National HIV Curriculum

Efavirenz (*Sustiva*)

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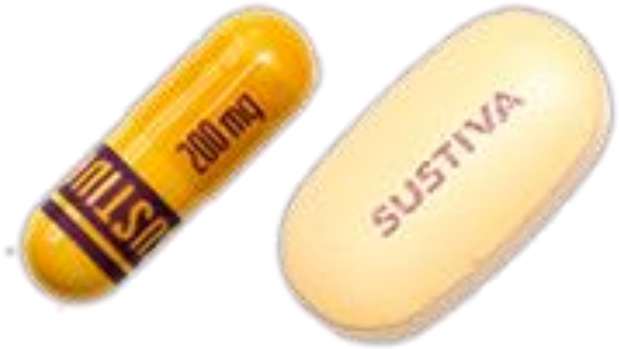
AETC AIDS Education & Training Center Program

Efavirenz (*Sustiva*)

Sustiva

[sus-TEE-vah]



200 mg 600 mg

NNRTI

Dose: 600 mg once daily on empty stomach, preferably at bedtime

INITIAL THERAPY

Efavirenz

Efavirenz
Summary of Key Studies

- Phase 3 Trials in Treatment-Naïve
  - ACTG 5202: EFV versus ATV/r, both with TDF-FTC or ABC-3TC
  - ENCORE-1: EFV 400 mg versus EFV 600 mg, with 2 NRTIs
  - ACTG 5095: PI-sparing regimens
  - ACTG 5142: LPV/r + EFV; LPV/r + NRTIs; EFV + NRTIs
  - GS-934: EFV + TDF-FTC versus EFV + ABC-3TC
  - ECHO: EFV + TDF-FTC versus RPV + TDF-FTC
  - THRIVE: EFV + 2NRTIs versus RPV + 2NRTIs
  - LAKE: EFV + ABC-3TC versus LPV/r + ABC-3TC
  - SUPPORT: EFV + ABC-3TC in underrepresented populations

Efavirenz
Summary of Key Studies

- Phase 3 Trials in Treatment-Experienced
  - 006: EFV + IDV, EFV + ZDV-3TV versus IDV + ZDV-3TC
  - ACTG 388: Efavirenz versus Nelfinavir, both with 3TC-ZVD + IDV
- Switch/Simplification Trials
  - ACTG 5116 (and 5125s): PI-sparing versus NRTI sparing regimens

TREATMENT EXPERIENCED

Efavirenz

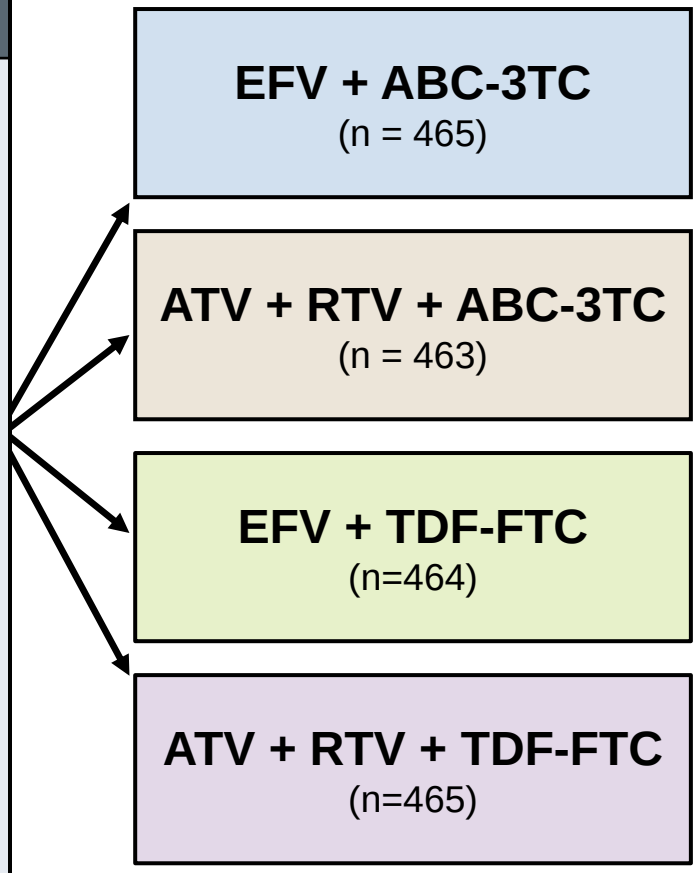
EFV versus ATV + RTV, both with ABC-3TC or TDF-FTC

ACTG 5202

EFV versus ATV/r, both with ABC-3TC or TDF-FTC
ACTG 5202: Study Design

Study Design: ACTG 5202

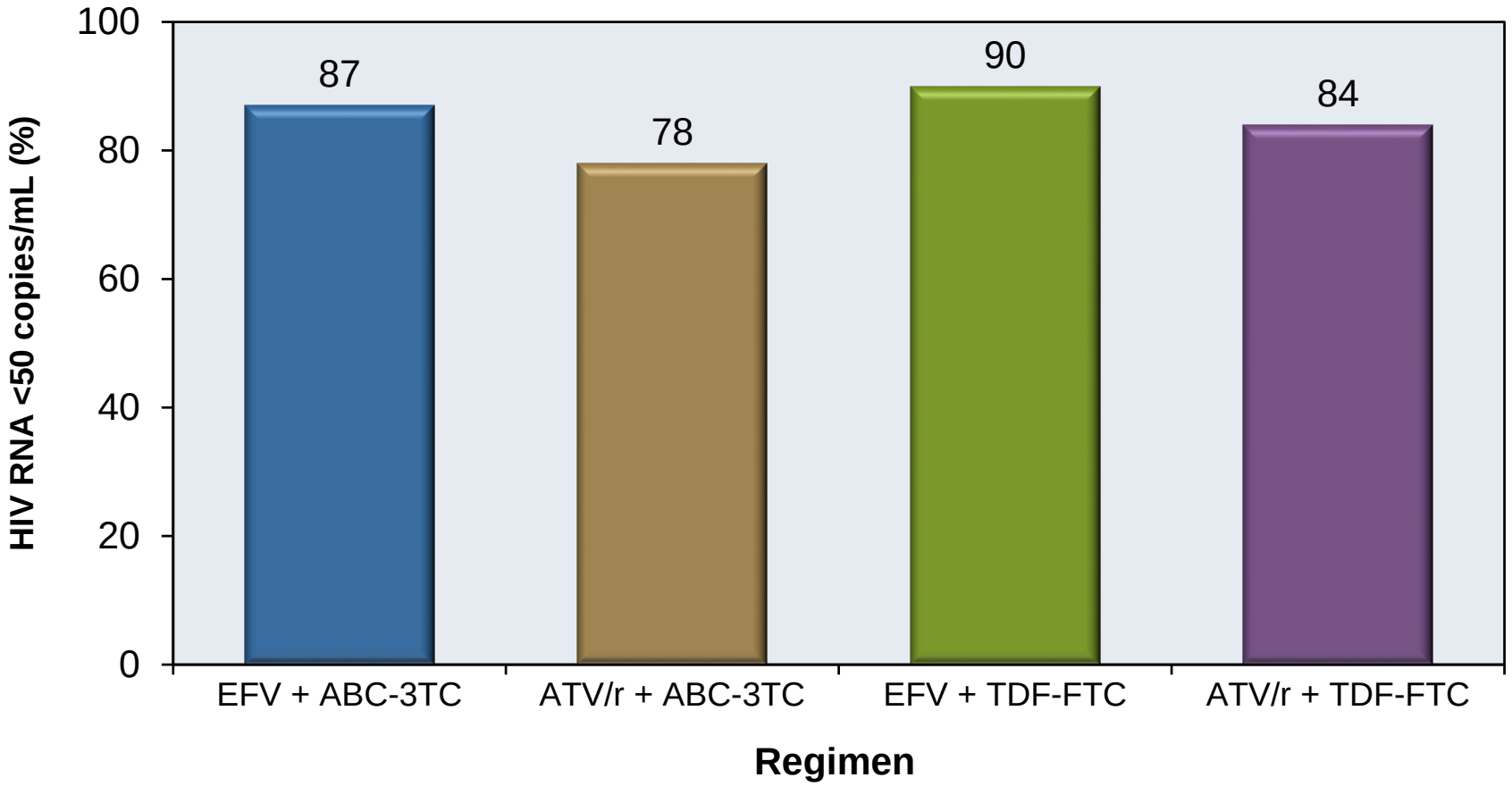
- **Background**: Randomized, phase 3b equivalence trial to evaluate open-label efavirenz against atazanavir + ritonavir, each with either double-blinded abacavir-lamivudine or tenofovir DF-emtricitabine, for initial treatment of HIV.
- **Inclusion Criteria (n = 1857)**
  - Age >16 years
  - Antiretroviral-naive
  - No major resistance mutations
- **Treatment Arms** (all medications once daily)
  - EFV 600 mg + ABC-3TC 600-300 mg
  - ATV 300 mg + RTV 100 mg + ABC-3TC 600-300 mg
  - EFV 600 mg + TDF-FTC 300-200 mg
  - ATV 300 mg + RTV 100 mg + TDF-FTC 300-200 mg



Source: Daar ES, et al. Ann Intern Med. 2011;154:445-56.

EFV versus ATV/r, both with ABC-3TC or TDF-FTC
ACTG 5202: Results

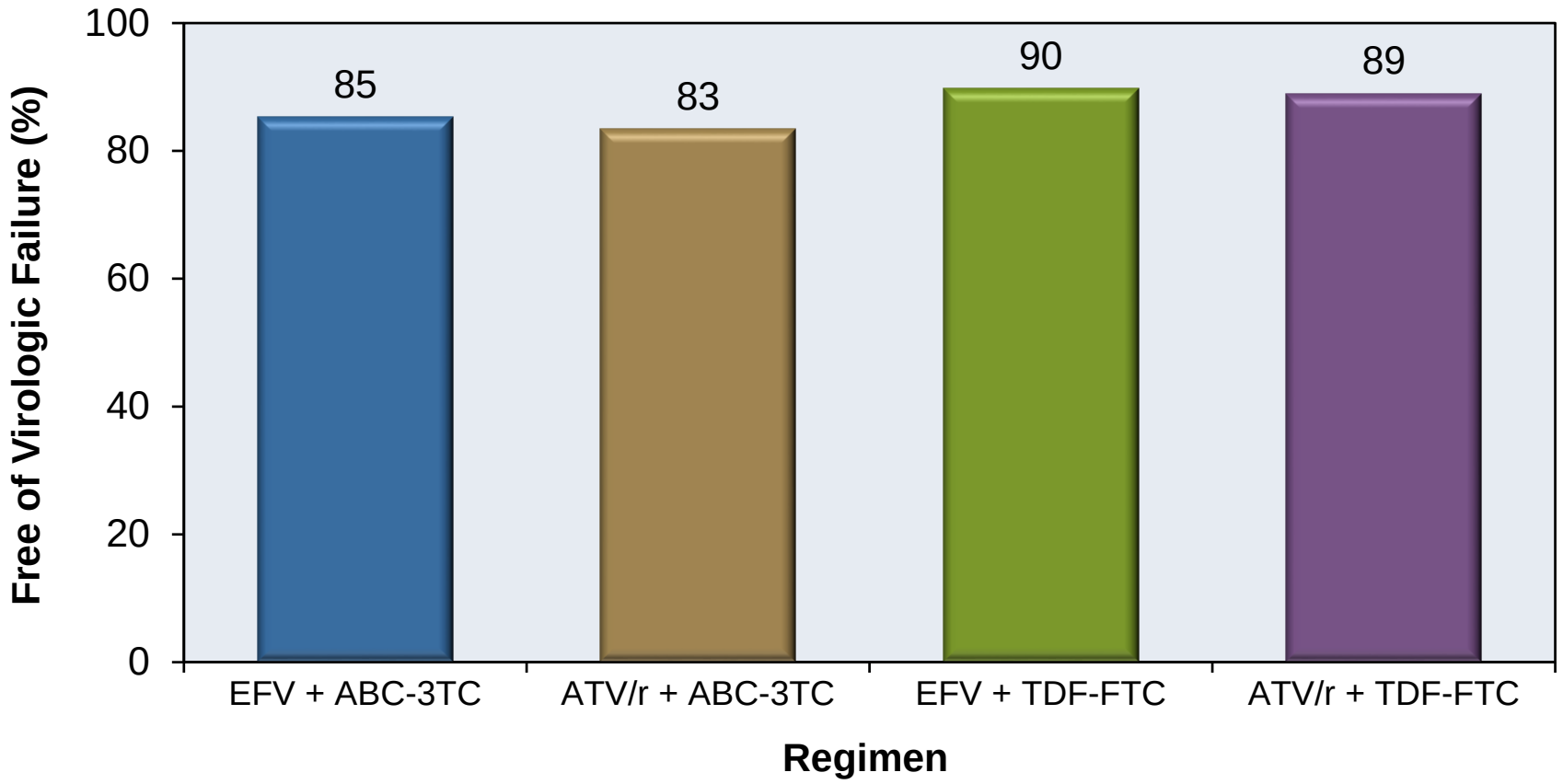
Week 48: Virologic Response



Source: Daar ES, et al. Ann Intern Med. 2011;154:445-56.

EFV versus ATV/r, both with ABC-3TC or TDF-FTC
ACTG 5202: Results

Week 96: Free of Virologic Failure

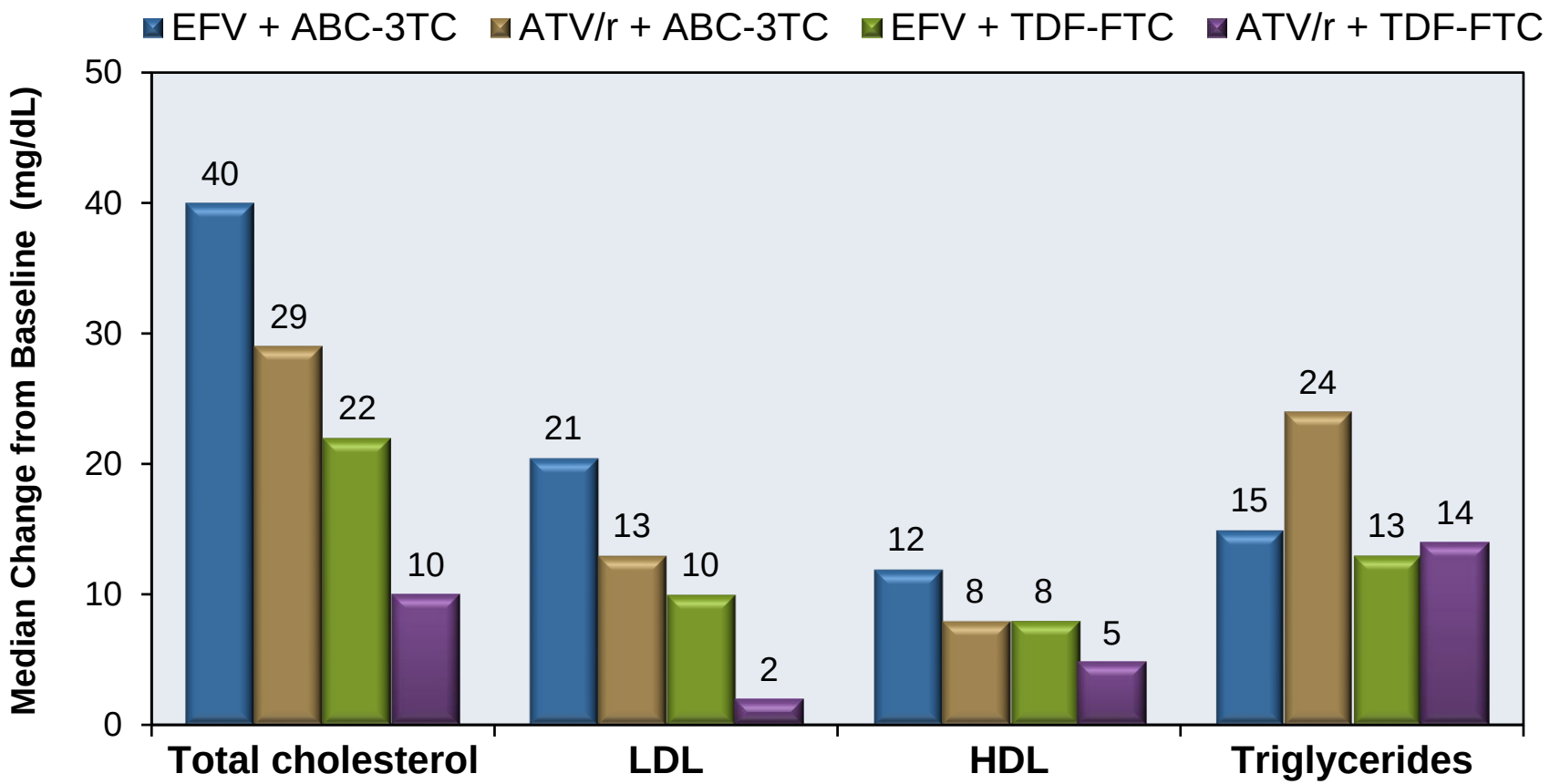


*Virologic failure = HIV RNA ≥1000 copies/mL between 16 and 24 weeks, or HIV RNA ≥200 copies/mL after 24 weeks.

Source: Daar ES, et al. Ann Intern Med. 2011;154:445-56.

EFV versus ATV/r, both with ABC-3TC or TDF-FTC
ACTG 5202: Results

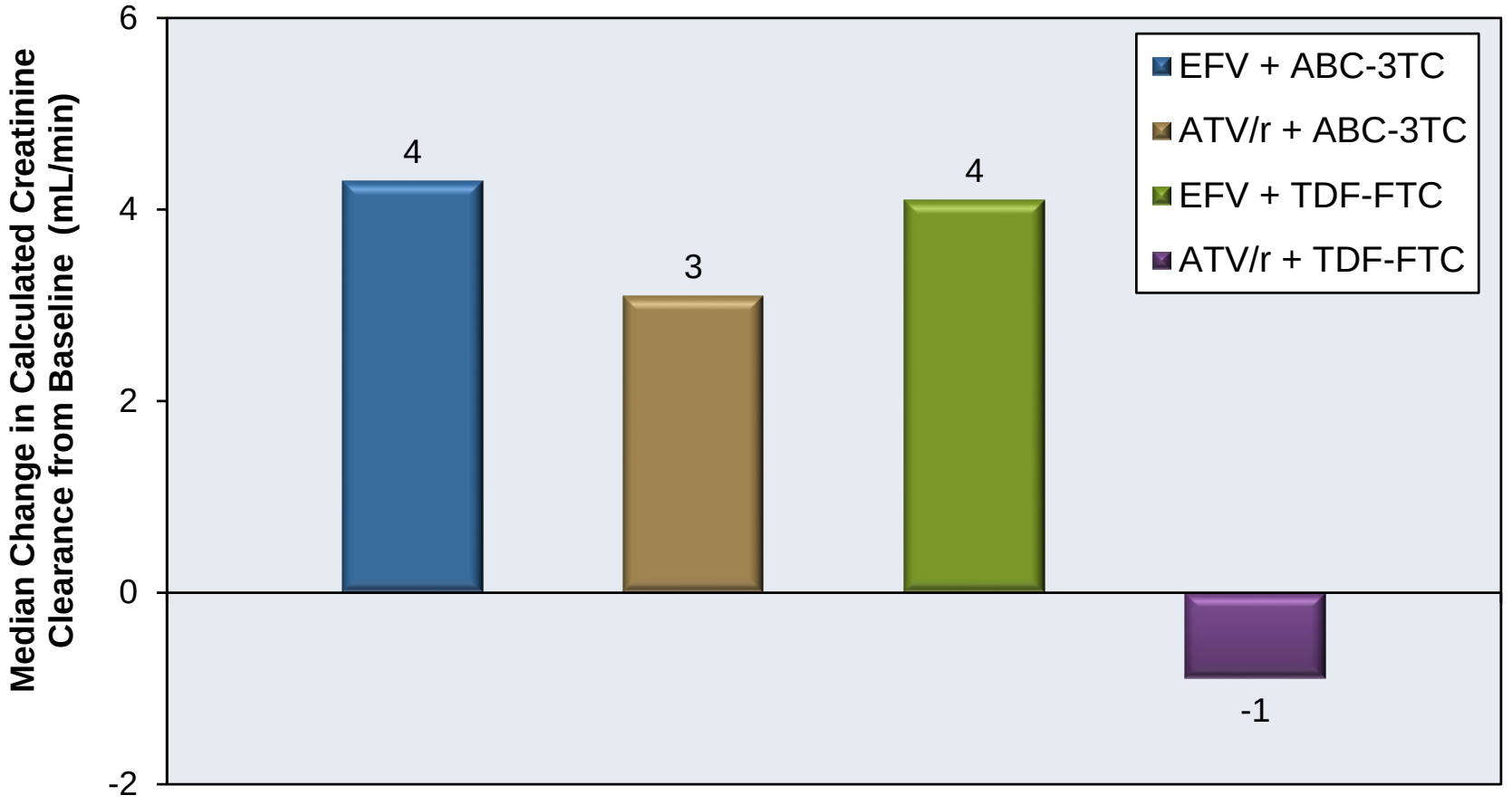
Week 48: Analysis of Lipids



Source: Daar ES, et al. Ann Intern Med. 2011;154:445-56.

EFV versus ATV/r, both with ABC-3TC or TDF-FTC
ACTG 5202: Results

Week 48: Change in Creatinine Clearance



Source: Daar ES, et al. Ann Intern Med. 2011;154:445-56.

EFV versus ATV/r with ABC-3TC or TDF-FTC
ACTG 5202: Conclusions

Conclusion: “Atazanavir plus ritonavir and efavirenz have similar antiviral activity when used with abacavir-lamivudine or tenofovir DF-emtricitabine.”

Source: Daar ES, et al. Ann Intern Med. 2011;154:445-56.

Efavirenz 400 mg versus 600 mg, with TDF-FTC

ENCORE1 Trial

Efavirenz 400 mg versus Efavirenz 600 mg, with TDF-FTC
ENCORE1: Study Design

Study Design: ENCORE1

- **Background**: Randomized, double-blind, placebo-controlled study comparing the safety and efficacy of two doses of efavirenz, in combination with co-formulated tenofovir DF and emtricitabine
- **Inclusion Criteria (n = 636)**
  - Antiretroviral-naïve
  - Age ≥16 years
  - HIV RNA ≥1000 copies/mL
  - CD4 count >50 and <500 cells/mm^3
- **Treatment Arms**
  - Efavirenz 400 mg QD + TDF-FTC QD
  - Efavirenz 600 mg QD + TDF-FTC QD

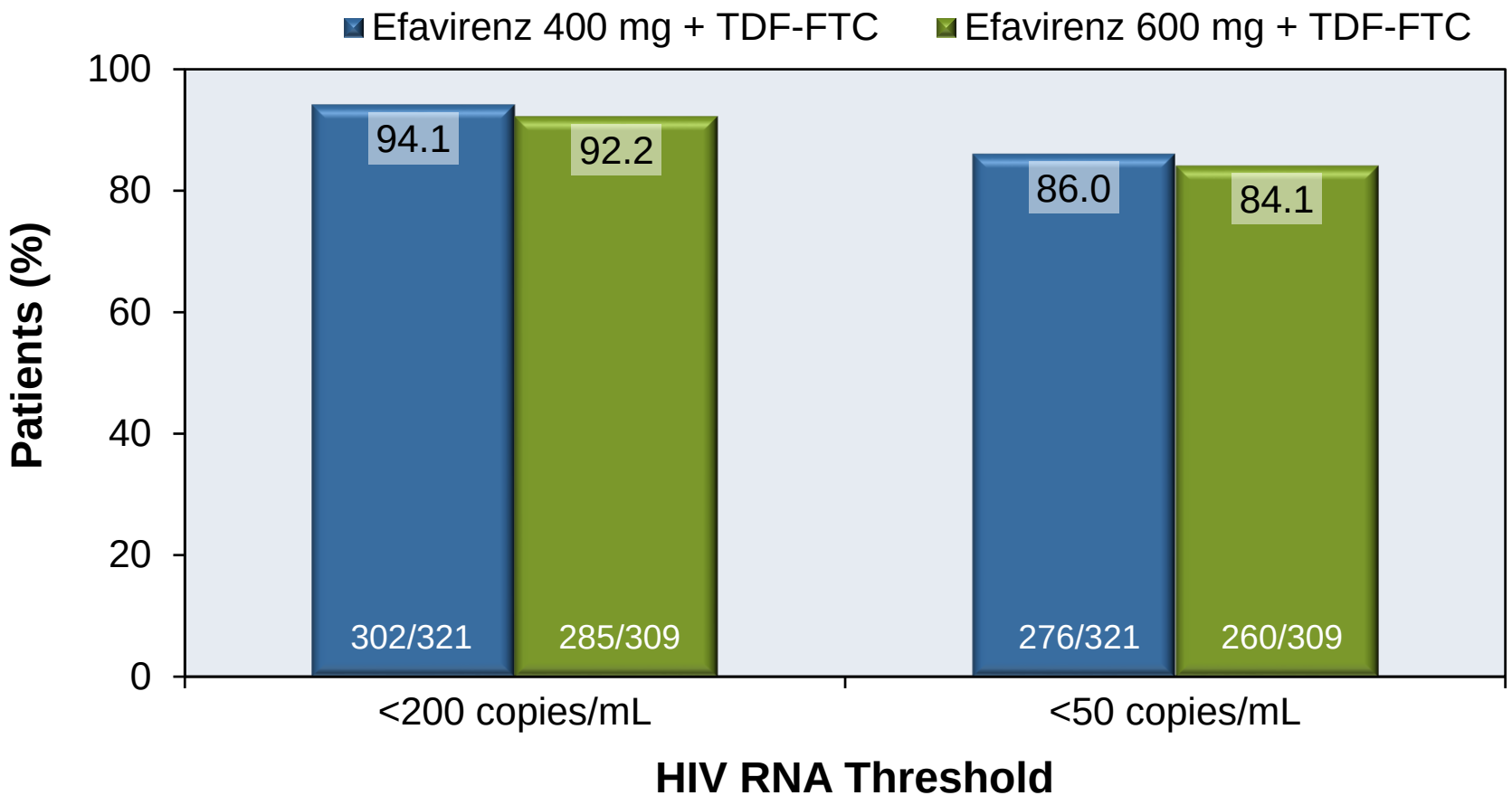
Efavirenz 400 mg + TDF-FTC QD
(n = 321)

Efavirenz 600 mg + TDF-FTC QD
(n = 309)

Source: ENCORE1 Study Group. Lancet. 2014;383:1474-82.

Efavirenz 400 mg versus Efavirenz 600 mg, with TDF-FTC
ENCORE1: Results

Week 48: Virologic Response (Modified Intention-to-Treat)



Source: ENCORE1 Study Group. Lancet. 2014;383:1474-82.

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Efavirenz 400 mg versus Efavirenz 600 mg, with TDF-FTC
ENCORE1: Results

Overall Adverse Events		
Variable	**EFV 400 mg** n (%)	**EFV 600 mg** n (%)
Number of adverse events	1173 (49.8%)	1182 (50.2%)
Serious adverse events		
Total number of serious adverse events	31 (46.2%)	36 (53.7%)
Number with serious adverse events	23 (7.17%)	22 (7.12%)
Number with serious adverse events related to study drug	3 (0.93%)	4 (1.29%)
Adverse events probably related to study drug		
Patients with adverse events related to study drug	118 (36.8%)	146 (47.2%)
Patients stopping drug due to drug related adverse event	6 (1.9%)	18 (5.8%)

Source: ENCORE1 Study Group. Lancet. 2014;383:1474-82.

Efavirenz 400 mg versus Efavirenz 600 mg, with TDF-FTC
ENCORE1: Conclusions

Interpretation: “Our findings suggest that a reduced dose of 400 mg efavirenz is non-inferior to the standard dose of 600 mg, when combined with tenofovir and emtricitabine during 48 weeks in ART-naive adults with HIV-1 infection. Adverse events related to the study drug were more frequent with 600 mg efavirenz than with 400 mg. Lower dose efavirenz should be recommended as part of routine care.”

Source: ENCORE1 Study Group. Lancet. 2014;383:1474-82.

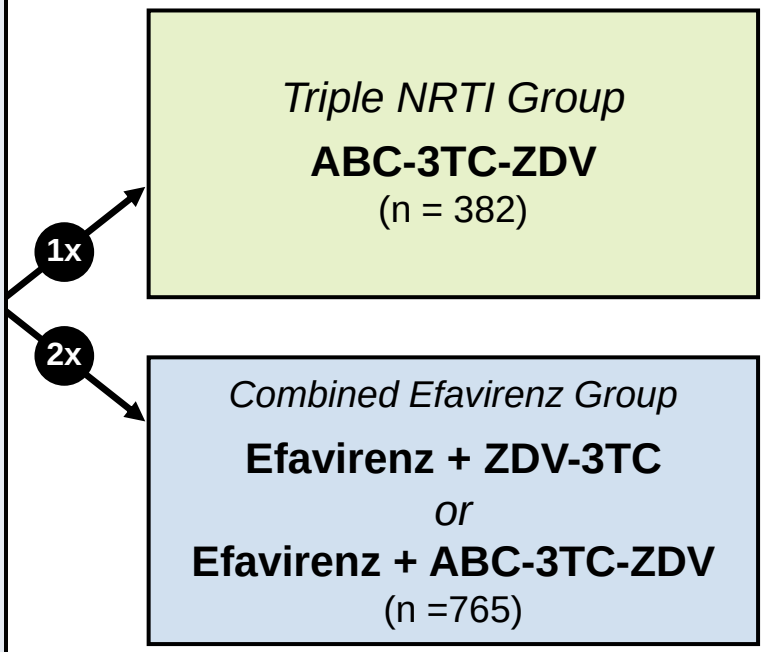
Triple NRTIs versus Efavirenz + 2-3 NRTIs

ACTG 5095 Trial

Triple NRTIs versus Efavirenz + 2-3 NRTIs
ACTG 5095: Study Design

Study Design: ACTG 5095

- **Background**: Randomized, double-blind, placebo-controlled, phase 3 trial comparing 3 protease inhibitor-sparing antiretroviral therapy regimens in antiretroviral-naïve patients
- **Inclusion Criteria (n = 1147)**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA ≥400 copies/mL
- **Treatment Arms**
  - Triple NRTI: ABC-3TC-ZDV
  - Combined Efavirenz: ZDV-3TC + Efavirenz*
  - Combined Efavirenz: ABC-3TC-ZDV+ Efavirenz*

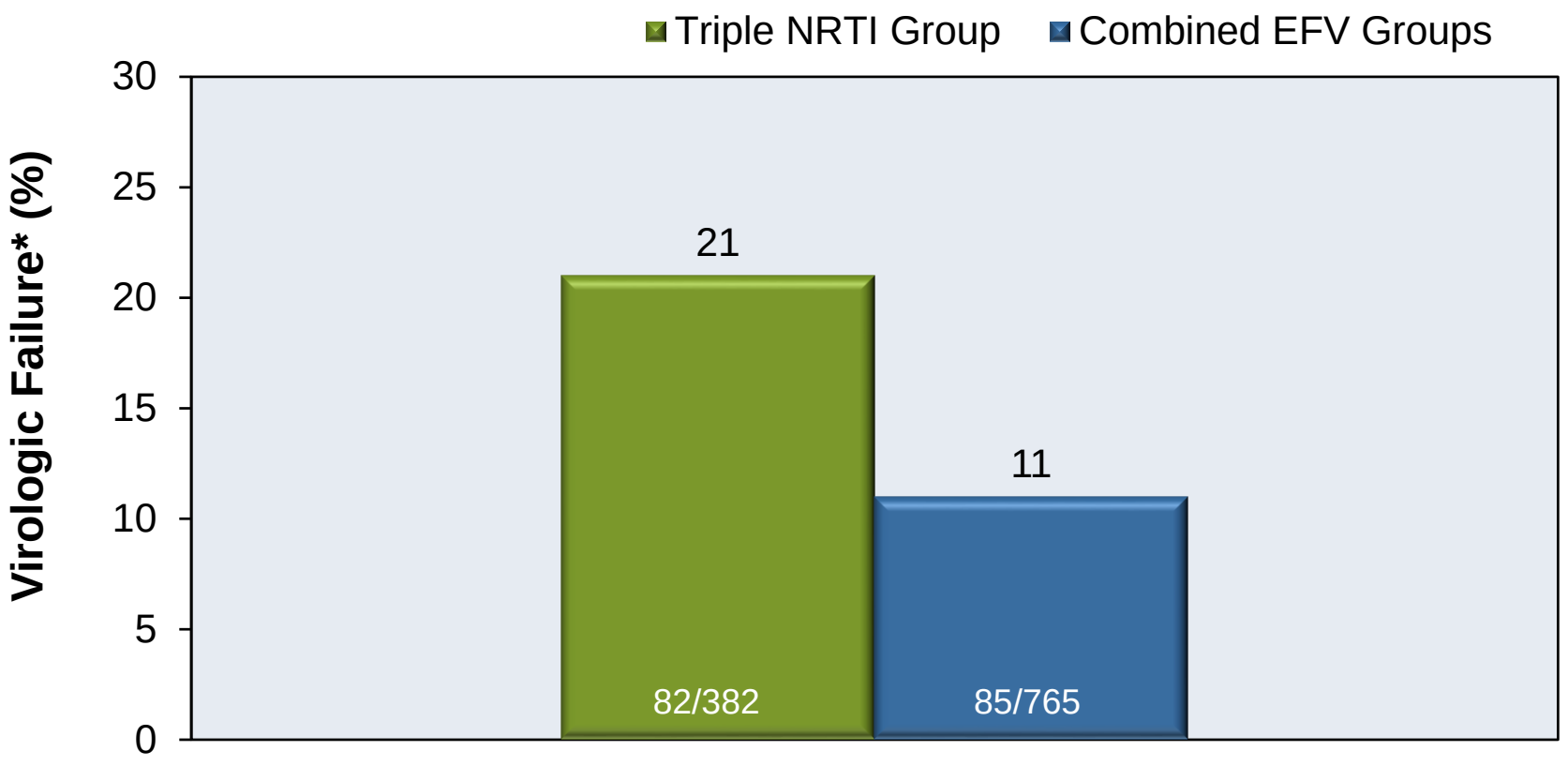


*Efavirenz arms combined for analysis

Source: Gulick RM, et al. N Engl J Med. 2004;350:1850-61.

Triple NRTIs versus Efavirenz + 2-3 NRTIs
ACTG 5095: Results

Week 48: Virologic Failure

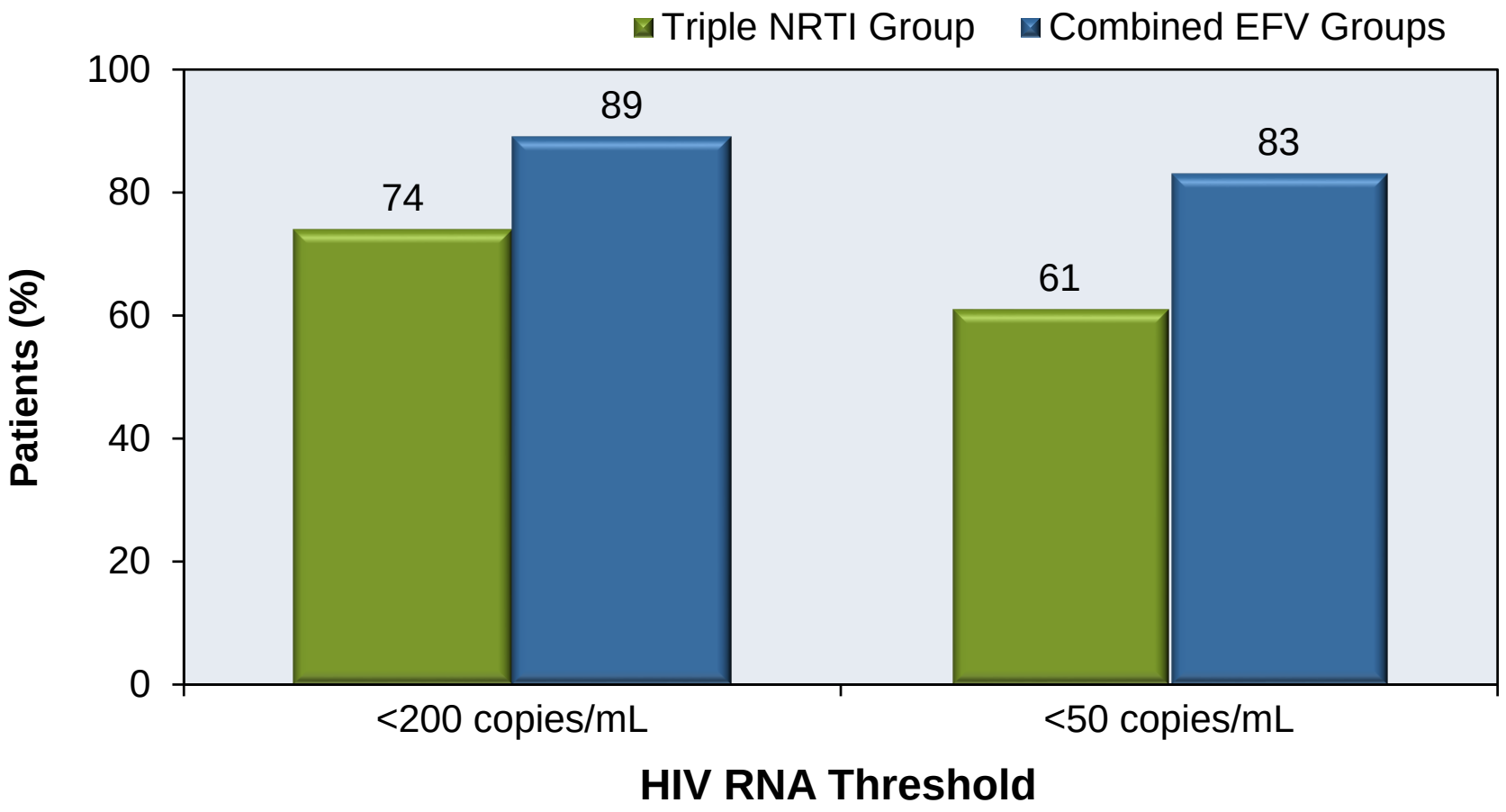


*Virologic failure = two successive HIV-1 RNA values ≥200 copies/mL ≥16 weeks after randomization

Source: Gulick RM, et al. N Engl J Med. 2004;350:1850-61.

Triple NRTIs versus Efavirenz + 2-3 NRTIs
ACTG 5095: Results

Week 48: Virologic Response



Source: Gulick RM, et al. N Engl J Med. 2004;350:1850-61.

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Triple NRTIs versus Efavirenz + 2-3 NRTIs
ACTG 5095: Conclusions

Conclusions: “In this trial of the initial treatment of HIV-1 infection, the triple-nucleoside combination of abacavir, zidovudine, and lamivudine was virologically inferior to a regimen containing efavirenz and two or three nucleosides.”

Source: Gulick RM, et al. N Engl J Med. 2004;350:1850-61.

Class-Sparing Regimens for Initial Treatment of HIV

ACTG 5142

EFV + NRTIs versus LPV/r + NRTIs versus LPV/r + EFV
ACTG 5142: Study Design

Study Design: ACTG 5142

- **Background**: Randomized, phase 3 trial comparing the efficacy, safety, and tolerability of 3 different class-sparing ARV regimens in antiretroviral naïve adults and adolescents with HIV
- **Inclusion Criteria (n = 753)**
  - Age ≥13 years
  - Antiretroviral naïve
  - HIV RNA ≥2,000 copies/mL
  - No CD4 restrictions
- **Treatment Arms**
  - EFV 600 mg QD + 2 NRTIs
  - LPV/r 400/100 mg BID + 2 NRTIs
  - LPV/r 533/133 mg BID + EFV 600 mg QD

PI-Sparing Group
Efavirenz + 2 NRTIs
(n = 250)

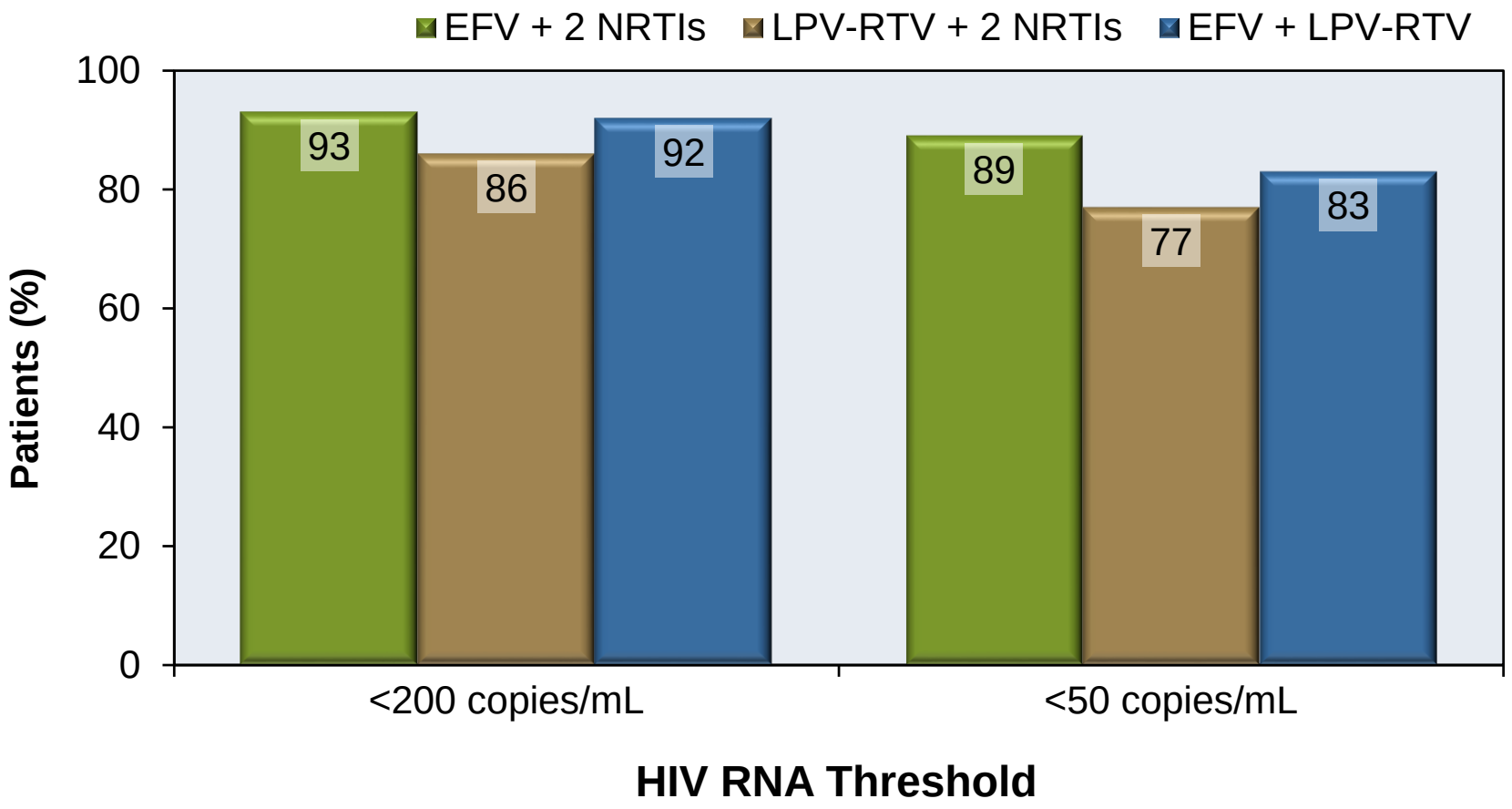
NNRTI-Sparing Group
Lopinavir-ritonavir + 2 NRTIs
(n = 253)

NRTI-sparing Group
Lopinavir-ritonavir + Efavirenz
(n = 250)

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

EFV + NRTIs versus LPV/r + NRTIs versus LPV/r + EFV
ACTG 5142: Results

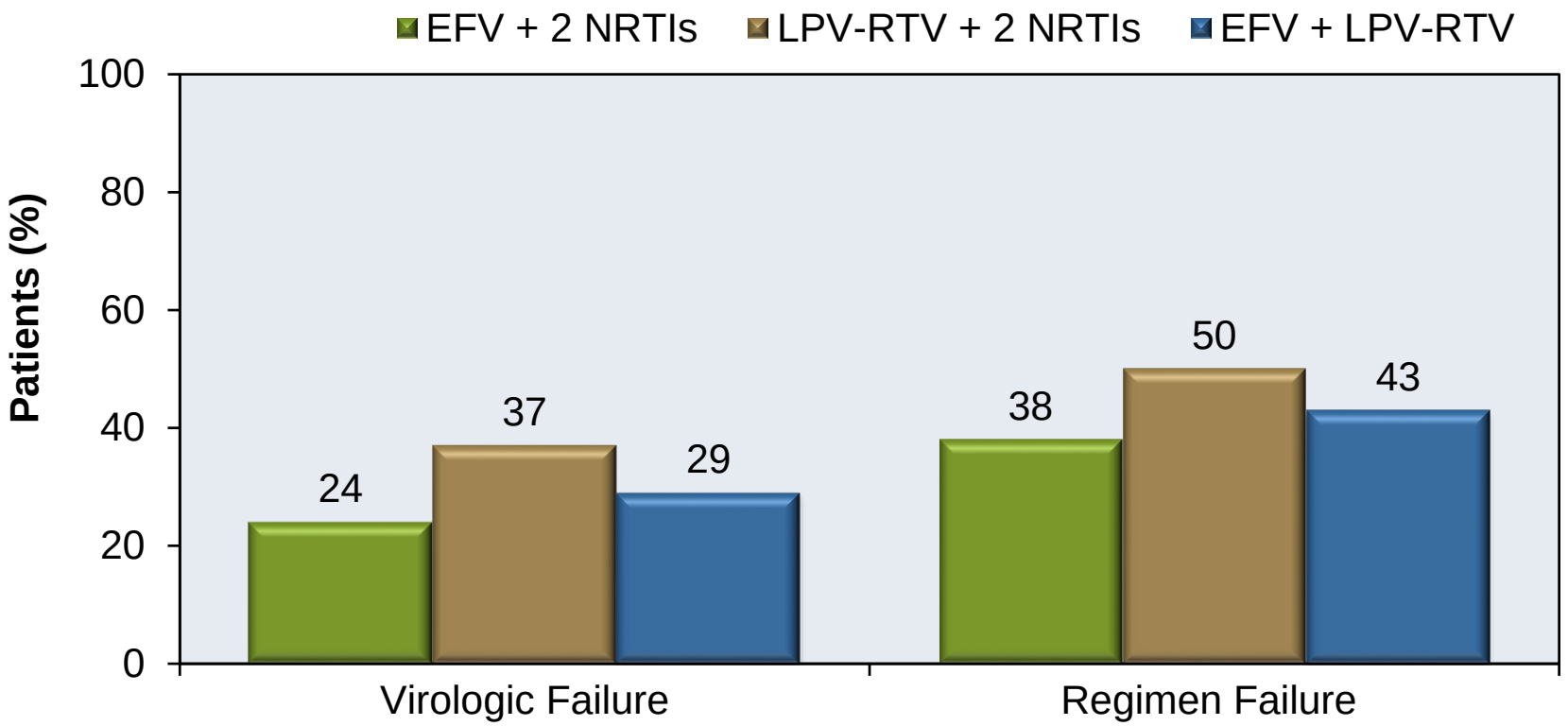
Week 96: Virologic Response



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

EFV + NRTIs versus LPV/r + NRTIs versus LPV/r + EFV
ACTG 5142: Results

Virologic or Regimen Failure



Virologic failure = lack of suppression of plasma HIV-1 RNA by 1 log10 or rebound before week 32 or a lack of suppression to <200 copies/mL or rebound after week 32.
Regimen failure = first of either virologic failure or toxicity-related discontinuation

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

EFV + NRTIs versus LPV/r + NRTIs versus LPV/r + EFV
ACTG 5142: Results

Summary of Resistance Mutations at Time of Virologic Failure*			
Variable	**EFV + 2 NRTIs** (%)	**LPV/r + 2NRTIs** (%)	**LPV/r + EFV** (%)
Virologic failure events	24	37	29
Any mutation	48	21	70
NRTI-associated mutation	30	19	11
M184V	17	17	0
K65R	7	0	2
NNRTI-associated mutation	43	3	66
K103N	24	0	55
Any protease mutation	85	78	80
Major protease mutation	0	0	4
Mutation associated with 2 classes	26	1	7

*Percentages of patients with mutations were calculated for those who had an available genotype at the time of virologic failure.

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

EFV + NRTIs versus LPV/r + NRTIs versus LPV/r + EFV
ACTG 5142: Conclusions

Conclusions: “Virologic failure was less likely in the efavirenz group than in the lopinavir-ritonavir group. The virologic efficacy of the NRTI-sparing regimen was similar to that of the efavirenz regimen but was more likely to be associated with drug resistance.”

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

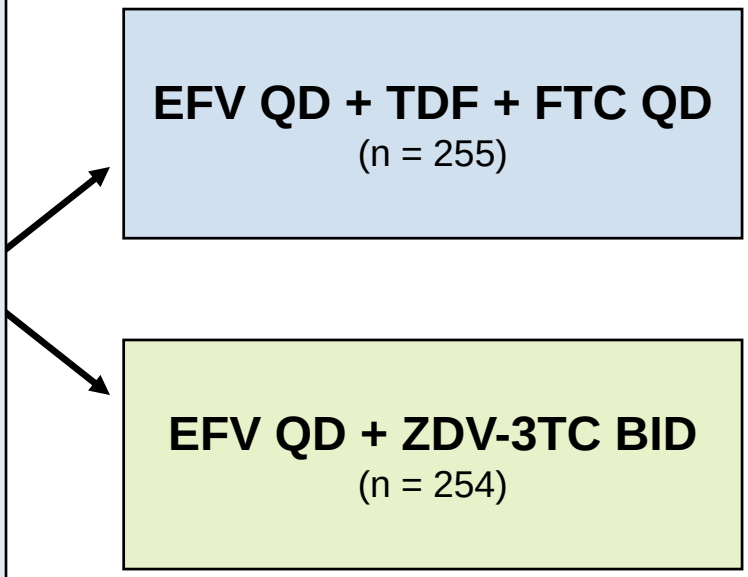
EFV + TDF + FTC versus EFV + ZDV-3TC

Study 934

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC
Study 934: Study Design

Study Design: STUDY 934

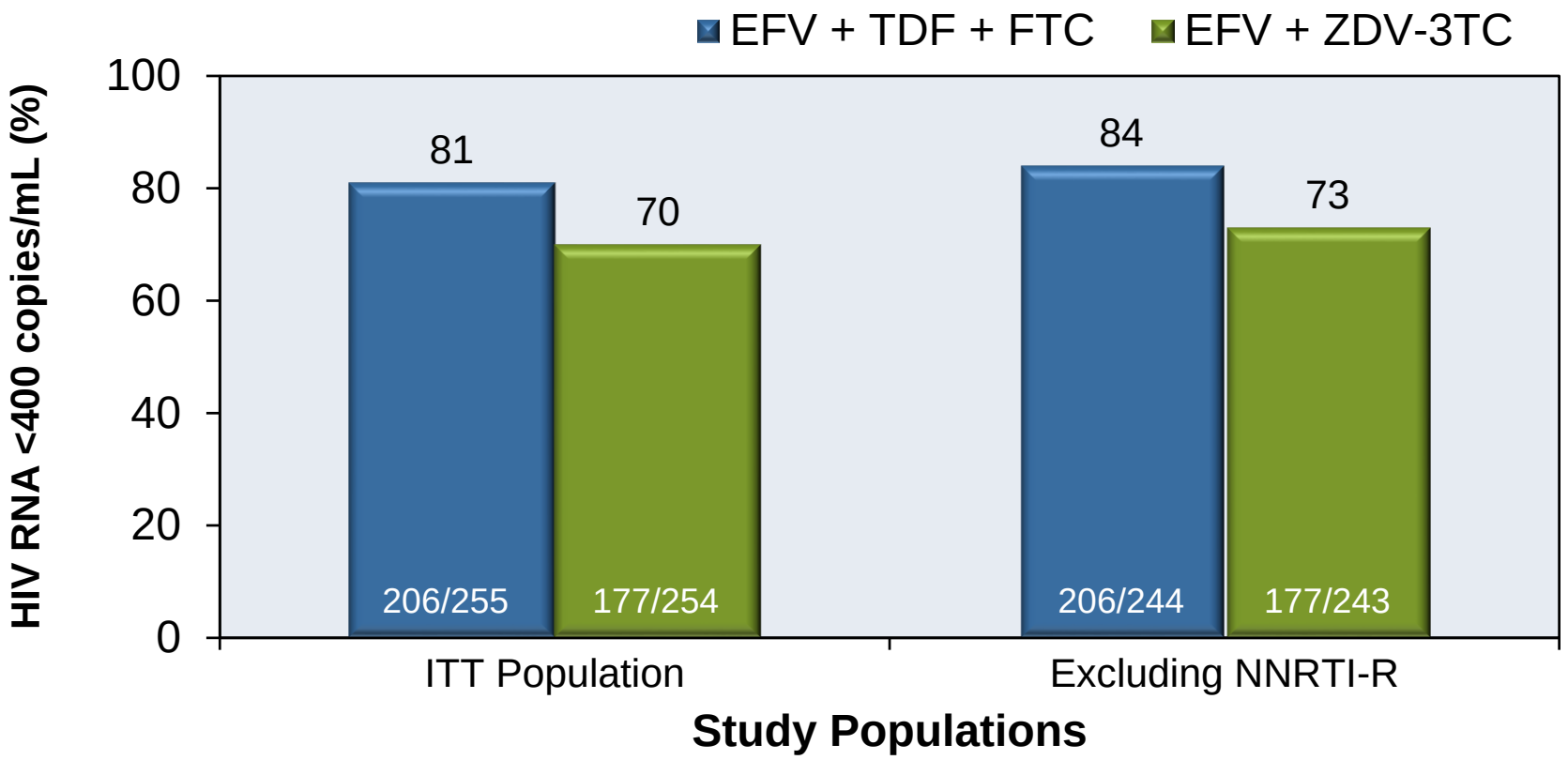
- **Background**: Randomized, open label phase 3 study comparing efavirenz plus either tenofovir DF and emtricitabine or fixed-dose zidovudine-lamivudine
- **Inclusion Criteria (n = 509)**
  - Antiretroviral-naïve adults
  - Age ≥18 years
  - HIV RNA ≥10,000 copies/mL
  - CD4 >50 cells/mm^3
  - No AIDS conditions in prior 30 days
- **Treatment Arms**
  - Efavirenz + tenofovir DF + emtricitabine
  - Efavirenz + zidovudine-lamivudine



Source: Gallant JE, et al. N Engl J Med. 2006;354:251-60.

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC
Study 934: Result

Week 48: Virologic Response (< 400 copies/mL)



ITT = Intention-to-Treat; NNRTI-R = Patients with baseline NNRTI mutations.

Source: Gallant JE, et al. N Engl J Med. 2006;354:251-60.

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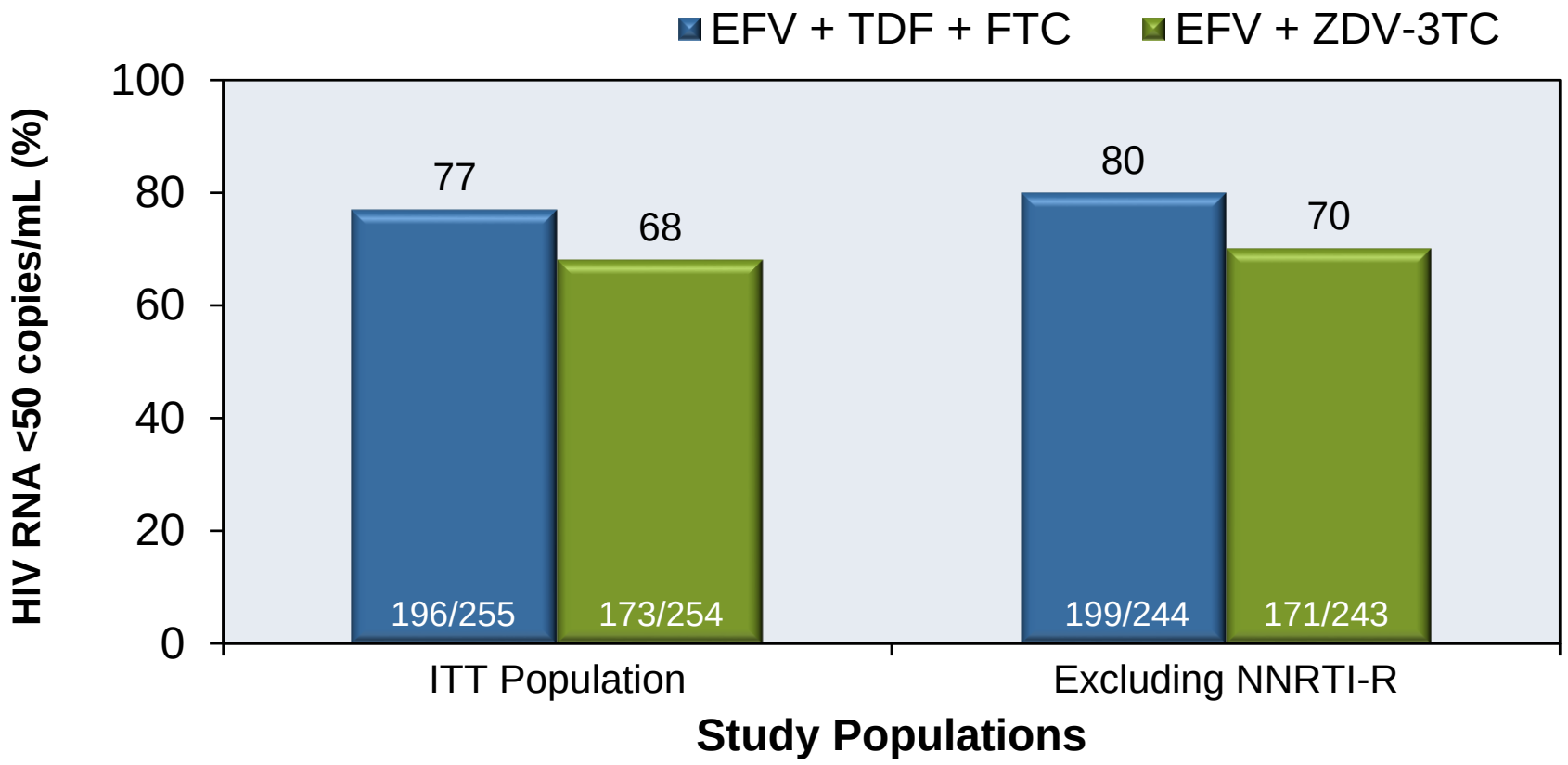
Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC
Study 934: Result

Week 48: Virologic Response (<50 copies/mL)

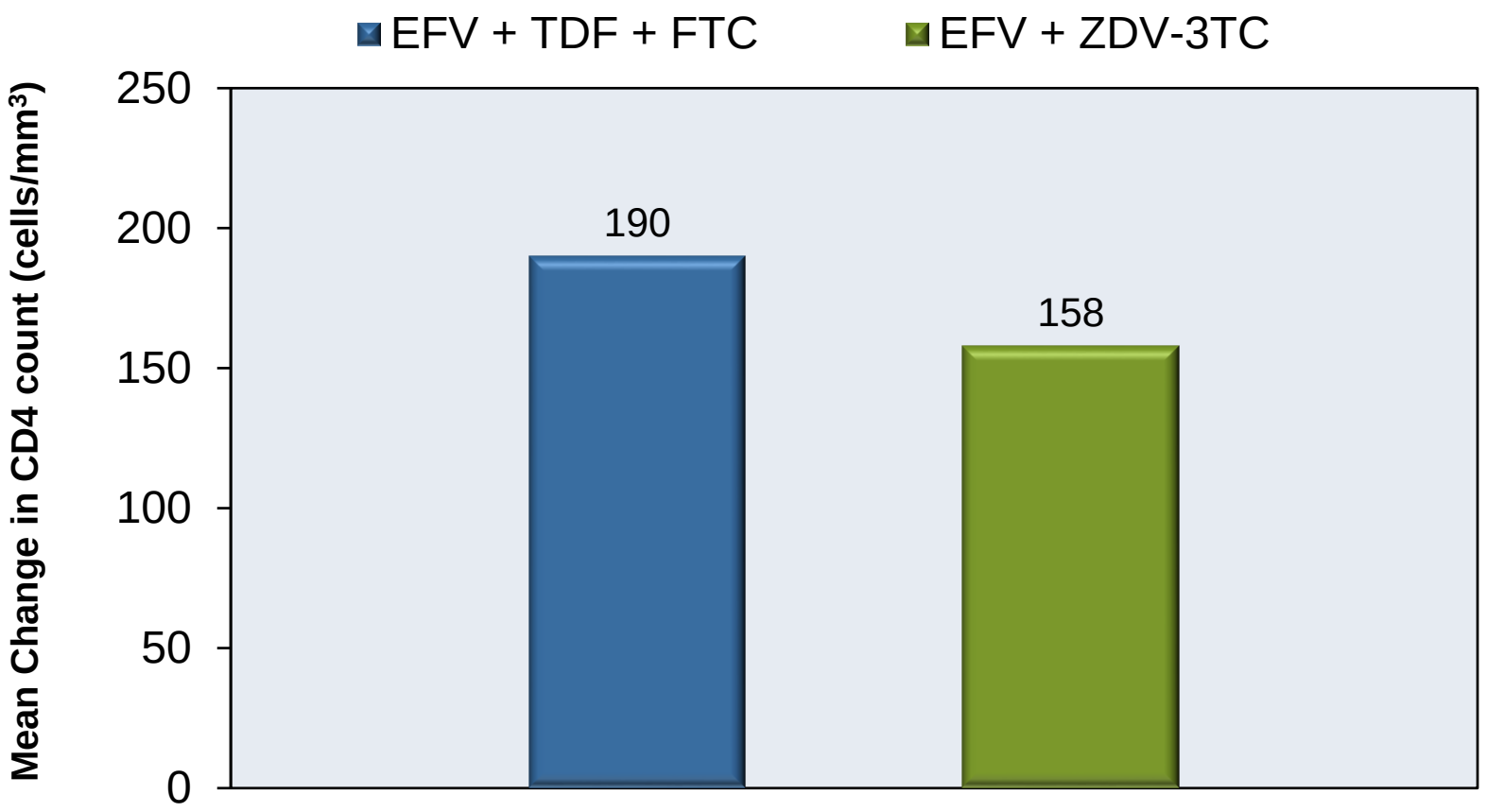


ITT = Intention-to-Treat; NNRTI-R = Patients with baseline NNRTI mutations.

Source: Gallant JE, et al. N Engl J Med. 2006;354:251-60.

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC
Study 934: Result

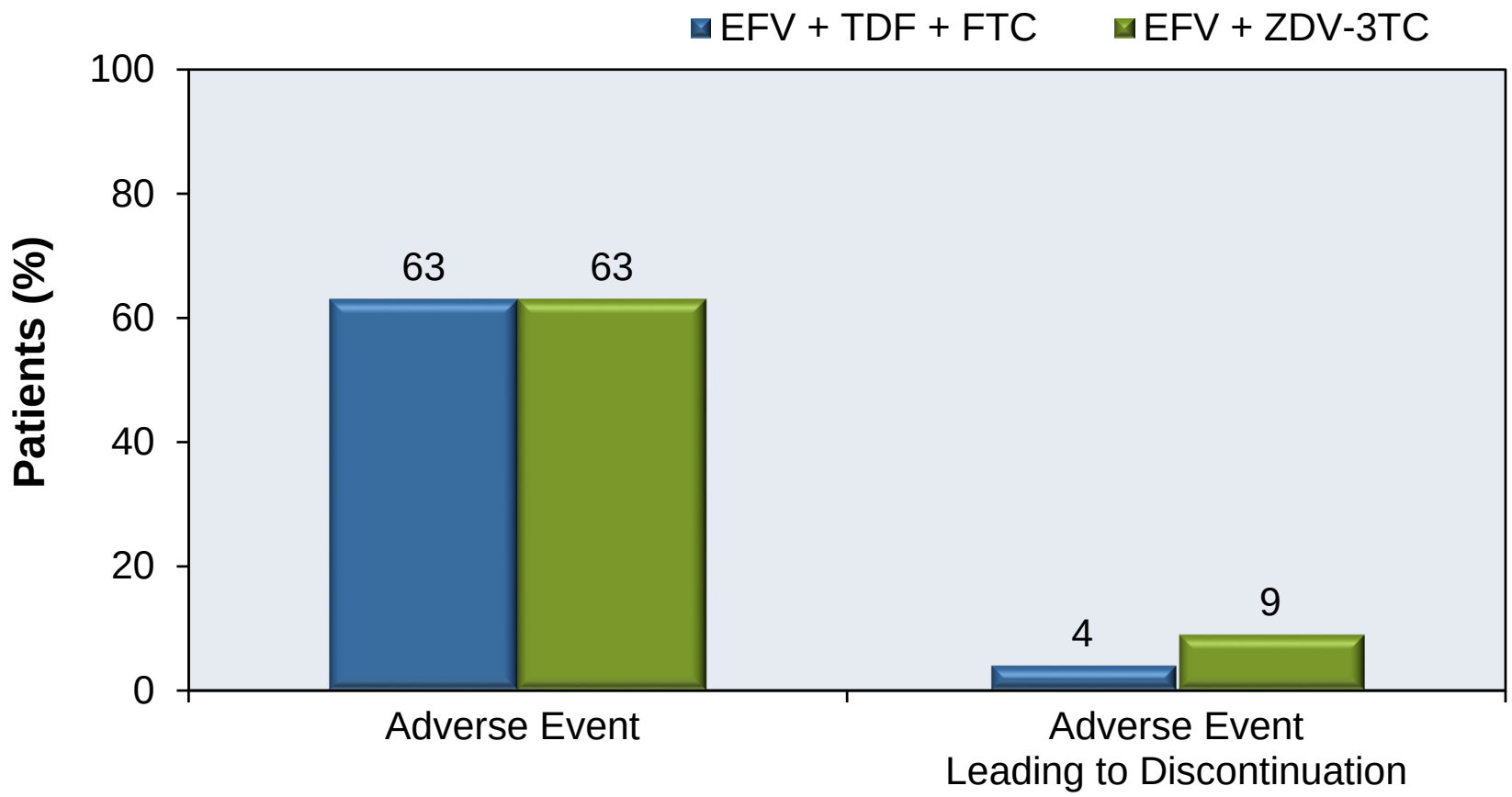
Week 48: Immunologic Response



Source: Gallant JE, et al. N Engl J Med. 2006;354:251-60.

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC
Study 934: Result

Adverse Events through 48 Weeks



Source: Gallant JE, et al. N Engl J Med. 2006;354:251-60.

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC
Study 934: Common Adverse Events

Treatment Emergent Adverse Events in ≥ 5% of Subjects in Either Arm		
	EFV + TDF + FTC (n = 257)	**EFV + ZVD-3TC** (n= 254)
Dizziness	8%	7%
Nausea	8%	6%
Diarrhea	7%	4%
Fatigue	7%	6%
Depression	4%	7%
Headache	5%	4%
Rash	5%	4%
Insomnia	4%	5%
Anemia	<1%	5%

Source: Gallant JE, et al. N Engl J Med. 2006;354:251-60

TDF+ FTC + Efavirenz versus ZDV-3TC+ Efavirenz
Study 934: Conclusions

Interpretation: “Through week 48, the combination of tenofovir DF and emtricitabine plus efavirenz fulfilled the criteria for noninferiority to a fixed dose of zidovudine and lamivudine plus efavirenz and proved superior in terms of virologic suppression, CD4 response, and adverse events resulting in discontinuation of the study drugs.”

Source: Gallant JE, et al. N Engl J Med. 2006;354:251-60.

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO Trial

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO: Study Design

Study Design: ECHO Study

- **Background**: Randomized, double-blind, phase 3 trial comparing rilpivirine and efavirenz in combination with a fixed background regimen consisting of tenofovir DF-emtricitabine in treatment-naïve adults with HIV
- **Inclusion Criteria (n = 690)**
  - Antiretroviral-naïve adults
  - Age ≥18 years
  - HIV RNA ≥5000 copies/mL
  - No resistance to any study drugs
- **Treatment Arms**
  - Rilpivirine + Tenofovir DF-Emtricitabine
  - Efavirenz + Tenofovir DF-Emtricitabine

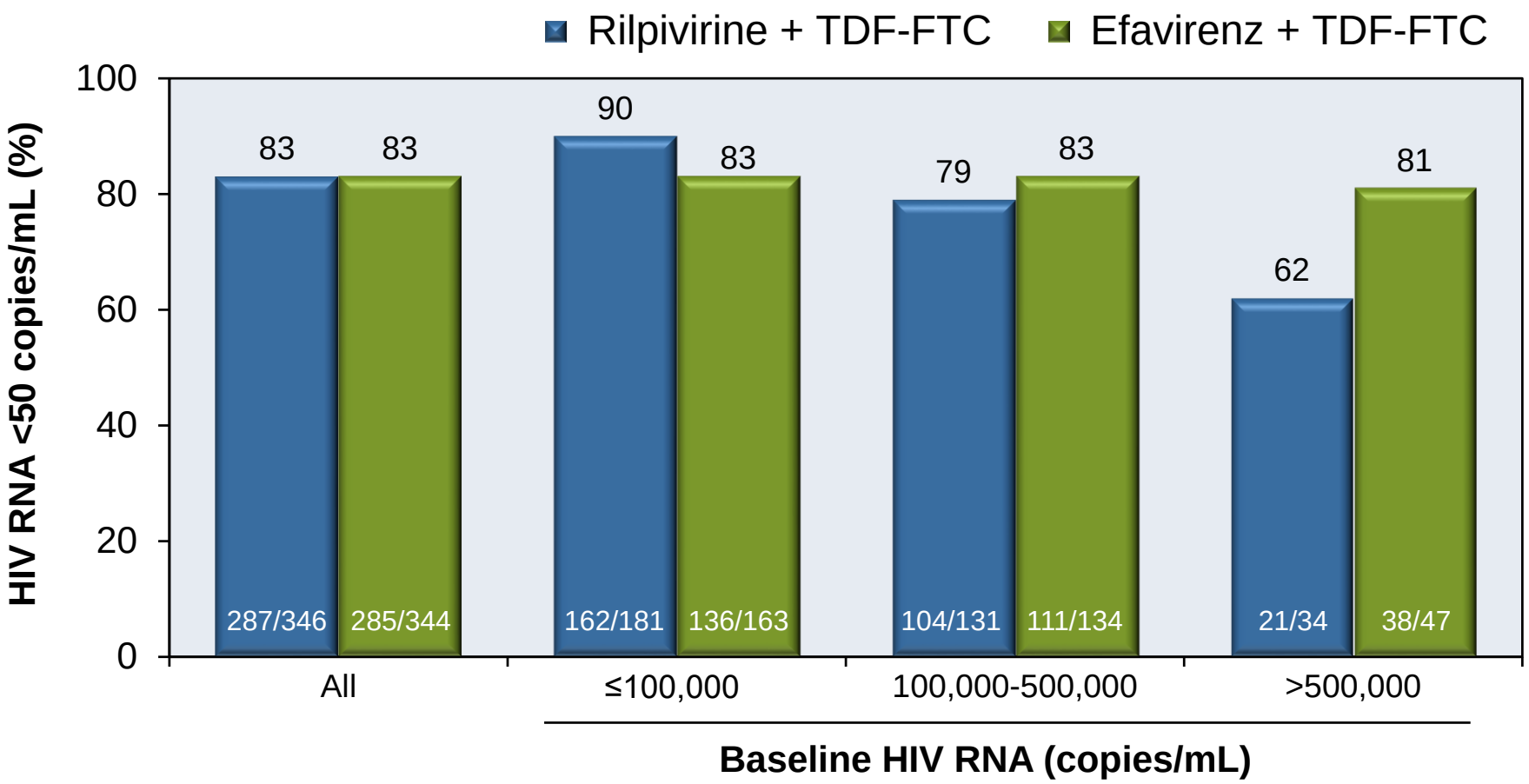
Rilpivirine + TDF-FTC QD
(n = 346)

Efavirenz + TDF-FTC QD
(n = 344)

Source: Molina J-M, et al. Lancet. 2011;378:238-46.

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO: Result

48 Week Virologic Response (ITT-TLOVR)



Source: Molina J-M, et al. Lancet. 2011;378:238-46.

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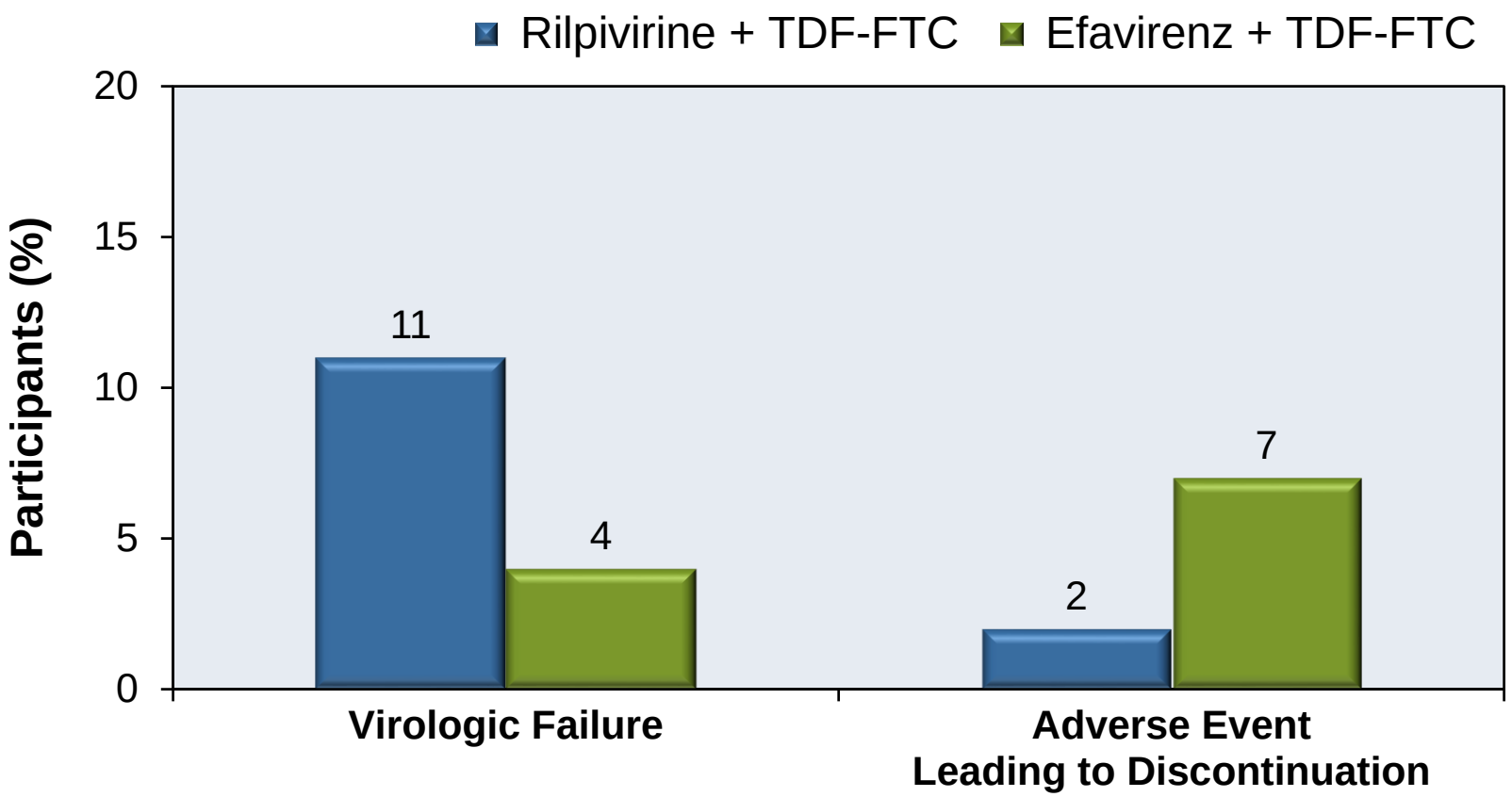
Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO: Result

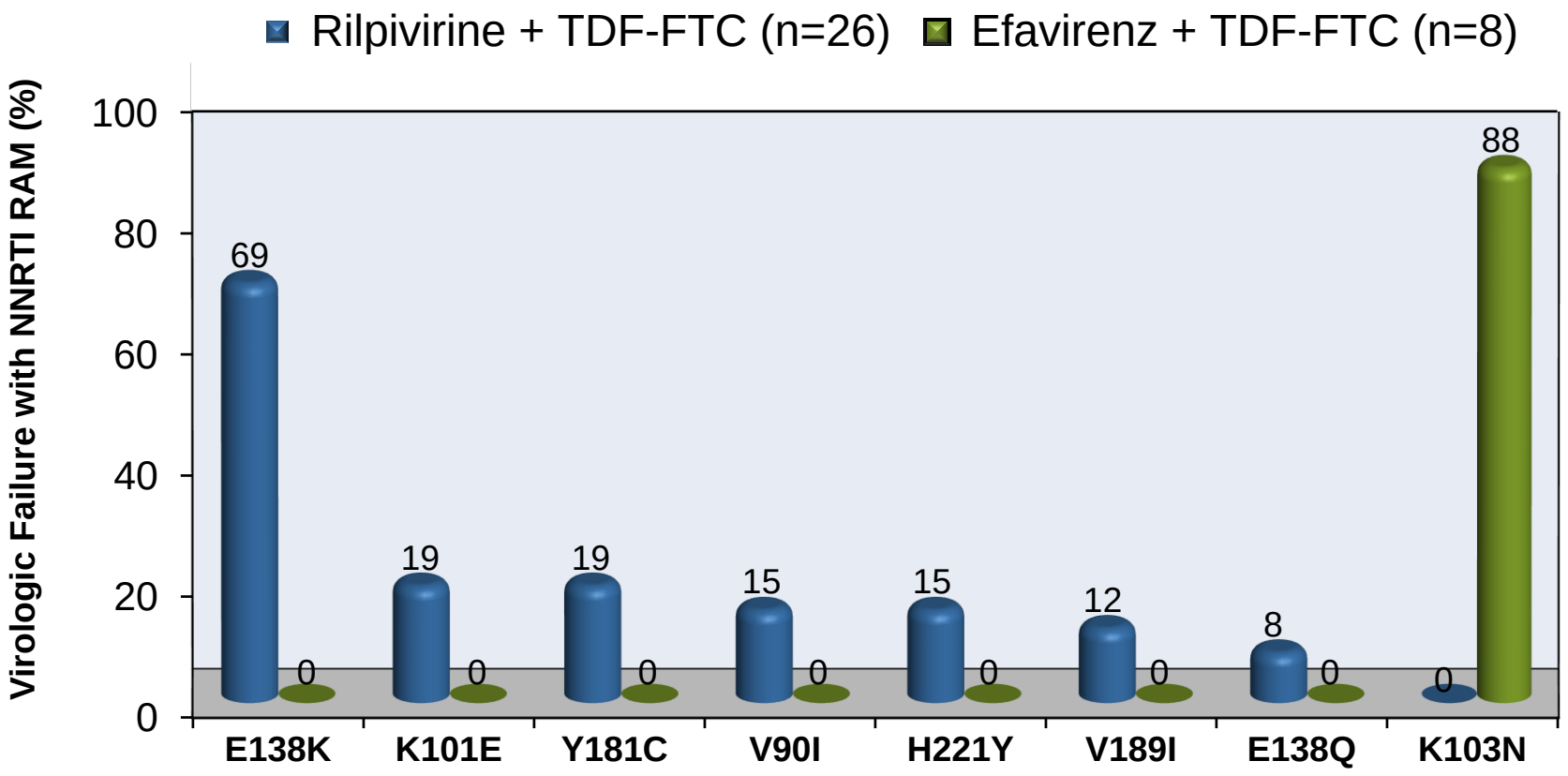
48 Week Virologic Failure and Discontinuations (ITT-TLOVR)



Source: Molina J-M, et al. Lancet. 2011;378:238-46.

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO: Resistance Results

Incidence of NNRTI Resistance Associated Mutations (RAMs)



Source: Molina J-M, et al. Lancet. 2011;378:238-46.

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO: Conclusions

Interpretation: “Rilpivirine showed non-inferior efficacy compared with efavirenz, with a higher virological-failure rate, but a more favourable safety and tolerability profile.”

Source: Molina J-M, et al. Lancet. 2011;378:238-46.

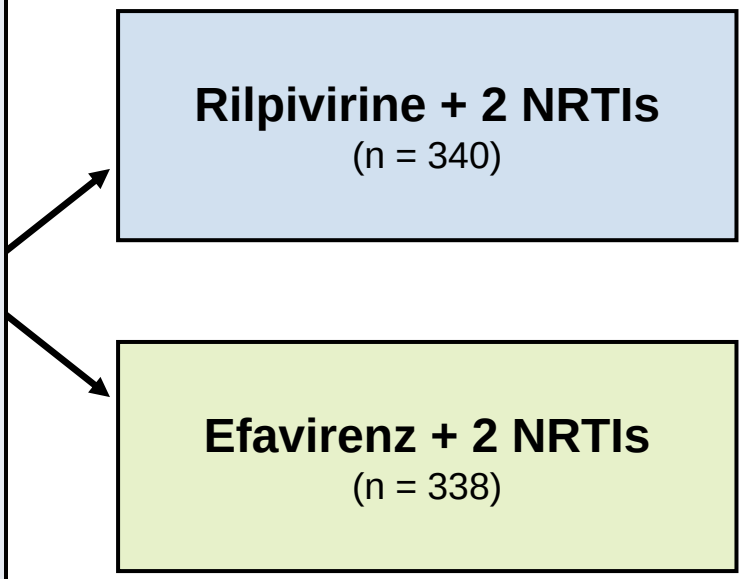
Rilpivirine versus Efavirenz, with 2 NRTIs

THRIVE Study

Rilpivirine versus Efavirenz, with 2 NRTIs
THRIVE: Study Design

Study Design: THRIVE

- **Background**: Randomized, double-blind, phase 3 trial comparing rilpivirine and efavirenz in combination with two nucleoside reverse transcriptase inhibitors in treatment-naïve adults with HIV
- **Inclusion Criteria (n = 680)**
  - Antiretroviral-naïve
  - Age ≥18 years
  - HIV RNA ≥5000 copies/mL
  - No resistance to any study drugs
- **Treatment Arms**
  - Rilpivirine + 2 NRTIs*
  - Efavirenz + 2 NRTIs*

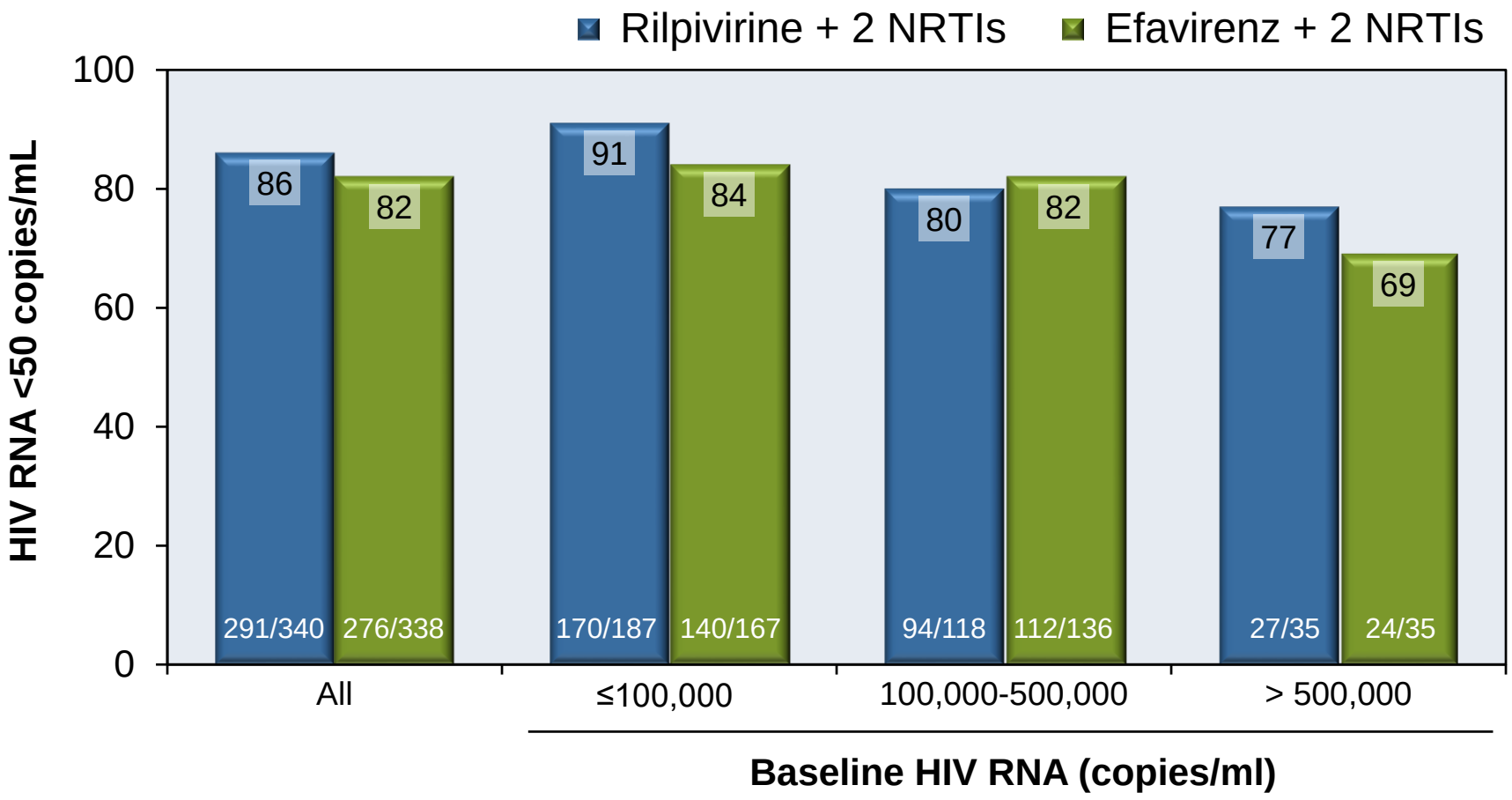


*Investigator-selected 2 NRTIs:
Tenofovir DF plus emtricitabine; zidovudine plus lamivudine; or abacavir plus lamivudine

Source: Cohen CJ, et al. Lancet. 2011;378:229-37.

Rilpivirine versus Efavirenz, with two background NRTIs
THRIVE: Result

48 Week Virologic Response (ITT-TLOVR)



Source: Cohen CJ, et al. Lancet. 2011;378:229-37.

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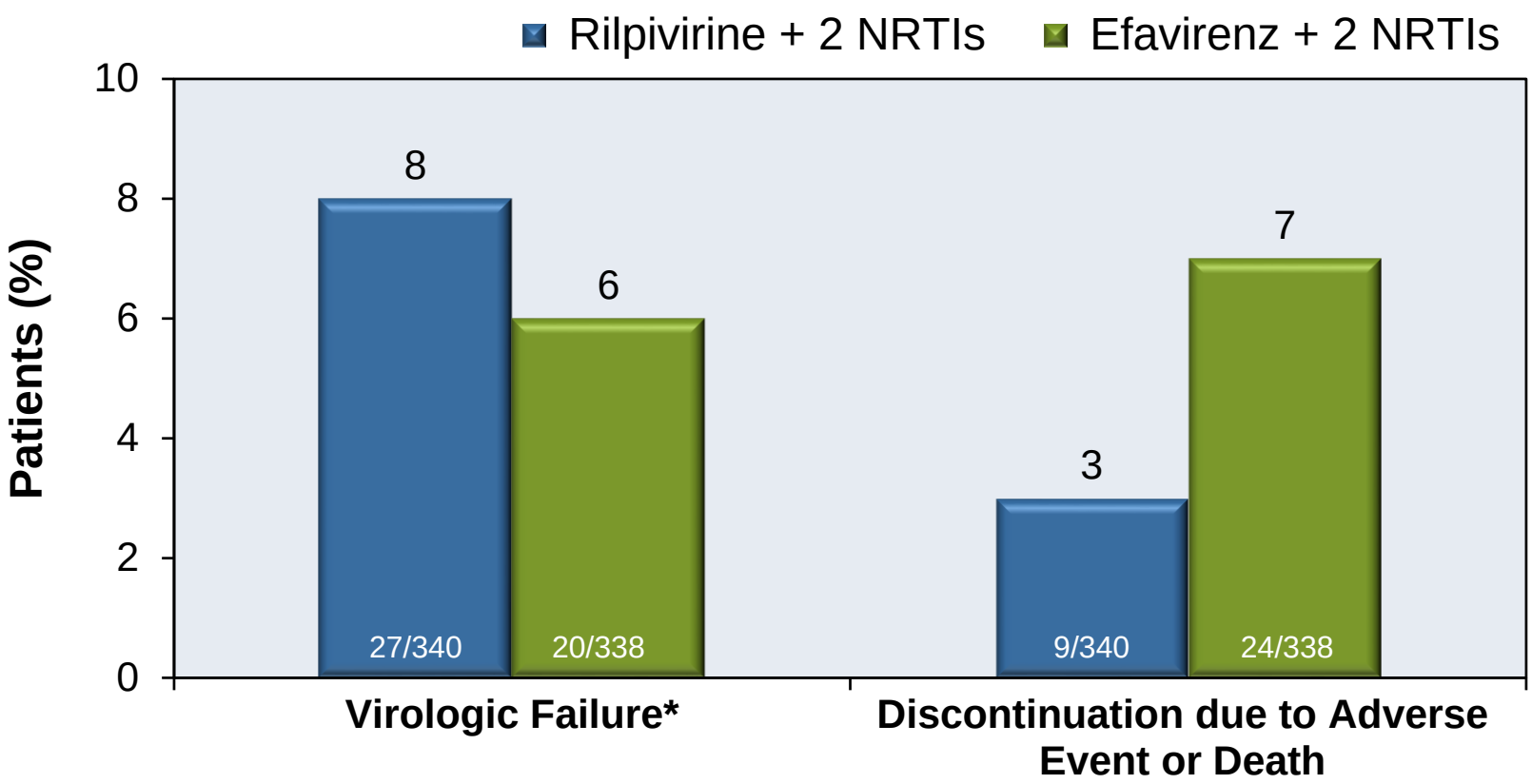
Rilpivirine versus Efavirenz, with two background NRTIs
THRIVE: Result

48 Week Virologic Failure and Discontinuations

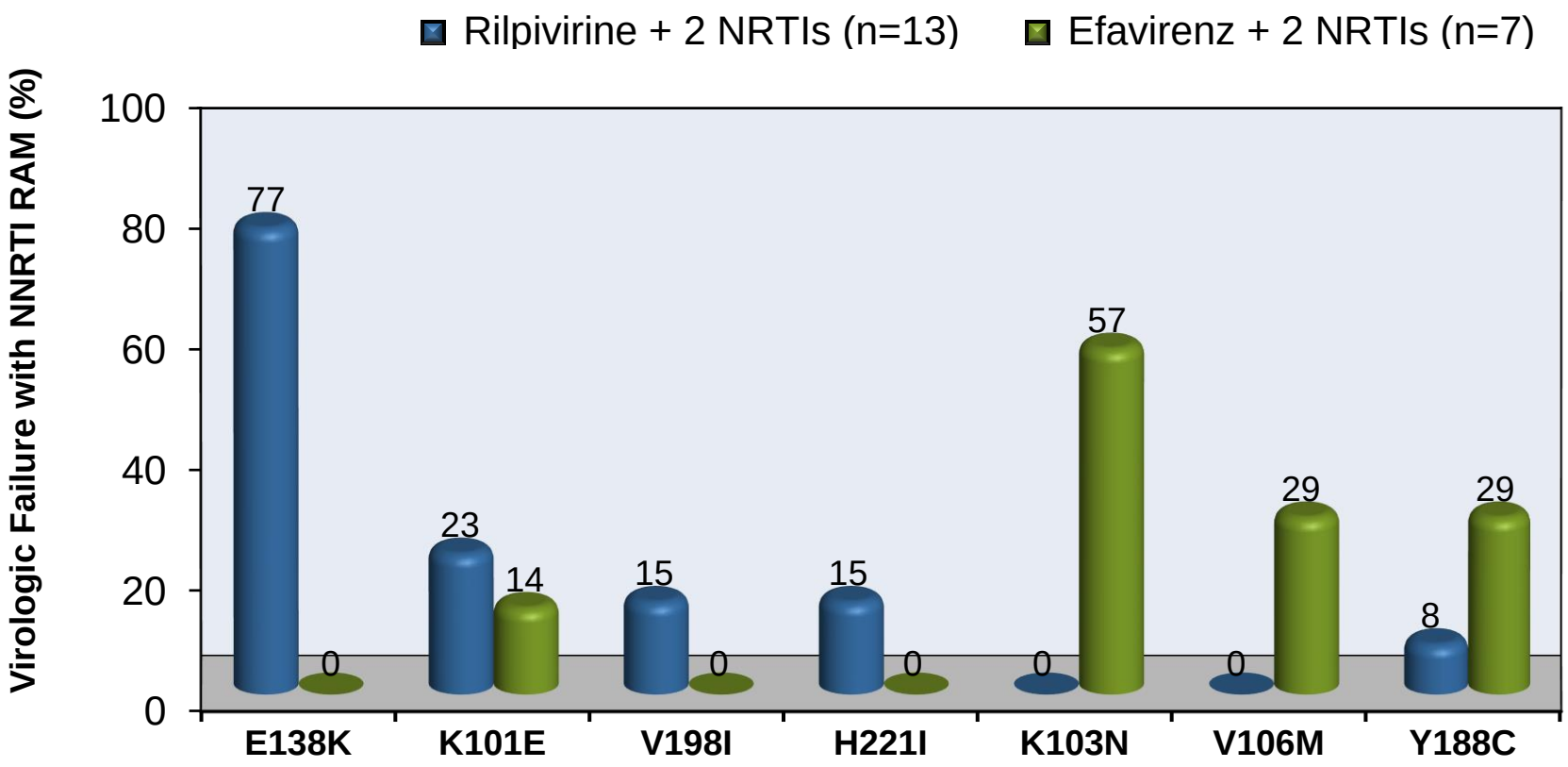


*Virologic failure includes those without emerging mutation at failure

Source: Cohen CJ, et al. Lancet. 2011;378:229-37.

Rilpivirine versus Efavirenz, with two background NRTIs
THRIVE: Resistance Results

Incidence of NNRTI Resistance Associated Mutations (RAMs)



Source: Cohen CJ, et al. Lancet. 2011;378:229-37.

Rilpivirine versus Efavirenz, with two background NRTIs
THRIVE: Result

Resistance Associated Mutations (RAMs)		
	Rilpivirine (n = 340)	**Efavirenz** (n = 338)
Virologic Failure with Resistance Data	27 (8%)	20 (6%)
Emergent NNRTI RAMs	59%	47%
Most Frequent NNRTI RAMs	E138K	K103N
Emergent NRTI RAMs	64%	33%
Most Frequent NRTI RAMs	M184I/V	M184V

Source: Cohen CJ, et al. Lancet. 2011;378:229-37.

Rilpivirine versus Efavirenz, with two background NRTIs
THRIVE: Conclusions

Interpretation: “Despite a slightly increased incidence of virological failures, a favourable safety profile and non-inferior efficacy compared with efavirenz means that rilpivirine could be a new treatment option for treatment-naive patients infected with HIV-1.”

Source: Cohen CJ, et al. Lancet. 2011;378:229-37.

Efavirenz versus Lopinavir-Ritonavir, with ABC-3TC

LAKE Trial

Efavirenz versus Lopinavir-Ritonavir, with ABC-3TC
LAKE: Study Design

Study Design: LAKE

- **Background**: Randomized study to compare the long-term efficacy and safety of efavirenz and lopinavir-ritonavir, each in combination with co-formulated abacavir-lamivudine, in antiretroviral-naïve adults with HIV
- **Inclusion Criteria (n = 126)**
  - Age ≥18 years
  - Antiretroviral-naïve
  - No recent opportunistic infection
  - No CD4 count or HIV RNA restrictions
  - HLA*B5701 testing not available at time of study
- **Treatment Arms**
  - Efavirenz 600 mg QD + ABC-3TC QD
  - Lopinavir-RTV 400/100 mg BID + ABC-3TC QD

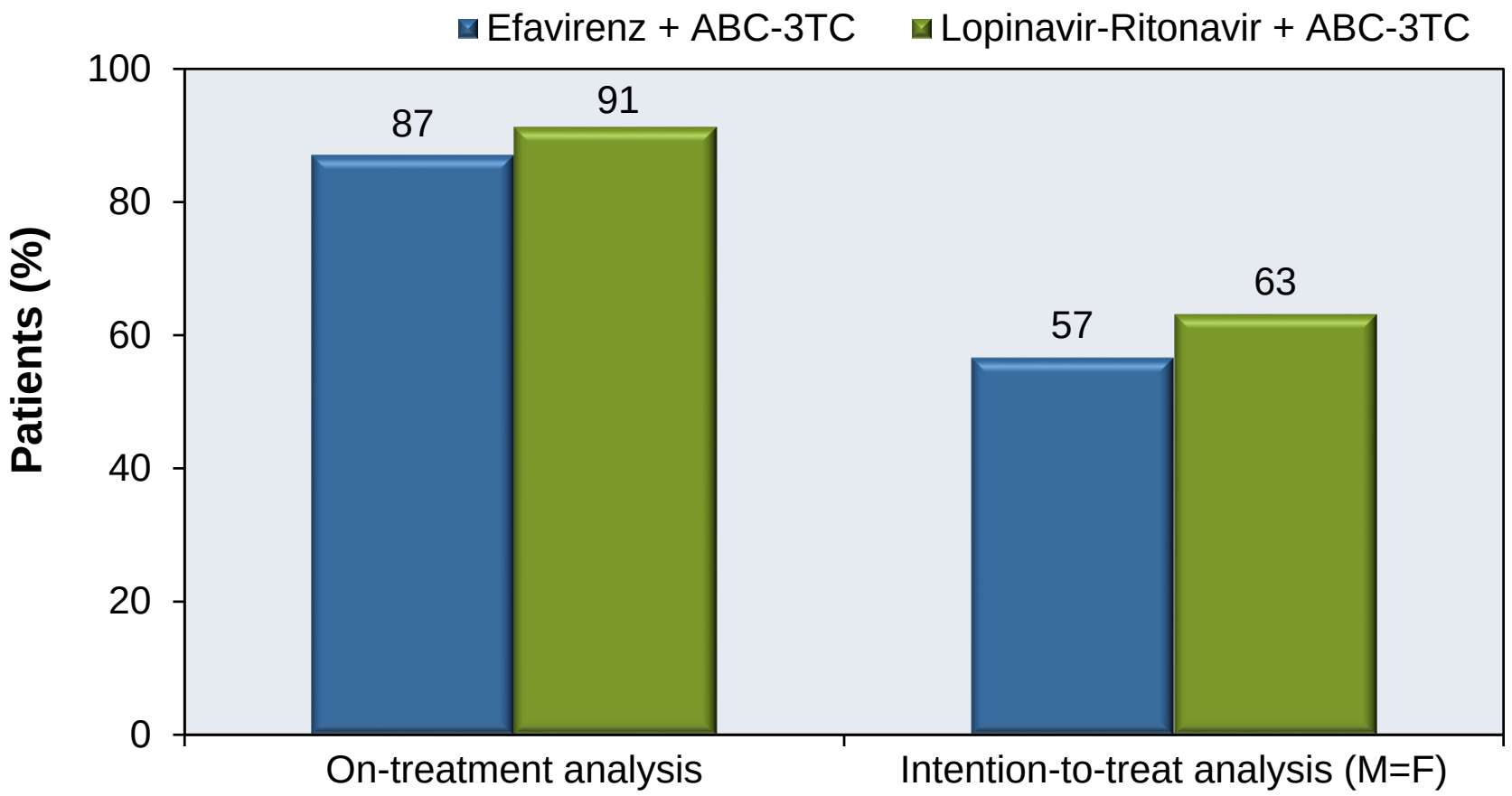
Efavirenz + ABC-3TC
(n = 321)

Lopinavir/r + ABC-3TC
(n = 309)

Source: Echeverría P, et al. Antiviral Res. 2010;85:403-8.

Efavirenz versus Lopinavir-Ritonavir, with ABC-3TC
LAKE: Results

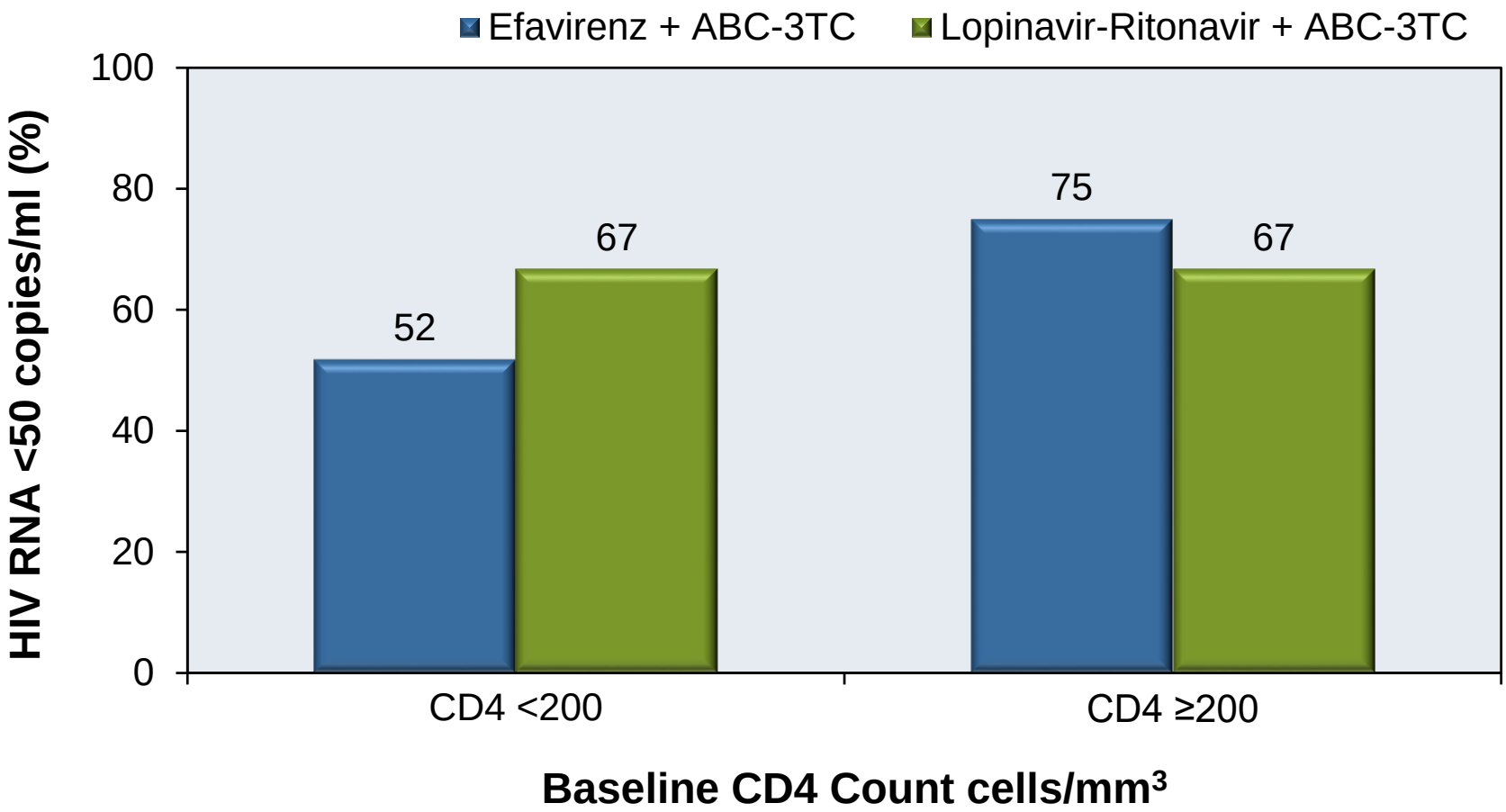
Week 48: Virologic Response



Source: Echeverría P, et al. Antiviral Res. 2010;85:403-8.

Efavirenz versus Lopinavir-Ritonavir, with ABC-3TC
LAKE: Results

Week 48: Virologic Response, by Baseline CD4 count (OT analysis)



Source: Echeverría P, et al. Antiviral Res. 2010;85:403-8.

National HIV Curriculum

Efavirenz versus Lopinavir/r, with ABC-3TC
LAKE: Conclusions

Conclusions: “Similar virological efficacy was observed for efavirenz and lopinavir/r, when administered with abacavir-lamivudine in antiretroviral-naïve patients, while immunological improvement was slightly superior for efavirenz. The higher rate of discontinuation due to toxicity in the efavirenz group was related to a higher incidence of hypersensitivity reaction. Nowadays, the use of the new formulation of lopinavir/r and the HLA-B*5701 genotype test before starting abacavir should improve the safety profiles of these regimens.”

Source: Echeverría P, et al. Antiviral Res. 2010;85:403-8.

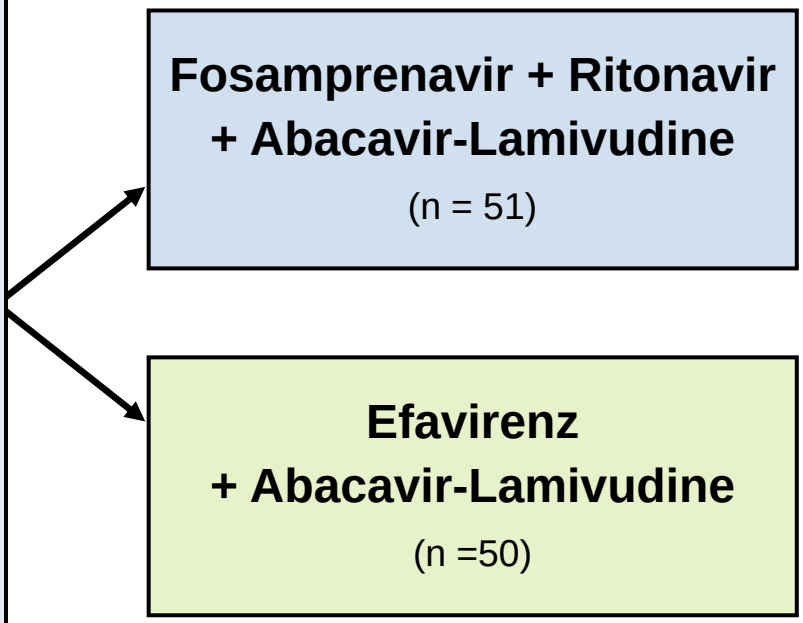
Fosamprenavir + ritonavir versus Efavirenz, with ABC-3TC

SUPPORT Trial

FPV/r versus EFV, both with ABC-3TC
SUPPORT: Study Design

Study Design: SUPPORT

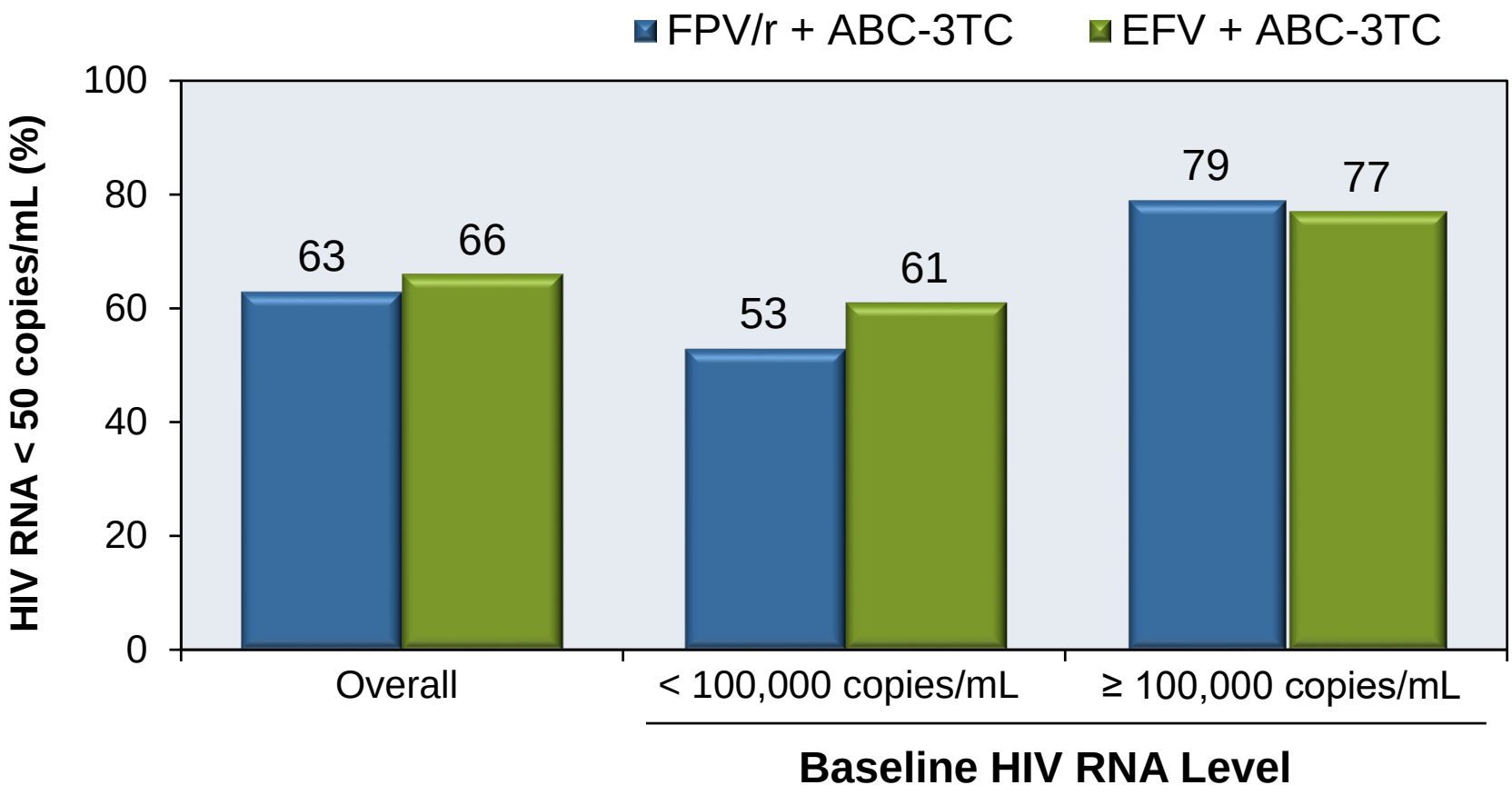
- **Background**: Randomized, open-label pilot study comparing ritonavir-boosted fosamprenavir versus efavirenz, both in combination with abacavir-lamivudine, in minority adults with HIV
- **Inclusion Criteria (n = 101)**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA > 5000 copies/mL
  - HLA-B*5701 negative
  - Minority race or ethnicity
- **Treatment Arms** (all medications once daily)
  - Fosamprenavir 1400 mg + Ritonavir 100 mg + Abacavir-lamivudine 600-300 mg
  - Efavirenz 600 mg + ABC-3TC 600-300 mg



Source: Kumar P, et al. BMC Infect Dis. 2013;13:269.

FPV/r versus EFV, both with ABC-3TC
SUPPORT: Results

Week 96: Virologic Response (Intention-to-treat, Missing=Failure)



Source: Kumar P, et al. BMC Infect Dis. 2013;13:269.

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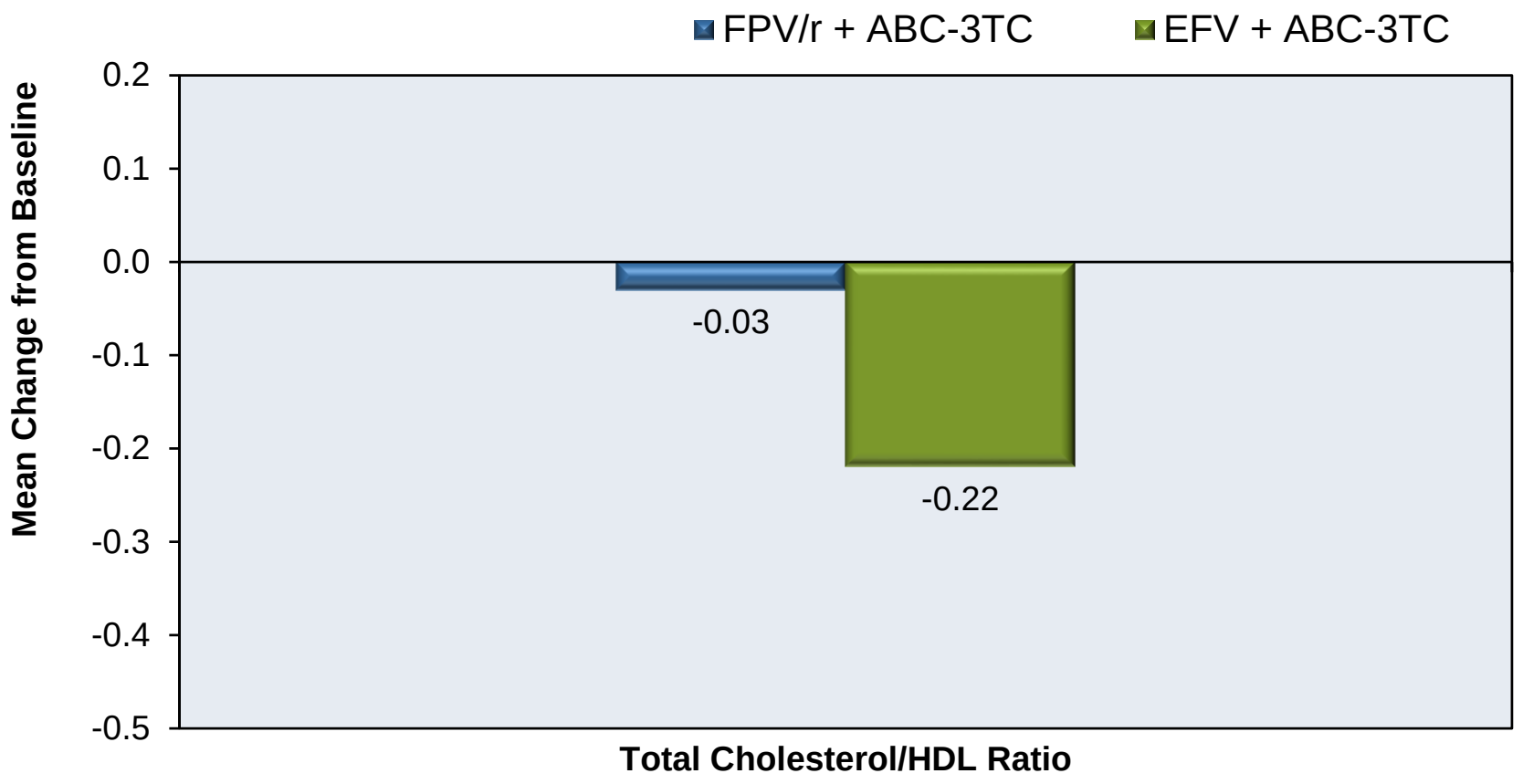
FPV/r versus EFV, both with ABC-3TC
SUPPORT: Results

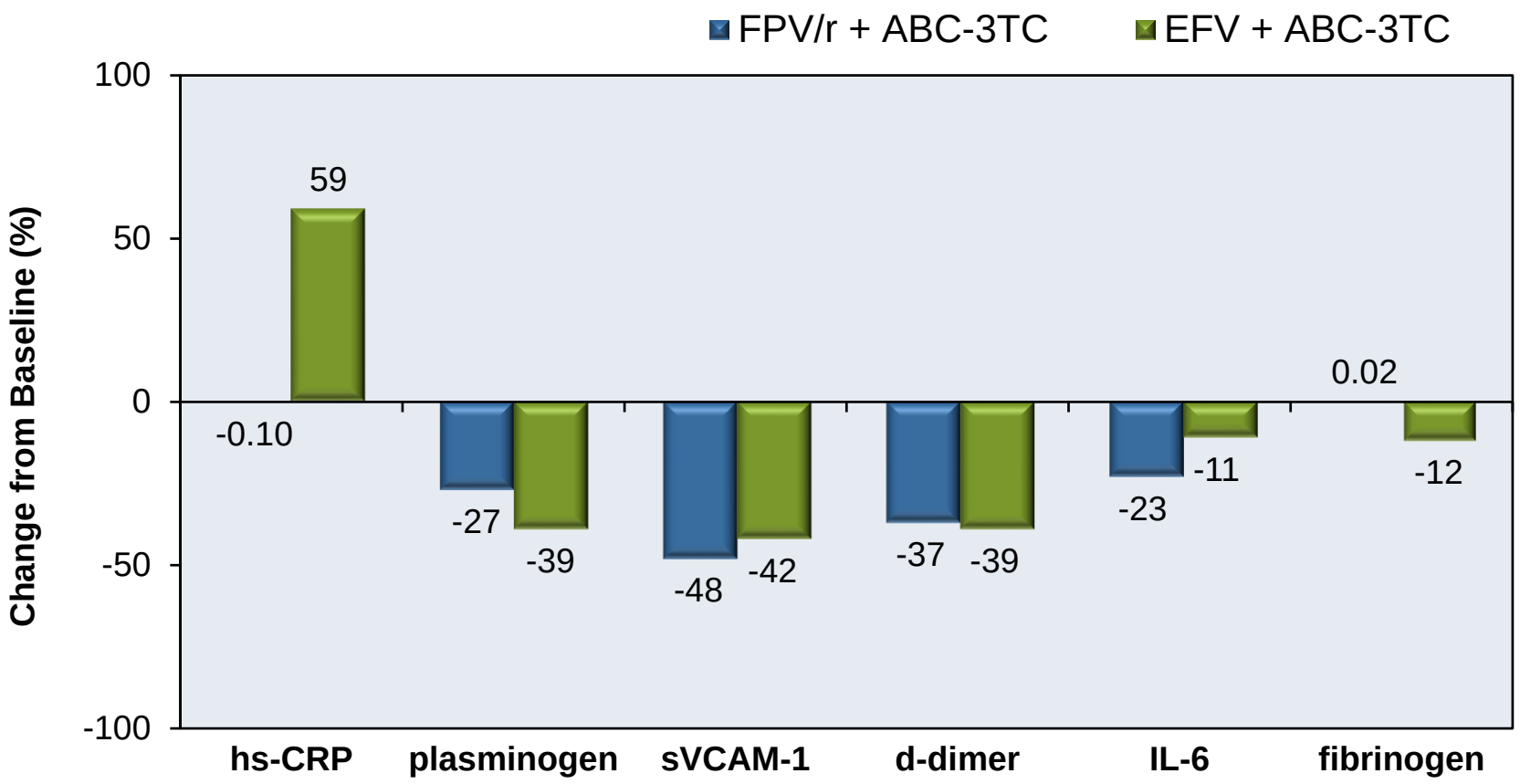
Week 96: Analysis of Lipids



Source: Kumar P, et al. BMC Infect Dis. 2013;13:269.

FPV/r versus EFV, both with ABC-3TC
SUPPORT: Results

Week 96: Analysis of Cardiovascular Biomarkers



Source: Kumar P, et al. BMC Infect Dis. 2013;13:269.

FPV/r versus EFV, both with ABC-3TC
SUPPORT: Conclusions

Conclusions: “In this study of underrepresented patients, treatment with abacavir/lamivudine combined with either fosamprenavir/ritonavir or efavirenz over 96 weeks, produced stable or declining biomarker levels except for hs-CRP, including significant and favorable decreases in thrombotic activity (reflected by d-dimer) and endothelial activation (reflected by sVCAM-1). Our study adds to the emerging data that some cardiovascular biomarkers are decreased with initiation of ART and control of HIV viremia.”

Source: Kumar P, et al. BMC Infect Dis. 2013;13:269.

TREATMENT EXPERIENCED

Efavirenz

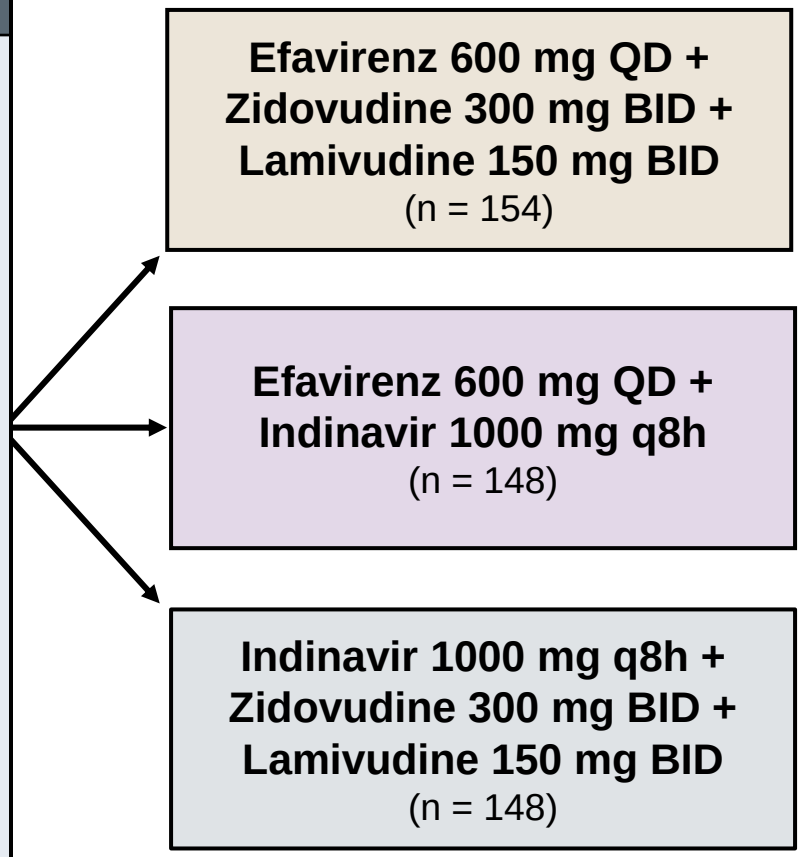
EFV + ZDV + 3TC vs. EFV + IDV vs. IDV + ZDV + 3TC

006 Trial

EFV + ZDV + 3TC vs. EFV + IDV vs. IDV + ZDV + 3TC
006: Study Design

Study Design: 006

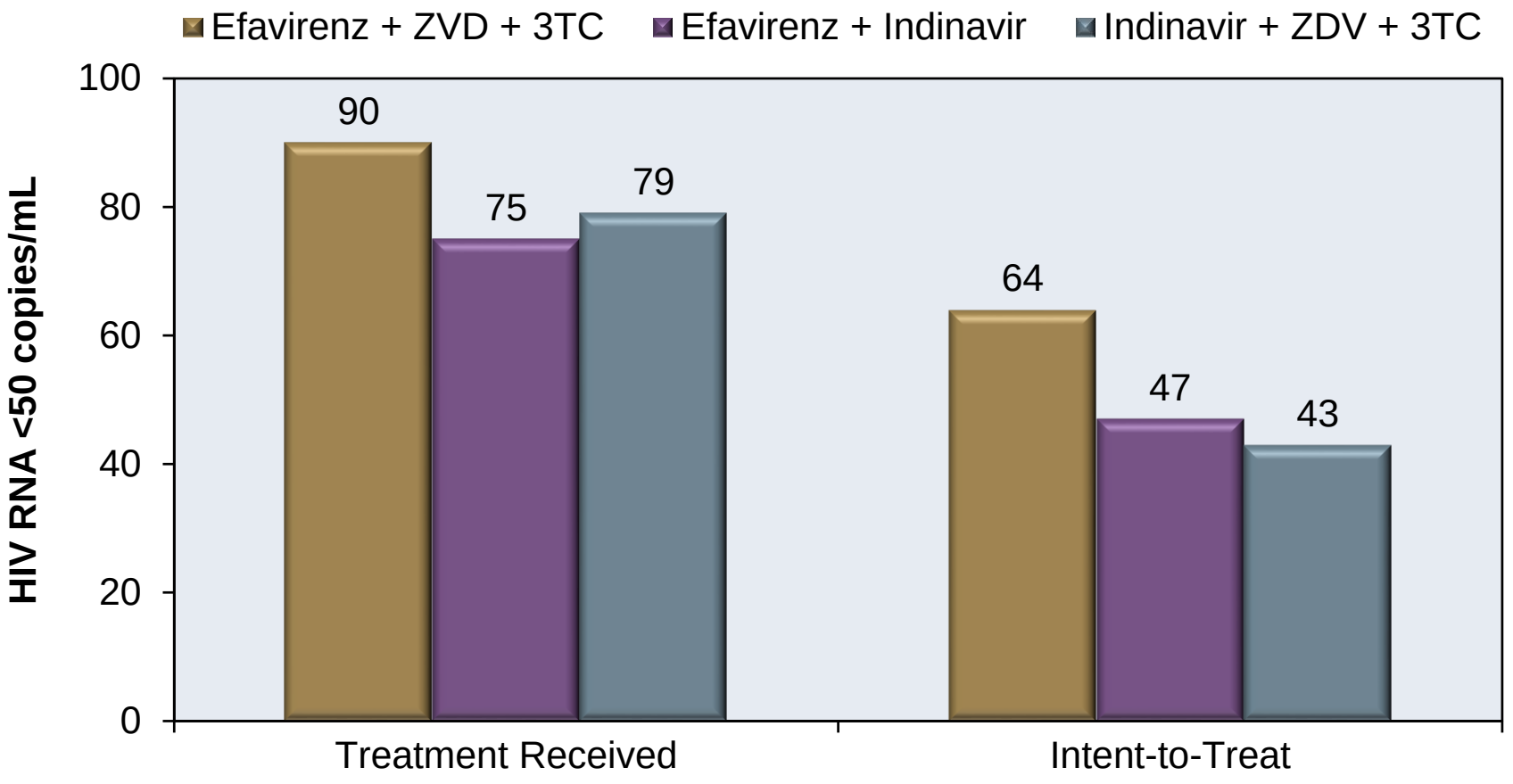
- **Background**: Open-label, randomized, phase 3 trial evaluating safety, efficacy and tolerability of efavirenz plus zidovudine plus lamivudine versus efavirenz plus indinavir versus indinavir plus zidovudine plus lamivudine in persons with HIV
- **Inclusion Criteria (n = 450)**
  - Age ≥13 years
  - Naïve to lamivudine, NNRTIs, PIs
  - CD4 >50 cells/mm^3
  - HIV RNA >10,000 copies/mL
  - No resistance to NRTIs or PIs
- **Treatment Arms**
  - EFV 600 mg QD + ZDV BID + 3TC BID
  - EFV 600 mg QD + IDV 1000 mg q8h
  - IDV 1000 mg q8h + ZDV BID + 3TC BID



Source: Staszewski S, et al. N Engl J Med. 1999;341:1865-73.

EFV + ZDV + 3TC vs. EFV + IDV vs. IDV + ZDV + 3TC
006: Results

Week 48: Virologic Response (Intention-to-Treat Analysis)



Source: Staszewski S, et al. N Engl J Med. 1999;341:1865-73.

EFV + ZDV + 3TC vs. EFV + IDV vs. IDV + ZDV + 3TC
006: Results

Adverse Effect	EFV + ZDV + 3TC	EFV + IND	IDV + ZDV + 3TC
Rash	34%	34%	18%
CNS Effects	58%	53%	26%
Nausea	15% (combined EFV groups)		27%
Vomiting	8% (combined EFV groups)		15%
Treatment Discontinuation	27%	Not reported	43%

Source: Staszewski S, et al. N Engl J Med. 1999;341:1865-73.

EFV + ZDV + 3TC vs. EFV + IDV vs. IDV + ZDV + 3TC
006: Conclusions

Conclusions: “As antiretroviral therapy in HIV-1-infected adults, the combination of efavirenz, zidovudine, and lamivudine has greater antiviral activity and is better tolerated than the combination of indinavir, zidovudine, and lamivudine.”

Source: Staszewski S, et al. N Engl J Med. 1999;341:1865-73.

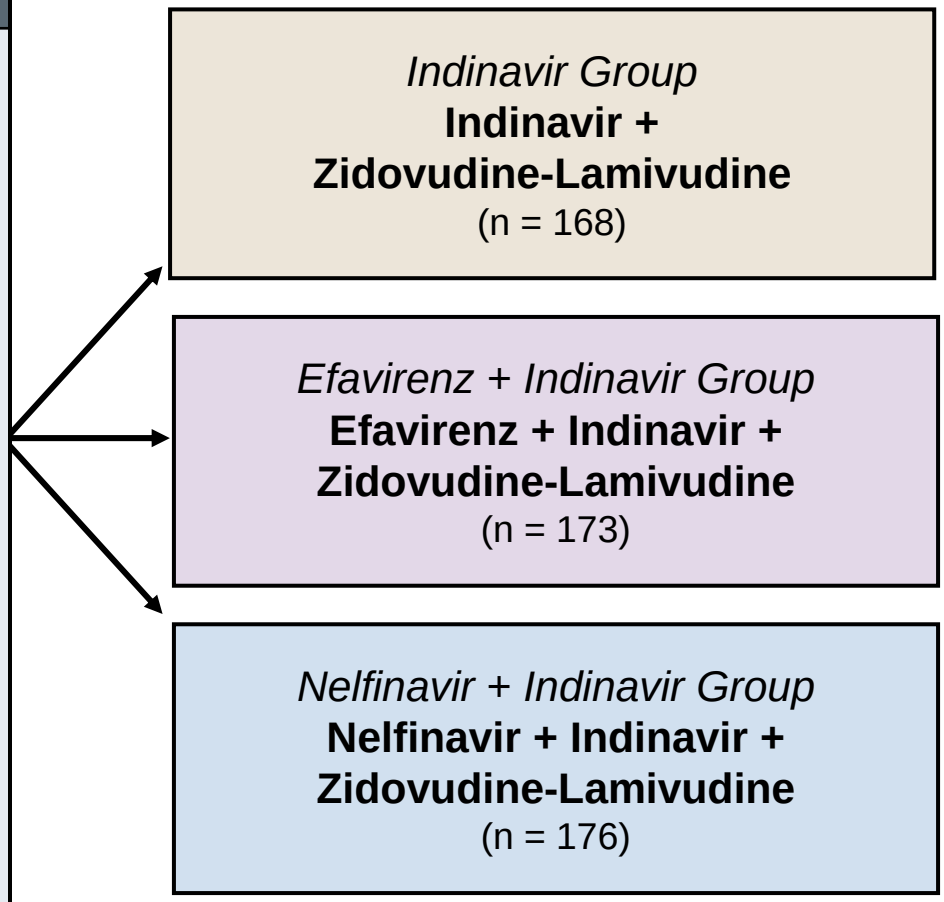
4-Drug Regimens versus 3-Drug Regimen

ACTG 388 Trial

4-Drug Regimens versus 3-Drug Regimen
ACTG 388: Study Design

Study Design: ACTG 388

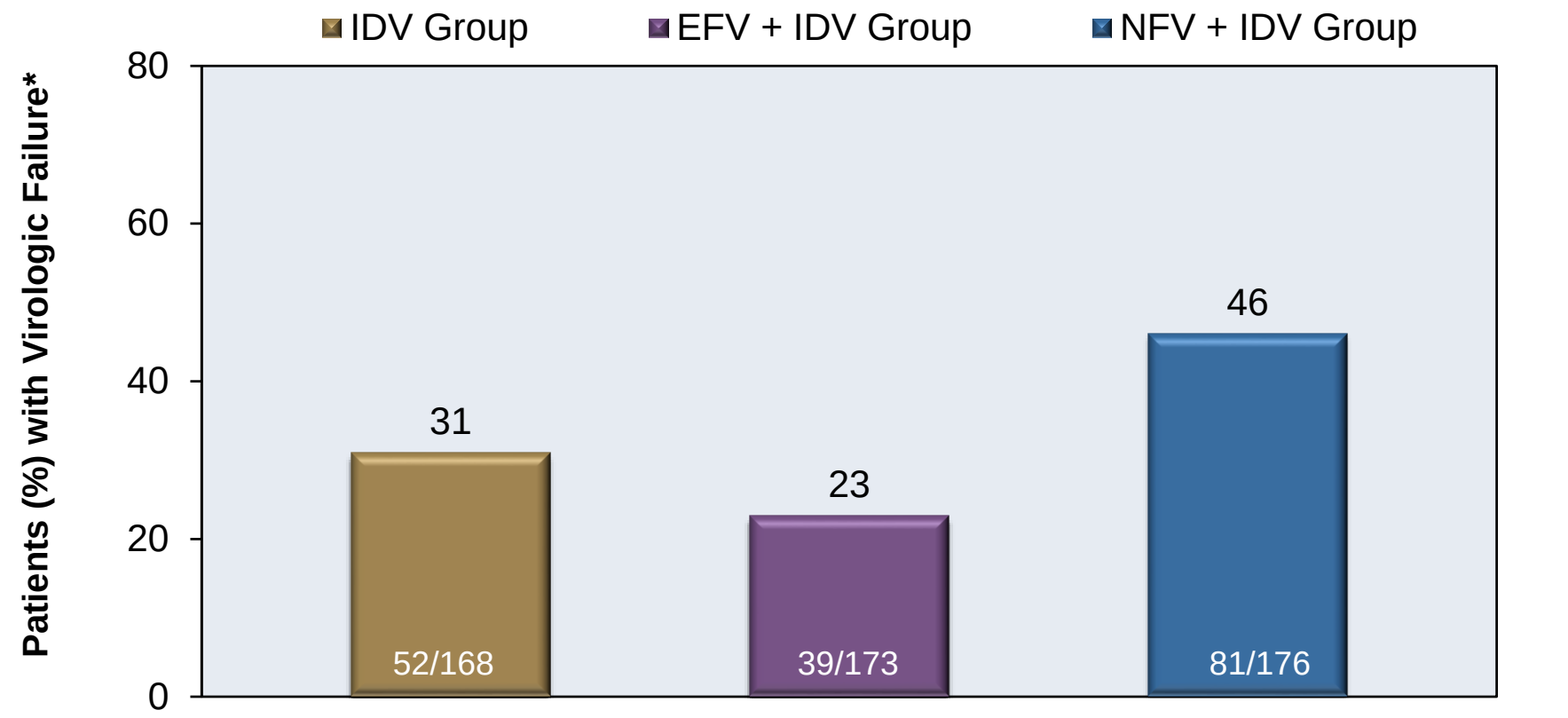
- **Background**: Randomized, controlled, phase 3 trial comparing the activity, safety, and tolerability of two different 4-drug regimens with a 3-drug regimen in advanced HIV disease
- **Inclusion Criteria (n = 517)**
  - Prior ART: only ZDV, d4T, DDI, ddC
  - CD4 ≤200 cells/mm^3
  - HIV RNA ≥80,000 copies/mL
  - No resistance to NRTIs or PIs
- **Treatment Arms**
  - IDV 800 mg TID + ZDV-3TC BID
  - EFV 600 mg QD + IDV 800 mg TID + ZDV-3TC BID
  - NFV 1250 mg BID + IDV 1000 mg BID + ZDV-3TC BID



Source: Fischl MA, et al. J Infect Dis. 2003;188:625-34.

4-Drug Regimens versus 3-Drug Regimen
ACTG 388: Results

Week 48: Virologic Failure



*Virologic failure = confirmed increase in HIV-1 RNA level greater than baseline or nadir values, failure to achieve HIV RNA <200 copies by week 24, or relapse (2 consecutive HIV-1 RNA levels ≥200 copies/mL after confirmed virologic response (HIV-1 RNA levels <200 copies/mL).

Source: Fischl MA, et al. J Infect Dis. 2003;188(5):625-34.

4-Drug Regimens versus 3-Drug Regimen
ACTG 388: Results

Clinical Toxicity and Laboratory Abnormalities			
Variable	**IDV only** (n = 168)	**EFV + IDV** (n = 168)	**NVF + IDV** (n = 168)
Nausea (+/- vomiting)	15	7	19
Diarrhea	4	3	16
Rash	2	7	3
Nephrolithiasis	22	5	8
Serum bilirubin >2.5x ULN	16	0	8
ANC <750 cells/mm^3	8	12	21
AST >5x ULN	6	11	8
Serum triglycerides >750 mg/dL	7	12	8

Source: Fischl MA, et al. J Infect Dis. 2003;188:625-34.

4-Drug Regimens versus 3-Drug Regimen
ACTG 388: Conclusions

Conclusions: “A 4-drug regimen containing efavirenz plus indinavir resulted in a superior virologic response, whereas one containing nelfinavir plus indinavir resulted in an inferior response and a greater likelihood of toxicity.”

Source: Fischl MA, et al. J Infect Dis. 2003;188:625-34.

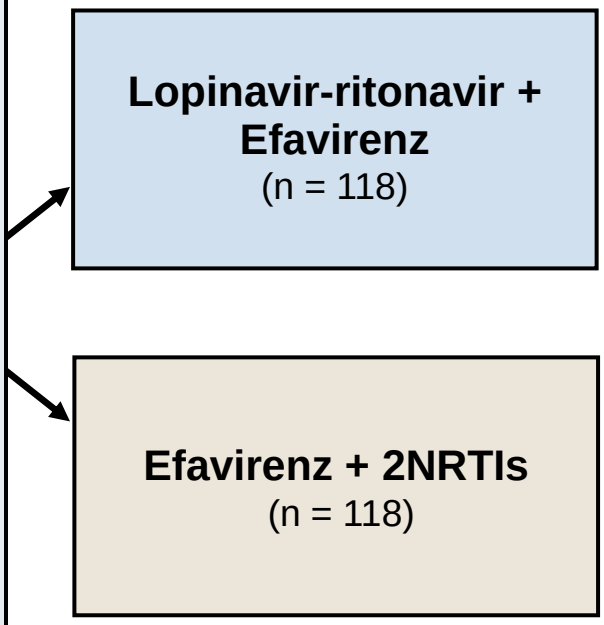
NRTI-Sparing Regimens following Viral Suppression

ACTG 5116

NRTI-sparing Regimens following Viral Suppression
ACTG 5116: Study Design

Study Design: ACTG 5116

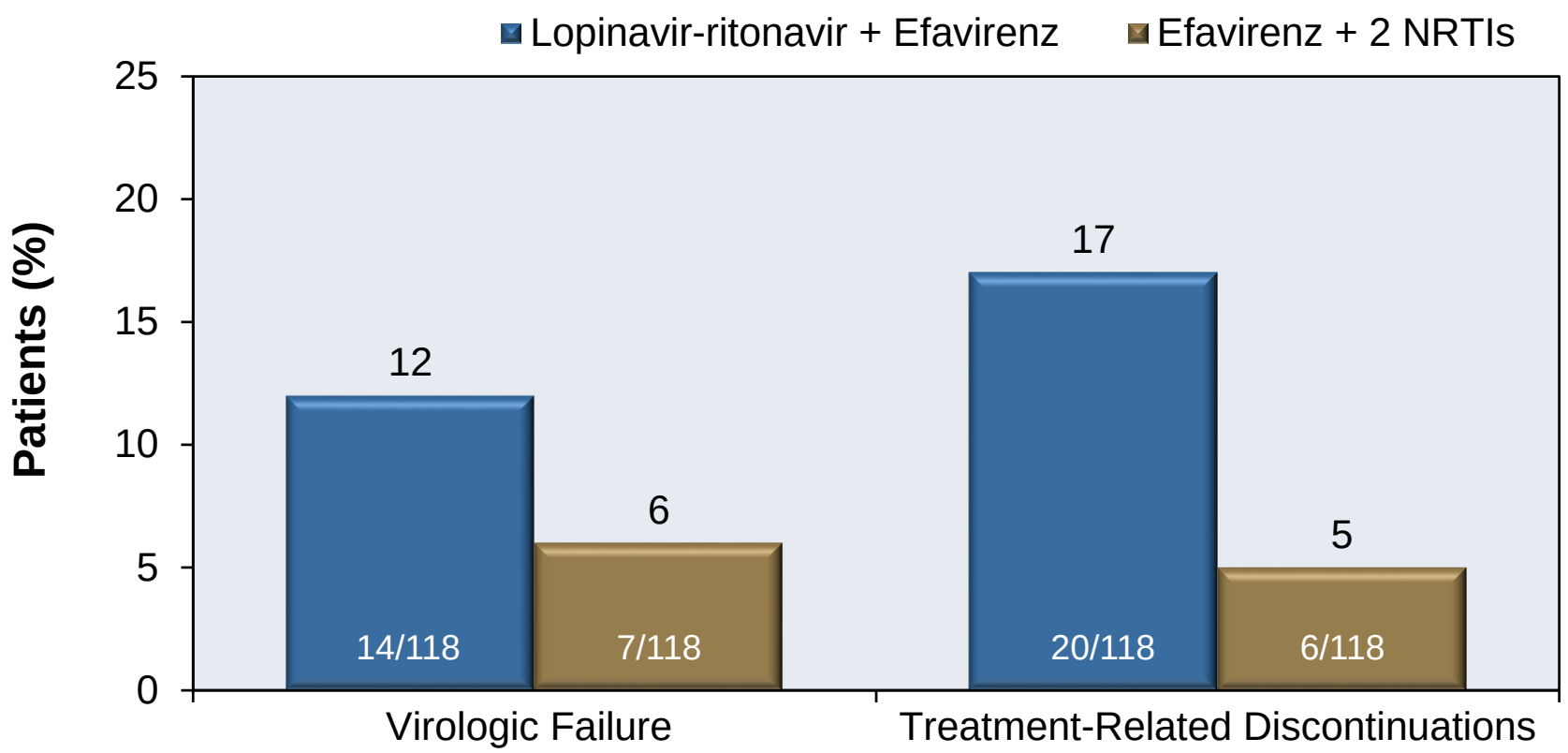
- **Background**: Randomized, open-label trial to compare NRTI-sparing regimen of lopinavir-ritonavir plus efavirenz versus efavirenz plus 2 NRTIs
- **Inclusion Criteria (n= 236)**
  - Prior ACTG 388 participants: HIV RNA ≤200 copies/mL on a first 3- or 4-drug ARV regimen
  - Non-ACTG 388 participants: stable first 3- or 4-drug NNRTI or PI-based regimen for ≥18 months without viral failure or resistance and HIV RNA ≤200 copies/mL
- **Treatment Arms**
  - Lopinavir-ritonavir 533/133 mg BID + Efavirenz 600 mg QD
  - Efavirenz 600 mg QD + 2 NRTIs



Source: Fischl MA, et al. AIDS. 2007;21:325-33.

NRTI-Sparing Regimens following Viral Suppression
ACTG 5116: Results

Week 48: Virologic Failure and Treatment-Related Discontinuations

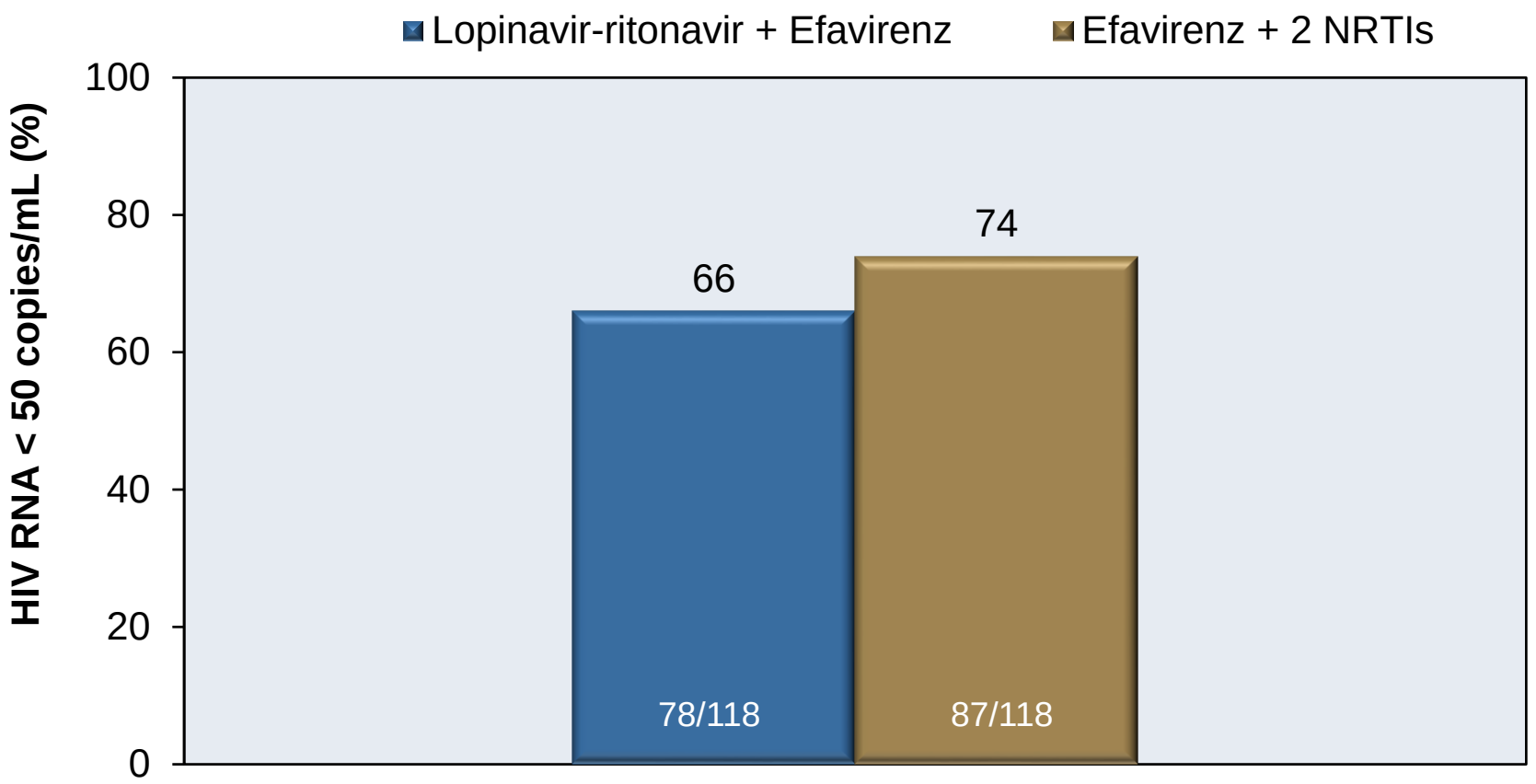


Virologic failure = two successive HIV-1 RNA values > 200 copies/mL

Source: Fischl MA, et al. AIDS. 2007;21:325-33.

Class-sparing Regimens following Viral Suppression
ACTG 5116: Results

Week 48: Virologic Response (Intent-to-Treat)



Source: Fischl MA, et al. AIDS. 2007;21:325-33.

NRTI-Sparing Regimens following Viral Suppression
ACTG 5116: Conclusions

Conclusions: “Switching to EFV + NRTI resulted in better outcomes, fewer drug-related toxicity discontinuations and a trend to fewer virologic failures compared to switching to LPV/r + EFV.”

Source: Fischl MA, et al. AIDS. 2007;21:325-33.

Acknowledgment

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