Low-Level Viremia Is Associated With Cumulative Adherence to Antiretroviral Therapy in Persons With HIV

Jose R. Castillo-Mancilla,1 Mary Morrow,2 Ryan P. Coyle,3 Stacey S. Coleman,3 Jia-Hua Zheng,4 Lucas Ellison,4 Lane R. Bushman,4 Jennifer J. Kiser,4 Peter L. Anderson,4 and Samantha MaWhinney2

1Division of Infectious Diseases, School of Medicine, University of Colorado-AMC, Aurora, Colorado, USA, 2Department of Biostatistics and Bioinformatics, Colorado School of Public Health, Aurora, Colorado, USA, 3University of Colorado Hospital, Aurora, Colorado, USA, and 4Colorado Antiviral Pharmacology Laboratory and Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado-AMC, Aurora, Colorado, USA

The drivers of low-level viremia (LLV) between 20 and 200 copies/mL remain unclear. In 1042 person-visits from 497 persons with HIV on tenofovir disoproxil fumarate–containing antiretroviral therapy (ART), the association between LLV and cumulative antiretroviral adherence (quantified using tenofovir diphosphate [TFV-DP] in dried blood spots) was assessed. Lower TFV-DP levels were associated with higher odds of LLV. As TFV-DP (fmol/punch) categories decreased from >1650 to 800–1650; 800–1650 to <800; and >1650 to <800, the adjusted odds ratios for LLV vs HIV VL <20 copies/mL were 2.0 (95% CI, 1.2–3.1), 2.4 (95% CI, 1.1–5.0), and 4.6 (95% CI, 2.2–9.9), respectively. This suggests that adherence could impact LLV.

Keywords. low-level viremia; adherence; dried blood spots; tenofovir diphosphat; antiretroviral therapy.

Achieving and sustaining an undetectable HIV viral load (VL) while on antiretroviral therapy (ART) can prevent progression to AIDS, development of drug resistance, and transmission [1, 2]. Durable viral suppression is accomplished with sustained ART adherence in the majority of persons with HIV (PWH). However, some PWH develop intermittent (ie, viral blips) or persistent low-level viremia (LLV), which is usually defined as an HIV VL that is above the lower limit of detection of a specific assay (ie, <20 or <50 copies/mL) but below the defined threshold for virologic failure of 200 copies/mL [1], or even 1000 copies/mL in some settings [3, 4]. This is not an uncommon finding in clinical practice, with estimates of up to 30% of PWH on ART experiencing LLV [4]. To date, the implications of LLV remain controversial, with some studies demonstrating an association with virologic failure [5] and, in cases of persistent LLV, drug resistance [6], while other studies show no adverse clinical outcomes in cases of intermittent viral blips [7].

In addition to its uncertain clinical significance, the root causes of LLV in PWH on ART also remain unclear. They include ongoing reactivation or budding of viral reservoirs [8], drug resistance [4], or even laboratory errors. Whether ART adherence influences LLV has also been evaluated, with some studies identifying an association with adherence measures such as unannounced pill counts [9] or medication event monitoring systems (MEMS) [10], while other studies did not find an association with a combination of pill count, self-report, and MEMS [11], or with low plasma drug concentrations (which can only inform recent dosing) [12]. However, no studies have evaluated whether LLV is associated with quantitative measures of cumulative ART adherence such as tenofovir diphosphate (TFV-DP) in dried blood spots (DBS), which was the aim of this study.

METHODS

We enrolled a prospective clinical cohort of adult (≥18 years) PWH receiving any tenofovir disoproxil fumarate–based regimen at the University of Colorado Hospital (UCH) between 2014 and 2017, as previously described [13]. Study participants were recruited at the time of a routine clinical visit where blood for HIV VL was being collected and had up to 3 visits (at least 14 days apart) within a 48-week period [13]. As all the study visits were performed at the time of a regular clinic visit, the first visit upon entry to the study did not have any specific HIV viral load requirement (ie, participants were not required to have an HIV VL of <20 copies/mL at entry). After signed informed consent, 4–6 mL of whole blood in EDTA was collected for DBS and prepared by spotting 25 μL onto 903 Protein Saver cards; DBS samples were allowed to dry for at least 2 hours and stored at −80°C until analysis [13]. Quantification of TFV-DP in DBS was performed from a 3-mm punch using a liquid chromatography/tandem mass spectrometry assay previously validated by our group [14, 15]. HIV VL in plasma was quantified using the Roche cobas 6800 HIV test at the UCH clinical laboratory, which is certified under the 1988 Clinical Laboratory Improvement Amendment (CLIA) [13]. Self-reported adherence was quantified using a validated visual analog scale, as previously reported in the cohort [13, 16]. The study was approved...
by the Colorado Multiple Institutional Review Board (COMIRB 
#13-2104) before the initiation of any study procedures.

To minimize the influence of recent initiation of ART on viral 
suppression, we only included study participants who had been 
on ART for at least 6 months at enrollment. For this analysis, 
person-visits from study participants were categorized into 1 of 
the following categories: (a) HIV VL <20 copies/mL (reference 
category); (b) HIV VL ≥20–<200 copies/mL; (c) HIV VL ≥200–
<1000 copies/mL; and (d) HIV VL ≥1000 copies/mL. TFV-DP 
in DBS was categorized based on our previous observations of 
its predictive value for future viremia, as follows: (a) ≥1650; (b) 
800–1650; and (c) <800 fmol/punch [17]. A generalized linear 
mixed model with a multinomial logistic link was used to esti-
mate the odds ratio (ORs) for each HIV VL category compared 
with <20 copies/mL by comparing the 2 lowest drug concen-
tration categories (<800 and 800–1650 fmol/punch) with the 
highest category (≥1650 fmol/punch), which was considered 
the reference. We selected a mixed model in order to include 
all available data as participants provided repeated measures 
(i.e., up to 3 in 48 weeks) and could change TFV-DP categories 
throughout the study. As our model was highly parameterized, 
ORs were adjusted (aORs) for covariates that remained sig-
nificant using backward selection and were not explained by 
TFV-DP category [13, 17]. Data are number (%), median (in-
terquartile range [IQR]), or aOR (95% CI), and a P value <.05 
was considered statistically significant. Statistical analyses were 
performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC,
USA), and R software, version 3.4.4.

RESULTS

From a total of 532 study participants (1199 person-visits) in 
whom drug concentrations were available [13], this analysis 
included 497 participants (1042 person-visits) in whom all clinical 
covariates for an adjusted analysis were available. The demo-
graphic characteristics of the study participants (at the first visit 
where drug concentrations were available) according to each 
HIV VL category are presented in Table 1. Overall, the median 
(IQR) age was 46 (37–52) years, and 72 (14%) of the study parti-
cipants were female. The racial distribution was consistent with 
the demographics of the HIV epidemic in Colorado (Table 1), 
as previously reported in this cohort [13]. The proportion of 
study participants with CD4+ T cells <200 cells/mm³ was the 
lowest (6%) for participants with HIV VL <20 copies/mL and 
highest (39%) for participants with HIV VL >1000 copies/mL 
(Table 1). Among participants with an HIV VL >1000 copies/ 
mL, boosted protease inhibitor– and integrase strand transfer 
inhibitor (INSTI)–based ART were predominant (Table 1). Overall, 
50% of participants were in the highest TFV-DP cat-
gen, and the proportion of participants in this category de-
creased from 56% in the <20 copies/mL HIV VL category to 3% 
in the >1000 copies/mL HIV VL category (Table 1). Figure 1 
shows this same relationship for all person-visits, where in the 
highest TFV-DP category the proportion of person-visits where 
the participants had an HIV VL <20 copies/mL was 83% com-
pared with 1% for an HIV VL >1000 copies/mL.

Table 2 shows the aOR for each HIV VL category according 
to a change in each TFV-DP category. When compared with 
the reference HIV VL category (<20 copies/mL), the aOR for 
an HIV VL of ≥20–<200 copies/mL increased by 2.0 (95% CI, 
1.2–3.1; P = .0048) and by 2.4 (95% CI, 1.1–5.0; P = .034) for a 
decrease in 1 category of TFV-DP from ≥1650 fmol/punch to 
800–1650 punch or from 800–1650 fmol/punch to <800 fmol/ 
punch, respectively (Table 2). Comparatively, the aOR for an 
HIV VL of ≥20–<200 copies/mL increased by 4.6 (95% CI, 
2.2–9.9; P < .0001) for a decrease in 2 categories of TFV-DP 
from ≥1650 to <800 fmol/punch (Table 2). We observed similar 
trends, albeit with a higher magnitude, for HIV VL categories of 
≥200–<1000 copies/mL (Table 2) and ≥1000 copies/mL (data 
not shown). When we limited our analysis to visits where HIV 
VL was always <200 copies/mL, our results were almost iden-
tical to those observed in the full cohort (Supplementary 
Table 1). Similarly, in an analysis that included self-reported adher-
ence in the last 3 months in the model, the odds of being in each 
HIV VL category were similar to the original model, although 
slightly attenuated (Supplementary Table 2). Last, we found a 
statistically significant difference when we compared median 
(IQR) concentrations of TFV-DP in DBS from person-visits 
where the HIV VL was <20 copies/mL with those where it was 
≥20–<200 copies/mL (1839 [1390–2521] vs 1580 [1153–2261] 
fmol/punch; P = .001) (Supplementary Figure 1).

We also evaluated the association between CD4+ T cells and 
LLV. In this analysis, adjusted by TFV-DP category and ART 
class, the odds of being in each HIV VL for every decrease in 
CD4+ T cells of 100 cells/mm³ were 1.1 (95% CI, 1.0–1.2; 
P = .031), 1.1 (95% CI, 0.9–1.3; P = .064), and 2.2 (95% CI, 1.4– 
3.4; P = .0006), respectively, for an HIV VL of ≥20–<200 copies/
/mL, ≥200–<1000 copies/mL, and >1000 copies/mL when com-
pared with <20 copies/mL.

DISCUSSION

In this study, we established that cumulative ART adherence, 
quantified using TFV-DP in DBS, was associated with LLV in 
the ≥20–<200 copies/mL range and with higher ranges of HIV 
VL (ie, ≥200 and >1000 copies/mL). Of interest, decreasing 
from the highest adherence category to the middle category 
(≥1650 fmol/punch to 800–1650 fmol/punch) resulted in a 
doubling of the odds of LLV, informing pharmacologic forgive-
lessness and sources of LLV. These results further expand our (and 
others’) previous findings, where TFV-DP in DBS was found to 
be strongly associated with viral suppression [13, 18], and 
suggest that changes in cumulative ART adherence play a sig-
nificant role in the development of LLV in PWH on ART. They
also support previous observations where changes in adherence (measured by self-report or pill counts) were associated with changes in residual viral replication below the limit of detection of most clinical assays [19–21]. However, they are contrary to another study (ACTG A5321) where antiretroviral drug concentrations in hair—which also quantify cumulative ART adherence—did not find an association with single-copy viremia [22]. This discrepancy could be explained because A5321 focused on a cohort of PWH with long-standing viral suppression who had participated in ART clinical trials and did not assess HIV VL in the 20–200 range [22]. Despite these discrepancies, our findings highlight the relevance that an objective and quantitative adherence measure can have in clarifying the different thresholds of viremia that are available in clinical practice.

While previous studies have explored root causes of LLV in PWH on ART [4], to our knowledge, this is the first study that has assessed its association and potential role with a measure of cumulative adherence. This is particularly relevant because we used an objective and reproducible adherence measure that is highly informative of virologic outcomes in PWH. Furthermore, the drug concentration categories that we used in our analyses have been previously found to be predictive of future viremia, even in PWH who are virologically suppressed. In this analysis, we demonstrate that these concentration thresholds can also

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Table 1. Demographics and Clinical Characteristics of the Study Participants at Their Entry Visit According to HIV Viral Load Category

| HIV VL, Copies/mL | No. (%) or Median (IQR) |
|-------------------|-----------------------|
| <20 n = 363 | 769 Person-Visits | |
| ≥20–<200 n = 74 | 157 Person-Visits | |
| ≥200–<1000 n = 27 | 42 Person-Visits | |
| ≥1000 n = 33 | 74 Person-Visits | |
| Total n = 497 | 1042 Person-Visits |

| Characteristic | No. (%) or Median (IQR) |
|---------------|-----------------------|
| Age, y | 46 (38–53) 48 (36–54) 44 (36–48) 40 (36–51) 46 (37–52) |
| Gender | Male 304 (84) 69 (93) 23 (85) 29 (88) 425 (86) |
| Female 59 (16) 5 (7) 4 (15) 4 (12) 72 (14) |
| Race | Black 69 (19) 15 (20) 9 (33) 2 (8) 95 (19) |
| White 213 (59) 36 (49) 13 (48) 19 (58) 261 (57) |
| Hispanic 65 (18) 20 (27) 3 (11) 9 (27) 97 (20) |
| Other 16 (4) 3 (4) 2 (7) 3 (9) 24 (5) |
| BMI, kg/m² | <18.5 16 (4) 2 (3) 0 (0) 1 (3) 18 (4) |
| ≥18.5–<25 149 (41) 31 (42) 13 (48) 19 (58) 212 (43) |
| ≥25–<30 122 (34) 24 (32) 8 (30) 10 (30) 164 (33) |
| ≥30 77 (21) 17 (23) 6 (22) 3 (9) 103 (21) |
| eGFR, mL/min/1.73 m² | 86 (73–101) 88 (75–104) 80 (73–99) 91 (80–109) 87 (74–102) |
| CD4⁺ T-cell count, cells/mm³ | <200 21 (6) 10 (14) 3 (11) 13 (39) 47 (9) |
| ≥200–<360 50 (14) 11 (15) 5 (19) 5 (15) 71 (14) |
| ≥350–<500 53 (15) 10 (14) 5 (19) 6 (18) 74 (15) |
| ≥500 239 (66) 43 (58) 14 (52) 14 (42) 305 (61) |
| Hematocrit, % | 45 (42–47) 45 (42–48) 45 (41–47) 43 (41–45) 45 (42–47) |
| Type of ART | NNRTI-based 117 (32) 12 (16) 2 (7) 2 (6) 133 (27) |
| INSTI-based 121 (33) 33 (45) 7 (26) 11 (33) 172 (35) |
| b/PI-based 87 (24) 16 (22) 12 (44) 14 (42) 129 (26) |
| Multiclass 38 (10) 13 (18) 6 (22) 6 (18) 63 (13) |
| Pharmacologic booster | No 200 (55) 32 (43) 6 (22) 9 (27) 247 (50) |
| Yes 163 (45) 42 (57) 21 (78) 24 (73) 250 (50) |
| TFV-DP in DBS, fmol/punch | <800 19 (5) 11 (15) 8 (30) 25 (78) 63 (13) |
| 800–1650 139 (36) 30 (41) 9 (33) 7 (21) 185 (37) |
| ≥1650 205 (56) 33 (45) 10 (37) 1 (3) 249 (50) |
| Self-reported adherence in the last 3 mo, % | 99 (90–100) 97 (90–100) 90 (68–96) 80 (60–90) 90 (90–100) |

Abbreviations: ART, antiretroviral therapy; b/PI, boosted protease inhibitor; BMI, body mass index; DBS, dried blood spots; eGFR, estimated glomerular filtration rate; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; TFV-DP, tenofovir diphosphate.
explain changes in concomitant viremia, thus expanding the utility of TFV-DP as an adherence biomarker in PWH on ART.

In addition to the novelty of our findings, the significance of our results should be emphasized based on their potential clinical implications. First, this analysis focused on LLV, which is frequently encountered in the clinic and for which a mechanistic explanation has not yet been established. Second, it underscores the role of adherence as a modifiable factor that could be targeted to address a clinical scenario where no management consensus is currently available [1]. Third, our results identified a specific group of PWH (ie, those with HIV VL between 20 and 200 copies/mL) in which timely counseling could be implemented to prevent an adverse clinical outcome such as virologic failure. Collectively, these features support the conduct of controlled clinical trials where the use of objective pharmacologic measures of adherence to complement the information provided by routine viral load monitoring is evaluated. Such studies could prove particularly useful in PWH who are not fully virologically suppressed (ie, HIV VL 20–1000 copies/mL), in whom resistance testing is not always feasible [23].

The strengths of our study include a large sample size that was prospectively enrolled within in a diverse real-world clinical cohort of PWH taking a variety of ART regimens. This allows for wide reach and applicability of our results in different populations. We also utilized a novel objective biomarker of cumulative adherence (TFV-DP in DBS) that is highly informative of concurrent suppression and future viremia. Among our weaknesses is that we were not able to differentiate participants who had persistent low-level viremia vs a viral blip. In addition, our study period (2014–2017) preceded the widespread use of TAF-based therapy and of second-generation INSTIs. However, we would anticipate similar results for PWH on TAF-based therapy. Furthermore, we limited our follow-up period to 48 weeks and lack data on the clinical outcomes (ie, virologic failure, residual inflammation) of the PWH with LLV. Finally, we did not evaluate any other potential drivers of LLV such as duration of viral suppression or disease stage at the initiation of treatment [4]; however, this was partially mediated by including only participants who had been on ART for at least 6 months. Additional studies focusing on modern ART regimens and on a more comprehensive and intensive evaluation of LLV and cumulative adherence are required.

In conclusion, we identified an association of LLV (HIV VL between 20 and 200 copies/mL) and a decrease in cumulative ART adherence measured using TFV-DP in DBS. These
findings emphasize the possible role that treatment adherence could play on the development of LLV and identify a potential interventional target to address this common clinical scenario. Future studies should evaluate whether TFV-DP in DBS can be used to identify patients with LLV in whom an adherence intervention would be beneficial.

Acknowledgments

We would like to thank the study participants and the personnel at the Colorado Antiviral Pharmacology Laboratory for their invaluable assistance and support of this study. We would also like to thank Dr. Steven Johnson, director of the University of Colorado Hospital HIV program, and the medical assistants (Nancy Olague, Brittany Limon, Ariel Cates, Maureen Sullivan, and Missy Sorrell) at the University of Colorado Hospital–Infectious Disease Group Practice for their invaluable contributions to and support of this study.

Financial support. This work was supported by the National Institutes of Health (K23AI104315 and R01AI145453 to J.C.M.; R01AI112298 to P.L.A.).

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Potential conflicts of interest. J.J.K and P.L.A. have received research support from Gilead Sciences paid to their institution. Other authors reported no conflicts of interest. 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.

Author contributions. J.C.M. led the conception and study design, obtained the funding and regulatory approvals, led all aspects regarding study monitoring, logistics, data and sample collection, and result interpretation, wrote the first manuscript draft, and contributed to all the edits for the subsequent drafts. M.M. performed data and statistical analysis and interpretation, generated figures and tables, and performed edits in subsequent versions. R.P.C. and S.S.C. performed participant consent, data and sample collection, data management, and data analysis and interpretation and made substantial edits and critical revisions of the manuscript. J.H.Z., L.E., and L.R.B. led the sample processing, directed and supported all aspects of the pharmacologic and drug concentration analysis, and data validation for the drug concentrations and made substantial edits and critical revisions of the manuscript. J.I.K. participated in the study design, adherence, and pharmacologic data interpretation and performed manuscript editing and critical revisions. P.L.A. co-led the study conception and design, assisted with obtaining the funding, supported the study monitoring and logistics, directed and supported all aspects of the pharmacologic and drug concentration analysis, collaborated with data interpretation, and made substantial edits and critical revisions of the original manuscript and all its subsequent versions. S.M. co-led the conception of the study design and conceptualization, performed the sample size calculation and data management, led the statistical analysis and interpretation, generated figures and tables, and made substantial edits and critical revisions of the manuscript.

Patient consent. 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).

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