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MAJOR ARTICLE

Antiretroviral Refill Histories as a Predictor of Future Human Immunodeficiency Virus Viremia

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Background. The use of adherence measures as markers for virologic failure (VF) has been studied. Yet, there is currently no single adherence metric recommended for VF. Antiretroviral prescription refill histories, for people living with human immunodeficiency virus (HIV), are readily accessible and can be easily quantified to an estimated adherence level.

Methods. Participants from a Midwestern US HIV clinic were retrospectively evaluated from 2018 to 2020. Refill histories (RH) and last HIV RNA for each participant were abstracted for each study year. RH were quantified as a percentage of days covered (PDC) and VF was defined as HIV RNA >200 copies/mL. PDC values were matched with subsequent year HIV RNA (matched pair). Sample *t* test were used to compare mean PDC level by viral suppression status and generalized estimating equations models were used to determine the predictability of PDC level for VF. An optimal PDC threshold for VF was determined using receiver operating characteristic curve analysis and Youden index.

Results. A total of 1056 participants contributed to 1923 matched pairs (PDC/HIV RNA); mean age was 48.3 years, 24% women, and 30.6% Black. PDC levels differed significantly based on dichotomized HIV RNA (2018–2019: >200: 40% [95% confidence interval {CI}, 33%–46%] vs ≤200: 85% [95% CI, 84%–87%], $P < .0001$; 2019–2020: >200: 45% [95% CI, 38%–51%] vs ≤200: 87% [95% CI, 86%–89%], $P < .0001$). Based on the Youden index value of 0.66 (sensitivity 0.77, specificity 0.89), the optimal PDC threshold predictive of VF was 52%.

Conclusions. Lower antiretroviral therapy (ART) adherence levels were predictive of future VF when PDC ≤52%.

Keywords. adherence; HIV viremia; pharmacy refill records; viral failure.

KEY POINTS

Pharmacy refill records are readily accessible and can be quantified into an adherence level to determine thresholds for prediction of HIV virologic failure. Patients with estimated adherence levels of ≤52% are most likely to experience virologic failure in the future.

BACKGROUND

Virologic suppression with antiretroviral therapy (ART) among people living with human immunodeficiency virus (PLWH) is the cornerstone of human immunodeficiency virus (HIV) treatment [1]. Sustained HIV virologic suppression reduces the risk for HIV-related comorbidities leading to improvements in long-term health outcomes [2, 3]. ART adherence levels >95% have traditionally been recommended for sustained HIV virologic suppression [4]. With the advent of newer, more potent ART regimens, adherence levels as low as 75% (dependent on regimen type) have been associated with virologic suppression when quantitatively evaluating prescription refill histories as a percentage of days covered (PDC) [5]. These lower thresholds possibly suggest some forgiveness in newer, potent ART regimens with a higher barrier to the development of HIV drug resistance.

Novel, innovative measures of ART adherence have been explored including analysis of antiretroviral concentrations in dried blood spots (DBSs), hair, and urine [6–11]. Concentration of tenofovir diphosphate (TFV-DP) levels in DBSs has been shown to be a viable predictor of viral suppression and future viremia in PLWH [8, 11]. However, these assays are not yet commercially available and are therefore used primarily in investigational settings. In clinical practice, providers often rely on prescription refill history data in conjunction with subjective patient reports to retrospectively evaluate ART adherence. Yet,

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subjective patient reports frequently overestimate actual adherence [12, 13] and often do not match the adherence portrayed by the refill history, leaving real-time, clinical decision making challenging.

In this longitudinal, retrospective cohort study, we aimed to evaluate whether adherence levels based on antiretroviral prescription refill data predict future HIV viremia and to identify an adherence threshold level associated with future HIV viremia.

METHODS

Study Design and Participants

We conducted a single-center, retrospective cohort study to evaluate the relationship(s) between ART adherence and future HIV viremia. A query of established patients receiving medical care at the University of Nebraska Medical Center HIV clinic, the Specialty Care Center, was collected from the electronic health record (EHR; Epic, Verona, Wisconsin). Participants were included in the study data set according to the following inclusion criteria: (1) living with HIV and ≥19 years of age and (2) prescribed ART for at least 6 months prior to the beginning of the study period. Participants were excluded from analysis for the following reasons: (1) industry study participation for receipt of ART; (2) lost to follow-up (ie, missing clinical care visit within 1 year) and/or missing HIV RNA data; or (3) relocated, incarcerated, or deceased during the study period.

Procedures and Outcomes

Study participant data from 1 January 2018 through 31 December 2020 were abstracted from the EHR. Collected data included demographic, socioeconomic, and clinical variables. Complete pharmacy refill histories were collected via the Nebraska Prescription Drug Monitoring Program (PDMP), EHR, or directly from the participant's pharmacy(s) by telephone for the calendar years 2018 and 2019 to calculate annual PDC values. PDC was calculated for the prescribed ART regimen as the following: total number of ART tablets, for complete ART regimen, dispensed within the respective study calendar year divided by 365 days multiplied by 100% [14, 15]. The upper limit of PDC value was not capped at 100% if the participant had received their ART regimen >12 times in the given study year period. HIV virologic failure was defined as HIV RNA >200 copies/mL.

The primary objective of the study was to assess whether annual PDC can predict virologic failure in the following year. We matched participant annual PDC level with the first reported HIV RNA in the following study calendar year (matched pair). Participants could have contributed to 1 or 2 matched-pair data depending on the availability of reported data variables for each time period (Figure 1). Secondary objectives included determining the minimum ART adherence threshold by PDC predictive of future viremia. Furthermore, we analyzed for predictive factors associated with poor ART adherence defined as a PDC below the observed minimum threshold level.

Last, a subanalysis to determine differences in minimum ART adherence thresholds by predictive of future viremia was

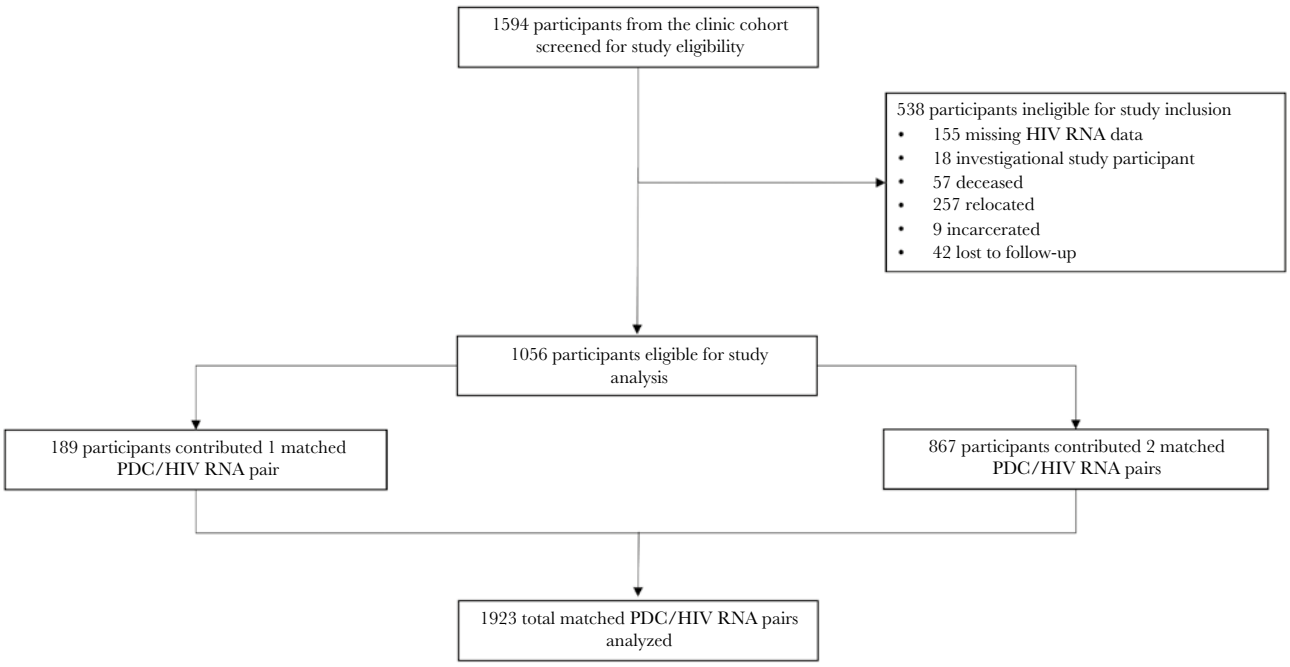

Figure 1. Study profile. One matched percentage of days covered (PDC)/human immunodeficiency virus (HIV) RNA pair represents the matched variables of 1 study-year PDC with the following year HIV RNA.

completed. We categorized all ART regimens as high barrier or non–high barrier. High-barrier ART regimens were defined as those anchored by a boosted protease inhibitor (PI) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) [16–18], a second-generation (dolutegravir or bictegravir) integrase strand transfer inhibitor (INSTI) plus 2 NRTIs [19–22], dual ART of boosted darunavir plus dolutegravir [23], or a multiclass ART regimen consisting of a combination of ≥3 ART classes including both a boosted PI and second-generation INSTI. All other ART regimens were considered non–high barrier.

Statistical Analysis

Descriptive statistics were used to summarize participant demographics and baseline characteristics. Counts and percentages were used for categorical data and mean and ranges for continuous data. HIV viral load was dichotomized at ≤200 or >200 copies/mL. The independent sample *t* test was used to compare the mean PDC level between the viral load groups using the previous year's PDC level stratified by year. A generalized estimating equation (GEE) approach was used to determine if PDC in the previous year predicted virologic failure in the following year. This approach accounts for the correlation within patients of HIV RNA and PDC since the same patients were evaluated between 2018 and 2020 and uses a compound symmetry covariance structure to account for the correlation. A receiver operating characteristic (ROC) curve was used to determine the optimal PDC cut point by the Youden index (Youden index = sensitivity + specificity – 1) based on the predictive model. The index is defined for all points of an ROC curve, and the maximum value of the index is used as a criterion for selecting the optimum adherence threshold. GEEs with a binomial distribution were used to model the probability of poor adherence using the log link function in univariate and multivariable analysis. Factors associated with PDC level at the $P < .15$ level were included in a multivariable model. A final model was performed using manual backward selection and only factors associated at the $P < .05$ level were included in the final model. All analyses were done using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

Patient Consent Statement

The University of Nebraska Medical Center Institutional Review Board (IRB 787-18-EP) has approved the design and procedures for this study.

RESULTS

A total of 1594 patients were initially screened for study analysis for the 3-year period between 1 January 2018 and 31 December 2020. The final study analysis consisted of 1056 patients (Figure 1). Mean age was 48.3 years, and 24.2% (n = 256) were cisgender female. Thirty percent (n = 323) were of Black race and 13.5% (n = 143) were of Hispanic ethnicity. More than half of the study population was covered by a commercial insurance provider (n = 607 [57.5%]) and/or supported by the state-operated AIDS Drug Assistance Program (n = 714 [67.6%]). At baseline, half were on INSTI-based ART (n = 575 [54.5%]) and the majority had an HIV RNA level ≤200 copies/mL (n = 940 [89%]). Mean PDC for all participants was similar between study years (2018: 81.4%; 2019: 82.1%). All patient baseline demographics are outlined in Table 1. One hundred eighty-nine patients contributed to single-year matched pairs and 867 patients contributed to 2 study-year matched pairs for a total of 1923 matched pairs analyzed (Figure 1).

Primary Endpoint

We aimed to determine if HIV virologic failure was predicted by the prior year's adherence level as defined by the annual PDC value. Table 2 highlights the viral suppression data by year. Similar results for HIV virologic failure were observed for each study year ranging from 7.3% to 8.8%. Matched pairs for 2018–2019 and 2019–2020 were analyzed to assess differences in mean PDC based on HIV virologic suppression (Table 3). Statistically significant differences in mean PDC were observed for both the 2018–2019 matched pairs (HIV RNA >200 vs ≤200 copies/mL: 40% [95% confidence interval {CI}, 33%–46%] vs 85% [95% CI, 84%–87%], respectively; $P < .0001$) and 2019–2020 matched pairs (HIV RNA >200 vs ≤200 copies/mL: 45% [95% CI, 38%–51%] vs 87% [95% CI, 86%–89%], respectively; $P < .0001$).

Secondary Endpoints

We used all study matched pairs data to generate an ROC curve and Youden index for PDC and HIV RNA to determine the optimal PDC threshold associated with future HIV viral failure. A PDC threshold of 52% was associated with HIV virologic failure with sensitivity and specificity of 0.77 and 0.89, respectively (Figure 2).

Univariate and multivariate analyses were performed using all sociodemographic characteristics to identify factors associated with adherence levels <52% (Table 4). The final, reduced multivariate model revealed race (Black vs White race: odds ratio [OR], 2.04 [95% CI, 1.5–2.8]; $P < .0001$) and other races vs White race (any race excluding White or Black: OR, 2.66 [95% CI, 1.4–5.0]; $P = .0026$]), marital status (participants not reporting a committed relationship [ie, single, divorced, separated, widowed] vs participants in a relationship: OR, 1.86 [95% CI, 1.2–2.8]; $P = .0033$), housing (homelessness vs stable housing: OR, 3.84 [95% CI, 2.3–6.5]; $P < .0001$), and insurance coverage (government-based insurance vs commercial insurance: OR, 1.72 [95% CI, 1.2–2.4]; $P = .0019$ and uninsured vs commercial insurance: OR, 9.85 [95% CI, 6.0–16.2]; $P < .0001$) as variables associated with lower adherence.

Subanalyses were completed to determine PDC threshold for HIV virologic failure based on each ART regimen's perceived barrier to the development of HIV drug resistance. The same but higher PDC threshold level was observed with

Table 1. Baseline Characteristics

Characteristic	Total Population (N = 1056)	Single-Year Matched Pair[a] (n = 189)	Dual-Year Matched Pair[b] (n = 867)
Age, y, mean (range)	48.3 (19–77)	46.3 (19–71)	48.8 (21–77)
Gender			
Male	784 (74.2)	139 (73.6)	645 (85.1)
Female	256 (24.2)	46 (24.3)	210 (13.5)
Transgender female	16 (1.6)	4 (2.1)	12 (1.4)
Race			
White	678 (64.2)	112 (59.3)	566 (65.3)
Black	323 (30.6)	66 (34.9)	257 (29.6)
Asian	27 (2.6)	4 (2.1)	23 (2.7)
American Indian/Pacific Islander	10 (1.0)	2 (1.1)	8 (0.9)
Multiracial	18 (1.6)	5 (2.6)	13 (1.5)
Ethnicity			
Hispanic	143 (13.5)	20 (10.6)	123 (14.2)
Non-Hispanic	913 (86.5)	169 (89.4)	744 (85.8)
Relationship status			
Single	594 (56.3)	119 (63.0)	475 (54.8)
Married/life partner	289 (27.4)	40 (21.2)	249 (28.7)
Divorced/separated	140 (13.3)	23 (12.1)	117 (13.5)
Widower	33 (3.0)	7 (3.7)	26 (3.0)
Housing status			
Stable housing	998 (94.5)	169 (89.4)	829 (95.6)
Homelessness	58 (5.5)	20 (10.6)	38 (4.4)
Urbanity			
Urban	909 (86.1)	170 (90.0)	739 (85.2)
Rural	147 (13.9)	19 (10.0)	128 (14.8)
Federal poverty level, %			
≤138	460 (43.6)	115 (60.9)	345 (39.8)
139–300	310 (29.4)	32 (16.9)	278 (32.1)
301–400	78 (7.4)	8 (4.1)	70 (8.1)
401–500	21 (2.0)	2 (1.1)	19 (2.1)
>500	12 (1.1)	0 (0.0)	12 (1.3)
Unknown	175 (16.5)	32 (16.9)	143 (16.4)
Health coverage			
Uninsured	66 (6.3)	19 (10.0)	47 (5.4)
Commercial	607 (57.5)	94 (49.7)	513 (59.2)
Government-funded[c]	383 (36.2)	76 (40.3)	307 (35.4)
ADAP assistance	714 (67.6)	122 (64.6)	592 (68.3)
Years prescribed ART, mean (range)	10.5 (1.3–38.0)	10.7 (1.3–38.0)	10.7 (1.7–37.8)
Baseline HIV RNA, ≤200 copies/mL	940 (89.0)	134 (70.9)	806 (93.0)
Baseline CD4 cell count, mean (range)	855 (2–2655)	864 (23–2037)	855 (5–2655)
Baseline ART regimen type			
NNRTI + 2 NRTIs	185 (17.5)	16 (8.5)	169 (19.5)
PI + 2 NRTIs	221 (20.9)	32 (16.9)	189 (21.8)
INSTI + 2 NRTIs	575 (54.5)	124 (65.6)	451 (52.0)
Multiclass[d]	60 (5.7)	13 (6.9)	47 (5.4)
Dual ART[e]	15 (1.4)	4 (2.1)	11 (1.3)
PDC, mean (range)			
2018	81.4 (0.0–133.0)	60.6 (0.0–117.0)	84.9 (0.0–133.0)
2019	82.1 (0.0–125.0)	68.9 (0.0–116)	84.8 (0.0–125.0)
Months to HIV RNA[f], mean (range)			
2018	5.0 (0.0–11.8)	5.3 (0.6–11.8)	4.6 (0.0–11.1)
2019	4.6 (0.0–11.9)	5.1 (0.1–11.9)	4.1 (0.0–11.3)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ADAP, AIDS Drug Assistance Program; ART, antiretroviral therapy; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PDC, percentage of days covered; PI, protease inhibitor.

[a]Denotes participants contributing only 1 study-year PDC paired with the following year's HIV RNA.

[b]Denotes participants contributing both study years' PDC paired with each subsequent following year's HIV RNA.

[c]Includes participants with Medicaid, Medicare, or Veterans Administration coverage.

[d]Nontraditional combination of ≥3 ART classes.

[e]Combination of 2 ART classes supported by clinical trial data (dolutegravir/lamivudine, dolutegravir/rilpivirine, boosted darunavir/dolutegravir).

[f]Denotes the time from end of study-year PDC collection to first HIV RNA in subsequent year.

Table 2. Viral Suppression by Study Year

Year	No. (% of Total) (n = 1056)	HIV RNA, No. (%)	
		>200 Copies/mL	≤200 Copies/mL
2018	985 (93.3)	72 (7.3)	913 (92.7)
2019	1039 (98.4)	91 (8.8)	948 (91.2)
2020	948 (89.8)	77 (8.1)	871 (91.9)

both non-high-barrier and high-barrier regimens (56%; Supplementary Figure 1), compared to the overall dataset PDC threshold of 52%.

DISCUSSION

In this retrospective cohort study, we used refill history data to quantify adherence levels, as PDC, and HIV RNA values to evaluate the relationship between PDC and future HIV virologic failure. We found PDC levels to be associated with future HIV virologic failure and identified a PDC of ≤52% as a threshold level predictive of future HIV viremia. Our findings suggest that PDC may be a useful real-time, clinical tool to identify patients at risk of future virologic failure.

Prior studies have explored various adherence markers for association with HIV virologic suppression. Self-reported adherence reports are extensively used in clinical practice but are limited by their subjectivity and often overestimate ART adherence [4, 13]. Antiretroviral concentrations in red blood cells via DBSs has been associated with both viral suppression and future viremia [8, 11, 24]. Emtricitabine (FTC) triphosphate and TFV-DP concentrations in DBSs allow for a view of short-term and intermediate-term adherence, respectively [8, 11, 24]. Antiretroviral concentrations in hair samples provide views of long-term adherence (~1 month) and have proven to be predictive of virologic outcomes as demonstrated in AIDS Clinical Trial Group study 5257 [25]. Yet, both DBS and hair sample analysis are not available at the point of care, currently limiting their use in the clinical setting. Point-of-care urine analysis of FTC and tenofovir salt (TFV) have been used in research settings as an adherence marker in patients receiving an FTC/TFV product for either preexposure prophylaxis or HIV infection [26–28]. Although these novel adherence analyses measuring concentrations of antiretrovirals in red blood cells, hair, and urine have found positive associations with virologic outcomes, the tests currently are not commercially available for clinical use and are not encompassing of all antiretrovirals [6–11]. Alternatively, refill history data are readily accessible through pharmacy communication, increased incorporation into EHR systems, and statewide PDMPs [29–31], allowing for quick calculation of an adherence level by PDC.

Table 3. Comparison of Prior-Year Mean Percentage of Days Covered With Human Immunodeficiency Virus RNA

Matched Pair[a], Year/PDC	HIV RNA, Copies/mL		*P* Value
	>200 Copies/mL	≤200 Copies/mL	
2018–2019			<.0001
No. (%)	72 (7.4)	902 (92.6)	
Mean PDC, %/100 (SD)	0.40 (0.29)	0.85 (0.23)	
2019–2020			<.0001
No. (%)	77 (8.1)	872 (91.9)	
Mean PDC, %/100 (SD)	0.45 (0.30)	0.87 (0.18)	

Abbreviations: HIV, human immunodeficiency virus; PDC, percentage of days covered; SD, standard deviation.

[a]Denotes 1 study-year PDC paired with the following year's HIV RNA.

Byrd and colleagues recently presented data from a prospective, cohort study using PDC as a marker for current HIV viral suppression [5]. Across all ART regimen types, the group identified a minimum PDC threshold for viral suppression of 82%. Subanalysis stratified by ART regimen type revealed further reductions in the minimum adherence threshold levels for current viral suppression: INSTI-based regimens, 75%; nonnucleoside reverse transcriptase inhibitor–based regimens, 78%; and PI-based regimens, 87% [5]. Our data, also using PDC, found a minimum threshold for future HIV viremia at 52%. While differences exist between the virologic endpoints with regard to timing (ie, current viral suppression vs future viral failure), both PDC studies may help to identify upper and lower bound adherence thresholds for HIV viral suppression and failure. Combining overall PDC thresholds from both studies, a PDC range between 52% and 82% is an intriguing adherence zone where the risk of the development of HIV drug resistance may be higher and the utilization of genotyping and/or adherence interventions may be warranted. Importantly, our subanalyses found similar but unexpectedly higher adherence thresholds for future HIV virologic failure between participants taking high-barrier ART regimens (PDC threshold level, 56%) vs non-high-barrier ART regimens (PDC threshold level, 56%) compared to the overall dataset (PDC threshold level, 52%). While the reasoning for these findings remains unclear, the subanalyses possibly highlight that future failure was not impacted by the ART barrier type (Supplementary Figure 1). Further research investigating the differences in viral failure based on ART regimen barrier would be beneficial to guide clinician real-time decision making in the setting of ART nonadherence.

An abundance of research currently exists around the predictive factors of ART nonadherence. Yet, the reasons for ART nonadherence are intrapersonal, cumulative, and often intertwined [32]. Our study data highlight populations most at risk of ART adherence ≤52% and future HIV viremia. We found that non-White race (specifically Black race), homelessness, government-based insurance, no insurance, and not being in a committed relationship were associated with adherence rates <52%. Higher rates of missed medical appointments and ART nonadherence were observed in a recent, cross-sectional study evaluating the effects of social determinants on HIV health outcomes [33]. Furthermore,

A

Youden	*Sensitivity*	*Specificity*	*PDC Threshold*
0.658	0.767	0.891	0.522
0.657	0.767	0.890	0.599
0.644	0.781	0.863	0.606
0.643	0.795	0.849	0.609
0.622	0.712	0.910	0.519
0.608	0.685	0.923	0.439
0.594	0.822	0.772	0.689
0.593	0.822	0.771	0.739
0.564	0.863	0.701	0.769
0.519	0.877	0.642	0.772
0.462	0.904	0.558	0.856

B

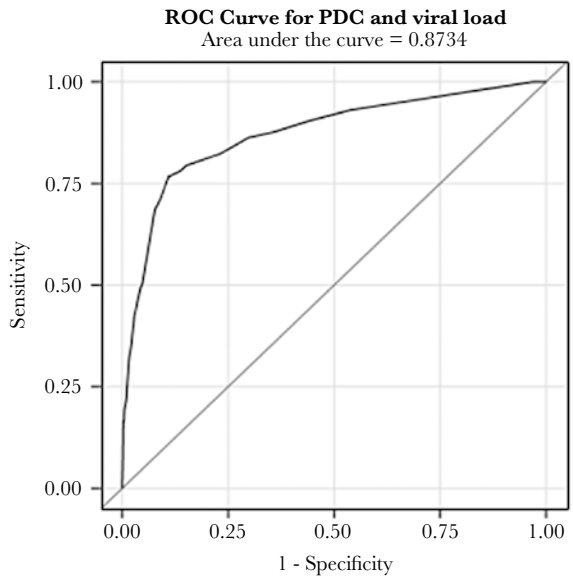

Figure 2. Determination of percentage of days covered (PDC) threshold for future human immunodeficiency virus (HIV) viremia. *A*, Sensitivity, specificity, and Youden J value based on PDC threshold level. *B*, Associated receiver operating characteristic (ROC) curve identified minimum PDC threshold for future HIV viremia, 0.52 or 52%.

social determinants are often interrelated and compound together to create a flywheel effect. For example, consider a PLWH with employer-based insurance who becomes newly unemployed. The resultant loss of income and insurance coverage could lead to a lack of ART access and subsequent nonadherence as well as potential homelessness without assistance of state or federal grant support. "Churning" or transitions in medical/prescription coverage secondary to income changes is common among PLWH [34]. Moreover, racial disparities in HIV care have been described in detail [35], with non-White PLWH exhibiting lower rates of ART adherence and viral suppression [36, 37]. Potential reasons for the racial differences in ART adherence and HIV outcomes include stigma [38, 39], provider mistrust [40, 41], and income inequality/poverty [42], among others. In conjunction with PDC prescription refill data, PLWH presenting with these social determinants may benefit from early, targeted adherence interventions and integrated team efforts to assist with socioeconomic barriers, such as housing support, insurance/grant access, etc, to improve ART adherence and virologic outcomes.

Table 4. Multivariate Predictors of Adherence Levels ≤52%[a]

Predictor	Odds Ratio	95% Confidence Limits		*P* Value
Race				
Black vs White	2.04	1.46	2.84	<.0001
Other vs White	2.66	1.41	5.02	.0026
Marital status				
Not in a relationship[b] vs in a relationship[c]	1.86	1.23	2.81	.0033
Housing status				
Homelessness vs stable housing	3.84	2.28	6.47	<.0001
Coverage				
Government-based[d] vs commercial	1.72	1.22	2.43	.0019
Uninsured vs commercial	9.85	5.99	16.19	<.0001

Representative of the final, reduced multivariate model including only variables significant at $P < .05$. Univariate model included the following variables: age, gender, race, ethnicity, marital status, housing status, urbanicity, Federal Poverty Limit, human immunodeficiency virus risk factor, insurance coverage.

[a]Expressed as a percentage of days covered ratio.

[b]Denotes relationship status of single, divorced, separated, or widower.

[c]Denotes relationship status of married or with life partner.

[d]Includes participants with Medicaid, Medicare, or Veterans Administration coverage.

We recognize our study has limitations. Most notably, its retrospective design introduces potential for misclassification bias. The generalizability of our results is limited as we only assessed a single, clinical cohort. PDC is an imperfect adherence marker and may be falsely high or low because dispensation of ART does not always result in ingestion. Additionally, some patients stop refilling their ART when they acquire a stockpile of medications due to hospitalizations, early refills, etc. Furthermore, our study used the first reported HIV RNA of each subsequent study year relative to PDC, which may not account for any HIV viremia after that time point.

In conclusion, our data suggest that ART adherence as measured by PDC is associated with future HIV viremia when levels are ≤52%. Our findings add to the current literature utilizing PDC as an adherence marker with associations for virologic outcomes and help define thresholds where direct adherence interventions may be indicated to prevent future HIV viremia and failure.

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

Author contributions. J. P. H., N. F., and S. H. B. designed the study. D. S. and J. P. H. contributed to the data collection. L. L. performed the statistical analyses. All authors analyzed and interpreted the data. D. S. and J. P. H. drafted the manuscript. All authors reviewed, critically revised, and approved the final manuscript.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Group ISS, Lundgren JD, Babiker AG, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med **2015**; 373:795–807.
2. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. N Engl J Med **1998**; 338:853–60.
3. Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet **2005**; 366:378–84.
4. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med **2000**; 133:21–30.
5. Byrd KK, Hou JG, Hazen R, et al. Antiretroviral adherence level necessary for HIV viral suppression using real-world data. J Acquir Immune Defic Syndr **2019**; 82:245–51.
6. Phillips TK, Gomba Y, Huang D, et al. Point-of-care urine tenofovir versus self-reported ART adherence in routine HIV care [abstract 183]. In: Conference on Retroviruses and Opportunistic Infections, Virtual, 6–10 March **2021**.
7. Baxi SM, Greenblatt RM, Bacchetti P, et al. Nevirapine concentration in hair samples is a strong predictor of virologic suppression in a prospective cohort of HIV-infected patients. PLoS One **2015**; 10:e0129100.
8. Castillo-Mancilla JR, Morrow M, Coyle RP, et al. Tenofovir diphosphate in dried blood spots is strongly associated with viral suppression in individuals with human immunodeficiency virus infections. Clin Infect Dis **2019**; 68:1335–42.
9. Gandhi M, Ameli N, Bacchetti P, et al. Atazanavir concentration in hair is the strongest predictor of outcomes on antiretroviral therapy. Clin Infect Dis **2011**; 52:1267–75.
10. Gandhi M, Ameli N, Bacchetti P, et al. Protease inhibitor levels in hair strongly predict virologic response to treatment. AIDS **2009**; 23:471–8.
11. Morrow M, MaWhinney S, Coyle RP, et al. Predictive value of tenofovir diphosphate in dried blood spots for future viremia in persons living with HIV. J Infect Dis **2019**; 220:635–42.
12. Pearson CR, Simoni JM, Hoff P, et al. Assessing antiretroviral adherence via electronic drug monitoring and self-report: an examination of key methodological issues. AIDS Behav **2007**; 11:161–73.
13. Simoni JM, Kurth AE, Pearson CR, et al. Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. AIDS Behav **2006**; 10:227–45.
14. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. Available at: http://www2.sas.com/proceedings/forum2007/043-2007.pdf. Accessed 13 July 2021.
15. McMahon JH, Jordan MR, Kelley K, et al. Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring. Clin Infect Dis **2011**; 52:493–506.
16. Clutter DS, Jordan MR, Bertagnolio S, Shafer RW. HIV-1 drug resistance and resistance testing. Infect Genet Evol **2016**; 46:292–307.
17. de Meyer S, Vangeneugden T, van Baelen B, et al. Resistance profile of darunavir: combined 24-week results from the POWER trials. AIDS Res Hum Retroviruses **2008**; 24:379–88.
18. Mo H, King MS, King K, et al. Selection of resistance in protease inhibitor-experienced, human immunodeficiency virus type 1-infected subjects failing lopinavir- and ritonavir-based therapy: mutation patterns and baseline correlates. J Virol **2005**; 79:3329–38.
19. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet **2017**; 390:2063–72.
20. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet HIV **2015**; 2:e127–36.
21. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine vs ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet HIV **2017**; 4:e536–46.
22. Sax PE, DeJesus E, Crofoot G, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. Lancet HIV **2017**; 4:e154–60.
23. Spinner CD, Kummerle T, Schneider J, et al. Efficacy and safety of switching to dolutegravir with boosted darunavir in virologically suppressed adults with HIV-1: a randomized, open-label, multicenter, phase 3, noninferiority trial: the DUALIS study. Open Forum Infect Dis **2020**; 7:ofaa356.
24. Morrow M, MaWhinney S, Coyle R, et al. Emtricitabine triphosphate in dried blood spots predicts future viremia in PWH. In: Conference on Retroviruses and Opportunistic Infections, Virtual, 6–10 March **2021**.
25. Gandhi M, Ofotokun I, Bacchetti P, et al. Hair antiretroviral levels strongly predict virologic outcomes in ACTG's A5257 trial [abstract 24]. In: Conference on Retroviruses and Opportunistic Infections, Boston, MA, 4–7 March **2018**.
26. Gandhi M, Bacchetti P, Okochi H, et al. Validation of a urine TFV immunoassay for real-time PrEP and ART adherence testing [abstract 464]. In: Conference on Retroviruses and Opportunistic Infections, Seattle, WA, 4–7 March **2019**.
27. Drain PK, Bardon AR, Simoni JM, et al. Point-of-care and near real-time testing for antiretroviral adherence monitoring to HIV treatment and prevention. Curr HIV/AIDS Rep **2020**; 17:487–98.
28. Gandhi M, Wang G, King R, et al. Development and validation of the first point-of-care assay to objectively monitor adherence to HIV treatment and prevention in real-time in routine settings. AIDS **2020**; 34:255–60.
29. Comer D, Couto J, Aguiar R, et al. Usefulness of pharmacy claims for medication reconciliation in primary care. Am J Manag Care **2015**; 21:486–93.
30. Comer D, Mearns E, Olivere L, Elliott DJ. Primary care provider perspectives on electronic medication refill history. Am J Med Qual **2017**; 32:43–7.
31. Manasco AT, Griggs C, Leeds R, et al. Characteristics of state prescription drug monitoring programs: a state-by-state survey. Pharmacoepidemiol Drug Saf **2016**; 25:847–51.
32. Kim J, Lee E, Park BJ, et al. Adherence to antiretroviral therapy and factors affecting low medication adherence among incident HIV-infected individuals during 2009-2016: a nationwide study. Sci Rep **2018**; 8:3133.
33. Menza TW, Hixson LK, Lipira L, Drach L. Social determinants of health and care outcomes among people with HIV in the United States. Open Forum Infect Dis **2021**; 8:ofab330.
34. Sommers BD, Rosenbaum S. Issues in health reform: how changes in eligibility may move millions back and forth between Medicaid and insurance exchanges. Health Aff (Millwood) **2011**; 30:228–36.
35. Andersen R, Bozzette SA, Shapiro MF, et al. Disparities in care for HIV patients: results of the HCSUS study. Santa Monica, CA: RAND Corporation; **2006**. Available at: https://www.rand.org/pubs/research_briefs/RB9171.html. Accessed 8 December 2021.
36. Beer L, Mattson CL, Bradley H, et al. Understanding cross-sectional racial, ethnic, and gender disparities in antiretroviral use and viral suppression among HIV patients in the United States. Medicine (Baltimore) **2016**; 95:e3171.
37. Geter A, Sutton MY, Armon C, Buchacz K; HIV Outpatient Study Investigators. Disparities in viral suppression and medication adherence among women in the USA, 2011-2016. AIDS Behav **2019**; 23:3015–23.
38. Algarin AB, Zhou Z, Cook CL, et al. Age, sex, race, ethnicity, sexual orientation: intersectionality of marginalized-group identities and enacted HIV-related stigma among people living with HIV in Florida. AIDS Behav **2019**; 23:2992–3001.
39. Brewer R, Hood KB, Moore M, et al. An exploratory study of resilience, HIV-related stigma, and HIV care outcomes among men who have sex with men (MSM) living with HIV in Louisiana. AIDS Behav **2020**; 24:2119–29.
40. Pellowski JA, Price DM, Allen AM, et al. The differences between medical trust and mistrust and their respective influences on medication beliefs and ART adherence among African-Americans living with HIV. Psychol Health **2017**; 32:1127–39.
41. Saha S, Jacobs EA, Moore RD, Beach MC. Trust in physicians and racial disparities in HIV care. AIDS Patient Care STDS **2010**; 24:415–20.
42. Xia Q, Robbins RS, Lazar R, et al. Racial and socioeconomic disparities in viral suppression among persons living with HIV in New York City. Ann Epidemiol **2017**; 27:335–41.