National HIV Curriculum

Mini-Lecture Series

Boosted Darunavir

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Disclosures

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Boosted Darunavir Basics

- **Medication**
  - Oral protease inhibitor (PI)
- **Administration**
  - Co-administered with Ritonavir (DRV/r) OR
  - Co-administered with Cobicistat as a fixed dose combination tablet (DRV/c)
  - Several drug-drug interactions due to ritonavir and cobicistat CYP3A inhibition
- **Indication**
  - Once daily DRV/r or DRV/c is indicated for the treatment of HIV-1 in adult and pediatric patients
  - Twice daily DRV/r can be used in treatment-experienced adults with certain PI resistance mutations

Source: Darunavir Prescribing Information and Darunavir-Cobicistat Prescribing Information.

Boosted Darunavir Basics

- **Testing Prior to Initiation**
  - Liver function tests if using DRV/r
  - Renal function if using DRV/c
  - Genotype especially for treatment experienced individuals
- **With Renal Impairment**
  - DRV/c is not recommended for severe renal impairment
- **With Hepatic Impairment**
  - DRV/c is not recommended for severe hepatic impairment
  - Close monitoring of liver function tests are recommended if using DRV/r

Source: Darunavir Prescribing Information and Darunavir-Cobicistat Prescribing Information.

Darunavir

Darunavir 800 mg → PI + Ritonavir 100 mg → Booster	Darunavir 600 mg → PI + Ritonavir 100 mg → Booster
Dosing: Once daily with food	Dosing: Twice daily with food

Darunavir-Cobicistat

Darunavir	Cobicistat
800 mg	150 mg
↳ PI	↳ Booster

Dosing: Once daily with food

Recommended Darunavir Dosing in Adult Patients

Treatment-Naïve and Treatment Experienced with no Darunavir Resistance-Associated Mutations

Darunavir	+	Ritonavir
800 mg		100 mg

Dosing: Once daily with food

Darunavir-Cobicistat
800 mg-150 mg

Dosing: Once daily with food

Treatment Experienced with ≥1 Darunavir Resistance-Associated Mutations

Darunavir	+	Ritonavir
600 mg		100 mg

Dosing: Twice daily with food

Source: Darunavir Prescribing Information and Darunavir-Cobicistat Prescribing Information.

Darunavir: Mechanism of Action

HIV Protease and Polypeptide Cleavage

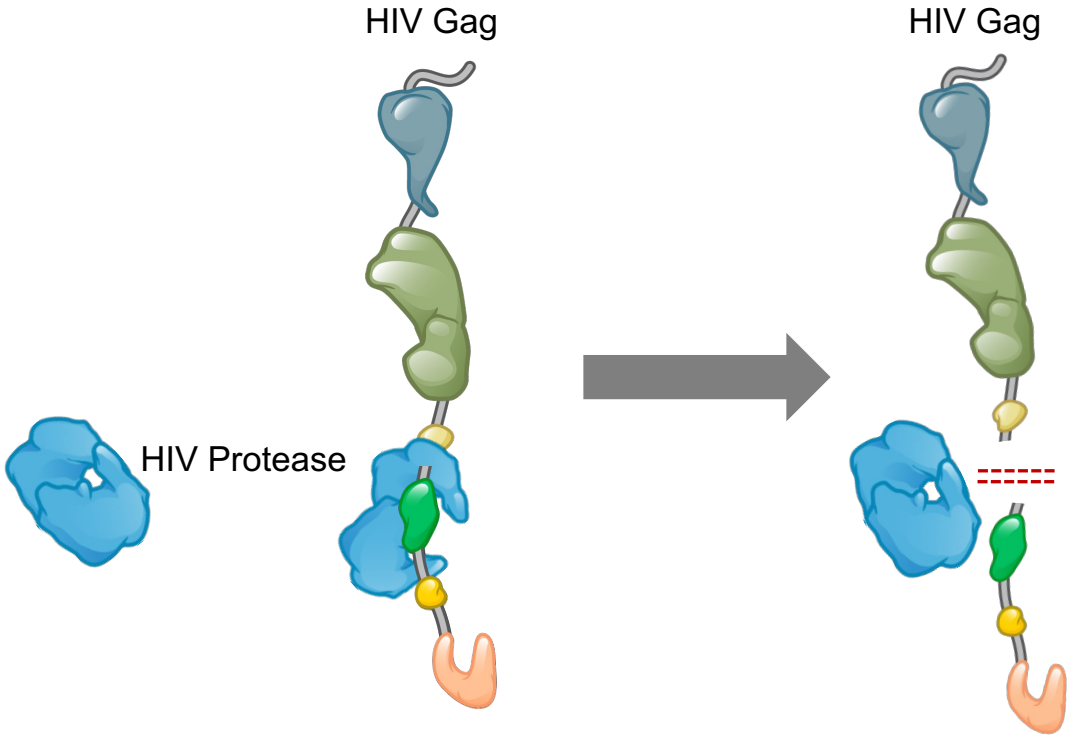

Illustration: *Cognition Studio, Inc.* and David H. Spach, MD

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Protease Inhibitors: Mechanism of Action

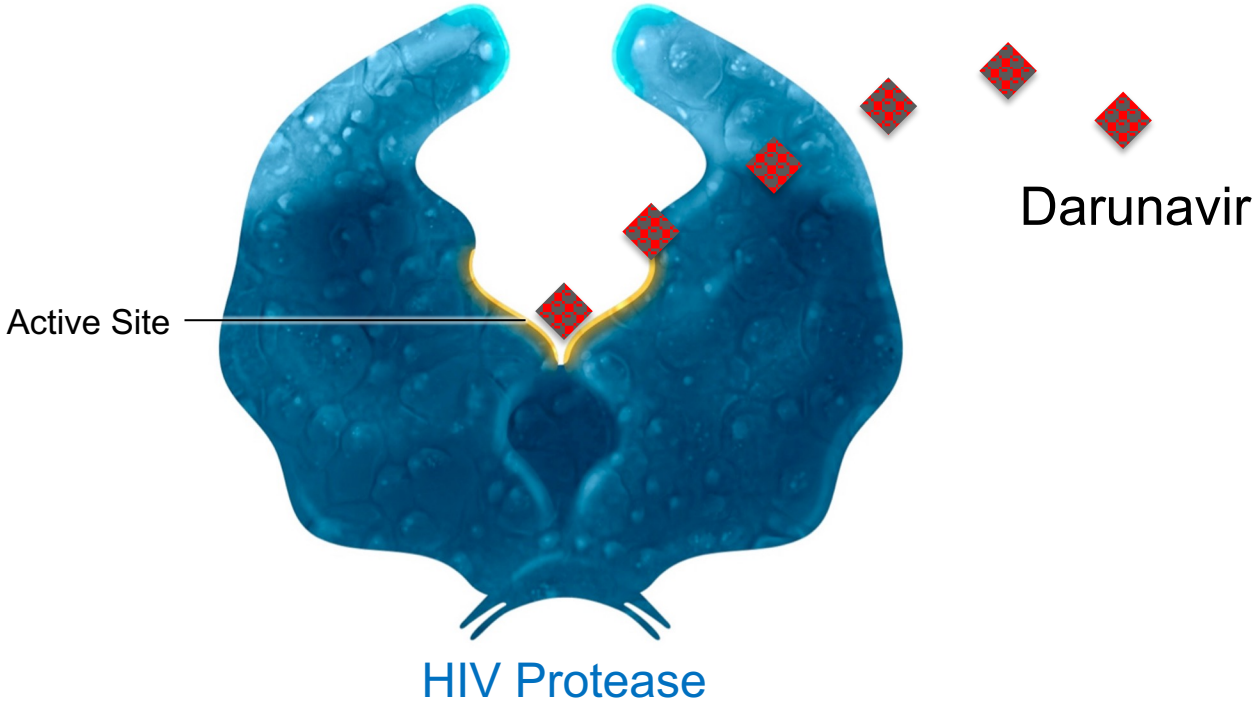


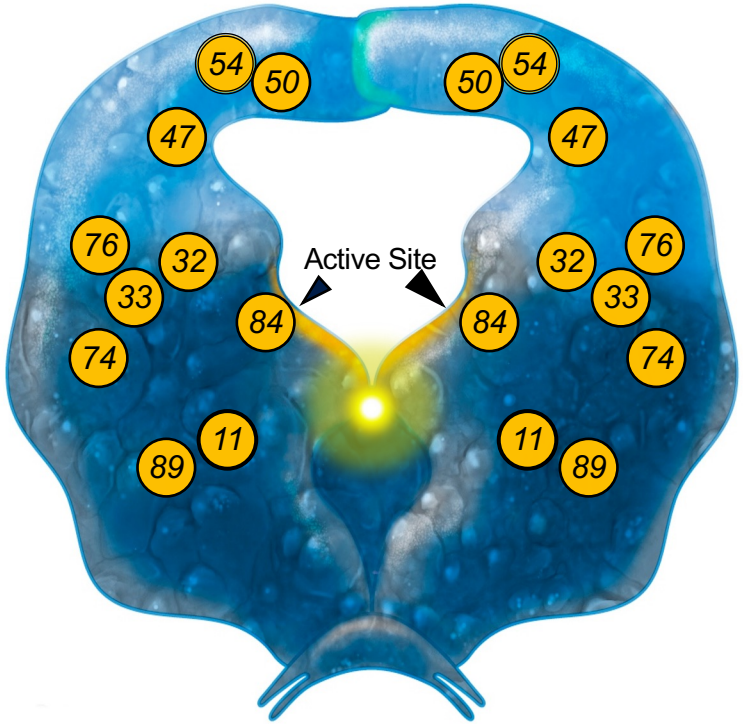
Illustration: *Cognition Studio, Inc.* and David H. Spach, MD

Resistance

HIV Protease and Darunavir Amino Acid Mutations

Darunavir Resistance-Associated Mutations

V11I
V32I
L33F
I47V
I50V
I54L
I54M
T74P
L76V
I84V
L89V



HIV Protease

Illustration: David H. Spach, MD and *Cognition Studio, Inc.*

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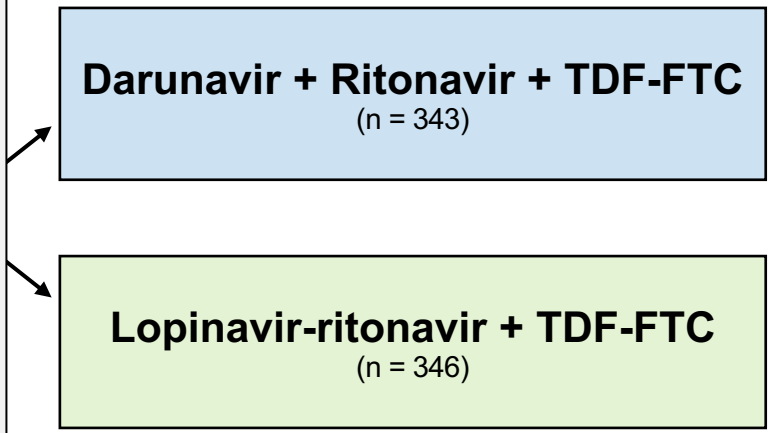
Key Clinical Trials

Once Daily Darunavir/r versus Lopinavir/r in Treatment-Naïve ARTEMIS: Study Design

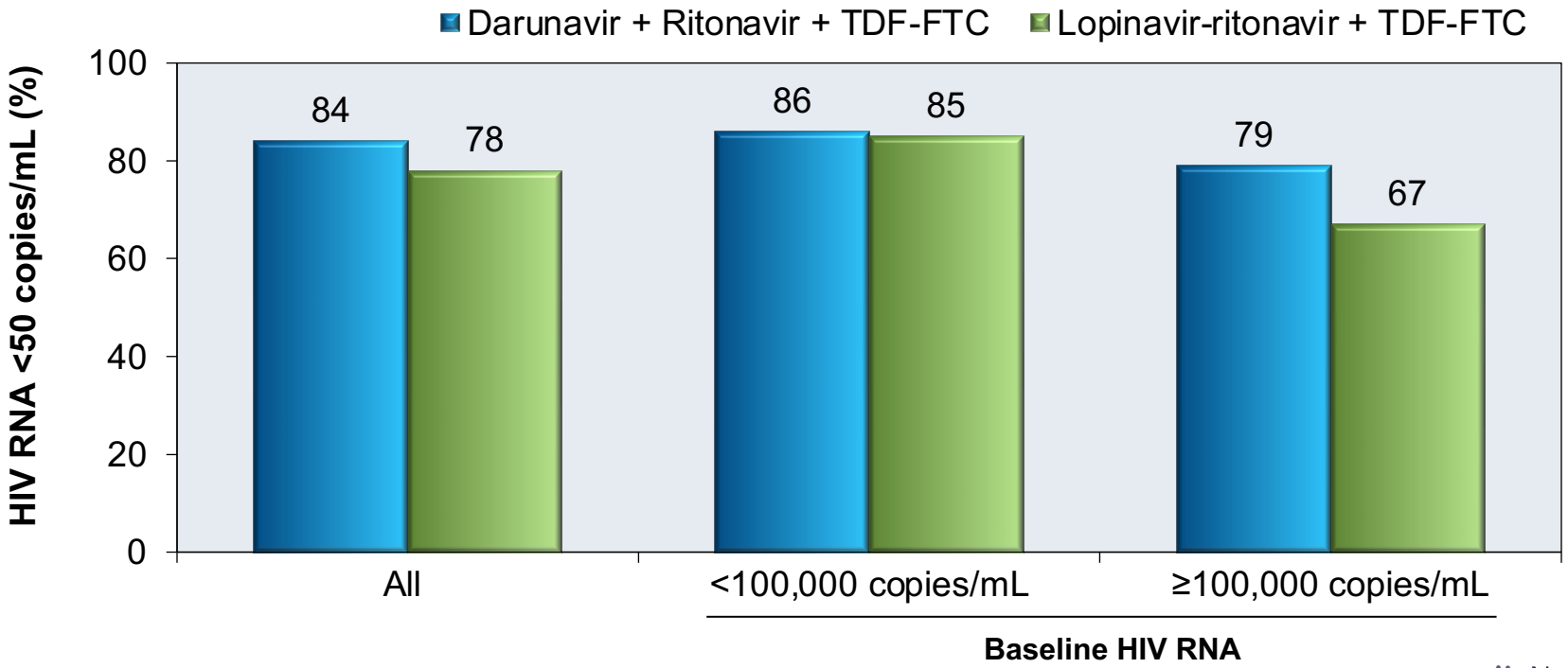
- **Background**: Randomized, open-label phase 3 trial comparing the efficacy and safety of once-daily darunavir + ritonavir with lopinavir-ritonavir in treatment-naïve persons with HIV
- **Inclusion Criteria** (n = 689)
  - Age >18 years
  - Antiretroviral-naïve
  - HIV RNA ≥5000 copies/mL
  - No AIDS-defining illness
- **Treatment Arms**
  - DRV 800 mg QD + RTV 100 mg QD + TDF-FTC
  - LPV/r 800/200 mg QD (or 400 mg bid) + TDF-FTC



Source: Ortiz R, et al. AIDS. 2008;22:189-97.

Once Daily Darunavir/r versus Lopinavir/r in Treatment-Naïve ARTEMIS: Results at 48 Weeks

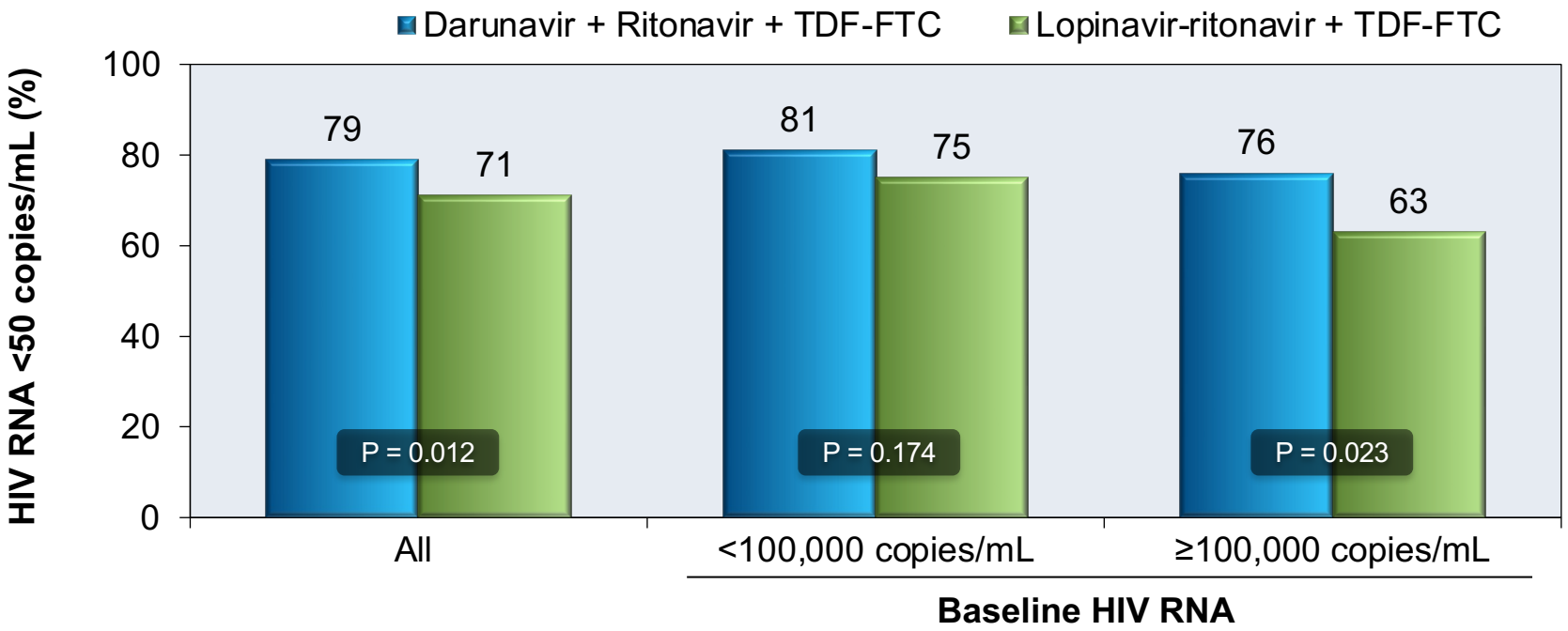
Week 48: Virologic Response (Intent-to-Treat Analysis)



Source: Ortiz R, et al. AIDS. 2008;22:189-97.

Once Daily Darunavir/r versus Lopinavir/r in Treatment-Naïve ARTEMIS: Results at 96 Weeks

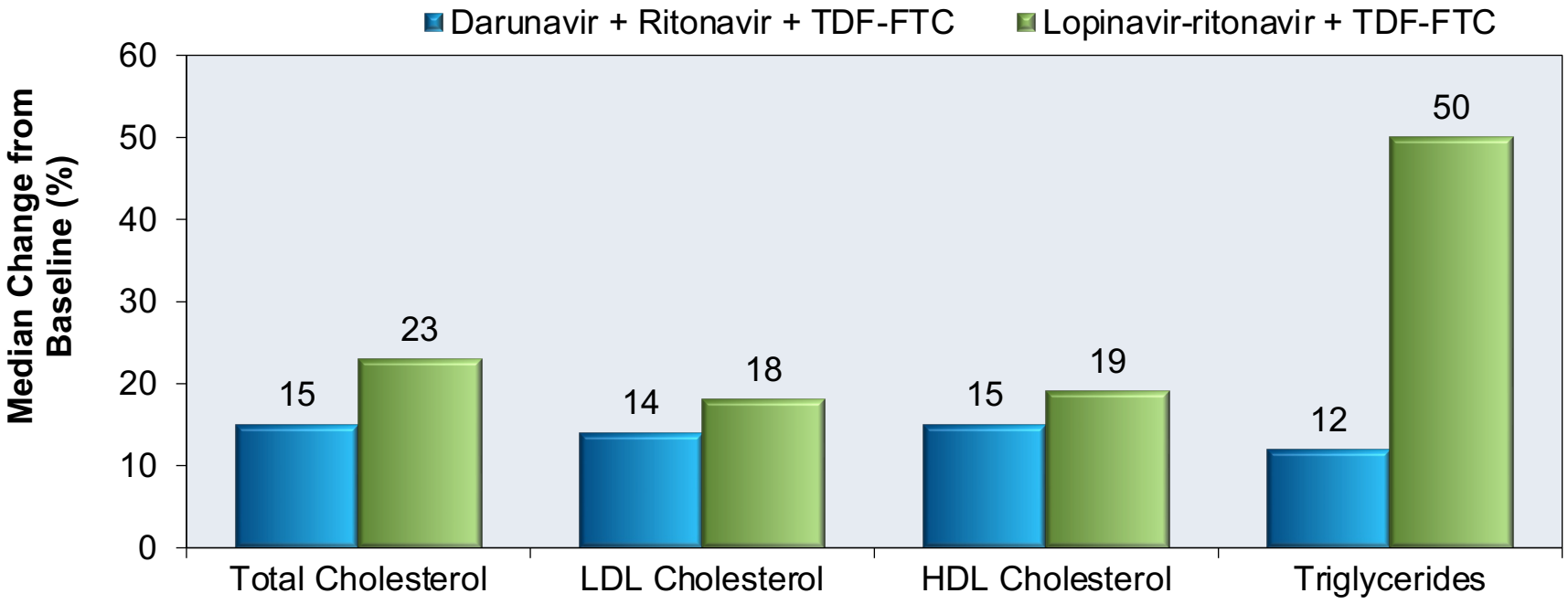
Week 96: Virologic Response (Intent-to-Treat Analysis)



Source: Mills AM, et al. AIDS. 2009;23:1679-88.

Once Daily Darunavir/r versus Lopinavir/r in Treatment-Naïve ARTEMIS: Results at 96 Weeks

Week 96: Analysis of Lipids



Source: Mills AM, et al. AIDS. 2009;23:1679-88.

Boosted Darunavir
Summary of Key Studies

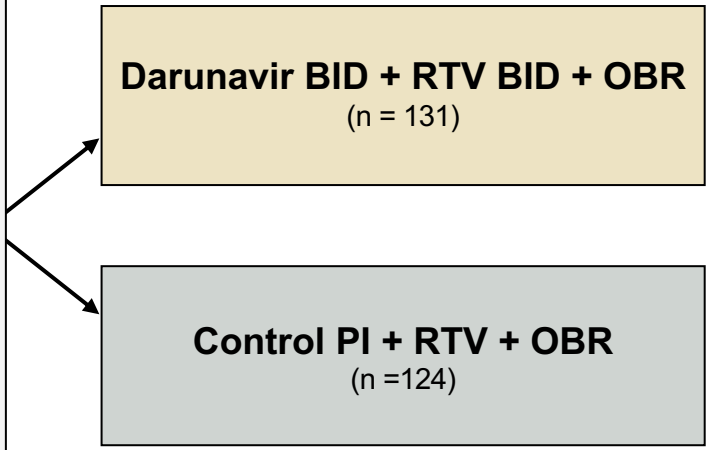
- **Trials in Treatment Naïve Adults**
  - [1,2]ARTEMIS: DRV/r versus LPV/r
    - Once-daily DRV/r was superior in virologic response to LPV/r, with a more favorable safety, gastrointestinal and lipid profile, in antiretroviral-naive patients

Efficacy of Darunavir-cobicistat is based on clinical trials establishing the efficacy of using DRV/r once daily in treatment naïve individuals

1Ortiz R, et al. AIDS. 2008;22:189-97.
2Mills AM, et al. AIDS. 2009;23:1679-88

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Study Design

- **Background**: Two randomized, phase 2b trials to compare the efficacy and safety of ritonavir-boosted darunavir with other protease inhibitors in treatment-experienced adults with HIV and PI resistance
- **Inclusion Criteria (n = 155)**
  - Age ≥18 years
  - HIV RNA >1000 copies/mL
  - On PI-containing regimen
  - Took>1 NRTI, and ≥1 NNRTI as part of failing regimen
  - At least 1 primary PI mutation at screening
- **Treatment Arms**
  - Darunavir 600 mg BID + Ritonavir 100 mg bid + OBR*
  - Investigator-selected control PI + OBR*

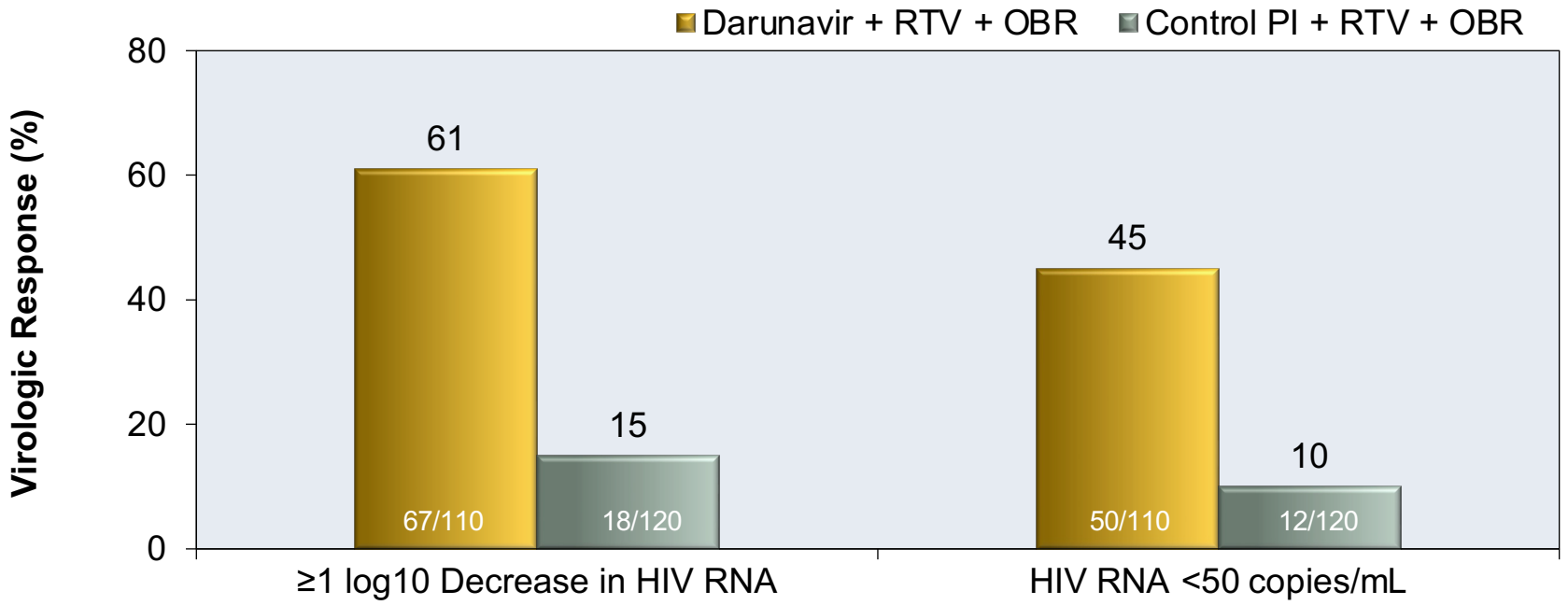


*OBR = Optimized background regimen: ≥2 NRTIs +/- enfuvirtide

Source: Clotet B, et al. Lancet. 2007;369:1169-78.

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Result

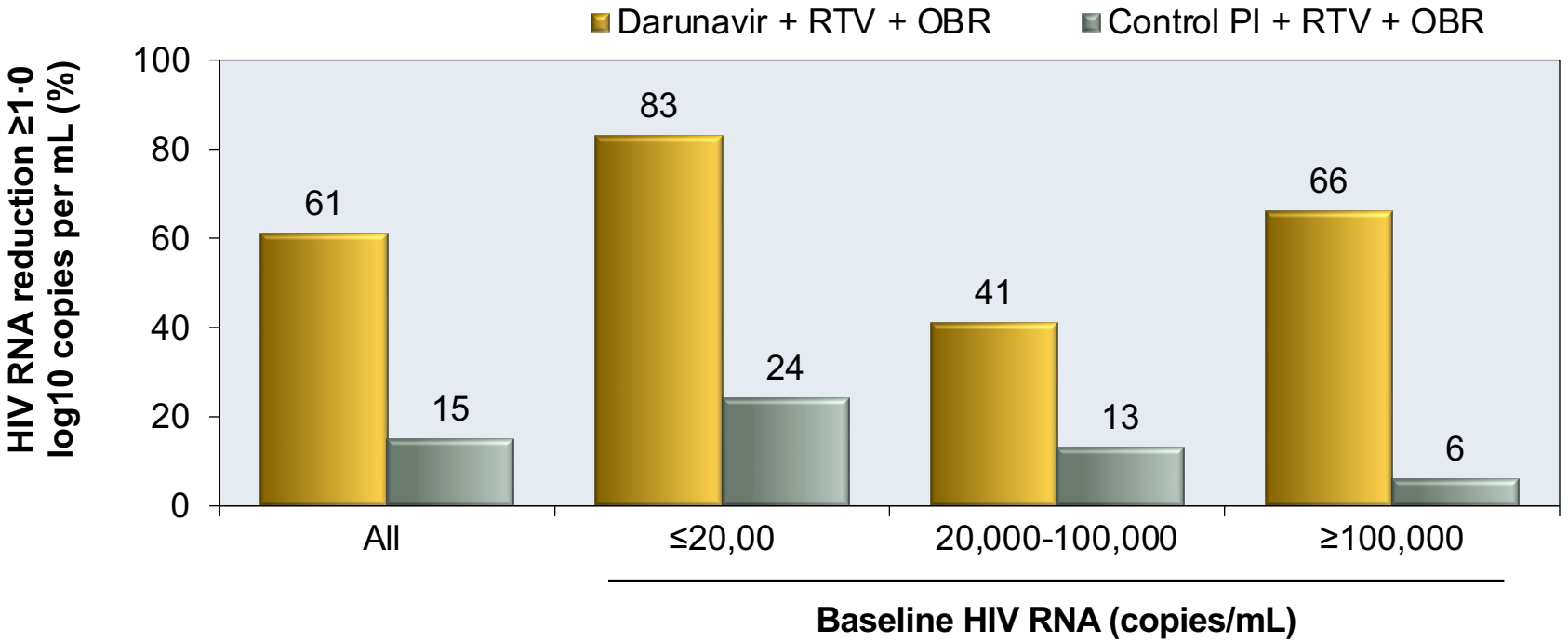
Week 48: Virologic Response



Source: Clotet B, et al. Lancet. 2007;369:1169-78.

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Result

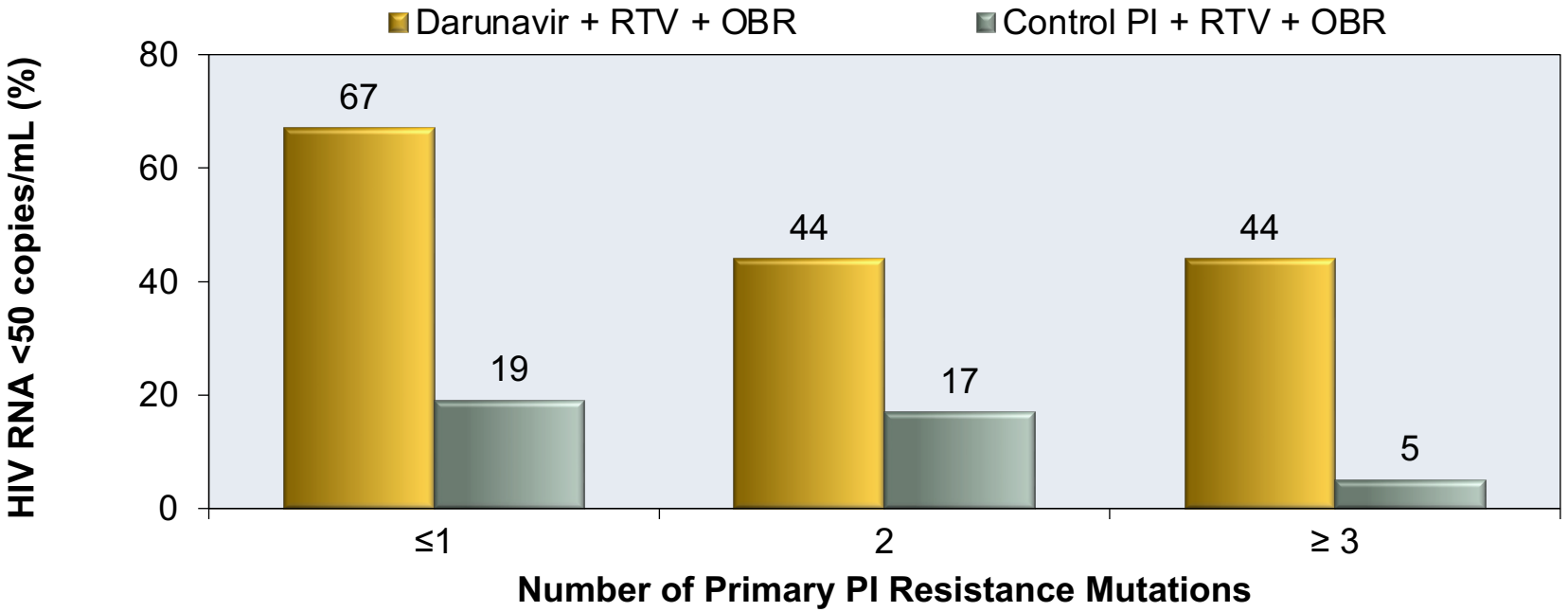
Week 48: Virologic Response (ITT-TLOVR)



Source: Clotet B, et al. Lancet. 2007;369:1169-78.

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Result

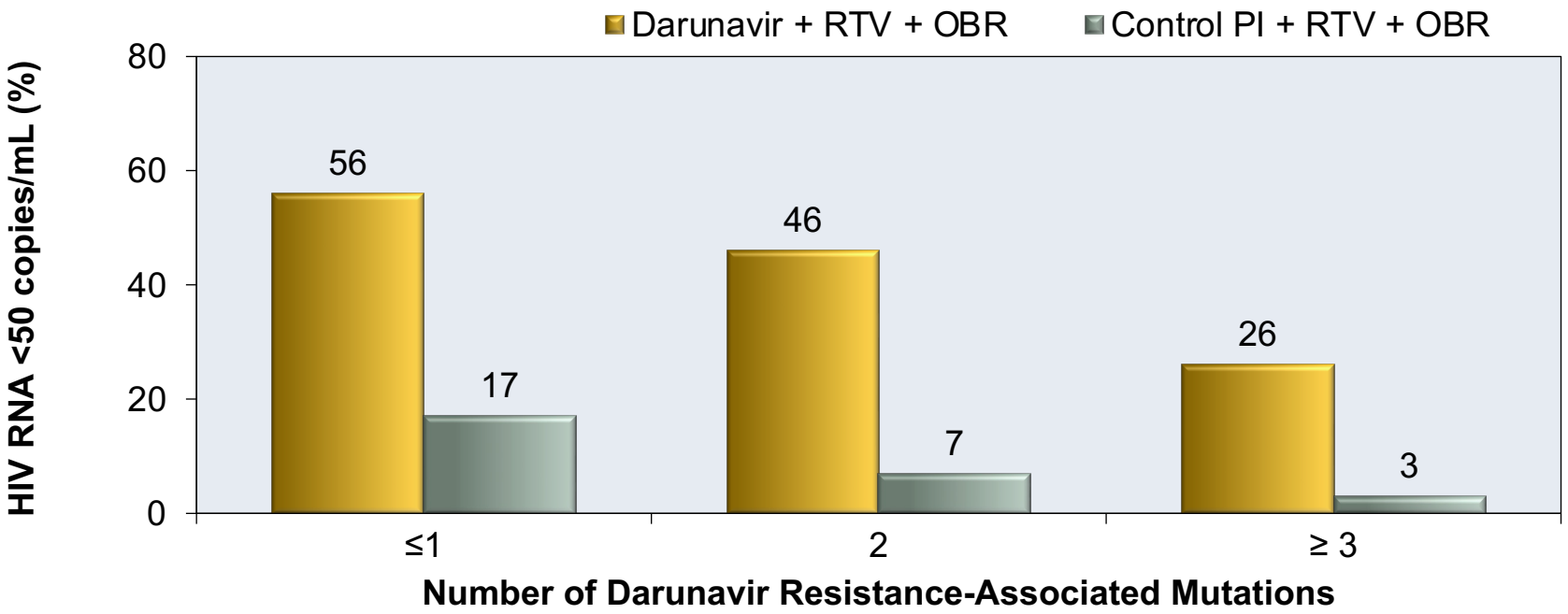
Week 48: Virologic Response, by Primary PI Mutations at Baseline



Source: Clotet B, et al. Lancet. 2007;369:1169-78.

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Result

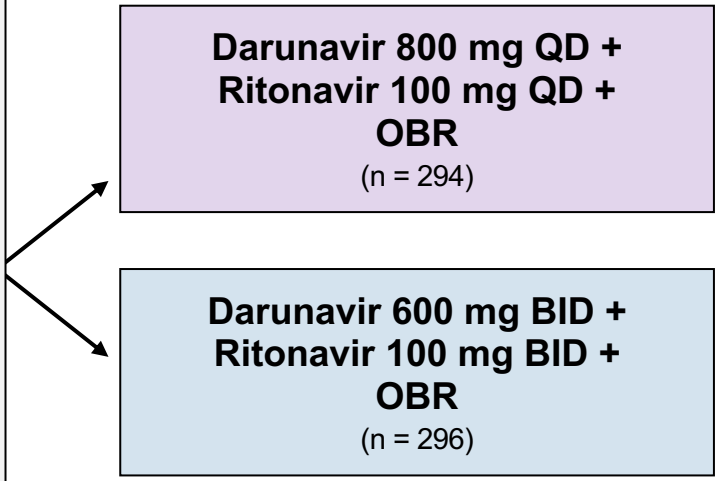
Week 48: Virologic Response, by DRV Resistance-Associated Mutations at Baseline



Source: Clotet B, et al. Lancet. 2007;369:1169-78.

Once-daily versus Twice-daily Darunavir in Treatment-Experienced ODIN: Study Design

- **Background**: Randomized, open-label phase 3 trial to compare once daily versus twice-daily dosing of ritonavir-boosted darunavir in treatment-experienced patients with HIV
- **Inclusion Criteria (n = 590)**
  - Age ≥18 years
  - On stable antiretroviral regimen for >12 weeks
  - HIV RNA >1000 copies/mL
  - CD4 count >200 cells/mm^3
  - No darunavir resistance-associated mutations
- **Treatment Arms**
  - Darunavir 800 mg QD + RTV 100 mg QD + OBR*
  - Darunavir 600 mg BID + RTV 100 mg BID + OBR

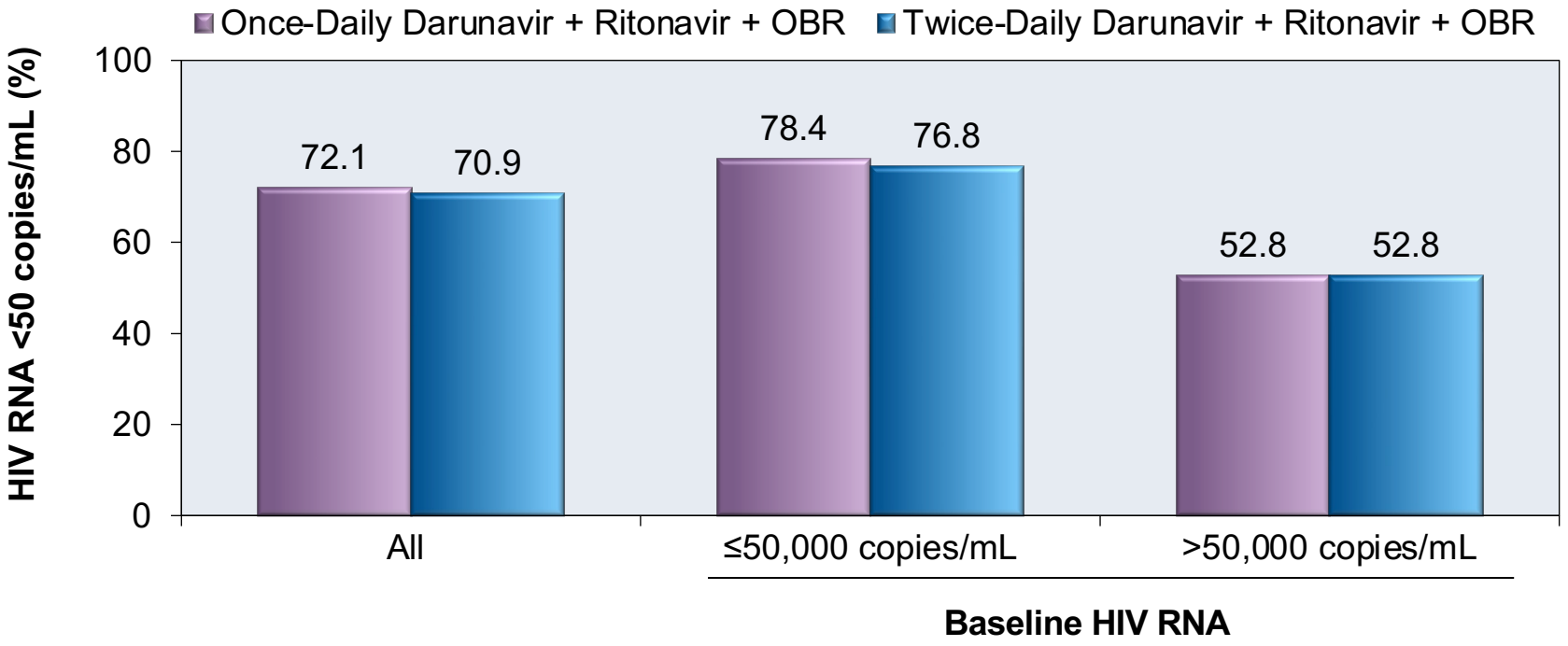


ODIN = Once-daily **D**arunavir **I**n treatment-experie**N**ced
*OBR = Optimized background regimen: ≥2 nucleoside reverse transcriptase inhibitors, investigator-selected

Source: Cahn P, et al. AIDS. 2011;25:929-39.

Once Daily versus Twice Daily Darunavir in ARV-Experienced ODIN: Result

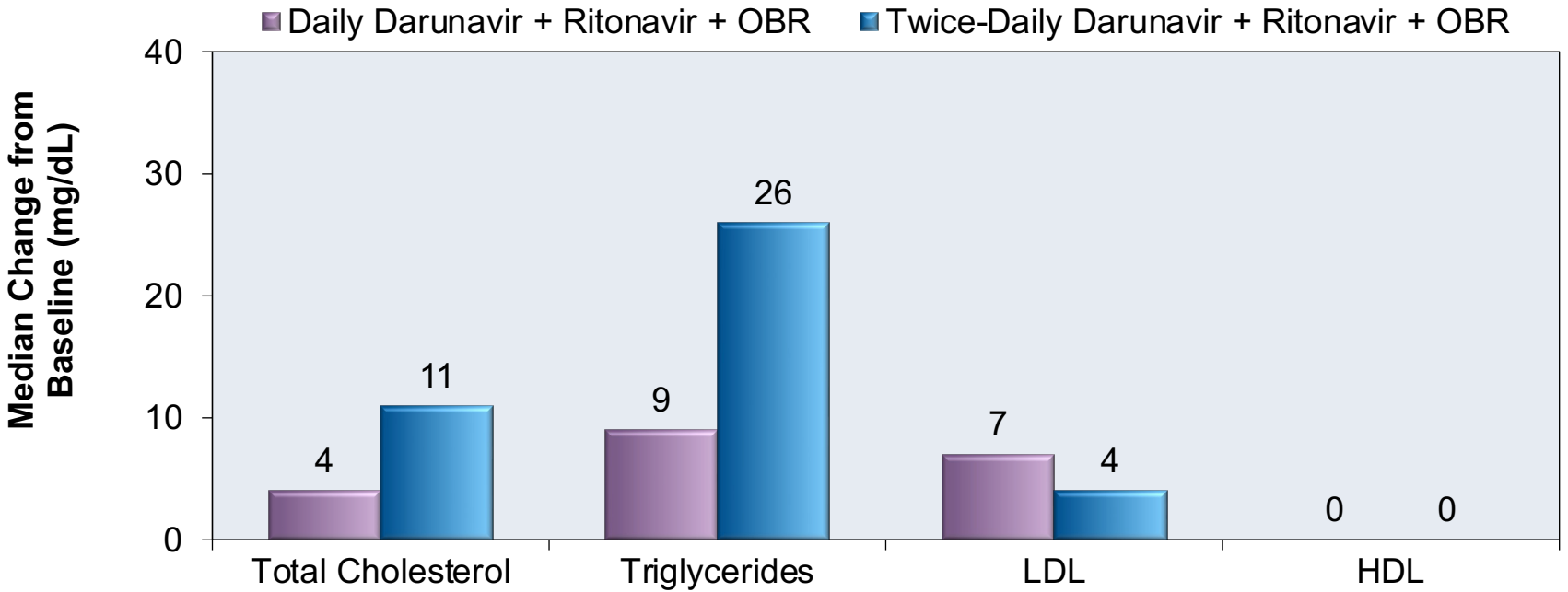
Week 48: Virologic Response (ITT-TLOVR)



Source: Cahn P, et al. AIDS. 2011;25:929-39.

Once-Daily versus Twice Daily Darunavir in ARV-Experienced
ODIN: Result (Impact on Lipids)

Week 48: Changes in Lipids from Baseline



Source: Cahn P, et al. AIDS. 2011;25:929-39.

Once Daily versus Twice Daily Darunavir in ARV-Experienced ODIN: Result

Adverse Events Possibly Related to Darunavir + Ritonavir (≥ 2% incidence in either arm)		
Symptom	**DRV + RTV + Once Daily + OBR** (n = 294)	**DRV + RTV + Twice Daily + OBR** (n = 296)
Nausea	10.9%	10.5%
Vomiting	9.9%	15.2%
Diarrhea	3.1%	5.4%
Rash	2.7%	2.7%
Headache	1.4%	2.0%

Source: Cahn P, et al. AIDS. 2011;25:929-39.

Boosted Darunavir: Summary of Key Studies

- **Trials in Treatment Naïve Adults**
  - [1,2]ARTEMIS: DRV/r versus LPV/r
    - Once-daily DRV/r was superior in virologic response to LPV/r, with a more favorable safety, gastrointestinal and lipid profile, in antiretroviral-naive patients
- **Trials In Treatment Experienced Adults with PI resistance**
  - [3]POWER 1 and 2: Switch to DRV-COBI-TAF-FTC or stay on PI + TDF-FTC
    - Using DRV/r 600/100 mg twice daily with OBR, had more effective virologic response plus favorable safety and tolerability, up to week 48, in treatment-experienced patients
  - [4]ODIN: Switch to DRV-COBI-TAF-FTC or stay on PI + TDF-FTC
    - Once-daily DRV/r 800/100 mg was non-inferior in virologic response to twice-daily DRV/r 600/100 mg at 48 weeks in treatment-experienced patients with no DRV RAMs

Source:
[1] Ortiz R, et al. AIDS. 2008;22:189-97.
[2] Mills AM, et al. AIDS. 2009;23:1679-88.
[3] Clotet B, et al. Lancet. 2007;369:1169-78.
[4] Cahn P, et al. AIDS. 2011;25:929-39.

Boosted Darunavir: Adverse Effects

- **Gastrointestinal**
  - Diarrhea and nausea
- **Hepatotoxicity**
  - Risk increased with pre-existing liver dysfunction, including chronic HBV or HCV
- **Skin Reactions**
  - Darunavir contains a sulfonamide moiety
  - Rash in approximately 8%
  - Stevens-Johnson syndrome in 0.1% of persons taking darunavir with cobicistat
- **Prior Sulfonamide Allergy**
  - Incidence and severity of rash similar with or without a history of sulfonamide allergy
  - History of sulfonamide allergy not a contraindication but monitoring recommended

Boosted Darunavir: Editor's Summary

- Oral PI available to be given with ritonavir or, in a fixed dose combination with cobicistat
- High genetic barrier to resistance
- DRV/c should not be used in patients with severe renal or severe hepatic impairment, but DRV/r remains an option
- Mostly associated with gastrointestinal adverse effects, such as diarrhea and nausea
- As an inhibitor of CYP3A, Cobicistat and Ritonavir can cause problematic interactions with drugs metabolized by CYP3A or drugs that induce or inhibit CYP3A

Acknowledgments

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AETC AIDS Education & Training Center Program

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