
CROI 2007 Update
New Agents: Maraviroc, TMC 278;
Drug Resistance Update

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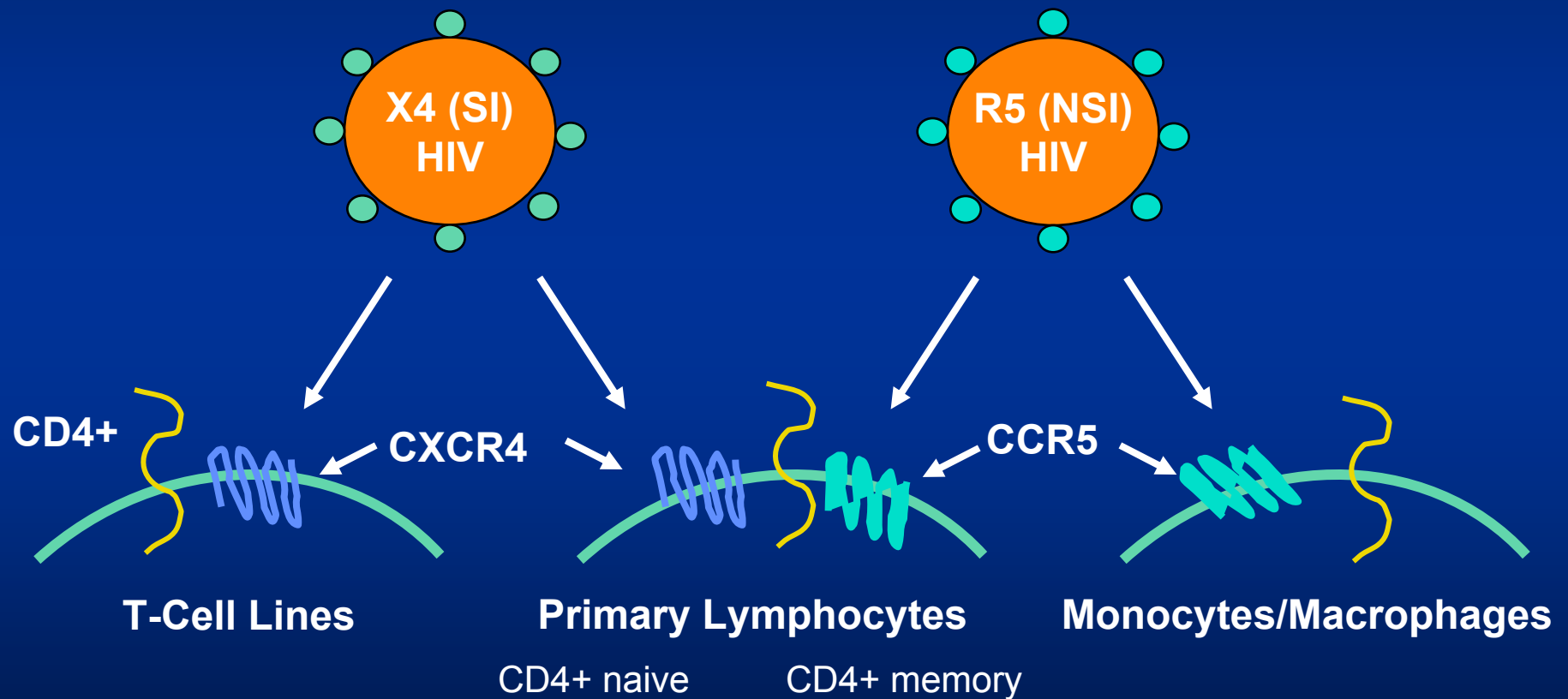
Outstanding sessions that you can view on the web

- International issues: breastfeeding (Session 7), HIV resistance in developing world (Session 59), benefits of circumcision (Abstract 155 LB), failure of first large female microbicide trial (Abstract 106 LB)
- Pathogenesis: HIV coreceptors (Session 12), immunopathogenesis of SIV and relevance to HIV (Session 8), review of immune reconstitution syndromes (Session 35), HIV restriction as possible therapeutic approach (Session 107)
- Drug resistance in naïve patients (Session 60), Low-frequency HIV resistance (Session 61)

Learning the names of new drugs

- Darunavir
- Etravirine
- Rilpivirine
- Maraviroc
- Vicriviroc
- Raltegravir
- Elvitegravir

Coreceptor Usage of HIV-1 Variants



Coreceptor Tropism by Treatment Status

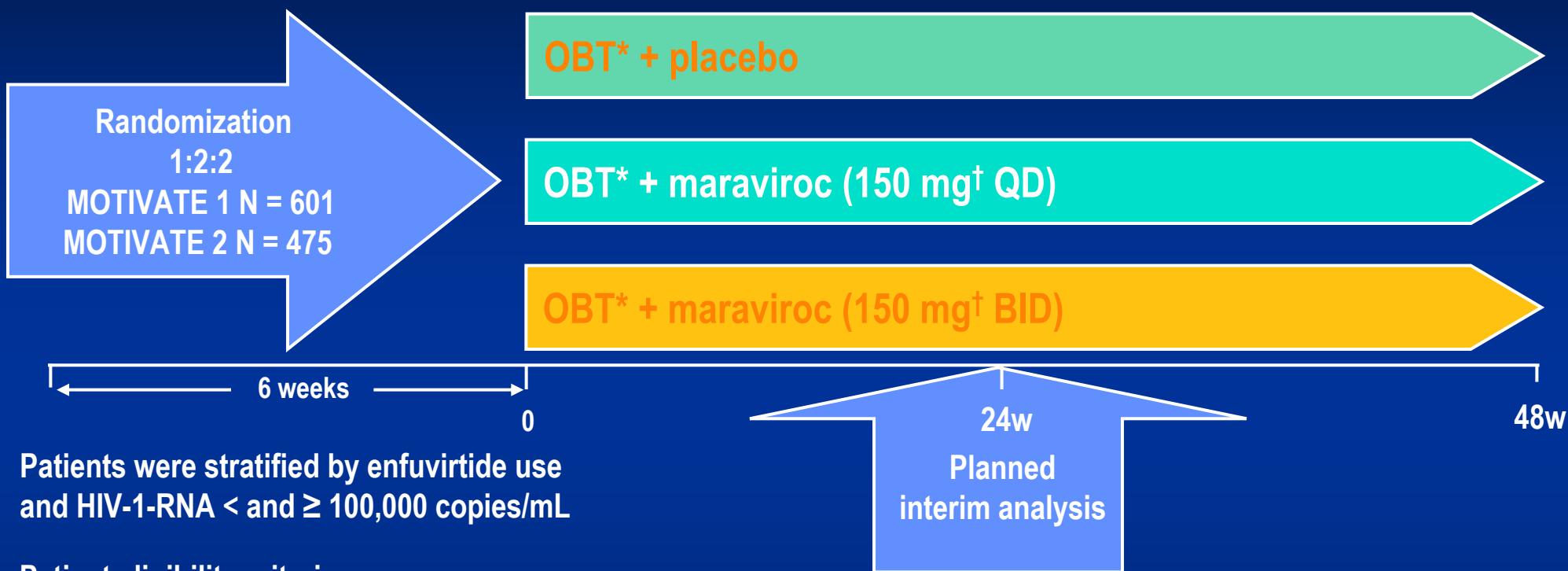
Study	Population	N	R5 Only, %	R5/X4, %	X4 Only, %
Demarest et al ^[1]	Naive	325	88	12	0
HOMER ^[2]	Naive	979	82	18	0.1
Moyle et al ^[3]	Naive	402	81	19	N/A
Demarest et al ^[1]	Experienced	117	67	28	5
Moyle et al ^[3]	Experienced	125	78	22	N/A
TORO ^[4]	Experienced	724	50	48	2
ACTG A5211 ^[5]	Experienced	391	49	47	4

1. Demarest J, et al. ICAAC 2004. Abstract H-1136.
2. Brumme ZL, et al. J Infect Dis. 2005;192:466-474.
3. Moyle G, et al. J Infect Dis. 2005;191:866-872
4. Melby T, et al. CROI 2006. Abstract 233.
5. Wilkin T, et al. CROI 2006. Abstract 655.

Challenges in CCR5 Inhibitor Development

- Tropism may be related to disease stage, not treatment experience
 - Higher prevalence of X4 virus in patients presenting with advanced disease
 - Trends toward later initiation of therapy may bias against use of CCR5 inhibitors
- Uncertain long-term safety of CCR5 inhibition
 - Atravirine development halted because of hepatotoxicity
 - ACTG 5211 demonstrated higher incidence of malignancy in raltegravir arm
- Uncertain risk/implications of X4 emergence
- Uncertain benefit in patients with mixed infection
 - Prior study of maraviroc in dual tropic/X4 patients showed safety but minimal virologic or immunologic benefit
- Cost and delay of initiating therapy because of need for tropism assay

MOTIVATE 1 and 2: Trial Design (Abstracts 104LB and 105LB)



Patient eligibility criteria:

- R5 HIV-1 infection
- HIV-1-RNA ≥ 5,000 copies/mL
- Stable pre-study ARV regimen, or no ARVs for ≥ 4 weeks
- Resistance to and/or ≥ 6 months' experience with ≥ one ARV from three classes (≥ two for PIs)

* OBT = optimized background therapy of 3–6 ARVs (PK boosting doses of RTV not counted as an ARV)

[†] Subjects receiving a PI (except TPV) and/or delavirdine in their OBT received 150 mg dose of MVC; all other subjects received 300 mg dose of MVC

Demographics and Baseline Characteristics

Treated N = 585	Placebo + OBT N = 118	MVC QD + OBT N = 232	MVC BID + OBT N = 235
Mean age, yrs (range)	46 (31–71)	46 (19–75)	46 (25–69)
Male, n (%)	106 (90)	210 (91)	212 (90)
White, n (%)	99 (84)	187 (81)	197 (84)
Median CD4 count*, cells/mm ³ (range)	163 (1–675)	168 (1–812)	150 (2–678)
Mean HIV-1 RNA*, log ₁₀ c/mL (range)	4.84 (3.46–6.02)	4.85 (3.20–6.75)	4.86 (3.26–6.88)
Enfuvirtide in OBT, %	42	43	46
≤ 2 active drugs in OBT [†] , %	66	69	76

Includes all patients who received at least one dose of study medication

* Baseline for each patient calculated as the mean of up to three pre-dose assessments (screening, randomization, and baseline visit);

[†] According to Overall Susceptibility Score; c/mL = copies/mL

MOTIVATE 1 – 24 week results

	Placebo	Maraviroc qd	Maraviroc BID
n	118	232	235
HIV RNA (log)	-1.03	-1.82*	-1.95*
VL < 400 (%)	31.4*	54.7*	60.4*
VL < 50 (%)	24.6*	42.2*	48.5*
CD4 change	+52*	+107*	+101*

- Similar results for patients with baseline VL >100K or < 100K; similar results for with and without T20 (T20 naïve patients not analyzed separately); maraviroc arms superior if composite OBT sensitivity ≤ 2

All groups received OBT

*P<0.001 versus OBT

MOTIVATE 1 & 2: Effect of Tropism Switch on CD4 count at Time of Failure

	Mean change in CD4 count from baseline, cells/mm ³		
Tropism result, Baseline → Treatment Failure	Placebo + OBT N = 209	MVC QD + OBT N = 414	MVC BID + OBT N = 426
All patients with treatment failure	14 (n=97)	49 (n=68)	71 (n=77)
R5 → R5	15 (n=80)	61 (n=18)	138 (n=17)
R5 → D/M or X4	67 (n=4)	37 (n=31)	56 (n=32)

- Approximately 8% of patients had a change in tropism result between screening and baseline, demonstrating the change in background tropism over a 4–6 week period in this population

Data excludes patients who had no tropism result at time of failure and patients with non-R5 virus at baseline

Summary of 24-week Interim Analyses of the MOTIVATE 1 and 2 trials

- Maraviroc (BID or QD) + OBT provided significantly superior virologic control compared to placebo + OBT in this ARV-experienced patient population
 - Virologic response was not affected by baseline viral load or inclusion of enfuvirtide in OBT
 - Superior virologic response with maraviroc was most pronounced in patients with ≤ 2 active drugs in their OBT
- Maraviroc (BID or QD) + OBT provided significantly superior increases in CD4 count compared to placebo + OBT

Summary of 24-week Interim Analyses of the MOTIVATE 1 and 2 trials

- There were no clinically relevant differences in the safety profile between maraviroc (BID or QD) and placebo treatment groups (especially with regard to hepatotoxicity and malignancy)
- Fewer patients receiving maraviroc experienced treatment failure compared to those receiving placebo, however more patients on maraviroc had a change in tropism result to D/M or X4 at time of failure
- Tropism switch was not associated with deleterious effects on CD4 counts previous to or at time of virologic failure
- Only a subgroup of treatment-experienced patients will have significant benefit from this drug determined by an expensive laboratory test

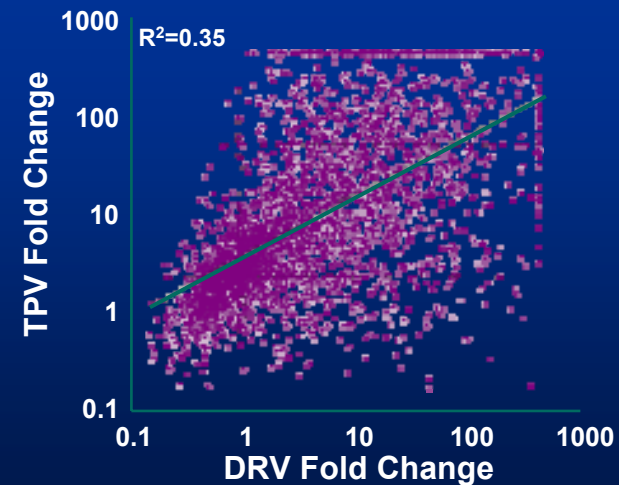
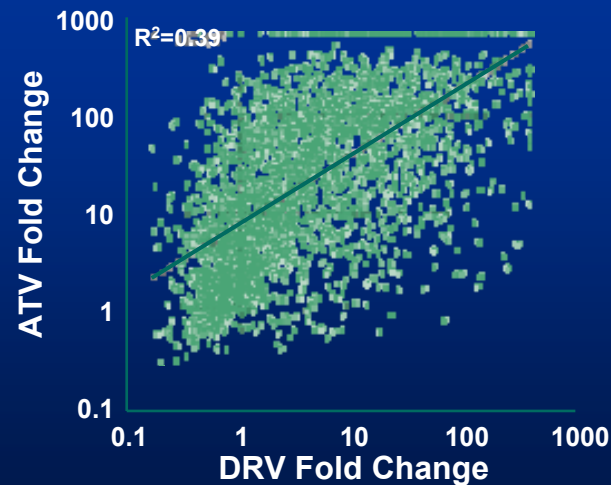
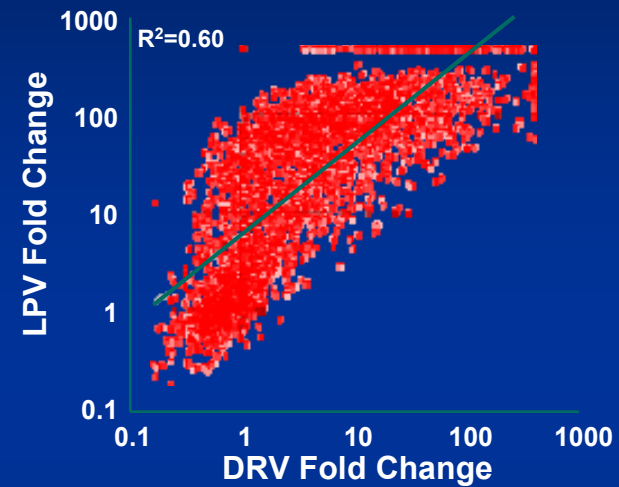
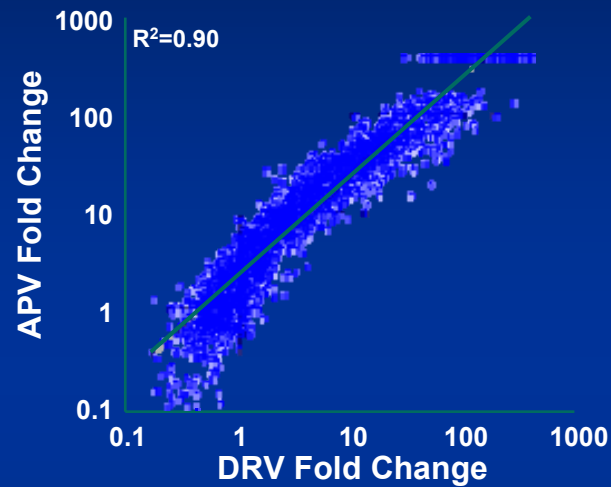
Maraviroc dosing in expanded access

- 150 mg BID if on PI (other than tipranavir)
- 300 mg BID if on tipranavir or if no NNRTI or PI is in regimen
- 600 mg BID with nevirapine or efavirenz
- Dose with concurrent TMC 125 not established
- Not anticipated to have drug interactions with raltegravir

Darunavir Cross Resistance (Abstract 607)

- Review of 2600 clinical isolates from Monogram database with at least 1 major PI mutation beginning May, 2006
- Isolates could not have mixture at any of the key darunavir mutations (V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, L89V)
- Hypothesis was that correlation between darunavir and amprenavir resistance would be high because of similar biochemical structure
- Goals were: to correlate DRV phenotypic resistance with other PIs; AND to correlate DRV genotypic mutation score with phenotypic resistance

DRV Cross Resistance



Results

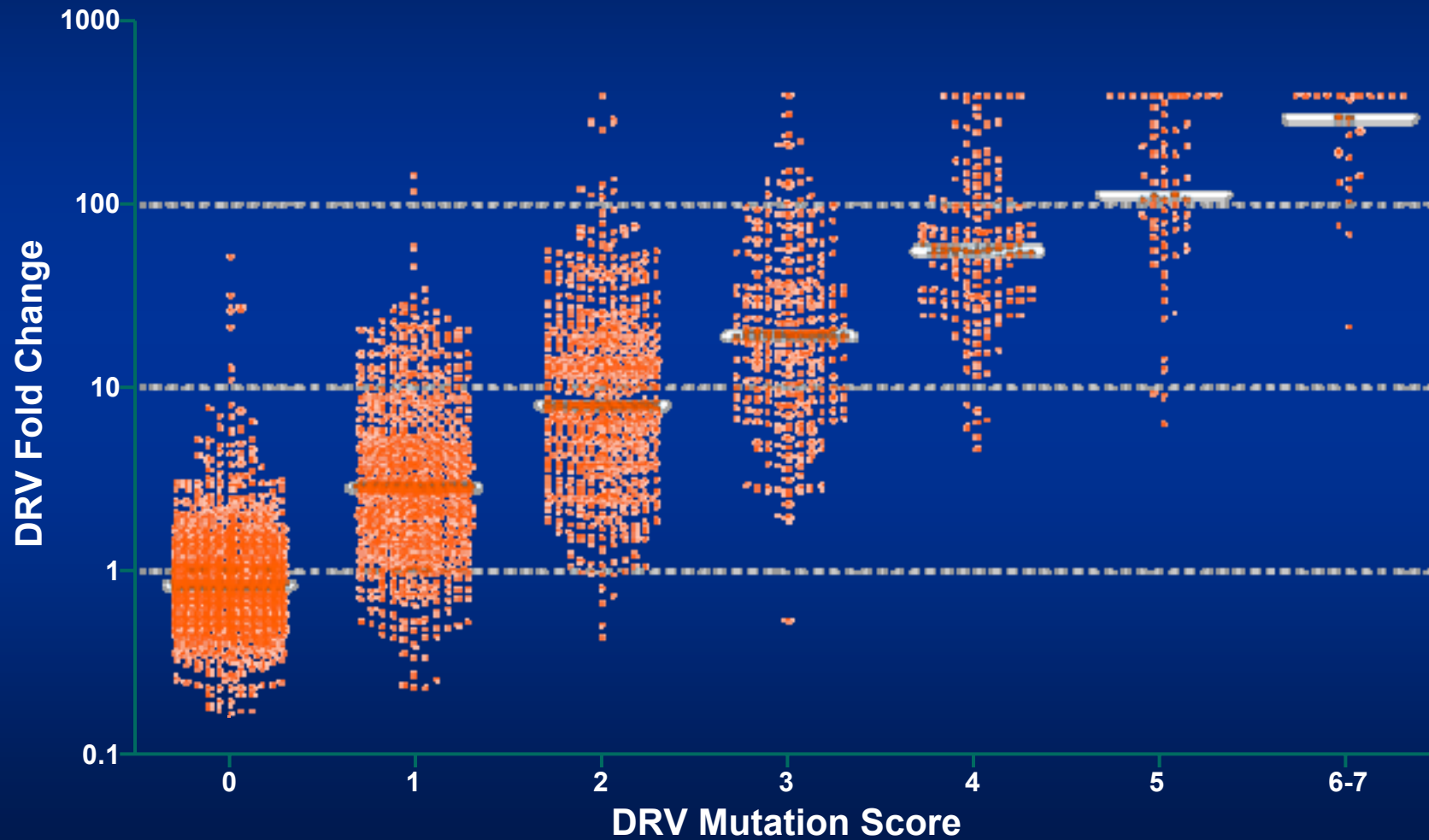
- the prevalence of phenotypic darunavir resistance was low (high level resistance 5%)
- darunavir resistance highly correlated with amprenavir resistance, although the prevalence of darunavir resistance was only 12% among amprenavir resistant isolates
- In AMP-resistant isolates, high level cross resistance to DRV infrequent (<17%) – ?due to higher DRV IQ or binding to PI active site
- 35% of DRV/r still at least partially S to TPV/rtv
- All DRV resistant isolates also fully resistant to LPV and AMP

Incidence of high level PI resistance in 2800 isolates (using higher clinical cutoff on Monogram PT Assay)

% highly resistant

DRV/r	5
TPV/r	22
LPV/r	42
AMP/r	57

DRV Mutation Score Performance



Revised Monogram Clinical Cutoffs for Darunavir (Abstract 610)

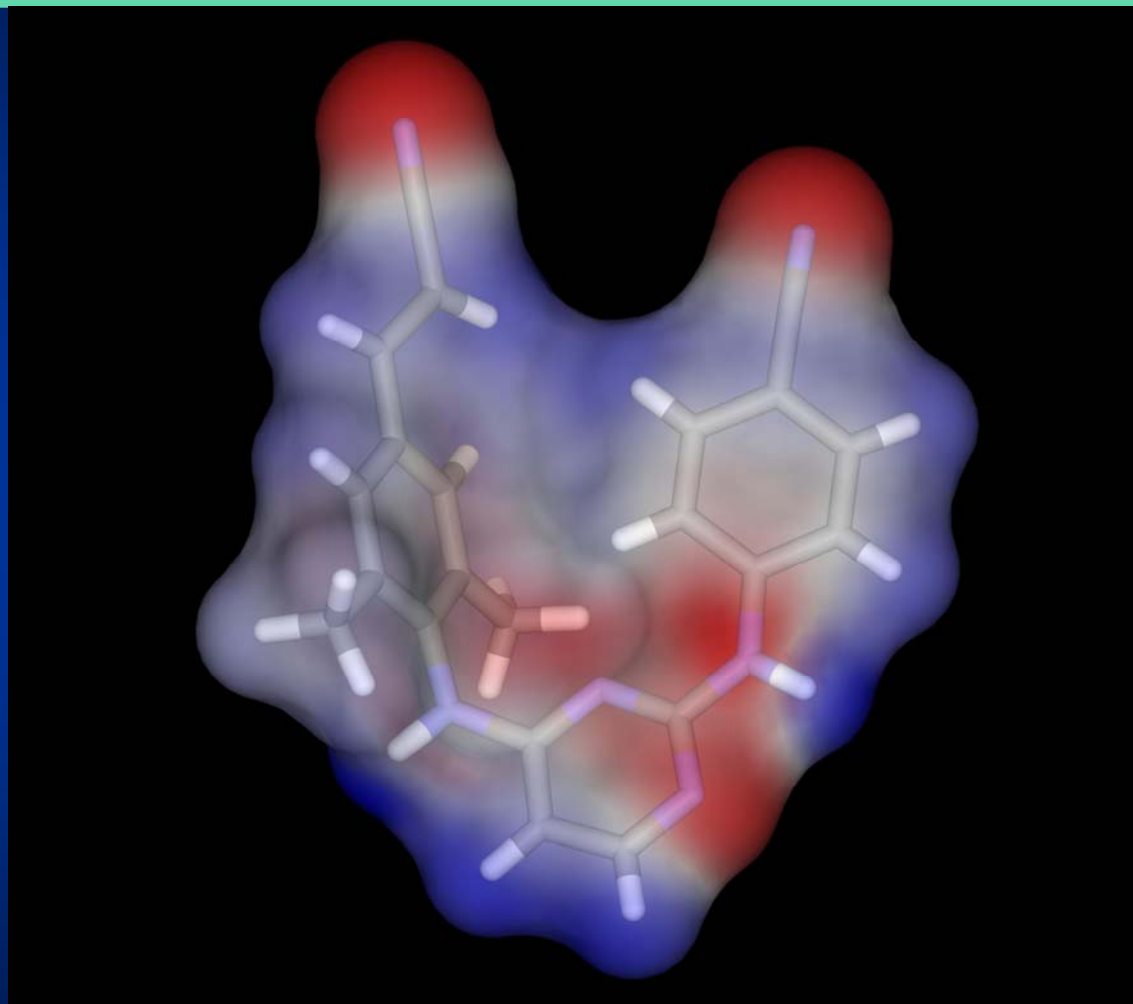
- Methods: review of patients for whom DRV was only active drug added at baseline in POWER 1, 2 and 3 (n=76)
- Virologic Response by baseline FC described:

Log HIV RNA change at week 2

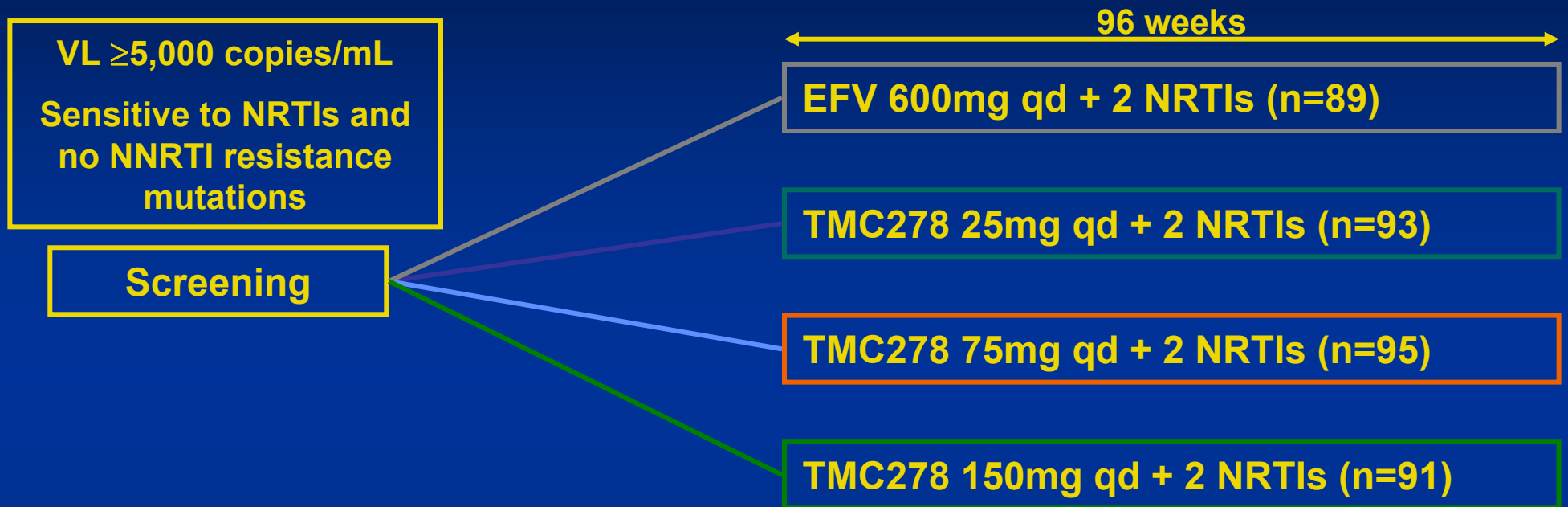
FC < 10	-1.7
FC 10 – 90	-1.2
FC > 90	-0.3

TMC 278 (Ralpivirine) – Background

- DAPY (diarylpyrimidine) NNRTI with half-life of 45 hours
- Active against 90% of a panel of 1500 isolates of NNRTI resistant viruses, whereas only 33% sensitive to efavirenz (de Bethune, Abstract 556, 12th CROI, 2005)
- Double mutant L100I and K103N associated with fold change of 5 in phenotypic sensitivity
- Mutations selected in vitro: L100I, V106I, Y181C, M230I
- Previous 7 day monotherapy study showed approximately 1.2 log HIV RNA reduction in naïve patients after qd dosing of 25 mg to 150 mg (Goebel, Abstract 160, 12th CROI, 2005)



TMC278-C204 Phase IIb, ARV-naïve Patients (Abstract 144LB)



- Randomized controlled study
- TMC278 blinded for all 3 dose groups versus open label efavirenz
- Stratification factors
 - Investigator-selected NRTI backbone: Combivir[®] (75.3%) or Truvada[®] (24.7%) (given as combination or individual components)
 - Region (Asia and Africa; US, Europe and Russia; Latin America)

Demographic and Baseline Characteristics

Characteristic	All TMC278* n=279	EFV 600mg n=89
Gender, % female	33.0	32.6
Race, % Caucasian	44	47
Age, years	35 (19–67)	35 (21–63)
VL, log ₁₀ copies/mL	4.84 (2.16–7.13)	4.88 (3.37–6.41)
VL, copies/mL	69,300 (144–13,600,000)	75,100 (2,320–2,570,000)
CD4 cell count, cells/mm ³	200 (5–758)	207 (3–970)
Duration of known HIV infection, years	1.0 (0–21)	1.0 (0–15)

Patient Disposition at Week 48

Primary Efficacy Endpoint, ITT Population

Parameter, n (%)	TMC278			
	25mg qd n=93	75mg qd n=95	150mg qd n=91	EFV 600mg n=89
VL <50 copies/mL*	75 (81)	76 (80)	70 (77)	72 (81)
Virologic failure	8 (9)	5 (5)	6 (7)	5 (6)
Death	0	1 (1) [†]	0	0
Discontinuation due to adverse event (AE)	6 (6)	5 (5)	9 (10)	5 (6)
Discontinuation for other reasons	4 (4)	8 (8)	6 (7)	7 (8)

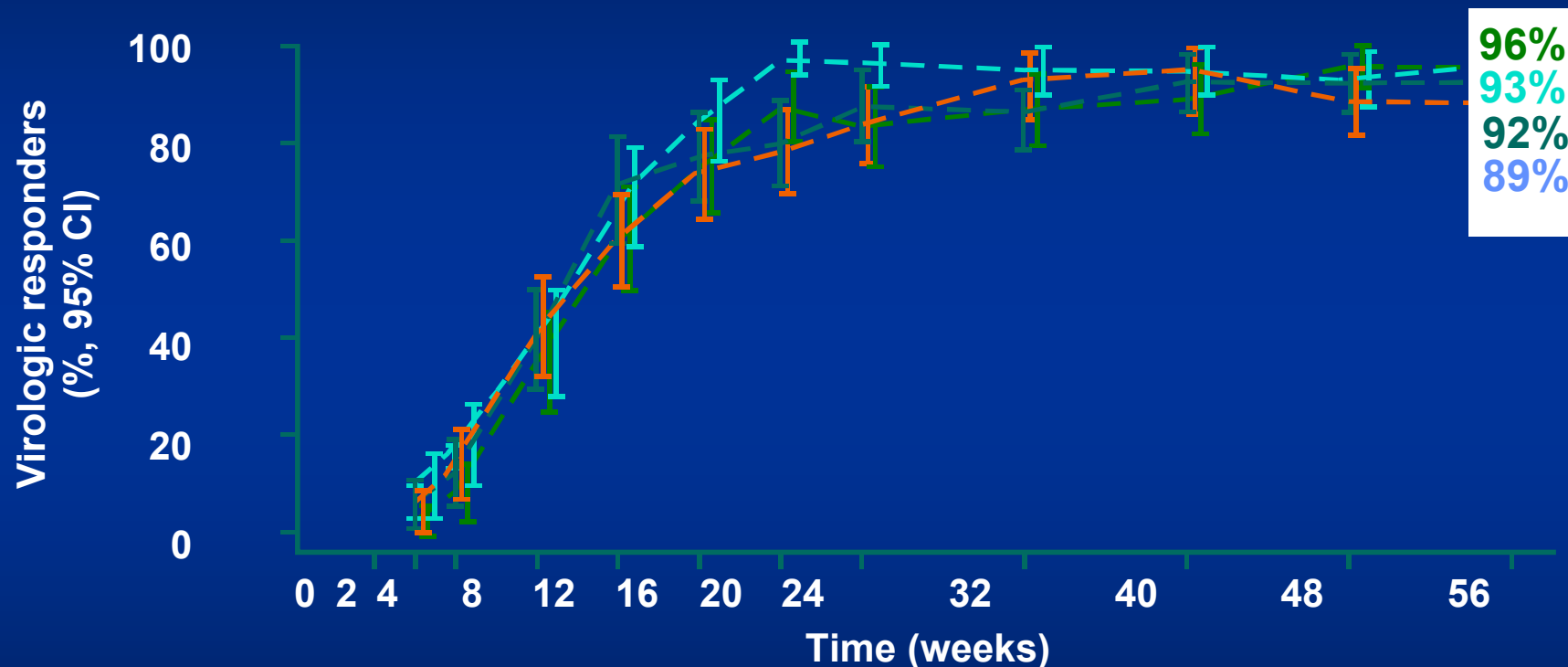
*TLOVR = time to loss of virologic response; NC=F = non-completer = failure; ITT = intent to treat.

Virologic response and loss of response need confirmation with subsequent VL measurement.

[†]Not related to TMC278

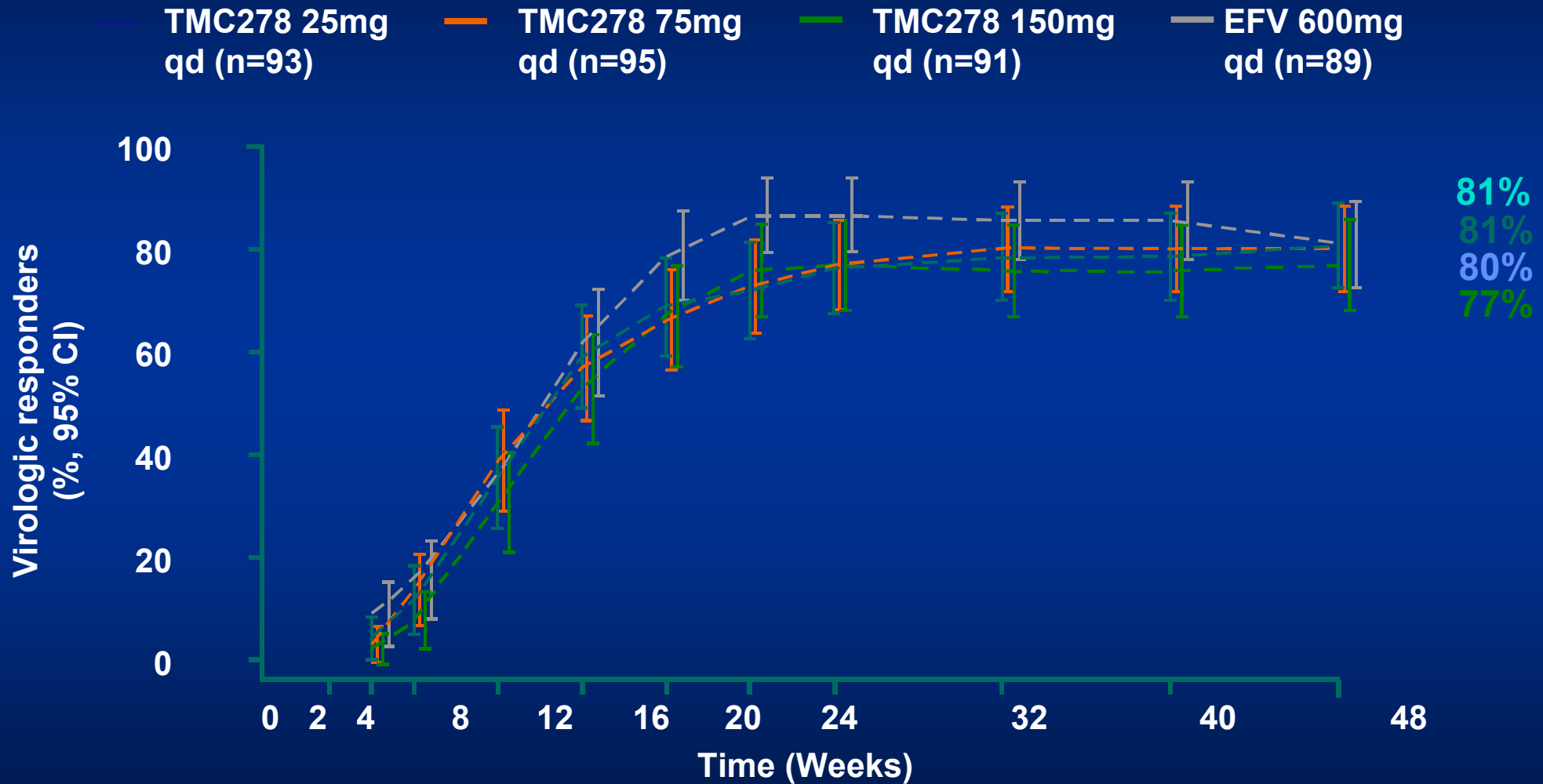
VL <50 Copies/mL Through 48 Weeks (Observed)

TMC278 25mg qd TMC278 75mg qd TMC278 150mg qd EFV 600mg qd



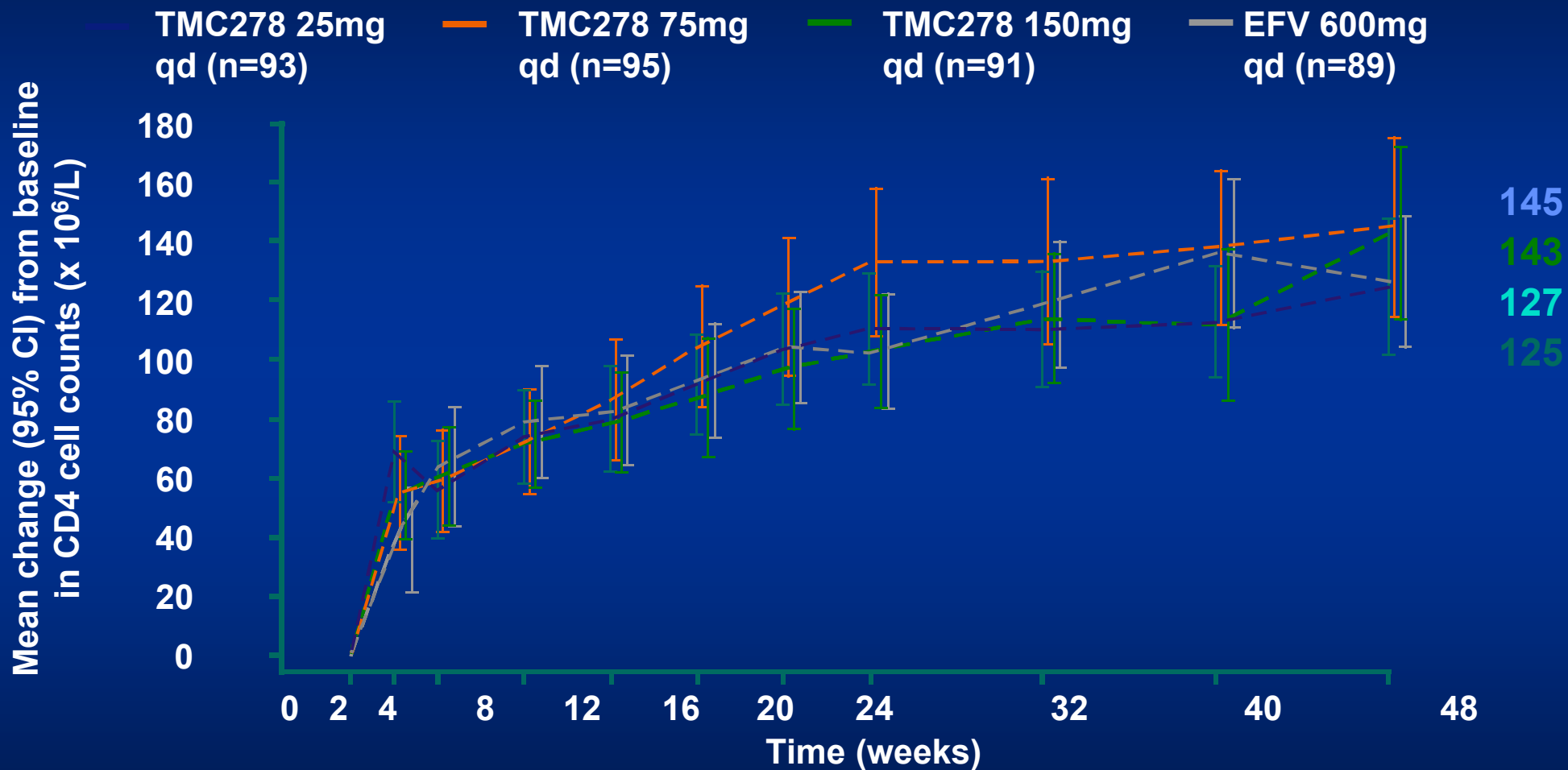
TMC278 25mg N =	8990	88	81	84	81	81	81	80	78	28
TMC278 75mg N =	9392	90	92	88	88	87	83	81	81	26
TMC278 150mg N =	8987	86	83	81	80	79	77	74	75	23
EFV 600mg N =	8384	82	83	79	80	80	80	79	76	27

VL <50 Copies/mL Through 48 Weeks (Primary Efficacy Endpoint, ITT Population)



CI = confidence interval

Change in CD4 Cell Count Through 48 Weeks



For premature discontinuations: data imputed with baseline value (NC=F)
For missing values: last observation carried forward (LOCF)

TMC 278-C204: Safety

- Higher incidence of vomiting, dizziness, somnolence, vertigo, abnormal dreams, and rash in efavirenz arm
- Higher incidence grade 3/4 severe adverse events in TMC 278 arms (study was not blinded to drug, only to TMC 278 dose)
- No difference in grade 3/4 laboratory abnormalities in EFV and TMC278 arms
- Mild increases in chol, LDL and TG in EFV arms versus TMC 278
- The 75mg dose, one pill once daily, has been selected for further development in treatment-naïve HIV patients

Commercial Resistance Testing Underestimates Resistance in Rx-Naïve Patients (Abstract 639)

- Commercial testing will not identify minor variants <20% of population
- Real-time PCR for specific point mutations can detect mutations with frequencies between 0.4 and 2% of viral population
- Screening for resistance using real-time PCR done in 205 treatment-naïve patients with “wild type HIV” by commercial assays and 302 treatment-naïve patients with at least 1 resistance mutation identified by commercial assays
- Real time PCR was done for the following point mutations: M41L, K70R, K103N, Y181C, M184V, T215F/Y

Commercial Resistance Testing Underestimates Resistance in Rx-Naïve Patients (Abstract 639)

Results:

- Sensitive RT PCR identified mutations in 30/205 (15%) isolates previously identified as wild type by commercial assays; 2% of these isolates were multidrug-resistant
- Of 302 patients harboring at least 1 mutation at baseline by commercial testing, 7% were found to harbor additional mutations by the more sensitive real time PCR assay
- Similar results have previously been demonstrated explaining treatment failure of ARV regimens due to occult baseline resistance, and in predicting vertical transmission of HIV by women receiving nevirapine during labor

Neurosyphilis and HIV (Abstract 375): Is follow up lumbar puncture necessary?

- Standard of care is repeat LP q 6 mos until CSF abnormalities normalize (WBC, protein, CSF VDRL)
- Methods: 68 patients with HIV, >20 WBC in CSF, suspected neurosyphilis, had f/u LP at 3 mos, then every 3 mos until CSF parameters normalized; normalization of serum RPR defined as 4 fold decline from baseline
- Demographics: 67 patients were men, 44 (70%) had early syphilis, median CD4 383, median CSF WBC 44; CSF VDRL was reactive in 43%

Neurosyphilis and HIV (Abstract 375): Is follow up lumbar puncture necessary?

Findings:

- Odds of CSF normalizing was 52x in patients whose serum RPRs had normalized as compared to patients in whom RPRs had not normalized
- At 7 months, RPR normalization predicted CSF normalization in 88%
- At 13 months, RPR normalization predicted CSF normalization in 96% of subjects