CNS HIV Anti-Retroviral Therapy Effects Research

University of California, San Diego

Low Atazanavir Concentrations in Cerebrospinal Fluid

Brookie Best, Scott Letendre, Parul Patel, David Clifford,
Ann Collier, Benjamin Gelman, Justin McArthur,
J. Allen McCutchan, David Simpson, Diane Holland, Igor Grant,
Edmund Capparelli and the CHARTER Study Group

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

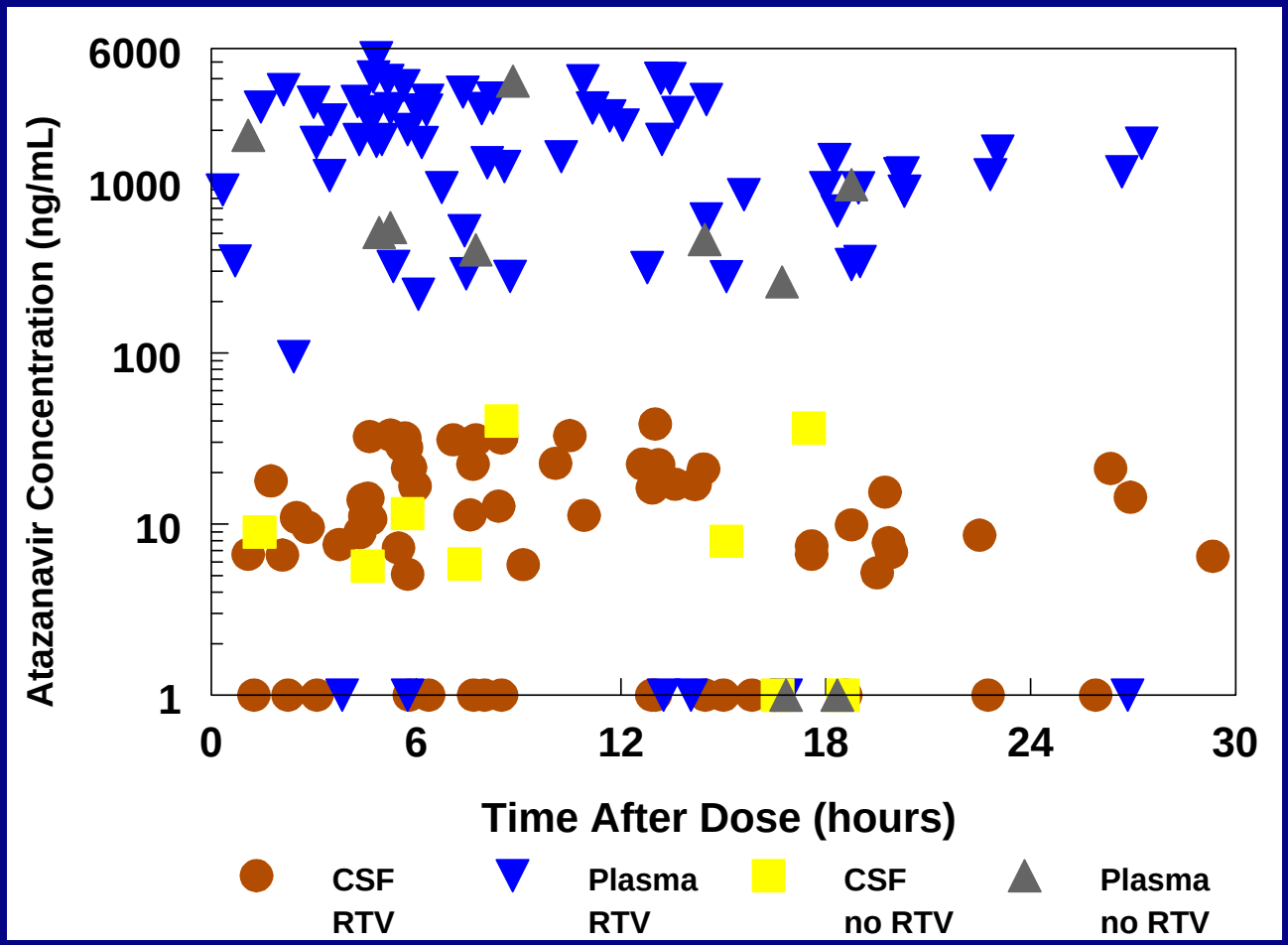
Atazanavir Penetration into CSF METHODS

- 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 (r2 = 0.96).

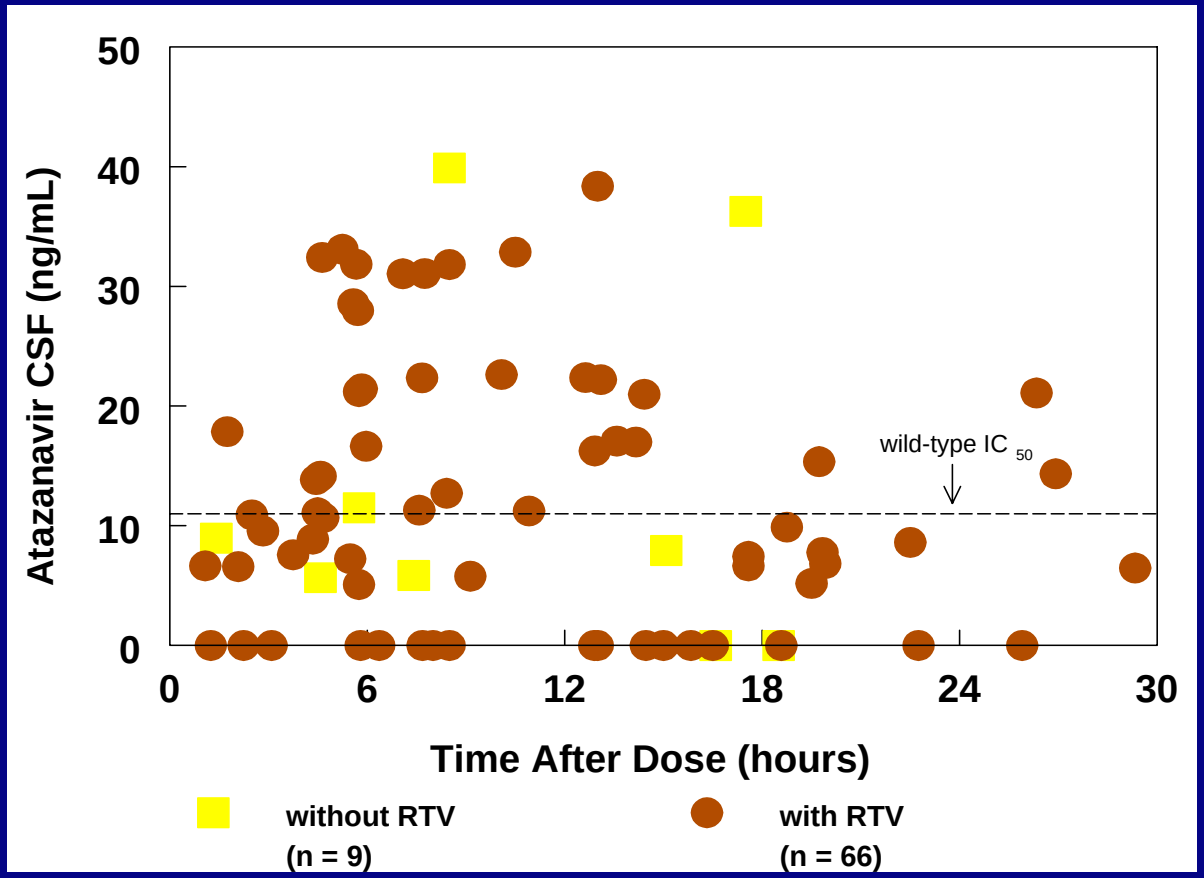
Atazanavir Penetration into CSF RESULTS

	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

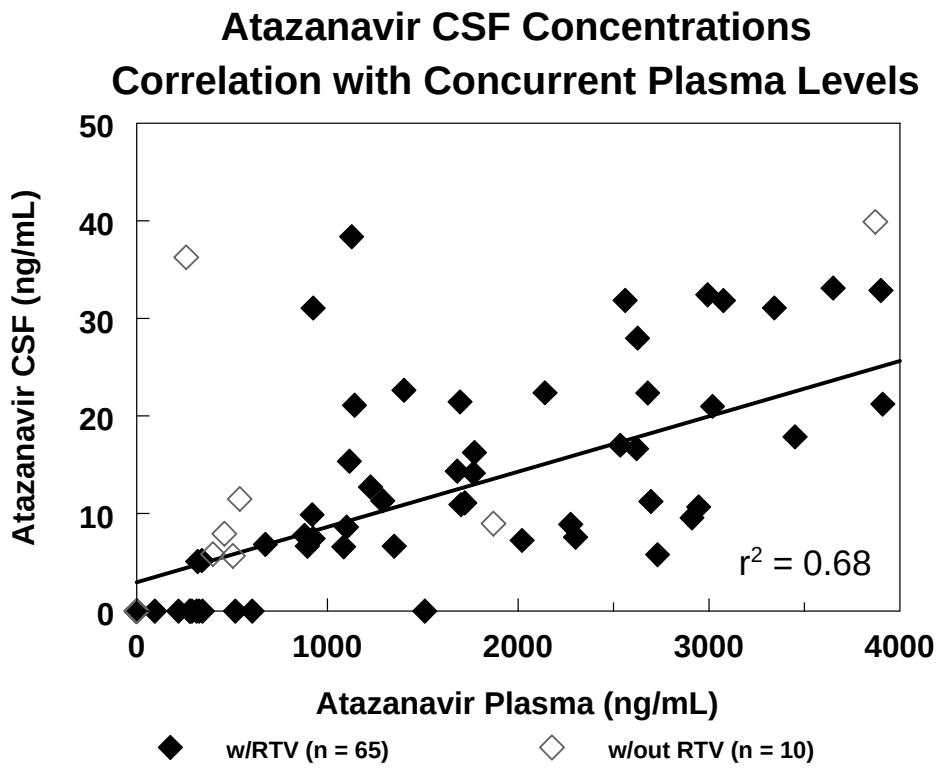
Atazanavir Penetration into CSF RESULTS



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

Brookie Best, Mallory Witt, Miguel Goicoechea, Carol Kemper, Robert Larsen, Catherine Diamond, Shelley Sun, Edmund Capparelli, Glenn Wagner, J. Allen McCutchan, Richard Haubrich, and the California Collaborative Treatment Group

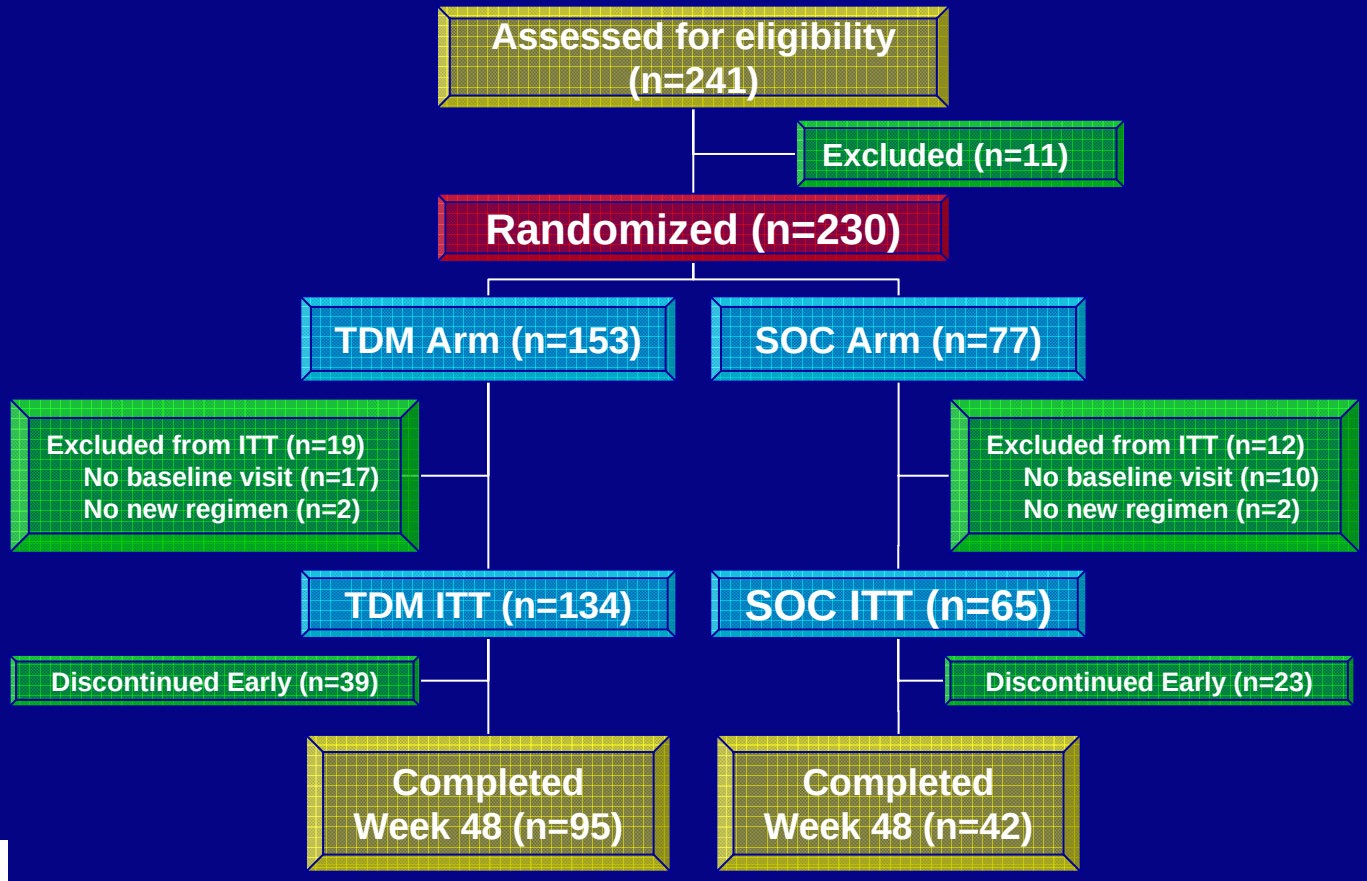
Improved ARV Exposure with TDM

- 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

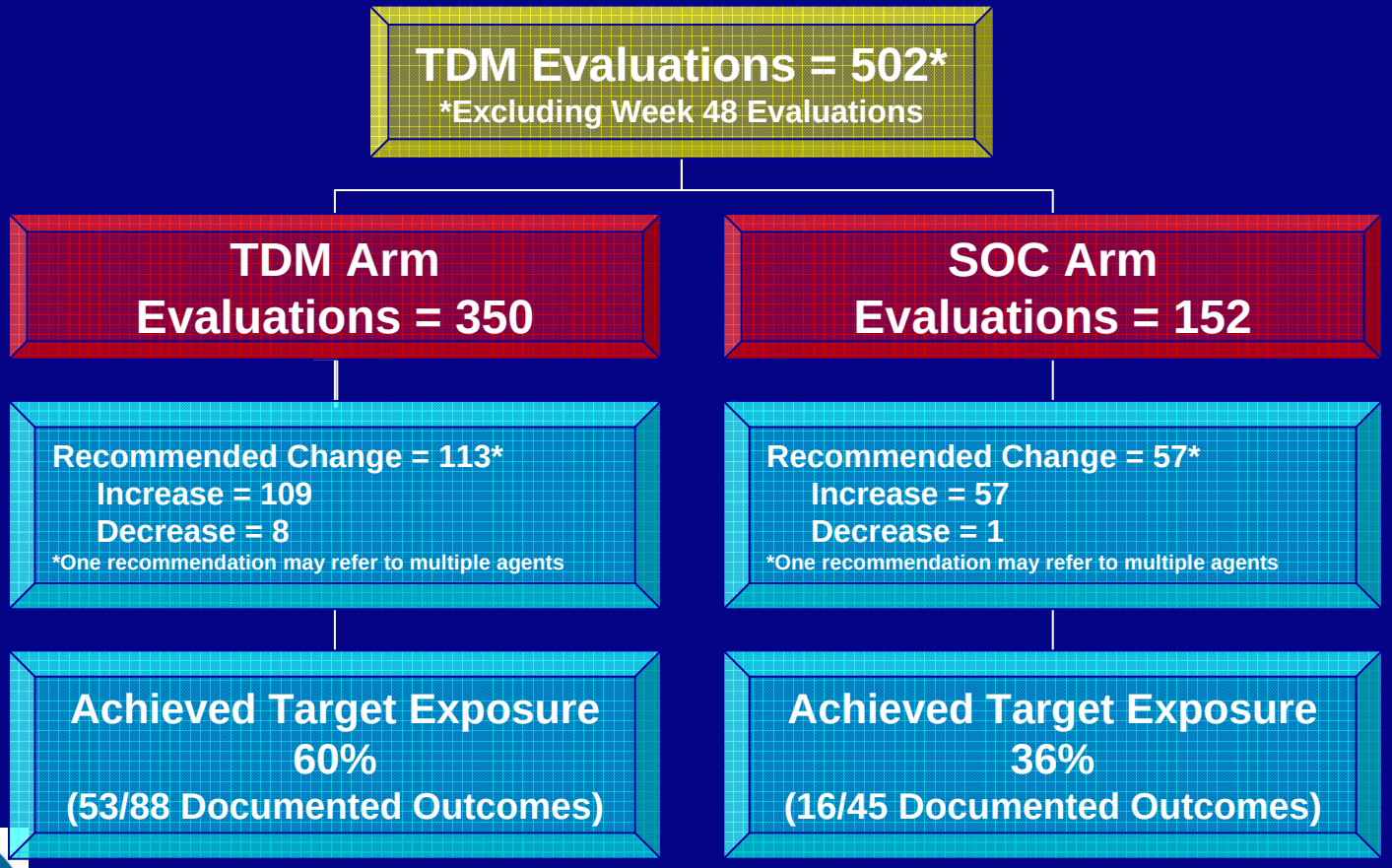
- CCTG 578: 5 center, randomized, 2x3 factorial study of TDM versus standard of care (TDM:SOC, 2:1 ratio) crossed with three adherence interventions
- PI and/or NNRTI plasma drug concentrations drawn at 0, 2, 4 hrs after witnessed dose at week 2Random samples at weeks 4, 6, 12, 18, 24, 32, 40 and 48
- 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



CCTG

Improved ARV Exposure with TDM RESULTS



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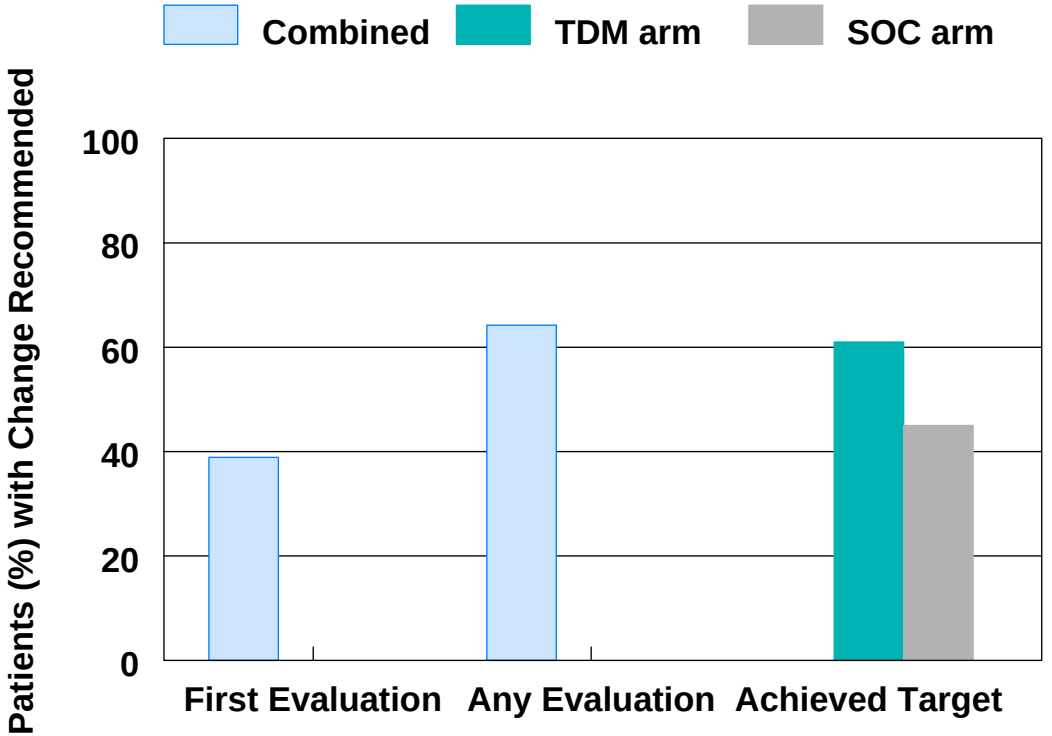

CCTG

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.
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- Quest Diagnostics

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

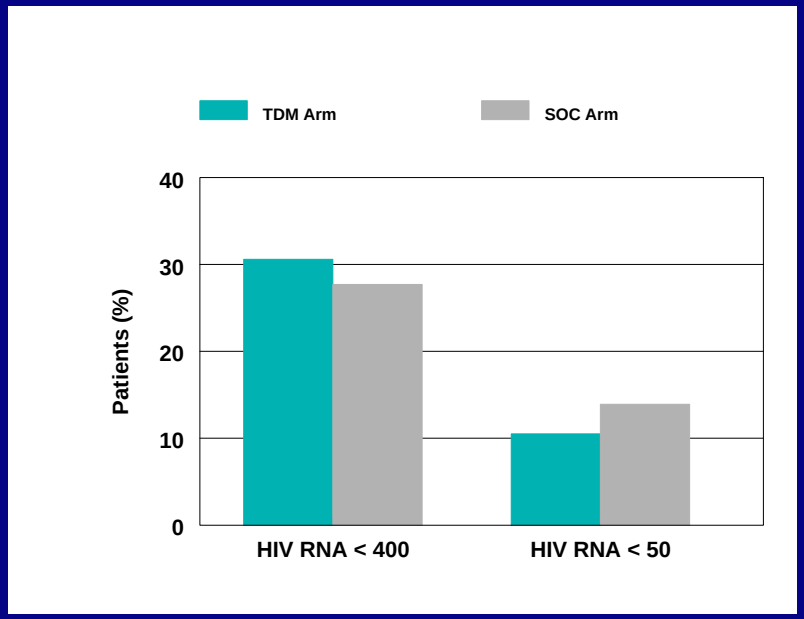
Improved ARV Exposure with TDM RESULTS

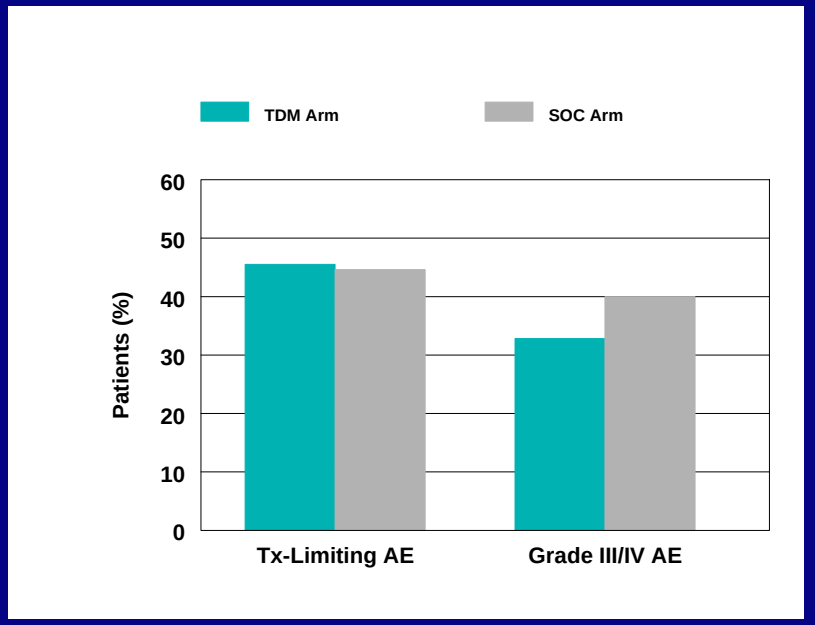
- 199 patients were included in the intent-to-treat population, with 137 completing 48 weeks of study
- Patient demographics and drop-outs were balanced
- 647 TDM evaluations were performed through Week 48
  - In 225 of 647 (35%, SE 2%), recommendation was made to change drug exposure and in the TDM 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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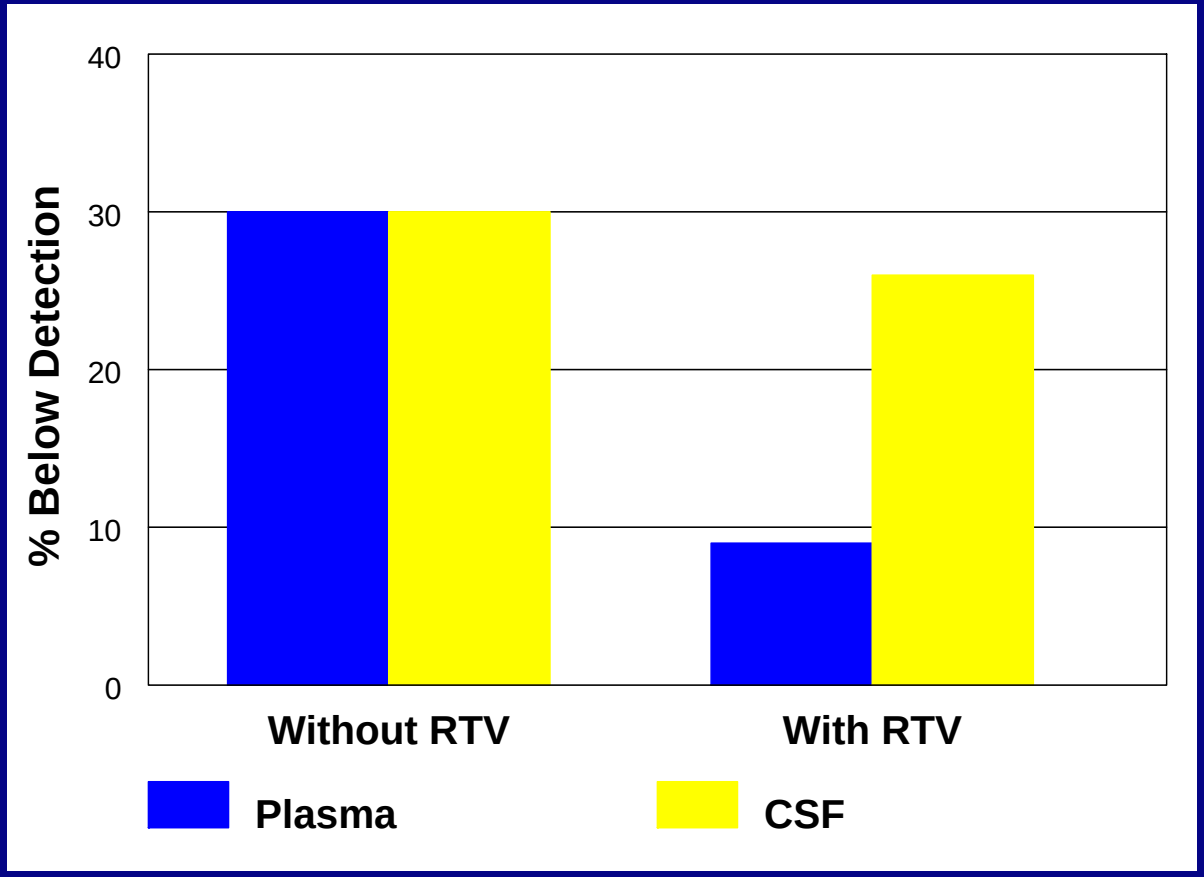
Demographics		Without RTV	With RTV
n (females/males)		9 (3/6)	48 (3/45)
Age (yrs)		44 ± 6	43 ± 8
Weight (kg)		77 ± 14	81 ± 13
Ethnicity:	White	2	24
	Black	4	19
	Hispanic	3	3
Concomitant Medications (n):	abacavir	8	16
	didanosine	3	12
	emtricitabine	0	16
	lamivudine	8	15
	tenofovir	0	42
	zidovudine	4	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_{10} copies/mL)		2.2 ± 1	2.5 ± 1.1
CSF RNA (log_{10} copies/mL)		2.1 ± 0.9	1.9 ± 0.4
Absolute CD4 (cells/mm^3)		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_{50} Comparison

- 55% (42/76) of CSF atazanavir concentrations were below the approximate IC50 for wild-type virus (~ 11 ng/mL)
  - 43% (33/76) of CSF concentrations still fell below wild-type IC50 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, Geraldes M, Giordano M, O'Mara E. Tissue compartment concentrations of atazanavir (ATV) in cerebrospinal fluid, seminal fluid and plasma in HIV + subjects.***