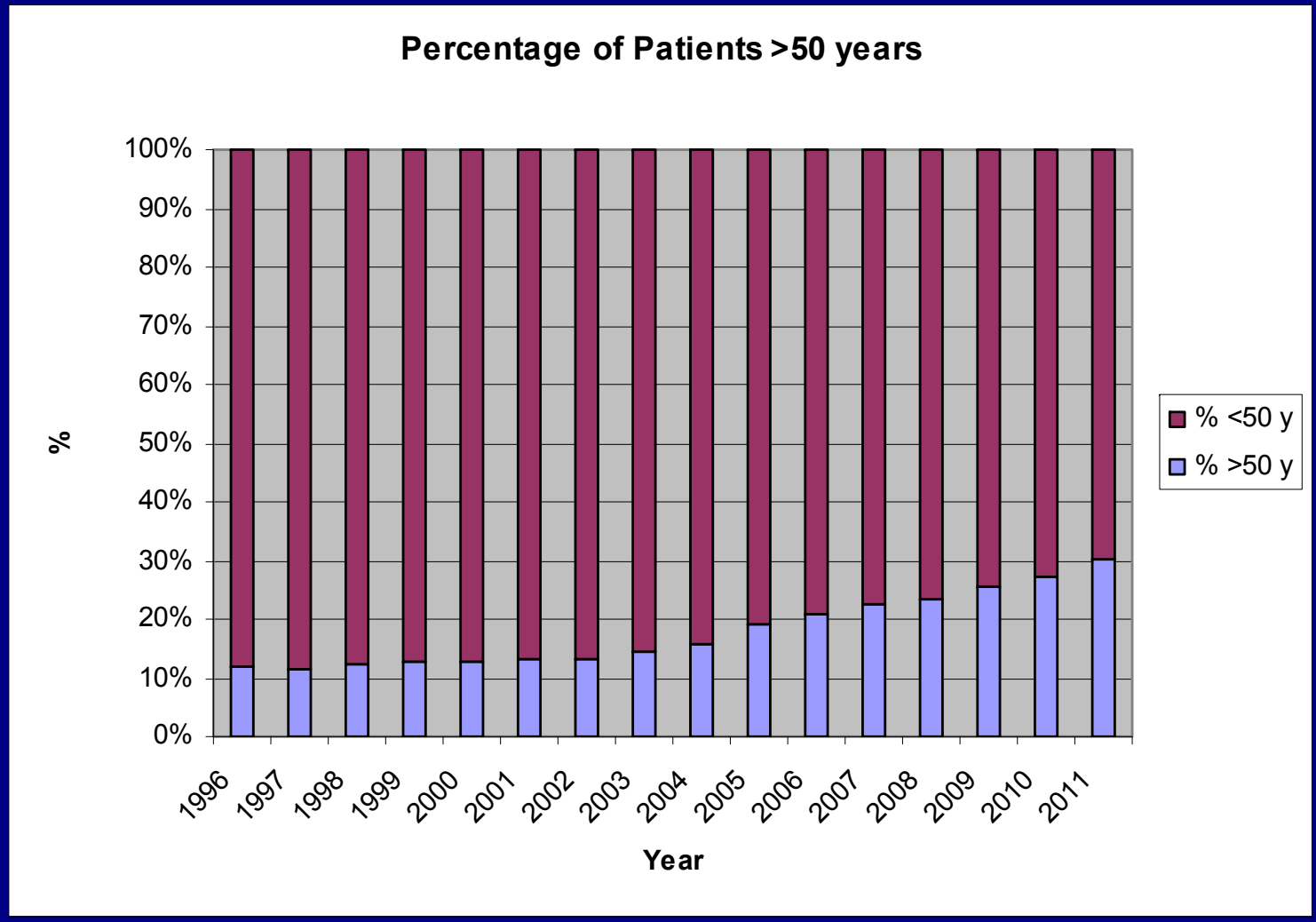
Kaletra update: what are the strengths?

Abbott Symposium, Turkey,

Sunday 27 November 2011

Jürgen Rockstroh,
Department of Medicine I, University of Bonn, Germany

Age distribution among active participants of the Bonn HIV Cohort Study over time



•Wasmuth JC, Rockstroh JK, personal communication

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

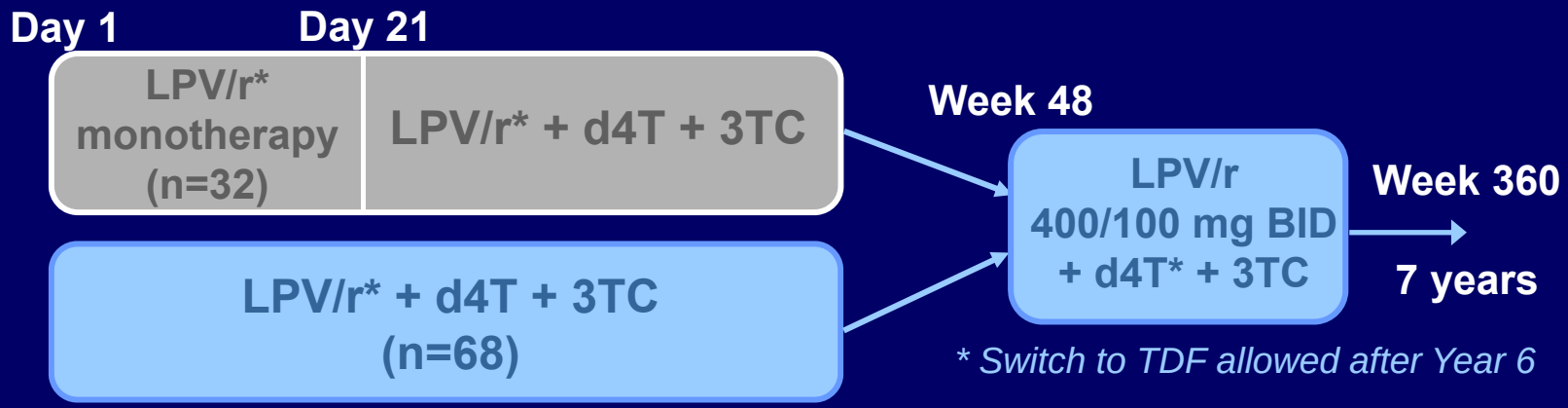
M97-720: LPV/r + d4T + 3TC in treatment-naïve adults with HIV-1 infection

Entry criteria

- Antiretroviral-naïve
- Plasma HIV-1 RNA >5,000 copies/mL
- No CD4 count restriction

Baseline characteristics

- Mean HIV-1 RNA: 77,400 copies/mL
- Mean CD4 count: 338 cells/mm^3



***LPV/r dosed at either 200/100 mg BID, 400/100 mg BID or 400/200 mg BID**

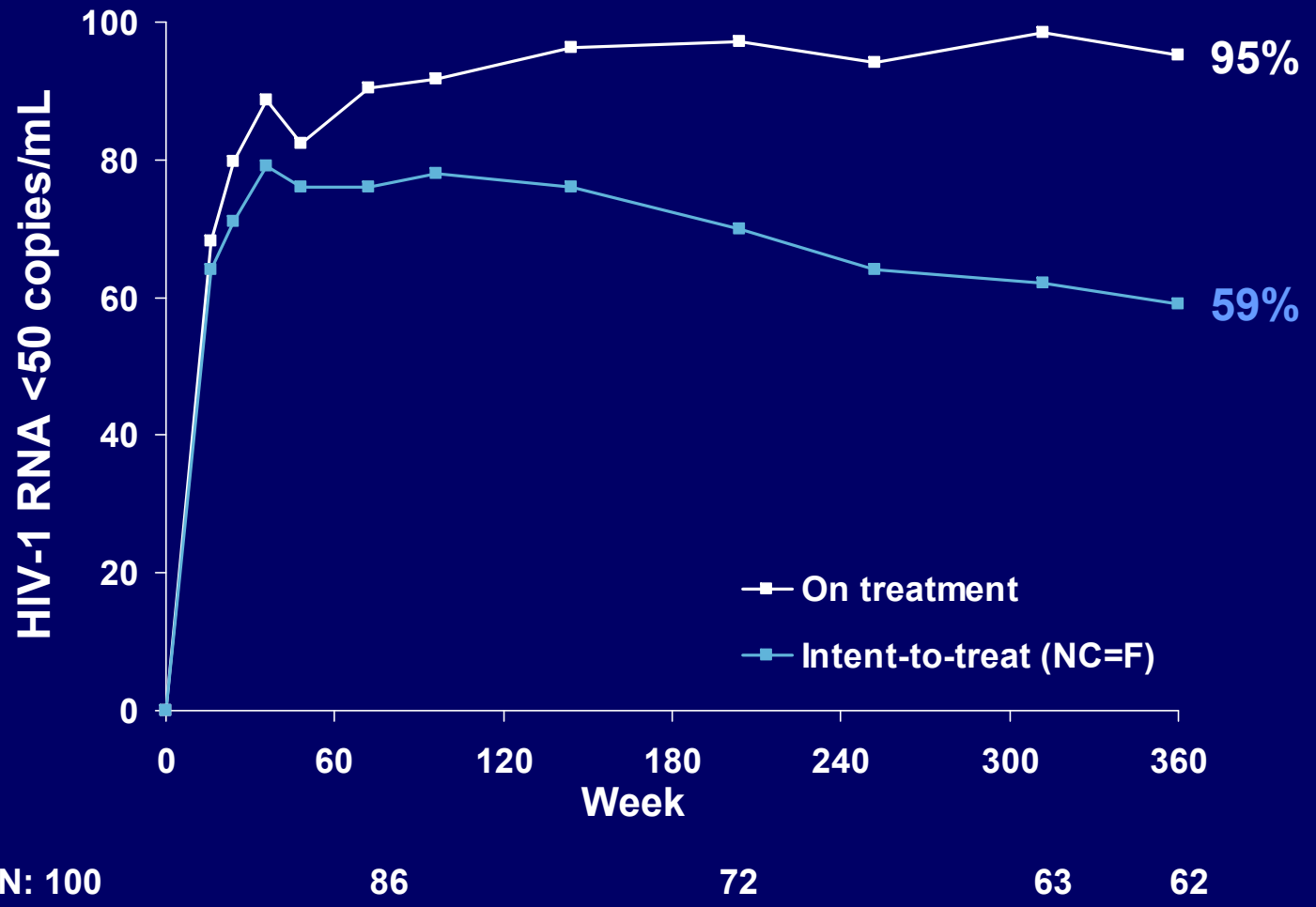
Primary endpoint

- Proportion of subjects with plasma HIV-1 RNA <400 copies/mL at Week 24 and duration of virologic response through Week 48

Murphy R. *et al., AIDS* 2001, 15:1–9

Study 720

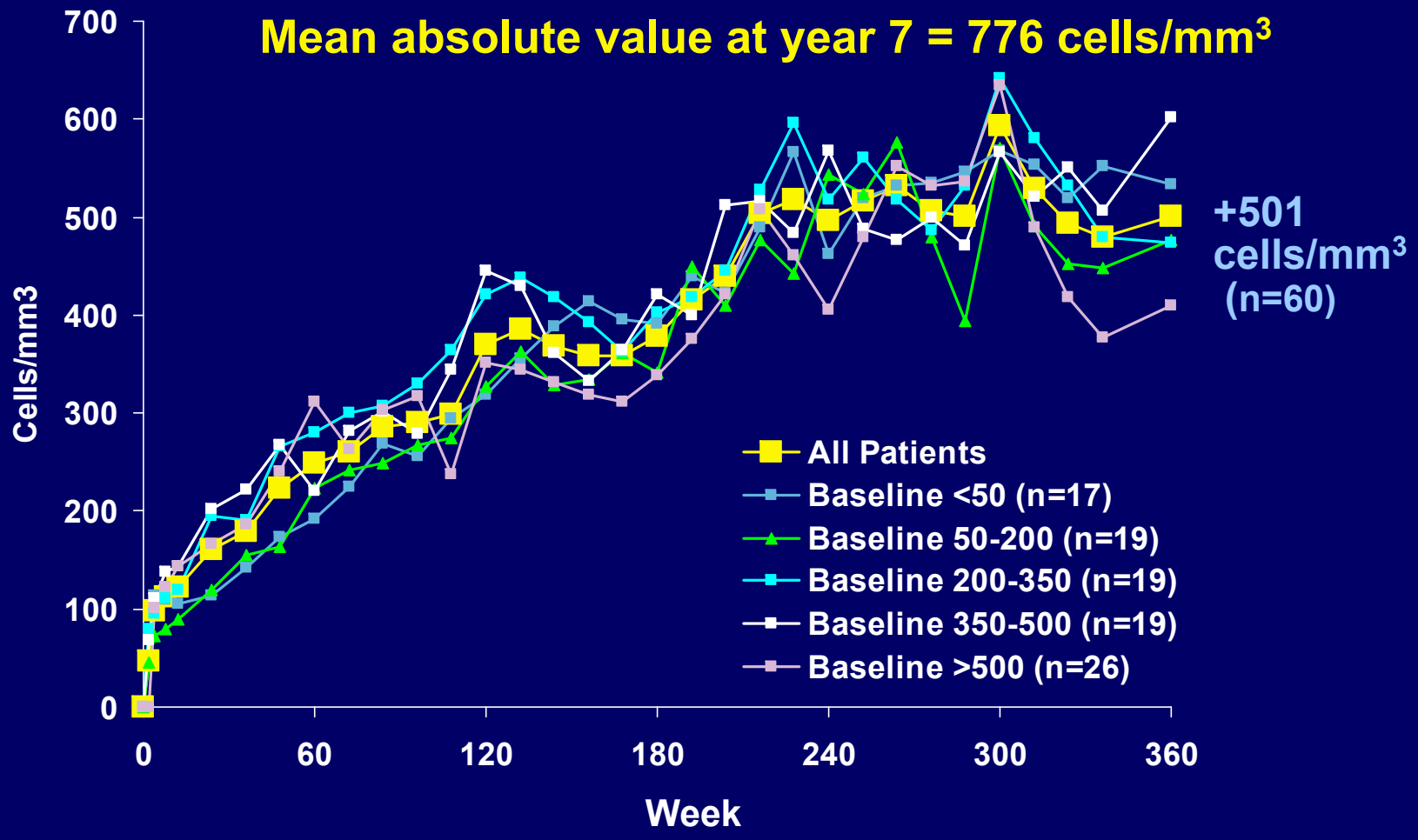
Virologic response
HIV-1 RNA <50 copies/mL through Week 360



N:	100	86	72	63	62

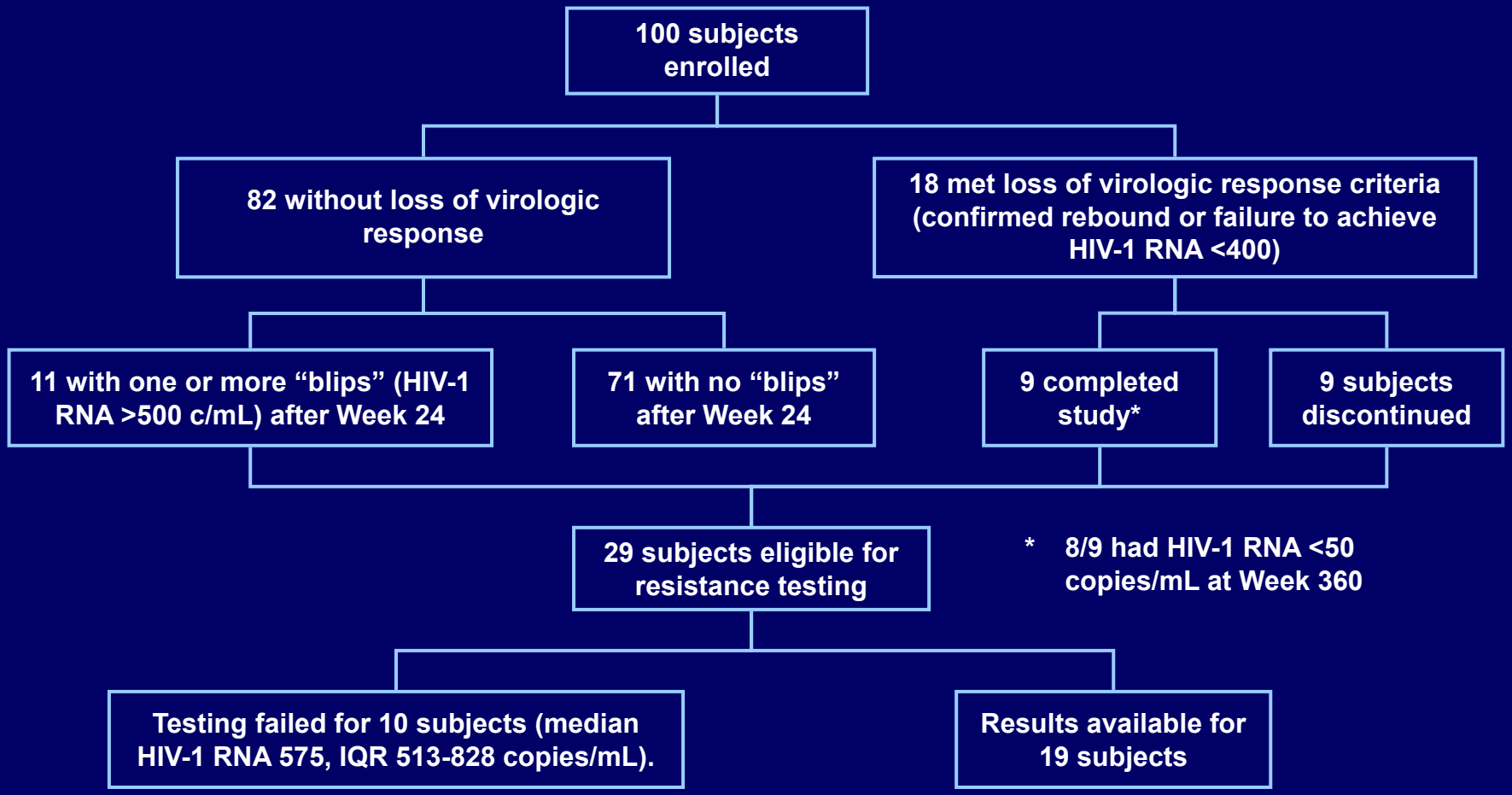
Murphy R. *et al.*, *10th EACS,* Dublin, Ireland, November 2005, #P7.9/3 **Study 720**

Mean change in CD4 Cell Count Through 7 years



Murphy R. *et al.*, *10th EACS,* Dublin, Ireland, November 2005, #P7.9/3 **Study 720**

Virologic disposition



Murphy R. *et al*., *10th EACS,* Dublin, Ireland, November 2005, #P7.9/3 **Study 720**

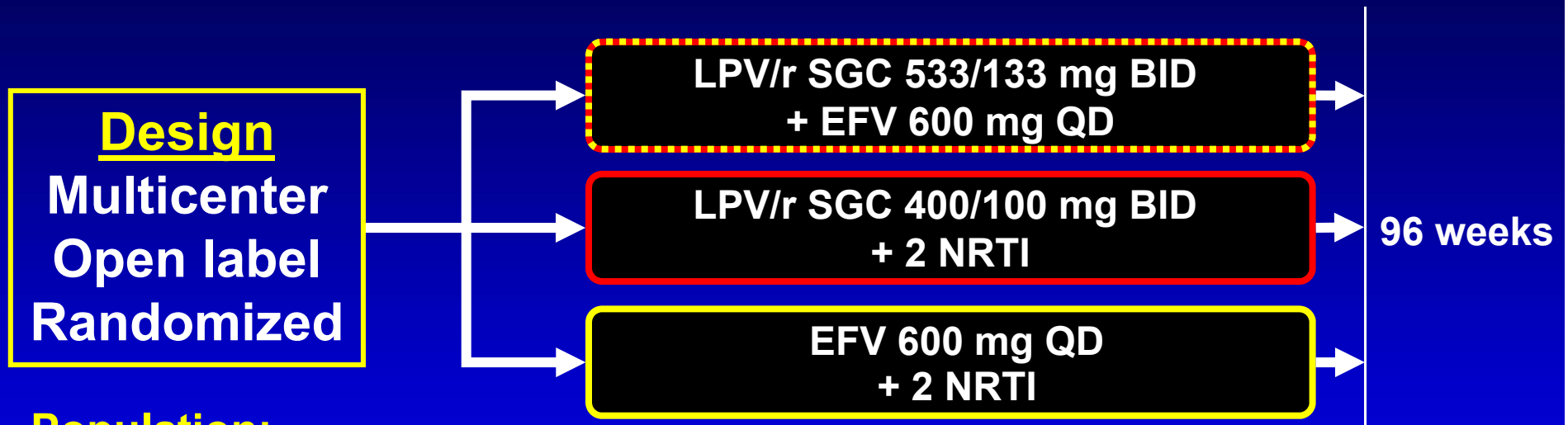
No detectable lopinavir or stavudine resistance through Week 360

Patients enrolled	**100**
Patients eligible for resistance testing	**29**
Patients with resistance data available*	**19/29**
LPV resistance (any primary/active site mutation)	**0**
d4T resistance (any TAM)	**0**
3TC resistance (M184V/I/T mutation)	**4/19 (21%)**

* **Testing failed in 10 patients due to low HIV RNA level (median 575, IQR 513-828 copies/mL)**

Murphy R. *et al*., *10th EACS,* Dublin, Ireland, November 2005, #P7.9/3 **Study 720**

A5142 Study Design



Population:

ARV-naïve
HIV RNA ≥2,000 c/mL
Any CD4 count

3TC + Investigator
Selection of
ZDV or d4T XR or TDF

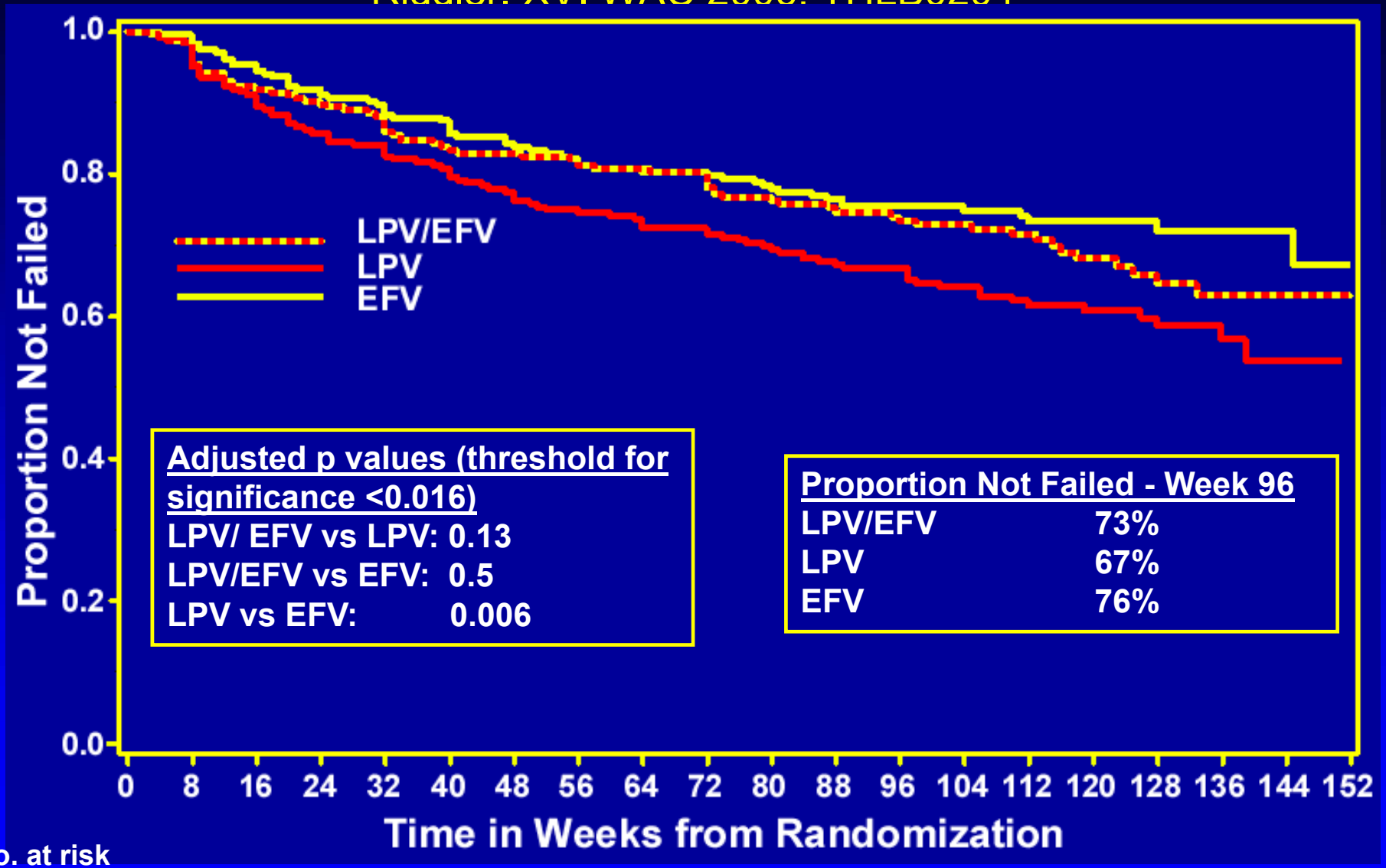
Stratification:

Selected NRTI (%)	
ZDV	42
d4T XR	24
TDF	34

Haubrich R et al., 14th CROI, Los Angeles 2007, #38

Time to Virologic Failure

Riddler. XVI WAC 2006: THLB0204



Adjusted p values (threshold for significance <0.016)

LPV/ EFV vs LPV: 0.13

LPV/EFV vs EFV: 0.5

LPV vs EFV: 0.006

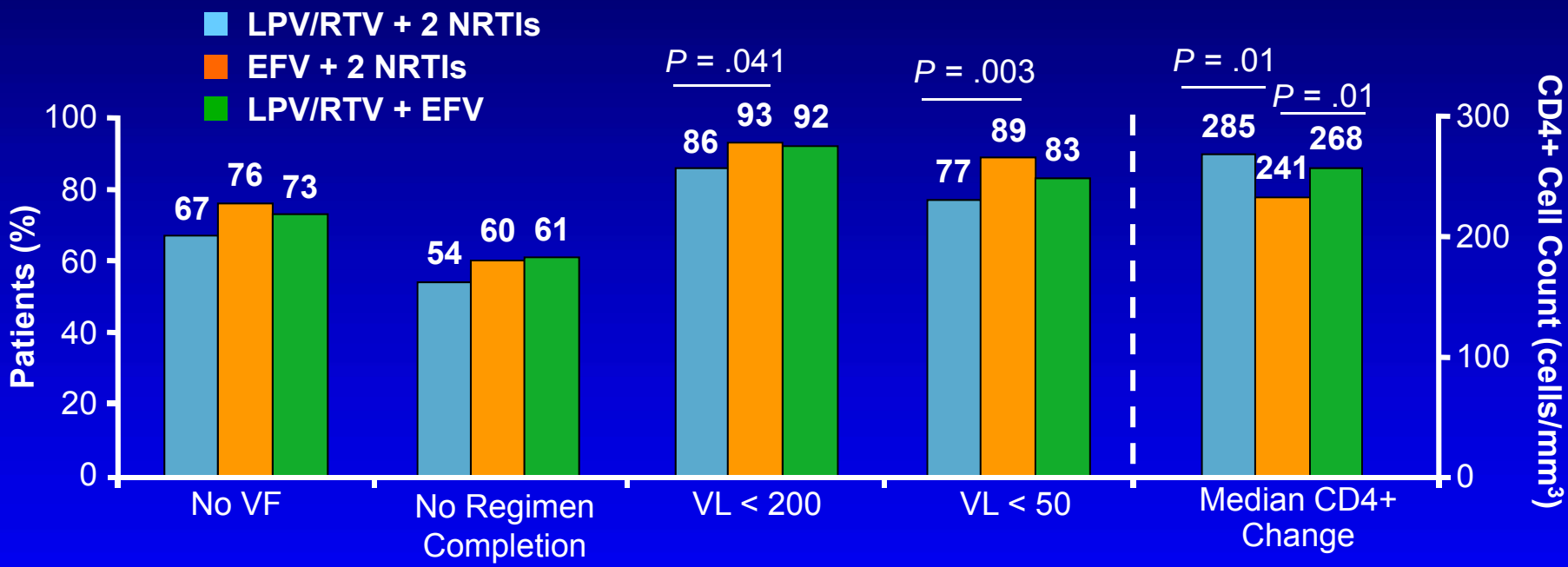
Proportion Not Failed - Week 96

LPV/EFV	73%
LPV	67%
EFV	76%

No. at risk

LPV/EFV	250	208	187	171	131	58	10
LPV	253	206	180	164	116	62	3
EFV	250	204	183	170	121	60	8

ACTG 5142: Outcomes at Week 96 (ITT)



- EFV + 2 NRTIs superior to LPV/RTV + 2 NRTIs in coprimary endpoint of time to virologic failure (*P* = .006)
- EFV + 2 NRTIs not significantly different to LPV/RTV + 2 NRTIs in coprimary endpoint of time to regimen completion (*P* = .02)
- LPV/RTV + 2 NRTIs superior to EFV + 2 NRTIs in CD4+ cell count change

Riddler S, et al. IAC 2006. Abstract THLB0204.

ACTG 5142
Preliminary analysis of mutations associated with resistance

	LPV/EFV	LPV	EFV
Pat. With virological failure	73	94	60
Number of genotypic resistance tests*	39	52	33
Number of NRTI mutations M184I / V K65R	4 (10%) 1 0	8 (15%) 7 0	11 (33%) 8 3
Number of NNRTI mutations K103N	27 (69%) 21	2 (4%) 0	16 (48%) 9
Number of primary PI mutations**	2	0	0
Mutations in 2 drug classes	2	2	10

* Some results are still pending

** 30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, 90M

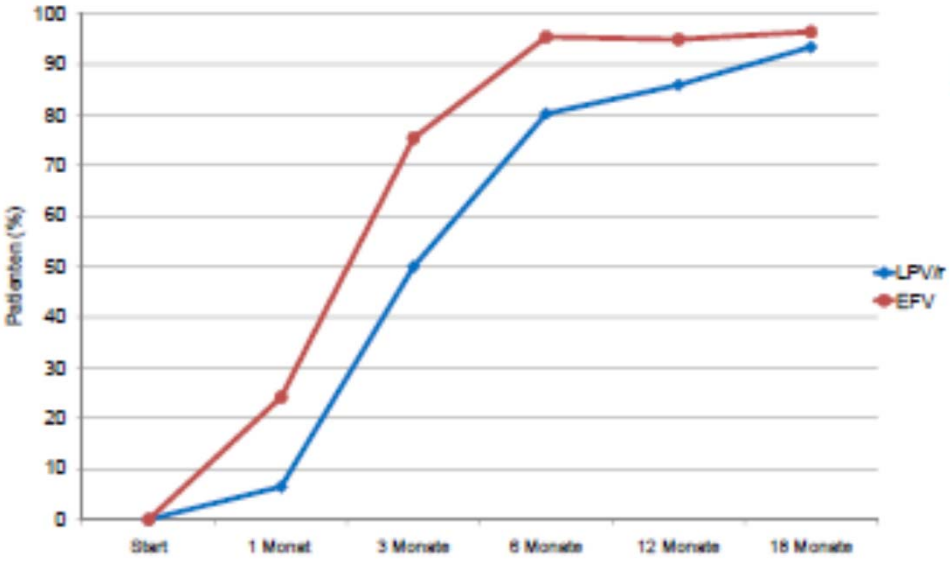
Adapted from Riddler et al., XVI International AIDS Conference, Toronto 2006, THLB0204

Efavirenz or lopinavir/r based firstline therapy: why do patients discontinue therapy ?

Tabke 1: Reasons for treatment discontinuation

	LPV/r	EFV
Gastrointestinal AE	9,8%	0,0%
CNS	0,0%	10,7%
Simplification	5,9%	1,3%
Lab. Toxicity	3,0%	2,7%
Pregnancy	0,0%	2,7%
Death	3,9%	0,0%
Compliance	3,9%	1,3%
Other	6,0%	8,1%

Figure 1: Percentage of patients with a viral load <50 copies/ml (on-treatment analyses)



Discontinuation rate was 24% in the EFV arm (n=75) and 24,5% in the LPV/r arm (n=102);p=0.938.

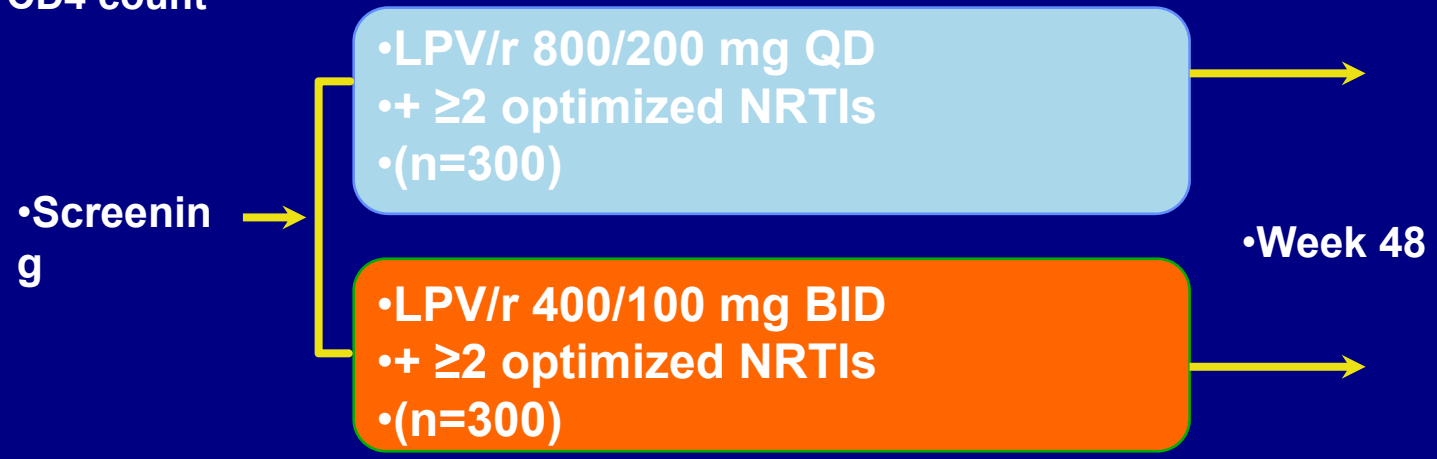
Gilhaus L, Weinzierl I et al., KIT 2010

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

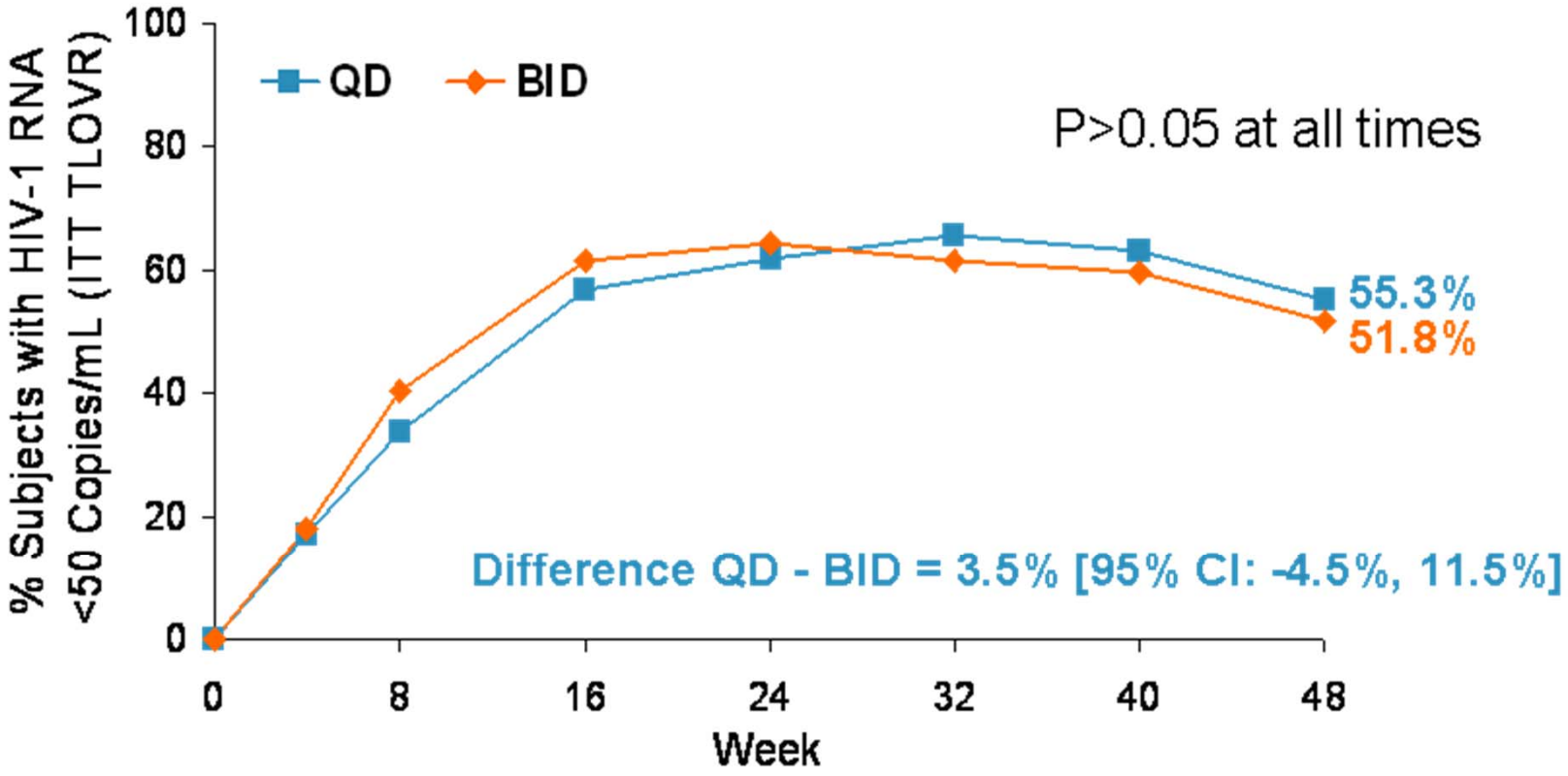
LPV/r QD *vs* BID in Treatment-Experienced Subjects M06-802 Study Design

- **Inclusion Criteria**
- HIV-1 infection
- ARV-experienced, lopinavir-naïve
- HIV-1 RNA >1000 c/mL on treatment regimen unchanged for ≥12 weeks
- Based on genotypic and treatment history, investigator considers LPV/r plus ≥2 NRTIs to be an appropriate treatment option
- Any CD4 count



- **Primary endpoint:** HIV-1 RNA <50 copies/mL at Week 48 (ITT TLOVR)
- Noninferiority assessed by 95% CI for the difference (QD *minus* BID) using a -12% threshold

Primary Efficacy Endpoint at Week 48
Proportion of Subjects Responding (ITT TLOVR)



Demonstrating non-inferiority of LPV/r QD to BID in treatment-experienced subjects

Abbott Virology

Number and % of Subjects with Moderate or Severe Drug-related Adverse Events Occurring in ≥2%*

	LPV/r QD (N=300) n (%)	LPV/r BID (N=299) n (%)	*P* value
Any Adverse Event	**82 (27.3)**	**76 (25.4)**	**NS**
GI Disorders			
Diarrhea	42 (14.0)	33 (11.0)	NS
Nausea	8 (2.7)	22 (7.4)	0.009
Abdominal pain	6 (2)	1 (0.3)	NS
Abdominal pain (upper)	2 (0.7)	6 (2.0)	NS
Vomiting	6 (2.0)	8 (2.7)	NS
Metabolism and Nutrition Disorders	7 (2.3)	4 (1.3)	NS
Hypercholesterolemia			

* in either treatment group

Abbott Virology

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

Summary of Resistance Analysis: Week 24–96

	Kaletra (N=326)	Nelfinavir (N=327)
HIV RNA above 400 copies/ml	74	123
Genotype available	51	96
PI or active site mutations*	0/51 (0%)†	44/96 (46%)†
3TC resistance*	19/51 (37%)	79/96 (82%)
TAMs (d4T)	0/51 (0%)	9/96 (9%)
Secondary mutations/polymorphisms† *	7/51 (14%)	48/96 (50%)

†Confirmed by phenotype<2.5 FC in IC_{50}

* p<0.001

M98-863

D Kempf et al., 10th CROI, Boston, 2003, #600
D. Kempf et al. *Antiviral Therapy* 2002;7:S119

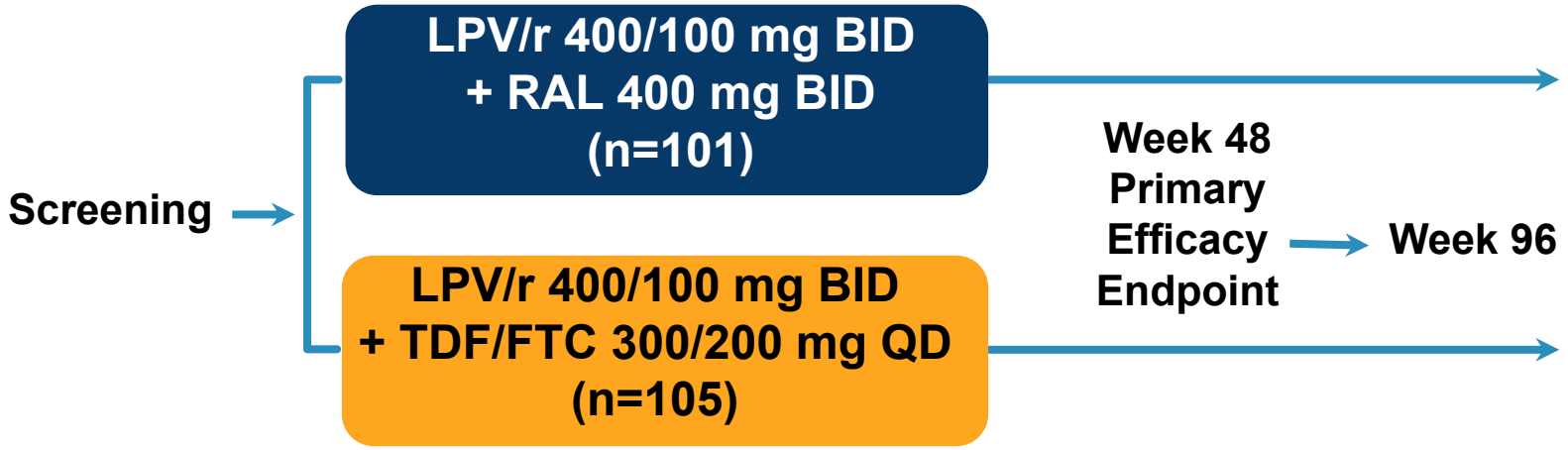
Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

LPV/r + RAL *vs*. LPV/r + TDF/FTC in Treatment-Naive Subjects: PROGRESS Study Design*

Inclusion Criteria for PROGRESS (M10-336)

- HIV-1 infection
- ARV-naïve
- Plasma HIV-1 RNA >1000 copies/mL
- Any $CD4^+$ T-cell count



Met Primary Endpoint of Noninferiority

- **Primary endpoint: plasma HIV-1 RNA <40 copies/mL at week 48 (FDA-TLOVR)**
- **FDA-TLOVR week 48: LPV/r + RAL=83.2%, LPV/r + TDF/FTC=84.8%**
- ***P*=0.850, difference -1.6%, 95% exact confidence interval (CI) -12.0%, 8.8%**
- **Safety and tolerability were similar at week 48**

* 3 subjects were randomized but not dosed

Baseline Demographics and HIV Disease Characteristics

Variable	LPV/r + RAL (N=101)	LPV/r + TDF/FTC (N=105)	Total (N=206)
Males, n (%)	88 (87.1)	86 (81.9)	174 (84.5)
Race			
White, n (%)	74 (73.3)	81 (77.1)	155 (75.2)
Black, n (%)	22 (21.8)	22 (21.0)	44 (21.4)
Other, n (%)	5 (4.9)	2 (1.9)	7 (3.4)
Mean age ± SD, years	39.8 ± 9.9	39.4 ± 11.2	39.6 ± 10.6
Mean BL HIV-1 RNA, $\log_{10}$ copies/mL (range)*	4.24 (2.0-6.0)	4.25 (2.7 – 6.0)	4.25 (2.0 – 6.0)
Mean BL $CD4^+$ T-cells/µL (range)	289.3 (5 – 668)	297.6 (5 – 743)	293.5 (5 – 743)

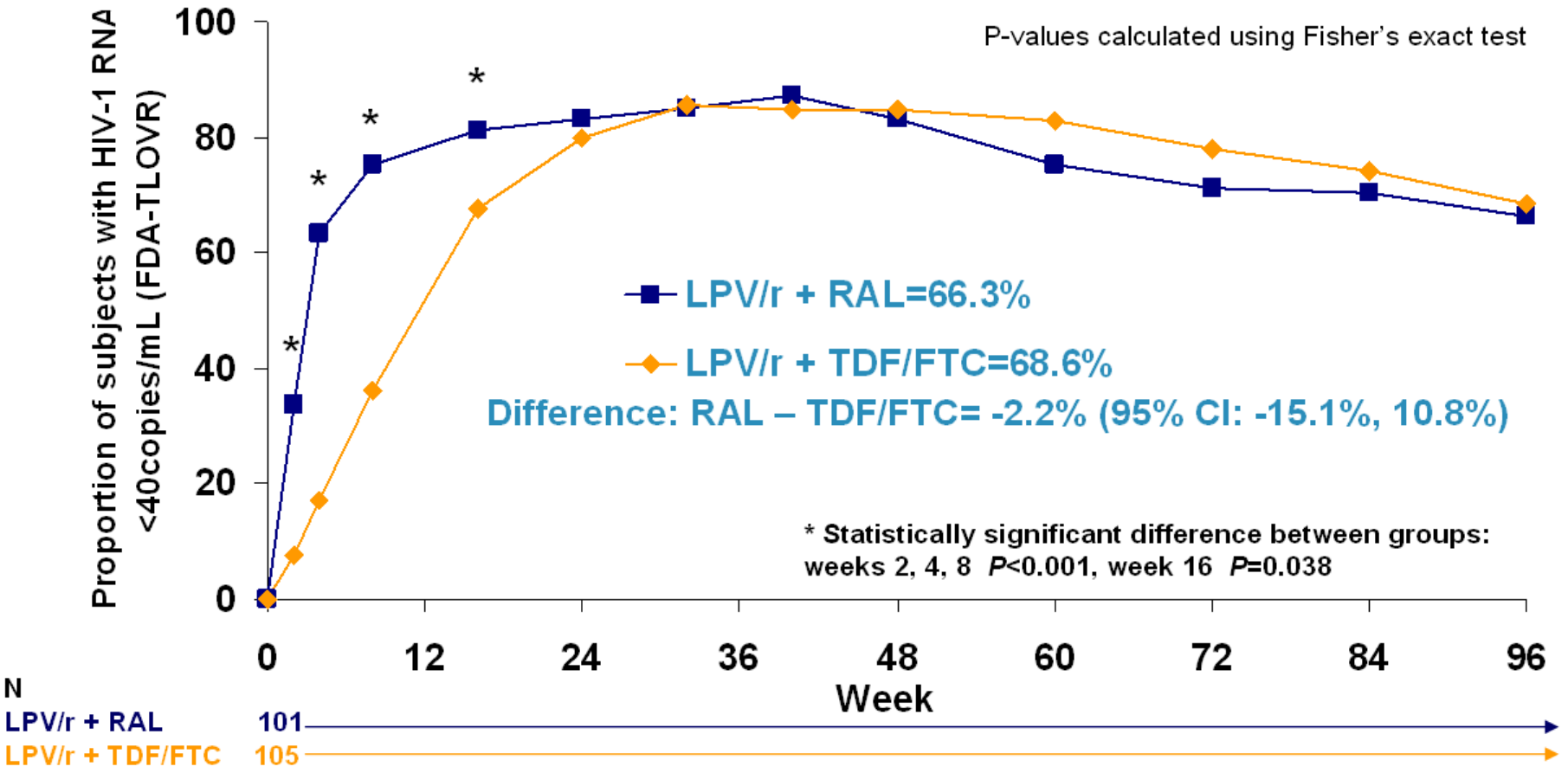
* Plasma HIV-1 viral loads determined using automated, quantitative RT-PCR assay (Abbott RealTime HIV-1 assay®)
Groups were compared using one-way ANOVA for continuous variables and Fisher's exact test for categorical variables.

Subject Disposition at Week 96

Reasons for Discontinuations	LPV/r + RAL (N=101) n (%)	LPV/r + TDF/FTC (N=105) n (%)	Total (N=206) n (%)
All Reasons*	19 (18.8)	15 (14.3)	34 (16.5)
Lost to Follow-Up	9 (8.9)	3 (2.9)	12 (5.8)
AE/HIV-related Event	5 (5.0)	4 (3.8)	9 (4.4)
Withdrew Consent	2 (2.0)	4 (3.8)	6 (2.9)
Virologic Failure	1 (1.0)	2 (1.9)	3 (1.5)
Other†	2 (2.0)	1 (1.0)	3 (1.5)
Noncompliance†	1 (1.0)	0 (0)	1 (0.5)
Pregnancy	0 (0)	1 (1.0)	1 (0.5)

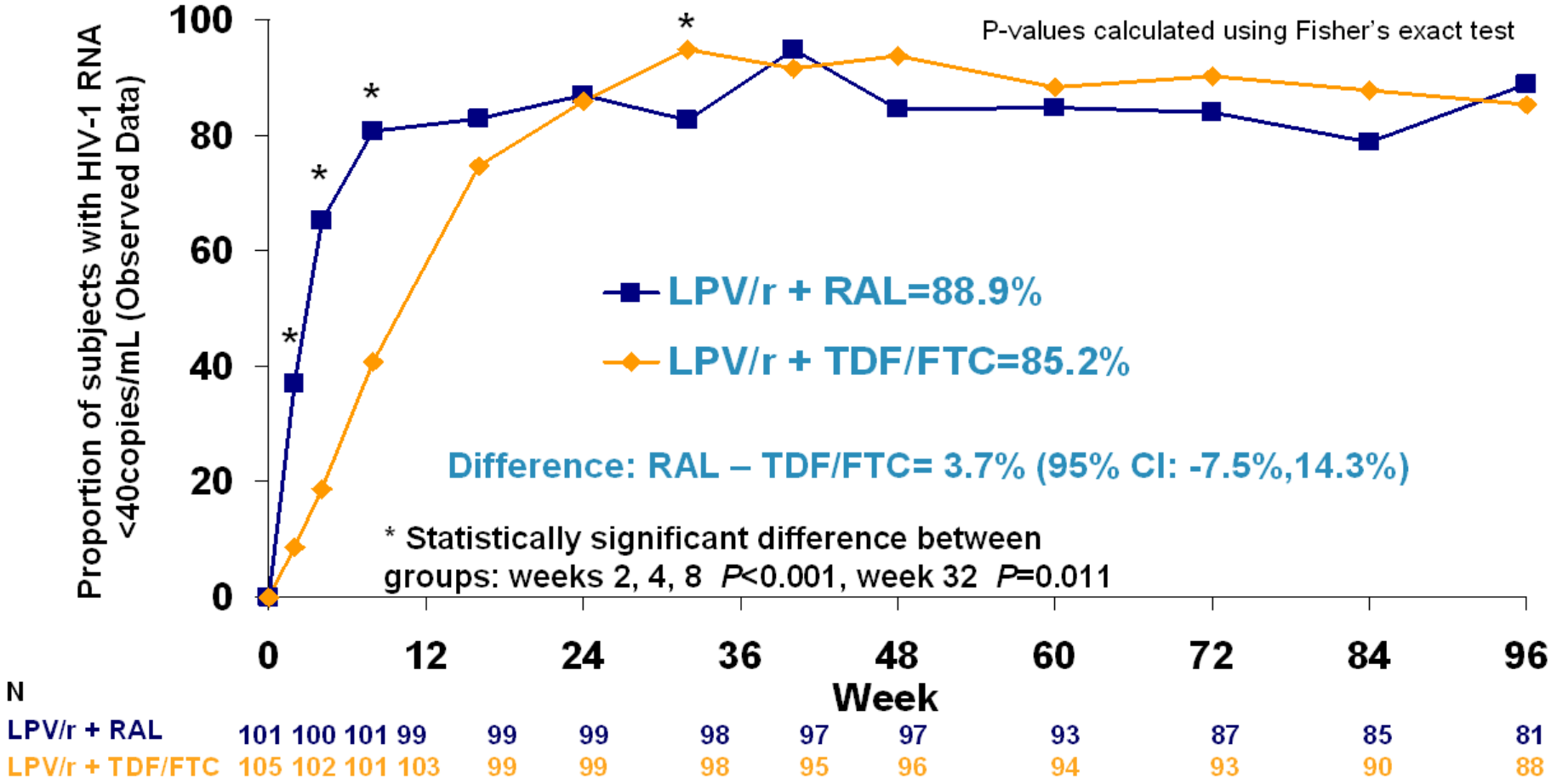
* *P*>0.05 for LPV/r +RAL vs. LPV/r + TDF/FTC comparison for each reason based on Fisher's exact test
† 1 LPV/r + RAL subject discontinued for two reasons: Noncompliance and Other

Proportion of Subjects Responding at Week 96 (FDA-TLOVR)



Week 96 FDA-TLOVR response for subjects with BL plasma HIV-1 RNA ≥100,000 copies/mL:
LPV/r + RAL= 6/15, LPV/r + TDF/FTC= 10/19

Proportion of Subjects Responding at Week 96 (Observed Data Analysis)



Week 96 OD response for subjects with BL plasma HIV-1 RNA ≥100,000 copies/mL:
LPV/r + RAL= 8/10, LPV/r + TDF/FTC= 12/15

Number and % of Subjects with Moderate or Severe Drug-Related Adverse Events*

	LPV/r + RAL (N=101) n (%)	LPV/r + TDF/FTC (N=105) n (%)
Any adverse event	**31 (30.7)**	**36 (34.3)**
Diarrhea	**8 (7.9)**	**17 (16.2)**
Hypercholesterolaemia†	**10 (9.9)**	**7 (6.7)**
Hypertriglyceridaemia†	**9 (8.9)**	**5 (4.8)**
Alanine Aminotransferase Increased	**3 (3.0)**	**1 (1.0)**
Hyperlipidaemia	**3 (3.0)**	**1 (1.0)**
Asthenia	**0 (0)**	**3 (2.9)**
Regurgitation	**0 (0)**	**3 (2.9)**

* Occurring in ≥2.0% in either treatment group
† Hypercholesterolaemia includes blood cholesterol increased, hypertriglyceridaemia includes blood triglycerides increased
P>0.05 for LPV/r + RAL *vs*. LPV/r + TDF/FTC comparison for each adverse event based on Fisher's exact test

Emergence of Resistance-Associated Mutations (RAMs)* Through 96 Weeks

13 subjects (8 LPV/r + RAL and 5 LPV/r + TDF/FTC) met the protocol-defined criteria for resistance testing

- FTC RAM was detected in 1 subject (week 40)
- RAL RAMs without LPV/r RAMs were detected in 2 subjects (weeks 48 and 65)
- RAL (week 16) and LPV/r (week 72) RAMs were detected in 1 subject

* Resistance was specified by the 2010 IAS-USA panel.

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

DHHS Guidelines: What to Start

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) The preferred regimens for nonpregnant patients are arranged by chronological order of FDA approval of components other than nucleosides and, thus, by duration of clinical experience.

NNRTI – Based Regimen **EFV/TDF/FTC[1] (AI)**	Comments: **EFV** should not be used during the first trimester of pregnancy or in women of childbearing potential trying to conceive or not using effective and consistent contraception
PI – Based Regimens (in alphabetical order) **ATV/r + TDF/FTC[1] (AI)** **DRV/r (once daily) + TDF/FTC[1] (AI)**	**TDF** should be used with caution in patients with renal insufficiency
INSTI – Based Regimen **RAL + TDF/FTC[1] (AI)**	**ATV/r** should not be used in patient who require >20mg omeprazole equivalent per day. Refer to Table 15a for dosing recommendations regarding interactions between ATV/r and acid-lowering agents
Preferred Regimen for Pregnant Women[2] **LPV/r (twice daily) +ZDV/3TC[1] (AI)**	

Alternative Regimens (that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)

NNRTI – Based Regimens (in alphabetical order) **EFV + ABC/3TC[1] (BI)** **RPV/TDF/FTC[1] (BI)** **RPV + ABC/3TC[1] (BIII)**	Comments: Use **RPV** with caution in patients with pretreatment HIV RNA >100,000 copies/mL
PI – Based Regimens (in alphabetical order) **ATV/r + ABC/3TC[1] (BI)** **DRV/r + ABC/3TC[1] (BIII)** **FPV/r (once or twice daily) = ABC/3TC[1] or TDF/FTC[1] (BI)** **LPV/r (once or twice daily) = ABC/3TC[1] or TDF/FTC[1] (BI)**	Use of proton pump inhibitors is contraindicated with **RPV** **ABC** should not be used in patients who test positive for HLA-B #5701
INSTI – Based Regimen **RAL + ABC/3TC[1] (BIII)**	Use **ABC** with caution in patients with known high risk of cardiovascular disease or with pretreatment HIV RNA >100,000 copies/mL. (See text) **Once-daily LPV/r** is not recommended in pregnant women

ddI + 3TC and unboosted FPV no longer recommended

US Department of Health and Human Services Guidelines; Revised October 14, 2011
Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

Discordance Between CSF and Plasma HIV in Patients with Neurological Symptoms Who Are Receiving Suppressive ART

Methods

- 11 cases of neurological symptoms in patients on stable ART for median of 13 months-median length of total ART was 12 years
  - Discordance defined as CSF VL >200 copies/mL while plasma <50 copies/mL **or** if CSF VL 1 log greater than plasma
  - no other infectious agents

Results

- MRI showed encephalitis in 9 patients and myelitis in 2 patients
- CSF VL median of 880 copies/mL (range, 558–12,885 copies/mL)
- 7/8 available patients had significant resistance mutations in the CSF HIV strains
  - In 5 patients, the virus present in the CSF was not sensitive to their current regimen
- Median 2008 CPE score was 2 (1 to 3) but 5 patients had a CPE score of <2
- Treatment modification in 10/11 patients based on genotypes & 2008 CPE score
  - 10/10 patients improved clinically within 4 weeks
  - 9/9 who had CSF drawn had a CSF HIV RNA <200 copies/mL within 6 weeks

Conclusion

- Despite suppression of plasma viremia with ART, HIV may replicate in CSF, with development of CSF HIV resistance resulting in acute or subacute neurological manifestations

1. Canestri A, *et al.* CID. 2010; 50:773–778

CPE score of Letendre

	4	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

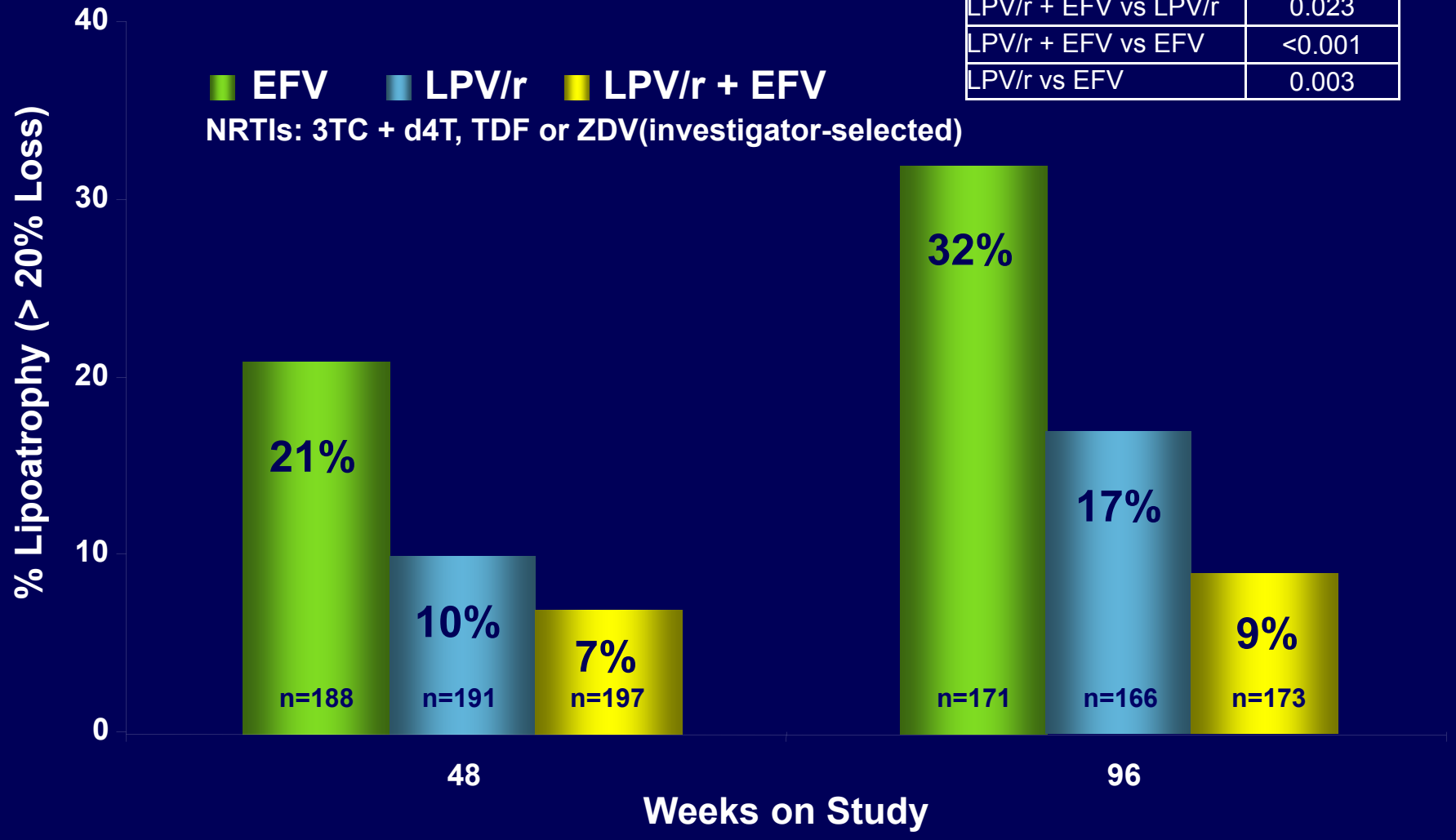
Letendre S et al. CROI 2010, Poster 430

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

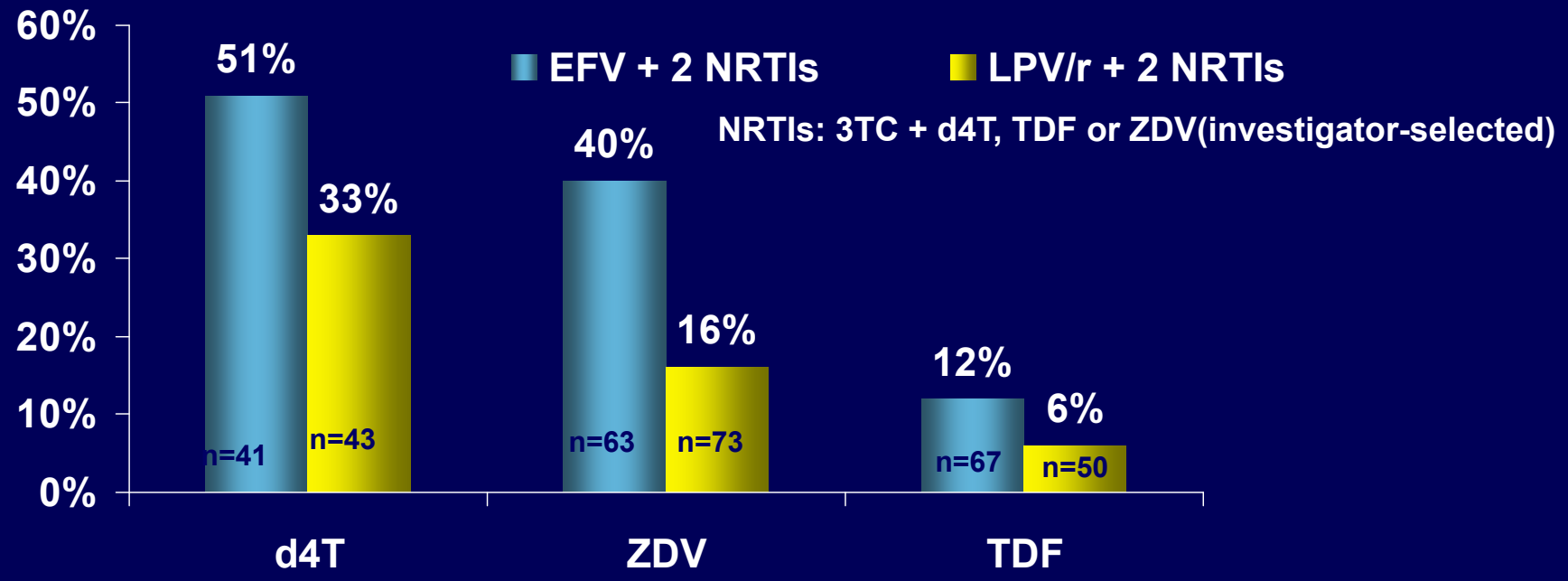
ACTG 5142: Lipoatrophy in LPV/r vs. EFV at Weeks 48 and 96

P values at week 96	
LPV/r + EFV vs LPV/r	0.023
LPV/r + EFV vs EFV	<0.001
LPV/r vs EFV	0.003



Haubrich R et al. *AIDS* 2009, (23) 1109-1128

ACTG 5142: Lipoatrophy in LPV/r vs EFV at Week 96 Within NRTI Subgroups



Logistic Regression Week 96 Lipoatrophy

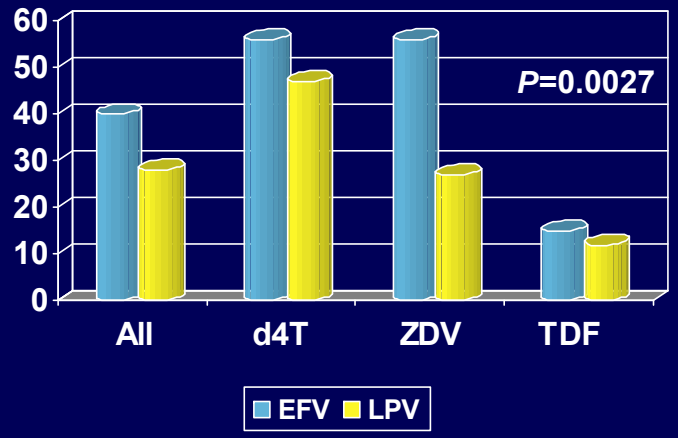
Model includes randomized arm and NRTI, for NRTI-containing regimens only

Factor	OR (95% CI)	*P* Value
EFV vs LPV/r	2.7 (1.5–4.6)	<0.001
d4T vs ZDV	1.9 (1.1–3.5)	0.029
TDF vs ZDV	0.24 (0.12–0.5)	<0.001

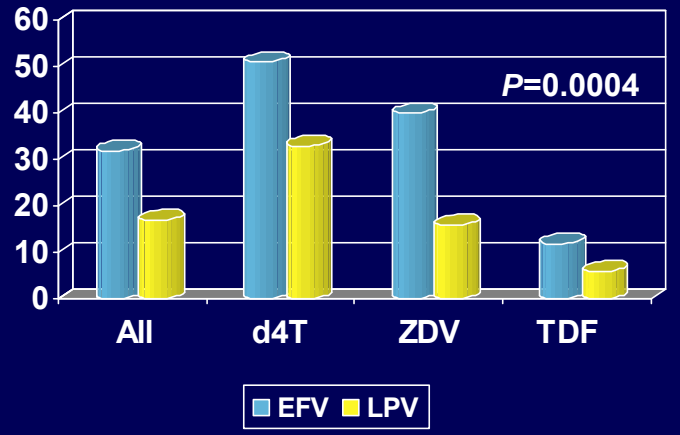
Haubrich R et al. *AIDS* 2009, (23) 1109-1128

ACTG 5142: Percentage of subjects with lipoatrophy by NRTI choice and lipoatrophy definition

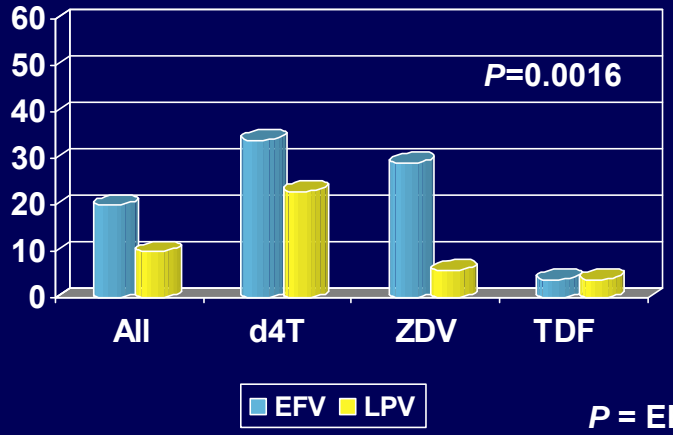
≥ 10% extremity fat loss



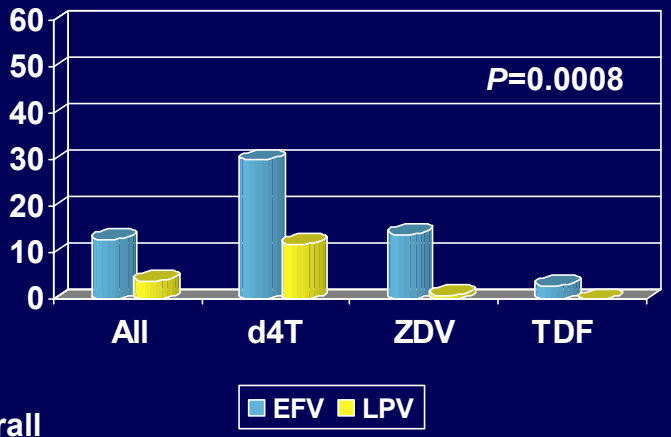
≥ 20% extremity fat loss



≥ 30% extremity fat loss



≥ 40% extremity fat loss



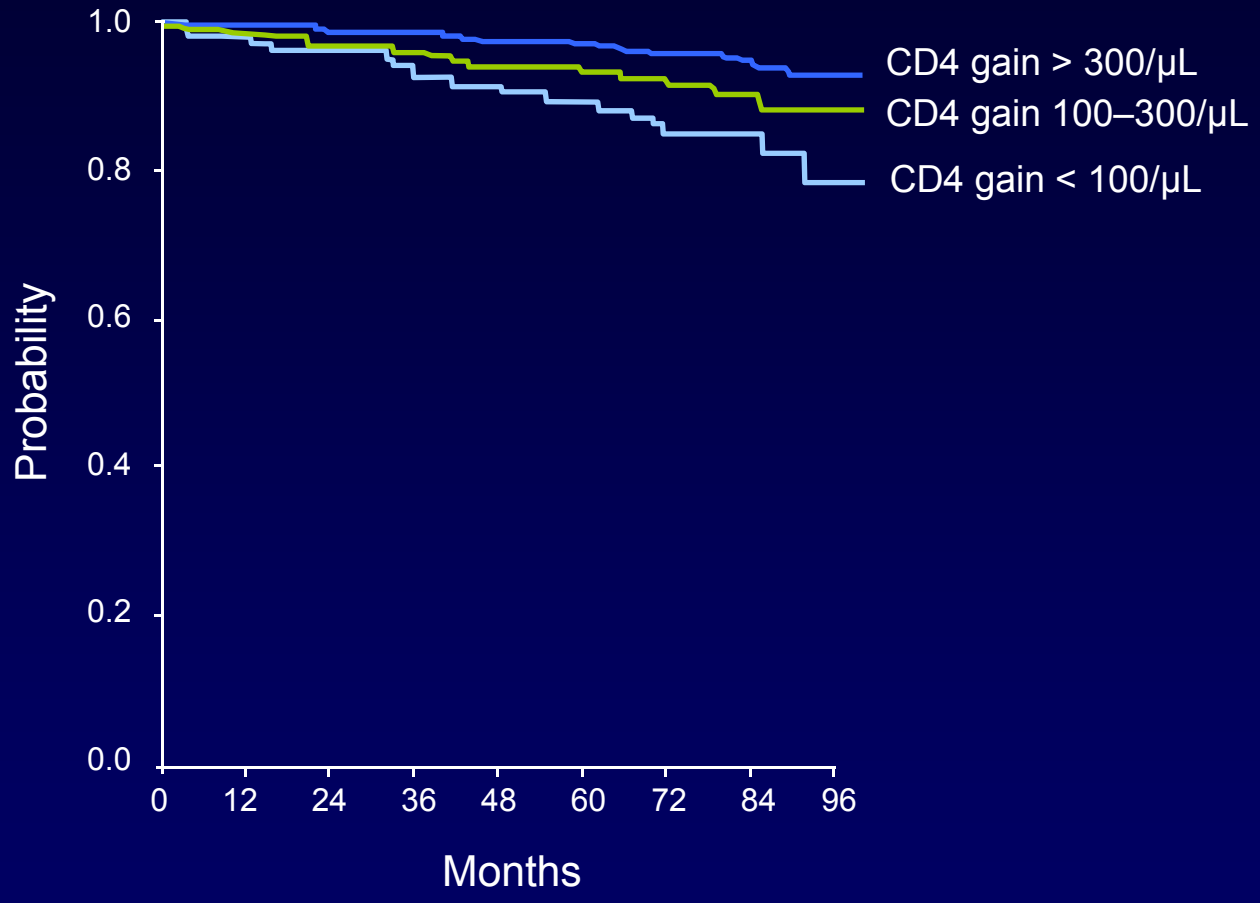
P **= EFV vs LPV overall adjusted for NRTI choice**

Haubrich R *et al*. *AIDS* 2009, (23) 1109-1128

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

Probability of remaining free of hepatic decompensation in HCV co-infected patients



Patients at risk									
CD4 gain > 300/µL	495	480	462	425	392	329	263	190	75
CD4 gain 100–300/µL	298	278	235	191	153	123	87	55	17
CD4 gain < 100/µL	193	161	138	116	92	77	53	31	13

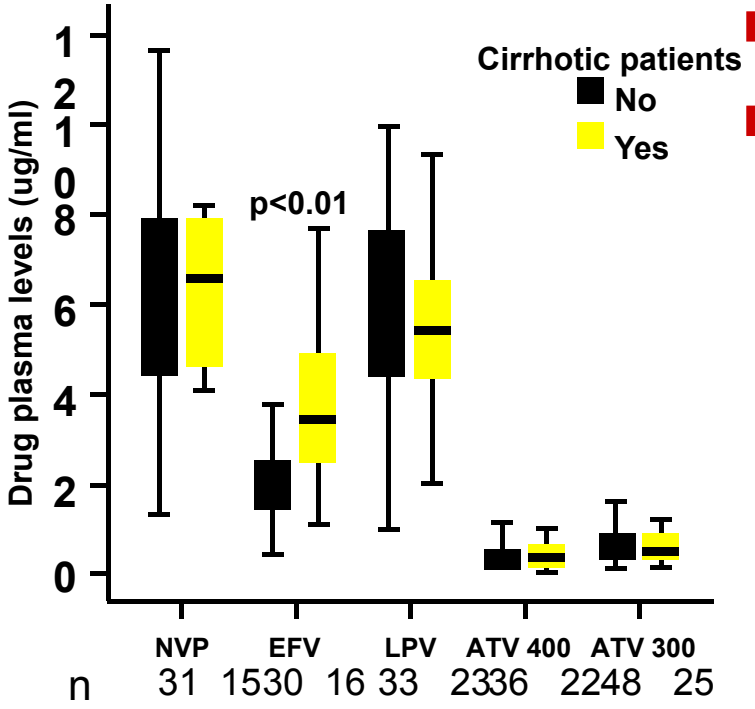
Adapted from Pineda et al. Hepatology 2007;46:622

Stage of liver fibrosis and levels of antiretrovirals

- Plasma drug levels in 279 pt HIV/HCV+ receiving NVP, EFV, LPV/r, ATV+RTV or ATV
- Liver fibrosis (Fibroscan); 37% F0–F1, 15% F2, 11% F3, 37% F4

Plasma drug levels according to liver fibrosis

	Cirrhosis	No cirrhosis	*p*
NVP	6.6 mg/mL	5.8 mg/mL	0.33
NVP >8 mg/mL	50%	27%	0.27
EFV	3.4 mg/mL	1.9 mg/mL	<0.001
EFV >4 mg/mL	31%	3%	<0.001



PIs: no difference cirrhosis vs no cirrhosis

- In compensated cirrhotics plasma levels of NNRTI, mainly EFV, may be increased, plasma levels of PI remain similar to non-cirrhotics

Barreiro P, *et al. HIV8*, Glasgow 2006, #PL 6.2

Kaletra update

- Longterm efficacy
- Once daily therapy
- Resistance aspects
- New treatment strategies
- Pregnancy
- CNS
- Lipoatrophy
- Liver disease

Thank you