Hormonal Contraception and Risk of Psychiatric and Other Noncommunicable Diseases in HIV-Infected Women

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Abstract

Background: Hormonal contraception use is common among human immunodeficiency virus (HIV)-infected women. Risk of psychiatric and other noninfectious complications of hormonal contraception use has not been described in this population.

Methods: We performed a retrospective cohort study of HIV-infected women receiving care in Tennessee from 1998 to 2008 to examine the risks of incident psychiatric and other noncommunicable diseases (NCDs), including cardiovascular, hepatic, renal, and malignant diseases, and hormonal contraception use, including depot medroxyprogesterone acetate (DMPA) and combined estrogen- and progestin-containing hormonal contraceptives. We used marginal structural models with inverse probability weights to account for time-varying confounders associated with hormonal contraception use.

Results: Of the 392 women included, 94 (24%) used hormonal contraception during the study period. Baseline psychiatric disease was similar between women who received and did not receive hormonal contraception. There were 69 incident psychiatric diagnoses and 72 NCDs. Only time-varying DMPA use was associated with increased risk of psychiatric disease (adjusted odds ratio [aOR] 3.70; 95% confidence interval [95% CI] 1.32–10.4) and mood disorders, specifically (aOR 4.70 [1.87–11.8]). Time-varying and cumulative combined hormonal contraception use were not statistically associated with other NCDs (aOR 1.64, 95% CI 0.64–4.12 and aOR 1.16, 95% CI 0.86–1.56, respectively). However, risk of incident NCDs was increased with cumulative DMPA exposure (per year exposure aOR 1.45, 95% CI 1.01–2.08).

Conclusions: Among HIV-infected women, DMPA was associated with risk of incident psychiatric diseases, particularly mood disorders, during periods of use. Cumulative DMPA exposure was also associated with risk of other NCDs. However, combined estrogen and progestin-containing hormonal contraception use was not statistically associated with risk of any NCDs.

Introduction

FOR ALL WOMEN OF CHILDBEARING AGE, effective family planning is important for reproductive autonomy, economic stability, reduction in abortions, and reduction in maternal morbidity and mortality. For women living with human immunodeficiency virus (HIV)-1 infection, family planning also reduces the risk of mother-to-child transmission of HIV-1.¹ Data published by the United Nations in 2010 estimated prevalence of contraception use (including all modern and traditional methods) to be 63% among women of

childbearing age in a marriage or union worldwide.² In the United States, recent data from the Women's Interagency HIV Study estimated that approximately 90% of HIV-infected women of childbearing age used some form of contraception. Hormonal contraceptive oral pills, patches or rings were used by 5%–10% of women and depot medroxyprogesterone acetate (DMPA) was used by 10% of women from 1998 to 2010.³

Hormonal contraception has been evaluated for its possible effects on HIV-1 transmission and disease progression. Hormonal contraception generally includes oral, patch, and

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ring formulations of combined estrogen and progestins, oral progestins, and injectable long-acting progestins. Use of hormonal contraception—and DMPA in particular—has been associated with an increased risk of HIV-1 acquisition in a number of prospective cohorts.^{4–10} Among HIV-infected women, hormonal contraception use has not been associated with accelerated HIV-1 disease progression or death.^{11–18}

In the general population with unknown HIV-1 infection status, hormonal contraception has been associated with adverse health outcomes, including psychiatric outcomes. Previous research has demonstrated an increased risk of thrombosis and cardiovascular events among women using estrogen-containing hormonal contraception.^{19–22} Metabolic effects, including increased bone metabolism, have been of concern, but have not been demonstrated in clinical studies.^{23–26} Lastly, while mood effects from hormonal contraception have been observed, particularly with DMPA use, most studies have not shown a consistently increased risk of adverse psychiatric events.^{27–31}

With effective antiretroviral therapy, noncommunicable diseases (NCDs) increasingly account for morbidity and mortality among persons living with HIV-1 infection^{32–35}. Cardiovascular diseases, liver disease, renal disease, metabolic diseases, and certain malignancies have been observed in HIV-infected populations at increased rates and, at times, at younger ages compared to uninfected populations^{36–40}. While multifactorial in their pathogenesis, these NCDs are hypothesized to occur more commonly in HIV-infected populations as a result of chronic inflammation and immune dysfunction that persist despite successful HIV-1 viral suppression.^{41,42} While subtle, the immunologic and inflammatory effects of hormonal contraception, including DMPA, may affect the development of these diseases in HIV-infected women.^{43–46}

Psychiatric diseases, including depression, are common in HIV-infected women.^{47–49} In HIV-infected women, depression has been associated with increased risk of neurocognitive decline, HIV disease progression, and mortality.^{50–52} The risk of depression observed in HIV-infected populations is multifactorial and includes changes in hypothalamic-pituitary axis associated with HIV-infection.⁵³ Additional hormonal changes due to hormonal contraception could lead to increased risk of psychiatric outcomes in HIV-infected women.

Among HIV-infected women, the potential immediate and delayed effects of hormonal contraception use on risk of NCDs, including psychiatric outcomes, cardiovascular disease, hepatic dysfunction, renal disease, metabolic disorders, malignancies, and mental illness, has not been described. To our knowledge, the risk of psychiatric outcomes associated with hormonal contraception has not been reported in HIV-infected women. In this retrospective cohort study of women with HIV-1 infection, we hypothesized that, compared with women who do not use hormonal contraception, women receiving hormonal contraception would experience higher rates of psychiatric and other NCDs.

Materials and Methods

We performed a retrospective cohort study among HIV-1 infected women receiving HIV care. The Vanderbilt Comprehensive Care Clinic is an HIV clinic in Nashville, Tennessee, that provides primary and subspecialty health care, including mental health services by licensed psychiatric

providers. Patients are seen at the clinic every 3–6 months. Data for this study were obtained from electronic medical records by data management specialists. For this study, female patients who entered care between January 1, 1998, and December 31, 2008, were included. Follow-up was censored at death, December 31, 2008, or at the last clinic visit when care was interrupted for more than one year. Women were included if they were between the ages of 18 and 45 years old at the time of clinic entry. Women were not censored after 45 years of age in order to examine possible delayed effects of hormonal contraception use. Women older than 45 years at clinic entry and women with a history of amenorrhea, menopause, thromboembolism (pulmonary embolism or deep vein thrombosis), hysterectomy, bilateral tubal ligation, or breast cancer were excluded, as they would not be eligible for hormonal contraception at study entry. Women who became pregnant during the study period had their follow-up time censored during the pregnancy. Age, race, year of cohort entry, history of injection drug use, CD4+ lymphocyte count, log₁₀ HIV-1 RNA, hepatitis C virus infection, antiretroviral use, previous hormonal contraception use, and history of psychiatric disease and NCDs prior to clinic entry were included as baseline covariates. Socioeconomic status, education, and medication adherence data were not available. Baseline clinical and demographic characteristics were compared between women with any hormonal contraception use and women without any hormonal contraception use during study follow-up with chi-squared and Wilcoxon rank sum tests.

The primary exposures of interest were time varying and cumulative use of hormonal contraception, including oral contraceptive pills, injectable contraceptives, and other formulations of hormonal delivery (transdermal patches and vaginal rings). Time-varying exposure status reflected whether or not a woman was recorded as receiving hormonal contraception at a given point in time and cumulative exposure reflected total duration of hormonal contraception exposure (regardless of current use status) at a given point in time. Thus, follow-up time for each woman who received any hormonal contraception was divided into periods of hormonal contraception use and nonuse. Exposure data were obtained and validated from medication lists recorded in the electronic medical record. In the clinic, physicians perform medication list reconciliation at every visit for all patients. DMPA is routinely available and administered at the clinic for women when prescribed. Pharmacy data were not available. A minimum of 30 days was required to meet criteria for exposure. Exposure time ended when the medication was removed from the medication list or listed as inactive. Data on nonhormonal forms contraception (i.e., barrier methods) were not available through medication review.

Hormonal contraception was categorized into two groups: combined hormonal contraception and DMPA. Combined hormonal contraception included pill, patch, and ring formulations of combined estrogen- and progestin-containing hormonal contraceptives. As the biologic effects and potential confounders may differ by hormonal contraception formulation, all outcome analyses were stratified by hormonal contraception category.

The outcomes of interest were incident psychiatric diseases and NCDs following the first clinic visit. While screening tools are not typically used, patients entering care in the clinic routinely undergo a thorough review of past

medical history, including psychiatric disease history. For this study, incident diagnoses were obtained through routine clinical assessment and documentation entered into the medical records by primary care physicians and mental health professions. Psychiatric diagnoses excluded substance abuse disorders. NCDs included cardiovascular disease, renal disease, hepatic diseases, metabolic diseases, and non-AIDS-defining malignancies (see Supplementary Table S1 for complete list of eligible diagnoses; Supplementary Data are available online at www.liebertpub.com/jwh). Psychiatric and NCD outcomes were examined separately given their different pathophysiology, morbidity, and mortality. Unadjusted incidence rates were calculated for the psychiatric outcomes and NCD categories by occurrence during hormonal contraception exposure time periods (while on or not on hormonal contraception, which included follow-up time for women who never received hormonal contraception). All psychiatric and NCD diagnoses captured during follow-up time were included in calculation of incidence rates and each woman could contribute multiple diagnoses. Incidence rate ratios were calculated using univariate Poisson models to compare rates of diagnoses between exposed and unexposed person-time.

Marginal structural models (MSM) were used to evaluate time-varying and cumulative hormonal contraception use and risk of psychiatric and NCDs outcomes in multivariate analyses. MSM use inverse probability weighting to account for time-varying, selective observations—for example, the nonrandomization of hormonal contraception use, as women who do and do not use hormonal contraception often differ by the potential confounders of age, race, health status, and social factors.⁵⁴ Weights in the MSM were created as the inverse predicted probability of the observed hormonal contraception history, estimated using logistic regression with the outcome being an indicator for hormonal contraception use and the predictors of baseline age, race, history of injection drug use, history of hepatitis C virus infection, year of first visit, hormonal contraception use prior to first visit, time since clinic entry, and the time-varying covariates of CD4+ lymphocyte count, log₁₀ HIV-1 RNA, an indicator for an AIDS-defining event (ADE), and antiretroviral therapy (ART) use. Sexual practices, relationship status, alcohol use, drug use, smoking status, and body mass index data were not available. Weights were stabilized in the standard manner and truncated at the 2.5th and 97.5th percentiles.

Primary models using pooled logistic regression were performed for incident psychiatric outcomes and NCDs (cardiovascular, hepatic, renal, metabolic, and cancer diagnoses) and were stratified by type of hormonal contraception. To further investigate psychiatric outcomes, we performed secondary analyses that examined mood disorders (depression and bipolar affective disorder), also stratifying by type of hormonal contraception. For each outcome, only the first event was included and the relationship between the outcome and hormonal contraception use (time-varying and cumulative use at the time of the event) was adjusted for baseline demographic and clinical covariates (as determined by available degrees of freedom), time-varying weights (described above), and month of follow-up. ART use was not included as an independent variable in primary models as it was included in the calculation of time-varying weights.

All reported *p* values are two-sided. All analyses were performed using R statistical software (version 2.15.2, www.r-project.org) and Stata 12.1 (Stata Corporation, College Station, TX). Analysis code is posted at <http://biostat.mc.vanderbilt.edu/ArchivedAnalyses>.

Results

There were 392 women who met the inclusion criteria. Of the 392 women, 94 (24%) received any form of hormonal contraception during follow-up. Table 1 describes the demographic and clinical characteristics of the women. The majority of women were non-white (65%) and a minority reported injection drug use as HIV-1 transmission risk factor (10%). Compared with nonusers, women who had any hormonal contraception use during follow-up were younger at clinic entry, followed in the clinic for longer duration, and had higher CD4+ lymphocyte counts. They were also more likely to have a history of hormonal contraception exposure prior to clinic entry. Women who used hormonal contraception had lower rates of nonpsychiatric NCDs and had similar rates of mental health illness at the time of entry. There was no difference in rates of ADEs or receipt of ART during follow-up between women who did or did not receive hormonal contraception.

For women who used hormonal contraception, the median total use of hormonal contraception was 1.08 years. There were a total of 156.4 person-years of hormonal contraception exposure (90.5 person-years of DMPA and 65.9 person-years of combined hormonal contraception exposure) and 852.6 person-years of no hormonal contraception exposure among all women in the cohort. The majority (94%) of combined hormonal contraception person-time was combined oral contraceptive pill use, including use of 19 different commercial brands. Combined hormonal contraception also included person-time of vaginal ring (NuvaRing[®]) use (0.1 person-years) and transdermal patch (OrthoEvra[®]) use (4.4 person-years).

There were a total of 69 psychiatric diagnoses and 72 NCDs observed during study follow-up. Table 2 lists the incidence rates (per 1000 person-years) for types of NCDs observed during hormonal contraception person-time and during person-time without any hormonal contraception exposure. Of the 69 psychiatric diagnoses, 48 (70%) were mood disorders (43 depression and 5 bipolar affective disorder diagnoses), 12 (17%) were anxiety disorders, 7 (10%) were psychotic disorders, and 2 (3%) were other (dementia and adjustment reaction). Compared with no hormonal contraception exposure, the incidence of psychiatric events was 2-fold higher during person-time with DMPA exposure (*p*=0.02) but was not statistically different during exposure time with combined hormonal contraception. After psychiatric diagnoses, the most common categories NCDs observed included cardiovascular and metabolic events. Compared to no hormonal contraception exposure, the incidence of cardiovascular events was nearly 3-fold increased during combined hormonal contraception use but this did not meet statistical significance (*p*=0.07).

Table 3 reports the results of the adjusted marginal structural models of hormonal contraception use and first NCD, excluding psychiatric outcomes (*n*=65). Results include models stratified by hormonal contraception category. After adjusting for covariates, cumulative DMPA use was associated with an increased risk of NCD events (per year of DMPA

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY POPULATION, ACCORDING TO HORMONAL CONTRACEPTIVE USE

	<i>Hormonal contraception users (n=94)</i>	<i>Hormonal contraception nonusers (n=298)</i>	<i>p</i>
Age at clinic entry in years, median (IQR)	27 (24–32)	33 (27–39)	<0.01 ¹
Non-white race	62 (66)	193 (65)	0.83 ²
Injection drug use as HIV-1 transmission risk factor	7 (7)	33 (11)	0.31 ²
Hormonal contraception use prior to clinic entry	20 (21)	4 (1)	<0.01 ²
CD4+ lymphocyte count (cells/ μ L) at clinic entry, median (IQR)	504 (350–704)	364 (191–601)	<0.01 ¹
Log ₁₀ HIV-1 RNA at clinic entry, median	3.6 (2.6–4.5)	4.1 (2.6–4.8)	0.07 ¹
Hepatitis C virus infection at clinic entry	5 (5)	36 (12)	0.06 ²
History of psychiatric diagnosis prior to clinic entry	16 (17)	47 (16)	0.77 ²
History of nonpsychiatric NCD prior to clinic entry	20 (21)	98 (33)	0.03 ²
Year of clinic entry, median (IQR)	2002 (2000–2005)	2003 (2000–2006)	0.16 ¹
Duration of follow-up in months, median (IQR)	42 (24–77)	15 (5–36)	<0.01 ¹
Any AIDS-defining event during follow-up	8 (9)	24 (8)	0.59 ²
Receipt of ART during follow-up	76 (81)	221 (74)	0.19 ²
Duration of hormonal contraception use in years, median (IQR)	1.08 (0.5–2.3)	–	

Percentages are in parentheses, except as noted.

Hormonal contraception users include women who received any hormonal contraception during the study period. Hormonal contraception nonusers refers to women who did not receive hormonal contraception during the study period.

¹Wilcoxon rank-sum test.

²Pearson chi-squared test.

ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; NCD, noncommunicable disease.

use, adjusted odds ratio [aOR] 1.45, 95% confidence interval [95% CI] 1.01–2.08) but time-varying DMPA use was not associated with risk of NCDs. Neither time-varying nor cumulative combined hormonal contraception use was statistically associated with risk of NCDs.

Table 4 reports the results of the adjusted marginal structural models of hormonal contraception use and first psychiatric outcome ($n=53$) and first mood disorder event ($n=41$). Given

the small number of outcomes, multivariate models included hormonal contraception variables (which reflect weighted probabilities based upon other time-varying covariates as described in “Materials and Methods”), age, race, and month of follow-up. Time-varying DMPA use was associated with nearly 4-fold increased risk of psychiatric outcomes (aOR 3.70, 95% CI 1.32–10.4) and nearly 5-fold increased risk of mood disorders (aOR 4.70, 95% CI 1.87–11.8).

TABLE 2. INCIDENCE AND INCIDENCE RATE RATIOS OF NONCOMMUNICABLE DISEASES ACCORDING TO HORMONAL CONTRACEPTION EXPOSURE

	<i>Incidence during person-time without any hormonal contraception exposure</i>	<i>Incidence during person-time of DMPA exposure</i>	<i>Incidence rate ratio¹ [95% CI]</i>	<i>Incidence during person-time of combined hormonal contraception exposure</i>	<i>Incidence rate ratio² [95% CI]</i>
All psychiatric disorders	61.0 (52)	132.7 (12)	2.2 [1.2–4.1]	75.9 (5)	1.2 [0.5–3.1]
Mood disorders	41.1 (35)	88.4 (8)	2.2 [1.0–4.6]	75.9 (5)	1.8 [0.7–4.7]
Anxiety disorders	10.6 (9)	33.1 (3)	3.1 [0.9–11.6]	0 (0)	–
Psychosis disorders	7.0 (6)	11.0 (1)	1.6 [0.2–13.0]	0 (0)	–
Other psychiatric	2.3 (2)	0 (0)	–	0 (0)	–
Cardiovascular	22.3 (19)	33.2 (3)	1.5 [0.4–5.0]	60.7 (4)	2.7 [0.9–8.0]
Metabolic	27.0 (23)	22.1 (2)	0.8 [0.2–3.5]	0 (0)	–
Hepatic	17.6 (15)	33.2 (3)	1.9 [0.5–6.5]	30.4 (2)	1.7 [0.4–7.5]
Renal	9.4 (8)	33.2 (3)	3.4 [0.9–13.3]	15.2 (1)	1.6 [0.2–12.9]
Malignancy	(0)	(0)	–	(0)	–

Incidence rates are per 1000 person-years. Frequencies of events are in parentheses.

Exposure time: Without any hormonal contraception, 852.6 person-years; during DMPA exposure, 90.5 person-years; during combined hormonal contraception, 65.9 person-years.

¹Incidence rate ratio of incidence during DMPA exposure vs. incidence without any hormonal contraception exposure.

²Incidence rate ratio of incidence during combined hormonal contraception exposure vs. incidence without any hormonal contraception exposure.

CI, confidence interval; DMPA, depot medroxyprogesterone acetate.

TABLE 3. MULTIVARIATE MARGINAL STRUCTURAL MODELS OF HORMONAL CONTRACEPTION USE AND NONCOMMUNICABLE DISEASES

	<i>Noncommunicable diseases, excluding psychiatric outcomes (n=65)</i>	
	<i>aOR [95% CI]</i>	<i>p</i>
Any hormonal contraception use		
Time-varying use	1.64 [0.65–4.12]	0.29
Cumulative use (per year)	1.16 [0.86–1.56]	0.32
DMPA use		
Time-varying use	1.15 [0.39–3.38]	0.80
Cumulative use (per year)	1.45 [1.01–2.08]	0.04
Combined hormonal contraception use		
Time-varying use	1.75 [0.55–5.56]	0.34
Cumulative use (per year)	1.04 [0.58–1.86]	0.91

Multivariate models included time-varying hormonal contraception use and time-varying cumulative hormonal contraception use as well as age, race, history of injection drug use, hormonal contraception use prior to clinic entry, noncommunicable diseases prior to clinic entry, year of clinic entry, month of follow-up, CD4+ lymphocyte count at clinic entry, log₁₀ HIV RNA at clinic entry, and hepatitis C virus infection at clinic entry. Time-varying hormonal contraception is weighted using inverse probability after adjusting for baseline age, race, history of injection drug use, history of hepatitis C virus infection, year of first visit, hormonal contraception use prior to first visit, time since clinic entry, and the time-varying covariates of CD4+ lymphocyte count, log₁₀ HIV-1 RNA, an indicator for an AIDS-defining event (ADE), and ART use.

aOR, adjusted odds ratio.

Discussion

In this retrospective cohort study of HIV-infected women, time-varying DMPA in was associated with an approximately 4-fold increased risk of incident psychiatric diagnosis and nearly 5-fold increased risk of mood disorders. Time-varying combined hormonal contraception use was not associated with psychiatric outcomes. Neither time-varying nor cumulative combined hormonal contraception use was sta-

tistically associated with an increased risk of incident NCDs after controlling for potential confounding variables. However, longer cumulative DMPA use was associated with an increased risk of NCDs.

This study is novel in our discovery of mental health risks associated with DMPA use in HIV-infected women. In analyses restricted to mood disorders, the risk associated with DMPA use was even greater. Importantly, women who used hormonal contraception did not differ compared with women who did not by known psychiatric disorders at the time of clinic entry, nor by race or history of intravenous drug use. In fact, women who received hormonal contraception were younger and healthier at clinic entry than women who did not receive hormonal contraception. In HIV-infected adults, studies have found that HIV disease stage and CD4+ lymphocyte count are independently associated with risk of depression.^{48,55} Biologically, the hormones of estrogen and progesterone are postulated to have mood effects not only due to the higher rates of depression in women compared with men (with periods of greatest risk occurring during times of hormone level fluctuations) but also due to experimental data demonstrating their effects on neuron signaling and neurocognitive function.^{56–59} The increased risk of depression in women has also been observed in HIV-infected populations.^{47,55} However, even with this biologic underpinning, results of clinical studies examining risk of mental health adverse effects of any hormonal contraception have been inconsistent. While some studies have shown emotional disturbances associated with hormonal contraception use, others have shown no effect or even a beneficial effect of hormonal contraception use.^{29,60–64}

DMPA use, though, has more consistently been shown to increase risk of depression. While a retrospective study that evaluated DMPA and risk of postpartum depression found no effect, a randomized trial of a long-acting injectable progestin demonstrated increased risk of postpartum depression.^{30,65} Another prospective study of young DMPA users also demonstrated increased risk of depressive symptoms, particularly prior to discontinuation.²⁸ Our study adds to the literature suggesting a link between mood disturbance and use of DMPA, and is the first to do so in an HIV-infected

TABLE 4. MULTIVARIATE MARGINAL STRUCTURAL MODELS OF HORMONAL CONTRACEPTION USE AND PSYCHIATRIC OUTCOMES

	<i>All psychiatric outcomes (n=53)</i>		<i>Only mood disorders (n=41)</i>	
	<i>aOR [95% CI]</i>	<i>p</i>	<i>aOR [95% CI]</i>	<i>p</i>
Any hormonal contraception use				
Time-varying use	3.04 [1.36–6.78]	<0.01	3.91 [1.73–8.84]	<0.01
Cumulative use (per year)	0.58 [0.22–1.50]	0.26	0.58 [0.22–1.54]	0.27
DMPA use				
Time-varying use	3.70 [1.32–10.4]	0.02	4.70 [1.87–11.8]	<0.01
Cumulative use (per year)	0.29 [0.05–1.72]	0.17	0.25 [0.05–1.23]	0.09
Combined hormonal contraception use				
Time-varying use	1.39 [0.36–5.42]	0.64	1.58 [0.39–6.32]	0.52
Cumulative use (per year)	0.78 [0.23–2.68]	0.69	0.84 [0.24–2.97]	0.79

Multivariate models included time-varying hormonal contraception use and time-varying cumulative hormonal contraception use as well as age, race, and month of follow-up. Time-varying hormonal contraception is weighted using inverse probability after adjusting for baseline age, race, history of injection drug use, history of hepatitis C virus infection, year of first visit, hormonal contraception use prior to first visit, time since clinic entry, and the time-varying covariates of CD4+ lymphocyte count, log₁₀ HIV-1 RNA, an indicator for an ADE, and ART use.

cohort of women. As depression has been associated with HIV disease progression and mortality in HIV-infected populations, these results highlight the need for close follow-up of women starting DMPA for depressive symptoms.^{50,51}

This study has a number of limitations. While comparable to patterns observed in other HIV-infected populations, a low percentage of women of childbearing age in our cohort used hormonal contraception during follow-up (less than 25%). Women who used hormonal contraception only did so on average for approximately one year. Additionally, with relatively few outcomes, NCDs were pooled in multivariate analyses rather than examined by categories (such as cardiovascular disease or metabolic diseases) or specific diagnoses (such as myocardial infarction). It is also possible that hormonal contraception may have different effects on NCDs. For example, a study by the Women's Interagency HIV Study in 2009 investigated the association of hormonal contraception and risk of metabolic diseases (dyslipidemia, hyperlipidemia, and disorders of glucose) in HIV-infected and at-risk women. Results of that study demonstrated the complexity of hormonal contraception effects: progestin-only hormonal contraception use was associated with slightly lower high-density lipoprotein and higher risk of insulin resistance, while use of combined forms of hormonal contraception was associated with increased high-density lipoprotein and was not associated with insulin resistance in both HIV-infected and HIV-uninfected women.⁶⁶ With few outcomes, we were limited to investigate differences in risk of specific NCDs by hormonal contraception exposure history.

An additional possible limitation to our study is that of unmeasured confounding. Women who use hormonal contraception differ from women who do not use hormonal contraception, as we observed in our cohort. Additionally, women who choose injectable forms of contraception may differ from those who choose oral formulations. In our study, we attempted to adjust for these confounders in a time-varying manner by marginal structural models. Marginal structural models weight time-varying hormonal contraception use by adjusting for a number of baseline demographic, comorbidities, and time-varying clinical covariates (including CD4+ lymphocyte count, ART use, and HIV-1 RNA level) that have been associated with risk of depression in HIV-infected adults. However, our data lack information about smoking status, alcohol use, socioeconomic status, education, medication adherence, and relationship status details, which may confound hormonal contraception use and risk of NCDs and psychiatric outcomes.

Thirdly, our study is limited due to its retrospective and observational design. Women who used any formulation of hormonal contraception may have had more regular follow-up with providers, and thus an ascertainment bias may have been present. As an observational study, misclassification bias may have occurred. Women using oral hormonal contraception may not regularly adhere to the medication and may have been classified as an active user erroneously. Given that its injectable formulation requires clinic visits, DMPA exposure misclassification is less likely, though may have occurred if a patient missed or was late for an injection and the medication list was not updated to reflect the lapse in coverage. Finally, as mood disorders are often episodic, it is possible that a new diagnosis of a mood disorder may not truly reflect incident disease. At clinic entry, however,

women who used any hormonal contraception did not differ from women who did not use hormonal contraception in their history of psychiatric diseases.

Lastly, this study is limited by the lack of HIV-uninfected women with whom to compare effects of hormonal contraception and these noninfectious outcomes. As HIV-1 infection and its treatment are associated with NCDs and psychiatric diseases, the interaction of HIV-1 infection and hormonal contraception on the risk of noninfectious morbidity could not be assessed in this study.

Studying NCDs represents unique challenges and limitations. For instance, we did not include pulmonary or hematologic diseases as outcomes and thus may have missed other important noninfectious morbidity related to hormonal contraception use. However, there is no standardized list of NCDs in the HIV literature. We chose to include the most common NCD categories (cardiovascular, malignancy, renal, hepatic, and metabolic) reported in HIV research, with the addition of psychiatric illnesses based upon preliminary analyses of our cohort.^{67,68} As psychiatric outcomes were the most common NCDs among women in our study regardless of hormonal contraception use, they represent important causes of noninfectious morbidity in this population.

Conclusions

This study is the first to examine risk for psychiatric outcomes and NCDs among HIV-infected women on hormonal contraception. Time-varying DMPA use was strongly associated with short-term risk of incident psychiatric diagnoses, particularly mood disorders. HIV providers should closely monitor women starting DMPA for depressive symptoms, which could impact adherence to antiretroviral therapy. However, unwanted pregnancies can also detrimentally affect mental health, and these psychiatric risks should not deter providers from providing hormonal contraception, as safe and effective family planning remains of paramount importance for women living with HIV-1 infection. After careful adjustment for time-varying confounders, we found no statistically associated immediate or delayed risk of cardiovascular, hepatic, renal, metabolic, or malignant NCDs and combined hormonal contraception use. These findings will need to be confirmed in larger cohorts of HIV-infected women.

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Author Disclosure Statement

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