Risk of HIV Infection in Depot-Medroxyprogesterone Acetate (DMPA) Users: A Systematic Review and Meta-analysis

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ABSTRACT:

Objective: As the HIV/AIDS epidemic continues to spread in Africa and Asia, use of the injectable contraceptive steroid DMPA is widespread and has been increasing. Since studies dating back to 1992 have suggested that DMPA may increase the transmission of HIV to women, we endeavored to determine if the extant epidemiological and biological evidence is sufficient to conclude that DMPA use constitutes a definite hazard to women's health.

Methods: We searched Medline using the search terms: contraceptives or contraception AND HIV and searched bibliographies of articles thus identified. We included in the meta-analysis all studies examining the association between use of DMPA (or injectable contraceptives comprising mostly DMPA) and the presence (cross-sectional studies, n = 8) or acquisition (longitudinal studies, n = 16) of HIV+ status in women, using a random effects

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models to estimate odds ratios (ORs; cross-sectional studies) and hazard ratios (HRs; longitudinal studies). Studies were excluded if the comparison group included women using any form of steroidal contraception.

***Results*: Statistically significant positive associations between DMPA use and HIV positivity were observed both in cross-sectional (OR = 1.41, 95% CI 1.15 - 1.73) and longitudinal studies (HR = 1.49, 95% CI 1.28 - 1.73). The biological plausibility of increased vulnerability to HIV infection due to progestational action (via thinning of the vaginal epithelial barrier and immunosuppression) as well as glucocorticoid agonistic immunosuppression, are discussed.**

***Conclusion*: The epidemiological and biological evidence now make a compelling case that DMPA adds significantly to the risk of male-to-female HIV transmission.**

Introduction

The HIV-AIDS epidemic continues to spread in the developing world, particularly in sub-Saharan Africa. While advocacy of condom use has been persistent and pervasive, family planning advocates have also pursued advocacy of steroidal contraceptives, even though these provide no protection against HIV transmission. In fact, evidence has accrued that links the use of steroidal contraception (SC, often referred to as "hormonal" contraception. We prefer the term "steroidal," since the compounds in question are, strictly speaking, steroid drugs and not actual hormones.) to increased risk of HIV transmission. In a 1999 meta-analysis,[1] Wang et al. observed a modest but significant association between HIV-1 seroconversion and oral contraceptive (OC) use. Since that time, injectable contraceptives (ICs)—especially DMPA—have been increasing in use compared to OCs. A number of studies have examined HIV-1 seroconversion as a function of IC use, and have found DMPA to facilitate HIV-transmission to an even greater extent than OCs. However, even though such evidence first appeared in the peer-reviewed literature over 20 years ago[2] and though this association has been examined in nearly two dozen studies since, no consensus has yet emerged as to the potential danger of HIV acquisition to women using DMPA. Even the authors of a systematic review as recent as 2013[3] declined to perform a meta-analysis of extant data, because the literature consisted of studies with "heterogeneous methods and mixed results." Most recently, two meta-analyses have appeared.[4,5] Importantly, these two reviews incorporated different criteria for inclusion and therefore summarized largely overlapping but somewhat different bodies of research, yet they reported almost identical, significant increased risks of HIV acquisition with DMPA use.

In the present article, we set out to assemble the literature pertaining to IC (particularly DMPA) and HIV acquisition and to quantify the overall findings of the worldwide literature. Considering the wide variation in population and primary study

methodology, we have endeavored to be as inclusive as possible in the meta-analysis, specifically aiming to avoid the imposition our own biases regarding quality criteria. Consequently, the present work contrasts sharply with both of the recently published meta-analyses by including many earlier studies, including many that had incorporated a less definitive, cross-sectional methodology.

We believe that the present work therefore provides a larger perspective on the role of contraceptive interventions in the unfolding of the global HIV-AIDS epidemic. Thus it may serve not only as potential confirmation of the work of others, but also as evidence of ways by which potential dangers that may be posed by the use of new interventions may be brought to light sooner. Such earlier warnings can impart life-saving information to both family planning practitioners and the women whose right it is make their own informed reproductive choices.

Methods

Eligibility Criteria and Study Selection

We searched the Medline data base using the terms "contraceptive" or "contraception" and HIV, to identify studies that examined HIV status or acquisition as a function of IC or DMPA use. We also searched bibliographies of studies so identified. All studies that reported risk estimates or crude data that could be converted into risk estimates were included, unless the comparison group also included women who were using some other form of steroidal contraception (e.g., a comparison between IC users and OC users). In our search, we did not impose any starting date criteria, so that the earliest relevant studies could be identified.

Since the overwhelming majority of women using IC use DMPA, we have endeavored, as much as possible, to focus on DMPA, especially in light of differences in affinity among synthetic progestins for progesterone and other steroid hormone receptors. Therefore, we have included all data specifically related to DMPA use, as well as data for which the progesterone agonist is not specified (as these refer mostly to DMPA), but have excluded data specifically pertaining to any other forms of IC (generally norethisterone) as well as data pertaining mostly or entirely to OCs.

A total of 34 studies were initially identified which contained data on the association of IC with HIV-1 seroconversion. Six studies[6-11] were excluded from the meta-analysis because the comparison group included women using other forms of SC, generally combined OCs. One study[12] was excluded because users of DMPA were lumped together with all "other" forms of contraception, and not separately analyzed. Of the remaining 25 reports, 4 were excluded[13-16] because their results were reported in subsequent papers as further follow-up on the same subjects. The meta-analysis therefore includes data from 24 studies reported in 23 papers[2, 17-38] (Ungchusak 1996[18] included both a cross-sectional and a longitudinal study). The eight cross-sectional and 16 longitudinal studies were analyzed separately.

Data Extraction and Analysis

All studies were reviewed to determine if they could provide OR (cross-sectional) or HR (longitudinal) effect size data. For studies which did not report ORs or HRs (e.g., those which reported ORs based on inappropriate comparisons[20] or those which reported incidence rate ratios or IRRs[18, 24, 26, 27]), we reconstructed, where possible, the raw data from which ORs or HRs could be calculated.

Some included studies used "crude" (unadjusted) data, whereas others reported data adjusted for a number of variables such as age, occupation, or marital status. We used multivariate-adjusted outcome statistics, where reported. Otherwise, we used either the reported unadjusted outcome statistics, or the basic 2x2 cell-type raw data.

Subjects of included studies differed substantially from study to study, e.g., in location (Asia versus Africa), employment (sex worker or not), age, condom use, etc. We therefore used the random effects model, which assumes that the various studies which are meta-analyzed represent a random sample of studies which represent the true effect.[39,40] We employed the statistical package "Comprehensive Meta-Analysis" (Version 2) by Biostat (Englewood Cliffs, NJ, USA).

Table I. Population Characteristics of Included Cross-sectional Studies.

Authors	Year of publication	Year(s) of study	Population size	Nation and locale	Subject source	Type of data presented
Siraprapasiri et al.[17]	1991	1989	238	Changmai, Thailand	CSW*	Crude OR
Rehle et al.[2]	1992	1990	356	Khon Kaen, Thailand	CSW	MLR**
Plourde et al.[20]	1992	1988-89	600	Nairobi, Kenya	STD clinic	Raw data
Kapiga et al.[21]	1994	1991-92	2,285	Dar-es-Salaam, Tanzania	family planning clinics	MLR
Ungchusak et al. [18]	1996	1990	271	Khon Kaen, Thailand	CSW	MLR
Taneepanichskul et al.[19]	1997	1993-94	376	northern Thailand	CSW	Crude OR
Kumwenda et al.[29]	2008	2003-05	1,686	Blantyre, Malawi	reproductive health clinics	CLR***
Leclerc et al.[30]	2008	2003-2006	4,549	Kenya, Lesotho, Malawi, Zimbabwe	General population	MLR

* Commercial sex workers, i.e. prostitutes

**Multiple Logistic Regression

***Conditional Logistic Regression

Table II. Population Characteristics of Included Longitudinal Studies

Authors	Yr of publication	Yr(s) of study	Pop. size	Nation and locale	Subject source	Months of follow-up	Follow up interval (months)	Type of data presented
Bulterys et al. [22]*	1994	1991-93	5,690	Butare, Rwanda	Prenatal clinics	24	24	Cum IR, MLR
Ungchusak et al.[18]	1996	1990-91	240	Khon Kaen, Thailand	CSW	3-12	3	IRR, MLR
Kiddugavu et al.[24]	2003	1994-99	5,117	Rakai, Uganda	General population	31	10	IRR, MLR
Baeten et al.[13, 14, 23]	2007	1993-97	779	Mombasa, Kenya	CSW	120	1	MV HR
Kleinschmidt et al.[26]	2007	1999-2001	551	Orange Farm, So. Africa	Family planning clinic	12	3	MV HR
Myer et al.[27]	2007	2000-04	4,073	Cape Town, So. Africa	General population	24	6,6, and 12	MV IRR
Kumwenda et al.[28]	2008	2003-05	787	Blantyre, Malawi	Reproductive health clinics	12	3	MV HR
Watson-Jones et al.[31]**	2009	2003-08	659	Tanzania	HSV2+ hotel/bar workers	30	3	Age-adj. HR
Reid et al.[32]	2010	2003-07	1,358	So. Africa, Zambia, Zimbabwe	HSV2+ from gen pop	18	3	MV HR
Feldblum et al.[33]	2010	2004-07	7,364	Africa & India	Microbicide trial "higher risk"	12	1	MV HR
Morrison et al. [15, 16, 25]	2010	1999-2004	6,109	Uganda, Zimbabwe, Thailand	family plan clinics	21.5	3	MSM HR
Heffron et al.[34]	2012	2004-10	3,790	7 African nations	sero-discordant. couples	12-24	3	MSM HR
Wand H, Ramjee G[35]	2012	Not reported	2,236	Durban, S. Africa	>90% from microbicide trial	Not reported	3	MV HR
Morrison et al.[36]	2012	2004-2007	5,567	South Africa	General population	9-24	3	MSM HR
McCoy [37]	2013	2003-2007	4,913	South Africa, Zimbabwe	Diaphragm/gel HIV prev. trial	24	3	MV HR
Crook et al. [38]	2014	2005-2009	8,663	S Africa, Uganda, Tanzania, Zambia	Microbicide trial sero-disc. couples	12	1	Inv. Prob. W'ted HR

*74% DMPA users; 26% used other forms of SC.
**67% DMPA users; 33% COC users.

Results

Data are presented as composites of tabular data and semi-logarithmic Forest plots for cross-sectional (Fig. 1) and longitudinal studies (Fig. 2). The combining of data from individual studies of both types, using a random effects model, produced a significantly positive cumulative point estimate of OR and HR, respectively, the latter showing a slightly stronger association (HR = 1.49; 95% CI: 1.28 – 1.73 v. OR = 1.41; 95% CI:

1.15 – 1.73). The consistency of the association between IC use and HIV acquisition is noteworthy in that out of the eight cross-sectional studies and 16 longitudinal studies, there are no outliers, i.e., the 95% CI of each study includes the pooled OR. Consistency across primary studies is also reflected by the fact that the overwhelming majority of both cross-sectional (88%) and longitudinal (75%) studies favor a positive association.

Figure 1

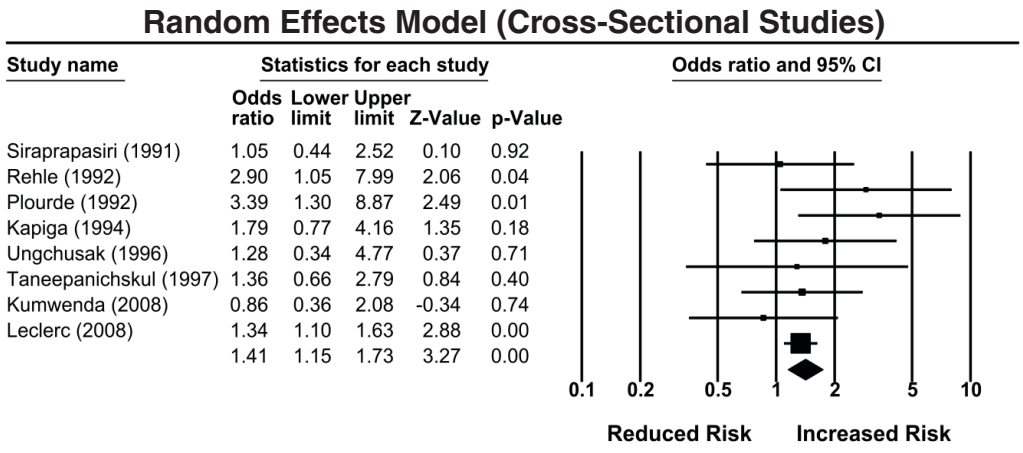
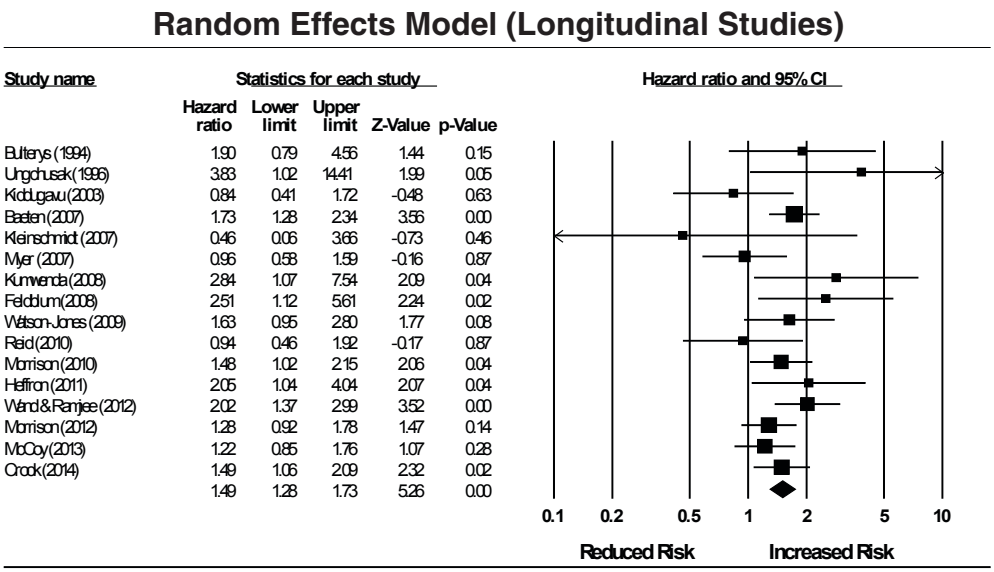


Figure 2



Discussion

Cumulatively, both cross-sectional and longitudinal studies show a significant positive association between HIV-1 positivity and IC use. However, the cross-sectional studies are considerably weaker than the longitudinal studies owing to their reporting only prevalence ORs, since the actual exposure to HIV among study participants was largely unknown. Hence, the cross-sectional studies comprise an early hint as to the potential of IC to increase HIV seroconversion rates, whereas the longitudinal studies provide a much clearer picture of the role of IC.

Importantly, the present review differs substantially from the other two meta-analyses[4,5]—both published in 2015—that examine the association between DMPA use and HIV acquisition. Morrison et al.[4] acquired and pooled individual participant data, thus including much reviously unpublished data. They also excluded several published studies whose authors did not participate in the meta-analysis or which otherwise did not meet rigorous inclusion criteria, such as having follow-up visits more than 6 months apart. Ralph et al.[5] restricted their analysis to published studies (as did we), but also used rigorous exclusion criteria such as not controlling for condom use and suffering a less than 30% loss-to follow-up. Both meta-analyses restricted inclusion to prospective studies and to subjects from sub-Saharan Africa. Hence, no data published prior to 2003 were included.

In contrast, we have made the present meta-analysis as inclusive as possible, including cross-sectional studies as well as longitudinal. Hence, we included the very earliest studies, going back to 1991.[17] Despite these substantial differences in the designs and data included in these meta-analyses, it is striking how all have come up with almost identical results.

Potential Biological Mechanisms

One of the classical effects of progesterone is immunosuppression, in terms of enabling tolerance of the presence of the fetus by the maternal immune system. Another classical effect is the luteal phase thinning of the vaginal epithelium. Evidence for both mechanisms playing a role in the consequent facilitation of disease transmission was reviewed by Wang, et al.[42] Marx et al.[43] experimentally demonstrated dramatically increased susceptibility of retroviral transmission of simian immunodeficiency virus (SIV) in Rhesus macaques (78% infection rate in progesterone-treated animals v. 10% in controls). Hence, the chronically high progestin levels that accompany use of any steroidal contraceptive, particularly injectable or implantable progestins, suggests the possibility of increasing susceptibility to HIV transmission, as Marx et al. observed in their 1999 meta-analysis of OC and HIV infection.

More recent data presented by Hujibrechts et al.,[44] however, suggest that DMPA, in addition to its progesterone agonist action, confers an additional measure of immunosuppression via agonistic interaction with the glucocorticoid receptor (GR), an effect not shared by norethisterone (whether used as the acetate—NET-A—or enanthate ester—NET-EN), for example. Thus, Hujibrechts et al. demonstrated the *in vitro* inhibition of

immune cytokine production and T-cell proliferation in the presence of MPA, as well as higher levels of surface HIV-1 coreceptors in MPA-treated T-cells, both effects occurring via GR activation. Tomasicchio et al.[45] recently demonstrated the *in vitro* facilitation of T-cell apoptosis via GR activation in the presence of contraceptive dose levels of MPA but not Net-A or physiological levels of progesterone, hence also suggesting that DMPA may facilitate the progression as well as transmission of HIV infection. Direct evidence of increased tranmission of HIV has recently been provided by Heffron et al.,[42] who demonstrated elevated HIV-1 RNA concentrations in endocervical secretions of HIV+ women using IC (mostly DMPA) v. women using OC.

Most recently, the meta-analyses of Morrison et al.[4] and Ralph[5] report similar, significant risk elevations with DMPA use (pooled HR: 1.50; 95% CI 1.24 – 1.83 and pooled HR: 1.40; 95% CI 1.16 – 1.69, respectively), but small, non-significant risk elevations for injectable NET-EN (pooled HR: 1.24; 95% CI 0.84 – 1.82 and pooled HR: 1.10; 95% CI 0.88 – 1.37, respectively) and null associations with COC use. While NET-EN data are scant, these data suggest the possibility that both NET-EN and DMPA contribute to risk by maintaining a high and constant progestin concentration, but DMPA provides its major risk increasing effect as a glucocorticoid agonist.

Potential Impact and Ethical Considerations

A remarkable finding of the present meta-analysis is the consistency of the positive association observed between DMPA use and the HIV transmission (Table 1) across many different populations in Africa and Asia, with large differences in lifestyle and sexual practices, the prevalence of other STIs such as HSV-2, and with many differences in study design, such as focusing on other outcome variables. While it must be acknowledged that the earlier studies are generally much weaker in design—especially due their cross-sectional nature—we believe that their inclusion gives a more accurate picture of the time frame during which useful information became available about the role of an elective intervention on the risk of acquiring a life-threatening infection.

We find it particularly noteworthy that the earlier, less rigorous cross-sectional studies, ignored in the other recent meta-analyses, provide almost identical findings to those of the more recent, rigorous, longitudinal studies. Indeed, it is troubling that, despite the often lethal effects of HIV infection and the even stronger association than has generally been observed with combined OC,[42] as well as the documentation of plausible mechanisms by which DMPA in particular can increase susceptibility, there has been a reluctance on the part of researchers to conclude that DMPA presents a significant hazard to women. Even as recently as 2013, Polis and Curtis tepidly concluded: "More definitive evidence for the existence and size of any potential effect could inform appropriate counseling and policy responses…."[47] Yet even greater emphasis on protecting "highly efficacious" contraception, at the expense of protecting the lives and health of the women concerned, can be found in the literature. Thus, Stephenson[48] opined that even if research "were to present a more compelling case to indicate that hormonal contraception increases the risk of HIV transmission, women could be advised that

such contraceptives do not protect against HIV and might increase susceptibility. But such advice would need to be weighed against the risks of rejecting safe and reliable contraception." Indeed, it is difficult to reconcile such a policy consideration to withhold the disclosure of the documented dangers of any elective medication for any reason, as such policy would clearly violate any reasonable standard of medical ethics and the need to obtain informed consent.

Conclusions

We conclude that the extant epidemiological literature, coupled with the documentation of plausible biological mechanisms by which DMPA has been shown to weaken both the epithelial and immunological barriers to HIV transmission, makes a compelling case that DMPA presents a substantial hazard to women of increased risk of HIV transmission from infected men to women, independent of the presence of other STIs. This result essentially confirms the findings of the two other meta-analyses examining this question. Yet it is troubling that there still seems to be a lack of urgency in providing this important knowledge to those women most exposed, DMPA being presently the most widely used form of steroidal contraception in sub-Saharan Africa.[4] Thus, Morrison et al.[4] merely "highlight the need to initiate randomized controlled trials to provide more definitive evidence of the effects of hormonal contraception, particularly DMPA, on HIV risk." Ralph et al.[5] also look forward to furthering research with a randomized trial. However, at least they acknowledge that such a trial, in light of the now documented danger of DMPA in increasing HIV acquisition risk "might violate the principle of equipoise required for a trial."[5] It seems to us that the ongoing widespread use of DMPA, without including substantial warnings to women using it about the increased HIV risk, may essentially constitute a very large scale trial that is already violative of patients' rights to give informed consent. Policymakers and practitioners should incorporate this knowledge accordingly, to ensure that a woman's right to make informed choices about her reproductive and general health is protected, and not subordinated to public policy concerns about population control.

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