National HIV Curriculum

Antiretroviral Therapy: 2021 Update

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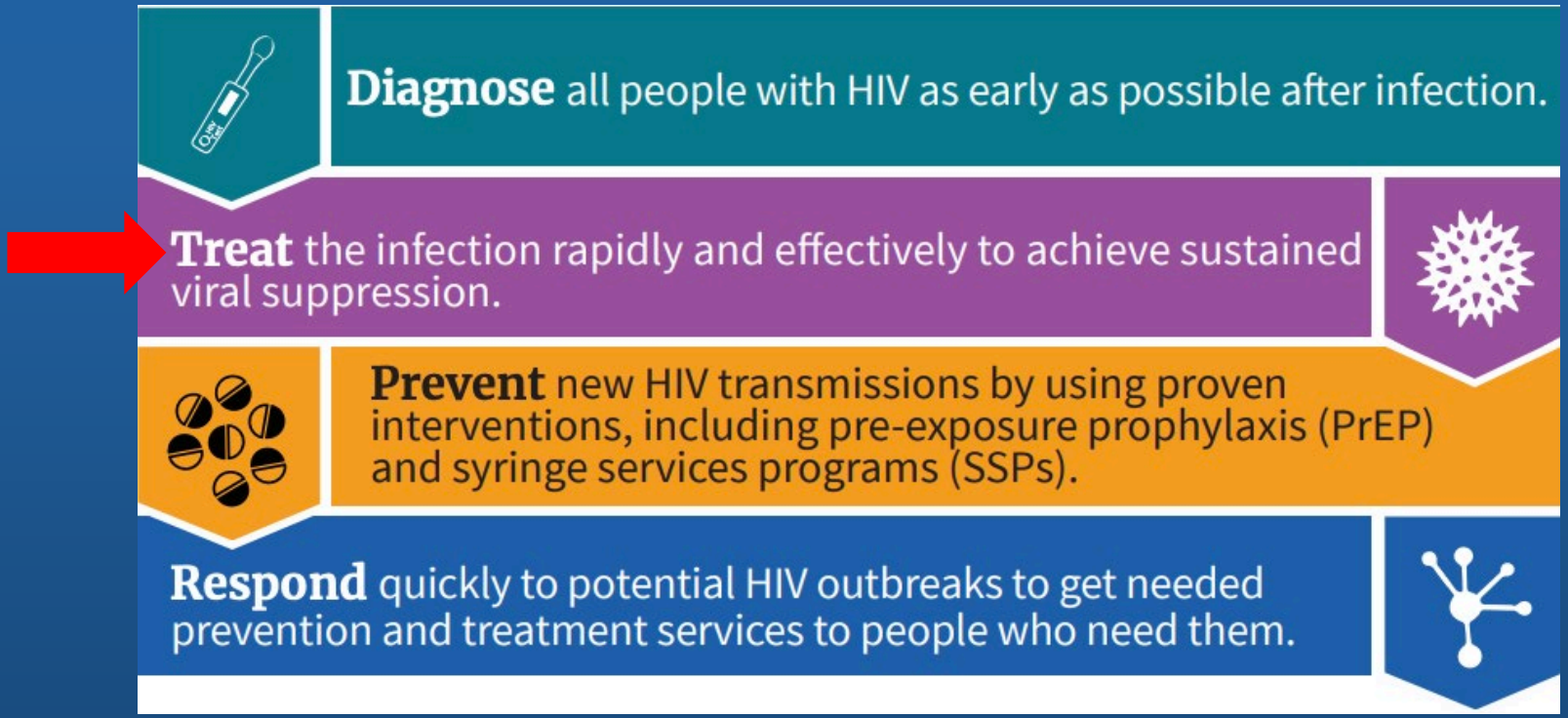
AETC AIDS Education & Training Center Program

Disclosures

Dr. Spach has no disclosures

Ending the HIV Epidemic (EHE)



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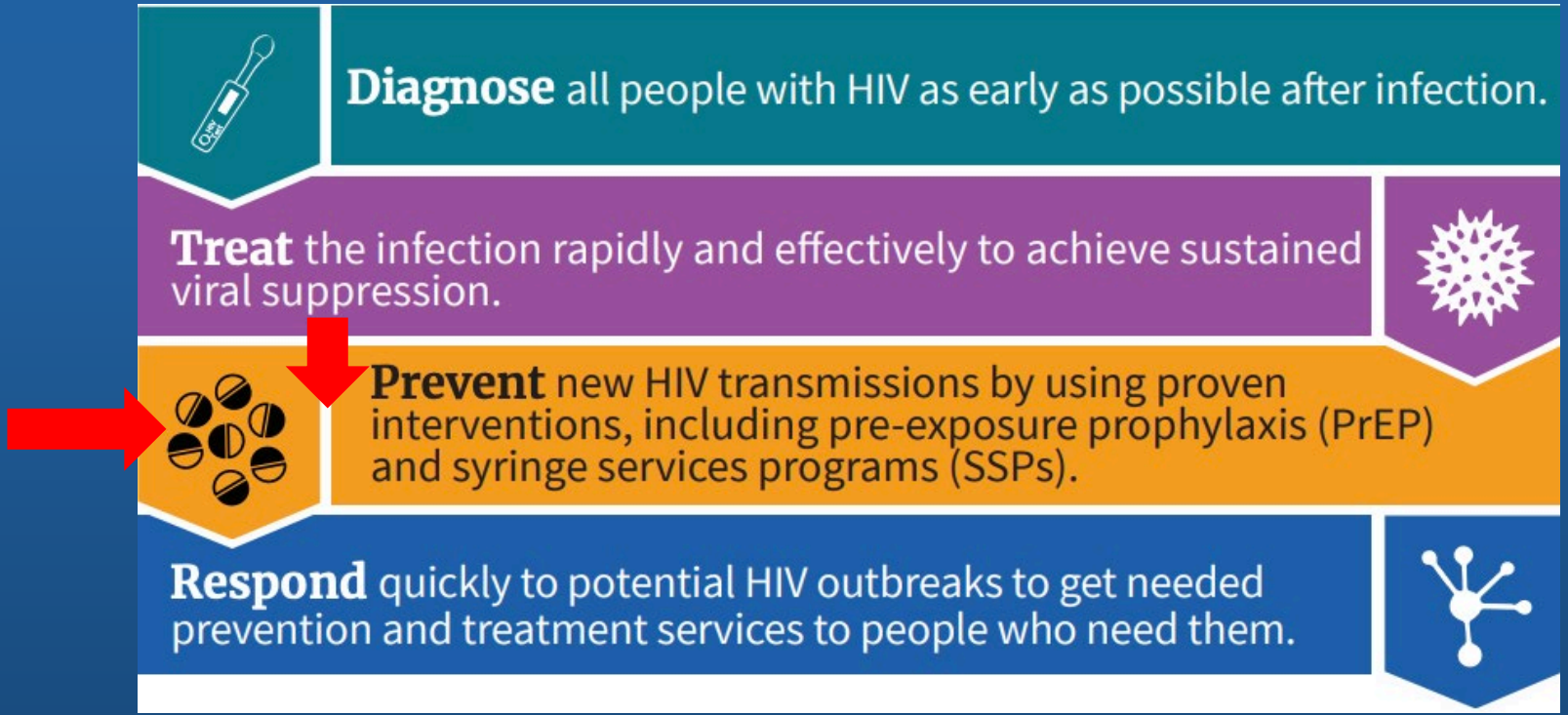
Ending the HIV Epidemic (EHE)



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Antiretroviral Therapy 2021: Outline

- **Initial Therapy**
  - Current HHS Antiretroviral Therapy Guidelines
- **Maintenance Therapy**
  - Consideration of 2-Drug Options
- **Salvage Therapy**
  - New options (Fostemsavir and Ibalizumab)
- **Future Therapy**
  - NRTTIs (Islatravir) and Capsid Inhibitor (Lenacapavir)

Initial Antiretroviral Therapy

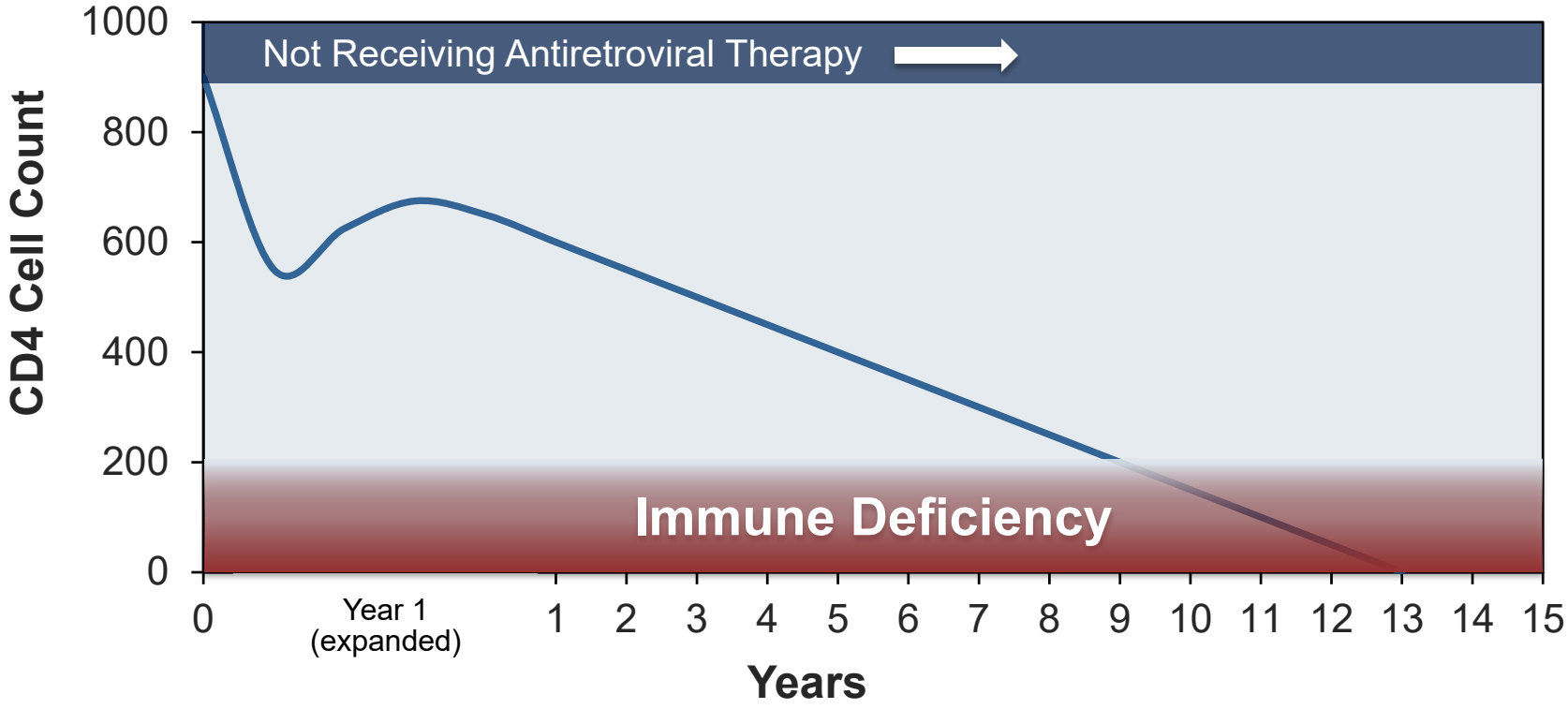
When to Start Antiretroviral Therapy

Initiating Therapy in Treatment-Naïve Persons

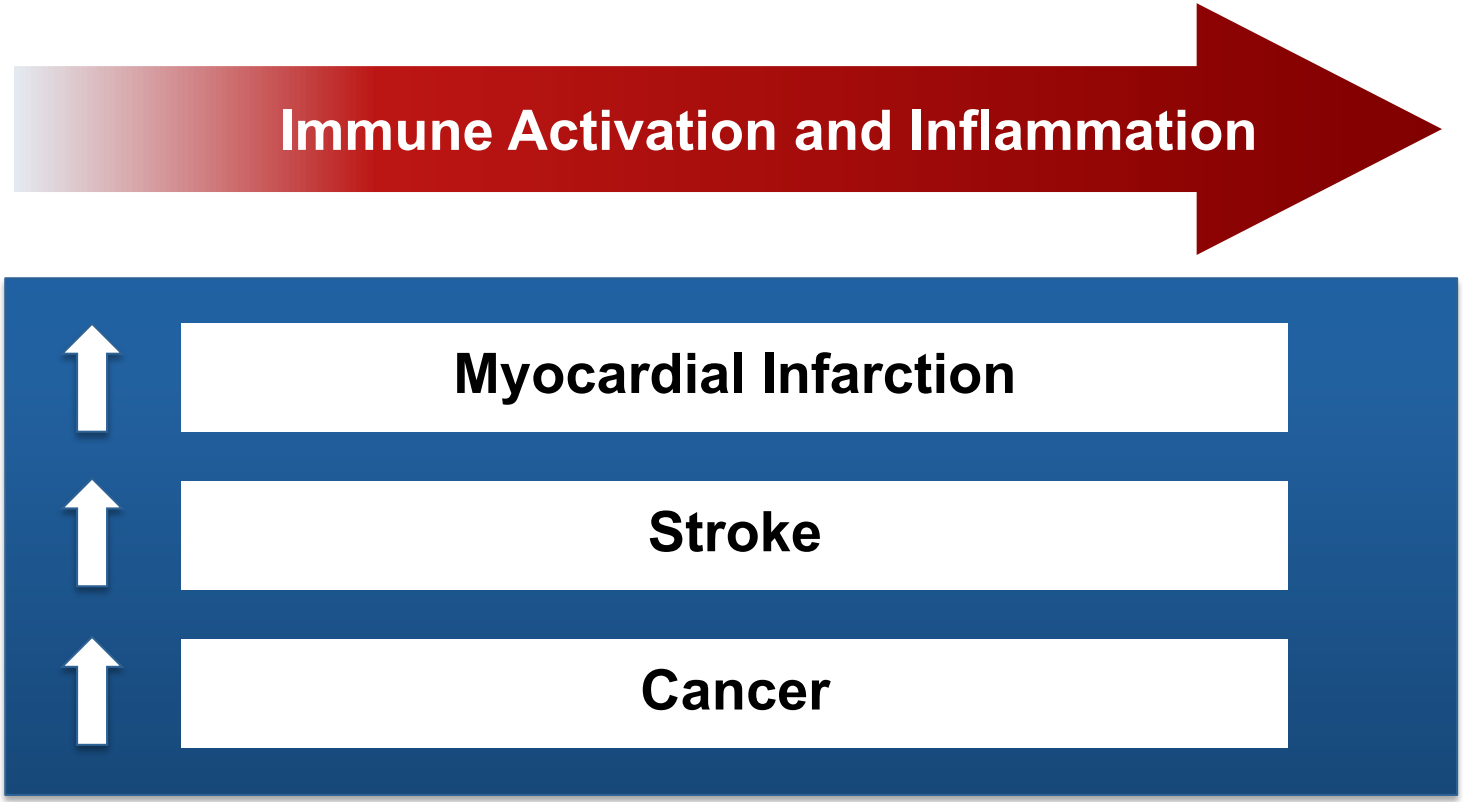
"Antiretroviral therapy is recommended for all persons with HIV to reduce morbidity and mortality (**AI**) and to prevent the transmission of HIV to others (**AI**).

Source: HHS Antiretroviral Therapy Guidelines. AIDS Info. December 18, 2019

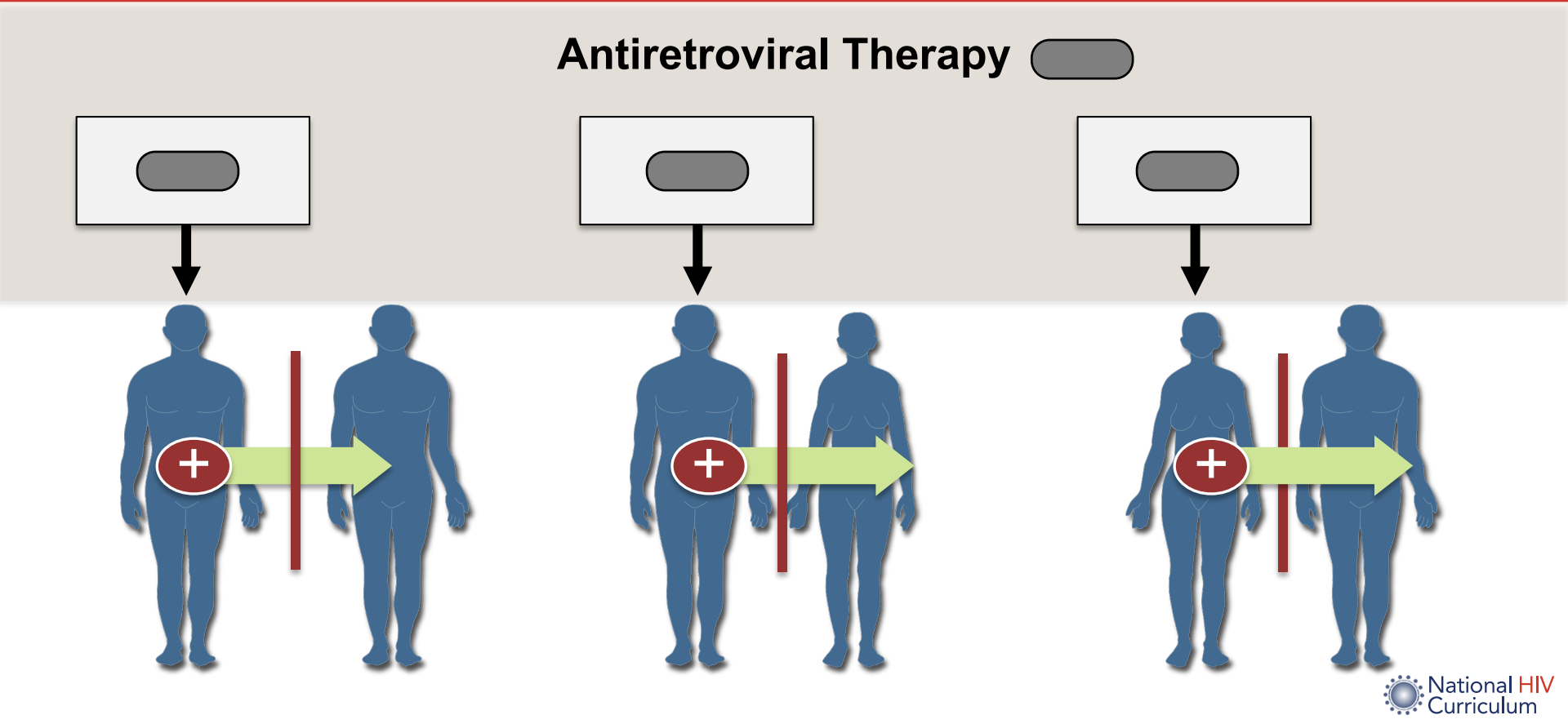
CD4 Cell Progression Without Antiretroviral Therapy



Chronic Immune Activation and Inflammation



HIV Treatment as Prevention



U = U (Undetectable equals Untransmittable)

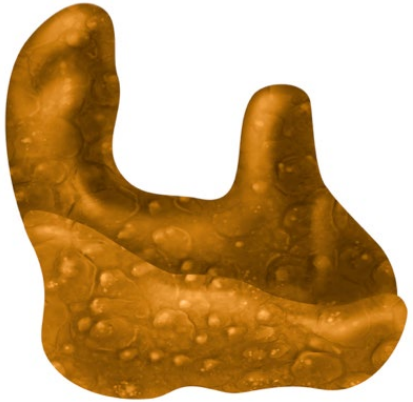
General Mechanisms for ARV Medications

Currently Available Antiretroviral Therapy
Mechanisms of Preventing HIV Replication

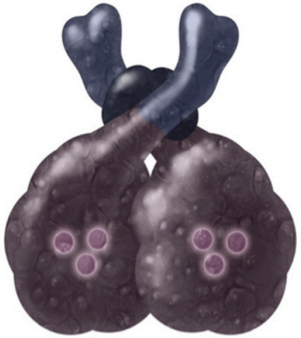
- Inhibition of HIV Enzymes
- Binding to HIV
- Binding to Human Cell Receptor to Block Virus-Host Interaction

HIV Enzymes

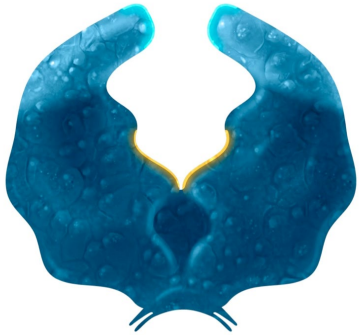
Reverse Transcriptase



Integrase

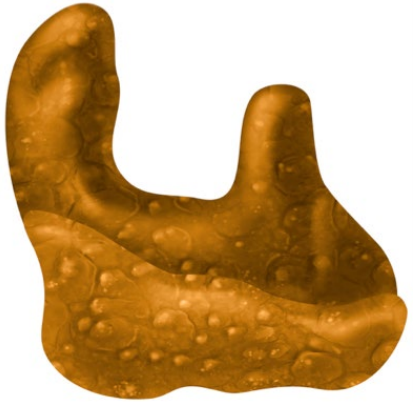


Protease



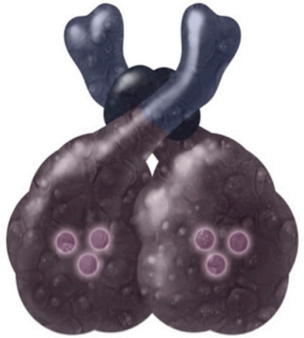
HIV Enzymes and Antiretroviral Drug Classes

Reverse Transcriptase



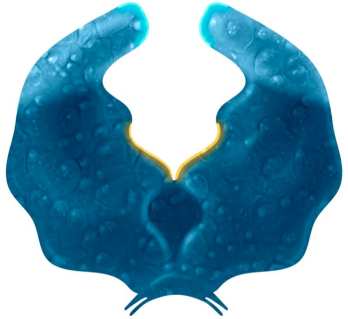
- Nucleoside RTI
- Nucleoside RTTI
- Non-Nucleoside RTI

Integrase



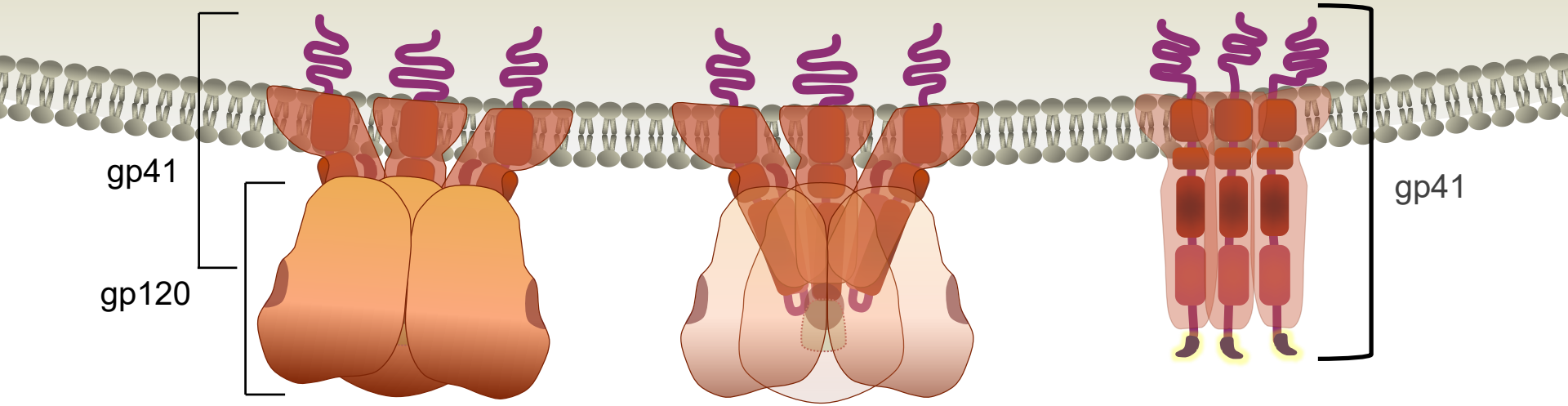
- Integrase Inhibitor

Protease



- Protease Inhibitor

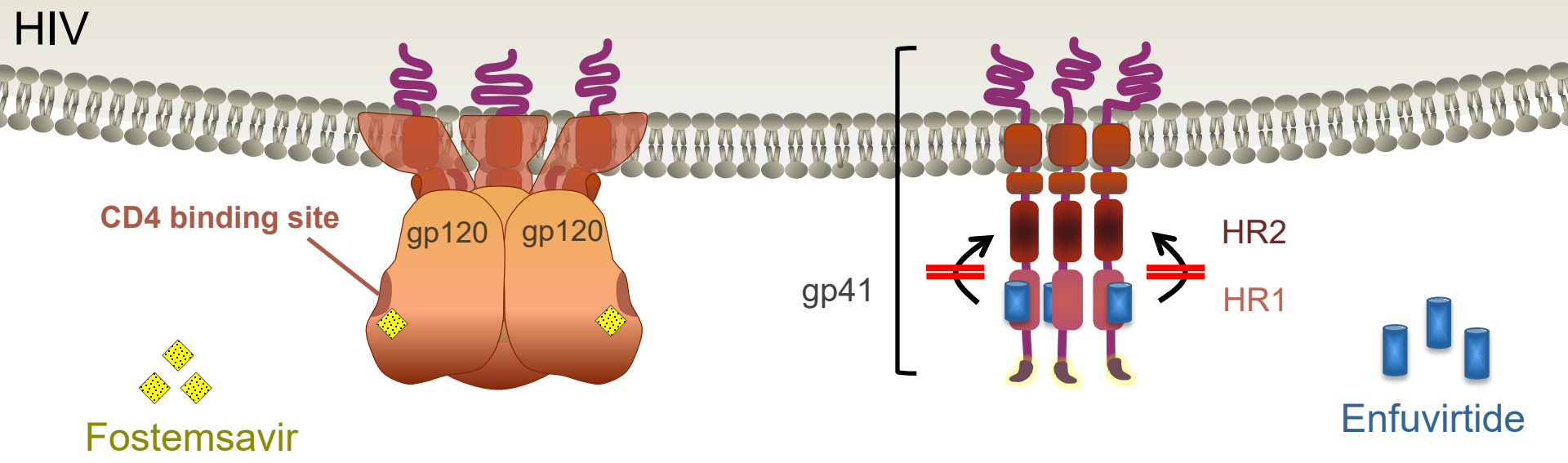
HIV Envelope



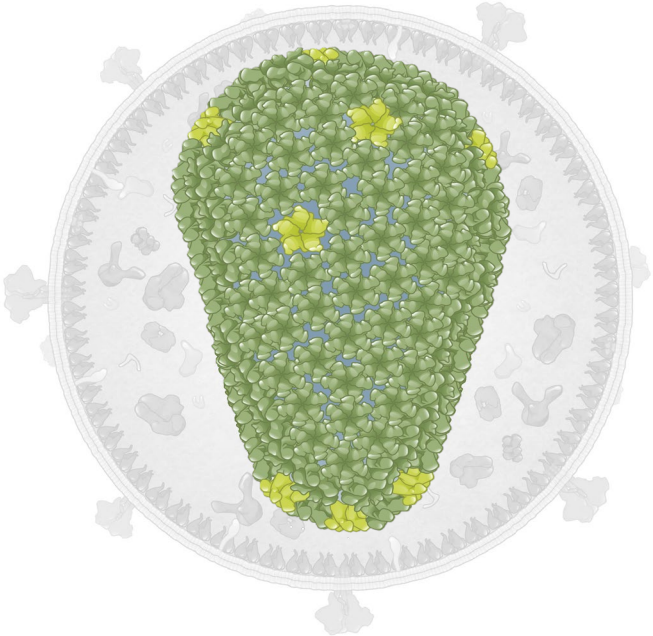
Binding to HIV Envelope (gp120 and gp41)

Attachment Inhibitors (gp120)

Fusion Inhibitors (gp41)



HIV Capsid



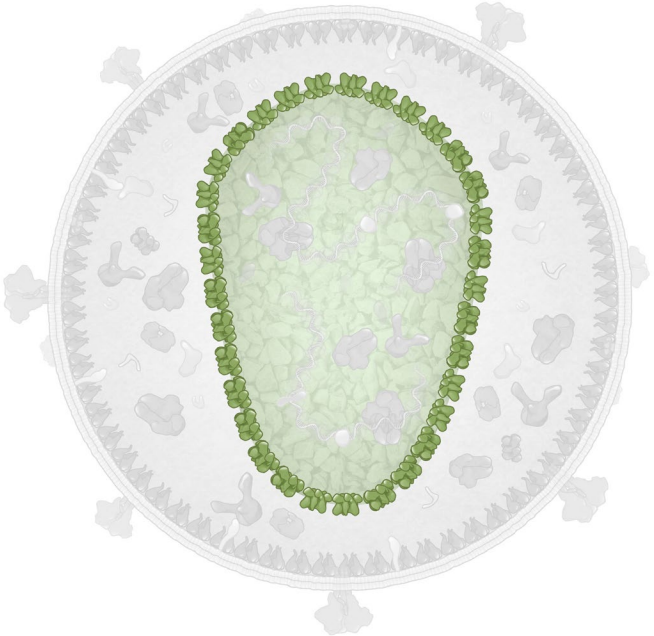


Illustration: Jared Travnicek (Cognition Studio) and David Spach, MD

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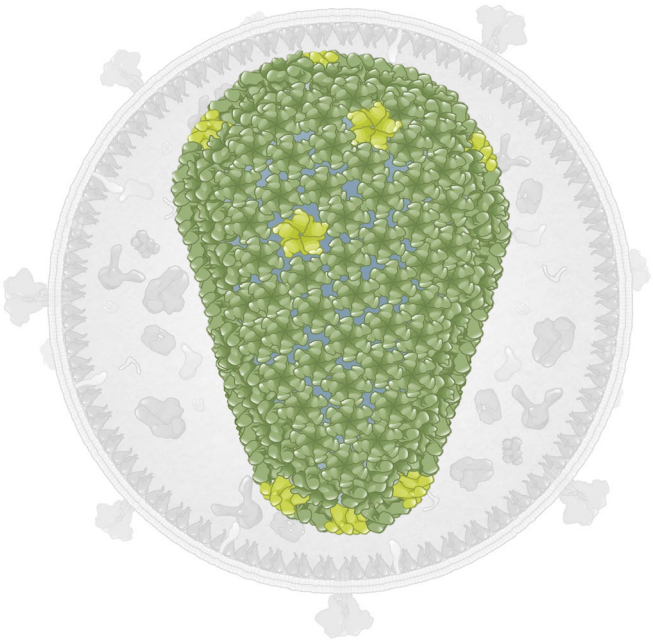
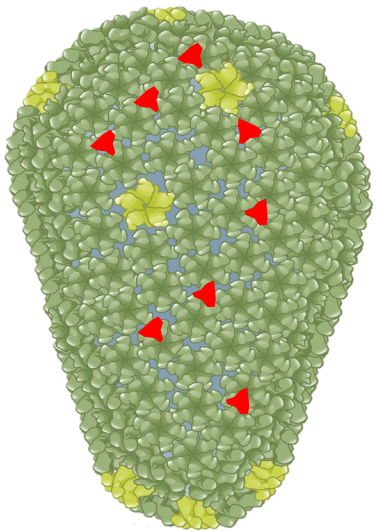
HIV Capsid Inhibitor





Capsid Inhibitor

Illustration: Jared Travnicek (Cognition Studio) and David Spach, MD

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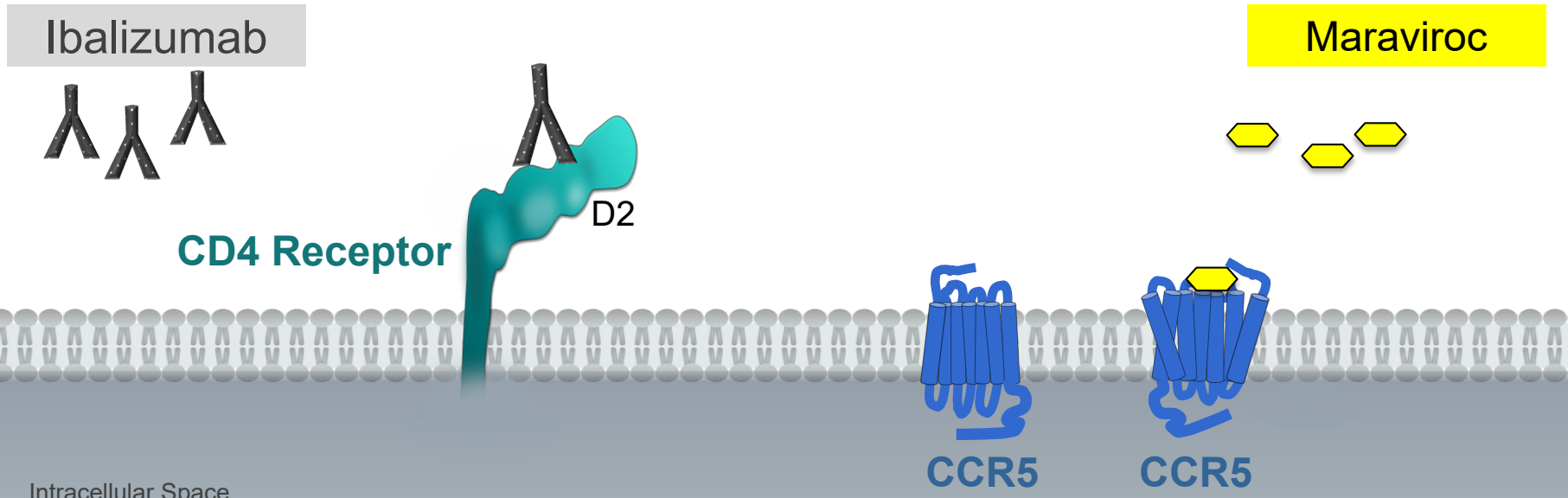
HIV Inhibitors that Bind to Human Cell Receptors

Post-Attachment Inhibitors

CCR5 Antagonists



What to Start

HHS Antiretroviral Therapy Guidelines: December 18, 2019
Recommended Initial Regimens for Most People with HIV

Anchor Drug		Backbone
INSTI	+	2 NRTIs
INSTI	+	1 NRTI

Source: HHS Antiretroviral Therapy Guidelines (December 18, 2019). AIDS Info.

HHS Antiretroviral Therapy Guidelines: December 18, 2019

Recommended Initial Regimens for Most People with HIV

INSTI + 2NRTIs	Rating
Bictegravir-TAF-FTC	AI
Dolutegravir-ABC-3TC (if HLA-B*5701 negative)	AI
Dolutegravir + TAF-FTC	AI
Dolutegravir + [TDF-FTC or TDF + 3TC]	AI
Raltegravir + [TDF-FTC or TDF + 3TC]	BI
Raltegravir + TAF-FTC	BII
INSTI + 1NRTI	**Rating**
Dolutegravir-Lamivudine (except: HIV >500,000 copies/mL, HBV, no genotype)	AI

Source: HHS Antiretroviral Therapy Guidelines (December 18, 2019).

HHS Antiretroviral Therapy Guidelines: December 18, 2019

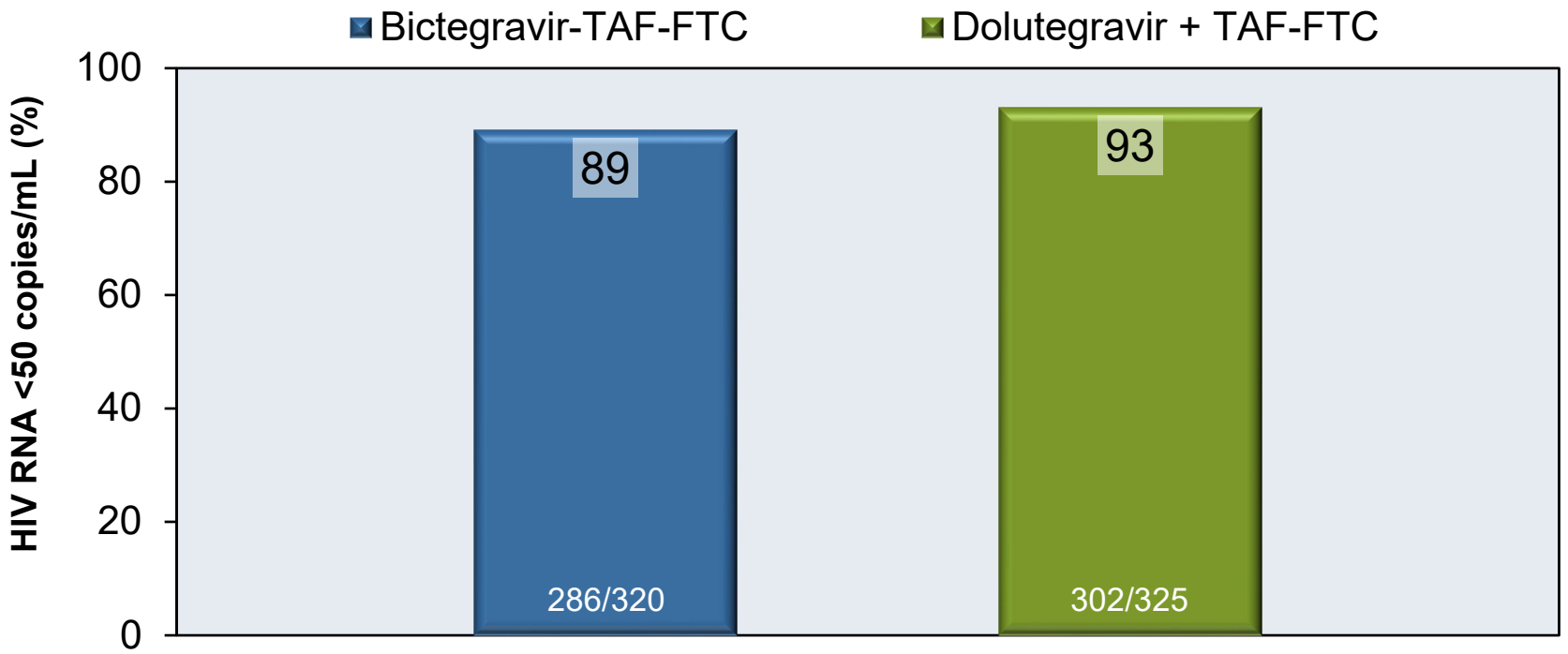
Recommended Initial Regimens for Most People with HIV

INSTI + 2NRTIs	Rating
Bictegravir-TAF-FTC	AI
Dolutegravir-ABC-3TC (if HLA-B*5701 negative)	AI
Dolutegravir + TAF-FTC	AI
Dolutegravir + [TDF-FTC or TDF + 3TC]	AI
Raltegravir + [TDF-FTC or TDF + 3TC]	BI
Raltegravir + TAF-FTC	BII
INSTI + 1NRTI	**Rating**
Dolutegravir-Lamivudine (except: HIV >500,000 copies/mL, HBV, no genotype)	AI

Source: HHS Antiretroviral Therapy Guidelines (December 18, 2019).

BIC-TAF-FTC vs. DTG + TAF-FTC as Initial Therapy
GS-380-1490 (Week 48): Results

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



Source: Sax PE, et al. Lancet. 2017;390:2073-82.

HHS Antiretroviral Therapy Guidelines: December 18, 2019

Recommended Initial Regimens for Most People with HIV

INSTI + 2NRTIs	Rating
Bictegravir-TAF-FTC	AI
Dolutegravir-ABC-3TC (if HLA-B*5701 negative)	AI
Dolutegravir + TAF-FTC	AI
Dolutegravir + [TDF-FTC or TDF + 3TC]	AI
Raltegravir + [TDF-FTC or TDF + 3TC]	BI
Raltegravir + TAF-FTC	BII
INSTI + 1NRTI	**Rating**
Dolutegravir-Lamivudine (except: HIV >500,000 copies/mL, HBV, no genotype)	AI

Source: HHS Antiretroviral Therapy Guidelines (December 18, 2019).

Dolutegravir-Lamivudine
2-Drug **Initial** Antiretroviral Therapy

Initial 2-Drug Therapy
Dolutegravir-Lamivudine

Time

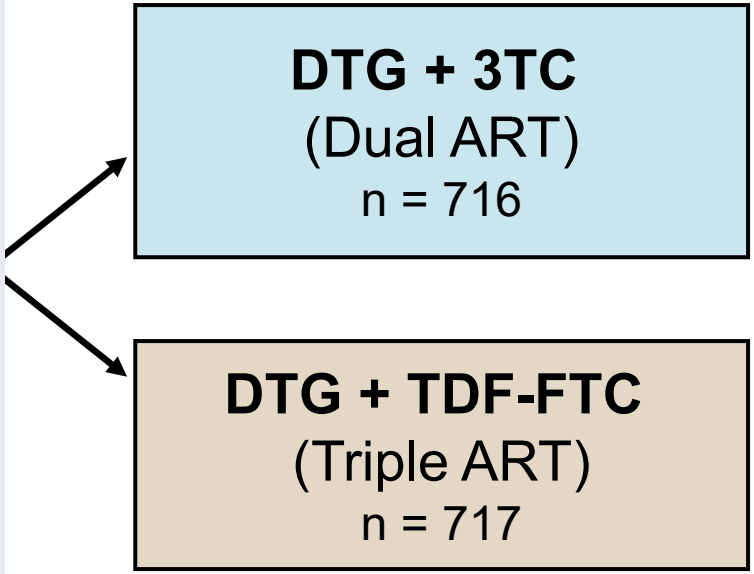
- HIV RNA <500,000 copies/mL
- HBsAg negative
- Results from genotype known

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and GEMINI 2: Background

Study Design: GEMINI 1 and 2

- **Background**:
  - Two identical, double-blind, multinational, noninferiority, randomized controlled trials that compared initial ART of dolutegravir plus lamivudine (DTG + 3TC) versus dolutegravir plus tenofovir-DF-emtricitabine (DTG + TDF-FTC)

- **Enrollment Criteria:**
  - Treatment-naïve adults
  - HIV RNA 1,000-500,000 copies/mL
  - No NRTI, INSTI, or major PI mutations
  - No chronic HBV
  - Not pregnant or breastfeeding

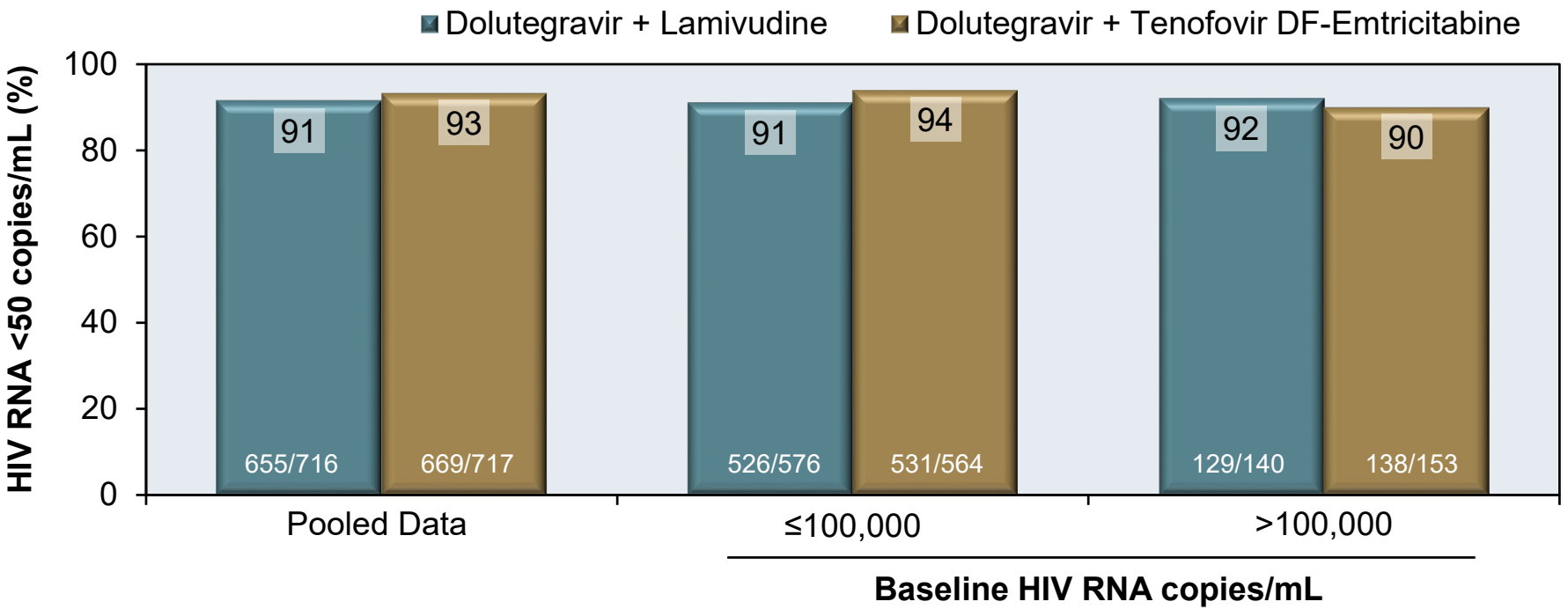


Source: Cahn P, et al. Lancet. 2019;393:143-55.

DTG + 3TC versus DTG + TDF-FTC as Initial ART

GEMINI 1 and GEMINI 2: Results by Baseline HIV RNA Level

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



Source: Cahn P, et al. Lancet. 2019;393:143-55.

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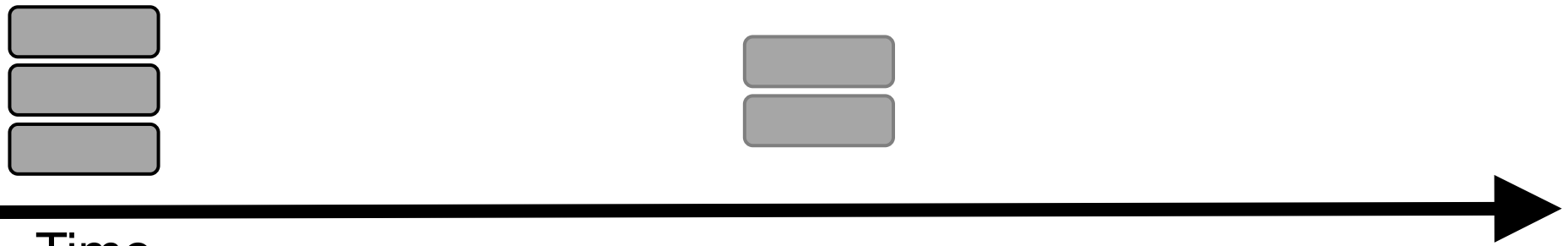
Options for Simplified Maintenance Therapy

Step Down **2-Drug Maintenance** Antiretroviral Therapy

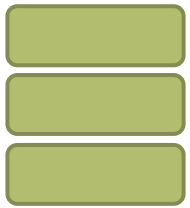
Initial Antiretroviral Therapy (3-Drug Therapy)	Maintenance (2-Drug Therapy)



- HIV RNA <50 copies/mL
- No prior virologic failure
- No HBV
- No resistance to either maintenance drug

Dolutegravir-Lamivudine
2-Drug **Maintenance** Antiretroviral Therapy

Initial Antiretroviral Therapy (3-Drug Therapy)	Dolutegravir-Lamivudine Maintenance (2-Drug Therapy)



Time

- HIV RNA <50 copies/mL
- Stable ARV regimen
- No prior virologic failure
- No HBV
- No resistance to dolutegravir or lamivudine

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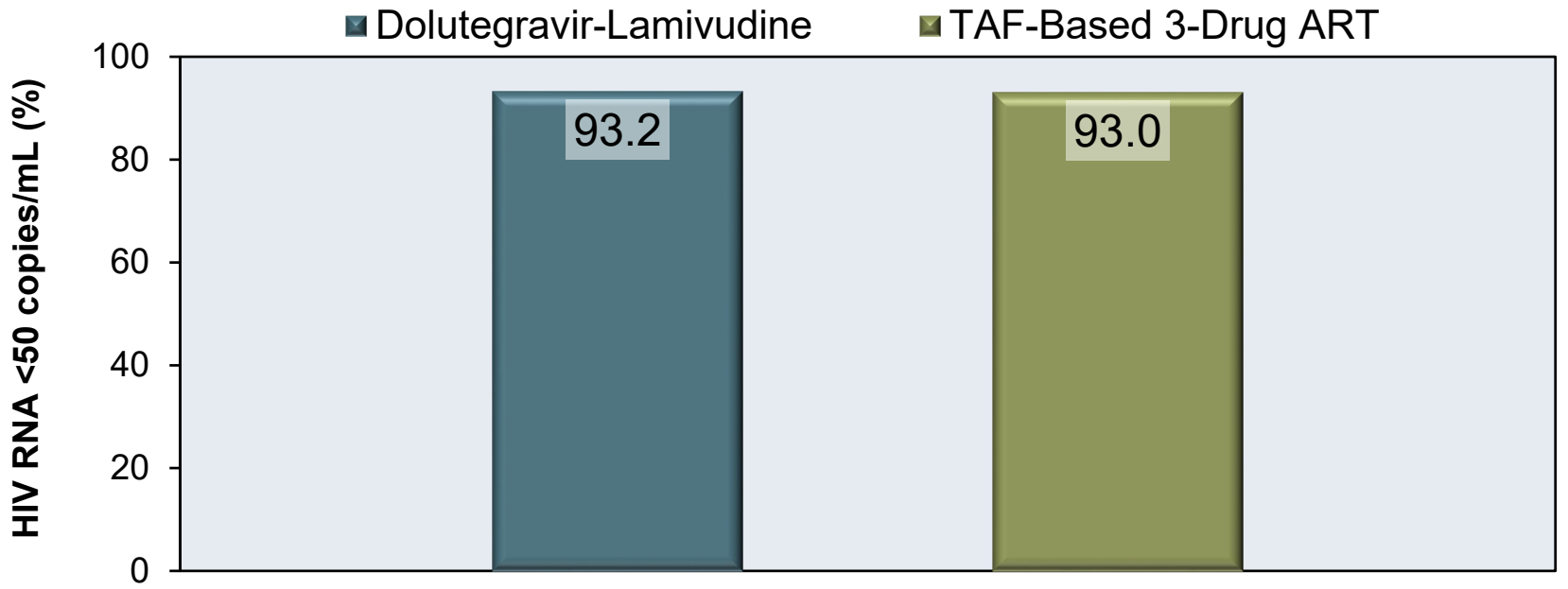
Switch to Dolutegravir-Lamivudine vs Continued TAF-Based 3-Drug ART
TANGO: Results

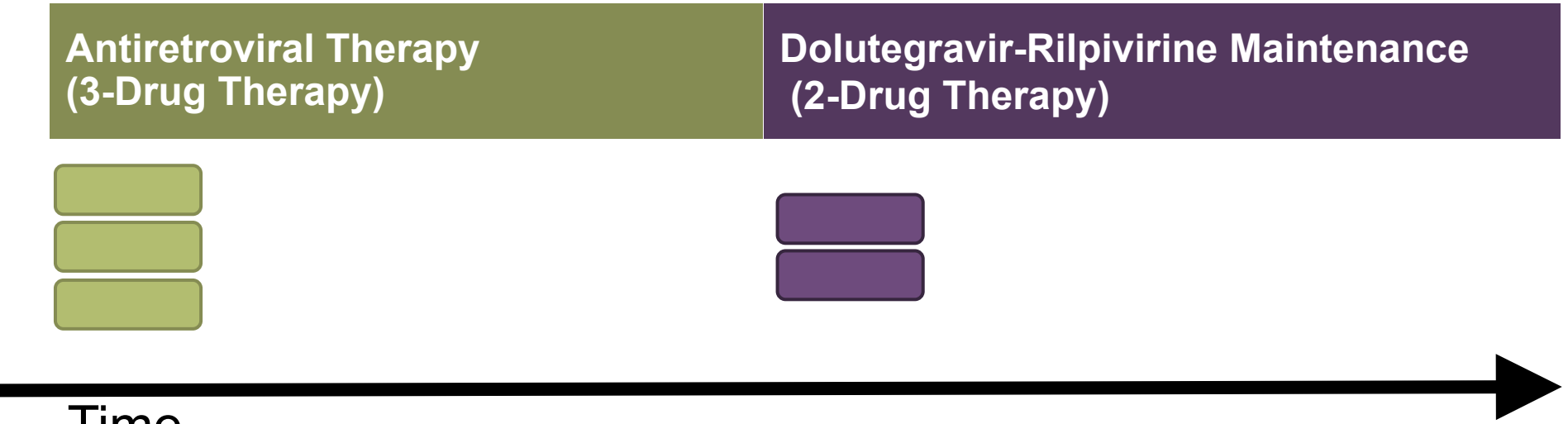
Week 48 Virologic Response (Intention-to-Treat Analysis)



Confirmed withdrawal for virologic failure: 0 in DTG/3TC arm, 1 in TAF-based ART arm

Source: van Wyk J, et al. Clin Infect Dis. 2020. Jan 6. [Epub ahead of print]

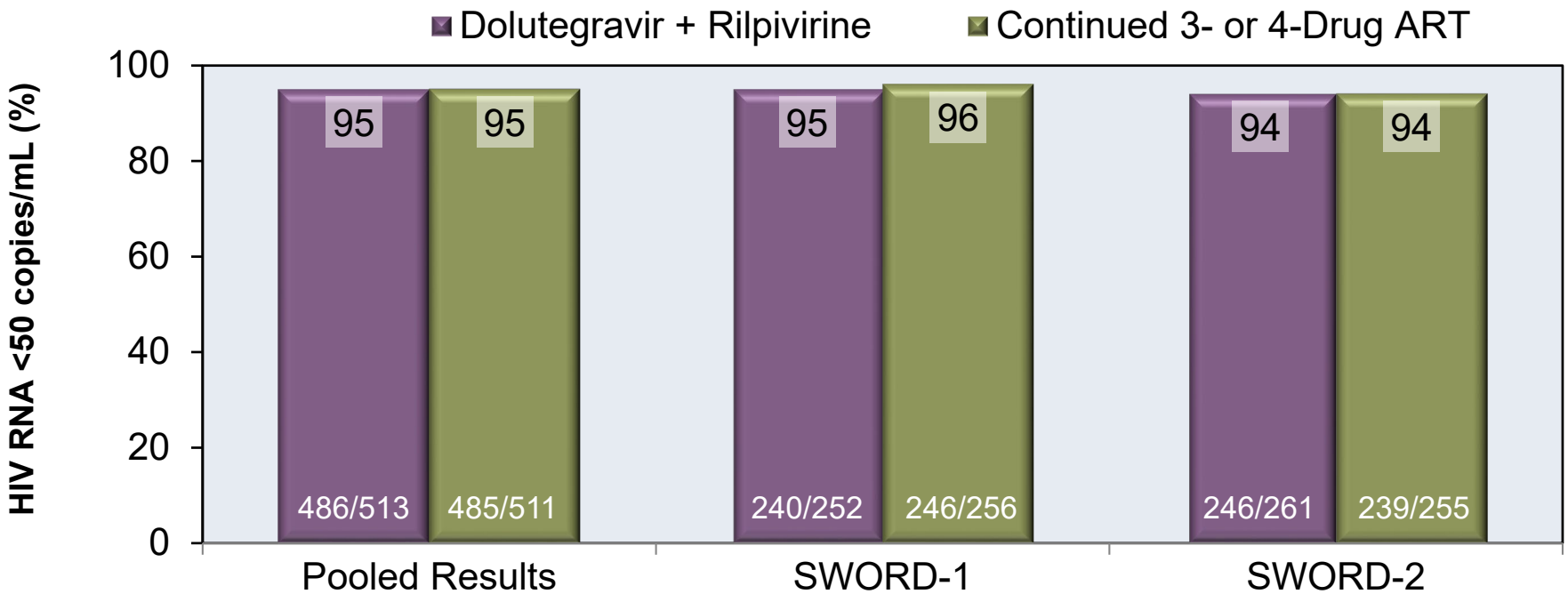
Dolutegravir-Rilpivirine
2-Drug **Maintenance** Antiretroviral Therapy



- HIV RNA <50 copies/mL for ≥6 months
- No prior virologic failure
- No resistance to either maintenance drug

Dolutegravir plus Rilpivirine as Maintenance Dual Therapy SWORD-1 and SWORD-2: Pooled Results at Week 48

Week 48 Virologic Response



Source: Llibre JM et al. Lancet. 2018;39:839-49.

Cabotegravir and Rilpivirine
Oral and Injectable Preparations

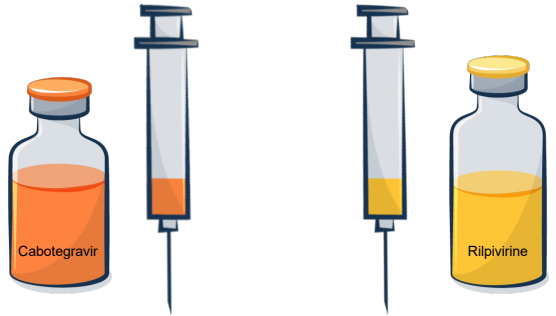
Oral Component

Cabotegravir + Rilpivirine

30 mg → INSTI

25 mg → NNRTI

Injection Component



Cabotegravir + Rilpivirine

200 mg/mL → INSTI

300 mg/mL → NNRTI

Source: Cabenuva Prescribing Information

Recommendations for Cabotegravir and Rilpivirine

- **Appropriate Use of Monthly CAB + RPV Intramuscular Injections:**
  - HIV RNA <50 copies/mL for ≥3 months
  - No baseline resistance to either medication
  - No prior virologic failures
  - No active HBV infection (unless also receiving HBV active Rx)
  - Not pregnant and are not planning on becoming pregnant
  - Not taking meds with significant DDI with oral or IM CAB or RPV

Source: HHS Antiretroviral Therapy Guidelines (February 24, 2021

Cabotegravir and Rilpivirine (*Cabenuva*)
Dosing Schedule

Oral Lead-In x 1 month (≥28 days)
Cabotegravir 30 mg daily +
Rilpivirine 25 mg daily

***Initiation Injections (x 1)**
Cabotegravir (600 mg): 3 mL IM +
Rilpivirine (900 mg): 3 mL IM

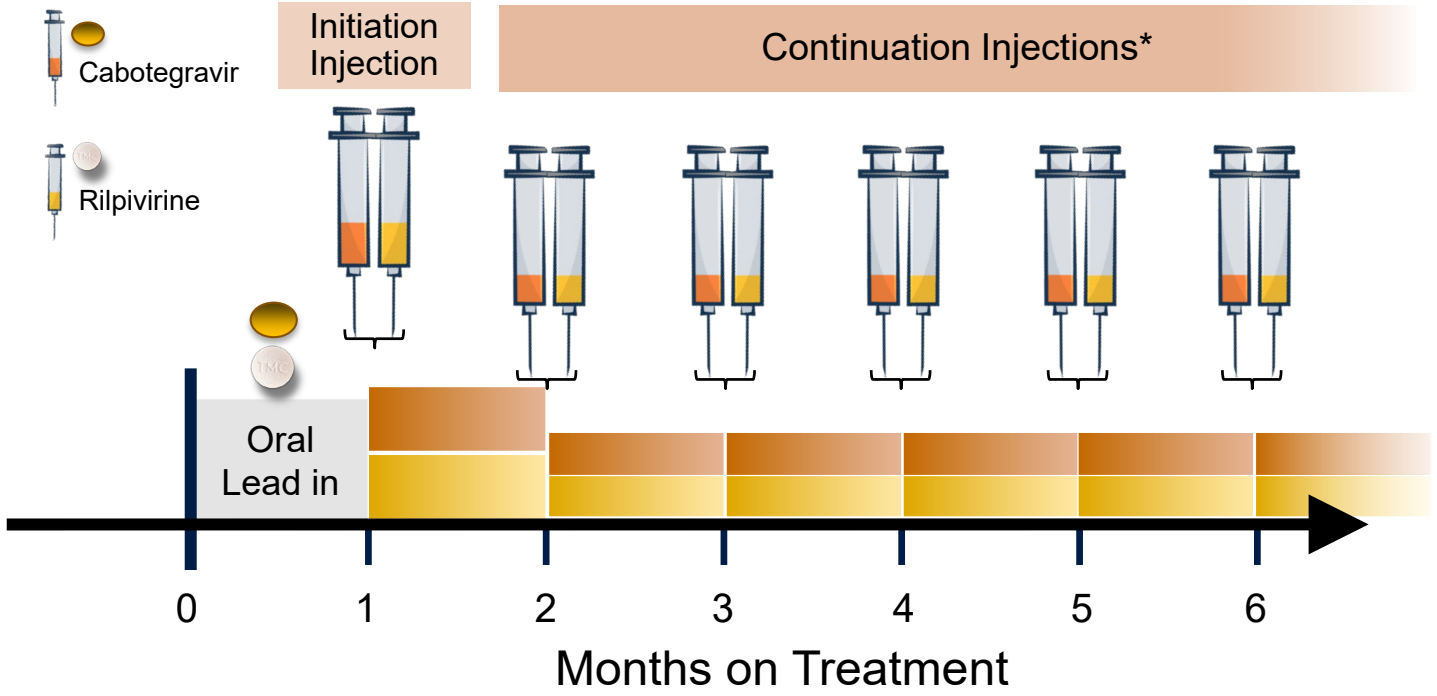
***Continuation Injections (Monthly)**
Cabotegravir (400 mg): 2 mL IM +
Rilpivirine (600 mg): 2 mL IM

*Administer injections at opposite gluteal sites (or at least 2 cm apart) and give both during the same visit.

Source: Cabenuva Prescribing Information

Cabotegravir and Rilpivirine Extended-Release Injectable Suspension

Dosing Schedule



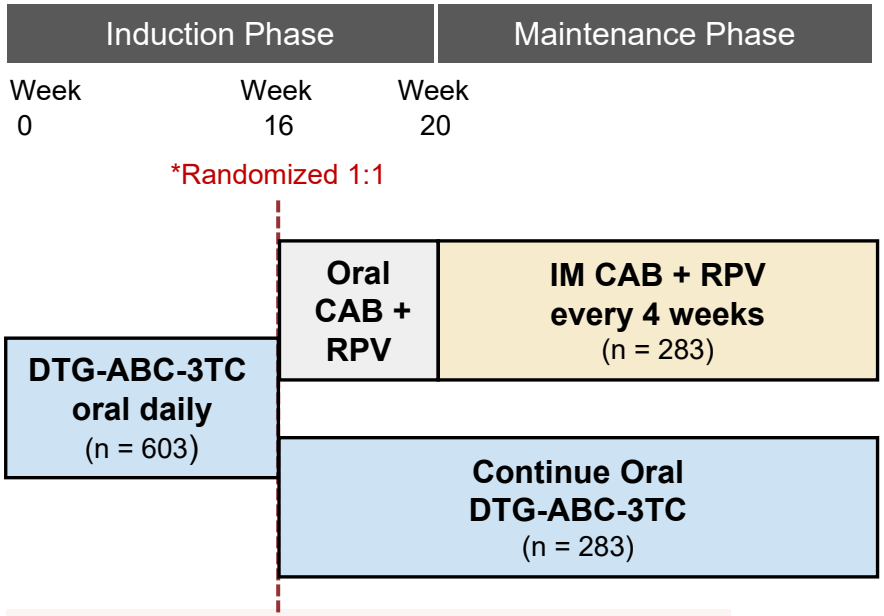
*May receive cabotegravir and rilpivirine up to 7 days before or after the date of the scheduled monthly injection dosing visit.

Source: Cabenuva Prescribing Information

Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study (48-Week Data): Design

Study Design:

- **Background**: Phase 3, randomized, open-label, trial assessing IM CAB + RPV after oral induction for treatment-naïve adults
- **Inclusion Criteria**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA ≥1,000 copies/mL
  - Any CD4 cell count
  - No chronic hepatitis B
  - No NNRTI resistance

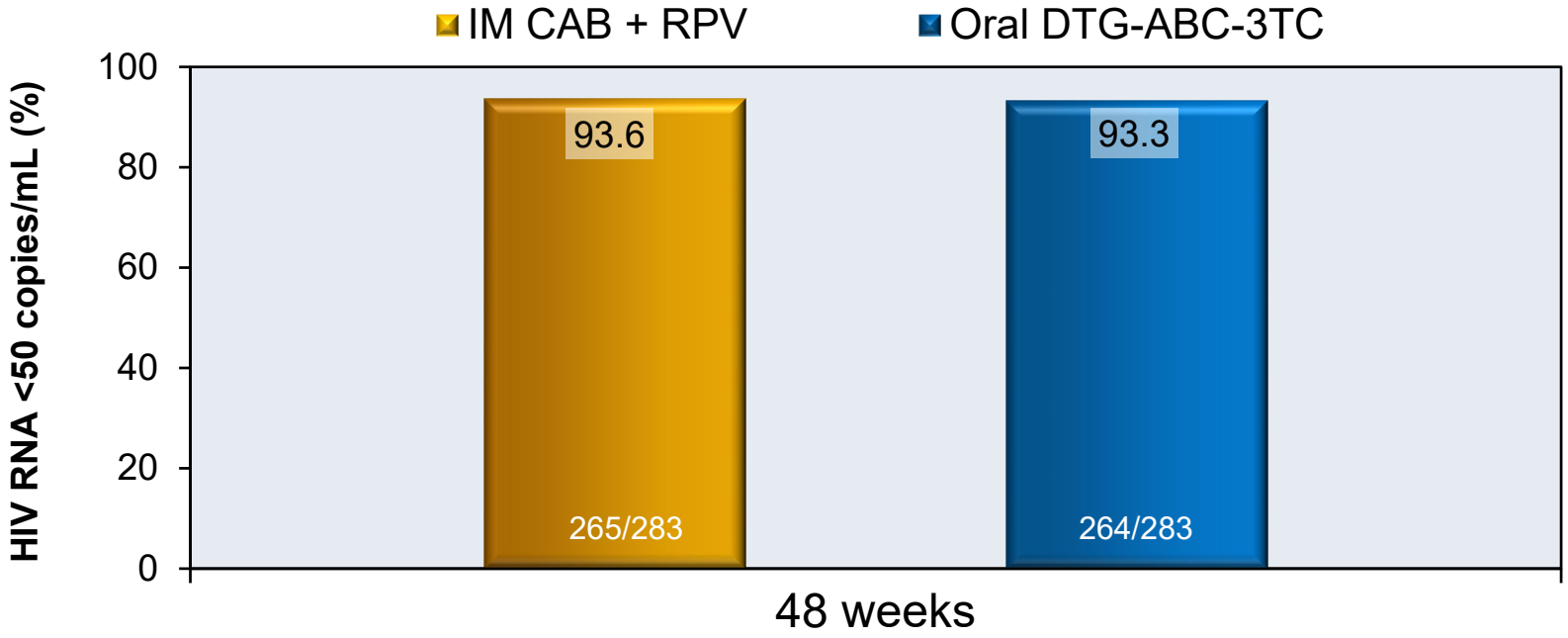


Oral lead in dosing: cabotegravir 30 mg daily and rilpivirine 25 mg daily x 4 weeks
Loading injections: cabotegravir 600 mg IM and 900 mg rilpivirine IM x 1
Maintenance injections: cabotegravir 400 mg IM and 600 mg rilpivirine IM monthly

Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study (48-Week Data): Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



*HIV RNA ≥50 copies/mL at 48 weeks: 2.1 % CAB-RPV, 2.5% DTG-ABC-3TC

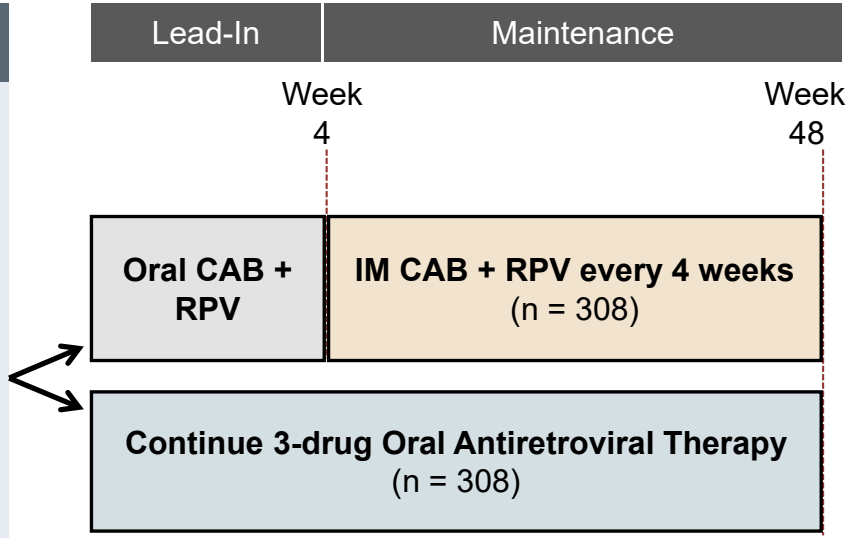
Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Design

Study Design:

- **Background**: Phase 3, randomized, open-label trial assessing IM cabotegravir plus IM rilpivirine after oral induction for adults taking a 3-drug oral antiretroviral therapy regimen

- **Inclusion Criteria**
  - Age ≥18 years
  - Taking 2NRTI + INSTI, NNRTI, or PI
  - Stable ARV regimen ≥6 months
  - HIV RNA <50 copies/mL ≥6 months
  - No history of virologic failure
  - No INSTI or NNRTI resistance (K103N allowed)
  - No chronic hepatitis B

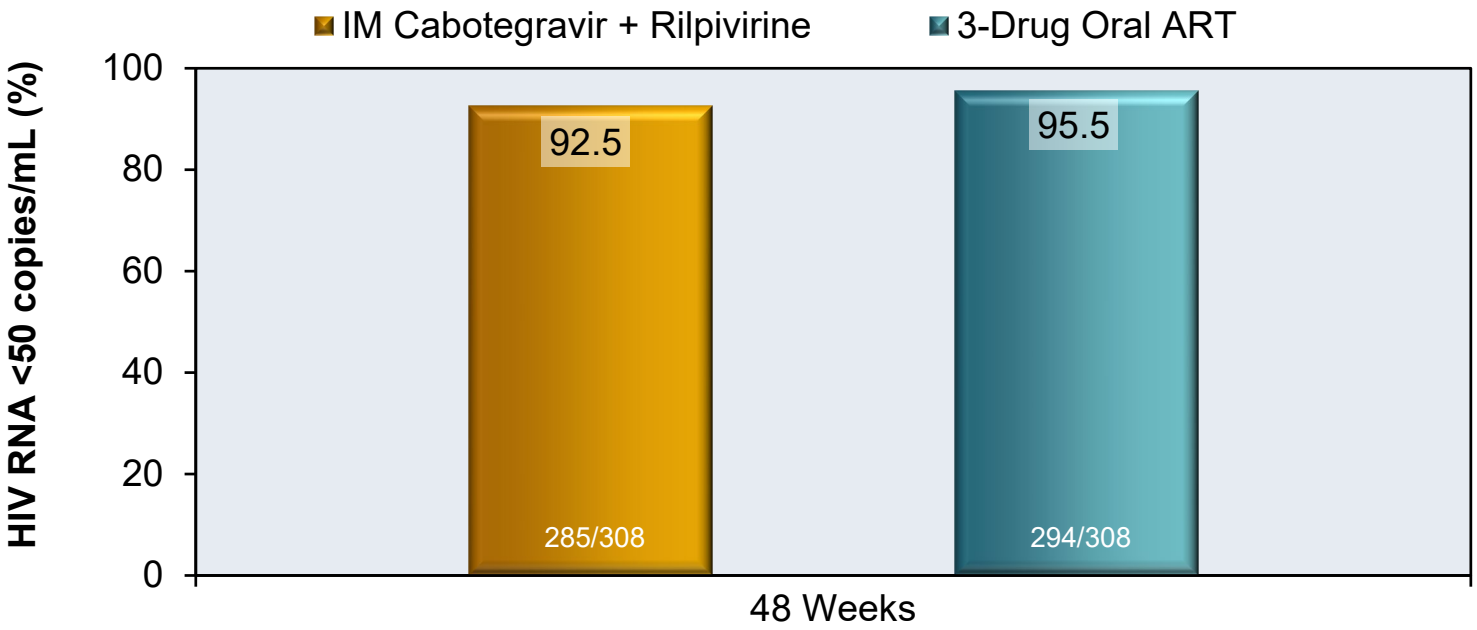


Abbreviations: CAB = cabotegravir; RPV = rilpivirine

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 48 weeks: 1.6 % CAB + RPV, 1.0% 3-drug oral ART

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

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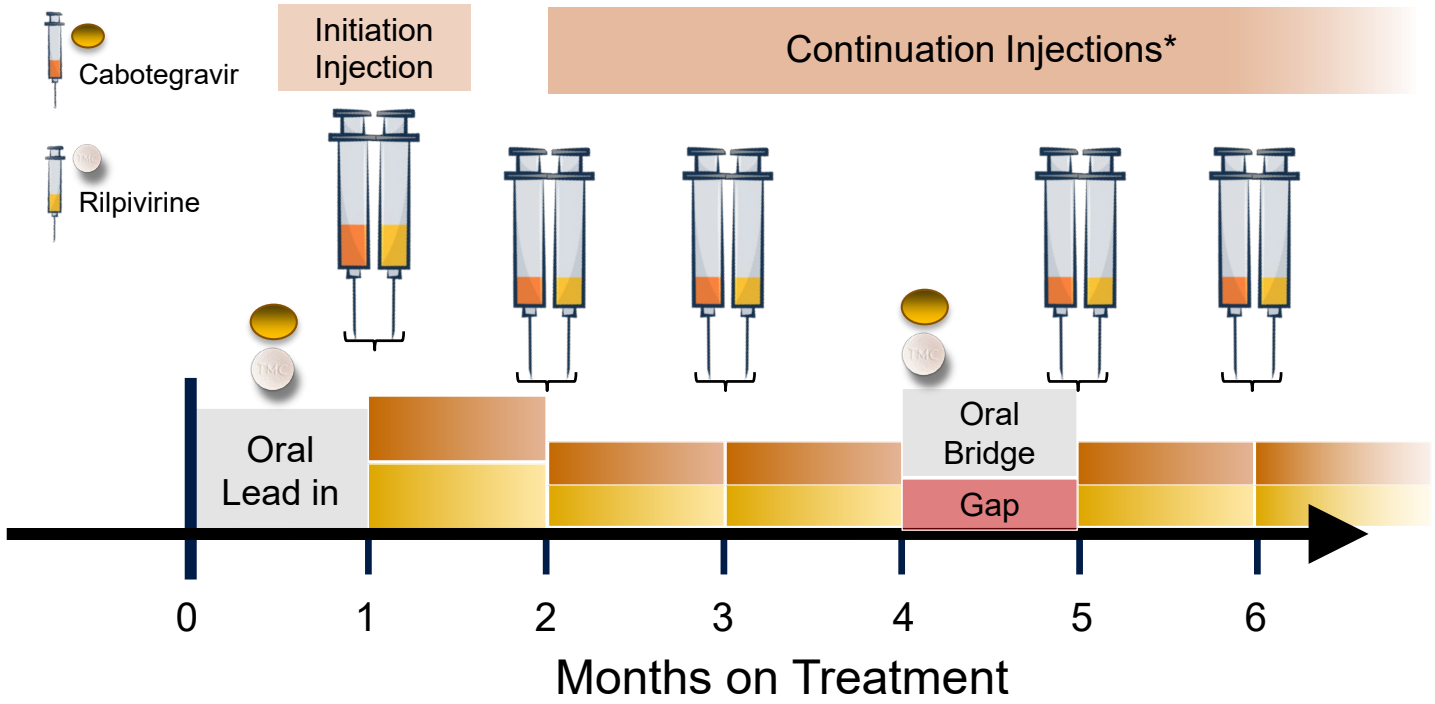
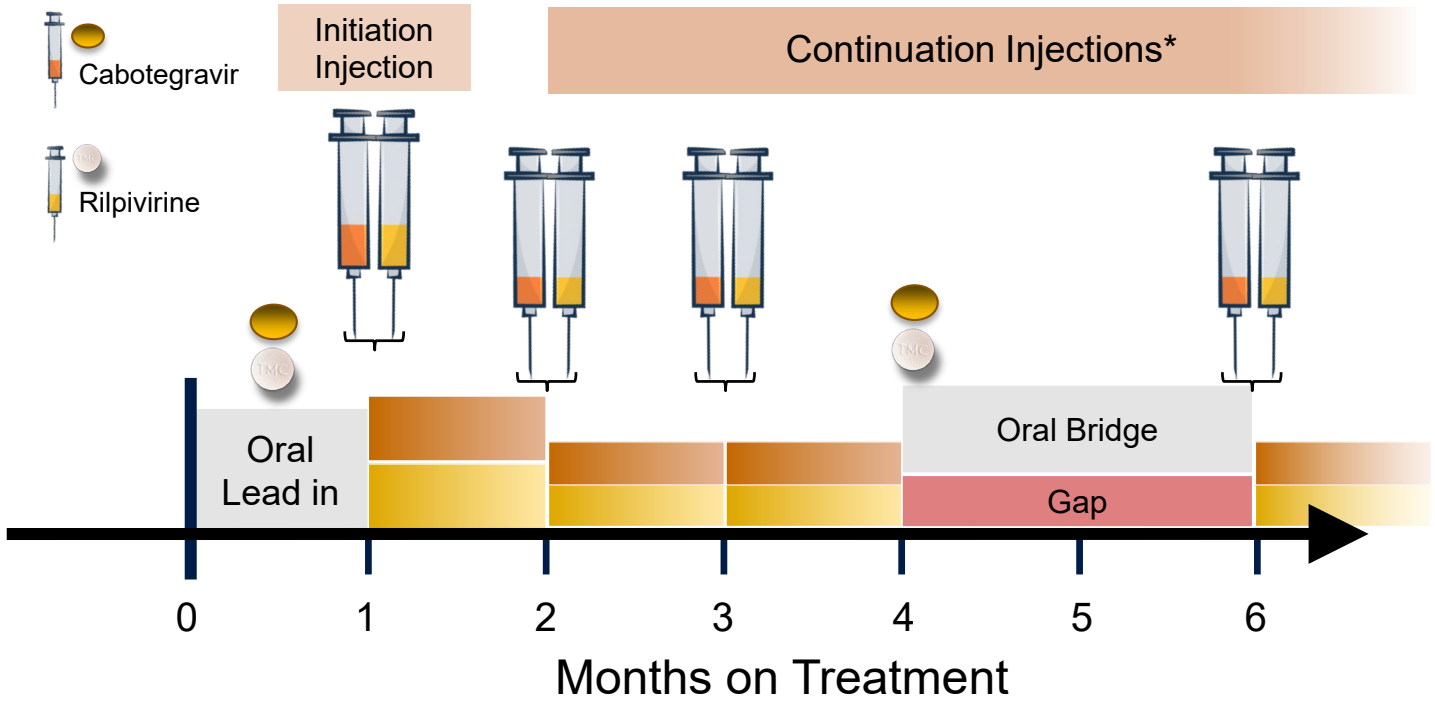
Cabotegravir and Rilpivirine
Dosing Schedule with Oral Bridge (for 1-2 months)



*May receive cabotegravir and rilpivirine up to 7 days before or after the date of the scheduled monthly injection dosing visit.

Source: Cabenuva Prescribing Information

Cabotegravir and Rilpivirine
Dosing Schedule with Oral Bridge (for 1-2 months)



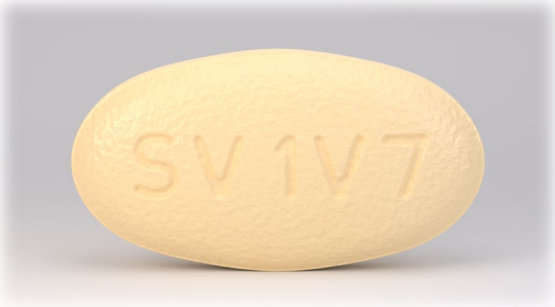
*May receive cabotegravir and rilpivirine up to 7 days before or after the date of the scheduled monthly injection dosing visit.

Source: Cabenuva Prescribing Information

New Salvage Therapy Options

Fostemsavir

- **Indication**:
  - Heavily treatment-experienced
  - Multidrug-resistant HIV
  - Failing their current ART

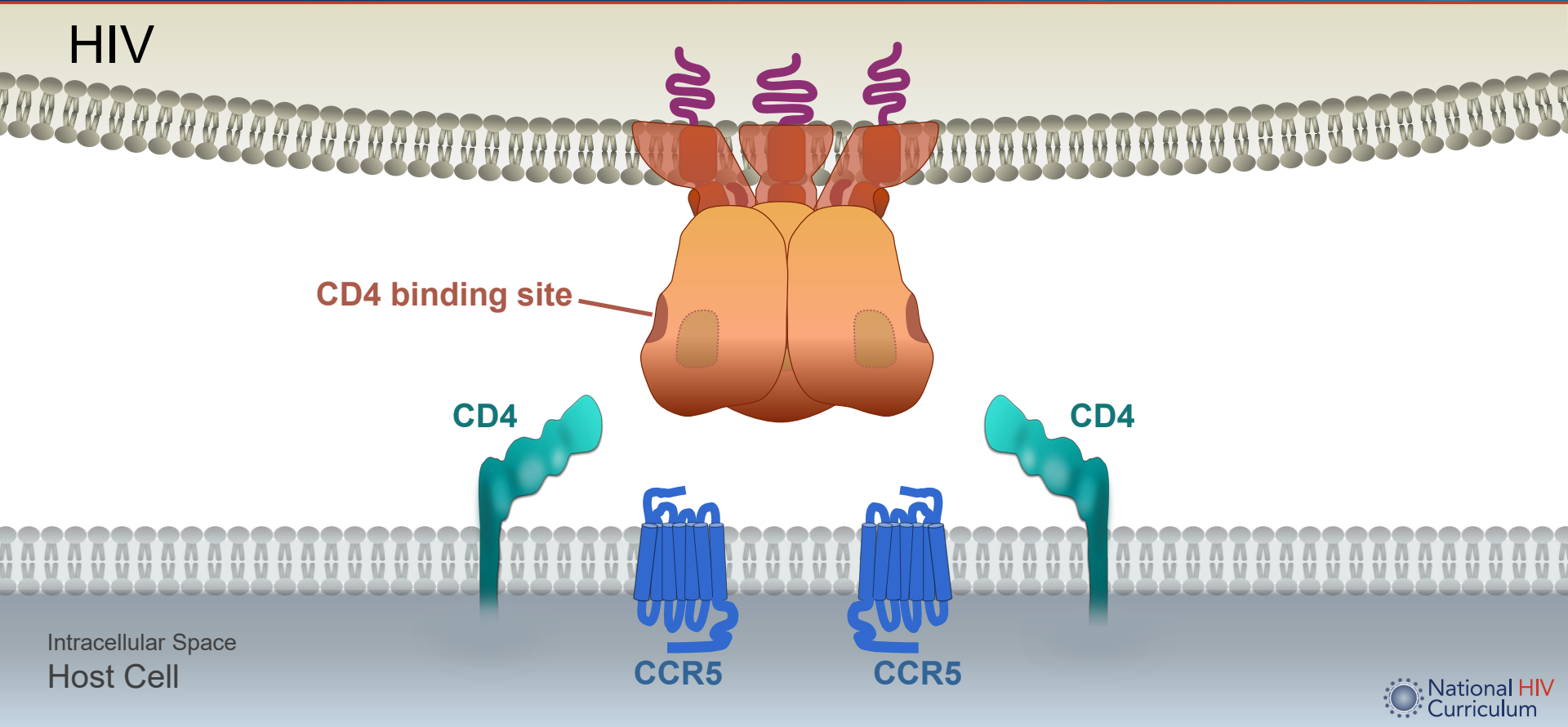


- **Dosing**:
  - 600 mg orally twice daily, with or without food

- **Contraindications**
  - Coadministration with strong cytochrome P450 (CYP) 3A inducers

Source: *Rukobia* Prescribing Information

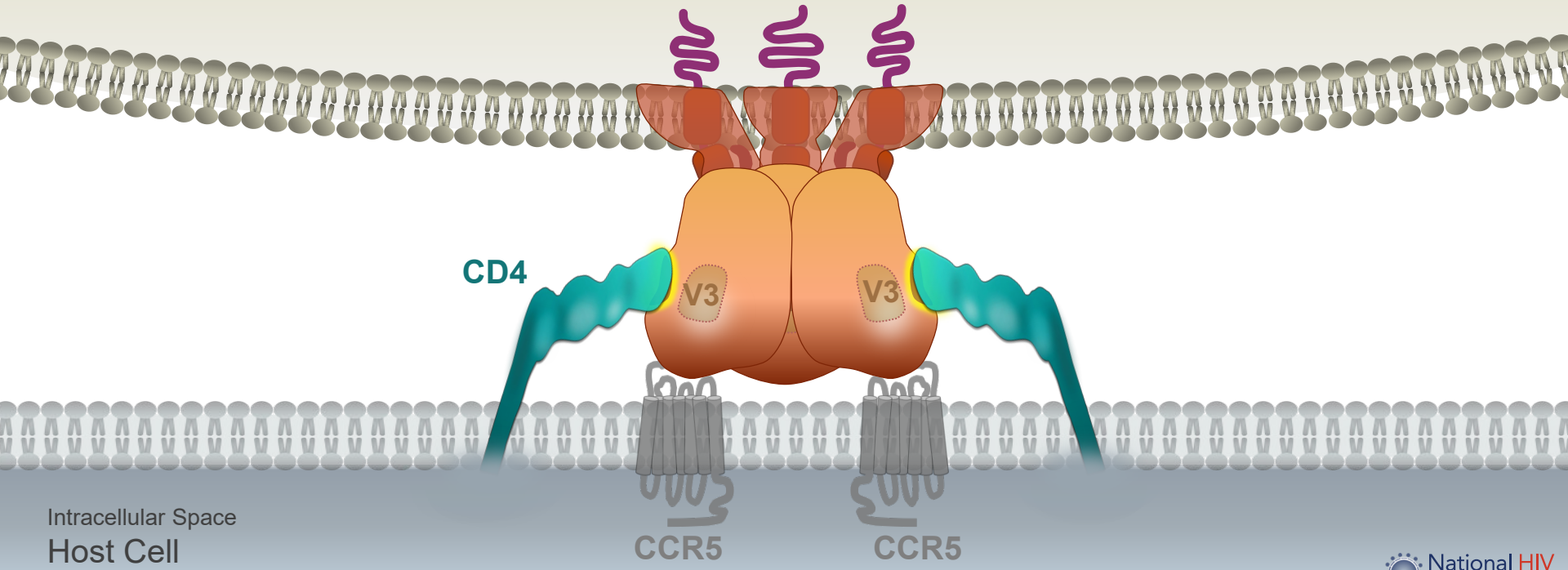
HIV Cell Entry



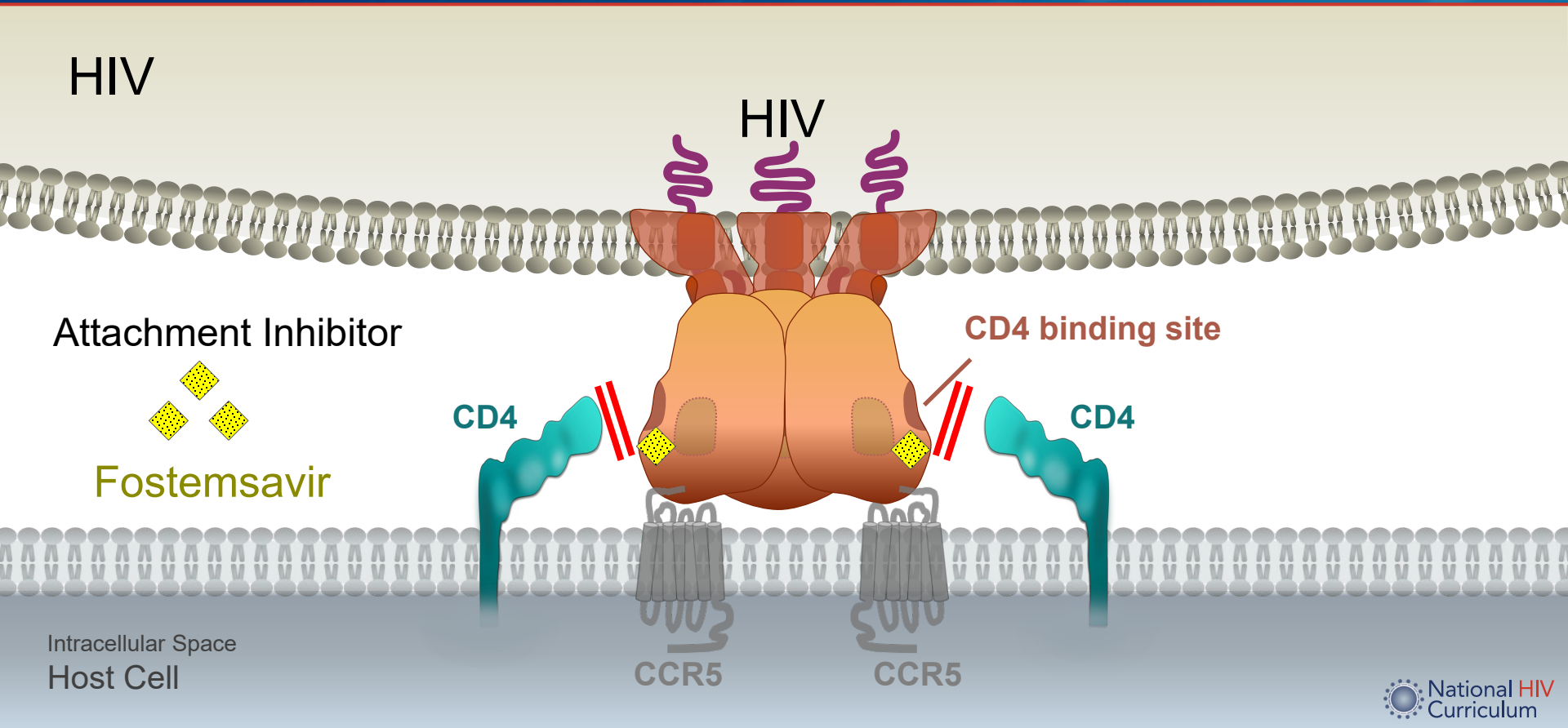
HIV Cell Entry

Attachment: Binding to Host Cell CD4 Receptor

HIV



HIV Entry Inhibitors: Attachment Inhibitor
Fostemsavir



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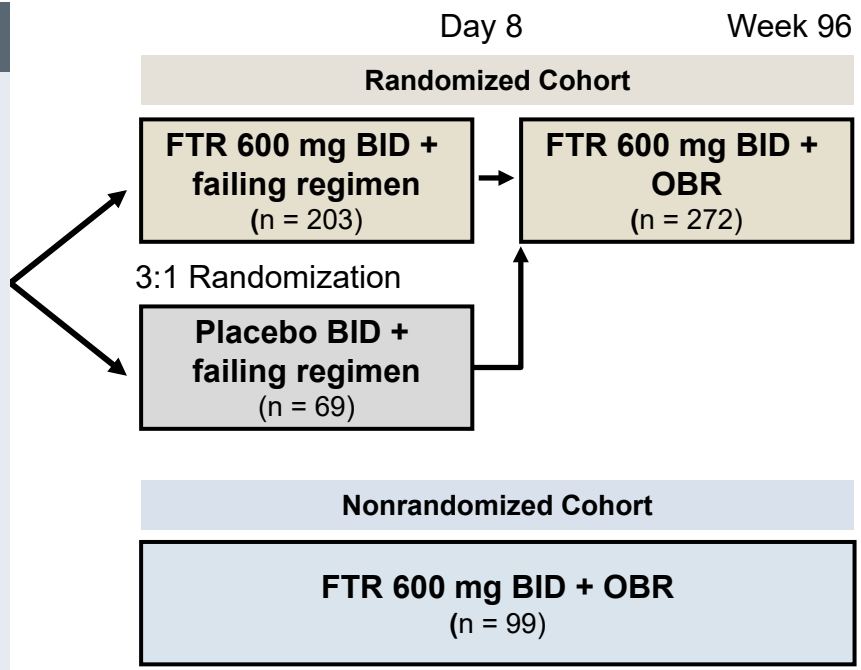
Fostemsavir (FTR) for Heavily Treatment Experienced BRIGHTE Study (Week 48): Background

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

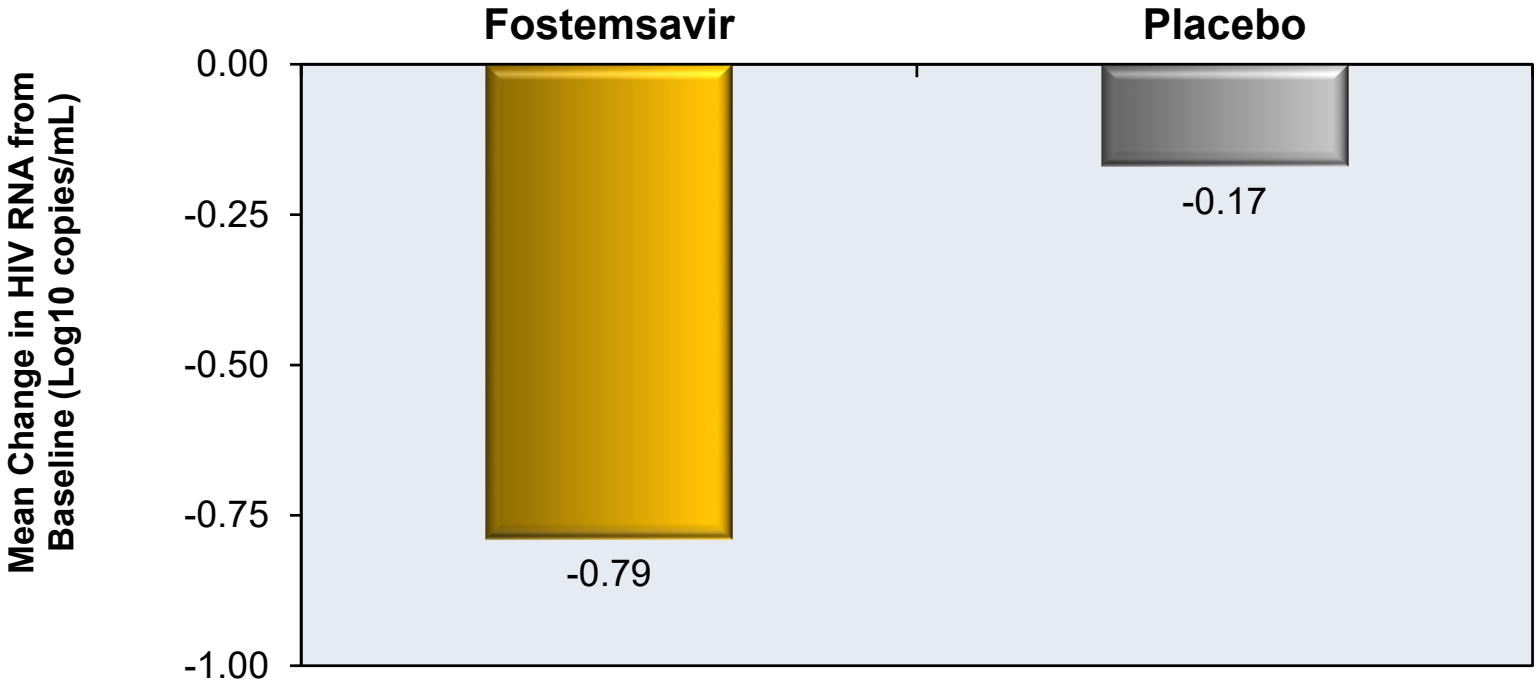


*Also a cohort with 0 remaining active agents; all given Fostemsavir 600 mg BID + OBR (n = 99)
*OBR = optimized background regimen

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

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

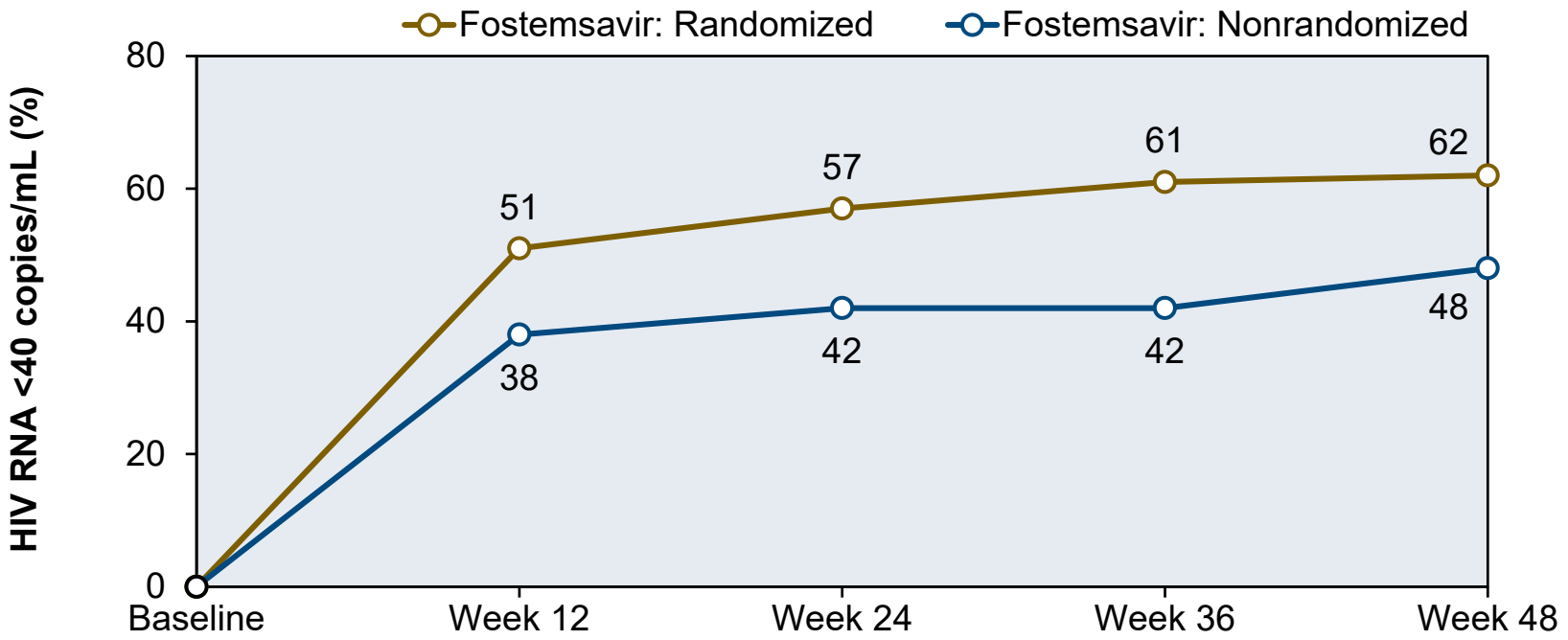
Baseline to Day 8 Change in HIV RNA Level



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

Fostemsavir (FTR) for Heavily Treatment Experienced 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.

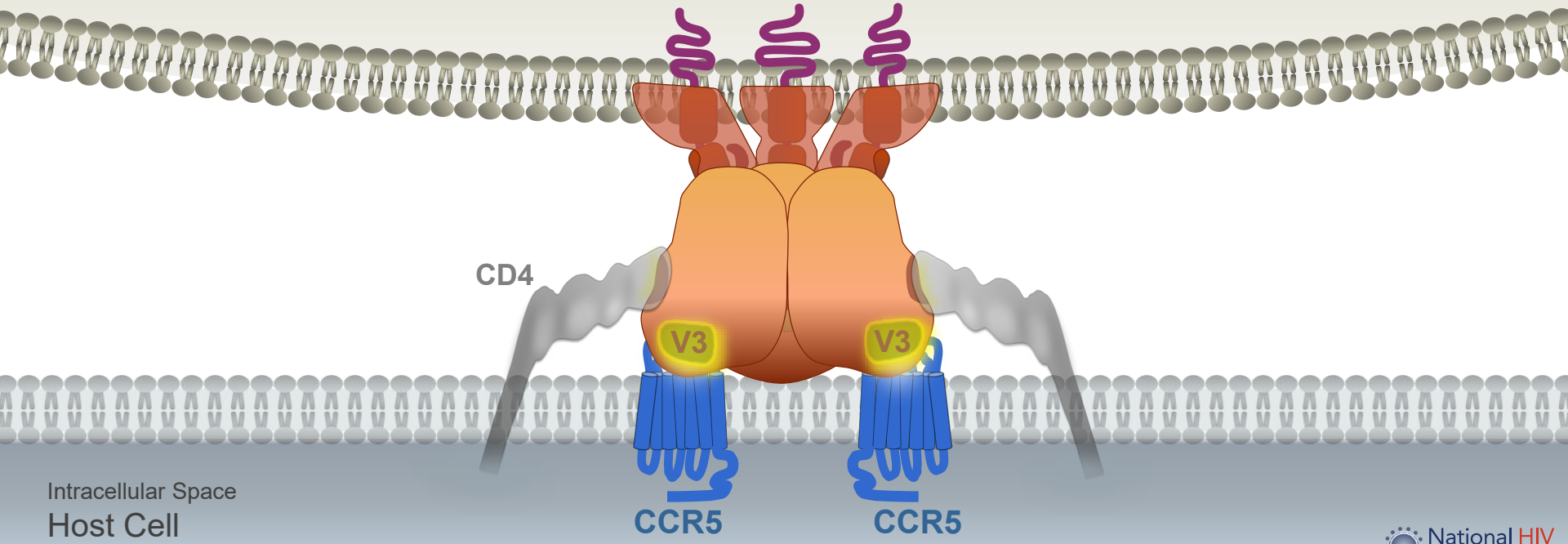
Ibalizumab

- **Indication**
  - Heavily treatment-experienced adults
  - multidrug resistant HIV-1
  - Failing their current antiretroviral regimen
- **Dosing (Intravenous)**
  - Loading dose: 2,000 mg IV
  - Maintenance dose: 800 mg IV every 2 weeks
- **Contraindications**
  - None

HIV Cell Entry

Co-Receptor Binding

HIV



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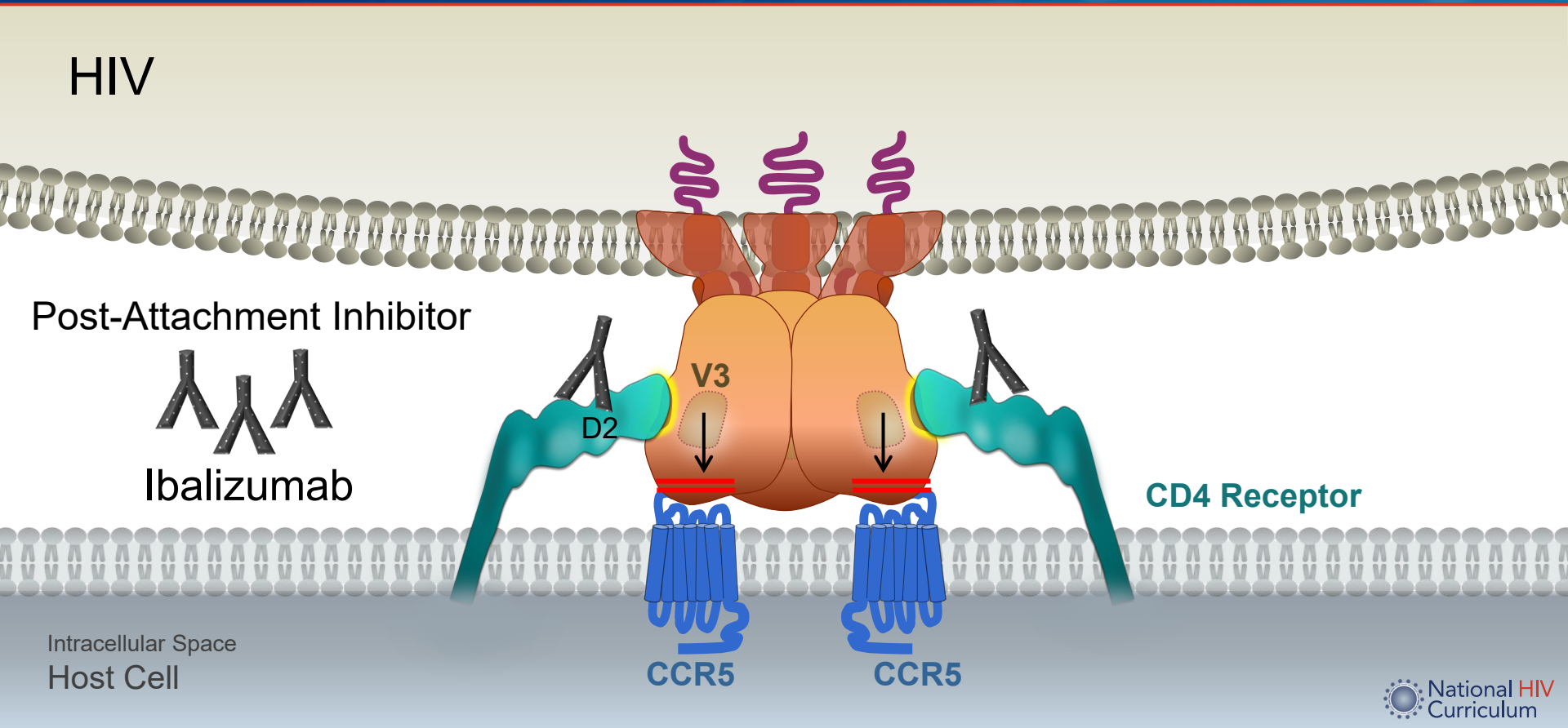
Ibalizumab

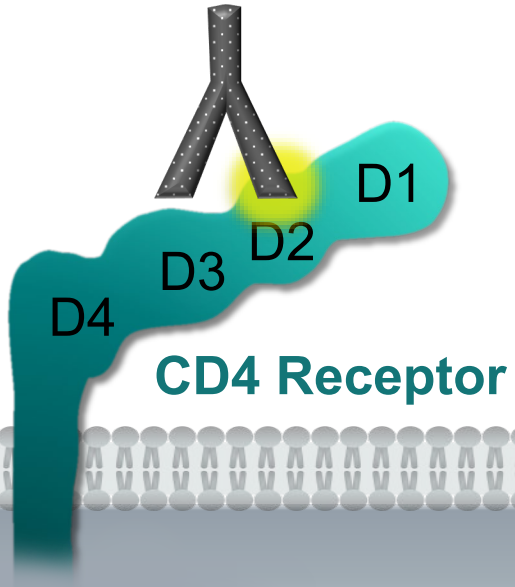


Post-Attachment Inhibitors

Ibalizumab

Monoclonal Antibody

Post-Attachment Inhibitor



Intracellular Space

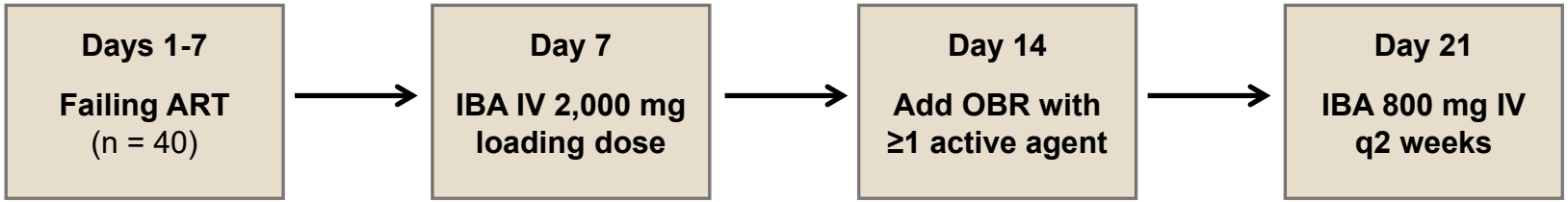
Host Cell

Ibalizumab Added to OBR for Adults Failing ART
TMB-301: Study Design

TMB-301: Study Design

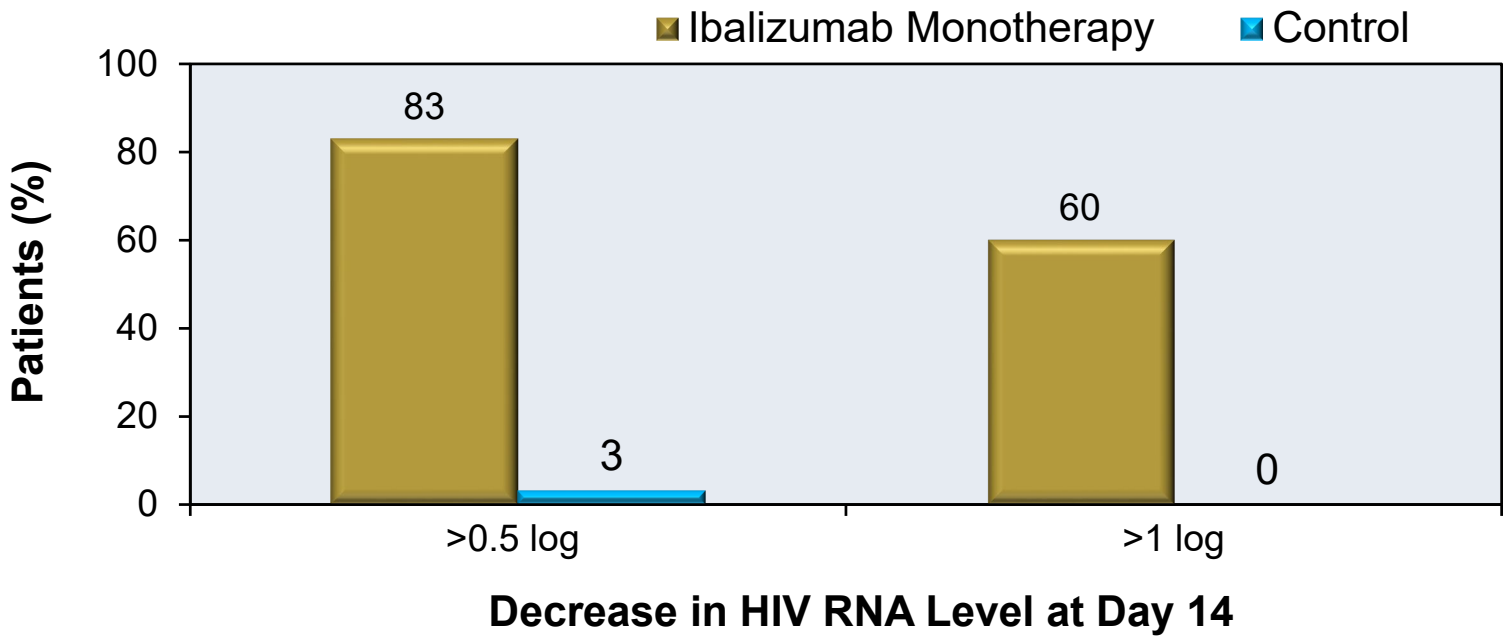
- **Study design:**
  - Single-arm, open label study of ibalizumab (IBA) added to OBR) for individuals failing ART
  - Primary endpoint: ≥0.5 $\log_{10}$ decrease in HIV RNA 7 days after initiating IBA therapy (day 14 of study)
  - Secondary endpoints: virologic outcomes, safety, and tolerability at 24 weeks

- **Inclusion Criteria:**
  - Adults with HIV, on ART for ≥6 months
  - HIV RNA >1,000 copies/mL
  - ≥3 class drug resistance (but ≥1 remaining active drug)



Source: Emu B, et al. N Engl J Med. 2018;379:645-54.

Ibalizumab Added to OBR for Adults Failing ART
TMB-301: Efficacy at Day 14

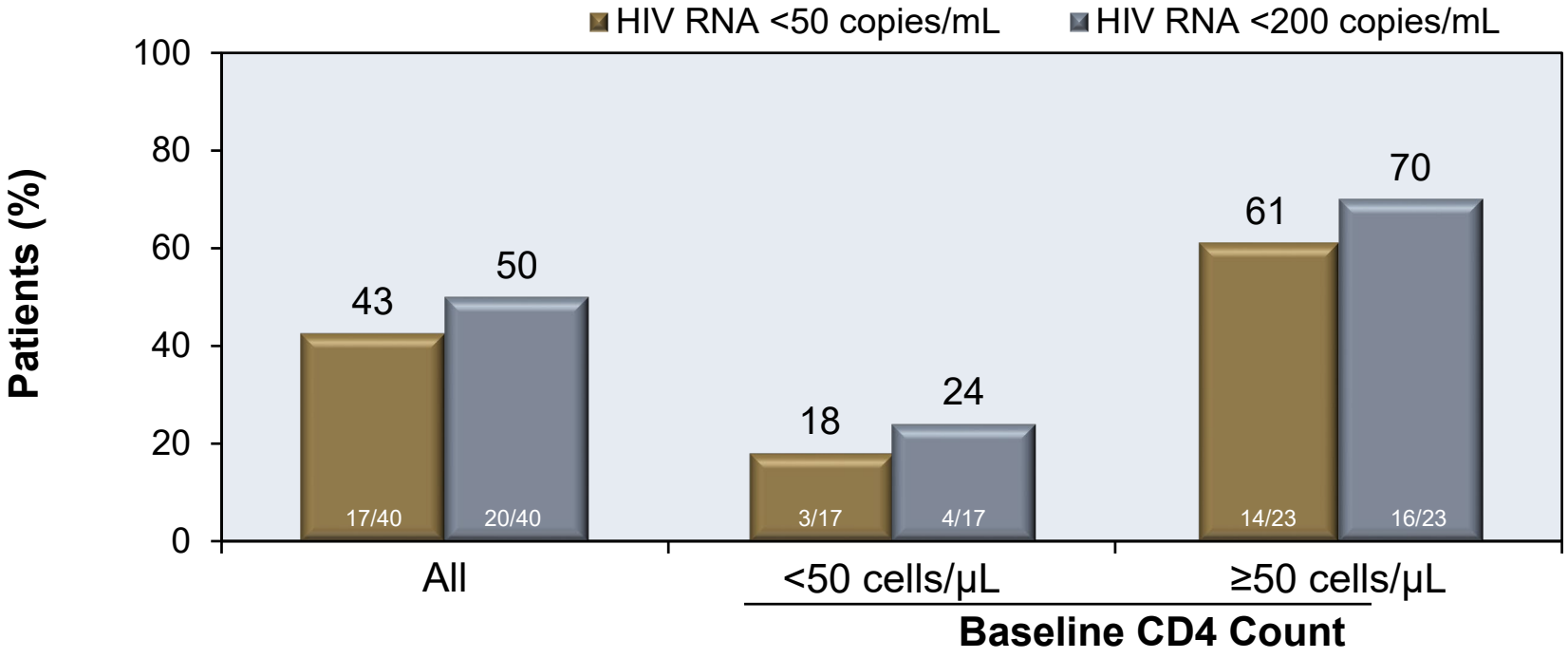


IBA Monotherapy = after 7 days of IBA added to failing ART (functional monotherapy)
Control = after 7 days of baseline failing ART

Source: Emu B, et al. N Engl J Med. 2018;379:645-54.

Ibalizumab Added to OBR for Adults Failing ART
TMB-301: Efficacy at Week 25, by Baseline CD4 Cell Count

Week 25 Virologic Response (Intention-to-Treat Analysis)



Source: Emu B, et al. N Engl J Med. 2018;379:645-54.

Promising Future Medications

Islatravir

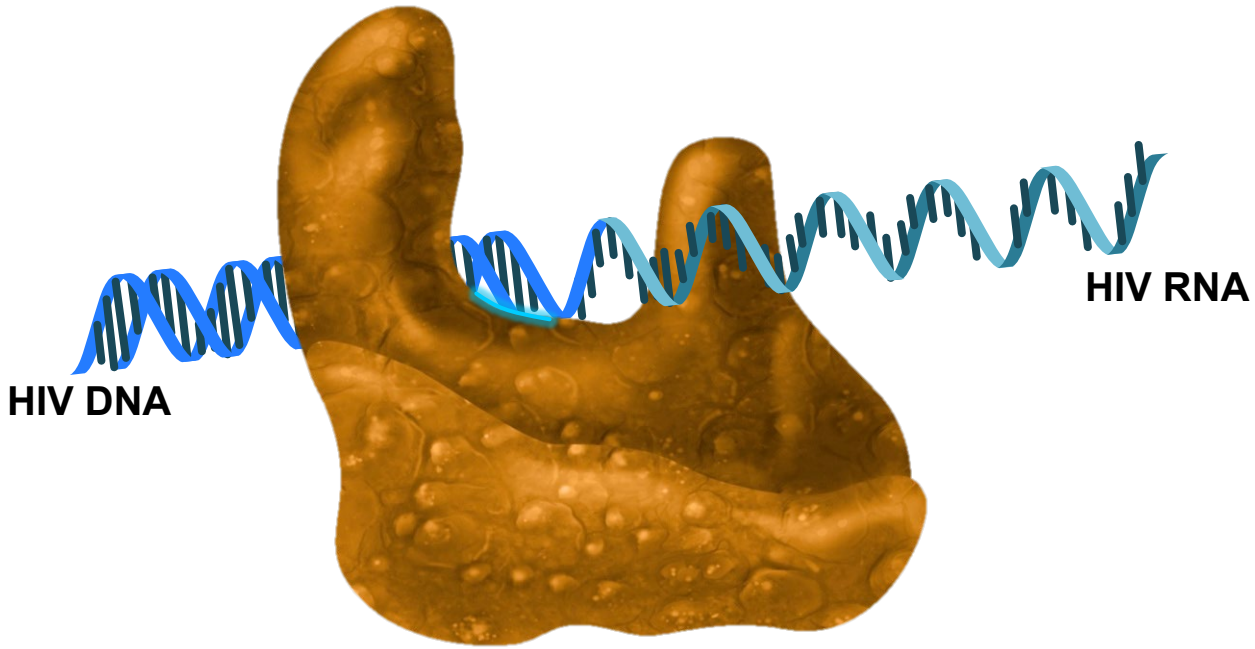
Islatravir (MK-8591, EFdA)

- Nucleoside Reverse Transcriptase **Translocation** Inhibitor (NRTTI)
- Nano-molar potency
- Half-life estimated at 191 hours
- High genetic barrier to resistance
- Broad activity against NRTI-resistant HIV
- Appear to have minimal or no metabolic adverse effects

How is a NRTTI different from an NRTI?

HIV Reverse Transcription

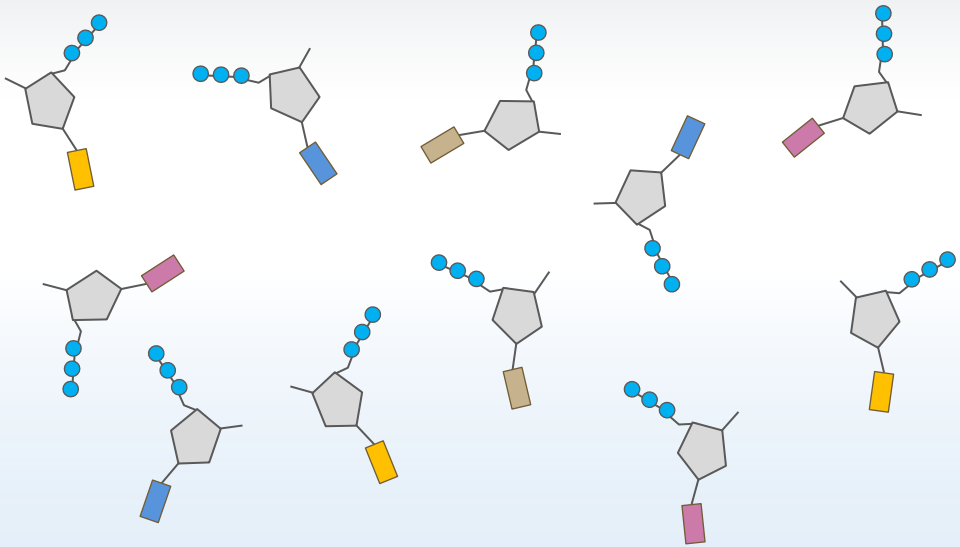
Conversion of HIV RNA to HIV DNA



Intracellular Pool of Nucleotides

Intracellular Space

Human Cell



Human Nucleotides

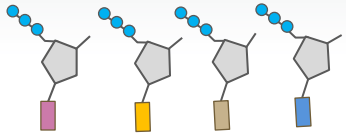


Illustration: David H. Spach, MD

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Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

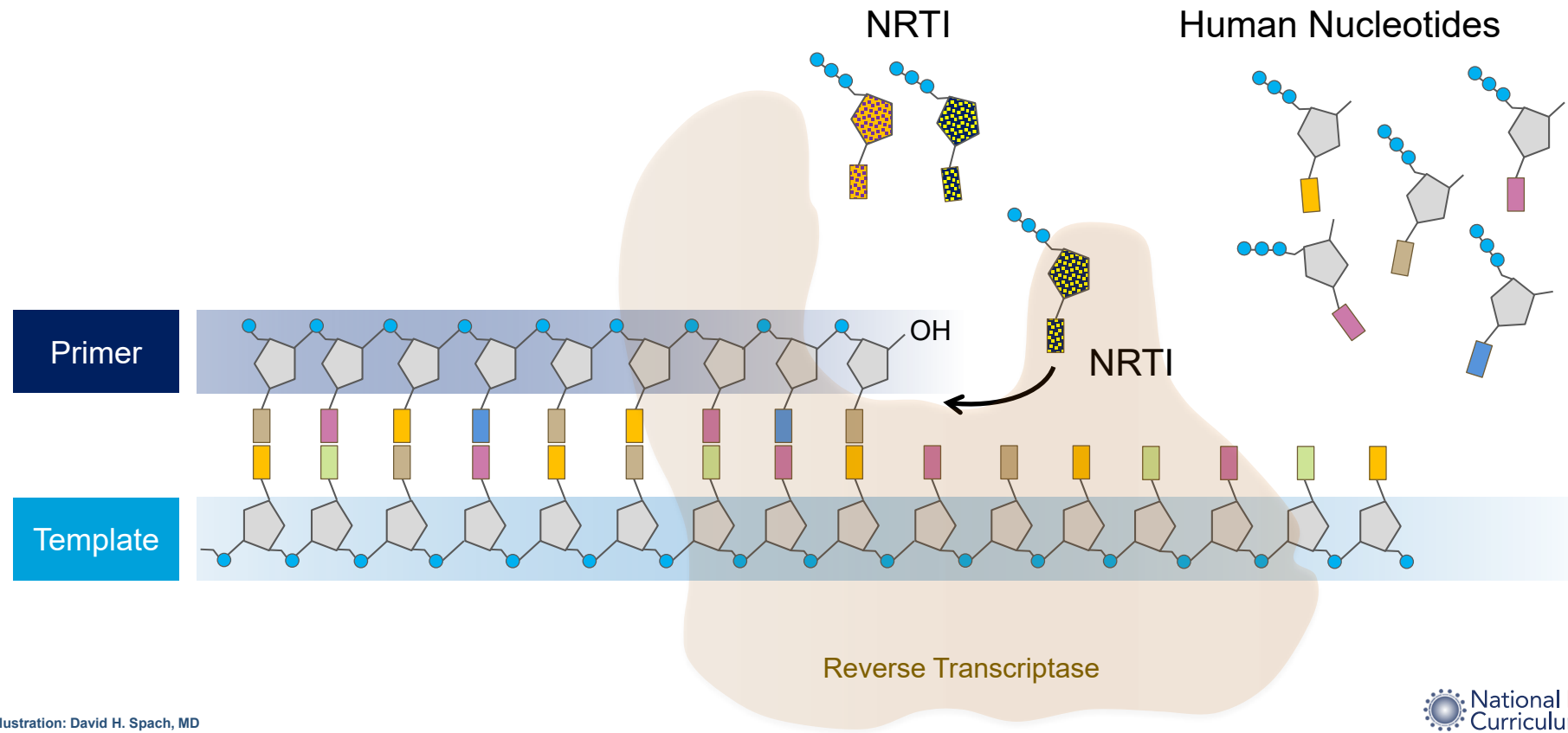

Illustration: David H. Spach, MD

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Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

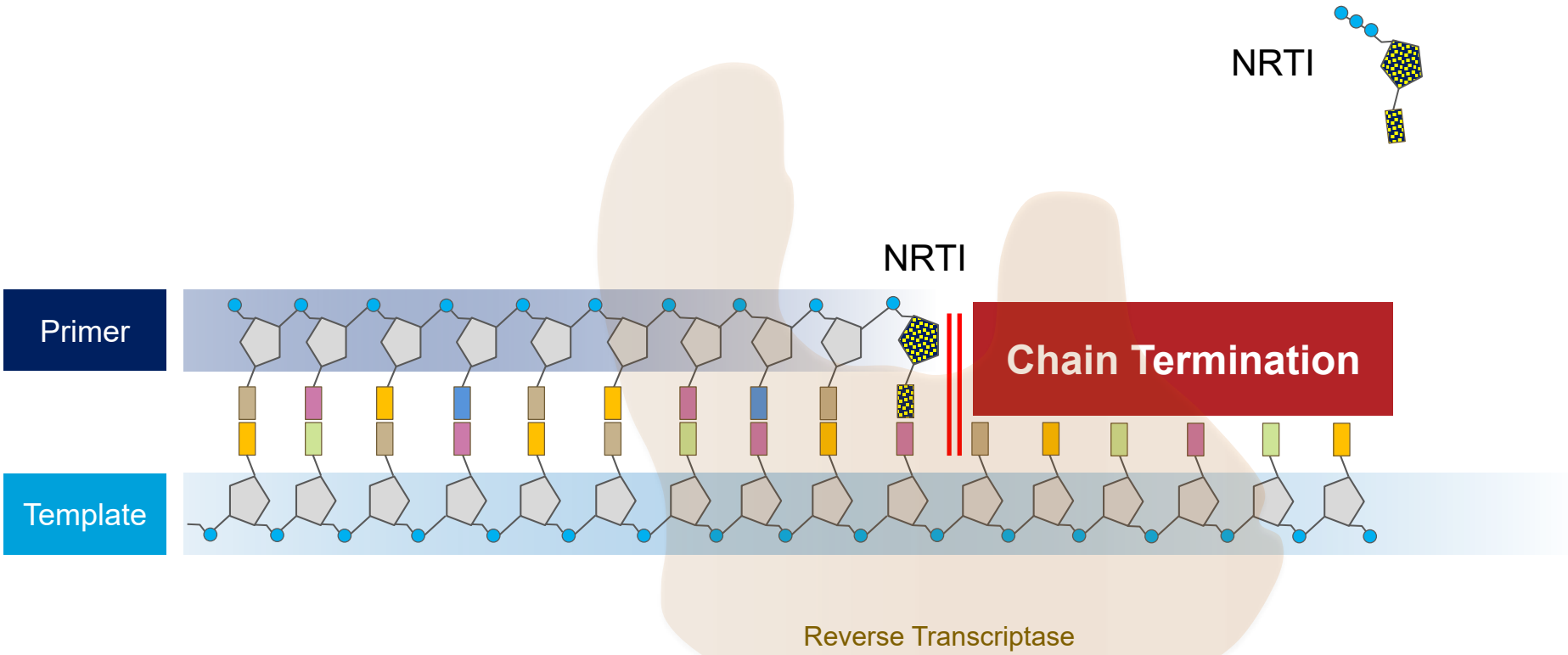
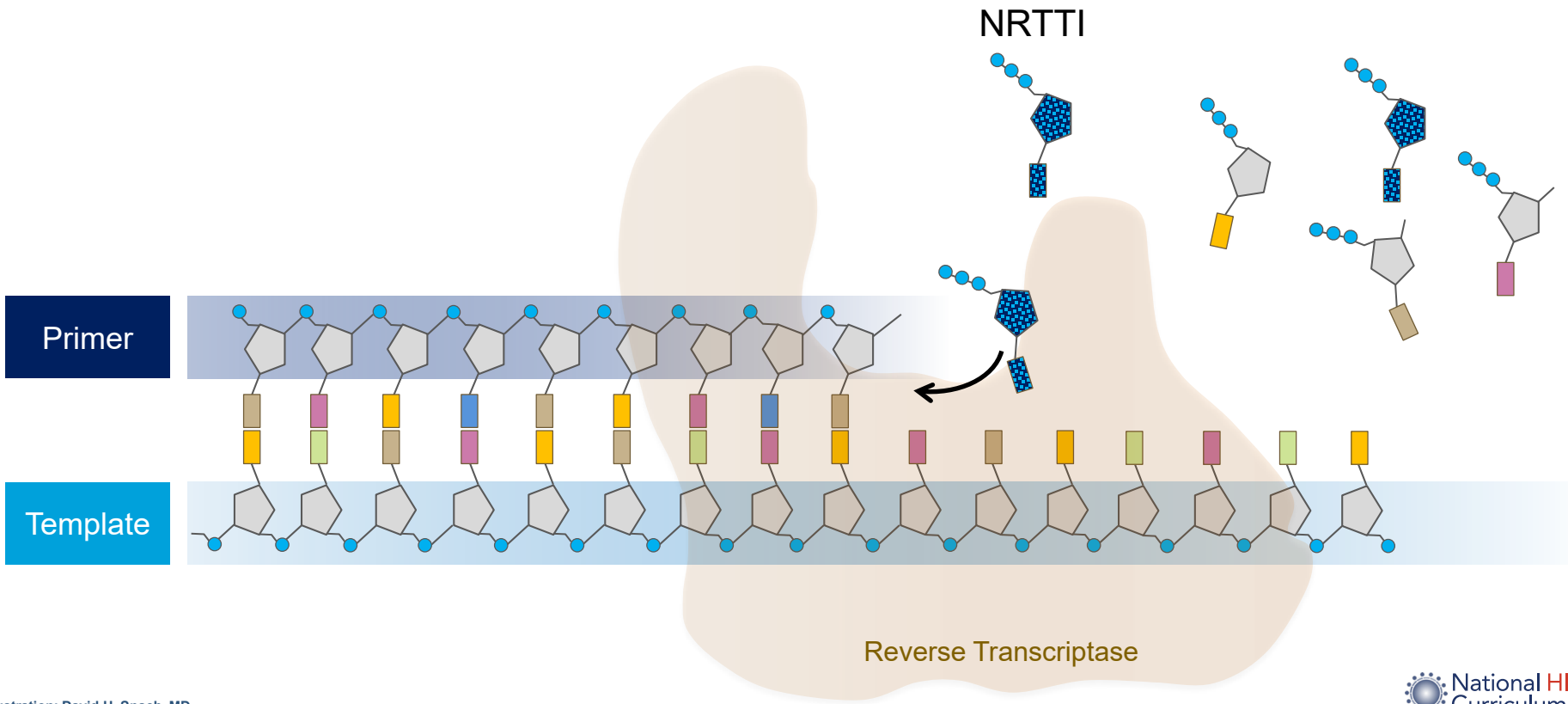


Illustration: David H. Spach, MD

Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)



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Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)

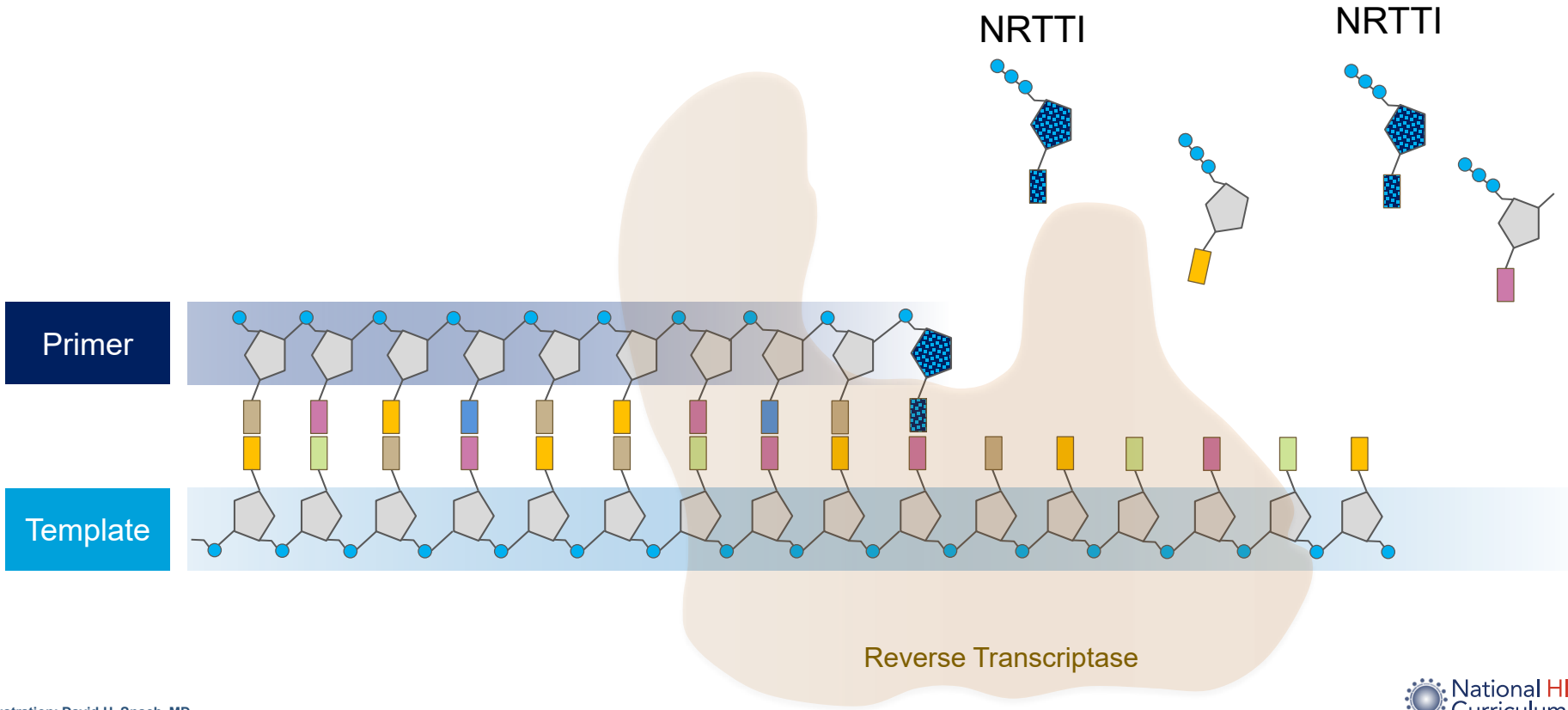

Illustration: David H. Spach, MD

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NRTTI Mechanism (1): Translocation Inhibition

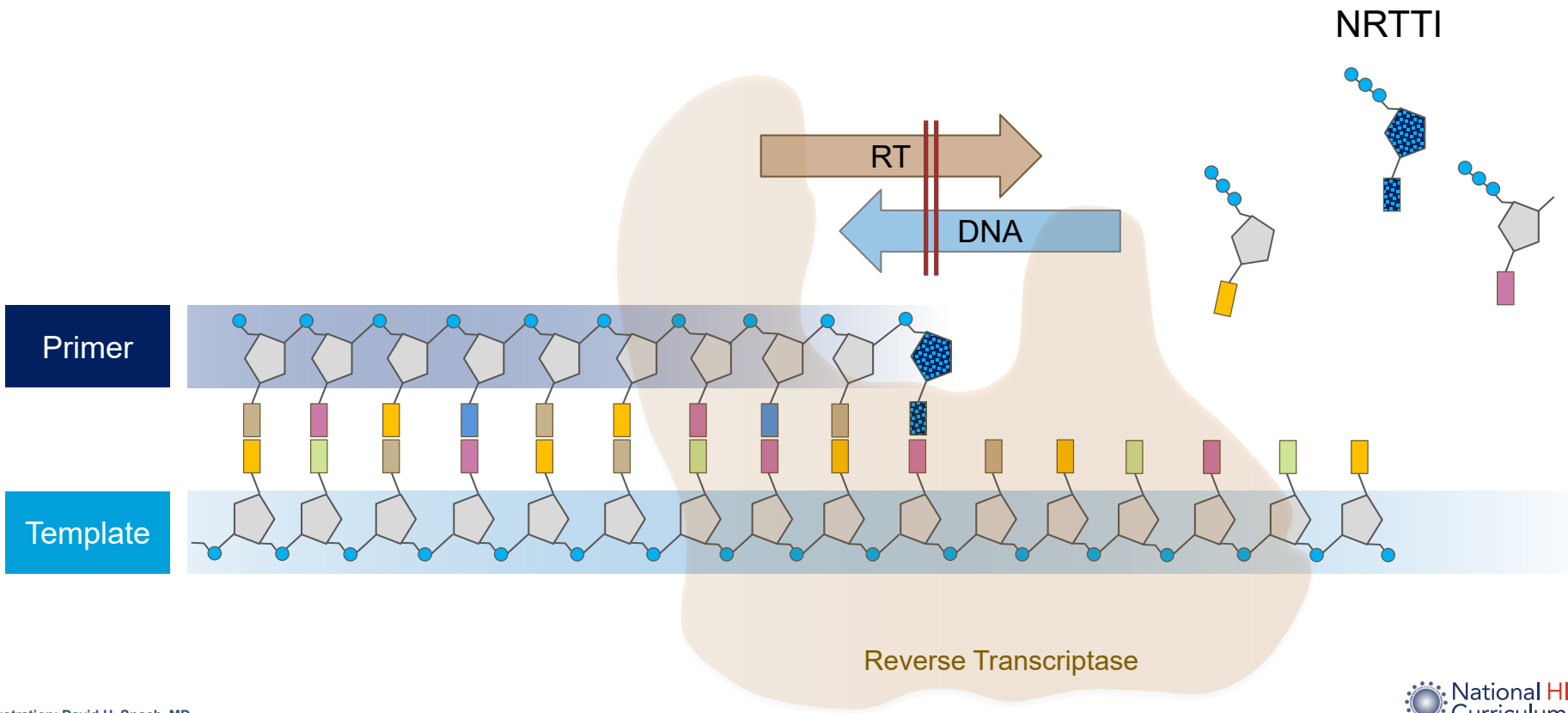

Illustration: David H. Spach, MD

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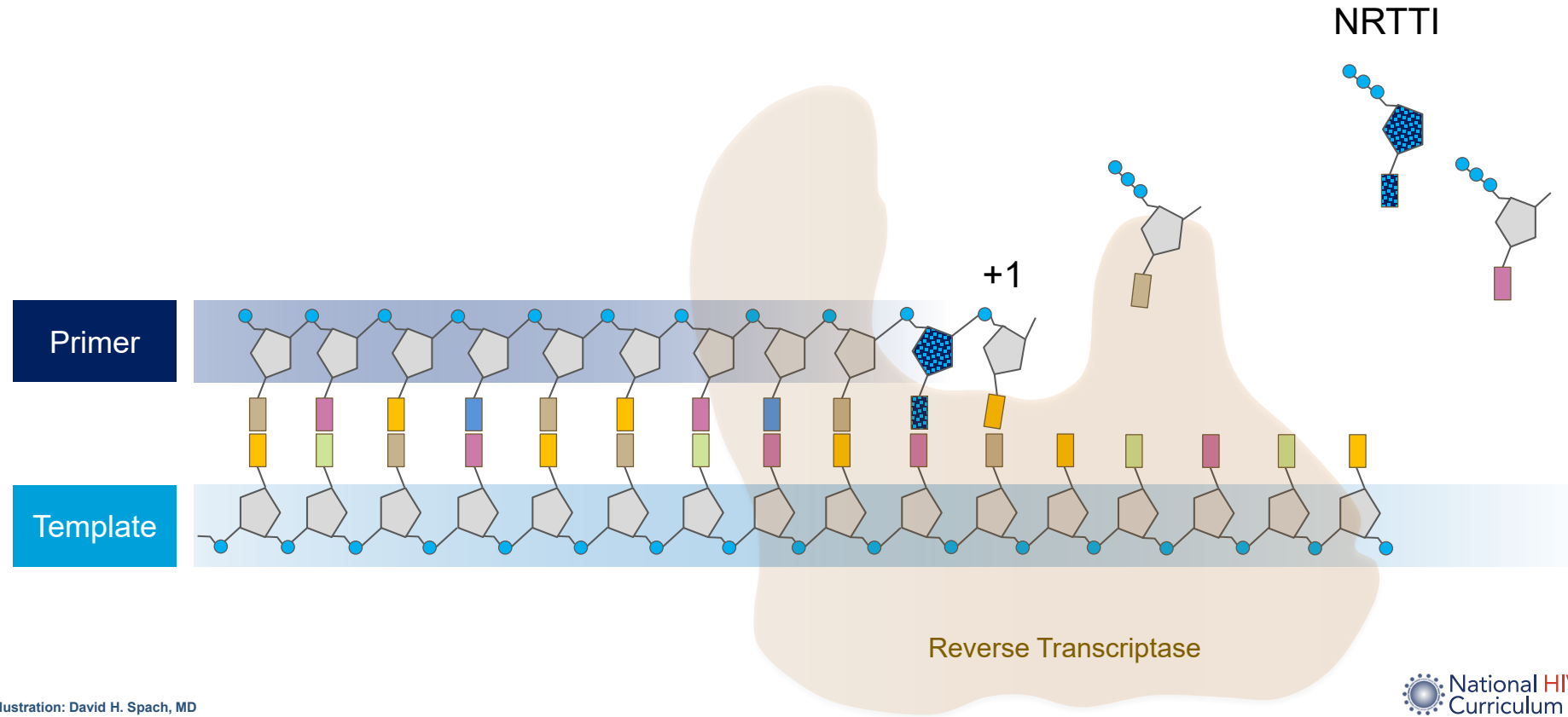
NRTTI Mechanism (2): Delayed Chain Termination



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NRTTI Mechanism (2): Delayed Chain Termination

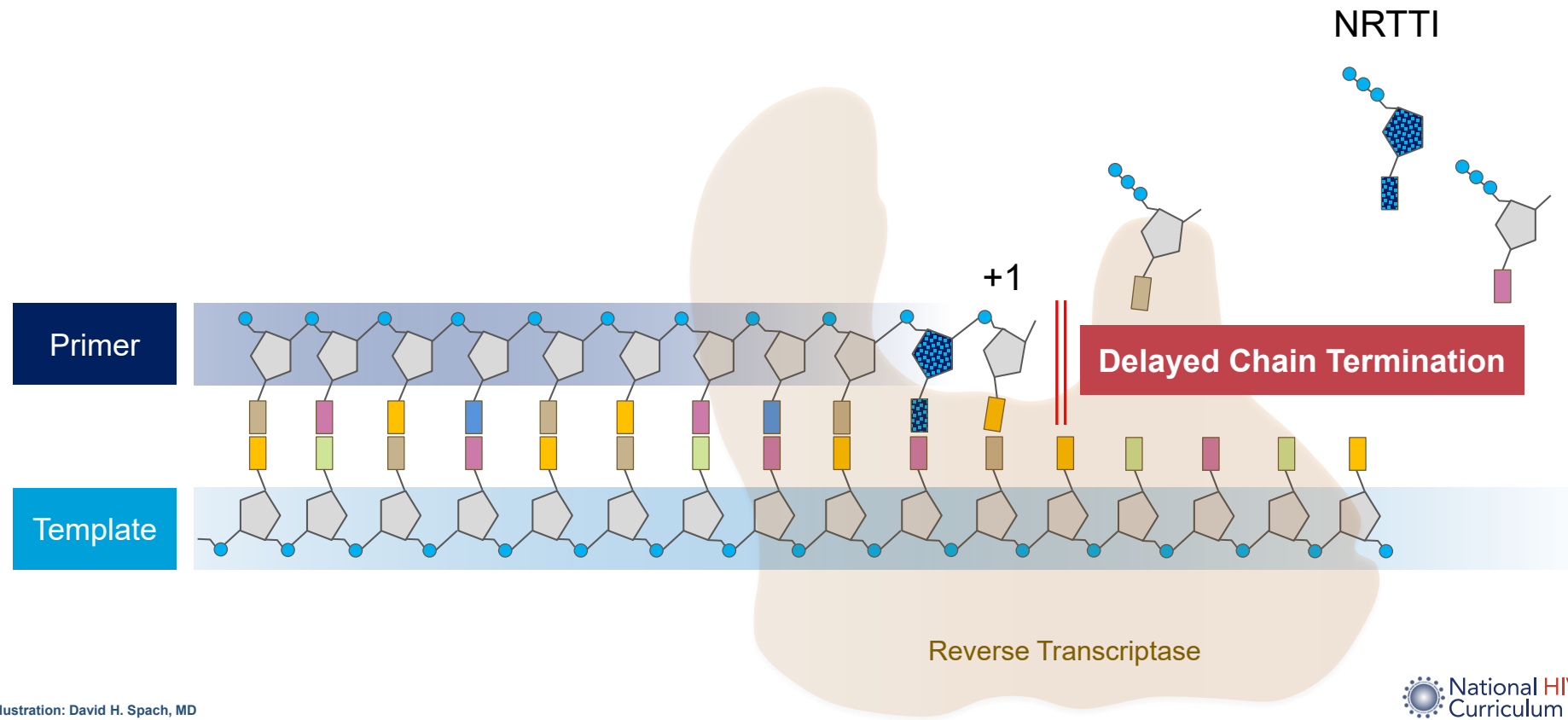

Illustration: David H. Spach, MD

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Islatravir (MK-8591, EFdA): Studies

- **Treatment**
  - Oral Daily Initial: islatravir 0.75 mg + doravirine 100 mg
  - Oral Daily Maintenance: islatravir 0.75 mg + doravirine 100 mg
  - Oral Daily Salvage: islatravir 0.75 mg + doravirine 100 mg
  - Oral Weekly Maintenance*: islatravir 20 mg + NNRTI MK-8507 (100-400 mg)
  - Injections: unknown dose frequency

- **PrEP**
  - Oral Monthly: islatravir 60 mg dosing
  - Implant Yearly: eluting islatravir implant (56 mg)
  - Injections: unknown dose and frequency

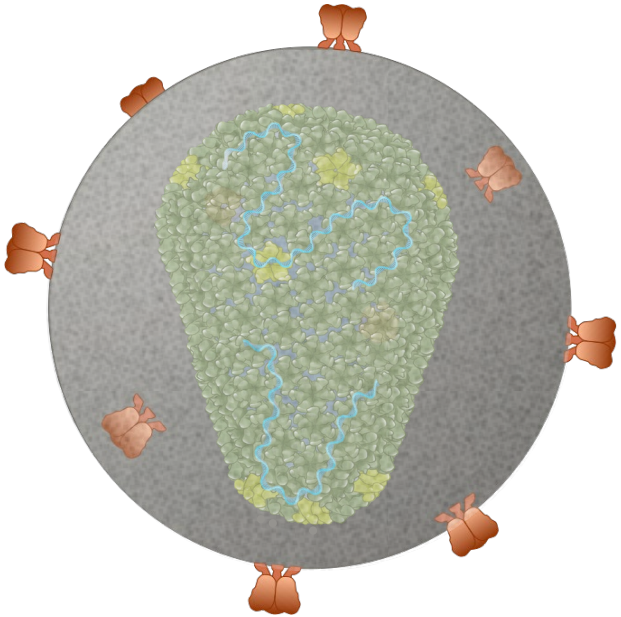
*Islatravir 20 mg weekly generates islatravir trough levels similar to islatravir 0.75 mg daily

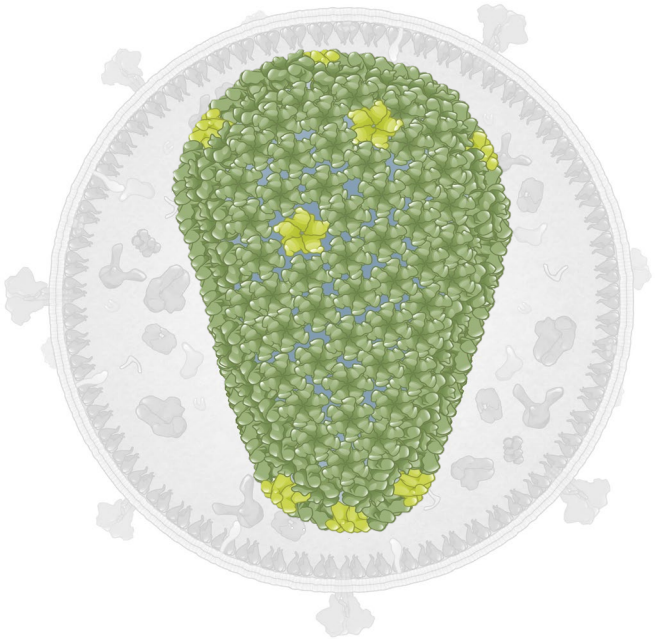
Lenacapavir

Lenacapavir (GS-6207):

- Capsid Inhibitor (multiple steps)
  - Capsid disassembly and nuclear transport
  - Virus production and release
  - Core assembly
- Pico-molar potency
- Oral formulation: Half-life estimated at 12 days
- High genetic barrier to resistance
- Broad activity against drug-resistant HIV
- Appear to be safe and well tolerated

HIV Capsid





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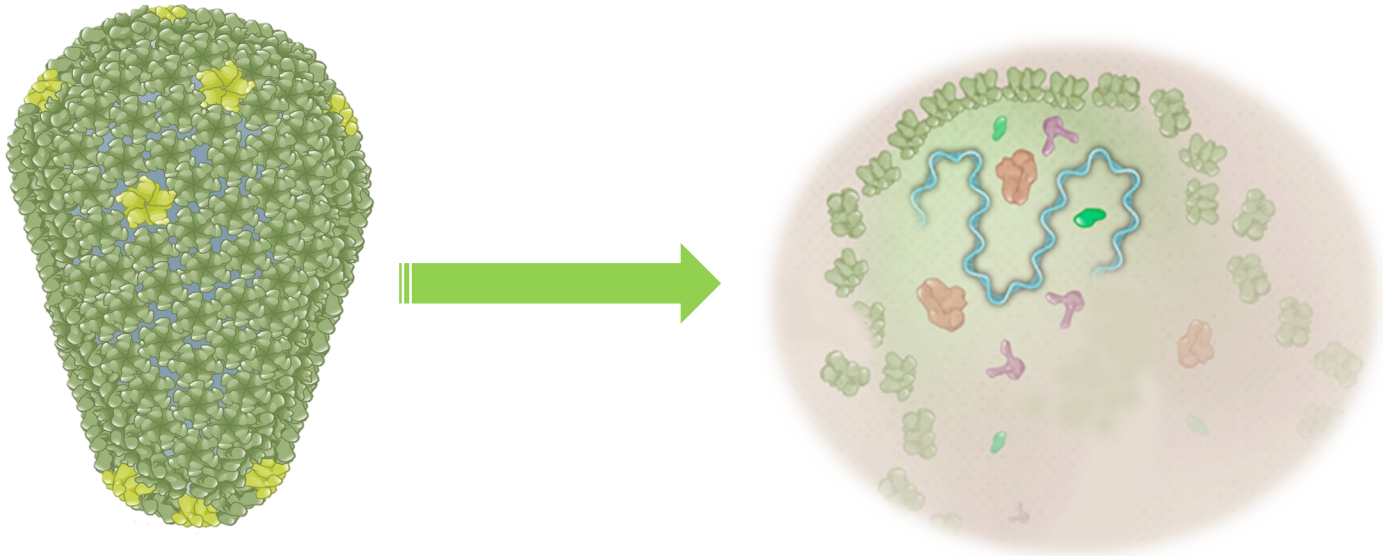
Capsid Disassembly



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Capsid Inhibitors: Bind to Capsid (p24) Hexamer Proteins

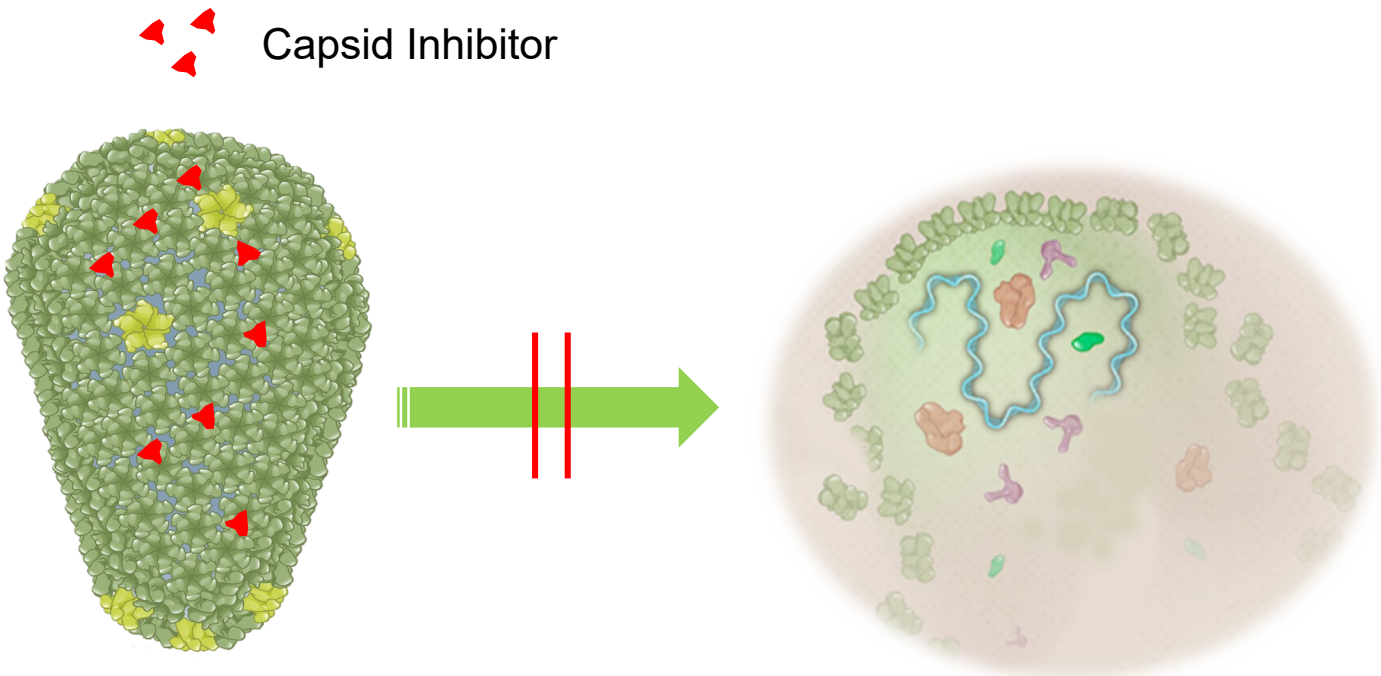

Illustration: Jared Travnicek (Cognition Studio) and David Spach, MD

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Lenacapavir (GS-6207): Studies

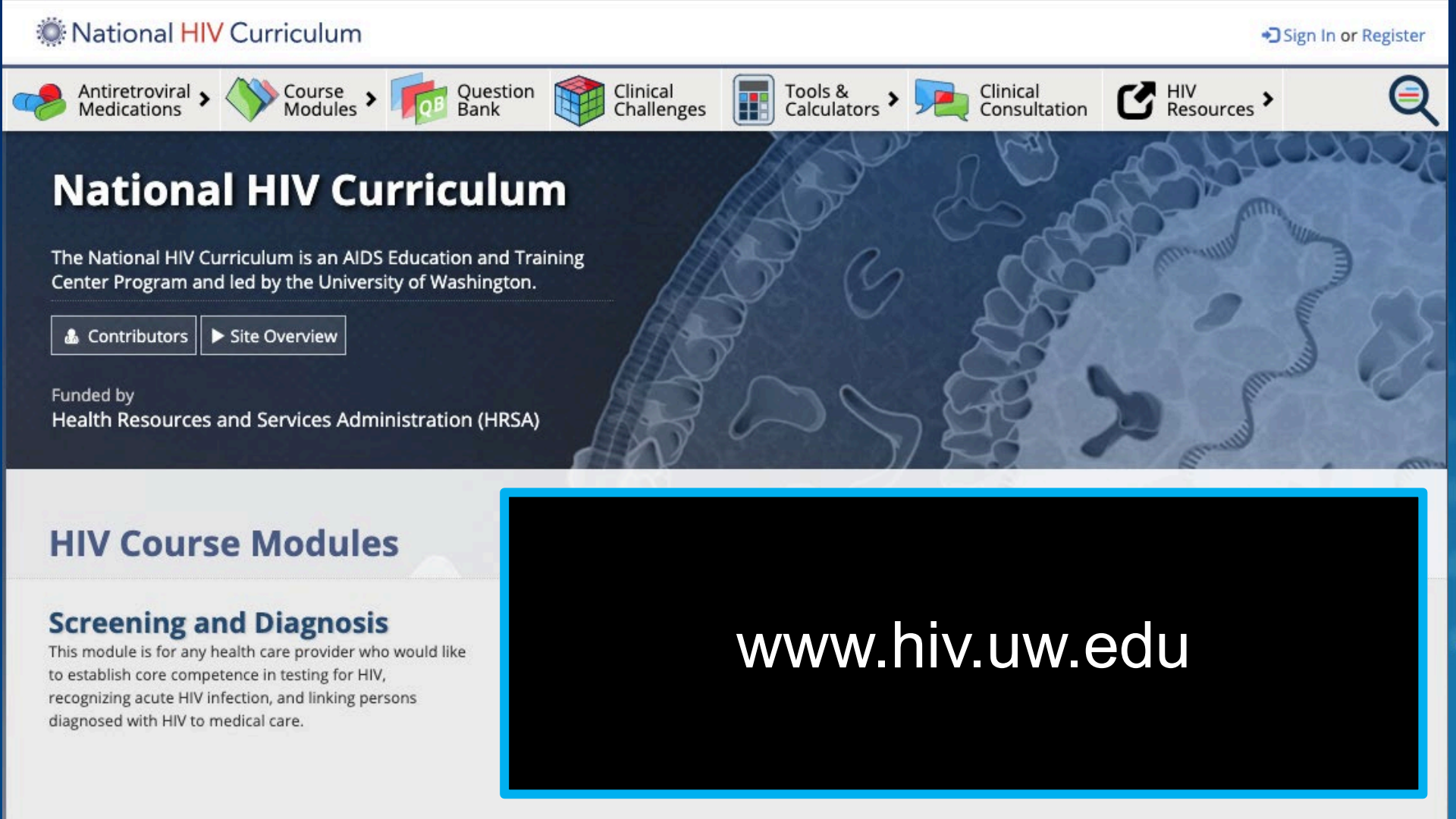
- **Treatment**
  - Oral Daily Initial
  - Subcutaneous Injections: every 6 months
- **PrEP**
  - Subcutaneous Injections: every 6 months

Long-Acting Lenacapavir and Islatravir

Gilead and Merck Announce Agreement to Jointly Develop and Commercialize Long-Acting, Investigational Treatment Combinations of Lenacapavir and Islatravir in HIV

– Collaboration to Focus on Oral and Injectable Formulations of Lenacapavir and Islatravir –

– Agreement Brings Together Potentially Complementary Medicines in Late-Stage Development with the Goal to Provide Innovative, Long-Acting Treatments in HIV –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This module is for any health care provider who would like to establish core competence in testing for HIV, recognizing acute HIV infection, and linking persons diagnosed with HIV to medical care.
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