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BRIEF REPORT

Use of Intrauterine Devices and Risk of Human Immunodeficiency Virus Acquisition Among Insured Women in the United States

Julia L. Marcus,[1] Jonathan M. Snowden,[2] Mara E. Murray Horwitz,[1] Sengwee Toh,[1] Casie Horgan,[1] Rong Chen Tilney,[1] Rajani Rajbhandari,[1] Soowoo Back,[1] Daniel J. Westreich[3]

[1]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts; [2]School of Public Health, Oregon Health & Science University—Portland State University; and [3]Department of Epidemiology, University of North Carolina at Chapel Hill

Concerns have been raised about progestin-containing contraceptives and the risk of human immunodeficiency virus (HIV) acquisition. Based on health insurance data from women in the United States with intrauterine device (IUD) insertions during 2011–2018, there was no increased risk of incident HIV diagnosis for levonorgestrel-releasing IUDs versus copper IUDs.

Keywords. human immunodeficiency virus; intrauterine devices; copper intrauterine devices; hormone releasing intrauterine devices; long-acting reversible contraception.

Progestins are commonly used in existing contraceptives, including intrauterine devices (IUDs), and are being evaluated in multipurpose prevention technologies, which are designed to simultaneously prevent 2 or more of unintended pregnancy, human immunodeficiency virus (HIV), and other sexually transmitted infections. However, concerns have been raised about progestins and HIV risk. Some observational studies have suggested an increased risk of HIV acquisition with the use of depot medroxyprogesterone acetate (DMPA) [1, 2]. In contrast, a randomized trial, Evidence for Contraceptive Options and HIV Outcomes (ECHO), recently found no substantial increase in HIV risk in women using DMPA compared with those using levonorgestrel-releasing implants or copper IUDs [3]. Nevertheless, some biological studies have suggested a potentially increased risk of HIV acquisition with levonorgestrel IUD use [4]. Although the use of IUDs is increasing globally, with IUDs now being the dominant contraceptive method in some countries [5], there have been no epidemiologic studies to date on levonorgestrel IUDs and HIV risk [1].

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Correspondence: J. Marcus, 401 Park Dr, Ste 401, Boston, MA 02215 (julia_marcus@harvardpilgrim.org).

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Comparisons of HIV risk by contraceptive method are often confounded by differences in condom use and other sexual behaviors [6]. However, among IUD users, the choice of IUD type may be largely independent of sexual behaviors. Thus, our objective was to estimate the effect of levonorgestrel IUD use, compared with copper IUD use, on risk of HIV acquisition.

METHODS

We conducted a cohort study using the IBM MarketScan Commercial Database, which included individual-level, deidentified data from approximately 129 million people with commercial employer–sponsored health insurance in the United States during 2010–2018. We identified women aged ≥15 years with billing codes indicating levonorgestrel IUD insertion or copper IUD insertion between 1 January 2011 and 31 March 2018 and with at least 1 year of prior health plan enrollment. We excluded women with prior evidence of an HIV infection (ie, HIV diagnoses, HIV genotype tests, or antiretroviral therapy use). Follow-up was until the earliest of the following occurrences: HIV diagnosis, IUD removal (without same-day reinsertion of the same IUD type), insertion of the comparator type of IUD, health plan disenrollment, death, or 31 March 2018. Women could reenter the cohort if they had multiple eligible exposure episodes.

We fit crude and inverse probability weighted Cox regression models to estimate hazard ratios (HRs) for incident HIV diagnosis by IUD type (levonorgestrel IUD compared with copper IUD). Logistic models for inverse probability weights included age at IUD insertion; year of IUD insertion; number of ambulatory visits in the prior year; live birth in the prior year; diagnoses of chlamydia, gonorrhea, and syphilis in the prior year; and other diagnoses in the prior year that may have affected clinical decisions about IUD type, including systemic lupus erythematosus, cirrhosis, liver cancer, breast cancer, and heavy or painful menses. We also included use of DMPA in the prior year because the ECHO trial could not rule out a smaller effect of DMPA use on HIV acquisition [3]. We stabilized the weights and assessed the balance in covariates between exposure groups before and after weighting. Statistical inference was derived with cluster robust sandwich variance estimation to account for multiple exposure episodes [7].

We conducted 2 sensitivity analyses. First, because a single HIV diagnosis code may represent a billing error rather than a true HIV diagnosis, we restricted incident HIV cases to women who had multiple HIV diagnosis codes on different dates of service, using the date of the initial diagnosis code as the HIV diagnosis date. Second, we explored the potential impact of an unmeasured confounder [8].

This study was approved by the Institutional Review Board at Harvard Pilgrim Health Care Institute with a waiver of written informed consent.

RESULTS

We identified 622 565 women with at least 1 levonorgestrel or copper IUD insertion from 1 January 2011 through 31 March 2018, with a mean of 1 insertion per woman (range 1–5). There were 541 635 levonorgestrel IUD insertions and 99 389 copper IUD insertions included in analyses of HIV incidence, with characteristics of IUD users before and after inverse probability weighting shown in Supplementary Table 1. The groups were similar with respect to health-care utilization in the prior year, while women using levonorgestrel IUD tended to be older than those using copper IUD. Having a recent live birth, breast cancer, or liver cancer were less common in women with levonorgestrel IUD insertions, and having heavy or painful menses was more common. The mean of the inverse probability weights was 1 (range 0.2–5.6), and covariates were well balanced by IUD type after weighting.

There were 89 incident HIV diagnoses in the levonorgestrel IUD group and 21 in the copper IUD group, with corresponding incidence rates per 1000 person-years of 0.11 and 0.15, respectively (Table 1). Compared with women with copper IUD insertions, women with levonorgestrel IUD insertions were not at increased risk of an HIV diagnosis in crude (HR 0.74, 95% confidence interval [CI] 0.46–1.19) or weighted analyses (HR 0.78, 95% CI 0.48–1.28). Results were similar when restricting to incident HIV cases with multiple diagnosis codes on different dates of service, with a weighted HR of 0.62 (95% CI 0.24–1.59).

We explored the impact a potential unmeasured confounder—specifically, Black race—could have had on the observed HR of 0.78. Black women have an approximately 8.5-fold higher lifetime risk of an HIV diagnosis compared with non-Black women [9]. Data are limited on the racial/ethnic backgrounds of levonorgestrel and copper IUD users specifically, but an estimated 12% of IUD users overall are Black [10]. Assuming an 8.5-fold higher risk of an incident HIV diagnosis in Black women compared with non-Black women in our cohort, and that 12% of levonorgestrel IUD users were Black, Black women would need to have constituted at least 43% of copper IUD users to move the HR from the observed 0.78 to 1.70 (ie, increased HIV risk with levonorgestrel IUD) with a lower confidence limit above the null value of 1.

DISCUSSION

Epidemiologic data on levonorgestrel IUD use and HIV risk have been lacking to date. In this large cohort study of insured women in the United States, we found no evidence that levonorgestrel IUD use was associated with increased HIV risk compared with copper IUD use. Indeed, although not statistically significant, the direction of the observed HRs was the opposite of what we had hypothesized, with a lower risk of incident HIV diagnosis among levonorgestrel IUD users compared with copper IUD users.

Our results provide some initial reassurance that existing levonorgestrel-containing contraceptives and emerging multipurpose prevention technologies will not increase the risk of HIV acquisition in women. Biological studies on levonorgestrel IUD use and potential HIV risk have had mixed results. Shanmugasundaram et al [11] observed local immune and inflammatory changes with levonorgestrel IUD use, including an increased density of T-cells in the cervix and endometrium, raising concerns about potentially increased HIV risk. In contrast, Achilles et al [12] observed a decrease in T-cells expressing the HIV coreceptor CC chemokine receptor 5 in the cervix and endometrium with levonorgestrel IUD use, suggesting that HIV risk would not be elevated. Although some women in the ECHO trial were randomized to receive levonorgestrel implants, there are no data from randomized studies on levonorgestrel IUDs and HIV risk [3]. Thus, observational studies such as ours are necessary to fill a critical research gap on the effect of levonorgestrel IUDs on HIV risks.

Our study had several limitations. First, although IUD type is unlikely to influence sexual behaviors, unmeasured confounding cannot be ruled out. However, our sensitivity analysis suggested that the degree of unmeasured confounding needed to produce an HR suggesting increased HIV risk with levonorgestrel IUD use would be implausibly strong. Second, we may have misclassified women previously diagnosed with HIV as having

Table 1. Incident Human Immunodeficiency Virus Diagnoses Among Women With Intrauterine Device Insertions, 2011–2018

	Women	Exposure Episodes	Events	Incidence Per 1000 Person-years	Crude HR (95% CI)	Weighted HR (95% CI)
Incident HIV diagnosis, ≥1						
Levonorgestrel IUD	531 551	541 635	89	0.11	0.74 (0.46–1.19)	0.78 (0.48–1.28)
Copper IUD	97 475	99 389	21	0.15	ref	ref
Incident HIV diagnosis, >1						
Levonorgestrel IUD	531 551	541 635	25	0.03	0.62 (0.25–1.58)	0.62 (0.24–1.59)
Copper IUD	97 475	99 389	7	0.05	ref	ref

Logistic models for inverse probability weights included age, year, and all of the following in the prior year: number of ambulatory visits, live birth, use of depot medroxyprogesterone acetate, and diagnoses of chlamydia, gonorrhea, syphilis, lupus, cirrhosis, liver cancer, breast cancer, and heavy or painful menses. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; IUD, intrauterine device; ref, reference.

incident HIV diagnoses, although we minimized this possibility by requiring at least 1 year of prior health plan enrollment and no HIV-related claims in all available history. We may have also misclassified women who were living with HIV but not yet diagnosed by the end of follow-up. In both scenarios, we expect any potential misclassification to have been nondifferential by IUD type. Third, despite our large sample size, there were few incident HIV diagnoses and, thus, wide CIs. Fourth, we cannot rule out the possibility that both types of IUDs similarly increase or decrease HIV risk, but our results can inform decision-making about IUD type among women who are seeking an IUD. Finally, our data set only included commercially insured women in the United States, potentially limiting generalizability to publicly insured and uninsured women, who may be at greater risk of HIV acquisition.

Our study also had strengths. First, our large sample size allowed us to evaluate a relatively rare exposure and outcome. Second, because most insurance plans cover the copper IUD and at least 1 type of progestin-releasing IUD, typically with no out-of-pocket costs, restricting to an insured population likely minimized potential bias related to differences in access to care.

In this large health insurance database, we found no increased risk of an incident HIV diagnosis among women using levonorgestrel IUDs compared with those using copper IUDs. These results may help allay concerns about progestins and HIV risk. Future studies should evaluate the association of levonorgestrel IUD use and HIV risk in other large-scale health-care databases that may include women at higher risk of HIV acquisition, such as those on Medicaid, and among women in non-US settings.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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