



HIV-1 Prevention and the Potential for Antiretroviral Resistance

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Outline

- Quick refresher on resistance
 - Principles, types, major vs. minor
- What have we learned in the last year and what do we still need to learn?
 - About resistance from oral or topical PrEP?
- Focus on resistance to NNRTIs
 - General features
 - Dapivirine and dapivirine ring (MTN-020)

Resistance Refresher: Principles

- HIV-1 can develop resistance to any ARV
 - If it's any good as an inhibitor of replication
- HIV-1 replication + drug = **resistance**
- No replication (3 drug ART) = **no resistance**
- Remove drug, resistance decays but...
 - Depends on mutation and drug
 - 184V (3TC/FTC) = **fast** vs. 103N (NNRTI) = **slow**

Types of Resistance

- Transmitted Resistance
 - Person is infected with resistant virus
 - Never exposed to ARVs
 - Partner rec'd ART, sdNVP or PrEP
 - Or, partner infected with resistant virus from a another partner: a “secondary” transmission
- Selected Resistance (most common)
 - Infected with wildtype virus
 - Resistance selected by sdNVP, ART, or PrEP

Major vs. Minor Resistance

- Major
 - $\geq 25\%$ of virions in a person are resistant
 - detected by standard population genotype
- Minor
 - $< 25\%$ of virions in a person are resistant
 - missed by standard genotype
 - detected by ASP, SGS, deep sequencing

What Have We Learned in 1 Year?

- No infection on PrEP, **no resistance** 😊
 - CAPRISA, iPrEX, TDF2, Partners PrEP
- No PrEP exposure, **rare** resistance **but infection** 😞
 - iPrEX, TDF2, Partners PrEP, FEM-PrEP

HIV-1 Drug Resistance from PrEP

- **Infrequent** cases of drug resistance among PrEP study participants who seroconverted while receiving active drug

Study	Infections on Study	
	# infected	# resistant to FTC or TDF
iPrEx	131	None
Partners PrEP	82	None
TDF2	33	1 placebo (K65R <1%)*
FEM-PrEP	68	1 placebo (M184V)* 4 FTC/TDF (M184V/I)**

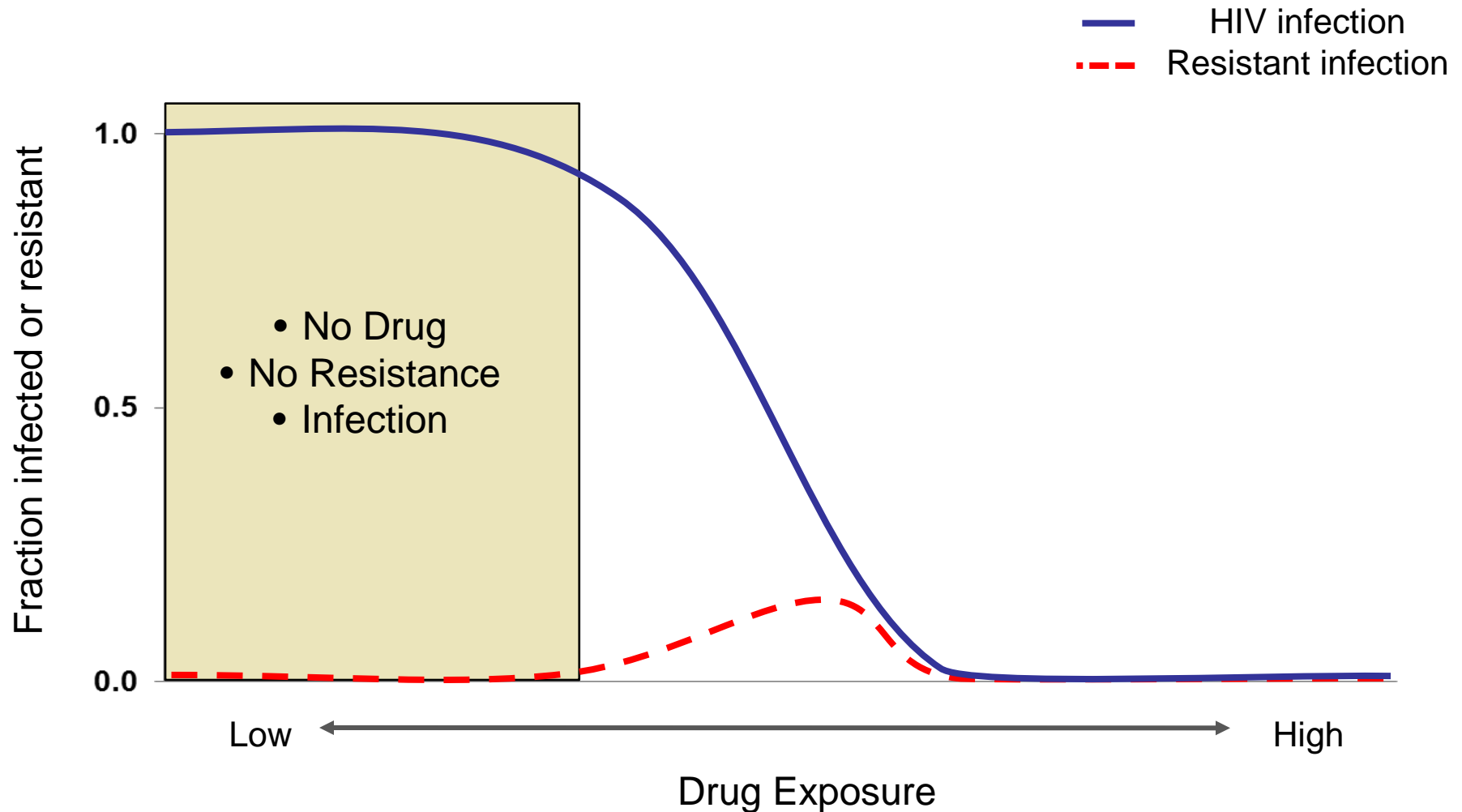
* Transmitted (primary) resistance can occur independent of PrEP, which likely explains resistance in the placebo arm

** 1 probable and 2 possible transmitted resistance; 1 uncertain timing of infection (HIV RNA detectable at first follow-up visit)

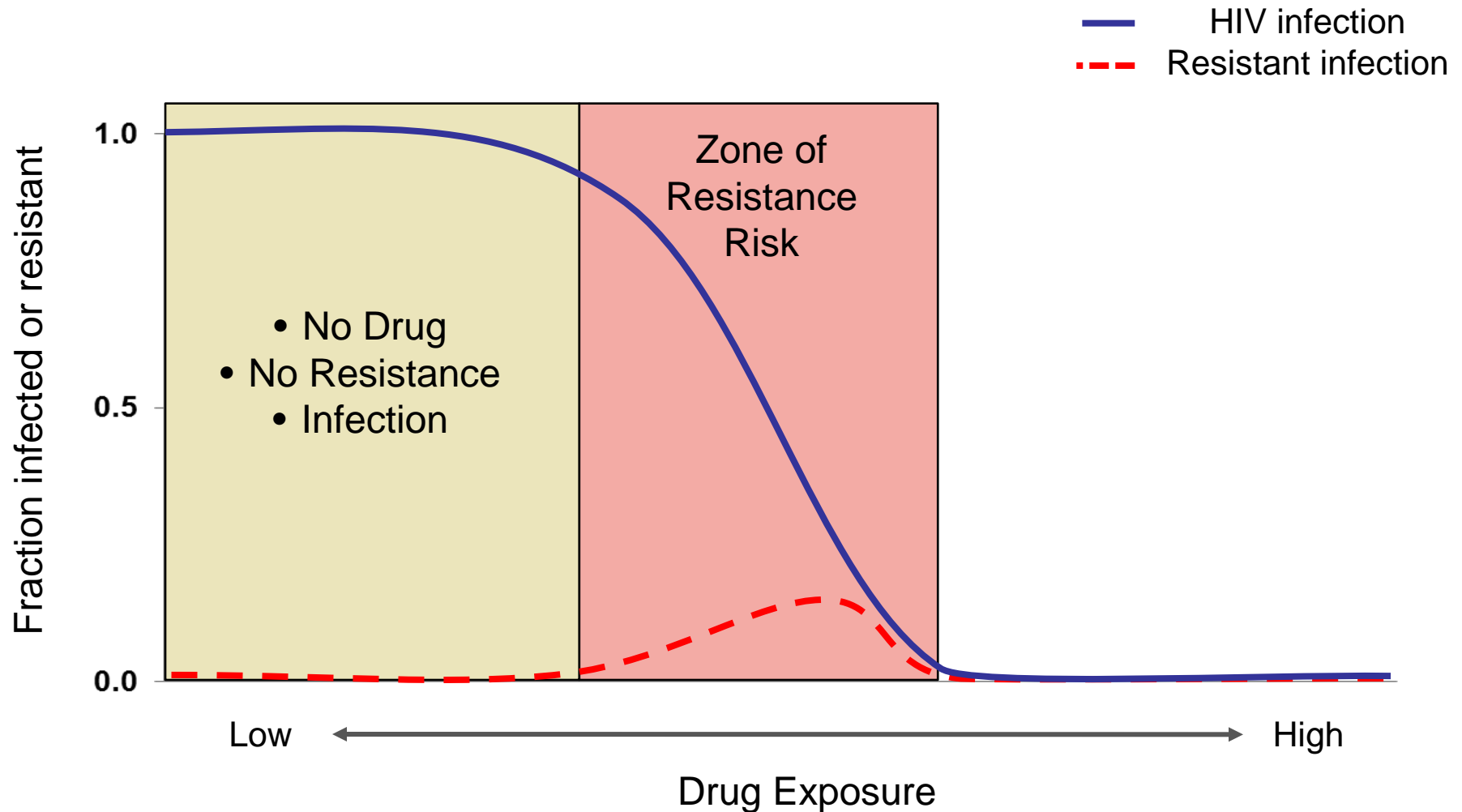
Infrequent Drug Resistance

- **Why?**
 - Risk of infection and drug exposure are **inversely** related
 - No or low drug exposure, no selection by drug, no resistance, but **infection**
 - Good exposure → **no infection & no resistance**
- **Resistance is still possible**
 - At drug exposures that permit infection but also provide selection of resistant variants
 - Appears to be uncommon

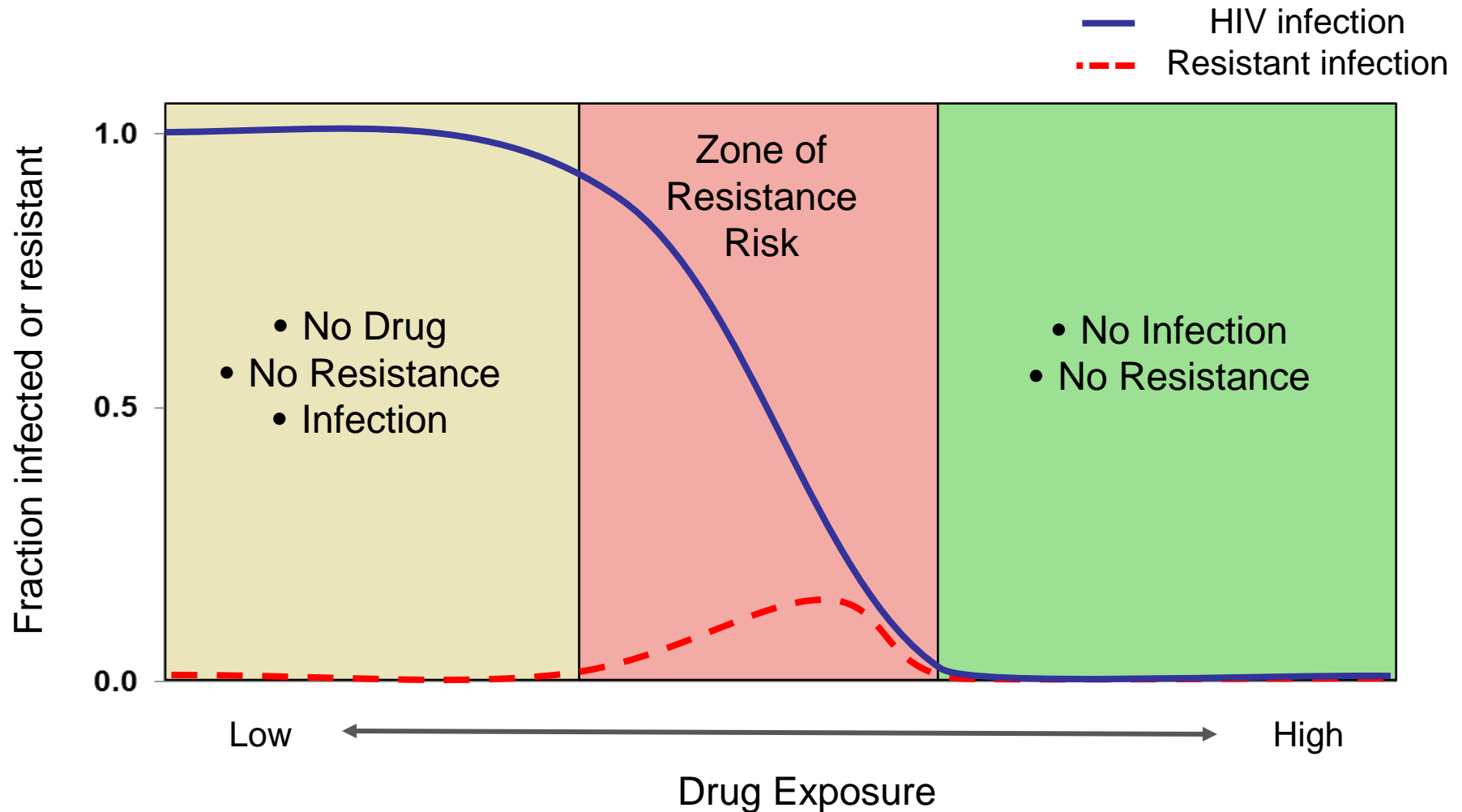
Theoretical Infection-Exposure-Resistance Relationships



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Theoretical Infection-Exposure-Resistance Relationships



What Have We Learned in 1 Year?

- Resistance more likely if PrEP given during unrecognized acute infection
 - iPrEX, TDF2, Partners PrEP, FEM-PrEP

Resistance More Likely if PrEP is Given During Unrecognized Acute Infection*

Study	Baseline infections	
	# infected	# resistant
iPrEx	10	2/2 active (M184V/I) 1/8 placebo (M184V)
Partners PrEP	14	2/8 active (1 K65R, 1 M184V)
TDF2	3	1/1 active (K65R, M184V, A62V)
FEM-PrEP	2	0/1 active

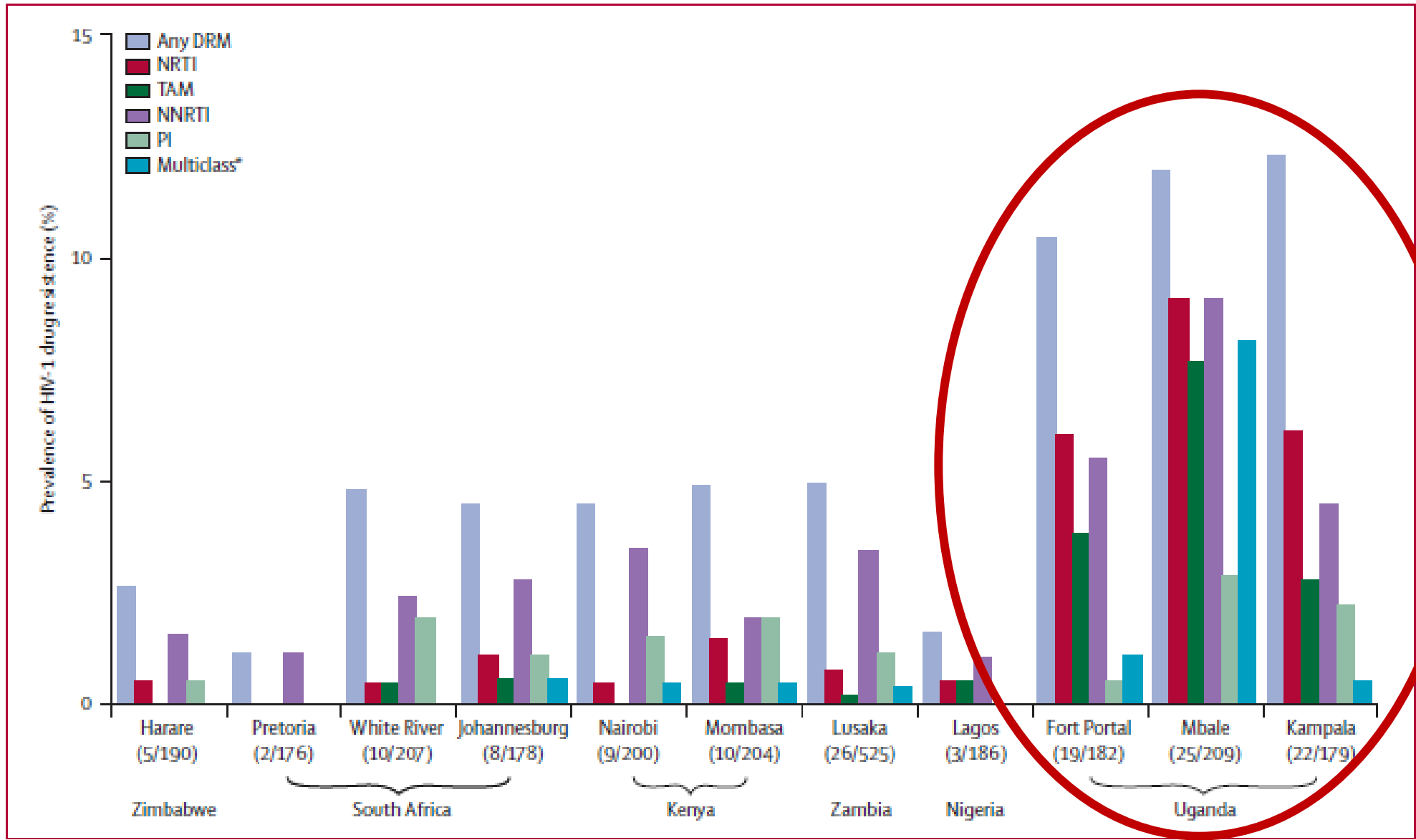
* Infection + incomplete suppression of replication selects resistance
Transmitted (primary) resistance can occur, independent of PrEP, which likely explains resistance in the placebo arm

What Have We Learned (con't)

- Topical PrEP (TNV gel), no systemic resistance
 - CAPRISA 004
 - No major or minor resistance
 - Relevant for MTN-020 (dapivirine ring)

What Have We Learned (con't)

- Resistance from ART is common
 - 15-20% of first-line therapy
 - Evidence of spread: prevalence pretherapy has increased in some countries from <5% to >12%
 - Uganda, Cameroon

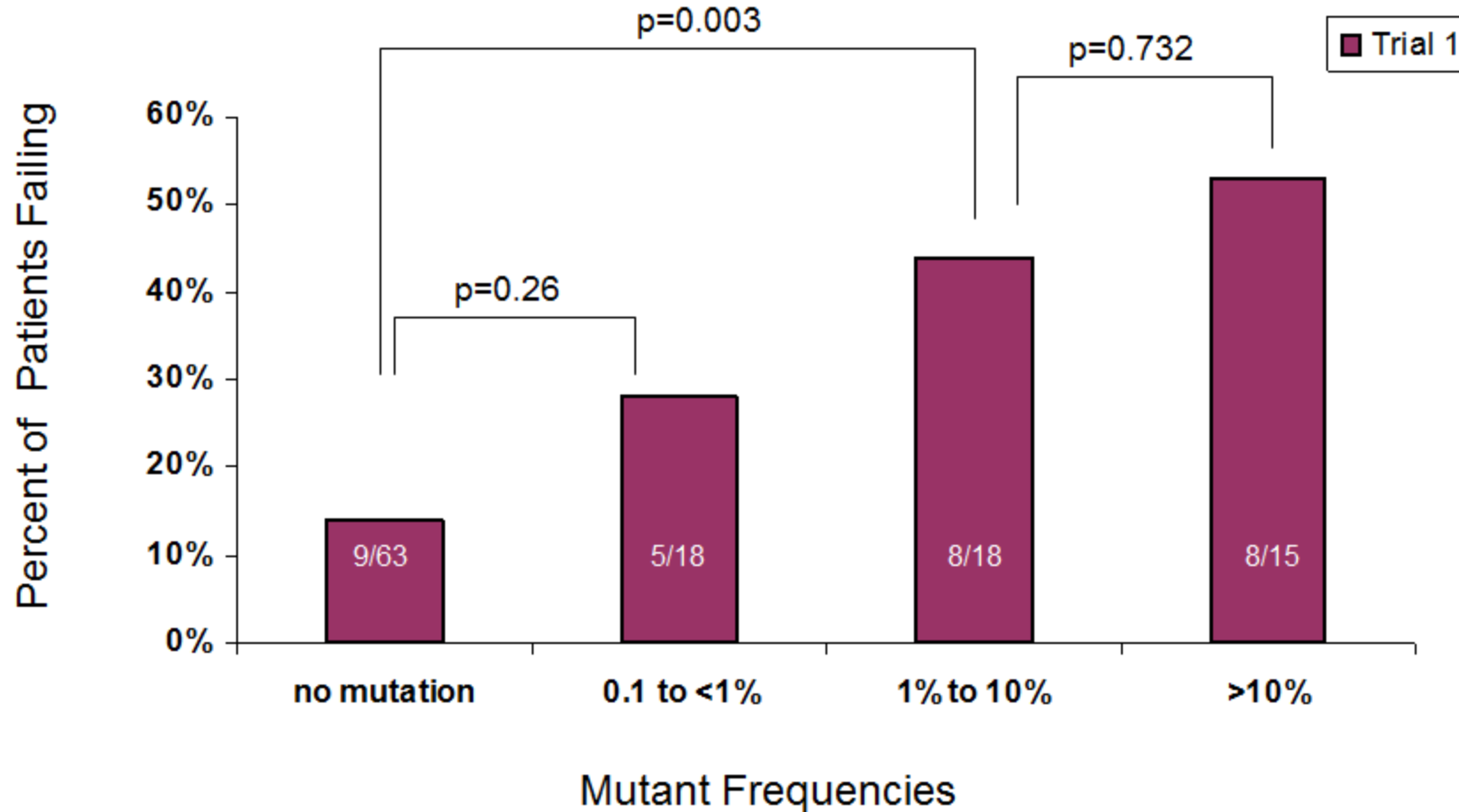


Hamers et al., Lancet Infectious Dis 2011

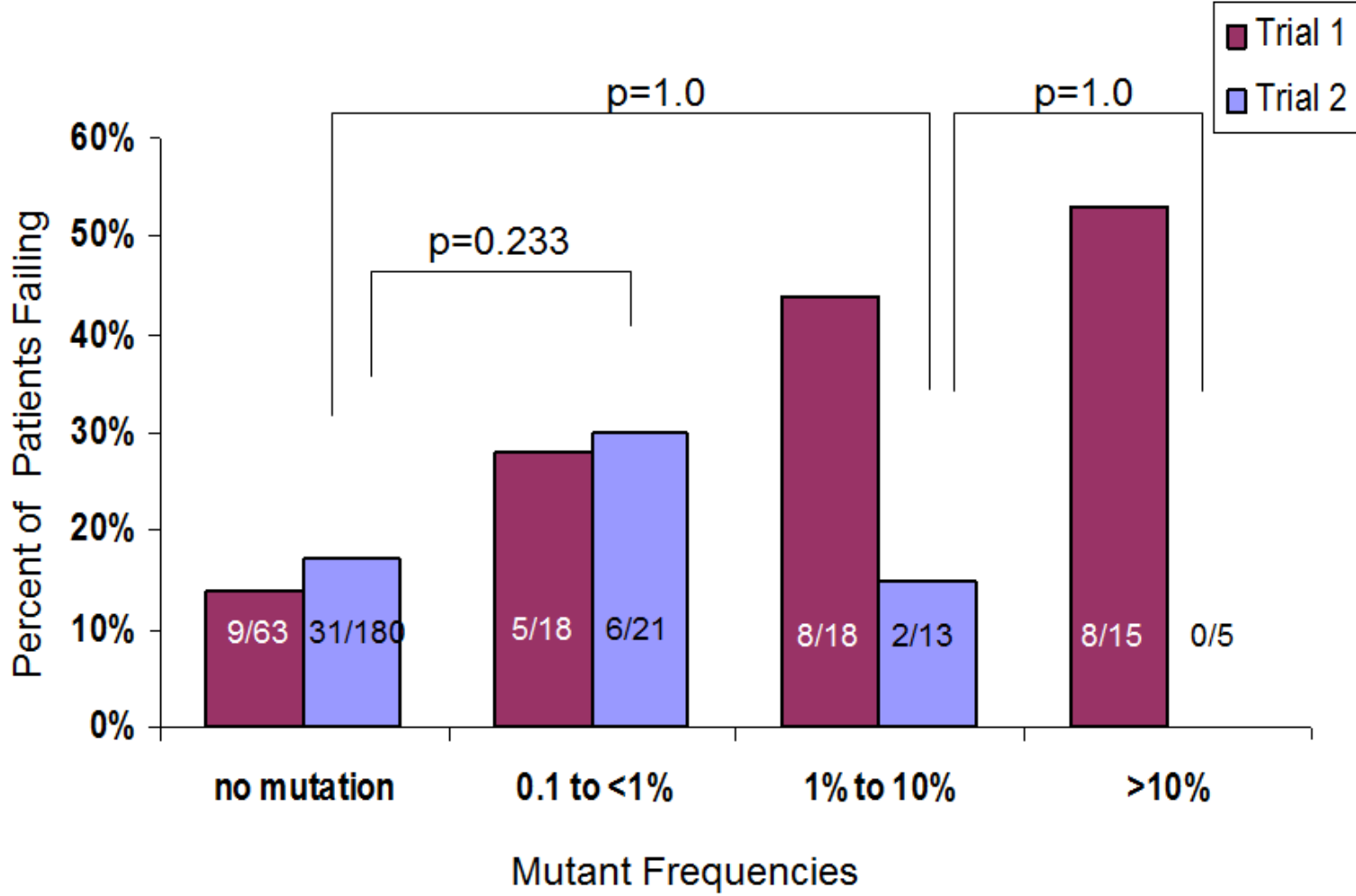
What do we need to Learn?

- What level of PrEP exposure, if any, results in infection + resistance?
- What is the significance of minor resistance
 - Thought we knew but...

A5208 Trial 1 (sdNVP): Risk of Failure vs. Mutation Frequency by Allele-Specific PCR



A5208 Trial 2 (no sdNVP): No Increased Risk of Failure vs. Mutation Frequency by Allele-Specific PCR in the NVP Arm



Not All Minor Resistance is the Same

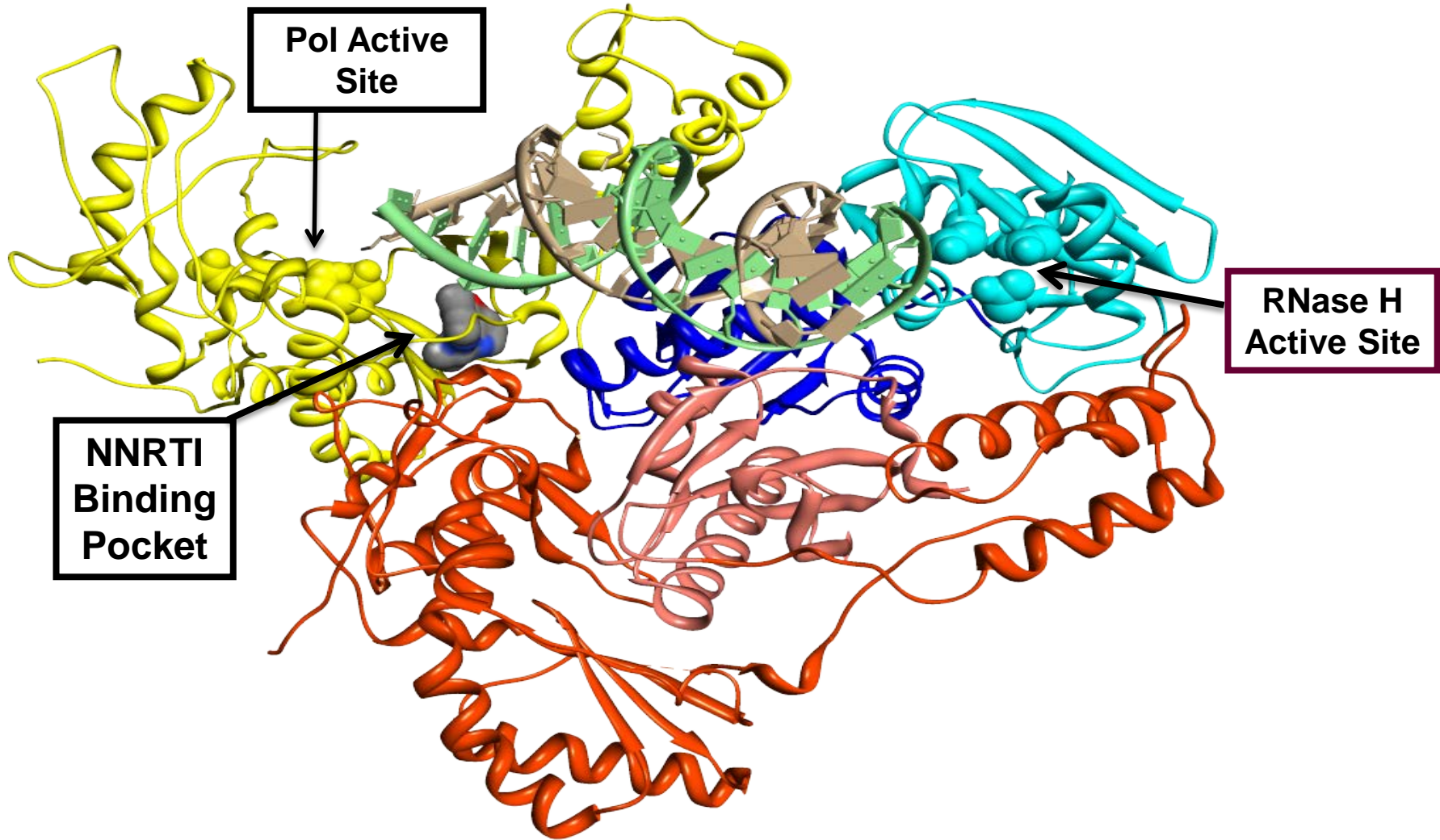
- Minor drug resistance after sdNVP is associated with increased risk of failure of NVP-containing ART
- Spontaneous, pre-existing resistance is not
- So, if we detect minor resistance in a person with uncertain prior drug exposure (e.g. PrEP), we don't know its significance
 - Working on additional ways to distinguish risk

NNRTIs and NNRTI Resistance

General Characteristics of NNRTIs

- Hydrophobic (water fearing) molecules
- Bind to a hydrophobic “grease pit” in HIV-1 RT near the catalytic site called the NNRTI binding pocket
- Inhibit RT function by multiple mechanisms
 - Distort the active site
 - Alter primer binding
 - Freeze RT in the open (non-catalytic) position

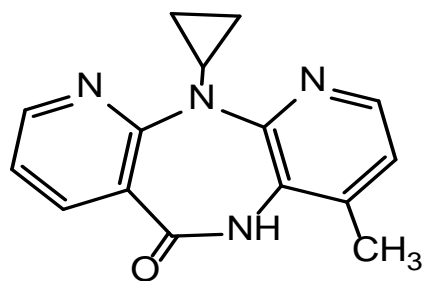
Structure of HIV-1 Reverse Transcriptase



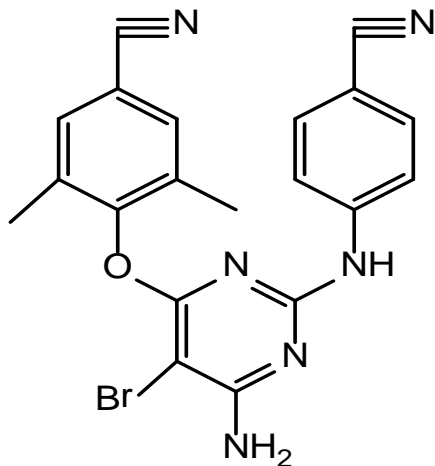
FDA-approved NNRTIs

- First generation
 - Delavirdine, Nevirapine, Efavirenz
- Second generation
 - Etravirine (TMC-125), Rilpivirine (TMC-278)

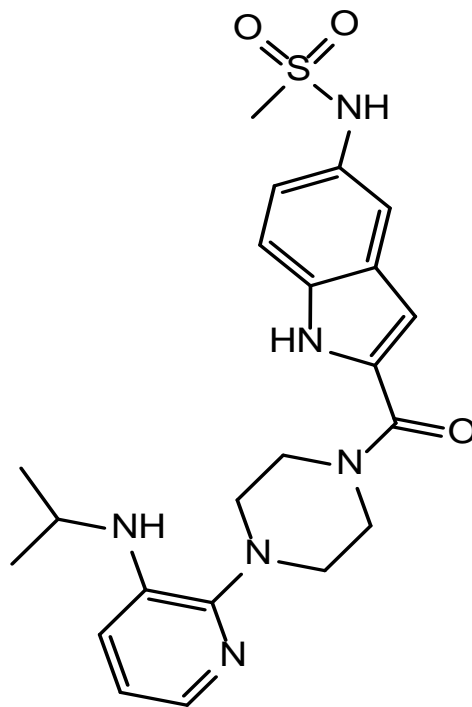
Structures of FDA-approved NNRTI



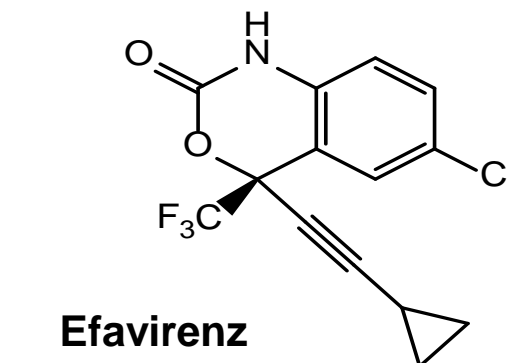
Nevirapine



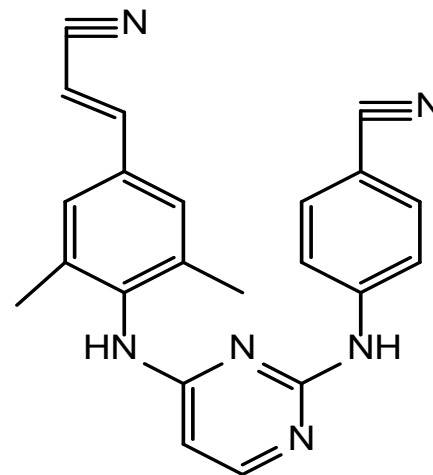
Etravirine



Delavirdine



Efavirenz



Rilpivirine

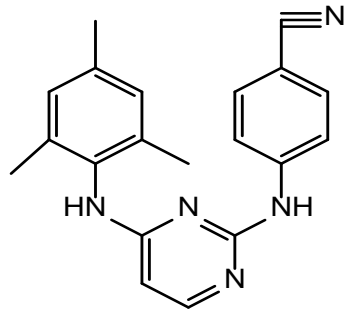
Multiple NNRTI Resistance Mutations

Efavirenz			L	K	K	V	V		Y	Y	G		P		
			100	101	103	106	108		181	188	190		225		
			I	P	N	M	I		C	L	S		H		
					S				I		A				
Etravirine ⁿ	V	A	L	K		V		E	V	Y		G		M	
	90	98	100	101		106		138	179	181		190		230	
	I	G	I*	E		I		A	D	C*		S		L	
				H				G	F	I*		A			
				P*				K	T	V*					
								Q							
Nevirapine			L	K	K	V	V		Y	Y	G				
			100	101	103	106	108		181	188	190				
			I	P	N	A	I		C	C	A				
					S	M			I	L					
										H					
Rilpivirine ^o				K				E	V	Y			H	F	M
				101				138	179	181			221	227	230
				E				A	L	C			Y	C	I
				P				G		I					L
								K*		V					
								Q							
								R							

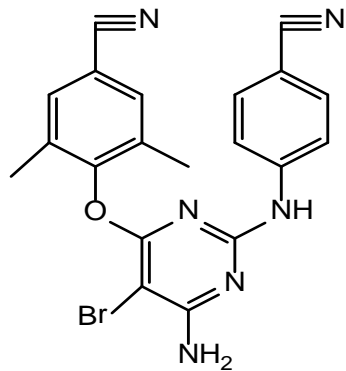
General Features of NNRTI Resistance

- The “grease pit” is not conserved
- Mutations decrease NNRTI binding
 - Direct loss of hydrophobic interaction (Y181C)
 - Closing of entry to the pit (K103N)
 - Steric hindrance (G190E)
- Some mutations have minimal effect on fitness
 - May persist after drug is withdrawn (K103N)
- Cross-resistance is common among NNRTI
 - Extensive for 1st generation
 - Less between 1st & 2nd generation but still problematic

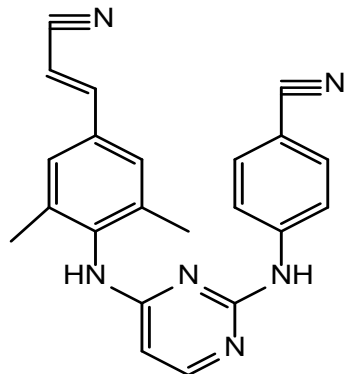
Dapivirine is an analog of ETV and RIL and binds to the same pocket. Figure shows overlay of the 3 drugs



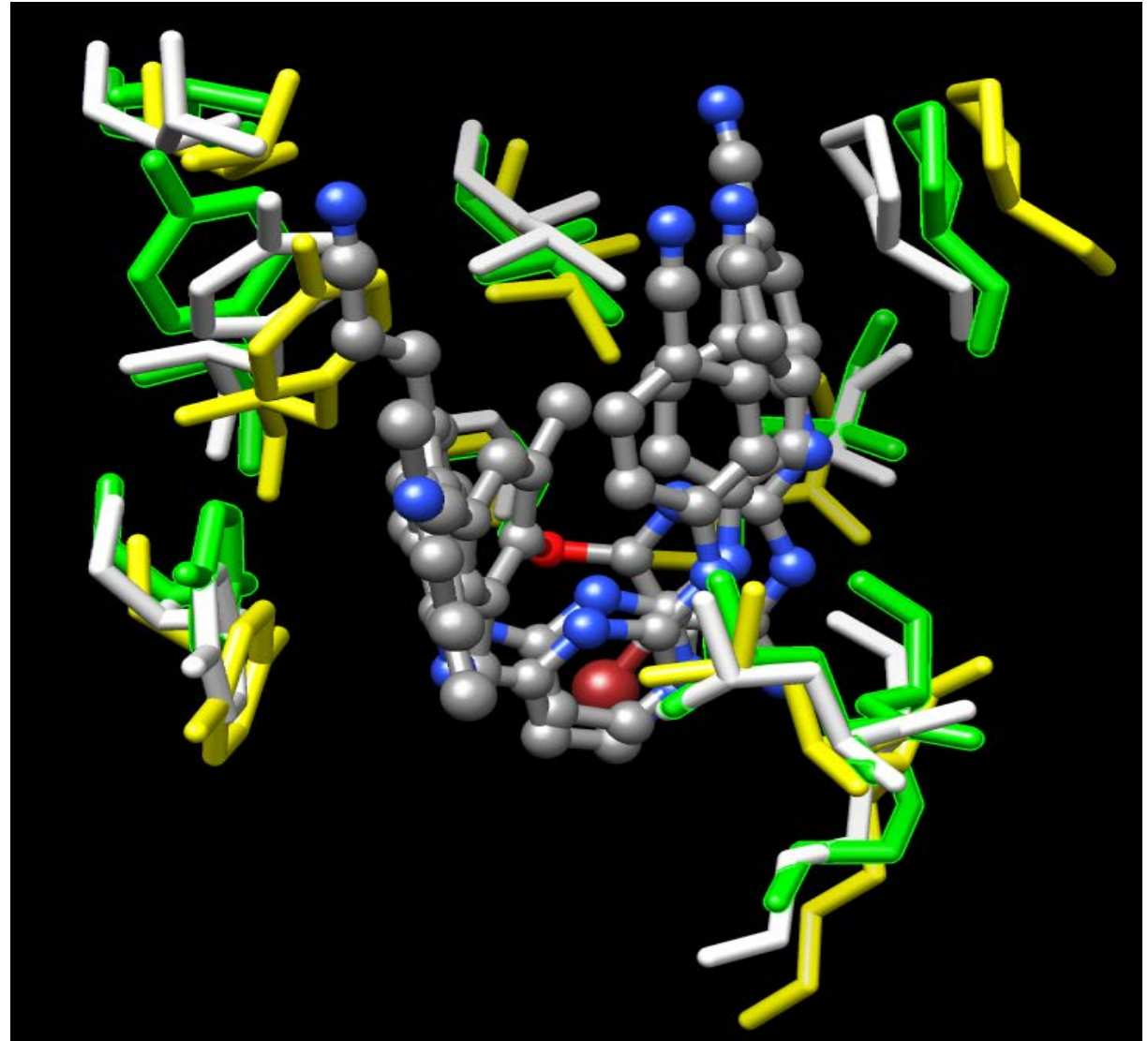
Dapivirine
TMC-120



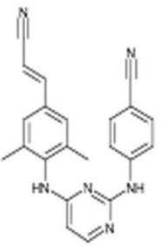
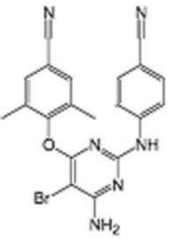
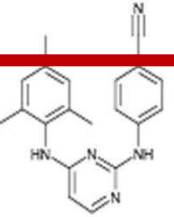
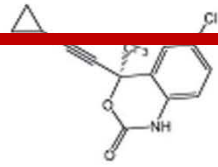
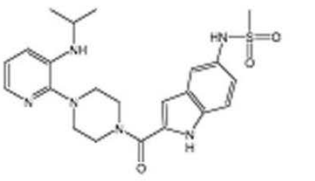
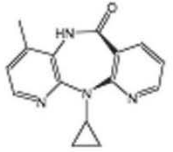
Etravirine
TMC-125



Rilpivirine
TMC-278



Cross Resistance

Compound	Chemical structure	EC ₅₀ in μM					
		Wild-type	K103N	Y181C	K103N/ Y181C	L100I	L100I/ K103N
TMC278		0.0004	0.0003	0.0001	0.0008	0.0005	0.008
TMC125		0.002	0.001	0.006	0.005	0.003	0.01
TMC120		0.001	0.004	0.008	0.044	0.016	>10
Efavirenz		0.001	0.039	0.002	0.04	0.038	> 10
Delavirdine		0.016	> 1	> 1	>10	> 1	N/A
Nevirapine		0.085	> 1	> 1	>100	0.6	N/A

Dapivirine (TMC-120) Ring

- Advantages
 - Very potent inhibitor of HIV-1 ($EC_{50} = 1 \text{ nM}$)
 - Local delivery, so systemic resistance unlikely
 - Very high local concentrations may inhibit resistance development as well as NNRTI-resistant HIV-1 that comes from an infected partner

Dapivirine (TMC-120) Ring

- Potential limitations

- Not active against high-level NNRTI resistant variants from a source partner
 - Uncommon now but could increase
- Selection of resistance in the GT of INFECTED women
 - Theoretically transmissible
- Resistance likely to be minor so more difficult to detect
 - MTN Virology Core will be prepared!

Take Home Messages

- Don't give PrEP (Dapivirine Ring) to HIV+'s
 - Screen carefully for acute infection
- Look hard for minor drug resistance among seroconverters in MTN-020/ASPIRE
 - Comparisons with placebo arm are key
- Monitor prevalence of NNRTI resistance in ART- naïve and -experienced persons in RLS
 - Transmission of NNRTI-resistant virus is likely to increase
 - Potential for dapivirine ring breakthrough exists



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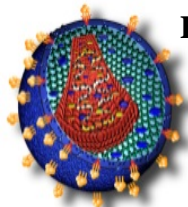
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**The women in Africa who participated in A5208
and the 10 study sites**



HIV Drug Resistance Program

National Cancer Institute at Frederick



Any Questions?