First-Line Antiretroviral Therapy for Treatment and Prevention:

The Past, Present and Future Best Options

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IAS-USA Guidelines 7/2008: When To Start

Clinical Condition and/or CD4 Count	Recommendations
Symptomatic HIV infection Asymptomatic CD4 *before* CD4 <350	Start ART

US DHHS Guidelines; Revised January 29, 2008. http://.aidsinfo.nih.gov/contentfiles/adultandadolescnetGL.pdf.

IAS-USA Guidelines 7/2008: When To Start

Clinical Condition and/or CD4 Count	Recommendations
Symptomatic HIV infection Asymptomatic CD4 *before* CD4 <350	Start ART
CD4 ≥ 350	Considerations: -HIV-1 RNA > 100,000 -CD4 decline > 100 cells/year -HBV infection -HCV infection -Cardiovascular disease -HIV-associated nephropathy -Mother-to-child transmission -Serodiscordant relationships

US DHHS Guidelines; Revised January 29, 2008. http://.aidsinfo.nih.gov/contentfiles/adultandadolescnetGL.pdf.

DHHS Guidelines 11/2008: When To Start

Clinical Condition and/or CD4 Count	Recommendations
• History of AIDS-defining illness • CD4 ≤ 350 • Pregnant women • HIVAN • HBV coinfection when HBV treatment is indicated	Start ART

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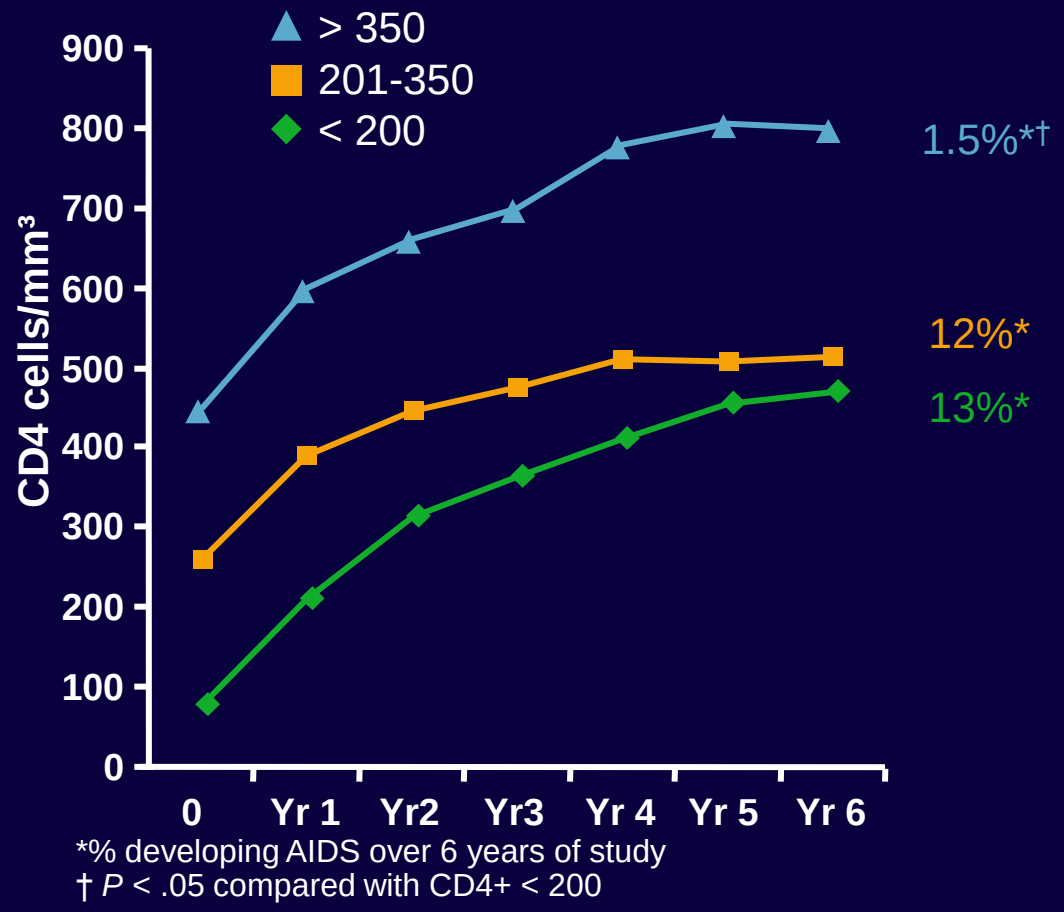
DHHS Guidelines 11/2008: When To Start

Clinical Condition and/or CD4 Count	Recommendations
• History of AIDS-defining illness • CD4 ≤ 350 • Pregnant women • HIVAN • HBV coinfection when HBV treatment is indicated	Start ART
CD4 > 350	Considerations: – Older age – Comorbidities – CD4 decline > 120 cells/year – Serodiscordant relationships

US DHHS Guidelines; Revised January 29, 2008. http://.aidsinfo.nih.gov/contentfiles/adultandadolescnetGL.pdf

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

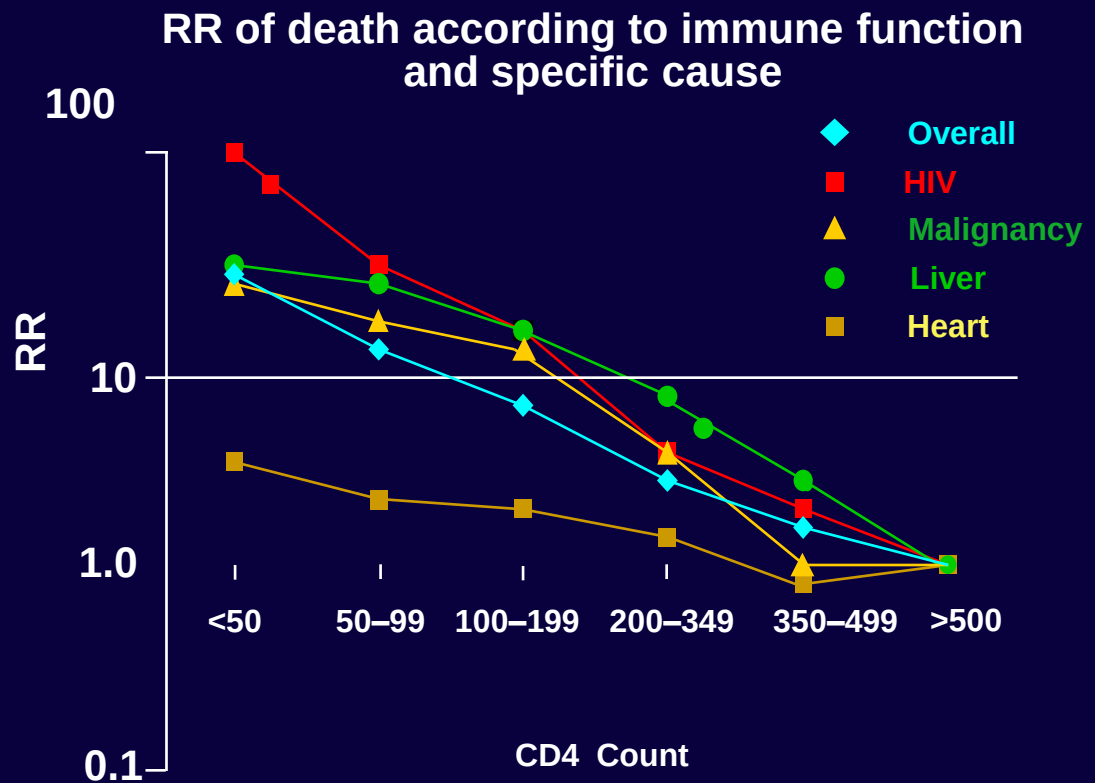
- Johns Hopkins HIV Cohort
- Patients with virologic suppression for up to 6 yrs (N=280)
- Only patients with baseline CD4 >350 returned to near normal CD4 count levels
- Rate of progression to AIDS or death significantly higher over time in patients with CD4 <200 and 201-350 vs. >350



Moore RD, et al. IAC 2006. Abstract THPE0109.

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

- Cohort of >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, suggesting role for immunosuppression in causes of death typically considered not HIV-related*

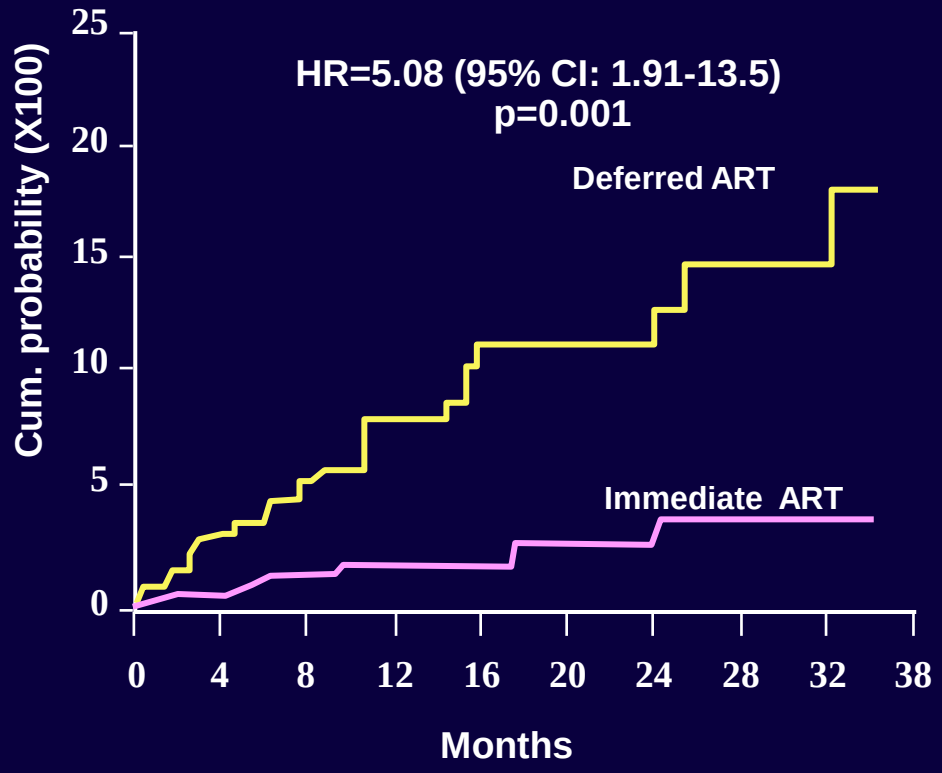


**Liver-related: Chronic viral hepatitis, liver failure (other); malignancy-related: malignancy, non-AIDS hepatitis; heart-related: MI, other CVD, other heart disease*

Weber R et al. 12th CROI; 2005; Boston. Abstract 595.

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



1. Emery S, *et al. 4th IAS*, Sydney 2007, #WEPEB018; 2. Marin B, *et al. ibid*, #WEPEB019

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[1]
  - ↑ 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)[2]

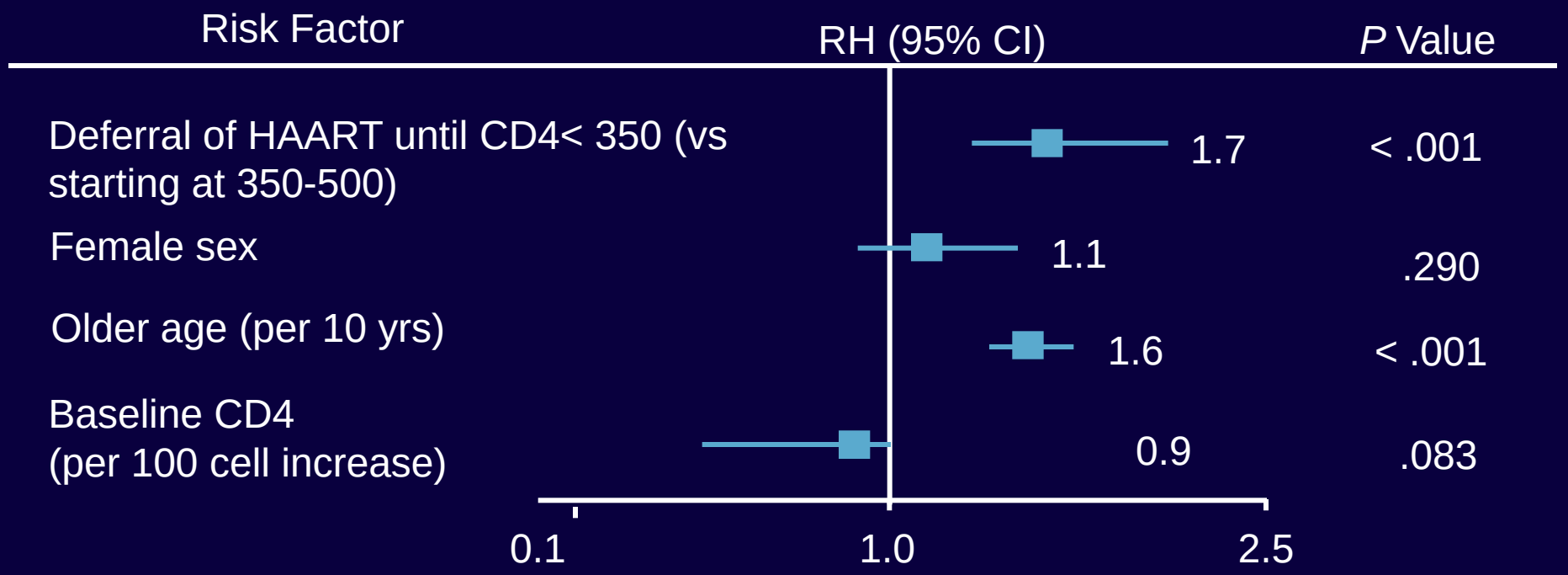
1. Kuller L, et al. CROI 2008. Abstract 139. 3. Calmy A, et al. CROI 2008. Abstract 140.

NA-ACCORD: Mortality with Early vs Deferred HAART

- NA-ACCORD includes 22 HIV research cohorts
- Current analyses:
  - 1. Patients with CD4 351-500 at visit between 1996-2006[1]
  - 2. Patients with CD4 >500 at visit between 1996-2006[2]
- Compared outcomes based on following definitions:
  - Early: initiated HAART within 1.5 years of first CD4 count in 351-500[1] or >500[2] range
  - Deferred: did not initiate HAART within 1.5 years of first CD4 count in those ranges
- Primary outcome: all-cause mortality

1. Kitahata, et al. ICAAC/IDSA 2008. Abstract 896b. 2 Kithata et al.CROI 2009. Abstratc 71..

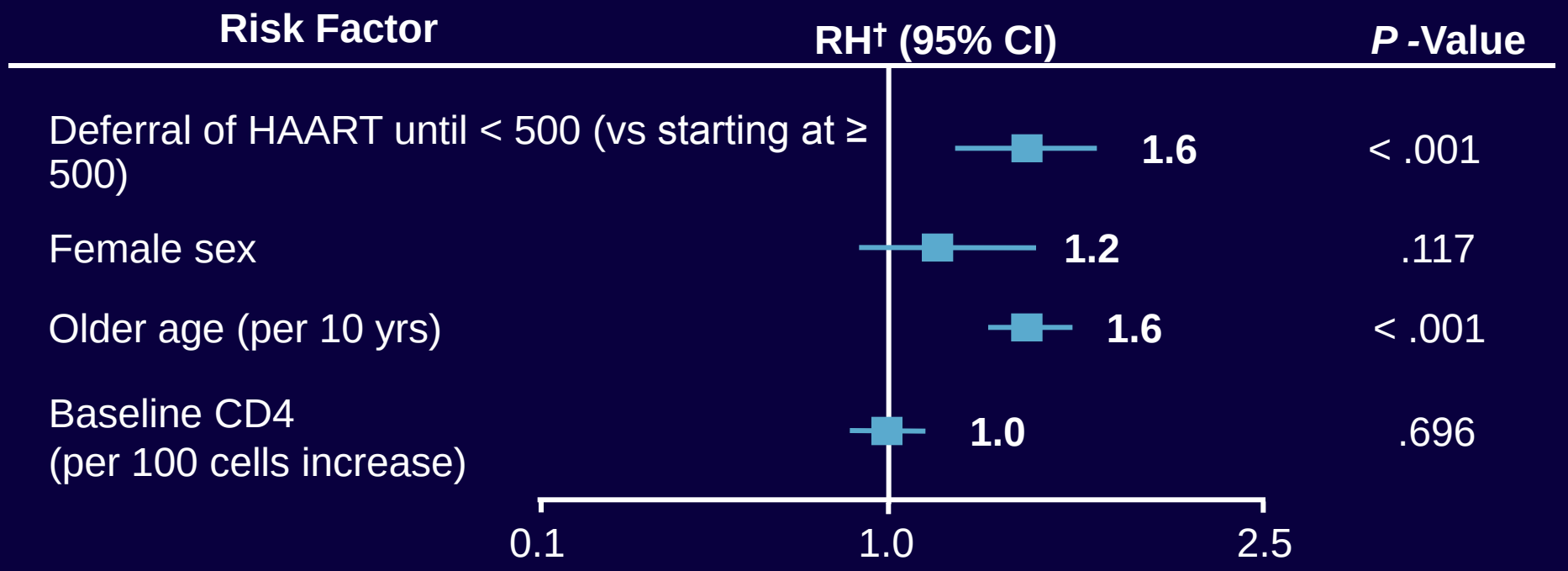
NA-ACCORD: Mortality with Early vs Deferred HAART (350-500 vs. >500 analysis)



- Increased risk of death with deferral unchanged when adjusted for IDU or for HCV coinfection, both independent predictors of mortality

Kitahata, et al. ICAAC/IDSA 2008. Abstract 896b.

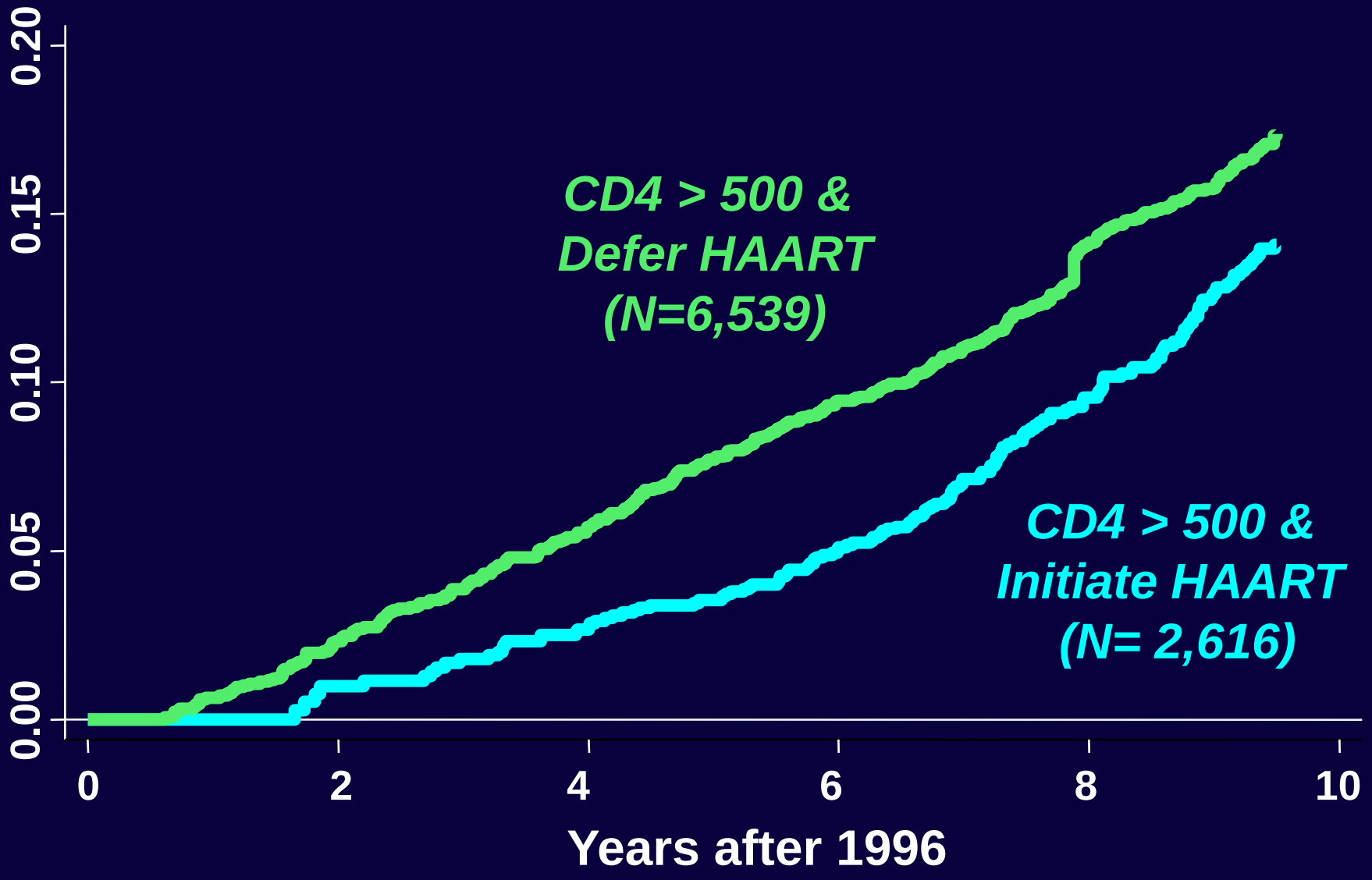
NA-ACCORD: Mortality with Early vs Deferred HAART (>500 vs. <500 analysis)



†Stratified by cohort and calendar year.

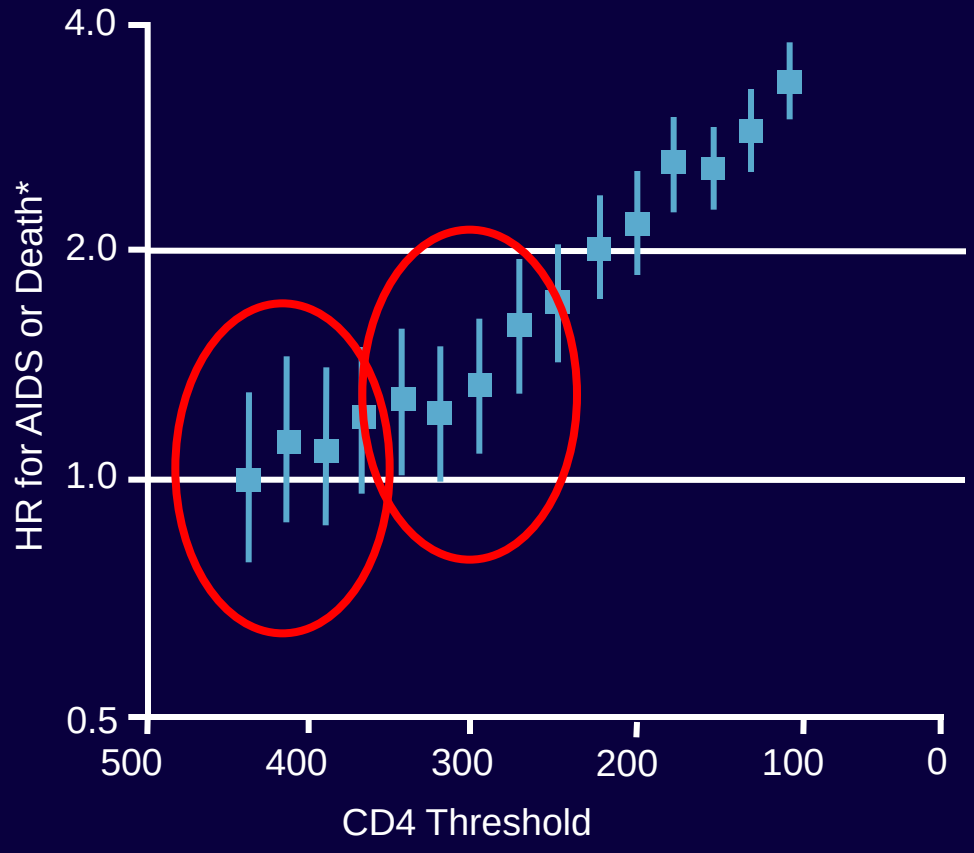
Kitahata MM, et al. CROI 2009. Abstract 71.

NA-ACCORD:
Cumulative Mortality Estimates



ART-CC: Prognosis based on CD4 count at initiation of ART

- ART Cohort Collaboration:15 cohorts from US and Europe (N = 24,444)



Comparison	HR* (95% CI)
1-100 vs 101-200	3.35 (2.99-3.75)
101-200 vs 201-300	2.21 (1.91-2.56)
201-300 vs 301-400	1.34 (1.12-1.61)
251-350 vs 351-450	1.28 (1.04-1.57)
351-450 vs 451-550	0.99 (0.76-1.29)

*Adjusted for lead-time and unobserved events.

Sterne J, et al. CROI 2009. Abstract 72LB.
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ART and Sexual Transmission: Data from CROI 2009

- Rakai study: 205 discordant couples
  - 20 positive partners started on ART based on standard guidelines
  - 34 transmissions among untreated couples (8.6/100 p-y) vs. 0 among treated couples (26.4 p-y of follow-up)

- Rwanda/Zambia study: 2993 discordant couples
  - 171 of the 175 transmissions occurred in untreated couples
  - 3.4 vs. 0.7 transmissions/100 p-y: 5-fold reduction in risk

1. Reynolds S, et al. CROI 2009, Abstract 52a. 2. Sullivan P, et al. CROI 2009, Abstract 52bLB.

“Our model suggests that massive scale-up of universal voluntary HIV testing with immediate initiation of ART could nearly stop transmission and drive HIV into an elimination phase in a high-burden setting within 1-2 years of reaching 90% of programme coverage.”

- Reuben M Granich, MD, et al. Lancet 2008;

When to Start: Conclusions

- Observational data concordant on starting therapy at CD4 >350
- Growing support in *some* studies for initiation at CD4 >500
- Unlike other treatable infectious diseases, the burden of proof is still on those who would treat early; deferral remains the default in the absence of data
- Prediction: In the future, we will ask “who should *not* be treated?”
  - Patients unready, unwilling, or unable to adhere
  - Long-term non-progressors or elite controllers?

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

IAS-USA Guidelines "Recommended"			
NNRTI-based regimen	EFV* NVP†	+	TDF/FTC† ABC§/3TC‡
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.

Hammer SM, et al. *JAMA.* 2008;300:555-570.

The Initial Regimen: DHHS Guidelines, 11/3/2008

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

US Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/Default.aspx.

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

EFV: Unbeaten in clinical trials

EFV Wins

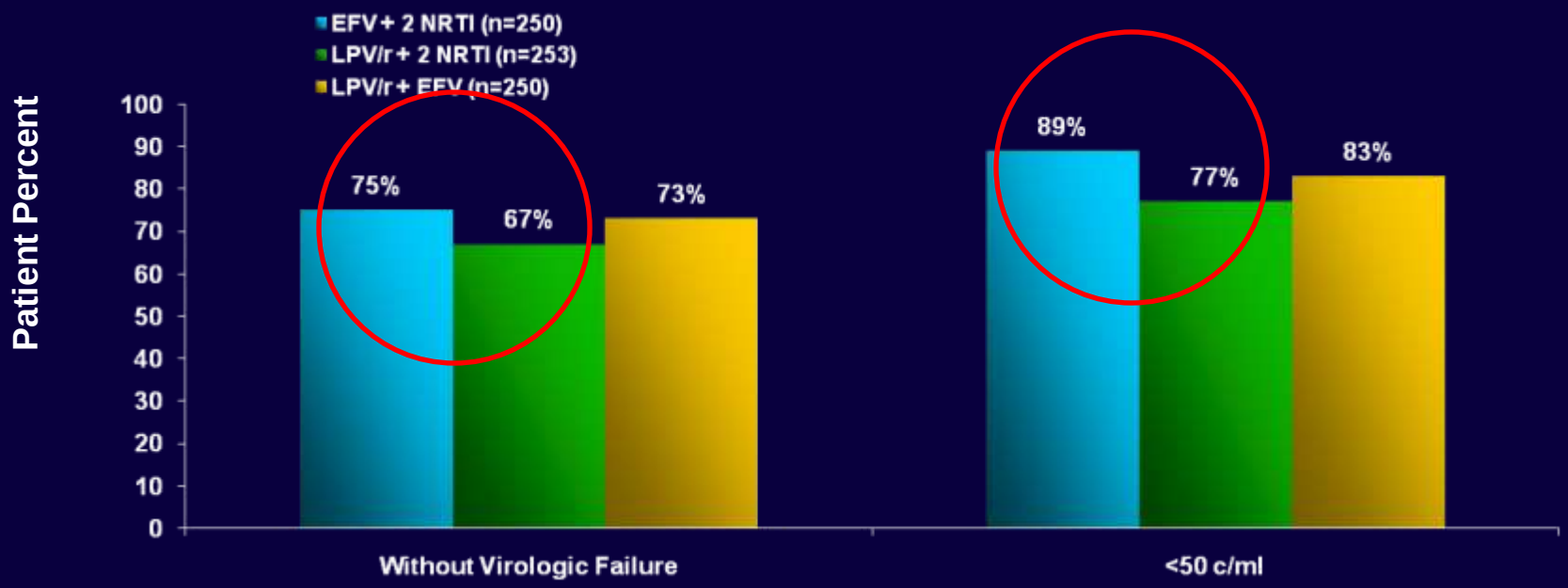
ABC:	ACTG 5095
d4T:	Class
IDV:	DMP 006
NFV:	ACTG 384, Initio
APV/r:	Class
SQV/r:	Focus
LPV/r:	ACTG 5142

A Draw

NVP:	2NN
ATV:	BMS 034
RAL:	STARTMRK

Cal Cohen (Adapted)

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

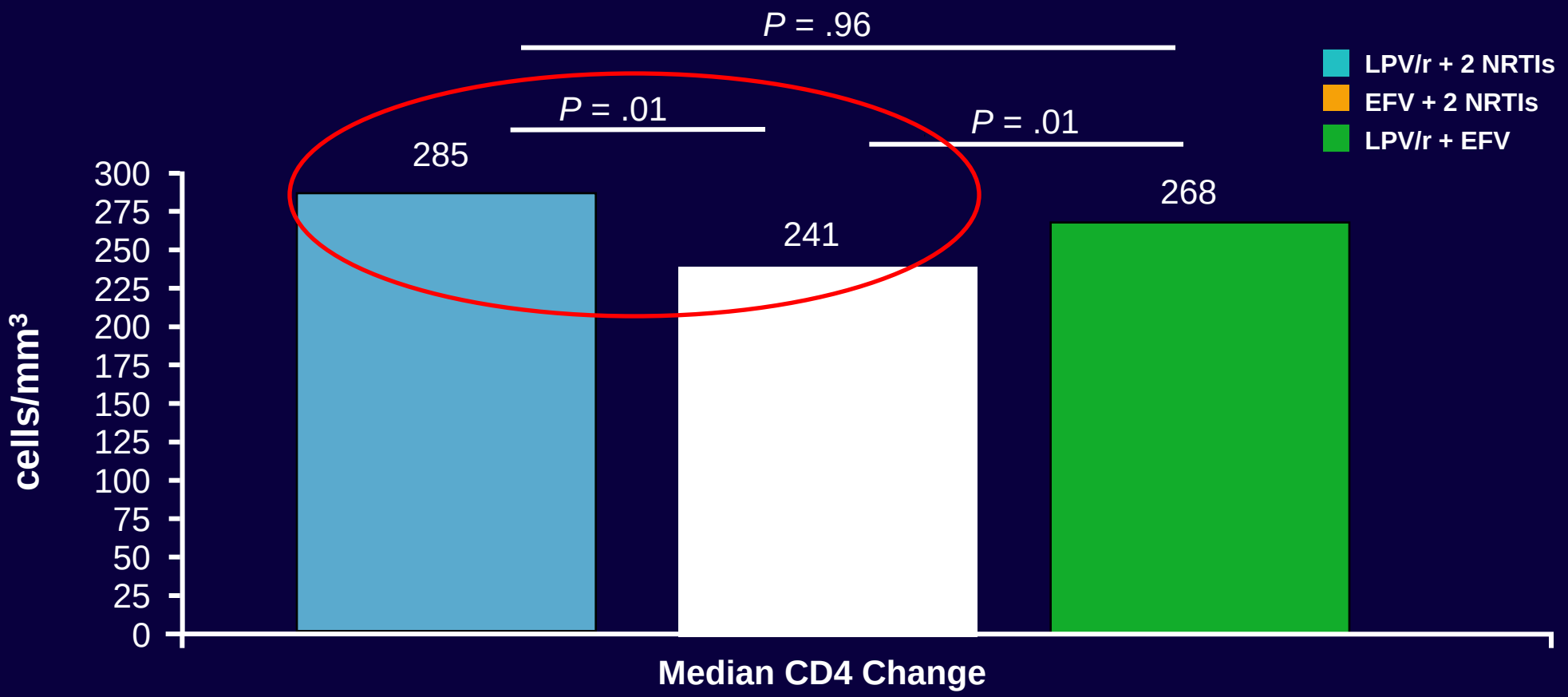
Greater day 7 VL reduction associated with 24, 48, and 96-week virologic response

Riddler SA, et al. *N Engl J Med* 2008;358:2095-106

Question 1: EFV vs. Boosted PI?

EFV	BOOSTED PI
•Gold standard for virologic efficacy •Easiest regimens (1-2 pills/d) •Minimal long-term toxicity •Favorable PK	•Better CD4 response than EFV (LPV/r: ACTG 5142) •Less resistance with failure •Preferred if risk for pregnancy •Preferred if baseline NNRTI (or NRTI?) resistance

ACTG 5142: Change in CD4 Count at Week 96



Riddler SA, et al. *N Engl J Med* 2008;358:2095-106

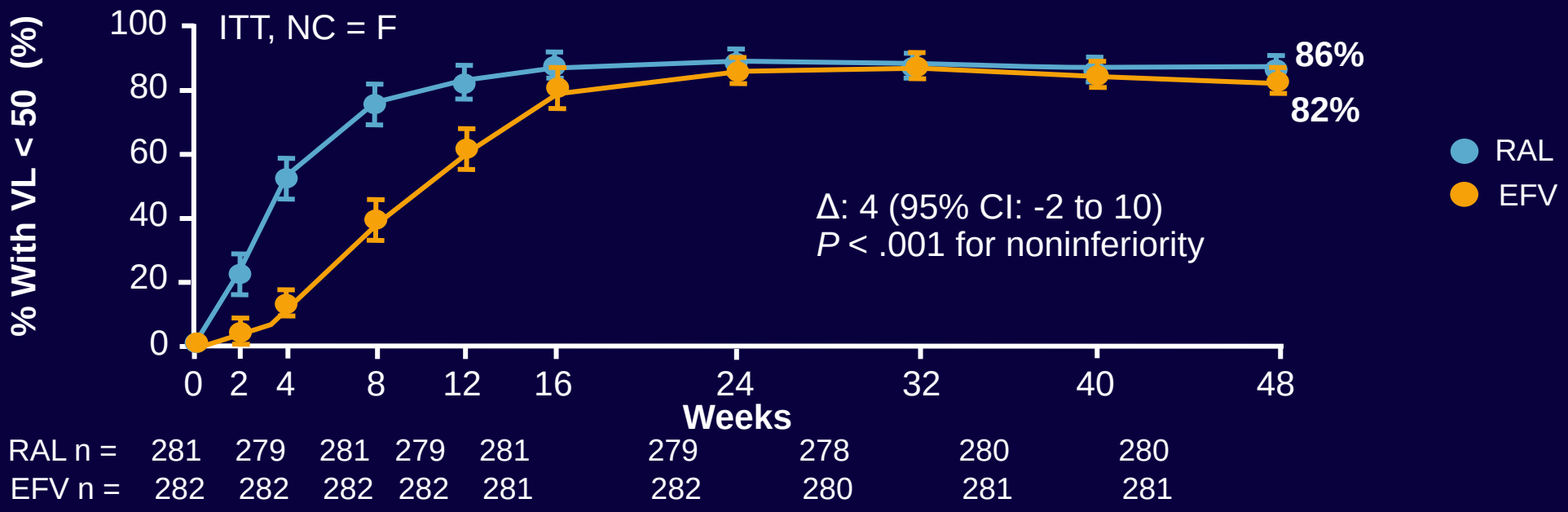
ACTG 5142: Resistance Mutations

Characteristic	LPV	EFV	LPV/ EFV
Observed viral failure, n	94	60	73
Genotypic assay available, n	52	33	39
Any PI mutations, n	20	13	18
Major PI mutations*	0	0	2
NNRTI mutations, n (%)	2 (4)	16 (48)	27 (69)
NRTI mutations, n (%)	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.

Riddler SA, et al. *N Engl J Med* 2008;358:2095-106

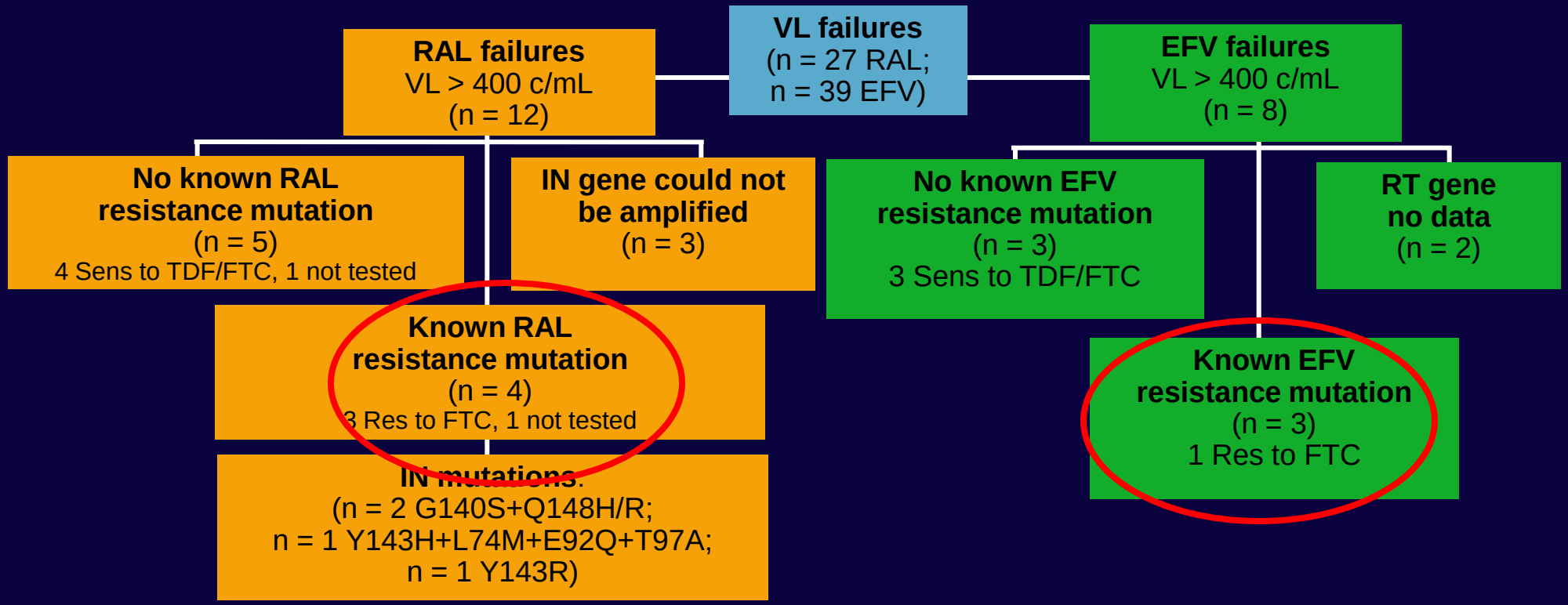
STARTMRK: Virologic and Immunologic Efficacy at Week 48



- Significantly shorter time to virologic response with RAL vs EFV (*P* < .001)
- Significantly greater CD4 count increase with RAL vs EFV
  - +189 vs +163; Δ: 26 (95% CI: 4-47)
- Fewer CNS events by Week 8 with RAL vs EFV (10.3% vs 17.7%; *P* = .015)

Lennox J, et al. ICAAC/IDSA 2008. Abstract 896a.

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

Lennox J, et al. ICAAC/IDSA 2008. Abstract 896a.

Question 1: EFV, boosted PI, or RAL?

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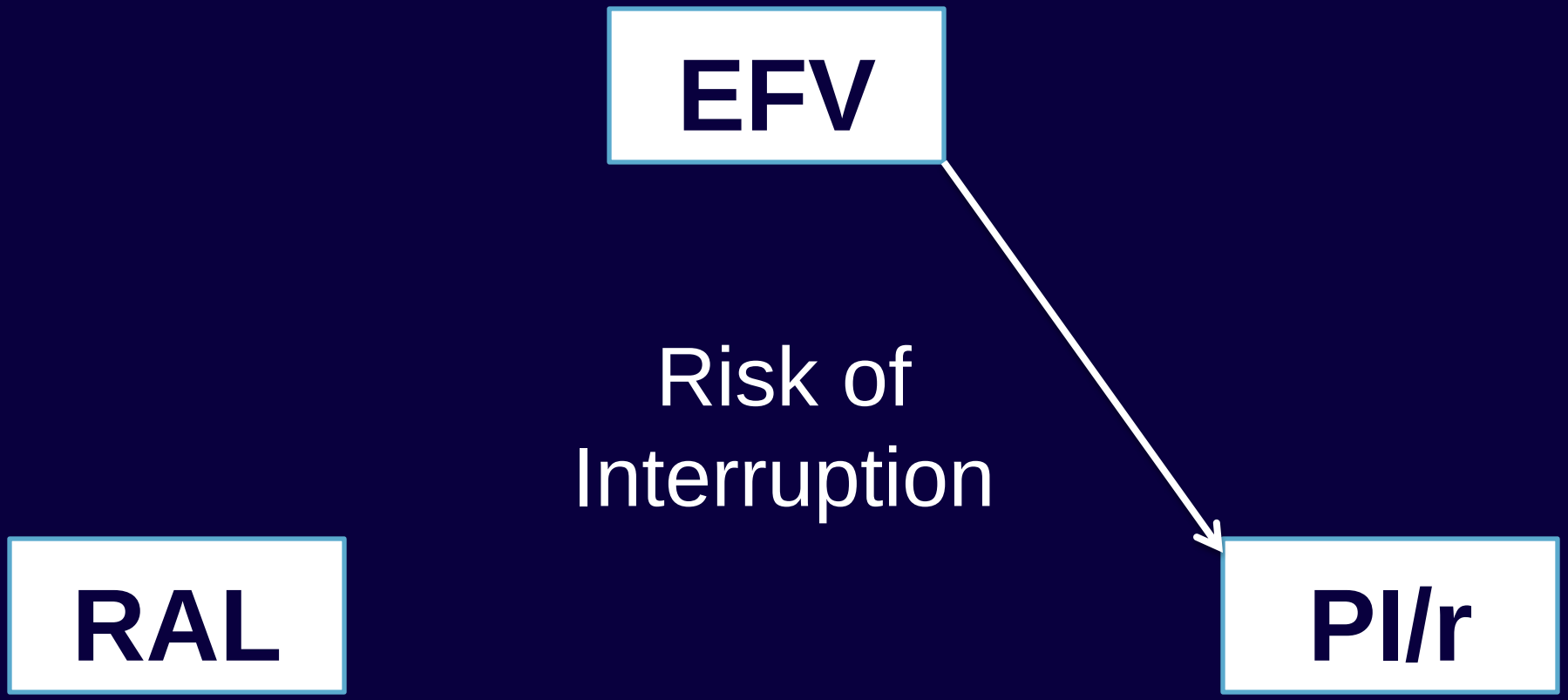

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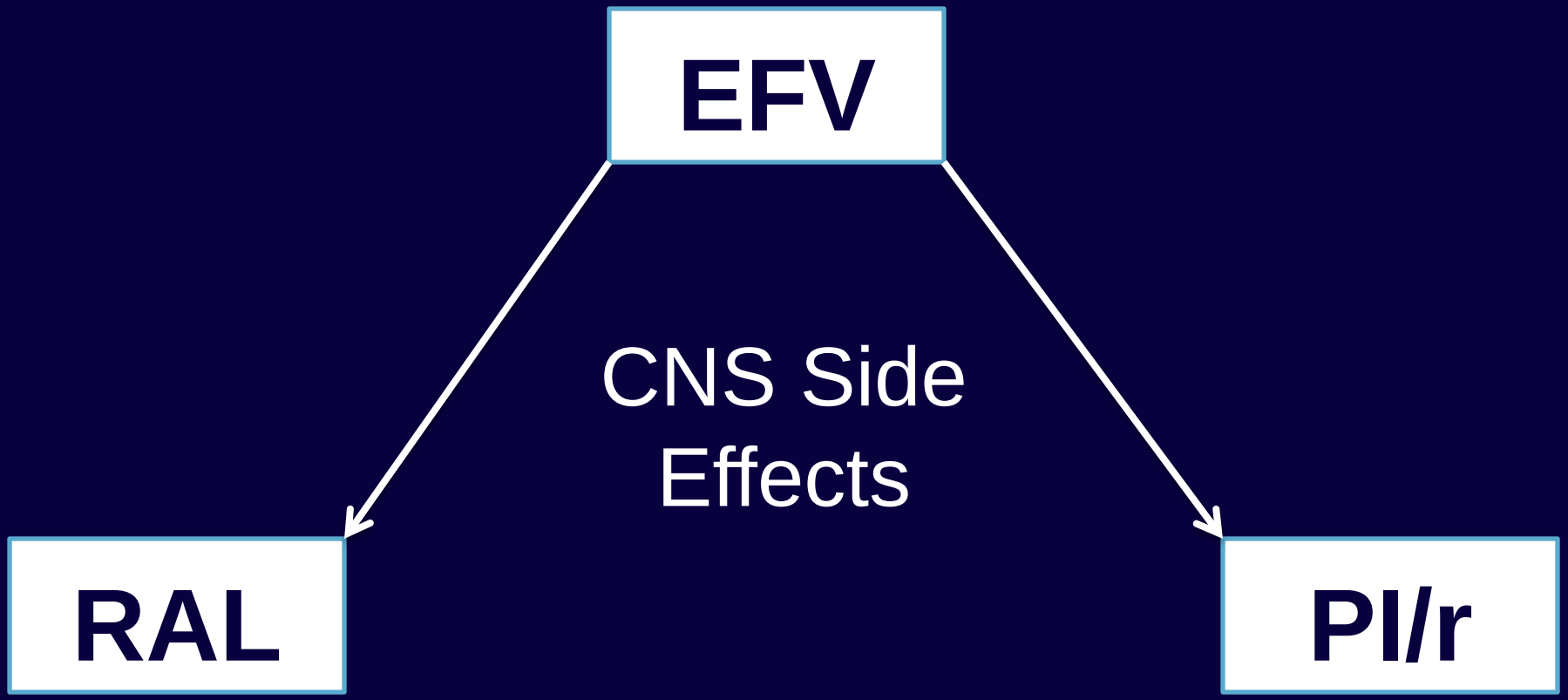

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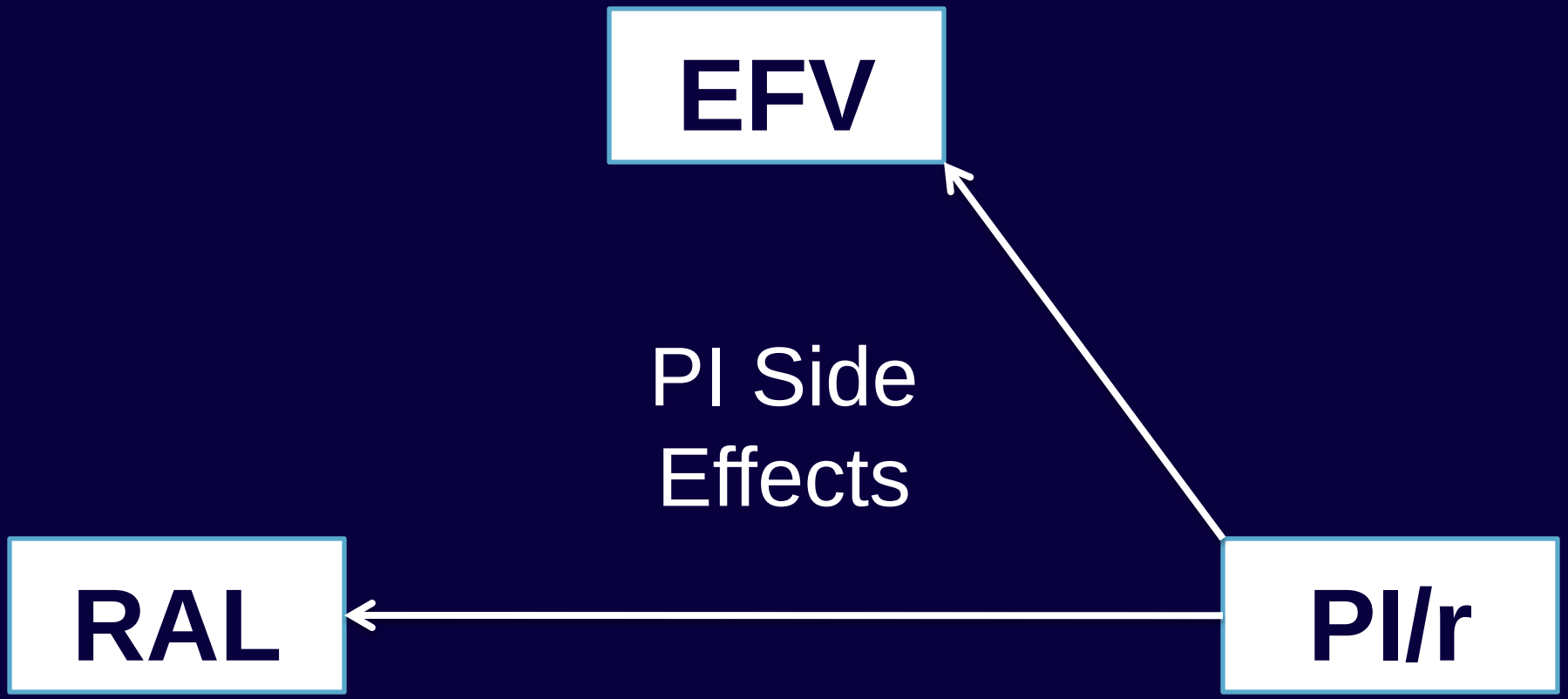

Question 2: Which Boosted PI?

PI/r	PROS	CONS
LPV/r	•Coformulated •No refrigeration •No food restrictions •Preferred for pregnancy	•Requires 200 mg/d of RTV •Metabolic toxicity •GI side effects

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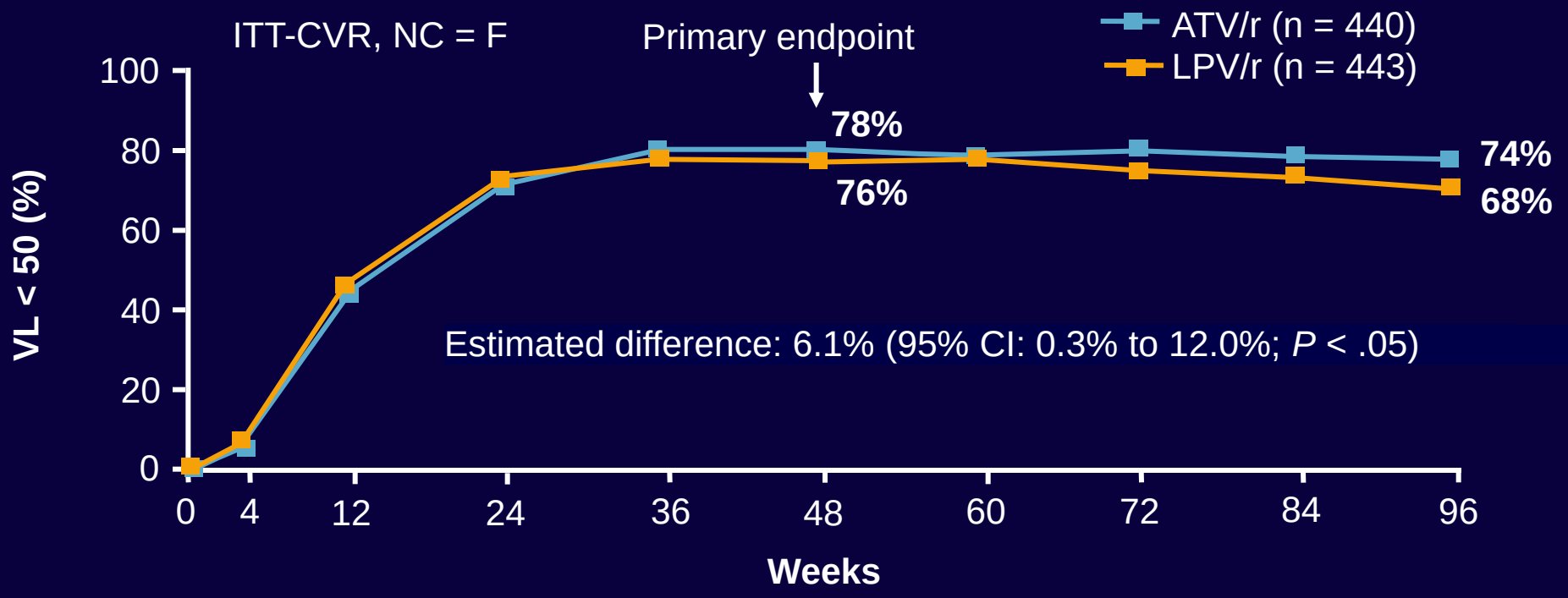
LPV/r	•Coformulated •No refrigeration •No food restrictions •Preferred for pregnancy	•Requires 200 mg/d of RTV •Metabolic toxicity •GI side effects
ATV/r	•Lowest pill burden (2/d) •Once daily dosing •Best GI tolerability •Least metabolic toxicity	•Gastric acid requirement •Food requirement •Jaundice & scleral icterus

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



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

Molina JM, et al. *Lancet.* 2008;372:646-55.

Question 2:Which Boosted PI?

PI/r	PROS	CONS
LPV/r	•Coformulated •No refrigeration •No food restrictions •Preferred for pregnancy	•Requires 200 mg/d of RTV •Metabolic toxicity •GI side effects
ATV/r	•Lowest pill burden (2/d) •Once daily dosing •Best GI tolerability •Least metabolic toxicity	•Gastric acid requirement •Food requirement •Jaundice & scleral icterus
FPV/r	•No food restrictions •QD dosing option (1400 + 100-200 mg of RTV)	•700/100 mg BID dose: no advantage over LPV/r •1400/100 mg QD dose: not as well studied as other PI/r options

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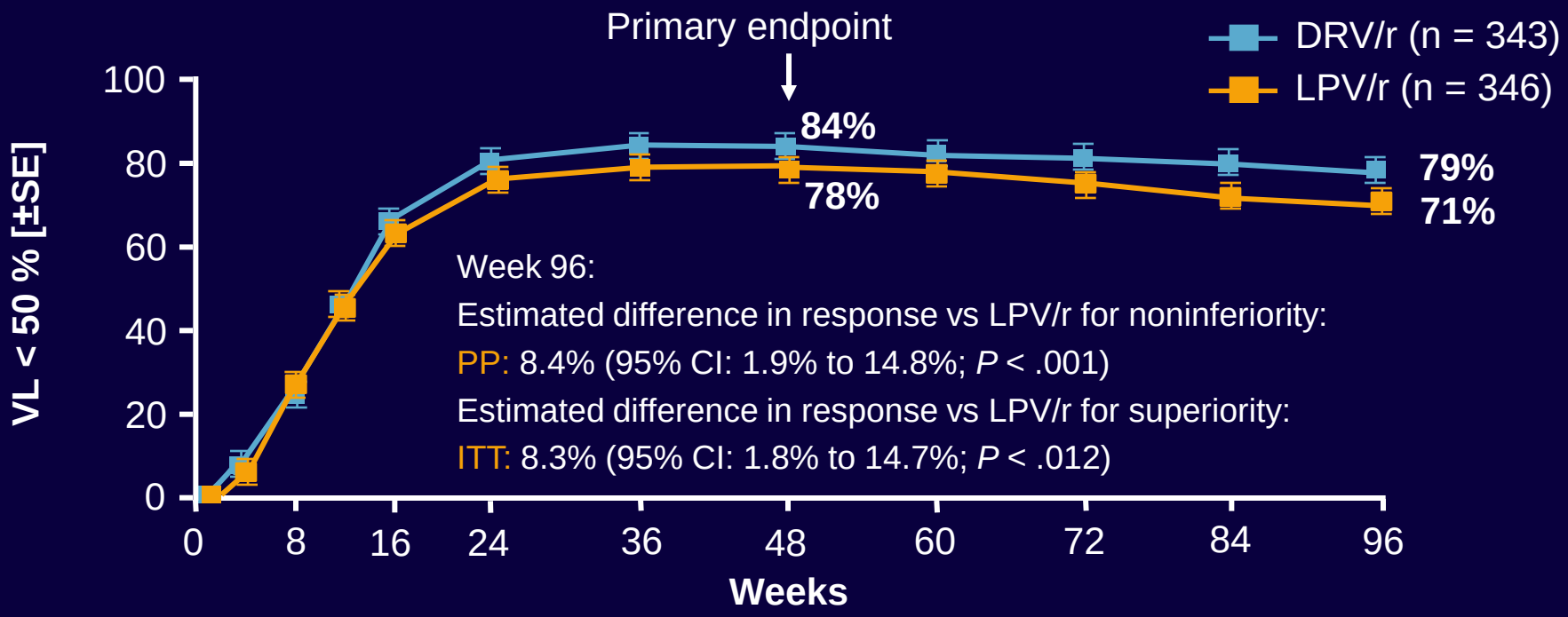
ATV/r	•Lowest pill burden (2/d) •Once daily dosing •Best GI tolerability •Least metabolic toxicity	•Gastric acid requirement •Food requirement •Jaundice & scleral icterus
FPV/r	•No food restrictions •QD dosing option (1400 + 100-200 mg of RTV)	•700/100 mg BID dose: no advantage over LPV/r •1400/100 mg QD dose: not as well studied as other PI/r options
DRV/r	•Superior to LPV/r (VL>100K) •Better tolerability and less hyperlipidemia (vs. LPV/r) •No gastric acid issues (vs. ATV/r) •Stronger data (vs. FPV/r)	•Rash

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)

Mills A, et al. ICAAC/IDSA 2008. Abstract 1250c.

The Argument Against PI "Sequencing"

- Failure of PI/r-based regimens rarely associated with PI resistance when used without baseline PI resistance
  - demonstrated for LPV/r, FPV/r, ATV/r, DRV/r
- Failure usually due to non-adherence rather than resistance
- Therefore, any PI/r should be active after failure of an initial PI/r (including the same PI)

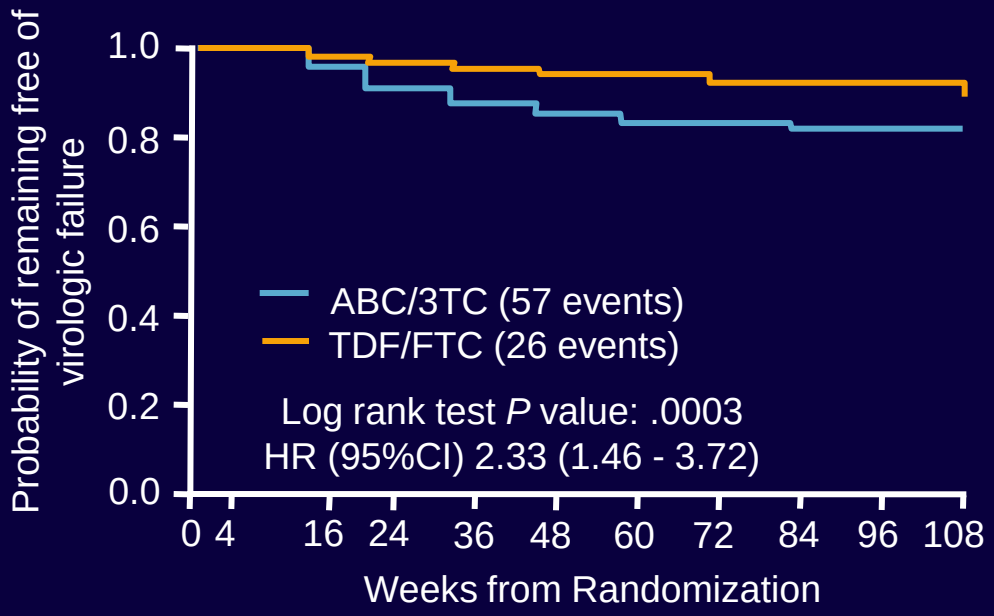
Question 3: Which NRTI Backbone?

NRTIs	PROS	CONS
TDF/FTC	•Superior to AZT/3TC •Less resistance than AZT/3TC or TDF/3TC •Favorable toxicity profile •Long-term data with EFV •Preferred for HBV coinfection	•Renal toxicity

Question 3: Which NRTI Backbone?

NRTIs	PROS	CONS
TDF/FTC	•Superior to AZT/3TC •Less resistance than AZT/3TC or TDF/3TC •Favorable toxicity profile •Long-term data with EFV •Preferred for HIV/HBV coinfection	•Renal toxicity
ABC/3TC	•Comparable to AZT/3TC, better CD4 response •Favorable toxicity profile •↓ risk of HSR with HLA B*5701 screening	•ABC HSR •Need for patient education +/- lab screening •Risk of MI? •Suboptimal at high viral loads?

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



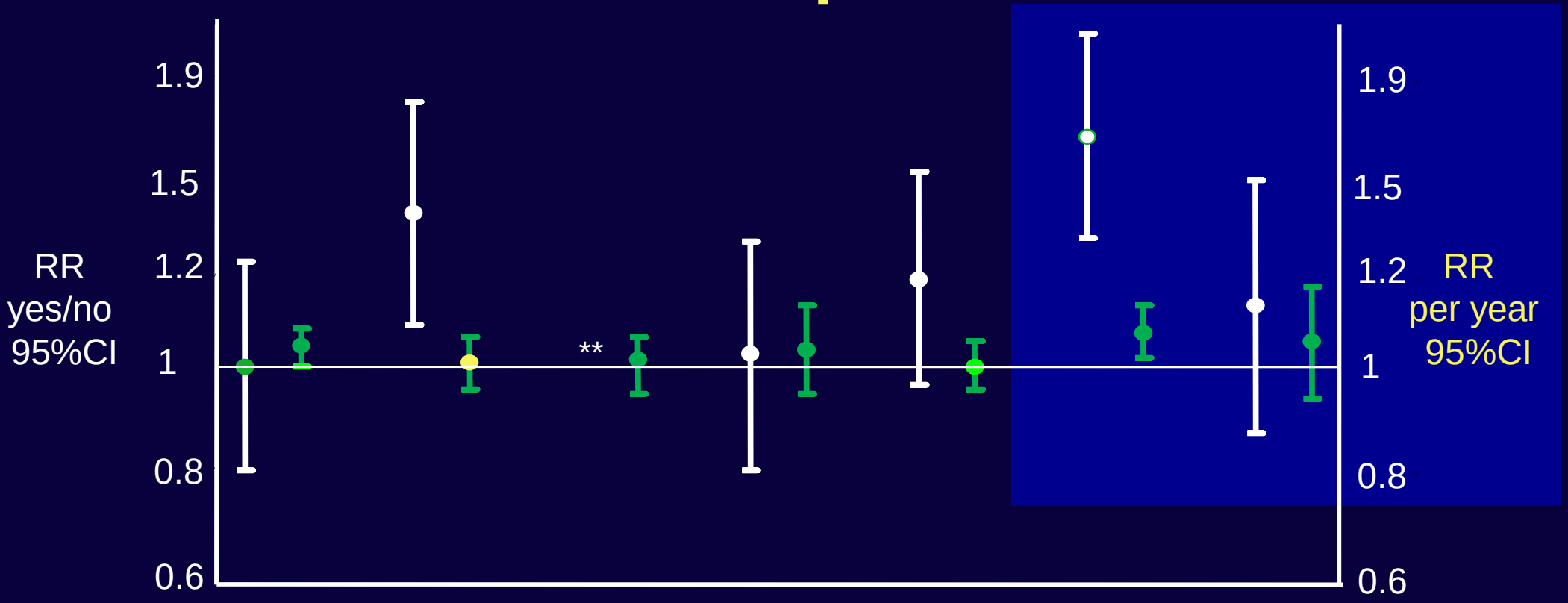
Outcome, n	ABC/3TC (n = 398)	TDF/FTC (n = 399)
Virologic failure (VF), total	57	26
▪ Early VF with no previous suppression to VL< 200	19	9
▪ Late VF with no previous suppression to VL< 200	9	2
▪ Late VF with previous suppression to VL< 200	29	15

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

Sax PE, et al. IAS 2008. Abstract THAB0303.

D:A:D: NRTIs and risk of MI:

recent* / cumulative exposure



	ZDV	ddI	ddC	d4T	3TC	ABC	TDF
#PYFU:	138,109	74,407	29,676	95,320	152,009	53,300	39,157
#MI:	523	331	148	405	554	221	139

* recent use= current or within last 6 mos **: not shown (low number of patient currently on ddC)

J Lundgren, et al CROI 2009, Abstr LB44

Summary of Studies Assessing Association Between ABC and Cardiovascular Risk

Study	Design	Event Ascertainment	N	Effect Found?
D:A:D	Prospective observational cohort	Prospective, predefined	33,347	YES
SMART	Observational analysis from RCT	Prospective, predefined	2,752	YES
FHDB	Case-control in observational cohort	Prospectively reported MI, retrospectively validated	289 cases 884 controls	YES
STEAL	RCT	Prospective	357	YES
GSK analysis	RCTs (54)	Retrospective database search	14,174	NO
ACTG/ ALLRT	LTFU from 5 RCTs	Retrospective: 2 independent reviewers	3,205	NO

Reiss P. CROI 2009.

Summary of Studies Assessing Association Between ABC and Cardiovascular Risk

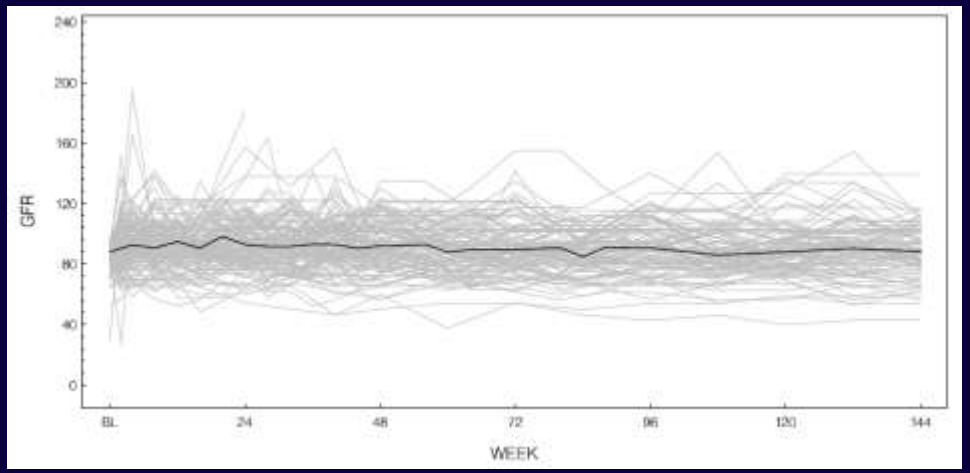
Study	Design	Event Ascertainment	N	Effect Found?	# with low/BLQ VL
D:A:D	Prospective observational cohort	Prospective, predefined	33,347	YES	Majority
SMART	Observational analysis from RCT	Prospective, predefined	2,752	YES	Majority
FHDB	Case-control in observational cohort	Prospectively reported MI, retrospectively validated	289 cases 884 controls	YES	Majority
STEAL	RCT	Prospective	357	YES	All
GSK analysis	RCTs (54)	Retrospective database search	14,174	NO	Few (2%)
ACTG/ ALLRT	LTFU from 5 RCTs	Retrospective: 2 independent reviewers	3,205	NO	None

Reiss P. CROI 2009.

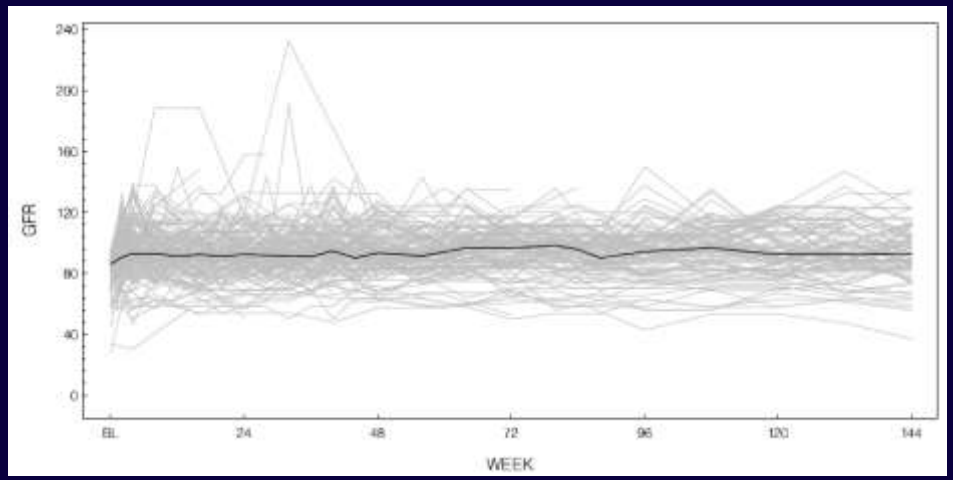
Individual Plots of GFR by MDRD in Patients Whose Baseline GFR are in the Lowest Quartile (25th Percentile)

GFR by MDRD

TDF

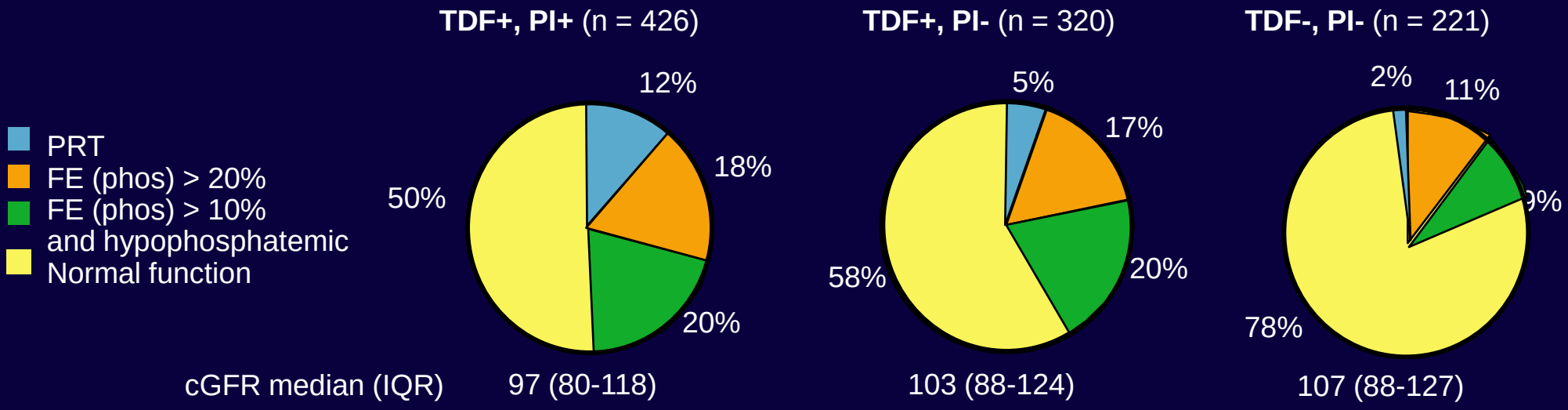


Control



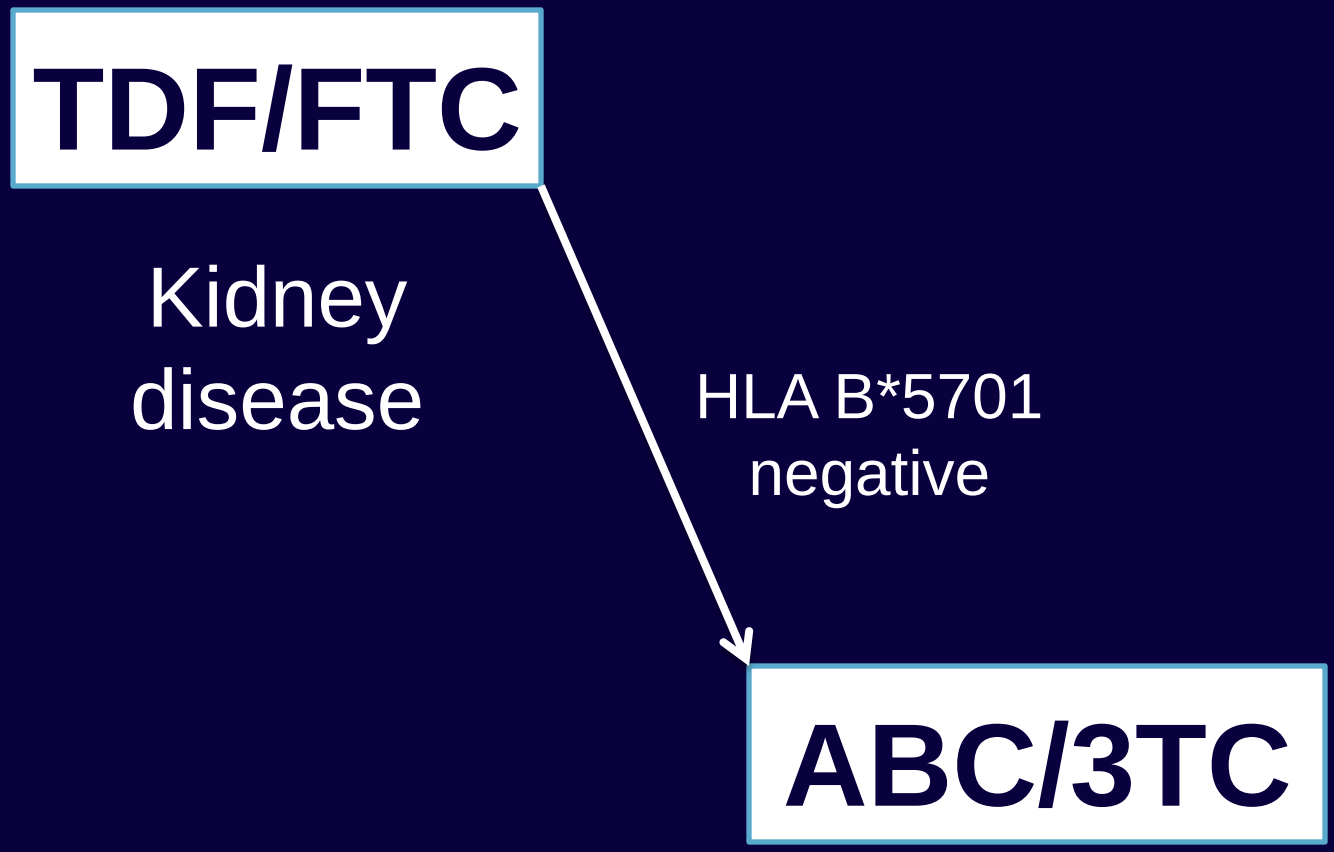
TDF and Proximal Renal Tubulopathy (PRT): Swiss Cohort

- Cross-sectional analysis (N = 1202)
- PRT = abnormalities in ≥ 3 of following : fractional excretion (FE) of phosphate or uric acid, urine prt/creat ratio euglycemic glucosuria
- Incidence highest in patients receiving TDF plus PI (vs no TDF, no PI): OR: 7.1 (95% CI: 2.5-19.8; *P* < .001)



Fux C, et al. CROI 2009. Abstract 743. Graphics reproduced with permission.

Question 3: Which NRTIs?



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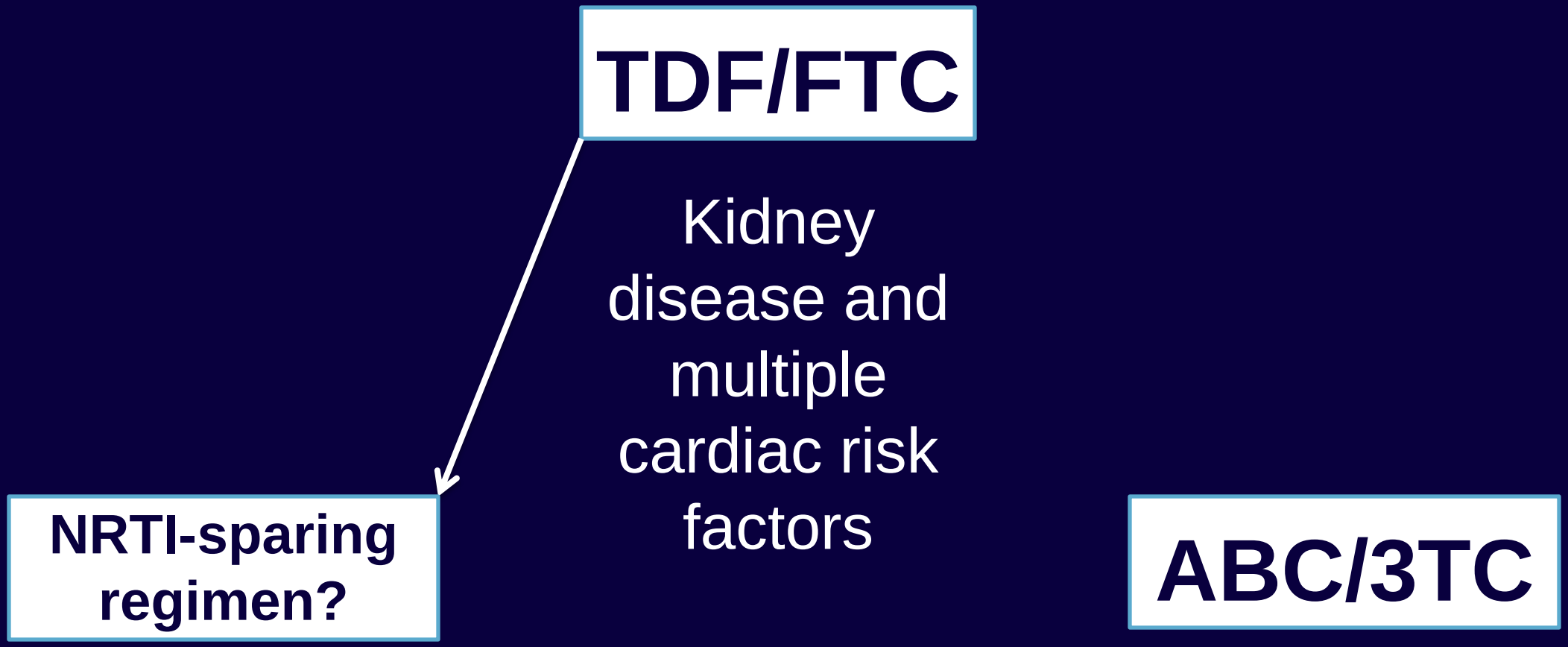

Examples of NRTI-Sparing Options

- 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

Future Options for Initial Therapy?

- 2 NRTIs + rilpivirine
- 2 NRTIs + RAL once daily
- TDF/FTC/EFV/GS9350 coformulation
- NRTI-sparing regimens

Conclusions: When and What to Start

- Growing support for earlier ART, including ART independent of CD4 count
- TDF/FTC now the preferred NRTI backbone for patients with without kidney disease
- Options for 1st PI now include 3 once-daily boosted PIs that use 100 mg of RTV
- RAL emerging as option for initial ART