Published in final edited form as:
J Acquir Immune Defic Syndr. 2009 December ; 52(5): 581–587.

Hormonal Contraception and Metabolic Outcomes in Women with or at Risk for HIV Infection

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Abstract

Introduction—The use of hormonal contraception (HC) is increasing in HIV-infected women. Both HC and HIV infection have been associated with adverse metabolic outcomes. We investigated the association of progestin-only and combined (estrogen/progestin) HC with disorders of glucose and lipid metabolism in HIV-infected and uninfected women.

Methods—Linear mixed models evaluated the association of HC type with fasting HDL, LDL, triglycerides, the homeostasis model assessment estimate of insulin resistance (HOMA-IR), and glucose in 885 HIV-infected and 408 HIV-uninfected women from the Women's Interagency HIV Study seen between October 2000 and September 2005.

Results—Compared to non-HC users, progestin-only HC was independently associated with lower HDL (-3mg/dL;95% confidence interval[CI]:-5,-1 in HIV-infected and -6mg/dL;95% CI:-9,-3 in HIV-uninfected women), greater HOMA (+0.86;95% CI:0.51,1.22 and +0.56;95% CI:0.12,1.01). Combined HC was associated with higher HDL(+5mg/dL;95% CI:2,7 and +5mg/dL;95% CI:3,7).

Conclusion—Progestin–only HC is associated with lower HDL and greater HOMA-IR than non-HC users. Combined HC may be preferred in HIV-infected women of reproductive age at risk for cardiovascular disease, but interactions with antiretroviral therapy that may impair contraceptive efficacy have been reported. Alternative HC methods that minimize adverse outcomes but maintain efficacy require further study.

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Keywords

HIV/AIDS; hormonal contraception; Depo Provera®; HDL; triglycerides

Introduction

Hormonal contraception (HC) is an issue of growing importance to HIV-infected women, most of whom are of reproductive age.[1] In the US, most HIV-infected individuals younger than 25 years of age are women,2 and the prevalence of HIV infection among women in this age group is increasing.2 Therefore, availability of effective, reversible birth control is crucial. While barrier contraception is central to the prevention of HIV transmission, these methods are less effective as contraceptives, having higher failure rates than, for example, intrauterine devices or hormonal contraceptives.3

In the general population, hormonal contraceptive use has been associated with an increased risk of metabolic dysregulation, especially lower serum high density lipoprotein (HDL) concentrations, hypertriglyceridemia, insulin resistance, and elevated serum glucose concentrations.[4-6] HIV disease has been associated with a similar pattern of metabolic dysregulation, and specific antiretroviral drugs may further worsen hypertriglyceridemia, insulin resistance, and glucose tolerance. HC may thus represent an additional risk factor for metabolic dysfunction in HIV-infected women.7 However, few if any studies have explored the impact of HC on metabolic outcomes in the context of HIV infection.

The aim of our study was to investigate the association of progestin-only HC (depot medroxyprogesterone acetate (DMPA), levonorgestrel implants) and combined HC (pill or patch containing estrogen and progestin) with disorders of glucose and lipid metabolism in an ethnically diverse cohort of HIV-infected and uninfected women. The outcomes of interest included fasting HDL, low density lipoprotein (LDL), HDL, triglycerides, glucose and insulin resistance as estimated by HOMA-IR.

Methods

Study population

Participants were HIV-infected and uninfected women enrolled in the Women's Interagency HIV Study (WIHS), an ongoing multicenter longitudinal cohort study of the progression of HIV infection in women. A total of 3766 women (2791 HIV-infected and 975 HIV-uninfected) were enrolled in either 1994-5 (n=2623) or 2001-2 (n=1143) from six sites: Bronx/Manhattan, Brooklyn, Washington D.C., Chicago, Los Angeles, and the San Francisco Bay Area. The seropositive cohort reflected the characteristics of the HIV/AIDS epidemic in US women.[8] The HIV-uninfected women were similar to the HIV-infected women in sociodemographic characteristics and HIV risk factors. The recruitment methods and baseline characteristics of enrollees have been reported elsewhere.[8, 9] Institutional review boards approved all protocols and informed consent forms, which were completed by all study participants. A structured interview, physical examination, and the collection of blood, urine, and cervicovaginal fluid samples were performed at each semiannual visit.

Beginning in October 2000, serum specimens for glucose, insulin, and lipids were collected after at least an 8-hour fast. This analysis reports on 875 HIV-infected and 406 HIV-uninfected women with fasting glucose, insulin, and lipid data available on at least one visit between October 2000 and September 2005 who met the following study criteria: 1) between the ages of 18 and 52 years and reported being post-menarchal and premenopausal for the duration of the study; 2) did not self-report a history of hysterectomy; and 3) did not have diabetes (i.e.

did not have a fasting plasma glucose greater than 125 mg/dL, report a diagnosis of diabetes, or report antidiabetic medication use). Women who met criteria for diabetes during follow up, were excluded from analysis beginning with the first visit diabetes was diagnosed. Women who became pregnant during follow-up (n=22) were excluded for the duration of the pregnancy and were then reincorporated into the study at their first post-delivery semiannual study visit. Among the 22 women who became pregnant, 34 pregnancies were reported (29 among HIV-uninfected women, 5 among HIV-infected). Of these, 20 occurred within 6 months of reported HC use (15 among HIV-uninfected women and 5 among HIV-infected).

Because the metabolic effects of combined estrogen and progestin contraceptives may differ significantly from those of progestin-only methods, those women using combined HC were evaluated separately from those using progestin-only HC. Both of these groups were compared with women who either used non-HC or did not contracept. Women could contribute to more than one contraceptive group during the course of the study as many of these women changed contraceptive method over time. Twenty-two of the 113 women who reported using combined HC at baseline remained on this method throughout the study period, as did 16 of the 133 women who reported using progestin-only HC at baseline. Forty-eight women changed HC method over the course of the study, and some changed methods more than once. There were 22 changes from a progestin-only to a combined HC method, 17 from combined to progestin-only HC, and 19 changes from one type of combined HC to another. The baseline visit for each participant was the first visit for which fasting laboratory information was available.

Statistical analysis

Within HIV serostatus groups, the association between the variables of interest and contraceptive use were compared and tested for statistical significance using a t-test for continuous characteristics, and chi square or Fisher's exact test for categorical characteristics. Variables with skewed distributions were normalized by transformation or categorized. The Wilcoxon rank sum test and Fisher's exact test were used when non-normality persisted.

Variables that were not normally distributed were transformed, if possible. Among HIV-uninfected women using progestin-only HC or comparators, triglycerides, HOMA, and glucose were log transformed. For HIV-uninfected women using combined HC and comparators, BMI, triglycerides, HOMA, glucose, and insulin were log transformed. Among HIV-infected women, for those using progestin-only HC and comparators, HDL was square root transformed, and triglycerides, LDL, waist circumference, hip circumference, glucose, and HOMA were log transformed. For those using combined HC and comparators, HDL was square root transformed, and triglycerides, HOMA, glucose, insulin, waist and hip circumference were log transformed. Neither AST, ALT, nor HIV viral load could be normalized through transformation for any of the applicable groups, thus all were categorized by interquartile ranges. Among HIV-infected women using progestin-only HC and comparators, CD4 count could also not be normalized through transformation, and interquartile ranges were used to categorize this variable.

Random coefficient multivariable linear mixed regression models were used to identify factors associated with HDL, LDL, triglycerides, HOMA-IR and glucose. HIV-infected and HIV-uninfected women were analyzed separately, as were those who used progestin-only HC and those using combined HC.

A review of the literature guided the selection of demographic and clinical covariates with previously demonstrated independent effects on lipid, insulin, and glucose levels. Only those covariates with a statistically significant ($P \leq 0.05$) unadjusted association with the outcome of interest (i.e., HDL, LDL, triglycerides, HOMA-IR, and glucose) were included in the analysis. Those variables that did not retain significance at the $P<0.05$ level in a multivariable model

were removed by backwards selection. During model selection, parameter estimates were obtained by maximum likelihood; parameter estimates in the final model were obtained by restricted/residual maximum likelihood.

Missing data is one of the central problems in longitudinal research.[10] We, therefore, used multiple imputation[11] via the SAS procedure MI. The percent of missing data ranged from less than 1% to 38%. By using multiple imputation, we were able to include all observations in our analysis. Imputation of the outcomes using the predictors under study minimizes bias in the relationship between predictors and outcomes.[12, 13]

Ten imputed data sets were created using all the variables considered in these analyses.[14] The following variables were used to impute the missing data: time (visit), progestin-only contraceptive use, HDL, LDL, triglycerides, HOMA-IR (or insulin in the glucose models), glucose, aspartate aminotransferase, alanine aminotransferase, waist circumference, hip circumference, HIV serostatus, age, race, education, employment, income, insurance, family history of diabetes, use of medications for dyslipidemia, alcohol use, and marital status. Body mass index was not included as it was less strongly associated with the outcomes of interest than either waist or hip circumference. Analyses of the imputed data sets were combined using Rubin's rule,[15] as implemented in the SAS procedure MIANALYZE.

Subgroup analysis

A subgroup analysis was conducted in HIV-infected women to evaluate the role of HIV-specific factors including CD4 count, HIV viral load, and antiretroviral therapy use (defined as current use of nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and/or protease inhibitors (PI)) on the relationship between HC and lipid levels, HOMA-IR, and glucose.[16] The same approaches to missing data and model building were used as described above. SAS version 9.1 was used for all statistical analyses.

Results

Among the HIV-infected and uninfected women included in the analysis, those who used HC were younger than those who did not (Table 1). HIV-infected and HIV-uninfected women who used combined HC were more likely to be white, and to be employed, and less likely to be current smokers than women who used progestin-only HC or non-HC/no contraception. Among HIV-uninfected women, those who used combined HC were more likely to be insured than women who did not. Among HIV-infected women, those who used combined HC were less likely than others to have a family history of cardiovascular disease and to be HCV seropositive. The CD4 count at time of entry into the study among women who used combined HC was higher than in those who used progestin-only HC or non-HC/no contraception. There was little difference in the use of antiretroviral therapy (ART) by drug class among the three contraceptive groups.

At baseline, HIV-infected as well as uninfected women who used progestin-only HC were more likely to have serum HDL concentrations less than 40 mg/dL than women using other forms of contraception (Table 2). In addition, among HIV-infected women, those using progestin-only HC were more likely to have triglycerides greater than or equal to 200 mg/dL than women using other forms of contraception. However, more than two-thirds of the women in all of the contraceptive groups had serum triglyceride concentrations in the normal range. There were no statistically significant differences in the percentages of women with abnormal glucose, HOMA-IR, or LDL.

In the multivariable model controlling for other clinical and sociodemographic variables, compared to women who did not contracept or who used non-HC, progestin-only HC was

associated with lower HDL and higher HOMA-IR in HIV-infected and HIV-uninfected women (Table 3). Combined HC was associated with higher HDL in HIV-infected and HIV-uninfected women. The association of combined HC with HOMA-IR was not statistically significant in either the HIV-infected or HIV-uninfected women. The association of combined and progestin HC with triglycerides, LDL, and glucose was not statistically significant with the exception of the small but statistically significant association of progestin HC use with lower glucose in HIV-uninfected women.

We next examined the association of HC and changes over time in these metabolic outcomes. In the multivariable models of the association of progestin-only HC, there was little change in HDL over time among HIV-infected women (change in HDL per 6 month visit: 0.01 mg/dL; 95% CI: -0.16, 0.19 mg/dL; p=0.87). In HIV-uninfected women, there was a small but statistically significant decrease in HDL over time (change in HDL per 6 month visit: -0.32 mg/dL; 95% CI: -0.59, -0.06 mg/dL; p=0.02). There was also little change in HOMA-IR over time among both HIV-infected and uninfected women (change in HOMA-IR per 6 month visit: -0.03; 95% CI: -0.06, 0.003; p=0.07; -0.02; 95% CI: -0.06, 0.02; p=0.32, respectively). In the multivariable models examining the association of combined HC, there was no statistically significant change in HDL over time, either among HIV-infected or HIV-uninfected women (change in HDL per 6 month visit: -0.03 mg/dL; 95% CI: -0.27, 0.22 mg/dL; p=0.80; change in HDL per 6 month visit:0.06 mg/dL; 95% CI: -0.12, 0.25 mg/dL; p=0.49, respectively). Neither progestin-only nor combined HC was statistically significantly associated with serum triglycerides, LDL or glucose in the longitudinal analyses (data not shown).

Among the HIV-infected women, addition of HIV-specific covariates to the multivariate model strengthened the association between progestin-only HC and HDL (estimate remained constant: -3 mg/dL per 6 month visit, p=0.021 to p=0.0052 after addition of HIV-specific covariates), and HOMA-IR (estimate increased: 1.13 per 6 month visit to 1.15 per 6 month visit, p<0.0001 for both). For the combined HC model, addition of HIV-specific covariates did not strengthen the associations between combined HC and any of the metabolic outcomes (data not shown).

The results using a complete-case analysis were similar, albeit less precise, to those presented using multiple imputation.

Discussion

In our large cohort of ethnically diverse HIV-infected and uninfected women, we found that progestin-only and combined HC impact metabolic outcomes differently. Progestin-only HC was associated with lower HDL and greater HOMA-IR in HIV-infected and uninfected women. On the other hand, combined HC was associated with higher HDL in HIV-infected and uninfected women. Addition of HIV-specific variables strengthened the association between progestin-only HC and lower HDL and higher HOMA-IR in HIV-infected women; the association between combined HC and any of the metabolic outcomes was not altered.

Our findings that progestin-only HC was associated with lower HDL are consistent with published studies in HIV-uninfected populations.[17] 18 19-22 While we noted that the HDL trajectory decreased over time in HIV-uninfected women, in particular, the clinical significance of the small, but significant six-month average decreases in HDL is unclear. Whether HDL levels improve once HIV-infected women discontinue progestin-only HC or whether NNRTI use (which has been associated with increased HDL23) might mitigate the negative effects of progestin-only HC on HDL levels also needs to be studied.

It was not surprising that there was little difference in LDL between hormonal contraceptive users and non-users. LDL is primarily influenced by the estrogen component in combined

hormonal contraceptives and less by progestin,[5] but even with combined hormonal contraceptive use, alterations in LDL levels are often not seen. However, some studies indicate that low-dose oral contraceptive pills are associated with increased proportions of small, dense LDL subfractions, most likely because of the increase in TG levels.[24] This change in the type of LDL particle is concerning as the small, dense LDL subfractions are more easily oxidized and thus more atherogenic than the normal LDL particles.

It was somewhat unexpected that serum triglyceride concentrations did not differ in HIV-infected or uninfected women between progestin users and non-users as DMPA has been associated with a mild increase in triglycerides in a prior study.[25] Our sample size may have been too small to detect a similar increase.

Progestin-only contraceptives such as DMPA and levonorgestrel implants have been consistently associated with worsening insulin resistance[19, 25-27] and with unfavorable alterations in insulin metabolism in general,[19-22] which are consistent with our findings. Some authors have also shown that longer exposure to these progestin-only methods may lead to more severe dysregulation of glucose levels and insulin responses.[19, 20, 28] We were unable to adequately assess the duration of exposure to HC with disorders in glucose metabolism because of frequent changes in contraceptive methods and the small sample size. This study should be re-evaluated with a larger sample size which might be available through collaborations among HIV observational cohorts that collect contraceptive and metabolic data. Patterns of contraceptive use should also be addressed to determine if frequent changes of contraceptive methods are characteristic of other cohorts as well.

Glucose, on the other hand, has been found to be adversely affected by both combined hormonal and progestin-only contraception. Formulations using higher doses of estrogen (50 mcg) have a more negative impact on insulin action and glucose metabolism than formulations that use lower doses of estrogen (20-35 mcg). With regards to the progestin component, Godsland and colleagues,[29] Wynn & Godsland,30 and Wynn and colleagues31 have consistently found that levonorgestrel containing oral contraceptive pills, regardless of the dose, produce consistently worse glucose outcomes than other progestins, even when controlling for estrogen dose. We were not powered to explore the impact of specific estrogen/progestin combinations on glucose outcomes in our study, thus the variety of progestins and estrogen doses used by study participants may have masked the impact of any specific combination. Interestingly, among HIV-uninfected women using progestin-only contraception, serum glucose levels were lower than among non-progestin users; the clinical significance of this decrease is unclear.

Our findings are important because research in the general population has demonstrated that the risk for metabolic dysfunction associated with HC use may be more pronounced in women with additional risk factors for metabolic dysfunction, including race/ethnicity[32] and past medical history.[33] Our study suggests that HIV infection is yet another of these additional risk factors. Furthermore, HC is becoming more common among HIV-infected women. In a retrospective cohort study of an urban clinic in New Orleans,[34] Clark and colleagues found that the use of DMPA in HIV-infected women increased from 9% between 1994-1996, to almost 17% between 2000-2002. As larger numbers of HIV-infected women choose HC and with the advent of newer progestin contraceptives, further study will be needed to evaluate the impact of these contraceptives on metabolic parameters and long-term cardiovascular risk.

There are limitations to the present work. We assumed that the missing data were missing at random, conditional on the set of measured variables included in this analysis. Given these assumptions, we used multiple imputation, which allowed maximal use of the observed information, to strengthen our results as opposed to using only those subjects with complete data for the variables of interest.[35] Confidence in our outcomes was reinforced by the fact that

the complete-case analyses were not different from the imputed analyses. Because this is an observational study, our results may be due to confounding by unmeasured factors. However, the richness of the WIHS dataset allowed us to assess and control for a wide variety of covariates that are commonly associated with metabolic outcomes. We were not able to determine the association of the specific types of progestin-only HC with metabolic outcomes, due to the small number of levonorgestrel implant users (n=3). We were also not able to assess the effects of the different antiretroviral medications on metabolic parameters, relative to HC type. Furthermore, while we observed that a small percentage of women became pregnant soon after initiating HC, we were not able to assess whether this was due to lack of adherence or to failure due to lower hormone levels. Further study is needed to determine whether pharmacokinetic alterations in serum contraceptive hormone levels (due to a possible interaction with antiretroviral therapy) is associated with contraceptive failure and increased unplanned pregnancies. Even though the WIHS with its large, ethnically diverse sample of women was the ideal cohort for this study, data on duration of HIV infection and duration of ART use is limited, and the sample sizes for women using either progestin-only or combined HC were small. Combining a variety of cohorts that collect this information on women would provide one option for further pursuing these studies.

Despite these study limitations, the longitudinal study design enabled us to assess the outcome trajectories over time in the context of the predictor variable and the covariates, which provided a stronger analysis than would have been possible with a cross-sectional design.

In conclusion, progestin-only HC is associated with negative metabolic outcomes in reproductive age women. In HIV-infected women, adjustment for HIV-related factors strengthened these negative associations, suggesting that progestin-only HC should be used with caution in HIV-infected women at risk for cardiovascular disease. Combined HC may be preferable in terms of metabolic risk, but interactions with both NNRTIs and PIs have been reported that may impair contraceptive efficacy.[36] Further research is needed to elucidate the mechanism by which HC might impact metabolic outcomes in HIV-infected women, and whether newer, alternative HC methods, such as the levonorgestrel intrauterine device, might be preferable, as it appears to exert its effect locally. HIV-infected women and their health care providers need to be aware of possible side effects of the different contraceptive formulations so that informed contraceptive choices can be made and appropriate follow-up care provided.

Acknowledgments

The authors would like to acknowledge the contributions of Michael Schneider, MS, and Susan Richman, MD to this research.

Funding: NIH F31NR009886

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington, DC Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases (UO1-AI-35004, UO1-AI-31834, UO1-AI-34994, UO1-AI-34989, UO1-AI-34993, and UO1-AI-42590) and by the National Institute of Child Health and Human Development (UO1-HD-32632). The study is co-funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. Funding is also provided by the National Center for Research Resources (UCSF-CTSI Grant Number UL1 RR024131). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. Dr. Tien is supported by the National Institute of Allergy and Infectious Diseases through K23 AI 66943. This material is also the result of work supported with resources and the use of facilities at the San Francisco, CA and the West Haven, CT Veterans Affairs Medical Center.

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J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2010 December 1.

Table 1

Sociodemographic and clinical variables at baseline comparing HIV-infected and HIV-uninfected women. (N=1293)*

	HIV-infected (N=875)				HIV-uninfected (N=406)			
	Combined hormonal contraception user (n=55)	Progestin-only user (N=88)	Non-hormonal contraception or no contraception (n=735)	p-value	Combined hormonal contraception user (n=58)	Progestin-only user (N= 45)	Non-hormonal contraception or no contraception (n=299)	p-value
Age (years)**	33 ± 8	31 ± 7	37 ± 7	<0.0001	28 ± 6	28 ± 7	33 ± 8	<0.0001
Race								
White, non-hispanic or other***	13 (24)	7 (8)	71 (10)	0.0005	19 (33)	6(13)	38 (13)	0.004
Hispanic***	16 (30)	38 (44)	215 (29)		12 (27)	14 (24)	85 (28)	
Black, non-hispanic***	25 (46)	41 (48)	449 (61)		25 (43)	27 (60)	176 (59)	
Employed***	28 (52)	27 (31)	263 (36)	0.027	38 (66)	15 (33)	146 (49)	0.005
Insured***	50 (94)	81 (94)	639 (87)	0.055	36 (80)	38 (66)	177 (59)	0.02
Current smoker***	11 (21)	35 (41)	341 (47)	0.001	12 (21)	22 (49)	154 (52)	<0.0001
Any alcohol consumption***	29 (55)	40 (47)	370 (51)	0.63	39 (67)	24 (55)	191 (64)	0.39
Family history of Type 2 diabetes***	10 (26)	18 (29)	192 (34)	0.46	16 (36)	6(18)	83 (36)	0.13
Family history of cardiovascular disease***	17 (44)	34 (55)	379 (67)	0.004	25 (56)	21 (64)	149 (64)	0.54
HCV seropositive***	5 (9)	12 (14)	167 (23)	0.014	6(11)	3(7)	36 (12)	0.57
Body mass index (kg/m^2)****	26 (24, 30)	28 (25, 31)	27 (24, 32)	0.52	26 (23, 32)	29 (25, 34)	27 (23, 33)	0.41
Waist circumference(cm)****	86 (78, 102)	88 (81, 97)	87 (79, 96)	0.80	82 (72, 94)	88 (79, 104)	86 (76, 98)	0.15
Hip circumference (cm)****	102 (92, 110)	101 (93, 107)	199 (92, 109)	0.78	100 (92, 110)	102 (95, 115)	100 (94, 112)	0.78
Current CD4 (cells/mm^3)****	526(387,746)	431 (317, 690)	431 (260, 609)	0.004	NA	NA	NA	NA
Current HIV RNA**** (copies/ml)	600(80,4600)	445 (80, 4900)	1000 (80, 13000)	0.15	NA	NA	NA	NA
NRTI use***	32 (59)	56 (65)	435 (59)	0.58	NA	NA	NA	NA
NNRTI use***	10 (19)	30 (35)	196 (27)	0.09	NA	NA	NA	NA
PI use***	20 (37)	24 (28)	204 (28)	0.35	NA	NA	NA	NA

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*
Percents may not sum to 100 due to missing data and rounding

**
Mean±SD

***
N(%)

****
Median(IQR)

NRTI = nucleoside reverse transcriptase inhibitor, NNRTI= non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor

Table 2

Metabolic Parameters at Baseline by HIV Status and Type of Contraceptive Use

	HIV-infected				HIV-uninfected			
	Contraception				Contraception			
	Combined hormonal	Progestin-only	Non-hormonal or none	P-value	Combined hormonal	Progestin-only	Non-hormonal or none	P-value
HDL (mg/dL)				0.05				0.01
<40 mg/dL	14 (25)	38 (45)	333 (34)	-	6 (10)	10 (24)	43 (10)	-
40-59 mg/dL	25 (46)	35 (42)	429 (44)	-	29 (47)	24 (59)	220 (52)	-
≥ 60 mg/dL	16 (27)	10 (12)	207 (21)	-	27 (44)	7 (17)	161 (38)	-
HOMA				0.25				0.53
≤ 2.5	36 (69)	45 (55)	573 (60)	-	44 (71)	25 (63)	258 (63)	-
>2.5	16 (31)	37 (45)	383 (40)	-	18 (29)	15 (38)	146 (36)	-
Triglycerides (mg/dL)				0.044				0.29
< 150 mg/dL	41 (75)	58 (70)	719 (74)	-	57 (92)	35 (85)	382 (90)	-
150 – 199 mg/dL	6 (11)	7 (8)	144 (15)	-	4 (6)	2 (5)	27 (6)	-
≥ 200 mg/dL	8 (15)	18 (22)	110 (11)	-	1 (2)	4 (10)	15 (4)	-
LDL (mg/dL)				0.13				0.26
< 100 mg/dL	22 (41)	42 (49)	506 (53)	-	31 (50)	19 (46)	225 (53)	-
100 – 129 mg/dL	20 (37)	20 (24)	291 (31)	-	25 (40)	11 (27)	130 (31)	-
130 – 159 mg/dL	11 (20)	13 (15)	111 (12)	-	4 (6)	9 (22)	49 (12)	-
≥ 160 mg/dL	1 (2)	6 (7)	38 (4)	-	2(3)	2(5)	20 (5)	-
Glucose (mg/dL)				0.26				0.1
< 100 mg/dL	54 (98)	77 (92)	898 (92)	-	55 (89)	41 (100)	390 (92)	-
100 – 125 mg/dL	1 (2)	6 (7)	76 (8)	-	7 (11)	0	34 (8)	-

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Table 3

Association of Combined Hormonal Contraception and Progestin-only Contraception with Lipid, Glucose, and HOMA-IR by HIV Status

	HIV-infected				HIV-uninfected			
	Combined HC N=55		Progestin-only HC N=88		Combined HC N=58		Progestin-only HC N=45	
	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
HDL	5 (2, 7)	0.001	-3 (-5, -1)	0.02	5 (3, 7)	<0.0001	-6(-9, -3)	<0.0001
HOMA	0.15 (-0.31, 0.62)	0.50	0.86 (0.51, 1.22)	<0.0001	0.12 (-0.17, 0.42)	0.41	0.56 (0.12, 1.01)	0.01
Triglycerides	2 (11, 17)	0.75	-12 (-24, 0.15)	0.056	6 (-2, 13)	0.14	-5 (-15, 5)	0.29
LDL	-3 (-10, 5)	0.46	3 (-2, 7)	0.28	2 (-1, 6)	0.21	1 (-5, 7)	0.67
Glucose	0.42 (-1, 2)	0.58	0.12 (-1, 2)	0.88	0.45 (-1, 2)	0.42	-2 (-4,-0.33)	0.02

Reference group: Non-hormonal contraceptive use or no contraception.

The following variables, in addition to time and contraceptive use, were controlled for in the final models:
HIV-infected on combined hormonal contraception: HDL: waist circumference, hip circumference, triglycerides, HOMA-IR, age, race, CD4 count, viral load, NNRTI-use, PI use; HOMA: waist circumference, hip circumference, family history of type 2 diabetes, HCV, ALT; Triglycerides: waist circumference, age, employment, race, ALT, HOMA-IR, CD4 count, NRTI-use, PI use; LDL: waist circumference, HOMA-IR, employment, HCV, income, AST, CD4 count, viral load, PI-use; Glucose: waist circumference, age, insulin, alcohol use, family history of type 2 diabetes, viral load.
HIV-infected on progestin-only contraception: HDL: waist circumference, hip circumference, triglycerides, HOMA-IR, age, education, family history of type 2 diabetes, alcohol use, NNRTI-use, viral load; HOMA: waist circumference, hip circumference HCV, ALT, NRTI-use, NNRTI-use; Triglycerides: waist circumference, hip circumference, age, employment, race, HOMA-IR, use of dyslipidemic medications, NNRTI-use, PI-use, viral load; LDL: waist circumference, HCV, AST, PI-use, viral load; Glucose: waist circumference, age, insulin, family history of type 2 diabetes, viral load
HIV-uninfected on combined hormonal contraception: HDL: waist circumference, triglycerides, HOMA-IR, race, alcohol use; HOMA: waist circumference, ALT, employment, alcohol use; Triglycerides: waist circumference, age, HOMA-IR, HCV, current smoker, use of dyslipidemic medications, race; LDL: waist circumference; Glucose: hip circumference, age, insulin, family history of type 2 diabetes, use of dyslipidemic medications
HIV-uninfected on progestin-only contraception: HDL: waist circumference, age, triglycerides, HOMA-IR, alcohol use; HOMA: waist circumference, hip circumference, ALT, education, alcohol use; Triglycerides: waist circumference, hip circumference, age, HOMA-IR, current smoker, use of dyslipidemic meds, race; LDL: waist circumference, HCV, alcohol use; Glucose: waist circumference, age, insulin.