AETC AIDS Education & Training Center Program Mountain West

Fostemsavir (*Rukobia*®)

The How, Why and When

David Hachey, PharmD, AAHIVP
Professor
Department of Family Medicine
Idaho State University

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Disclosures

No conflicts of interest or anything to disclose

Objectives

- Compare the mechanism of action of fostemsavir (FTR) to other antiretrovirals
- Describe the relevant pharmacokinetic characteristics of FTR
- Review the clinical trial highlights that led to the approval of FTR
- Discuss the place in therapy where FTR may be of benefit

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Case

- 57 yo male with 30 year history of HIV, neuropathy, lipodystrophy, and chronic diarrhea. He has complete class resistance to NRTIs and NNRTIs. The patient had a trophile and it came back as dual-mixed; VL 50,000 and CD4 150.
- Currently takes
  - Atorvastatin 10 mg daily
  - Gabapentin 400 mg three times daily
  - Omeprazole 40 mg daily
  - Tramadol 50 three times daily
  - Cymbalta 60 mg daily
- *Would FTR be an option for this person?*

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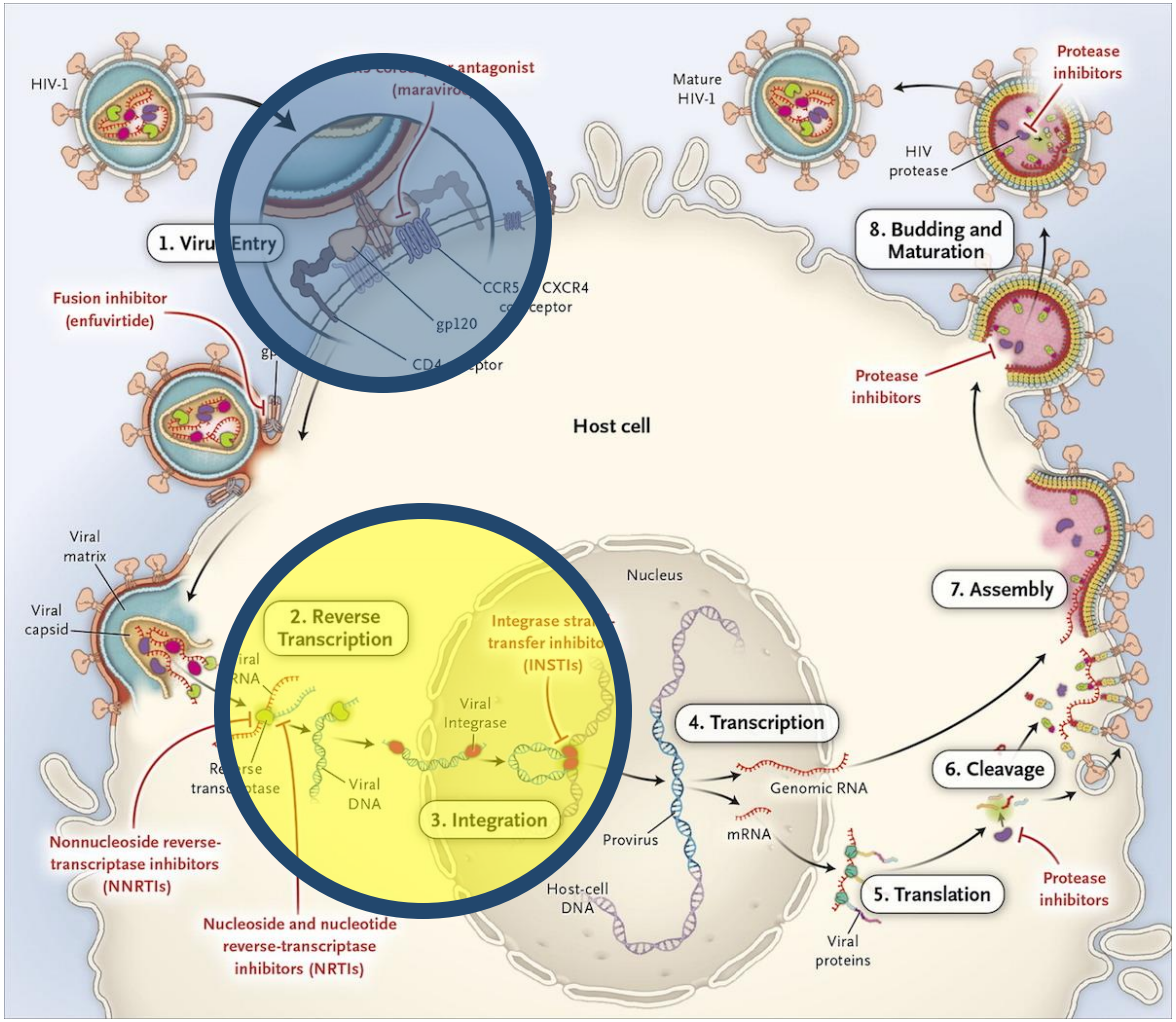
FTR Activity and Kinetics

HIV Life Cycle



Source: Gandhi M, Gandhi RT. Single-pill combination regimens for treatment of HIV-1 infection. N Engl J Med. 2014;371:248-59.

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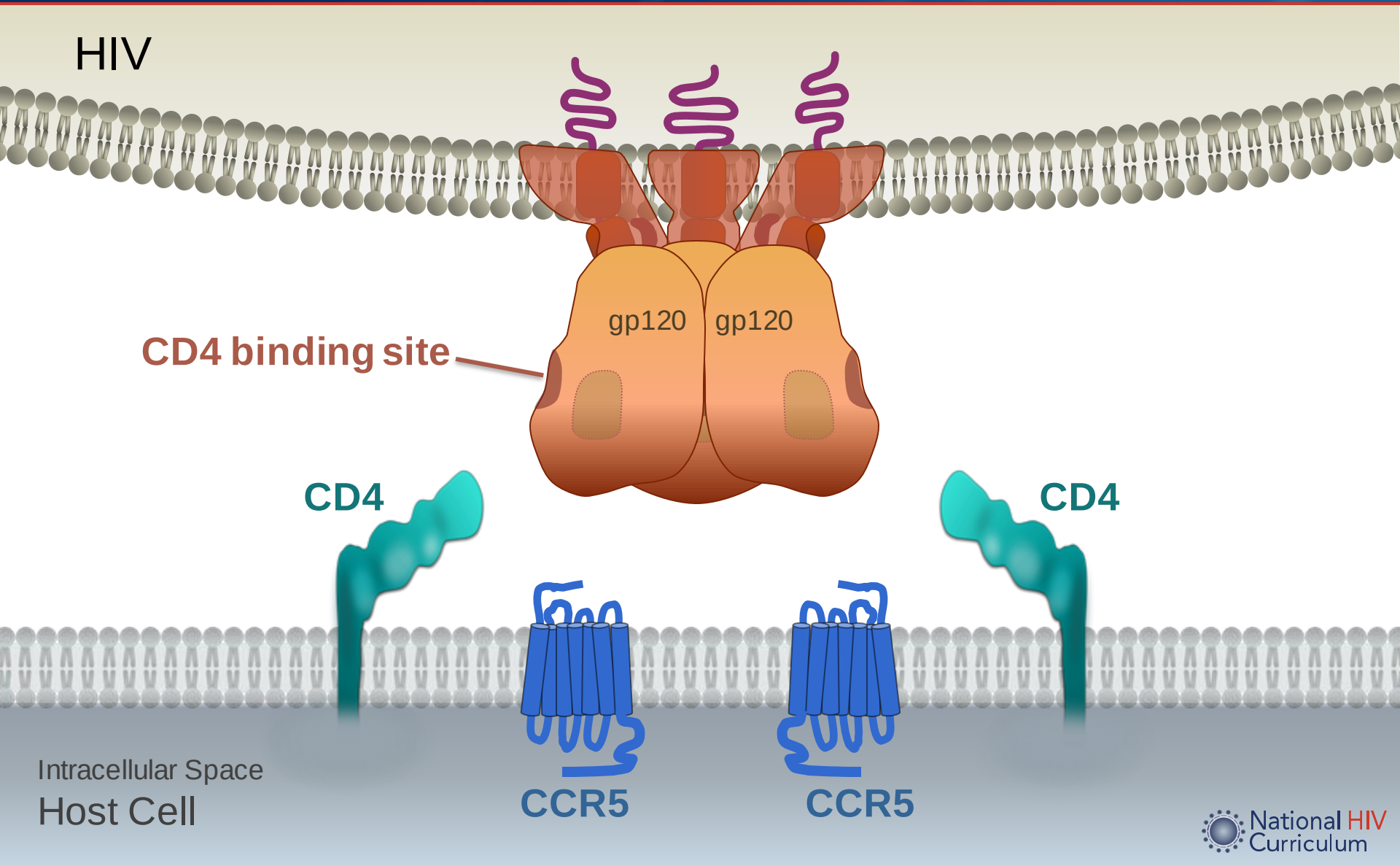
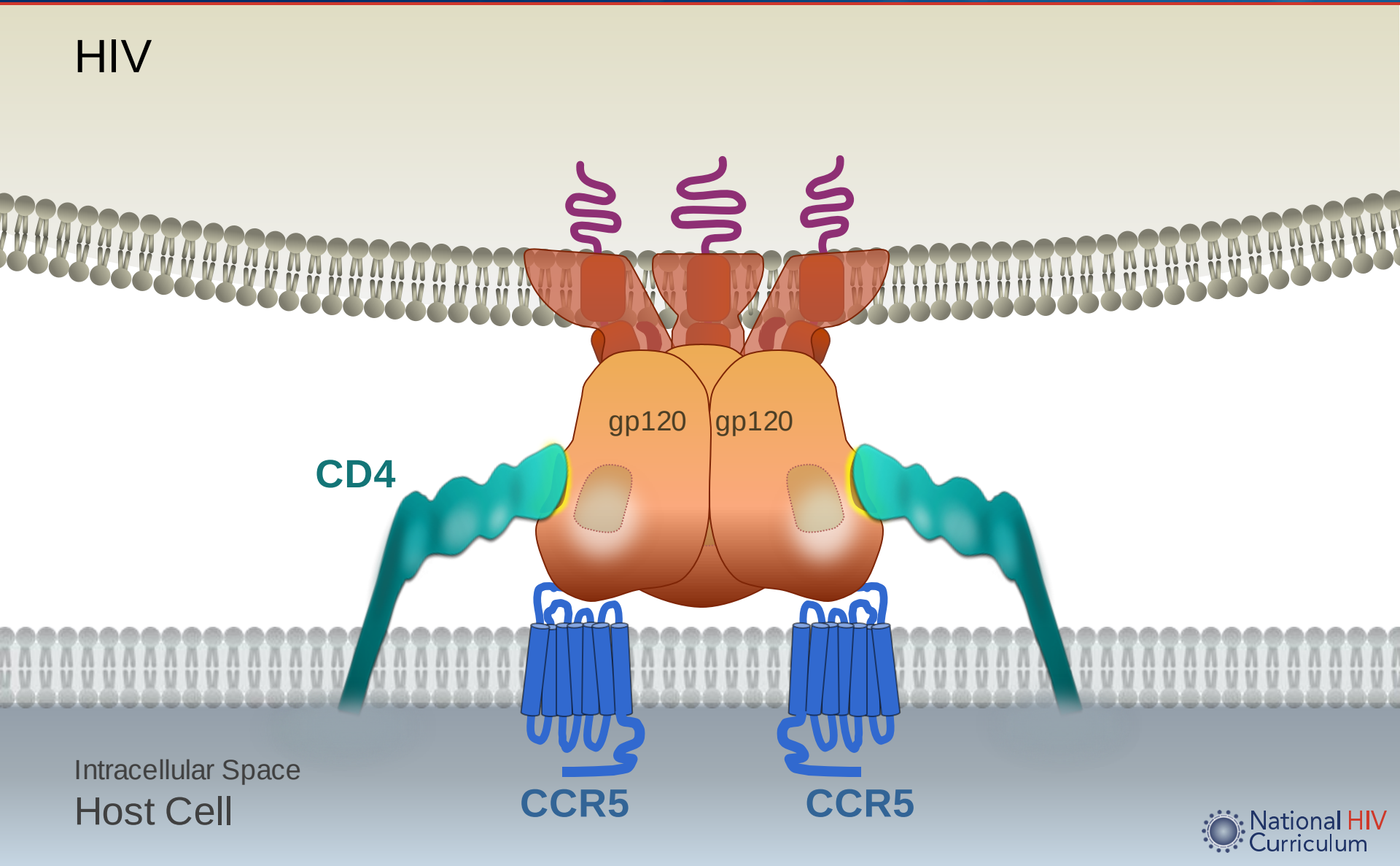
HIV Cell Entry

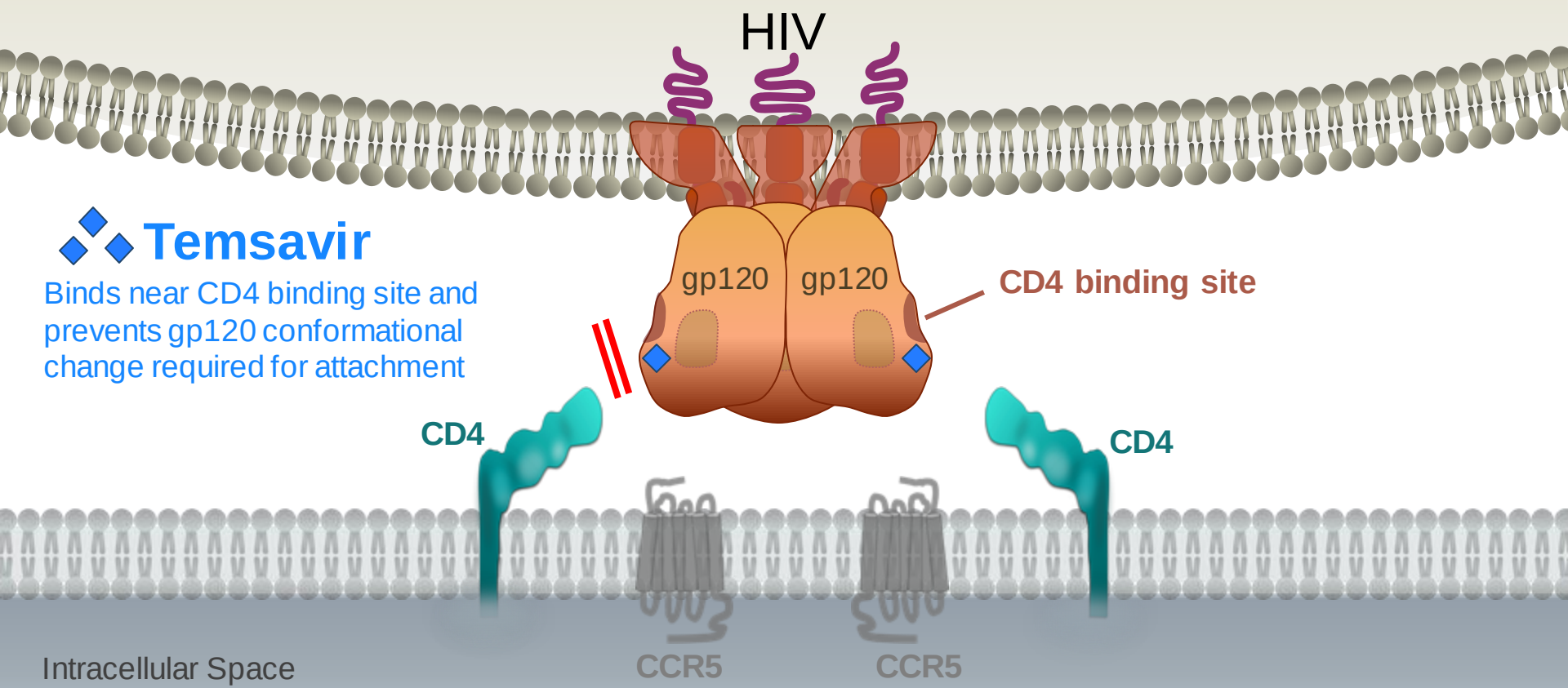


HIV Cell Entry
HIV gp120 Attachment to Host Cell CD4 Receptor



HIV Entry Inhibitors: Attachment Inhibitors
Fostemsavir—prodrug converted to Temsavir

HIV



Relevant Pharmacokinetics

- Absorption
  - **Fos**temsavir is a prodrug of the active moiety temsavir
  - Can be taken with or without food
- Metabolism
  - Major routes are hydrolysis (36%) and oxidation by CYP3A4 (21%)
  - May **inhibit** organic anion transporting polypeptide (OATP)
- Excretion
  - No adjustments needed in patients with impaired renal function OR dialysis

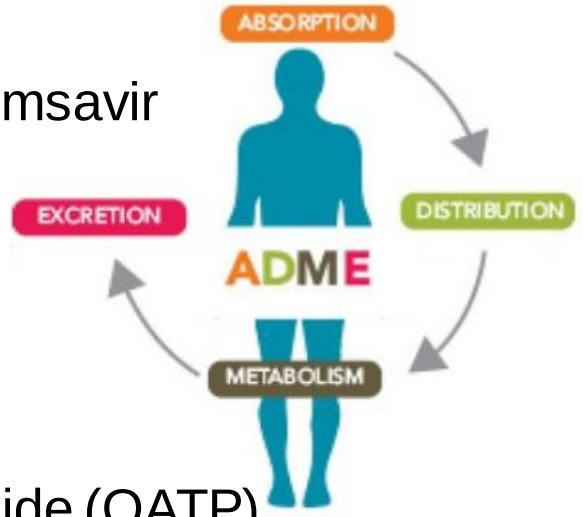


IMAGE: http://www.emdocs.net/toxcards-general-principles-of-toxicokinetics/

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FTR Drug Interactions

- Drugs that lower FTR:
  - **Strong** CYP3A4 inducers may reduce FTR activity
    - Carbamazepine, phenytoin
    - *Rifampin*
    - St John's wort
- FTR may increase concentrations of:
  - Grazoprevir or voxilaprevir via OATP inhibition
  - Ethinyl estradiol
  - Statins
    - Rosuvastatin, Atorvastatin, Fluvastatin, Pitavastatin, Simvastatin
- Safe to use with:
  - ARVS
    - Atazanavir/ritonavir
    - Darunavir/cobicistat
    - Darunavir/ritonavir with and without etravirine
    - Etravirine
    - Maraviroc
    - Raltegravir
    - Tenofovir disoproxil fumarate
  - Others
    - Methadone
    - Norethindrone
    - *Rifabutin* with and without ritonavir
    - Buprenorphine/naloxone
    - Famotidine

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Fostemsavir in Treatment-Experienced Patients
BRIGHTE Study

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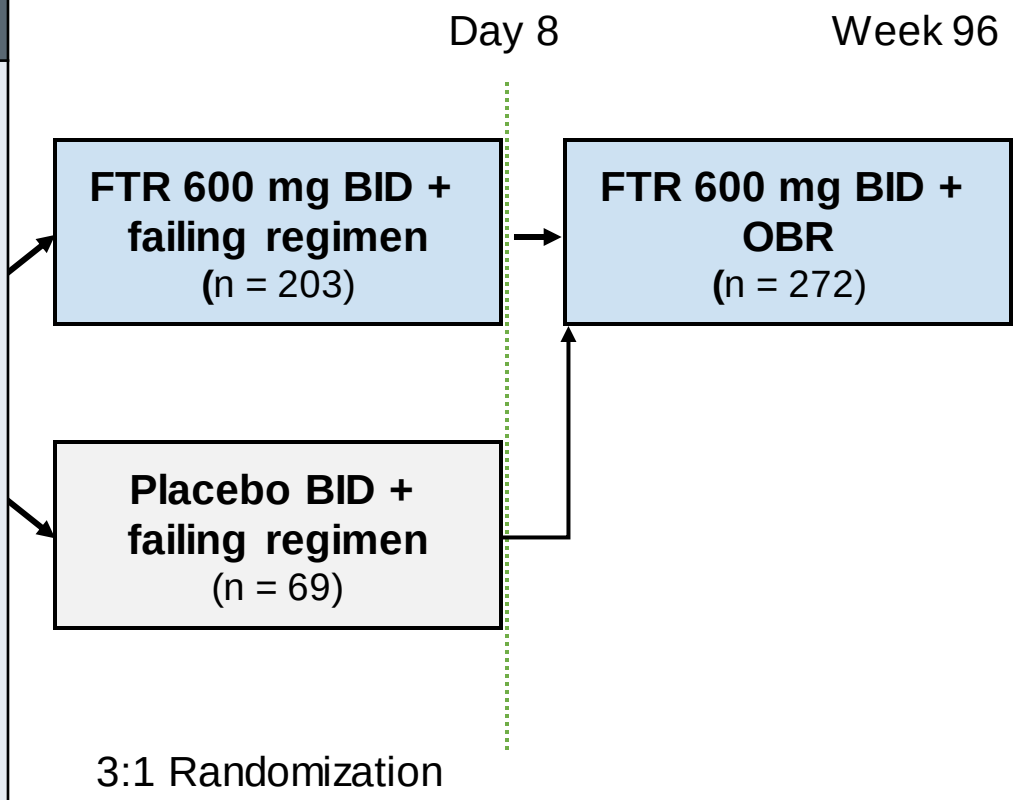
Fostemsavir (FTR) for Heavily Treatment Experienced BRIGHTE Study: Background

Study Design: BRIGHTE

- **Background**:
  - Phase 3, randomized, multicenter, placebo-controlled, non-inferiority trial evaluating attachment inhibitor fostemsavir (FTR) in salvage ART
- **Enrollment Criteria:**
  - Highly ART-experienced adults
  - Failing current ART regimen
  - HIV RNA >400 copies/mL
  - Multiclass ART resistance
  - At least one fully active agent
  - Unable to construct viable regimen



*Also a cohort with 0 remaining active agents; all given Fostemsavir 600 mg BID + OBR (n = 99)
*OBR = optimized background regimen

Source: Kozal M, et al. N Engl J Med. 2020;382:1232-43.

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Fostemsavir (FTR) for Heavily Treatment Experienced BRIGHTE Study: Baseline Characteristics

Baseline Characteristics	Randomized (n = 272)	Non-Randomized (n = 99)
Age, years, median (range)	48 (18-73)	50 (17-72)
Male sex, n (%)	200 (74)	89 (90)
White, n (%)	184 (68)	74 (74)
Black/African American, n (%)	60 (22)	23 (23)
HIV RNA 1,000-100,000 copies/mL, n (%)	161 (59)	75 (76)
HIV RNA >100,000 copies/mL, n (%)	80 (29)	15 (15)
CD4 count—cells/mm^3, median (range)	99 (0-1160)	41 (0-641)
2 fully active agents in OBR, %	42	0
1 fully active agent in OBR, %	52	19
0 fully active agents in OBR, %	6	81

*Most common ARV's in OBR: DTG, DRV, TDF, ETR, MVC, ENF, IBA

Source: Kozal M, et al. N Engl J Med. 2020;382:1232-43.

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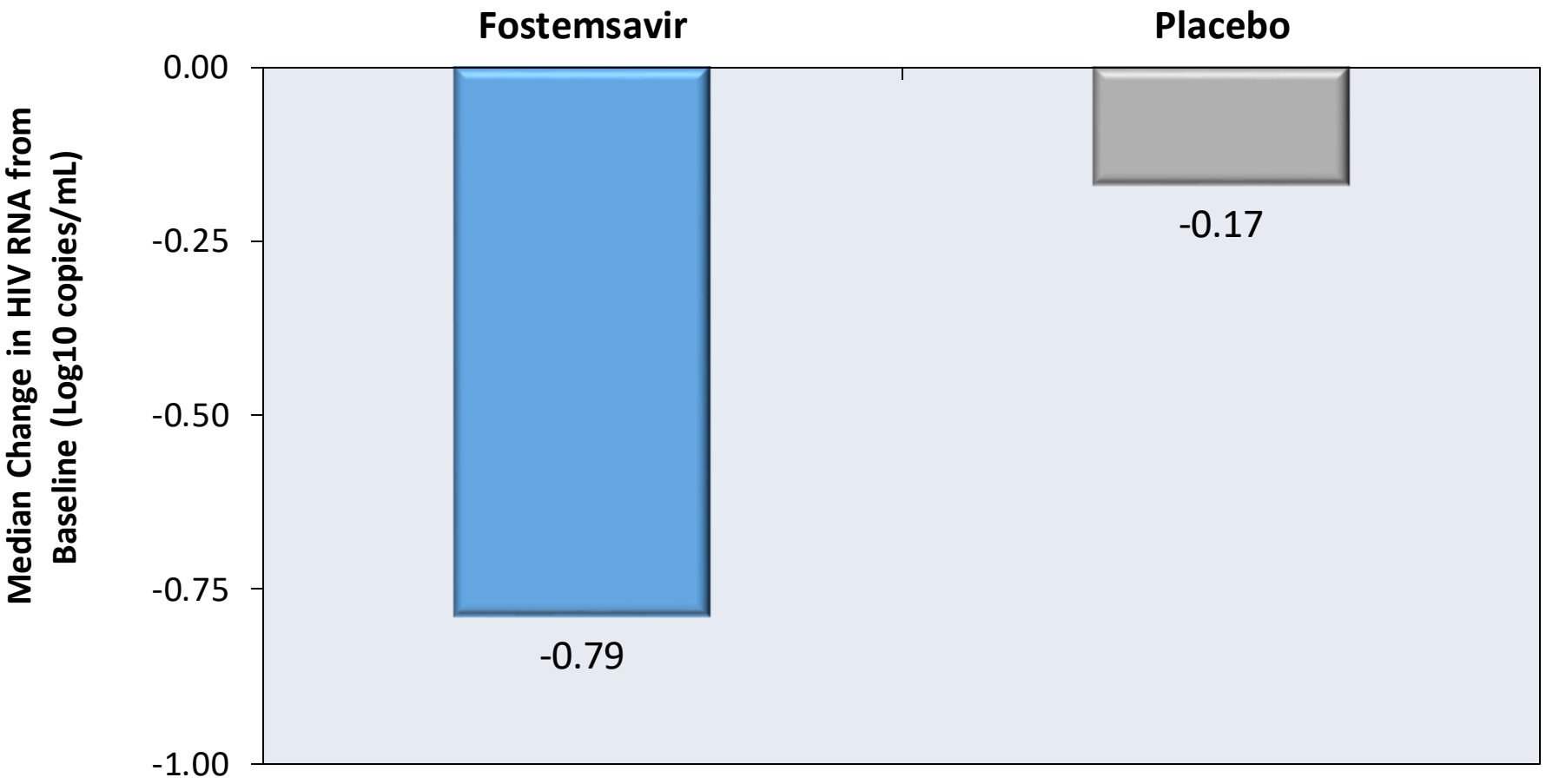
Fostemsavir (FTR) for Heavily Treatment Experienced BRIGHTE Study: Results

Baseline to Day 8 Change in HIV RNA Level



Source: Nettles RE, et al. Ray N, et al. J Infect Dis. 2012;206:1002-11.

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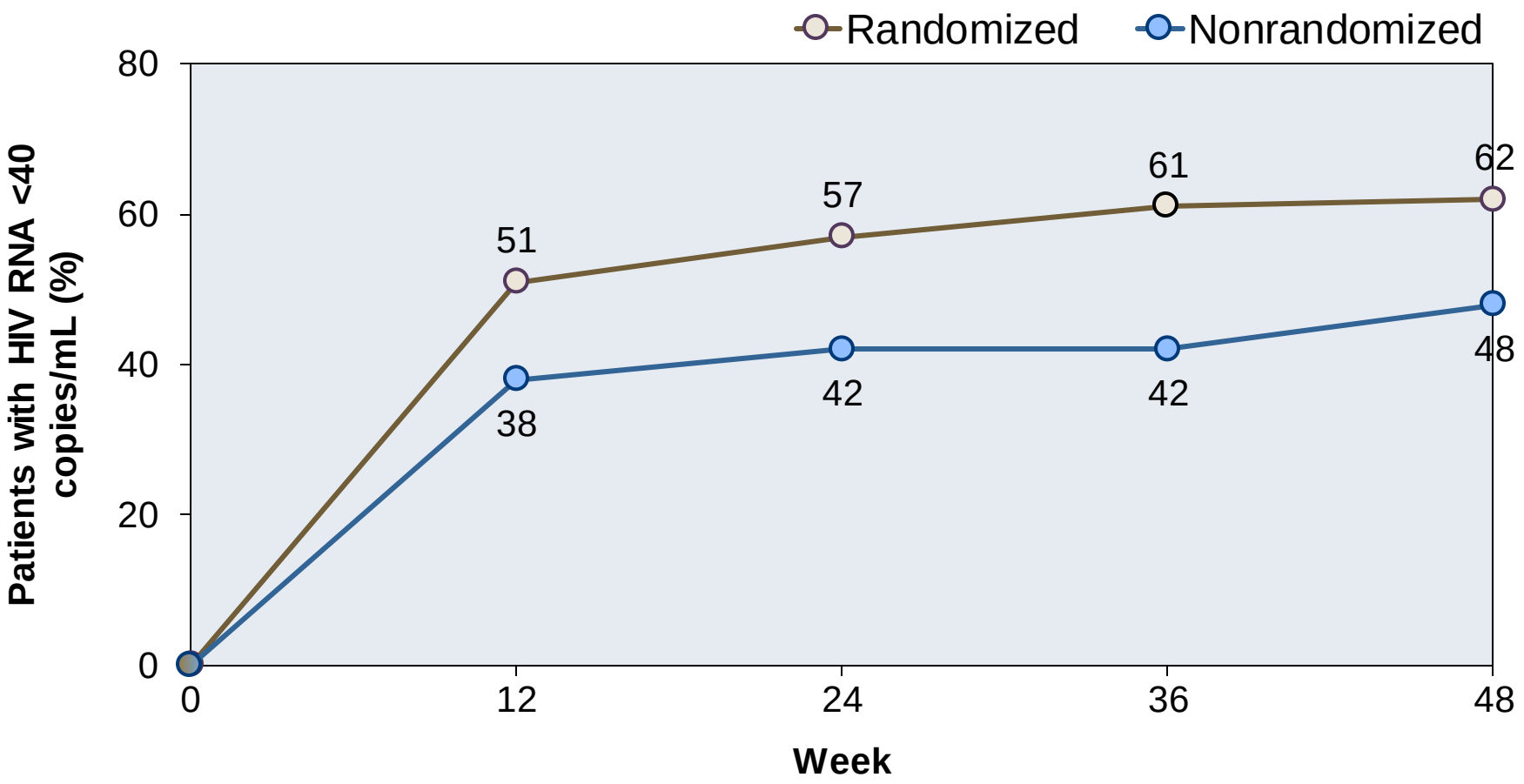
Fostemsavir (FTR) for Heavily Treatment Experienced BRIGHTE Study: Results

Virologic Response Through Week 48 (HIV RNA <40 copies/mL)



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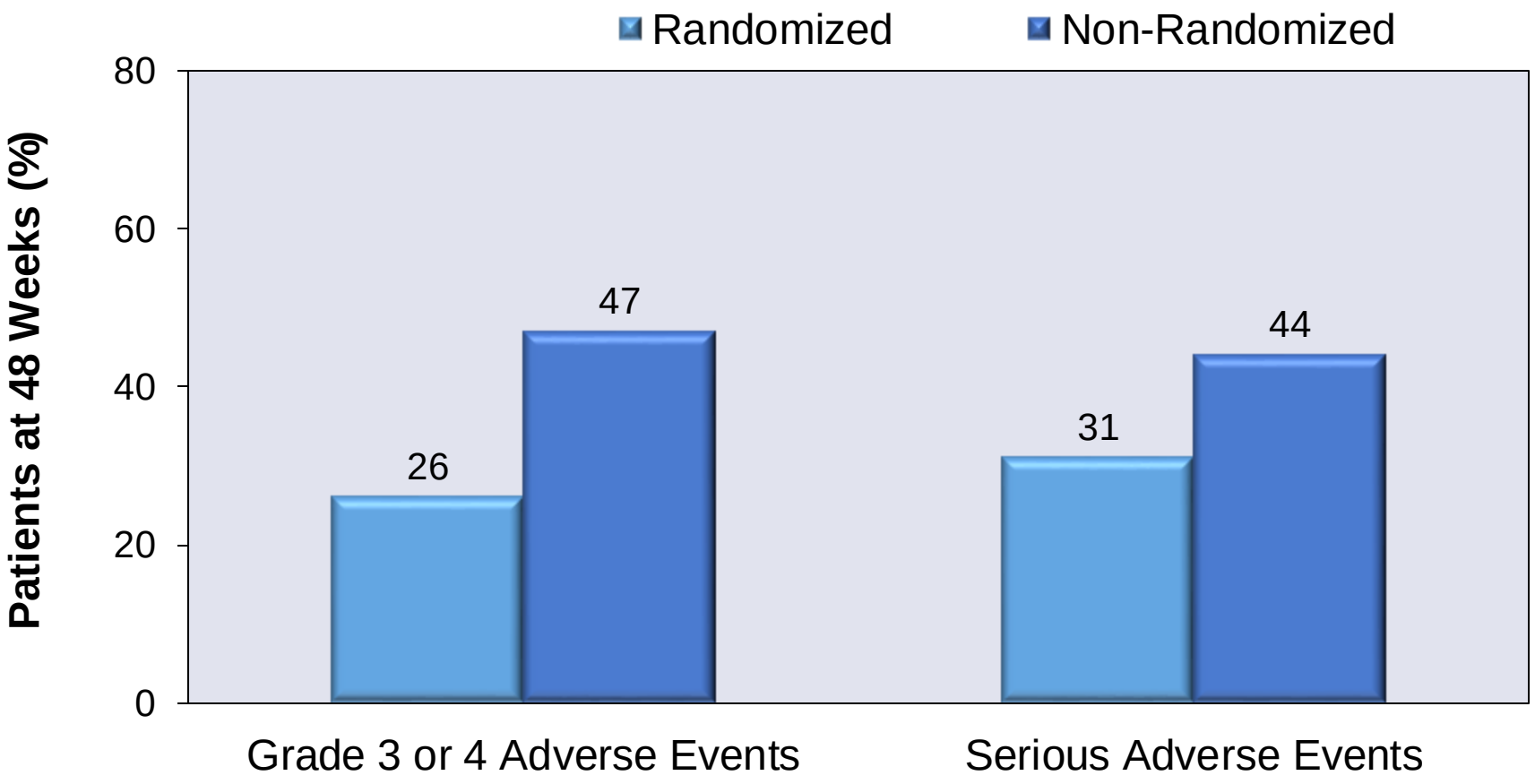
Fostemsavir (FTR) for Heavily Treatment Experienced BRIGHTE Study: Results

Adverse Events



Source: Kozal M, et al. N Engl J Med. 2020;382:1232-43.

Fostemsavir (FTR) for Heavily Treatment Experienced BRIGHTE Study: Results

Adverse Events

- Nearly 90% of patients described at least one adverse event, but serious events were attributed to infections from advanced HIV
- Adverse events led to discontinuation in only 7% of patients

- GI side effects
  - Nausea (10%)
  - Diarrhea (4%)
  - Abdominal pain (3%)
  - Dyspepsia (3%)
  - Vomiting (2%)
- CNS
  - Headache (4%)
  - Fatigue (3%)
  - Sleep disturbance (3%)

Source: Kozal M, et al. N Engl J Med. 2020;382:1232-43. / Package Inster

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Fostemsavir (FTR) for Heavily Treatment Experienced BRIGHTE Study: Conclusion

Conclusion: “In patients with multidrug-resistant HIV-1 infection with limited therapy options, those who received fostemsavir had a significantly greater decrease in the HIV-1 RNA level than those who received placebo during the first 8 days. Efficacy was sustained through 48 weeks.”

Source: Kozal M, et al. N Engl J Med. 2020;382:1232-43.

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Place in Therapy

Case

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Tale of the Tape

- Pros
  - Completely new class
  - Manageable side effect profile and drug interactions
  - Compatible with other ARVs
  - No food restrictions
  - Safe in renal disease
- Cons and Unknowns
  - Twice daily dosing
  - Hepatic impairment
    - Concentrations may increase
  - Costs
  - Resistance

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FTR Take Home Points

- Works by **blocking** the **attachment** of the virus to CD4 at gp 120
  - Works regardless of R5/X4 status
- Oral tablet taken twice daily with or without food
- Few interactions, but need to avoid **CYP3A4 inducers**
- Safe in renal impairment and hemodialysis
- Use is reserved for ‘heavily treatment-experienced adults with multidrug resistance’
- Several unknowns

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Acknowledgment

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