

# Hot Topics in Antiretroviral Therapy



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# DHHS Guidelines 11/2008: When To Start

Clinical Condition and/or CD4 Count	Recommendations
<ul style="list-style-type: none"><li>• History of AIDS-defining illness</li><li>• CD4 <math>\leq</math> 350</li><li>• Pregnant women</li><li>• HIVAN</li><li>• HBV coinfection when HBV treatment is indicated</li></ul>	Start ART

# DHHS Guidelines 11/2008: When To Start

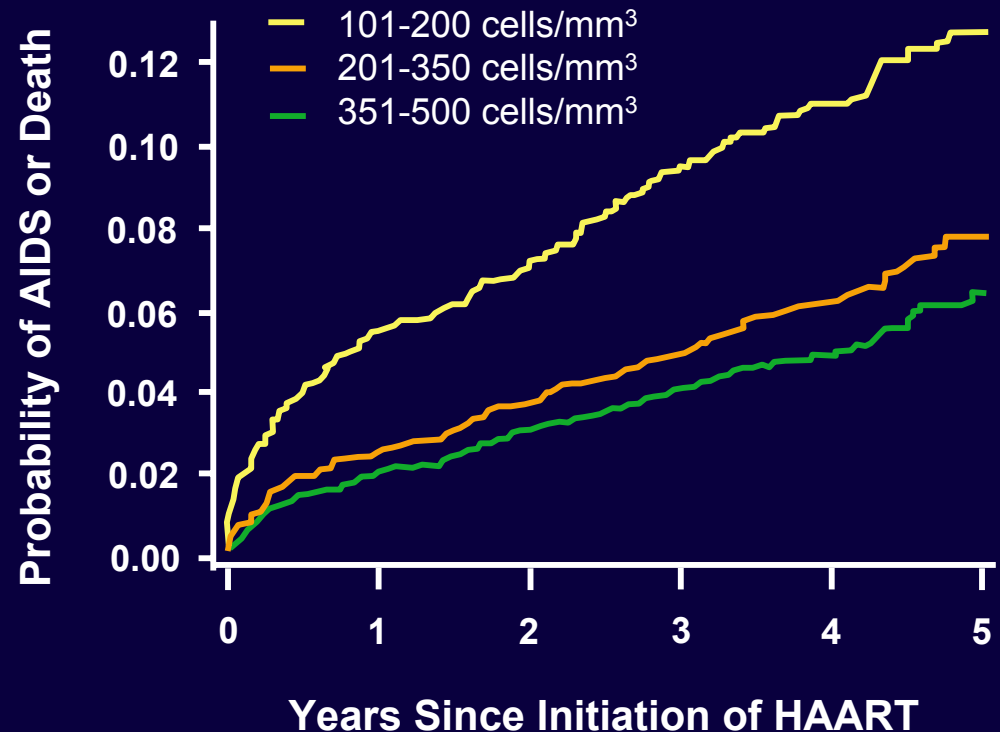
Clinical Condition and/or CD4 Count	Recommendations
<ul style="list-style-type: none"><li>• History of AIDS-defining illness</li><li>• CD4 <math>\leq</math> 350</li><li>• Pregnant women</li><li>• HIVAN</li><li>• HBV coinfection when HBV treatment is indicated</li></ul>	Start ART
CD4 > 350	<ul style="list-style-type: none"><li>• Optimal time to initiate ART not well defined</li><li>• Consider patient scenarios and comorbidities</li></ul>

# HAART and Survival Based on Initial CD4 Count

- Modeled data from ART Cohort Collaborative
- 10,855 pts, >61,000 person-years of F/U
- 934 progressed to AIDS or died
- IDUs excluded from model

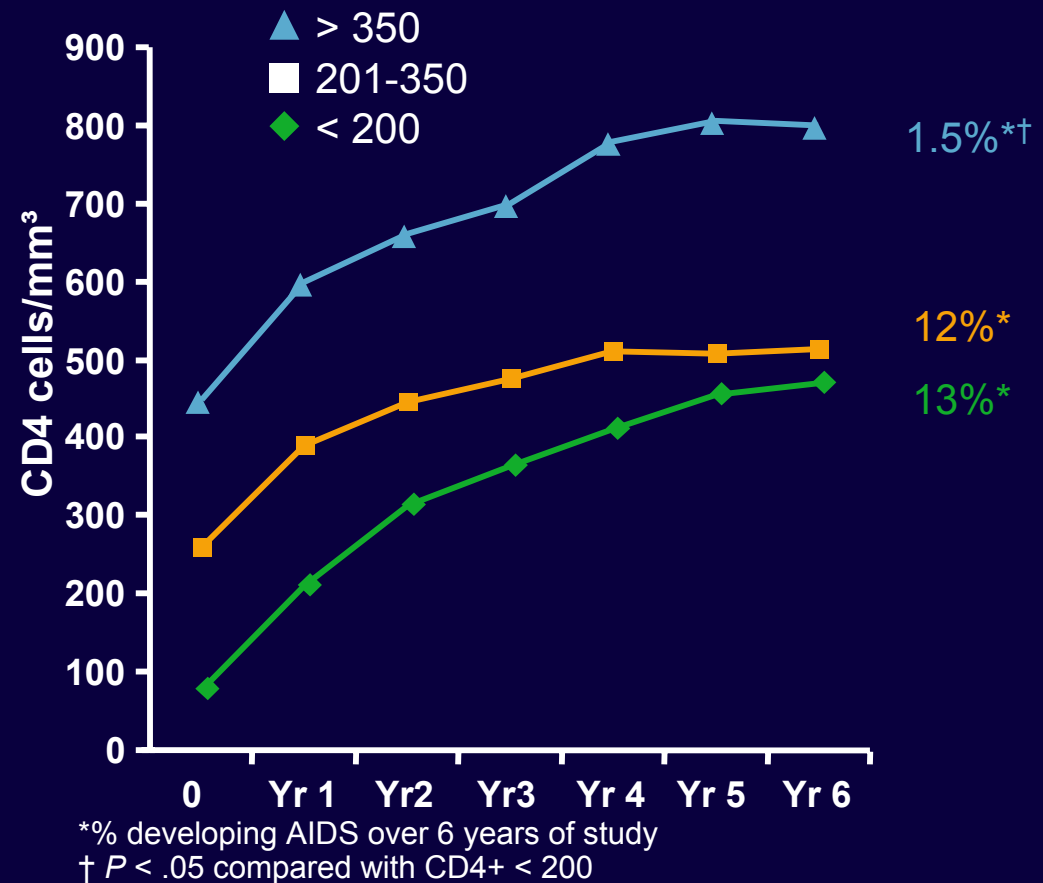
	< 200 vs 201-350	< 350 vs 351-500
Hazard ratio for AIDS (95% CI)	3.68 (3.01-4.51)	1.52 (1.10-2.10)
Hazard ratio for AIDS or death (95% CI)	2.93 (2.41-3.57)	1.26 (0.94-1.68)

Cumulative Probability of AIDS/Death by CD4 Count at Initiation of ART

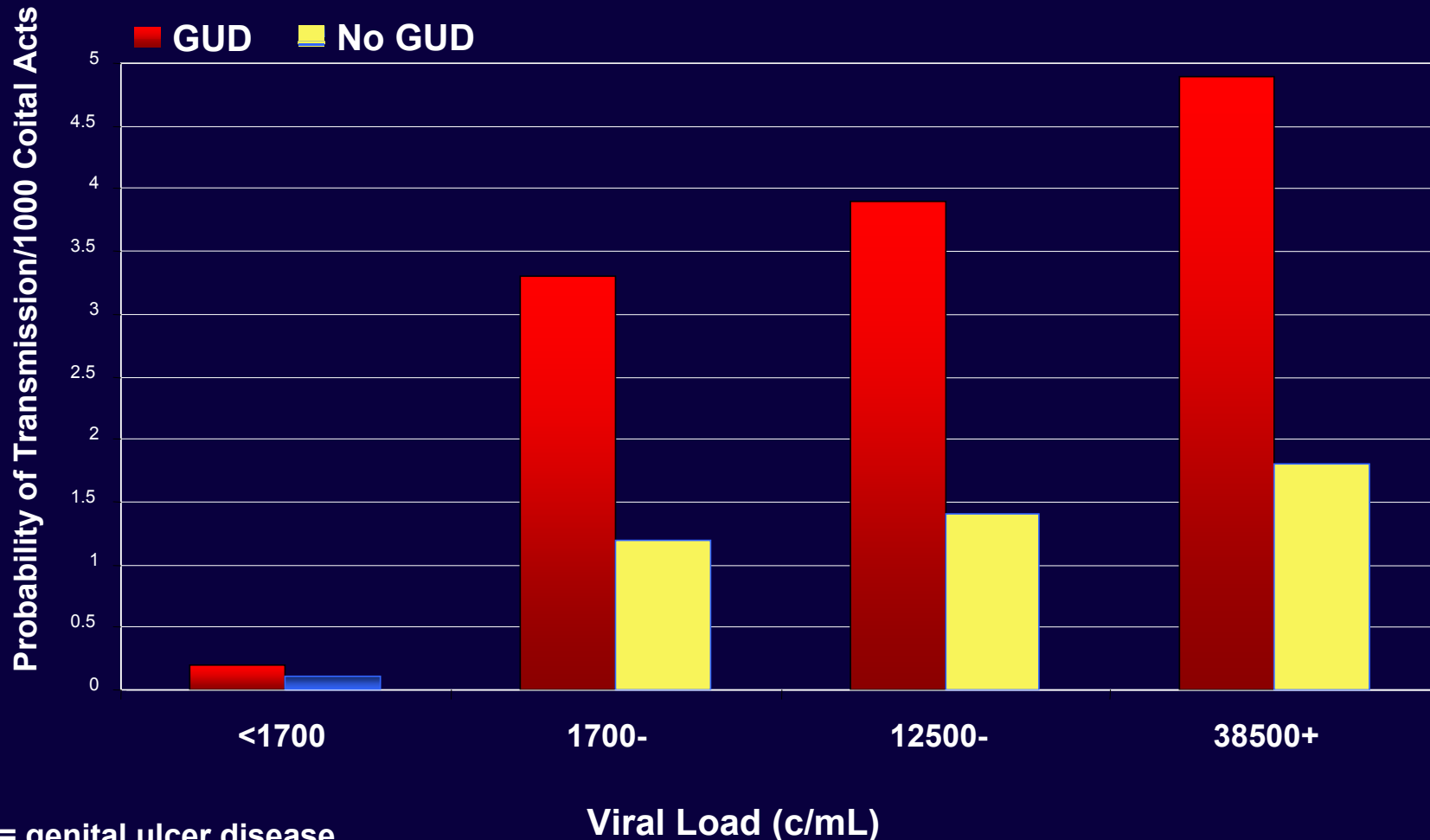


# Pre-HAART CD4 Predicts Progression to AIDS: Johns Hopkins Cohort

- Johns Hopkins HIV Cohort
- Patients with virologic suppression for up to 6 yrs (N=280)
- Only patients with baseline CD4 >350 returned to near normal CD4 count levels
- Rate of progression to AIDS or death significantly higher over time in patients with CD4 <200 and 201-350 vs. >350



# Viral Load Affects Probability of HIV Heterosexual Transmission

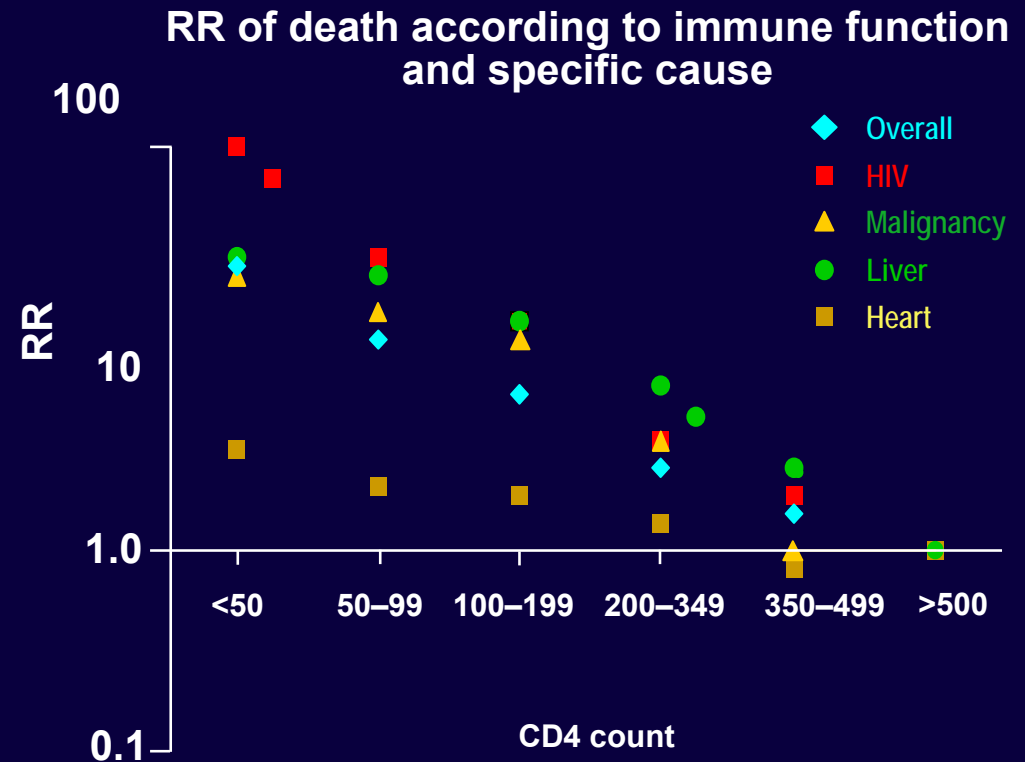


GUD = genital ulcer disease.

Gray R et al. *Lancet*. 2001;357:1149-1153.

# D:A:D Study: CD4 Count Associated with Risk of Non-HIV Related Death

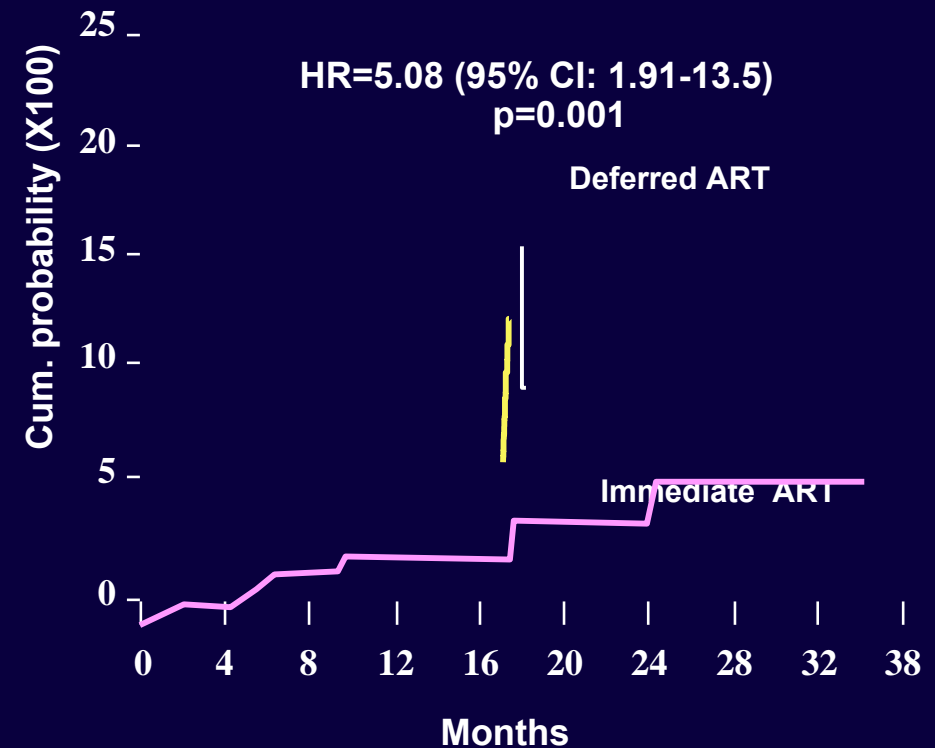
- >23,000 pts in Europe, Australia, USA
- 1248 (5.3%) deaths 2000–2004 (1.6/100 person-years)
  - Of these, 82% on ART
- Both HIV- and non-HIV-related mortality\* associated with CD4 depletion



\*Liver-related: Chronic viral hepatitis, liver failure (other);  
malignancy-related: malignancy, non-AIDS hepatitis;  
heart-related: MI, other CVD, other heart disease

# SMART: Patients not on ART at Randomization

- Subset: ART-naïve or not on ART at randomization
  - Immediate ART: n=249 (131 naïve)
  - Deferred ART: n=228 (118 naïve)
- Greater risk of OI, OI/death, serious non-AIDS event with deferred ARV
- >5-fold increased risk with deferred ARV



# Molecular Risk Factors for Mortality During Treatment Interruption

- SMART: High baseline levels and increases in hsCRP, amyloid A, IL-6, and D-dimer correlated with increased risk of death<sup>[1]</sup>
  - ↑ in med. concentration of IL-6 (TI: +60%; VS: +12%) and D-dimer (TI: +5%; VS: 0%) in first month of trial
  - Increases in IL-6 and D-dimer correlated with increasing VL in TI arm
  - Markers predictive of mortality after adjusting for CD4 and VL
- Staccato: Increased VL during treatment interruption correlated with markers of inflammation and endothelial dysfunction (s-VCAM-1, IL-10, and MCP-1)<sup>[2]</sup>



# The Pros and Cons of a Randomized Trial

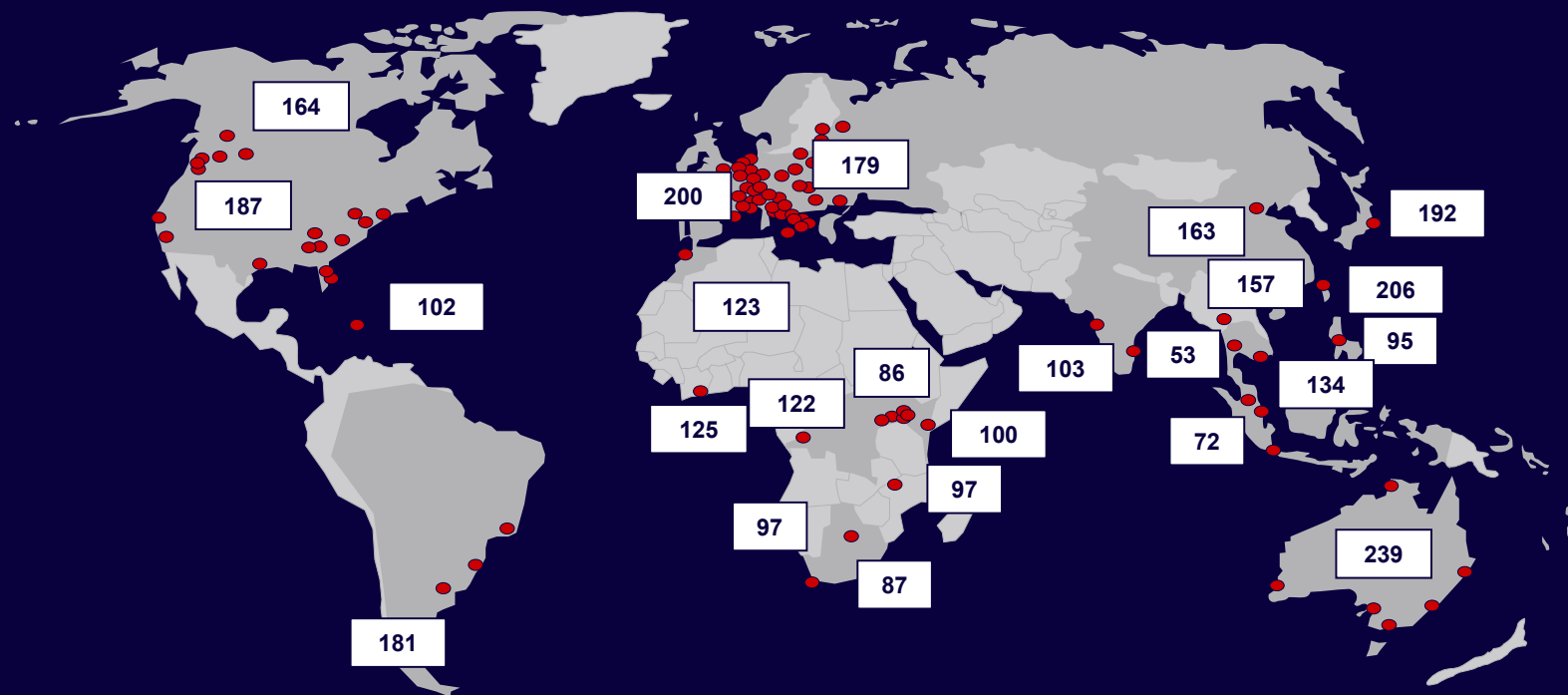
## PROS

- Could provide the definitive answer about when to start therapy

## CONS

- Previous attempts to enroll such trials have failed
- Expensive
- Observational data already compelling
- Will the question or the chosen CD4 thresholds still be relevant by the time the results are available?

# CD4 Count at ART Initiation, 2003-5



- Since 2000, CD4 count at initiation
  - has increased in Sub-Saharan Africa from 50 to 100
  - has remained stable in developed countries stable at ~150–200,
  - Is lower in U.S. than in many other resource-rich nations

# The Initial Regimen: DHHS Guidelines, 11/2008

NRTIs	NNRTIs	PIs
<b>PREFERRED</b>		
TDF/FTC	EFV	ATV/r
		DRV/r QD
		LPV/r QD or BID
		FPV/r BID
<b>ALTERNATIVE</b>		
ABC/3TC	NVP	ATV
AZT/3TC		FPV
ddl + (3TC or FTC)		FPV/r QD
		SQV/r BID

# The Initial Regimen: IAS-USA Guidelines, 7/2008

IAS-USA Guidelines “Recommended”			
NNRTI-based regimen	EFV*	+	TDF/FTC† ABC§/3TC‡
	NVP†		
PI-based regimen	LPV/r		
	ATV/r		
	FPV/r		
	SQV/r		

\*Except during first trimester of pregnancy or in women with high pregnancy potential.

† Or lamivudine.

‡Possible increased risk of CVD; possible increased risk of failure with high viral load.

§Or emtricitabine.

# Choosing the Initial Regimen: The 3 Questions

- EFV or a boosted PI (or RAL)?
- If a boosted PI, which one?
- Which NRTI backbone?

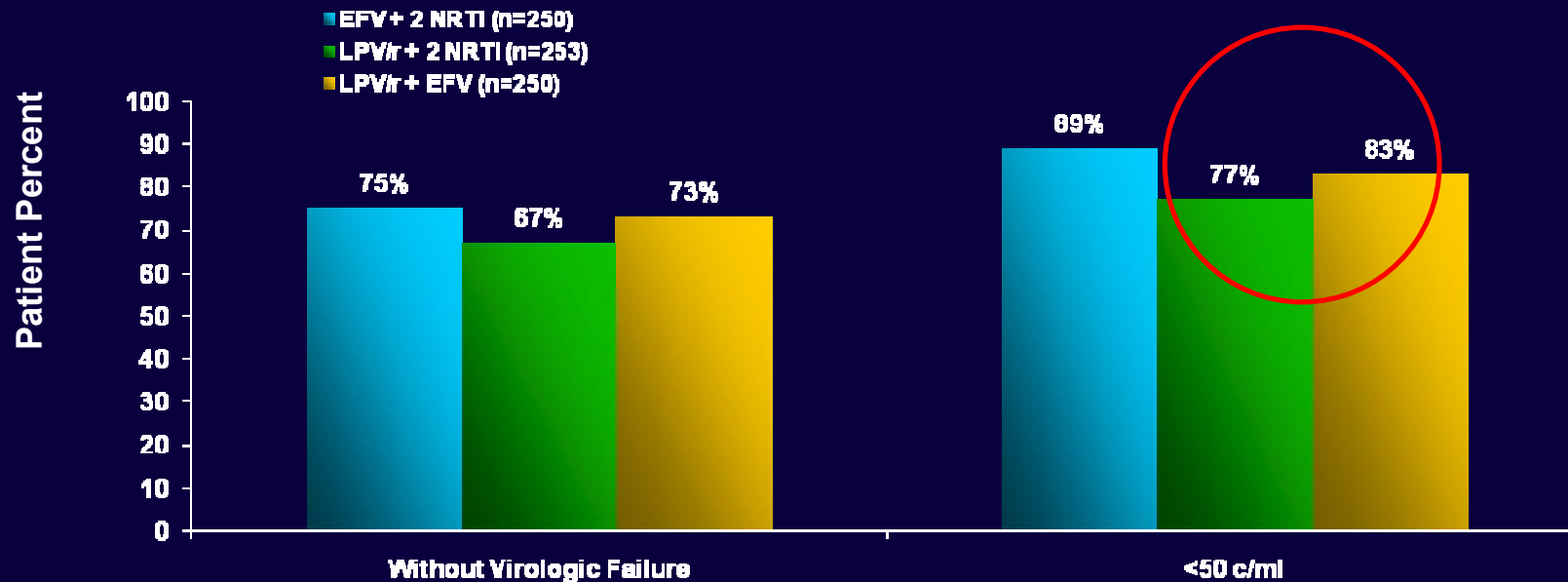
# Question 1: EFV vs. Boosted PI?

## EFV

- Gold standard for virologic efficacy
- Easiest regimens (1-2 pills/d)
- Minimal long-term toxicity
- Favorable PK

# ACTG 5142: 96 week ITT outcomes

## EFV vs. LPV/r vs. LPV/r + EFV



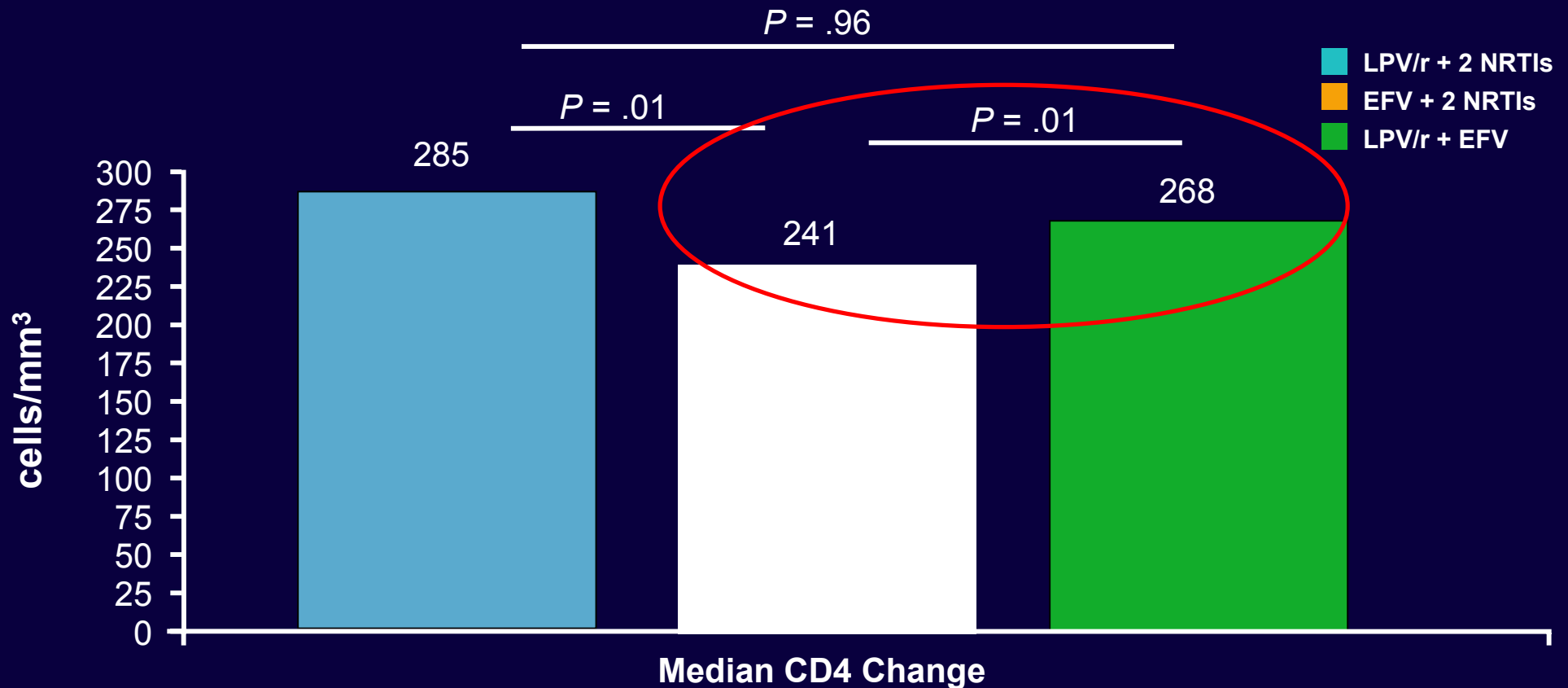
Regimen	N	Day 7 Δ VL
EFV + 2 NRTIs	193	-1.48
LPV/r + 2 NRTIs	182	-1.17
EFV + LPV/r	200	-1.23

Greater day 7 VL reduction associated with 24, 48, and 96-week virologic response

# Question 1: EFV vs. Boosted PI?

EFV	BOOSTED PI
<ul style="list-style-type: none"><li>•Gold standard for virologic efficacy</li><li>•Easiest regimens (1-2 pills/d)</li><li>•Minimal long-term toxicity</li><li>•Favorable PK</li></ul>	<ul style="list-style-type: none"><li>•Better CD4 response than EFV (LPV/r: ACTG 5142)</li><li>•Less resistance with failure</li><li>•Preferred if risk for pregnancy</li><li>•Preferred if baseline NNRTI (or NRTI?) resistance</li><li>•Less lipoatrophy?</li></ul>

# ACTG 5142: Change in CD4 Count at Week 96



# ACTG 5142: Resistance Mutations

	LPV	EFV	LPV/ EFV
Observed viral failure, n	94	60	73
	52	33	39
Any PI mutations, n	20	13	18
	0	0	2
NNRTI mutations, n (%)	2 (4)	16 (48)	27 (69)
	8 (15)	11 (33)	4 (10)
Mutations in 2 classes, n (%)	2 (4)	10 (30)	2 (5)

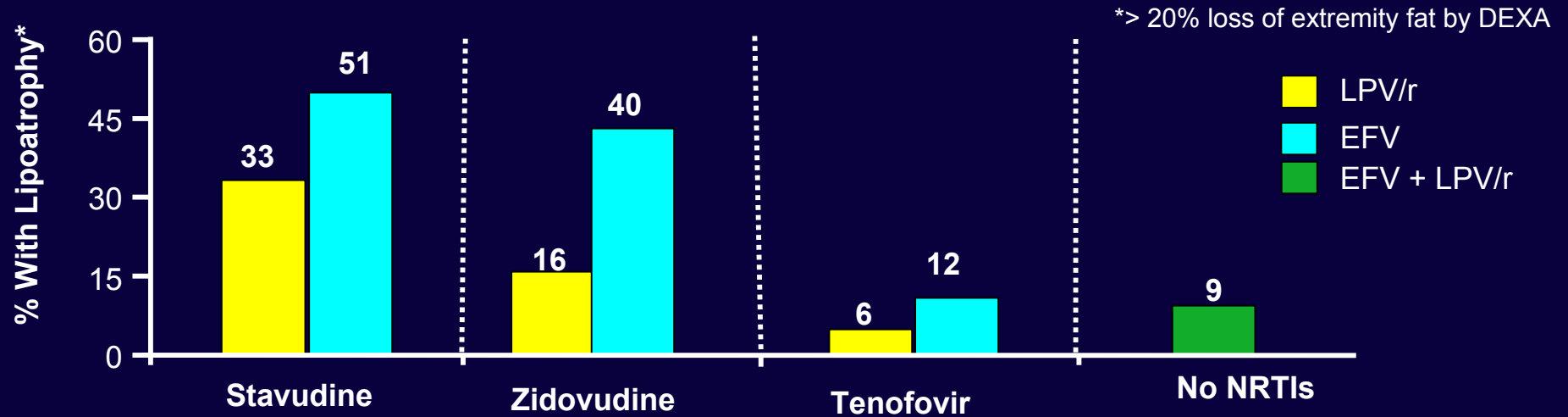
\*Defined as 30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, or 90M.

# “Styles” of Non-Adherence Have Different Implications for Resistance

Two patients with ~70% adherence:

- Wild Wilbert:
  - Skips his meds on weekends when he uses drugs
  - Long half-lives of NNRTIs (especially EFV) may protect him from resistance
- Bad Bradford:
  - Spends several weeks in jail every few months
  - High risk for NNRTI resistance due to prolonged treatment interruptions

# ACTG 5142: Lipoatrophy\* at Week 96

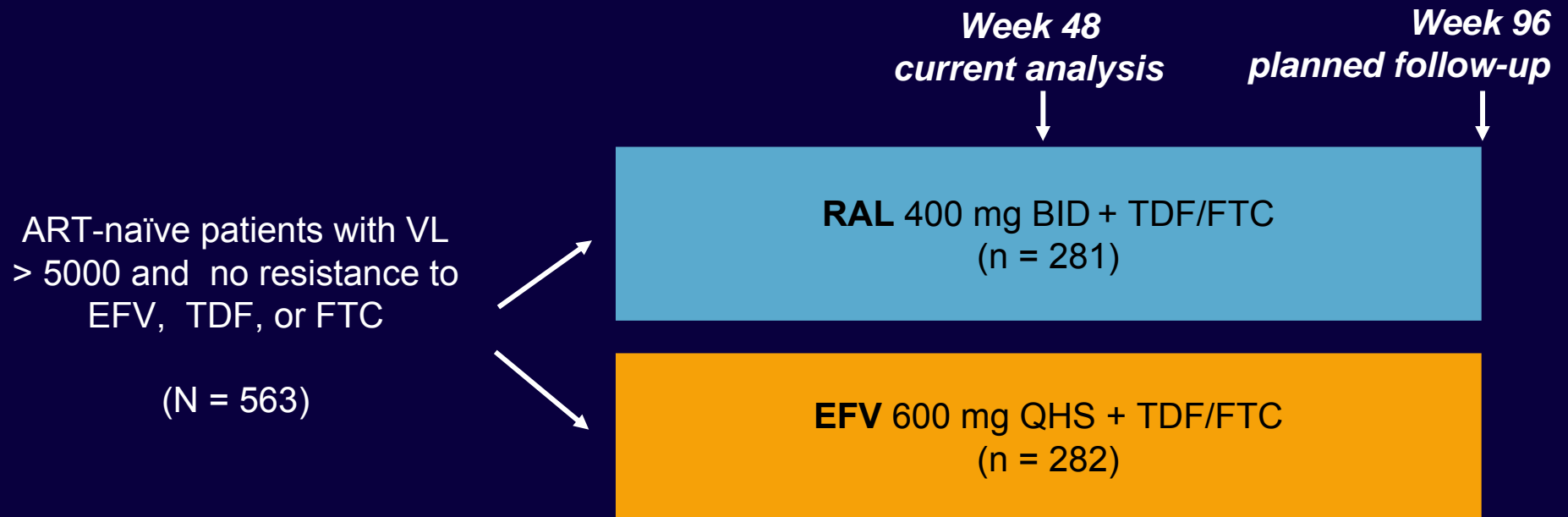


## Risk Factors for Lipoatrophy at Week 96 (Logistic Regression)\*

Factor	OR (95% CI)	P Value
EFV vs LPV/r	2.7 (1.5-4.6)	< .001
d4T vs ZDV	1.9 (1.1-3.5)	.029
TDF vs ZDV	0.24 (0.12-0.5)	< .001

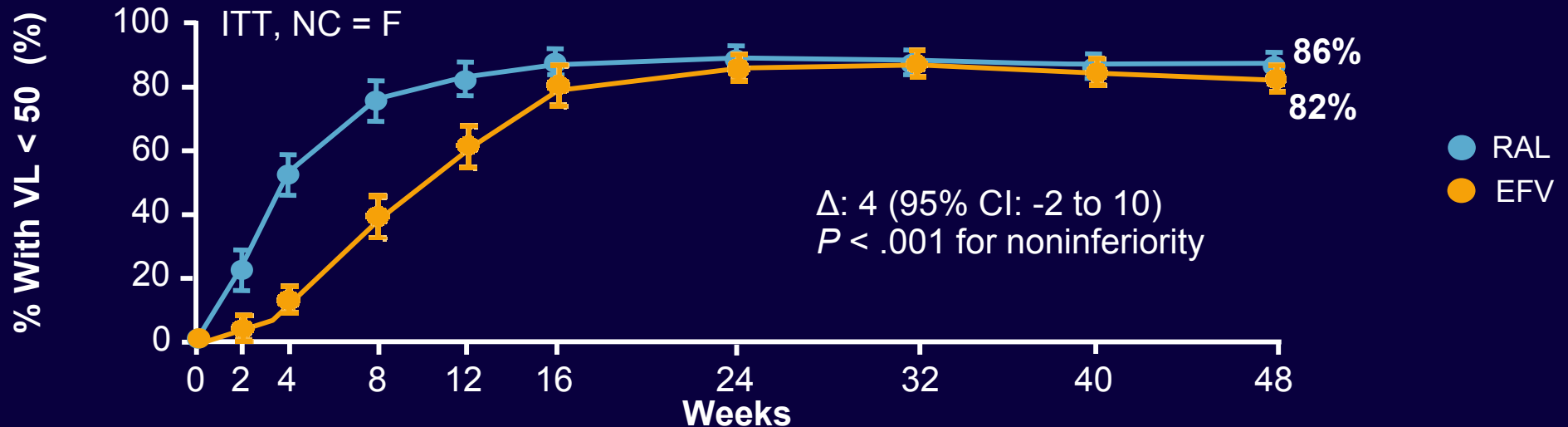
\*Excludes NRTI-sparing arm.

# STARTMRK Phase III: RAL vs EFV in ART-Naive Patients



- Primary endpoint: VL < 50 at Week 48
- Secondary endpoints: CD4 count, safety, and tolerability
- 53% of patients had VL > 10<sup>5</sup> c/mL; 47% of patients had CD4 counts < 200 at baseline

# STARTMRK: Virologic and Immunologic Efficacy at Week 48



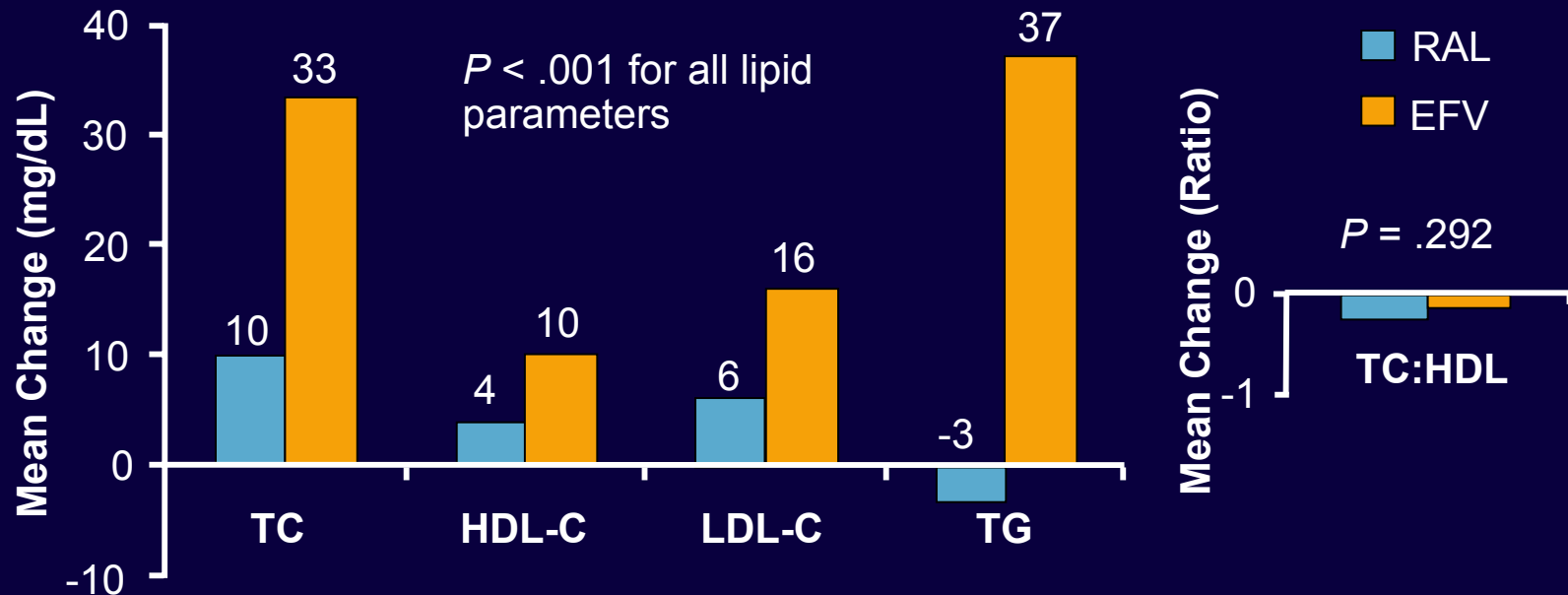
RAL n =	281	279	281	279	281	279	278	280	280
EFV n =	282	282	282	282	281	282	280	281	281

- Significantly shorter time to virologic response with RAL vs EFV ( $P < .001$ )
- Significantly greater CD4 count increase with RAL vs EFV
  - +189 vs +163;  $\Delta: 26$  (95% CI: 4-47)

# STARTMRK: AEs at Week 48

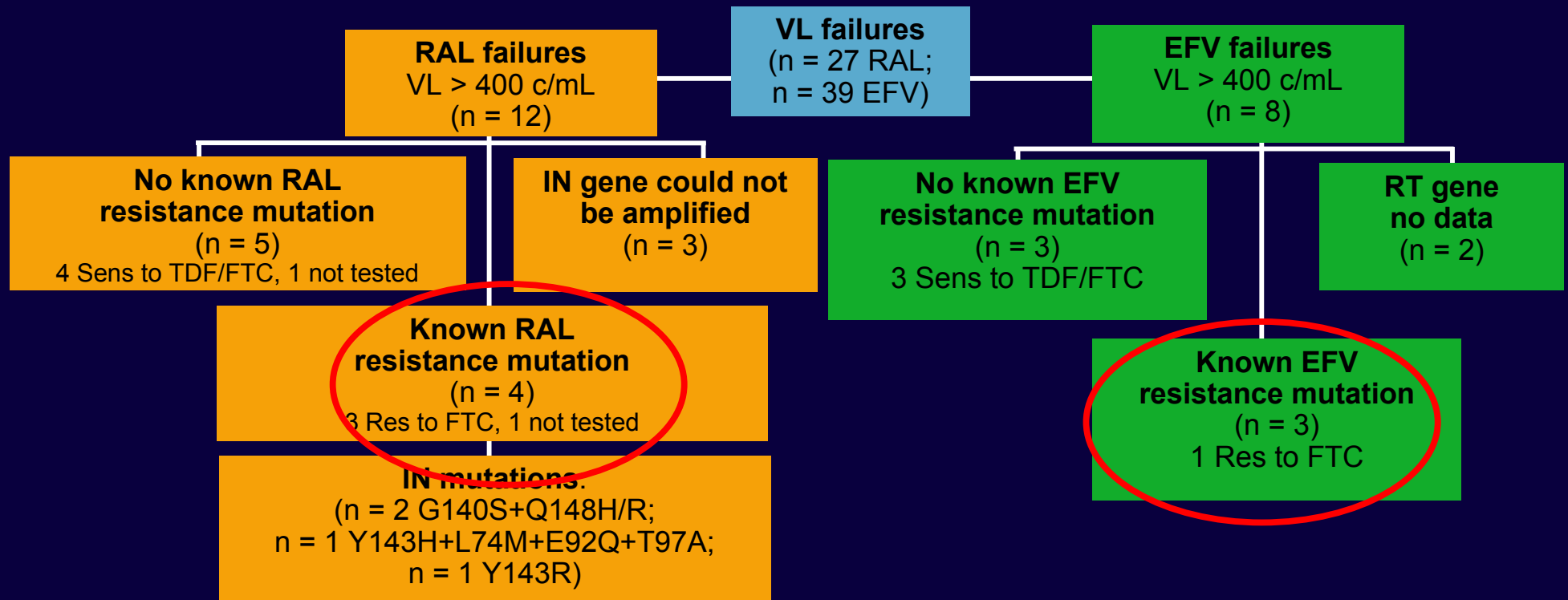
- Moderate/severe drug-related clinical AEs more frequent in EFV vs RAL arm (32% vs 16%;  $P < .001$ )
  - Serious clinical AEs in 10% of patients in both arms
- Fewer patients experienced CNS events by Week 8 with RAL vs EFV (10.3% vs 17.7%;  $P = .015$ )
- Malignancies developed in 1 patient in RAL arm vs 9 patients in EFV arm
  - KS (n = 7), anal cancer (n = 1), NHL (n = 1), bone cancer (n = 1)

# STARTMRK: Lipid Changes From Baseline to Week 48



- Fewer patients initiated lipid-lowering therapy with RAL vs EFV (3 vs 11)
  - 4 patients in each arm increased lipid-lowering therapy
- Greater increases in all lipid parameters including HDL in EFV arm, no overall difference in TC:HDL ratio

# STARTMRK: Week 48 Resistance in Patients With Virologic Failure\*

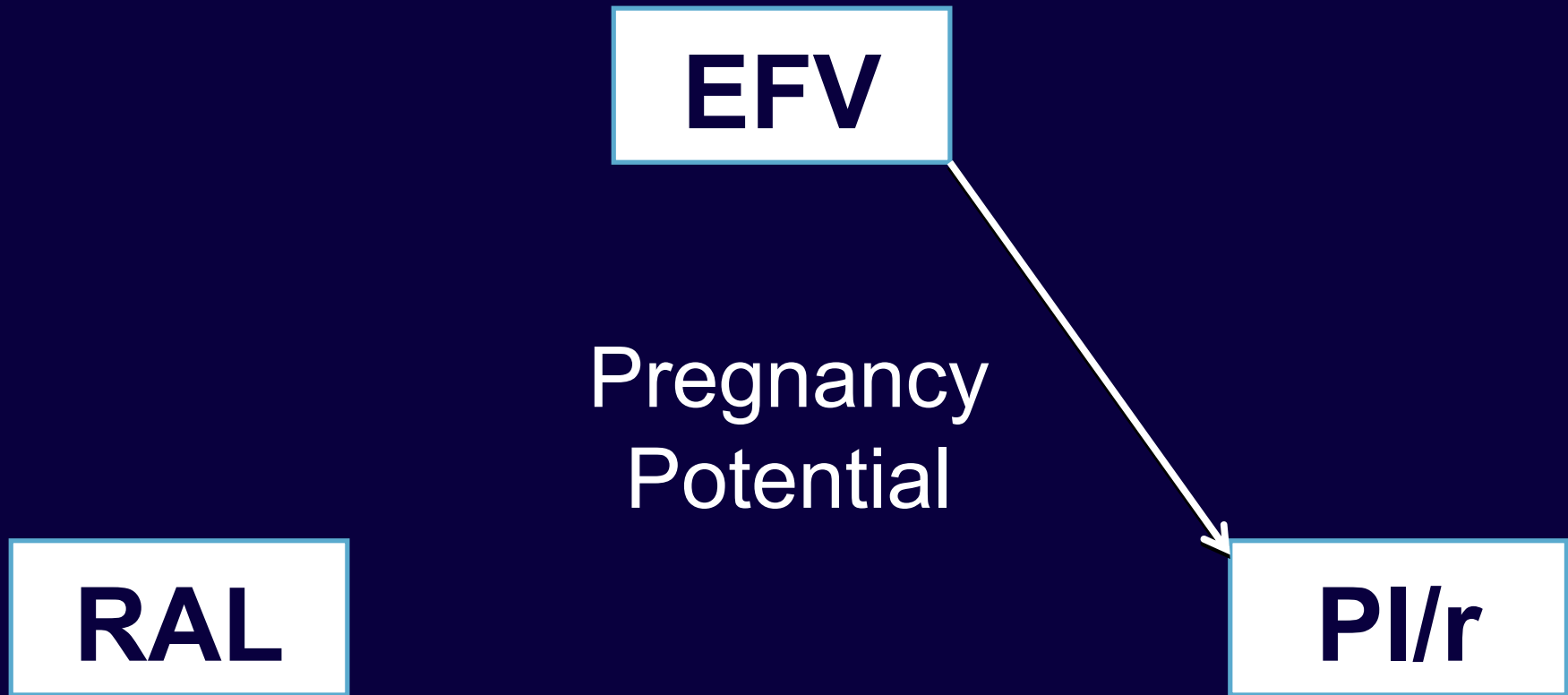


## \*Virologic failure:

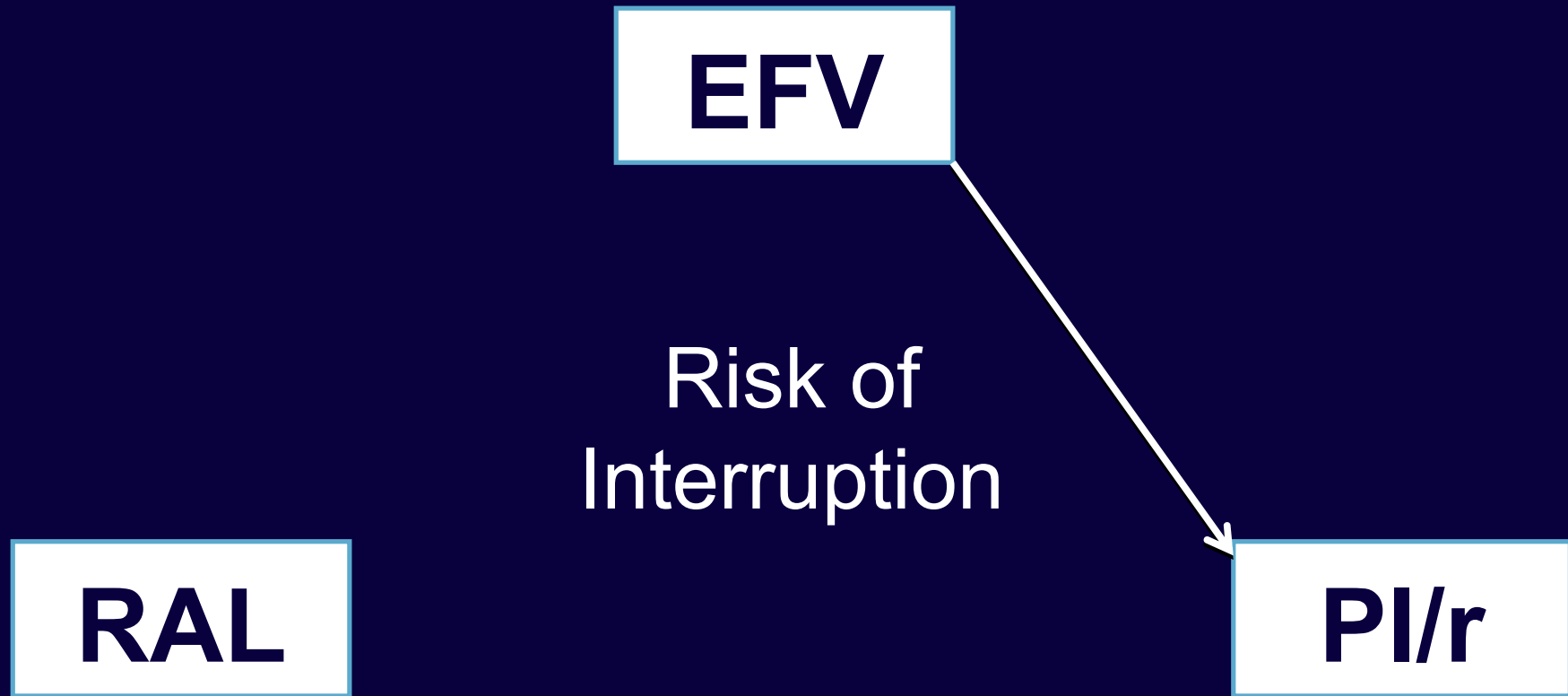
Nonresponder: VL > 50 c/mL at time of discontinuation or VL > 50 c/mL at Week 24

Virologic rebound: VL > 50 c/mL on 2 consecutive tests at least 1 week apart after initial response

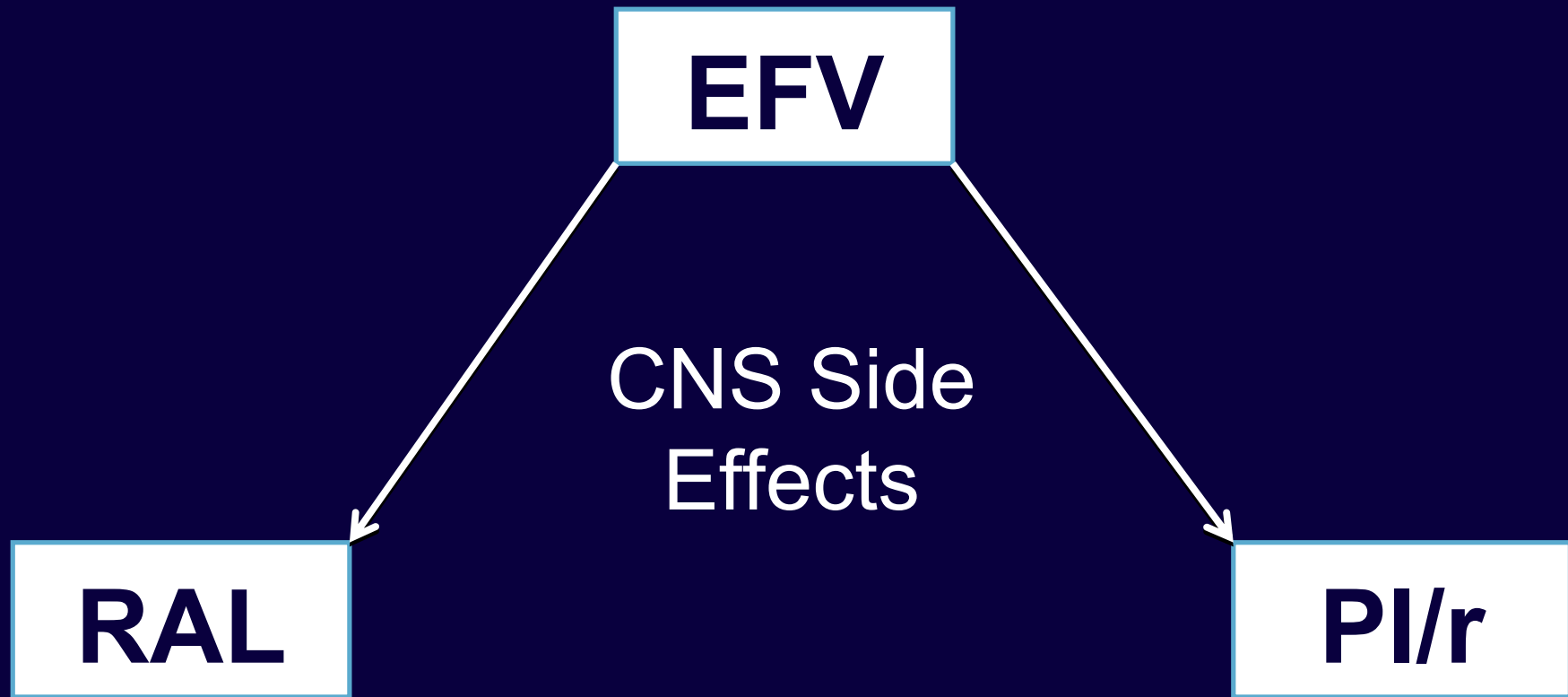
# Question 1: EFV, boosted PI, or RAL?



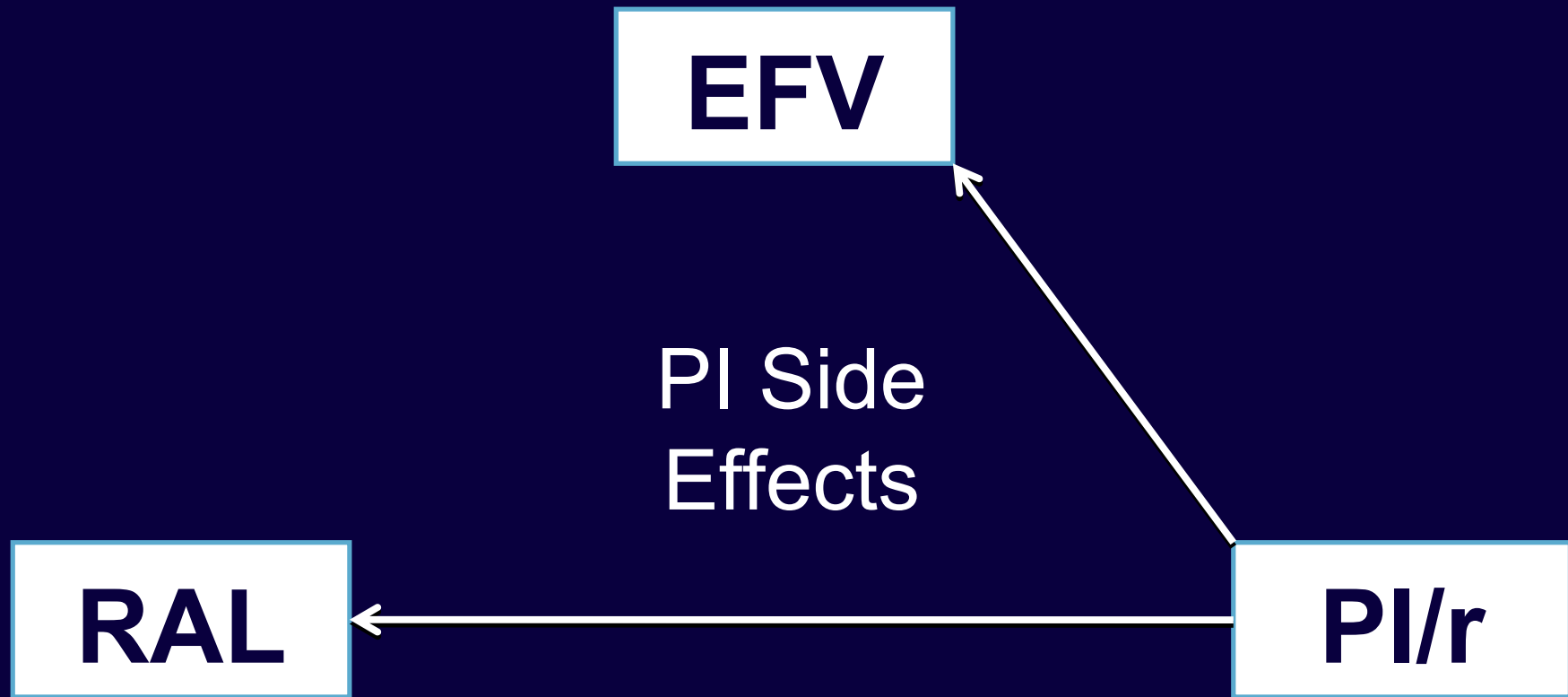
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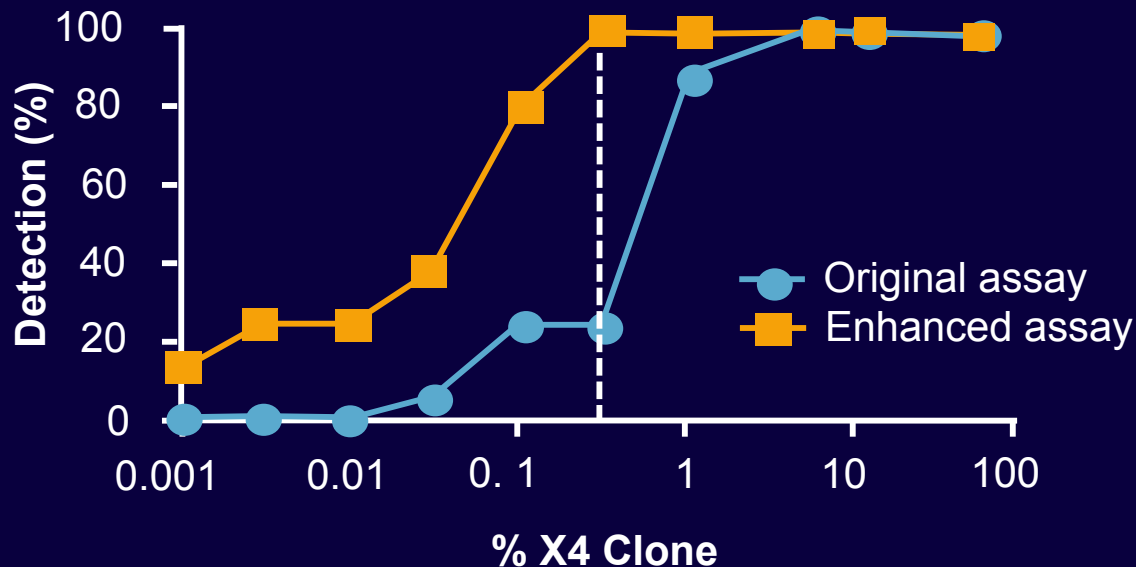


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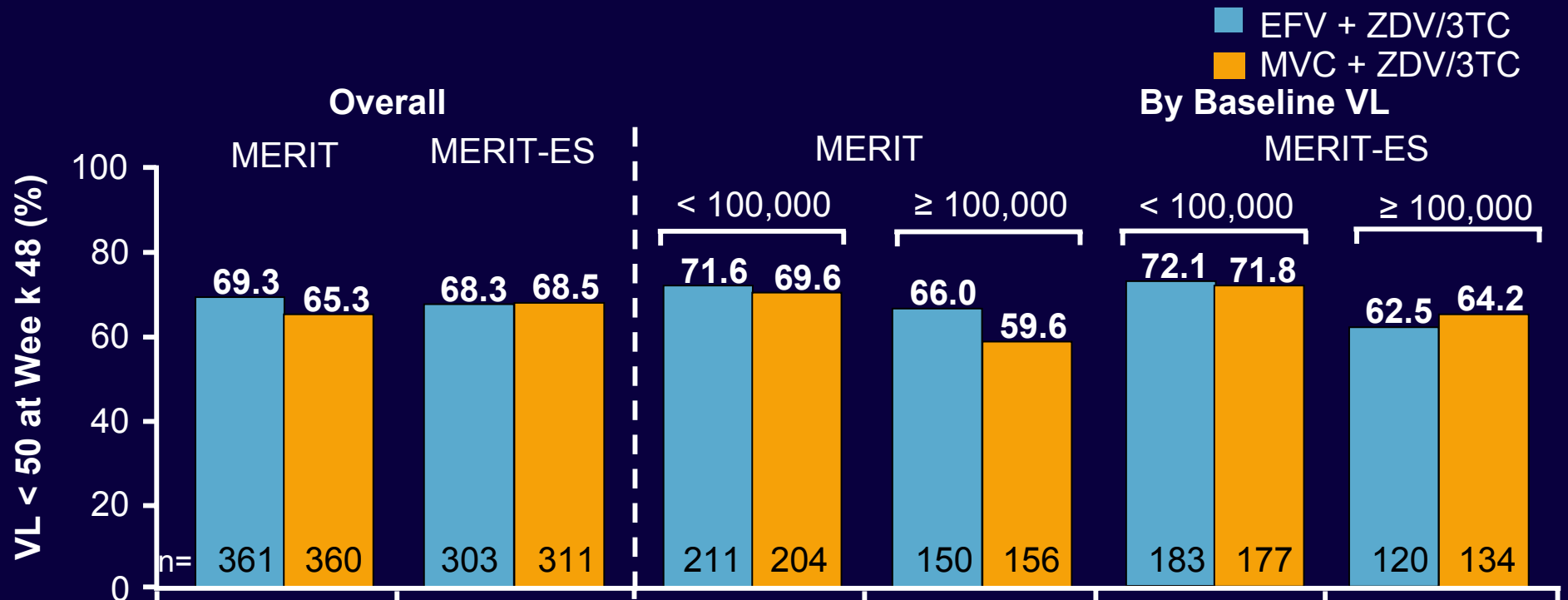
# Enhanced Sensitivity Tropism Assay For Detection of CXCR4-Using Virus

- Enhanced assay highly sensitive in detecting X4-using variants comprising 0.3% of viral populations



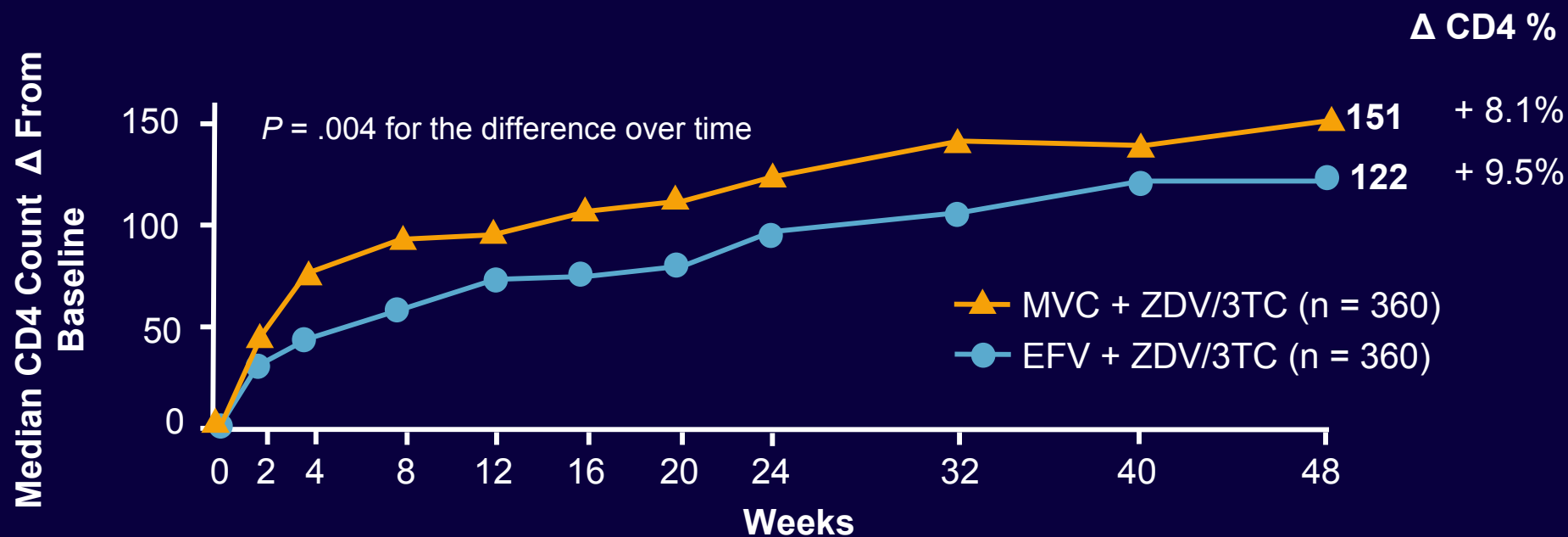
# Reanalysis of Virologic Efficacy in MERIT With Enhanced Tropism Assay

- Enhanced sensitivity tropism assay resulted in reclassification of 15% of patients from R5 to D/M at screening
  - Noninferiority criteria (rates of VL < 50) met when D/M patients excluded



# Effect of Maraviroc on CD4 Counts

- Analysis of MERIT study<sup>[1]</sup>



- In separate study, addition of MVC in 9 patients with undetectable VL but CD4 counts < 250 on current ART regimen did not significantly increase CD4 count recovery with 5 mos of follow-up (*P* > .39)<sup>[2]</sup>

1. Lazzarin A, et al. ICAAC/IDSA 2008. Abstract 1248.

2. Paez S, et al. ICAAC/IDSA 2008. Abstract 1247.

# Maraviroc for Initial Therapy

## PROS

- Greatest likelihood of R5 virus in ART-naïve patients
- Non-inferior to EFV with *Trofile ES* assay
- Well tolerated
- Preserves other classes for later use

## CONS

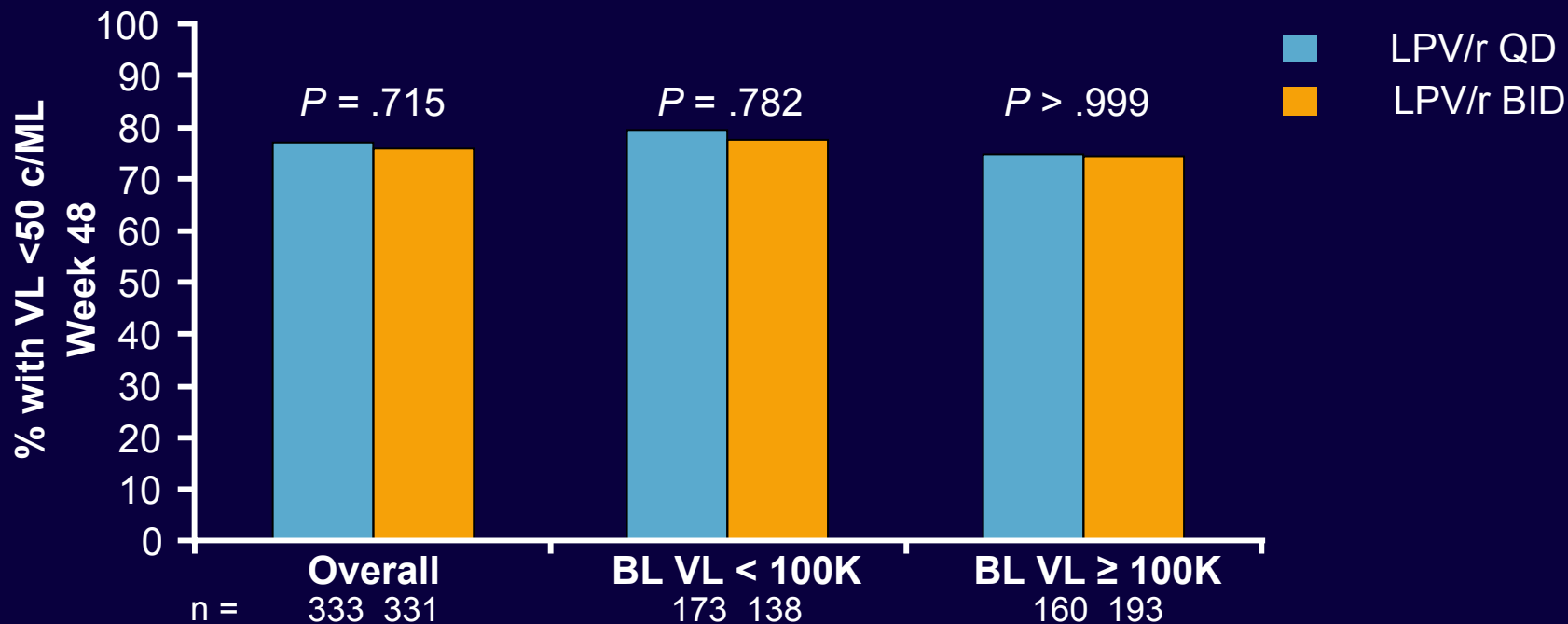
- Need for baseline tropism testing
- Twice-daily dosing
- Lack of long-term safety & efficacy data

# Question 2: Which Boosted PI?

PI/r	PROS	CONS
LPV/r	<ul style="list-style-type: none"><li>•Coformulated</li><li>•No refrigeration</li><li>•No food restrictions</li><li>•Preferred for pregnancy</li></ul>	<ul style="list-style-type: none"><li>•Requires 200 mg/d of RTV</li><li>•Metabolic toxicity</li><li>•GI side effects</li></ul>

# M05-730: LPV/r QD vs. BID < 50 c/mL at Week 48 (ITT, NC = F)

- LPV/r SGC vs tablet compared for 1st 8 weeks of study only, then all received tablet
- QD noninferior to BID: 76% vs 75% (95% CI: -5% to 8%)

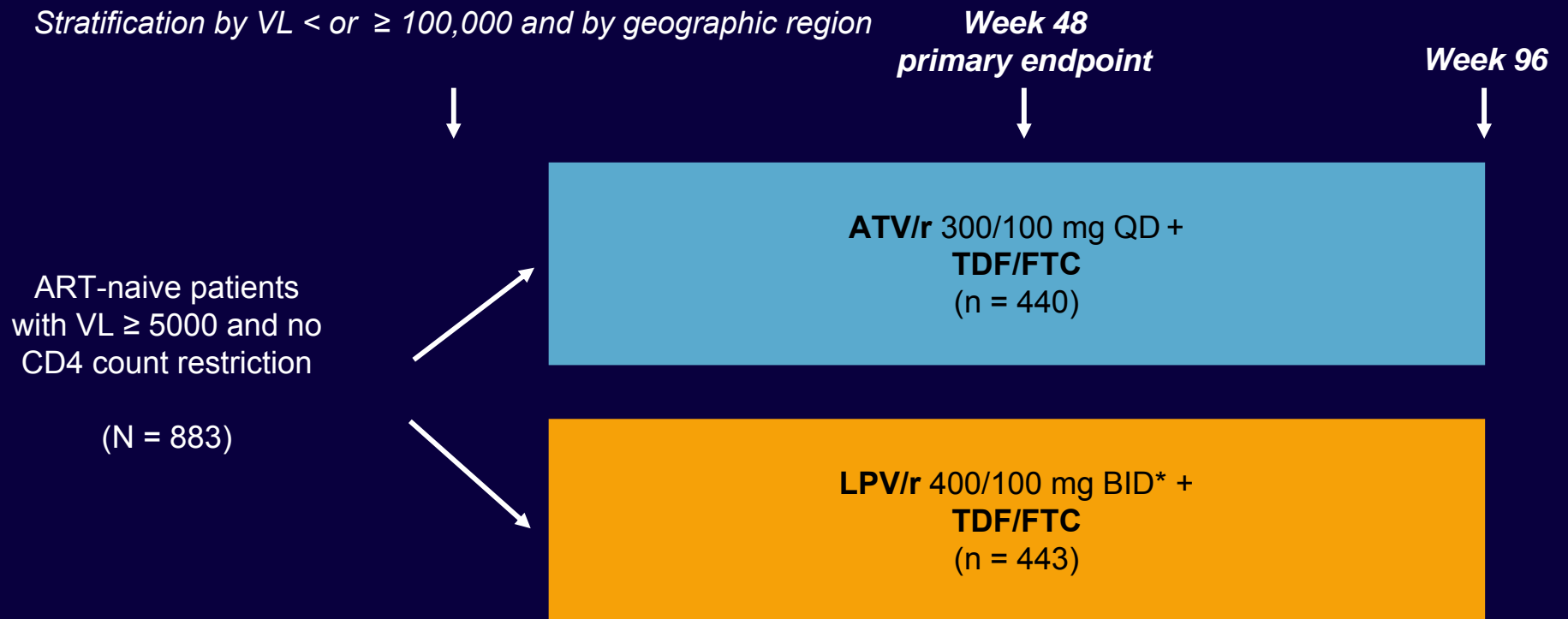


Similar CD4 increases at Week 48 with LPV/r QD (+186) vs BID (+197)

# Question 2: Which Boosted PI?

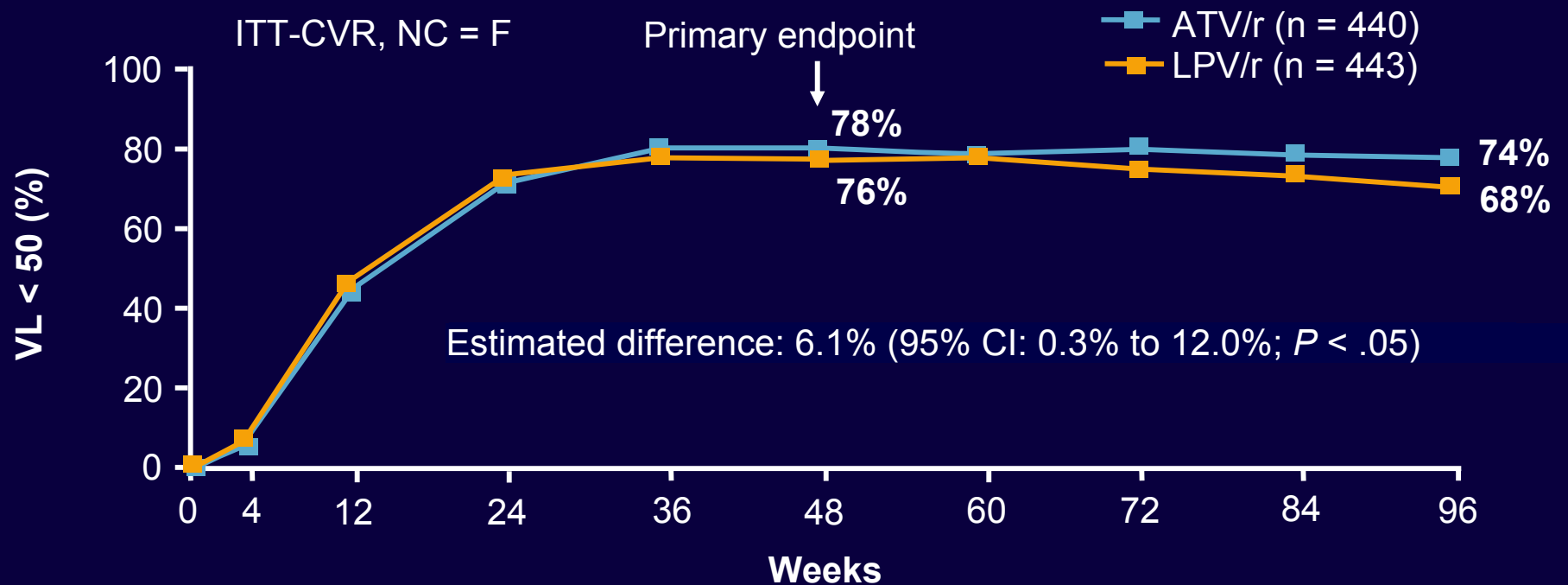
PI/r	PROS	CONS
<b>LPV/r</b>	<ul style="list-style-type: none"><li>• Coformulated</li><li>• No refrigeration</li><li>• No food restrictions</li><li>• Preferred for pregnancy</li></ul>	<ul style="list-style-type: none"><li>• Requires 200 mg/d of RTV</li><li>• Metabolic toxicity</li><li>• GI side effects</li></ul>
<b>ATV/r</b>	<ul style="list-style-type: none"><li>• Lowest pill burden (2/d)</li><li>• Once daily dosing</li><li>• Best GI tolerability</li><li>• Least metabolic toxicity</li></ul>	<ul style="list-style-type: none"><li>• Gastric acid requirement</li><li>• Food requirement</li><li>• Jaundice &amp; scleral icterus</li></ul>

# CASTLE: ATV/r vs LPV/r in ART-Naive Patients



\*LPV/r administered as soft-gel capsules through Week 48; tablet formulation administered after Week 48 where available.

# CASTLE: Week 96 Response to ATV/r vs LPV/r in Naive Patients



Supportive analyses:

ITT-TLOVR: VL < 50: ATV/r 70%; LPV/r 63%; 6.6% (0.4% to 12.7%)

OT-VR-OC: VL < 50: ATV/r 89%; LPV/r 88%; 1.6% (-3.1% to 6.2%)

Molina JM, et al. ICAAC/IDSA 2008. Abstract 1250d.

# CASTLE: Virologic Failure and Resistance at Week 96

Resistance Analysis, n	ATV/r (n = 438)	LPV/r (n = 443)
Patients with virologic failure	28	29
Patients with genotypes at baseline and virologic failure	26	26
▪ Major PI mutations	1*	0
▪ M184V/I	5	7
▪ K65R	1	0

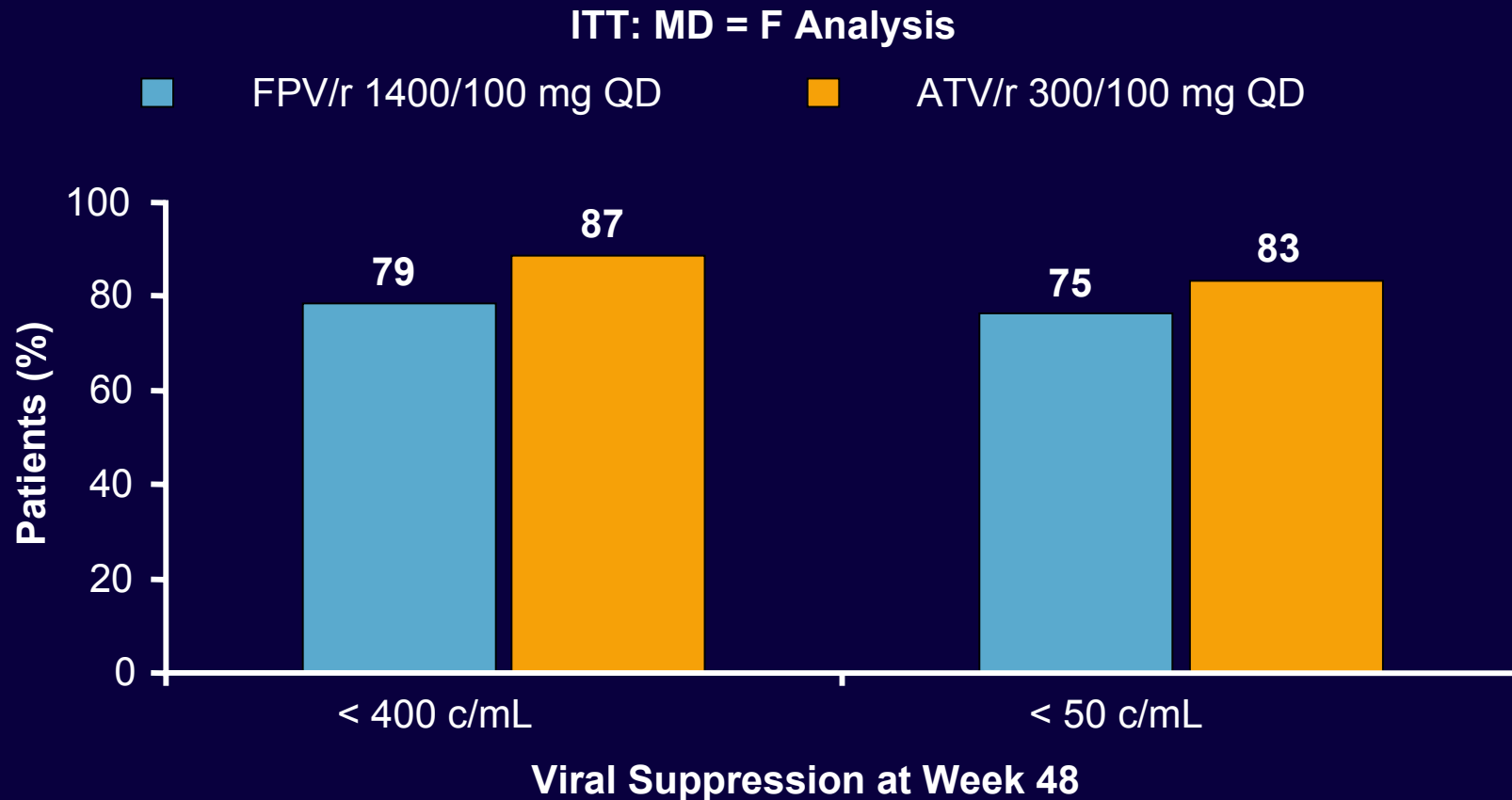
\*1 patient failed with L10F, V32I, K43T, M46I, A71I, G73S, L90M. A second patient on ATV/r who failed by Week 48 with N88S and M46I subsequently resuppressed VL and was not included.

- Higher discontinuation rate with LPV/r vs ATV/r (16% vs 21%, respectively)

# Question 2: Which Boosted PI?

PI/r	PROS	CONS
<b>LPV/r</b>	<ul style="list-style-type: none"><li>• Coformulated</li><li>• No refrigeration</li><li>• No food restrictions</li><li>• Preferred for pregnancy</li></ul>	<ul style="list-style-type: none"><li>• Requires 200 mg/d of RTV</li><li>• Metabolic toxicity</li><li>• GI side effects</li></ul>
<b>ATV/r</b>	<ul style="list-style-type: none"><li>• Lowest pill burden (2/d)</li><li>• Once daily dosing</li><li>• Best GI tolerability</li><li>• Least metabolic toxicity</li></ul>	<ul style="list-style-type: none"><li>• Gastric acid requirement</li><li>• Food requirement</li><li>• Jaundice &amp; scleral icterus</li></ul>
<b>FPV/r</b>	<ul style="list-style-type: none"><li>• No food restrictions</li><li>• QD dosing option (1400 + 100-200 mg of RTV)</li></ul>	<ul style="list-style-type: none"><li>• 700/100 mg BID dose: no advantage over LPV/r</li><li>• 1400/100 mg QD dose: not well studied compared to other PI/r options</li></ul>

# ALERT: FPV/r vs ATV/r in ART-Naive Patients, 48-week results



# FPV/r 1400/100 mg QD in ART-Naive Patients

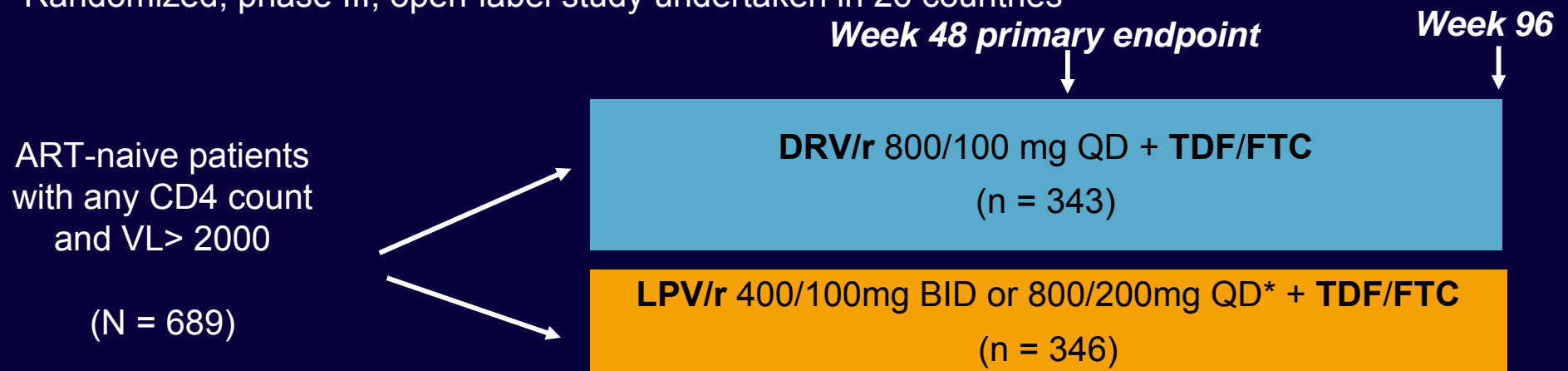
- COL100758: FPV/r 1400/200 mg vs 1400/100 mg QD (+ ABC/3TC) in 115 naive patients (96-wk data)
  - 1400/100 mg: greater virologic suppression by ITT analysis, better adherence, fewer early withdrawals, better lipid profile<sup>[2]</sup>
  - Virologic failure in 5/58 (9%) of 1400/100 mg arm and 8/57 (14%) of 1400/200 mg arm: no major PI mutations, 2/13 developed M184V<sup>[3]</sup>
- FPV/r switch study (N = 209): randomized switch from FPV/r 1400/200 to 1400/100 mg QD after suppression  $\geq$  3 mos (24-wk data)<sup>[4]</sup>
  - 1400/100 mg noninferior; suppression maintained: 1 virologic failure
  - Greater decrease in triglycerides with switch

# Question 2: Which Boosted PI?

PI/r	PROS	CONS
LPV/r	<ul style="list-style-type: none"> <li>•Coformulated</li> <li>•No refrigeration</li> <li>•No food restrictions</li> <li>•Preferred for pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>•Requires 200 mg/d of RTV</li> <li>•Metabolic toxicity</li> <li>•GI side effects</li> </ul>
ATV/r	<ul style="list-style-type: none"> <li>•Lowest pill burden (2/d)</li> <li>•Once daily dosing</li> <li>•Best GI tolerability</li> <li>•Least metabolic toxicity</li> </ul>	<ul style="list-style-type: none"> <li>•Gastric acid requirement</li> <li>•Food requirement</li> <li>•Jaundice &amp; scleral icterus</li> </ul>
FPV/r	<ul style="list-style-type: none"> <li>•No food restrictions</li> <li>•QD dosing option (1400 + 100-200 mg of RTV)</li> </ul>	<ul style="list-style-type: none"> <li>•700/100 mg BID dose: no advantage over LPV/r</li> <li>•1400/100 mg QD dose: not well studied compared to other PI/r options</li> </ul>
DRV/r	<ul style="list-style-type: none"> <li>•Superior to LPV/r (VL&gt;100K)</li> <li>•Better tolerability and less hyperlipidemia (vs. LPV/r)</li> <li>•No gastric acid issues (vs. ATV/r)</li> <li>•Stronger data (vs. FPV/r)</li> </ul>	<ul style="list-style-type: none"> <li>•Rash</li> </ul>

# ARTEMIS: DRV/r vs LPV/r in Treatment-Naive Patients

- Randomized, phase III, open-label study undertaken in 26 countries



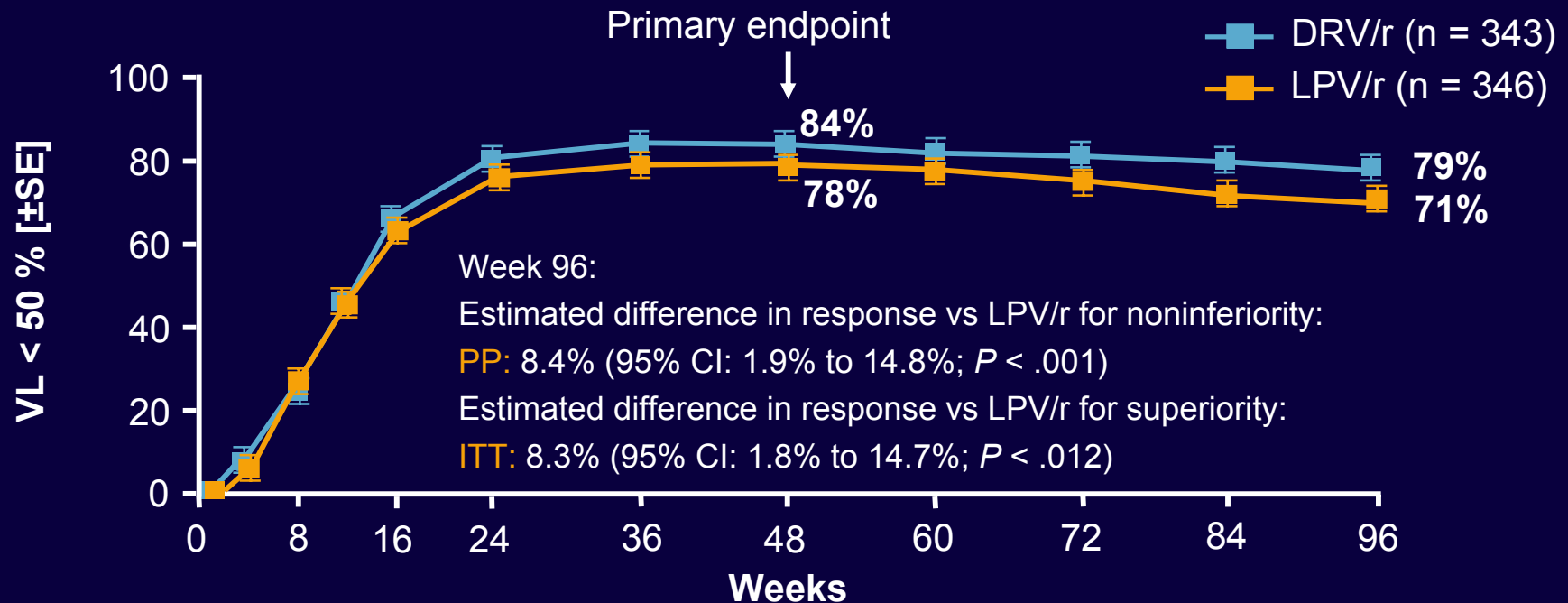
- Baseline disease characteristics in DRV/r vs LPV/r arms

- Median VL: 70,800 vs 62,100
- Median CD4 count: 228 vs 218

- 83% of patients switched from capsule to tablet formulation of LPV/r during study; switch made according to local regulatory approval and drug availability

\*Dosing based on regulatory approval; 77% of patients received BID dosing.

# ARTEMIS: Week 96 Response to DRV/r vs LPV/r in Naive Patients



- Superiority at Week 96 also observed when DRV/r (n = 343) compared with subset of patients treated with twice-daily LPV/r only (n = 258)
  - 79% vs 72% ( $P = .038$ )

# Question 3: Which NRTI Backbone?

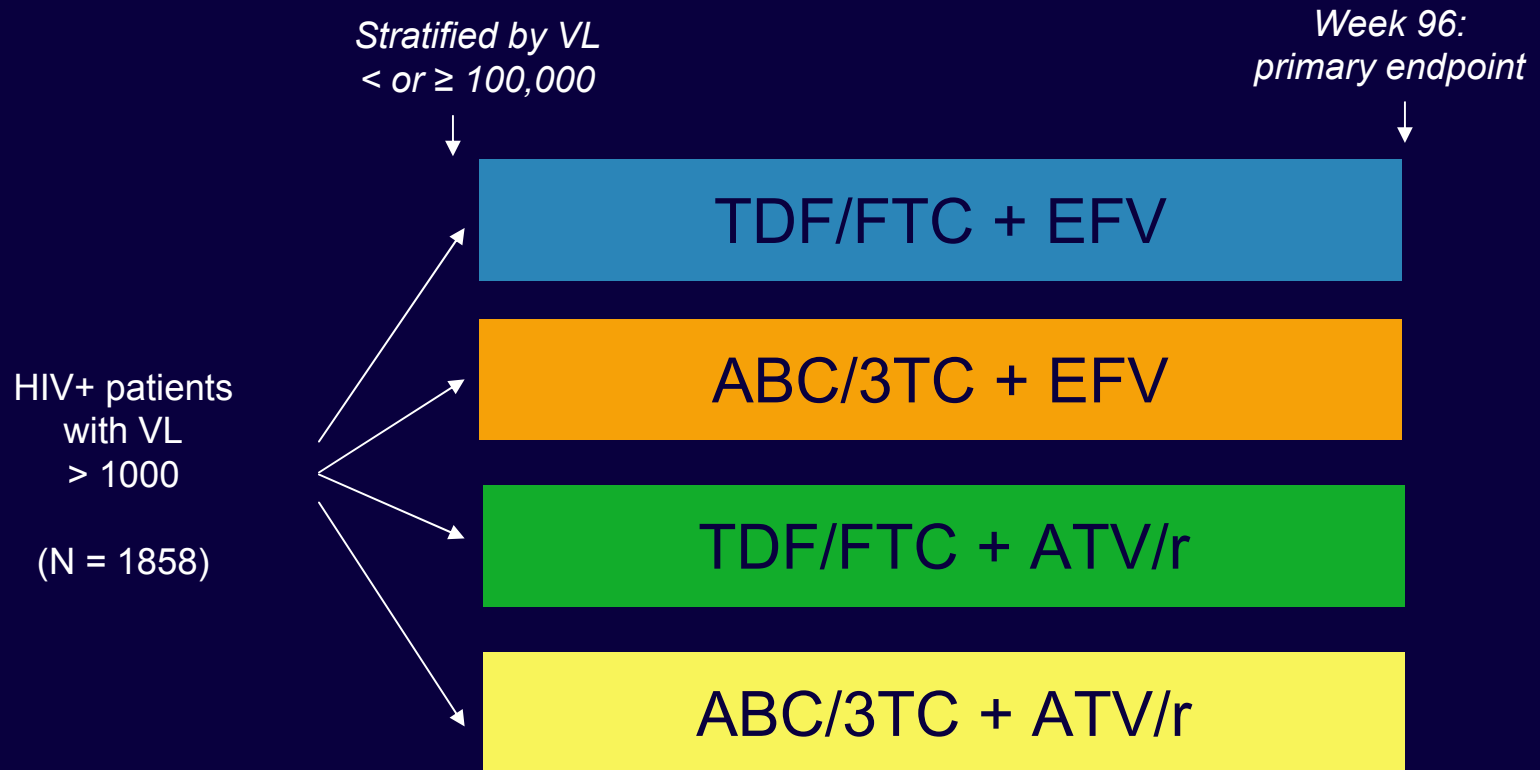
NRTIs	PROS	CONS
<b>TDF/FTC</b>	<ul style="list-style-type: none"><li>•Superior to AZT/3TC</li><li>•Less resistance than AZT/3TC or TDF/3TC</li><li>•Favorable toxicity profile</li><li>•Long-term data with EFV</li><li>•Preferred for HBV coinfection</li></ul>	<ul style="list-style-type: none"><li>•Renal toxicity</li></ul>

# Question 3: Which NRTI Backbone?

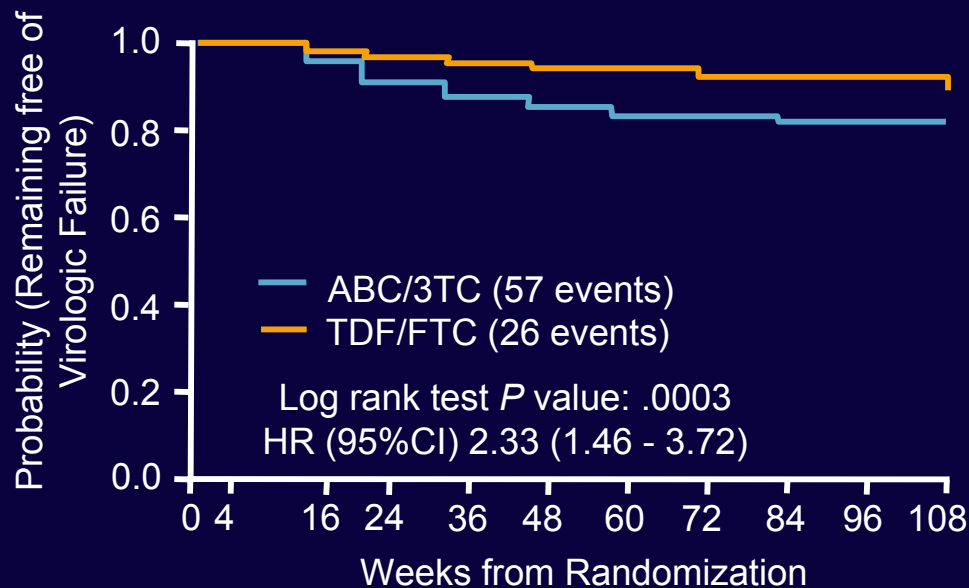
NRTIs	PROS	CONS
<b>TDF/FTC</b>	<ul style="list-style-type: none"><li>• Superior to AZT/3TC</li><li>• Less resistance than AZT/3TC or TDF/3TC</li><li>• Favorable toxicity profile</li><li>• Long-term data with EFV</li><li>• Preferred for HIV/HBV coinfection</li></ul>	<ul style="list-style-type: none"><li>• Renal toxicity</li></ul>
<b>ABC/3TC</b>	<ul style="list-style-type: none"><li>• Comparable to AZT/3TC, better CD4 response</li><li>• Favorable toxicity profile</li><li>• ↓ risk of HSR with HLA B*5701 screening</li></ul>	<ul style="list-style-type: none"><li>• ABC HSR</li><li>• Need for patient education +/- lab screening</li><li>• Risk of MI?</li><li>• Suboptimal at high viral loads?</li></ul>

# ACTG 5202: ABC/3TC vs TDF/FTC + EFV or ATV/r

- Randomized, double-blind, open-label, phase IIIb study



# ACTG 5202: Shorter Time to VF in Pts With High VL Receiving ABC/3TC



Outcome, n	ABC/3TC (n = 398)	TDF/FTC (n = 399)
Virologic failure (VF), total	57	26
▪ Early VF with no previous suppression to VL < 200	19	9
▪ Late VF with no previous suppression to VL < 200	9	2
▪ Late VF with previous suppression to VL < 200	29	15

- Similar proportions in each arm with VL < 50 at Wk 48 ( $P = .20$ ) by ITT (switching NRTIs  $\neq$  failure)
- Post hoc analysis: for subjects achieving 2 VL < 50 on therapy, no significant difference in risk of viral rebound between arm ( $P = .247$ )

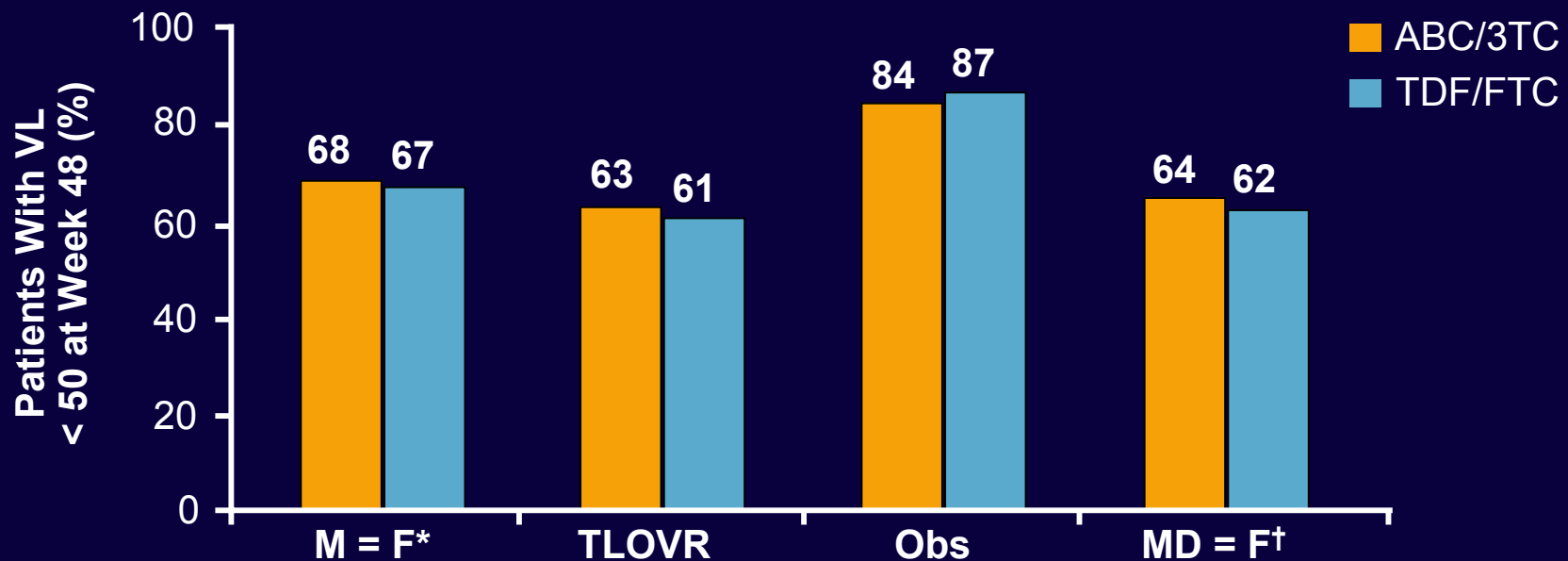
# ACTG 5202: Immunologic Response and Adverse Events

- Similar increases in CD4 count in both arms, reaching approximately 400 by Week 96
- No association of suspected drug hypersensitivity and virologic failure
  - Rates of suspected HSR similar between arms
  - Most patients with suspected HSR did not experience virologic failure

Adverse Events, %	ABC/3TC (n = 398)	TDF/FTC(n = 399)
Any grade 3/4 event*	33	19
■ Lipid abnormalities	10	3
■ Gastrointestinal	7	5
■ General body	14	10
Suspected drug HSR	7	7

\*Occurring in  $\geq 5\%$  of patients reported.

# HEAT: Virologic and Immunologic Outcomes at Week 48



\*NRTI switches allowed.

†NRTI switches counted as failure.

LPV/r could be switched to FPV/r.

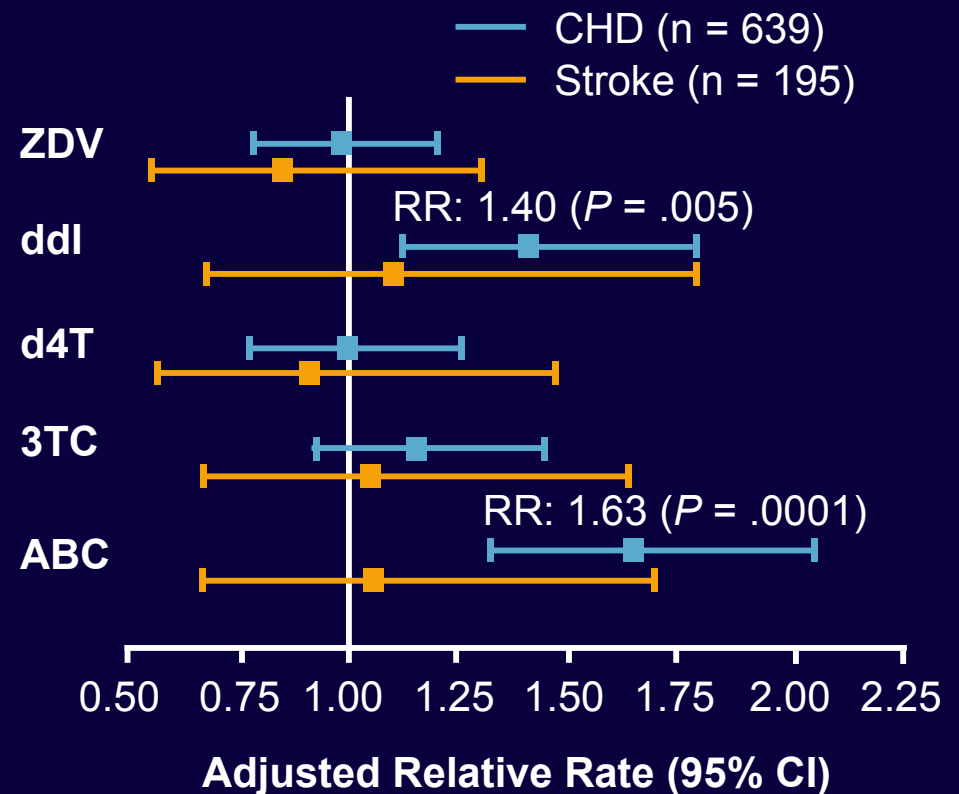
- Numerically greater median CD4 count increases with ABC/3TC vs TDF/FTC:
  - +201 vs +173 at Week 48, respectively

# ACTG 5202: Possible Explanations For Differing Results vs Similar Trials

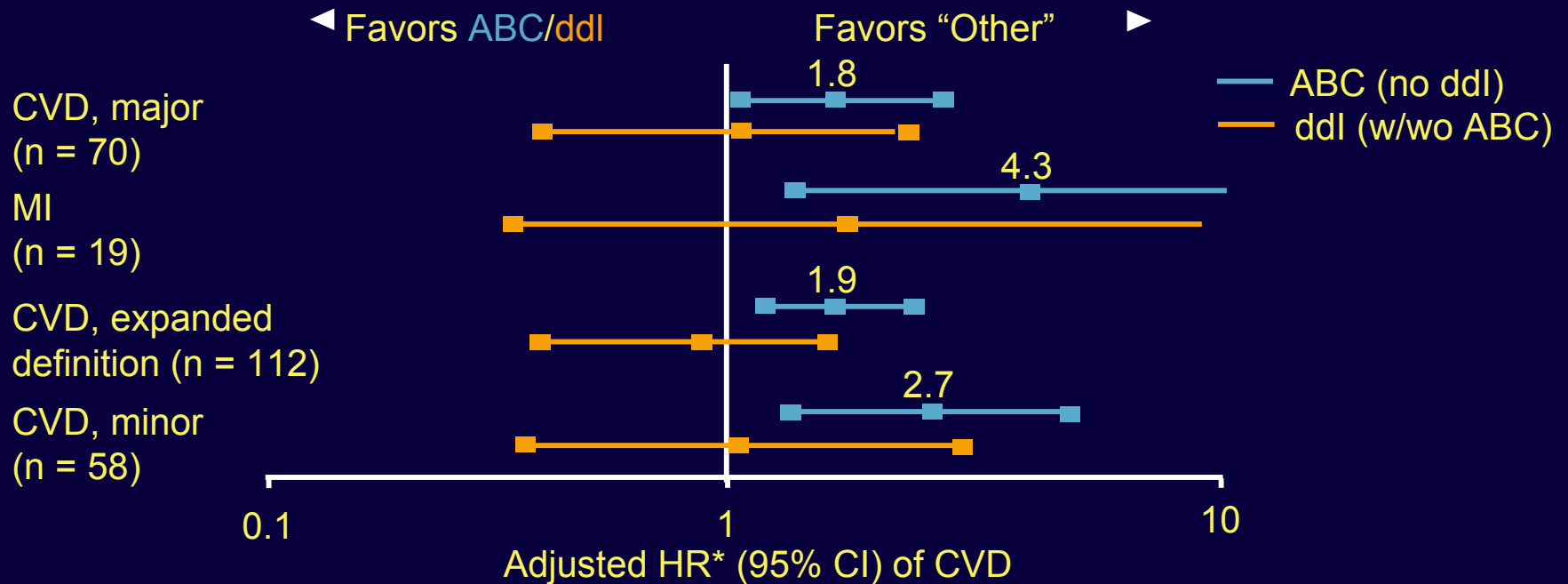
- Differing study designs
  - Duration of follow-up
  - Endpoints: different definitions/timepoints for virologic failure; TLOVR vs % with VL < 50
  - Larger vs smaller sample size
  - ABC/3TC compared with different NRTI strategies: ZDV/3TC, TDF/FTC
  - Different 3rd drug used: ATV/r, EFV, LPV/r, FPV/r

# D:A:D Study: Recent Use of ABC, ddl Associated With Increased Risk of MI

- Current or recent (within 6 mos) use of ABC or ddl associated with ↑ relative risk of MI
  - 90% ↑ risk of MI with recent ABC
  - 49% ↑ risk of MI with recent ddl
  - Risk most prominent in individuals with underlying CVD risk factors
- ↑ risk no longer observed in patients who had discontinued ABC or ddl for > 6 mos



# SMART: Current Use of ABC But Not ddl Associated With Increased CV Risk



- Increased risk of CVD events with use of ABC detected only among patients with  $\geq 5$  CV risk factors at baseline (adjusted HR: 3.1)
  - However, difference in risk between patients with vs without these factors failed to reach statistical significance

# Question 3: Which NRTIs?

**C**

Decreased  
kidney  
function

HLA B\*5701  
negative

**ABC/3TC**



# Question 3: Which NRTIs?

**C**

Decreased  
kidney  
function and  
multiple  
cardiac risk  
factors

**NRTI-sparing  
regimen?**

**ABC/3TC**

# Examples of NRTI-Sparing Options

## ■ PI/r + NNRTI

- LPV/r + EFV: well studied and effective, but poorly tolerated with significant hyperlipidemia
- ATV/r + EFV: not well studied, easier and likely to be better tolerated with better lipid profile; need for increased ATV/r dose (400/100 mg QD)
- DRV/r + EFV: not studied; ARTEMIS dose of DRV/r (800/100 QD) OK?

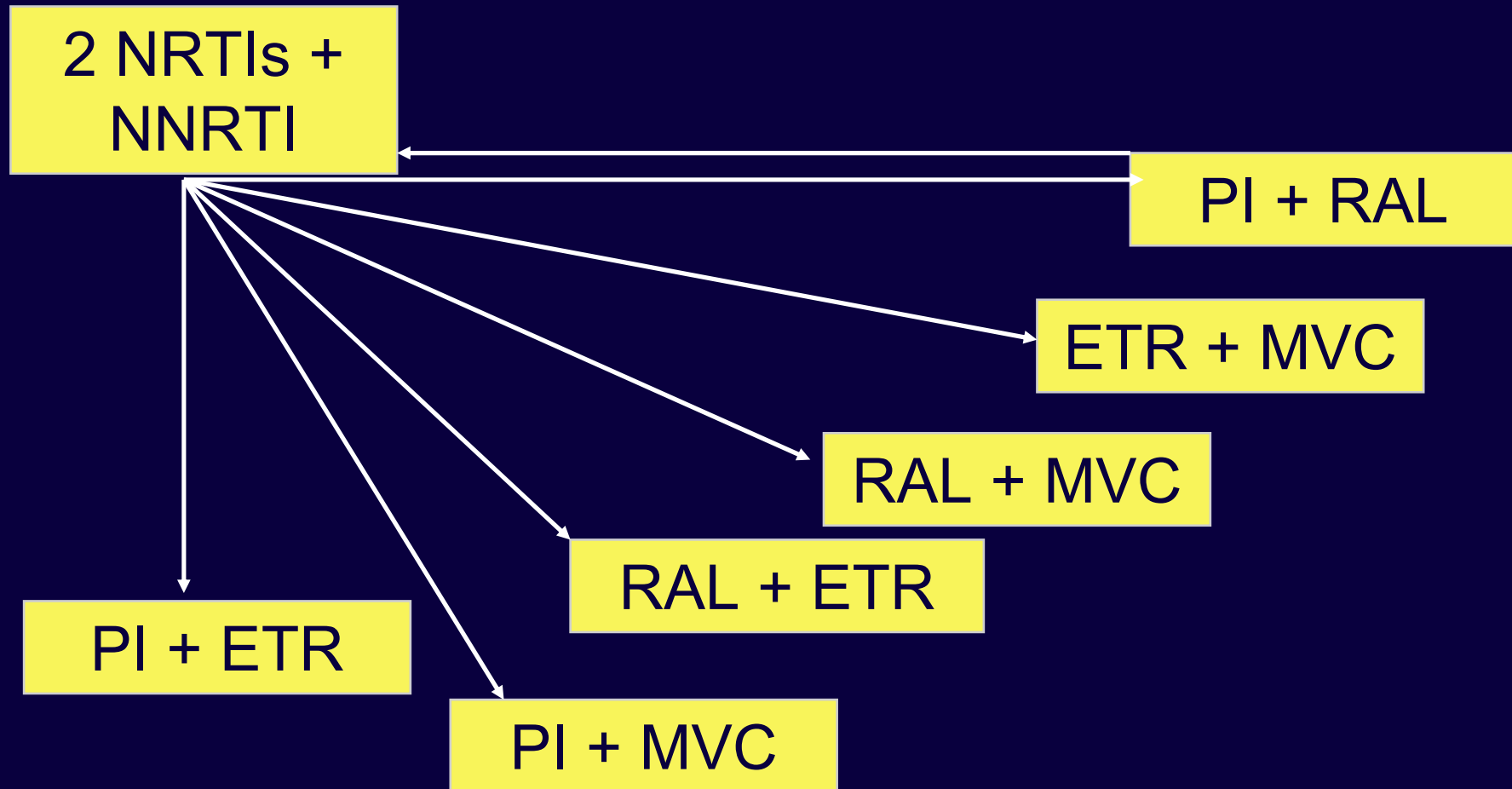
## ■ PI or PI/r + RAL

- Under study, including RAL + ATV 300 mg BID

## ■ RAL + NNRTI

- No data; low barrier to resistance with both drugs

# New Sequencing Options for First Failure



# Starting Therapy: The Basic Questions

- Is the patient ready?
- Does the patient meet guidelines criteria for starting?
- If not, is there a reason to start anyway?
- Is there baseline resistance?
- Assuming no resistance, which regimen?
  - EFV, a boosted PI, or RAL?
  - If a PI, which one?
  - Which NRTI backbone?

# The Next Drugs?

- Rilpivirine: NNRTI with promise for initial therapy. Probable cross-resistance with ETR
- Elvitegravir: Once-daily boosted integrase inhibitor. Cross-resistance with RAL
- Vicriviroc: Once-daily boosted CCR5 inhibitor. Will be ineffective in patients who fail MVC with D/M-tropic virus

