National HIV Curriculum

Fostemsavir

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Disclosures

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

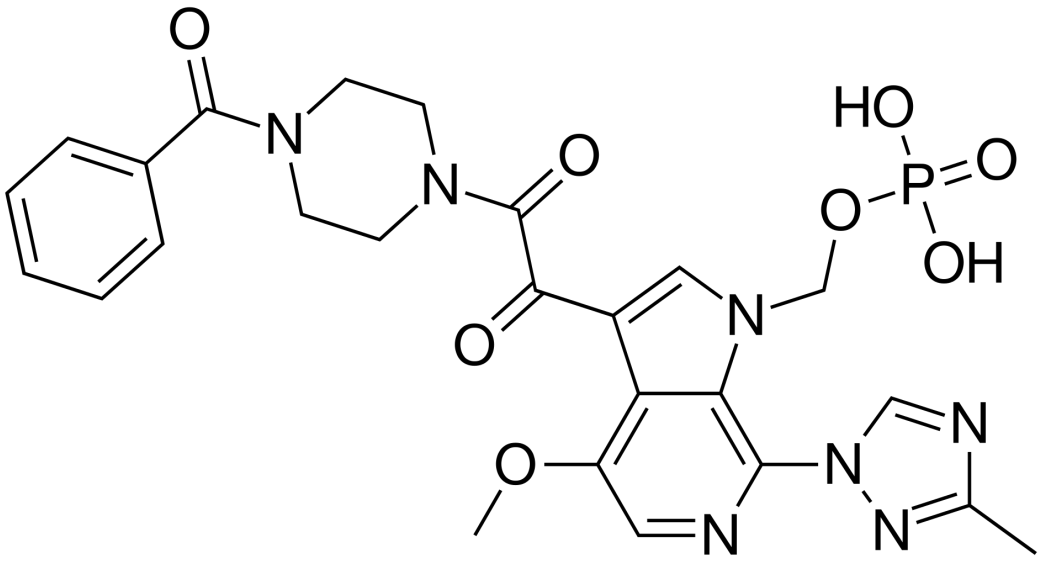
Fostemsavir

600 mg

Attachment Inhibitor

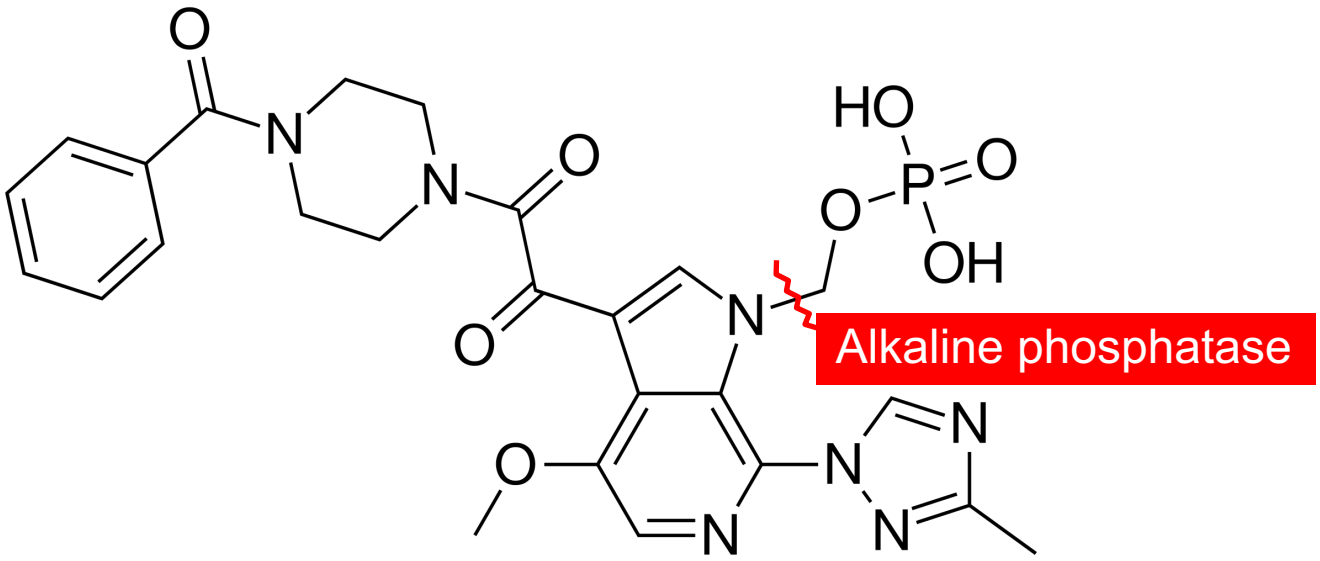
Dose: 1 tablet twice daily with or without food

Fostemsavir



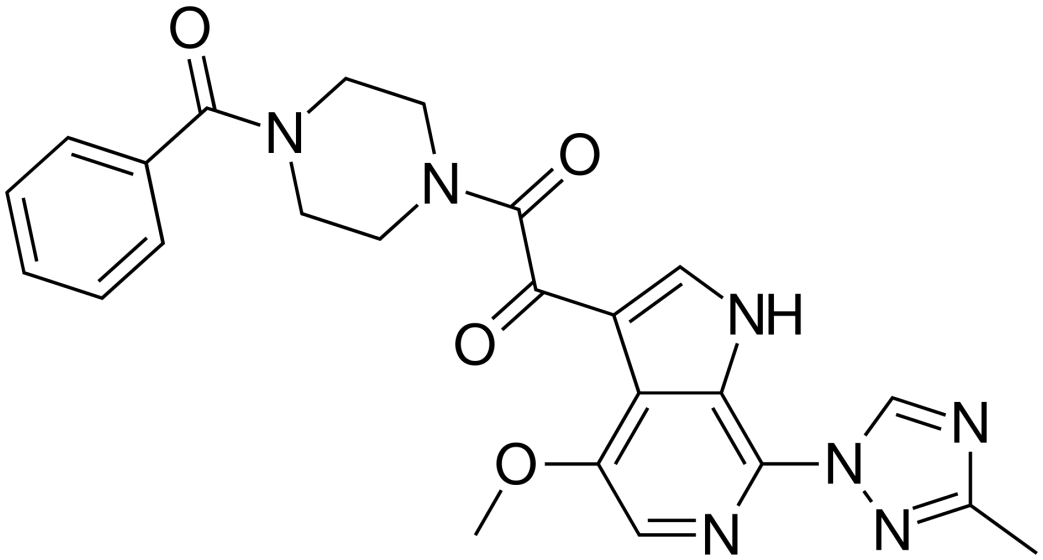
Fostemsavir is a prodrug of temsavir

Fostemsavir: Hydrolysis by Alkaline Phosphatase



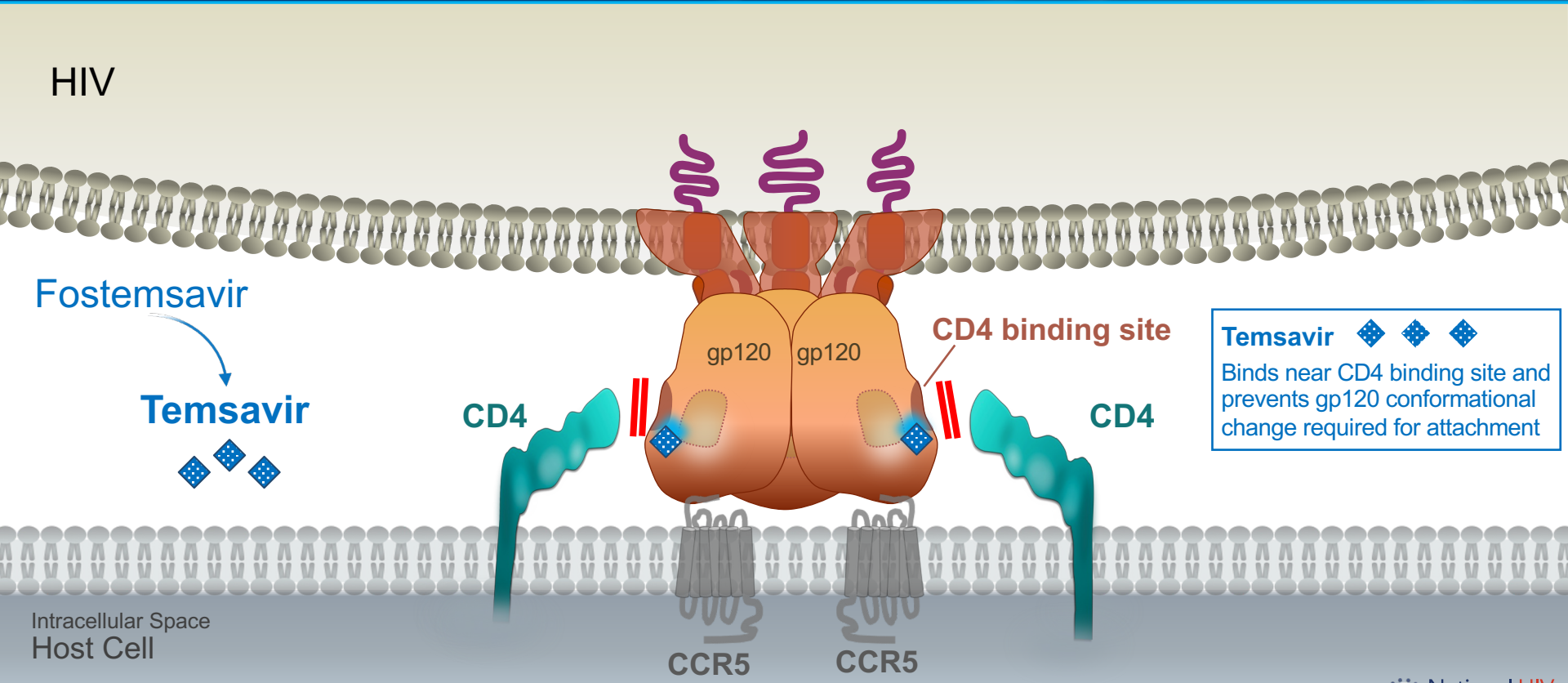
Fostemsavir undergoes hydrolysis on the luminal surface of the small intestine brush border membranes

Temsavir (Active Drug)



HIV Entry Inhibitors

Fostemsavir: Attachment Inhibitor



Temsavir

Binds near CD4 binding site and prevents gp120 conformational change required for attachment

Illustration: David H. Spach, MD

National HIV Curriculum

Fostemsavir

- **Indication**
  - Heavily treatment-experienced adults with multidrug-resistant HIV-1
- **Drug-drug interactions**
  - Avoid: strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort), grazoprevir, voxilaprevir, >30 mcg/day ethinyl estradiol
  - Use with caution if prolonged QTc or taking meds known to cause torsade de pointes
  - Consider statin dose adjustment (use lowest possible statin starting dose)
- **Use during pregnancy**
  - Insufficient data

Source: Fostemsavir Prescribing Information

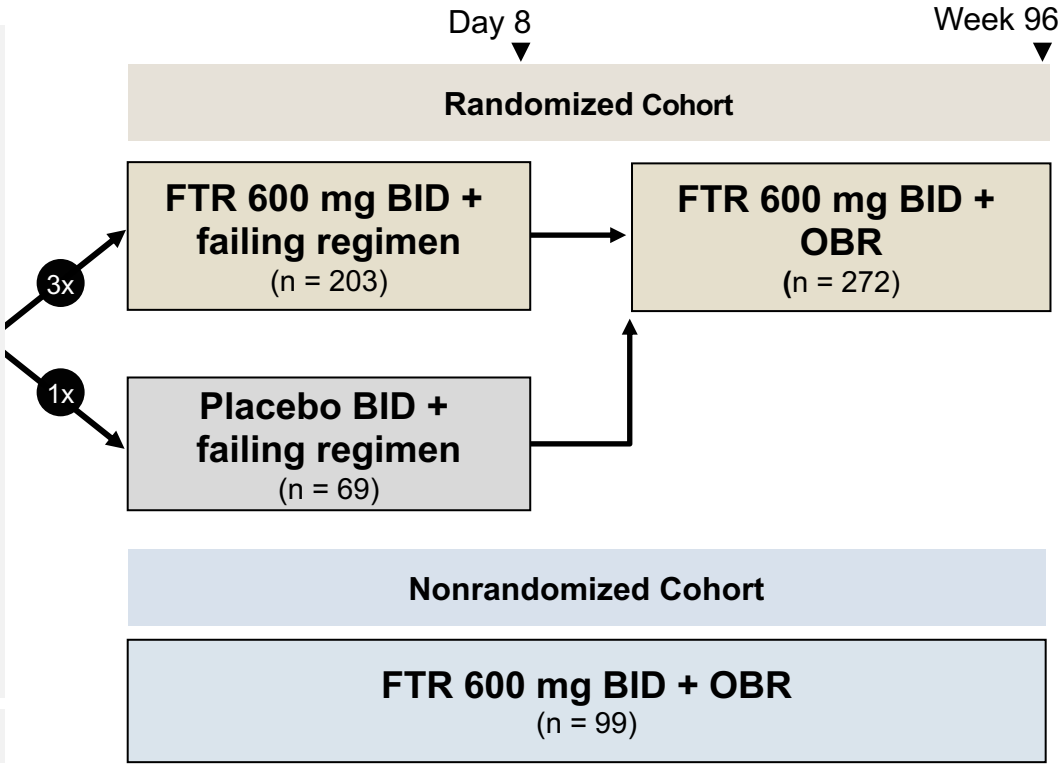
Fostemsavir for Heavily Treatment-Experienced Individuals

BRIGHTE Study (Week 48 Data)

Fostemsavir for Heavily Treatment-Experienced Individuals
BRIGHTE Study (Week 48): Background

- **Background**
  - Phase 3, randomized, placebo-controlled, non-inferiority trial evaluating fostemsavir (FTR) in salvage ART
- **Enrollment Criteria:**
  - Highly ART-experienced adults
  - Virologic failure on current ART
  - HIV RNA >400 copies/mL
  - Multiclass ART resistance
  - At least one fully active agent (for randomized cohort)

*OBR = optimized background regimen



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

Fostemsavir for Heavily-Treatment Experienced Individuals
BRIGHTE Study (Week 48): Baseline Characteristics

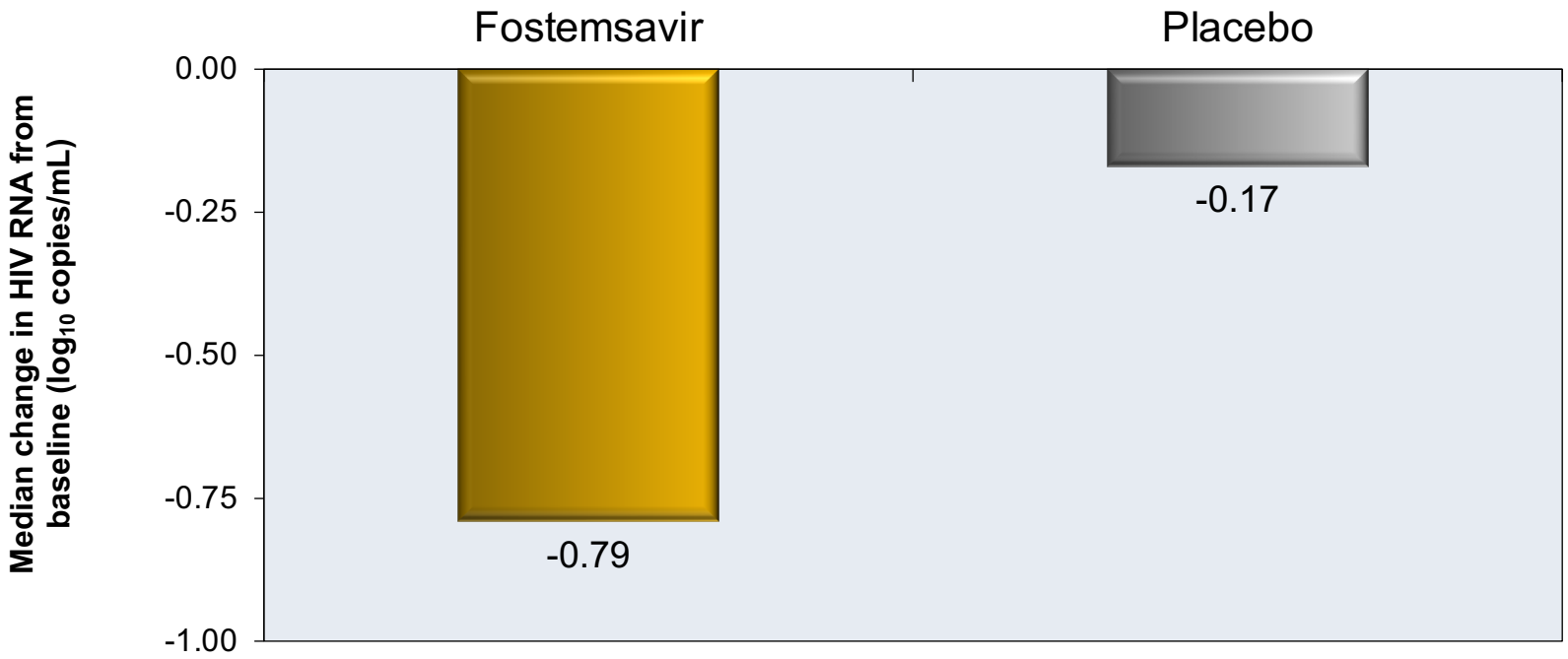
Baseline Characteristics	Randomized (n = 272)	Non-Randomized (n = 99)
Age, years, median (range)	48 (18-73)	50 (17-72)
Male sex, n (%)	200 (74)	89 (90)
White, n (%)	184 (68)	74 (74)
Black/African American, n (%)	60 (22)	23 (23)
HIV RNA 1,000-100,000 copies/mL, n (%)	161 (59)	75 (76)
HIV RNA >100,000 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: dolutegravir, boosted darunavir, tenofovir DF, etravirine, maraviroc, enfuvirtide, ibalizumab

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

Fostemsavir for Heavily Treatment-Experienced Individuals BRIGHTE Study (Week 48): Results

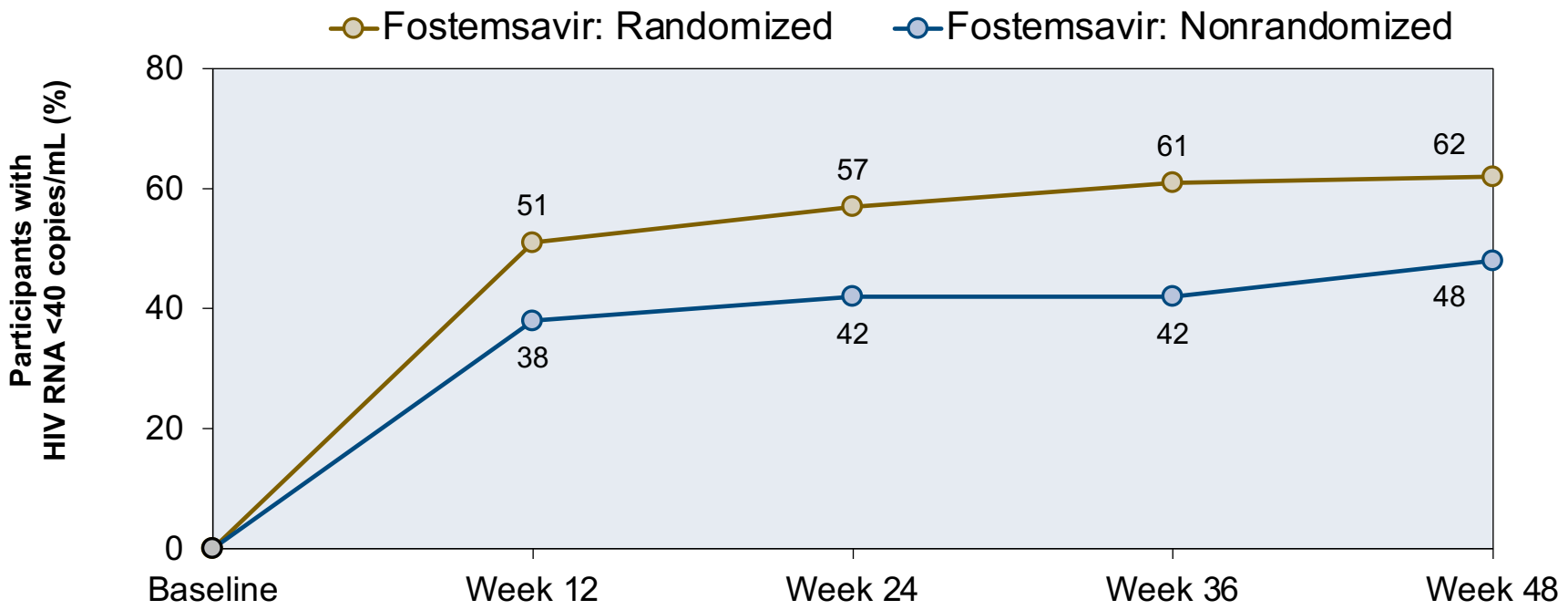
Baseline to Day 8 Change in HIV RNA Level (Randomized Cohort)



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

Fostemsavir for Heavily Treatment-Experienced Individuals
BRIGHTE Study (Week 48): Results

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



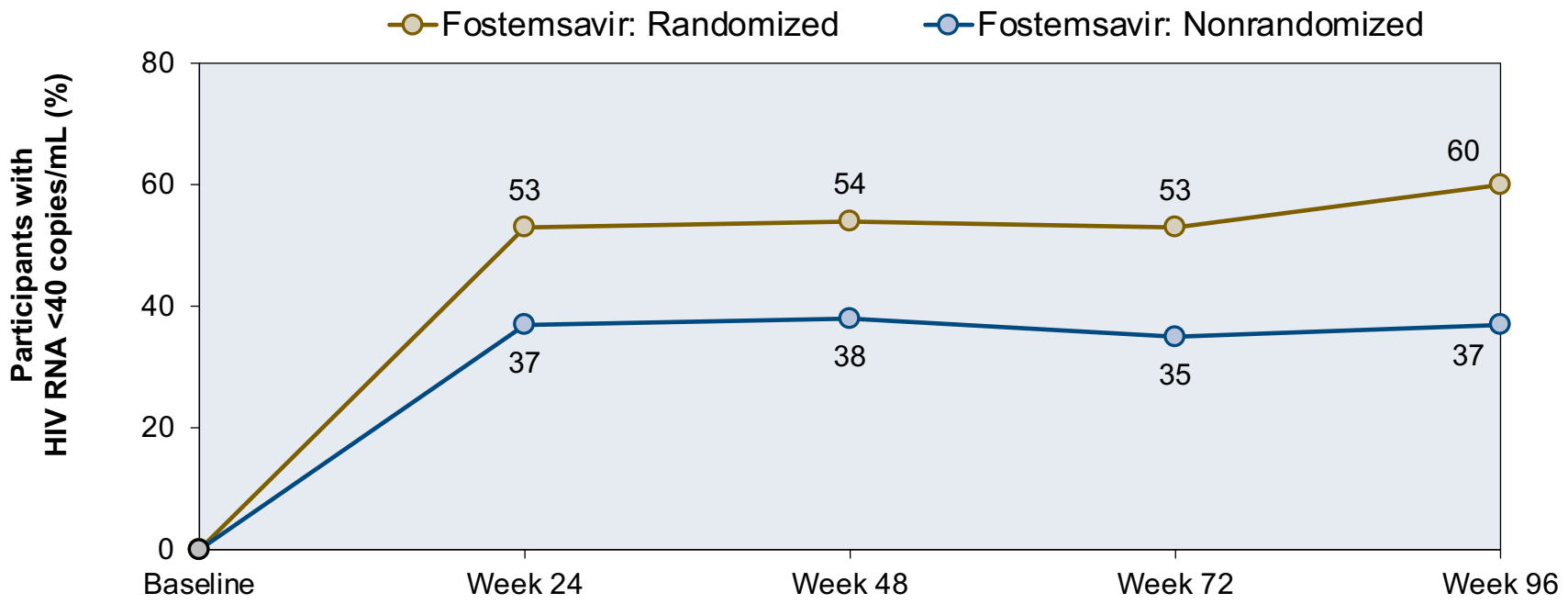
Source: Kozal M, et al. N Engl J Med. 2020;382:1232-43.

Fostemsavir for Heavily Treatment-Experienced Individuals

BRIGHTE Study (Week 96 Data)

Fostemsavir for Heavily Treatment-Experienced Individuals
BRIGHTE Study (Week 96): Results

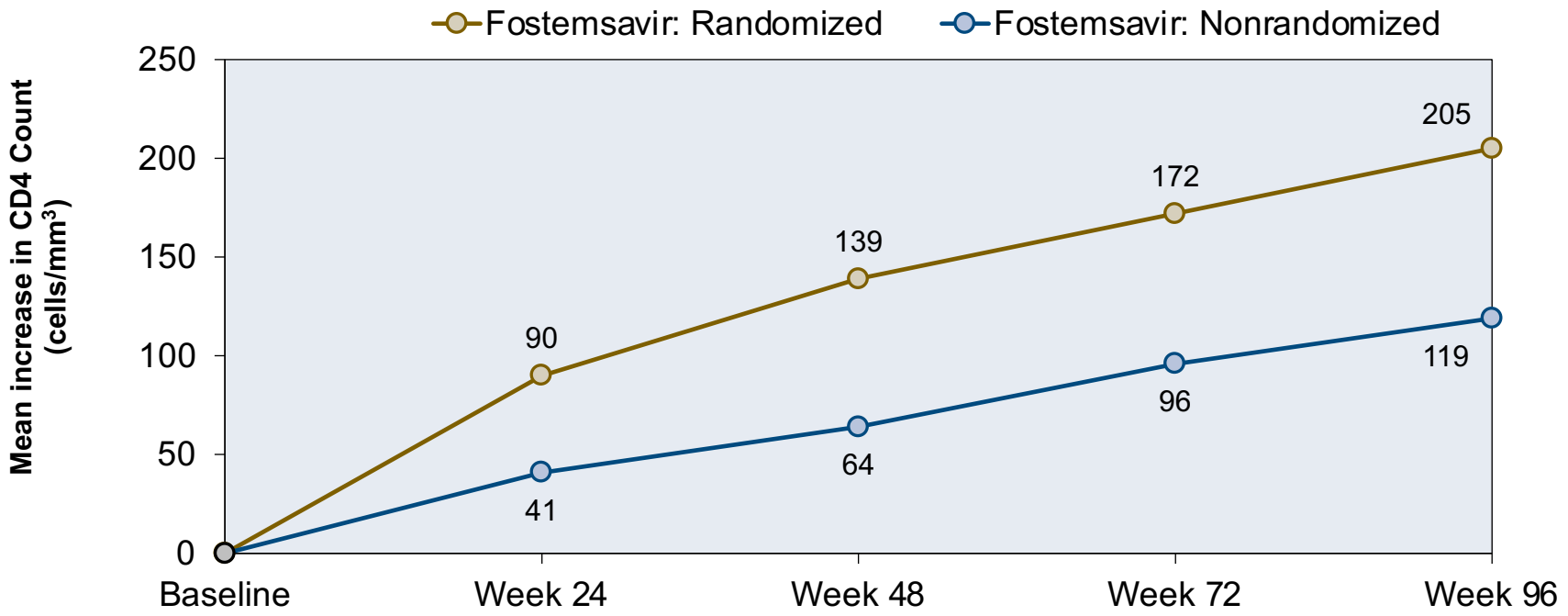
Virologic Response Through Week 96 (HIV RNA <40 copies/mL)



Source: Lataillade M, et al. Lancet HIV. 2020;7:e740-51.

Fostemsavir for Heavily Treatment-Experienced Individuals
BRIGHTE Study (Week 96): Results

Mean Change in CD4 T-Cell Count Through Week 96



Source: Lataillade M, et al. Lancet HIV. 2020;7:e740-51.

Fostemsavir for Heavily Treatment-Experienced Individuals
BRIGHTE Study (Week 96): Results

Adverse Events (AEs)	Randomized (n = 272)	Non-Randomized (n = 99)
Any AE, n (%)	249 (92)	98 (99)
Drug-related grade 2-4 AEs, n (%)	57 (21)	22 (22)
Nausea	9 (3)	5 (5)
Diarrhea	6 (2)	3 (3)
Headache	6 (2)	1 (1)
Vomiting	4 (1)	2 (2)
Fatigue	3 (1)	2 (2)
Asthenia	2 (<1)	2 (2)
Drug-related AE leading to discontinuation, n (%)	7 (3)	7 (3)
Drug-related serious AE, n (%)	9 (3)	3 (3)

Source: Lataillade M, et al. Lancet HIV. 2020;7:e740-51.

Fostemsavir Resistance

Fostemsavir for Heavily Treatment-Experienced Individuals
BRIGHTE Study (Week 96): Virologic Failures

	Randomized (n = 272)	**Non-Randomized** (n = 99)
Number of virologic failures	69/272 (25%)	50/99 (51%)
With gp120 RAPs at screening (of those with genotypic data)	43/68 (63%)	26/48 (54%)
Virologic failures with post-baseline data	53	45
With emergent gp120 (*env*) RAS	29/53 (55%)	33/45 (73%)
S**375**H/I/M/N/T	19/53 (36%)	21/45 (47%)
M**426**L/I	18/53 (34%)	23/45 (51%)
M**434**I/L	6/53 (11%)	5/45 (11%)
M**475**I/L/V	8/53 (15%)	5/45 (11%)

Abbreviation: RAPs = Resistance-associated polymorphisms; RAS = Resistance-associated substitutions

Source: Fostemsavir Prescribing Information

Fostemsavir (FTR): Resistance Testing & Cross Resistance

- FTR can be used regardless of HIV-1 tropism
- Standard genotype testing does not give FTR resistance information
- Certain viral subtypes, such as AE, may have reduced susceptibility, but are rare
- HIV with resistance mutations in the gp120 envelope subunit due to virologic failure on ibalizumab or maraviroc may have reduced susceptibility to FTR, but are rare
- Viruses resistant to the gp41 inhibitor enfuvirtide typically retain susceptibility to FTR
- Other entry inhibitors tend to retain activity in the presence of FTR resistance mutations

Source: Fostemsavir Prescribing Information

Fostemsavir: Summary

- Oral, twice-daily, CD4 attachment inhibitor
- Typically used as part of salvage antiretroviral therapy for heavily-treatment experienced individuals
- Can be combined with other entry inhibitors (ibalizumab, enfuvirtide, maraviroc if R5-tropic), other salvage antiretrovirals, and/or optimized background regimen
- Overall, well tolerated with few drug-drug interactions, though need to consider interactions with strong CYP3A4 inducers, estradiol, statins, and drugs that may prolong the QTc or cause torsade de pointes
- Resistance mutations in the gp120 envelope subunit may develop with virologic failure

Acknowledgments

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