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An Investigation of the Possible Interaction between the Use of Vitamin C and Highly Active Anti-Retroviral Therapy (HAART) Adherence and Effectiveness in Treated HIV+ Women

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Abstract

Objectives—Our goal in this study was to examine how Vitamin C interacts with antiretroviral therapy in individuals with HIV. We specifically evaluated how Vitamin C impacts highly active antiretroviral therapy (HAART) adherence and HAART effectiveness as adjudicated by HIV viral loads and CD4 cell counts. Women served as their own controls, comparing periods of Vitamin C usage with periods of non-usage.

Design—An intra-individual, cross-sectional comparative study ‘nested’ in the WIHS observational cohort study

Subjects—Women in the Women’s Interagency HIV Study (WIHS).

Outcome Measures—Adherence, CD4 count and Viral load.

Results—Our study population was drawn from 2,813 HIV+ participants who contributed 44,588 visits in WIHS from October, 1994 to April, 2009. Among them, there were 1,122 Vitamin C users with 4,954 total visits where use was reported. In the multivariate model adjusting for age, education, race, income, drug use, Vitamin C use order and depression score, there was a 44% increase in the odds of $\geq 95\%$ HAART adherence among participants during their period of

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Conflict of Interest Statement:

None declared.

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Vitamin C use compared to when they were not using Vitamin C (OR=1.44; 95% CI=1.1–1.9; P-value=0.0179). There was an association with Vitamin C usage and CD4 counts on viral loads.

Conclusion—Vitamin C usage appears to be associated with improved adherence. Future Vitamin C studies should target specific HAART drugs, and prospective clinical outcomes.

Introduction

In populations with chronic or terminal diseases, complementary and alternative medicines (CAM) have been shown to have higher usage than the general population, likely due to the belief that CAM may reduce disease symptoms or side effects from conventional treatments^{1–5}. In the early HIV-era, CAM usage was high, due to HIV's debilitating effects and a paucity of effective treatment options^{6–9}. CAM covers a diverse group of treatment and products utilized by many health professionals. The National Center of Complementary and Alternative Medicine (NCCAM) finds providing a definition to suit the field challenging due to the broad and rapidly changing practices. However, CAM can be classified into broad categories that include natural products, mind and body medicine and manipulative and body-based practices. Natural products include minerals and vitamins such as Vitamin C that are often sold as dietary supplements. The use of these dietary supplements beyond sole nutritional need and dietary requirements are often considered CAM.¹⁰ Vitamin C can be considered a nutraceutical in certain cases, as it is found to be a dietary supplement that provides medical and health benefits.¹¹

The research on the interaction between Vitamin C and HIV has been limited, concentrated mainly in animal models and mechanistic hypotheses^{12, 13}. Evidence of decreased plasma ascorbate concentrations in HIV patients suggest that vitamin C requirements may be higher in those with HIV infection compared to regularly reported norms.¹⁴ Limited studies have found a reduction in antiretroviral concentrations with Vitamin C intake and that high doses of vitamin C may significantly reduce indinavir plasma concentrations.^{15, 16} However, other studies have shown that adverse events of other antiretrovirals, such as zidovudine's effects on leukopenia, may be prevented by Vitamin C supplementation in animal models.^{17, 18}

We conducted an intra-individual, cross-sectional comparative study to evaluate how Vitamin C interacts with antiretroviral therapy in individuals with HIV. We specifically evaluated how Vitamin C impacts HAART adherence and HAART effectiveness as adjudicated by HIV viral loads and CD4 cell counts. Even minor changes in HAART adherence have been associated with dramatic changes in HIV RNA levels, CD4+ counts, morbidity and survival in individuals with HIV.^{19, 20}

Methods

WIHS Study Design

The Women's Interagency HIV Study (WIHS) was initiated in 1994 to examine the natural and treated history of HIV disease among women in response to its rising epidemic. The study design of WIHS is detailed elsewhere²¹. The original enrollment recruited 2,054 HIV-infected and 569 HIV-uninfected women from six study sites (Chicago, Los Angeles, San Francisco, Washington D.C., Brooklyn and the Bronx) around the United States. Women visit a study site every 6 months. During each visit, structured interviews are performed to collect data on sociodemographics characteristics, substance use and sexual behaviors, health care utilization, antiretroviral therapy use and patterns, other treatments, and disease outcomes. In addition, physical and obstetric/gynecologic examinations are performed by the medical staff and biological specimens are collected. The local institutional review board at each site has approved the study protocol and all women have given their written informed consent. In the WIHS, comprehensive information on CAM use

was collected annually (at only odd-numbered visits) from study enrollment until March 2002.

Comparative Study Design

The WIHS is an observational cohort study. Unlike controlled experiments, use of therapies in observational studies is not from random assignment and unbalanced distributions of participants' characteristics and antiretroviral drug use history might bias estimated exposure effects. To account for this, an intra-individual cross-sectional comparative study 'nested' in the WIHS observational cohort study was conducted. First, we determined all visits where participants reported usage of Vitamin C and then defined its paired control visit based on four criteria: visit from the same individual occurring within 12 months where the antiretroviral drug regimen is unchanged, but the patient no longer reports Vitamin C usage. All data were collected after usage of Vitamin C. Allowing patients to serve as their own controls eliminated many potential confounders, while evaluating the effect of Vitamin C on adherence and outcomes.

Exposures of interest

Vitamin C usage was a dichotomous variable indicating whether the participants used Vitamin C or not.

Covariates

Covariance selection was based on prior knowledge of factors that affect adherence and outcomes, available data, and the hypothesis to be examined. The following covariates were selected as potential confounders in evaluating the interaction between Vitamin C use and antiretroviral therapy use and effectiveness: Age in visits (<35, 35–50 and 50+), race/ethnicity (white, black, Hispanic and other), education (less than high school, some high school, or college and above), income (1= \$12,000+, 0=less than \$12,000), depression score, Vitamin C use order (0="from no reported Vit-c" to Vit-c use"; 1="Vit-c use" to "no reported Vit-c use") and drug use (1=use, 0=no use). In evaluating the interaction between Vitamin C use and antiretroviral effectiveness, adherence ($\geq 95\%$ or not) as a confounder was also included into model. See Table 2 and Table 3 for detailed covariate combination.

Study outcomes

The definition of HAART at any study visit in WIHS was guided by the DHHS/Kaiser Panel [DHHS/Kaiser 2008] guidelines²⁰. We examined HAART adherence both as a binary variable of having HAART adherence level $\geq 95\%$ as this cutoff and as a multi-categorical measure (HAART adherence level=100%, 95–99%, 75–94%, <75% and "haven't taken any of my prescribed medications")^{19, 20}. We assessed HAART outcomes by current CD4 cell counts and HIV viral load measurements.

Statistical analysis

To account for correlated responses from the same woman, for the HAART adherence response variable, generalized linear modeling of PROC GENMOD for repeated measures with generalized estimating equations (GEE) was used for both the binary (e.g. 95% or not) and multinomial adherence outcomes; for the continuous study outcomes of continuous HIV viral load and CD4+ cell counts, a random effect linear mixed model was fit and appropriate transformation performed. Selected covariates (age, education, race, drug use, income, Vitamin C use order and depression score) were adjusted for in the models.²²

Results

Study Population Characteristics

Our study population was drawn from 2,813 HIV+ participants who contributed 44,588 visits in WIHS from October, 1994 to April, 2009. Among them, there were 1,122 Vitamin C users with 4,954 total visits where use was reported.

Matched pairs Population Characteristics

After selecting and matching participants, 558 Vitamin C visits were found among 365 women who also had non Vitamin C-usage periods. Among them, 462 pairs were “from Vitamin C use” to “no reported Vitamin C use” and 96 pairs were “from no reported Vitamin C use” to reported Vitamin C use”. Each pair represented a case and control from the same participant using the same antiretroviral regimen.

Consistent with the WIHS group as a whole, the majority of participants were between the ages of 35–50 but the Vitamin C group had more white women and higher incomes than the overall cohort, (Table 1).

HAART adherence

Univariate and multivariate Generalized Linear Models (GENMOD) with binomial and multinomial distributions were conducted to explore the relationship between Vitamin C usage and HAART adherence. Both models indicated Vitamin C usage may be associated with significantly increase HAART adherence, regardless of whether adherence is treated as a binary or multi-categorical outcome variable (Table 2). In the multivariate model adjusting for age, education, race, income, drug use and depression score, there was a 44% increase in the odds of $\geq 95\%$ HAART adherence among participants during their period of Vitamin C use compared to when they were not using Vitamin C (OR=1.44; 95% CI=1.1–1.9; P-value=0.0179). A multinomial distribution of adherence usage found a 21% improvement in adherence in the Vitamin C period, (OR=1.21; 95% CI=1.01–1.46; P-value=0.0411). Participants who used Vitamin C for general health were more likely to have 95% HAART adherence compared to visits where they did not use Vitamin C (OR=1.45; CI=1.01–2.09; P-value=0.049). Participants who used Vitamin C every day were more likely to have 95% HAART adherence compared to visits where they did not use Vitamin C (OR=1.40; CI=1.01–1.94; P-value=0.0439).

CD4+T cell counts and viral load

Mixed models for repeated measures were conducted to analyze the relationship between Vitamin C usage and HAART effectiveness in term of CD4+T cell counts and viral loads (Table 3). There was no evidence that the same participants had significant differences in CD4 cell counts or HIV viral loads in their periods of Vitamin C use versus participants' periods of non-use of Vitamin C.

Discussion

We found a 44% improvement in HAART adherence examined binomially when women are taking Vitamin C compared to when they are not and a 21% improvement when examined via a multinomial model. Interestingly while participants who used Vitamin C daily they had 40% better adherence during those periods of usage compared to when they did not use Vitamin C. We did not see any changes in CD4+ T cell counts or viral load by Vitamin C use, but we were not able to follow these patients longitudinally given the restrictions of our study design. CAM use may be associated with self-empowerment forming a relationship

with improved adherence to traditional medicines.²³ This concept needs further exploration, as a possible reason Vitamin C usage was associated with HAART adherence.

Our study had some limitations that deserve mention. First, we used self-reported CAM and medication adherence, both of which are topics that participants may not feel comfortable disclosing. Recall bias is another factor that may influence the results provided by participants. However, previous WIHS research has shown that self-reported medication use is consistent with objective measures of HIV outcome, such as CD4+ T cell count, and HIV viral load.^{24, 25} While we adjusted for education and race status, we did not have information on other health promoting behaviors other than Vitamin C from this cohort. Most limiting to our analysis was that we were unable to follow women over time due to the cross-sectional matching of our study design. We found no association among Vitamin C usage and HIV treatment outcomes, such as viral loads and CD4+ T cell counts, which may translate to a lack of association or may mean that increases in adherence take time to impact concrete biological outcomes. Furthermore, the efficacy of varying dosages of Vitamin C was unable to be observed since Vitamin C was treated as a binomial variable. Finally, although patients serving as their own controls eliminated many potential confounders, and the models were also adjusted by some variables that we knew might have an effect to outcomes, it is also possible that some variables were missed.

Previously we studied whether CAM use is associated with the timing of HAART initiation, by examining 1,034 HIV-infected women in the WIHS cohort who contributed 4,987 person visits over six years of follow-up. At any time point, the cumulative incidence of HAART initiation among any CAM user was higher than that among non-CAM users. After adjusting for potential confounders, any CAM use was associated with 1.34 times (95% confidence interval CI: 1.09, 1.64) greater likelihood of HAART initiation than non-CAM users.²⁶ Additionally, we have found that CAM usage is correlated with effective use of HAART, with a 19% increase in our multivariate model of CAM users having greater than 95% adherence than non-CAM users.²⁷ Our current data is consistent with our previous data that clearly shows some association among supplements and CAM modalities and HAART adherence. We believe the adherence data is consistent enough over many studies that the next logical step is a long term Vitamin C intervention trial to examine clinical outcomes such as CD4 counts and viral load.

Use of herbs in the HIV population has been shown to be similar in the HAART and pre-HAART eras with many potential herb-drug interactions not considered by patients.²⁸⁻³¹ A survey of HIV patients in London found that 20% of them were using herbals that could potentially adversely affect HAART usage.³² A recent study by Qato et al. found that nearly 50% of individuals with a poor or fair self-reported health status used dietary supplements.³³ Many of these supplements have known interactions with the same metabolic pathways as HAART treatments, as many of these treatments are metabolized by cytochrome P450 (CYP450) enzymes, including CYP3A4, CYP2B6, and others.³⁴ However, many of these interactions have only been shown in vitro and depend on dosage and frequency.³⁵

We conducted a cross-sectional matched analysis of women examining the impact of Vitamin C usage. We found significantly increased HAART adherence during periods of Vitamin C usage compared to when the same women were not consuming Vitamin C. Due to the potential impact this simple inexpensive intervention may have on HIV-positive women, we believe a large community-based clinical trial is indicated.

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Abbreviations

WIHS	Women's Interagency HIV Study
CAM	complementary and alternative medicines
HAART	highly active antiretroviral therapy

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Table 1

Characteristics of Vitamin C users at baseline visit: whole WIHS versus paired dataset

Characteristics	Vitamin C users in whole WIHS (1122 users contributed 4954 visits)	Vitamin C users in paired dataset (365 users contributed 558 pairs visits)	P value
Age, N (%)			0.2251
<35	488(43.49)	140 (38.36)	
35–50	587(52.32)	208 (56.99)	
50+	47(4.19)	17 (4.66)	
Race, N (%)			<0.0001
White	206(18.36)	32 (8.77)	
Black	618(55.08)	185 (50.68)	
Hispanic	255(22.73)	143 (39.18)	
Other	43(3.83)	5 (1.37)	
Education			<0.0001
Less than high school	351(31.28)	160(43.84)	
Completed high school	327(29.14)	102(27.95)	
Some college and above	443(39.48)	103(28.22)	
Income, N (%)			<0.0001
\$12,000+	485(43.23)	103(28.22)	
<=\$12,000	609(54.28)	255(69.86)	

Table 2

Association between adherence and Vitamin C use

MODEL	OUTCOME VARIABLE	UNIVARIATE			MULTIVARIATE		
		OR	95% CI	P-value	OR	95% CI	P-value
GENMOD with binomial distribution	Adherence>=95% or not	1.3	[1.0, 1.7]	0.0372	1.44	[1.1, 1.9]	0.0179
GENMOD with multinomial distribution	Adherence has 5 levels: 1=100% of the time 2=95–99% 3=75–94% 4=<75% 5=I haven't taken any of my prescribed medications	1.19	[1.01, 1.39]	0.0369	1.21	[1.01, 1.46]	0.0412

Univariate model: Model includes an intercept and an indicator of Vitamin C use or not

Multivariate model: Model includes an intercept, an indicator of Vitamin C use or not, age, education, race, drug use, depression score, Vit-c use order and income

OR, odds ratio; CI, confidence interval

Table 3

Association between Vitamin C and CD4+ T cell counts, viral load

Model	OUTCOME VARIABLE	UNIVARIATE			MULTIVARIATE		
		Estimate	95% CI	P-value	Estimate	95% CI	P-value
MIXED	CD4+T cell counts	-7.99	[-24.4, 8.4]	0.34	-12.36	[-30.1, 5.4]	0.1713
MIXED	Log(viral load)	-0.1469	[-0.29, 0.003]	0.0543	-0.1147	[-0.27, 0.04]	0.1448

Univariate model: Model includes an intercept and an indicator of Vitamin C use or not

Multivariate model: Model includes an intercept, an indicator of Vitamin C use or not, age, education, race, drug use, depression score, income, Vit-c use order and adherence
CI, confidence interval