HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2017 November 13.

Published in final edited form as:

AIDS. 2016 November 13; 30(17): 2571–2576. doi:10.1097/QAD.0000000000001229.

Levonorgestrel in contraceptives and multipurpose prevention technologies: does this progestin increase HIV risk or interact with antiretrovirals?

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Keywords

hormonal contraception; HIV; progestins; levonorgestrel; multipurpose prevention technologies; antiretrovirals

Introduction

Mounting observational evidence suggests that use of certain types of hormonal contraception, specifically the progestin-only injectable depot medroxyprogesterone acetate (DMPA), may be associated with an increased risk of HIV acquisition in women.[1] This relationship has been examined in several observational studies and is currently being assessed in a randomized trial, the ECHO study (NCT02550067). As evidence continues to evolve, it is also necessary to critically examine knowledge gaps for other contraceptive progestins. Levonorgestrel is used in many existing contraceptives and is being evaluated for use in multipurpose prevention technologies (MPTs). MPTs are designed to simultaneously prevent two or more of the following: unintended pregnancy, HIV, and other sexually transmitted infections (STIs). Potential drug-drug interactions and side effect profiles must also be considered in developing products, including some MPTs, which would contain levonorgestrel and antiretrovirals (ARVs). Vaginal rings containing dapivirine or tenofovir (NCT02235662) for HIV prevention combined with levonorgestrel as a contraceptive are in development as MPTs.

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SLH conceived of the topic; CBP drafted the outline and managed the overall writing process; all authors contributed components to the writing and endorsed the final version.

How does levonorgestrel compare to other progestins?

Although all progestogens are steroid hormones that bind and activate progesterone receptors, synthetic progestins and naturally occurring progesterone differ in chemical structure and steroid receptor binding profiles that may mediate important non-contraceptive physiologic effects and may impact HIV acquisition risk. A variety of progestins are used in hormonal contraceptives, and belong to three main chemical families: progesterone derivatives (pregnanes), testosterone derivatives (estranes and gonanes), and spironolactone derivatives. Most contraceptive progestins (including levonorgestrel) are testosterone derivatives, with some notable exceptions: DMPA is a pregnane, and drospirenone is derived from spironolactone. Levonorgestrel and norethindrone enanthate (NET-EN; a two-monthly injectable contraceptive used primarily in South Africa) are both testosterone-derivatives, and as such, are more similar to each other than to DMPA. Despite their biochemical differences, DMPA and NET-EN have frequently been grouped together by researchers when assessing HIV acquisition risk since both are injectables used in high HIV prevalence populations.

Progestins differ significantly in binding affinities for all steroid receptors, including progesterone, androgen, mineralocorticoid, and glucocorticoid receptors.[2] Stimulation of glucocorticoid receptors with cortisol (natural ligand) influences inflammation and immune system signaling. Progestins have different binding affinities for glucocorticoid receptors: DMPA binds at 29-59% of total specific binding relative to cortisol whereas levonorgestrel binds at 1-8% and NET-EN binds at 0-2%.[3]

Which current and future products contain levonorgestrel?

Levonorgestrel is currently formulated in many existing contraceptives, and is being studied in several products in development (Table 1), in the form of oral contraceptive pills (OCPs) and emergency contraception pills, transdermal patches, vaginal rings, injectables, intrauterine devices (IUDs) and subdermal implants. Levonorgestrel is the first progestin incorporated into MPTs. Several MPT intravaginal rings containing a progestin plus an ARV for HIV prevention (such as tenofovir or dapivirine) or a combination of active ingredients (such as zinc acetate, carrageenan, and an ARV for simultaneous prevention of HIV, herpes simplex virus-2, and human papillomavirus) are in development.[4]

What biological and immunological evidence is available for levonorgestrel and risk of HIV acquisition?

Multiple biological and immunological mechanisms exist by which progestins could theoretically impact HIV acquisition risk.[5] At a cellular level, progestins and other sex steroid hormones act via interactions with steroid receptors that result in alterations in gene transcription and cellular functions.[6] Glucocorticoid receptors have an important role in immune regulation and exert complex actions on the primary immune cell targets for HIV infection; representing a potential mechanism by which progestin exposure could alter HIV acquisition risk. Currently, limited data support or refute hypothetical mechanisms of progestin impact on HIV acquisition risk. Adding further complexity, many researchers have

grouped hormonal contraceptives groups by type (e.g. OCPs or injectables) rather than by specific progestin, limiting levonorgestrel-specific data. Progress has been slow, in part given the lack of a biomarker for HIV acquisition risk. Researchers have therefore studied a range of immune and tissue responses to steroid hormones.

Interpretation of hormonally-driven immunomodulatory changes in women is also challenging due to potentially important environmental differences between individuals and populations that may influence secretion of immunomodulatory molecules. However, some researchers have evaluated levonorgestrel using *ex vivo* and human studies. One recent study evaluated specific progestogens by testing their impact on peripheral blood mononuclear cells collected from healthy premenopausal women at mid-cycle. Investigators found that DMPA, but not progesterone or levonorgestrel, inhibited cytokine production.[7] In a cohort of Sub-Saharan African women, samples collected prior to HIV seroconversion compared to samples from non-seroconverting women were analyzed by contraceptive and genital tract infection status. Most biomarker changes associated with DMPA were different than changes associated with levonorgestrel, and for many biomarkers, presence of genital infection amplified changes, suggesting that both specific progestin and genital tract environment (including infections) are important determinants of HIV acquisition risk.[8]

Lectins are carbohydrate-binding proteins that may interfere with HIV-specific binding necessary for viral transmission. In a cross sectional study using a lectin microarray to evaluate the glycome in the vaginal fluid of women using contraception, DMPA users had differences in carbohydrate binding patterns as compared to women using OCPs, levonorgestrel IUDs, or no hormonal contraception [9]. These data suggest that changes in some of carbohydrate epitopes associated with immune function in the reproductive tract differ for women using DMPA compared to women using levonorgestrel-based methods or no contraceptives. Finally, HIV target cells in the genital tract (CCR5+ T-cells) decreased after initiation of levonorgestrel IUD compared to baseline.[10] Though few, these studies suggest that levonorgestrel is unlikely to increase risk for HIV acquisition.

What epidemiological evidence is available on levonorgestrel and risk of HIV acquisition?

A recent systematic review summarized epidemiological data published through January 15, 2016 on various hormonal contraceptive methods and risk of HIV acquisition in women.[1] Authors used a quality assessment framework to determine which studies were considered to be higher quality, although all currently available analyses are based on observational data, and therefore vulnerable to residual or uncontrolled confounding. Below, we describe results from higher-quality studies, with specific focus on levonorgestrel-containing contraceptives.

Oral contraceptive pills

Most data do not suggest that OCPs increase a woman's risk of HIV acquisition. Among eleven currently available higher-quality studies assessing OCPs and risk of HIV acquisition, [11-23] one reported a marginally significant increase in risk (adjHR 1.50, p=0.05), while ten reported non-significant estimates (ranging from adjIRR 0.66 to adjHR 1.80).[1] Studies

did not specify if the OCPs contained levonorgestrel, although it is a common progestin in OCPs used in sub-Saharan Africa. Furthermore, most estimates pertained to combined oral contraceptive pills (COCs), which contain both progestin and estrogen. Only one study separately assessed COCs and progestin-only pills, and reported similar point estimates (adjHR 0.86 (95% CI: 0.58-1.28) and adjHR: 0.98 (95% CI: 0.56-1.73), respectively).[18] In COCs, the relative contribution of the progestin component (versus the estrogen component) to HIV risk is unknown and may be important; some researchers hypothesize that estrogen may protect against HIV acquisition.[24] Thus, while existing data on OCPs and risk of HIV acquisition are generally reassuring, our ability to draw conclusions specific to levonorgestrel based on currently available OCP data is limited.

Implants

The daily systemic dose of levonorgestrel for implants is lower than for OCPs, and similar to or lower than what might be expected for intravaginal rings. Only two higher-quality studies assessed levonorgestrel-containing contraceptive implants: adjHR for Norplant® [12, 25]: 1.6 (95% CI: 0.5-5.7) and adjHR for either Norplant® or Jadelle® [13]: 0.96 (95% CI: 0.29-1.34). Thus, while data are sparse and 95% CIs are wide, neither study suggested a statistically significant increased risk of HIV acquisition in women using levonorgestrel-containing implants.

Will drug interactions occur if levonorgestrel is used in products containing ARVs?

Simultaneous use of ARVs and levonorgestrel-containing contraceptives

Levonorgestrel is metabolized hepatically through the cytochrome P-450 isoenzyme 3A4 (CYP3A4). ARVs that induce CYP3A4, including non-nucleoside reverse transcriptase inhibitors (NNRTIs) (such as efavirenz or nevirapine) and protease inhibitors (such as nelfinavir or ritonavir), could decrease contraceptive efficacy by increasing the metabolism of levonorgestrel, thus lowering bioavailable levels.[26]

Contraceptive failures have been observed among levonorgestrel implant users taking certain ARVs, including specific NNRTIs. While pregnancy among levonorgestrel implant users is rare (0.4 per 100 woman-years) [27], in a study of 570 HIV-positive levonorgestrel implant-using women, 2.8% (n=16) became pregnant, 15 of whom were using efavirenz-based ARV regimens.[28] Another study of levonorgestrel implant users found a pregnancy incidence of 4.2 per 100 person-years among users of efavirenz-based ARV and 1.0 per 100 person-years among users of nevirapine-based ARV.[29] In a pharmacokinetic study of HIV-positive implant users, levonorgestrel serum concentrations decreased 47% by 24 weeks among women using efavirenz-based ARV, and 15% of these women became unintentionally pregnant within one year, compared to women either using nevirapine-based ARV or no ARV, who had no pregnancies and no change in serum levonorgestrel levels.[30]

Certain ARVs may lower levonorgestrel levels in users of levonorgestrel emergency contraceptive pills. In healthy HIV-negative subjects who took two 0.75 mg doses of levonorgestrel 12 hours apart, the area under the curve at 12 hours was reduced by 56%, and

maximum levonorgestrel serum concentration was reduced 41% after 14 days of efavirenz.[31] However, in a small study of nine women taking COCs (ethinyl estradiol/norgestrel), levonorgestrel levels were higher both among women taking nevirapine-based ARV and HIV-positive women not on ARVs compared with HIV-negative women.[32]

Potential for drug interactions for ARVs in MPTs in development (tenofovir, dapivirine)

Tenofovir is a nucleoside reverse transcriptase inhibitor not metabolized by the CYP450 system,[26] so may not be subject to interactions with levonorgestrel. In a pharmacokinetic study, women using levonorgestrel implants who were using either tenofovir-based pre-exposure prophylaxis or placebo had similar levonorgestrel levels, and no pregnancies were reported.[33]

Dapivirine is an NNRTI that has been used vaginally in ring and gel formulations and has a very low systemic concentration, [34] which is unlikely to alter hepatic CYP450 metabolism of co-administered drugs. However, it remains unclear whether higher dapivirine concentrations in the vagina could impact local metabolism by CYP450 enzymes expressed in vaginal tissue; additional studies are needed.[35]

Implications

With respect to HIV acquisition risk, levonorgestrel-specific data, either from biological or immunological studies, or from epidemiological studies, are sparse. However, existing data generally do not indicate an association between levonorgestrel and increased risk of HIV acquisition in women. Most published biological studies comparing levonorgestrel to DMPA show different impacts on immunomodulatory molecules, suggesting that levonorgestrel is unlikely to impart similar biological and immunological changes to those seen with DMPA which may be associated with increased HIV risk. Epidemiological data on OCPs and HIV acquisition is of limited value to understand the relationship between levonorgestrel and HIV risk. Few epidemiological studies on levonorgestrel implants and HIV risk are available; none suggest an increased HIV risk. Epidemiological data on NET-EN (another testosterone derivative progestin) are more reassuring with respect to risk of HIV acquisition than are data on DMPA, a progesterone-derivative progestin. No epidemiological data are currently available on levonorgestrel-containing IUDs and risk of HIV acquisition. Theoretically, drug-drug interactions may be of concern between levonorgestrel and ARVs, although the extent to which this is problematic is uncertain. Studies suggest decreased levonorgestrel levels and contraceptive failures with efavirenz; evidence to date does not suggest such an effect for nevirapine. Little is known about the potential interactions with other ARVs that are candidates for MPTs. Assessing the potential for drug interactions between levonorgestrel and dapivirine prior to clinical studies of dapivirine-containing MPT rings would be useful.

Given the leading role of levonorgestrel in current and future contraceptive and MPT products, it is critical to elucidate the relationship between levonorgestrel and HIV acquisition, and potential levonorgestrel/ARV interactions, particularly with ARVs used in MPTs. The nearly complete CHIC (NCT01873170) and Zim CHIC (NCT02038335) studies are aimed at closing some of these critical research gaps, including controlled and verified

progestin exposure in women with respect to measured changes in immune cells and soluable mediators. The recently completed ASPIRE study [36] and the ongoing ECHO trial (http://echo-consortium.com) are likely to provide additional epidemiological information about levonorgestrel implants and risk of HIV acquisition. Future biological, immunological, and epidemiological analyses should, where possible, provide disaggregated estimates by progestin type, delivery method, and dose (both systemic and local). Drug interaction studies should focus on clinical outcomes, such as ovulation and pregnancy, rather than pharmacokinetic outcomes alone. Such studies would fill a critical research gap in the search for effective MPTs, and the ongoing need to understand the role of progestins in risk of HIV acquisition.

Acknowledgments

Funding: Support for drafting this manuscript was provided by the Guttmacher Institute (Dr. Polis), the Microbicide Trials Network (grant AI 068633, Dr. Hillier), and the US National Institutes of Health/National Institute of Allergy and infectious Diseases (NIH R01-AI102835, Dr. Achilles).

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Table 1

Current and future contraceptives containing levonorgestrel

Contraceptive Formulation	Current products (levonorgestrel dosage)	Products in development (levonorgestrel dosage)
Oral Pills	• Combined oral contraceptives, co-formulated with ethinyl estradiol, multiple formulations (0.05-0.15mg) • Levonorgestrel-only oral contraceptive pill formulations * (0.075-0.1mg) • Emergency contraception (1.5mg)	
Patch		• Levonorgestrel-only patch (6.5mg and 12.5mg doses being studied), Health Decisions • Co-formulated with ethinyl estradiol (2.6mg), Agile Therapeutics
Vaginal Ring		• Levonorgestrel-only ring (170mg), Bayer • Levonorgestrel co-formulated with tenofovir (dosage unknown), CONRAD • Levonorgestrel co-formulated with dapivirine (32mg and 320mg levonorgestrel), IPM • Levonorgestrel (potentially) co-formulated with zinc acetate, carrageenan, and an antiretroviral (dosage unknown), Population Council
Injectable		• Levonorgestrel butanoate injection (20mg), Health Decisions
IUD	• Levonorgestrel IUD (52mg), approved for 5 year use, Mirena® Bayer • Levonorgestrel IUD (52mg), currently approved for 3 year use, Liletta® Odyssea Pharma SPRL • Levonorgestrel IUD (13.5mg), approved for 3 year use, Skyla® Bayer	• Levonorgestrel IUD (52mg), in clinical trials for efficacy up to 7 years, Liletta® Odyssea Pharma SPRL
Implant	• Levonorgestrel implant (2 × 75 mg levonorgestrel rods), approved for 5 year use *, Jadelle® Bayer • Levonorgestrel implant (2 × 75 mg levonorgestrel rods), approved for 4 year use *,	

Contraceptive Formulation	Current products (levonorgestrel dosage)	Products in development (levonorgestrel dosage)
	Sino-implant (II)® Shanghai Dahua Pharmaceutical Co., Ltd	

* not available in the United States