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MAJOR ARTICLE

Vitamin C Urinary Loss and Deficiency in Human Immunodeficiency Virus (HIV): Cross-sectional Study of Vitamin C Renal Leak in Women With HIV

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Background. Reduced plasma vitamin C (vitC) concentrations in human immunodeficiency virus (HIV) may result from abnormal urinary excretion: a renal leak. VitC renal leak indicates underlying nutritional dysregulation independent of diet. We hypothesized that increased renal leak prevalence in HIV would be associated with deficient vitC concentrations.

Methods. We conducted an outpatient cross-sectional study of 96 women (40 HIV [PWH] and 56 without HIV [PWOH]) at the National Institutes of Health and Georgetown University. Renal leak was defined as abnormal urinary vitC excretion at fasting plasma concentrations <43.2μM, 2 SDs below vitC renal threshold in healthy women. To determine the primary outcome of renal leak prevalence, matched urine and plasma samples were collected the morning after overnight fast. Secondary outcomes assessed group differences in mean plasma vitC concentrations and prevalence of vitC deficiency. Exploratory outcomes assessed clinical parameters associated with renal leak. VitC was measured by high-performance liquid chromatography with coulometric electrochemical detection.

Results. PWH had significantly higher renal leak prevalence (73%vs14%; OR (odds ratio):16; *P*<.001), lower mean plasma vitC concentrations (14μMvs50μM; *P*<.001), and higher prevalence of vitC deficiency (43%vs7%; OR:10; *P*<.001) compared with PWOH, unchanged by adjustments for confounding factors. Significant predictors of renal leak included antiretroviral therapy (ART), Black race, older age, and metabolic comorbidities but not viral load or CD4 count. When compared with other chronic disease cohorts, PWH had the highest prevalence of renal leak and vitC deficiency (*P*<.001).

Conclusions. High prevalence of vitC renal leak in HIV was associated with vitC deficiency, ART use, and race/ethnicity differences.

Keywords. HIV; antiretroviral therapy; vitamin C; ascorbate; renal leak.

Vitamin C is an important antioxidant nutrient required for many enzymatic functions in humans [1, 2]. Low vitamin C concentration in chronic diseases, even if nondeficient, may have consequences for disease pathogenesis and wellbeing [3–6]. Cohorts with human immunodeficiency virus (HIV) have been shown to have lower vitamin C concentrations compared with seronegative controls, even with optimal dietary intake [7–11]. Findings were attributed to increased oxidative stress and antioxidant utilization in HIV [7, 9]. Beyond utilization, low vitamin C concentrations may also result from impaired renal reabsorption of vitamin C, resulting in abnormal or increased urinary loss: a renal leak [12–14]. In healthy individuals, at plasma vitamin C concentrations 2 SDs below sex-specific renal thresholds (the minimal elimination threshold [MET]), vitamin C is fully reabsorbed in the proximal renal tubules by sodium-dependent vitamin C transporter 1 (SVCT1), and no vitamin C is excreted into urine. A renal leak occurs when there is inappropriate urinary excretion at low plasma concentrations below the MET [12]. Renal leak indicates underlying nutritional pathophysiology that is independent of dietary intake [12]. For a chronic disease like HIV with accelerated antioxidant utilization, renal leak could increase the risk of vitamin C deficiency.

Renal leak assessment in chronic disease serves 2 key functions. First, renal leak characterizes the scope and contribution of abnormal vitamin C urinary loss to low vitamin C concentrations [12, 15]. Second, because renal leak incorporates both fasting plasma and urine measurements using a specific vitamin C assay, renal leak outcomes are an effective means of investigating disease-specific factors that contribute to vitamin C

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nutritional pathophysiology and disease pathogenesis [12, 15]. In recent studies, we showed that participants with diabetes had 5-fold higher odds of renal leak compared with nondiabetic controls [12]. There was an even higher, 16-fold, odds of renal leak observed in Fabry disease, a rare chronic disease associated with renal tubular dysfunction, indicating that renal leak may reflect underlying renal tubular dysfunction [15]. Like Fabry disease and diabetes, HIV is a chronic disease with complex multifactorial pathophysiology that includes chronic inflammation, increased antioxidant requirements, renal tubular dysfunction, and low plasma vitamin C concentrations [12, 15–21]. However, in populations with HIV, the relationship between renal leak, low vitamin C concentrations, and vitamin C deficiency is unknown. An understanding of renal leak prevalence and the contributory factors could provide foundational information in uncovering disease-related vitamin C pathophysiology in populations with HIV.

This study had 3 main objectives. The first was to determine the relationship between renal leak prevalence, vitamin C plasma concentrations, and vitamin C deficiency in female participants with HIV (PWH) and without HIV (PWOH). The second was to investigate the demographic and clinical factors associated with vitamin C renal leak. The third was to understand how renal leak outcomes in HIV vary from previously studied cohorts with diabetes and Fabry disease [12, 15]. We hypothesized that PWH would have a higher prevalence of vitamin C renal leak, reduced plasma vitamin C concentrations, and higher prevalence of vitamin C deficiency. We tested our hypotheses using sex-specific renal leak criteria and a sensitive/specific vitamin C assay.

METHODS

Study Design & Setting

This was an outpatient cross-sectional cohort study. There were 2 study locations: the National Institutes of Health Clinical Center's metabolic unit, Bethesda, Maryland (ClinicalTrials.gov NCT00071526), and Georgetown University, Washington, DC (ClinicalTrials.gov NCT00000797). The research protocols were approved by the institutional review boards (IRBs) of both institutions.

Participants

Recruitment

Participants were recruited from the Washington, DC, Women's Interagency HIV Study (WIHS), now combined with the Multicenter AIDS Cohort Study (MACS) (DC MACS/WIHS Combined Cohort Study [DC MWCCS]) and from the Washington, DC, area community. In accordance with the IRB-approved protocols in both institutions, PWH were recruited from MWCCS, while PWOH were recruited from both MWCCS and the community. Recruitment was conducted using recruitment flyers and advertisements displayed in the community, social media, and online registries.

Inclusion/Exclusion Criteria

Among the MWCCS participants, there were no additional inclusion/exclusion criteria beyond the MWCCS requirements [22]. Among participants recruited from the community, inclusion criteria comprised participants aged 18–65 years. Exclusion criteria included acute or chronic illness, alcohol abuse or tobacco use, and use of chronic medications. Exclusion criteria were chosen to avoid confounding the study findings, given the reported association of these conditions with vitamin C dysregulation.

Assessment of Vitamin C Renal Leak

Renal leak was assessed using matched urine and plasma vitamin C measurements, as previously described [12, 15]. Briefly, approximately 2 weeks prior to study sampling, participants were instructed to avoid vitamin C supplements. Participants fasted overnight and arrived at the research center the morning of the study visit. Participants were then instructed to empty their bladder. After a 1-hour interval, urine and blood samples were obtained for vitamin C measurements, chemistry, and related studies. See Supplementary Methods for additional details on sampling approaches, measures to minimize bias, dietary considerations, and assay measurements.

Study Outcomes

The primary outcome was difference in vitamin C renal leak prevalence between PWH and PWOH. Vitamin C renal leak was defined as the presence of urinary fasting plasma concentrations below 43.2 μM, the MET in women [12]. Secondary outcomes were between-group differences in mean plasma vitamin C concentrations and prevalence of vitamin C deficiency, defined as plasma vitamin C concentrations below 11 mol/L [23]. Exploratory outcomes evaluated associations between clinical variables and renal leak outcome in all participants.

Study Size Considerations

As noted in recent renal leak publications, there were no actual, extant data upon which to base a sample size calculation [12, 15]. Sample size calculations of a related single-site study were based on scant anecdotal evidence indicating substantial differences in 24-hour urinary vitamin C excretion between nondiabetic controls and the diabetes cohort. In the combined cohort of participants from the National Institutes of Health and the MWCCS cohort, sample size was effectively determined by logistical constraints and participant willingness, rather than any a priori sample size calculations.

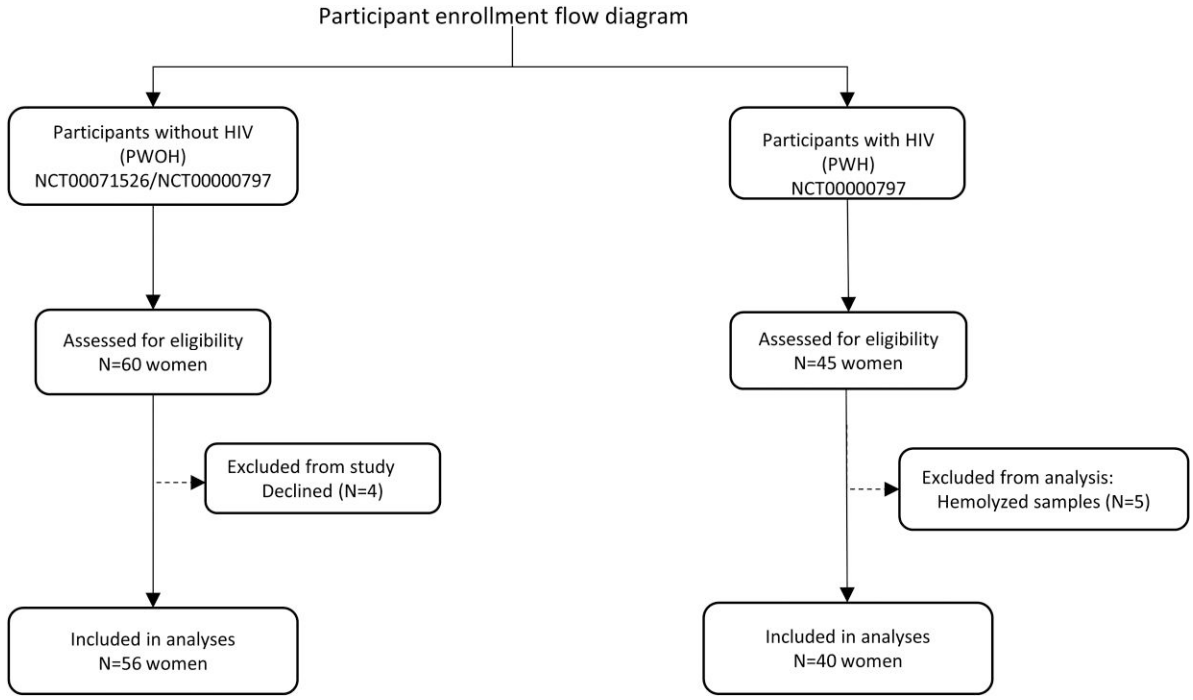

Figure 1. Enrollment and patient flow of study participants with HIV (PWH) and without HIV (PWOH). Abbreviation: HIV, human immunodeficiency virus.

Statistical Methods

In this cross-sectional study, descriptive statistics were calculated for baseline characteristics of study participants. Counts and proportions were used for categorical variables, accompanied by Pearson's chi-square test or Fisher's exact tests, as indicated by expected cell counts, while means and SDs were used for continuous variables, accompanied by Welch's *t* test or Wilcoxon-Mann-Whitney tests, as indicated by approximate normality. The primary outcome of vitamin C renal leak prevalence in PWH versus PWOH was assessed using group-specific proportions accompanied by a series of unadjusted and covariate-adjusted odds ratios (ORs) estimated via logistic regression [24]. The secondary outcome evaluating group differences (estimated shifts) in mean plasma vitamin C concentrations was assessed using linear regression analyses. Exploratory analyses reported multiplicity-adjusted *P* values for groups of related variables' respective associations with the primary endpoint of renal leak via Wald-type tests for non-zero logistic regression coefficients . See Supplementary Methods for additional description of statistical methods.

RESULTS

Baseline Characteristics of Study Cohorts

A total of 105 female volunteers were assessed for eligibility in both study groups. Of the 60 PWOH assessed, 4 were unable to participate (Figure 1). Among PWH, all 45 who were assessed were studied; however, data from 5 participants were excluded from the primary analysis due to sample hemolysis (Figure 1). A total of 96 participants were included in the primary analyses, 40 PWH and 56 PWOH (Figure 1). The baseline characteristics of participants in both groups are shown in Table 1. The racial/ethnic composition of both groups was different, with significantly more Black/non-Hispanic PWH versus PWOH (84% vs 48%) (Table 1). The mean age was higher in PWH (53 vs 37 years; $P < .05$), whereas body mass index (BMI) was not significantly different ($P > .05$) (Table 1). Among the baseline clinical parameters, compared with PWOH, PWH had lower estimated glomerular filtration rate (eGFR) (84 vs 111 mL/min/1.73 m^2; $P < .05$) and a higher prevalence of hypertension (70% vs 27%; $P < .05$) and tobacco use (54% vs 4%; $P < .05$) (Table 1).

Vitamin C Renal Leak Prevalence in Participants With HIV and Participants Without HIV

Almost all PWOH had no detectable vitamin C in urine at plasma concentrations below the MET (Figure 2*A*). In contrast, almost all PWH had detectable vitamin C in urine at plasma vitamin C concentrations below the MET: a renal leak (Figure 2*B*). Renal leak prevalence was significantly higher in PWH versus PWOH (73% vs 14%; unadjusted OR: 15.8; 95% confidence interval [CI]: 5.7, 43.9; $P < .001$) (Figure 2*C*). The odds of renal leak in the PWH versus PWOH cohort remained significant when adjusted for medical comorbidities (adjusted OR: 94; 95% CI: 5.6, 1592.3; $P = .002$) (Figure 2*C*, Table 1) and active tobacco

Table 1. Baseline Characteristics of Female Participants With HIV and Those Without HIV

	PWOH (n = 56)	PWH (n = 40)
Demographics & Anthropometrics: mean (SD) or n (%)		
Race/ethnicity,[a] n (%)		
Black/non-Hispanic	27 (48)	34 (84)
White/non-Hispanic	25 (45)	5 (13)
Other	4 (7)	1 (3)
Age,[b] y	37 (14)	53 (7)
BMI, kg/m^2	29 (8)	28 (6)
Systolic blood pressure, mmHg	117 (13)	123 (21)
Diastolic blood pressure,[b] mmHg	70 (9)	77 (12)
Clinical laboratory: mean (SD)		
Fasting glucose,[b] mg/dL	88 (11)	86 (36)
Hemoglobin A1c,[b] %	5.3 (0.4)	6.2 (2)
eGFR,[c] mL/min/1.73 m^2	111 (21)	84 (24)
Chronic medical conditions: n/total (%)		
Hypertension[b,d]	15/56 (27)	28/40 (70)
Hyperlipidemia[e]	9/48 (19)	1/12 (8)
Diabetes[f]	7/56 (13)	5/40 (13)
Metabolic syndrome[g]	1/54 (2)	2/25 (8)
Obesity[h]	20/56 (36)	15/40 (38)
Chronic kidney disease[i]	1/56 (2)	4/33 (12)
Elevated liver enzymes[j]	2/56 (2)	4/33 (12)
Tobacco use	2/56 (4)	19/35 (54)
HIV parameters: mean (SD) or n/total (%)		
Duration of HIV diagnosis, y	…	17 (7)
CD4 count, cells/mm^3	…	739 (282)
CD4 count >300 cells/mm^3	…	32/37 (97)
Viral load, copies/mL	…	494 (1863)
Viral load <50 copies/mL	…	30/37 (91)
ART use, any	…	32/37 (86)
ART use, by class		
Nucleoside RTI	…	32/32 (100)
Tenofovir	…	18/32 (56)
TDF	…	14/32 (44)
TAF	…	4/32 (13)
Non-nucleoside RTI	…	11/32 (34)
Protease inhibitors	…	13/32 (41)
Integrase inhibitor	…	14/32 (44)
Entry inhibitor	…	1/32 (3)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CD4, cluster of differentiation number 4 estimated blood cell count; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; PWH, participants with HIV; PWOH, participants without HIV; RTI, reverse transcriptase inhibitor; SBP, systolic blood pressure; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Racial categories were based on National Institutes of Health reporting guidelines on racial and ethnic categories (NOT-OD-15-089). "Other" comprises Asian, Hispanic and Latino, and multiethnic subjects.

[b]Variables that are statistically different between groups ($P < .05$).

[c]The eGFR was calculated using the Modification of Diet in Renal Disease v4 (MDRD4) equation: [186 × (creatinine/88.4) − 1.154 × (age) − 0.203 × (0.742 if female) × (1.210 if Black)].

[d]Any indication of hypertension: SBP ≥130 mmHg or DBP ≥80 mmHg, self-report, or use of antihypertensive medications.

[e]Defined as high-density lipoprotein (HDL) <40 mg/dL or triglycerides >150 mg/dL or low-density lipoprotein (LDL) >130 mg/dL.

[f]Diabetes: any indication of diabetes based on clinical history, medication use, or laboratory values (hemoglobin A1c >6.5% or fasting glucose >126 mg/dL).

[g]Metabolic syndrome: based on American Association of Clinical Endocrinology 2003 criteria.

[h]Obesity: BMI >30 kg/m^2.

[i]Chronic kidney disease: eGFR <60 mL/min/1.73 m^2.

[j]Elevated liver enzymes: aspartate aminotransferase ≥35 units/L or alanine aminotransferase ≥36 units/L.

use (adjusted OR: 27; 95% CI: 6.4, 113.4; $P < .001$) (Figure 2*C*, Table 1). Change-in-effect analyses adjusting for group differences in baseline demographic, anthropometric, and clinical parameters (Table 1) did not change the significant association between HIV-positive status and renal leak (Supplementary Table 1).

Plasma Vitamin C Concentrations and Prevalence of Vitamin C Deficiency in Participants With and Without HIV

The mean plasma vitamin C concentration was significantly lower in PWH versus PWOH (mean ± SD: 14 ± 12 μM vs 50 ± 23 μM; $P < .001$) (Figure 2*D*), even with adjustments for higher prevalence of medical comorbidities and tobacco use in PWH versus PWOH ($P = .027$ and $P < .001$, respectively). Change-in-effect analyses adjusting for group differences in baseline demographic, anthropometric, and clinical variables did not change the significant association between HIV-positive status and low plasma vitamin C concentrations (Supplementary Table 2). The prevalence of vitamin C deficiency was significantly higher in PWH versus PWOH (43% vs 7%; OR: 9.6; 95% CI: 2.9, 31.7; $P < .001$) (Figure 2*E*).

Variables Associated With Vitamin C Renal Leak in All Participants

Exploratory analyses were performed to evaluate demographic and clinical variables associated with vitamin C renal leak (Figure 3), with category-based multiplicity adjustments (see Methods). Among the demographic and anthropometric parameters, Black/non-Hispanic participants had significantly higher odds of having a renal leak compared with White/non-Hispanic participants ($P = .013$) (Figure 3). Older age and higher BMI were also associated with increased renal leak ($P < .001$ and $P = .001$, respectively) (Figure 3). Among the clinical variables assessed via single-predictor regression, renal leak was associated with higher systolic blood pressure ($P = .047$), higher diastolic blood pressure ($P = .004$), hypertension ($P < .001$), obesity ($P = .022$), lower eGFR ($P < .001$), and elevated liver enzymes ($P = .033$). Among the HIV-related variables, renal leak was associated with antiretroviral therapy (ART) use ($P < .001$) but not duration of HIV diagnoses, CD4 count, or viral load ($P = .364$ for all).

Comparative Renal Leak Outcomes in Participants With and Without HIV and Previously Studied Cohorts With Diabetes and Fabry Disease

Across the 4 groups, a higher renal leak prevalence was associated with lower mean plasma vitamin C concentrations ($P < .001$) (Figure 4*A*) and a higher prevalence of vitamin C deficiency ($P < .001$) (Figure 4*B*). In this continuum of chronic diseases studied, PWH had the highest renal leak prevalence, lowest plasma vitamin C concentrations, and highest prevalence of vitamin C deficiency (Figure 4).

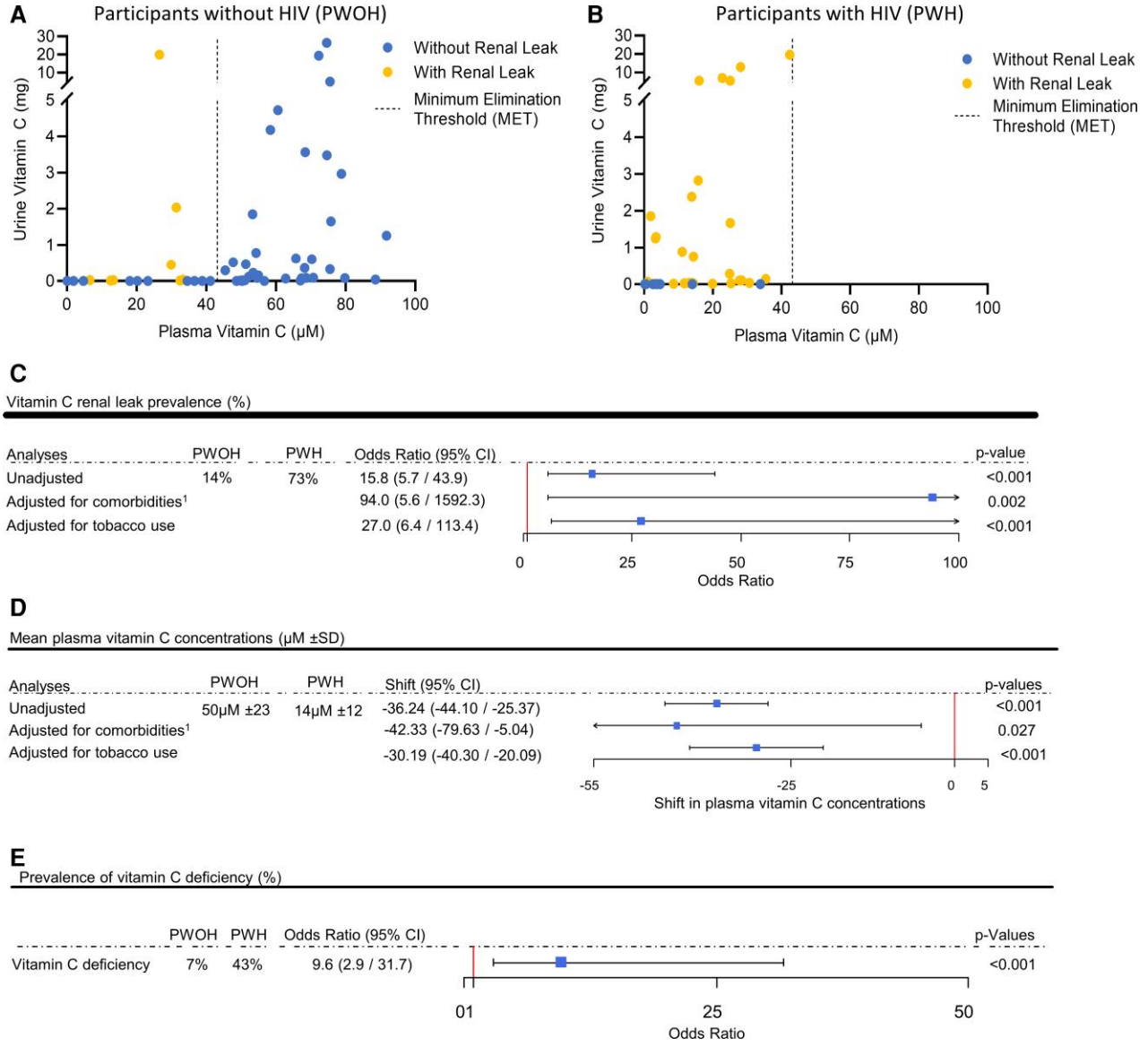

Figure 2. Vitamin C renal leak prevalence, mean plasma concentrations, and prevalence of deficiency in participants with HIV (PWH) and without HIV (PWOH). *A*, *B*, Urinary vitamin C excretion as a function of plasma vitamin C concentrations in PWOH (*A*) and PWH (*B*). Renal leak symbol (yellow circles), including those that appear to be on the *x*-axis, indicate vitamin C amounts above 0.01 mg. *C*, Vitamin C renal leak prevalence with and without adjustments for medical comorbidities and tobacco use. Squares indicate odds ratios, with horizontal lines indicating 95% CIs. *D*, Mean plasma vitamin C concentrations, with and without adjustment for medical comorbidities and tobacco use. Squares indicate estimated shift in mean plasma vitamin C, with horizontal lines indicating 95% CIs. *E*, Prevalence of vitamin C deficiency. The square indicates the odds ratio, with the horizontal line indicating 95% CI. *P* values are shown for estimated shift. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus. [1]Comorbidities include chronic medical conditions (Table 1, see Supplementary Methods).

DISCUSSION

We investigated the prevalence and clinical characteristics of vitamin C renal leak in PWH and PWOH, with renal leak indicating the abnormal urinary excretion of vitamin C when plasma concentrations are at least 2 SDs below the renal threshold [12]. Our findings showed a significantly higher prevalence of vitamin C renal leak and vitamin C deficiency in PWH compared with PWOH. The HIV–renal leak association remained significant following statistical adjustments for potentially confounding factors: medical comorbidities, tobacco use, and demographic differences. Renal leak was associated with ART use, medical comorbidities, and demographic parameters, but not viral load, CD4 count, or duration of HIV diagnosis. This study is the first description of vitamin C renal and nutritional dysregulation in HIV and suggests an increased risk of renal leak–mediated vitamin C deficiency in PWH, independent of dietary intake.

To broaden the context of our findings, we analyzed renal leak outcomes in PWH and PWOH, compared with diabetes

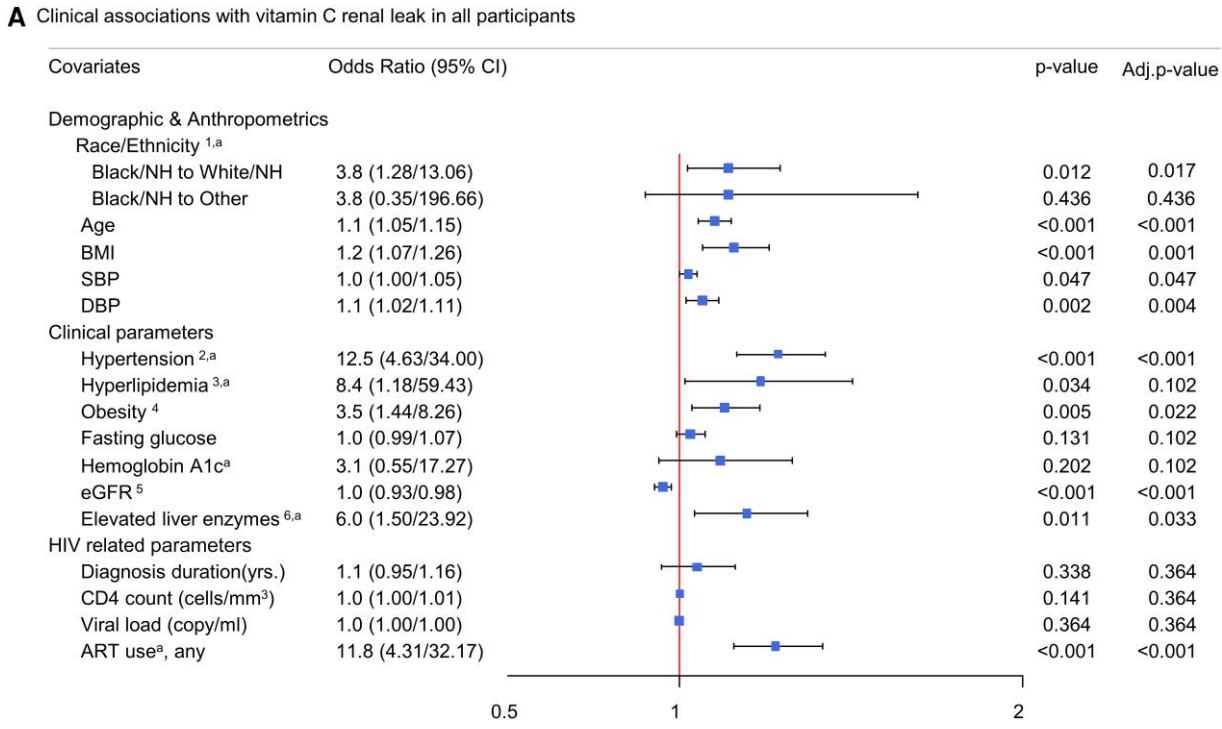

Figure 3. Demographic and clinical variables and their predictive association with vitamin C renal leak in all participants. Squares indicate odds ratios, with horizontal lines indicating 95% CIs. Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CD4, cluster of differentiation number 4; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; NH, non-Hispanic; RTI, reverse transcriptase inhibitor; SBP, systolic blood pressure. [1]Black and White groups were composed of non-Hispanic participants. "Other" comprised Asians, those of Hispanic/Latino ethnicity, and multiracial participants. [2]Hypertension was defined as participants with any indication of hypertension: SBP ≥130 mmHg or DBP ≥80 mmHg, self-report, or use of antihypertensive medications. [3]Hyperlipidemia was defined as participants with either high-density lipoprotein (HDL) <40 mg/dL or triglycerides >150 mg/dL or low-density lipoprotein (LDL) >130 mg/dL. [4]Obesity was defined as participants with a BMI >30 kg/m^2. [5]The eGFR for all groups was calculated using the Modification of Diet in Renal Disease v4 (MDRD4). [6]Elevated liver enzymes were defined as aspartate transaminase (AST) ≥35 units/L or alanine transaminase (ALT) ≥56 units/L. [a]Values were adjusted (divided by 10) to fit the scale of the forest plot.

and Fabry disease cohorts who were previously studied using the same methodology for renal leak assessment and vitamin C measurements (see Methods) [12, 15]. Across all groups, there was a relationship between a higher group prevalence of renal leak, low vitamin C concentrations, and a high prevalence of vitamin C deficiency, with the highest degree of vitamin C dysregulation and deficiency in PWH ($P < .001$) (Figure 4). Other investigators reported higher vitamin C values than those reported here [7–11]. Prior findings may be explained by nonspecific vitamin C measurements, lack of adjustment for variations in sex and medical comorbidities, and collection of samples from nonfasted subjects. Due to postprandial fluctuations in vitamin C measurements, the use of nonfasting measurements may artifactually inflate plasma vitamin C concentrations and underestimate the true prevalence of vitamin C deficiency [13, 14, 25].

Among the HIV-related parameters, the use of ART was significantly associated with renal leak (Figure 3). Of the 86% of PWH on ART, 100% were on a nucleoside reverse transcriptase inhibitor (NRTI), with smaller proportions on a non-nucleoside reverse transcriptase inhibitor (NNRTI) (34%), protease inhibitor (41%), and integrase inhibitor (44%) and 1 participant on an entry inhibitor (Table 1). We found no association with HIV disease severity biomarkers CD4 count or viral load, suggesting that immune suppression did not contribute to the study findings. However, given that 97% had a CD4 count greater than 300 cells/mm^3 and 91% had a suppressed viral load less than 50 copies/mL, findings should be viewed in the context of a generally well-treated cohort.

It is uncertain whether ART use alone accounts for the much higher renal leak prevalence in PWH compared with the other chronic diseases (Figure 4). Nevertheless, there are several potential mechanisms in which ART may directly or indirectly contribute to increased odds of renal leak. The first possibility is that vitamin C renal leak is secondary to ART-induced renal tubular dysfunction and renal impairment [15, 26]. Renal leak describes an aberrant process in which proximal renal tubular reabsorption of vitamin C is dysregulated, resulting in abnormal excretion into urine [12]. Antiretroviral therapies, including NRTIs like tenofovir, are associated with renal tubular dysfunction and renal failure [26, 27]. In our study cohort, 56% of PWH on ART were taking tenofovir (Table 1), but

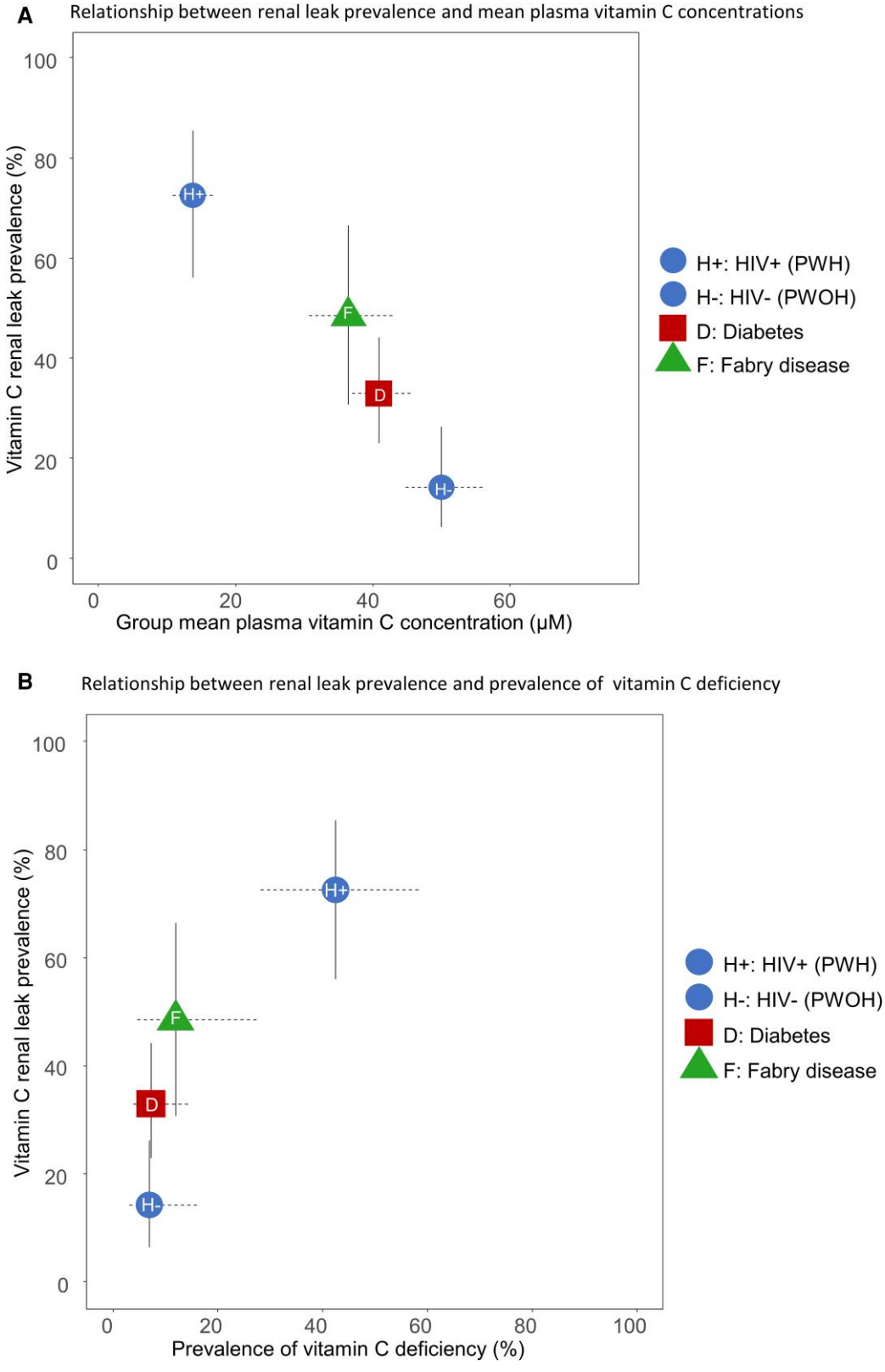

Figure 4. Comparative renal leak outcomes in PWH, PWOH, and previously studied cohorts with diabetes and Fabry disease. Relationship between renal leak prevalence and mean plasma vitamin C concentrations (*A*) and the prevalence of vitamin C deficiency (*B*) in the 4 groups. Abbreviations: HIV, human immunodeficiency virus; PWH, participants with HIV; PWOH, participants without HIV.

our study was inadequately powered for subgroup analysis evaluating the effects of individual ART drugs and/or classes on renal leak outcomes. In our study of participants with Fabry disease, a rare chronic disease associated with renal tubular dysfunction, we found a significantly high prevalence of vitamin C renal leak [15]. While renal tubular function was not specifically assessed in this HIV study, we found a significant association between reduced renal function (eGFR) and vitamin C renal leak. The second possibility is that ART may have a direct drug effect that is specific to vitamin C transporters in the kidney, although, to date, this has not been tested experimentally. The third possibility is that ART-associated renal leak may be indirectly related to ART-induced metabolic complications in HIV. Antiretroviral therapy has been associated with HIV lipodystrophy, a severe form of metabolic syndrome, with an estimated 40–50% prevalence in individuals with HIV characterized by fat redistribution and cardiometabolic risk [28, 29]. Like other obesity-related conditions, HIV lipodystrophy is associated with increased inflammation and oxidative stress [21, 30, 31], which may potentially contribute to vitamin C dysregulation. The relationship between altered metabolism and vitamin C dysregulation is supported by our study findings that showed significant associations between renal leak and metabolic comorbidities (obesity, hypertension, hyperlipidemia), as well as other studies showing low plasma vitamin C concentrations in obesity and diabetes [12, 32]. Mechanistic and longitudinal clinical studies will be needed to investigate relationships between ART, renal leak, and vitamin C deficiency in PWH, but also PWOH on ART for either preexposure prophylaxis in HIV prevention, or treatment of chronic viral infections such as hepatitis. Independent of ART, longitudinal studies are also needed to investigate the clinical implications of renal leak–mediated vitamin C deficiency in PWH with non-scorbutic plasma concentrations, particularly with comorbidities associated with low plasma vitamin C concentrations, including obesity-related conditions such as diabetes and HIV lipodystrophy, neuropsychiatric health outcomes, and low bone density [12, 32–37].

There were several notable demographic associations with renal leak, including older age and Black/non-Hispanic race/ethnicity. While the association with older age is consistent with findings in diabetes, the association with race/ethnicity has not been previously reported and may have several explanations [12]. First, findings may be skewed by the comparatively higher enrollment of Black, non-Hispanic PWH as well as the combined study cohort. Independent of statistical considerations, a second explanation is that HIV- and/or ART-induced vitamin C dysregulation exerts a disproportionately more severe nutritional and metabolic pathophysiology in Black individuals compared with other racial groups. Metabolic phenotypes display race-based differences, with Black individuals having comparatively higher rates of insulin resistance despite lower visceral/hepatic fat and triglyceride levels [38, 39]. These factors may be exacerbated by socioeconomic factors such as food insecurity, low income, and poverty [32]. Comprehensive longitudinal studies will be needed to investigate the disparate metabolic and nutritional outcomes across race/ethnic groups and the confluence of clinical, nutritional, and socioeconomic contributory factors.

There are several strengths of the study presented here. One is the foundational basis of the study design: a sex-specific vitamin C renal leak criteria based on vitamin C depletion-repletion and pharmacokinetics studies coupled with a highly sensitive and specific vitamin C measurement. Second, the study methodology for assessing vitamin C renal leak status was specifically designed to minimize bias. In addition, PWH were recruited from the DC MWCCS. The study of this unique cohort is a strength as it includes many participants from underserved, vulnerable, and high-risk communities. Study of the MWCCS cohort may also be a limitation as findings in this unique cohort may not be generalizable to all PWH, despite adjustments for potential confounding factors. Additionally, our limited data and sample size precluded a more detailed analyses of how race/ethnicity and socioeconomic factors (poverty, income, and food insecurity) potentially contribute to vitamin C renal leak and low plasma vitamin C concentrations. Last, while the cross-sectional study design provided is a necessary first step in understanding prevalence and clinical associations, findings are a snapshot in time and do not include dynamic or longitudinal outcomes, nor is causation determined.

Taken together, the data here indicate that HIV is associated with a significant degree of vitamin C dysregulation and deficiency. While mechanisms and long-term clinical implications can be addressed in future studies, current findings suggest a need for proactive preventative measures to prevent deficiency in all PWH, such as monitoring vitamin C concentrations, optimizing dietary intake, and supplementation when necessary. Our findings emphasize the need for dietary intake guidelines to account for altered vitamin C requirements in HIV and other chronic diseases [40].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. Conceptualization: M. L., I. E., P.-C. V., S. J. P., S. K. Methodology: M. L., I. E., P.-C. V., S. J. P, S. K. Investigation: M. L., I. E., P.-C. V., S. J. P., H. T., Y. W., S. K., K. M. Resources: M. L., S. K. Data Curation: P.-C. V., I. E., K. J. W., and M. L. Writing—original draft: I. E., P.-C. V., K. J. W., M. L. Writing—review and editing: I. E., P.-C. V., K. J. W., K. M., S. J. P., S. K., and M. L. Funding acquisition: M. L., S. K. Supervision: M. L., I. E., S. K. Formal analysis: P.-C. V., I. E., K. J. W., and M. L. All co-authors have read and approved the final version.

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Data availability. Data described in the manuscript will be made available upon request pending application and approval.

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