

44th ICAAC—What I Thought You'd Like to Know

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PRESENTATIONS ON ONCE A DAY REGIMENS

H-577 VEST QD—24 week data

- Patients on PI plus 2+ NRTI with VL<50 c/ml switched to non-PI regimen
- Goal of 300 patients—186 presently randomized
- 150 on EFV/ddI EC/3TC (all qd) and 150 on EFV with current NRTIs
- No difference in VL BLQ at week 24 (86% both)
- No significant difference in adverse events and no pancreatitis with ddI
- At baseline, 57% had 100% adherence with PI—at week 24, 73% had 100% adherence with EFV ($p<.05$)

H-561--CD4 Cell Count Changes after ddl Dose Reduction (400 → 250mg) in ddl EC +TDF HAART

Patients classified as CD4 cell decline >50 or ≤ 50 cells/mm³ during HAART with ddl 400 + TDF existed or not

ddl 400+ TDF + NNRTI/PI
>12 months

n = 39

CD4 decline group
n = 20

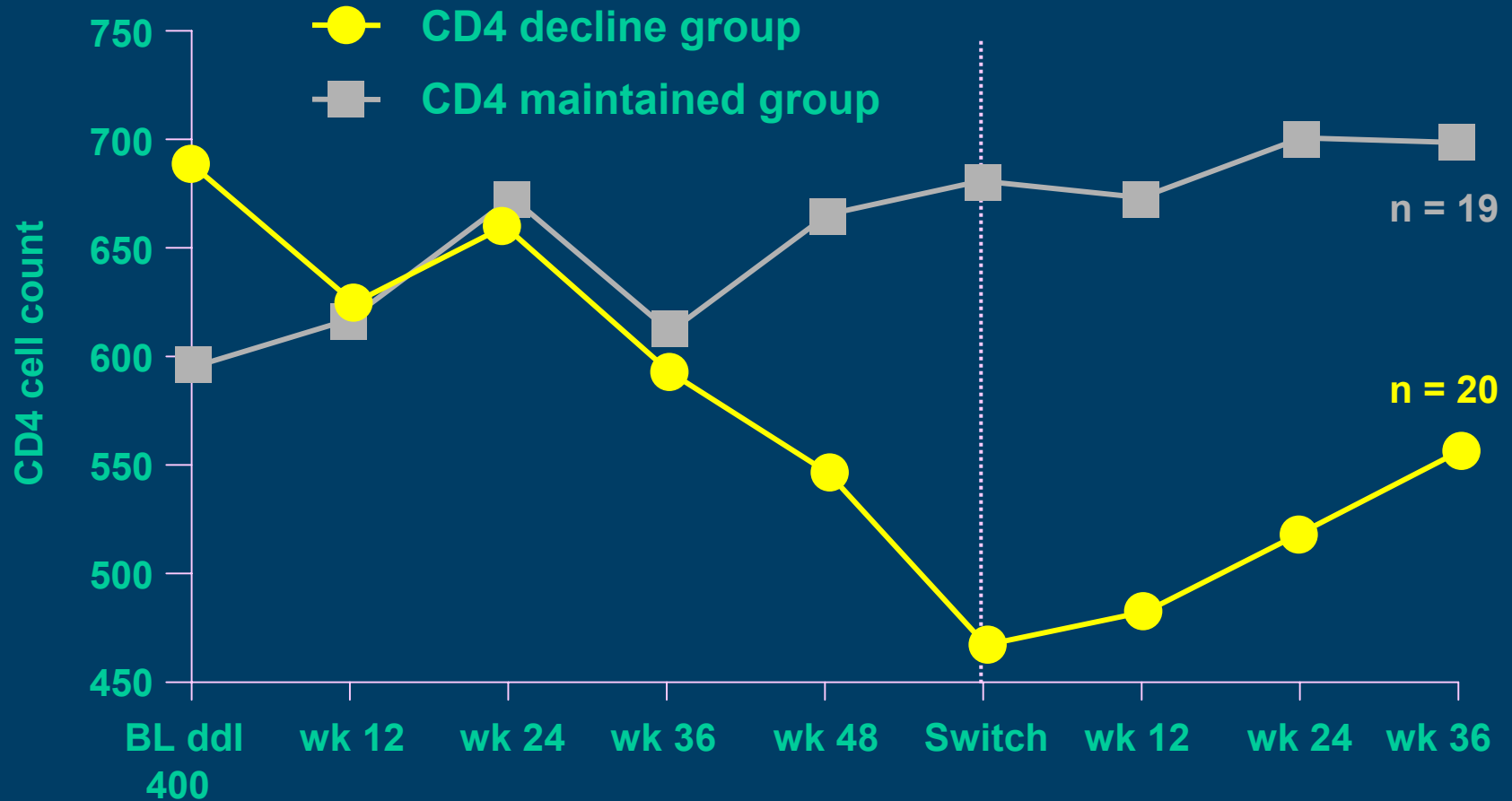
CD4 maintained group
n = 19

Mean decline of 86 cells ($p=0.017$)

Mean increase of 85 cells ($p=ns$)

ddl 250+ TDF + NNRTI/PI

H-561 (cont.) CD4 Cell Counts Before and After ddl Dose Reduction (mean, cells/mm³)



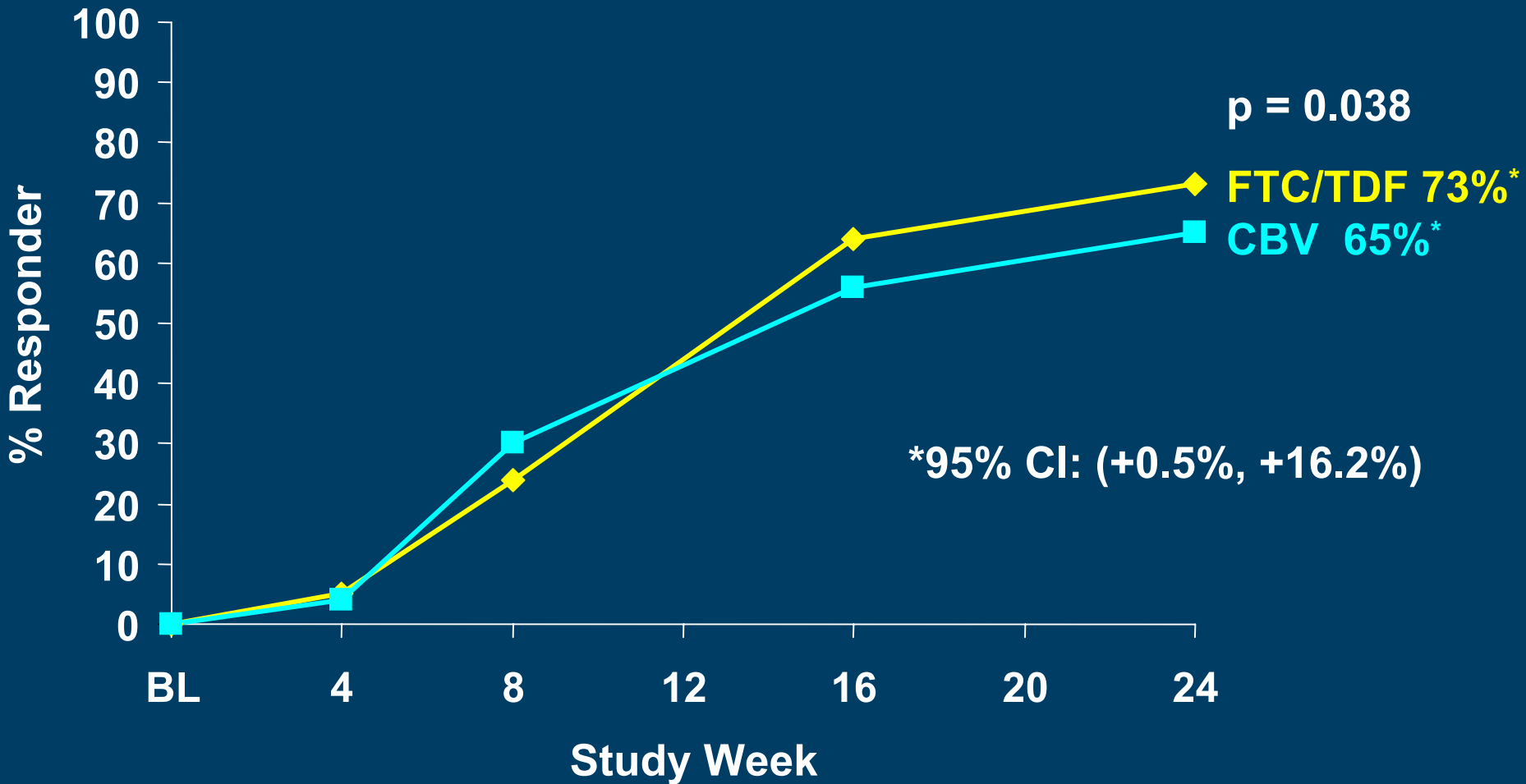
2 studies with TDF qd regimens

- **TZV #2 qd with TDF #1 qd**
- HAART naïve—123 pts.
- At week 24—64% with $vl < 50$ c/ml (ITT)
- 27 patients d/c'd regimen due to 12 A.E. (8 with ABC HSR, 2 nausea, 1 “mood swings”, 1 cancer)
- Rest due to protocol issues
- +80 median change CD4
- **TDF/FTC/EFV vs. COM/EFV**
- 73% TDF group (n=255) vs. 65% COM group (n=254) with $vl < 50$ at week 24 (p=.03)
- BL $vl > 100k$ —67% with TDF went to < 50 vs. 54% COM (p=.02)
- K103N and M184V equal in both arms; no K65R

H-1137c--Study 934

TLOVR <50 c/mL

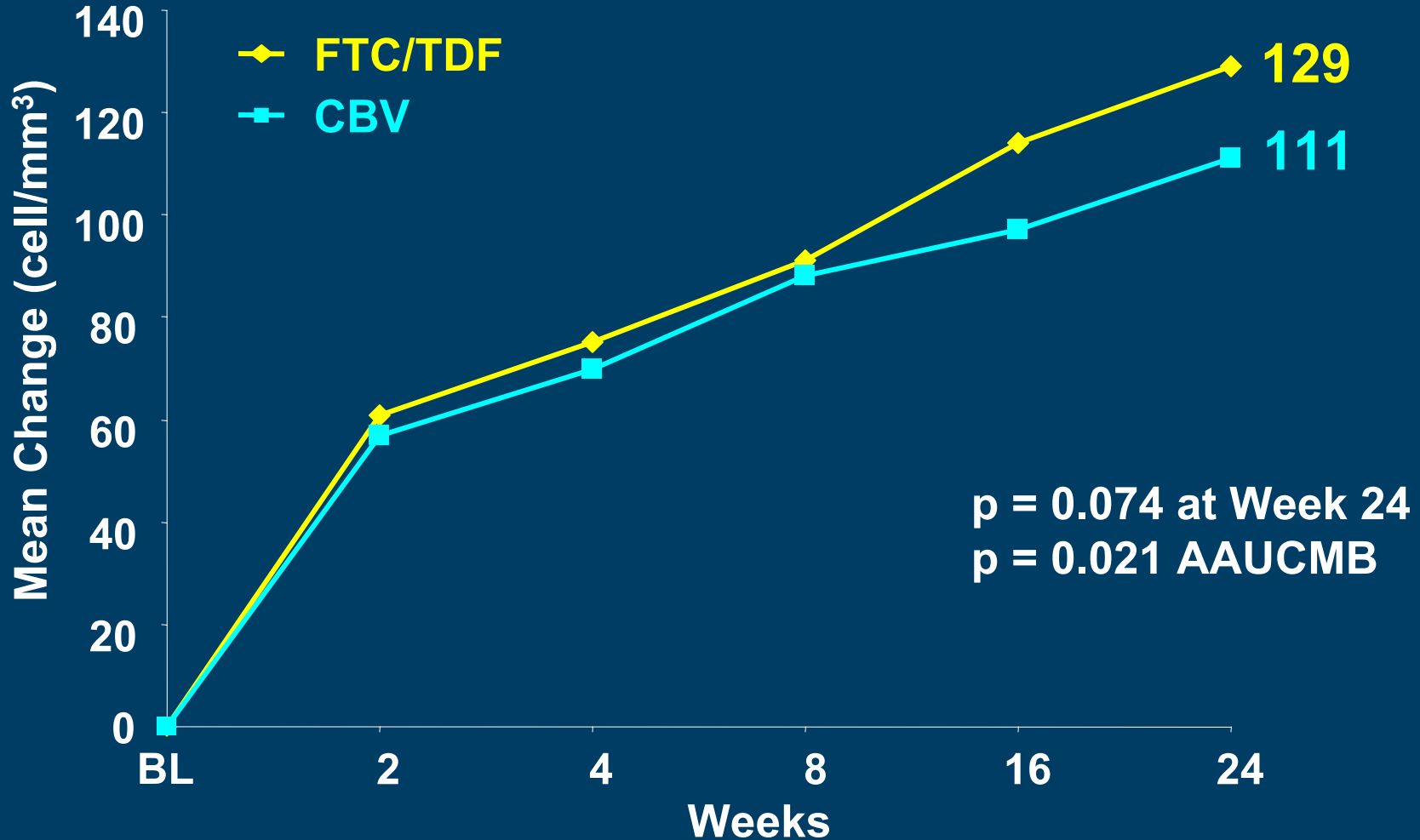
ITT (n = 509)



H-1137c

CD4 Mean Change from Baseline

H-1137c-Gazzard, B. et al, 44th ICAAC



H-866 PK and Safety Assessment of QD vs. BID T-20

180 mg ENF QD + OB

(180 mg QD → 90 mg BID)
Group A

Group B
(90 mg BID → 180 mg QD)

90 mg ENF BID + OB

Day 1

Start dosing VL sample

Day 3

VL sample

Day 7

VL sample
Intensive PK

Day 8

Dosage crossover
QD → BID
BID → QD

Day 14

VL sample
Intensive PK

OB – Optimized background; VL – Viral load; QD – Once daily; BID – Twice daily; ENF – enfuvirtide; PK – pharmacokinetic(s)

Baseline patient demographics

	Group A (<i>QD</i> → <i>BID</i>)	Group B (<i>BID</i> → <i>QD</i>)	Total
Number of patients, N (%)	19 (51)	18 (49)	37 (100)
Randomization Stratum (HIV-1 RNA copies/mL) n(%)			
<50,000	6 (32)	4 (22)	10 (27)
50,000 – 300,000	11 (58)	11 (61)	22 (60)
>300,000	2 (10)	3 (17)	5 (13)
Baseline HIV-1 RNA [1] (log ₁₀ copies/mL, median)	4.93	5.09	4.98
Baseline CD4 cell count [2] (cells/mm ³ , median)	72	67	72
Baseline CD4 cell count, N (%)			
<100 cells/mm ³	11 (58)	10 (56)	21 (57)
≥100 cells/mm ³	8 (42)	8 (44)	16 (43)
Baseline GSS = 0 [3], N (%)	9 (47)	6 (33)	15 (41)

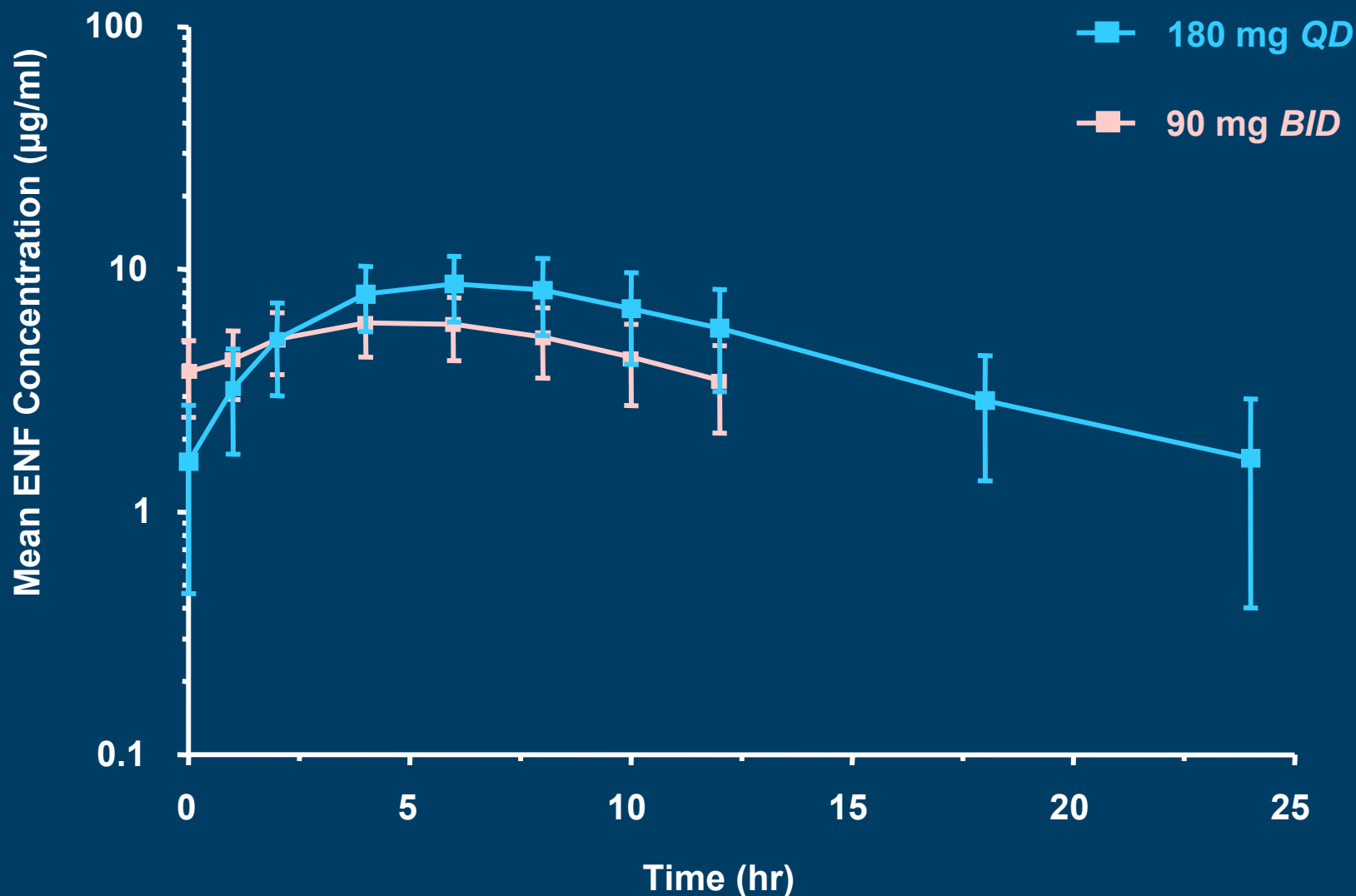
[1] Baseline HIV-1 RNA was the average of last two log₁₀ HIV-1 RNA results obtained prior to initiating ENF.

If one of the values was missing, the non-missing value was used

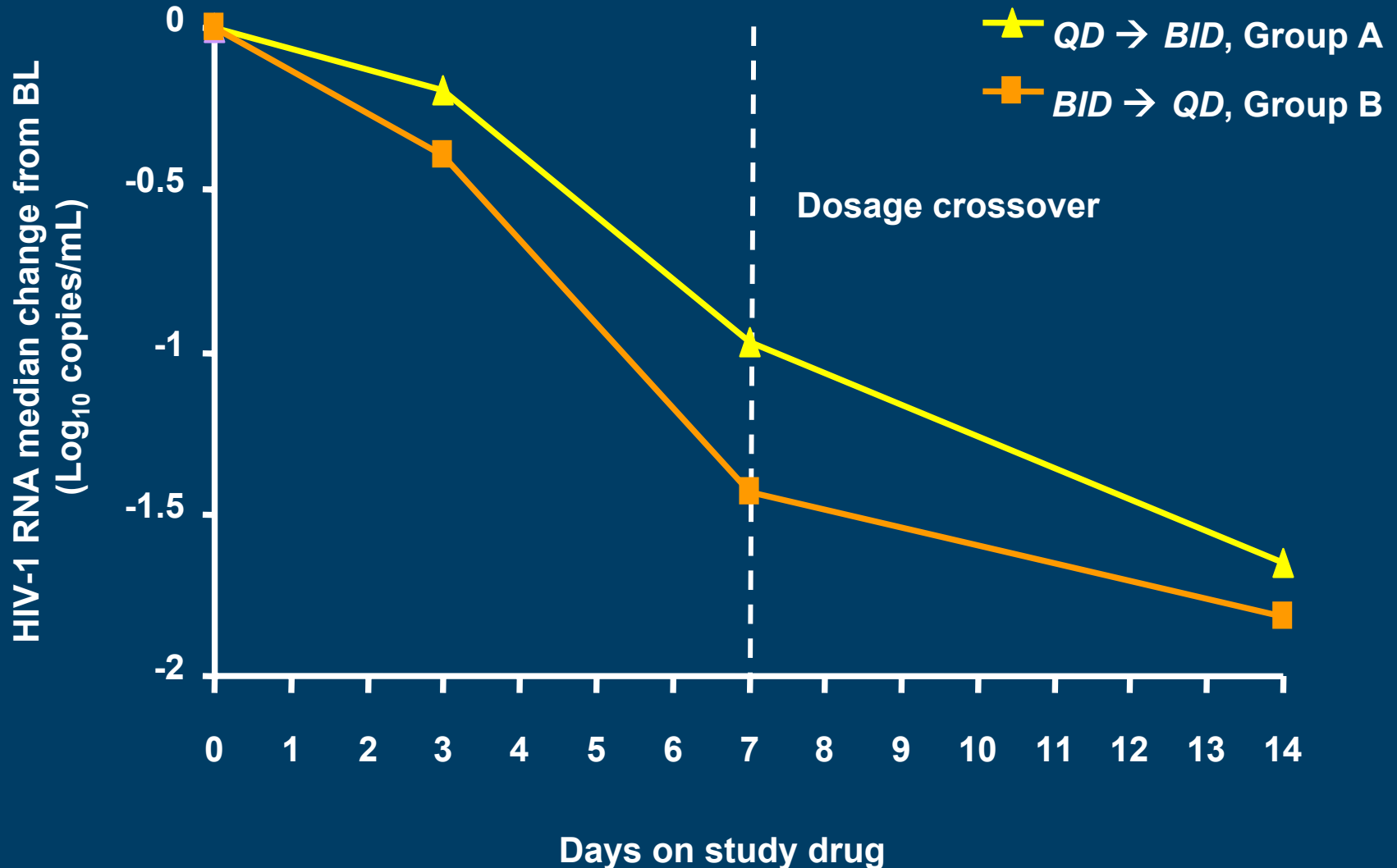
[2] Screening CD4 result was used if the baseline result was unavailable

[3] GSS – genotype sensitivity score –the total number of drugs in the actual OB regimen to which a patient’s virus showed genotypic sensitivity

Steady-state mean ENF plasma concentration-time profile following SC administration of ENF in the 180 mg *QD* or 90 mg *BID* regimen



Log₁₀ RNA median change from baseline



Incidence of most frequently reported treatment-emergent adverse events by preferred term; safety analysis population

Preferred Term	180 mg <i>QD</i> (N=36) n (%)	90 mg <i>BID</i> (N=35) n (%)
Flatulence	3 (8)	1 (3)
Nausea	3 (8)	4 (11)
Cough	2 (6)	0
Vomiting (NOS)	2 (6)	2 (6)
Abdominal distension	1 (3)	2 (6)
Diarrhea (NOS)	1 (3)	3 (9)
Dizziness	0	2 (6)
Insomnia	0	2 (6)
Parasthesia	0	2 (6)
Proctitis herpes	0	2 (6)

NOS = not otherwise specified

Other Notes on Enfuvirtide (T-20) from TORO

- **Week 12 Response as Predictor of Outcome**
 - 395/620 with $\geq \downarrow 1$ log₁₀ VL at wk12 with 79% sustaining that to wk96
 - 225/620 with $\leq \downarrow 1$ log₁₀ VL at wk12 with only 9% having $\geq \downarrow 1$ log₁₀ VL at wk96
 - Similar responses for CD4 (if >50 cell \uparrow wk12—sustained)
- **Elevated Serum IgE levels with T-20**
 - 48.3% at BL and but only 3.6% at wk8 and 4.7% wk24
 - In OB only, 48.9% BL and 3.6% wk8 and 5.6% wk24
 - No correlation b/w IgE levels and CD4
 - At BL, stat. sig correlation b/w \uparrow IgE & \uparrow eos., but not later

Notes on Lipids

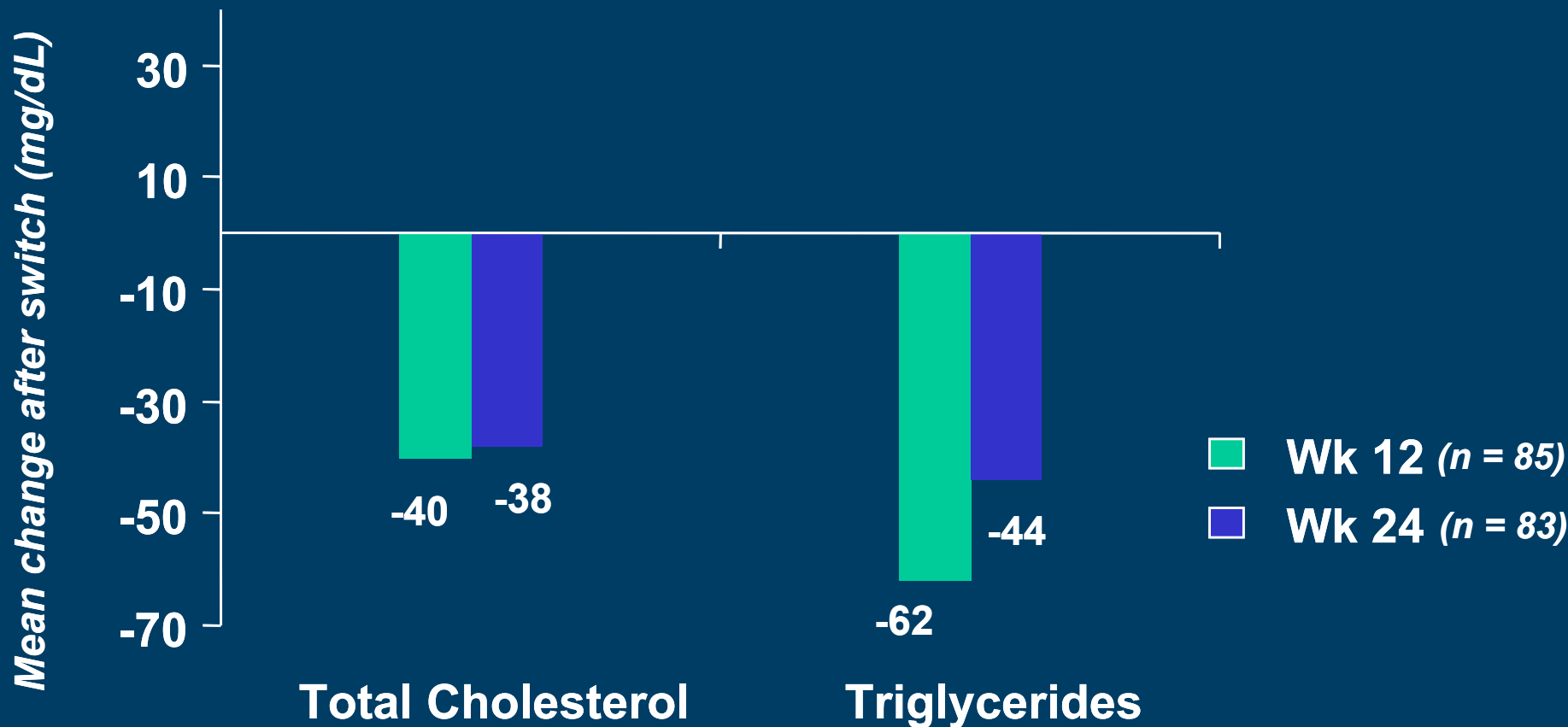
- **H-158—TDF for D4T and effect on lipids**

- Substudy 903E—open label change from D4T to TDF
- 24 week data—85 patients switched. 81/82 with VL<50 at week 24
- Δ cholesterol-- \downarrow 38 mg/dl, Δ TG-- \downarrow 44mg/dl, Δ LDLC \downarrow 17mg/dl
- See next 2 slides.

- **H-156—Increase HDL with FPV in HAART naïve pts**

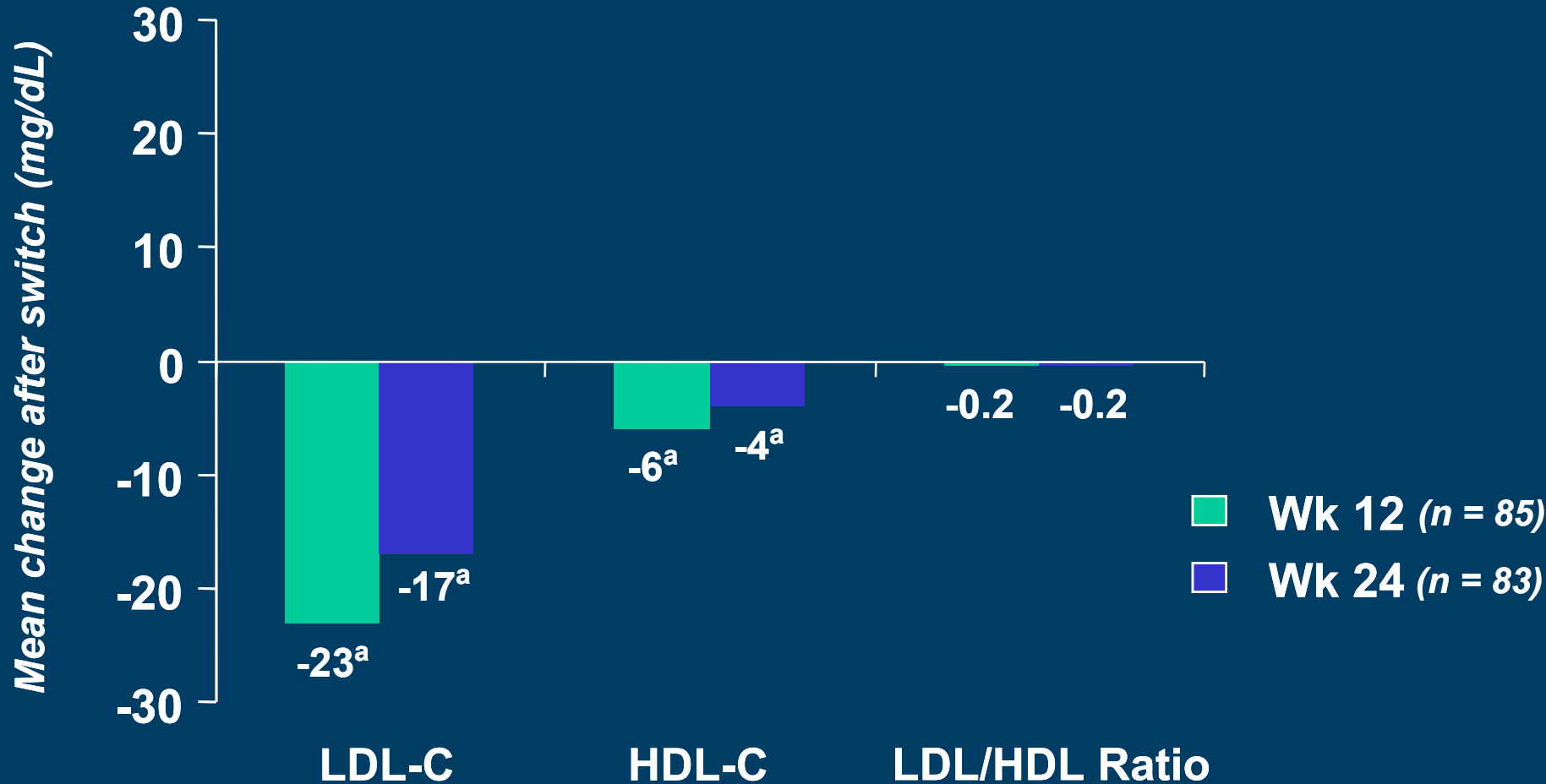
- F/U of NEAT study—Efficacy study of FPV (vs. NFV)
- 37% increase in HDL at 48 week and 22% increase HDL with NFV (significant overlap of confidence intervals)
- No significant change in total cholesterol or TG for either

H-158: Mean Change (after d4T → TDF Switch) in Fasting Cholesterol and Triglycerides



$p < 0.001$ for all observations

H158: Mean Change (after d4T → TDF) Switch in Fasting LDL-C & HDL-C



a. $p < 0.001$

Resistance and Failures

**...no, I don't mean the Democrats and
earlier this month!**

H-173—Prevalence of ARV Resistance in the US in 2003

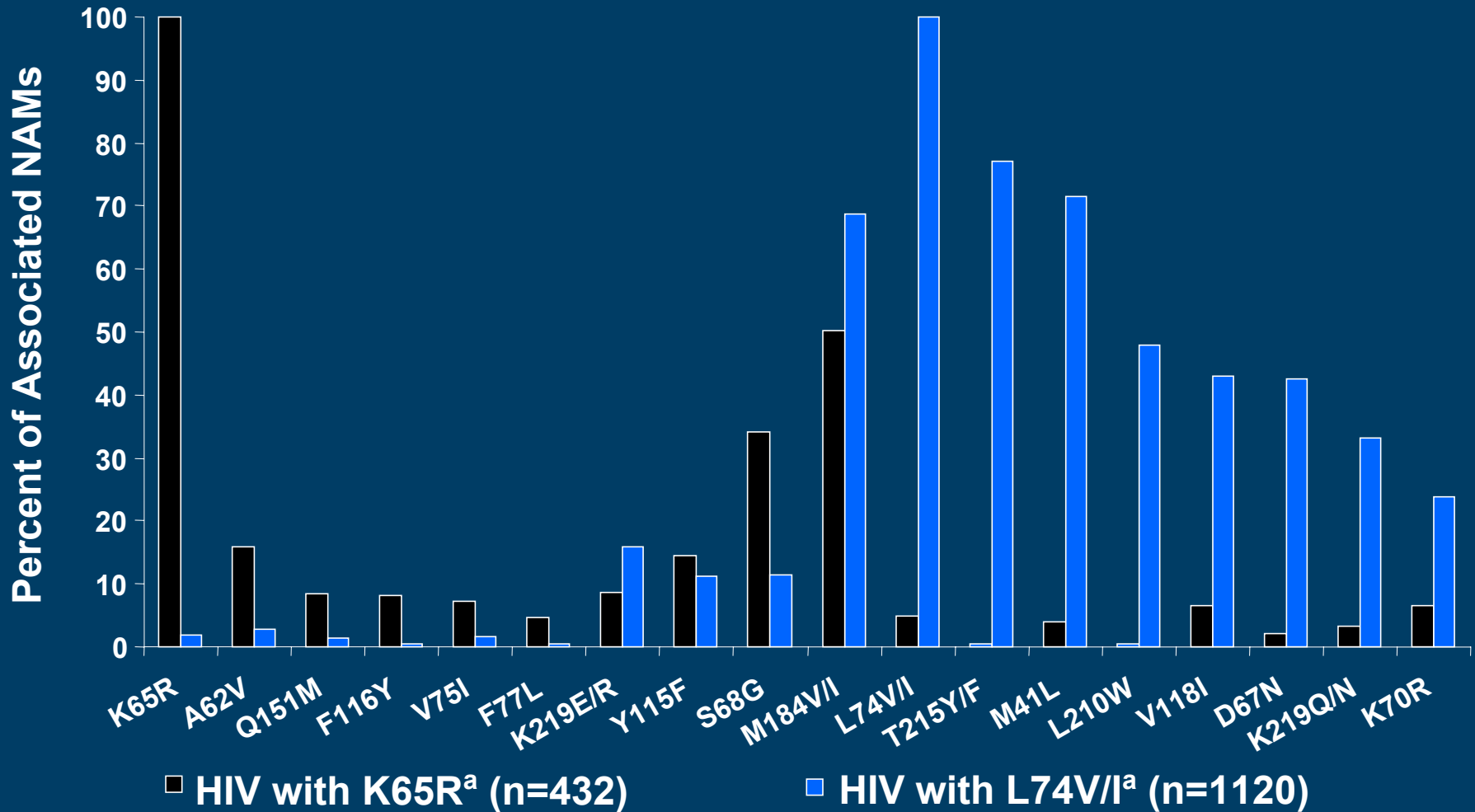
- Retrospective review of Virologic Co. data on 317 HIV+ HAART naïve patients in 40 cities in 2003
- 23% with at least one drug resistance
- 18% with reduced susceptibility to ≥ 1 NNRTI (but only 3% K103N)
- 6% with reduced susceptibility to ≥ 1 PI (but only 2% with any PI mutation)
- Only .9% with any reduced susceptibility to any NRTI but 8% with any NRTI mutation
- Of these patients—27% Caucasian, 23% African American, 24% MSM (where known)

H-176: Resistance Evolution With Stable HAART

- **98 pts in UNC CAR with virologic failure and no change HAART between 2 genotypes \geq 30 days apart**
- **PI-55%, NNRTI-14%, both-14%, NRTI only-15%**
- **1st geno—86 with \geq 1 mutations, median 3 (1-18)**
- **2nd geno—91 with at least 1, median 4 (1-18)**
 - 27% 1 new mutations, 12% 2 new mut., 21% 3+ new mut.
 - Incidence of 13/100 person-month (95% CI—11-16)

Statistically significant \uparrow risk mutations if no mutations at BL, CD4<200, or on HAART 2-5 yrs

H-178: The K65R and L74V/I Mutations Associate with Distinct Patterns of NAMs



a. Mixtures with wild-type excluded

McColl DJ. 44th Annual ICAAC October 30-November 2, 2004, Washington, DC, USA. Poster #H-178

H-579—Race as a Predictor of Failure

- **Retrospective analysis of 626 pts Atlanta VA cohort—African-American vs. Caucasian**
- **EFV and LPVr based therapies only**
- **626 patients**

Immunologic Failure if CD4 <50 cells after ≥ 3 mo. Rx

Virologic Failure if VL >400 c/ml after at least 3 mo. Rx

Multivariate Cox Modeling done

Results

All—AA protective for IF (HR=.64) but not VF (HR=.85)

EFV—AA protective for IF (.63) but not VF (.92)

LPVr—Race not predictive at all (IF and VF >.85 HR)

H-1134—Viral Blips—Intermittent Low Level HIV-1 Viremia

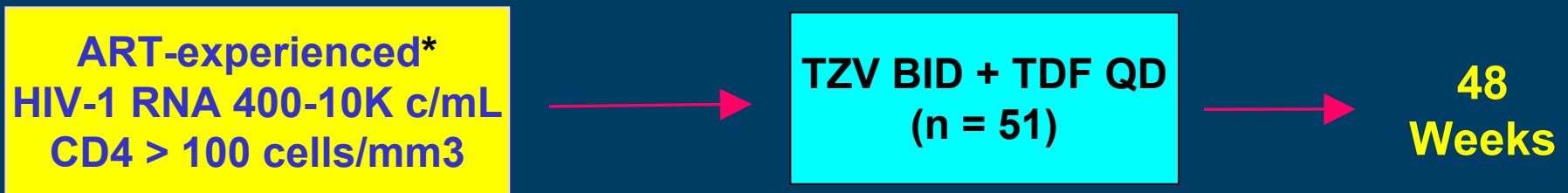
- **10 pts with VL BLQ (10-79 mo) and occasional “blips”—median blip 79 c/ml (range 51-201)**
 - VL checked 3x/week for 12-16wks and geno checked with any ↑VL
- **18 blips total with median 0.67 blip/mo (0-1.67)**
- **Median duration of blips were 60 hours**
- **Sent to 2 labs—kappa for blips 4.4%**
- **No correlation with any demographics, CD4, type of regimen, clinical condition at time of blip**
- **No genotype changes with any blip**
- **Conclusion: Blips of <120 c/ml—may be lab error**

H-183: Resistance in Patients with LPVr Monotherapy

- **Virologic Failure if 2+ VL >400c/ml or never <400**
- **33 patients failed from 2 studies combined**
- **8 met definition of this failure**
- **Genotypic data—most develop minor LPV mutations (63, 93, 76, 77)**
- **Only 1 patient developed phenotypic resistance despite rising VL with LPVr monotherapy**
- **24 week data from 18 patients on LPVr monotherapy (failed NNRTI based)—13/18 VL<75, 2 Virologic failure, 3 D/C due to diarrhea**

H-563– TZV+TDF for Early Virologic Failure

Phase IV, single-arm, open-label, multicenter study



Baseline Characteristics

- 61% prior PI and 39% prior NNRTI
- CD4 median – 436 (142 – 1291)
- ≤ 2 NRTI mutations or K65R

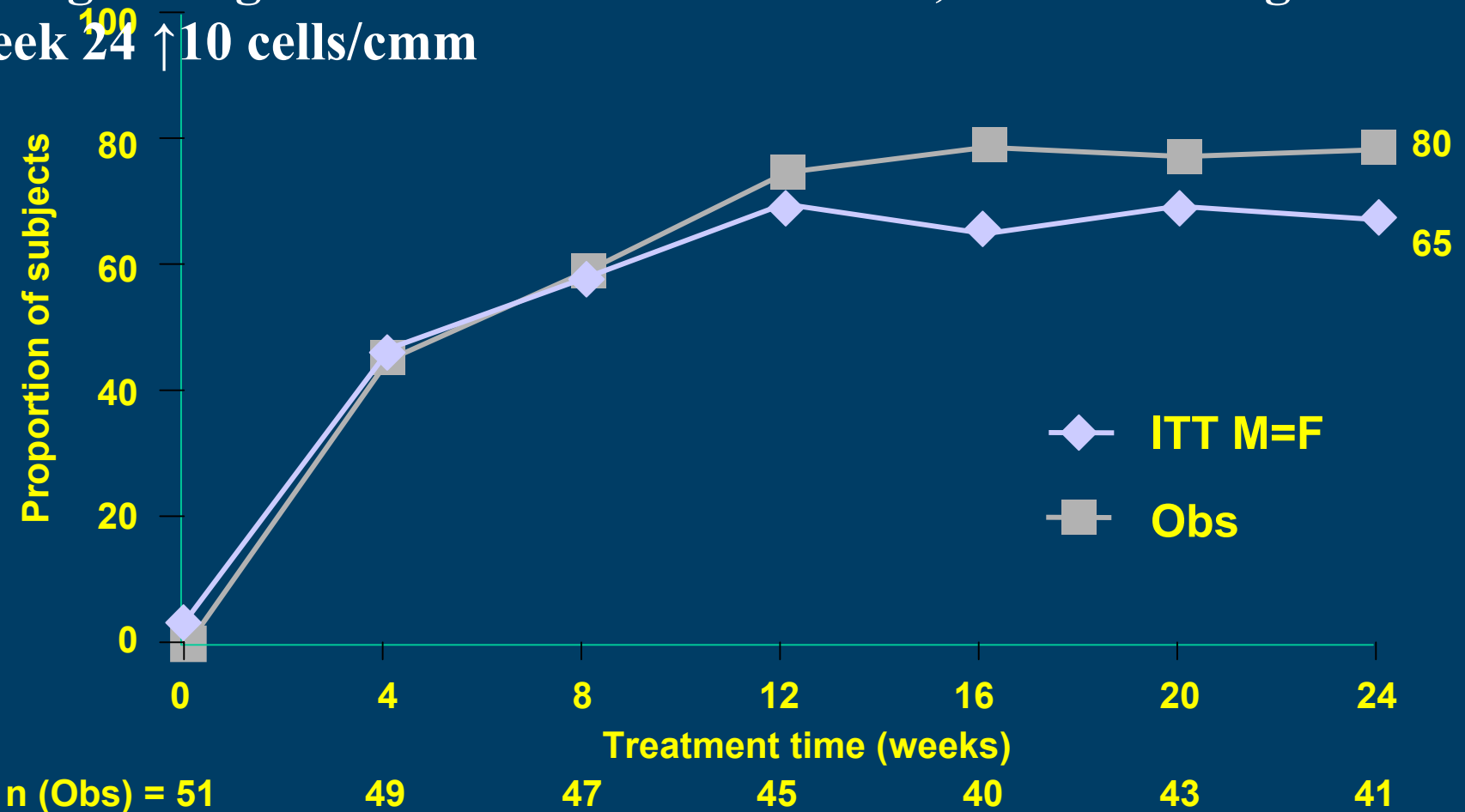
***Initial ART regimen composed of ZDV (or d4T) + 3TC + PI or NNRTI**

Key exclusion criteria: Screening genotype with > 2 NRTI-associated mutations or K65R

H-563

Virologic Response (HIV-1 RNA <50 c/mL) Through WK 24

No sig. change CD4 but median 463 at BL; median change at week 24 ↑10 cells/cmm



Miscellaneous Notes on a Variety of Subjects

Syphilis—A New Epidemic

- **As *T. pallidum* is not one subspecies, vaccine will be hard to generate. Also, need to grow spirochetes in rabbits so hard to get sufficient numbers for analysis.**
- **Very limited data on any therapy other than PCN.**
- **Large scale study now on azithromycin but early failures are being reported.**
- **Although CDC notes that 2 fold reduction by 6months for +ve response, but may be closer to 12 months (esp. if HIV+)**
- **Also, 21% did not respond to PCN therapy at 12months in HIV+ patients as evidenced by ↓ VDRL titer (Rofls, NEJM, 2004)**

HCV/HIV Studies-H-156—Predictability of SVR in HCV/HIV with pegIF α and RBV

- From the APRICOT study
- Peg IF α 180ug/wk plus RBV 800mg qd
- 289 patients treated with this regimen in trial
- 116/289 had SVR (HCV VL BLQ) at end of 72 wk post-therapy follow up
- Of the 116—99 had >2 log drop HCV VL at week 4 of therapy. Overall, 52% of 289 had such a drop at week 4. **HOWEVER, 114/116 had +ve response at week 12**
- Of the 116—51 genotype 1 and 59 genotype 2/3
- Cannot recommend testing yet at week 4

H-1757—Long Term F/U of HCV/HIV Treated Patients

- **Retrospective analysis of 351 patients rx'd in Madrid Spain**
- **All had some form of therapy for HCV but SVR in 77 pts only (22%)**
 - 22/119 with IF only, 17/106 with IF-RBV, 38/126 with pegIF-RBV
 - No difference in demographics or genotypes in LT responders and not. No difference in HIV course either
 - Of the 274 non sustained responders, 90% had persistent elevated LFTs and 4% developed cirrhosis and 2 died of ESLD

HCV/HIV/HBV—all 3 together

- **V-1153—HCV clearing in triple infected patients**
 - HIV/HCV/HBV infected and HBsAg+
 - Cross sectional study comparing these patients to HBsAg-
 - From Spain
 - 68% HCV VL neg if sAg+ vs. 10% if sAg- ($p < .01$)
 - No difference if HBV VL + or – ; and no difference if on TDF or 3TC
 - Multivariate analysis shows only sAg+ difference in these groups
 - Has been seen in HCV/HBV patients but never studied in HIV+ patients also

Anemia Therapy and Quality of Life

- **H-1761—Q2wk Epo Alpha for anemia**
 - Hgb <12 and stable HAART ≥4 wks.
 - Excluded if OI, HCV on IFN/RBV, pregnant, ferritin<40
 - 292 enrolled, 222 evaluated
- **Median Hgb—11.1 (range 7.2-12.8)**
- **EpoA 40K units Q2wk until Hgb>14; restarted when <11 again**
- **24wk—208 pts, mean Hgb ↑ 2.6g/dl, All QOL measures increased significantly (p<.001)**
- **Serious AE— 1 htn, 1 neutropenia, 8.9% diarrhea**

2 Other Studies Worth Noting

- **H-868: Stability of LPVr at Higher Temperatures**
- Studied stability of capsules at 35° and 45°C
- 35° (95F)--can last 30 days but take on moisture and lose structure by 60 days
- 45° (113F)--capsules break after 24 hours
- Implications for Africa and military
- **H-166: BMD in AA HIV+ Pts**
- X-sectional study of BMD in 267 HIV+ pts at Walter Reed
- DEXA scans—all volunteer
- 6% osteoporosis and 40% osteopenia
- NOT related to HAART, CD4, or years of disease
- Only univariate analysis done—only AA race found significant risk for ↓BMD