NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Integrase Strand Transfer Inhibitors on the Horizon

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Investigational

Integrase Strand Transfer Inhibitors (ISTIs) on the Horizon

1. Elvitegravir and “Quad Pill”
2. Dolutegravir and “572-Trii”

Investigational

Antiretroviral Therapy: Investigational

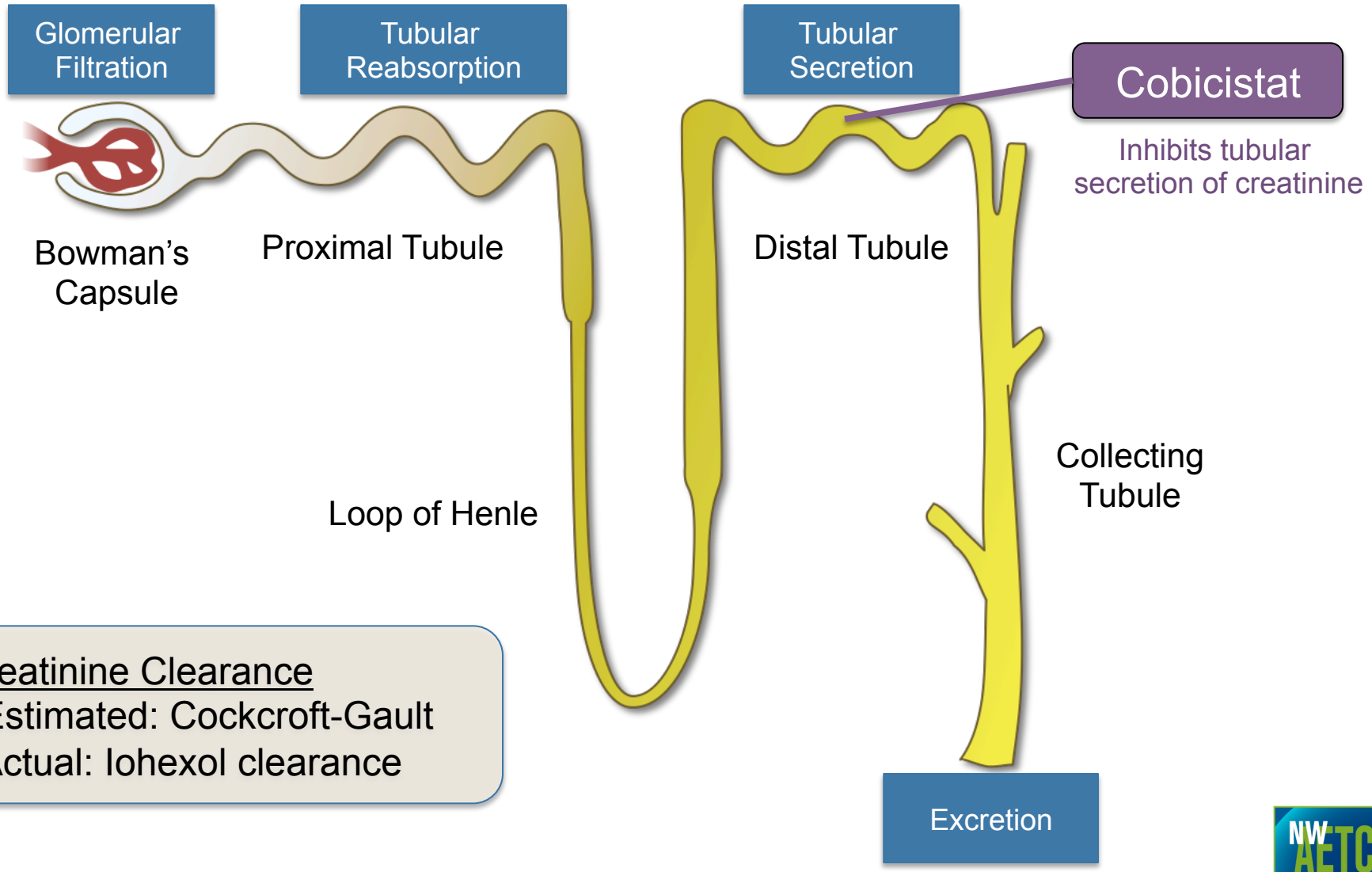
Elvitegravir

Investigational

Elvitegravir, formerly GS-9137

- **Class**: integrase strand transfer inhibitor
- **Approval Status**: Filed for NDA October 2011
- **Dose (Requires Boosting)**
  - Standard Dosing: 150 mg once daily with food
  - With Atazanavir + Ritonavir or Lopinavir-Ritonavir: 85 mg once daily
- **Fixed Dose "Quad Pill"**: Elvitegravir-Cobicistat-Tenofovir-Emtricitabine
- **Metabolism**: via cytochrome P450 (CYP) 3A4
- **Pregnancy**: category unknown
- **Adverse Events**:
  - Well tolerated
  - Cobicistat decreases estimated Creatinine clearance

Urine Formation



Creatinine Clearance
- Estimated: Cockcroft-Gault
- Actual: Iohexol clearance

Investigational

Summary of Key Elvitegravir Studies

- Phase 3 Trials in Treatment Naïve
  - Study 102: “Quad Pill” versus EFV-TDF-FTC (*Atripla*)
- Phase 3 Trial: Treatment Naive
  - Study 103: “Quad Pill” versus RTV + ATZ +TDF-FTC
- Phase 3 Trials in Treatment Experienced
  - Study 145: Elvitegravir versus Raltegravir

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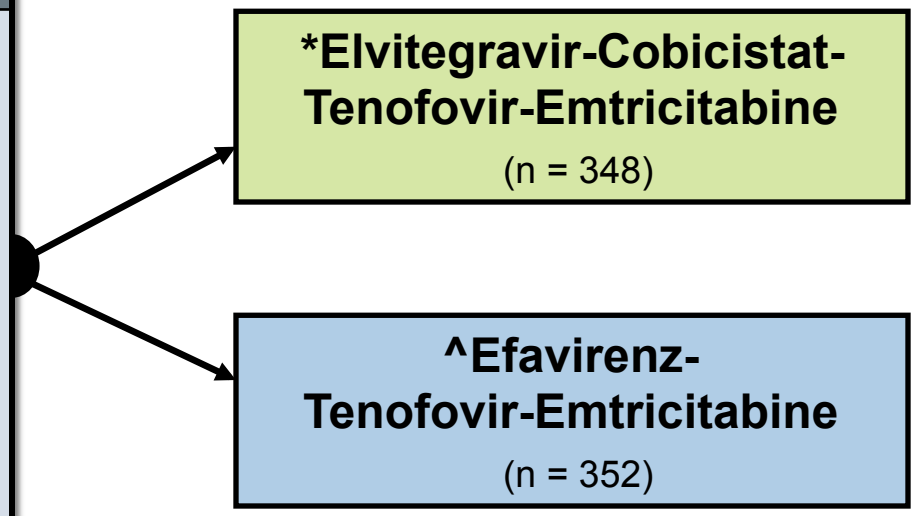
Elvitegravir-Cobicistat-TDF-FTC versus Efavirenz-TDF-FTC
Study 102: Design

Study Design

Protocol
- N = 700
- Randomized, Double-blind
- Phase 3 trial at 130 study sites
- Conducted in U.S. and Puerto Rico
- Age ≥ 18
- Antiretroviral naive
- No baseline NRTI, NNRTI mutations
- HIV RNA ≥ 5,000 copies/ml
- No AIDS condition in previous 30 days



*Dosing: Elvitegravir (150 mg); Cobicistat (150 mg); Tenofovir (300 mg); Emtricitabine (200mg)

^Dosing: Efavirenz (600 mg); Tenofovir (300 mg); Emtricitabine (200mg)

Source: Gilead Sciences Press Release, August 15, 2011.

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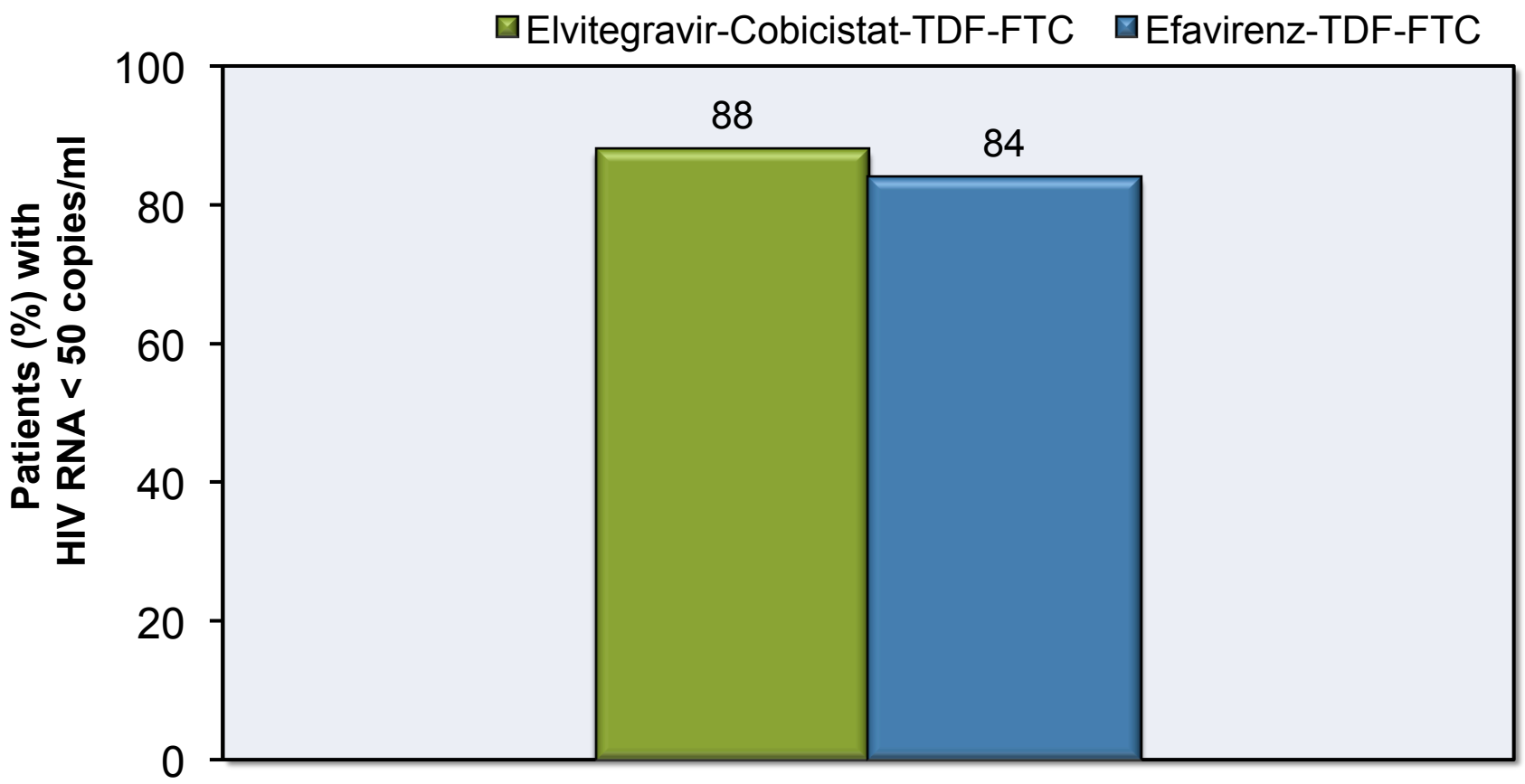
Elvitegravir-Cobicistat-TDF-FTC versus Efavirenz-TDF-FTC
Study 102: Week 48 Results

Week 48: Virologic Response (ITT-TLOVR*)



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

Source: Gilead Sciences Press Release, August 15, 2011.

Investigational

Elvitegravir-Cobicistat-TDF-FTC versus + RTV + ATZ + TDF-FTC
Study 103: Design

Study Design

Protocol

- N = 708
- Double-blind, randomized, phase 3 trial
- Age ≥ 18
- Antiretroviral naive
- No baseline NRTI, NNRTI, or PI mutations
- HIV RNA ≥ 5,000 copies/ml
- CD4 > 50 cells/mm^3
- No AIDS condition in previous 30 days

***Elvitegravir-Cobicistat-Tenofovir-Emtricitabine**
(n = 353)

^Ritonavir + Atazanavir Tenofovir-Emtricitabine
(n = 355)

*Dosing (QD): Elvitegravir (150 mg); Cobicistat (150 mg); Tenofovir (300 mg); Emtricitabine (200mg)

^Dosing (QD): Ritonavir (100 mg); Atazanavir (300 mg); Tenofovir (300 mg); Emtricitabine (200mg)

Source: Gilead Sciences Press Release, September 19, 2011.

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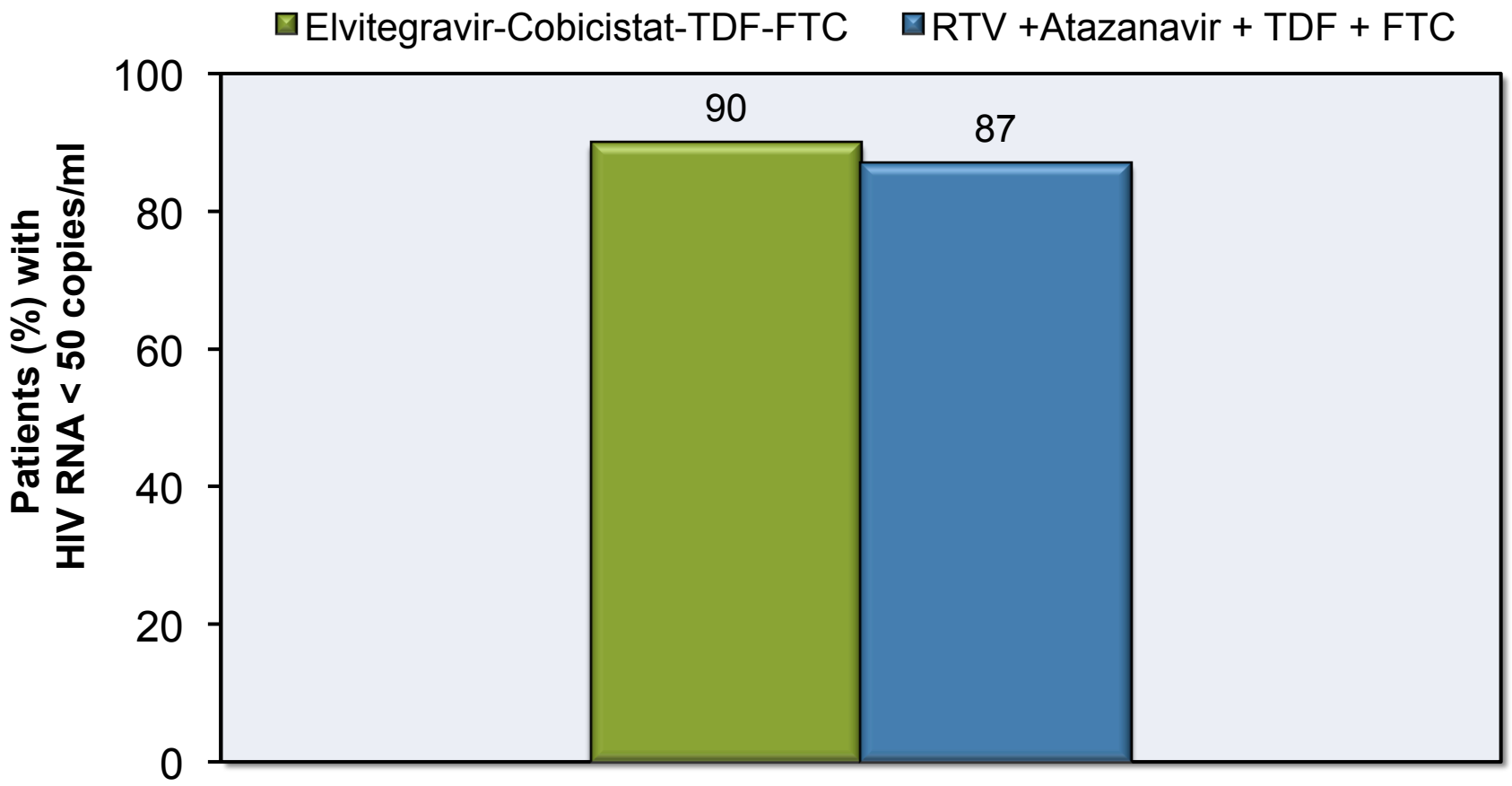
Elvitegravir-Cobicistat-TDF-FTC versus + RTV + ATZ + TDF-FTC
Study 103: Week 48 Results

Week 48: Virologic Response (ITT-TLOVR*)



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

Source: Gilead Sciences Press Release, September 19, 2011.

Investigational

Elvitegravir versus Raltegravir in Treatment Experienced
Study 145: Design

Study Design

Protocol

- N = 702
- Double-blind, double-dummy, randomized
- Phase 3 trial, 96 weeks
- Treatment-experienced patients
- Age ≥ 18
- Resistance to at least 2 classes
- Stable regimen for at least 30 days
- HIV RNA ≥ 1,000 copies/ml
- No AIDS condition in previous 30 days

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

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

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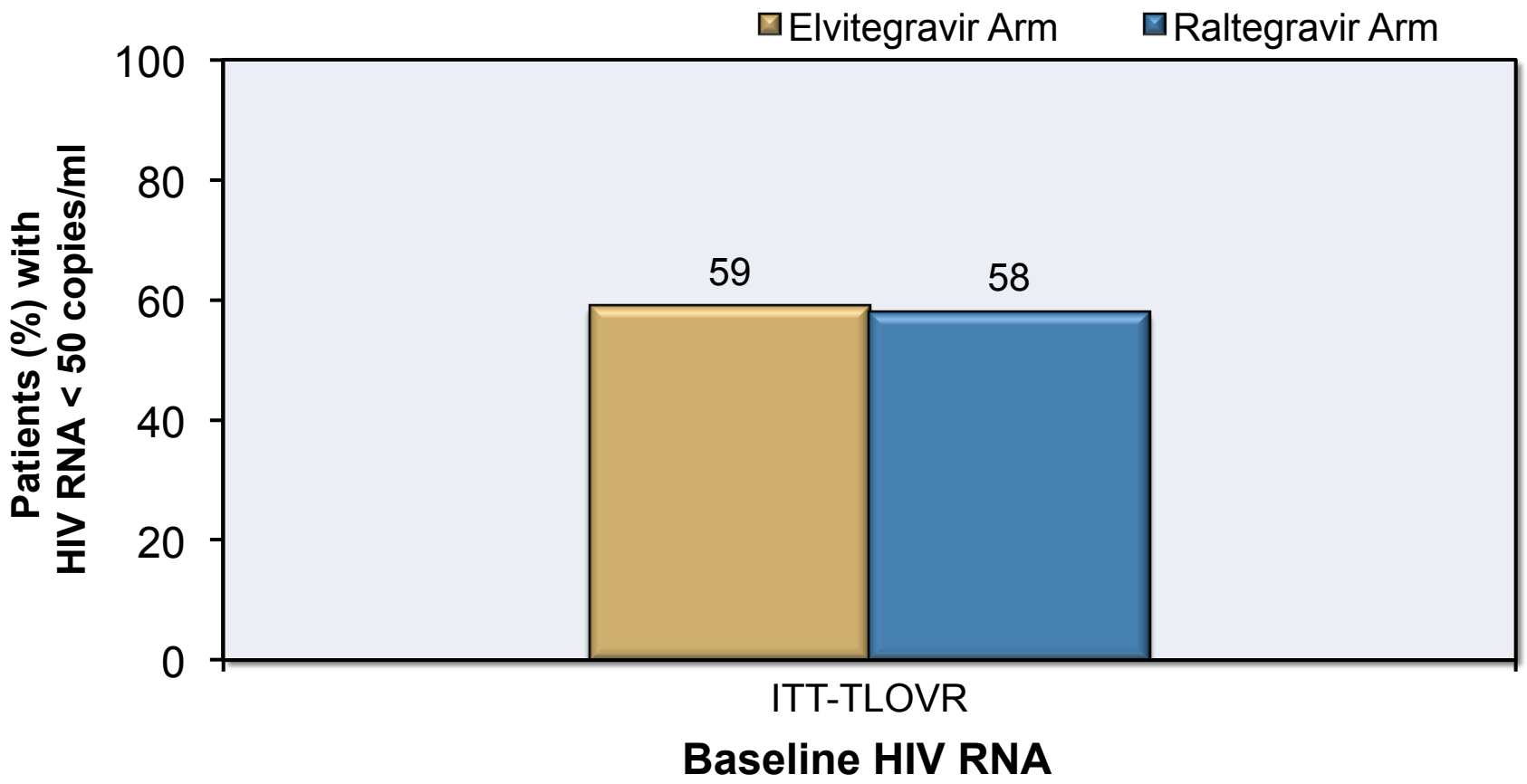
Elvitegravir versus Raltegravir in Treatment Experienced
Study 145: Week 48 Results

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.

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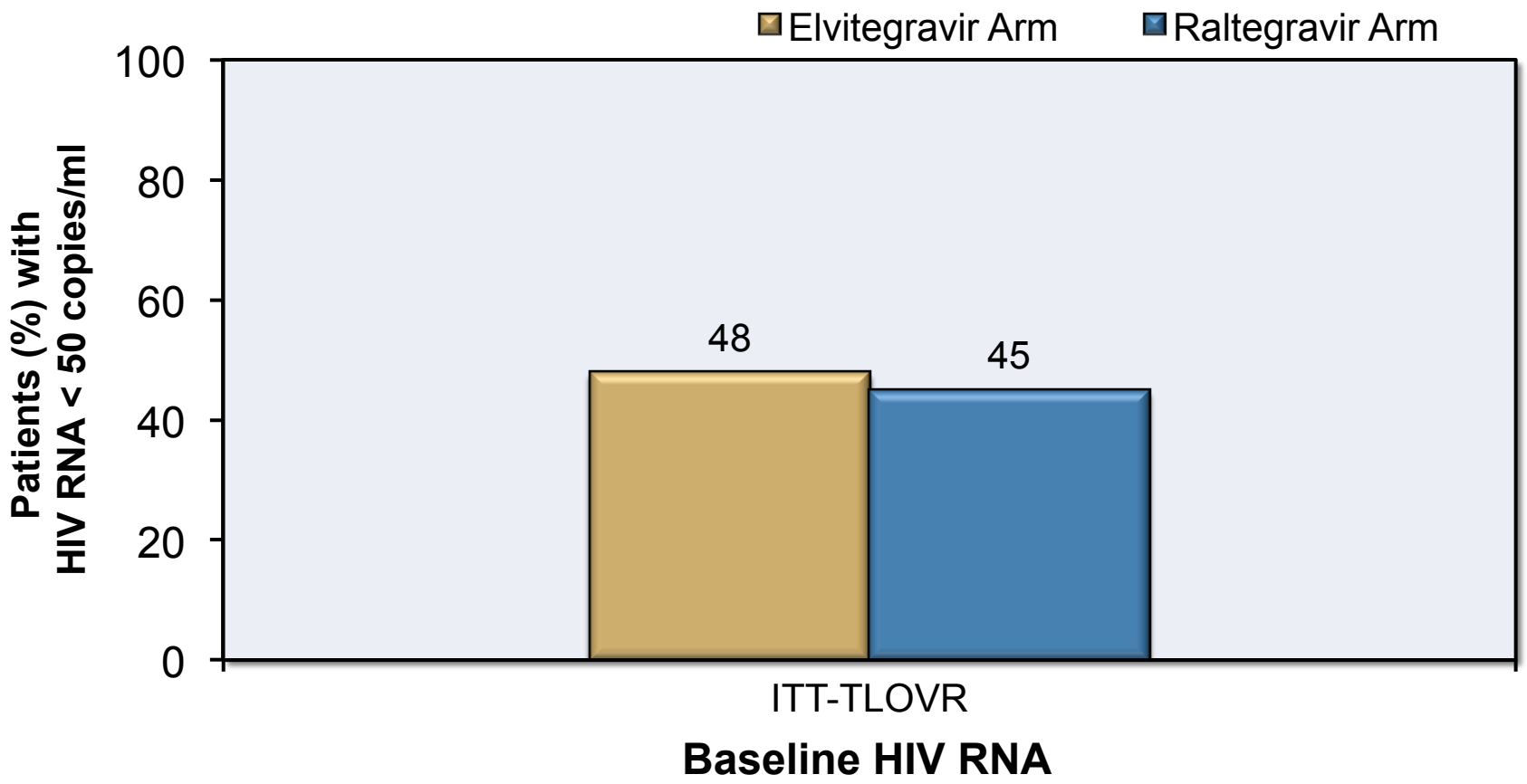
Elvitegravir versus Raltegravir in Treatment Experienced
Study 145: Week 96 Results

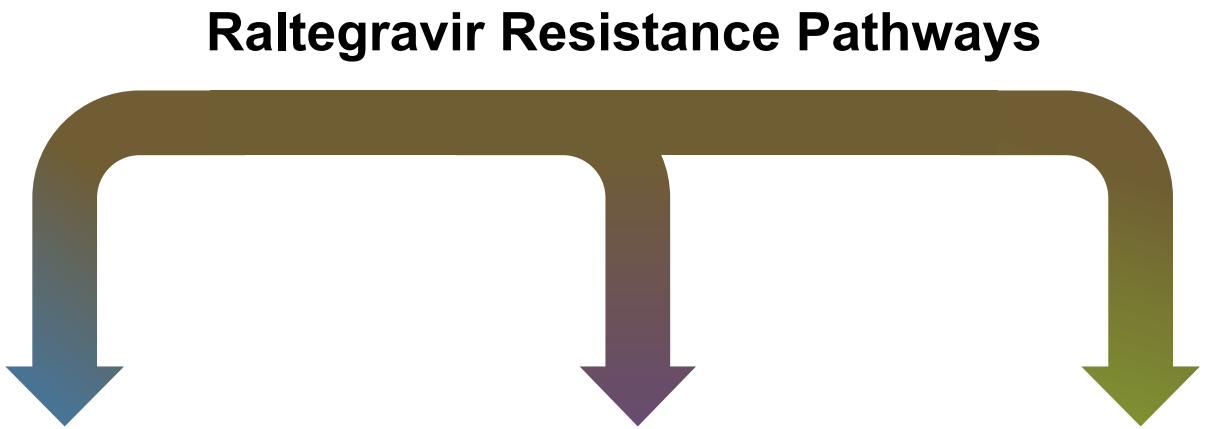
Week 96: Virologic Response (ITT-TLOVR*)



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

Source: Gilead Sciences Press Release, December 9, 2011.

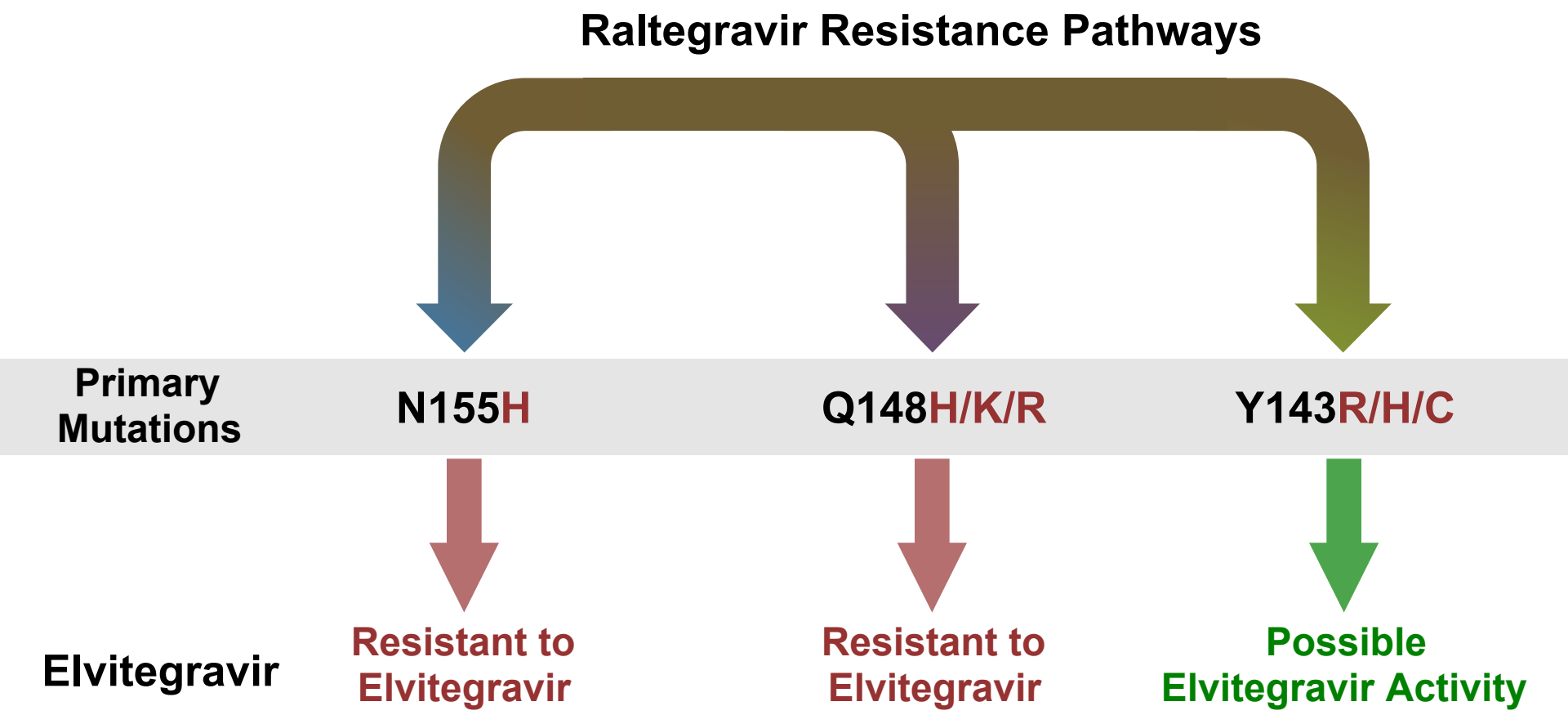
Raltegravir and Elvitegravir Cross Resistance



Source: Metifiot M, et al. Viruses. 2010;2:1347-66.

Investigational

Raltegravir and Elvitegravir Cross Resistance

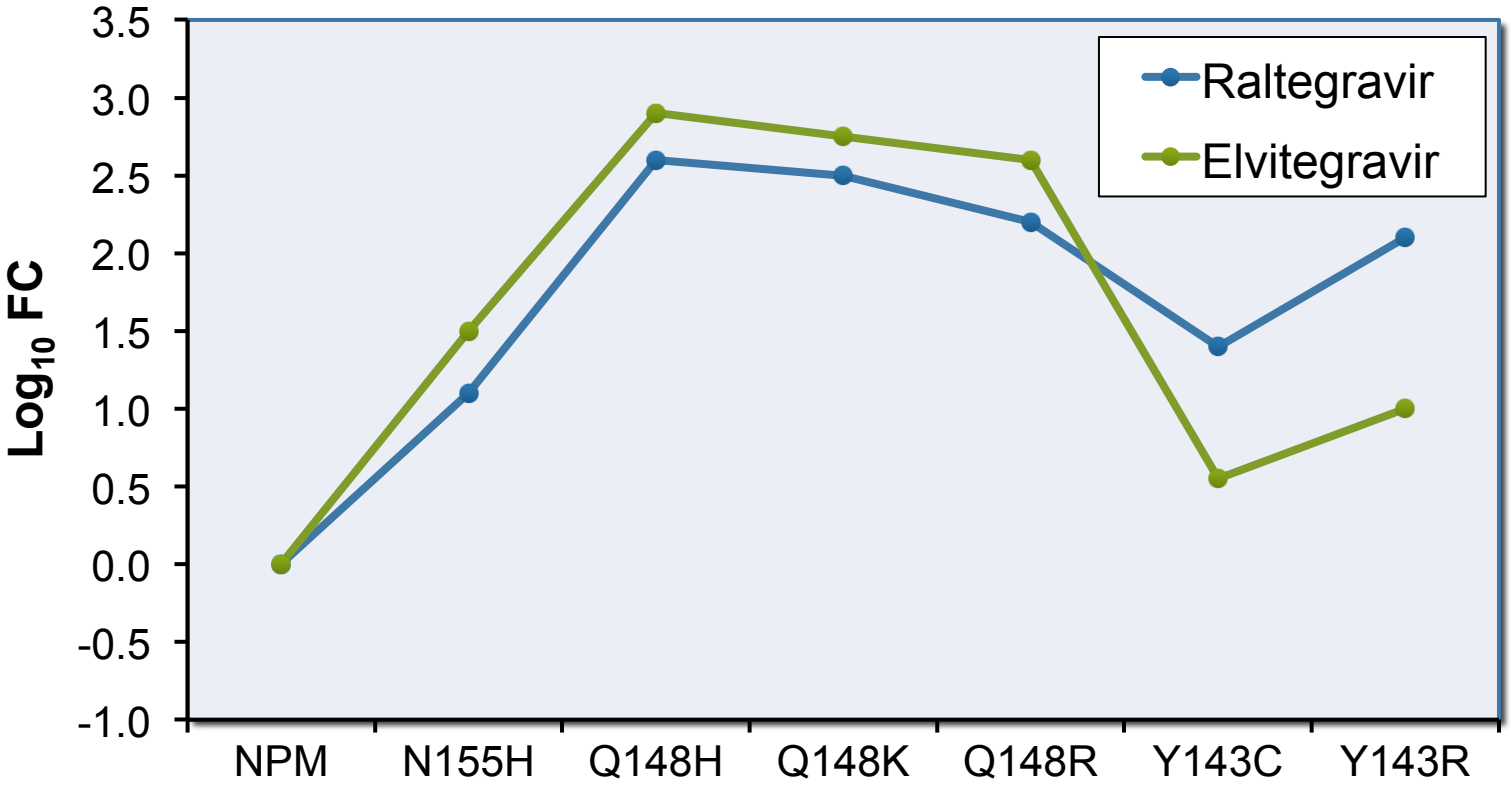


Source: Metifiot M, et al. Viruses. 2010;2:1347-66.

Investigational

Raltegravir and Elvitegravir: Cross Resistance

Graphical Representation of Mean log10 Fold Change Values for Different Genotype



NPM = no primary mutation

Source: Van Wesenbeeck L, et al. Antimicrob Agents Chemother. 2011;55:321-5.

Investigational

Elvitegravir
Summary Points

- **Pros**
  - Efficacy similar to efavirenz and raltegravir
  - Attractive once daily dosing
  - Fixed-dosed “Quad Pill” regimen: one pill once a day
  - Well tolerated

- **Cons**
  - Requires boosting (with cobicistat or ritonavir)
  - High cross-resistance with raltegravir
  - Requires taking with food

- **Clinical Use**
  - Attractive first line agent as fixed drug combination pill
  - Not likely used in patients with raltegravir resistance

Investigational

Antiretroviral Therapy: Investigational

Dolutegravir

Investigational

Dolutegravir, formerly S/GSK-572

- **Class**: integrase strand transfer inhibitor
- **Approval Staus**: Not FDA Approved; in Phase 3 Trials
- **Dose (with or without food)**:
  - Treatment Naive: 50 mg once daily
  - Treatment Experienced, ISTI-Naive: 50 mg once daily
  - ISTI Resistant: 50 mg twice daily
- **Fixed Dose Combination**: Abacavir-Lamivudine-Dolutegravir (*572-Trii*)
- **Pregnancy**: category unknown
- **Adverse Events**:
  - Small increases in serum creatinine (inhibition of creatinine secretion)

Investigational

Dolutegravir: Summary of Key Studies

- Phase 2b Trial in Treatment Naïve
  - SPRING-1: Dose-ranging Dolutegravir versus Efavirenz
- Phase 2b Trials in Treatment Experienced
  - VIKING I: Dolutegravir 50 mg QD added to failing regimen
  - VIKING II: Dolutegravir 50 mg BID added to failing regimen

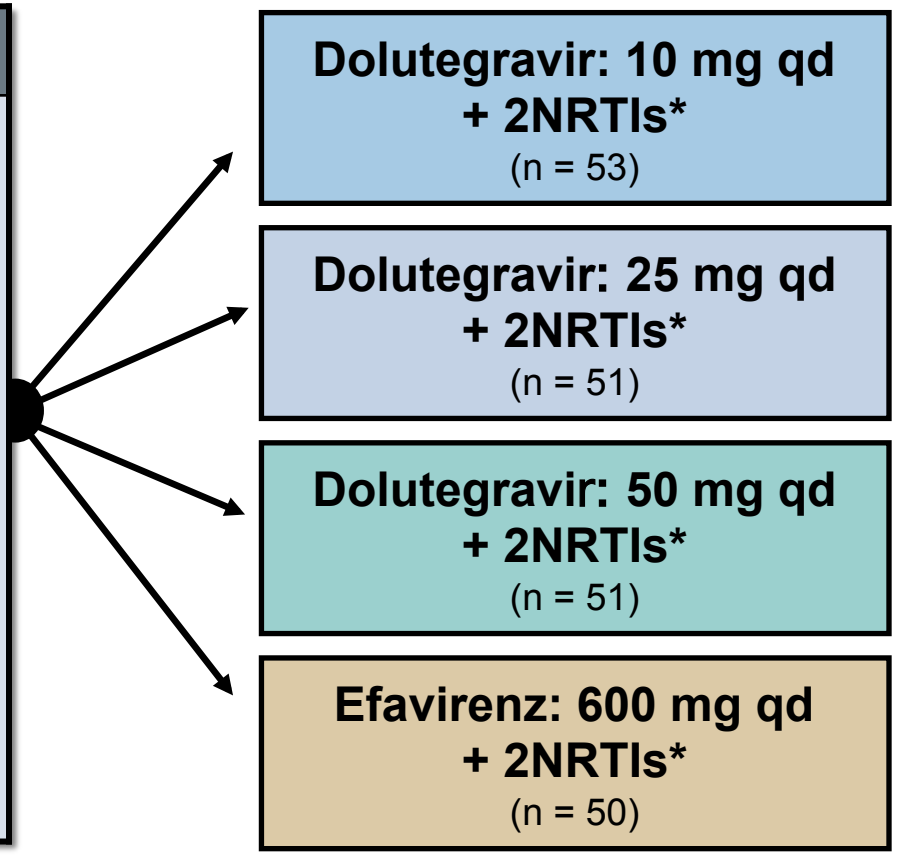
Investigational

Dolutegravir ("572") vs. Efavirenz in ARV-Naive
SPRING-1: Study Design

Study Design

Protocol

- N = 205
- Dose ranging, partially-blinded
- Multicenter, phase 2b trial
- Antiretroviral therapy-naïve
- Age ≥ 18
- HIV RNA > 1,000 copies/ml
- CD4 > 200 cells/mm^3
- No baseline NNRTI mutations
- Randomized to one of 4 arms
- All given 2 NRTIs*



*2 NRTIs: Tenofovir-Emtricitabine + (67%); Abacavir-Lamivudine (33%)

Source: van Lunzen J, et al. Lancet Infect Dis 2011;12:111-8.

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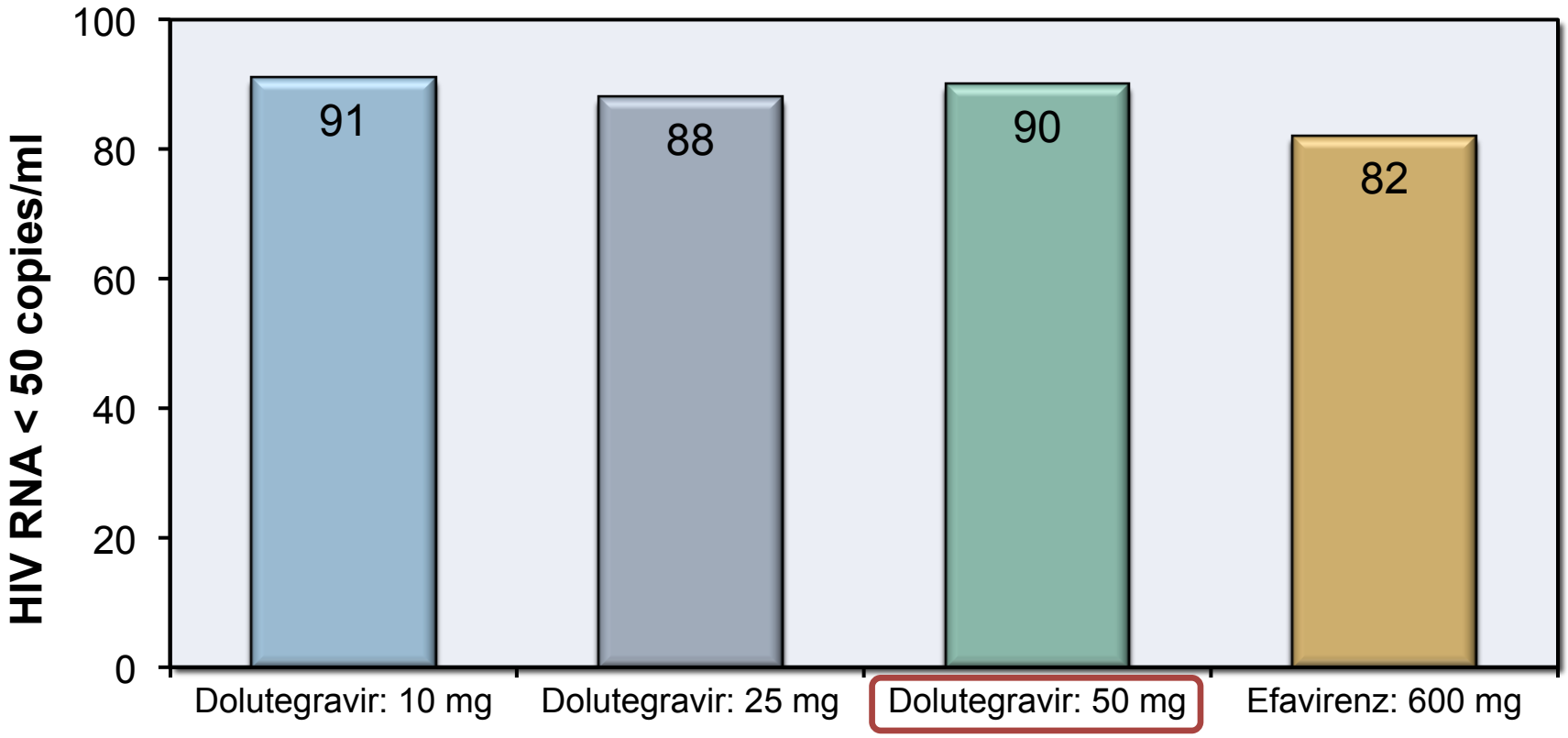
Dolutegravir ("572") vs. Efavirenz in ARV-Naive SPRING-1: Study Results

48 Week Data: Virologic Response (TLOVR)



All regimens included 2 NRTIs: Tenofovir-Emtricitabine or Abacavir-Lamivudine

Source: van Lunzen J, et al. Lancet Infect Dis 2011;12:111-8.

Investigational

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

Cohort I (N = 27); Cohort II (N = 24)

Single arm, Phase II Trial

Documented raltegravir resistance

Documented resistance to $\geq$ 3 ARV classes

HIV RNA > 1,000 copies/ml (Median HIV RNA= 4.3 $\log_{10}$ copies/ml

Day 0 to 10: Raltegravir replaced with Dolutegravir

Day 11 to Week 24: Dolutegravir + OBR

Source: Soriano V, et al. 13th EACS 2011: Abstract PS1/2LB.

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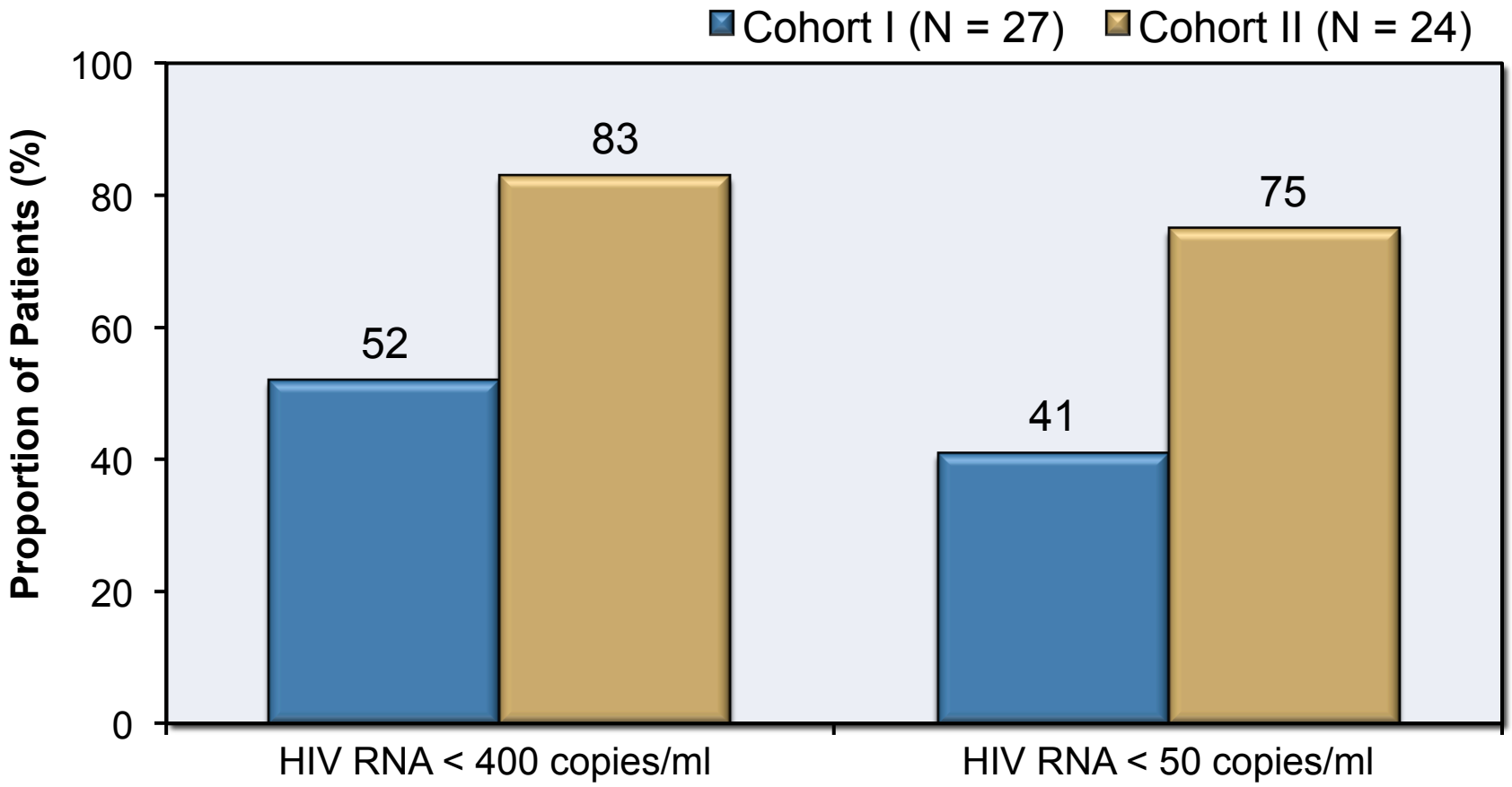
Dolutegravir in Patients with Raltegravir Resistance
VIKING Study (Cohorts I & II): Week 24 Results



Source: Soriano V, et al. 13th EACS 2011: Abstract PS1/2LB.

Investigational

Dolutegravir Activity Against Raltegravir-Resistant HIV

- **Minimal or no Impact on Dolutegravir Activity**
  - N155H +/- secondary mutations
  - Y143R/H/C +/- secondary mutations
  - Q148H/K/R single mutations

- **Significant Decrease in Dolutegravir Activity**
  - Q148H/K/R + secondary mutations (G140S/A; E138K/A)
  - G118R (not reported in vivo)
  - Dolutegravir 50 mg BID appears active

Investigational

Dolutegravir: Program in Development

- Phase 3 Program In Development: Treatment Naive
  - SPRING 2: Dolutegravir versus Raltegravir
  - SINGLE: Dolutegravir-ABC-3TC versus Efavirenz-TDF-FTC
- Phase 3 Program In Development: Treatment Experienced
  - SAILING: Dolutegravir versus Raltegravir (integrase naïve)

Investigational

Dolutegravir
Summary Points

- **Pros**
  - Efficacy similar to efavirenz
  - Convenient (one pill per day without meal restrictions)
  - Plans for fixed drug Tri-572
  - Effective in patients with raltegravir failure
- **Cons**
  - Lacking phase 3 data
  - Tri-572 with HIV RNA > 100,000 copies/ml due to abacavir
- **Clinical Use**
  - Very attractive as 2nd line regimen and salvage
  - Possible first line agent with fixed-drug preparation

End