National HIV Curriculum

# Maraviroc

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# Disclosures

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

# Maraviroc

**150 mg and 300 mg**

Entry Inhibitor

Dosing: twice daily dosing, with or without food

# Maraviroc: Indications and Dosing

- **Indication**
  - In combination with other antiretroviral agents for adults (and children ≥2 kgs) who have only CCR5-tropic HIV-1
  - Requires HIV Tropism Assay testing before use
  - Not recommended for initial treatment of HIV-1 infection
- **Preparations**
  - Tablets: 25-mg, 75-mg, 150-mg, and 300-mg
  - Oral Solution: 20 mg per mL clear, colorless, strawberry-flavored
- **Dosing**
  - Twice daily dosing, with dose dependent on interactions with other medications
  - Take with or without food

Source: Maraviroc Prescribing Information

# Maraviroc: Dosing Adjustments with Concomitant Medications

| Maraviroc: Recommended Dosage in Adults | |
|---|---|
| **Concomitant Medications** | **Dose** |
| Potent cytochrome P450 (CYP)3A inhibitors[a] (+/- potent CYP3A inducer) | 150 mg twice a day |
| Noninteracting concomitant medications[b] | 300 mg twice a day |
| Potent and moderate CYP3A inducers (without a potent CYP3A inhibitor)[c] | 600 mg twice a day |

[a] Potent CYP3A inhibitors (+/- potent CYP3A inducer) including: clarithromycin, cobicistat, elvitegravir/ritonavir, itraconazole, ketoconazole, nefazodone, protease inhibitors (except tipranavir/ritonavir), telithromycin.

[b] Noninteracting concomitant medications include all medications that are not potent CYP3A inhibitors or inducers such as: dolutegravir, enfuvirtide, nevirapine, all nucleoside reverse transcriptase inhibitors (NRTIs), raltegravir, and tipranavir/ritonavir.

[c] Potent and moderate CYP3A inducers (without a potent CYP3A inhibitor) including: carbamazepine, efavirenz, etravirine, phenobarbital, phenytoin, and rifampin.

Source: Maraviroc Prescribing Information

# Maraviroc: Dosing Based on Renal Function

**Recommended Maraviroc Dosage in Adults Based on Renal Function**

| Concomitant Medications | Dosage of Maraviroc Based on Renal Function | | |
|---|---|---|---|
| | CrCl ≥30 mL/min | CrCl <30 mL/min | End-Stage Renal Disease on Regular Hemodialysis |
| Potent CYP3A inhibitors (with or without a CYP3A inducer)[a] | 150 mg twice daily | Contraindicated | Contraindicated |
| Noninteracting concomitant medications[b] | 300 mg twice daily | 300 mg twice daily | 300 mg twice daily[d] |
| Potent and moderate CYP3A inducers (without a potent CYP3A inhibitor)[c] | 600 mg twice daily | Contraindicated | Contraindicated |

[a] Potent CYP3A inhibitors (with or without a CYP3A inducer) including: clarithromycin, cobicistat, elvitegravir/ritonavir, itraconazole, ketoconazole, nefazodone, protease inhibitors (except tipranavir/ritonavir), telithromycin.
[b] Noninteracting concomitant medications include all medications that are not potent CYP3A inhibitors or inducers such as: dolutegravir, enfuvirtide, nevirapine, all NRTIs, raltegravir, and tipranavir/ritonavir.
[c] Potent and moderate CYP3A inducers (without a potent CYP3A inhibitor) including: carbamazepine, efavirenz, etravirine, phenobarbital, phenytoin, and rifampin.
[d] Maraviroc dosing should be decreased to 150 mg twice daily if patients experience symptoms of postural hypotension

Source: Maraviroc Prescribing Information

# Maraviroc: Mechanism of Action

# Host Cellular Co-Receptors Involved in HIV Entry

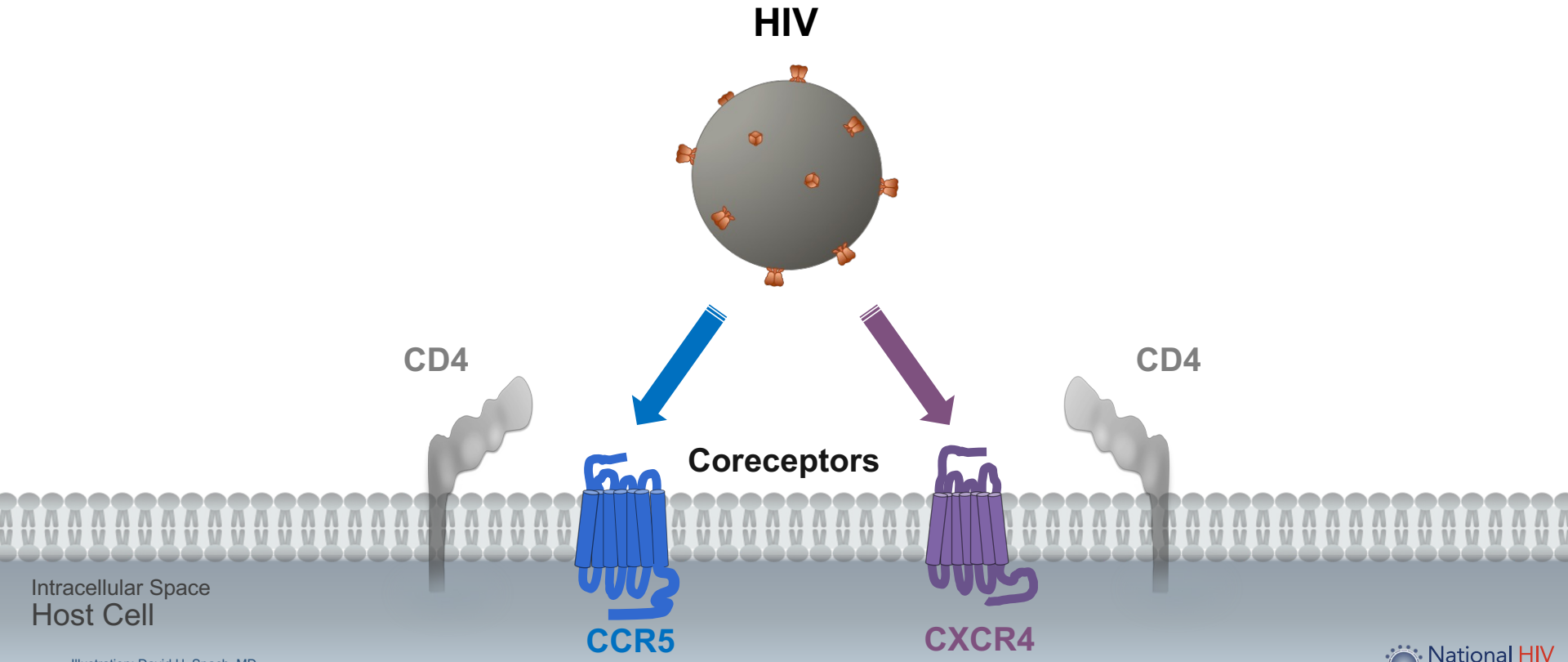


Illustration: David H. Spach, MD

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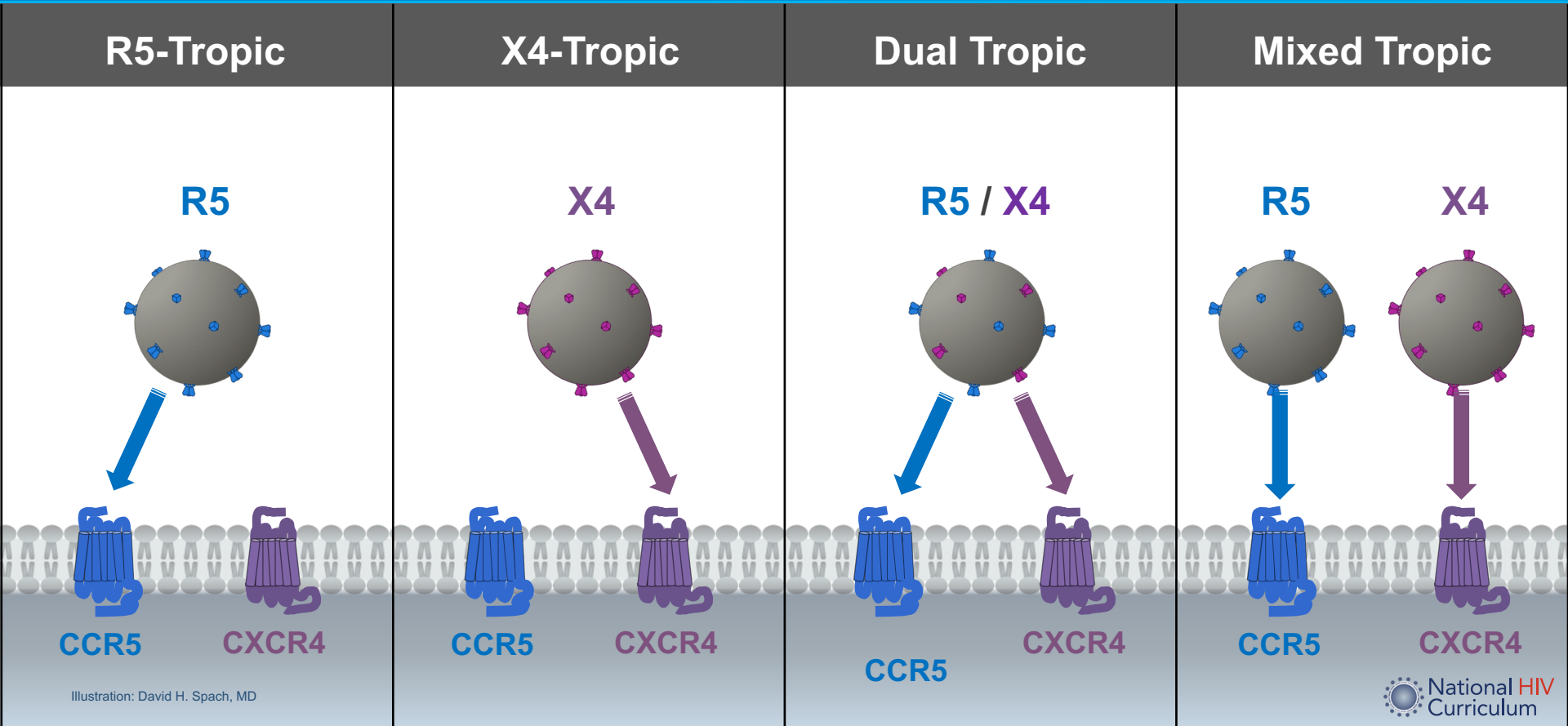
# HIV Tropism


R5-Tropic
X4-Tropic
Dual Tropic
Mixed Tropic
R5
X4
R5 / X4
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X4
CCR5
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Illustration: David H. Spach, MD
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# Maraviroc: Mechanism of Action

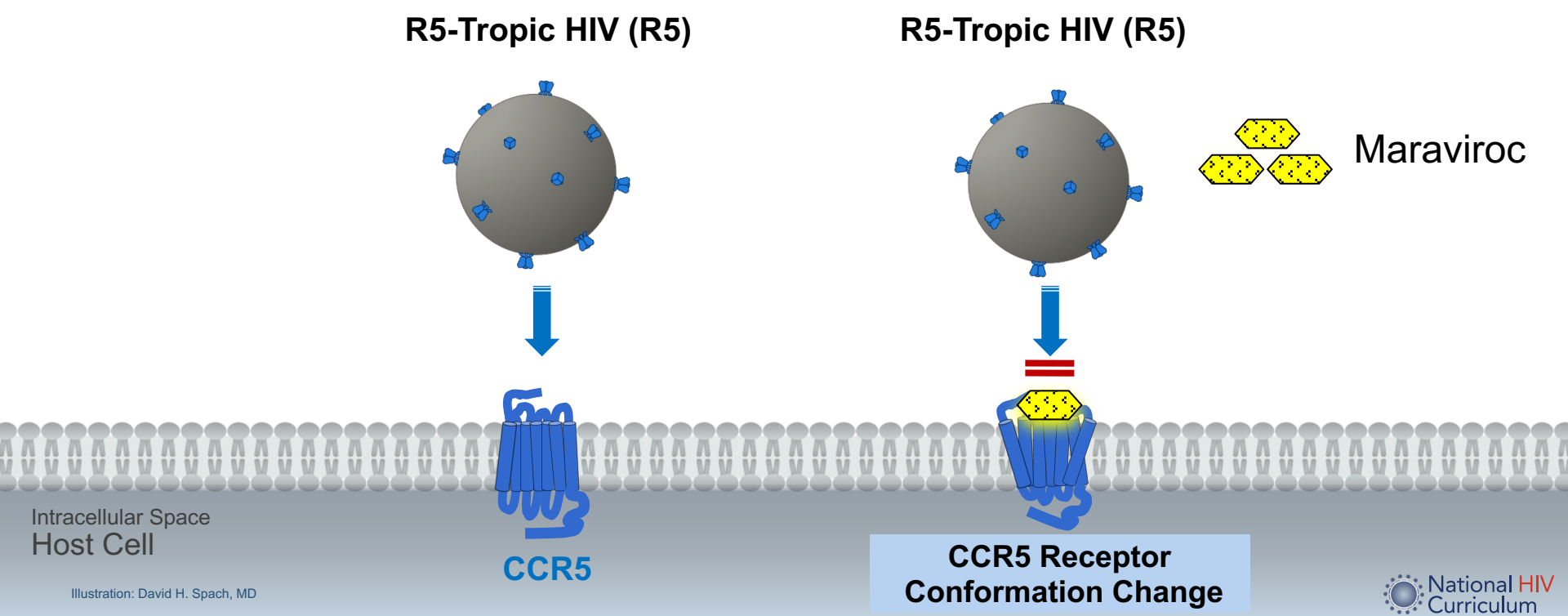
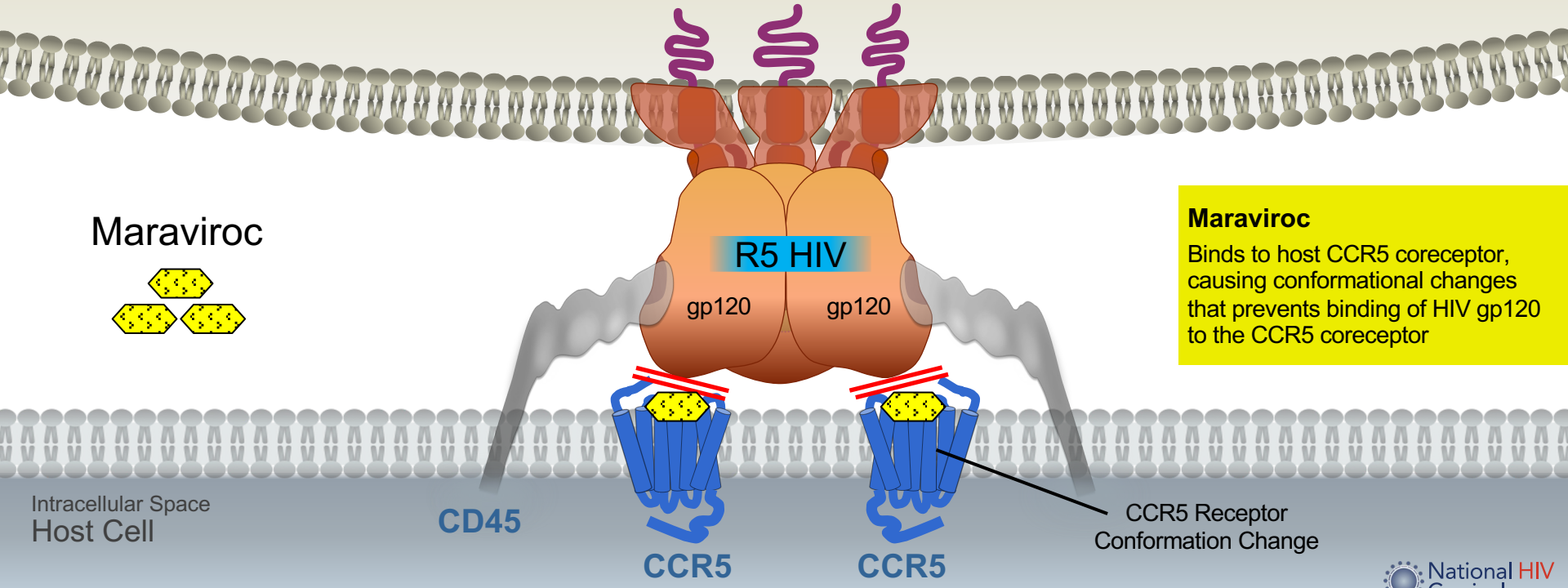



Illustration: David H. Spach, MD

# HIV Entry Inhibitor: CCR5 Antagonist

Maraviroc

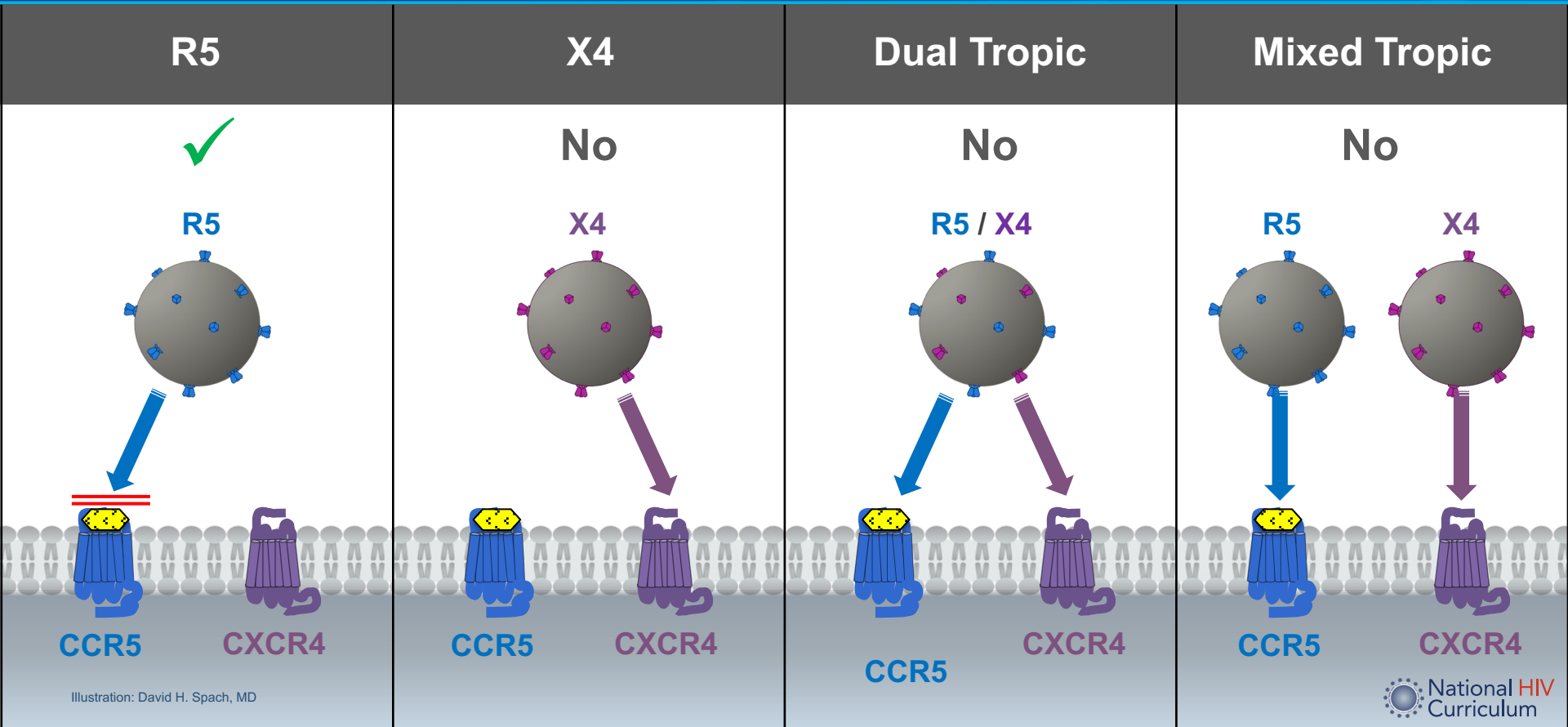



**Maraviroc**

Binds to host CCR5 coreceptor, causing conformational changes that prevents binding of HIV gp120 to the CCR5 coreceptor

# Coreceptor Tropism Results: Maraviroc Indication

Maraviroc



# Key Clinical Trials

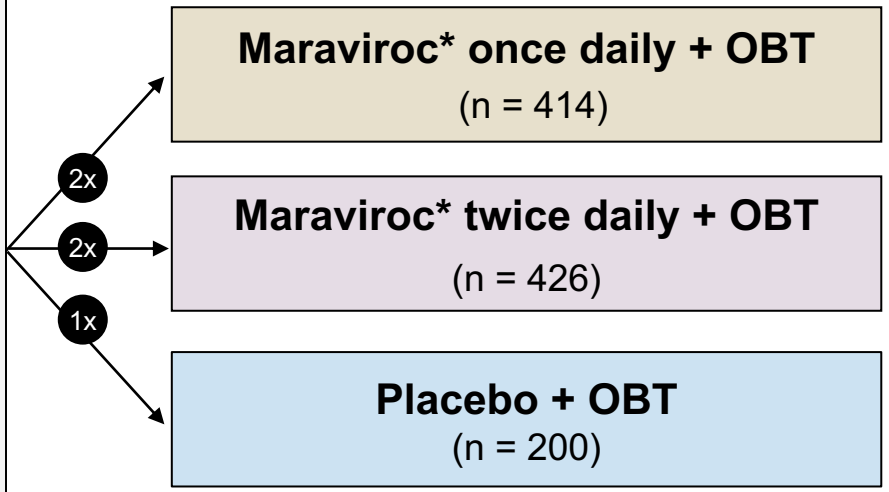
# Maraviroc: Summary of Key Studies

- **Trials in Treatment Naïve**
  - [1]MERIT: Maraviroc (QD or BID + ZDV-3TC versus Efavirenz + ZDV-3TC)
    - Maraviroc inferior to efavirenz for virologic suppression
- **Trials In Treatment-Experienced Persons**
  - [2]MOTIVATE 1 & MOTIVATE 2: Maraviroc (QD or BID) + OBT
    - Maraviroc + OBT significantly greater virologic suppression than OBT alone
- **Switch Trials**
  - [3]ROCnRal (ARNS 157): Switch to 2-drug Maraviroc + Raltegravir
    - In treatment-experienced patients, maraviroc + raltegravir lacked virological robustness

[1]Cooper DA, et al. J Infect Dis. 2010;201:803-13.
[2]Gulick RM, et al. N Engl J Med. 2008;359:1429-41.
[3]Katlama C, et al. J Antimicrob Chemother. 2014;69:1648-52.

# Maraviroc in Patients with Multiclass Antiretroviral Drug Resistance
# MOTIVATE 1 and 2: Study Design

- **Background:** Two parallel, randomized, double-blind, placebo-controlled, phase 3 trials comparing 2 does of maraviroc in treatment-experience persons
- **Inclusion Criteria**
  - Age ≥16 years
  - Treatment experienced
  - Resistance to ≥ 3 ARV classes
  - Only R5-tropic HIV
  - Stable ARV regimen or no regimen for ≥4 weeks with HIV RNA ≥ 5,000 copies/mL




*MVC dosing:
- 300 mg daily or BID with PI-containing regimens
- 150 mg daily or BID with all other regimens

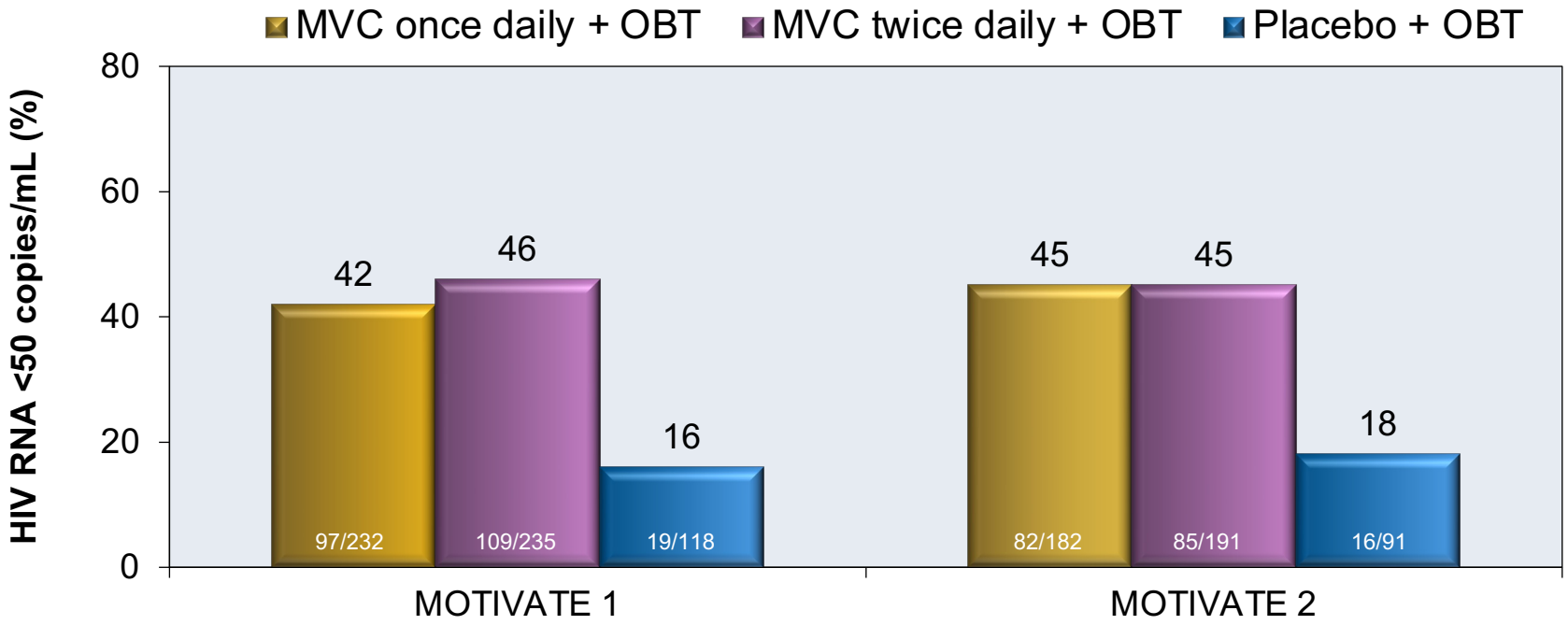
OBT = Optimized Background Therapy (3-6 agents)

**MOTIVATE** = **M**araviroc versus **O**ptimized **T**herapy in **V**iremic **A**ntiretroviral **T**reatment-**E**xperienced Patients

Source: Gulick RM, et al. N Engl J Med. 2008;359:1429-41.

# Maraviroc in Patients with Multiclass Antiretroviral Drug Resistance MOTIVATE 1 and 2: Results

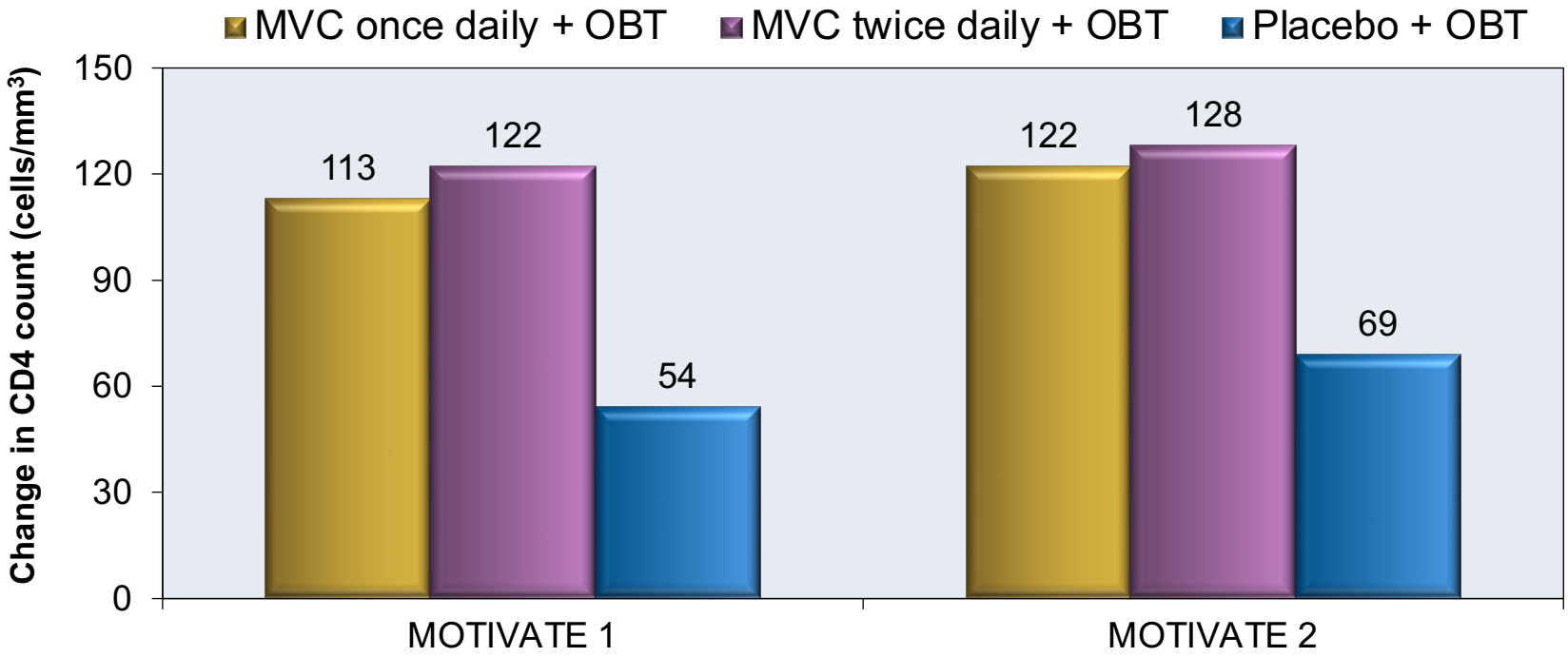
## Week 48: Virologic Response (ITT, missing=nonresponse)




Source: Gulick RM, et al. N Engl J Med. 2008;359:1429-41.

# Maraviroc in Patients with Multiclass Antiretroviral Drug Resistance MOTIVATE 1 and 2: Results

## Week 48: Change in CD4 Cell Count from Baseline




Source: Gulick RM, et al. N Engl J Med. 2008;359:1429-41.

# Maraviroc in Patients with Multiclass Drug Resistance
## MOTIVATE 1 and 2: Adverse Events

**Grade 2-4 Adverse Events (all causes) Occurring in ≥ 5% of Patients**
MOTIVATE 1 and MOTIVATE 2 Study Populations Combined

| Adverse Event | Maraviroc QD + OBT (n = 414) | Maraviroc BID + OBT (n = 426) | Placebo (n = 219) |
|---|---|---|---|
| Diarrhea | 43 (10%) | 32 (8%) | 20 (10%) |
| Fatigue | 13 (3%) | 21 (4%) | 13 (6%) |
| Fever | 9 (2%) | 24 (6%) | 9 (4%) |
| Headache | 22 (5%) | 9 (2%) | 12 (6%) |
| Nausea | 25 (6%) | 25 (6%) | 15 (7%) |
| Upper respiratory infection | 16 (4%) | 20 (5%) | 3 (1%) |

Abbreviations: OBT = optimized background therapy; QD = once daily; BID = twice daily

Source: Gulick RM, et al. N Engl J Med. 2008;359:1429-41.

# Adverse Effects

# Maraviroc: Potential Severe Drug Reactions

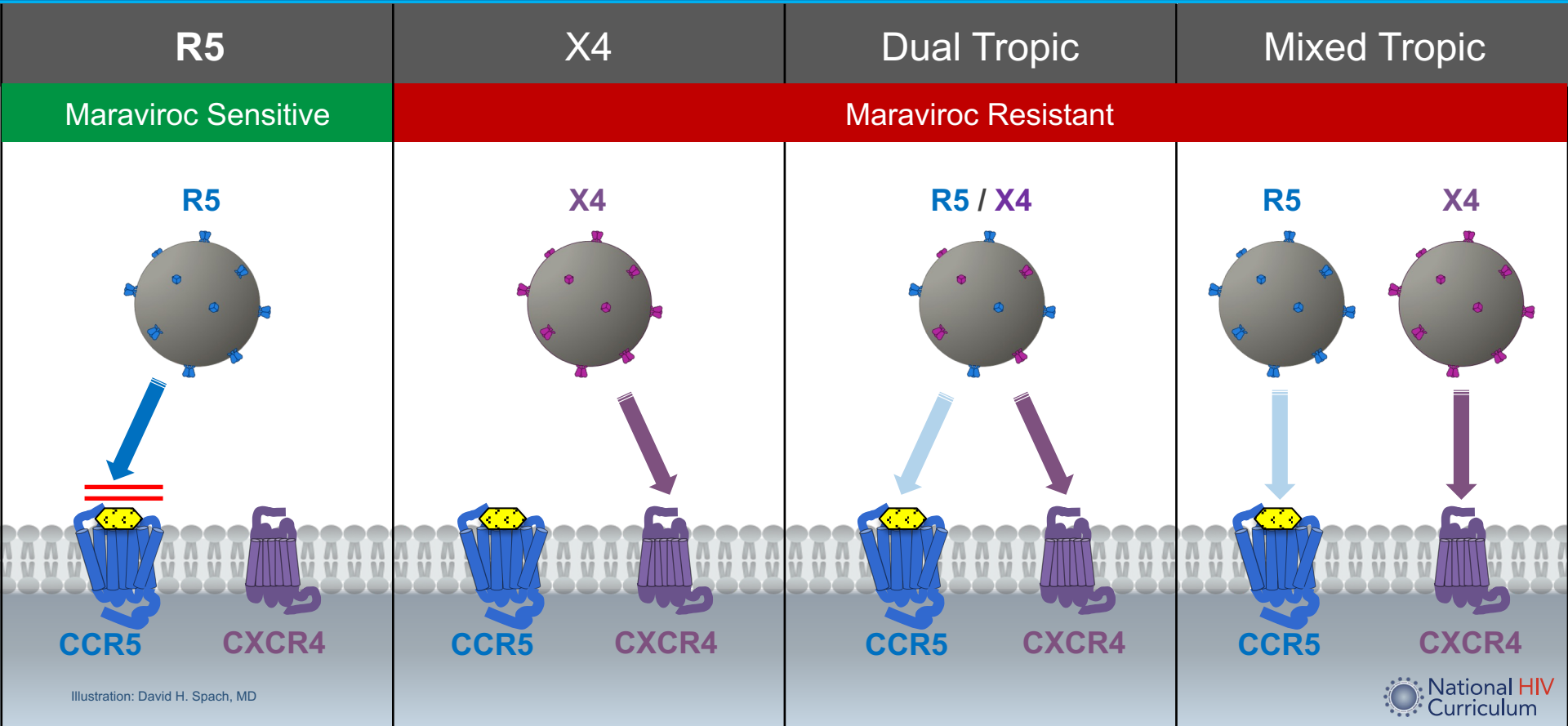
- **Hepatotoxicity** (*Black Box Warning*)
  - Maraviroc can cause severe hepatotoxicity +/-severe skin & hypersensitivity reactions
  - Severe skin rash or systemic allergic reactions may develop prior to hepatotoxicity
- **Skin rash or systemic allergic reactions**
  - Maraviroc may cause severe severe skin and hypersensitivity reactions +/- hepatoxicity
  - Reactions include fever, eosinophilia, elevated IgE, or other systemic symptoms
- **Timing and Evaluation of Severe Maraviroc-Related Drug Reaction**
  - Timing of severe reactions is approximately 1 month after starting maraviroc
  - Persons taking maraviroc should have immediate evaluation if they develop any of the following: sign or symptoms of hepatitis, a severe skin rash or systemic allergic reaction

Source: Maraviroc Prescribing Information

# Resistance

# Resistance to Maraviroc: Change in Viral Tropism

Maraviroc



# Resistance to Maraviroc: HIV Binds to CCR5 in Presence of Maraviroc

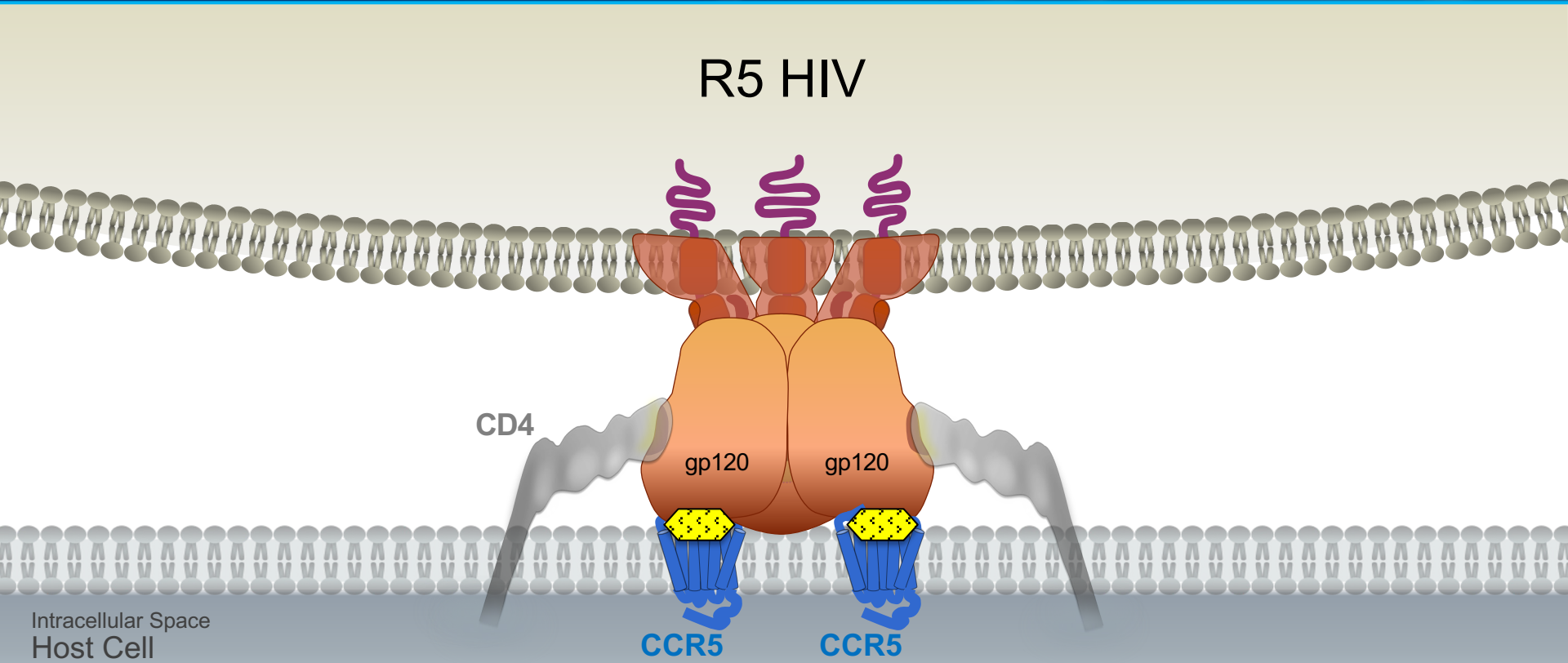



Illustration: David H. Spach, MD

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# Maraviroc: Summary

- Oral, twice-daily HIV entry inhibitor that selectively binds to human C-C chemokine receptor 5 (CCR5)
- Need to perform HIV tropism assay prior to use
- Typically used as part of salvage antiretroviral therapy for heavily-treatment experienced individuals
- Can be combined with other entry inhibitors (ibalizumab, enfuvirtide, fostemsavir), and other salvage antiretroviral medications
- Generally well tolerated with few long-term adverse effects or drug interactions, though rarely
- Rarely may cause hepatotoxicity and/or severe skin and allergic reactions

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