A CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV Therapies and Therapeutic Strategies

REPORTING FROM THE

13th European AIDS Conference (EACS) and the 49th Annual Meeting of the Infectious Diseases Society of America (IDSA)

Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Studies in Antiretroviral Naïve Patients

Paul Sax, MD
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

EACS Guidelines: When to Start

- Initiation of ART
  - ART is always recommended if CD4 count <350 cells/mm3
  - Serodiscordant couples: Early ART should be considered and actively discussed

Condition	Current CD4 + lymphocyte count[II, III]	
	350-500	>500
Asymptomatic HIV infection	C	D
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:		
HIV-associated kidney disease	R	R
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers	R	R
Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy	C	C
Autoimmune disease — otherwise unexplained	C	C
High risk for CVD(>20% estimated 10 yr risk) or history of CVD	C	C
Chronic viral hepatitis		
HBV requiring anti-HBV treatment	R	R
HBV not requiring anti-HBV treatment	C/R [IV]	D
HCV for which anti-HCV treatment is being considered or given	R [V]	D [VI]
HCV for which anti-HCV treatment not feasible	R	C

C = CONSIDER. D = DEFER. R = RECOMMENDED

www.eacs.eu. (October 2011)

EACS Guidelines: Initial Combination Regimen

- Changes:
  - RAL (now recommended)
  - SQV/r (now alternative)

Select 1 drug in column A and 1 NRTI combination in column B (*)	A	B	REMARKS
Recommended (**)	NNRTI	ABC/3TC (VI) or TDF/FTC	TDF/FTC co-formulated ABC/3TC co-formulated EFV/TDF/FTC co-formulated
	EFV (I) NVP (II)	TDF/FTC	
	or ritonavir-boosted PI		
	ATV/r (III) DRV/r (III) LPV/r (IV)	ABC/3TC (VI) or TDF/FTC	ATV/r: 300/100 mg qd DRV/r: 800/100 mg qd LPV/r: 400/100 mg bid or 800/200 mg qd
	ITI		
	RAL	TDF/FTC	RAL: 400 mg bid
Alternative	SQV/r FPV/r MVC (V)	ZDV/3TC ddI/3TC or FTC (VII)	SQV/r: start with 500/100 mg then change to 1000/100 mg bid after one week FPV/r: 700/100 mg bid or 1400/200 mg qd ZDV/3TC co-formulated

www.eacs.eu. (October 2011)

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)**

PI – Based Regimens (in alphabetical order)
- **ATV/r + TDF/FTC[1] (AI)**
- **DRV/r (once daily) + TDF/FTC[1] (AI)**

INSTI – Based Regimen
- **RAL + TDF/FTC[1] (AI)**

Preferred Regimen for Pregnant Women[2]
- **LPV/r (twice daily) +ZDV/3TC[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

TDF should be used with caution in patients with renal insufficiency

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

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)**

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)**

INSTI – Based Regimen
- **RAL + ABC/3TC[1] (BIII)**

Comments:
Use **RPV** with caution in patients with pretreatment HIV RNA >100,000 copies/mL

Use of proton pump inhibitors is contraindicated with **RPV**

ABC should not be used in patients who test positive for HLA-B #5701

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 on pregnant women

ddI + 3TC and unboosted FPV no longer recommended

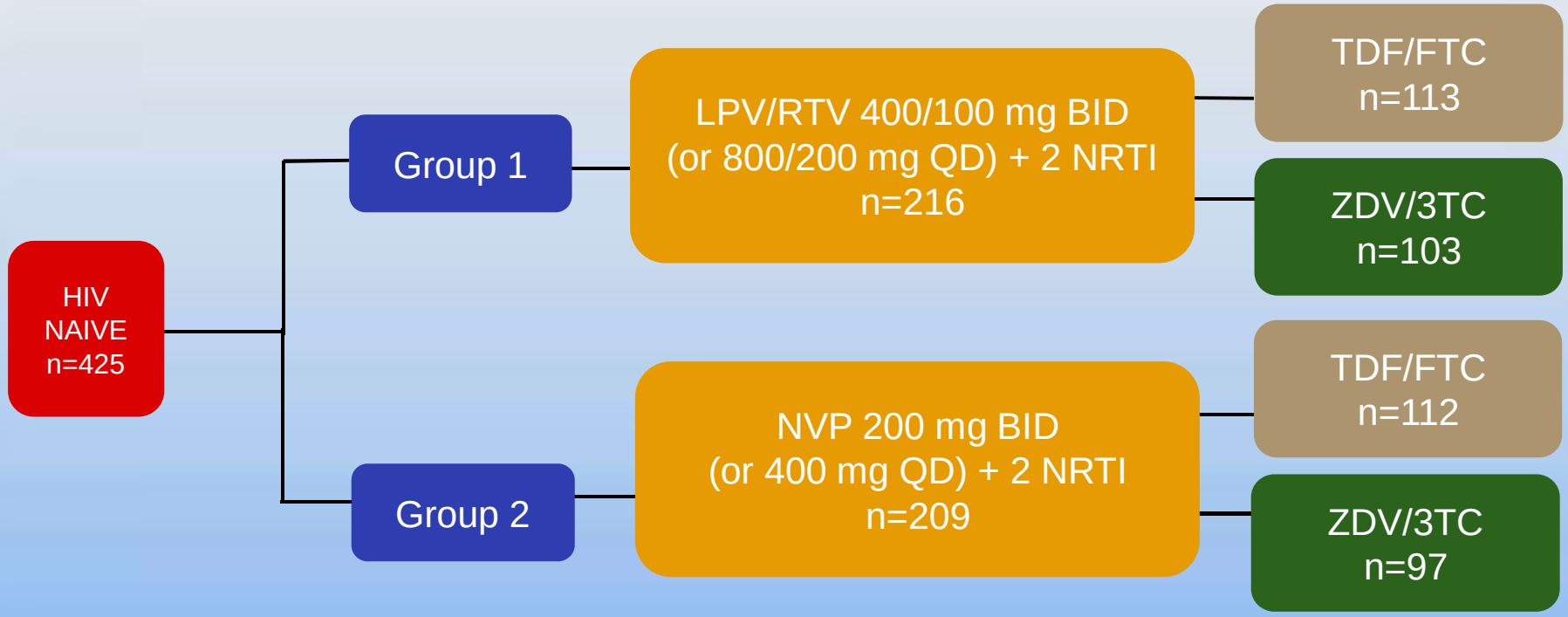
US Department of Health and Human Services Guidelines; Revised October 14, 2011
Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

What to Start: Comparison of Guidelines

Regimen	DHHS	IAS	EACS
EFV/TDF/FTC	Preferred	Recommended	Recommended
DRV/r + TDF/FTC	Preferred	Recommended	Recommended
ATV/r + TDF/FTC	Preferred	Recommended	Recommended
RAL + TDF/FTC	Preferred	Recommended	Recommended
EFV + ABC/3TC	Alternative	Alternative	Recommended
LPV/r + TDF/FTC	Alternative	Alternative	Recommended
ATV/r + ABC/3TC	Alternative	Alternative	Recommended
DRV/r + ABC/3TC	Alternative	Alternative	Recommended
NVP + TDF /FTC		Alternative	Recommended

US Department of Health and Human Services Guidelines; Revised October 14, 2011
Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf; Thompson MA, et al. JAMA 2010;304(3):321-333; www.eacs.eu (October, 2011).

Lubumbashi Trial: Nevirapine vs. Lopinavir/r in ARV-naïve (Democratic Republic of the Congo)



Previous single NVP dose allowed (PMTCT) if >1year

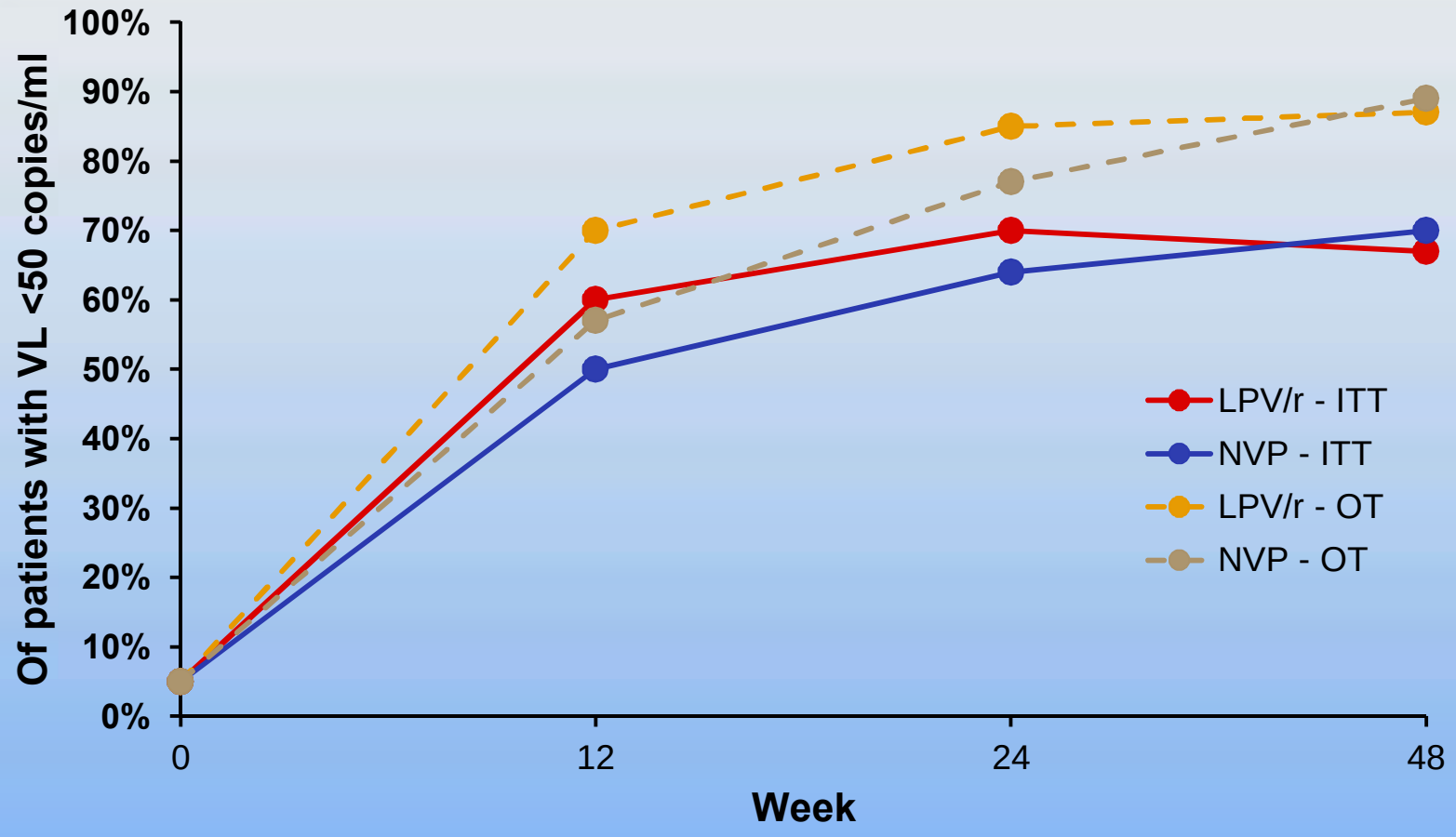
Clumeck N et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/3.

Lubumbashi Trial: Baseline Characteristics

	LPV/RTV (n=216)	NVP (n=209)
CD4 count (cell/µL)-Median (Range)	170 (1-434)	165 (1-711)
CD4 count< 100/µL	28.7%	29.6%
HIV RNA (log copies/ml-Median)	135 403	148 815
HIV RNA > 100 000 copies/ml	53.2%	55%
Hb (g/dL), median, range	11 (8.5-20)	10.8 (8.5-16)
Hep B Surface Antigen, positive, n (Percentage)	22 (10.1%)	18 (8.6%)
Hep C Antibody, positive, n (Percentage)	8 (3.7%)	7 (3.3%)
HBV+HCV positive, n (Percentage)	1 (0.5%)	1 (0.5%)

Clumeck N et al. 11TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/3.

Lubumbashi Trial: Virologic Results



Clumeck N et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/3.

Lubumbashi Trial: Virological Failures and Resistance

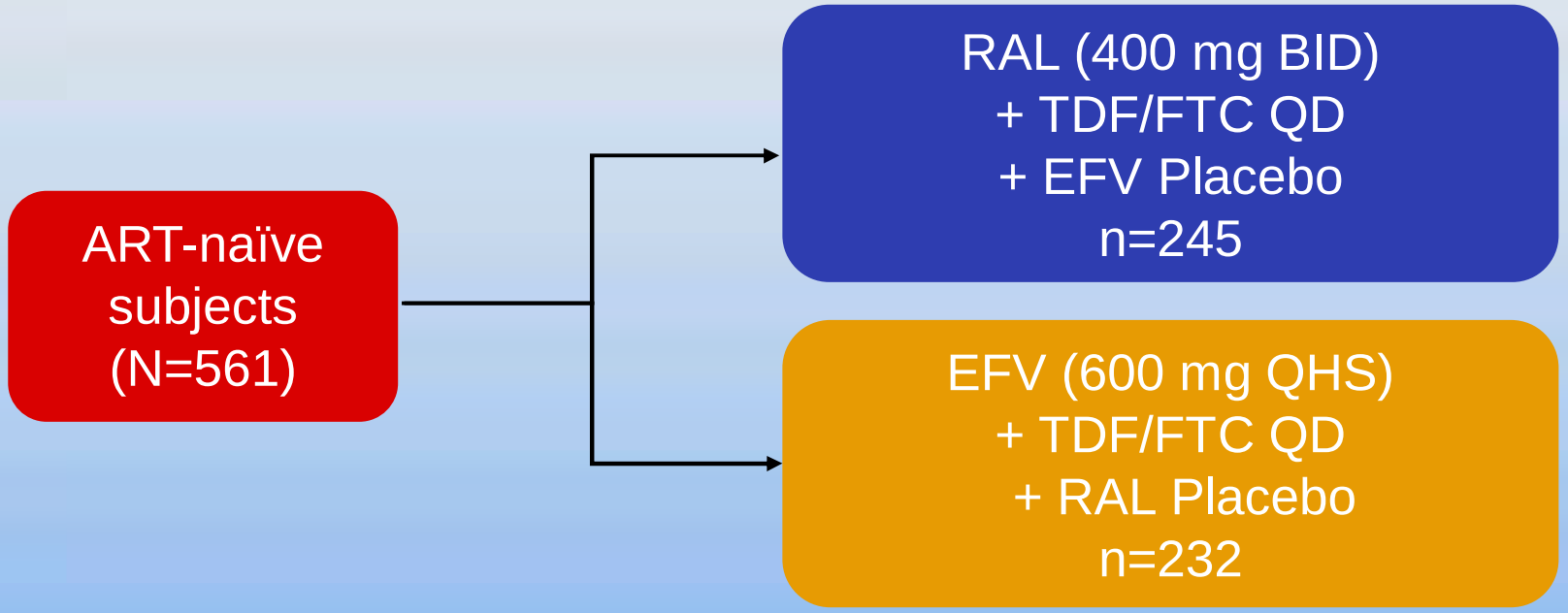
Treatment outcome (ITT) W48, missing or lost FU = failure	LPV/r n = 216	NVP n = 209	*P*
Protocol defined therapeutic failure			
WHO HIV clinical stage III or IV	3	4	
Virologic failure (VL>1000 c/ml)	7	19	0.0144
Changement of treatment for toxicity	2	2	
NRTI mutations	1 (20%)	13/15(87%)	
M184V	1	10	
K65R	0	6	
NNRTI mutations	0	13/15(87%)	
K103N	0	10	
Major PI mutations	0	0	
Mutations in 2 classes	0	11	

3/15 subjects (2F;1M) on NVP had drug resistance mutations for NNRTI; all failed at week 24 NNRTI-NRTI use as a first line, was associated with a significant higher virologic failure rate and number of drug resistance mutations in both RTI classes

Clumeck N et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/3.

STARTMRK: RAL vs. EFV at 192 Weeks

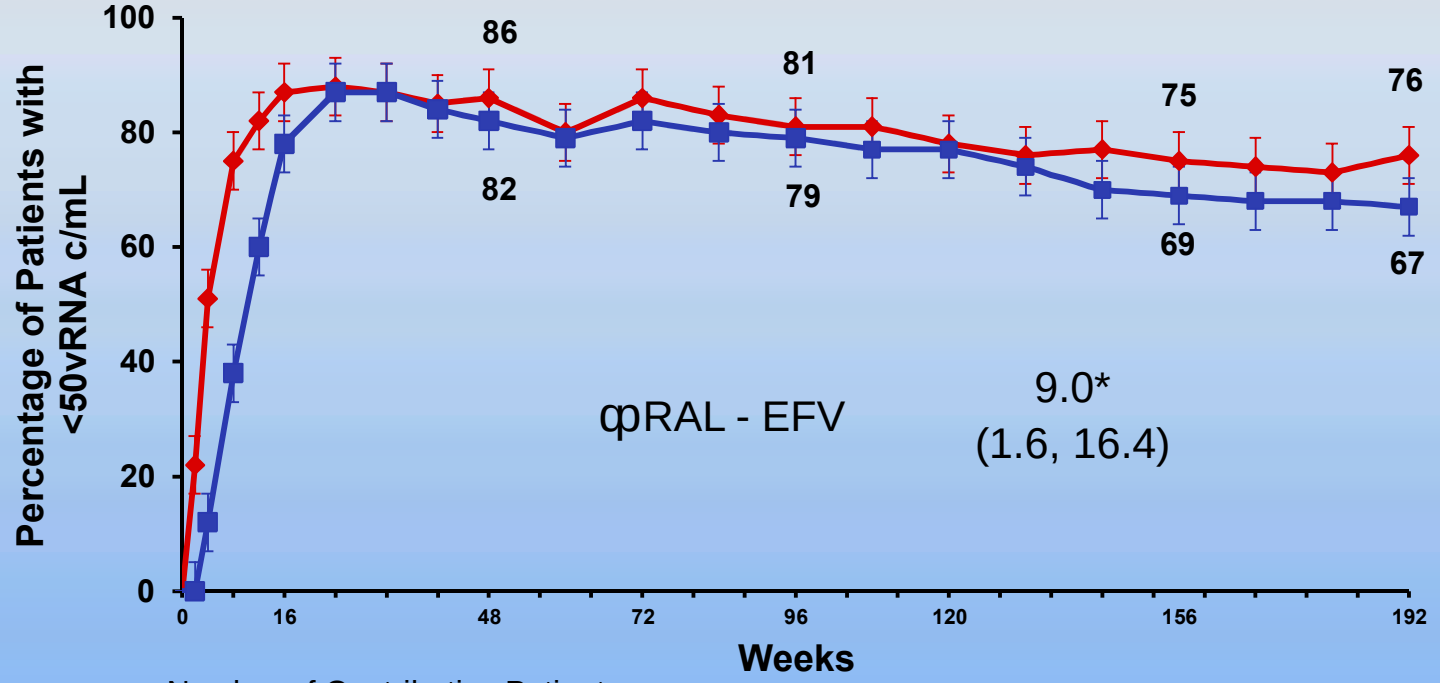
Randomized (1:1), double blind



DeJesus E et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 405.
Rockstroh J et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/1.

Proportion of Patients with <50 RNA c/mL Over Time (Primary NC=F Approach)

- No differences by age, gender, region, race, hepatitis co-infection, baseline plasma RNA level >100,000 copies/mL, CD4 count Ò200 cells/mm3, viral subtypes
- Better CD4 cell recovery in the RAL group RAL - EFV(95% CI): 60 (24, 95)



Number of Contributing Patients

Raltegravir group	281	281	280	281	281	277	281	281
Efavirenz group	282	281	281	282	282	281	282	282

DeJesus E et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 405.
Rockstroh J et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/1.

Proportion of Patients with HIV RNA < 50 copies/mL (NC=F)

	Raltegravir	Efavirenz	Treatment Difference‡
	n/N (%)	n/N (%)	% (95% CI)
Week 48	241/280 (86.1)	230/281 (81.9)	4.2 (-1.9, 10.3)
Week 96	228/281 (81.1)	222/282 (78.7)	2.4 (-4.3, 9.0)
Week 144	217/280 (77.5)	197/281 (70.1)	7.3 (0.0, 14.5)
Week 192	214/281 (76.2)	189/282 (67.0)	9.0 (1.6, 16.4)

ÿ 95% CIs and p-values for non-inferiority for treatment differences in percent response were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screen HIV RNA>50,000 copies/mL or Ò50,000 copies/mL). Raltegravir is considered non-inferior to Efavirenz if the lower bound of the 95% CI for the difference in percent response is above -12 percentage points. It can be further concluded that Raltegravir is superior to Efavirenz if the lower bound exceeds zero.

DeJesus E et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 405.
Rockstroh J et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/1.

Summary of Efficacy at Week 192

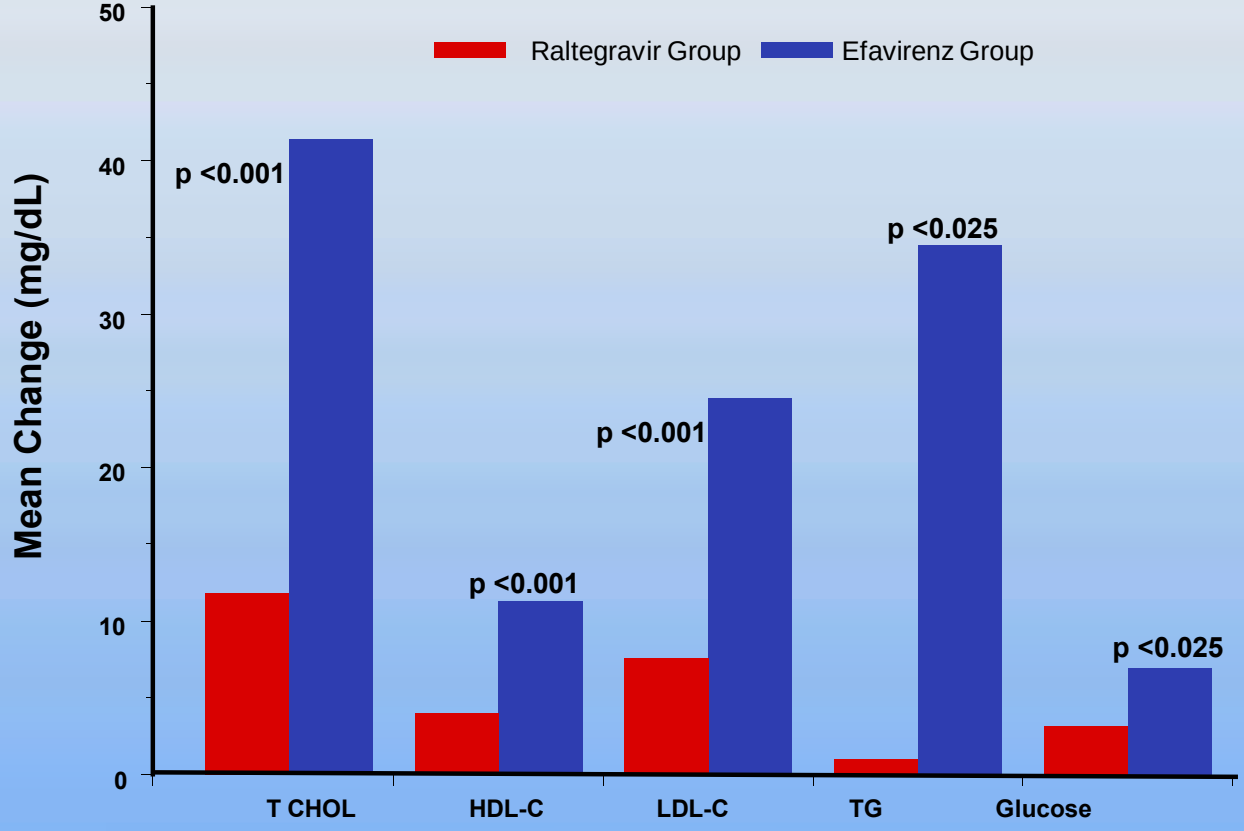
	Proportion of Patients (%, n/N) with HIV RNA < 50 copies/mL			CD4 Cell Count, Change from BL (cells/mm^3)
	NC=F	TRD=F	OF	OF‡
RAL (N=281)	76.2 (214/281)	86.3 (214/248)	91.1 (214/235)	360.7
EFV (N=282)	67.0 (189/282)	76.2 (189/248)	85.1 (189/222)	300.9
RAL - EFV†,§	9.0* (1.6, 16.4)	10.1* (3.3, 17.0)	6.0* (0.1, 12.2)	59.8 (24.1, 95.4)

À Difference between RAL and EFV (95%CI)
* p-value for non-inferiority <0.001
§ RAL is considered non-inferior to EFV if the lower bound of the 95% CI for the difference in % response was above -12%, and superior to EFV if the lower bound exceeds 0.
ÿ BL values carried forward for virologic failures.

DeJesus E et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 405.
Rockstroh J et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/1.

Mean Change from BaselineÀ in Metabolic Parameters at Week 192

- The change from baseline in the Total CHOL:HDL-C ratio was -0.17 for the RAL group and 0.02 for EFV group (p=0.177).

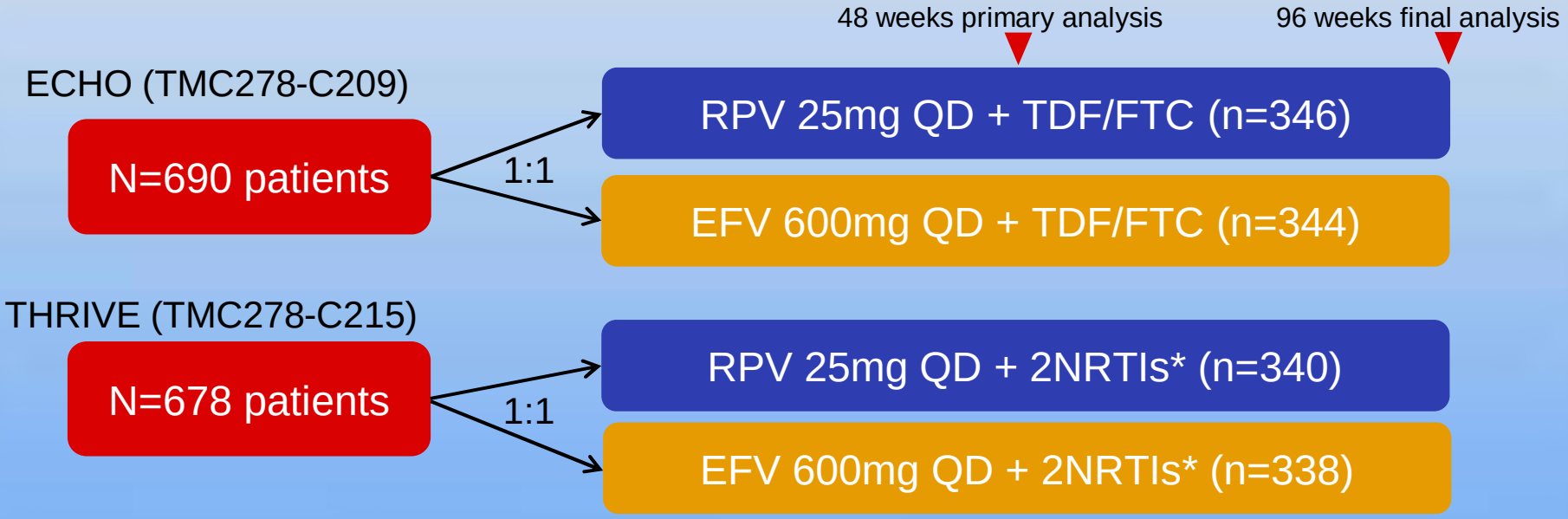


ÀLast Obs. Carry Forward (LOCF) approach is applied for missing data due to increased lipids (e.g., use of rescue therapy).

DeJesus E et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 405.

Factors Associated with Increased Response in ECHO and THRIVE

- Inclusion criteria: viral load (VL) ≥5K: no NNRTI RAMs; sensitivity to the NRTIs
- Primary objective: demonstrate non-inferiority (12% margin) vs. EFV in confirmed virologic response (VL <50 copies/mL ITT-TLOVR) at Week 48
- Stratification factors by screening VL (both) and NRTI background (THRIVE only)



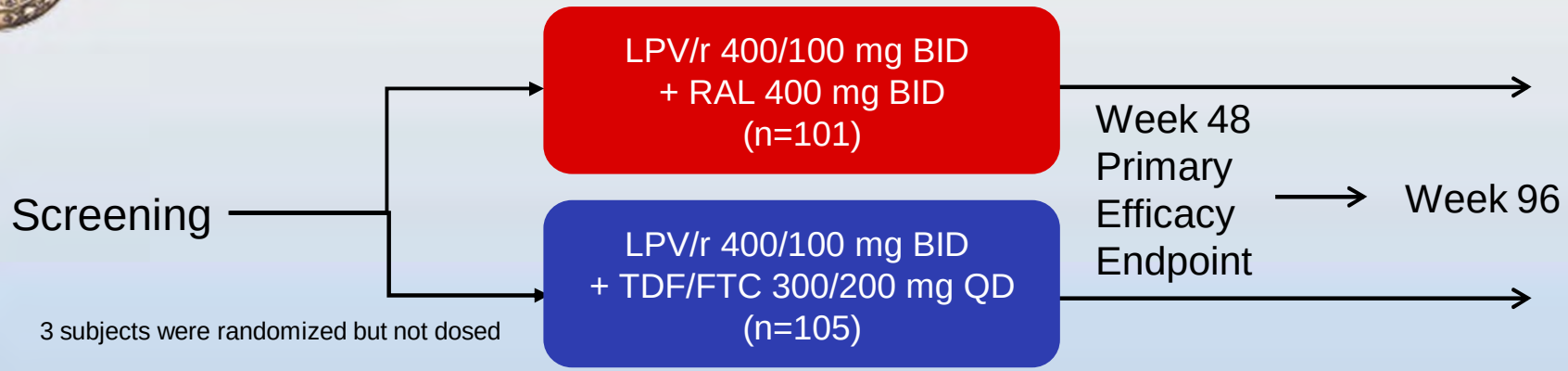
Brochot A et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS12/7.

Factors Associated with Increased Response in ECHO and THRIVE

RPV N=652	EFV N=599
Treatment adherence	no BLQ
RPV exposure	Treatment adherence
Baseline viral load	Baseline viral load
Fold change at baseline	EFV exposure
Baseline CD4 count	Fold change at baseline
no BLQ	Background regimen
Trial	

Brochot A et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS12/7.

PROGRESS 96-Weeks: Study Design and Baseline Characteristics

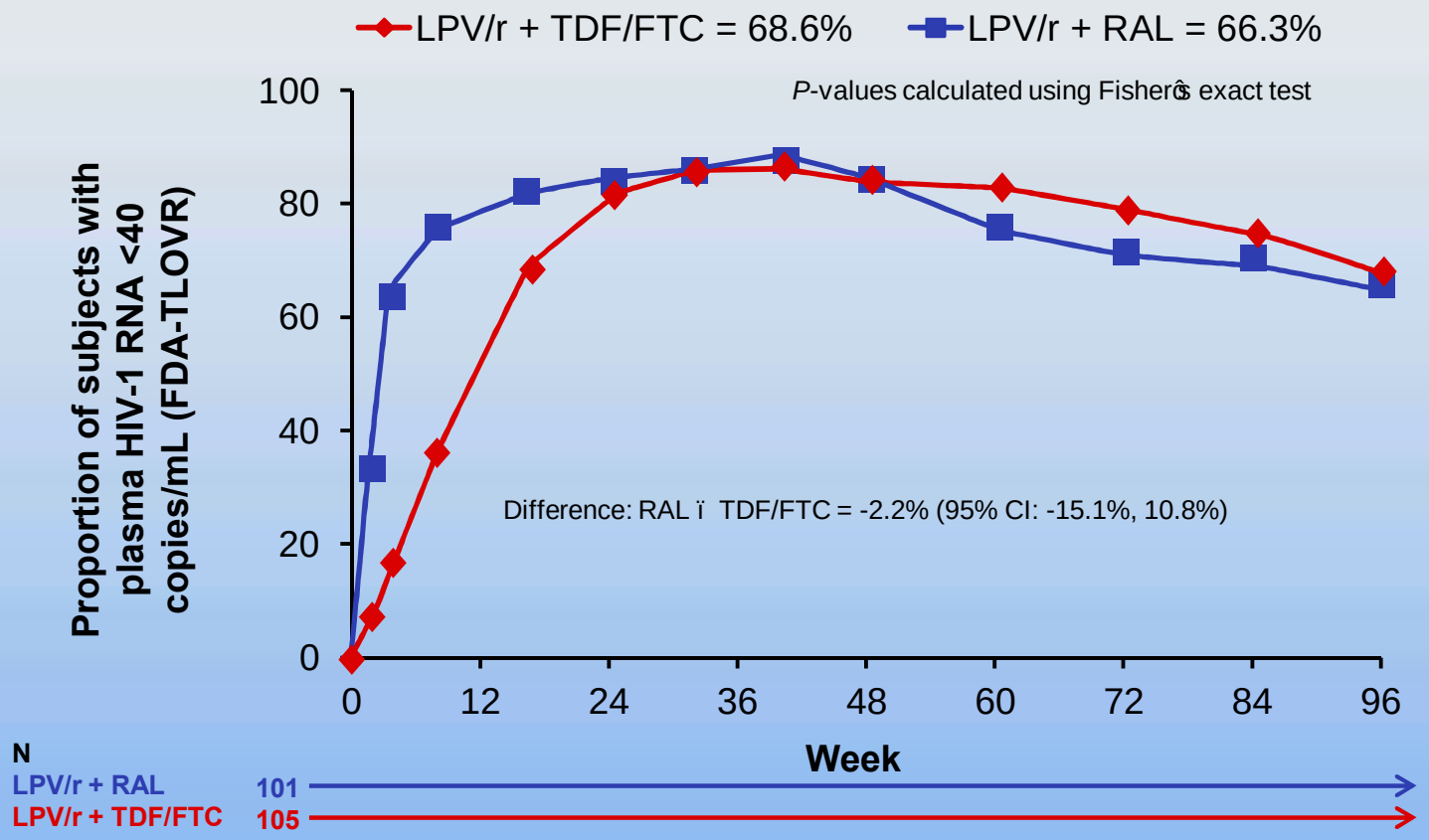


Variable	LPV/r + TDF/FTC (n=101)	LPV/r + TDF/FTC (n=105)	Total (n=206)
Males, n (Percentage)	88 (87.1)	86 (81.9)	174 (84.5)
Race			
White, n (Percentage)	74 (73.3)	81 (77.1)	155 (75.2)
Black, n (Percentage)	22 (21.8)	22 (21.0)	44 (21.4)
Other, n (Percentage)	5 (4.9)	2 (1.9)	7 (3.4)
Mean Age ± SD, years	39.8 ± 9.9	30.4 ± 11.2	39.6 ± 10.6
Mean plasma HIV-1 RNA, log_{10} copies/mL (range)*	4.24 (2.0 ï 6.0)	4.25 (2.7 ï 6.0)	4.25 (2.0 ï 6.0)
Mean CD4* T-cells/mm^3 (range)	289.3 (5-668)	297.6 (5 ï 743)	293.5 (5 ï 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 Fisherôs exact test for categorical variables

Trinh R et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 406.

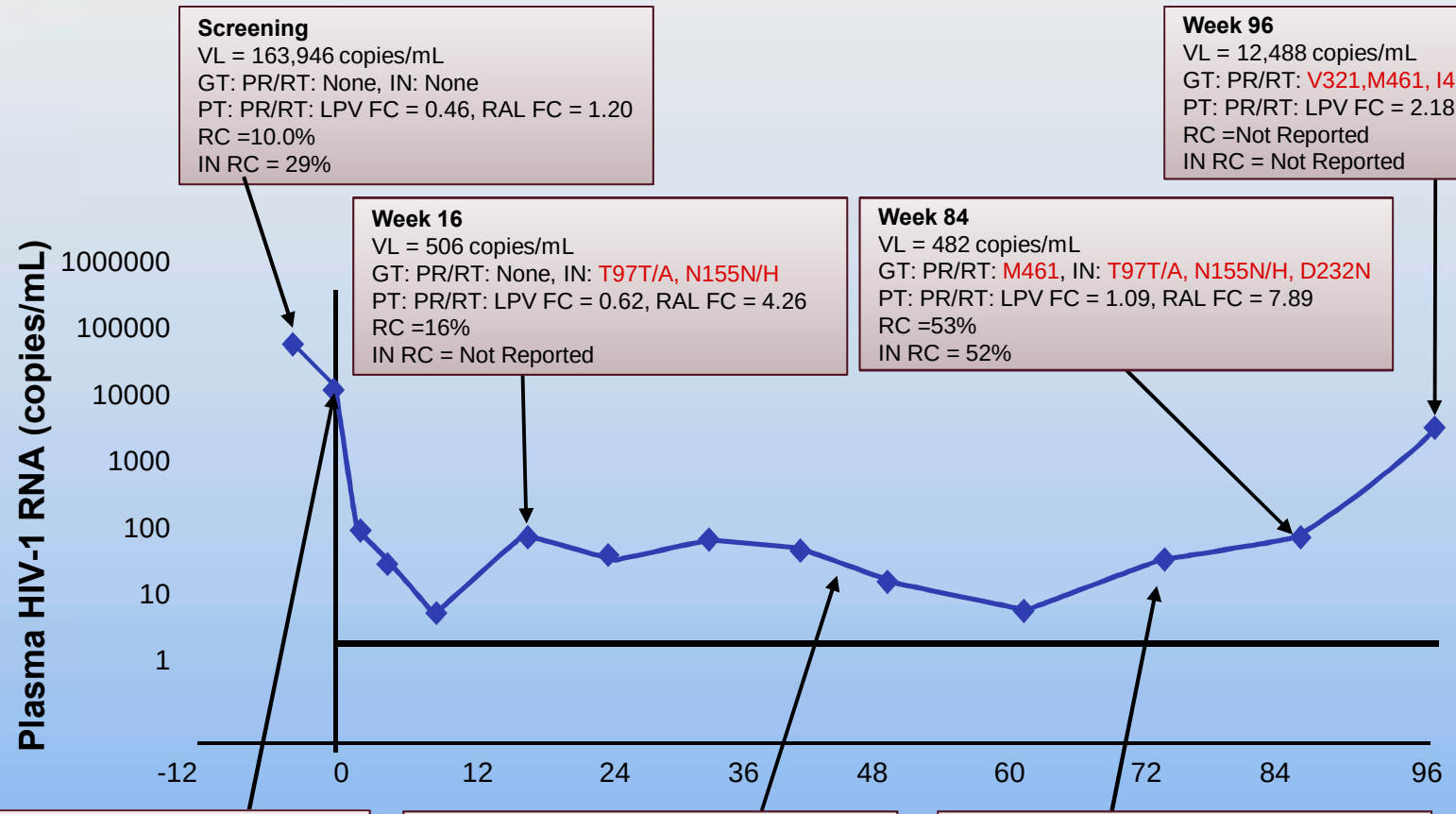
PROGRESS 96-Weeks: Proportion of Subjects Responding at Week 96 (FDA-TLOVR)



*Statistically significant difference between groups: weeks 2,4,8 *P*<0.001; week 16 *P*=0.038

Trinh R et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 406.

PROGRESS 96-Weeks: HIV-1 RNA Levels for Subject with LPV/r and RAL Resistance-Associated Mutations



Screening
VL = 163,946 copies/mL
GT: PR/RT: None, IN: None
PT: PR/RT: LPV FC = 0.46, RAL FC = 1.20
RC =10.0%
IN RC = 29%

Week 16
VL = 506 copies/mL
GT: PR/RT: None, IN: T97T/A, N155N/H
PT: PR/RT: LPV FC = 0.62, RAL FC = 4.26
RC =16%
IN RC = Not Reported

Week 84
VL = 482 copies/mL
GT: PR/RT: M461, IN: T97T/A, N155N/H, D232N
PT: PR/RT: LPV FC = 1.09, RAL FC = 7.89
RC =53%
IN RC = 52%

Week 96
VL = 12,488 copies/mL
GT: PR/RT: V321,M461, I47V IN: N155H
PT: PR/RT: LPV FC = 2.18, RAL FC = 14
RC =Not Reported
IN RC = Not Reported

Baseline
VL = 37,920 copies/mL
GT: PR/RT: None, IN: None
PT: PR/RT: LPV FC = 0.63, RAL FC = 0.96
RC =48.0%
IN RC = Not Reported

Week 40
VL = 331 copies/mL
GT: PR/RT: None, IN: T97T/A, N155H
PT: PR/RT: LPV FC = 0.57, RAL FC = 5.536
RC =44%
IN RC 29%

Week 72
VL = 233 copies/mL
GT: PR/RT: M461, IN: N155H
PT: PR/RT: LPV FC = 1.17, RAL FC = 4.217
RC =58%
IN RC = 65%

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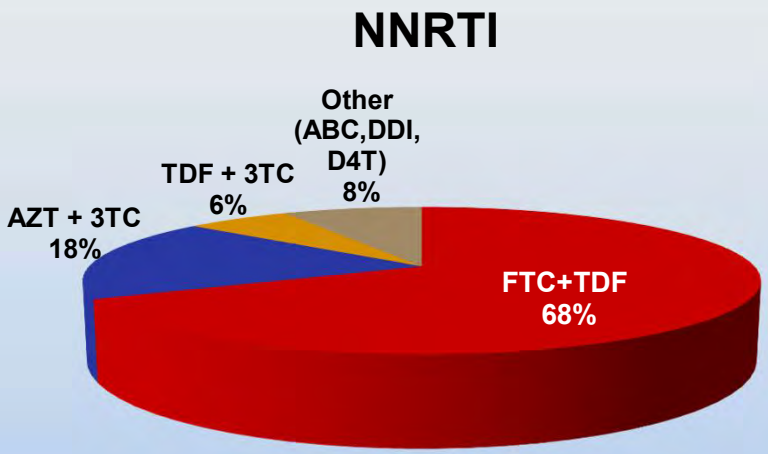
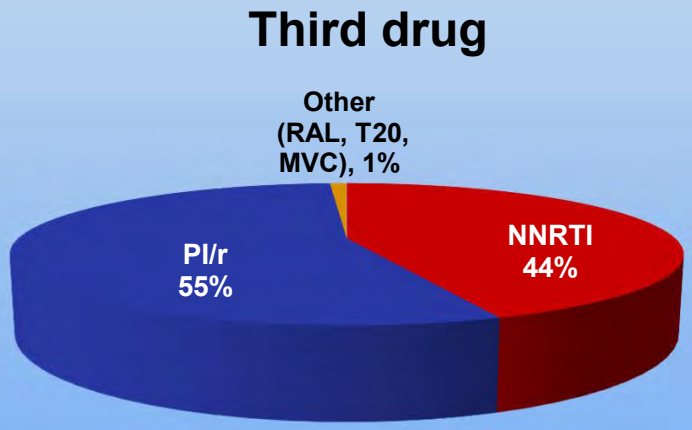
Viral Load and Time to Suppression Italian Cohort Analysis

Variable	Overall N=1430
Male, n (%)	1071 (75.8)
Age (years), Median (IQR)	39 (33-46)
Pre-HAART plasma HIV-RNA (Log_{10} copies/ML)	5.1 (4.5-5.5)
Pre-HAART CD4 (cells/mm^3) Median (IQR)	202 (80-309)
Risk factor, N (%)	
Heterosexual	376 (39.0)
Homosexual	362 (37.6)
IDU	120 (12.5)
Sexual	93 (9.6)
Other/unknown	13 (1.3)
CDC C stage, n (%)	73 (15.0)
Transmitted drug resistance, n (%)	142 (9.9)
Subtype, n (%)	
B	1003 (71.5)
C	64 (4.6)
CRF02_AG	67 (4.8)
F	45 (3.2)
Other	223 (15.9)

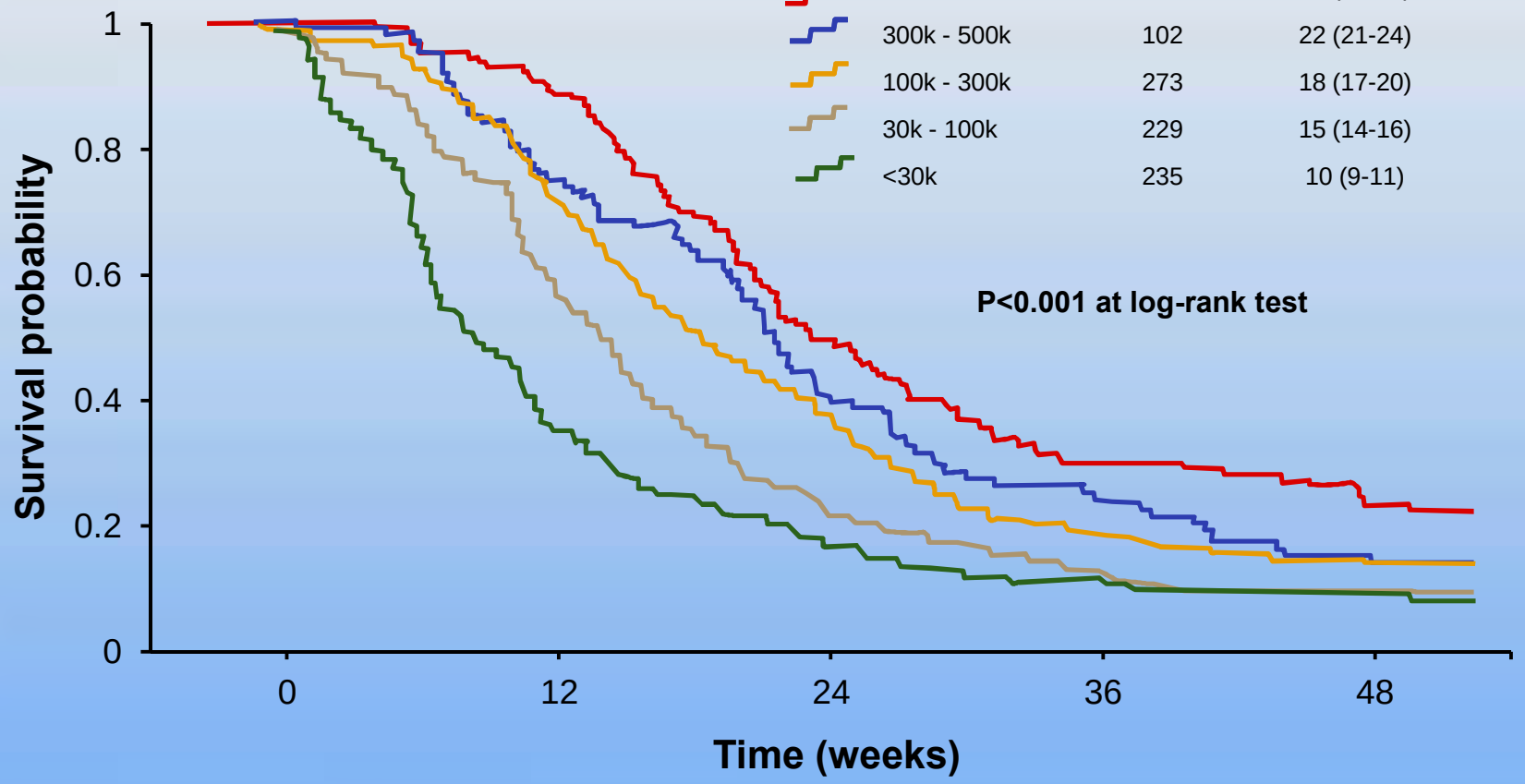




Perno CF et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS11/5.

Viral Load and Time to Suppression

Pre-HAART Viremia ranges (copies/mL)	No.	Median Time (95% CI) to achieve VS (weeks)	Probability of VS at 48 weeks
>500k	135	23 (21-25)	84%
300k - 500k	102	22 (21-24)	93%
100k - 300k	273	18 (17-20)	93%
30k - 100k	229	15 (14-16)	98%
<30k	235	10 (9-11)	99%



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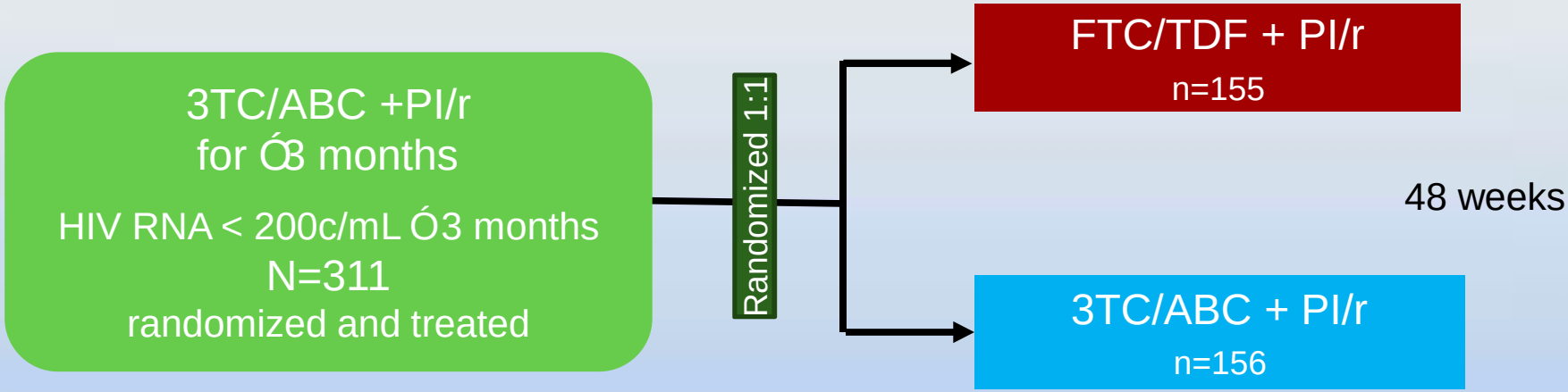
Studies in Antiretroviral Experienced Patients

Calvin Cohen, MD
CRI New England
Harvard Vanguard Medical Associates
Boston, Massachusetts

Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

SWIFT: Switching from 3TC/ABC to FTC/TDF



No prior history of resistance to study drugs
No CD4 restriction
Stratified by PI: 32% LPV/r vs. 68% Non-LPV/r

	LPV/r	ATV+RTV	FPV+RTV 100mg	FPV+RTV 200mg	DRV+RTV
FTC/TDF	48/155 (31%)	62/155 (40%)	22/155 (14%)	12/155 (8%)	9/155 (6%)
3TC/ABC	53/156 (34%)	60/156 (38%)	12/156 (8%)	19/156 (12%)	11/156 (7%)

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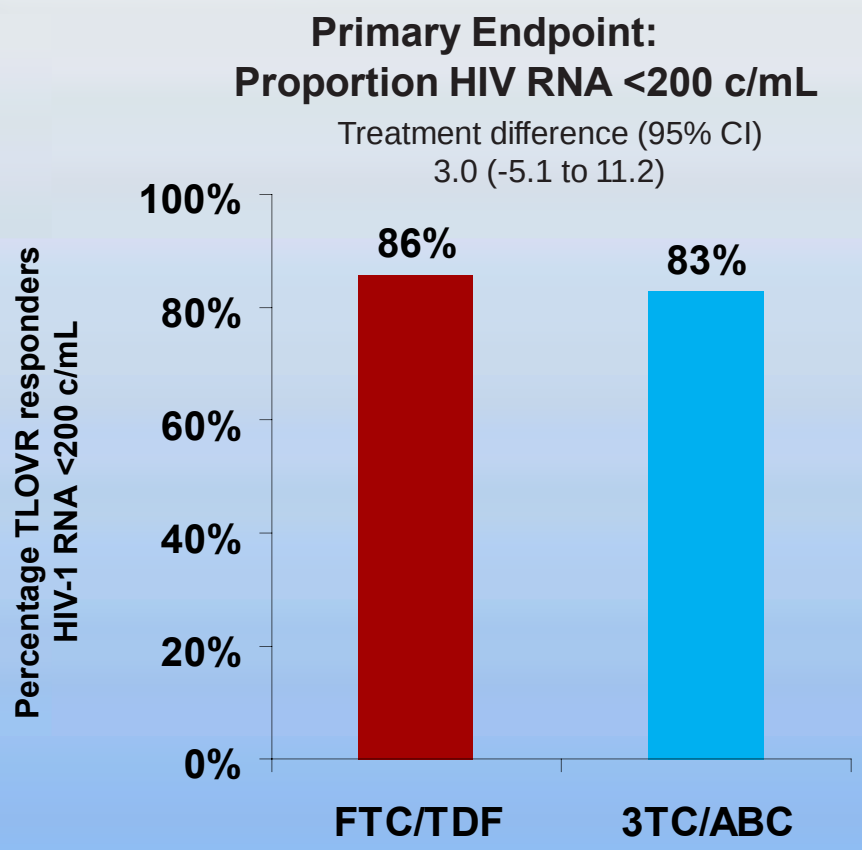
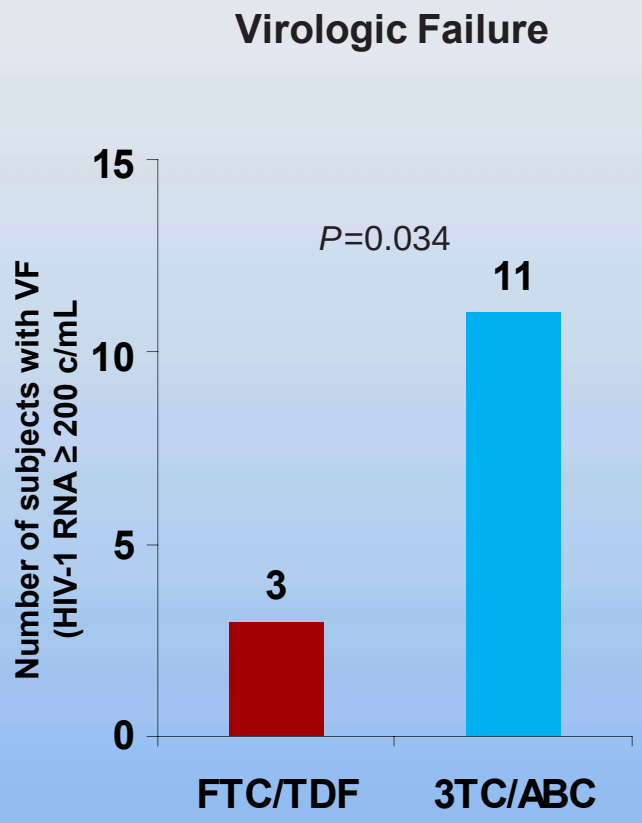
SWIFT: Virologic Response through Week 48 (TLOVR)





*TLOVR failure includes: virologic failure, premature discontinuation for any reason, ARV modifications

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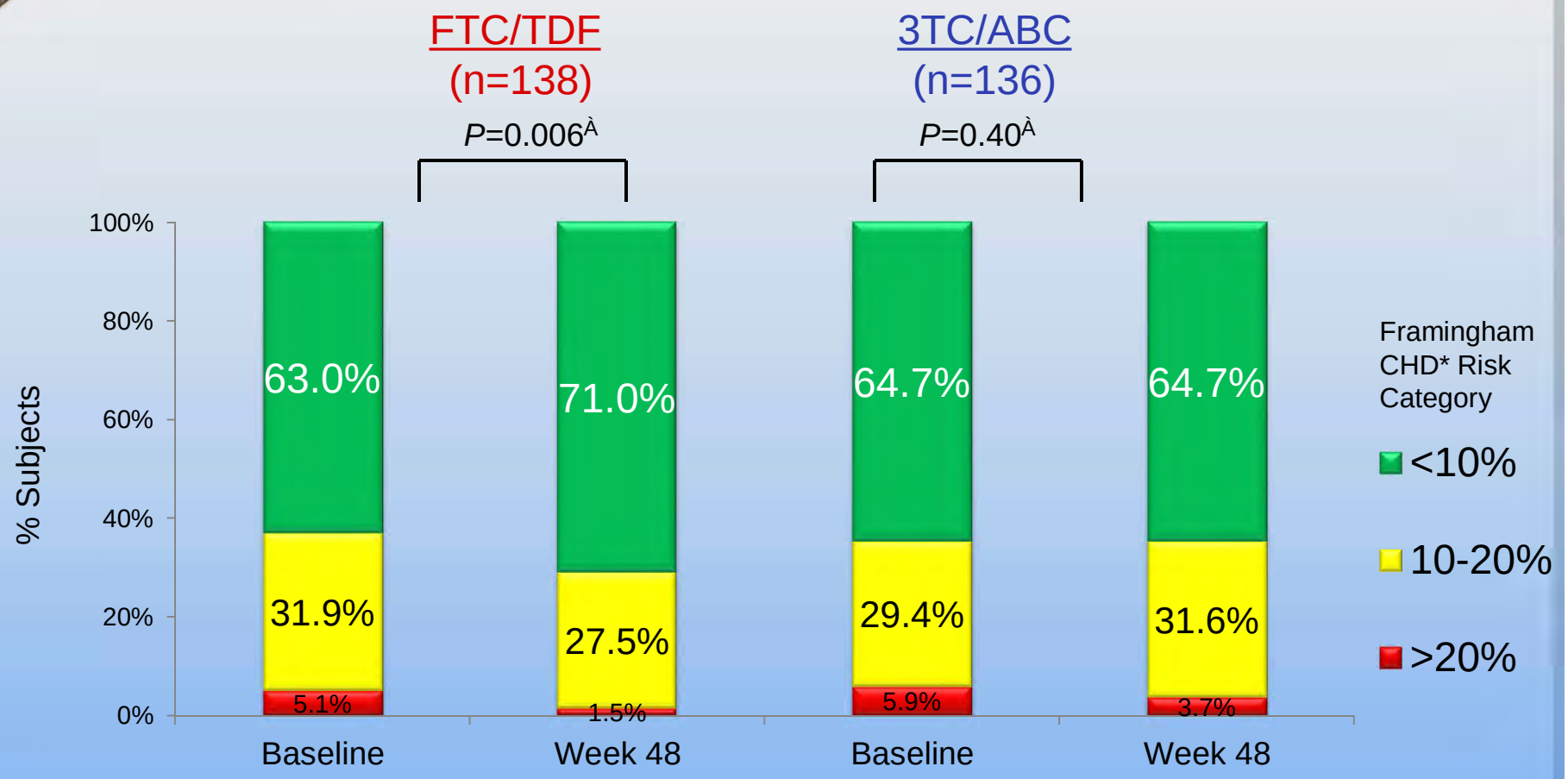
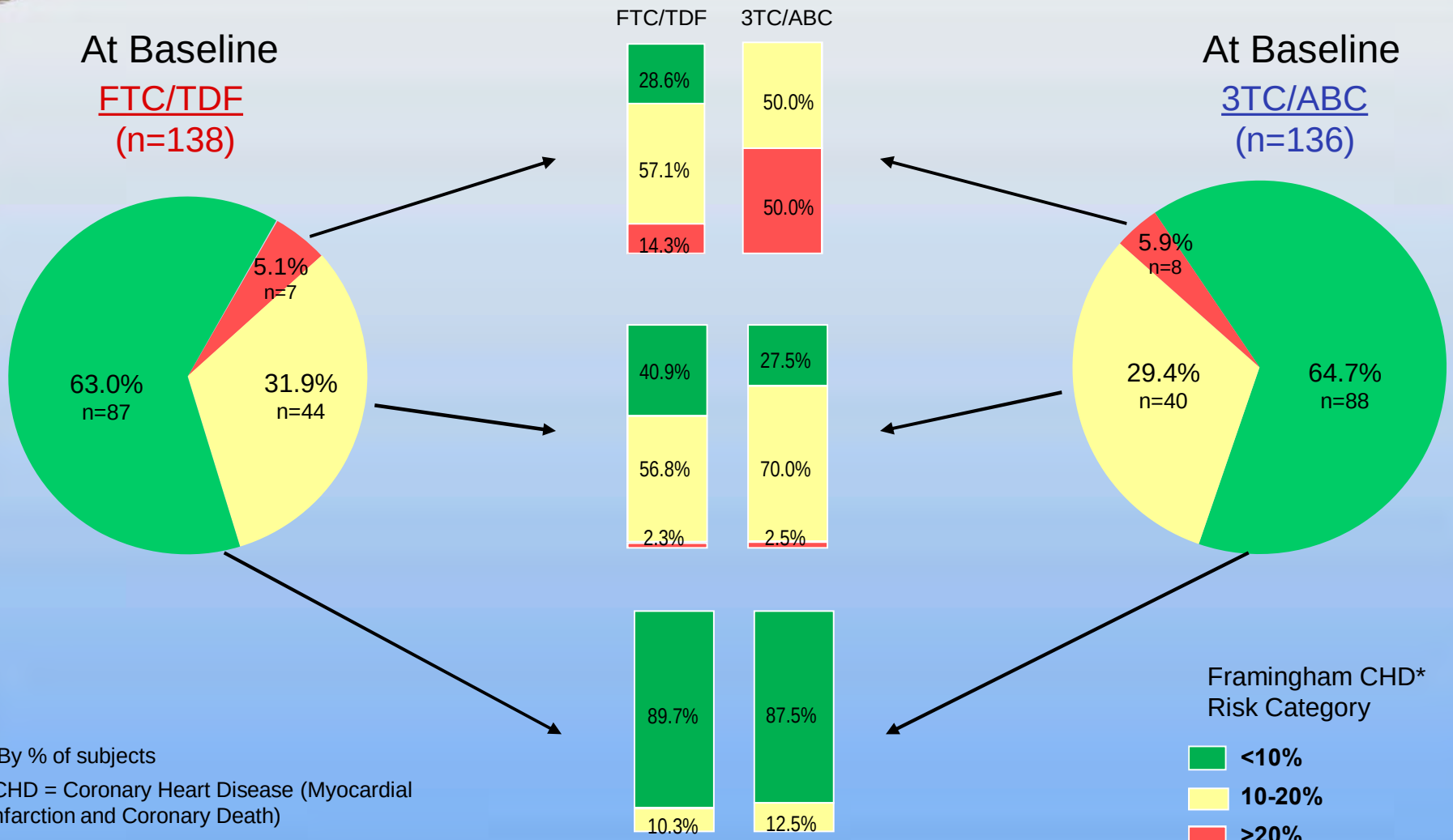
SWIFT: Change in 10-Year CHD* Risk Category by Framingham Score



*CHD = Coronary Heart Disease (Myocardial Infarction and Coronary Death)
À *P*-value from Wilcoxon signed-rank test for within group comparison on Framingham score
ÿ *P*-value from Wilcoxon rank-sum test for between group comparison on Framingham score

DeJesus et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 401.

Categorical Shifts by Framingham Scores from Baseline to Week 48*

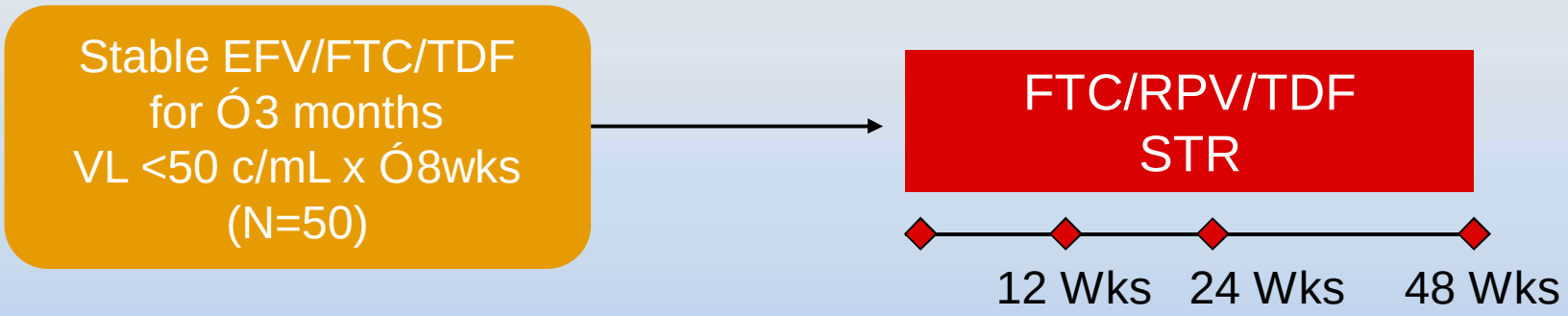


*By % of subjects

*CHD = Coronary Heart Disease (Myocardial Infarction and Coronary Death)

DeJesus et al. 49th IDSA; Boston, MA; October 20-23, 2011; Abst. 401.

Switching EFV/TDF/FTC to RPV/TDF/FTC



Primary endpoint: Percentage of subjects with HIV-1 RNA <50 c/mL at week 12 after switching - ITT population Snapshot analysis

Secondary endpoints: Safety and tolerability of FTC/RPV/TDF over 24 & 48 weeks
HIV-1 RNA <50 c/mL at Week 24 and Week 48 after switching
Pharmacokinetics of RPV after switching from EFV

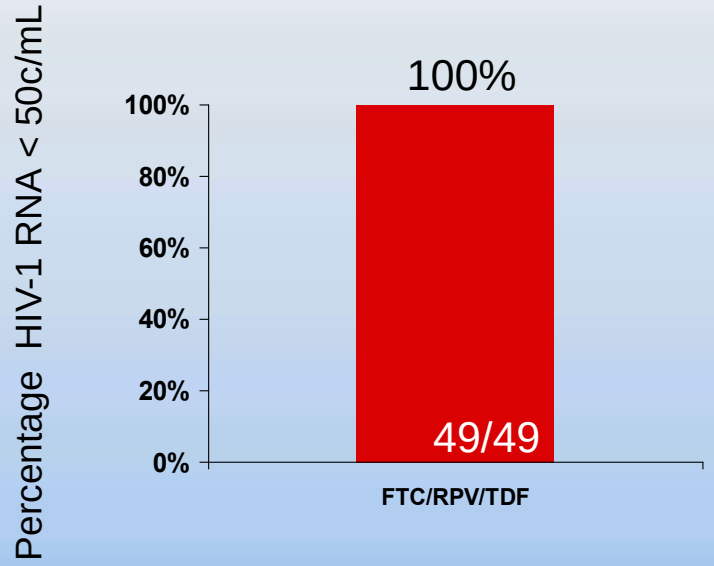
Cohen C et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. LBPS 10/4.

Baseline Characteristics and Virologic Results

Baseline Parameters

Baseline parameter	FTC/RPV/TDF N=49
Male, percentage	92
Median age, years	39
Race, percentage Caucasian	80
Median treatment duration prior to switch, years	2.5
Median CD4 cell count, cells/mm^3	653

Virologic Results

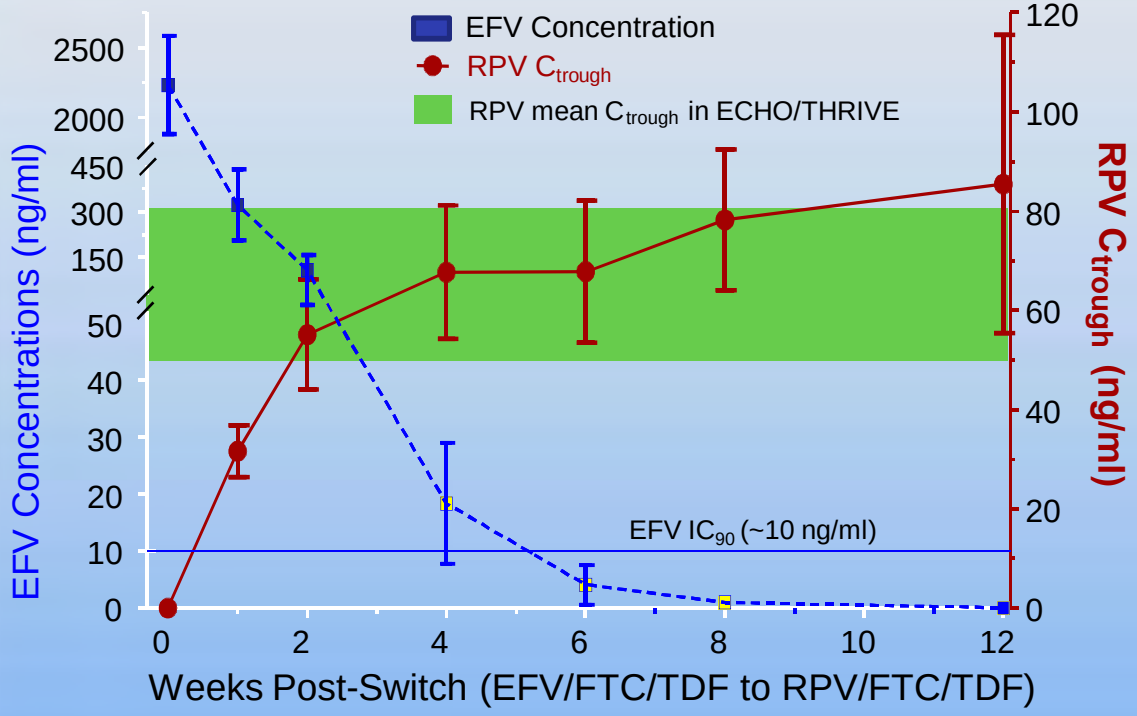


- Sum: 100% of subjects (95% CI 93%-100%) remained virologically suppressed thru the week 12 visit

Cohen C et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. LBPS 10/4.

Secondary Endpoint: RPV PK after Switching from EFV

Mean (95% CI) Rilpivirine (C_{trough}) and EFV Concentrations



- EFV mean C_{trough} above IC_{90} (~10 ng/ml*) up to ~4 weeks
- No subject had RPV below quantifiable levels at any visit
- RPV mean C_{trough} within historic range by 2 weeks

Week	RPV C_{trough} Mean (%CV), ng/ml
2	52 (47)
4-12	66 (51) - 84 (76)

Cohen C et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. LBPS 10/4.

Safety Summary

- Drug related treatment-emergent Aes
  - Gr 1 (in >2 subjects)
    - Nausea (n = 2)
    - Insomnia (n = 2)
    - Flatulence (n = 2)
  - Gr 2 AEs (n=1 each)
    - Fatigue
    - Incr bilirubin
  - No Gr 3 or 4 AEs

Visit	Mean Serum Creatinine mg/dL (SD*)	Mean Change mg/dL (SD*)
Baseline	0.97 (0.177)	-
Week 4	1.04 (0.176)	0.07 (0.094)
Week 8	1.05 (0.177)	0.07 (0.103)
Week 12	1.09 (0.193)	0.11 (0.110)

RPV inhibits OCT2 (renal transporter) in vitro for tubular secretion of creatinine

Cohen C et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. LBPS 10/4.

48 Week Pilot Study: Maintenance with Raltegravir + Nevirapine

- N=20, all virologically suppressed (<40c/mL) on NVP containing regimens
  - N=10 with a boosted PI
  - N=9 with TDF/FTC
  - N=1 with TDF
- Time with VL < 40c/mL:
  - median 55 months (IQR 37-98 mo)
- Design
  - Continue NVP BID, start RAL BID and stop all other ARVs
- Baseline characteristics:
  - 16 males, median age 51 (range 34-69)
  - Nadir CD4 median 190/mm3 (IQR 68-258)
  - All raltegravir naive

Reliquet V et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PE7.3/3.

48 Week Pilot Study: Maintenance with Raltegravir + Nevirapine

- Results1:
  - All remain virologically suppressed at all visits thru week 48
    - One discontinuation at week 24 due to BID schedule
  - PI subset: CD4 count incr. from 688/mm3 to 842/mm3 (p=0.004)
  - TDF subset: Significant decline in Total Chol/HDL ratio (due to incr in HDL): 4.55 to 3.8 (p=0.004)
  - PK study: No drug-drug interaction of RAL and NVP
- Conclusion
  - Novel 2 drug regimen can maintain suppression thru 48 weeks in pts with hx of long term suppression on NVP based regimen
- Note: Similar study of RAL + Etravirine2 in suppressed pts (n=18) reported two VF by week 48

(1) Reliquet V et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PE7.3/3., (2) Calin R et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PE7.9/1.

VIKING: The Activity of Dolutegravir in Patients With Raltegravir Resistance

- 50 mg QD DTG showed activity in pts with RAL resistance
  - Higher DTG dose leads to higher drug exposure
- Design: Pts. viremic, > 3 class ARV resistance including integrase
  - Day 1-11: Replace RAL with DTG
    - Or add DTG if not currently on RAL
  - Day 12: start optimized regimen
- Dose: DTG 50mg QD (Cohort I) and 50mg BID (Cohort II)
  - Cohort II subjects should have Ó1 fully active ART in OBR

Soriano V et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/2.

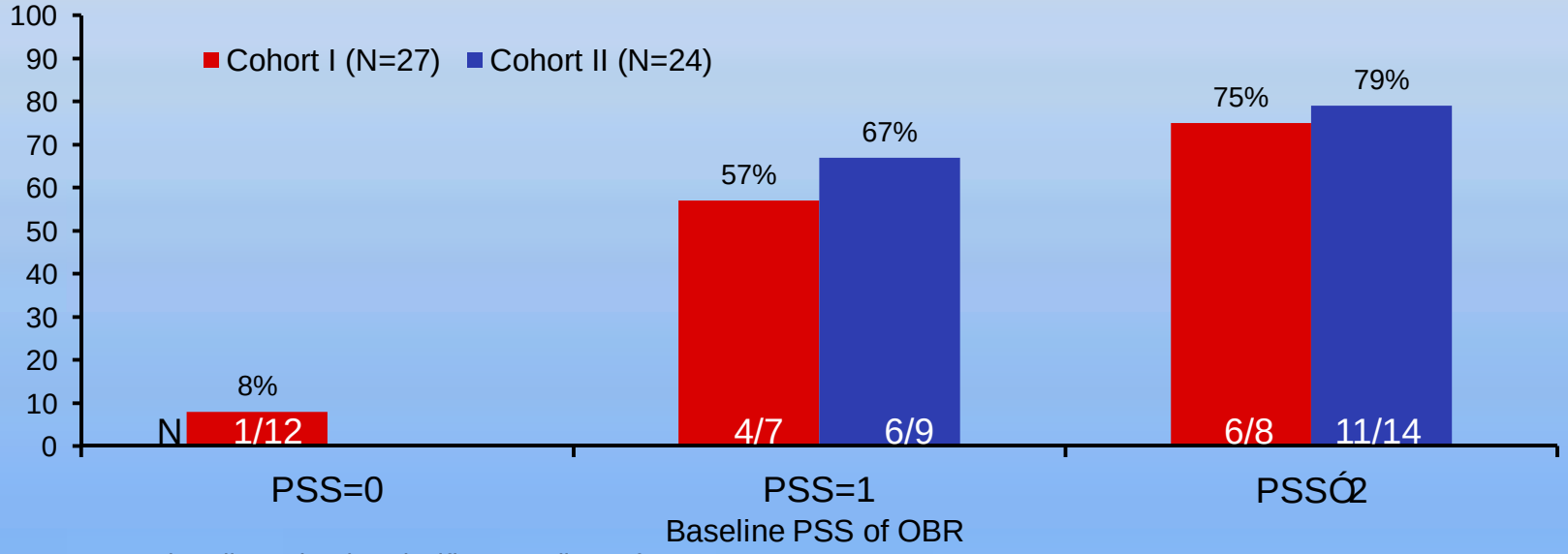
VIKING: Baseline Characteristics

	Cohort I (n=27)	Cohort II (n=24)
Age in years, median (range)	48 (19-61)	47 (33-68)
Male gender, n (percentage)	25 (93%)	18 (75%)
CD4+ cells/mm^3, median (IQR)	114 (44-227)	202 (19-384)
Plasma HIV-1 RNA log_{10} c/mL, median (IQR)	4.5 (3.9-4.9)	4.3 (3.9-4.8)
Current RAL failure, n (percentage)	21 (78%)	20 (83%)
Duration on RAL, months Median (range)	27 (3-41)	29 (10-63)
Baseline RAL FC, median (range)	>161 (0.67->Max)	>128 (0.78->Max)
Prior ART		
PSS of failing regimen=0: n (%)	18 (67%)	15 (63%)
Prior treatment with: n (%)		
etravirine	19 (70%)	11 (46%)
enfuvirtide	22 (81%)	13 (54%)
darunavir/rtv	23 (85%)	14 (58%)

Soriano V et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/2.

Week 24 Response (<50 c/mL; TLOVR) by Phenotypic Score of OBR and Safety of higher dose

- DTG safety for 50 mg BID dose:
- No safety related discontinuations
- N=6 Drug related AEs
  - Mild Diarrhea (n=2) only AE in >1 subject
- N=6 treatment emergent Grade 3/4 lab AEs
  - Gr 3 ALT(n=1), bilirubin (n=2), lipids (n=2); Grade 4 leukopenia (n=1)



Higher CD4 count at baseline only other significant predictor of response

Soriano V et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS1/2.

Association of Regimen Pill Count and Costs of Care

- Study analysis of a large US Multistate Medicaid database
  - Time Jan 2005 – Dec 2009
- Objective: Explore the relationship between number of pills in an HIV regimen vs. costs of care
  - Cohort limited to pts receiving 2 NRTIs plus a third agent
- Adherence data from pharmacy refill records
  - Note: Lab results not available

Conclusions:

- Significantly higher refill adherence with STR
- Costs of care lower on STR vs. 2+ tablet regimen due to:
  - Lower cost of third drug (EFV vs. mainly PI based regimens)
  - Significantly fewer hospitalizations, with lower cost for both in-pt and out-pt care

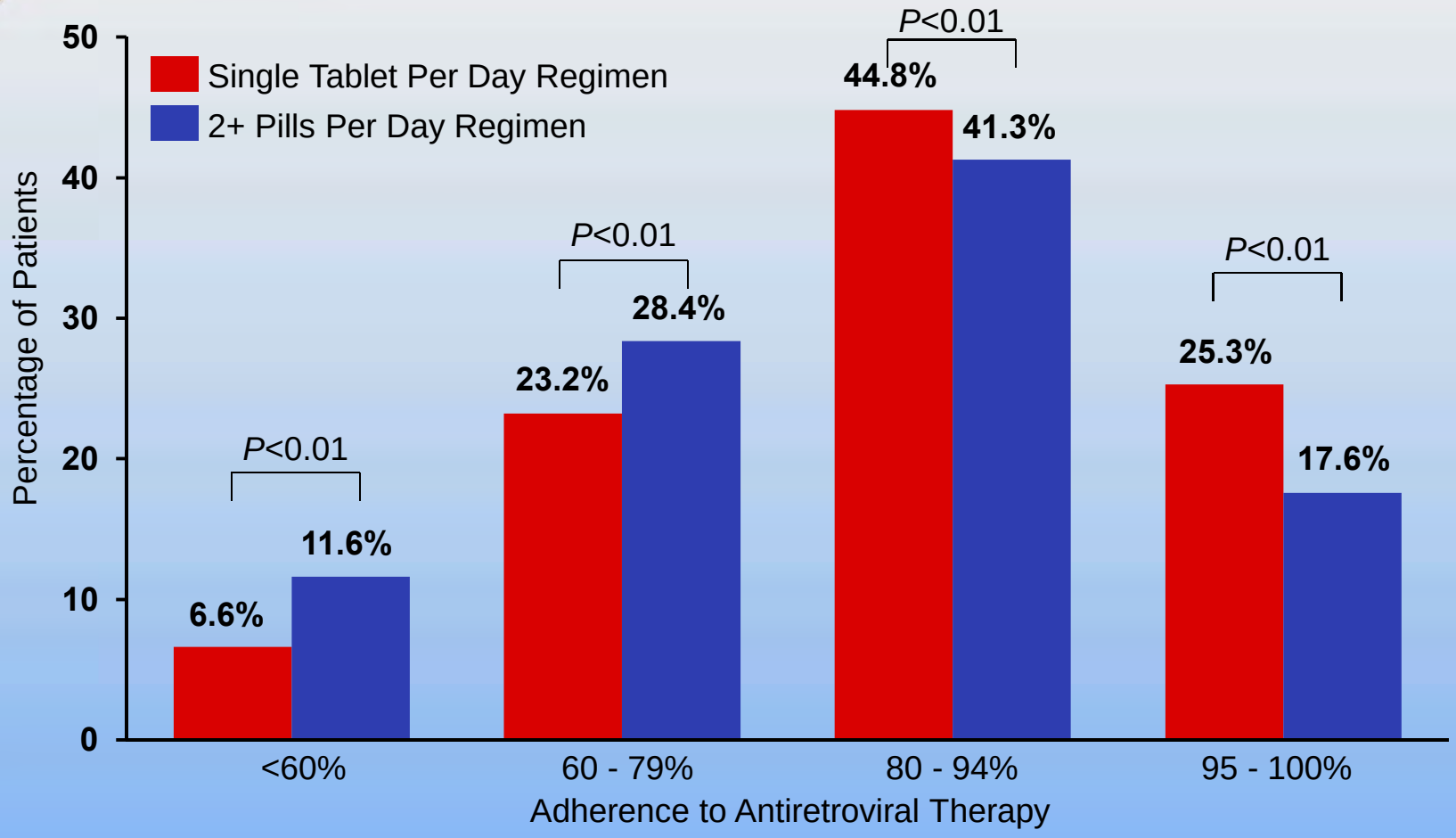
Cohen C et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PE7.5/7.

Patient Characteristics

Characteristic	Single Tablet Per Day Regimen	2+ Tablet Per Day Regimen	Overall
N	1,838	5,945	7,783
Female	48.6%	48.7%	48.7%
Age			
Mean (SE)	41.4 (0.3)	41.5 (0.2)	41.5 (0.1)
55+ years	9.8%	11.1%	10.9%
Mean (SE) Charlson Comorbidity Index	0.7 (0.03)	0.6 (0.02)	0.6 (0.02)
ART Classes Received (in addition to 2 NRTIs)			
NNRTIs	100.0%	26.1%	43.5%
Protease Inhibitors	---	73.6%	56.2%
Co-formulated boosted protease inhibitor	---	40.3%	---
Protease inhibitor + pharmacokinetic enhancer (separate pills)	---	39.6%	---
Protease inhibitor unboosted	---	20.1%	---
Other third agents	---	1.5%	1.1%
Mean (SE) follow-up duration (days)	348 (6.5)	429 (4.8)	409 (4.1)

Cohen C et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PE7.5/7.

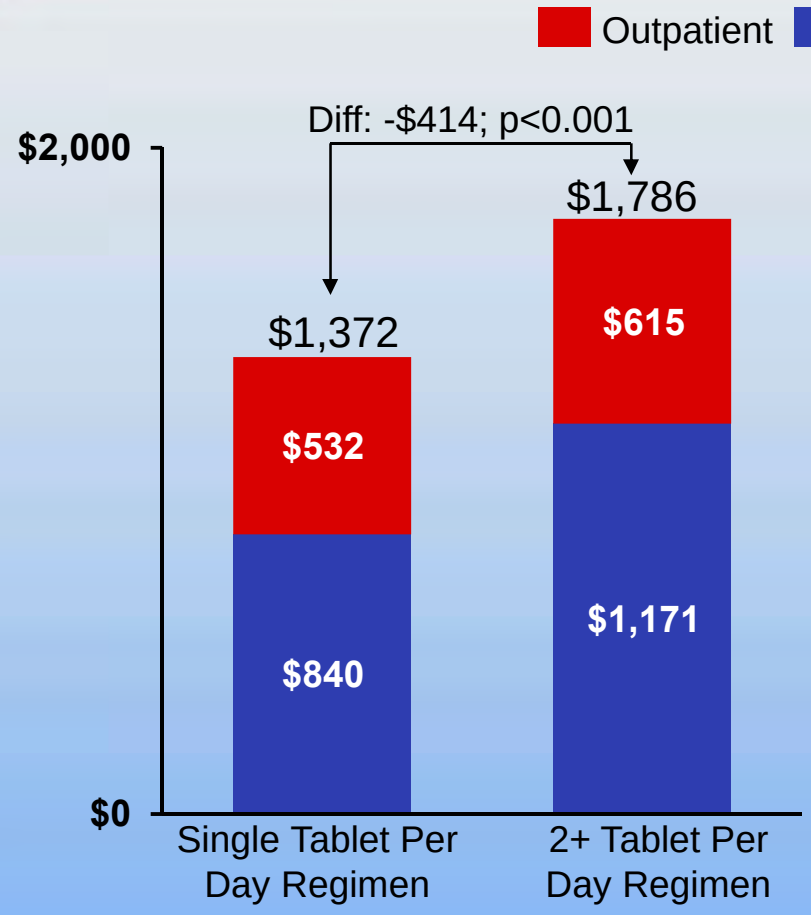
Adherence: On time Pharmacy Refills by Number of Tablets per Day

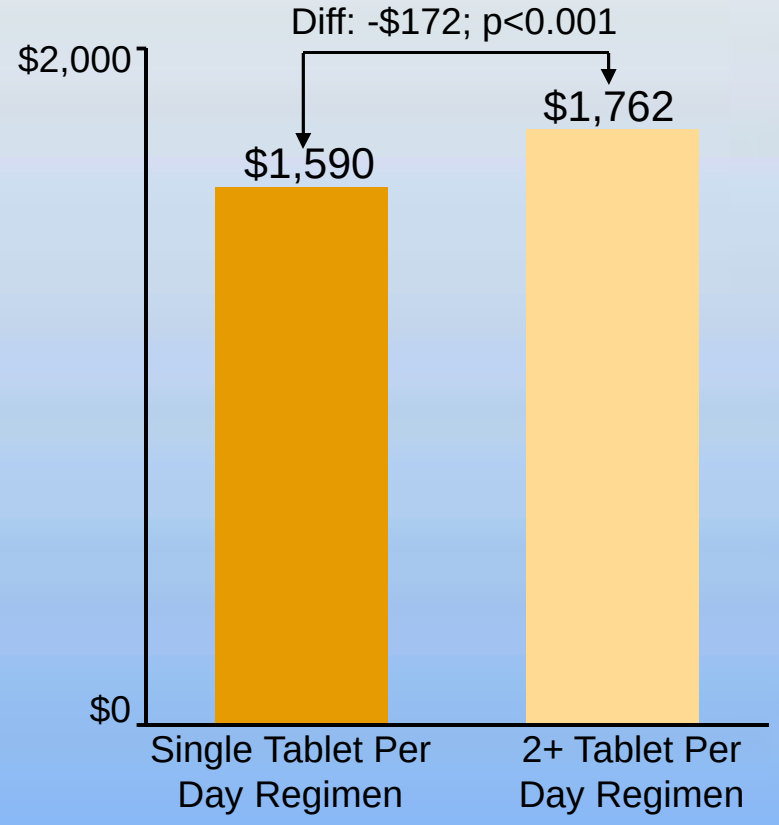


Patients on a once daily single tablet regimen consistently achieved higher adherence levels than patients on 2+ pills PI based regimens

Cohen C et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PE7.5/7.

Medical and Pharmacy Costs Per Patient, Per Month (All-Cause, Unadjusted)





Sum: Patients on a once daily single tablet regimen had 17% lower health care costs compared to patients receiving a 2+ PI based regimen

Cohen C et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PE7.5/7.

A CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV Therapies and Therapeutic Strategies

REPORTING FROM THE

13th European AIDS Conference (EACS) and the 49th Annual Meeting of the Infectious Diseases Society of America (IDSA)

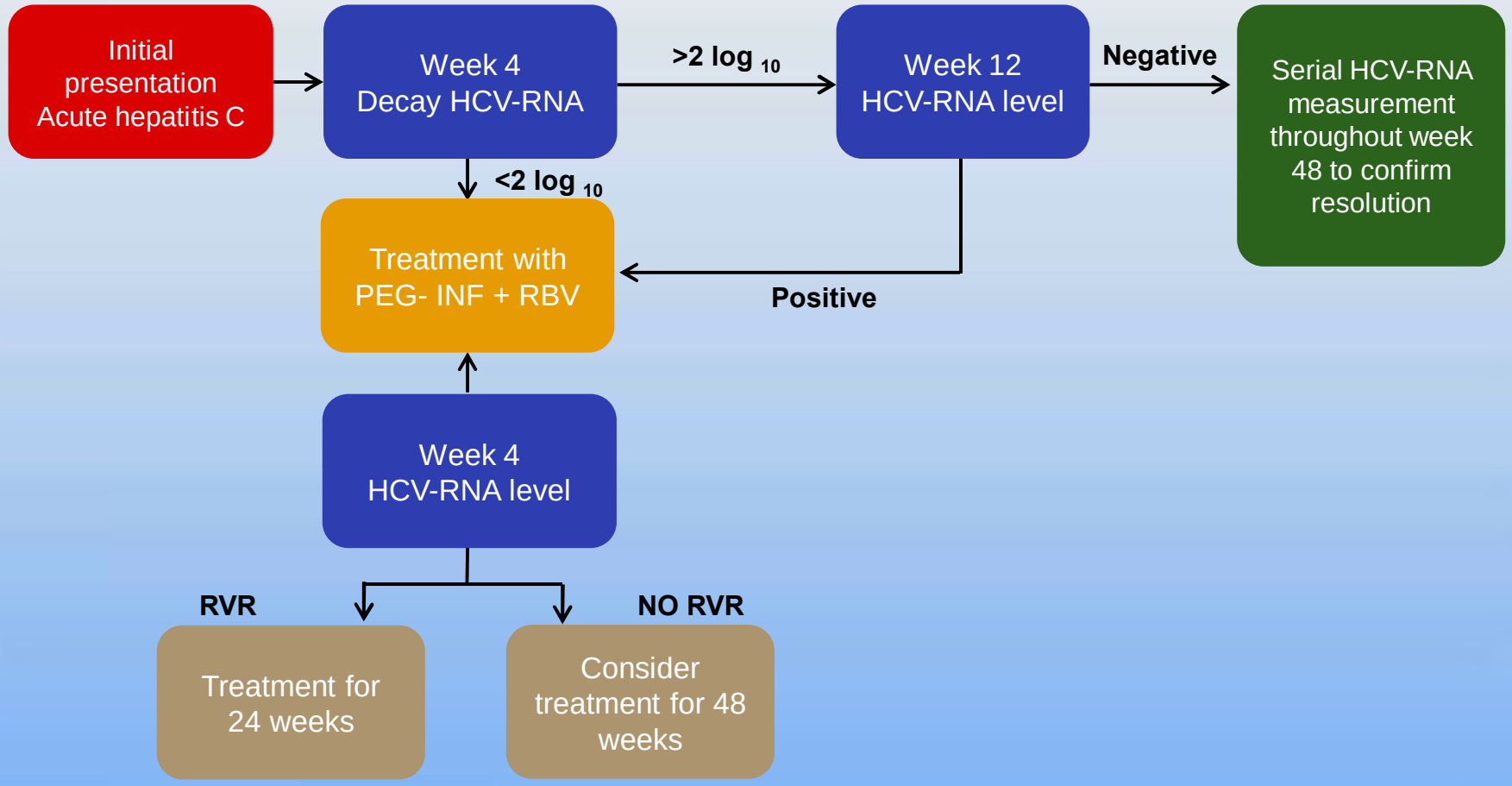
Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Management: Hepatitis Co-infection and other comorbidities

Edwin DeJesus, MD, FACP
Medical Director,
Orlando Immunology Center
Orlando, Florida

Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

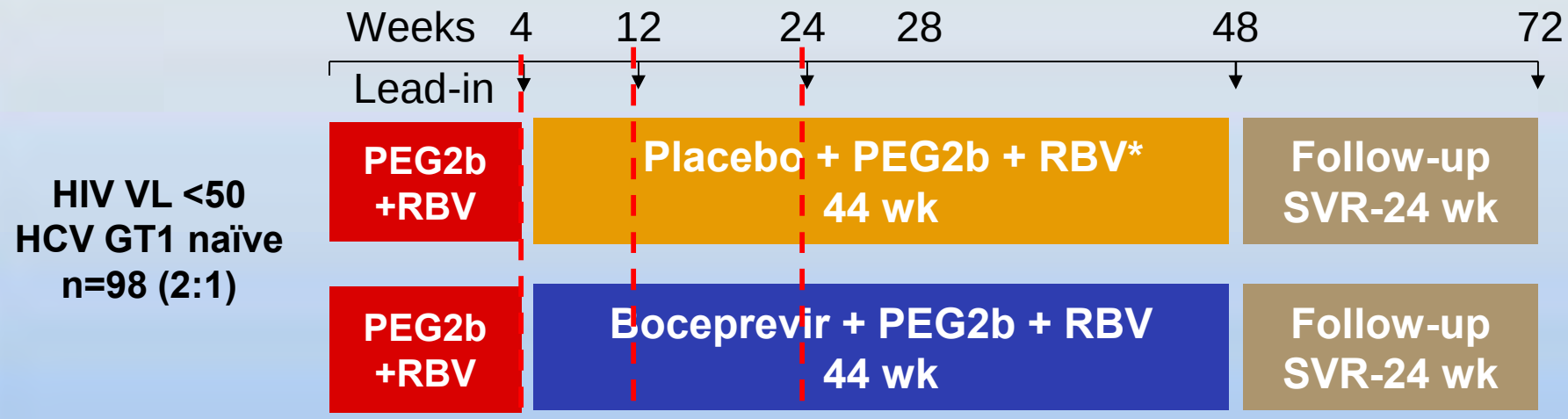
EACS GUIDELINES Update: Management of acute HCV in HIV+



www.eacs.eu (October, 2011).

BOC + PEG/RBV for HCV/HIV Co-Infection (interim analysis)

Phase II, BOC-double-blinded 800mg TID, PEG2b 1.5µg/kg QW/RBV WB



- >90% pts reached W12 or 24 or had DC at the time of analysis
- Futility rules: W12: <2 $\log_{10}$ decline; W24: HCV RNA $\geq$ LLOQ
- BL characteristics were well balanced, but cirrhosis: 1-control, 4-BOC

Sulkowski M et al. 49TH IDSA; Boston, MA; October 20-23, 2011; Abst. LB-37.

Use of Antiretroviral Therapy

	PR	B/PR
Any*	34 (100)	64 (100)
HIV Protease Inhibitors†	31 (91)	54 (84)
ATV/r	13 (38)	20 (31)
Lopinavir/r	10 (29)	16 (25)
Darunavir/r	7 (21)	12 (19)
NRTIs††	33 (97)	60 (94)
Integrase Inhibitors	4 (12)	11 (17)
CCR5 antagonists	1 (3)	1 (2)

* To maintain blinding in this continuing study, data is only shown where at least 1 patient in each treatment group is represented.
À HIV PIs included ATVr, DRV/r, LPV/r, fAMP/r, SAQ/r
À À NRTIs included TDF, ABC, 3TC, FTC

Sulkowski M et al. 49TH IDSA; Boston, MA; October 20-23, 2011; Abst. LB-37.

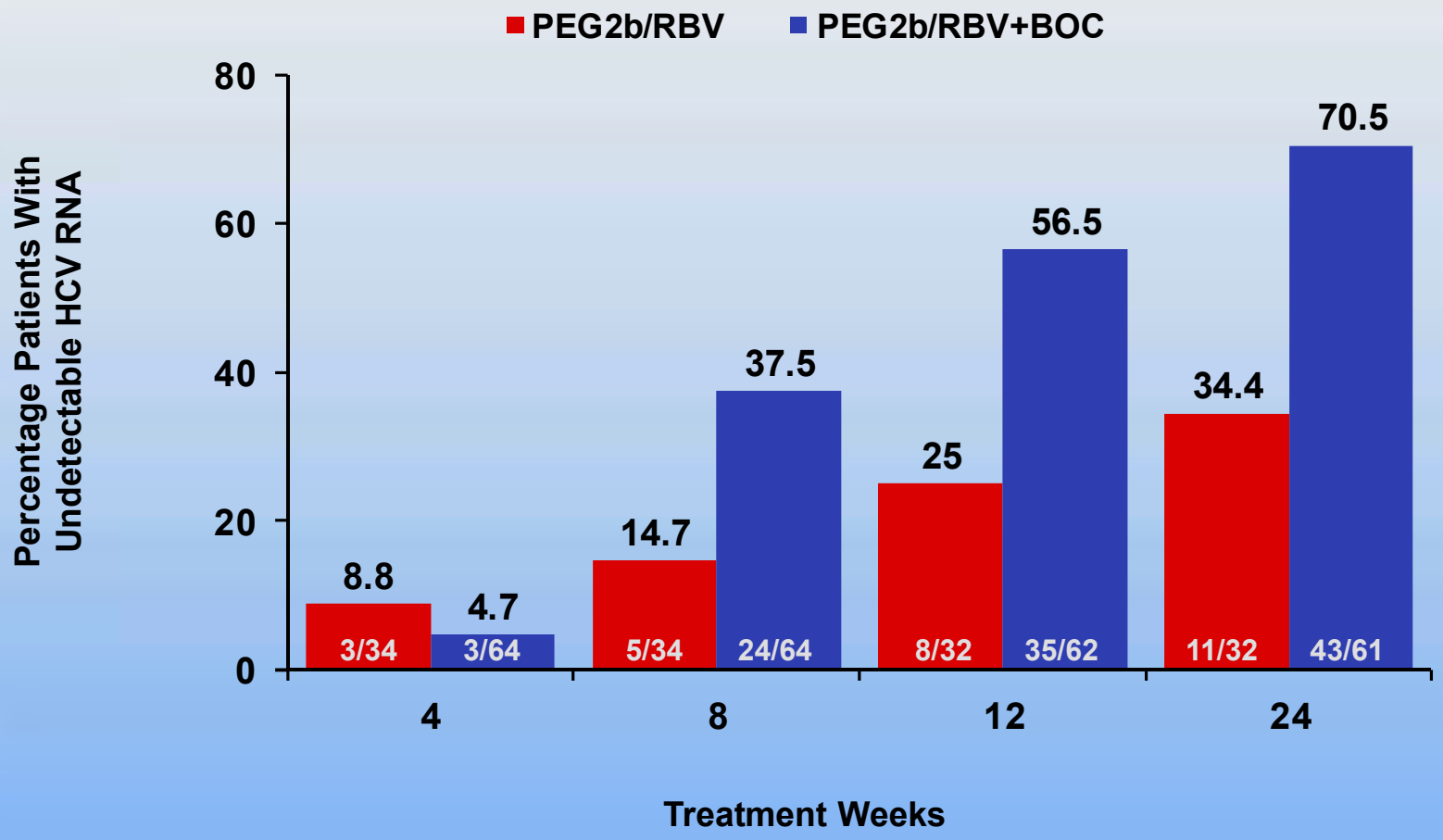
Patient Disposition

	PEG2b/RBV	PEG2b/RBV + BOC
Treated, n (Percentage)	34 (100%)	64 (100%)
Discontinued during treatment phase, n (Percentage)	14 (41%)	16 (25%)
Due to AE, n (Percentage)	3 (9%)	9 (14%)
Due to treatment failure, n (Percentage)	11 (32%)	3 (5%)
Other reasons	0	4 (6%)
Completed treatment phase, n (Percentage)	1 (3%)	2 (3%)
Ongoing, n (Percentage)	19 (56%)	46 (72%)

Most commons AE > 10% Nurtropenia, dysgeusia, vomiting pyrexia, h/a, ↓ appetite

Sulkowski M et al. 49TH IDSA; Boston, MA; October 20-23, 2011; Abst. LB-37.

Virologic Response Over Time (% HCV RNA Undetectable)



Sulkowski M et al. 49TH IDSA; Boston, MA; October 20-23, 2011; Abst. LB-37.

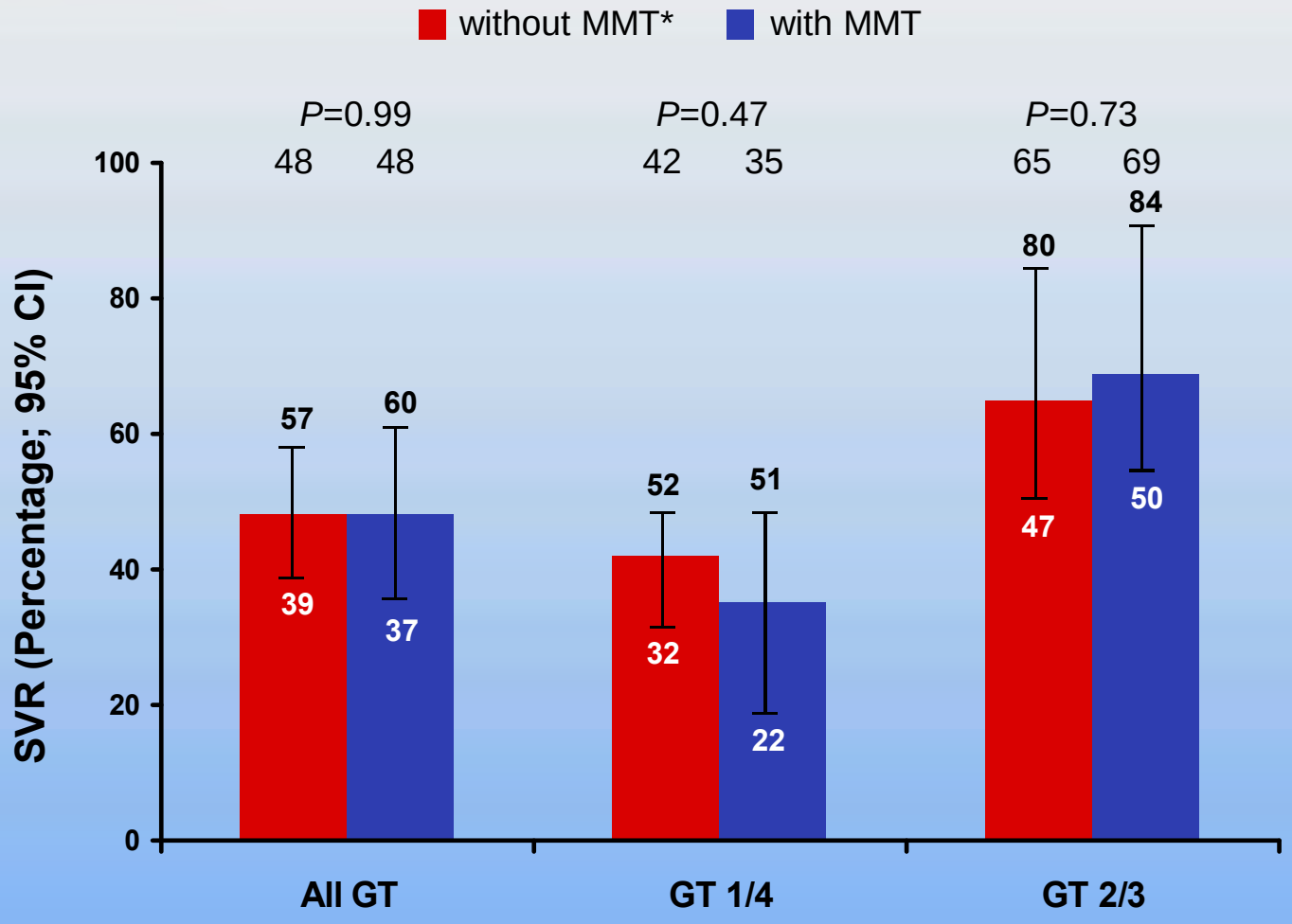
Methadone Maintenance Therapy Does Not Influence the Outcome of HCV Therapy

- Evaluation of rate of response to HCV treatment with pegylated interferon (PEG-IFN) plus ribavirin (RBV) in patients undergoing MMT

Characteristic	Patients without MMT (n=133)	Patients under MMT (n=31)	p
Age (years)	42.2 (36.8 - 47.4)	41.4 (37.5 - 45.2)	0.42
Male sex, n (Percentage)	102 (76.7)	71 (87.7)	0.04
Body mass index (kg/m2)*	25.2 (22.7 - 27.6)	24.7 (22.1 - 27.4)	0.31
HIV positive, n (Percentage)	34 (26)	22 (26.8)	0.89
IL28B CC, n (Percentage)‡	29 (44.6)	15 (34.1)	0.48
Genetype 1/4, n (Percentage)	96 (72.2)	48 (59.2)	0.07
HCV viral load (log_{10} IU/mL)*	6.2 (5.6 - 6.7)	6.1 (5.5 - 6.8)	0.59
ALT (U/l)*	79.5 (45 - 112)	62 (38.9 - 105)	0.23
Cirrhosis at baseline, n (Percentage)	8 (7)	9 (13.2)	0.16
Depression, n (Percentage)	10 (7.5)	5 (6.2)	0.83

Neukam K et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS7/5.

Influence of MMT on SVR Intention-to-treat Analysis

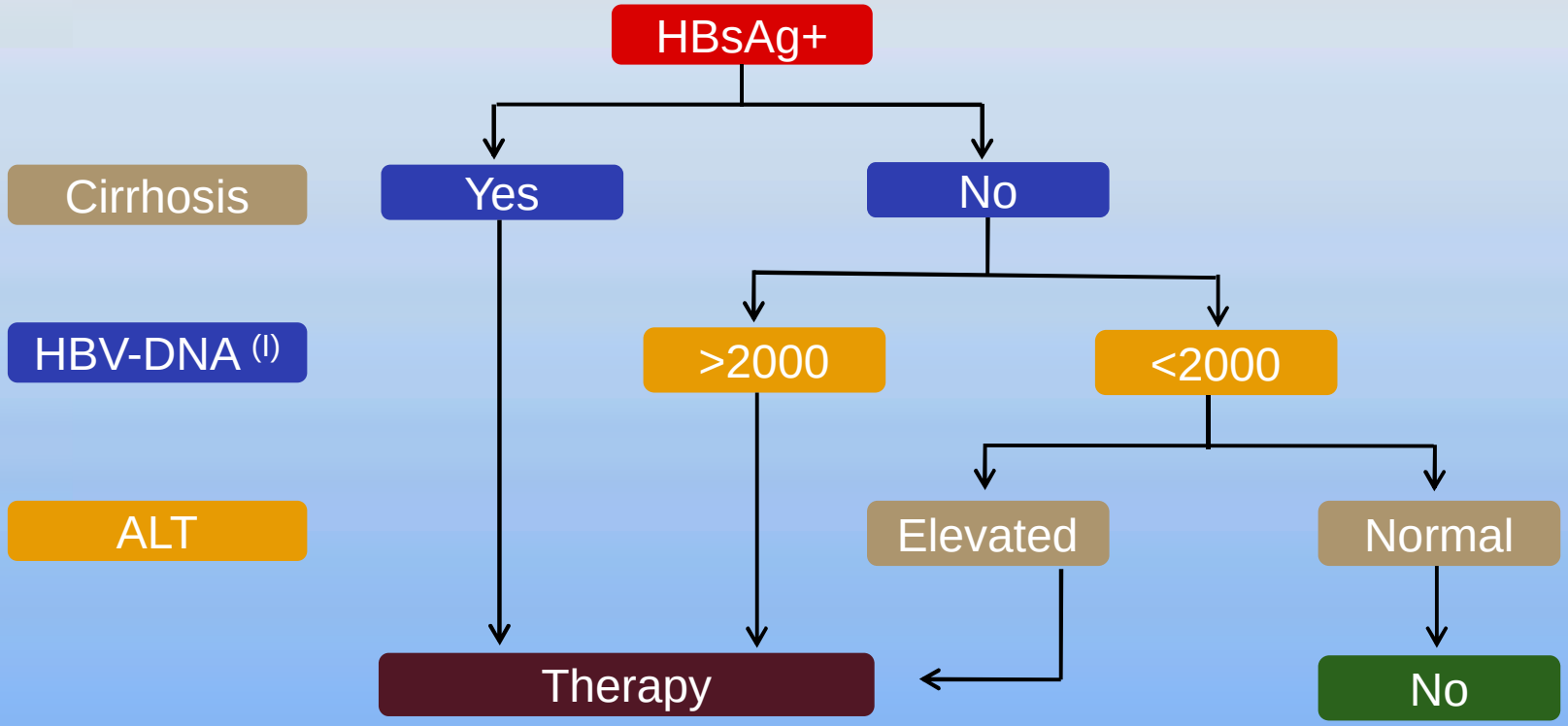


*MMT= methadone maintenance therapy

Neukam K et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS7/5.

EACS GUIDELINES Update: HBV Infection in HIV+

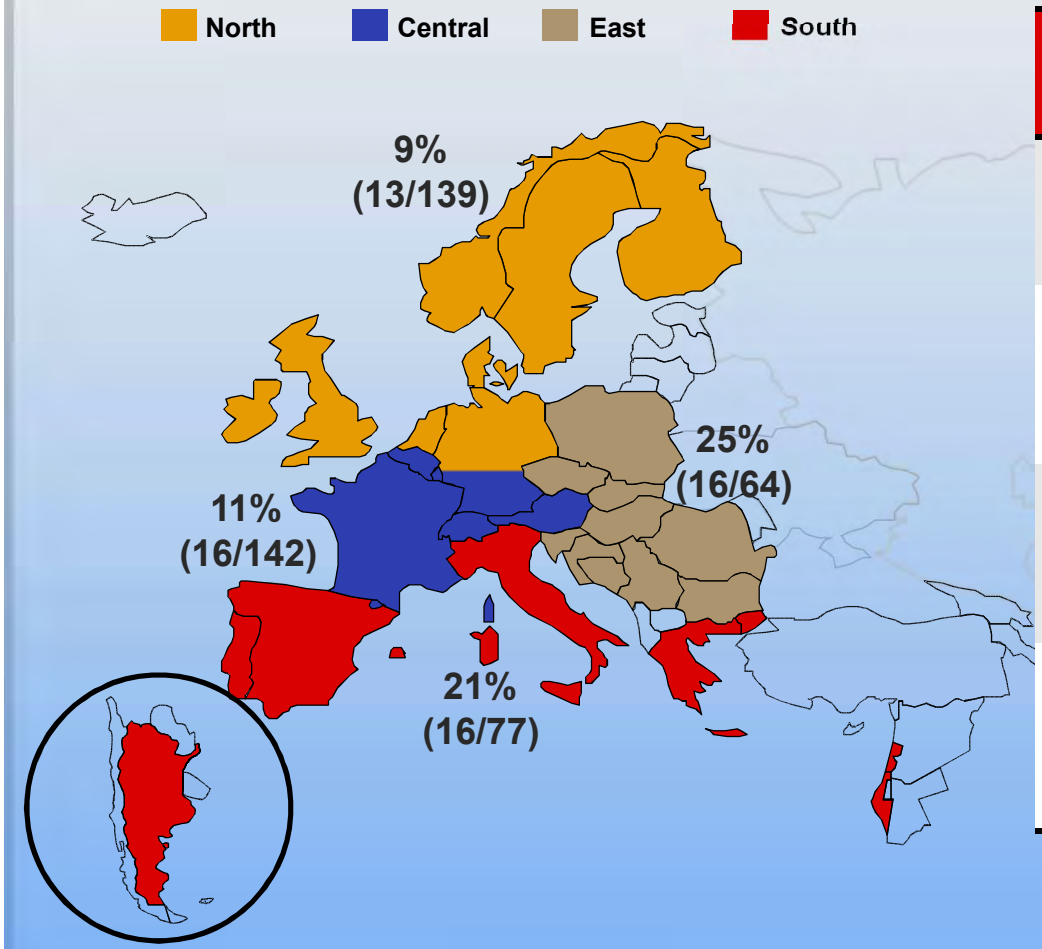
- In patients with significant liver fibrosis (F2-F3), anti-HBV treatment might be considered even when serum, HBV-DNA is below 2000 IU/mL and liver enzymes are not elevated.



(I): IU/mL

www.eacs.eu (October, 2011).

Prevalence of anti-HDV Ab in HBsAg+ patients in EuroSIDA



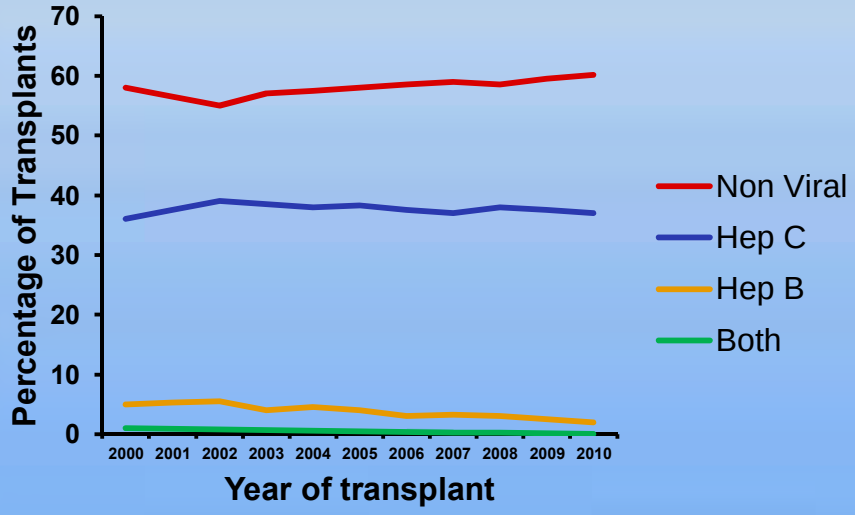
Total no. patients	16,597
HBsAg+	1,319 (7.9%)
Anti-HDV Ab+	61/422 (14.5%) (95% CI: 11.1-17.8)
HDV-RNA+	31/38 (81.6%) (95% CI: 69.3-93.9%)
Median follow-up in HBs-AG+ patients	90.2 months (95% CI: 51.1-135.2)

Soriano V et al. 13TH EACS; Belgrade, Serbia; October 12-15, 2011; Abst. PS9/5.

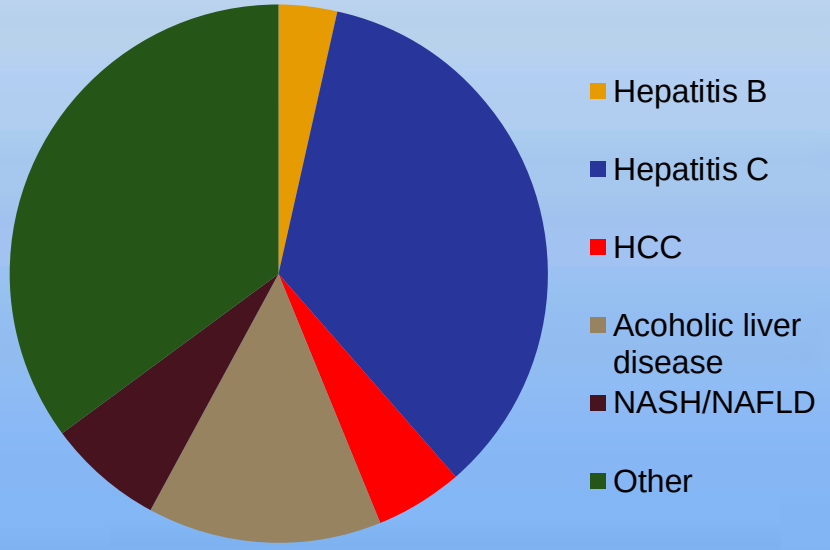
Trends in Hepatitis B and C Liver Transplants

- OPTN data liver transplants from January 2000-December 2010
  - 65,891 total: 61,752 unique (4,139 re-transplants)
  - 2000-2006 increased by 39%, 2006-2010 decreased by 3%
  - Viral Hepatitis (42%): HBV (4%), HCV (37.3%), both (0.8%)
    - no significant change in 10 yrs
  - Non viral hepatitis (58%): alcoholic, NASH, HCC, Autoimmune, others

Trends in Liver Transplants Associated with Viral Hepatitis, United States, 2000-2010



Distribution of Liver Transplants by Indication, 2010



Klevins RM et al. 49TH IDSA; Boston, MA; October 20-23, 2011; Abst. 1194.

EACS GUIDELINES Update: Cancer Screening Methods

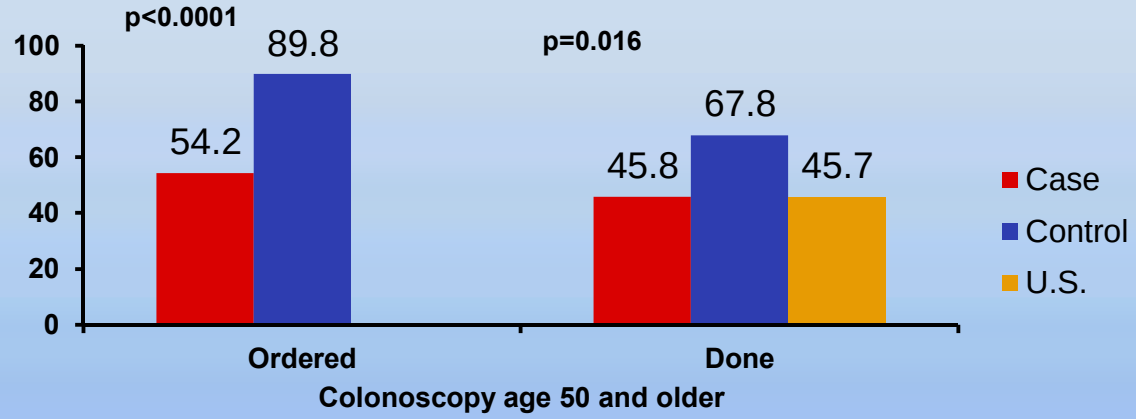
Problem	Patients	Procedure	Evidence of Benefit	Screening Interval	Additional Comments
Anal cancer	Homosexual men	Digital rectal exam ±Papanicolau test	Unknown advocated by some experts	1-3 years	If Pap test abnormal, anoscopy
Breast cancer	Women 50-70 yrs	Mammography	ŹBreast cancer morality	1-3 years	
Cervical cancer	Sexually active women	Papanicolau test	ŹCervical cancer morality	1-3 years	Target age group should include at least the age range 30 to 59 years. Longer screening interval if prior screening tests repeatedly negative
Colorectal cancer	Persons 50-75 yrs	Faecal Occult Blood test	ŹColorectal cancer morality	1-3 years	Benefit is marginal
Hepatocellular carcinoma	Persons with cirrhosis	Ultrasound and alphafoetoprotein	Diagnosis earlier allowing for improved ability for surgical eradication	Every 6 months	
Prostate cancer	Men > 50 yrs	Digital rectal exam ±prostate specific antigen (PSA)	Use of PSA is controversial	1-3 years	Pros: ŷearly diagnosis Con: Over treatment, noŹ cancer-related morality

*Screening recommendations derived from the general population. These screenings should preferably be done as part of national general population-screening programs. Although non-Hodgkinôs lymphoma has a higher incidence in HIV-infected patients than in the general population, it is currently unknown whether it can be screened Careful examination of skin should be performed regularly to detect cancers such as Kaposiôs sarcoma, basal cell carcinoma and malignant melanoma.

www.eacs.eu (October, 2011).

Cancer Screening Rates Among HIV and Non-HIV Patients

- To evaluate compliance with the ACS screening guidelines between HIV pts cared by ID vs HIV negatives cared by IM
- Retrospective, 78 HIV pts, matched to controls
  - 56.4% of the HIV pts also had a primary care provider



- HIV pts cared by ID were less likely to have routine screening for cervical, breast and colon cancer, irrespectively if they have a primary care provider

Johnson L et al. 49TH IDSA; Boston, MA; October 20-23, 2011; Abst. 481.

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