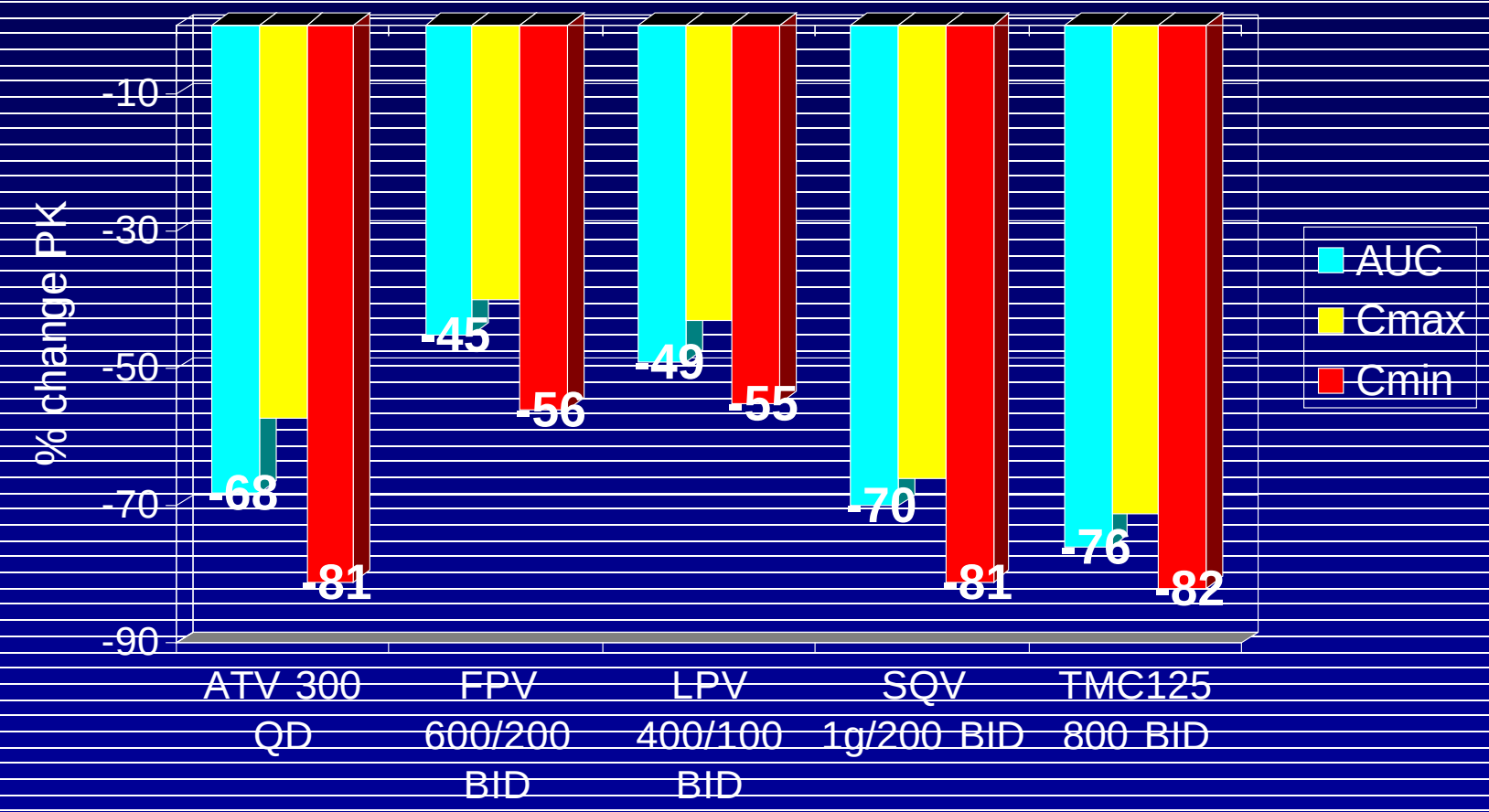
REPORT FROM

13th Conference on Retroviruses and Opportunistic Infections (CROI)

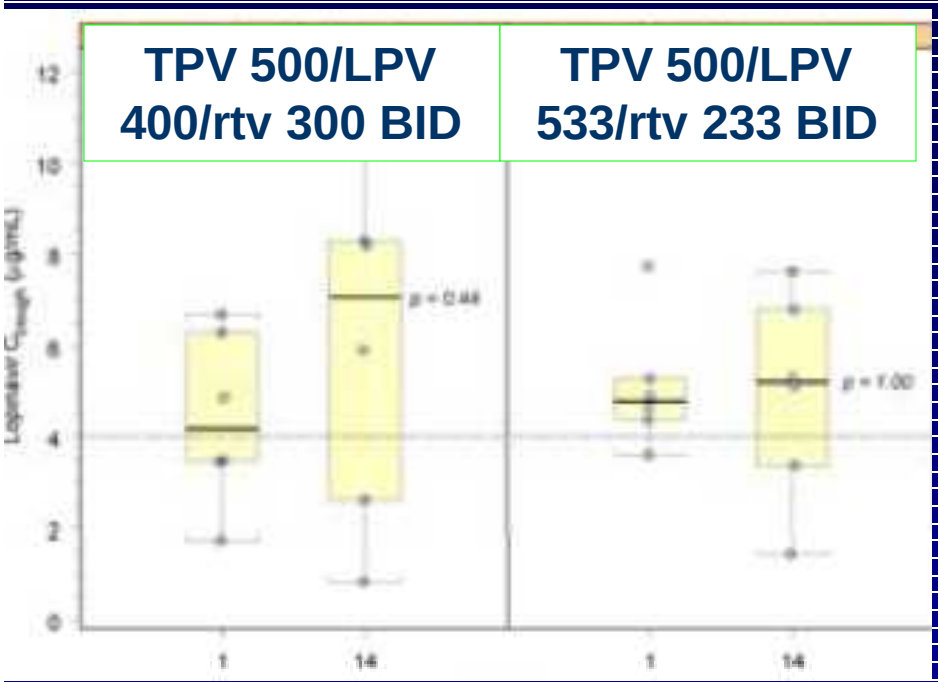
February 5–8, 2006
Denver, CO

Tipranavir Significantly Reduces Concentrations of Other ARVs



[Leith et al. 5th IWCPHT 2004, #5.1; Scholler et al. #583, CROI 2006; Sabo et al. 7th IWCPHT 2006, #41]

Dosing PIs with Tipranavir



- TDM study (n=20):
  - **a) TPV 500/LPV 533/rtv 233 mg BID**
    - 74% achieved therapeutic LPV Ctrough
  - **b) TPV 500/FPV 1400/rtv 200 mg BID**
    - 67% achieved therapeutic APV Ctrough

TDM recommended!

- 2 dosing strategies studied in 13 pts on stable LPV/r, VL≤50
- LPV levels generally ↑ vs 400/100 mg BID alone but variability also ↑↑

[Harris et al. #584; Peytavin et al. #591, CROI 2006]

Atazanavir/PI Combinations

ATV 300 mg QD + LPV 400/100 mg BID

- ATV Cmin slightly > vs. ATV 300 mg/100 mg QD

ATV 200/SQV 1500 mg BID

- SQV levels << vs. SQV/r, 75%> 100 ng/mL
- ATV levels ≈ ATV 400 mg QD

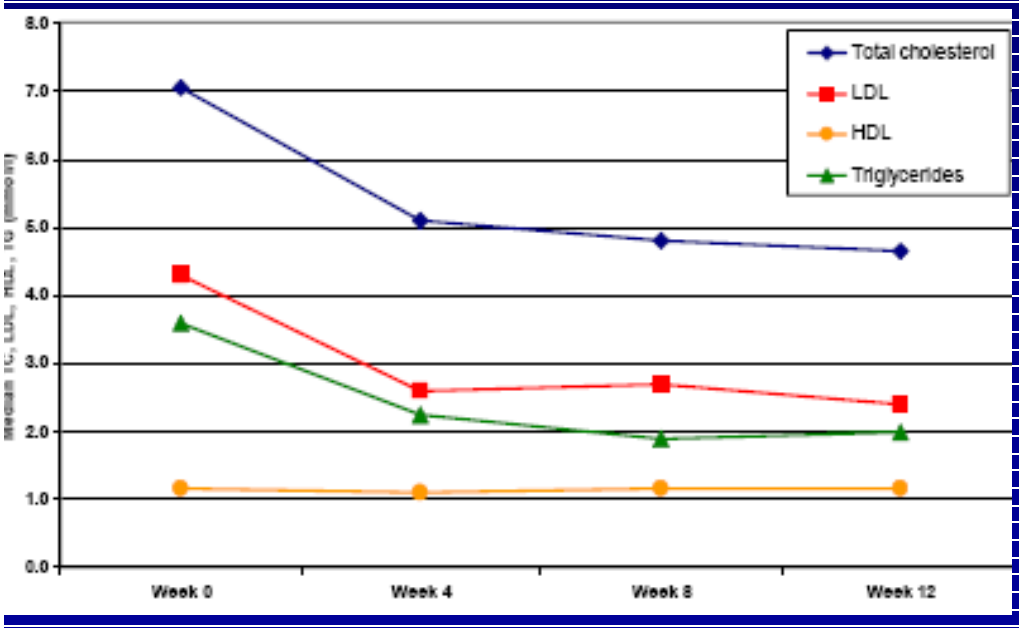
ATV 400 mg/FPV 1400 mg QD

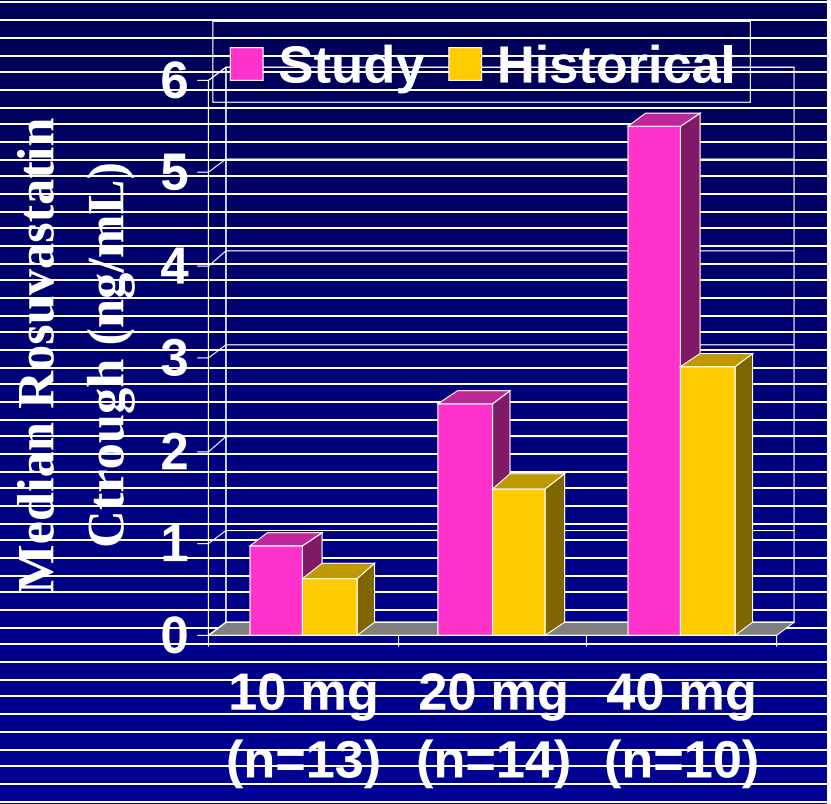
- APV AUC ↑ 78%, C_{24} ↑ 283% vs. FPV 1400 mg QD (~FPV 1400 mg BID)
- ATV AUC ↓ 33%, C_{24} ↓ 57% vs. ATV 400 mg QD

[Pham et al. #585; King et al. #586; Clay et al. #587, CROI 2006]

Rosuvastatin + Lopinavir/rtv in HIV-infected subjects (n=22)

- Pts stable on LPV/r (VL<400) with TC>6.2 mmol/L treated with rosuvastatin 10 mg for 12 weeks
- ROS dose ↑ at wks 4, 8 if target lipids not achieved

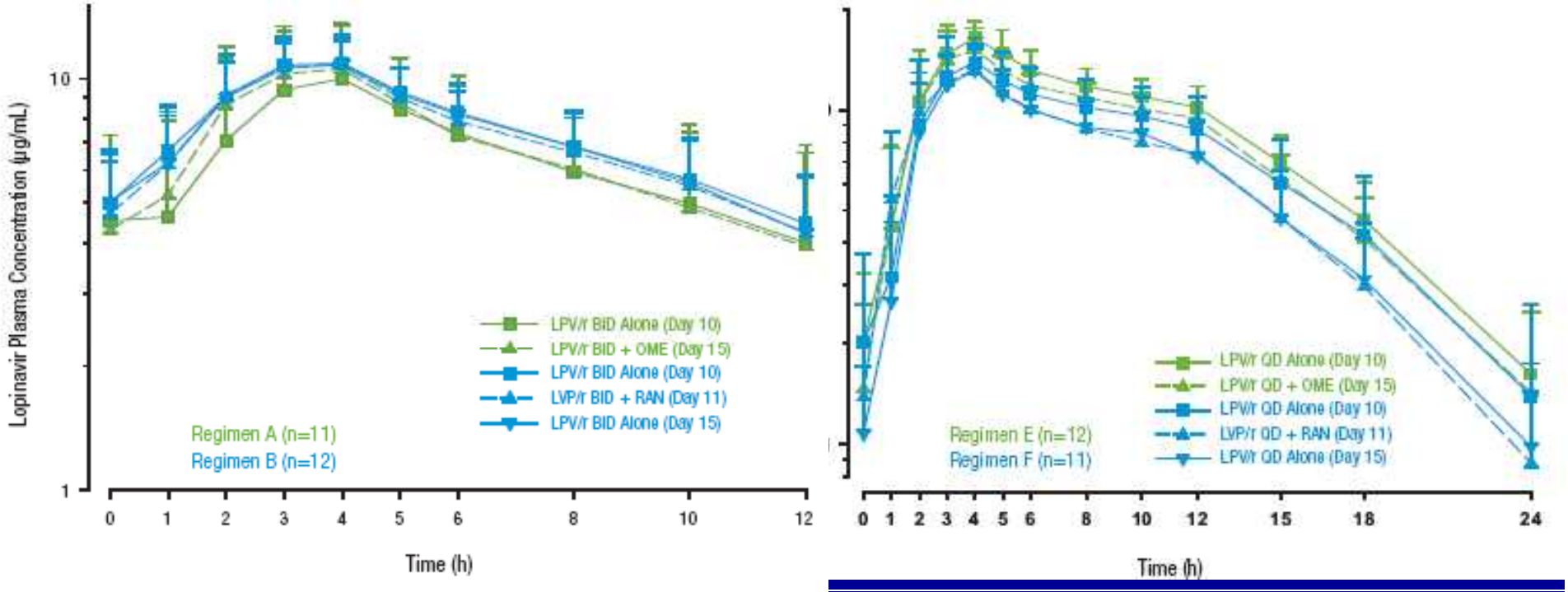




- ↑ ROS Ctrough compared to historical controls
- ROS is Pgp substrate?

[van der Lee et al. CROI 2006, #588]

No Effect of Ranitidine or Omeprazole on Kinetics of QD or BID Lopinavir/r Tablets



LPV/r BID + OMP 40 mg QD x 5/7 LPV/r QD + RAN 150 mg QD

[Klein et al. CROI 2006, #578]

Negative Dual Interaction between Efavirenz & Carbamazepine

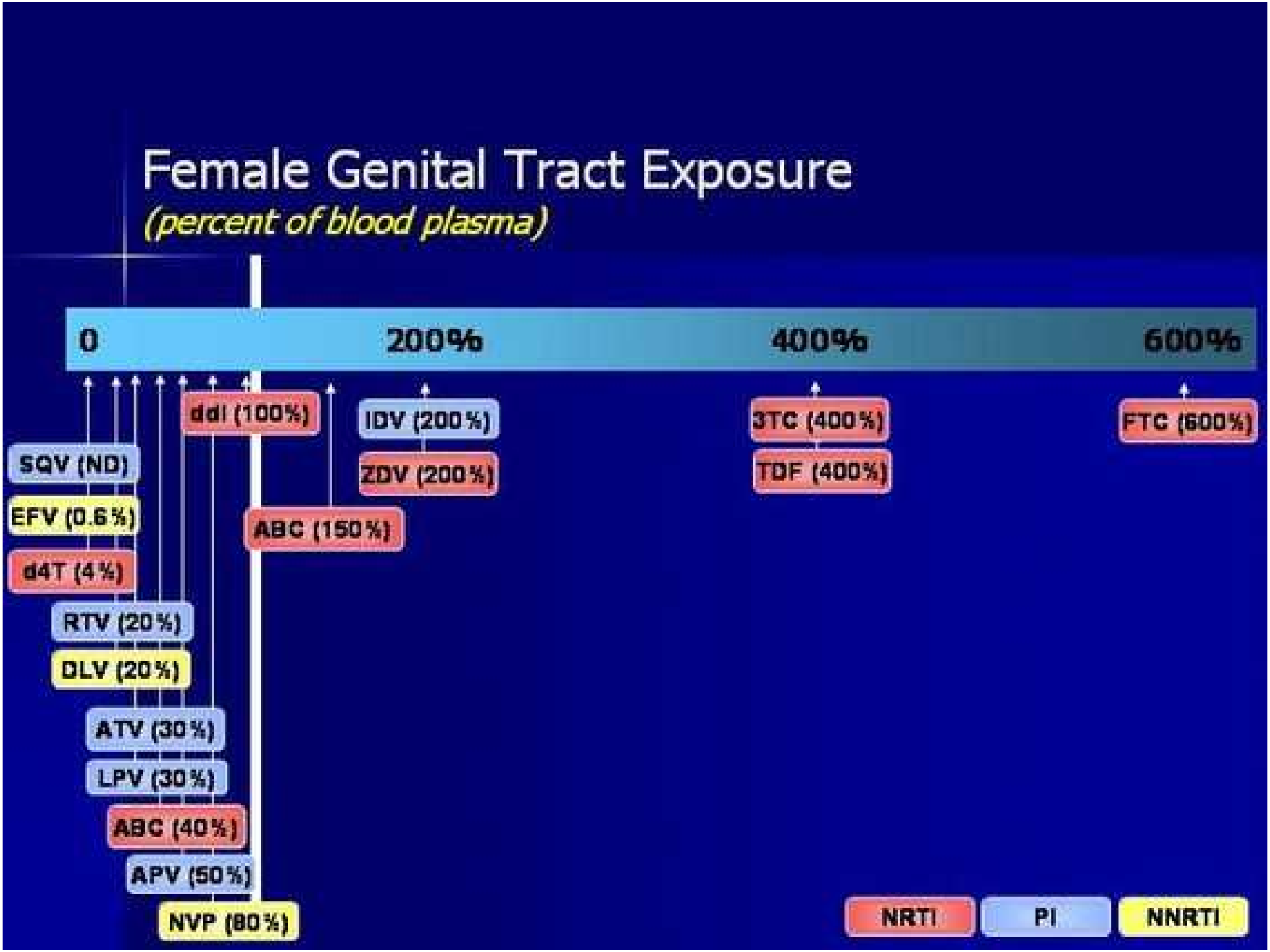
- Co-administration of EFV 600 mg QD with CBZ 400 mg QD in healthy subjects:
  - ↓ AUC 36%, Cmax 21%, Cmin 47% of EFV
  - ↓ AUC 27%, Cmax 20%, Cmin 35% of CBZ
  - kinetics of active CBZE metabolite unchanged
- Recommendations on dose adjustment not available; use alternate anticonvulsant

[Kaul et al. CROI 2006, #575a]

Low Antiretroviral Exposures in Pregnancy

- Nelfinavir
  - 45% had NFV Cmin <1 mg/L (n=40); 1500 mg BID, 2/8 still low
- Lopinavir
  - Cohort 1) regular dose throughout preg., adequate Ctrough
  - Cohort 2) low LPV in 2nd trimester; used 533/133 mg BID in 3rd trimester
  - Difference in weight of women between 2 groups?
- Tenofovir 600 mg at onset of labour:
  - maternal AUC, Cmax < non-pregnant
  - Cord blood:maternal ratio 0.65, low infant TDF
  - phase 2: mother 900 mg x 1; infant 4 mg/kg ASAP after birth

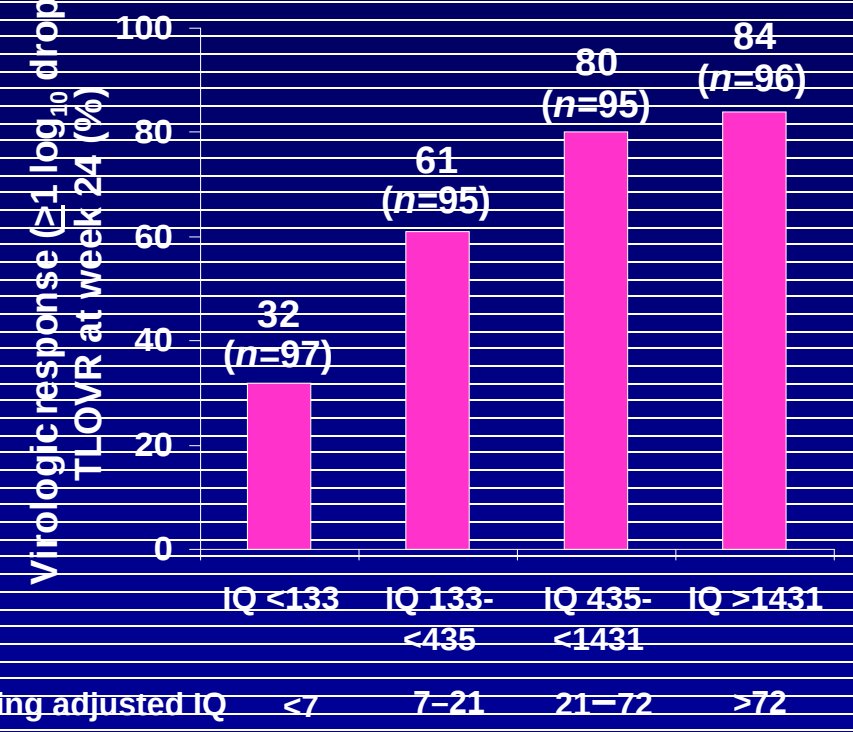
[Rodman et al. #708; Khuong-Josses et al. #707; Lyons et al. #709; Mirochnick et al. #710, CROI 2006]


Female Genital Tract Exposure
(percent of blood plasma)
0
200%
400%
600%
ddI (100%)
IDV (200%)
3TC (400%)
FTC (600%)
SQV (ND)
ZDV (200%)
TDF (400%)
EFV (0.6%)
ABC (150%)
d4T (4%)
RTV (20%)
DLV (20%)
ATV (30%)
LPV (30%)
ABC (40%)
APV (50%)
NVP (80%)
NRTI
PI
NNRTI

PK/PD analyses of TMC114

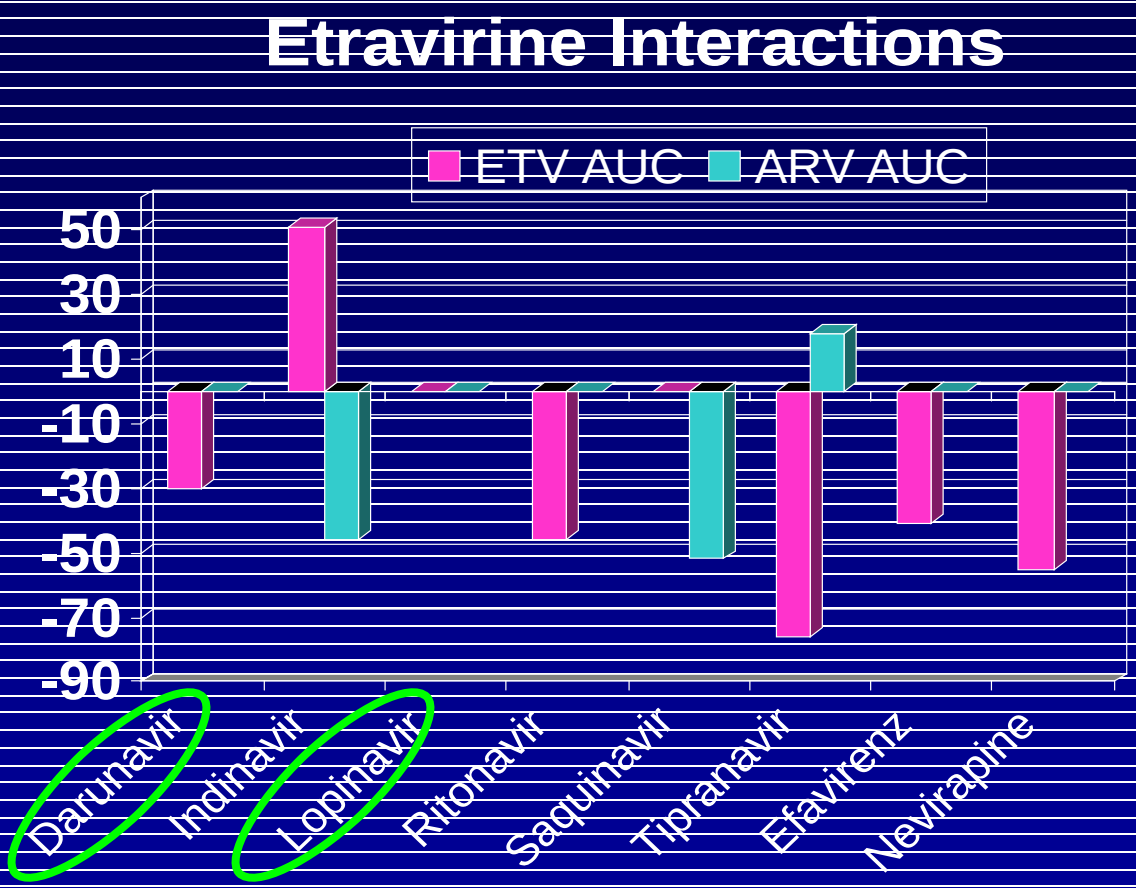
- PK from POWER I and POWER II
  - Blood sampling in 468 subjects randomized to TMC114 arms
  - IQ = $\frac{\text{Steady state TMC114 } C_{0h}}{\text{Baseline TMC114 } EC_{50}}$
- Found significant relationship between TMC114 PK and efficacy
  - IQ was strongest predictor of virologic response

Virologic response at Week 24 by TMC114 IQ C_{0h}



Etravirine (TMC-125)

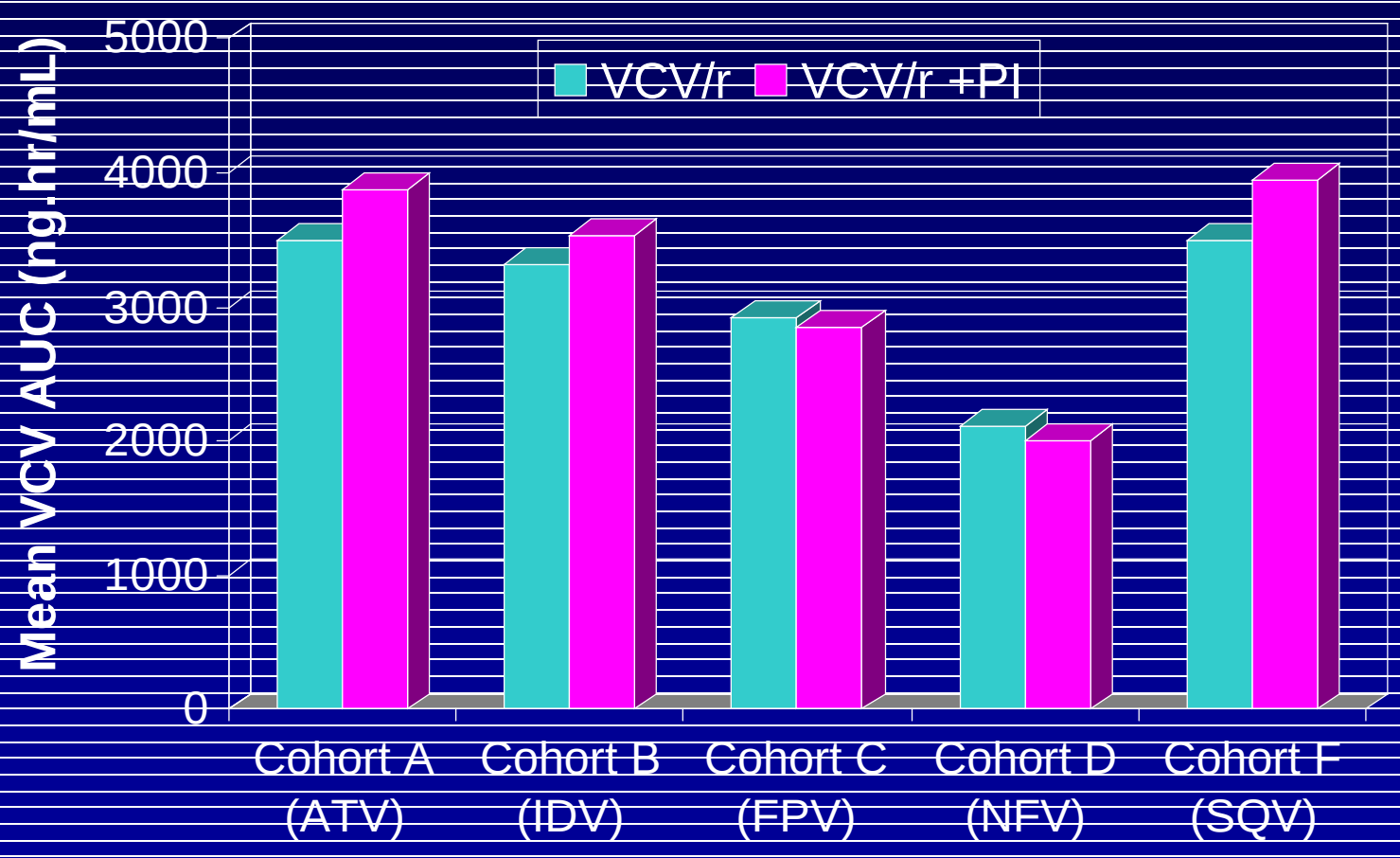
- NNRTI
- 200 mg BID
  - food ↑ absorption 51%
- Metabolized by CYP and GT, CYP3A4 inducer
- Sildenafil:
  - 57% ↓ sildenafil AUC



- Avoid combining with SQV, IDV, TPV, EFV, NVP

[Harris et al. #575b; Boffito et al. #575c; Scholler et al. #583; CROI 2006; Scholler-Gyure et al. 7th IWCPHT 2006, #45]

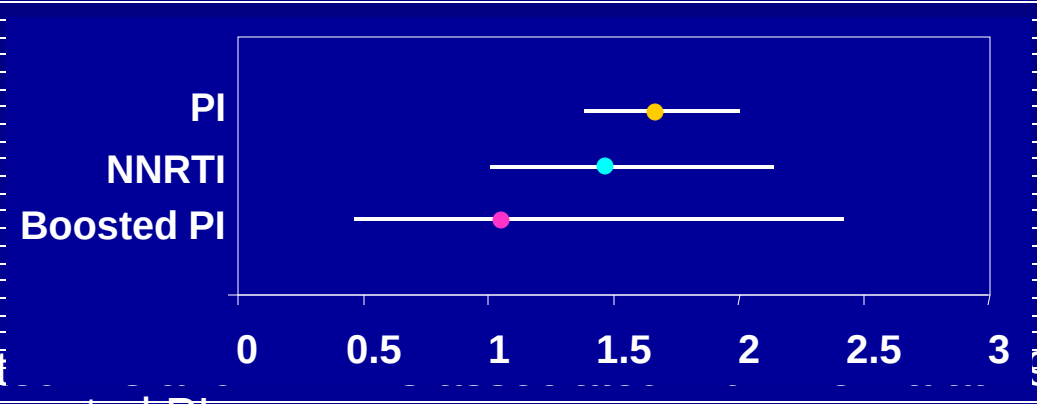
Vicriviroc Can Be Added to Boosted PI Regimens



[Sansone et al. #582, CROI 2006]

Adherence: Boosted PIs are more forgiving of suboptimal performance than non-boosted PIs or NNRTIs

- HOMER Cohort study of 1634 patients (1996–2003) with 2 VL <500 c/mL followed until VL failure (VL ≥1000 c/mL; median follow-up 29 months)
  - ART: 46% PI, 39% NNRTI, 15% boosted PI
  - Adherence calculated and stratified ≥95% or <95% based on pharmacy scripts filled
- 606 pts (37%) experienced breakthrough viremia
- <95% adherence most strongly associated with breakthrough for PI and NNRTI, but not boosted PI



- Conclusion: Unboost[illegible]95% adherence, but not boosted PIs

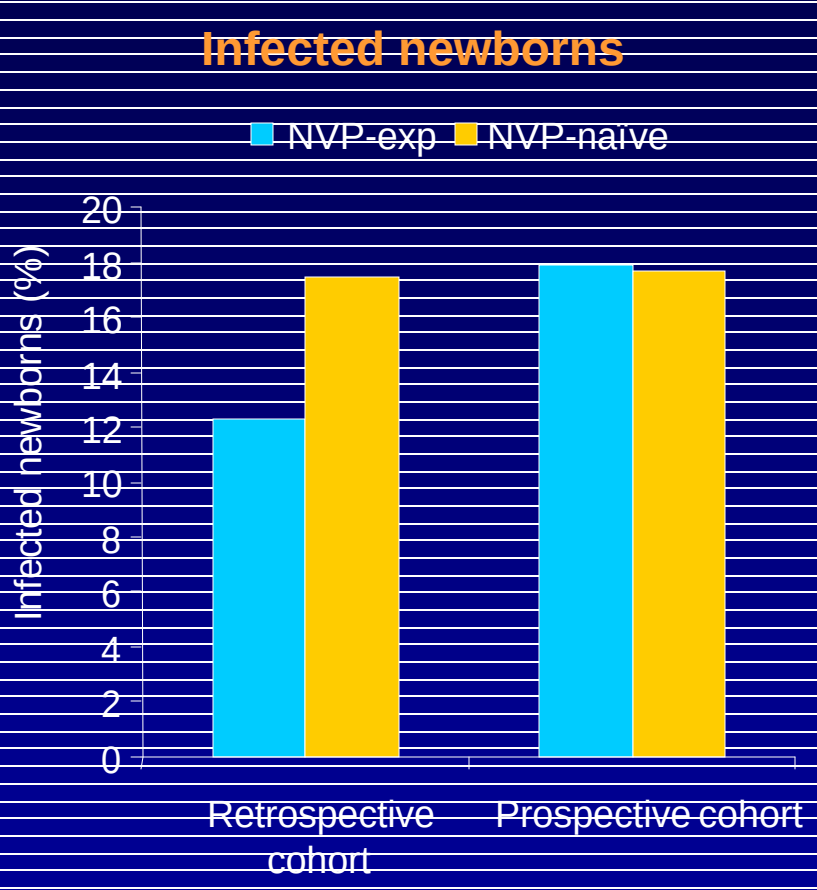
Transmission & Pathogenesis

Male circumcision for prevention of HIV transmission

- Prevalence of male circumcision (MC) varies by country and region:
  - US prevalence 55%, Europe lower
- On population basis, MC rates associated with HIV prevalence:
  - African countries with <20% MC have significantly higher prevalence than countries with >80% MC
  - Multiple cohort studies support long-term effect of risk reduction in those with MC
- Biologically plausible mechanisms for protection by MC include: 9-fold fewer HIV targets in stratified epithelium vs mucosal inner foreskin; infection studies
- 3 randomized, controlled trials of MC vs control accrued:
  - First study of 3520 subjects in S Africa stopped by DSMB; RR of infection 0.4 with MC; 4% adverse events
- WHO concludes that MC should be made available, but awaits 2 ongoing studies for firm recommendation

Repeated single-dose NVP in subsequent pregnancies

- Two cohorts studied:[1]
  - Retrospective: pts from HIVNET-012 with previous ZDV (*n*=41) or NVP (*n*=57) use
  - Prospective: pts who were NVP-naïve (*n*=63) or received prior NVP (*n*=30)
- No significant differences in rate of infected infants in both cohorts
- Consistent results presented from separate cohorts (Soweto, *n*=76; Abidjan, *n*=35)[2]
- Results are still not conclusive (lack of resistance, HIV RNA, CD4+ data, possible drop-out of infants because of death in the retrospective cohorts)



1. Eure C, *et al. 13th CROI*, Denver 2006, #125; 2. Martinson N, *et al. ibid*, #722

Treatment interruptions

TIME-BASED

Staccato (wk on/wk off)[1]

- Stopped for failure

Trivacan[2]

- 2 months off/4 months on
- Ongoing

Windows[3]

- 8 weeks on/8 weeks off
- Completed

ISS / PART[4]

- 1, 2, 3 months off
- Completed

CD4-GUIDED

Staccato[1]

- 350 on/off
- Completed 96 weeks

Trivacan[2]

- 250 on/350 off
- Stopped early

SMART[5]

- 250 on/350 off
- Stopped early

1. Ananworanich J, *et al. 13th CROI*, Denver 2006, #102; 2. Danel C, *et al. ibid*, #105LB; 3. Marchou B, *et al. ibid*, #104; 4. Palmisiano L, *et al. ibid,* #103;; 5. El-Sadr W, *et al. ibid,* #106LB

SMART Study

- Study design:
  - Eligibility: CD4+ >350 cells/mm^3
- Randomization:
  - Viral suppression (VS) arm: Continuous ARV
  - Drug conservation (DC) arm: No ARV until CD4+ <250 cells/mm^3, then treat until CD4+ >350 cells/mm^3 (verified), then stop
- 5472 patients enrolled; stopped early by DSMB
- Primary endpoint: Clinical events / death
- 3.7 (DC) vs 1.5 (VS) events / 100 pt-yrs
  - Relative Risk 2.5; $p<0.0001$
- Consistent results for all subgroups; eg, by baseline and nadir CD4+ counts

Conclusion

- This strategy cannot be recommended

SMART Study: Primary endpoint and components

Endpoints	# Pts with events	Relative Risk
Progression of disease or death	164	2.5
Death	84	1.9
Serious HIV events	21	6.1
Severe complications*	114	1.5
*CVD, renal, hepatic events (fatal/nonfatal)		

Trivacan Study

- Patients on suppressive HAART with CD4 >350 cells/mm^3 and VL <300 c/mL in Côte D'Ivoire randomized to:
  - Continuous therapy (*n*=110)
  - CD4+ guided therapy (On at 250 cells/mm^3, Off at 350 cells/mm^3) (*n*=216)
  - 2 months Off, 4 months On therapy (*n*=325)
- End-points: Death or serious morbidity
- CD4-guided arm 2.6-fold higher event rate over continuous therapy strategy (95% CI 1.3–5.6; *p*=0.001)
- Consistent with SMART results
- Time-based arm was is ongoing

Staccato: STI with higher CD4+ thresholds

- Eligibility: ARV naïve; treated with 2 NRTI/boosted PI
  - HIV RNA <50 c/mL, CD4+ >350 cells/mm^3
- Randomized to:
  - Continuous ARV (*n*=154)
  - Stop ARV >350 cells/mm^3, restart <350 cells/mm^3 (*n*=299)
  - In interruption arm after 96 weeks all patients restarted therapy
- Primary endpoint: Progression to AIDS/death (no difference) and proportion of CD4 >350 cells/mm^3 at end of randomization (higher in continuous arm) and after resuming ARV (no difference)

	CD4-guided arm	Continuous arm	*p*
AIDS events	0	0	
Deaths	1	1	
% <50 c/mL	91%	92%	
Time on ARV	37.5%	99%	
Oral candidiasis	3.5%	0%	0.04
Neuropathy	1.9%	4.6%	0.03

Ananworanich J, *et al. 13th CROI,* Denver 2006, #102

"Time-based" STIs
Window Study

- Continuous ART (n=203) vs STI (n=200) with 8 weeks on/8 weeks off (96-week study)
- Eligible: CD4+ ≥450 cells/mm^3 and HIV RNA ≤200 c/mL for ≥ 6 months
  - Exclude: CD4+ nadir <100 cells/mm^3, ABC or NVP in regimen, HBV infection
- Primary endpoint: confirmed CD4+ <300 cells/mm^3
  - *n*=403; 362/403 complete 96 weeks
  - Overall baseline CD4+ = 744 cells/mm^3
- ITT failures: 7 on STI arm, 3 on continuous arm (*p*=NS)
  - STI arm: 52% time on ART (vs 100% in continuous arm)
  - % <400 c/mL *: 81% (STI arm) vs 90% (continuous); *p*=0.02
  - No AIDS events
  - Thrombocytopenia: STI arm (*n*=9), continuous arm (*n*=2)

*After 8 weeks on therapy

Comparison of CD4-Guided Treatment Interruption Studies

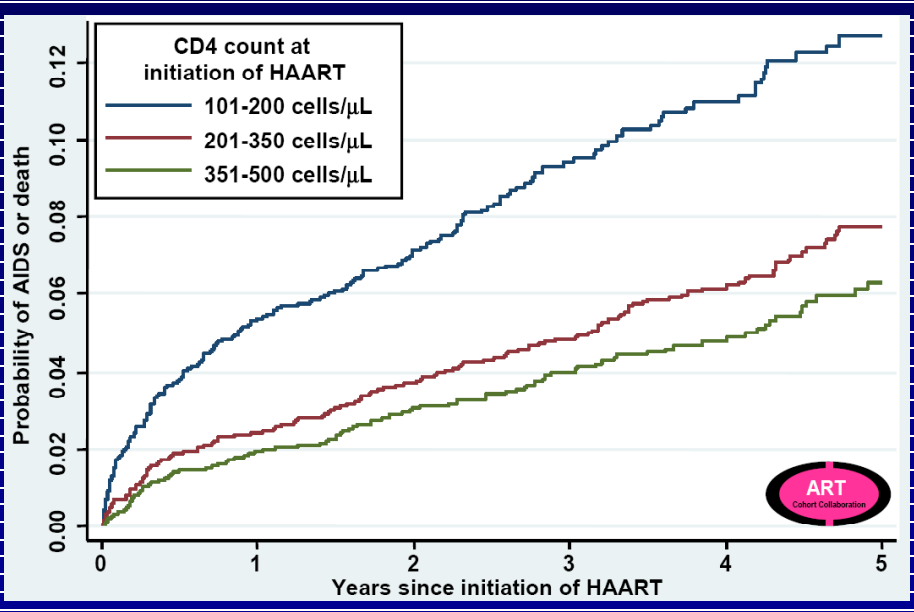
	Staccato	Trivacan	SMART
# of pts	430	326	5472
PY FU (in STI arm)	490	?	3062
CD4 at Stop	350	350	350
CD4 at Start	350	250	250
Median age (years)	35	34	46
AIDS, death/100PY			
STI	0.2	17.6	3.1
CT	0.4	6.7	1.4
Time on ARV before study (months)	15	7	72

ARV Therapy – Current

Clinical outcomes related to timing of initiation of ART

- Timing of initiation of ART in naïve subjects (*n*=10,885) in the ART Cohort Collaboration (ART-CC)
  - Median follow-up 2.7 years
- Hazard ratio for progression to AIDS or death by CD4+ cells at initiation of ART
  - <200 vs 201–350 cells/mm^3 HR 2.93 (95% CI: 2.41, 3.57)
  - 201–350 vs 351–500 cells/mm^3 HR 1.26 (95% CI: 0.94, 1.68)
- Trend favoring outcomes for ART initiation at >350/mm^3 CD4+ T-cells

Cumulative probability of AIDS/death according to CD4+ count at initiation of HAART



Sterne J, *et al. 13th CROI*, Denver 2006, #525 (courtesy of ART Cohort Collaboration)

Toxicity in relationship to the timing of initiation of ART

- HIV Outpatient Study (HOPS) cohort prospectively followed >8000 patients
- Assessed relationship between timing of ART and development of select toxicities
- CD4+ ≥200 cells/mm^3 associated with decreased risk of toxicity

Factor	Condition		
	Renal	PN	LipA
Cases/ Total	113/ 2156	301/ 2222	176/ 361
Pre-HAART CD4+ cells/mm^3 Adjusted OR (95% CI) vs <200 cells/mm^3			
200–349	0.5 (0.3, 0.8)	0.6 (0.5, 0.9)	0.4 (0.2, 0.8)
350–499	0.7 (0.4, 1.2)	0.6 (0.4, 0.9)	0.3 (0.2, 0.6)
≥500	0.3 (0.2, 0.6)	0.7 (0.5, 0.9)	0.5 (0.3, 0.9)

PN = peripheral neuropathy
LipA = lipoatrophy

Lichtenstein K, *et al. 13th CROI,* Denver 2006, #769

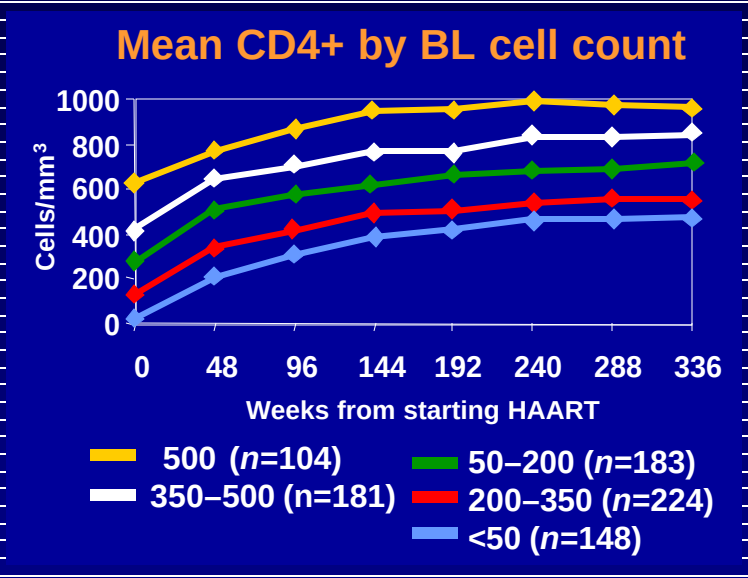
Long-term CD4+ response to ART

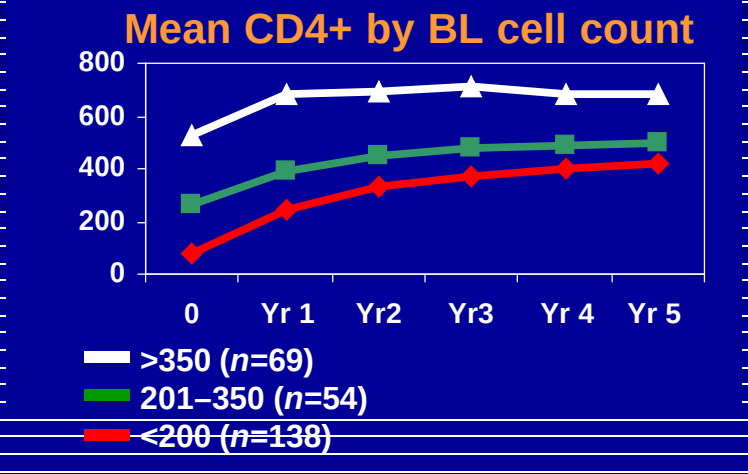
Dutch ATHENA cohort (*n*=840)[1]

- ART started 1/97–6/98 (7 yr follow-up)
- Annual increase in CD4+ declined with longer follow-up ($p<0.0001$)
- Smaller annual increase with:
  - Older age
  - Time with HIV RNA >500 c/mL

JHU HIV clinical cohort (5-yr follow-up)[2]

- ≥1year follow-up after initiation of ART
- Persistent HIV RNA <400 c/mL during ART
- Multivariate analysis of risk for reduced CD4+ response
  - IDU
  - Gender, race, type of ART are NOT associated with CD4+ change

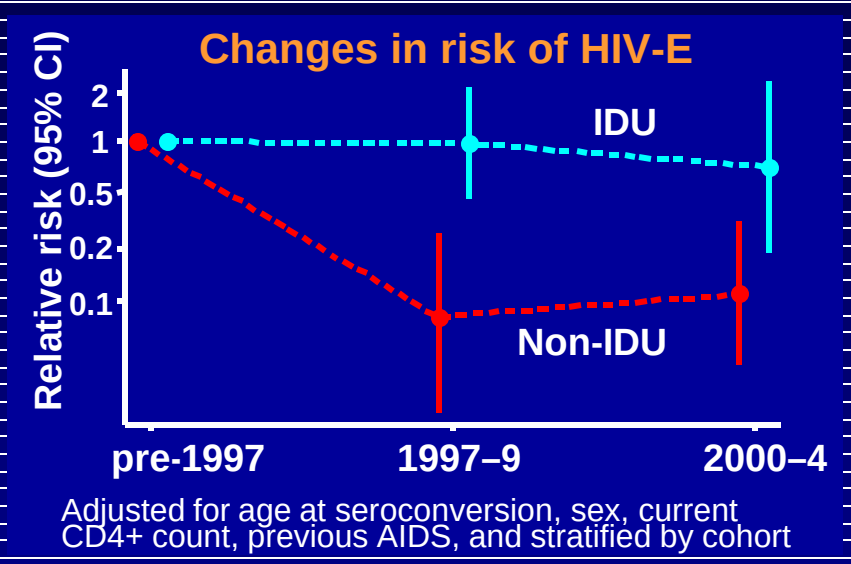




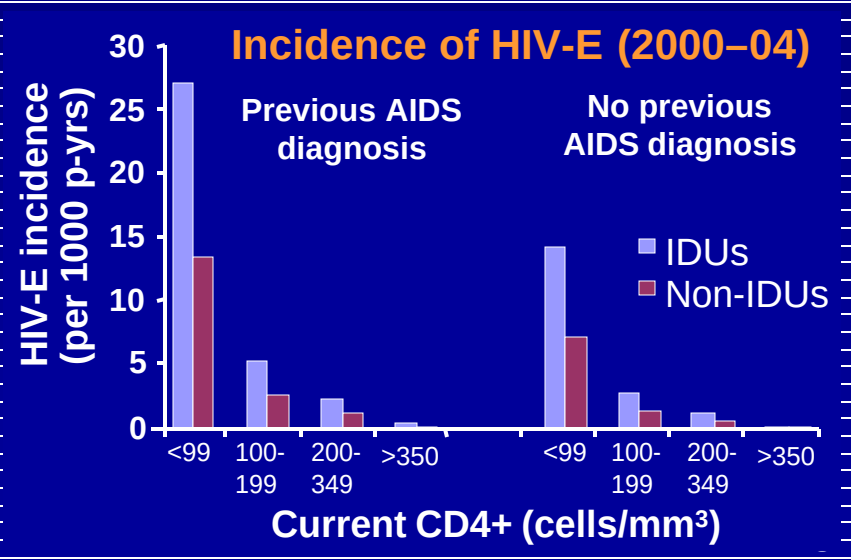
1. Gras L, *et al. 13th CROI,* Denver 2006, #530; 2. Keruly J, *et al. ibid,* #529

HIV encephalopathy in the HAART era

- 7948 seroconverters in EU, Australia, Canada (CASCADE)
- Among non-IDUs, risk of HIV encephalopathy (HIV-E) fell substantially:
  - Pre-1997 vs 1997–99; RR: 0.08, 95% CI 0.02–0.27
  - Pre-1997 vs 2000–04; RR: 0.11, 95% CI 0.04–0.32
- Estimated incidence of HIV-E in 2000–04 ⇧ at lower CD4+ among those with previous AIDS diagnosis and IDUs
- ⇩ in HIV-E incidence at the same CD4+ levels in the HAART ERA suggests a direct effect of HAART on the pathology of HIV-E



Adjusted for age at seroconversion, sex, current CD4+ count, previous AIDS, and stratified by cohort



Mussini C, *et al. 13th CROI,* Denver 2006, #351

Antiretroviral effectiveness in the CNS

- HIV+ subjects in CHARTER study (*n*=833)
  - Paired plasma & CSF samples
- "Penetration-Effectiveness [P-E] Score" determined by:
  - Pharmacokinetics
  - Pharmacodynamics
  - Drug characteristics
- Higher P-E score correlated with lower CSF viral load ($p<0.0001$)
  - Independent of plasma VL
  - P-E Score <1.5 nearly doubled odds of having detectable VL in CSF

ARV penetration-effectiveness score

	1	0.5	0
NRTIs	ABC ZDV	FTC 3TC d4T	ddI TDF ddC
NNRTIs	DLV NVP	EFV	
PIs	APV + RTV IDV + RTV LPV/r	APV ATV ATV + RTV IDV	NFV RTV SQV SQV + RTV TPV + RTV
Fusion inhibitors			ENF

- Relationship between P-E score and risk of CNS disease uncertain

BMS-089: RTV-boosted vs unboosted ATV in ART-naïve patients

- 3TC + d4T XR + ATV + RTV vs ATV

	ATV 300 + RTV (*n*=95) *n* (%)	ATV 400 (*n*=105) *n* (%)
Treated	95 (100)	104 (99)
D/C before Wk 48	11 (12)	10 (10)
Adverse event	8 (8)	1 (<1)
Death	0 (0)	1 (<1)
Other	3 (3)	8 (8)
Virologic failure	3 (3)	10 (10)
Never suppressed but on study at Wk 48	0 (0)	2 (2)
Rebound	3 (3)	6 (6)
D/C due to poor virologic response	0 (0)	2 (2)

- Total bilirubin elevation (≥2.5 x ULN): 59% (ATV + RTV), 20% (ATV)

48-week results

% undetectable (ITT)

	ATV + RTV	ATV
HIV RNA:		
<400 c/mL	86%	85%
<50 c/mL	75%	70%

Resistance mutations

	ATV + RTV	ATV
I50L	0	1
I50I/L +/- G73G/S	0	2
M184M/V, M184V	1	7

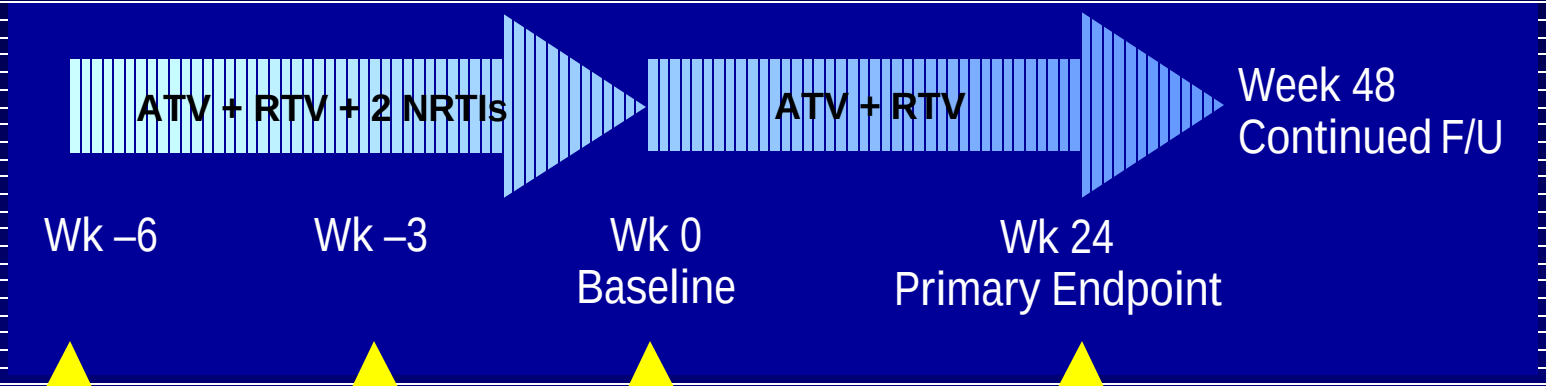
Lipids

	ATV + RTV	ATV
TC	+15%	+6%
LDL	+23%	+16%
HDL	+30%	+29%
TG	+26%	–3%

- ATV + RTV non-inferior to ATV

Malan N, *et al. 13th CROI,* Denver 2006, #107LB

ACTG 5201: Boosted ATV alone for maintenance



Inclusion criteria: CD4+ ≥250 cells/mm^3, HIV RNA <50 c/mL for ≥48 weeks, no history of virologic failure (*n*=36;)

Confirmed HIV RNA <50 c/mL

D/C NRTIs (*n*=34)

91% without virologic failure by Wk 24 (lower 90% CI= 85%)

- 8 semen samples: all <150 c/mL
- Virologic failures (*n*=3)
  - No PI mutations in any failures
  - No ATV plasma levels in 2/3