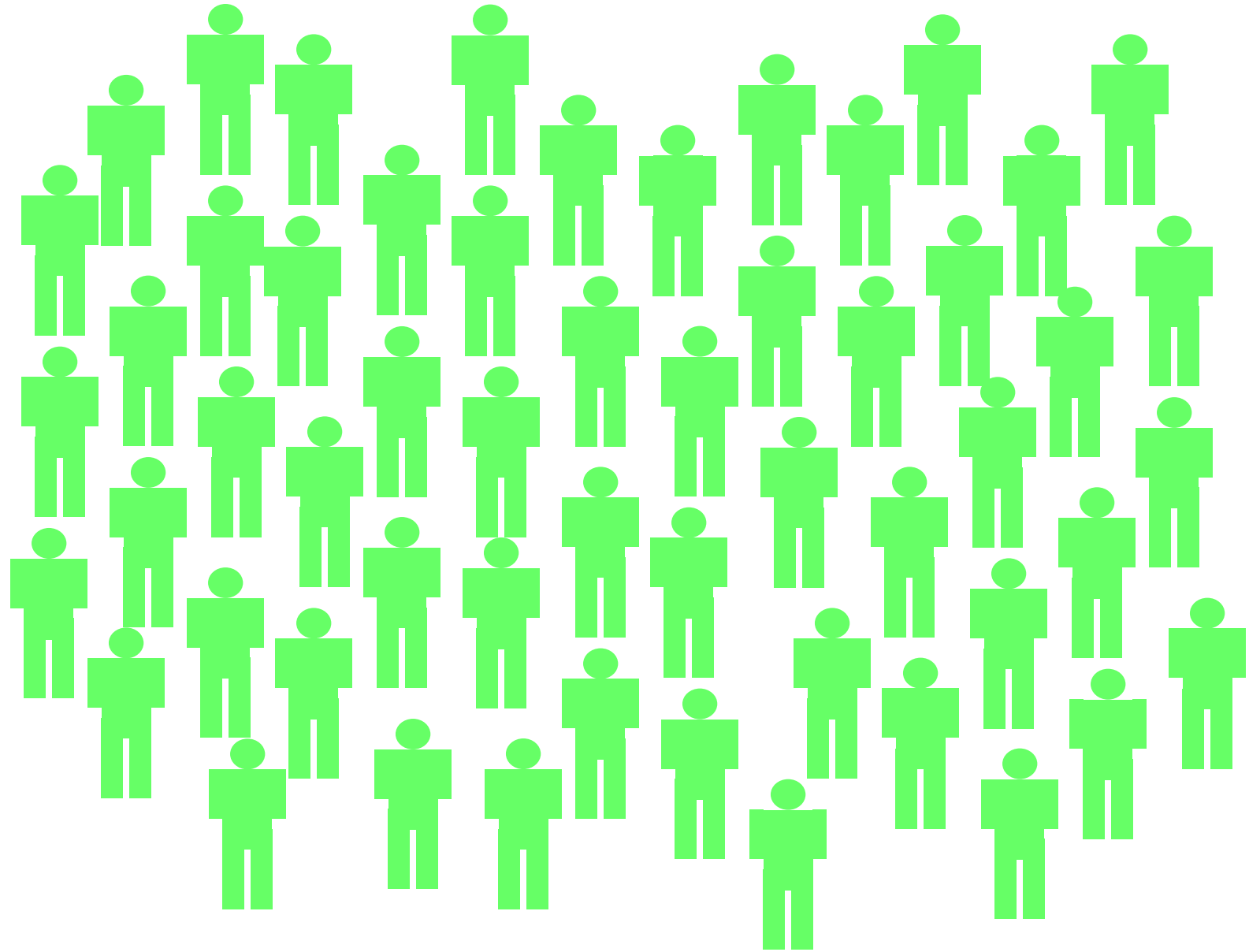


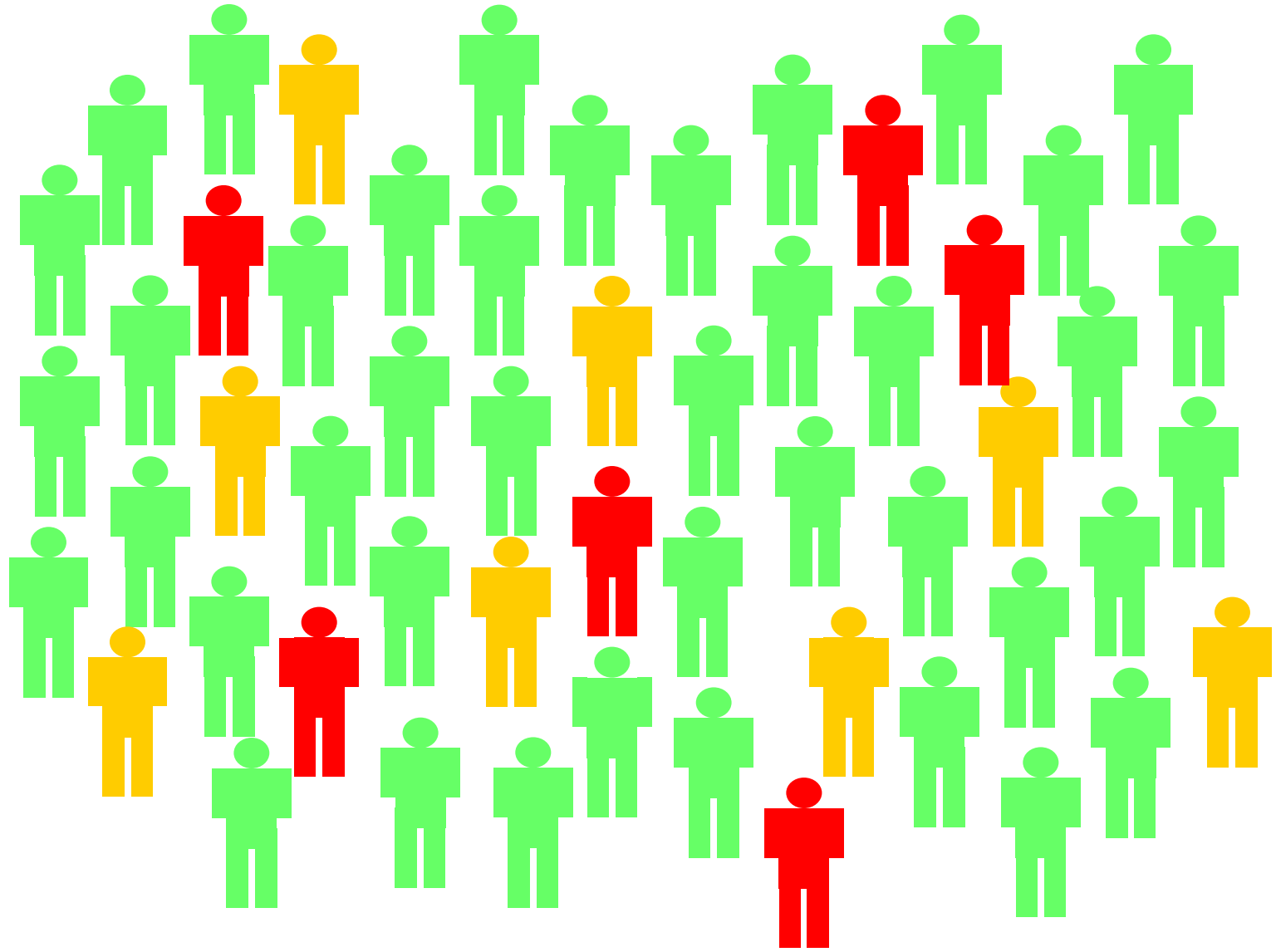
Pharmacologic Disposition Difference Between Males and Females

Stan Louie
Associate Professor
University of Southern California

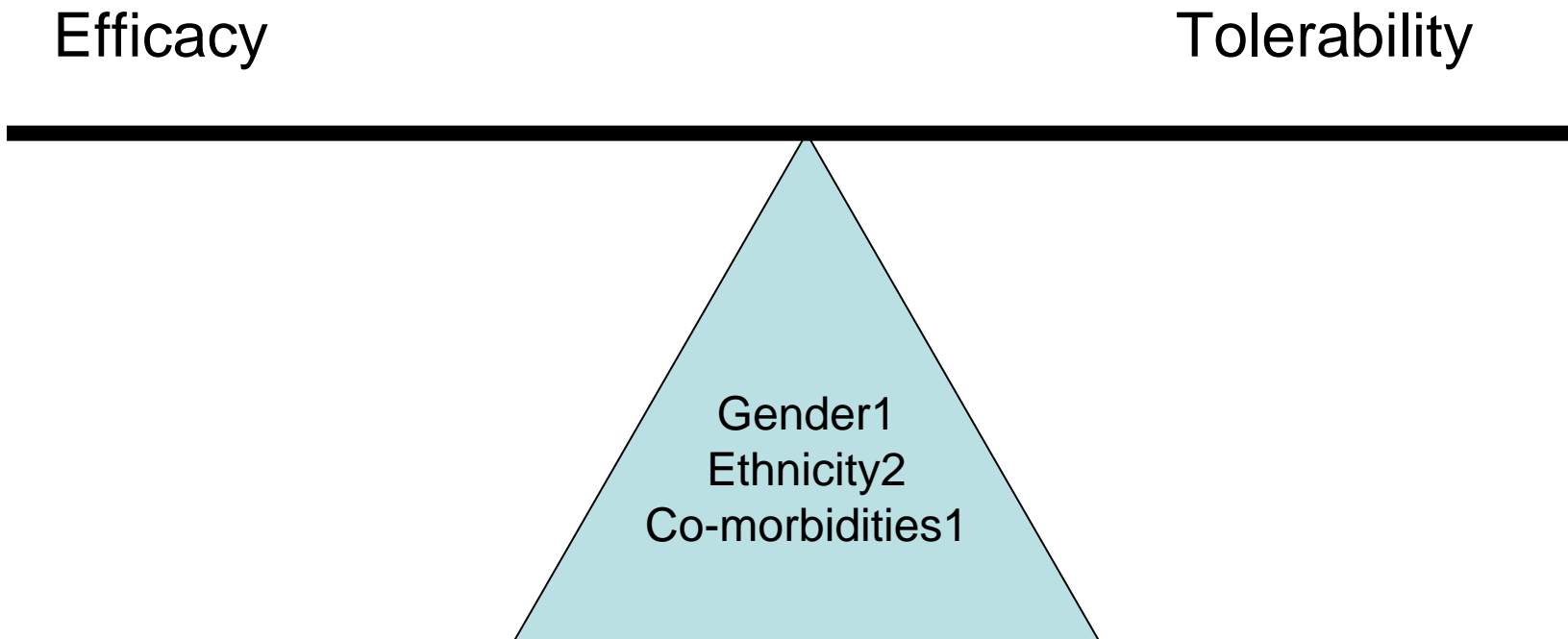
Patients with the Same Diagnosis



Pharmacologic Response to Therapy



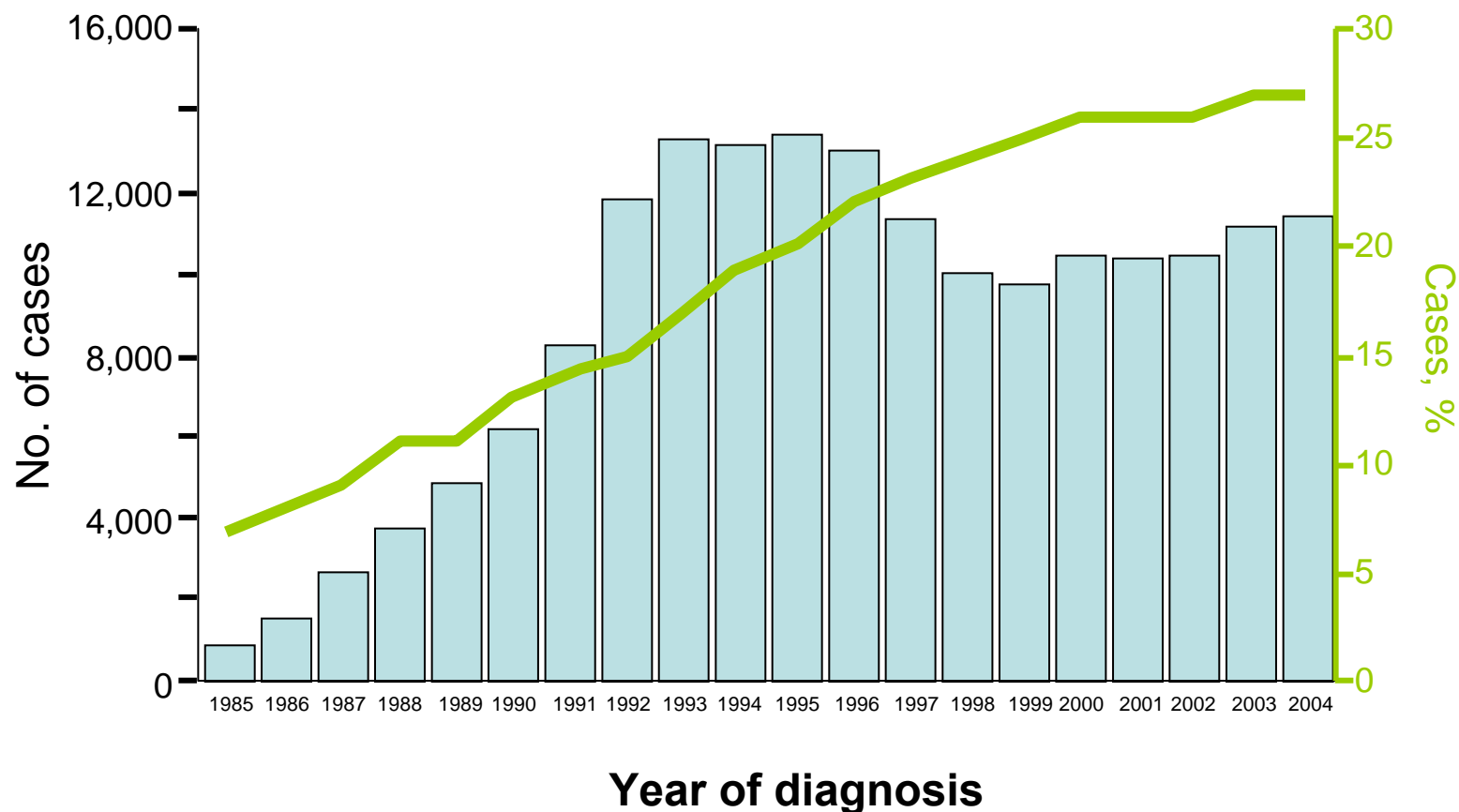
Consideration of Gender, Ethnicity and Co-morbidities When Selecting ARVs



1. DHHS Guidelines 2005
2. Butcher RO. J Natl Med Assoc 2005; 97: 1093-1100

Number and Proportion of AIDS Cases Among Female Adults and Adolescents

1985-2004—United States



Note. Data have been adjusted for reporting delays.

CDC. Available at: www.cdc.gov/hiv/topics/surveillance/resources/slides/index.htm. Accessed February 26, 2007.

Adverse Events

Treatment of Women With HIV/AIDS: HAART Adverse Events

- Higher prevalence of adverse events in women
 - Ritonavir-associated nausea and vomiting: 66% vs 27%¹
 - Women are also nearly 3 times as likely to have adverse events when treated with ddl¹
- Some common side effects more prevalent in men (nelfinavir-associated diarrhea 10% vs 23%)
- Side effects have special importance for women
 - When women discontinue HAART medications, it is most frequently because of side effects²
 - 2 times as likely as men to discontinue because of side effects²

¹ Squires K, et al. 13th IAC; Durban, South Africa. Abstract TuOr54.

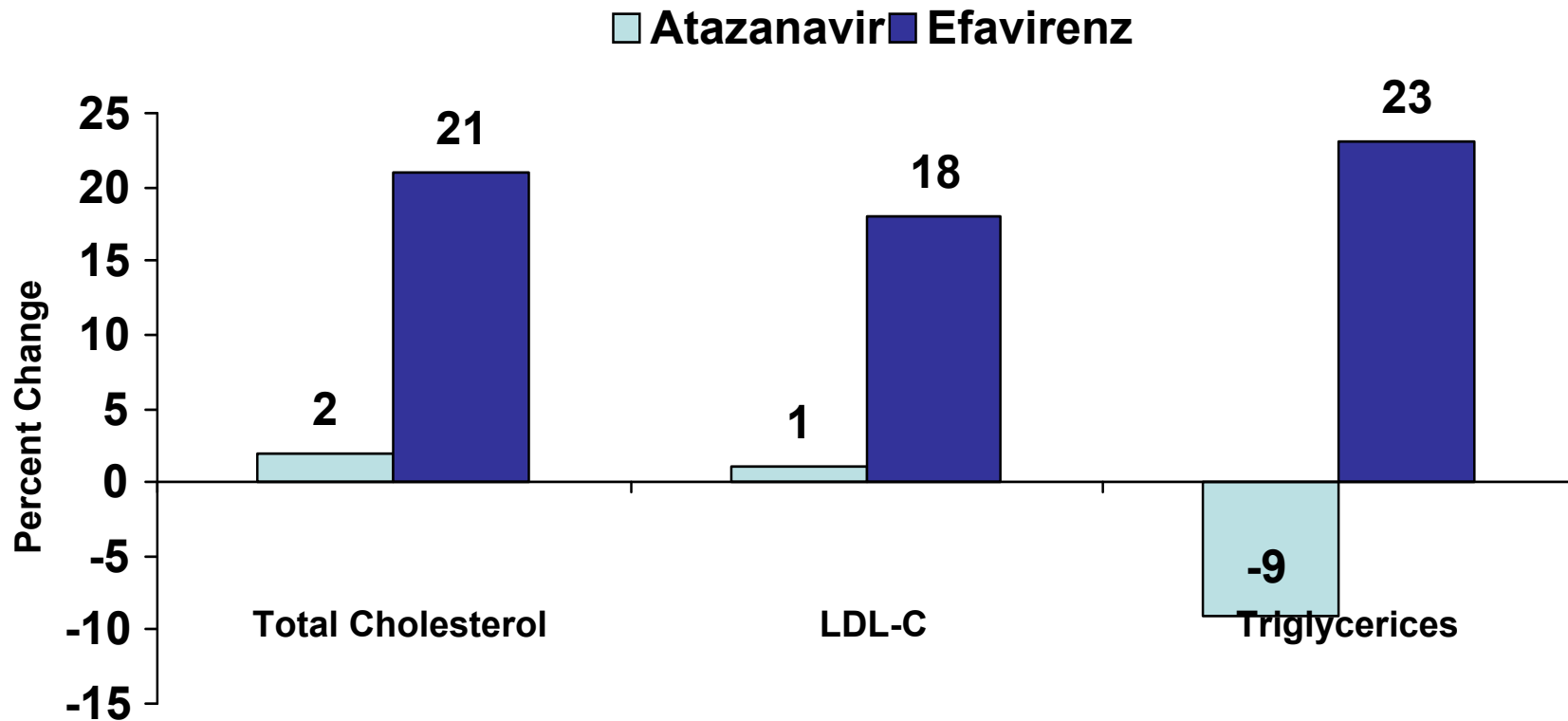
² Hirschhorn LR, et al. 12th IAC; 1998; Geneva, Switzerland. Abstract 12443.

Lipid Fractions May Differ Between African-American and Caucasian HIV-Infected Women Treated With PIs

- 32 Caucasian and 10 African-American women receiving PIs + 2 NRTIs
- African-American women were older, and significantly more were overweight (80% vs 47%)
- During treatment with PI, no differences found in:
 - Fasting insulin, fasting glucose, or HOMA-IR
- African-American women showed:
 - Significantly higher HDL-C
- Caucasian women showed:
 - Higher LDL-C, triglycerides

Comparative Effects of HAART on Lipid Levels

Changes in Lipids at 48 Weeks

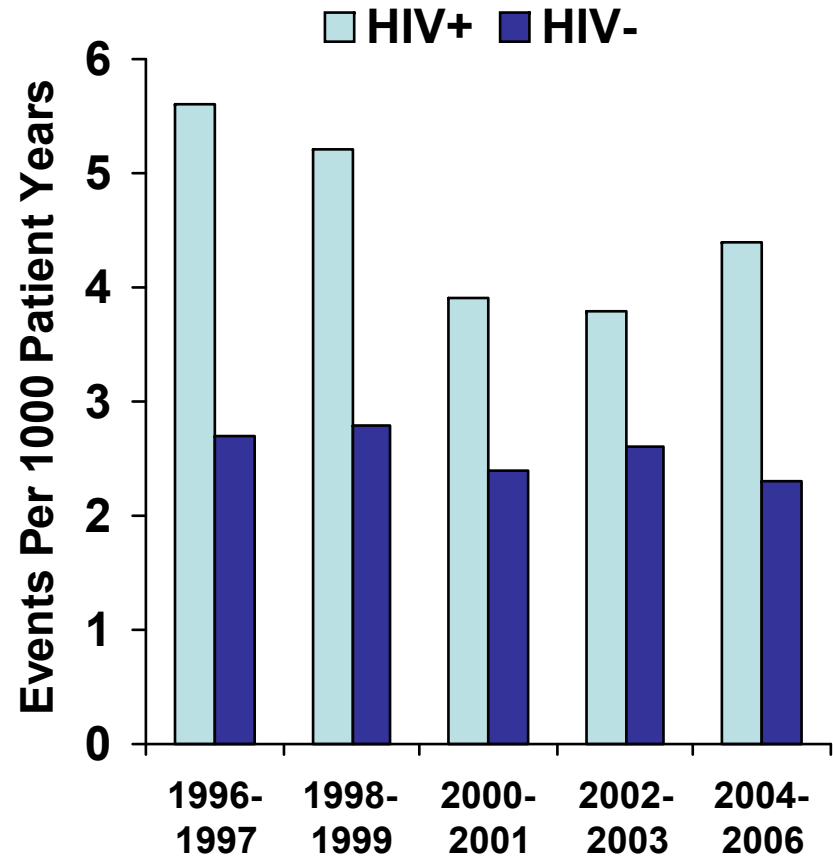


N=810 treatment-naïve patients treated with either atazanavir or efavirenz in a 3-drug regimen. Efficacy equivalent between 2 regimens.

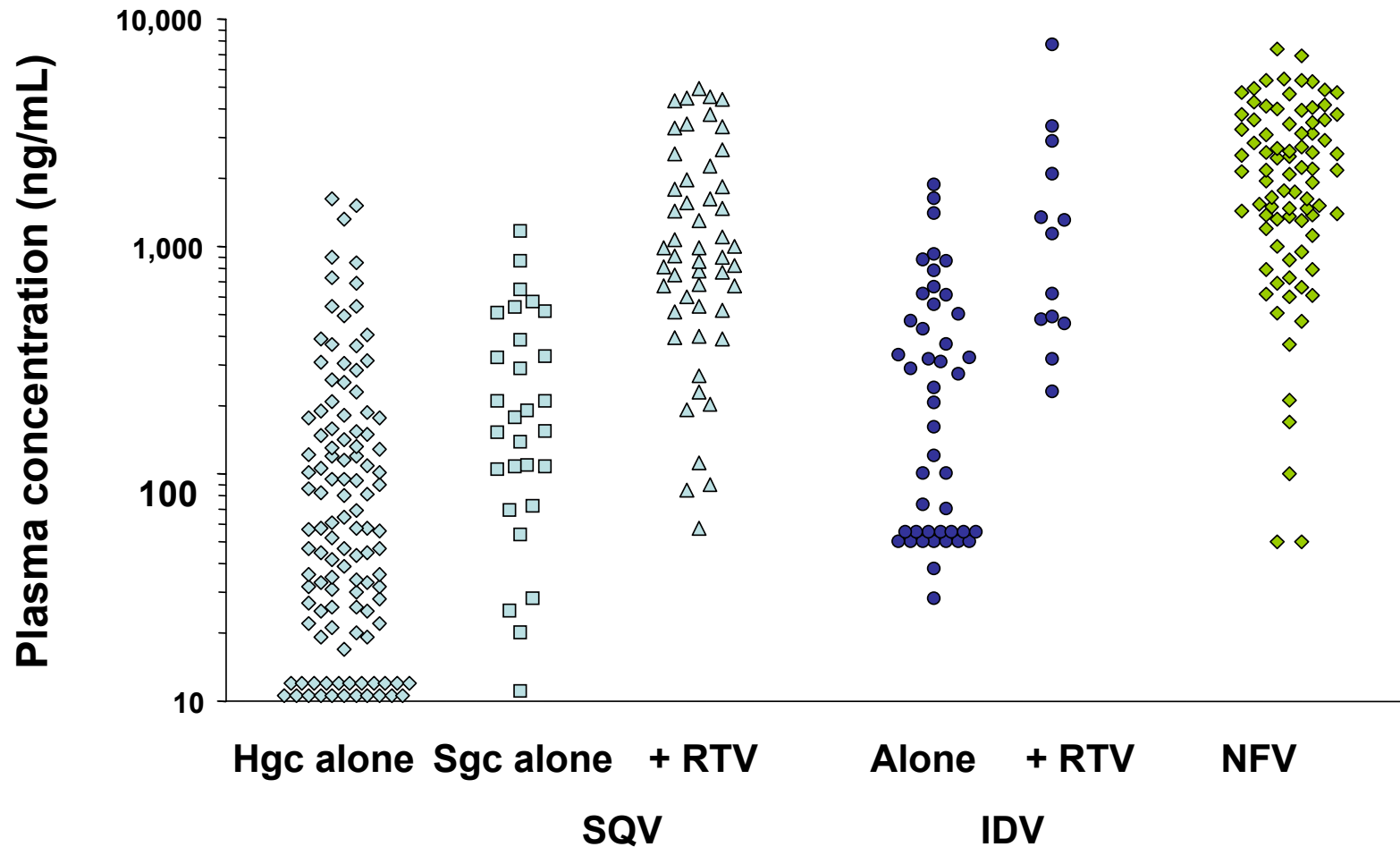
Risk of Myocardial Infarction Hospitalization Higher in HIV+ Women

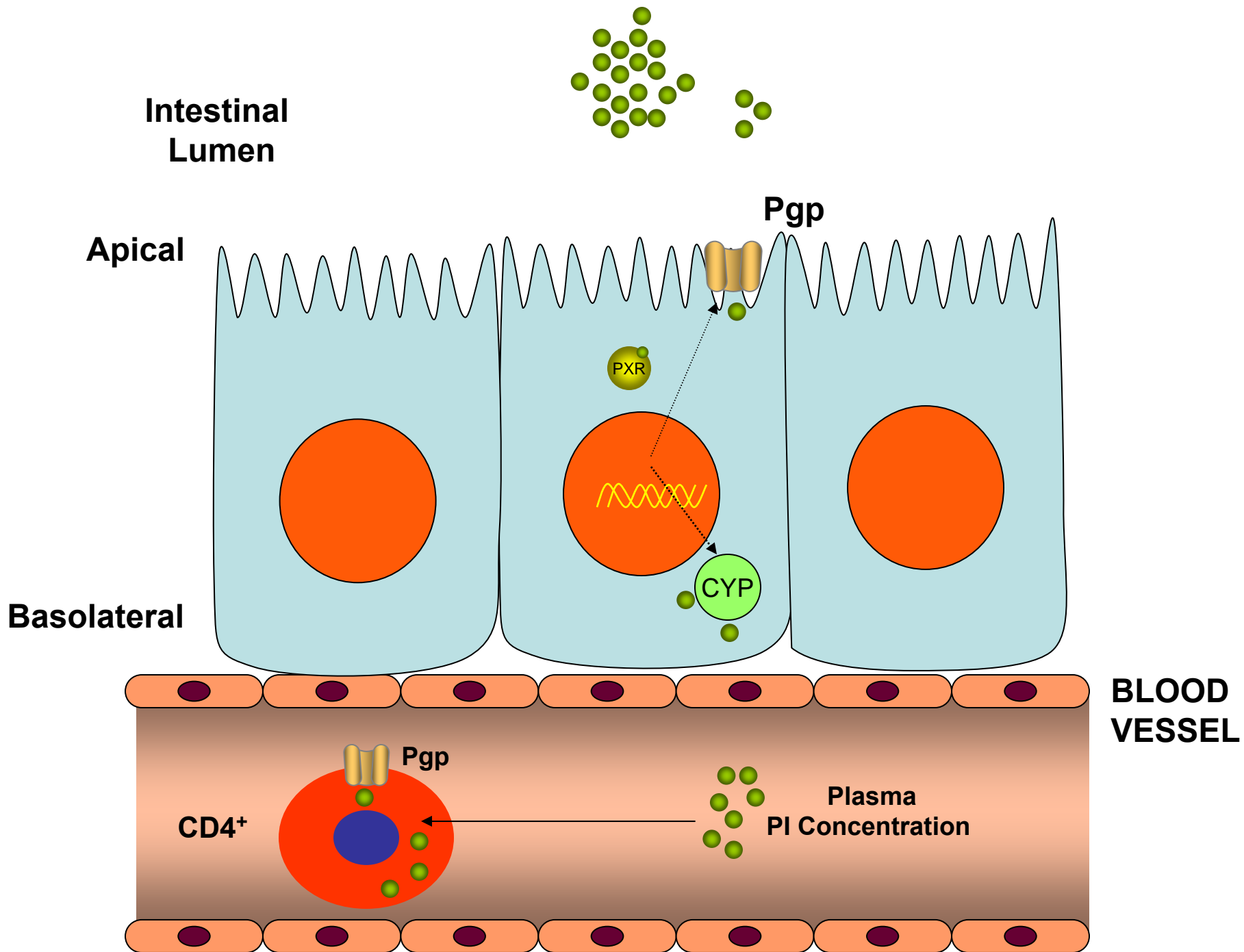
Kaiser Permanente Northern California Surveillance Cohort

- MI hospitalizations significantly higher among HIV+ patients compared with HIV- health plan members
- HIV+ women had 3.99 times relative risk of MI hospitalization

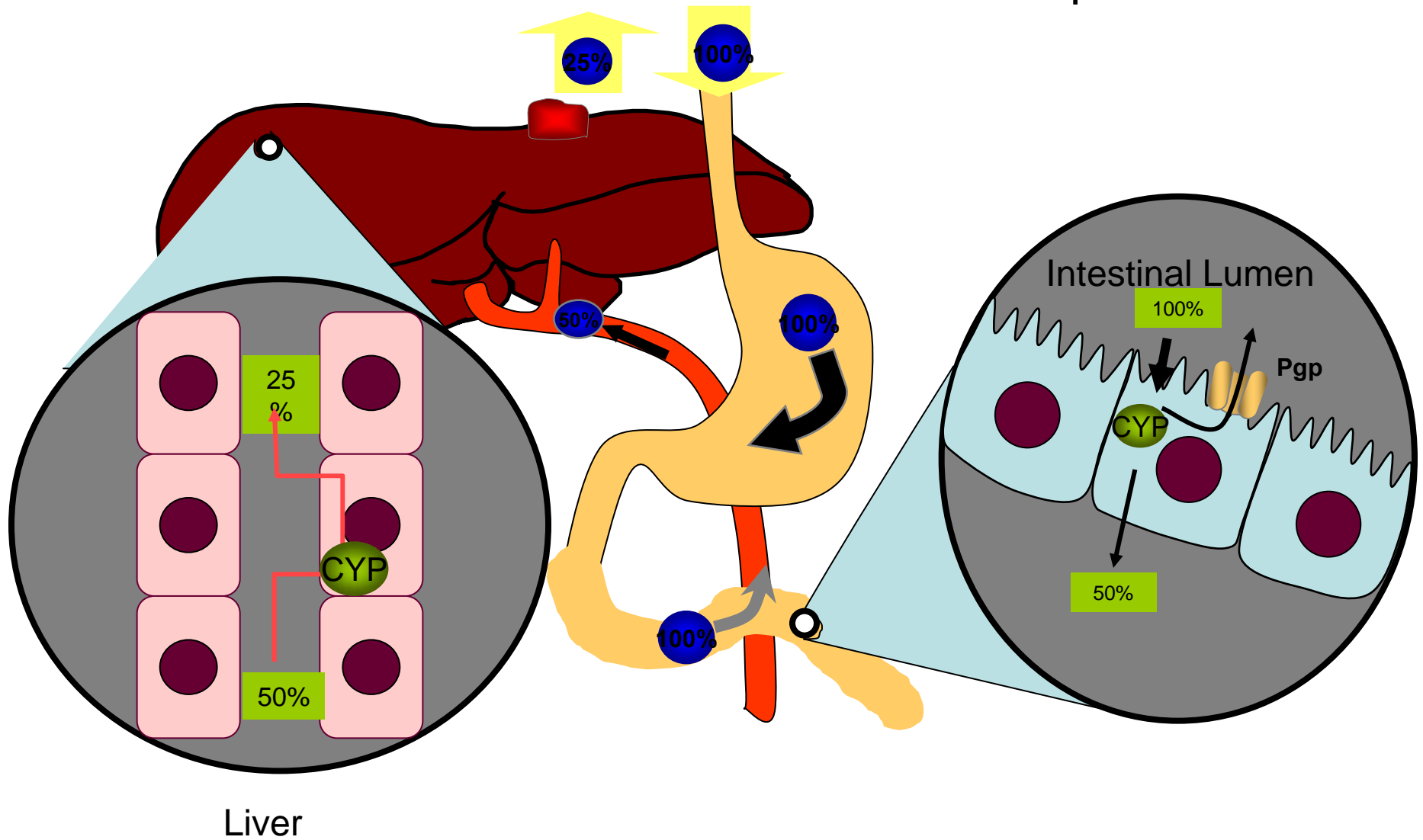


Interindividual Variation in Trough Concentrations of SQV, IDV, and NFV



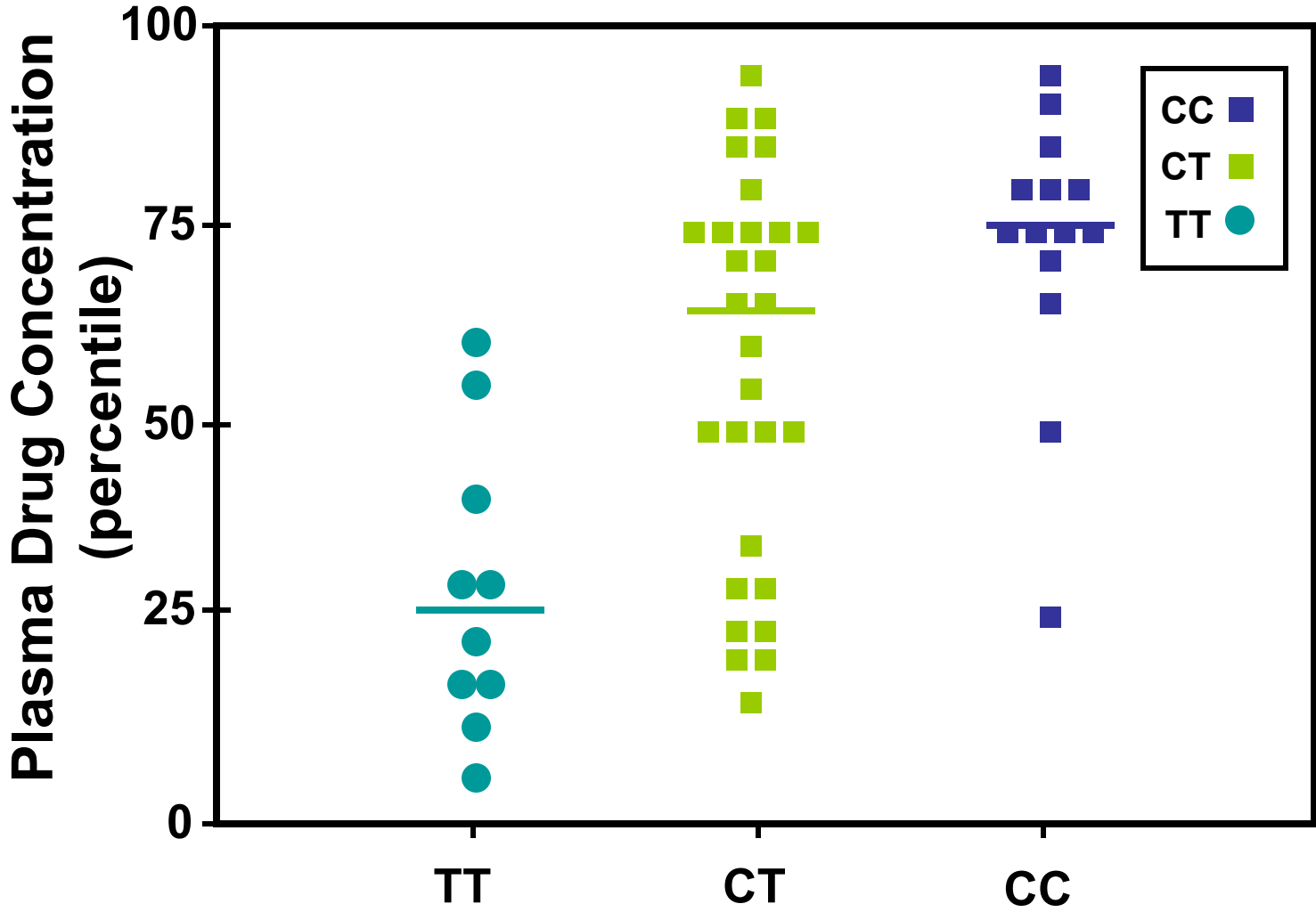


Role of CYP 450 Mediated Metabolism and P-glycoprotein Interaction and Its Influence on Absorption



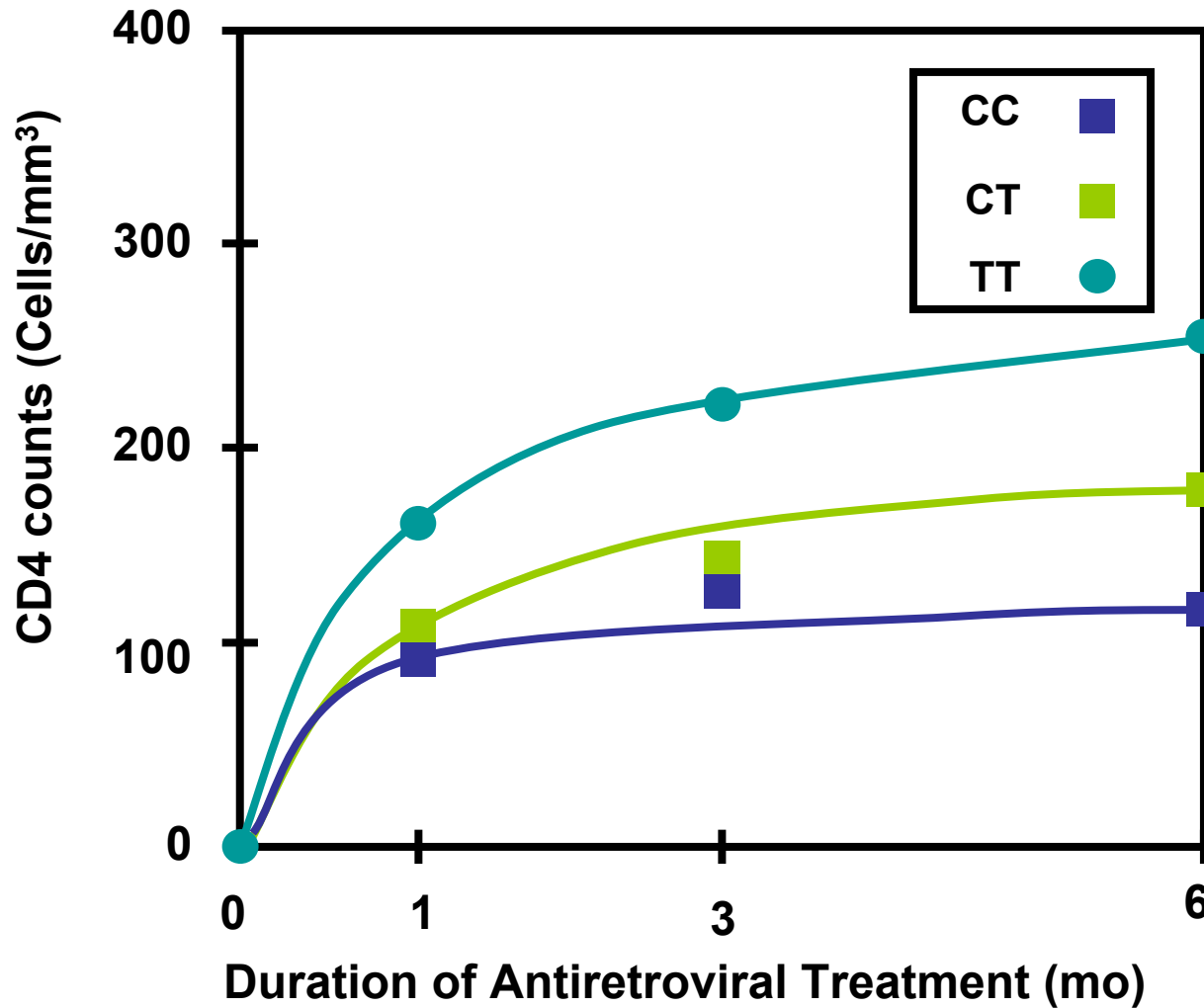
Adapted from: Bailey, DG, et al. Br J Clin Pharmacol 1998;46:101-110

Nelfinavir Plasma Levels With Regards to MDR-1 Polymorphism



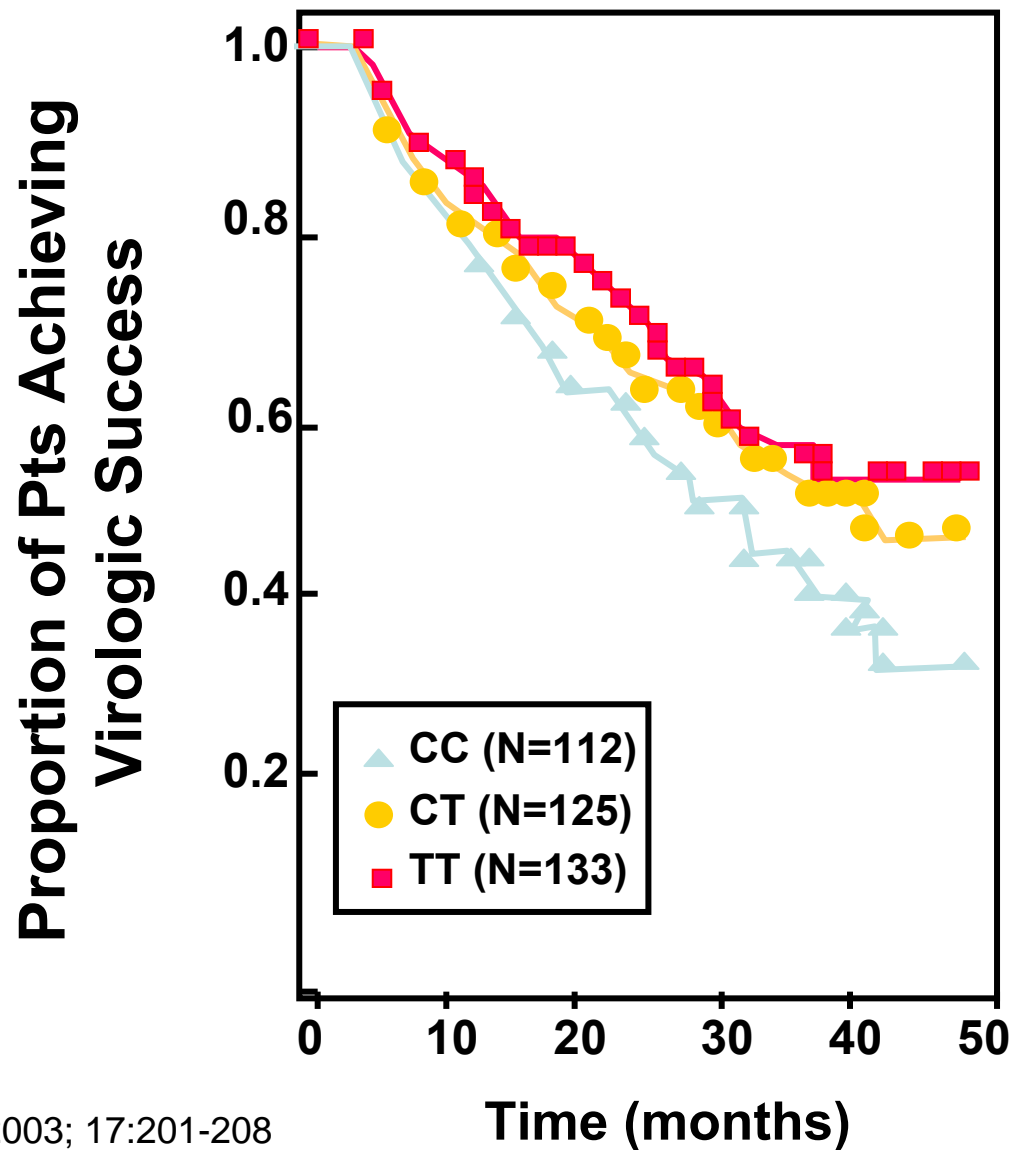
Fellay J et al Lancet 2000

CD4 Count Response with Regards to MDR-1 Polymorphism

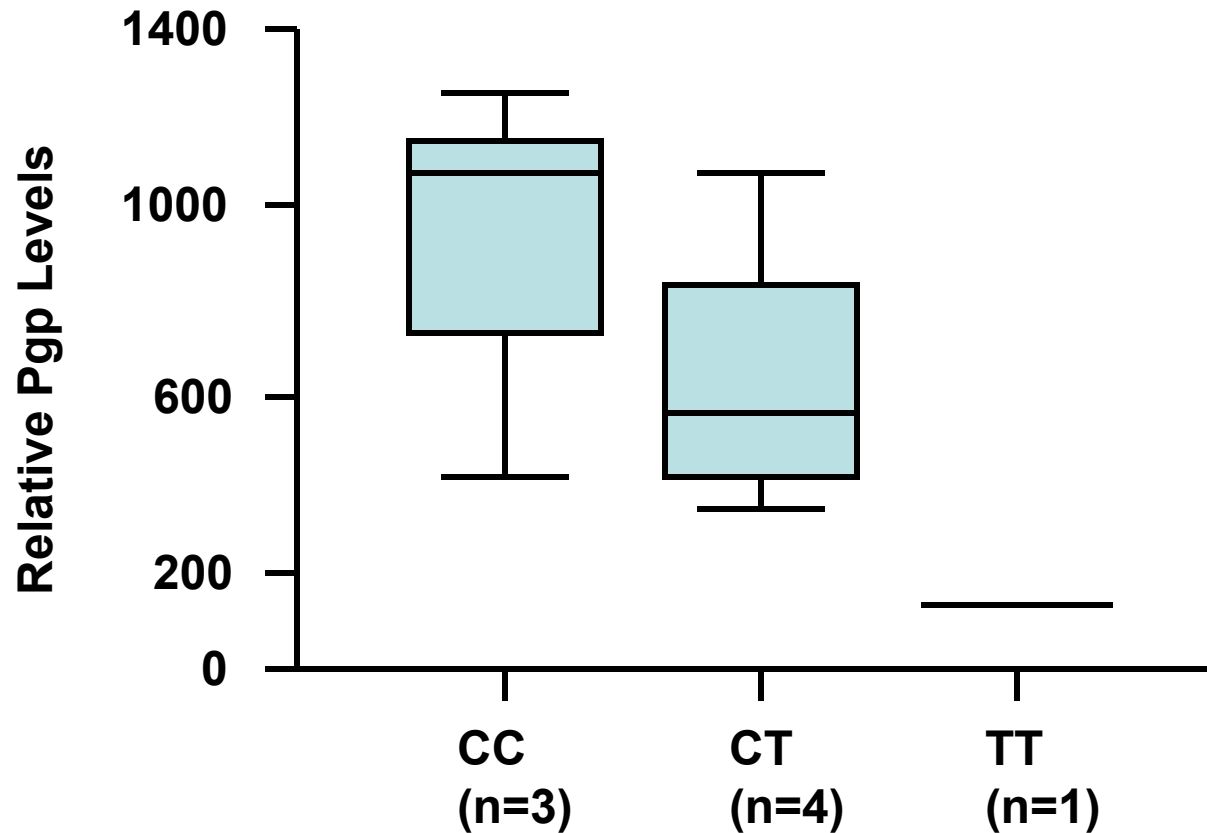


Fellay J et al Lancet 2000

Impact of MDR-1 Genotype on Virologic Response



Functional Pgp Polymorphism Exon 26 C3435T



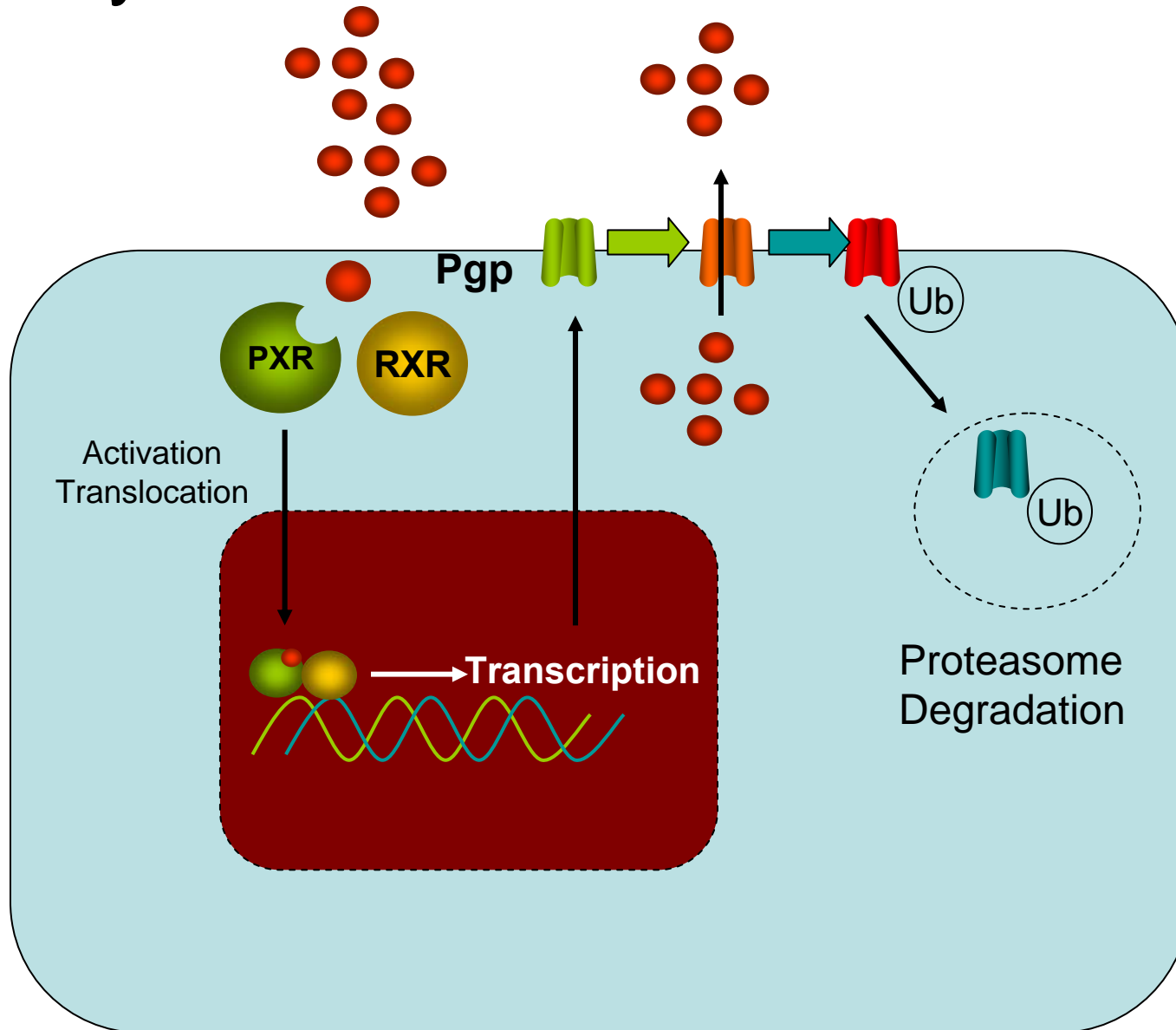
Hoffmeyer S et al Proc Natl Acad Sci 2000; 97:3473-8

Ethnic Differences of MDR1 exon 26 C3435T Polymorphism

	CC(%)	CT(%)	TT(%)
Caucasians	26	48	26
African American	68	31	1
Chinese	32	42	26
Southwest Asian	15	38	47

From: Ameyaw MM et al. Pharmacogenetics 2001; 11:217-221.

Biosynthesis and Elimination of Pgp



Gender Difference

Advantages and Disadvantages of PI-Based HAART

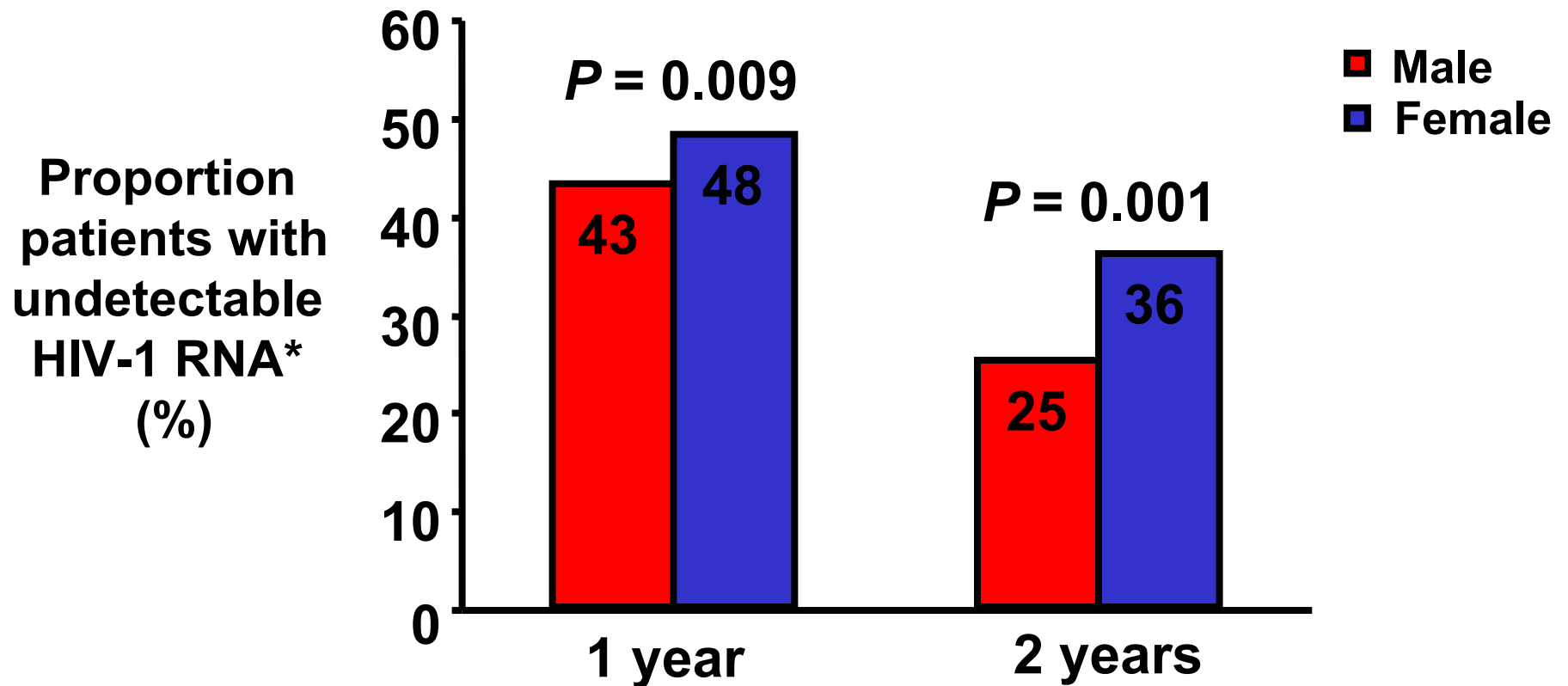
Advantages

- Demonstrated long-term efficacy
- Potential immune benefit beyond antiviral effect
- High barrier to resistance (boosted)
 - Preservation of both PI and NRTI options upon failure
- Lower rates of transmission of primary PI resistance
- No known teratogenicity; less likely to cross placenta
- No CD4 restrictions
- QD dosing available with LPV/r, ATV, and FPV/r for treatment-naïve patients (alternative regimens)

Disadvantages

- Lipid and metabolic abnormalities (agent specific)
- Higher pill burden (agent specific)
- CYP3A4 inhibitors and substrates
- Gastrointestinal side effects
- Drug-drug interactions

Sex and Virologic Response to HAART



* Plasma viral load <400 copies/mL

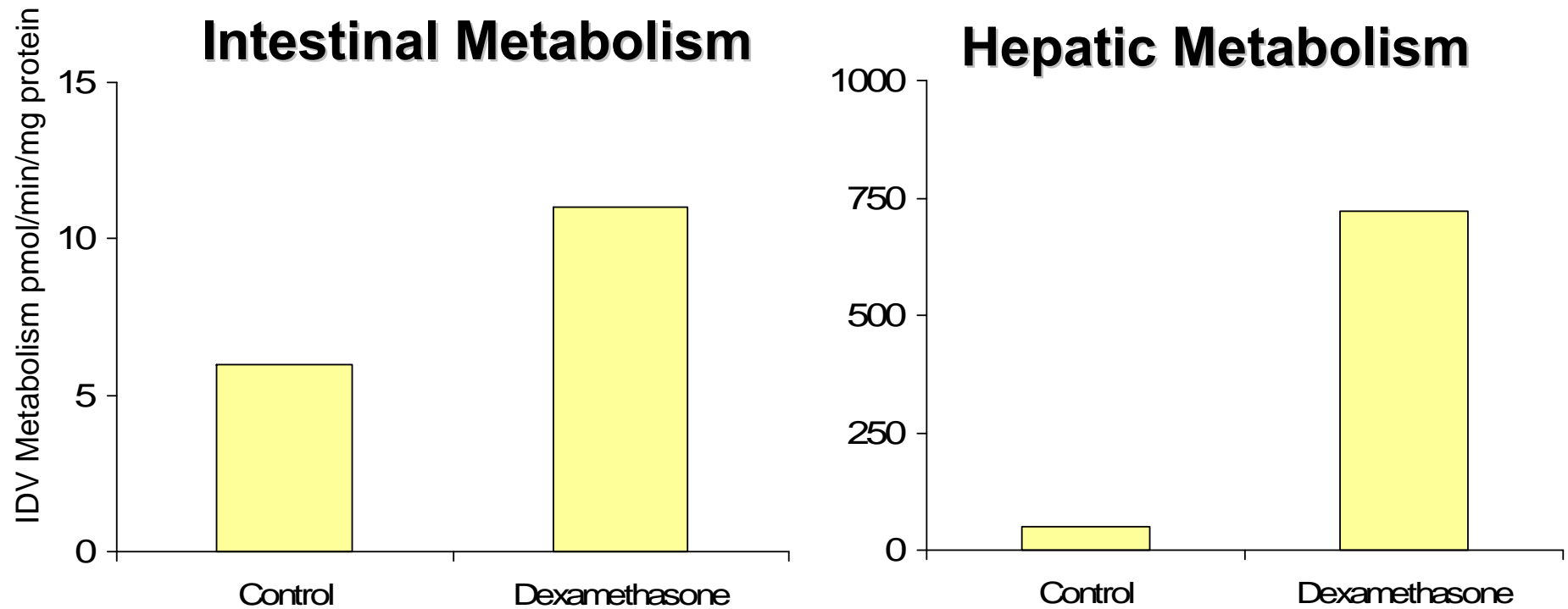
Sex and Virologic Response to HAART: Observational Study

- Case-control observational sex comparison
- 162 women matched with 324 men
 - All ART-naïve
 - Matched by CD4 cell count and VL
- Received 2 NRTIs + nelfinavir
- Followed for 2 years

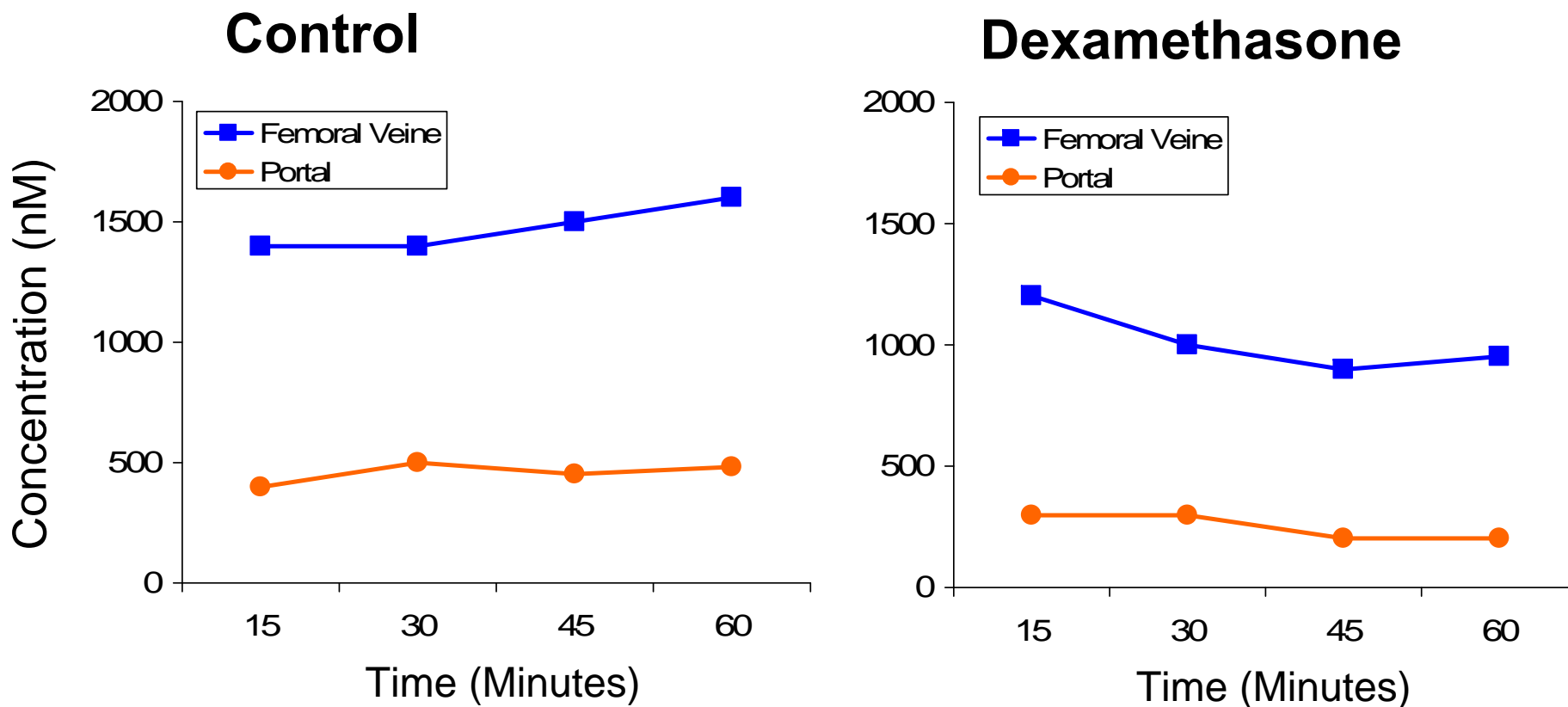
Mechanisms Of Sex Based PK Differences

- Women may on the average express lower levels of p-glycoprotein
 - If drug is pure substrate for P450 3A4 tends to have lower concentrations in women
 - If substrate for both P450 3A4 *and* PGP tends to have higher levels in women
- Counter-evidence: indinavir is a substrate for both, and has equivalent concentrations in women and men

Effect of DEX on the Intestinal and Hepatic Metabolism of IDV (5 mM) in Rats



Mean Concentrations of IDV in Systemic Circulation of Control (A) and DEX-treated (B) Rats During Portal (E) and Femoral (F) Vein Infusion at a Constant Rate of 12 mg/min



Indinavir Clearance in Females versus Males

	Male	Female
Clearance	89 ml/min/kg	41 ml/min/kg

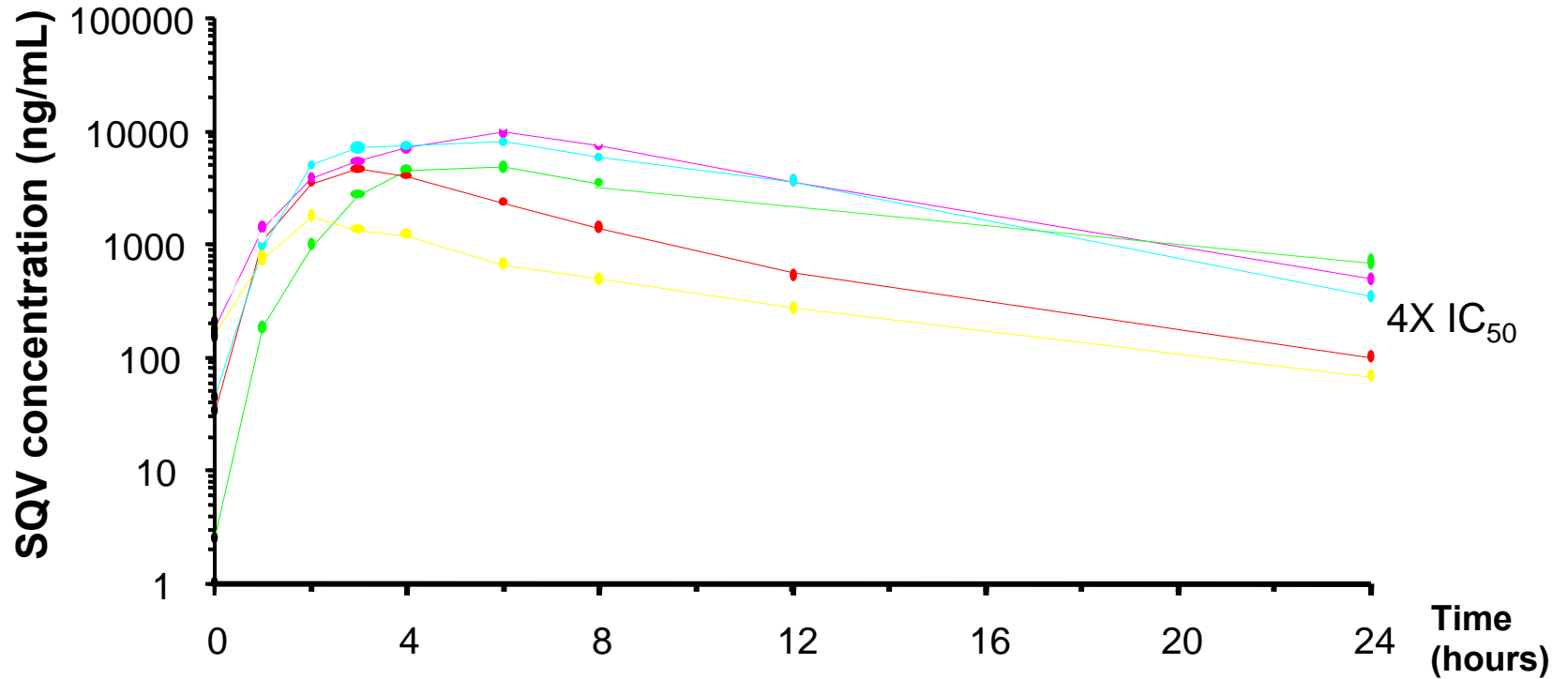
Sex-Based Pharmacokinetics Differences of NVP, EFV and SQV

Drug	Difference in Woman versus Men
Atazanavir	↑ 20% AUC
Efavirenz	↑ 30% C _{min}
NVP	↑ 20% C _{min}

Drug	Women	Men	P-value
Nevirapine TDM ¹	6.7 mg/L	5.5 mg/L	0.0006
Efavirenz TDM ²	3.0 mg/L	2.3 mg/L	<0.0001
Saquinavir AUC ³	20 mg-hr/L	14.9 mg-hr/L	0.04
Saquinavir C _{min}	0.30 mg/L	0.13 mg/L	0.001

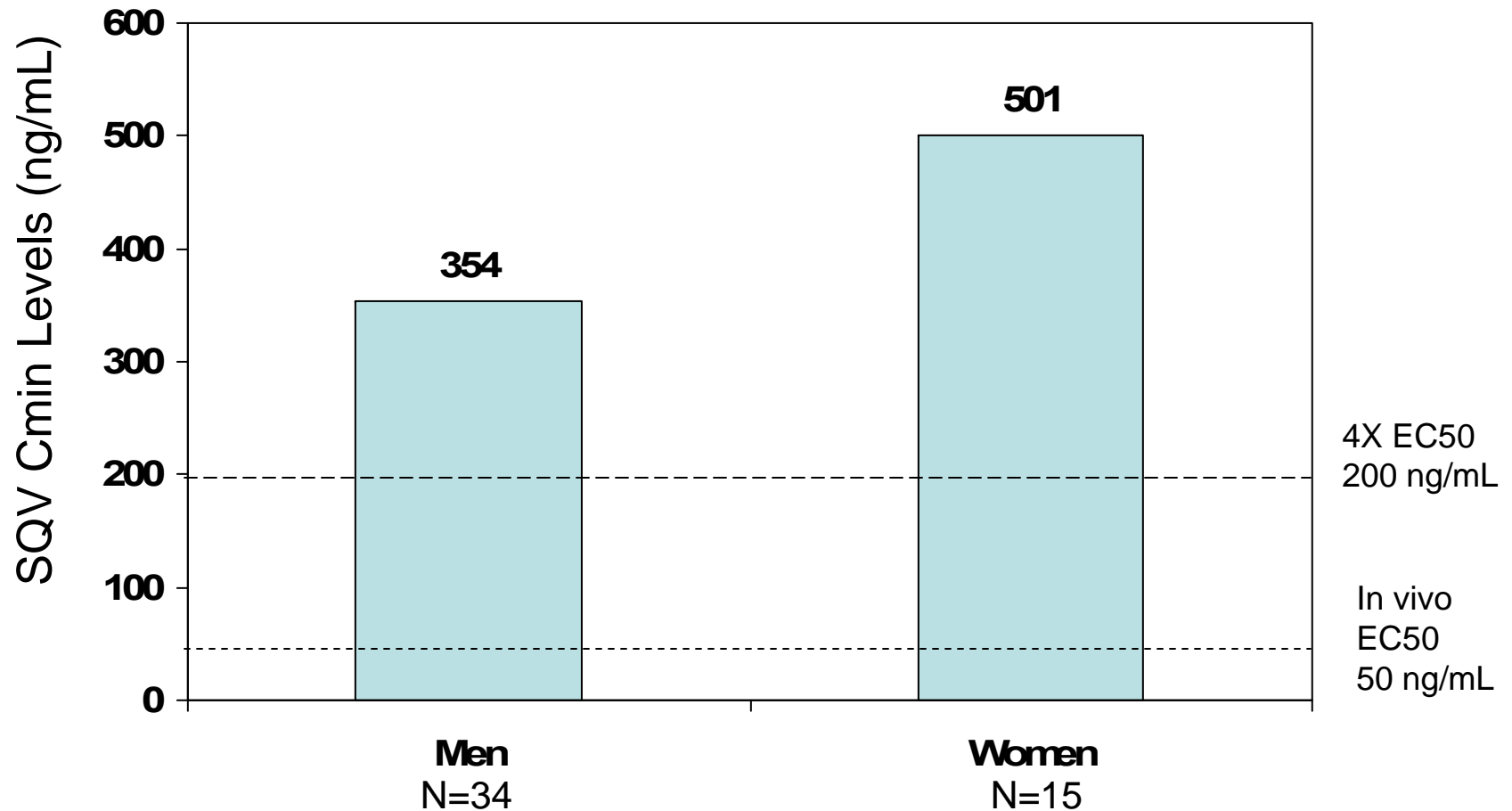
¹La Porte et al, ²Burger et al, *4th International Wksp on Clinical Pharmacology in HIV, March 2003, #10, #15*
Fletcher et al, 2nd IAS Conference on HIV Pathogenesis and Treatment, July 2003, #128

PHARMACOKINETIC PROFILES WEEK 4



	<u>C_{last}</u> (ng/mL)	<u>C_{max}</u> (ng/mL)	<u>AUC_(0-24h)</u> (ng-h/mL)
N	6	6	6
Min	68	1,720	10,542
Median	429	6,435	66,920
Max	1,750	13,400	137,563
Geometric Mean	336	5,875	49,777

Median Cmin for Men and Women



J Montaner. FOCUS Trial Update at Frankfurt Resistance Conference, 2001

Gender Differences in Lopinavir/r Soft-Gel Pharmacokinetics

- Pharmacokinetics of lopinavir/r (400/100) soft gel determined in 40 men and 38 women
 - Well balanced as to race
 - 31% white, 31% black, 31% Hispanic, 4% Asian
- Lopinavir pharmacokinetics did not differ between men and women
- Women had 20% higher ritonavir AUC, C_{\max} , and trend toward faster oral clearance
- Clinical significance of differences unclear

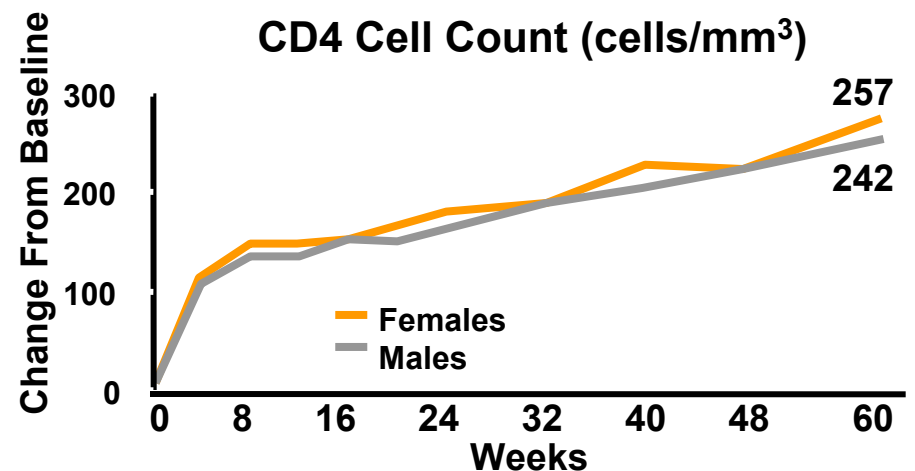
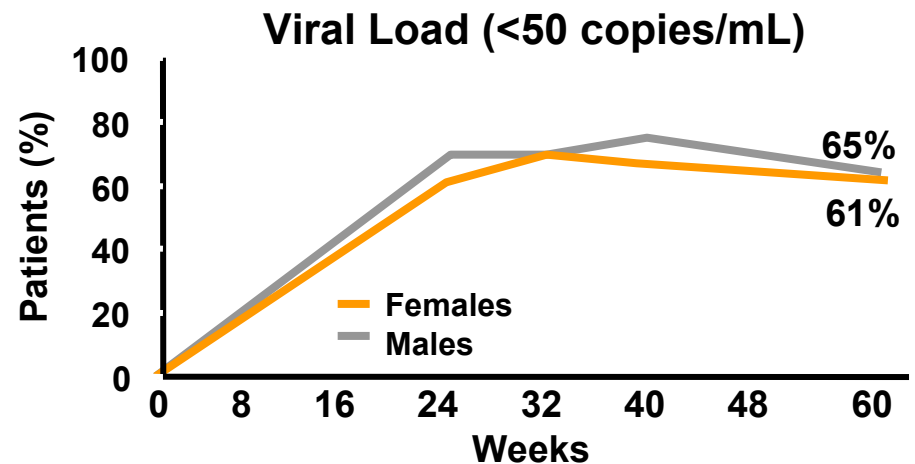
Lopinavir/Ritonavir Virologic and Immunologic Outcomes Do Not Differ by Gender

- 326 lopinavir/ritonavir patients (soft-gel formulation)
 - Female/male: 20% vs 80%
 - African American: 50% vs 18%
 - Caucasian: 33% vs 62%
 - Hispanic: 15% each
- Grade 3/4 adverse events
 - Female/male
 - Diarrhea: 11% vs 18%
 - Nausea: 14%* vs 6%
 - Dyspepsia: 8%* vs 2%
 - Vomiting: 6% vs 2%
 - Triglycerides >750 mg/dL: 2%* vs 13%

* $P < 0.05$ vs males.

Intent-to-treat analysis (missing values=failure).

Cernohous P, et al. 14th IAC; 2002, Barcelona, Spain. Abstract WePeB5972.



Absence of Gender Differences in Fosamprenavir Efficacy and Safety

- 3 clinical trials of fosamprenavir±ritonavir in treatment-naïve (NEAT and SOLO) and experienced (CONTEXT) patients
 - 25% of total were female
- No differences in viral load response
- No gender differences (in treatment-naïve studies) in rates of discontinuation
- Rates of grade 2-4 adverse events similar in all studies
- Women had generally lower rates of grade 2-4 treatment-related adverse events
 - Especially triglyceride elevations

Darunavir Efficacy and Safety by Gender, Age, and Race

- Combined 24-week analysis of POWER 1, 2, and 3 studies of darunavir
- No difference between men and women in response to darunavir with <10 baseline resistance fold change
- No gender, age, or race differences in outcomes, including pharmacokinetic variables
 - Higher mean AUC exposure (16.8%) in women in POWER 1 and 2 integrated analysis

The Pharmacokinetics Of Nelfinavir Are Similar In Men And Women

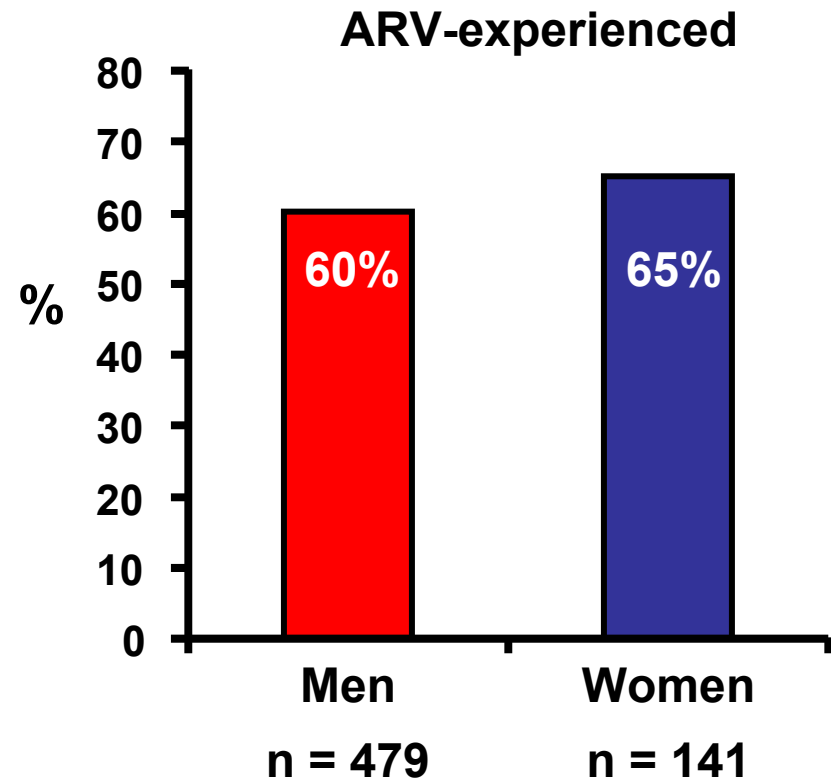
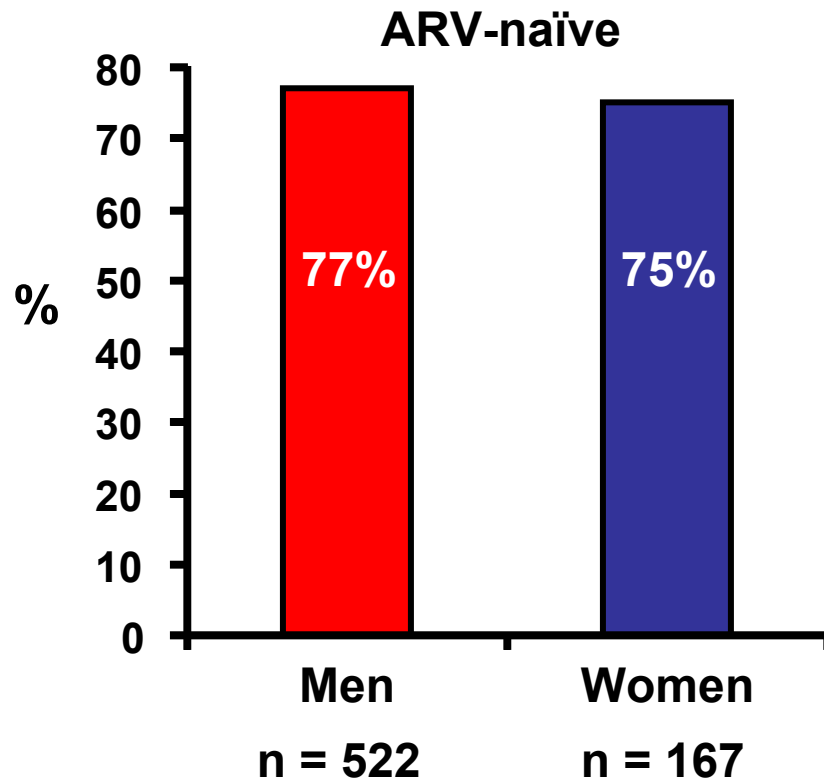
Results from a study in African-American patients with HIV infection receiving nelfinavir 1250 mg *bid*

Parameter	Women (n = 15)	Men (n = 15)
C _{max} (mcg/ml)	5.86 ± 1.38	5.60 ± 2.53
C _{min} (mcg/ml)	1.26 ± 0.74	1.34 ± 1.64
t _{1/2} (hours)	3.85 ± 1.58	3.83 ± 2.71
AUC ₀₋₁₂ (mcg-h/ml)	41.24 ± 11.06	41.95 ± 24.36
Vd (L/kg)	2.61 ± 1.12	2.47 ± 1.21

Nelfinavir is Equally Effective in Women and Men

Proportion <400 copies/ml at most recent visit.

Nelfinavir-based HAART taken for mean 52.2 (men) or 47.8 (women) months



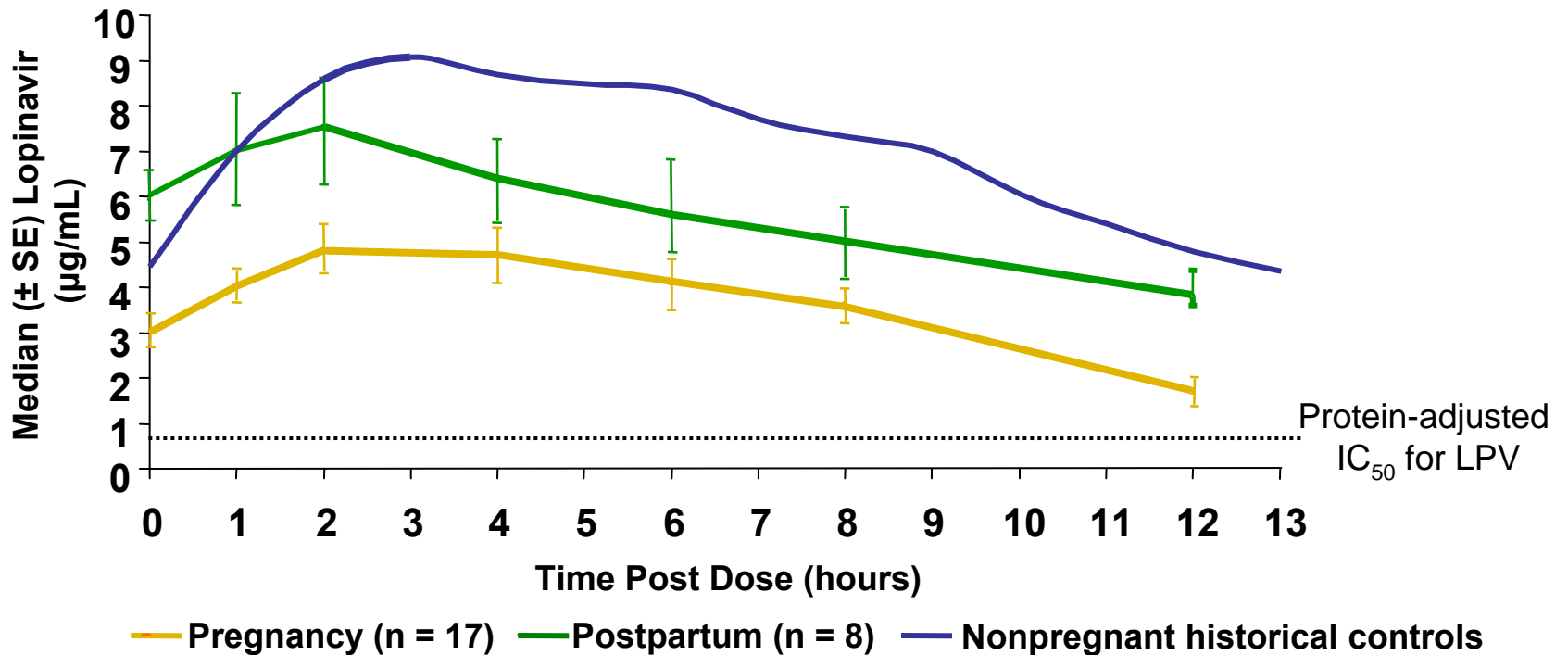
$P > 0.3$ for men vs women

Drug Concentrations In Pregnancy

- Nelfinavir concentrations ~40% lower in 27 pregnant women compared to 48 controls¹
- Case report of low NFV concentrations in pregnancy returning to normal post-partum²
- Indinavir AUC lower in pregnancy³
 - Results not present if indinavir used with ritonavir
 - Cytochrome P450 activity increased
 - Results returned to normal post-partum
 - Effect of pregnancy on nelfinavir concentrations variable

¹Wit et al, 2nd IAS conference, #129; ²Angel et al, AIDS 2001;15:417; ³Kosel et al AIDS 2003;17:1195;

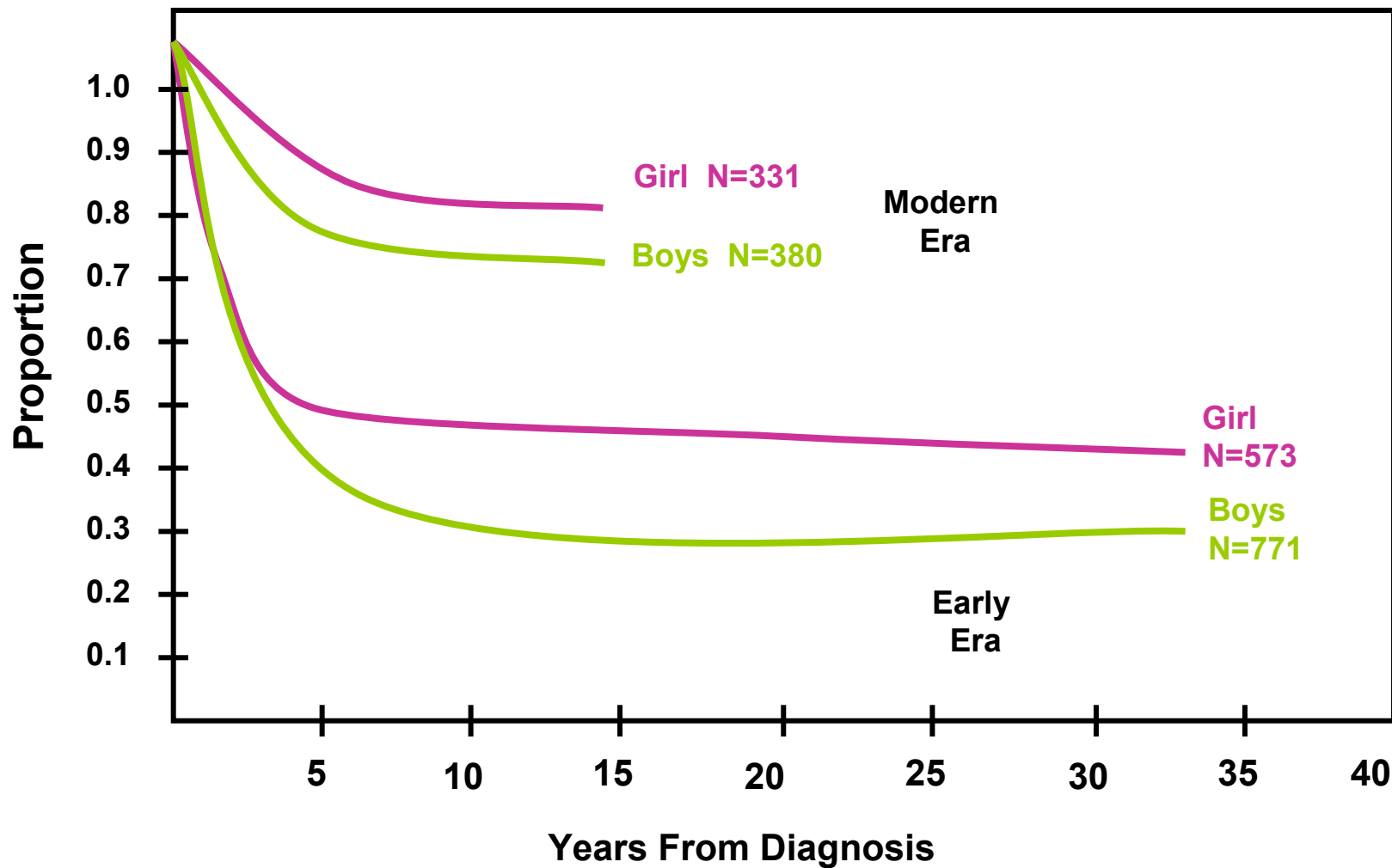
Reduced Lopinavir Plasma Concentrations in Pregnancy



- Note also abstract 4644 – NVP plasma exposure reduced in pregnant vs nonpregnant women

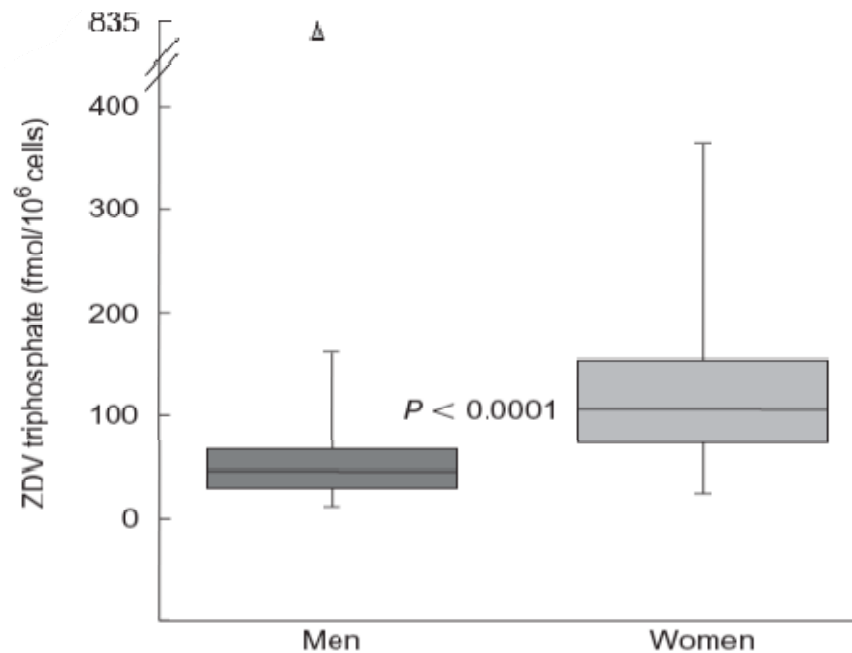
Gender Difference: Toxicity Towards Pharmacologic Agents

Gender Difference in Response to Anti-leukemic Effect



Adapted from Lilleyman and Lennard. Lancet 1994; 343: 1188-1190

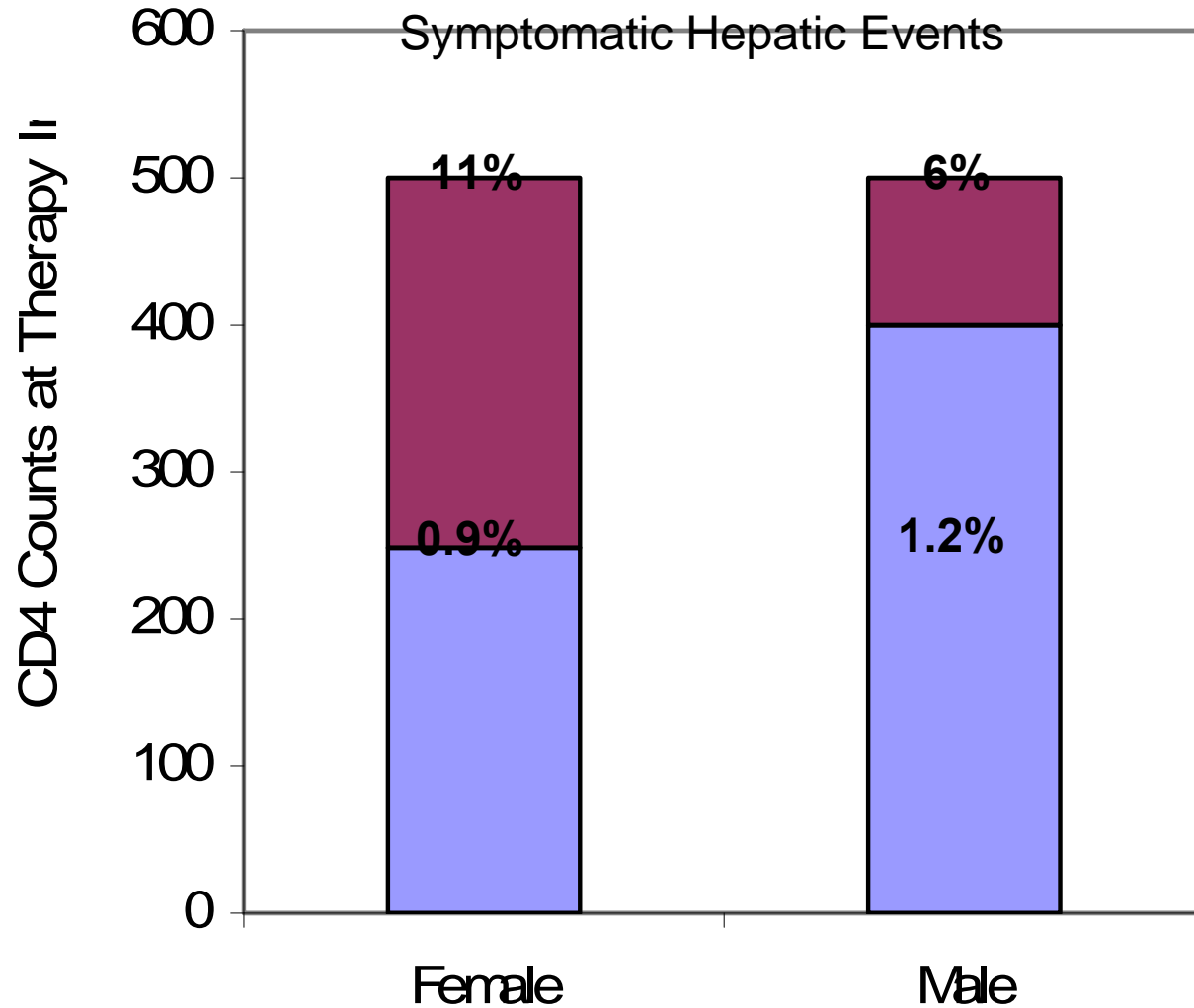
Impact of Sex on Intracellular Nucleotide Analogs



Impact of IC Nucleotide Levels and Virologic Impact

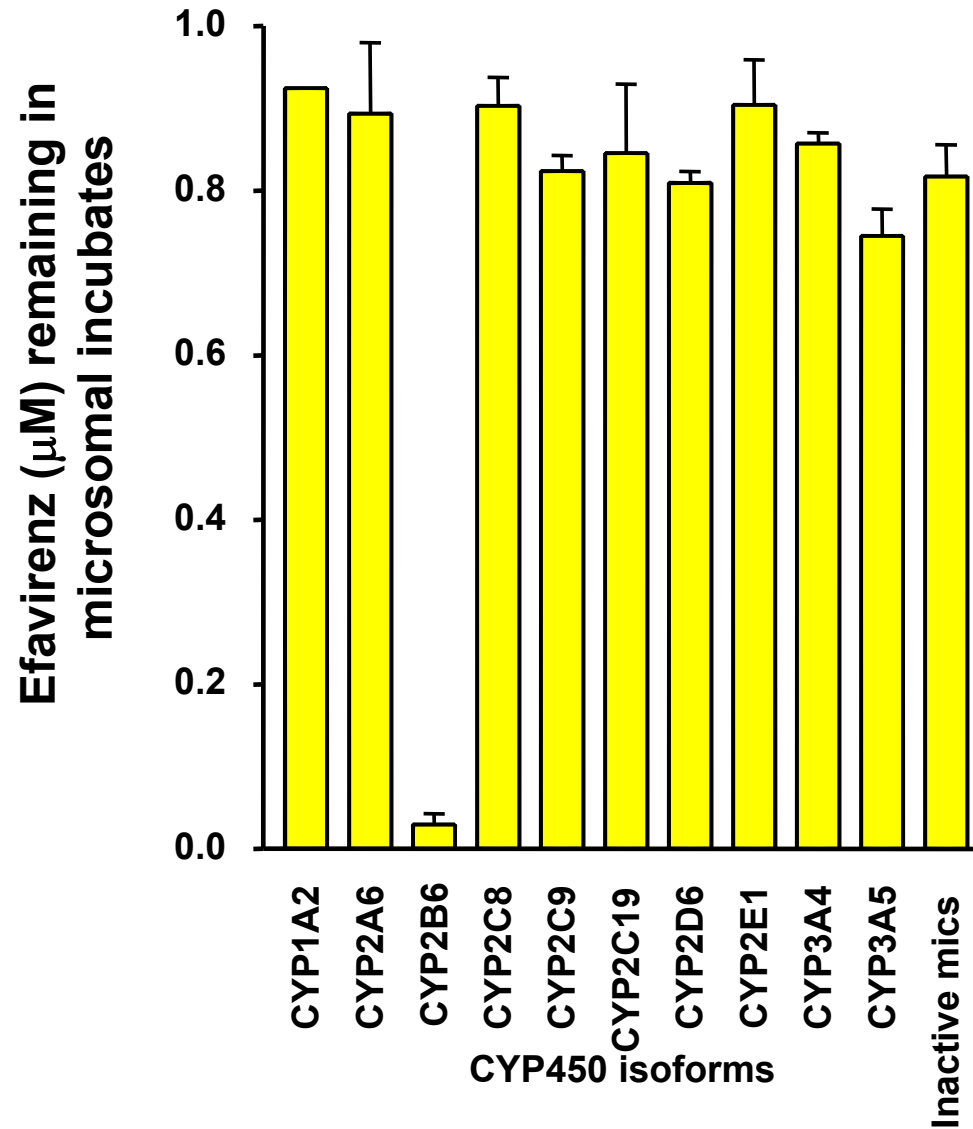
QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Gender Difference in the Incidence of Hepatic Events Related to Viramune (Nevirapine)

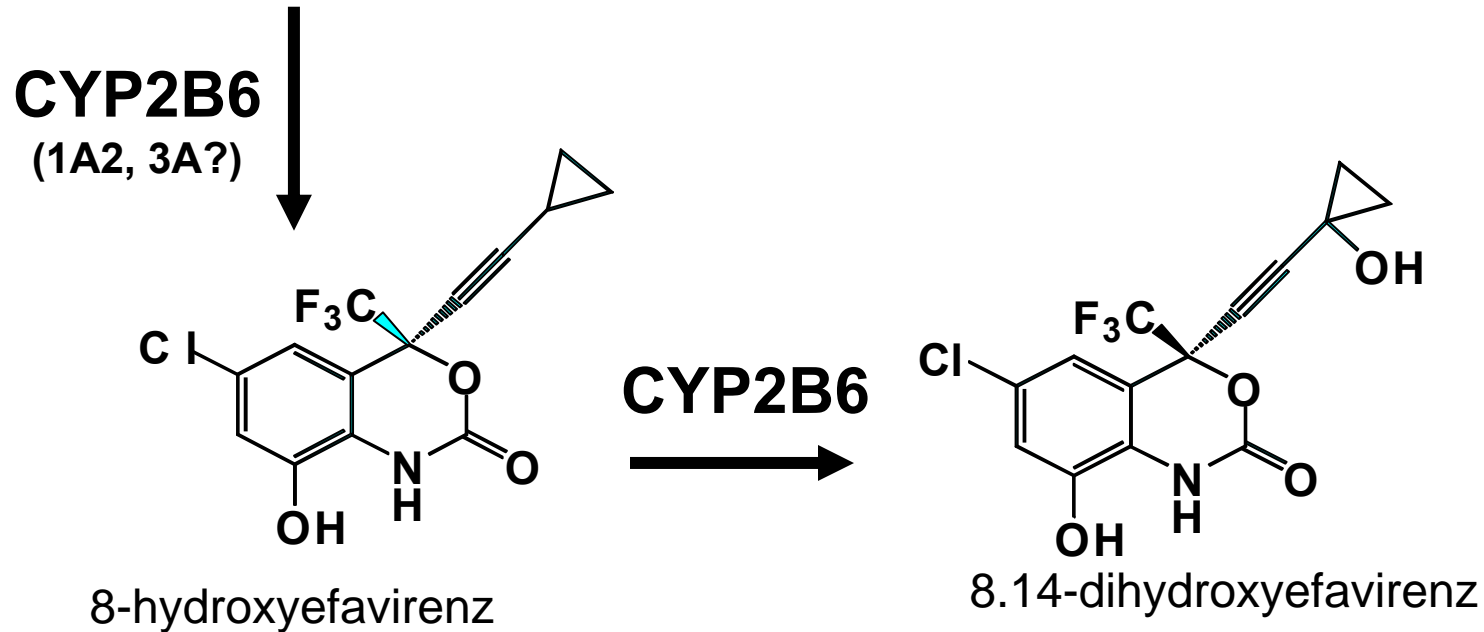
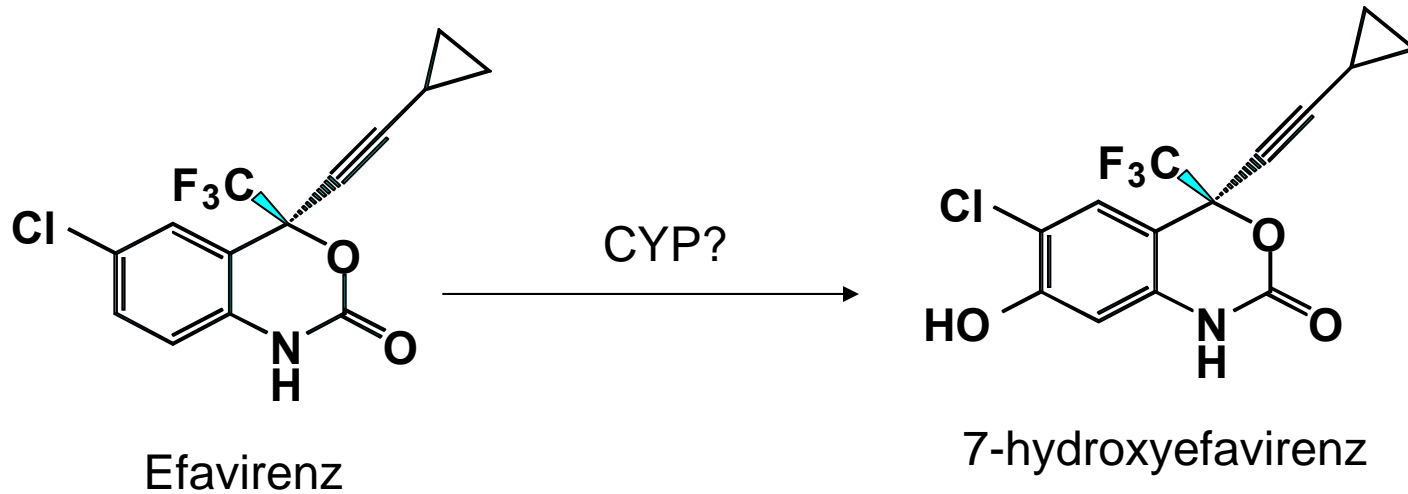


Viramune Prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc

CYP2B6 Catalyses The Metabolism Of Efavirenz (1 μ m)

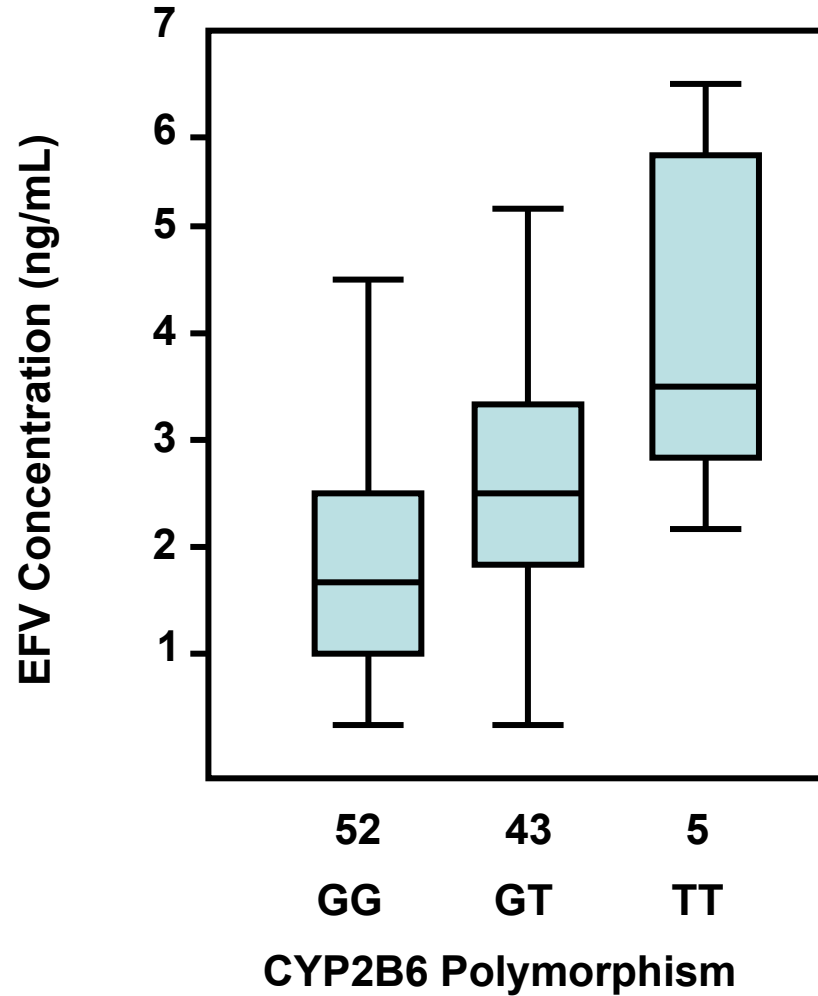


Human Metabolism of Efavirenz

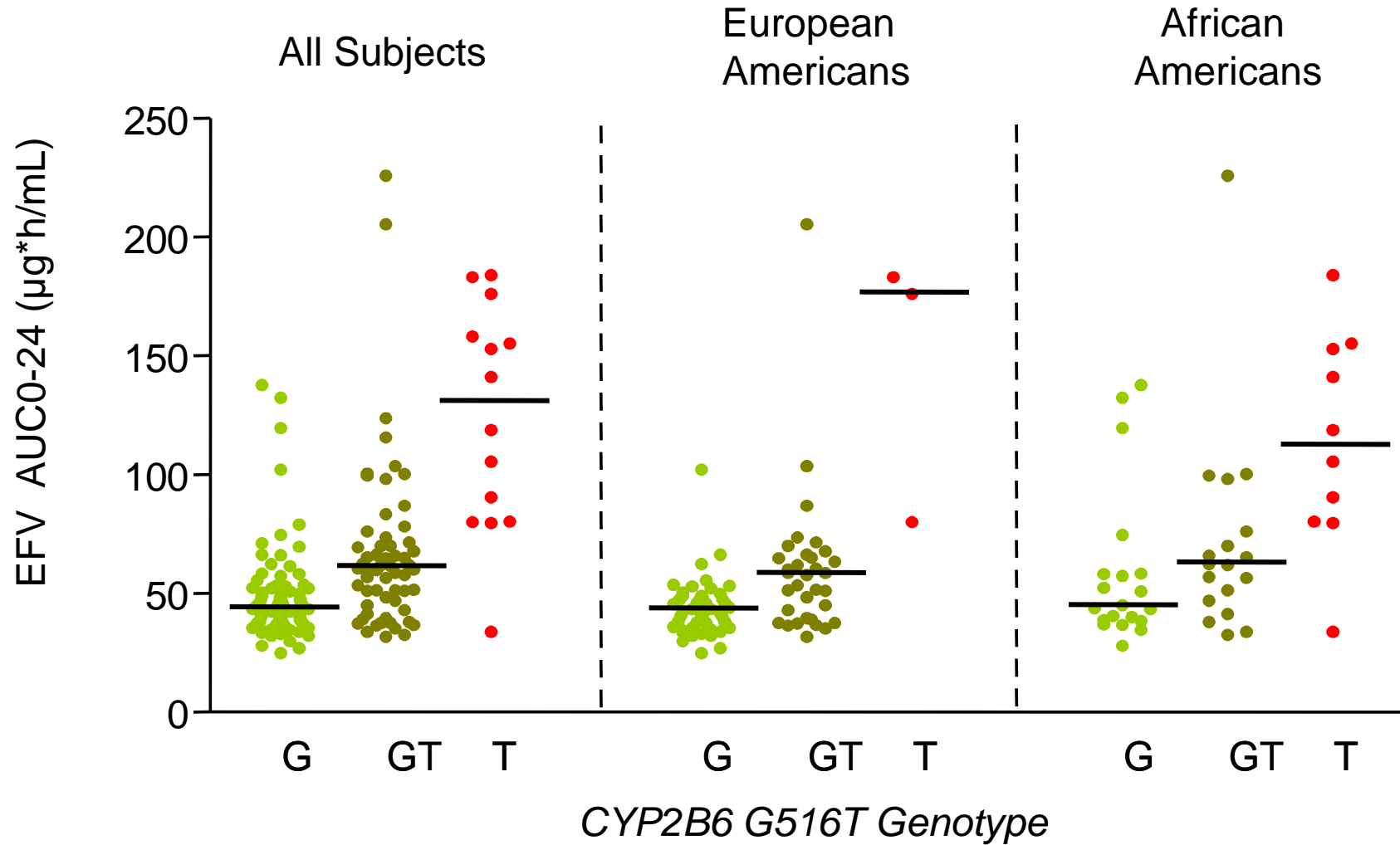


(Ward et al., J Pharmacol Exp Ther 2003)

Efavirenz Concentration in Relationships with CYP2B6 Polymorphism



CYP2B6 G516T (Exon 4) and Efavirenz Plasma Levels: A5097s



Haas et al, *AIDS* 2004;18:2391

Host Genetics and Efavirenz: ACTG studies A5095/5097s)

Efavirenz Levels

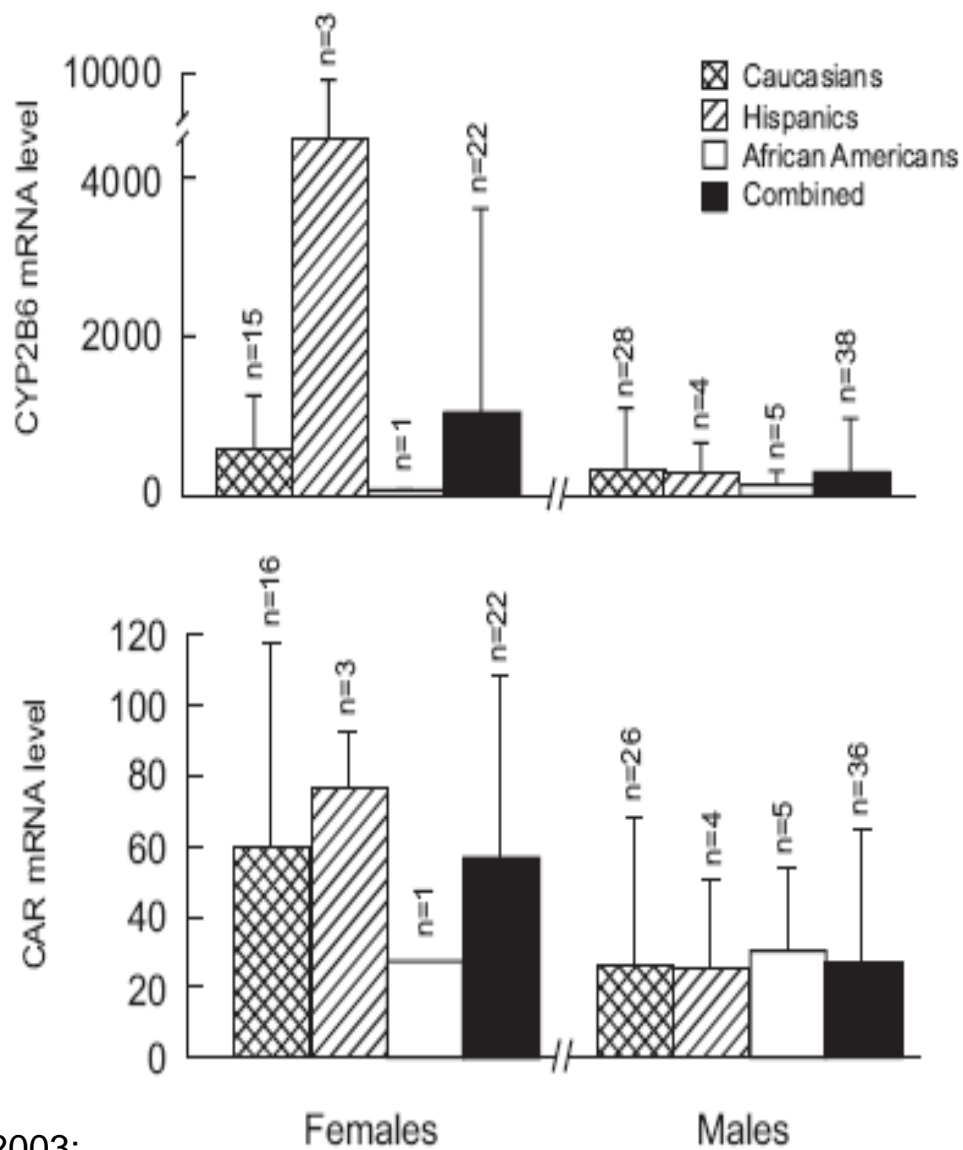
- EFV plasma levels were greater in blacks and Hispanics than in whites (Ribaud et al, 11th CROI).

	<u>Median EFV AUC_{0-24h}</u>
Blacks	58 $\mu\text{g}\cdot\text{hr}\cdot\text{mL}^{-1}$
Hispanics	66 $\mu\text{g}\cdot\text{hr}\cdot\text{mL}^{-1}$
Whites	46 $\mu\text{g}\cdot\text{hr}\cdot\text{mL}^{-1}$

(overall $P \leq 0.001$ for all comparisons)

- There was much overlap in the distribution of PK parameters between racial/ethnic populations.

Difference in Expression of CAR and CYP2B6



Lamba V et al JPET 2003;

Lecture Highlight

- Gender difference may be due to difference in absorption and elimination
- Gender difference in outcomes (e.g. viral suppression or drug related toxicity) is dependent on the substrate
- The role of hormones has not been fully elucidated