New NRT(T)I and NNRTI

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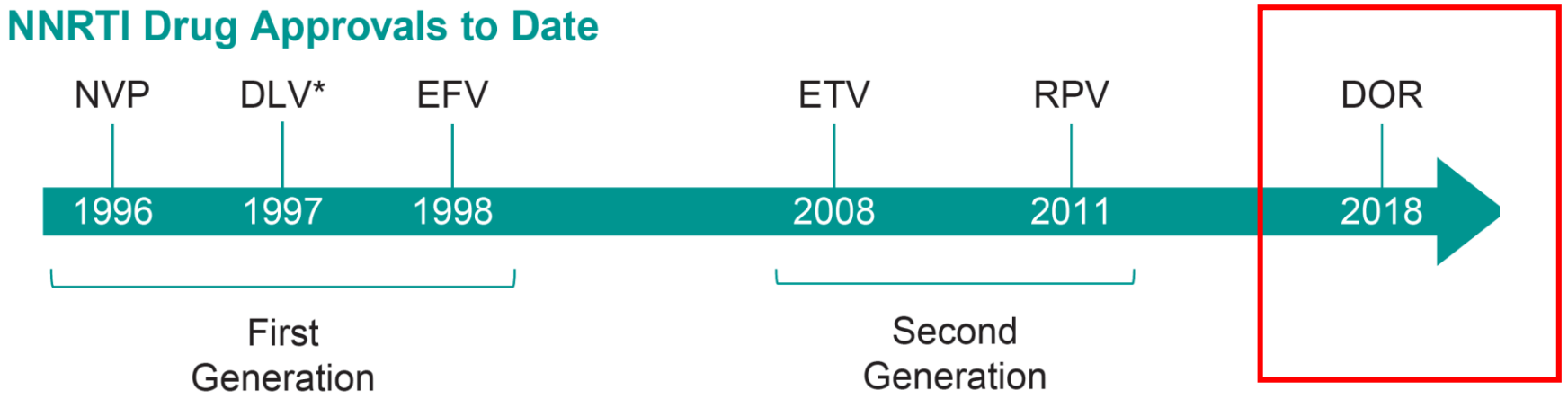
Brief History of NNRTI Class

- Six drugs in this class are currently approved by regulatory authorities (DLV*, EFV, ETR, NVP, RPV and DOR)
- Efavirenz (EFV), the most widely used NNRTI for over a decade, was removed from the preferred list in the US guidelines due to CNS tolerability issues
- Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has recently been approved (August 2018) as a single entity, and as a fixed-dose combination with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) (DOR/3TC/TDF) as once-daily oral treatment for HIV-1 infection in treatment-naïve adults



*Anticipate discontinuation in October 2018.

DOR=doravirine; DVL=delavirdine; EFV=efavirenz; ETR=etravirine; NNRTI=nonnucleoside reverse transcriptase inhibitor; NVP=nevirapine; RPV=rilpivirine.

Abstract #545, Presented at IDWeek; San Francisco, CA; October 3–7, 2018.

Doravirine: A Novel NNRTI

Delstrigo™
doravirine/lamivudine/
tenofovir disoproxil fumarate

Pifeltro™
doravirine
100 mg tablets

Approval Timeline

- US: Pifeltro and Delstrigo (Aug. 30, 2018)
- Canada: Pifeltro (Oct 12, 2018); Delstrigo (Nov. 9, 2018)
- EU: Positive opinion for Pifeltro and Delstrigo (Sept 20, 2019); Pifeltro (Nov. 23, 2018)

Do we really need of a new NNRTI?

PROs

Durability
Tolerability
CNS safety
Metabolic safety
Cost

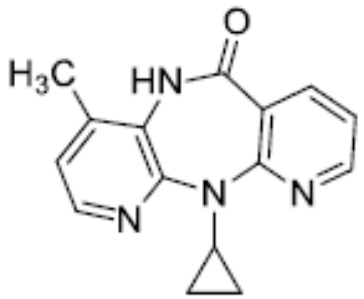
Rilpivirine-based STR is the NNRTI most used

CONs/Concerns

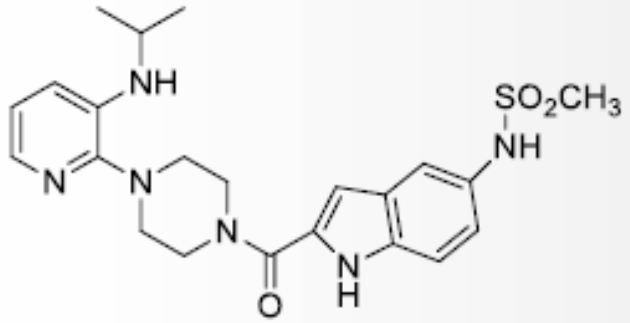
Potency (restriction by VL)
Food effetc
DDIs (gastric ph modifiers)
Low genetic barrier
Poor activty in NNRTI-exp

Approved HIV NNRTIs

Nevirapine (NVP)
(1996)

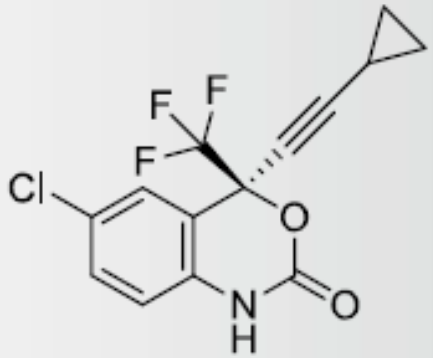


Delavirdine (DLV)
(1997)

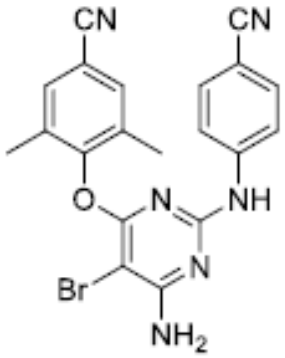


Rarely use

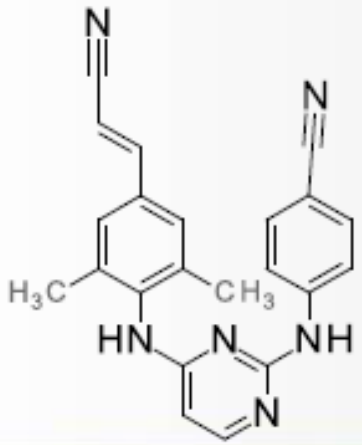
Efavirenz (EFV)
(1998)



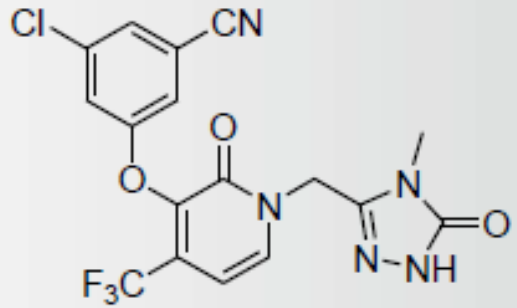
Etravirine (ETR)
(2008)



Rilpivirine (RPV)
(2011)



Doravirine (MK-1439)



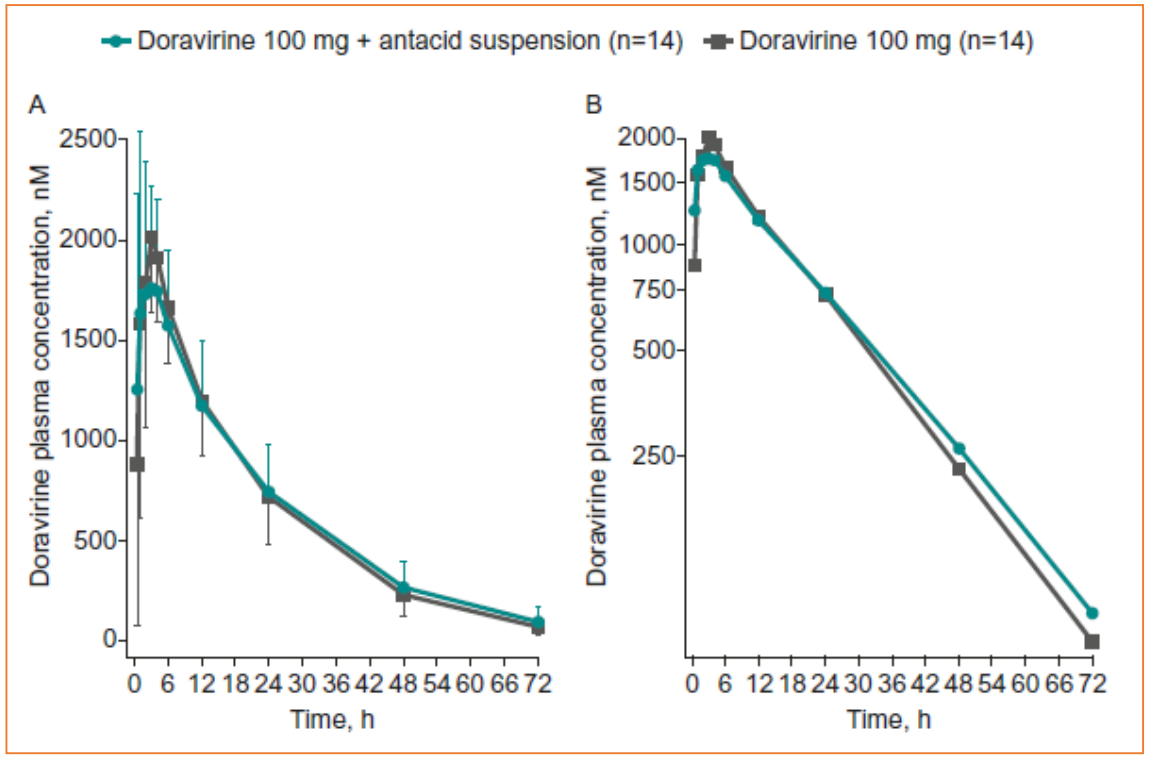
Doravirine Clinical Pharmacokinetics

- **<u>Absorption:</u>**
  - Median Tmax, oral: ~2 hours
  - Food effect: **no meaningful effect** on C_{max} or AUC
  - Gastric pH modifiers: **no meaningful effec**t on C_{max} or AUC

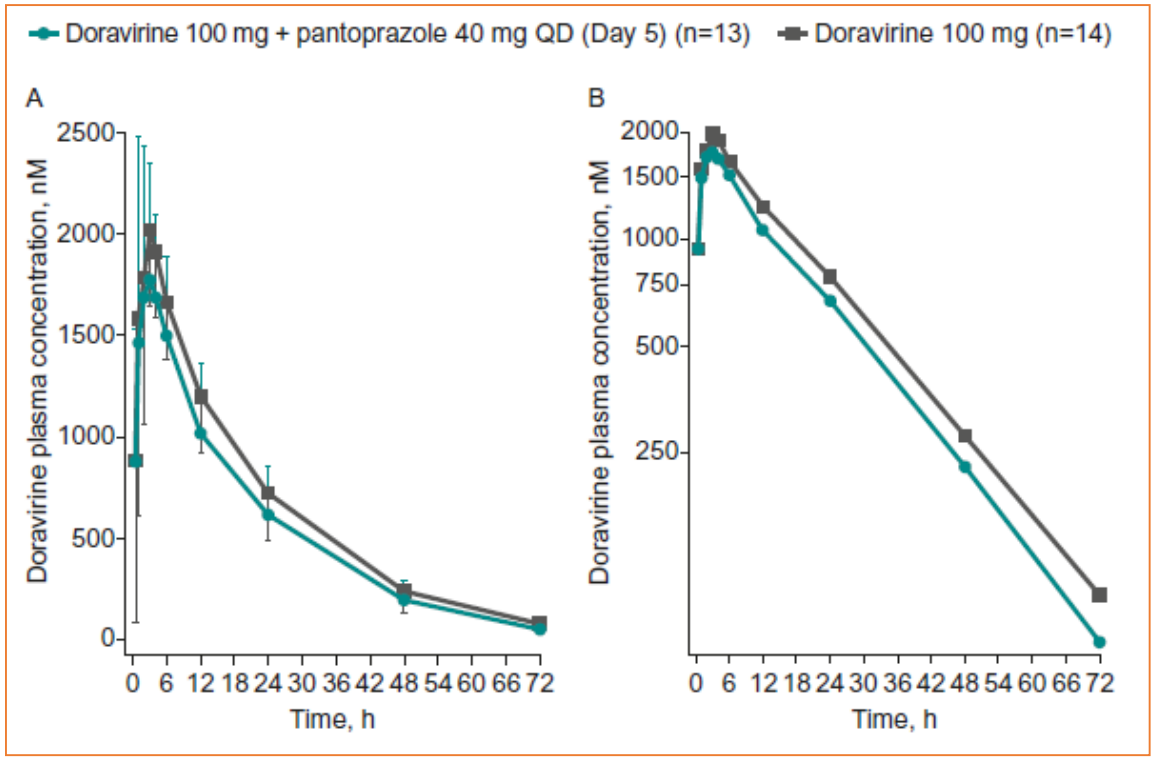
No clinically meaningful effect on DOR Pharmacokinetics when DOR is Coadministered With an *Aluminum/ Magnesium-containing Antacid or Pantoprazole*

Study Design: This was an open-label, 3-period, fixed-sequence study in healthy males and females 31–60 years of age

Single Dose of Doravirine With or Without Single Dose of Aluminum/Magnesium-Containing *Antacid Suspension*



Single Dose of Doravirine With or Without Multiple QD Doses *of Pantoprazole*



Khalilieh S et al. IAS; July 23-26, 2017; Paris, France. Abstract MPOEB0334.

No Effect of Food on DOR Bioavailability: Results from Two Pharmacokinetic Studies in Healthy Subjects

Comparison of fed and fasted pharmacokinetic parameters (GMRs) of single-dose DOR 100 mg administered as a single-entity or fixed dose combination tablet in healthy subjects

Parameter	GMR (90% CI) fed/fasted	
	DOR alone; n=14	DOR FDC; n=14 (fed) and 13 (fasted)
$AUC_{0-\infty}$	1.16 (1.06-1.26)	1.10 (1.01-1.20)
AUC_{0-last}	1.18 (1.08-1.29)	1.10 (1.01-1.20)
C_{max}	1.03 (0.89-1.19)	0.95 (0.80-1.12)
C_{24}	1.36 (1.19-1.55)	1.26 (1.13-1.41)

The $AUC_{0-\infty}$ and C_{24} values were slightly increased for DOR in the fed vs fasted state in both studies; however, the *differences were not considered clinically meaningful*. Additionally, DOR C_{max} remained unchanged after fed and fasted conditions for both formulations.

Behm MO et al. *Clin Drug Investig.* 2017;37(6):571–579.

Doravirine Clinical Pharmacokinetics

- **Absorption:**
  - Median Tmax, oral: ~2 hours
  - Food effect: no meaningful effect on C_{max} or AUC
  - Gastrxci pH modifyers: no meaningful effect on C_{max} or AUC

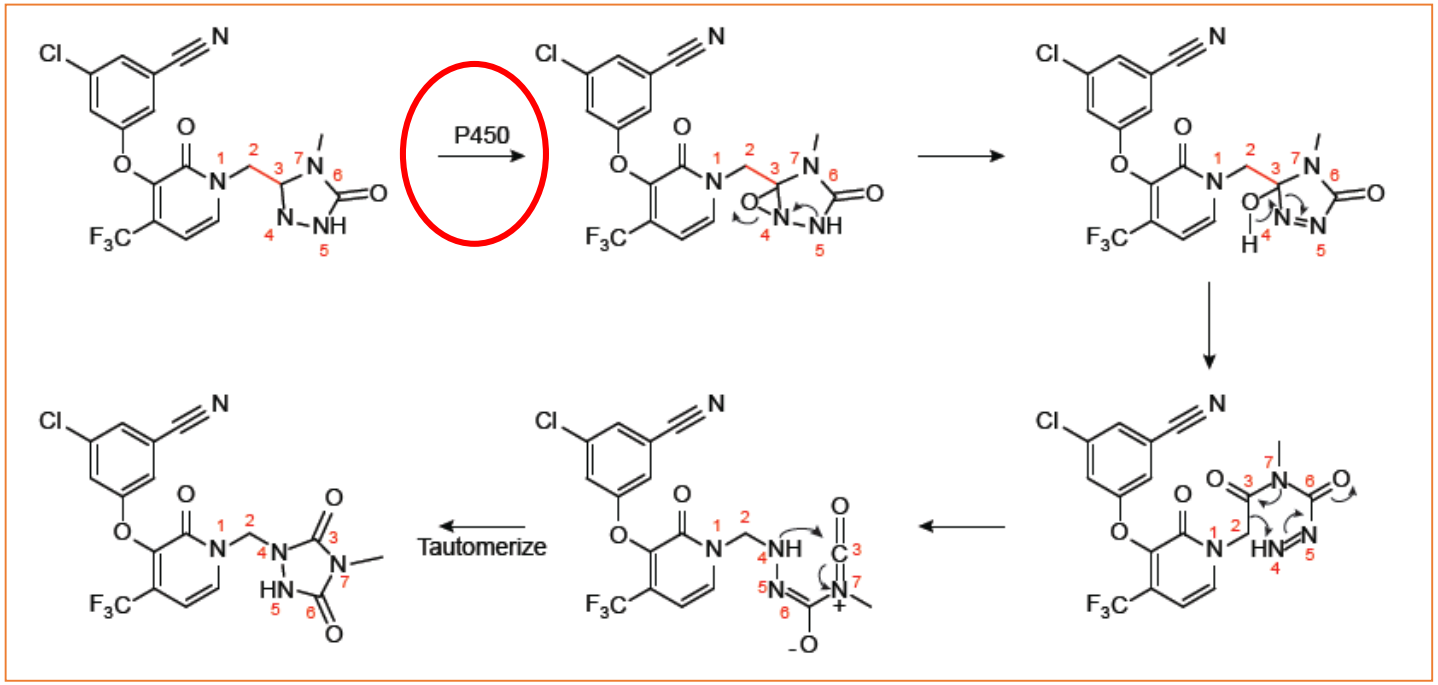
- **Metabolism:**
  - Oxidative metabolism **via CYP3A**

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

Metabolism of DOR by CYP3A4

- Following oral administration, doravirine was the major circulating species. M9 was the major metabolite in plasma and urine

Proposed mechanism for the novel rearrangement reaction that results in the formation of M9



Fillgrove K et al. Presented at ISSX 2016. Abstract P212

Preclinical Pharmacokinetics

Doravirine is not an inhibitor of major CYPs and UGT1A1 at concentrations well above the clinical C_{max} (~3µM)

Reversible inhibition of marker enzyme activities in pooled human liver microsomes

CYP	Probe Reaction	IC_{50} Control Inhibitor (µM)	IC_{50} Doravirine (µM)
1A2	Phenacetin O-Deethylation	0.0074 α-Naphthoflavone	>100 (0%)[†]
2B6	Bupropion Hydroxylation	0.74 Ticlopidine	>100 (2.1 ± 3.4%)
2C8	Amodiaquine N-Deethylation	0.23 Montelukast	>100 (17 ± 6.3%)
2C9	Diclofenac 4-Hydroxylation	0.74 Sulfaphenazole	>100 (28 ± 2.6%)
2C19	S-Mephenytoin 4-Hydroxylation	0.20 Benzylnirvanol	>100 (46 ± 1.9%)
2D6	Dextromethorphan O-Demethylation	0.083 Quinidine	>100 (7.4 ± 1.2%)
3A4	Midazolam 1-Hydroxylation	0.027 Ketoconazole	>100 (0%)
3A4	Testosterone 6β-Hydroxylation	0.022 Ketoconazole	>100 (35 ± 0.52%)
UGT1A1	Estradiol 3-O-Glucuronidation	3.2 Nifedipine	>100

[†]The values in parentheses represent the percent inhibition (mean ± standard deviation) observed at 100µM.

Sanchez R et al. ISSX 2015 Poster.

Risk for interaction of DOR with drug transporters is null or very low

15.1.3. Evaluation of Inhibition of Drug Transporters by DOR

Table 52. Table Effect of DOR on the Activity of Human Uptake and Efflux Transporters

Transporter	IC_{50} (µM)	Maximum Concentration Tested (µM)
BCRP	51±4	75
P-gp	>100 (0%)	100
BSEP	>50 (2%)	50
OATP1B1	39±2	75
OATP1B3	31±4	75
OAT1	>75 (13%)	75
OAT3	16±0.7	75
OCT2	67±9	75
MATE1	>50 (28%)	50
MATE2	>50 (39%)	50

BCRP = breast cancer resistance protein; DOR = doravirine (MK-1439); MATE = multi-antimicrobial extrusion protein; OATP = organic-anion-transporting polypeptide; P-gp = P-glycoprotein

Final Doravirine review, FDA, 2018

DORAVIRINE: POTENTIAL FOR DDIs

- **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

DOR as a Victim Drug

DOR is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of DOR. Coadministration of DOR and drugs that induce CYP3A result in decreased plasma concentrations of DOR. Coadministration of DOR and drugs that inhibit CYP3A result in increased plasma concentrations of DOR.

The table below includes results of DDI studies between DOR and CYP3A inhibitors and CYP3A inducers.

Table 23. Changes in Pharmacokinetic Parameter Values of DOR in the Presence of Coadministered Drug

Coadministered Drug	Regimen of Coadministered Drug	Geometric Mean Ratio (90% CI) of DOR Pharmacokinetics With/Without Coadministered Drug (No Effect=1.00)		
		AUC[1]	C_{max}	C_{24}
Ketoconazole	400 mg QD	3.06 (2.85, 3.29)	1.25 (1.05, 1.49)	2.75 (2.54, 2.98)
Rifampin	600 mg QD	0.12 (0.10, 0.15)	0.43 (0.35, 0.52)	0.03 (0.02, 0.04)
Rifabutin	300 mg QD	0.50 (0.45, 0.55)	0.99 (0.85, 1.15)	0.32 (0.28, 0.35)
Ritonavir[2]	100 mg BID	3.54 (3.04, 4.11)	1.31 (1.17, 1.46)	2.91 (2.33, 3.62)
Efavirenz[3]	600 mg QD[4]	0.38 (0.33, 0.45)	0.65 (0.58, 0.73)	0.15 (0.10, 0.23)
	600 mg QD[5]	0.68 (0.58, 0.80)	0.86 (0.77, 0.97)	0.50 (0.39, 0.64)

AUC = area under the curve; CI = confidence interval; QD = once daily; BID = twice daily; DOR = doravirine

[1] AUC_{inf} for single-dose, $AUC_{0\text{-}24}$ for once daily.

[2] A single DOR 50-mg dose (0.5 times the recommended approved dose) was administered.

[3] Interaction was assessed following the cessation of efavirenz therapy.

[4] The first day following the cessation of efavirenz therapy and starting of DOR 100 mg QD

[5] 14 days following the cessation of efavirenz therapy and DOR 100 mg QD

DORAVIRINE DDIS

Not a perpetrator of DDI

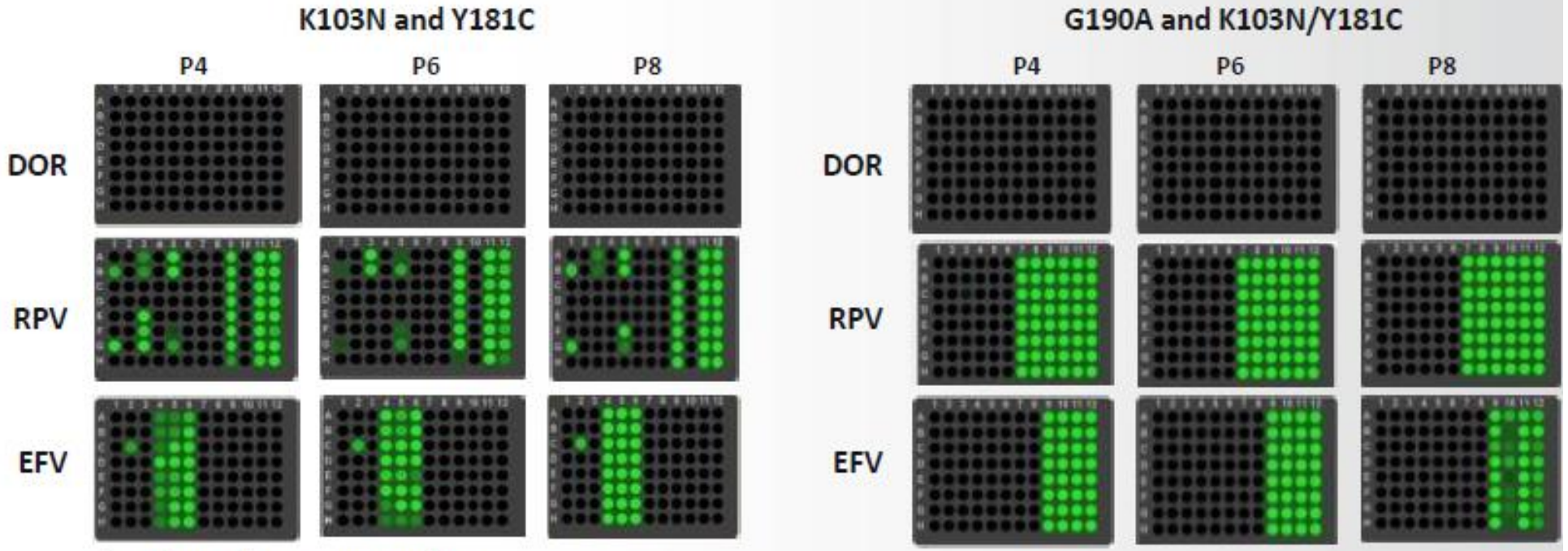
Victim of strong inducers

- AUC < 88% with rifampicin — Avoid
- AUC < 50% with rifabutin — Increase daily dose to 100 mg BD

PK affected by strong inhibitors

- AUC > 254% — No dose adjustment

Resistance Selection with NNRTI Resistance Viruses at Clinically Relevant Drug Concentrations Predicts Clinical Efficacy

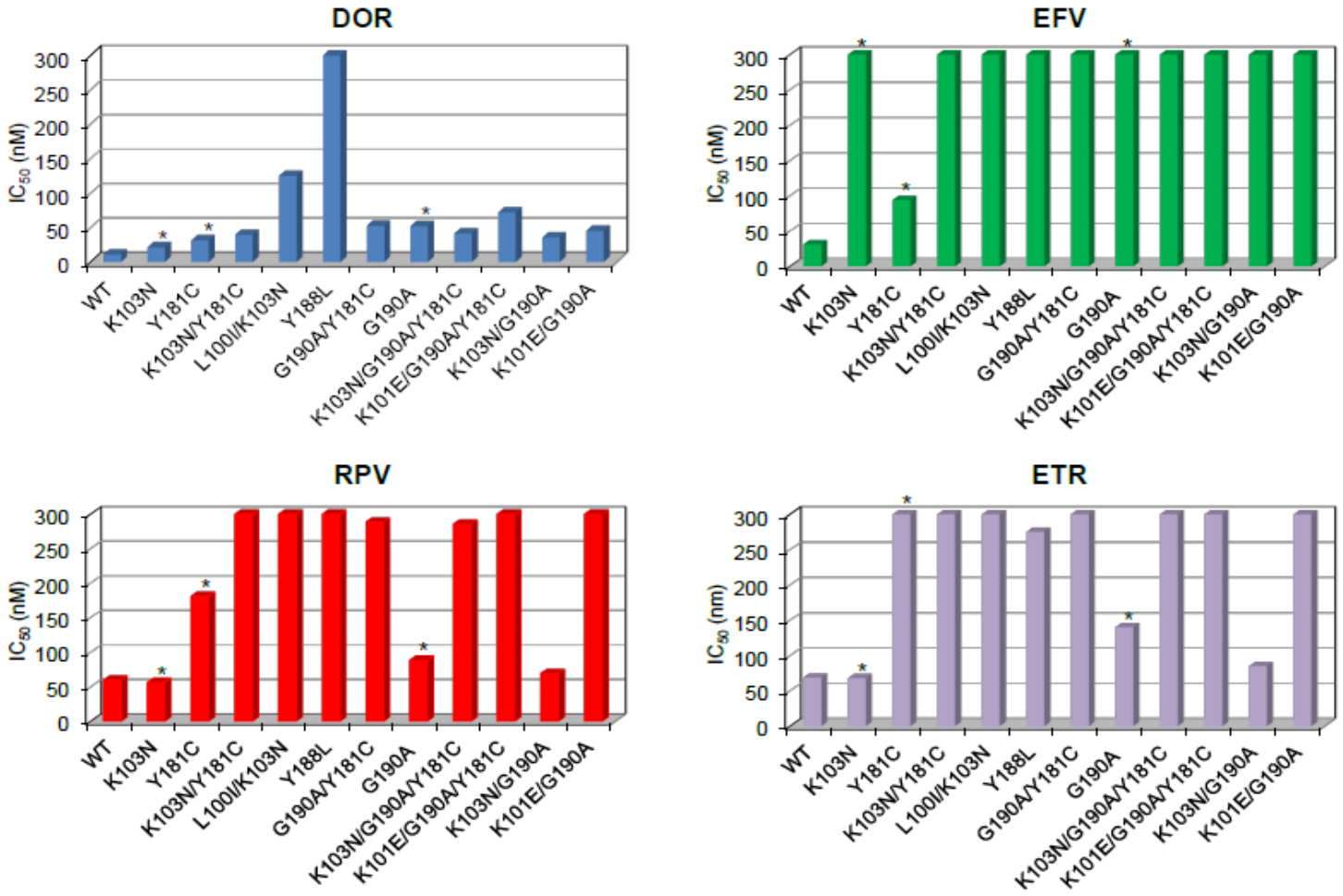


*P indicates the passage number.

- No viral breakthrough was observed for DOR in the selection with K103N, Y181C, G190A, and K103N/Y181C mutants
- Viral breakthrough was detected for RPV and EFV in the selection with K103N, Y181C, and K103N/Y181C mutants (except EFV with Y181C mutant)

Data are Consistent with Clinical Profile of EFV and RPV

Suppression of Prevalent NNRTI-associated Mutants

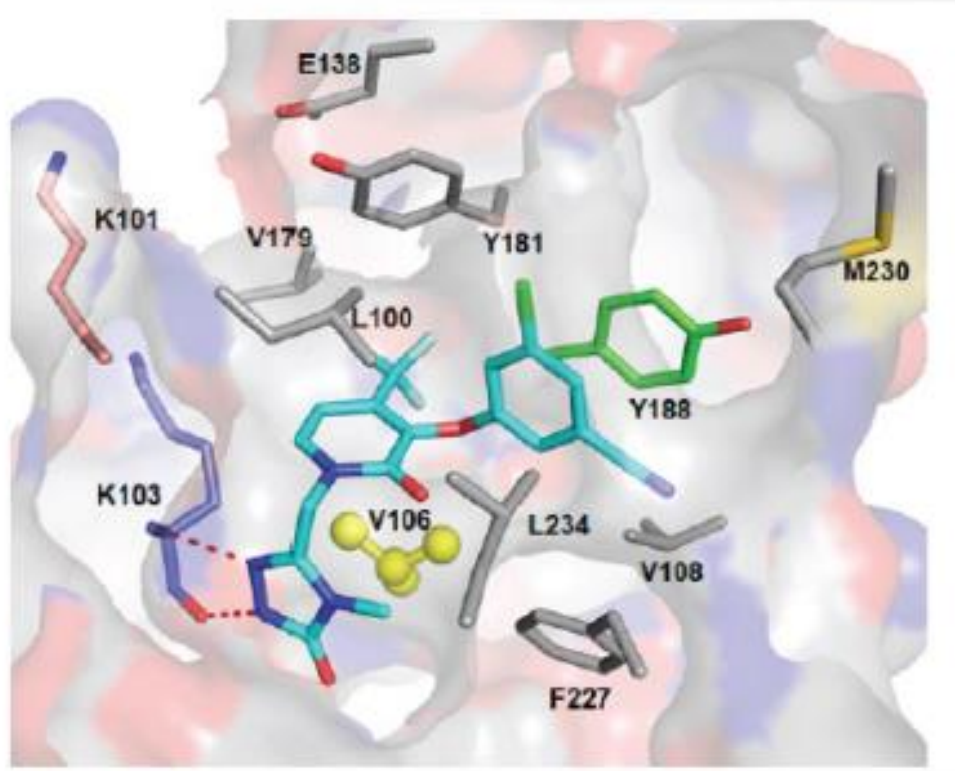


- Doravirine retains antiviral potency against the most prevalent NNRTI-associated resistant mutations

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.

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.

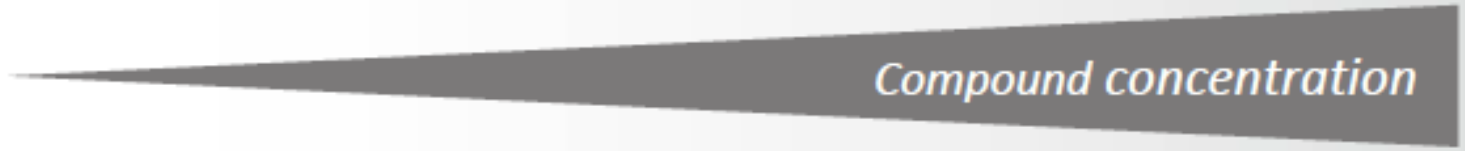
The X-ray Structure of DOR With HIV Reverse Transcriptase (RT) is Consistent the Observed Resistance Profile



Doravirine interacts with backbone of K103 (not side chain)
No interaction with Y181, L100, E138, K101[2]

1. Côté B, Burch JD, Asante-Appiah E, et al. *Bioorg Med Chem Lett*. 2014;24(3):917-922
2. Feng M, Wang D, Grobler JA, et al. *Antimicrob Agents Chemother*. 2015;59(1):590-598.

DOR Resistance Develops via a Distinct Mutation Pathway in In Vitro Resistance Selection Studies



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.

In Vitro Resistance Selection with Doravirine (MK-1439), a Novel Nonnucleoside Reverse Transcriptase Inhibitor with Distinct Mutation Development Pathways

The mutants selected by doravirine are susceptible to RPV and EFV and mutants selected by RPV and EFV, are susceptible to doravirine.

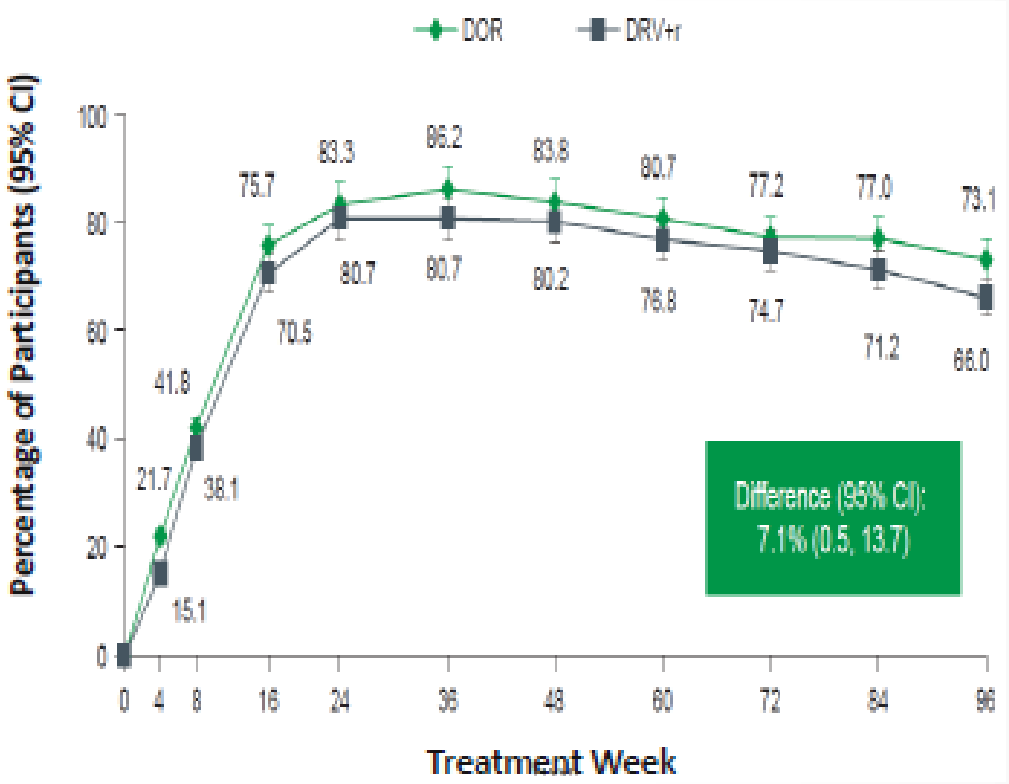
Feng, AAC 2014

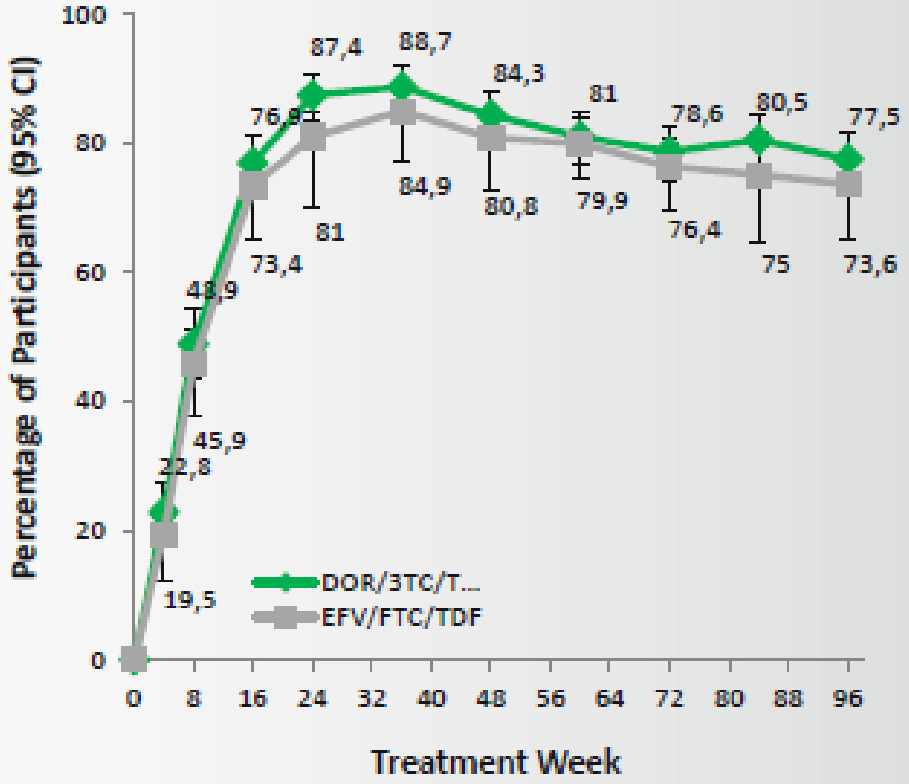
Susceptibility of selected mutant viruses to NNRTIs.

Phase 2 and 3 Clinical Program for DOR and DOR/3TC/TDF

	PN	Comparator / Population
Phase 2	**030** **DRIVE-BEYOND** NCT02629822	DOR/3TC/TDF in TN participants with transmitted resistance to NNRTIs
Phase 3	**018** **DRIVE-FORWARD** **NCT02275780**	**DOR vs. boosted-darunavir (with FTC/TDF or ABC/3TC) in TN adults**
	021 **DRIVE-AHEAD** **NCT02403674**	**DOR/3TC/TDF vs. EFV/FTC/TDF in TN adults**
	024 **DRIVE-SHIFT** NCT02397096	DOR/3TC/TDF in participants switching from other regimens

DOR Ph3 Trials Efficacy at 96 Weeks:
DRIVE-FORWARD (DOR vs DRV) and DRIVE-AHEAD (DOR vs EFV)





DOR shows greater efficacy than DRV at Week 96

DOR/3TC/TDF is non-inferior to EFV/FTC/TDF at Week 96

Proportion with HIV-1 RNA <50 c/mL

Table 21. Summary of Resistance Emergence in Virologic Failures From PN018 DRIVE-FORWARD and PN021 DRIVE-AHEAD

	PN018 DRIVE-FOWARD		PN021 DRIVE-AHEAD	
	DOR N=383	DRV N=383	DOR N=364	EFV N=364
Virologic Failures[1,2]	21/383 (5.5%)	16/383 (4.2%)	22/364 (6%)	21/364 (6%)
Virologic Failures with Resistance Data[3,4]	7/21 (33%)	9/16 (56%)	20/22 (91%)	20/21 (95%)
With Genotypic Resistance Emergence[5]	2/7 (29%)	0/9 (0%)	9/20 (45%)	12/20 (60%)
With Phenotypic Resistance Emergence[5]	1/7 (14%)	0/9 (0%)	6/20 (30%)	12/20 (60%)

DOR = doravirine (MK-1439); DRV = darunavir; EFV = efavirenz.
[1] Confirmed HIV-1 RNA ≥400 copies/mL after response of HIV-1 RNA <50 copies/mL at any time during the study OR discontinued with HIV-1 RNA ≥400 copies/mL at or after week 4.
[2] Number and proportion. Denominator is number of subjects in treatment arm.
[3] Baseline and postbaseline resistance data.
[4] Number and proportion. Denominator is number of subjects with virologic failure.
[5] Number and proportion. Denominator is number of subjects with resistance data.

DOR does not appear to provide an advantage in resistance barrier over other approved NNRTIs.

Final Doravirine review, FDA, 2018

Genotypic and Phenotypic Resistance Observed in DRIVE-FORWARD and DRIVE-AHEAD

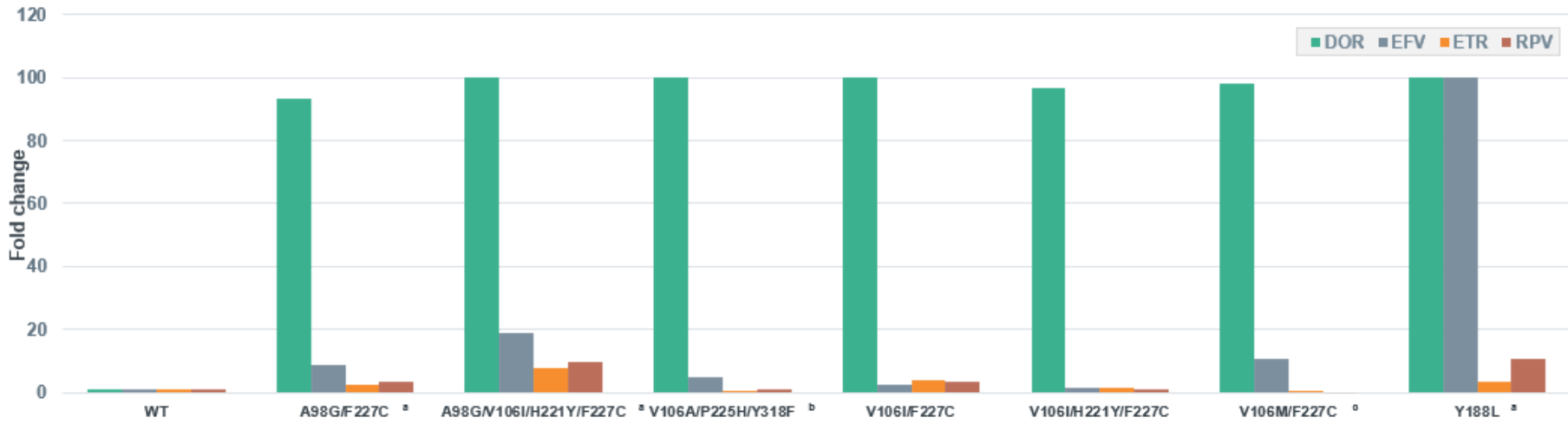
			NNRTI mutation			NRTI mutation			
			Geno	Pheno (fold-change)		Geno	Pheno (fold-change)		
PDVF or D/C	WK[b]	VL (c/mL)	mutation	DOR	EFV	mutation	3TC	FTC	TDF
PDVF	24	7527	A98G/F227C	>93	9.0	M184V	>75	>61	S
PDVF	24	33250	A98G/V106I/H221Y/F227C	>110	19	M184V	>116	>90	S
PDVF	24	80038	V106A/P225H/Y318F	>210	4.8	K65R	12	7.7	1.6
PDVF	24	12691	V106I/F227C	>105	2.5 (S[d])	No	S	S	S
D/C	24	55708	V106I/H221Y/F227C[c]	>96	1.7 (S)	M184V	>100	>57	S
PDVF	24	71727	V106M/F227C	>98	11	M184V/K65R	76	76	0.4
PDVF	48	1256	Y188L	>181	>120	M184V	>103	>83	S

PDVF=protocol-defined virological failure; D/C =Discontinued [b] Weeks at PDVF or D/C; [c] From DRIVE-FORWARD, the rest of mutations were from DRIVE-AHEAD; [d] susceptible

- The combined rate of NNRTI and NRTI mutations from the doravirine arms of DRIVE-FORWARD and DRIVE-AHEAD was 0.9% (7/747).
- The rate from the efavirenz (EFV) arm in DRIVE-AHEAD was 12/363 (3.3%). As shown, most patients with doravirine-associated resistance required ≥1 mutation except for Y188L.
- Among the 7 doravirine-resistant clinical mutants, 5 were susceptible to etravirine.

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.

Susceptibility of DOR-Resistant Clinical Isolates to NNRTIs



		A98G/F227C[a]	A98G/V106I/H221Y/F227C[a]	V106A/P225H/Y318F[b]	V106I/F227C	V106I/H221Y/F227C[b]	V106M/F227C[c]	Y188L[a]
DOR	1.0	>93	>110	>210	>105	>96	>98	>181
EFV	1.0	9.0 (R)	19 (R)	4.8 (R)	2.5 (S)	1.7 (S)	11.0 (R)	>120 (R)
ETR	1.0	2.8 (S)	7.9 (PS)	0.7 (S)	4.0 (PS)	1.5 (S)	0.6 (S)	3.4 (PS)
RPV	1.0	3.8 (R)	10 (R)	1.0 (S)	3.4 (R)	1.2 (S)	0.4 (S)	11 (R)

Performed by Monogram Biosciences

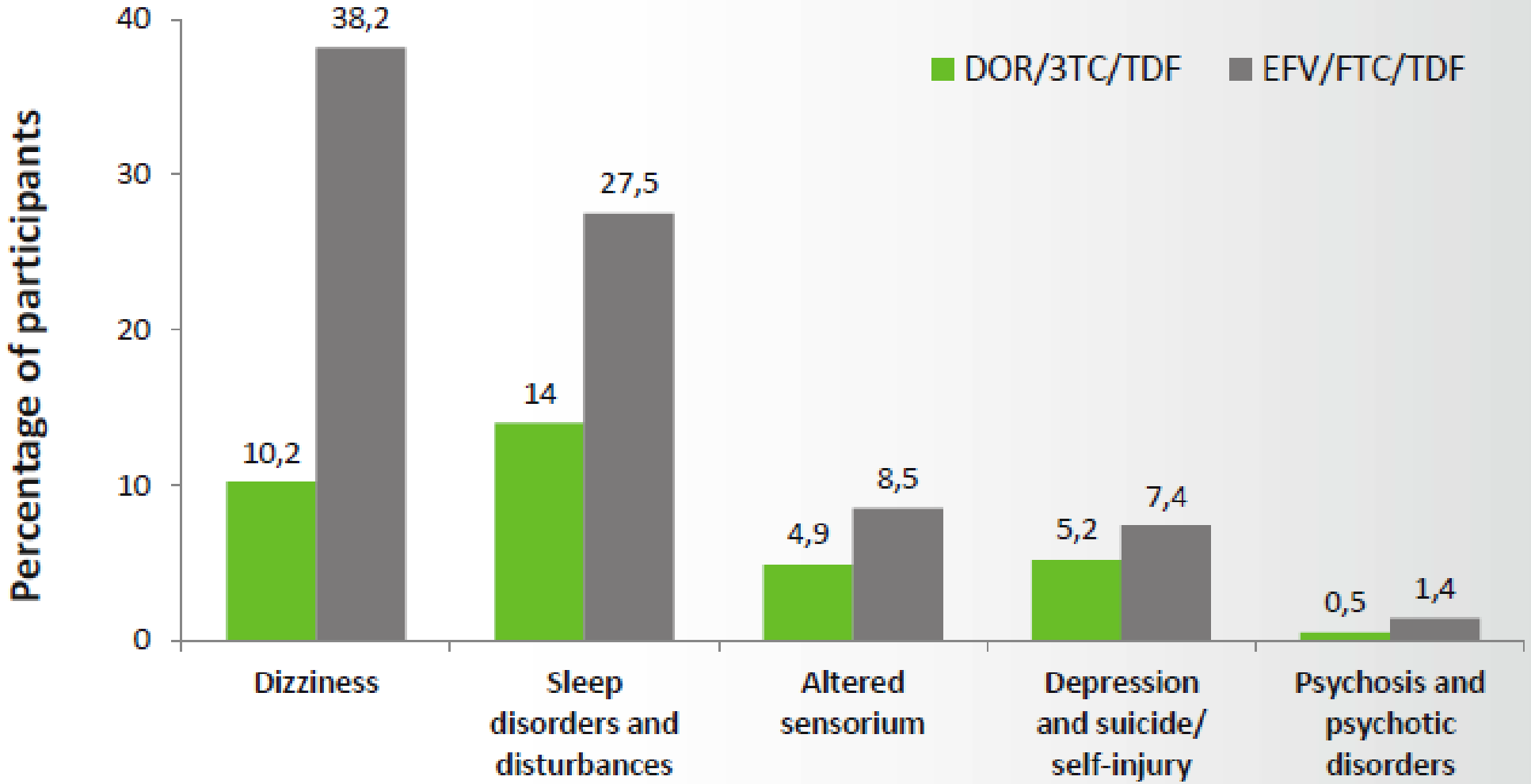
[a] With NRTI mutation M184V; [b] with NRTI K65R mutation; [c] with NRTI M184V/K65R mutation

S=susceptible; PS=partial susceptible; R=resistant.

Fold-change cut-off: EFV=3; RPV= 2; ETR=2.9-10

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.

Neuropsychiatric Adverse Events (Predefined) at Week 96

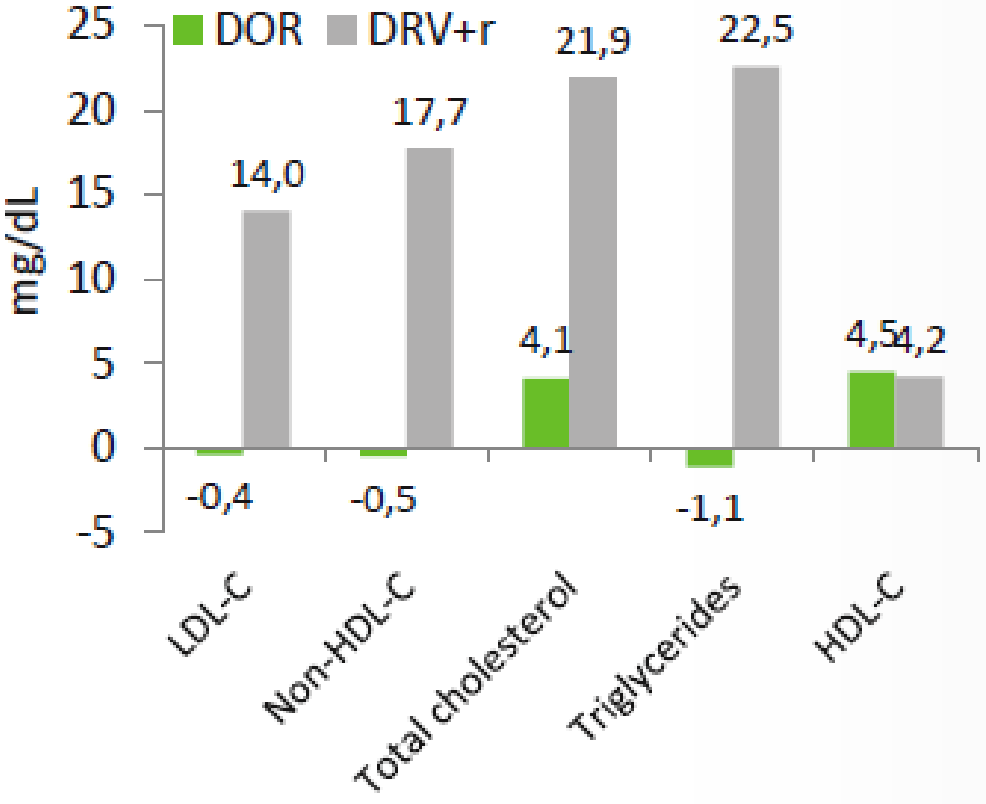


Difference (95% CI)

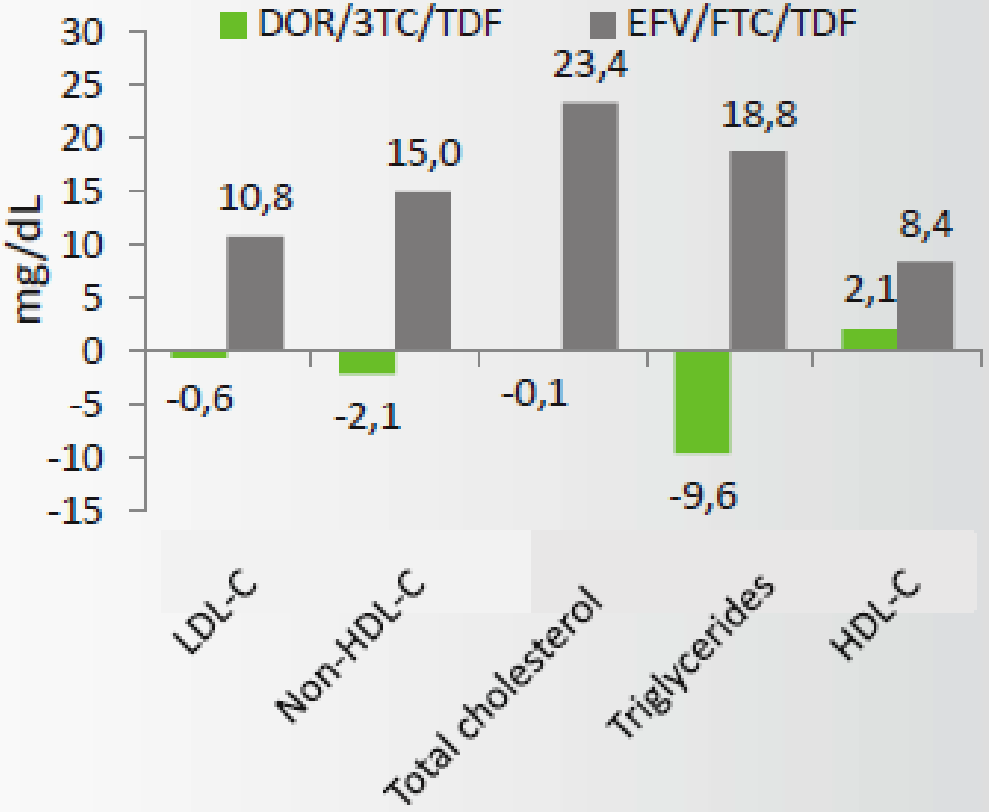
Dizziness	Sleep disorders and disturbances	Altered sensorium	Depression and suicide/ self-injury	Psychosis and psychotic disorders
-28.0 (-33.9, -22.1)	-13.5 (-19.3, -7.6)	-3.6 (-7.4, 0.1)	-2.2 (-5.9, 1.4)	-0.8 (-2.7, 0.8)

At Week 96, DOR Exhibits a More Favorable Lipid Profile

DRIVE-FORWARD (DOR vs DRV)



DRIVE-AHEAD DOR/3TC/TDF vs EFV/FTC/TDF

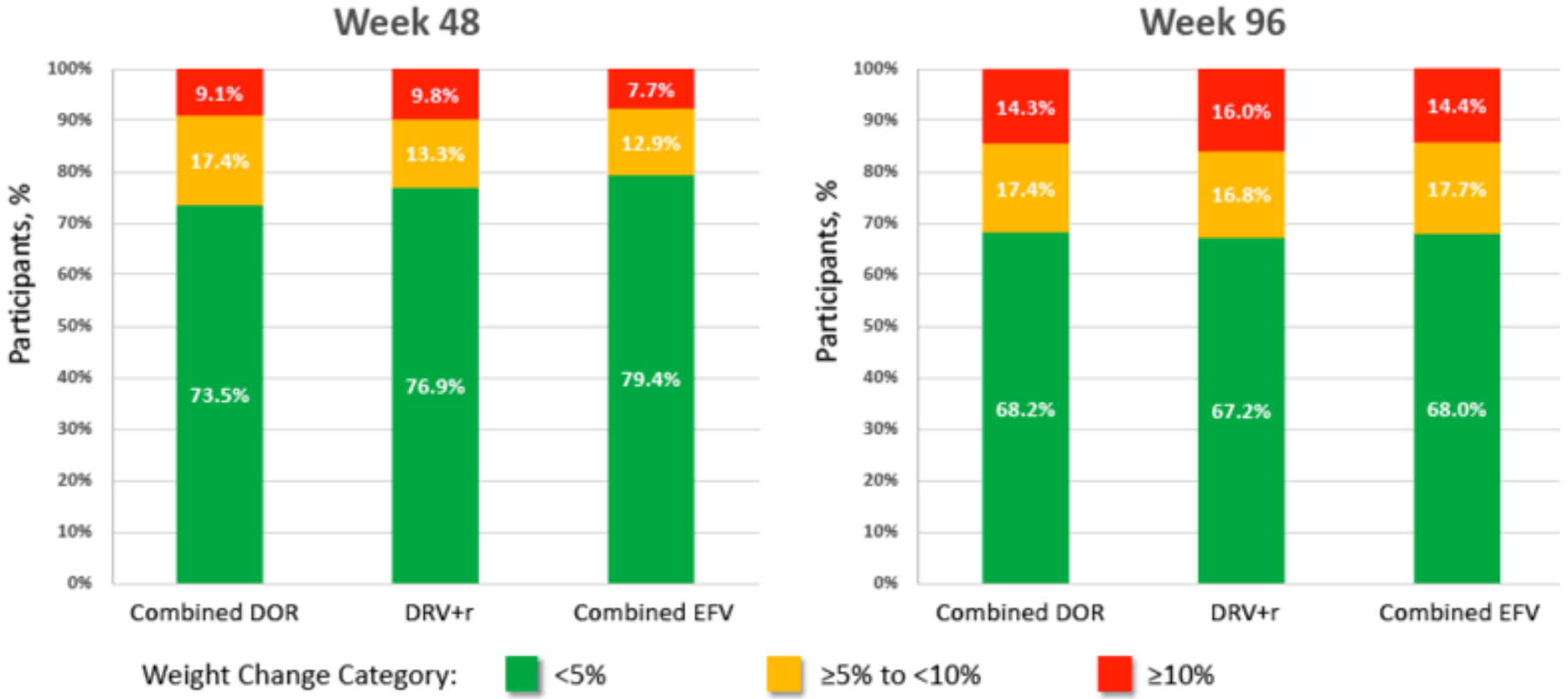


Fasting Lipids, Change from Baseline at Week 96

EFFECT OF DORAVIRINE ON BODY WEIGHT AND BODY MASS INDEX IN TREATMENT NAÏVE ADULTS WITH HIV-1

C. Orkin[1], R. Elion[2], M. Thompson[3], J. Rockstroh[4], Z.J. Xu[5], E.A. Martin[5], C. Hwang[5], P. Sklar[5], F. Alvarez Bognar[5]

Summary of Weight Change Category



DORAVIRINE STRENGHTS

- Few drug interactions, in particular none with acid-reducing agents.
- Can be taken with or without food.
- A more favorable lipid profile, lower incidence of rash, and fewer CNS side effects than efavirenz.
- A novel resistance pathway, with activity against viruses with K103N or Y181C mutations. By contrast, the V106I and F227C mutations selected by doravirine *do not cause in vitro resistance to either rilpivirine or etravirine* — and may induce hypersusceptibility to certain NRTIs.

DORAVIRINE WEAKNESSES

- HIV treatment guidelines now list **integrase inhibitor based regimens as preferred for initial therapy**, and the drug has not been compared to an integrase inhibitor in any clinical trial.

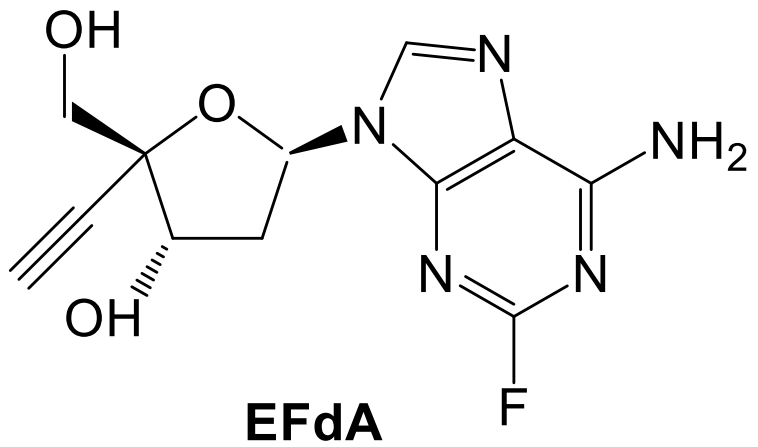
- The single tablet option contains tenofovir disoproxil fumarate, which has more renal and bone toxicity than tenofovir alafenamide.

CLINICAL SCENARIOS FOR DORAVIRINE USE

- Those who can't tolerate integrase inhibitors.
- Someone looking for efavirenz or rilpivirine alternatives within the same drug class, due to concerns over CNS side effects or use of acid-reducing agents, respectively.
- As part of a switch strategy for patients with susceptible virus
- As a cost-saving strategy, depending on listed and negotiated prices — in particular for the single tablet, since the non-doravirine components are generic.
- Doravirine is also under study with the potent and long-acting agent MK-8591 as part of a two-drug strategy. MK-8591 is an NRT**T**I, the second T standing for "translocation".

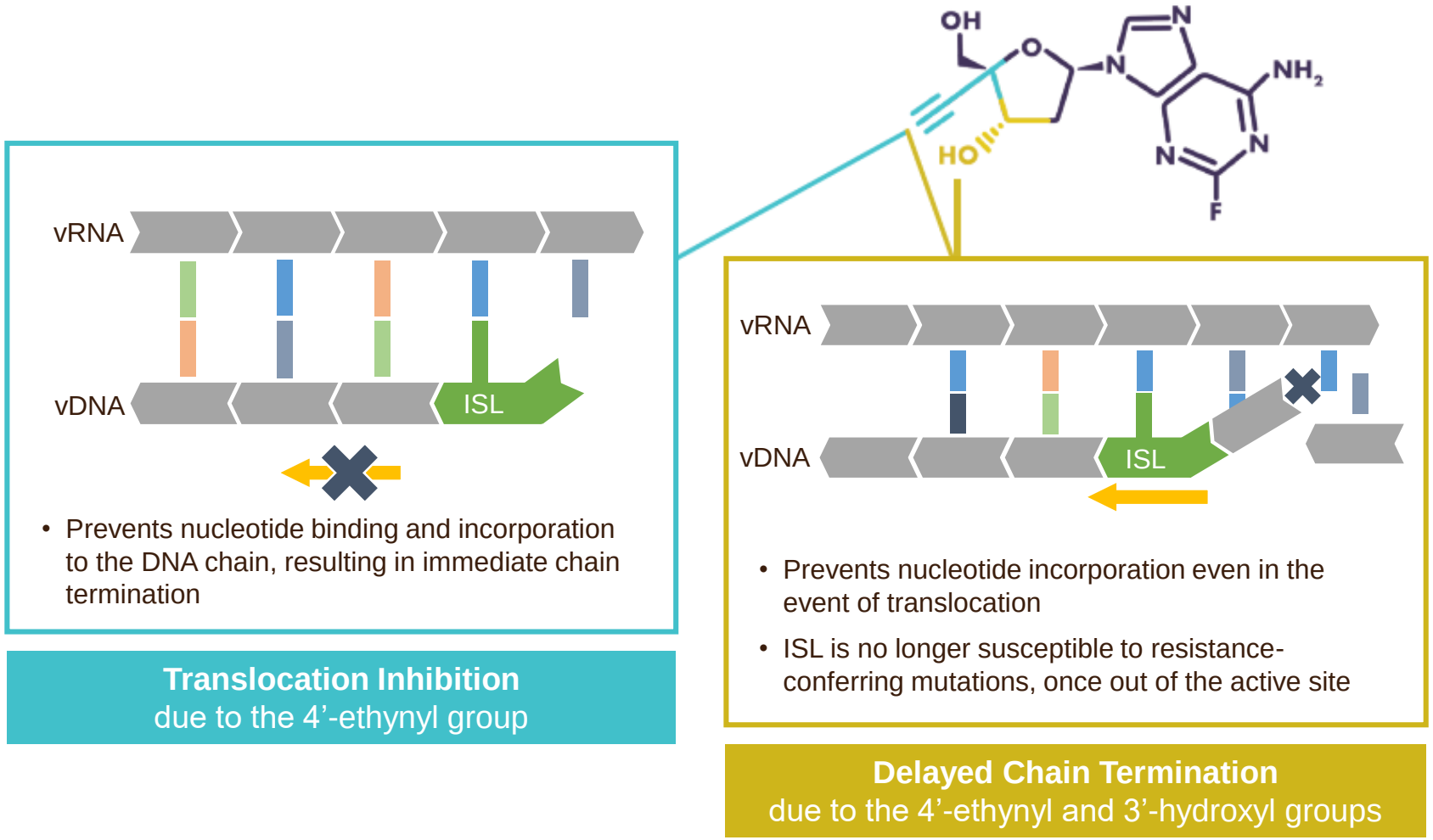
MK-8591: A Novel Nucleoside With a Unique Mechanism of Action

- MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA), licensed from Yamasa
- First-in-class nucleoside reverse transcriptase translocation inhibitor (NRT**T**I)
  - Inhibits HIV replication through multiple mechanisms
  - Potent antiviral activity (PBMC EC_{50} = 0.2 nM) with broad subtype and mutant coverage (HIV-1, HIV-2, MDR strains)
  - Additive with respect to antiviral potency with 15 FDA-approved antiviral agents including lamivudine, emtricitabine, and tenofovir
  - No/weak inhibition of human DNA polymerases α, β, and γ
  - In a Phase 2 clinical trial (NCT03272347) for the treatment of HIV-1 infection with once daily (QD) administration of 0.25 mg, 0.75 mg, or 2.25 mg in combination with doravirine



EFdA

Grobler JA, et al. Long-acting oral and parenteral dosing of MK-8591 for HIV treatment or prophylaxis. Presented at: CROI 2016; February 22-25, 2016; Boston, MA.

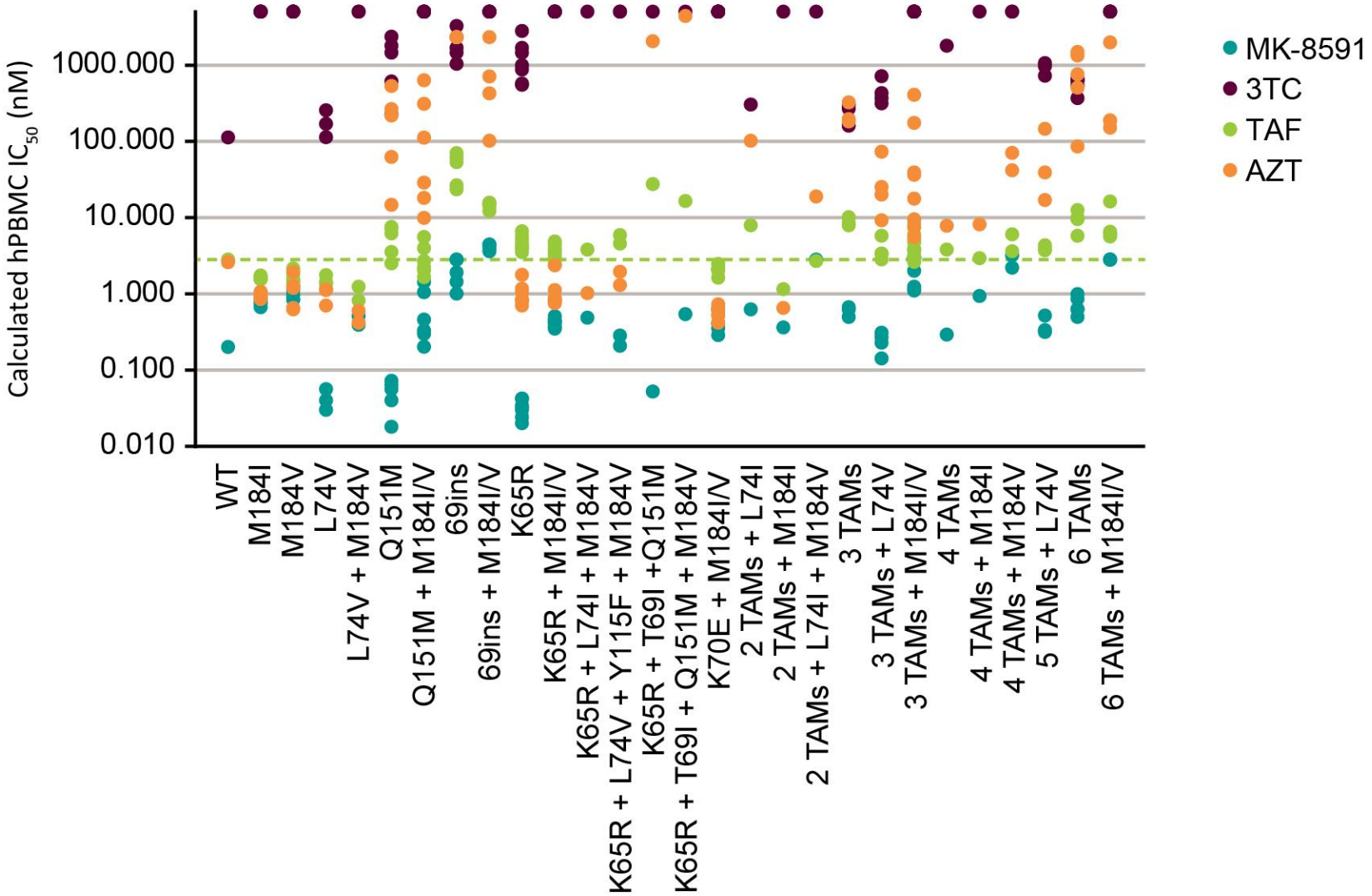


Multiple mechanisms contribute to the high potency of ISL against HIV-1 and drug-resistant variants as well as its high barrier to resistance

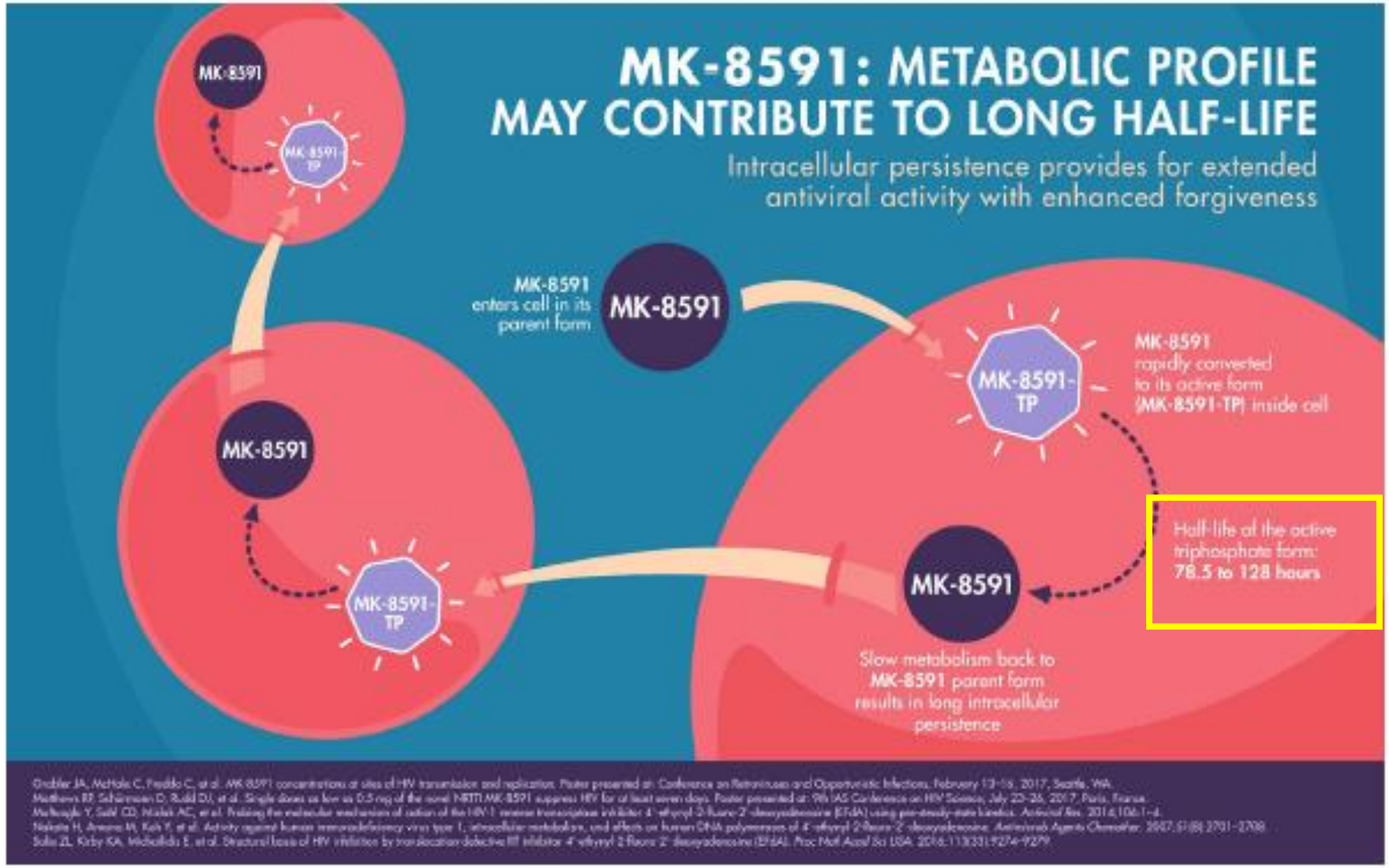
Incorporation of the analog results in either immediate stalling of polymerization or delayed termination after incorporation of the next complementary nucleotide ; the latter mechanism renders the newly synthesized DNA resistant to ATP- or pyrophosphate-mediated drug removal (excision)

Adapted from Molina J-M, et al. Presented at IAS 2019; Oral Presentation #WEAB0402LB and Poster #LBPED46.

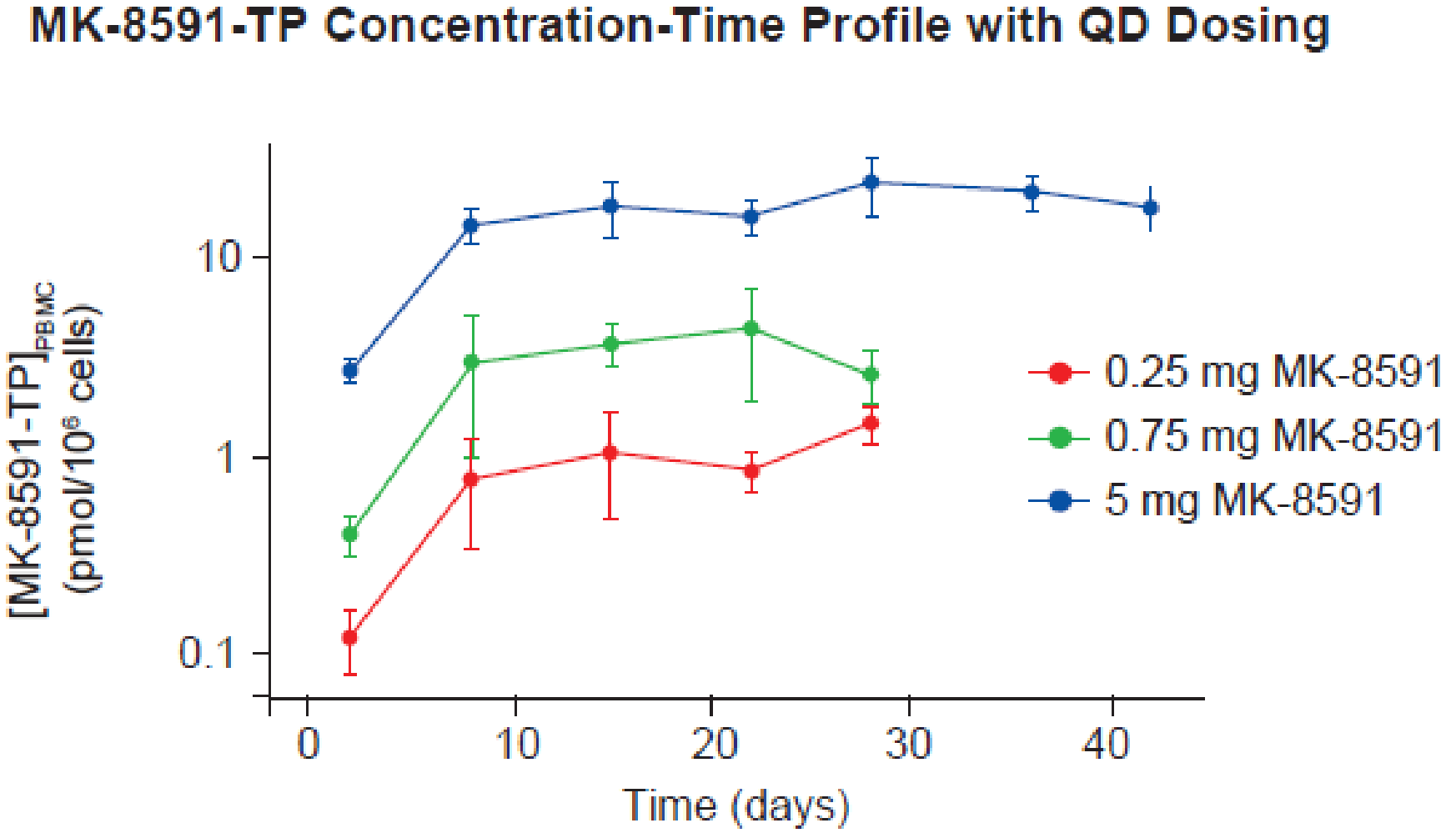
MK-8591 is More Potent Against Most Resistant Mutants Than Approved NRTIs



Antiviral Activity of MK-8591 and NRTIs Requires Intracellular Phosphorylation to Their Active Anabolites

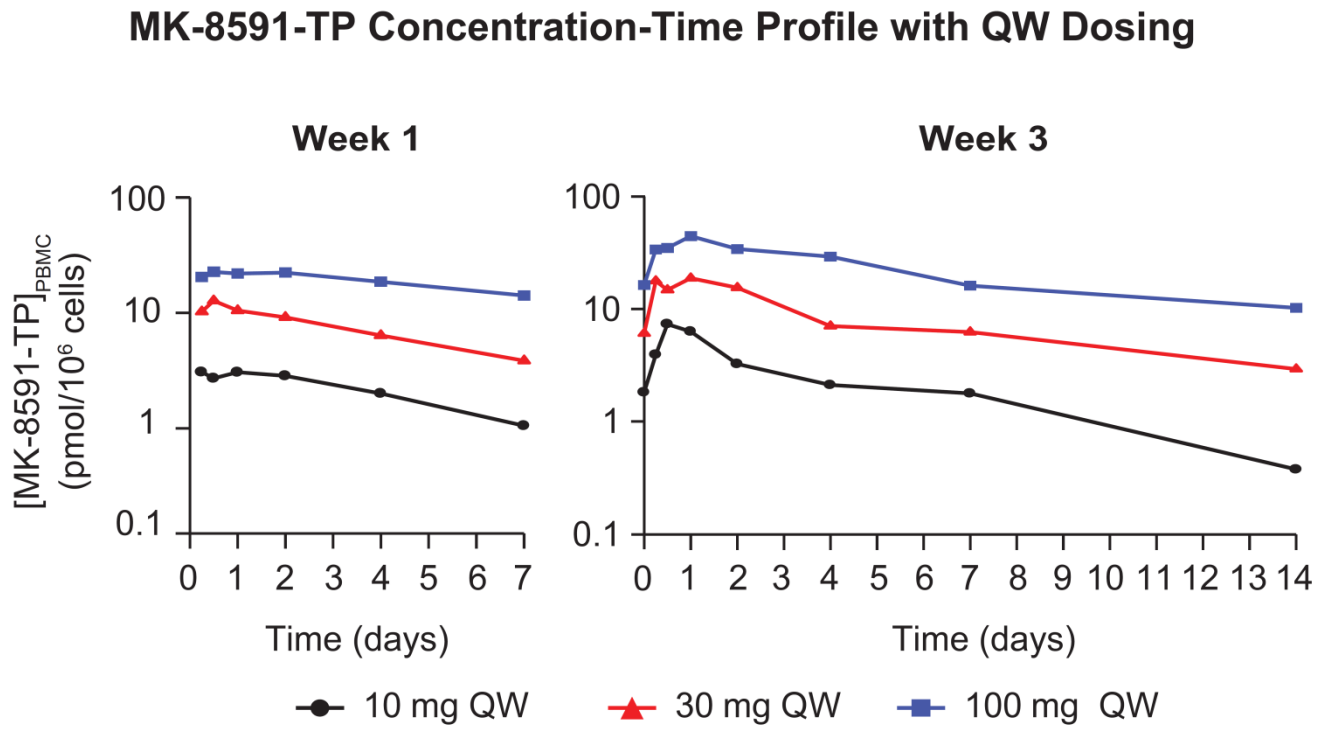


MK-8591-TP Accumulates to High Levels at Low Doses in Humans and Exhibits a Long Intracellular $t_{1/2}$



GROBLER, MK-8591 PK STUDY, CROI 2019

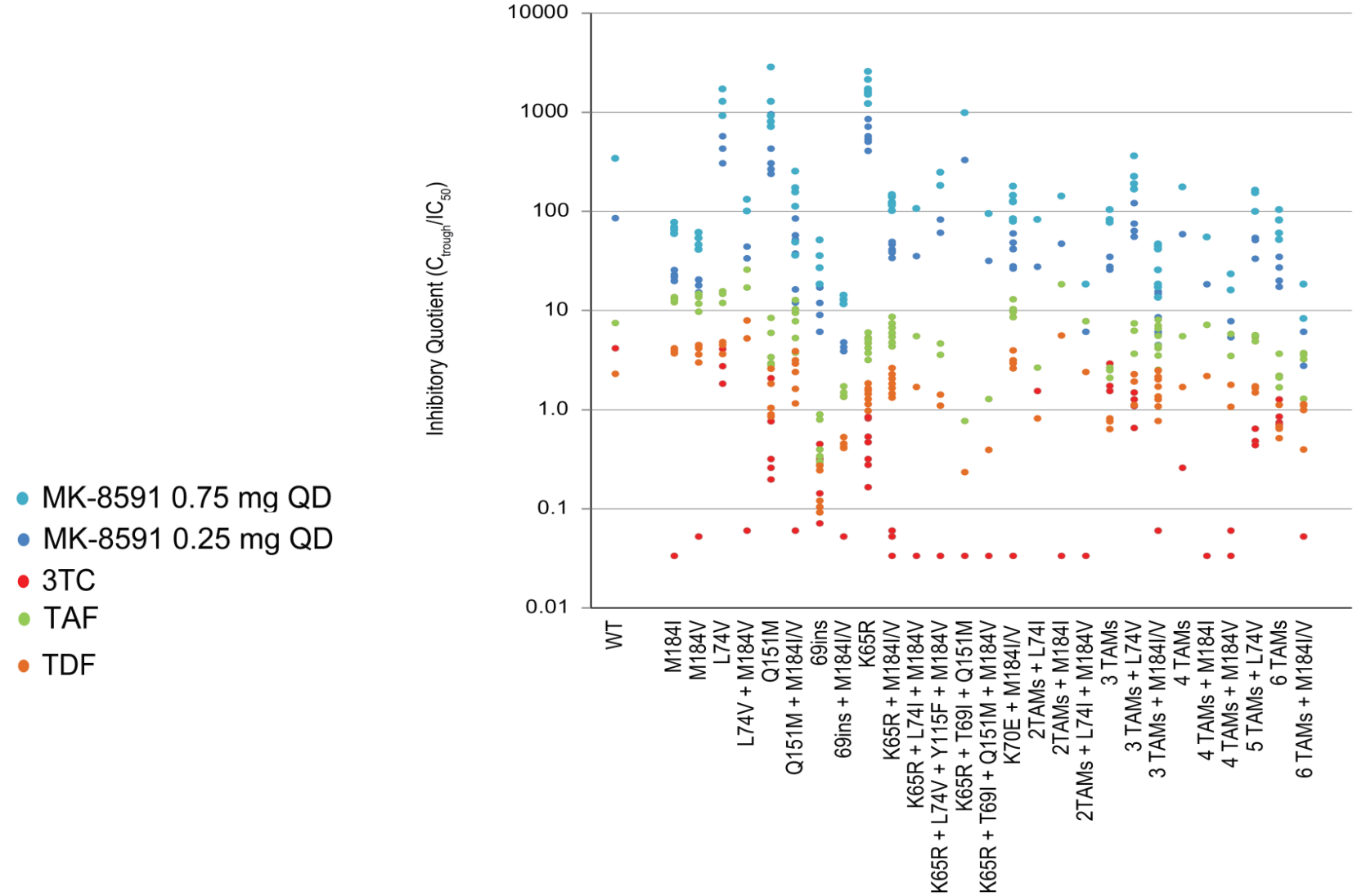
MK-8591-TP Accumulates to High Levels at Low Doses in Humans and Exhibits a Long Intracellular $t_{1/2}$ [2/2]



Matthews, CROI 2018
Grobler et al., CROI 2016

GROBLER, MK-8591 PK STUDY, CROI 2019

Inhibitory Quotients of MK-8591 and NRTIs Against Wild-Type and NRTI-Resistant HIV-1



Islatravir + Doravirine and Lamivudine in Treatment-naïve Adults: 24-week Results

Subjects:

- 121 HIV-1 infected treatment-naïve adults with pre-treatment HIV-1 RNA ≥ 1,000 c/mL and CD4+ T-cell count > 200 cells/mm^3

Methods:

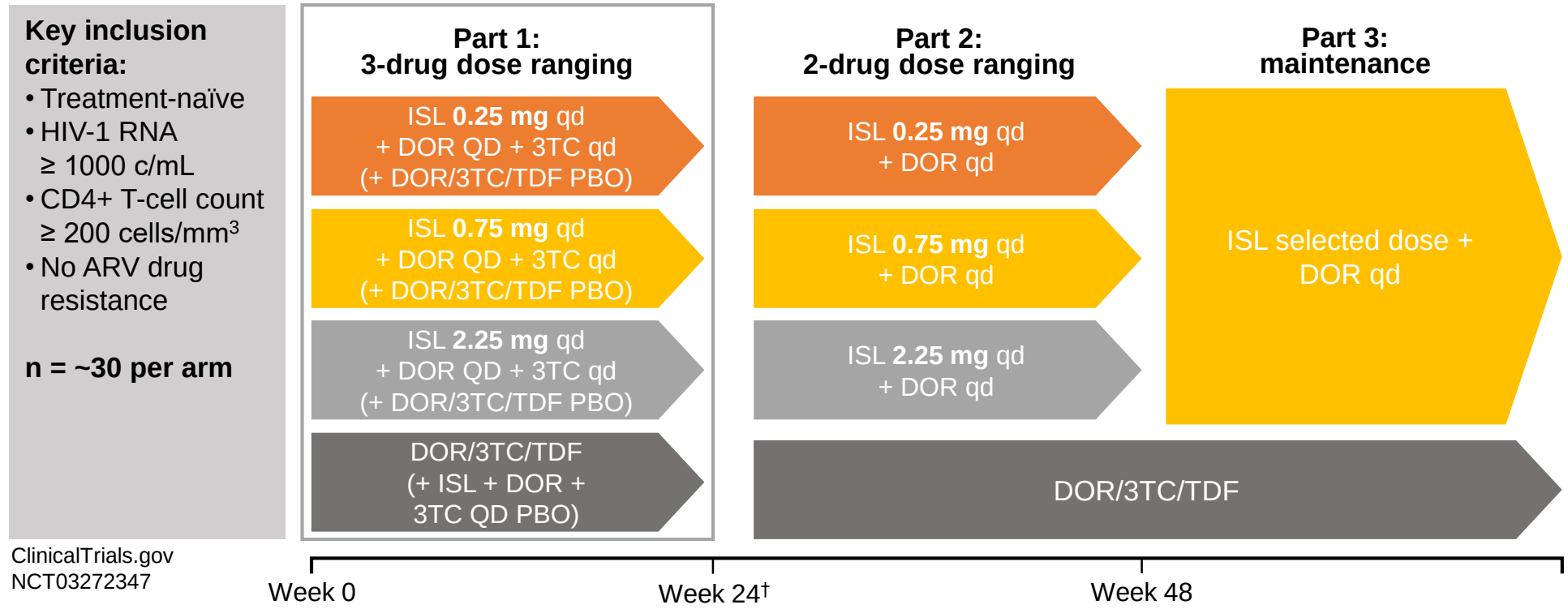
- Subjects randomized to ISL 0.25, 0.75 or 2.25 mg, each + doravirine & lamivudine or DOR/3TC/TDF

Study Design

Key inclusion criteria:

- Treatment-naïve
- HIV-1 RNA ≥ 1000 c/mL
- CD4+ T-cell count ≥ 200 cells/mm^3
- No ARV drug resistance

n = ~30 per arm



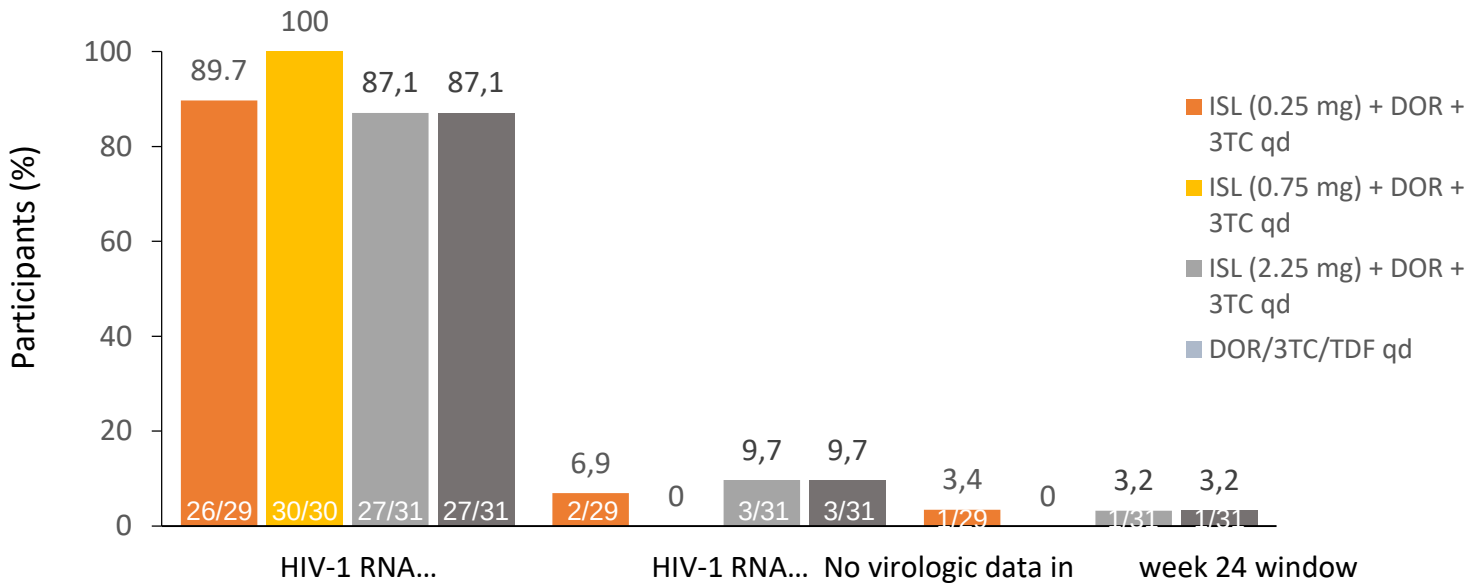
ClinicalTrials.gov
NCT03272347

†After 24 weeks of dosing in Part 1, participants who are virologically suppressed (HIV-1 RNA < 50 c/mL) at Week 20 visit and have not met any viral failure criteria are eligible to switch to Part 2 of the trial at Week 24. Participants with HIV-1 RNA levels ≥ 50 c/mL at Week 20 will remain in Part 1 until the HIC-1 RNA is < 50 c/mL and they have not met any of the viral failure criteria, at which point they transition to part 2 at their next visit.

Adapted from Molina J-M, et al. Presented at IAS 2019; Poster #LBPED46.

Islatravir + Doravirine and Lamivudine in Treatment-naïve Adults: 24-week Results

Virologic Outcomes at Week 24, Snapshot Analysis



Other Findings:

- No protocol-defined virologic failure
- No discontinuations due to AEs
- No dose-related AEs or lab abnormalities

KEY MESSAGES: ISL + DOR + 3TC demonstrated high efficacy and a favorable safety profile in this phase 2 study.

Adapted from Molina J-M, et al. Presented at IAS 2019; Poster #LBPED46.

Islatravir + Doravirine in Treatment-naïve Adults: 48-week Trial

Subjects:

- 123 treatment-naïve patients

Methods:

- For 1st 24 weeks, ISL-treated patients also had DOR + 3TC
- After 24 weeks of treatment, those who achieved VL < 50 c/mL switched to 2-drug regimen of ISL + DOR

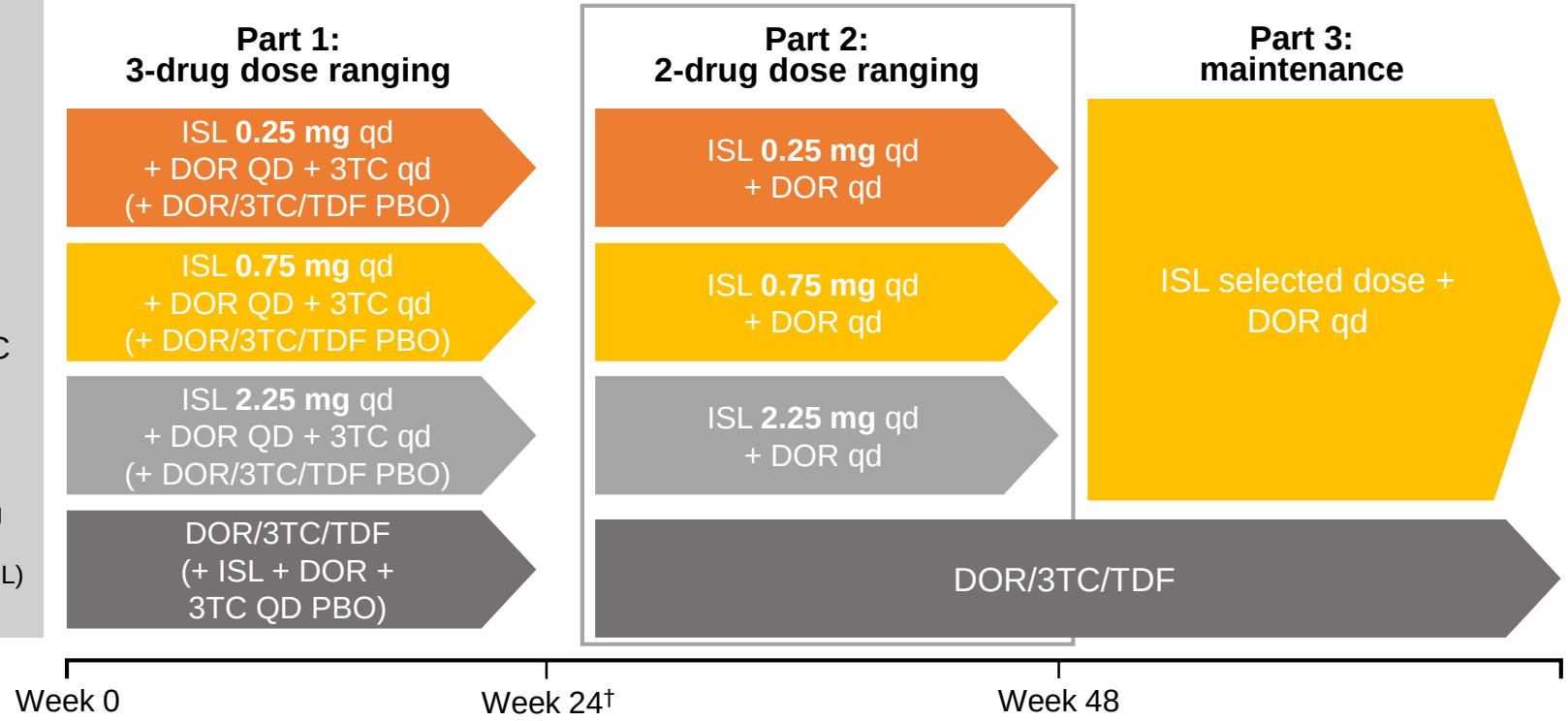
Study Design

Key inclusion criteria:

- Treatment-naïve
- HIV-1 RNA ≥ 1,000 c/mL
- CD4+ T-cell count ≥ 200 cells/mL
- No ARV drug resistance
- No active hepatitis C virus (HCV) co-infection or active HBV co-infection

Stratification by screening HIV-1 RNA level (≤ 100,000 or > 100,000 c/mL)
N= ~30 per arm

ClinicalTrials.gov
NCT03272347



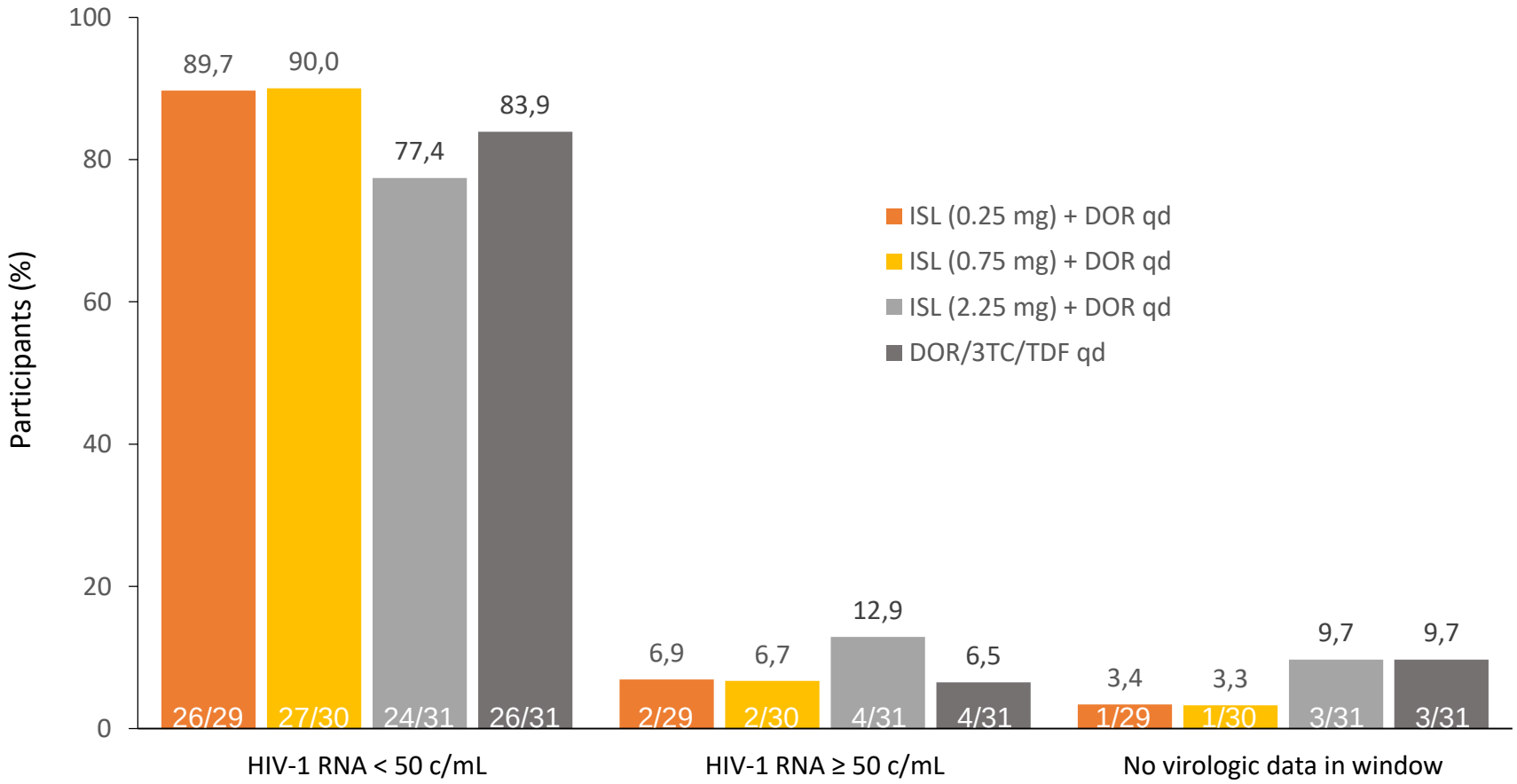
†After 24 weeks of dosing in Part 1, participants who are virologically suppressed (HIV-1 RNA < 50 c/mL) at Week 20 visit and have not met any viral failure criteria are eligible to switch to Part 2 of the trial at Week 24. Participants with HIV-1 RNA levels ≥ 50 c/mL at Week 20 will remain in Part 1 until the HIC-1 RNA is < 50 c/mL and they have not met any of the viral failure criteria, at which point they transition to part 2 at their next visit.

Continued on next slide→

Adapted from Molina J-M, et al. Presented at IAS 2019; Oral Presentation #WEAB0402LB.

Islatravir + Doravirine in Treatment-naïve Adults: 48-week Trial (cont'd)

Virologic Outcomes at Week 48, Snapshot Analysis



- All participants with protocol-defined virologic failure had VL < 80 c/mL at 48 weeks
- No participants met the criteria for resistance testing

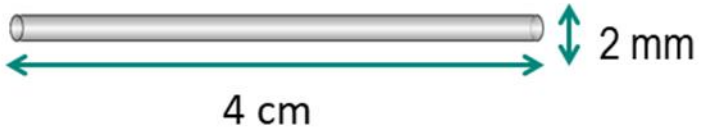
Adapted from Molina J-M, et al. Presented at IAS 2019; Oral Presentation #WEAB0402LB.

ISLATRAVIR Implant design similar to Nexplanon®

- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator

- Initial trial uses prototype implant

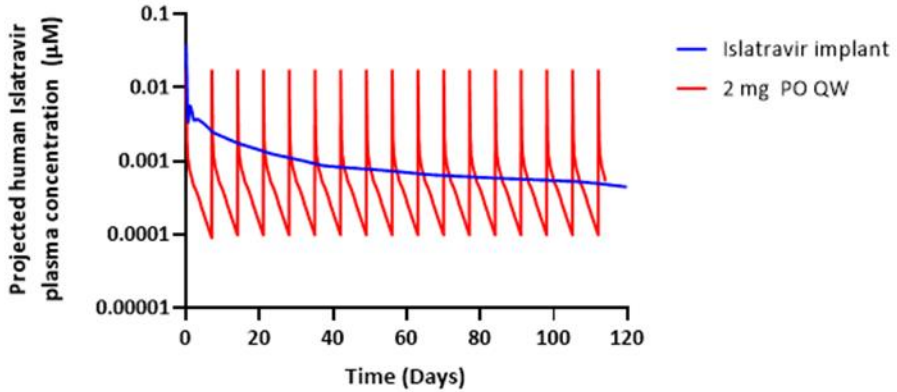
Polymer + **ISL**



Nexplanon®

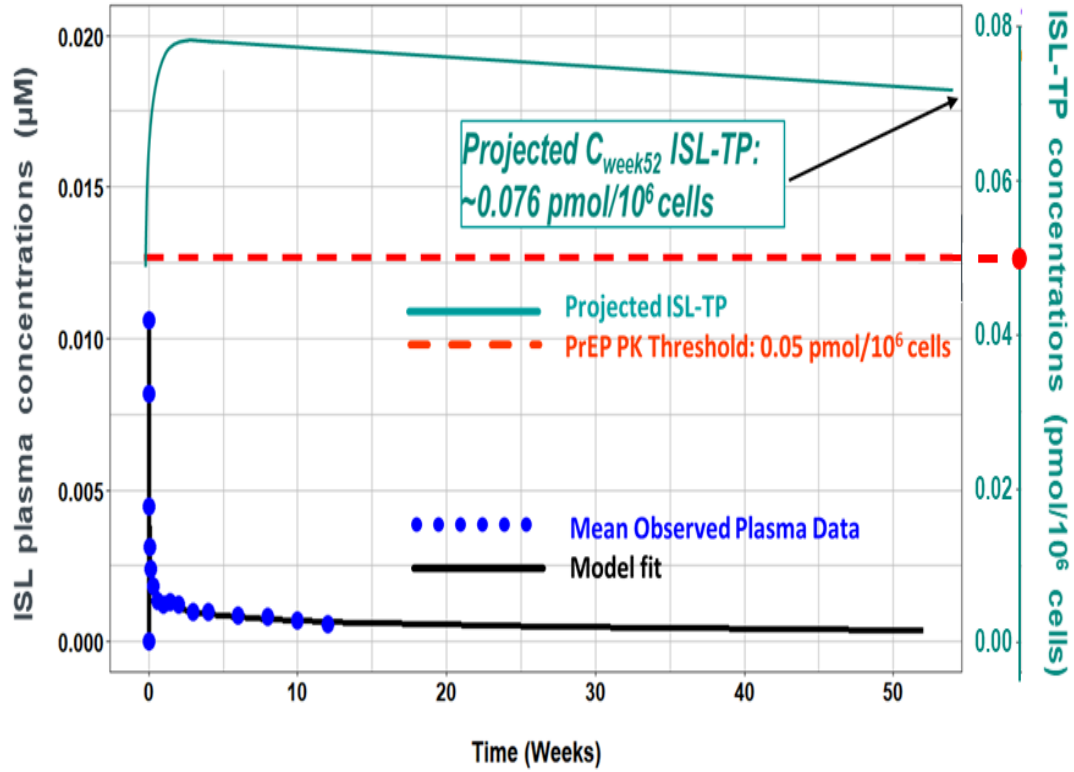
XRCT of ISL implant

Simulated Human PK Profiles



R. Matthews IAS 2019.

62mg Implant projected lead to concentrations above threshold for at least 12 months



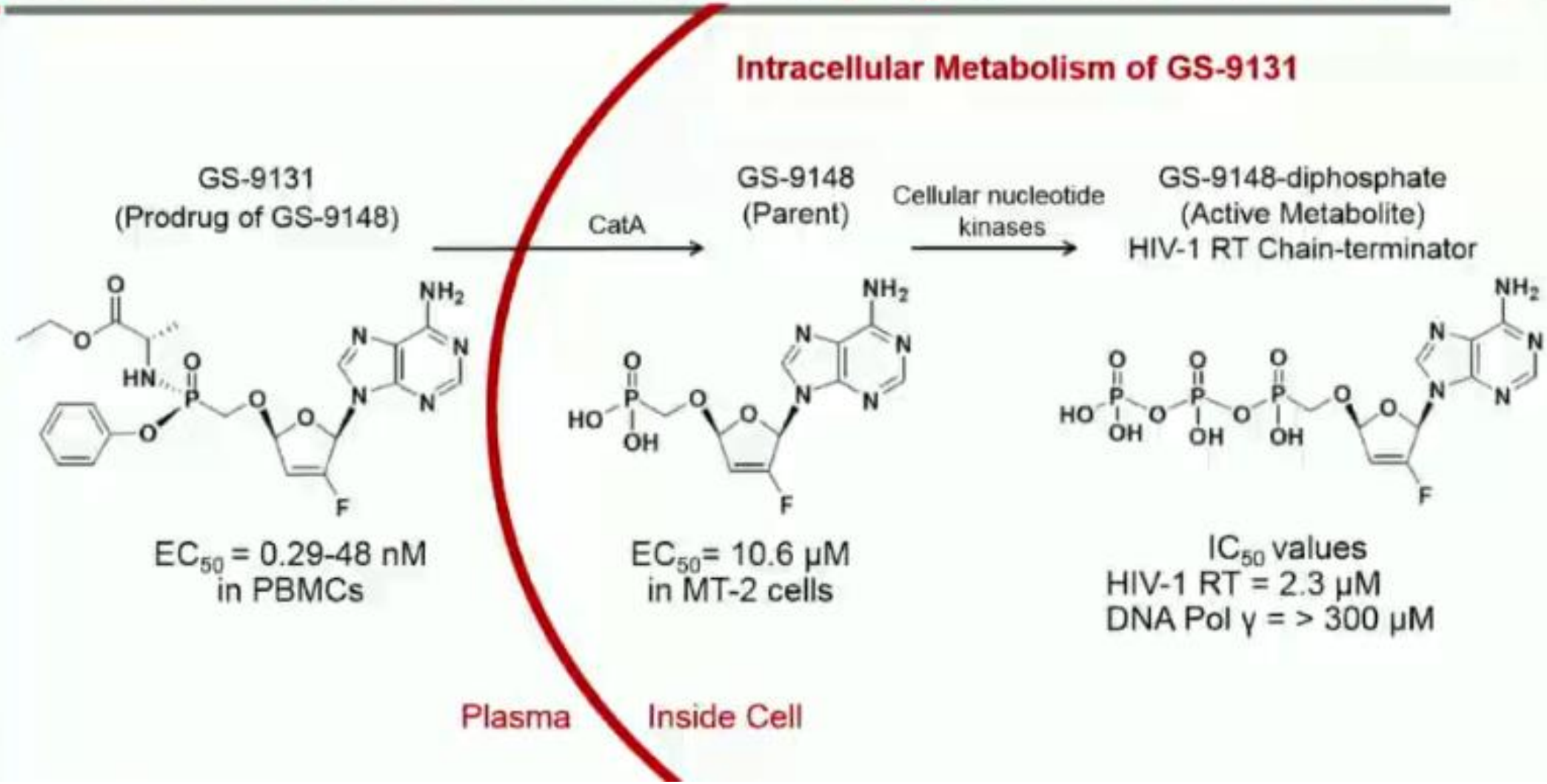
- 62 mg implant will continue to release through 52 weeks
- ISL-TP should be above threshold (0.05 pmol/10^6 cells) for >12 months
  - Projected concentration at 12 months: **0.076 pmol/10^6 cells**
  - Projected time at which concentration falls below 0.05 pmol/10^6 cells: 68-70 weeks (**~16 months**)

- ISL protype implants were generally well-tolerated, with no discontinuations due to an AE and no severe implant-related AEs
- No laboratory or other signs of systemic reactions
- Local tolerability (erythema, induration) generally mild and possibly dose dependent
- Both implants (54 and 62 mg) had concentrations above PK threshold at 12 weeks
- 62 mg implant projected to be well above threshold at 12 months and likely for several months beyond

Supports potential of the ISL implant as a once yearly PrEP option

R. Matthews IAS 2019.

GS-9131 is a Novel NRTI with Activity Against NRTI-Resistant HIV-1



GS-9131 Maintains Activity Against HIV-1 with NRTI Resistance

NRTI Mutation	Susceptibility of HIV-1 to NRTIs							
	GS-9131	GS-9148	TFV	FTC	ABC	ddI	ZDV	d4T
K65R								
M184V								
L74V								
K65R+M184V								
K70E+M184V								
L74V+M184V								
4-TAM (4Y)								
4-TAM (4F)								
4-TAM (4Y)+M184V								
6 TAMs								
6TAMs+M184V								
T69-insertion+4TAMs								
Q151M								
Q151M Complex								
Q151M Complex+M184V								

Green: FC < lower cut-off or <2.5 if not defined
Yellow: FC ≥ lower cut-off < upper cutoff
Red: FC ≥ upper cut-off or 10-fold if not defined

Thanks

Giovanni Di Perri
Andrea Calcagno
Antonio D’Avolio
Micol Ferrara
Nicola Forni
Amedeo de Nicolò
Chiara Carceri
Alice Trentalange
Chiara Polifroni
Alice Ianniello

Cristina Tettoni
Letizia Marinaro
Gloria Palazzo
Alessandro Lazzaro
Veronica Pirriatiore
Roberto Angilletta
Maurizio Milesi
Jessica Cusato
Marco Milesi

Minimal DDIs

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.