National HIV Curriculum

Rilpivirine (*Edurant*)

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AETC AIDS Education & Training Center Program

Rilpivirine (*Edurant*)

Edurant

[ee' dur ant]

25 mg

NNRTI

Dose: 1 tablet once daily with a meal

Rilpivirine
Summary of Key Studies

- Phase 2b Trial
  - C204 Dose Ranging Study: Rilpivirine versus Efavirenz
- Phase 3 Trials
  - ECHO (TMC278-C209): Rilpivirine versus Efavirenz
  - THRIVE (TMC278-C215): Rilpivirine versus Efavirenz

ANTIRETROVIRAL THERAPY

Rilpivirine

*Rilpivirine (*Edurant*)

- **Class**
  - Non-nucleoside reverse transcriptase inhibitor
- **Approval**
  - FDA-approved May 20, 2011
- **Indication**
  - In combination with other ARVs for treatment-naïve adults
- **Dosing**
  - 25 mg^ tablet once daily (with a meal)
- **Metabolism**
  - Primarily in liver via cytochrome P450 (CYP 3A4) enzymes
- **Adverse Events**
  - Depression, insomnia, headache, and rash

Rilpivirine Dose-Ranging versus Efavirenz, with 2NRTIs

C204

Rilpivirine (TMC-278) vs. Efavirenz, with 2NRTIs in ARV-Naive
C204: Study Design

Study Design: C204

- **Background**: Randomized, phase IIb, dose-ranging, international study of rilpivirine compared with efavirenz, all in combination with 2 NRTIs in treatment-naïve persons with chronic HIV.
- **Inclusion Criteria (n = 368)**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA ≥5,000 copies/mL
  - No baseline NNRTI mutations
- **Treatment Arms**
  - Rilpivirine 25, 75, or 150 mg daily + 2 NRTIs*
  - Efavirenz 600 mg daily + 2 NRTIs*

Rilpivirine: 25 mg + 2 NRTIs
(n = 93)

Rilpivirine: 75 mg + 2 NRTIs
(n = 95)

Rilpivirine: 150 mg + 2 NRTIs
(n = 91)

Efavirenz: 600 mg + 2 NRTIs
(n = 89)

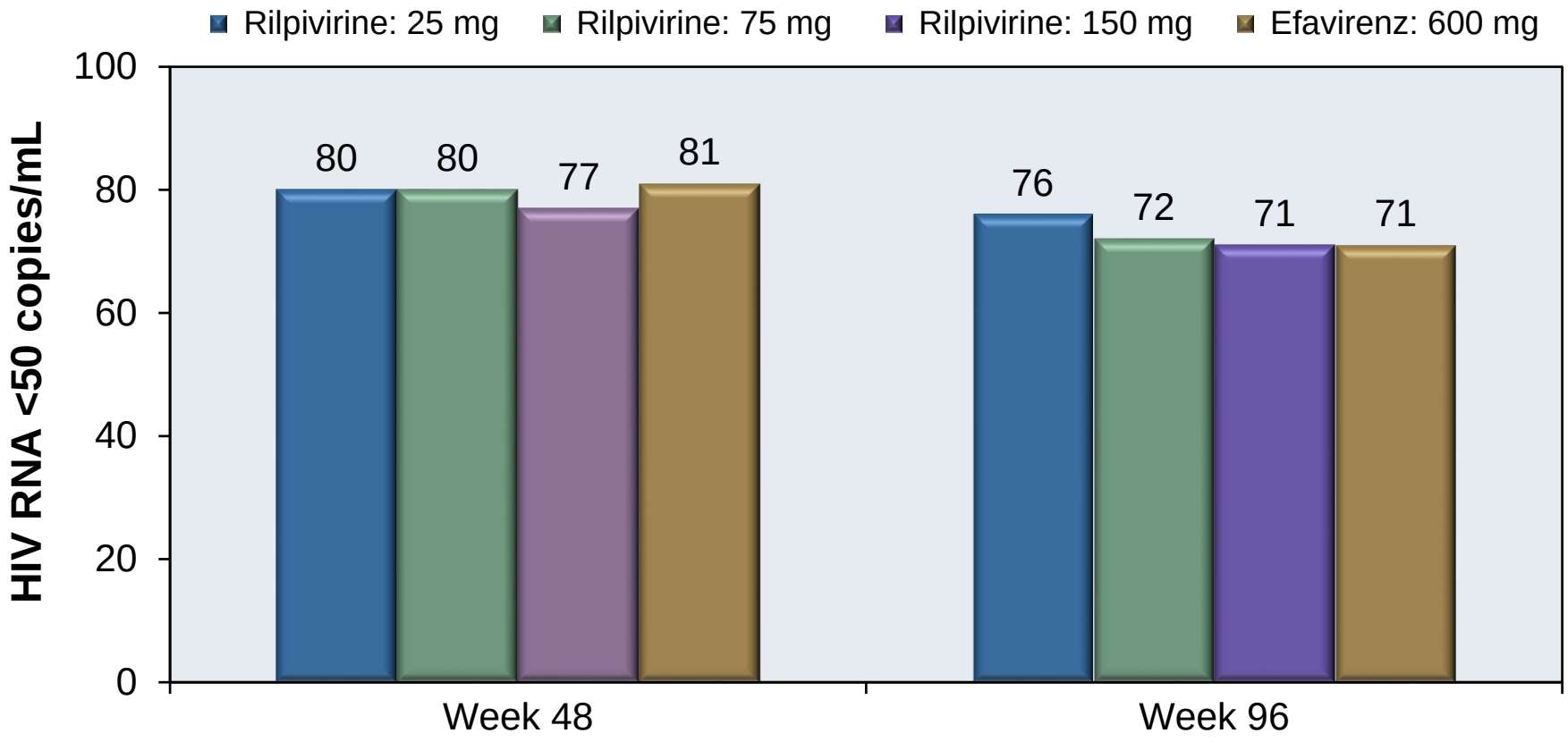
*2 NRTIs: Zidovudine + Lamivudine (75%); Tenofovir DF + Emtricitabine (25%)

Source: Pozniak AL, et al. AIDS. 2010;24:55-65.

Rilpivirine (TMC-278) vs. Efavirenz, with 2NRTIs in ARV-Naive

C204: Results

48 and 96 Week Data: Virologic Response (ITT)



All regimens included 2 NRTIs: Zidovudine + Lamivudine (75%); Tenofovir + Emtricitabine (25%)

Source: Pozniak AL, et al. AIDS. 2010;24:55-65.

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Rilpivirine (TMC-278) vs. Efavirenz, with 2NRTIs in ARV-Naive
C204: Conclusions

- **Conclusion**: “All TMC278 doses demonstrated potent and sustained efficacy comparable with efavirenz in treatment-naive patients over 96 weeks. TMC278 was well tolerated with lower incidences of neurological and psychiatric adverse events, rash and lower lipid elevations than those with efavirenz. TMC278 25 mg once daily was selected for further clinical development.”

Source: Pozniak AL, et al. AIDS. 2010;24:55-65.

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 adult 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

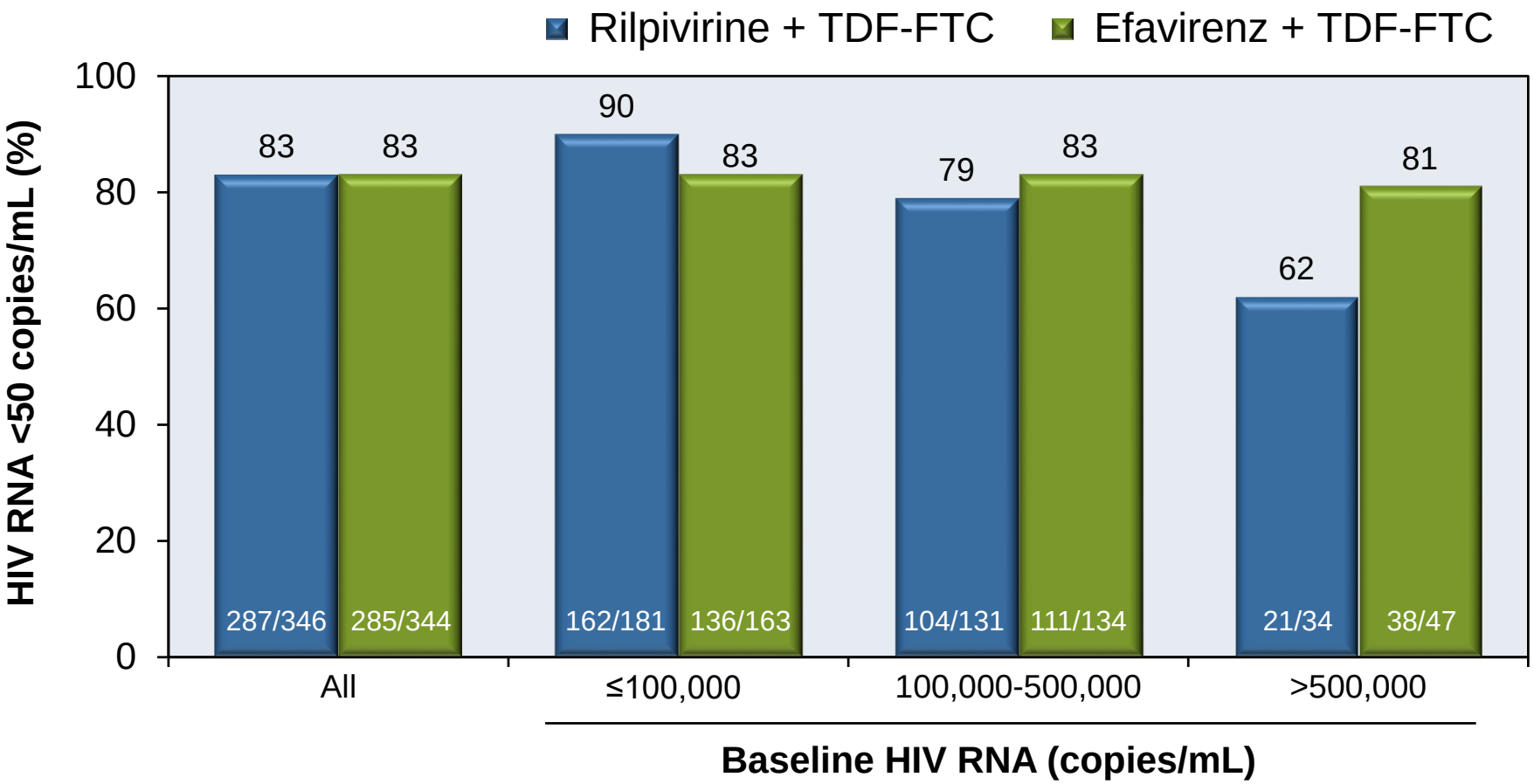
Rilpivirine + TDF-FTC QD
(n = 346)

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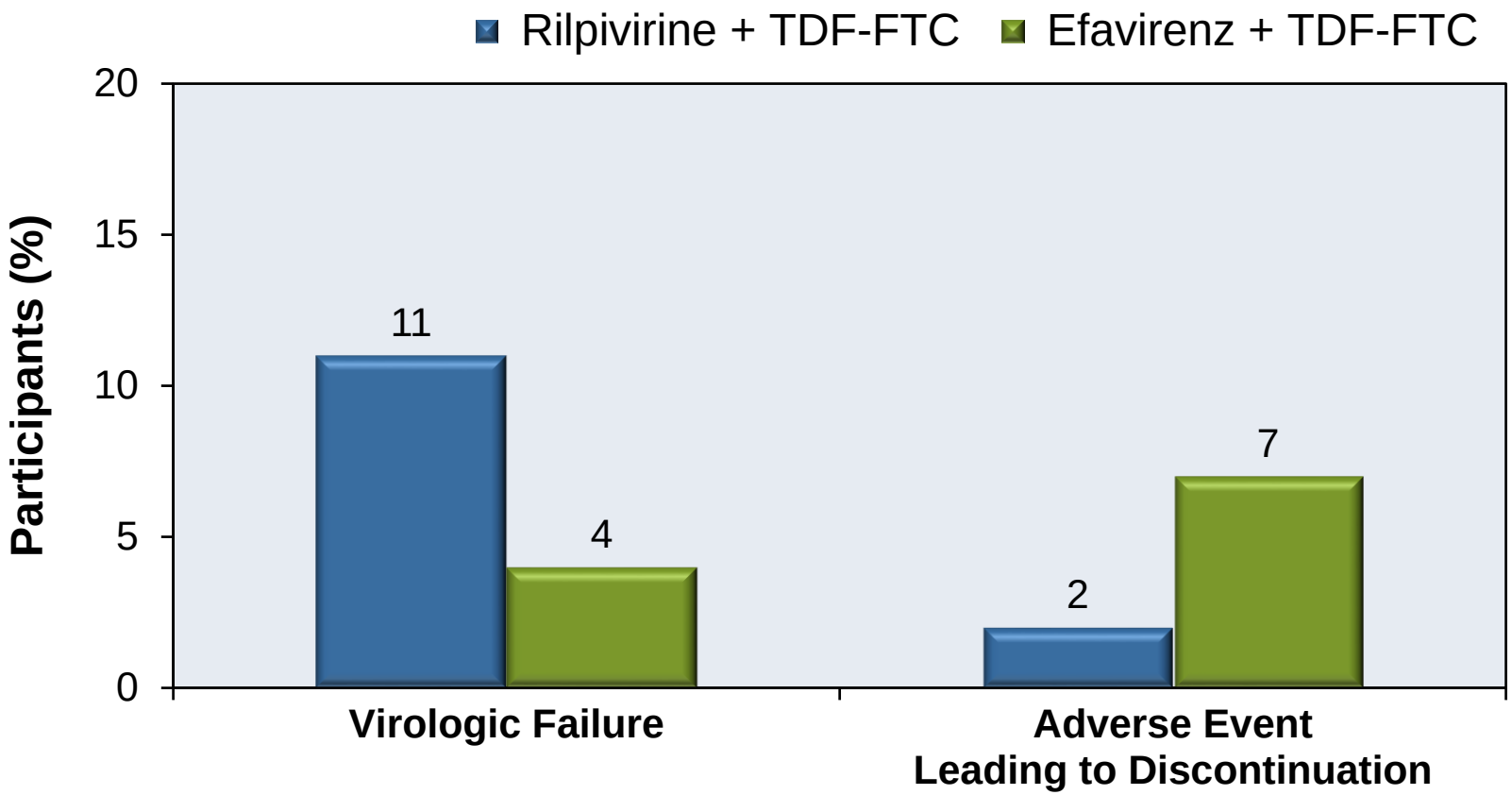
Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO: Result

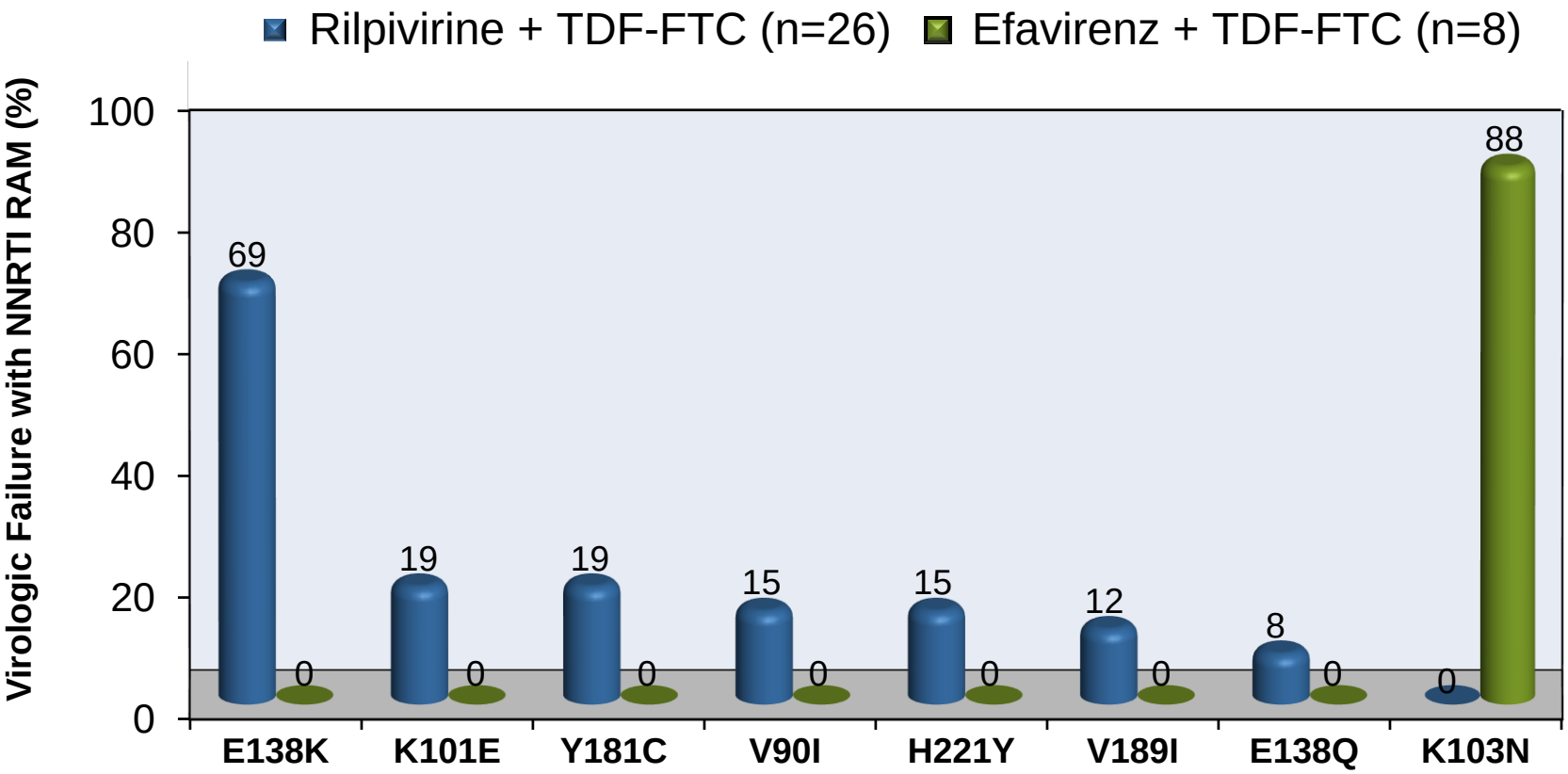
48 Week Virologic Failure and Discontinuations (ITT-TLOVR)



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.

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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 patients
  - Age ≥18 years
  - HIV RNA ≥5000 copies/mL
  - No resistance to any study drugs
- **Treatment Arms**
  - Rilpivirine + 2 NRTIs*
  - Efavirenz + 2 NRTIs*

Rilpivirine + 2 NRTIs
(n = 340)

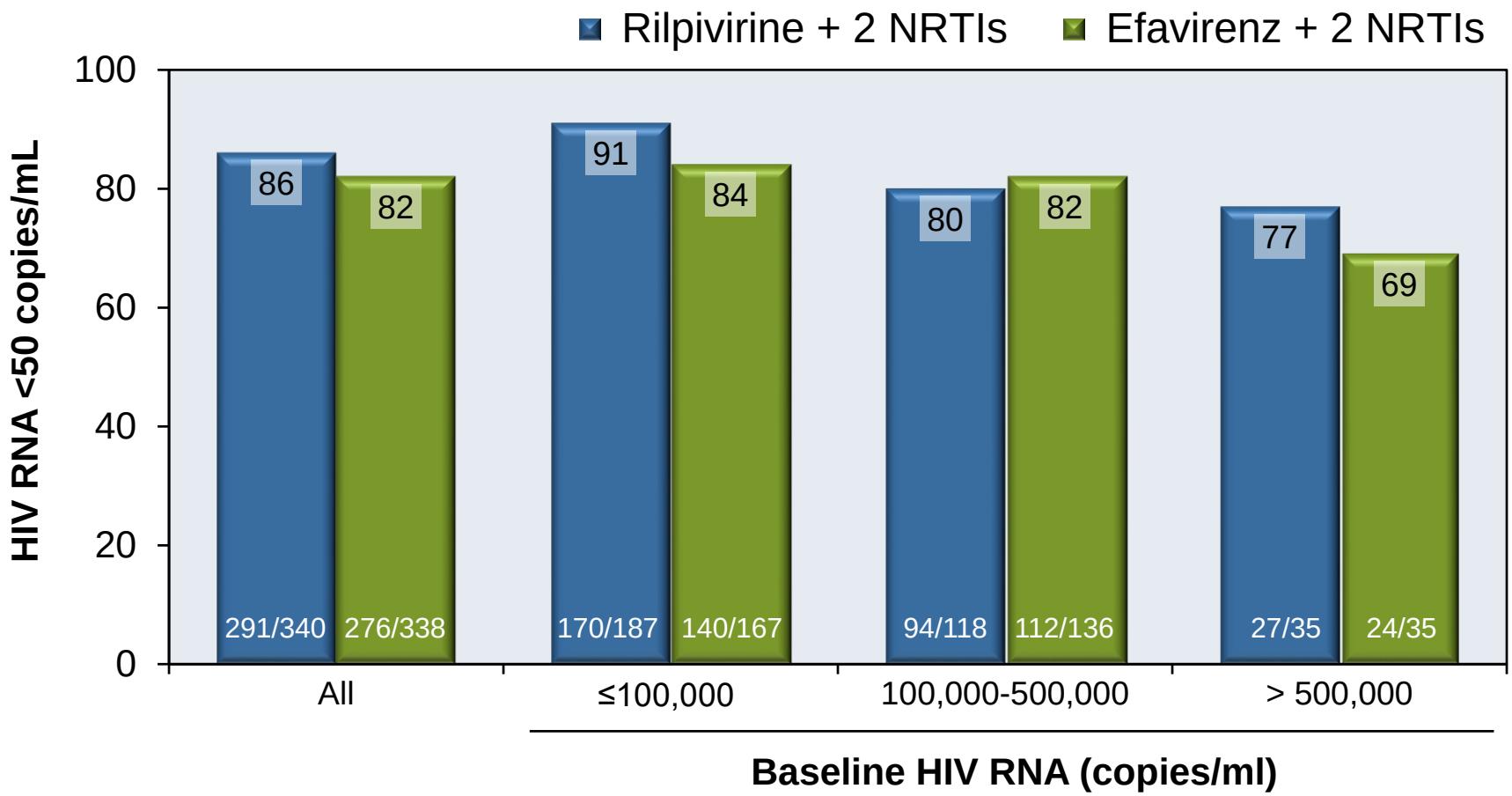
Efavirenz + 2 NRTIs
(n = 338)

*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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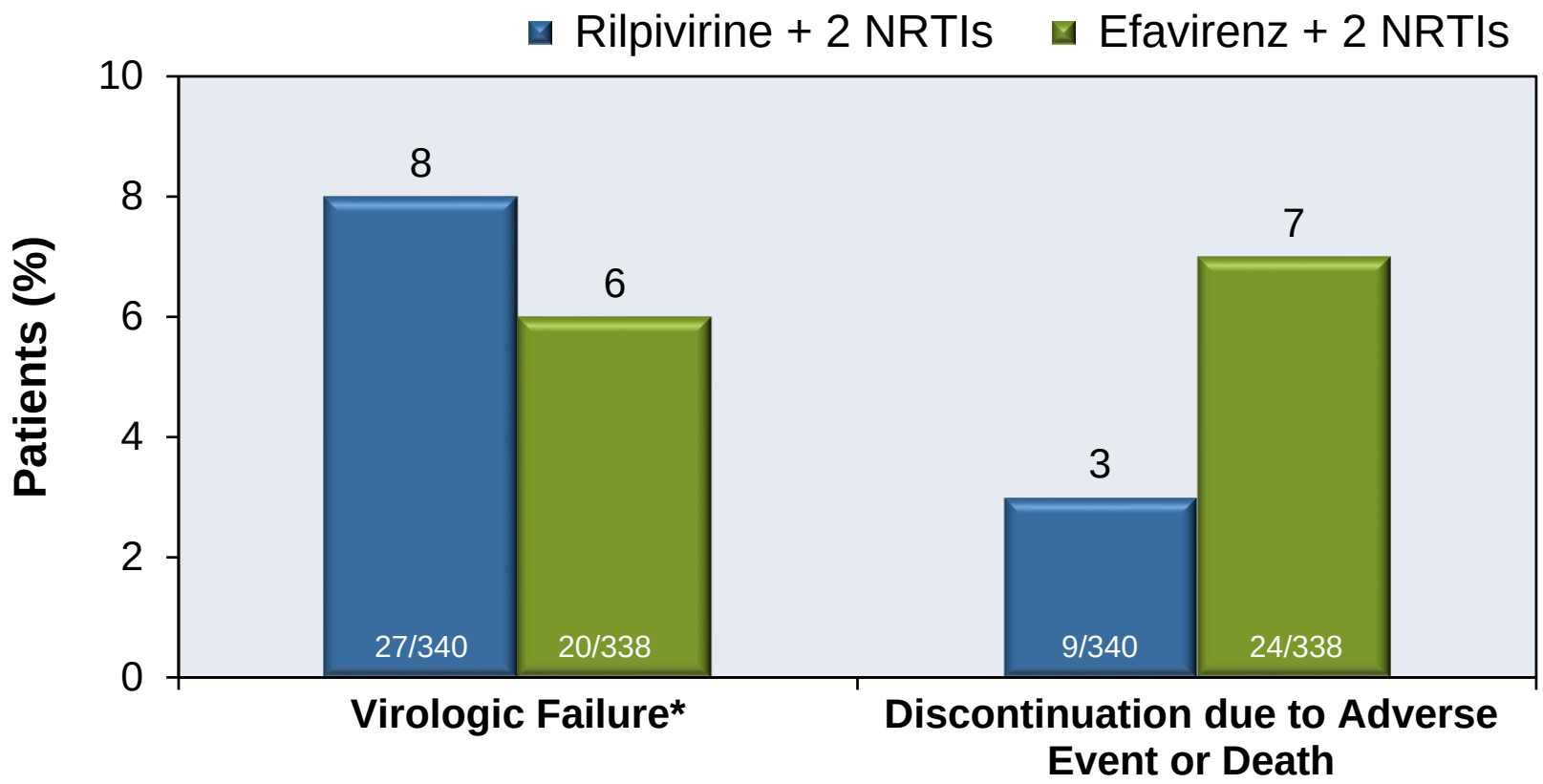
Rilpivirine versus Efavirenz, with two background NRTIs
THRIVE: Result

48 Week Virologic Failure and Discontinuations

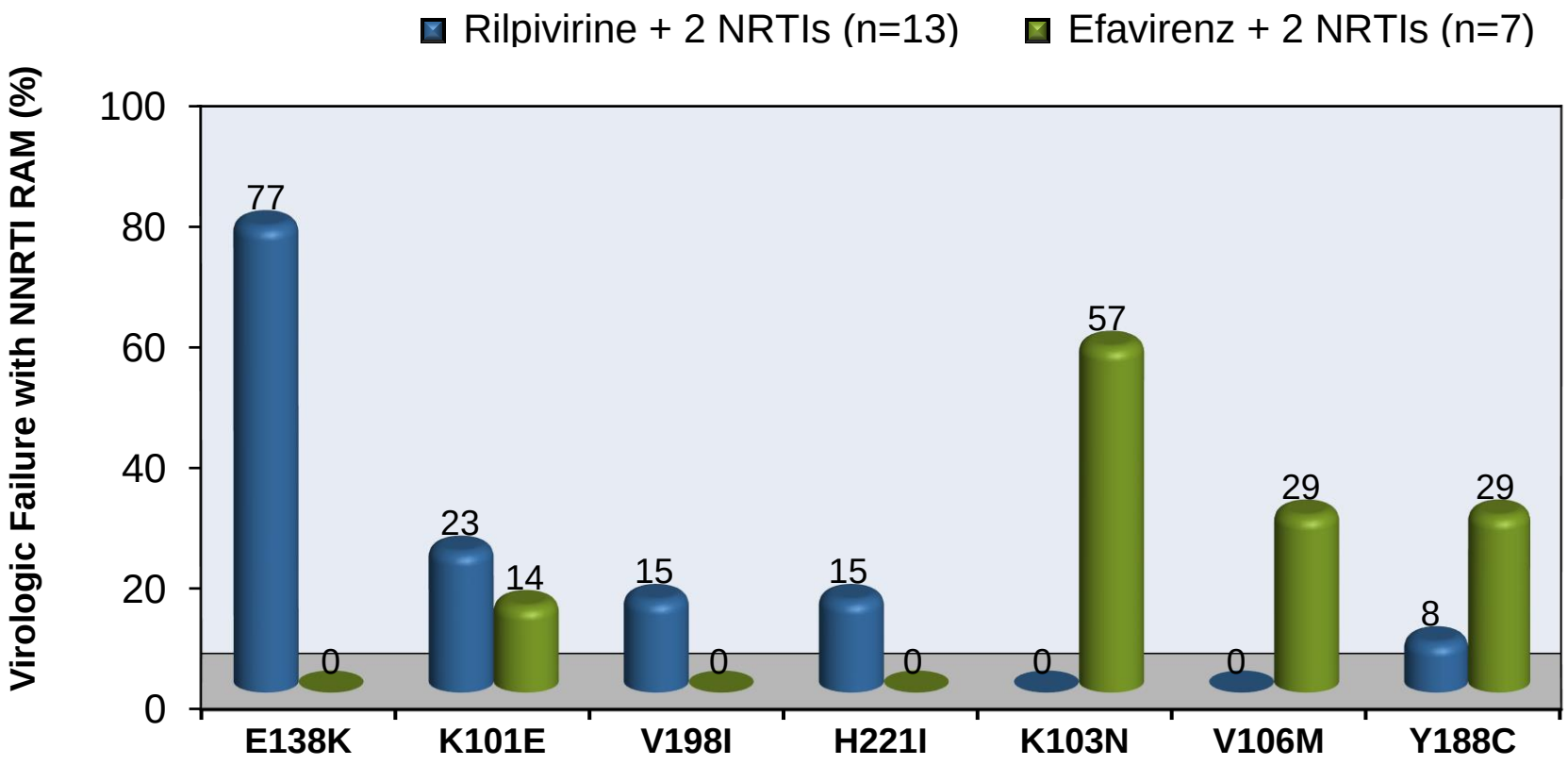


*Virologic failure includes those without emerging mutation at failure

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.

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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.

Rilpivirine vs. Efavirenz in Treatment-Naïve Patients

ECHO & THRIVE (Pooled 48 Week Data)

Rilpivirine vs. Efavirenz in Antiretroviral-Naïve Patients
ECHO and THRIVE Pooled 48 Week Data: Design

Study Design: ECHO & THRIVE

- **Background:** Randomized, double-blind, double-dummy Phase 3 trials comparing rilpivirine with efavirenz
- **Inclusion Criteria**
  - Age ≥ 18
  - Antiretroviral-naïve
  - HIV RNA ≥ 5,000 copies/ml
  - No baseline NNRTI mutations
- **Treatment Arms**
  - RVP or EFV plus 2 NRTIs*

ECHO

- **Rilpivirine: 25 mg qd + TDF-FTC (n = 346)**
- **Efavirenz: 600 mg qd + TDF-FTC (n = 344)**

THRIVE

- **Rilpivirine: 25 mg qd + 2NRTIs (n = 340)**
- **Efavirenz: 600 mg qd + 2NRTIs (n = 338)**

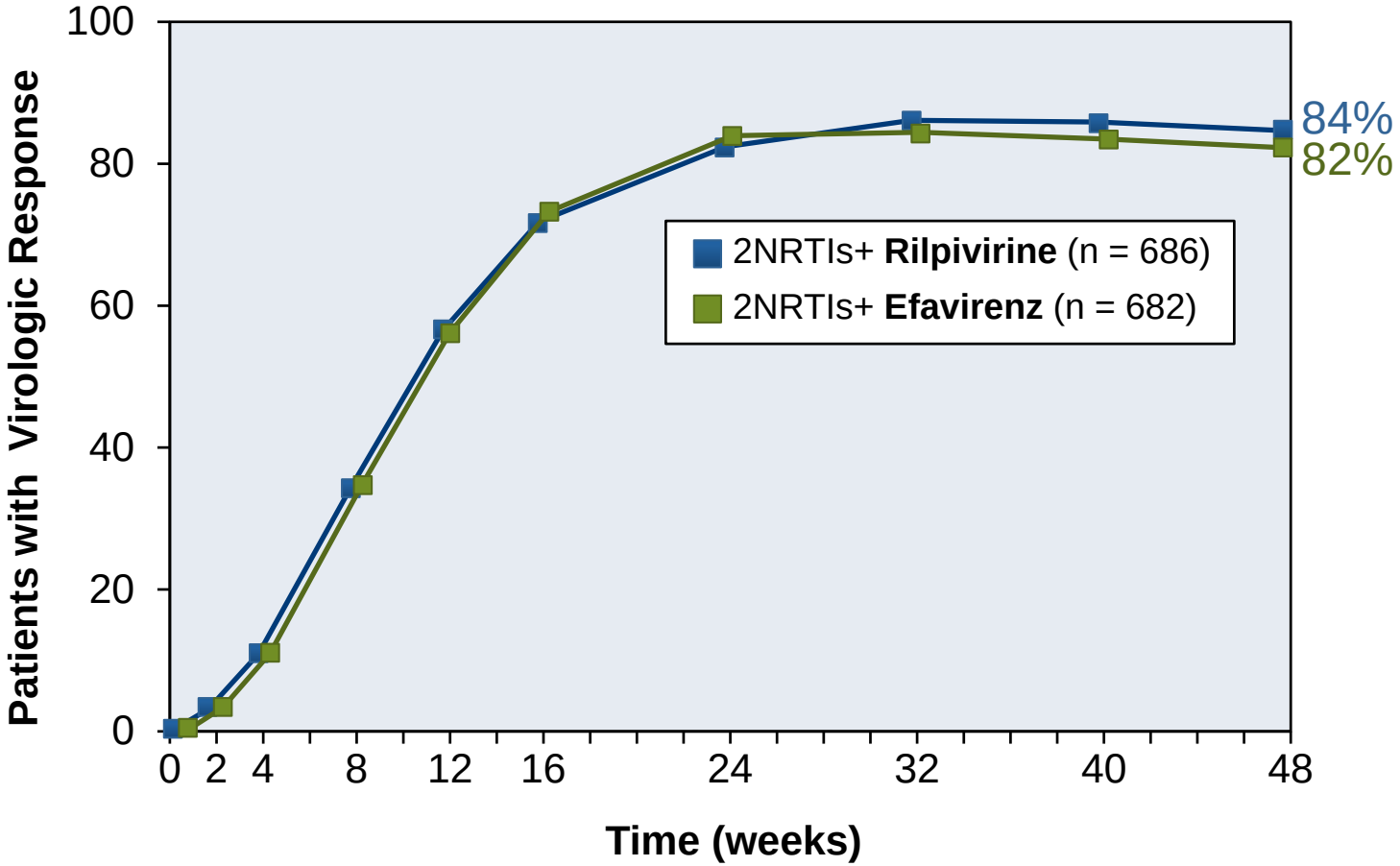
*__ECHO__: 2NRTIs = Tenofovir DF-Emtricitabine

*__THRIVE__: 2NRTIs = Tenofovir DF + Emtricitabine; Zidovudine + Lamivudine; Abacavir + Lamivudine

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

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

Virologic Response (ITT-TLOVR) over 48 Weeks



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

Rilpivirine vs. Efavirenz in Antiretroviral-Naïve Patients
ECHO and THRIVE Pooled 48 Week Data: Resistance

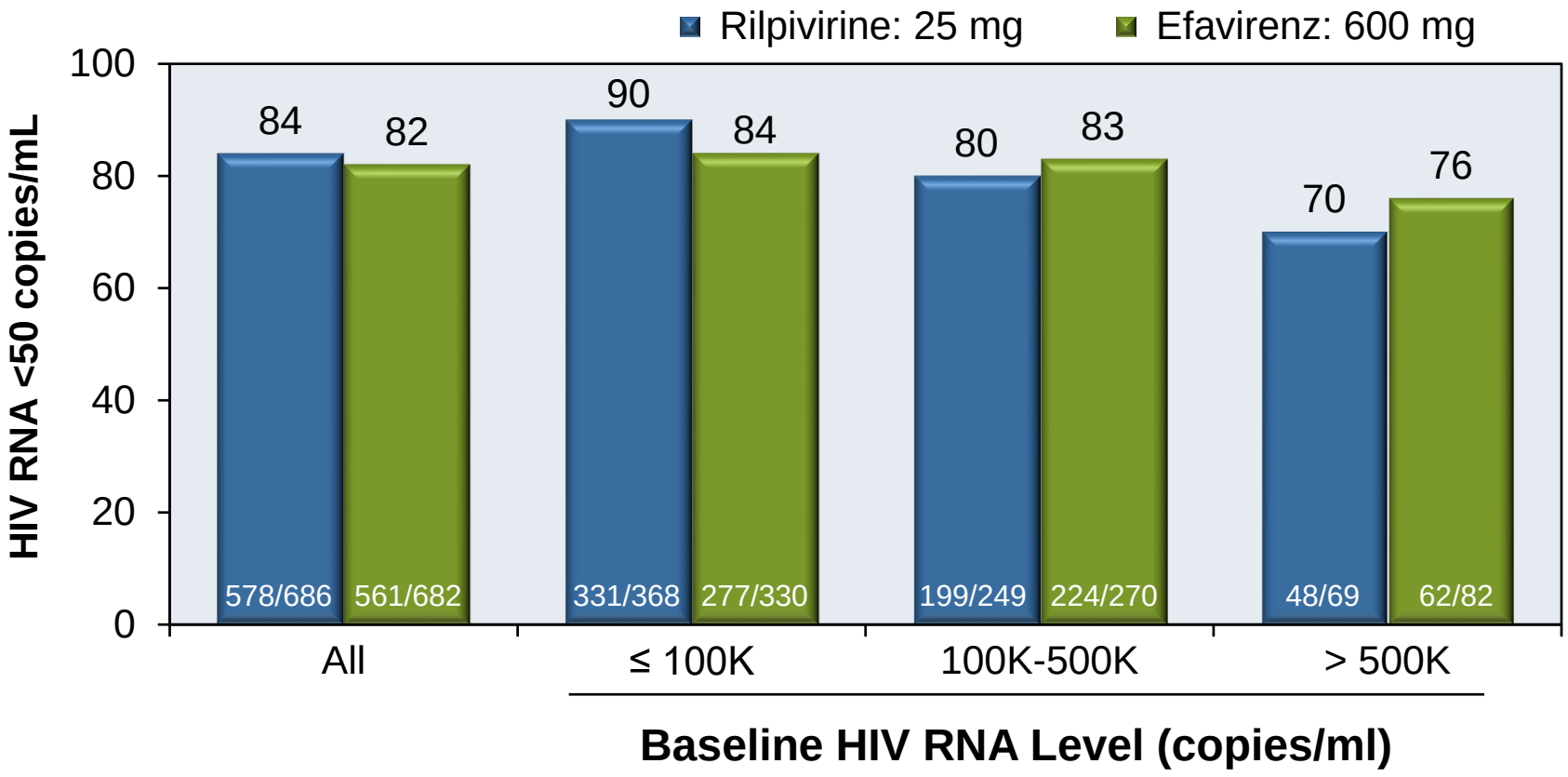
Resistance Findings in ECHO and THRIVE Studies: 48 Week Pooled Data		
	Rilpivirine arms (n = 686)	**Efavirenz arms** (n = 682)
Virologic failure with resistance data, n	62	28
No NNRTI or NRTI RAMs	29%	43%
Emergent NNRTI RAMs	63%	54%
Most Frequent NNRTI RAMs	E138K (72%)	K103N (73%)
Emergent NRTI RAMs	68%	32%
Most Frequent NRTI RAMs	M184I (69%)	M184V (67%)

NOTE: 31 (50%) of 62 rilpivirine failures were phenotypically resistant to rilpivirine
28 (90%) of 31 rilpivirine failures were phenotypically cross-resistant to etravirine

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

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

48 Week Data: ITT-TLOVR Outcome by Baseline Viral Load



All regimens included 2 NRTIs

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

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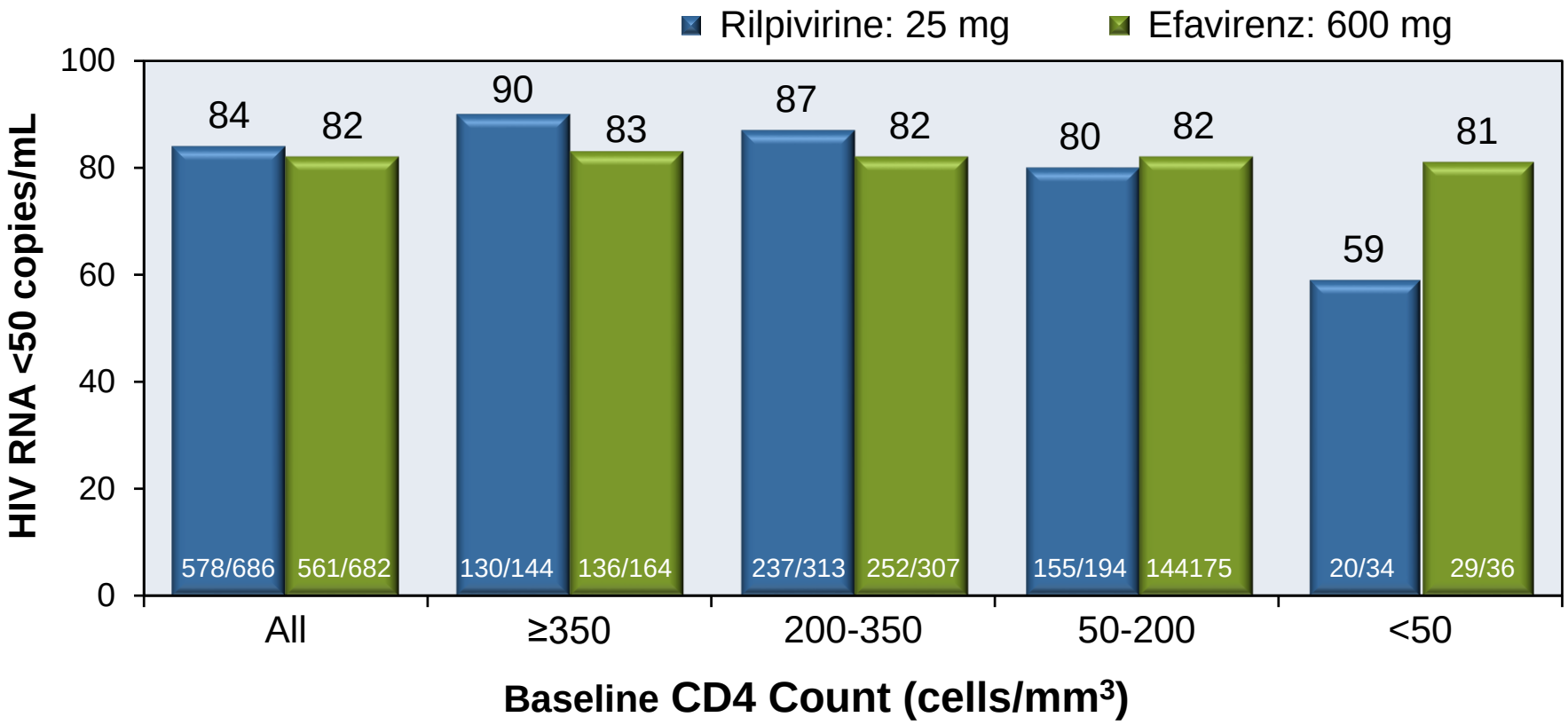
Rilpivirine vs. Efavirenz in Antiretroviral-Naïve Patients
ECHO and THRIVE Pooled 48 Week Data: Results

48 Week Data: ITT-TLOVR Outcome by Baseline CD4 Cell Count



All regimens included 2 NRTIs

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

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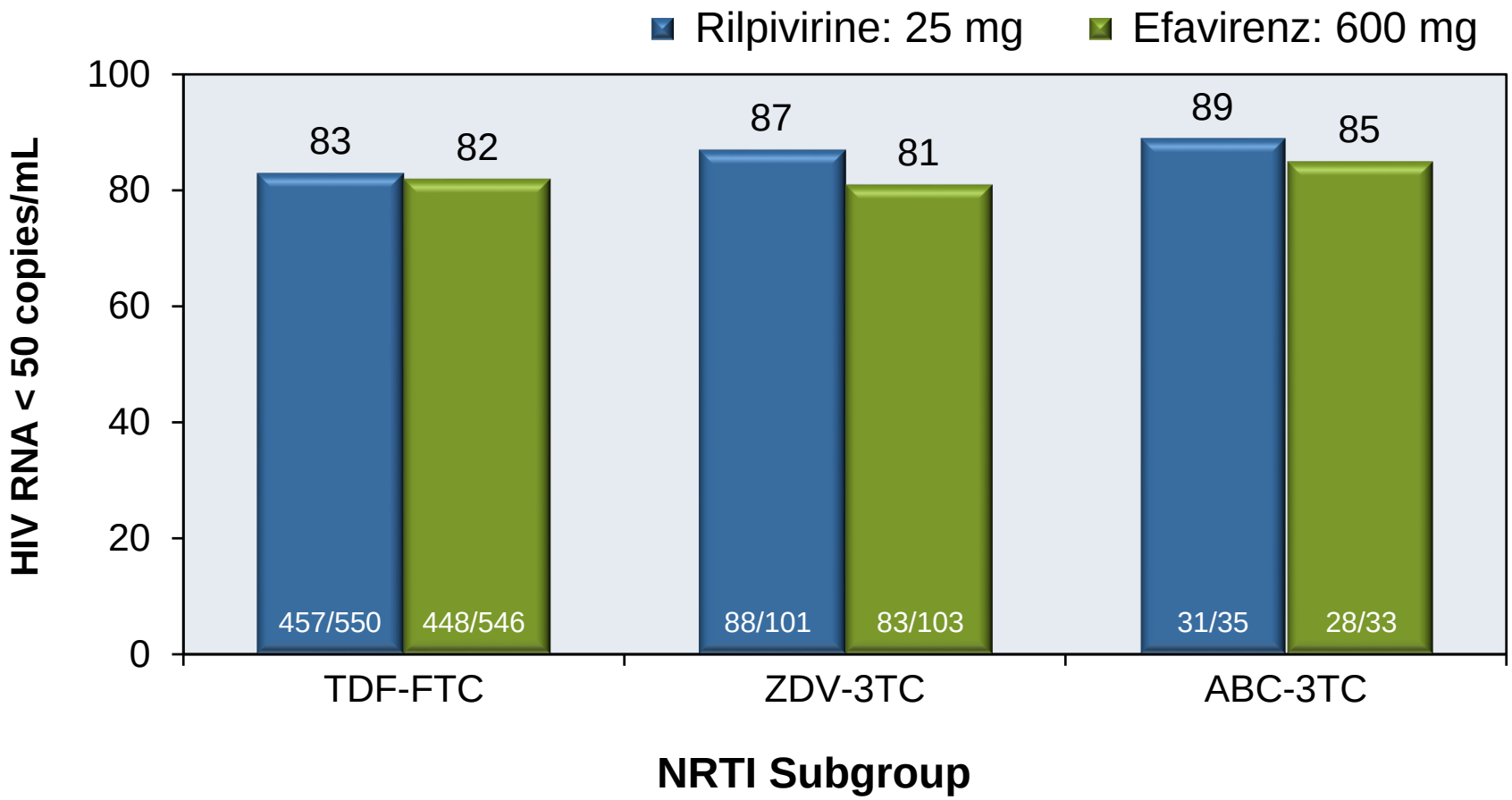
Rilpivirine vs. Efavirenz in Antiretroviral-Naïve Patients
ECHO and THRIVE Pooled 48 Week Data: Results

48 Week Data: ITT-TLOVR Outcome by NRTI Subgroup



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

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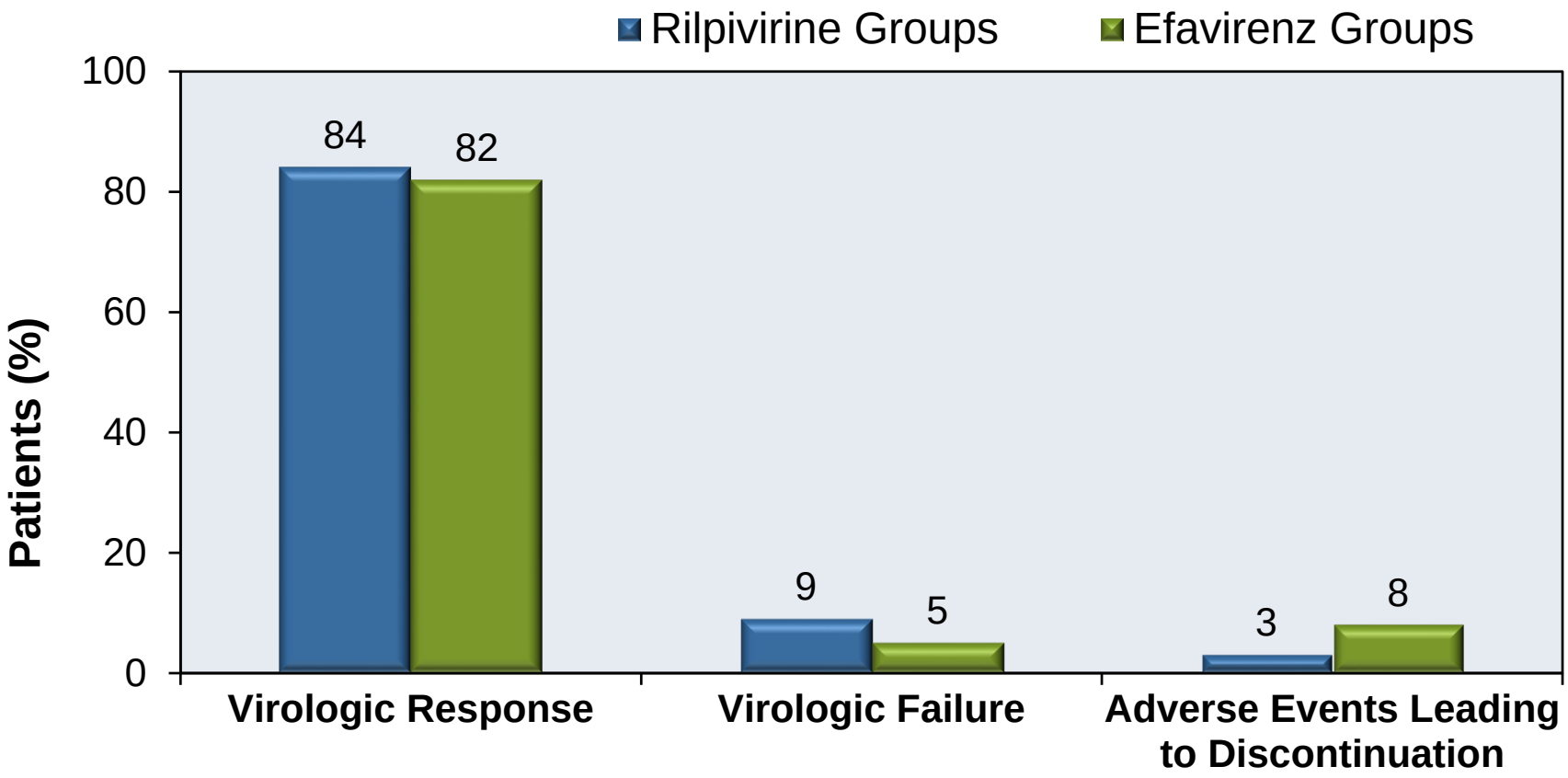
Rilpivirine vs. Efavirenz in Antiretroviral-Naïve Patients

ECHO and THRIVE Pooled 48 Week Data: Results

48 Week Pooled Efficacy and Safety Data



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

Rilpivirine vs. Efavirenz in Antiretroviral-Naïve Patients
ECHO and THRIVE Pooled 48 Week Data: Conclusions

Conclusions: "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."

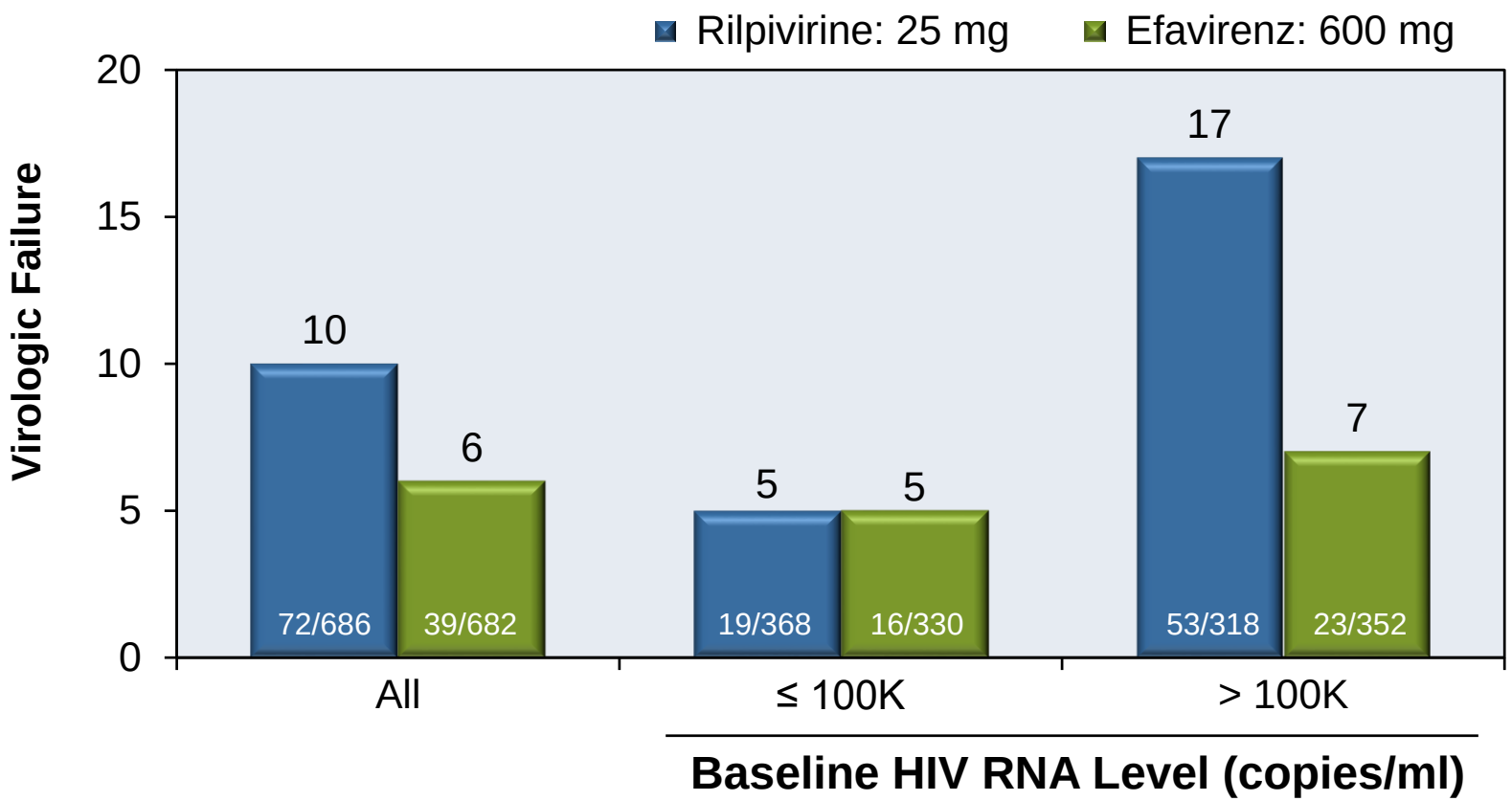
Source: Cohen C, et al. J Acquir Immune Defic Syndr. 2012:60:33-42.

Rilpivirine vs. Efavirenz

ECHO & THRIVE (Week 48 Pooled Resistance Data)

Rilpivirine vs. Efavirenz in ARV-Naive
ECHO and THRIVE Resistance: Virologic Failure Results

Virologic Failure: 48 Week Data



All regimens included 2 NRTIs

Source: Rimsky L, et al. JAIDS. 2012;59:39-46.

Rilpivirine vs. Efavirenz in ARV-Naive
ECHO and THRIVE Resistance : Conclusions

Conclusions: “Virologic failure and treatment-emergent reverse transcriptase RAMs were similar at low baseline VL but more frequent at high baseline VL in rilpivirine-treated than in efavirenz-treated patients. The frequent emergence of E138K, especially in combination with M184I, in rilpivirine VFs is a unique finding of these trials..”

Source: Rimsky L, et al. JAIDS. 2012;59:39-46.

SWITCH STUDIES

Rilpivirine

RESISTANCE DATA IN PRESCRIBING INFORMATION

Rilpivirine

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

	Rilpivirine + 2NRTIs	Efavirenz + 2NRTIs
Subjects with evaluable resistance data	87	43
Emerging NNRTI Substitution (any)	62%	53%
V90I	13%	2%
K101E/P/T/Q	20%	9%
K103N	1%	40%
E138K/A/Q/G	40%	2%
E138K + M184I	25%	0%
V179I/L/D	6%	7%
Y181C/I/S	10%	2%
V189I	8%	2%
H221Y	9%	0%
Emerging NRTI Substitution (any)	57%	30%
M184I/V	54%	26%
K65R	9%	2%
2° Mutations: A62V, D67N/G,K70E, Y115F, T215S/T,K219E/R	21%	2%

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

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

	Rilpivirine + 2NRTIs	Efavirenz + 2NRTIs
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K101E/P/T/Q	20%	9%
K103N	1%	40%
E138K/A/Q/G	40%	2%
E138K + M184I	25%	0%
V179I/L/D	6%	7%
Y181C/I/S	10%	2%
V189I	8%	2%
H221Y	9%	0%
Emerging NRTI Substitution (any)	57%	30%
M184I/V	54%	26%
K65R	9%	2%
2° Mutations: A62V, D67N/G,K70E, Y115F, T215S/T,K219E/R	21%	2%

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

Acknowledgment

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