

# Identification of Novel Factors That Influence Atazanavir Exposure in a Diverse Population of HIV-Infected Women Under Conditions of Actual Use

M Gandhi<sup>1</sup>, SJ Gange<sup>2</sup>, C Ponath<sup>1</sup>, K Anastos<sup>3</sup>, P Bacchetti<sup>1</sup>, G Sharp<sup>4</sup>, M Cohen<sup>5</sup>, M Young<sup>6</sup>, A Levine<sup>6</sup>, H Minkoff<sup>7</sup>, RM Greenblatt<sup>1</sup>; Women's Interagency HIV Study (WIHS)

<sup>1</sup>Univ of California, San Francisco, San Francisco, CA; <sup>2</sup>Johns Hopkins Univ Bloomberg Sch of Publ Hlth, Baltimore, MD; <sup>3</sup>Albert Einstein Univ, Bronx, NY; <sup>4</sup>NIAID/NIH, Bethesda, MD; <sup>5</sup>Cook County Hosp, Chicago, IL; <sup>6</sup>Georgetown University, Washington DC; <sup>7</sup>Univ of Southern California, Los Angeles<sup>7</sup>

Monica Gandhi MD  
405 Irving Street, 2<sup>nd</sup> flr  
SF, CA 94122  
415-502-6285 (O);  
415-476-8528 (fax)  
[monica.gandhi@ucsf.edu](mailto:monica.gandhi@ucsf.edu)

## Introduction

•PK studies for FDA approval performed in HIV- patients or relatively homogenous HIV+ populations

•PK studies in large, diverse populations under conditions of actual use identify factors that contribute to variability in ARV exposure during chronic therapy

•Women's Interagency HIV Study (WIHS): Multicenter, prospective cohort of HIV-infected women



## Objectives

- 1) Calculate exposure metrics for atazanavir from intensive PK studies in large numbers of women under conditions of actual use
- 2) Identify the factors that significantly contribute to ATV exposure in multivariate models

## Methods

•Enrolled **122 WIHS women on ATV** into intensive PK studies: 8 time points for ATV levels over 24 hrs

•**No restrictions** on interacting medications, lab abnormalities, pregnancy, substance abuse, diet (simulated during study), liver, renal abnormalities, etc. Data collected on all these parameters

•**Objective 1:** Areas under the curves (AUCs) from intensive PK data calculated using the trapezoidal rule; other PK metrics calculated in STATA/SE version 9.2

•**Objective 2:** Univariate analyses by linear regression between log-transformed AUC and covariates.

Multivariable models constructed by manual forward stepwise selection using predictors with smallest p-values

## Results

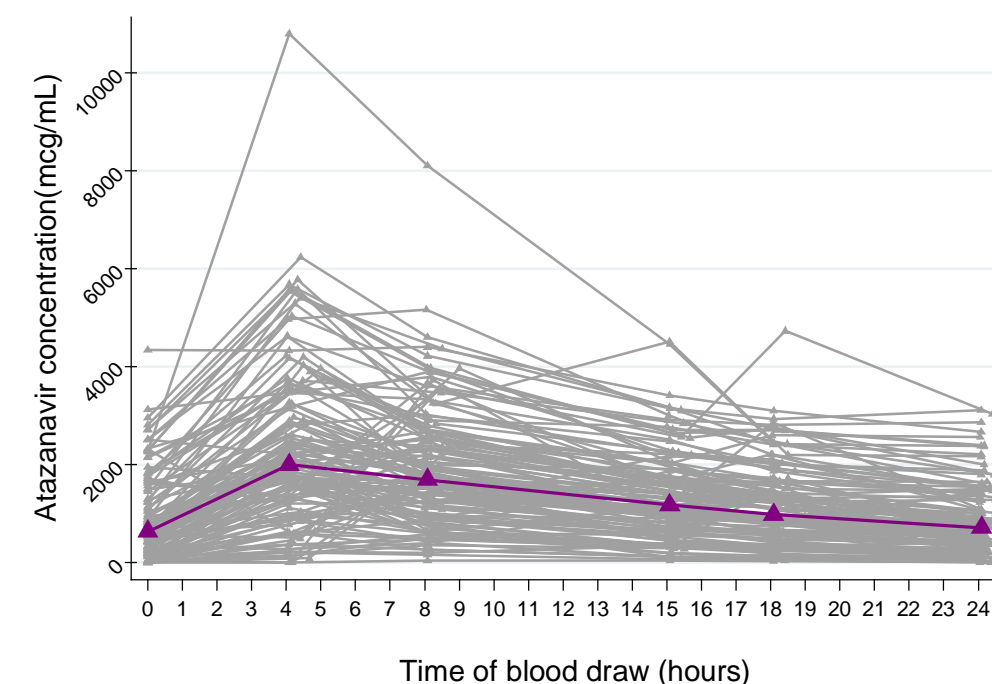
**Table 1:** Summary exposure metrics for 122 WIHS women on ATV

AUC (mcg <sup>1</sup> x h/mL)	C <sub>min</sub> (mcg/mL)	C <sub>max</sub> (mcg/mL)	t <sub>max</sub> (hrs)	CL/F (ml/h)
32.3 (0.72-131.0)	0.56 (0-2.81)	2.31 (0.04-10.8)	4.33 (0-18.5)	9.41 (2.23 834.5)

**Table 2:** Patient covariates and univariate relationship to AUC (N=122)

Covariate	number (%)	Effect on AUC ↑ or ↓
Age (median, range)	45 (22-67) years	↑ 1.2-fold (1.0-1.4) per decade, p 0.10
Race (White; AA; Latina; Other)	14%, 63%, 19%, 4%	↑ 1.1 (0.8-1.5) black versus other, p 0.64
Hepatitis C positive	37 (30%)	↑ 1.3-fold (1.0-1.9), p 0.08
Creatinine clearance <60 (MDRD)	18 (15%)	↑ 1.7-fold (1.1-2.7), p 0.03
Current smoker	68 (56%)	↑ 1.2-fold (0.9-1.7), p 0.23
Total bilirubin (median, range) mg/dL	1.3 (0.2-6.9)	↑ 1.9-fold (1.1-3.0) per doubling, p 0.01
Ongoing diarrhea (>3 soft stools/day)	18 (15%)	↓ 0.6 (0.4-0.9), p 0.02
Crack cocaine more than once a month	10 (8%)	↑ 1.8-fold (1.0-3.1), p 0.05
Currently menstruating	19 (16%)	↓ 0.8 (0.6-1.0), p 0.10
Patients on concomitant ritonavir	98 (80%)	↑ 3.5 (2.5-4.8), p < 0.001
Use of antacids (PPIs or H <sub>2</sub> blockers)	20 (16%)	↓ 0.7 (0.4-1.0), p 0.07
Current oral or injectable hormone use	7 (6%)	↓ 0.4 (0.2-0.7), p 0.003

**Figure 1:** ATV AUC curves for 122 pts (purple line – median) showing interindividual variability in real-life setting



**Table 3:** Multivariate model: Effects of predictors on ATV exposure

Covariate	Fold ↑ or ↓ on AUC
Use of ritonavir	↑ 3.19 (2.3-4.4), p <0.0005
Exogenous hormone use	↓ 0.53 (0.30-0.91), p 0.023
Creatinine clearance <60	↑ 1.58 (1.05-2.38), p 0.028
For every doubling in bilirubin	↑ 1.14 (1.01-1.28), p 0.037

\*Adjusted for age, race, weight, ongoing diarrhea, hepatitis C, crack use, menstrual status, use of antacids

## Summary

•Intensive PK studies in “real-world” populations without restrictive exclusion criteria may reveal factors that impact drug exposure in chronic treatment

•24 hour intensive PK studies in 122 WIHS women on ATV under conditions of actual use performed, PK parameters calculated

•Results showed expected boosting of exposure by RTV and the association between ATV levels and bilirubin

•Exogenous hormones (OCPs/HRT) and moderate renal impairment influenced ATV exposure in multivariate models (crack cocaine and diarrhea also significant in bivariate models)

•Further examination of the impact of these parameters on ATV outcomes in chronically treated patients is needed.

University of California  
San Francisco

