Income Inequality Is Associated With Low Cumulative Antiretroviral Adherence in Persons With Human Immunodeficiency Virus

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Background. The adherence biomarker tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is associated with viral suppression and predicts future viremia. However, its association with social determinants of health (SDoH) in people with human immunodeficiency virus (PWH) remains unknown.

Methods. Dried blood spots for TFV-DP were longitudinally collected from a clinical cohort of PWH receiving tenofovir disoproxil fumarate-based therapy (up to 3 visits over 48 weeks) residing in 5 Colorado counties. To assign SDoH, zip codes at enrollment were matched with SDoH data from AIDSVu (https://aidsvu.org/). The SDoH included household income, percentage living in poverty, education level, and income inequality (quantified using Gini coefficient, where 0 and 1 represent perfect income equality and inequality, respectively). Log-transformed TFV-DP concentrations were analyzed using a mixed-effects model to estimate percentage change (95% confidence interval) in TFV-DP for every significant change in the SDoH and adjusted for relevant covariates including age, gender, race, estimated glomerular filtration rate, body mass index, hematocrit, CD4+ T-cell count, antiretroviral drug class, and 3-month self-reported adherence.

Results. Data from 430 PWH totaling 950 person-visits were analyzed. In an adjusted analysis, income inequality was inversely associated with TFV-DP in DBS. For every 0.1 increase in the Gini coefficient, TFV-DP concentrations decreased by 9.2% (−0.5 to −17.1; P = .039). This remained significant after adjusting for human immunodeficiency virus viral suppression, where a 0.1 increase in Gini was associated with a decrease of 8.7% (−0.3 to −17.9; P = .042) in TFV-DP.

Conclusions. Higher income inequality was associated with lower cumulative antiretroviral adherence. These findings support the need for further research on how SDoH impact adherence and clinical care.

Keywords. adherence; dried blood spots; income inequality; social determinants of health; tenofovir diphosphate.

Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS), an objective pharmacologic measure of cumulative adherence, has been associated with viral suppression [1] and predicts future viremia in persons with human immunodeficiency virus (PWH) [2]. Current research acknowledges the importance of developing objective adherence metrics to replace less precise self-reported adherence [1, 3, 4]. More objective measures of adherence can be used to quantify the impact of sociostructural factors, such as food insecurity, on adherence [5, 6]. However, research remains limited on the use of novel, clinically meaningful adherence measures to study the impact of social determinants of health (SDoH) on adherence and clinical outcomes.

Social determinants of health are defined as “the conditions in which people are born, grow, live, work and age, as well as the complex, interrelated social structures and economic systems that shape these conditions” [7]. Social determinants of health include aspects of the social (eg, discrimination, income, education), physical (eg, place of residence, living conditions, infrastructure, transportation), and health services environments (eg, access to and quality of care) [7]. As demonstrated by the human immunodeficiency virus (HIV) treatment cascade, even when people are diagnosed and access antiretroviral therapy (ART), 1 in 5 people still have a detectable HIV viral load [8]. Factors contributing to viremia include suboptimal adherence and/or persistence, as well as drug resistance [8], with adherence being the greatest predictor of viral suppression and clinical outcomes [9, 10]. Previous research has established that
individual changes in behavior and access to ART alone are not enough to address disparities in adherence to treatment in HIV/acquired immune deficiency syndrome (AIDS) [11], yet there is a lack of focus on the impact of SDoH. This represents a significant knowledge gap given the importance of these nonclinical factors on HIV outcomes [12]. Although previous research has recognized the impact of SDoH on adherence [12] and viral suppression [13], most studies have estimated adherence through subjective methods, such as self-report, which is bound with inherent constraints that can limit its interpretability. To date, how population-level SDoH influence objective measures of adherence remains unknown. To address this gap, this study aimed to examine potential associations between SDoH and concentrations of TFV-DP in DBS as a biomarker of adherence.

METHODS

Patient Consent Statement
The study participants’ written consent was obtained before any study procedures. The study was approved by the Colorado Multiple Institutional Review Board (COMIRB 13-2104).

Study Design and Participants
Persons with HIV receiving any tenofovir disoproxil fumarate (TDF)-based regimen (any duration of time), who attended a regular clinical visit where HIV viral load (VL) was routinely collected, were prospectively enrolled into a clinical cohort at the University of Colorado Hospital (UCH) Infectious Diseases Group Practice between 2014 and 2017, as previously described [1]. After informed consent was signed, whole blood (4–6 mL in ethylenediaminetetraacetic acid [EDTA]) was collected for DBS, and participants were observed for up to 3 routine visits over 48 weeks, allowing for a minimum of 14 days between visits [1]. Three-month self-reported adherence was also evaluated at each visit using a validated visual analog scale that ranged from 0% to 100% [1, 14], and HIV VL was measured through the Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory at UCH using quantitative polymerase chain reaction (Roche COBAS 6800; detection range of 20–10,000,000 copies/mL).

Quantification of Tenofovir Diphosphate in Dried Blood Spots
After collection, 25 μL whole blood in EDTA were spotted 5 times onto Whatman 903 Protein saver cards, which were allowed to dry for at least 2 hours and up to overnight. Once dry, cards were stored frozen at −80°C until assay from a 3-mm punch using a previously validated liquid chromatography-tandem mass spectrometry method [1, 15].

Social Determinants of Health
Zip code at enrollment was matched with the relevant SDoH data from 2016 obtained from AIDSVu [https://aidsvu.org/] [16]. We excluded any participant who resided outside of the state of Colorado (n = 6) as there would not be enough aggregate data points from those locations to adequately study the SDoH impact. Social determinants of health data by zip code included household income, percentage living in poverty, education level, and income inequality, which was quantified using the Gini coefficient. Derived from the Lorenz curve, the Gini coefficient "is based on the comparison of cumulative proportions of the population against cumulative proportions of income they receive, and it ranges between 0 (perfect equality) and 1 (perfect inequality)" [17].

Statistical Analysis
In this subanalysis, TFV-DP concentrations in DBS were log transformed to address skewness. Log-transformed TFV-DP concentrations were analyzed using a mixed-effects model to estimate the percentage change in drug concentrations for every significant change in the SDoH. We initially evaluated a model in which each individual SDoH (ie, household income, percent living in poverty, education level and income inequality) was the primary predictor of interest, and then we evaluated a model that adjusted for potential confounders that were selected a priori, including age, gender, race, body mass index (BMI), type of ART anchor drug class (nonnucleoside-based, boosted protease inhibitor-based, integrase inhibitor-based or multiclass), estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease [MDRD] equation), CD4+ T-cell count, and hematocrit (HCT), as previously described in our cohort [1, 2, 18, 19]. Model results are presented as percentage change (95% confidence interval [CI]) in TFV-DP concentrations in DBS for every significant change in each SDoH. All results are reported with no adjustment for multiple comparisons, because they were considered to be hypothesis generating. Other data are presented as number (%), median (interquartile range [IQR]), or geometric mean (95% CI). Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC). Figures were created using R (https://www.r-project.org/, Vienna, Austria) and GraphPad Prism 8 (GraphPad Software, La Jolla, CA). A P < .05 was considered to be statistically significant.

RESULTS

Study Population
The main study cohort enrolled a total of 807 PWH, drug concentrations of which were available in 532 participants (1199 person/visits), as previously reported [1, 2]. From these, a total of 950 person-visits from 430 participants, encompassing 81 zip codes within 5 Colorado counties (Denver, Arapahoe, Jefferson, Adams, and Douglas), were included in the present analysis. The baseline demographic and clinical characteristics of the study participants included in this subanalysis are presented in Table 1. The median age
of the study participants was 45 (IQR, 36–52) years, and 15% of the study cohort were women. The majority of the study participants (n = 233, 54%) self-identified as white and 22% and 19% self-identified as black and Hispanic, respectively. A total of 256 participants (60%) had a CD4+ T-cell count greater than 500 cells/mm³, and 300 participants (70%) had an HIV VL of less than 20 copies/mL (Table 1).

Tenofovir Diphosphate in Dried Blood Spots and Social Determinants of Health

The Gini coefficient quartiles with their estimated TFV-DP concentrations in DBS, according to each zip code evaluated in the study population, are presented in Figure 1, and the associations of TFV-DP in DBS with each SDoH are presented in Table 2. After adjusting for age, gender, race, eGFR, BMI, HCT, CD4+ T-cell count, antiretroviral drug class, and 3-month self-reported adherence, only the Gini coefficient was inversely associated with TFV-DP in DBS. For every 0.1 increase in Gini coefficient, the concentrations of TFV-DP in DBS decreased by 9.2% (−17.1 to −0.5; \( P = .039 \)). To assess the robustness of our findings, we performed a sensitivity analysis adjusting for HIV viral suppression (<20 copies/mL). In this analysis, Gini coefficient remained significant, because a 0.1 increase in Gini was associated with a decrease of 8.7% (−0.3 to −17.9; \( P = .042 \)) in TFV-DP in DBS for participants with the same HIV VL status (suppressed or viremic).

For the remaining SDoH, we observed a 0.2% (−3.3 to 3.0; \( P = .90 \)) decrease and a 3.5% (−8.8 to 2.1; \( P = .22 \)) decrease in TFV-DP in DBS for every $10,000 increase in median household income and for every 10% increase in persons with high school diploma or equivalent, respectively. In contrast, for every 10% increase in the population living in poverty, we observed a 1.9% (−6.0 to 10.5; \( P = .65 \)) increase in the concentrations of TFV-DP in DBS (Table 2).

Figure 2 shows the adjusted the geometric means (95% CI) of TFV-DP concentrations in DBS according to the median of each Gini coefficient quartile estimated from our study population. To estimate the concentrations of TFV-DP in DBS, the continuous covariates were set to their mean values for the study cohort considering a white male taking an integrase inhibitor (age = 45 years, BMI = 25 kg/m², HCT = 45%, eGFR = 88 mL per min/1.73 m², CD4+ T-cells = 575 cells/mm³, and 3-month self-reported ART adherence = 98%). For Gini coefficient values 0.367, 0.408, 0.455, and 0.528, TFV-DP in DBS concentrations were 1864, 1792, 1713, and 1597 fmol/punch, respectively.

DISCUSSION

In this study, higher income inequality (quantified using the Gini coefficient) was associated with lower TFV-DP concentrations in PWH taking TDF-based ART. Given that TFV-DP is a biomarker of cumulative ART adherence, these findings suggest that adherence may be influenced by population-level characteristics, such as income inequality, and may impact individual-level health outcomes. A substantial amount of research supports the inverse association between income inequality and population health [20–22]. For example, as previously described by the income inequality hypothesis, an individual’s health can be impacted by the distribution of income in the place where an individual lives [17]. Building on this hypothesis, our study raises the following questions: “why” does a population-based metric such as income inequality impact individual ART adherence (and potentially clinical outcomes), and “how” should we use this information to further our efforts aimed at decreasing overall HIV disease burden, morbidity, and transmission.

Available research provides multiple hypotheses to explain the impact of income inequality on individual health outcomes. First, within an established social hierarchy, income

### Table 1. Demographic and Clinical Characteristics of the Study Population

| Characteristic | Participants Included in Analysis (n = 430) |
|----------------|------------------------------------------|
| Age (years)    | 45 (36–52)                               |
| Gender         |                                          |
| Female         | 66 (15%)                                 |
| Male           | 364 (85%)                                |
| Race/Ethnicity |                                          |
| Black          | 96 (22%)                                 |
| White          | 233 (54%)                                |
| Hispanic       | 83 (19%)                                 |
| Other          | 18 (4%)                                  |
| Body Mass Index (kg/m²) |                            |
| <18.5          | 18 (4%)                                  |
| 18.5–25        | 179 (42%)                                |
| 25–30          | 143 (33%)                                |
| >30            | 90 (21%)                                 |
| eGFR (mL/min)  | 88 (74–104)                              |
| Hematocrit (%) | 45 (42–47)                               |
| CD4+ T-cell count (cells/mm³) |                        |
| <200           | 48 (11%)                                 |
| 200–350        | 59 (14%)                                 |
| 350–500        | 67 (16%)                                 |
| >500           | 256 (60%)                                |
| ART Drug Class |                                          |
| NNRTI-based    | 112 (26%)                                |
| INSTI-based    | 158 (37%)                                |
| b/PI-based     | 109 (25%)                                |
| Multiclass     | 51 (12%)                                 |
| HIV Viral Load (copies/mL) |                          |
| <20            | 300 (70%)                                |
| 20–200         | 74 (17%)                                 |
| ≥200           | 56 (13%)                                 |
| 3-month self-reported adherence (%) | 98% (90%–100%)                |

Abbreviations: ART, antiretroviral therapy; b/PI, boosted protease inhibitor; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; INSTI, integrase strand-transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor.
inequality can cause psychosocial harm to an individual due to actual or perceived social status, or lack thereof, as well as access to mobility and resources [23]. People who have a higher income may not experience more happiness and lower stress. In fact, as previously argued by Yu et al [24], individuals would still be “more likely to compare themselves to those richer, which may deteriorate their subjective well-being”. Furthermore, wherever a person might be located on the continuum of individual income level within a particular community, living and experiencing income inequality can result in psychosocial stress [25], which could further support a possible explanation for the impact of income inequality on drug adherence observed in our study. Second, individuals with lower socioeconomic status relative to those with high socioeconomic status living within the same area could become more prone to suboptimal adherence due to an inability to access adequate healthcare (including financial constraints, limited transportation, inflexible employers, among other challenges) [12]. This finding is supported by another study from our cohort in which PWH with a mental

| Social Determinant of Health                                      | Percentage Change in TFV-DP in DBS | 95% CI        | P Value |
|------------------------------------------------------------------|-----------------------------------|---------------|---------|
| 0.1 increase in income inequality (Gini coefficient)             | −9.2%                             | −17.1 to −0.5 | .039    |
| 10% increase in population living in poverty                     | 1.9%                              | −6.0 to 10.5  | .66     |
| 10% increase in persons with high school diploma or equivalent   | −3.5%                             | −8.8 to 2.1   | .22     |
| $10 000 increase in median household income                      | −0.2%                             | −3.3 to 3.0   | .90     |

Abbreviations: CI, confidence interval; DBS, dried blood spots; TFV-DP, tenofovir diphosphate.

*Adjusted for age, sex, race, estimated glomerular filtration rate [eGFR], body mass index [BMI], hematocrit [HCT], CD4+ T-cell count, antiretroviral drug class, and 3-month self-reported adherence.

Figure 1. (a) Gini coefficient category and (b) estimated tenofovir diphosphate (TFV-DP) concentrations in dried blood spots (DBS) according to zip code of the study population in the state of Colorado (insert in left top corner). Darker shades of blue in (a) represent more income equality, whereas lighter shades of green in (b) represent lower concentrations of TFV-DP in DBS. NA, not applicable.

Table 2. Percentage Change in TFV-DP Concentrations in DBS According to a Meaningful Change in Each Evaluated Social Determinant of Health

Figure 2. Adjusted (adjusted for age, sex, race, estimated glomerular filtration rate [eGFR], body mass index [BMI], hematocrit [HCT], CD4+ T-cell count, antiretroviral drug class, and 3-month self-reported adherence) tenofovir diphosphate (TFV-DP) concentrations in dried blood spots by Gini coefficient quartiles estimated from the study population. Covariates set to the following: (1) age, 45 years; (2) BMI, 25 kg/m²; (3) HCT, 45%; (4) eGFR, 88 ml per min/1.73 m²; (5) CD4+ T cells, 575 cells/mm³; (6) 3-month self-reported adherence, 98%; (7) gender, male; (8) race, white; (9) antiretroviral therapy anchor drug class, integrase strand-transfer inhibitor. CI, confidence interval; GM, geometric mean.
health disorder who were engaged in mental healthcare had higher adherence (both by TFV-DP in DBS and self-report) than PWH with a mental health disorder who were not engaged in mental healthcare, and comparable adherence to PWH without a mental health disorder [18]. Thus, having access to support services positively impacted adherence. Third, societal-structural arguments highlight the association between inequality and the development, or not, of public and private health services [26]. Differences between the rich and the poor impact decision making for the expansion of social services and health access, thus creating multilayered health challenges [17]. For example, in a community with a discrepancy between the rich and the poor, could societal level factors lead to higher disease prevalence, delayed care, and low adherence due to the tensions between how and where those with affluence decide to invest in local health? Our findings support the need for comprehensive national efforts to shift the focus away from individual-level health to better understand community-level factors [23] that impact ART adherence, and how this new information can play a critical role in the development of effective strategies to improve clinical care in HIV and end the HIV/AIDS epidemic.

In addition to the social influences that income inequality can have on ART adherence, biological factors could also explain some of our findings. For example, a recent study identified an association between low concentrations of antiretrovirals in hair and food insecurity in women, hypothesizing that poor nutrition and low caloric intake could decrease drug absorption [5]. This study supports previous research in Africa that has identified food insecurity, a SDoH, as a barrier to ART adherence [27–29]. Research has also explored links between the biological effects of social exposures and experiences and various physiologic pathways including stress responses, the sympathetic nervous system, and the hypothalamic-pituitary-adrenal axis to investigate the potential biological manifestations of social conditions and their impact in HIV-related clinical outcomes [30, 31]. Future research is needed to elucidate the intersection between SDoH and biological and clinical outcomes in PWH.

The strengths of our study include the evaluation of a large, real-world clinical cohort combined with SDoH data from the well established, HIV-focused database (AIDSVu), which supports the generalizability of our findings. In addition, the clinical application of population-level SDoH data is a novel approach to better understand how social factors may influence an individual’s adherence and potential future health outcomes. Limitations include that the participants enrolled in the study were already receiving HIV care, thus our study did not capture PWH who might not have access to care. In addition, due to the nature of how SDoH data are reported in the AIDSVu database, zip code-level data were used as an approximation for an individual’s potential experience of SDoH because it was the finest resolution of data that we could use based on what was collected from study participants at the time of enrollment. Thus, because the data we are using are zip code level, they are not an exact measurement or reflection of each person’s experience. The limitation of these data and the database could provide a varied representation of the inequities experienced by an individual when compared with a population in a particular zip code. Furthermore, our analysis was limited to 5 counties in the state of Colorado and should be replicated in other areas to increase generalizability. Finally, this study did not include all SDoH that may impact a person’s adherence. Future research is needed to better understand the complex interactions between SDoH and ART adherence, including a more comprehensive evaluation of SDoH in diverse settings and populations.

CONCLUSIONS

In summary, we demonstrated that higher income inequality is associated with lower cumulative adherence as measured with TFV-DP in DBS. Extending clinically significant objective measures of adherence from an individual into a population level will be indispensable to understand the impact of community-wide SDoH on ART adherence. For much of our history in fighting the HIV epidemic, we have focused on individual-level change to decrease risk, transmission, and disease burden. However, as we enter a new era with increasing capability to conduct real-time, point-of-care measurements of adherence, we have the opportunity to extend the use of these clinical measurements as tools to better understand the population and community-wide challenges that are preventing us from further decreasing the global burden of HIV disease and ending the HIV epidemic.

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