Antiretroviral Regimen and Suboptimal Medication Adherence Are Associated With Low-Level Human Immunodeficiency Virus Viremia

Christina Konstantopoulos,[1,2] Heather Ribaudo,[3] Kathleen Ragland,[4] David R. Bangsberg,[5] and Jonathan Z. Li[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Meharry Medical College, Nashville, Tennessee; [3]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, Massachusetts; [4]Division of HIV/AIDS, San Francisco General Hospital, University of California; [5]Massachusetts General Hospital, Harvard Medical School, Boston

Episodes of human immunodeficiency virus low-level viremia (LLV) are common in the clinical setting, but its association with antiretroviral therapy (ART) regimen and adherence remains unclear. Antiretroviral therapy adherence was evaluated in participants of the Research on Access to Care in the Homeless cohort by unannounced pill counts. Factors associated with increased risk of LLV include treatment with a protease inhibitor (PI)-based regimen (ritonavir-boosted PI vs nonnucleoside reverse-transcriptase inhibitor: adjusted hazard ratio [HR], 3.1; $P = .01$) and lower ART adherence over the past 3 months (HR, 1.1 per 5% decreased adherence, adjusted; $P = .050$). Patients with LLV may benefit from ART adherence counseling and potentially regimen modification.

Keywords. adherence; antiretroviral therapy; low-level viremia.

Low-level viremia (LLV) is commonly defined as detectable levels of human immunodeficiency virus (HIV) in plasma, but less than 1000 HIV RNA copies/mL. Low-level viremia is of clinical importance because it is associated with a greater risk of virologic failure [1], emergence of drug resistance [2], and immune activation [3]. Episodes of LLV can be relatively common among patients on antiretroviral therapy (ART) [4]. Although several studies have been conducted, the exact cause of LLV is still uncertain. Potential etiologies include the development of drug resistance, reactivation of the latent viral reservoirs, and the ART regimen. However, few studies have evaluated the effect of ART adherence on LLV risk, and the results have been conflicting, with some studies showing a correlation between decreased ART adherence and LLV [5], and others finding no association between ART adherence and LLV risk [6]. In addition, the studies that have reported an association of ART regimen with risk of LLV have been unable to control for differential rates of ART adherence as a confounding factor.

In this study, we studied a cohort of patients infected with HIV with rigorous ART adherence, and we monitored these patients to determine whether suboptimal ART adherence, ART regimen, or other factors were independently associated with risk of LLV. The Research on Access to Care in the Homeless (REACH) cohort comprised HIV-infected participants who were recruited from homeless shelters, free meal programs, and low-income single-room occupancy hotels in San Francisco. Participants on 3-drug combination ART were invited to participate in a rigorous adherence monitoring substudy that involved unannounced visits to the participants in the community every 3–6 weeks for pill counts. This measure of ART adherence has been associated with viral suppression [7], emergence of ART resistance [8], and disease progression [9]. We determined the association between ART adherence, ART regimen, and other factors with risk of LLV by using both univariate and multivariable Cox proportional hazard analysis. We also evaluated the association between suboptimal ART adherence and outcome after the LLV episode.

METHODS

The Research on Access to Care in the Homeless cohort was a prospective study of homeless and marginally housed individuals infected with HIV in San Francisco. A subset of this cohort was enrolled in the REACH Adherence Monitoring Cohort (AMC) and were observed between 1997 and 2008, during which adherence was evaluated approximately every month by unannounced pill counts in the community [10]. Participants of the REACH AMC who were virologically suppressed (<50 HIV RNA copies/mL) for at least 3 months were included.

Wilcoxon rank-sum and Fishers exact tests were used to assess differences in baseline characteristics for those with and without an episode of LLV (50–1000 HIV RNA copies/mL).

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Correspondence: Jonathan Z. Li, MD, Division of Infectious Diseases, Brigham and Women's Hospital, 65 Landsdowne St, Rm 421, Cambridge, MA 02139 (jli22@partners.org).

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Univariate and multivariable Cox proportional hazard modeling were used to determine factors associated with the presence of LLV. Participants were censored at the time of virologic failure or conclusion of the AMC study. Adherence over the prior 1, 2, and 3 months (recent ART adherence) were analyzed in a time-updated analysis, and the most significant variable was used for multivariable modeling to evaluate the association between the presence of LLV and recent ART adherence, $CD4^+$ cell count, ART regimen, and duration on current ART regimen. Antiretroviral therapy regimen categories included nonnucleoside reverse transcriptase (NNRTI), ritonavir-boosted protease inhibitors (PI/r), or unboosted protease inhibitor (PI)-based regimens. Modification of the effect of recent adherence on LLV by ART regimen (ie, an interaction between ART regimen and adherence) was evaluated in the Cox proportional hazard model. The association between ART regimen and recent ART adherence was also evaluated in a Wilcoxon rank-sum analysis of ART adherence stratified by regimen (NNRTI vs combined PI-based ART).

Kruskal-Wallis testing was used to evaluate differences in ART adherence by outcome after initial episode of LLV. The 3 possible outcomes at the subsequent viral load measurement were viral resuppression (<50 HIV RNA copies/mL), persistent LLV, and virologic failure (>1000 HIV RNA copies/mL).

RESULTS

Thirty-seven of 128 REACH participants were found to have an episode of LLV after at least 3 months of virologic suppression. No significant differences were seen in the baseline demographics of participants with and without LLV, with the exception of ART regimen (Table 1). A smaller proportion of participants with LLV was receiving an NNRTI, and a larger proportion was on a PI-based regimen.

Univariate Cox proportional hazard analysis showed that the use of PI-based regimens was significantly associated with increased risk of LLV (Table 2). There was also weak evidence to suggest an association between average ART adherence over the past 3 months and risk of LLV (hazard ratio [HR], 1.1; $P = .07$) that was also apparent in adjusted analysis. In multivariable Cox proportional hazard analysis, ART adherence over the past 3 months was associated with risk of LLV at an HR of 1.1 per 5% decrease in adherence ($P = .050$). A higher risk of LLV was also apparent for participants on PI regimens compared with those on NNRTIs, with an HR of 3.1 on multivariable analysis for both PI/r and PI-based regimens ($P = .01$ and $P = .02$, respectively). No differences were seen in the risk of LLV between ritonavir-boosted and unboosted regimens (HR, 1.0; $P = .94$). Associations between baseline $CD4^+$ count and duration on current regimen with risk of LLV were not apparent (Table 2). An interaction between ART regimen and adherence was not detected, and no consistent differences were seen in mean adherence levels between participants treated with NNRTI- or PI-based regimens (Supplementary Figure 1).

We also performed a sensitivity analysis by evaluating ART adherence as a categorical variable: <80%, 80%–94%, and ≥95% adherence over the past 3 months. On multivariable analysis, participants in the lowest adherence category (<80%) were found to have the highest risk of LLV compared with those at the highest adherence levels of ≥95% (HR, 2.2; $P = .06$; Supplementary Table 1).

Table 1. Baseline Demographics of Participants Stratified by Presence of LLV[a]

Baseline Characteristics	Cases (N = 37)	Controls (N = 91)	*P* Value
Median age, years	45	45	.63
Male, N (%)	29 (78%)	64 (70%)	.39
Median baseline $CD4^+$ count[b]	459	442	.97
Median months on current regimen	20	14	.15
ART regimen, N (%)[c]			
NNRTI	7 (19%)	38 (42%)	.04
PI/r	20 (54%)	38 (42%)	
PI	10 (27%)	15 (16%)	

Abbreviations: ART, antiretroviral therapy; LLV, low-level viremia; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted protease inhibitor.

[a] Cases were those who experienced LLV, and controls maintained virologic suppression.

[b] $CD4^+$ count measured in cells/mm^3.

[c] The most common NNRTIs were nevirapine (54%) and efavirenz (46%). The most common PIs included atazanavir (37%), lopinavir (29%), and nelfinavir (23%).

Table 2. Univariate and Multivariable Cox Proportional Hazard Models of Factors Associated With Low-Level HIV Viremia

	Univariate		Multivariable	
Predictors	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Adherence over past 3 months, per 5% decrease	1.1 (0.99–1.17)	.07	1.1 (0.99–1.2)	.050
Baseline $CD4^+$ count	1.0 (0.99–1.0)	.86	1.0 (0.99–1.0)	.87
Duration on current regimen (months)	1.0 (0.99–1.0)	.21	1.0 (0.99–1.0)	.10
ART regimen				
PI/r vs NNRTI	2.7 (1.1–6.4)	.03	3.1 (1.3–7.4)	.01
PI vs NNRTI	3.0 (1.1–6.4)	.03	3.1 (1.2–8.3)	.02
PI/r vs PI	0.9 (0.4–1.9)	.79	1.0 (0.4–2.1)	.94

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted protease inhibitor.

We further analyzed the impact of recent adherence by studying the 3 possible outcomes after the initial episode of LLV: suppressed, persistent LLV, or virologic failure. We found no significant difference in ART adherence by outcome, although there were only a limited number of participants with persistent LLV or virologic failure (suppressed [N = 15] vs persistent LLV [N = 5] vs virologic failure [N = 4]: median 90% adherence vs 91% vs 82%, Kruskal-Wallis; $P = .68$; Supplementary Figure 2).

DISCUSSION

In this study, we evaluated participants of the REACH cohort with rigorous ART adherence monitoring and found that suboptimal ART adherence was associated with an increased risk of LLV. A 5% decrease in adherence contributed to an approximately 10% increase in risk of LLV after controlling for potential confounders. In addition, ART regimen was also associated with risk of LLV because participants on a PI-based regimen had 3 times the risk of having an LLV episode compared with those receiving an NNRTI-based regimen.

Although it is generally assumed that suboptimal ART adherence plays a role in LLV episodes, relatively few studies have explored this point. The studies that have been performed have shown conflicting results, with one study reporting an association between ART adherence and LLV risk [5] and another showing no significant association [6]. However, both of these studies evaluated only the narrow spectrum of patients with viral load blips, and neither study was able to evaluate the concurrent impact of ART regimen. The results of this study are also supported by the findings of our previous analysis of REACH participants, which showed that suboptimal adherence was associated with levels of residual viremia as detected by the ultrasensitive single-copy assay in participants with HIV RNA <50 copies/mL [11]. Although LLV and residual viremia are often considered to arise from different mechanisms, these results support the interpretation that these processes should be thought of as a continuum and may arise due to similar etiologies.

There have been previous studies that have reported an association between PI-based regimens and an elevated risk of LLV [12, 13]. However, these studies were limited by the lack of rigorous adherence monitoring, and they were unable to exclude suboptimal PI regimen adherence as the actual cause of the association with LLV. Controlling for adherence, we found that PI-based regimen was associated with 3 times the risk of LLV. We found no evidence of an interaction between ART regimen and recent ART adherence on the risk of LLV, nor did we find consistent differences in medication adherence by ART regimen in this cohort. This result suggests that active viral replication is more likely on a PI-based regimen and provides an explanation for the observation that raltegravir intensification studies have shown increases in 2-long terminal repeat circles among participants receiving PI-based ART, a result that suggests incomplete viral suppression before the treatment intensification [14]. Possible explanations for this finding include ART class- and drug-specific differences in pharmacokinetics and tissue penetration. Previous studies have demonstrated that inadequate tissue penetration of ART can lead to an increased risk of active viral replication within tissue compartments [15]. Additional studies are needed to further explore the mechanisms behind these results.

Limitations of this study include the limited numbers of participants due to the intensive nature of the adherence monitoring. There were also limited numbers of post-LLV outcomes for analysis, making it difficult to detect an association between adherence and post-LLV outcome. There was also heterogeneity in the ART regimens of this "real-world" cohort and limited power to discern drug-specific differences in LLV risk. Although the most commonly used PI in this study was atazanavir, a large subset of participants was on older PIs such as lopinavir and nelfinavir. A large study of atazanavir-based ART regimens did not show a significantly increased risk of LLV [16], suggesting that newer PI-based regimens may be associated with less risk of LLV. Other limitations of this study include a lack of therapeutic drug levels and tissue sample availability to determine the mechanism behind our findings. Lastly, samples were unavailable to perform drug resistance testing of samples with LLV.

CONCLUSIONS

Using a cohort of participants with rigorously defined ART adherence, we showed that both adherence and ART regimen can affect the risk of LLV in patients infected with HIV. These results suggest that adherence counseling should be a key component of the clinical response to detectable LLV, but that choice of ART regimen may also impact LLV. Understanding the factors associated with LLV is an important step towards improved patient care and has implications for efforts to eradicate HIV.

Supplementary Material

Supplementary material is available online at *Open Forum Infectious Diseases* (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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References

1. Greub G, Cozzi-Lepri A, Ledergerber B, et al. Intermittent and sustained low-level HIV viral rebound in patients receiving potent antiretroviral therapy. AIDS **2002**; 16:1967–9.
2. Li JZ, Gallien S, Do TD, et al. Prevalence and significance of HIV-1 drug resistance mutations among patients on antiretroviral therapy with detectable low-level viremia. Antimicrob Agents Chemother **2012**; 56:5998–6000.
3. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. AIDS **2004**; 18:981–9.
4. Ryscavage P, Kelly S, Li JZ, et al. Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients. Antimicrob Agents Chemother **2014**; 58: 3585–98.
5. Podsadecki TJ, Vrijens BC, Tousset EP, et al. Decreased adherence to antiretroviral therapy observed prior to transient human immunodeficiency virus type 1 viremia. J Infect Dis **2007**; 196:1773–8.
6. Miller LG, Golin CE, Liu H, et al. No evidence of an association between transient HIV viremia ("Blips") and lower adherence to the antiretroviral medication regimen. J Infect Dis **2004**; 189:1487–96.
7. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS **2000**; 14:357–66.
8. Bangsberg DR, Acosta EP, Gupta R, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. AIDS **2006**; 20:223–31.
9. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS. **2001**; 15:1181–3.
10. Moss AR, Hahn JA, Perry S, et al. Adherence to highly active antiretroviral therapy in the homeless population in San Francisco: a prospective study. Clin Infect Dis **2004**; 39:1190–8.
11. Li JZ, Gallien S, Ribaudo H, et al. Incomplete adherence to antiretroviral therapy is associated with higher levels of residual HIV-1 viremia. AIDS **2014**; 28:181–6.
12. Geretti AM, Smith C, Haberl A, et al. Determinants of virological failure after successful viral load suppression in first-line highly active antiretroviral therapy. Antivir Ther **2008**; 13:927–36.
13. Taiwo B, Gallien S, Aga E, et al. Antiretroviral drug resistance in HIV-1-infected patients experiencing persistent low-level viremia during first-line therapy. J Infect Dis **2011**; 204:515–20.
14. Buzon MJ, Massanella M, Llibre JM, et al. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. Nat Med **2010**; 16:460–5.
15. Fletcher CV, Staskus K, Wietgrefe SW, et al. Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues. Proc Natl Acad Sci U S A **2014**; 111:2307–12.
16. White KL, Wei X, Zhong L, et al. Efficacy of first-line ARV regimens: an exploratory "target not detected" analysis. In: Conference on Retroviruses and Opportunistic Infections. Boston, MA, March 3–6, 2014 (Abstract 546).