

# The Risk of Virologic Failure Decreases with Duration of Continuous Viral Suppression, for

## Adherence Levels Above 50%

M. Rosenblum<sup>1</sup>, S. G. Deeks<sup>1</sup>, M. J. van der Laan<sup>2</sup>, D. R. Bangsberg<sup>3</sup>

<sup>1</sup>University of California, San Francisco, USA; <sup>2</sup>University of California, Berkeley, USA; <sup>3</sup>Harvard Medical School, Boston, USA.



Correspondence:  
David R. Bangsberg, MD  
Massachusetts General Hospital  
Harvard Medical School  
Harvard Initiative for Global Health  
617-852-5083  
david\_bangsberg@harvard.edu



### Background

The degree of residual virus in the reservoir is known to be higher during the first year of antiretroviral therapy as compared to later in the course of treatment (Palmer et al, PNAS 2008). Theoretically, the degree of antiretroviral drug exposure necessary to achieve and maintain viral suppression will therefore be higher during early therapy, and decline with time. We tested this hypothesis by determining if the degree of treatment adherence necessary to prevent failure differs based on duration of therapy.

### Methods

- All subjects were identified from the a cohort of HIV+ homeless and marginally housed individuals (REACH)
- Eligible subjects included those who were receiving combination antiretroviral therapy and who agreed to monthly unannounced pill visits.
- Virologic failure was defined as HIV RNA > 50 c/ml.
- For each participant, his/her data was included starting at the first month of viral suppression during adherence monitoring and continuing until virologic failure occurred or the adherence monitoring period ended.
- Adherence was categorized into four levels (0–49%, 50–74%, 75–89%, and 90–100% pills taken).
- We used a marginal structural model, and controlled for confounding by CD4 nadir, regimen characteristics, past adherence, age, sex, depression, ethnicity, and drug/alcohol use, among others.
- Targeted maximum likelihood estimation was used, and inference was based on the nonparametric bootstrap using 500 iterations.

### Characteristics at Start of Adherence Monitoring

Characteristic	Among Subjects Achieving Viral Suppression (n=221) <sup>[1]</sup>	Missing (%)
Non-Caucasian (%)	127 (57%)	3 (1%)
Male (%)	149 (67%)	10 (5%)
Median age (IQR)	44.1 (10.5)	0
<b>Antiretroviral Treatment</b>		
PI <sup>[2]</sup> -based (%)	55 (25%)	0
NNRTI <sup>[3]</sup> -based (%)	81 (37%)	0
PI-NNRTI <sup>[2,3]</sup> -based (%)	15 (7%)	0
RTV <sup>[4]</sup> only (%)	7 (3%)	0
RTV-boosted <sup>[5]</sup>	63 (29%)	0
Once daily therapy (%)	81 (37%)	0
Median months on current regimen (IQR)	7 (14)	0
Median number of ARVs experienced (IQR)	2 (2)	5 (2%)
No prior ARV regimens (%)	100 (46%)	5 (2%)
Mono or dual nucleoside exposure (%)	80 (37%)	5 (2%)

<sup>[1]</sup> During adherence monitoring

<sup>[2]</sup> PI: protease inhibitor

<sup>[3]</sup> NNRTI: non-nucleoside reverse transcriptase inhibitor

<sup>[4]</sup> RTI: reverse transcriptase inhibitor

<sup>[5]</sup> RTV-boosted: Ritonavir-boosted protease inhibitor

### Participant Characteristics during Follow-up:

Characteristic during Followup	Among Subjects Achieving Viral Suppression <sup>[1]</sup> (n=221)	Missing (%)
Intravenous drug use (%) <sup>[6]</sup>	23 (10%)	32 (14%)
Crack use (%) <sup>6</sup>	27 (12%)	32 (14%)
Slept on street or in shelter (%) <sup>6</sup>	5 (2%)	46 (21%)
Mean days intoxicated in past month (SD)	3.6 (7.2)	32 (14%)
Median nadir CD4/ml (IQR)	202 (280)	5 (<1%)
Median CD4/ml (IQR)	389 (345)	5 (<1%)
Person-months with pill box organizer use (%) <sup>[7]</sup>	274 (45%)	0 (0%)
Mean duration of viral suppression in months (SD)	3.9 (3.1)	0 (0%)
Mean viral load at month of failure, in log copies/ml (IQR)	2.7 (1.0)	0 (0%)
Median pill count adherence (IQR)	0.94 (0.22)	97 (8%)
Median Time on Regimen During Adherence Monitoring (IQR)	23	0 (0%)

<sup>[6]</sup> Reported in last 30 days at least once during follow-up

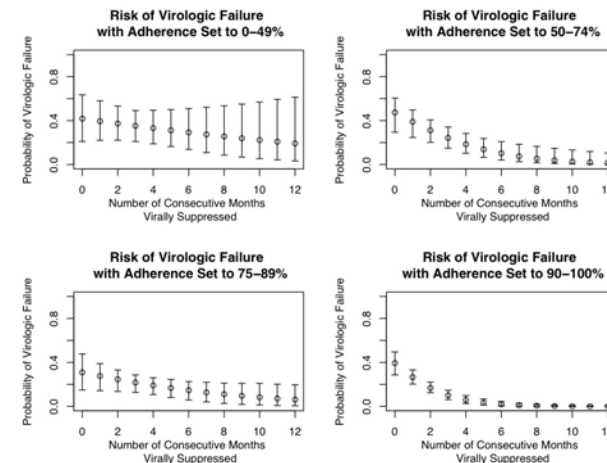
<sup>[7]</sup> Excluding subject-months with missing data

### Results of Statistical Analysis

Probability of Virologic Failure, at set levels of adherence, within subpopulations defined by duration of continuous suppression

- Comparing the probability of failure just after achieving suppression vs. after 12 consecutive months of suppression, there was a statistically significant decrease in the probability of virologic failure for those with at least 50% adherence.
- The estimated decrease in risk of failure was 0.45 (95% CI 0.28–0.70) at 50-74% adherence, 0.25 (CI 0.05–0.50) at 75-89% adherence, and 0.39 (CI 0.29–0.52) at 90-100% adherence.
- For adherence levels below 50%, estimated risk of failure decreased, but this was not statistically significant.

Estimates and 95% Confidence Intervals for the Risk of Virologic Failure, at Four Levels of Adherence, Given Duration of Continuous Viral Suppression



### Conclusions and Implications

- The risk of virologic failure, for any given level of adherence above 50%, declines over time.
- While high level adherence is required to maximize the probability of durable viral suppression, the range of adherence capable of sustaining viral suppression increases with the duration of continuous viral suppression.
- These data suggest that once the virus is fully controlled, the level of drug exposure necessary to maintain such control declines; however, we cannot rule out selection bias as an alternative explanation.

This study was funded by NIMH 54907 and was conducted at the UCSF Clinical and Translational Science Initiative Tenterlin Clinical Research Center, NIH U54 RR023566-01. Dr. Bangsberg received additional funding from NIAAA 015287. HIV RNA kits were donated by Roche. Michael Rosenblum was supported by a Ruth L. Kirschstein National Research Service Award (NRSA) under NIH/NIMH grant 5 T32 MH-19105-19. Mark van der Laan was supported by NIH grant R01 A1074345-01.