



Boosted Protease Inhibitors are More Forgiving of Suboptimal Adherence than Non-boosted Protease Inhibitors or Non-Nucleoside Reverse Transcriptase Inhibitors

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Abstract

Introduction: Interpretations of HIV adherence data to date suggest that the highest levels of adherence (e.g., >95%) are important for viral suppression. However, differences by regimen have often been ignored.

Methods: We assessed the relation between adherence to different regimens and viral suppression rates in subjects in the HOMER cohort of 1634 British Columbians with at least 2 consecutive viral loads <500 c/mL. Time zero was the 1st of at least 2 consecutive viral loads <500 c/mL. Event date for breakthrough was the second of two viral loads >1000 c/mL and censoring occurred on the event date, time of last viral load, or June 30, 2003, whichever was first. ARV adherence over every 2 dispensing periods was calculated as: # days of medication supplied / # days between refill dates. Cox models were constructed controlling for sex, age, injection drug use, CD4 count, AIDS diagnosis, provider treatment experience, and year of starting ARVs. Adherence was assigned using a time updated pharmacy refill measure and was dichotomized as >95% vs. <95%. Primary outcome was time to viral breakthrough and models were constructed separately for PI, NNRTI, and boosted-PI regimens.

Results: Demographics included 1376 (84.2%) males and 383 (23.4%) subjects with a history of injection drug use, median age of 39 years (IQR 33-46), and a median CD4 count of 200 cells/mm³ (IQR 80-350) and median follow-up of 29 months. 752 (46.0%) initiated a PI, 631 (38.6%) an NNRTI, and 251 (15.4%) a boosted PI-based regimen. 606 (37.1%) subjects had viral breakthrough. In adjusted analyses, <95% adherence was most strongly associated with breakthrough with PIs [HR 1.78 (1.41-2.24)], followed by NNRTIs [HR 1.47 (1.01-2.14)]. In contrast, there was no relation between <95% adherence and breakthrough for boosted PIs [HR 1.05 (0.46-2.42)].

Conclusions: The lack of a relation between adherence and maintained suppression at a threshold of 95% adherence suggests that boosted PIs are more forgiving of non-adherence than either PIs alone or NNRTIs. These results may be explained in part by higher trough concentrations with respect to the IC90 of the virus, higher genetic barrier to resistance of PIs vs. NNRTIs, and prolonged half-lives due to the ritonavir boosting. For individuals at high risk of suboptimal adherence, using boosted PI-based regimens may achieve higher effectiveness rates. Adherence studies should address these differences between regimens in the evaluation of their results.

Introduction

Background on Magnitude of HIV Adherence

- Adherence to ARVs is vital to suppression of HIV
- Differences in the magnitude of adherence associated with the development of resistance have emerged
- Differences amongst ARVs in the magnitude of adherence required to maintain HIV suppression is poorly understood

Study Aim

- To determine whether the magnitude of ARV adherence needed to maintain HIV suppression after achieving an undetectable HIV viral load using a pharmacy-based refill derived time updated measure of adherence differed by ARV regimen

HAART Observational Medical Evaluation and Research (HOMER) Cohort

- ARV distribution in British Columbia (BC) directed by HIV/AIDS Drug Treatment Program of BC Centre for Excellence in HIV/AIDS
- Prescriptions provided through designated pharmacies in BC
- Study data extracted from Centre's monitoring and evaluation system

Methods

Subject Eligibility

- HIV+
- ARV-naïve
- Age > 18 years
- Initiated ARVs between 8/1/96 - 6/30/03
- Had at least 2 consecutive HIV viral loads < 500 copies/mL
- CD₄ and viral loads measured within 6 mo of initial ARV start date

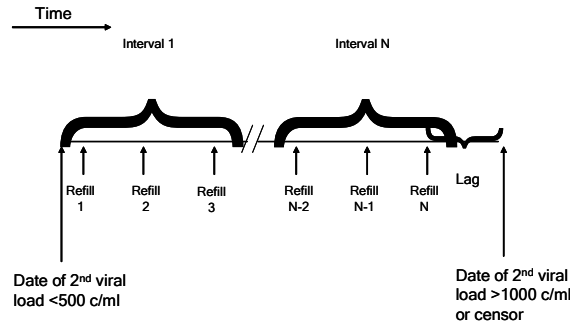
Main Outcome Measure

- Virological breakthrough = 2nd of at 2 consecutive HIV viral load measurements ≥ 1000 copies/mL
 - Allows for inclusion of pharmacy data proximal to event date
 - Avoids inclusion of adherence data after breakthrough event

Adherence Measure

- Based on medications dispensed
- # pills dispensed/# pills prescribed per day/# days between refills x 100%
- Assessed for a single drug (NNRTI, PI or boosted PI) or for each adherence interval per subject
 - Allowed to change with regimen change
- Refill interval = duration between any 2 consecutive refills
 - Days supply varied between and within subjects

Schematic of Adherence Measure



Statistical Analyses

- Analysis approach:
 - Cox proportional hazard regression assessing relation between breakthrough and time updated adherence measure
 - Adherence measure dichotomized at 95%
 - Subjects censored at 2nd of 2 consecutive HIV VL ≥ 1000 copies/mL
 - Event-free subjects right-censored as of 6/30/03
 - Subjects lost to follow-up censored at date of last known contact
 - Test for effect modification by regimen using interaction term in Cox model

Results

Baseline Characteristics (N=1634)

Median age (IQR)	37 years (32-43)
Male sex	1376 (84%)
History of IDU	383 (23%)
AIDS diagnosis	180 (13%)
Median CD4 (IQR)	200 cells/cm ³ (80-350)
Median HIV VL (IQR)	120,000 copies/mL (40,000-309,500)
Median follow-up	29 mo
PI-based regimen	752 (46%)
NNRTI-based regimen	631 (39%)
Boosted-PI based regimen	251 (15%)

Univariate Analyses of <95% Adherence and Breakthrough by Regimen

Regimen	Unadjusted Hazard Ratio [HR, (95% CI)]
Single PI-based	1.92 (1.52, 2.42)
NNRTI-based	1.58 (1.09, 2.29)
Boosted PI-based	1.28 (0.57, 2.86)

Results: Multivariate Analyses of Factors Associated with Virologic Breakthrough (Adherence Measured as Time-Varying Covariate) by Regimen

Variable	Adjusted Hazard Ratios* [HR, (95% CI)]		
	Single PI	NNRTI	Boosted PI
Adherence < 95%	1.68 (1.38, 2.01)	1.47 (1.01, 2.14)	1.05 (0.46, 2.42)
Male sex	0.89 (0.72-1.12)	1.00 (0.68, 1.46)	—
IDU history	1.37 (1.15-1.63)	1.47 (1.08, 2.02)	1.69 (0.86, 3.34)
Age	0.84 (0.65, 1.08)	0.98 (0.96-1.00)	0.98 (0.95, 1.01)
AIDS diagnosis	0.87 (0.74, 1.01)	0.80 (0.45, 1.43)	—
CD4 count	0.93 (0.89, 0.96)	0.88 (0.81, 0.95)	0.98 (0.76, 1.27)
HIV viral load	1.06 (0.89, 1.26)	1.12 (0.83, 1.51)	0.63 (0.33, 1.11)
Prior to guideline change	1.47 (1.16, 1.85)	1.01 (0.32, 3.21)	—

— = not included in adjusted model for that regimen

Conclusions

- Highest levels of adherence associated with higher rates of maintained suppression for PIs and NNRTIs
- Clinically important threshold for boosted PIs may be lower than 95%
- Results may be confounded by
 - Indication
 - Pre-existing resistance
- Formal test for interaction was not significant
- Further evaluation of differences between regimens in adherence needed