sampling schedules and analytical methods in order to yield meaningful and comparable results. Currently all injectable progestin-only contraceptives are categorized together in the Medical Eligibility Criteria for Contraceptive Use and there is concern for this entire class of highly effective and widely available injectable contraceptives if no progress is made differentiating these methods.

As indicated by World Health Organization guidance, women should be informed and counseled about the risks and benefits of their contraceptive options, including the potential

effect of progestin-only injectables on HIV risk [5]. Furthermore, women and couples at high risk of HIV acquisition considering using progestin-only injectables should be informed about how to minimize their risk of HIV acquisition. Importantly, continued expansion of the hormonal and non-hormonal contraceptive method mix should remain a priority. Specific characteristics of injectable contraceptives, including the ability to use them discretely, make them popular and widely used in many populations. Development of new contraceptive injectable options with formulations that exhibit low immunosuppressive activity, potentially including alternative progestins to MPA, should also be considered. An understanding of whether such progestins could be delivered subcutaneously would be important, and could potentially benefit from the service delivery advantages provided by the Uniject system. Finally, DMPA-IM and DMPA-SC remain important options for many women, including women living with and at risk of HIV. Many women may benefit from access to a contraceptive with the potential for self-administration like Sayana® Press, particularly if it does not increase HIV acquisition risk.

Acknowledgments

FUNDING

Support for drafting this manuscript was provided by the Guttmacher Institute (C.B.P.), and National Institutes of Health (NIH) under award number R01 HD083026 (J.P.H., Z.H.) and R01 AI102835 (S.L.A.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Guttmacher Institute or the NIH.

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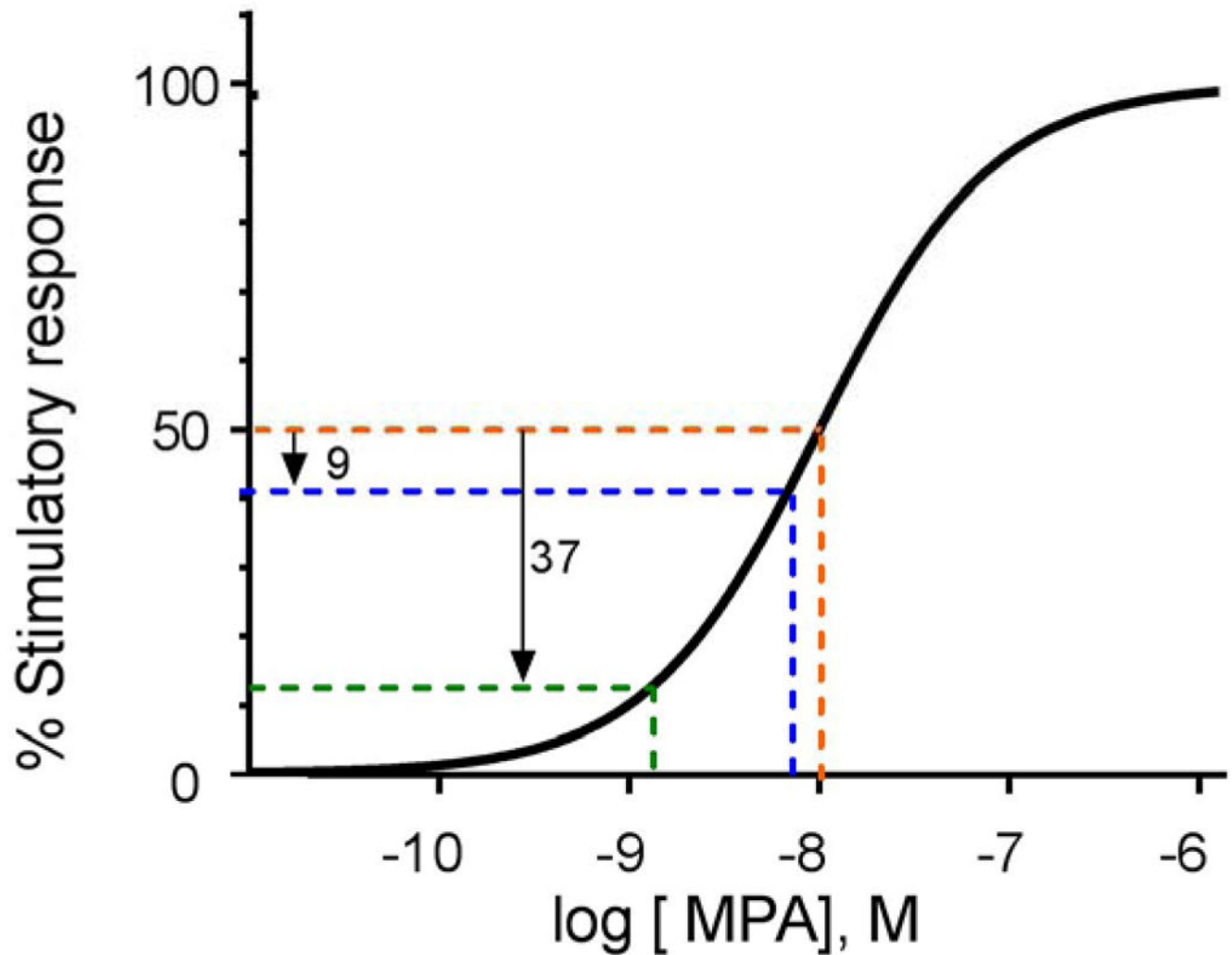


Figure 1. Relationship between dose response and concentration of MPA

The orange line depicts a 50% increase in a given stimulatory response for a woman using DMPA-IM (versus a woman using no hormonal contraception), assuming that the EC₅₀ value (potency) for that particular biological response occurs at 10 nM MPA (3.8 ng/mL; -8 on the log scale). If we assume that DMPA-SC reduces MPA intracellular concentrations by 31% (from 10 nM assumed with DMPA-IM to 6.9 nM assumed with DMPA-SC), that particular stimulatory response would theoretically be predicted to drop by 9 percentage points, to 41% (blue line) instead of 50% (orange line). If we assume that DMPA-SC reduces intracellular concentrations by 85% (from 10 nM assumed with DMPA-IM to 1.5 nM assumed with DMPA-SC), that particular stimulatory response would be theoretically predicted to drop by 37 percentage points, to 13% (green line) instead of 50% (orange line). Note that the actual EC₅₀ for specific biological responses varies depending on the cell type and target gene, and cannot be predicted. The sigmoidal shaped curve with a Hill slope of one is based on theoretical predictions,[86] and supported by *ex vivo* data, as discussed in the text.