Incomplete Adherence to Antiretroviral Therapy is Associated with Higher Levels of Residual HIV-1 Viremia

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Abstract

BACKGROUND: The persistence of HIV-1 in the latent reservoir is reflected in the frequent detection of residual HIV-1 viremia below 50 copies/m despite long-term antiretroviral therapy (ART). Incomplete ART adherence is common even in individuals who maintain virologic suppression <50 copies/mL, but its effect on residual viremia is unknown. We hypothesize that incomplete ART adherence may lead to active viral replication and higher levels of residual HIV-1 viremia, even for individuals with apparently successful virologic suppression.

METHODS: Medication adherence and residual viremia <50 copies/mL were quantified in participants of the REACH cohort of homeless and marginally housed individuals with HIV/AIDS. Participants (N=64) had at least 6 months of virologic suppression <50 copies/mL and were in the adherence monitoring cohort with unannounced pill counts on a random day at the participants' usual place of residence every 3-6 weeks. Residual viremia was measured by the single-copy assay.

RESULTS: The median duration of virologic suppression was 10.5 months [Q1-Q3: 7.5-18.4 months] and the median average ART adherence over the prior 1 and 2 months was 94% [Q1-Q3: 79%-100%] and 93% [Q1-Q3: 82%-98%], respectively. Average ART adherence over the past 2 months was associated with levels of residual HIV viremia (Spearman r = -0.25, P=0.04). One-third of participants with 100% ART adherence over the previous 2 months had detectable residual viremia. In multivariate regression analysis, ART adherence over the past 2 months, but not duration of virologic suppression, CD4+ T cell count, or ART regimen, was significantly associated with levels of residual HIV-1 viremia (P=0.004). Detectable residual viremia was associated with virologic failure (>50 copies/mL) in univariate Cox proportional hazard analysis (HR 2.08, P=0.02). However, in multivariate analysis, only ART adherence was associated with risk of virologic failure (HR 1.21, P<0.001).

CONCLUSIONS: Incomplete ART adherence was associated with higher levels of residual HIV-1 viremia, which may reflect new rounds of HIV replication even when an individual's viral load is <50 copies/mL. However, residual viremia was also detected in some individuals despite 100% measured ART adherence, suggesting that a component of residual viremia may originate from ongoing release of HIV-1 from the latent reservoir.

Background

- HIV-1 persistence is reflected in the frequent detection of residual viremia despite long-term antiretroviral therapy (ART)[1].
- Whether residual viremia is caused by HIV-1 release from the latent reservoir or from active viral replication is controversial.
- Incomplete ART adherence is common in chronically-treated patients as 100% ART adherence is not needed for HIV-1 suppression <50 copies/mL[2-5].
- The impact of incomplete ART adherence on residual viremia is unknown.

Objectives

1. **Determine the association between suboptimal ART adherence and levels of residual HIV-1 viremia.**
2. **Evaluate the relationship between ART adherence and residual viremia with risk of subsequent virologic failure.**

Methods

Data Sources, Study, and Subject Selection

- Participants were enrolled in the Research on Access to Care in the Homeless (REACH) cohort.
- Recruited from San Francisco homeless shelters, free meal programs, and low-income single-occupancy hotels.
- Inclusion Criteria:
  - On cART with ≥6 months of virologic suppression <50 HIV-1 RNA copies/mL.
  - Enrolled in the REACH Adherence Monitoring Cohort with unannounced pill counts every 3-6 weeks.
  - Available plasma for residual viremia measurement.
- Residual viremia measured by the single-copy assay[6].

Statistical Analysis

- Substance abuse defined as evidence of hazardous drinking or any illicit drug use in prior 90 days.
- Associations between residual viremia and ART adherence by Spearman correlation and Wilcoxon rank sum testing.
- Univariate and multivariable regression analysis using SAS 9.2.
- Virologic failure defined as HIV-1 RNA >50 copies/mL with sensitivity analysis using HIV-1 RNA ≥200 and ≥1000 copies/mL.

Table 1: Characteristics of the Study Participants

Characteristic	Median or % (N)	Q1-Q3
Age (years)	46	39-51
Male sex % (N)	81% (52)	
Ethnicity % (N)		
White	45% (29)	
Black	39% (25)	
Hispanic	8% (5)	
Others	8% (5)	
Substance abuse (%)	34% (22)	
cART % (N)		
NNRTI	47% (30)	
PI (boosted)	23% (15)	
PI (unboosted)	19% (12)	
Both NNRTI and PI	8% (5)	
CD4+ count (cells/μl)	477	321-728
Duration of viral suppression (months)	10.5	7.5-18.4
ART adherence over prior 1 month	94%	79%-100%
ART adherence over prior 2 months	93%	82%-98%

Results

Patient Characteristics

- 64 participants met the inclusion criteria and had evaluable single-copy assay results (**Table 1**).
- Median time of virologic suppression was 10.5 months [Q1-Q3, 7.5-18.4 months].
- Median ART adherence was 94% [Q1-Q3, 79%-100%] in the past month and 93% [Q1-Q3, 82%-98%] over the past 2 months.

Relationship Between Residual HIV-1 Viremia and ART Adherence

- Average ART adherence over the past 2 months was significantly associated with levels of residual viremia (Spearman r = -0.25, P=0.04).
- 33% (4/12) of participants had detectable residual viremia despite 100% ART adherence over the past 2 months.
- ART adherence over the past 2 months was significantly associated with residual viremia (P=0.004), even after controlling for duration of virologic suppression, CD4+ cell count, and ART regimen.

Table 2: Cox Proportional Hazard Models of Virologic Failure

Virologic Failure Definition	Factors	Univariate		Multivariable	
		HR [95% CI]	P-value	HR [95% CI]	P-value
VL >50 copies/mL	Detectable RV[1]	2.08 [1.13-3.81]	**0.02**	1.58 [0.85-2.93]	0.15
	CD4+ cell count[2]	1.05 [0.99-1.11]	0.10	1.05 [0.99-1.12]	0.11
	ART adherence[3]	1.21 [1.12-1.32]	**<0.001**	1.21 [1.11-1.33]	**<0.001**
	Substance abuse[4]	1.83 [1.0-3.35]	**0.049**	1.57 [0.84-2.93]	0.16
VL ≥200 copies/mL	Detectable RV[1]	1.55 [0.74-3.22]	0.24	1.19 [0.57-2.49]	0.65
	CD4+ cell count[2]	1.08 [1.0-1.16]	0.05	1.10 [1.02-1.19]	**0.02**
	ART adherence[3]	1.14 [1.05-1.23]	**0.003**	1.19 [1.07-1.31]	**<0.001**
	Substance abuse[4]	2.31 [1.12-4.74]	0.02	1.70 [0.82-3.56]	0.16
VL ≥1000 copies/mL	Detectable RV[1]	1.86 [0.78-4.43]	0.16	1.40 [0.58-3.41]	0.45
	CD4+ cell count[2]	1.07 [0.99-1.17]	0.11	1.10 [1.00-1.21]	**0.04**
	ART adherence[3]	1.14 [1.03-1.25]	**0.007**	1.17 [1.06-1.31]	**0.003**
	Substance abuse[4]	1.54 [0.66-3.56]	0.32	1.07 [0.45-2.53]	0.88

[1]Detectable residual viremia by the single-copy assay. [2]Per 50 CD4+ cell/ul decrease. [3]Average past 2 months, per 5% decrease in adherence. [4]Any drug use in the past 3 months or hazardous alcohol use in the past month. Abbreviations: HR, hazard ratio; VL, viral load; RV, residual viremia.

Detectable Residual Viremia and Risk of Virologic Failure

- Detectable residual viremia, ART adherence, and recent substance abuse were all associated with virologic failure (HIV-1 RNA >50 copies/mL) on univariate analysis (**Table 2**).
- On multivariable analysis, only ART adherence was significantly associated with virologic failure.
- In a sensitivity analysis, ART adherence and CD4+ count were both associated with viral rebound ≥200 copies/mL and ≥1000 copies/mL.

Conclusions

- Residual HIV-1 viremia was detectable despite 100% measured ART adherence.
- Incomplete ART adherence was associated with higher levels of residual HIV-1 viremia.
- Detectable residual viremia was associated with viral rebound >50 copies/mL, but not after taking into account ART adherence, CD4+ count, and recent substance abuse.

Implications

- **Residual HIV-1 viremia may be due to both HIV release from the latent reservoir and active viral replication during incomplete ART adherence.**
- **ART adherence counseling to counter pill fatigue may have benefits even in the setting of apparently successful virologic suppression.**

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