



**CNS HIV Anti-Retroviral Therapy Effects Research**  
University of California, San Diego

## **Low Atazanavir Concentrations in Cerebrospinal Fluid**

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# Atazanavir Penetration into CSF

- ◆ HIV Neurocognitive Impairment is prevalent despite the use of combination antiretroviral therapy
- ◆ Potent protease inhibitors (PI) may not penetrate into the CNS in therapeutic concentrations, which may allow ongoing replication and injury
- ◆ Atazanavir, a commonly used PI, is 86% bound to plasma proteins, leaving 14% free to penetrate into the CNS
- ◆ Objective
  - To determine the extent of atazanavir penetration into the cerebrospinal fluid of HIV-infected individuals

# Atazanavir Penetration into CSF

## METHODS

- ◆ CHARTER is an on-going, multi-center, observational study to determine the effects of potent antiretroviral therapy on HIV-associated neurological disease.
- ◆ Single random plasma and CSF samples were drawn within an hour of each other from subjects taking atazanavir (ATV) with or without ritonavir (RTV) between October 2003 and October 2005.
  - Daily doses of ATV included 300-400 mg alone, and 300-400 mg with RTV
- ◆ Samples were assayed by rapid, automated enzyme immunoassays (ARK ATV-Tests™, ARK Diagnostics, Inc. Sunnyvale, CA).
  - Plasma validation inter-assay precision was < 9.2% CV and accuracy was within 11% deviation. Calibration standards ranged from 0.25 to 8 mcg/mL with a sensitivity of 0.128 mcg/mL.
  - CSF validation, inter-assay precision and accuracy were within 18% at 5ng/mL, and within 15% for remaining controls.
  - Concentrations from the ARK method strongly correlated with those from a validated HPLC method ( $r^2 = 0.96$ ).

CHARTER

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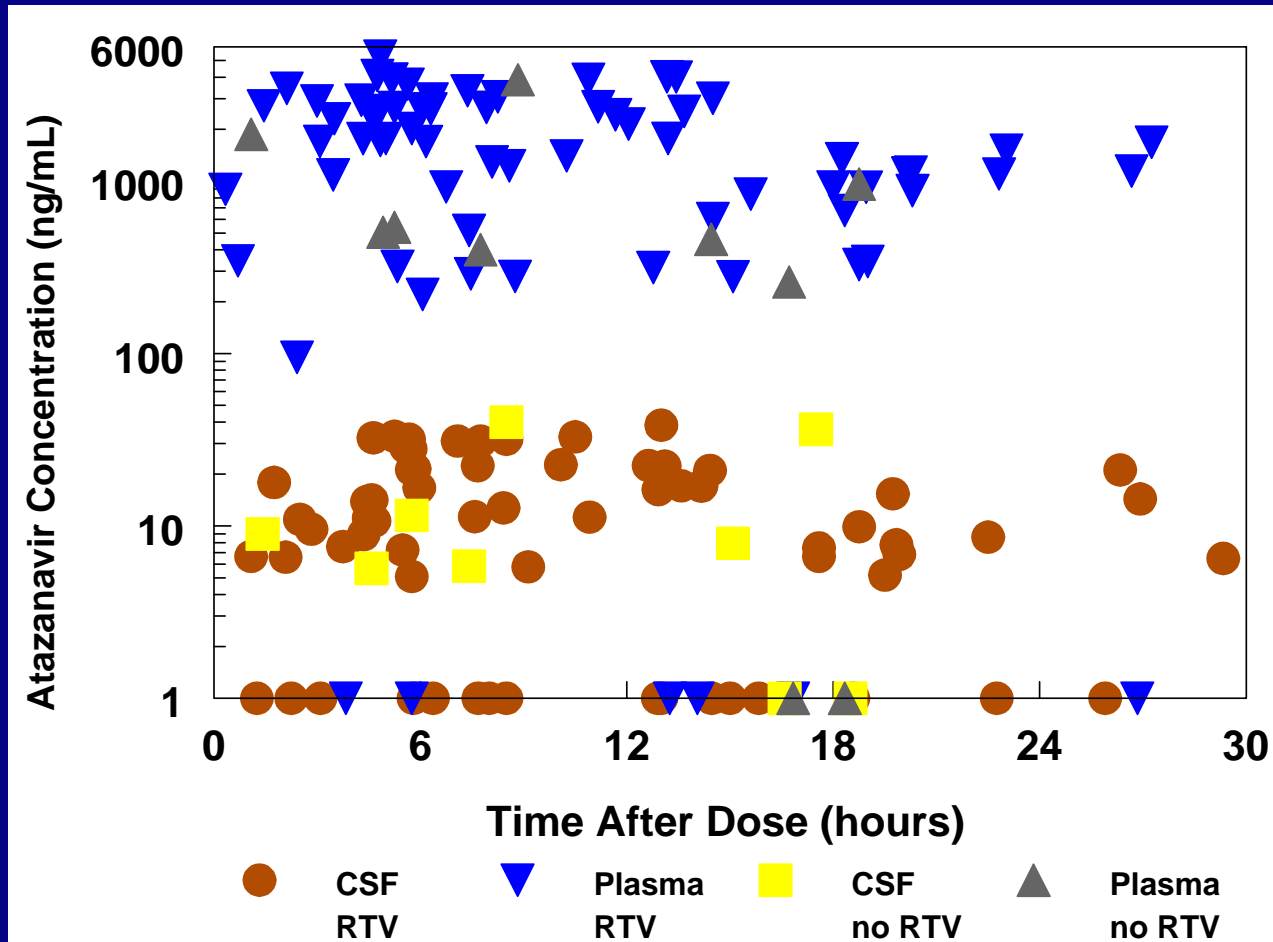
# Atazanavir Penetration into CSF RESULTS

	Without RTV	With RTV
Plasma		
number of samples	11	69
median conc. (ng/mL)	460	1510
range	BQL – 3871	BQL – 5295
Time post dose (hrs)	10.2 ± 7.2	10.7 ± 7.2
CSF		
number of samples	10	66
median conc. (ng/mL)	6.9	10.3
range	BQL – 40	BQL – 38.4
Time post dose (hrs)	9.5 ± 7	10.6 ± 7.1
CSF/Plasma Ratio		
number of sample pairs	7	59
median	0.0146	0.007
range	0.005 – 0.139	0 – 0.034

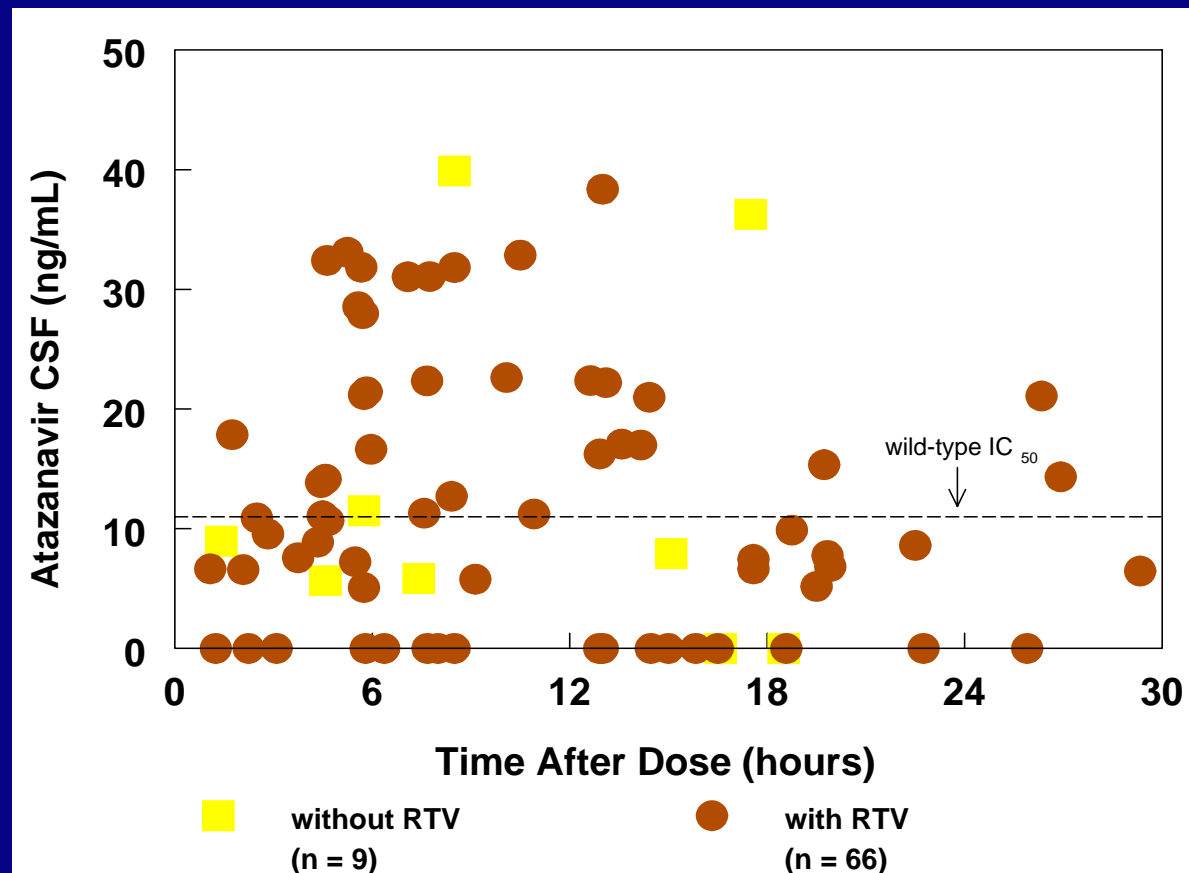
CHARTER

CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

# Atazanavir Penetration into CSF RESULTS



# Atazanavir Penetration into CSF RESULTS





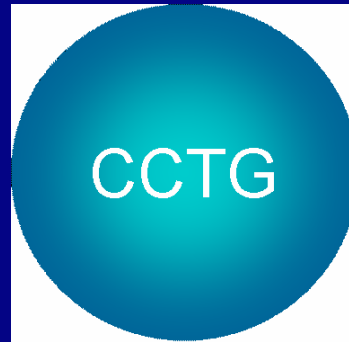
# Atazanavir Penetration into CSF

## CONCLUSIONS

- ◆ Atazanavir concentrations in CSF are 100 fold lower than plasma concentrations, even with RTV-boosting
- ◆ Observed CSF concentrations are less than the estimated free concentration in plasma (~210 ng/mL), suggesting active transport out of the CSF
- ◆ Increasing atazanavir plasma exposure may increase CSF penetration
- ◆ Atazanavir CSF concentrations do not consistently exceed the wild-type  $IC_{50}$ , and may not protect against CSF viral replication



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# **Improved Antiretroviral Exposure with Therapeutic Drug Monitoring**

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# Improved ARV Exposure with TDM

- ◆ Antiretroviral efficacy and toxicity have been associated with plasma drug concentrations
- ◆ Therapeutic drug monitoring (TDM) may prove a useful tool to detect and correct inappropriately high or low drug concentrations
- ◆ The clinical utility of TDM in HIV therapy is controversial. The objective of this study was to define
- ◆ Objective:
  - To define the proportion of patients that may benefit from TDM, and
  - To define the rate at which TDM interventions achieve target antiretroviral exposure compared to standard of care

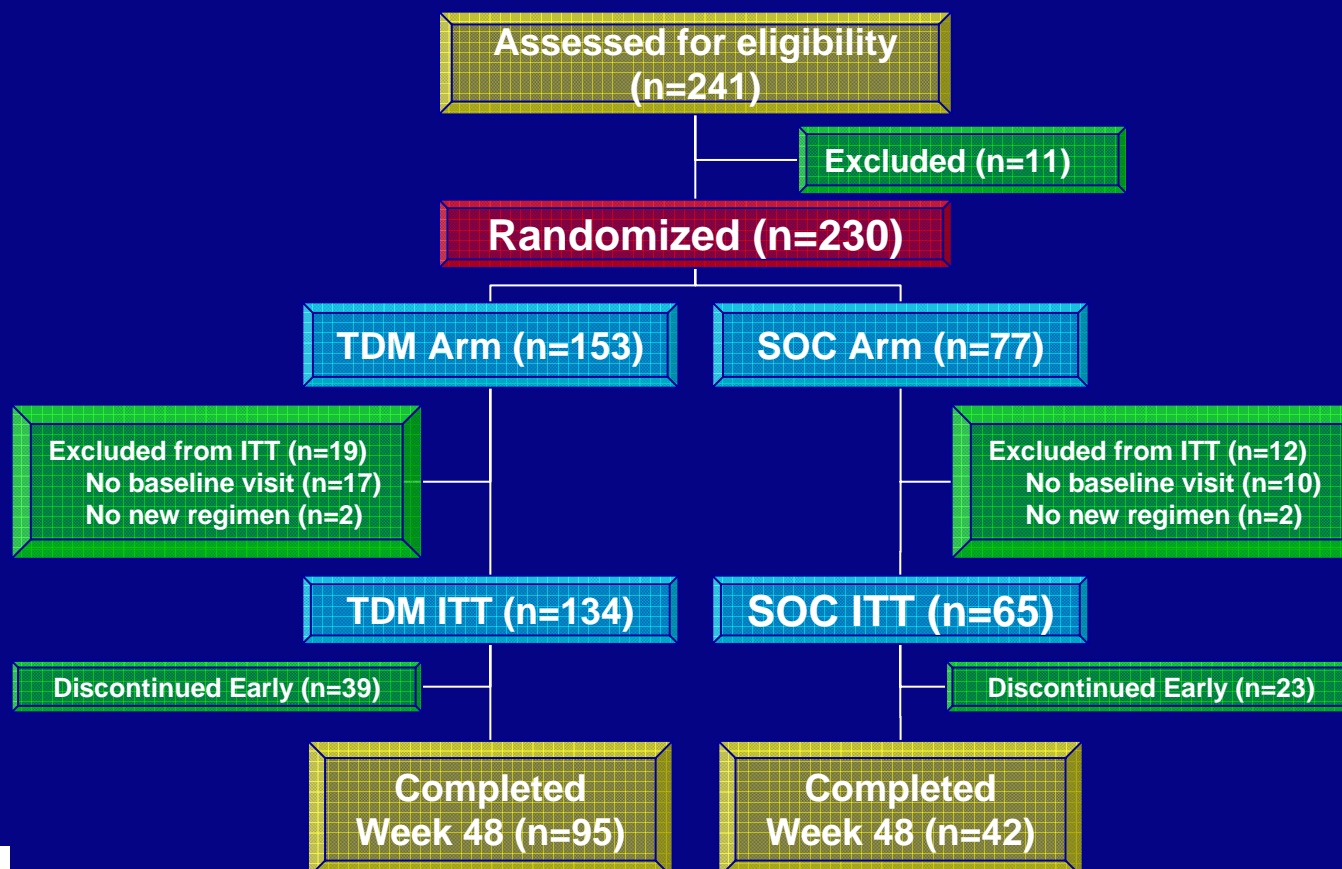
# Improved ARV Exposure with TDM

## METHODS

- ◆ **CCTG 578: 5 center, randomized, 2x3 factorial study of TDM versus standard of care (TDM:SOC, 2:1 ratio) crossed with three adherence interventions**
- ◆ **PI and/or NNRTI plasma drug concentrations drawn at 0, 2, 4 hrs after witnessed dose at week 2 Random samples at weeks 4, 6, 12, 18, 24, 32, 40 and 48**
- ◆ **Validated reverse-phase HPL**
- ◆ **Individual patient's pharmacokinetic parameters estimated in real-time using Bayesian methods**
- ◆ **Expert committee (blinded to randomization) reviewed data (TDM, HIV RNA, CD4, toxicity) and recommended regimen changes as appropriate**
- ◆ **Site investigators received recommendations only for patients in the TDM group**



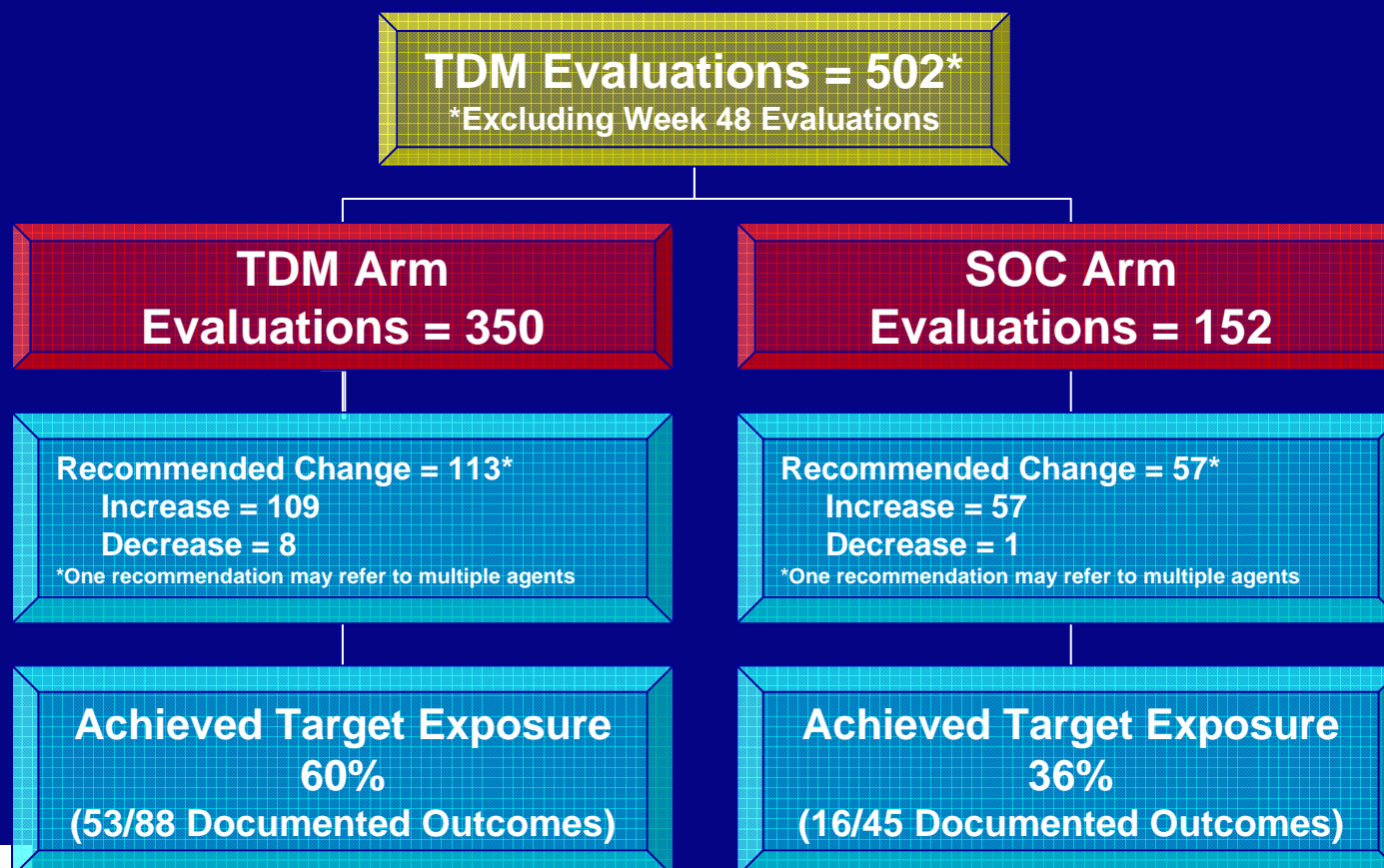
# Improved ARV Exposure with TDM RESULTS



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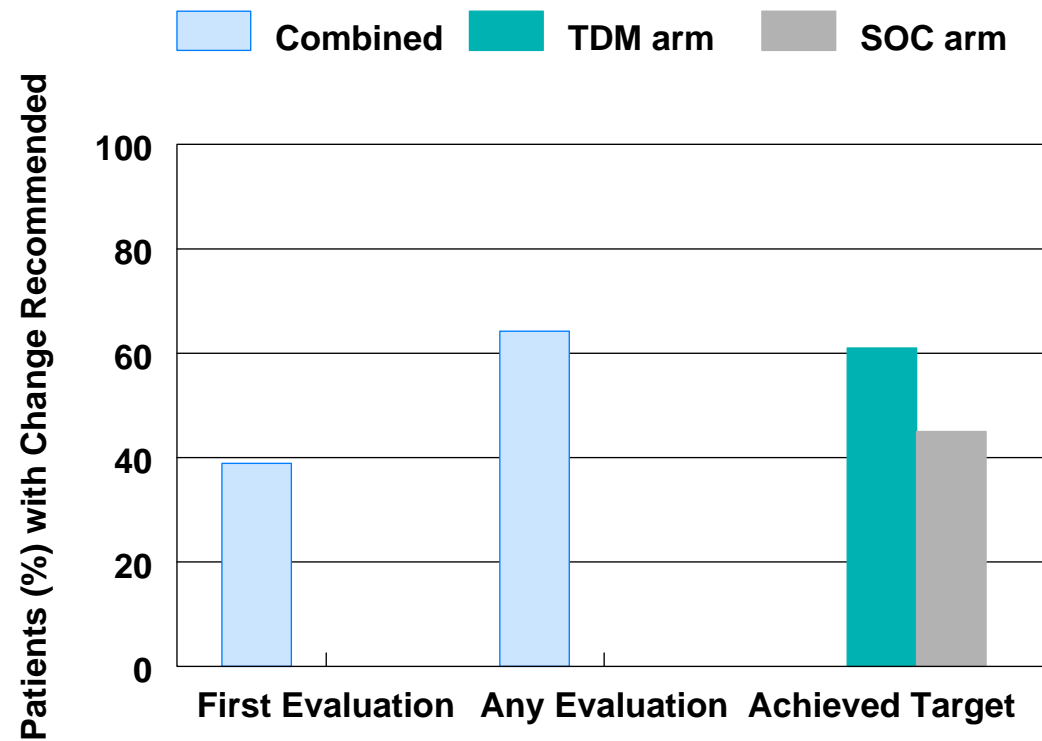
# Improved ARV Exposure with TDM RESULTS



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# Improved ARV Exposure with TDM RESULTS



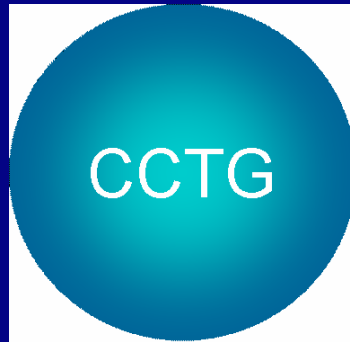
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# Improved ARV Exposure with TDM

## CONCLUSIONS

- ◆ More than 1/3 of patients (39%) had suboptimal antiretroviral exposure at the start of a new regimen and may benefit from TDM.
- ◆ Nearly 2/3 of patients (64%) had suboptimal exposure at some point during the first year of a new regimen.
- ◆ For evaluations of suboptimal antiretroviral exposure, TDM doubles the likelihood of reaching target antiretroviral exposure.
- ◆ Larger randomized studies are needed to:
  - Refine the population needing TDM
  - Define the clinical benefit of this intervention



## Acknowledgments

- ◆ We wish to thank all of the patients and staff of this study.
- ◆ California Collaborative Treatment Group (CCTG) UARP CC02-SD-003 and CH05-SD-607-005, UARP IS02-SD-701
- ◆ Rand Corporation, NIMH, National Institutes of Health
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- ◆ Quest Diagnostics



<b>Demographics (ITT Population)</b>	<b>TDM</b>	<b>SOC</b>
<b>N</b>	<b>134</b>	<b>65</b>
<b>HIV RNA (mean)</b>	<b>5.18</b>	<b>5.12</b>
<b>CD4 (mean)</b>	<b>180</b>	<b>211</b>
<b>Prior AIDS Diagnosis (%)</b>	<b>47.8</b>	<b>40</b>
<b>Age (mean)</b>	<b>40.1</b>	<b>39.3</b>
<b>Sex (% male)</b>	<b>79.1</b>	<b>84.6</b>
<b>Race (%)</b>		
<b>Caucasian</b>	<b>29.9</b>	<b>32.3</b>
<b>Hispanic</b>	<b>49.2</b>	<b>49.2</b>
<b>African-American</b>	<b>15.7</b>	<b>12.3</b>
<b>Other</b>	<b>5.2</b>	<b>6.2</b>
<b>Weight (kg)</b>	<b>74.7</b>	<b>75.4</b>
<b>Treatment-naïve (%)</b>	<b>29.1</b>	<b>30.8</b>
<b>Completed Study Week 48 (%)</b>	<b>71</b>	<b>65</b>

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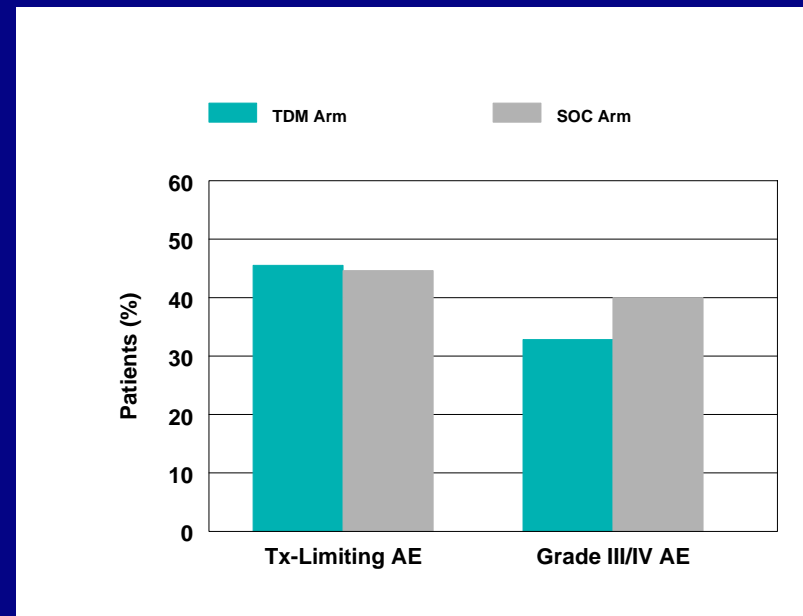
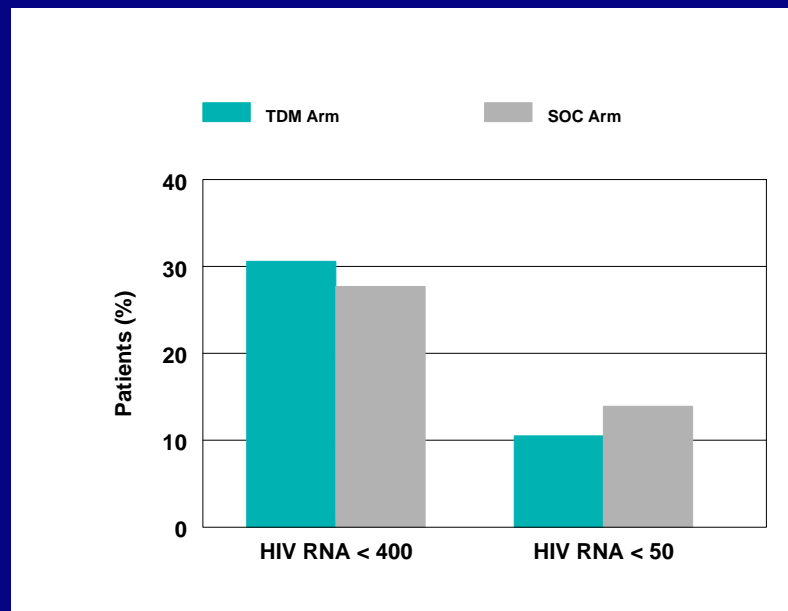
# Improved ARV Exposure with TDM RESULTS

- ◆ 199 patients were included in the intent-to-treat population, with 137 completing 48 weeks of study
- ◆ Patient demographics and drop-outs were balanced
- ◆ 647 TDM evaluations were performed through Week 48
  - In 225 of 647 (35%, SE 2%), recommendation was made to change drug exposure and in the TDM arm, 77% of the recommendations were implemented by clinicians
- ◆ 502 TDM evaluations were performed prior to the final (Week 48) study visit, with 170 recommendations to change
  - Of subjects with documented outcomes, 60% of the evaluations in the TDM arm and 36% in SOC arm achieved target exposure

# Improved ARV Exposure with TDM RESULTS

- ◆ Proportion of patients with a change recommended:
  - 39% at first evaluation
  - 64% at some point during the 48 weeks of study
- ◆ Rates of efficacy and toxicity endpoints were similar in both arms (Figures 4a/b), but the study was not powered to detect these differences
- ◆ Patients with treatment-limiting toxicity had higher maximum concentrations but not minimum concentrations or average concentrations,  $p=0.01$  at week 24

# Improved ARV Exposure with TDM RESULTS





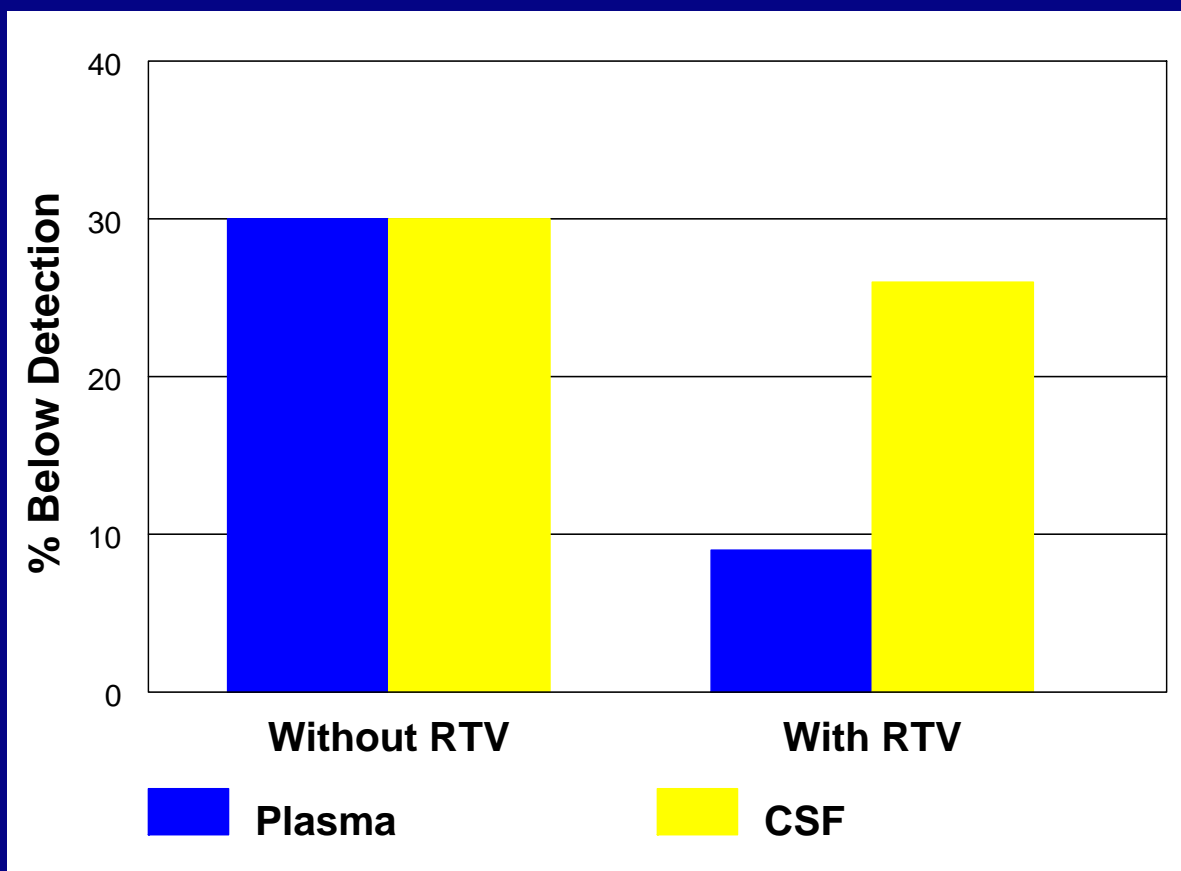
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<i>Demographics</i>		Without RTV	With RTV
n (females/males)		9 (3/6)	48 (3/45)
Age (yrs)		44 ± 6	43 ± 8
Weight (kg)		77 ± 14	81 ± 13
Ethnicity:	White	2	24
	Black	4	19
	Hispanic	3	3
Concomitant Medications (n):	abacavir	8	16
	didanosine	3	12
	emtricitabine	0	16
	lamivudine	8	15
	tenofovir	0	42
	zidovudine	4	8
EFV, T20, FPV, LPV, NVP, d4T		0	1 per drug
Time on regimen (months)		5.8 ± 5.7	9.4 ± 7.2
Serum Creatinine (mg/dL)		1.2 ± 1.1	1.1 ± 0.4
Albumin (g/dL)		4 ± 0.6	4.2 ± 0.5
CSF Protein		41.2 ± 14	43.8 ± 19
Plasma RNA (log <sub>10</sub> copies/mL)		2.2 ± 1	2.5 ± 1.1
CSF RNA (log <sub>10</sub> copies/mL)		2.1 ± 0.9	1.9 ± 0.4
Absolute CD4 (cells/mm <sup>3</sup> )		445 ± 231	401 ± 225



# Atazanavir Penetration into CSF

## RESULTS: Below Detection



# Atazanavir Penetration into CSF

## RESULTS: Below Detection

- ◆ 80 plasma and 76 CSF samples were evaluated from 57 participants
- ◆ CSF atazanavir concentrations were approximately 1% of the corresponding plasma concentrations
- ◆ 9/80 plasma and 20/76 CSF samples were below detection
  - 9 pairs of plasma/CSF were BQL, probably due to non-adherence (3 on ATV alone and 6 on ATV-RTV).
  - For 11 CSF BQL samples with measurable plasma ATV, the median plasma concentration was 315 ng/mL, compared with a median plasma concentration of 2,080 ng/mL for 48 samples with detectable atazanavir in CSF.

# Atazanavir Penetration into CSF

## RESULTS: IC<sub>50</sub> Comparison

- ◆ 55% (42/76) of CSF atazanavir concentrations were below the approximate IC<sub>50</sub> for wild-type virus (~ 11 ng/mL)
  - 43% (33/76) of CSF concentrations still fell below wild-type IC<sub>50</sub> after excluding specimens below detection in both plasma and CSF (probable non-adherence).
- ◆ Atazanavir plasma and CSF concentrations were correlated ( $r^2=0.68$ )

## Additional Background

- ◆ In the ATARITMO-Study, 2 of 12 patients whose virus was suppressed in plasma developed measurable virus in CSF while on ATV/r maintenance therapy.
  - Vernazza P, Daneel S, Schiffer V, Decosterd L, Hirschel B and the Swiss HIV Cohort S. *Viral suppression in CSF and genital tract in ritonavir-boosted "atazanavir only" maintenance therapy (ATARITMO-Study)*. IAS Conf HIV Pathog Treat 2005 Jul 24-27;3rd:Abstract No. WeOa0204
- ◆ Randall et. al observed CSF atazanavir concentrations approximately 1% of plasma concentrations in 7 HIV+ patients.
  - Randall D, Agarwala S, Mummaneni V, Geraldles M, Giordano M, O'Mara E. *Tissue compartment concentrations of atazanavir (ATV) in cerebrospinal fluid, seminal fluid and plasma in HIV + subjects.*