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Hormonal Contraception and HIV Acquisition: Reanalysis using Marginal Structural Modeling

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Introduction

In 2007 we published the results of a large multicenter cohort study designed specifically to investigate whether hormonal contraceptive (HC) use increased HIV acquisition [1]. The HC-HIV Study enrolled 4,450 HIV-negative women in Uganda and Zimbabwe ages 18-35 years that had either been using depot-medroxyprogesterone acetate (DMPA) or combined oral contraceptives (COCs) for at least 3 months or no hormonal method. Women were followed every 12 weeks for a median of 21.5 months. Overall, we found no significant increased risk of HIV acquisition for either DMPA or COCs adjusting for demographic and sexual risk factors [1]. In a pre-specified subgroup analysis, we found that while HSV-2 positive women using hormonal contraception had no increased HIV risk, HSV-2 negative women who used either DMPA or COCs were at increased HIV acquisition risk. In a subsequent analysis, we also found that young women (18-24 years) who used DMPA or COCs were at increased risk of HIV acquisition while older women (≥ 25 years) using hormonal contraception appeared to be at decreased HIV risk [2].

During the HC-HIV Study more than 30% of participants switched their contraceptive method. The decision to switch contraceptive use was found to be associated with participants' use of condoms, their sexual behavioral risk, and their partners' behavioral risks – all risk factors for HIV acquisition in the HC-HIV Study dataset. Furthermore, these HIV risk factors changed over time and may both predict subsequent hormonal contraceptive use and be predicted by past hormonal contraceptive exposure and thus were found to be time-dependent confounders. Use of conventional Cox proportional hazard regression modeling as applied in the original analysis [1] cannot satisfactorily adjust for

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time–dependent confounding and likely produced a biased estimate of the effect of hormonal contraceptive exposure on HIV acquisition [3, 4].

Marginal structural modeling (MSM) is a statistical method that accounts for measured time-dependent confounding and reduces corresponding selection bias that may be present with observational study designs [5]. The MSM approach, through the use of inverse probability of exposure weighting, seeks to mimic the results that would be obtained in a study when the exposure variable is randomized [3, 6]. Given the time-varying hormonal contraceptive exposure and potential time-dependent confounding in the HC-HIV Study, we decided to replicate our original study analysis [1] using marginal structural modeling.

Methods

Study methods have been described in detail elsewhere [1]. Briefly, between 1999 and 2004, we enrolled and followed women seeking reproductive and general health care services in Uganda and Zimbabwe. Participants were age 18-35 years, not pregnant, HIV-1-uninfected, sexually active, and had been using either no hormonal contraceptive method, DMPA or COCs for at least 3 months. Enrolled women were followed quarterly for 15-24 months. Each study visit included administration of a standardized questionnaire, a physical examination, and HIV-1, STI and pregnancy testing,

We tested for HIV-1 using an algorithm described previously [1]. To accurately time incident HIV-1 infections, DNA PCR was performed retrospectively on serial visit specimens. We used PCR testing for gonorrhea and chlamydia (Amplicor^{R} CT/NG, Roche Diagnostics), an ELISA to test for HSV-2 antibodies (Focus Diagnostics) and microscopy to diagnose vaginal infections (trichomonas, bacterial vaginosis, yeast) [1].

Analysis Population and Variable Definition

The analysis population consisted of participants with at least one follow-up visit with valid HIV-1 results [1]. The outcome was the number of days from the baseline visit to the date of the first positive HIV-1 result or the last study contact.

All variable definitions and the final analysis model used in the original analysis were imitated as closely as possible in the reanalysis. However, HC exposure time was divided into equal monthly intervals rather than using visit segments as in the original analysis. This allowed HC exposure to be defined more precisely and to be analyzed using the MSM approach with equal length time intervals for each participant.

Statistical Methods

We pre-specified several potential time-dependent confounders – condom use, participant behavioral risk, primary partner risk, and coital frequency – to be considered in the MSM reanalysis. To avoid introducing finite-sample bias (through including too many potential time-dependent confounders) we used Cox proportional hazard regressions and logistic regressions adjusted for repeated observations to evaluate bivariable associations between potential time-dependent confounders and HIV acquisition and HC exposure [7]. If a potential time-dependent confounder was associated ($p<0.05$) with HIV acquisition and predicted subsequent HC exposure, and also was predicted by past HC exposure, it was considered a time-dependent confounder [6]. Accordingly, we identified three time-dependent confounders: any condom use, participant behavioral risk, and primary partner risk. The ‘inconsistent condom use’ variable included in the original analysis was not significantly associated with HIV acquisition and was therefore replaced with ‘any condom use’ in the reanalysis.

The stabilized inverse probability of weights were obtained using multinomial logistic regressions of HC exposure versus identified time-dependent confounders and time-independent covariates specified by the original analysis (e.g., age, site, living with partner) as well as other potential baseline confounders (including education, baseline STI history, coital frequency, and breastfeeding).

We used a weighted Cox proportional hazard model to estimate the effect of HC exposure on HIV acquisition. We calculated 95% confidence intervals for estimated hazard ratios using the robust sandwich estimate of the covariance matrix [8].

We tested three variables for effect modification of the HC-HIV relationship; enrolment HSV-2 infection status and study site (considered in the original analysis) and age (not considered in the original analysis). Because interaction terms for each of these variable were statistically significant ($p \leq 0.05$), we report strata-specific results.

We performed several sensitivity analyses to assess the robustness of our final model to the inclusion of time-dependent confounders. These included using the stabilized inverse probability of weights including adding coital frequency (a variable that did not meet the criteria for time-dependent confounding) and dropping primary partner risk (a time-dependent confounder) from calculation of the weights.

Data analyses were conducted using SUDAAN version 8.0.1 (RTI International, Research Triangle Park, NC, USA) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

In this reanalysis 4,435 African participants contributed 93,303 person-months. At baseline, 34.7% participants used COCs, 34.2% used DMPA and 31.1% were in the non-hormonal group. Participant characteristics remain as previously reported [1].

Hormonal contraception and HIV acquisition: MSM reanalysis results

213 incident HIV infections occurred in 7,775 years of follow-up for an overall incidence rate of 2.7 per 100 woman years (wy); 4.0 per 100wy in Zimbabwe and 1.6 per 100wy in Uganda. HIV incidence among the COC, DMPA, and NH group participants, respectively, was 2.6, 3.0, and 2.6 per 100wy.

To ascertain how closely we replicated the original study results, we compared adjusted hazard ratios for DMPA and COC for HIV acquisition using the new data structure (including contraceptive use categorized by month) before using MSM with the original study results. We found effect measures for DMPA (adjusted hazard ratio (AHR)=1.25, 95% CI 0.89-1.77) and COC use (AHR=1.05, 95% CI 0.73-1.52) that were very similar to the original published results (Table 1). Using the full MSM approach we found that DMPA (AHR=1.48, 95% CI 1.02-2.15) but not COC use (AHR=1.19, 95% CI 0.80-1.76) was significantly associated with HIV acquisition adjusting for covariates.

We evaluated whether the addition or deletion of time-dependent variables into the MSM weightings would change the effect estimates for DMPA and COC use. The addition of time-varying coital frequency (which did not meet our criteria as a time-dependent confounder) into the MSM weightings resulted in little change to the effect estimates for DMPA and COC use. When primary partner risk was deleted from the MSM weightings (thus deleting a known time-dependent confounder), AHRs for DMPA and COC use moved towards unity but did not change in direction.

Effect modification of the HC-HIV relationship

Analysis stratified by age at enrolment—While HIV incidence was higher among younger (18-24 years) than older women (≥ 25 years) overall, we found a significant interaction between hormonal contraceptive use and age (Table 2). Among young women both DMPA (AHR=2.76, 95% CI 1.62-4.72) and COC use (AHR=2.02, 95% CI 1.15-3.55) were associated with an increased risk of HIV acquisition (Table 2). Among older women, neither DMPA (AHR=0.81, 95% CI 0.48-1.39) nor COC use (AHR=0.73, 95% CI 0.42-1.26) was associated with HIV risk. We also considered the hormonal contraception effect when dividing the younger age group into women ages 18-20 years and 21-24 years. Among the youngest women (18-20 years), there was a strong increased risk of HIV acquisition for both DMPA (AHR=9.29, 95% CI 2.72-31.69) and COC users (AHR=3.68, 95% CI 0.88-15.31). Among women ages 21-24 years, an increased HIV risk remained for DMPA (AHR=1.95, 95% CI 1.06-3.58) and COC users (AHR=1.67, 95% CI 0.90-3.09) but the effect was mitigated.

Analyses Stratified by HSV-2 Status at Enrolment—HIV incidence was higher among HSV-2 positive participants than HSV-2 negative participants at enrolment (Table 2). We found a significant interaction between hormonal contraception and HSV-2 status similar to that reported in the original study results. Among HSV-2 positive participants, neither DMPA (AHR=1.03, 95% CI 0.67-1.59) nor COC use (AHR=1.07, 95% CI 0.69-1.65) appeared to increase HIV risk, adjusting for covariates. However, among HSV-2 negative participants, HIV acquisition risk was statistically significantly higher for DMPA (AHR=4.49; 95% CI 1.98-10.17) but not COC users (AHR=2.06 95% CI 0.87-4.92) compared with the non-hormonal group.

While the interaction between hormonal contraception and site was weaker than for either age or HSV-2 infection status, it attained statistical significance for DMPA (p=0.05). For Uganda, we found evidence of an increased risk for DMPA (AHR=2.09, 95% CI 1.07-4.08) but not COC users (AHR=1.64, 95% CI 0.80-3.39). In Zimbabwe, neither DMPA (AHR=1.14, 95% CI 0.73-1.78) nor COC use (AHR=0.96, 95% CI 0.61-1.51) was associated with HIV acquisition.

Discussion

Using marginal structural modeling to replicate the original HC-HIV Study analysis, we found that DMPA use was marginally associated with an increased risk of HIV acquisition while COC use was not. We also found that young women and HSV-2 negative women using hormonal contraception, particularly DMPA, were at increased HIV acquisition risk, while older women and HSV-2 positive women were not.

We believe that the use of marginal structural models to analyze the HC-HIV study data represents an important improvement over our previously reported analysis [1] for two reasons. First, the MSM approach is able to analyze longitudinal data subject to time-dependent confounding such as found in the HC-HIV study [5, 9, 10]. Secondly, simulations have shown that inclusion of measured confounders in the MSM approach resulted in a decrease in bias even when all true confounders are not measured [11]. The reanalysis results are consistent with these findings in that adding each time-dependent confounder individually into the overall model resulted in small increases in the adjusted hazard ratios for hormonal contraceptive use from their originally reported levels towards those reported in the final MSM model.

The MSM approach has become increasingly recognized as a preferred method to analyze longitudinal data subject to time-dependent confounding [5, 9, 10] especially in cohort

studies of HIV infection and the effect of HAART on HIV disease progression [9, 10, 12]. Nevertheless, like all statistical approaches, MSM depends on certain assumptions. The validity of the reanalysis assumes that all confounders were measured and sufficient to adjust for confounding and selection biases. These assumptions, however, are also required for the use of more standard statistical methods if their parameters are used for causal interpretation [6].

The finding that DMPA use was associated with an increased risk of HIV acquisition contrasts with some, but not all, previous longitudinal studies. Nine other prospective studies have examined the relationship between DMPA and HIV acquisition [2, 13-21]; none have used marginal structural modeling. Three studies found a significantly increased HIV risk associated with DMPA use [13, 19, 21, 22], two of which were conducted among high-risk populations (e.g., sex workers). The largest and methodologically strongest study conducted among high-risk populations (Curtis, personal communication) found an effect estimate for DMPA use (AHR=1.73, 95% CI 1.28-2.34) [13] similar to what we report in this reanalysis.

Our finding of no overall increase in HIV risk among COC users is in agreement with most previous longitudinal studies. Two of the 12 previous prospective studies examining COC use and HIV acquisition found a significantly increased risk of HIV associated with COC use [13, 23] while ten [15-17, 20, 21, 24-28] did not.

We found that the association between hormonal contraceptive use and HIV risk was modified by age. Young women using DMPA and COCs were at increased HIV risk compared to young women not using hormonal contraception. A similar age interaction was found in a study of injectable contraception and HIV acquisition conducted in South Africa[18]. However, no age interaction was found in the Mombasa sex worker study as similar raised effect estimates were seen for DMPA and COC users in both younger and older age groups (personal communication, Baeten). While the mechanism for this age interaction is not clear, it is plausible that physiologic differences between younger and older women could interact with hormonal contraception. For example, more young women and women taking COCs have cervical ectopy and the size of ectopy is larger among these groups [29-31]. It is also possible that differences in local or systemic immunity between younger and older women could account for these findings as hormonal contraception can also affect immune function [32-36]. Alternatively, our ability to accurately measure risk behaviors and thus control for confounding could differ between younger and older women.

We also confirmed the effect modification of the HC-HIV relationship by HSV-2 infection status reported in the original study manuscript [1]. The interaction between hormonal contraceptive use and HSV-2 serostatus was not replicated in the Mombasa sex worker study. In that study the hazard ratio for DMPA use among HSV-2 negative women was very high but the power to detect a modification effect was low due to small numbers of HSV-2 negative women [13]. No other studies have evaluated the effect of HSV-2 infection status on hormonal contraception and HIV acquisition.

We noted that although pregnancy was not found to be a significant risk factor for HIV acquisition in this study [37], it remains an important analytic issue. Because most pregnancies occurred in the non-hormonal group, censoring pregnancies from analyses or considering pregnancy as a time-varying confounder would likely introduce bias or increase the variability of estimates due to informative censoring or exchangeability concerns. Thus, analyses involving pregnancy should be further explored using alternative statistical approaches.

While the results of this reanalysis are not definitive, and should be carefully examined through additional research, if confirmed, they would have wide-ranging implications for

family planning provision in Sub-Saharan Africa. First, many family planning programs in Sub-Saharan Africa are organized primarily to provide hormonal contraception, especially COCs and DMPA. Provision of additional family planning methods such as IUDs at many family planning service provision points would require additional training and supervision and intensified management of commodities. Additionally, outreach of family planning services to rural areas is currently being promoted and implemented through community-based distribution of DMPA by lower-level service providers. This strategy would need reconsideration. Finally, much HIV prevention research targeting women assumes low numbers of women becoming pregnant (to preserve initial randomization and study power). Many studies strongly promote DMPA and COC use to achieve this goal. Research studies may need to revisit this strategy and offer alternative contraceptive options, such as IUDs, to achieve low pregnancy rates.

In summary, our reanalysis of the HC-HIV Study database using marginal structural modeling should reduce bias in the initial study findings. We found that DMPA but not COC use was associated with increased HIV acquisition overall. Young and HSV-2 negative women using hormonal contraception, particularly DMPA, were at increased HIV risk and may need alternative, highly effective contraceptive options to limit their fertility. In addition, promotion of condoms and monogamous relationships among hormonal contraceptive users and their partners needs to be actively implemented.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Adjusted Hazard Ratios (AHR) for HIV Acquisition by Contraceptive Group: Original Analysis and Marginal Structural Modeling (MSM) Reanalysis

Factor	Adjusted Hazard Ratio (95% CI)					
	Original Analysis[1]	P	New Data Structure[2] (No Weights)	P	MSM Reanalysis[2] (With Weights)	P
Contraceptive group						
Non-HC	1.00		1.00		1.00	
COC	0.99 (0.69, 1.42)	0.94	1.05 (0.73, 1.52)	0.78	1.19 (0.80, 1.76)	0.39
DMPA	1.25 (0.89, 1.78)	0.20	1.25 (0.89, 1.77)	0.20	1.48 (1.02, 2.15)	0.04

[1] Adjusted for time-varying contraceptive group, site, living with partner, age, time-varying participant behavioral risk, time-varying primary partner risk, time-varying coital frequency and time-varying consistent condom use.

[2] Adjusted for time-varying contraceptive group, site, living with partner, age, baseline participant behavioral risk, baseline primary partner risk, baseline coital frequency and baseline any condom use.

Table 2

HIV Incidence Rates and Adjusted Hazard Ratios for Incident HIV Infection by Age group, Enrolment HSV-2 Infection Status, and Contraceptive Exposure Group: Marginal Structural Modeling (MSM) Reanalysis[1]

	N/wy (incidence rate per 100wy)	Adjusted Hazard Ratio (95% Confidence Interval)	P-value
Age group: ≤ 24			
No HC use	33/1475 (2.2)	1.00	
COC	38/1035 (3.7)	2.02 (1.15, 3.55) [2]	0.014
DMPA	47/1079 (4.4)	2.76 (1.62, 4.72) [2]	<0.001
Total	118/3588 (3.3)	NA	
Age group: > 24			
No HC use	41/1332 (3.1)	1.00	
COC	25/1367 (1.8)	0.73 (0.42, 1.26) [3]	0.258
DMPA	29/1489 (1.9)	0.81 (0.48, 1.39) [3]	0.448
Total	95/4187 (2.3)	NA	
HSV-2 negative at enrolment			
No HC use	15/1454 (1.0)	1.00	
COC	21/1136 (1.8)	2.06 (0.87, 4.92) [4]	0.102
DMPA	24/1143 (2.1)	4.49 (1.98, 10.17) [4]	<0.001
Total	60/3732 (1.6)	NA	
HSV-2 positive at enrolment			
No HC use	59/1309 (4.5)	1.00	
COC	42/1233 (3.4)	1.07 (0.69, 1.65) [5]	0.772
DMPA	51/1371 (3.7)	1.03 (0.67, 1.59) [5]	0.887
Total	152/3912 (3.9)	NA	

[1] Adjusted for time-varying contraceptive group, site, living with partner, age, baseline participant behavioral risk, baseline primary partner risk, baseline coital frequency and baseline any condom use.

[2] Contraceptive exposure based on 42959 months and 116 infections.

[3] Contraceptive exposure based on 50192 months and 95 infections.

[4] Contraceptive exposure based on 44711 months and 58 infections.

[5] Contraceptive exposure based on 46863 months and 152 infections.