

Antiretroviral Therapy Options from a Clinician's Point of View



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DHHS (2009) & IAS-USA Guidelines (2010): Preferred Initial Regimens

Preferred Agents for First-Line Therapy	
NRTIs	▪ TDF/FTC
Plus a third agent	
NNRTI	▪ EFV
Boosted PI	▪ ATV/r
	▪ DRV/r
INSTI	▪ RAL

Choosing the Initial Regimen: The 4 Questions

- EFV, a boosted PI, or RAL?
- If a boosted PI, which one?
- Which NRTI backbone?
- Something else?

Question 1: EFV vs. PI/r vs. RAL?

EFV

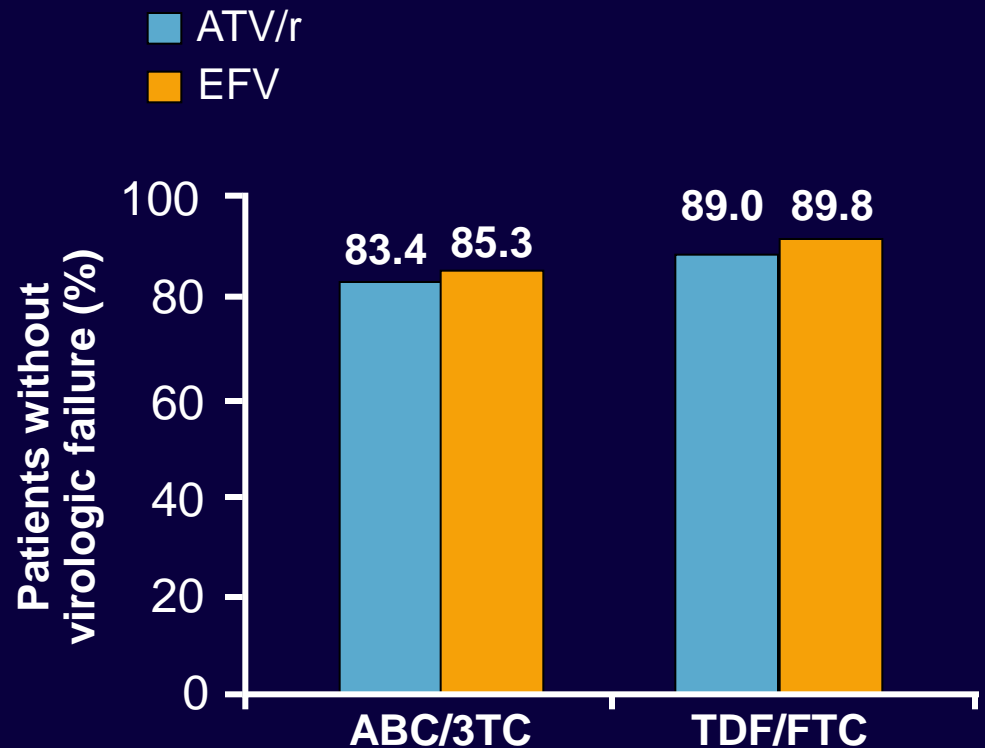
- Gold standard for virologic efficacy
- Easiest regimens (1-2 pills/d)
- Minimal long-term toxicity
- Favorable PK

Question 1: EFV vs. PI/r vs. RAL?

EFV	<ul style="list-style-type: none">•Gold standard for virologic efficacy•Easiest regimens (1-2 pills/d)•Minimal long-term toxicity•Favorable PK
PI/r	<ul style="list-style-type: none">•Can be as effective as EFV (ATV/r in ACTG 5202)•Better CD4 response than EFV (LPV/r in ACTG 5142, ATV/r in 5202)•Less resistance with failure•Preferred if risk for pregnancy

ACTG 5202: ATV/r vs EFV Comparison

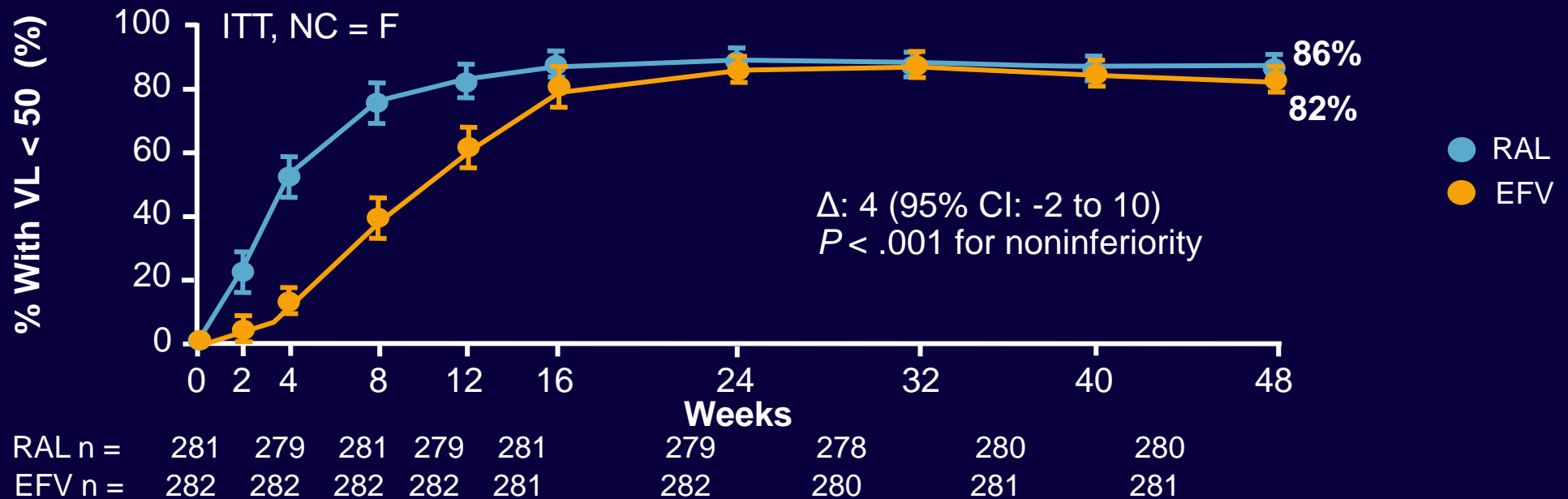
- Similar time to virologic failure with ATV/r vs EFV with either ABC/3TC or TDF/FTC in overall population analysis
 - With ABC/3TC, HR: 1.13 (95% CI: 0.82-1.56)
 - With TDF/FTC, HR: 1.01 (95% CI: 0.70-1.46)
- More resistance at VF with EFV vs ATV/r plus ($P < .001$)
- Greater lipid increases with EFV vs ATV/r ($P < .05$) but minimal difference in total/HDL cholesterol ratio



Question 1: EFV vs. PI/r vs. RAL?

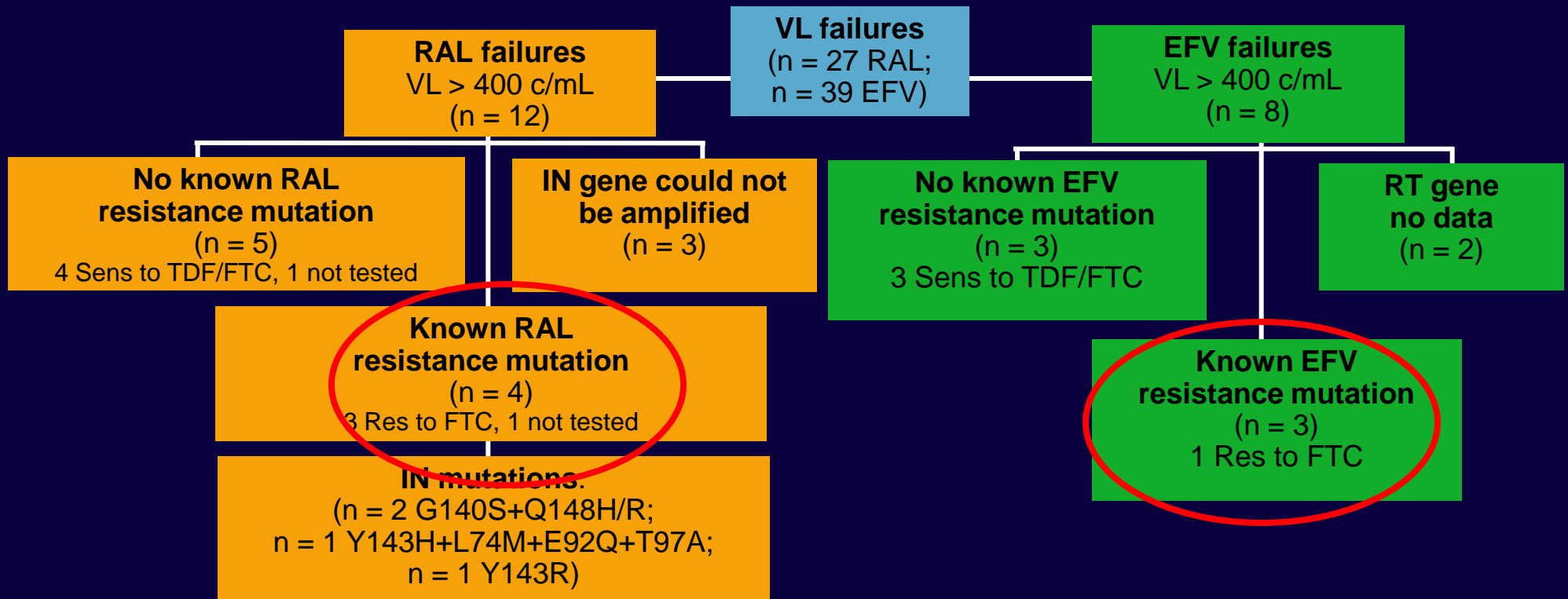
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RAL	<ul style="list-style-type: none">•As effective as EFV with better tolerability (STARTMRK)•Lipid neutral•Requires twice-daily dosing•Resistance risk similar to EFV

STARTMRK: Virologic and Immunologic Efficacy at Week 48



- Shorter time to virologic response with RAL vs EFV ($P < .001$)
- Greater CD4 increase with RAL vs EFV
 - +189 vs +163; $\Delta: 26$ ($P=0.0184$)
- Fewer CNS events by Week 8 with RAL vs EFV (10.3% vs 17.7%; $P = .015$)

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 2: Which Boosted PI?

PI/r	PROS	CONS
ATV/r	<ul style="list-style-type: none">• Superior to LPV/r at 96 wks (CASTLE)• Lowest pill burden (2/d)	<ul style="list-style-type: none">• Gastric acid requirement• Food requirement• Jaundice & scleral icterus

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DRV/r	<ul style="list-style-type: none">•Superior to LPV/r (VL>100K, ARTEMIS)•Better tolerability and less hyperlipidemia (vs. LPV/r)•No gastric acid issues (vs. ATV/r)	<ul style="list-style-type: none">•Food requirement•Rash

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LPV/r	<ul style="list-style-type: none">•Coformulated•No food restrictions•Preferred for pregnancy	<ul style="list-style-type: none">•Requires 200 mg/d of RTV•Metabolic toxicity•GI side effects•Risk of MI in D:A:D

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FPV/r	<ul style="list-style-type: none"> •No food restrictions 	<ul style="list-style-type: none"> •700/100 mg BID dose: no advantage over LPV/r •1400/100 mg QD dose: not as well studied as other PI/r options

Question 3: Which NRTI Backbone?

NRTIs	PROS	CONS
TDF/FTC	<ul style="list-style-type: none">•Best backbone with EFV•Only studied backbone with RAL•Preferred for HBV coinfection	<ul style="list-style-type: none">•Renal toxicity•Possible increased risk with PIs•Bone density?

Question 3: Which NRTI Backbone?

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TDF/FTC	<ul style="list-style-type: none">•Best backbone with EFV•Only studied backbone with RAL•Preferred for HBV coinfection	<ul style="list-style-type: none">•Renal toxicity•Possible increased risk with PIs•Bone density?
ABC/3TC	<ul style="list-style-type: none">•Lack of renal toxicity	<ul style="list-style-type: none">•Need for HLA B*5701 screening to avoid ABC HSR•Inferior to TDF/FTC with VL >100,000•Possible increased risk of MI•ACTG 5202 safety/tolerability data

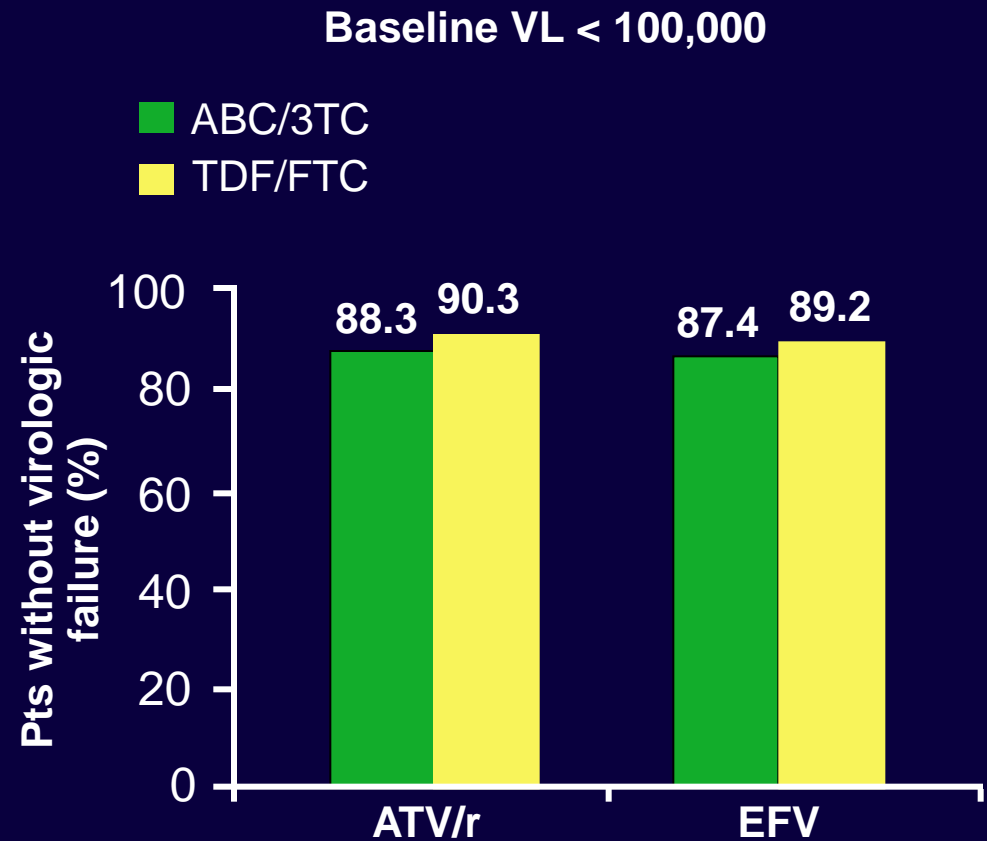
ACTG 5202: Virologic Failure With ABC/3TC vs TDF/FTC

Baseline VL \geq 100,000:

- Shorter time to VF with ABC/3TC vs TDF/FTC
 - With EFV, HR: 2.22 (1.19-4.14)
 - With ATV/r, HR: 2.46 (1.20-5.05)

Baseline VL < 100,000:

- Similar time to VF with ABC/3TC vs TDF/FTC
 - With ATV/r, HR: 1.26 (0.76-2.05)
 - With EFV, HR: 1.23; (0.77-1.96)



ACTG 5202: Safety and Tolerability for ABC/3TC vs TDF/FTC in Low VL Stratum

- Shorter time to grade 3/4 safety event with ABC/3TC vs TDF/FTC when combined with EFV ($P = .03$) but not with ATV/r ($P = .44$)
- Shorter time to treatment modification with ABC/3TC vs TDF/FTC with ATV/r ($P = .018$) or EFV ($P = .005$)
 - Partially due to suspected ABC HSR (no HLA B*5701 screening)
- Greater lipid increases with ABC/3TC vs TDF/FTC, regardless of assignment to ATV/r or EFV

Abacavir and Cardiovascular Risk

- Conflicting data from multiple cohort studies and clinical trials
- If there is an increased risk:
 - it is greatest in patients with multiple cardiovascular risk factors
 - pathogenesis unknown, but not due to metabolic factors
 - Inflammation, endothelial function, platelet reactivity/function?
- Cardiovascular risk of untreated HIV probably greater than risk of any specific drug

Tenofovir and Renal Risk

- TDF can cause two types of nephrotoxicity:
 - Glomerular: decreased kidney function
 - Tubular: Fanconi's syndrome, phosphate wasting
- Low risk, especially with initial therapy or when combined with EFV
- Boosted PIs increase tenofovir levels and may increase nephrotoxicity, though incidence has been low in trials of 1st line therapy
- Tubular toxicity not detected by creatinine alone. Look for glycosuria, proteinuria, phosphate wasting

Which NRTI Backbone?

TDF/FTC

Kidney
disease

HLA B*5701
negative,
VL <100,000,
low CV risk

ABC/3TC

Which NRTI Backbone?

TDF/FTC

HLA B*5701
positive,
high CV risk,
(or VL
>100,000?)

Kidney
disease

**NRTI-sparing
regimen?**

ABC/3TC

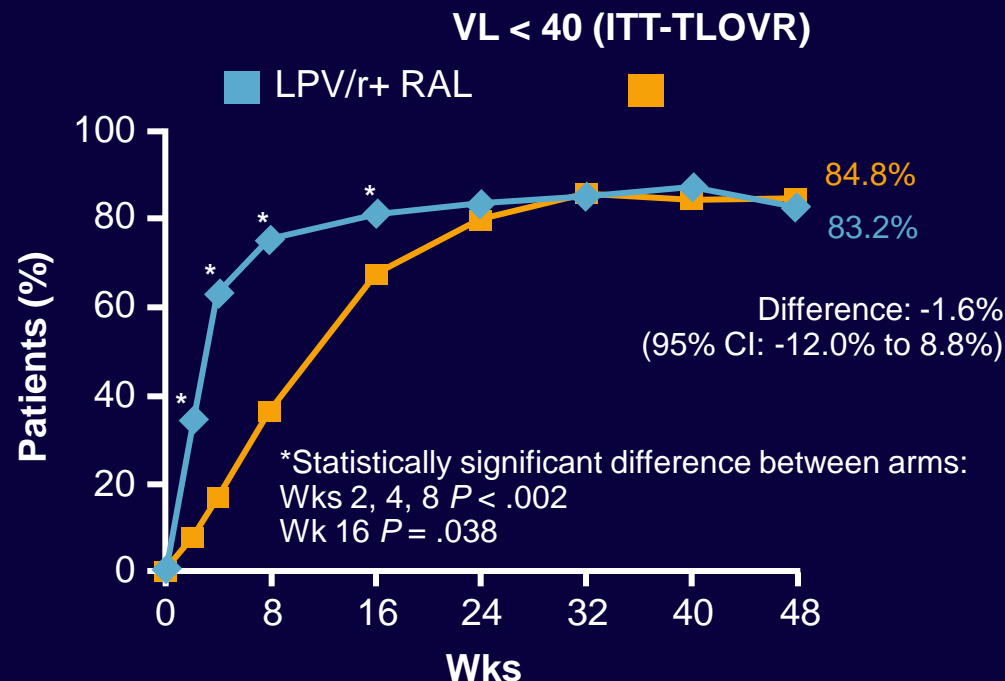
Question 4: Something Else?

NRTI-Sparing Options

- PI/r + NNRTI
- PI or PI/r + RAL
- PI/r monotherapy
- MVC + PI/r

PROGRESS: LPV/r + RAL vs LPV/r + NRTIs in ART-Naive Patients

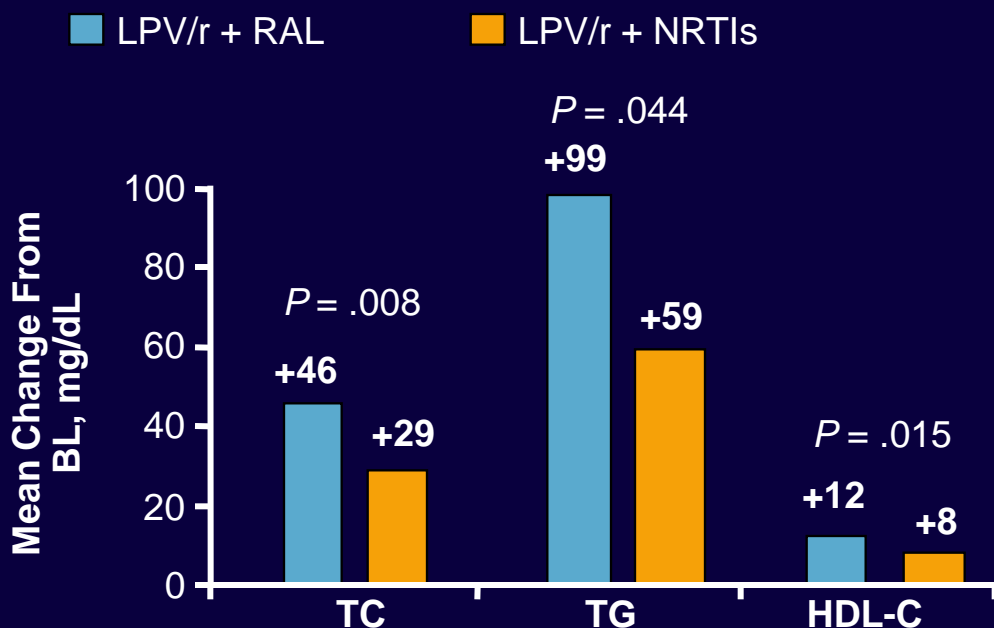
- Randomized, open-label, multicenter phase III trial in ART-naive pts with VL > 1000
 - LPV/r 400/100 mg BID + RAL 400 mg BID (n = 101) vs
 - LPV/r 400/100 mg BID + TDF/FTC (n = 105)
- Relatively low mean baseline VL: 4.25 log₁₀



- Similar CD4 gain at Wk 48
 - LPV/r + RAL: 215
 - LPV/r + NRTIs: 245

PROGRESS: Lipids and Adverse Events at Wk 48

- Mean increases in TC, TG, and HDL-C from BL to Wk 48 significantly greater in RAL arm vs NRTI arm

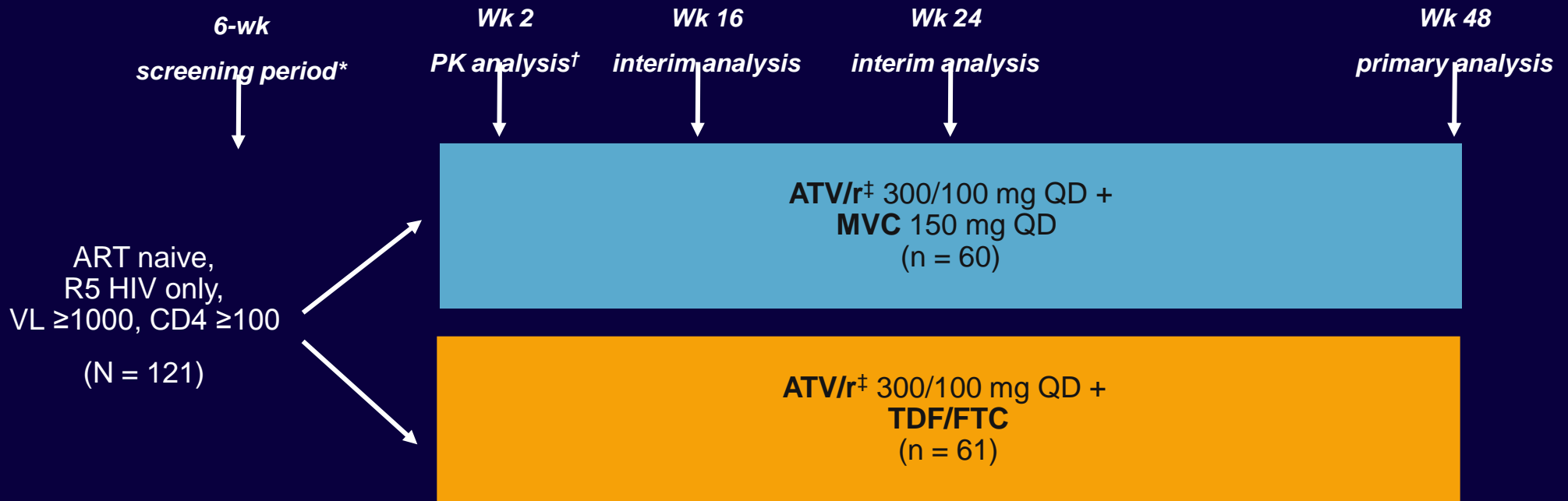


Resistance Development at VF	LPV/RTV + RAL	LPV/RTV + NRTIs
Met criteria for resistance testing	4	3
▪ INSTI mutation (N155H)	1	0
▪ NRTI mutations (M184V)	0	1

- Grade 3/4 laboratory events did not differ between arms, except higher risk of CPK > 4 x ULN in RAL arm
 - 12.9% vs 3.8% ($P = .023$)

A4001078: ATV/r + MVC vs ATV/r + TDF/FTC in ART-Naïve Patients

- Randomized, multicenter, open-label phase IIb pilot study



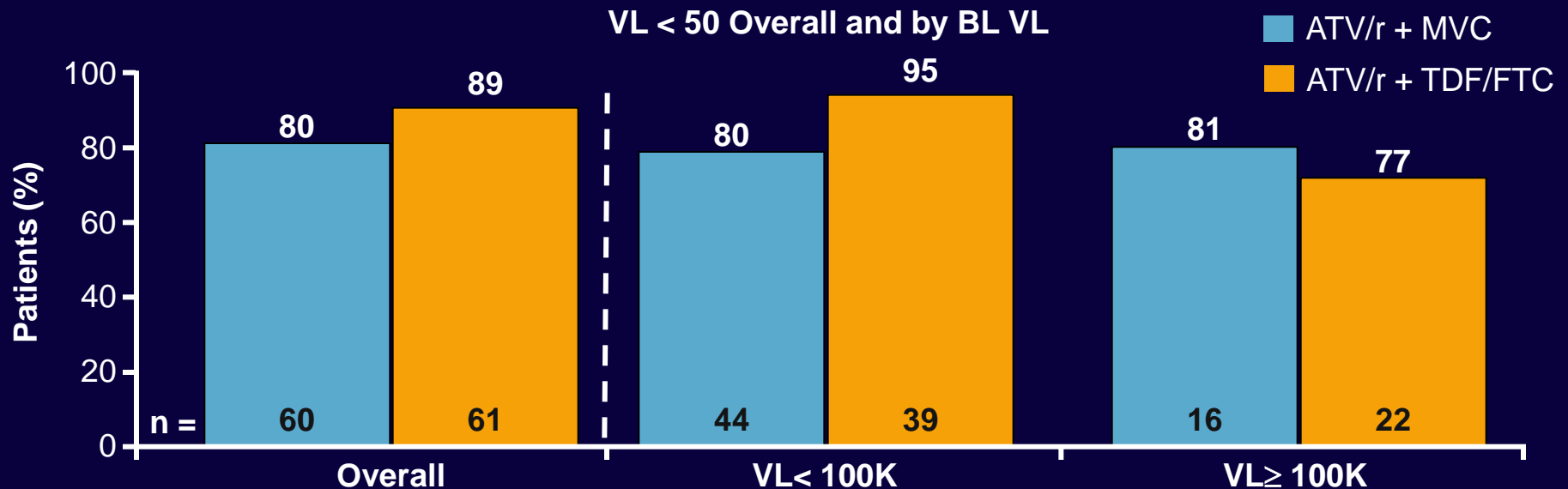
*Prior to randomization.

[†]PK analysis of MVC exposure in 15 MVC recipients.

[‡]Pts without VF but with jaundice and/or scleral icterus allowed to switch ATV/r to DRV/r or LPV/r if desired.

Not powered for statistical comparisons.

A4001078: ATV/r + MVC vs ATV/r + TDF/FTC—Wk 24 Interim Analysis

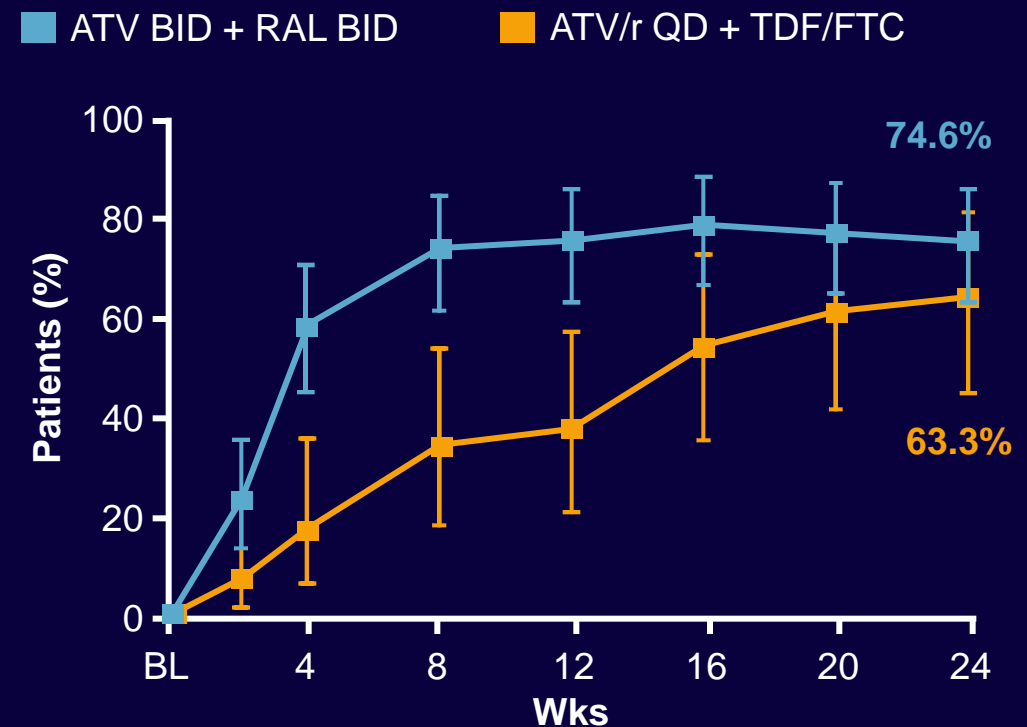


- CD4 increases similar
 - ATV/r + MVC: 195
 - ATV/r + TDF/FTC: 173
- Grade 3/4 hyperbilirubinemia
 - ATV/r + MVC: 59.3%
 - ATV/r + TDF/FTC: 49.2%
- 5 pts in MVC arm, 1 pt in TDF/FTC arm switched to DRV/r per protocol for jaundice or scleral icterus

SPARTAN: Pilot Study of ATV + RAL vs ATV/r + TDF/FTC in Naive Pts

- Randomized, noncomparative, open-label, multicenter pilot study in ART-naive patients with VL ≥ 5000
 - ATV 300 mg BID + RAL 400 mg BID (n = 63) vs
 - ATV/r 3001/00 mg QD + TDF/FTC (n = 31)
- Mean BL VL 4.9 log₁₀

1° Endpoint: VL < 50 Through Wk 24 (CVR*, NC = F)



*CVR = modified ITT.

SPARTAN: Wk 24 Results

Resistance Through Wk 24, n	ATV + RAL (n = 63)	ATV/RTV + TDF/FTC (n = 30)
Virologic failure (HIV-1 RNA > 50 copies/mL)	11	8
▪ BL HIV-1 RNA > 250,000 copies/mL	8	4
Evaluable for resistance testing * (HIV-1 RNA > 400 copies/mL)	6	1
Genotypic and phenotypic RAL resistance		
▪ N155H	2	NA
▪ Q148R	1	NA
▪ Q148R + N155H + T97A	1	NA
Phenotypic RAL resistance without genotypic evidence of resistance	1	NA
ATV resistance	0	0
TDF/FTC resistance	NA	0

- No significant changes in fasting lipids observed in either arm
- Trial terminated at Wk 24 due to resistance data and grade 4 bilirubin abnormalities (21%) with experimental regimen vs control arm (0%)

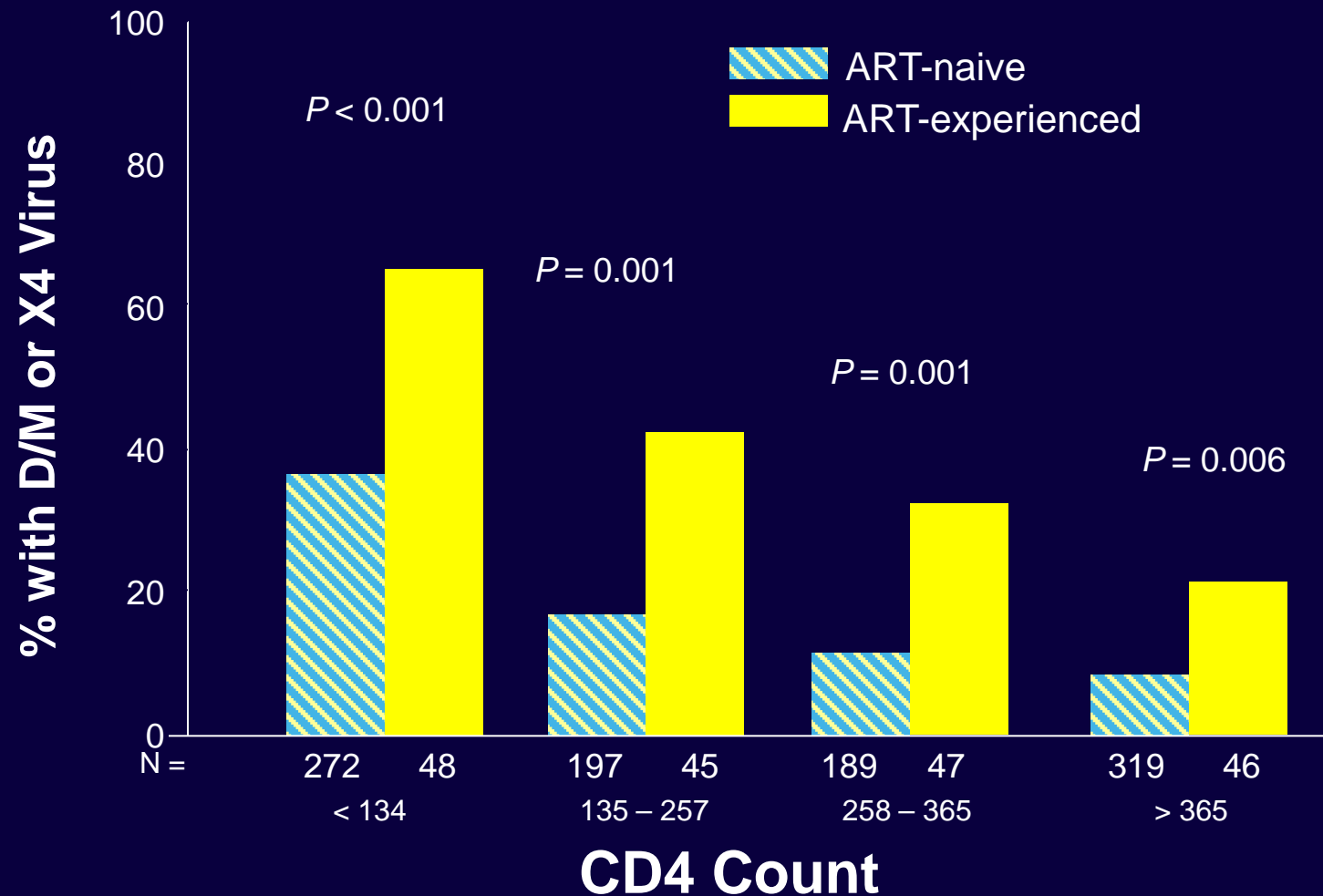
*Criteria for resistance testing:

- VL \geq 400 at or after Wk 24
- Rebound to VL \geq 400 at any time
- Discontinued before achieving VL < 50 after Wk 8 with last VL \geq 400

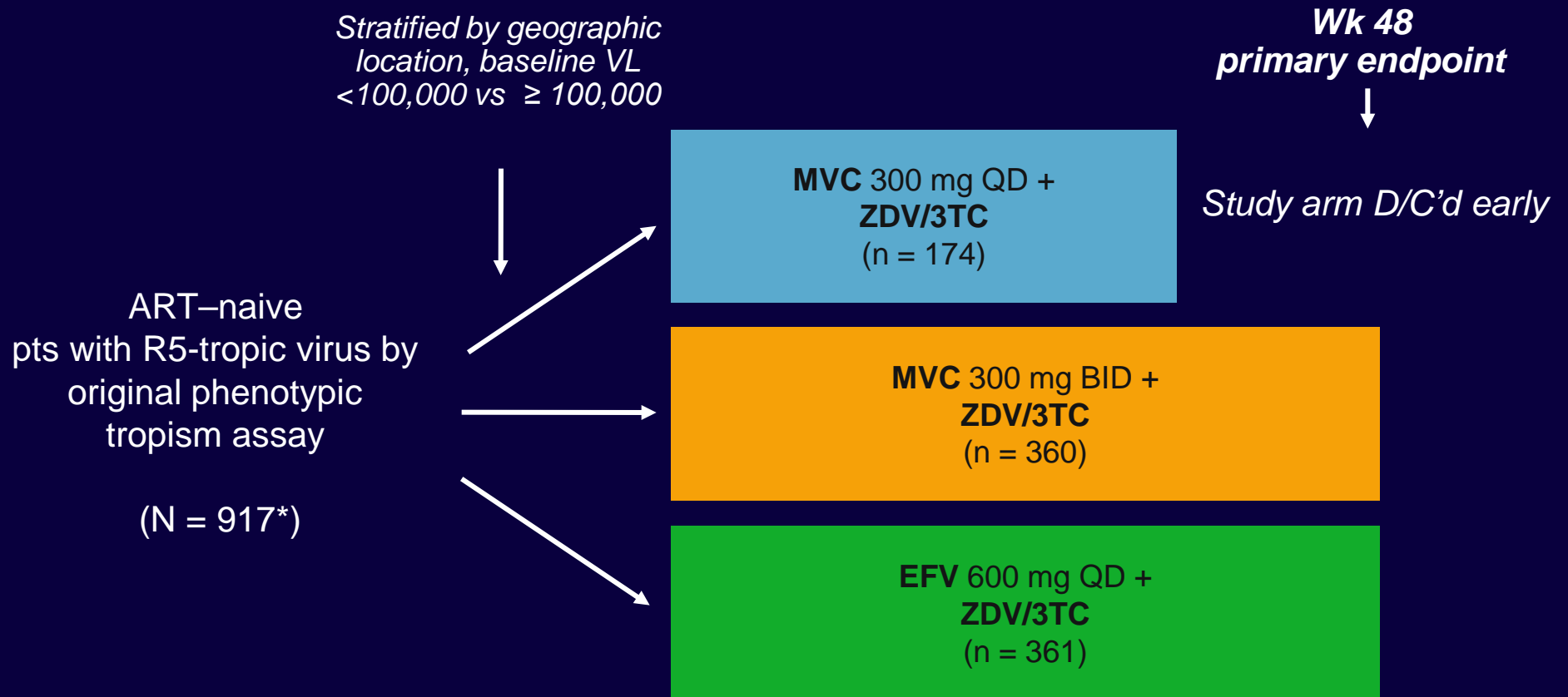
Potential New First-Line Options

- CCR5 inhibitor-containing regimens
- “Quad”: elvitegravir/cobicistat/TDF/FTC
- Cobicistat as PI booster, including possible coformulations
- S/GSK1349572 (including coformulation with ABC/3TC)
- Rilpivirine, including coformulation with TDF/FTC
- RAL once-daily

Tropism Profiles in SCOPE and HOMER Cohorts: Treatment and CD4 Counts



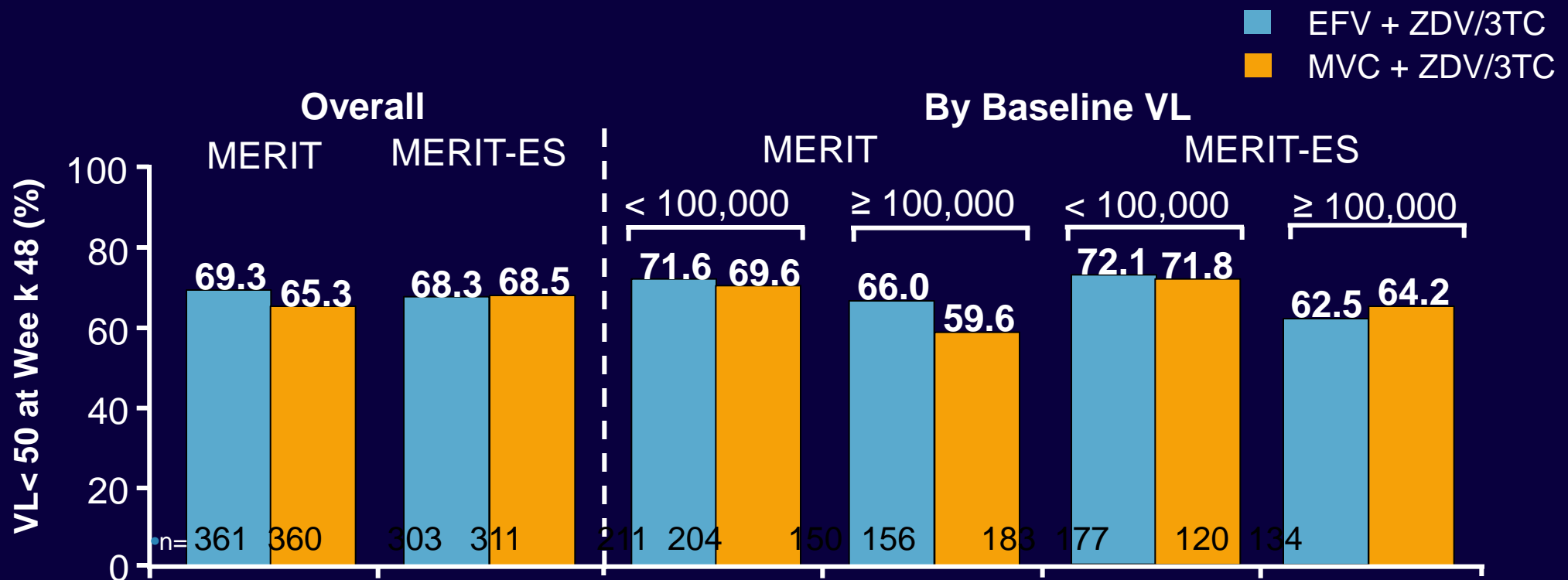
MERIT: MVC vs EFV in Treatment-Naive Patients



*22 patients not treated; analysis limited to patients receiving ≥ 1 dose of BID MVC or EFV.

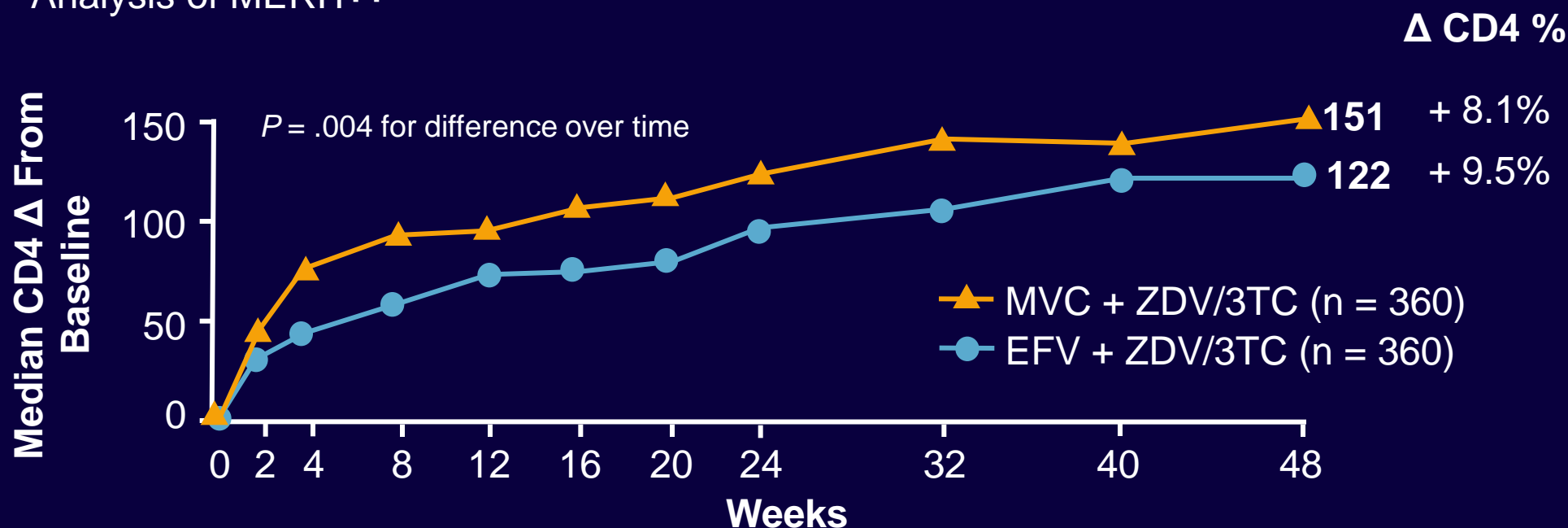
MERIT-ES: Reanalysis of Virologic Efficacy With Enhanced Tropism Assay

- Enhanced phenotypic tropism assay resulted in reclassification of 15% of pts 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^[1]



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

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

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

Intensification of Stable ART in Pts With Suboptimal CD4 Counts

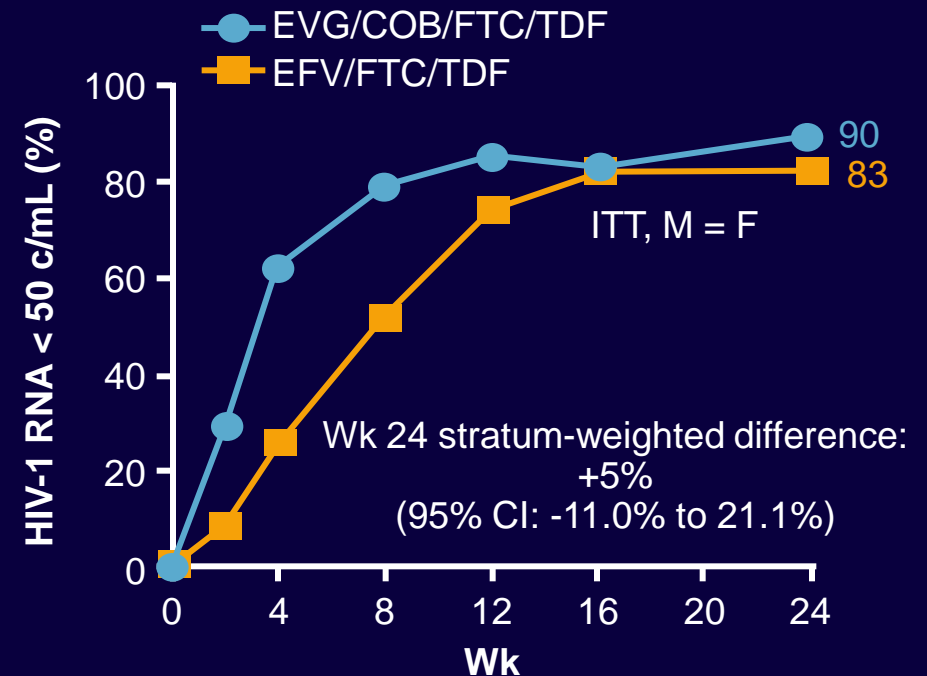
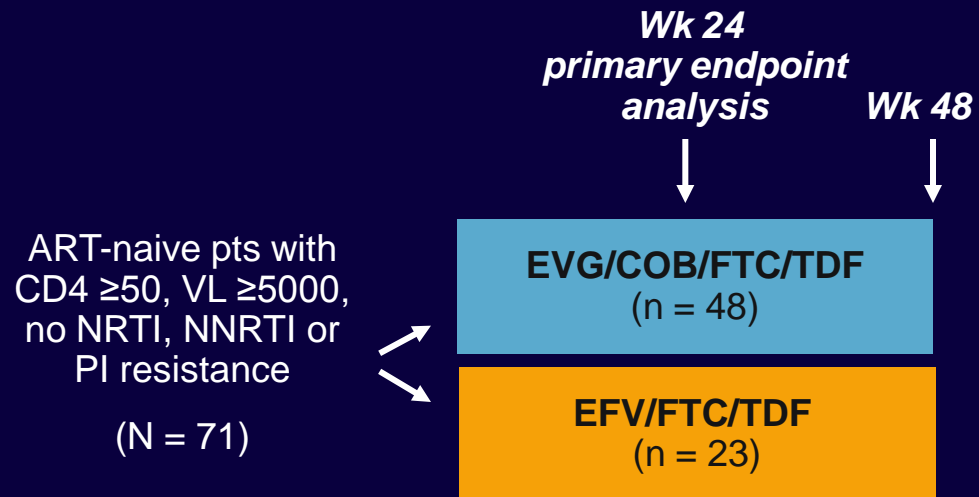
- ACTG 5256: MVC added for 24 wks in 32 pts with VL < 50 for ≥ 48 wks on stable ART but CD4 < 250^[1]
 - Intensification not associated with clinically significant CD4 gain
 - Median CD4 increase at Wk 22/24: +12 (90% CI: 1-22)
 - Decrease in CD4/CD8 activation and improvements in markers of apoptosis, but not correlated with change in CD4 count
- RAL intensification not associated with significant CD4 increase in suppressed pts with low CD4 counts^[2]

Potential New Options

- CCR5 inhibitor-containing regimens
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Cobicistat-Boosted EVG + FTC/TDF vs. EFV/FTC/TDF in Naive Pts: Phase II trial

- Cobicistat (GS-9350, COB): investigational CYP3A inhibitor (boosting agent)
- Elvitegravir (EVG): investigational integrase inhibitor

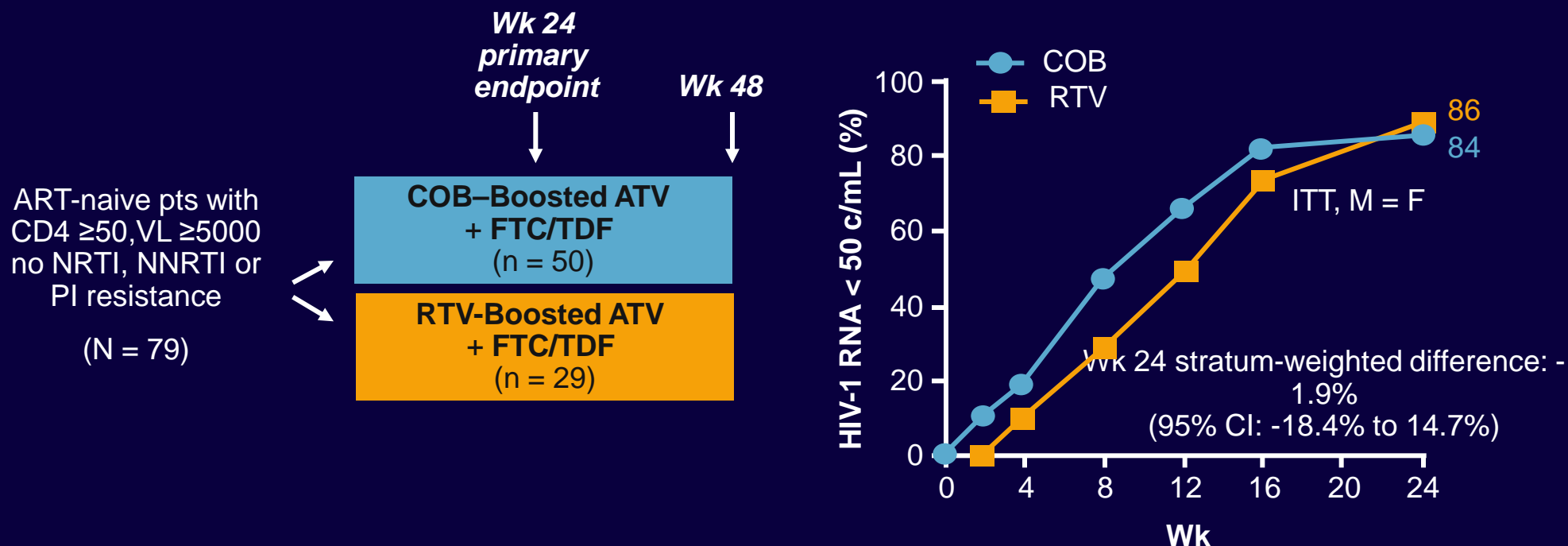


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Cobicistat-Boosted ATV Virologic Efficacy Similar to ATV/r in Naive Pts

- Phase II study comparing cobicistat (GS-9350) vs RTV as boosting agent for atazanavir

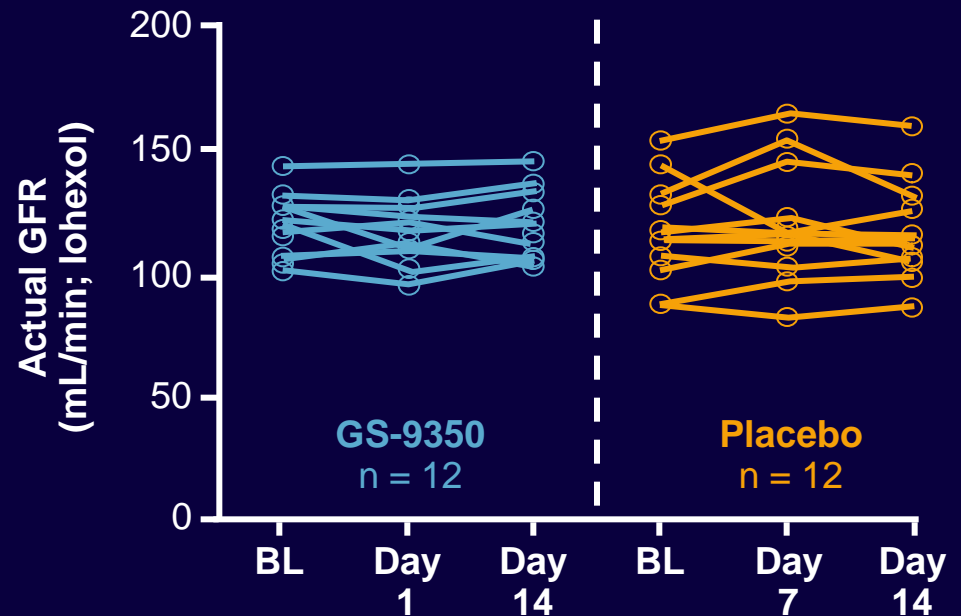


Cobicistat: AEs When Combined With EVG/FTC/TDF or ATV/r + TDF/FTC

AEs, n (%)	EVG/COB/TDF/FTC (n = 48)	EFV/FTC/TDF (n = 23)	COB + ATV + FTC/TDF (n = 50)	RTV + ATV TDF/FTC (n = 29)
Grade 1-4 AEs related to randomized drug	17 (35)	13 (57)	10 (20)	7 (24)
Abnormal dreams, nightmares	5 (10)	8 (35)	0	0
Dizziness	0	3 (13)	0	0
Fatigue	4 (8)	3 (13)	1 (2)	2 (7)
Somnolence	2 (4)	2 (9)	0	0
Diarrhea	4 (8)	1 (4)	3 (6)	3 (10)
Nausea	2 (4)	1 (4)	5 (10)	1 (3)
Bilirubin, total	0	0	40/49 (82)	25 (86)
Creatinine (grade 1)	1 (2)	0	6 (12)	0
Δ mean serum creatinine from BL to Wk 24, mg/dL	+ 0.14	+ 0.04	+ 0.18	+ 0.14
Δ mean eGFR from BL to Wk 24, mL/min	- 18	- 7	- 15	- 14

Cobicistat Appears to Alter Estimated GFR, Not Actual GFR

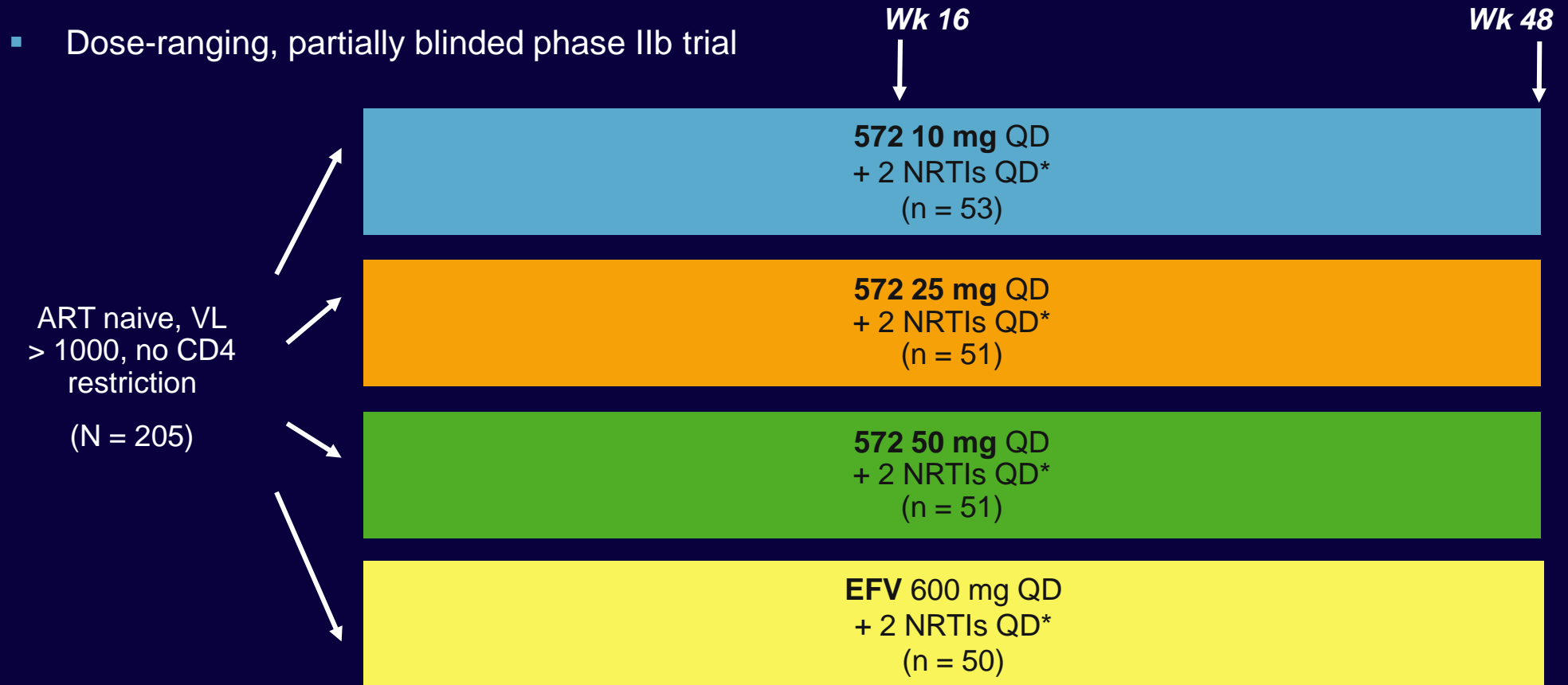
- Most creatinine excretion occurs by filtration, but 10-15% excreted by active tubular secretion
- Lower estimated GFR for GS-9350 appears due to inhibition of tubular secretion
 - Separate study of 7-day GS-9350 150 mg monotherapy vs placebo in healthy volunteers demonstrated no impact of GS-9350 on actual GFR (measured by iohexol clearance) despite lower estimated GFR (Cockcroft- Gault) with GS-9350 vs placebo



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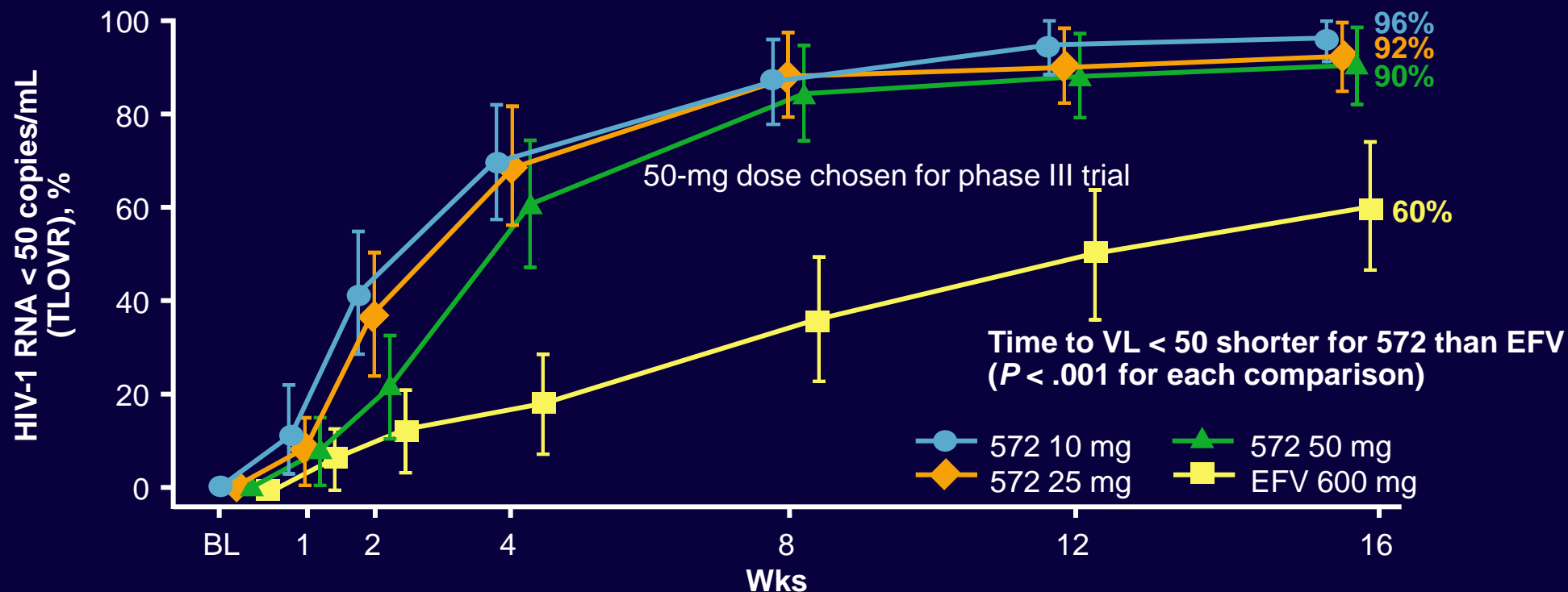
SPRING-1: S/GSK1349572 vs EFV in Treatment-Naive Patients



*NRTIs individually selected by trial investigators (TDF/FTC, 67%; ABC/3TC, 33%).

†After Wk 48, all patients continue at dose selected for phase III trial.

SPRING-1: Virologic Response to S/GSK1349572 vs EFV at Wk 16



- CD4 count increases 153-176 on 572 vs 116 on EFV
- No serious adverse events related to 572

VIKING: S/GSK1349572 in RAL-Resistant Patients

- International, multicenter, single-arm, phase II study in 27 patients with RAL resistance
 - S/GSK572 50 mg QD to replace RAL in failing regimen (or added if RAL already d/c) for 10 days of functional monotherapy
 - Day 11-Wk 24: S/GSK572 50 mg QD continued and regimen optimized
 - Median fold-change in RAL susceptibility at BL: 161 (range: 0.6 - > 166)
 - Median S/GSK572 FC at BL: 1.5 (range: 0.6-35)
- Stratified by BL integrase genotype
 - Group 1: Q148 + ≥ 1 secondary resistance mutations (n = 9)
 - Group 2: All others (N155H and Y143H pathways) and single mutations at Q148 (n = 18)

VL Response at Day 11	Group 1 (n = 9)	Group 2 (n = 18)
< 400 or $\geq 0.7 \log_{10}$ c/mL decline, %	33	100
Change from baseline, \log_{10} c/mL	-0.72	-1.82

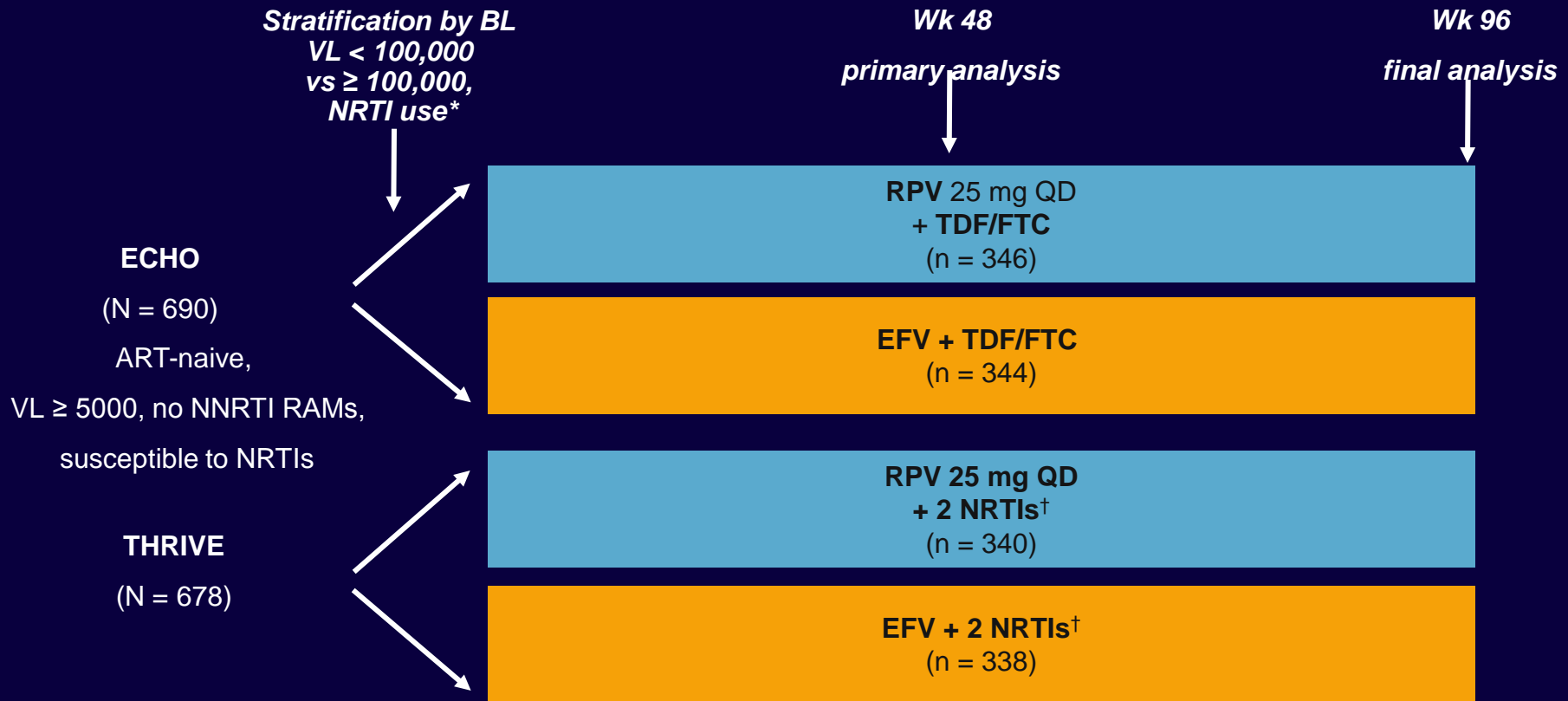
- Day 1 FC to 572 highly predictive of Day 11 virologic response ($r = 0.79$; $P < .001$)
- Among 18 paired isolates evaluated on Day 1 and Day 11, no evidence of emergent RAL mutations
 - In 17 subjects, < 2 FC in susceptibility
 - In 1 subject, ~ 6 FC in susceptibility

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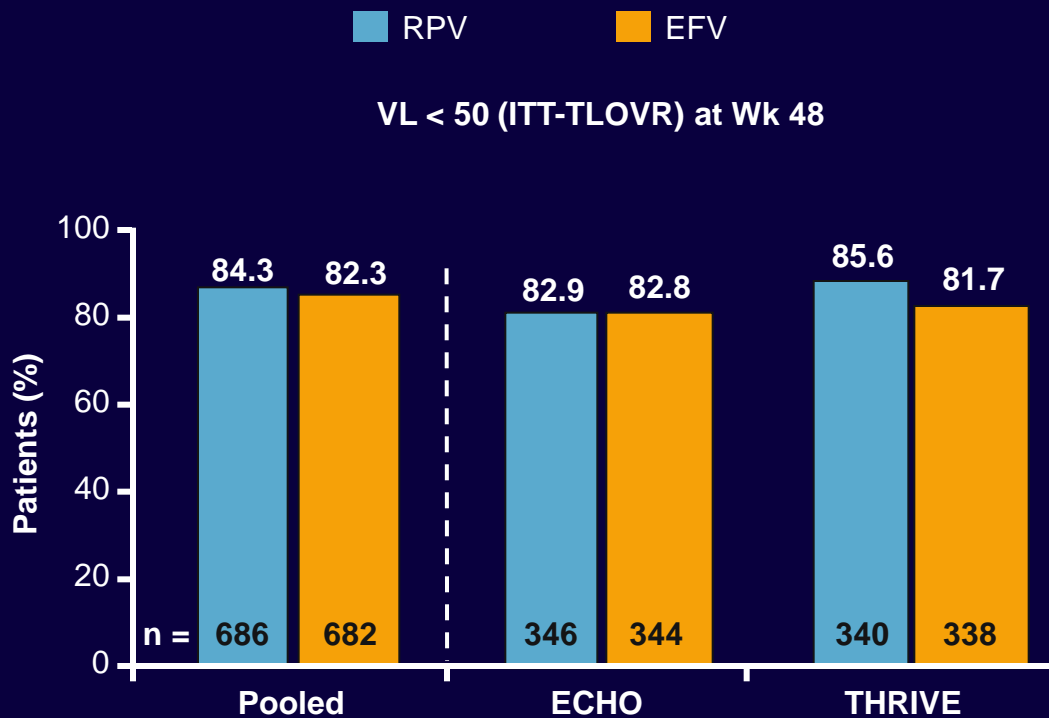
ECHO, THRIVE: Rilpivirine vs EFV in Treatment-Naive Patients

- Randomized, double-blind phase III trials



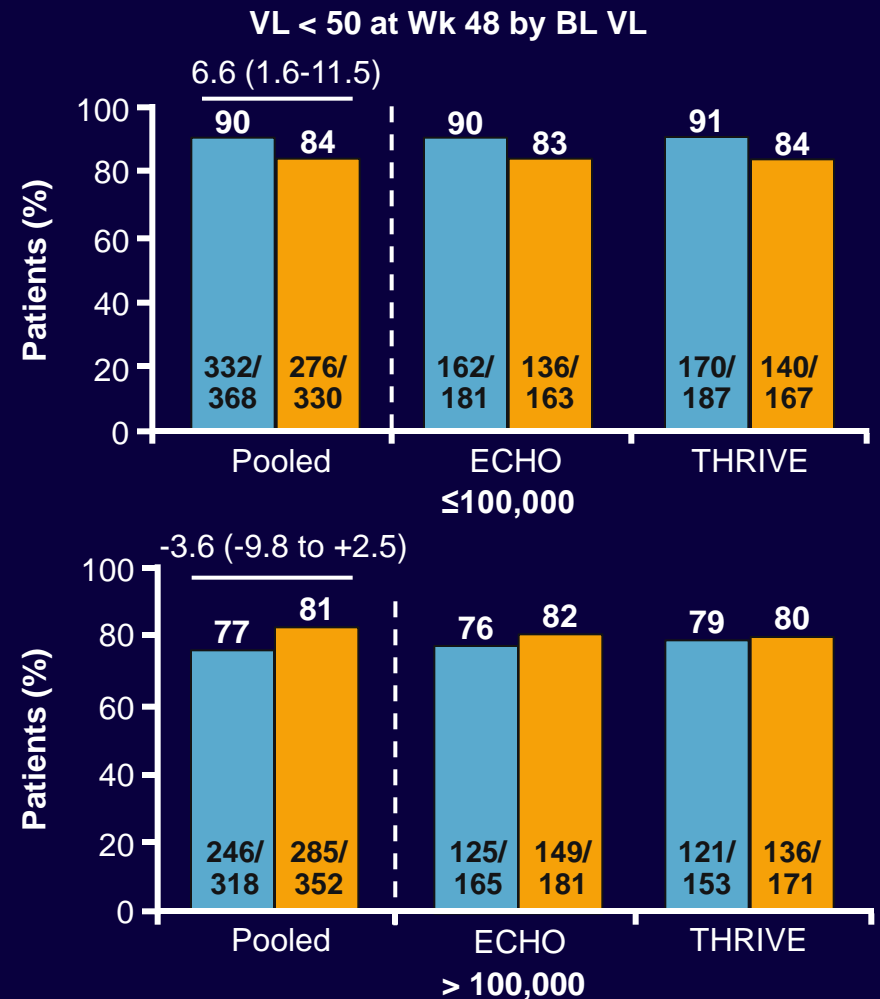
*THRIVE only. †Selected by investigator from ABC/3TC, TDF/FTC, ZDV/3TC.

ECHO, THRIVE: Rilpivirine vs EFV in Treatment-Naive Patients

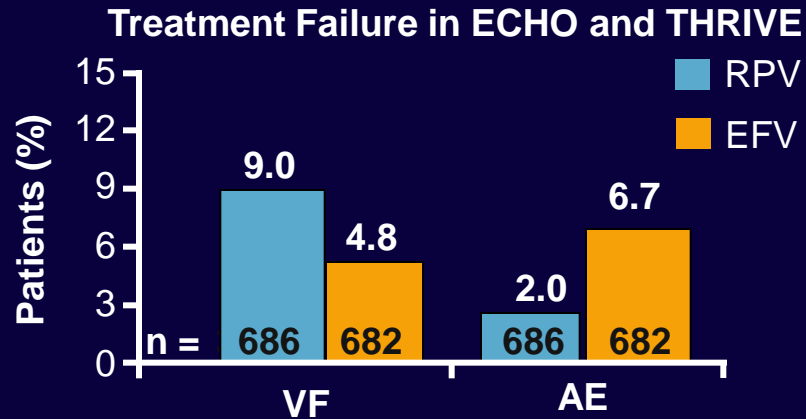


* $P < .0001$ for noninferiority at -12% margin.

Cohen C, et al. AIDS 2010. Abstract THLBB206. Graphics used with permission.



ECHO, THRIVE: Treatment Failure, Resistance, and Adverse Events



Resistance at Virologic Failure

Wk 48 Outcome	Rilpivirine (n = 686)	Efavirenz (n = 682)
VF with resistance data, n	62	28
No NNRTI or NRTI RAMs,%	29	43
≥ 1 Emergent NNRTI RAM,%	63	54
▪ Most frequent NNRTI RAM	E138K	K103N
≥ 1 Emergent NRTI RAMs, %	68	32
▪ Most frequent NRTI RAM	M184I	M184V

Adverse Events and Discontinuation

Wk 48 Outcome, %	Rilpivirine (n = 686)	Efavirenz (n = 682)	P Value
DC for AE	3	8	.0005
Most Common AEs of Interest, %			
Any neurologic AE	17	38	< .0001
Any psychiatric AE	15	23	.0002
Any rash	3	14	< .0001

Potential New Options

- CCR5 inhibitor-containing regimens
- “Quad”: elvitegravir/cobicistat/TDF/FTC
- Cobicistat as PI booster, including possible coformulations
- S/GSK1349572 (including coformulation with ABC/3TC)
- Rilpivirine, including coformulation with TDF/FTC
- RAL once-daily

***“Prediction is difficult,
especially when it involves the future”***

-Vice President Dan Quayle

Predictions involving the future - 1

- *Something* will eventually replace TDF/FTC/EFV for initial therapy
 - TDF/FTC/RPV?
 - Better tolerability, but efficacy and resistance concerns
 - Once daily RAL?
 - Data in 2/11. Well tolerated but not coformulated
 - “Quad”?
 - Phase III studies in progress. Concern about creatinine elevation
 - S/GSK1349572
 - Attractive 1st agent, but depends on what happens with earlier entries
- For the foreseeable future, boosted PIs will remain the best choice for patients with unreliable adherence
 - Will cobicistat replace ritonavir?

Predictions involving the future - 2

- Generics: the wild card:
 - Generic 3TC, EFV, SQV coming
 - For the first time, preferred agents will be available as generics
 - Will 3rd party payers notice?
 - Will coformulations no longer be covered?
 - Will the bar be higher for development of new first-line agents?
 - Need to show superior efficacy and/or safety rather than non-inferiority and improved convenience
- Will there be a pipeline for treatment-experienced patients?

The Next Drugs?

- Rilpivirine: Cross-resistance with ETR
- Elvitegravir: Cross-resistance with RAL
- S/GSK1349572: Activity against *some* RAL-resistance virus
- New CCR5 antagonists: Won't help those who can't take MVC due to tropism. Vicriviroc development halted
- Maturation inhibitors: Bevirimat development halted

