National HIV Curriculum

Dolutegravir (*Tivicay*)

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AETC AIDS Education & Training Center Program

Dolutegravir (*Tivicay*)

Tivicay
[TIV-eh-kay]

Dolutegravir
50 mg

INSTI

- Treatment Naïve: 50 mg once daily with or without food
- Coadministered with certain UGT1A or CYP3A inducers: 50 mg twice daily with or without food
- INSTI-experienced with certain substitutions: 50 mg twice daily with or without food
- Clinically suspected INSTI resistance: 50 mg twice daily with or without food

Dolutegravir (*Tivicay*)

- **Class**: integrase strand transfer inhibitor (INSTI)
- **Approval Status**: approved for persons 12 and older
- **Dose (with or without food)**:
  - Treatment Naïve: 50 mg once daily
  - Treatment Experienced, INSTI-Naive: 50 mg once daily
  - INSTI Resistant: 50 mg twice daily
  - Coadministration of Certains Inducers: 50 mg twice daily
- **Metabolism**: glucuronidation via UGT 1A1
- **Adverse Events**:
  - Small increases in serum creatinine (benign inhibition of creatinine secretion)

Dolutegravir

Recommended Dolutegravir Dosing	
Adult Population	**Recommended Dose**
Treatment-naïve *or* Treatment-experienced INSTI-naïve	50 mg once daily
Coadministered with potent UGT1A/CYP3A inducer: Efavirenz Fosamprenavir/ritonavir Tipranavir/ritonavir Rifampin	50 mg twice daily
INSTI-experienced with certain INSTI mutations* *or* Clinically suspected INSTI resistance	50 mg twice daily
Poor virologic response associated with Q148 Substitution plus ≥2 INSTI mutations	

Source: Dolutegravir Prescribing Information

Dolutegravir
Summary of Key Studies

- Phase 2b Trials in Treatment Naïve
  - SPRING-1: Dose-ranging Dolutegravir vs. Efavirenz + 2NRTIs
- Phase 3 Trials in Treatment Naïve
  - SPRING 2: Dolutegravir + 2NRTIs vs Raltegravir + 2NRTIs
  - FLAMINGO: Dolutegravir vs. Ritonavir-boosted Darunavi
  - GS-380-1489: Dolutegravir + TAF-FTC versus Bictegravir-TAF-FTC
  - ING 116070: Dolutegravir CSF levels and virologic response in CSF
- Phase 2a Trial in Treatment Naïve & Experienced
  - ING 111521: 10-Day, dose-ranging, dolutegravir monotherapy trial
  - IMPAACT P1093: Dolutegravir in infants, children, and adolescents

Dolutegravir
Summary of Key Studies

- Phase 2b Trials in Treatment Experienced
  - VIKING 1 & 2: Dolutegravir 50 mg QD added to failing regimen
  - VIKING 2: Dolutegravir 50 mg BID added to failing regimen
- Phase 3 Trials in Treatment Experienced
  - DAWNING: Dolutegravir 50 mg QD vs. LPV-RTV in salvage regimen
  - SAILING: Dolutegravir 50 mg QD vs. Raltegravir in salvage regimen
  - VIKING 3: Dolutegravir 50 mg BID in patients with INSTI resistance
  - VIKING-4: Dolutegravir 50 mg BID in patients with INSTI resistance (with placebo-controlled 7-day monotherapy phase)
- Phase IV Switch Studies
  - DUALIS: Dolutegravir + boosted PI as maintenance
  - NEAT 022: CV Risk Switching from boosted PI to Dolutegravir
  - DOMONO: Dolutegravir 50 mg QD Monotherapy vs. 3-drug treatment

INITIAL THERAPY

Dolutegravir

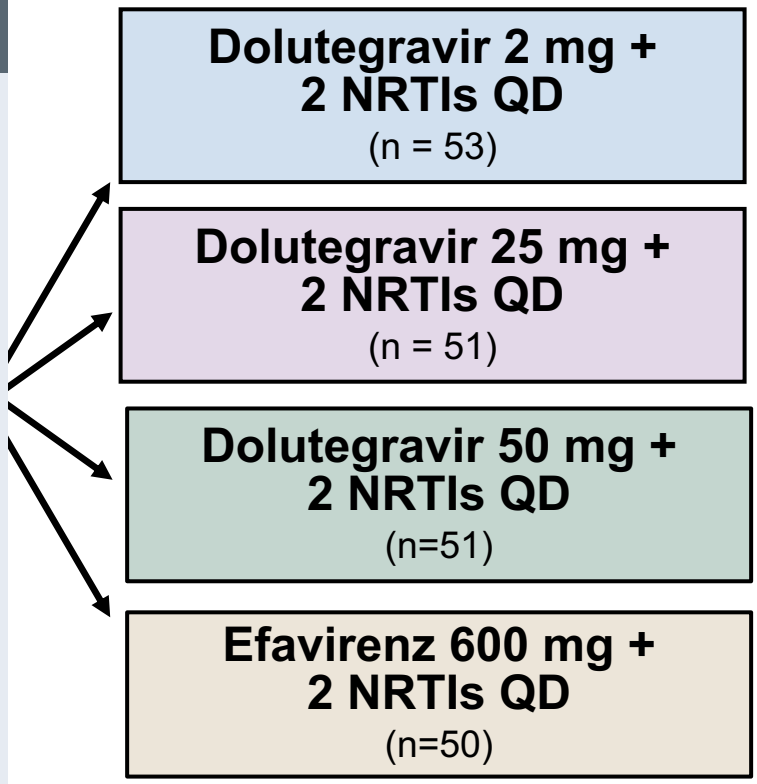
Dolutegravir vs. Efavirenz in Antiretroviral Naive

SPRING-1 Study

Dolutegravir versus Efavirenz in ARV-Naïve
SPRING-1: Study Design

Study Design: SPRING-1

- **Background**: Dose-ranging, partially-blinded phase 2b trial in antiretroviral-naïve persons with HIV to select a dolutegravir dose for phase 3 trials.
- **Inclusion Criteria (n = 205)**
  - Age ≥18
  - Antiretroviral-naïve
  - CD4 >200 cells/mm^3
  - HIV RNA >1,000 copies/mL
  - No NNRTI mutations
- **Treatment Arms**
  - Dolutegravir: 2, 10, or 50 mg daily + 2 NRTIs*
  - Efavirenz: 600 mg daily + 2 NRTIs*

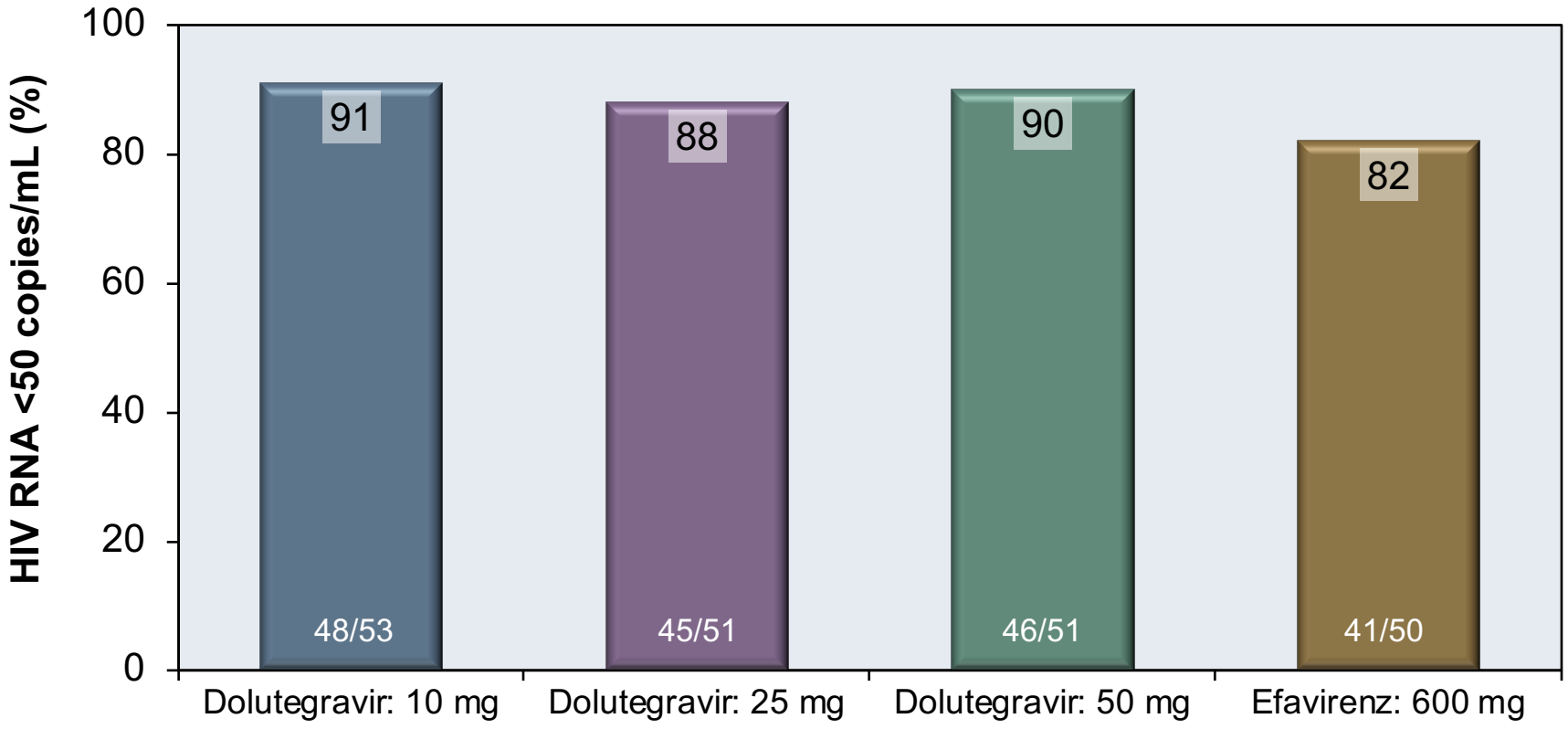


*2 NRTIs = Tenofovir DF-Emtricitabine or Abacavir-Lamivudine

Source: van Lunzen J, et al. Lancet Infect Dis. 2012;12:111-8.

Dolutegravir versus Efavirenz in ARV-Naïve
SPRING-1: Results

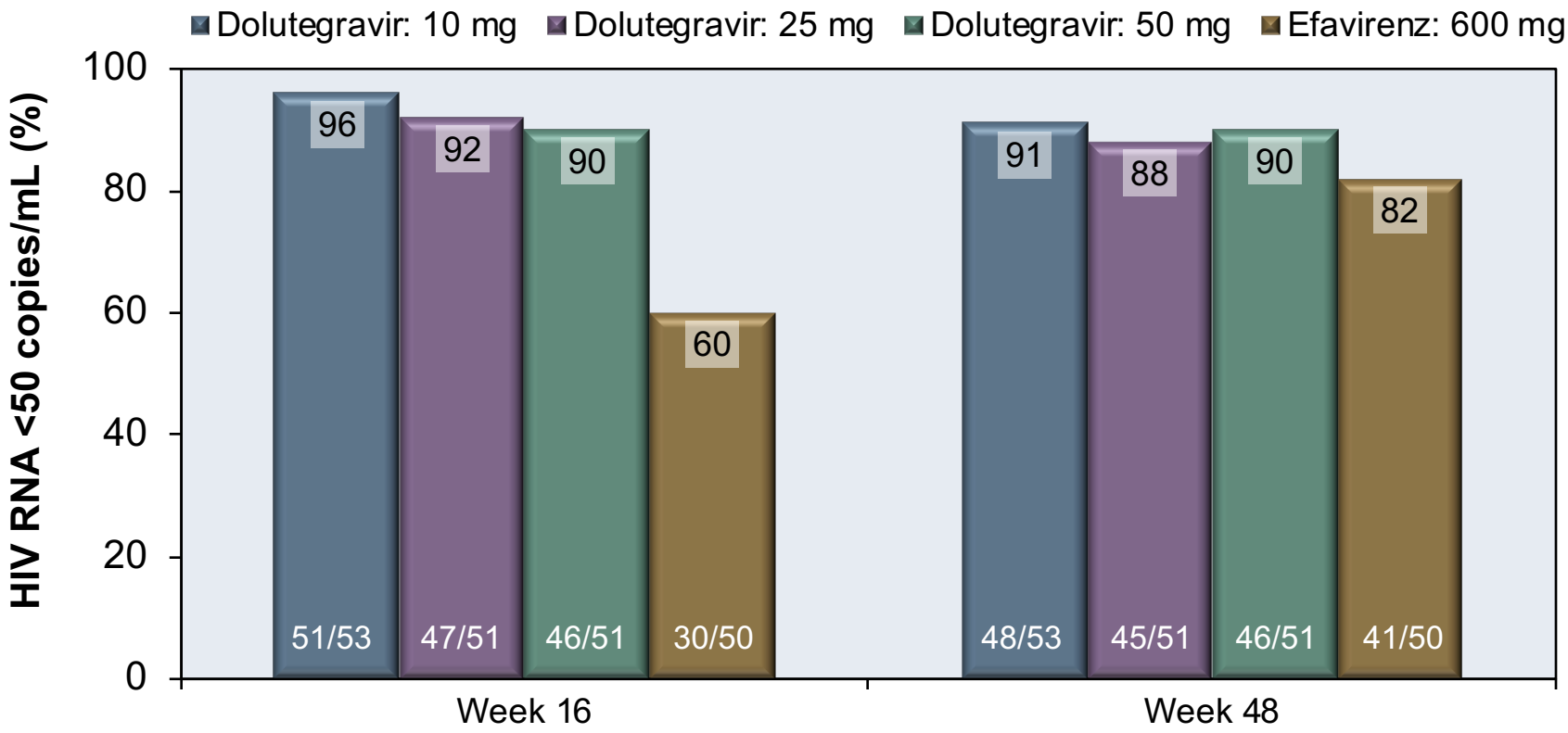
Week 48 Virologic Response (TLOVR)



Source: van Lunzen J, et al. Lancet Infect Dis. 2012;12:111-8.

Dolutegravir versus Efavirenz in ARV-Naïve
SPRING-1: Results

Week 16, 24, and 48 Virologic Response (TLOVR)



Source: van Lunzen J, et al. Lancet Infect Dis. 2012;12:111-8.

Dolutegravir versus Efavirenz in ARV-Naive
SPRING-1: Adverse Events

Adverse Effect	DTG 10 mg	DTG 25 mg	DTG 50 mg	DTG Subtotal	EFV 600 mg
Serious Adverse Events	3 (6%)	1 (2%)	4 (8%)	8 (5%)	4 (8%)
Nausea	7 (13%)	6 (12%)	6 (12%)	19 (12%)	3 (6%)
Diarrhea	4 (8%)	3 (6%)	5 (10%)	12 (8%)	3 (6%)
Dizziness	2 (4%)	0	3 (6%)	5 (3%)	9 (18%)
Headache	2 (4%)	4 (8%)	4 (8%)	10 (6%)	1 (2%)
Fatigue	1 (2%)	3 (6%)	1 (2%)	5 (3%)	4 (8%)
Insomnia	0	0	3 (6%)	3 (2%)	4 (8%)
Abnormal Dreams	1 (2%)	0	0	1 (<1%)	3 (6%)
Rash	2 (4%)	0	0	2 (1%)	4 (8%)

Source: van Lunzen J, et al. Lancet Infect Dis. 2012;12:111-8.

Dolutegravir versus Efavirenz in ARV-Naive
SPRING-1: Conclusions

Interpretation: “Dolutegravir was effective when given once daily without a pharmacokinetic booster and was well tolerated at all assessed doses. Our findings support the assessment of once daily 50 mg dolutegravir in phase 3 trials.”

Source: van Lunzen J, et al. Lancet Infect Dis. 2012;12:111-8.

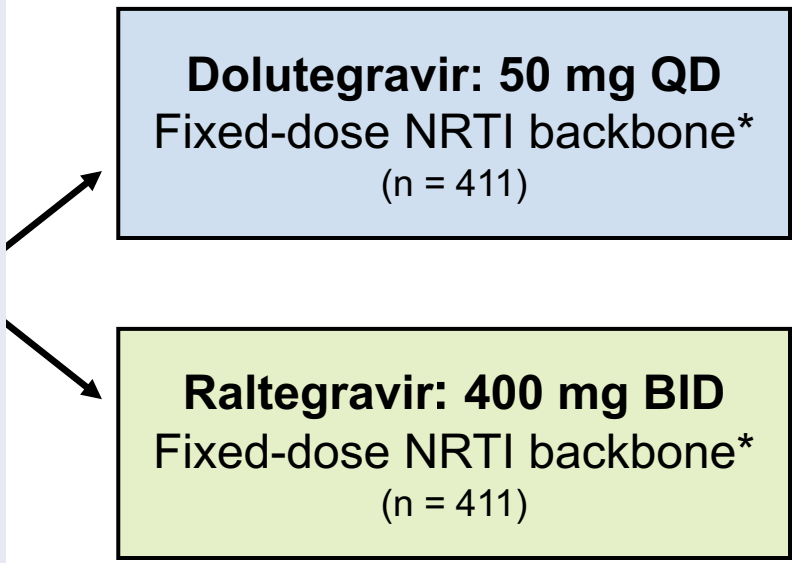
Dolutegravir vs. Raltegravir

SPRING-2 Study

Dolutegravir versus Raltegravir
SPRING-2: Design

Study Design: SPRING-2

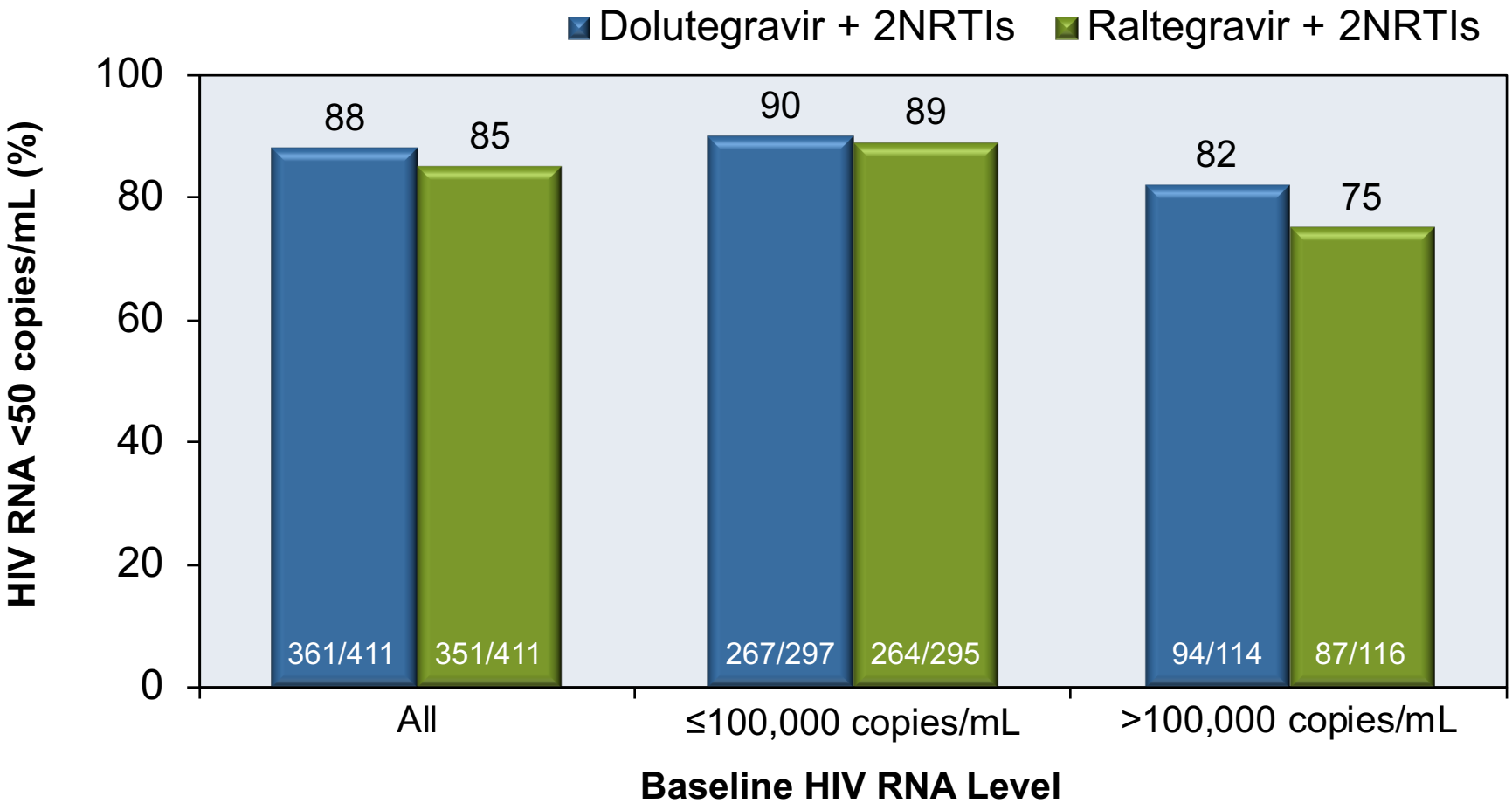
- **Background**: Randomized, double-blind study, phase 3 trial comparing dolutegravir versus raltegravir, both with 2NRTI backbone in persons with HIV.
- **Inclusion Criteria (n = 822)**
  - Antiretroviral-naïve
  - Age ≥18
  - HIV RNA ≥1,000 copies/mL
  - No active CDC AIDS condition
- **Treatment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



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

Dolutegravir versus Raltegravir
SPRING-2: Results

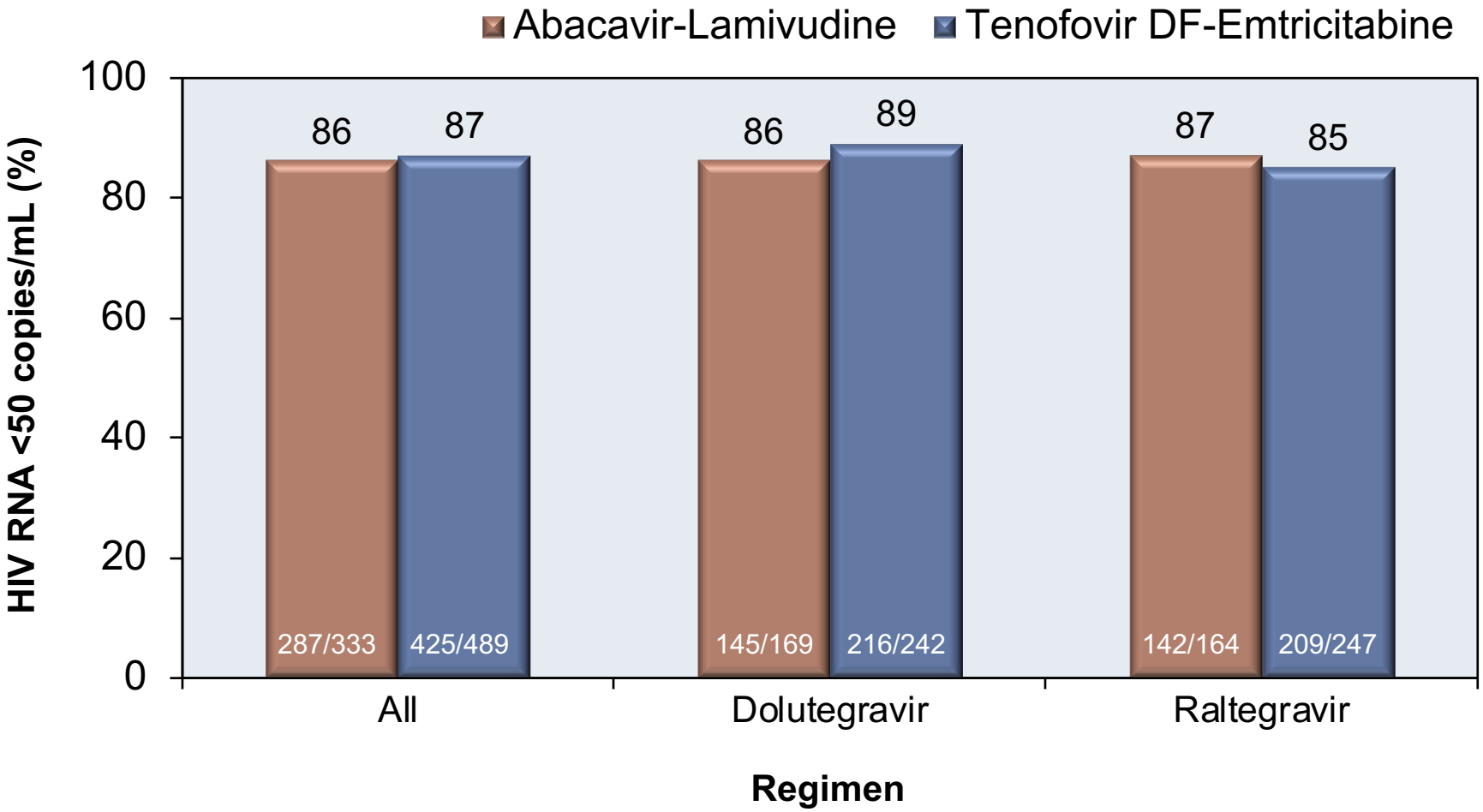
Week 48: Virologic Response, by Baseline HIV RNA



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.”

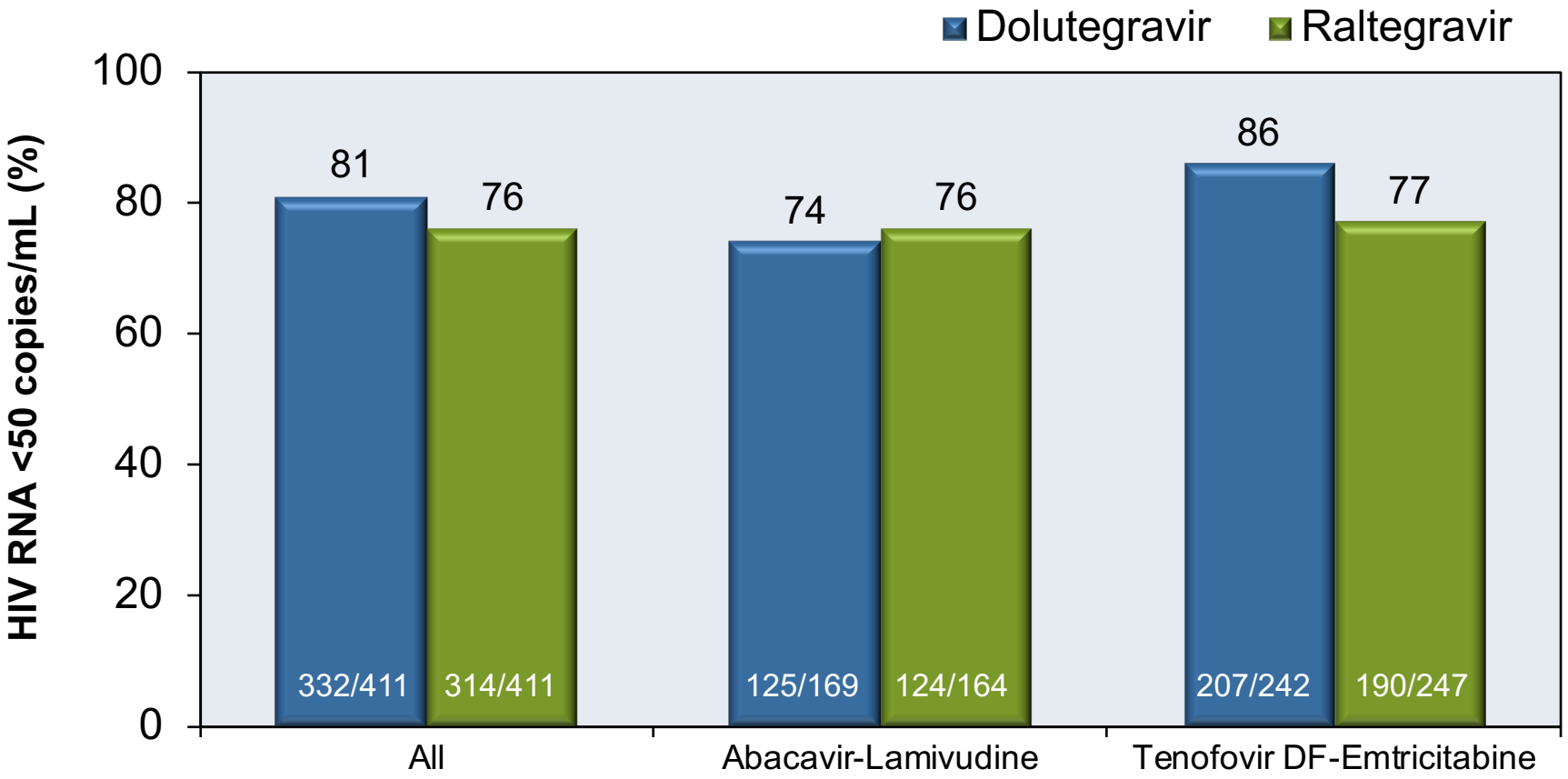
Source: Raffi F, et al. Lancet. 2013;381:735-43.

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.”

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

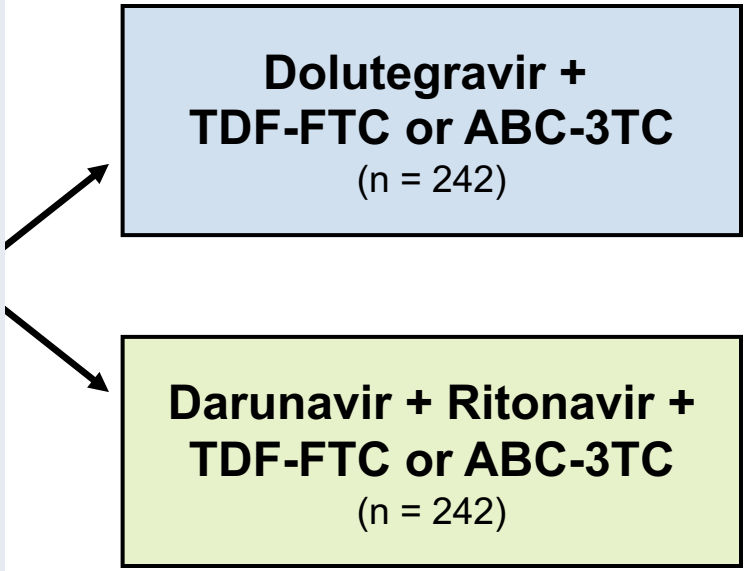
Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs

FLAMINGO

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Study Design

Study Design: FLAMINGO

- **Background**: Randomized, open label phase 3b study comparing dolutegravir to darunavir-ritonavir with fixed-dose NRTI backbone in antiretroviral-naïve persons with HIV.
- **Inclusion Criteria (n = 484 analyzed)**
  - Antiretroviral-naïve
  - Age ≥18
  - HIV RNA ≥1,000 copies/mL
  - No active class C conditions
  - No resistance to NRTIs or protease inhibitors
- **Treatment Arms (once daily)**
  - Dolutegravir 50 mg + 2 NRTIs*
  - Darunavir 800 mg + Ritonavir 100 mg + 2 NRTIs*

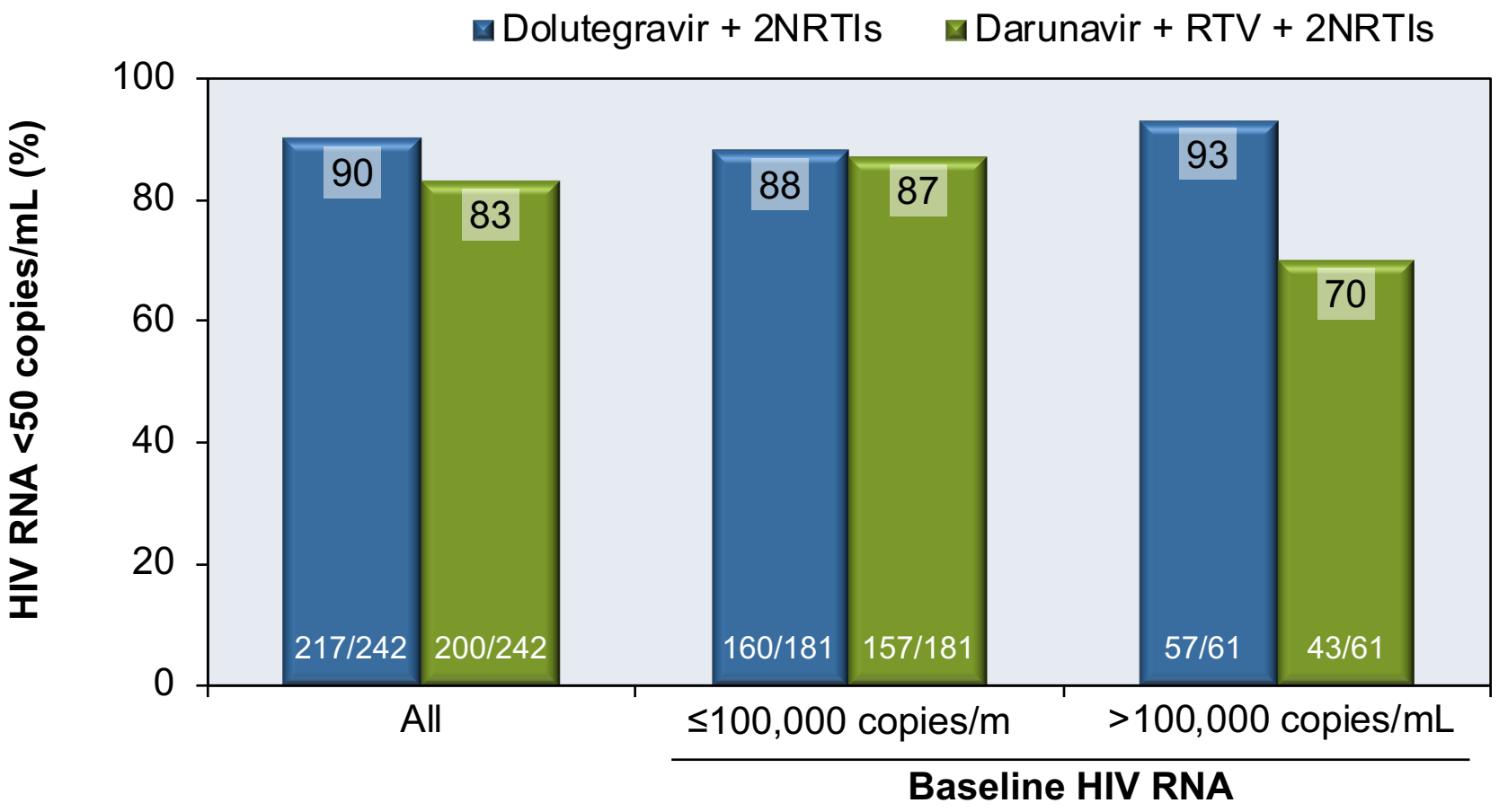


*2 NRTIs = tenofovir-emtricitabine or abacavir-lamivudine (with negative HLA-B*5701 testing).

Source: Clotet B, et al. Lancet. 2014;383:2222-31.

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Results

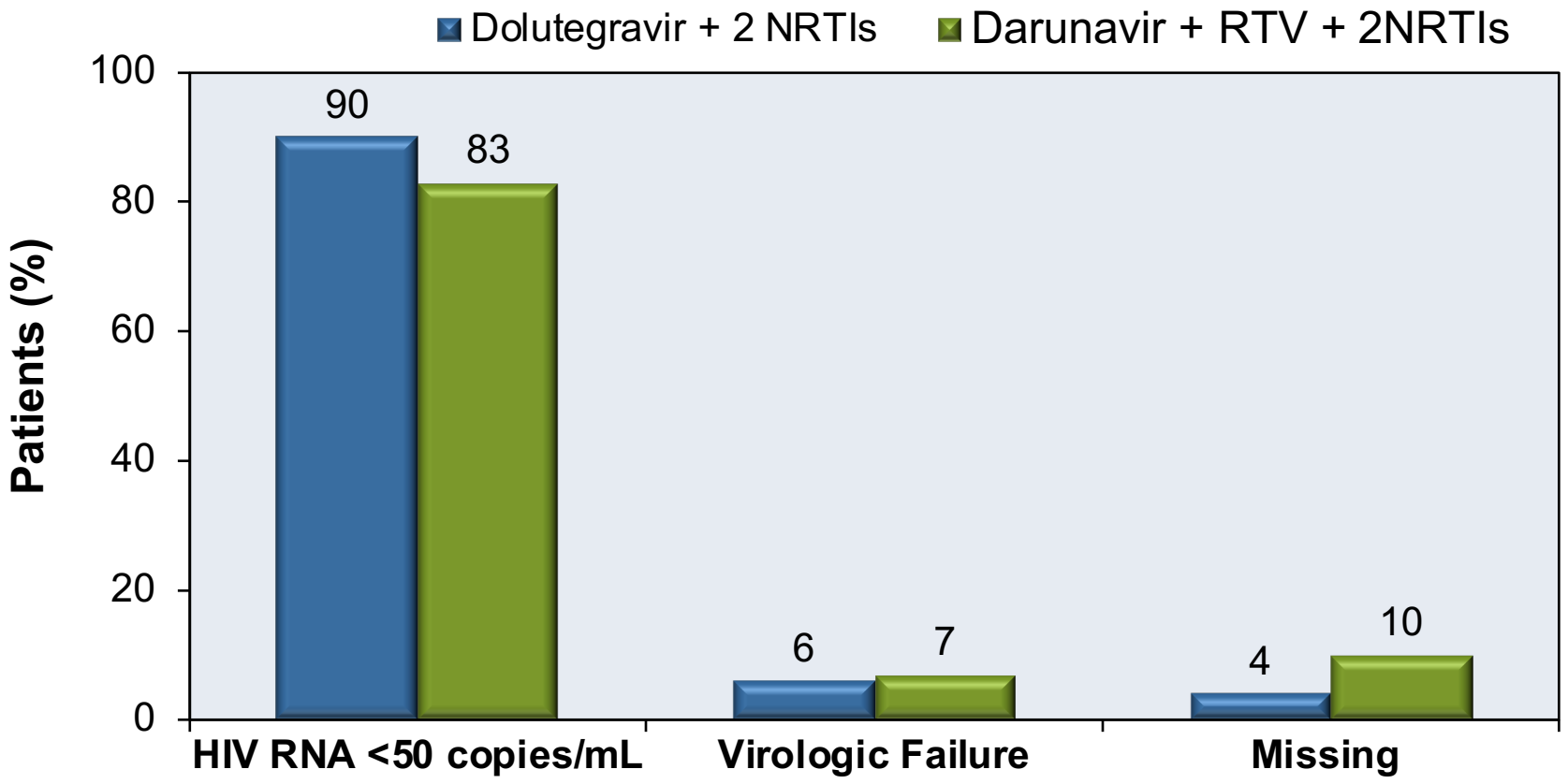
Week 48 Virologic Response, by Baseline HIV RNA Level



Source: Clotet B, et al. Lancet. 2014;383:2222-31.

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Results

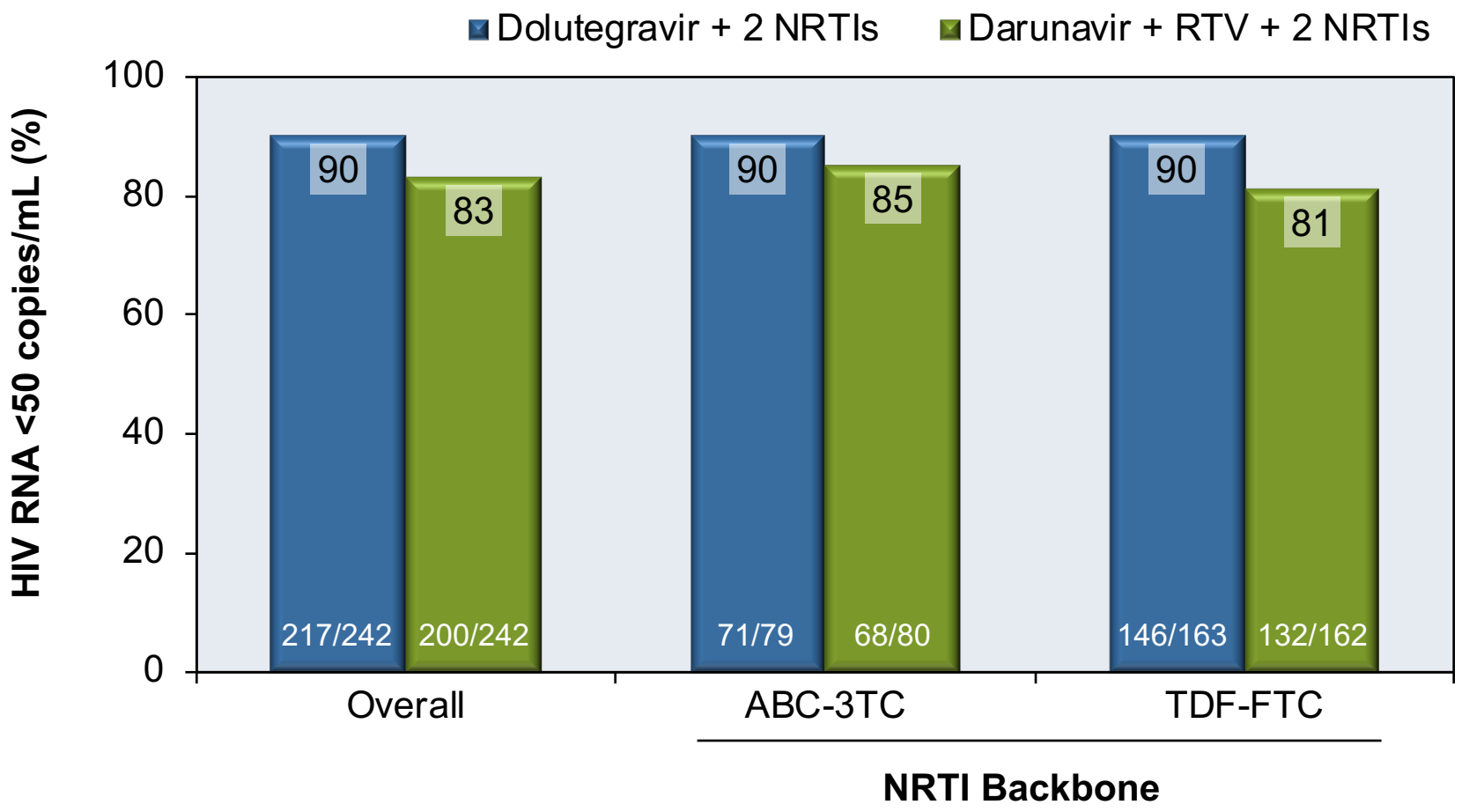
48 Week Virologic Outcomes (Modified Intent-to-Treat Analysis)



Source: Clotet B, et al. Lancet. 2014;383:2222-31.

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Results

Week 48 Virologic Response, by Background Dual NRTI Therapy



Source: Clotet B, et al. Lancet. 2014;383:2222-31.

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Common Adverse Events

Treatment Emergent Adverse Events in ≥ 5% of Subjects in Either Arm		
	DTG + 2 NRTIs (n = 242)	**DRV + RTV + 2 NRTIs** (n= 242)
Dizziness	17%	29%
Nausea	16%	18%
Headache	15%	10%
Nasopharyngitis	9%	8%
Upper respiratory infection	5%	10%
Insomnia	7%	6%
Cough	5%	7%
Vomiting	6%	6%
Fatigue	6%	5%

Source: Clotet B, et al. Lancet. 2014;383:2222-31.

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Common Adverse Events (continued)

Treatment Emergent Adverse Events in ≥ 5% of Subjects in Either Arm		
	DTG + 2 NRTIs (n = 242)	**DRV + RTV + 2 NRTIs** (n = 242)
Pyrexia	5%	6%
Dizziness	6%	5%
Rash	4%	6%
Back Pain	4%	5%
Pharyngitis	3%	5%
Bronchitis	2%	5%
Sinusitis	2%	5%
Depression	5%	2%
Arthralgia	2%	5%

Source: Clotet B, et al. Lancet. 2014;383:2222-31.

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Conclusions

Interpretation: “Once-daily dolutegravir was superior to once-daily darunavir plus ritonavir. Once-daily dolutegravir in combination with fixed-dose NRTIs represents an effective new treatment option for HIV-1-infected, treatment-naive patients.”

Source: Clotet B, et al. Lancet. 2014;383:2222-31.

Dolutegravir + ABC-3TC and CSF HIV-1 RNA Levels

ING116070 Study

Dolutegravir + ABC-3TC and Impact on CSF HIV RNA Levels
ING116070 Study: Design

Study Design: ING116070

- **Background**: Single arm, phase 3b, open-label, multi-center trial to evaluate the distribution and antiviral activity of dolutegravir + abacavir-lamivudine in CSF in persons with HIV.
- **Inclusion Criteria (n = 13)**
  - Antiretroviral-naïve
  - Age ≥18 years
  - HIV RNA ≥5,000 copies/mL
  - CD4 count ≥200 cells/mm^3
  - No active CDC AIDS condition (except KS)
- **Treatment Arm (n = 12)**
  - Dolutegravir (QD) + Abacavir-lamivudine

→ **Dolutegravir + ABC-3TC**
(n = 12)

Source: Letendre SL, et al. Clin Infect Dis. 2014;59;1032-7.

Dolutegravir + ABC-3TC and Impact on CSF HIV RNA Levels
ING116070 Study: Design

CSF Findings in Patients on Dolutegravir + Abacavir-Lamivudine		
Cerebrospinal Fluid (CSF) Parameter	**Week 2**	**Week 16**
Mean CSF DTG Concentration total, ng/mL	16.2	12.6
CSF/Total Plasma Ratio for DTG Concentration	0.47	0.55
CSF HIV-1 RNA <50 copies/mL	11/12 (92%)	11/11 (100%)
CSF HIV-1 RNA <2 copies/mL	ND	11/12 (92%)

Source: Letendre SL, et al. Clin Infect Dis. 2014;59;1032-7.

Dolutegravir + ABC-3TC and Impact on CSF HIV RNA Levels
ING116070 Study: Conclusions

Conclusions: "The dolutegravir concentrations in CSF were similar to unbound plasma concentrations and exceeded the in vitro 50% inhibitory concentration for wild-type HIV (0.2 ng/mL), suggesting that dolutegravir achieves therapeutic concentrations in the central nervous system. The HIV-1 RNA reductions were similar in CSF and plasma."

Source: Letendre SL, et al. Clin Infect Dis. 2014;59;1032-7.

TREATMENT-NAÏVE AND TREATMENT EXPERIENCED

Dolutegravir

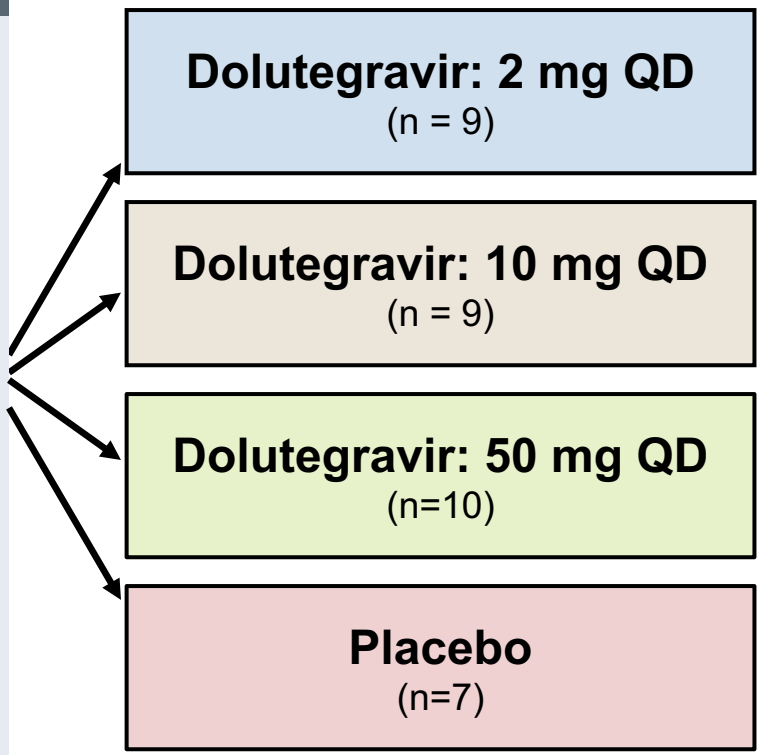
Dolutegravir 10-Day, Dose-Ranging, Monotherapy Study

ING111521

Dolutegravir Dose-Ranging Monotherapy
ING111521 Study: Design

Study Design: ING111521

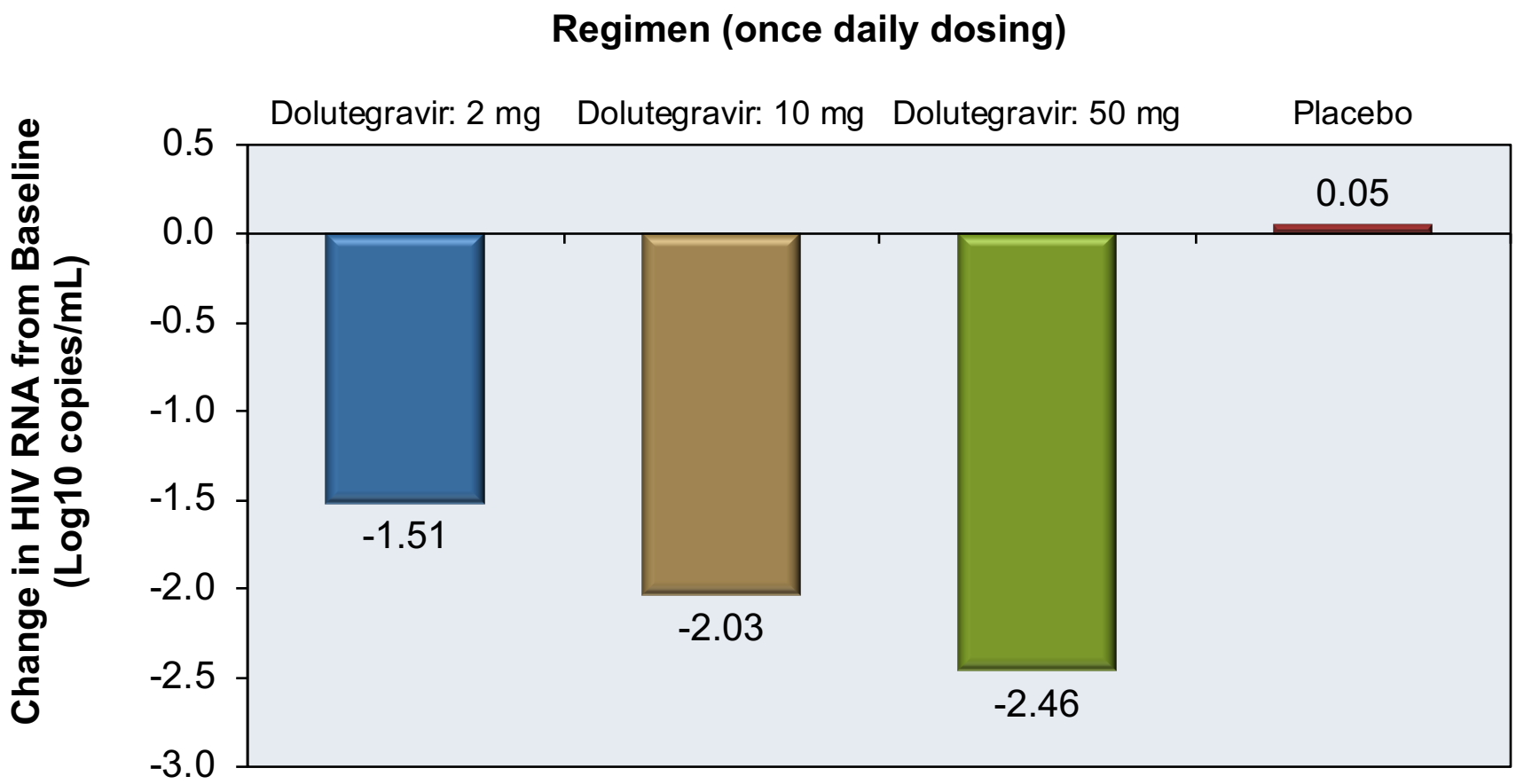
- **Background**: Randomized, double-blind, dose-ranging,10-day, phase 2a study to evaluate antiviral activity, safety, and pharmacokinetics and pharmacodynamics of dolutegravir in pesons with HIV.
- **Inclusion Criteria (n = 35)**
  - Antiretroviral-naïve and antiretroviral-experienced
  - Integrase strand transfer inhibitor-naïve
  - Age ≥18 and ≤65 years
  - CD4 ≥100 cells/mm^3
  - HIV RNA ≥5,000 copies/mL
  - No AIDS conditions
- **Treatment Arms**
  - Dolutegravir 2, 10, or 50 mg daily, or placebo



Source: Min S, et al. AIDS. 2011;25:1737-45.

Dolutegravir Dose-Ranging Monotherapy
ING111521 Study: Results

Baseline to Day 11: Change in Baseline HIV RNA Level

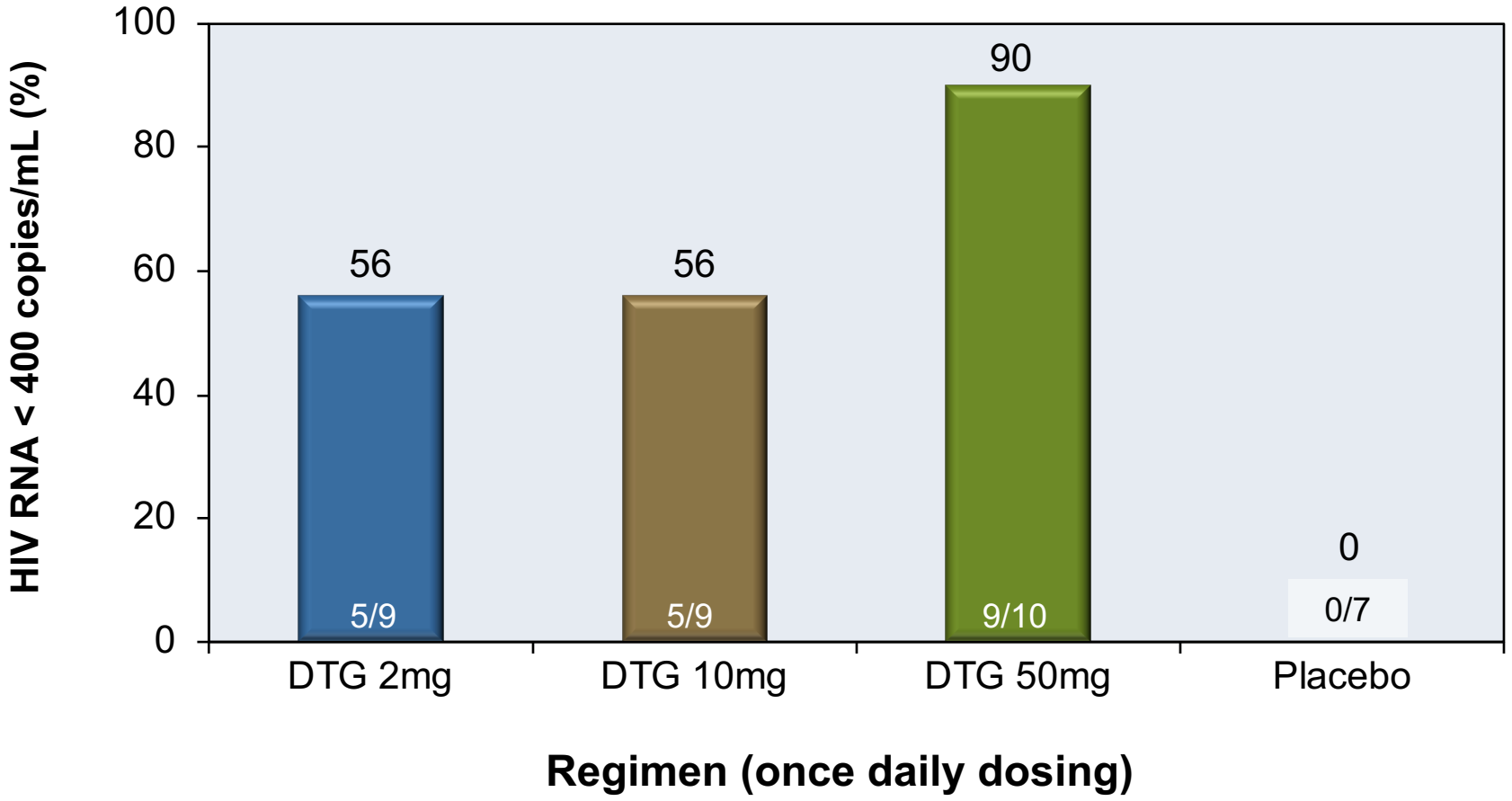


Source: Min S, et al. AIDS. 2011;25:1737-45.

National HIV Curriculum

Dolutegravir Dose-Ranging Monotherapy
ING111521 Study: Results

Baseline to Day 11: Patients with Suppressed Viral Load at Nadir



Source: Min S, et al. AIDS. 2011;25:1737-45.

Dolutegravir Dose-Ranging Monotherapy
ING111521 Study: Conclusion

Conclusion: “Dolutegravir demonstrated potent antiviral activity, good short-term tolerability, low pharmacokinetic variability, and a predictable pharmacokinetics/pharmacodynamics relationship, which support once daily dosing without a pharmacokinetic booster in integrase-naive patients in future studies.”

Source: Min S, et al. AIDS. 2011;25:1737-45.

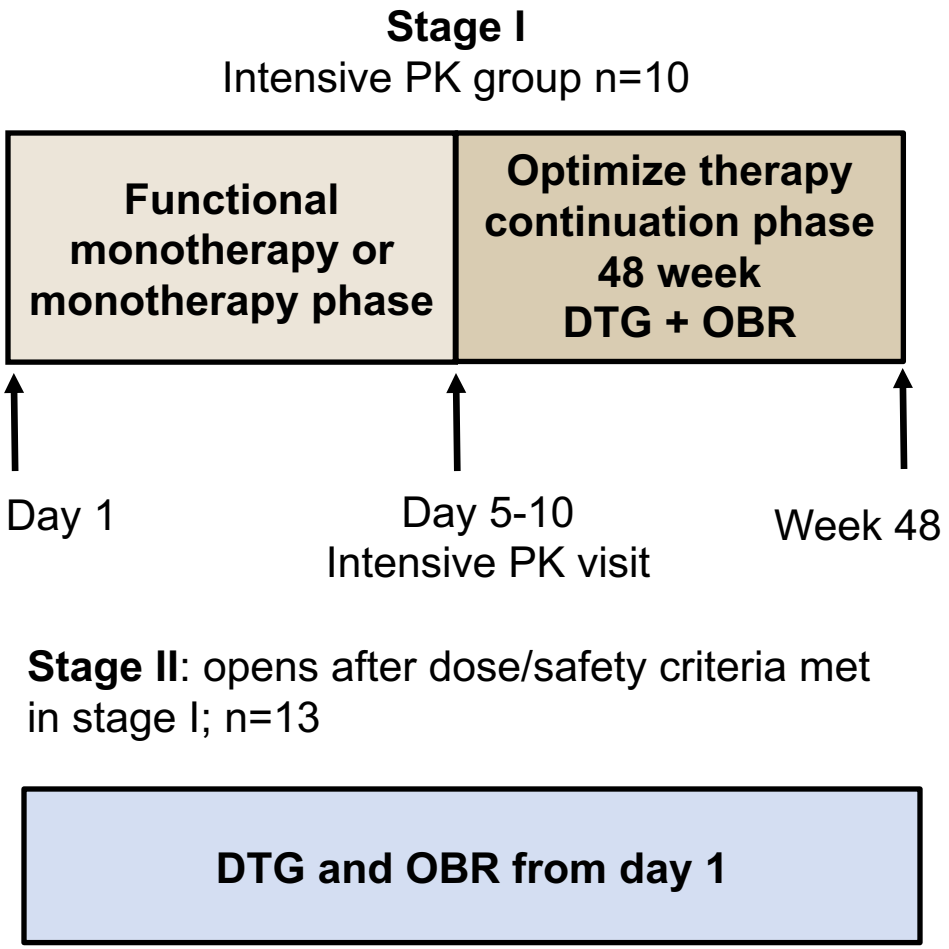
Dolutegravir in Treatment-Experienced Adolescents

IMPAACT P1093

Dolutegravir in Treatment-Experienced Adolescents
IMPAACT P1093: Study Design

Study Design: IMPAACT P1093

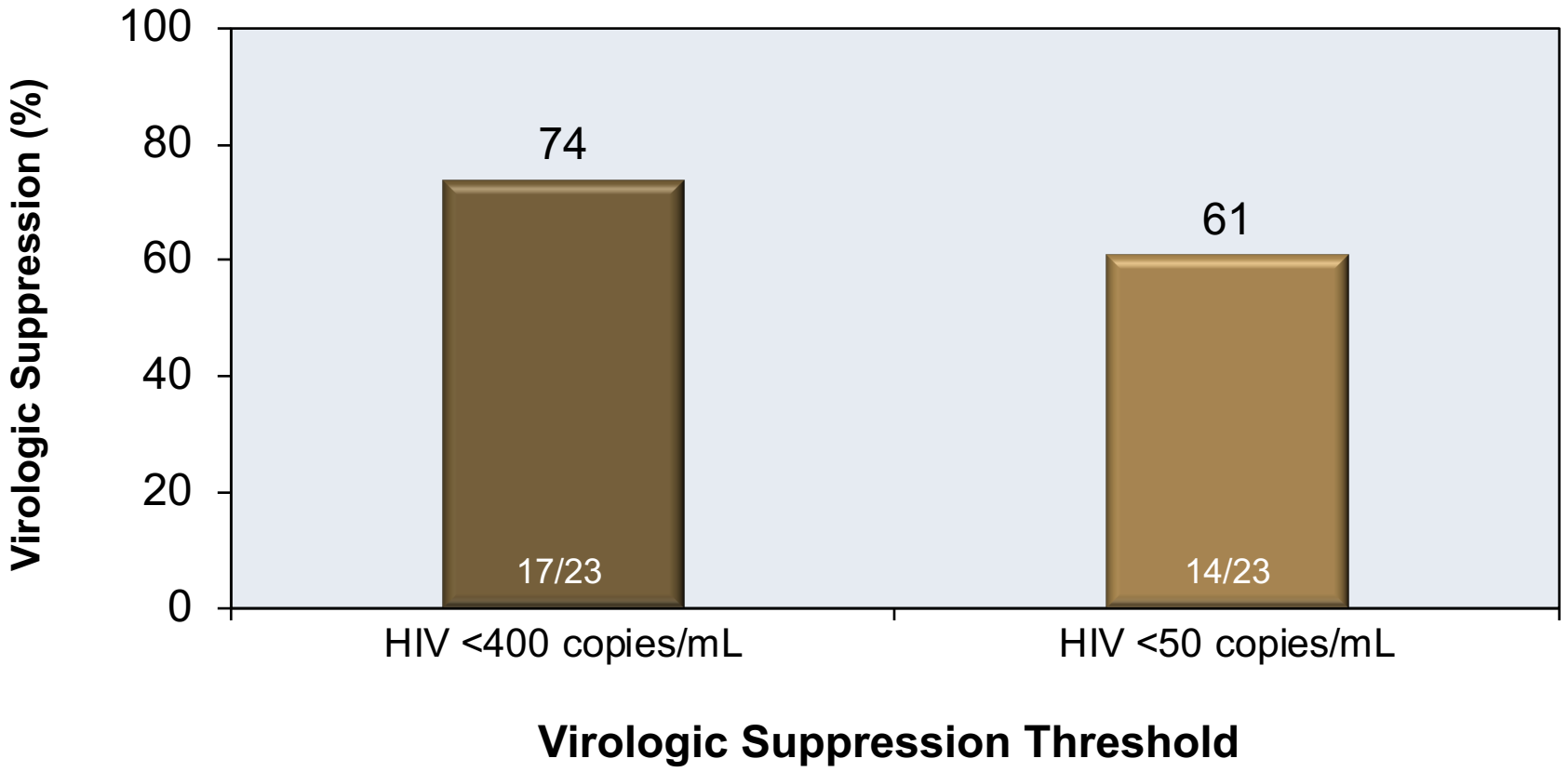
- **Background**: Open-label, non-randomized phase I/II study treatment-experienced adolescents with HIV
- **Inclusion Criteria (n = 23)**
  - Age 12 to <18 years of age
  - Antiretroviral-experienced
  - Naïve to integrase inhibitors
  - HIV RNA >1,000 copies/mL
  - Genotype showing sensitivity to at least one other active antiretroviral agent
- **Treatment Arms**
  - Dolutegravir monotherapy, then dolutegravir with optimized background regimen



Source: Viani RM, et al. Pediatr Infect Dis J. 2015;34:1207-13.

Dolutegravir in Treatment-Experienced Adolescents
IMPAACT P1093: Results

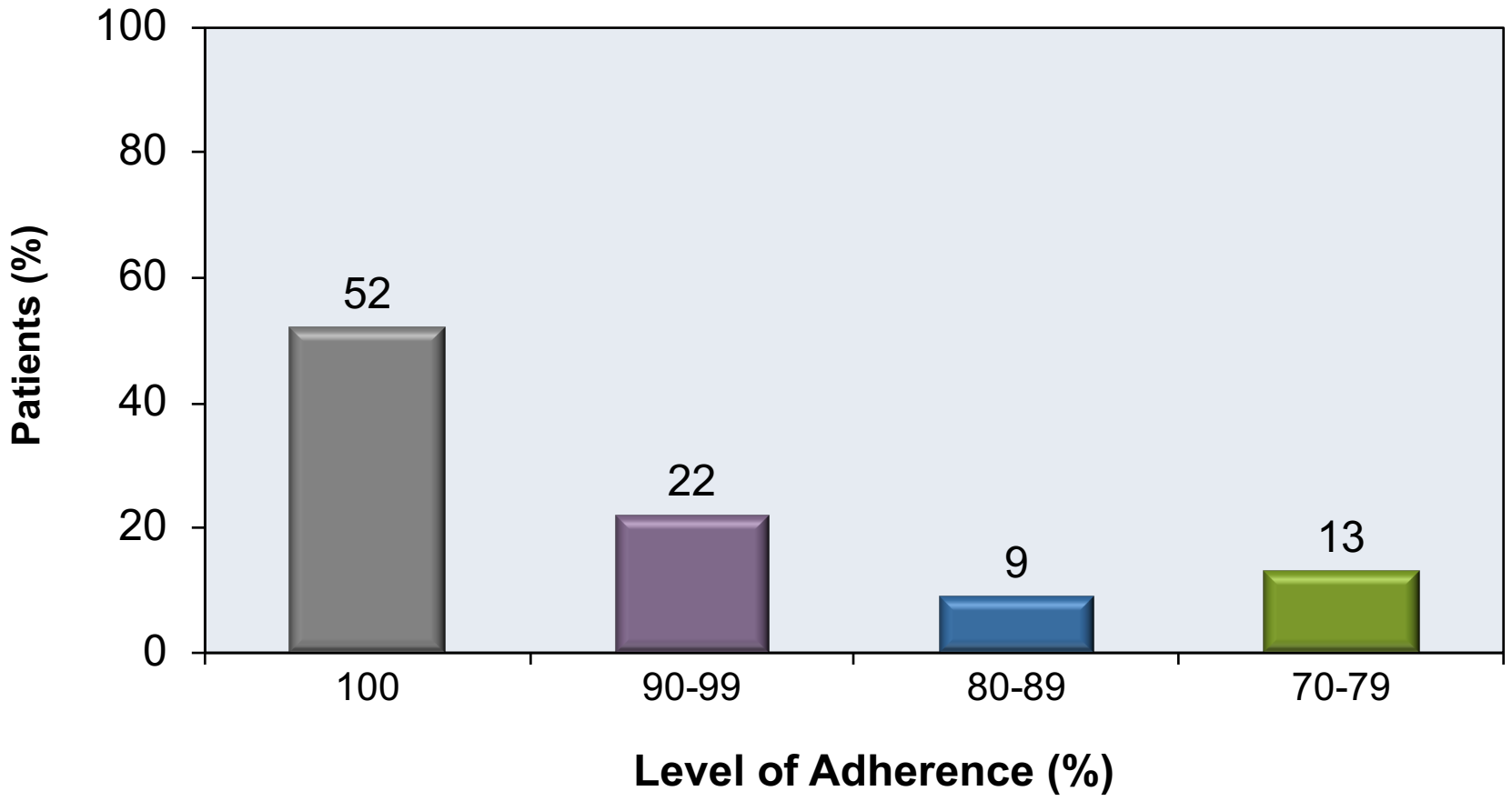
Week 48: Virologic Response



Source: Viani RM, et al. Pediatr Infect Dis J. 2015;34:1207-13.

Dolutegravir in Treatment-Experienced Adolescents
IMPAACT P1093: Results

Week 48: Patient-Reported Adherence



Source: Viani RM, et al. Pediatr Infect Dis J. 2015;34:1207-13.

Dolutegravir in Treatment-Experienced Adolescents
IMPAACT P1093: Conclusions

Conclusions: “Dolutegravir achieved target PK exposures in adolescents. Dolutegravir was safe and well tolerated, providing good virologic efficacy through week 48.”

Source: Viani RM, et al. Pediatr Infect Dis J. 2015;34:1207-13.

TREATMENT EXPERIENCED

Dolutegravir

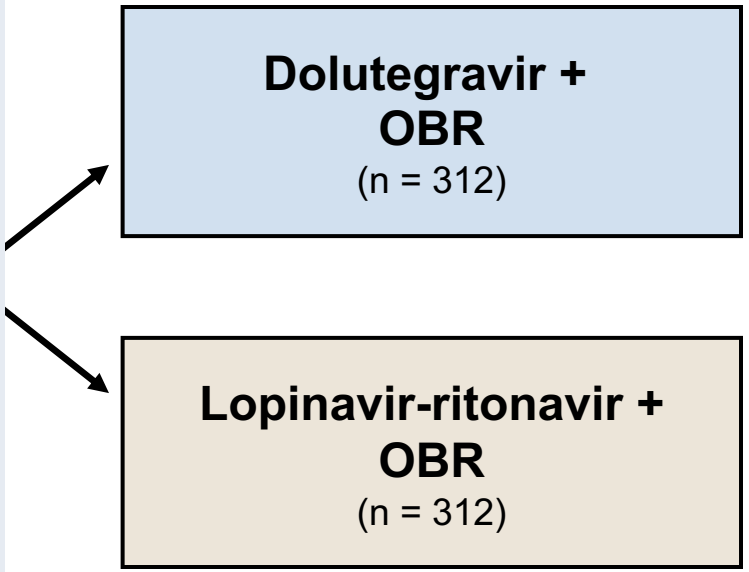
Dolutegravir versus Lopinavir-Ritonavir in Second-Line Treatment

DAWNING

Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Study Design

Study Design: DAWNING

- **Background**: Randomized, open-label, multinational, non-inferiority phase 3b trial comparing dolutegravir to boosted lopinavir, each with optimized background regimen (OBR) after failure of NNRTI-based first-line ART
- **Inclusion Criteria**
  - Antiretroviral-experienced adults
  - Virologic failure on NNRTI plus 2 NRTI's
  - HIV RNA ≥400 copies/mL at 2 consecutive visits
  - INSTI and PI-naïve
  - ≥1 active NRTI available based on genotype
  - HBV and HCV allowed
- **Treatment Arms**
  - Dolutegravir 50 mg daily + investigator-selected OBR (including at least 1 active NRTI)
  - Lopinavir + ritonavir* + investigator-selected OBR (including at least 1 active NRTI)



*Once-daily lopinavir 800 mg + ritonavir 200 mg or twice daily lopinavir 400 mg + 100 mg, based on investigator discretion

Source: Aboud M, et al. Lancet Infect Dis. 2019;19:253-64.

Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Baseline Characteristics

Baseline Characteristics in DAWNING Study		
	DTG + OBR (n = 312)	**LPV-RTV + OBR** (n = 312)
Age, mean	37.5	38.7
Women, n, %	116 (37%)	103 (33%)
Hispanic or Latino	105 (34%)	109 (35%)
African American or African	130 (42%)	112 (36%)
Viral hepatitis (HBV, HCV, or both)	35 (11%)	38 (12%)
WHO category C (AIDS)	107 (34%)	95 (30%)
Mean HIV RNA, $\log_{10}$ copies/mL	4.2	4.2
HIV RNA >100,000 copies/mL	70 (22%)	63 (20%)
CD4 count <200 cells/mm^3	166 (53%)	151 (48%)

Source: Aboud M, et al. Lancet Infect Dis. 2019;19:253-64.

Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Previous ART History

Previous Antiretroviral History in DAWNING Study		
	DTG + OBR (n = 312)	**LPV-RTV + OBR** (n = 312)
Duration prior ART, median, weeks	86.4	90.9
Previous NNRTI therapy		
Efavirenz	242 (78%)	242 (78%)
Nevirapine	70 (22%)	69 (22%)
Previous NRTI therapy		
Tenofovir DF	181 (58%)	186 (60%)
Zidovudine	89 (29%)	89 (29%)
Stavudine	15 (5%)	9 (3%)
Lamivudine or emtricitabine	311 (99%)	310 (99%)

Source: Aboud M, et al. Lancet Infect Dis. 2019;19:253-64.

Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Optimized Background Regimens

Optimized background regimens (OBRs) in DAWNING Study Second-Line ART		
	DTG + OBR (n = 312)	**LPV-RTV + OBR** (n = 312)
NRTIs in second-line regimen		
Zidovudine plus lamivudine	132 (42%)	121 (39%)
Tenofovir DF plus lamivudine or emtricitabine	128 (41%)	134 (43%)
Tenofovir DF plus zidovudine	36 (12%)	41 (13%)
Abacavir plus lamivudine	7 (2%)	7 (2%)
Stanford genotype susceptibility score in background ART		
0 to <1	30 (10%)	36 (12%)
1 to <2	223 (71%)	212 (68%)
2	61 (20%)	64 (21%)
>2	0	0

Source: Aboud M, et al. Lancet Infect Dis. 2019;19:253-64.

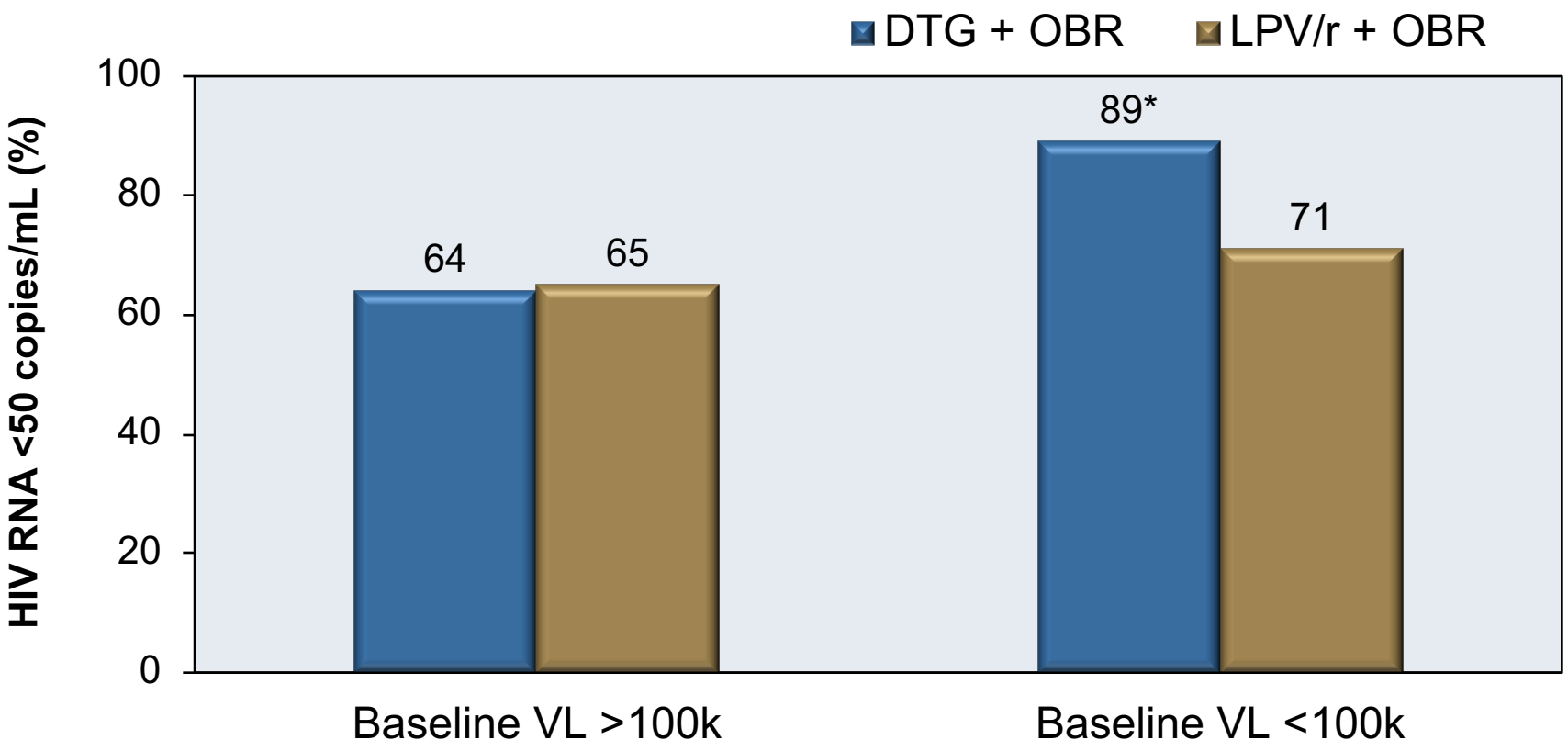
Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Baseline NRTI Resistance

Baseline NRTI Resistance-Associated Mutations in DAWNING Study		
	DTG + OBR (n = 312)	**LPV-RTV + OBR** (n = 312)
K65R	95 (30%)	92 (29%)
K70E	33 (11%)	37 (12%)
M184I/V only	77 (25%)	85 (27%)
M184I/V plus any other NRTI mutation	184 (59%)	167 (54%)
TAM's	71 (23%)	81 (26%)
Other major NRTI mutation	90 (29%)	88 (28%)

Source: Aboud M, et al. Lancet Infect Dis. 2019;19:253-64.

Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Results

Virologic Suppression Rate at 48 Weeks by Baseline Viral Load

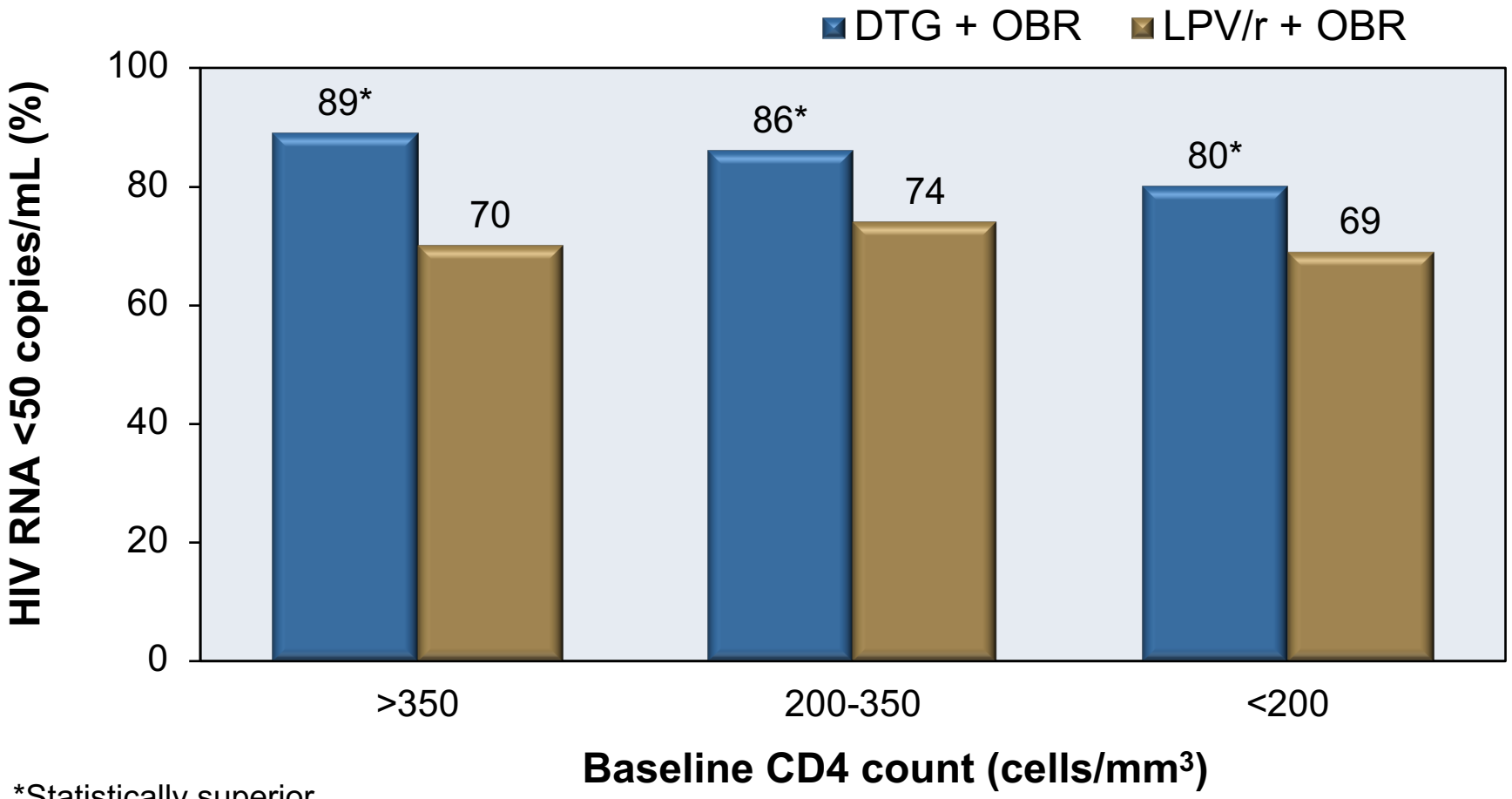


*Statistically superior

Aboud M, et al. Lancet Infectious Dis, 2019;19:253-64.

Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Results

Virologic Suppression Rate at 48 Weeks by Baseline CD4 Count

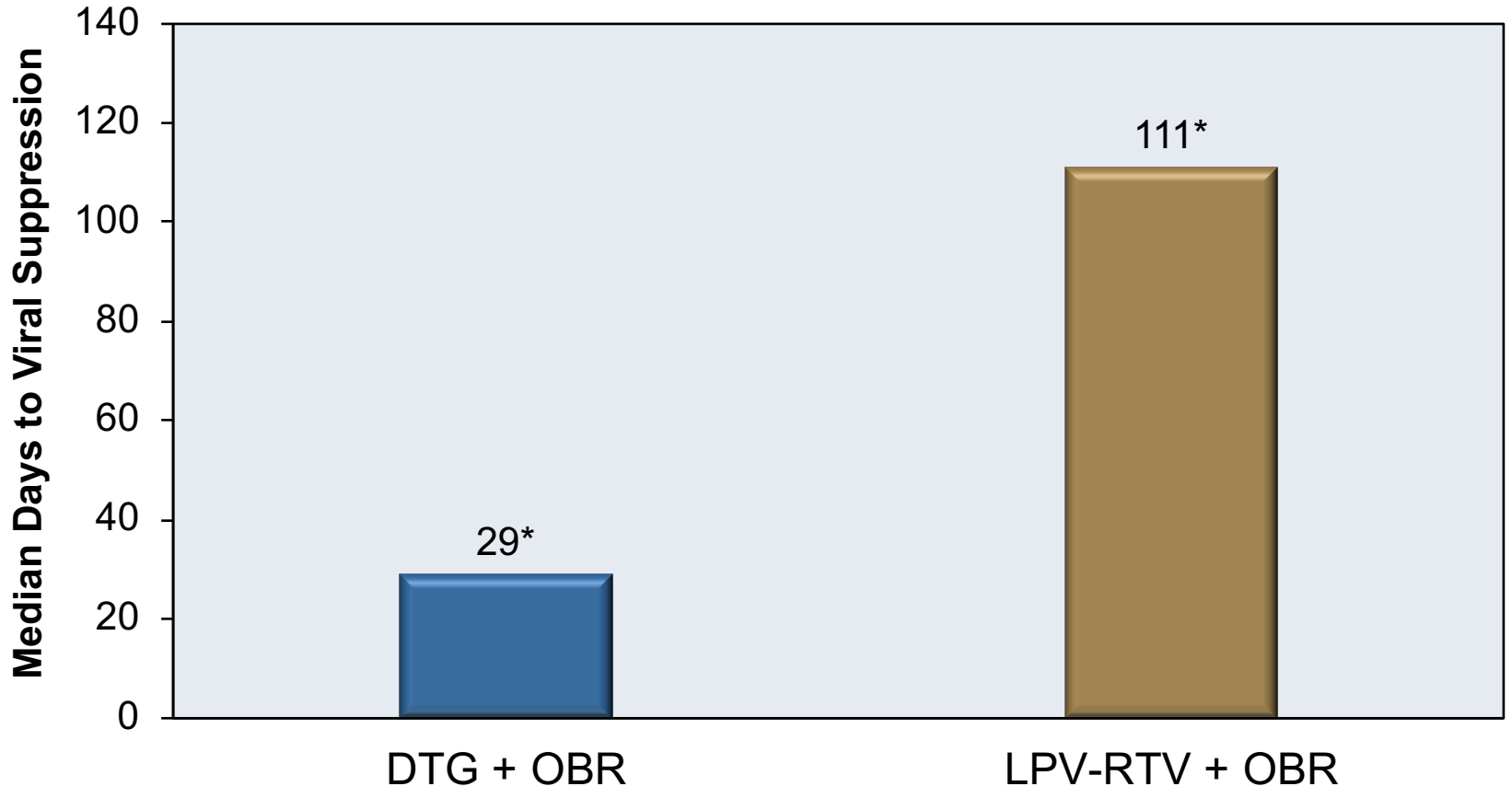


*Statistically superior

Aboud M, et al. Lancet Infectious Dis, 2019;19:253-64.

Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Results

Median Days to Viral Suppression



*Statistically superior

Aboud M, et al. Lancet Infectious Dis, 2019;19:253-64.

Dolutegravir vs Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Adverse Events

Treatment-Related Adverse Events (AEs) in DAWNING Study		
	DTG + OBR (n = 312)	**LPV-RTV + OBR** (n = 312)
Any AE	50 (16%)	119 (38%)
Grade 2-4 AE	11 (4%)	44 (14%)
AEs that occurred in ≥ 2% of participants in either group		
Diarrhea	1 (<1%)	23 (7%)
Nausea	0	6 (2%)

Source: Aboud M, et al. Lancet Infect Dis. 2019;19:253-64.

Dolutegravir versus Lopinavir-Ritonavir in Second-Line Treatment
DAWNING: Conclusions

Interpretation: “When administered with two NRTIs, dolutegravir was superior to ritonavir-boosted lopinavir at 48 weeks and can be considered a suitable option for second-line treatment.”

Source: Aboud M, et al. Lancet Infect Dis. 2019;19:253-64.

Dolutegravir in Patients with Raltegravir-Resistant HIV

VIKING (Cohorts I & II)

Dolutegravir in Patients with Raltegravir Resistance
VIKING Study (Cohorts I & II): Study Design

Day 1	Day 11	Week 24

Functional Monotherapy Phase	Continuation Phase
Cohort I: Dolutegravir: 50 mg QD	**Cohort I**: Dolutegravir: 50 mg QD + OBR
Cohort II: Dolutegravir: 50 mg BID	**Cohort II**: Dolutegravir: 50 mg BID + OBR

Study Design: VIKING

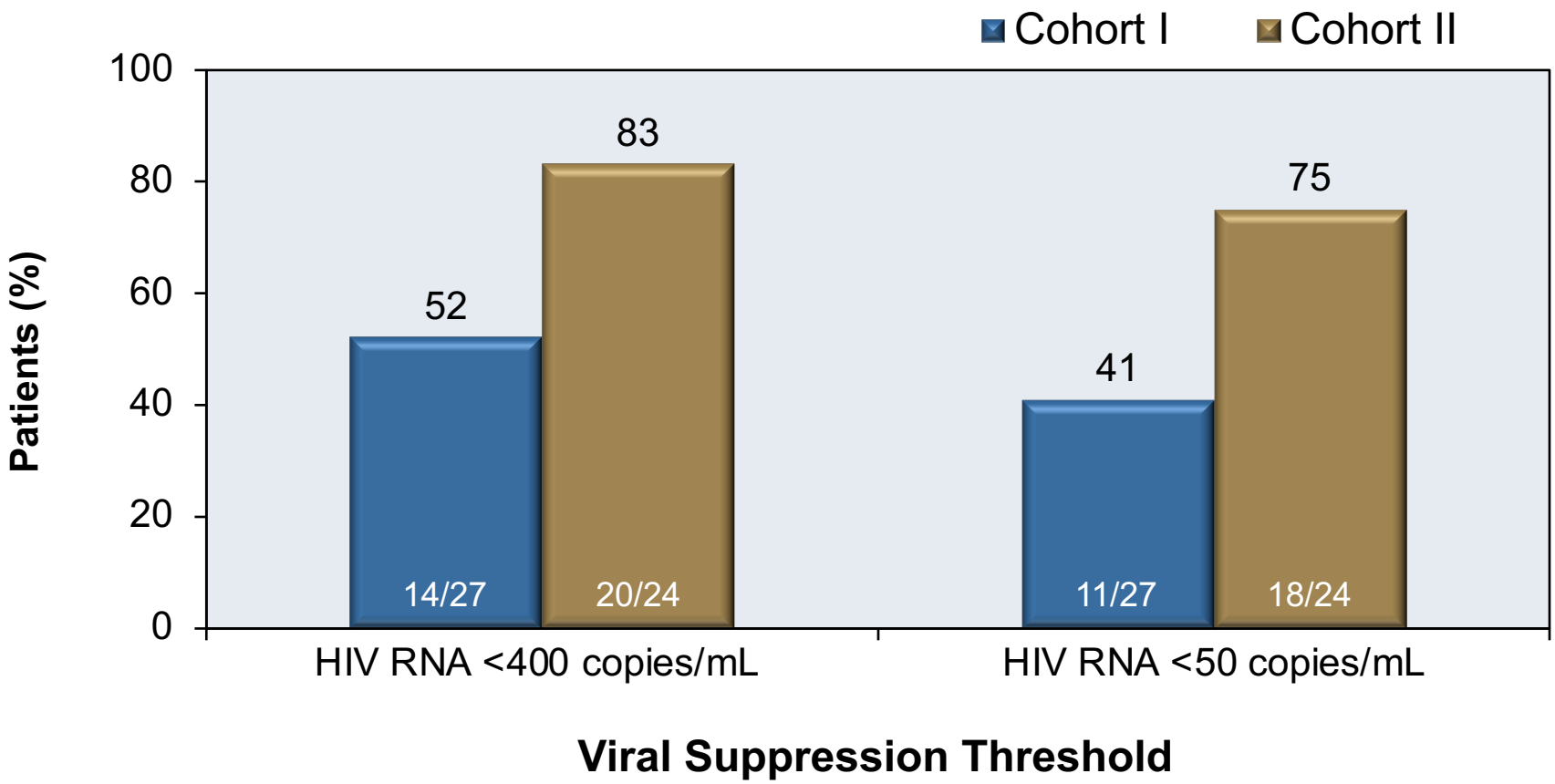
- **Background**: Single-arm, phase 2b trial evaluating efficacy of once daily or twice daily dolutegravir in patients with integrase resistance
- **Inclusion Criteria (n=51)**
  - Age ≥18 years
  - HIV RNA >1,000 copies/mL
  - Documented resistance ≥3 ARV classes, including integrase inhibitors
- **Treatment Arms**
  - Cohort I*: dolutegravir 50 mg once daily
  - Cohort II*: dolutegravir 50 mg twice daily

*Failing regimen continued during day 1-10, then replaced with OBR through week 24

Source: Eron JJ, et al. J Infect Dis. 2013;207:740-8.

Dolutegravir in Patients with Raltegravir Resistance
VIKING Study (Cohorts I & II): Results

Week 24 Virologic Response



Source: Eron JJ, et al. J Infect Dis. 2013;207:740-8.

Dolutegravir in Patients with Raltegravir Resistance
VIKING Study (Cohorts I & II): Conclusions

Conclusion: “Dolutegravir 50 mg twice daily with an optimized background provided greater and more durable benefit than the once-daily regimen. These data are the first clinical demonstration of the activity of any integrase inhibitor in subjects with HIV-1 resistant to raltegravir.”

Source: Eron JJ, et al. J Infect Dis. 2013;207:740-8.

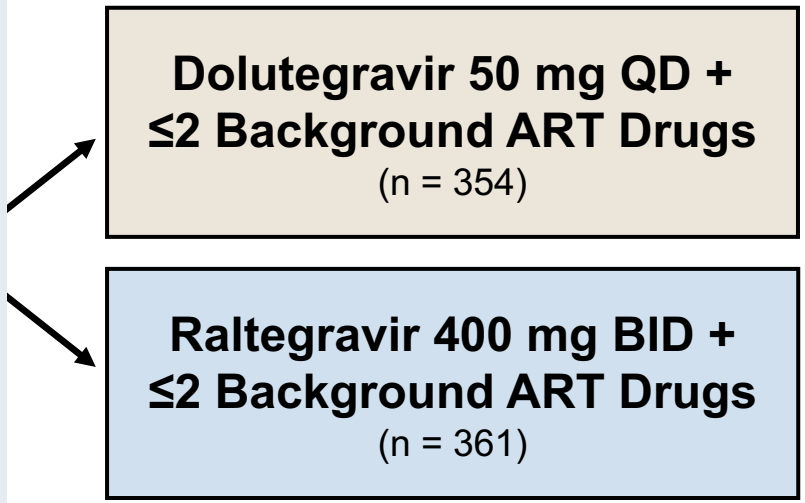
Dolutegravir versus Raltegravir in Treatment Experienced

SAILING Study

Dolutegravir versus Raltegravir in Treatment Experienced
SAILING: Study Design

Study Design: SAILING

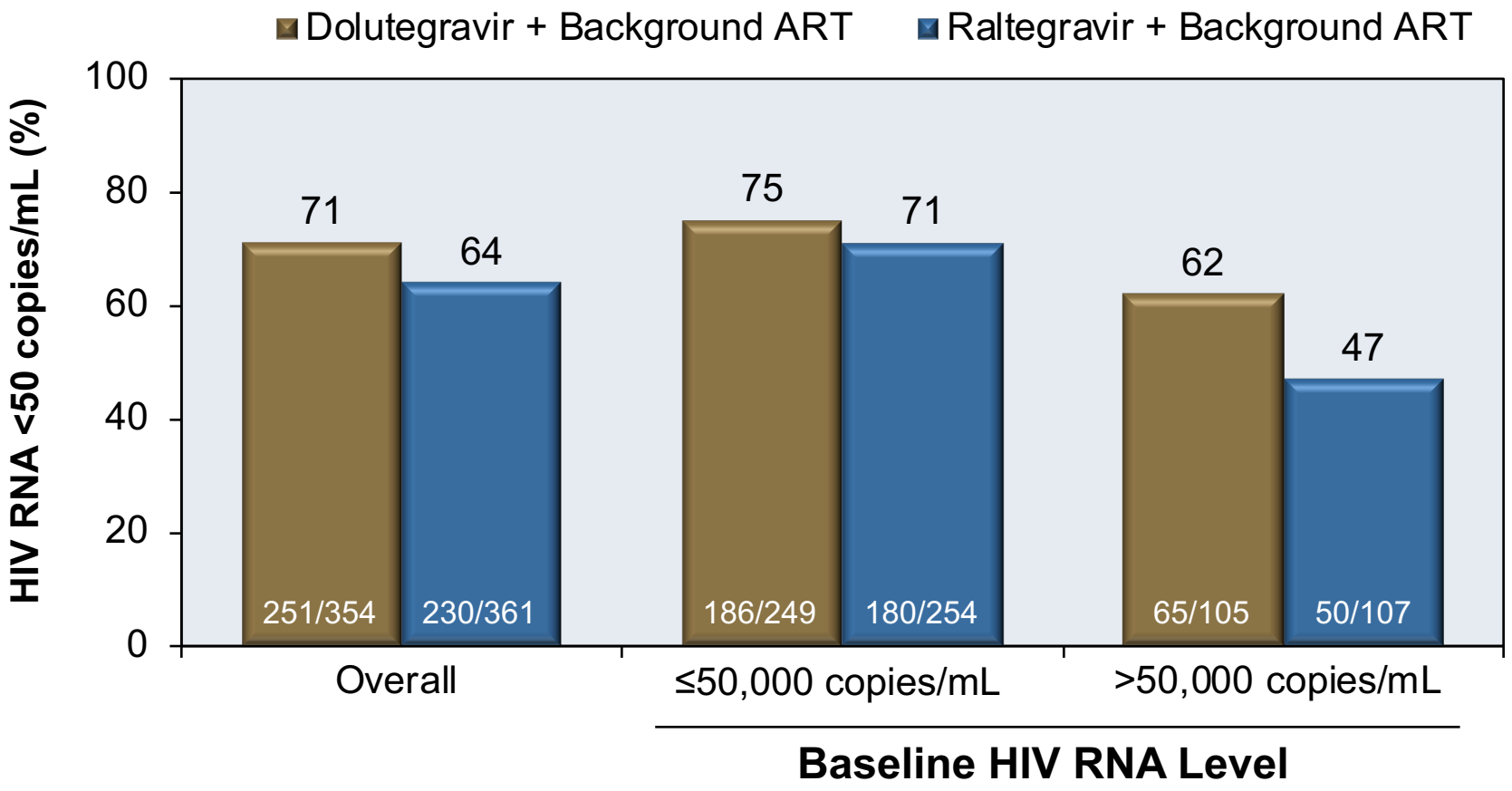
- **Background**: Randomized, double-blind, active-control phase 3 trial evaluating efficacy, safety, and emergent resistance with dolutegravir versus raltegravir in antiretroviral-experienced, integrase inhibitor-naïve patients with at least 2-class resistance
- **Inclusion Criteria (n = 715)**
  - Age ≥18
  - Resistance to ≥2 ARV classes
  - Integrase inhibitor-naïve
  - 2 consecutive HIV RNA ≥400 copies/mL (unless >1000 copies/mL at screening)
- **Treatment Arms**
  - Dolutegravir + up to 2 background ARTs
  - Raltegravir + up to 2 background ARTs



Source: Cahn P, et al. Lancet. 2013;382:700-8.

Dolutegravir versus Raltegravir in Treatment Experienced
SAILING: Results

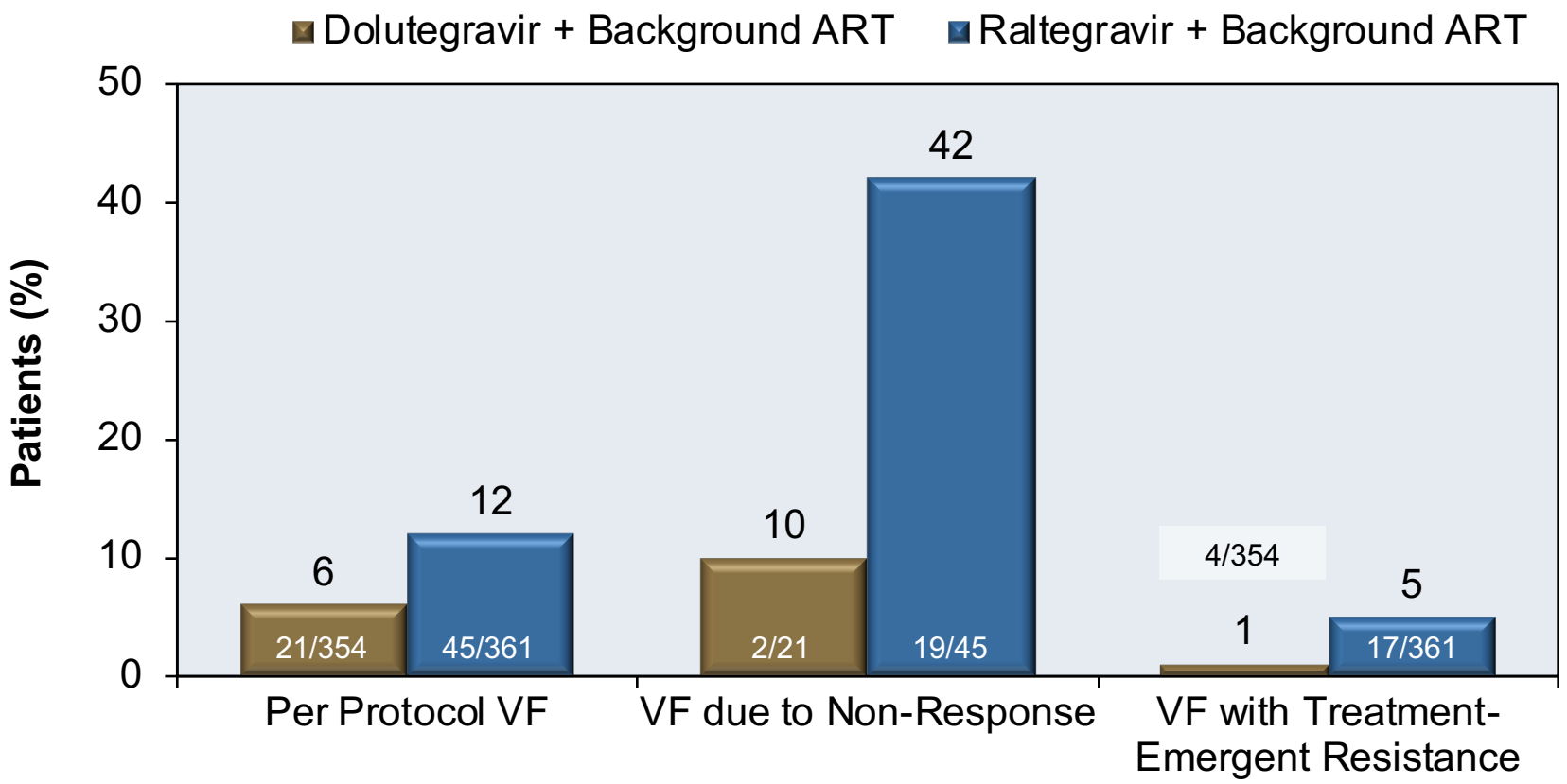
Week 48 Virologic Response, By Baseline HIV RNA Level



Source: Cahn P, et al. Lancet. 2013;382:700-8.

Dolutegravir versus Raltegravir in Treatment-Experienced
SAILING: Results

Week 48 Virologic Failure



VF = Virologic Failure

Source: Cahn P, et al. Lancet. 2013;382:700-8.

Dolutegravir versus Raltegravir in Treatment Experienced
SAILING Study: Conclusion

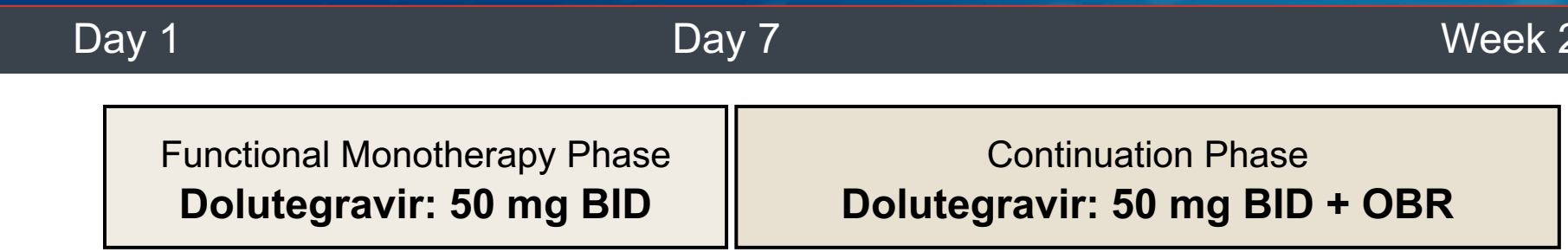
Interpretation: “Once-daily dolutegravir, in combination with up to two other antiretroviral drugs, is well tolerated with greater virological effect compared with twice-daily raltegravir in this treatment-experienced patient group.”

Source: Cahn P, et al. Lancet. 2013;382:700-8.

Dolutegravir in Patients with Integrase-Resistant HIV

VIKING-3

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-3: Study Design



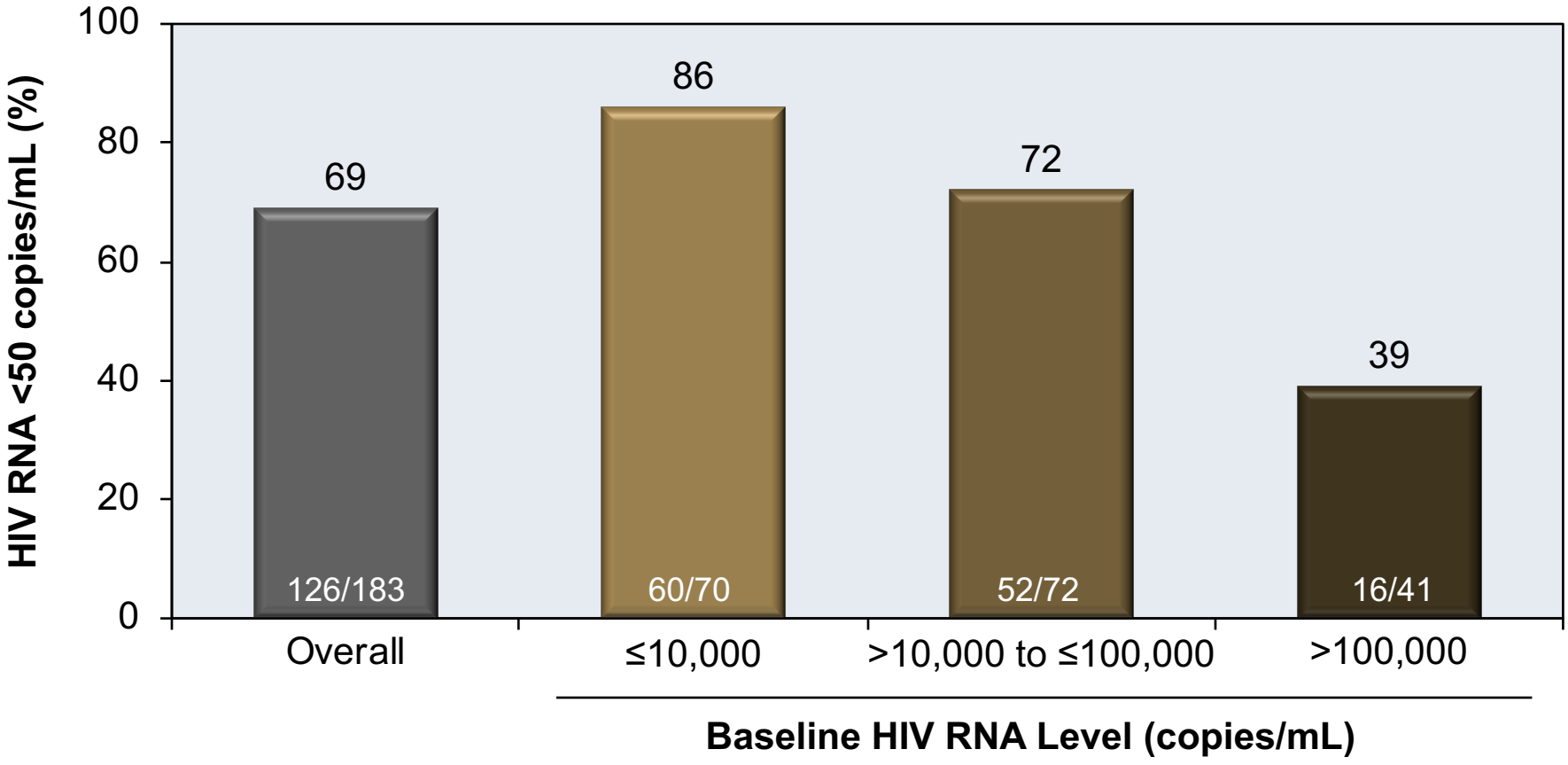
Study Design: VIKING-3

- **Background**: Single arm, open-label, phase 3 trial to determine the efficacy of twice daily dolutegravir in patients with integrase resistance
- **Inclusion Criteria (n=183)**
  - Age ≥18
  - Antiretroviral experienced, resistance to raltegravir and/or elvitegravir
  - Resistance to 2 classes of ARVs (in addition to integrase resistance)
  - HIV RNA ≥500 copies/mL
  - At least one fully active drug for optimized background regimen
  - Dolutegravir naïve
- **Treatment arm**: Dolutegravir 50 mg twice daily, with OBR added on day 7

Source: Castagna A, et al. J Infect Dis. 2014;210:354-62.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-3: Results

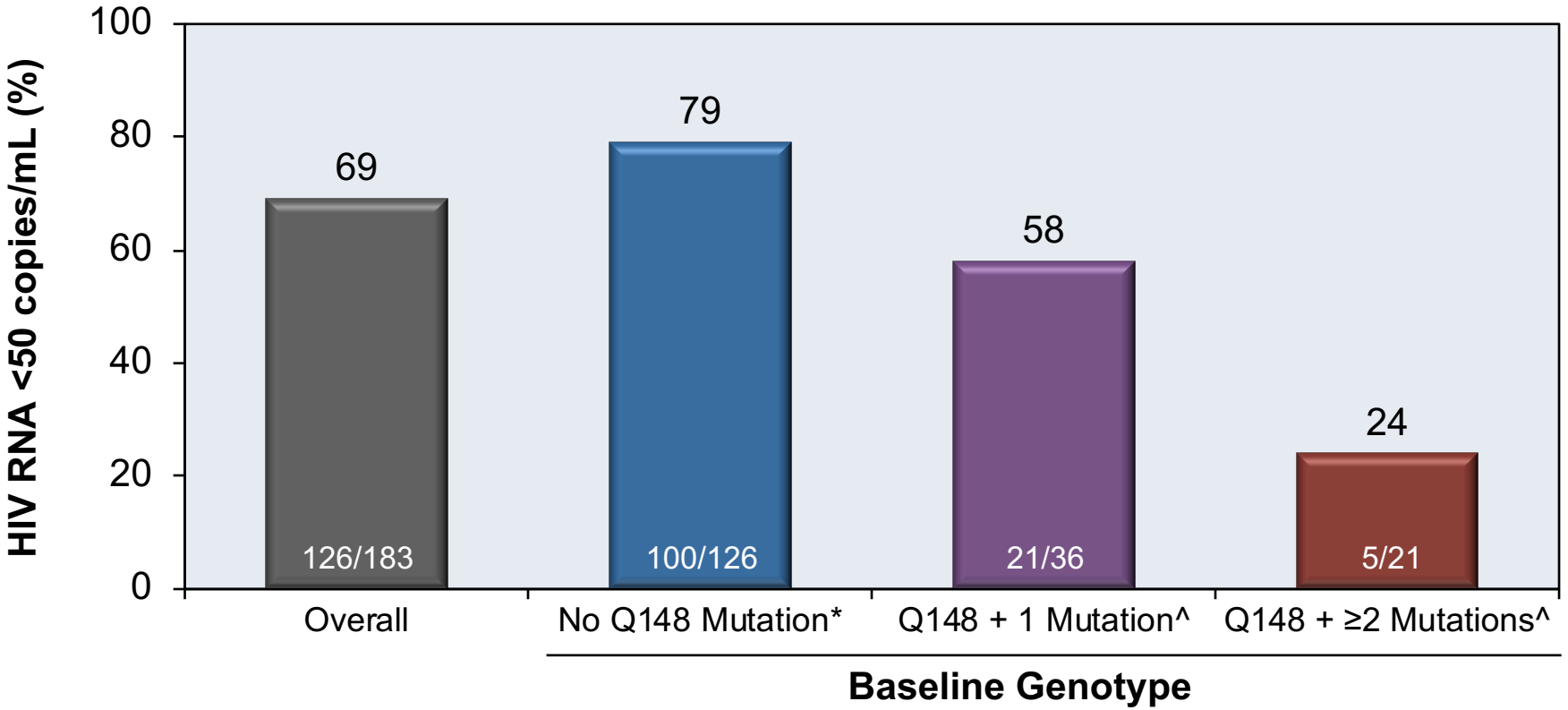
24 Week Virologic Response, by Baseline HIV RNA Level



Source: Castagna A, et al. J Infect Dis. 2014;210:354-62.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-3: Results

24 Week Virologic Response, by Baseline Genotype

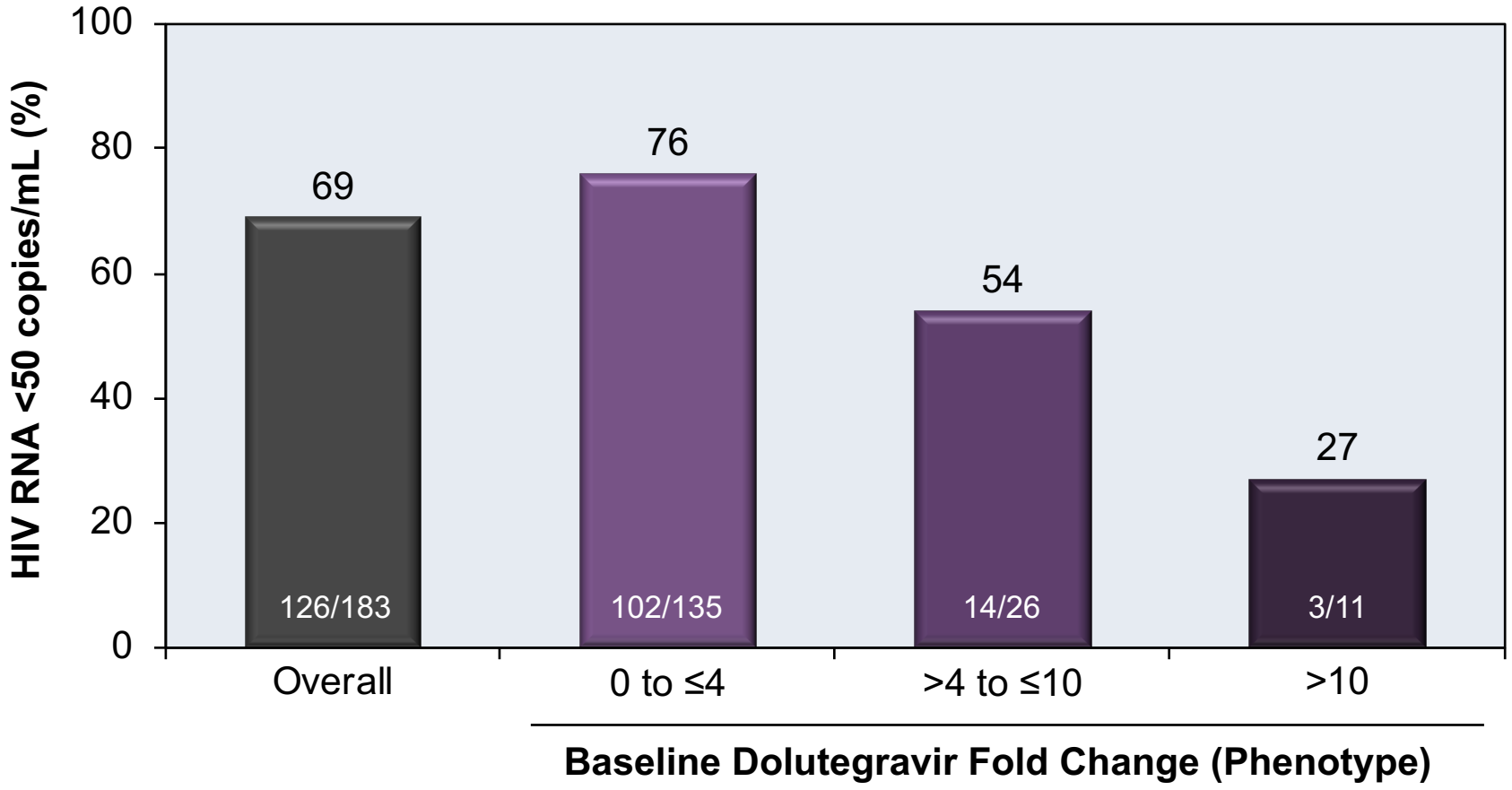


*Included primary INI-resistance mutations N155H, Y143C/H/R, T66A or E92Q or only historical evidence of resistance
^Secondary mutations from G140A/C/S, E138A/K/T or L74I.

Source: Castagna A, et al. J Infect Dis. 2014;210:354-62.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-3: Results

24 Week Virologic Response, by Baseline Phenotype



Source: Castagna A, et al. J Infect Dis. 2014;210:354-62.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-3: Conclusions

Conclusions: “Dolutegravir 50 mg BID-based therapy was effective in this highly treatment-experienced population with integrase inhibitor-resistant virus.”

Source: Castagna A, et al. J Infect Dis. 2014;210:354-62.

Dolutegravir in Patients with Integrase-Resistant HIV

VIKING-4

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-4: Study Design

Day 1 | Day 8 | Week 48

Functional Monotherapy Phase	Continuation Phase
Dolutegravir: 50 mg BID or Placebo	**Dolutegravir: 50 mg BID + OBR**

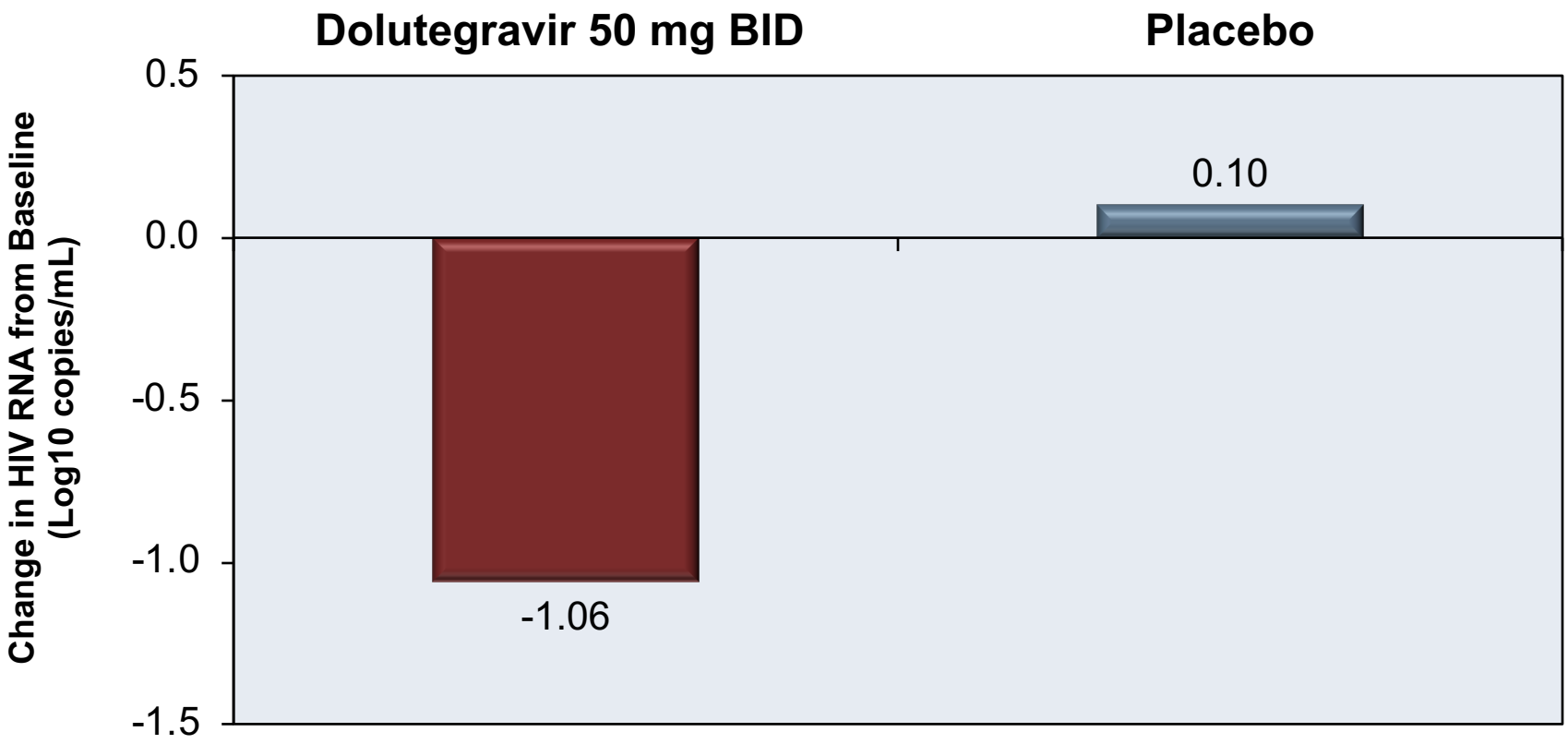
Study Design: VIKING-4

- **Background:** Single-arm, open-label, phase 3 trial to evaluate short-term antiviral efficacy of dolutegravir in persons with HIV who have integrase resistance
- **Inclusion Criteria**
  - Age ≥18 years old
  - ARV experienced, dolutegravir naïve,
  - Documented Resistance to ≥3 ARV classes, including raltegravir or elvitegravir
  - HIV RNA ≥1,000 copies/mL
- **Treatment Arms (n = 30 randomized)**
  - Day 0 to 7: Dolutegravir: 50 mg BID or Placebo
  - Day 8 to Week 24: Dolutegravir 50 mg BID + optimized background regimen

Source: Akil B, et al. Antivir Ther. 2015;20:343-8.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-4: Results

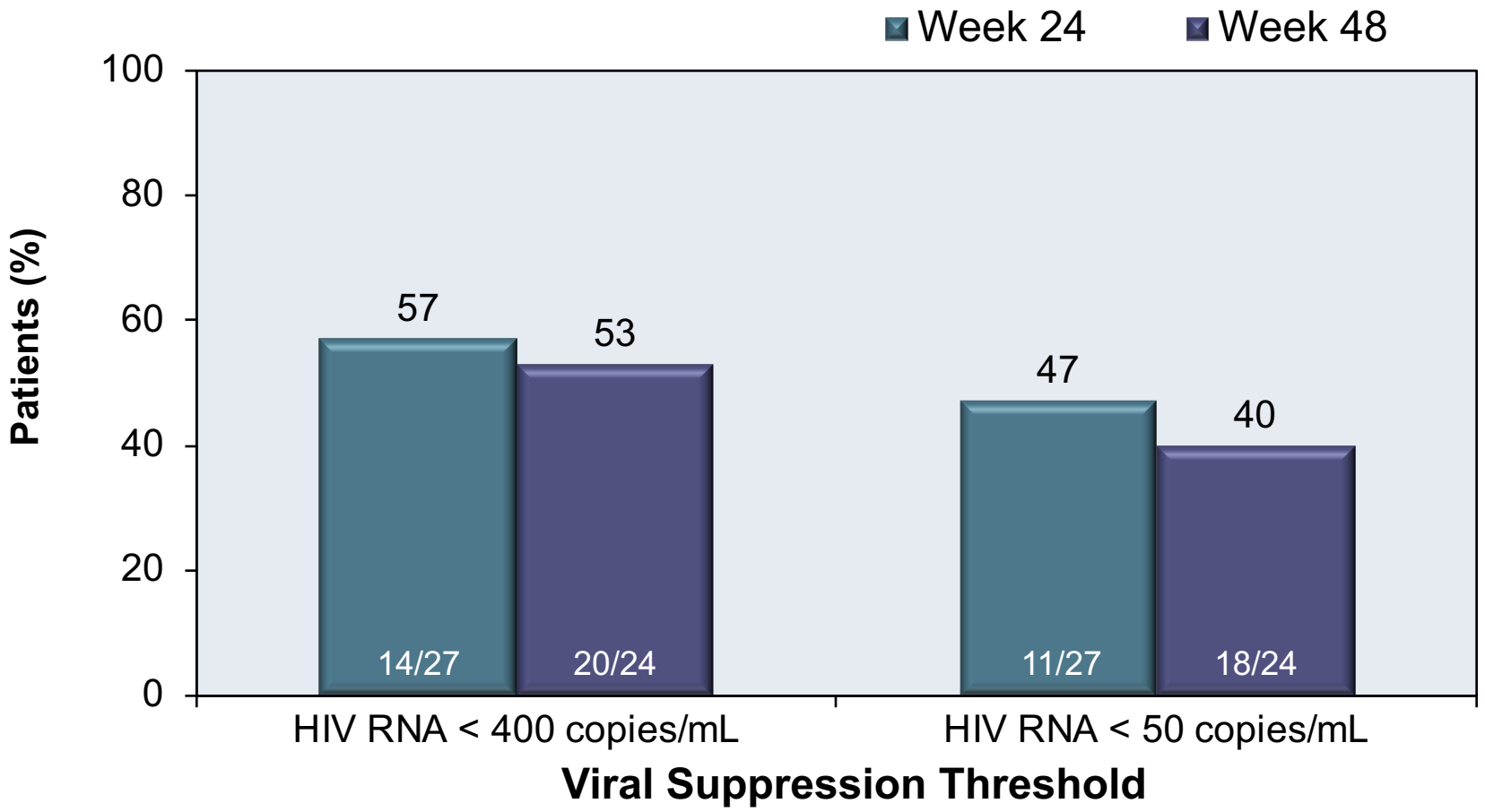
Baseline to Day 8: Change in Viral Load (in Functional Monotherapy Phase)



Source: Akil B, et al. Antivir Ther. 2015;20:343-8.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-4: Results

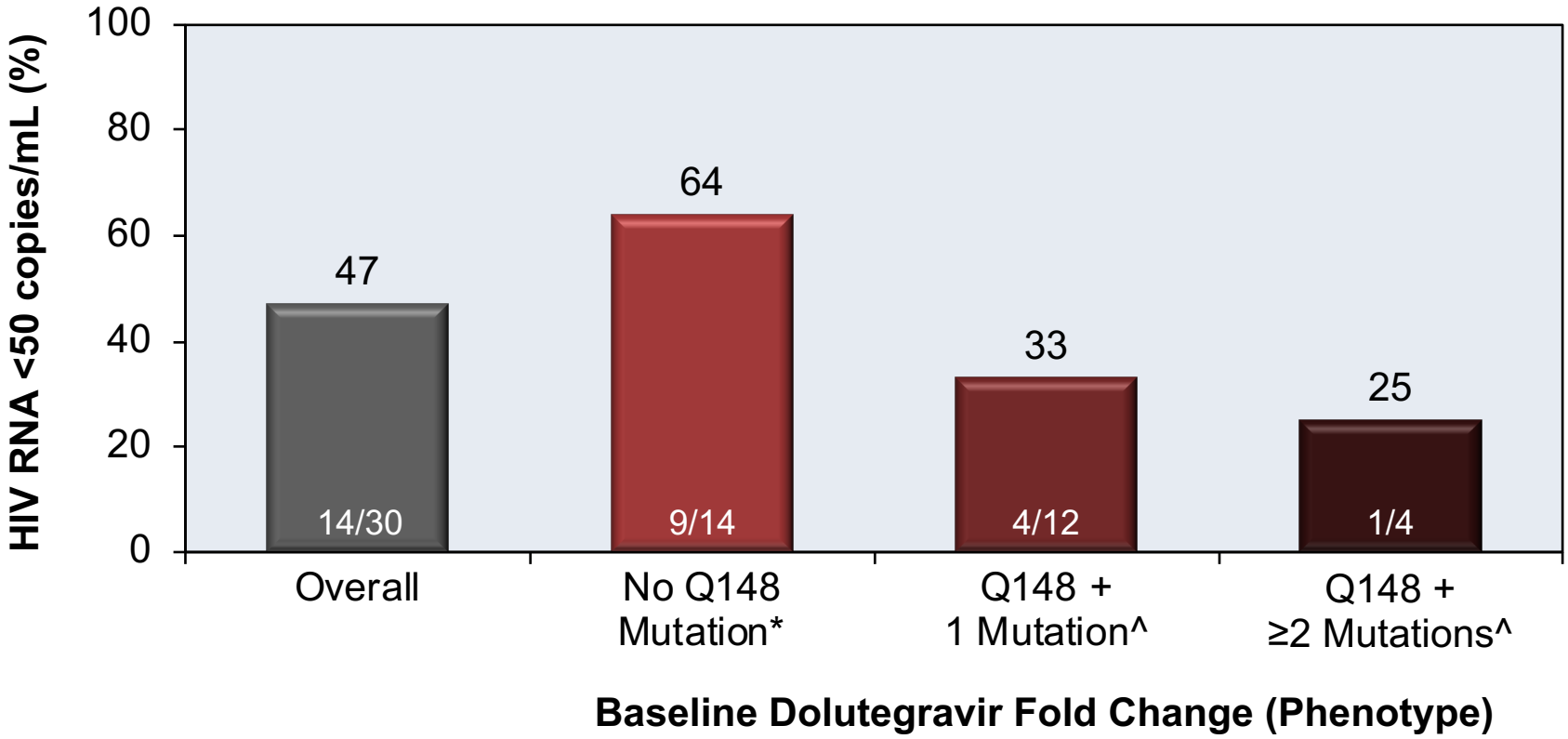
Week 24 and 48 Virologic Response in Dolutegravir-Treated Patients



Source: Akil B, et al. Antivir Ther. 2015;20:343-8.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-4: Results

Week 24 Virologic Response, by Baseline Genotype

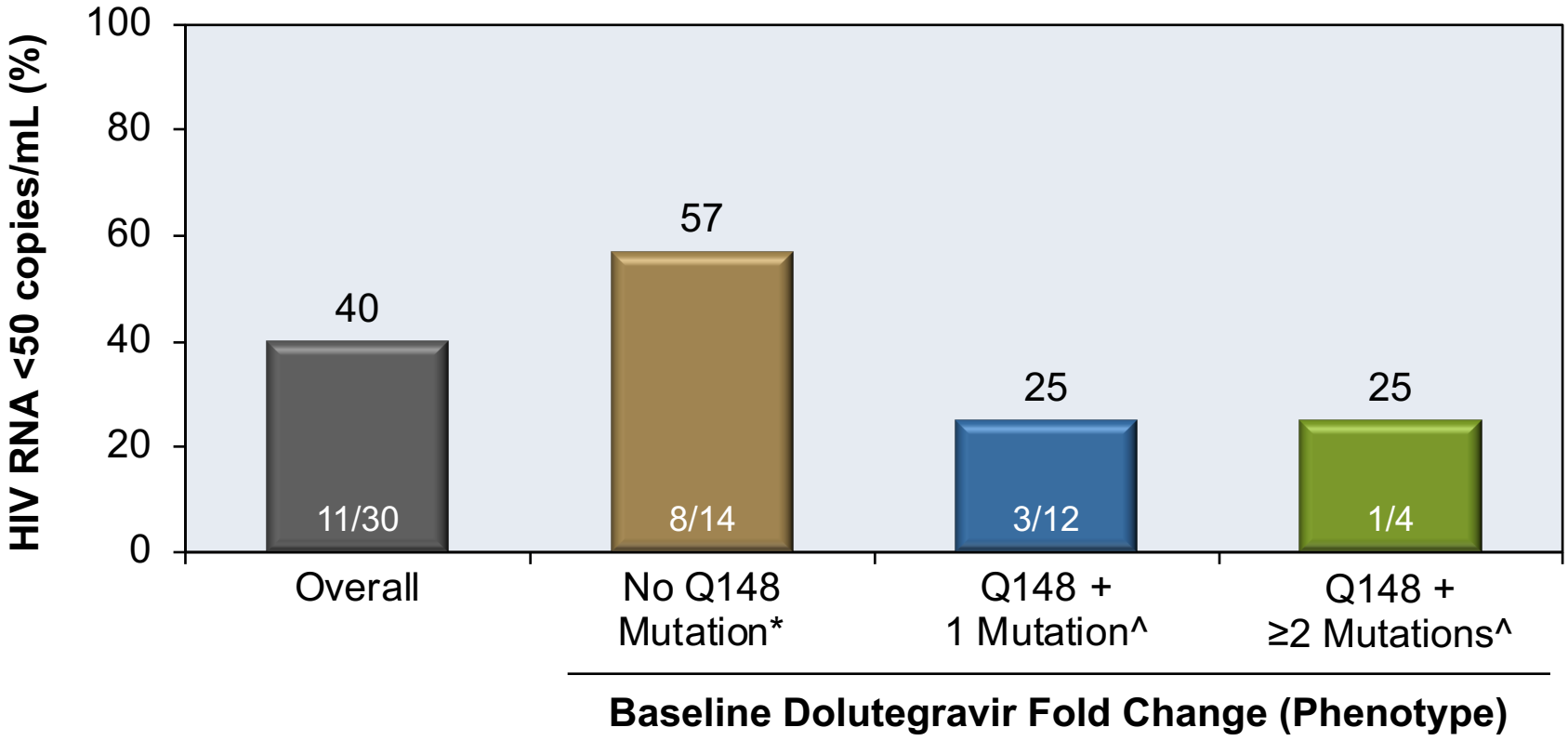


*Included primary INI-resistance mutations N155H, Y143C/H/R, T66A or E92Q or historical evidence of resistance
^Secondary mutations from G140A/C/S, E138A/K/T and L74I.

Source: Akil B, et al. Antivir Ther. 2015;20:343-8.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-4: Results

Week 48 Virologic Response, by Baseline Genotype

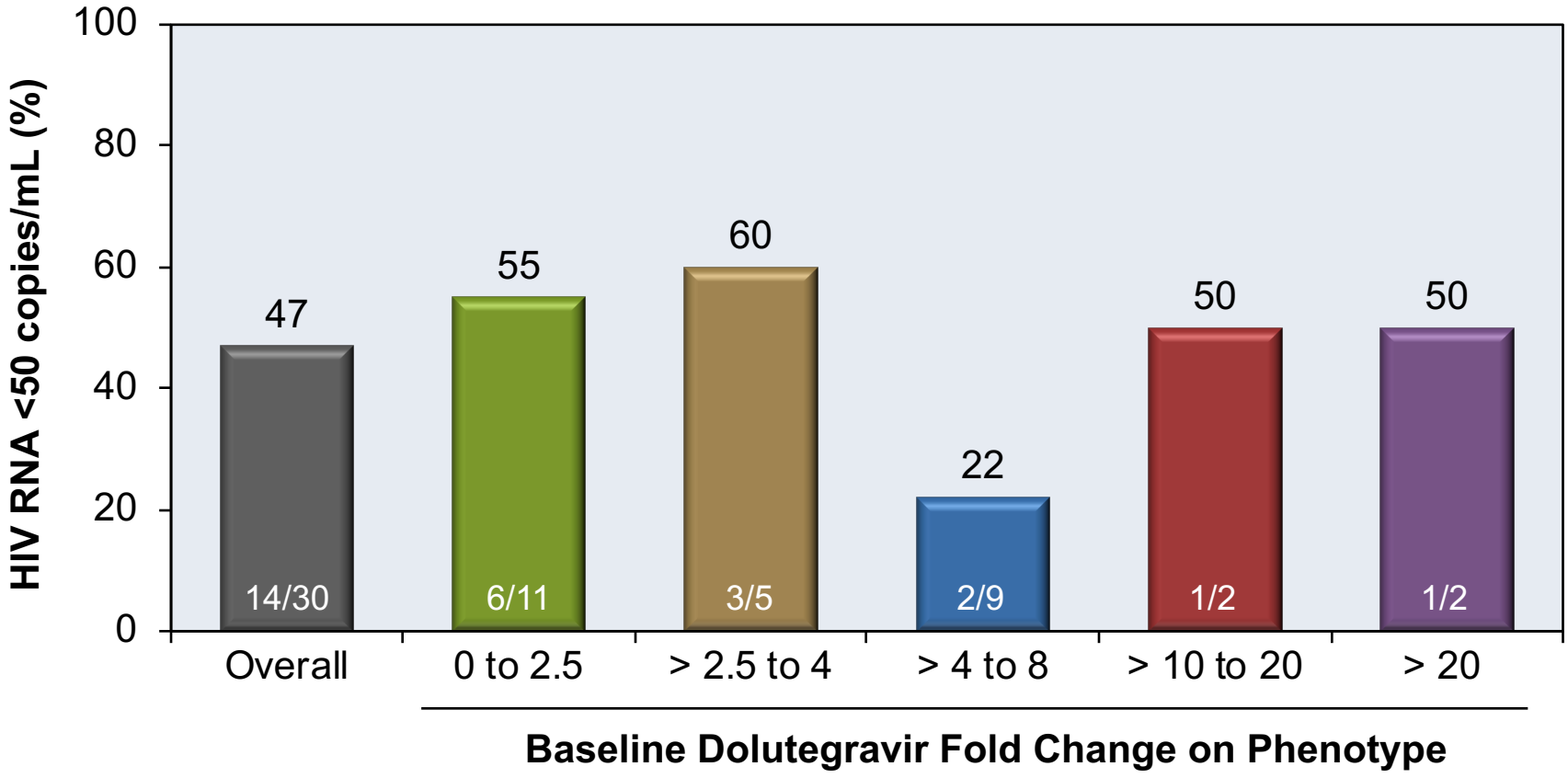


*Included primary INI-resistance mutations N155H, Y143C/H/R, T66A or E92Q or historical evidence of resistance
^Secondary mutations from G140A/C/S, E138A/K/T and L74I.

Source: Akil B, et al. Antivir Ther. 2015;20:343-8.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-4: Results

Week 24 Virologic Response, by Baseline Phenotype*

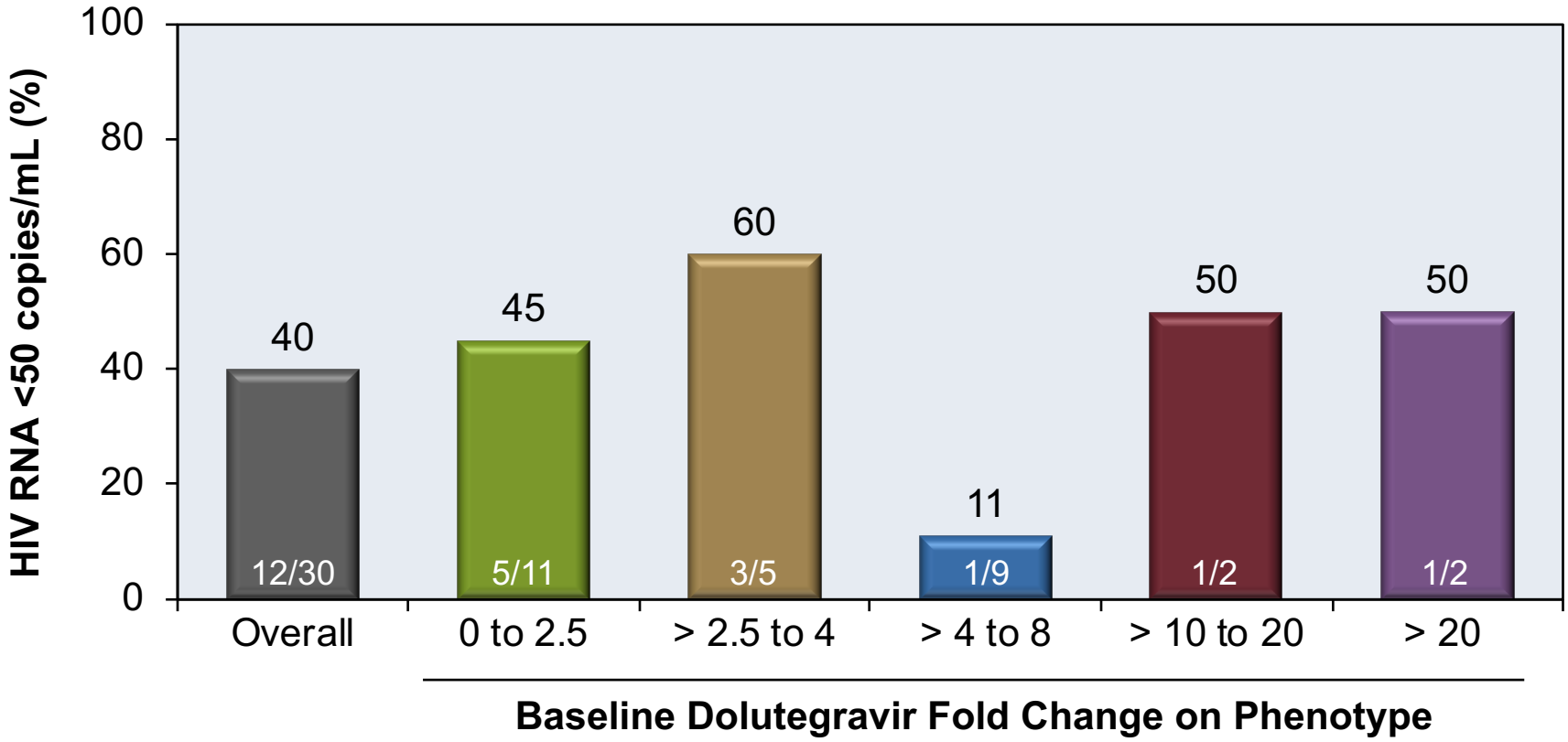


*Missing phenotypic resistance data on 1 subject

Source: Akil B, et al. Antivir Ther. 2015;20:343-8.

Dolutegravir in Patients with Integrase Inhibitor Resistance
VIKING-4: Results

Week 48 Virologic Response, by Baseline Phenotype



*Missing phenotypic resistance data on 1 subject

Source: Akil B, et al. Antivir Ther. 2015;20:343-8.

Dolutegravir in Patients with Raltegravir Resistance
VIKING-4: Conclusions

Conclusions: “The observed day 8 antiviral activity in this highly treatment-experienced population with INI-resistant HIV-1 was attributable to dolutegravir. Longer-term efficacy (after considering baseline ART resistance) and safety during the open-label phase were in-line with the results of the larger VIKING-3 study.”

Source: Akil B, et al. Antivir Ther. 2015;20:343-8.

SWITCH STUDIES

Dolutegravir

Dolutegravir + Boosted-Darunavir as Maintenance Therapy

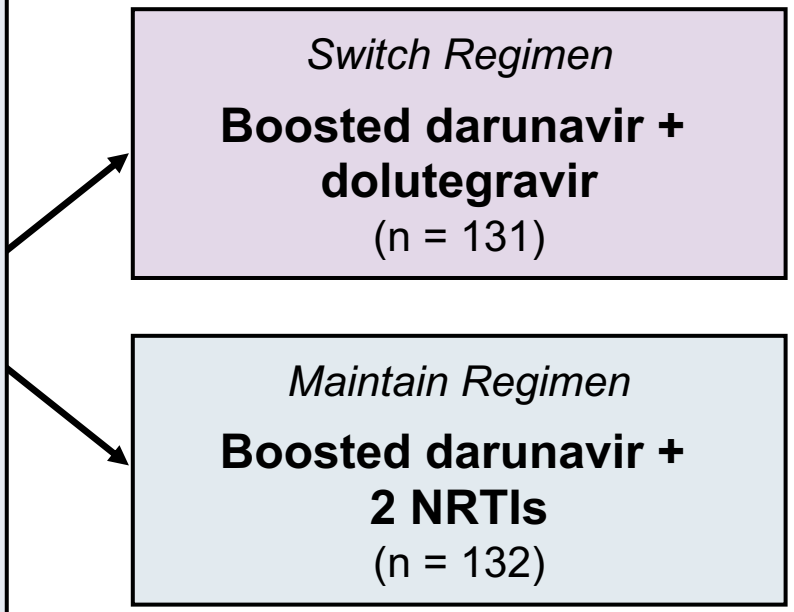
DUALIS

Switch to Boosted DRV + DTG vs Continue Boosted DRV + 2 NRTI's
DUALIS: Background

Study Design: DUALIS

- **Background**:
  - Randomized, open label, multicenter phase 3 non-inferiority trial comparing a switch to boosted darunavir + dolutegravir to continued boosted darunavir + 2 NRTIs

- **Enrollment Criteria:**
  - Age ≥18 years
  - HIV RNA <50 copies/mL for >6 months
  - Taking boosted darunavir + 2 NRTI's
  - One HIV RNA level >200 copies/mL within past 6 months allowed, as long as subsequently returned to <50 copies/mL
  - Estimated GFR >50 mL/min
  - No active hepatitis B, AIDS-defining condition, or severe hepatis impairment



Primary endpoint: virologic response at 48 weeks by FDA snapshot

Source: Spinner CD, et al. Open Forum Infect Dis. 2020;7(9):ofaa356.

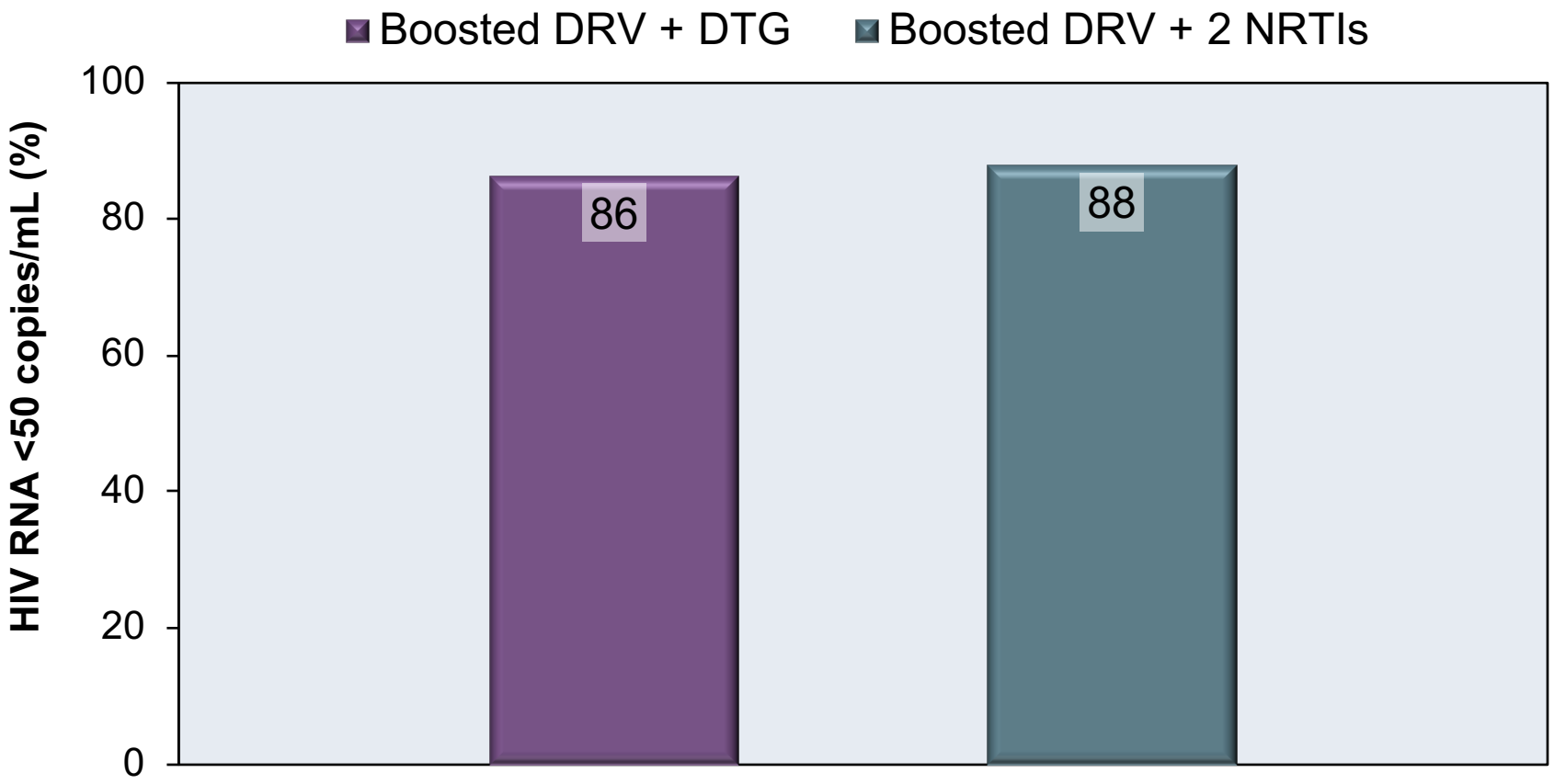
Switch to Boosted DRV + DTG vs Continue Boosted DRV + 2 NRTI's
DUALIS: Baseline Characteristics

Characteristic	Boosted DRV + DTG (n = 131)	Boosted DRV + 2 NRTIs (n = 132)
Age, years, median (IQR)	47 (39-55)	48 (40-53)
Male sex, n (%)	115 (88)	122 (92)
White, n (%)	118 (90)	118 (89)
MSM, n (%)	90 (69)	92 (70)
eGFR, median (IQR), mL/min	92 (70-104)	92 (81-106)
Baseline CD4, median (IQR)	609 (401-818)	585 (453-823)
NRTIs at baseline, n (%)		
Tenofovir-DF-emtricitabine	110 (84)	94 (71)
Tenofovir-alafenamide-emtricitabine	11 (8)	13 (10)
Abacavir-lamivudine	9 (7)	23 (17)

Source: Spinner CD, et al. Open Forum Infect Dis. 2020;7(9):ofaa356.

Switch to Boosted DRV + DTG vs Continue Boosted DRV + 2 NRTI's
DUALIS: Results

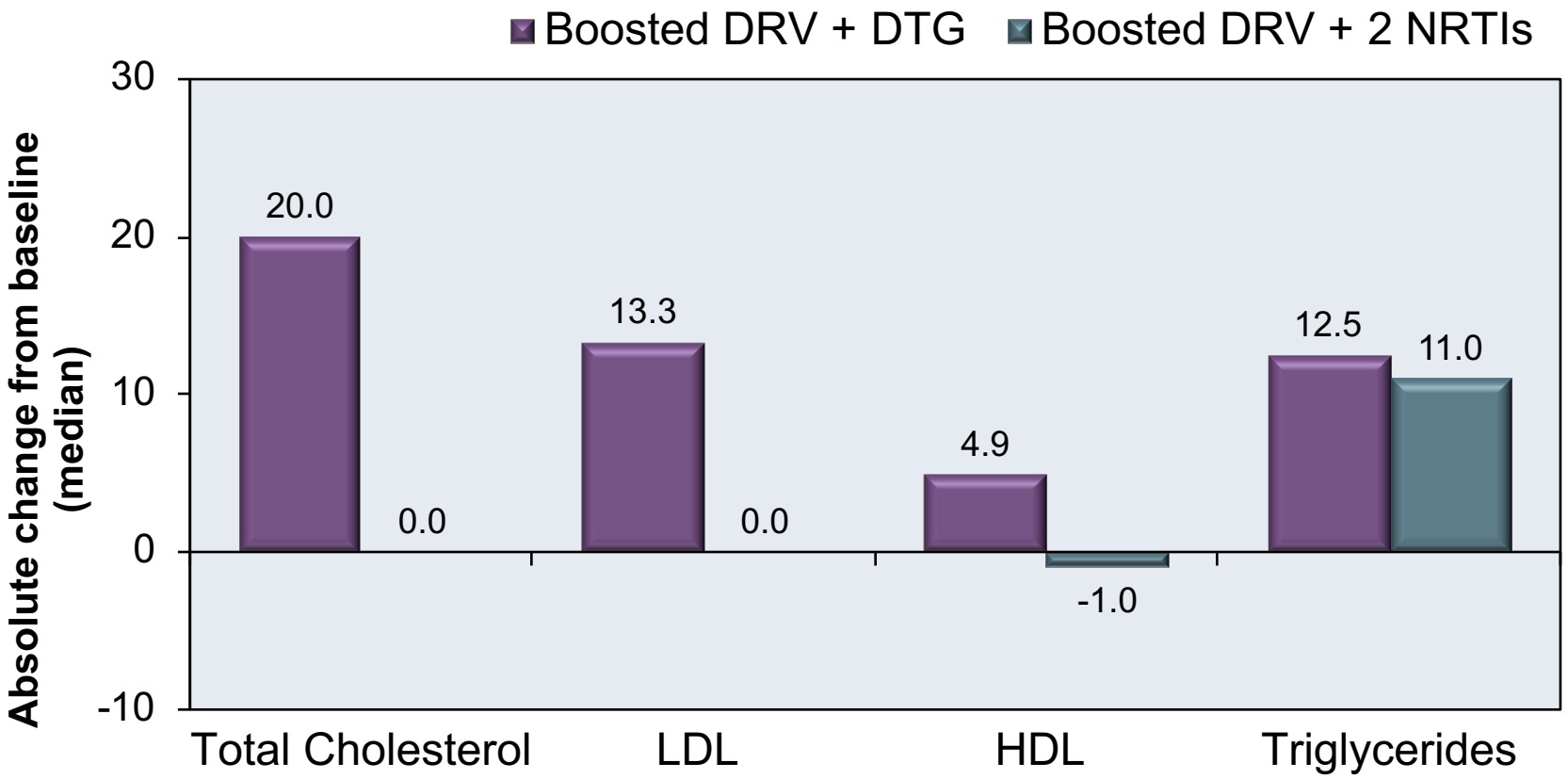
Week 48 Virologic Response (Intention-to-Treat Analysis)



Source: Spinner CD, et al. Open Forum Infect Dis. 2020;7(9):ofaa356.

Switch to Boosted DRV + DTG vs Continue Boosted DRV + 2 NRTI's
DUALIS: Results

Week 48 Changes in Serum Lipid Parameters



Source: Spinner CD, et al. Open Forum Infect Dis. 2020;7(9):ofaa356.

Switch to Boosted DRV + DTG vs Continue Boosted DRV + 2 NRTI's
DUALIS: Conclusions

Conclusions: "Switching to dolutegravir plus boosted darunavir was noninferior to continuing 2 nucleoside reverse transcriptase inhibitors plus boosted darunavir in subjects already treated with 2 nucleoside reverse transcriptase inhibitors plus boosted darunavir."

Source: Spinner CD, et al. Open Forum Infect Dis. 2020;7(9):ofaa356.

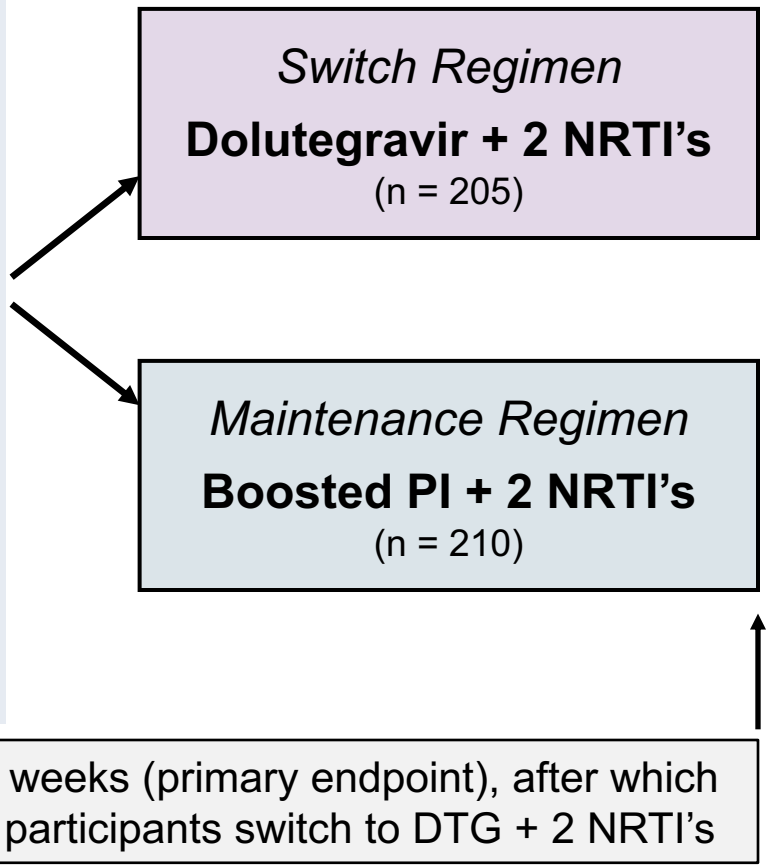
Switch from Boosted PI to Dolutegravir

NEAT 022

Switching from a Boosted PI to Dolutegravir
NEAT 022: Design

Study Design

- **Background**: Randomized, open-label, multicenter trial in Europe evaluating the impact of switching from a boosted PI to dolutegravir in virologically suppressed persons with older age or elevated cardiovascular risk.
- **Inclusion Criteria**
  - Age ≥50 years or Framingham 10-year estimated cardiovascular event risk >10%
  - HIV RNA <50 copies/mL for ≥24 weeks
  - On 2 NRTI's + boosted PI
  - No prior virologic failure and no genotypic resistance mutations



Source: Gatell JM, et al. AIDS. 2017;31:2503-14.

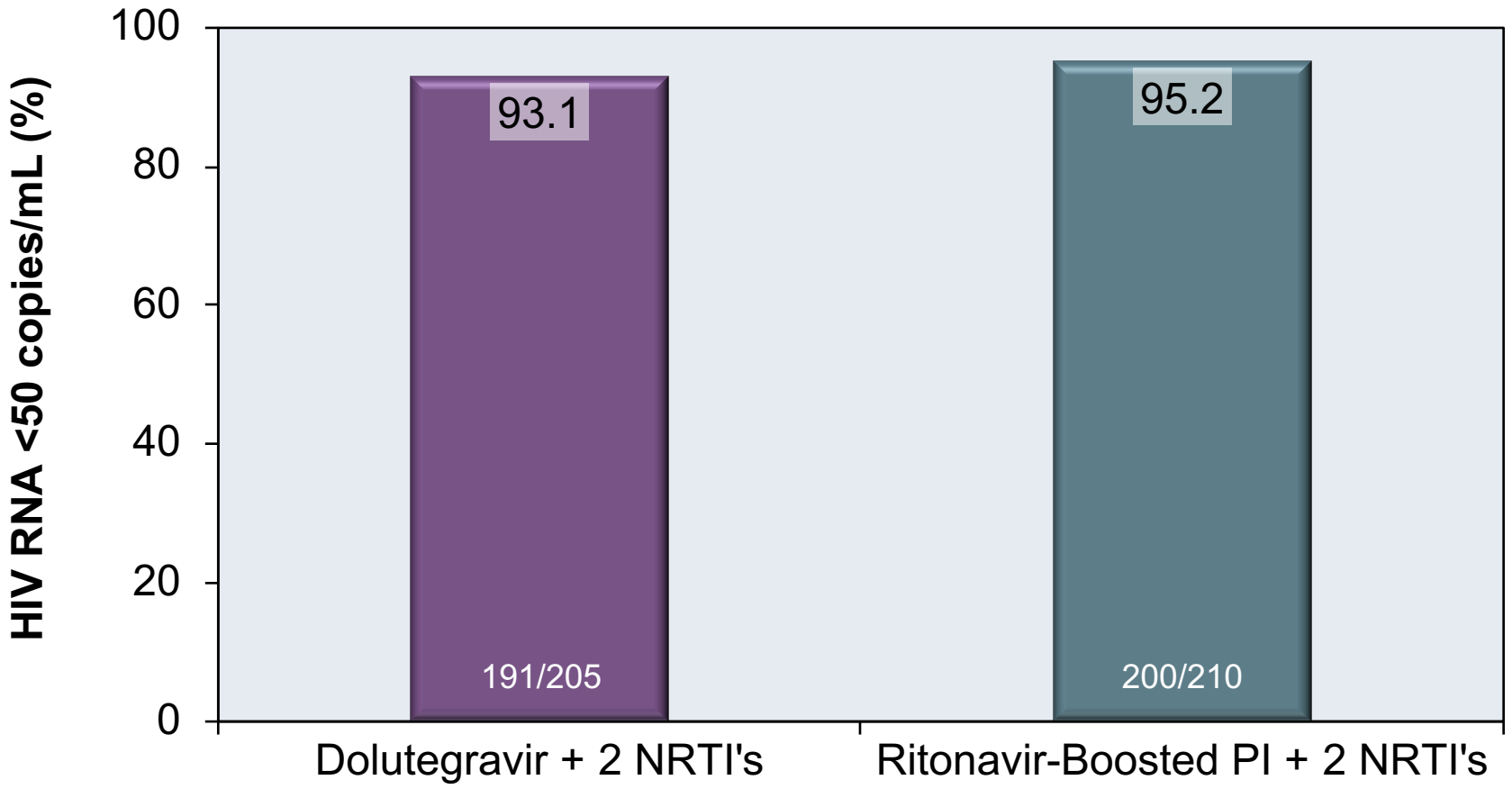
Switching from a Boosted PI to Dolutegravir
NEAT 022: Baseline Regimens

Baseline Regimens in NEAT 022 Study		
	DTG + 2 NRTI's (n = 205)	**PI/r + 2 NRTI's** (n = 210)
NRTI Backbone		
Tenofovir DF-Lamivudine	134 (65.4%)	135 (64.3%)
Abacavir-Lamivudine	63 (30.7%)	67 (31.9%)
Other	8 (3.9%)	8 (3.8%)
Boosted PI		
Darunavir + ritonavir	105 (51.5%)	107 (51.0%)
Atazanavir + ritonavir	77 (37.7%)	74 (35.2%)
Other	22 (10.7%	29 (13.8%)

Source: Gatell JM, et al. AIDS. 2017;31:2503-14.

Switching from a Boosted PI to Dolutegravir
NEAT 022: Results

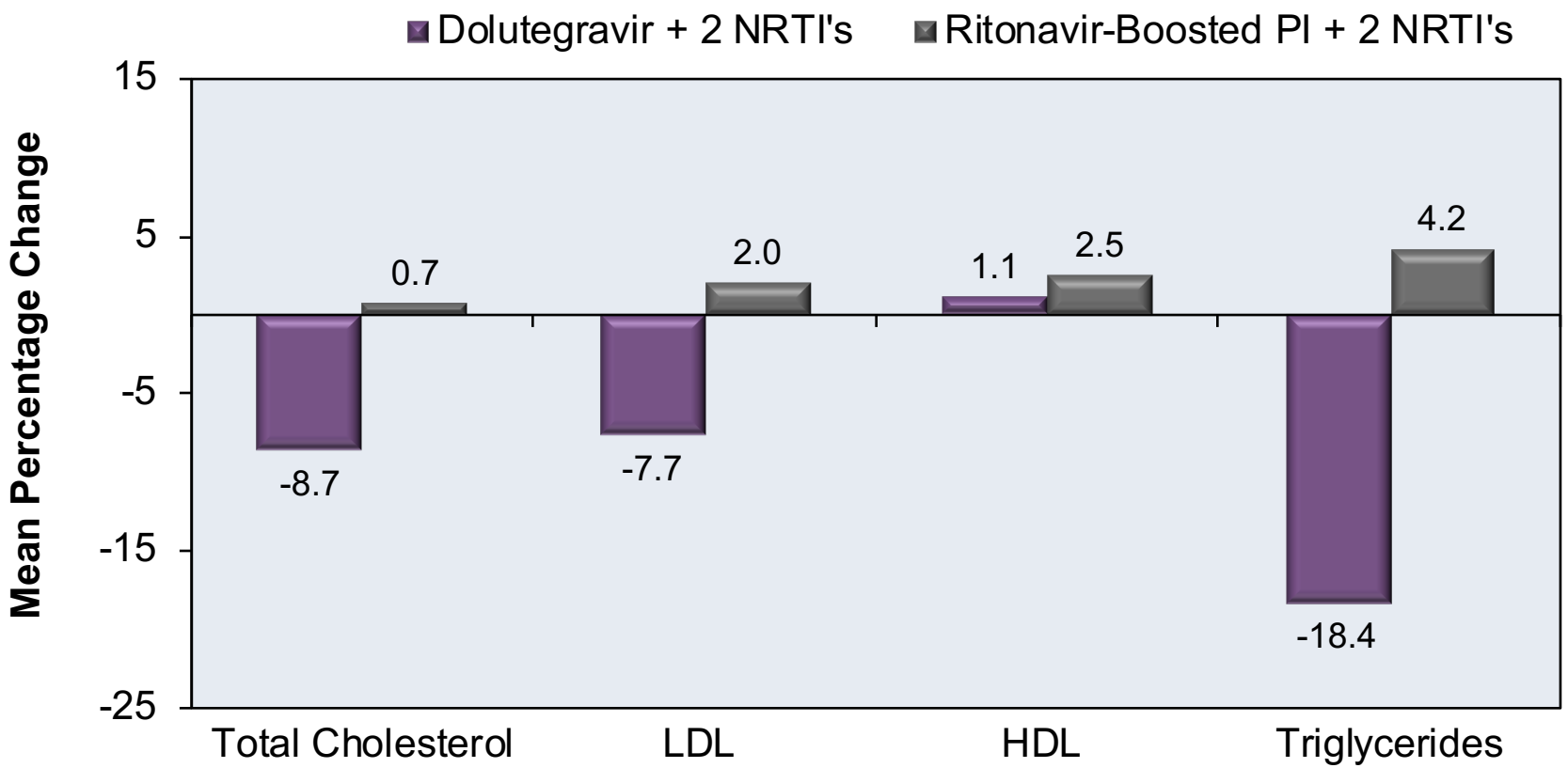
Week 48: Virologic Response by FDA Snapshot Analysis (ITT)



Source: Gatell JM, et al. AIDS. 2017;31:2503-14.

Switching from a Boosted PI to Dolutegravir
NEAT 022: Results

Mean Percentage Change in Lipids at 48 Weeks



Source: Gatell JM, et al. AIDS. 2017;31:2503-14.

Switching from a Boosted PI to Dolutegravir
NEAT 022: Conclusion

Interpretation: “Switching to a dolutegravir regimen in virologically suppressed HIV type 1 patients with high cardiovascular disease risk was noninferior, and significantly improved lipid profiles.”

Source: Gatell JM, et al. AIDS. 2017;31:2503-14.

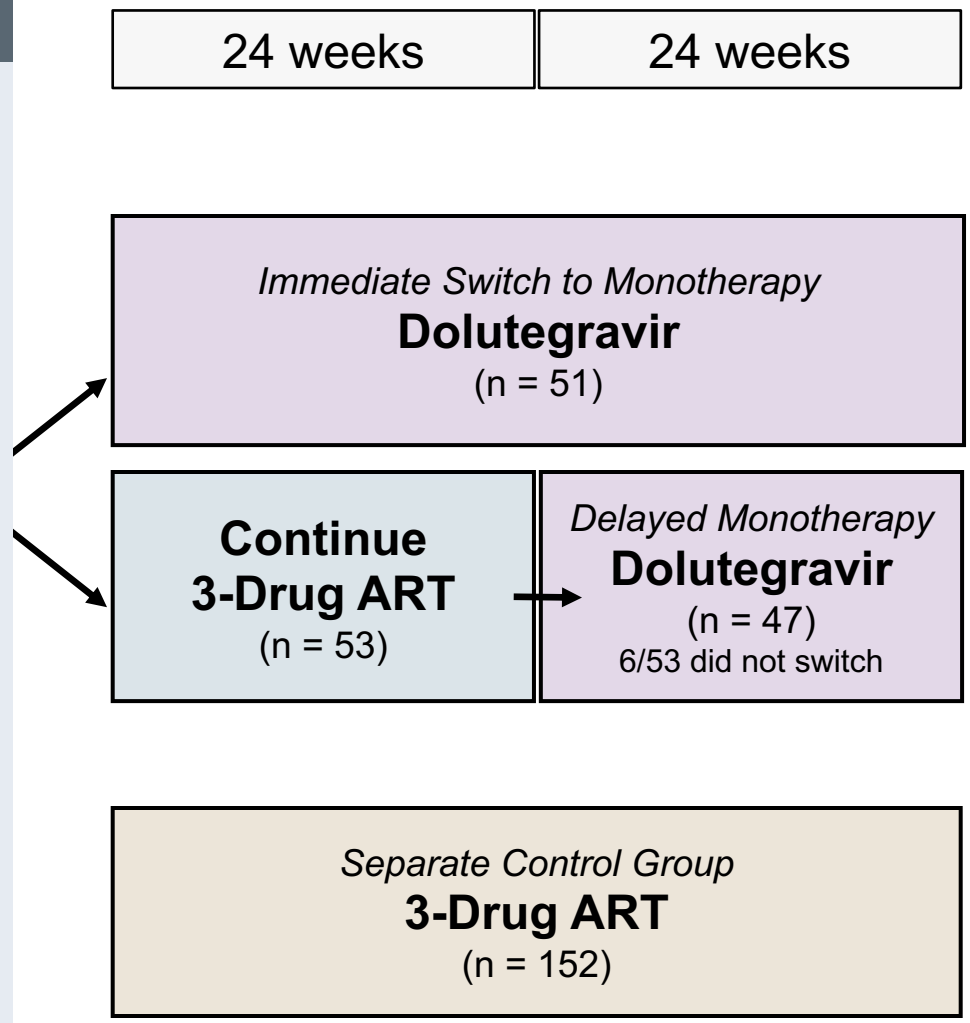
Dolutegravir as Maintenance Monotherapy

DOMONO

Dolutegravir as Maintenance Monotherapy
DOMONO: Design

Study Design: DOMONO

- **Background**: Randomized, open-label, phase 2, non-inferiority trial conducted at 2 centers in Netherlands to determine if dolutegravir monotherapy is noninferior to combination antiretroviral therapy in maintaining viral suppression.
- **Inclusion Criteria:**
  - Age ≥18 years old
  - On 3-drug ART
  - HIV RNA <50 copies/mL for ≥6 months
  - HIV RNA zenith <100,000 copies/mL
  - CD4 count nadir >200 cells/mm^3
  - No baseline HIV drug resistance
  - No history of virologic failure
  - No HBV co-infection
- Dolutegravir Regimen
  - Dolutegravir 50 mg once daily



Source: Wijting I, et al. Lancet HIV. 2017;4;e547-54.

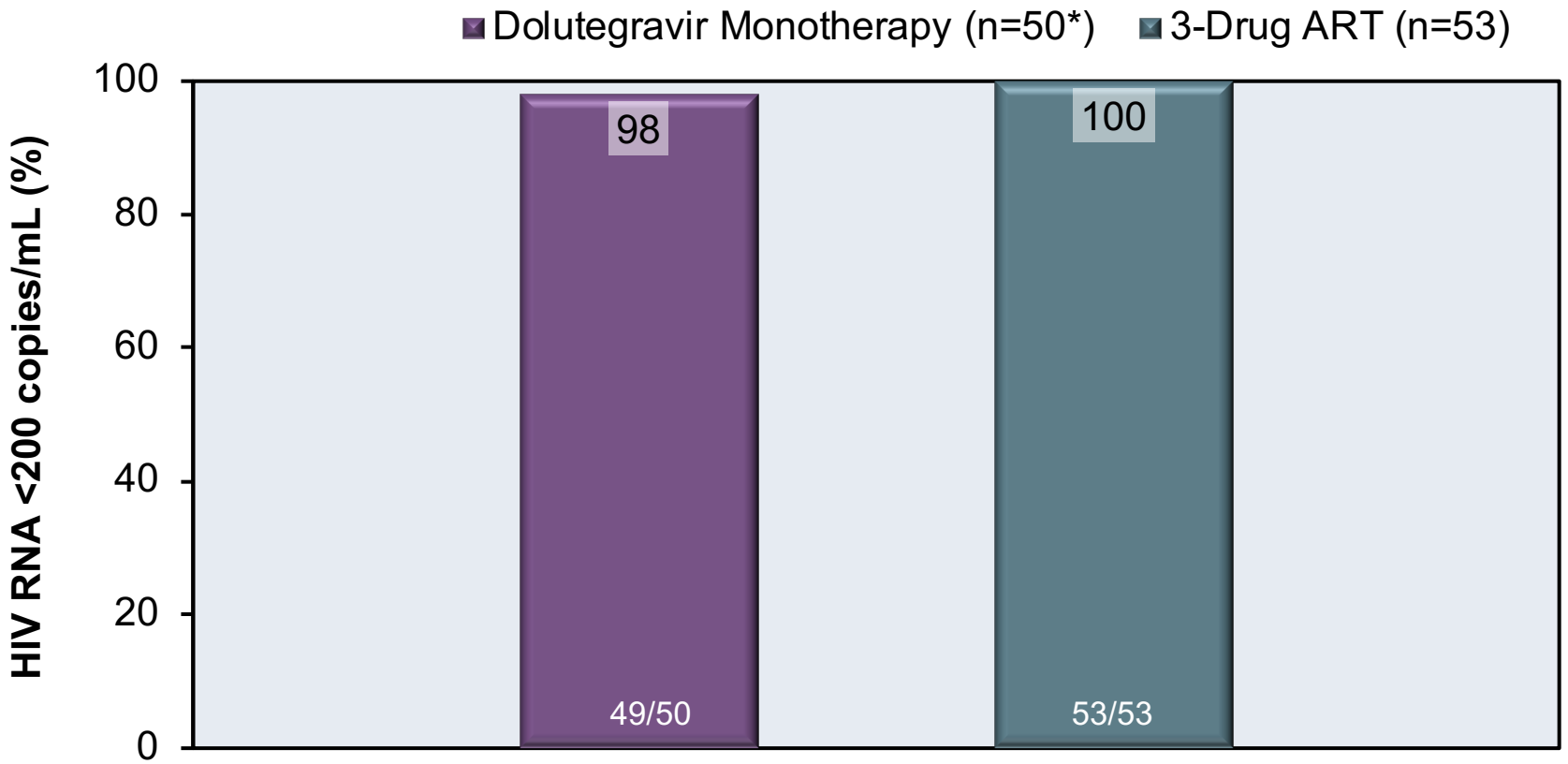
Dolutegravir as Maintenance Monotherapy
DOMONO: Baseline Characteristics

Baseline Characteristic	Immediate Switch to DTG Monotherapy (n = 51)	Delayed Switch to DTG Monotherapy (n = 53)
Age (median, years)	46	45
Male, %	47	48
MSM, %	80	77
Caucasian ethnicity, %	86	79
On TDF before switch, %	86	85
On NNRTI + 2 NRTI's before switch, %	80	81
On PI + 2 NRTI's before switch, %	4	2
On INSTI + 2 NRTI's before switch, %	14	17
Receiving a STR before switch, %	63	77
Time on ART (median, months)	35	43
HIV RNA zenith (median, copies/mL)	29,300	44,877
CD4 T-cell nadir (median, cells/mm^3)	320	380

Source: Wijting I, et al. Lancet HIV. 2017;4;e547-54.

Dolutegravir as Maintenance Monotherapy
DOMONO: 24-Week Results

Week 24 Virologic Suppression

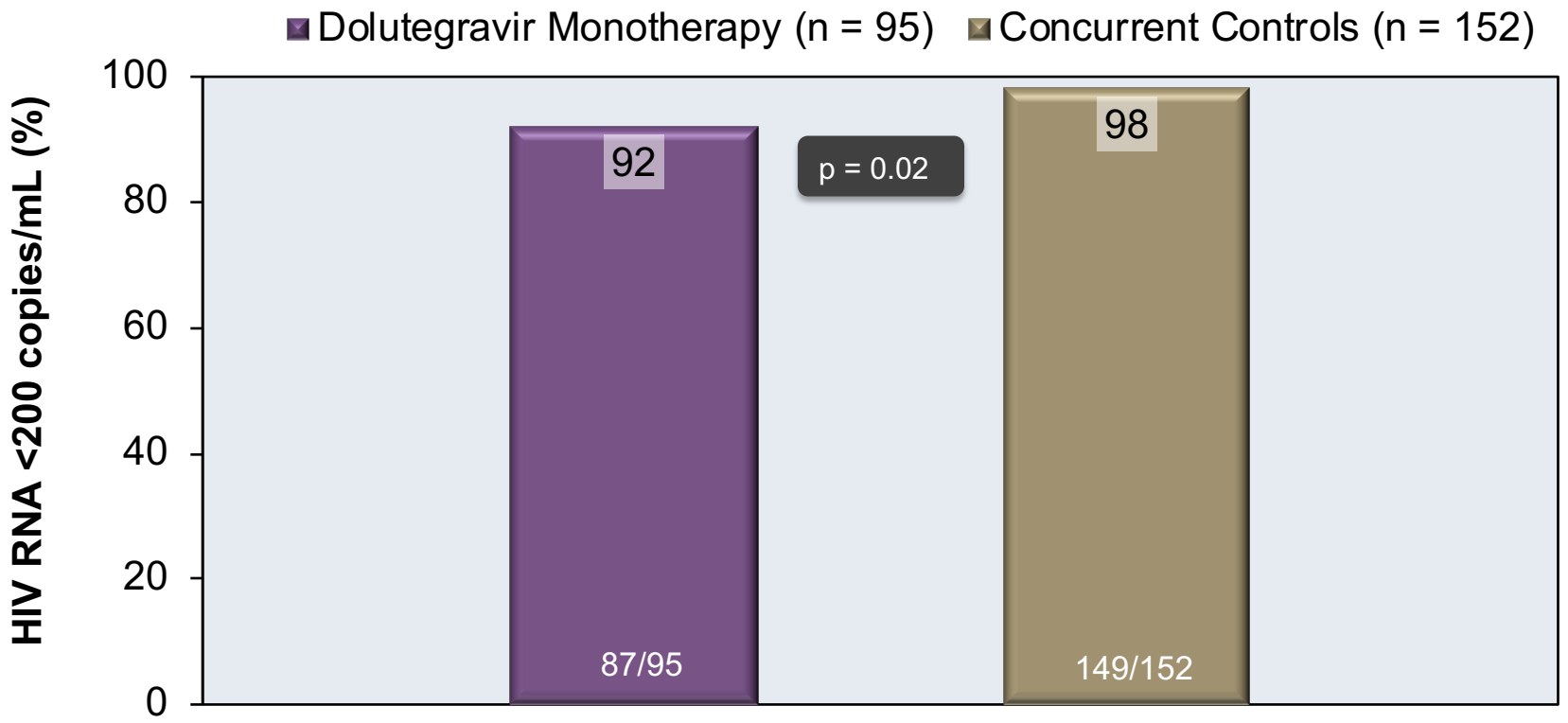


*One of 51 participants in the immediate DTG switch arm discontinued treatment after 12 weeks because of disturbed sleep (HIV RNA <50 copies/mL at the time)

Source: Wijting I, et al. Lancet HIV. 2017;4;e547-54.

Dolutegravir as Maintenance Monotherapy
DOMONO: 48-Week Results

Week 48 Virologic Suppression (Entire Study Population)



- Study stopped early; 8 virologic failures in dolutegravir arm, 3 with INSTI resistance (N155H, R263K, S230R)
- RNA at failure 678-4,990 copies/mL with one exception (71,600 copies/mL); all reported >95% adherence and all suppressed with re-initiation of cART

Source: Wijting I, et al. Lancet HIV. 2017;4;e547-54.

Dolutegravir as Maintenance Monotherapy
DOMONO: Conclusion

Interpretation: “Dolutegravir monotherapy was non-inferior to combination ART at 24 weeks. However, virological failure continued to occur thereafter and led to dolutegravir resistance. Dolutegravir should not be used as maintenance monotherapy.”

Source: Wijting I, et al. Lancet HIV. 2017;4;e547-54.

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