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MAJOR ARTICLE

Food Insecurity Is Associated With Low Tenofovir Diphosphate in Dried Blood Spots in South African Persons With HIV

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Background. Food insecurity has been linked to suboptimal antiretroviral therapy (ART) adherence in persons with HIV (PWH). This association has not been evaluated using tenofovir diphosphate (TFV-DP) in dried blood spots (DBSs), a biomarker of cumulative ART adherence and exposure.

Methods. Within a prospective South African cohort of treatment-naive PWH initiating ART, a subset of participants with measured TFV-DP in DBS values was assessed for food insecurity status. Bivariate and multivariate median-based regression analysis compared the association between food insecurity and TFV-DP concentrations in DBSs adjusting for age, sex, ethnicity, medication possession ratio (MPR), and estimated glomerular filtration rate.

Results. Drug concentrations were available for 285 study participants. Overall, 62 (22%) PWH reported worrying about food insecurity and 44 (15%) reported not having enough food to eat in the last month. The crude median concentrations of TFV-DP in DBSs differed significantly between those who expressed food insecurity worry versus those who did not (599 [interquartile range {IQR}, 417–783] fmol/punch vs 716 [IQR, 453–957] fmol/punch; $P = .032$). In adjusted median-based regression, those with food insecurity worry had concentrations of TFV-DP that were 155 (95% confidence interval, −275 to −35; $P = .012$) fmol/punch lower than those who did not report food insecurity worry. Age and MPR remained significantly associated with TFV-DP.

Conclusions. In this study, food insecurity worry is associated with lower TFV-DP concentrations in South African PWH. This highlights the role of food insecurity as a social determinant of HIV outcomes including ART failure and resistance.

Keywords. adherence; antiretroviral therapy; dried blood spots; food insecurity; tenofovir diphosphate.

South Africa has the highest number of people with human immunodeficiency virus (PWH) and fourth-highest prevalence of human immunodeficiency virus (HIV) globally, with an estimated 7.8 million cases in 2020 [1]. Several drivers of this high prevalence have been proposed, including social determinants of health (SDoH) such as low income and food insecurity [2]. Of note, South Africa has experienced an increase in food insecurity between 2020 and 2022; food insecurity presently affects >20% of its population due to natural disasters, political unrest, supply chain challenges, and the coronavirus disease 2019 pandemic [3, 4]. Defined as the lack of regular access to safe and nutritious foods for normal growth and development as well as an active and healthy life, food insecurity is a recognized determinant of HIV outcomes via several proposed pathways [5]. These include poor medication absorption from malnutrition, as well as poor medication adherence due to fears or actual experience of increased ART side effects in the absence of adequate nutritional intake; cost-reducing behaviors such as selling medication or skipping clinic visits for other competing priorities; and associated mental health comorbidities such as depression and anxiety [6–8].

Access to antiretroviral therapy (ART) has increased the proportion of PWH who are engaged in care and have achieved viral suppression [9]. However, durable ART adherence is still required for sustained viral suppression. Poor adherence to

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ART medications can lead to adverse HIV outcomes such as viremia, virologic failure, antiretroviral resistance, and HIV transmission [10]. While ART alone is known to reduce disease burden, SDoH (including food insecurity) are also influential in determining a patient's access to, and empowerment in, utilizing these medications effectively over time, during a lifelong course of disease management [2, 8, 11–17].

Research on ART adherence has usually relied on measures that are subject to reporting bias and cannot confirm medication ingestion [18]. Antiretroviral concentrations in urine, hair, and dried blood spots (DBSs) can address some of these limitations, as they can serve as both measures of adherence and pharmacokinetics (ie, absorption, distribution, metabolism, and excretion) in a single test. Tenofovir diphosphate (TFV-DP) in DBSs—a quantitative measure of cumulative ART adherence to tenofovir-based regimens—is easily collected and is a highly informative ART adherence measure that is predictive of HIV outcomes including viral suppression, future viremia, drug resistance, virologic failure, and endothelial/immune activation [10, 18–20].

Prior research in the United States (US) has demonstrated an inverse association between food insecurity and pharmacologically measured ART adherence quantified using antiretroviral drug concentrations in hair [21]. Another study has linked income inequality with ART concentrations measured in DBSs [13]. To date, no studies have evaluated the relationship between food insecurity and a DBS-based adherence biomarker in a resource-limited setting. To address this gap, we evaluated whether food insecurity was associated with drug concentrations of TFV-DP in DBSs in South African PWH.

METHODS

Patient Consent Statement

All patients provided informed written consent prior to their participation in the study. The study was approved by the University of KwaZulu-Natal (KZN) Biomedical Research Ethics Committee and the Emory University and MassGeneral Brigham institutional review boards.

Overview

A secondary data analysis of the KZN HIV/AIDS Drug Resistance Surveillance Study (ADReSS) in South Africa was conducted [22, 23]. The primary exposures of interest were self-reported measures of food insecurity in the last month. The primary outcome of interest in this subanalysis was cumulative ART adherence, measured using TFV-DP in DBSs. Covariates of interest included sociodemographic and clinical factors such as age, sex, race, ethnicity, education, income, wealth index, employment, distance to HIV clinic, psychological distress, medication possession ratio (MPR), and estimated glomerular filtration rate (eGFR). Univariate, bivariate, and multivariate relationships identified significant associations between exposure variables and TFV-DP concentration using an $\alpha = .05$ level with no adjustments for multiple comparisons. Significantly associated covariates with both the primary exposure and outcome variables were used in a stratified analysis to explore potential effect modification or confounders.

Study Design

The parent study ADReSS was an observational nested case-control study conducted in KZN, South Africa, to assess ART response and resistance among those initiating first-line ART (efavirenz/tenofovir disoproxil fumarate/emtricitabine). Study enrollment of 1000 ART-naive patients took place at 2 clinics, R. K. Khan Hospital and Bethesda District Hospital Clinic, between July 2014 and September 2016, as previously described [10, 23]. Inclusion criteria required participants to be ≥18 years of age when first-line ART was initiated consisting of tenofovir disoproxil fumarate (TDF) and emtricitabine, plus efavirenz (a single-tablet regimen) or nevirapine, which were provided by South African Health authorities. PWH were excluded if they had any prior ART except for single-dose nevirapine for HIV vertical transmission prevention.

Participants were then followed prospectively with HIV RNA measurement (viral load [VL]) obtained at 6 months, 12 months, and annually thereafter to identify cases and controls. Cases were participants who had met criteria for virologic failure, defined as HIV-1 VL >1000 copies/mL after receiving ≥5 months of ART, and controls were participants without virologic failure (participants who had VL ≤1000 copies/mL) matched 2:1 by study site, sex, closest age, and duration of ART (Figure 1). At the follow-up study visit where case-control status was determined, DBS samples were obtained to quantify TFV-DP concentrations. At the same visit, participants completed surveys with questions regarding the primary exposure of interest—food insecurity—as well as secondary covariates of interest such as socioeconomic status, stigma, ART challenges, and mental health assessments. Participants remained blinded to their virologic failure status until completion of the survey; subsequently, participants followed clinic protocols for adherence counseling and a confirmation of VL. This temporary participant blinding was intended to avoid any influence on survey responses, without delay in appropriate care. Additional data such as VL, $CD4^+$ T-cell count, and serum creatinine were collected throughout the study duration at 6-month intervals.

Data Collection

Whole blood for DBSs was collected in ethylenediaminetetraacetic acid tubes and 25 μL was spotted 5 times onto 903 protein saver cards. The concentrations of TFV-DP in DBSs were quantified from a 3-mm punch using a validated liquid chromatography–tandem mass spectrometry assay with a limit of quantification of 25 fmol/sample [24]. Blood for HIV VL,

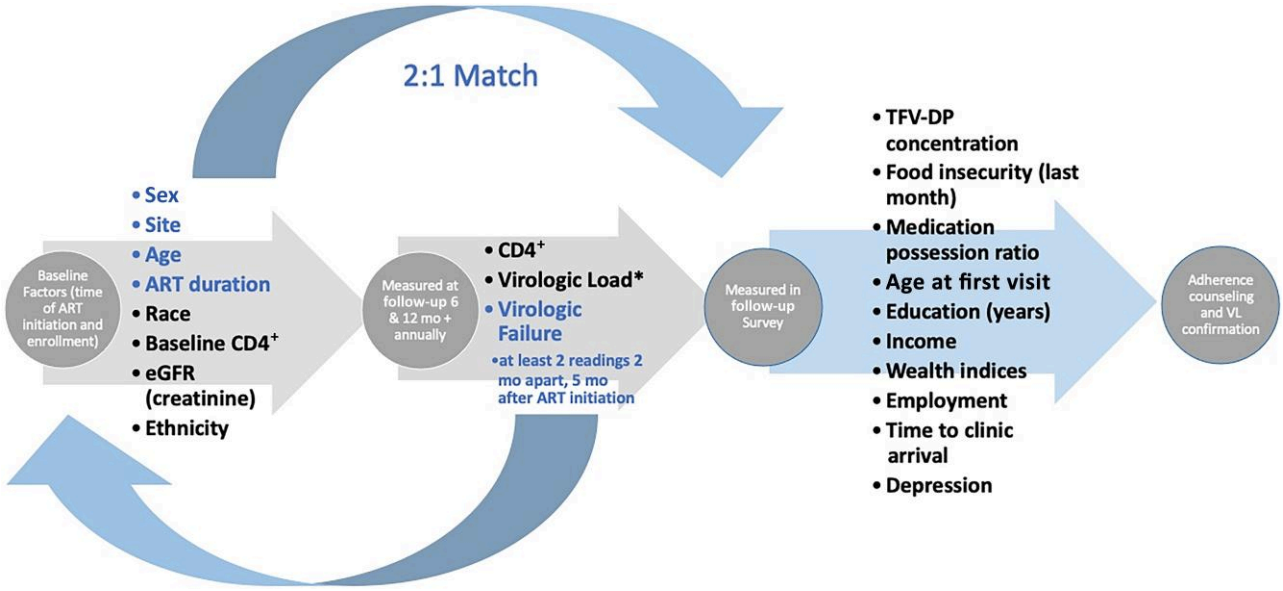

Figure 1. At the initial study visit, baseline characteristics were noted such as sex, age, race, and study site. Testing was obtained for participants' baseline $CD4^+$ T-cell count and serum creatinine. Subsequent blood samples for plasma human immunodeficiency virus type 1 RNA viral load (VL) and $CD4^+$ T-cell count were obtained at 6 months, 12 months, and annually thereafter. Virologic failure status was defined in participants whose VL values exceeded 1000 copies/mL in at least 2 readings, 2 months apart, after a minimum of 5 months of antiretroviral therapy (ART). Participants with virologic failure were matched 1:2 to participants without virologic failure (<1000 copies/mL) by age, sex, site, and ART duration. Participants completed a follow-up study visit survey, where questions regarding socioeconomic status, stigma, ART challenges, and mental health assessments were included. At this visit, dried blood spots were also obtained to quantify tenofovir diphosphate concentrations. Subsequently, participants followed clinic protocols for adherence counseling and a confirmation of VL. *To assess for virologic failure. Abbreviations: ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; TFV-DP, tenofovir diphosphate; VL, viral load.

$CD4^+$ T-cell count, and blood chemistries were obtained per local standard of care [22]. Participants responded to a questionnaire containing adapted validated psychosocial scales (including the World Health Organization [WHO] wealth index [25, 26], Household Food Insecurity Access Scale measures [modified] [27], and psychological distress screening using the Kessler-10 scale [28, 29]). Food security was assessed with the following 3 questions: "In the past 4 weeks, did you worry that you and your family would not have enough food?"; "In the past 4 weeks, was the amount of food you and your family has to eat enough, sometimes not enough, or often not enough to eat?"; and "In the past 4 weeks, how many times did you and anyone in your family go an entire day and night without food because there was not enough food?" For each food security measure, respectively, any participant answer indicating having ever worried, ever not had enough to eat, or ever gone 24 hours without food in the last 4 weeks was considered as food insecure. Participants with a Kessler-10 score >20 were considered psychologically distressed. The MPR, which was estimated using the number of days' supply for all pharmacy fills of ART medication in a particular time period divided by the number of days in that period multiplied by 100, was corrected with an adjustment for values >100% caused by early refills and was used to estimate participants' medication adherence [30]. Collected response variables were composited into variables of interest for analysis in R software (version 2022.02.2) (R Foundation for Statistical Computing, Vienna, Austria, 2017).

Data Analysis

The primary study outcome of this secondary analysis was TFV-DP in DBS samples. Concentrations of TFV-DP in DBSs that were below the limit of quantification were imputed to 12.5 fmol/punch, as previously described [31]. Serum creatinine measured at baseline (closest value to enrollment within a period 1 year prior to enrollment and up to 90 days after) were used to calculate eGFR using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) 2021 formula [32]. Preliminary analyses examined the relationship between concentrations of TFV-DP in DBSs and food insecurity, as well as other variables of interest using Wilcoxon rank-sum tests for categorical variables and Spearman correlation for continuous variables ($P < .05$). The relationships between predictors, food insecurity measures, and participant characteristics were analyzed using either χ^2 or Fisher exact test for categorical characteristics, as appropriate, and Wilcoxon rank-sum tests for continuous variables. Crude differences in TFV-DP concentrations compared by covariates of interest were then calculated using median-based regression. Standard error was calculated using the bootstrapping method.

Table 1. Participant Characteristics in the HIV AIDS Drug Resistance Surveillance Study (ADReSS) Cohort Nested Case-Control Subset (N = 285)

Characteristic	No. (%) or Median (IQR)
Food insecurity worry in last month	
Never experienced	207 (72)
Experienced	62 (22)
Missing[a]	16 (6)
Enough to eat in last month	
Always	235 (83)
Not always	44 (15)
Missing	6 (2)
24 h without food in last month	
Never experienced	266 (93)
Experienced	14 (5)
Missing	5 (2)
Age at first visit, y	31 (26–38)
Sex	
Male	119 (42)
Female	166 (58)
Race	
Black or mixed race	275 (96)
Indian	10 (4)
Ethnicity	
Zulu	220 (77)
Xhosa	33 (12)
Other	22 (8)
Missing	10 (4)
Education, y	11 (9–12)
Income	
No	71 (25)
Yes	209 (73)
Missing	5 (2)
Wealth indices[a,b]	
Wealth index 1	0.2 (−1.1 to 1.5)
Wealth index 2	−0.7 (−0.9 to 0.5)
Employment	
Unemployed	99 (35)
Employed	168 (59)
Other	13 (4)
Missing	5 (2)
Time to clinic arrival, min	
<30	79 (28)
30–60	178 (62)
>60	22 (8)
Missing	6 (2)
Psychological distress[c]	
No	254 (89)
Yes	22 (8)
Missing	9 (3)
eGFR[d], mL/min/1.73 m²	
>90	210 (74)
60–90	26 (9)
<60	4 (1)
Missing[a]	45 (16)
MPR[e], %	
≥100	96 (34)
85–99	82 (29)
<85	106 (37)
Missing	1 (0.3)
TFV-DP concentration[f], fmol/punch	696 (443–938)
CD4⁺ T-cell count at follow-up, cells/μL	371 (223–520)
HIV RNA load at follow-up, copies/mL	40 (24–150)
Virologic failure	
No	193 (68)
Yes	92 (32)

Abbreviations: eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IQR, interquartile range; MPR, medication possession ratio; TFV-DP, tenofovir diphosphate.

[a]More than 5% of responses missing.

[b]Wealth indices missing 17 responses each (6%).

[c]Psychological distress was considered in participants scoring ≥20 on the Kessler-10 scale.

[d]eGFR missing in 166 participants (58%).

[e]MPR percentage missing 1 response (<1%).

[f]TFV-DP concentrations below the lower limit of quantification were imputed to 12.5 fmol/punch.

An adjusted multivariate model using median-based regression was created to include covariates that were significantly associated with TFV-DP concentration in bivariate analyses. Additional variables decided based on prior literature (sex and ethnicity) were also added into the model [10]. The adjusted median-based regression model measuring the association between food insecurity and TFV-DP concentration thus included age, sex, ethnicity, and MPR. Potential confounders and effect modifiers were identified with stratified analysis. While eGFR had fewer participant data available, a sensitivity analyses was conducted to account for it in the adjusted regression model as it remained of interest based on the literature [32]. An additional version of the adjusted model was created without MPR to determine its impact on the relationship between food insecurity and TFV-DP concentration.

An additional analysis was conducted with an aggregated food insecurity measure, which combined 2 of the food security measures that asked about food insecurity worry in the last month and lack of food in the last month. Responses indicating whether participants had ever worried and/or had a lack of food were scaled categorically with the following options: food insecure, partially food insecure, or food secure. This aggregated food insecurity measure was then compared to TFV-DP in crude and adjusted models using the same model covariates: age, sex, ethnicity, and MPR.

RESULTS

The parent cohort enrolled a total of 1000 treatment-naive PWH who initiated first-line ART [22]. This subanalysis included data from 285 PWH in whom TFV-DP concentrations in DBS were available, 92 (32%) of whom had virologic failure. Demographic and baseline clinical characteristics of the study participants are shown in Table 1. Overall, 166 (58%) of the

participants were women, 275 (96%) were Black including 2 participants who identified as mixed race, 220 (77%) identified as ethnically Zulu, 209 (73%) reported having an income, and 168 (59%) were employed. The median age at first visit was 35 (interquartile range [IQR], 26–38) years, the number of years of education attained was 11 (IQR, 9–12), and the wealth index resolved on 2 principal component analyses was 0.2 and −0.7. Clinically, 22 (8%) participants screened positive for psychological distress, 30 (10%) had an eGFR <90 mL/minute/1.73 m^2, and 106 (37%) had an MPR <85%. Examining secondary outcome measures, the median baseline $CD4^+$ T-cell count was 286 (IQR, 171–386) cells/μL, which increased to 371 (IQR, 223–520) cells/μL at the time concurrent with DBS testing.

The median TFV-DP concentration in DBS for the whole cohort was 696 (IQR, 443–938) fmol/punch (Table 1). In the month prior to being surveyed, 62 (22%) participants reported experiencing worry about food insecurity and 44 (15%) participants reported that they had insufficient food to eat. An additional 14 (5%) participants reported going 24 hours without eating due to insufficient food; given this limited sample size of affirmative responses, this variable was not included in further analyses.

Bivariate analyses indicated a significant association between food insecurity worry and TFV-DP concentrations in DBS (Table 2). Study participants who reported food insecurity worry had a lower median TFV-DP concentration compared to those without food insecurity worry (599 [IQR, 417–783] fmol/punch vs 716 [IQR, 453–957] fmol/punch; $P = .031$). PWH who reported insufficient food in the last month also had lower TFV-DP concentrations compared to those who always had enough to eat, although the association was not statistically significant (613 [IQR, 480–838] fmol/punch vs 699 [IQR, 419–943] fmol/punch; $P = .361$). Significant associations were additionally found in bivariate analyses comparing median TFV-DP concentrations to both age and MPR. The median TFV-DP concentration was positively correlated with age ($\rho = 0.26$; $P < .001$). Median TFV-DP concentrations were lower among participants with <85% MPR compared to those with at least 100% MPR (602 vs 789 fmol/punch; $P < .001$). No significant associations were found between TFV-DP and sex, race, ethnicity, education, wealth indices, employment, time to clinical arrival, psychological distress, eGFR, or having enough to eat in the last month ($P > .09$ for all variables; Table 2).

To identify potential confounders or effect modifiers on the association between food insecurity and concentrations of TFV-DP in DBS, further analyses were conducted. In bivariate analyses examining differences in covariates among measures of food insecurity, significant associations were found between food insecurity worry and age, ethnicity, wealth, and employment status (Supplementary Table 1). There were no significant associations found between food insecurity worry and sex, race, education, income, time to clinic arrival, psychological distress, eGFR, or MPR (Supplementary Table 1). Based on this, age was considered a potential effect modifier or confounder.

Using median-based regression modeling, Table 3 shows the crude and adjusted relationships between food insecurity,

Table 2. Participant Characteristics in Relation to Tenofovir Diphosphate Concentrations in Dried Blood Spots

Characteristic	TFV-DP Concentration in DBS (fmol/punch)	
	Median (IQR) or Correlation Coefficient	*P* Value
Food insecurity worry in last month		.031*
Never experienced	716 (453–957)	
Experienced	599 (417–783)	
Enough to eat in last month		.361
Always	699 (419–943)	
Not always	613 (480–838)	
Age at first visit, y	0.26	<.001*
Sex		.298
Male	717 (488–1006)	
Female	668 (435–894)	
Race		.988
Black	692 (448–937)	
Indian	774 (137–1203)	
Ethnicity		.371
Zulu	667 (418–935)	
Xhosa	741 (552–913)	
Other	746 (462–1001)	
Education, y	−0.04	.486
Income		.947
No	670 (447–938)	
Yes	696 (443–938)	
Wealth index 1[a]	0.1	.093
Wealth index 2[a]	0.03	.599
Employment		.713
Unemployed	630 (405–928)	
Employed	707 (501–940)	
Other	658 (496–895)	
Time to clinic arrival, min		.223
<30	664 (415–826)	
30–60	713 (462–972)	
>60	595 (396–912)	
Psychological distress		.308
No	700 (445–944)	
Yes	642 (407–782)	
eGFR[a], mL/min/1.73 m^2		.204
>90	702 (478–941)	
60–90	739 (455–1022)	
<60	265 (13–610)	
MPR, %		<.001*
≥100	789 (586–1036)	
85–99	677 (476–930)	
<85	602 (302–856)	

Data are presented as median (IQR) or Spearman correlation coefficient. *P* values compare mean values of TFV-DP between groups, calculated using Wilcoxon rank-sum tests for categorical variables and Spearman rank correlation for continuous variables.

Abbreviations: DBS, dried blood spots; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MPR, medication possession ratio; TFV-DP, tenofovir diphosphate.

[a]More than 5% missing data.

*$P < .05$.

covariates of interest, and median TFV-DP concentrations in DBS. Similar to the Wilcoxon rank-sum results in Table 2, food insecurity worry in the last month was crudely associated with lower concentrations of TFV-DP, although without statistical significance (−112 [95% confidence interval {CI}, −232 to 8] fmol/punch; $P = .069$). In an adjusted model that included age, sex, ethnicity, and MPR, food insecurity worry became significantly associated with median TFV-DP concentration, showing that PWH who reported food insecurity worry had a median concentration of TFV-DP in DBS that was 155 fmol/punch lower compared to those who reported no worry (95% CI, −275 to −35 fmol/punch; $P = .012$). Age remained significantly associated with TFV-DP in both crude and adjusted models. Both models showed that median TFV-DP in DBS was 16 fmol/punch higher for every increasing year of age (95% CI, 9–22; $P < .001$, adjusted model). MPR <85% also was significantly associated with a decrease in TFV-DP concentration compared to an MPR of 100% in both crude and adjusted models (crude model: −183 [95% CI, −294 to −72] fmol/punch, $P = .002$; adjusted model: −151 [95% CI, −271 to −31] fmol/punch, $P = .015$).

In a sensitivity analysis that added eGFR to the adjusted model, though with fewer total participant observations (n = 215), food insecurity, age, and MPR <85% remained significant predictors of decreased TFV-DP concentration (Table 3). No significant crude associations were found between median TFV-DP concentration and having enough to eat in the last month, sex, race, ethnicity, education, income, wealth indices, employment, time to clinic arrival, psychological distress, or eGFR. In another adjusted model excluding MPR, food insecurity worry still accounted for 139 fmol/punch lower concentrations of TFV-DP (95% CI, −232 to −46 fmol/punch; $P = .004$) when compared to no food insecurity worry (Table 3).

In a bivariate analysis comparing an aggregated food insecurity measure to median TFV-DP concentration, a stepwise reduction in median TFV-DP concentration was noted among increasing severity of food insecurity (food secure, 716 [IQR, 450–961] fmol/punch vs partially food insecure, 611 [IQR, 423–754] fmol/punch vs food insecure, 595 [IQR, 441–787] fmol/punch; $P = .079$). In an adjusted analysis, food-insecure participants had a median 129 fmol/punch lower concentration compared to those who were food secure (95% CI, −238 to −18 fmol/punch; $P = .023$).

DISCUSSION

In this study, we identified an inverse association between TFV-DP in DBS, a measure for cumulative ART adherence and exposure, and the experience of food insecurity in PWH in South Africa who were taking first-line TDF-based therapy. This is consistent with a previous US-based study where food insecurity was associated with lower cumulative ART drug concentrations quantified in hair [21]. Furthermore, the study found that the relationship between food insecurity and ART concentrations persisted both with and without the inclusion of MPR in the model, suggesting that low medication adherence may only partially explain our observations and that an objective measure of adherence and exposure may more readily identify these differences [21]. For example, previous studies have proposed that food insecurity may impact pharmacokinetic drug absorption if participants are unable to take medications with a meal, which can be particularly impactful for tenofovir absorption [21, 33–36]. Collectively, our findings support the premise that SDoH (in this case, food insecurity) could adversely impact drug adherence and bioavailability and on that addressing these factors using novel adherence measures could improve ART adherence and clinical outcomes.

Compared to the worry of not having enough food, the relationship between TFV-DP and actually having enough food in the last month was less robust, although demonstrating similar directionality. In a sensitivity analysis where food insecurity measures were aggregated, this directionality was maintained: An increased number of reported food insecurity measures corresponded with a decreased TFV-DP concentration. However, with food insecurity worry being the strongest singular predictor of the food insecurity measures, this suggests that the component of worrying about food security may play a role in ART adherence. This worry may be a contextual indication of longer-term wealth instability versus the more focused measure of whether food insecurity was directly experienced in the last 4-week period. It is also plausible that worry may act as a surrogate for mental health comorbidities such as stress, anxiety, or depression, which have been implicated in bidirectional relationships with both food insecurity and ART adherence [2, 6, 7, 29, 37]. In this study, though only a small proportion of participants reported psychological distress, those participants tended to have lower concentrations of TFV-DP. Furthermore, it is possible that psychological distress among participants may have been undercounted due to varied sensitivity of the Kessler-10 scale among the Black South African demographic [29].

Regarding clinical translation, several inferences can be derived from our findings. In our cohort, food-insecure participants had a median TFV-DP concentration that was 155 fmol/punch lower than those who had no food insecurity worry (median concentration of TFV-DP, ∼700 fmol/punch). This reduction is consistent with approximately missing 1 TDF dose per week [38]. Moreover, extrapolating to previously published literature, PWH with similar TFV-DP concentrations to those who experienced food insecurity worry in our cohort were at greater risk for various adverse HIV outcomes such as loss of viral suppression, future viremia, or virologic failure with HIV drug resistance [10, 19, 39]. In a US study,

Table 3. Median-Based Regression Models of Food Insecurity and Tenofovir Diphosphate Concentrations in Dried Blood Spots

Characteristic	Median Difference in TFV-DP in DBS (fmol/punch)			
			Sensitivity Analyses	
	Single Variable Median Regression[a] (95% CI) (n = 285)	Adjusted Median Regression Model[b] (95% CI) (n = 258)	Adjusted Median Regression Model With eGFR[c] (95% CI) (n = 215)	Adjusted Median Regression Model With MPR Removed[d] (95% CI) (n = 259)
Food insecurity worry in last month[e]				
Never	Ref	Ref	Ref	Ref
Ever	−112 (−232 to 8)	−155 (−275 to −35)*	−195 (−320 to −71)*	−139 (−232 to −46)*
Enough to eat in last month				
Always	Ref	…	…	…
Not always	−77 (−192 to 38)	…	…	…
Age at first visit (per y)	16 (10–23)*	16 (9–22)*	16 (8–23)*	16 (10–22)*
Sex				
Male	Ref	Ref	Ref	Ref
Female	−47 (−135 to 41)	−40 (−157 to 78)	−35 (−155 to 86)	−23 (−137 to 91)
Race				
Black	Ref	…	…	…
Indian	62 (−497 to 621)	…	…	…
Ethnicity				
Zulu	Ref	Ref	Ref	Ref
Xhosa	71 (−55 to 197)	42 (−123 to 207)	55 (−113 to 222)	96 (−68 to 261)
Other	39 (−158 to 234)	71 (−162 to 303)	87 (−130 to 304)	93 (−116 to 302)
Education (y)	3 (−24 to 31)	…	…	…
Income				
No	Ref	…	…	…
Yes	26 (−107 to 160)	…	…	…
Wealth index 1[e]	11 (−11 to 33)	…	…	…
Wealth index 2[e]	15 (−14 to 45)	…	…	…
Employment				
Employed	Ref	…	…	…
Unemployed	−76 (−194 to 41)	…	…	…
Other	−48 (−280 to 184)	…	…	…
Time to clinic arrival (min)				
<30	Ref	…	…	…
30–60	45 (−64 to 154)	…	…	…
>60	−60 (−266 to 146)	…	…	…
Psychological distress				
No	Ref	…	…	…
Yes	−29 (−196 to 138)	…	…	…
eGFR (mL/min/1.73 m^2)[e]				
>90	Ref	…	Ref	…
60–90	8 (−195 to 211)	…	−40 (−281 to 201)	…
<60	−182 (−834 to 470)	…	−350 (−1261 to 561)	…
MPR (%)				
≥100	Ref	Ref	Ref	…
85–99	−91 (−257 to 75)	−47 (−173 to 81)	−74 (−211 to 64)	…
<85	−183 (−294 to −71)*	−151 (−271 to −31)*	−137 (−263 to −11)*	…

Abbreviations: CI, confidence interval; DBSs, dried blood spots; eGFR, estimated glomerular filtration rate; MPR, medication possession ratio; Ref, reference group; TFV-DP, tenofovir diphosphate.

[a]Single variable median regression: crude relationship between individual variables and TFV-DP concentration.

[b]Adjusted median-based regression: relationship between food insecurity and TFV-DP concentration adjusted for age, sex, ethnicity, and MPR.

[c]Adjusted median-based regression with eGFR: relationship between food insecurity and TFV-DP concentration adjusted for age, sex, ethnicity, MPR, and eGFR.

[d]Adjusted median-based regression with MPR removed: relationship between food insecurity and TFV-DP concentration adjusted for age, sex, and ethnicity.

[e]More than 5% missing data.

*$P < .05$.

PWH with TFV-DP between 700 and 1250 fmol/punch had 33 times greater odds of viral suppression than those with TFV-DP <350 fmol/punch. In comparison, PWH with TFV-DP between 351 and 699 fmol/punch, analogous to the concentration observed in our food insecurity worry group, had only 9 times greater odds of suppression than the study reference group—almost a 4-fold reduction [31]. Similarly, in a South African cohort of postpartum women with HIV, study participants with TFV-DP concentrations in DBS in the 350–699 fmol/punch range had higher odds of future viremia (~3.4) compared to a reference group of women with TFV-DP >1850 fmol/punch, whereas those with TFV-DP concentrations >700 fmol/punch did not show significant odds of future viremia [39]. Beyond the individual impact of food insecurity on ART adherence, our findings could have concrete public health implications, as focusing on access to food in PWH would not only improve their overall health by allowing proper nutrition, but would also impact their adherence and could lead to a reduction in HIV transmission.

Our study did not identify the previously observed associations between eGFR, sex, race, or ethnicity and TFV-DP concentrations in DBS [39, 40]. This may be due to a limited sample size and decreased heterogeneity among groups of study participants, reducing the power of this analysis. In this study, >95% of participants identified as Black. Additionally, ethnicities were local to the South African population, and did not include Latinx or Hispanic participants as traditionally studied in a US context. Previous studies describing race, ethnicity, and TFV-DP in DBS have, to our knowledge, only been described among participants in the US, where additional sociostructural predictors may have influenced the relationship [21]. However, this does not impact our conclusions. Future studies where the association of this (and other) SDoH in more diverse populations are needed.

Among the strengths of our study are the large clinical cohort from where this substudy is derived, the wide range of SDoH collected, and the use of a novel and validated adherence biomarker that has been utilized effectively in South African cohorts [10, 33]. Limitations include the lack of availability of other known predictors of TFV-DP drug concentrations such as hematocrit, body mass index, and the temporal relationship between meals and ART dosing [40, 41]. Additional predictors of ART adherence such as substance abuse, depression and anxiety, traditional or herbal medicine use, HIV stigma and discrimination, and healthcare worker dissatisfaction were also either unavailable or underreported, potentially due to social desirability bias among these stigmatized participants [2, 7, 11]. The use of MPR as a proxy for ART adherence also has its limitations, due to imperfect sensitivity and assumption that all pills distributed by the pharmacy were consumed appropriately and consistently [42]. Larger structural issues not addressed in our study, such as medication access, pharmacy stockouts, drug prices, and food costs [2, 11, 43], should also be examined in the future.

In conclusion, food insecurity worry is significantly associated with low cumulative ART adherence and bioavailability. While an overall high proportion of adherence to ART regimens is reported in sub-Saharan Africa, SDoH remain influential in an individual patient's likelihood to remain adherent and effectively absorb their treatment [44]. The WHO has recognized that holistic treatment of PWH must address SDoH, including a focus on nutritionally based interventions where applicable [45]. The observed rise in the prevalence of food insecurity should be considered within HIV intervention planning to better meet the needs of PWH at risk for suboptimal ART concentrations. Future research delineating the mechanisms through which food insecurity impacts ART adherence and exposure could help prevent adverse HIV treatment outcomes [10].

Supplementary Data

Supplementary materials are available at *Open Forum 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

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