

# HIV Treatment: What to Start

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# Learning Objectives

Upon completion of this presentation, learners should be better able to:

- Assess current guidelines for selection of initial antiretroviral regimens, including the advantages and disadvantages of each
- Appraise the drugs and regimens currently being investigated in phase III clinical trials and their potential role in practice



# Off-Label Disclosure

The following off-label/investigational uses will be discussed in this presentation:

- Investigational agents: elvitegravir, cobicistat, rilpivirine, S/GSK1349572
- Investigational coformulations using investigational and approved agents



# Case

- A 30 year old accountant is referred to you by his dentist, who found oral thrush on exam.
- He is found to be HIV+ with a CD4 count of 83 and a viral load of 192,000
- Genotype shows pan-susceptible virus
- He does not have chronic hepatitis B or C. Renal function, liver enzymes, and fasting lipid profile are normal
- He does not use illicit drugs. He has no chronic medical conditions except HTN, well controlled on an ARB
- He says he is ready to start ART. He has no preferences about regimen



# Case

- What would you do now?
  1. Defer ART until he has seen an adherence counselor and has kept several follow-up appointments
  2. Start 2 NRTIs plus EFV
  3. Start 2 NRTIs plus a boosted PI
  4. Start 2 NRTIs plus RAL
  5. Start an NRTI-sparing regimen

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

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

# Other regimens categories (DHHS)

- Alternative (BI)
- Acceptable (CI)
- Acceptable but more definitive data are needed (CIII)
- May be acceptable but should be used with caution (CI-III)
- Not recommended

# 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?

	PROS	CONS
EFV	<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>•PK forgiving of missed doses</li></ul>	<ul style="list-style-type: none"><li>•CNS side effects</li><li>•Teratogenicity</li><li>•Genetic barrier: resistance with interruption</li><li>•Poorer CD4 response than with other classes</li></ul>

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PI/r	<ul style="list-style-type: none"><li>•As effective as EFV (ATV/r in ACTG 5202)</li><li>•Less resistance with failure</li><li>•Preferred in pregnancy</li></ul>	<ul style="list-style-type: none"><li>•Greater pill burden</li><li>•GI side effects</li></ul>

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PI/r	<ul style="list-style-type: none"><li>•As effective as EFV (ATV/r in ACTG 5202)</li><li>•Less resistance with failure</li><li>•Preferred in pregnancy</li></ul>	<ul style="list-style-type: none"><li>•Greater pill burden</li><li>•GI side effects</li></ul>
RAL	<ul style="list-style-type: none"><li>•As effective as EFV with better tolerability (STARTMRK)</li><li>•Lipid neutral (vs. EFV, PI/r)</li></ul>	<ul style="list-style-type: none"><li>•No long-term data</li><li>•Twice-daily dosing</li><li>•Resistance risk similar to EFV</li><li>•Expensive</li></ul>

# Case

- The patient wants a once-daily regimen and says he can't afford the time to adjust to EFV side effects. What do you choose?
  1. 2 NRTIs + LPV/r
  2. 2 NRTIs + DRV/r
  3. 2 NRTIs + ATV/r
  4. Convince him to take EFV
  5. 2 NRTIs plus once-daily RAL

## Question 2: Which Boosted PI?

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

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

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<b>LPV/r</b>	<ul style="list-style-type: none"><li>• Coformulated</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><li>• Risk of MI in D:A:D</li></ul>

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<b>LPV/r</b>	<ul style="list-style-type: none"> <li>• Coformulated</li> <li>• No food restrictions</li> <li>• Preferred for pregnancy</li> <li>• Least expensive</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> <li>• Risk of MI in D:A:D</li> </ul>
<b>FPV/r</b>	<ul style="list-style-type: none"> <li>• No food restrictions</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 as well studied as other PI/r options</li> </ul>

# Case

- Which NRTI backbone do you choose?
  1. TDF/FTC
  2. ABC/3TC (after HLA B\*5701 testing)
  3. AZT/3TC
  4. I would use an NRTI-sparing regimen

# Question 3: Which NRTI Backbone?

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

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<b>ABC/3TC</b>	<ul style="list-style-type: none"><li>•Lack of renal toxicity</li></ul>	<ul style="list-style-type: none"><li>•Need for HLA B*5701 screening to avoid ABC HSR</li><li>•Inferior to TDF/FTC with VL &gt;100,000</li><li>•Increased risk of MI?</li><li>•ACTG 5202 safety/tolerability data</li></ul>

# 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 1<sup>st</sup> 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,  
(VL>100,000?)

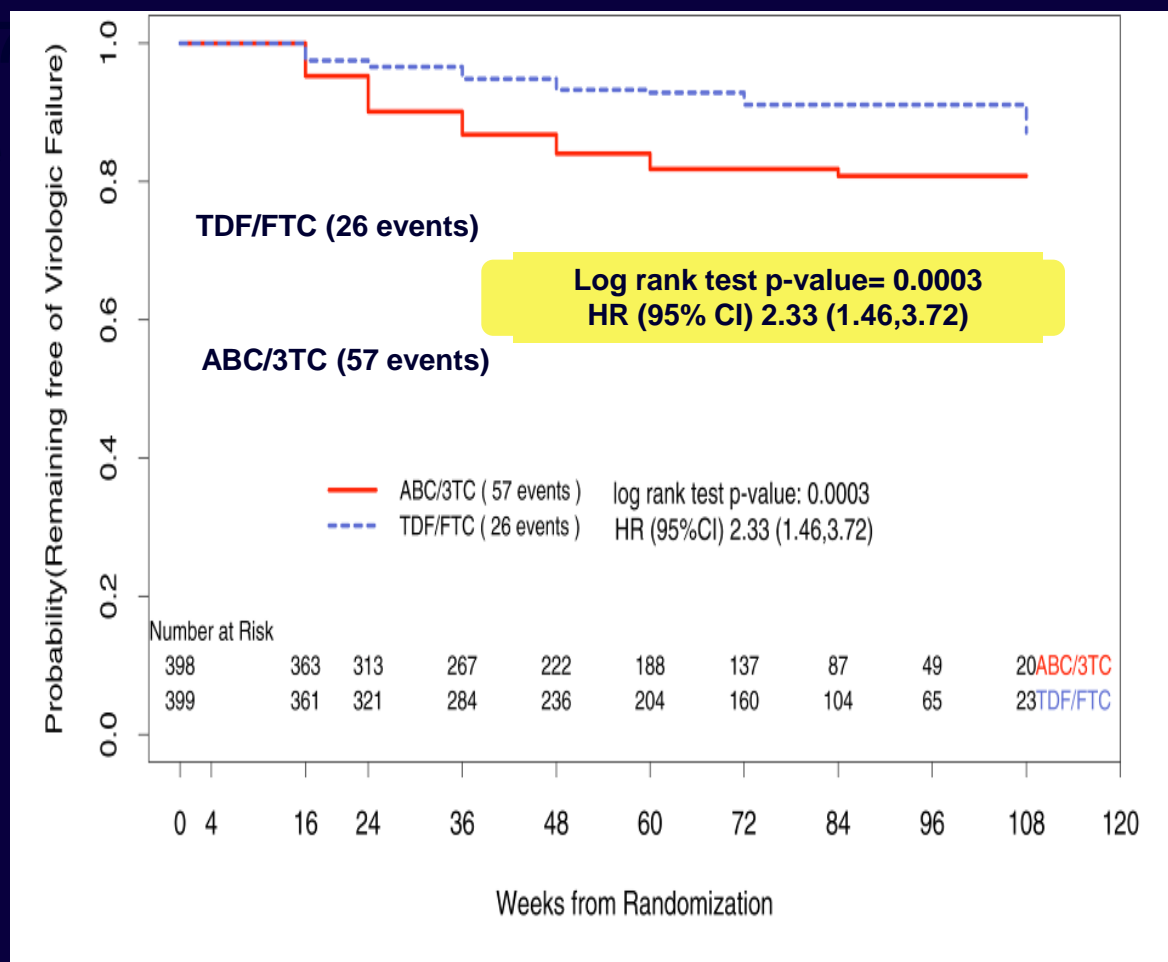
Kidney  
disease

**NRTI-sparing  
regimen?**

**ABC/3TC**

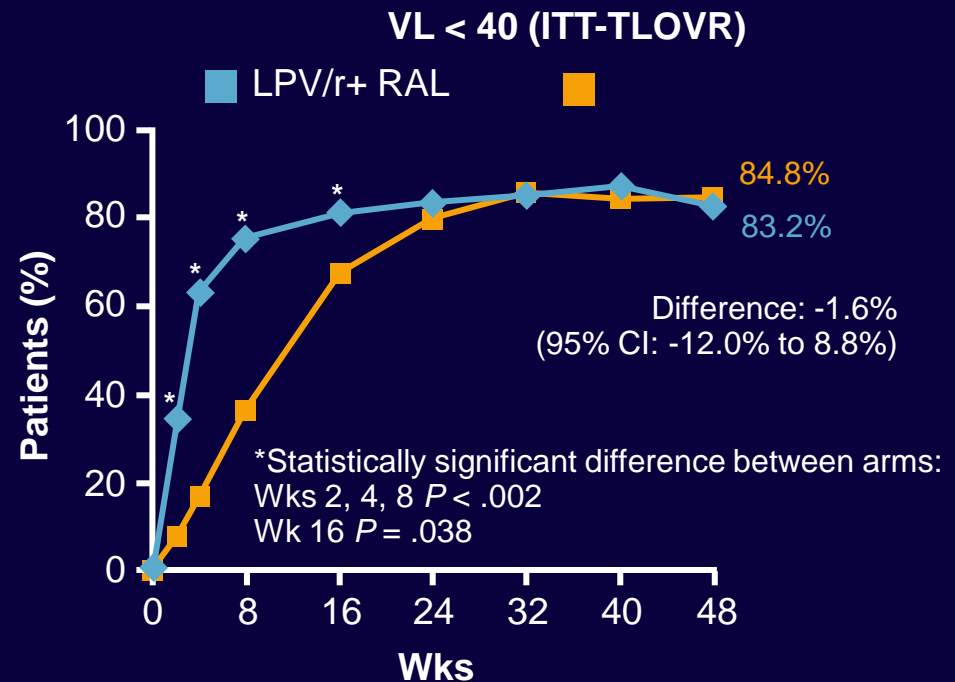
# ACTG 5202: ABC/3TC vs. TDF/FTC

## Primary Virologic Endpoint (High VL Stratum at DSMB Action)



# 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 log<sub>10</sub>



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

# Potential New First-Line Options

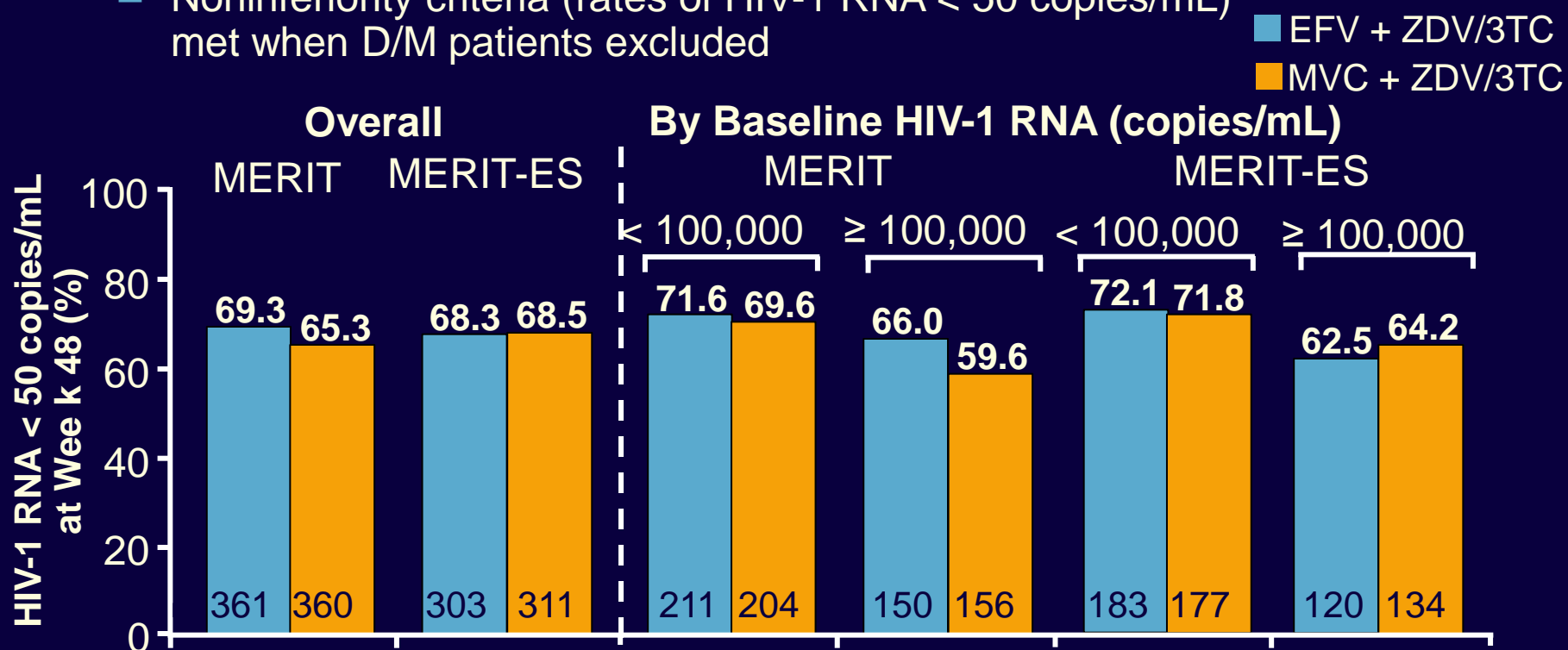
- CCR5 inhibitor-containing regimens
- “Quad”: elvitegravir/cobicistat/TDF/FTC
- Cobicistat as PI booster, including possible coformulations
- Dolutegravir (including coformulation with ABC/3TC)
- Rilpivirine, including coformulation with TDF/FTC

# What about maraviroc?

	PROS	CONS
MVC	<ul style="list-style-type: none"><li>•R5 virus more likely with early/initial therapy</li><li>•Very well tolerated</li><li>•Greater CD4 count than with EFV</li><li>•High barrier to resistance</li></ul>	<ul style="list-style-type: none"><li>•No long-term data</li><li>•Twice-daily dosing</li><li>•Studied only with ZDV/3TC</li><li>•Requires baseline tropism testing</li><li>•Complex dosing</li></ul>

# MERIT: Reanalysis With Enhanced Sensitivity Phenotypic Tropism Assay

- 15% of patients reclassified from R5 to D/M at screening when retested with enhanced sensitivity phenotypic tropism assay
  - Noninferiority criteria (rates of HIV-1 RNA < 50 copies/mL) met when D/M patients excluded



# Determination of Viral Tropism

- Phenotypic assay used in clinical trials involving CCR5 antagonists to determine viral tropism<sup>[1,2]</sup>
- Genotyping of env V3 loop may be an alternative to phenotyping<sup>[3,4]</sup>
  - Less costly and faster, though some assays inferior to phenotypic assay<sup>[5]</sup>
- Genotypic<sup>[6]</sup> and phenotypic<sup>[7]</sup> assays available for determining tropism from PBMC proviral DNA

1. Gulick RM, et al. *N Engl J Med.* 2008;359:1429-1441. 2. Cooper DA, et al. *J Infect Dis.* 2010;201:803-813. 3. Harrigan PR, et al. IAS 2009. Abst WELBA101. 4. McGovern R, et al. CROI 2010. Abs 92. 5. Wilkin TJ, et al. ICAAC 2010. Abs. H-932a. 5. Swenson LC, et al. *J Acquir Immun Defic Syndr.* 2010;54:506-510. 6. Toma J, et al. ICAAC 2010. Abs H-921.

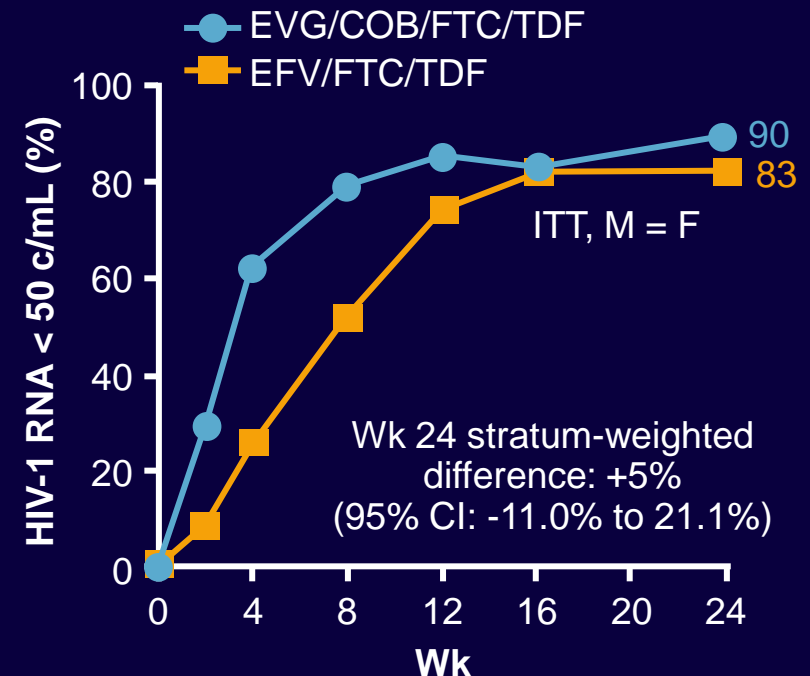
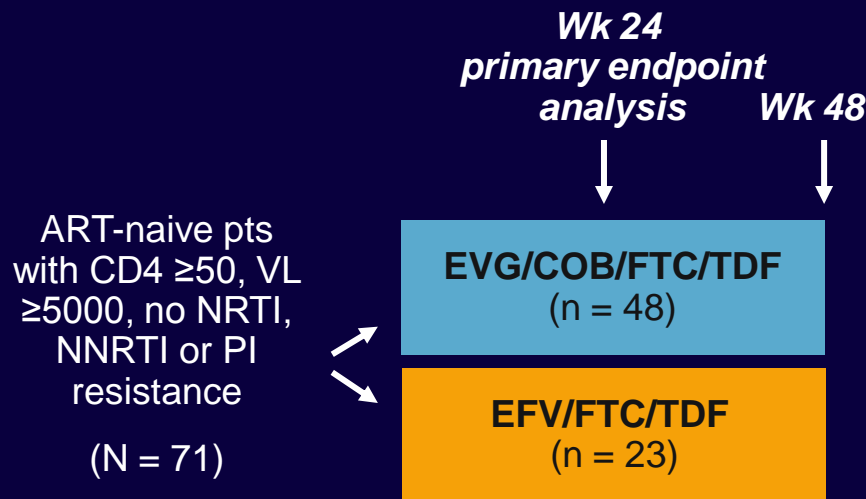
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# Cobicistat-Boosted EVG + FTC/TDF vs. EFV/FTC/TDF in Naive Pts: Phase II trial

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

- Elvitegravir (EVG): investigational integrase inhibitor

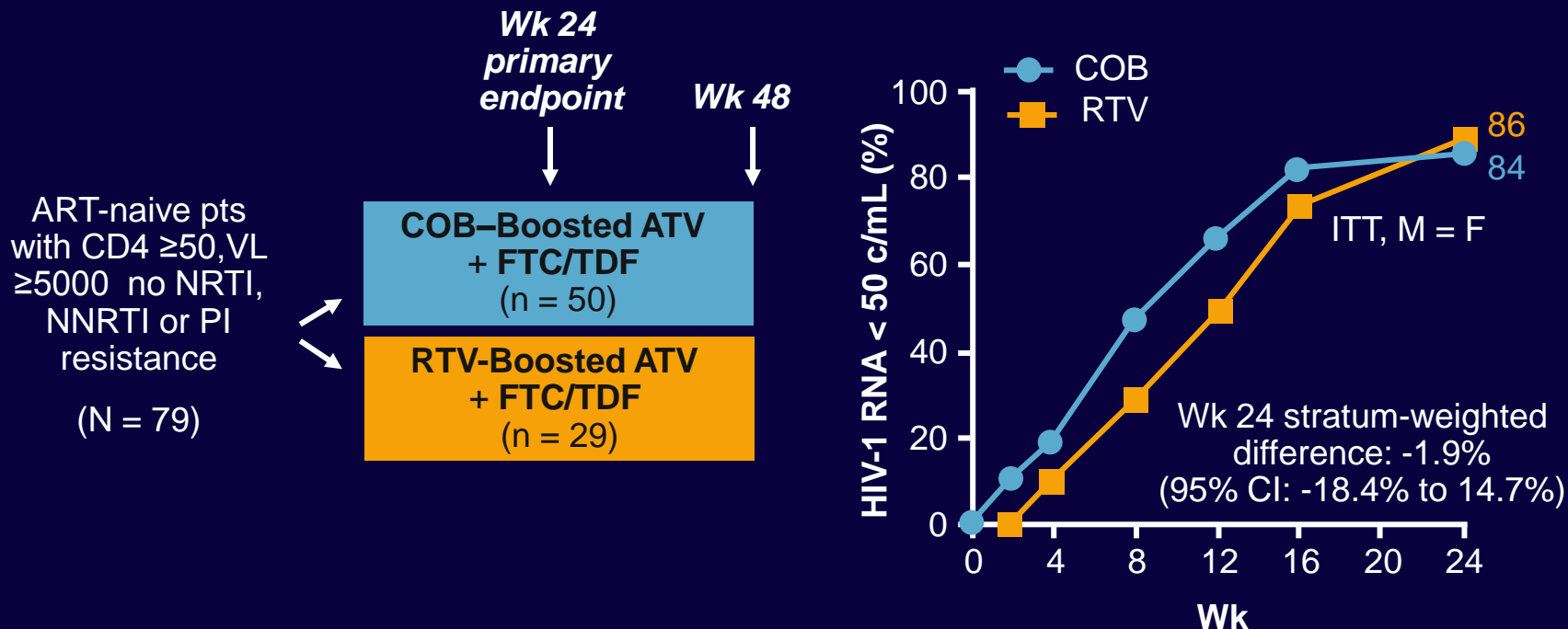


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# Cobicistat-Boosted ATV Virologic Efficacy Similar to ATV/r in Naive Pts

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



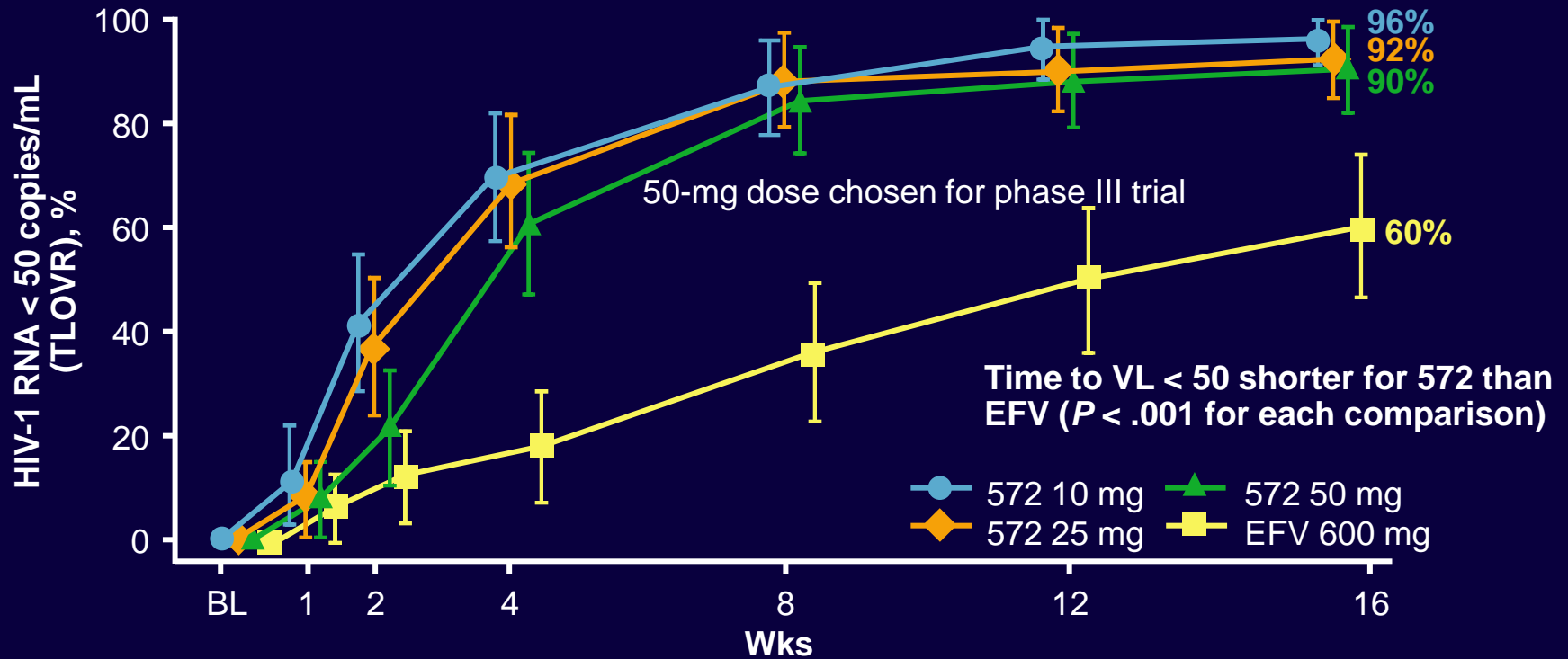
# Cobicistat: AEs When Combined With EVG/FTC/TDF or ATV/r + TDF/FTC

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

# Potential New Options

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

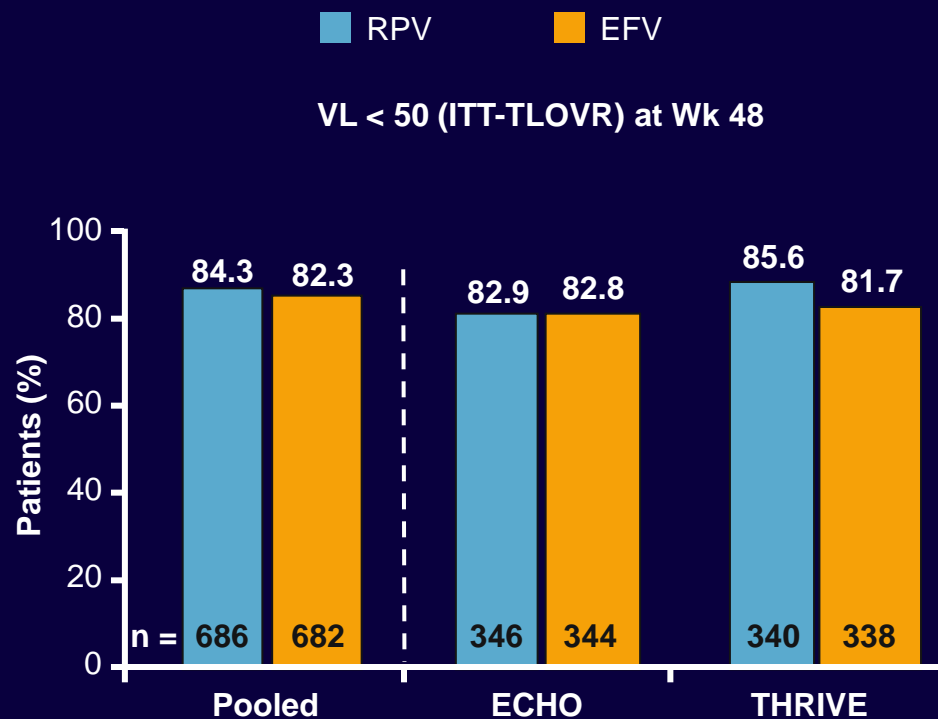


- CD4 count increases 153-176 on 572 vs 116 on EFV
- No serious adverse events related to 572

# Potential New Options

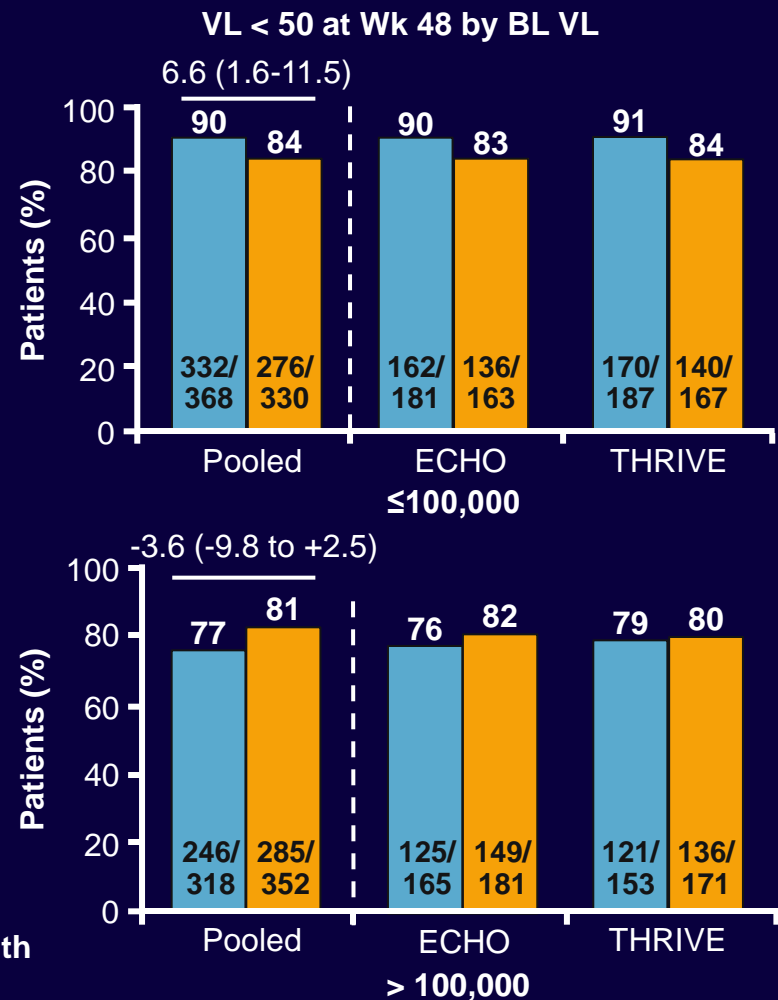
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# ECHO, THRIVE: Rilpivirine vs EFV in Treatment-Naive Patients



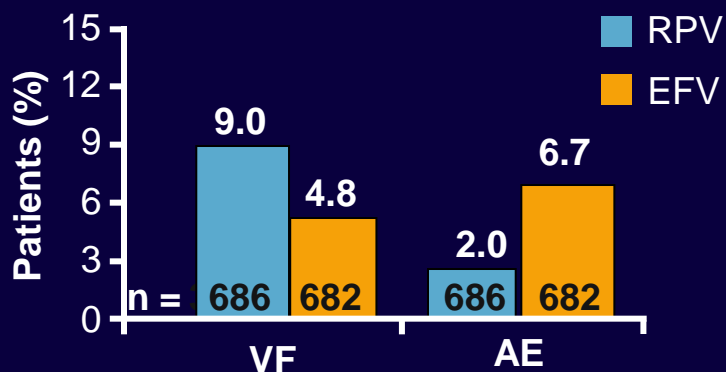
\**P* < .0001 for noninferiority at -12% margin.

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



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

Treatment Failure in ECHO and THRIVE



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
<b>Most Common AEs of Interest, %</b>			
Any neurologic AE	17	38	< .0001
Any psychiatric AE	15	23	.0002
Any rash	3	14	< .0001

# Predictions (and questions) involving the future

- There will soon be new options for initial therapy
  - TDF/FTC/RPV?
    - Better tolerability, but efficacy and resistance concerns
  - “Quad”?
    - Phase III studies in progress. Concern about creatinine elevation
  - Dolutegravir + ABC/3TC coformulation
    - Attractive 1<sup>st</sup> agent, but depends on what happens with earlier entries
    - Use of ABC/3TC
- Boosted PIs will remain the best choice for patients with unreliable adherence
  - Will cobicistat replace ritonavir?

# Predictions (and questions) involving the future

- Generics: the wild card:
  - Generic 3TC, EFV, SQV coming
  - For the first time, preferred agents will be available as generics
  - Will 3<sup>rd</sup> 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

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**Features**

- [Johns Hopkins Point of Care Technology Center \(POC-IT\)](#)
- [The Choice of the Nucleoside Backbone in Initial Therapy](#)

**New Developments**

**Announcements**

- [Johns Hopkins POC-IT Center launches the first comprehensive, on-line decision support tool designed to assist clinicians in the diagnosis, management and treatment of HIV/AIDS \(HIV Guide\)](#)

**Question of the Week**

Why are many PI's "boosted" with ritonavir? Wouldn't it have made much more sense for one manufacturer to have created a strong enough drug on its own, without having to add another drug for only boosting purposes?  
*10-29-2004*

**Literature Review**

- [Nelfinavir Plasma Concentrations are Low During Pregnancy](#)  
By John G. Bartlett, M.D.
- [Incidence of HIV Superinfection Following Primary Infection](#)  
By John G. Bartlett, M.D.

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