Sep 21st, 2:25 PM - 3:10 PM

HIV Resistance and Care Update

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HIV Resistance and Care Update

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Division of Health Protection/IDI-HIV

September 21, 2018

Go to **www.menti.com** and use the code **13 35 33**

1

Grab your phone

2

Go to www.menti.com

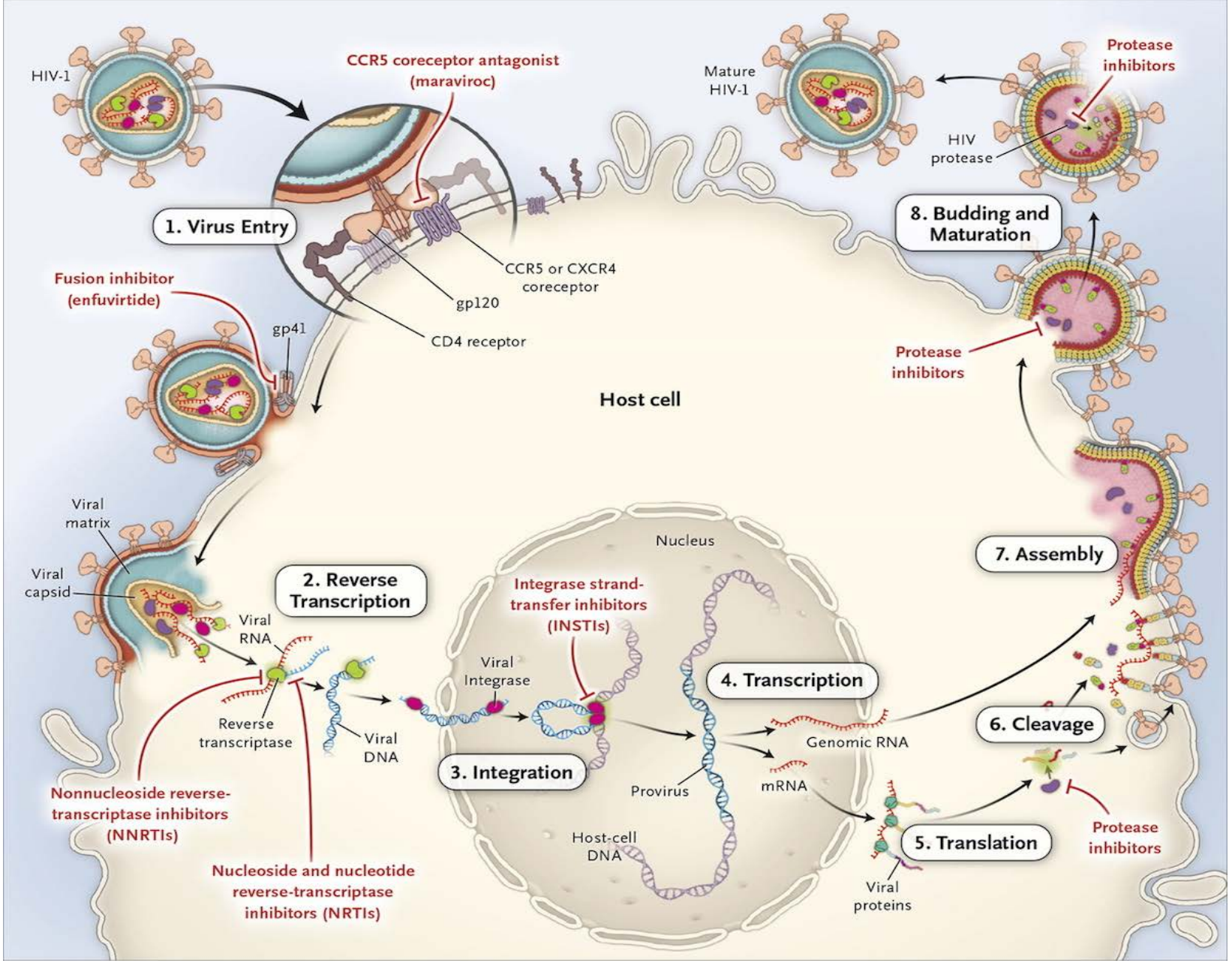
3

Enter the code 13 35 33 and vote!

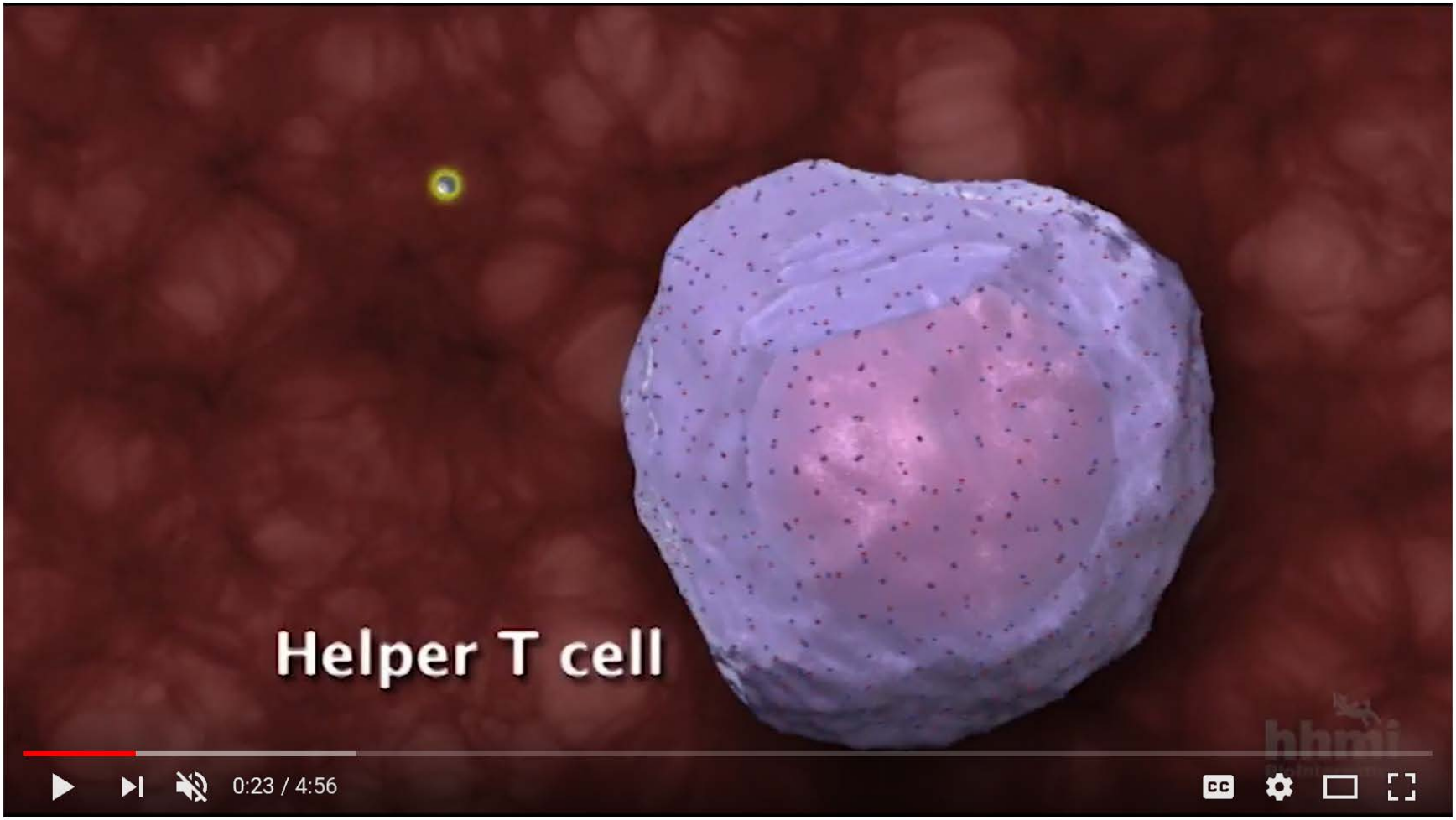
Objectives

- Summarize the HIV replicative cycle
- Describe the mechanism of action of ARVs
- Visualize how mutations & resistance occurs
- Define current HIV treatment guidelines
- Illustrate resistance via clinical case presentations

No Disclosures

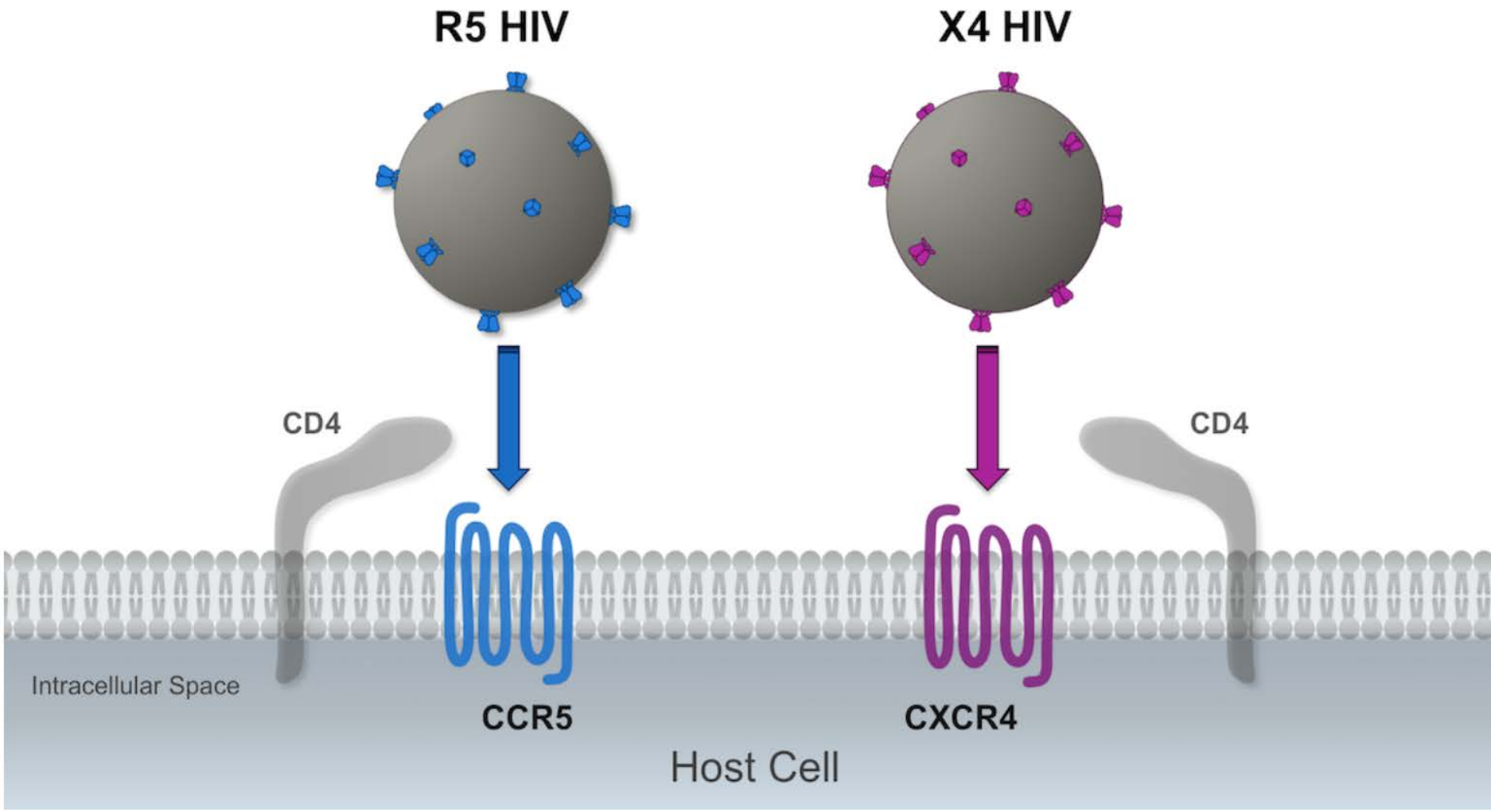


https://www.hiv.uw.edu/go/antiretroviral-therapy/general-information/core-concept/all#hiv-life-cycle-antiretroviral-drug-targets



https://youtu.be/PlSvywlLuNw

Mixed-Tropic HIV



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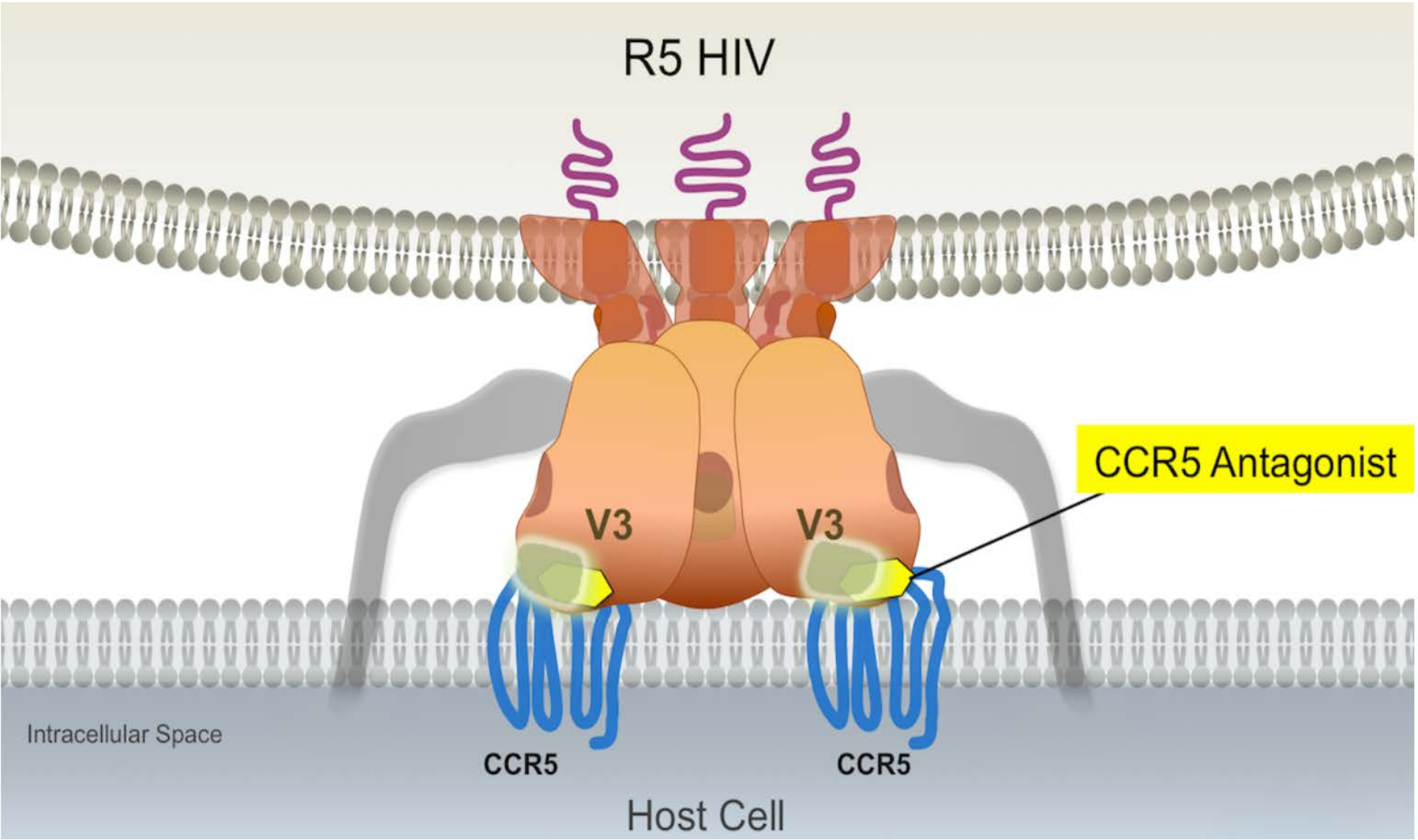
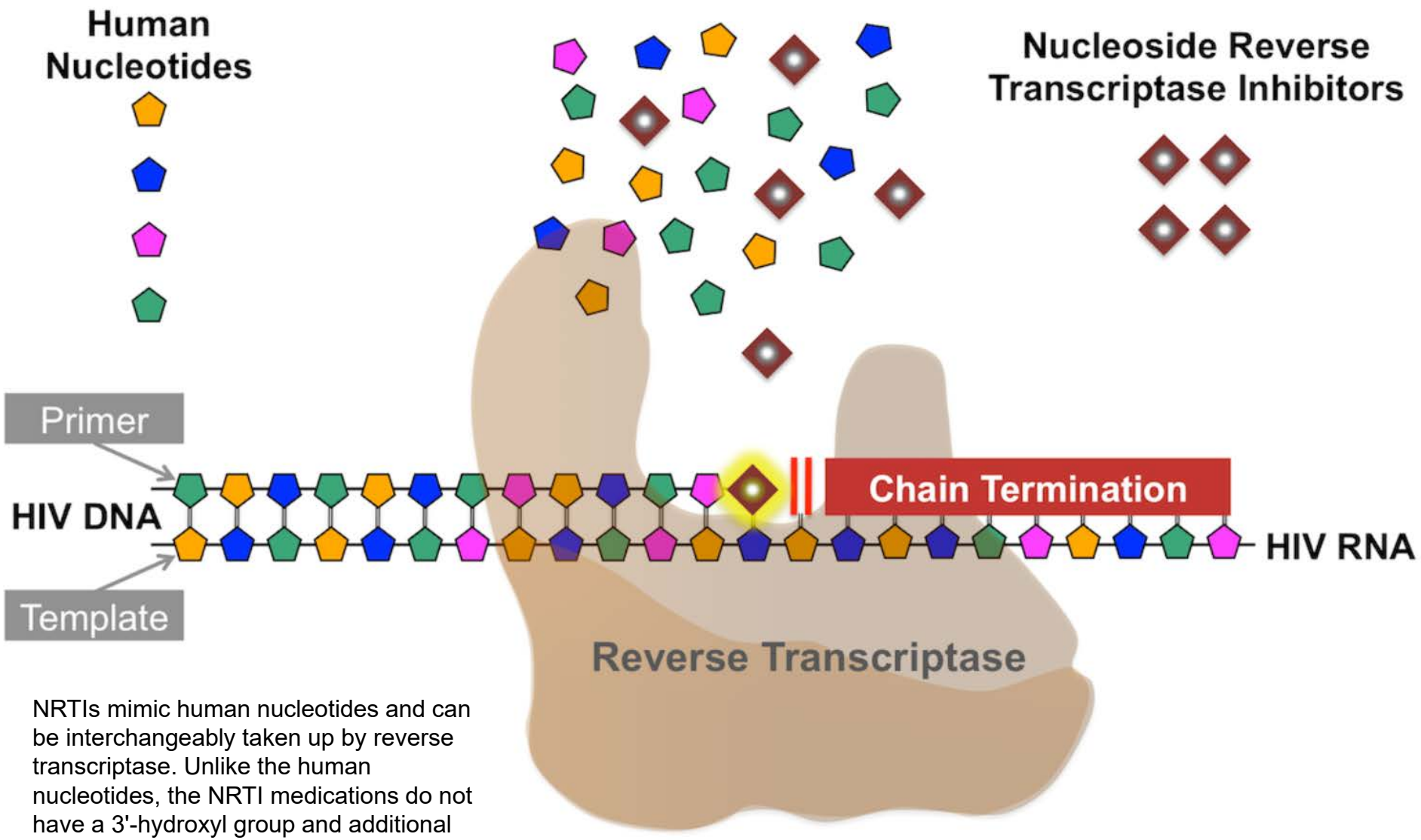


Resistance to maraviroc can occur when R5-tropic HIV-1 develops mutations that facilitate the gp120-CCR5 coreceptor binding despite maraviroc attachment to the CCR5 coreceptor and receptor conformational changes. When this type of resistance occurs, the binding of HIV-1 gp120 occurs with enhanced affinity at the CCR5 N-terminal domain region

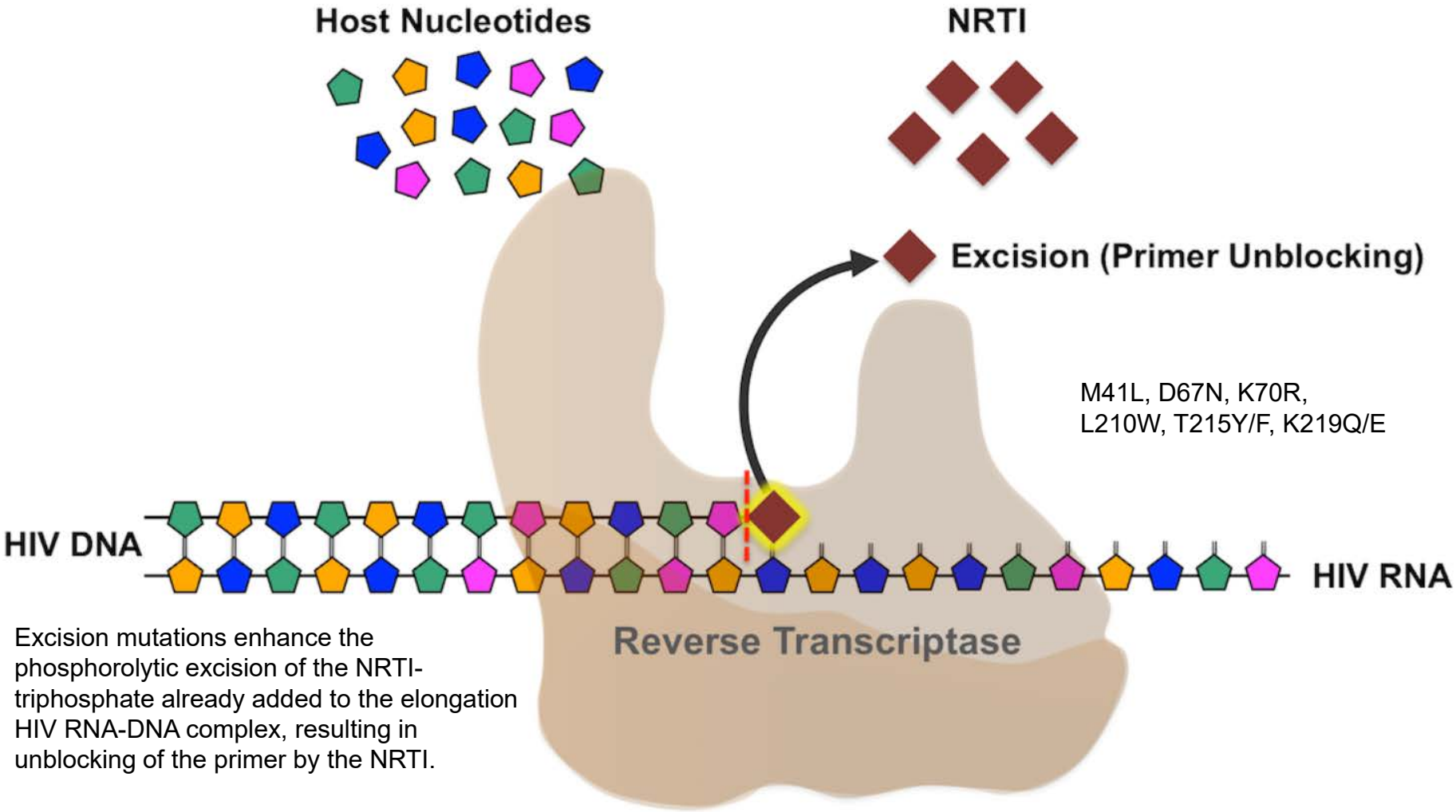
https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all



NRTIs mimic human nucleotides and can be interchangeably taken up by reverse transcriptase. Unlike the human nucleotides, the NRTI medications do not have a 3'-hydroxyl group and additional nucleotides can not be added to the NRTI drug, hence the name chain terminator

https://www.hiv.uw.edu/go/antiretroviral-therapy/general-information/core-concept/all#hiv-life-cycle-antiretroviral-drug-targets

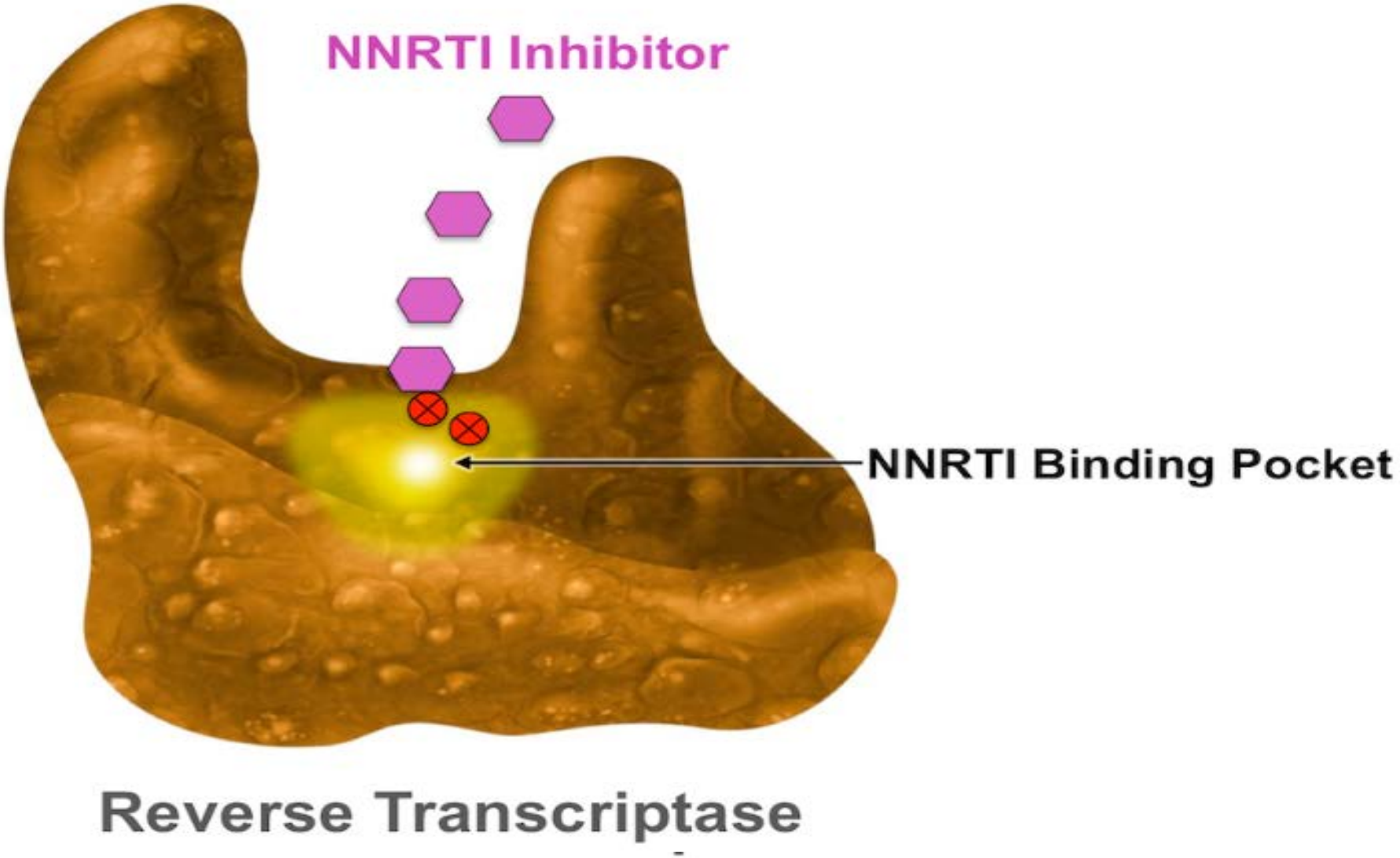
Excision of incorporated NRTI by promoting pyrophosphorolysis (primer unblocking)



Excision mutations enhance the phosphorolytic excision of the NRTI-triphosphate already added to the elongation HIV RNA-DNA complex, resulting in unblocking of the primer by the NRTI.

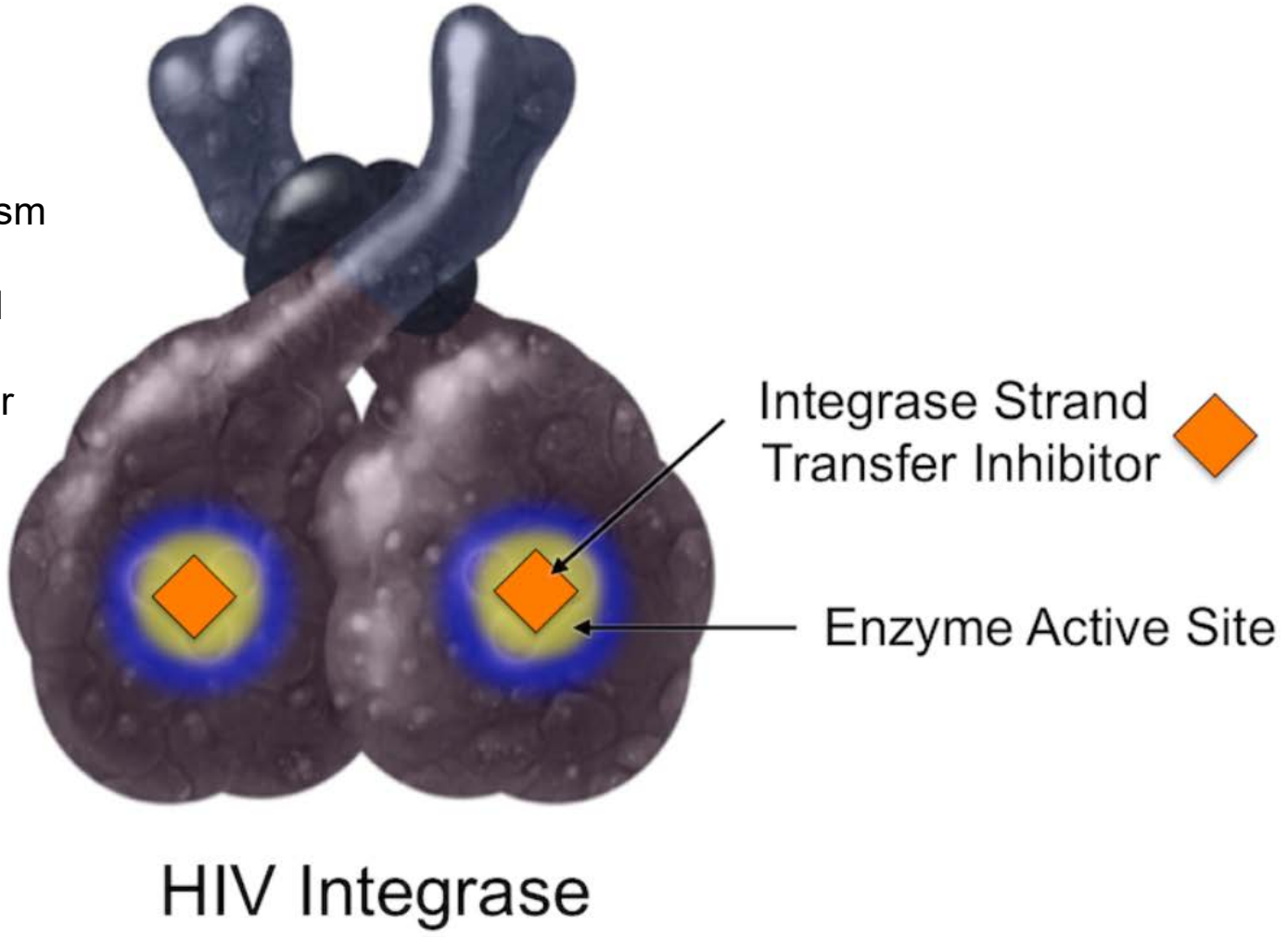
https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all

Reduced Access to NNRTI Binding Pocket

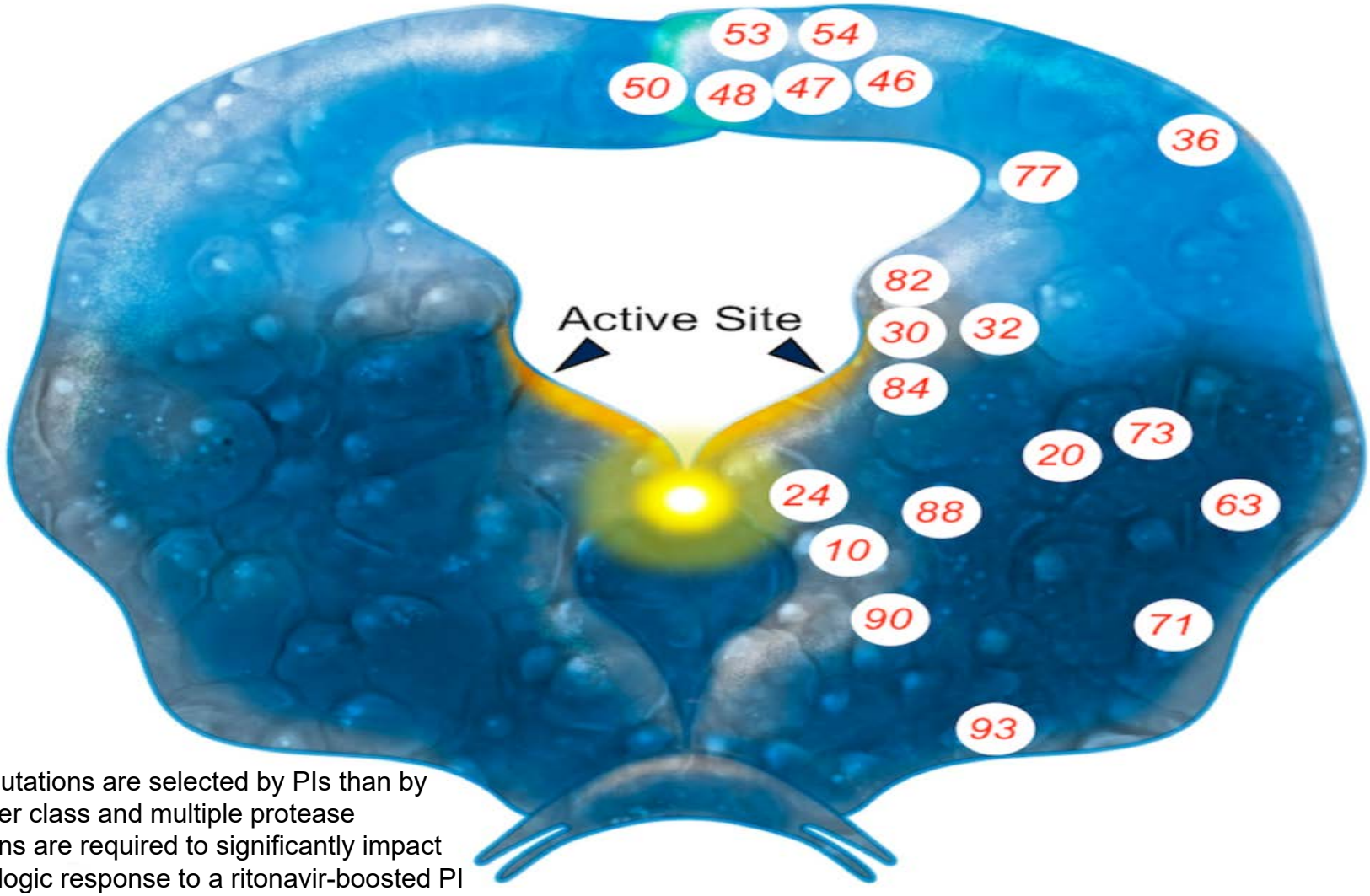


https://www.hiv.uw.edu/go/antiretroviral-therapy/general-information/core-concept/all#hiv-life-cycle-antiretroviral-drug-targets

HIV integrase inhibitors utilize multiple mechanism to block the integrase strand transfer step and are thus referred to as integrase strand transfer inhibitors (INSTIs)



https://www.hiv.uw.edu/go/antiretroviral-therapy/general-information/core-concept/all#hiv-life-cycle-antiretroviral-drug-targets



More mutations are selected by PIs than by any other class and multiple protease mutations are required to significantly impact the virologic response to a ritonavir-boosted PI

https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all

Samuel H. Pepkowitz, MD, Medical Director
345 Oyster Point Blvd
South San Francisco, CA 94080 - Tel: (800) 777-0177

Patient Name	DOB	Patient ID/Medical Record #	Gender	Monogram Accession #
Date Collected	Date Received	Date Reported	Mode	Report Status
Referring Physician			Reference Lab ID/Order #	
Comments			**HIV-1 Subtype:** B	

Drug		GenoSure®MG	Assessment*	Comments
Generic	Brand			

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Patient Name	DOB	Patient ID/Medical Record #	Gender	Monogram Accession #
Date Collected	Date Received	Date Reported	Mode	Report Status

* Assessment of drug susceptibility is based upon detected mutations and interpreted using an advanced proprietary algorithm (version 16).
♦ Interpretation algorithms for ritonavir-boosted protease inhibitors appropriate for the following dosages: AMP/r 600mg/100mg BID; ATV/r 300mg/100mg QD; IDV/r 800mg/200mg BID; LPV/r 400mg/100mg BID; SQV/r 1000mg/100mg BID; TPV/r 500mg/200mg BID; and DRV/r 600mg/100mg BID.
* **Mixtures** are indicated by amino acids separated by a slash. Deletions in the amino acid sequence are indicated by a ^ symbol.

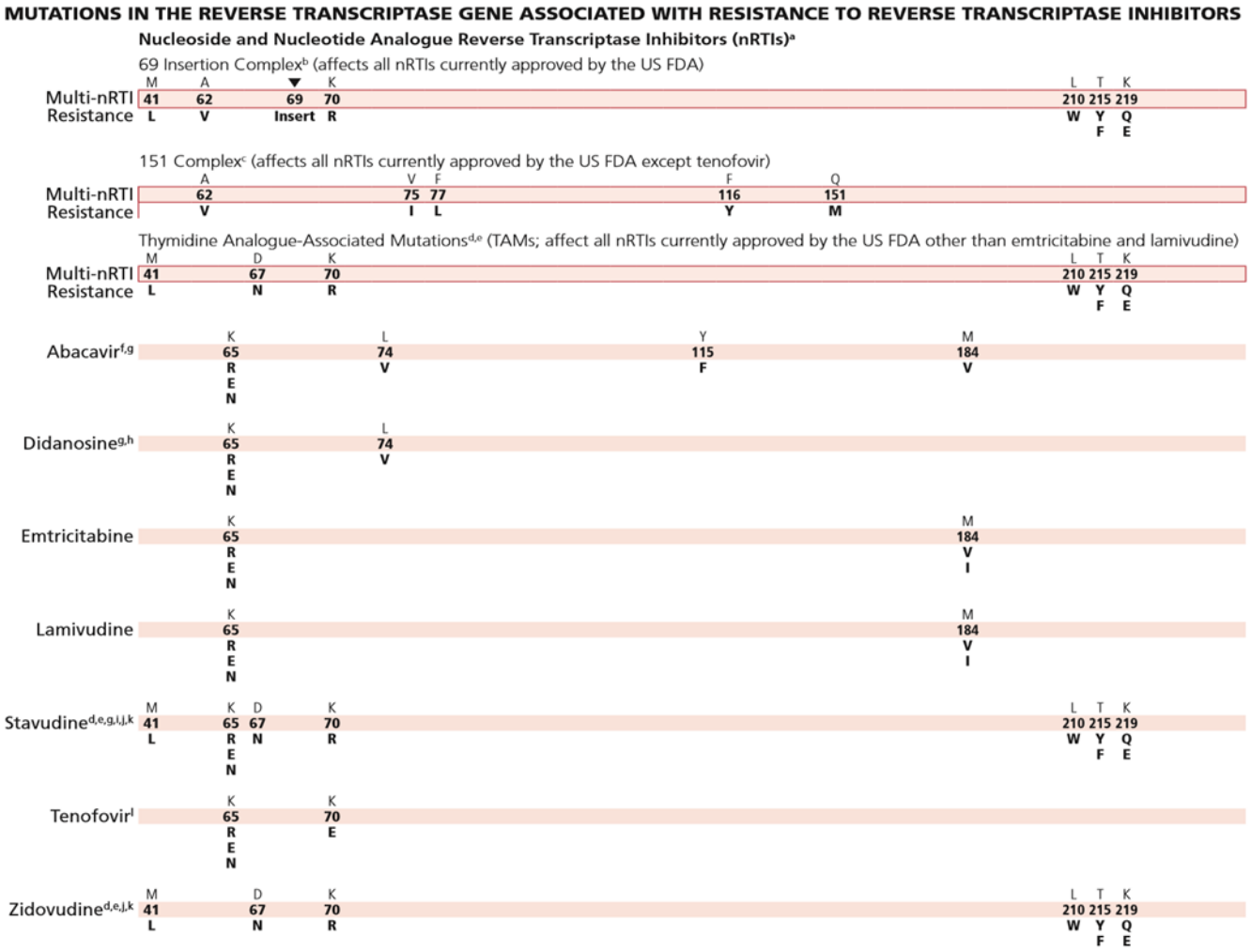
Summary of Mutations Observed

RT K13R, Q102K, K103N, I142T, C162S, Q197E, R211K, A272S, V276I, R277K, V292I, E297V, I326V, A327V, Y339F, P345Q, M357I, K358R, T377V, V381I, T386I, A400T

PR V11I, I64V, K70R, A71V, I72E, V77I, I93L

PI	**Indinavir**	Crixivan / r♦	A71V	**IDV/r**	**Sensitive**
	Lopinavir	Kaletra♦	A71V	**LPV/r**	**Sensitive**
	Nelfinavir	Viracept	A71V	**NFV**	**Sensitive**
	Ritonavir	Norvir	A71V	**RTV**	**Sensitive**
	Saquinavir	Invirase / r♦	A71V	**SQV/r**	**Sensitive**
	Tipranavir	Aptivus / r♦	A71V	**TPV/r**	**Sensitive**

Major Mutations



MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]

69 Insertion Complex[b] (affects all nRTIs currently approved by the US FDA)

	M	A	▼	K	L	T	K
Multi-nRTI Resistance	41	62	69 Insert	70	210	215	219
	L	V	R		W	Y	Q
						F	E

151 Complex[c] (affects all nRTIs currently approved by the US FDA except tenofovir)

	A	V	F	F	Q
Multi-nRTI Resistance	62	75	77	116	151
	V	I	L	Y	M

Thymidine Analogue-Associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)

	M	D	K	L	T	K
Multi-nRTI Resistance	41	67	70	210	215	219
	L	N	R	W	Y	Q
					F	E

	K	L	Y	M
Abacavir[f,g]	65	74	115	184
	R	V	F	V
	E			
	N			

	K	L
Didanosine[g,h]	65	74
	R	V
	E	
	N	

	K	M
Emtricitabine	65	184
	R	V
	E	I
	N	

	K	M
Lamivudine	65	184
	R	V
	E	I
	N	

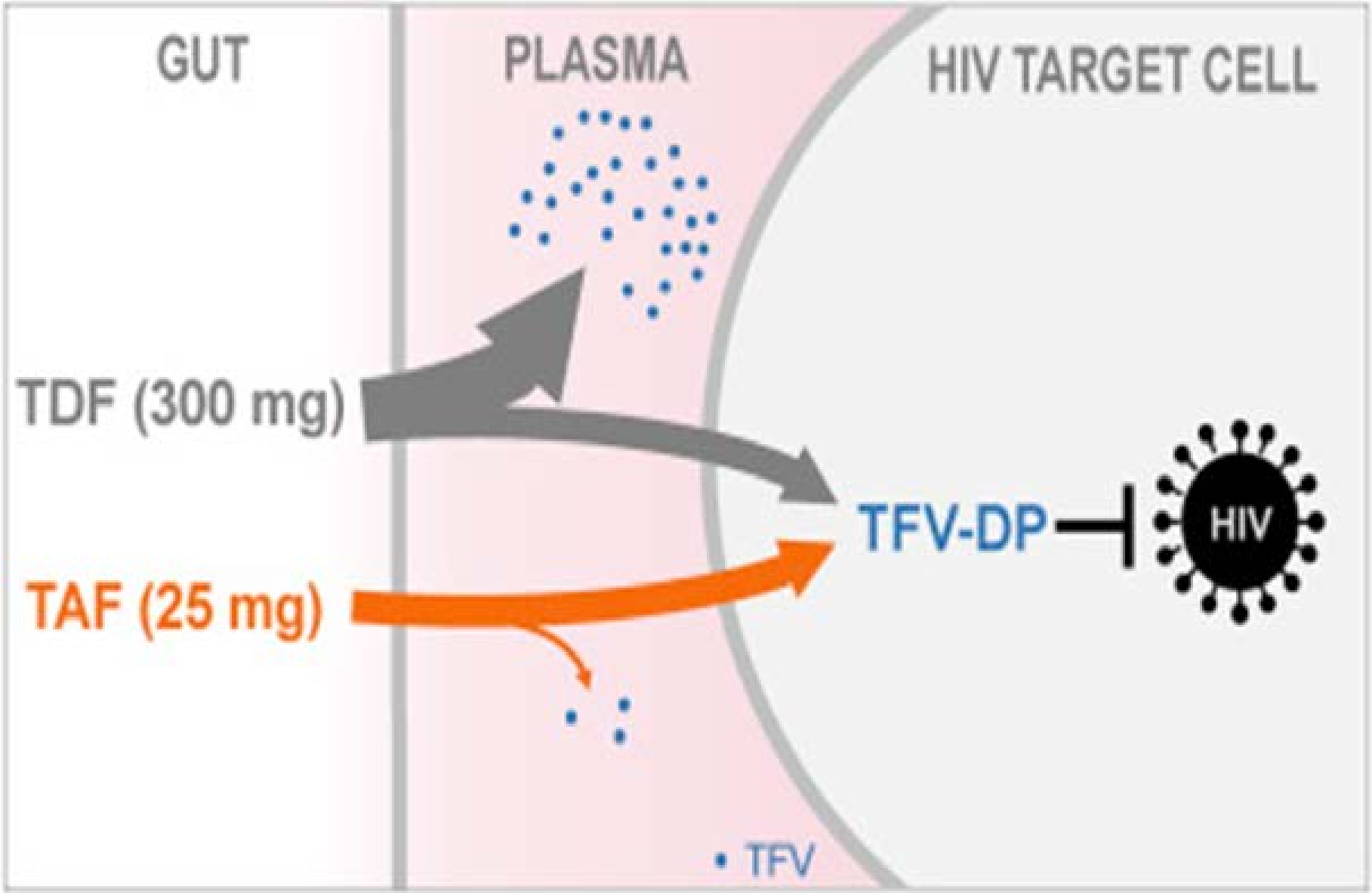
	M	K	D	K	L	T	K
Stavudine[d,e,g,i,j,k]	41	65	67	70	210	215	219
	L	R	N	R	W	Y	Q
		E				F	E
		N					

	K	K
Tenofovir[l]	65	70
	R	E
	E	
	N	

	M	D	K	L	T	K
Zidovudine[d,e,j,k]	41	67	70	210	215	219
	L	N	R	W	Y	Q
					F	E

https://hivdb.stanford.edu/pages/download/resistanceMutations_handout.pdf

https://www.iasusa.org/sites/default/files/2017-drug-resistance-mutations-hiv-1-figure.pdf



http://www.sciencedirect.com/science/article/pii/S0166354215300310

ANTIRETROVIRAL (ARV) REGIMENS FOR ART-NAÏVE PATIENTS

Recommended Regimen Options

INSTI Based

• DTG + ABC**/3TC* **Triumeq™**	• DTG + TAF/FTC* or TDF/FTC*
• EVG/cobi***/TAF/FTC **Genvoya™**	• RAL### + TDF/FTC* or TAF/FTC*
• EVG/cobi***/TDF/FTC **Stribild™**	• BIC (Bictegravir)/TAF/FTC **Biktarvy™**

Recommended Initial Regimens in Certain Clinical Situations

Effective and tolerable but have some disadvantages when compared with the above recommended regimens, or have less supporting data from randomized clinical trials. However, one of the following regimens may be the preferred regimens in certain clinical situations.

PI Based¥	**NNRTI Based**
• (DRV/cobi*** or DRV/r) + TAF/FTC* or TDF/FTC*	• EFV + TDF/FTC* **Atripla™**
• (DRV/cobi*** or DRV/r) + ABC**/3TC*	• EFV + TAF/FTC*
• (ATV/cobi*** or ATV/r) + TAF/FTC* or TDF/FTC*	• RPV# + TDF/FTC* **Complera™**
• (ATV/cobi*** or ATV/r) + ABC**/3TC* (##)	• RPV# + TAF/FTC* **Odefsey™**
INSTI Based	**If TDF, TAF or ABC cannot be used**
• RAL### + ABC**/3TC* (##)	• DRV/r + RAL (twice daily)#
	• LPV/r¥¥ (twice daily) + 3TC* (twice daily)

July 18, 2018: Symtuza™ FDA Approved

Aug. 30, 2018: Delstrigo™ / Pifeltro™ (doravirine)

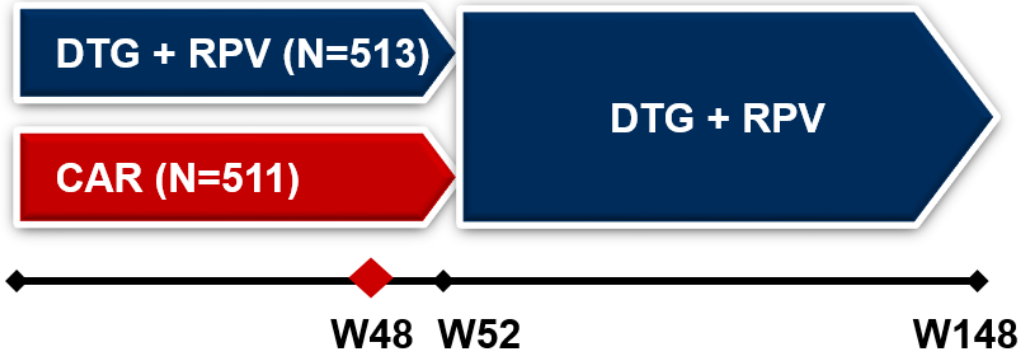
Study Design and Virological Outcomes at W48

Two randomized, multicenter, open-label studies

HIV Suppressed Adults
HIV-1 RNA <50 c/mL
x 12 months

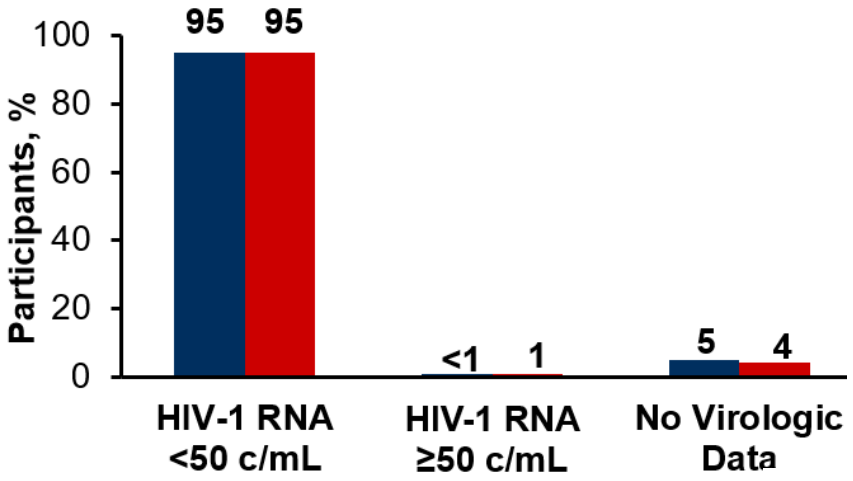
Stable ART x 6 months
INSTI / NNRTI / PI + 2 NRTIs
1st or 2nd ART with no change due to VF

HBV negative



Primary Endpoint[1]

- Non-inferiority established for DTG + RPV vs CAR in virologic suppression (HIV-1 RNA <50 c/mL) at W48 using Snapshot margin of 8% for pooled studies[1]
  - Difference (95%CI): -0.2 (-3.0, 2.5)*
- Non-inferiority was also demonstrated regardless of 3rd agent class[2]



CAR: Continue ART
* Adjusted for age and baseline 3rd agent

1. Llibre JM, et al. CROI 2017; Seattle, WA. Abstract 2421
2. Orkin C, et al. EACS 2017. Milan, Italy. Poster BPD 1/5

Bictegravir/Emtricitabine/Tenofovir Alafenamide

Study 1490: B/F/TAF vs DTG + FTC/TAF in Treatment-Naïve Adults

Virologic Outcome at Week 48 by FDA Snapshot Analysis

On the basis of clinical trial results, the Panel classifies BIC/TAF/FTC as one of the Recommended Initial Regimens for Most Adults with HIV (Mar. 27, 2018)

HIV-1 RNA < 50 copies/mL **HIV-1 RNA ≥ 50 copies/mL** **No HIV-1 RNA Data**

Mean changes in CD4 cell count (cells/μL) at Week 48: +180 BIC vs +201 DTG (p=0.10)

B/F/TAF vs. DTG + FTC/TAF: Non-inferior efficacy at Week 48

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

Treatment Emergent Adverse Events (AEs) Through Week 48

% Subjects	B/F/TAF n=320	DTG + FTC/TAF n=325
All grade AEs (≥ 5% in either arm)		
Headac		
Diarrhe		
Nausea		
Nasoph		
Fatigue		
Influenz		
Lympha		
Arthralg		
Insomn		
Upper r		
Pyrexia		
Back pa		
Drug-related AEs*	18%	26%

B/F/TAF **E/C/F/TAF** **DTG/ABC/3TC** **D/C/F/TAF**

Integrase Strand Transfer Inhibitor

Protease Inhibitor

subjects
vs.
related

elated AEs
exact test)

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

Relative Bioavailability of D/C/F/TAF STR: Whole, Split, or Crushed Tablet

Randomized, open-label, singe dose D/C/F/TAF, cross-over study in 30 HIV negative volunteers assessing (i) whole tablet, (ii) two halves of a pill-cutter split tablet, and (iii) crushed tablet with the powder mixed in apple sauce

Relative bioavailability assessed to determine if exposures meet bioequivalence standard of 90% confidence intervals for mean difference falling within 80%-125%

- **DRV, COBI, and FTC:**
  - Overall, plasma concentrations over 24 hours for each method of administration were similar at all timepoints
- **TAF:**
  - Whole vs. split tablet: bioequivalent (mean ratio 97%; 90%CI 90 to 105)
  - Whole vs. crushed tablet: ~20% reduced AUC (mean ratio 81%; 90%CI 75 to 88)

Authors' Conclusions:

- Split versus whole tablet: No relevant impact on the bioavailability of D/C/F/TAF components
- Crushed tablet: The clinical relevance has not been assessed but is expected to be minimal due to the wide therapeutic window for TAF

AUC: area under the concentration-time curve, CI: confidence interval, D/C/F/TAF: darunavir / cobicistat / emtricitabine / tenofovir alafenamide

Brown K, et al. EACS 2017. Milan, Italy. #PS 8/3.

‡

Switch to DTG+3TC in Patients with Virological Suppression >12 Months

Pilot, monocentric, single arm, study in heavily pre-treated patients

Stable on ARV > 12 months
VL < 50c/mL > 12 months
No resistance associated mutations on INI (GT on RNA or DNA)
Tolerability issues with pre-switch ART

N=27 → **Switch to DTG + 3TC**

week: BL 6 12 24 48 96

Baseline (BL) characteristics	
Median age, years (range)	59 (41-77)
Male, n (%)	20 (74%)
Median CD4 cell count	601
M184V prevalence on RNA, DNA and historical genotype, n (%)	17 (63%)
Median duration ARV, months (range)	215 (22-329)
Median duration on last ARV, months (range)	51 (13 – 108)
Pre-Switch HAART regimens, n (%) TDF containing PI/r containing RAL containing	 13 (48%) 22 (81%) 7 (26%)

* Fatigue n=2, gastrointestinal discomfort n=1, weight increase n=1

At Wk 48 :

- 24/27 (89%) patients maintained VL < 50 c/mL
- 2 DC AEs* at Wk 16 and 24
- 1 re-intensification at Wk 18, due to blip

At Wk 96 :

- No additional DC after Wk 48
- 1 patient experienced blip
- eGFR change was -6mL/min/1.76m² at Wk104
- History of M184V/I was without deleterious impact on efficacy of DTG + 3TC through Wk 102
- All subjects had excellent adherence prior to entry and rigorous follow-up during study

This small pilot study supports the concept of maintenance regimen of DTG + 3TC

Reynes J, et al. IAS 2017, Paris, France. Poster #MOPEB0322. Reynes J, et al. EACS 2015, Barcelona, Spain. Poster #PE8/81

Ibalizumab-uiyk

Trogarzo™

- CD4-directed post-attachment HIV-1 inhibitor (CCR5 & CXCR4)
  - required for the entry of HIV-1 virus particles into host cells
  - recombinant humanized monoclonal antibody
- Loading dose: 2,000mg / Maintenance: 800mg every 2 wks
  - 4 vials: dilution in 250mL of 0.9% Sodium Chloride Injection
  - Infuse over 15-30 minutes
  - Observe 1 hour after administration for the first infusion
  - No RXN: can be reduced to 15 minutes thereafter
- Heavily treatment-experienced adults;
  - multidrug resistant HIV-1 infection / failing current ARVs
- Most common adverse reactions
  - Diarrhea (8%), dizziness (8%), nausea (5%), rash (5%)

Trial TMB 301 Virologic Outcomes (Snapshot Algorithm) at Week 25

	TROGARZO (N=40)
HIV RNA < 50 copies/mL at Week 25	43%
HIV RNA ⩾ 50 copies/mL at Week 25*	45%
HIV RNA < 200 copies/mL at Week 25	50%
HIV RNA ⩾ 200 copies/mL at Week 25**	38%
No virologic data at Week 25	
Discontinued due to AE or death	13%

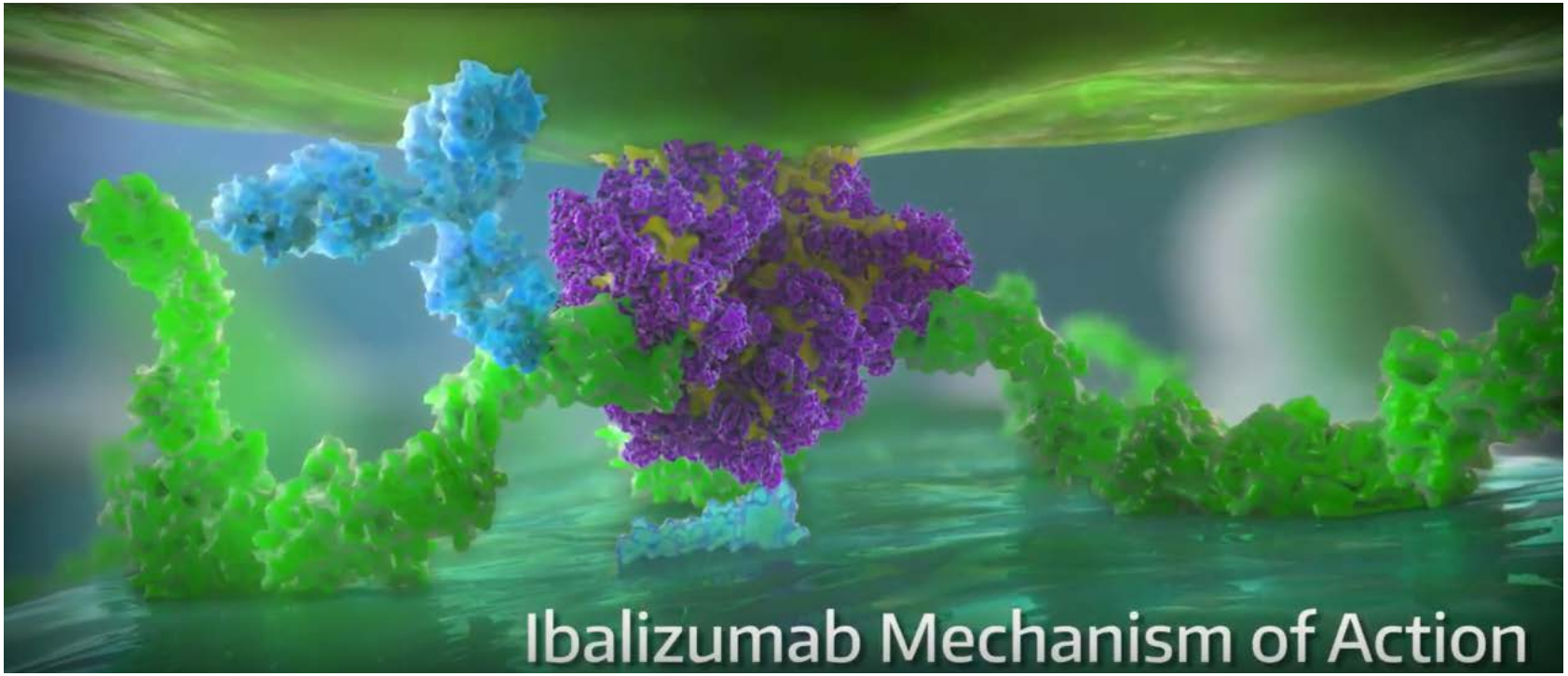
*included subjects who had ≥ 50 copies/mL in the Week 25 window, subjects who discontinued study drug due to lack of efficacy, and subjects who discontinued study drug for reasons other than an AE, death and at the time of discontinuation had a viral value ≥ 50 copies/mL

**included subjects who had ≥ 200 copies/mL in the Week 25 window, subjects who discontinued study drug due to lack of efficacy, and subjects who discontinued study drug for reasons other than an AE, death and at the time of discontinuation had a viral value ≥ 200 copies/mL

wholesale acquisition cost of $118,000/year

THERA technologies

We Protect Lives.



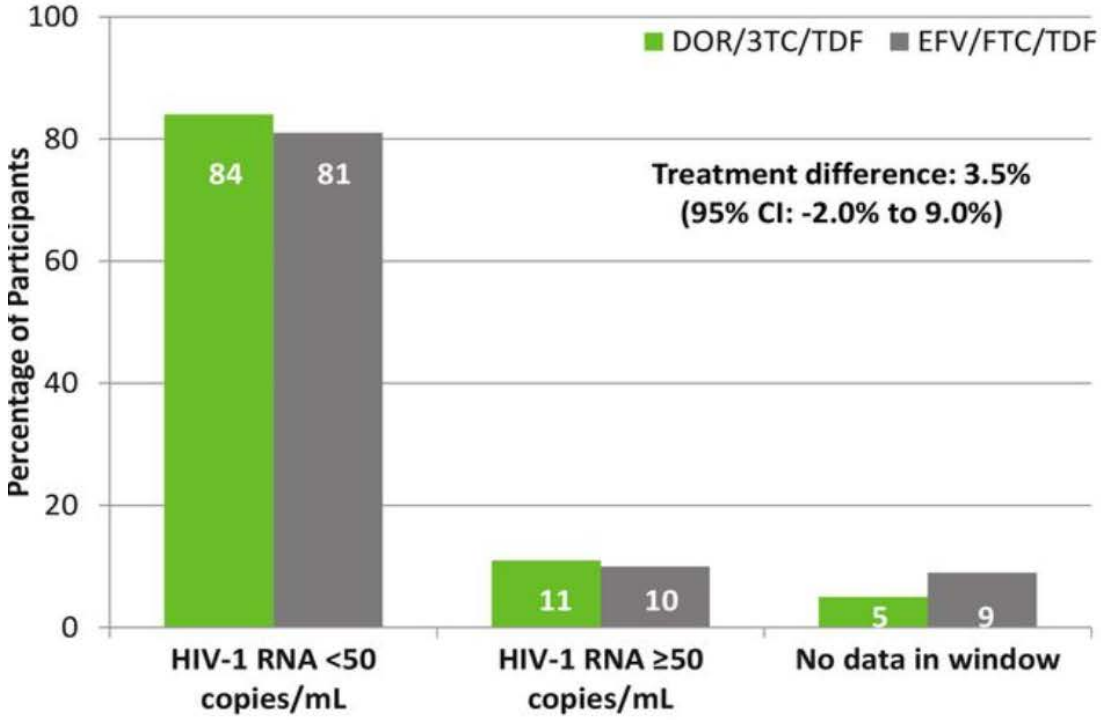
https://www.youtube.com/watch?v=rPf9rqBbrNQ&feature=youtu.be&t=07s

Doravirine

- NNRTI with activity against resistance to common NNRTI mutations (K103N, Y181C, G190A)
- QD dosing without regard to food
- Low potential for drug-drug interactions
- Co-formulated with 3TC/TDF
- DRIVE-FORWARD[1]
  - In Phase 3 clinical trial of ART naïve patients, DOR non-inferior to DRV/r in combination w/ 2 NRTI-backbone in terms of virologic suppression at 48 weeks
  - Superior lipid profile with DOR
  - Efficacy similar regardless of baseline HIV RNA level

Molina, CROI 2017, Abstract 45LB

DRIVE-AHEAD: Key Findings



Outcome at Wk 48, n (%)	DOR/3TC/TDF (n = 364)	EFV/FTC/TDF (n = 364)
PDVF	22 (6.0)	14 (3.8)
Genotyped	23	24
Primary NNRTI* resistance	6 (1.6)	12 (3.3)
Primary NRTI*	5 (1.4)	5 (1.4)

*See slide notes for specific mutations.

- DOR/3TC/TDF non-inferior to EFV/FTC/TDF at week 48
- Similar efficacy of DOR vs. EFV in baseline HIV VL >100K

Squires, IAS 2017, Abstract TUAB0104LB

Slide credit: clinicaloptions.com

DHHS 2017 Guidelines

Recommendations for Use of Antiretroviral Drugs during Pregnancy

	NRTIs	NNRTIs	PIs	Entry Inhibitors	Integrase Inhibitors
Preferred	ABC*/ 3TC TDF/ (3TC or FTC)		ATV/r DRV/r (twice daily)		RAL (twice daily)
Alternate	ZDV/ 3TC	RPV EFV***	LPV/r (twice daily)		DTG
Insufficient Data	TAF/FTC	Odefsey™			
Not Recommended	ABC*/3TC/ZDV ddI + d4T# ddC	NVP** ETR	FPV SQV/r IDV/r TPV/r NFV RTV (as single PI)	T20 MVC	Stribild™ Genvoya™ Cobicistat June 4: Prezcobix

** Use ABC only for HLA-B*5701 negative patients*

*** Use with caution: use only if CD4 count < 250*

**** anencephaly, microphthalmia, cleft palate*

 # Implicated in death of a client: severe lactic acidosis with hepatic steatosis with or without pancreatitis

March 18, 2018
FDA Drug Safety Alert

Botswana identified neural tube defects in 4 infants born to 426 women who initiated a DTG-based regimen prior to pregnancy, & who were still receiving it at the time of conception

In response to the FDA alert, interim guidance has been issued by the HHS Antiretroviral Guidelines Panels regading dolutegravir (DTG).[2] The Office of AIDS Research Advisory Council will be reviewing for proposed guideline changes. The interim recommendations of the Panels are as follows[3]:

- Health care providers are encouraged to counsel women of childbearing age with HIV currently receiving DTG about this newly identified potential risk.
- Pregnant women with HIV who are currently taking DTG should not stop their ARV therapy and should speak with their health care provider for additional guidance.
- Women of childbearing age with HIV who desire to become pregnant should discuss alternative ARV regimen options with their health care provider.
- Women of childbearing age with HIV who are not planning to become pregnant may be on DTG-based regimens provided their pregnancy test before initiation of therapy is negative, and they consistently use a reliable contraceptive method.
- Health care providers are encouraged to report all pregnancy data to the Antiretroviral Pregnancy Registry (1-800-258-4263; http://www.apregistry.com).

https://www.cdc.gov/ncbddd/birthdefects/data.html
http://www.who.int/bulletin/volumes/94/1/14-151365/en/

Preliminary Data Suggest Increased Risk of Neural Tube Defects (NTDs) With Dolutegravir (DTG) Exposure at Conception

Tsepamo: birth outcomes surveillance study / Summary of Key Conclusions

- Unplanned analysis of ongoing birth outcomes surveillance study among Botswanan women with and without HIV infection detected preliminary increase in prevalence of NTDs among infants exposed to DTG **at conception**
- NTD prevalence: DTG exposure **at conception**: 4/426 (**0.94%**; 95% CI: 0.37% - 2.4%)
  - 1 case each- encephalocele, anencephaly, myelomeningocele, iniencephaly
- NTD prevalence: other subgroups
  - non-DTG ART at conception (0.12%), efavirenz at conception (0.05%),
  - DTG started during pregnancy (0.00%), and HIV-negative women (0.09%)
- At latest analysis, July 2018:
  - NTD prevalence: DTG exposure **at conception**: 4/596 (**0.67%**; 95% CI: 0.26% - 1.7%)
  - NTD prevalence: DTG started **in pregnancy**: 1/3104 (**0.03%**; 95% CI: 0.01% - 0.18%)

Investigators suggest that this preliminary, early signal needs further data and analysis

Source: 22nd International AIDS Conference
Released: July 27, 2018

Go to **www.menti.com** and use the code **13 35 33**

1

Grab your phone

2

Go to www.menti.com

3

Enter the code 13 35 33 and vote!

Number 1

- 45 yo TGF transferring care; diagnosed with HIV 7 years ago
  - Client unaware of what ARVs she has "been on" in the past
  - Reports taking one pill a day
- Genotype demonstrates: L10I, K103N
- HIV-VL: 120,000
- CD4: 184 / 14%
- CBC/CMP: WNL

What should we do at this time?

A. Start Azithromycin, Bactrim DS & Atripla™
B. Start Bactrim DS & Complera™
C. Start Triumeq™
D. Start Bactrim DS & Genvoya™
E. Start Bactrim DS & hold ARVs for now
F. Watch & Wait

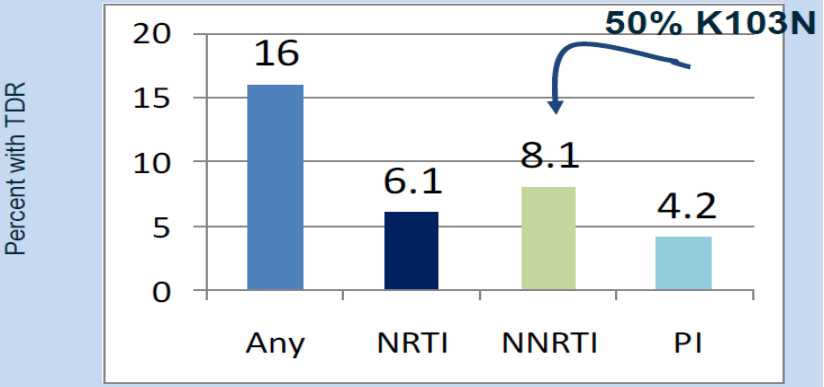
Mutations: L10I, K103N

HIV-VL: 120,000

CD4: 184 / 14%

US Transmitted Drug Resistance: Newly Diagnosed

- 2007 CDC surveillance for TDR detected 16% of pts with new HIV diagnosis & mutations
  - Most common: NNRTI
  - 83% had single mutation



Primary Resistance in Young Pts: 55 recently infected pts (16-24 yo) from 15 US cities; approx. 50% AA; 25% Hisp.

Resistance	By Genotype	By Phenotype
Overall	18%	22%
NNRTI	15%	18%
PI	3.6%	5.5%
NRTI	4%	4%

Kim D, et al. 17th CROI; San Fran; February 16-19, 2010. Abst. 580; Viani R, et al. 13th CROI, Denver 2006; #21.

Acknowledgment: Elizabeth Race, MD MPH

Genotype: genetic code of the sample virus is compared to the wild type
Phenotype: sample of HIV is grown with each ARV

http://hivdb.stanford.edu/
http://www.iasusa.org/resistance_mutations

Records Arrive

Genotype:

- M184V, P225H

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Potential Low-Level Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

NRTI	ABC	AZT	D4T	DDI	FTC	3TC	TDF
M184V	15	-10	-10	10	60	60	-10
Total	15	-10	-10	10	60	60	-10

NNRTI	EFV	ETR	NVP	RPV
K103N	60	0	60	0
P225H	45	0	45	0
Total	105	0	105	0

Mutations: L10I, K103N, M184V, P225H

HIV-VL: 120,000

CD4: 184 / 14%

The next day additional records arrive

84V, 63P, 190Q, 65N

What do we do now?

A. Refer or call someone
B. Bactrim DS & Symtuza™
C. Bactrim DS & Stribild™
D. Bactrim DS & Review Stanford HIV Database
E. Watch & Wait

Mutations: L10I, K103N, M184V, P225H, 84V, 63P, 190Q, 65N

HIV-VL: 120,000

CD4: 184 / 14%

Dosage Considerations

- There is evidence for low-level **DRV** resistance. If **DRV** is administered it should be used twice daily.

nelfinavir (NFV)	High-Level Resistance		
saquinavir/r (SQV/r)	High-Level Resistance	**efavirenz (EFV)**	High-Level Resistance
tipranavir/r (TPV/r)	Intermediate Resistance	**etravirine (ETR)**	Intermediate Resistance

NRTI

- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication.

M184V	15	-10	-10	10	60	60	-10
Total	45	-20	20	40	75	75	20

NNRTI	EFV	ETR	NVP	RPV
K103N	60	0	60	0
G190Q	60	45	60	45
P225H	45	0	45	0
Total	165	45	165	45

Mutations: L10I, K103N, M184V, P225H,
84V, 63P, 190Q, 65N

HIV-VL: 120,000

CD4: 184 / 14%

Number 2

- 38 yo AAM entering into care
  - Client unaware of what ARVs he has "been on" in the past
  - Reports taking several types of pills over the years with many SEs
  - Points to: AZT, CBV, TDF, Truvada, Kaletra, DTG, Descovy, Evotaz
- Archive genotype demonstrates:
  - 36I, 62V, 219Q, 138A, 179D, 190A, 318F, 101Q, 143C, 230R
- HIV-VL: 98,000
- CD4: 86 / 4.1%
- eGFR: 61

What should we do at this time?

A. Refer or call someone else
B. Start Azithromycin, Bactrim DS & Biktarvy™
C. Start Bactrim, Descovy™ & Evotaz™
D. Start Bactrim DS & review Stanford HIV DB
E. Start Bactrim & Watch & Wait

Archive genotype demonstrates:
36I, 62V, 219Q, 138A, 179D, 190A, 318F, 101Q, 143C, 230R

HIV-VL: 98,000

CD4: 86 / 4.1%

eGFR: 61

Mutations Review

Integrase Strand Transfer Inhibitors	
bictegravir (BIC)	Low-Level Resistance
dolutegravir (DTG)	Intermediate Resistance
elvitegravir (EVG)	Intermediate Resistance
raltegravir (RAL)	High-Level Resistance

INSTI	BIC	DTG	EVG	RAL
Y143C	5	5	10	60
S230R	10	20	20	20
Y143C + S230R	5	5	5	0
Total	20	30	35	80

Dosage Considerations

- There is evidence for intermediate **DTG** resistance. If **DTG** is used, it should be administered twice daily.

Chart Review: Records Obtained

CCC called: Descovy™ + Prezcobix™

HIV-VL decr. to 26,000

CD4: 132/6%

Review of all available (R) tests (archived):

36I, 62V, 63P/S, 65R, 184I/V, 219Q, 138A, 179D, 190A, 230L, 318F, 101Q, 103R, 143C, 230R, 74M, 151I

Repeat resistance testing without new mutations

What should we do at this time?

A. Refer or call someone else
B. Start Azithromycin, Bactrim DS & Biktarvy™
C. Start Bactrim, Genvoya™ & Prezista™
D. Start Bactrim DS & review Stanford HIV DB
E. Start Bactrim & Watch & Wait

Mutations: 36I, 62V, 63P/S, 65R, 184I/V, 219Q, 138A, 179D, 190A, 230L, 318F, 101Q, 103R, 143C, 230R, 74M, 151I

HIV-VL: 26,000

CD4: 132 / 6%

eGFR: 61

Genotypic Score	https://hivdb.stanford.edu/
0 – 9	Susceptible
10 – 14	Potential Low-Level Resistance
15 – 29	Low-Level Resistance
30 – 59	Intermediate Resistance
≥ 60	High-Level Resistance

Integrase Strand Transfer Inhibitors	
bictegravir (BIC)	Low-Level Resistance
dolutegravir (DTG)	Intermediate Resistance
elvitegravir (EVG)	Intermediate Resistance
raltegravir (RAL)	High-Level Resistance

INSTI	BIC	DTG	EVG	RAL
Y143C	5	5	10	60
S230R	10	20	20	20
Y143C + S230R	5	5	5	0
Total	20	30	35	80

Dosage Considerations

- There is evidence for intermediate **DTG** resistance. If **DTG** is used, it should be administered twice daily.

Descovy + Prezcobix: TDF (60), FTC (95), DRV (0) – monotherapy

Changed ARVs: AZT (-10: close monitoring), Prezcobix (0) + DTG (30: twice day)

Follow-up: HIV-VL: <40 and CD4: 201/12%. eGFR: 70, Hgb: 13.7

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That which is not good for the bee-hive cannot be good for the bees.

Marcus Aurelius