National HIV Curriculum

Mini-Lecture Series

Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine

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Disclosures

Dr. Kalapila has no financial conflicts of interest or disclosures.

Darunavir-Cobicistat-Tenofovir alafenamide-Emtricitabine (DRV-COBI-TAF-FTC)

Darunavir	Cobicistat	Tenofovir alafenamide	Emtricitabine
800 mg	150 mg	10 mg	200 mg
↳ PI	↳ Booster	↳ NRTI	↳ NRTI

Dosing: Once daily with food

Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine Single-Tablet Regimen

- **Indication:** Complete regimen for treatment of HIV-1 in persons weighing ≥40 kg:
  - No prior antiretroviral treatment history, *or*
  - Virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ART for ≥6 months and have no known resistance to darunavir or tenofovir
- **Testing Prior to Initiation**
  - Renal function
  - Serologic testing for hepatitis B (HBV) virus infection
- **With Renal or Hepatic Impairment**
  - Not recommended if estimated CrCl <30 mL/min
  - Not recommended with severe hepatic impairment (Child-Pugh C)

Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine Mechanism of Action

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): Mechanism of Action

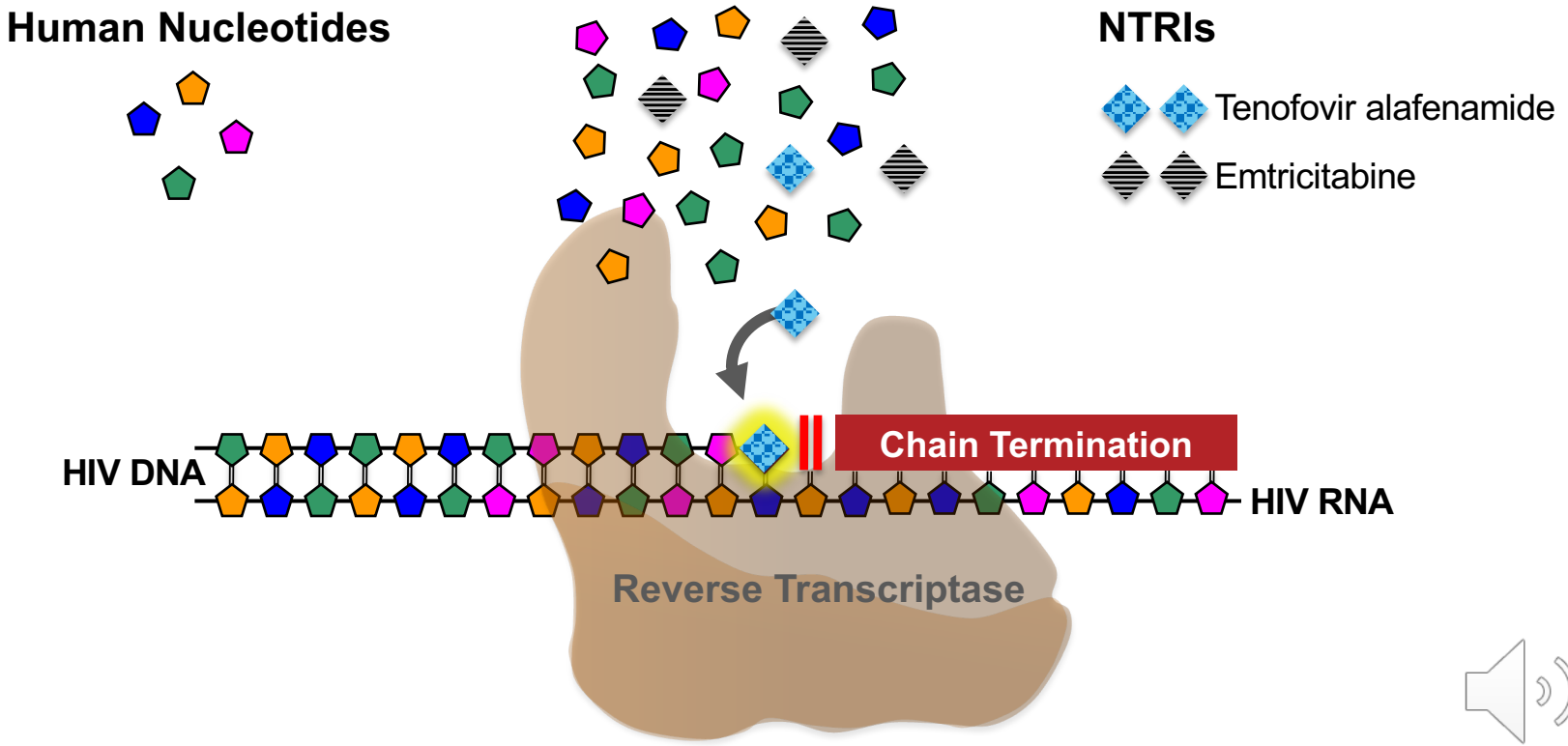

Illustration: David H. Spach, MD

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HIV Protease and Polypeptide Cleavage

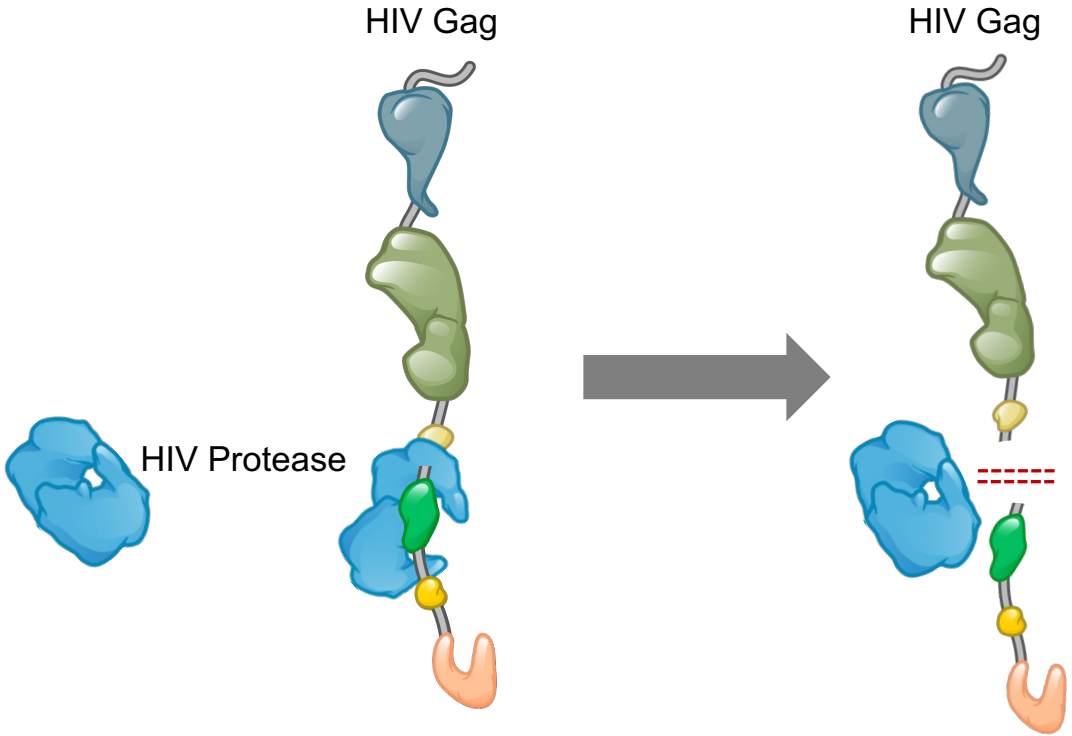

Illustration: *Cognition Studio, Inc.* and David H. Spach, MD

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Protease Inhibitors: Mechanism of Action

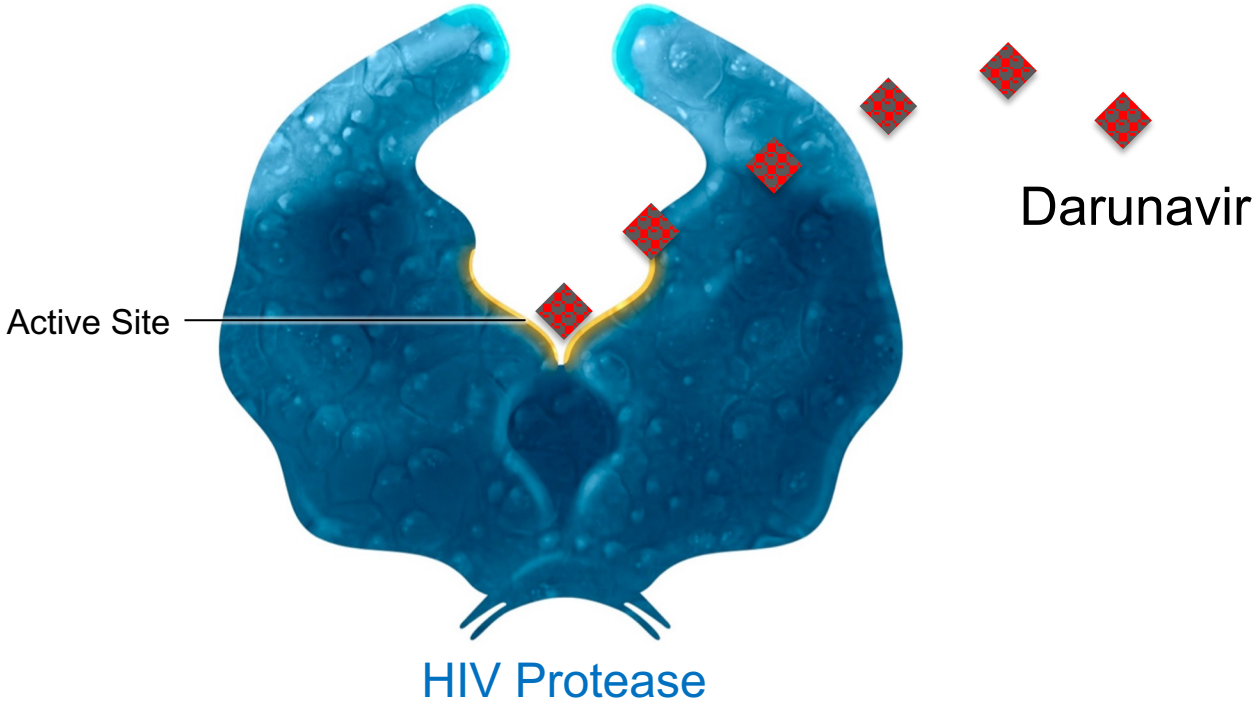

Illustration: *Cognition Studio, Inc.* and David H. Spach, MD

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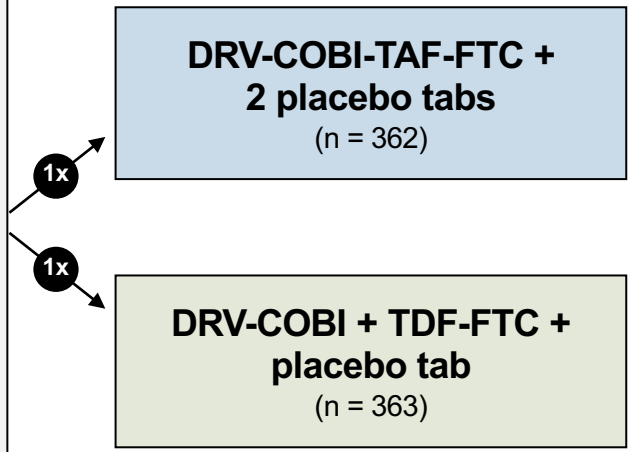
Key Clinical Trials

DRV-COBI-TAF-FTC vs DRV-COBI + TDF-FTC as Initial ART
AMBER: Design

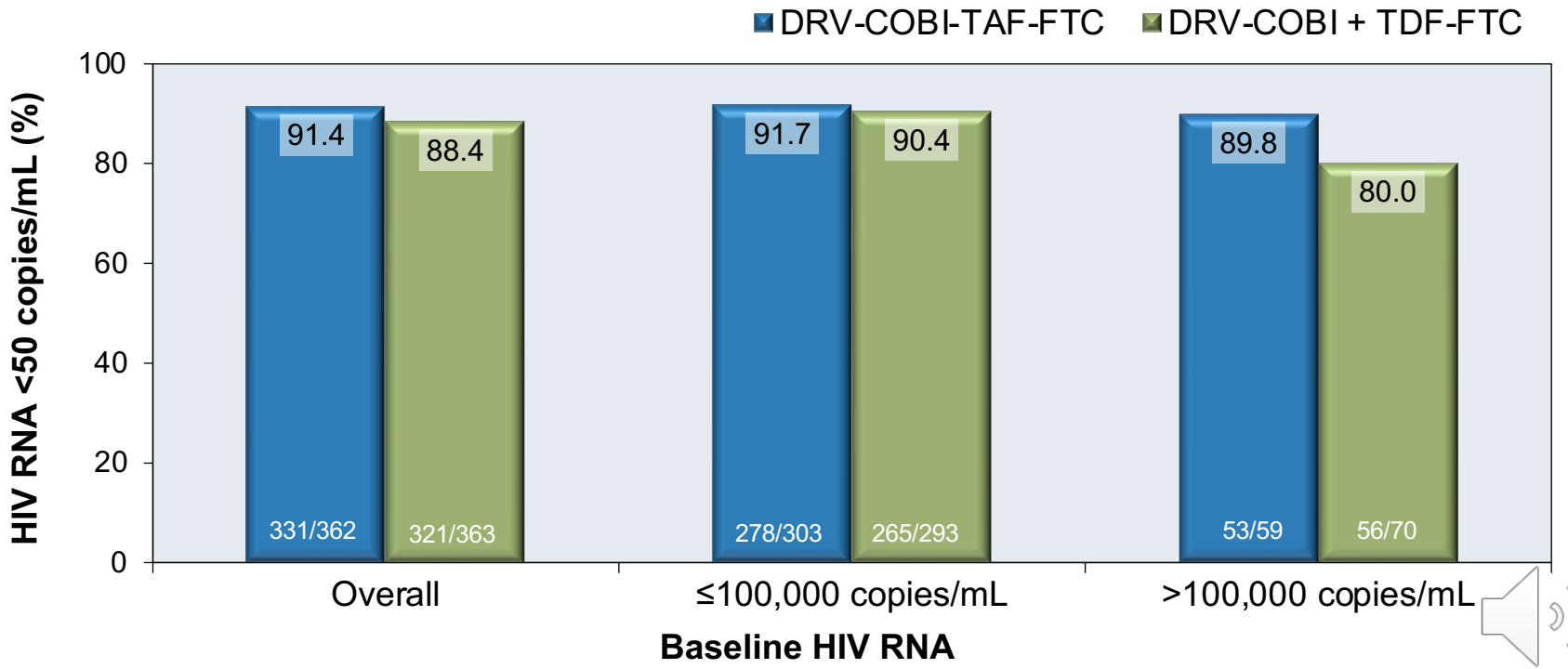
- **Background**: Randomized, double-blind, active-controlled, international, phase 3 study evaluating the efficacy and safety of the single-tablet regimen DRV-COBI-TAF-FTC compared with DRV-COBI + TDF-FTC for treatment-naïve individuals
- **Inclusion Criteria (n = 725)**
  - Age ≥18 years
  - Antiretroviral naïve
  - CD4 count >50 cells/mm^3
  - HIV RNA ≥1,000 copies/mL
  - eGFR ≥70 mL/min
  - Genotypic sensitivity to DRV, TDF, and FTC
  - No hepatitis B or C
  - Not pregnant
  - No AIDS-defining condition within 30 days



Source: Eron JJ, et al. AIDS. 2018;32:1431-42.

DRV-COBI-TAF-FTC vs DRV-COBI + TDF-FTC as Initial ART
AMBER: Results

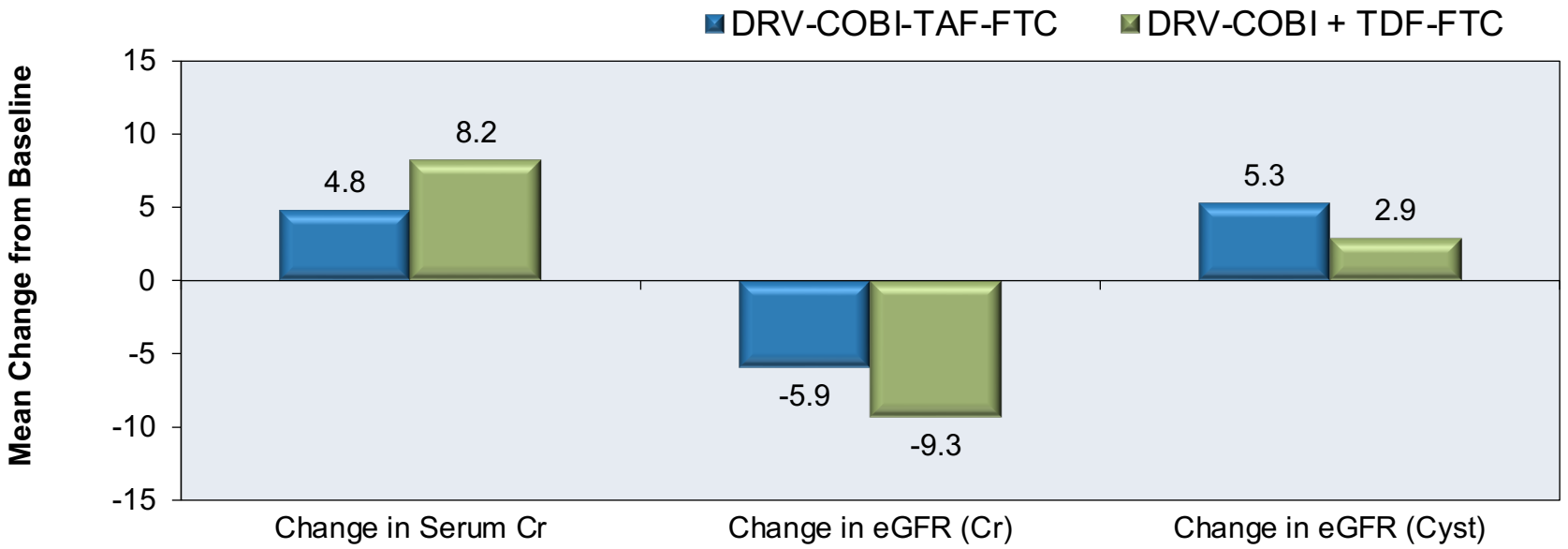
Week 48: Virologic Response by FDA Snapshot Analysis, ITT



Source: Eron JJ, et al. AIDS. 2018;32:1431-42.

DRV-COBI-TAF-FTC vs DRV-COBI + TDF-FTC as Initial ART
AMBER: Results

Week 48: Change in Serum Creatinine and Estimated GFR



Abbreviations: Cr = creatinine (measured in µmol/L); eGFR = estimated glomerular filtration rate (measured in mL/min/1.73m^2, calculated using CKD-EPI); Cyst = cystatin C

Source: Eron JJ, et al. AIDS. 2018;32:1431-42.

DRV-COBI-TAF-FTC vs DRV-COBI + TDF-FTC as Initial ART
AMBER: Results

Week 48: Change in Urinary Markers of Tubular Dysfunction

Mean Change in Markers of Proximal Tubulopathy at Week 48

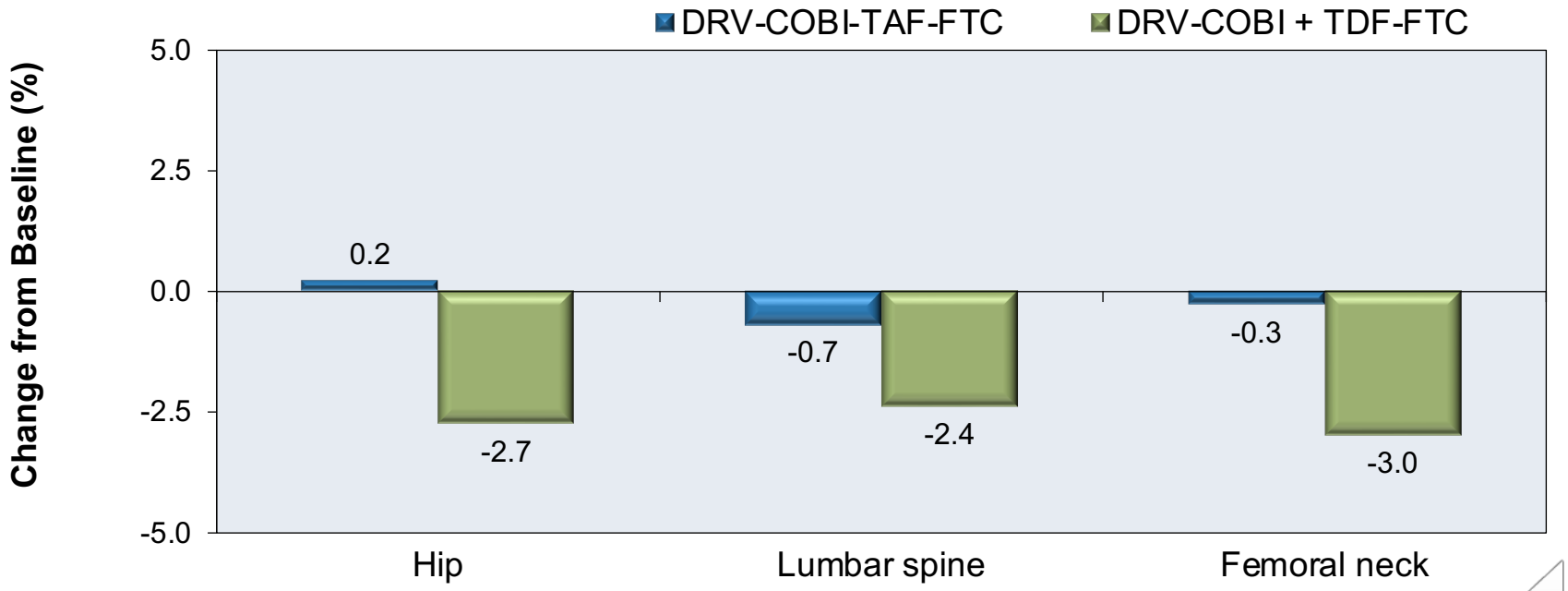
	DRV-COBI-TAF-FTC (n = 362)	DRV-COBI + TDF-FTC (n = 363)
UPCR (mg/g)	-22.42	-10.34
UACR (mg/g)	-2.45	-0.58
RBP:Cr (µg/g)	16.84	401.12
β2M:Cr (µg/g)	-100.58	837.63

UPCR = urine protein to creatinine ratio; UACR = urine albumin to creatinine ratio
RBP:Cr = retinol binding protein to creatinine ratio; β2M:Cr = beta-2-microglobulin to creatinine ratio

Source: Eron JJ, et al. AIDS. 2018;32:1431-42.

DRV-COBI-TAF-FTC vs DRV-COBI + TDF-FTC as Initial ART
AMBER: Results

Week 48: Percentage Change in Bone Mineral Density*



*This is from a bone mineral density substudy (n = 113 participants in TAF arm, 99 in control arm)

Source: Eron JJ, et al. AIDS. 2018;32:1431-42.

DRV-COBI-TAF-FTC vs DRV-COBI + TDF-FTC as Initial ART
AMBER: Results

Median Change in Fasting Lipid Parameters at Week 48

	DRV-COBI-TAF-FTC (n = 362)	DRV-COBI + TDF-FTC (n = 363)
TC (mg/dL)	28.6	10.4
LDL (mg/dL)	17.4	5.0
HDL (mg/dL)	4.3	1.5
TC:HDL ratio	0.2	0.08
Triglycerides (mg/dL)	23.9	14.2

TC = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein

Source: Eron JJ, et al. AIDS. 2018;32:1431-42.

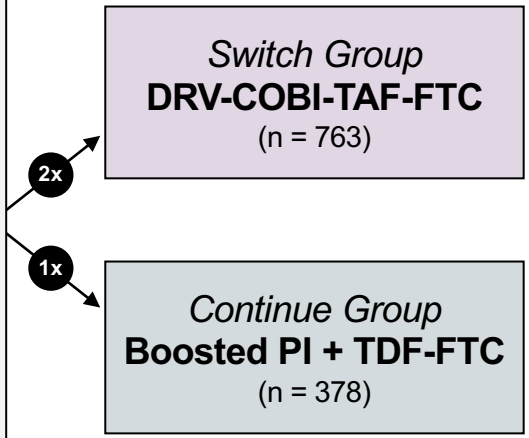
Darunavir-Cobicistat-Tenofovir alafenamide-Emtricitabine Summary of Key Studies

- **Trials in Treatment Naïve Adults**
  - AMBER: DRV-COBI-TAF-FTC versus DRV-COBI + TDF-FTC
    - DRV-COBI-TAF-FTC achieved a high virologic suppression rate and was non-inferior to DRV-COBI + TDF-FTC

[1]Eron JJ, et al. AIDS. 2018;32:1431-42.

DRV-COBI-TAF-FTC vs Continue Boosted PI + TDF-FTC
EMERALD: Design

- **Background**: Randomized, open-label, active-controlled, international, phase 3 study evaluating the efficacy and safety of switching to the single-tablet regimen DRV-COBI-TAF-FTC versus continuing a boosted PI + TDF-FTC
- **Inclusion Criteria (n = 1,141)**
  - Age ≥18 years
  - Antiretroviral experienced
  - HIV RNA ≤50 copies/mL for >2 months*
  - Taking a PI plus ritonavir or cobicistat
  - Regimen stable for ≥6 months
  - eGFR ≥50 mL/min
  - No prior virologic failure on a DRV-based regimen
  - Virologic failure on non-DRV-based regimen allowed
  - Not pregnant or breastfeeding



*One HIV RNA 50-200 copies/mL within prior 12 months allowed

Source: Orkin C, et al. Lancet HIV. 2018;5:e23-e34.

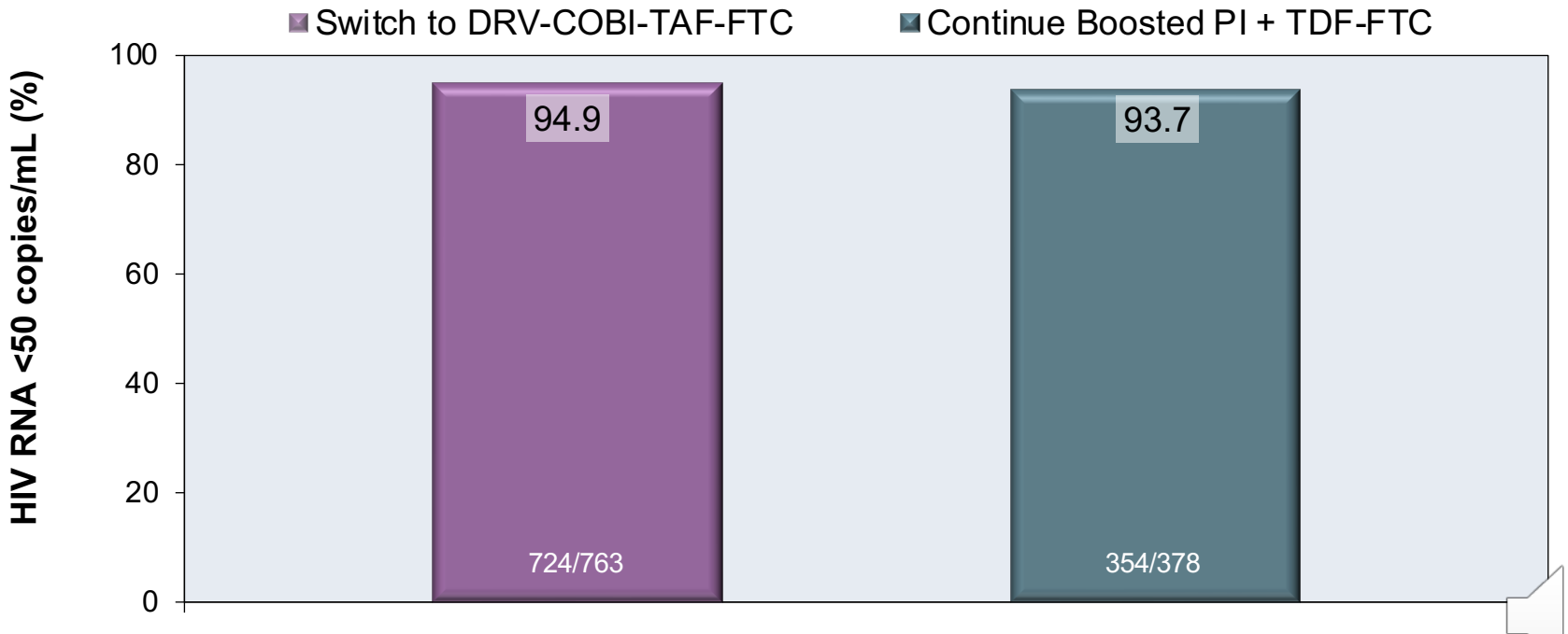
DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC
EMERALD: Baseline Characteristics

EMERALD Study: Baseline Characteristics		
	DRV-COBI-TAF-FTC ***Switch Group*** (n = 763)	**Boosted PI + TDF-FTC** ***Continue Group*** (n = 378)
CD4 Count (cells/mL)	630	624
Time since HIV diagnosis (years)	9.3	8.9
Time since first ART (years)	6.2	5.8
Previous use of >5 ARV's	59	58
Previous virologic failure	15	14
Boosted darunavir at screening (%)	70	70
Boosted atazanavir at screening (%)	22	22
Boosted lopinavir at screening (%)	8	8

Source: Orkin C, et al. Lancet HIV. 2018;5:e23-e34.

DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC
EMERALD: Results

Week 48: Virologic Response by FDA Snapshot Analysis, ITT



Source: Orkin C, et al. Lancet HIV. 2018;5:e23-e34.

DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC
EMERALD: Results

Week 48: Virologic Outcomes

EMERALD Study Virologic Outcomes

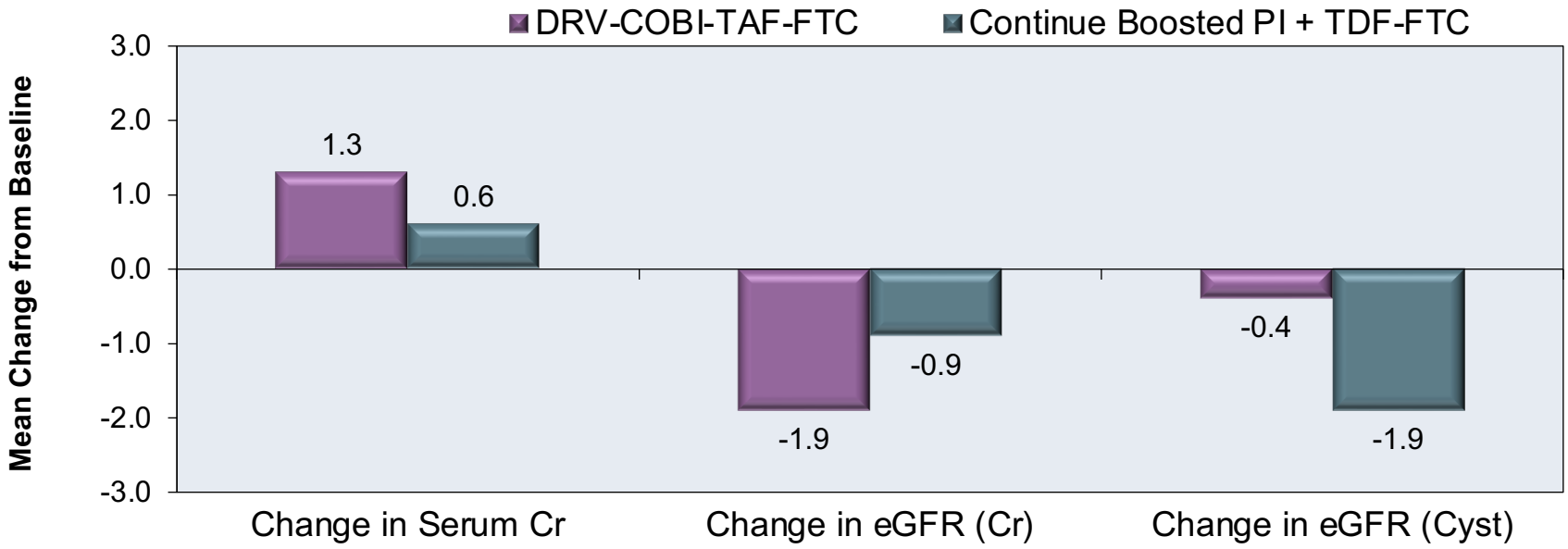
	DRV-COBI-TAF-FTC *Switch Group* (n = 763)	Boosted PI + TDF-FTC *Continue Group* (n = 378)
Virologic rebound rate through 48 weeks*	2.5%	2.1%
HIV RNA <50 copies/mL at 48 weeks	94.9%	93.7%
HIV RNA ≥50 copies/mL at 48 weeks	0.8%	0.5%
No virologic data at 48 weeks	4.3%	5.8%

*HIV RNA ≥50 copies/mL or premature discontinuation with last HIV RNA ≥50copies/mL

Source: Orkin C, et al. Lancet HIV. 2018;5:e23-e34.

DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC
EMERALD: Results

Week 48: Change in Serum Creatinine and Estimated GFR



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eGFR = estimated glomerular filtration rate (measured in mL/min/1.73 m^2, calculated using CKD-EPI)
Cyst = cystatin C

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DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC
EMERALD: Results

Week 48: Change in Urinary Markers of Tubular Dysfunction

Mean Change in Markers of Proximal Tubulopathy at Week 48

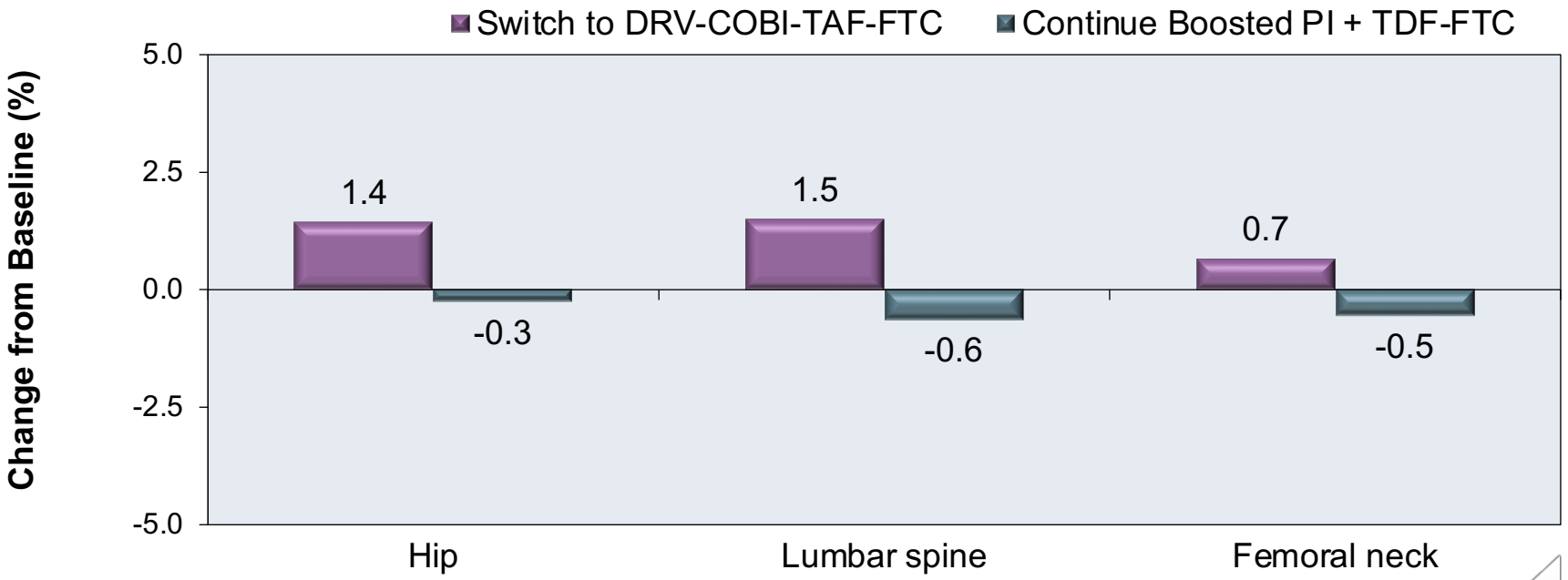
	DRV-COBI-FTC-TAF *Switch Group* (n = 763)	Boosted PI + TDF-FTC *Continue Group* (n = 378)
UPCR (mg/g)	-33.9	-6.43
UACR (mg/g)	-3.2	1.3
RBP:Cr (mg/g)	-630.5	1037.1
β2M:Cr (mg/g)	-1454.7	1371.3

UPCR = urine protein to creatinine ratio; UACR = urine albumin to creatinine ratio
RBP:Cr = retinol binding protein to creatinine ratio; β2M:Cr = beta-2-microglobulin to creatinine ratio

Source: Orkin C, et al. Lancet HIV. 2018;5:e23-e34.

DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC
EMERALD: Results

Week 48: Change in Bone Mineral Density



This is from a bone mineral density substudy (n = 209 participants in switch arm, 108 in control arm)

Source: Orkin C, et al. Lancet HIV. 2018;5:e23-e34.

DRV-COBI-TAF-FTC vs Continue a Boosted PI + TDF-FTC
EMERALD: Results

Median Change in Fasting Lipid Parameters at Week 48

	DRV-COBI-FTC-TAF *Switch Group* (n = 763)	Boosted PI + TDF-FTC *Control Group* (n = 378)
TC (mg/dL)	19.7	1.3
LDL (mg/dL)	15.7	1.9
HDL (mg/dL)	3.0	-1.0
TC:HDL ratio	0.2	0.1
Triglycerides (mg/dL)	6.0	5.0

TC = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein

Source: Orkin C, et al. Lancet HIV. 2018;5:e23-e34.

Darunavir-Cobicistat-Tenofovir alafenamide-Emtricitabine Summary of Key Studies

- **Trials in Treatment Naïve Adults**
  - [1]AMBER: DRV-COBI-TAF-FTC versus DRV-COBI + TDF-FTC
    - DRV-COBI-TAF-FTC achieved a high virologic suppression rate and was non-inferior to DRV-COBI + TDF-FTC

- **Trials In Adults with Virologic Suppression**
  - [2]EMERALD: Switch to DRV-COBI-TAF-FTC or stay on PI + TDF-FTC
    - DRV-COBI-TAF-FTC is safe and efficacious as a potential switch option for the treatment of HIV-1 infection in adults with viral suppression, if a single tablet regimen is needed

[1]Eron JJ, et al. AIDS. 2018;32:1431-42.
[2]Orkin C, et al. Lancet HIV. 2018;5:e23-e34.

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Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine Adverse Effects

- **Gastrointestinal**
  - Diarrhea (9%) and nausea (6%) in persons taking taking darunavir with cobicistat
- **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

Darunavir-Cobicistat-Tenofovir Alafenamide-Emtricitabine Editor's Summary

- Oral, once-daily single tablet combination antiretroviral therapy with a high genetic barrier to resistance
- It is a large pill which, some individuals may find difficult to swallow
- It should not be used in patients with severe renal or severe hepatic impairment
- The medication is mostly associated with gastrointestinal adverse effects, such as diarrhea and nausea
- As an inhibitor of CYP3A, COBI can cause problematic interactions with drugs metabolized by CYP3A or drugs that induce or inhibit CYP3A

Acknowledgments

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