

Raltegravir (*Isentress*)

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Raltegravir (*Isentress*)

Isentress
[eye-SEN-tris]

Isentress



400 mg



INSTI

Isentress HD



600 mg



Dosing

- Treatment naïve: 400 mg twice daily or 1200 mg (2x 600 mg) once daily, with or without food
- Treatment experienced: 400 mg twice daily with or without food
- Coadministered with Rifampin: 800 mg twice daily

Raltegravir (*Isentress*)

- **Approval Status:** Approved by United States FDA October 12, 2007
- **Indications and Usage**
 - Indicated in combination with other antiretrovirals for the treatment of HIV
- **Class & Mechanism**
 - Integrase strand-transfer inhibitor (INSTI)
- **Dosing**
 - 400 mg tablet twice daily for adults in treatment-naïve or treatment experienced
 - 600 mg tablet (2 tablets) once daily in treatment-naïve
 - 800 mg twice daily for adults if co-administered with rifampin
- **Dosage Forms**
 - Film-coated tablets, for oral use
 - Chewable tablets, for oral use (NOT bioequivalent to film-coated tablets)
 - Oral suspension (NOT bioequivalent to film-coated tablets)
- **Adverse Events (AE's)**
 - headache, insomnia, nausea, rash, CPK elevation

Raltegravir

Summary of Key Studies

- Phase 3 Trials in Treatment Naïve
 - STARTMRK: Raltegravir versus Efavirenz
 - SPRING-2: Raltegravir versus Dolutegravir
 - SHIELD: Raltegravir plus Abacavir-Lamivudine
 - ARDENT (ACTG 5257): Raltegravir vs. Darunavir/r vs. Atazanavir/r
- Once Daily Raltegravir for Treatment Naïve
 - QDMRK: Raltegravir 800 mg QD versus Raltegravir 400 mg BID
 - ONCEMRK: Raltegravir 1200 mg QD versus Raltegravir 400 mg BID
- Dual Therapy with Raltegravir for Treatment Naïve
 - PROGRESS: Lopinavir/r + TDF versus Lopinavir/r + Raltegravir
 - SPARTAN: Raltegravir plus Atazanavir/r versus 2NRTIs + Atazanavir
 - RADAR: Raltegravir plus Darunavir/r versus TDF-FTC + Darunavir/r
 - ACTG 5262: Raltegravir plus Darunavir/r
 - NEAT001/ANRS143: Raltegravir + DRV/r vs TDF-FTC + DRV/r

Raltegravir

Summary of Key Studies

- Phase 3 Trials in Treatment Experienced
 - BENCHMRK: OBT + Raltegravir versus OBT + Placebo
 - GS-183-0145: Elvitegravir/r versus Raltegravir
 - SAILING: Raltegravir versus Dolutegravir
 - 005: OBT + Raltegravir versus OBT alone
 - ACTG 5244: Treatment intensification with Raltegravir
- Dual Therapy in Treatment Experienced
 - SECOND-LINE: Lopinavir/r + Raltegravir vs. NtRTIs
 - SELECT: Lopinavir/r + Raltegravir vs. NRTIs

Raltegravir

Summary of Key Studies

- Switch Trials
 - SWITCHMRK 1 & 2: Switch from Lopinavir/r to Raltegravir
 - SPIRAL: Switch from PI/r to Raltegravir
 - CHEER: Switch from Enfuvirtide to Raltegravir
 - EASIER (ANRS 138): Switch from Enfuvirtide to Raltegravir
 - ROCnRAL (ANRS 157): Raltegravir + Maraviroc
 - HARNESS: 3-drug ART to [Raltegravir + ATZ/r or ATZ/r + TDF/FTC]
- Raltegravir in Early HIV
 - UW 300 PIC: Raltegravir + 3-Drug Rx versus 3-Drug Rx
 - OPTIPRIM-ANRS 147: DRV/r + TDF-FTC +/- [RAL + MVC]
- Raltegravir in PrEP
 - RALPEP: RAL + TDF-FTC versus Lopinavir/r + TDF-FTC
- Raltegravir in Pregnancy
 - PANNA: Raltegravir + background regimen in pregnancy

INITIAL THERAPY

Raltegravir

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

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

STARTMRK: Study Design

Study Design: STARTMRK Study

- **Background:** Randomized, double-blind phase 3 study comparing the safety and efficacy of raltegravir with efavirenz, in combination with co-formulated tenofovir DF and emtricitabine for persons with HIV.
- **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

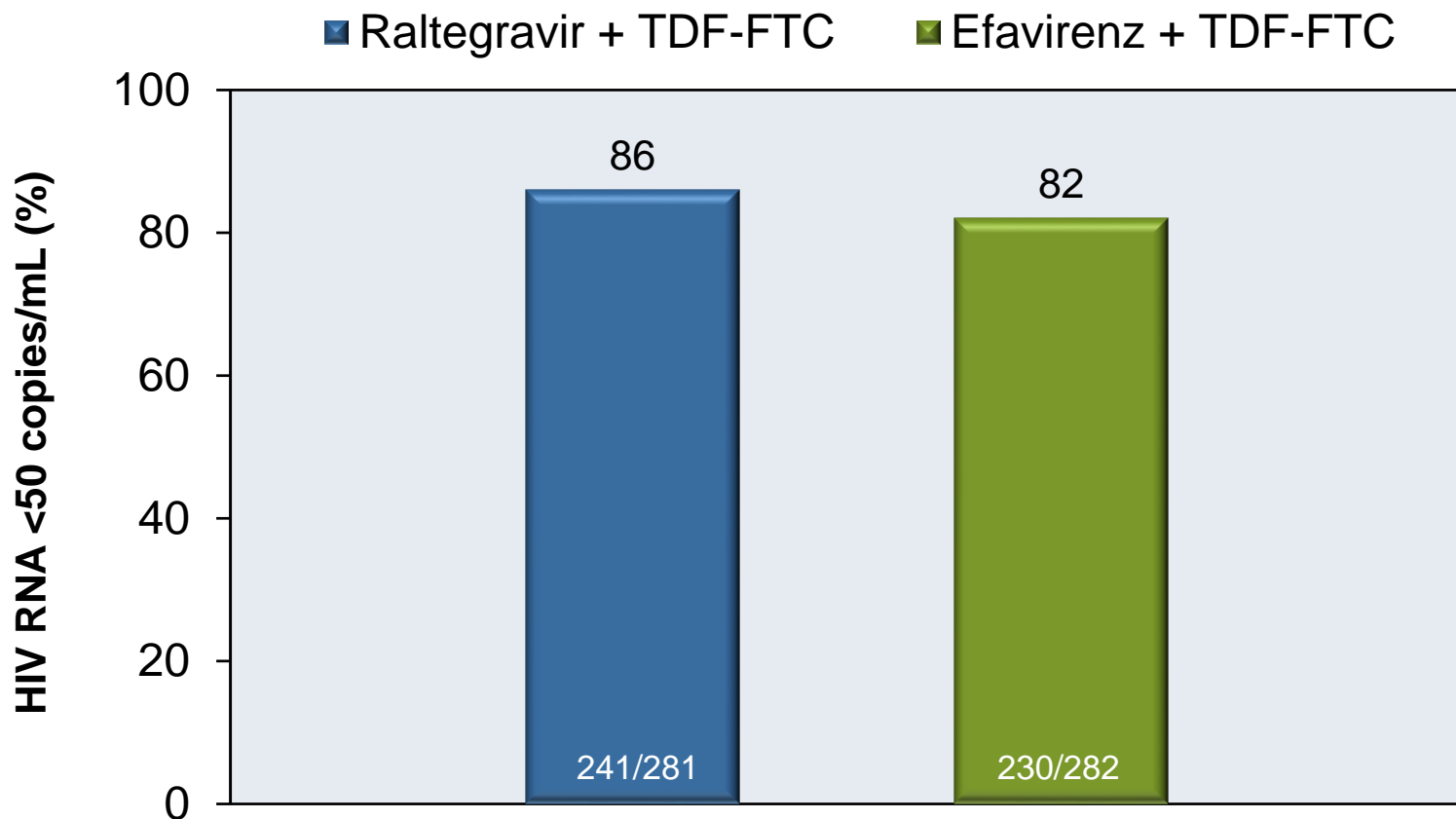
**Raltegravir BID +
TDF-FTC**
(n = 281)

Efavirenz + TDF-FTC
(n = 282)

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

STARTMRK: Result

Week 48: Virologic Response (Primary Analysis, M=F)

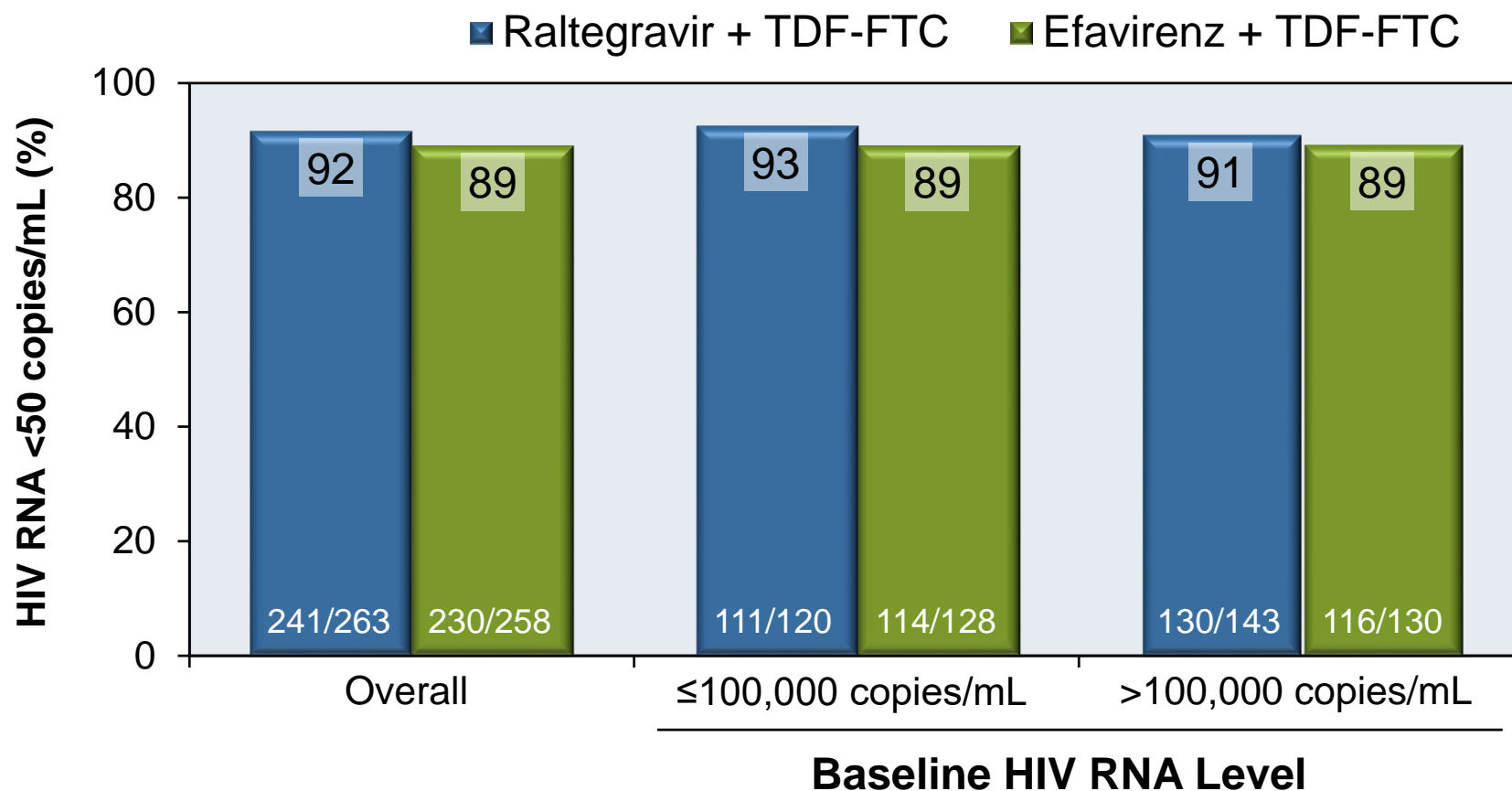


Source: Lennox JL, et al. Lancet. 2009;374:796-806.

Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC

STARTMRK: Result

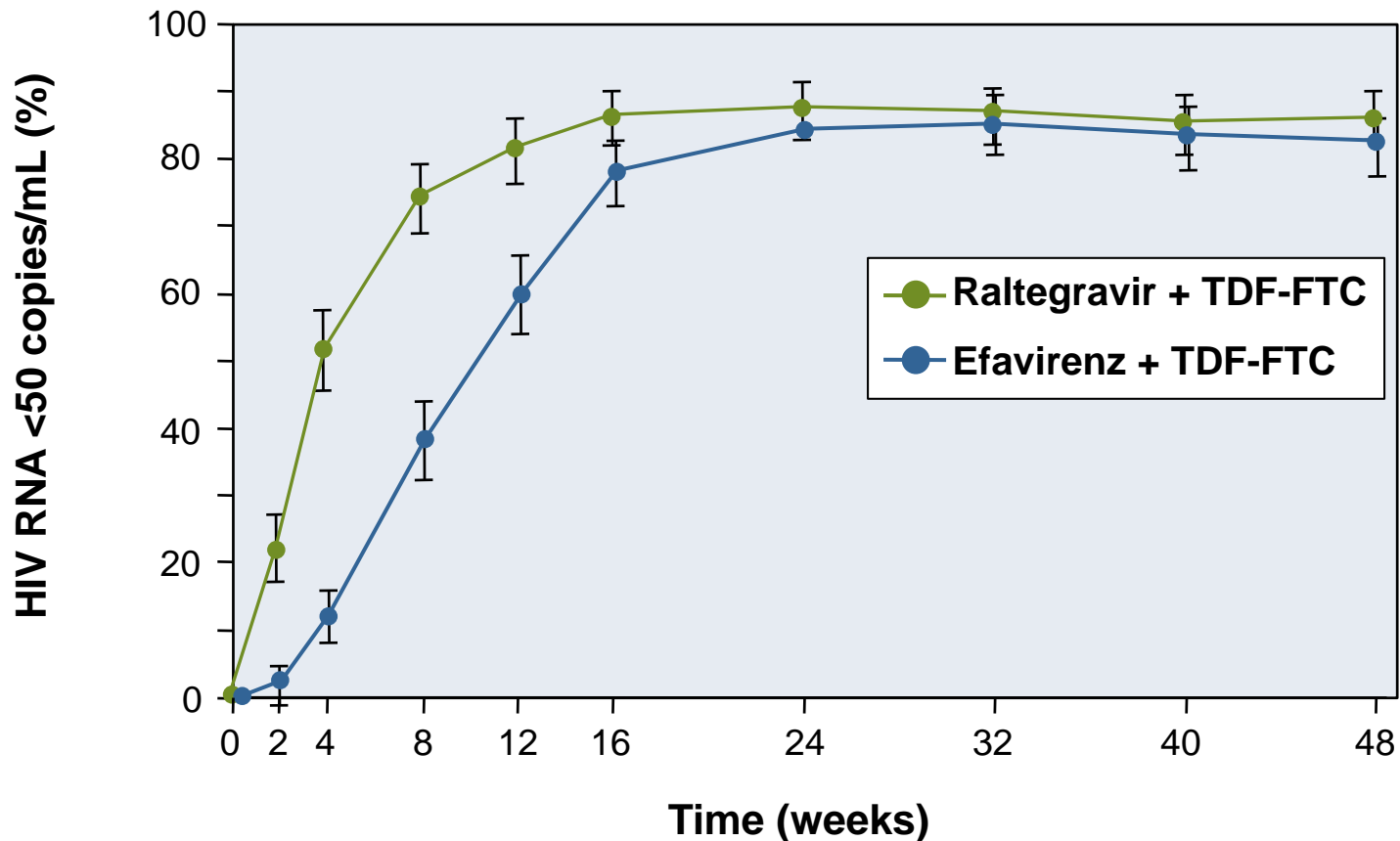
Week 48 Virologic Response (Observed-Failure Method)



Raltegravir versus Efavirenz in Combination Therapy

STARTMRK Trial: Results

Week 48 Virologic Response

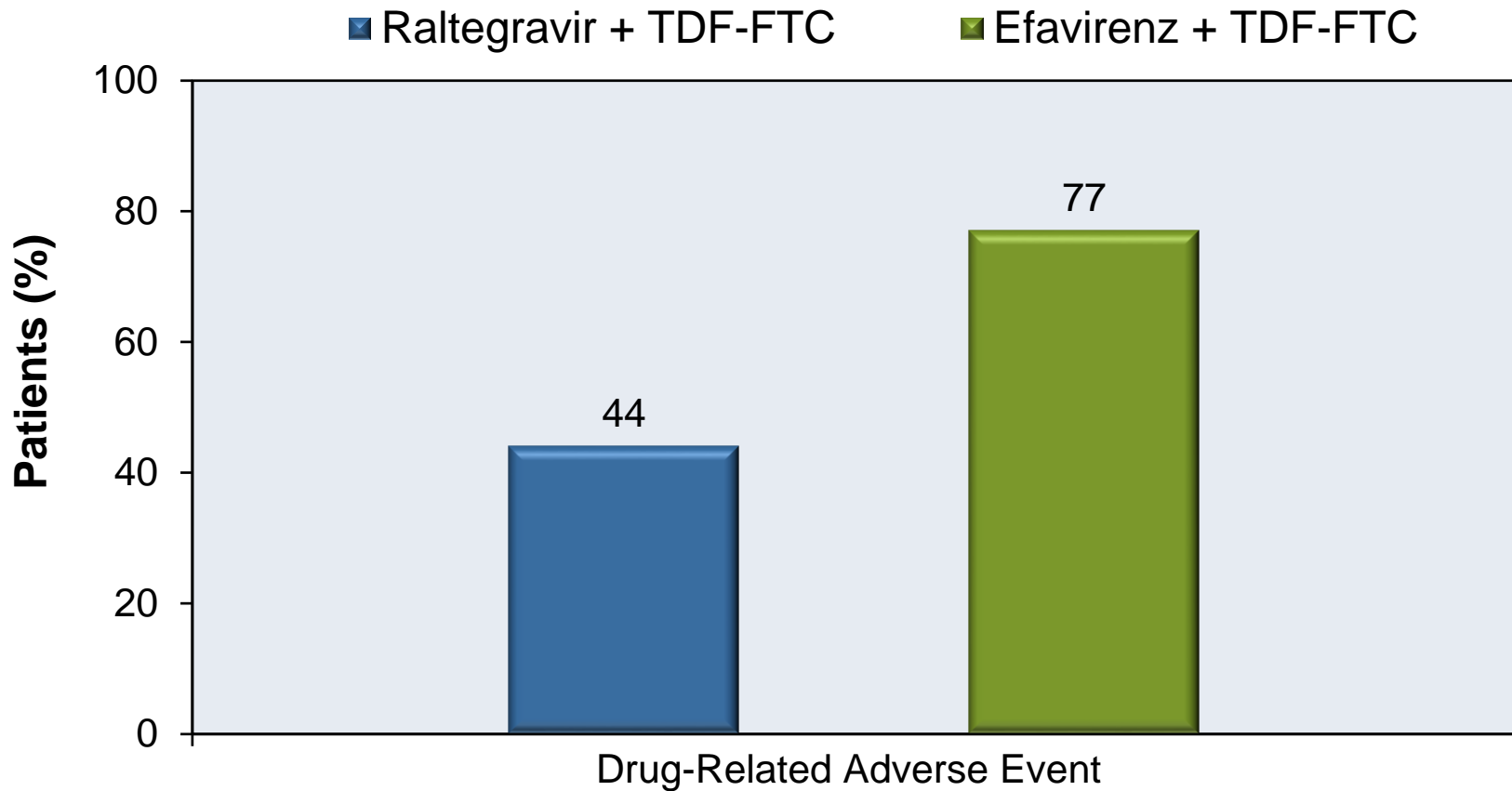


Source: Lennox JL, et al. *Lancet*. 2009;374:796-806.

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

STARTMRK: Result

Adverse Events through 48 Weeks

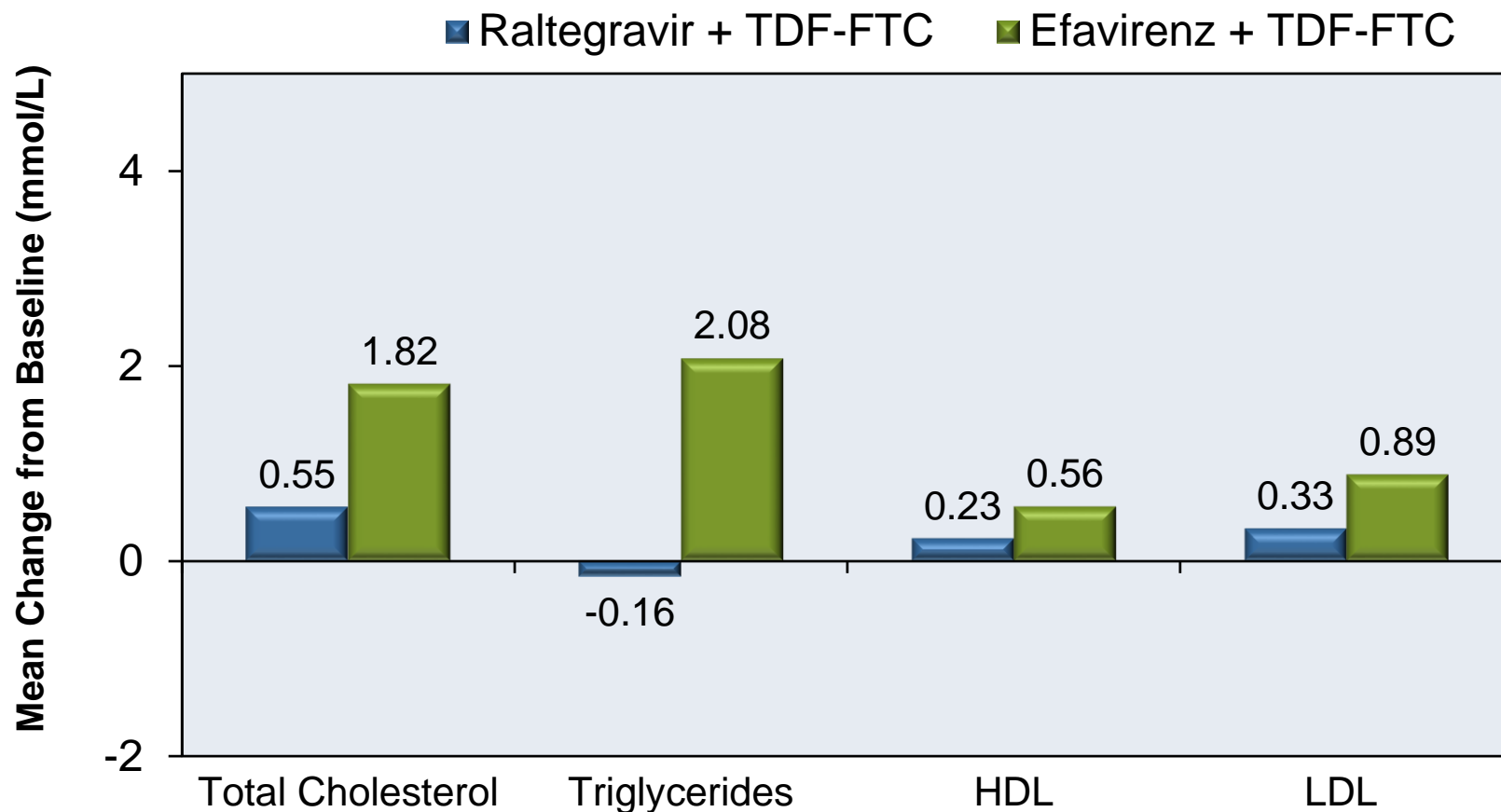


Source: Lennox JL, et al. Lancet. 2009;374(9692):796-806.

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

STARTMRK: Result

Week 48: Changes in Lipid Concentrations



Source: Lennox JL, et al. *Lancet*. 2009;374(9692):796-806.

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 (IRIS)	6%	4%

Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC STARTMRK: Conclusions

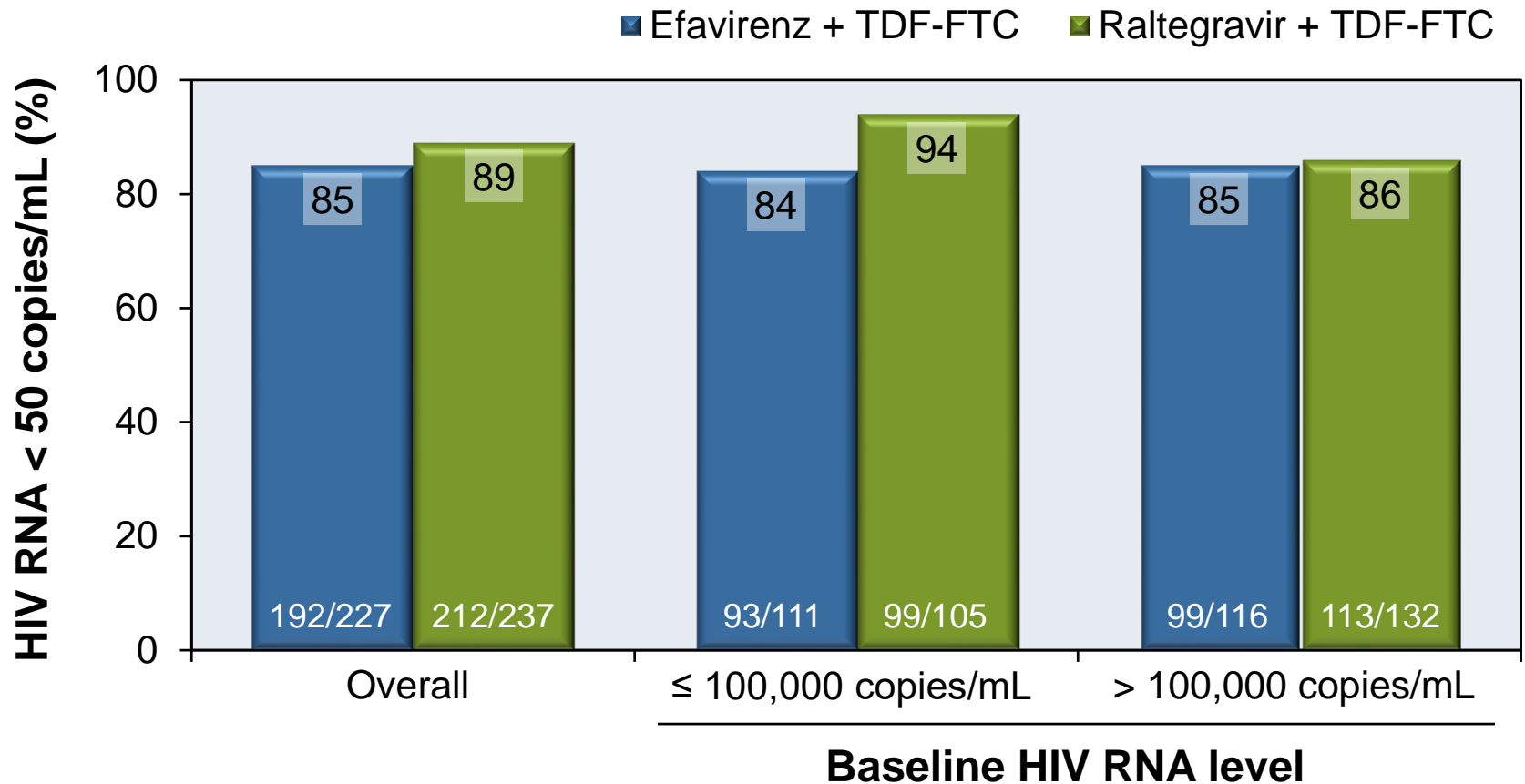
Interpretation: “Raltegravir-based combination treatment had rapid and potent antiretroviral activity, which was non-inferior to that of efavirenz at week 48. Raltegravir is a well tolerated alternative to efavirenz as part of a combination regimen against HIV-1 in treatment-naive patients.”

Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC
STARTMRK Trial: 156 Week Data

Raltegravir versus Efavirenz in Combination Therapy

STARTMRK: Results at Week 156

Week 156: Virologic Response (Observed Failure Method)



Raltegravir versus Efavirenz in Combination Therapy STARTMRK Trial: Results at Week 156

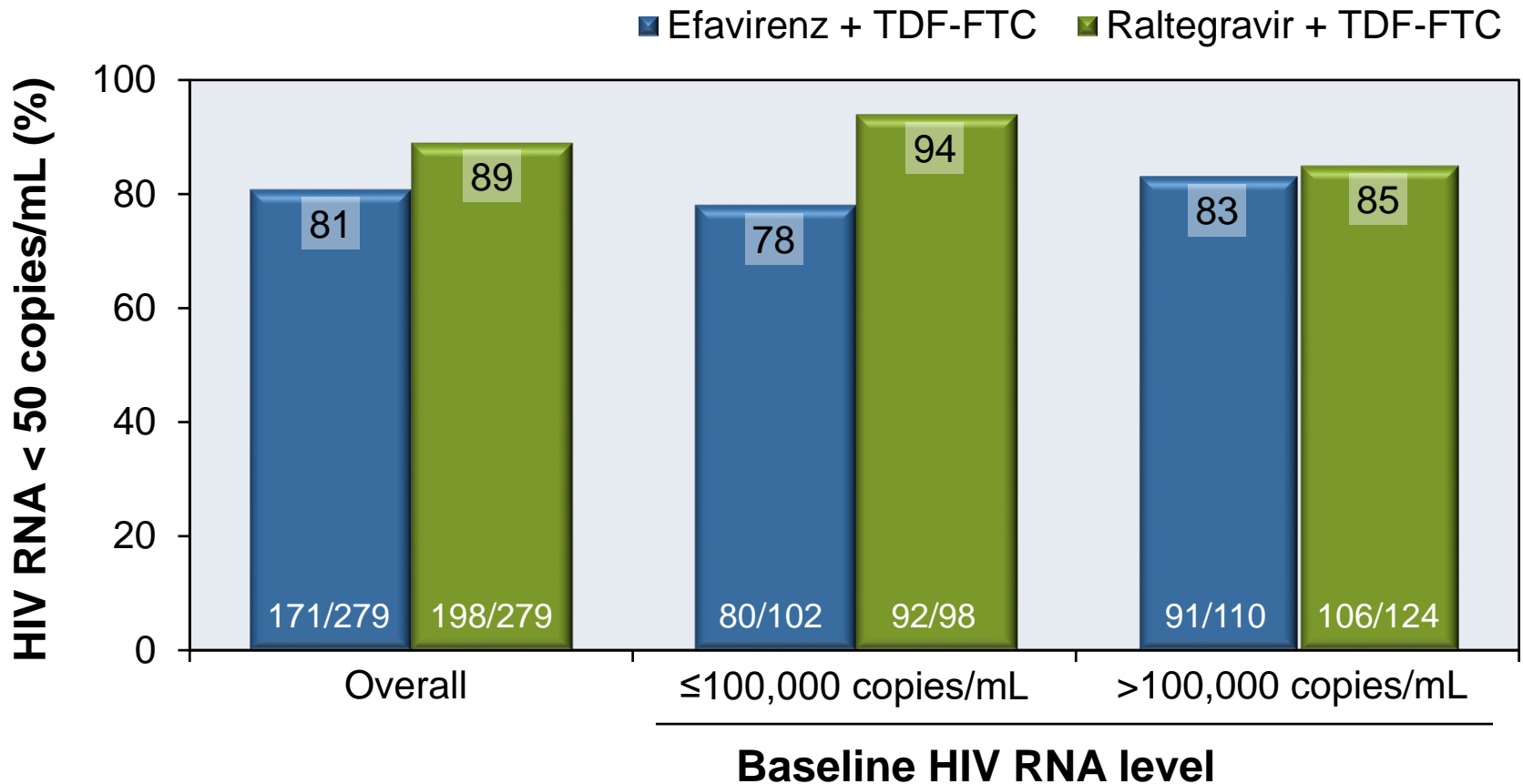
Conclusions: “When combined with tenofovir/emtricitabine in treatment-naive patients, raltegravir produced durable viral suppression and immune restoration that was at least equivalent to efavirenz through 156 weeks of therapy. Both regimens were well tolerated, but raltegravir was associated with fewer drug-related clinical adverse events and smaller elevations in lipid levels.”

Raltegravir + TDF-FTC versus Efavirenz + TDF-FTC
STARTMRK Trial: 240 Week Data

Raltegravir versus Efavirenz in Combination Therapy

STARTMRK: Results at Week 240

Week 240: Virologic Response (Observed Failure Method)



Source: Rockstroh JK, et al. J Acquir Immune Defic Syndr. 2013;63:77-85.

Raltegravir versus Efavirenz in Combination Therapy

STARTMRK: Results at Week 240

Conclusions: “In this exploratory analysis of combination therapy with tenofovir/emtricitabine in treatment-naïve patients at week 240, vRNA suppression rates and increases in baseline CD4 counts were significantly higher in raltegravir than efavirenz recipients. Over the entire study, fewer patients experienced neuropsychiatric and drug-related adverse events in the raltegravir group than in the efavirenz group. Based on better virologic and immunologic outcomes after 240 weeks, raltegravir/tenofovir/emtricitabine seemed to have superior efficacy compared with efavirenz/tenofovir/emtricitabine.”

Dolutegravir vs. Raltegravir
SPRING-2 Study

Dolutegravir versus Raltegravir

SPRING-2: Design

Study Design: SPRING-2

- **Background:** Randomized, double-blind study, phase 3 trial comparing dolutegravir versus raltegravir, both with 2NRTI backbone for persons with HIV.
- **Inclusion Criteria (n = 822)**
 - Antiretroviral-naïve patients
 - Age ≥ 18 years
 - HIV RNA $\geq 1,000$ copies/mL
 - No active CDC AIDS condition
- **Treatment Arms**
 - Dolutegravir + 2NRTIs
 - Raltegravir + 2NRTIs
 - Fixed dose 2NRTIs* = TDF-FTC or ABC-3TC

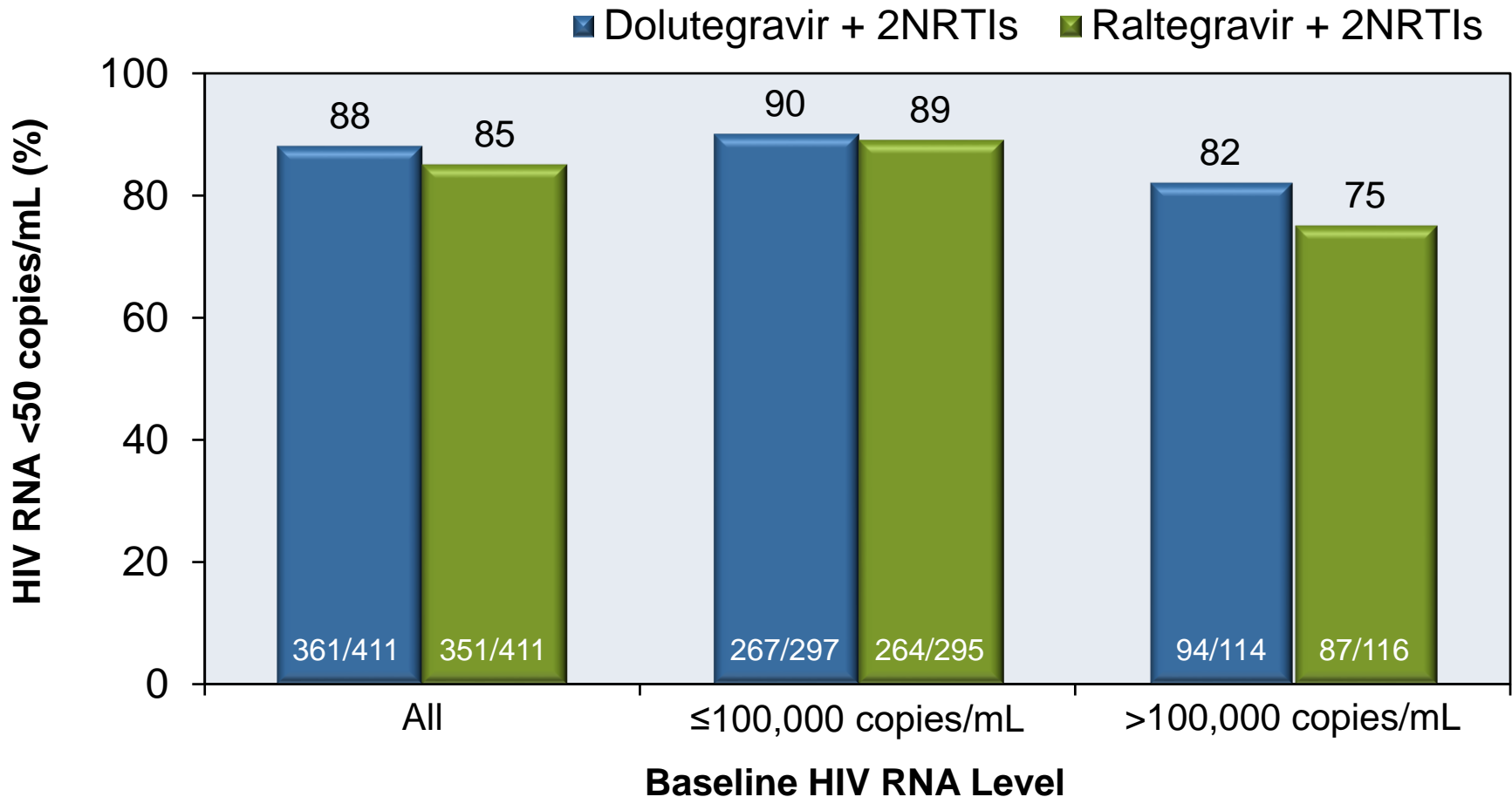
Dolutegravir: 50 mg QD
Fixed-dose NRTI backbone*
(n = 411)

Raltegravir: 400 mg BID
Fixed-dose NRTI backbone*
(n = 411)

Dolutegravir versus Raltegravir

SPRING-2: Results

Week 48: Virologic Response, by Baseline HIV RNA

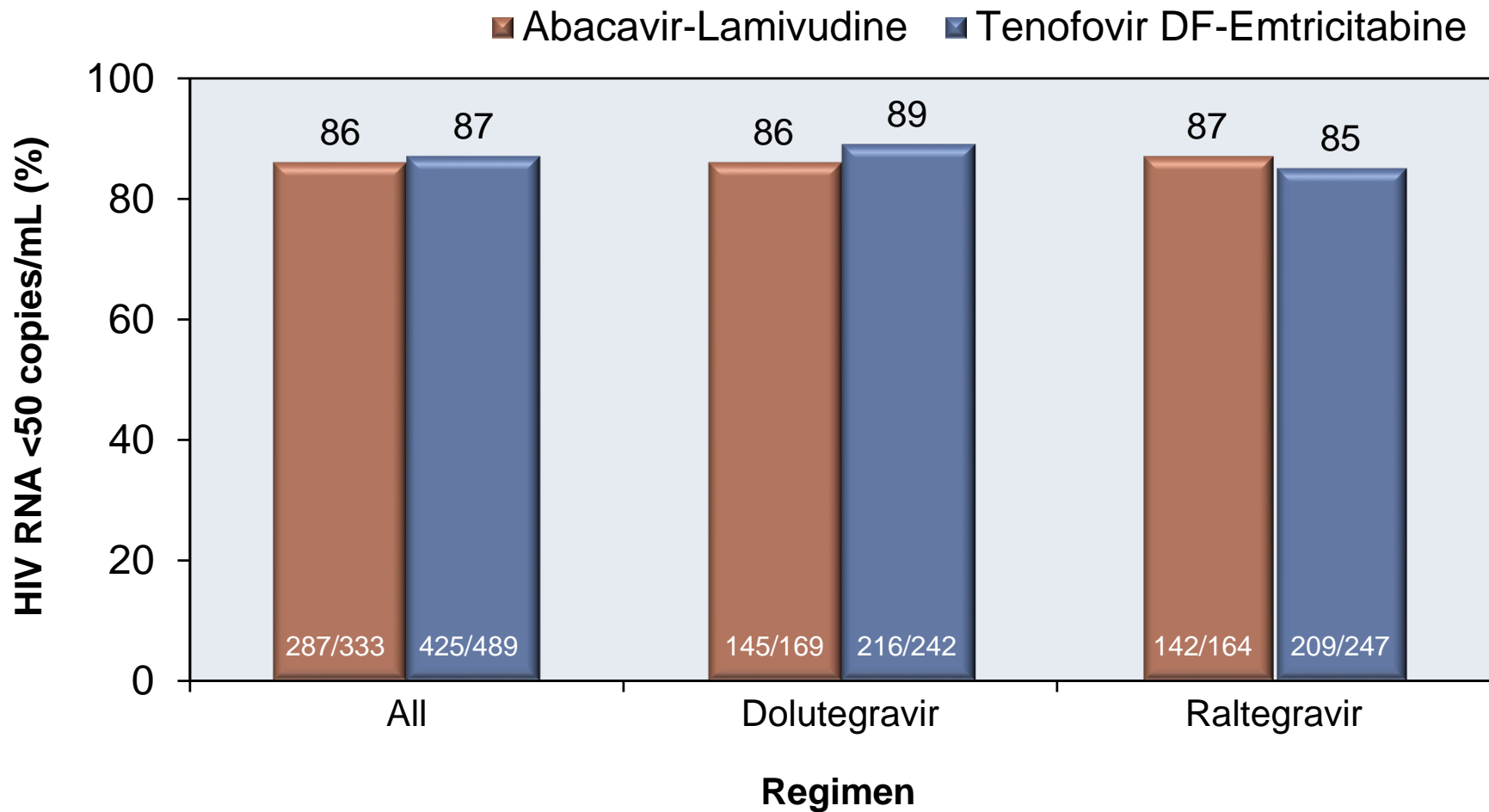


Source: Raffi F, et al. Lancet. 2013;381:735-43.

Dolutegravir versus Raltegravir

SPRING-2: Results

Week 48: Virologic Response, by NRTI Component



Source: Raffi F, et al. Lancet. 2013;381:735-43.

Dolutegravir versus Raltegravir

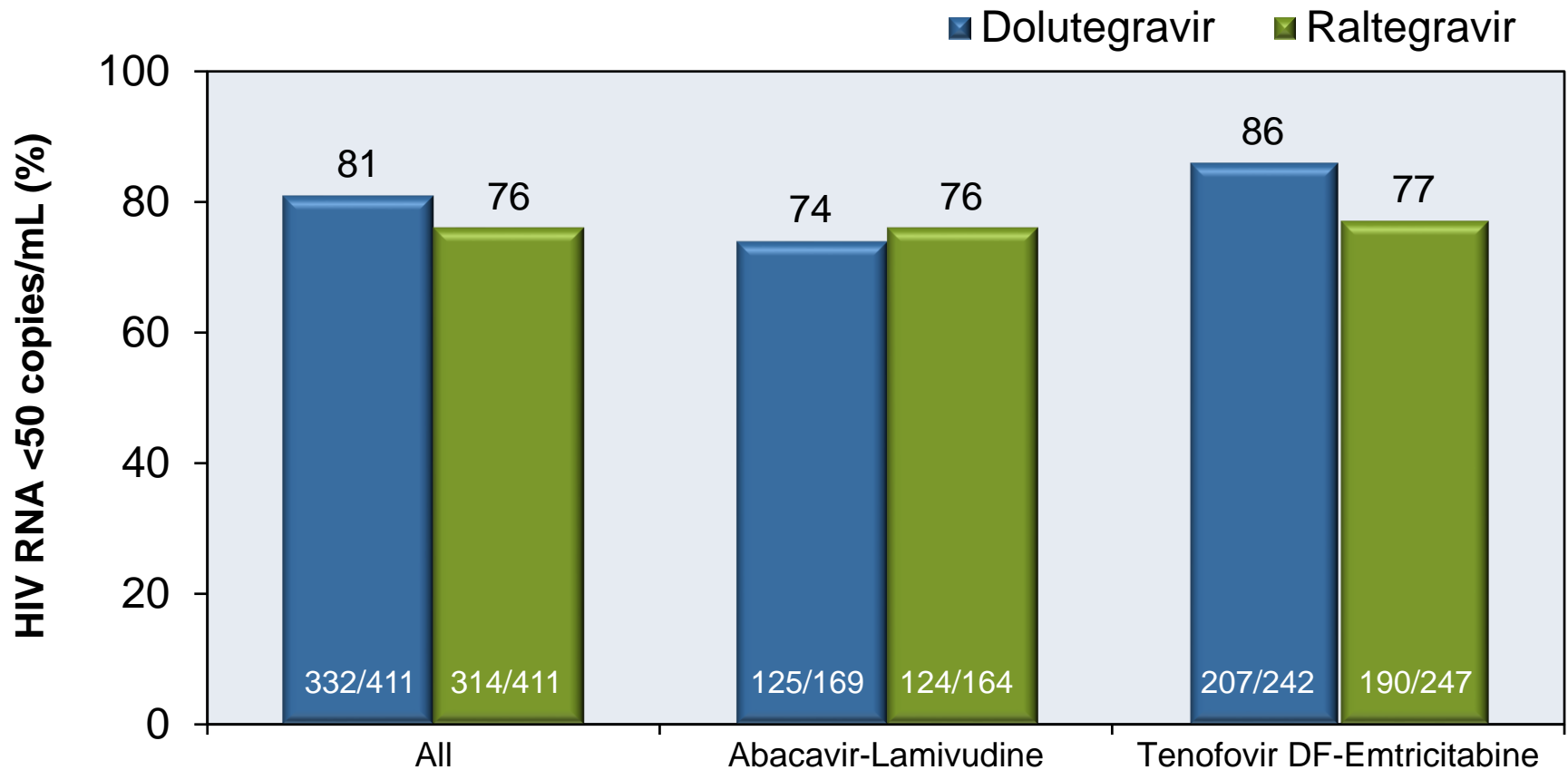
SPRING-2: Conclusions

Interpretation: “The non-inferior efficacy and similar safety profile of dolutegravir compared with raltegravir means that if approved, combination treatment with once-daily dolutegravir and fixed-dose nucleoside reverse transcriptase inhibitors would be an effective new option for treatment of HIV-1 in treatment-naive patients.”

Dolutegravir vs. Raltegravir
SPRING-2 Study: Week 96 Data

Dolutegravir + 2NRTIs versus Raltegravir + 2NRTIs SPRING-2 (Week 96): Results

Week 96 Virologic Response: Background Dual NRTI Therapy



Source: Raffi F, et al. Lancet Infect Dis. 2013;13:927-35.

Dolutegravir versus Raltegravir SPRING-2 (Week 96): Conclusions

Interpretation: “At week 96, once-daily dolutegravir was non-inferior to twice-daily raltegravir in treatment-naive, patients with HIV-1. Once-daily dosing without requirement for a pharmacokinetic booster makes dolutegravir-based therapy an attractive treatment option for HIV-1-infected treatment-naive patients.”

Raltegravir + Abacavir-Lamivudine
SHIELD Trial

Raltegravir + Abacavir-Lamivudine SHIELD: Study Design

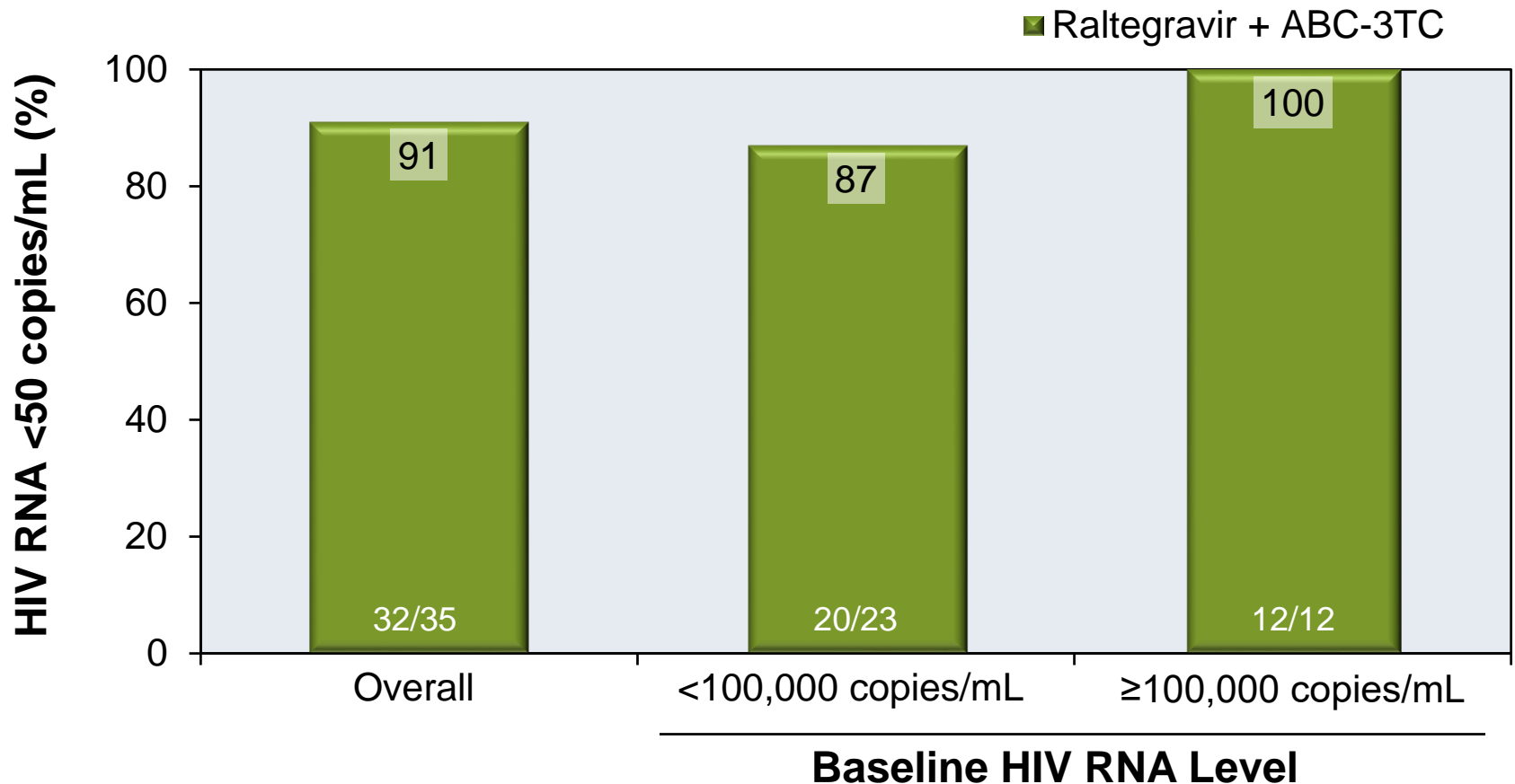
Study Design: SHIELD

- **Background:** Open-label, prospective, pilot trial evaluating efficacy of raltegravir in combination with abacavir-lamivudine in treatment-naïve persons with HIV.
- **Inclusion Criteria (n = 37)**
 - Age ≥ 18 years
 - Antiretroviral therapy naïve
 - HIV RNA > 1000 copies/mL
 - HLA-B*5701 negative
 - No resistance to any study drug
- **Treatment Arm**
 - Raltegravir 400 mg BID + Abacavir-Lamivudine QD

**Raltegravir 400 mg BID +
Abacavir-Lamivudine QD**
(n = 37)

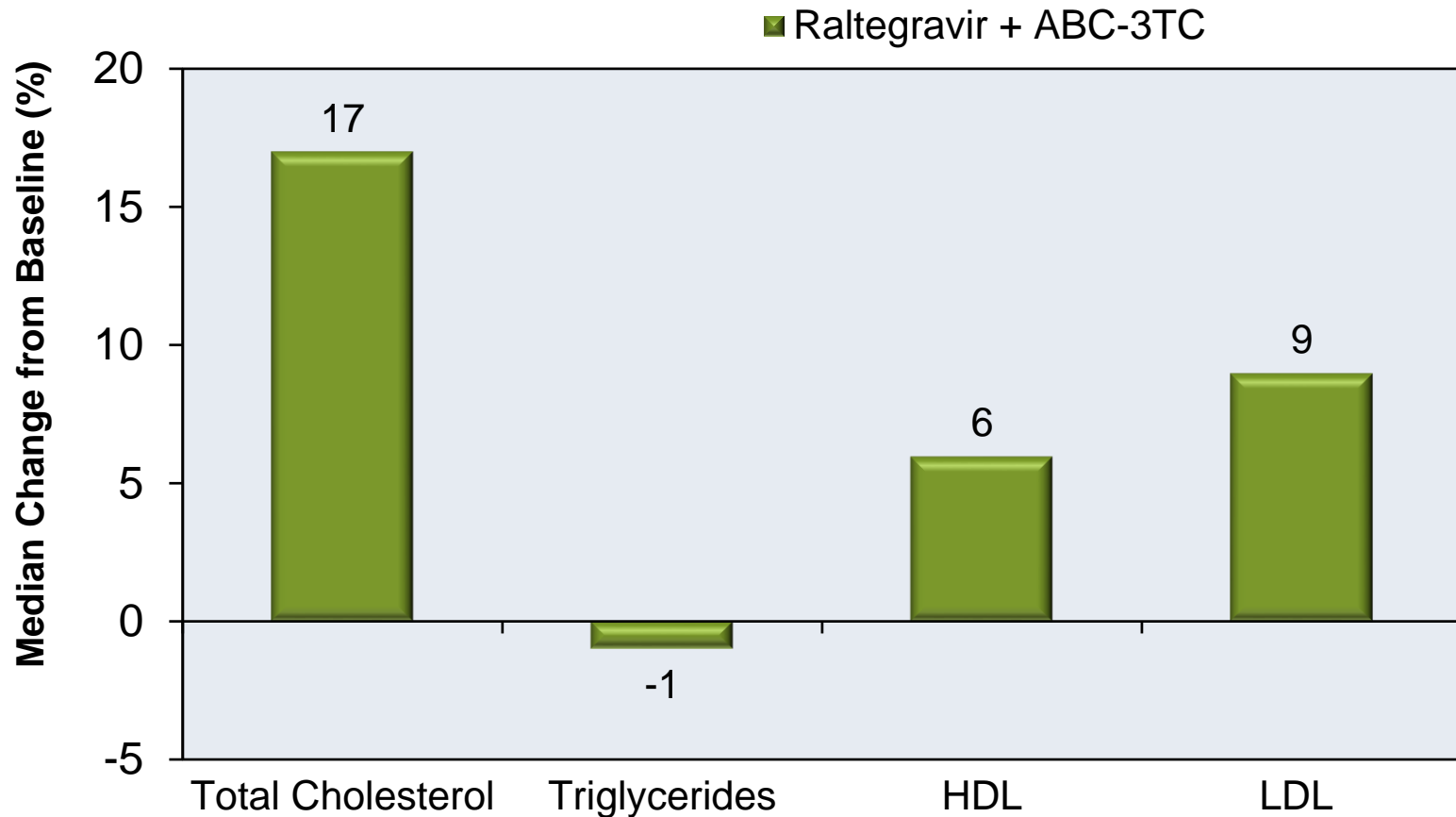
Raltegravir + Abacavir-Lamivudine SHIELD: Result

Week 48: Virologic Response (missing/discontinuation = failure)



Raltegravir + Abacavir-Lamivudine SHIELD: Result

Week 48: Changes in Lipid Concentrations



Source: Young B, et al. HIV Clin Trials. 2010;11:260-9.

Raltegravir + Abacavir-Lamivudine SHIELD: Conclusions

Conclusions: “In this pilot study, abacavir/lamivudine plus raltegravir was effective and generally well-tolerated over 48 weeks with modest changes in fasting lipids.”

Raltegravir vs Darunavir/r vs Atazanavir/r
ARDENT (ACTG 5257) Trial

Raltegravir vs Darunavir/r vs Atazanavir/r ARDENT (ACTG 5257): Study Design

Study Design: ARDENT (ACTG 5257)

- **Background:** Open-label, randomized, phase 3 trial evaluating virologic efficacy and tolerability of 3 NNRTI-sparing antiretroviral therapy regimens for persons with HIV.
- **Inclusion Criteria (n = 1809)**
 - Age ≥18 years
 - Antiretroviral-naïve
 - CD4 >200 cells/mm³
 - HIV RNA >1,000 copies/mL
 - No resistance to NRTIs or PIs
- **Treatment Arms**
 - ATZ 300 mg + RTV 100 mg + TDF-FTC
 - RAL 400 mg BID + TDF-FTC
 - DRV 800 mg + RTV 100 mg + TDF-FTC

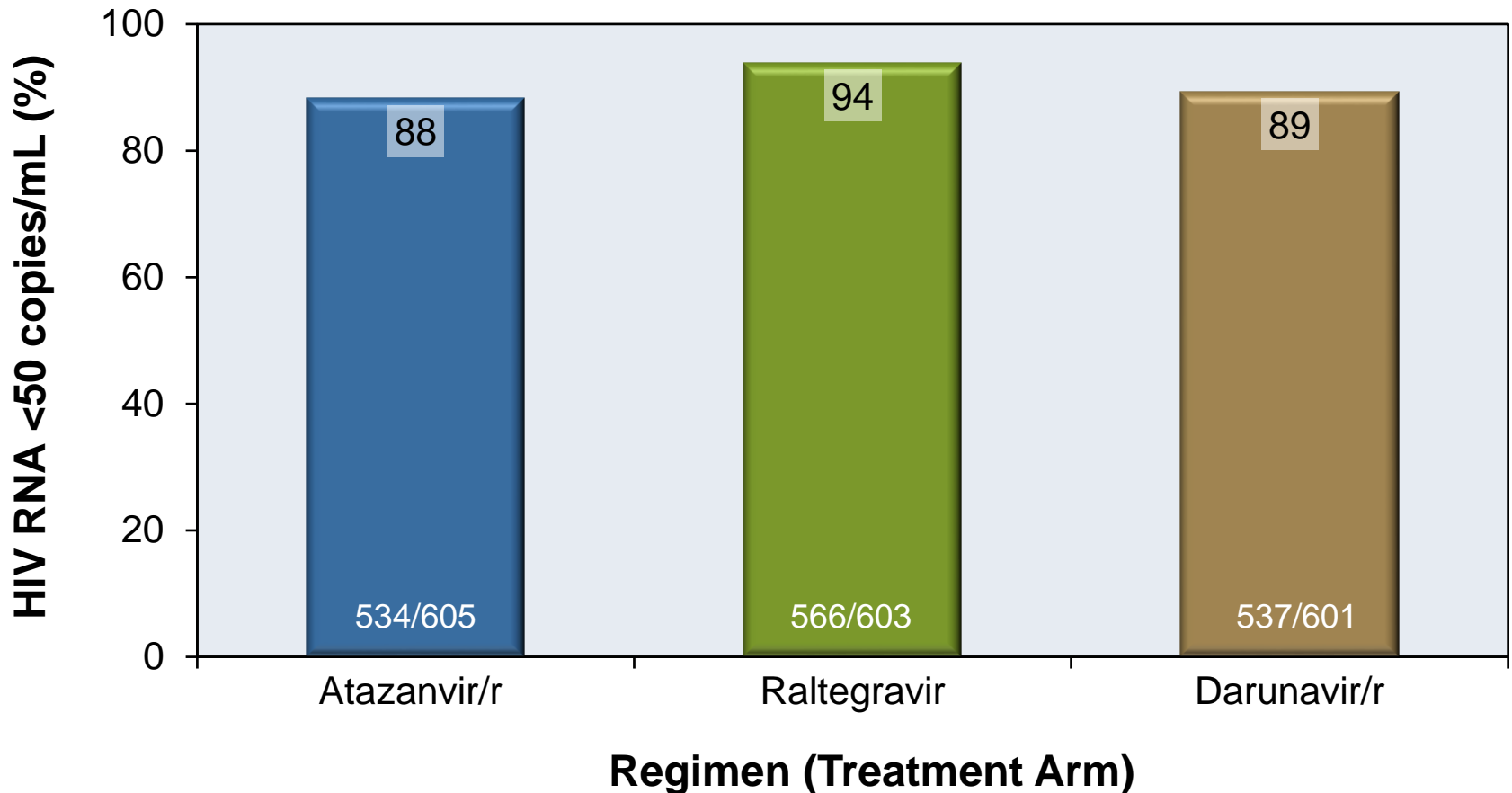
**Atazanavir 300 mg QD +
RTV 100 mg QD + TDF-FTC QD**
(n = 605)

**Raltegravir 400 mg BID +
TDF-FTC QD**
(n = 603)

**Darunavir 800 mg QD +
RTV 100 mg QD + TDF-FTC QD**
(n = 601)

Raltegravir vs Darunavir/r vs Atazanavir/r ARDENT (ACTG 5257): Results

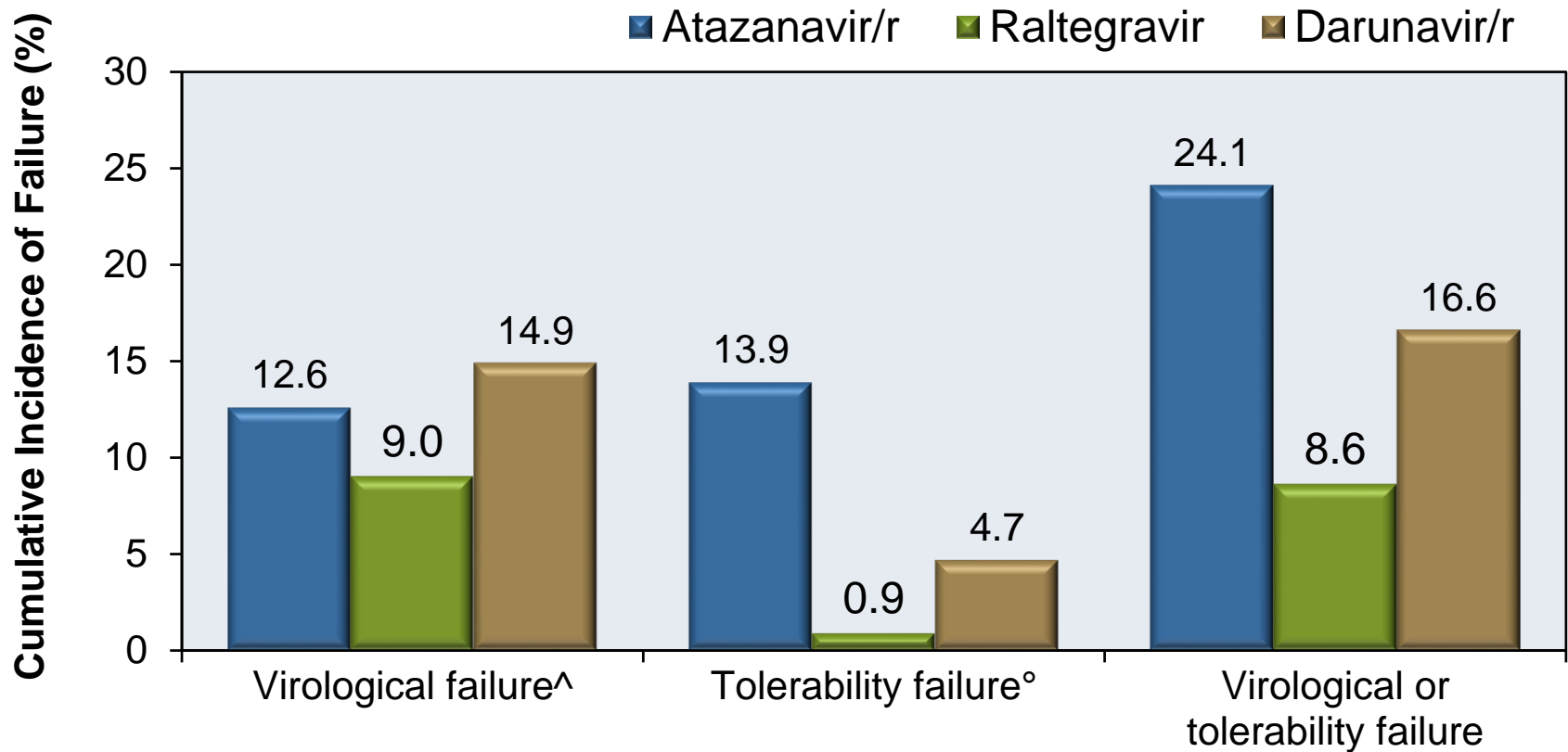
Week 96: Virologic Response (ITT analysis)



Source: Lennox JL, et al. Ann Intern Med. 2014;161:461-71.

Raltegravir vs Darunavir/r vs Atazanavir/r ARDENT (ACTG 5257): Results

Week 96: Virologic and Tolerability Failures



[^]Virological failure: HIV RNA >1,000 copies/mL after 16 weeks or >200 copies/mL after 24 weeks

[°]Tolerability failure: discontinuation of raltegravir, darunavir/r, or atazanavir/r for toxicity

Source: Lennox JL, et al. *Ann Intern Med.* 2014;161:461-71.

Raltegravir vs Darunavir/r vs Atazanavir/r ARDENT (ACTG 5257): Results

Genotype Resistance Testing in ACTG 5257			
Variable	Atazanavir/r	Raltegravir	Darunavir/r
Virologic failure (n)	95	85	115
Genotype testing complete	75	65	99
Any resistance	9	18	4
PI resistance	0	0	0
NRTI-only resistance	8	7	3
FTC	5	7	3
TDF	2	0	0
TDF and FTC	1	0	0
INSTI-only resistance	1	1	1
NRTI and INSTI resistance	0	10	0
RAL and FTC	0	7	0
RAL, TDF and FTC	0	3	0

Source: Lennox JL, et al. Ann Intern Med. 2014;161:461-71.

Raltegravir vs Darunavir/r vs Atazanavir/r ARDENT (ACTG 5257): Conclusions

Conclusion: “Over 2 years, all 3 regimens attained high and equivalent rates of virologic control. Tolerability of regimens containing raltegravir or ritonavir-boosted darunavir was superior to that of the ritonavir-boosted atazanavir regimen.”

INITIAL THERAPY: ONCE DAILY

Raltegravir

Raltegravir 800 mg Once Daily versus 400 mg Twice Daily
QDMRK Trial

[Raltegravir 800 mg Once Daily or 400 mg Twice Daily] + TDF-FTC QDMRK: Study Design

Study Design: QDMRK Study

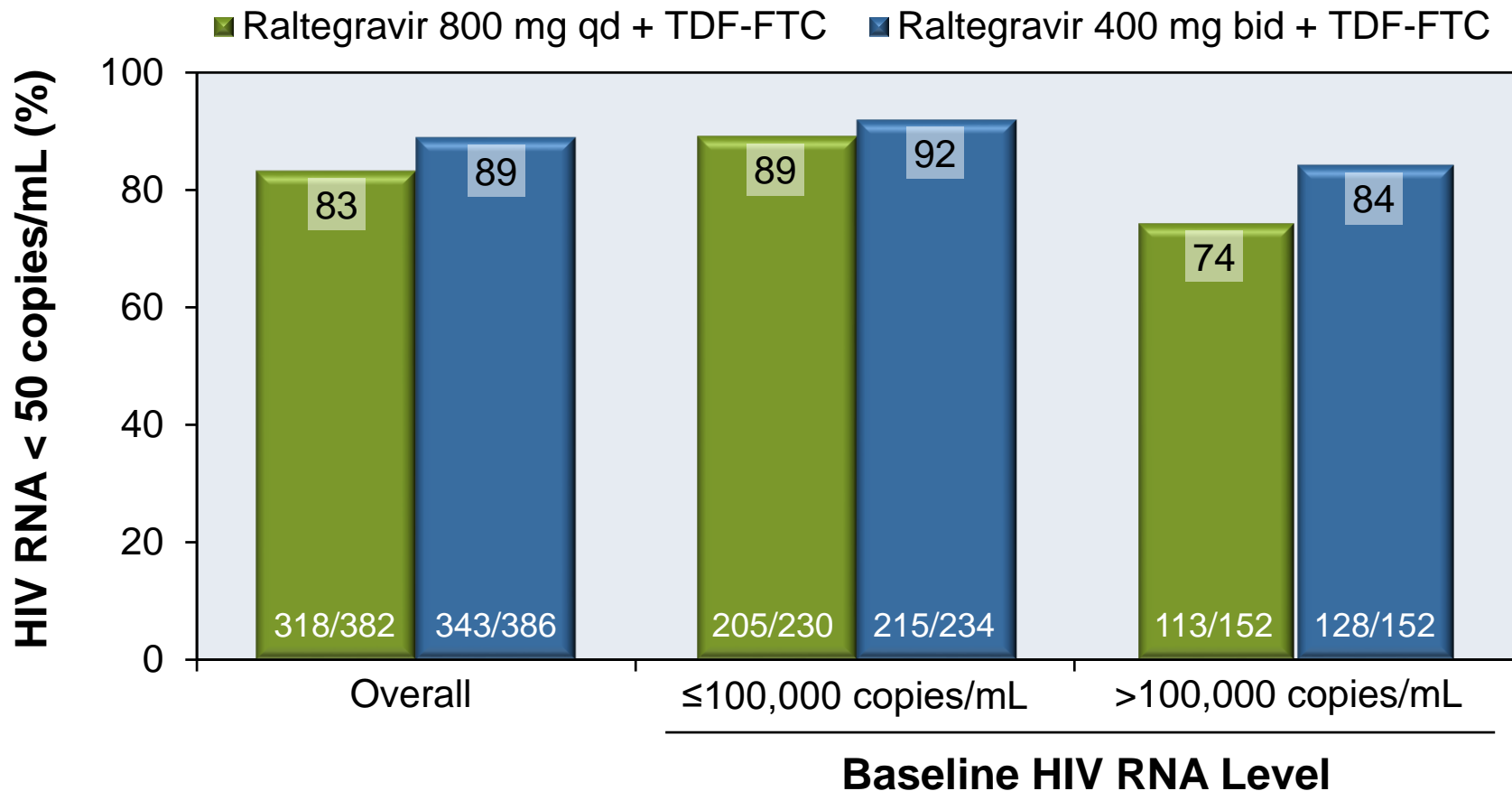
- **Background:** Randomized, double-blind, phase 3 trial in antiretroviral-naïve persons with HIV to compare the efficacy of once-daily with twice-daily Raltegravir.
- **Inclusion Criteria (n = 775)**
 - Age ≥18 years
 - Antiretroviral-naïve
 - HIV RNA >5,000 copies/mL
 - No CD4 criteria
 - No relevant mutations
- **Treatment Arms**
 - Raltegravir 800 mg QD + TDF-FTC
 - Raltegravir 400 mg BID + TDF-FTC

**Raltegravir 800 mg QD +
TDF-FTC**
(n = 386)

**Raltegravir 400 mg BID +
TDF-FTC**
(n = 389)

[Raltegravir 800 mg Once Daily or 400 mg Twice Daily] + TDF-FTC QDMRK: Results

Virologic Response: Week 48 (non-completer = failure)



[Raltegravir 800 mg Once Daily or 400 mg Twice Daily] + TDF-FTC QDMRK: Conclusions

Interpretation: “Despite high response rates with both regimens, once-daily raltegravir cannot be recommended in place of twice-daily dosing.”

Raltegravir 1200 mg Once Daily versus 400 mg Twice Daily
ONCEMRK Trial

Raltegravir 1200 mg Once Daily versus 400 mg Twice Daily ONCEMRK: Study Design

Study Design: ONCEMRK STUDY

- **Background:** Randomized, double-blind, phase 3 trial in antiretroviral-naïve adults with HIV comparing raltegravir 1200 mg once-daily with raltegravir 400 mg twice-daily, both in combination with tenofovir DF-emtricitabine.
- **Inclusion Criteria (n = 797 received treatment)**
 - Age ≥18 years
 - Antiretroviral-naïve
 - HIV RNA ≥1,000 copies/mL
- **Treatment Arms**
 - *Raltegravir 1200 mg QD + TDF-FTC
 - Raltegravir 400 mg BID + TDF-FTC

2x

1x

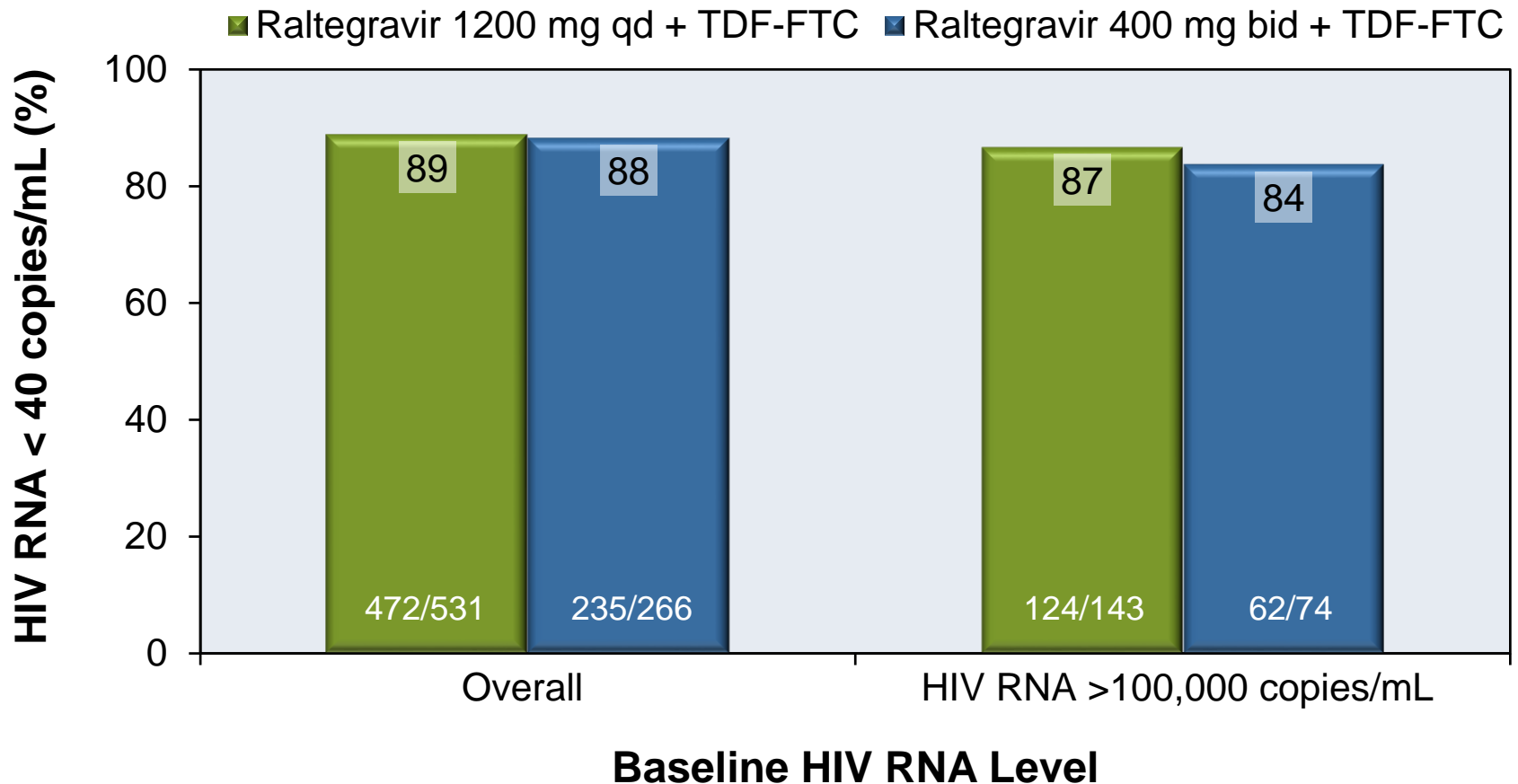
**Raltegravir 1200 mg QD +
TDF-FTC**
(n = 531)

**Raltegravir 400 mg BID +
TDF-FTC**
(n = 266)

*The 1200 mg dose of raltegravir given as two 600 mg tablets

Raltegravir 1200 mg Once Daily versus 400 mg Twice Daily ONCEMRK: Result

Week 48: Virologic Response (non-completer = failure)



Raltegravir 1200 mg Once Daily versus 400 mg Twice Daily ONCEMRK: Conclusions

Conclusions: “A once daily raltegravir 1200 mg regimen was non-inferior compared with raltegravir 400 mg twice daily for initial treatment of HIV-1 infection. These results support the use of raltegravir 1200 mg once daily for first-line therapy.”

INITIAL THERAPY: DUAL THERAPY

Raltegravir

Lopinavir-RTV + Raltegravir vs. Lopinavir-RTV + TDF-FTC
PROGRESS Trial

Lopinavir-RTV + Raltegravir vs. Lopinavir-RTV + TDF-FTC

PROGRESS: Study Design

Study Design: PROGRESS

- **Background:** Randomized, open-label non-inferiority trial comparing efficacy, safety, and tolerability of lopinavir-ritonavir with either raltegravir or tenofovir DF-emtricitabine in treatment-naïve persons with HIV.
- **Inclusion Criteria (n = 206)**
 - Antiretroviral-naïve patients
 - Age ≥18 years
 - HIV RNA ≥1000 copies/mL
 - Antiretroviral therapy naïve
 - No resistance to lopinavir, TDF, or FTC
- **Treatment Arms**
 - Lopinavir-RTV BID + Raltegravir BID
 - Lopinavir-RTV BID + TDF-FTC QD

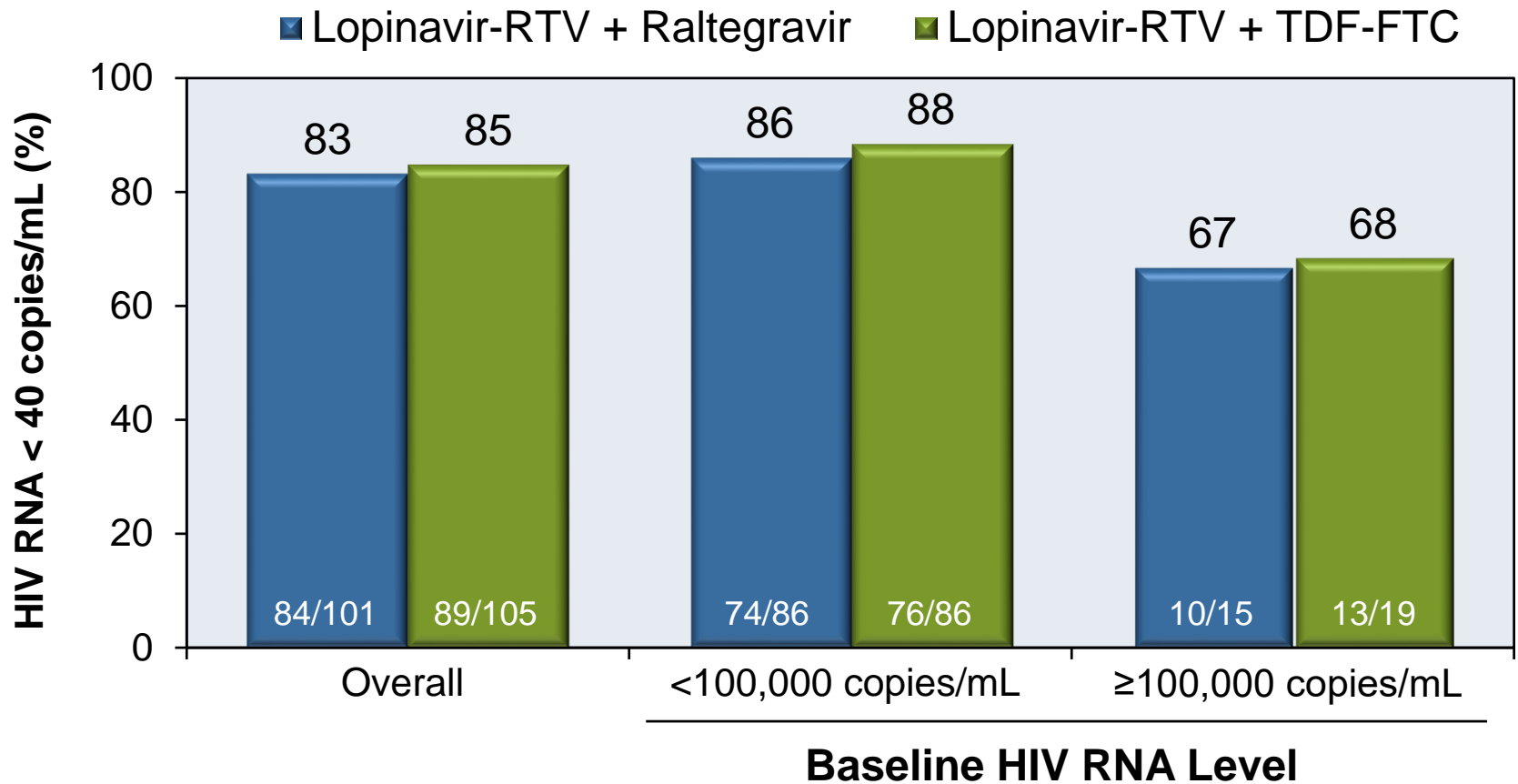
**Lopinavir-ritonavir BID +
Raltegravir BID +**
(n = 101)

**Lopinavir-ritonavir BID +
TDF-FTC QD**
(n = 105)

Lopinavir-RTV + Raltegravir vs. Lopinavir-RTV + TDF-FTC

PROGRESS: Result

Week 48 Virologic Response (FDA-TLOVR Algorithm)



Lopinavir-RTV + Raltegravir vs. Lopinavir-RTV + TDF-FTC

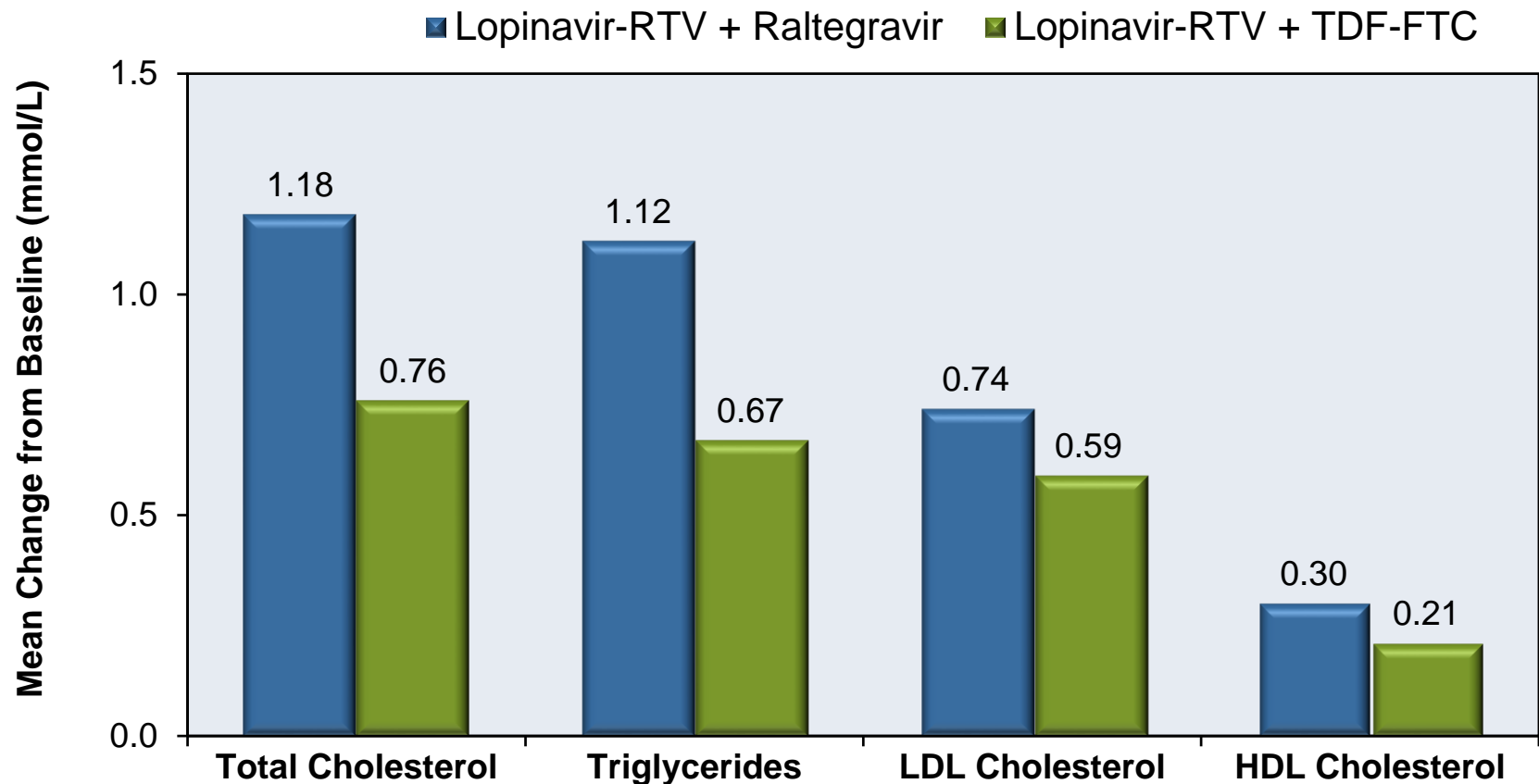
PROGRESS: Result

Possibly/probably Treatment-Related Moderate to Serious Adverse Events Occurring in $\geq 2\%$ of Subjects in Either Arm		
Variable	LPV-RTV + RAL (n = 101)	LPV-RTV + TDF-FTC (n = 105)
Any adverse event (%)	27.7%	27.6%
Hyperlipidemia	13.9%	8.6%
Diarrhea	7.9%	13.3%
Alanine Aminotransferase increased	2%	1%

Lopinavir-RTV + Raltegravir vs. Lopinavir-RTV + TDF-FTC

PROGRESS: Result

Week 48: Analysis of Lipids



Source: Reynes J, et al. HIV Clin Trials. 2011;12:255-67.

Lopinavir-RTV + Raltegravir vs. Lopinavir-RTV + TDF-FTC

PROGRESS: Conclusions

Conclusions: “The HIV treatment regimen of LPV/r + RAL resulted in noninferior efficacy and comparable safety and tolerability compared with a traditional NRTI-containing regimen through 48 weeks of treatment. These results support further evaluation of the LPV/r + RAL regimen.”

Raltegravir + Atazanavir vs. Atazanavir/r + TDF-FTC
SPARTAN Trial

Atazanavir + Raltegravir versus Atazanavir/r + TDF-FTC

SPARTAN: Study Design

Study Design: SPARTAN

- **Background:** Randomized, open-label, noncomparative phase 2b trial evaluating the efficacy, safety, and resistance profile of a NRTI-and ritonavir-sparing regimen containing atazanavir and Raltegravir in persons with HIV.
- **Inclusion Criteria (n = 94)**
 - Age ≥ 18 years
 - Antiretroviral-naïve
 - HIV RNA ≥ 5000 copies/mL
 - No CD4 count restrictions
- **Treatment Arms**
 - Atazanavir 300 mg BID + Raltegravir 400 mg BID
 - Atazanavir 300 mg + RTV 100 mg QD + TDF-FTC

2x

**Atazanavir 300 mg BID +
Raltegravir 400 mg BID**
(n = 63)

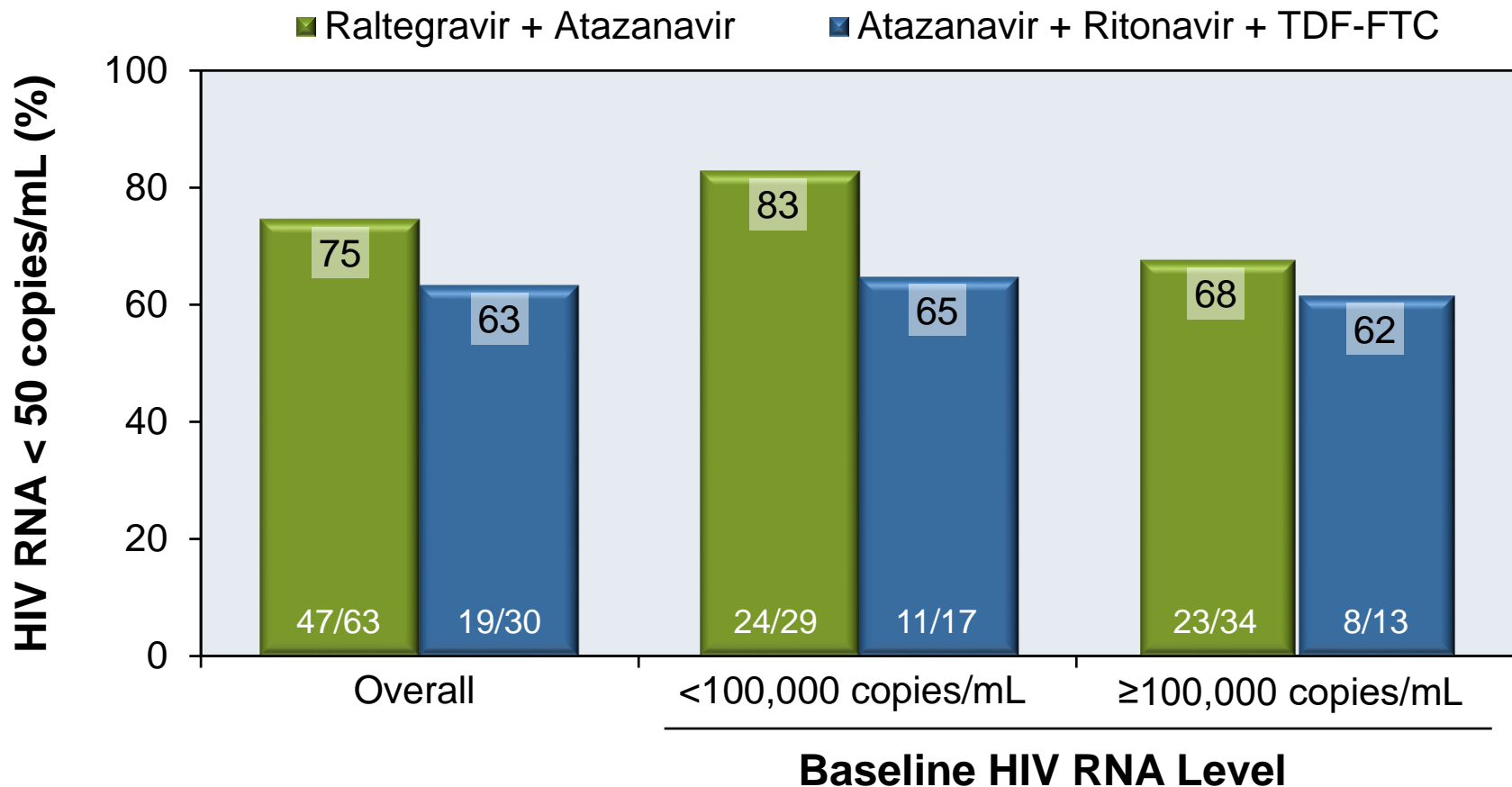
1x

**Atazanavir 300 mg QD +
RTV 100 mg QD +
TDF-FTC QD**
(n = 31)

Atazanavir + Raltegravir versus Atazanavir/r + TDF-FTC

SPARTAN: Result

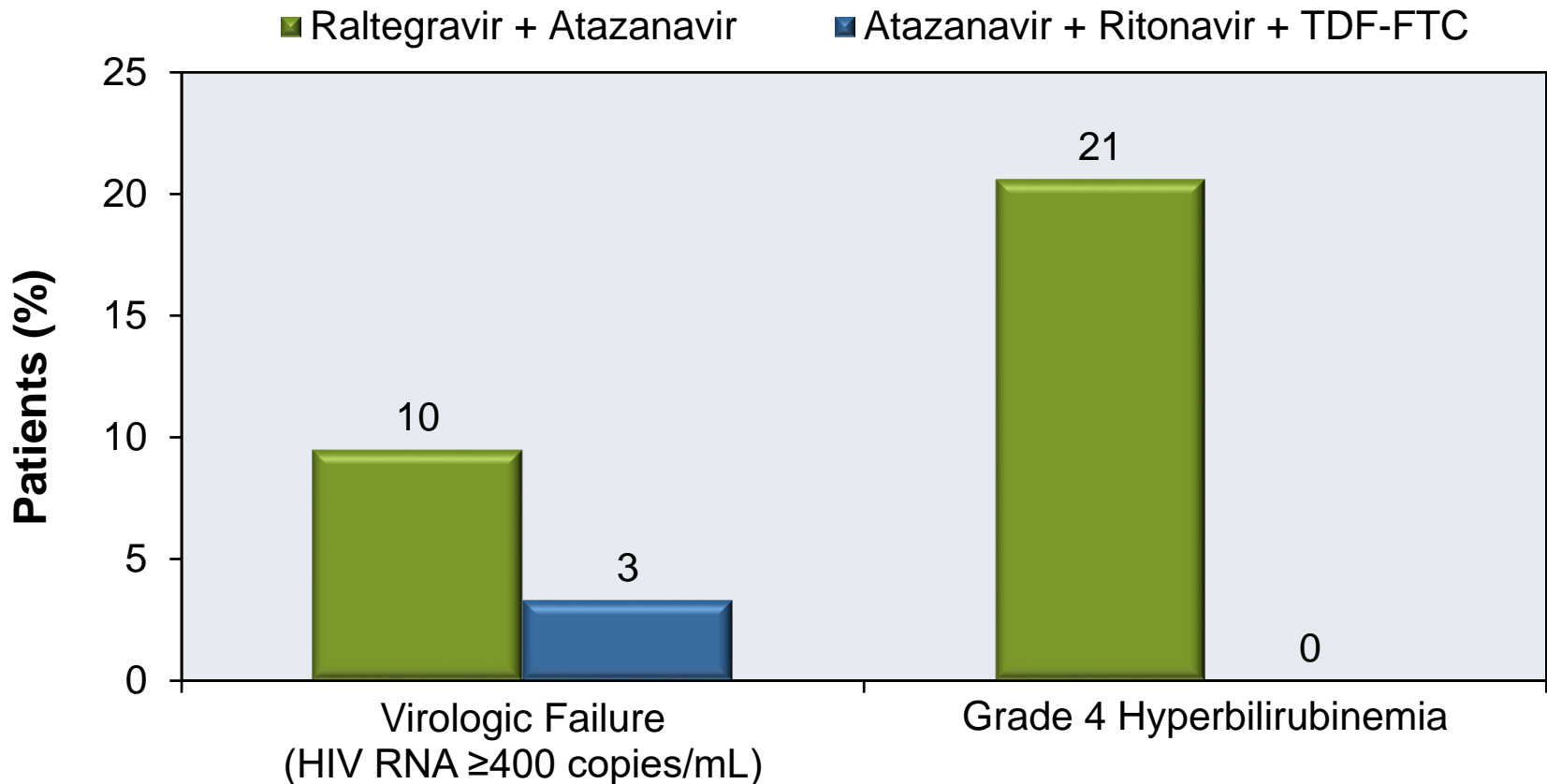
Week 24: Virologic Response (non-completer = failure)



Atazanavir + Raltegravir versus Atazanavir/r + TDF-FTC

SPARTAN: Result

Virologic Failure and Hyperbilirubinemia



Atazanavir + Raltegravir versus Atazanavir/r + TDF-FTC SPARTAN: Conclusions

Conclusions: “ATV + RAL, an experimental NRTI- and RTV-sparing regimen, achieved virologic suppression rates comparable to current standards of care for treatment-naïve patients. The overall profile did not appear optimal for further clinical development given its development of resistance to RAL and higher rates of hyperbilirubinemia with twice-daily ATV compared with ATV/RTV.”

Raltegravir + Darunavir/r versus TDF-FTC + Darunavir/r
RADAR Trial

Raltegravir + Darunavir/r versus TDF-FTC + Darunavir/r

RADAR: Study Design

Study Design: RADAR

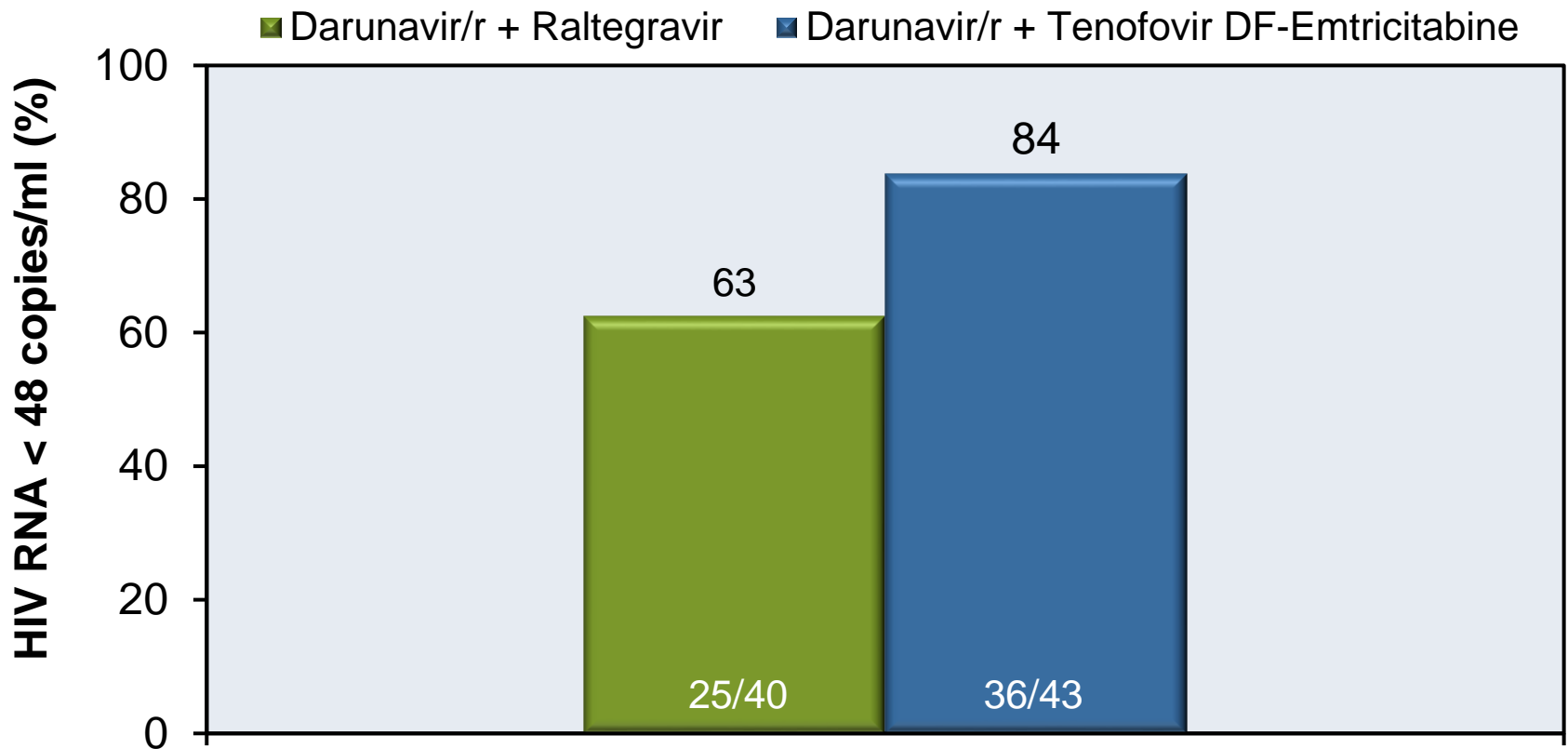
- **Background:** Randomized, open-label, pilot study to evaluate the efficacy and safety of raltegravir plus boosted darunavir versus tenofovir DF-emtricitabine plus boosted darunavir.
- **Inclusion Criteria (n = 85)**
 - Age ≥ 18 years
 - Antiretroviral-naïve
 - HIV RNA $> 5,000$ copies/mL
 - CD4 > 100 cells/mm³
 - No resistance to TDF, FTC, or DRV (resistance to RAL was not tested at baseline)
- **Treatment Arms**
 - Darunavir 800 mg QD + RTV 100 mg QD + Raltegravir 400 mg BID
 - Darunavir 800 mg + RTV 100 mg QD + TDF-FTC QD

Darunavir QD + Ritonavir QD + Raltegravir BID
(n = 42)

Darunavir QD + Ritonavir QD + TDF-FTC QD
(n = 43)

Raltegravir + Darunavir/r versus TDF-FTC + Darunavir/r RADAR: Result

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

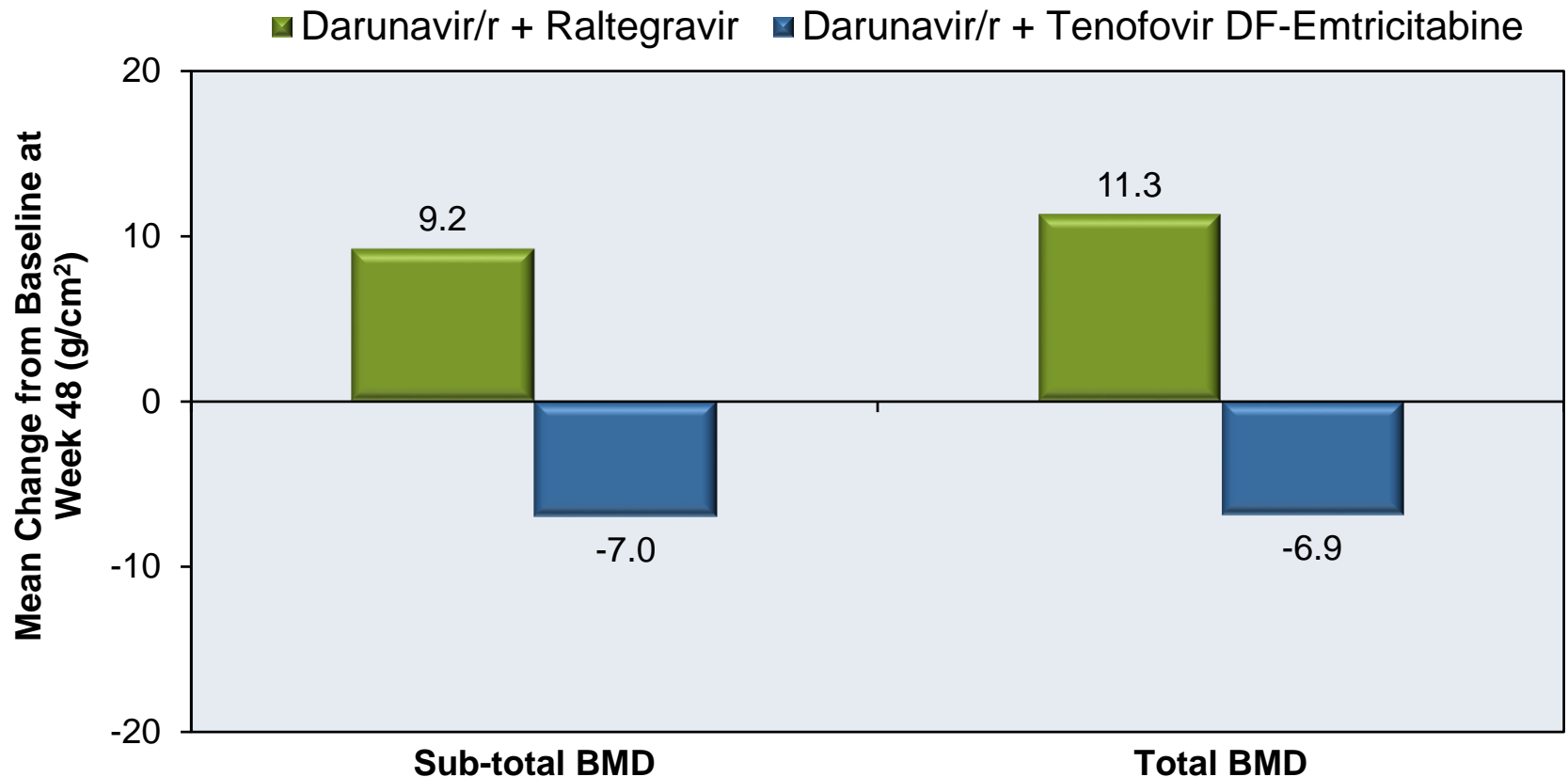


Virologic Failure: Darunavir/r + RAL (N = 15); Darunavir/r + TDF-FTC (N = 7)

Source: Bedimo RJ, et al. PLoS One. 2014;9:e106221.

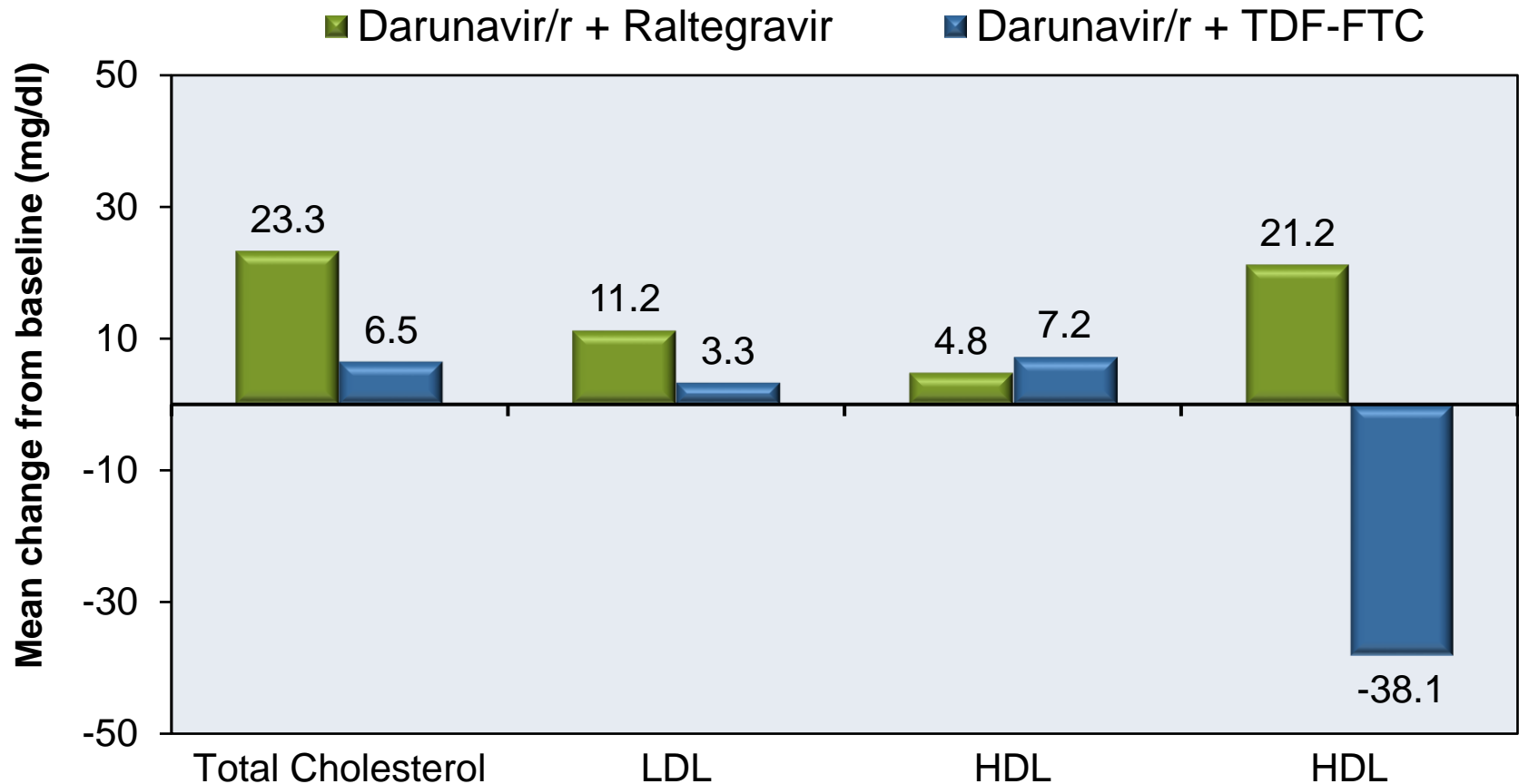
Raltegravir + Darunavir/r versus TDF-FTC + Darunavir/r RADAR: Result

Week 48: Bone Mineral Density Results



Raltegravir + Darunavir/r versus TDF-FTC + Darunavir/r RADAR: Result

Week 48: Change in Plasma Lipids from Baseline



Source: Bedimo RJ, et al. PLoS One. 2014;9:e106221.

Raltegravir + Darunavir/r versus TDF-FTC + Darunavir/r RADAR: Conclusions

Conclusion: “The NRTI-sparing regimen raltegravir + darunavir/ritonavir did not achieve similar week 48 virologic efficacy compared with tenofovir/emtricitabine plus darunavir/ritonavir, but was better with regard to markers of bone health.”

Raltegravir plus Ritonavir-Boosted Darunavir
ACTG 5262 Trial

Raltegravir plus Ritonavir-Boosted Darunavir ACTG 5262: Study Design

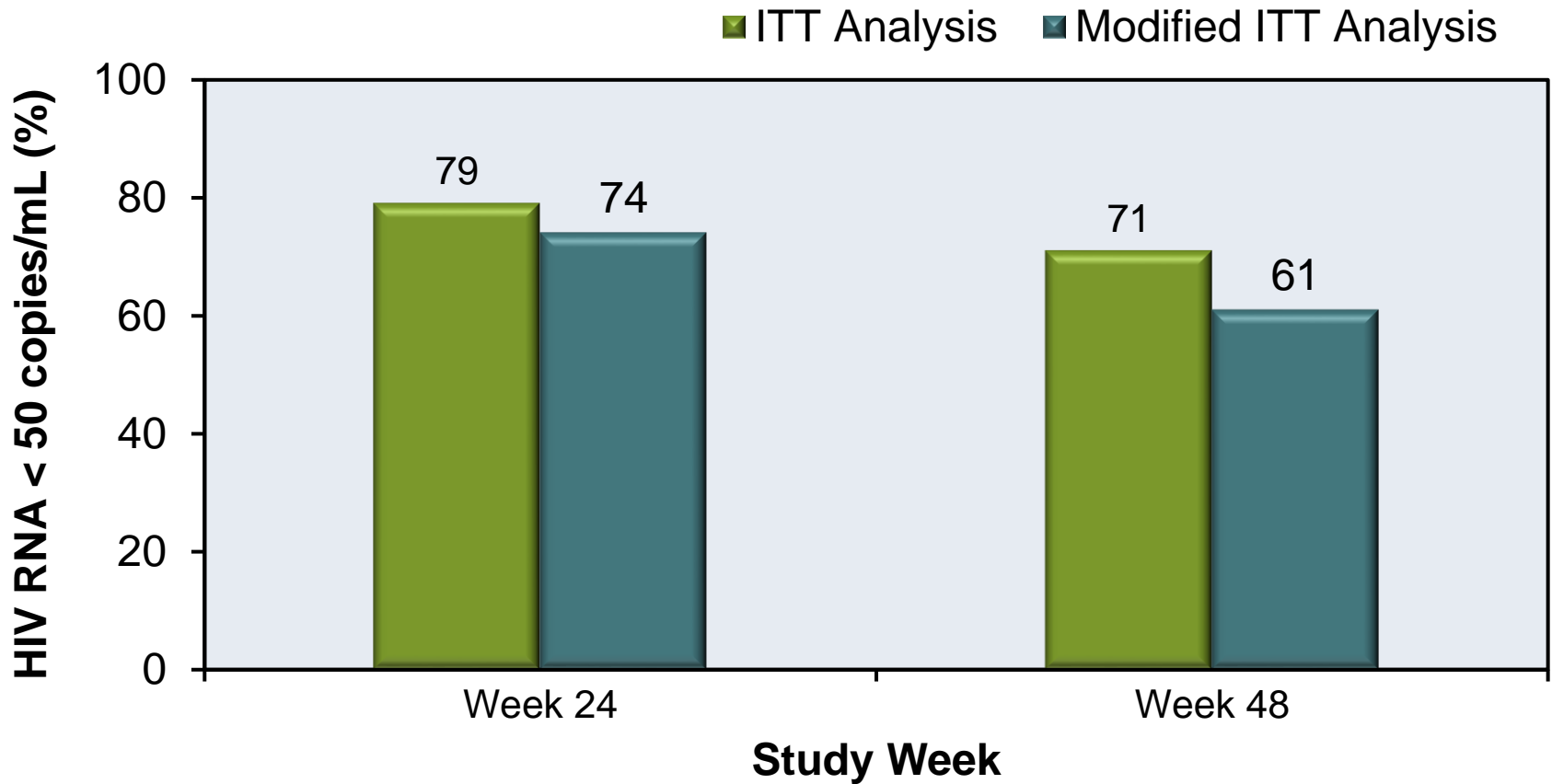
Study Design: ACTG 5262

- **Background:** Open-label, single-arm, phase 2 study evaluating the efficacy of a NRTI-sparing regimen consisting of boosted darunavir plus raltegravir in persons with HIV.
- **Inclusion Criteria (n = 112)**
 - Age \geq 18 years
 - Antiretroviral-naïve
 - HIV RNA \geq 5000 copies/mL
 - More than one darunavir resistance-associated mutation (RAM) or known major integrase RAM
- **Treatment Arm**
 - Darunavir 800 mg + Ritonavir 100 mg QD + Raltegravir 400 mg BID

**Darunavir 800 mg QD +
Ritonavir 100 mg QD +
Raltegravir 400 mg BID**
(n = 112)

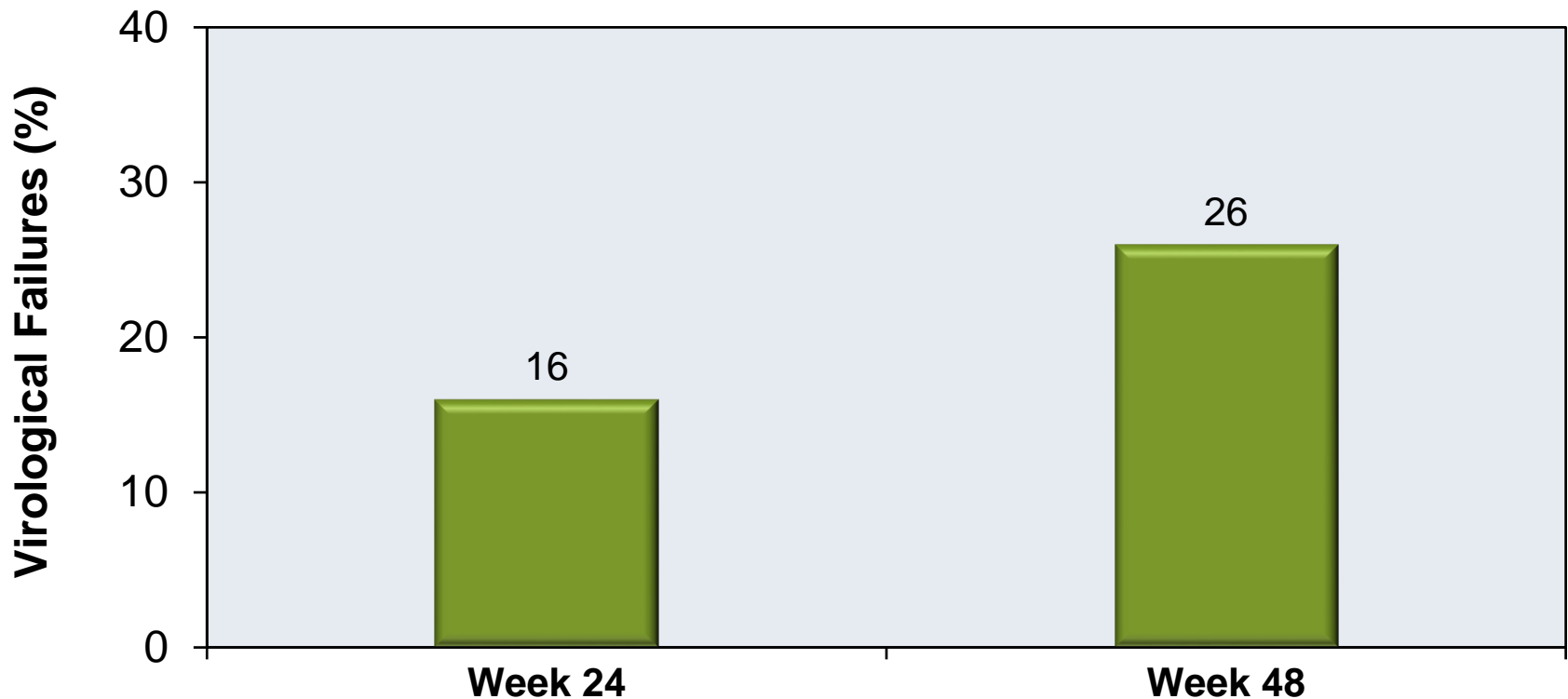
Raltegravir plus Ritonavir-Boosted Darunavir ACTG 5262 Trial: Result

Week 24 and Week 48: Virologic Efficacy



Raltegravir plus Ritonavir-Boosted Darunavir ACTG 5262 Trial: Result

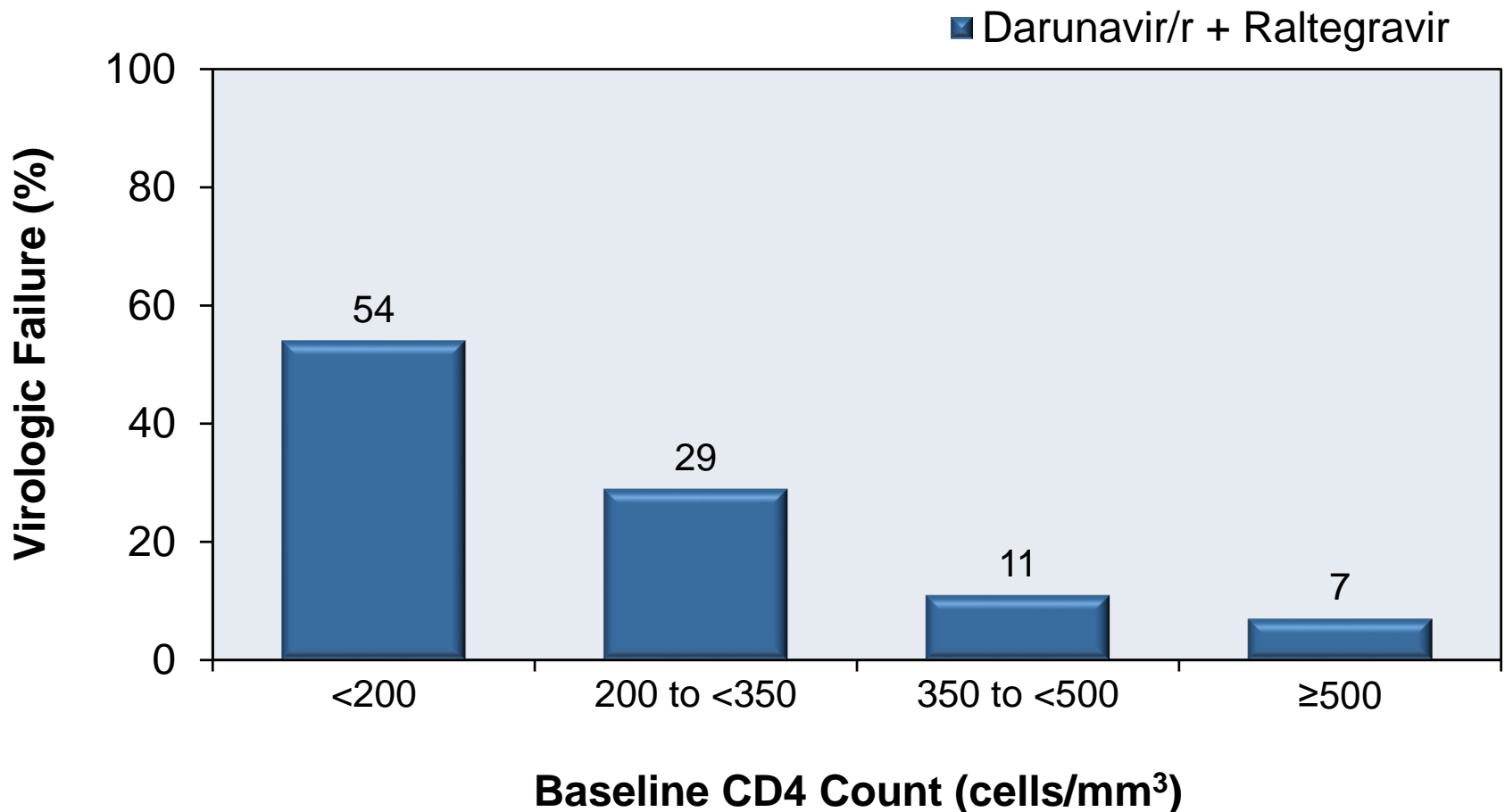
Week 24 and Week 48: Virologic Failure (Intent-to-Treat Analysis)



Virologic failure associated with baseline HIV RNA >100,000 copies/mL and lower CD4 count

Raltegravir plus Ritonavir-Boosted Darunavir ACTG 5262: Result

Virologic Failure, by Baseline CD4 Count



Raltegravir plus Ritonavir-Boosted Darunavir ACTG 5262: Conclusions

Conclusion: “DRV/r + RAL was effective and well tolerated in most patients, but virological failure and integrase resistance were common, particularly in patients with baseline viral load more than 100,000 copies/ml.”

Raltegravir plus Ritonavir-Boosted Darunavir
NEAT001/ANRS 143 Trial

Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Study Design

Study Design: NEAT001/ANRS 143

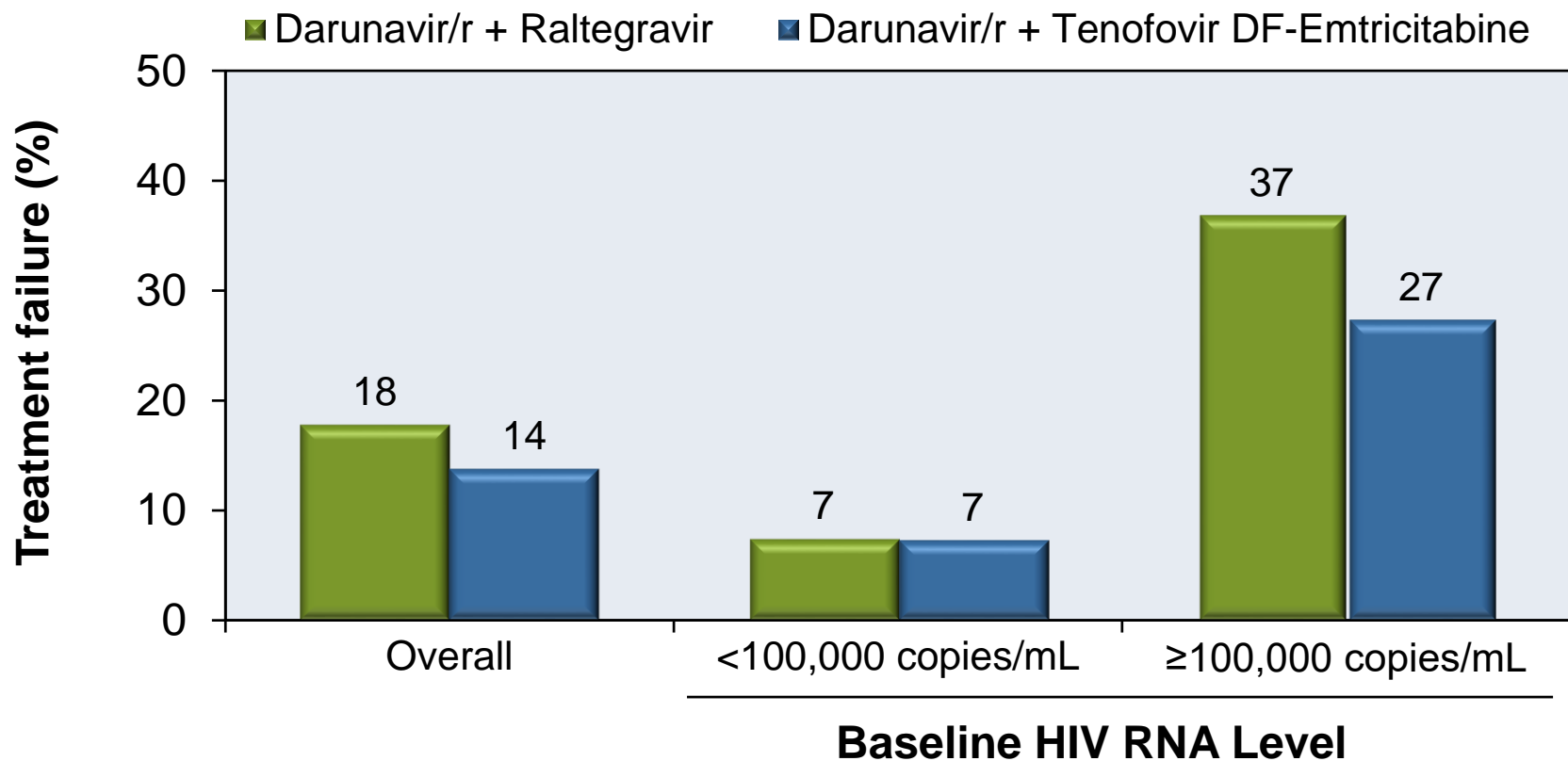
- **Background:** Randomized, open-label, non-inferiority trial study to evaluate the efficacy and safety of a NtRTI-sparing regimen of raltegravir and boosted darunavir vs. combination tenofovir DF-emtricitabine and boosted darunavir.
- **Inclusion Criteria (n = 805)**
 - Age ≥ 18 years
 - Antiretroviral-naïve
 - HIV RNA $> 1,000$ copies/mL
 - CD4 < 500 cells/mm³
 - No major resistance mutations
- **Treatment Arms**
 - Darunavir 800 mg QD + Ritonavir 100 mg QD + Raltegravir 400 mg BID
 - Darunavir 800 mg QD + Ritonavir 100 mg QD + TDF-FTC QD

**Darunavir + Ritonavir QD
+ Raltegravir BID**
(n = 401)

**Darunavir + Ritonavir QD
+ TDF-FTC QD**
(n = 404)

Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Result

Week 96: Treatment Failure, by Baseline HIV RNA*

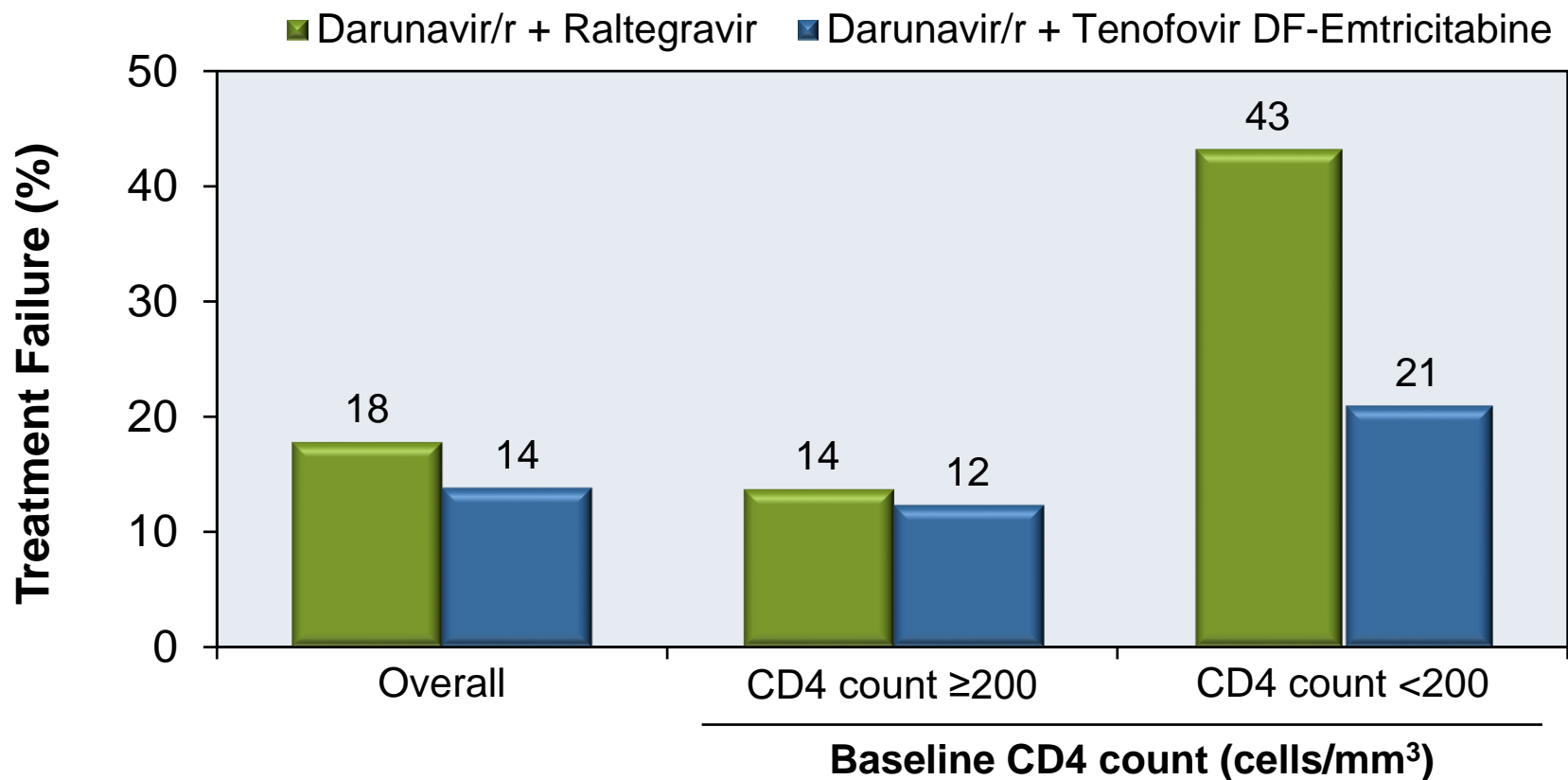


*Kaplan-Meier estimates of proportion of patients reaching endpoints)

Source: Raffi F, et al. Lancet. 2014;384:1942-51.

Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Result

Week 96: Treatment Failure, by Baseline CD4 Count*

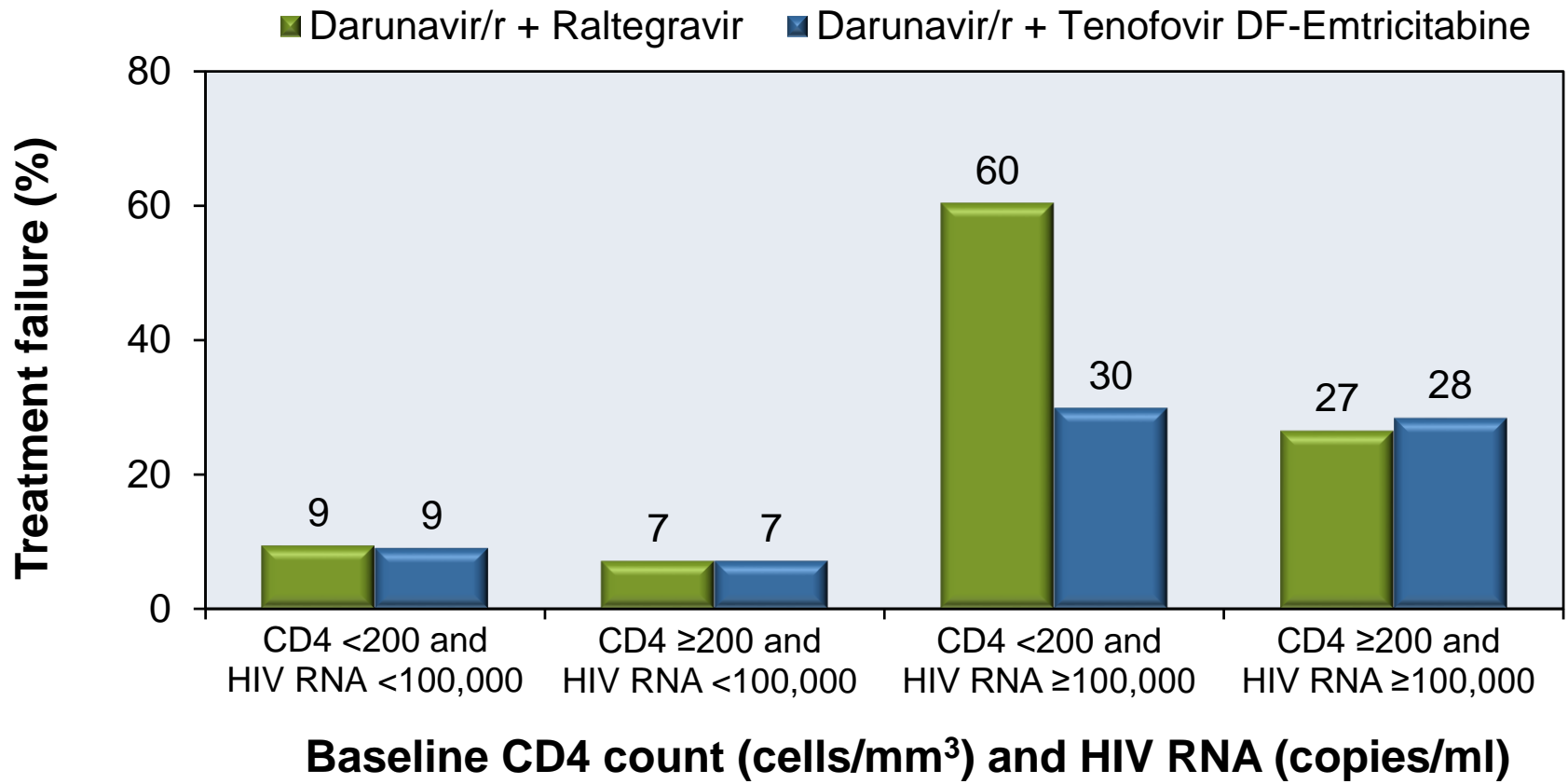


*Kaplan-Meier estimates of proportion of patients reaching endpoints)

Source: Raffi F, et al. Lancet. 2014;384:1942-51.

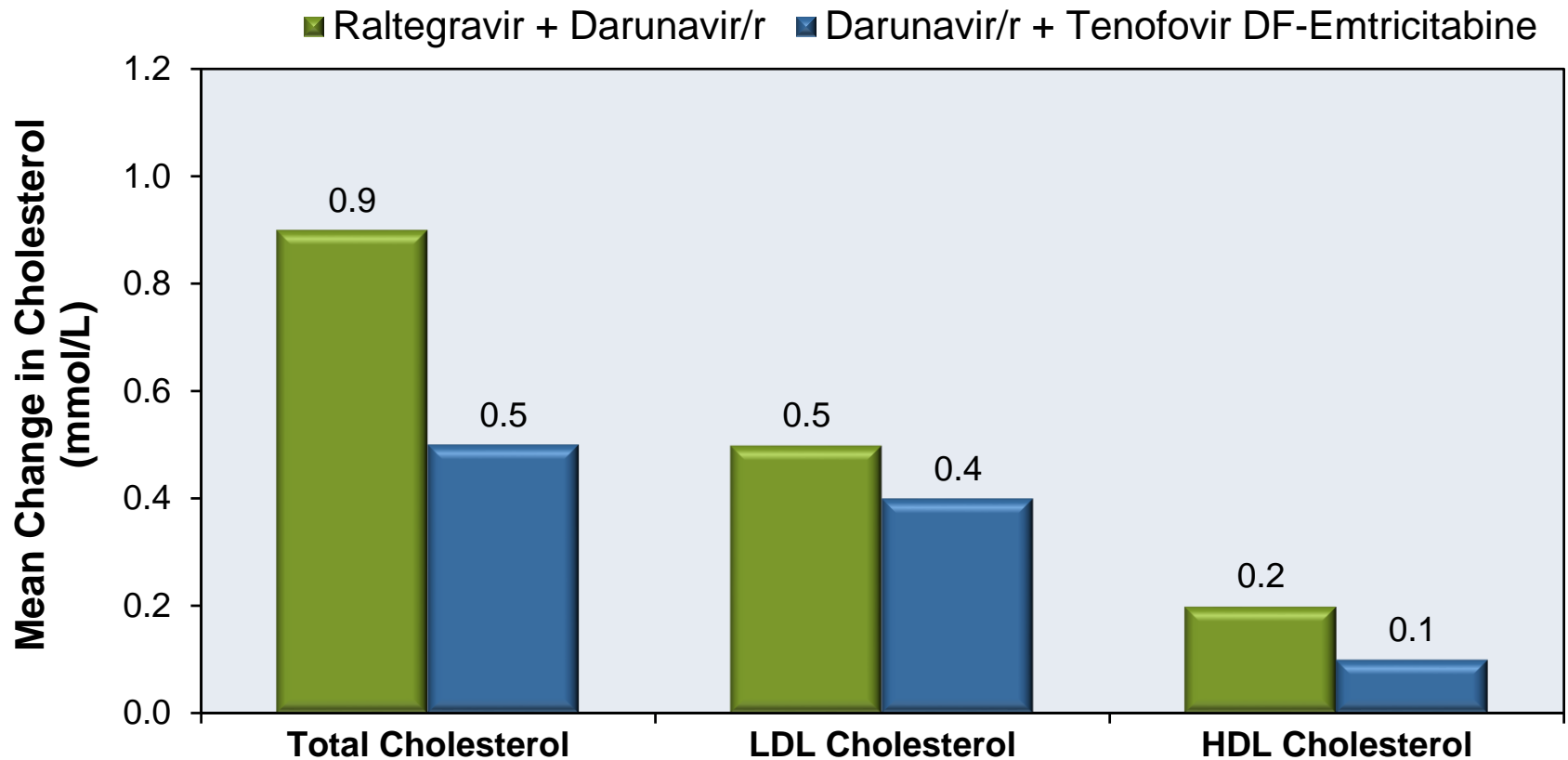
Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Result

Week 96: Treatment Failure, by HIV RNA and CD4 Count (combined effects)



Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Result

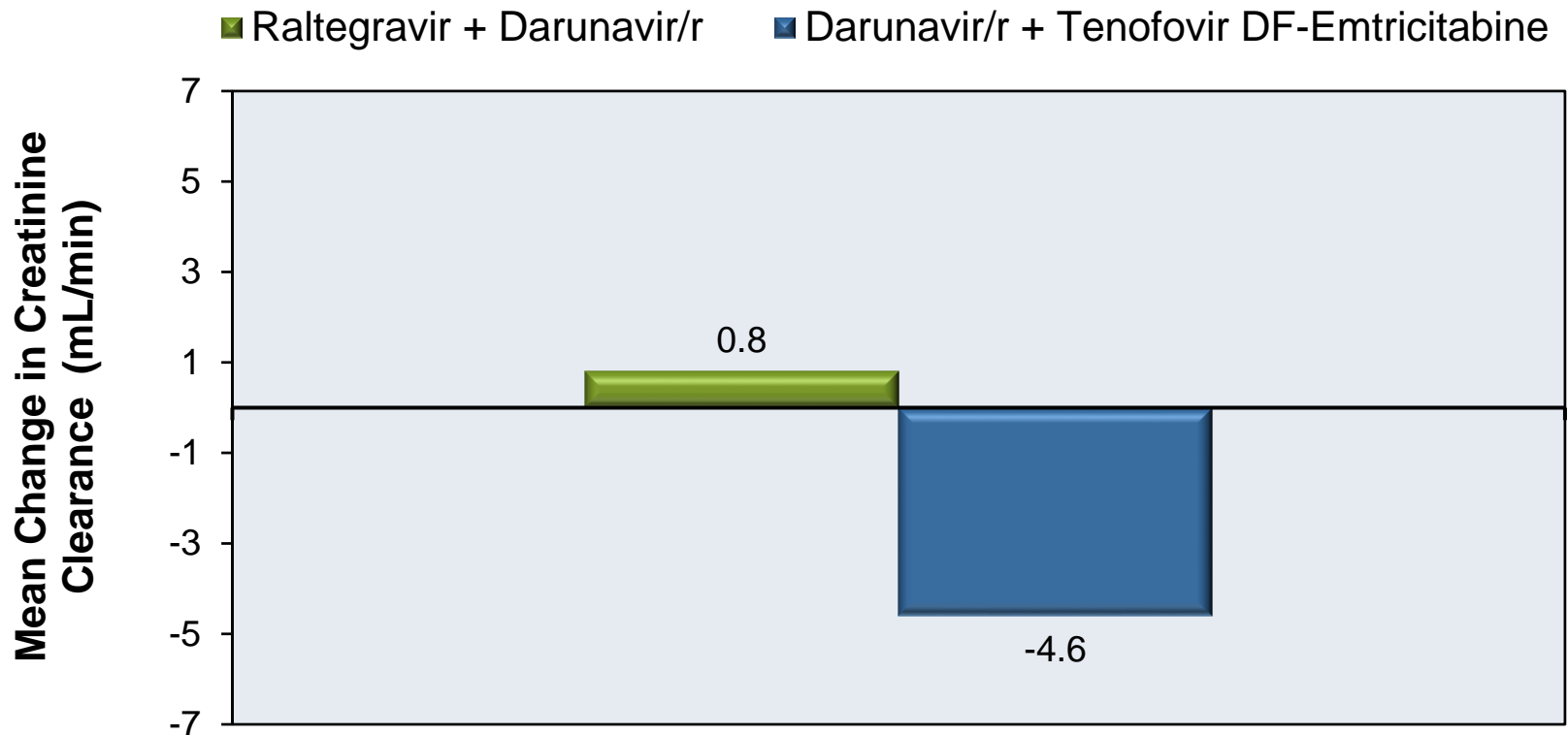
Week 96: Change in Lipids from Baseline



Source: Raffi F, et al. Lancet. 2014;384:1942-51.

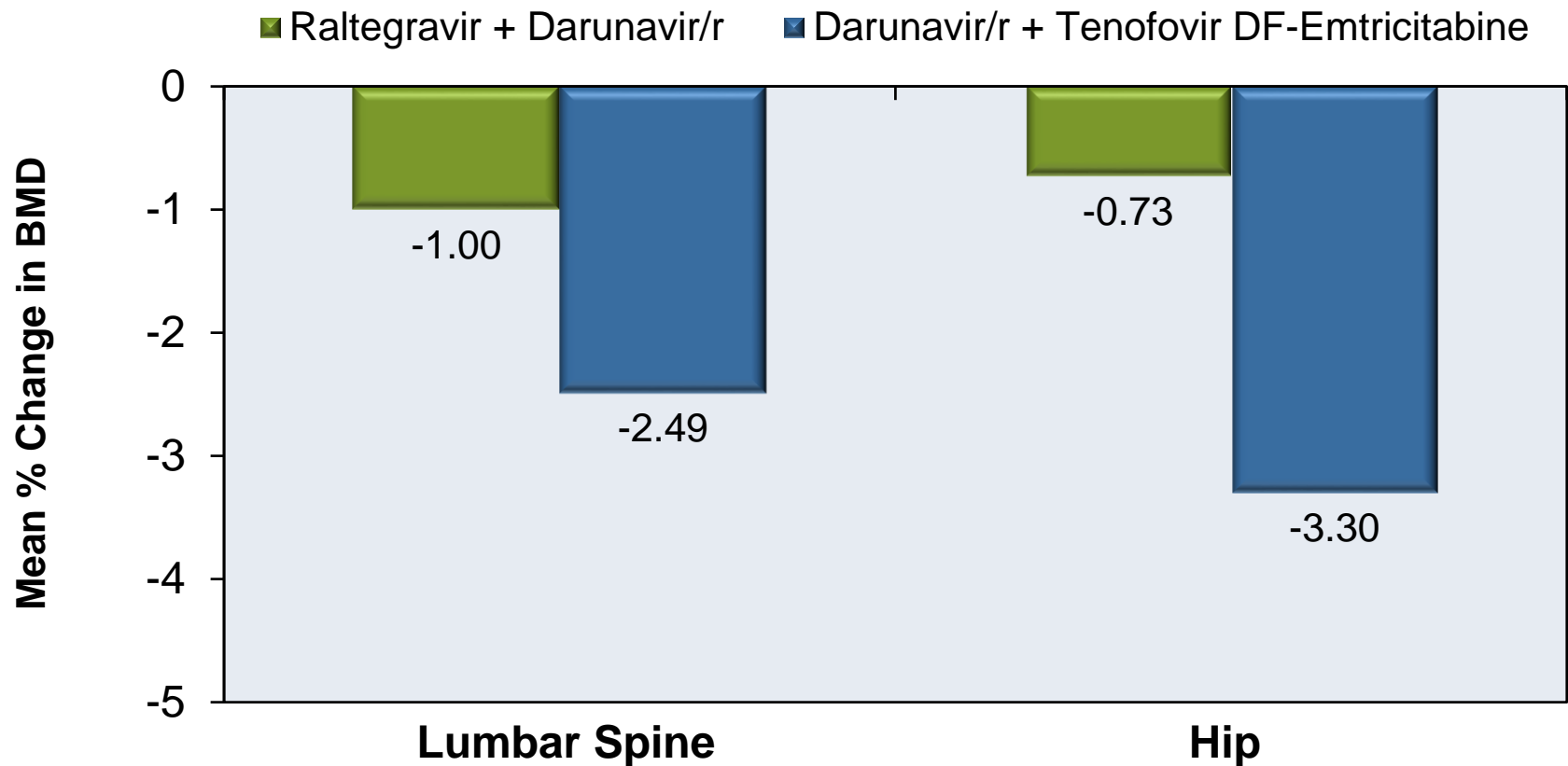
Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Result

Week 96: Change in Creatinine Clearance from Baseline



Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Substudy Result

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



Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Result

Analysis of Virologic Failures and Emerging Genotypic Resistance

Genotype Resistance Testing in NEAT001/ANRS143

Resistance Testing and Results	RAL + DRV/r (n = 401)	DRV/r + TDF/FTC (n = 404)
Patients who underwent genotype resistance testing at virological failure	29	13
Major resistance mutations detected	6	0
Reverse transcriptase	1*	0
Protease	0	0
Integrase	5**	0

*K65R mutation; **N155H mutation

Darunavir/r + Raltegravir versus Darunavir/r + TDF-FTC NEAT001/ANRS143: Conclusions

Interpretation: “Our NtRTI-sparing regimen was non-inferior to standard treatment and represents a treatment option for patients with CD4 cell counts higher than 200 cells per μL .”

TREATMENT EXPERIENCED

Raltegravir

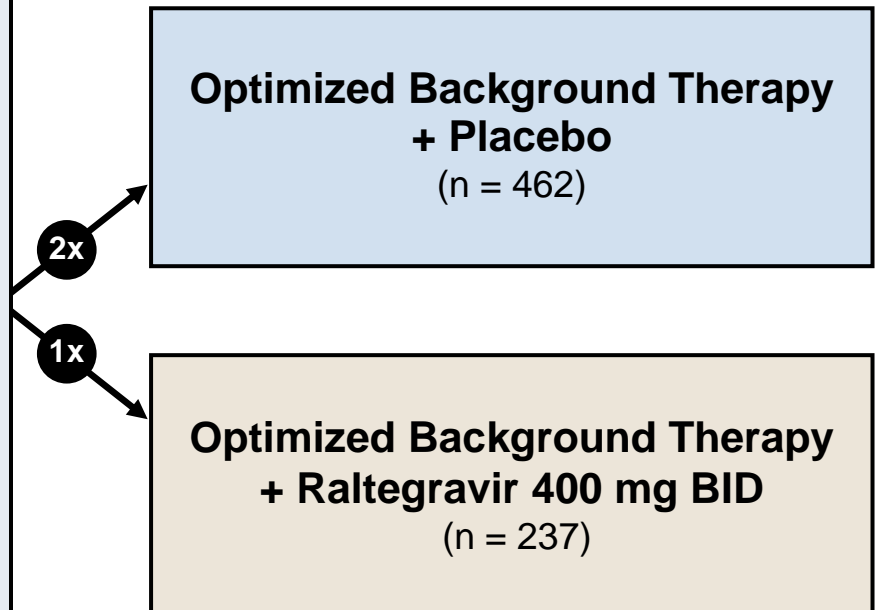
Raltegravir + Optimized Background Therapy for Resistant HIV
BENCHMRK 1 and 2

Raltegravir with Optimized Background Therapy for Resistant HIV

BENCHMARK 1 and 2: Study Design

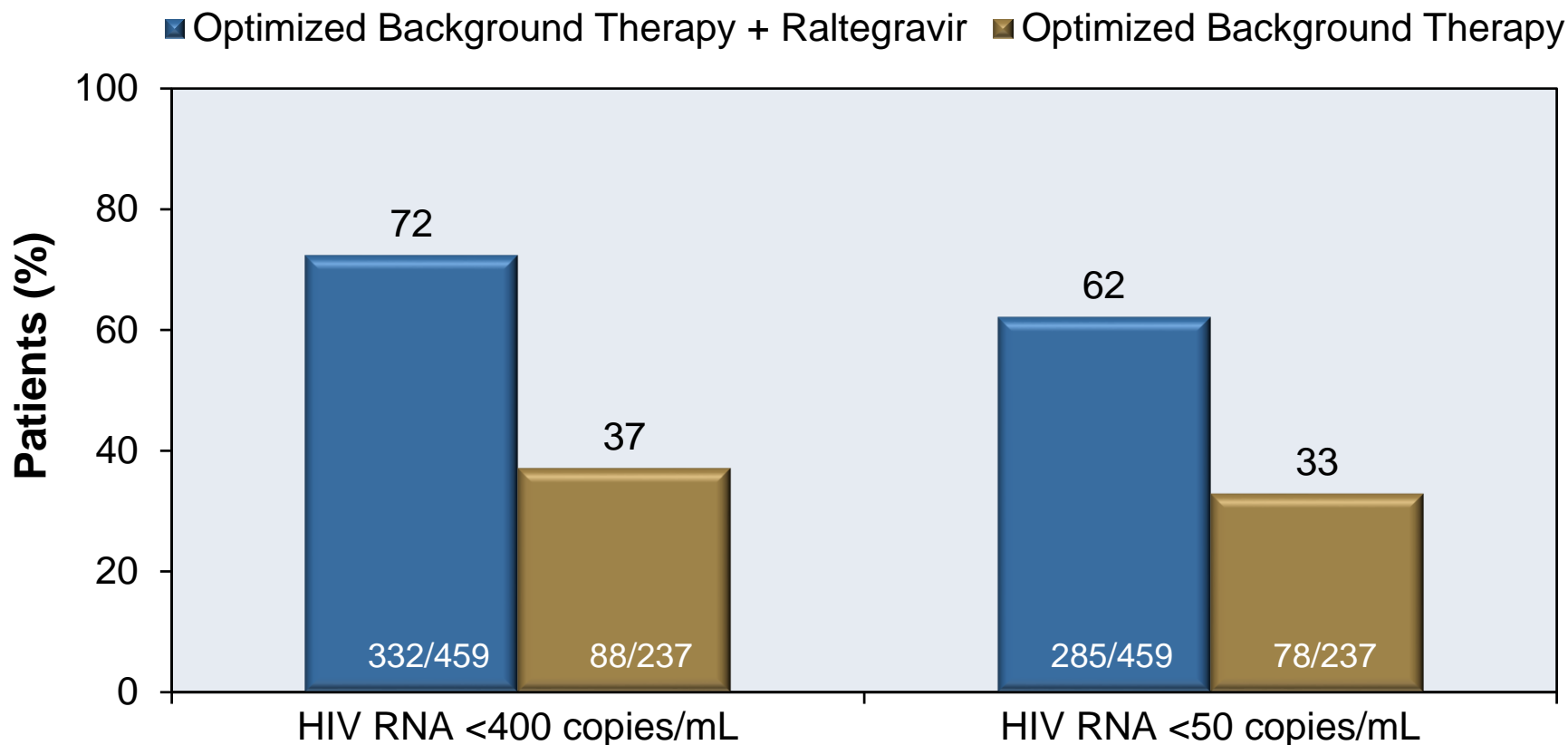
Study Design: BENCHMARK 1 and 2

- **Background:** Two identical randomized, double-blind, phase 3 trials conducted in different geographic areas to evaluate the efficacy of raltegravir plus an optimized background therapy in persons with HIV resistant to at least one drug in each of three antiretroviral classes.
- **Inclusion Criteria (n = 699 combined)**
 - Age ≥ 16 years
 - HIV RNA > 1000 copies/mL on ART
 - Documented resistance to at least 1 drug in NRTI, NNRTI, and PI classes
- **Treatment Arms**
 - OBT + Placebo
 - OBT + Raltegravir 400 mg BID



Raltegravir with Optimized Background Therapy for Resistant HIV BENCHMARK 1 and 2: Results

Week 48: Virologic Response (Non-completion Counted as Failure)

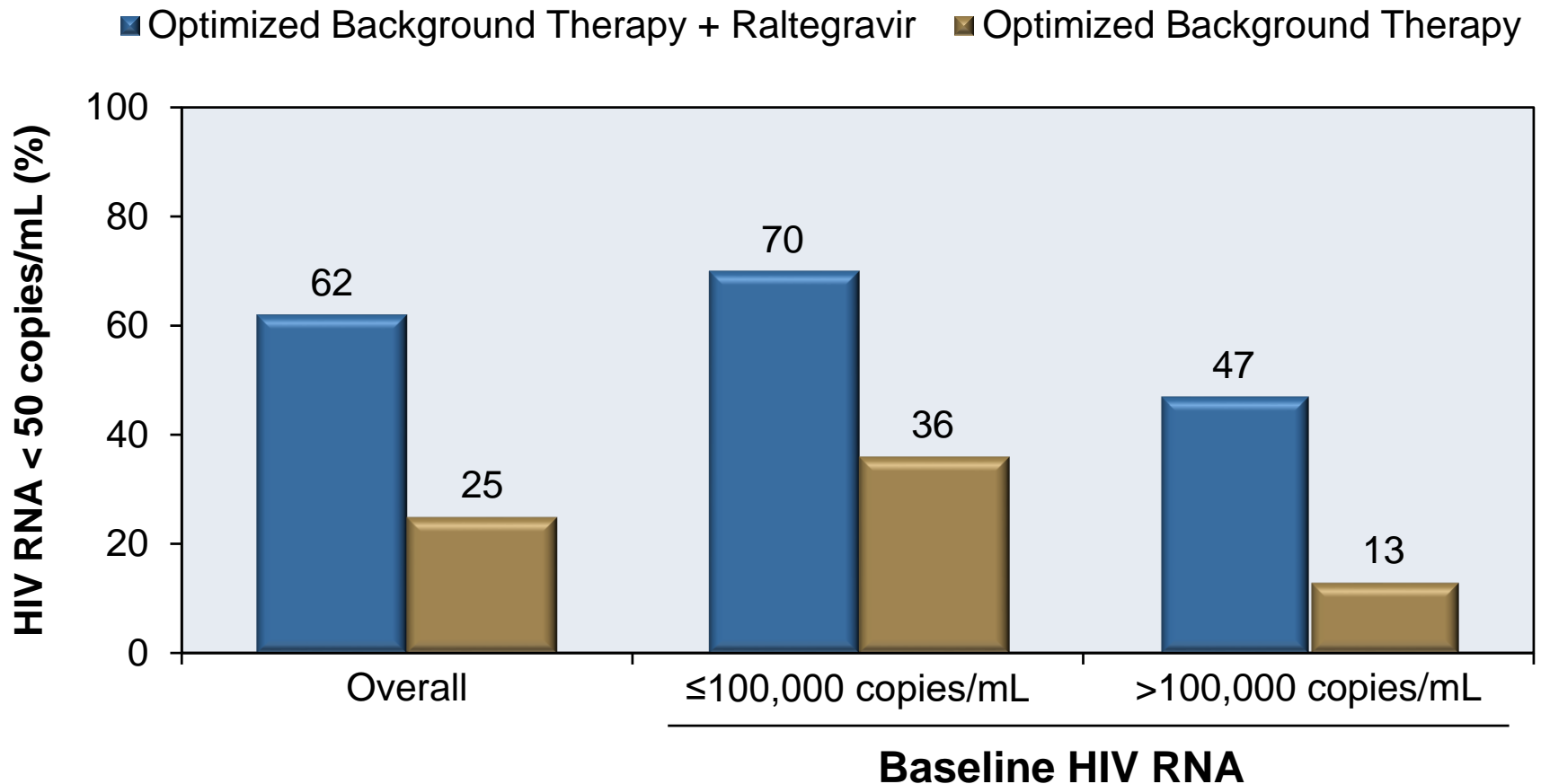


Raltegravir with Optimized Background Therapy for Resistant HIV BENCHMRK 1 and 2: Conclusions

Conclusions: “In HIV-infected patients with limited treatment options, raltegravir plus optimized background therapy provided better viral suppression than optimized background therapy alone for at least 48 weeks.”

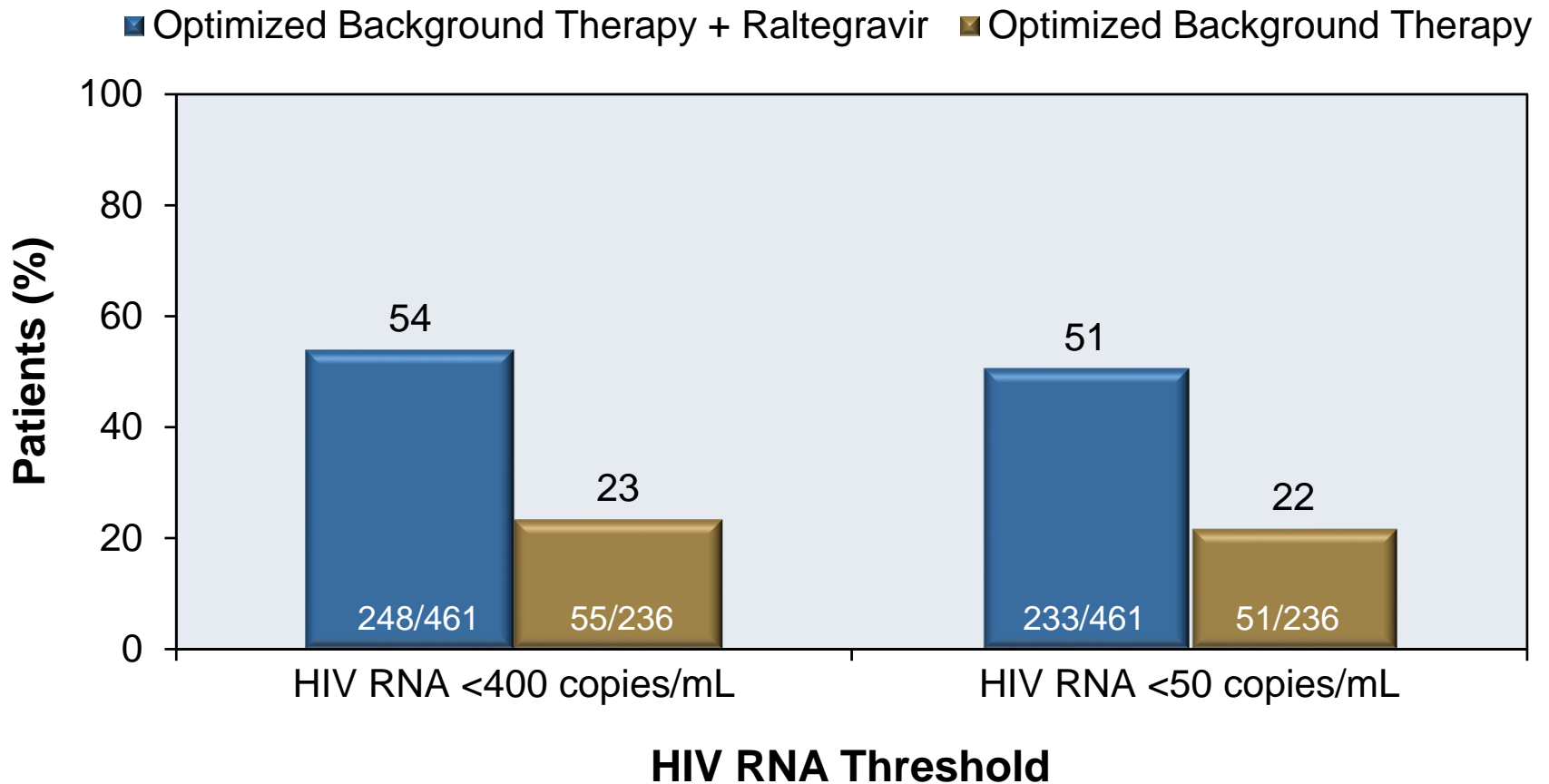
Raltegravir with Optimized Background Therapy for Resistant HIV BENCHMARK 1 and 2: Results

Week 96: Virologic Response, by Baseline HIV RNA



Raltegravir with Optimized Background Therapy for Resistant HIV BENCHMARK 1 and 2: Results

Week 156: Virologic Response (Non-completion Counted as Failure)



Elvitegravir versus Raltegravir in Treatment-Experienced
GS-183-0145

Elvitegravir versus Raltegravir in Treatment Experienced Study 0145: Design

Study Design: 0145

- **Background:** Randomized, double-blind phase 3 study comparing the safety and efficacy of elvitegravir versus raltegravir with efavirenz, in combination with background regimen.
- **Inclusion Criteria (n = 702)**
 - Treatment-experienced persons with HIV
 - Age ≥ 18 years
 - HIV RNA ≥ 1000 copies/mL
 - Stable regimen for at least 30 days
 - Resistance to at least 2 classes
 - No AIDS condition in prior 30 days
- **Treatment Arms**
 - Elvitegravir + TDF-FTC
 - Raltegravir + Background (RTV + PI + 3rd Drug)

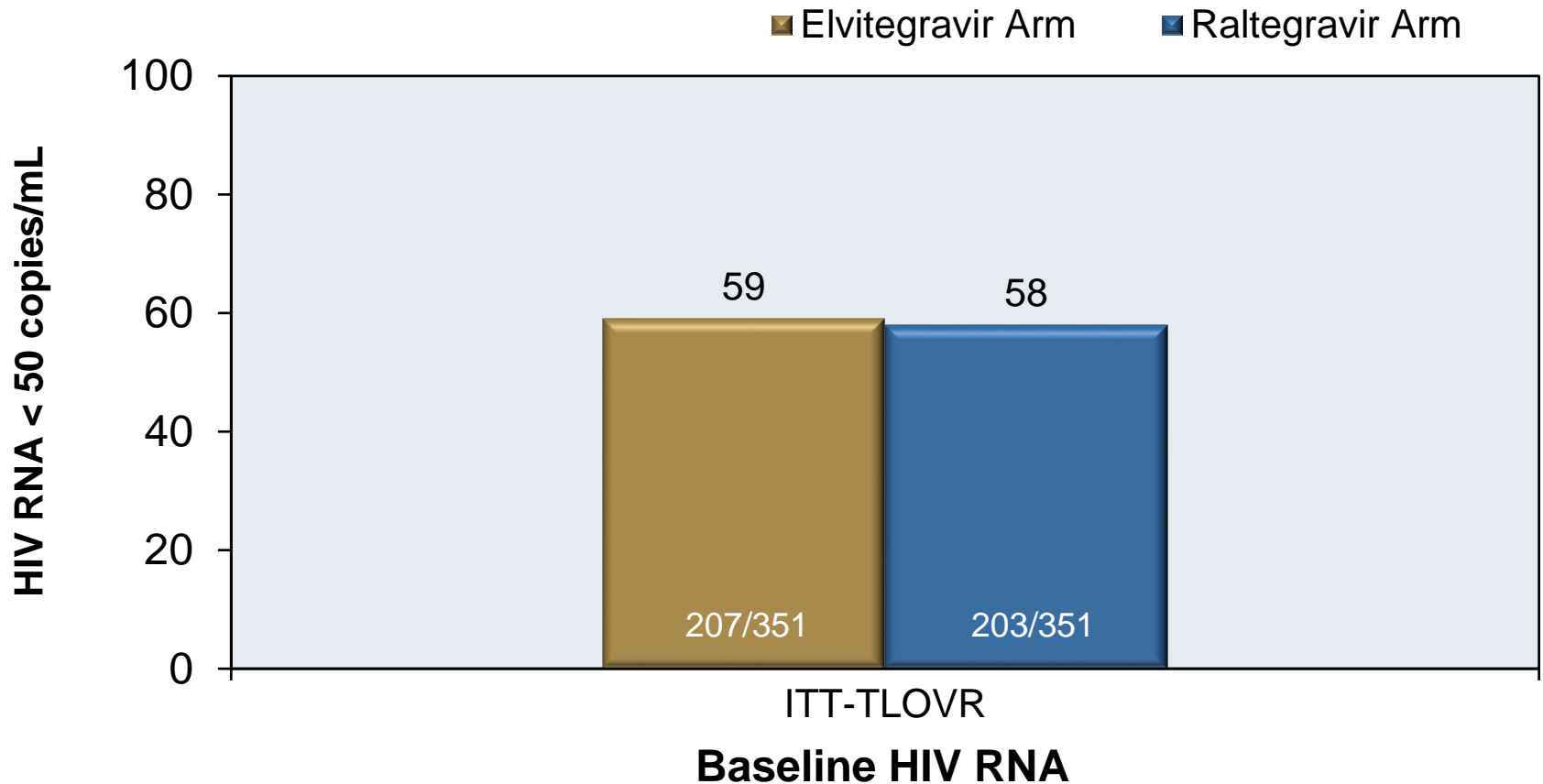
Elvitegravir* (150 mg QD) +
Ritonavir + Protease Inhibitor +
3rd Antiretroviral Agent
(n = 351)

Raltegravir (400 mg BID)
Ritonavir + Protease Inhibitor +
3rd Antiretroviral Agent
(n = 351)

*Elvitegravir dose reduced to 85 mg QD with ritonavir-atazanavir and ritonavir-lopinavir

Elvitegravir versus Raltegravir in Treatment Experienced Study 0145: Results

Week 48: Virologic Response (ITT-TLOVR*)

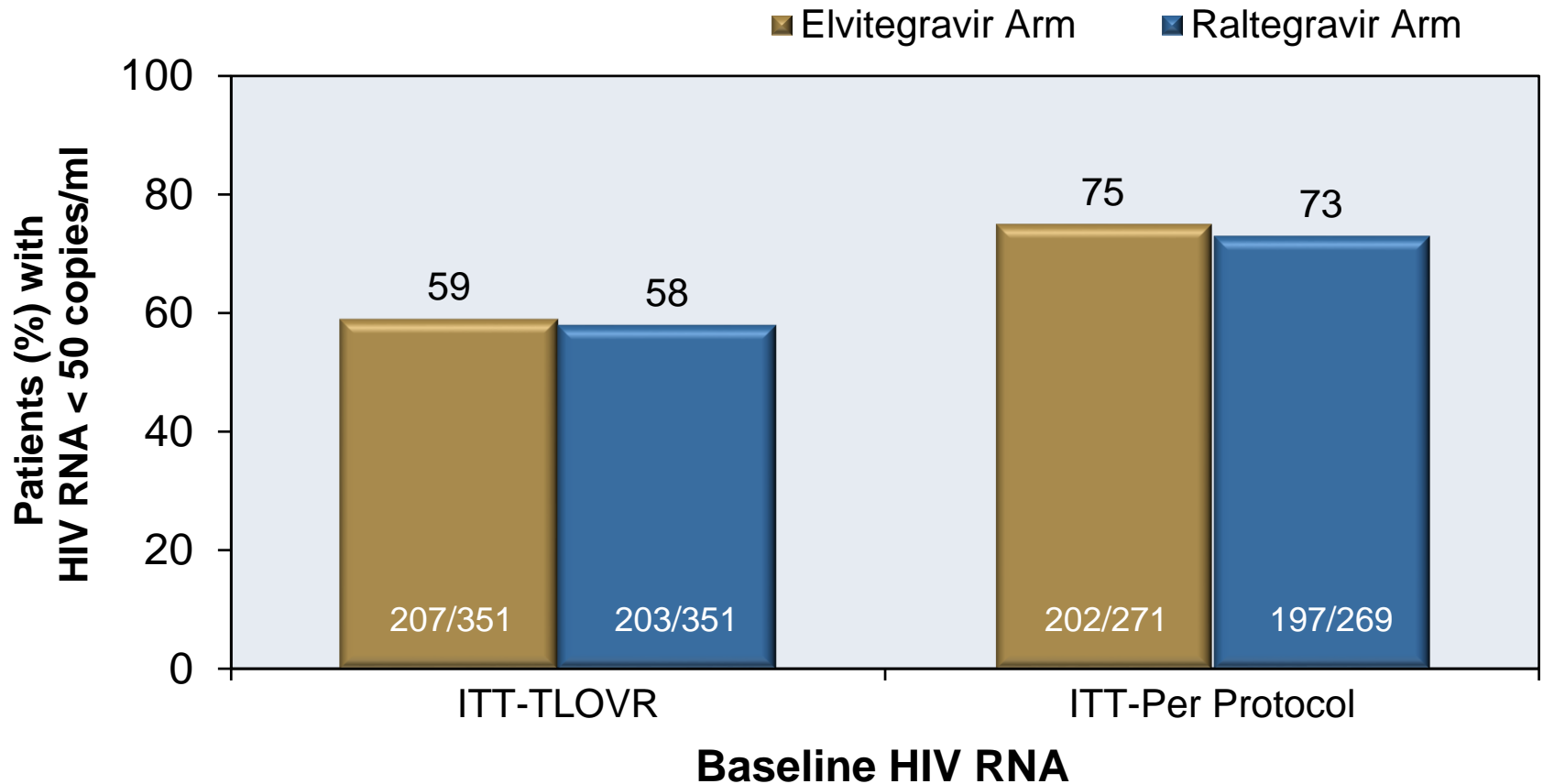


*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response

Source: Molina JM, et al. Lancet. 2012;12:27-35.

Elvitegravir versus Raltegravir in Treatment Experienced Study 0145: Results

Week 48: Virologic Response (ITT-TLOVR and Per Protocol*)

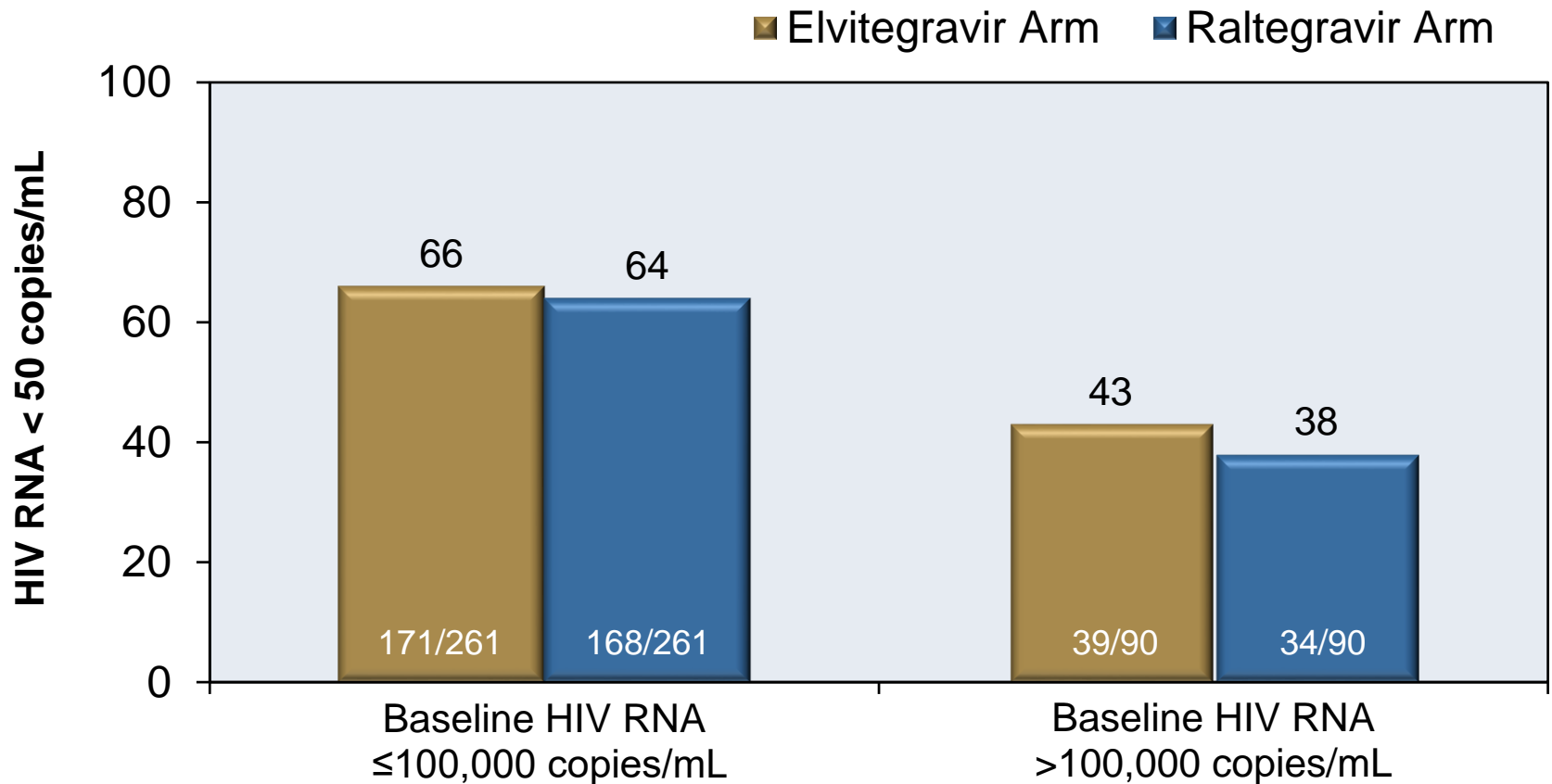


*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response

Source: Molina JM, et al. Lancet. 2012;12:27-35.

Elvitegravir versus Raltegravir in Treatment Experienced Study 0145: Results

Week 48: Virologic Response (mITT)



*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response

Source: Molina JM, et al. *Lancet*. 2012;12:27-35.

Elvitegravir versus Raltegravir in Treatment Experienced Study 0145: Results

Resistance Development by Week 48		
Subjects with Virologic Failure	Elvitegravir (n = 61)	Raltegravir (n = 75)
Any NRTI-Resistance	7 of 59 (12%)	10 of 75 (13%)
Any PI-Resistance	4 of 59 (7%)	3 of 75 (4%)
Any Integrase-Resistance	16 of 60 (27%)	15 of 72 (21%)
T66I/A	7 (12%)	0%
E92Q	5 (8%)	1 (1)%
T97A	3 (5%)	3 (4)%
Y143R/H/C	0%	1 (1)%
S147G	3 (5%)	0%
Q148R/H	3 (5%)	4 (6)%
N155H	3 (5%)	9 (13)%

Source: Molina JM, et al. Lancet. 2012;12:27-35.

Elvitegravir versus Raltegravir in Treatment Experienced Study 0145: Conclusions

Interpretation: “Elvitegravir used in combination with a ritonavir-boosted protease inhibitor in treatment-experienced patients has similar efficacy and safety to raltegravir. Since elvitegravir can be given once a day compared with twice a day for raltegravir, elvitegravir might improve patients' adherence.”

Dolutegravir versus Raltegravir in Treatment Experienced
SAILING Study

Dolutegravir versus Raltegravir in Treatment Experienced SAILING: Study Design

Study Design: SAILING

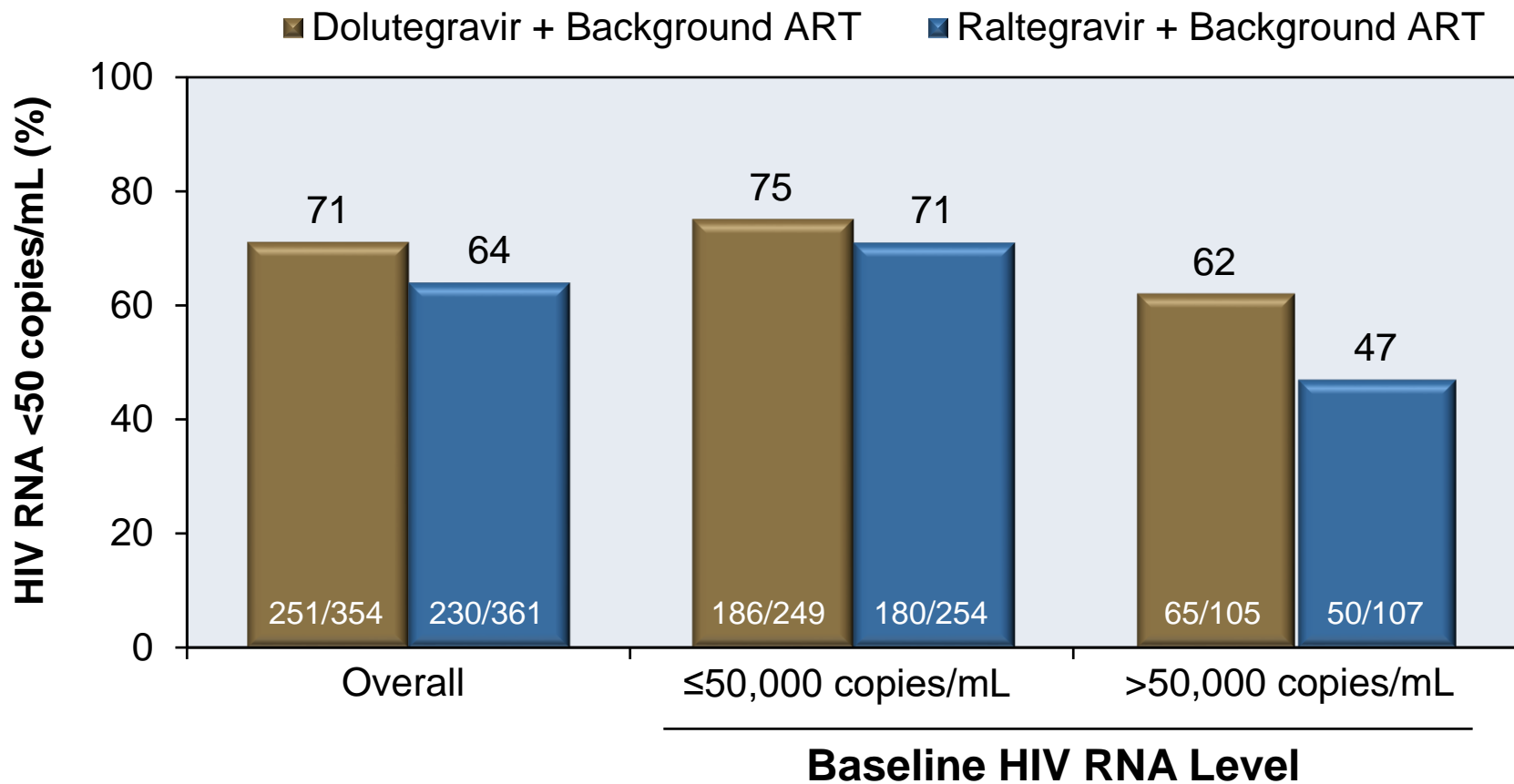
- **Background:** Randomized, double-blind, active-control phase 3 trial evaluating efficacy, safety, and emergent resistance with dolutegravir versus raltegravir in antiretroviral-experienced, integrase inhibitor-naïve persons with HIV who have at least 2-class resistance.
- **Inclusion Criteria (n = 715)**
 - Age ≥ 18 years
 - Resistance to ≥ 2 ARV classes
 - Integrase inhibitor-naïve
 - 2 consecutive HIV RNA ≥ 400 copies/mL (unless $> 1,000$ copies/mL at screening)
- **Treatment Arms**
 - Dolutegravir + up to 2 background ARTs
 - Raltegravir + up to 2 background ARTs

**Dolutegravir 50 mg QD +
 ≤ 2 Background ART Drugs**
(n = 354)

**Raltegravir 400 mg BID +
 ≤ 2 Background ART Drugs**
(n = 361)

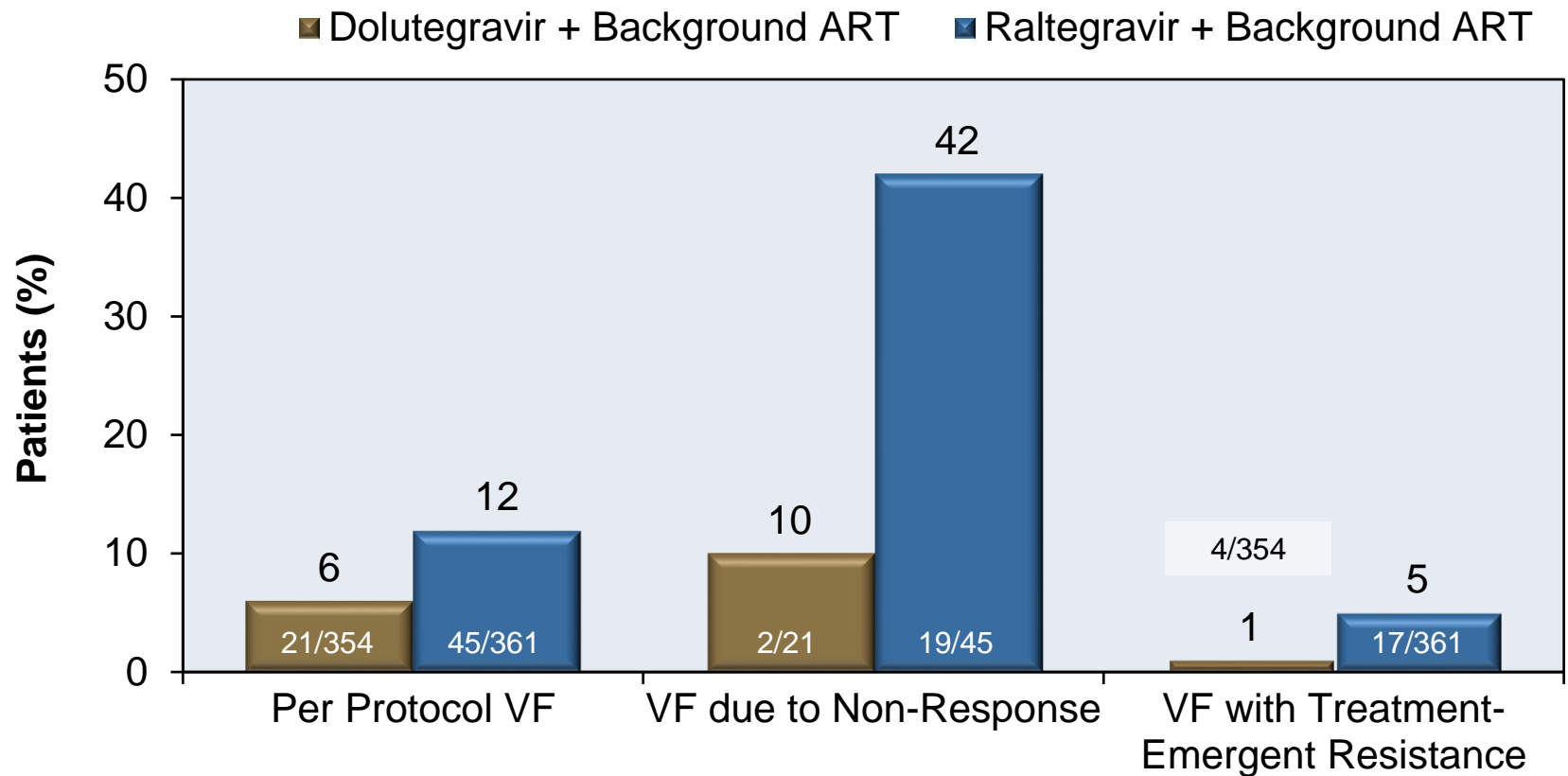
Dolutegravir versus Raltegravir in Treatment Experienced SAILING: Results

Week 48 Virologic Response, By Baseline HIV RNA Level



Dolutegravir versus Raltegravir in Treatment-Experienced SAILING: Results

Week 48 Virologic Failure



VF = Virologic Failure

Dolutegravir versus Raltegravir in Treatment Experienced SAILING Study: Conclusion

Interpretation: “Once-daily dolutegravir, in combination with up to two other antiretroviral drugs, is well tolerated with greater virological effect compared with twice-daily raltegravir in this treatment-experienced patient group.”

Raltegravir plus OBT in Patients with Multidrug-Resistant HIV
005 Trial

Raltegravir plus OBT in Patients with Multidrug-Resistant HIV 005: Study Design

Study Design: 005

- **Background:** Randomized, double-blind, dose-ranging, placebo-controlled phase 2 trial to evaluate raltegravir compared to placebo, with optimized background therapy (OBT), in patients with multidrug-resistant HIV.
- **Inclusion Criteria (n = 179)**
 - Age ≥ 18 years
 - Antiretroviral-experienced with resistance to at least 1 NNRTI, 1 NRTI, and 1 PI
 - CD4 count >50 cells/mm³
 - HIV RNA $>5,000$ copies/mL
 - Non-pregnant, no HCV coinfection
- **Treatment Arms (All Received OBT)**
 - Raltegravir 200 mg, 400 mg, or 600 mg BID
 - Placebo

**Raltegravir 200 mg BID
+ OBT**
(n = 44)

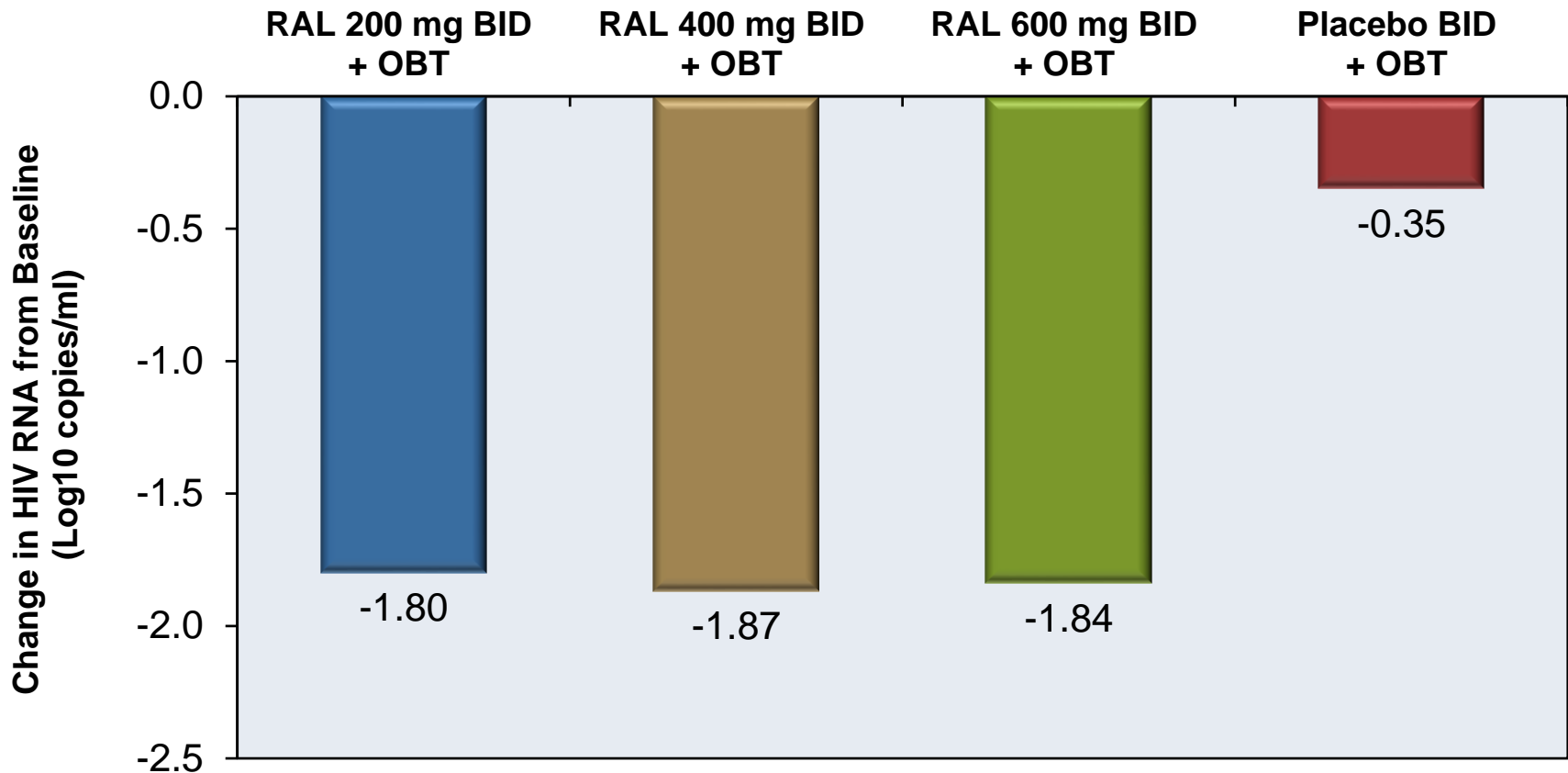
**Raltegravir 400 mg BID
+ OBT**
(n = 45)

**Raltegravir 600 mg BID
+ OBT**
(n=45)

**Placebo
+ OBT**
(n=45)

Raltegravir plus OBT in Patients with Multidrug-Resistant HIV 005: Results

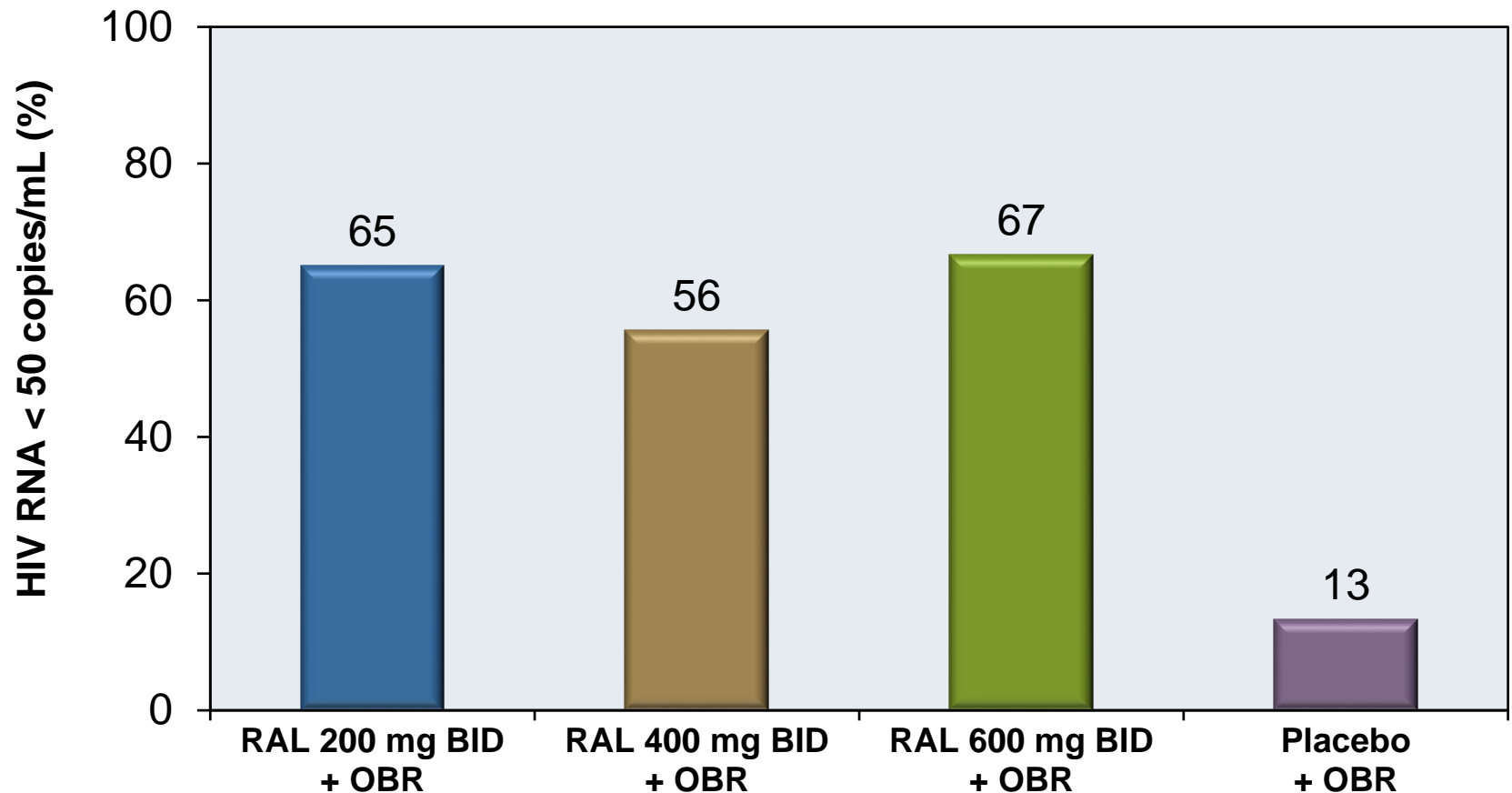
Week 24: Change from Baseline Viral Load



Source: Grinsztejn B, et al. Lancet. 2007;369:1261-9.

Raltegravir plus OBT in Patients with Multidrug-Resistant HIV 005: Results

Week 24: Virologic Response



Source: Grinsztejn B, et al. Lancet. 2007;369:1261-9.

Raltegravir plus OBT in Patients with Multidrug-Resistant HIV 005: Conclusions

Interpretation: “In patients with few remaining treatment options, raltegravir at all doses studied provided better viral suppression than placebo when added to an optimised background regimen. The safety profile of raltegravir is comparable with that of placebo at all doses studied.”

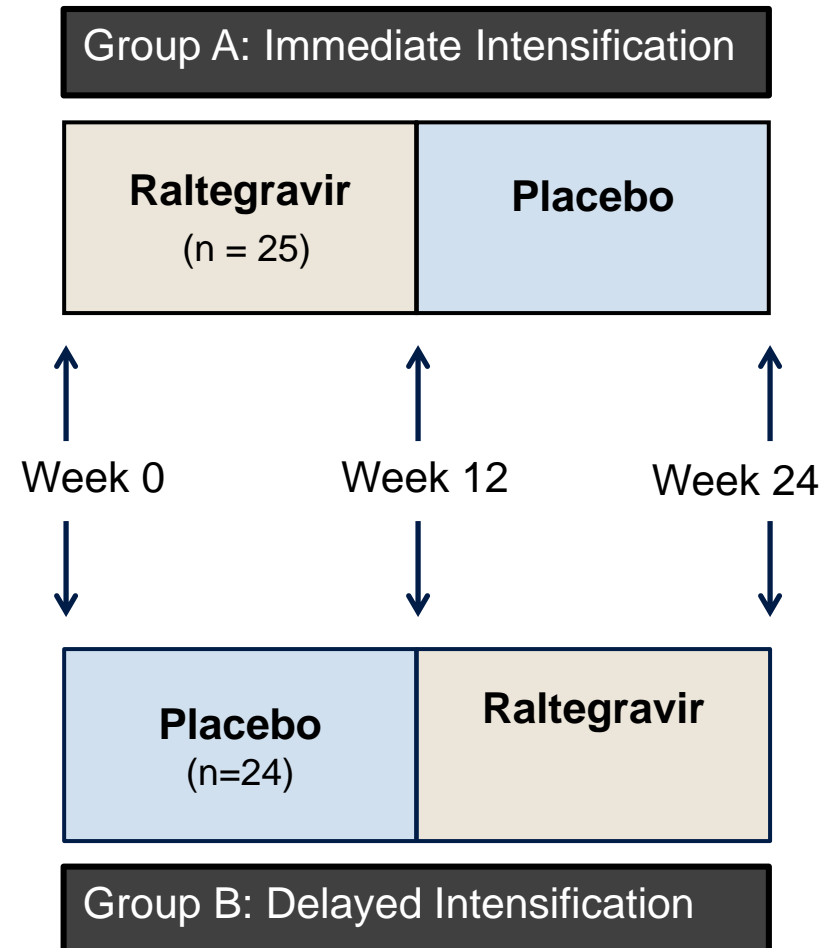
Raltegravir Intensification with Residual Low-Level Viremia
ACTG 5244 Trial

Raltegravir Intensification with Residual Low-Level Viremia

ACTG 5244: Study Design

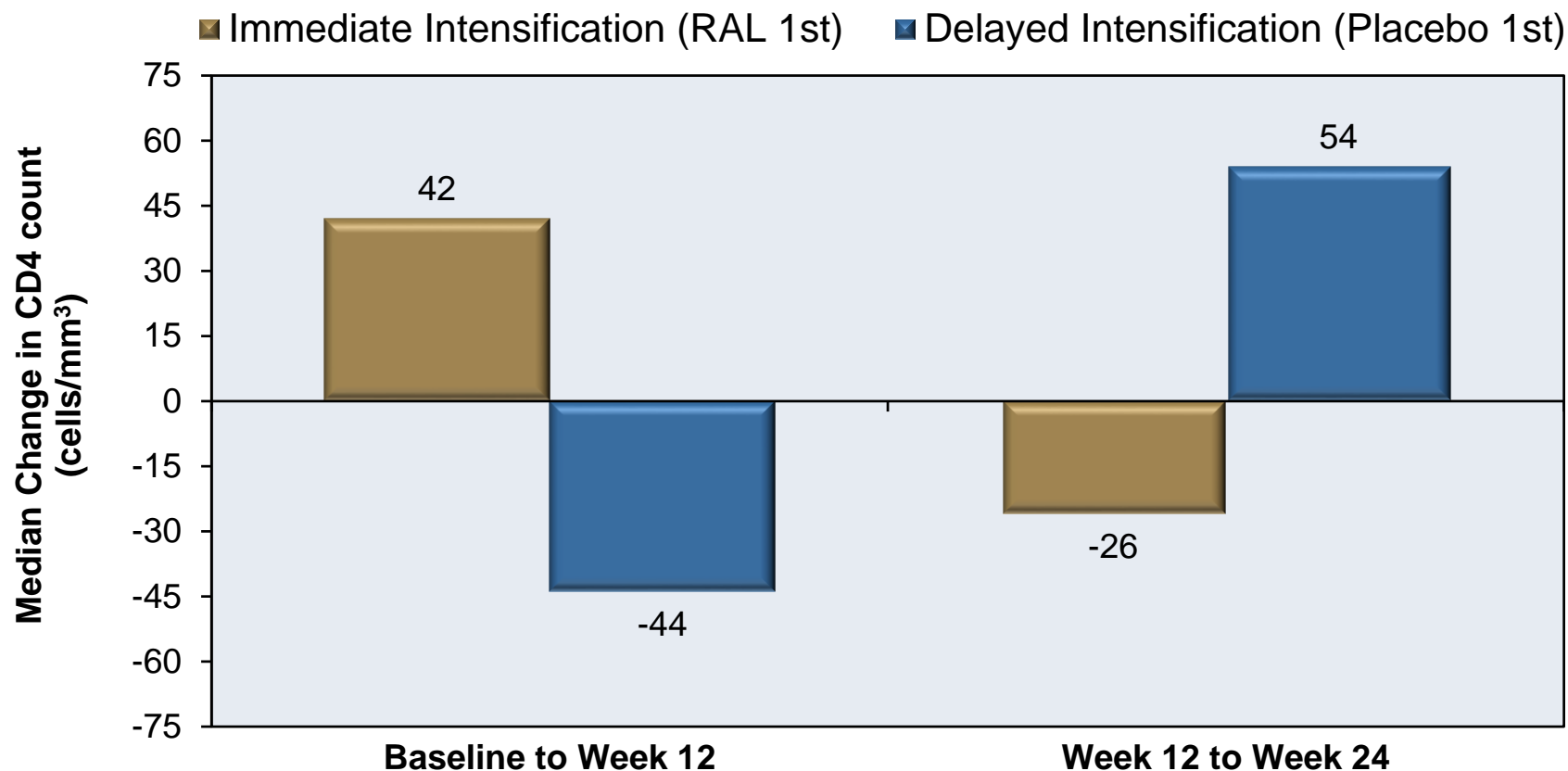
Study Design: ACTG 5244

- **Background:** Randomized, double-blind, placebo-controlled, crossover trial evaluating effect of raltegravir intensification on patients taking ART with low-level residual viremia.
- **Inclusion Criteria (n = 53)**
 - ART-experienced but INSTI-naïve
 - On ART for ≥ 12 months on 2 NRTIs + either NNRTI or PI
 - HIV RNA < 50 copies/mL for ≥ 6 months
 - Detectable viremia by single copy assay
 - Pretreatment HIV RNA $> 100,000$ copies/mL
 - No history of documented virologic failure
 - Detectable viremia by single-copy assay
- **Treatment Arms (crossed over at 12 weeks)**
 - Group A: entry regimen + RAL 400 mg BID
 - Group B: entry regimen + placebo



Raltegravir Intensification with Residual Low-Level Viremia ACTG 5244: Results

Effect of Raltegravir Intensification on CD4 Counts



Raltegravir Intensification with Residual Low-Level Viremia ACTG 5244: Conclusions

Conclusion: “In this randomized, double-blind cross-over study, 12 weeks of raltegravir intensification did not demonstrably reduce low-level plasma viremia in patients on currently recommended ART. This finding suggests that residual viremia does not arise from ongoing cycles of HIV-1 replication and infection of new cells. New therapeutic strategies to eliminate reservoirs that produce residual viremia will be required to eradicate HIV-1 infection.”

DUAL ARV THERAPY IN TREATMENT EXPERIENCED

Raltegravir

Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs
SECOND-LINE Trial

Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SECOND-LINE: Study Design

Study Design: SECOND-LINE

- **Background:** Randomized, parallel, open-label trial to compare dual therapy with lopinavir-ritonavir plus raltegravir with WHO 2nd line standard-of-care regimen of lopinavir-ritonavir plus NRTIs in persons with HIV.
- **Inclusion Criteria (n=541)**
 - Age ≥16 years
 - Received first-line ART with 2 NRTIs + 1 NNRTI for ≥24 weeks (no change in past 12 weeks)
 - No virologic failure
 - Naïve to PIs and integrase inhibitors
- **Treatment Arms**
 - Lopinavir-ritonavir + Raltegravir
 - Lopinavir-ritonavir + NRTIs

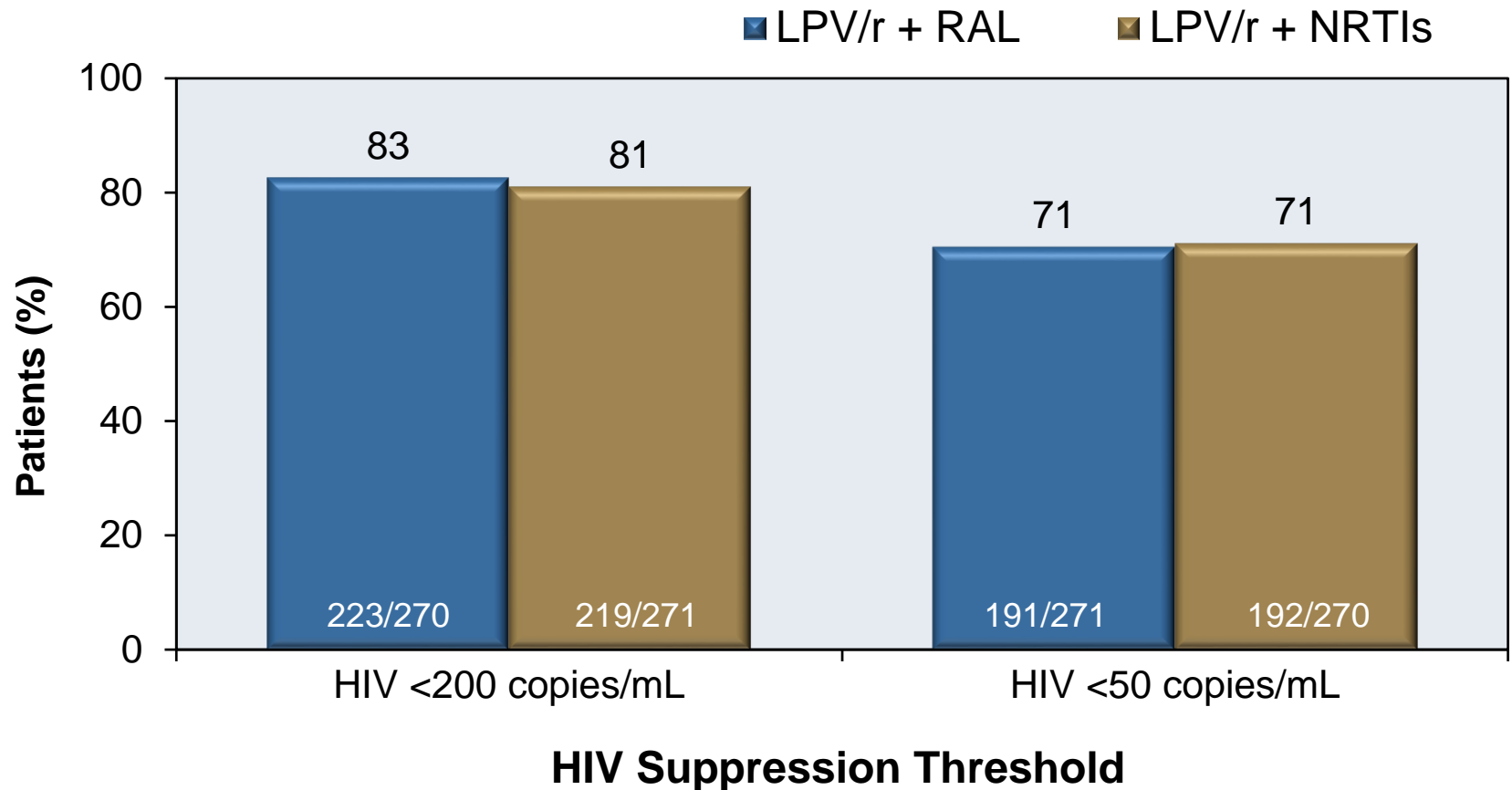
**Lopinavir-ritonavir 400-100 mg
(QD or divided BID) +
Raltegravir 400 mg BID**
(n = 271)

**Lopinavir-ritonavir 400-100 mg
(QD or divided BID) +
NRTIs**
(n =270)

Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SECOND-LINE: Result

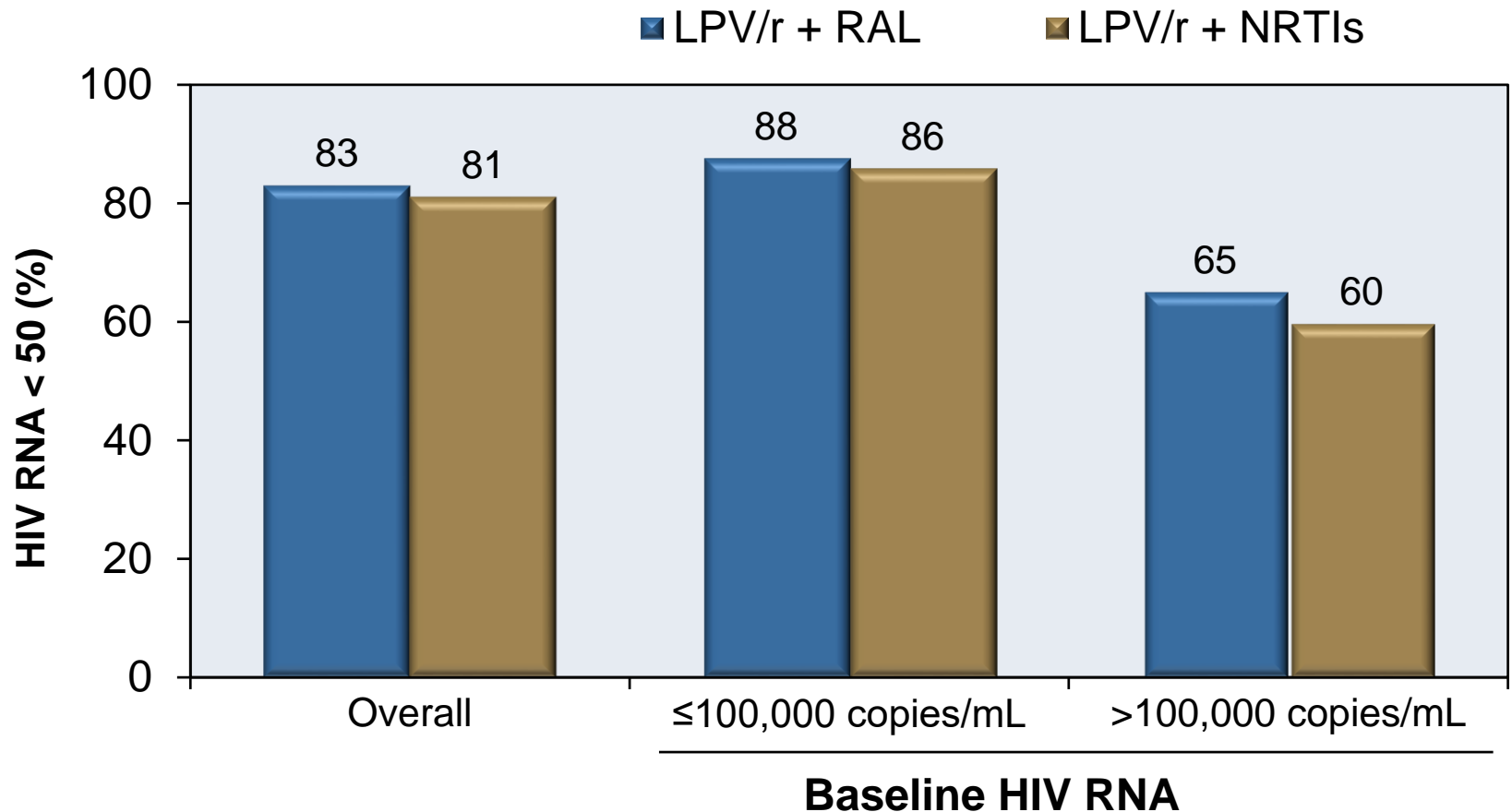
Week 48: Virologic Response (Modified ITT)



Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SECOND-LINE: Result

Week 48: Virologic Response (Modified ITT), by Baseline HIV RNA



Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SECOND-LINE: Result

Emergent Resistance Associated Mutations (RAMs) with Virologic Failure		
	Raltegravir (n = 271)	Control (NRTIs) (n = 270)
Virologic Failure with Resistance Data (Protease and reverse transcriptase)	42%	43%
Virologic Failure with Resistance Data (Integrase)	47%	46%
NtRTI-associated RAMs	0%	14%
Protease inhibitor-associated RAMs	0%	0%
Integrase inhibitor-associated RAMs	14.9%	0%
No new RAMs in protease, reverse transcriptase, or integrase	83%	86%

Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SECOND-LINE: Conclusion

Interpretation: “The raltegravir regimen was no less efficacious than the standard of care and was safe and well tolerated. This simple NtRTI-free treatment strategy might extend the successful public health approach to management of HIV by providing simple, easy to administer, effective, safe, and tolerable second-line combination antiretroviral therapy.”

Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs
SELECT Trial

Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SELECT: Study Design

Study Design: SELECT

- **Background:** Randomized, phase 3, open-label trial to compare dual therapy with lopinavir-ritonavir plus raltegravir with WHO 2nd line standard-of-care regimen of lopinavir-ritonavir plus NRTIs in persons with HIV.
- **Inclusion Criteria (n=412)**
 - Age ≥18 years
 - On initial ART containing NNRTI for ≥24 weeks
 - No virologic failure
 - Naïve to protease inhibitors
 - No known broad NRTI resistance
- **Treatment Arms***
 - Lopinavir-ritonavir + Raltegravir
 - Lopinavir-ritonavir + 2 or 3 NRTIs

**Lopinavir-ritonavir 400-100 QD
+ Raltegravir 400 mg BID**
(n = 258)

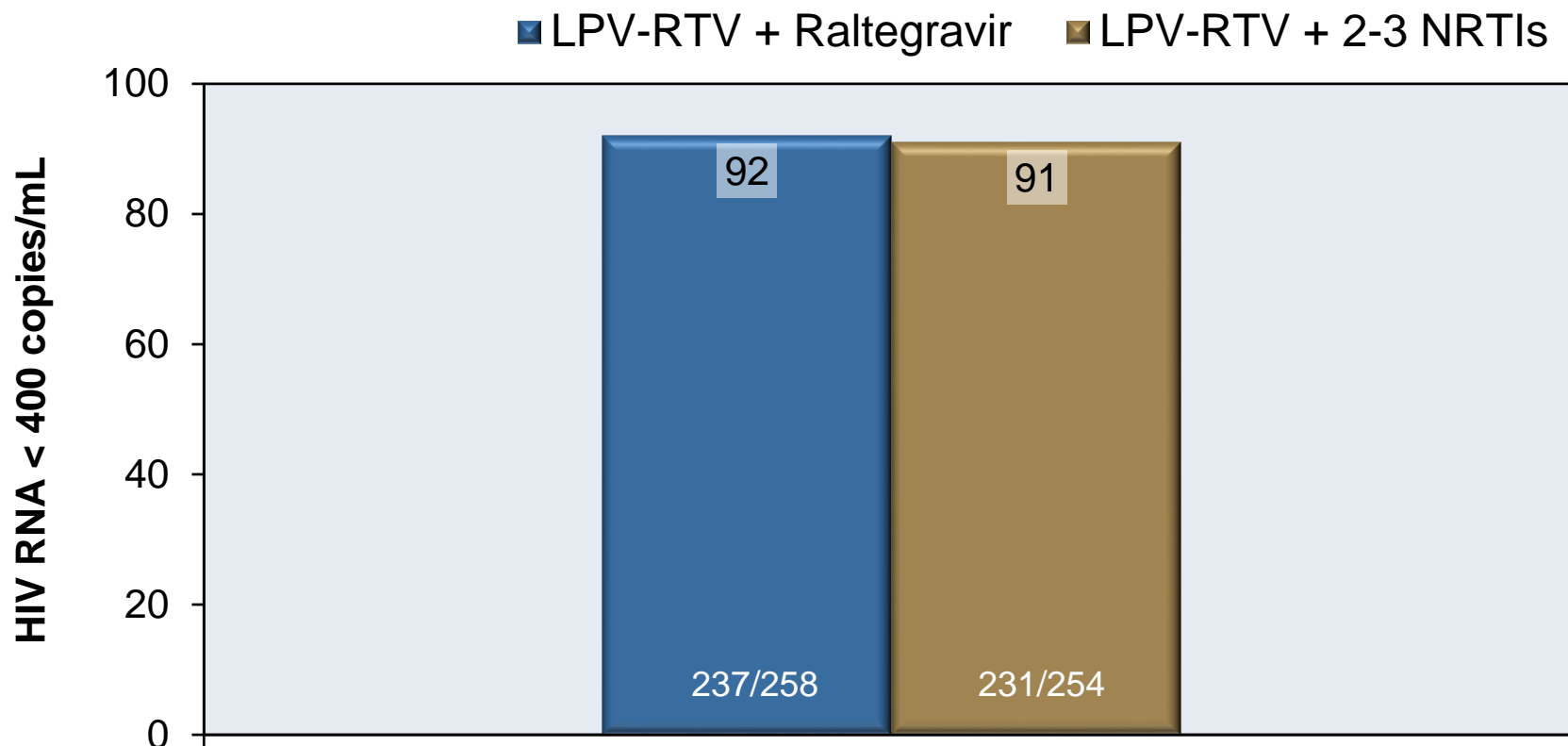
**Lopinavir-ritonavir 400-100 QD
+ 2-3 NRTIs**
(n = 254)

*95% in RAL group and 97% in NRTI group had at least 1 NRTI RAM at baseline

Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SELECT: Results

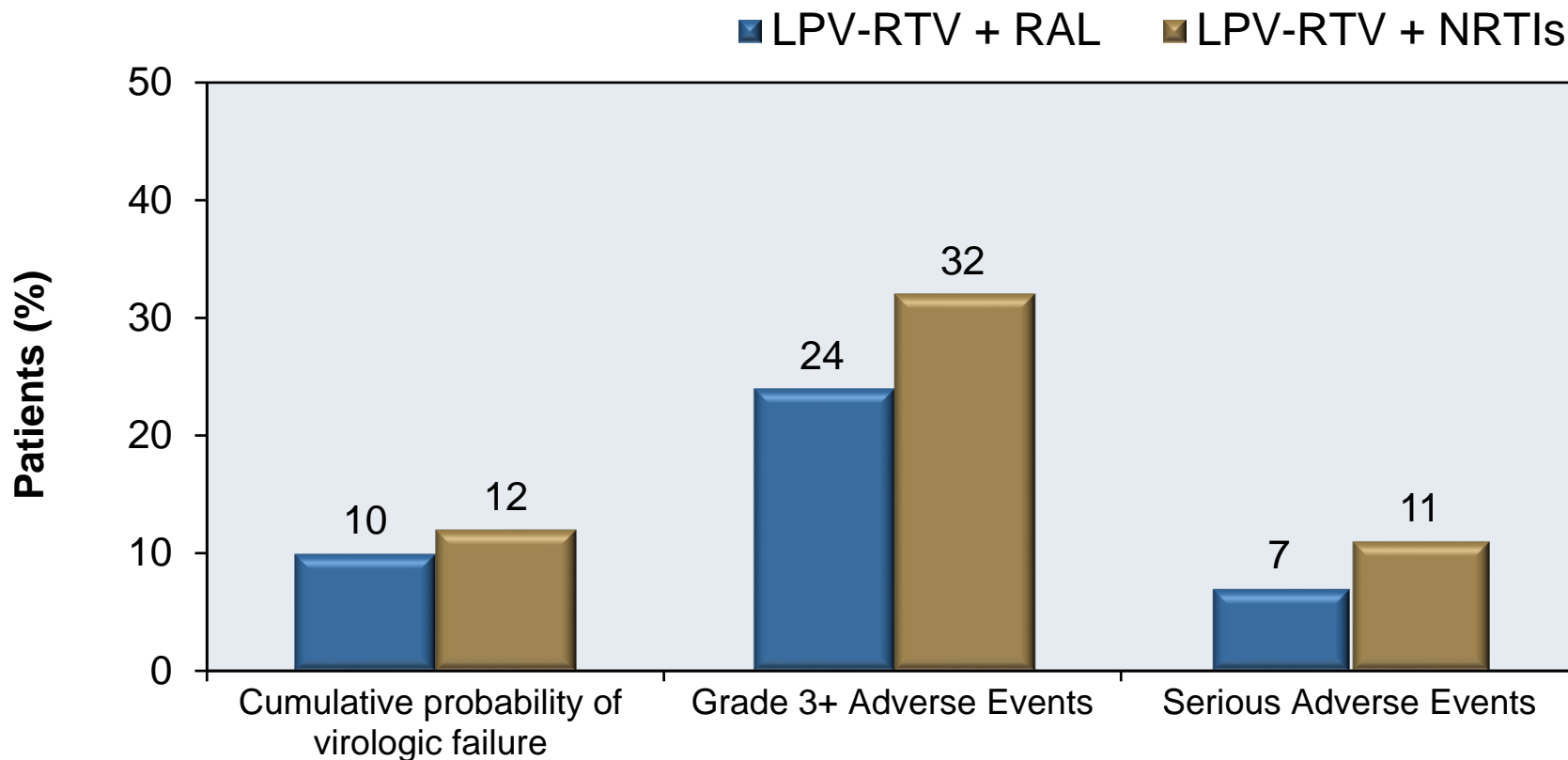
Week 48: Virologic Response (Missing Data Ignored)



Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SELECT: Results

Virologic Failure and Adverse Events



Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SELECT: Results

HIV Resistance Testing at Virologic Failure		
	LPV-RTV + RAL (n = 258)	LPV-RTV + NRTIs (n = 254)
Patients with virologic failure, n (%)	46 (18%)	50 (20%)
Any mutation at virologic failure	85%	90%
New resistance mutations at virologic failure	26%	29%

Lopinavir-Ritonavir plus either Raltegravir or 2-3 NRTIs

SELECT: Conclusions

Interpretation: “In settings with extensive NRTI resistance but no available resistance testing, our data support WHO's recommendation for ritonavir-boosted lopinavir plus NRTI for second-line antiretroviral therapy. Ritonavir-boosted lopinavir plus raltegravir is an appropriate alternative, especially if NRTI use is limited by toxicity.”

SWITCH TRIALS

Raltegravir

Switching from Lopinavir-Ritonavir to Raltegravir
SWITCHMRK 1 & 2 Trials

Switching from Lopinavir-Ritonavir to Raltegravir

SWITCHMRK 1 & 2 Trials: Study Design

Study Design: SWITCHMRK 1&2

- **Background:** Randomized, double-blind, double-dummy trial evaluating switch from lopinavir-ritonavir to raltegravir in combination with background therapy.
- **Inclusion Criteria (n = 707 combined)**
 - Age ≥ 18 years
 - HIV RNA < 50 copies/mL for ≥ 3 months
 - On lopinavir-ritonavir
 - CD4 count ≥ 100 cells/mm³
 - No lipid-lowering agent for 12 weeks
- **Treatment Arms***
 - Raltegravir 400 mg BID + background therapy
 - Lopinavir-ritonavir 400-100 mg BID + background therapy

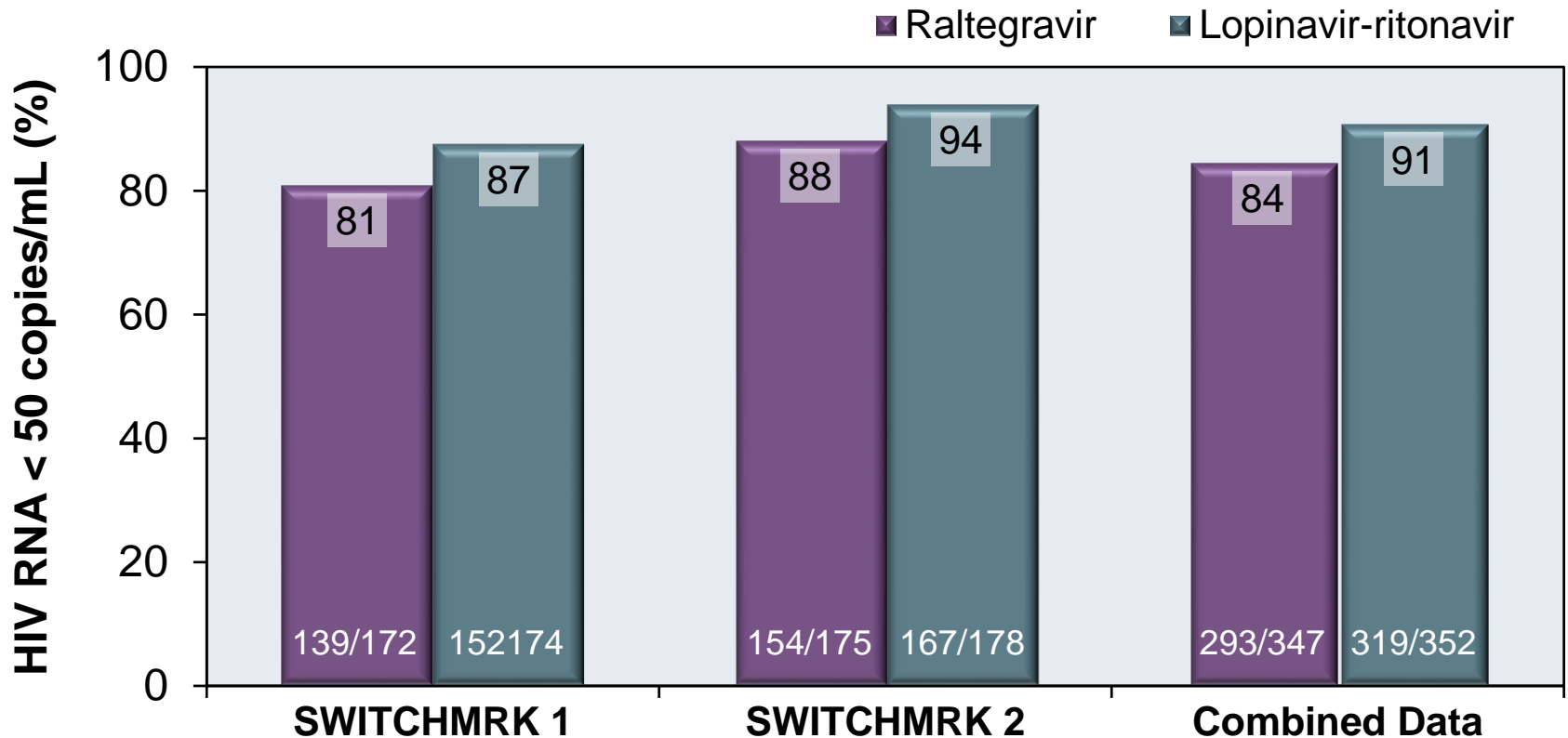
Switch Arm
Raltegravir 400 mg BID
(n = 353)

Continuation Arm
Lopinavir-ritonavir 400-100 mg BID
(n = 354)

*Background therapy in both groups included at least 2 NRTIs

Switching from Lopinavir-Ritonavir to Raltegravir SWITCHMRK 1 & 2 Trials: Results

Week 24: Virologic Response (Non-Completion Counted as Failure)



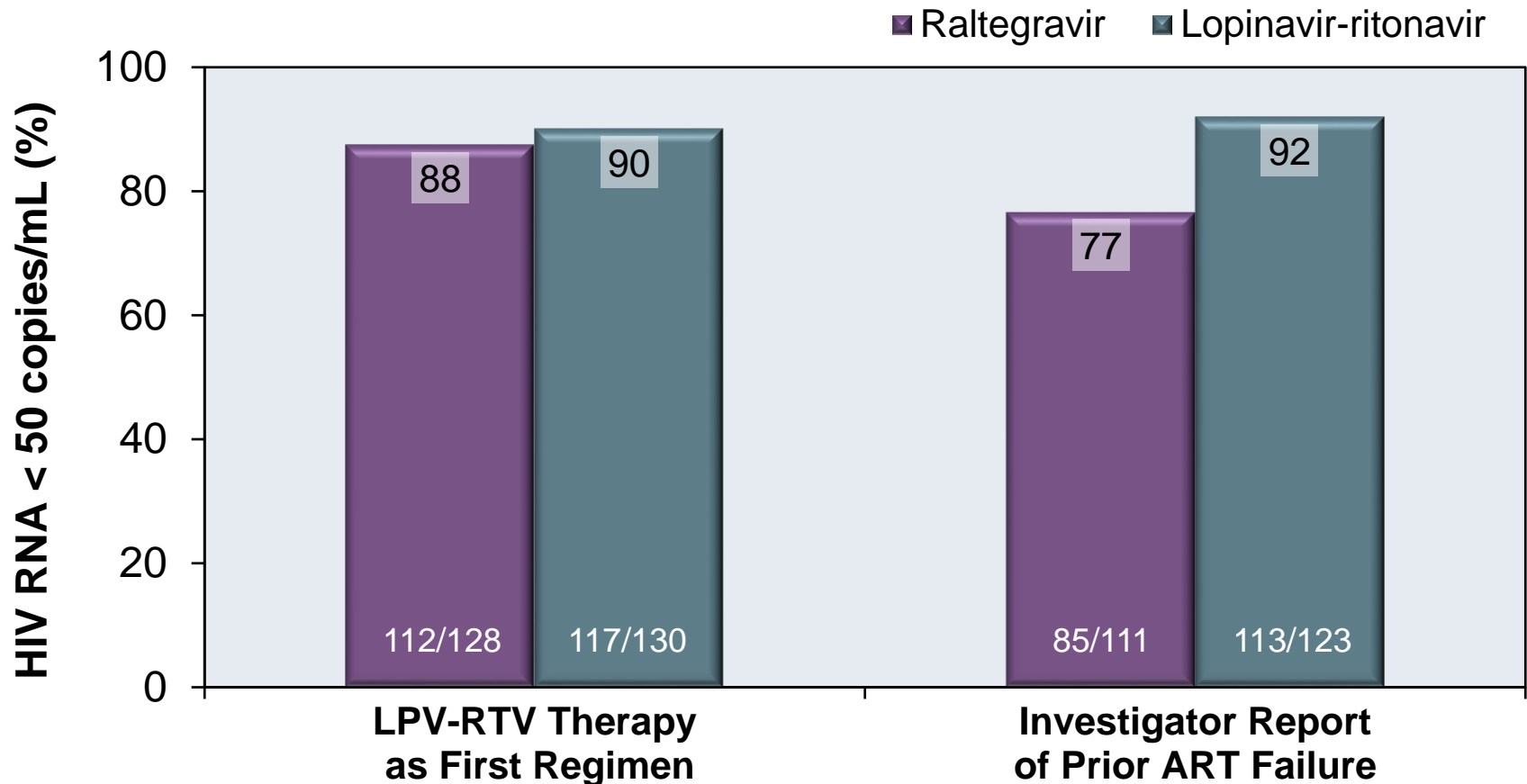
Virologic Failure: Lopinavir-Ritonavir (N = 4); Raltegravir (N = 12)

Source: Eron JJ, et al. *Lancet*. 2010;375:396-407.

Switching from Lopinavir-Ritonavir to Raltegravir

SWITCHMRK 1 & 2 Trials: Results

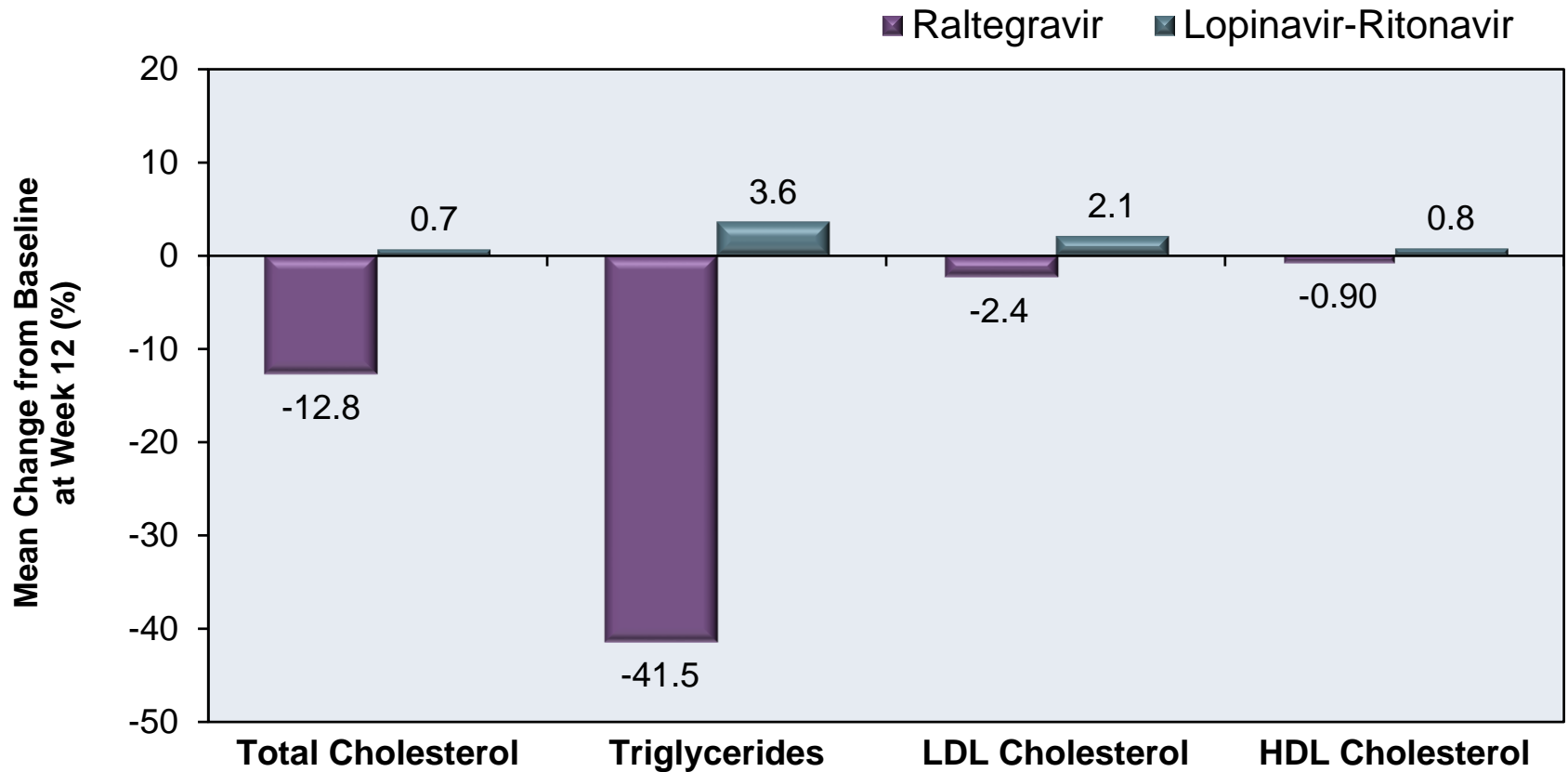
Week 24: Virologic Response (Non-Completion Counted as Failure)



Switching from Lopinavir-Ritonavir to Raltegravir

SWITCHMRK 1 Trial: Results

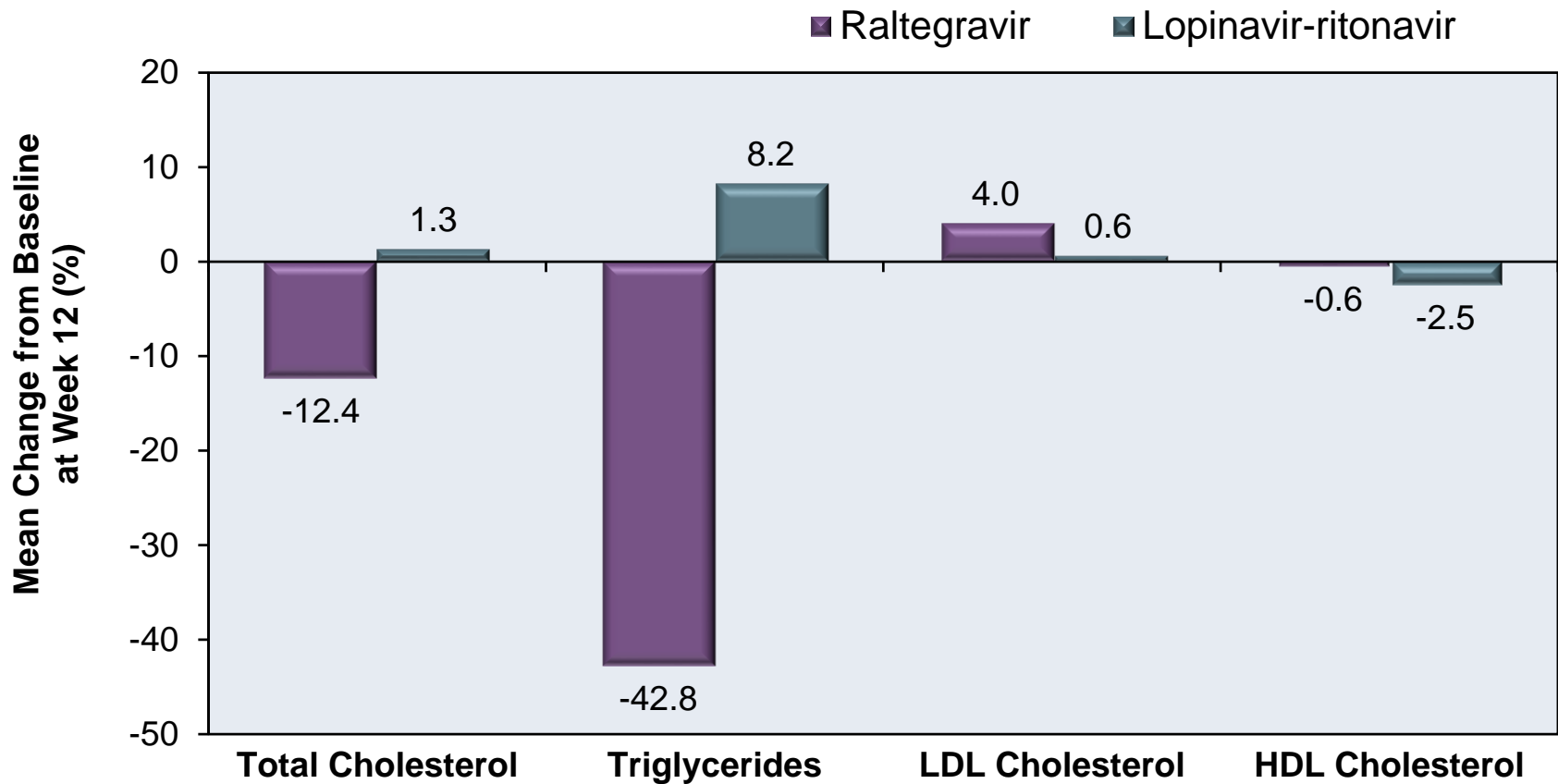
SWITCHMRK 1 Week 12: Analysis of Lipids



Switching from Lopinavir-Ritonavir to Raltegravir

SWITCHMRK 2 Trial: Results

SWITCHMRK 2 Week 12: Analysis of Lipids



Switching from Lopinavir-Ritonavir to Raltegravir SWITCHMRK 1 & 2 Trials: Conclusions

Interpretation: “Although switching to raltegravir was associated with greater reductions in serum lipid concentrations than was continuation of lopinavir-ritonavir, efficacy results did not establish non-inferiority of raltegravir to lopinavir-ritonavir.”

Switch from Protease Inhibitor to Raltegravir
SPIRAL Trial

Switch from Protease Inhibitor to Raltegravir SPIRAL Trial: Study Design

Study Design: SPIRAL

- **Background:** Randomized, open-label trial evaluating switch from a ritonavir-boosted protease inhibitor to raltegravir in persons with HIV.
- **Inclusion Criteria (n = 273)**
 - Age ≥ 18 years
 - HIV RNA < 50 copies/mL for ≥ 6 months
 - No prior raltegravir treatment
- **Treatment Arms***
 - Raltegravir 400 mg BID + background therapy
 - Ritonavir-boosted protease inhibitor + background therapy

Switch Arm
Raltegravir 400 mg BID
(n = 139)

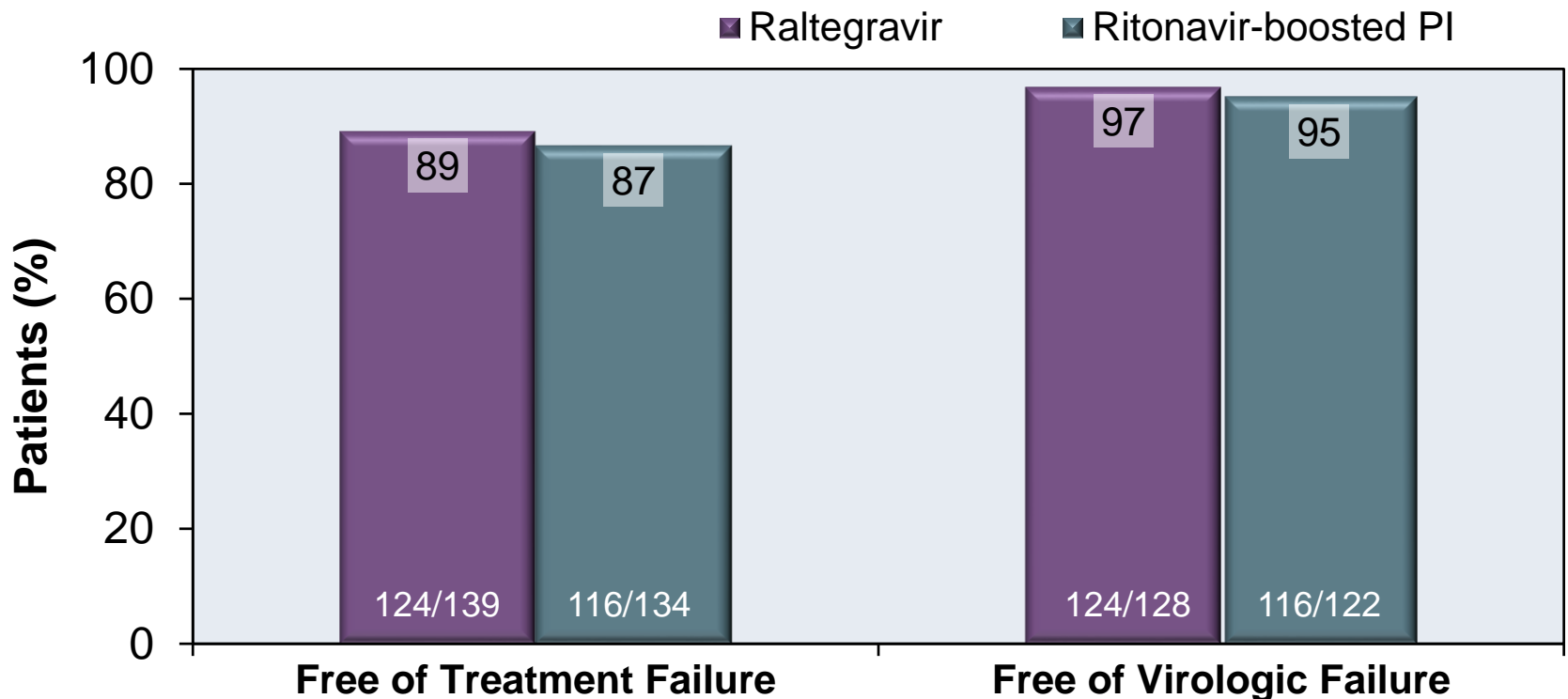
Continuation Arm
Ritonavir-boosted PI
(n = 134)

*Background therapy in both groups included at least 2 additional ARVs

Source: Martinez E, et al. AIDS. 2010;24:1697-1707.

Switch from Protease Inhibitor to Raltegravir SPIRAL Trial: Results

Week 48: Free of Treatment Failure and Virologic Failure



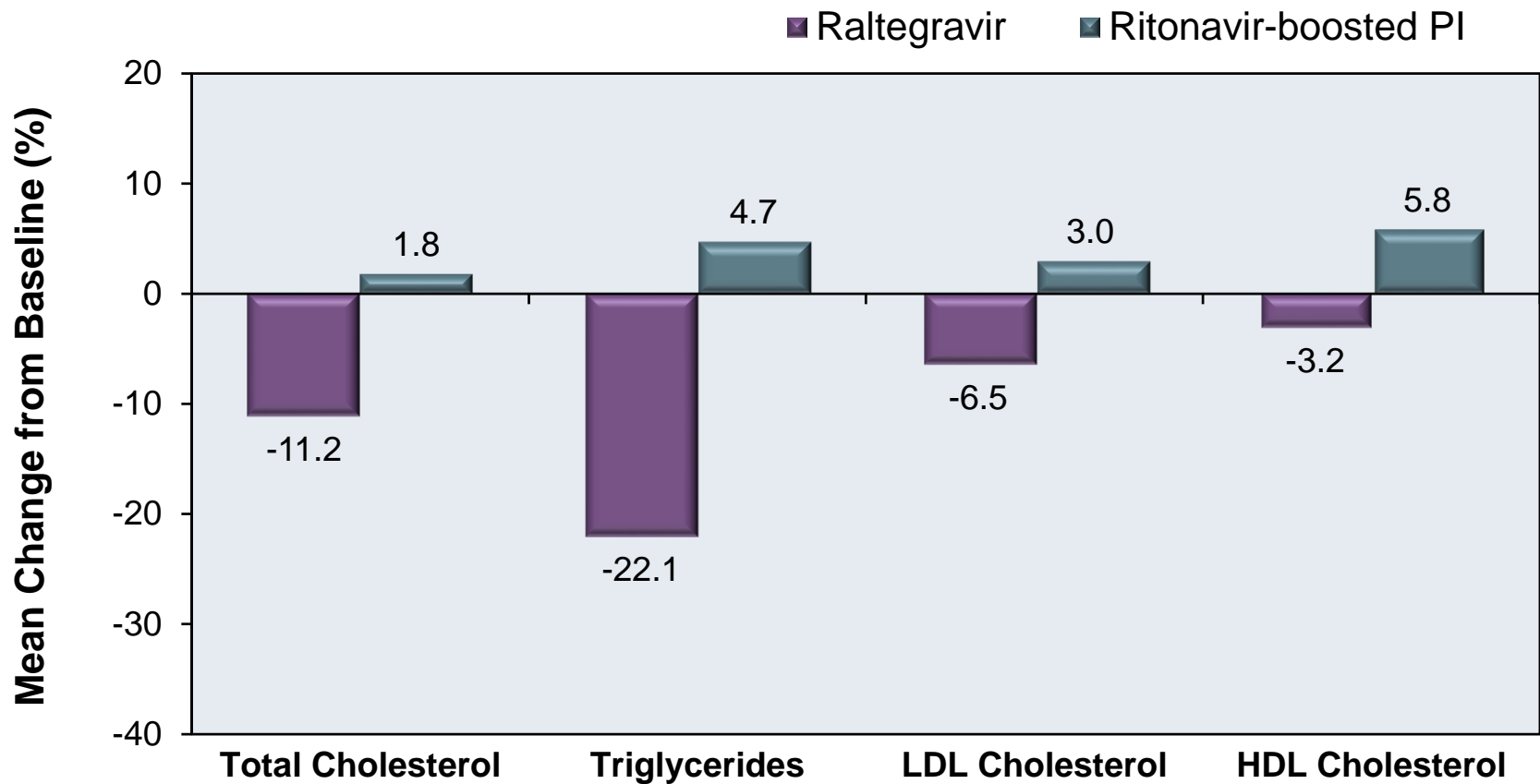
*Treatment failure: virologic failure, withdrawal of consent, discontinuation, loss to follow-up, progression to AIDS, or death.

Source: Martinez E, et al. AIDS. 2010;24:1697-1707.

Switch from Protease Inhibitor to Raltegravir

SPIRAL: Result

Week 48: Analysis of Lipids



Source: Martinez E, et al. AIDS. 2010;24:1697-1707.

Switch from Protease Inhibitor to Raltegravir SPIRAL Trial: Conclusions

Conclusion: “In patients with sustained virological suppression on ritonavir-boosted protease inhibitor-based therapy, switching from ritonavir-boosted protease inhibitor to raltegravir demonstrated noninferior efficacy and resulted in a better lipid profile at 48 weeks than continuing ritonavir-boosted protease inhibitor.”

Switch from Enfuvirtide to Raltegravir
CHEER Trial

Switch from Enfuvirtide to Raltegravir

CHEER: Study Design

Study Design: CHEER

- **Background:** Prospective, nonrandomized, open-label, historical control study evaluating switch from enfuvirtide to raltegravir in virologically suppressed adults with HIV.
- **Inclusion Criteria (n =52)**
 - Age ≥ 18 years
 - HIV RNA < 50 copies/mL (by PCR) or < 75 copies/mL (by bDNA) for ≥ 6 months
 - No prior treatment with integrase inhibitors
- **Treatment Arm**
 - Raltegravir + background antiretroviral regimen (patients served as own controls)

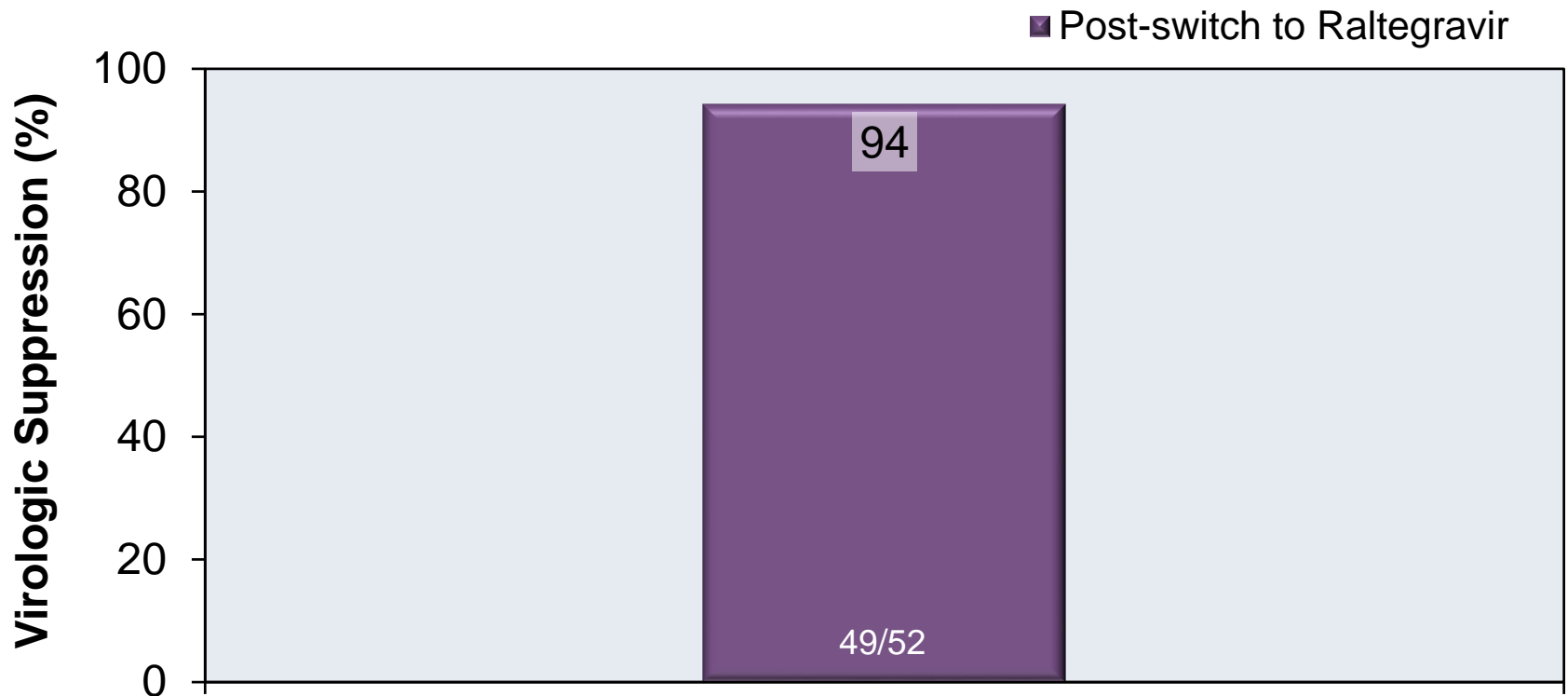
**Raltegravir 400 mg BID +
background ART**

(n = 52)

Switch from Enfuvirtide to Raltegravir

CHEER: Results

Week 24: Virologic Response (Non-completer=Failure, ITT Analysis)



Switch from Enfuvirtide to Raltegravir

CHEER: Conclusions

Conclusions: “In treatment-experienced patients on a stable virologically suppressive enfuvirtide-containing regimen, raltegravir can safely be substituted for enfuvirtide.”

Switch from Enfuvirtide to Raltegravir with Multidrug-Resistant HIV

EASIER ANRS 138 Trial

Switch from Enfuvirtide to Raltegravir in Multidrug-Resistant HIV

EASIER ANRS 138: Study Design

Study Design: EASIER ANRS 138

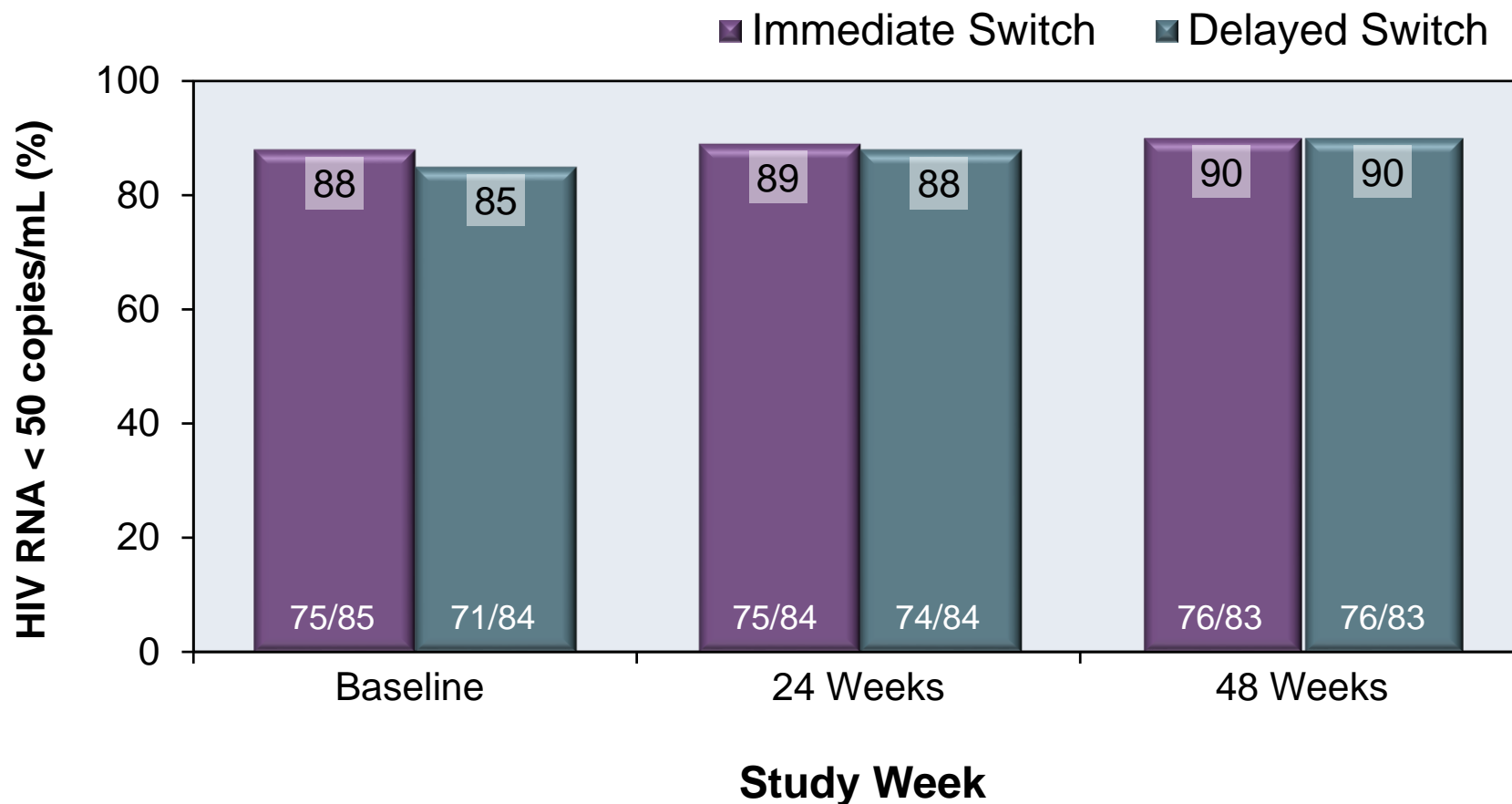
- **Background:** Open label, randomized trial evaluating switching from enfuvirtide-based therapy to raltegravir-based therapy, in virologically suppressed patients with multidrug resistant HIV-1 infection.
- **Inclusion Criteria (n = 170)**
 - Age ≥ 18 years
 - HIV RNA < 400 copies/mL for > 3 months
 - History of triple class failure (PI, NRTI, NNRTI)
 - Integrase inhibitor naïve
- **Treatment Arms**
 - Raltegravir 400 mg BID + background regimen
 - Enfuvirtide + background regimen x 24 weeks, then switch enfuvirtide to raltegravir 400 mg BID

Immediate Switch Arm
**Raltegravir 400 mg BID
+ Background Regimen**
(n = 84)

Delayed Switch Arm
**Enfuvirtide x 24 weeks, then
Raltegravir 400 mg BID +
Background Regimen**
(n = 84)

Switch from Enfuvirtide to Raltegravir in Multidrug-Resistant HIV EASIER ANRS 138: Results

Virologic Response (Intent-to-Treat Analysis, censoring missing data)

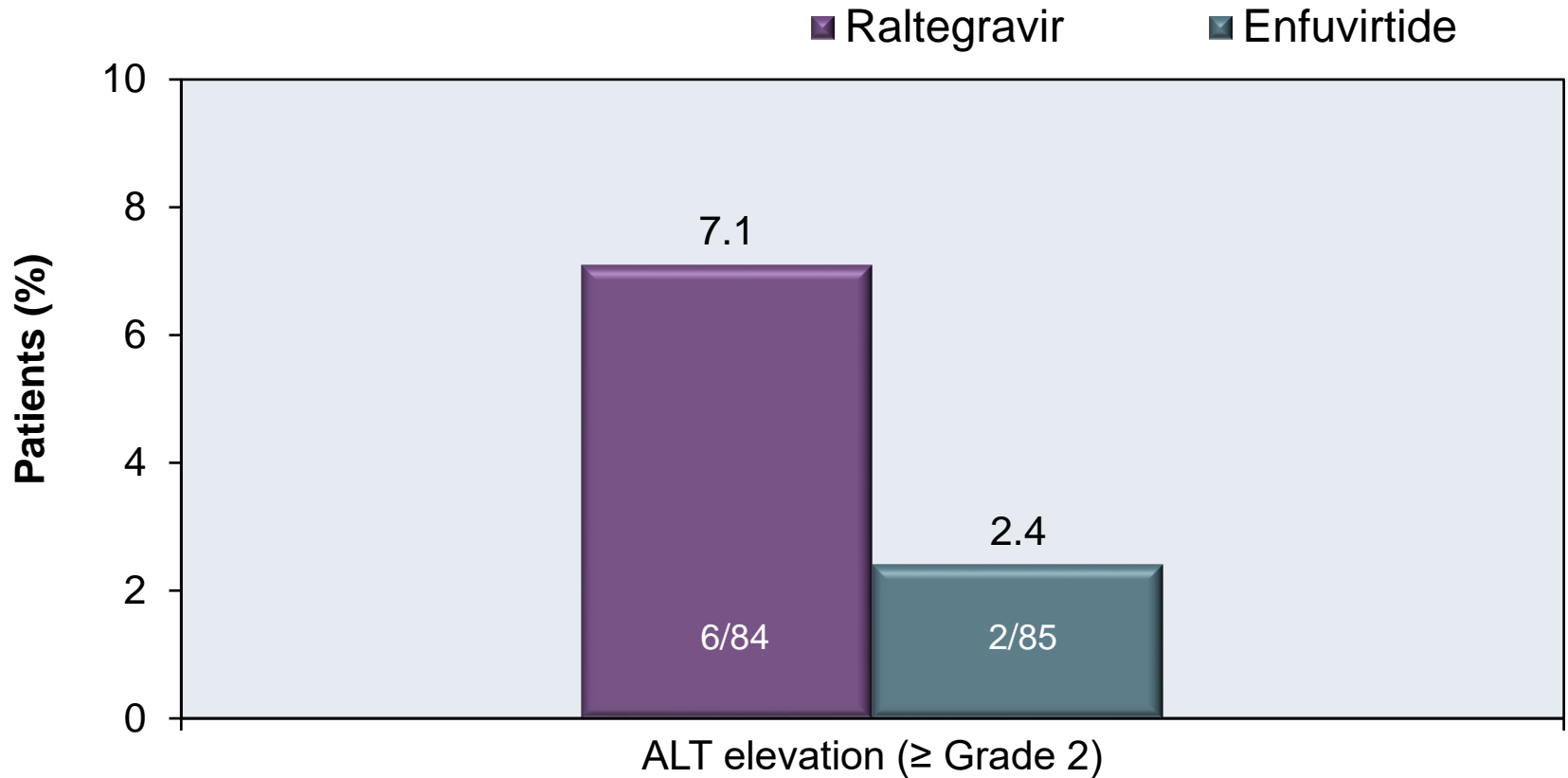


Switch from Enfuvirtide to Raltegravir in Multidrug-Resistant HIV EASIER ANRS 138: Conclusions

Conclusions: “In well-suppressed patients with multidrug-resistant HIV infection, a switch from enfuvirtide to raltegravir is generally well tolerated and has sustained antiviral efficacy when combined with a potent background regimen.”

Switch from Enfuvirtide to Raltegravir in Multidrug-Resistant HIV EASIER ANRS 138: Incidence of ALT Elevations

Week 24: ALT Elevation



Source: de Castro N, et al. AIDS Res Ther. 2016;13:17.

Switch from Enfuvirtide to Raltegravir in Multidrug-Resistant HIV

EASIER ANRS 138: Risk Factors for ALT Elevation

Multivariate Analysis of Baseline Risk Factors for ALT Elevation (\geq Grade 2)		
RISK FACTORS	Odds Ratio	p value
Use of boosted tipranavir	3.66	0.022
ALT elevation (\geq Grade 1)	10.3	< 0.001
Alcohol use (> 2 times/week)	0.39	0.281
Liver disease (steatosis/cirrhosis)	0.89	0.899

Maraviroc plus Raltegravir
ROCnROL (ANRS 157) Trial

Maraviroc + Raltegravir ROCNal (ANRS 157): Study Design

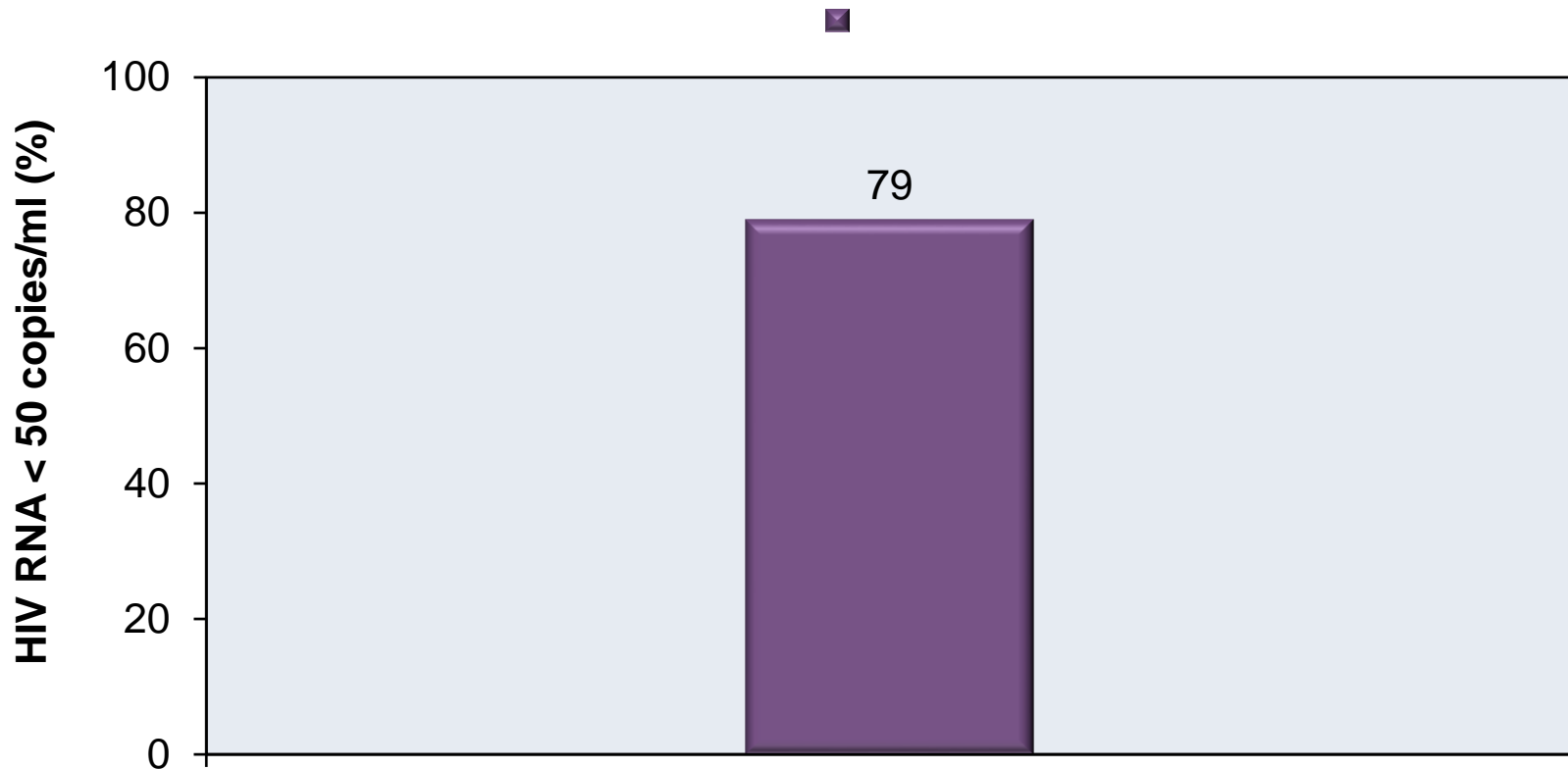
Study Design: ROCnRAL (ANRS 157)

- **Background:** Pilot, phase II, single-arm trial to evaluate capacity of a dual regimen of raltegravir plus maraviroc to maintain viral suppression in virally suppressed adults with HIV who have hyperlipidemia.
- **Inclusion Criteria (n = 44)**
 - Adults
 - On ART for ≥ 5 years
 - Naïve to INSTIs and maraviroc
 - HIV RNA < 200 copies/mL x 24 months and < 50 copies/mL for ≥ 12 months
 - R5 tropism
- **Switch Treatment Arm**
 - Raltegravir 400 mg BID + Maraviroc 300 mg BID

**Raltegravir 400 mg BID +
Maraviroc 300 mg BID**
(n = 44)

Maraviroc + Raltegravir ROCnRal (ANRS 157): Result

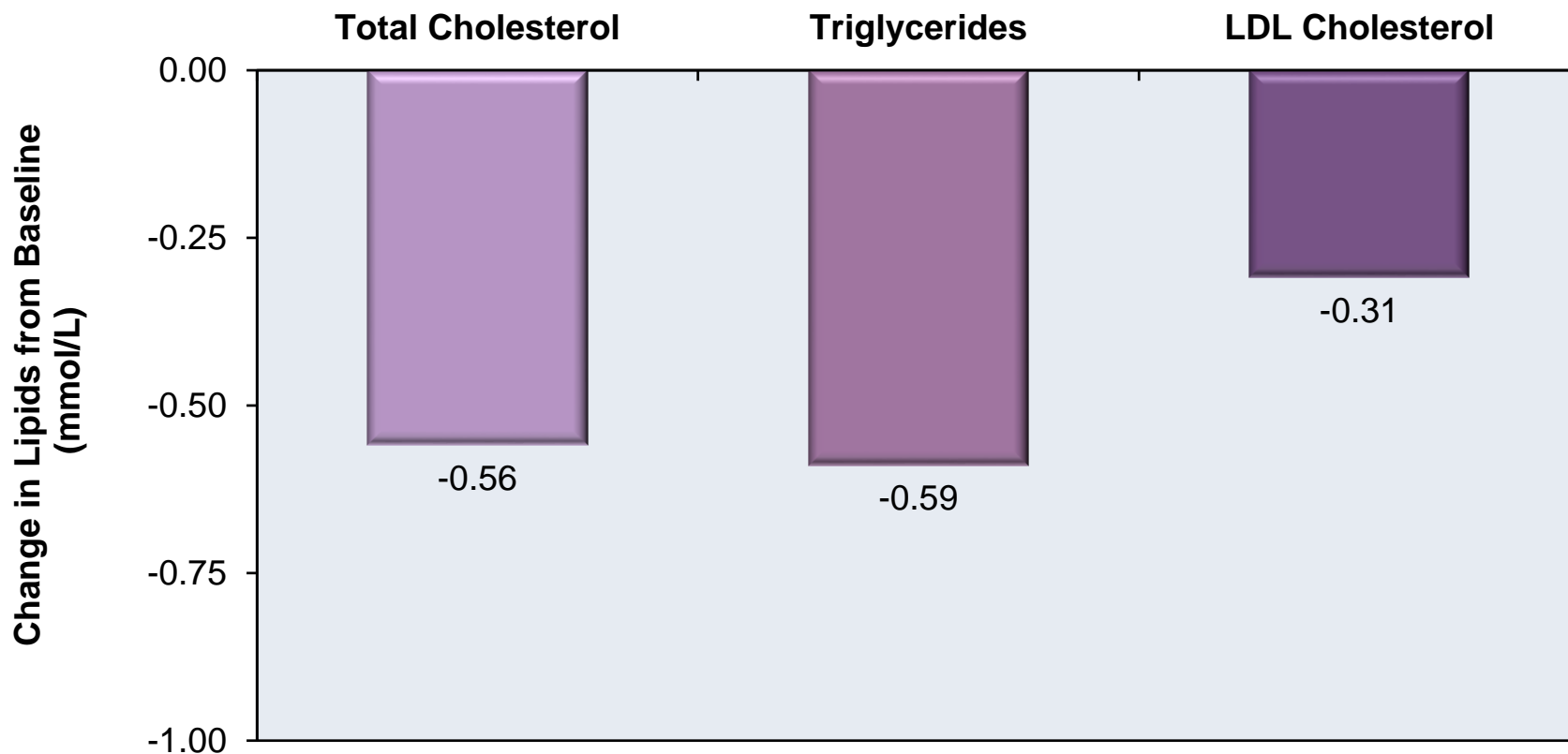
Week 24 Virologic Response



Source: Katlama C, et al. J Antimicrob Chemother. 2014;69:1648-52.

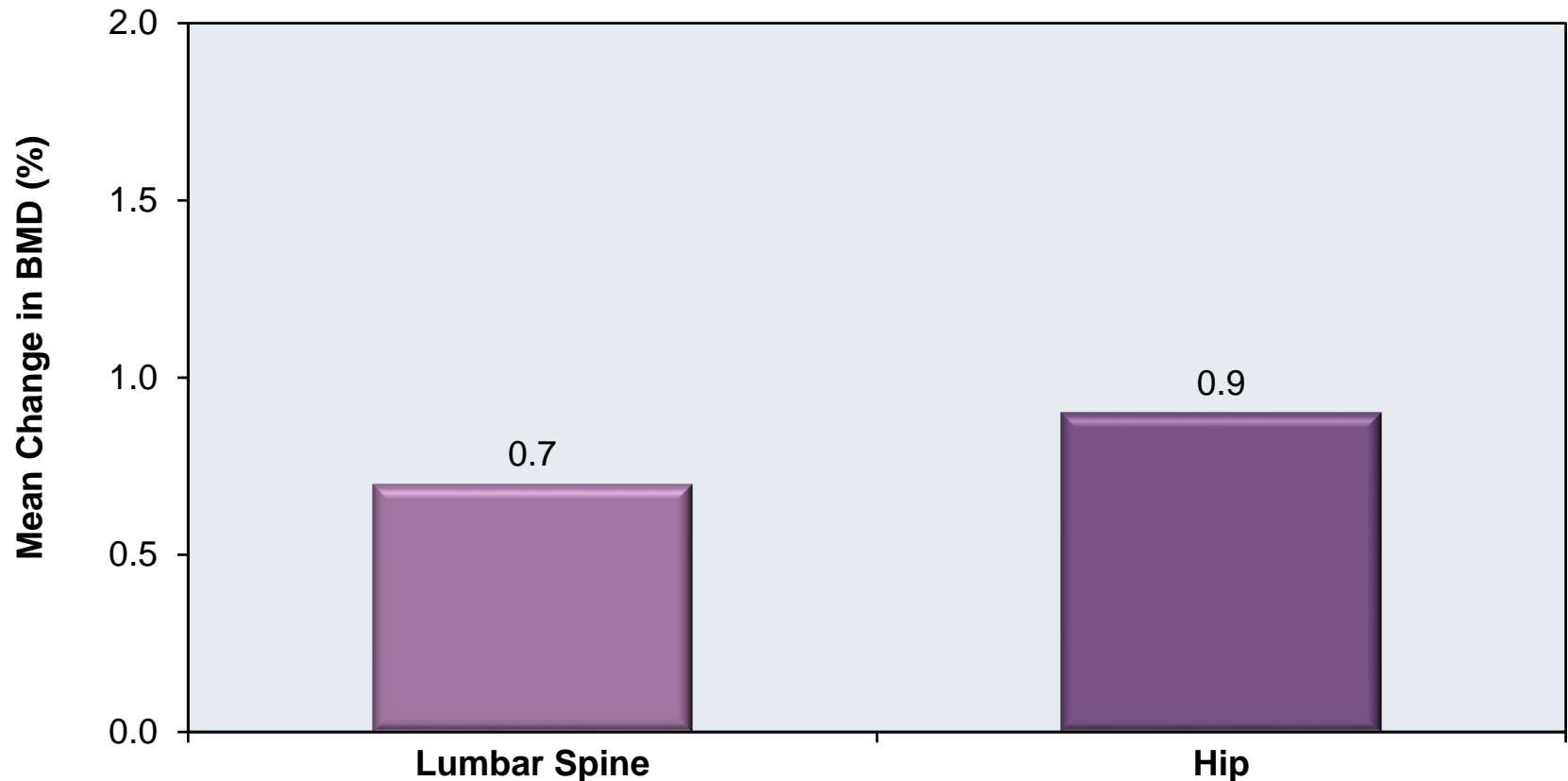
Maraviroc + Raltegravir ROCnRal (ANRS 157): Result

Analysis of Lipids on Dual Therapy (Median time = 19.4 weeks)



Maraviroc + Raltegravir ROCNal (ANRS 157): Result

Change in Bone Mineral Density from Baseline (Median interval: 26 wks)



Maraviroc + Raltegravir ROCnRal (ANRS 157): Conclusions

Conclusions: “In long-term-experienced patients, maraviroc/raltegravir therapy lacks virological robustness despite a benefit in lipid profile and bone density.”

Switch to Atazanavir-RTV with Either Raltegravir or TDF-FTC

HARNESSTrial

Switch to Atazanavir-ritonavir with Either Raltegravir or TDF-FTC

HARNESS: Study Design

Study Design: HARNESS

- **Background:** Open label, prospective, randomized, parallel group trial evaluating switching from stable ARV regimen (2 NRTIs + 3rd agent, excluding atazanavir) to ritonavir-boosted atazanavir with either raltegravir 400 mg BID or TDF-FTC.
- **Inclusion Criteria (n = 109)**
 - Age ≥18 years
 - HIV RNA <50 copies/mL for ≥3 months
 - Single HIV RNA <40 copies/mL in past 30 days
 - No history of virologic failure or resistance
- **Treatment Arms**
 - Atazanavir + RTV QD + Raltegravir 400 mg BID
 - Atazanavir + RTV QD + TDF-FTC QD

2x

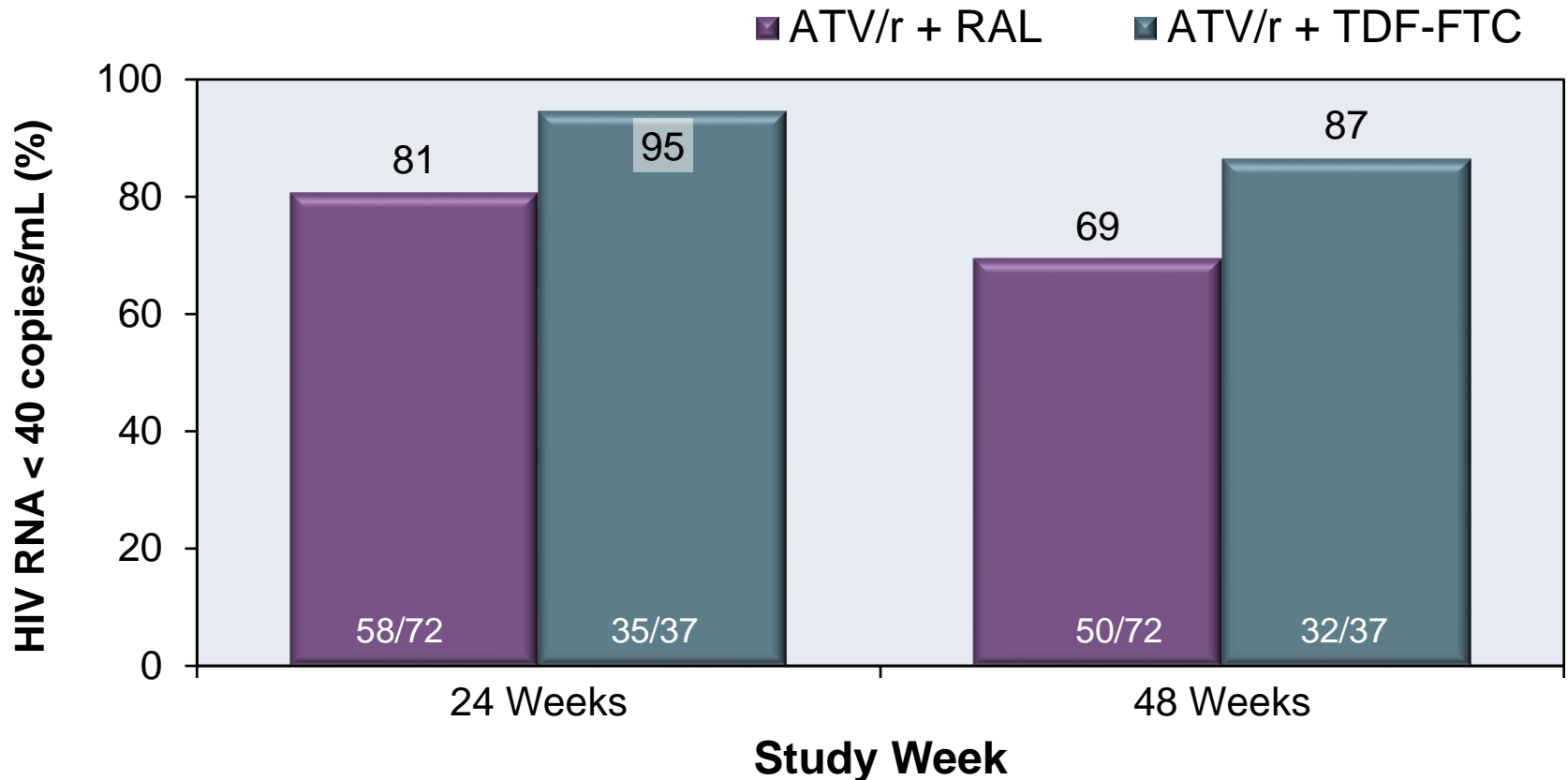
**Atazanavir QD + Ritonavir QD
+ Raltegravir 400 mg BID**
(n = 72)

1x

**Atazanavir QD + Ritonavir QD
+ TDF-FTC QD**
(n = 37)

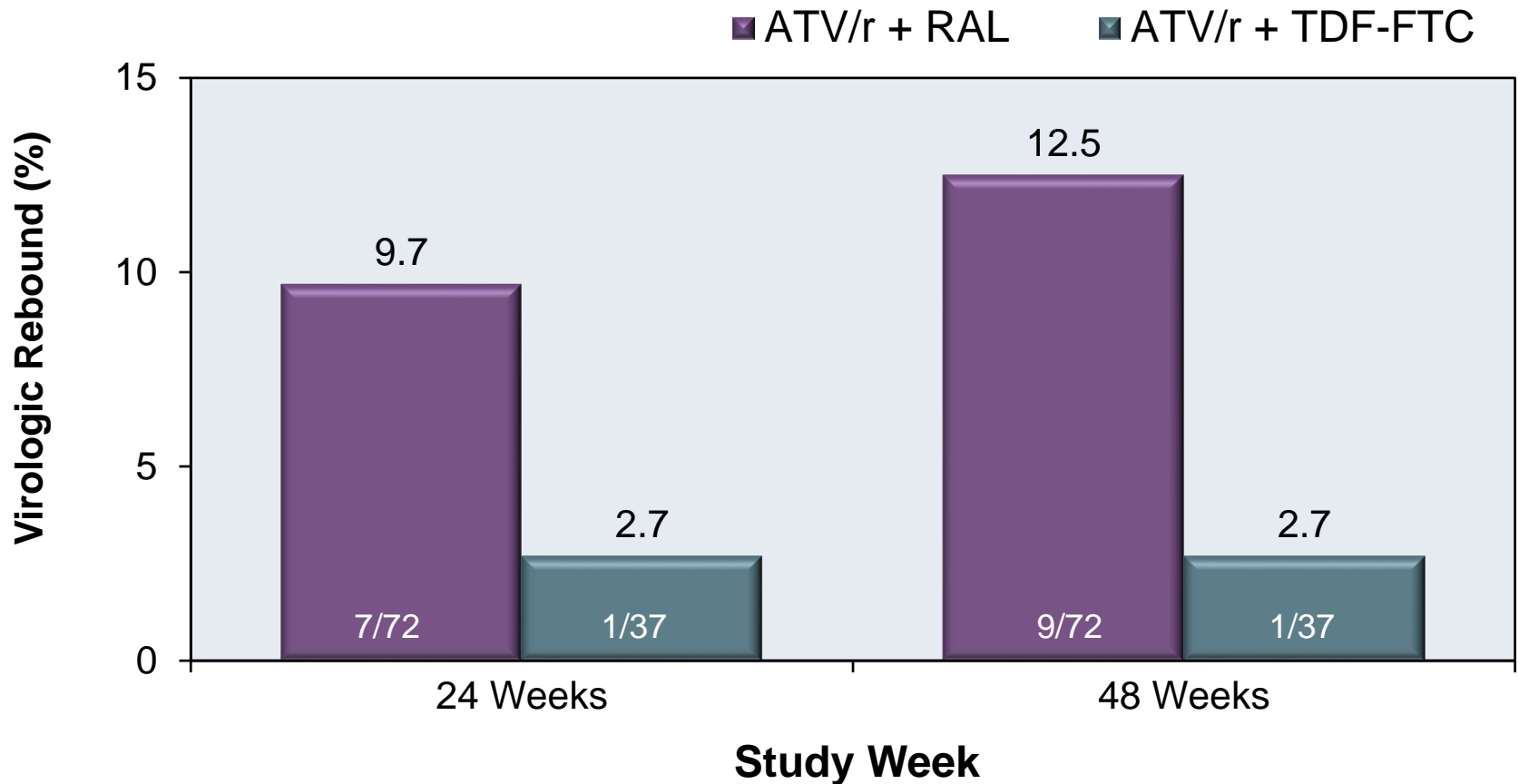
Switch to Atazanavir-ritonavir with Raltegravir or TDF-FTC HARNES: Results

Week 24 and 48: Virologic Response (Intent-to-Treat Analysis)



Switch to Atazanavir-ritonavir with Raltegravir or TDF-FTC HARNES: Results

Week 24 and 48: Virologic Rebound



Source: van Lunzen J, et al. J Acquir Immune Defic Syndr. 2016;71:538-43.

Switch to Atazanavir-ritonavir with Raltegravir or TDF-FTC HARNES: Conclusions

Conclusion: “In conclusion, switching to ATV/r + RAL resulted in a higher virological rebound rate than switching to ATV/r plus tenofovir disoproxil fumarate/emtricitabine.”

SPECIAL POPULATIONS

Raltegravir

Raltegravir plus Standard ART in Early HIV Infection
UW PIC 330 Trial

Raltegravir plus Standard ART in Early HIV Infection

UW 330 PIC: Study Design

Study Design: UW 300 PIC

- **Background:** Pilot, open-label, randomized, phase 3 trial evaluating impact of adding raltegravir to standard ART during early HIV.
- **Inclusion Criteria (n = 92)**
 - Age ≥ 18 years
 - Antiretroviral-naïve
 - HIV RNA ≥ 500 copies/mL < 14 days of study entry
 - Early HIV infection*
- **Treatment Arms**
 - RAL 400 mg BID + 2 NRTIs + [NNRTI or PI QD]
 - 2 NRTIs + [NNRTI or PI QD]

Raltegravir Group
**Raltegravir plus
2 NRTIs plus [NNRTI or PI]**
(n = 5)

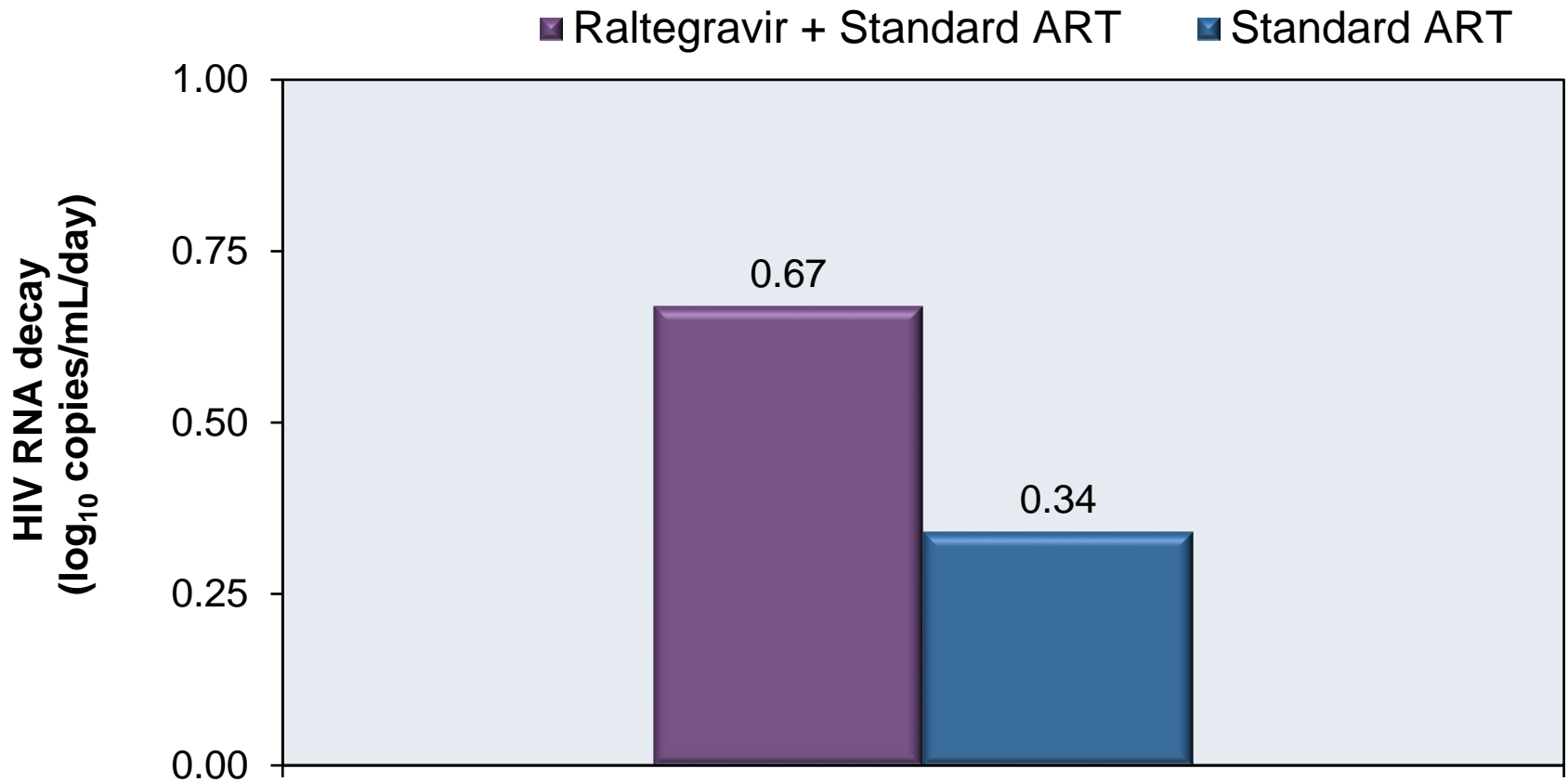
Standard ART
2 NRTIs plus [NNRTI or PI]
(n = 5)

*Early HIV defined as current positive HIV EIA and western blot with either a negative HIV EIA in past 6 months or negative point-of care test or nonreactive less sensitive HIV EIA in past month

Raltegravir plus Standard ART in Early HIV Infection

UW 330 PIC: Results

First Phase Plasma HIV RNA Decay



Raltegravir plus Standard ART in Early HIV Infection UW 330 PIC: Conclusions

Interpretation: “Our results suggest homogeneity of responses in cell-associated RNA, HIV DNA, CD4(+) T-cells with replication-competent virus, and 2LTR circles with early HIV in both ART groups. The kinetics of 2LTR DNA did not reflect the kinetics of plasma HIV RNA decline following ART initiation.”

Optimization of Primary HIV Infection Treatment
OPTIPRIM-ANRS 147 Trial

Optimization of Primary HIV Infection Treatment

OPTIPRIM-ANRS 147: Study Design

Study Design: OPTIPRIM-ANRS 147

- **Background:** Open label, randomized, phase 3 trial comparing intensive ART started during primary HIV infection to standard triple-drug ART.
- **Inclusion Criteria (n = 92)**
 - Primary HIV infection* with either symptoms or CD4 count <500 cells/mm³
 - Recruited from 33 French hospitals
 - No post-exposure prophylaxis in prior 6 months
- **Treatment Arms**
 - 1) Raltegravir 400 mg BID + Maraviroc 150 mg BID + Darunavir 800 mg QD + Ritonavir 100 mg QD + Tenofovir DF-Emtricitabine QD
 - 2) Darunavir 800 mg QD + Ritonavir 100 mg QD + Tenofovir DF-Emtricitabine QD

Intensive ART
RAL + MVC + DRV/r + TDF-FTC
(n = 45)

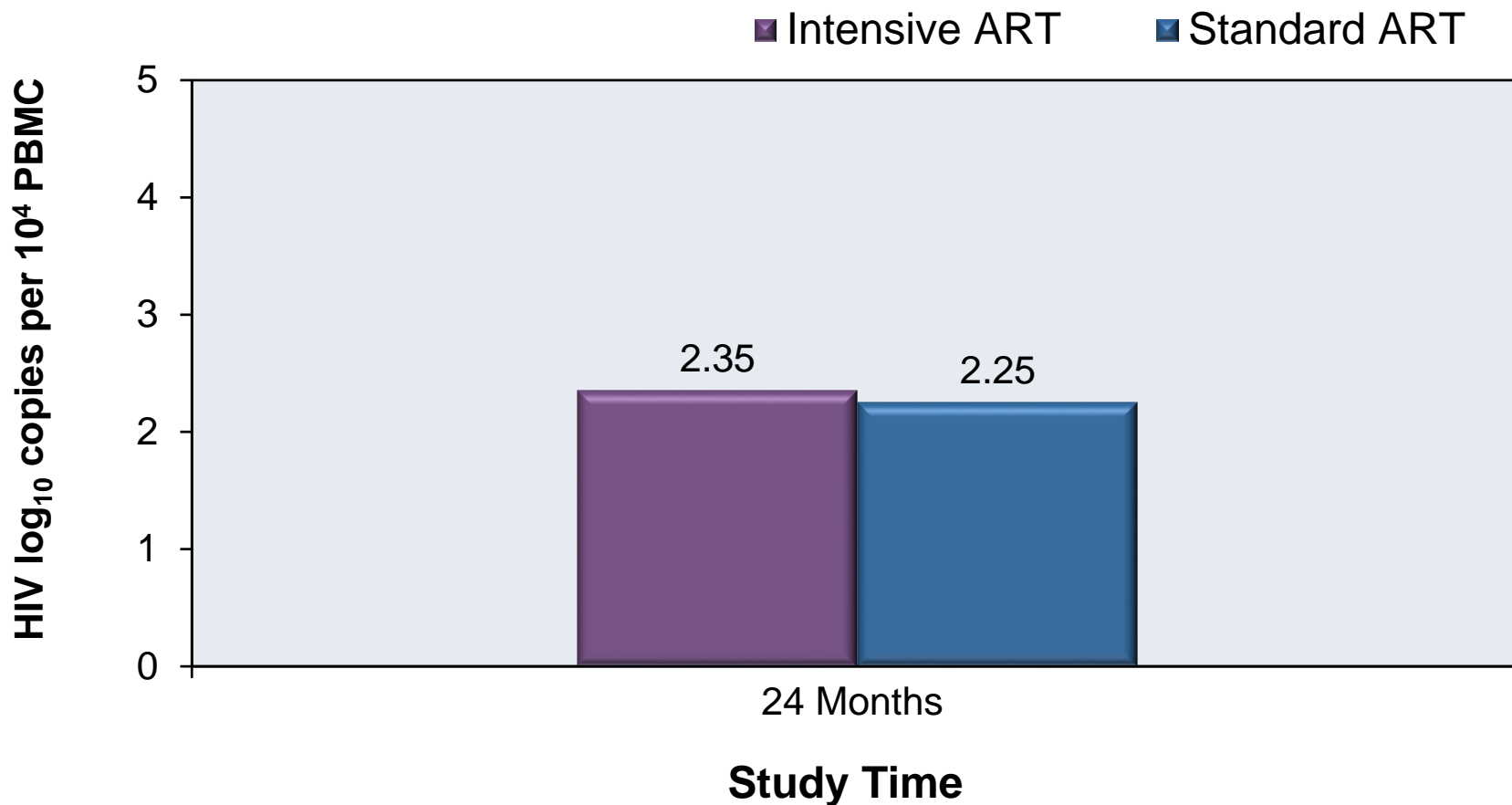
Standard ART
TDF-FTC + DRV/r
(n = 45)

*Primary HIV defined as detectable plasma HIV RNA with incomplete Western blot (≤ 4 bands), irrespective of ELISA result and p24 antigenemia, documented within 8 days before inclusion.

Optimization of Primary HIV Infection Treatment

OPTIPRIM-ANRS 147: Results

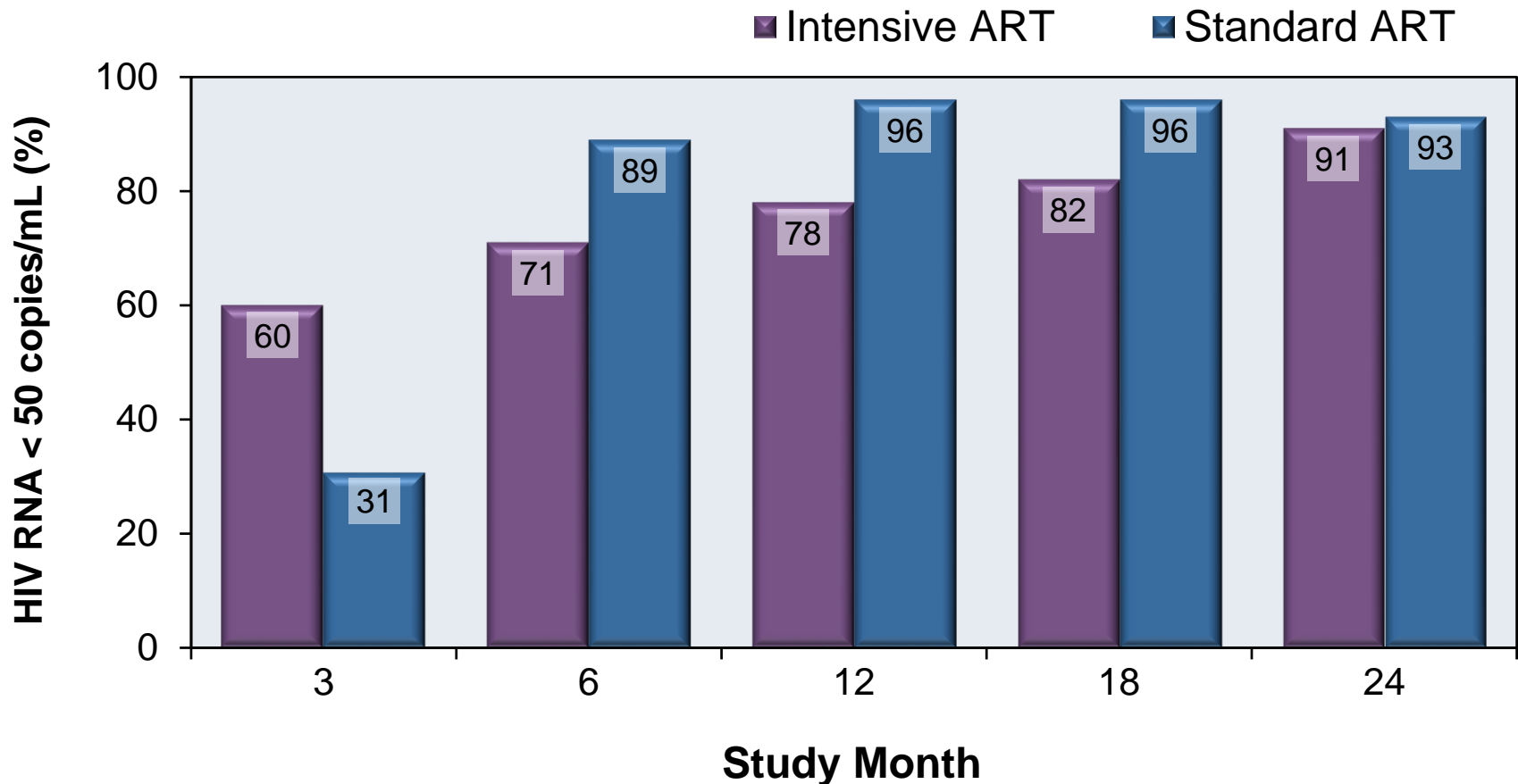
Week 24: Primary Virologic Outcome (Modified ITT Analysis)



Optimization of Primary HIV Infection Treatment

OPTIPRIM-ANRS 147: Results

Virologic Response by Study Month



Optimization of Primary HIV Infection Treatment

OPTIPRIM-ANRS 147: Conclusions

Interpretation: “After 24 months, cART intensified with raltegravir and maraviroc did not have a greater effect on HIV blood reservoirs than did standard cART. These results should help to design future trials of treatments aiming to decrease the HIV reservoir in patients with primary HIV-1 infection.”

Raltegravir vs. Lopinavir-ritonavir, both with 2NRTIs for nPEP

RALPEP Trial

Raltegravir vs. Lopinavir-ritonavir, both with 2NRTIs for nPEP

RALPEP: Study Design

Study Design: RALPEP

- **Background:** Open label, prospective, randomized trial evaluating two regimens for post-exposure prophylaxis following sexual exposure.
- **Inclusion Criteria (n = 243)**
 - Age ≥ 18 years
 - Recruited from hospital ER in Barcelona following potential sexual exposure to HIV
- **Treatment Arms**
 - TDF-FTC QD + Raltegravir 400 mg BID
 - TDF-FTC QD + Lopinavir-ritonavir QD

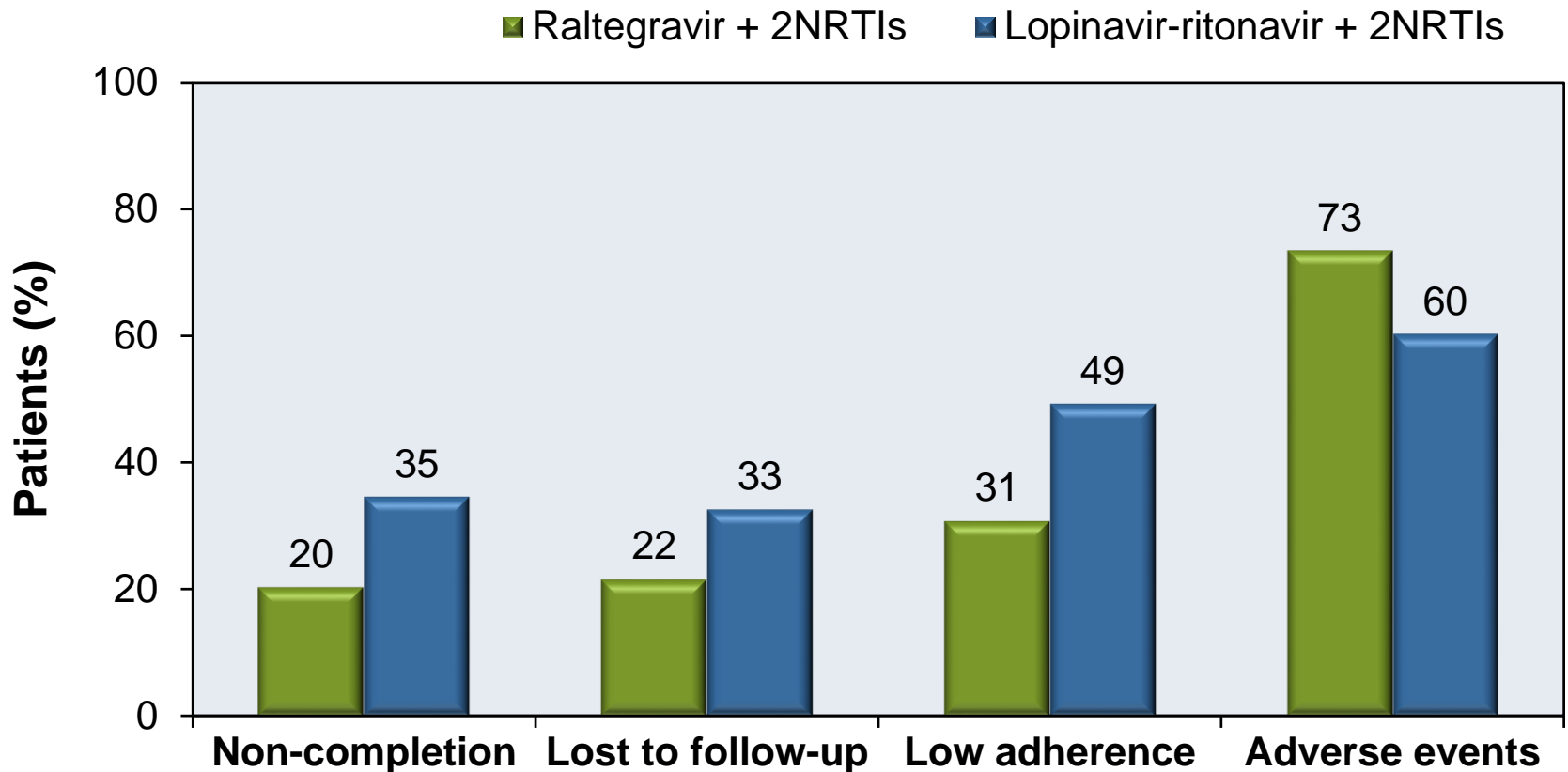
**TDF-FTC QD +
Raltegravir BID**
(n = 121)

**TDF-FTC QD +
Lopinavir-ritonavir QD**
(n = 122)

Raltegravir vs. Lopinavir-ritonavir, both with 2NRTIs for nPEP

RALPEP: Results

28-Day PEP Outcome Measures



Raltegravir vs. Lopinavir-ritonavir, both with 2NRTIs for nPEP

RALPEP: Conclusions

Conclusions: “Although we found no differences between arms regarding PEP non-completion, poor adherence and adverse events were significantly higher in patients allocated to tenofovir disoproxil/emtricitabine plus ritonavir-boosted lopinavir. These data support the use of raltegravir as the preferred third drug in current PEP recommendations.”

Raltegravir in Pregnancy

PANNA Trial

Raltegravir in Pregnancy

PANNA: Study Design

Study Design: PANNA Network Study

- **Background:** Open-label, nonrandomized, phase 4 trial evaluating the effects of pregnancy on the pharmacokinetics of raltegravir and its safety and efficacy in pregnant women with HIV.
- **Inclusion Criteria (n =52)**
 - Age ≥ 18 years
 - Taking raltegravir 400 mg BID ≥ 2 weeks prior to initial assessment in 3rd trimester of pregnancy
 - On raltegravir for optimization/intensification of 3-drug regimen or as alternative to another ART medication
- **Treatment Arm**
 - Raltegravir + background antiretroviral regimen

**Raltegravir 400 mg BI+
Background ART**

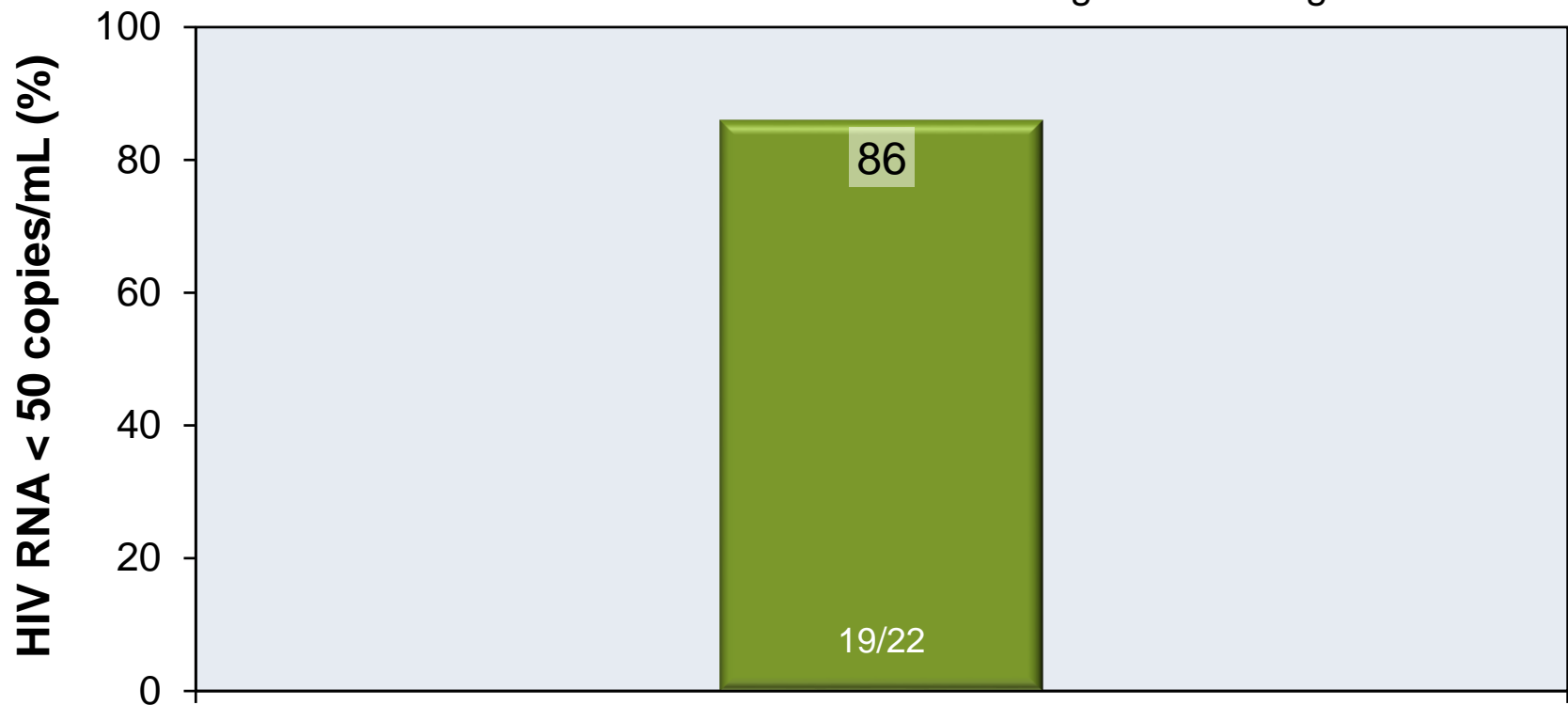
(n = 22)

Raltegravir in Pregnancy

PANNA: Results

Virologic Suppression at Delivery

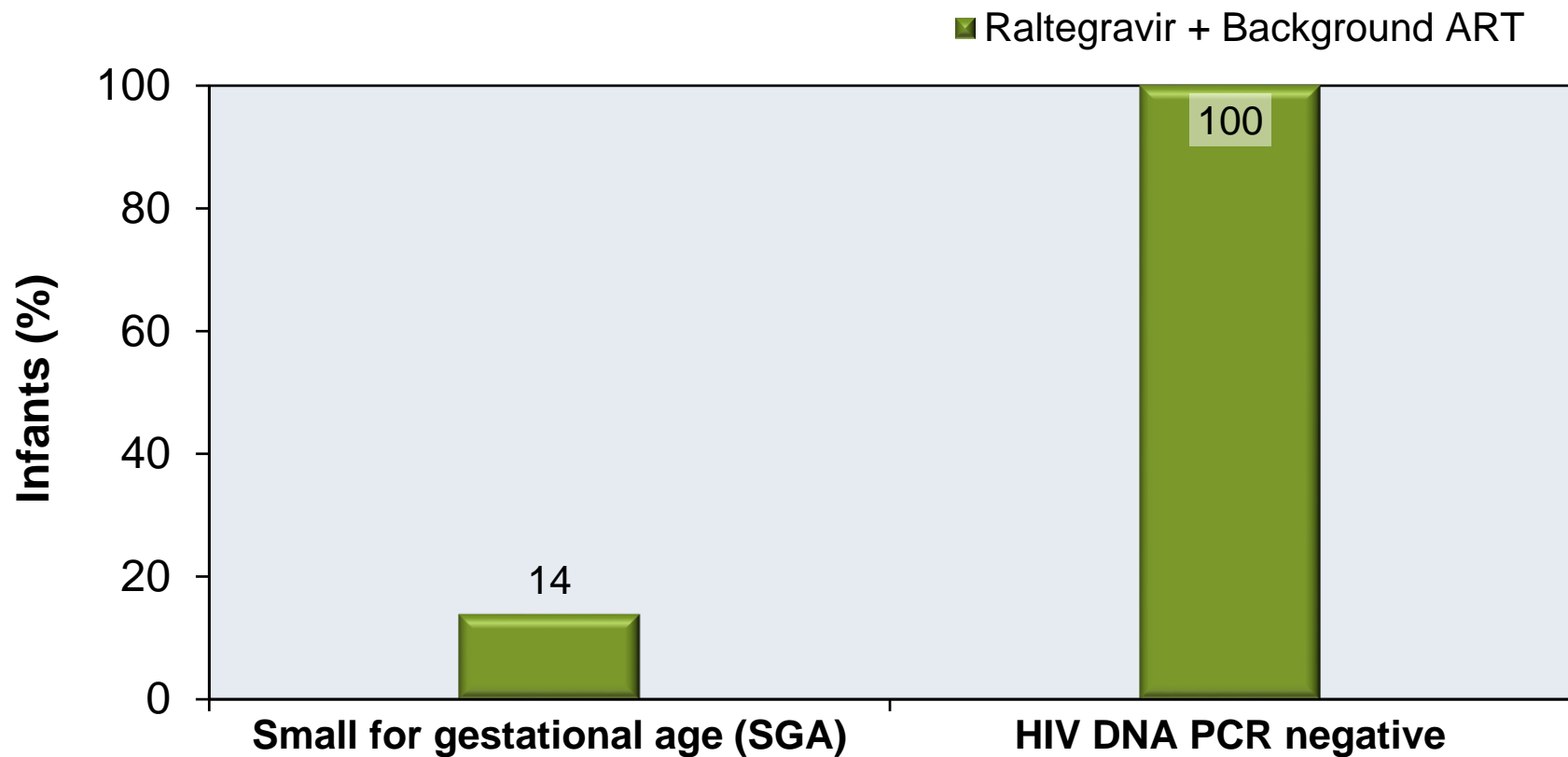
■ Raltegravir + Background ART



Raltegravir in Pregnancy

PANNA: Results

Pregnancy Outcomes



Raltegravir in Pregnancy

PANNA: Conclusions

Conclusions: “Raltegravir was well tolerated during pregnancy. The pharmacokinetics of raltegravir showed extensive variability. The observed mean decrease in exposure to raltegravir during third trimester compared to postpartum is not considered to be of clinical importance. Raltegravir can be used in standard dosages in HIV-infected pregnant women.”

Acknowledgment

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