# Persistent Low-level Viremia is Associated with Low Protease Inhibitor Levels in Hair


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Women's Interagency HIV Study

## Introduction

- The goal of combination antiretroviral therapy (ART) is to suppress plasma HIV RNA (viral load, VL) below the assay limit of detection.
- HIV-infected patients on ART still experience episodes of low-level viremia (LLV) below 500 copies/mL.
- Persistent LLV is associated with antiretroviral (ARV) drug resistance and regimen failure, but its etiology and optimal management are not known.
- Concentration of ARVs in hair is a validated measure of long-term systemic drug exposure (weeks to months).
- We evaluated factors associated with intermittent and persistent LLV, including long-term ARV exposure measured by the concentration of ARVs in hair, in a cohort of HIV-infected women receiving protease-inhibitor (PI)-based ART.

## Methods

- HIV-infected women enrolled in the Women's Interagency HIV Study (WIHS) receiving ART for at least 1 year with VL < 500 copies/mL were evaluated from Oct 2003- Sept 2014 for these outcomes:

| Viral load outcome | Definition |
|---|---|
| Persistent LLV | ≥2 consecutive detectable VL <500 copies/ml |
| Transient LLV | <2 consecutive detectable VL <500 copies/ml |
| Viral suppression | VL below assay limit of detection for all visits |

- Participants who had a single VL ≥ 500 copies/mL or discontinued ART were excluded from analyses.
- Multivariable logistic regression examined demographic and clinical factors associated with persistent and transient LLV versus viral suppression.
- Concentrations of lopinavir, atazanavir, and darunavir were measured from 1-2 cm segments of 10-30 scalp hairs using liquid chromatography/tandem mass spectrometry and divided into quartiles by drug.
- Generalized mixed linear models with binary distribution and logit link examined the association between hair ARV concentration quartile and persistent and transient LLV, adjusting for demographic and clinical factors.

## Results

**KEY FINDINGS**

- Women receiving PI-based ART commonly experience LLV, similar to previous reports from predominantly male cohorts.
- Self-reported non-Hispanic African-American race was associated with persistent and transient LLV in models that adjusted for self-reported adherence.
- Persistent LLV was more likely to occur among women with lower protease inhibitor levels in hair, a marker of lower systemic drug exposure.

**Table 1. Viral load outcome prevalence and follow-up**

| Viral load outcome | Number of participants (%), N = 730 | Number of person-visits (%), N=6,266 | Person-visits follow-up Median (Q1, Q3) | Maximum viral load Median (Q1, Q3) |
|---|---|---|---|---|
| Persistent LLV | 90 (12%) | 1046 (17%) | 12 (4, 17) | 235 (131, 342) |
| Transient LLV | 167 (23%) | 1966 (31%) | 12 (5, 18) | 120 (64, 215) |
| Viral suppression | 200 (27%) | 1799 (29%) | 6.5 (4, 15.5) | -- |

**Table 2: Factors associated with persistent LLV (excluding hair ARV concentration)**

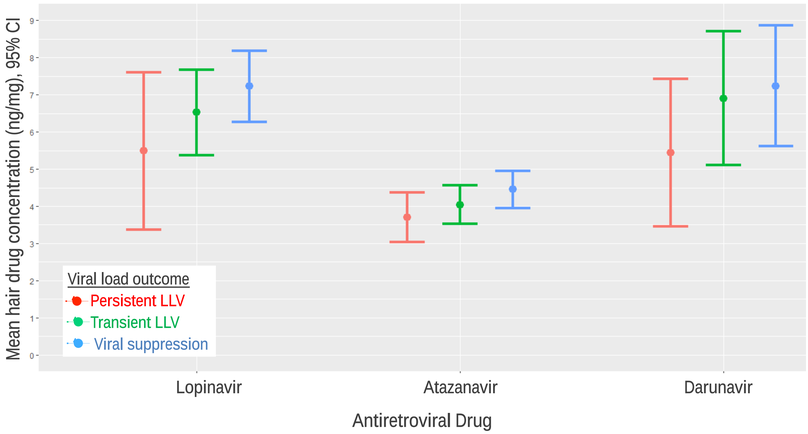
| Baseline Characteristic | Persistent LLV N=90 | Virologic suppression N=200 | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Age ≥40 years | 57 (63) | 130 (65) | 0.93 (0.55, 1.56) | 1.05 (0.59, 1.89) |
| Self-reported African-American race | 48 (53) | 92 (46) | 1.34 (0.82, 2.21) | **1.85 (1.03, 3.30)** |
| Pre-ART VL >100,000 copies/ml | 20 (22) | 29 (15) | 1.69 (0.89, 3.18) | 1.66 (0.85, 3.23) |
| Pre-ART CD4 <200 cells/mm$^3$ | 9 (26) | 25 (31) | 0.78 (0.32, 1.89) | -- |
| Self-reported adherence <95% | 12 (13) | 22 (11) | 1.24 (0.58, 2.63) | 1.55 (0.70, 3.44) |
| ART initiation after 2000 | 40 (44) | 78 (39) | 1.25 (0.76, 2.07) | 1.12 (0.60, 2.11) |

**Table 3: Factors associated with transient LLV (excluding hair ARV concentration)**

| Baseline Characteristic | Transient LLV N=167 | Virologic suppression N=200 | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Age ≥40 years | 113 (68) | 130 (65) | 1.13 (0.73, 1.74) | 0.96 (0.58, 1.58) |
| Self-reported African-American race | 100 (60) | 92 (46) | **1.75 (1.16, 2.66)** | **1.91 (1.20, 3.04)** |
| Pre-ART VL >100,000 copies/ml | 27 (16) | 29 (15) | 1.14 (0.64, 2.01) | 1.18 (0.65, 2.17) |
| Pre-ART CD4 <200 cells/mm$^3$ | 10 (26) | 25 (31) | 0.77 (0.33, 1.83) | -- |
| Self-reported adherence < 95% | 24 (14) | 22 (11) | 1.35 (0.73, 2.51) | 1.28 (0.67, 2.46) |
| ART initiation after 2000 | 62 (37) | 78 (39) | 0.92 (0.61, 1.41) | 1.33 (0.79, 2.22) |

## Results

**Figure 1: ARV concentrations in hair (mean, 95% confidence interval) among HIV-infected women receiving PI-containing ART by LLV status (n=440 with available hair PI levels).**




- After adjusting for demographic and clinical factors including race and self-reported adherence, *lower hair ARV quartile* was significantly associated with persistent LLV (OR 2.5, 95%CI 1.1–5.8) but not transient LLV (OR 1.5, 95%CI 0.8–2.9).

## Conclusions

- In this large cohort of HIV-infected women receiving PI-based ART, over one-third experienced either transient or persistent LLV.
- Persistent LLV (but not transient LLV) was more likely to occur among women with lower protease inhibitor exposure as estimated by hair concentrations.
- These findings suggest that improving ARV exposure could prevent LLV and its adverse consequences.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