CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV THERAPIES AND THERAPEUTIC STRATEGIES

Reporting From

THE XIX INTERNATIONAL AIDS CONFERENCE (AIDS 2012)

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

HIV Prevention

David Cooper, MD, DSc
Director and Professor,
Kirby Institute, University of New South Wales
Sydney, Australia

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

The Washington D.C. Declaration

To turn the tide against the HIV/AIDS epidemic we must:

1. Increase targeted new investments
2. Ensure evidence-based HIV prevention, treatment and care
3. End stigma, discrimination, legal sanctions
4. Markedly increase HIV testing, counseling and linkages to prevention, care and support services
5. Provide treatment for all pregnant and nursing women
6. Expand access to ARV treatment to all in need
7. Identify, diagnose and treat TB
8. Accelerate research
9. Mobilization and meaningful involvement of affected communities

http://www.2endaids.org/read.html

Parallel Challenges, Parallel Opportunities

	ART for HIV Prevention	PrEP for HIV Prevention
Adherence	Necessary for efficacy	Necessary for efficacy
Sexual Risk-Taking	*Principal question is whether risk-taking would be sufficient to undermine prevention benefits*	
Antiretroviral Resistance	Established risk, associated with poor adherence, rising in Africa	In trials, only with use in acute infection. Must be weighed against infections averted.
Who Will Use?	In theory, all HIV+s. Life-long	Target to those at highest risk. Season of highest risk.
Who Will Pay?	Rising need = rising costs	Where to fit in the priority list?

Mugo N, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB04.

PrEP (Like ART) Works When Taken

	Blood Samples with Tenofovir Detected	HIV Protection Efficacy in Randomized Comparison
Partners PrEP (FTC/TDF arm)	81%	75%
TDF2	79%	62%
iPrEx	51%	44%
FEM-PrEP	26%	6%

There is a clear dose-response between evidence of PrEP use & efficacy

Baeten et al N Engl Med 2012; Grant et al N Engl J Med 2010; Van Damme et al N Engl J Med 2012; Thigpen et al N Engl J Med 2012; Mugo N, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB04.

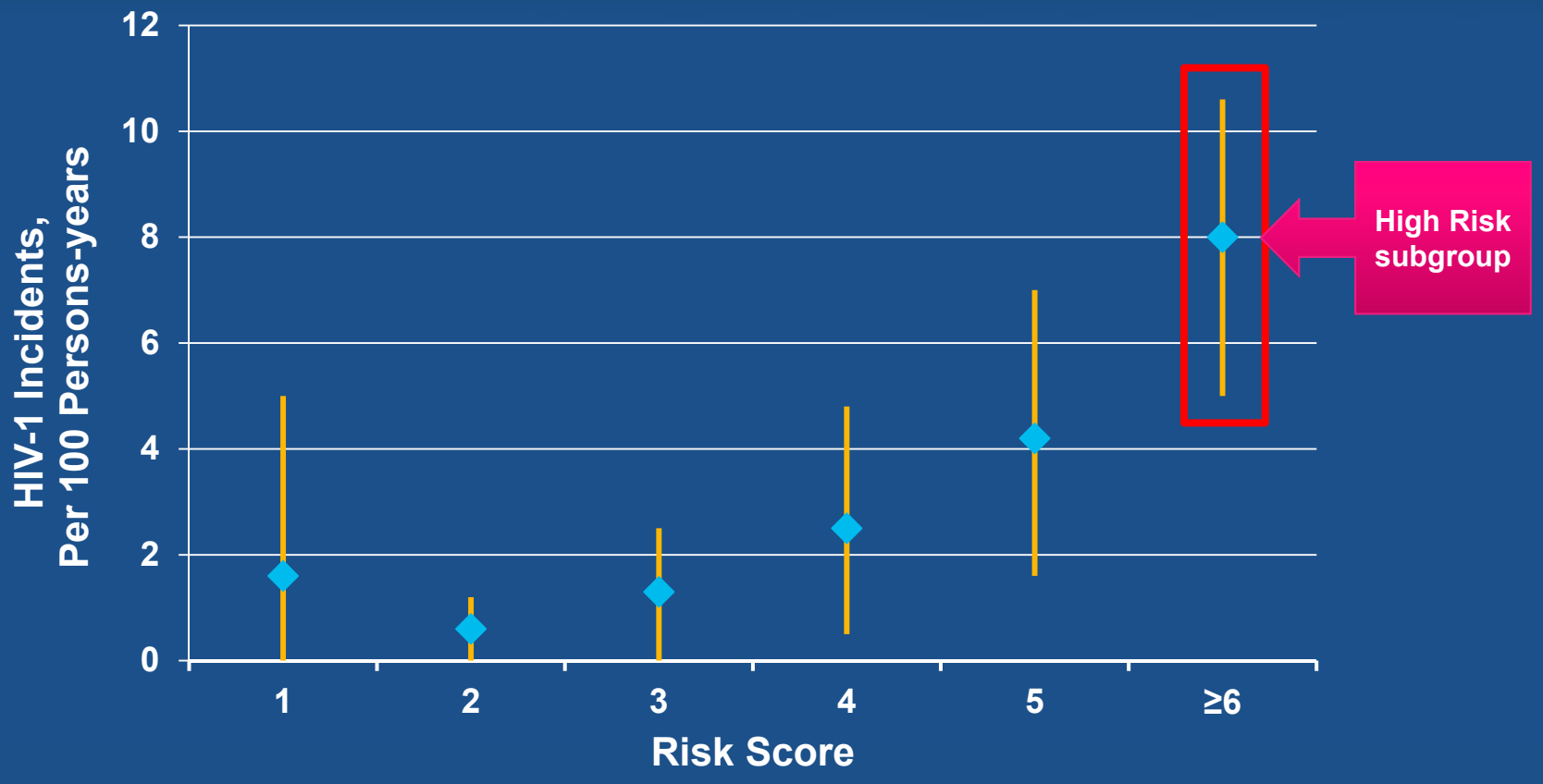
Partners PrEP Sub-study: PrEP Efficacy Among Higher-risk HIV-1 Serodiscordant Couples

- **Objective: Identify and assess efficacy of PrEP among a subgroup of higher-risk heterosexual HIV-1 serodiscordant couples**
- **HIV-1 Risk Score for Serodiscordant Couples: Novel risk scoring tool, made up of a discrete combination of baseline clinical and behavioral factors, that would define HIV-1 transmission risk**

Age of HIV-uninfected partner	
20 years or less	4
21-30 years	1
More than 30 years	0
Number of children	
0	2
1-2	1
3 or more	0
Male HIV-uninfected partner uncircumcised	
Yes	1
No	0
Married and/or cohabiting	
Yes	1
No	0
Unprotected sex with partnership, prior 30 days	
Yes	2
No	0
Plasma viral load, HIV-1 infected partner	
50,000 copies or higher	3
10,000-49,999 copies	1
Less than 10,000 copies	0
Total score (≥6=higher risk, ≥4 if viral load not done)	

Kahle E, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAC0102.

Partners PrEP Sub-study: HIV-1 Incidence by Risk Score in PrEP Placebo Arm



Comparable incidence to FemPrEP (5/100) and VOICE (6/100)

Kahle E, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAC0102.

Partners PrEP Sub-study: PrEP Efficacy Results

Partners PrEP Primary mITT Analysis	TDF	FTC/TDF	Placebo
Number of HIV-1 infections	17	13	52
HIV-1 incidence, per 100 person-years	0.65	0.50	1.99
HIV-1 protection efficacy, vs. placebo (95%CI)	67% (44-81%)	75% (55-87%)	
p-value	<0.001	<0.001	

High Risk Subgroup Analysis mITT	TDF	FTC/TDF	Placebo
Number of HIV-1 infections	7	6	28
HIV-1 incidence, per 100 person-years	1.34	1.10	5.01
HIV-1 protection efficacy, vs. placebo (95%CI)	72% (35-88%)	78% (46-91%)	
p-value	0.001	<0.001	

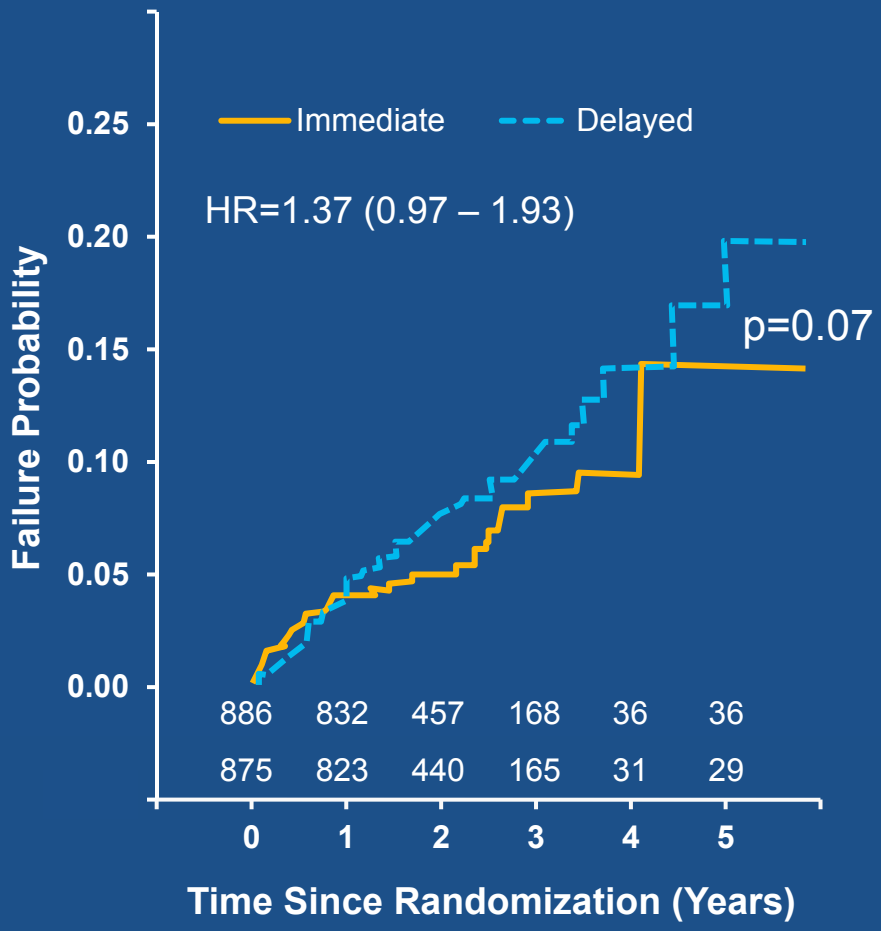
Kahle E, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAC0102.

HPTN 052: Effect of Early vs. Delayed Initiation of ARV Therapy on Clinical Outcomes

- HIV+ adults (CD4+350-550/μL) from Africa, Asia, and South America randomized to ART immediately or after CD4+ <250/μL or AIDS (Delayed)
- Primary Clinical Event:
  - Death
  - WHO Stage 4
  - Tuberculosis
  - Severe bacterial infection
  - Targeted serious non-AIDS events
    - Serious cardiovascular/vascular disease, Serious liver disease, End stage renal disease, Non-AIDS malignancy, Diabetes mellitus
- All events underwent blinded independent review using standardized criteria
  - ACTG Diagnoses Appendix (Appendix 60) and WHO criteria

Grinsztejn BE, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB05.

HPTN 052: Primary Events

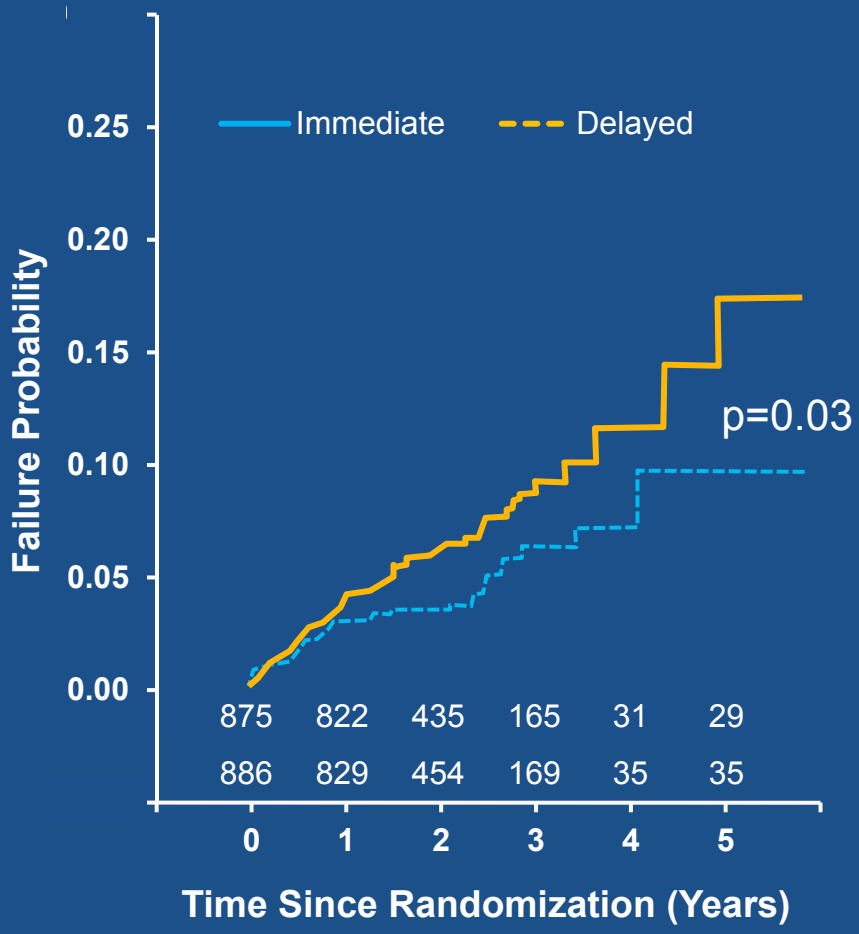


Number of Subjects Experiencing ≥1 Event		
	Delayed	**Immediate**
Any Primary event	77 (9%)	57 (6%)
AIDS event	61	40
Deaths	15	11
Primary event associated	4	1
Deaths from other causes	11	10
Non-AIDS events	9	12
Diabetes mellitus	5	4
Non AIDS malignancy	3	3
Cardiovascular/Vascular	1	3
Serious liver disease	0	2
End stage renal disease	0	0

Grinsztejn BE, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB05.

HPTN 052: AIDS Events

Time to First AIDS-Defining Disease



Number of Subjects Experiencing ≥1 Event		
	Delayed	Immediate
Tuberculosis	34 (4%)	17 (2%)
Serious bacterial infection	13 (1%)	20 (2%)
WHO Stage 4 event	19 (2%)	9 (1%)
Oesophageal candidiasis	2	2
Cervical carcinoma	2	0
Cryptococcosis	0	1
HIV-related encephalopathy	1	0
Herpes simplex, chronic	8	2
Kaposi's sarcoma	1	1
CNS Lymphoma	1	0
Pneumocystis pneumonia	1	0
Septicemia	0	1
HIV Wasting	2	0
Bacterial pneumonia	1	2

Grinsztejn BE, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB05.

Optimization of HIV Care and Service Delivery: Doing More with Less

- HIV Treatment Strategy
- Monitoring ART
- Dosing
- Service Delivery

Boyd M and Cooper D. Lancet. Published online July 23, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61154-4

Randomized Controlled Trials of Clinical and Immunological Monitoring of People Receiving ART

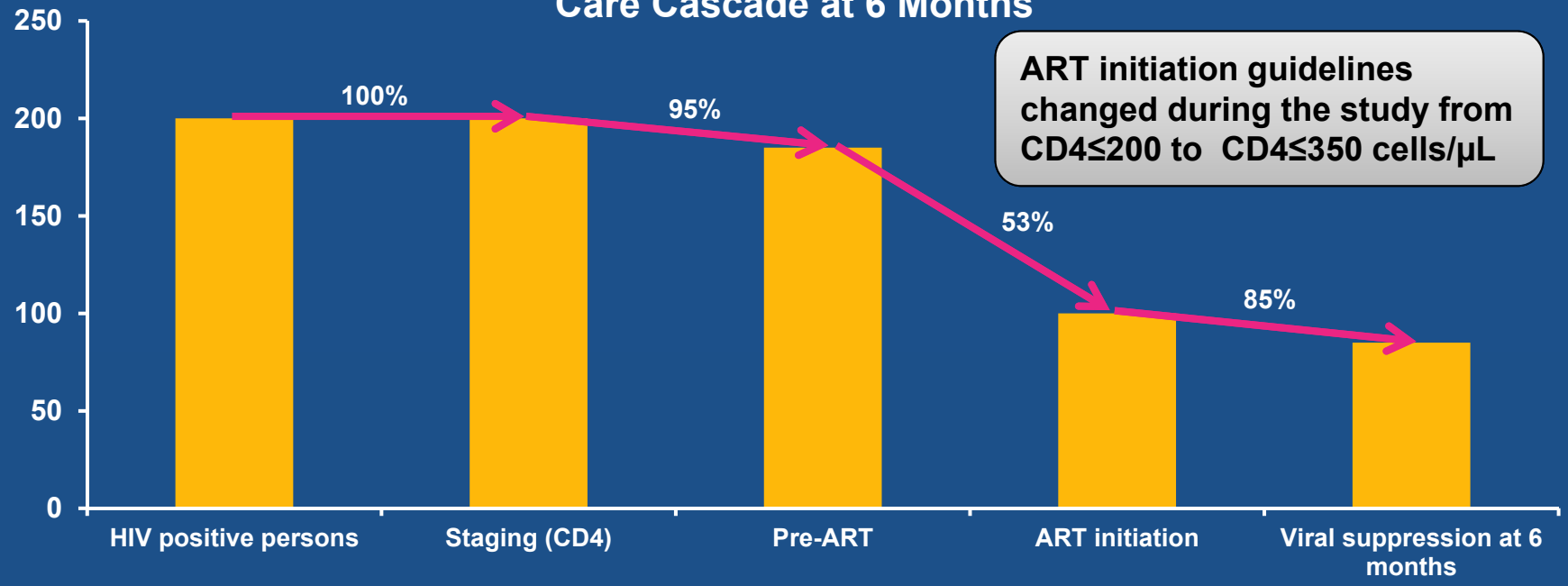
	Location	Participants (n)	Comparison	Conclusion
DART	Uganda, Zimbabwe	3321	Laboratory and clinical monitoring vs. clinical monitoring only	ART can be delivered safely without routine laboratory monitoring; differences in disease progression suggest a role for monitoring of CD4 cell count from the second year of treatment
AIDS Support Organization	Uganda	1094	Clinical monitoring alone vs. clinical and quarterly CD4 cell count vs. clinical plus quarterly CD4 cell count and viral load	Routine laboratory monitoring is associated with improved health and survival compared with clinical monitoring alone
PHPT-3 Study	Thailand	716	Virolological vs. immunological monitoring (both once every 3 months)	Viral load monitoring might be less important than regular safety, tolerability, adherence, and immunological monitoring
ANRS/ESTHER	Cameroon	256	Clinical vs. laboratory monitoring (viral load and CD4 cell count, once every 6 months)	Supports WHO's recommendation for laboratory monitoring of ART, although the small differences between the strategies suggest that clinical monitoring alone could be used

Boyd M and Cooper D. Lancet. Published online July 23, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61154-4

Improving Testing & Linkage to Care

- Strategies that have worked
  - Home based HIV testing
  - Point of Care CD4 count
  - Community delivery of ART

HBCT: Number of People at Each Stage of the Testing to Linkage to Care Cascade at 6 Months



* Barnabas TasP 2012

Mugo N, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB04.

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV THERAPIES AND THERAPEUTIC STRATEGIES

Reporting From

THE XIX INTERNATIONAL AIDS CONFERENCE (AIDS 2012)

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

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV THERAPIES AND THERAPEUTIC STRATEGIES

Reporting From

THE XIX INTERNATIONAL AIDS CONFERENCE (AIDS 2012)

Treatment-Naïve Patients

Joseph Eron, MD
Professor,
University of North Carolina School of Medicine
Chapel Hill, NC

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

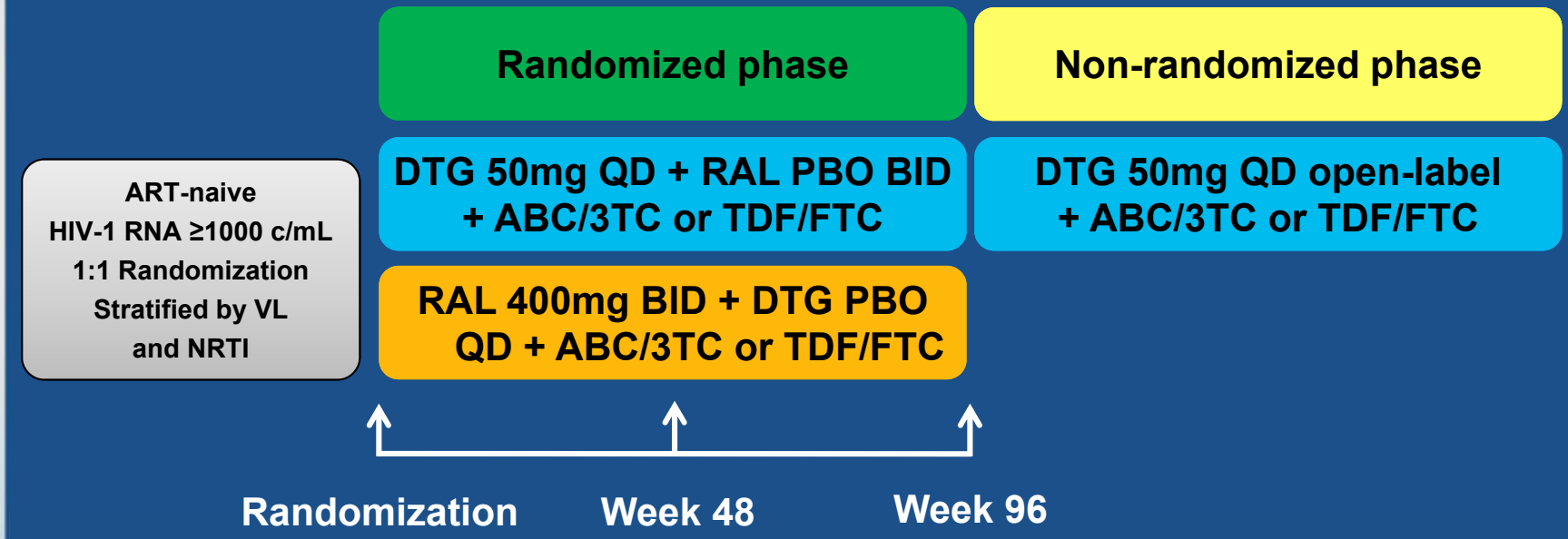
New IAS-USA Treatment Guidelines

- All adults with HIV-1 should be offered cART regardless of CD4 ccount.
  - The strength of the recommendation and the quality of the data increase as CD4 cell count decreases
- cART should be initiated early following TB diagnosis
  - Within 2 weeks in patients with low (< 50 cells/mm^3) CD4 cell counts
- Early cART needs to be monitored carefully in patients with cryptococcal and TB meningitis and very early therapy (within 2 weeks) may have increased risk.
- ABC/3TC with EFV or ATV/r are recommended regimens when HIV RNA < 100,000 c/mL and HLA-B*5701 is negative
- FDC rilpivirine/TDF/FTC and elvitegravir/cobisistat/TDF/FTC (pending approval) are alternative first line regimens.
  - Rilpivirine regimens should be avoided if BL HIV RNA > 100,000 c/mL

Thompson MA, et al. *JAMA. 2012;308(4):387-402*

SPRING-2: Dolutegravir vs. Raltegravir in ARV-naïve Patients

Phase III, randomized, double-blind, double-placebo, multicenter, parallel-group, non-inferiority study

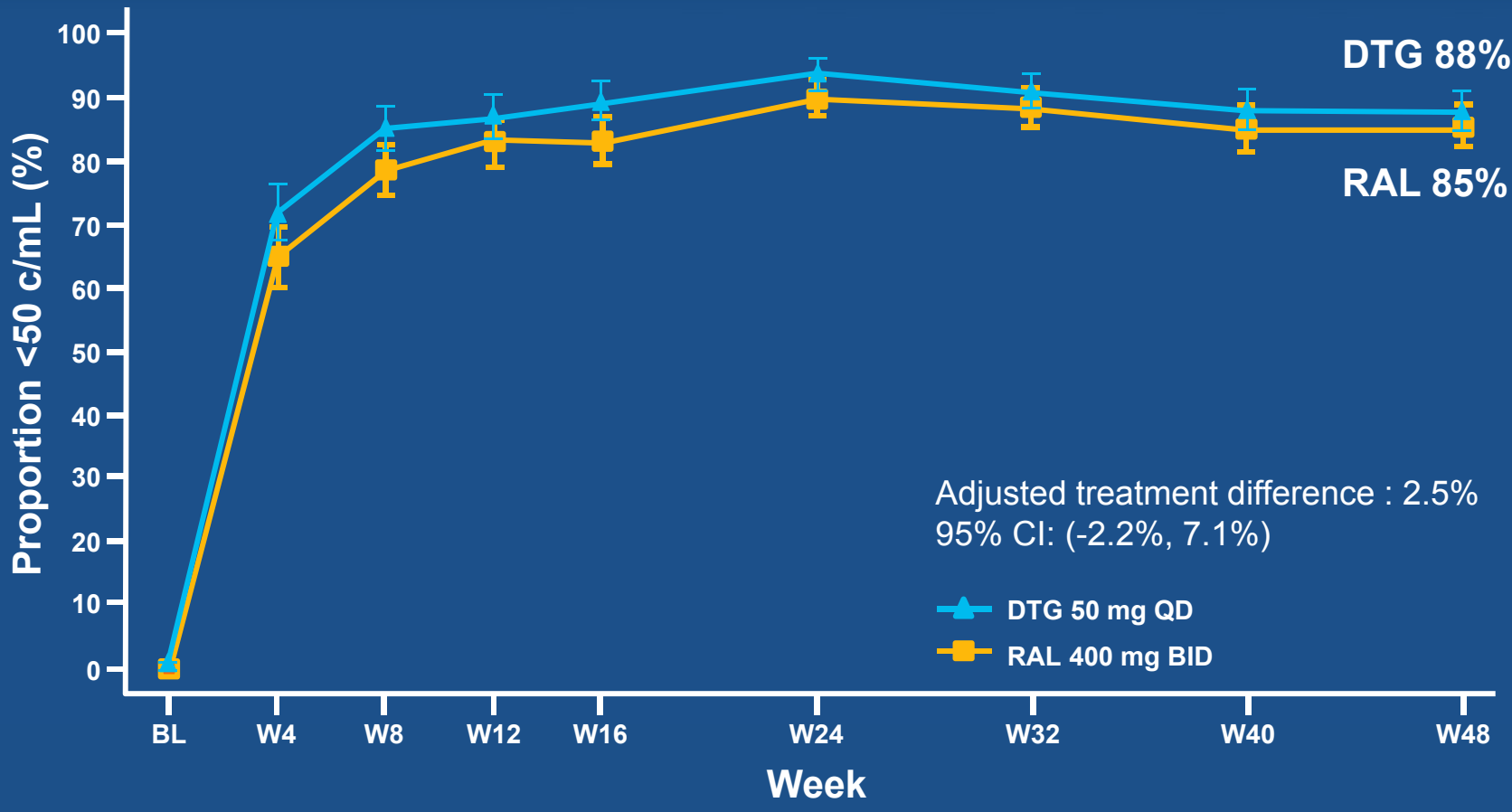


SPRING-2: Baseline Characteristics

		DTG 50 mg QD n=411	RAL 400 mg BID n=411
Age	Median (years)	37	35
Gender	Male	85%	86%
Race	White	84%	86%
	African American/African heritage	12%	9%
Baseline HIV-1 RNA	Median (log_{10} c/mL)	4.52	4.58
	>100,000 c/mL	28%	28%
Baseline $CD4^+$	Median (cells/mm^3)	359	362
	<200 cells/mm^3	13%	12%
Hepatitis coinfection	HBV	2%	2%
	HCV	10%	9%
Investigator-selected NRTIs	TDF/FTC	59%	60%
	ABC/3TC	41%	40%

Raffi F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB04.

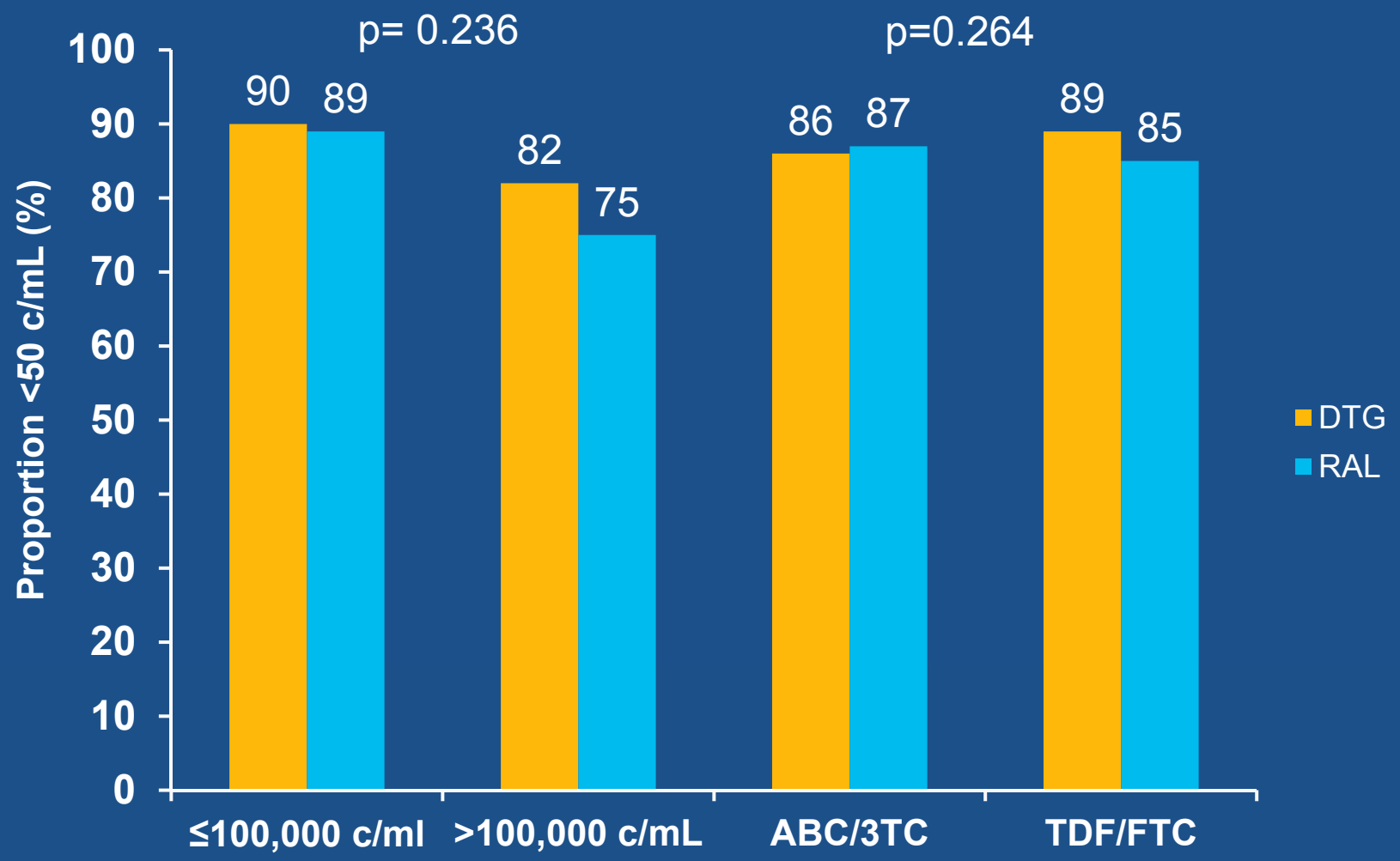
SPRING-2: Outcomes at Week 48



Median CD4 change (Week 48): DTG and RAL +230
Adverse Event profile similar

Raffi F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB04.

SPRING-2: Treatment Differences at Week 48 by Baseline HIV RNA and NRTIs



Raffi F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB04.

SPRING-2: Resistance

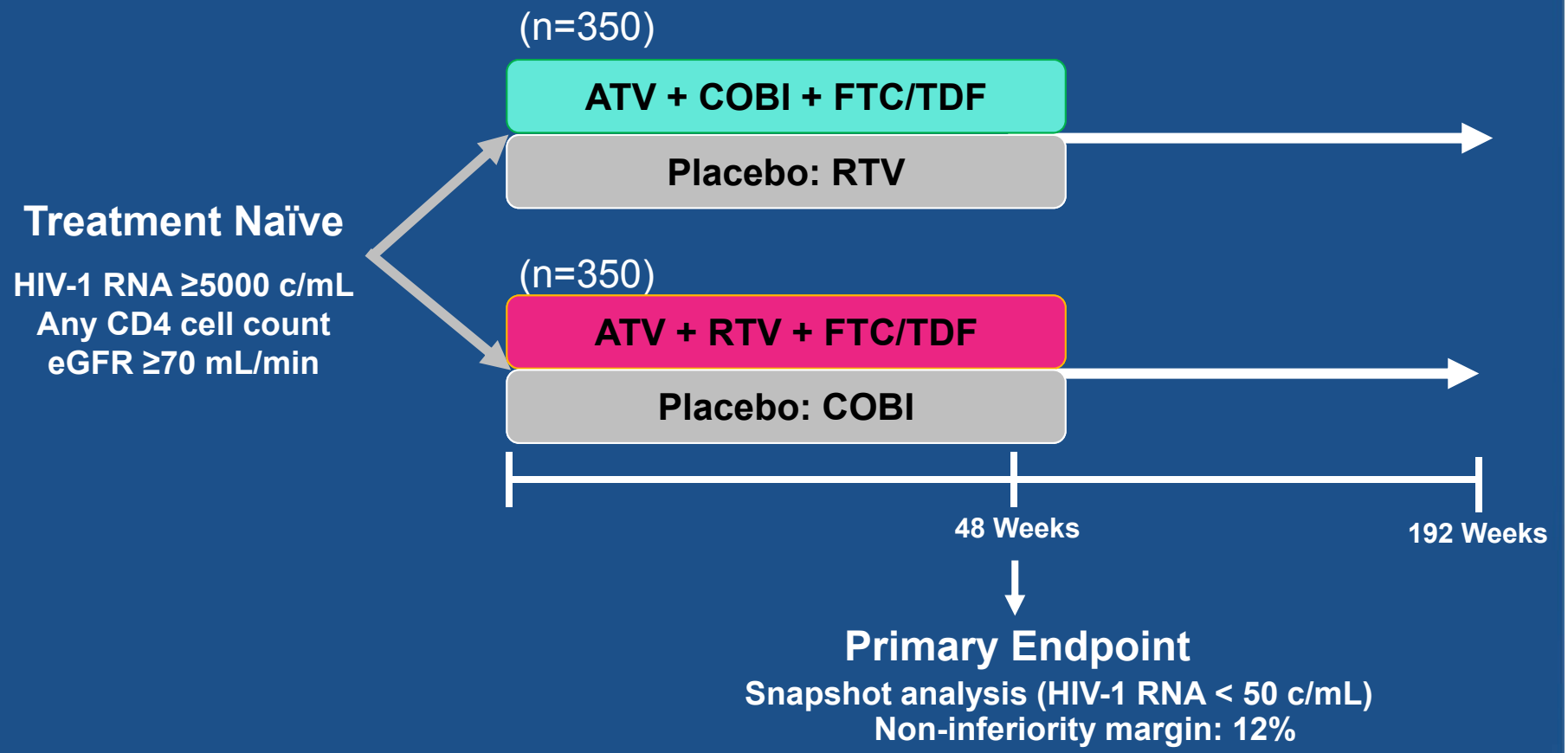
	DTG 50 mg QD n=411	RAL 400 mg BID n=411
Subjects with PDVF	**20 (5%)**	**28 (7%)**
IN genotypic results at BL and time of PDVF	8	18
INI-r mutations	**0**	**1/18 (6%)[a]**
PR/RT genotypic results at BL and time of PDVF	12	19
NRTI-r mutations	**0**	**4/19 (21%)[b,c,d]**

Mutations by subject in the RAL 400 mg BID arm:
a T97T/A, E138E/D, V151V/I, N155H + A62A/V, K65K/R, K70K/E, M184V
b, c, d A62A/V (n=1), M184M/I (n=1), M184M/V (n=1)

Raffi F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THLBB04.

Study 114:
Cobicistat vs. Ritonavir as Pharmacoenhancers

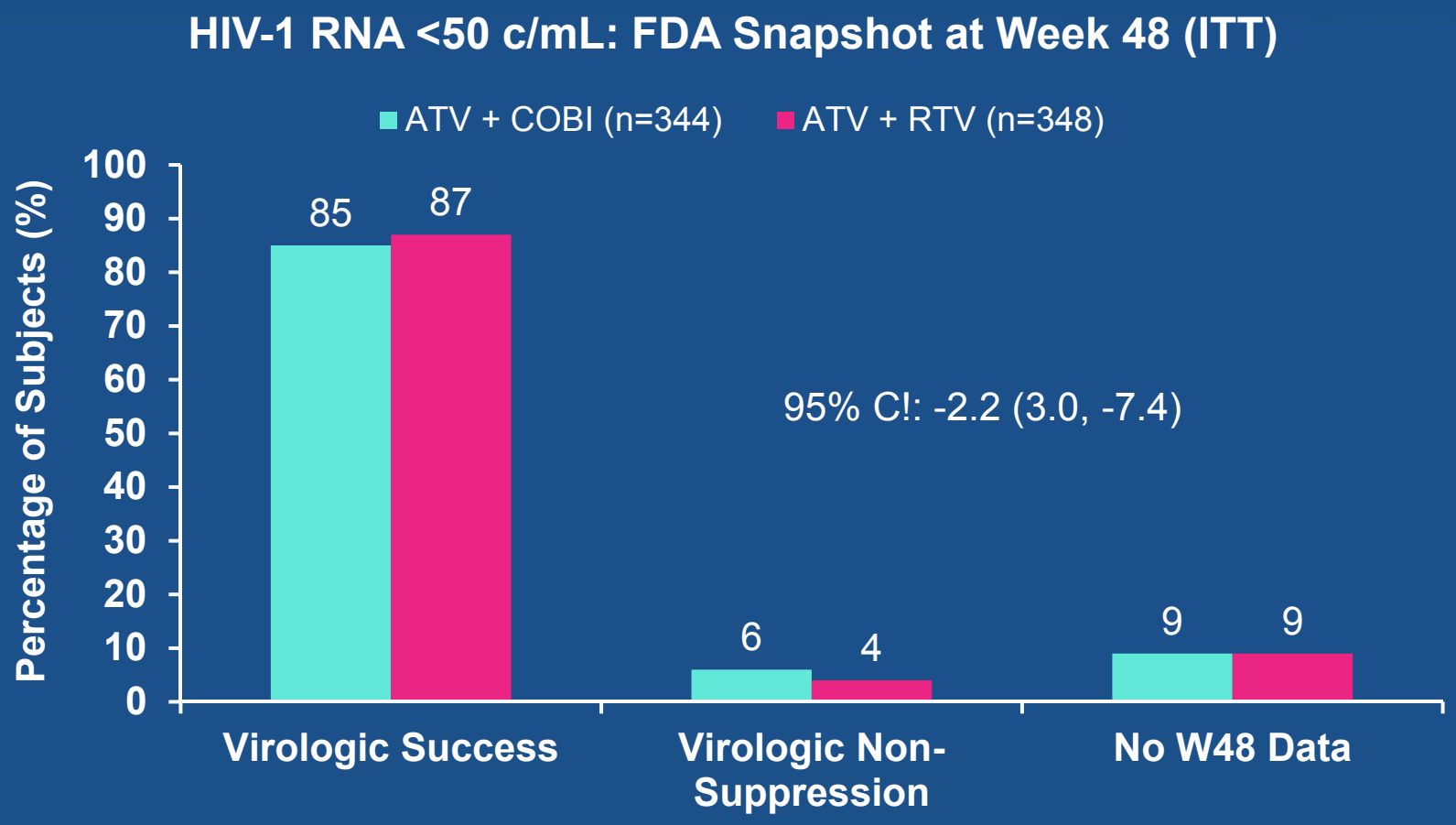
Randomized, double-blind, double dummy, active-controlled, international study



Randomization stratified by screening HIV-1 RNA (≤ vs >100,000 c/mL)

Gallant J, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0103.

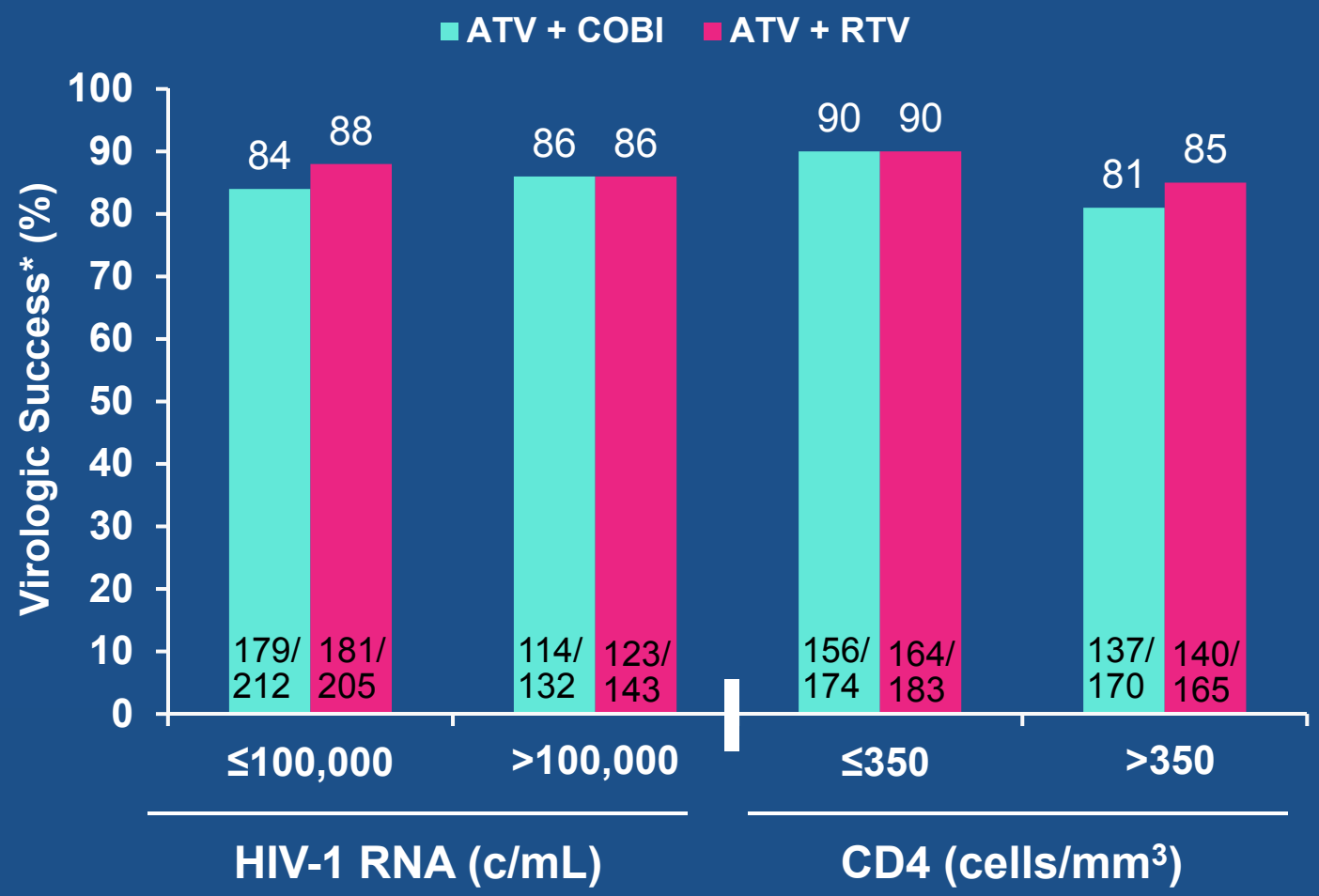
Study 114: Outcomes at Week 48



CD4 Change: COBI +213 vs. RTV +219 (p=0.67)
Resistance: COBI 2 (0.6%) vs. RTV 0 (both M184V/I)

Gallant J, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0103.

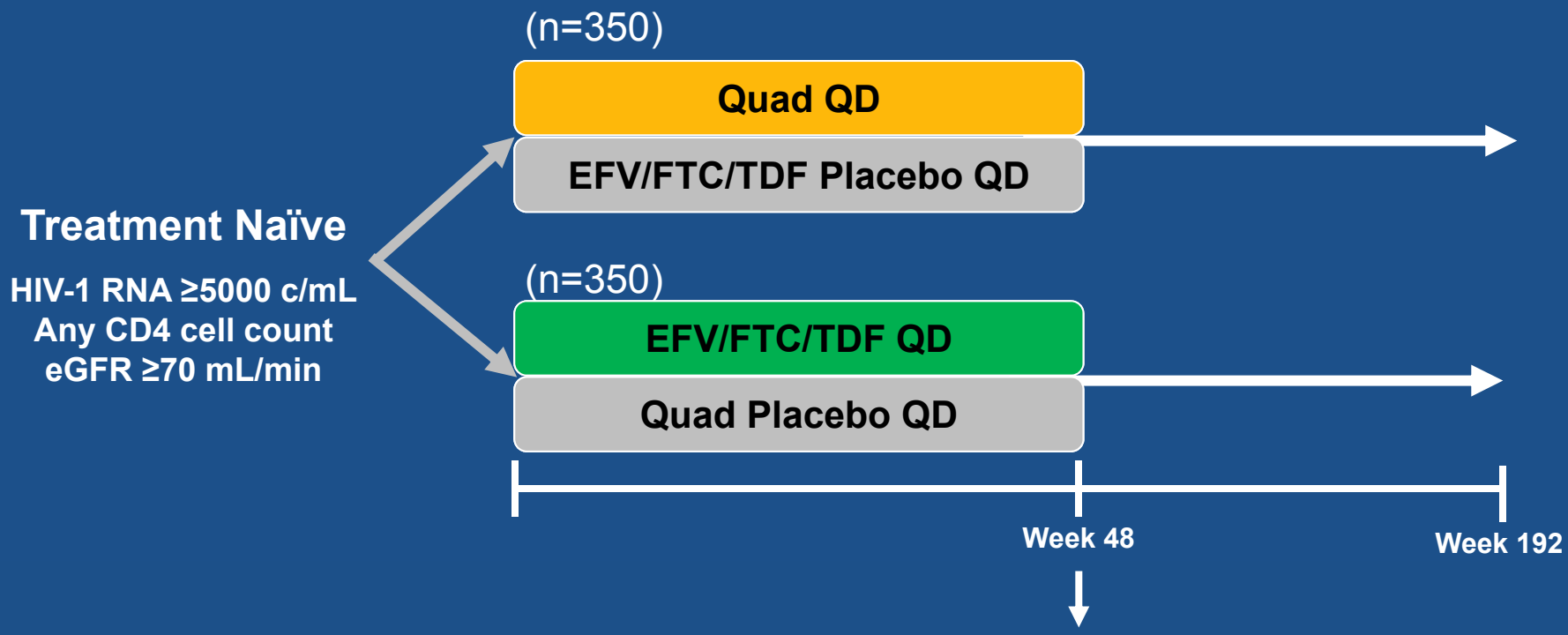
Study 114: Virologic Success by Baseline HIV-1 RNA and CD4 Subgroups



Gallant J, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0103.

Study 102: EVG/COBI/TDF/FTC vs. EFV/TDF/FTC

Randomized, double-blind, double dummy, active-controlled, international study



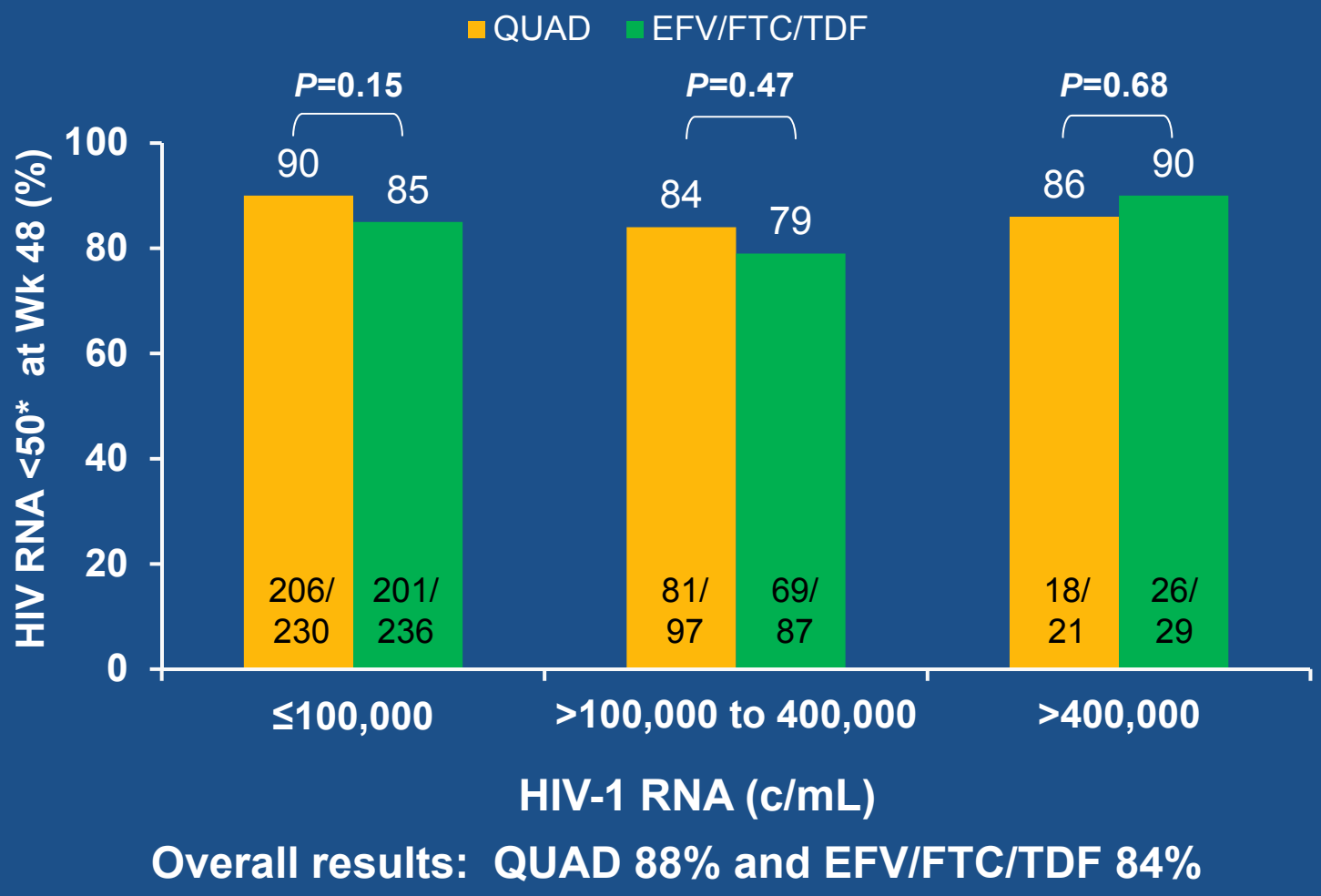
Primary Endpoint

HIV-1 RNA < 50 c/mL at Week 48
FDA snapshot analysis (ITT)
Non-inferiority margin: 12%

Randomization stratified by screening HIV-1 RNA (≤ vs >100,000 c/mL)

Sax P, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE028.

Study 102: Efficacy by Baseline HIV RNA Level

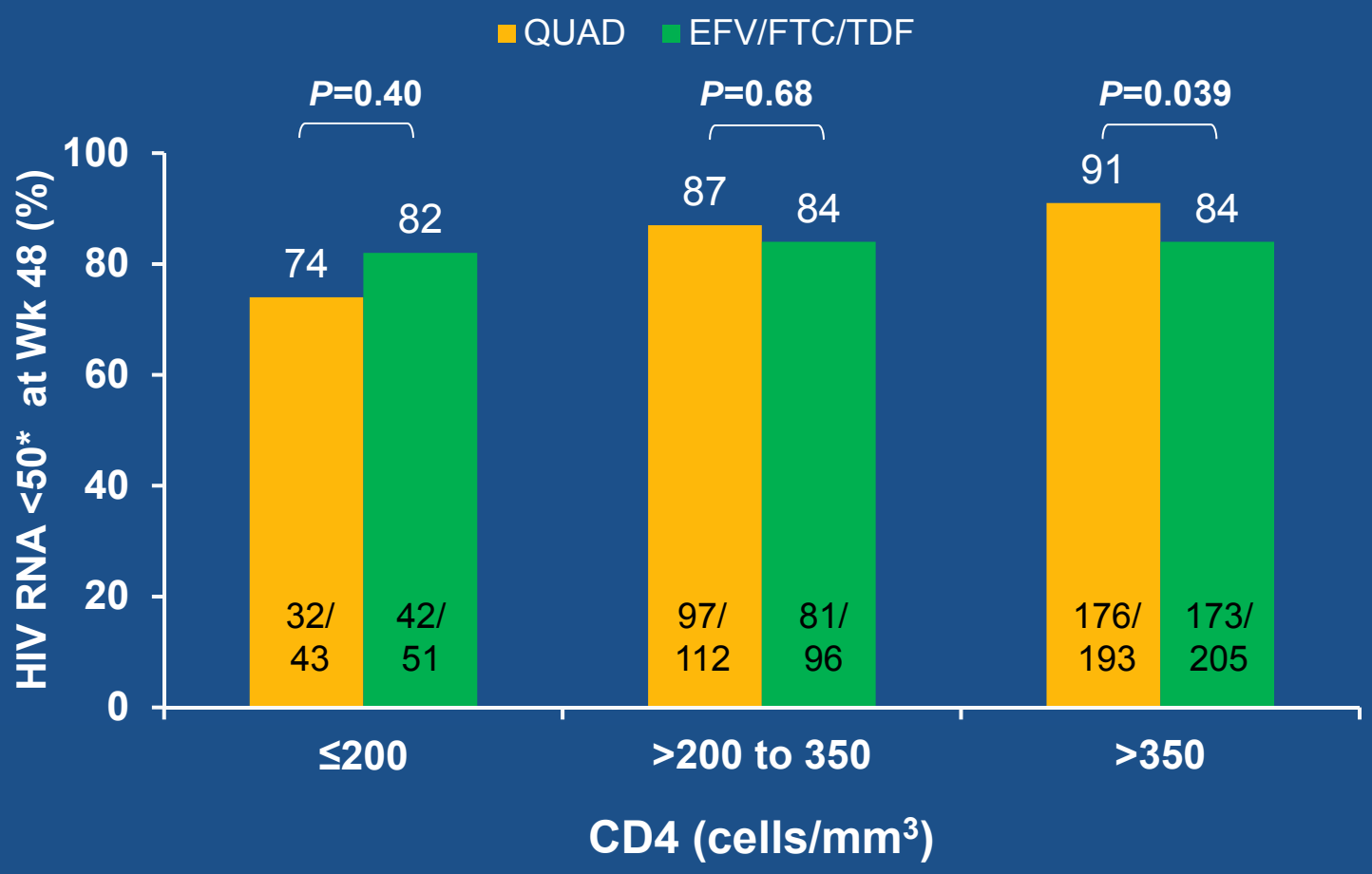


Overall results: QUAD 88% and EFV/FTC/TDF 84%

* FDA Snapshot algorithm

Sax P, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE028.

Study 102: Efficacy by Baseline CD4 Level

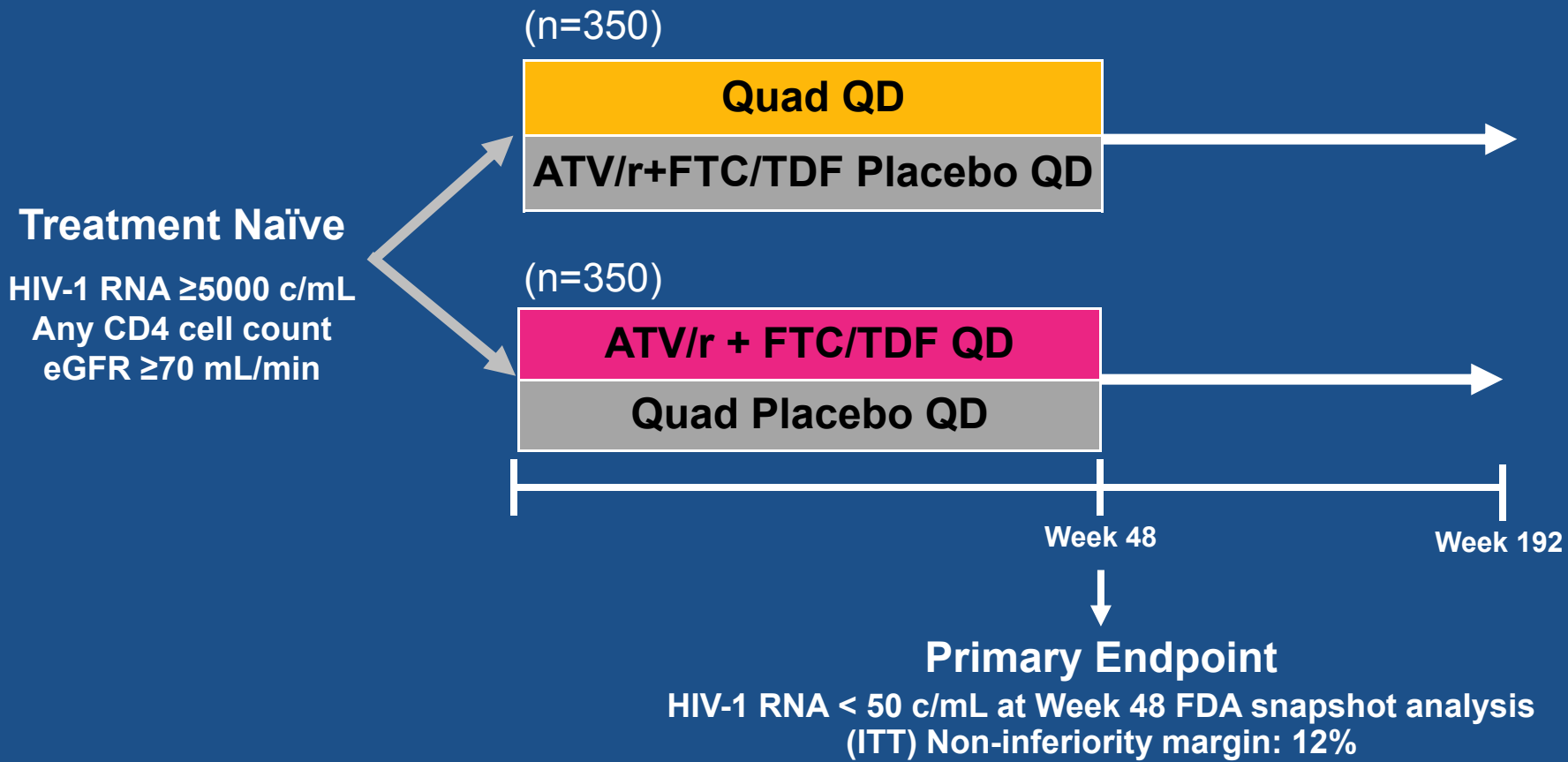


* FDA Snapshot algorithm

Sax P, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE028.

Study 103: EVG/COBI/TDF/FTC vs. ATV/r + TDF/FTC

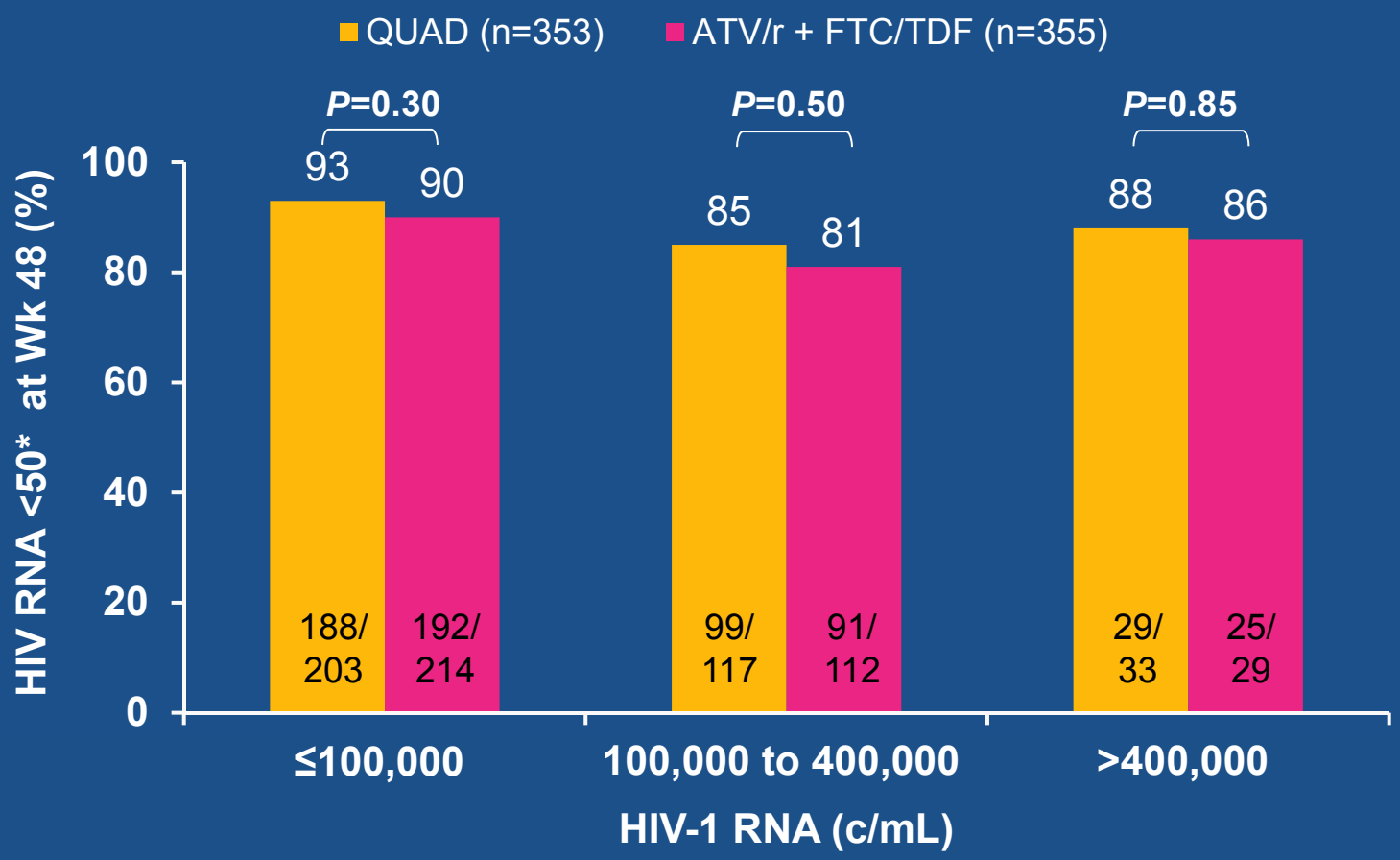
Randomized, double-blind, double dummy, active-controlled, international study



Randomization stratified by screening HIV-1 RNA (≤ vs >100,000 c/mL)

DeJesus E, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE043.

Study 103: Efficacy by Baseline HIV-1 RNA Level

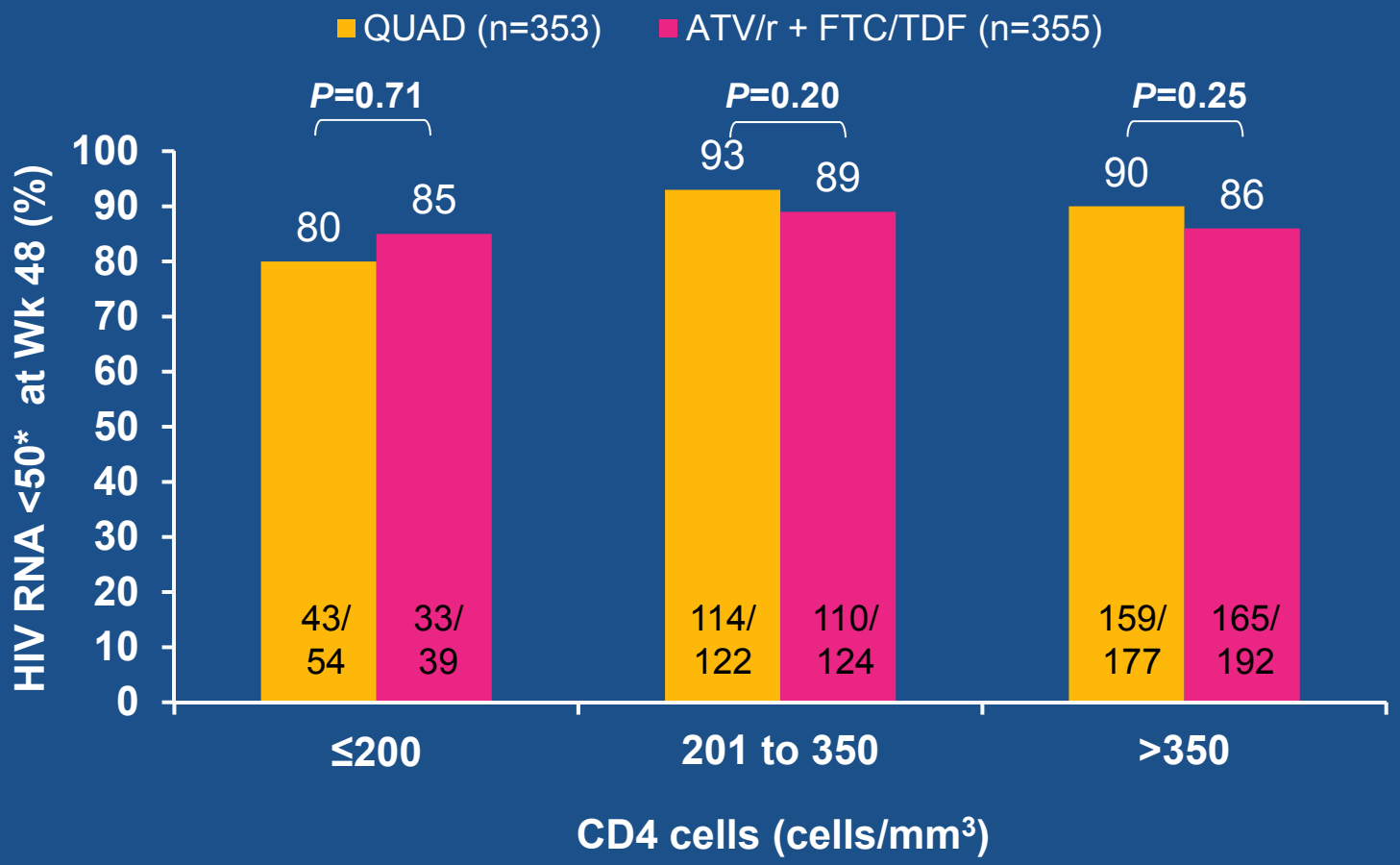


Overall results: QUAD 90% and ATV/r FTC/TDF 87%

* FDA Snapshot algorithm

DeJesus E, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE043

Study 103: Efficacy by Baseline CD4 Subgroups

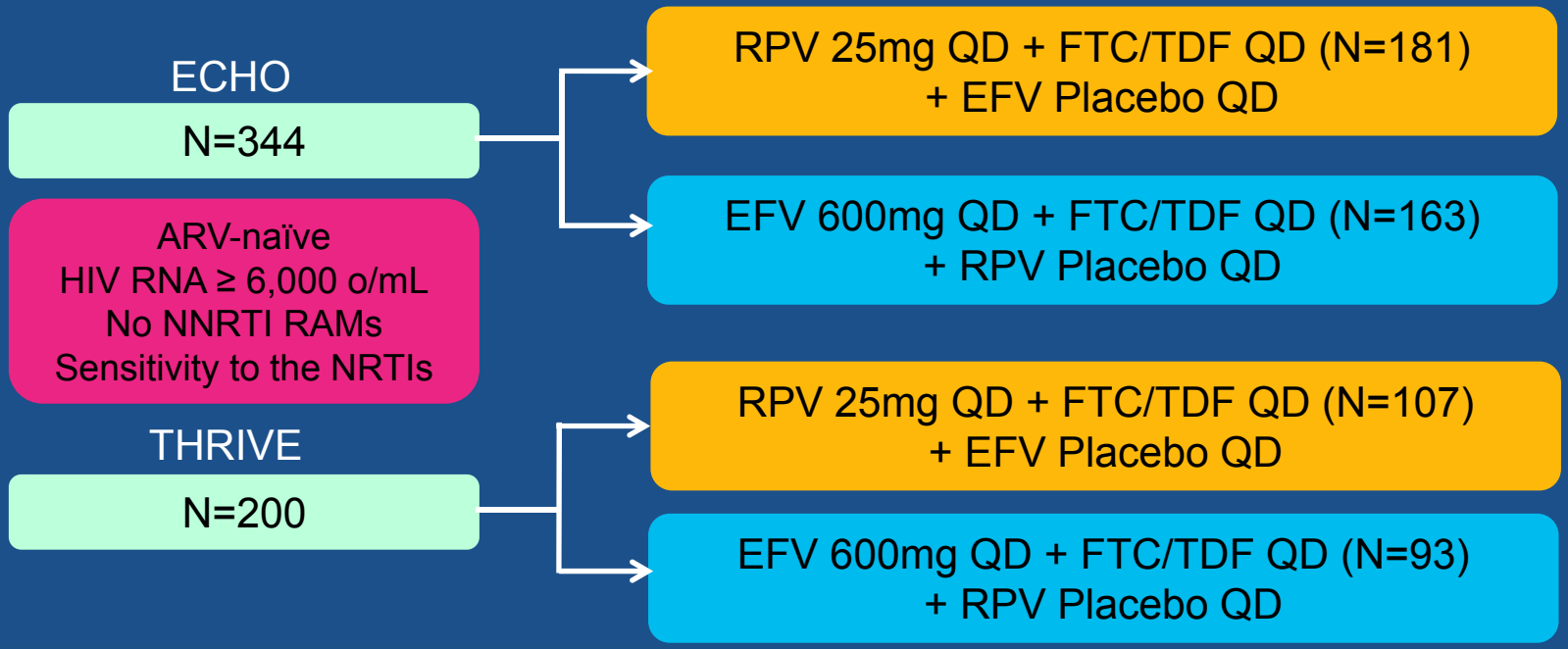


* FDA Snapshot algorithm

DeJesus E, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE043.

Pooled ECHO and THRIVE: RPV vs. EFV (Week 48) in Patients with HIV RNA ≤100,000 c/mL

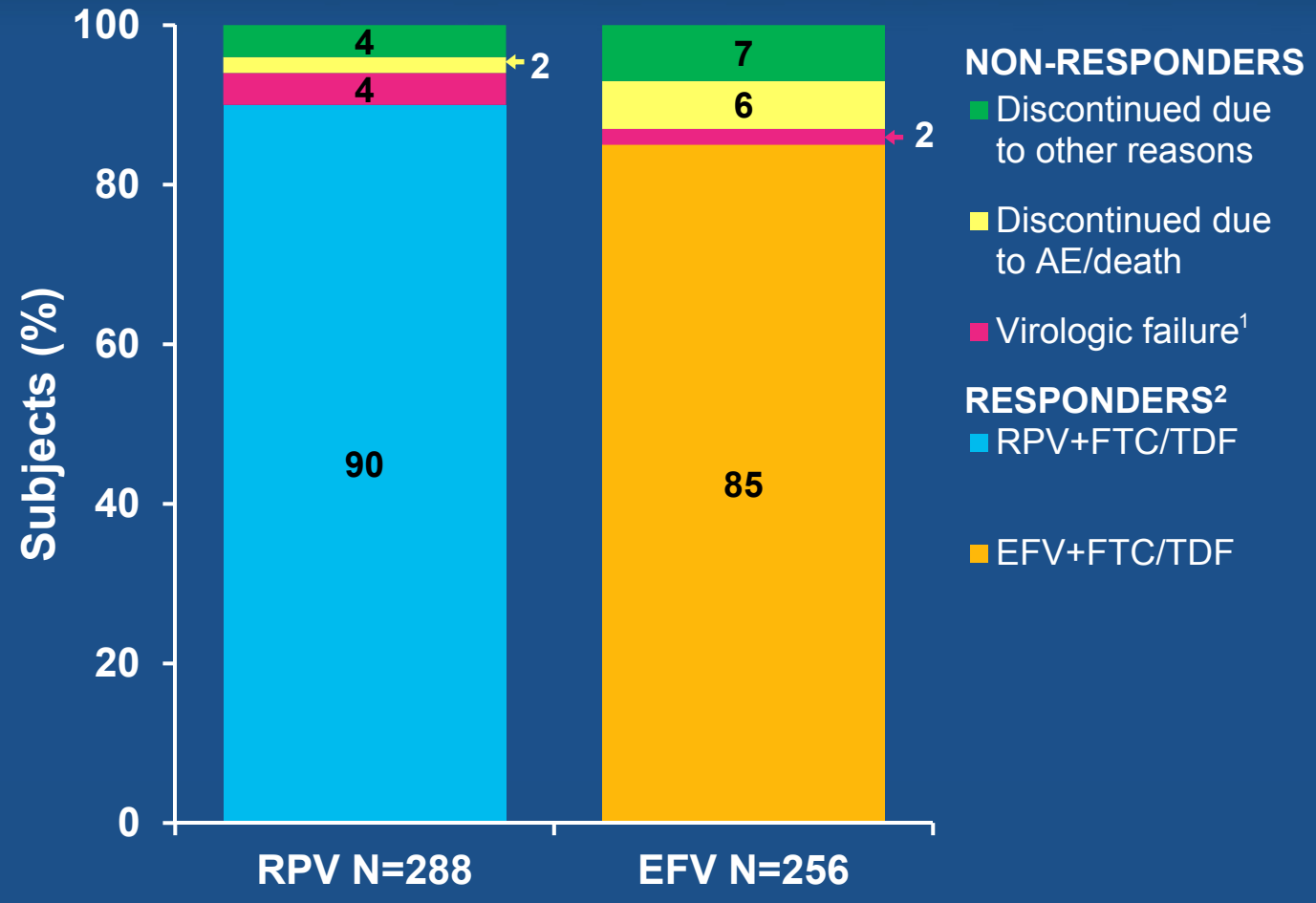
Randomized, double-blind, double-dummy, multicenter, 96-week studies



The overall study randomized 1368 subjects (ECHO, N=690; THRIVE, N=678). In ECHO, all subjects received FTC/TDF as the NRTI backbone. In THRIVE, N(t)RTI backbone was based on investigator choice, FTC/TDF (60%); AZT/3TC (30%); ABC/3TC (10%)

Rimsky L, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0302.

Pooled ECHO and THRIVE: Outcomes at Week 48 in Patients with HIV RNA ≤100,000 c/mL

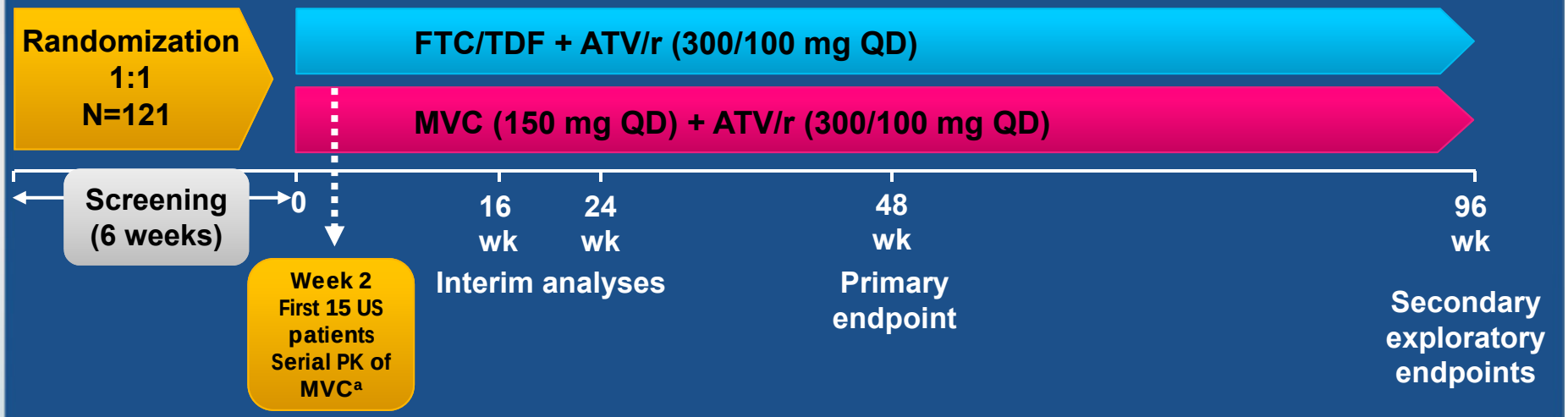


1 Responders-subjects with viral load <50 copies/mL, ITT-TLOVR algorithm
2 VF determined by TLOVR in the ITT Population; confirmed response before Week 48 and confirmed rebound (rebounders) at or before Week 48, or no response before Week 48 (never suppressed)

Rimsky L, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0302.

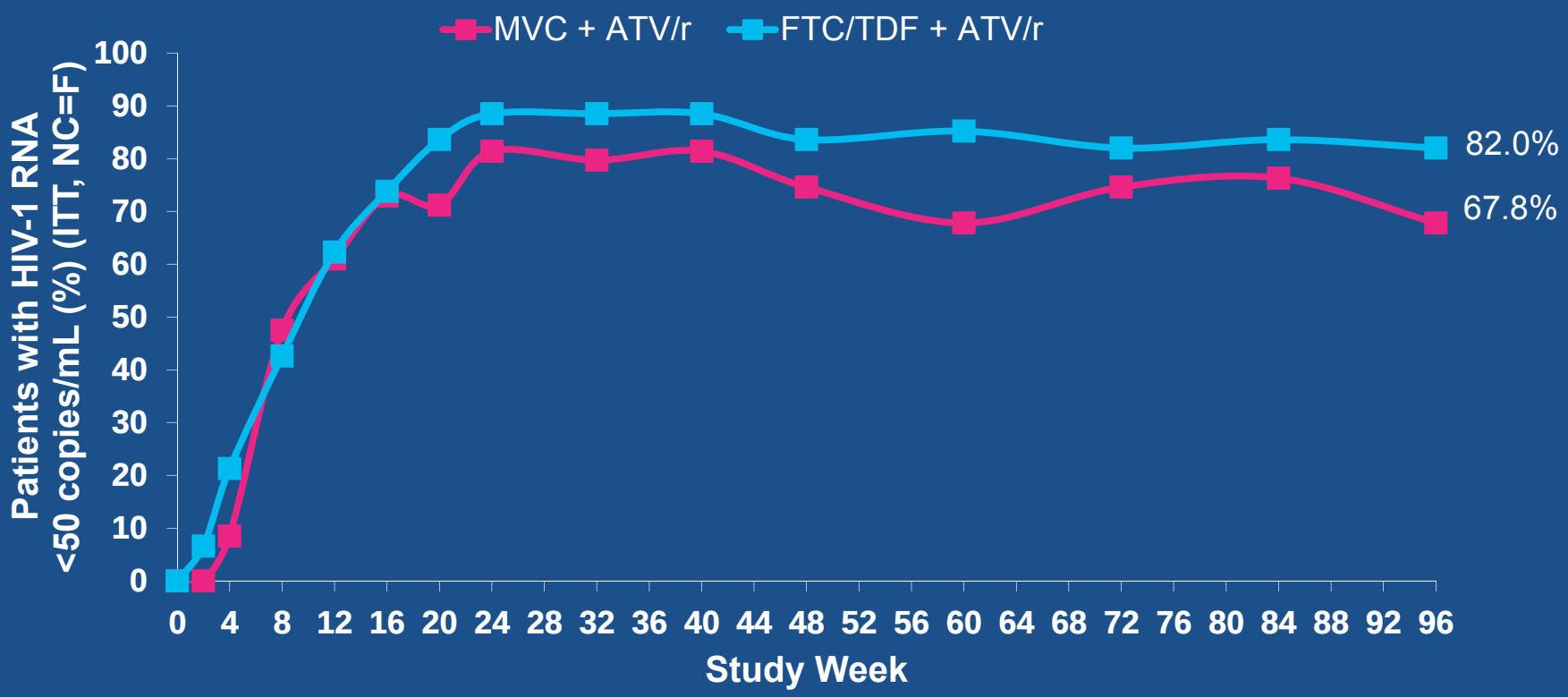
Study A4001078: ATV/r + MVC or FTC/TDF

Open-label, 96-Week Phase 2b Pilot Study Enrolling Patients with R5 HIV



Mills A, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0102.

Study A4001078: Outcomes at Week 96



CD4 response: FTC/TDF 264 vs. MVC 240 cells/mm^3

No resistance mutations or tropism change were seen in patients with VF

Mills A, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0102.

Study A4001078: Subjects with Detectable Viremia at Week 96

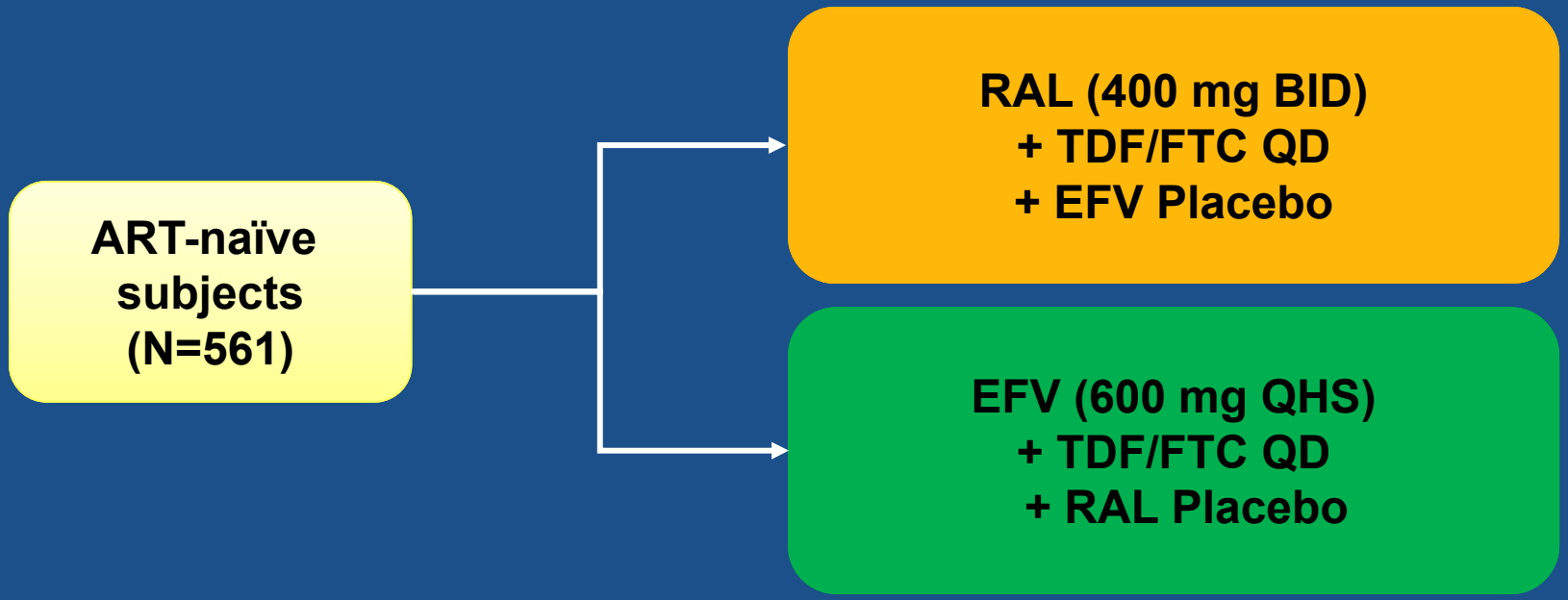
	HIV-1 RNA, copies/mL					
	Baseline	Week 48	Week 60	Week 72	Week 84	Week 96
MVC + ATV/r						
A	<100,000	**<50**	**<50**	**<50**	**<50**	7670
B	<100,000	**<50**	**<50**	135	66	73
C	<100,000	**<50**	**<50**	**<50**	**<50**	54
D[a]	<100,000	57	70	**<50**	*Missed visit*	81
E	≥100,000	81	102	145	**<50**	109
F	<100,000	167	99	**<50**	53	93
G	<100,000	87	**<50**	231	463	222
H[b]	<100,000	51	**<50**	137	<50	1200
FTC/TDF+ATV/r						
I	<100,000	**<50**	**<50**	**<50**	**<50**	77

a Ran out of medication and missed visits
b Missed dosing due to vomiting

Mills A, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0102.

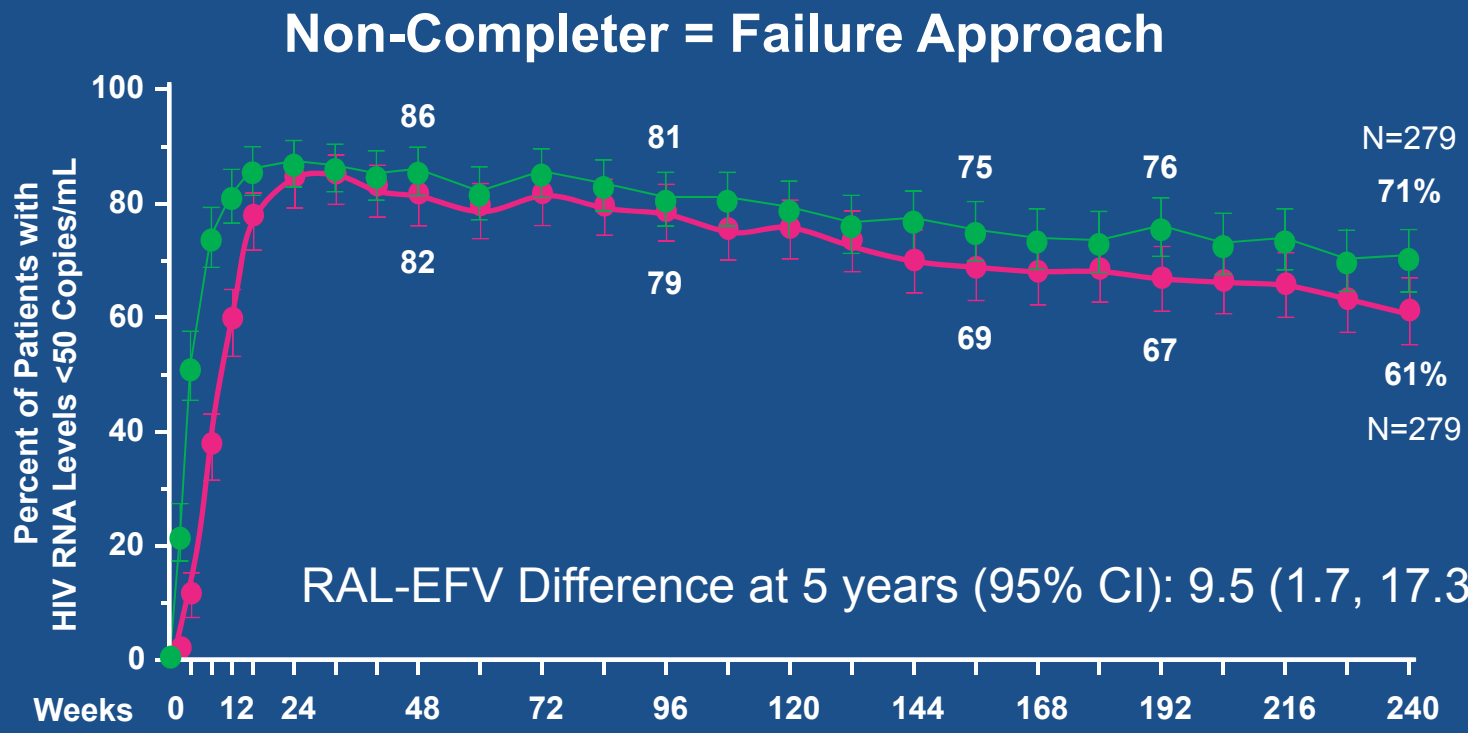
STARTMRK: Raltegravir vs. Efavirenz at 5 years

Randomized (1:1), double blind, study



Rockstroh J, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. LBPE19.

STARTMRK: Outcomes Through 5 Years



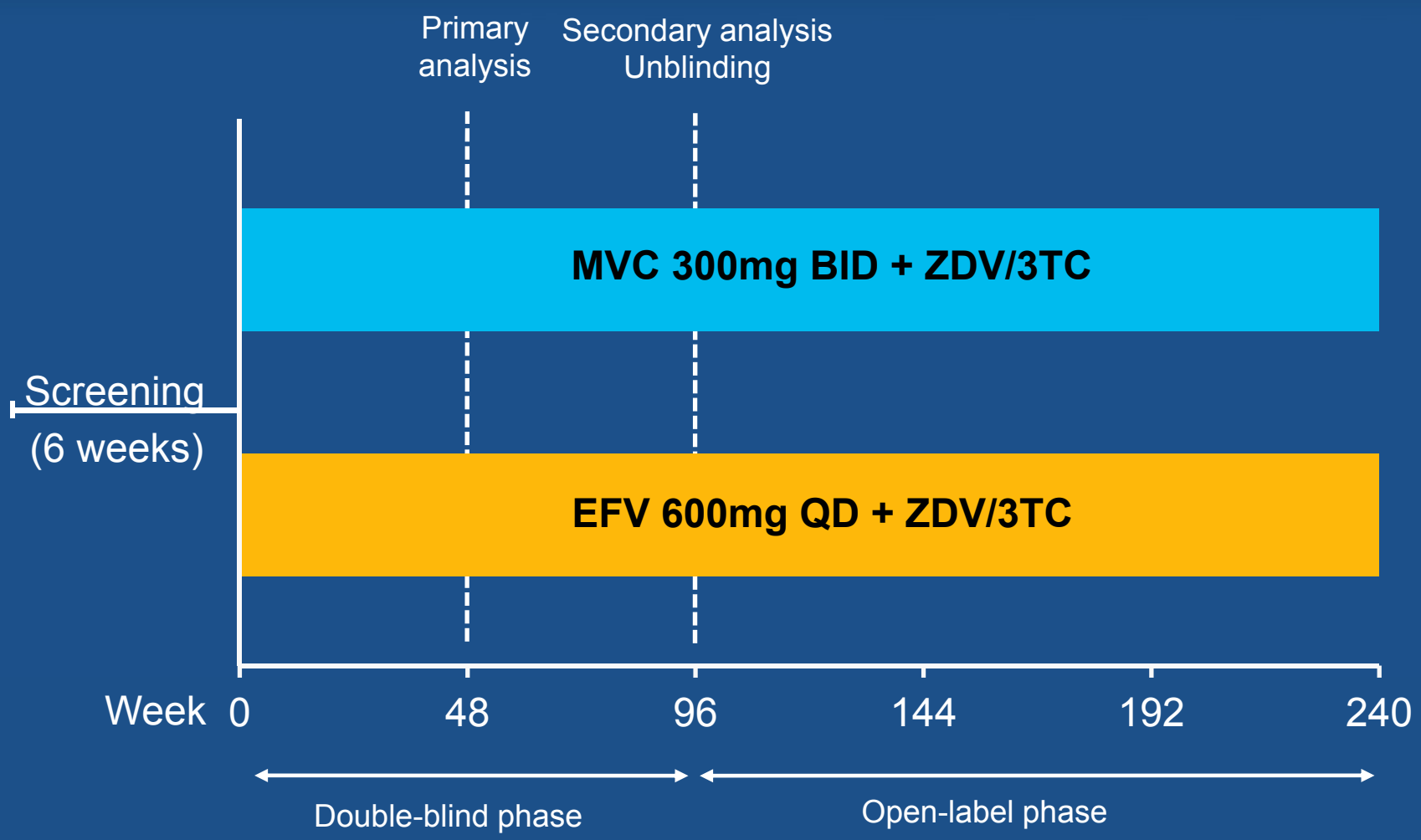
*At 5 years: P-value for non-inferiority <0.001; Met criteria for superiority.

Delta CD4 at 5 years: RAL 374 vs. EFV 312 cells/mm3

Any resistance over 5 years: RAL 2.5% vs. EFV 4.3%

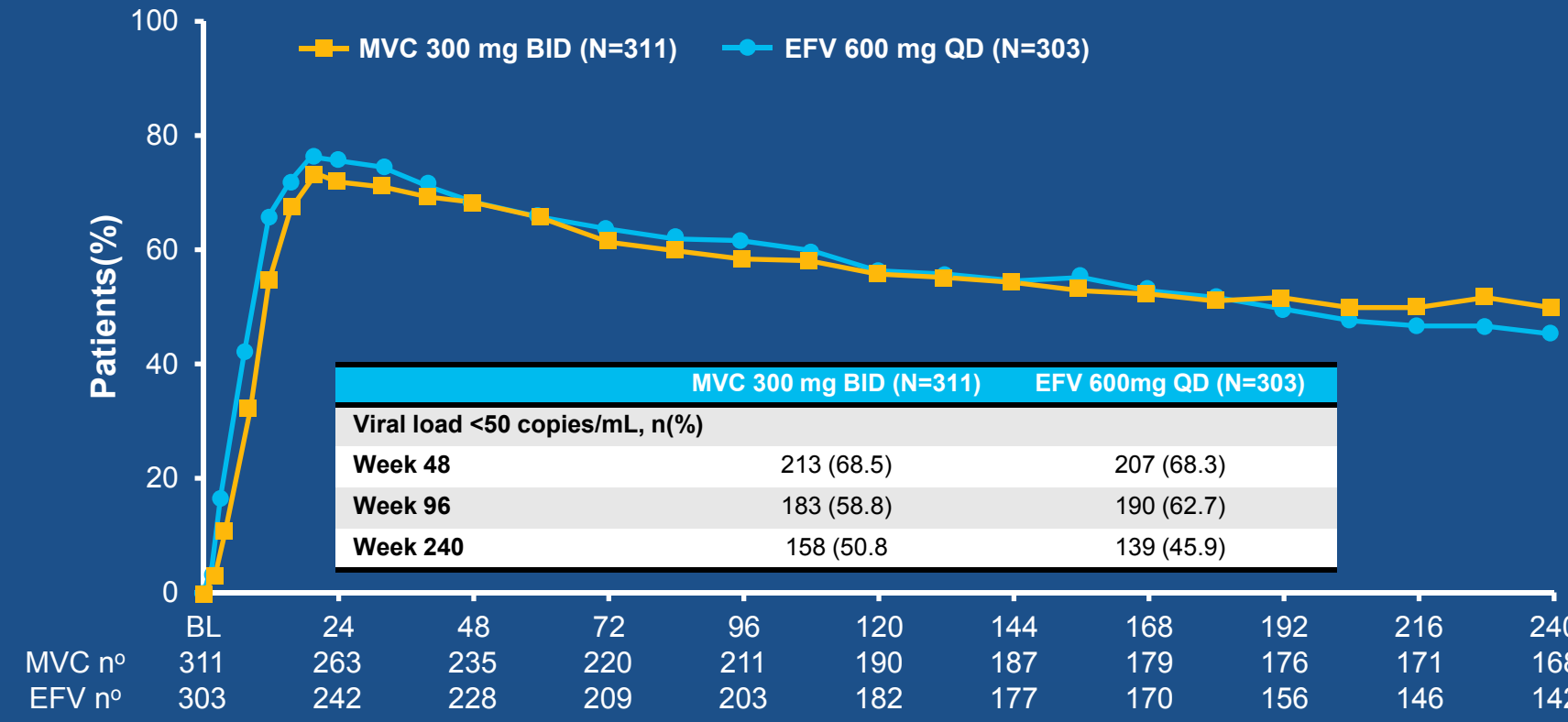
Rockstroh J, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. LBPE19.

MERIT: Maraviroc vs. Efavirenz at 5 years



Cooper D, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE026.

MERIT: Outcomes at 5 Years (R5 Trofile ES Cohort)



	MVC 300 mg BID (N=311)	EFV 600mg QD (N=303)
Viral load <50 copies/mL, n(%)		
Week 48	213 (68.5)	207 (68.3)
Week 96	183 (58.8)	190 (62.7)
Week 240	158 (50.8	139 (45.9)

CD4 Change at 240 weeks: MVC + 293 vs. EFV +271 (P=NS)

Cooper D, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE026.

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV THERAPIES AND THERAPEUTIC STRATEGIES

Reporting From

THE XIX INTERNATIONAL AIDS CONFERENCE (AIDS 2012)

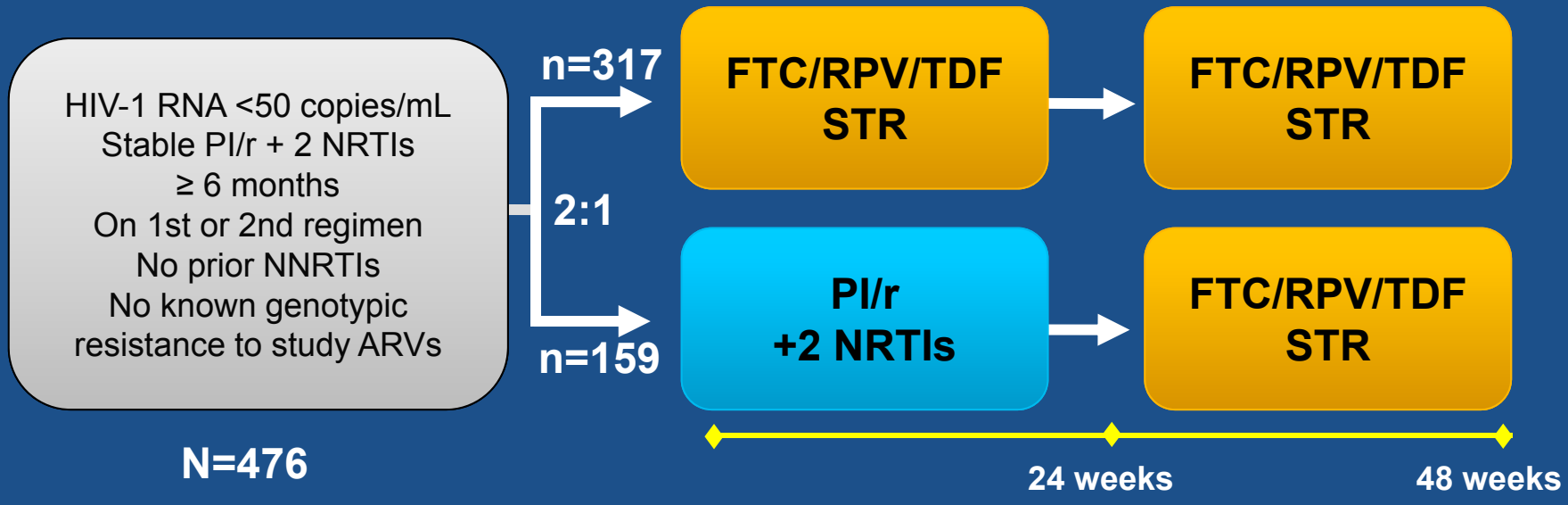
Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Treatment Experienced Patient Studies

Calvin Cohen, MD
Research Director, CRI New England
Clinical Instructor, Harvard Medical School
Boston, Massachusetts

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

SPIRIT: Switching from PI/r to Rilpivirine



- Primary Endpoint:
  - Non-inferiority (12% margin) to PI + RTV + 2 NRTIs by FDA snapshot analysis HIV-1 RNA <50 c/mL at 24 weeks

SPIRIT: Baseline Demographics and Regimens

Variable	FTC/RPV/TDF N = 317	PI/r + 2 NRTIs N = 159
Median age (years)	42	43
Female	14%	9%
Race		
White	76%	78%
Black	19%	14%
Latino Ethnicity	16%	20%
Median years since on ART	2.9	2.6
Mean CD4 cell count, cells/mm^3 (SD)	576 (237)	600 (259)

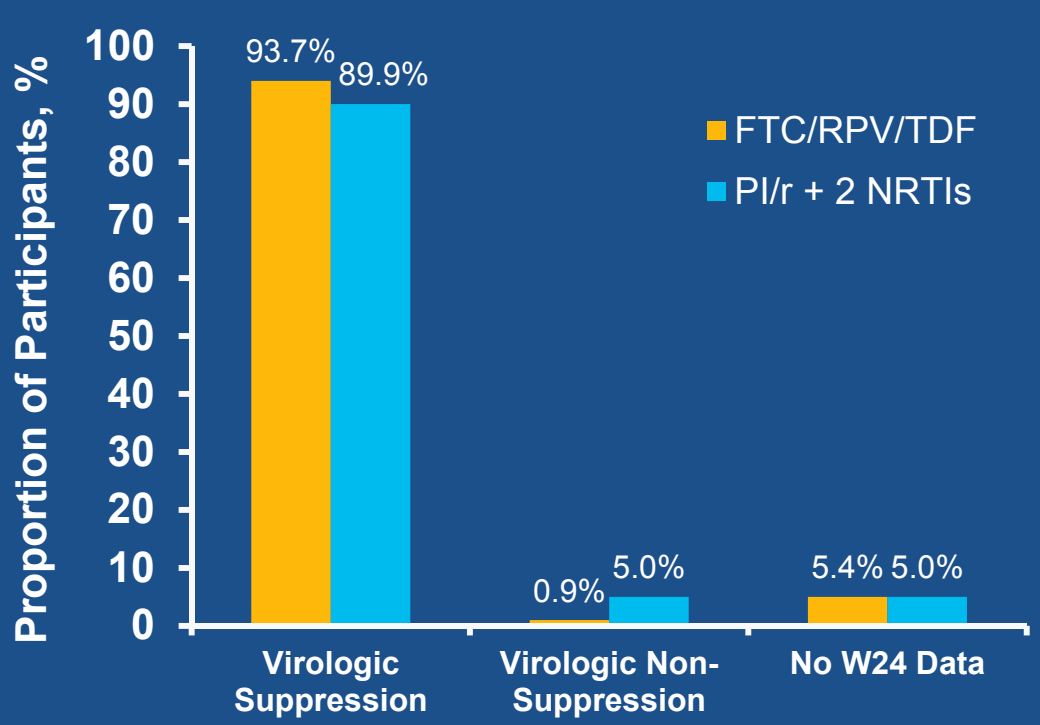
NRTI	
FTC/TDF	80.9%
3TC/ABC	13.2%

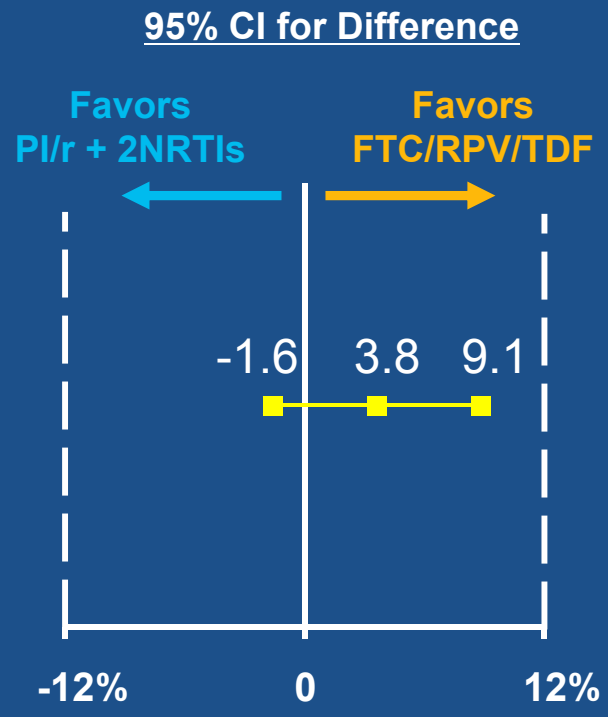
RTV-boosted PI	
ATV	37.0%
LPV	32.6%
DRV	20.2%

Palella F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0104.

SPIRIT: Virologic Suppression at Week 24 (Primary Endpoint)

FDA Snapshot Analysis – ITT Population

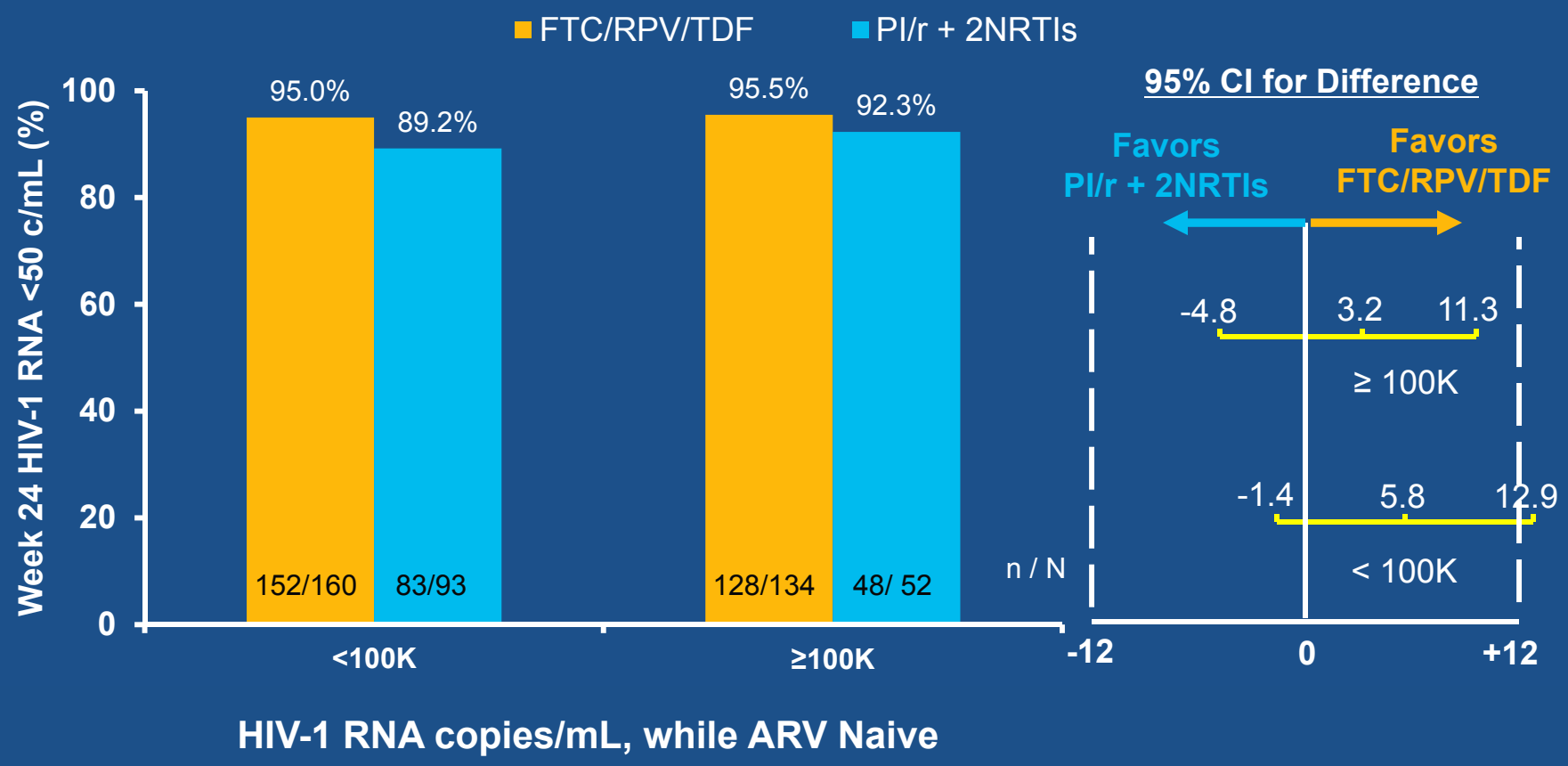




Change in CD4 count (cells/mm^3) : FTC/RPV/TDF +20 vs. PI/r +32 (p=0.28)

Palella F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0104.

SPIRIT:
Pre-Treatment Viral Load and Outcomes

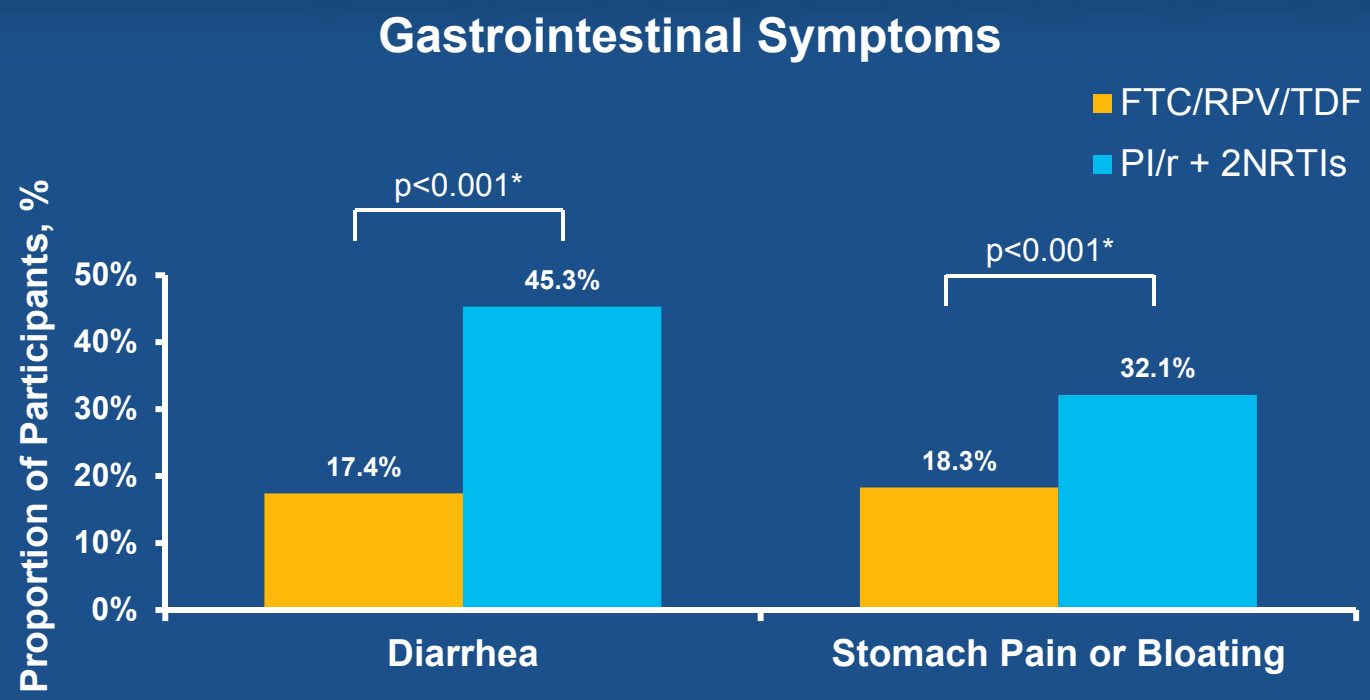


- N=17 (5.4%) had pretreatment K103N mutation – all maintain VL<50 on RPV**

**White, et al. IHDRW 2012; Sitges, Spain. #49

Palella F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0104.

SPIRIT: Adverse Events



- Switch to RPV: Significantly less fatigue, memory loss, headache, depression, and increased treatment satisfaction (all p<0.03)
- Reasons for DC on RPV: back pain/hot flush/sweats, cough/dyspnea/throat tightness/fatigue, depression, depression/agitation/anxiety, insomnia, renal impairment/glycosuria/proteinuria

Palella F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0104.

SPIRAL Study: Post hoc assessment of response by NRTIs

- SPIRAL: Pts suppressed on PI/r based regimen
  - Randomized to stay on PI/r or change to RAL

RAL arm	ABC/3TC	TDF/FTC	95% CI ABC-TDF
Treatment failure	11%	11%	0.15 (-17.9 – 11.6)
Virologic failure	3.7%	4.1%	-.41 (-8.3 – 14.4%)

PI/r Arm	ABC/3TC	TDF/FTC	95% CI ABC-TDF
Treatment failure	14.8%	17.1%	-2.33 (-16.1 – 16.7)
Virologic failure	7.4%	5.7%	1.7 (-18 – 8.0%)

  - Conclusion: Both NRTIs similarly active in both arms

Martinez E , et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE093.

Inflammatory Marker Changes with NRTI Switches

- Pts suppressed on ABC/3TC based regimen (majority with PI/r)
- Randomized to stay (n=13) or switch to TDF/FTC (n=14)

Median Biomarker Levels at 6 Months

	3TC/ABC	FTC/TDF	P-value
hsCRP (IQR), µg/mL	1.8 (0.9, 3.3)	1.3 (0.6, 2.6)	0.04
Inflammation/Coagulation Rank Composite (IQR)	16.3 (13.5, 19.5)	8.8 (7.2, 12.8)	0.001
Vascular Rank Composite, (IQR)	12.0 (10.8, 14.8)	12.2 (11.1, 14.9)	0.82

- Conclusion: switching from ABC/3TC to TDF/FTC-based ART in suppressed pts. may significantly reduce inflammation

- (hsCRP), interleukin-6 (IL-6), and D-dimer; Vascular rank composite = average of ranks for soluble inter-cellular adhesion molecule (sICAM-1), serum thrombomodulin (sTM), von Willebrand Factor (VWF), and asymmetric dimethylarginine (ADMA)

Alozie O, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THPE093.

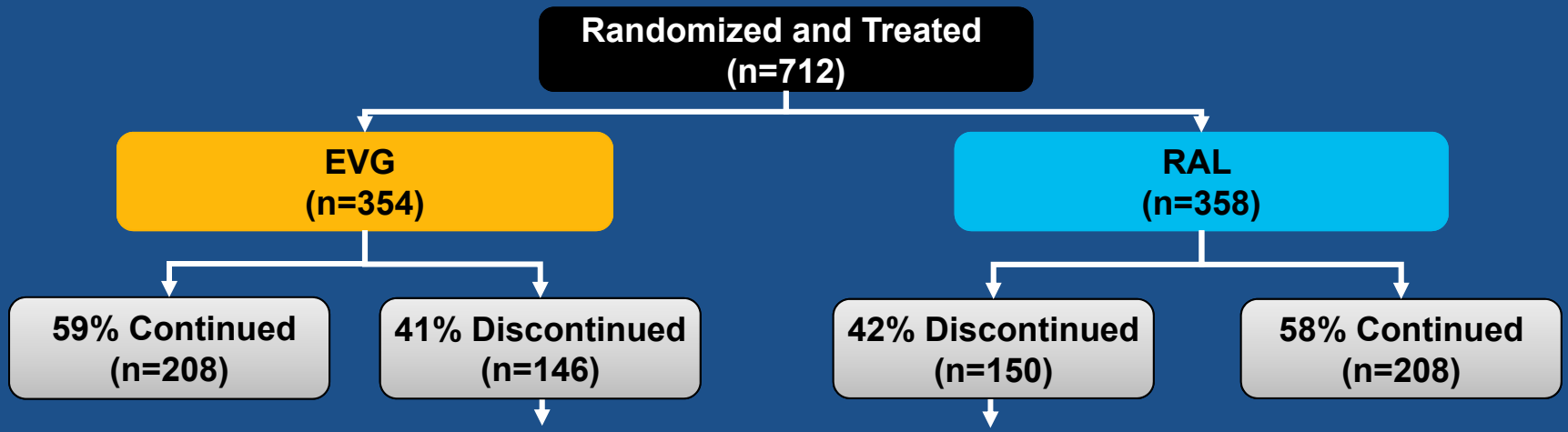
Notable Investigational Antiretrovirals

	NRTI	NNRTI	Protease Inhibitor	Entry Inhibitor	Integrase Inhibitor
Phase 3					elvitegravir dolutegravir
Phase 2	apricitabine DAPD dexelvucitabine festinavir GS-7340	BILR 355 lersivirine		BMS-663068 cenicriviroc ibalizumab PF-232798	S/GSK'744
Phase 1/2	amdoxovir BMS-986001 elvucitabine	GSK 2248761	TMC 310911	HGS004	

Adapted from: Gulick R, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB01

Study 145: Elvitegravir vs. Raltegravir in Treatment Experienced Patients

Eligible Pts: Treatment experienced and/or resistance to 2 or more ARV classes and VL > 1000 c/mL on current regimen

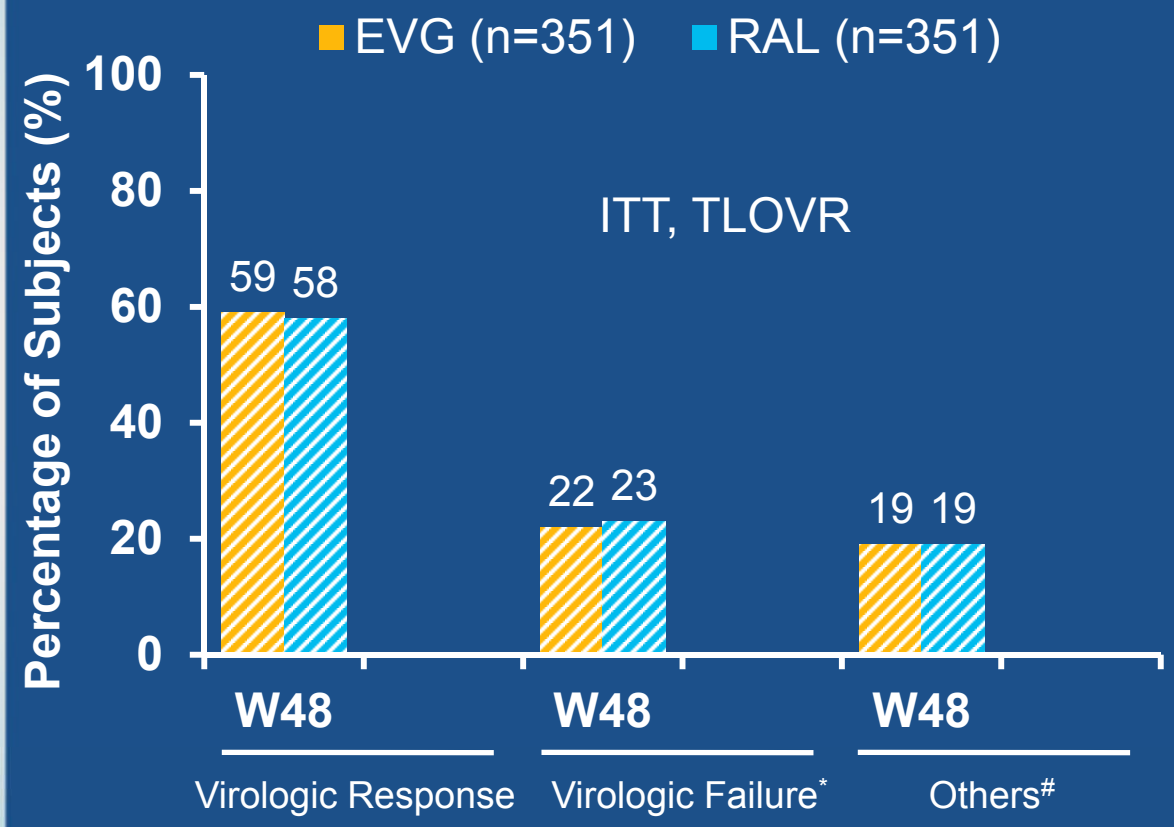


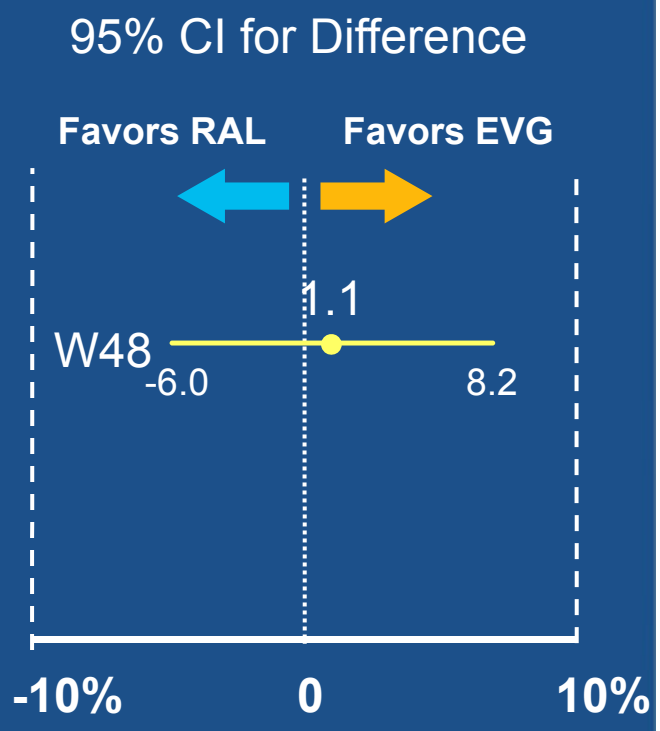
Most common Reasons in >10 arm

39	Patient non-compliance	34
30	Withdrew consent	17
29	Lost to follow-up	31
17	Lack of efficacy	21
11	Adverse event	15
11	Protocol violation	14

Elion R, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0105.

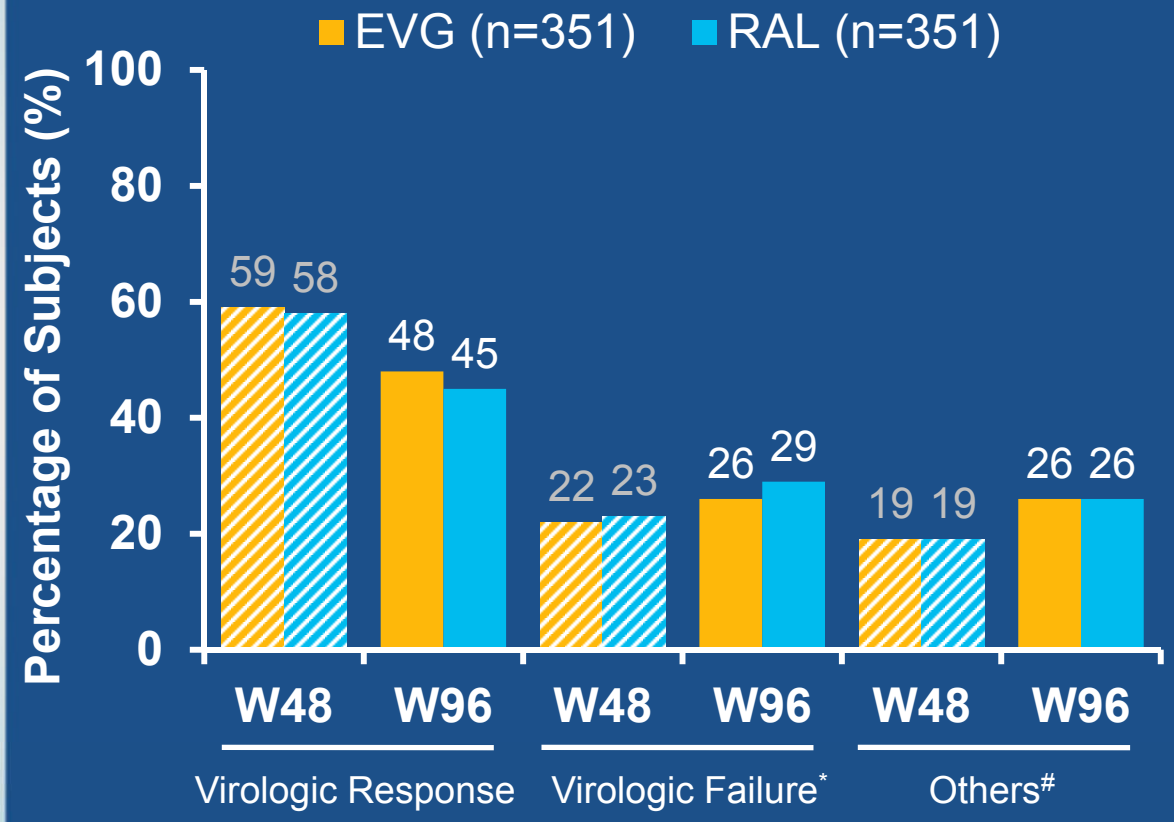
Study 145: HIV-1 RNA <50 c/mL Weeks 48 and 96

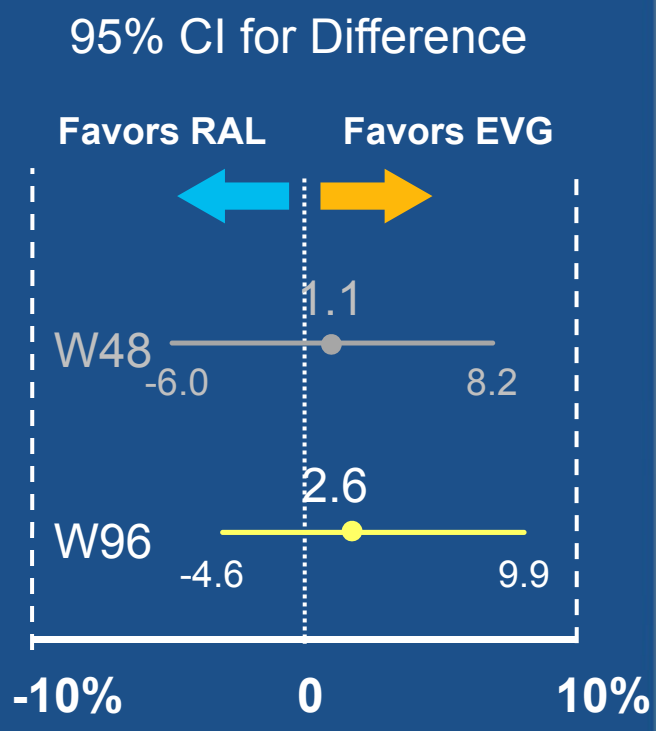




Elion R, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0105.

Study 145:
HIV-1 RNA <50 c/mL Weeks 48 and 96





Elion R, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0105.

Study 145: Adverse Events Significantly Different Between Arms

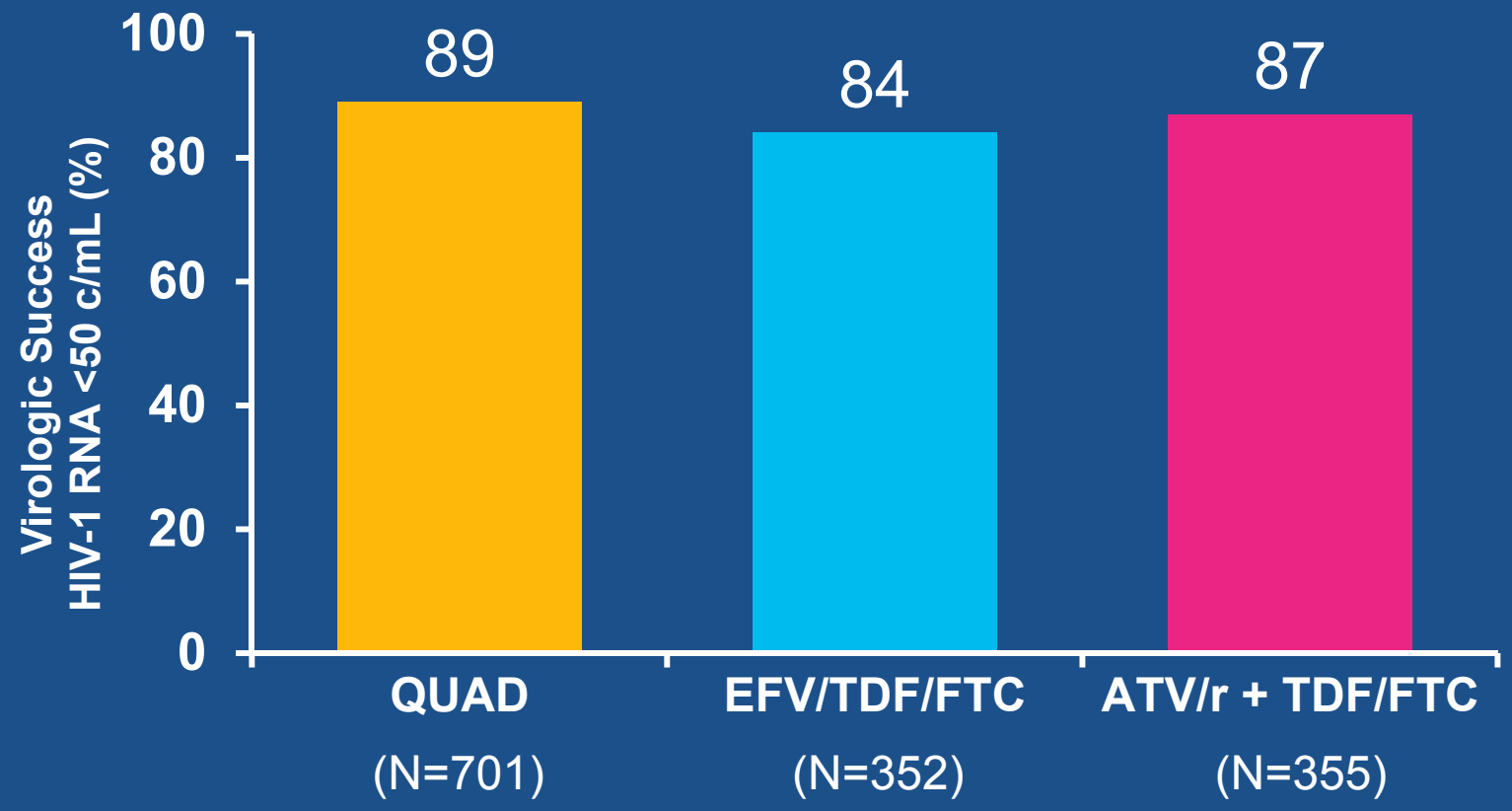
Grade 2-4 Adverse Event in >5%	EVG (n=354)	RAL (n=358)
Any Grade 2-4 AE at Week 96	68%	68%
Diarrhea*	13%	8%

Grade 3-4 laboratory abnormality	EVG (n=354)	RAL (n=358)
Any Grade 3-4 laboratory abnormality	37%	42%
AST**	2%	6%
ALT**	2%	5%
GGT**	3%	7%

*P=0.02
**P≤0.05

Elion R, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0105.

Studies 102 and 103: Combined QUAD Resistance Analysis



High and comparable efficacy of all regimens compared

White IWDR 2012; Abst. 4.

Studies 102 and 103: Genotypic and Phenotypic Analysis of the QUAD Virologic Failures with Emergent Resistance

Virology Patient	Genotype											Phenotype[a]		
	NRTI			INSTI								Fold-Change vs WT		
				Primary				Secondary				EVG	TFV	FTC
1	A62A/V	K65R	M184V			Q148R				G140C		>198	1.59	>84
2	A62A/V	K65R	M184V		E92Q				H51H/Y	L68V		149	1.49	>89
3		K65R	M184V		E92Q						S153A	111	1.07	>108
4	ND			T66T/I	E92E/Q		N155N/H				E157E/Q	54	ND	ND
5			M184V		E92E/Q	Q148Q/R	N155H/N					51	0.72	>108
6			M184V		E92Q							44	0.46	>121
7			M184V		E92Q							36	0.46	>76
8			M184V				N155H					36	0.54	>126
9			M184I		E92Q							28	0.48	>104
10			M184V			Q148R						23	0.74	>126
11			M184V	T66T/I	E92E/Q							5.55	0.64	>153
12		K65K/R	M184M/I									1.78	0.67	116
13			M184V									1.05	0.44	>88

- PhenoSense PR/RT or IN (Monogram Biosciences). Phenotype above the defined assay cutoffs are colored red (FC above the biological or lower clinical cut-off) or green (at or below the cut-off)

All patients with phenotypic resistance to a component of QUAD had a primary resistance-associated mutation

ND= no data due to assay failure.

White IWDR 2012; Abst. 4.

Potential Cross Resistance between Integrase Inhibitors: RAL, EVG and DTG

INSTI	Virology Patient										
	1	2	3	4	5	6	7	8	9	10	11
EVG	>198	149	111	54	51	44	36	36	28	23	5.6
RAL	28	6.2	3.8	6.0	12	3.6	3.0	11	3.3	8.7	1.8

Biological Cut-Offs: EVG 2.5; RAL 1.5
Mead fold change value for EVG was >67-fold
Mean fold change value for RAL = 7.9-fold

Viking Study: DTG in Patients Who Failed RAL

- 75% achieved VL <50 c/mL by wk 24
- 5/24 patients (21%) experienced virologic failure
- 3 had treatment-emergent integrase resistance mutations
  - Pt 1: T97T/A, E138E/K, N155H
  - Pt 2: E92E/Q, T97T/A
  - Pt 3: E138E/K, N155H
  - All had increase in phenotypic resistance to >40x to DTG

White IWDR 2012; Abst. 4; Vavro IWDR 2012; Abst. 5.

FEM-PREP: Potential Resistance with PrEP

Clinical Resistance (geno/pheno)	Status at Enrollment			
	RNA Positive		RNA Negative	
	Placebo N=1	FTC/TDF N=1	Placebo N=35	FTC/TDF N=33
K65R	0	0	0	0
K70E	0	0	0	0
M184I	0	0	0	1
M184V	0	0	1	3
Minor Variant				
K65R	0	0	0	0
K70E	0	0	1 (0.56%)	0
M184I	0	0	1 (0.72%)	0
M184V	0	0	0	1 (0.66%)

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV THERAPIES AND THERAPEUTIC STRATEGIES

Reporting From

THE XIX INTERNATIONAL AIDS CONFERENCE (AIDS 2012)

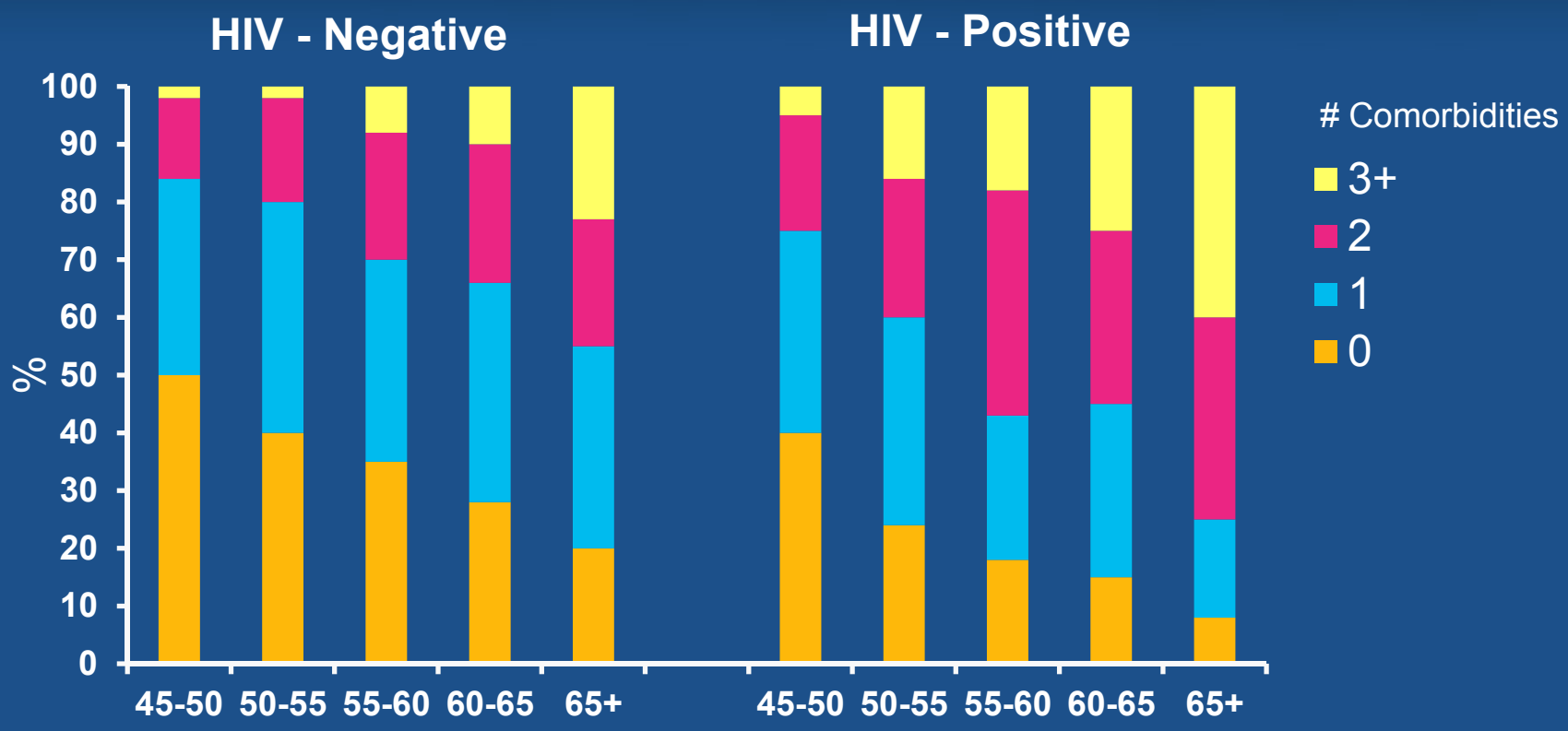
Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Adverse Events and Metabolics

Graeme Moyle, MD, MB, BS
Associate Director of HIV Research
Chelsea & Westminster Hospital
London, UK

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

Amsterdam Aging Cohort: Comorbidity by Age and HIV Status



	HIV - Negative					HIV - Positive				
Mean Number of AANCC	0.68	0.80	1.03	1.15	1.47	0.89	1.35	1.52	1.65	2.04
Number of Participants	166	108	70	53	34	159	111	86	62	52

After Adjustment: HIV infection, duration and ART duration were risks for comorbidities

Schouten J, et al. !4th IWCADRH; Washington, DC; July 19-21, 2012; O24

ATV/r vs. DRV/r in Healthy Volunteers for 4 Weeks

	Difference at week 4 (week 4 - week 0)		
	ATV/r (n=10)	DRV/r (n=10)	p value
Total cholesterol, mg/dl	11.6 (5)	30.9 (7.35)	0.041
HDL cholesterol, mg/dl	1.55 (1.55)	2.31 (1.55)	0.495
LDL cholesterol, mg/dl	4.25 (3.87)	25.52 (7.35)	0.017
Total: HDL cholesterol	0.06 (0.15)	0.42 (0.21)	0.174
Triglycerides, mg/dl	32.8 (9.74)	17.7 (14.2)	0.545
Apolipoprotein A1, mg/dl	17.7 (10.6)	15.06 (6.2)	0.940
Apolipoprotein B, mg/dl	12.4 (6.2)	23 (4.42)	0.257
AIx-75, %	3.15 (3.84)	-0.35 (1.91)	0.762

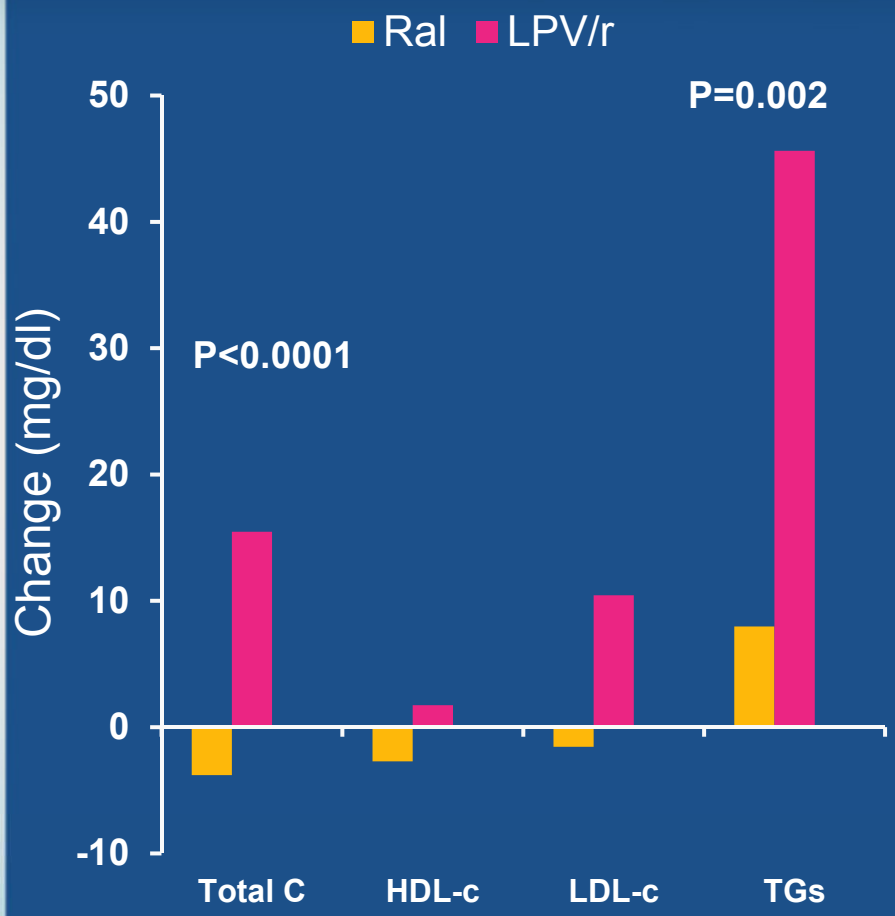
Values reported as mean (SE) unless otherwise stated

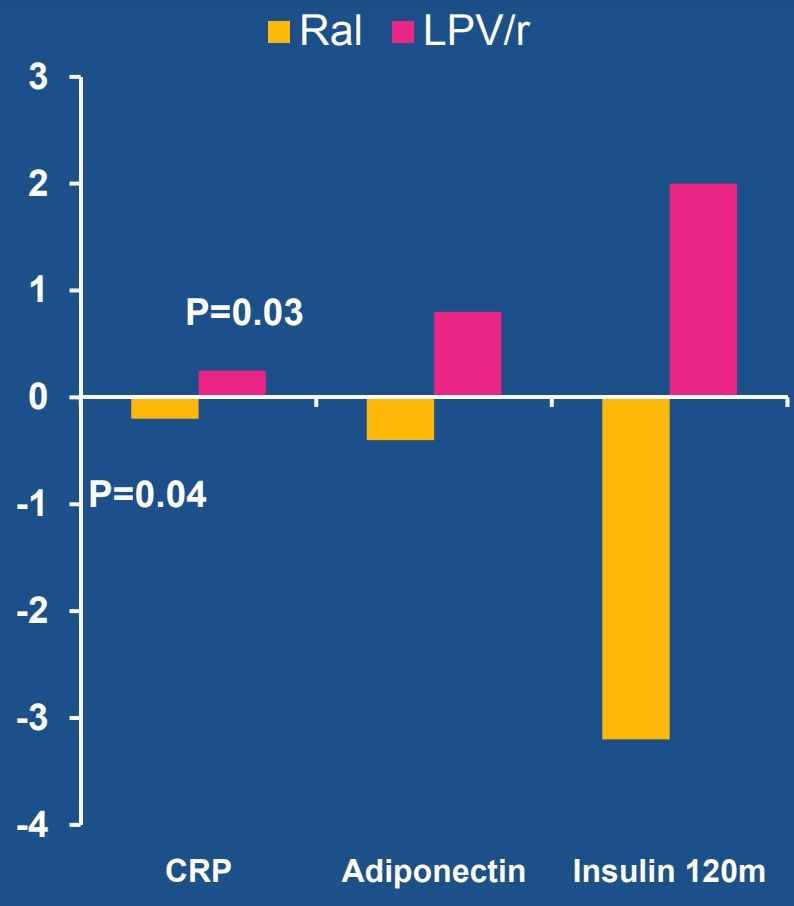
- ATV/r associated with lower post-prandial arterial stiffness (AIx-75) by tonometry than DRV/r

Arm	'Stiffness' ΔiAUC, h% (SE)
ATV/r (n=10)	-27.60 (11.63)
DRV/r (n=10)	0.08 (4.68)

Lee F, et al. !4th IWCADRH; Washington, DC; July 19-21, 2012; O12

Raltegravir vs Lopinavir/r in Volunteers for 2 Weeks: Change from Baseline in Lipids and Biomarkers



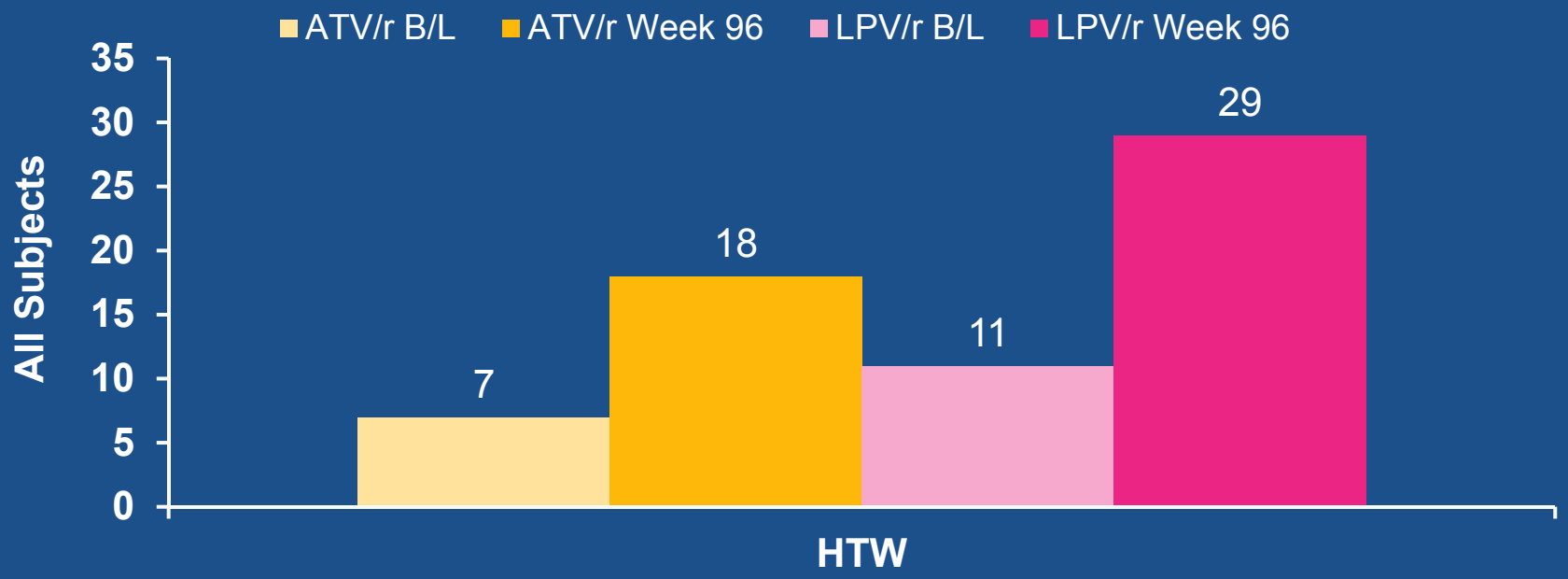


P values = versus baseline

Moyle G, et al. !4th IWCADRH; Washington, DC; July 19-21, 2012; O14

CASTLE: Emergent Hypertryglyceridemic Waist (HTW) Phenotype at Through Week 96 by TDF/FTC +ATV/r vs. LPV/r

New onset of HTW phenotype for combined genders increased by 10.4% on ATV/r and 18.2% on LPV/r over 96 weeks



- Significant differences in changes in VAT, SAT and limb fat changes were noted between ATV/r and LPV/r among subjects with the lowest baseline BMI (<22) and lowest baseline CD4 cell counts (<50)
- In patients taking LPV/r, a gain in fat, in particular VAT, is often associated with a notable increase in TG levels and may increase the risk of cardiovascular diseases

HTW= hypertriglyceridemic waist phenotype (HWC=high waist circumference, HTG=high triglycerides)

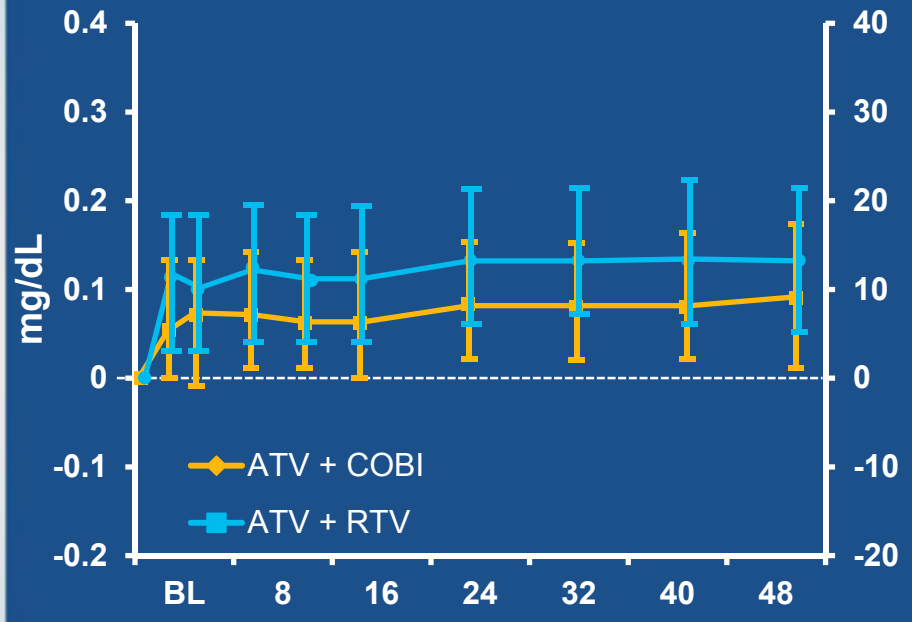
Moyle G, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. MoPE081

SPRING 2: Renal Safety

		DTG 50 mg QD n=411	RAL 400 mg BID n=411
Creatinine			
Median change (IQR) from baseline (mg/dL)	Week 48	0.14 (0.08, 0.20)	0.06 (0.00, 0.10)
Maximum emergent toxicity	Grade 1	10 (2%)	7 (2%)
	Grade 2	1 (<1%)	0
Urine albumin/creatinine			
Median change (IQR) from baseline (mg/mmol CR)	Week 48	0.00 (-0.30, 0.20)	0.00 (-0.20, 0.20)

GS 114: Changes in Serum Creatinine and eGFR

Change in Serum Creatinine, Median [IQR]



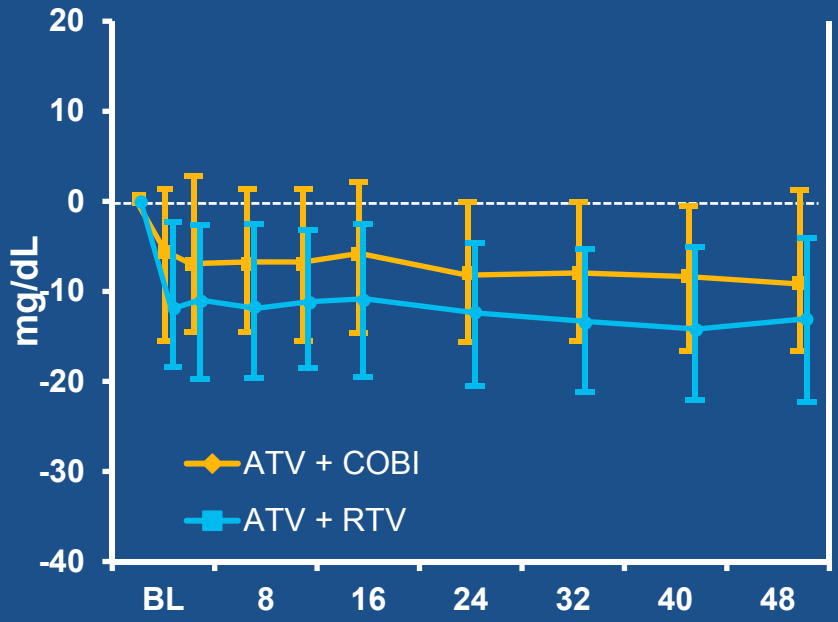
Change in Cr at Week 48

ATV + COBI: 0.13 mg/dL

ATV + RTV: 0.09 mg/dL

(*P*<0.001)

Change in eGFR, Median [IQR]



Change in eGFR at Week 48

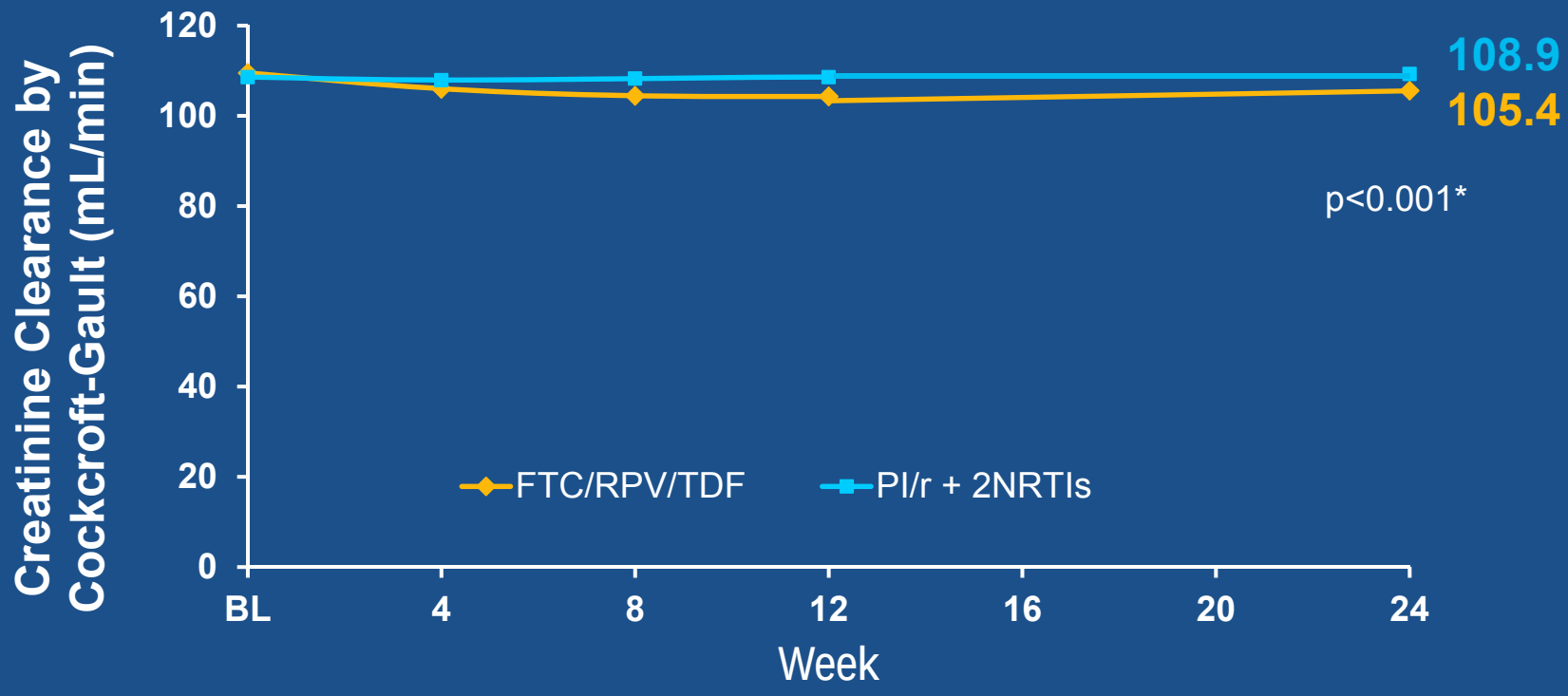
ATV + COBI: -12.9 mL/min

ATV + RTV: -9.1 mL/min

(*P*<0.001)

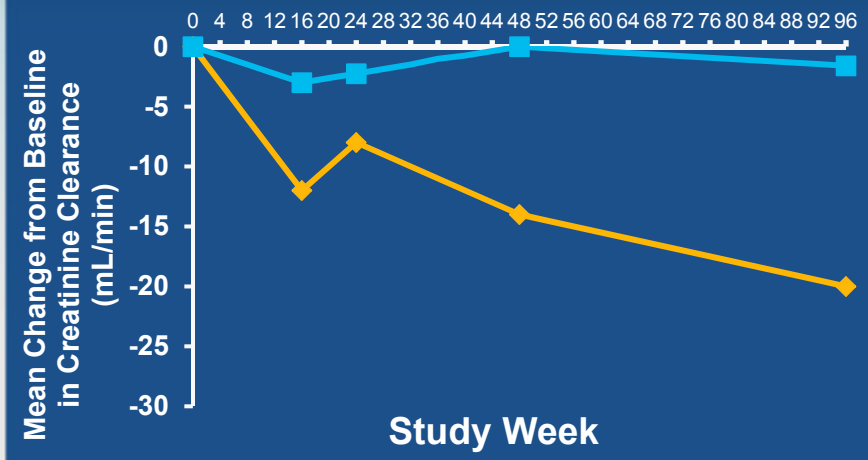
Gallant J, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0103

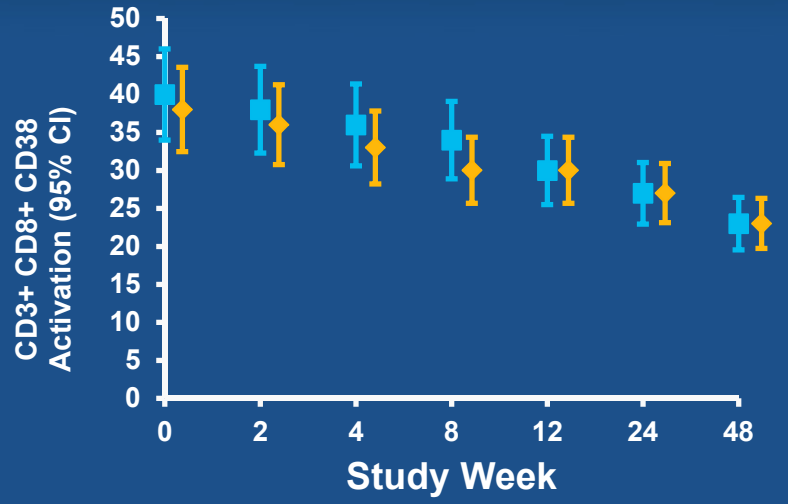
SPIRIT: Change from Baseline to Week 24 in eGFR (Cockcroft-Gault)

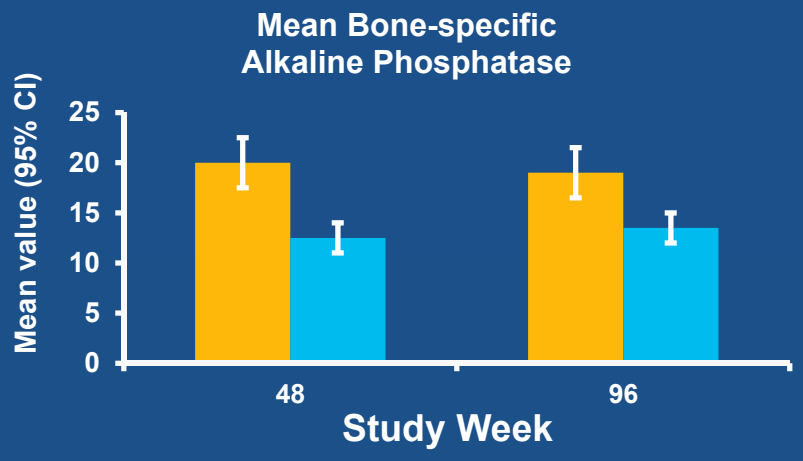


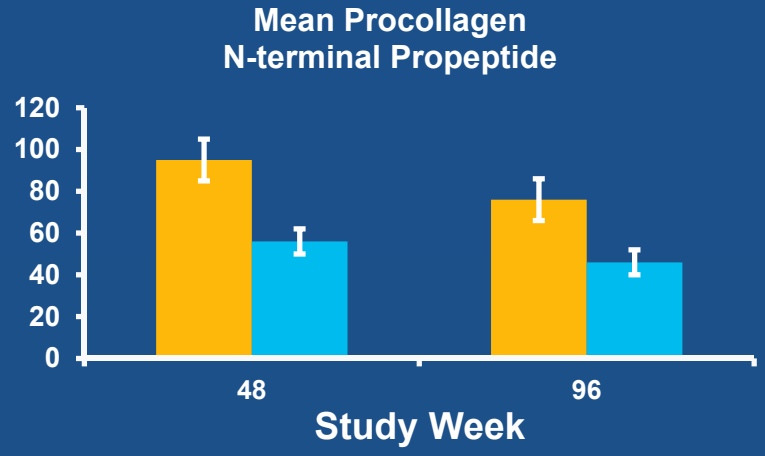
Palella F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0104

Study A4001078: Renal, Immune Activation and Bone Outcomes Week 96





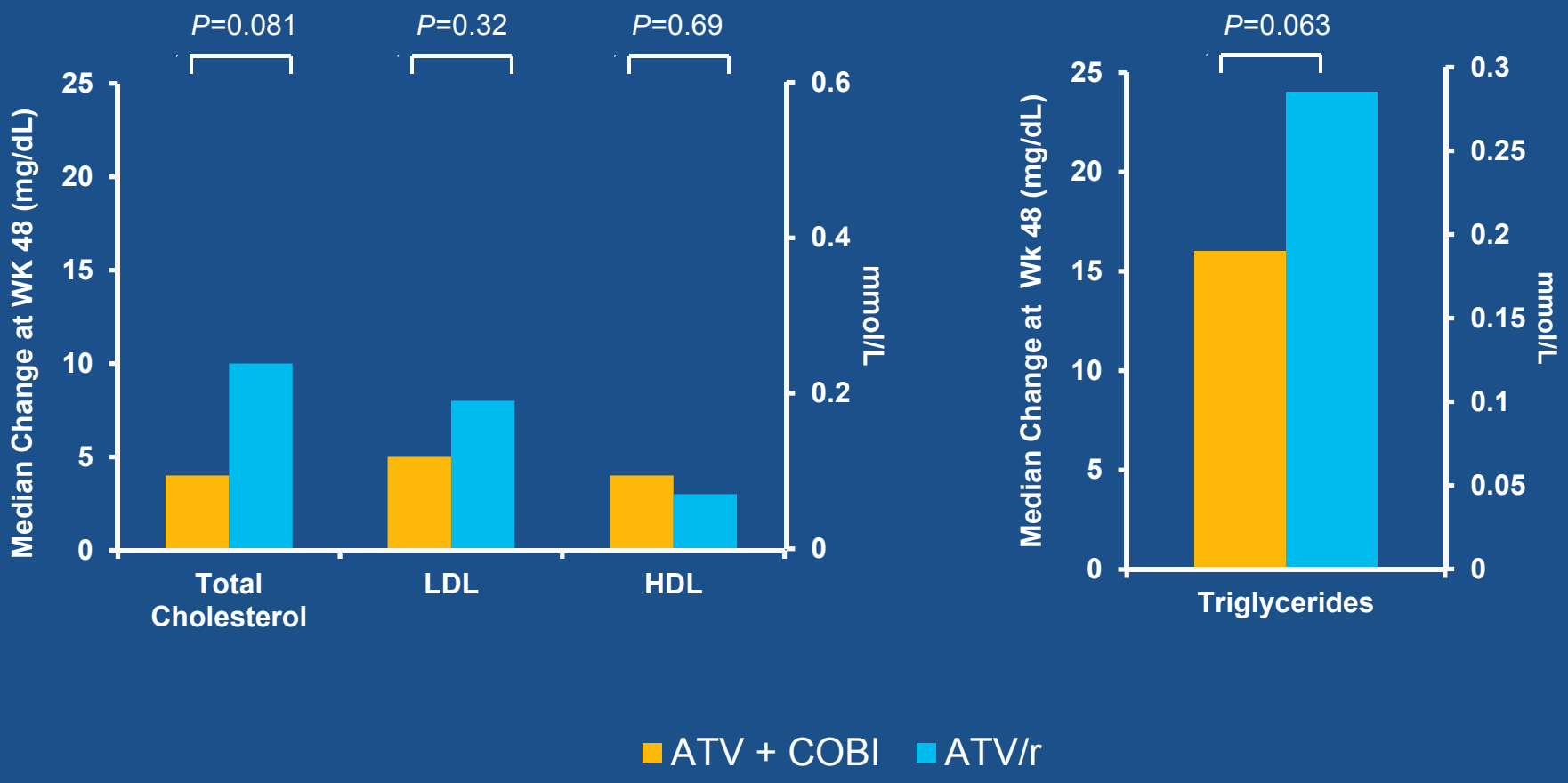




FTC/TDF + ATV/r (n=61) MVC + ATV/r (n=60)

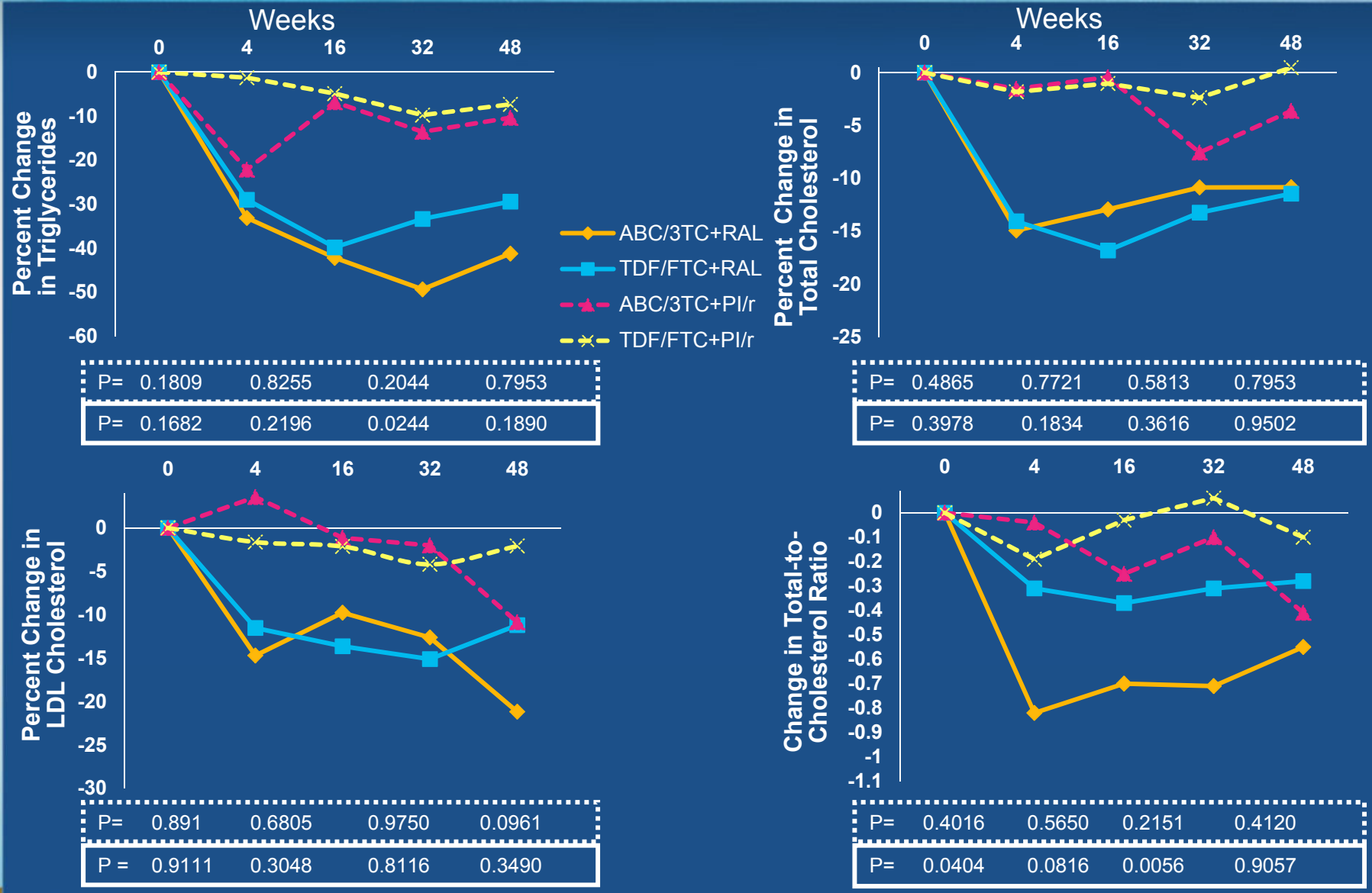
Mills A, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0102

GS 114: Changes in Fasting Lipids



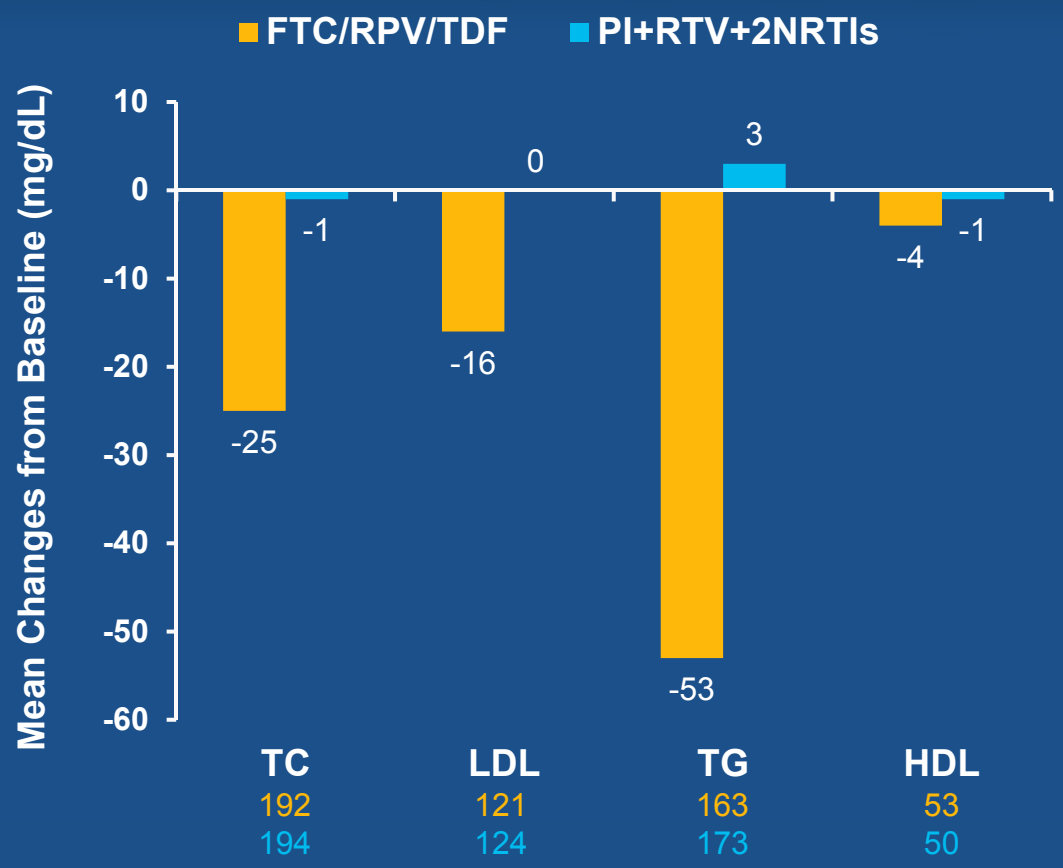
Gallant J, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0103

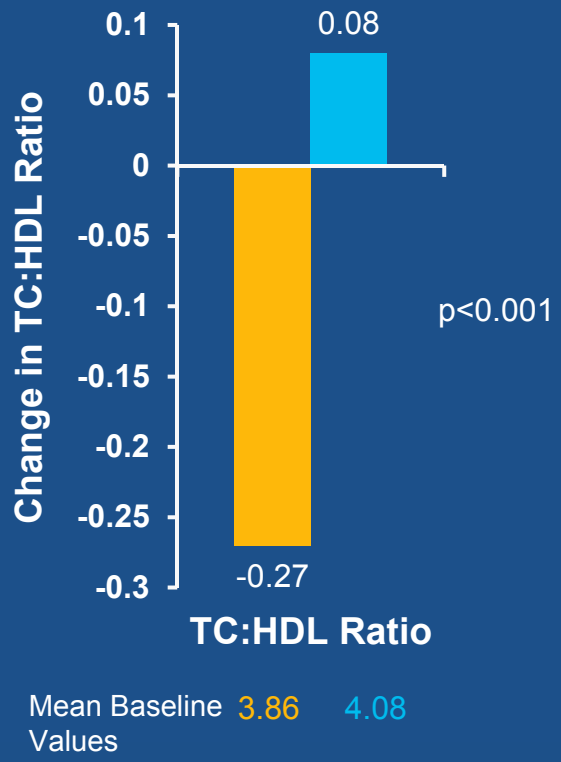
SPIRAL: Change in Key Lipids by NRTI Backbone



Msrtinez E et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUPE093

SPIRIT: Changes from Baseline to Week 24 in Fasting Lipids



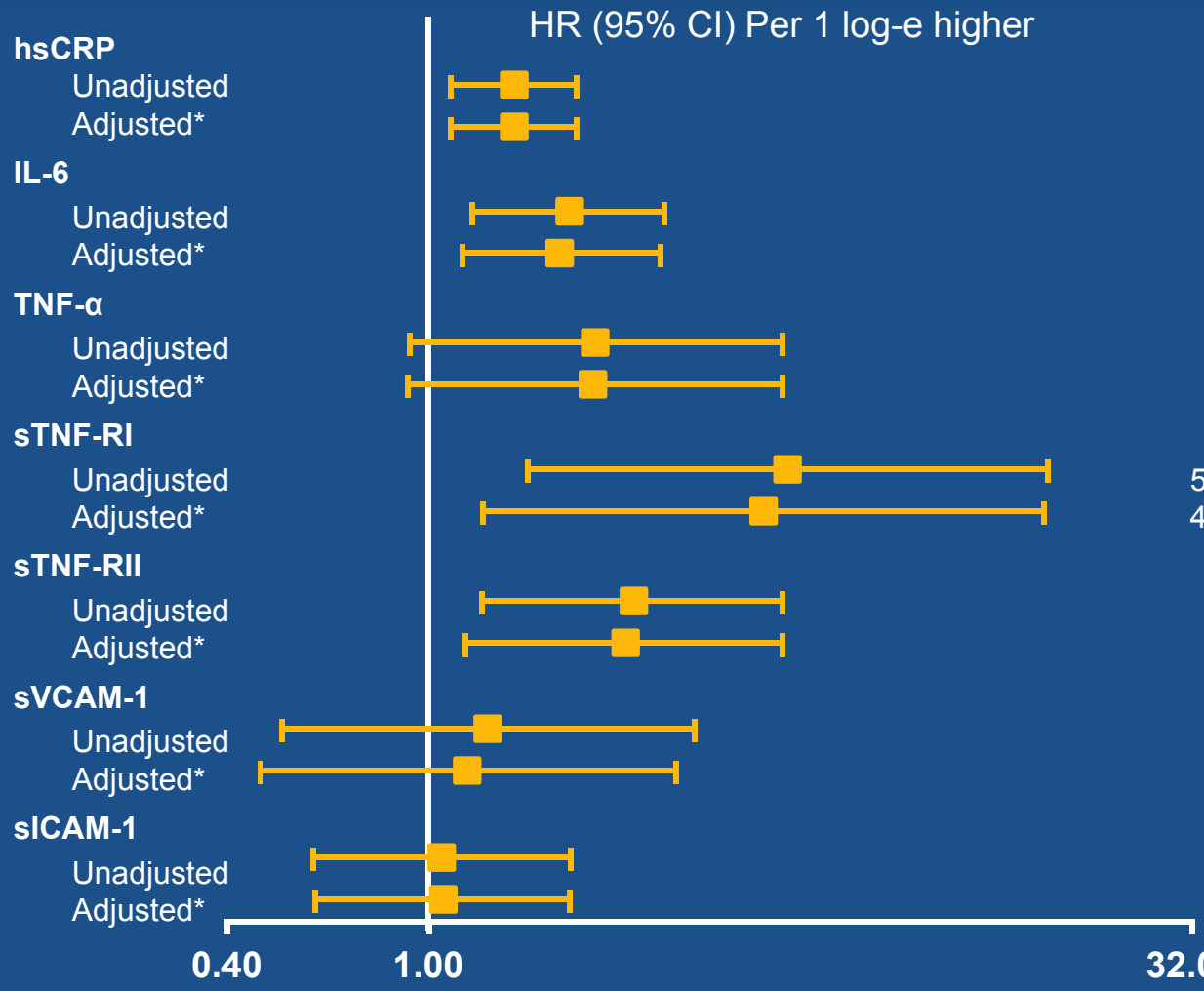


- Switching to FTC/RPV/TDF STR resulted in a greater improvement in 10-year Framingham Risk Score at Week 24 compared to PI+RTV+2NRTIs (p=0.001)

TC = Total Cholesterol, LDL = Low-Density Lipoprotein, TG = Triglycerides, HDL = High-Density Lipoprotein
p<0.001 for all comparisons between treatment groups using ANOVA

Palella F, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. TUAB0104

ACTG 5224s: Baseline Associations with Time to First AIDS or Non-AIDS Event



* Adjusted for ART and baseline CD4
HR= hazard ratio from Cox Proportional Hazard model

McComsey G, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. LBB06

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV THERAPIES AND THERAPEUTIC STRATEGIES

Reporting From

THE XIX INTERNATIONAL AIDS CONFERENCE (AIDS 2012)

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

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV THERAPIES AND THERAPEUTIC STRATEGIES

Reporting From

THE XIX INTERNATIONAL AIDS CONFERENCE (AIDS 2012)

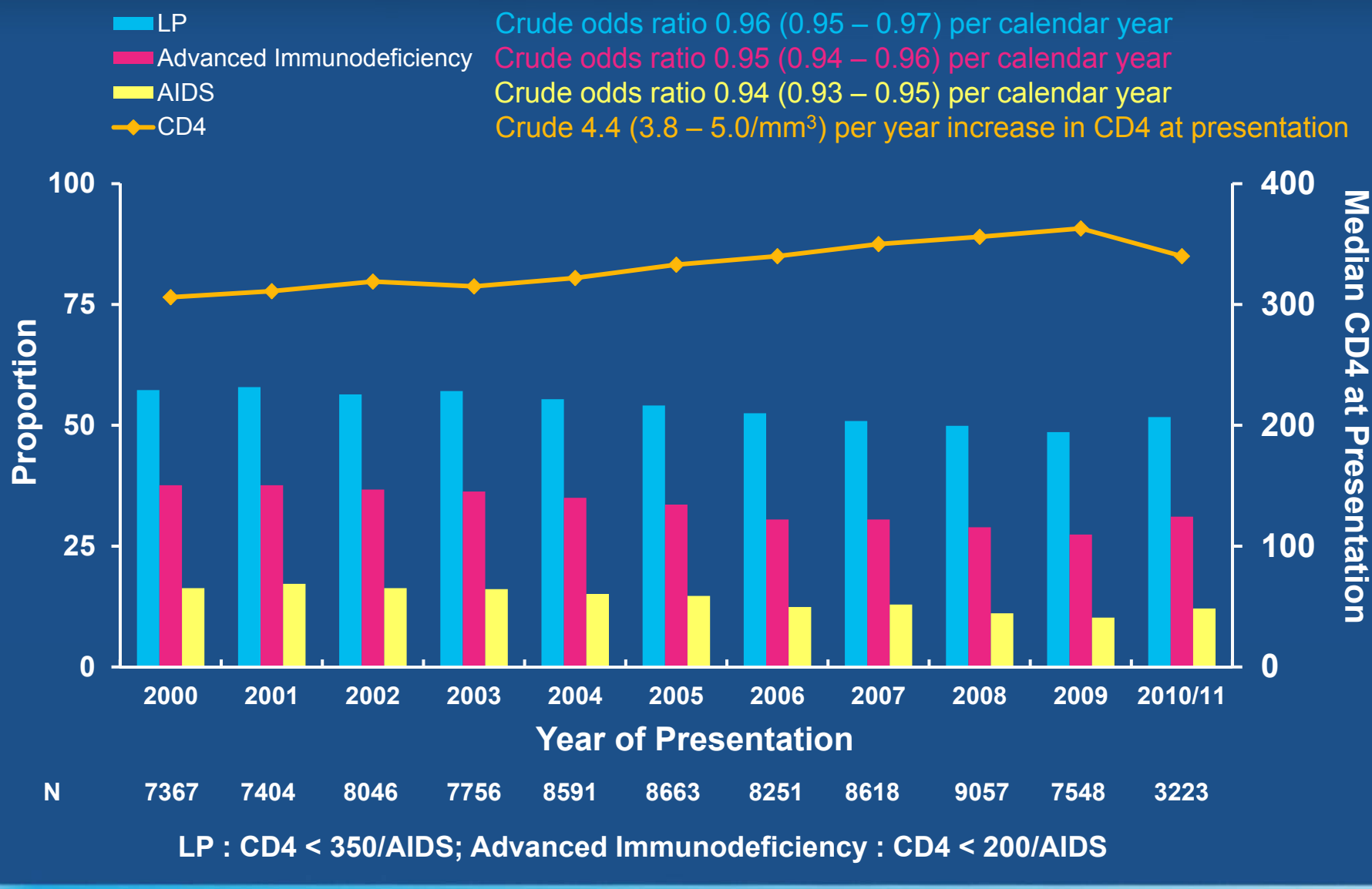
Management

Jürgen Rockstroh, MD

Department of Medicine I,
University of Bonn, Germany

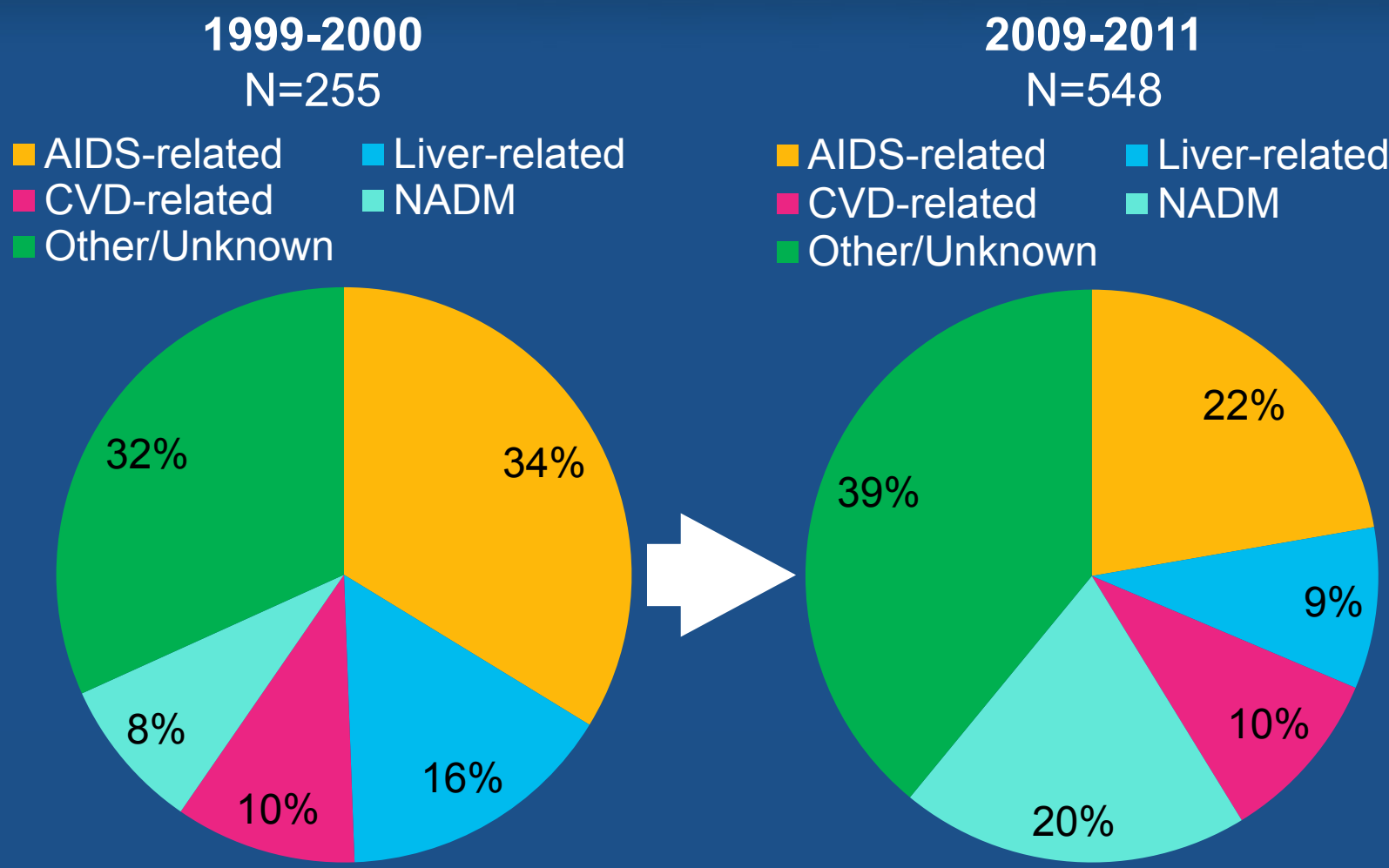
Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Late Presentation in the COHERE Cohort



Lundgren J, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THAB0303.

Changes in Causes of Death Over Time



- 3,802 deaths in 49,734 HIV positive individuals followed for 304,695 person-years
- Death rate fell from 17.4 deaths per 1000 py in 1999-2000 to 8.3 deaths in 2009-2011

Weber R, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THAB03104.

Cirrhosis After Primary HCV in HIV+ Men

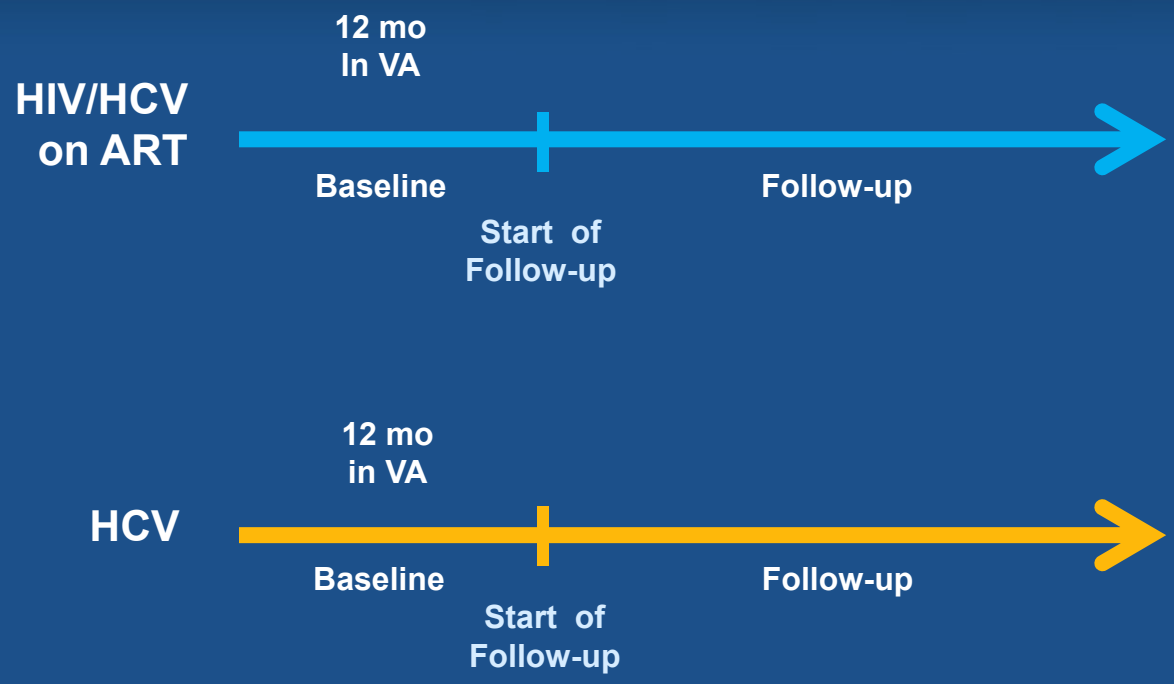
Pt	Age	CD4	HIV VL	HCV geno	pegIFN+RBV Rx	Time to initial biopsy	Initial biopsy stage (0-4)	Evidence of other liver disease	Time to 2nd biopsy	2nd biopsy stage (0-4)	Time to decompensated cirrhosis	Time to death or transplant
1	39	53 (3%)	<400	1a	failed	8 mo	3	none	2 yr (explant)	4	17 mo	Transplant 2 yr
2	55	200 (7%)	<50	1a	refused	4 mo	2	steato-hepatitis grade 2	Not done	Not done	2 ½ yr	Death 2 ¾ yr
3	40	381 (15%)	155	1a	1 dose, refused	3 ¼ yr	3	none	4 yr	4	3 ½ yr	[alive 6 ½ yr]
4	54	442 (40%)	221	1a	refused	3 ½ yr	3	steato-hepatitis grade 1	4 ½ yr	4	6 ½ yr	Death 7 yr

Increased Sinai cohort size, Follow-up:

- 15 patients persistently infected > 2 years after primary HCV
- 4 patients developed decompensated cirrhosis in 17 months to 6 ½ years

Fierer D. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0101.

Study Design: Retrospective Cohort Study from the Veterans Aging Cohort Study Virtual Cohort



Study Endpoint

Death

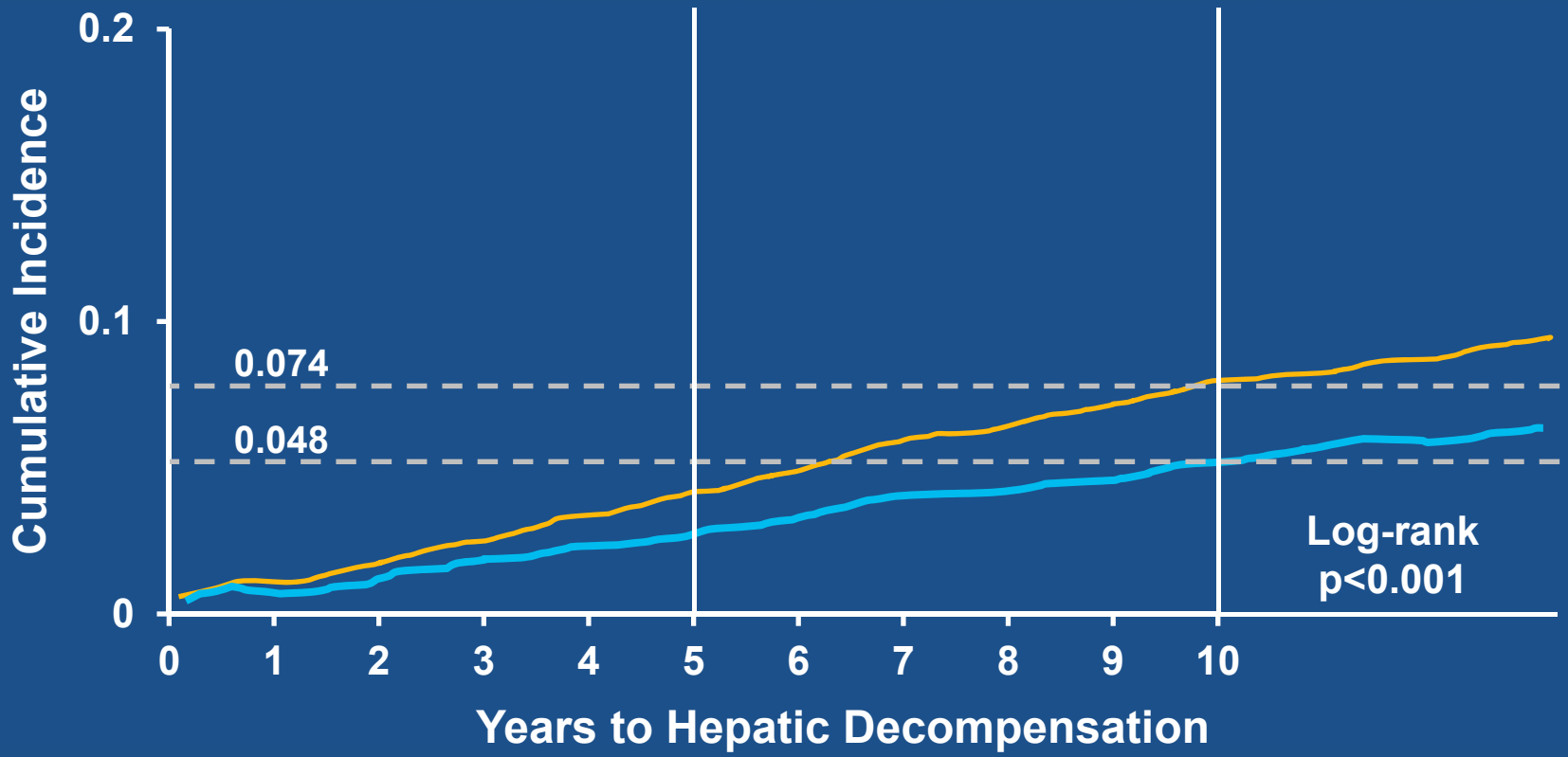
HCV Therapy

Last Visit Before Sept. 30, 2010

- **Study Aim:** To compare the incidence of hepatic decompensation between ART-treated HIV/HCV-coinfected and HCV-monoinfected pts
- **Hepatic decompensation** was defined as a hospital diagnosis indicated by ICD-9 code or two or more outpatient diagnoses of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage

Lo Re V, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0102.

Standardized Cumulative Incidence of Hepatic Decompensation*

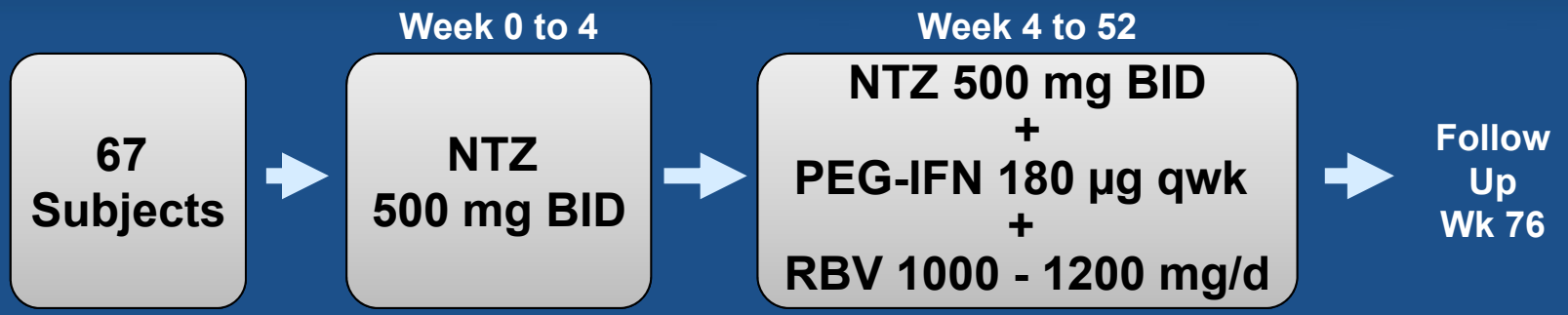


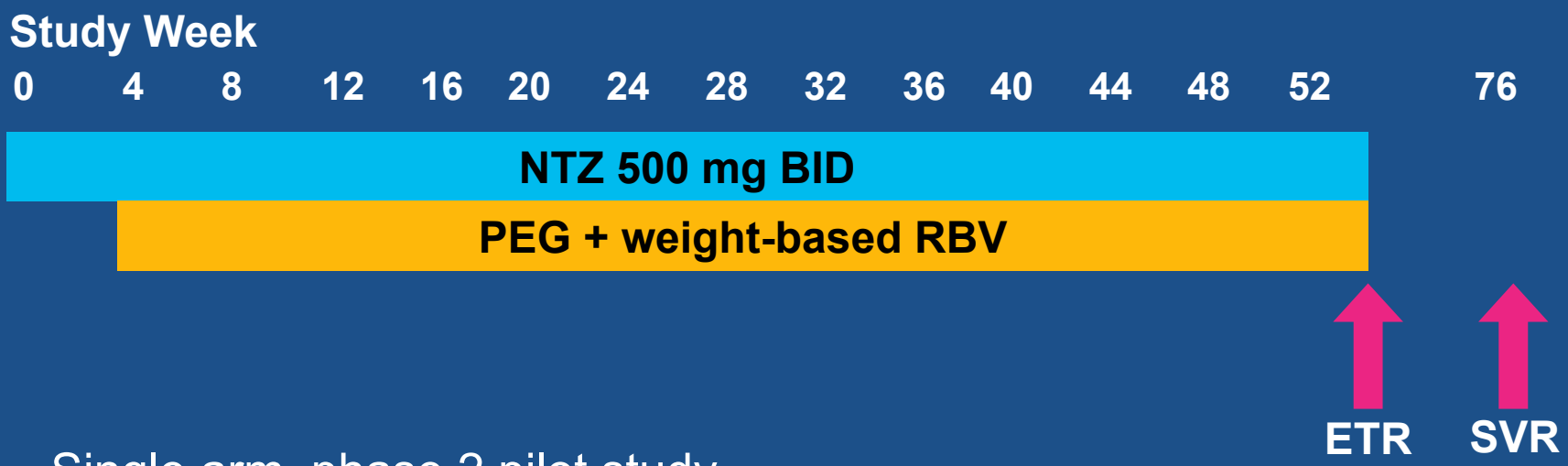
- HD risk was 83% higher in the coinfected group (aHR 1.83, 95% confidence interval [CI] 1.54 to 2.18)

* Based on competing risk regression analysis.

Lo Re V, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0102.

Study Design

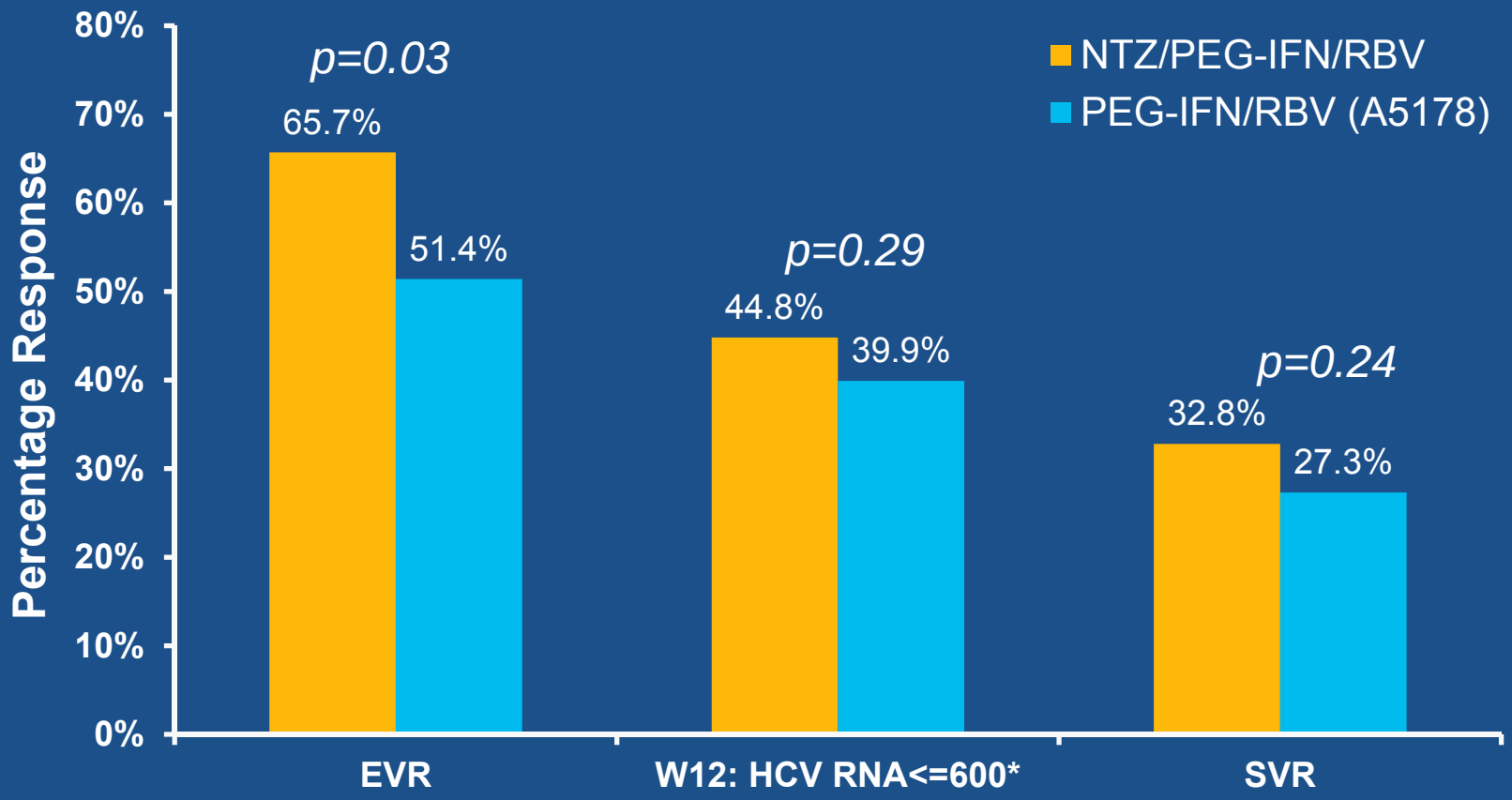




- Single arm, phase 2 pilot study
- Powered to conclude cEVR >40% and EVR >50%
  - Historical control A5178 (PEG/RBV in G1 HCV/HIV)

Amarosa V, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0103.

Virologic Response: Historical Comparison

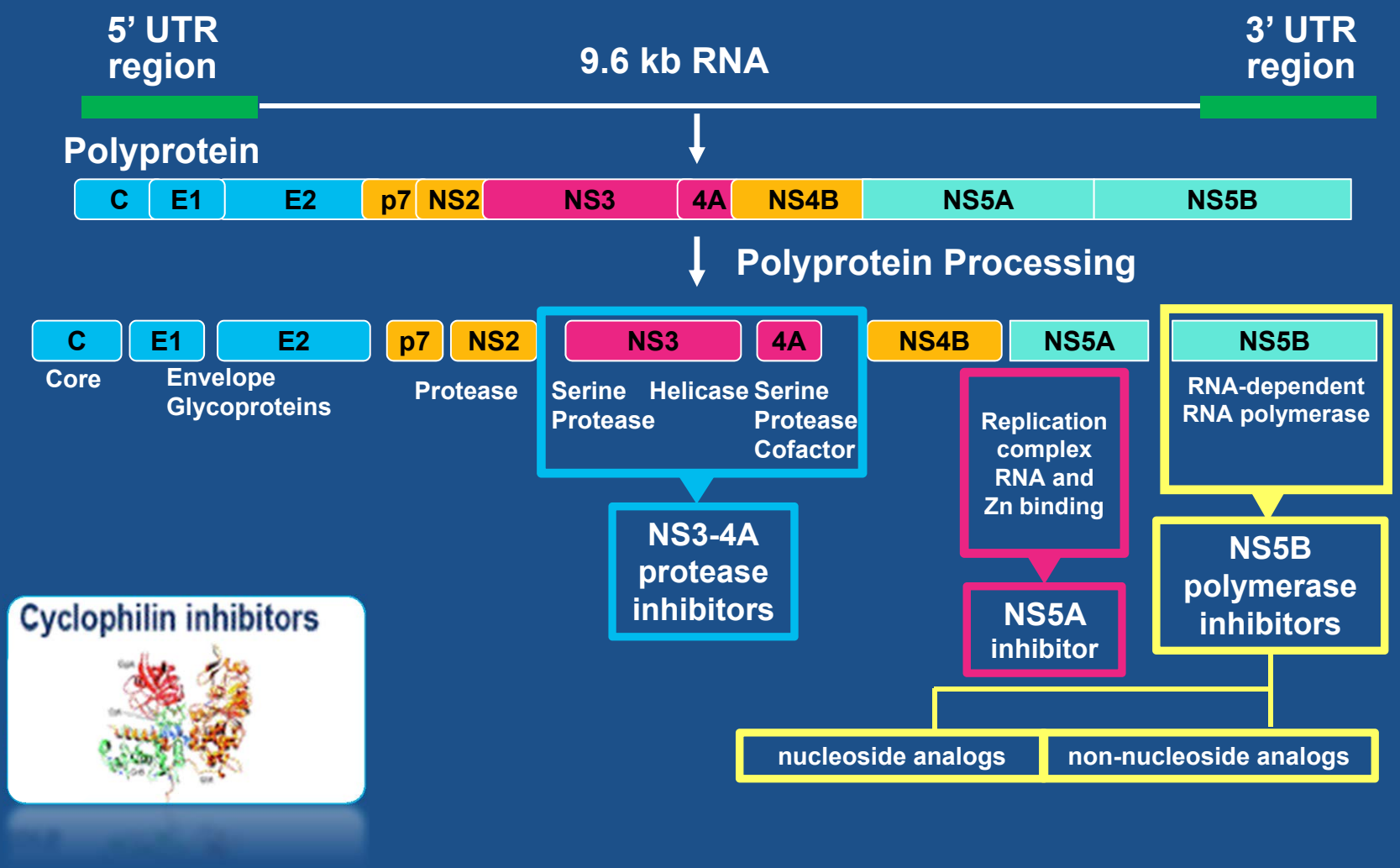


Responders (N):	44	94	30	73	22	50
Total (N):	67	183	67	183	67	183

* In A5269, at 12 weeks of triple therapy (study week 12); P-values are from one-sided Fisher's exact tests.

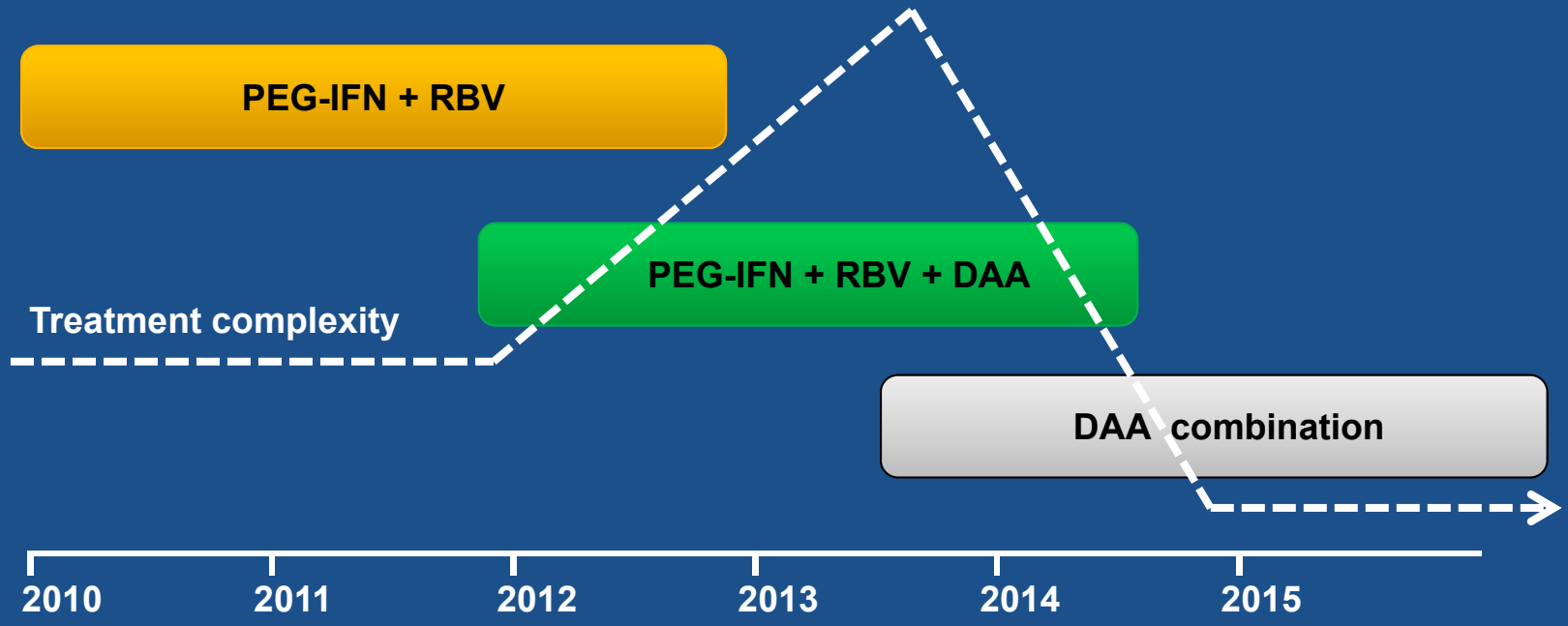
Amarosa V, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0103.

Multiple Direct Antiviral Targets



Adapted from McGovern et al, Hepatology, 2008;48:1700-1708
Terrault N. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0104.

DAA Development Timeline



Dore G. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THSS0202.

Dore GJ. Med J Aust 2012;196:629-632

HCV Treatment Strategies

Phase I (IFN-based therapy, 2012-2014):

- Treat primarily as liver disease
- Target treatment to F2-4
- Increase disease staging (i.e. Fibroscan assessment)
- Community-based disease staging (i.e. Portable Fibroscan)
- Expand treatment access: Prisons, Methadone clinics, Rural & Regional, Nurse Practitioners/Consultants, GPs , ID specialists

Phase II (IFN-free therapy, 2014 and beyond):

- Treat primarily as infectious disease
- Treat all stages of disease
- Major involvement of infectious disease and primary care clinics, with advanced disease in liver clinics
- Strategies to optimize adherence
- ? Treatment as prevention

Dore G. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THSS0202.

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV THERAPIES AND THERAPEUTIC STRATEGIES

Reporting From

THE XIX INTERNATIONAL AIDS CONFERENCE (AIDS 2012)

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