Darunavir overview

Dr Mike Youle
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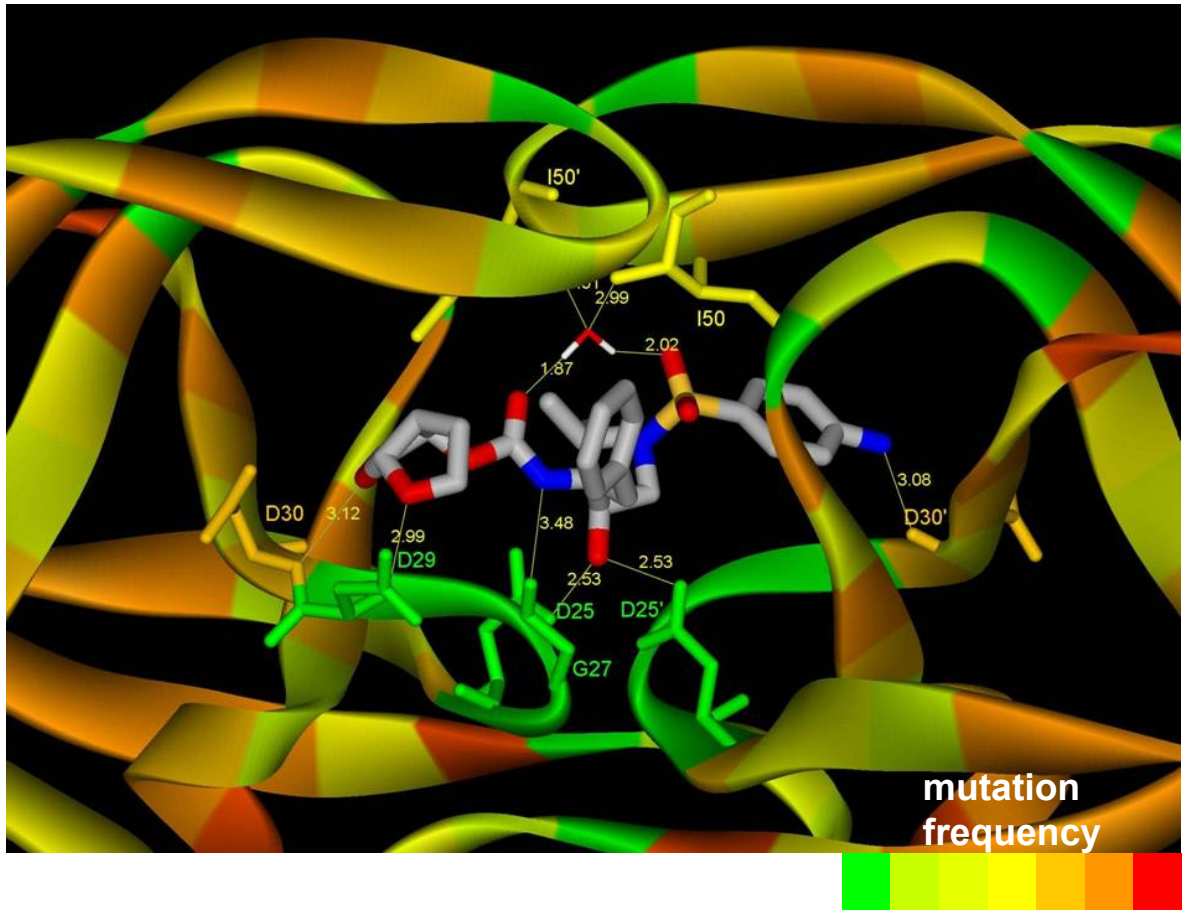
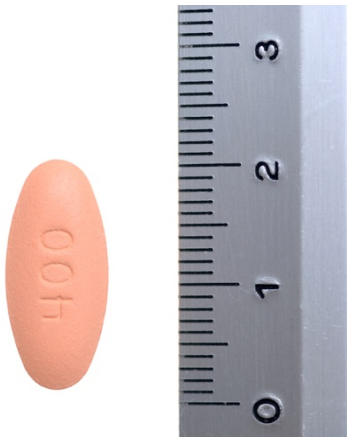
London

PREZISTA binding within HIV-1 protease



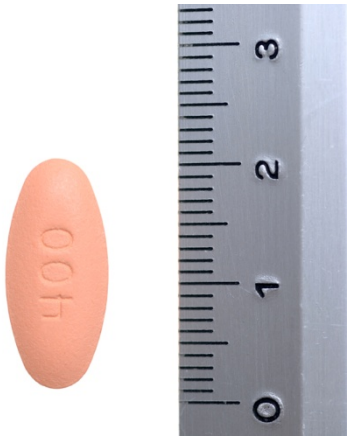
Data on file. Tibotec BVBA, Mechelen, Belgium

Once daily dosing with PREZISTA/r 800/100mg



PREZISTA 400mg*

RTV 100mg*



PREZISTA 400mg*

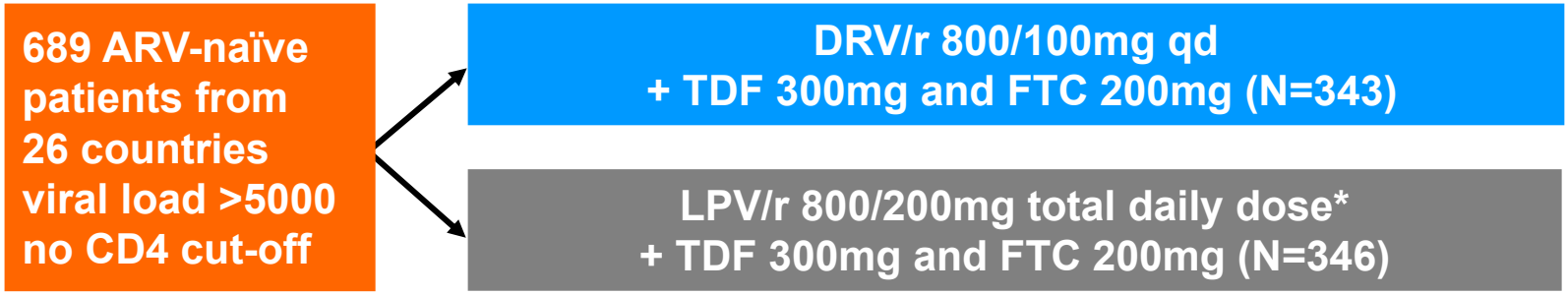
*All measurements in cm

ARTEMIS study

Naïve versus Kaletra

Efficacy and safety of darunavir/ritonavir 800/100mg once-daily versus lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients at 96 weeks: ARTEMIS (TMC114-C211)

Phase III study design



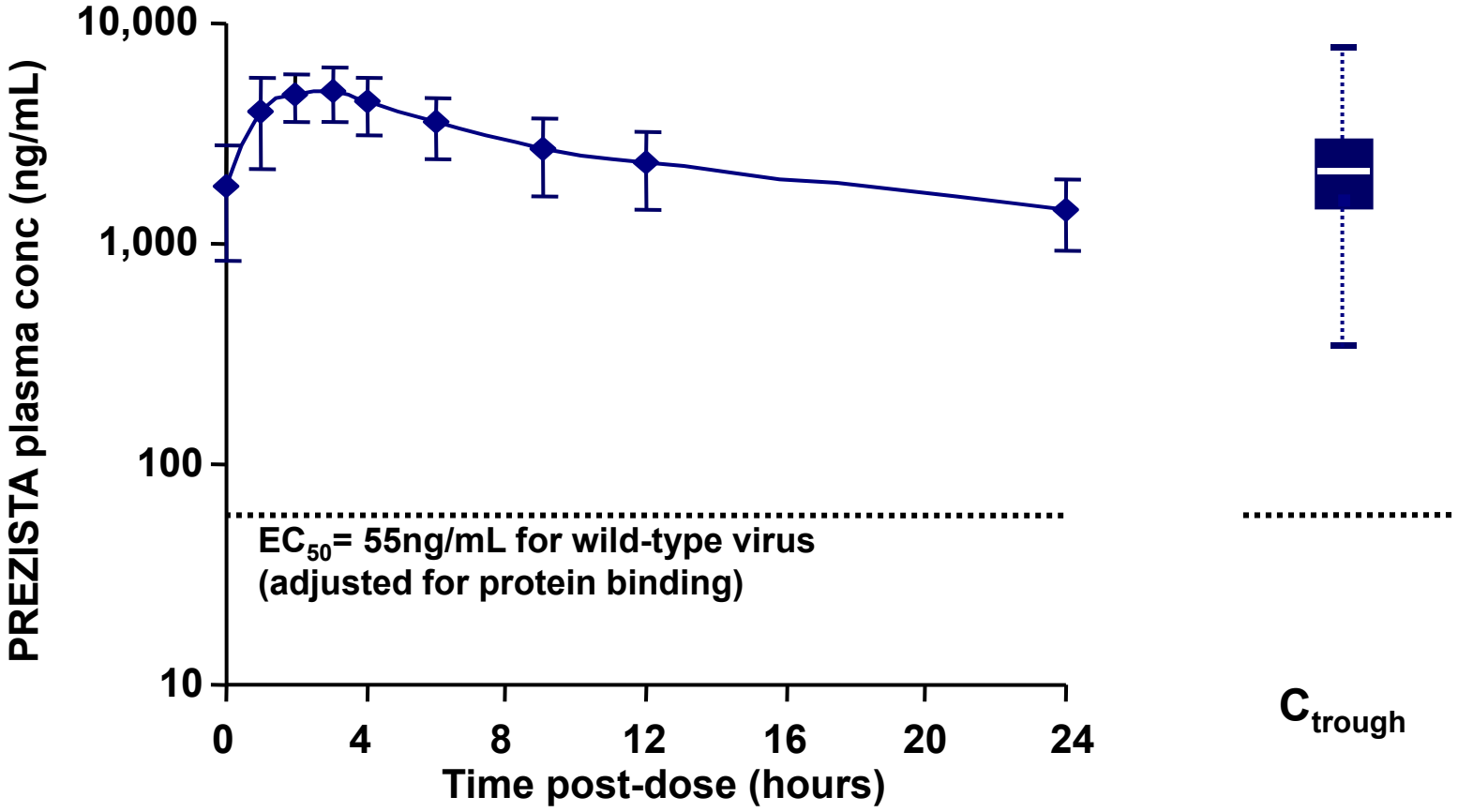
LPV dosing		LPV formulation	
qd =	15%	Capsule only =	12%
bid =	75%	Tablet only =	2%
bid/qd =	11%	Capsule/tablet switch =	86%

*qd or bid dosing was based on regulatory approval for naïve patients; switch from capsule to tablet (Meltrex) was made according to local regulatory approval and drug availability

TDF = tenofovir ; FTC = emtricitabine

Mills T, et al. 48th ICAAC/46th IDSA 2008. Abstract H-1250c

ARTEMIS: PREZISTA plasma concentrations for once-daily PREZISTA/r 800/100mg



PK substudy – week 4 data
(mean ± SD; n=9)

Population PK study
(median, IQR, range; n=335)

DeJesus E, et al. 47th ICAAC 2007. Presentation H-718b

ARTEMIS: Baseline characteristics

	DRV/r (N=343)	LPV/r (N=346)
Baseline demographics		
Female, n (%)	104 (30)	105 (30)
Mean age, years (±SD)	36 (9)	35 (9)
Caucasian, n (%)	137 (40)	153 (44)
Black, n (%)	80 (23)	71 (21)
Hispanic, n (%)	77 (22)	77 (22)
Asian, n (%)	44 (13)	38 (11)
Baseline disease characteristics		
Median HIV-1 RNA, copies/mL (range)	70,800 (835–5,580,000)	62,100 (667–4,580,000)
Median CD4 cell count, cells/mm^3 (range)	228 (4–750)	218 (2–714)
HBV/HCV co-infected, n (%)	43 (13)	48 (14)
Stratification factors		
CD4 cell count <200 cells/mm^3, n (%)	141 (41)	148 (43)
HIV-1 RNA ≥100,000 copies/mL, n (%)	117 (34)	120 (35)

SD = standard deviation; HBV = hepatitis B virus; HCV = hepatitis C virus

Mills T, et al. 48th ICAAC/46th IDSA 2008. Abstract H-1250c

ARTEMIS: Patient disposition at Week 96 analysis

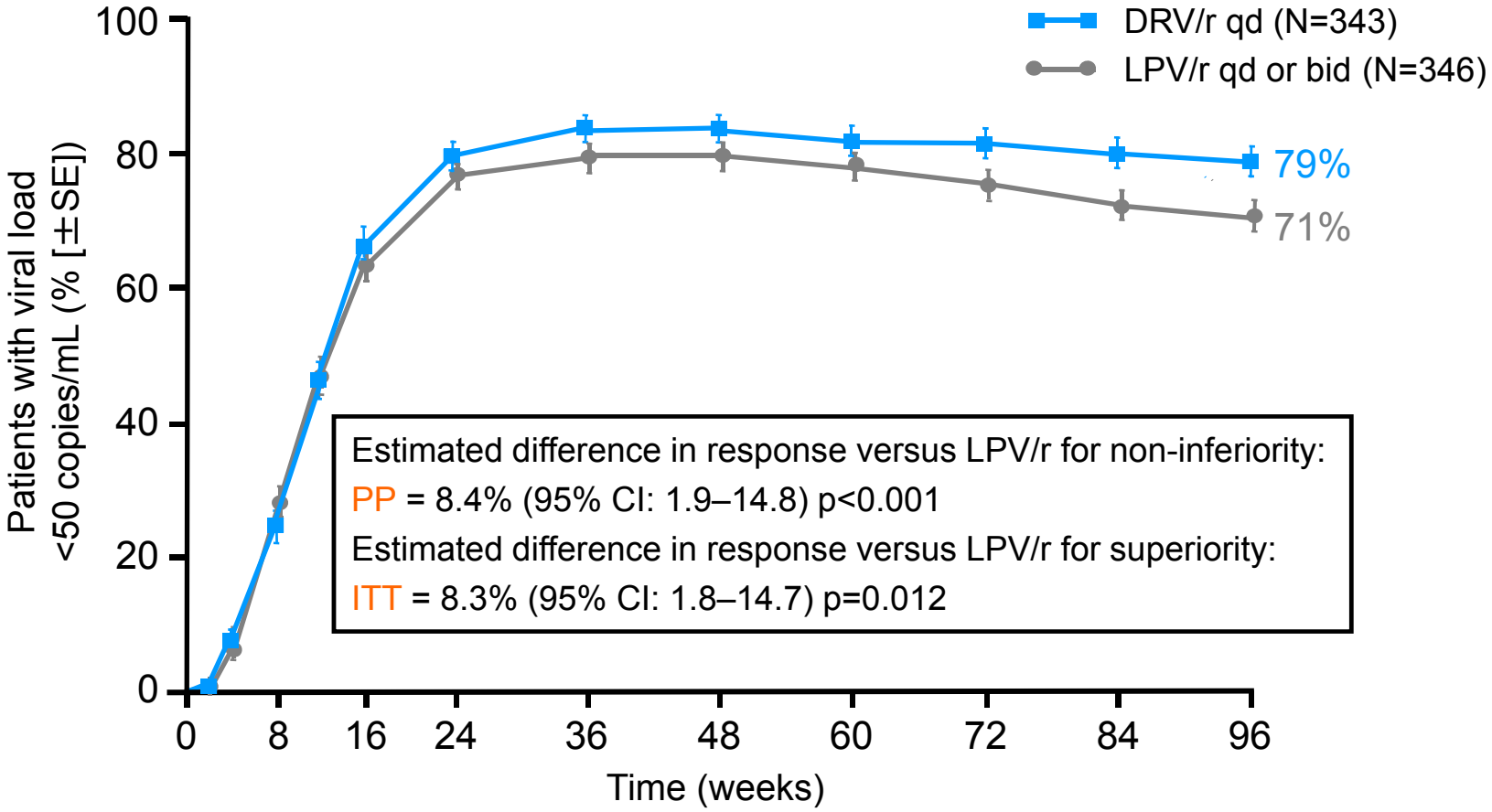
Incidence, n (%)	DRV/r (N=343)	LPV/r (N=346)
Discontinuation	59 (17)	81 (23)
AE*	13 (4)	32 (9)
Lost to follow-up	18 (5)	11 (3)
Withdrawal of consent	11 (3)	10 (3)
VF	3 (1)	8 (2)
Pregnancy	6 (2)	3 (1)
Non-compliance to study protocol	3 (1)	7 (2)
Other	5 (1)	10 (3)

*Includes six deaths (one in DRV/r group; five in LPV/r group)
Table includes all data up to the point when the last patient reached Week 96
Mean exposure was 93 weeks (range 0–130 weeks)

SE = standard error

Mills T, et al. 48th ICAAC/46th IDSA 2008. Abstract H-1250c

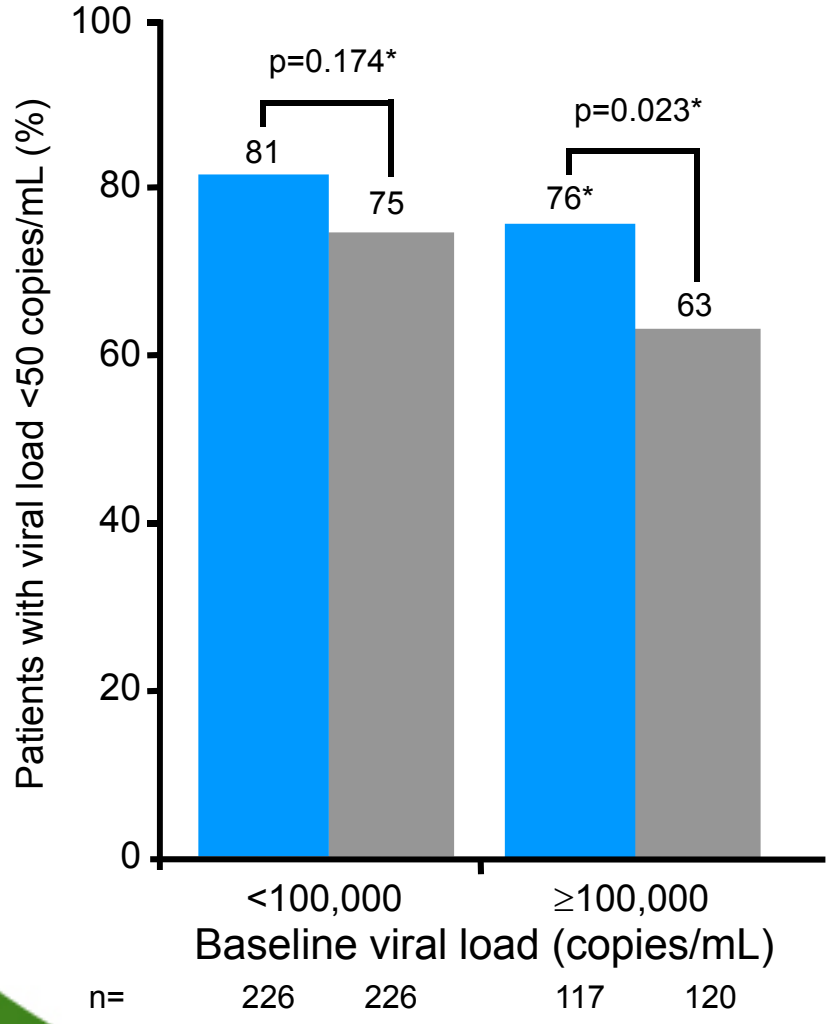
ARTEMIS: Viral load <50 copies/mL to Week 96 (ITT-TLOVR)*

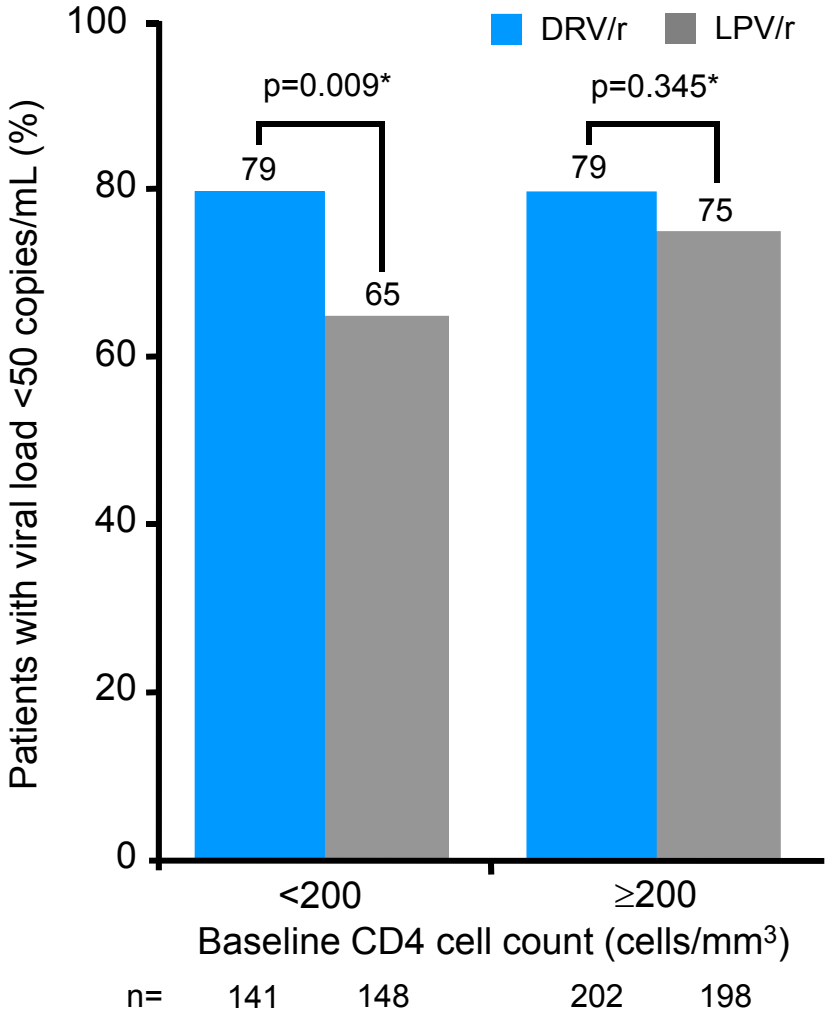


*Estimated from a logistic regression model including treatment and stratification factors (baseline $\log_{10}$ viral load and baseline CD4 cell count)

Mills T, et al. 48th ICAAC/46th IDSA 2008. Abstract H-1250c

ARTEMIS: Confirmed response by stratification factor (baseline viral load or CD4) at Week 96 (ITT-TLOVR)

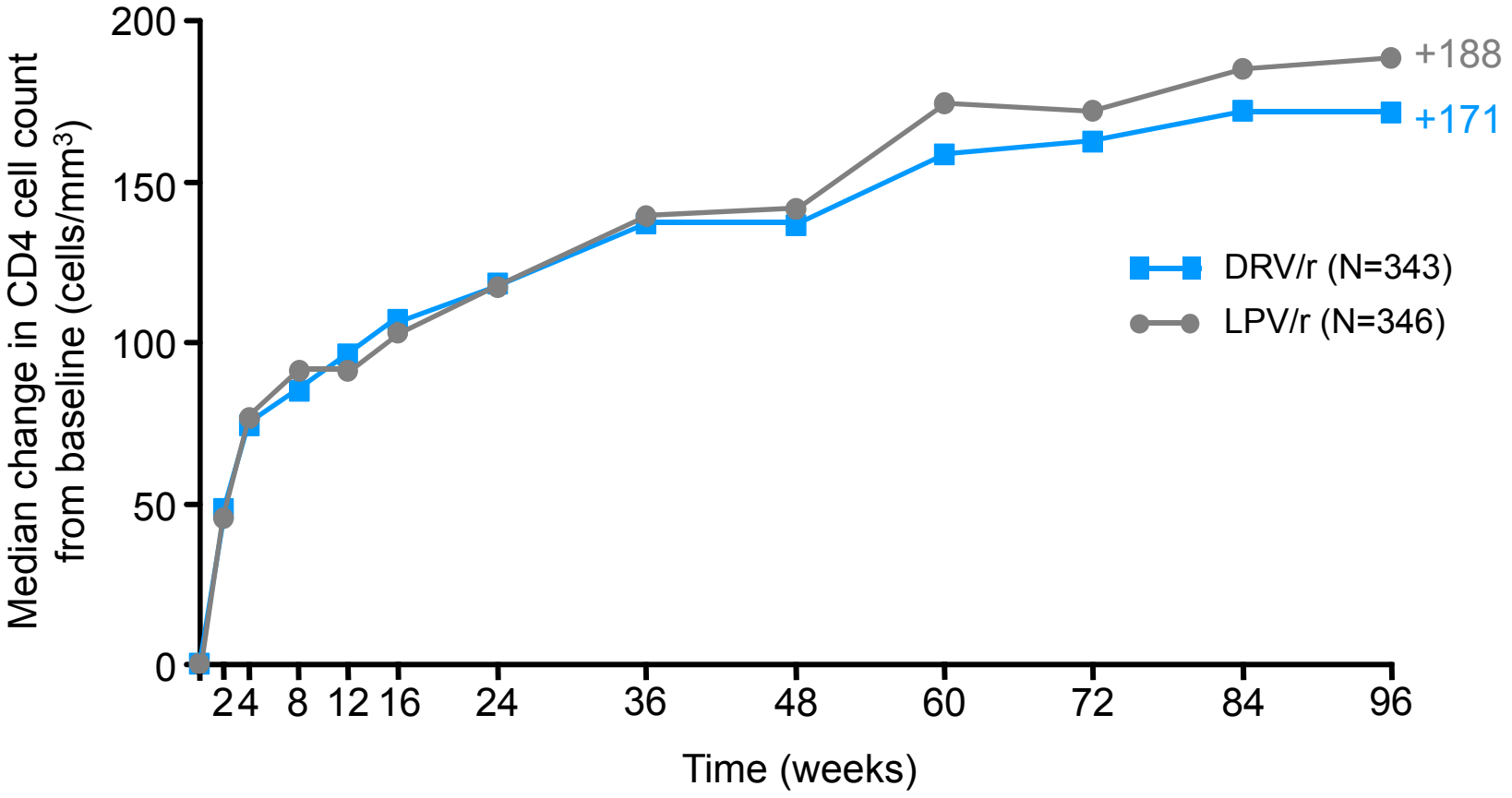




*Chi-square test

Mills T, et al. 48th ICAAC/46th IDSA 2008. Abstract H-1250c

ARTEMIS: Median change in absolute CD4 cell count to Week 96 (ITT-NC=F)



NC=F = non-completer = failure

Mills T, et al. 48th ICAAC/46th IDSA 2008. Abstract H-1250c

ARTEMIS: development of resistance in VFs

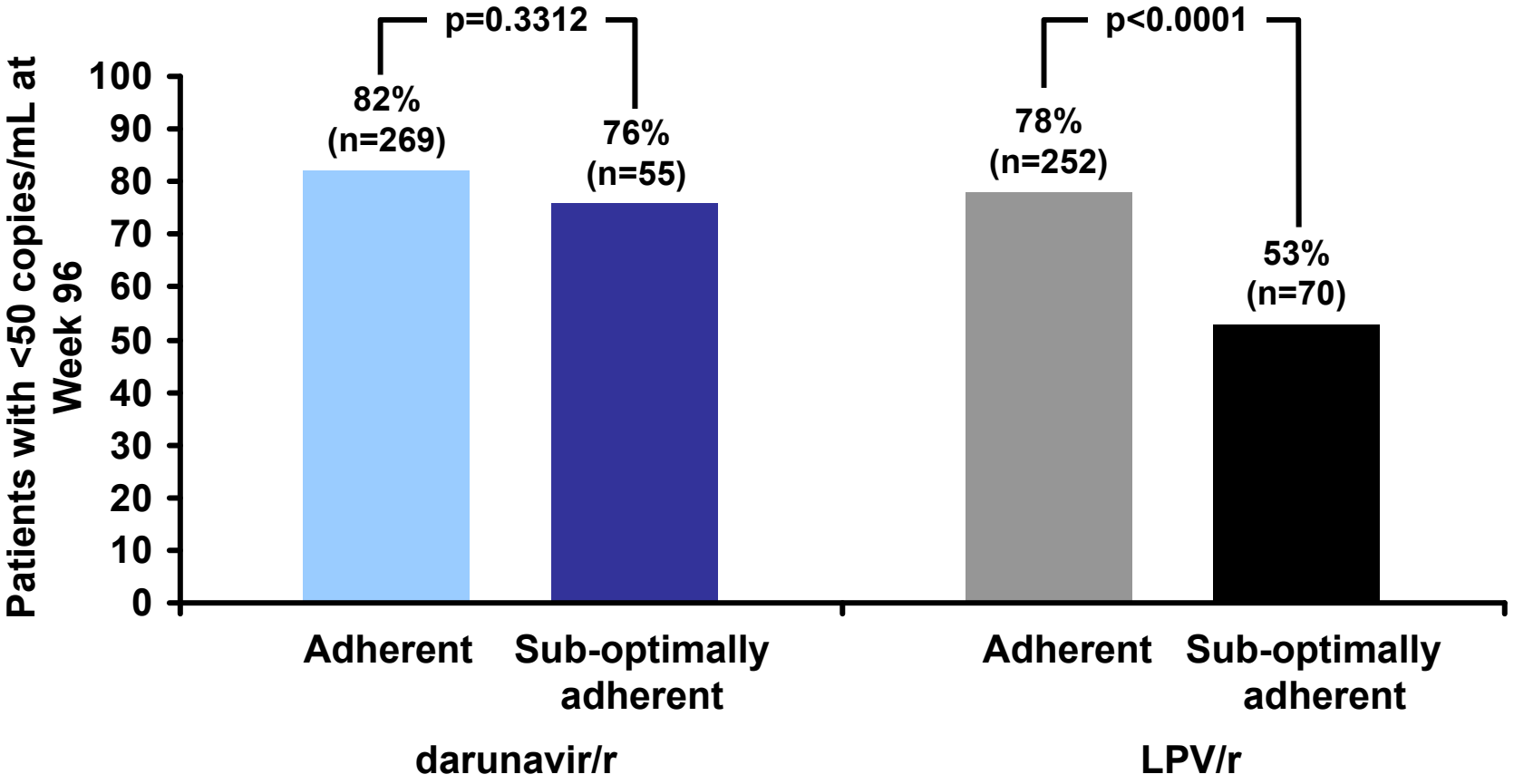
Number of patients, n	DRV/r (n=343)	LPV/r (n=346)
VFs	40	59
Paired genotypes	31	46
Developing major (IAS-USA) PI RAMs[1]	0	0
Developing minor (IAS-USA) PI RAMs[1]	4	7
Developing major non-polymorphic PI RAMs[2]	0	0
Developing minor non-polymorphic PI RAMs[2]	1	2
Developing (IAS-USA) NRTI RAMs[1]	2	5
Paired phenotypes	30	43
Loss of susceptibility to any PI*	0	0
Loss of susceptibility to FTC	1	4
Loss of susceptibility to TDF	0	0

*DRV, LPV, APV, ATV, IDV, NFV, SQV and TPV

1. Johnson VA, et al. Top HIV Med 2007;15:119–25
2. Molina JM, et al. ICAAC/IDSA 2008. Abstract H-1250d

Dierynck I, et al. 16th CROI 2009. Poster 655

ARTEMIS: percentage of patients with HIV-1 RNA <50 copies/mL at Week 96 by adherence



Note: adherence based on average % adherence Week 4 through Week 96

Nelson M, et al. 16th CROI 2009. Poster 575

ARTEMIS: Grade 2–4 AEs at least possibly related to treatment over 96 weeks (≥2% incidence)

	DRV/r (N=343)	LPV/r (N=346)
Mean exposure (weeks)	*95.0*	*91.4*
Any grade 2–4 AE at least possibly related‡	**80 (23)**	**119 (34)**
Gastrointestinal AEs (all types), n (%)	23 (7)	52 (15)
Diarrhea	14 (4)*	38 (11)
Nausea	6 (2)	10 (3)
Rash (all types), n (%)	9 (3)	5 (1)

*p<0.001 vs LPV/r; no other AEs showed a statistically significant difference between the two treatment arms; ‡Laboratory abnormalities reported as AEs are not shown in the table

- No additional case of grade 2–4 rash was seen for DRV/r after Week 48
- Grade 2–4 treatment-related hepatitis was reported in one patient (<1%) in each arm
- No renal serious AEs and no treatment discontinuations due to renal AEs were reported over 96 weeks

Mills T, et al. 48th ICAAC/46th IDSA 2008. Abstract H-1250c

ARTEMIS: Conclusions from 96-week analysis

- The use of once-daily DRV/r 800/100mg + TDF/FTC in treatment-naïve patients
  - resulted in sustained virologic and immunologic responses
  - was generally well tolerated, with a favorable safety profile
  - superiority was driven by better virologic response and fewer discontinuations due to AEs compared with LPV/r
- In comparison to the LPV/r arm in treatment-naïve patients
  - for efficacy, once-daily DRV/r 800/100mg was non-inferior and statistically superior
  - significantly lower rates of diarrhea were seen with DRV/r
  - DRV/r was associated with smaller median increases in triglycerides and total cholesterol

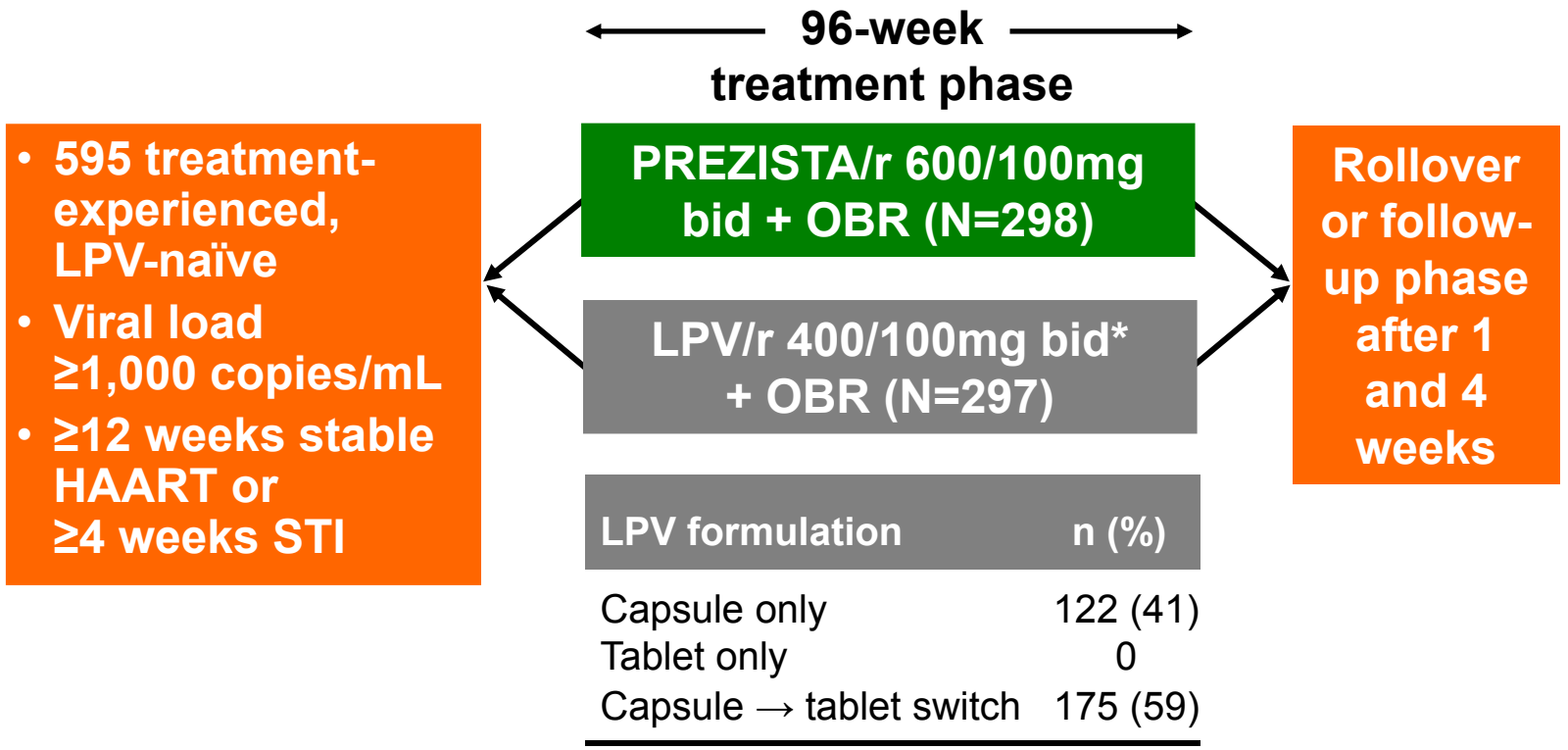
Mills T, et al. 48th ICAAC/46th IDSA 2008. Abstract H-1250c

TITAN study

Treatment-experienced versus Kaletra

Phase III TITAN week 96 final analysis: efficacy/safety of PREZISTA/ritonavir (PREZISTA/r) vs lopinavir/ritonavir (LPV/r) in LPV/r- naïve, treatment-experienced patients

Study design



LPV formulation	n (%)
Capsule only	122 (41)
Tablet only	0
Capsule → tablet switch	175 (59)

*LPV/r patients were allowed to switch to new formulation upon its approval by the regulatory authorities and upon availability for use in the study; STI = structured treatment interruption
OBR = optimised background regimen, ≥2 ARVs (NRTIs ± NNRTIs; enfuvirtide disallowed)

Bánhegyi D, et al. 9th ICDTHI 2008. Abstract P22

TITAN: Baseline characteristics

	PREZISTA/r (N=298)	LPV/r (N=297)
Demographics		
Male, n (%)	229 (77)	241 (81)
Mean age, years (SD)	41 (9.0)	41 (8.6)
Disease characteristics		
Mean viral load, log_{10} copies/mL (SD)	4.33 (0.79)	4.28 (0.81)
Median CD4 cell count, cells/mm^3 (range)	235 (3–831)	230 (2–1,096)
CDC class C, n (%)	101 (34)	94 (32)
Structured treatment interruption, n (%)	64 (21)	71 (24)
Previous ARV experience, n (%)		
NRTIs: ≥4	156 (52)	151 (51)
NNRTIs: ≥1	225 (76)	229 (77)
PIs: 0	94 (32)	93 (31)
PIs: 1	108 (36)	115 (39)
PIs: ≥2	96 (32)	89 (30)
Number of sensitive NRTIs in OBR, n (%)*		
0	31 (11)	42 (15)
1	69 (24)	75 (26)
≥2	188 (65)	171 (59)
Geometric median FC (range)		
DRV	0.6 (0–37)	0.6 (0–44)
LPV	0.7 (0–74)	0.8 (0–74)
LPV FC >10, n (%)	29 (10)	29 (10)

*Phenotypes determined by Antivirogram®

SD = standard deviation; CDC = Centers for Disease Control and Prevention; ARV = antiretroviral; FC = fold change in EC_{50}

Bánhegyi D, et al. 9th ICDTHI 2008. Abstract P22

TITAN: Patient disposition at Week 96 analysis

Incidence, n (%)	PREZISTA/r (N=298)	LPV/r (N=297)
Discontinuation	81 (27)	110 (37)
AE*	23 (8)	24 (8)
Lost to follow-up	13 (4)	13 (4)
Withdrew consent	10 (3)	12 (4)
VF	8 (3)	43 (15)
Non-compliant to protocol	16 (5)	7 (2)
Other	11 (4)	11 (4)

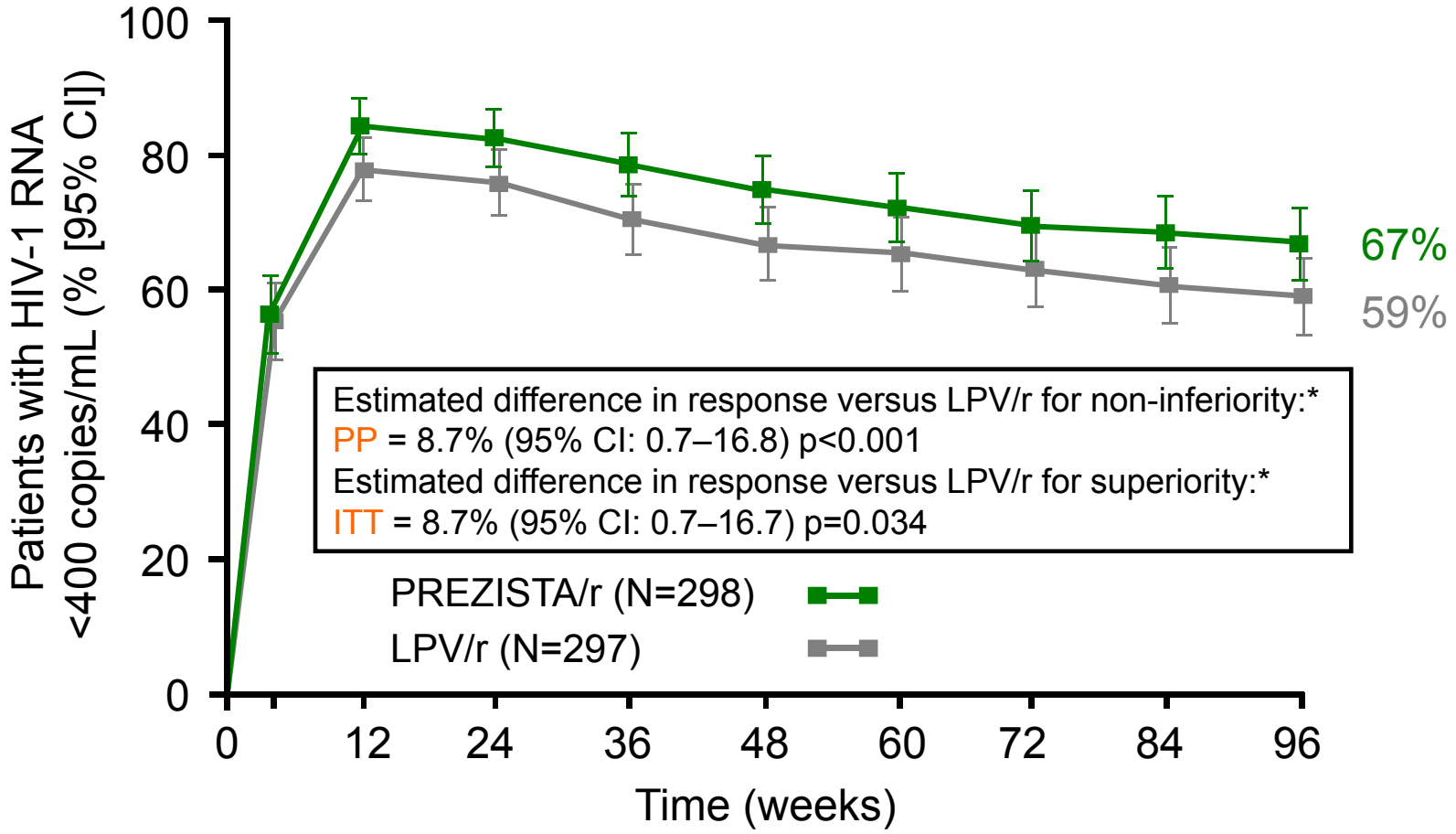
*Includes six deaths (two in PREZISTA/r group and four in LPV/r group, all of which were considered not or doubtfully related to the protease inhibitor [PI])

Table includes all data up to the point when the last patient reached Week 96

Mean exposure was 81 weeks in the PREZISTA/r arm and 76 weeks in the LPV/r arm

Bánhegyi D, et al. 9th ICDTHI 2008. Abstract P22

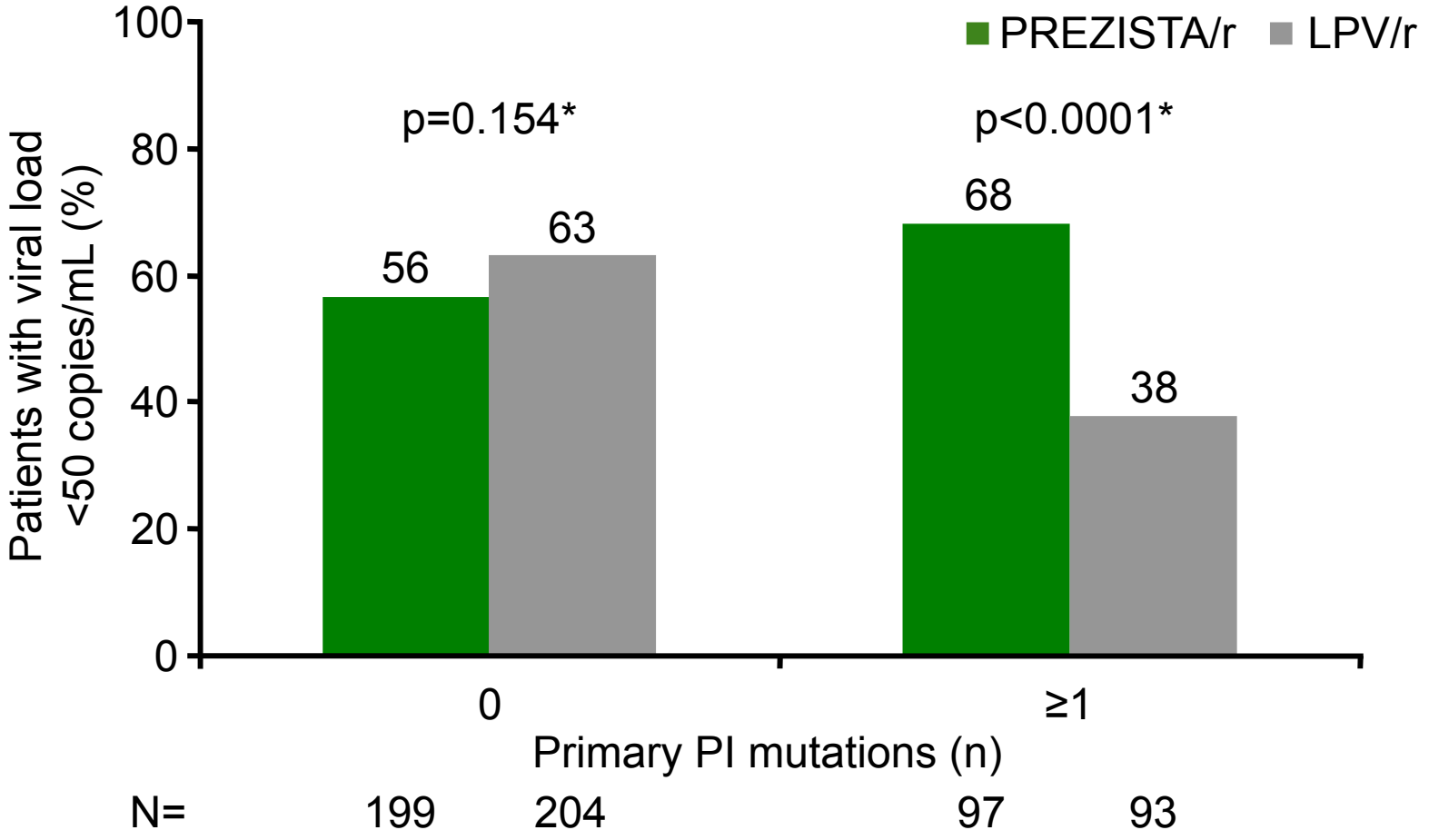
TITAN: Viral load <400 copies/mL to Week 96 (ITT-TLOVR)



*Derived from a logistic regression model including use of an NNRTI in the OBR as factor and baseline $\log_{10}$ plasma viral load as covariate; PP = per protocol

Bánhegyi D, et al. 9th ICDTHI 2008. Abstract P22

TITAN: Viral load <50 copies/mL at Week 96 by number of primary PI mutations[1]

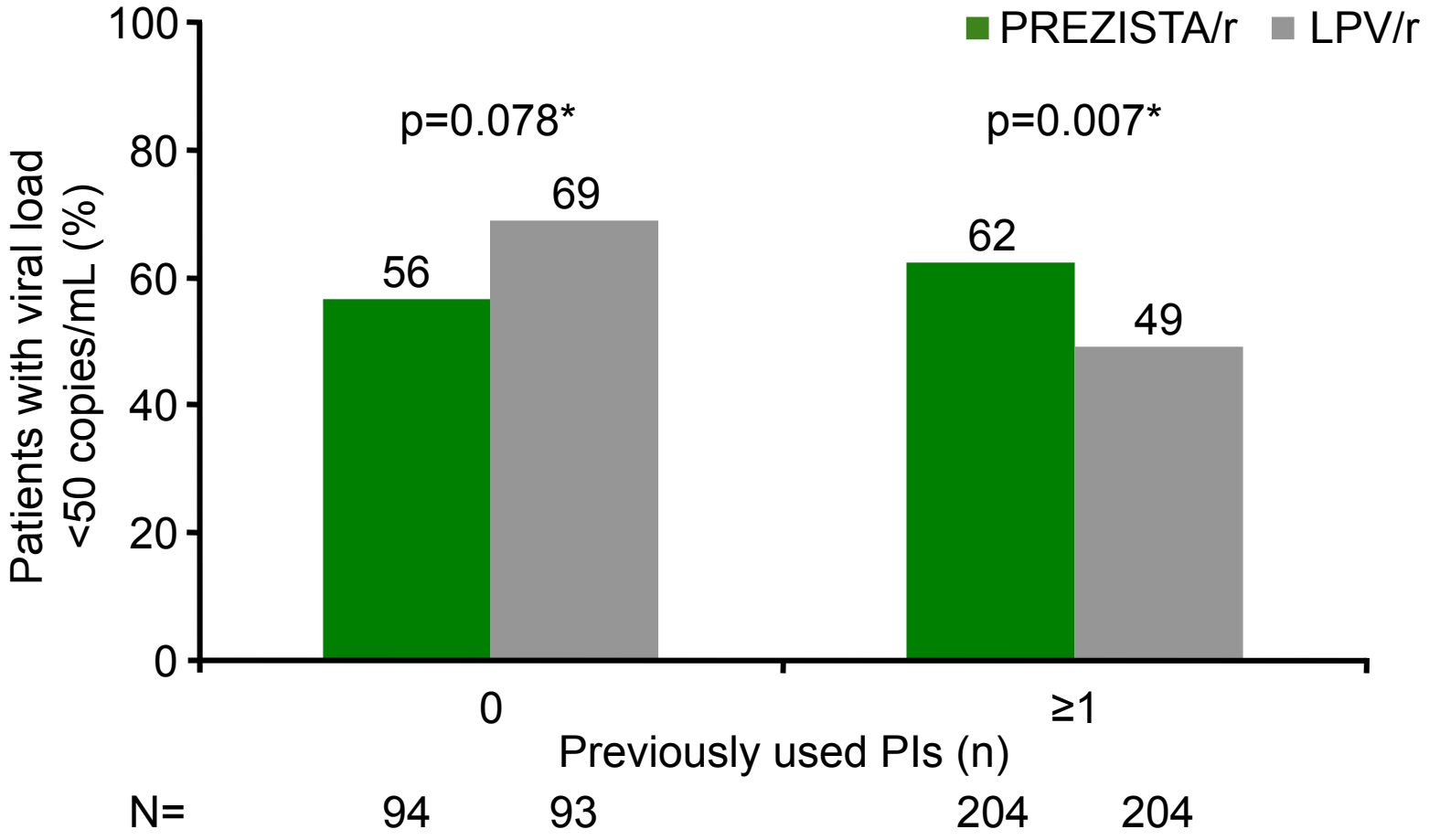


[1]Johnson VA, et al. Top HIV Med 2007;15:119–25

*Chi-square test

Bánhegyi D, et al. 9th ICDTHI 2008. Abstract P22

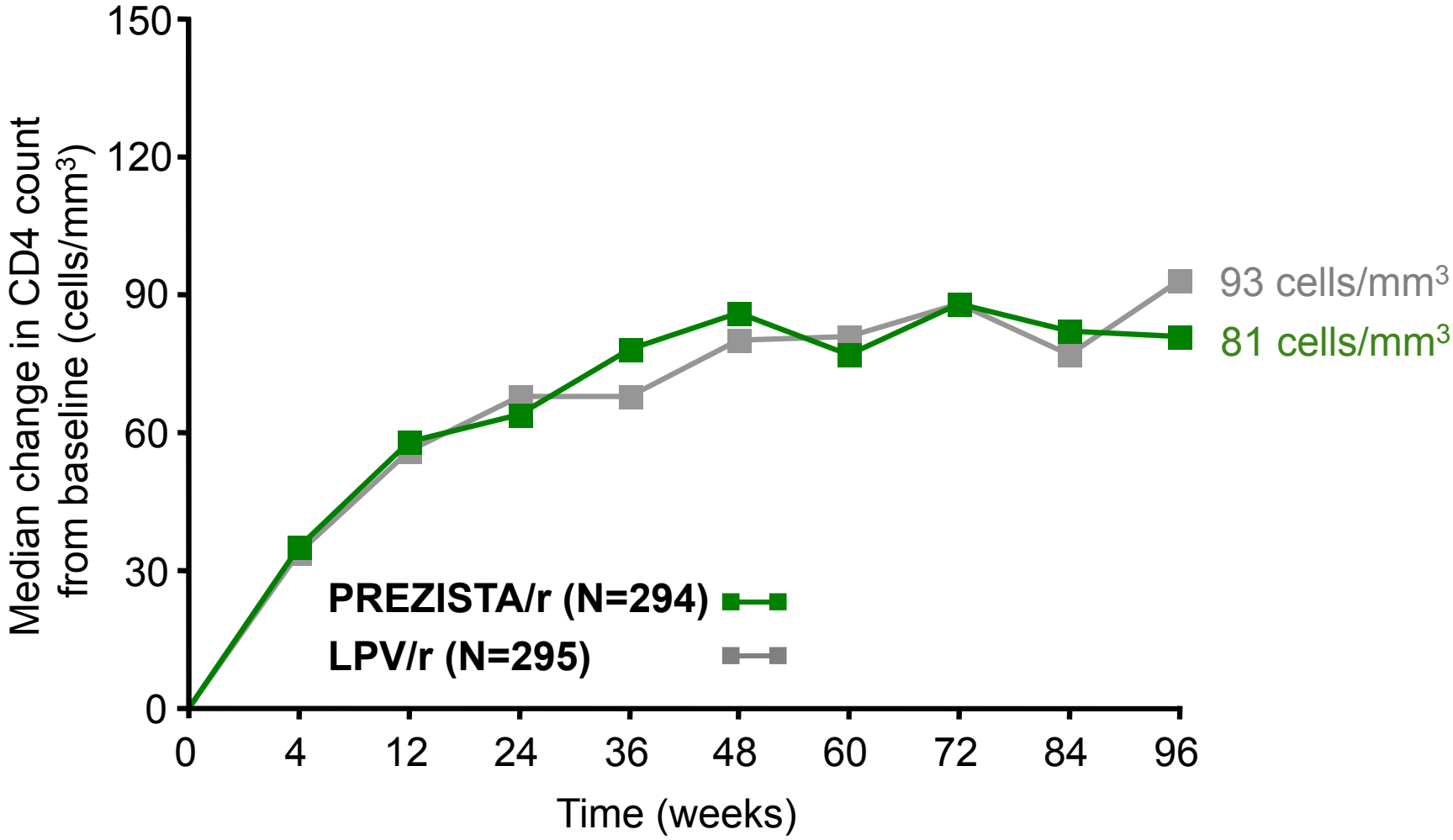
TITAN: Viral load <50 copies/mL at Week 96 by number of previously used PIs



*Chi-square test

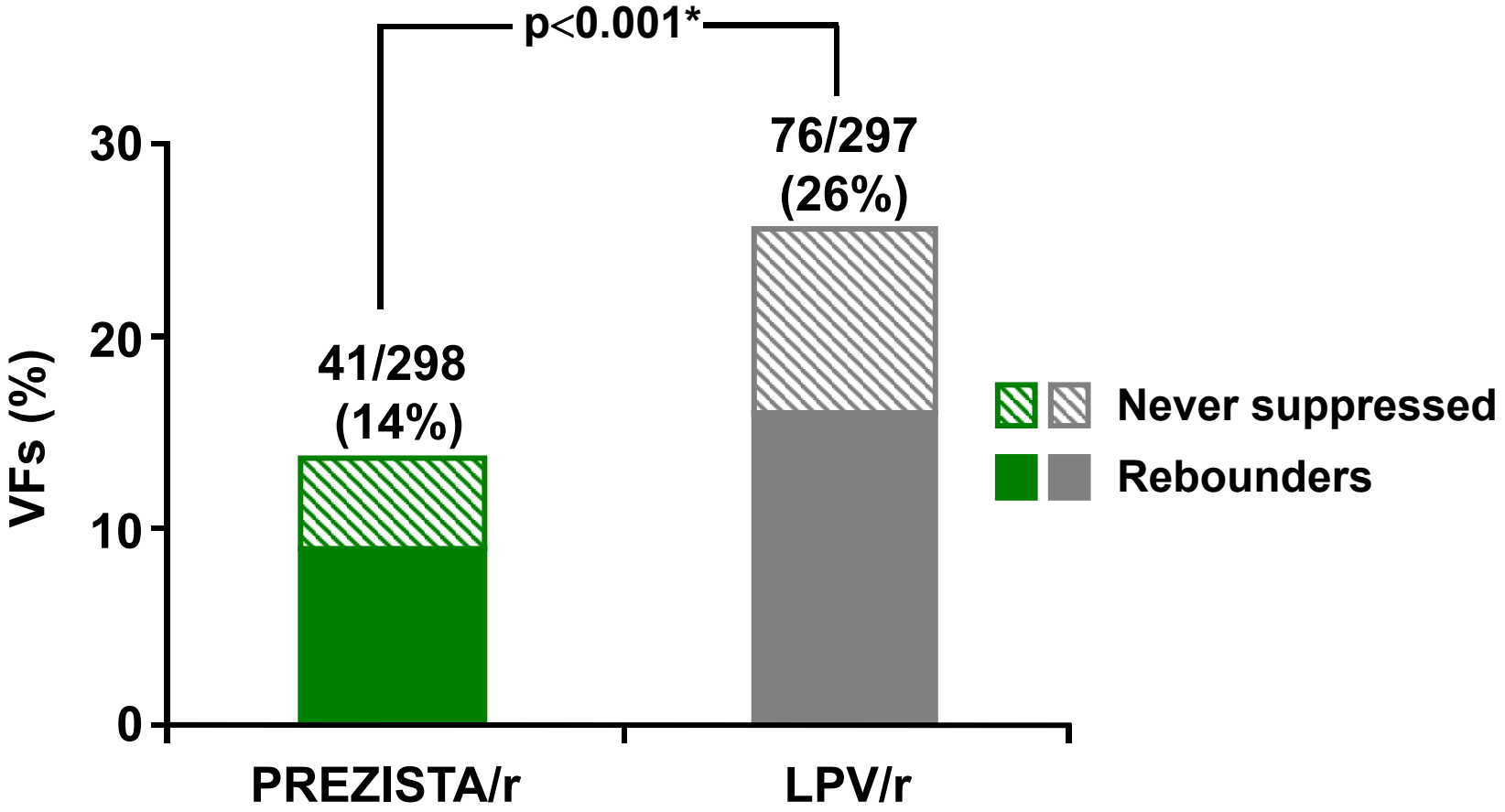
Bánhegyi D, et al. 9th ICDTHI 2008. Abstract P22

TITAN: Median change in absolute CD4 cell count over time to Week 96 (ITT-NC=F)



Bánhegyi D, et al. 9th ICDTHI 2008. Abstract P22

VFs were less frequent in the PREZISTA/r arm than in the LPV/r arm



- 48 week analysis: 31 VFs in the PREZISTA/r arm and 65 VFs in the LPV/r arm

***Exact Chi-Squared Test; TITAN 96 week analysis**

De Meyer S, et al. 9th ICDTHI 2008. Abstract O424

TITAN: Conclusions from final 96-week analysis

- Results of this analysis confirmed the results of the Week 48 primary analysis, demonstrating that PREZISTA/r is non-inferior and superior to LPV/r in virological response (VL <400 copies/mL, TLOVR) in treatment-experienced patients
- PREZISTA/r patients were approximately half as likely to experience VF than LPV/r patients
- Significantly greater efficacy (VL <50 copies/mL, TLOVR) was shown with PREZISTA/r compared to LPV/r in the presence of ≥1 primary PI mutation and in patients who had received ≥1 PI
- PREZISTA/r continued to demonstrate a good safety and tolerability profile over 96 weeks and was associated less frequently with diarrhoea and changes in triglycerides and total cholesterol than LPV/r

Bánhegyi D, et al. 9th ICDTHI 2008. Abstract P22

POWER studies

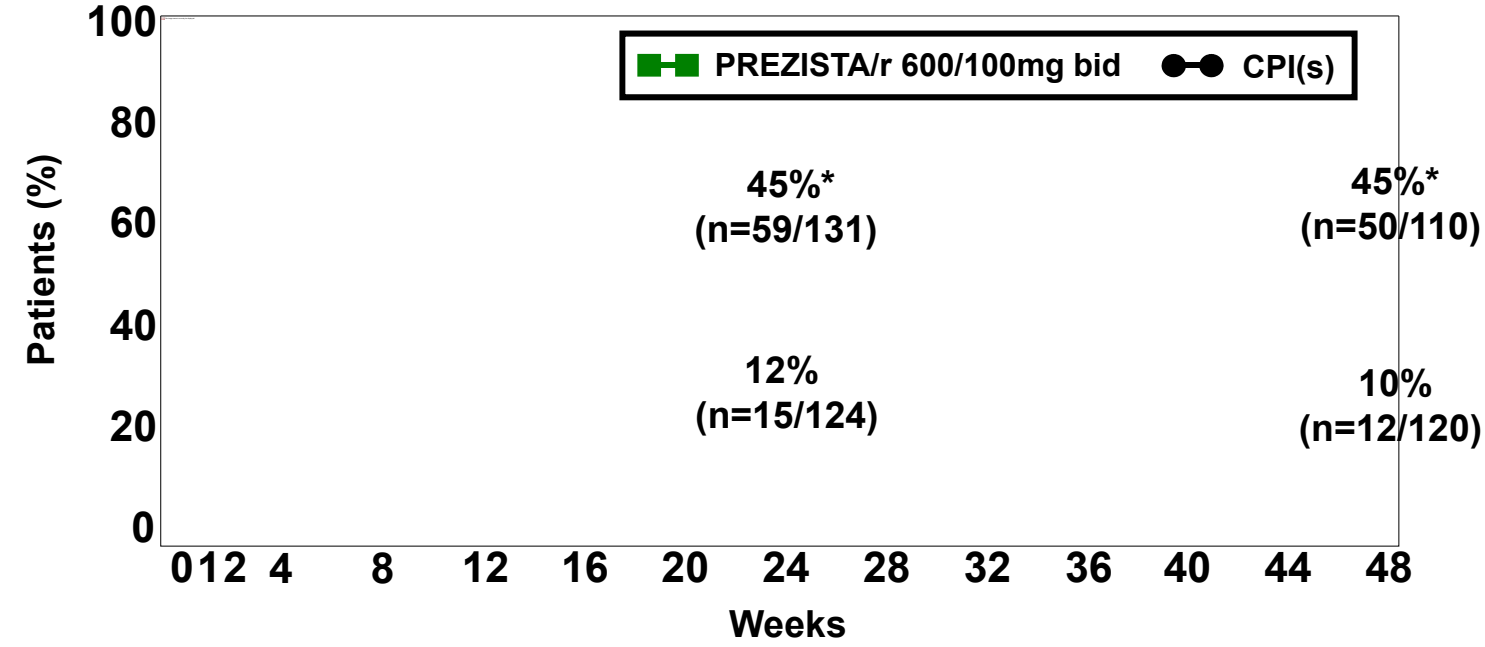
POWER 1 and 2: BL characteristics

	PREZISTA/r 600/100mg bid n=131	CPI(s) n=124
Demographics		
Male (%)	89	88
Mean age (years)	44	44
Disease characteristics		
CDC class C (%)	36	43
Mean duration of infection (years)	12.0	12.9
Mean VL (log_{10} copies/mL; SD)	4.61 (0.69)	4.49 (0.78)
Median CD4 count (cells/mm^3; range)	153 (3–776)	163 (3–1,274)
Previous ARV experience		
Mean duration (months; SD)		
NRTI	100 (48)	106 (45)
NNRTI	28 (24)	23 (15)
PI	65 (29)	65 (28)
Fusion inhibitor (ENF)	14 (11)	11 (9)
Genotypic and phenotypic information		
Median primary PI mutations* (n; range)	3 (0–5)	3 (0–5)
Median PI resistance-associated mutations* (n; range)	8 (0–12)	8 (1–13)
≥1 sensitive† PI available (%)	36	39
≥1 sensitive† NRTI in OBR (%)	72	73

*IAS-USA October 2004;
†susceptibility was determined by Antivirogram®

Clotet B, et al. Lancet 2007;369:1169–78

POWER 1 and 2: patients with VL <50 copies/mL over time to Week 48 (ITT-TLOVR)

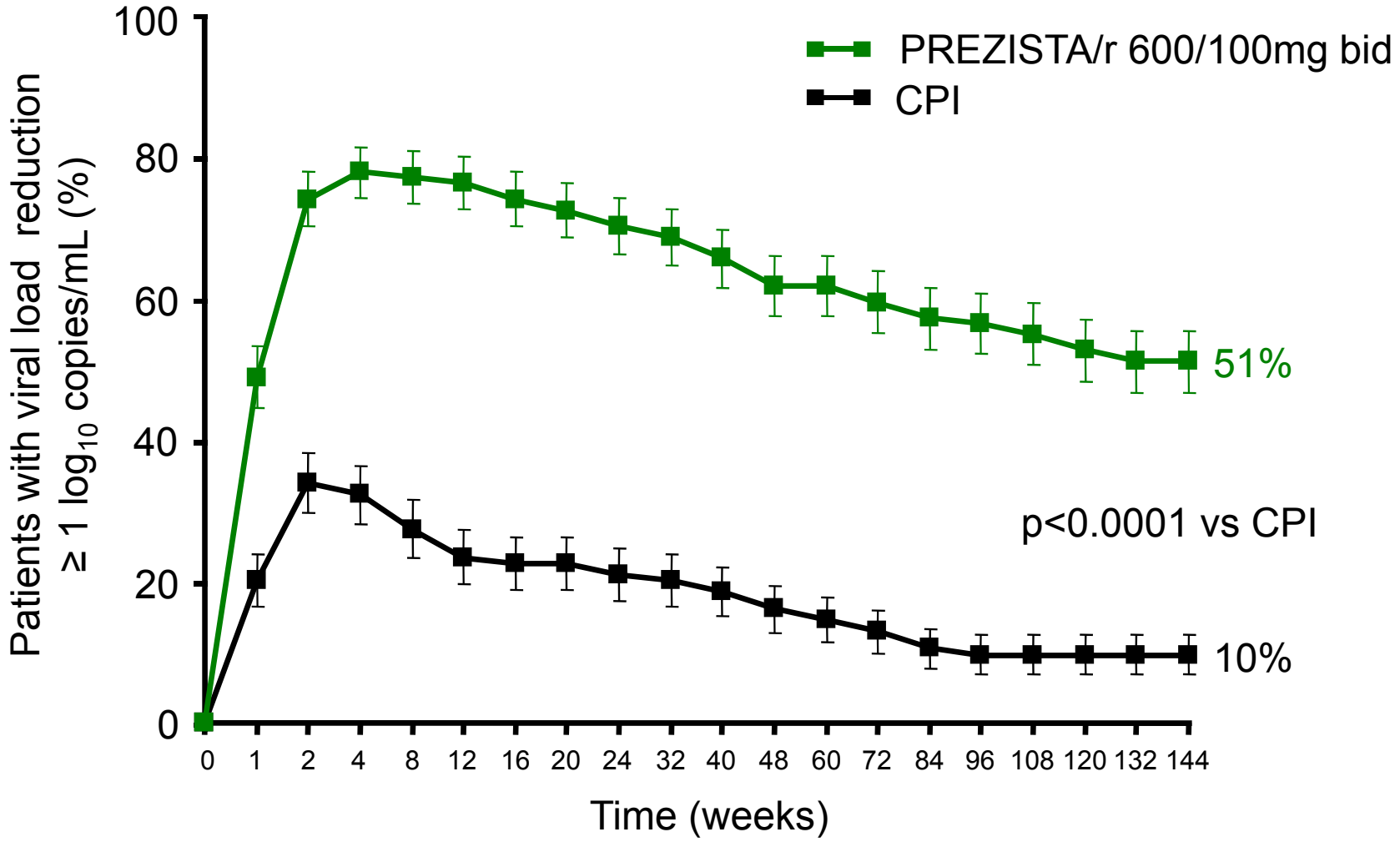


PREZISTA/r	n= 131	131	131	130	120	110
CPI(s)	n= 124	124	124	124	121	120

*p<0.001 vs CPI(s)

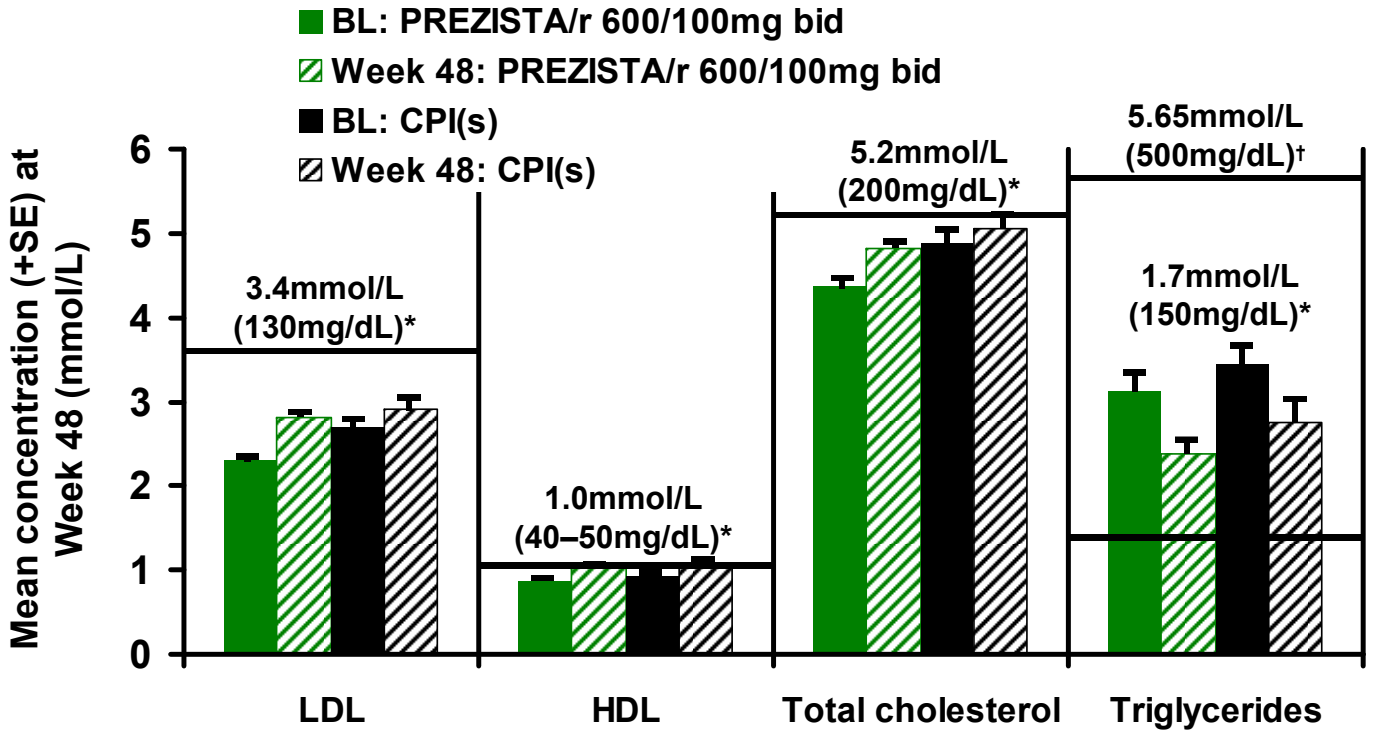
Clotet B, et al. Lancet 2007;369:1169–78

POWER 1 and 2: Viral load reduction ≥1 $\log_{10}$ copies/mL to Week 144 (ITT-TLOVR)



Katlama C, et al. 9th ICDTHI 2008. Abstract P21

Treatment-emergent laboratory abnormalities: lipid levels at Week 48



*Normal lipid levels and †very high triglyceride levels taken from the Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (JAMA.2001;285:2486–97)

Clotet B, et al. Lancet 2007;369;1169–78

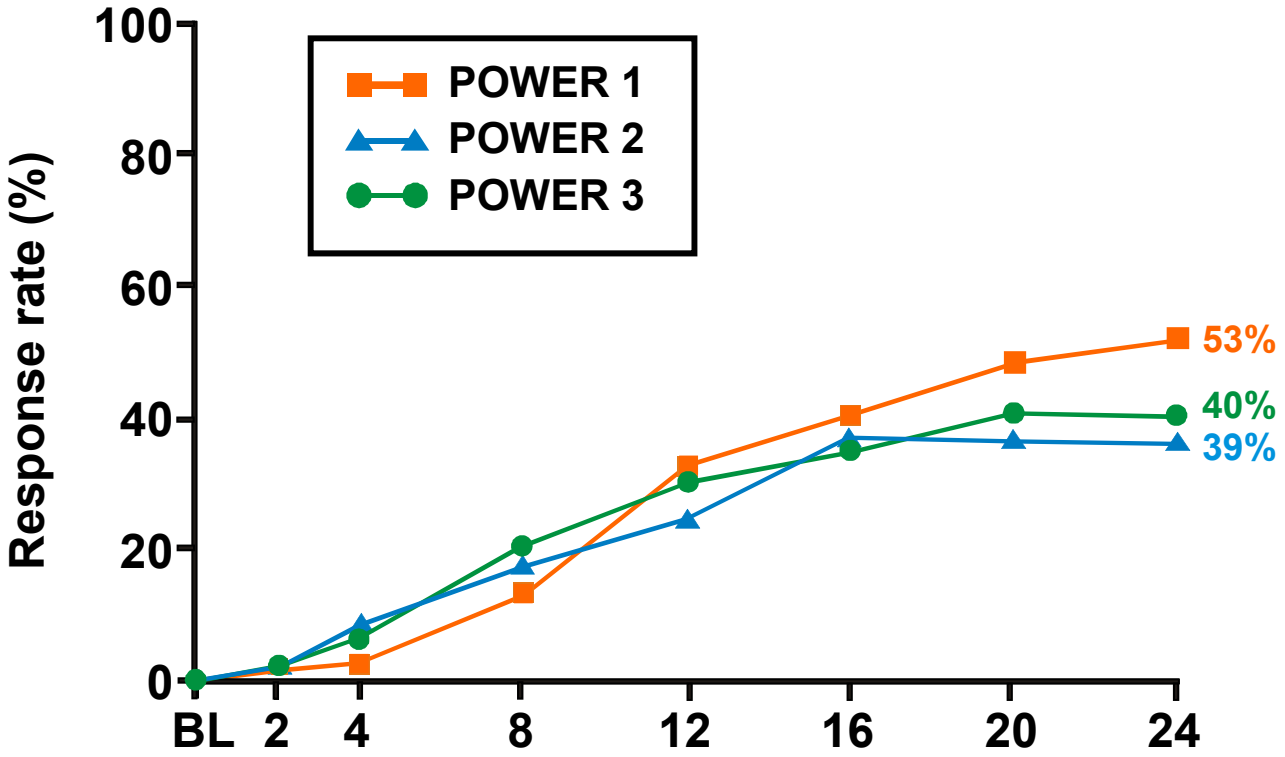
POWER 1 and 2: Grade 2–4 treatment-related AEs over 144 weeks (incidence ≥2%)

	PREZISTA/r 600/100mg bid (N=131)	CPI (N=124)
Median exposure (weeks)	***144***	***21***
Grade 2–4 AEs, n (%)*		
Abdominal pain	**3 (2)**	**1 (1)**
Constipation	**3 (2)**	**1 (1)**
Diarrhoea	**3 (2)**	**5 (4)**
Headache	**6 (5)**	**3 (2)**
Gynaecomastia	**3 (2)**	**0**
Rash (all types)	**2 (2)**	**2 (2)**

*Laboratory abnormalities reported as AEs not included in the table

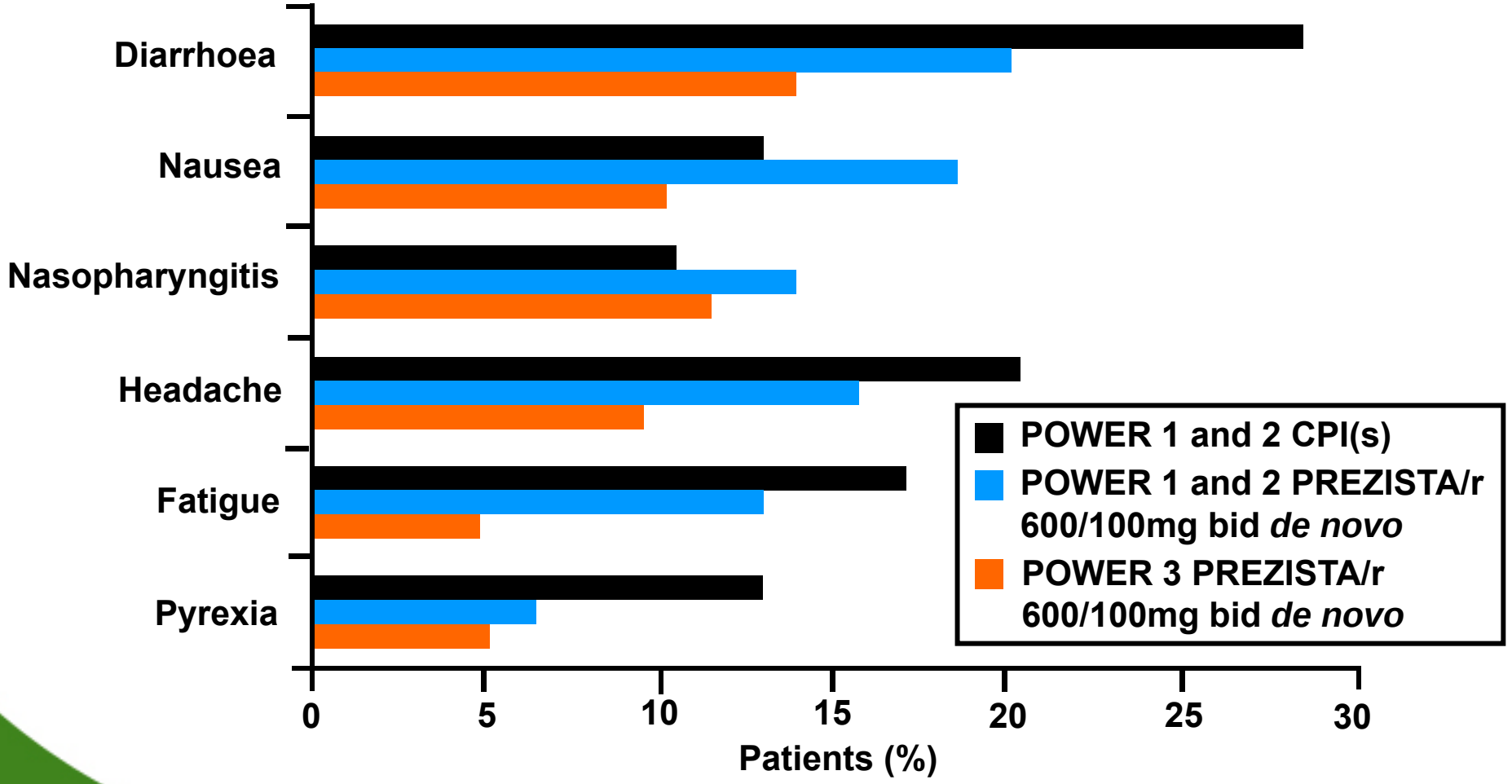
Katlama C, et al. 9th ICDTHI 2008. Abstract P21

POWER 1, 2 and 3: PREZISTA/r 600/100mg bid patients with plasma VL <50 copies/mL at Week 24 (ITT-TLOVR)



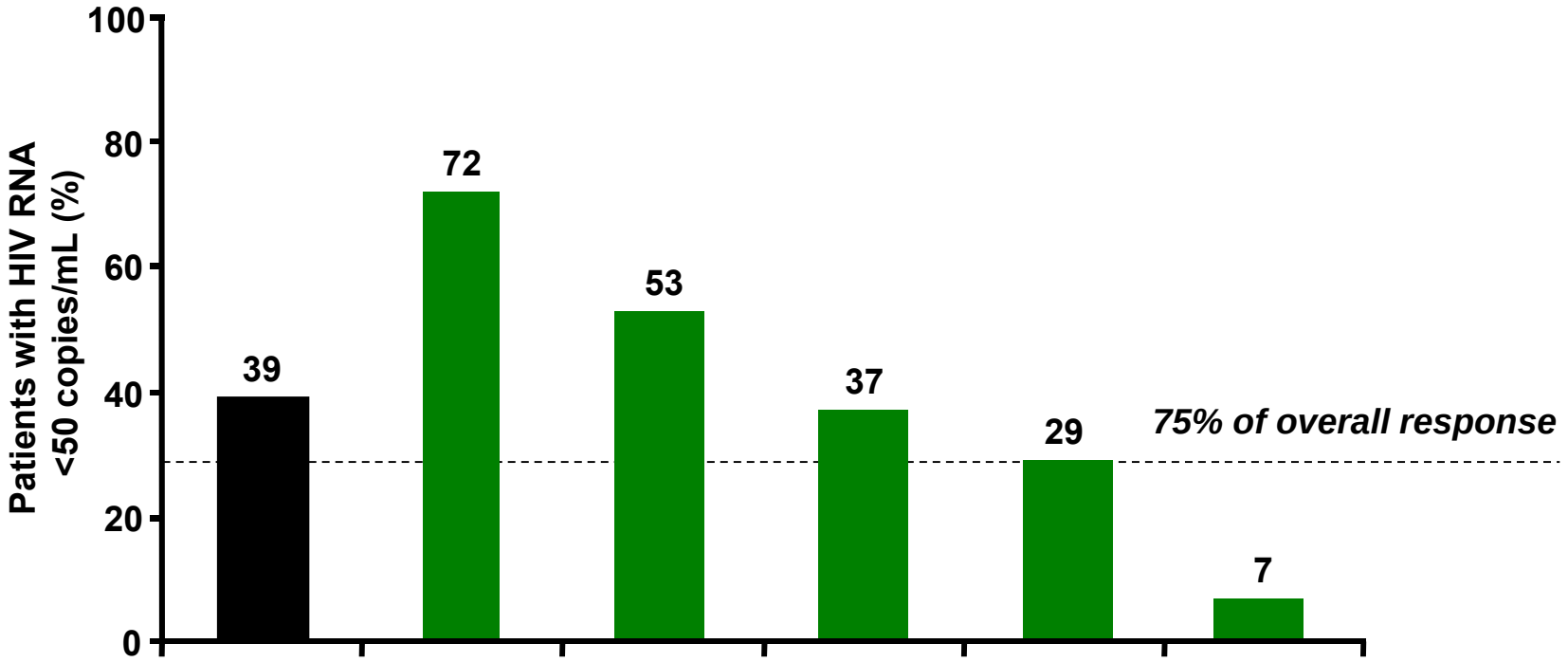
Molina JM, et al. 16th IAC 2006. Abstract TUPE0060

Treatment-emergent AEs reported in ≥10% of patients, regardless of severity or causality



Rockstroh J, et al. 8th ICDTHI 2006. Abstract P28

POWER and DUET: Virological response (HIV RNA <50 copies/mL, TLOVR non-VF censored) at Week 24 by number of 2007 DRV RAMs at baseline in PREZISTA/r patients who did not use/who re-used ENF



2007 DRV RAMs (n)*	Overall	0	1	2	3	≥4
Patients (n)	741	89	195	193	120	135
Median IAS-USA PI RAMs (n)	13	10	12	13	14	15

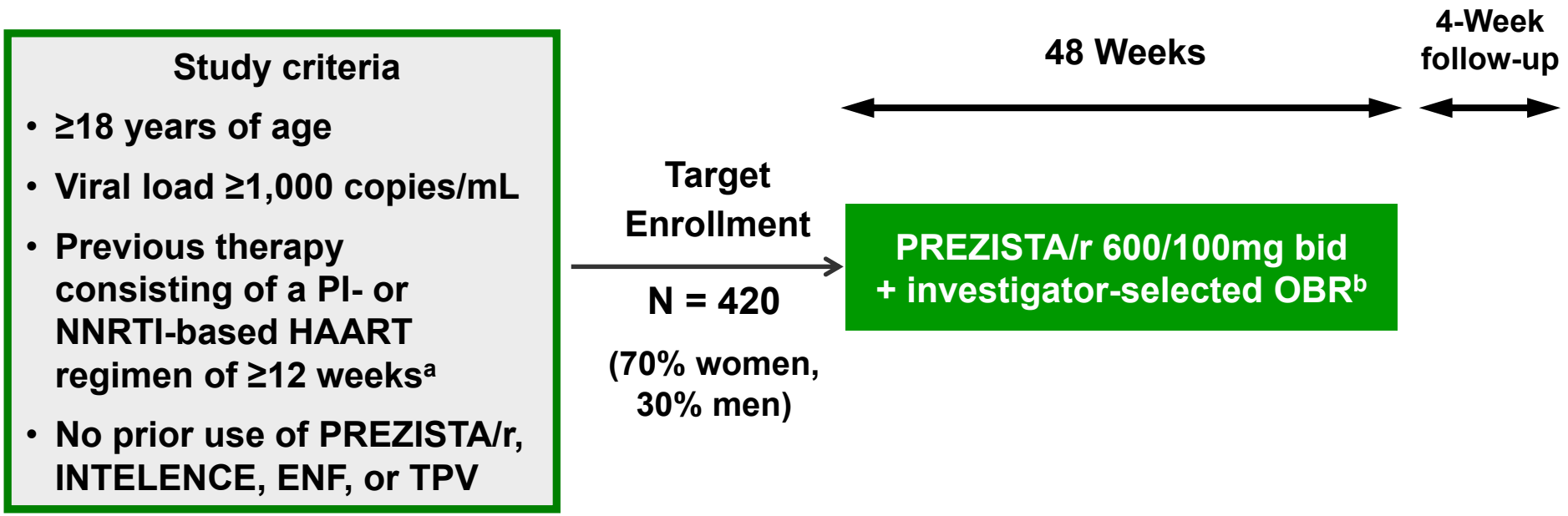
*When a mixture of different mutations was detected at a certain position, only one mutation per position was taken into account to determine the number of mutations
The horizontal line shows the value defined as diminished response (75% of overall response rate of 39% = 29%)

De Meyer S, et al. 6th EHDRW 2008. Abstract 54

GRACE

Experienced study focussing on women

GRACE Study Design

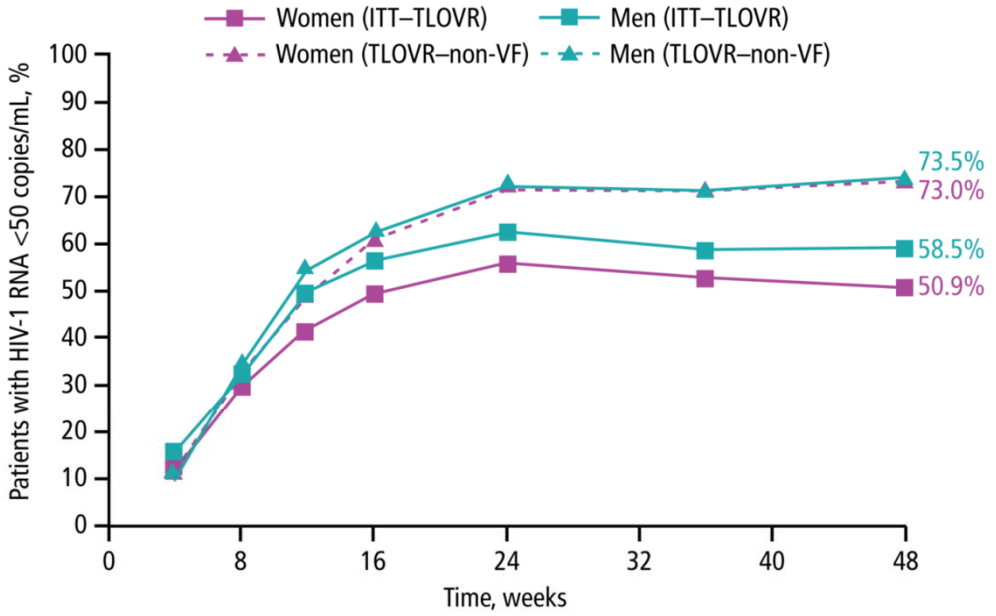


- Patients at participating sites who were eligible for participation in GRACE could be enrolled into single-arm prospective substudy
  - Virologic suppression defined as achieving VL <50 copies/mL at Week 48

[a]Patients were allowed to enter the study on treatment interruption of ≥4 weeks; [b]Investigator-selected NRTIs and NNRTIs were allowed; ENF, TPV or agents from novel classes were not allowed; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OBR, optimized background therapy; ENF, enfuvirtide; TPV, tipranavir

Squires, K et al. 5th IAS 2009. Poster MOPEB042

GRACE: Patients Who Achieved VL <50 copies/mL at Week 48 (ITT-TLOVR and TLOVR-non-VF Censored)



Women (ITT–LOVR), N	287	287	287	287	287	287	287
Women (TLOVR–non-VF), n	266	252	244	236	222	212	200
Men (ITT–LOVR), N	142	142	142	142	142	142	142
Men (TLOVR–non-VF), n	136	132	131	128	122	117	113

- In the ITT–TLOVR analysis, which treats all study discontinuations as failures, virologic response rate was higher in men than women; the adjusted difference between women and men was -9.6% (95% CI: -19.9%, 0.7%)
- After accounting for differential rates of discontinuation for men and women due to reasons other than VF, via the TLOVR-non-VF censored analysis, response rates were similar between sexes; the adjusted difference between women and men was -3.9% (95% CI: -13.9%, 6.0%)

The 95% confidence interval (CI) crossed zero for both ITT and non-VF censored analyses; the 95% CI only included –15% in the ITT–TLOVR analysis.; difference in response adjusted for baseline VL and CD4 count; ITT, intent-to-treat; TLOVR, time-to-loss of virologic response; VF, virologic failure

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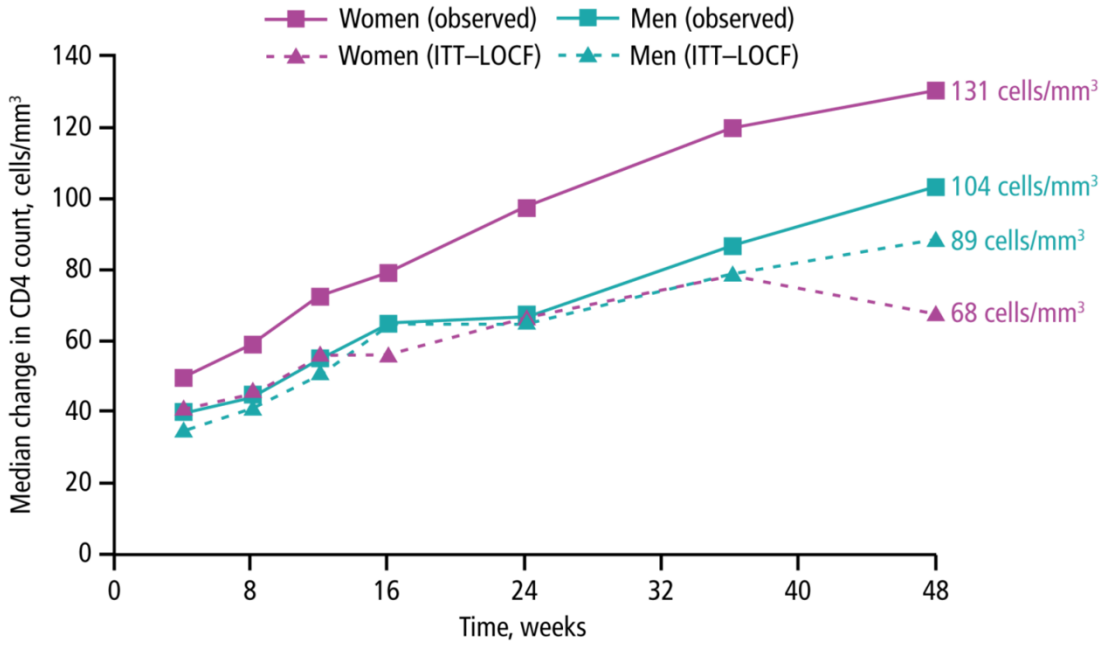
GRACE: Median Change in CD4+ Cell Count from Baseline to Week 48 (Observed and ITT-LOCF)



Women (observed), n	255	243	239	234	215	206	188
Women (ITT–LOCF), N	287	287	287	287	287	287	287
Men (observed), n	133	128	125	125	120	113	105
Men (ITT–LOCF), N	142	142	142	142	142	142	142

- Median change from baseline to Week 48 in the observed CD4+ count was higher in women than men
- Median change from baseline to Week 48 in CD4+ count for the ITT–LOCF analysis was similar in women and men

The least-squares mean difference between sexes in the observed and ITT–LOCF analyses, adjusted for baseline viral load and CD4+ count, was 34 cells/mm^3 (95% confidence interval [CI]: 0.4, 68; *P*=.047) and 11 cells/mm^3 (95% CI: –18, 39; *P*≥.05), respectively; ITT, intent-to-treat; LOCF, last observation carried forward

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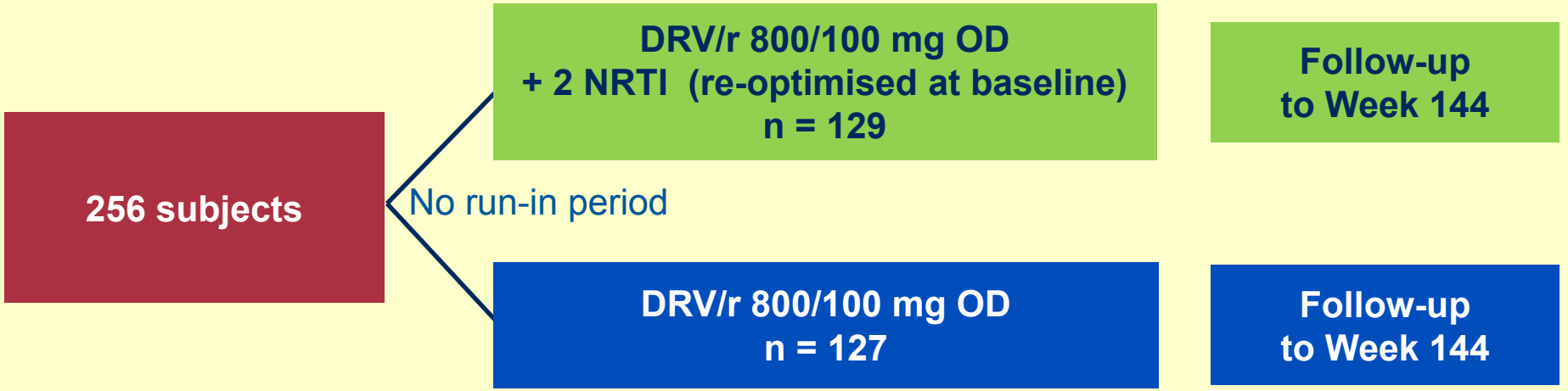
MONET study

Darunavir monotherapy in suppressed patients

MONET - Trial Design

- Taking 2 NRTI + either NNRTI or boosted PI at screening (stratified)
- No prior use of darunavir (DRV)
- HIV RNA <50 copies/mL for at least 6 months,
- No history of virological failure



SC ← 30 days → BL ← 4, 12, 24, 36, 48 weeks

Primary Endpoint: HIV RNA<50 at week 48 (TLOVR). Per Protocol, Switch = Failure

- 2 consecutive HIV RNA > 50 copies/mL (Roche Amplicor HIV-1 Monitor assay 1.5)
- Stopping DRV/r
- Starting NRTIs in the monotherapy arm
- Stopping NRTIs in the triple therapy arm (switches in NRTIs were permitted at any time).

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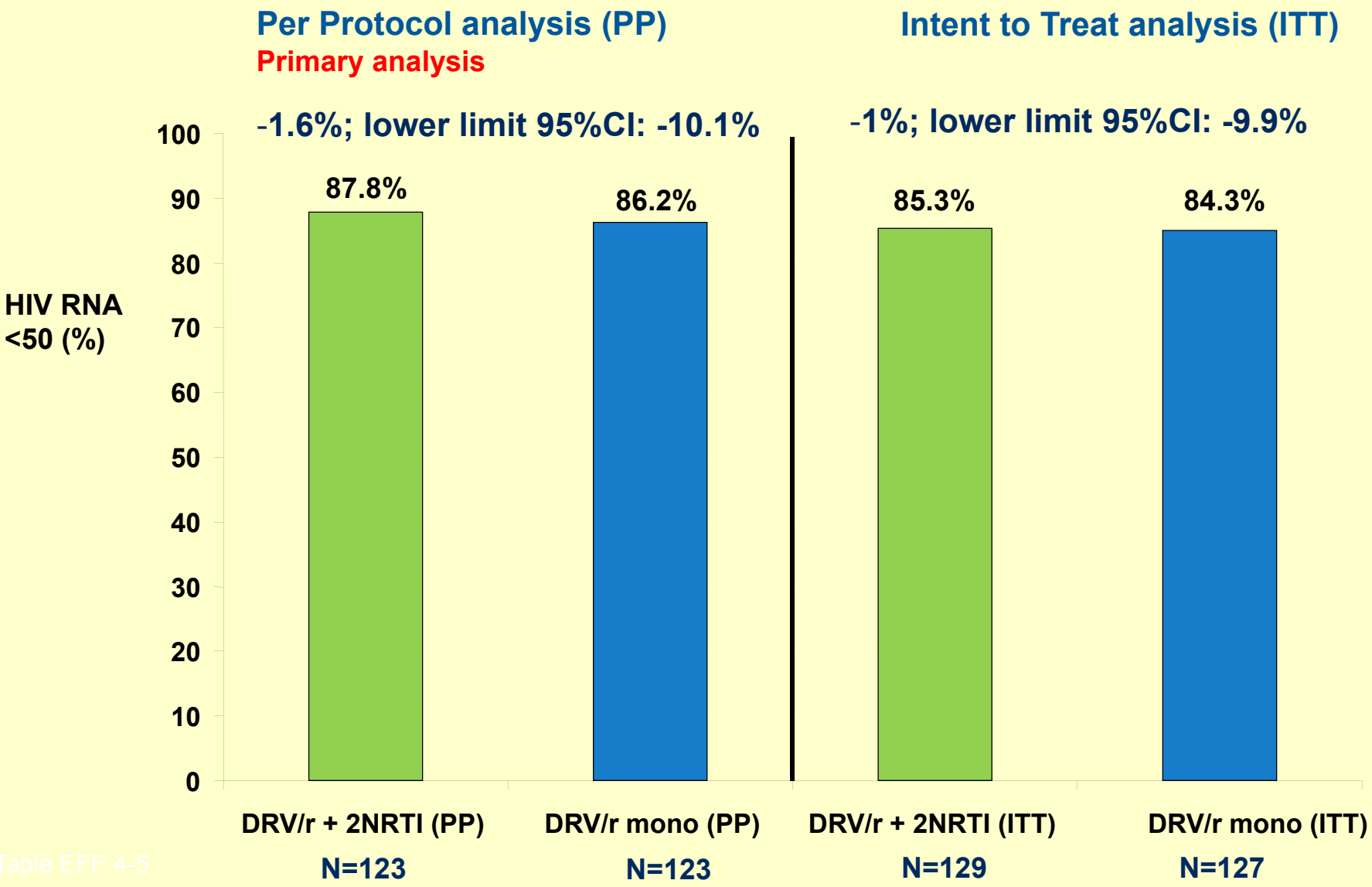
MONET trial:

HIV RNA <50 copies/mL at Week 48, TLOVR, S = F



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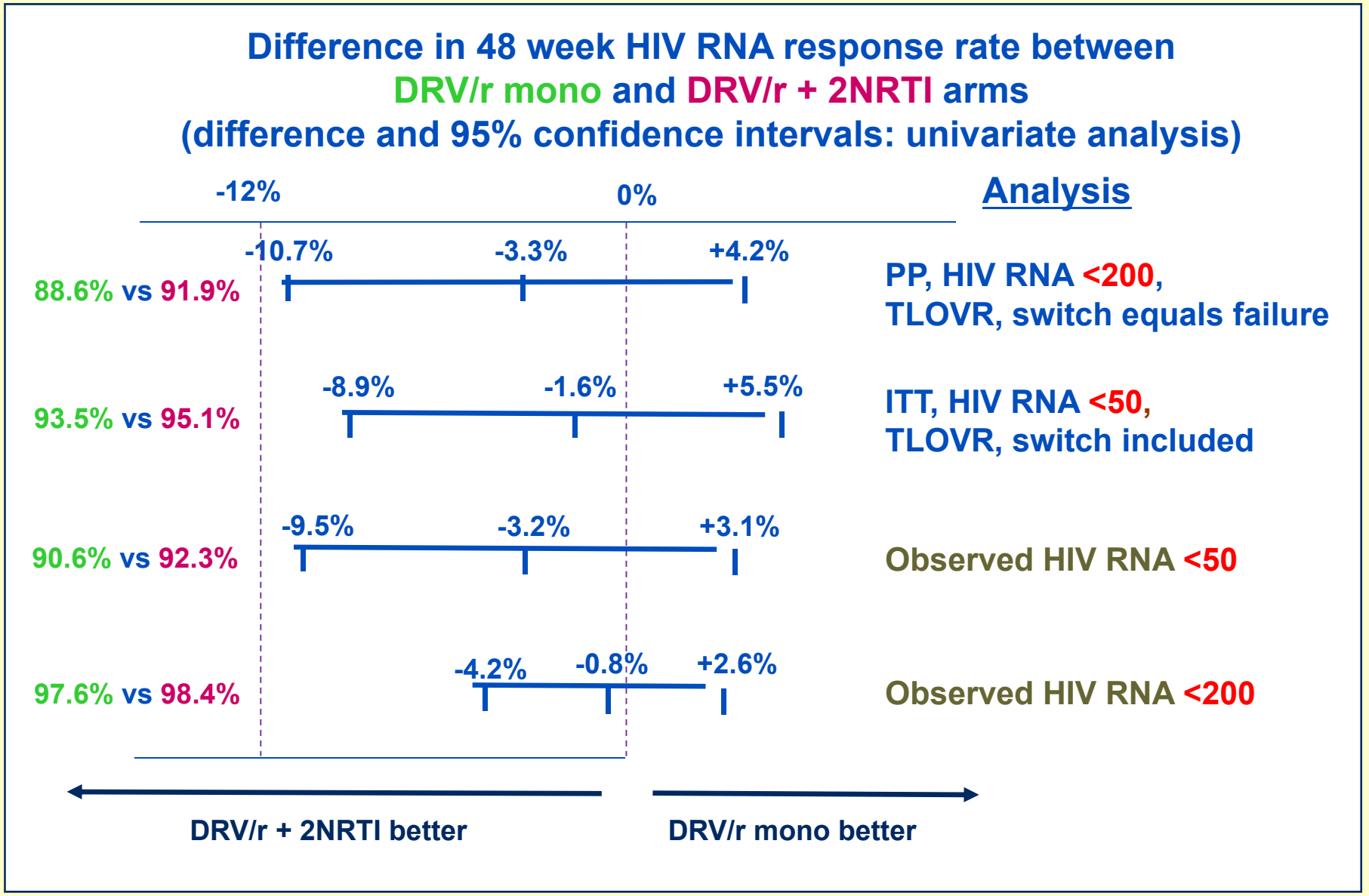
MONET trial: sensitivity analyses



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MONET: Outcome of "double blips" in HIV RNA DRV/r + 2NRTI arm (7 patients)

Patient number	Highest HIV RNA on trial	Change in ARVs	HIV RNA at Week 48
1	294 and 116	No	<50
2	54000 and 3400	No - stopped drug	<50
3	78 and 50	No	<50
4	164 and 67	No	<50
5	989 and 59	No	<50
6	746 and 2230	No	**2230**
7	128 and 548	No	<50

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MONET: Outcome of "double blips" in HIV RNA DRV/r mono arm (11 patients)

Patient number	Highest HIV RNA	Change in ARVs	HIV RNA at Week 48
1	140 and 133	No change (sinusitis)	<50
2	59 and 214	ZDV/3TC/NVP	<50
3	132 and 139	LPV/r mono	<50
4	539 and 862	TDF/FTC/EFV	<50
5	158 and 140	**ABC/3TC**/DRV/r	<50
6	40500 and 628	No change (stopped drug)	<50
7	51 and 80	No change (Hep C)	<50
8	106 and 268	**TDF/FTC**/DRV/r	<50
9	722 and 157	**TDF/FTC**/DRV/r	<50
10	779 and 267	**ABC/3TC**/DRV/r	<50
11	67 and 810	DRV/r (stopped drug)	**810**

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MONET: Drug resistance (Week 72 data)

Genotypic results	DRV/r + 2NRTI N= 129	DRV/r mono N= 127
Patients with at least 1 successful genotype	14	24
No primary PI, DRV or NRTI mutations	13/14 (92.9%)	23/24 (95.8%)
M184V	1	0
Primary IAS-USA PI mutations	1	1
DRV mutations	0	1

1 patient per arm had any evidence of genotypic resistance
No patients had phenotypic resistance to DRV

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Conclusions

- In the MONET trial, darunavir/ritonavir monotherapy showed consistently non-inferior efficacy versus triple antiretroviral drug treatment at Week 48.
- The efficacy results were sustained in several sensitivity analyses: looking only at virological endpoints, stratified by baseline Hepatitis C co-infection, looking at HIV RNA elevations above 200 copies/mL.
- Most elevations in HIV RNA were low level (50-200 copies/mL), and patients were re-suppressed <50 copies/mL at last visit, either on the original randomised treatment or with intensified treatment.

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Conclusion

- DRV/r is a generally well-tolerated drug in both treatment-experienced patients at a dose of 600/100 mg bid, and treatment-naïve patients at a dose of 800/100 mg qd
  - favourable GI tolerability
  - limited changes of lipids (triglycerides and total cholesterol)
- Studies evaluating DRV/r 800/100 mg qd in treatment-experienced patients are underway


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