National HIV Curriculum

Rilpivirine-Tenofovir DF-Emtricitabine (*Complera*)

David H. Spach, MD
Brian R. Wood, MD

Last Updated: December 12, 2022

Rilpivirine-Emtricitabine-Tenofovir DF (*Complera)*

Rilpivirine-Tenofovir DF-Emtricitabine

25 mg → NNRTI

300 mg → NRTI

200 mg → NRTI

Dose: 1 tablet once daily with food

Image Source: AIDS Info.org

Rilpivirine-Tenofovir DF-Emtricitabine (*Complera*)

- ***Complera* Components**:
  - Rilpivirine 25 mg
  - Tenofovir disoproxil fumarate (DF) 300 mg
  - Emtricitabine 200 mg
- **Dosing**:
  - 1 tablet once daily with food
- **Common Adverse Events (≥2%)**
  - Depression, insomnia, headache

Source: Food and Drug Administration. Edurant (package insert). 2012

Rilpivirine-Tenofovir DF-Emtricitabine
Summary of Key Phase 3 Studies

- **Trials in in Treatment-Naïve Adults**
  - ECHO: RPV + TDF-FTC versus EFV + TDF-FTC
  - THRIVE: RPV + 2NRTIs versus EFV + 2NRTIs
  - STaR: RPV-TDF-FTC versus EFV-TDF-FTC
- **Switch Trials in Adults with Virologic Suppression**
  - SPIRIT: Switch to RPV-TDF-FTC from ritonavir-boosted PI + 2NRTIs
  - Near-Rwanda: Switch to RPV-TDF-FTC from NVP-based regimen

Abbreviations: RPV = rilpivirine; TDF-FTC = tenofovir DF-emtricitabine; EFV = efavirenz; NRTIs = nucleoside reverse transcriptase inhibitors; EFV-TDF-FTC = efavirenz-tenofovir DF-emtricitabine; RPV-TDF-FTC = rilpivirine-tenofovir DF-emtricitabine; PI = protease inhibitor; NVP = nevirapine

Rilpivirine-Tenofovir DF-Emtricitabine

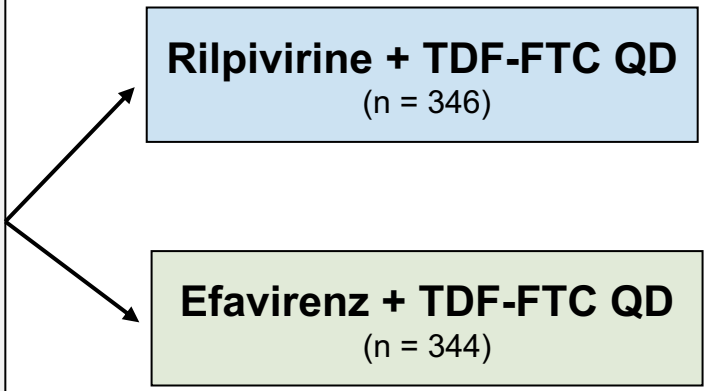
Trials in Treatment Treatment-Naïve Adults

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO Trial

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

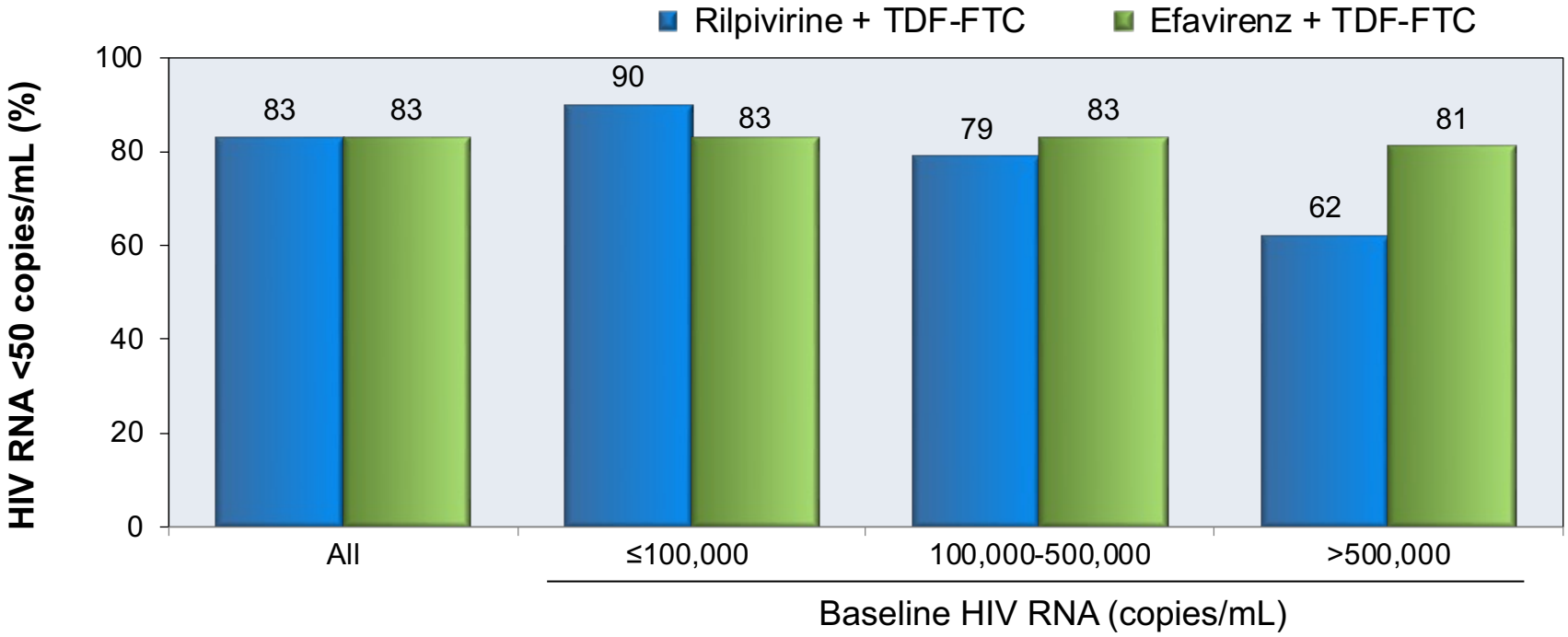
- **Background**: Randomized, double-blind, phase 3 trial comparing rilpivirine and efavirenz in combination with a fixed background regimen consisting of tenofovir DF-emtricitabine in treatment-naïve adults with HIV
- **Inclusion Criteria (n = 690)**
  - Antiretroviral-naïve adults
  - Age ≥18 years
  - HIV RNA ≥5,000 copies/mL
  - No resistance to any study drugs
- **Treatment Arms**
  - Rilpivirine + Tenofovir DF-Emtricitabine
  - Efavirenz + Tenofovir DF-Emtricitabine



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

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

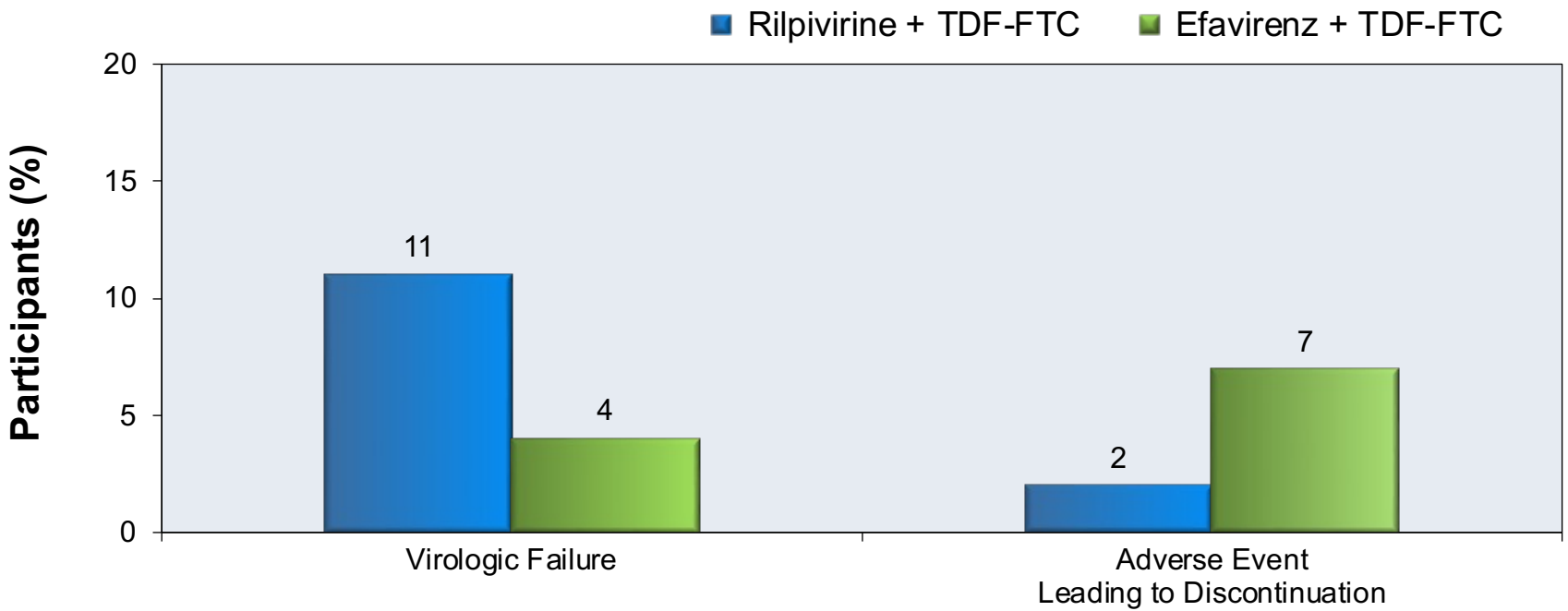
48 Week Virologic Response (Intention-to-Treat)



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

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

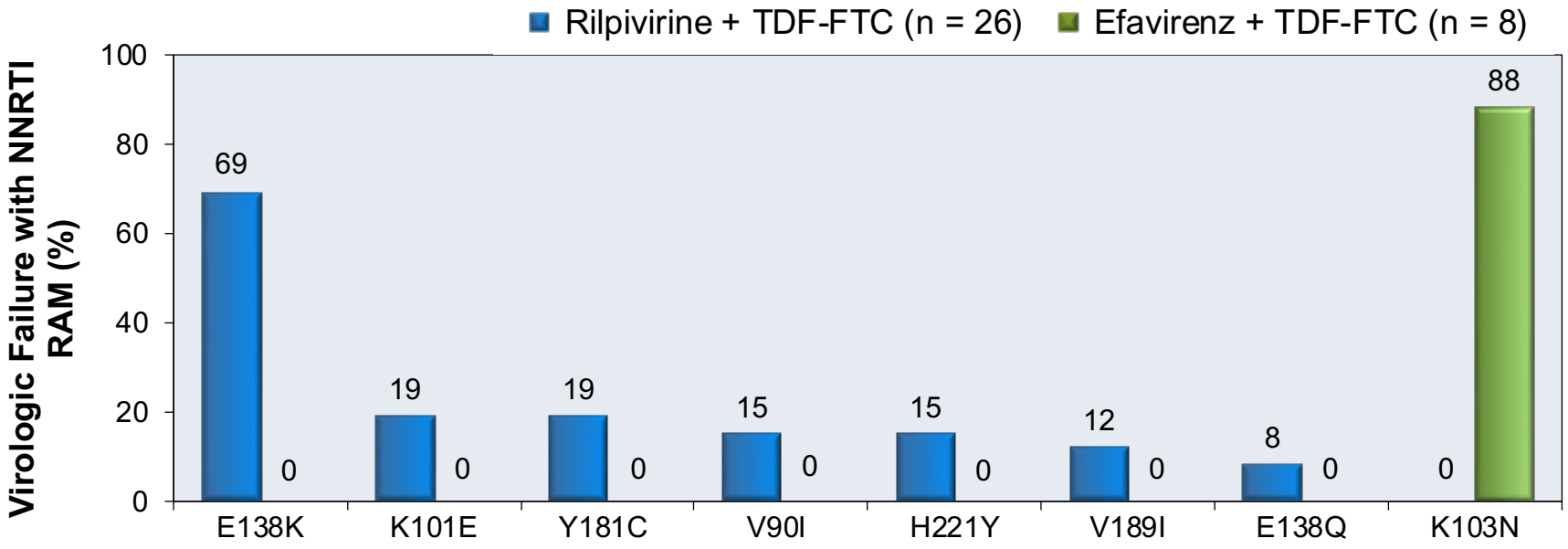
48 Week Virologic Failure and Discontinuations (Intention-to-Treat)



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)

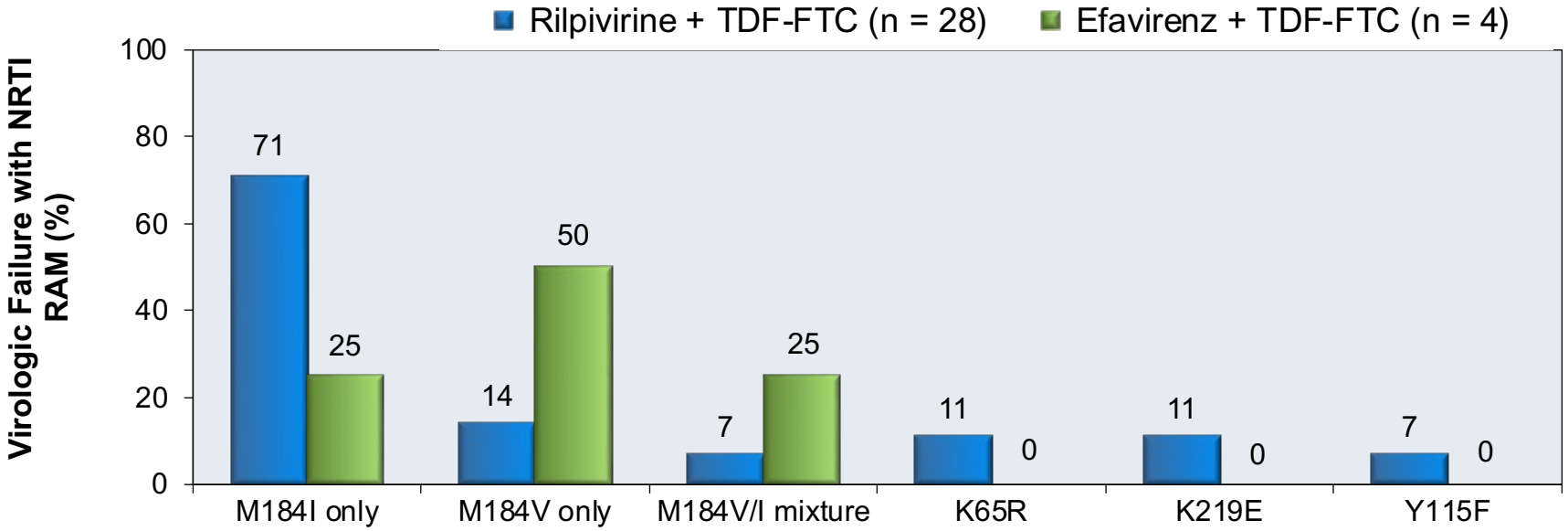


The percentages represent the number of participants who developed each specific NNRTI RAM out of the number of participants who developed any NNRTI RAM in that arm of the trial (the n listed at the top of the graph).

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

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).

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.”

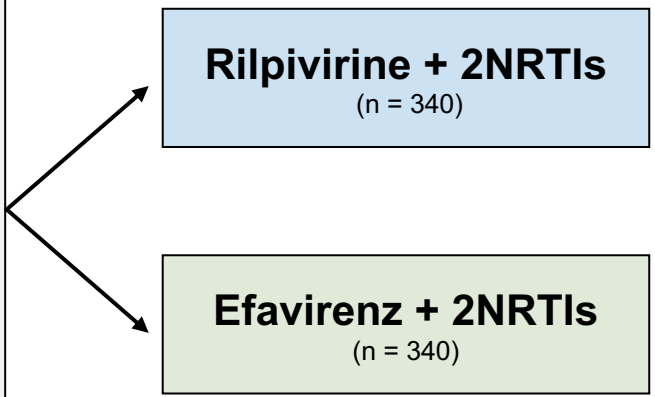
Source: Molina J-M, et al. Lancet. 2011;378:238-46.

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

THRIVE Trial

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

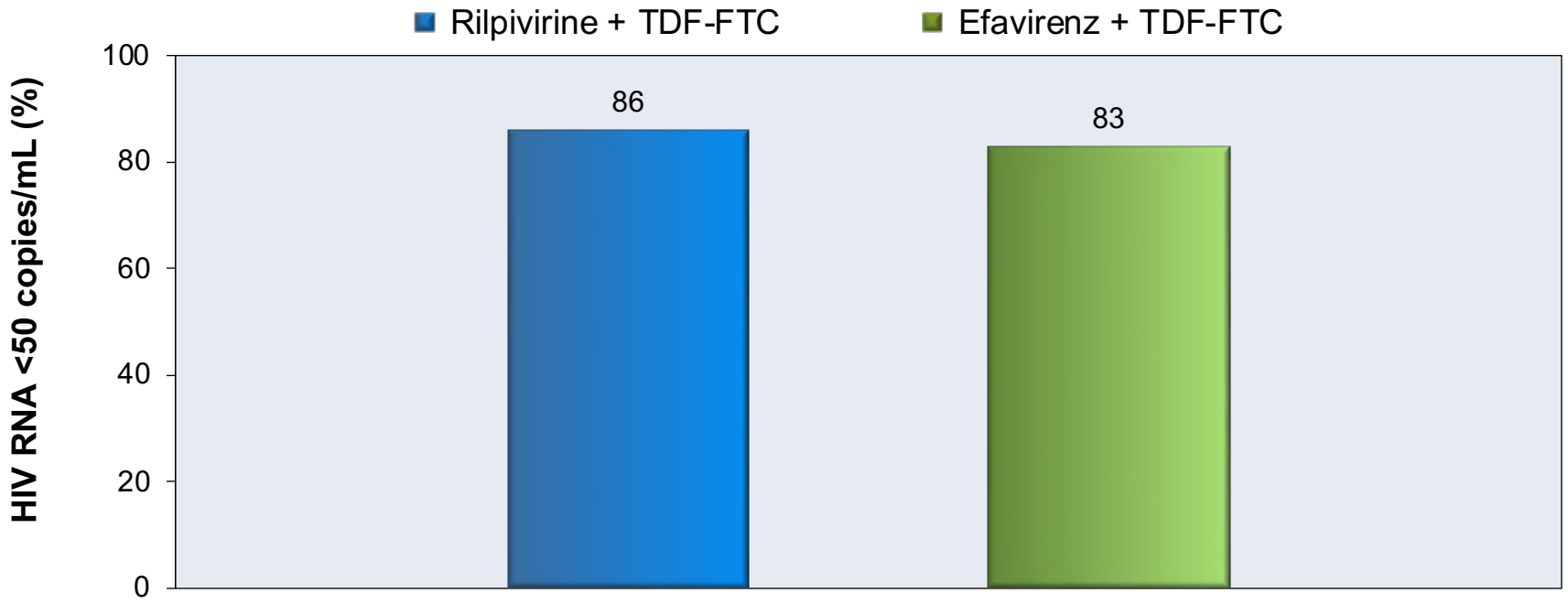
- **Background**: Randomized, double-blind, phase 3 trial comparing rilpivirine and efavirenz in combination with a fixed background regimen consisting of tenofovir DF-emtricitabine in treatment-naïve adult with HIV
- **Inclusion Criteria (n = 690)**
  - Antiretroviral-naïve adults
  - Age ≥18 years
  - HIV RNA ≥5,000 copies/mL
  - No resistance to any study drugs
- **Treatment Arms**
  - Rilpivirine + 2NRTIs
  - Efavirenz + 2NRTIs



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

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
THRIVE: Results

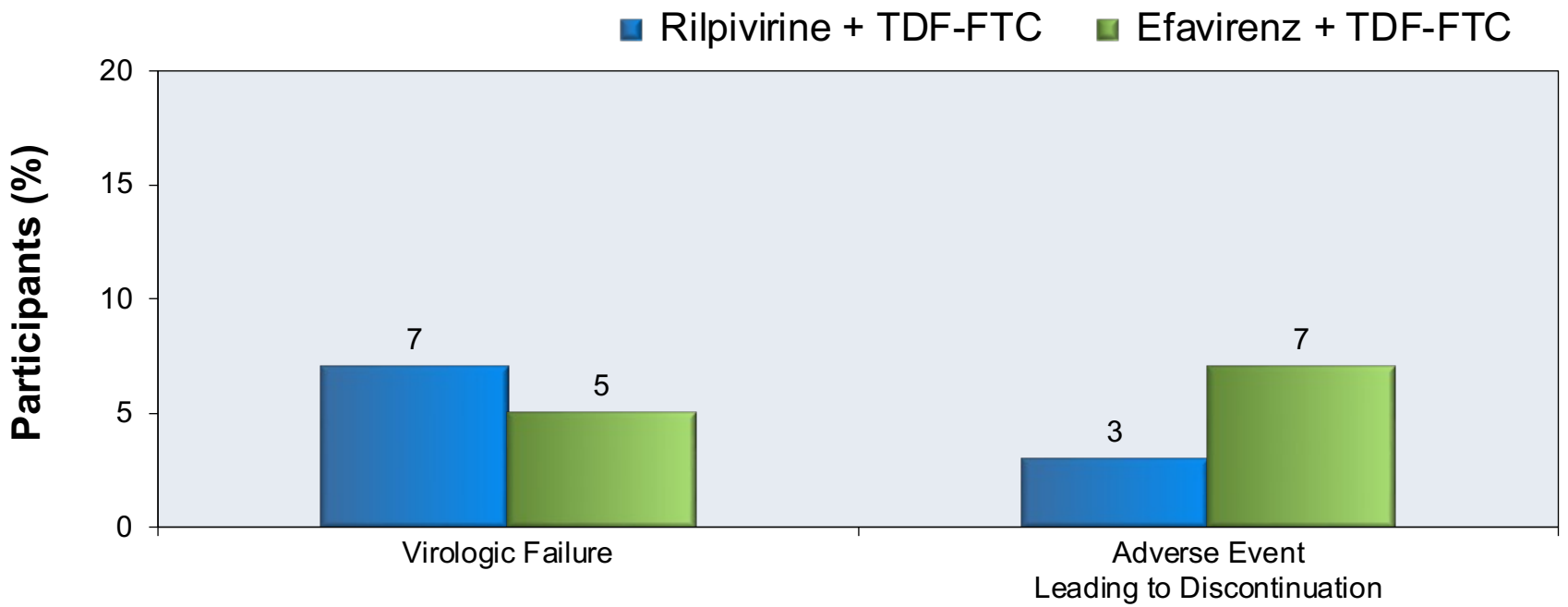
48 Week Virologic Response



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

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
THRIVE: Results

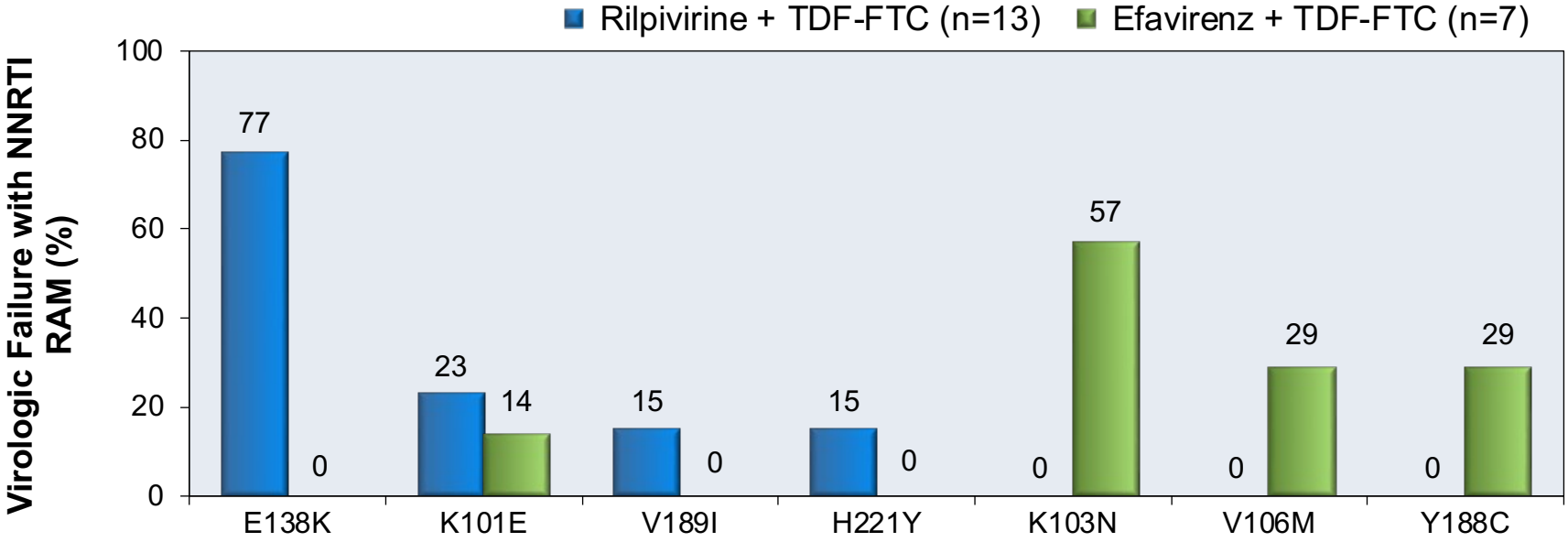
48 Week Virologic Failure and Discontinuations



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

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

Incidence of NNRTI Resistance Associated Mutations (RAMs)

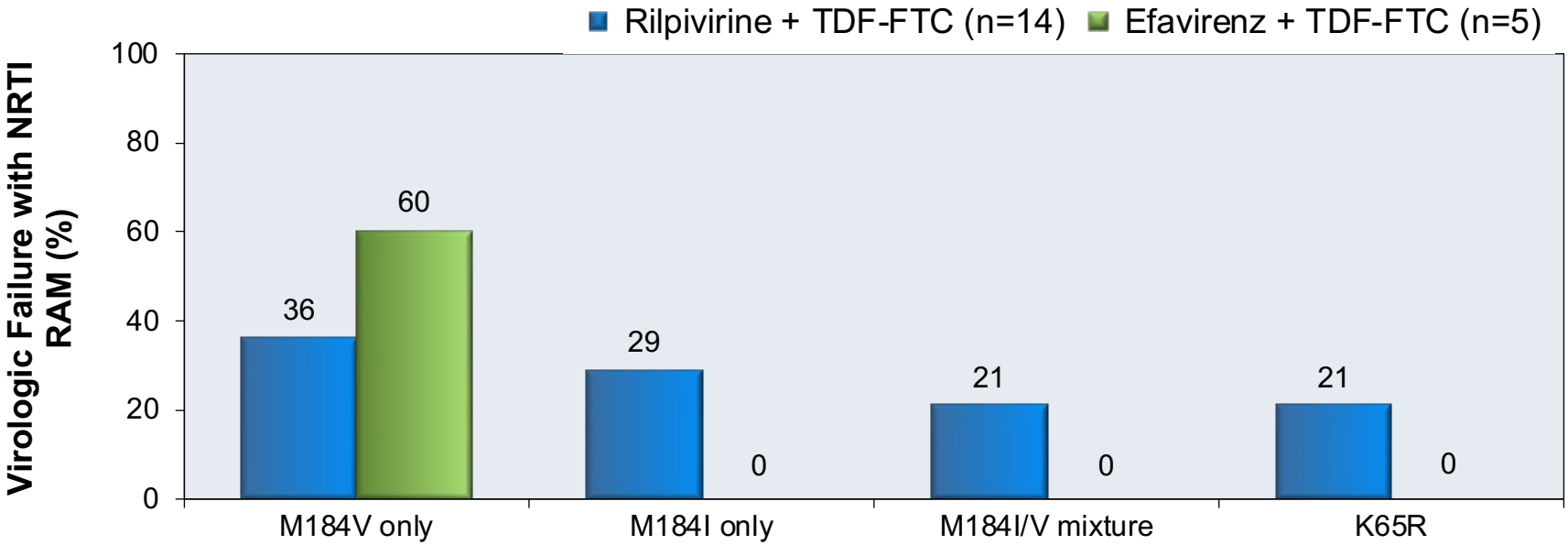


The percentages represent the number of participants who developed each specific NNRTI RAM out of the number of participants who developed any NNRTI RAM in that arm of the trial (the n listed at the top of the graph).

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

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
THRIVE: 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).

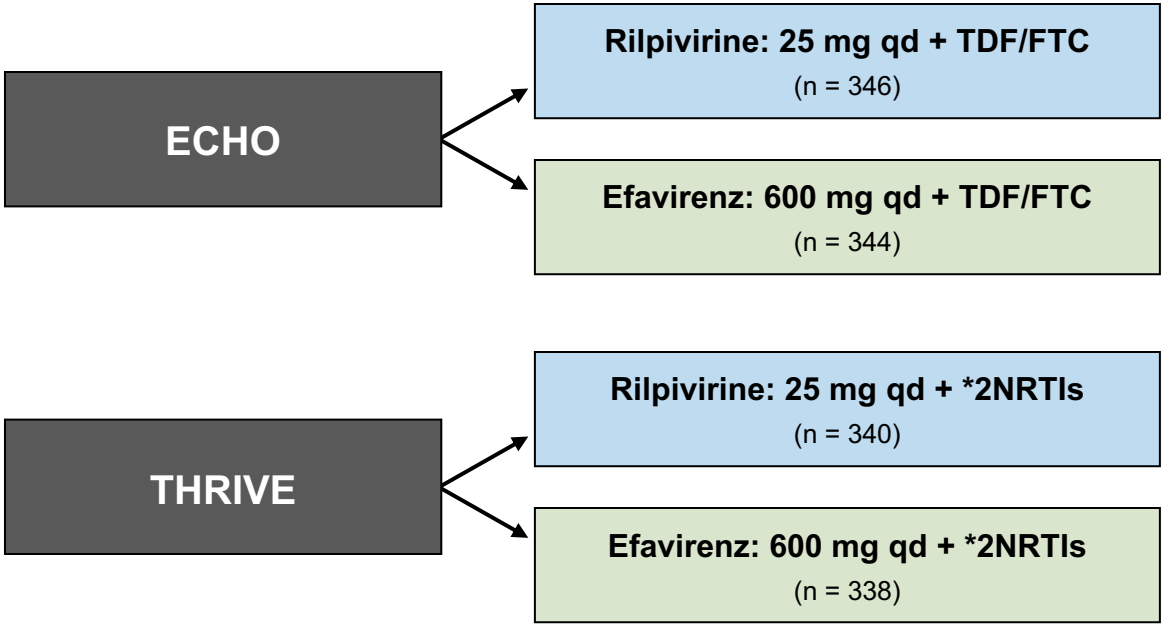
Source: Cohen CJ, et al. Lancet. 2011;378:229-37.

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
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.

Rilpivirine vs. Efavirenz in ARV-Naive ECHO and THRIVE Pooled Data: Study Design

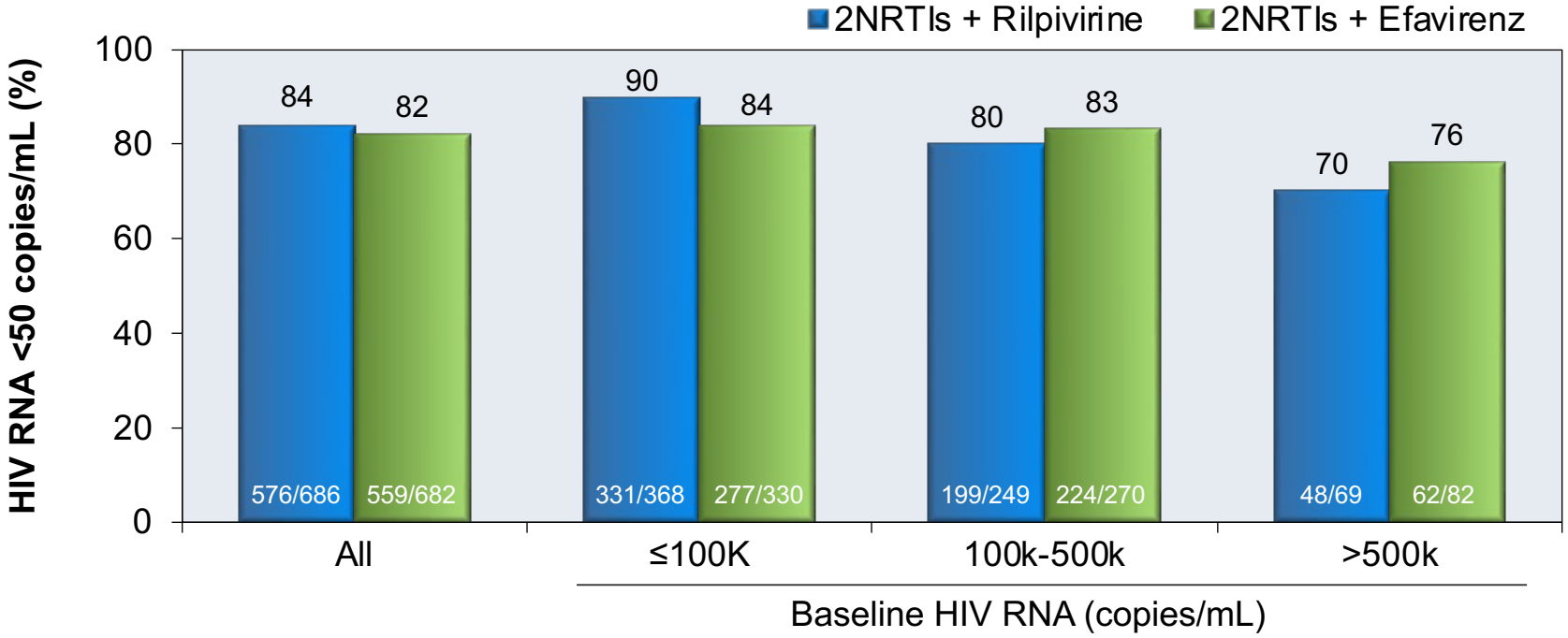


***2 NRTIs:** Tenofovir + Emtricitabine; Zidovudine + Lamivudine; Abacavir + Lamivudine

Source: Cohen CJ, et al. J Acquir Immune Defic Syndr. 2012:60:33-42.

Rilpivirine vs. Efavirenz in ARV-Naïve ECHO and THRIVE Pooled Data: Week 48 Results

Week 48 Virologic Response Stratified by Baseline HIV RNA

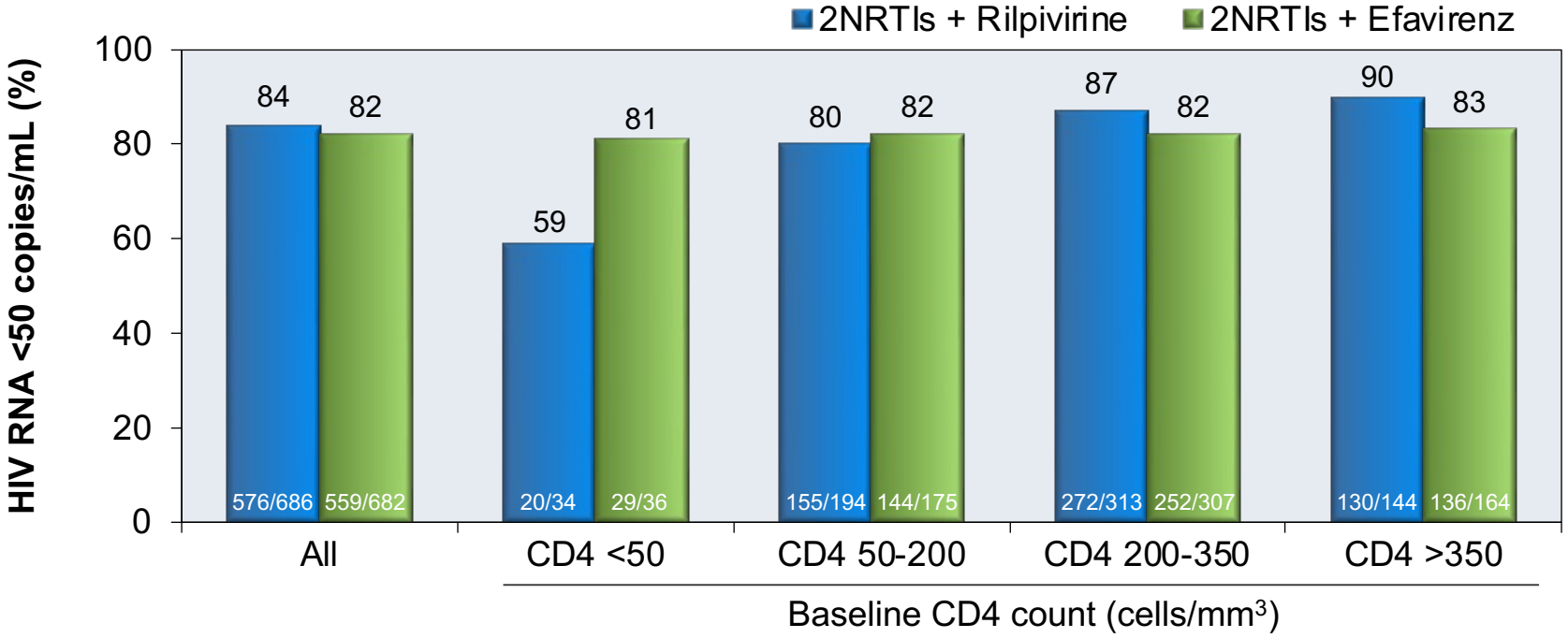


Source: Cohen CJ, et al. J Acquir Immune Defic Syndr. 2012:60:33-42.

National HIV Curriculum

Rilpivirine vs. Efavirenz in ARV-Naïve ECHO and THRIVE Pooled Data: Week 48 Results

Week 48 Virologic Response Stratified by Baseline CD4 Count



Source: Cohen CJ, et al. J Acquir Immune Defic Syndr. 2012:60:33-42.

Rilpivirine vs. Efavirenz in ARV-Naive ECHO and THRIVE Pooled Data: Week 48 Results

Treatment-Emergent Adverse Events (AEs)		
	Rilpivirine (n = 686)	Efavirenz (n = 682)
Treatment-related AE ≥grade 2, n (%)	109 (16)	212 (31)
AE leading to permanent discontinuation, n (%)	23 (3)	52 (8)
Any neurologic AE, n (%)	117 (17)	258 (38)
Any psychiatric AE, n (%)	102 (15)	155 (23)
Rash, n (%)	21 (3)	93 (14)

Source: Cohen CJ, et al. J Acquir Immune Defic Syndr. 2012:60:33-42.

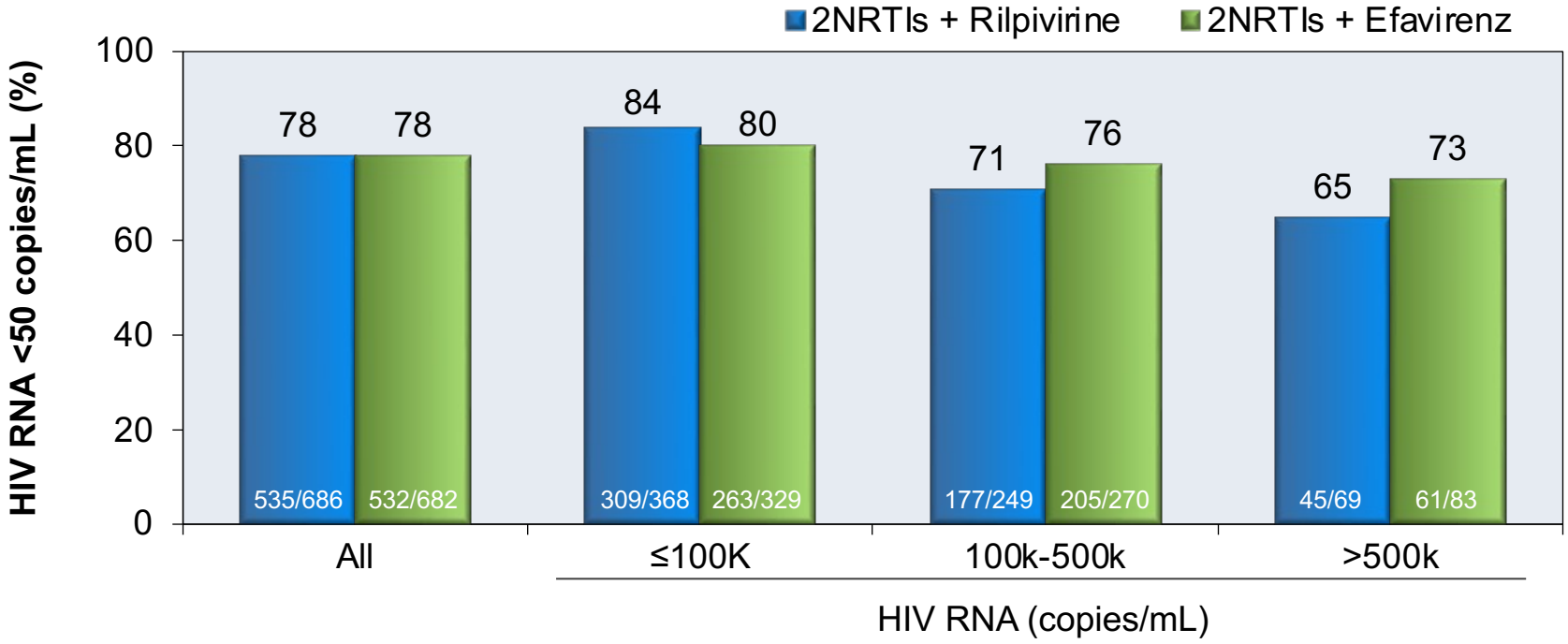
Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO & THRIVE Week 48 Pooled Data: Conclusions

Interpretation: “At week 48, rilpivirine 25 mg once daily and efavirenz 600 mg once daily had comparable response rates. Rilpivirine had more virologic failures and improved tolerability versus efavirenz.”

Source: Cohen CJ, et al. J Acquir Immune Defic Syndr. 2012:60:33-42.

Rilpivirine vs. Efavirenz in ARV-Naïve ECHO and THRIVE Pooled Data: Week 96 Results

Week 96 Virologic Response Stratified by Baseline HIV RNA

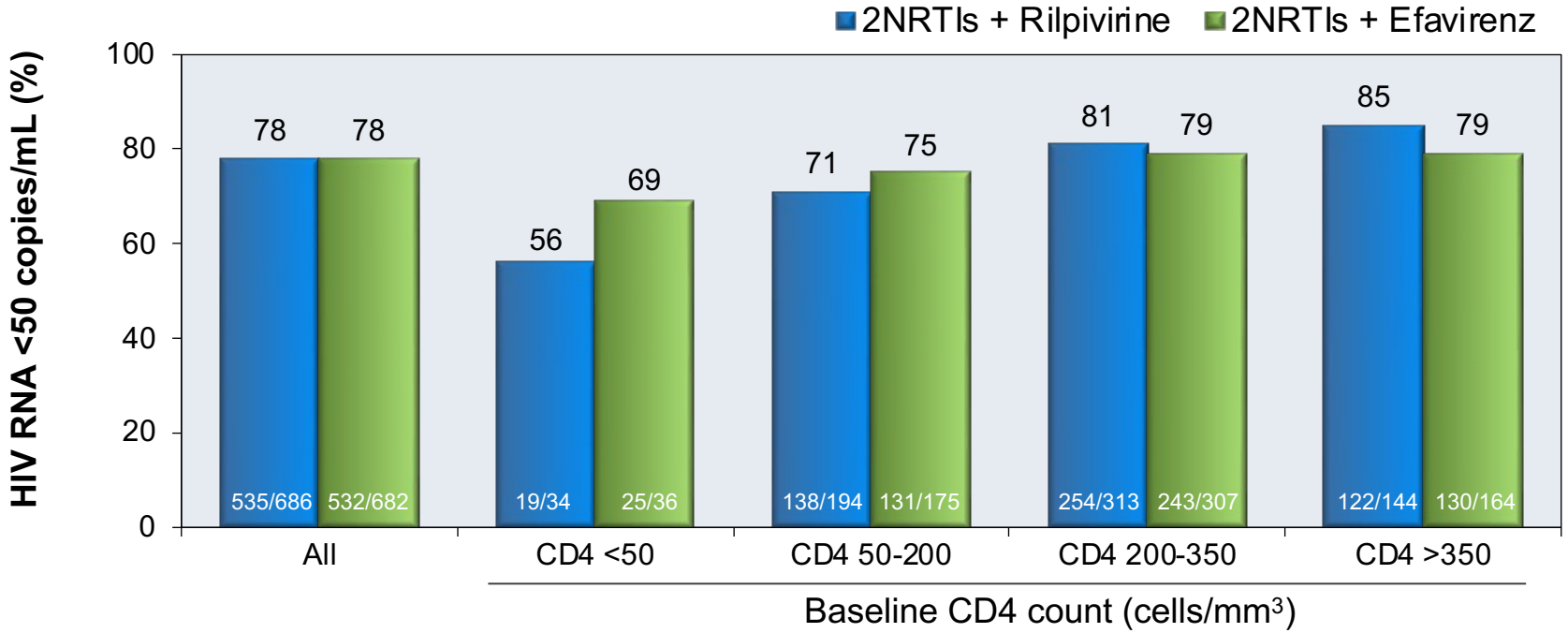


Source: Cohen CJ, et al. AIDS. 2013;27:939-50.

National HIV Curriculum

Rilpivirine vs. Efavirenz in ARV-Naïve ECHO and THRIVE Pooled Data: Week 96 Results

Week 96 Virologic Response Stratified by Baseline CD4 count



Source: Cohen CJ, et al. AIDS. 2013;27:939-50.

National HIV Curriculum

Rilpivirine vs. Efavirenz in ARV-Naive ECHO and THRIVE Pooled Data: Week 96 Results

Virologic Failure & Resistant Associated Mutations (RAMs)		
	Rilpivirine (n = 686)	Efavirenz (n = 682)
Virologic failure, n (%)	96 (14)	52 (8)
Any emergent NNRTI RAM, n (%)	51 (59)	23 (55)
Most frequent emergent NNRTI RAM	E138K	K103N
Any emergent NRTI RAM, n (%)	48 (56)	11 (26)
Most Frequent NRTI RAMs	M184I	M184V

NOTE: A majority of virologic failure instances occurred within the first 48 weeks in both arms.

Source: Cohen CJ, et al. AIDS. 2013;27:939-50.

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO & THRIVE Week 96 Pooled Data: Conclusions

Interpretation: “Rilpivirine 25 mg q.d. and efavirenz 600 mg q.d. had comparable responses at week 96. Rilpivirine had more virologic failures but improved tolerability versus efavirenz. The majority of virologic failures occurred in the first 48 weeks.”

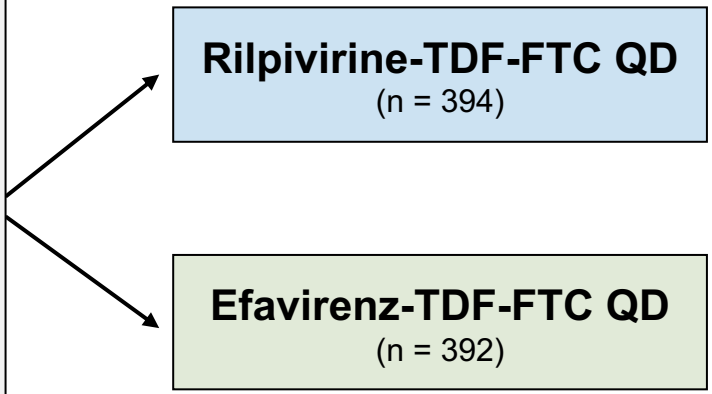
Source: Cohen CJ, et al. AIDS. 2013;27:939-50.

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

STaR Trial

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC STaR Study: Design

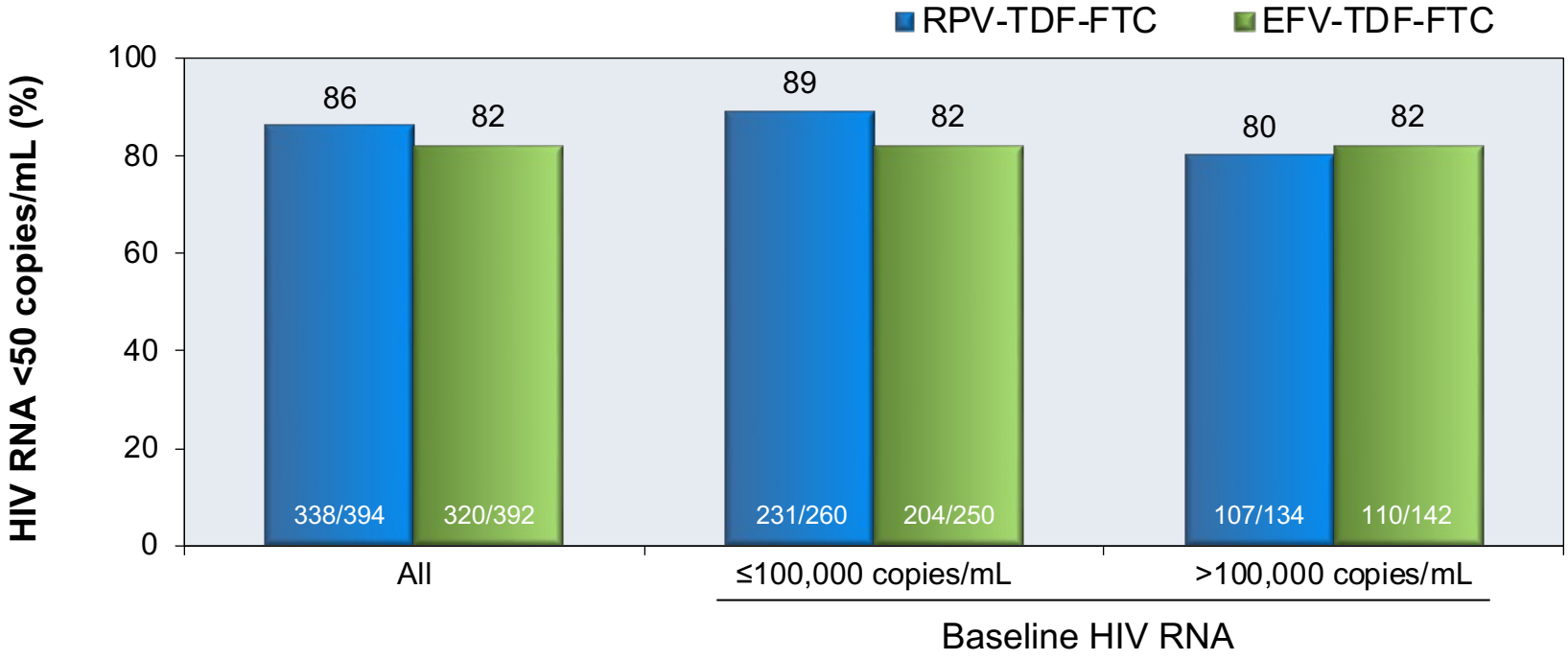
- **Background**: Randomized, open-label, phase 3b trial comparing safety and efficacy of two single-tablet regimens, RPV-TDF-FTC and EFV-TDF-FTC, in treatment-naïve adults with HIV
- **Inclusion Criteria (n = 786)**
  - Antiretroviral-naïve adults
  - Age ≥18 years
  - HIV RNA ≥2,500 copies/mL
  - No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



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

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

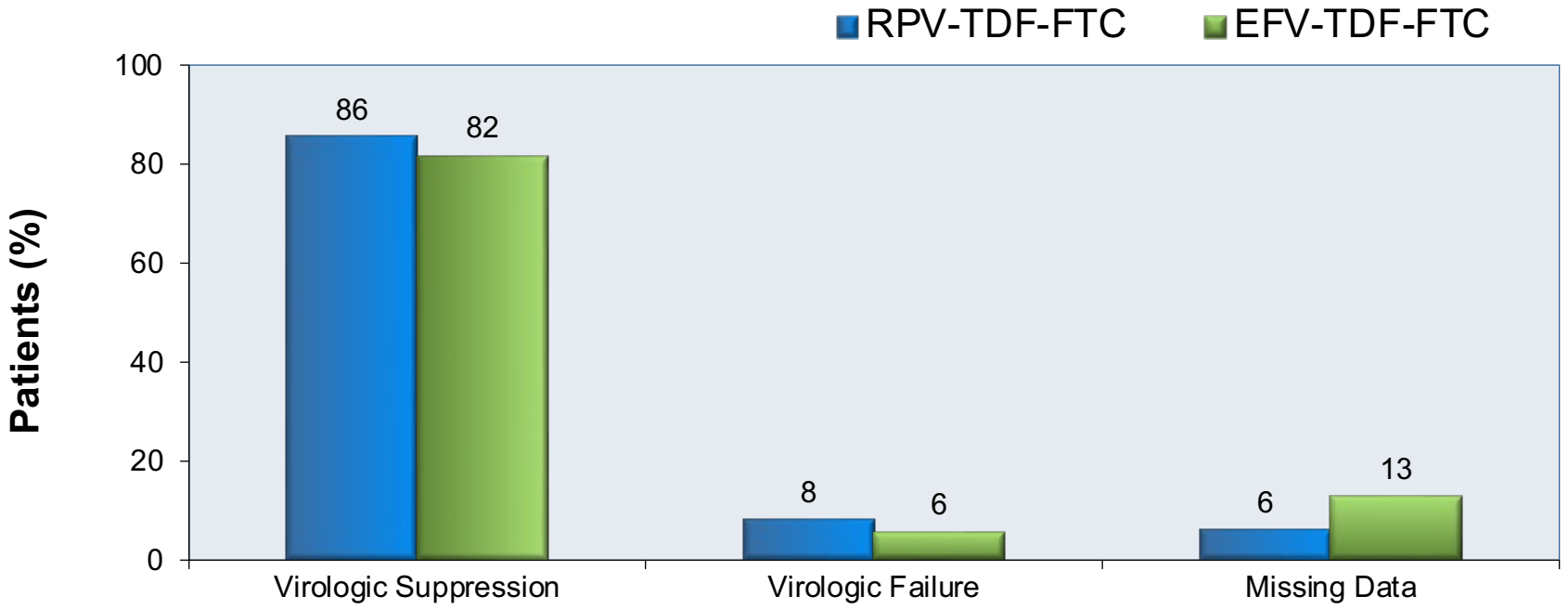
Week 48 Virologic Response (Intent-to-Treat Analysis)



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

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC
STaR: Results

48 Week Virologic Outcomes



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

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.”

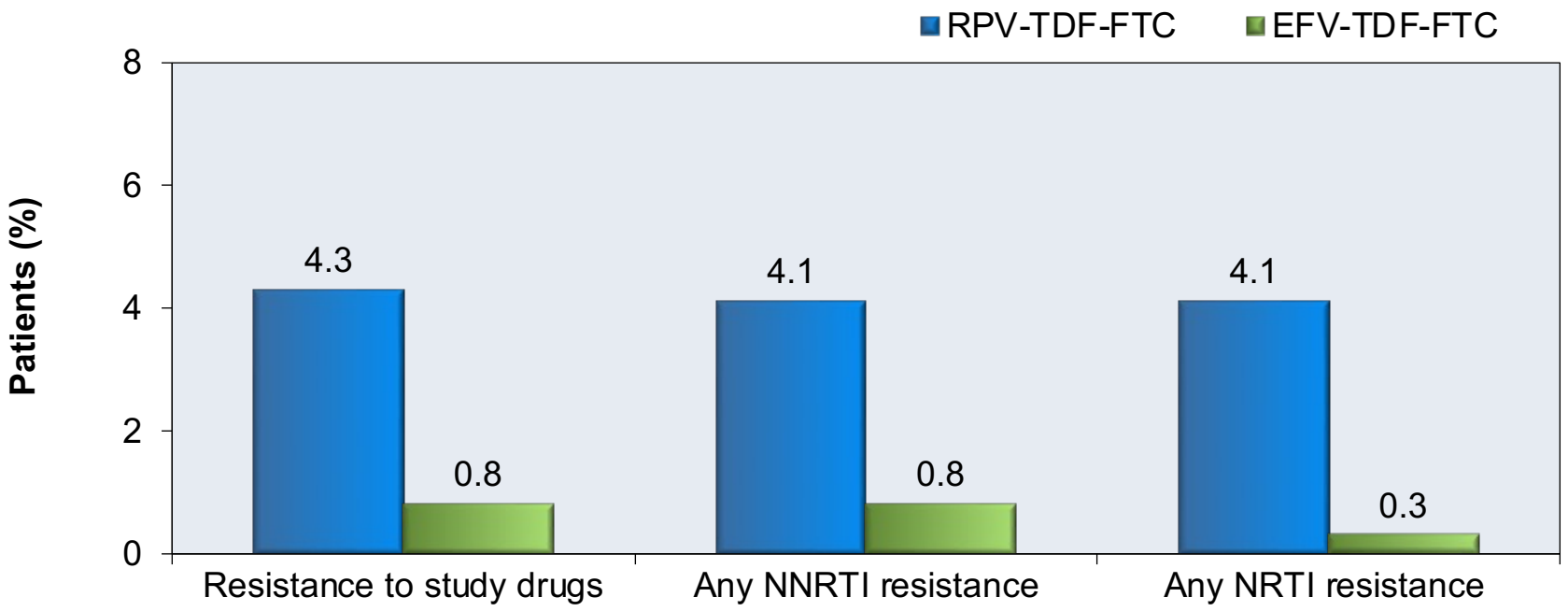
Source: Cohen CJ, et al. AIDS. 2014;28:989-97.

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

STaR Trial: Week 96 Resistance Data

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

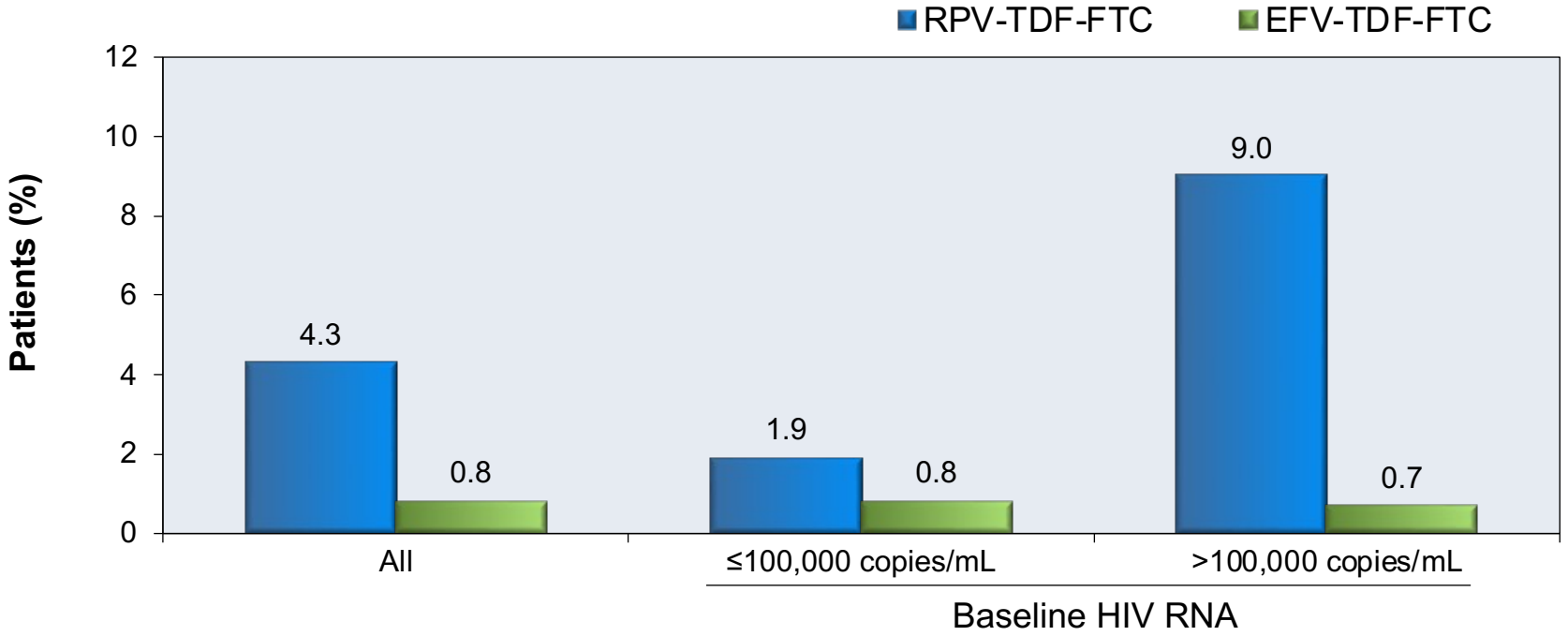
Development of Genotypic Resistance at Week 48



Source: Porter D, et al. J Acquir Immune Defic Syndr. 2014;65:318-26.

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

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



Source: Porter D, et al. J Acquir Immune Defic Syndr. 2014;65:318-26.

RPV-FTC-TDF versus EFV-FTC-TDF
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 ≤ 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.”

Source: Porter D, et al. J Acquir Immune Defic Syndr. 2014;65:318-26.

Rilpivirine-Tenofovir DF-Emtricitabine

Switch Studies in Adults with Virologic Suppression

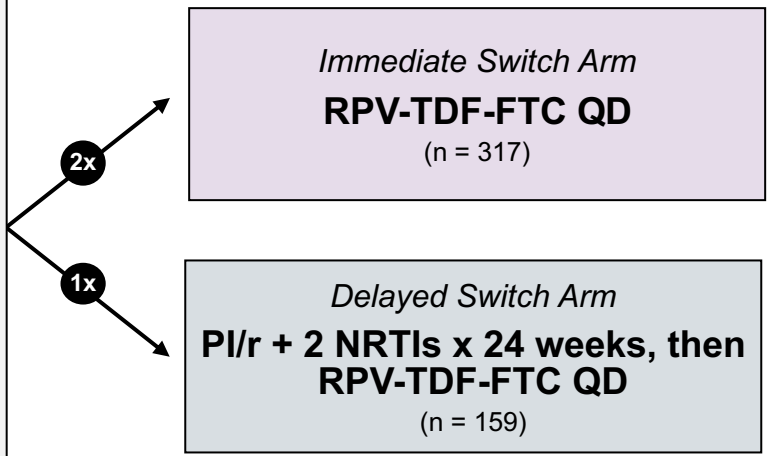
Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen

SPIRIT STUDY

National HIV Curriculum

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Study Design

- **Background**: Open-label, randomized, phase 3b trial evaluating switching from ritonavir-boosted PI plus 2 NRTIs to single-tablet regimen of rilpivirine-tenofovir DF-emtricitabine once daily
- **Inclusion Criteria**
  - Age ≥18 years
  - HIV RNA <50 copies/mL for ≥6 months
  - On PI with ritonavir ≥6 months
  - No known resistance to study drugs
- **Treatment Arms**
  - Rilpivirine-tenofovir DF-emtricitabine
  - PI with ritonavir (PI/r) + 2 NRTIs x 24 weeks, then rilpivirine-tenofovir DF-emtricitabine



Source: Palella FJ, et al. AIDS. 2014;28:335-44.

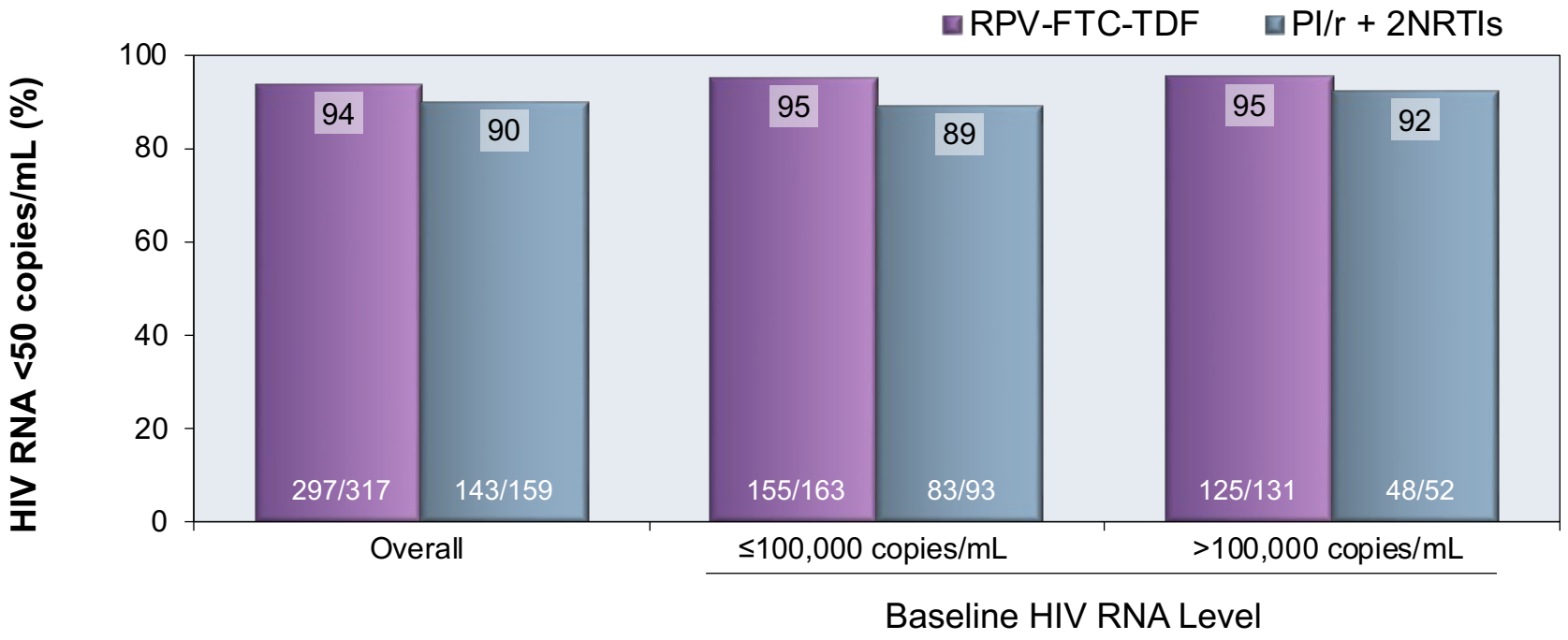
Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Study Design

Baseline Antiretroviral Regimens		
	Immediate Switch Arm (n = 317)	**Delayed Switch Arm** (n= 159)
NRTI at Screening		
TDF-FTC	80.4%	81.8%
ABC-3TC	13.2%	13.2%
Ritonavir-Boosted PI at Screening		
Atazanavir	38.5%	34.0%
Lopinavir	30.6%	36.5%
Darunavir	19.9%	20.8%
Fosamprenavir	7.9%	7.5%
Saquinavir	1.9%	1.3%

Source: Palella FJ, et al. AIDS. 2014;28:335-44.

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Results

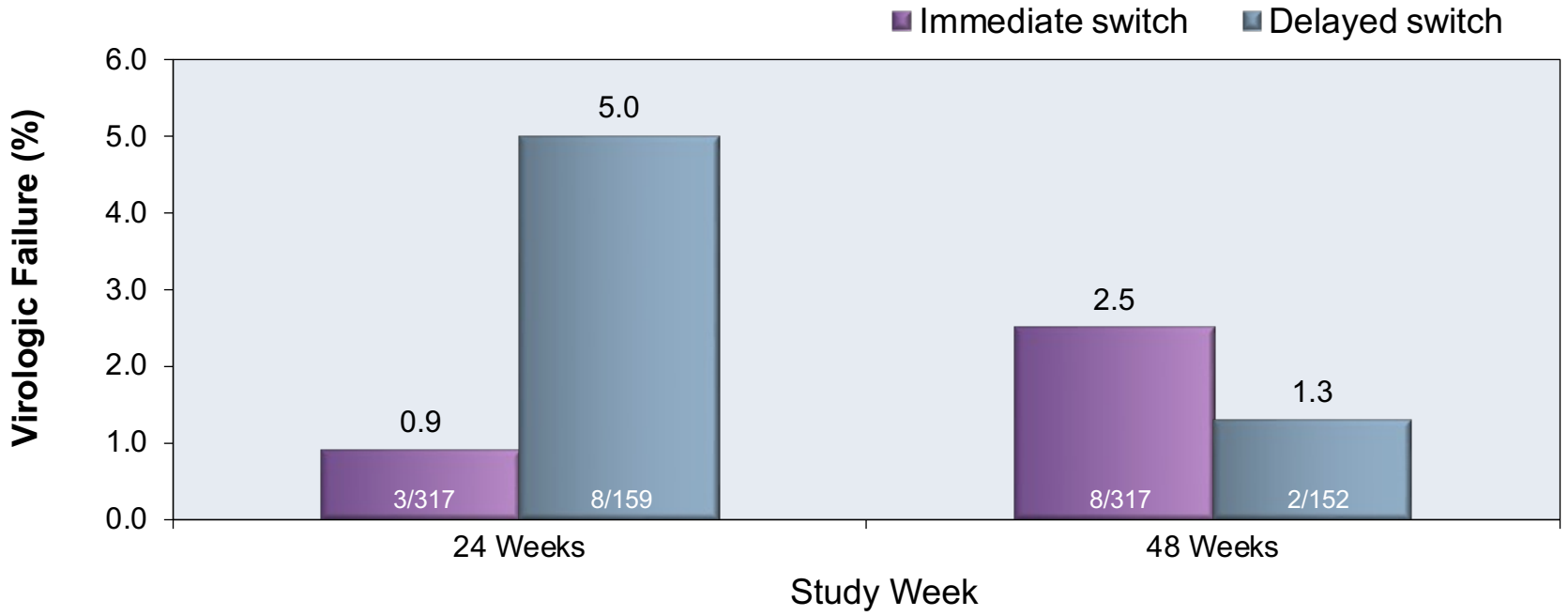
Week 24 Virologic Response (Intent-to-Treat Analysis)



Source: Palella FJ, et al. AIDS. 2014;28:335-44.

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Results

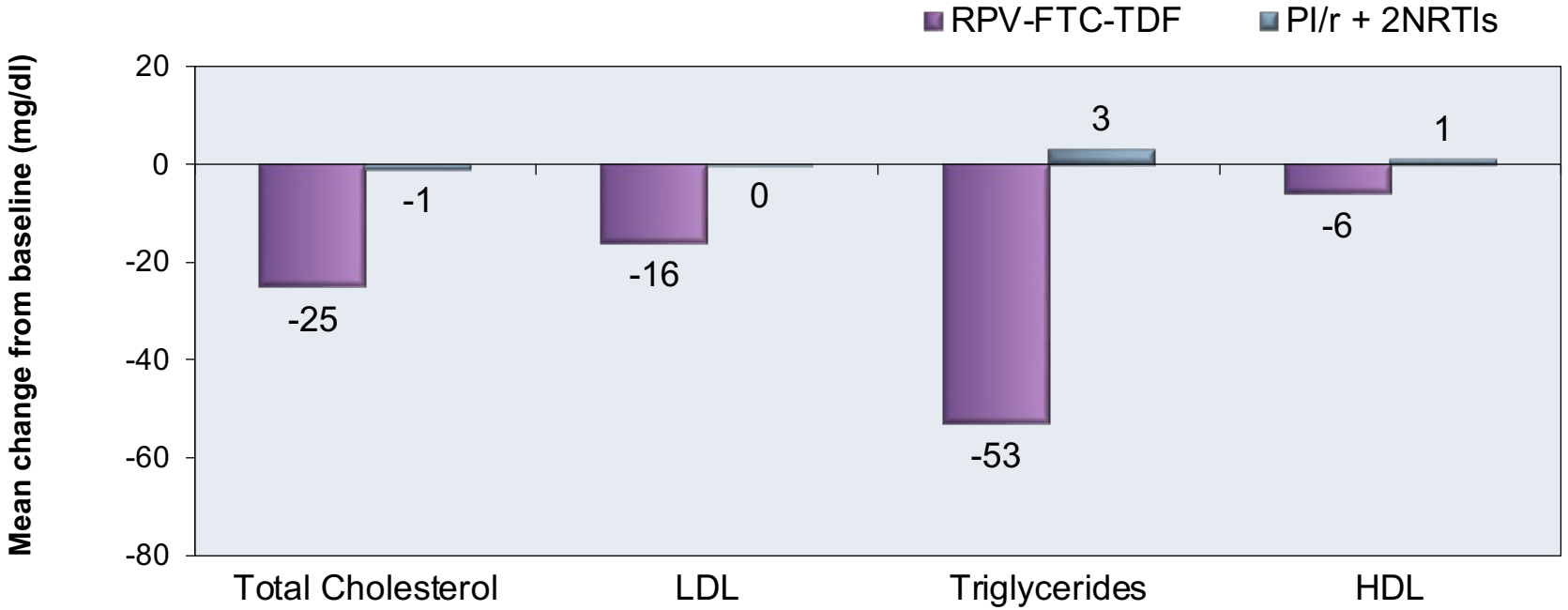
Virologic Failure (HIV RNA ≥50 copies/mL) at Weeks 24 and 48



Source: Palella FJ, et al. AIDS. 2014;28:335-44.

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Results

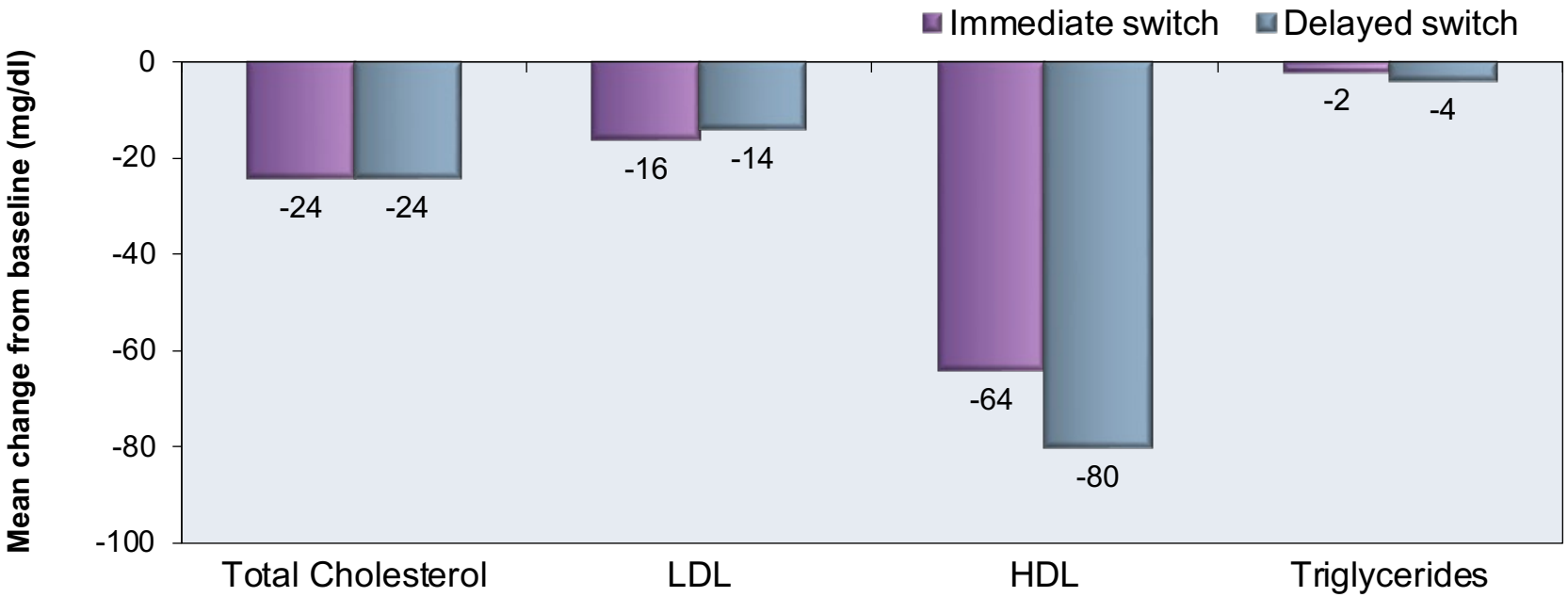
Week 24: Change in Plasma Lipids from Baseline



Source: Palella FJ, et al. AIDS. 2014;28:335-44.

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Result

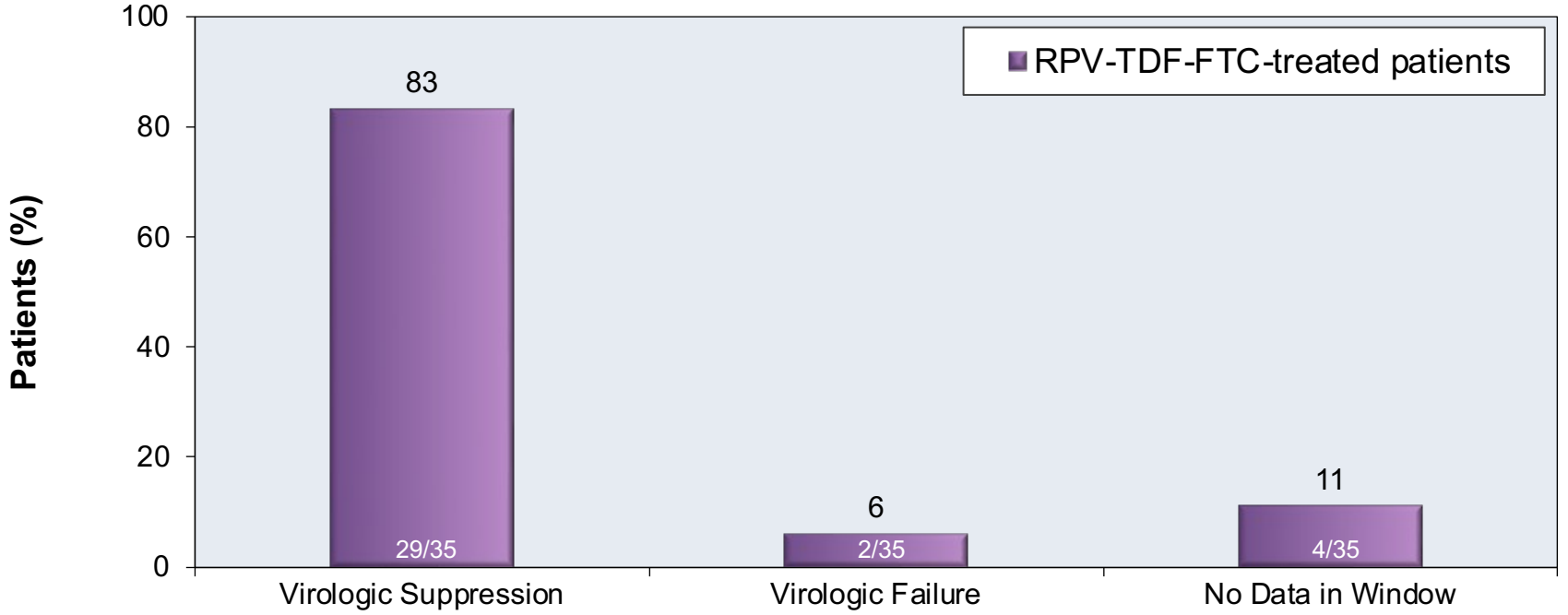
Week 48: Change in Plasma Lipids from Baseline



Source: Palella FJ, et al. AIDS. 2014;28(3):335-44.

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Result

Week 48 Virologic Outcomes in Patients with Resistance Mutations*



*Pre-existing NRTI or NNRTI resistance mutations by baseline proviral DNA or historical RNA genotype

Source: Porter DP, et al. HIV Clin Trials. 2016;17:29-37.

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
Spirit: Conclusions

Conclusion: “Switching to the STR RPV/FTC/TDF from an RTV-boosted protease inhibitor regimen in virologically suppressed, HIV-1-infected participants maintained virologic suppression with a low risk of virologic failure, while improving total cholesterol, LDL, and triglycerides.”

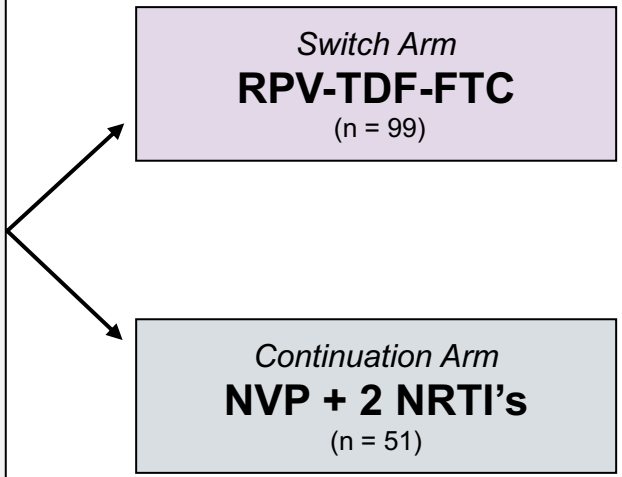
Source: Palella FJ, et al. AIDS. 2014;28:335-44.

Switch RPV-TDF-FTC from NVP-Based Regimen

Near-Rwanda Trial

Switch to RPV-TDF-FTC from NVP-Based Regimen Near-Rwanda: Study Design

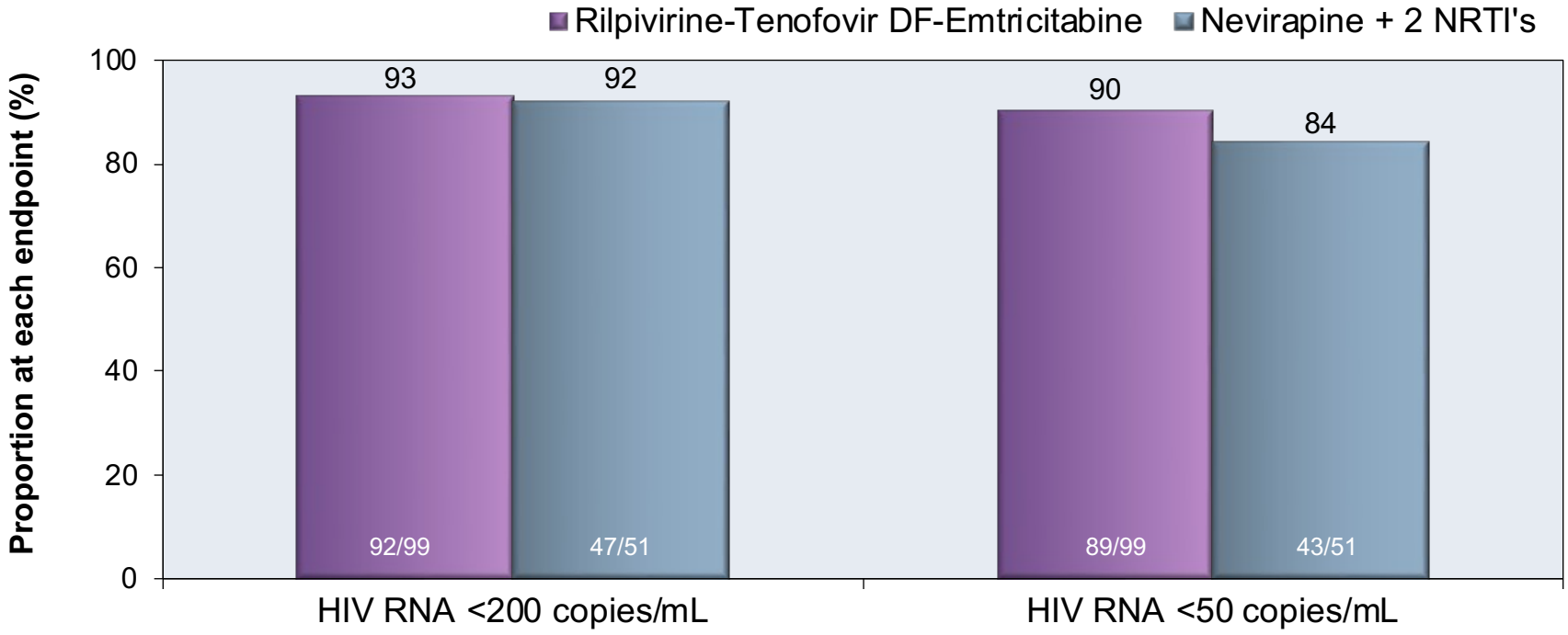
- **Background**: Randomized, open-label, single-center, noninferiority study conducted in Rwanda to evaluate a switch from a nevirapine (NVP)-based regimen to a single tablet regimen of rilpivirine-tenofovir DF-emtricitabine (RPV-TDF-FTC)
- **Inclusion Criteria (n = 150 enrolled)**
  - Rwandan adults with HIV-1 infection
  - HIV RNA <50 copies/mL within 12 months of screening
  - HIV RNA <50 copies/mL at screening visit
  - On NVP + lamivudine + 2nd NRTI ≥12 months
  - No prior virologic failure
  - No prior ART change except NRTI substitution
  - eGFR >60 mL/min and Hemoglobin >8 g/dL
  - No active TB or pregnancy
- **Treatment Arms (2:1 randomization)**
  - Continue NVP + 2 NRTIs
  - Switch to RPV-FTC-TDF



Source: Collins SE, et al. Open Forum Infect Dis. 2016;3:ofw141.

Switch to RPV-TDF-FTC from NVP-Based Regimen Near-Rwanda: Results

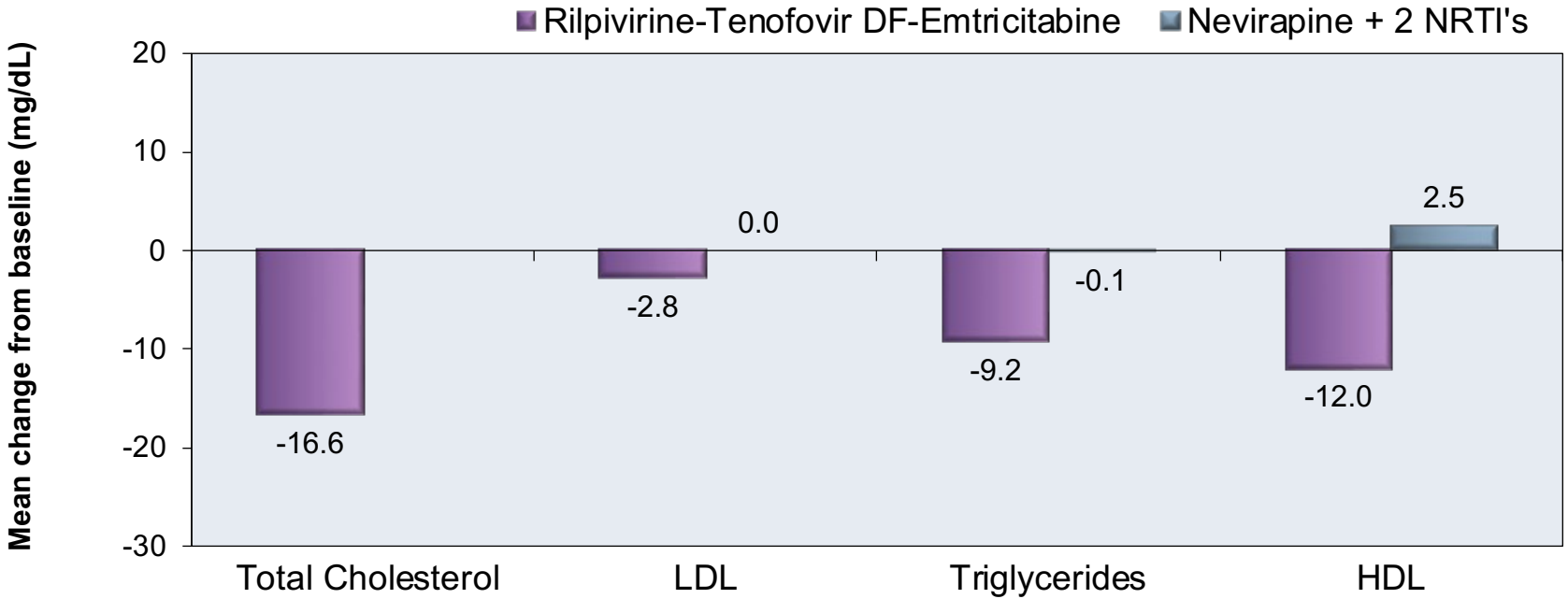
24 Week Virologic Response (FDA Snapshot Analysis)



Source: Collins SE, et al. Open Forum Infect Dis. 2016;3:ofw141.

Switch to RPV-TDF-FTC from NVP-Based Regimen Near-Rwanda: Results

Week 24: Change in Plasma Lipids from Baseline



Source: Collins SE, et al. Open Forum Infect Dis. 2016;3:ofw141.

Switch to RPV-TDF-FTC from NVP-Based Regimen Near-Rwanda: Conclusions

Conclusions: “A switch from nevirapine-based ART to rilpivirine-emtricitabine-tenofovir disoproxil fumarate had similar virologic efficacy to continued nevirapine-based antiretroviral therapy after 24 weeks with few adverse events.”

Source: Collins SE, et al. Open Forum Infect Dis. 2016;3:ofw141.

Acknowledgments

The **National HIV Curriculum** is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award totaling $1,021,448 with 0% financed with non-governmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, or the U.S. Government. For more information, please visit HRSA.gov. This project is led by the University of Washington's Infectious Diseases Education and Assessment (IDEA) Program.

AETC AIDS Education & Training Center Program

National HIV Curriculum

IDEA INFECTIOUS DISEASES EDUCATION & ASSESSMENT