

Efavirenz-Tenofovir DF-Emtricitabine (*Atripla*)

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Efavirenz-Tenofovir DF-Emtricitabine



Efavirenz-Tenofovir DF-Emtricitabine

600 mg



NNRTI

300 mg



NRTI

200 mg



NRTI

Dose: 1 tablet once daily on an empty stomach

Efavirenz-Tenofovir DF-Emtricitabine

- **Atripla Components:**
 - Efavirenz 600mg
 - Tenofovir disoproxil fumarate: 300 mg
 - Emtricitabine: 200 mg
- **Dosing:**
 - 1 tablet daily on empty stomach (bedtime dosing recommended to minimize side effects)
- **Pregnancy**
 - May cause fetal harm when administered during the first trimester of pregnancy
- **Common Adverse Events (≥10%)**
 - Nausea, diarrhea, headache, dizziness, depression, insomnia, abnormal dreams, rash

Efavirenz-Tenofovir DF-Emtricitabine

Summary of Key Phase 3 Studies

- **Trials in Treatment Naïve**

- ASSERT: ABC-3TC + EFV versus TDF-FTC plus EFV
- STUDY 934: TDF + FTC + EFV versus ZDV-3TC + EFV
- STARTMRK: RAL + TDF- FTC versus EFV + TDF-FTC
- ECHO: RPV + FTC-TDF versus EFV + FTC-TDF
- STaR: RPV-FTC-TDF versus EFV-TDF-FTC
- SINGLE: DTG + ABC-3TC versus EFV-TDF-FTC
- STUDY 102: EVG-COBI-FTC-TDF versus EFV-TDF-FTC

- **Switch Trials**

- Study 115 SWEET: Switch from EFV + AZT-3TC to EFV + TDF-FDC
- STUDY 073: Simplification to EFV-FTC-TDF

Efavirenz-Tenofovir DF-Emtricitabine

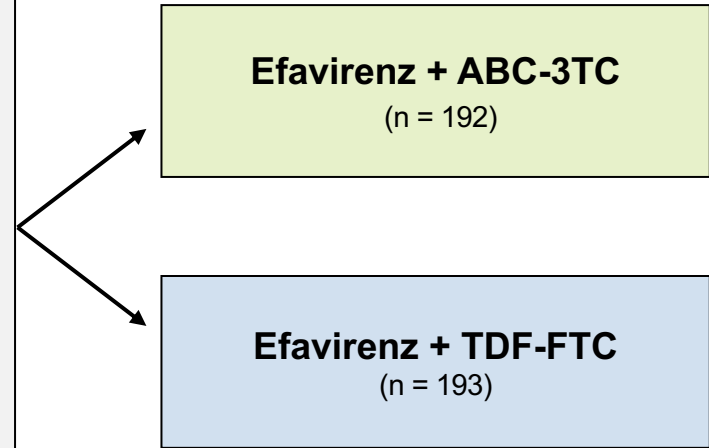
Trials in Treatment Treatment-Naïve Adults

EFV + ABC-3TC versus EFV + TDF-FTC
ASSERT Trial

Efavirenz + ABC-3TC versus Efavirenz + TDF-FTC

ASSERT: Study Design

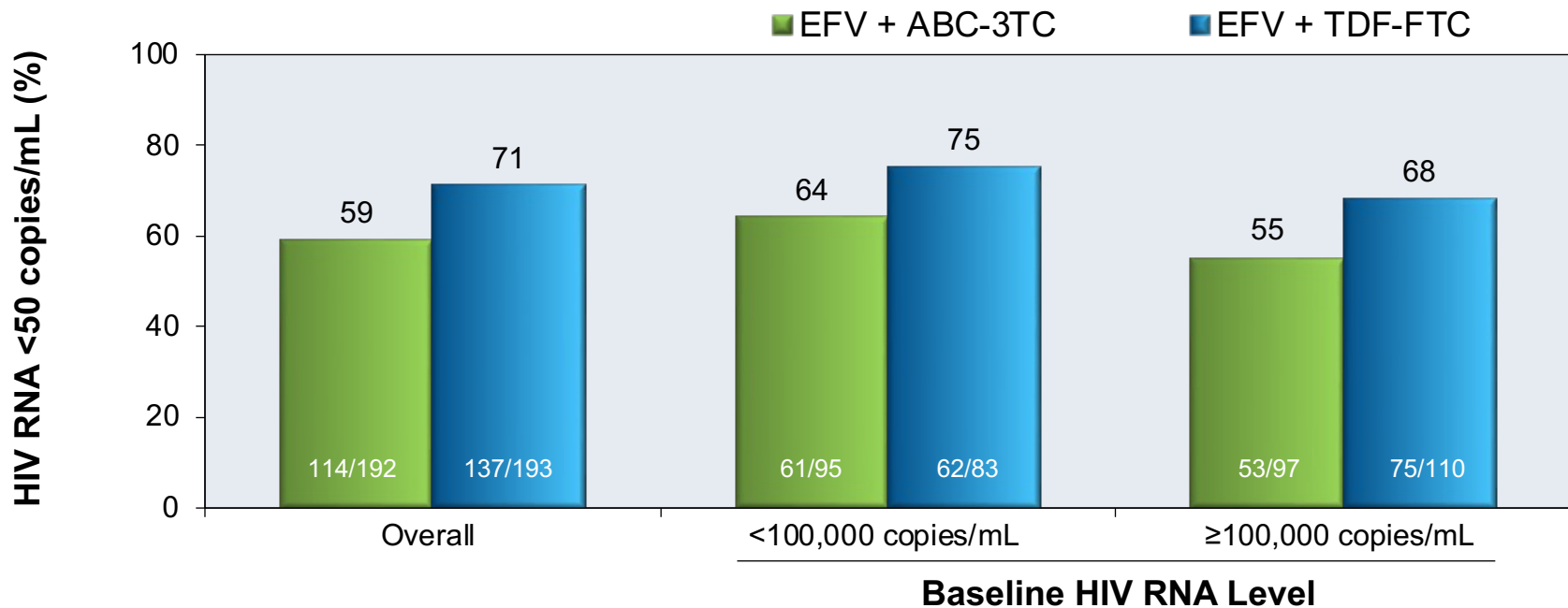
- **Background:** Randomized, open label, phase 3 study comparing tenofovir DF-emtricitabine plus efavirenz with zidovudine-lamivudine plus efavirenz in antiretroviral-naïve adults with HIV
- **Inclusion Criteria (n = 385)**
 - Antiretroviral-naïve adults
 - Age ≥ 18 years
 - HIV RNA $\geq 1,000$ copies/mL
 - HLA-B*5701 negative
 - CrCl ≥ 50 mL/min
 - No AIDS-defining condition or HBV infection
- **Treatment Arms**
 - Efavirenz + abacavir-lamivudine
 - Efavirenz + tenofovir DF-emtricitabine



Efavirenz + ABC-3TC versus Efavirenz + TDF-FTC

ASSERT: Results

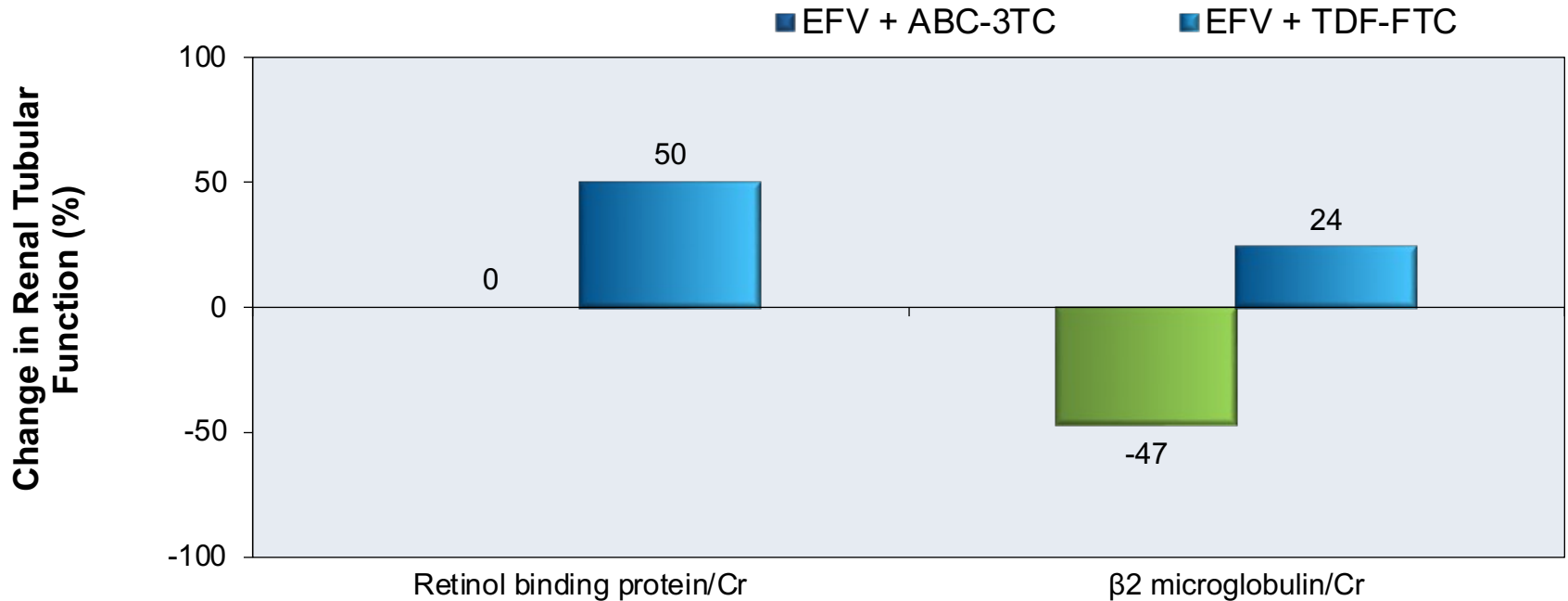
Week 48 Virologic Response (Intent-to-Treat Analysis)



Efavirenz + ABC-3TC versus Efavirenz + TDF-FTC

ASSERT: Renal Biomarkers

Week 48: Changes in Markers of Renal Tubular Function from Baseline



Efavirenz + ABC-3TC vs. Efavirenz + TDF-FTC

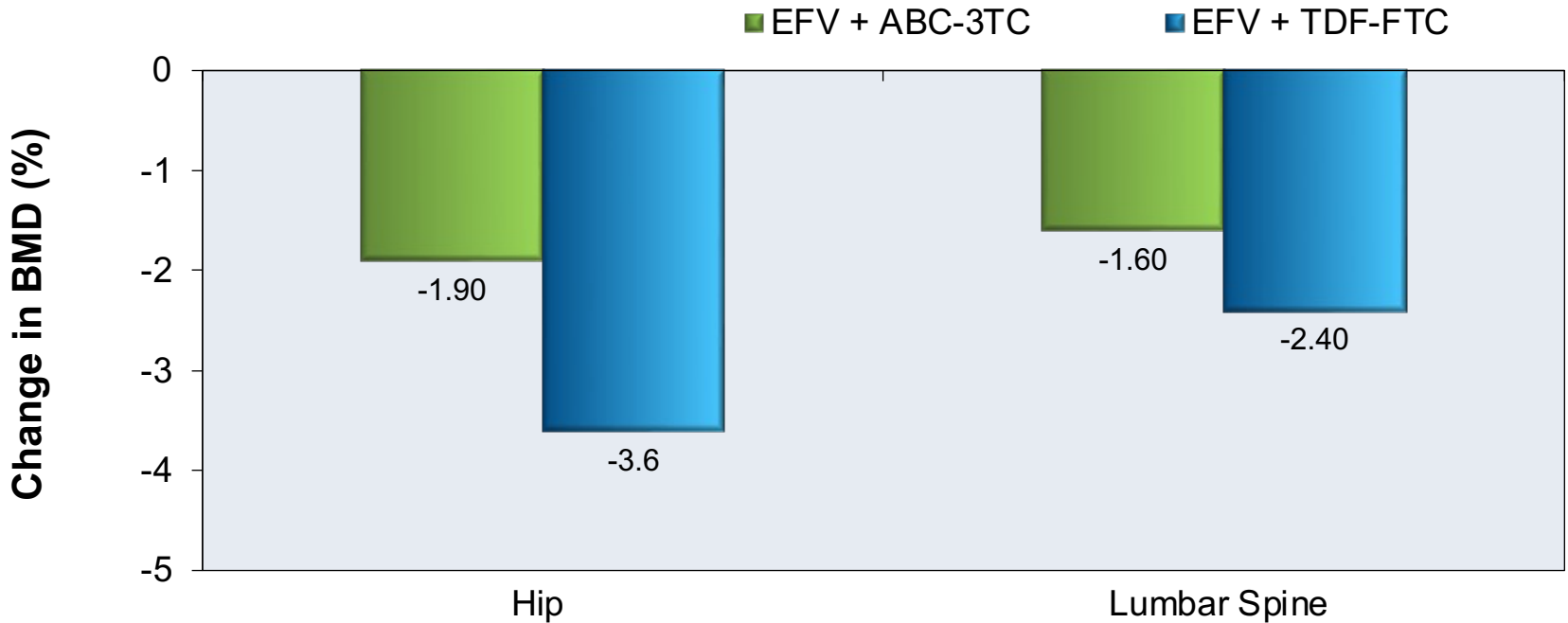
ASSERT: Conclusions

Interpretation: “The study showed no difference in estimated glomerular filtration rate between the arms, however, increases in markers of tubular dysfunction were observed in the tenofovir/emtricitabine arm, the long-term consequence of which is unclear. A significant difference in efficacy favoring tenofovir/emtricitabine was observed.”

Efavirenz + ABC-3TC versus Efavirenz + TDF-FTC

ASSERT: Bone Effects

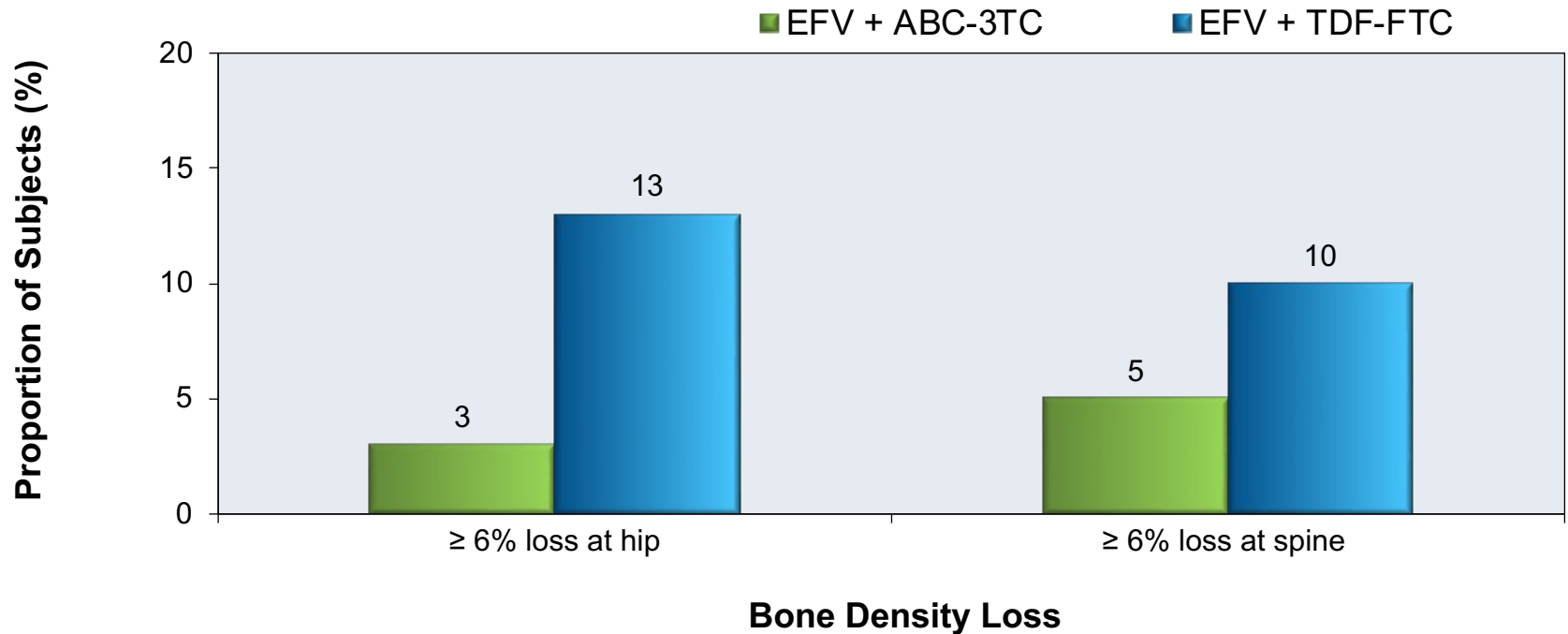
Week 48: Changes in Spine and Hip Bone Mineral Density from Baseline



Efavirenz + ABC-3TC versus Efavirenz + TDF-FTC

ASSERT: Bone Effects

Week 48: Proportion of Subjects with Decrease in BMD from Baseline



EFV + TDF + FTC versus EFV + ZDV-3TC
Study 934

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

Study 934: Study Design

- **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/mm³
 - No AIDS conditions in prior 30 days
- **Treatment Arms**
 - Efavirenz + tenofovir DF + emtricitabine
 - Efavirenz + zidovudine-lamivudine

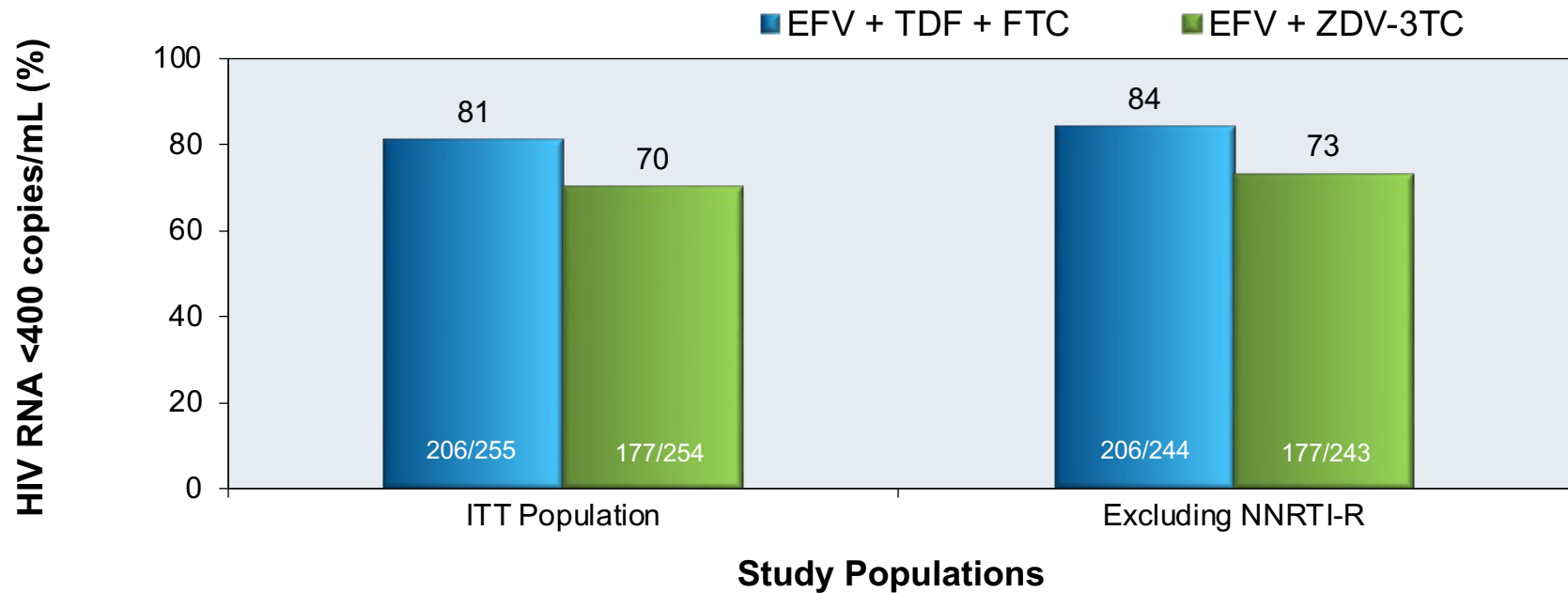
EFV QD + TDF + FTC QD
(n = 255)

EFV QD + ZDV-3TC BID
(n = 254)

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

Study 934: Results

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

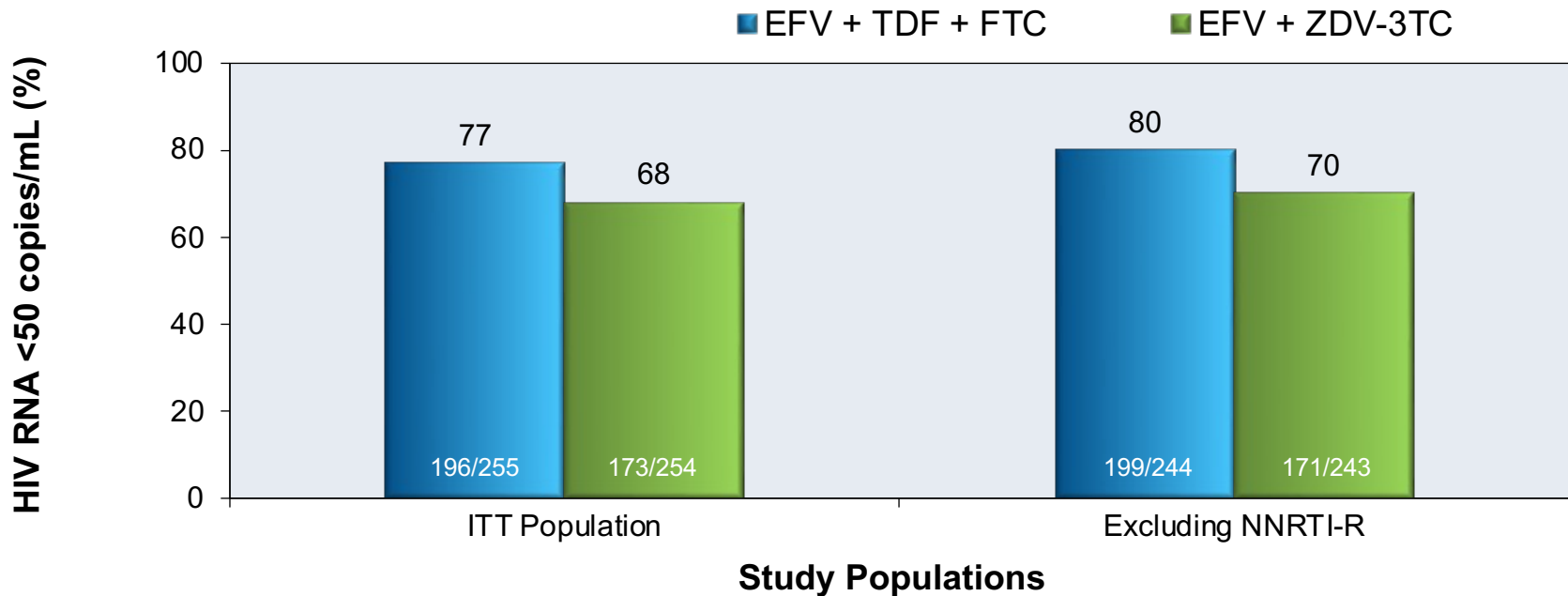


Abbreviations: ITT = Intention-to-Treat; NNRTI-R = Patients with baseline NNRTI mutations.

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

Study 934: Results

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

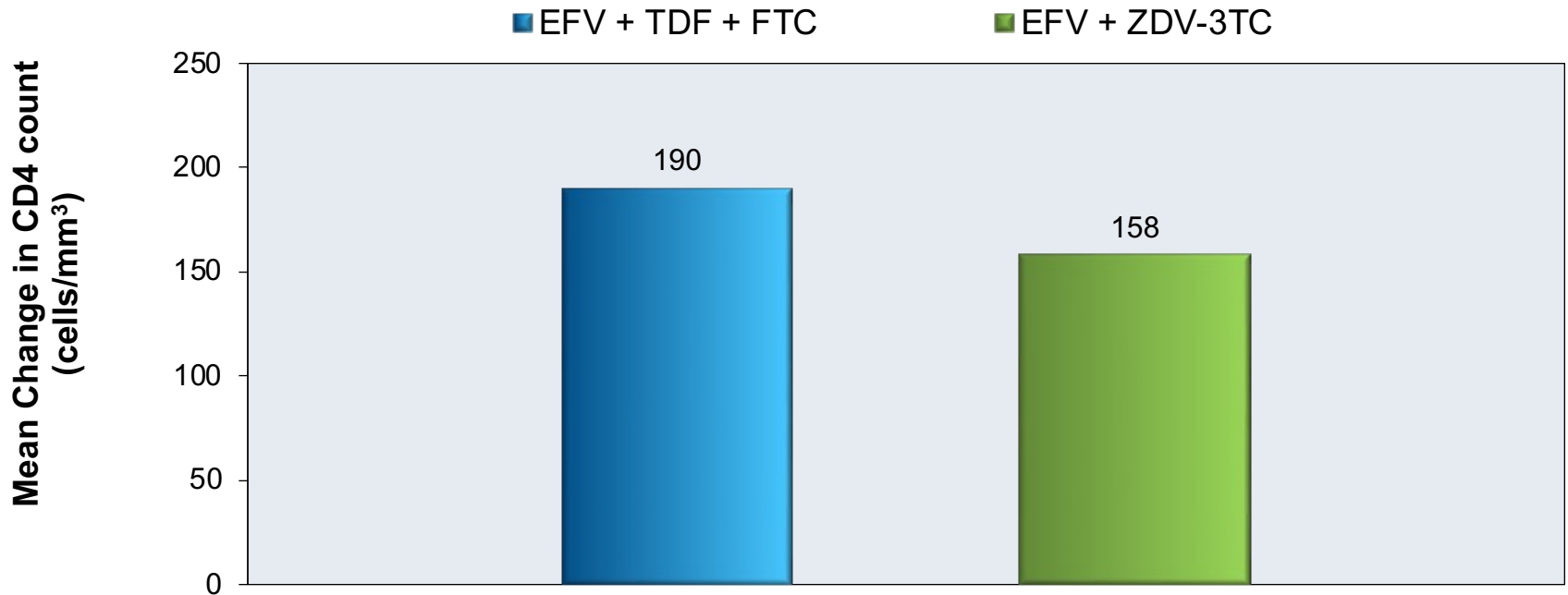


Abbreviations: ITT = Intention-to-Treat; NNRTI-R = Patients with baseline NNRTI resistance mutations.

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

Study 934: Results

Week 48: Immunologic Response

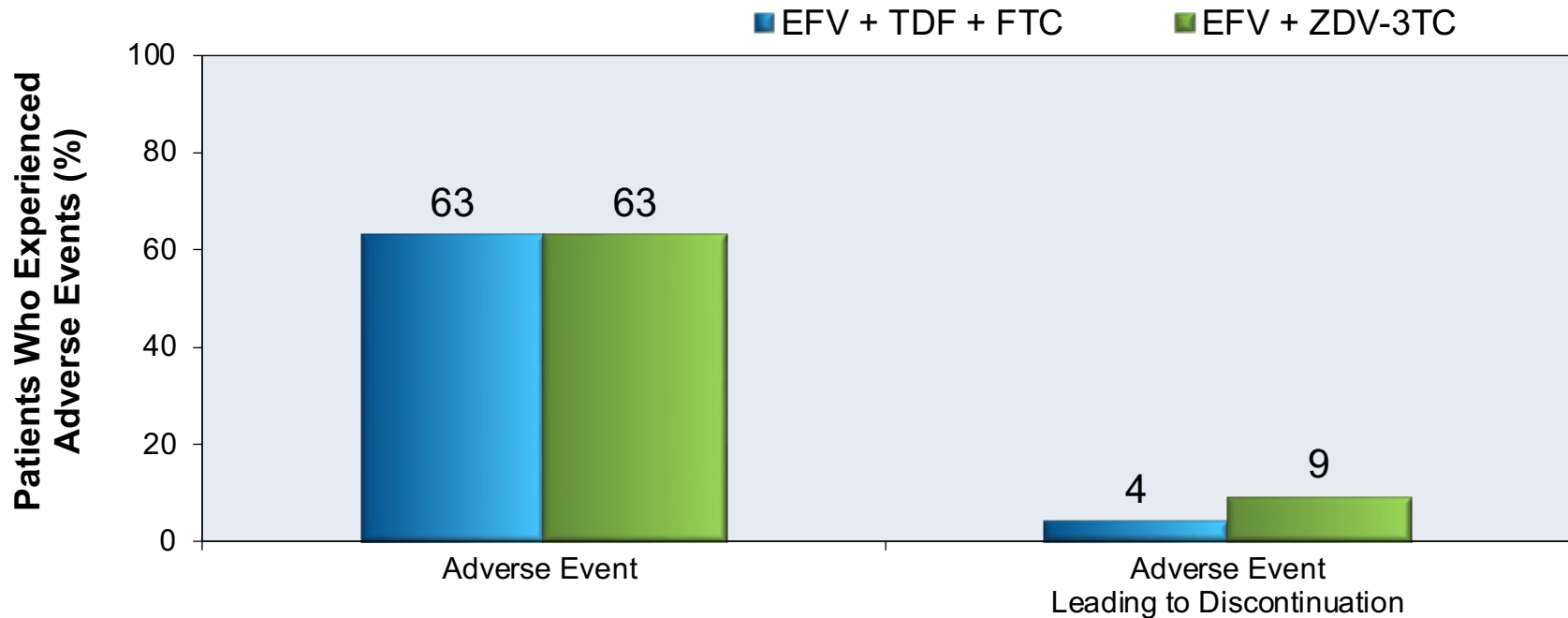


Source: Gallant JE, et al. N Engl J Med. 2006;354:251-60.

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

Study 934: Results

Adverse Events Through 48 Weeks



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

Study 934: Common Adverse Events

Treatment Emergent Adverse Events in $\geq 5\%$ 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%

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.”

Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC
STARTMRK Trial

Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC

STARTMRK: Study Design

- **Background:** Randomized, double-blind, phase 3 study comparing the safety and efficacy of raltegravir versus efavirenz, each in combination with tenofovir DF and emtricitabine
- **Inclusion Criteria (n = 569)**
 - Antiretroviral-naïve patients
 - Age ≥18 years
 - HIV RNA ≥5000 copies/mL
 - No resistance to EFV, TDF, or FTC
- **Treatment Arms**
 - Raltegravir + TDF-FTC
 - Efavirenz + TDF-FTC

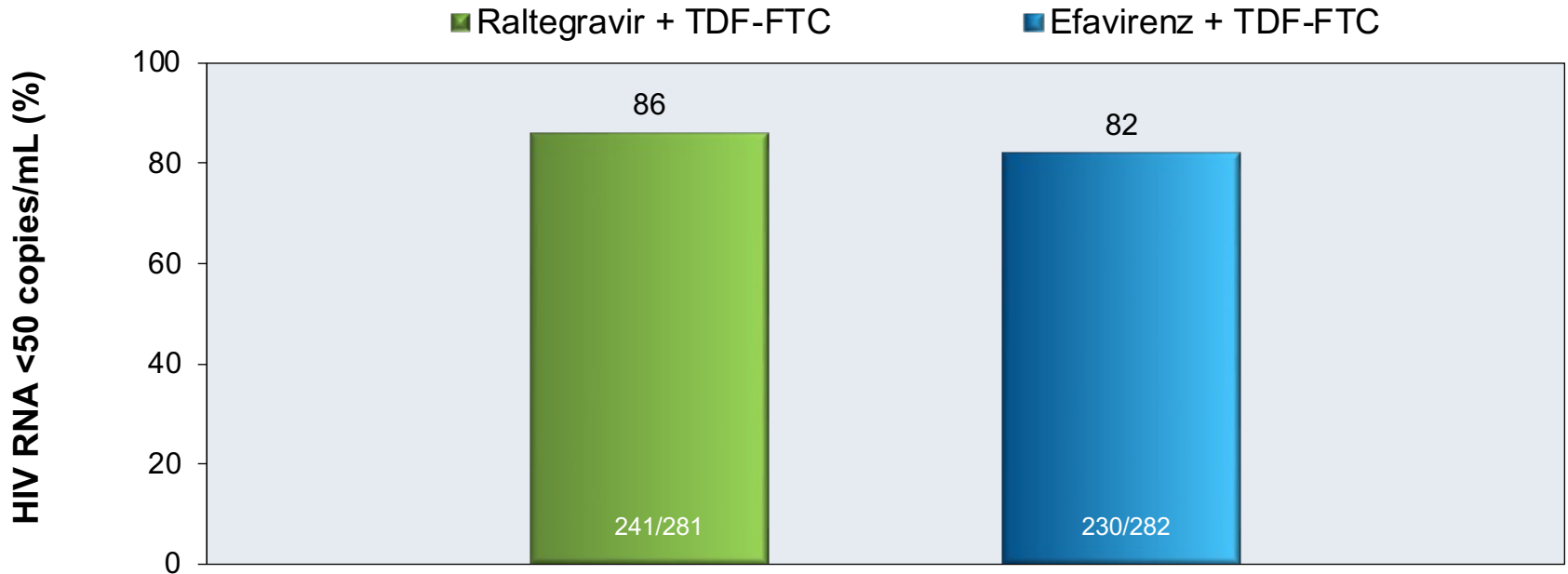
Raltegravir BID + TDF-FTC
(n = 281)

Efavirenz + TDF-FTC
(n = 282)

Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC

STARTMRK: Results

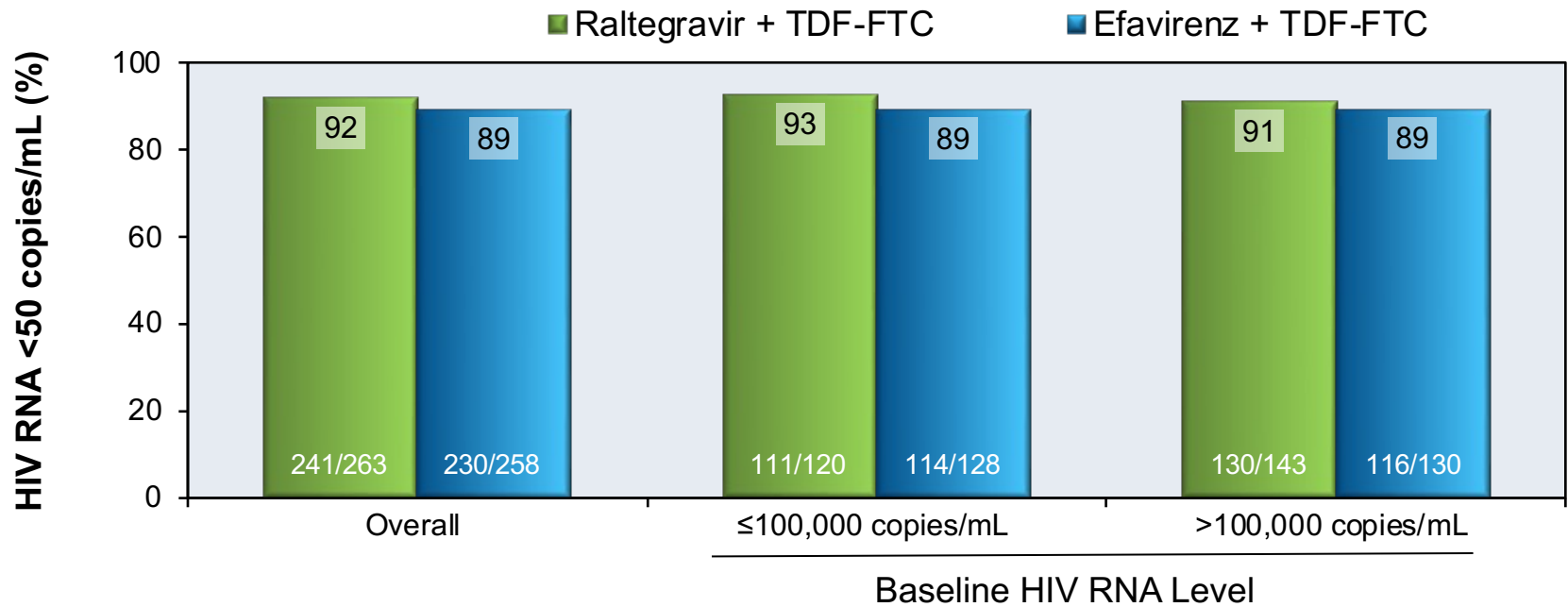
Week 48: Virologic Response (Primary Analysis, Missing=Failure)



Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC

STARTMRK: Results

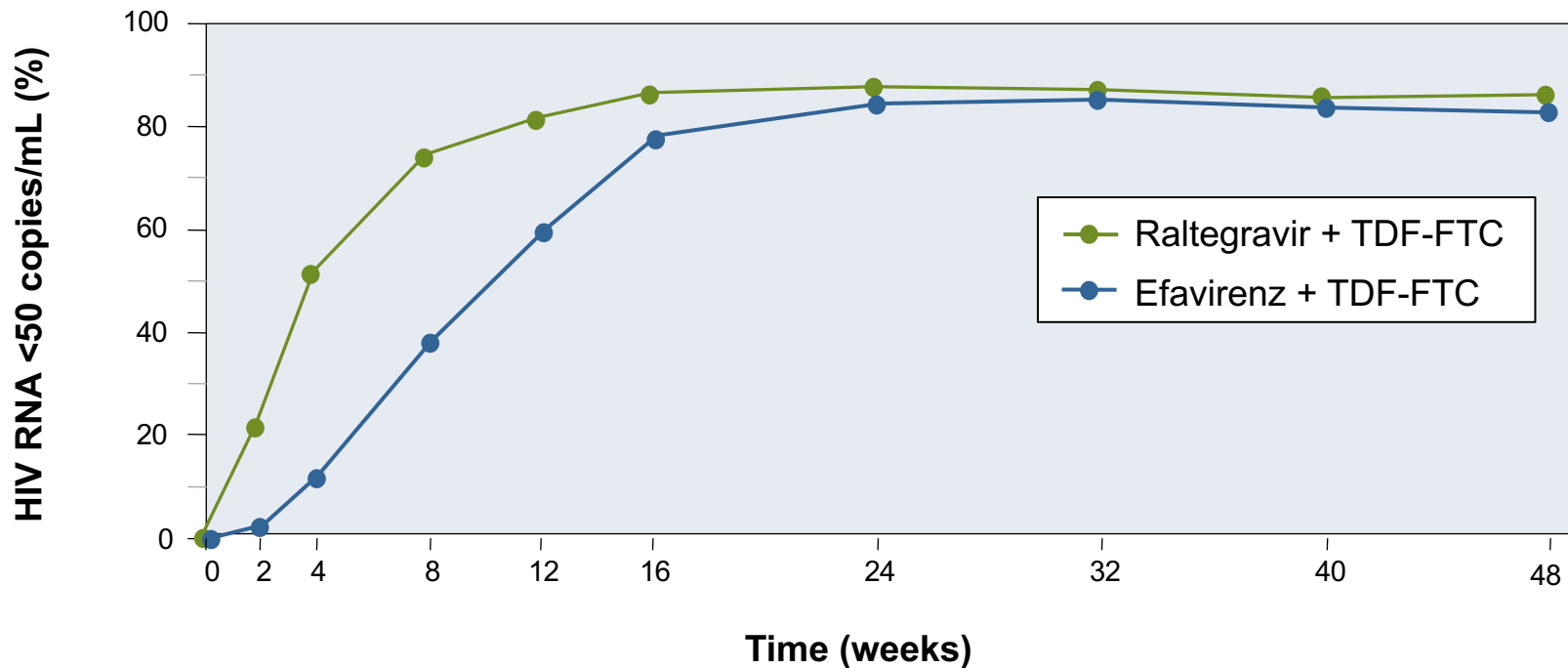
Week 48 Virologic Response (Observed-Failure Method)



Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC

STARTMRK: Results

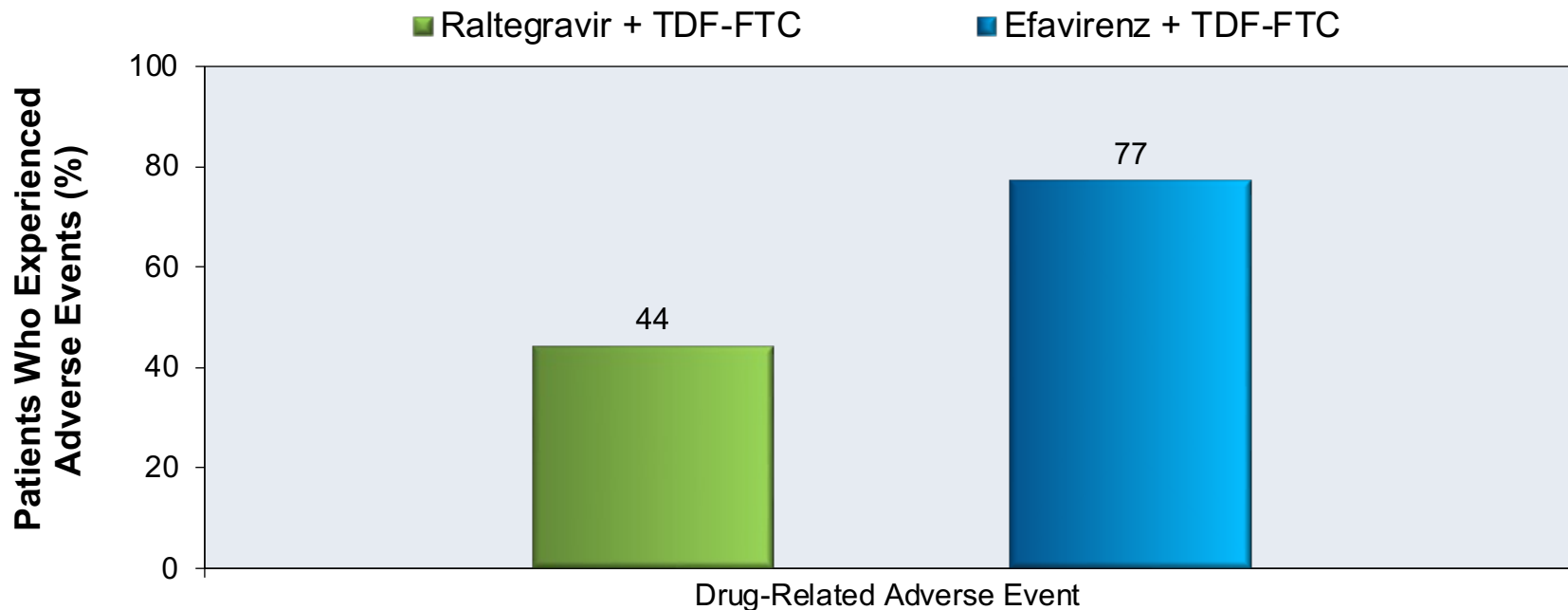
Week 48 Virologic Response



Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC

STARTMRK: Results

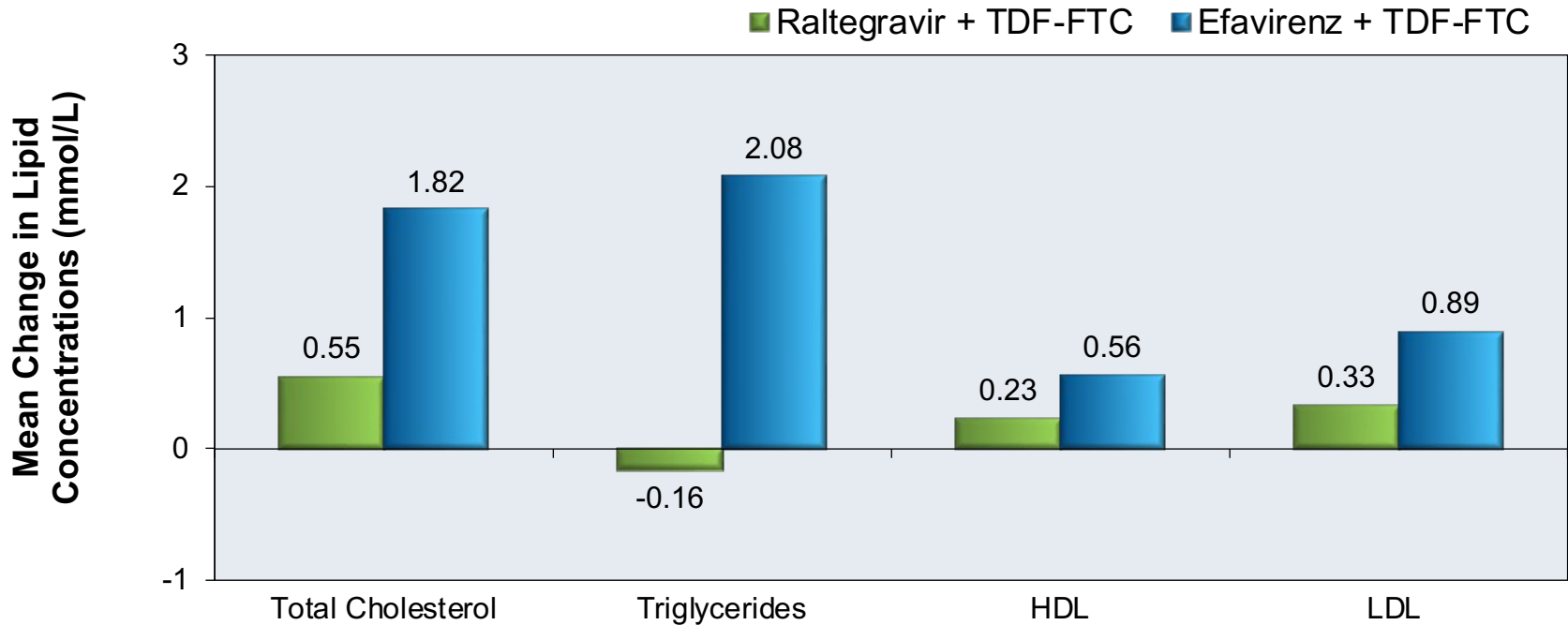
Adverse Events through 48 Weeks



Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC

STARTMRK: Results

Week 48: Changes in Lipid Concentrations from Baseline



Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC

STARTMRK: Common Adverse Events

Treatment Emergent Adverse Events in >10% of Subjects in Either Arm		
	RAL + TDF-FTC (n = 281)	EFV + TDF-FTC (n = 282)
Dizziness	6%	34%
Headache	9%	14%
Abnormal dreams	7%	13%
Immune Reconstitution Inflammatory Syndrome	6%	4%

Source: Lennox JL, et al. Lancet. 2009;374:796-806.

Raltegravir + TDF-FTC vs. Efavirenz + TDF-FTC

STARTMRK: Conclusions

Interpretation: “Raltegravir-based combination treatment had rapid and potent antiretroviral activity, which was non-inferior to that of efavirenz at week 48. Raltegravir is a well tolerated alternative to efavirenz as part of a combination regimen against HIV-1 in treatment-naive patients.”

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO Trial

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Study Design

- **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 ≥5,000 copies/mL
 - No resistance to any study drugs
- **Treatment Arms**
 - Rilpivirine + Tenofovir DF-Emtricitabine
 - Efavirenz + Tenofovir DF-Emtricitabine

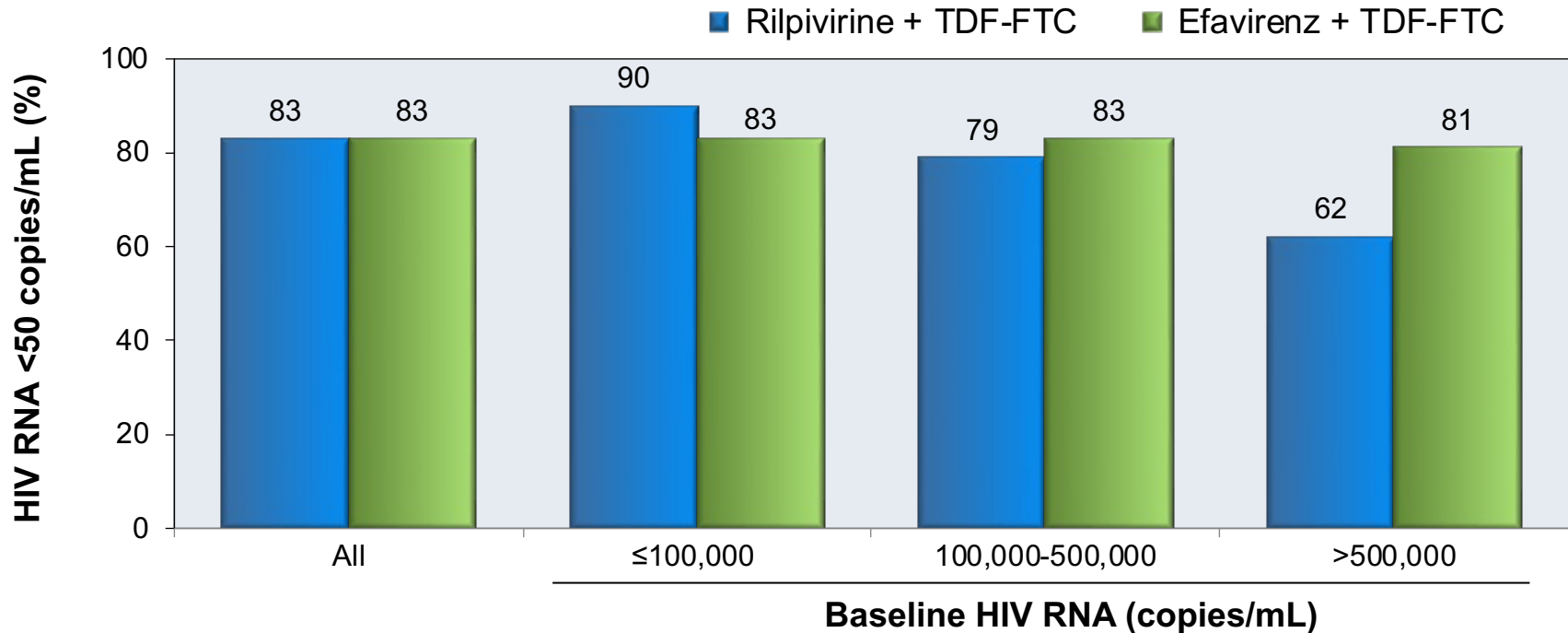
Rilpivirine + TDF-FTC QD
(n = 346)

Efavirenz + TDF-FTC QD
(n = 344)

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Results

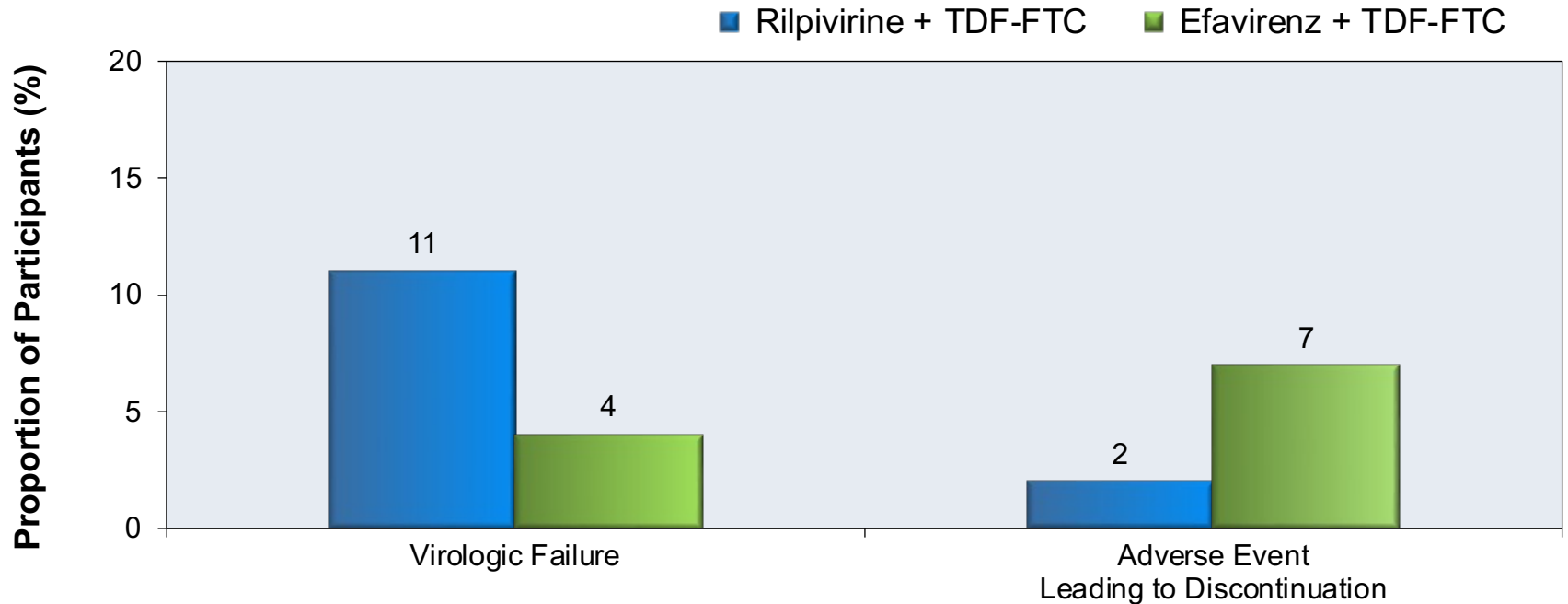
48 Week Virologic Response (Intention-to-Treat)



Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Results

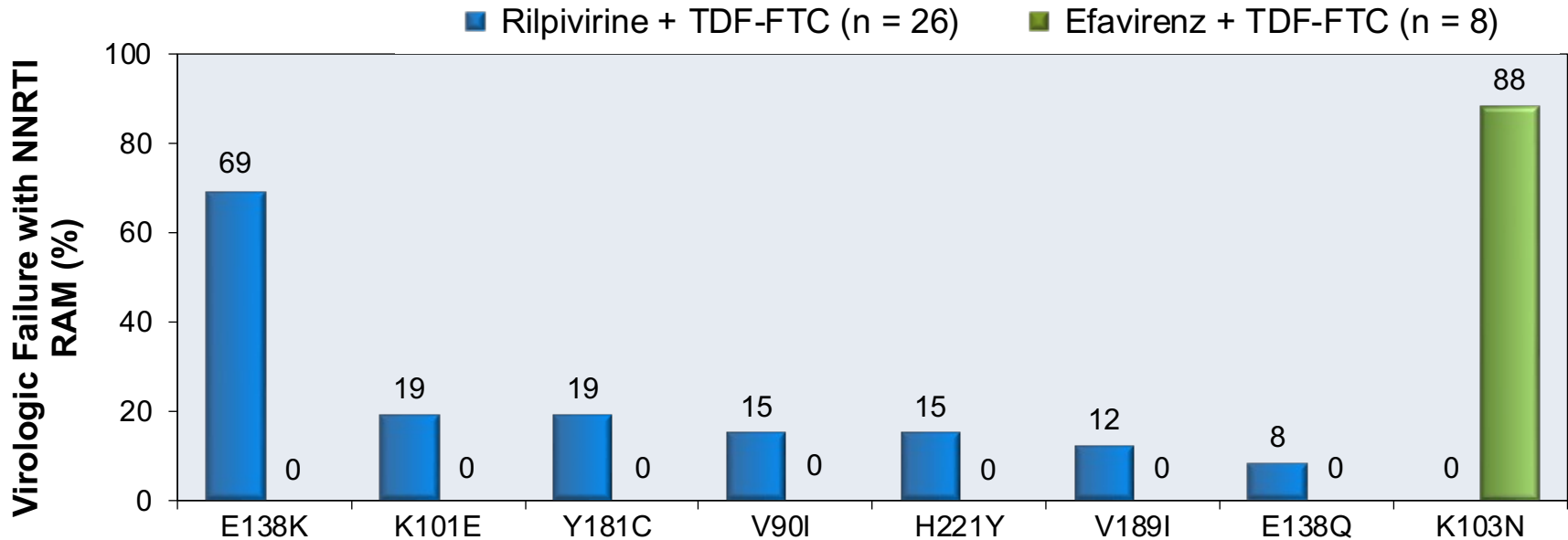
48 Week Virologic Failure and Discontinuations (Intention-to-Treat)



Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Resistance Results

Incidence of NNRTI Resistance Associated Mutations (RAMs)

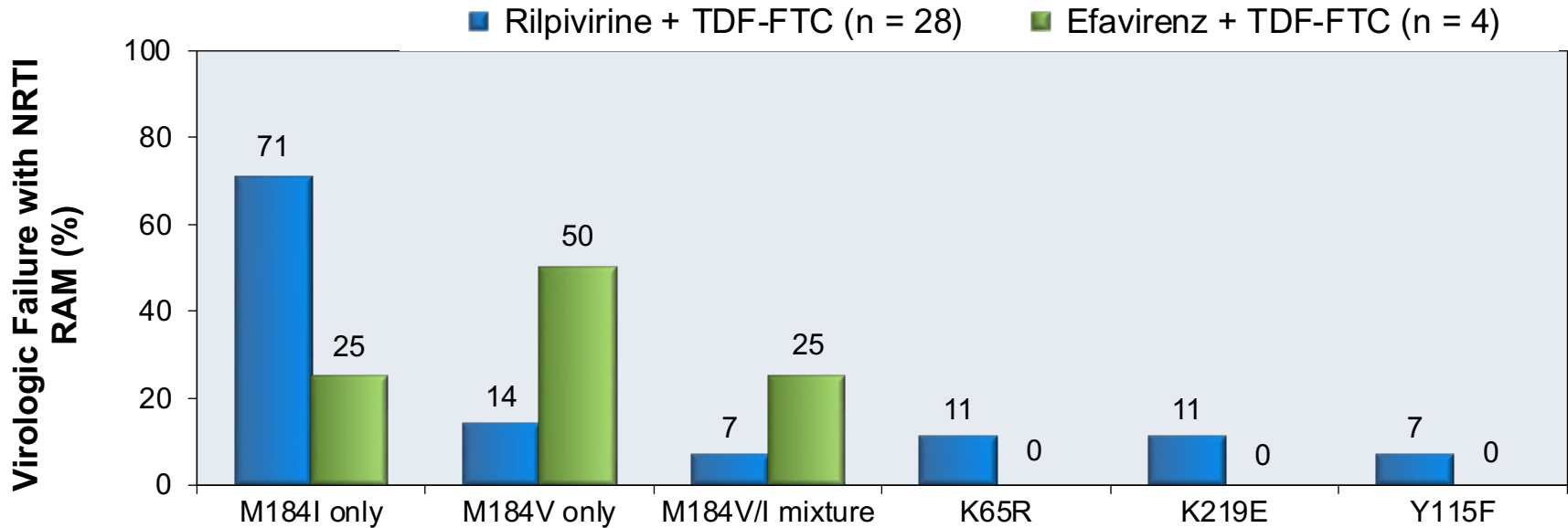


The percentages represent the number of participants who developed each specific NNRTI RAM out of the number of participants who developed any NNRTI RAM in that arm of the trial (the n listed at the top of the graph).

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Resistance Results

Incidence of NRTI Resistance Associated Mutations (RAMs)



The percentages represent the number of participants who developed each specific NRTI RAM out of the number of participants who developed any NRTI RAM in that arm of the trial (the n listed at the top of the graph).

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Conclusions

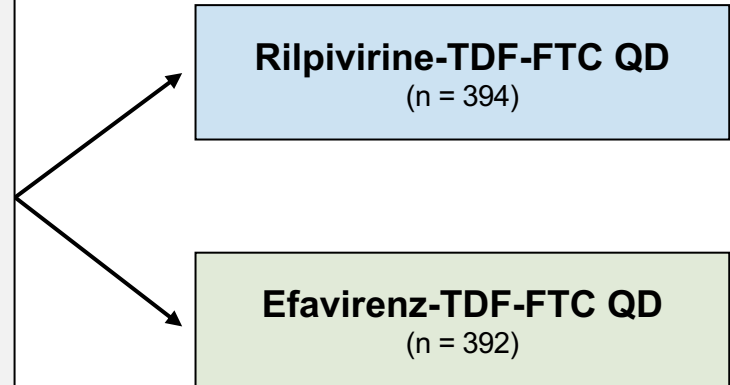
Interpretation: “Rilpivirine showed non-inferior efficacy compared with efavirenz, with a higher virological-failure rate, but a more favourable safety and tolerability profile.”

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC
STaR Trial

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

STaR Study: Design

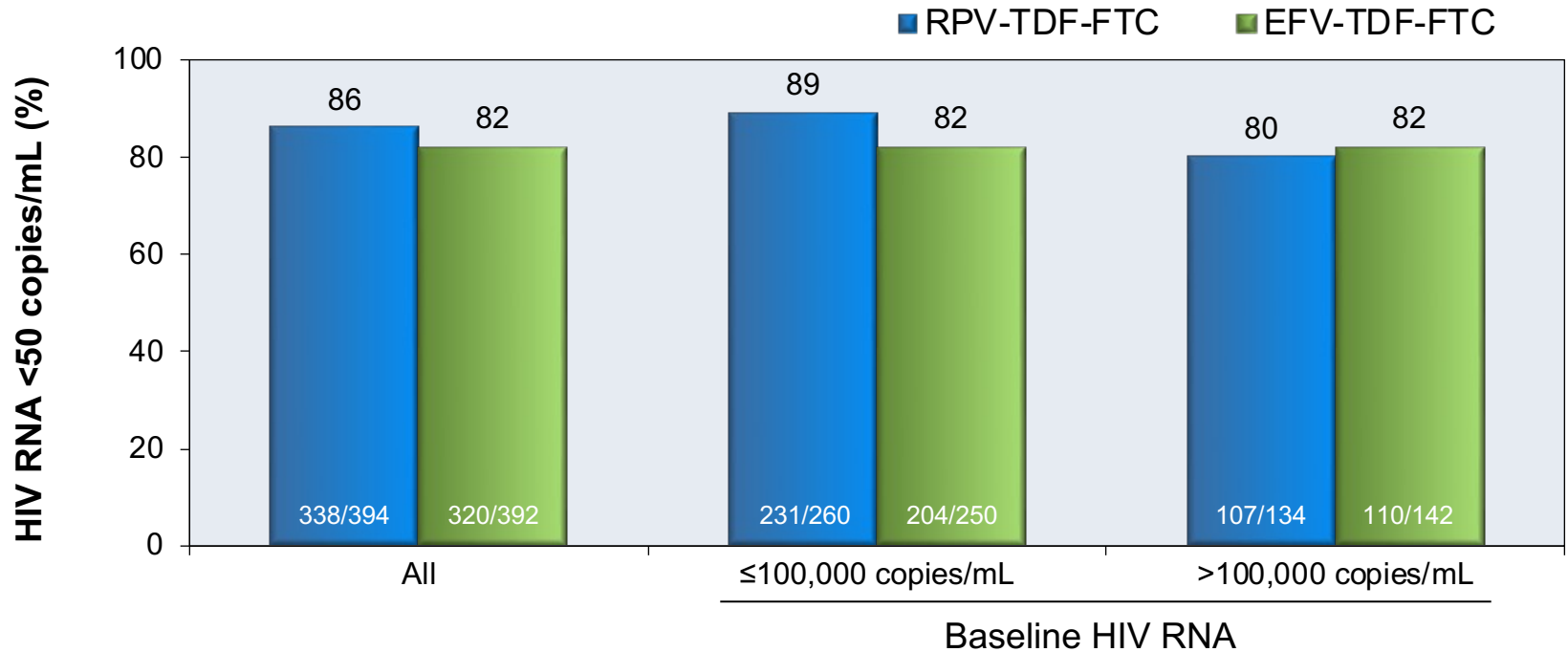
- **Background:** Randomized, open-label, phase 3b trial comparing safety and efficacy of two single-tablet regimens, RPV-TDF-FTC and EFV-TDF-FTC, in treatment-naïve adults with HIV
- **Inclusion Criteria (n = 786)**
 - Antiretroviral-naïve adults
 - Age ≥18 years
 - HIV RNA ≥2,500 copies/mL
 - No resistance to EFV, RPV, TDF, or FTC
- **Treatment Arms**
 - Rilpivirine-tenofovir DF-emtricitabine
 - Efavirenz-tenofovir DF-emtricitabine



Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

STaR: Results

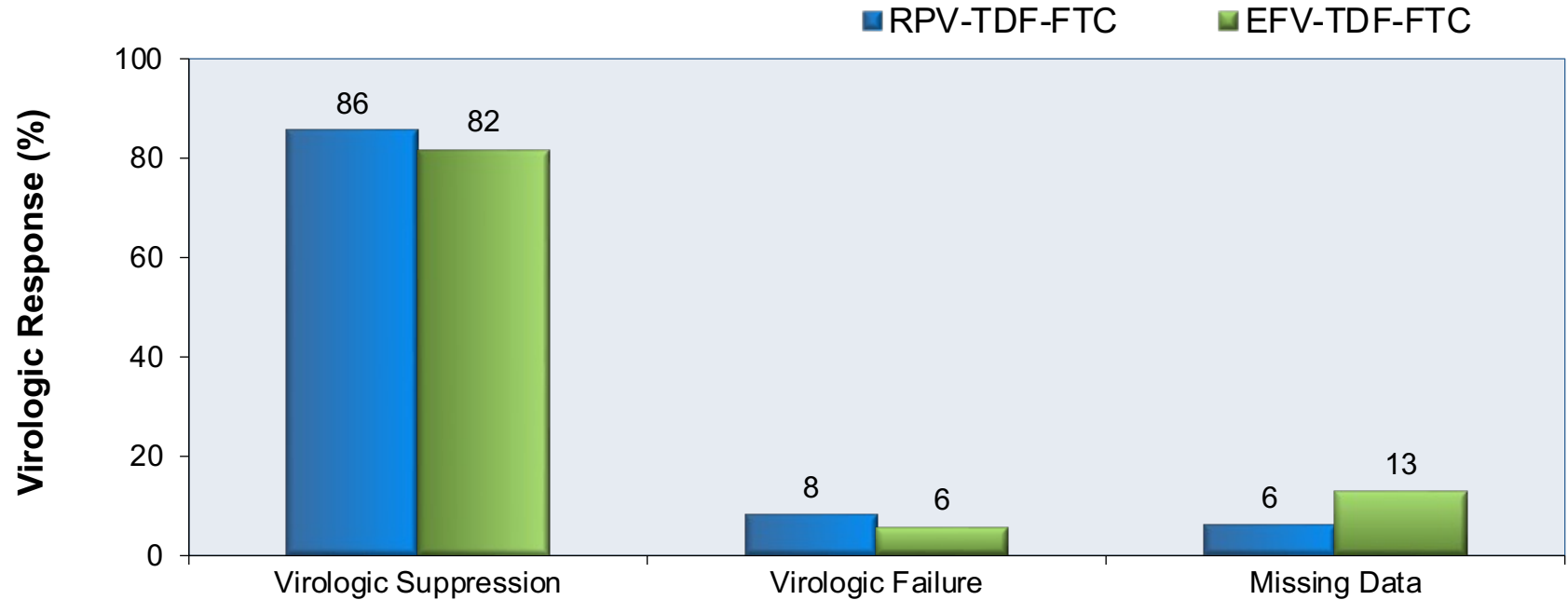
Week 48 Virologic Response (Intent-to-Treat Analysis)



Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

STaR: Results

48 Week Virologic Outcomes



Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

STaR: Common Adverse Events

Treatment Emergent Adverse Events in > 5% of Subjects in Either Arm		
	RPV-TDF-FTC (n = 392)	EFV-TDF-FTC (n = 394)
Dizziness	6.6%	22.2%
Insomnia	9.6%	14.0%
Somnolence	2.5%	6.9%
Headache	12.4%	13.5%
Abnormal Dreams	5.8%	24.5%
Depression	6.6%	8.9%
Anxiety	5.1%	8.4%
Folliculitis	5.3%	1.0%
Rash	6.1%	12.0%

Source: Cohen CJ, et al. AIDS. 2014;28:989-97.

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

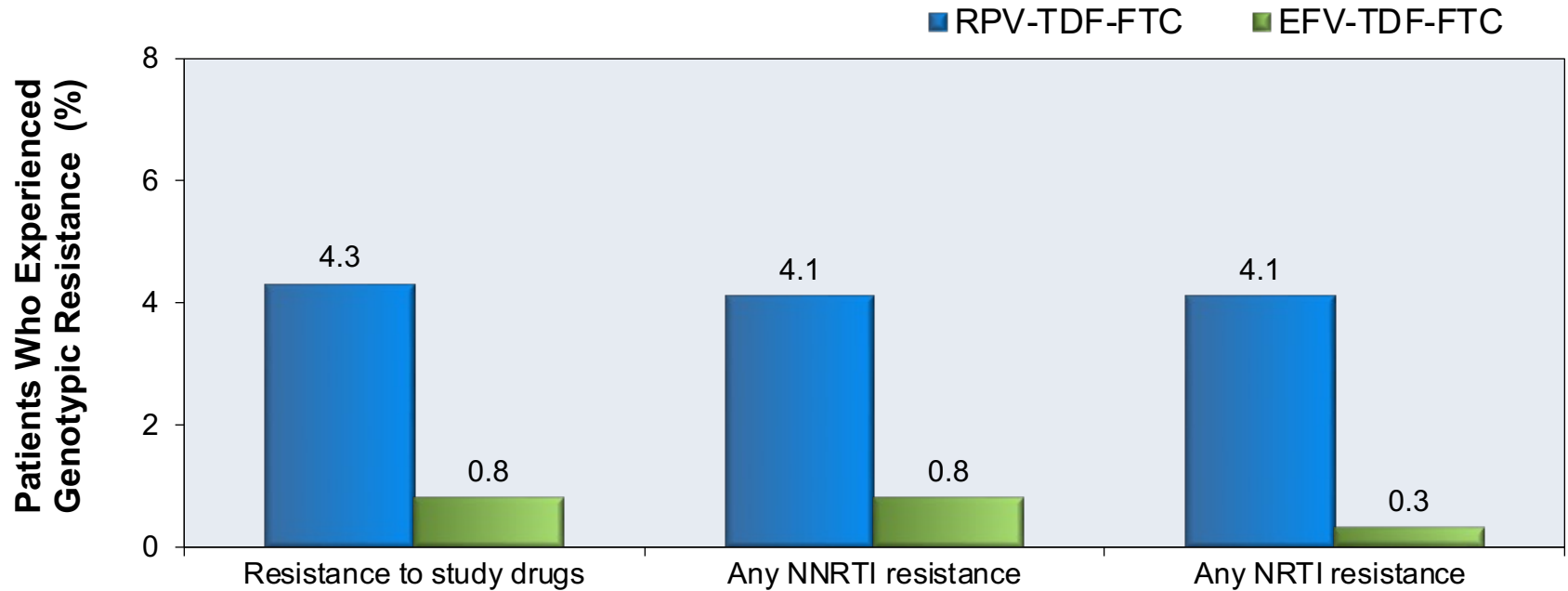
STaR: Conclusions from Primary Analysis

Conclusion: “In treatment-naïve participants, RPV/FTC/TDF demonstrated noninferior efficacy and improved tolerability compared with EFV/FTC/TDF, as well as a statistically significant difference in efficacy for participants with baseline HIV-1 RNA 100,000 copies/mL or less at week 48.”

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC
STaR Trial: Week 96 Resistance Data

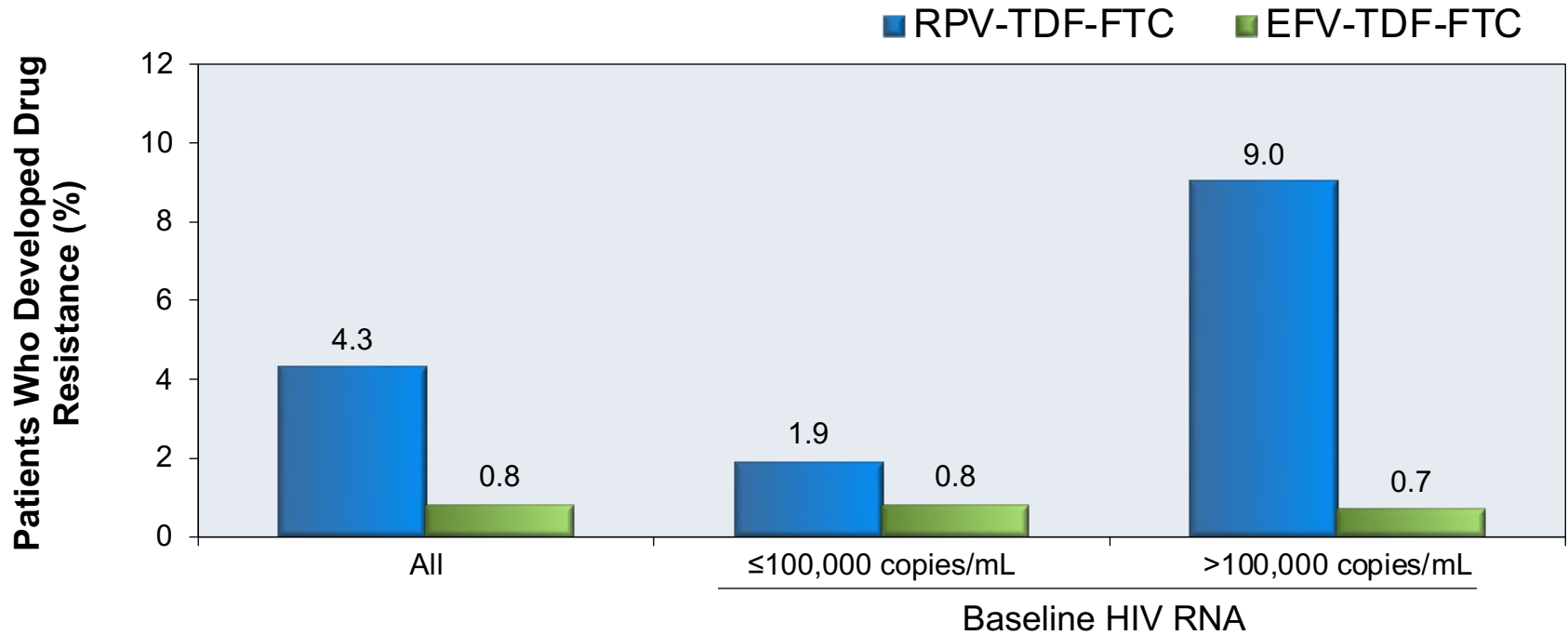
Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC STaR Resistance Analysis: Result

Development of Genotypic Resistance at Week 48



Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC STaR Resistance Analysis: Result

Development of Resistance to Study Drugs at 48 weeks, by Viral Load



Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC STaR Resistance Analysis: Conclusions

Conclusions: “Among subjects in the primary resistance-associated populations (RAP), resistance development to RPV/FTC/TDF consisted of NNRTI and NRTI mutations and was more frequent than resistance development to EFV/FTC/TDF. In subjects with baseline viral load $\leq 100,000$ copies/mL, resistance development was low ($<2\%$) for both RPV/FTC/TDF and EFV/FTC/TDF arms and less frequent compared with subjects with baseline viral load $>100,000$ copies/mL, for RPV/FTC/TDF.”

Dolutegravir + ABC-3TC versus Efavirenz-TDF-FTC
SINGLE Study

Dolutegravir + ABC-3TC versus Efavirenz-TDF-FTC SINGLE Study: Design

- **Background:** Randomized, double-blind study, phase 3 trial comparing dolutegravir + abacavir-lamivudine with efavirenz-tenofovir DF-emtricitabine
- **Inclusion Criteria (n = 833)**
 - Antiretroviral-naïve adults
 - Age ≥ 18 years
 - HIV RNA $\geq 1,000$ copies/mL
 - No active CDC AIDS-defining condition
- **Treatment Arms**
 - Dolutegravir (QD) + Abacavir-Lamivudine
 - Efavirenz-Tenofovir DF-Emtricitabine

Dolutegravir + ABC-3TC

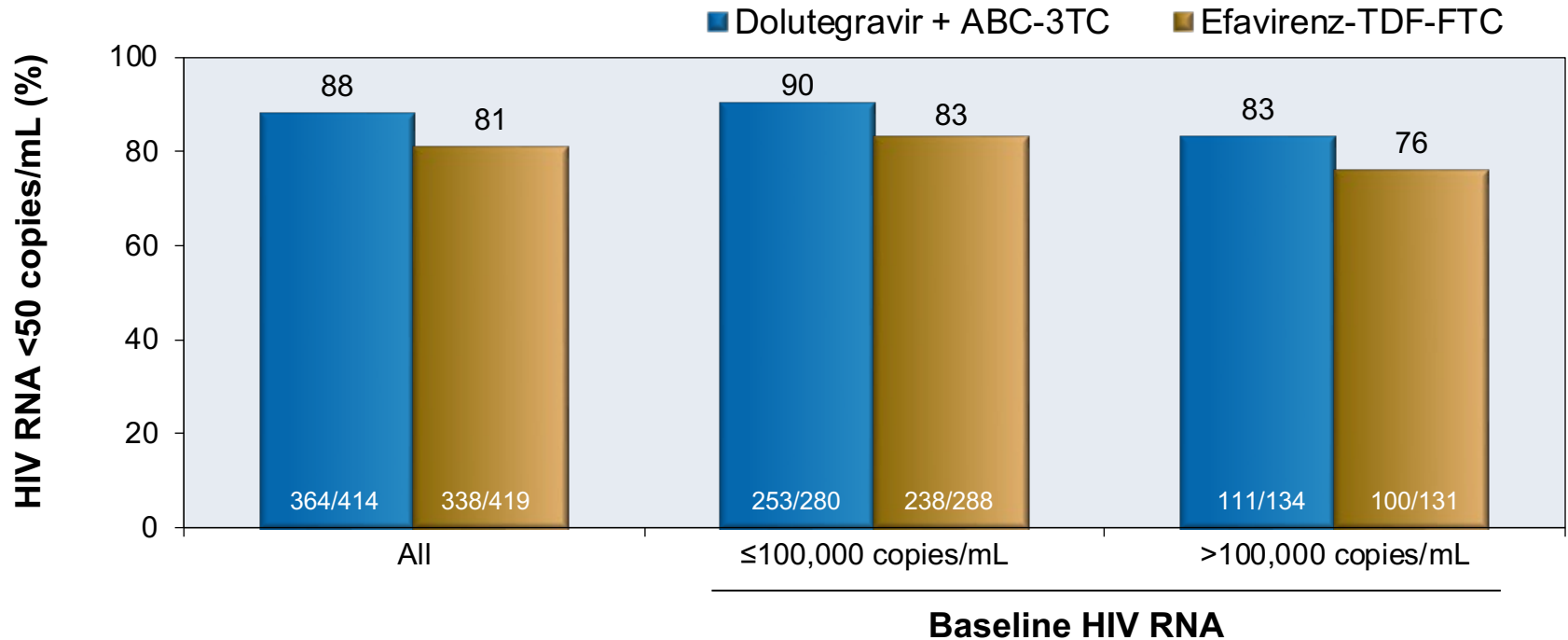
(n = 414)

Efavirenz-TDF-FTC

(n = 419)

Dolutegravir + ABC-3TC versus Efavirenz-TDF-FTC SINGLE Study: Results

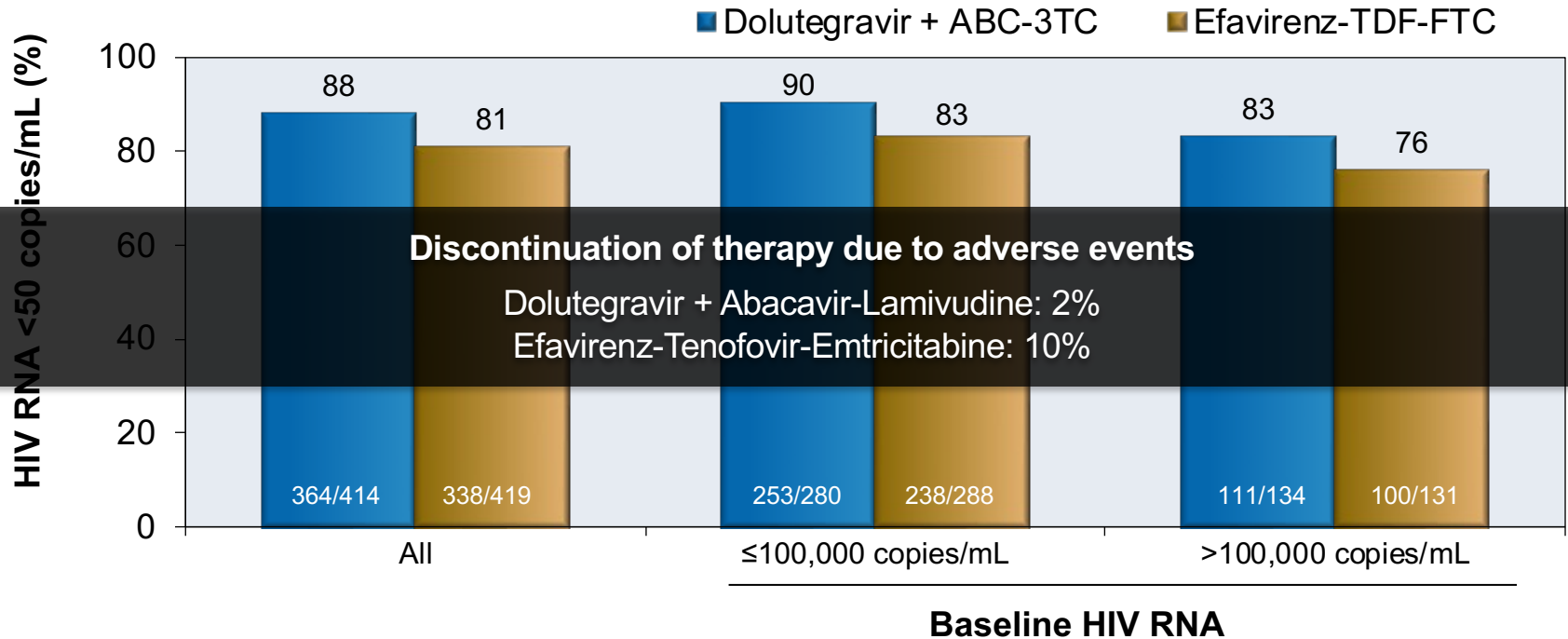
Week 48 Virologic Response (Intention-to-Treat Analysis)



Source: Walmsley SL, et al. N Engl J Med. 2013;369:1807-18.

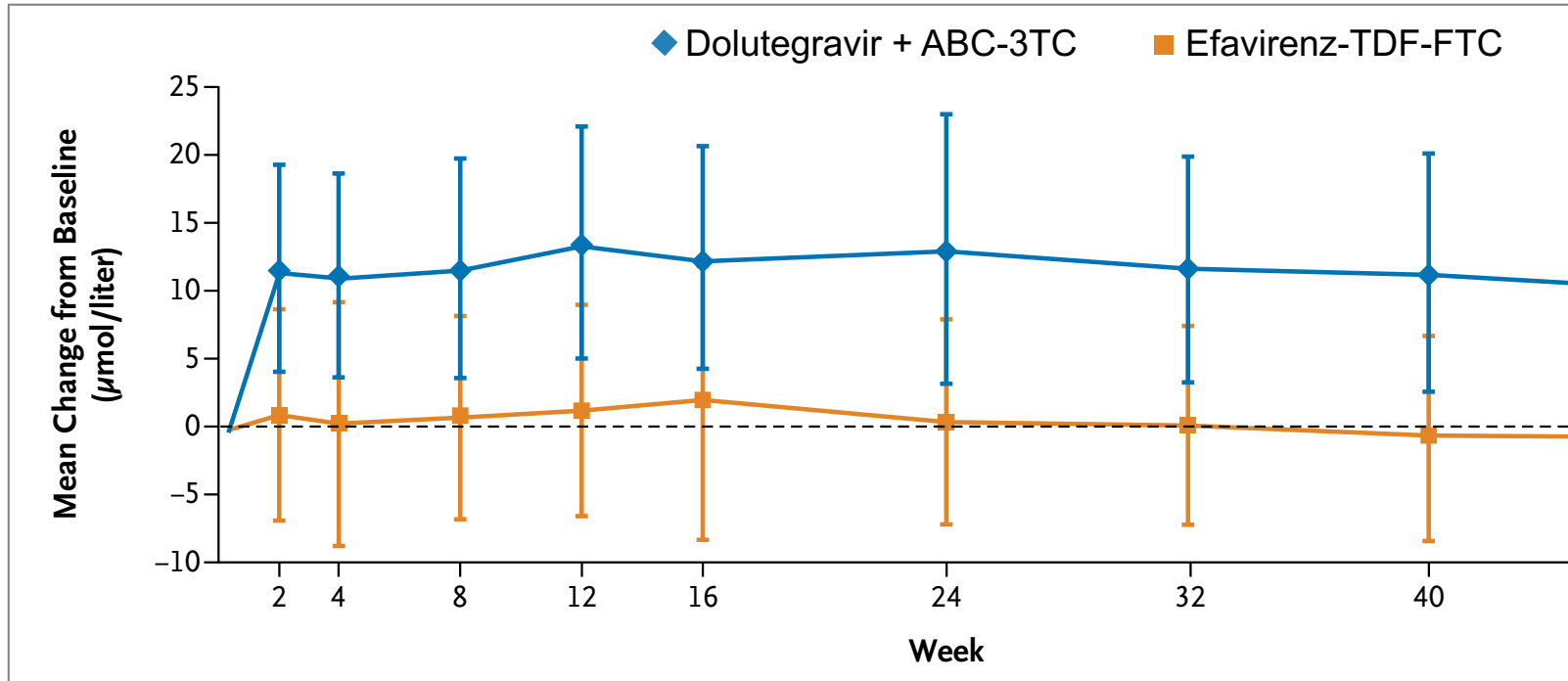
Dolutegravir + ABC-3TC versus Efavirenz-TDF-FTC SINGLE Study: Results

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



Dolutegravir + ABC-3TC versus Efavirenz-TDF-FTC SINGLE Study: Results

Mean Change from Baseline in Serum Creatinine Levels



Source: Walmsley SL, et al. N Engl J Med. 2013;369:1807-18.

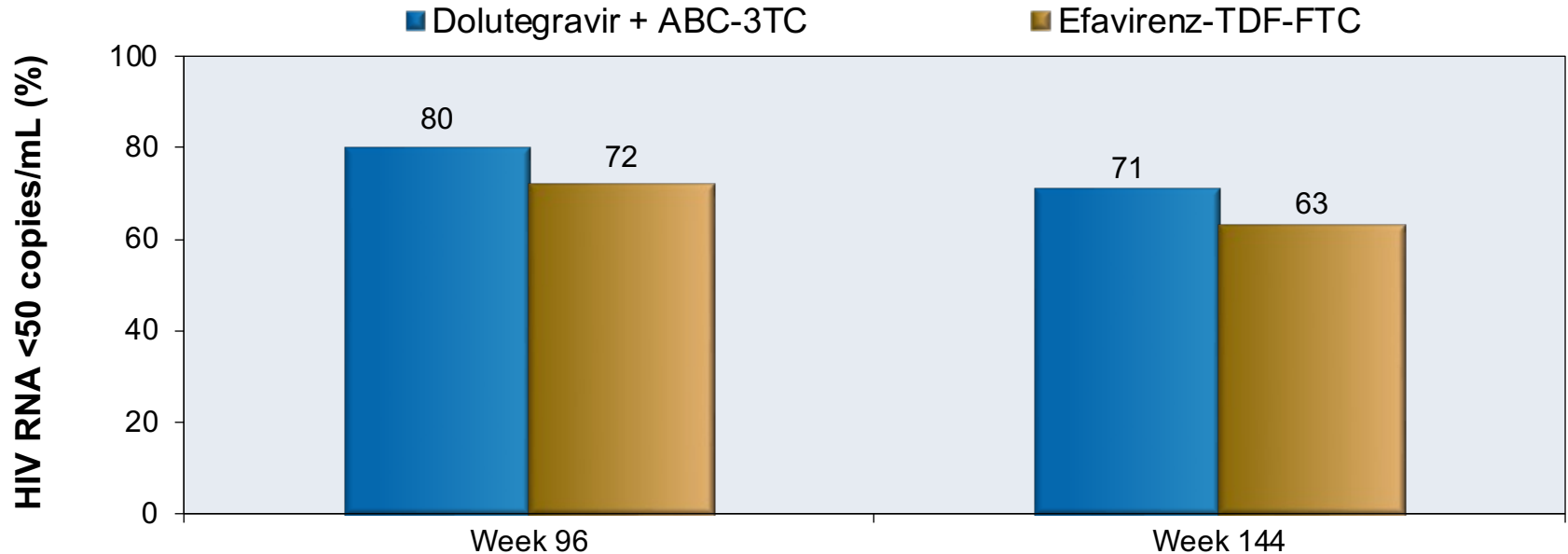
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Dolutegravir + ABC-3TC versus Efavirenz-TDF-FTC SINGLE Study: Conclusions

Conclusions: “Dolutegravir plus abacavir-lamivudine had a better safety profile and was more effective through 48 weeks than the regimen with efavirenz-tenofovir DF-emtricitabine.”

Dolutegravir + ABC-3TC versus Efavirenz-TDF-FTC SINGLE Study: Results

Week 96 and Week 144 Virologic Response (Intention-to-Treat Analysis)



Dolutegravir + ABC-3TC versus Efavirenz-TDF-FTC SINGLE Study: Results

Treatment-Emergent Adverse Events (AEs >5%)				
	DTG-ABC-3TC (n = 414)		EFV-TDF-FTC (n = 419)	
	Week 96	Week 144	Week 96	Week 144
Any, %	44	+1	67	+1.2
Dizziness, %	7	+0	33	+0.2
Abnormal dreams, %	7	+0	16	+0.2
Nausea, %	11	+0.2	12	+0
Insomnia, %	10	+0	6	+0.7
Diarrhea, %	6	+0	8	+0
Fatigue, %	7	+0	7	+0
Headache, %	6	+0	7	+0
Rash, %	<1	+0	8	+0

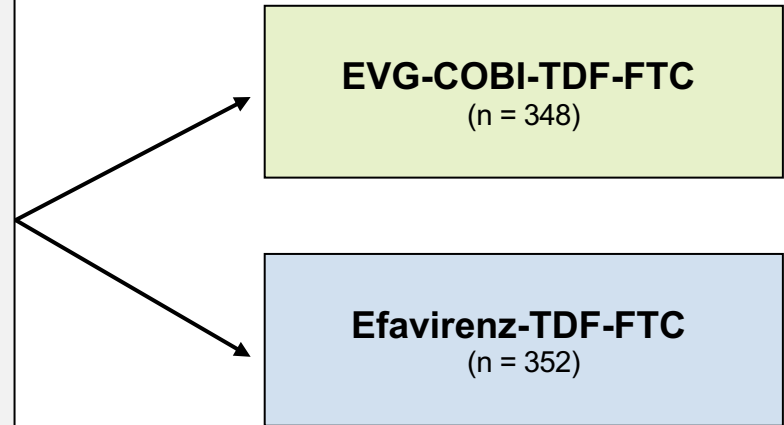
Source: Walmsley SL, et al. J Acquir Immune Defic Syndr. 2015;70:515-19.

Elvitegravir-Cobicistat-TDF-FTC versus Efavirenz-TDF-FTC
Study 102

Elvitegravir-Cobicistat-TDF-FTC versus Efavirenz-TDF-FTC

Study 102: Design

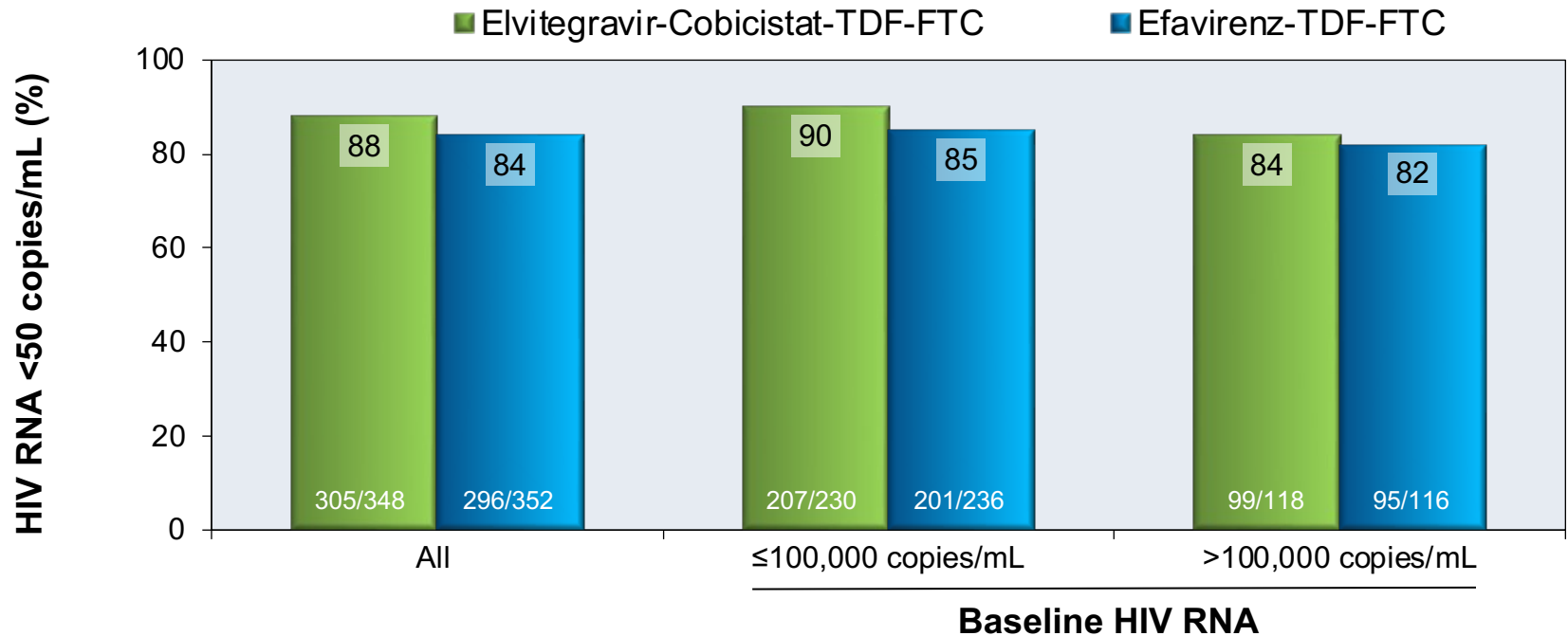
- **Background:** Randomized, double-blind, phase 3 trial comparing elvitegravir-cobicistat-tenofovir DF-emtricitabine with efavirenz-tenofovir DF-emtricitabine
- **Inclusion Criteria (n = 700)**
 - Antiretroviral-naïve adults
 - Age ≥18 years
 - HIV RNA ≥5,000 copies/mL
 - No AIDS conditions in previous 30 days
- **Treatment Arms**
 - Elvitegravir-Cobicistat-TDF-FTC
 - Efavirenz-TDF-FTC



Elvitegravir-Cobicistat-TDF-FTC versus Efavirenz-TDF-FTC

Study 102: Results

Week 48 Virologic Response



Elvitegravir-Cobicistat-TDF-FTC versus Efavirenz-TDF-FTC

Study 102: Common Adverse Events

Treatment-Emergent Adverse Events in $\geq 10\%$ of Subjects in Either Group		
	EVG-COBI-TDF-FTC (n = 348)	EFV-TDF-FTC (n = 352)
Diarrhea	23%	19%
Nausea*	21%	14%
Fatigue	11%	13%
Upper Respiratory Tract Infection	14%	11%
Dizziness [^]	7%	24%
Headache	14%	10%
Abnormal Dreams [^]	15%	27%
Insomnia [†]	9%	14%
Depression	9%	11%
Rash [§]	6%	12%

*p < 0.016; [^]p < 0.001; [†]p < 0.031; [§]p = 0.009

Source: Sax PE, et al. Lancet. 2012;379:2439-48.

Elvitegravir-Cobicistat-TDF-FTC versus Efavirenz-TDF-FTC Study 102: Conclusions

Interpretation: “This study met the primary endpoint of non-inferiority of elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/COBI/TDF/FTC) to efavirenz/emtricitabine/tenofovir (EFV/TDF/FTC) and demonstrates the robust antiviral efficacy of the only integrase inhibitor-based single tablet regimen for initial HIV treatment, irrespective of viral load.”

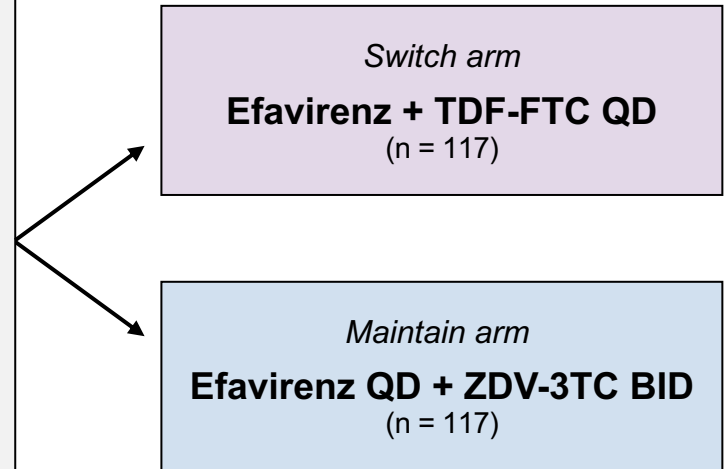
Efavirenz-Tenofovir DF-Emtricitabine
Switch Studies

Switch from Efavirenz + ZDV-3TC to Efavirenz + TDF-FTC
SWEET Trial

Switch to Efavirenz + TDF-FTC

SWEET: Study Design

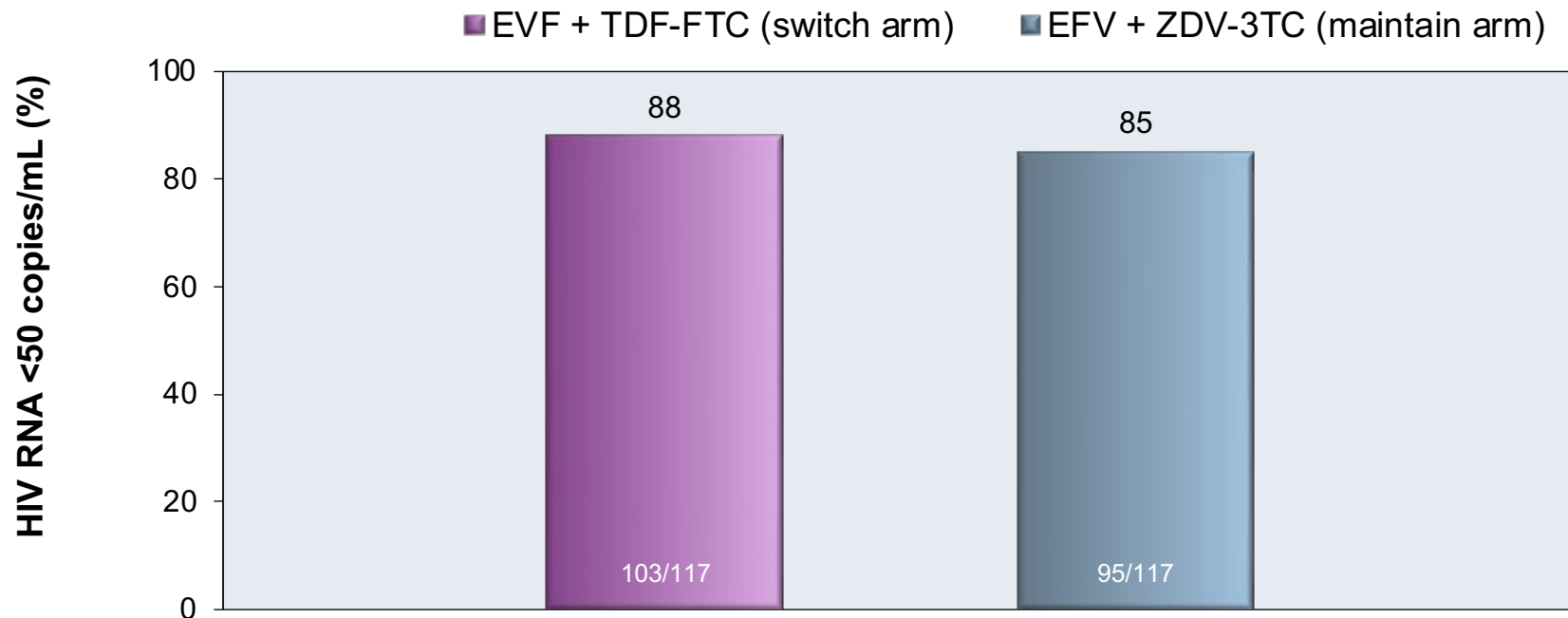
- **Background:** Randomized, controlled, open-label, phase 3 trial evaluating a simplification strategy for patients suppressed on efavirenz-based ART by switching from twice-daily zidovudine-lamivudine to once-daily tenofovir DF-emtricitabine in adults with HIV
- **Inclusion Criteria (n = 234)**
 - Age ≥ 18 years
 - On EFV + ZDV-3TC for >6 months
 - No resistance to study drugs
 - HIV RNA <400 copies/mL for ≥ 3 months and HIV RNA <50 copies/mL on 2 occasions
- **Treatment Arms**
 - Efavirenz + TDF-FTC
 - Efavirenz + ZDV-3TC



Switch to Efavirenz + TDF-FTC

SWEET: Results

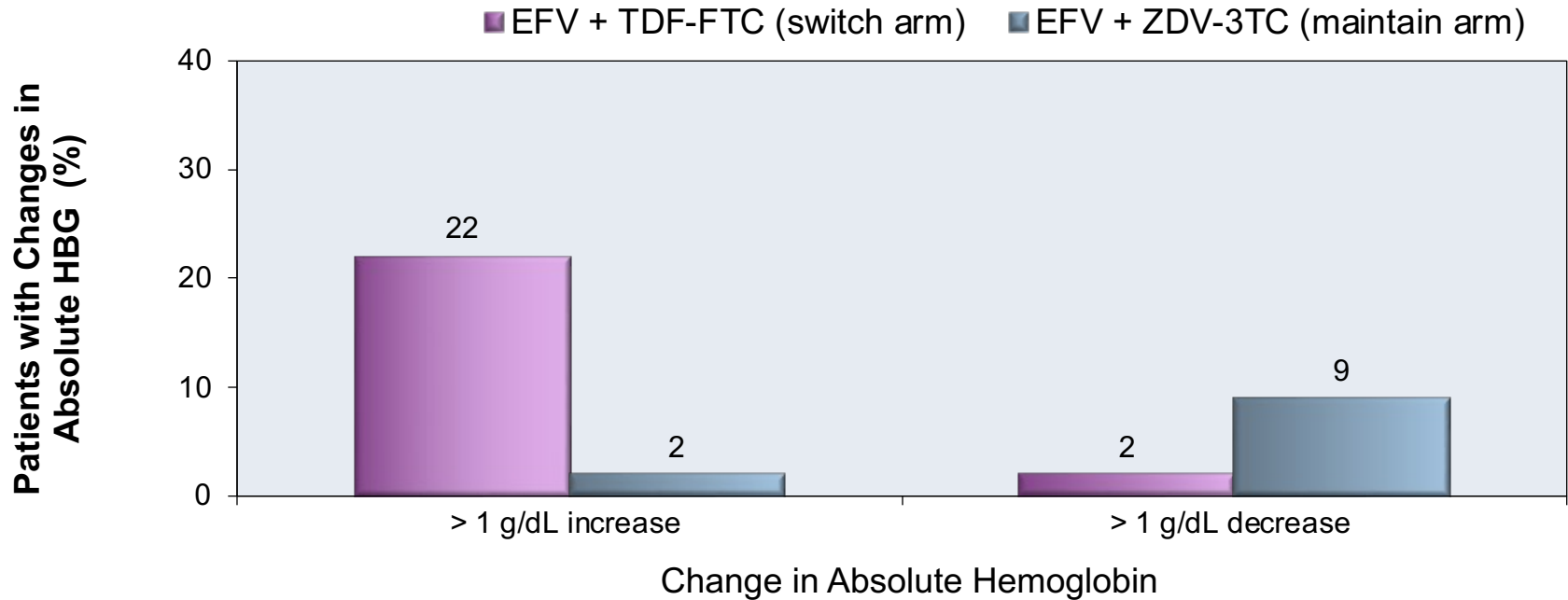
Week 48 Virologic Response (Intention-to-Treat Analysis, Missing=Failure)



Switch to Efavirenz + TDF-FTC

SWEET: Results

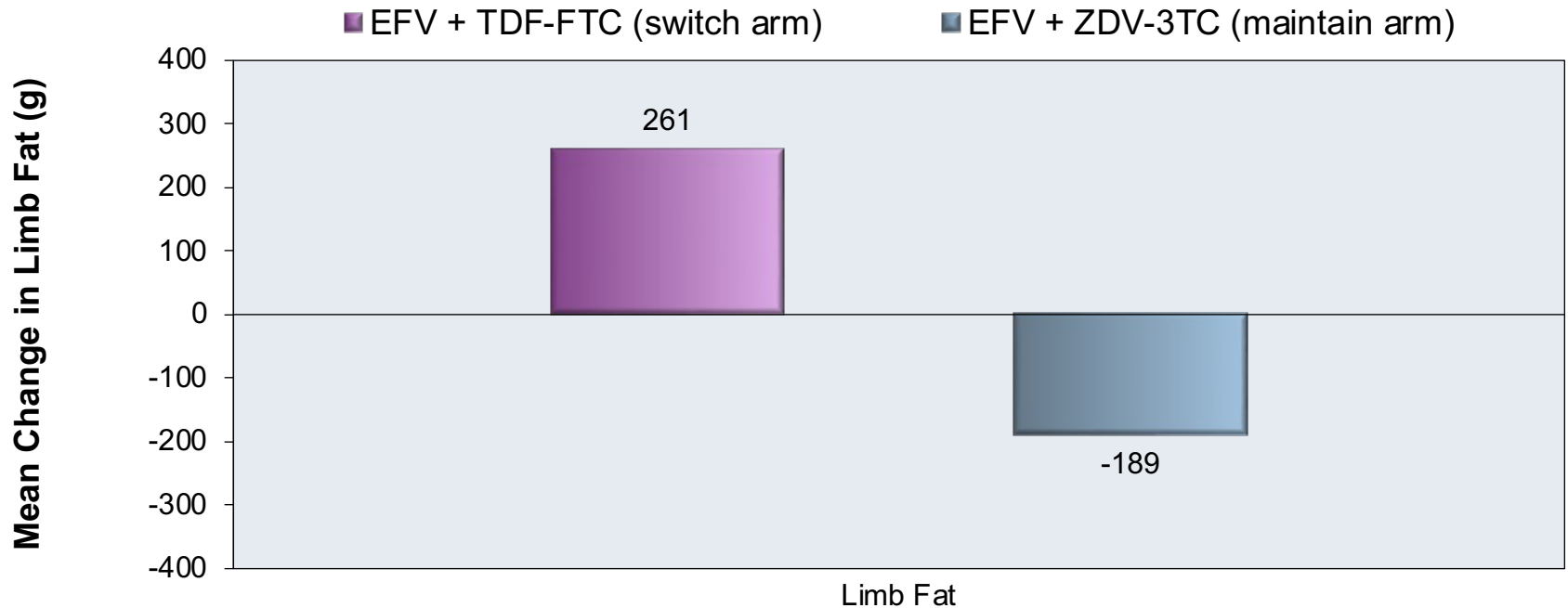
Week 48: Patients with Change in Absolute Hemoglobin from Baseline



Switch to Efavirenz + TDF-FTC

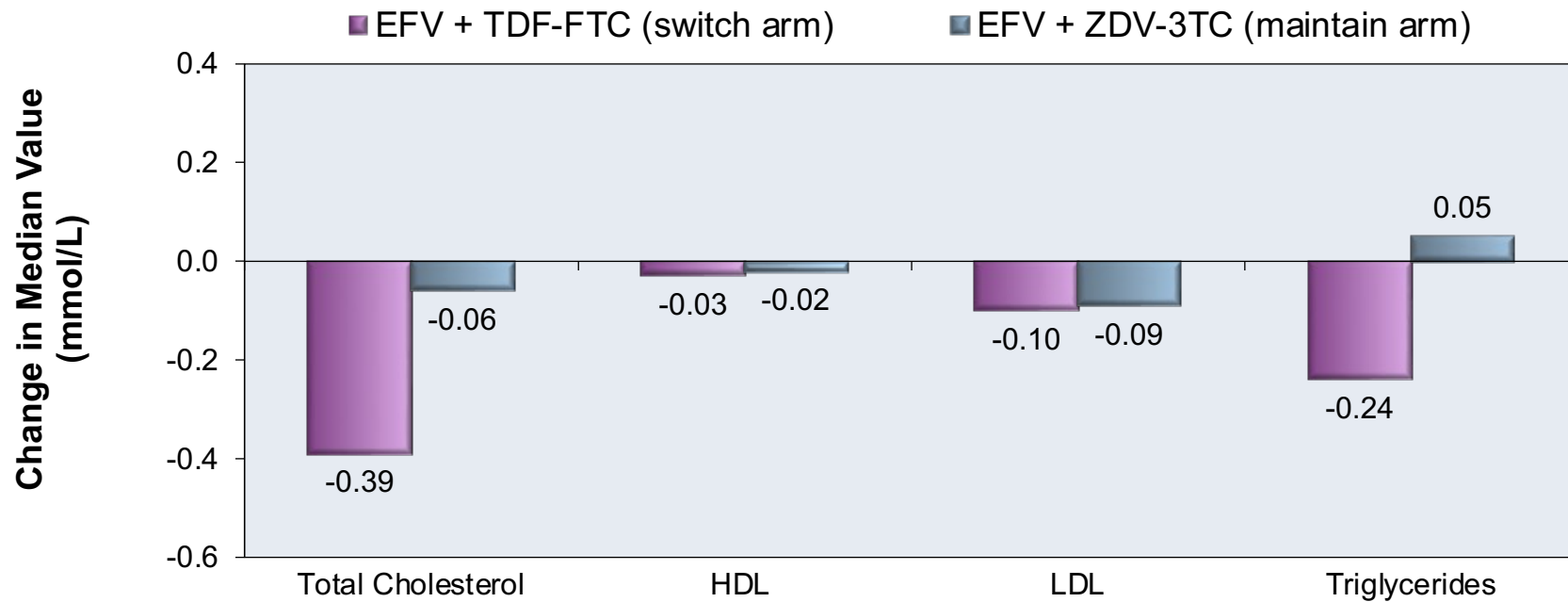
SWEET: Results

Week 24: Change in Limb Fat from Baseline



Switch to Efavirenz + TDF-FTC SWEET: Results

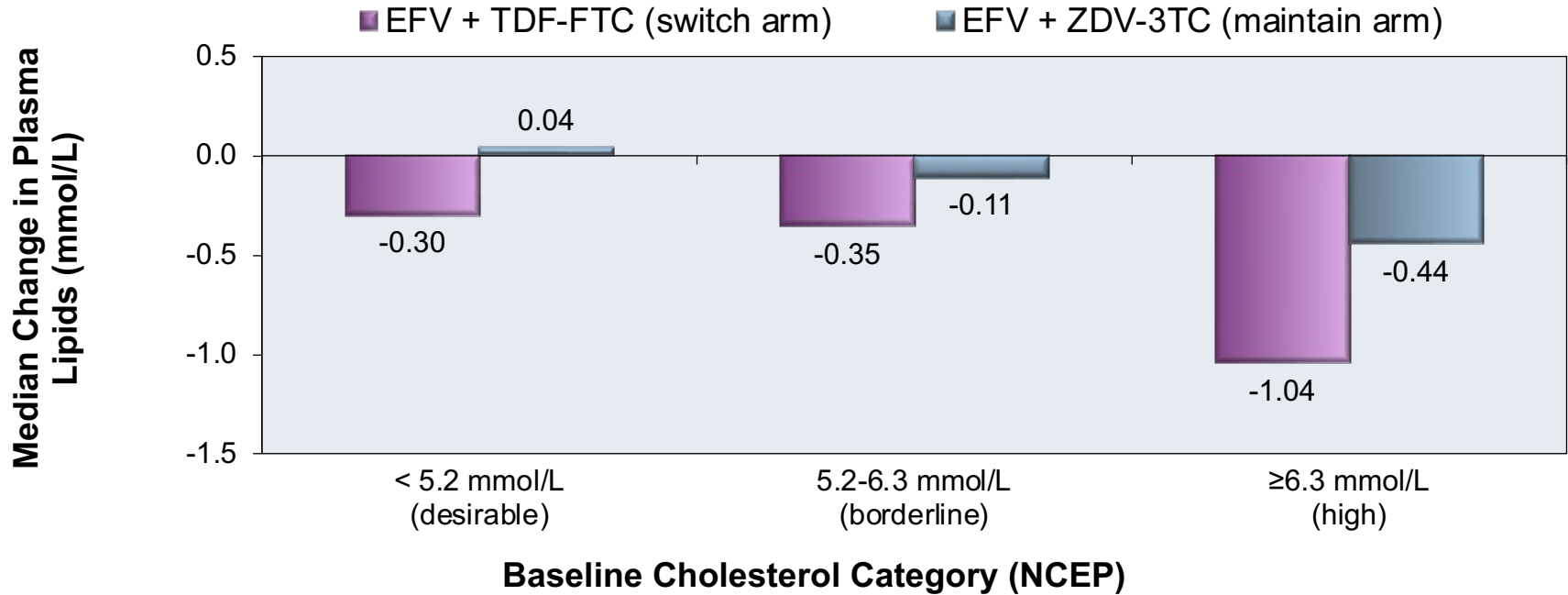
Week 24: Change in Plasma Lipids from Baseline



Switch to Efavirenz + TDF-FTC

SWEET: Results

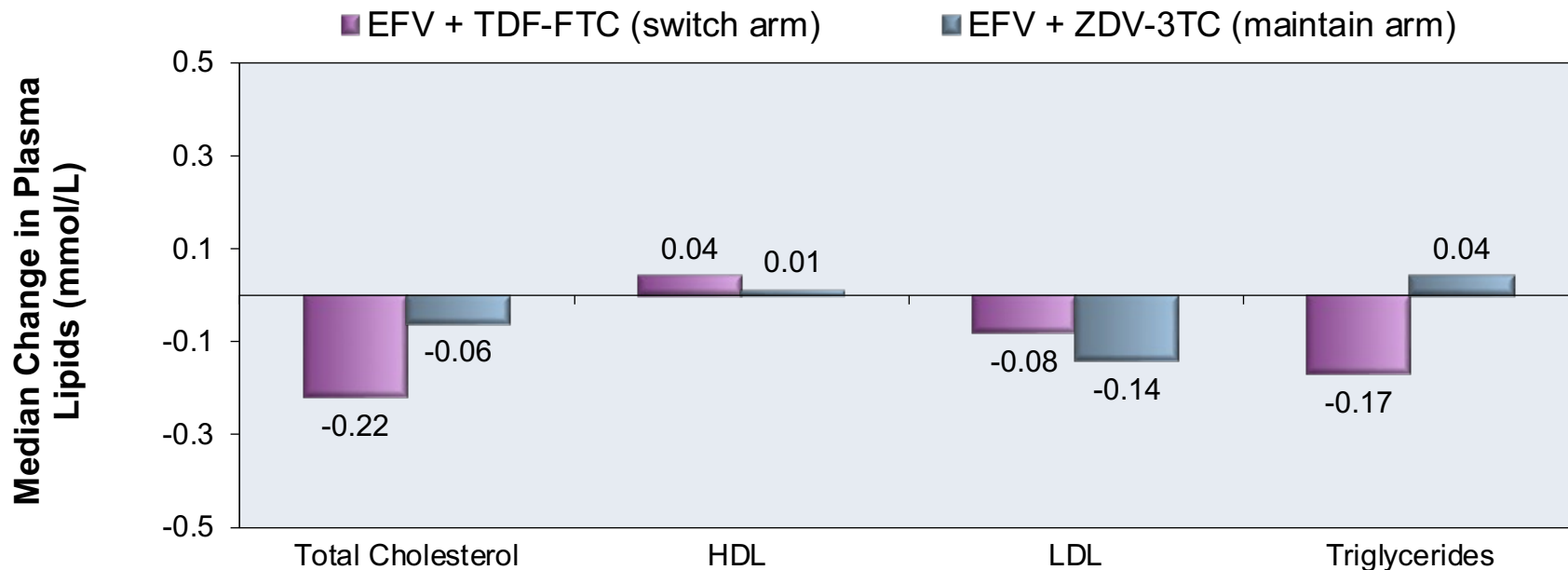
Week 24: Change in Plasma Lipids, by Baseline Cholesterol



Switch to Efavirenz + TDF-FTC

SWEET: Results

Week 48: Change in Plasma Lipids from Baseline



Switch to Efavirenz + TDF-FTC

SWEET: Results

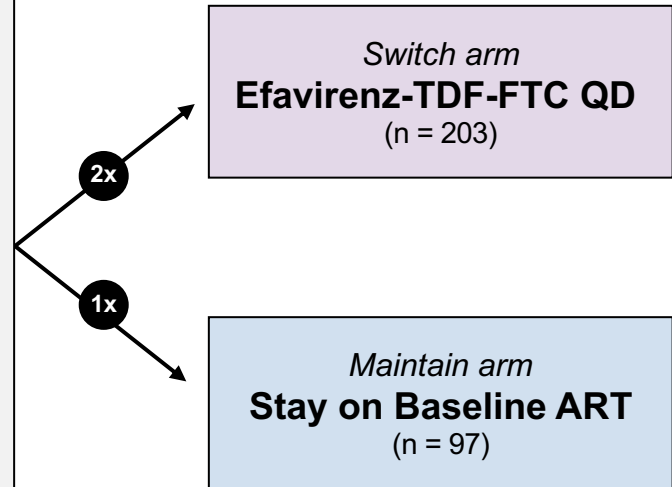
Interpretation: “Switching from zidovudine/lamivudine to tenofovir disoproxil fumarate/emtricitabine in persons on efavirenz therapy maintains virological control, establishes a once-daily regimen, results in improvements in hemoglobin and key lipid parameters, and preserves and restores limb fat relative to continuation of zidovudine/lamivudine.”

Simplification to Efavirenz-TDF-FTC
STUDY 073

Simplification to Efavirenz-TDF-FTC

Study 073: Study Design

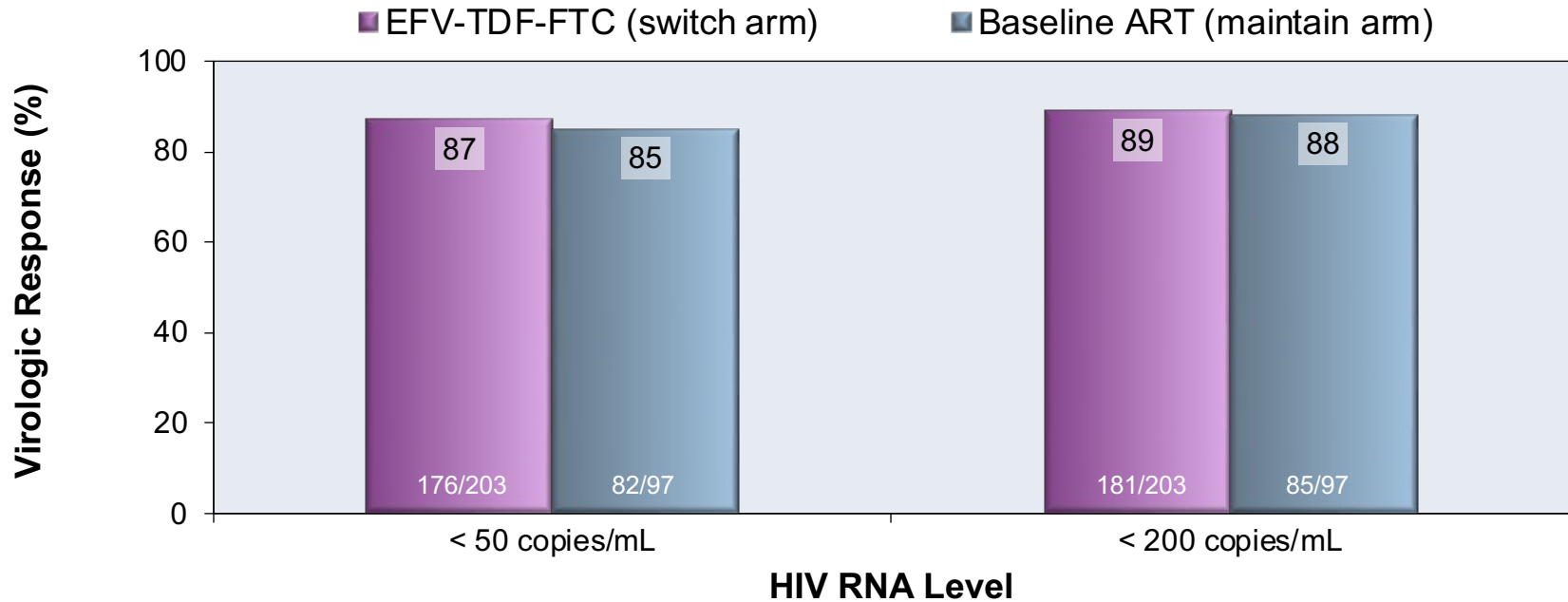
- **Background:** Randomized, controlled, open-label, phase 3 trial evaluating a simplification strategy for patients suppressed on baseline ART by switching to a single-tablet regimen of efavirenz-tenofovir DF-emtricitabine once daily
- **Inclusion Criteria (n = 300)**
 - Age ≥ 18 years
 - HIV RNA ≤ 200 copies/mL for ≥ 3 months
 - No new AIDS-defining conditions in past 30 days
 - On 1st ART regimen or viral suppression on previous protease inhibitor-based therapy at time of prior therapy switch
- **Treatment Arms**
 - Switch arm: Efavirenz-tenofovir DF-emtricitabine
 - Stay arm: maintain baseline ART



Simplification to Efavirenz-TDF-FTC

Study 073: Results

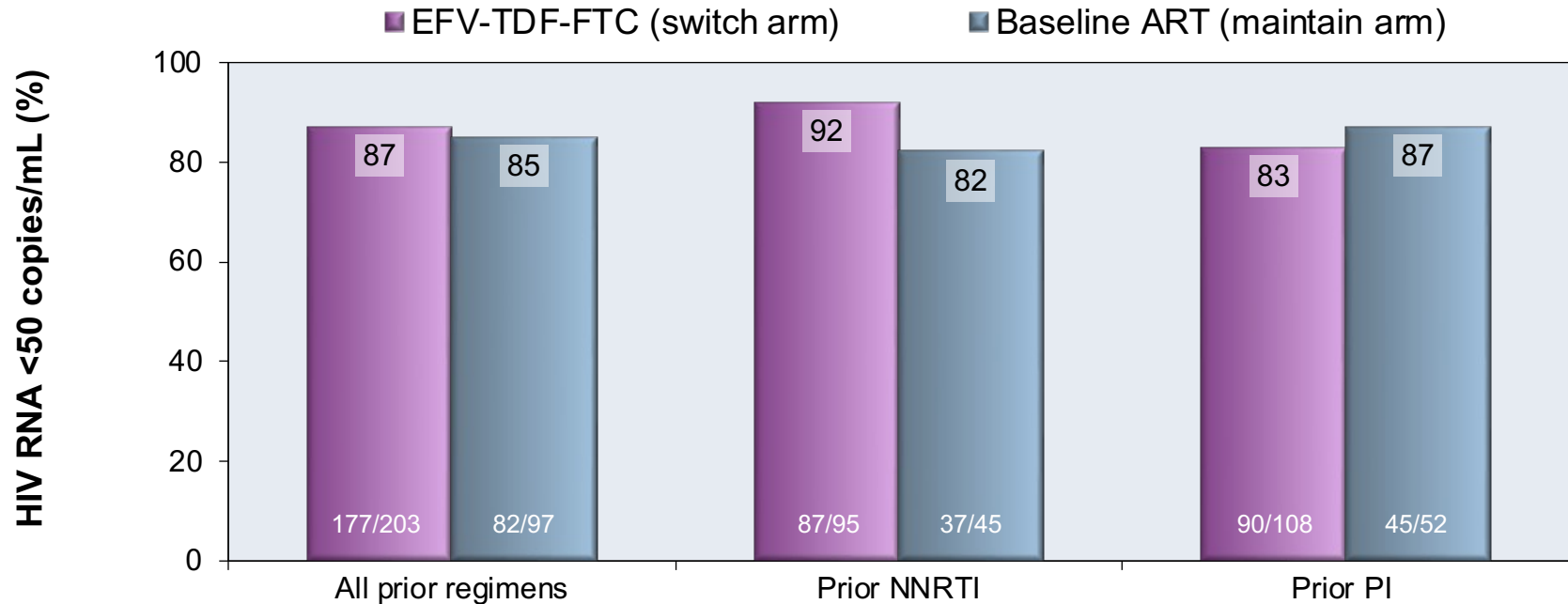
Week 48 Virologic Response by RNA Threshold



Simplification to Efavirenz-TDF-FTC

Study 073: Subgroup Analysis Result

Week 48 Virologic Response, by Baseline Regimen (Intent-to-Treat, Noncompletion = Failure)



Simplification to Efavirenz-TDF-FTC

Study 073: Conclusions

Interpretation: “Simplification to EFV/FTC/TDF maintained high and comparable rates of virologic suppression versus stay on baseline regimen (SBR) through 48 weeks.”

Acknowledgments

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