Pharmacology Update 2005

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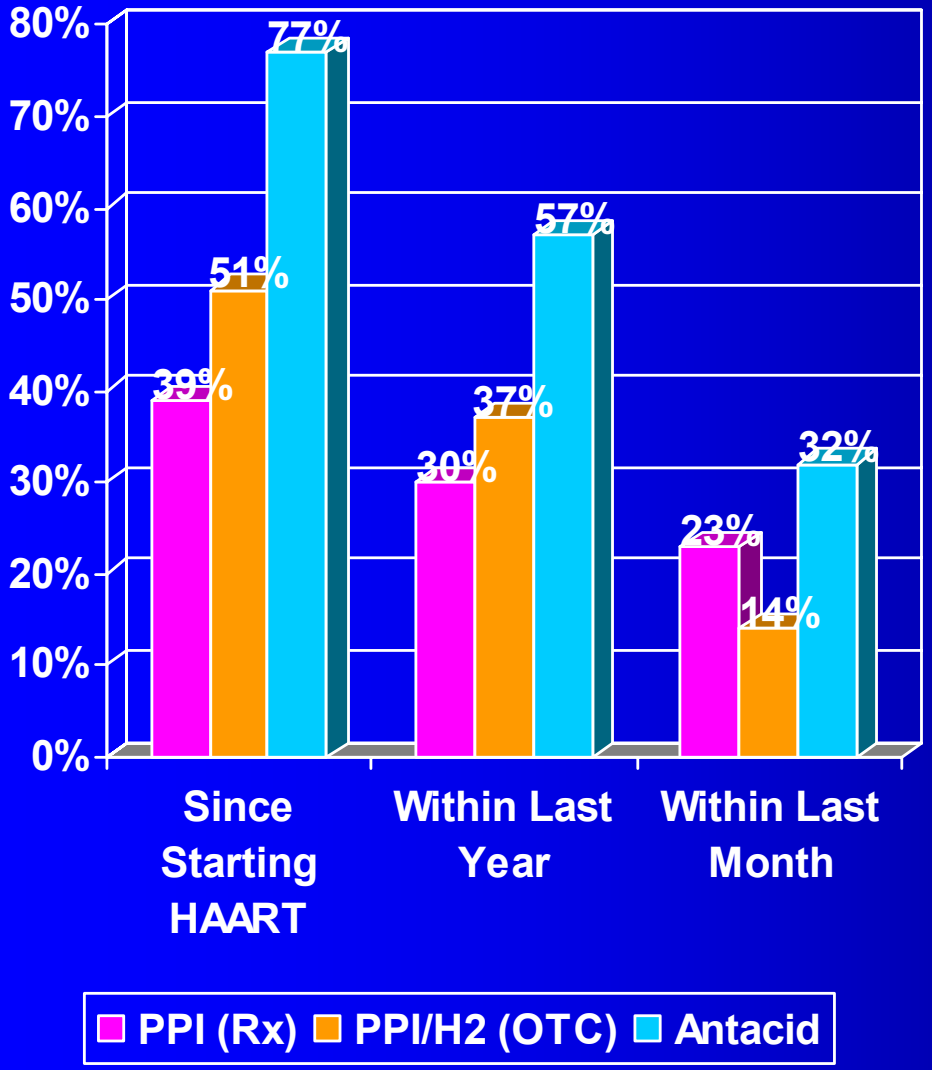
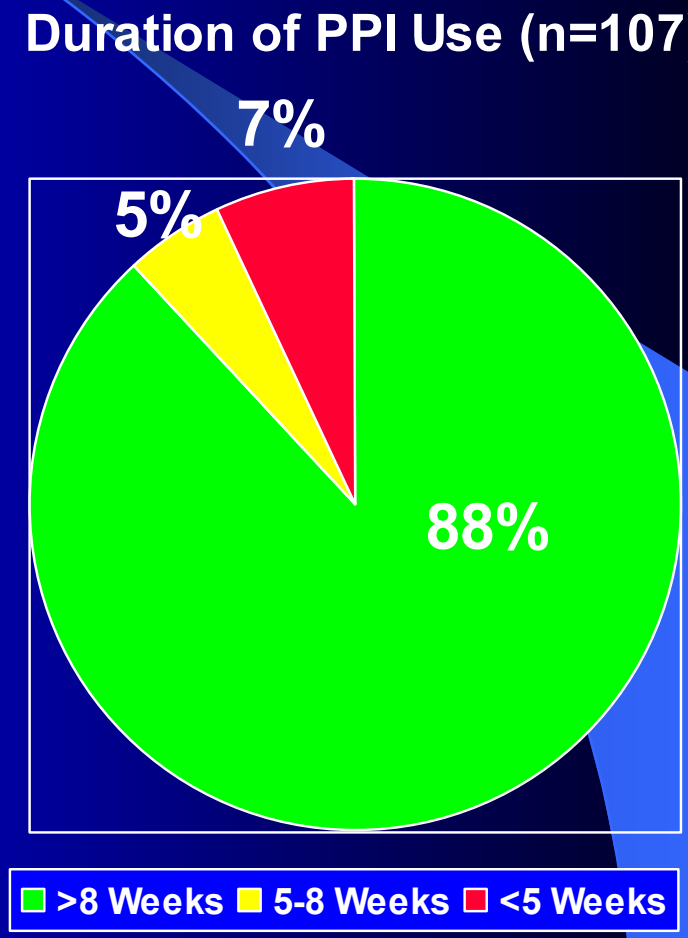
I'm having a *Maalox* moment!!!

Gastric Hypoacidity in HIV

- ≤20% incidence in HIV (unrelated to CD_4)
- Antacids, ddI tablets, H2-blockers or proton pump inhibitors (PPI) also affect gastric pH
- **Can lead to drug malabsorption:**
  - Atazanavir solubility ↓↓ as pH ↑
  - Also indinavir, delavirdine, keto/itraconazole

Use of Gastric Modifying Agents with HAART (n=200)





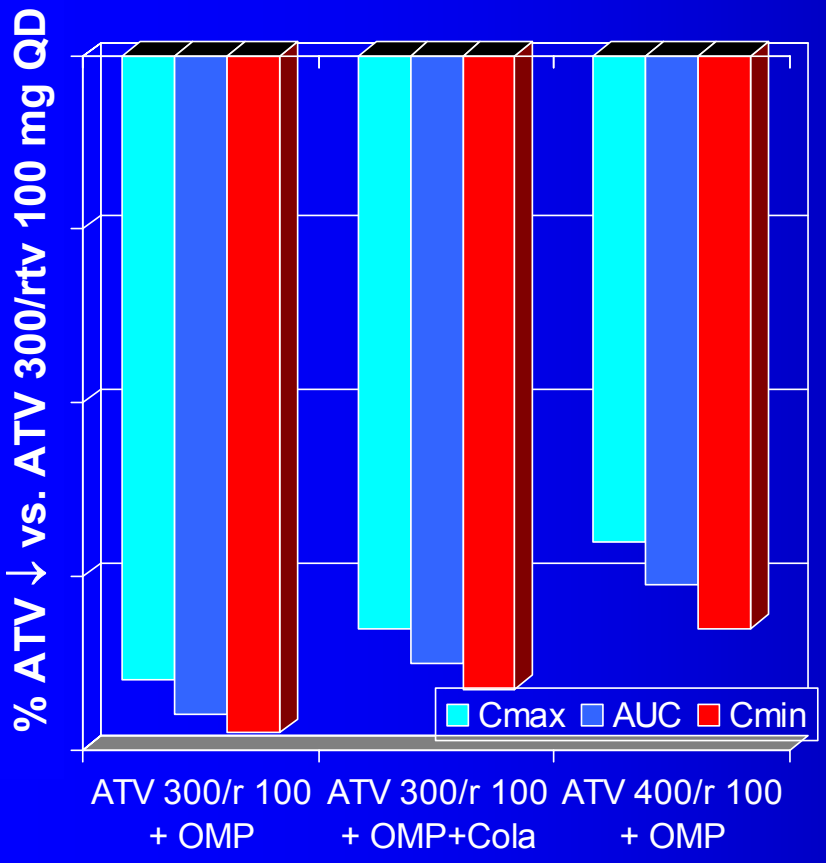
[Luber et al. 7th ICDTH 04, #206]

How Gastric Modifiers Affect Antiretroviral Absorption

- ddI tablets, antacids:
  - Temporarily ↑ gastric pH
  - *Dose ARVs 1 hour before/2 hrs after antacids*
- H2 blockers, PPI:
  - Steadily blocks secretion of gastric acid
  - *May need to alter gastric pH via acidic beverage*
  - *Using ritonavir as a booster may/may not help*

Atazanavir Exposure Is Significantly Reduced by Omeprazole

Omeprazole 40 mg QD in Healthy Subjects (n=48)

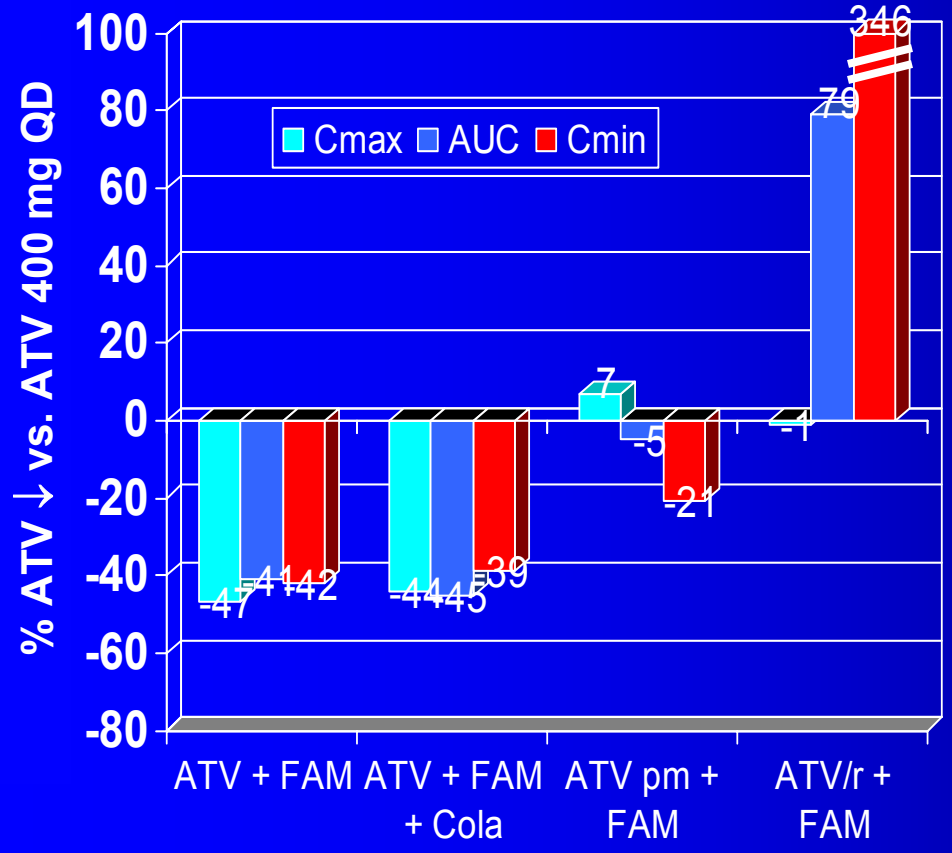


- Atazanavir exposure ↓↓ 70-80% with PPI
  - Effect not corrected with cola or rtv boost
- In this study, OMP was given 2 hours prior to ATV/r
- Ongoing study of ATV+ OMP 20 mg

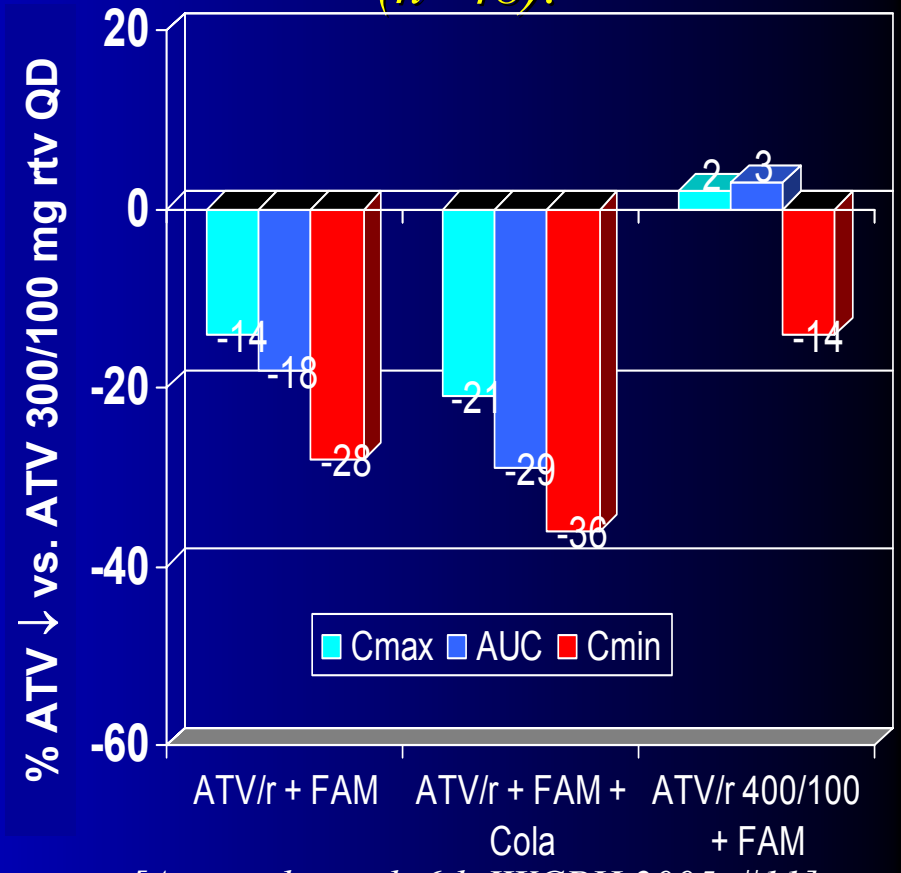
[Agarwala et al. CROI 2005, #658]

Atazanavir Exposure Is Reduced ~40% by Famotidine

Atazanavir 400mg + Famotidine 40 mg BID in Healthy Subjects (n=60)



Boosted Atazanavir + Famotidine 40 mg BID in Healthy Subjects (n=48):



[Agarwala et al. 6th IWCPH 2005, #11]

Clinical Implications of Coadministering Atazanavir and Gastric Modifying Agents

	ATV + H2 (n=20)	ATV + PPI (n=15)
Mean ATV Cmin (ug/mL)	1.12	0.65
suboptimal ATV Cmin (<0.27 ug/mL)	4 (20%)	6 (40%)
# on ATV/r	2/4	5/6

**Reference Cmin:*

ATV 400 mg QD: 0.273 ug/mL

ATV 300/rtv 100 mg QD: 0.862 ug/mL

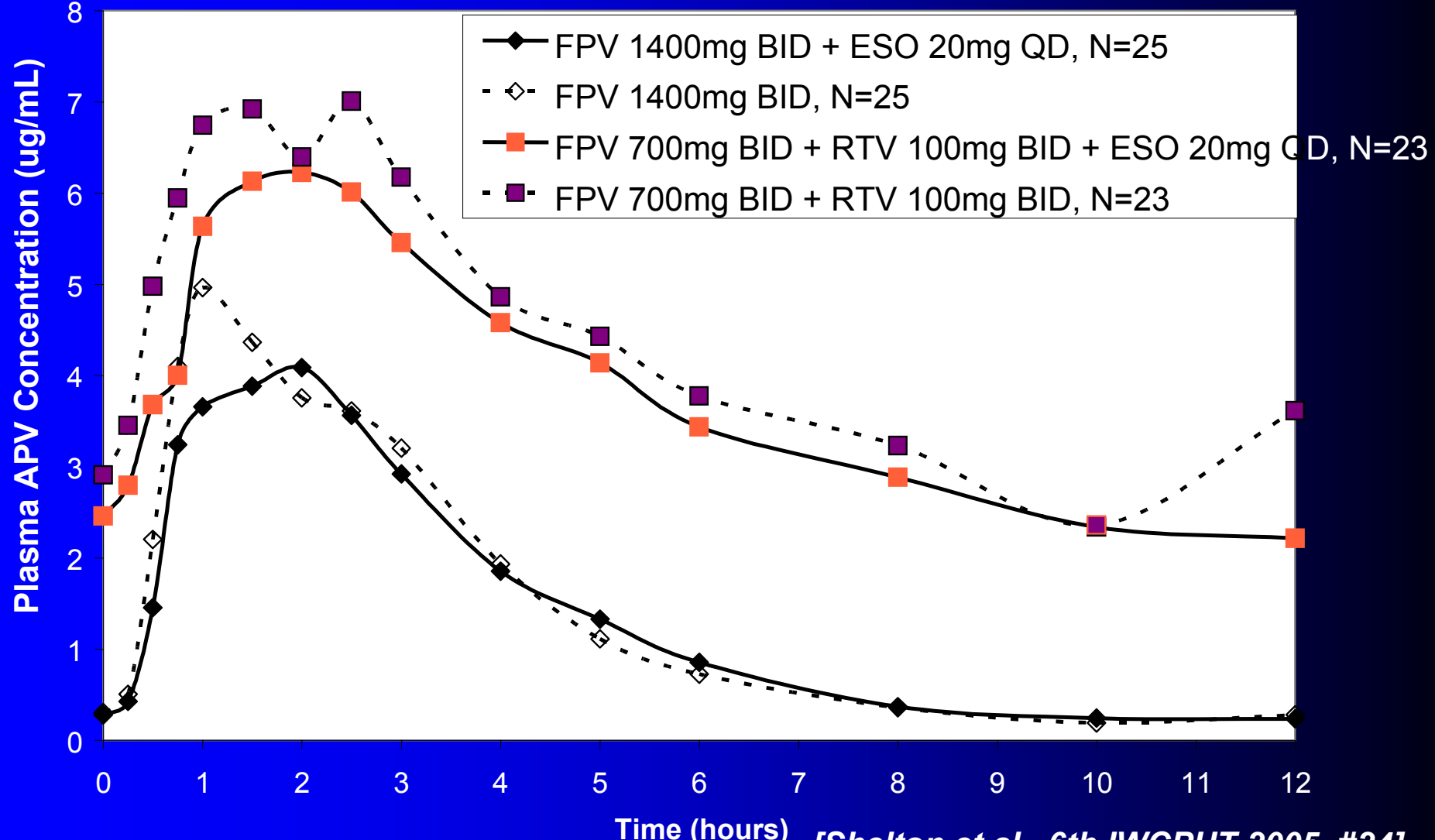
- Survey of clinic patients on ATV and PPIs or H2B
- ATV Cmin levels available on 34 patients prior to intervention
- Suboptimal ATV levels observed, even with boosted ATV

[Farthing et al. 7th ICTHI, P289]

Dosing Atazanavir with Gastric Modifying Agents

- Antacids:
  - Give ATV 2 hours before/1 hr after
- Proton-pump inhibitors: AVOID COMBINATION
- H2-blockers:
  - To achieve ATV levels ≅ 400 mg QD:
    - dose ATV 10 hours after H2 blocker
    - use ATV 300/rtv 100 mg QD
  - To achieve ATV exposure ≅ 300/100 mg QD:
    - Use ATV 400/rtv 100 mg QD

Fosamprenavir +/- rtv May Be Coadministered with Esomeprazole Without Dose Adjustment



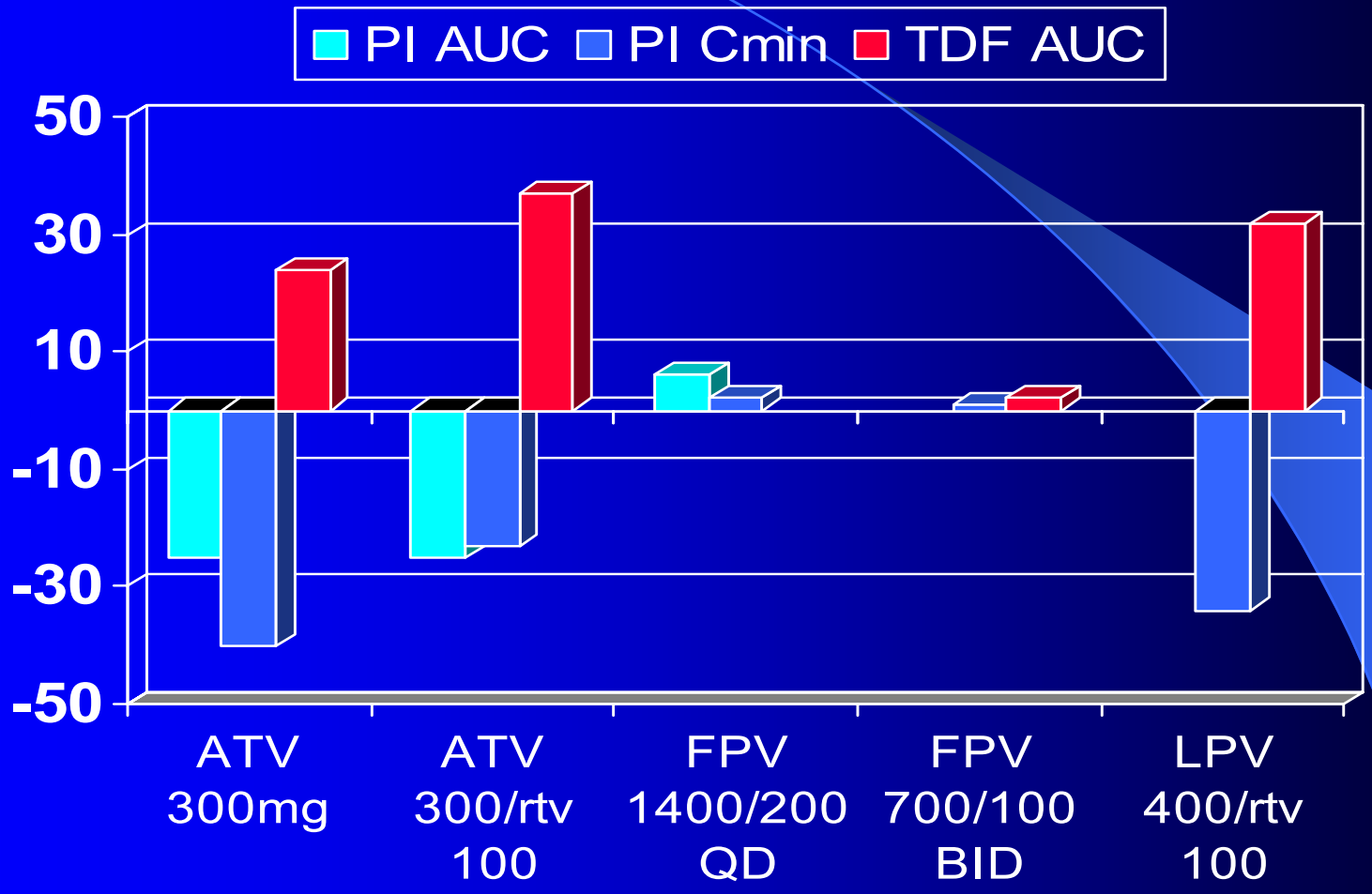
[Shelton et al. 6th IWCPHT 2005, #24]

Gastric Modifying Agents and Protease Inhibitors

ARV	ddI tabs/antacids	H2-blockers	PPI
atazanavir	89% ↓ Cmax, 87% ↓ AUC *(space >1 hr apart)*	41% ↓ AUC, 42% ↓ Cmin *(**NOT** corrected with cola; give ATV 10 hrs after H2 or use ATV/r.)*	**76%** ↓ AUC, **78%** ↓ Cmin *(**NOT** corrected with RTV or acidic drink)*
Indinavir	84% ↓ *(space >1 hr apart)*	7% ↑ Cmax, 2% ↓ AUC, 18% ↓ Cmin *(clinically insig)*	47% ↓AUC, 55% ↓ Cmin *(corrected when boosted with RTV 200mg)*
fos-amprenavir	35% ↓ Cmax, 18% ↓ AUC *(may give together)*	51%↓ Cmax, 30% ↓ AUC, no change C12	no effect on FPV steady-state PK (FPV or FPV/r)
tipranavir	25-29% ↓ in AUC, Cmax and C12 *(space >1 hr apart)*	? *(Use with caution.)*	? *(Use with caution.)*
lopinavir/r, saquinavir, nelfinavir	PI kinetic parameters not affected.		

Tenofovir Interactions

Tenofovir-PI Interactions



- PIs not affected by TDF: IDV, NFV, RTV, TPV

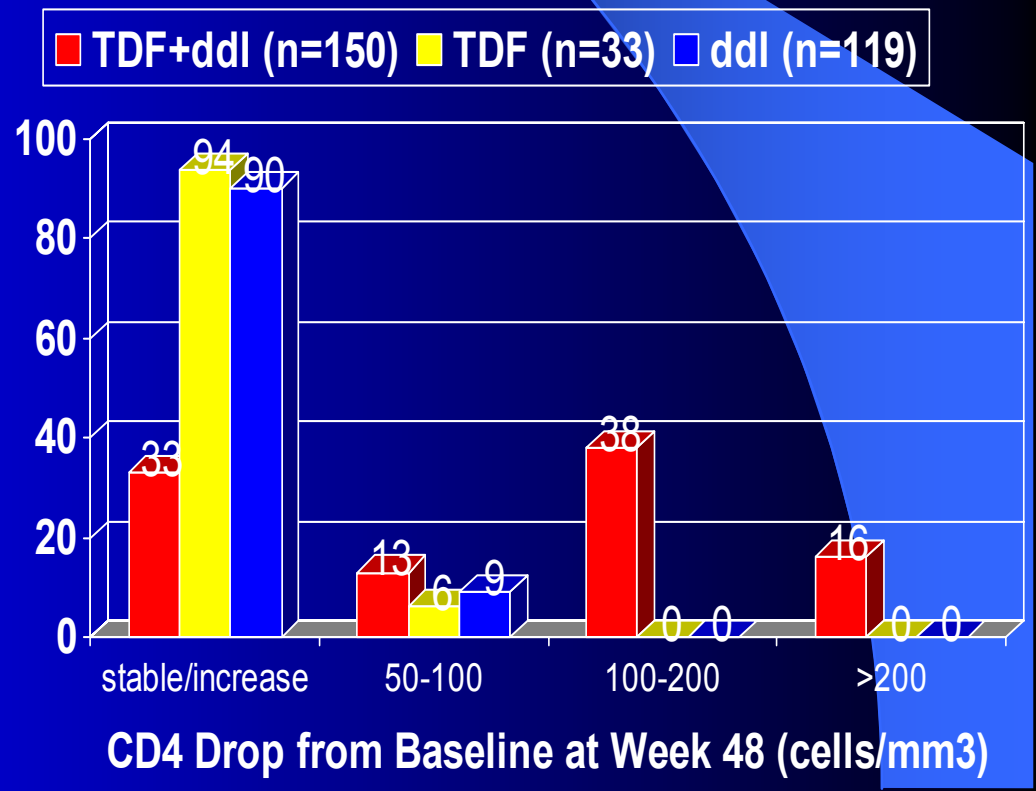
[6th IWCPHT #10, 16, 32, 34, 55]

Potential for CD4 Decline with ddI/Tenofovir

- Observed in various cohorts of patients virally suppressed on combination
- Declines of >200-300 cells in some by 1 year
- Predictors: weight, baseline CD4, ddI dose (400 mg>250 mg)

[Negredo et al. AIDS 04, ICAAC 04 #H561, Karrer et al. CROI 05 #588]

Retrospective study:
n=302, VL< 50 copies/mL, baseline CD4 450-700 cells/mm3



Tenofovir Inhibits Purine Nucleoside Phosphorylase (PNP)

- PNP is a ubiquitous enzyme that catalyses the breakdown of endogenous purines and ddI:
  - ↑ ddI concentrations
  - ↑ intracellular concentrations of dATP & dGTP
    - impairs T-cell maturation & differentiation, apoptosis
    - PNP deficiency (rare autosomal syndrome) causes cellular immunodeficiency disease
    - may also lead to favoured incorporation of endogenous dATP/dGTP by HIV-RT vs. purine NRTI-TP (i.e., ↓ efficacy of purine analogues such as ABC or ddI)

[Kakuda et al. AIDS 2004;18:2442-4.]

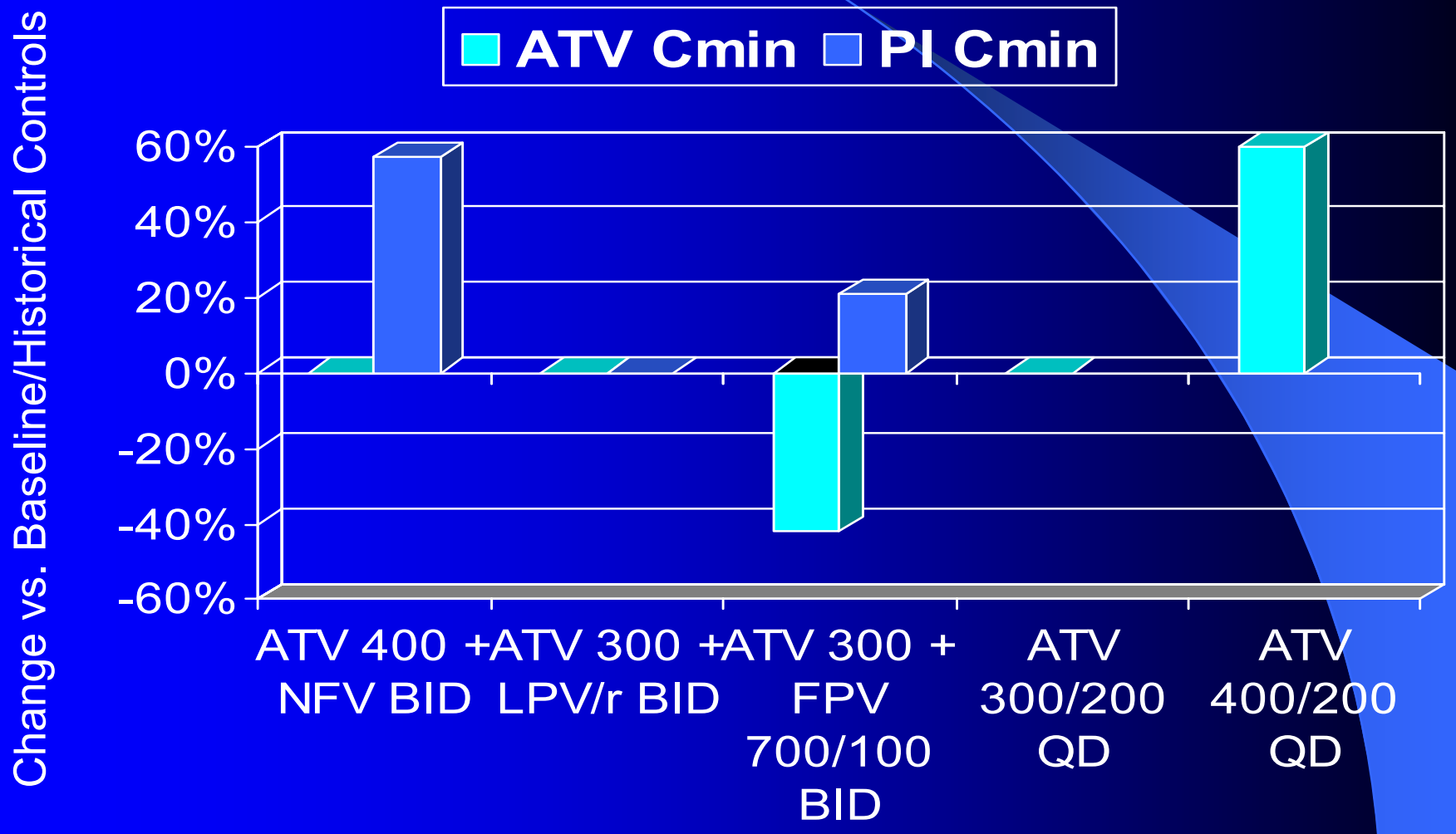
CD4 Declines in Patients on Tenofovir Regimens without ddI

- Retrospective review of 103 subjects on TDF without ddI and VL<400 copies/mL
- 18/103 subjects (17%) had CD4 declines
  - mean time on TDF 23 months (10-39), duration viral suppression 20 months (6-37)
  - 56% on PI/rtv, 28% on 3-4 NRTIs alone
  - Baseline CD4 395 (211-1259)
- Changes in CD4:
  - Average ↓ 253 cells (-88 to -901) by 12 months (6-34)

[Luber et al.6th IWCPHT #53.]

Double PI Combinations

Atazanavir-PI Combinations



[6th IWCPHT # 90, 56, 93, 91]

Other Double PI Boosting Attempts

- FPV 700/LPV 400/rtv 100-200 mg BID:
  - APV Cmin ↓ 72%, no change LPV
- NFV 1250/IDV 400/rtv 100 mg BID:
  - N=16 Thai women
  - therapeutic Cmin: 9/12 IDV, 12/12 NFV
  - at 6 months, 6/16 D/C, 4/11 had VL<400
- SQV 1600/rtv 100 vs. SQV 1600-2000/ATV 400 mg QD:
  - Rtv>>ATV as booster
  - SQV Cmin 87 vs. <30 ng/mL; no effect on ATV
- SQV 2000 mg + rtv 100 or keto 400 mg QD:
  - Rtv >> keto as booster
  - SQV Cmin 310 vs 40 ng/mL (target >100)

[6th IWCPHT # 69, 87, 89, CROI 655]

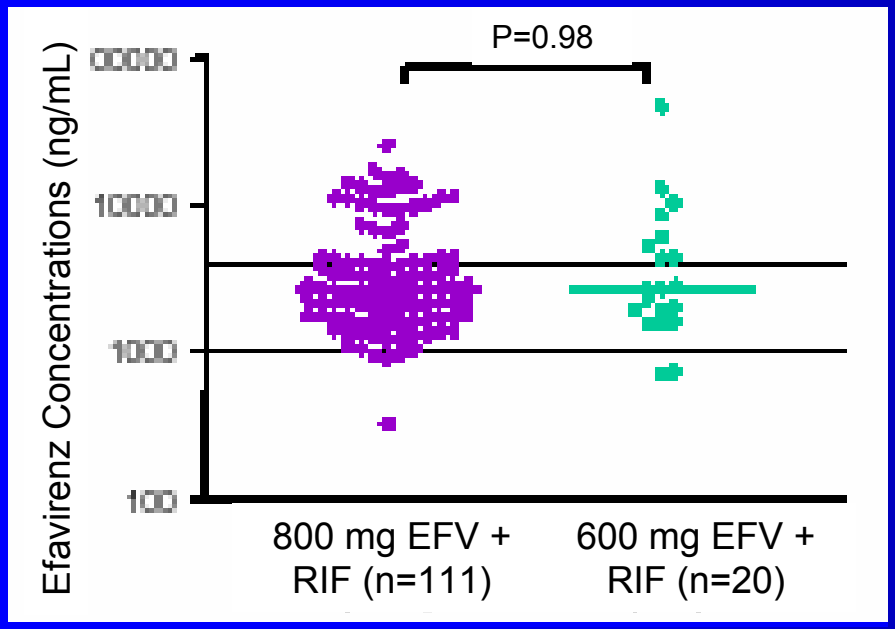
Efavirenz + TB Therapy

- PK interaction between EFV & RIF:
  - 30% ↑ Cl, 25% ↓ Cmin, 22% ↓ AUC of EFV
  - Recommend using EFV 800 mg with RIF
- However, several abstracts suggest that EFV 600 mg may provide therapeutic levels
  - 2 retrospective surveys of TDM databases
  - 1 prospective cohort study (n=17)
- Role for EFV TDM during TB therapy
  - ↓ NVP observed with RIF in Thai cohort

[Soy et al. 6th IWCPH #15; Almond et al. 6th IWCPH #19; Sheehan et al. 6th IWCPH #28; Friedland et al. CROI 2005, #891; Autar et al. 6th IWCPH #21]

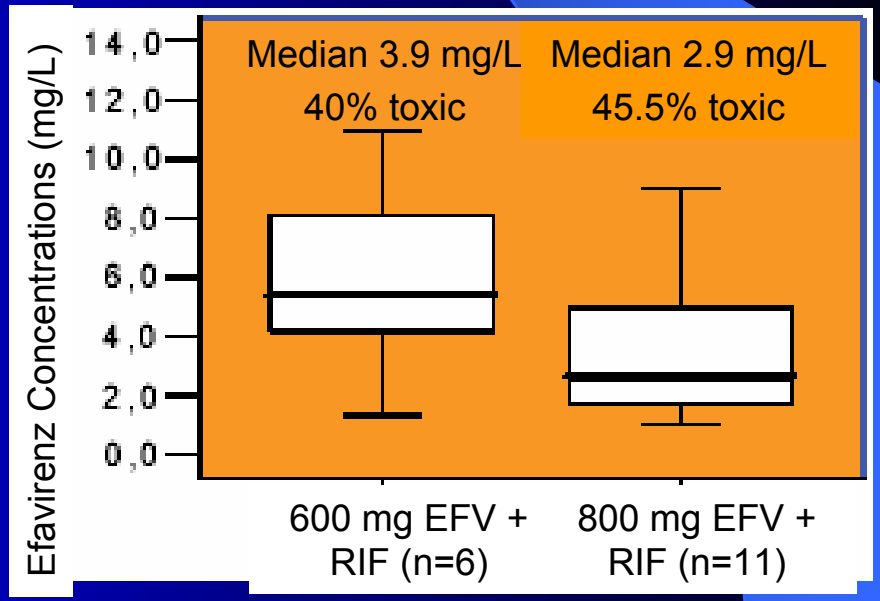
Efavirenz Concentrations in the Presence of Rifampin

- Retrospective survey of HIV+ subjects taking RIF + EFV 600 mg or 800 mg (n=131)
- No difference in EFV levels between 600-800 mg groups (median 2698 vs 2612 ng/mL)



[Almond et al. 6th IWCPH #19]

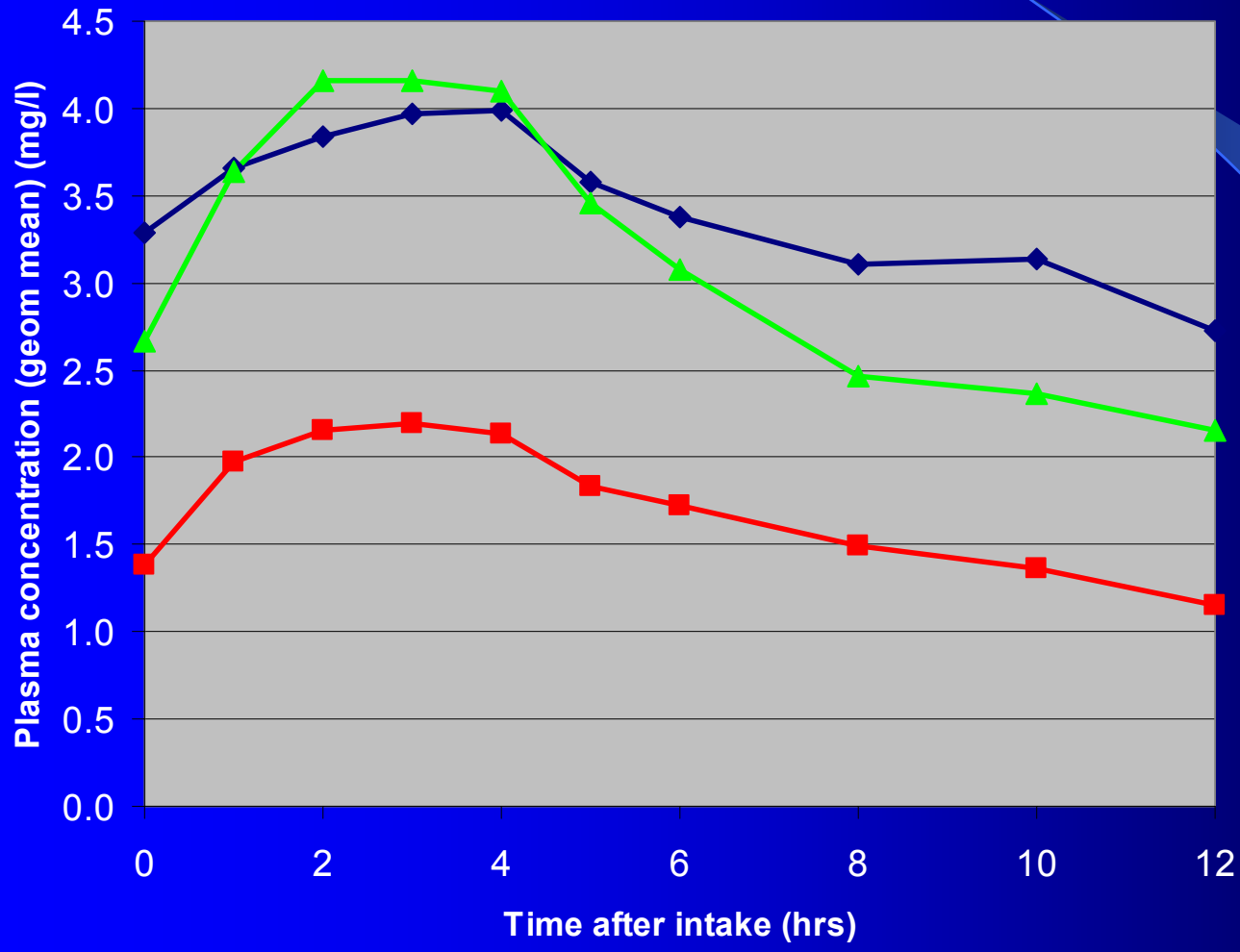
- Retrospective survey of HIV+ subjects taking RIF + EFV 600 mg or 800 mg (n=16)
- No correlation between EFV levels and dose; all EFV conc. were therapeutic



[Sheehan et al. 6th IWCPH #28]

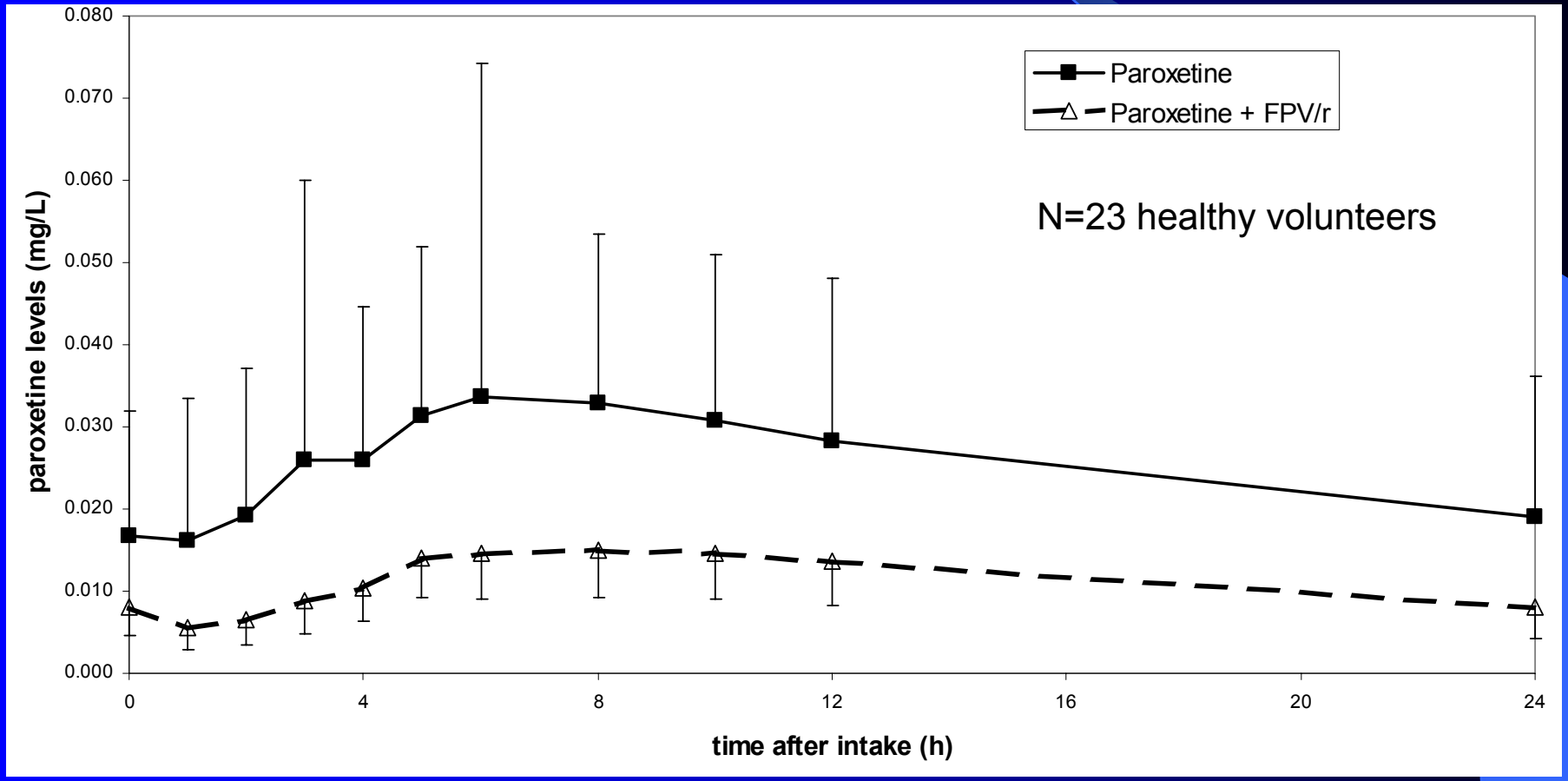
Other Drug Interactions

Lopinavir/rtv Reduces Lamotrigine Exposure by 50%



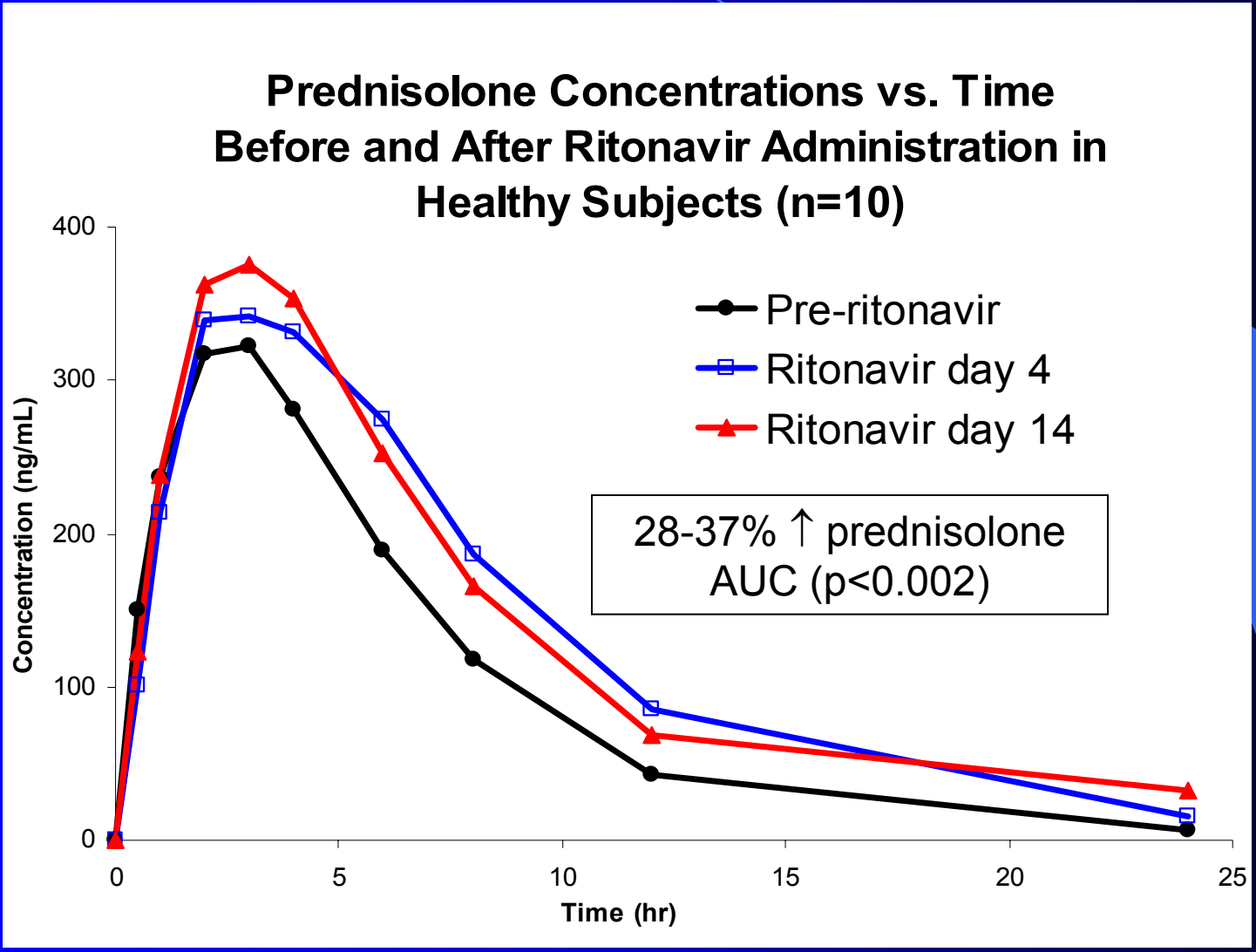
[van der Lee et al. 6th IWCPH #12]

Paroxetine Exposure is ↓ 50% When Given with Fosamprenavir 700/rtv 100 mg BID



[Burger et al. 6th IWCPH #13]

Prenisolone Exposure Is Increased With Ritonavir 200 mg BID



[Penzak et al. 6th IWCPH #14]

Lopinavir/r + Rosuvastatin

- 14 subjects on LPV/r with VL<400 & TC >6.2 mmol/L were treated with rosuvastatin x 12/7
- Rosuvastatin started at 10 mg/d, ↑ per lipid algorithm; dosage by week 12 was 20 mg (n=4) or 40 mg/d (n=10)
- LPV Cmin not affected by rosuvastatin
- Attempting to analyze rosuvastatin levels

[van der Lee et al. 6th IWCPH #25]

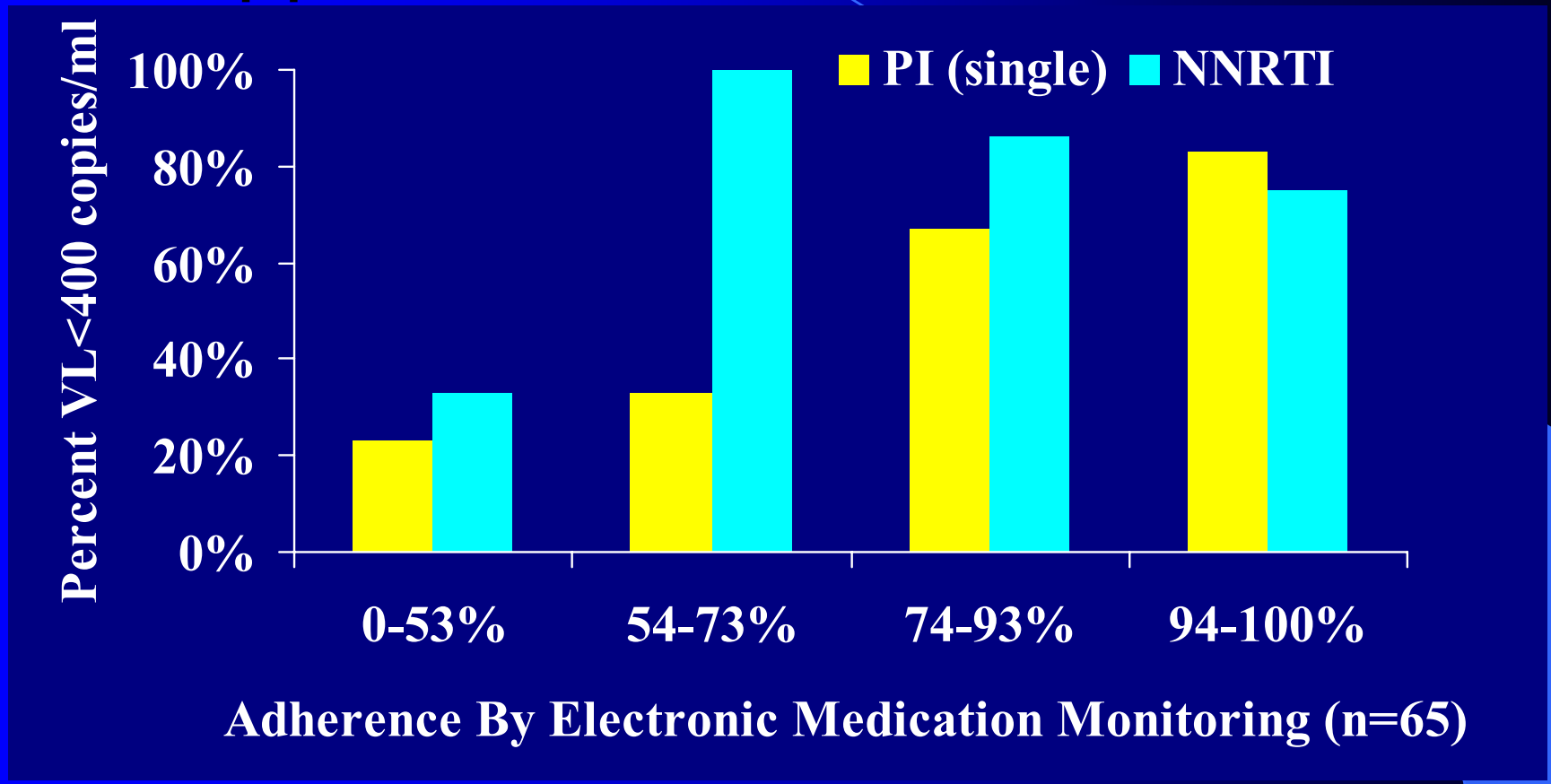
Adherence

95% Adherence Not Necessary for NNRTI Regimens

- Recruited 109 patients (56 on single PIs, 53 on NNRTI), followed median 9.1 months
  - Median 43.9 yrs, CD4 323, VL 2.5 log, 2 prior ARV regimens
- Adherence measured by unannounced pill count and electronic med monitoring
- Primary outcome was VL<400 copies/mL

Bangsberg et al 12th CROI 2005 # 616

NNRTI Regimens Can Lead to Viral Suppression at <95% Adherence



- Near complete adherence improves the probability of durable viral suppression for all regimen types

Bangsberg et al 12th CROI 2005 # 616

Adherence to QD vs. BID Regimens

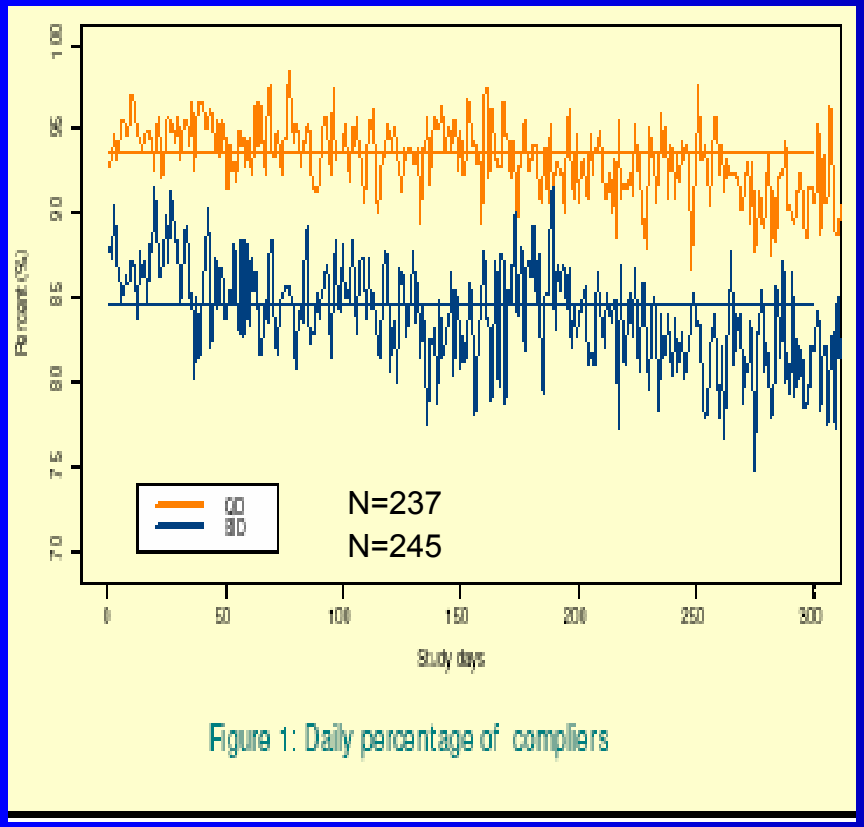


Figure 1: Daily percentage of compliers

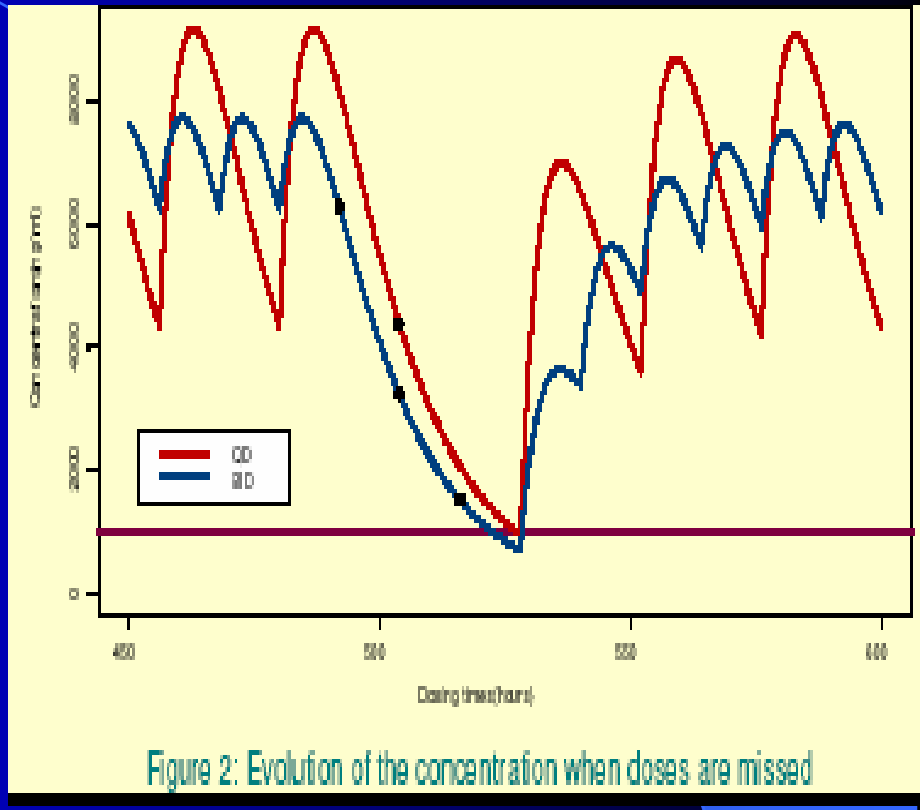


Figure 2: Evolution of the concentration when doses are missed

- Adherence: 93.5% QD vs. 84.5% BID, p<0.0001
- Pm dose missed more frequently in BID arm

- Consequence of missing 1 QD dose = missing 3 consecutive BID doses
- Such a delay was observed almost twice as often in the QD vs. BID groups

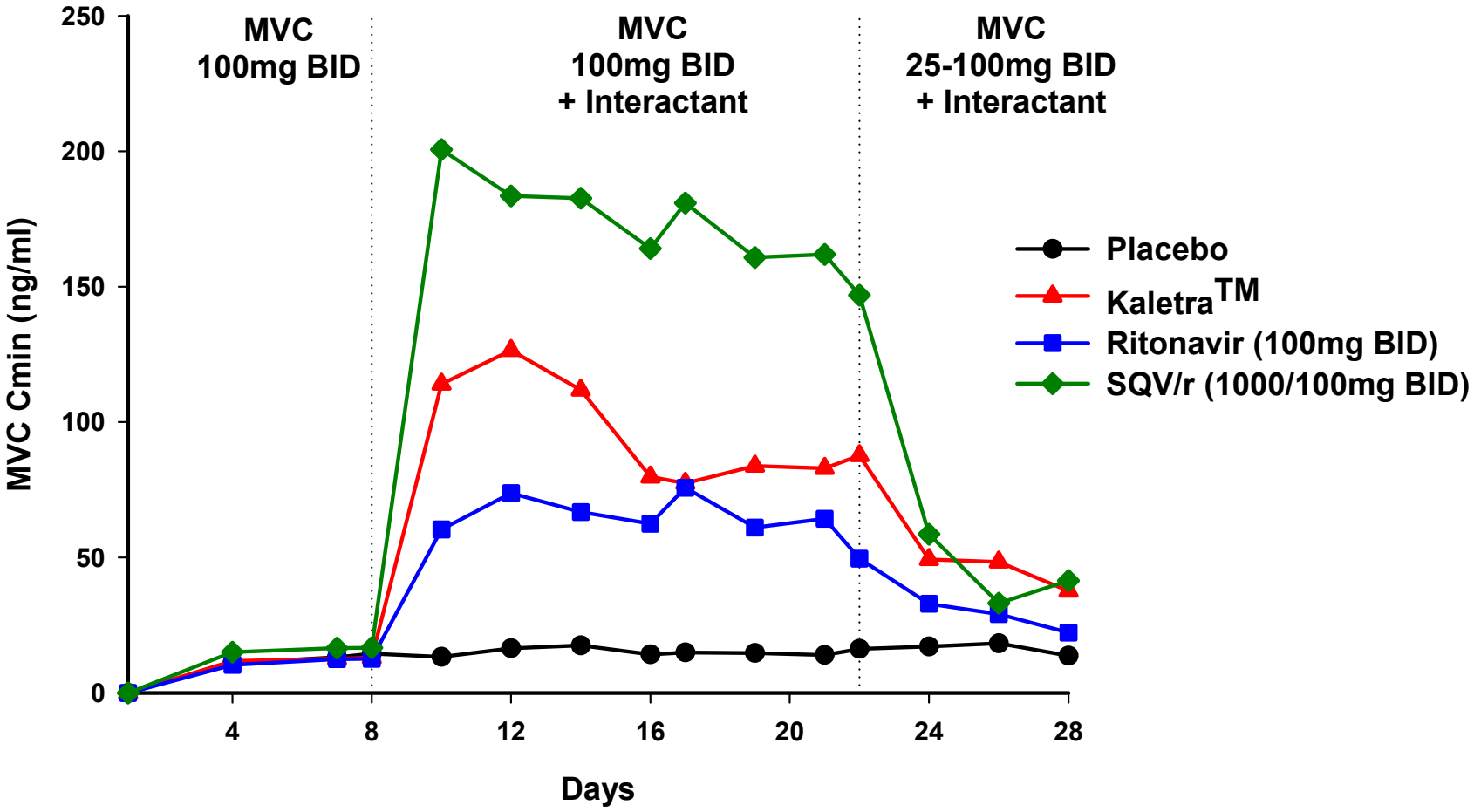
[Vrijens et al. 6th IWCPH #3]

New Drugs

CCR5 Antagonists

	Maraviroc, MVC (Pfizer)	873140 (GSK)	417690, SCH-D (SCH)
Doses under study	100-300 mg BID	400-600 mg BID	5-15 mg QD, 10-50 mg BID
Metabolism	3A4, Pgp	3A4, 2C19 (minor), weak 3A inhibitor	3A4
Food effect	↓ ≤50% AUC	↑ AUC 47-63%	
Inducers	↓AUC 70% (EFV, RIF)		↓ AUC 81% (EFV)
Inhibitors	↑ AUC 2.5-9.8 fold (PIs, keto)	↑ AUC 7.7 fold (LPV/r)	↑ AUC 400-500% (LPV, rtv)
Tenofovir	No interaction		No interaction

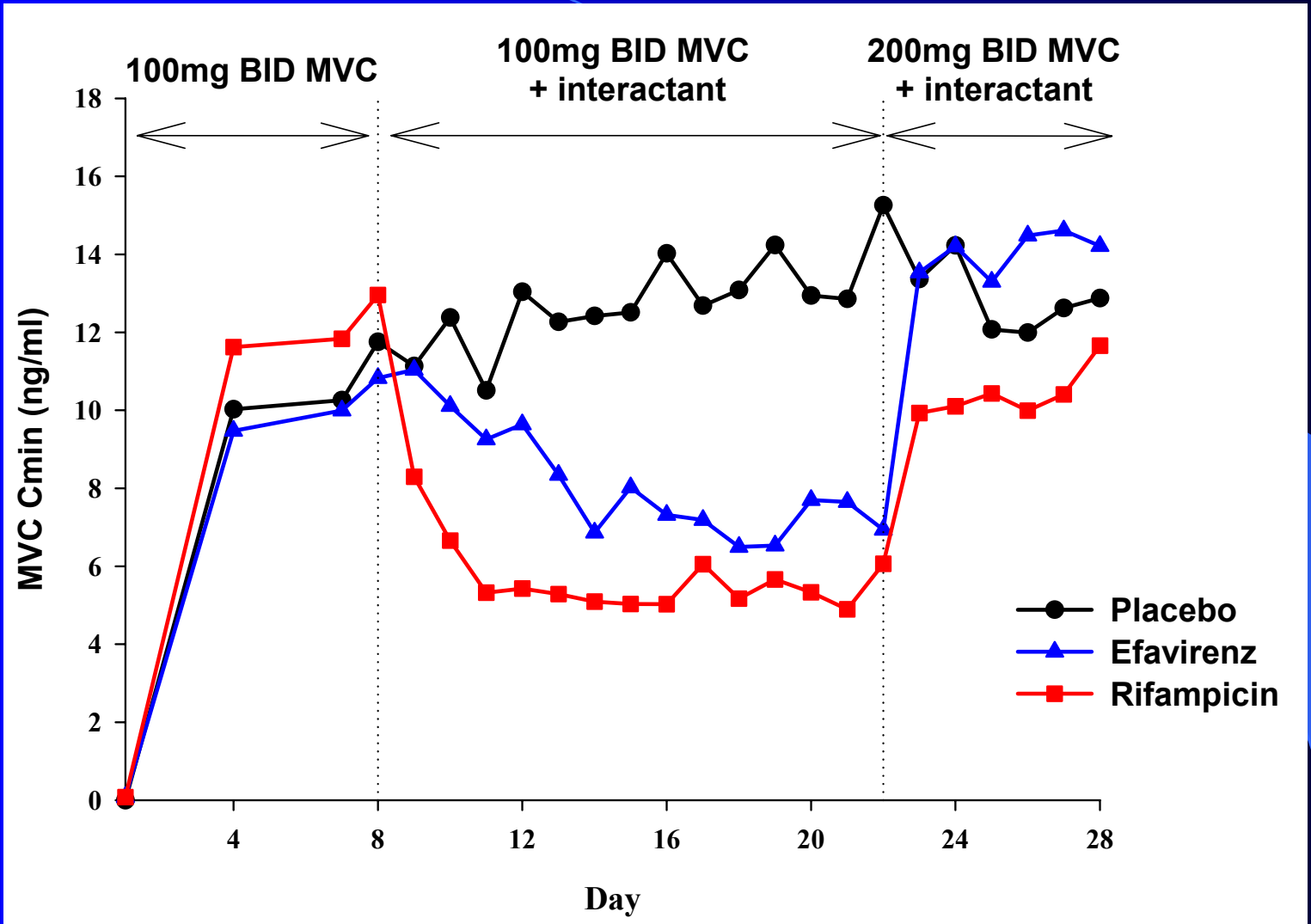
Maraviroc + Metabolic Inhibitors



- Effect of P450 inhibitors can be corrected by dose adjustment (1/2 MVC dose)

[Muirhead et al. 6th IWCPH #76]

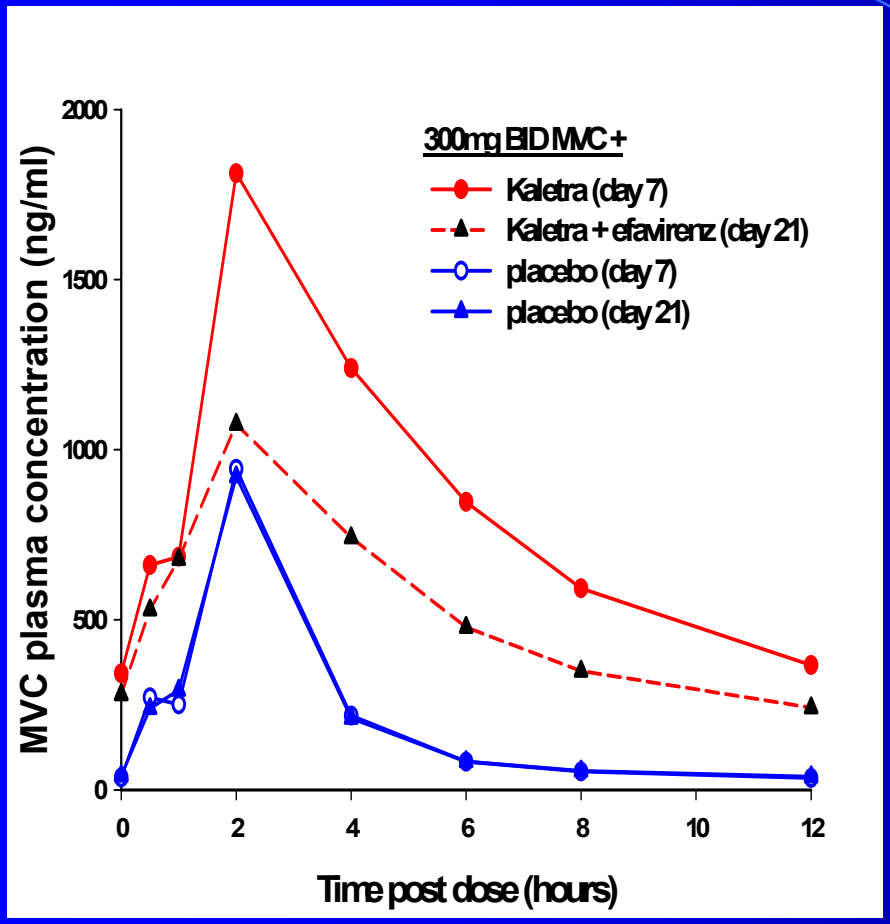
Maraviroc + Metabolic Inducers

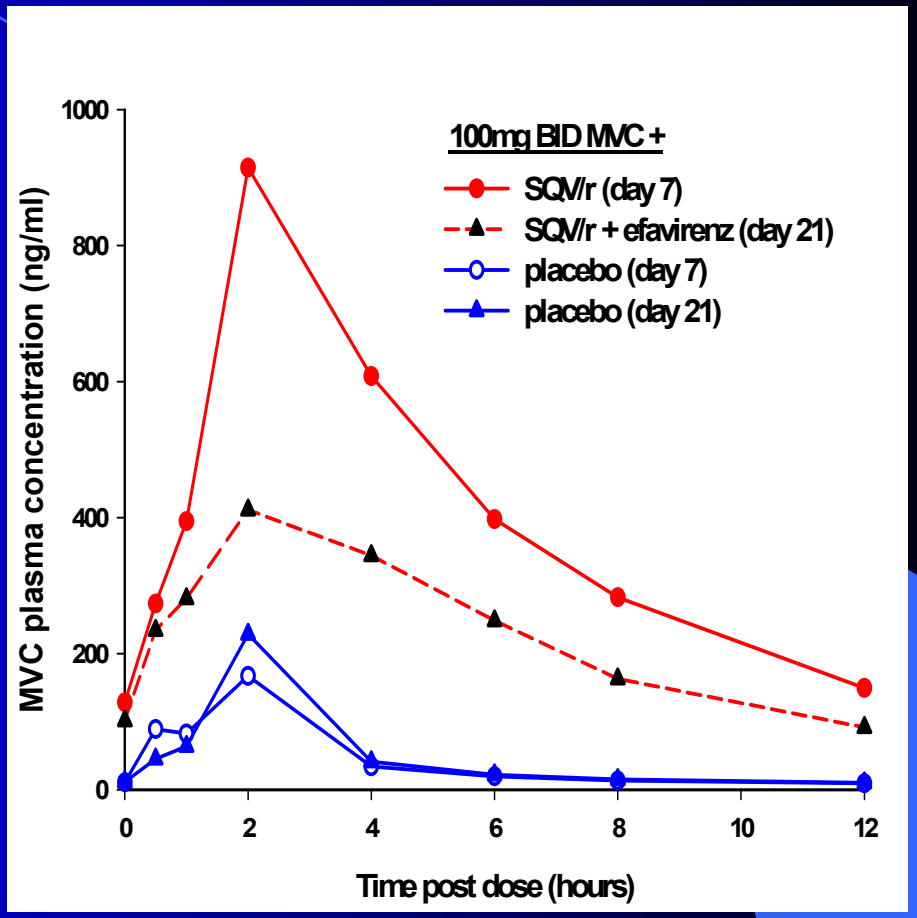


- Effect of P450 inducers can be corrected by dose adjustment (2x MVC dose)

[Muirhead et al. 6th IWCPH #76]

Maraviroc + PIs and EFV





- Efavirenz approximately halves the effect of the CYP3A4 inhibitors

[Muirhead et al. 6th IWCPH #76]

TMC Drugs (Tibotec)

- TMC 114 (PI): 400/100 rtv mg BID
  - No interaction with omeprazole 20 mg QD or ranitidine 150 mg BID
- TMC 125 (NNRTI): 800 mg BID
  - Significant food effect (give with food)
  - No interaction with ddI-EC (given 2 hrs before)
- TMC 278 (NNRTI): 25, 75, 150 mg QD
  - Take with food (↑ AUC 45%)
  - Tenofovir AUC ↑ 24%, Cmax ↑ 21%, Cmin ↑ 24%, no effect on TMC278

[Hoetelmans et al. 6th IWCPH #17, 29, 18]