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MAJOR ARTICLE

Food Insecurity Is Associated With Lower Levels of Antiretroviral Drug Concentrations in Hair Among a Cohort of Women Living With Human Immunodeficiency Virus in the United States

Anna M. Leddy,[1] Lila A. Sheira,[2] Bani Tamraz,[3] Craig Sykes,[4] Angela D. M. Kashuba,[4] Tracey E. Wilson,[5] Adebola Adedimeji,[6] Daniel Merenstein,[7] Mardge H. Cohen,[8] Eryka L. Wentz,[9] Adaora A. Adimora,[10] Ighovwerha Ofotokun,[11] Lisa R. Metsch,[12] Janet M. Turan,[13] Peter Bacchetti,[14] and Sheri D. Weiser[1,2]

[1]Division of Prevention Science, Department of Medicine, University of California–San Francisco, San Francisco, California, USA; [2]Division of HIV, ID and Global Medicine, Department of Medicine, University of California–San Francisco, San Francisco, California, USA; [3]Department of Clinical Pharmacy, University of California–San Francisco, San Francisco, California, USA; [4]Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [5]Department of Community Health Sciences, State University of New York Downstate Health Sciences University, School of Public Health, Brooklyn, New York, USA; [6]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, USA; [7]Department of Family Medicine, Georgetown University Medical Center, Washington, DC, USA; [8]Department of Medicine, Stroger Hospital, Chicago, Illinois, USA; [9]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [10]School of Medicine and Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [11]Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA; [12]Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA; [13]Department of Health Care Organization and Policy, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama, USA; and [14]Department of Epidemiology and Biostatistics, University of California–San Francisco, San Francisco, California, USA

Background. Food insecurity is a well-established determinant of suboptimal, self-reported antiretroviral therapy (ART) adherence, but few studies have investigated this association using objective adherence measures. We examined the association of food insecurity with levels of ART concentrations in hair among women living with human immunodeficiency virus (WLHIV) in the United States.

Methods. We analyzed longitudinal data collected semiannually from 2013 through 2015 from the Women's Interagency HIV Study, a multisite, prospective, cohort study of WLHIV and controls not living with HIV. Our sample comprised 1944 person-visits from 677 WLHIV. Food insecurity was measured using the US Household Food Security Survey Module. ART concentrations in hair, an objective and validated measure of drug adherence and exposure, were measured using high-performance liquid chromatography with mass spectrometry detection for regimens that included darunavir, atazanavir, raltegravir, or dolutegravir. We conducted multiple 3-level linear regressions that accounted for repeated measures and the ART medication(s) taken at each visit, adjusting for sociodemographic and clinical characteristics.

Results. At baseline, 67% of participants were virally suppressed and 35% reported food insecurity. In the base multivariable model, each 3-point increase in food insecurity was associated with 0.94-fold lower ART concentration in hair (95% confidence interval, 0.89 to 0.99). This effect remained unchanged after adjusting for self-reported adherence.

Conclusions. Food insecurity was associated with lower ART concentrations in hair, suggesting that food insecurity may be associated with suboptimal ART adherence and/or drug absorption. Interventions seeking to improve ART adherence among WLHIV should consider and address the role of food insecurity.

Keywords. food insecurity; antiretroviral therapy; adherence; ART concentrations in hair; women living with HIV.

Food insecurity was associated with lower antiretroviral therapy (ART) concentrations in hair, an objective measure of drug adherence and exposure, among women living with human immunodeficiency virus. Programs seeking to improve ART adherence should address food insecurity among this population.

Food insecurity, which refers to having limited or uncertain availability of nutritionally adequate and safe food [1], is a well-established determinant of suboptimal antiretroviral therapy (ART) adherence [2–6]. Research among women living with human immunodeficiency virus (WLHIV) in the United States has demonstrated that current, previous, and persistent food insecurity are associated with reduced ART adherence measured by self-report and unannounced pill counts [7, 8]. Evidence suggests that people living with HIV (PLHIV) who are food insecure may avoid taking ART when they do not have enough food to eat due to fears or actual experiences of acute hunger and/or increased

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Correspondence: A. M. Leddy, 550 16th St., 3rd floor, San Francisco, CA 94158 (anna.leddy@ucsf.edu).

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side effects such as nausea or vomiting from taking ART on an empty stomach [2, 9, 10]. PLHIV experiencing food insecurity also have described having to make trade-offs between using their limited resources to access food instead of medical care or transport costs to the clinic, often resulting in missed ART doses [2]. Additionally, food insecurity is associated with increased risk of substance use [11] and poor mental health outcomes including depression, anxiety, and stress [12, 13], which have been associated with suboptimal ART adherence [14, 15].

The vast majority of studies that examine the relationship between food insecurity and ART adherence have measured adherence through self-report [6, 7], which is susceptible to recall and social desirability bias [16]. Other studies that have examined the relationship between food insecurity and ART adherence have used unannounced pill counts [5, 8, 17, 18] and pharmacy refills [19] to measure adherence. Unannounced pill counts have been associated with concurrent viral suppression [16, 20], and pharmacy refills have demonstrated strong predictive validity of both viral load and CD4 cell counts [16, 21, 22]. However, the validity of such measures rests on the assumption that the number of pills remaining in unannounced pill counts reflects the number of pills dispensed minus the number of pills consumed, that pharmacy refill records are complete, and that patients consume all their pills before they receive a pharmacy refill [16]. If these assumptions are not met, these measures may be inaccurate [16, 23].

Concentrations of ART in hair is an objective and validated measure of drug adherence and exposure [24–28]. Prior research has demonstrated that the concentration of ART in hair is strongly and independently associated with viral suppression [24, 25] and is a stronger predictor of viral suppression than self-reported adherence [26, 29]. Few studies have examined the effect of sociostructural factors, such as food insecurity, on concentrations of ART in hair as a marker of ART adherence and exposure. In addition to influencing ART adherence, food insecurity may play an important role in drug exposure, given that some antiretrovirals (ARVs), such as atazanavir (ATV) and darunavir (DRV), need to be taken with food to facilitate absorption [30, 31]. Research examining the relationship between social-structural determinants, such as food insecurity, and ART adherence and exposure must use the most objective measures, such as concentrations of ART in hair, to justify and inform intervention approaches. Accordingly, in this study, we examined the association of food insecurity with concentrations of ART in hair as an objective measure of ART adherence and exposure among WLHIV in the United States. We also assessed the relationship between food insecurity and ART hair concentrations after adjusting for self-reported adherence to determine whether food insecurity was associated with aspects of adherence and drug exposure not captured by self-reported adherence.

METHODS

Study Population

Established in 1993, the Women's Interagency HIV Study (WIHS) is a large, multisite, prospective, observational, cohort study of WLHIV and demographically similar controls in the United States [32]. Data are collected semiannually through interviews, physical exams, and laboratory tests. Participants provide informed consent for all study procedures and are compensated for their time.

Since 2013, the Food Insecurity Sub-Study of the WIHS has included measures of food insecurity and dietary intake in semiannual interviews at all 10 sites (Bronx, New York; Brooklyn, New York; Washington, D.C.; San Francisco, California; Chicago, Illinois; Chapel Hill, North Carolina; Atlanta, Georgia; Miami, Florida; Birmingham, Alabama; and Jackson, Mississippi). We analyzed longitudinal data collected every 6 months from April 2013 through March 2015 among participants enrolled in WIHS from these sites. Hair samples were collected from all WLHIV reporting ARV use since their last study visit and were subsequently tested for concentrations of DRV, ATV, raltegravir (RAL), and dolutegravir (DTG). DRV, ATV, RAL, and DTG were selected for analysis as they were the most commonly used drugs in the cohort for which the hair assays were developed. We identified 677 women (1943 person-visits) who were eligible for inclusion in this analysis because they were HIV seropositive; on DRV, ATV, RAL, or DTG; had stored hair samples; and were enrolled in the food insecurity substudy between April 2013 and March 2015. Seven women were excluded because they had an insufficient amount of hair collected to meet assay requirements. The final sample for this analysis comprised 670 women.

Concentration of ART in Hair

Hair samples (approximately 10–20 strands) were cut close to the scalp from the occipital region at each visit among consenting WIHS participants on ART [24, 26]. The portions subsequently analyzed were those most proximal to the head (at least 1 cm in length or 1 month's worth of growth) and represented 1–5 mg of hair. ATV, RAL, DRV, and DTG concentrations in hair samples were determined by validated liquid chromatography-mass spectrometry methods with stable isotopically labeled ATV-d_5, RAL-d_6, DRV-d_9, and DTG-^{13}C-d_5 used as internal standards. Due to the varied extraction efficiencies of the drugs, 3 extraction solvents (70:30 methanol:water with 2% formic acid for ATV and RAL, 70:30 methanol:water for DRV, and 50:50 methanol:acetonitrile with 2% formic acid for DTG) were required. Following extraction, chromatographic separation was achieved under gradient conditions on a Waters Sunfire C18 (2.1 × 50 mm, 3.5 μm) analytical column for ATV and RAL and on a Waters Atlantis T3 (50 × 2.1 mm, 3 μm) analytical column for DRV and DTG. All compounds

were detected on an AB Sciex API-5000 triple quadrupole mass spectrometer using electrospray ionization in the negative ion mode for ATV and RAL and in the positive ion mode for DRV and DTG. Calibration ranges were 0.1 to 100 ng/mL for ATV and RAL, 0.05 to 50 ng/mL for DRV, and 0.005 to 10 ng/mL for DTG. Calibration standards and quality control samples for all 3 assays met precision and accuracy criteria of 15%.

Predictor

Food insecurity was measured using the validated 18-item US Household Food Security Survey Module (HFSSM) [1, 33]. The HFSSM measures uncertainty about household food supplies and insufficient diet quality and food quantity among adults and their children in the past 12 months [1]. The module includes 18 items that range in severity from worrying about running out of food to not eating for a whole day. Participants report whether or not they have experienced each situation (0 = no, 1 = yes), and scores are summed. This continuous measure of food insecurity has scores that range from 0 to 18, with higher scores being indicative of increased severity of food insecurity. The internal consistency of the HFSSM was high in the sample (Cronbach's alpha, 0.91). To facilitate interpretation, the food insecurity variable was rescaled so that a 1-unit increase corresponds to a 3-point increase in the HFSSM score.

Outcome

The outcome was concentration of DRV, ATV, RAL, or DTG in hair samples, with undetectable concentrations set to equal the limit of detection. The concentrations were reported for each drug, and a participant could contribute a maximum of 2 drugs per visit. A general concentration level variable was programmed as the main outcome, which was log-transformed to satisfy assumptions of normality and to better reflect the clinical importance of differences between concentrations. A fixed effect for drug was included in all models to account for differing concentrations of the different drugs, and all models allowed for distinct residual variances for the different drugs.

Covariates

Covariates were selected based on prior research on factors associated with food insecurity, ART adherence, and pharmacology. Sociodemographic covariates included age at visit (per 10 years), race/ethnicity (non-Hispanic white, Hispanic, black/African American, or other), annual household income (≤$12 000, $12 001–$24 000, $24 001–$36 000, $36 001–$75 000, ≥ $75 001), education (high school education or more compared with less than high school education), self-reported illicit substance use since the last visit, and self-reported adherence. Illicit substance use was defined as self-reported cocaine, crack, heroin, methamphetamine, hallucinogens, club drugs, nonprescribed narcotics, or any other illicit recreational drugs, excluding any form of marijuana, in the last 6 months or since the last visit.

We also examined kidney and liver function as they can independently affect the pharmacology of DRV, ATV, RAL, and DTG. Kidney function was measured using the estimated glomerular filtration rate (EGFR, mL/min; calculated using the Chronic Kidney Disease–Epidemiology Collaboration equation) [34]. Given that renal function does not affect DRV, we treated all observations of DRV as having a fixed, typical EGFR value of 100, allowing us to measure the effect of renal function on hair concentrations of the other drugs. We found strong evidence for a nonlinear effect of EGFR on hair concentrations, so the variable was subsequently modeled with a linear spline, allowing it to have different effects below and above 100 mL/min. EGFR results are presented per 10-point increase. Liver function was measured using the alanine aminotransferase (IU/L) test, the aspartate aminotransferase (IU/L) test, and the gamma-glutamyltransferase (IU/L) test. All of these measures were log base 2–transformed to better meet the linearity assumption and to prevent overly influential outliers. None of the measures of liver function were statistically significantly associated with ART concentrations in hair in unadjusted models and were therefore not included in the multivariable models. However, EGFR was statistically significantly associated with concentrations of ART in hair and was therefore included in the multivariable models.

Self-reported ART adherence was assessed by asking participants to indicate how often they took their ARVs as prescribed in the past 6 months. Response options ranged from 1 (100% of the time) to 5 (I haven't taken any of my prescribed medications). This measure has been found to predict CD4 cell count and viral load as well as, or better than, other measures of self-reported adherence [35].

Statistical Analyses

Summary statistics were examined at study baseline (ie, the first visit a participant contributed during the study period). Next, we conducted multiple 3-level linear regressions that accounted for repeated visits and multiple drug concentrations for each participant. We evaluated each predictor in a model with just the predictor and the 4-category drug classification as the 2 fixed effects. A multivariable model adjusting for sociodemographic and clinic characteristics was subsequently conducted. We then ran the same multivariable model but also adjusted for self-reported ART adherence to see if the relationship between food insecurity and ART concentration in hair persisted after adjusting for self-reported ART adherence. Estimated regression coefficients were exponentiated and interpreted as the relative difference in the hair concentration per unit increase in each predictor. All analyses were done using Stata 14 (StataCorp LP, College Station, TX).

This research was conducted as part of the WIHS and was approved by the institutional review boards at all WIHS study sites.

RESULTS

Sample Characteristics

The median age was 49 years (interquartile range, 42–55), and the majority of the sample was black/African American (n = 464, 70%; Table 1). More than half of the sample (n = 345, 54%) had an annual household income of ≤$12 000, and 35% (n = 237) reported some degree of food insecurity. The proportion reporting food insecurity was similar in women included in this sample and in other women living with HIV in the WIHS (35% vs 37%). More than half of the women in this sample (n = 439, 67%) were virally suppressed, and 82% (n = 550) self-reported adhering to their ART regimen 95% of the time or more.

Table 1. Sociodemographic and Clinical Characteristics of Women Living With Human Immunodeficiency Virus in the Women's Interagency HIV Study at the First Visit in the Food Insecurity Substudy (n = 670)

Characteristic	N (%)
Sociodemographic characteristic	
Food security	
High	422 (64)
Marginal	92 (14)
Low	70 (11)
Very low	75 (11)
Age, median (IQR), y	49 (42 to 55)
Race/Ethnicity	
Non-Hispanic white	75 (11)
Hispanic	110 (17)
Black/African American	464 (70)
Other	13 (2)
Annual household income	
≤$12 000	345 (54)
$12 001–$24 000	143 (23)
$24 001–$36 000	71 (11)
$36 001–$75 000	47 (7)
≥$75 001	30 (5)
High school education or more	429 (65)
Any illicit substance use since last visit	57 (9)
Clinical characteristics	
Self-reported adherence, %	
100	344 (51)
95–99	206 (31)
75–94	86 (13)
<75	31 (5)
Virally suppressed	439 (67)
Estimated glomerular filtration rate, median (IQR), IU/L	94 (73 to 109)
Liver enzymes, median (IQR), IU/L	
Aspartate transaminase	21 (17 to 27)
Alanine transaminase	17 (12 to 24)
Gamma-glutamyltransferase	25 (17 to 41)
Antiretroviral therapy regimens	
Atazanavir	225 (34)
Darunavir	232 (35)
Dolutegravir	83 (12)
Raltegravir	128 (19)
Concentration of antiretroviral drug in hair,[a] median (IQR), ng/mg	
Atazanavir	1.0 (0.2 to 1.5)
Darunavir	1.7 (1.1 to 2.2)
Dolutegravir	−0.9 (−2.1 to −0.4)
Raltegravir	0.4 (−0.3 to 0.9)

Abbreviation: IU, international units; IQR, interquartile range.

[a]On the $\log_{10}$ scale.

Association Between Food Insecurity and ART Concentrations in Hair

In the single predictor models (Table 2), each 3-point increase in food insecurity was associated with a 0.93-fold lower ART concentration in hair (95% confidence interval [CI], 0.88–0.98; $P < .01$). Older age was associated with higher ART concentration in hair. Compared with non-Hispanic white race/ethnicity, Hispanic, black/African American, and other race/ethnicity had higher ART concentrations in hair. Higher EGFRs were associated with decreased ART concentrations in hair and with a larger effect in the range above 100 than below 100. Compared with women who self-reported 100% ART adherence, women with lower self-reported adherence had lower concentrations of ART in hair.

In the adjusted model, controlling for sociodemographic characteristics and clinical characteristics including kidney function, every 3-point increase in food insecurity was associated with 0.94-fold lower ART concentration in hair (95% CI, 0.89–0.99; $P < .05$). Older age remained statistically significantly associated with higher ART concentrations in hair as did Hispanic, black/African American, and other race/ethnicities compared with non-Hispanic white. Kidney function also remained statistically significantly associated with lower ART concentrations in hair.

With self-reported adherence added to the adjusted model, the relationship between food insecurity and ART concentrations in hair remained unchanged (fold effect, 0.94; 95% CI, 0.89–1.00; $P < .05$).

DISCUSSION

In this study, food insecurity was associated with reduced concentrations of ART in hair among WLHIV in the United States, suggesting that food insecurity may be associated with suboptimal ART adherence and exposure. To our knowledge, this is one of the first studies to explore a structural driver of ART hair concentrations and the first to examine the association between food insecurity and ART hair concentrations. Findings support the growing body of evidence that demonstrates that food insecurity may be associated with reduced ART adherence and provides the first evidence to suggest that food insecurity may be associated with a combined measure of adherence and exposure [2–6].

Interestingly, the effect of food insecurity on ART concentrations in hair persisted after adjusting for self-reported ART

Table 2. Adjusted Associations Between Food Insecurity and Antiretroviral Therapy Concentrations in Hair Among Women Living With Human Immunodeficiency Virus in the Women's Interagency HIV Study

Characteristic	Single-predictor Model[a] Fold-effect[b] (95% CI)	Adjusted Model[a] Fold-effect[b] (95% CI)	Adjusted Model[a] + Self-reported Adherence Fold-effect[b] (95% CI)
Food insecurity score (continuous, per 3 points)	0.93 (.88–.98)**	0.94 (.89–.99)*	0.94 (.89–1.00)*
Age at visit (per 10 years)	1.20 (1.10–1.30)***	1.12 (1.02–1.22)*	1.11 (1.02–1.21)*
High school education or more	1.03 (.88–1.21)	1.08 (.92–1.27)	1.07 (.91–1.25)
Race/ethnicity			
Non-Hispanic white	(reference)	(reference)	(reference)
Hispanic	1.34 (1.00–1.78)*	1.44 (1.08–1.93)*	1.46 (1.09–1.95)*
Black/African American	1.52 (1.19–1.93)***	1.67 (1.31–2.13)***	1.70 (1.33–2.17)***
Other	1.85 (1.05–3.24)*	1.98 (1.14–3.44)*	1.99 (1.15–3.45)*
Annual household income			
≤$12 000	(reference)	(reference)	(reference)
$12 001–$24 000	0.91 (.78–1.05)	0.93 (.80–1.07)	0.93 (.81–1.08)
$24 001–$36 000	0.98 (.80–1.19)	1.02 (.83–1.24)	1.03 (.84–1.26)
$36 001–$75 000	0.86 (.68–1.09)	0.91 (.72–1.16)	0.92 (.72–1.17)
≥$75 001	0.80 (.57–1.10)	0.87 (.63–1.21)	0.88 (.63–1.22)
Illicit substance use since last visit	0.88 (.71–1.09)	0.93 (.75–1.15)	0.97 (.79–1.21)
EGFR (per 10 points when values are below 100)	0.91 (.88–0.94)***	0.93 (.90–.97)***	0.94 (.90–.97)***
EGFR (per 10 points when values are above 100)	0.84 (.78–.90)***	0.88 (.81–.95)**	0.88 (.81–.95)**
Aspartate transaminase, $\log_2$	1.01 (.93–1.10)	…	…
Alanine transaminase, $\log_2$	1.04 (.97–1.12)	…	…
Gamma-glutamyltransferase, $\log_2$	1.04 (.98–1.11)	…	…
Self-reported adherence, %			
100	(reference)	…	(reference)
95–99	0.95 (.85–1.06)	…	0.97 (.87–1.08)
75–94	0.77 (.66–.91)**	…	0.81 (.69–.95)**
<75	0.80 (.62–1.04)	…	0.80 (.62–1.05)

n = 637. Effects only apply to atazanavir, raltegravir, or dolutegravir, not darunavir.

Abbreviations: CI, confidence interval; EGFR, estimated glomerular filtration rate.

[a]All models include terms and options to allow the 4 drugs (darunavir, atazanavir, raltegravir, or dolutegravir) to have differing mean levels and differing residual variation. Only the relative (multiplicative) effects of the characteristics are assumed to be the same across drugs.

[b]Hair levels were logarithmically transformed for modeling purposes because raw differences of a given magnitude have differing meanings depending on whether hair levels are high or low and differing meanings across different drugs, while relative differences of a given magnitude remain comparably meaningful in these different situations. Regression coefficients were back-transformed from the log scale to obtain fold-effects.

*$P < .05$, **$P < .01$, ***$P < .001$.

adherence. There are 2 possible explanations for this finding. First, food insecurity may have an independent effect on drug absorption, separate from adherence. As described above, ATV and DRV must be taken with food to facilitate drug absorption [30, 31]. For example, taking ATV with a light meal (357 kcal) results in a 70% increase in the area under the curve (AUC) compared with fasting state [30]. Further, although integrase inhibitors such as DTG and RAL can be taken without regard to food, high-fat meals are known to increase the plasma AUC of these medications as well [36, 37]. For example, taking 50 mg of DTG with a high-fat meal (870 kcal) results in a 66% increase in AUC compared with fasting state [36]. Thus, individuals who experience food insecurity or uncertain access to food may not always be able to take such drugs with food, which could lead to poor or less extensive drug absorption. Second, it is also possible that the relationship between food insecurity and ART concentrations in hair is explained by adherence behaviors not captured in the self-reported adherence measure (eg, underreporting missed doses). Prior research has found that self-reported adherence is prone to social desirability and recall bias and, therefore, may not be completely capturing the adherence behaviors of participants [16]. As noted earlier, food insecurity has been associated with suboptimal adherence through a variety of mechanisms including fears of side effects/acute hunger from taking ART on an empty stomach, competing needs, substance use, and negative mental health outcomes including depression [2, 7, 11, 13]. It will be important for future research to tease apart how much of the relationship between food insecurity and ART concentrations in hair is explained by ART adherence vs drug exposure. Such information could provide important insights into the role food insecurity plays in ART adherence behavior and, separately, drug absorption.

Findings from this study suggest that ensuring consistent access to nutritious and high-quality food may be an important

intervention to improve ART adherence and absorption among PLHIV. The World Health Organization [38], the Joint United Nations Programme on HIV/AIDS [39], and the World Food Programme [40] all recommend the integration of food and nutritional support into HIV care and treatment services. Some researchers have assessed the influence of food assistance programs on ART adherence among PLHIV and have largely demonstrated improvements in adherence [41–45]. However, few of these studies have utilized randomized, controlled designs, and the vast majority have been conducted in resource-limited settings, particularly in Africa. Our findings suggest that such interventions may also be relevant in the United States. Studies of such interventions should utilize randomized, controlled trial designs and should assess whether food assistance programs for PLHIV are associated with improved ART adherence and exposure.

There were several limitations of this study. The observational design of WIHS limits our ability to infer causality. We also lacked hair data on participants who were on ART regimens other than those that included DRV, ATV, RAL, and DTG. Our findings, therefore, may not apply to other ART regimens. Future research should explore the relationship between food insecurity and hair concentrations of other ART regimens. Additionally, we did not use other objective measures of adherence, such as unannounced pill counts or medication event monitoring system caps, which may have better enabled us to determine whether the effects we found were due to drug absorption vs adherence.

Despite these limitations, our study has strengths. We utilized longitudinal data, which allowed us to examine the relationship between food insecurity and ART concentrations in hair over time. Additionally, the use of ART concentrations in hair in our analysis was a strength as it is an objective and valid measure of ART adherence and drug exposure [24–27].

CONCLUSIONS

We found that food insecurity was associated with lower levels of concentrations of ART in hair, which serve as a biomarker of adherence and a measure of drug exposure. This relationship persisted after adjusting for self-reported ART adherence, suggesting that food insecurity may independently affect ART absorption or adherence behaviors not captured by self-report. Future research is needed to unpack the relationships between food insecurity, ART absorption, and adherence. The results from this study support the need for HIV care and treatment services to address food insecurity among WLHIV to improve their ART adherence behaviors and/or drug absorption.

Notes

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