NEW NRTIs and NNRTIs

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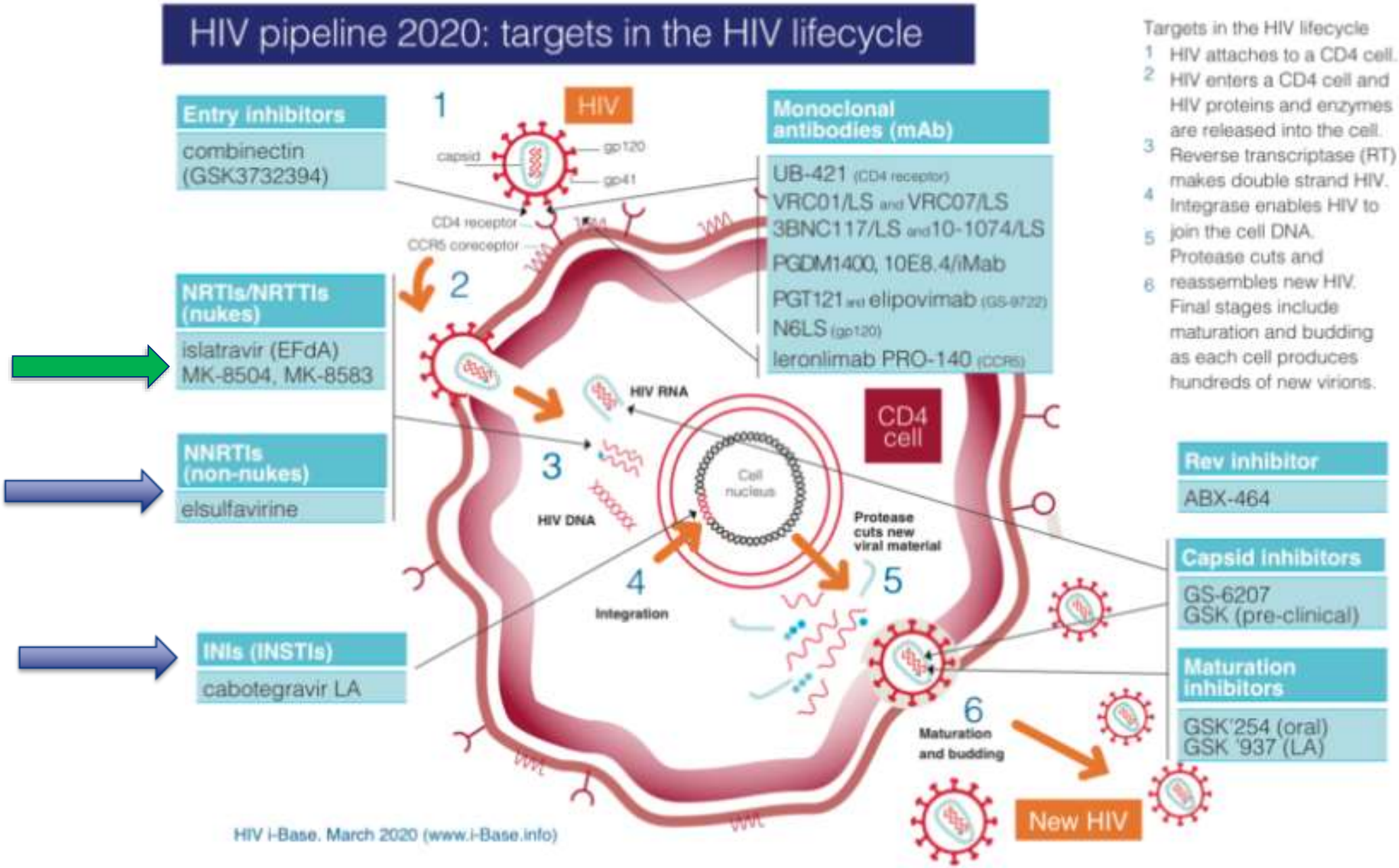
HIV pipeline 2020: targets in the HIV lifecycle



Targets in the HIV lifecycle

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
3. Reverse transcriptase (RT) makes double strand HIV.
4. Integrase enables HIV to join the cell DNA.
5. Protease cuts and reassembles new HIV.
6. Final stages include maturation and budding as each cell produces hundreds of new virions.

HIV i-Base. March 2020 (www.i-Base.info)

Doravirine Clinical Pharmacokinetics 1

- Absorption:
  - Median Tmax, oral: ~2 hours
  - **Food effect: no meaningful effect** on C_{max} or AUC
  - Exposures (AUC, C_{max}) increase less than dose proportionally

- Metabolism:
  - **Oxidative metabolism via CYP3A**

- Elimination:
  - Plasma peak concentrations decline in a monoexponential manner**; with a terminal half-life of ~15 h**
  - Minimal renal elimination <10% of dose

Doravirine Clinical Pharmacokinetics 2

- Intrinsic Factors:
  - **Age (adults, elderly), gender,** and HIV infection have no clinically meaningful effect on MK-1439 PK based on Phase 1 trials and preliminary Phase 2 popPK analysis

- Factors:
  - **Potential victim of CYP3A4 inhibitors and inducers**
  - **Not an inhibitor of CYP enzymes or UGT1A1** (IC_{50} > 100 µM); unbound C_{max} at 100 mg is ~0.7 µM, far below IC_{50}
    - Not an inducer of CYP1A2, 2B6. Very weak inducer of CYP3A4 in vitro (at 10 µM; 3 - 23% increases in mRNA relative to rifampin. No increase in enzyme activity)
  - **No clinically relevant interactions anticipated with hepatic or renal transporters**(OATP1B1/1B3, OAT1/3, OCT2)
    - **Not affected by P-gp** modulators and unlikely to be affected by BCRP modulators

Comparison of PK & Dosing Considerations

	DOR	Rilpivirine (RPV)	Etravirine (ETR)	Efavirenz (EFV)
Mainly metabolized by	CYP3A4	CYP3A4	CYP3A4, CYP2C9, CYP2C19	CYP2B6 (primary), CYP2A6, CYP3A4
Interactions with: NRTIs	No meaningful effect	none	None	None
Darunavir/ritonavir	Not expected based on ritonavir DDI study	None	None	None
Integrases	No meaningful effect	**Contraindicated:** EVG/c	**Contraindicated:** EVG/c Do not coadminister ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r	**Contraindicated:** EVG/c, EVG (when used with PI/r)
Antacids	No meaningful effect	Administer 2 hrs prior/2hrs after RPV	None	None
Antimycobacterials	Large decrease in DOR by multiple doses of both rifampin and rifabutin. Not to be coadministered with rifampin. Requires dose adjustment to 100 mg BID if coadministered with rifabutin	Contraindicated: Rifampin, Rifapentine Additional dose of RPV during rifabutin	Contraindicated: Rifampin, Rifapentine	None
Azole Antifungals	3 fold increase by Ketoconazole, likely no clinical meaningful effect	None	Use with caution	Avoid itraconazole; voriconazole dose adjustment necessary.
PPIs	No meaningful effect	Contraindicated	None	None
Statins	Atorvastatin: no meaningful effect	None	None	None
HCV DAA	Grazoprevir/elbasvir: no meaningful effect Ledipasgvir/sofosbuvir: no meaningful effect	**Contraindicated:** Paritaprevir/ Ritonavir plus Dasabuvir, **Concomitant use:** Daclatasvir, sofosbuvir, Elbasvir/Grazoprevir, Ledipasvir/Sofosbuvir (if used with TDF, monitor for TDF toxicity), Simeprevir	**Contraindicated:** Elbasvir/ Grazoprevir, Paritaprevir/ Ritonavir plus Dasabuvir, Simeprevir **Concomitant use:** Daclatasvir, sofosbuvir, Ledipasvir/ Sofosbuvir (if used with TDF, monitor for TDF toxicity)	**Contraindicated:** Elbasvir/ Grazoprevir, Paritaprevir/ Ritonavir plus Dasabuvir, Simeprevir **Concomitant use:** Daclatasvir, sofosbuvir, Ledipasvir/ Sofosbuvir (if used with TDF, monitor for TDF toxicity)
Narcotic analgesics	Not studied	None	None	None

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed June 24, 2017.

Doravirine Has a Distinct Mutation Development Pathway

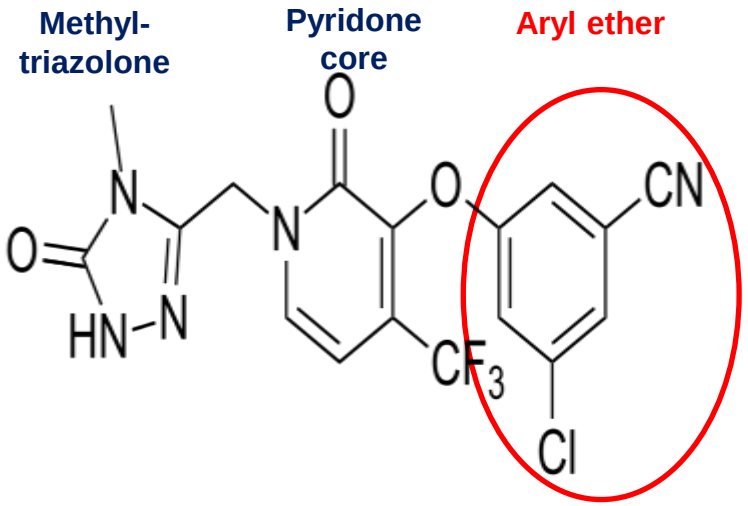
NNRTI		Mutation Pathway		
DOR	1	V106A	·····	V106A/F227L
	2	V106A	→ V106A/L234I →	V106A/L234I/F227L or V108I
EFV	1	L100I	·····	L100I/K103N
	2	L100I	→ L100I/V179D →	L100I/V179D/P225H or M230L
	3	K103N	·····	L100I/K103N
RPV	1	E138K	→ E138K/L100I →	E138K/L100I/V179I
	2	E138K	·····	E138K/V106A
	3	K101P	·····	K101P/V179I

*Experiments were performed under low multiplicity conditions in MT4GFP cells. The fitness of V106A mutant is only 25% of WT virus

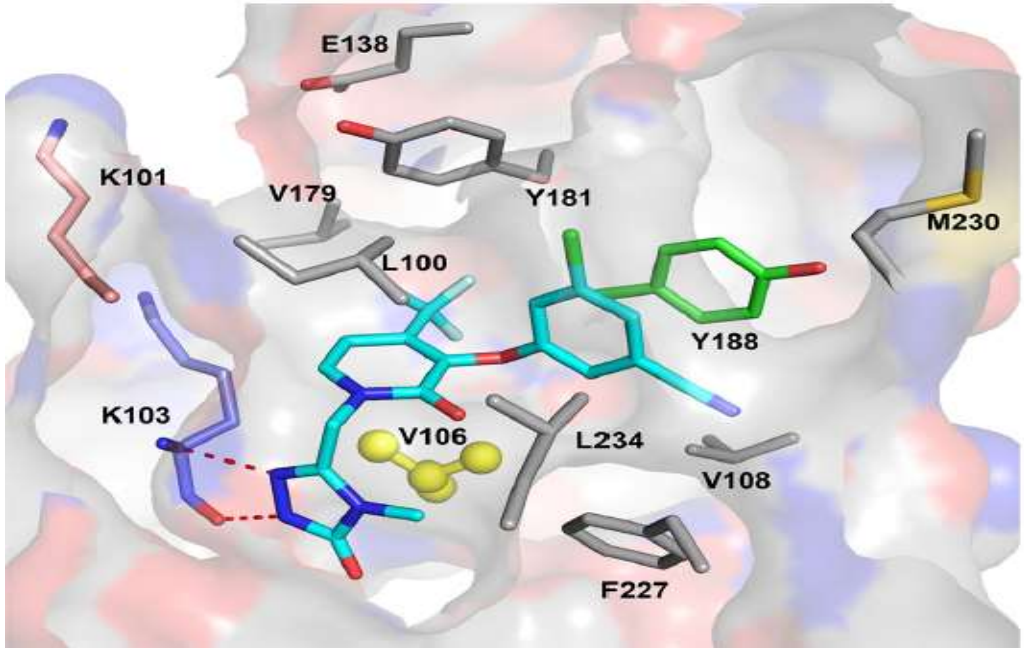
- DOR displays distinct mutation development pathways compared to EFV and RPV during in vitro resistance selection

Feng M., Wang D., Grobler JA., Hazuda DJ. et al. In vitro resistance selection with doravirine (MK-1439), a novel nonnucleoside reverse transcriptase inhibitor with distinct mutation development pathways. *Antimicrob. Agents Chemother.* 59(1):590-598. 2015

Impact of mutations in codons Y181 and Y188

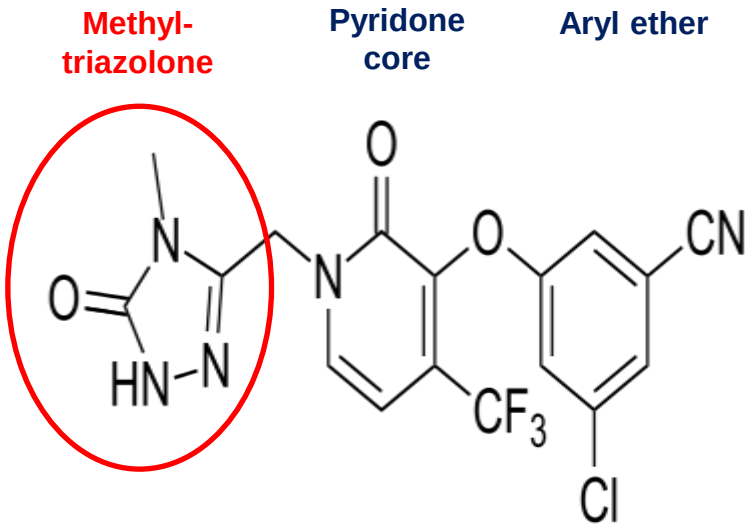


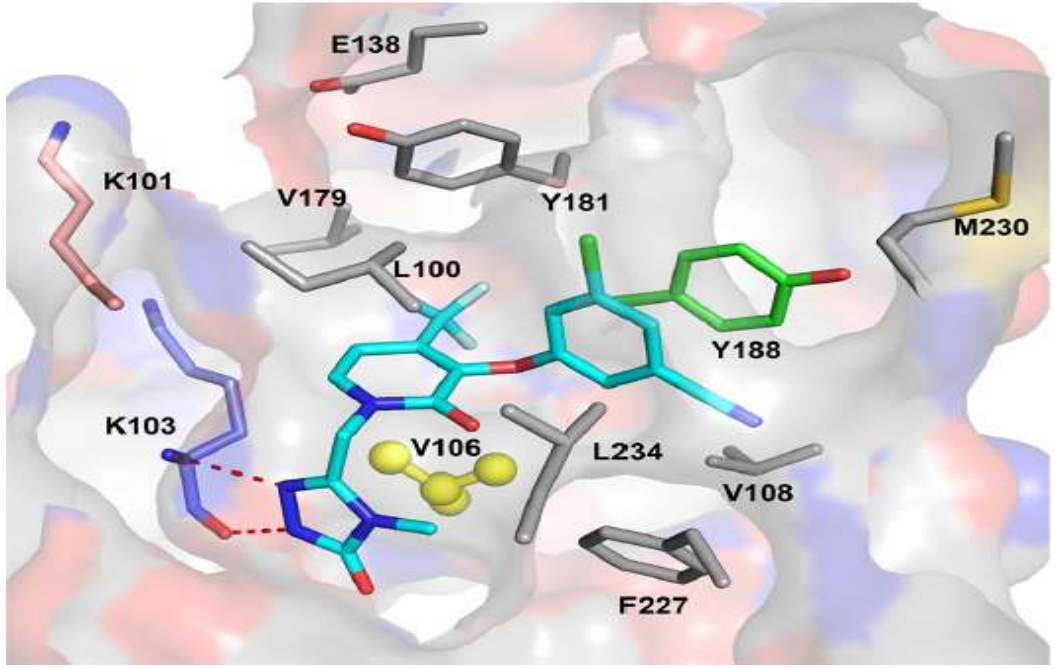
- Y181 does not play an important role in the binding of DOR to RT, given the long distance between the cyanochlorophenol group of DOR and Y181
- The cyanochlorophenol moiety forms π-π stacking with Y188, and the Y188L substitution eliminates the π–π interactions and creates a clash with DOR



Feng M, Wang D, Grobler JA, Hazuda DJ., et al. In vitro resistance selection with doravirine (MK-1439), a novel nonnucleoside reverse transcriptase inhibitor with distinct mutation development pathways. Antimicrob Agents Chemother. Jan;59(1):590-8. 2015

Impact of mutations in codon K103

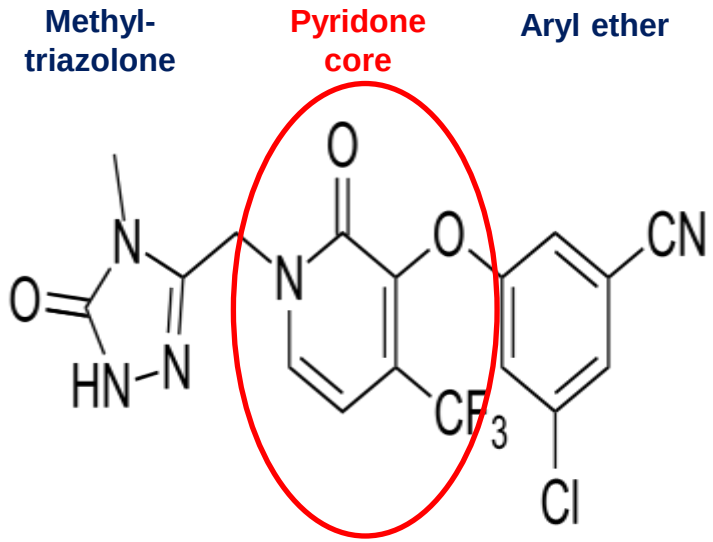




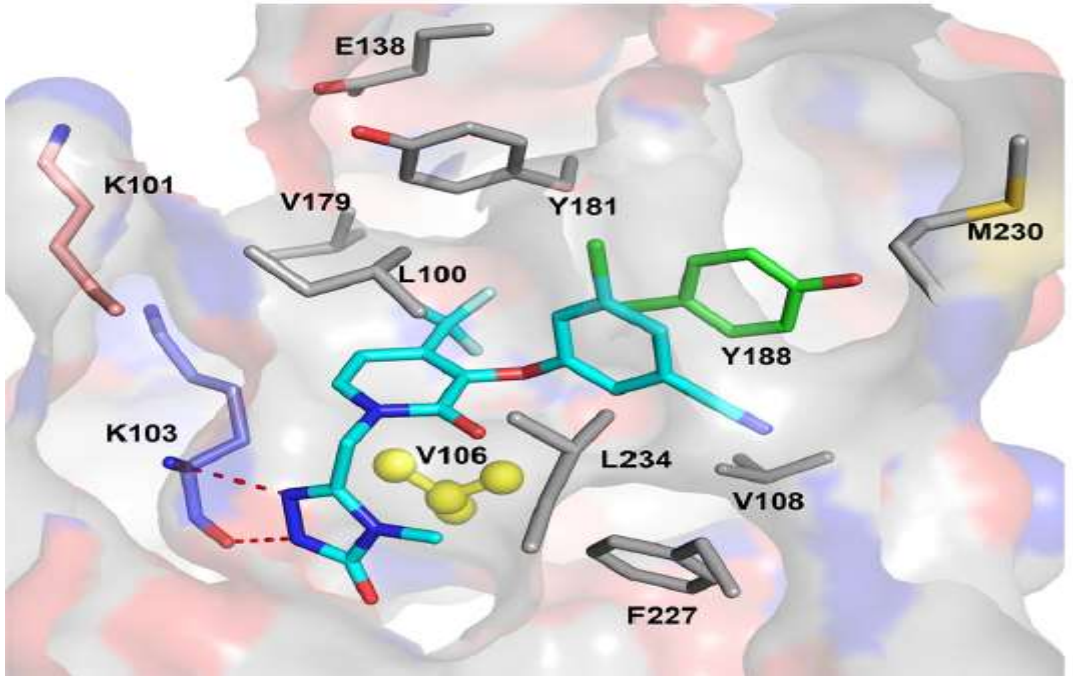
- The nitrogen atoms in the methyl-triazolone ring interact with the backbone, but not with the side chain, of K103 via two hydrogen bonds
- As a result, the impact of the K103N substitution on the interactions between the residue and DOR is minimal, as the interactions between N103 and the DOR triazole ring remain intact

Feng M, Wang D, Grobler JA, Hazuda DJ., et al. In vitro resistance selection with doravirine (MK-1439), a novel nonnucleoside reverse transcriptase inhibitor with distinct mutation development pathways. Antimicrob Agents Chemother. Jan;59(1):590-8. 2015

Impact of mutations in codon V106



- The side chain of V106 is close to the central ring of DOR, with a distance of 3.5 Å based on the X-ray structure. It appears that the isopropyl group on the Val side chain makes van der Waals interactions with DOR in the NNRTI binding pocket. Replacement of the isopropyl group with a methyl group (V106A) **weakens the interactions between RT and DOR**



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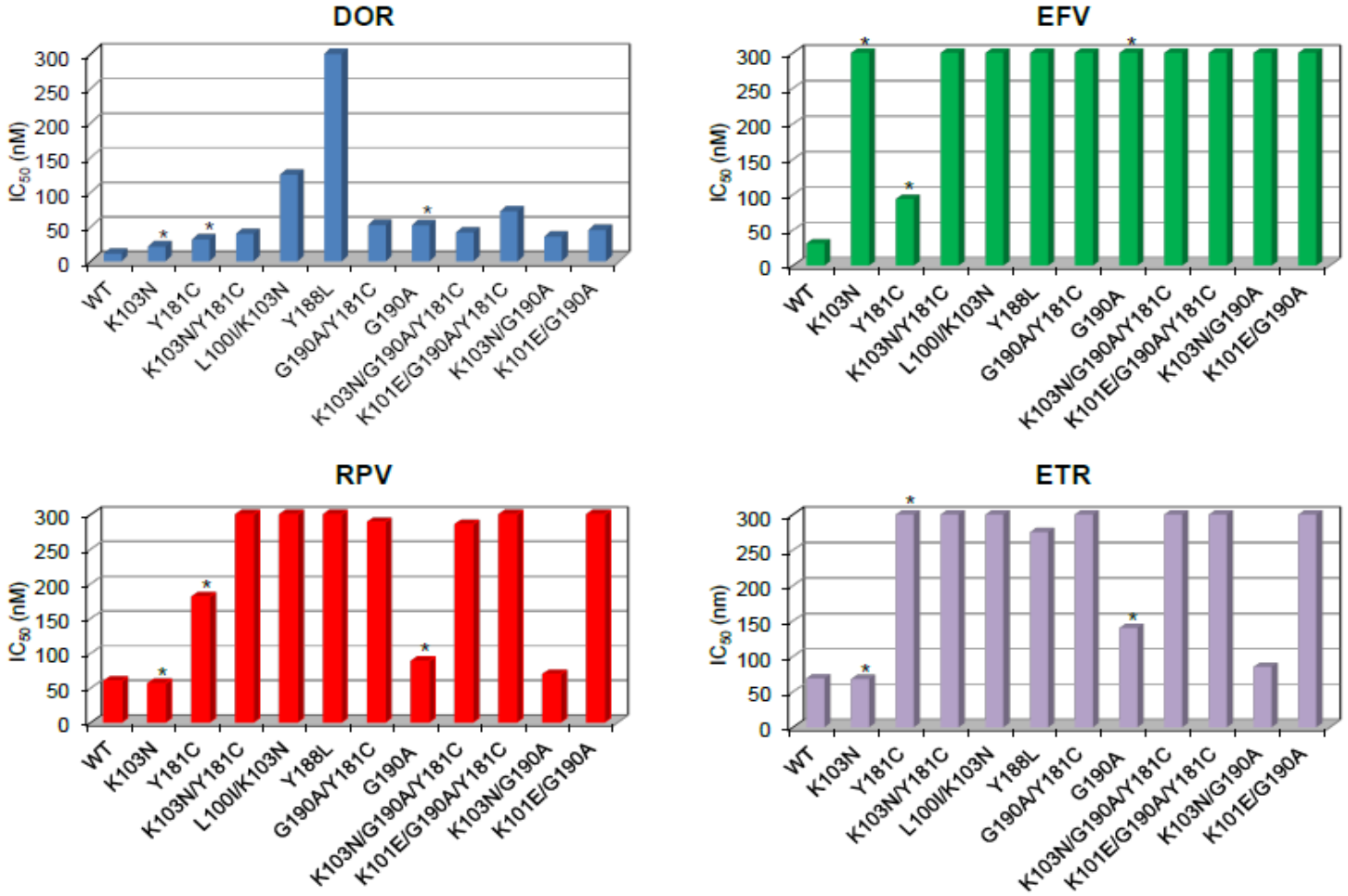
Suppression of Prevalent NNRTI-associated Mutants

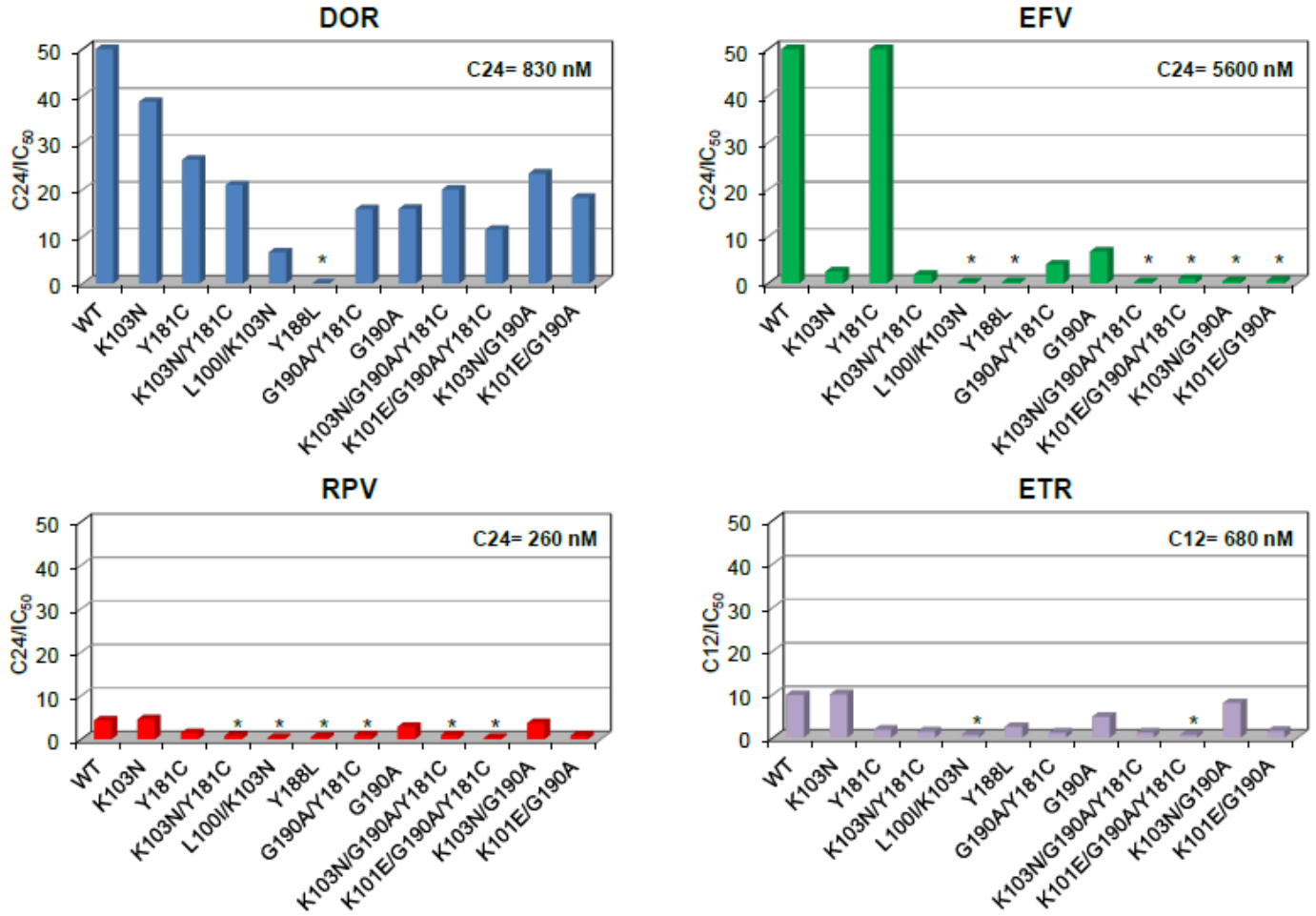


- Doravirine retains antiviral potency against the most prevalent NNRTI-associated resistant mutations

Note: The sequence of mutant viruses in X-axis represents the relative prevalence in patients who have failed with NNRTI-containing regimen based on Stanford HIV drug resistance database. *The top 3 transmitted mutant viruses.

Lai, MT, XU, M, Ngo, W, et al. Characterization of Doravirine-Selected Resistance Patterns from Participants in Treatment-Naïve Phase 3 Clinical Trials. Presented at the 22nd International AIDS Conference; Amsterdam, Netherlands; 23-27 July 2018.

Suppression of Prevalent NNRTI-associated Mutants



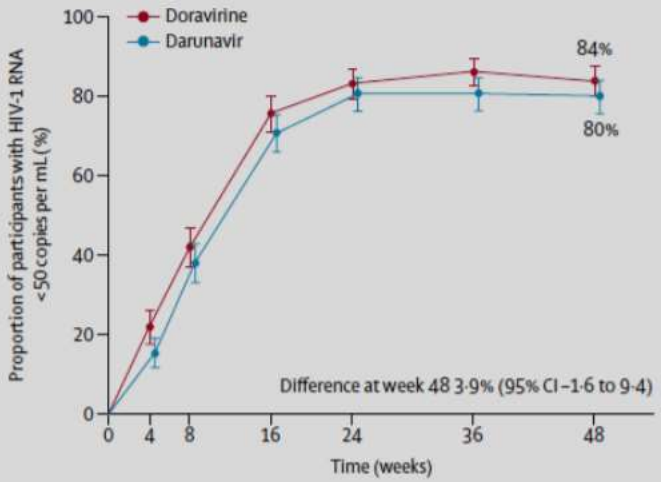
*Represent the C_{trough}/IC_{50} ratio below 1.

- The 100% NHS IQ (C_{trough}/IC_{50}) determined for doravirine is superior to EFV, RPV for WT, and most NNRTI-resistant viruses

Lai, MT, XU, M, Ngo, W, et al. Characterization of Doravirine-Selected Resistance Patterns from Participants in Treatment-Naïve Phase 3 Clinical Trials. Presented at the 22nd International AIDS Conference; Amsterdam, Netherlands; 23-27 July 2018.

Doravirine versus ritonavir-boosted darunavir in **antiretroviral-naive** adults with HIV-1 (**DRIVE-FORWARD**): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial

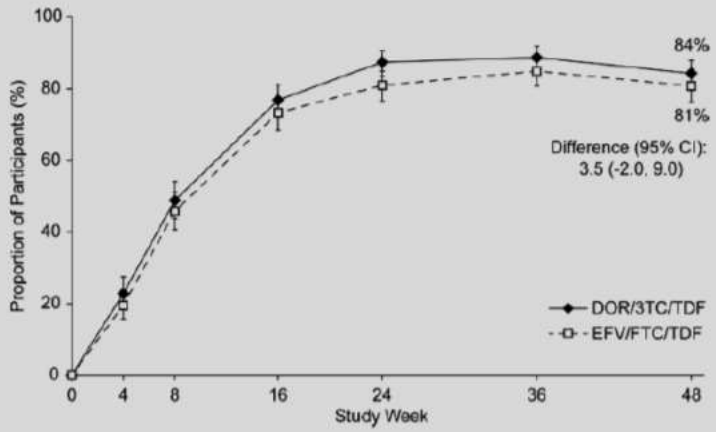
J.M Molina et al ; Lancet HIV 2018



Non-compliance at week 24
V106I, H221Y, and F227C

Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in **Treatment-naive** Adults With Human Immunodeficiency Virus–1 Infection: Week 48 Results of the **DRIVE-AHEAD** Trial

C.Orkin et al ; CID 2018



Y188L; Y318Y/F; V106I, F227C; V106V/I, H221H/Y, F227C; F227C; V106A, P225H, Y318Y/F; V106M/T, F227C/R

*In Phase 3 trials : **7 of 747** participants (**0.9%**) developed resistance to DOR*

DRIVE-AHEAD Week 96

Resistance Analysis at Week 96

- No additional viral drug resistance to DOR between Week 48 and 96

	DOR/3TC/TDF (N=364) Week 0-96		EFV/FTC/TDF (N=364) Week 0-96	
Resistance Analysis Population				
Participants discontinued early without PDVF, n (%)	39 (11%)		62 (17%)	
Participants with PDVF, n (%)	34 (9%)		28 (8%)	
	Non-responder	Rebounder	Non-responder	Rebounder
	6	28	4	24
Resistance Analysis Results				
Resistance test successfully performed[1], n	34		33	
DOR resistance[2]	6 (1.6%)		–	
NRTI resistance[2]	5 (1.4%)		5 (1.6%)	
EFV resistance[2]	–		13 (3.8%)	

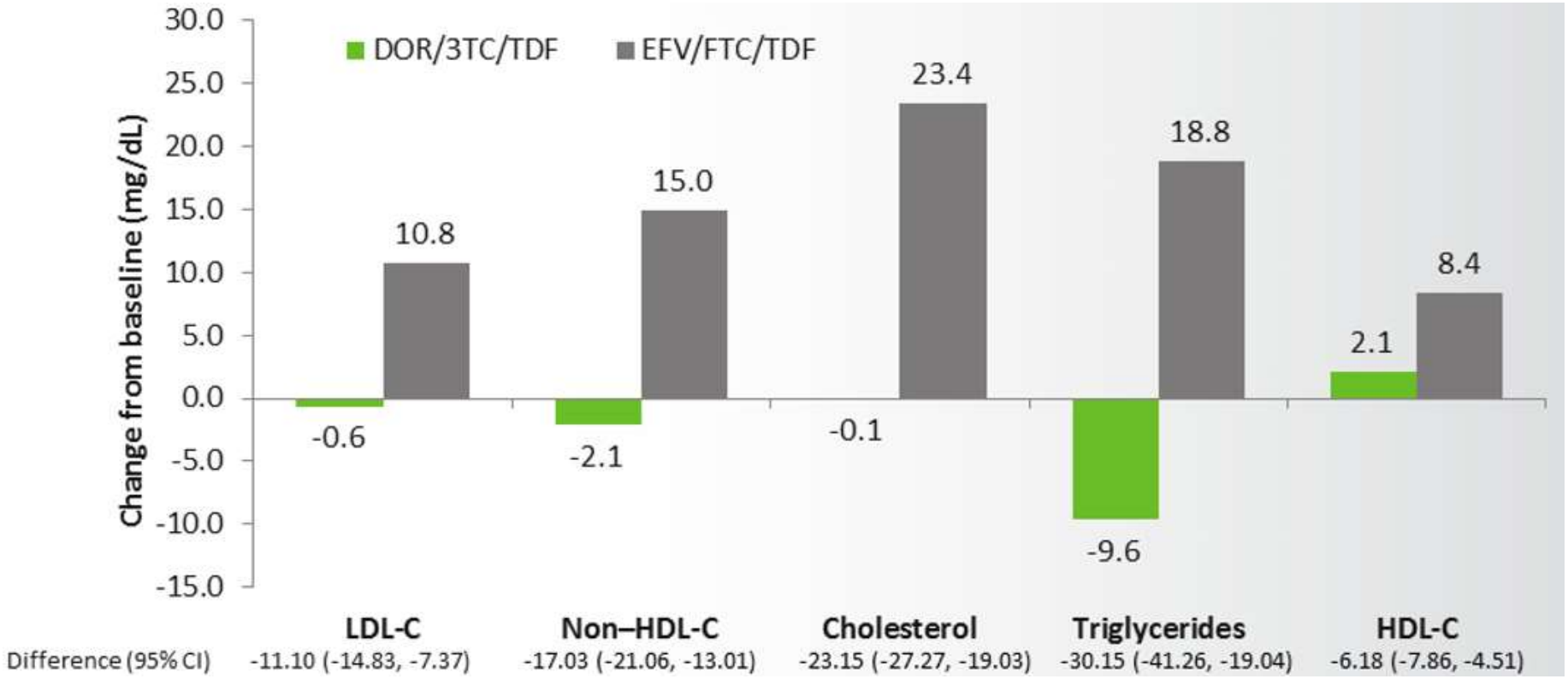
[1] Analysis was performed to identify both genotypic and phenotypic resistance

[2] Represents participants with HIV-1 that had both genotypic and phenotypic resistance for respective drug

Orkin et al. ID Week 2018

DRIVE-AHEAD Week 96

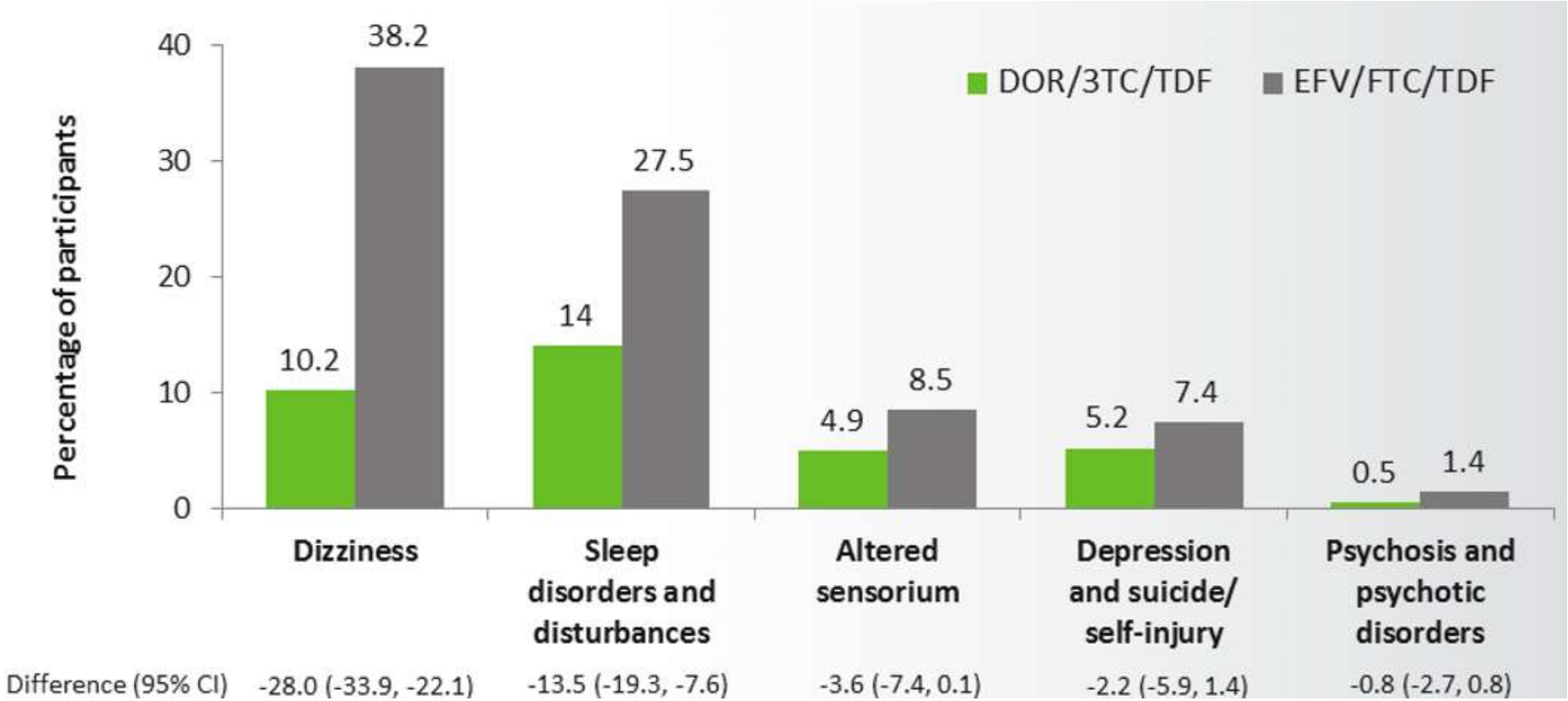
Fasting Lipids: Change from Baseline at Week 96



Orkin et al. ID Week 2018

DRIVE-AHEAD Week 96

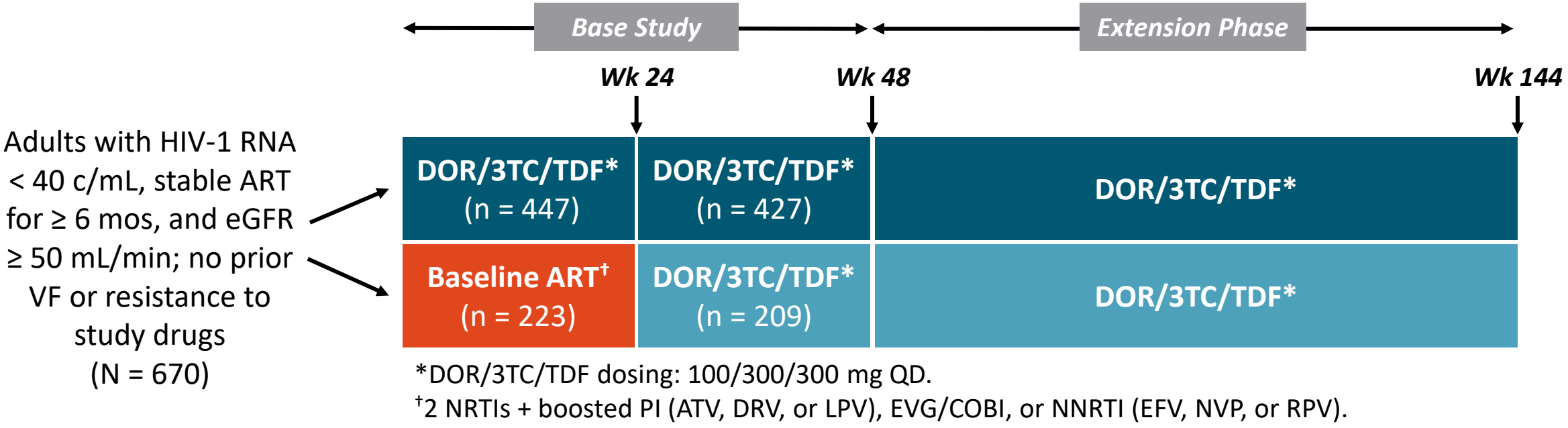
Neuropsychiatric Adverse Events (Predefined) at Week 96



Orkin et al. ID Week 2018

DRIVE-SHIFT: Study Design

- International, randomized, open-label phase III noninferiority study[1,2]



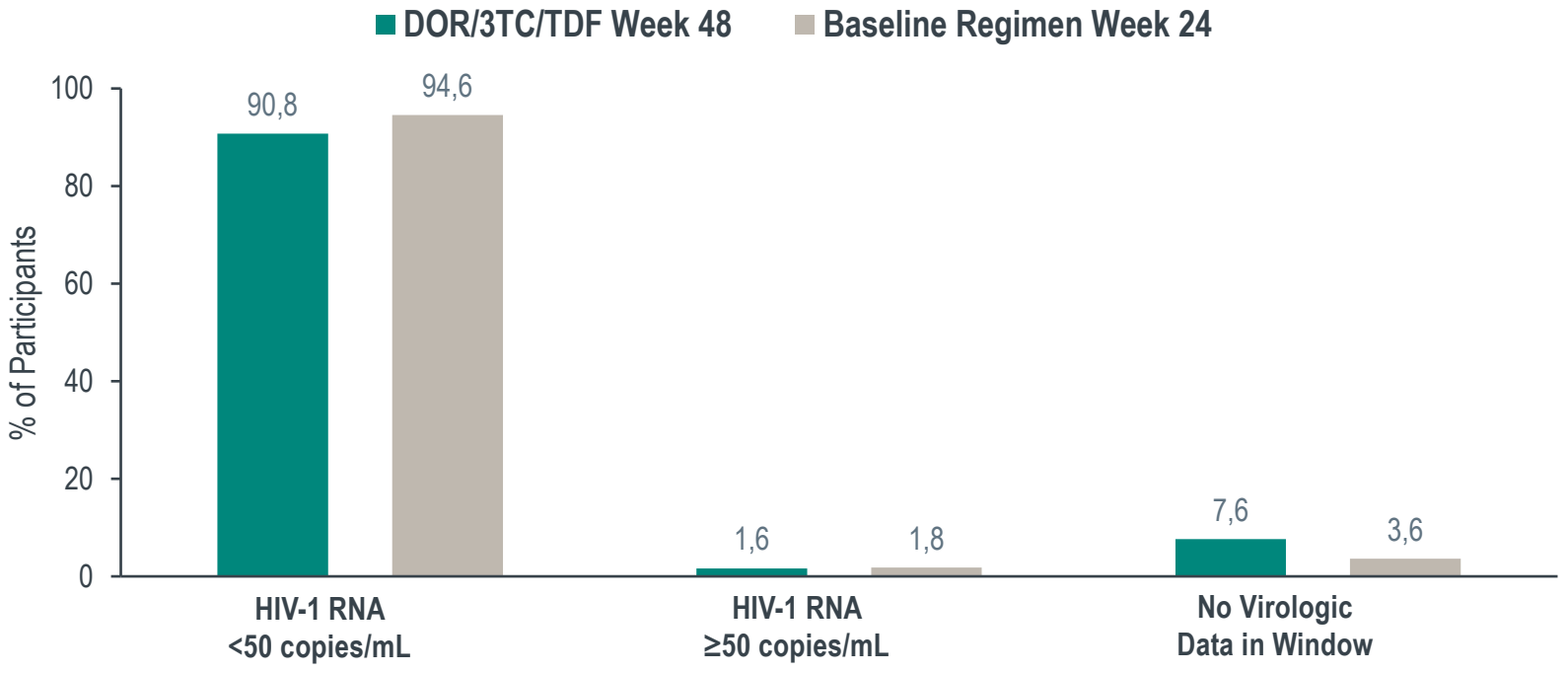
*DOR/3TC/TDF dosing: 100/300/300 mg QD.
†2 NRTIs + boosted PI (ATV, DRV, or LPV), EVG/COBI, or NNRTI (EFV, NVP, or RPV).

- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 in **immediate switch arm** vs Wk 24 in **delayed switch arm**[2]

1. Kumar. AIDS 2020. Abstr OAB0605. 2. Johnson. JAIDS. 2019;81:463.

DRIVE-SHIFT Week 48

Virologic Outcomes (FDA Snapshot Approach): DOR/3TC/TDF Week 48 vs Baseline Regimen Week 24

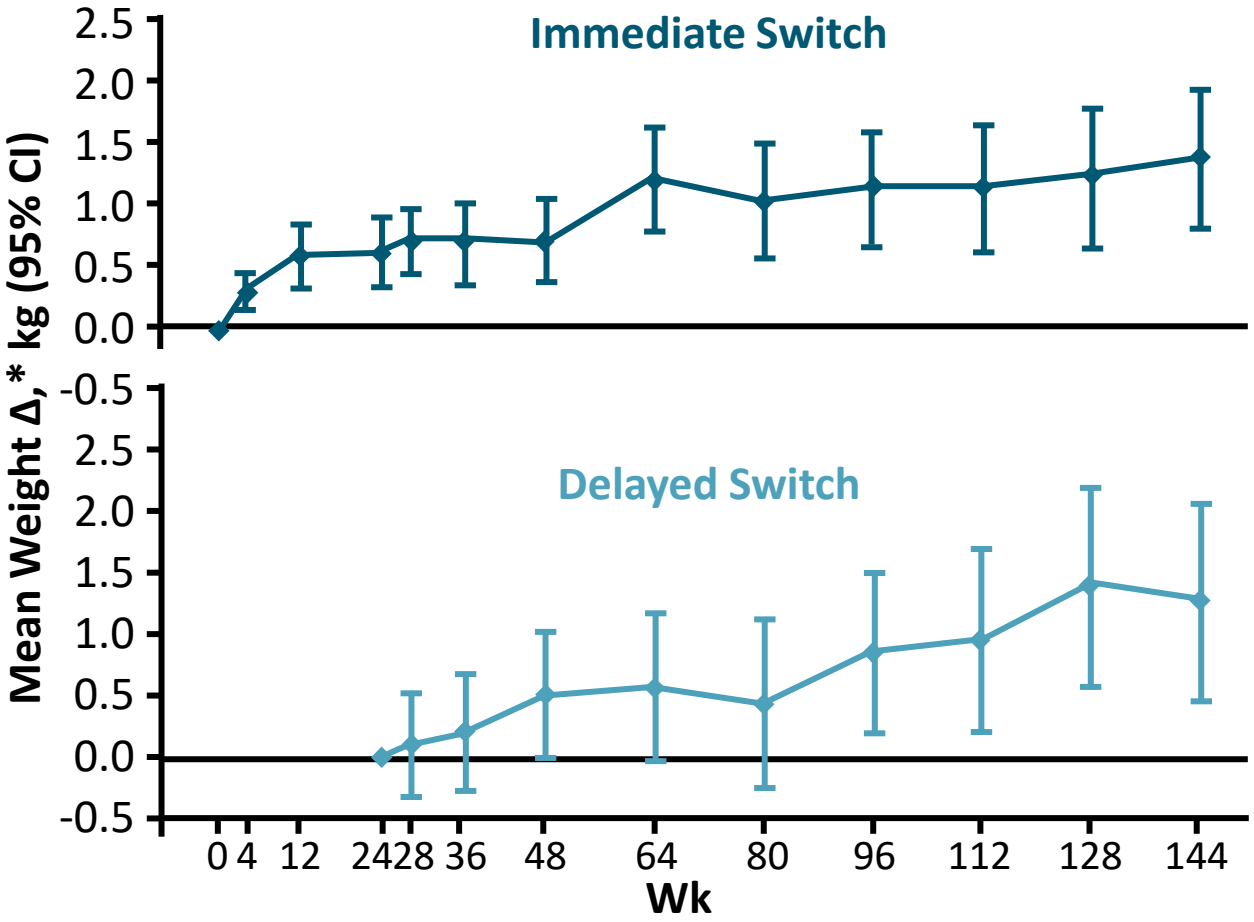


	HIV-1 RNA <50 copies/mL	HIV-1 RNA ≥50 copies/mL
Difference	-3.8%	-0.2%
(95% CI)	(-7.0 , 0.3)†	(-2.5, 2.1)‡

†DOR/3TC/TDF is non-inferior to the Baseline Regimen if the lower bound of the 95% CI is above -8 percentage points.
‡DOR/3TC/TDF is non-inferior (not adjusted for multiplicity) to the Baseline Regimen if the upper bound of the 95% CI is below 4 percentage points

Johnson M, Kumar P, Molina JM, et al. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr. 2019;81(4):463-472. https://www.ncbi.nlm.nih.gov/pubmed/30985556

DRIVE-SHIFT: Post-Switch Mean Weight Change



Mean Weight Δ,* kg (95% CI)	Immediate Switch	Delayed Switch
Wk 24	0.7 (0.4 to 0.9)	NA
Wk 48	0.7 (0.4 to 1.1)	0.5 (0 to 1.0)
Wk 96	1.1 (0.7 to 1.6)	0.8 (0.2 to 1.5)
Wk 144	1.4 (0.8 to 1.9)	1.2 (0.4 to 2.0)

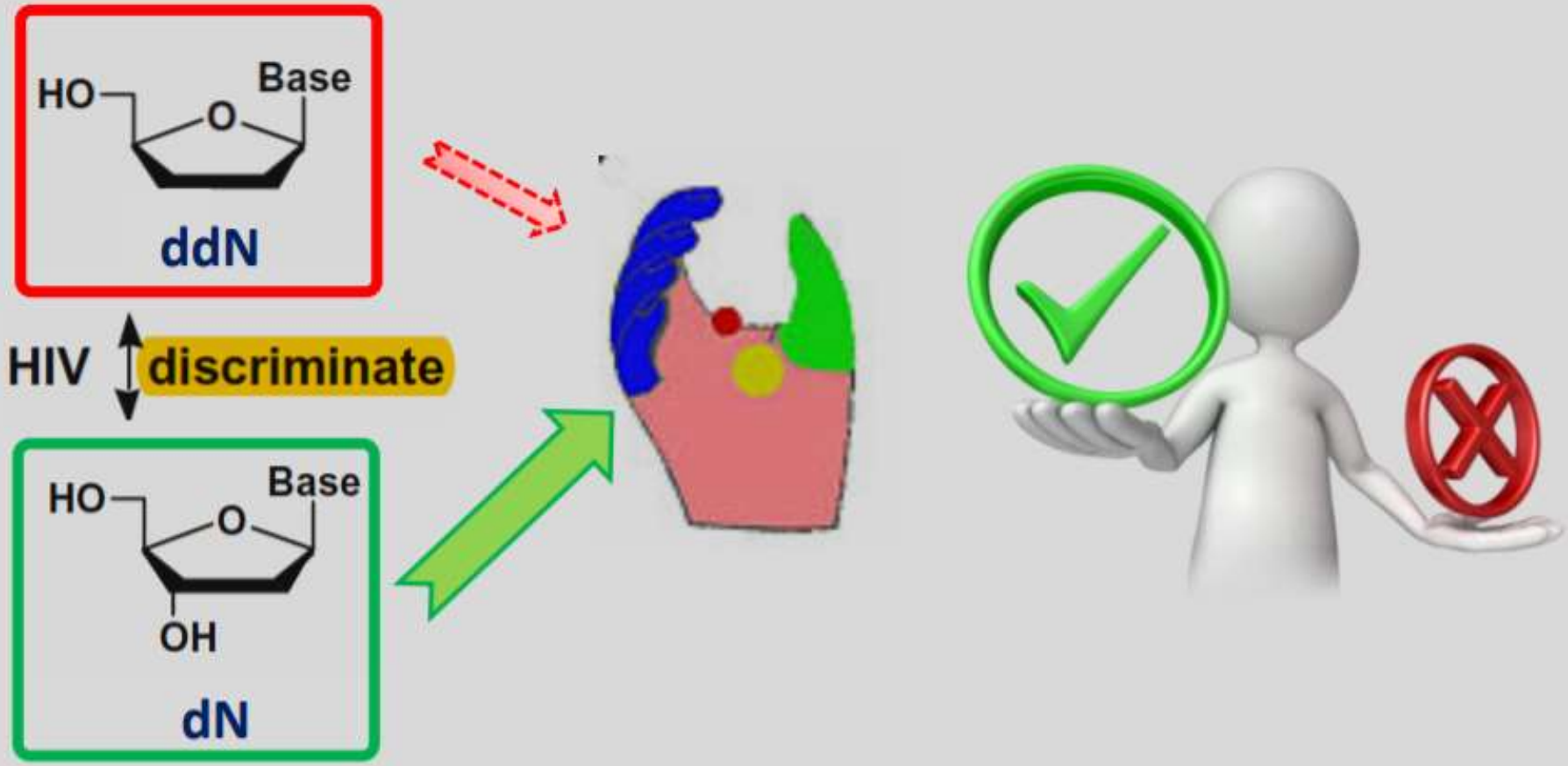
*Adjusted for weight at switch, race (black vs nonblack), ethnicity (Hispanic vs other), sex, age, BL CD4+ cell count, and HIV-1 RNA.

Kumar. AIDS 2020. Abstr OAB0605. Reproduced with permission.

Slide credit: clinicaloptions.com

Which postioning for DOR (alone or STR) in the clinical setting?

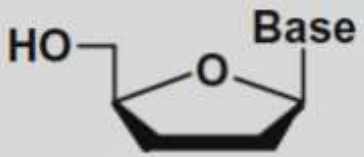
- Naive?
- Switch
    INI-intolerant
    RPV-intolerant or resistant
    RPV-sparing
- MDR



*All approved anti-HIV NRTIs **lack a 3'-hydroxyl** moiety and, thus, act as **chain terminators** following their incorporation into the nascent DNA chain*

*The **absence of a 3'-OH** imparts detrimental properties to these inhibitors, including reduced intracellular phosphorylation to the active triphosphate form and **reduced RT binding affinity***

H.Ohrui ; The Chemical Record 2006

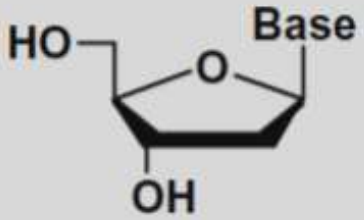


ddN

HIV discriminate

*These **EdN analogs**, unlike the existing approved nucleoside reverse transcriptase inhibitors, **possess a 3'-OH** in their sugar moiety; however, they **cause viral DNA chain termination**, resulting in RT inhibition*

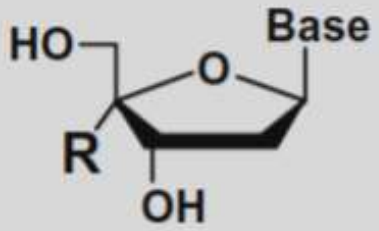
E.I Kodama et al ; AAC 2001

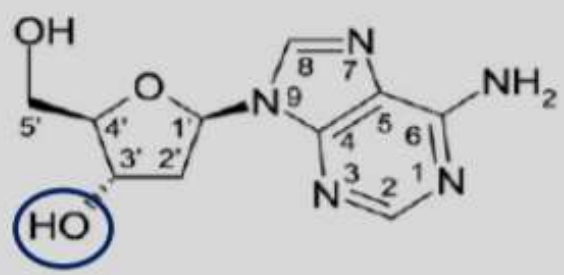


dN

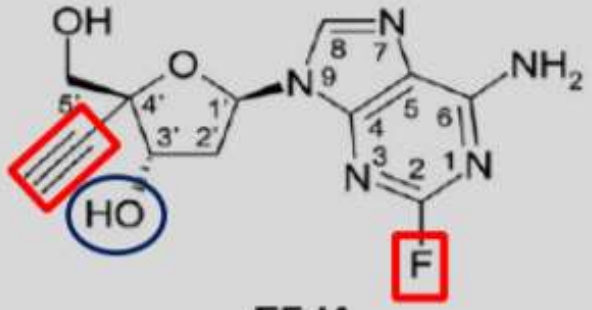
HIV

cannot discriminate





dA



EFdA

Islatravir

4'-ethynyl-2-fluoro-2'- deoxyadenosine (**EFdA**; MK-8591)

Probing the molecular **mechanism of action** of the HIV-1 reverse transcriptase inhibitor 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) using **pre-steady-state kinetics**

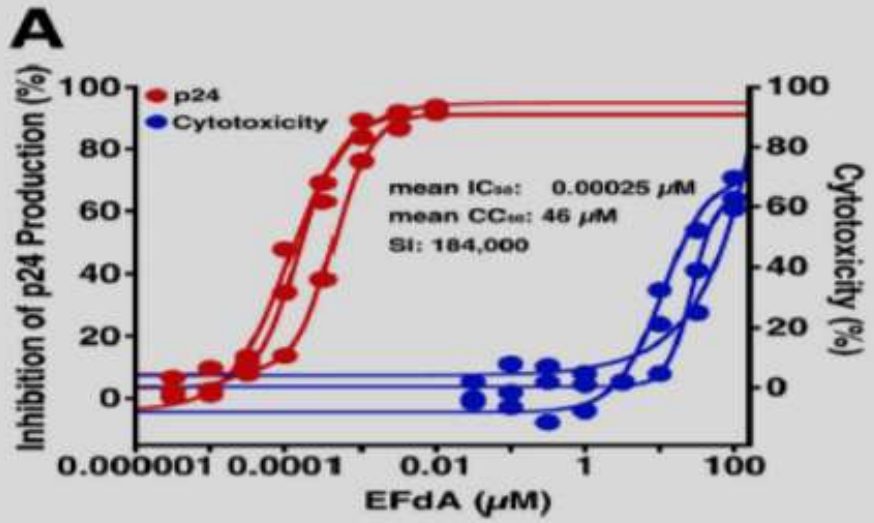
Y.Muftuoglu et al ; Ant.Res. 2014

Pre-steady-state rate constants for incorporation of EFdA-TP or dATP by RT and pol γ.[a]

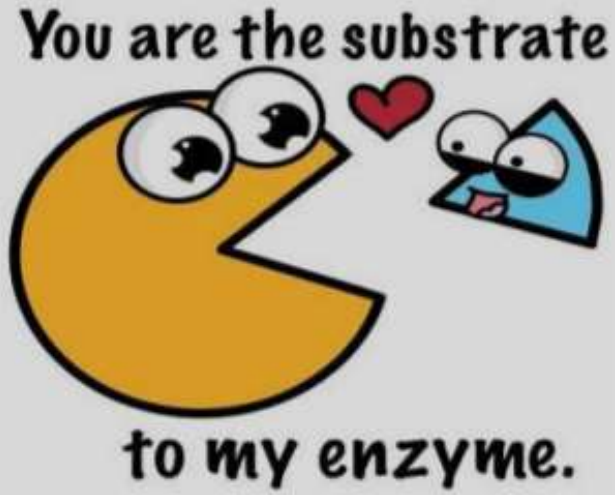
Enzyme	Nucleotide or analog	k_{pol} (s^{-1})	K_d (μM)	Efficiency[b] ($\mu M^{-1} s^{-1}$)	Discrimination[c]
RT	dATP	8.0 ± 0.7	3.8 ± 0.8	2.1	0.47
	EFdA-TP	5.8 ± 0.3	1.3 ± 0.2	4.5	
pol γ[d]	dATP	220 ± 16	3.2 ± 0.7	69	4.300
	EFdA-TP	0.29 ± 0.02	18 ± 4	0.016	

*The **striking discrimination by pol γ** in contrast with the **preference of EFdA over dATP** by RT indicates EFdA is a **very promising RT inhibitor***

*EFdA can likely be used in the clinical setting to treat HIV patients with **low doses** and minimal mitochondrial-based toxicity*



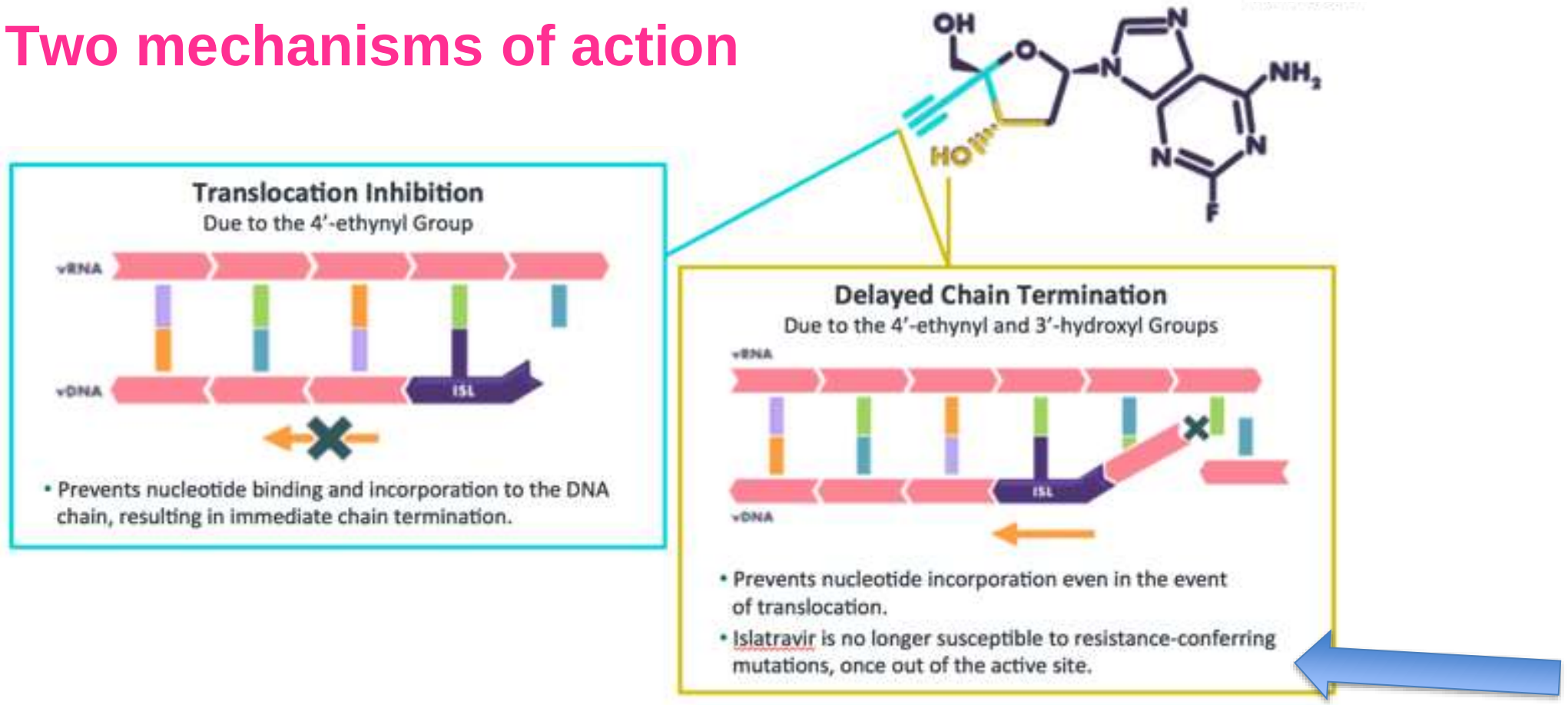
C.A Stoddart et al ; AAC 2015



Islatravir

First-in-class nucleoside reverse transcriptase **translocation** inhibitor [NRTTI]
Formerly known as MK-8591

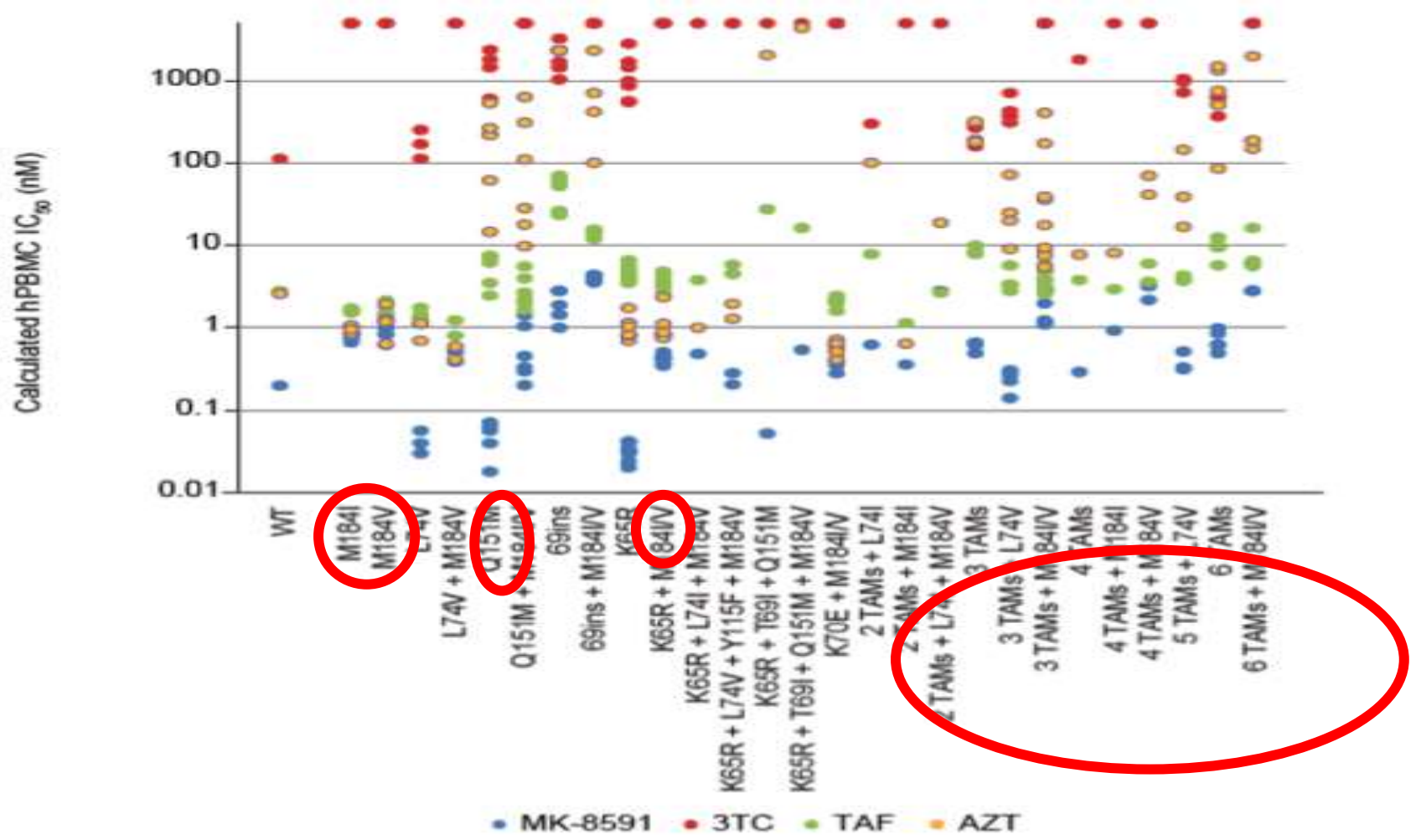
Two mechanisms of action



https://www.natap.org/2019/EACS/EACS_81.htm

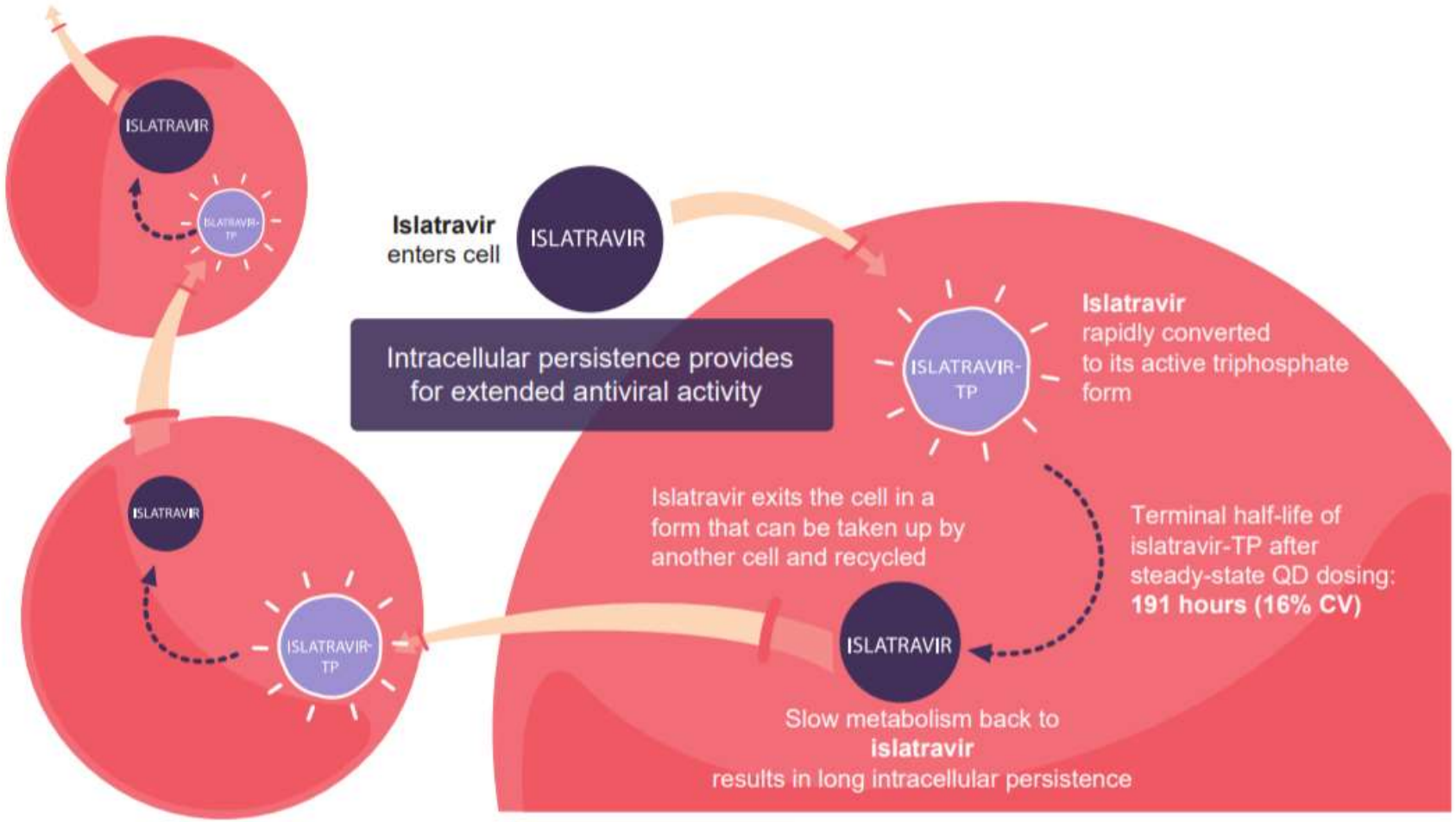
MK-8591: Activity Against NRTI-Resistant Strains

Common NRTI mutations, including M184I/V, thymidine analog mutations, K65R, and K70E, confer low fold-shifts in antiviral potency, and islatravir retains greater IQs against these NRTI-resistant viruses than those of TDF, TAF, and 3TC with WT virus.



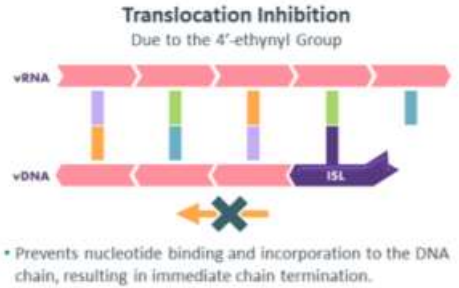
Grobler CROI 2019 #481

Figure 2. Islatravir Properties Contribute to Differentiated Pharmacokinetic (PK) and Long Half-life

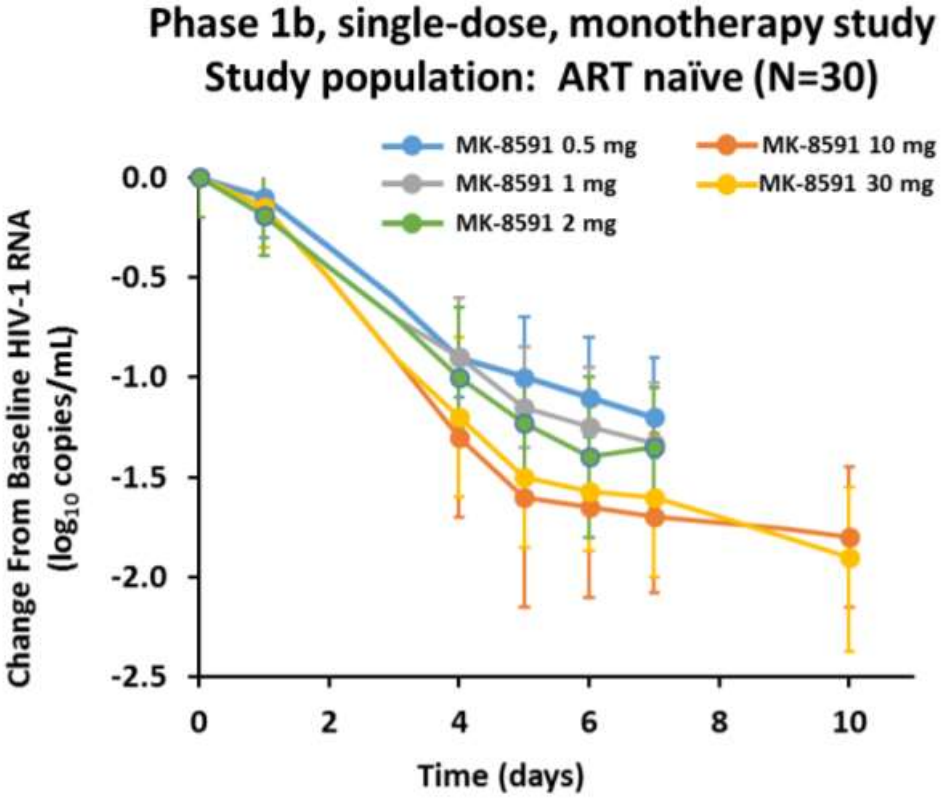


NRTTI

Islatravir (MK-8591)

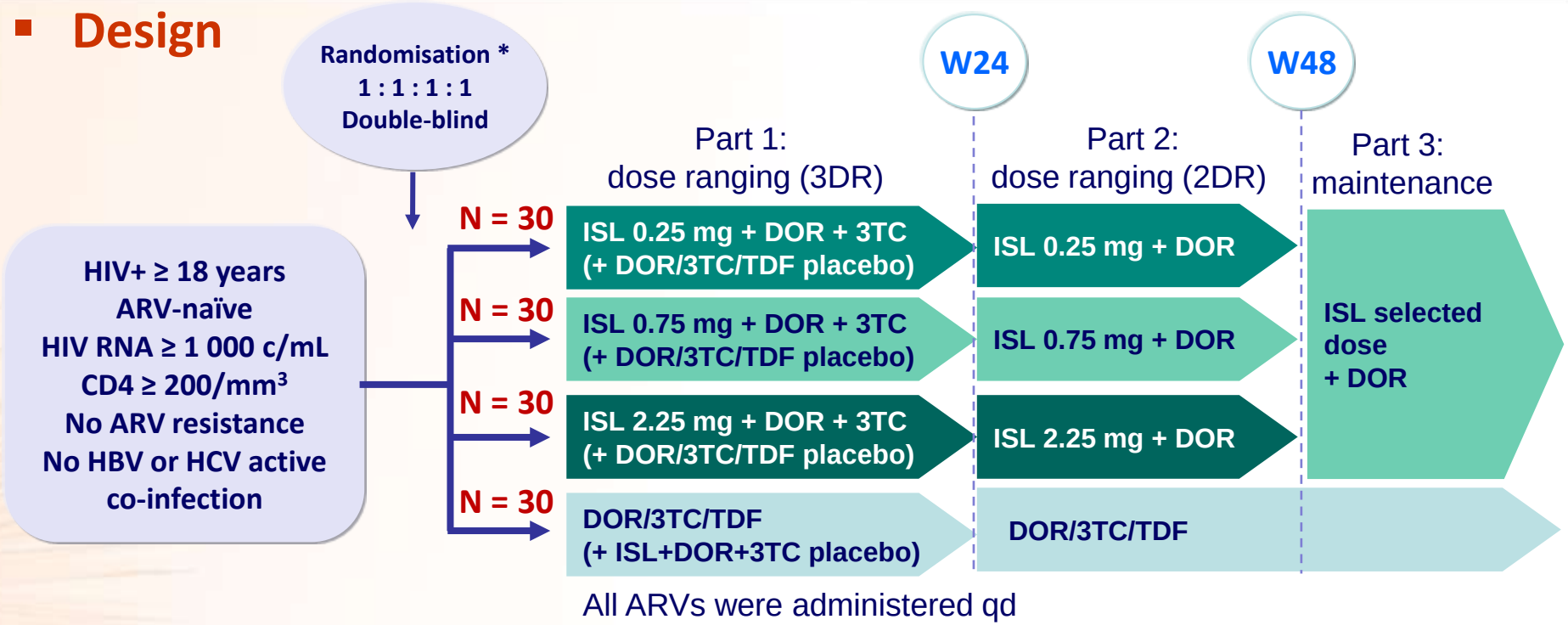


- Nucleoside RT translocation inhibitor (NRTTI)
- Potent at low doses: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days
- High barrier to resistance
- Long intracellular half-life (78-120 h)
  - Potential for once daily, once weekly or less frequent dosing



DRIVE2Simplify Study: Islatravir + Doravirine Phase 2

Design



* Randomisation stratified by HIV RNA (≤ or > 100 000 c/mL)

Primary endpoints

- Proportion of participants achieving HIV RNA < 50 c/mL at W24 (ITT- snapshot)
- Proportion of participants achieving HIV RNA < 50 c/mL at W48 (ITT- snapshot)
- Number of participants experiencing adverse events
- Number of participants discontinuing study drug due to adverse events

DRIVE2Simplify

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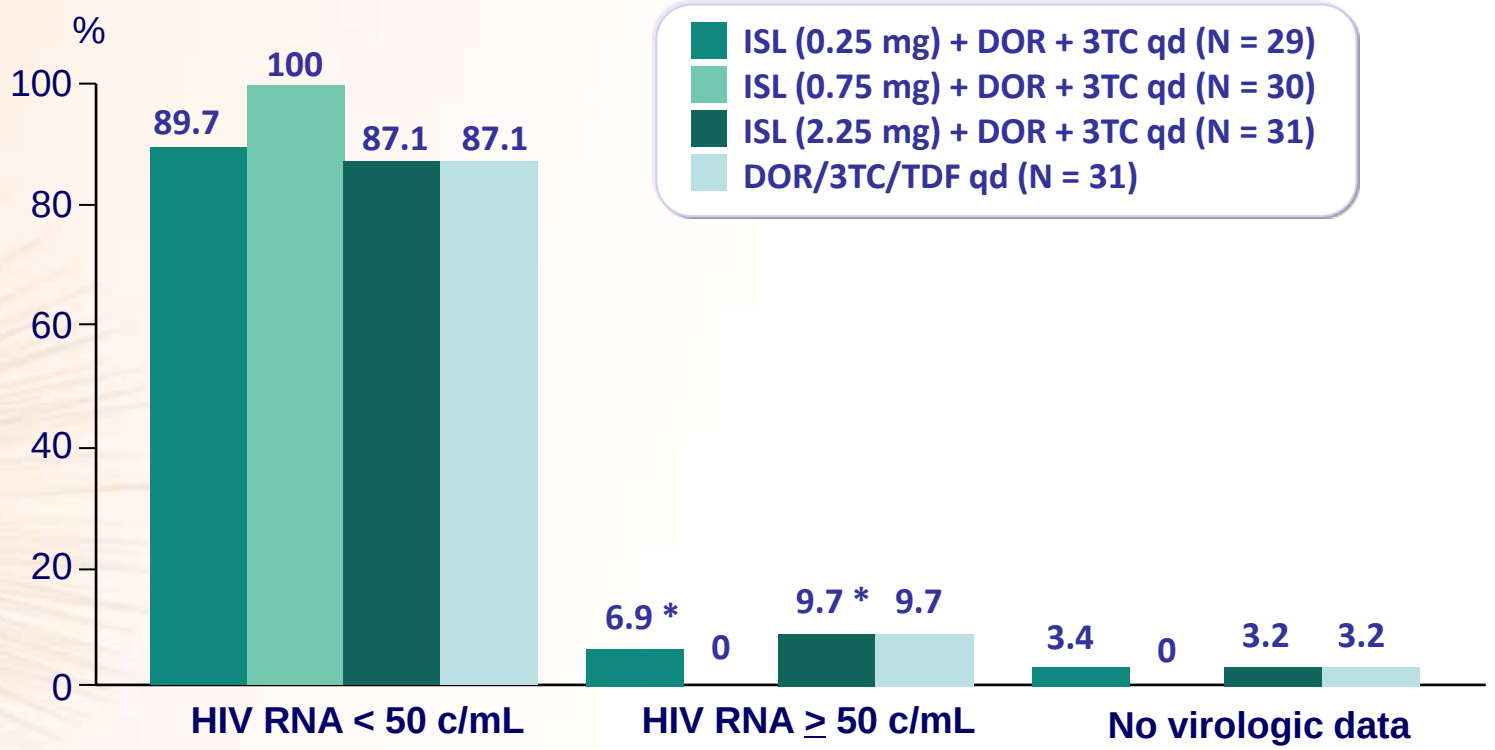
DRIVE2Simplify Study: Islatravir + Doravirine Phase 2

Virologic outcome at W24 (ITT, snapshot)



* 5 patients on ISL (2 in arm 0.25 mg, 3 in arm 2.25 mg) had HIV RNA between 50 and 200 c/mL at W24

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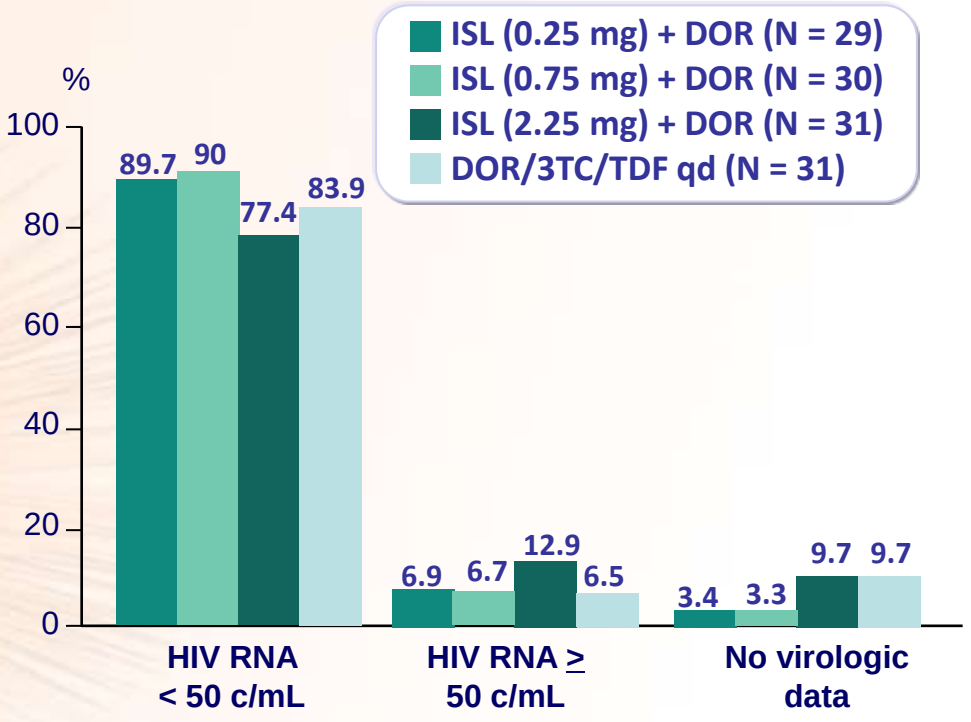
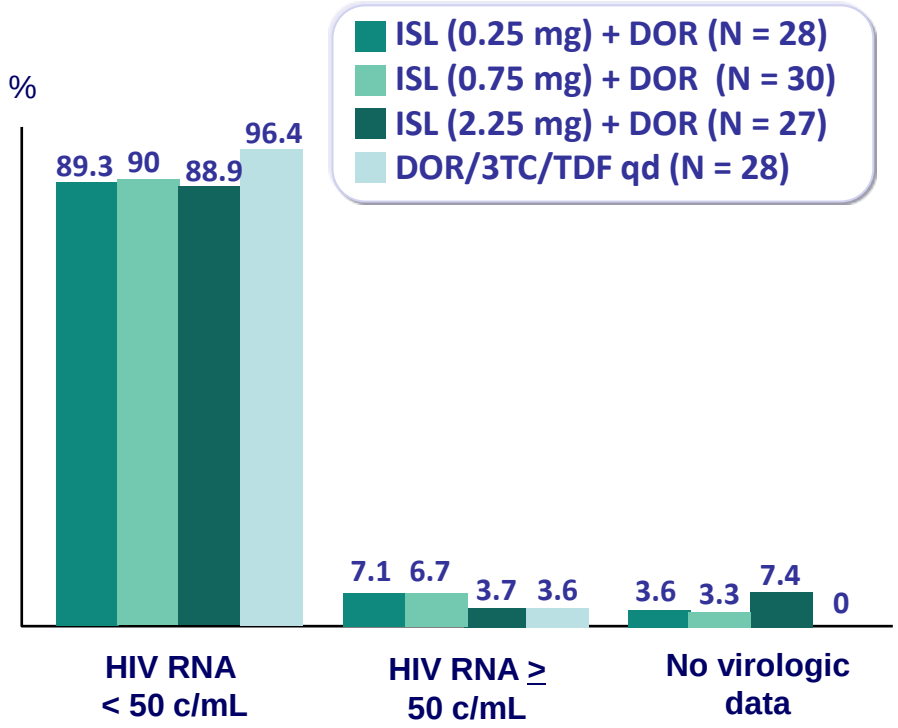
DRIVE2Simplify Study: Islatravir + Doravirine Phase 2

Virologic outcome at W48 (ITT, snapshot)

All patients



Outcome 24 weeks after entering part 2



- 5 virologic rebounds (2 in arm 0.25 mg, 2 in arm 0.75 mg, 1 in arm DOR/3TC/TDF) between W24 and W48 and 1 non-responder (arm 2.25 mg), all with HIV RNA between 50 and 200 c/mL and confirmatory sample < 80 c/mL

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DRIVE2Simplify Study: Islatravir + Doravirine Phase 2

Adverse events

	ISL 0.25 mg + DOR + 3TC N = 29	ISL 0.75 mg + DOR + 3TC N = 30	ISL 2.25 mg + DOR + 3TC N = 31	DOR/TDF/3TC N = 31
≥ 1 adverse event, %	72.4	86.7	61.3	77.4
Drug-related adverse event, N	0	3	4	6
Serious adverse event, N	1	2	0	2
Discontinuation for AE, N	0	0	2	1
Adverse event with incidence > 10%, N				
Diarrhea	0	4	2	5
Nausea	1	4	3	3
Bronchitis	2	4	0	4
Nasopharyngitis	1	4	1	3
Sinusitis	3	0	0	1
Syphilis	2	3	2	4
Vitamin D deficiency	0	4	2	1
Arthralgia	1	2	4	1
Pain in extremity	3	0	0	0
Headache	4	2	4	2

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DRIVE2Simplify Study: Islatravir + Doravirine Phase 2

Grade 3 or 4 laboratory abnormalities

	ISL 0.25 mg + DOR + 3TC N = 29	ISL 0.75 mg + DOR + 3TC N = 30	ISL 2.25 mg + DOR + 3TC N = 31	DOR/TDF/3TC N = 31
Fasting triglycerides, grade 3, N	2	0	0	0
ALT, grade 3, N	0	1	2	1
Creatine kinase, grade 3 / grade 4, N	3 / 0	0 / 2	0 / 3	1 / 1

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DRIVE2Simplify Study: Islatravir + Doravirine Phase 2

Conclusion

- Participants who initiated on ISL + DOR in combination with 3TC and switched to ISL + DOR had high efficacy at W48 as measured by proportion with HIV RNA < 50 c/mL similar to DOR/3TC/TDF
- No participant in any treatment group met criteria for resistance testing (All confirmed HIV RNA for protocol-defined virologic failure was < 80 c/mL)
- ISL + DOR was generally well- tolerated
- Few drug-related adverse events (7.8% overall)
- Rate of discontinuation for adverse event was low (2.2%)

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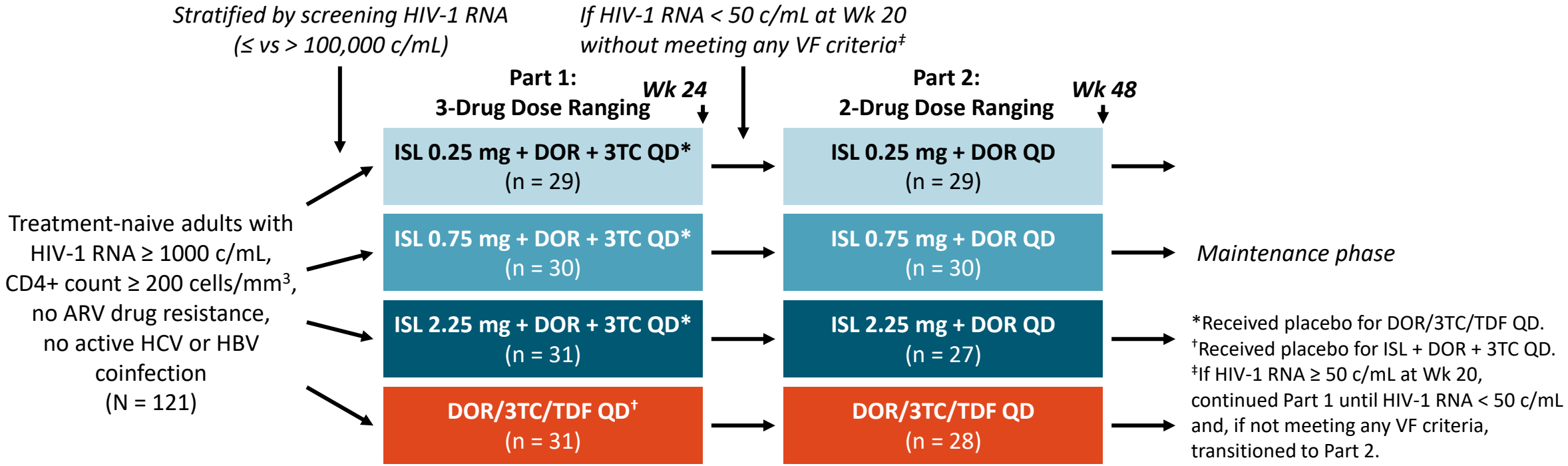
P011: Analysis of patients discontinuing international, randomized, double-blind phase IIb trial with PDVF

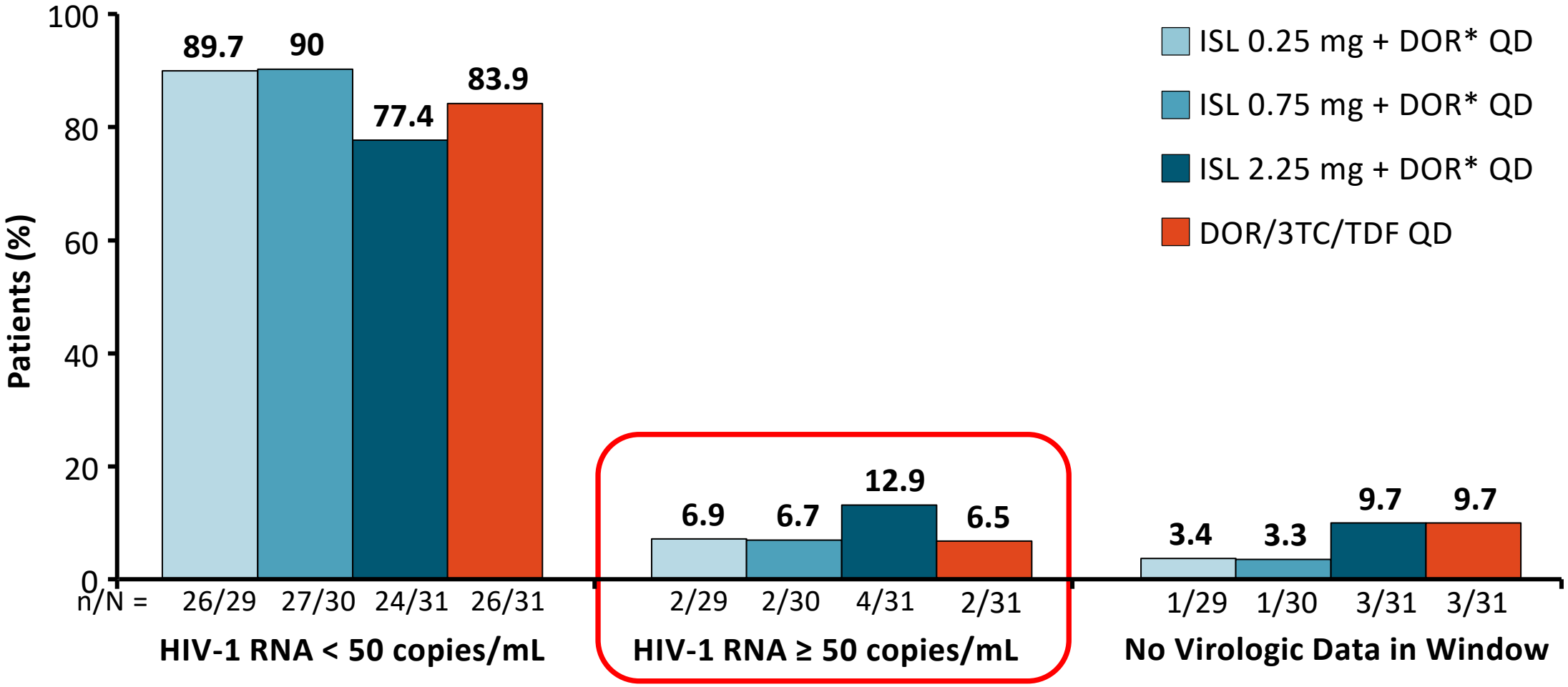
- **P011: Study Design**



- PDVF defined as: viral rebound (HIV-1 RNA ≥ 50 c/mL after initial response < 50 c/mL on study; or confirmed HIV-1 RNA > 1 log increase from nadir after a > 1 log decrease vs BL on study); or nonresponse (HIV-1 RNA ≥ 200 c/mL at any time from Wk 24 through Wk 48; or confirmed HIV-1 RNA ≥ 50 c/mL at Wk 48)
- Initial PDVF HIV-1 RNA level must be confirmed by subsequent measurement within 2 wks

Orkin. AIDS 2020. Abstr OAB0302. DeJesus. AIDS 2020. Abstr OAB0305.

P011: Virologic Outcomes Through Wk 48 (FDA Snapshot)



*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR during the Wk 24-48 period of the study.

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P011: Protocol Defined Virologic Failure at Wk 48

- HIV-1 RNA levels at second assessment to confirm PDVF were < 80 copies/mL in all patients with PDVF; no patient met criteria for resistance testing (HIV-1 RNA > 400 copies/mL)
- No evidence that PDVF was associated with drug pharmacokinetics

Outcome at Wk 48	ISL 0.25 mg + DOR QD (n = 29)	ISL 0.75 mg + DOR QD (n = 30)	ISL 2.25 mg + DOR QD (n = 31)	DOR/3TC/TDF QD (n = 31)
PDVF, n (%)				
▪ Nonresponse	0	0	1 (3.2)	0
▪ Rebound with HIV-1 RNA > 50 c/mL	2 (6.9)	2 (6.7)	0	1 (3.2)
▪ Rebound with HIV-1 RNA > 200 c/mL	0 (0)	0	0	0
HIV-1 RNA ≥ 50 c/mL not classified as PDVF, n (%)				
▪ Early d/c	0	0	3 (9.7)	1 (3.2)
▪ Reason for early d/c	--	--	2 LTFU; 1 withdrawal	1 protocol violation

Orkin. AIDS 2020. Abstr OAB0302.

P011: HIV-1 RNA by Study Visit for Patients With PDVF at Wk 48

- HIV-1 RNA before suppression
- HIV-1 RNA ≥ 50 and < 200 c/mL after suppression
- HIV-1 RNA < 50 c/mL after suppression
- HIV-1 RNA ≥ 200 c/mL after suppression

Patient: Treatment Group	BL CD4+ Cell Count, cells/ mm^3	HIV-1 RNA, copies/mL (PDVF Confirmation Value)												
		BL	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
1: ISL 0.25 + DOR + 3TC	299	66,774	927	927	94	70	< 50	< 50	< 50	< 50	< 50	<50	< 50	< 50	**51** (79)
2: ISL 0.25 + DOR + 3TC	464	153,790	3551	3551	552	412	106	< 50	132 (< 50)	**93** (55)					
3: ISL 0.75 + DOR + 3TC	334	626,957	1497	1497	665	248	151	151	< 50	**87** (58)					
4: ISL 0.75 + DOR + 3TC	370	4916	147	147	62	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	**77** (53)	
5: ISL 2.25 + DOR + 3TC*	365	413,236	4244	4244	1098	772	424	343	172	81	85	84	103	72	**93**(50)
6: DOR/3TC/TDF	414	437,894	2951	2951	771	534	75	< 50	< 50	**59** (55)					

*Patient switched treatment without PDVF.

- 3 of 6 patients who switched to new regimen had low level viremia at 42-day follow-up after switch

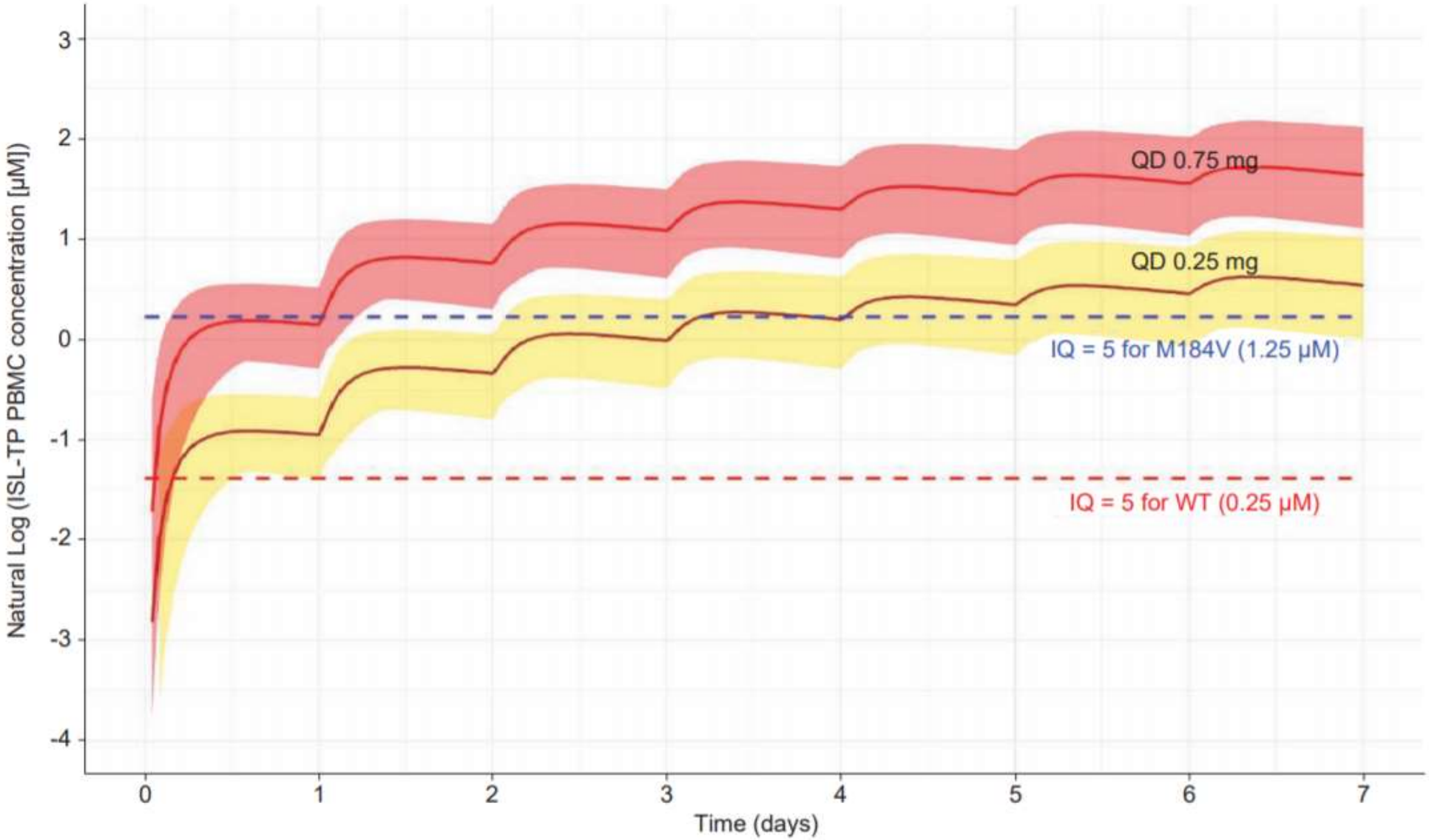
Orkin. AIDS 2020. Abstr OAB0302.

P011: Conclusions

- ART induction with ISL + DOR + 3TC followed by simplification to ISL + DOR demonstrated comparable Wk 48 efficacy vs DOR/3TC/TDF in treatment-naive patients
  - Low rate of PDVF
  - HIV-1 RNA remained < 200 copies/mL in all patients discontinuing for PDVF
    - HIV-1 RNA levels at second assessment to confirm PDVF were < 80 copies/mL in all patients with PDVF
    - No patient met criteria for resistance testing (HIV-1 RNA > 400 copies/mL)
  - 3 of 6 patients who switched to new regimen had low level viremia at 42-day follow-up after switch

Orkin. AIDS 2020. Abstr OAB0302.

Figure 6. ISL 0.75 mg QD Simulations Predict Antiviral Activity Against WT and M184V Virus



NRTTI

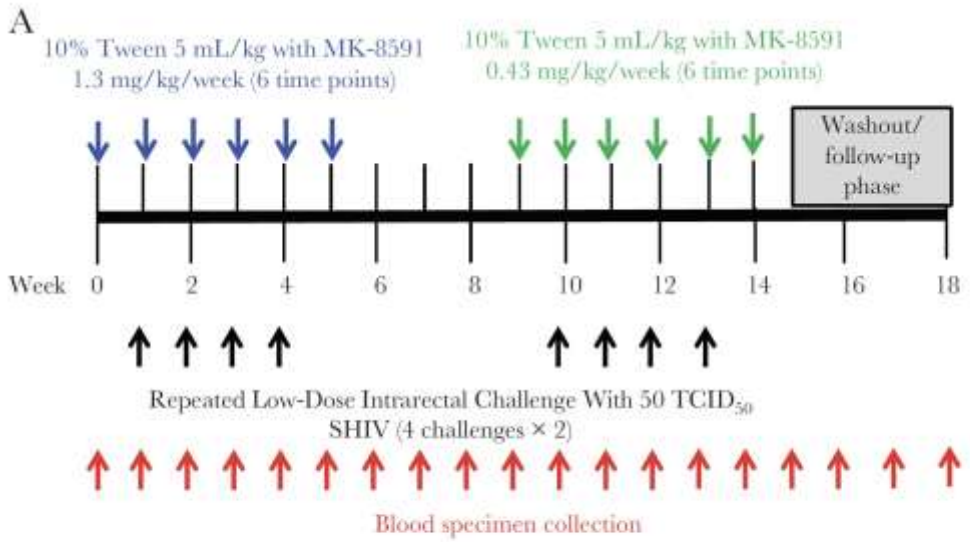
Islatravir (ISL)

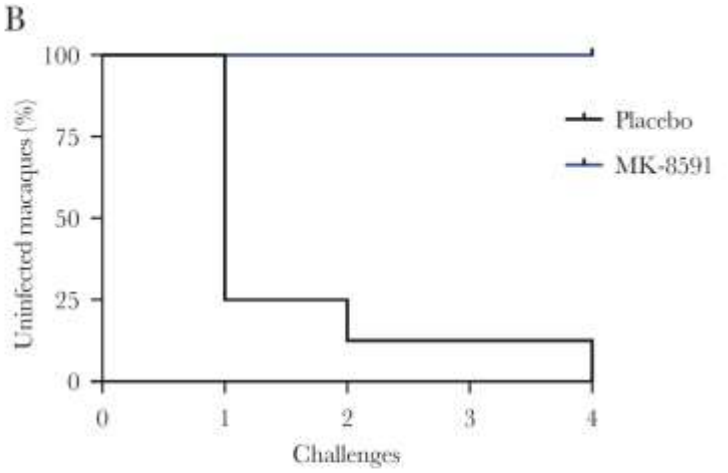
- **Phase 3 trials of ISL/DOR (0.75 mg/100 mg):**
  - Switch studies: from BIC/FTC/TAF (n=578)[1] or other 2- or 3-drug regimen (n=578)[2]
  - Highly treatment-experienced participants (at least 3 class resistance) (n=100)[3]
  - Treatment naïve participants: DOR/ISL vs. BIC/FTC/TAF (n=680)[4]

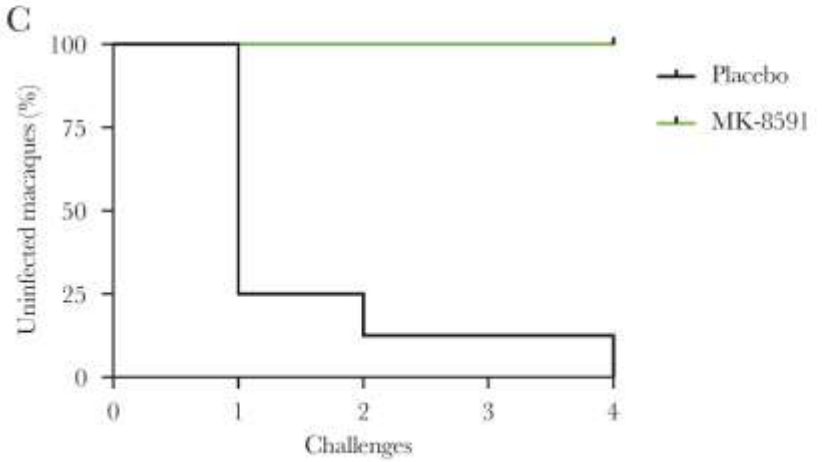
<u>Future possibilities:</u>

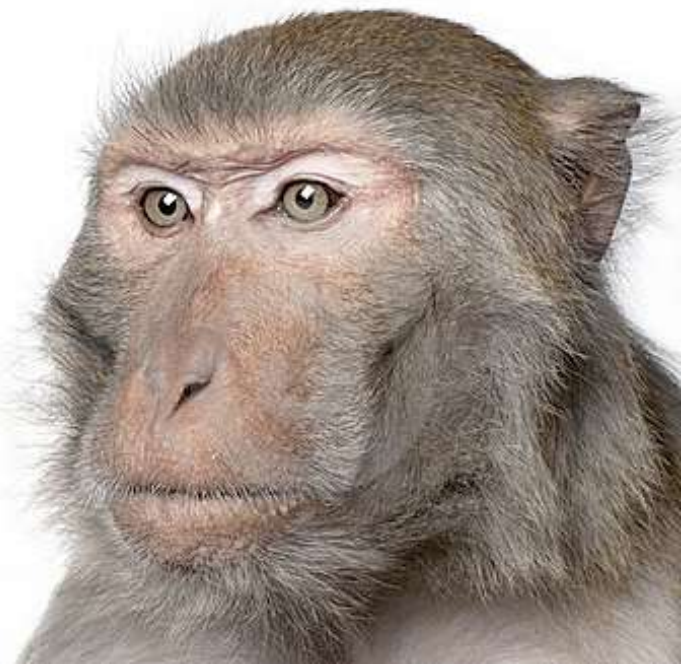
- In SIV model, weekly oral ISL provided effective post-exposure prophylaxis[5]
- May have applications for PrEP
  - Phase 2 trial in people at low risk of HIV: once monthly oral (60, 120 mg)[6]
  - Promising PK results with ISL implant[7]

Islatravir PO once <u>weekly</u> protects macaques







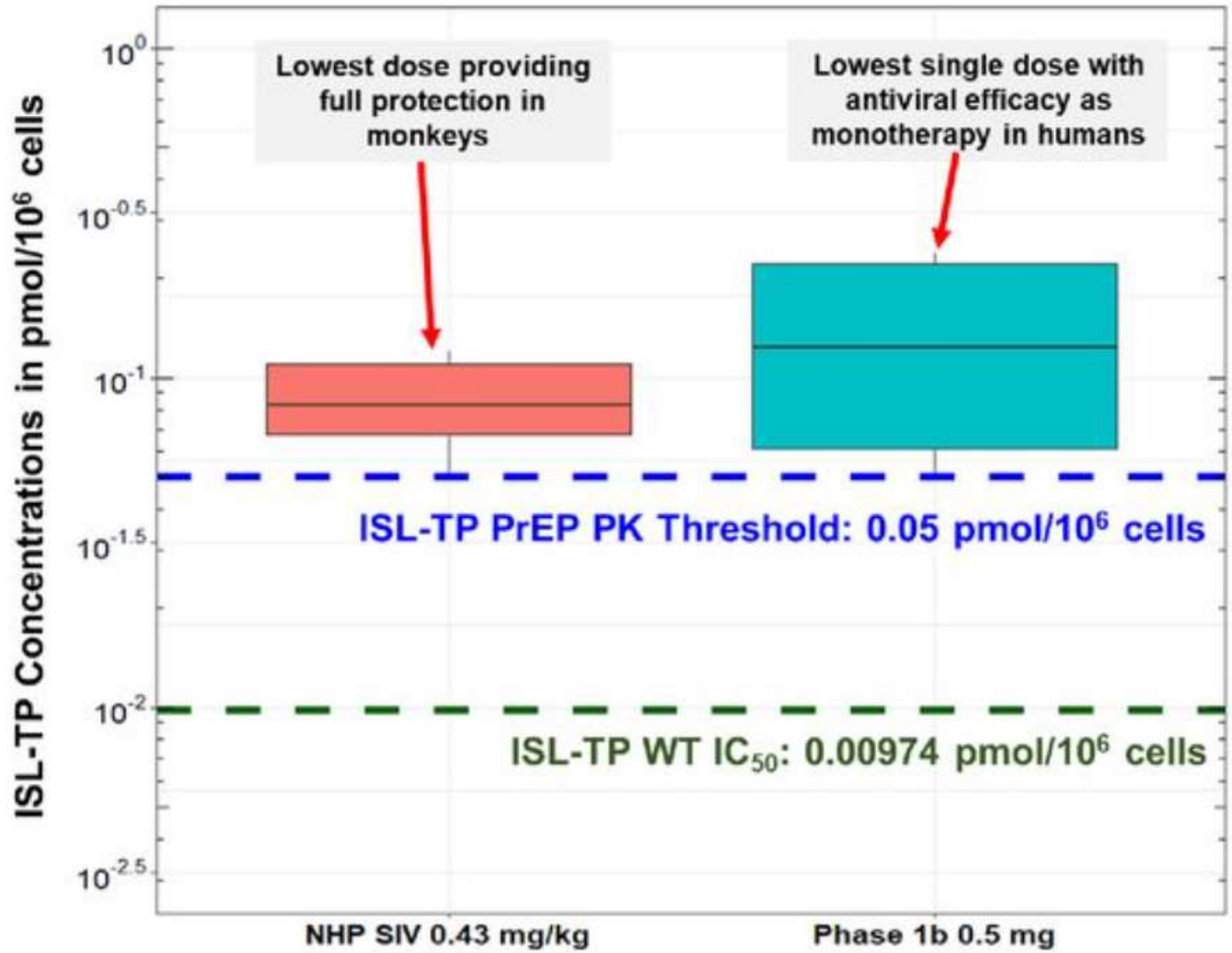


Markowitz M, et al. J Infect Dis. 2020;221(9):1398-1406

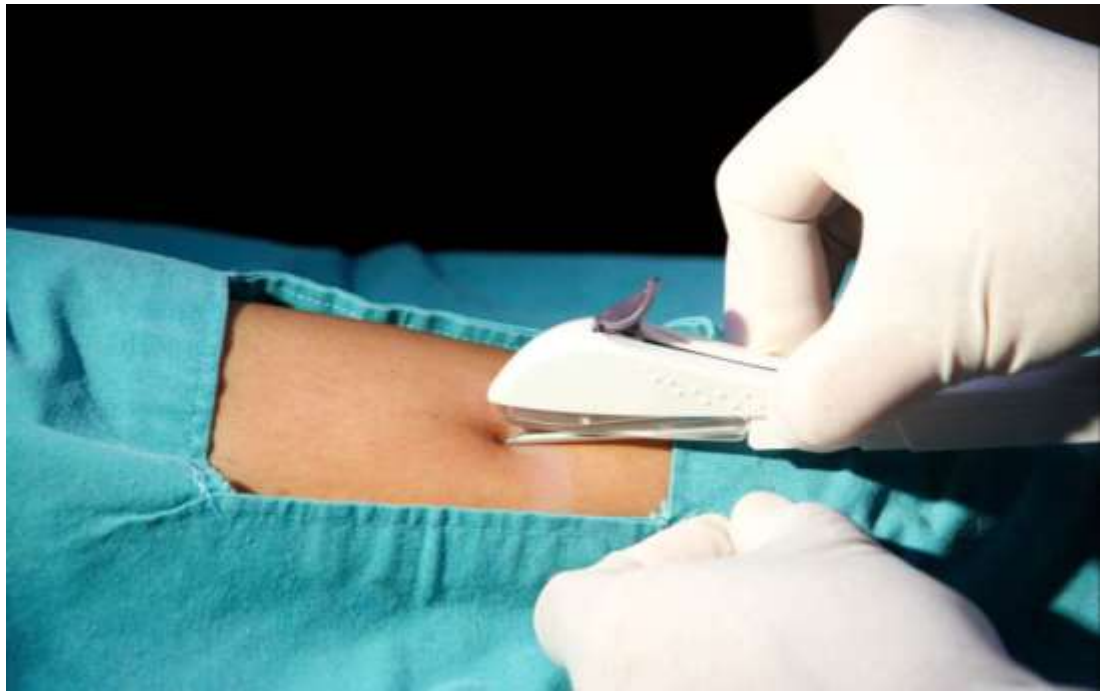
Translational PK/PD Modeling Supports PrEP Exposure Threshold of 0.05 pmol/10^6 Cells ISL-TP

- Threshold of **0.05 pmol/10^6 cells** supported by:
  - ISL rhesus macaque SIV study
  - Efficacious concentrations at 0.5 mg
- 0.05 pmol/10^6 cells = ~5.0x in vitro IC_{50}
  - In vitro WT IC_{50} of ISL-TP is ~0.01 pmol/10^6 cells
  - 0.05 pmol/10^6 cells ISL-TP also covers in vitro IC_{50} for M184I/V

Goal is to maintain concentrations above 0.05 pmol/10^6 cells for the entire duration of implant placement

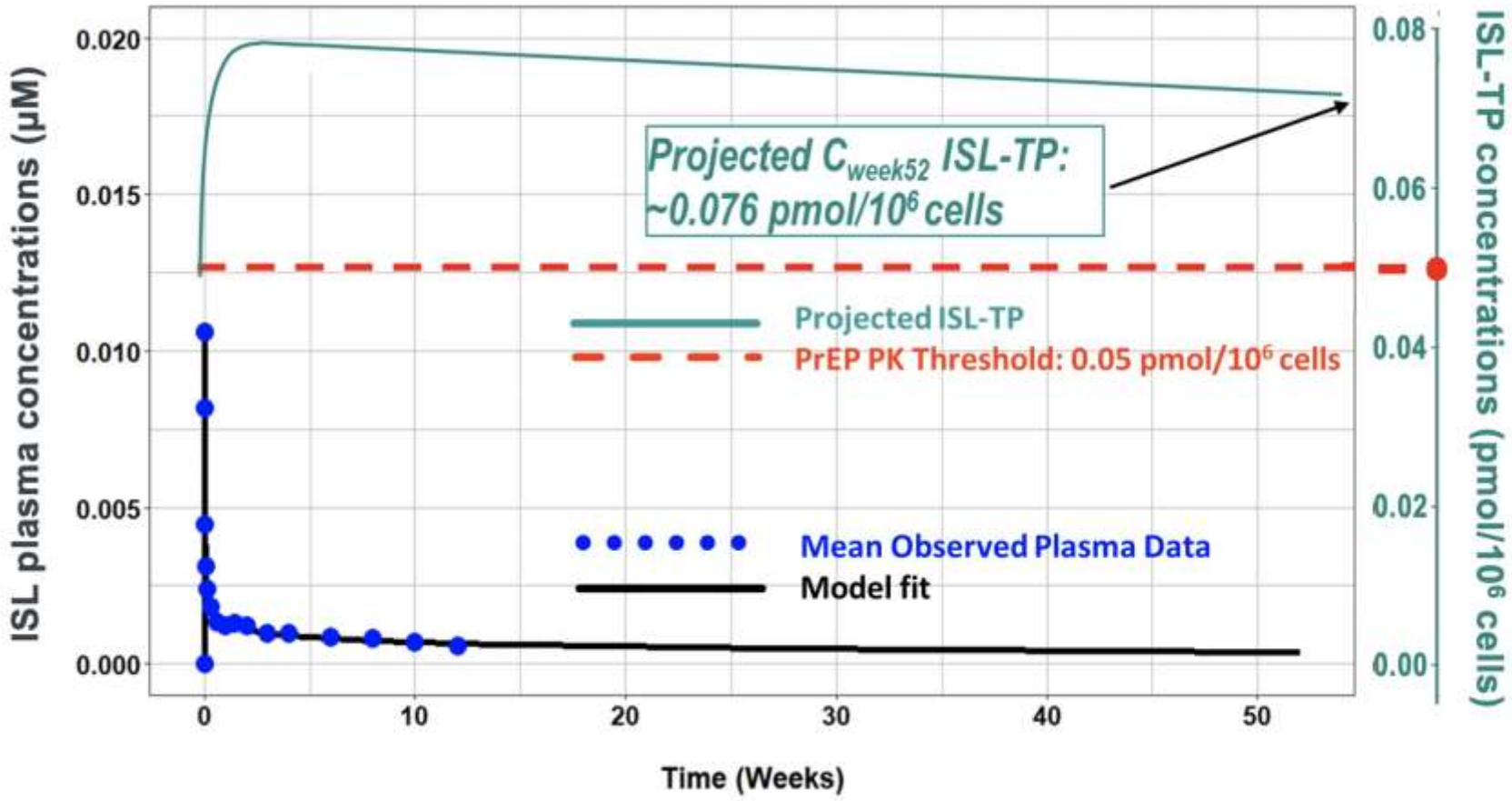


Islatravir prototype similar to Nexplanon



https://www.sfaf.org/collections/beta/islatravir-a-potential-prep-hiv-drug-now-being-tested/

Islatravir levels predicted to last 1 year



Matthews RP, et al. IAS 2019 Mexico City. Abstract TUAC0401LB
http://programme.ias2019.org/Programme/Session/167

Thank you

Edward Jenner, the pioneer of smallpox vaccine, sees off the anti-vaccinators (1868)