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Effect of hormonal contraceptive use on virologic response to antiretroviral therapy among women in Rakai, Uganda

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Abstract

Objective: Effective contraceptive counseling for HIV-infected women on antiretroviral therapy (ART) is complicated by the fact that little is known about potential interactions between hormonal contraception (HC) and ART, which share common hepatic metabolic pathways. In theory, these drugs may interact to decrease ART efficacy, decrease HC efficacy, or increase side effects. Decreased ARV drug levels could lead to drug resistance, treatment failure, and potentially increased mortality. In addition, regimen complexity or pill burden may contribute to non-adherence of either ART or HC regimens, and could thus lower efficacy of either regimen. Our objective was to strengthen the evidence base regarding the effect of HC on virologic response to ART among HIV+ women in Rakai, Uganda.

Design: Retrospective analysis of clinical and questionnaire data from 433 Ugandan women initiating ART.

Methods: Using a modified Poisson regression model, we assessed the effect of HC on failure to suppress viral load at 12 months after ART initiation or ART regimen change or death within one year of ART initiation among sexually active women in Rakai, Uganda. We also assessed whether HC use was associated with poorer adherence to ART.

Results: We did not find that HC use was associated with increased risk of failure, nor did we find that HC use was associated with poorer adherence to ART.

Conclusions: Our results are consistent with current WHO recommendations for HC use among HIV+ women on ART.

Keywords: family planning, hormonal contraception, HIV, antiretroviral therapy, drug interactions, Uganda

Introduction

Use of an effective contraceptive method increases women's reproductive control, reduces the demand for abortion, and decreases maternal morbidity and mortality.[1] When used by HIV-infected (HIV+) women who wish to avoid pregnancy, contraception is also an effective way to reduce mother-to-child HIV transmission.[2] Hormonal contraceptives (HC) are among the most effective methods of pregnancy prevention. The World Health Organization recommends that HIV+ women, including those on antiretroviral therapy (ART), can generally use HC with two exceptions: (1) women on ritonavir-boosted protease inhibitors are not recommended to use certain HC methods due to concerns about potential decreased contraceptive effectiveness, and (2) women with AIDS who are not clinically well on ART are not recommended to receive insertion of an intrauterine device (IUD) due to concerns about pelvic inflammatory disease.[3] For women on ART and HC, consistent condom use is still recommended to prevent HIV transmission to sexual partners and to provide backup protection against pregnancy.

Effective contraceptive counseling for HIV+ women on ART is complicated by the fact that little is known about potential interactions between HC and ART, which share common hepatic metabolic pathways. In theory, these drugs may interact to decrease ART efficacy, decrease HC efficacy, or increase side effects.[4] Decreased ARV drug levels could lead to drug resistance, treatment failure, and potentially increased mortality. Encouragingly, CD4+ counts and HIV viral loads (VL) do not appear to be affected by HC use in women on ART in the United States.[5, 6] Furthermore, HC does not appear to be associated with clinically significant changes in levels of saquinavir,[7] zidovudine,[8] nevirapine, efavirenz or nelfinavir in pharmacokinetic studies.[9] The potential for poorer adherence to ART among women on other

medications including HC should be considered in studies examining potential interactions between HC and ART, since regimen complexity or pill burden may contribute to non-adherence of either regimen, and could thus lower efficacy of either regimen.[10] To our knowledge, the effect of HC on virologic suppression among HIV+ women on ART in sub-Saharan Africa has not been studied. Our objective was to assess the effect of HC on virologic suppression among sexually active HIV+ women on ART in Rakai, Uganda, and to examine whether HC use was associated with poorer adherence to ART.

Methods

The Rakai HIV Care Program is a community HIV care service provided to the Rakai District of Uganda, with regularly scheduled visits for patient monitoring and free drug resupply. Clients are typically seen weekly for the first month, every two weeks until month 3, and monthly until 12 months. Depending on adherence status, patients are then followed every two or three months. A variety of family planning services are available to clients, including condoms and HC. ART is provided for individuals with CD4 cell count $\leq$250 cells/mm^3 and/or WHO clinical stage IV disease, and standard first-line regimens include zidovudine or stavudine, lamivudine, and nevirapine or efavirenz. A record of drug regimens, adherence to ART, CD4 and VL measurements (performed every 6 months), contraceptive use, and pregnancies are stored in electronic clinic records. Our analytical sample was drawn from sexually active women who initiated ART within the Rakai Health Sciences Program (RHSP) HIV care program after January 10, 2006 (when we began collecting information on HC use within ART clinic records), had information at baseline on viral load (VL), and had provided consent for use of their medical records for research purposes. We excluded women diagnosed with tuberculosis within the first

year of ART, since tuberculosis treatment may impact response to ART.[11] HIV-1 viral load testing was performed using the Roche Amplicor 1.5 Monitor assay (Roche Diagnostics, Indiana, USA) with a lower limit of detection of 400 copies/mL.

We assessed the effect of HC use as reported at ART initiation on a composite failure outcome which included (a) failure to achieve virologic suppression at 12 months after ART initiation (regardless of prior suppression), defined as viral load ≥400 copies/mL, (b) switch from first-line to second-line therapy within one year (unless due to drug toxicity), or (c) death. A small proportion of women (8%, 35/433) were missing a 12-month VL measurement. For seven of these women, we imputed information using VL measurements taken 6 and 18 months after ART initiation. We assumed undetectable VL at 12 months in five women with undetectable VL at 6 and 18 months, detectable VL at 12 months in one woman with detectable VL at 6 and 18 months, and detectable VL at 12 months in one woman with undetectable VL at 6 months and a high VL (910,626 copies/mL) at 18 months. The remaining 28 women were considered lost to follow up, and a sub-analysis included loss to follow up as part of the composite failure outcome. We did not have information indicating that loss to follow up results in higher rates of virologic failure, but this sub-analysis was performed as a sensitivity test under this conservative assumption.

Use of HC was defined as an affirmative response to questions on use of either oral contraceptive pills (OCPs), injectable contraception (depo-medroxyprogesterone acetate), or hormonal implants. We assumed non-use of a method if information on that individual method was missing. We considered the following variables (measured at ART initiation) as potential

confounders: age, marital status, current pregnancy status, consistency of condom use during past six months, number of sex partners during past six months, and last CD4 measurement prior to ART initiation (taken within 0-3 months prior to ART initiation). We also performed a sub-analysis to assess whether OCPs and injectables had different effects on virologic suppression.

Since some women died or were lost to follow up prior to 12 months after ART initiation, our original analysis was unable to control for adherence to ART throughout the first year of treatment. Thus, a second analysis was restricted to women who remained alive and on ART for at least one year after ART initiation. In this analysis, exposure was defined as ever vs. never use of HC during the first year of ART treatment, and our composite outcome included failure to achieve virologic suppression or switch in ART regimen. This analysis considered age, marital status, and CD4 count at ART initiation, as well as consistency of condom use, experience of pregnancy, and number of sex partners over time, and self-reported adherence to ART at 0-6 and at 6-12 months. Adherence to ART was calculated as the average percentage of days each patient reported taking ARVs as prescribed, and this measure has been shown to reflect true adherence.[12, 13] We compared ART adherence as reported at 6 and 12 months by baseline use of injectables, OCPs or no HC method.

Statistical analysis

We calculated descriptive statistics for baseline characteristics, and examined whether HC users were significantly different from their counterparts using the nonparametric Mann-Whitney U test to evaluate differences in medians, and Pearson's chi-square or Fischer's exact test for categorical variables. Since our outcome could be considered common (>10%), we estimated

the relationship between HC use and our composite outcome using a "modified" Poisson regression model with a robust error variance to obtain prevalence risk ratios (PRR).[14] In multivariable analysis, we controlled for all factors associated with HC and the composite outcome at $p \leq 0.25$ in univariable analysis. We tested for differences in adherence by HC use using Pearson's chi-square test. All analyses were done using Stata/SE 10.1 for windows.[15] We received ethical approval for this analysis of clinical data from the Science and Ethics Committee of the Uganda Virus Research Institute and the Ugandan National Council for Science and Technology.

Results

We analyzed data from 433 female ART initiators (**Table 1**). A small proportion of women (10%) were age 18-24, over half (56%) were age 25-34, and about a third (34%) were over 35 years old. A very small proportion (5%) had never been married, but only 56% were currently married or cohabitating. The majority (87%) reported zero or one recent sexual partner, but about 8% reported two or more partners (5% had missing information). About 8% of women were pregnant at ART initiation. At baseline, half of the sample reported never using condoms, 13% reported sometimes using condoms, and 38% reported always using condoms. Women had a median CD4 cell count of 191 cells/mm^3 at baseline (taken within 0-3 months prior to ART initiation).

About 15% of women reported HC use at baseline. Among HC users, over three-quarters (77%) reported use of injectables, while the remainder reported use of OCPs. HC users were significantly less likely to be pregnant at baseline (0% vs. 9%, $p<0.01$) and to report always

using condoms (18.2% vs. 41.1%, p=0.01). We found no significant differences by HC use in age, marital status, number of recent sexual partners, or CD4 count near ART initiation at $p \leq 0.05$. Age and number of recent sexual partners were considered for potential inclusion in multivariable analysis given p-values$\leq$0.25.

Among 405 individuals with complete information, 52 (13%) met the criteria for treatment failure (**Table 2**). Failure was significantly associated with age (p=0.04), but the following variables were also considered for inclusion in multivariable analysis given p-values$\leq$0.25: marital status, condom use, number of sex partners, and CD4 count prior to ART initiation. Including the 28 women lost to follow up as failures increased the proportion meeting the criteria for failure to 80/433 women (18%). Women lost to follow up did not significantly differ on any baseline characteristics.

In univariable regression, use of any HC method at baseline was not associated with failure (PRR: 1.20, p=0.59), even when loss to follow up was included as part of the composite failure outcome (PRR: 1.28, p=0.33) (**Table 3**). When we controlled for three variables associated with both HC use at baseline and failure at $p \leq 0.25$ (age, consistency of condom use, and number of recent sexual partners), PRRs were slightly attenuated and remained non-significant (PRR: 1.10, p=0.78, PRR: 1.23, p=0.41 including losses to follow up as failures). OCP use, reported only among 15 women, appeared to be marginally associated with an increased risk of failure in univariable analysis (PRR: 2.14, p=0.09), but was not significant after controlling for age, condom use, and number of sexual partners (PRR: 1.73, p=0.26).

Next, we conducted a sensitivity analysis in which we restricted the analysis to 280 women who had a documented 6 and 12 month follow up visit after ART initiation, as well as complete information on adherence throughout the first year of ART use, to assess the relationship between ever use of HC and failure to achieve virologic suppression at 12 months or drug regimen change. As in the main analysis, age and condom use remained significantly associated with ever use of HC (**Table 4**). Ever use of HC was not significantly associated with failure in univariable analysis (PRR: 1.23, p=0.56), or after adjusting for age, consistency of condom use, number of recent sexual partners, and reported adherence at 12 months (PRR: 1.00, p=0.99). Two factors were significantly associated with virologic failure: (1) having multiple sexual partners (PRR: 2.23, p=0.04) and (2) ART adherence <95% at 6-12 months (PRR: 2.15, p=0.05). Neither OCPs nor injectables were significantly associated with failure in univariable (PRR: 1.92, p=0.24 for OCPs and PRR: 0.95, p=0.90 for injectables) or multivariable analysis (PRR: 1.22, p=0.74 for OCPs and PRR: 0.83, p=0.66 for injectables).

ART adherence appeared to improve over time. Only 28% of women reported 100% adherence 0-6 months after ART initiation, while 75% reported 100% adherence during the second half of the year. Using chi-square tests, we assessed whether adherence (at 6 and 12 months) was associated with HC use as reported 6 months prior, or as reported concurrently. We found no statistically significant differences in ART adherence for use of any HC method, or for OCPs and injectables separately (data not shown).

Discussion

We did not find that HC use was associated with increased risk of failure as measured by failure to suppress viral load at 12 months after ART initiation or regimen change or death within one

year on ART, nor did we find evidence that HC use was associated with poorer adherence to ART. Our results are consistent with current WHO recommendations for HC use among HIV+ women on ART.

We assessed virologic (as opposed to immunologic) failure, since immunologic criteria for identifying ART failure perform poorly in Rakai and immunologic failure has been shown to lag behind virologic failure.[16, 17] However, the optimal VL threshold for defining virological failure has not been determined.[18] We assessed VL at 12 months after ART initiation for two main reasons. First, adherence to ART was poor at the start of ART initiation, so using earlier (6 month) VL measurement could have limited our ability to detect any effects of potential drug interactions between ART and HC. ART adherence improved dramatically between months 0-6 (28% reporting perfect adherence) and months 6-12 (75% reporting perfect adherence). Second, given variation in individual contraceptive use over time, using a VL measurement taken much later (i.e., 18 months and beyond) could have increased the potential for exposure misclassification in our primary analysis. The overall proportion of women reporting HC use remained consistent over time: 15% reported HC use at baseline (95% CI: 12-19), 14% reported HC use at 6 months (95% CI: 10-17), and 13% reported HC use at 12 months (95% CI: 10-17) (chi-square test for trend=0.55). However, HC use over time was inconsistent in individual women. Among 78 women who ever used HC in the first 12 months after ART initiation, and who provided information at baseline, six months, and twelve months, 28% initiated HC use at 6 or 12 months, 38% discontinued HC use at 6 or 12 months, 18% fluctuated in HC use over the three visits, and only 15% reported HC use at all three visits.

Our analysis has several limitations. Data were drawn from a clinical database, which had limited variables available. We were unable to control for factors such as alcohol use, education, socioeconomic status, and parity, which may be related to use of HC, ART adherence, and virologic suppression.[19] Use of HC was self-reported, intensity and duration of HC use may have varied, and some non-users may have been exposed to HC subsequently to baseline measurement, resulting in potential exposure misclassification. However, analyses incorporating information on HC use at the 6 and 12 follow up visits suggested similar results as our main analysis.

Women in sub-Saharan Africa may be more likely to enroll in HIV care[20] and to initiate ART than men.[21] As access to ART increases, an increasingly larger number of reproductive-age women will require counseling on simultaneous use of HC and ART. Among all women initiating ART in our sample, 15% (95% CI: 12-19) reported use of HC at baseline. This proportion is comparable with the 19% (95% CI :18-21) of all HIV+ women (regardless of ART use) who reported use of HC in Rakai between 2004 and 2006.[22] Despite the personal and public health impacts of unintended pregnancies to HIV+ women, providers in some settings are reluctant to give HC to women on ART,[4] highlighting the importance of providing definitive information on best practices for counseling HIV+ women on ART who wish to prevent pregnancy.

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Table 1. HC use by demographic, sexual, and health characteristics at ART initiation

	Total n=433 n (%)	**No HC use at baseline n=367 (85%)** n (%)	**HC use at baseline N=66 (15%)** n (%)	**p-value for χ^2**
Failure (detectable VL at 12 months, regimen change, or death)†	52 (13)	43 (13)	9 (15)	0.54
Age (years)				0.10
18-24	43 (10)	38 (10)	5 (8)	
25-34	242 (56)	197 (54)	45 (68)	
35-60	148 (34)	132 (36)	16 (24)	
Marital status				0.95
Never married	23 (5)	20 (6)	3 (5)	
Married/cohabitating	242 (56)	206 (56)	36 (55)	
Previously married	168 (39)	141 (38)	27 (41)	
Pregnant at baseline	33 (8)	33 (9)	0 (0)	<0.01
Condom use				0.01
Never	216 (50)	173 (47)	43 (65)	
Sometimes	54 (13)	43 (12)	11 (17)	
Always	163 (38)	151 (41)	12 (18)	
Sex partners past 6 months				0.17
None or one	375 (87)	322 (88)	53 (80)	
2-10	35 (8)	28 (8)	7 (11)	
Missing information	23 (5)	17 (5)	6 (9)	
CD4 0-3 months prior to ART initiation, n (median)‡	393 (191)	331 (191)	62 (192)	0.92

† Excludes 28 individuals presumably alive at 12 months, but without a 12 (or 6 and 18) month VL measurement

‡ 40 individuals excluded as final CD4 measurement prior to ART initiation was not within 0-3 months of ART initiation, p-value for Mann-Whitney U test.

Table 2. Association between ART failure (detectable viral load, drug regimen change, or death) over 12 months and demographic, sexual, and health characteristics at ART initiation

	Total n=405	**No failure n=353 (87%)**	**Failure n=52 (13%)**	**p-value for χ^2**
	n	n (%)	n (%)	
HC use				0.24
None	345	302 (88)	43 (12)	
Oral contraceptive pill	15	11 (73)	4 (27)	
Injection	45	40 (89)	5 (11)	
Age (years)				0.04
18-24	42	36 (86)	6 (14)	
25-34	224	188 (84)	36 (16)	
35-60	139	129 (93)	10 (7)	
Marital status				0.08
Never married	21	19 (90)	2 (10)	
Married/cohabitating	231	208 (90)	23 (10)	
Previously married	153	126 (82)	27 (18)	
Pregnant at baseline	30	27 (90)	3 (10)	0.78
Condom use				0.23
Never	204	178 (87)	26 (13)	
Sometimes	50	40 (80)	10 (20)	
Always	151	135 (89)	16 (11)	
Sex partners past 6 months				0.21
None or one	348	304 (87)	44 (13)	
2-10	34	27 (79)	7 (21)	
Missing information	23	22 (96)	1 (4)	
CD4 0-3 months prior to ART initiation, n (median)[‡]	393 (191)	318 (196)	47 (157)	0.08

[‡] 12 individuals excluded as final CD4 measurement prior to ART initiation was not within 0-3 months of ART initiation, p-value for Mann-Whitney U test.

Table 3. Univariable and multivariable associations between HC use at baseline and ART failure

	Univariable PRR			Multivariable PRR		
	PRR	**95% CI**	**p**	**PRR**	**95% CI**	**p**
Detectable VL at 12 mos, regimen switch, or death[†]						
Any HC at baseline vs. no HC	1.20	0.62-2.34	0.59	1.10	0.57-2.12	0.78
OCPs at baseline vs. no HC	2.14	0.88-5.17	0.09	1.73	0.67-4.47	0.26
Injectables at baseline vs. no HC	0.89	0.37-2.14	0.80	0.86	0.37-1.99	0.72
Detectable VL at 12 mos, regimen switch, death, or loss to follow-up[†]						
Any HC at baseline vs. no HC	1.28	0.78-2.11	0.33	1.23	0.75-2.02	0.41
OCPs at baseline vs. no HC	1.51	0.63-3.59	0.36	1.37	0.55-3.41	0.49
Injectables at baseline vs. no HC	1.22	0.69-2.15	0.50	1.19	0.69-2.06	0.53
Detectable VL at 12 mos, regimen switch (restricted to one-year survivors)[‡]						
Any HC ever vs. no HC	1.23	0.61-2.50	0.56	1.00	0.50-2.01	0.99
Ever OCPs vs. no HC	1.92	0.65-5.73	0.24	1.22	0.38-3.92	0.74
Ever injectables (unless also used OCPs during year) vs. no HC	0.95	0.40-2.24	0.90	0.83	0.35-1.93	0.66

[†] Multivariable analysis controlled for age at ART initiation, consistency of self-reported condom use during past six months, and number of sexual partners during past six months

[‡] Multivariable analysis controlled for age at ART initiation, consistency of self-reported condom use during last 1.5 years, number of recent sexual partners during last 1.5 years, and self-reported ART adherence from 6 to 12 months after ART initiation

Table 4. Associations between ever use of HC during the first year of ART use with demographic, sexual, and health characteristics at ART initiation among women with complete follow up at 6 and 12 months post-ART initiation

	Total n=280 n (%)	**Never HC use n=202 (72%)** n (%)	**Ever HC use n=78 (28%)** n (%)	**p-value for χ^2**
Failure (detectable VL at 12 mos or regimen change)	31 (11)	21 (10)	10 (13)	0.53
Age (years) at ART initiation				0.05
18-24	24 (9)	16 (8)	8 (10)	
25-34	160 (57)	108 (53)	52 (67)	
35-60	96 (34)	78 (39)	18 (23)	
Marital status at ART initiation				0.98
Never married	15 (5)	11 (5)	4 (5)	
Married/cohabitating	177 (63)	127 (63)	50 (64)	
Previously married	88 (31)	64 (32)	24 (31)	
Ever pregnant	55 (20)	45 (22)	10 (13)	0.09
Ever condom use				0.01
Never	39 (14)	26 (13)	13 (17)	
Inconsistently over time	66 (24)	57 (28)	9 (12)	
Always	175 (63)	119 (59)	56 (72)	
Sex partners				0.33
Always none or one	233 (83)	170 (84)	63 (81)	
Ever 2-10	34 (12)	25 (12)	9 (12)	
Missing information	13 (5)	7 (3)	6 (8)	
ART adherence from 0-6 mos				0.71
100%	78 (28)	55 (27)	23 (29)	
95-99.9%	109 (39)	77 (38)	32 (41)	
<95%	93 (33)	70 (35)	23 (29)	
ART adherence from 6-12 mos				0.22
100%	209 (75)	155 (77)	54 (69)	
95-99.9%	27 (10)	20 (10)	7 (9)	
<95%	44 (16)	27 (13)	17 (22)	
CD4 0-3 mos prior to ART initiation, n (median)[‡]	251 (189)	182 (188)	69 (200)	0.56

[‡] 29 individuals excluded as final CD4 measurement prior to ART initiation was not within 0-3 months of ART initiation, p-value for Mann-Whitney U test.

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