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ORIGINAL PAPER

Engagement in Mental Health Care is Associated with Higher Cumulative Drug Exposure and Adherence to Antiretroviral Therapy

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Abstract

Mental health (MH) disorders are more prevalent among persons living with HIV compared to the general population, and may contribute to suboptimal adherence to antiretroviral therapy (ART). Tenofovir-diphosphate (TFV-DP), the phosphorylated anabolite of tenofovir (TFV), is a biomarker with a 17-day half-life in red blood cells. TFV-DP can be measured in dried blood spots (DBS) using liquid chromatography/tandem mass spectrometry (LC-MS/MS) to assess adherence and cumulative drug exposure to tenofovir disoproxil fumarate (TDF)-based ART. From a larger clinical cohort ($N = 807$), TFV-DP concentrations and a paired HIV viral load were available from 521 participants at their enrollment visit. We used multivariable linear regression to evaluate the association between TFV-DP in DBS and engagement in MH care. After adjusting for clinical covariates, participants with MH disorders who were engaged in MH care had 40% higher TFV-DP compared to participants with MH disorders who were not engaged in MH care ($p < 0.001$), and similar TFV-DP to participants without MH disorders ($p = 0.219$). Further research is needed to identify the mechanism(s) for these findings, with the goal of optimizing engagement and retention in MH care strategies to improve ART adherence and clinical outcomes in PLWH with MH disorders.

Keywords Tenofovir-diphosphate · Dried blood spots · Adherence · Antiretroviral therapy · Mental health

Resumen

Las enfermedades mentales (EMs) son más frecuentes en personas que viven con VIH (PVIH), y pueden reducir la adherencia a la terapia antirretroviral (TARV). El difosfato de tenofovir (DF-TFV), el anabolito activo del tenofovir (TFV), tiene una vida media de 17 días en los eritrocitos y es cuantificable en gotas de sangre desecada (GSD) mediante cromatografía liquida y espectrometría de masa. El DF-TFV sirve come medida de adherencia y exposición acumulativa a la TARV basada en el fumarato de tenofovir disoproxil (TDF). En este estudio analizamos las concentraciones de DF-TFV en 521 PVIH derivadas de una cohorte clínica de 807 PVIH tratadas con TDF, con el objetivo de identificar si existe alguna asociación entre el DF-TFV y el cuidado activo de una EM en pacientes con este diagnóstico. Usando regresión lineal múltiple ajustada, en este análisis encontramos una reducción del 40% en las concentraciones de DF-TFV en las PVIH recibiendo tratamiento de una EM en comparación con las PVIH con un diagnóstico de EM sin recibir tratamiento activo ($p<0.001$), pero concentraciones similares a las de PVIH sin diagnóstico de EM ($p=0.219$). Las causas de estas diferencias deben ser investigadas en estudios adicionales con el fin de optimizar el tratamiento activo de las EMs y mejorar la adherencia a la TARV en PVIH con EMs.

Introduction

Mental health (MH) disorders are more prevalent among persons living with HIV (PLWH) compared to the general population, and may contribute to suboptimal adherence to antiretroviral therapy (ART) [1–3]. Given that durable ART adherence is required to achieve viral suppression and improve immune function [4], the presence of MH disorders

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in PLWH has the potential to worsen clinical outcomes [5], including viral suppression [6], and negatively affect retention in care [1, 3, 5, 7, 8].

Most research on the intersection between ART adherence and MH has focused on depression, and has generally found decreased ART adherence in PLWH with this condition [1, 3, 5, 9–13]. Specifically, one study of 1910 PLWH found that participants with depression had higher odds of being nonadherent compared to those without a MH disorder [13]. However, studies assessing adherence have been hindered by the lack of a gold-standard measure of ART adherence, which likely has led to the inconsistent results across studies [1]. For example, in a recent meta-analysis, 58% (32/62) of the included studies showed significantly lower ART adherence in the setting of clinical depression, while the other 42% found no difference [1]. Self-report is the most commonly used method to measure adherence in clinical practice, but is susceptible to recall errors and social desirability bias [1, 14, 15]. Other available ART adherence measures include unannounced pill counts, pharmacy refill data, electronic drug monitoring (EDM), directly-observed therapy (DOT), and quantification of antiretroviral (ARV) drug concentrations in various compartment and tissue biomatrices [e.g. in plasma, urine, dried blood spots (DBS), or hair] [1, 14, 16, 17]. However, despite this wide-range of available measures, little is known about their association with MH in PLWH.

An informative biomarker for quantifying ART adherence and cumulative drug exposure to tenofovir (TFV)-containing ART is tenofovir-diphosphate (TFV-DP) in DBS. TFV-DP is the phosphorylated anabolite of TFV and has a 17-day half-life in red blood cells (RBCs), which are abundant in DBS [18–21]. Based on this unique pharmacology, we have previously demonstrated that TFV-DP concentrations in DBS are strongly associated with viral suppression in PLWH [22], predict efficacy of HIV pre-exposure prophylaxis (PrEP) [23], and are correlated with other measures of adherence [20, 24]. Given that approximately 85% of PLWH are prescribed TFV-based ART [25], measurement of TFV-DP in DBS has the potential for widespread practical utility to objectively quantify adherence. However, whether this adherence and exposure biomarker is also associated with MH care in PLWH remains unknown, which was the focus of this analysis.

Methods

Study Design and Participant Characteristics

This study was a sub-analysis from a previously published study, which has been described elsewhere [22]. Briefly, study participants were prospectively recruited and enrolled, on a first-come, first-served basis, from the University of Colorado Hospital (UCH) Infectious Disease Group Practice (IDGP), which currently serves over 1900 PLWH and has integrated MH care into the infrastructure through three MH care providers. Urgent and same-day appointments are available, and patients can see their HIV provider and MH provider on the same clinic visit day, improving attendance to MH appointments. Eligible participants were at least 18 years old, taking tenofovir disoproxil fumarate (TDF) as part of their ART, and had blood drawn for routine HIV viral load (VL) at the time of study visits. There were no exclusions based on length of time on current ART or comorbid diagnoses. After informed consent, participants had four to six mL of whole blood drawn in an EDTA tube during their clinical blood draw. Participants were compensated $10 upon completion of their blood draw. Enrollment began in June 2014 and follow-ups were completed in July 2017. In this study, we performed a cross-sectional analysis from the enrollment visit only. Given we are only using the enrollment visit in this sub-analysis, this is equivalent to a case (viremic)—control (suppressed) study, which is the most efficient study design in this context, as viremia is a relatively rare event [26].

Quantification of TFV-DP in DBS

Intracellular TFV-DP concentrations in DBS were quantified using a previously validated method [18–20]. Briefly, 25 µl of whole blood were pipetted five times onto a Whatman 903 Protein Saver card, which were allowed to dry at room temperature for at least two hours and up to overnight, before being stored at − 80 °C until analysis. Quantification of TFV-DP was accomplished by assaying a 3-mm punch via liquid chromatography/tandem mass spectrometry (LC–MS/MS), as previously validated [18–20].

Self-reported Adherence

Participants were asked to self-report their three-month adherence to their current ART using a previously validated visual analog scale (VAS) [22, 27], which ranged from 0 to 100%, and had marks at every 10% interval. If a participant's response was unclear (i.e. a mark or circle between two percentages), they were asked to write a specific percent of ART adherence during this period of time.

HIV Viral Load

HIV-1 quantitative polymerase chain reaction (PCR) with the Roche cobas 6800 System at the University of Colorado Hospital's Clinical Laboratory [Clinical Laboratory Improvement Amendment of 1988 (CLIA)-certified] was used for VL assessment, with a detection range of

20–10,000,000 copies/mL. An HIV VL of < 20 copies/mL defined viral suppression.

Demographics and Clinical Data for MH Disorders and Engagement in MH Care

Electronic medical records of study participants were retrospectively reviewed by study personnel to determine the presence or absence of active MH disorders, and identify if participants were engaged in MH care for those with MH disorders. Beyond problem list documentation, provider notes and scanned records were reviewed to maximize accuracy of diagnoses, to verify diagnoses as active problems, and to capture information on out-of-clinic MH care (if applicable). If the provider notes and/or diagnoses were unclear, the UCH IDGP psychiatric provider was consulted to provide clarification. MH diagnoses were grouped into: (a) anxiety disorders [e.g. generalized anxiety disorder (GAD), obsessive compulsive disorder, post-traumatic stress disorder, phobias], (b) mood disorders [e.g. major depressive disorder (MDD), dysthymia, bipolar disorder, cyclothymia, mood disorders not otherwise specified], (c) substance use disorders (e.g. abuse of alcohol, amphetamines, cocaine, opiates/narcotics), or d) other disorders (e.g. schizophrenia, schizoaffective disorder, borderline personality disorder, psychosis not otherwise specified). Participants were able to be classified into multiple diagnosis groups (e.g. a participant with both GAD and MDD would be included in both the anxiety and mood disorders groups). Therefore, as multiple participants had more than one MH diagnosis, the total number of MH diagnoses is larger than the total sample size. Engagement in MH care was defined as at least one visit to any provider that addressed and managed a MH disorder within the previous 12 months.

Statistical Analyses

Enrollment visit TFV-DP concentrations (fmol/punch) were log transformed to address right-skewed data, then back-transformed after analysis into geometric mean (GM) concentrations with 95% confidence intervals (CIs) [28]. For participants with TFV-DP levels that were below the assay's limit of quantification (BLQ), concentrations were imputed a value of 12.5 fmol/punch, which is between zero and the lower limit of quantification [22]. Multivariable linear regression model predictors were age, gender, race, body mass index (BMI), estimated glomerular filtration rate (eGFR), $CD4^+$ T cell count, ART class, duration on current ART, use of a pharmacokinetic (PK) booster (either ritonavir or cobicistat), and engagement in MH care. The first model's outcome was (log)TFV-DP concentrations, and the second model's outcome was three-month self-reported adherence. In both adjusted analyses, continuous covariates were set to the mean values of all participants (age = 45 years; BMI = 26 kg/m^2; eGFR = 89 $mL/min/1.73\ m^2$; $CD4^+$ T-cells = 609 $cells/mm^3$) in order to quantify group TFV-DP GMs (95% CIs) in addition to group TFV-DP percent differences (95% CIs), and to quantify three-month adherence, for someone with average participant characteristics. Pearson's Chi squared test of independence was used to assess proportion of viral suppression (< 20 copies/mL) across groups, to assess differences in proportions of the number and types of MH diagnoses among those with MH disorders, and to assess proportion of viral suppression between just the two MH groups. A significance level of 0.05 was assumed for all hypothesis tests. All statistical analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Figures were created using GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA).

Results

Demographics

From a total of 807 participants enrolled in the parent study [22], TFV-DP concentrations and a paired HIV VL were available from 521 participants at their enrollment visit. Of these 521, 234 (45%) did not have a MH disorder, compared to 287 (55%) that did. Of the 286 participants excluded from this analysis because they did not have a paired TFV-DP concentration, all were virologically-suppressed, and 116 (41%) did not have a MH disorder, compared to 170 (59%) that did. When comparing the proportion of participants with and without a MH disorder between the included and excluded participants, we found the groups were not significantly different ($\chi^2 = 1.43$, $p = 0.233$). Demographic characteristics for the 521 participants included in this analysis are shown in Table 1. Overall, 347 (67%) of 521 were virologically-suppressed (< 20 copies/mL). Among the 204 participants with at least one MH disorder and were engaged in MH care (referred to as "engaged"), 143 (70%) were virologically-suppressed, similar to what was observed in participants without MH disorders (160/234, 68%), compared to only 44 (53%) of 83 participants with at least one MH disorder and were not engaged in MH care (referred to as "not engaged") ($\chi^2 = 8.34$, $p = 0.015$).

Regarding current ART across groups, a greater percentage of participants without MH disorders were on a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen (35%) compared to both MH groups (engaged: 21%; not engaged: 18%). Similarly, a larger proportion of both MH groups were taking an integrase strand transfer inhibitor (INSTI)-based regimen (engaged: 44%; not engaged: 41%) compared to those without MH disorders (27%).

Table 1 Demographic characteristics of the study population ($N=521$)

		No mental health Dx n (%) or median (IQR)	Mental health Dx, engaged n (%) or median (IQR)	Mental health Dx, not engaged n (%) or median (IQR)
Variable	Group	234 (45)	204 (39)	83 (16)
Age		47 (38, 53)	45 (36, 53)	40 (32, 50)
Gender	Male	202 (86)	177 (87)	68 (82)
	Female	32 (14)	27 (13)	15 (18)
Race	Black	48 (21)	34 (17)	17 (20)
	White	119 (51)	131 (64)	48 (56)
	Hispanic	56 (24)	30 (15)	13 (16)
	Other	11 (5)	9 (4)	5 (6)
BMI (kg/m^2)	< 18.5	6 (3)	7 (3)	8 (10)
	18.5–25	92 (39)	86 (42)	40 (48)
	25–30	83 (35)	66 (32)	24 (29)
	> 30	51 (22)	45 (22)	11 (13)
eGFR (mL/min/1.73 m^2)		87 (75, 104)	86 (73, 101)	90 (77, 101)
CD4$^+$ T-cells (cells/mm^3)	< 200	27 (12)	16 (8)	15 (18)
	200–350	28 (12)	29 (14)	21 (25)
	350–500	30 (13)	31 (15)	14 (17)
	> 500	149 (64)	128 (63)	33 (40)
Current ART duration (months)	< 1	11 (5)	5 (2)	5 (6)
	1–3	15 (6)	16 (8)	13 (16)
	3–6	12 (5)	13 (6)	5 (6)
	> 6	196 (84)	170 (83)	60 (72)
ART class	NNRTI	81 (35)	42 (21)	15 (18)
	b/PI	56 (24)	49 (24)	26 (31)
	INSTI	63 (27)	90 (44)	34 (41)
	Multiclass	34 (15)	23 (11)	8 (10)
PK booster	No	124 (53)	99 (49)	30 (36)
	Yes	110 (47)	105 (51)	53 (64)
HIV VL (copies/mL)	> 20	74 (32)	61 (30)	39 (47)
	< 20	160 (68)	143 (70)	44 (53)

Dx diagnosis, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *ART* antiretroviral therapy, *PK* pharmacokinetic, *MH* mental health, *VL* viral load

Distribution of MH Diagnoses

Table 2 shows the proportions of participants in the MH groups by number and type of diagnosed MH disorders. Among the 287 participants with MH disorders, 204 (71%) were engaged in MH care, and most had one MH diagnosis (engaged: 46%; not engaged: 58%). The most prevalent MH diagnosis group was mood disorders (77%). There was a greater percentage of anxiety disorders in the engaged group (48%) compared to the not engaged group (33%) ($\chi^2=5.77$, $p=0.016$). Additionally, there was a greater percentage of mood disorders in the engaged group (80%) compared to the not engaged group (67%) ($\chi^2=5.51$, $p=0.019$). Finally, there was a greater percentage of substance use disorders in the not engaged group (43%) compared to the engaged group (28%) ($\chi^2=5.98$, $p=0.015$).

TFV-DP Concentrations in DBS and Engagement in MH Care

The TFV-DP concentrations according to demographic and clinical characteristics in the parent study have been previously described [22]. Regarding engagement in MH care, Table 3 shows that participants in the engaged group had an average of 42% (95% CI 17–73) higher TFV-DP concentrations in DBS compared to the not engaged group ($\beta=0.35$, $SE=0.10$, $p<0.001$). Those without MH disorders had an average of 27% (95% CI 5–53) higher TFV-DP concentrations in DBS compared to the not engaged group ($\beta=0.24$, $SE=0.10$, $p=0.015$). In a multivariable linear regression that adjusted for age, gender, race, BMI, eGFR, CD4$^+$ T-cell count, ART class, duration on current ART, and use of a PK booster, we found these differences in

Table 2 Distribution of mental health diagnoses and detectable viremia in the study population according to engagement in mental health care ($N=287$)

		Mental health Dx, engaged n (%)	Mental health Dx, not engaged n (%)	χ^2 (DF)	p value
Variable	Group	204 (71)	83 (29)		
Number MH Dx	1	94 (46)	48 (58)	4.65 (2)	0.098
	2	76 (37)	28 (34)		
	≥3	34 (17)	7 (8)		
Anxiety Dx	No	106 (52)	56 (67)	5.78 (1)	0.016
	Yes	98 (48)	27 (33)		
Mood Dx	No	40 (20)	27 (33)	5.51 (1)	0.019
	Yes	164 (80)	56 (67)		
Substance use Dx	No	146 (72)	47 (57)	5.98 (1)	0.015
	Yes	58 (28)	26 (43)		
Other Dx	No	187 (92)	80 (96)	2.03 (1)	0.155
	Yes	17 (8)	3 (4)		
HIV VL (copies/mL)	> 20	61 (30)	39 (47)	7.59 (1)	0.006
	< 20	143 (70)	44 (53)		

Due to participants with multiple MH disorders that can be either in the same or different categories, the sum of all MH diagnoses (449) is greater than the sample size of participants with at least one MH disorder (287)

Dx diagnosis, *MH* mental health, *DF* degrees of freedom, *VL* viral load

Table 3 Unadjusted and adjusted TFV-DP concentrations by group

	Unadjusted			Adjusted[a]		
	n (%)	TFV-DP [GM (95% CI)] fmol/punch	t-statistic (DF), p value	n (%)	TFV-DP [GM (95% CI)] fmol/punch	t-statistic (DF), p value
No mental health Dx	234 (45)	1438 (1304, 1584)	2.44 (520), 0.015	232 (45)	1414 (1180, 1695)	2.57 (518), 0.011
Mental health Dx, engaged	204 (39)	1538 (1457, 1794)	3.58 (520), < 0.001	204 (39)	1546 (1273, 1877)	3.47 (518), < 0.001
Mental health Dx, not engaged	83 (16)	1135 (964, 1337)	REF	83 (16)	1103 (886, 1374)	REF

Unadjusted analysis $N=521$; adjusted analysis $N=519$ ($n=2$ removed for missing BMI)

TFV-DP tenofovir-diphosphate, *DF* degrees of freedom, *REF* reference group, *Dx* diagnosis, *GM* geometric mean, *95% CI* 95% confidence interval, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *ART* antiretroviral therapy, *PK* pharmacokinetic

[a]Adjusted for: age, gender, race, BMI, eGFR, CD4 + T-cell count, ART class, duration on current ART, use of PK booster; continuous covariates set to mean values: age (45 years), BMI (26 kg/m^2), eGFR (89 mL/min/1.73 m^2), CD4$^+$ T-cells (609 cells/mm^3)

TFV-DP concentrations in DBS according to MH group remained significant (Table 3 and Fig. 1). Participants in the engaged group had an average of 40% (95% CI 16–70) higher TFV-DP concentrations in DBS compared to the not engaged group ($\beta=0.34$, SE = 0.10, $p<0.001$). Similarly, participants without MH disorders had an average of 28% (95% CI 5–55) higher TFV-DP concentrations in DBS compared to the not engaged group ($\beta=0.25$, SE = 0.10, $p=0.011$). There was no significant difference in TFV-DP concentrations between the engaged group and those without MH disorders, in both the unadjusted analysis ($p=0.106$) and the adjusted analysis ($p=0.219$).

Self-reported Adherence and Engagement in MH Care

Data on three-month self-reported adherence in the study population has been described elsewhere [22]. In this analysis, three-month self-reported adherence data was available for 482 (93%) of 521 participants at enrollment. In an unadjusted analysis (Table 4), participants in the engaged group reported 9% (95% CI 5–13) higher three-month adherence compared to the not engaged group ($\beta=9.27$, SE = 1.94, $p<0.001$). Similarly, those without MH disorders reported 11% (95% CI 8–15) higher three-month

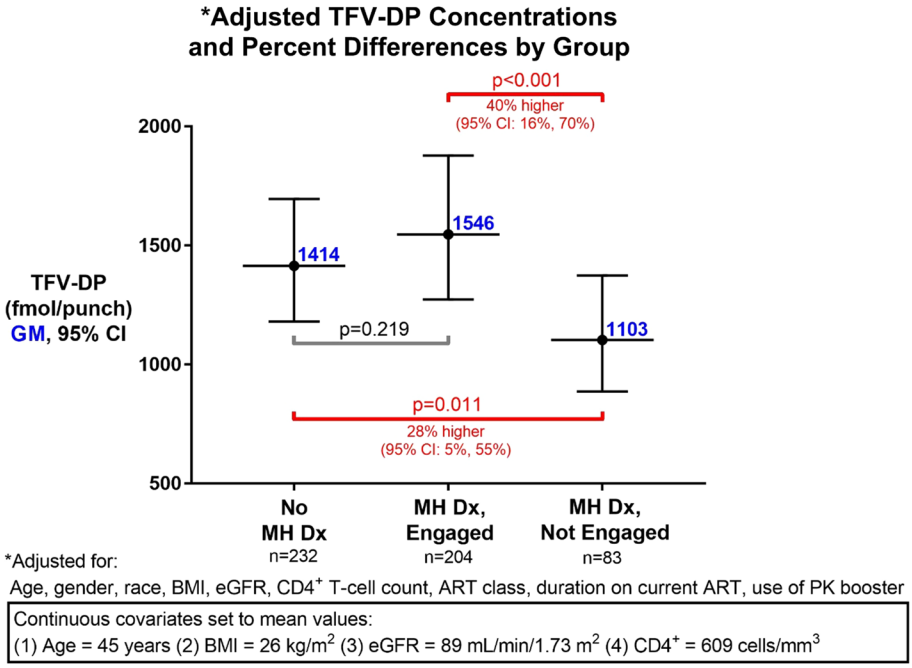

Fig. 1 Adjusted TFV-DP concentrations and percent differences by group ($N=519$). *TFV-DP* tenofovir-diphosphate, *GM* geometric mean, *95% CI* 95% confidence interval, *Dx* diagnosis, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *ART* antiretroviral therapy, *PK* pharmacokinetic

Table 4 Unadjusted and adjusted mean three-month self-reported adherence by group

	Unadjusted			Adjusted[a]		
	n (%)	Three-month SR adherence (% [95% CI])	t-statistic (DF), p value	n (%)	Three-month SR adherence (% [95% CI])	t-statistic (DF), p value
No mental health Dx	218 (45)	94 (92, 96)	6.00 (481), < 0.001	216 (45)	89 (85, 93)	5.25 (479), < 0.001
Mental health Dx, engaged	193 (40)	92 (90, 94)	4.77 (481), < 0.001	193 (40)	86 (82, 90)	3.87 (479), < 0.001
Mental health Dx, not engaged	71 (15)	83 (79, 86)	REF	71 (15)	79 (74, 84)	REF

Unadjusted analysis $N=482$; adjusted analysis $N=480$ ($n=2$ removed for missing BMI)

SR self-reported, *DF* degrees of freedom, *REF* reference group, *Dx* diagnosis, *GM* geometric mean, *95% CI* 95% confidence interval, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *ART* antiretroviral therapy, *PK* pharmacokinetic

[a]Adjusted for: age, gender, race, BMI, eGFR, CD4 + T-cell count, ART class, duration on current ART, use of PK booster; continuous covariates set to mean values: age (45 years), BMI (26 kg/m^2), eGFR (89 mL/min/1.73 m^2), CD4$^+$ T-cells (609 cells/mm^3)

adherence compared to the not engaged group ($\beta=11.47$, SE = 1.91, $p<0.001$). Table 4 and Fig. 2 show that these differences in self-reported adherence remained significant after adjusting for the same covariates used in the previous model with TFV-DP, where the engaged group reported 7% (95% CI 4–11) higher three-month adherence compared to the not engaged group ($\beta=7.26$, SE = 1.87, $p<0.001$). Similarly, participants without MH disorders reported 10% (95% CI 6–13) higher three-month adherence compared to the not engaged group ($\beta=9.78$, SE = 1.86, $p<0.001$). There was no significant difference in three-month self-reported adherence between the engaged group and those without MH disorders, in both the unadjusted analysis ($p=0.112$) and the adjusted analysis ($p=0.061$).

Discussion

In this study, we described the relationship between TFV-DP in DBS and engagement in MH care among a clinical cohort of PLWH. Compared to participants with MH disorders who were not engaged in MH care, we found higher TFV-DP concentrations in DBS in PLWH with MH disorders who were engaged in MH care and in PLWH without MH disorders. These relationships did not change after adjusting for real and plausible confounding variables, were similar when assessing three-month self-reported ART adherence as the outcome variable, and translated into higher proportions of viral suppression between

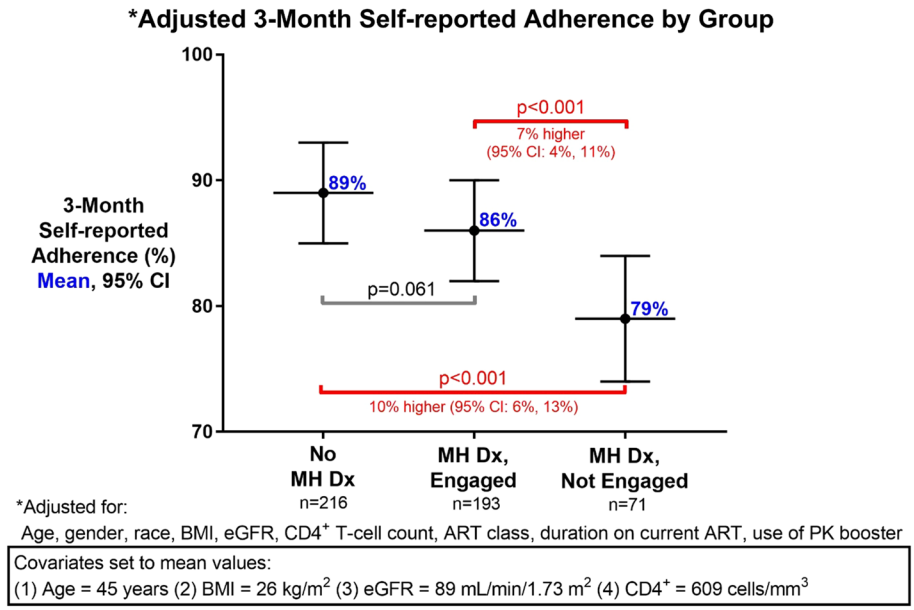

Fig. 2 Adjusted 3-month self-reported adherence by group ($N=480$). *95% CI* 95% confidence interval, *Dx* diagnosis, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *ART* antiretroviral therapy, *PK* pharmacokinetic

these groups. Collectively, these findings highlight a clear association between engagement in MH care with ART adherence and virologic suppression in PLWH with MH disorders.

Engagement in MH care is an important area in HIV research that needs to be addressed further in order to improve clinical outcomes [1, 5, 9], retention in care [2, 7], and help control the HIV epidemic through reduced transmission [11, 29–31]. Our results suggest that engaging PLWH who have MH disorders into MH care could help improve ART adherence and exposure and rates of viral suppression, thereby decreasing the likelihood of HIV transmission. Therefore, promoting engagement in MH care has the potential to enhance the progress of Undetectable = Untransmittable (U = U) and may also help decrease stigma—not only with regards to HIV, but with MH disorders and MH care/treatment at large—by showing both the clinical and social benefits of engagement in MH care.

Beyond the clinical benefits of decreased duration and/or burden of MH disorders [5, 32], engagement in MH care allows for more consistent monitoring of concomitant medications and substance use to avoid and limit drug–drug interactions, and to verify treatment efficacy and safety [33–35]. Additionally, initiating antidepressant therapy in PLWH with diagnosed depression has been associated with improved ART adherence [36–39]. Such improvements in adherence could be, in part, due to the reinforcement of MH medication adherence at the time of a MH clinic visit, which often results in an improvement in ART adherence. The converse could also be true, that is, that those who are more consistent with attendance to clinic appointments and ART dosing are more likely to be adherent to MH medications and/or MH care.

Parallel to the influence of engagement in MH care on ART adherence, our findings could also be explained by improvements in functioning associated with clinical improvements in a MH disorder. Such improvements in functioning may be evident by increases in motivation and organization that lead to increased ART adherence, or decreased frequency of other behaviors associated with lower ART adherence, such as substance use [40, 41]. An additional explanation of our findings could be unrecognized drug–drug interactions (DDIs) between ARVs, psychiatric medications, and/or substance use [33, 34, 41], which could differentially affect ARV exposure (specifically for TFV), leading to higher or lower TFV-DP concentrations. Many DDIs are known and documented for FDA-approved drugs, but it is often very difficult to identify all of them. For example, one study of coinfected HIV/Hepatitis C (HCV) participants being treated with a TDF-based regimen for HIV, and sofosbuvir (SOF) for HCV, found an unexpected DDI, where TFV-DP concentrations in DBS increased between 4.3-fold (for those on SOF + ribavirin) and 17.8-fold (for those on co-formulated ledipasvir/SOF) [42]. Further research on the potential mechanisms that drive ARV exposure in PLWH with MH disorders taking MH medications is needed.

Strengths of our study include a large and diverse sample size from a clinical cohort of PLWH taking a wide range of ART regimens for variable lengths of time, and the use of a novel measure of ART adherence and exposure. While we limited our analysis to those with available TFV-DP concentrations at enrollment, our results from this viremic-enriched cohort found significant differences between groups, and these differences may have been even more pronounced if the entire study population had been included. Limitations include the retrospective nature of the MH data collection,

as we relied solely on chart abstraction to identify MH disorders as active problems and determine if participants were engaged in MH care. Additionally, the definition of engagement in MH care defined as a visit to any provider that managed a MH disorder in the previous 12 months represented a large range, which could have introduced larger variability. However, some patients who are legitimately engaged in MH care only see their provider once a year, or are stable to the point where they no longer see a MH provider but have their HIV PCP refill MH medications. We did not want to inaccurately categorize these participants as not engaged in MH care. Similarly, while we identified substance use disorders, this analysis did not explore differences according to substance type, frequency, or quantity of substance use. Finally, our clinic has the advantage of having an integrated MH care system which other clinics may not have. This could have influenced the proportion of participants with MH disorders who were engaged in MH care, and limits the generalizability of our findings. However, efforts to integrate HIV and MH care are becoming more popular [43]. While our clinic has this advantage, not all of our patients are a part of this integrated care, as it is not required. As such, our clinic setting is likely quite similar to other sites that offer both HIV and MH care. Additional research to address these gaps and better understand the interactions between ART adherence and MH is needed. For example, a study in which TFV-DP is used in tandem with self-reported adherence and HIV VL to assess clinical and/or behavioral outcomes in PLWH with MH disorders would provide valuable insight.

In summary, our results demonstrate that engagement in MH care is associated with higher TFV-DP concentrations in DBS, higher three-month self-reported ART adherence, and higher proportions of viral suppression. Our findings provide further evidence for prioritizing MH care utilization for PLWH, especially for those with MH disorders, as engagement in MH care has been linked to increased retention in HIV primary care [2, 5], improved clinical outcomes [5], and decreased mortality risk [5, 44]. Further research is needed to identify the mechanism(s) for these findings, with the goal of optimizing engagement and retention in MH care strategies to improve ART adherence and clinical outcomes in PLWH with MH disorders.

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Conflict of interest No conflicts of interest were reported from all remaining authors. Each author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts of interest that the editors consider relevant to the content of the manuscript have been disclosed.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Colorado Multiple Institutional Review Board (COMIRB; protocol 13-2104) and was registered at ClinicalTrials.gov (NCT02012621).

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