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Doravirine

Jehan Budak, MD
Associate Editor, National HIV Curriculum
Assistant Professor of Medicine
Division of Allergy and Infectious Diseases
University of Washington

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Disclosures

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Doravirine Basics

- **Medication**
  - Oral, once daily, non-nucleoside reverse transcriptase inhibitor (NNRTI)
- **Administration**
  - Few drug-drug interactions, can give with proton pump inhibitors, and no food requirements
- **With Renal Impairment**
  - No adjustment with mild, moderate, or severe renal impairment
- **With Hepatic Impairment**
  - No dose adjustment for Child-Pugh A or B; insufficient data for C
- **Pregnancy**
  - Insufficient data for use in pregnancy
- **Common Adverse Effects** (≥5%)
  - Nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, abnormal dreams

Doravirine

100 mg

↳ NNRTI

Dose: 1 tablet once daily with or without food

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Doravirine: NNRTI Mechanism of Action

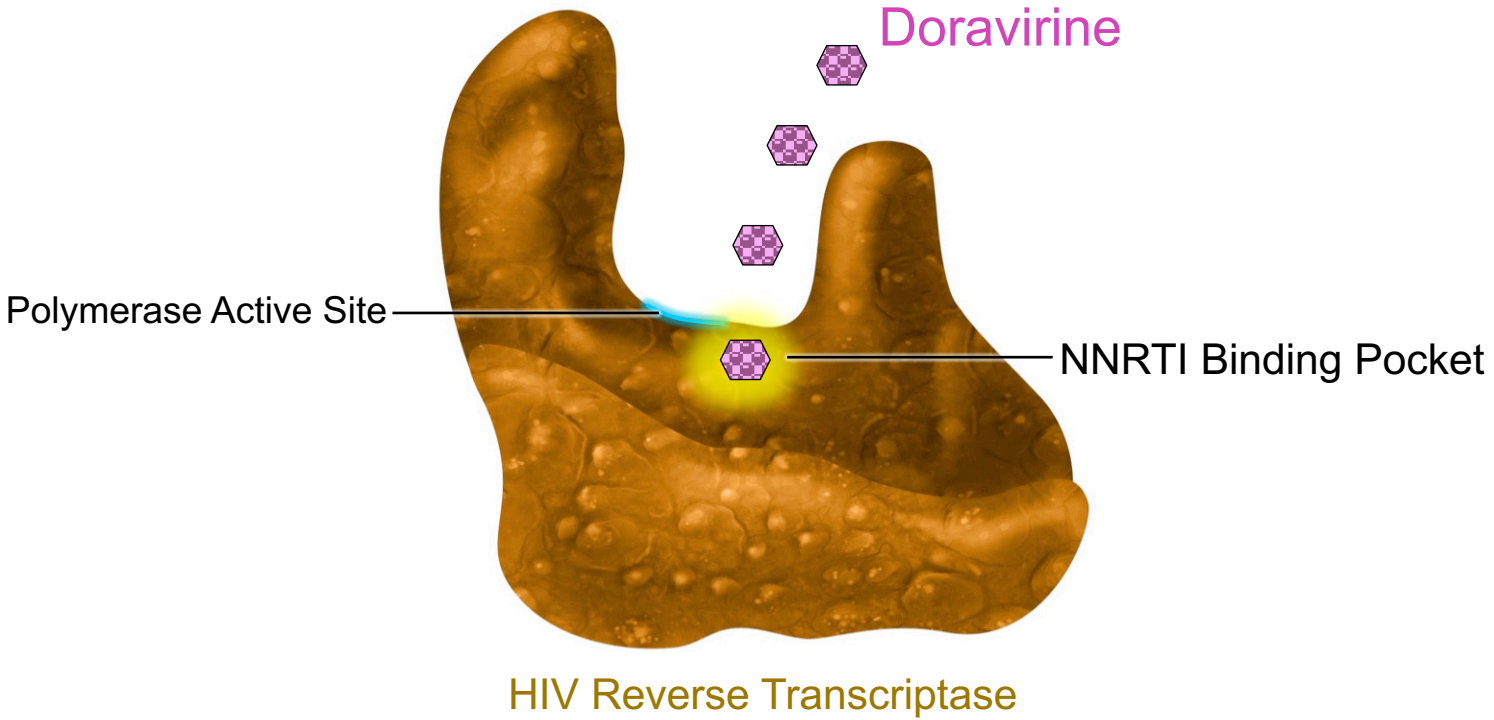

Illustration: *Cognition Studio, Inc.* and David H. Spach, MD

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Doravirine: Key Studies

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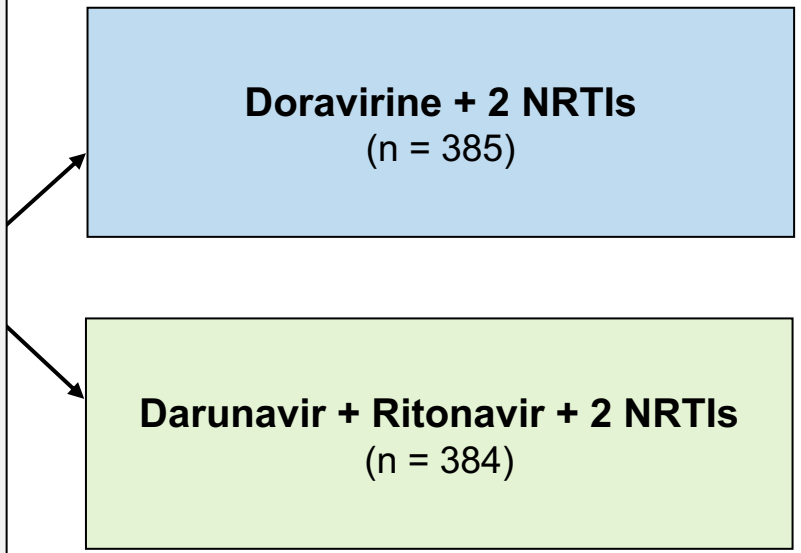
Key Doravirine Studies

- DRIVE FORWARD
- DRIVE AHEAD
- DRIVE SHIFT

Doravirine + 2 NRTIs vs. Darunavir + Ritonavir + 2 NRTIs
DRIVE FORWARD: Design

- **Design**
  - Randomized, double-blind, phase 3 study comparing doravirine plus 2 NRTIs with darunavir, boosted with ritonavir, in combination with 2 NRTIs as initial antiretroviral therapy
- **Inclusion Criteria**
  - Antiretroviral-naïve adults
  - HIV RNA ≥1,000 copies/mL
  - No resistance to any study drug
- **Regimens** (all once daily)
  - Doravirine (100 mg) + 2 NRTIs
  - Darunavir (800 mg) + Ritonavir (100 mg) + 2 NRTIs



Source: Molina J-M, et al. Lancet HIV. 2018;5:e211-20.

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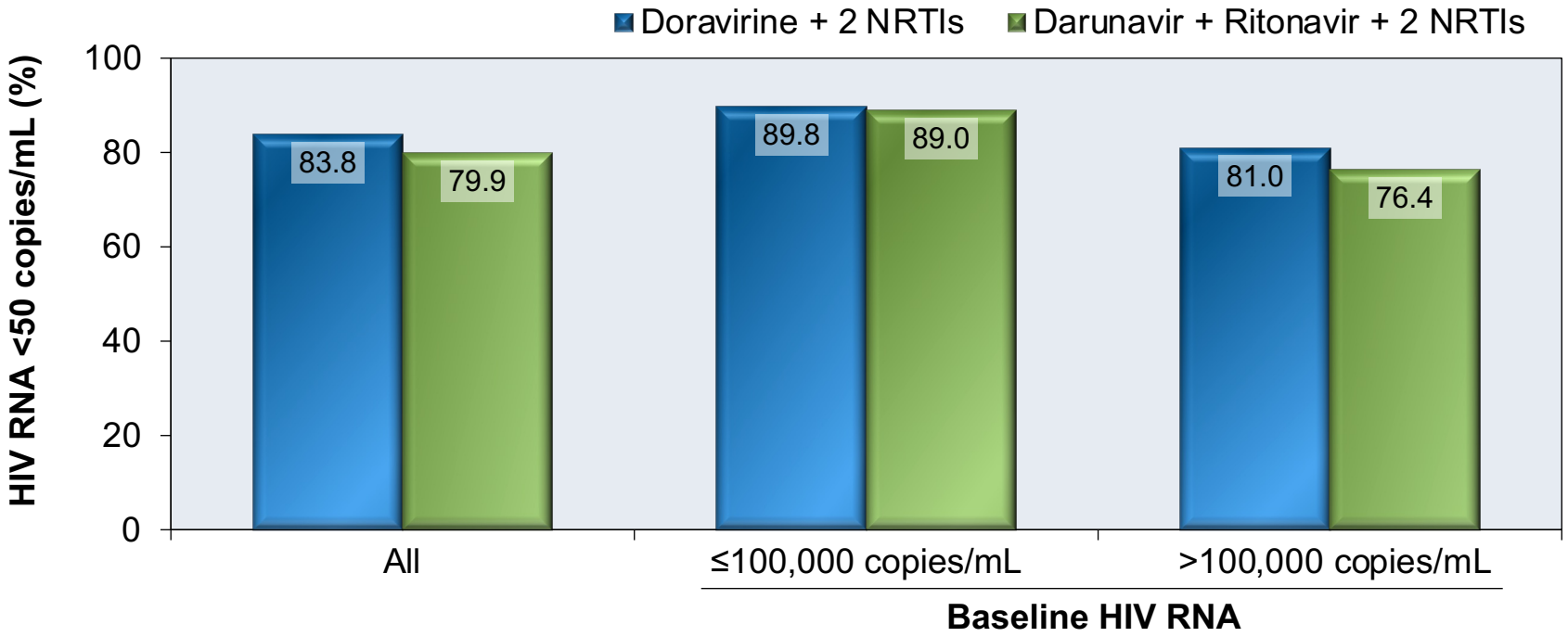
Doravirine + 2 NRTIs vs. Darunavir + Ritonavir + 2 NRTIs
DRIVE FORWARD: 48 Week Results

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



Source: Molina J-M, et al. Lancet HIV. 2018;5:e211-20.

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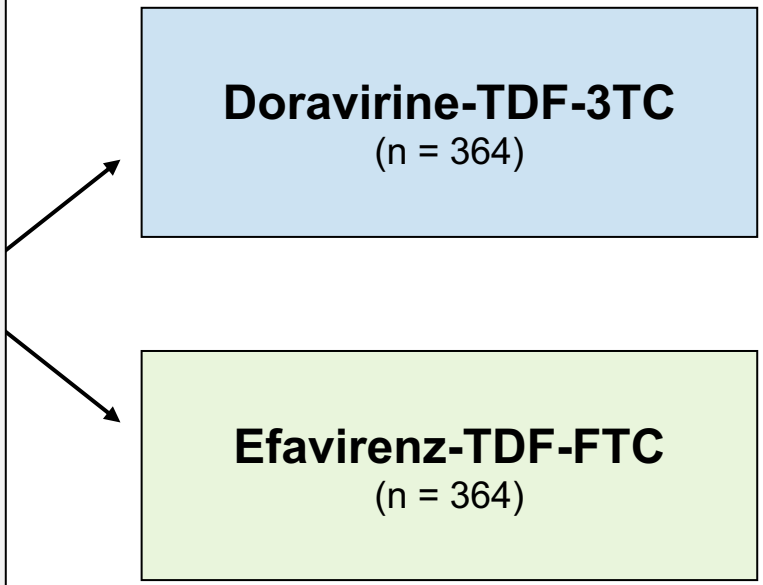
Doravirine-TDF-3TC versus Efavirenz-TDF-FTC as Initial Therapy
DRIVE AHEAD: Design

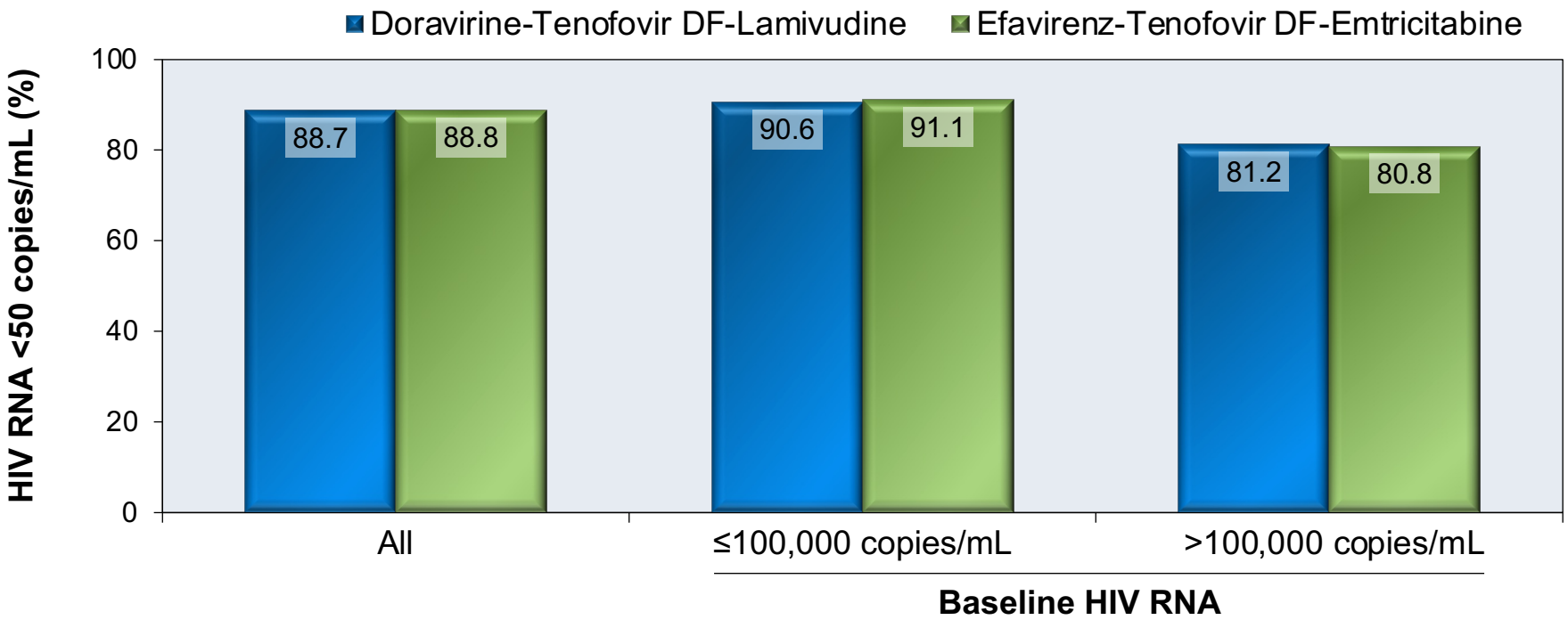
- **Design**
  - Randomized, double-blind, phase 3 study comparing fixed dose doravirine-tenofovir DF-lamivudine with fixed dose efavirenz-tenofovir DF-emtricitabine as initial antiretroviral therapy
- **Inclusion Criteria**
  - Antiretroviral-naïve adults
  - HIV RNA ≥1,000 copies/mL
  - No resistance to any study drug
- **Regimens**
  - Doravirine-TDF-3TC (100/300/300 mg) daily
  - Efavirenz-TDF-FTC (600/300/200 mg) daily



Source: Orkin C, et al. Clin Infect Dis. 2019;68:535-44.

Doravirine-TDF-3TC versus Efavirenz-TDF-FTC as Initial Therapy
DRIVE AHEAD: 48 Week Results

Week 48 Virologic Response (Observed Failure)



Source: Orkin C, et al. Clin Infect Dis. 2019;68:535-44.

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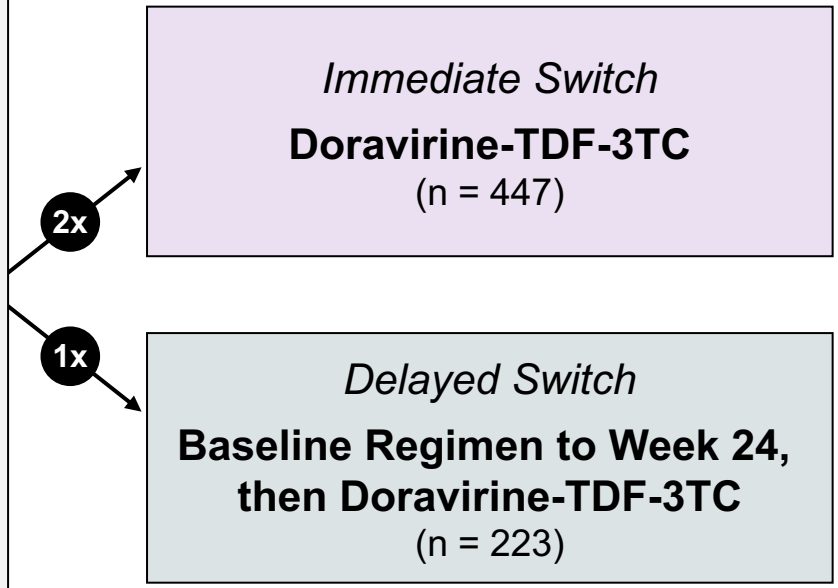
Switch to Doravirine-TDF-3TC versus Continued Baseline Regimen DRIVE SHIFT: Design

- **Design**
  - Open-label, non-inferiority trial
  - Adults with suppressed HIV RNA while taking 2 NRTIs plus anchor drug, randomized (2:1) to immediately switch to fixed-dose doravirine-tenofovir-DF-lamivudine or continue the baseline regimen with delayed switch at 24 weeks
- **Inclusion Criteria**
  - Adults with suppressed HIV RNA ≥6 months
  - No history of virologic failure
- **Baseline Regimen**
  - 2 NRTIs + (boosted protease inhibitor, boosted elvitegravir, or NNRTI)



Source: Johnson M, et al. J Acquir Immun Defic Syndr. 2019;81:463-72.

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Switch to Doravirine-TDF-3TC versus Continued Baseline Regimen
DRIVE SHIFT: Baseline Antiretroviral Regimens

DRIVE SHIFT Baseline Antiretroviral Regimens

Anchor Agent, n (%)	Immediate Switch (n = 447)	Delayed Switch (n = 223)
Boosted PI	316 (70.7)	156 (70.0)
Darunavir	166 (37.1)	82 (36.8)
Atazanavir	96 (21.5)	43 (19.3)
Lopinavir	54 (12.1)	31 (13.9)
Elvitegravir-cobicistat	25 (5.6)	12 (5.4)
NNRTI	106 (23.7)	55 (24.7)
Efavirenz	78 (17.4)	36 (16.1)
Nevirapine	17 (3.8)	12 (5.4)
Rilpivirine	11 (2.5)	7 (3.1)

*Most common NRTI backbone in both arms: TDF/FTC (73.8% in immediate switch, 69.1% in delayed switch)

Source: Johnson M, et al. J Acquir Immun Defic Syndr. 2019;81:463-72.

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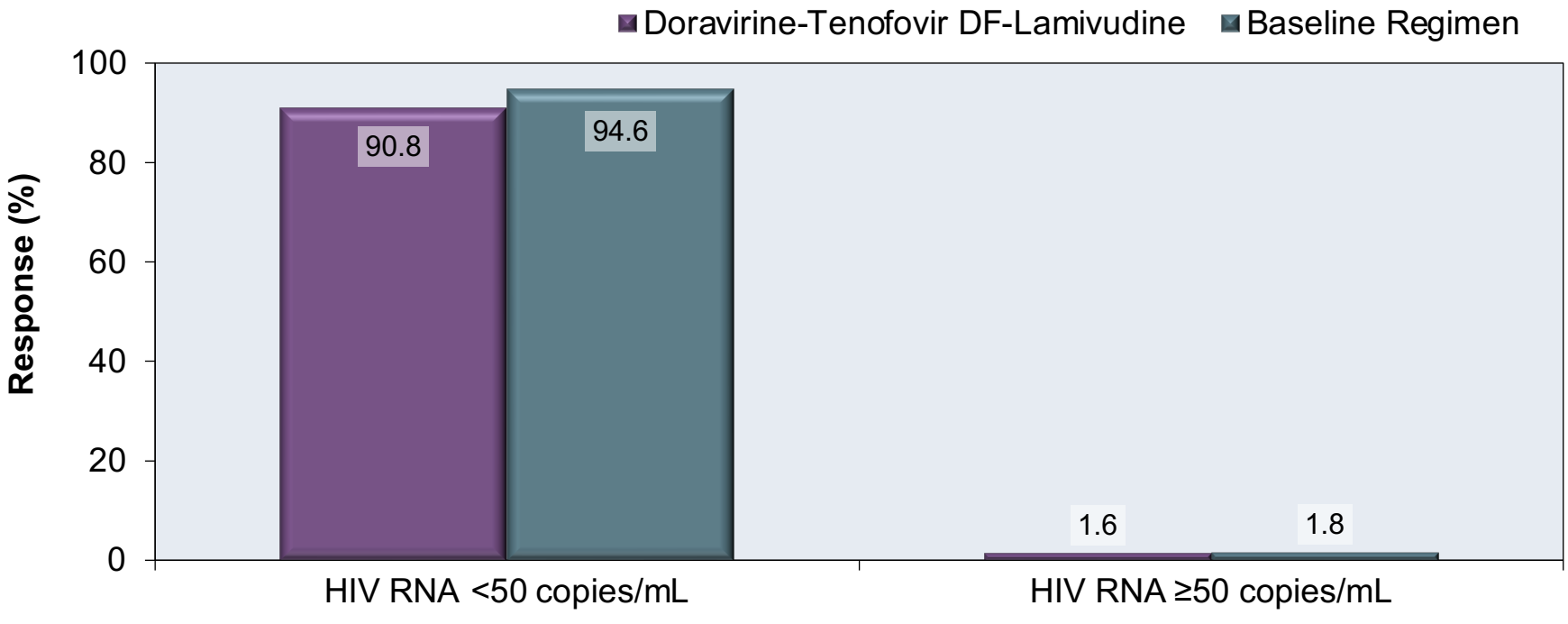
Switch to Doravirine-TDF-3TC versus Continued Baseline Regimen DRIVE SHIFT: Results

Week 48 Doravirine-TDF-3TC vs Week 24 Baseline Regimen (FDA snapshot)



Source: Johnson M, et al. J Acquir Immun Defic Syndr. 2019;81:463-72.

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Summary of Phase 3 Doravirine Trials

Study	Population	Outcome
DRIVE-FORWARD[1]	Treatment-Naïve	Doravirine + 2 NRTIs is non-inferior to Darunavir + Ritonavir + 2 NRTIs
DRIVE-AHEAD[2]	Treatment-Naïve	Doravirine-TDF-3TC is non-inferior to Efavirenz-TDF-FTC
DRIVE-SHIFT[3]	Treatment-Experienced	Immediate or delayed switch to Doravirine-TDF-3TC is non-inferior to baseline ART

[1]Molina J-M, et al. Lancet HIV. 2018;5:e211-20.
[2]Orkin C, et al. Clin Infect Dis. 2019:68:535-44.
[3]Johnson M, et al. J Acquir Immun Defic Syndr. 2019;81:463-72.

Doravirine is Weight Neutral

- Weight gain over 96 weeks was low with doravirine use[1]
- Two clinical trials looking into switch to doravirine after weight gain
  - [2]Do IT (A5391): Doravirine for Persons With Excessive Weight Gain on INSTIs and TAF
  - [3]DeLiTE: Can INSTI-associated Weight Gain be Halted or Reversed With a Switch to DOR/3TC/TDF?
- Consider doravirine in persons who have experienced or are hesitant about the potential of antiretroviral-related weight gain

Source

[1]Orkin C, et al. AIDS. 2021;35:91-9.

[2]DO IT: https://clinicaltrials.gov/ct2/show/NCT04636437

[3]DeLiTE: https://clinicaltrials.gov/ct2/show/NCT04665375

Doravirine: Resistance

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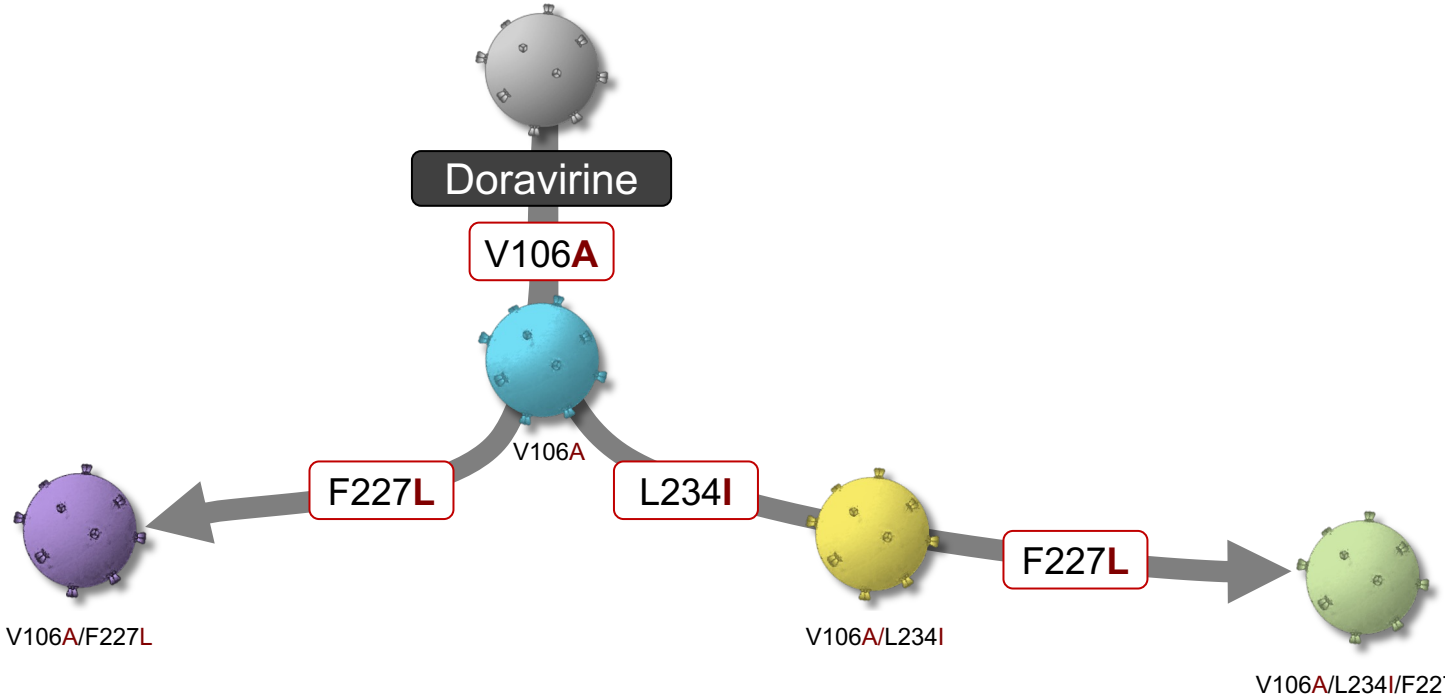
Doravirine *In Vitro* Resistance Pathways with HIV Subtype B



Source: Feng M, et al. Antimicrob Agents Chemother. 2015;59:590-8.

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Doravirine: Development of Drug Resistance with Virologic Failure

- Available data suggest doravirine has high genetic barrier to resistance[1]
- In four doravirine clinical trials <1% of participants experienced treatment failure with doravirine resistance[1]
- With virologic failure on doravirine in clinical trials, the most prevalent treatment-emergent mutations were at positions 106 (V106A/I/M) and 227 (F227C/L)[2,3]

Source

[1]Asante-Appiah E, et al. Antimicrob Agents Chemother. 2021;65:e0121621.
[2]Martin EA, et al. J Acquir Immune Defic Syndr. 2020;85:635-42.
[3]Johnson M, et al. J Acquir Immune Defic Syndr. 2019;81:463-72.

Impact of Doravirine Resistance

Impact of Most Common Resistance Mutations that Develop with Doravirine Virologic Failure				
NNRTI	**Resistance Associated Mutation**			
	V106A	**V106I**	**V106M**	**F227C**
Doravirine	High-Level	Low level	Intermediate	High-Level
Efavirenz	Intermediate	Susceptible	High-Level	Intermediate
Etravirine	Susceptible	Low level	Susceptible	Susceptible
Rilpivirine	Susceptible	Low level	Susceptible	Susceptible

Source: Stanford Resistance Database

Doravirine Activity with Prior NNRTI Virologic Failure Resistance

- Common mutations K103N and G190A have no impact on doravirine
- DRIVE BEYOND study showed good virologic response with doravirine-TDF-3TC in 10 persons with baseline K103N or G190A
- Single mutations with V106A, Y188L, G190E, or M230L confer high-level resistance to doravirine
- Avoid doravirine with mutations that confer intermediate or high-level resistance

Source
Martin EA, et al. J Acquir Immune Defic Syndr. 2020;85:635-42.
Asante-Appiah E, et al. Antimicrob Agents Chemother. 2021;65:e0121621
Wong A, et al. J Acquir Immune Defic Syndr. 2019;82:e47-e49.

Impact of NNRTI RAMs on Doravirine

No Impact on Doravirine
K103N; G190A

Potential Low-level Doravirine Resistance	Low-level Doravirine Resistance
K101P; E138K; Y181C	K101E; Y181C; K103N + Y181C; H221Y

Intermediate-level Doravirine Resistance
L100I + K103N; V106M; P225H; F227L; Y318F

High-level Doravirine Resistance
V106A; Y188L; G190E; M230L

Source: Stanford Resistance Database

Doravirine: Summary

- Oral, once-daily NNRTI available alone or in a fixed dose combination
- Typically used in treatment experienced or to address ART weight gain
- Most common treatment emergent mutations were V106I and F227L
- Retains full activity with a K103N and G190A mutations
- Well-tolerated with few drug-drug interactions
- Can take with or without food and can take with proton pump inhibitors

Acknowledgments

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