New oral anti-HIV drugs: which suggestions for the clinicians from PK data?

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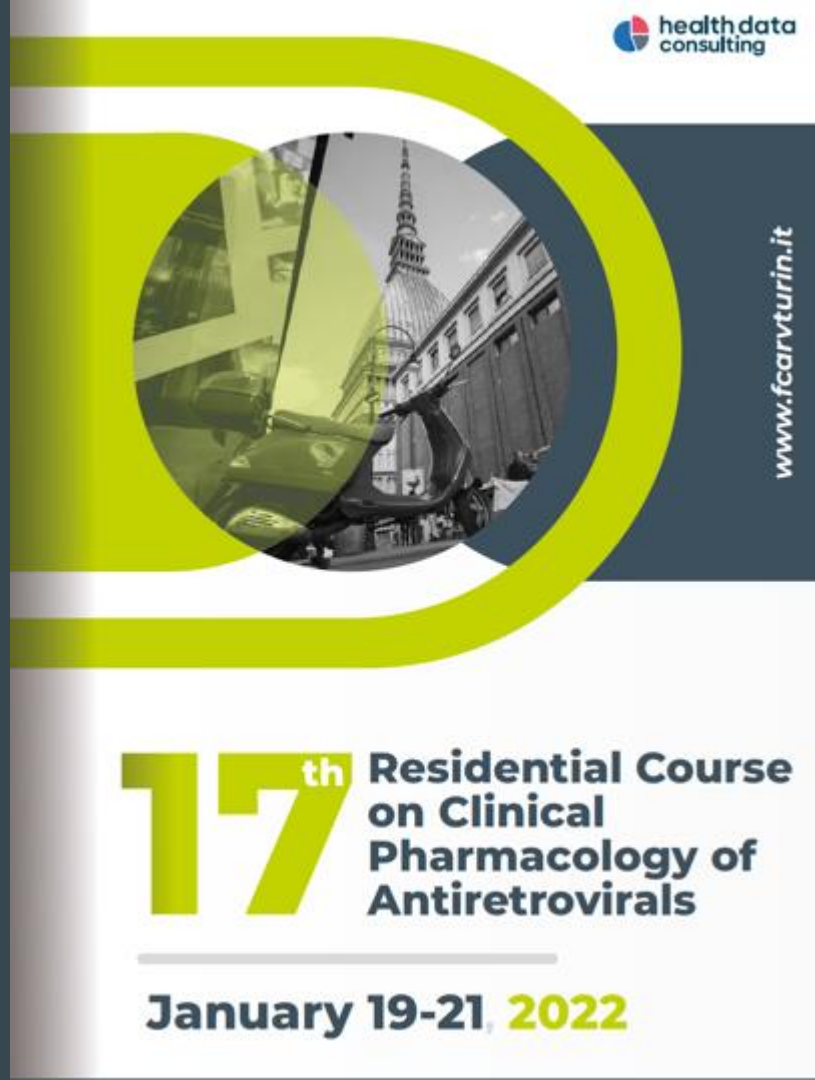
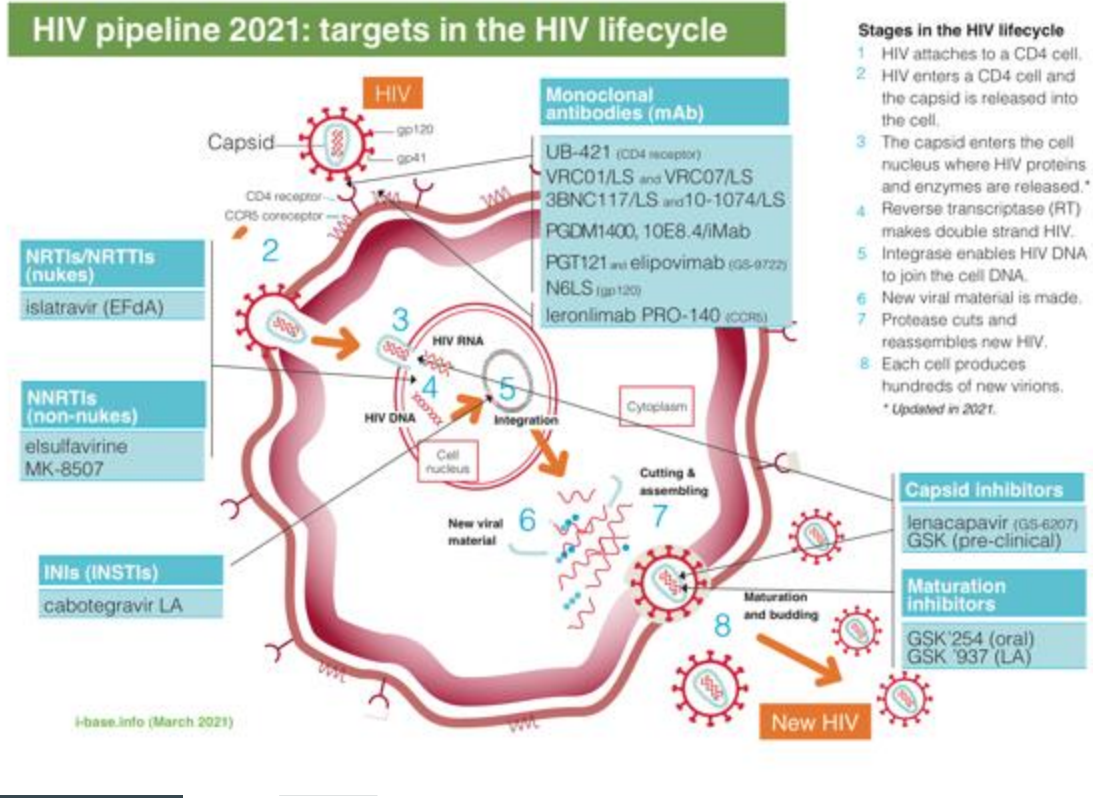
Micol Ferrara, MD
Department of Medical Sciences
Infectious Diseases
University of Torino



HIV Pipeline 2021

Doravirine
Fostemsavir
GSK3640254
Islatravir
MK-8507 (long acting)



Doravirine

Doravirine pharmacokinetics characteristics

Doravirine is a substrate for CYP3A4 (less extent CYP3A5), but unlike other NNRTIs, **does not impact the expression of CYP3A4 or other major drug-metabolizing enzymes**

- No inhibitor or substrate of major drug transporters indicated a low potential for interactions with substrates of BCRP, P-gp, OATP1B1, OATP1B3, BSEP, OAT1, OAT3, OCT2, MATE1, and MATE2K
- Passive permeability appeared to be the major driver of uptake of doravirine into hepatocytes
- Rapidly absorbed: median Tmax of 1–4 h. Plasma concentrations declined in a single exponential phase. T ½ : 12–19 h

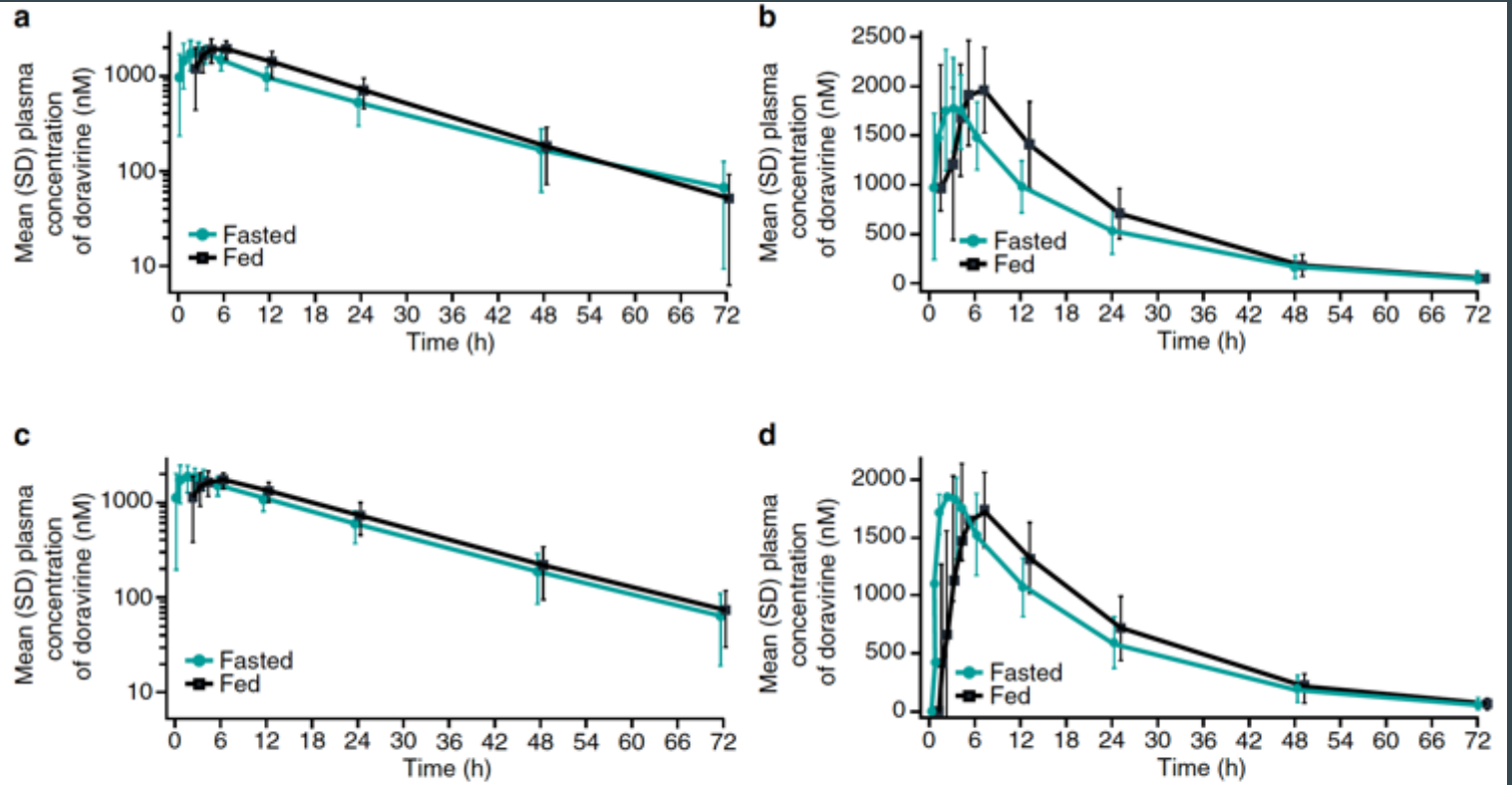
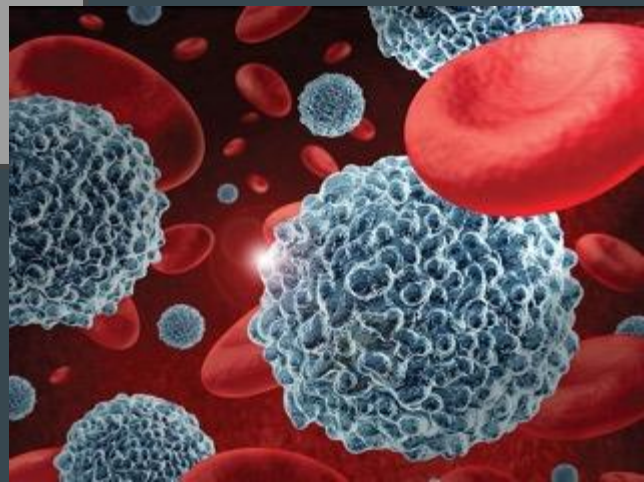


Fig. 1 Plasma concentration–time profiles (semi-log scale) of doravirine 100 mg under fed and fasted conditions in Trial 1, doravirine alone **a** on a logarithmic scale, and **b** on a linear scale, and Trial 2, doravirine fixed-dose combination **c** on a logarithmic scale, and **d** on a linear scale. *SD* standard deviation

16% increase in doravirine exposure as a STR or part of a fixed-dose combination, not clinically relevant

Behm M.O. et al, Clin Drug Investig (2017) 37:571–579

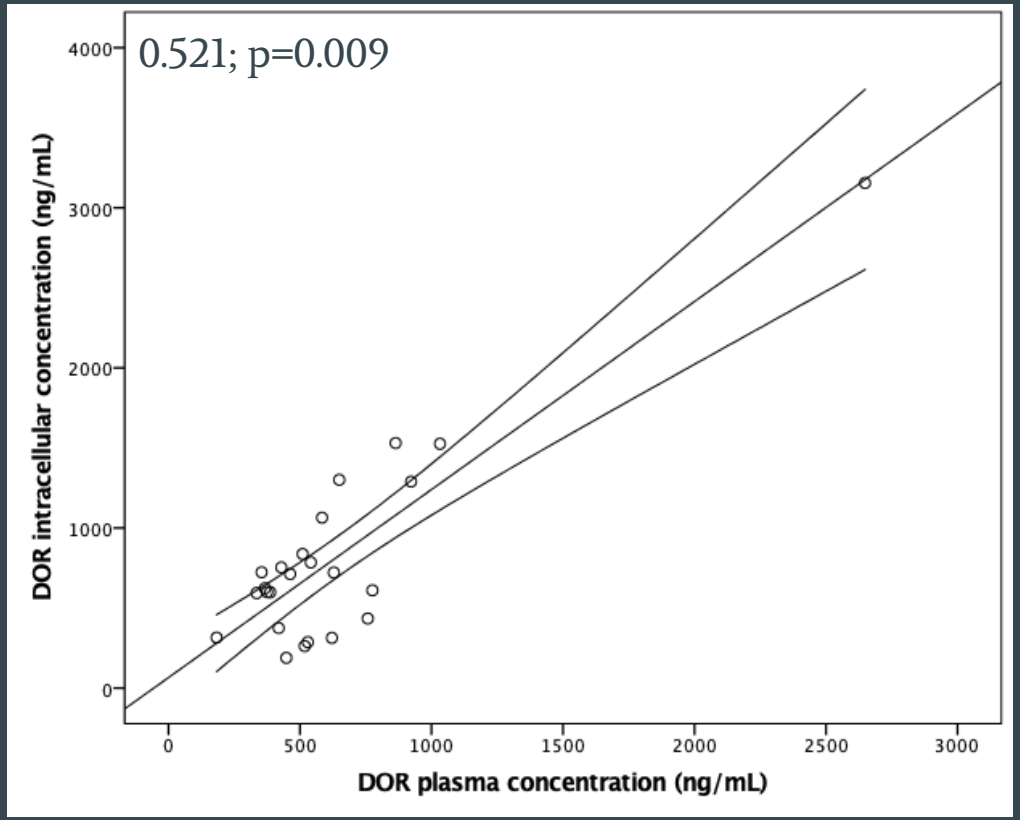
Intracellular penetration?



Correlation between Doravirine plasma and intra-PBMCs concentration

26 pts
M 77%
Median age (IQR) 56.5 (36.0-73.0) yrs
BMI 26.6 (24.5-28.8)

Dual tp: 30%
Triple tp: 70%



Amedeo di Savoia Hospital, unpublished data

Doravirine plasma and intra-PBMCs accumulation in real life setting

C_{trough}	DOR PBMCs	DOR plasma	DOR PBMCs/plasma ratio	DOR plasma[1] reference value
Geomean ng/mL (CI95%)	838.5 (564.7-1112.4)	659.0 (454.1-864.0)	1.308 (1.080-1.536)	396

1.Liverpool HIV drug interaction: https://www.hiv-druginteractions.org/prescribing_resources

Validation of a UHPLC-MS/MS Method to Quantify Twelve Antiretroviral Drugs within Peripheral Blood Mononuclear Cells from People Living with HIV

Pharmaceuticals, 2020

Amedeo De Nicolò [1,*], Alice Ianniello [1], Micol Ferrara [1], Valeria Avataneo [1], Jessica Cusato [1], Miriam Antonucci [1], Elisa De Vivo [1], Catriona Waitt [2], Andrea Calcagno [1], Alice Trentalange [1], Giampiero Muccioli [3], Stefano Bonora [1], Giovanni Di Perri [1] and Antonio D'Avolio [1]

Median Trough Concentrations (IQR)

Drugs	*n*	Plasma (ng/mL)	PBMC (ng/mL)	PBMC/Plasma Ratio
MVC	1	68 (na *)	163 (na)	2.40 (na)
RPV	1	80 (na)	399 (na)	4.98 (na)
DTG	34	913 (616–1392)	270 (156–450)	0.26 (0.14–0.53)
RAL	2	138 (136–na)	43 (40–na)	0.31 (0.29–na)
COBI	17	49 (6–142)	204 (63–686)	3.52 (3.15–4.48)
DRV	31	2389 (1523–3963)	935 (581–1642)	0.34 (0.23–0.57)
ATV	21	778 (424–1547)	1429 (552–3255)	1.53 (1.01–2.72)
RTV	29	82 (47–389)	497 (278–845)	3.81 (2.07–6.70)
ELV	1	228 (na)	1641 (na)	7.20 (na)
ETV	5	514 (78–763)	2137 (500–3126)	5.51 (3.01–6.03)

REAL LIFE SCENARIO

Comorbidity

CKD

Comedications

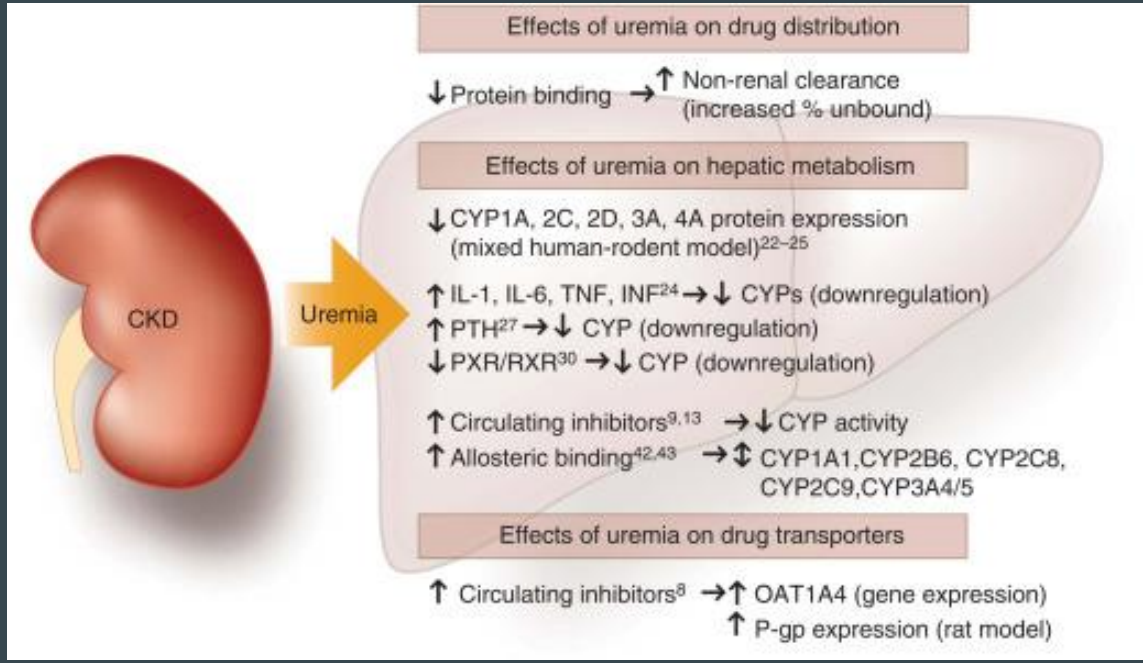
multivitamins

Severe Renal Impairment Has Minimal Impact on Doravirine Pharmacokinetics

Akrom W.et al, AAC 2018

- Severe renal impairment, however, has been shown to increase the AUC, Cmax, and t[1/2] of a range of drugs that are primarily metabolically eliminated via CYP enzymes

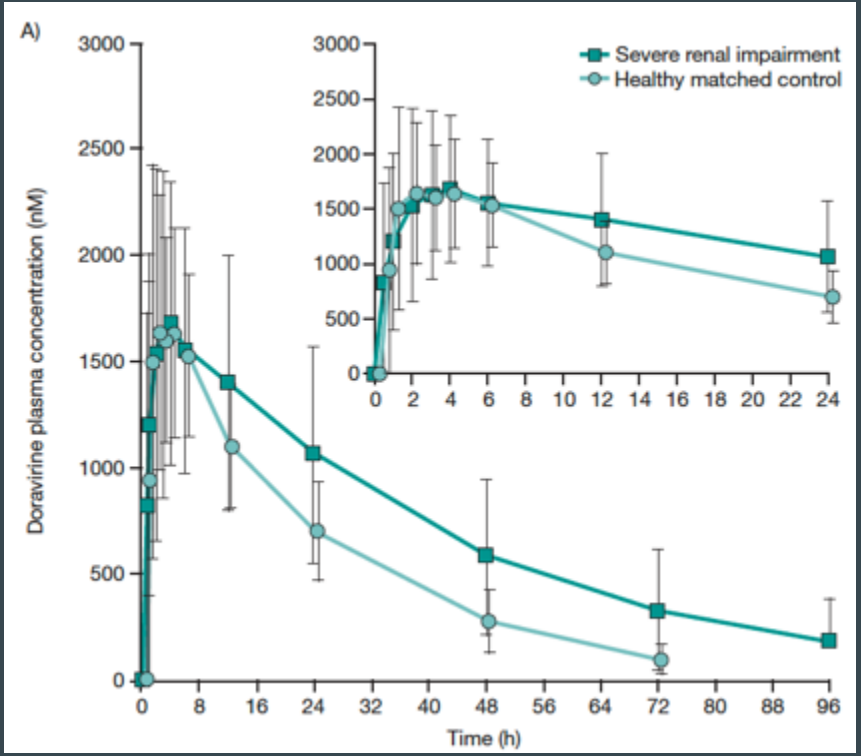
- The increases in the PK exposure are attributed to both
- increased oral bioavailability
- decreased clearance, due to decreased expression of gut and liver metabolic enzymes as well as inhibition of enzymes by uremic toxins

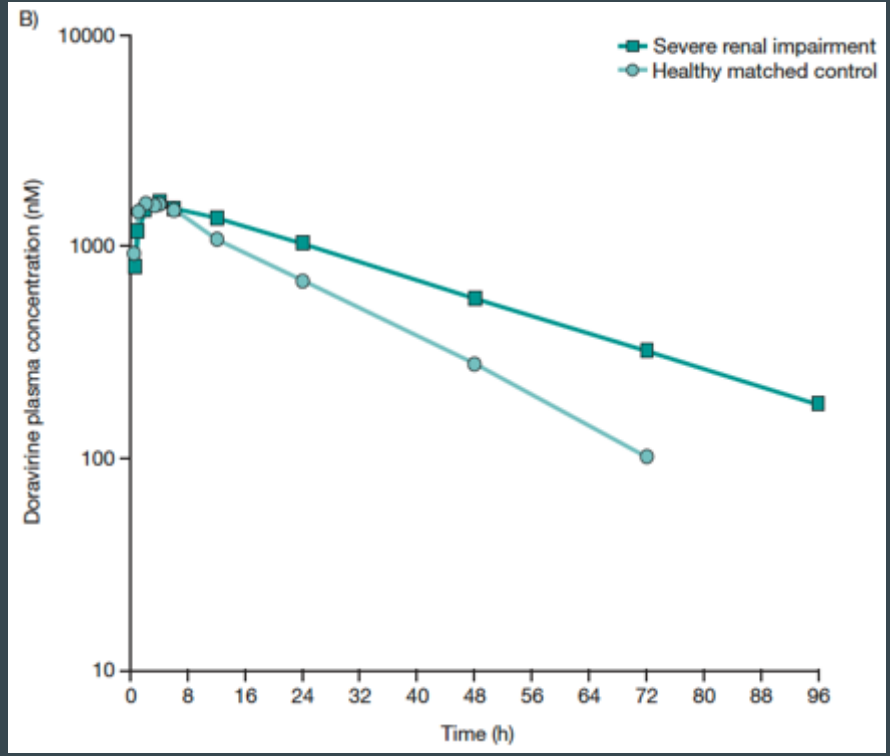


Pichette V. et al , 2003 Curr Drug Metab 4:91–103.; Yeung C.K. et al., Kidney International(2014)85, 522–528523

TABLE 1 Baseline characteristics of subject groups (severe renal impairment and healthy matched controls)

Characteristic, unit	Subjects with severe renal impairment	Healthy matched controls
Enrolled, *n*	8	8
Female, *n* (%)	2 (25.0)	3 (37.5)
Age, mean yr (range)	60.8 (51–69)	60.0 (52–69)
Height, mean cm (range)	170.9 (155.2–184.0)	172.5 (160.4–181.2)
Weight, mean kg (range)	90.9 (71.1–128.1)	90.9 (81.6–98.3)
BMI,[a] mean kg/m^2 (range)	31.2 (21.3–37.8)	30.6 (27.6–33.4)
Race, *n* (%)		
Black	3 (37.5)	1 (12.5)
White	5 (62.5)	7 (87.5)
Ethnicity, *n* (%)		
Hispanic or Latino	3 (37.5)	5 (62.5)
Non-Hispanic and non-Latino	5 (62.5)	3 (37.5)
eGFR[b], arithmetic mean in ml/min/1.73 m^2 (range)	19.6 (9–27)	104.8 (84–126)





The modest increase in doravirine AUC in subjects with severe renal impairment observed in this study is well within the ranges of exposures shown to be generally well tolerated in these previous studies

Akrom W.et al, AAC 2018

Drug Interactions Between Preferred and Alternative ART Options and Common Concomitant Medications

No interaction expected | Potential interaction | Do not coadminister

HIV Drug[1,2]	Multivitamins	Iron	Antacids	H2RA Antagonists	Proton Pump Inhibitors
BIC					
DTG					
RAL					
EVG/COBI					
Boosted ATV					
Boosted DRV					
DOR					
EFV					
RPV					

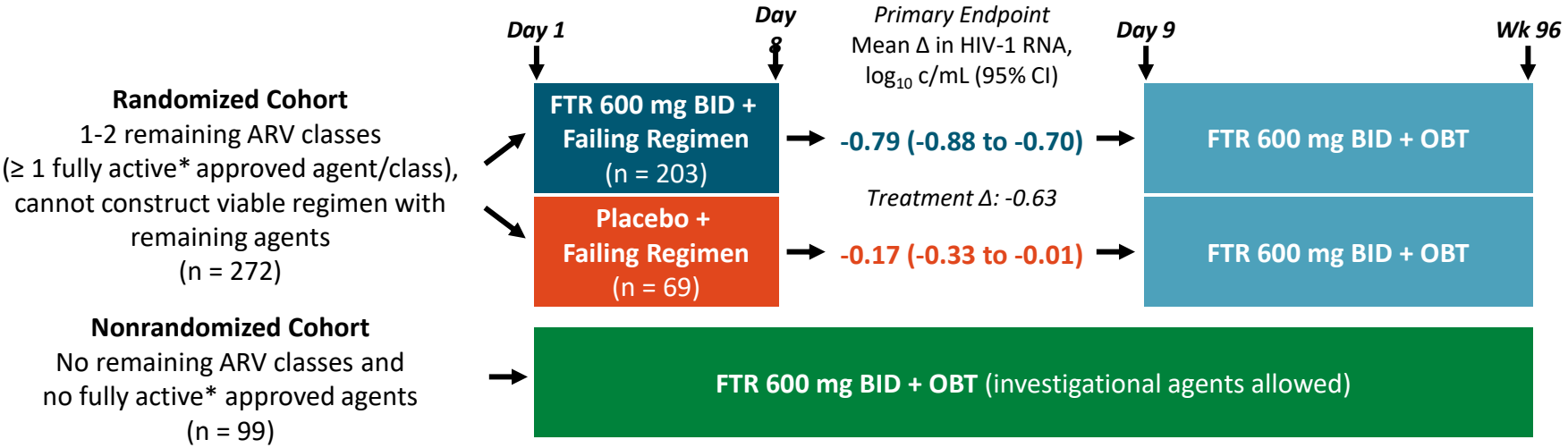
No drug–drug interactions are expected with these agents and the NRTIs

1. DHHS. ART Guidelines 2021. 2. hiv-druginteractions.org/checker

Slide credit: clinicaloptions.com

Fostemsavir

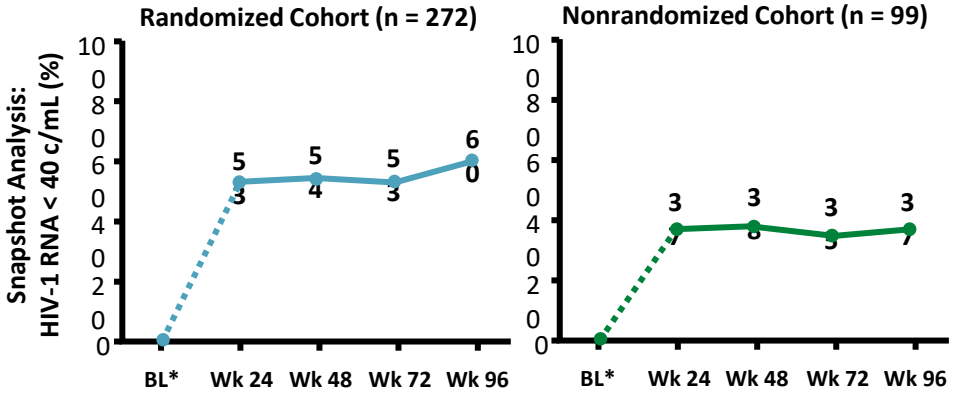
BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults With Multidrug-Resistant HIV



*No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV.

Kozal. NEJM. 2020;382:1232. Pialoux. AIDS 2018. Abstr THPEB045.

BRIGHTE: Virologic and Safety Outcomes Through 96 Wks



Outcome at Wk 96, n (%)	Randomized (n = 272)	Nonrandomized (n = 99)
HIV-1 RNA < 40 c/mL	163 (60)	37 (37)
HIV-1 RNA ≥ 40 c/mL	81 (30)	43 (43)
No virologic data	28 (10)	19 (19)
▪ D/c due to AE or death	15 (6)	14 (14)

*Snapshot analysis excluded BL data; 1 patient had BL HIV-1 RNA < 40 c/mL.

- Cumulative safety outcomes through Wk 96 for all treated patients
  - Drug-related AEs: grade 2-4, 21%; serious, 3%
  - AEs leading to d/c: 7%
  - Death: 8%; most due to AIDS-related events or acute infections, 1 deemed treatment-related (IRIS)

Lataillade. IAS 2019. Abstr MOAB0102.

Slide credit: clinicaloptions.com

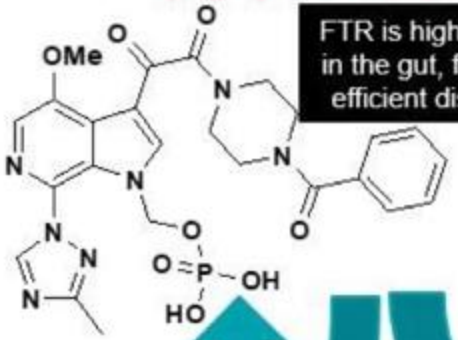
Pharmacokinetics characteristics

- gp-120 attachment inhibitor, approved 600 mg BID
- Metabolism: via hepatic esterase-mediated hydrolysis and, in a minor part, cytochrome P450 (CYP) 3A4- mediated oxidation
- Extrection : urine (44–51%), feces (33%), and bile (5%)
- Substrate of P-glycoprotein and breast cancer resistance protein (BCRP)
- Inhibitory activity toward BCRP and organic anion transporter protein 1B1/3 (OATP1B1/3) → increase plasma [ ] rosuvastatin [35] and oral contraceptives containing ethinylestradiol [36] OATP1B1/3 and BCRP substrates
- Volume of distribution: 29,5 L following intravenous administration
- Protein binding : 76.5% in patients with severe hepatic impairment, compared to 81% in volunteers with normal hepatic function

Rukobia. Package insert. ViiV Healthcare; 2020; Moore K et al, J Int AIDS Soc. 2018; US Food & Drug Administration. Rukobia (fostemsavir): US prescribing information. 2020; Magee M, 9th international AIDS society conference on HIV science. 2017.

FTR – Water Soluble Prodrug

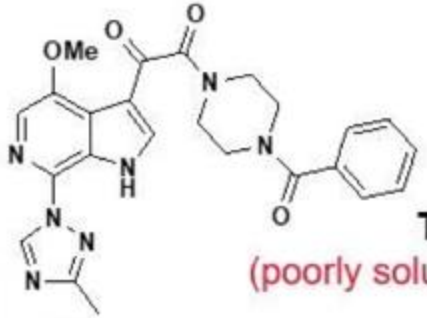
(highly soluble, poorly permeable)



FTR is highly soluble in the gut, facilitating efficient dissolution

FTR is converted to TMR by alkaline phosphatase in the gastrointestinal lumen

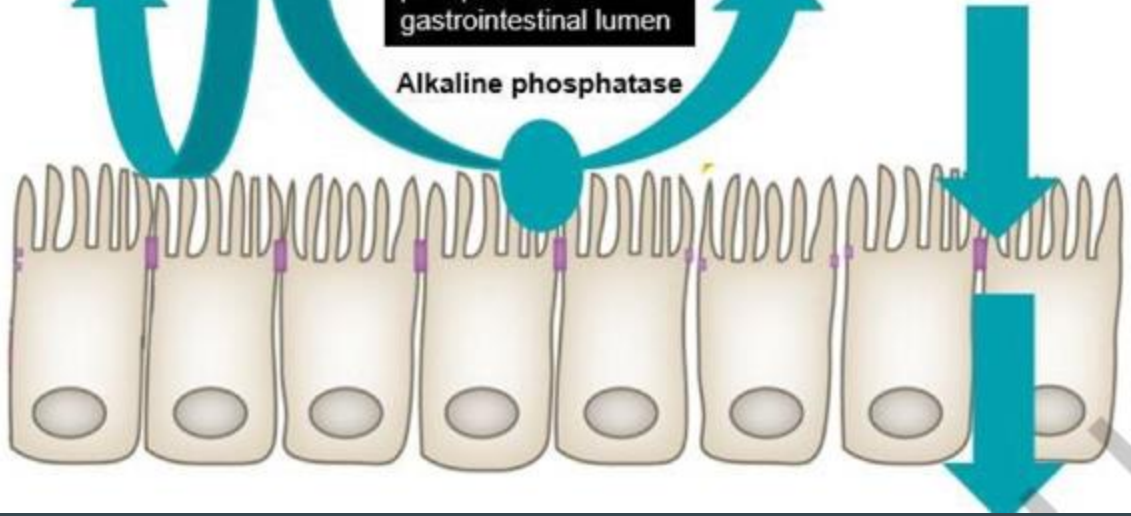
Alkaline phosphatase



TMR - Active

(poorly soluble, highly permeable)

TMR is then rapidly absorbed due to its efficient membrane permeability[1]



Intestinal epithelia

Conversion to TMR pre-systemically, with no measurable FTR in most samples

Brown J, et al. J Pharm Sci 2013; **102**:1742–1751

Pharmacokinetics characteristics

- No considerable pharmacological interaction nor reduction in the antiretroviral potency in HTE patients with INSTI or ibalizumab

- Co-administration with strong CYP3A4 inducers should be avoided due to significant decrease in drug exposure and possible loss of virological response. Co-administration with rifampin, a potent CYP and P-glycoprotein inducer, reduces temsavir Cmax and AUC by 76% and 82% [34], respectively

- The tablet can be taken with or without food.

US Food & Drug Administration. Rukobia (fostemsavir): US prescribing information. 2020; Magee M, 9th international AIDS society conference on HIV science. 2017.

Low-dose Fostemsavir Extended Release Relative Bioavailability Study

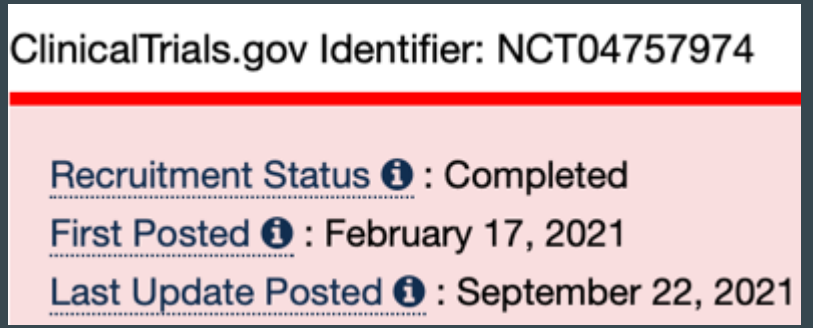
https://clinicaltrials.gov

A Two-Part Randomized Study to Evaluate the Relative Bioavailability of Temsavir Following Single Dose Administration of Fostemsavir 600 mg Tablets vs Fostemsavir 200 mg BID Tablets

Evaluate the Effect of Food on Bioavailability of Selected Fostemsavir 200 mg Tablet Formulation in Healthy Adult Participants

InterventionalOpen-label Randomized Clinical Trtial
32 participants, USA

Last update Sept 2021, not available results



Outcome Measures

Go to

Primary Outcome Measures :

1. Part 1: Area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable time point (AUC[0-t]) of temsavir [Time Frame: Predose (Day 1) until 72 hour post dose]
2. Part 1: AUC from time zero extrapolated to infinite time (AUC[0-infinity]) of temsavir [Time Frame: Predose (Day 1) until 72 hour post dose]
3. Part 1: Maximum observed plasma concentration (Cmax) [Time Frame: Predose (Day 1) until 72 hour post dose]

Secondary Outcome Measures :

1. Part 1: Time to Cmax (Tmax) of temsavir [Time Frame: Predose (Day 1) until 72 hour post dose]
2. Part 1: Elimination half-life (T1/2) of temsavir [Time Frame: Predose (Day 1) until 72 hour post dose]
3. Part 1: Concentration at 12 hours post-dose of temsavir [Time Frame: 12 hours post-dose]
4. Part 1 and Part 2: Number of participants with clinically significant change from Baseline in vital signs and clinical laboratory parameters [Time Frame: Baseline (Day -1) until end of follow up at 4 weeks]
5. Part 1 and Part 2: Number of participants reporting adverse events (AEs) and serious adverse events (SAEs) [Time Frame: Baseline (Day -1) until end of follow up at 4 weeks]
6. Part 2: AUC [0-t] of temsavir [Time Frame: Predose (Day 1) until 72 hour post dose]
7. Part 2: AUC [0-infinity] of temsavir [Time Frame: Predose (Day 1) until 72 hour post dose]
8. Part 2: Cmax of temsavir [Time Frame: Predose (Day 1) until 72 hour post dose]

REAL LIFE SCENARIO

Comorbidity

CKD

Comedications

Methadone/Buprenorphine

Effect of Renal and Hepatic Impairment on the Pharmacokinetics of Temsavir, the Active Moiety of Fostemsavir

Magee M. et al., The Journal of Clinical Pharmacology 2021, 61(7) 939–953

Table 1. Subject Demographics for the Renal Impairment and Hepatic Impairment Studies

	Renal Impairment Study					
	Group A Normal N = 6	Group B Mild N = 6	Group C Moderate N = 6	Group D Severe N = 6	Group E ESRD N = 6	Total N = 30
Age, y, mean (SD)	57.0 (3.6)	66.3 (5.6)	64.0 (9.9)	60.0 (8.0)	44.8 (5.0)	58.4 (9.9)
Sex, n (%)						
Male	3 (50.0)	4 (66.7)	3 (50.0)	5 (83.3)	4 (66.7)	19 (63.3)
Female	3 (50.0)	2 (33.3)	3 (50.0)	1 (16.7)	2 (33.3)	11 (36.7)
BMI, kg/m^2 mean (SD)	28.7 (4.1)	27.8 (3.1)	29.5 (3.7)	27.1 (3.7)	26.4 (4.2)	27.9 (3.7)
Height, cm, mean (SD)	161.0 (11.0)	168.0 (6.6)	165.1 (9.6)	167.8 (11.8)	173.3 (8.3)	167.0 (9.8)
Weight, kg, mean (SD)	74.6 (14.9)	78.2 (5.5)	80.1 (8.1)	76.2 (12.3)	79.2 (13.6)	77.7 (10.8)
Race, n (%)						
White	5 (83.3)	5 (83.3)	4 (66.7)	4 (66.7)	1 (16.7)	19 (63.3)
Black or African American	1 (16.7)	0	2 (33.3)	2 (33.3)	5 (83.3)	10 (33.3)
American Indian or Alaska Native	0	1 (16.7)	0	0	0	1 (3.3)
Ethnicity, n (%)						
Hispanic/Latino	5 (83.3)	0	3 (50.0)	3 (50.0)	0	11 (36.7)
Not Hispanic/Latino	1 (16.7)	6 (100.0)	3 (50.0)	3 (50.0)	6 (100.0)	19 (63.3)

Effect of Renal and Hepatic Impairment on the Pharmacokinetics of Temsavir, the Active Moiety of Fostemsavir

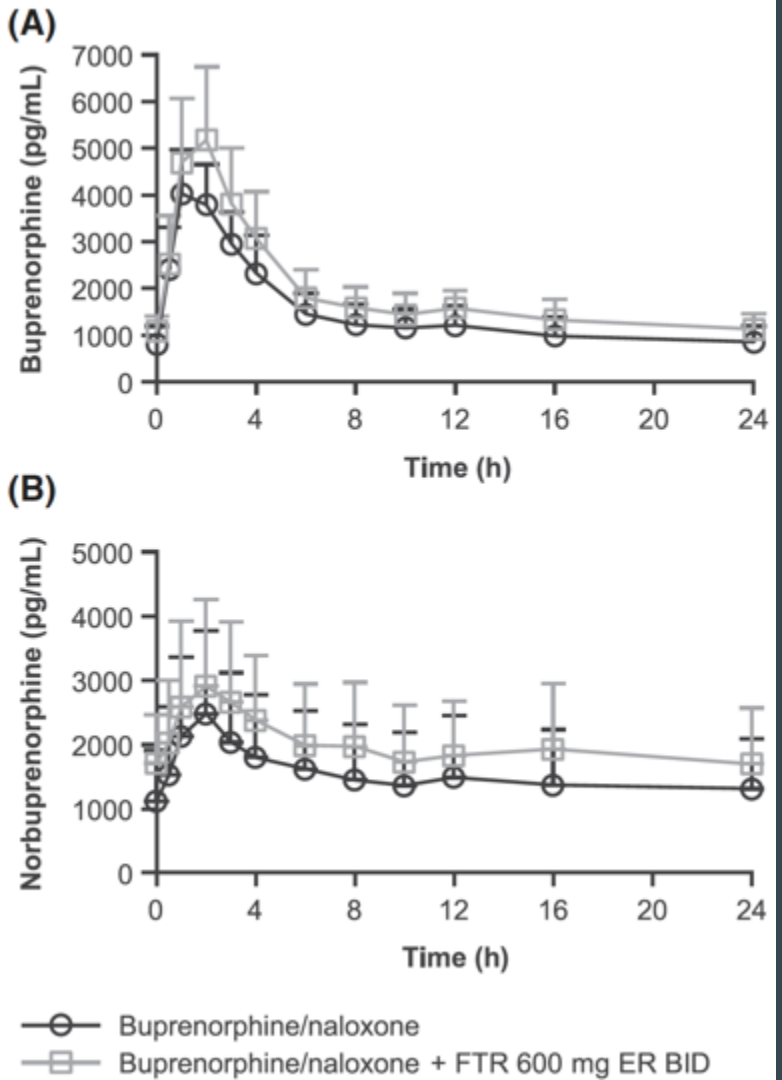
Magee M. et al., The Journal of Clinical Pharmacology 2021, 61(7) 939–953

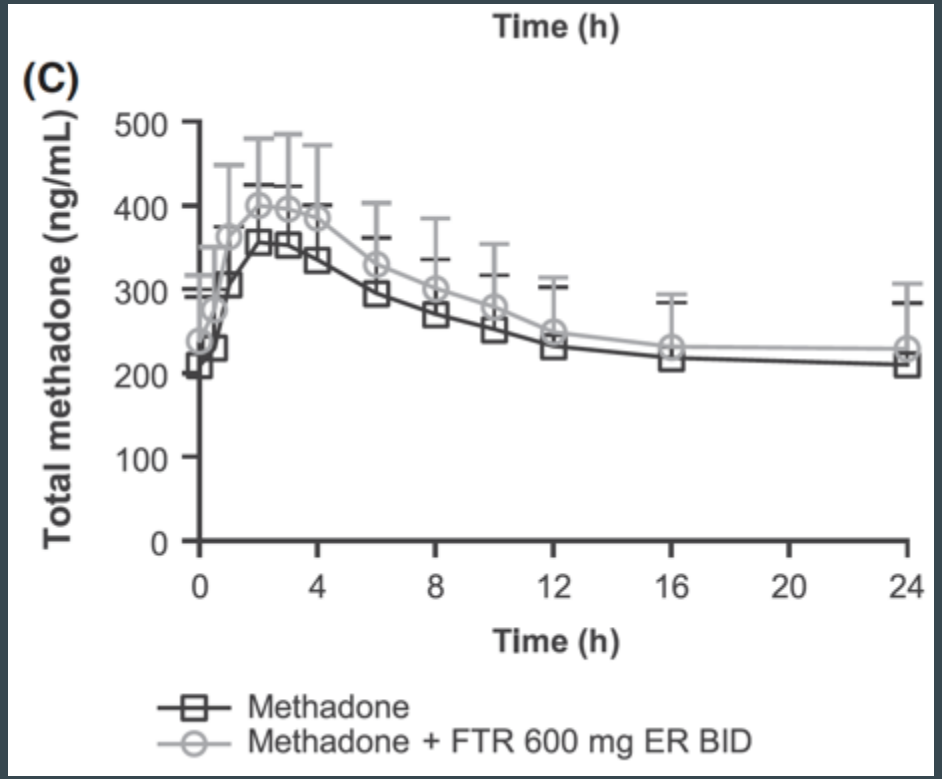
- In patients with renal dysfunction, higher plasma exposures are expected compared to normal function, 43% reduction in temsavir clearance was observed in patients with severe impairment
- No change in dosage was indicated for patients with hepatic and renal impairment, due to the safe range of exposure and lack of identified safety concerns.
- A decrease in temsavir CLR was observed with increasing severity of renal impairment, but no apparent effect of renal function (eGFR or CLcr) on temsavir PK
- Protein binding tended to decrease with increasing severity of renal impairment, there was no clear relationshi between unbound temsavir exposure and the severity of renal impairment
- No clinically relevant differences in temsavir PK were observed in patients with ESRD on HD

Methadone and buprenorphine pharmacokinetics and pharmacodynamics when coadministered with fostemsavir to opioid-dependent, human immunodeficiency virus seronegative participants

Moore K. et al., Br J Clin Pharmacol. 2019;85:1771–1780

- TMR has 2 human plasma metabolites, BMS-646915 and BMS-930644 both lack anti-HIV activity
- BMS-930644 low circulating concentrations,
- In vitro in human liver microsomes CYP3A4 and BRCP inhibitor
- All P-gp substrates, but not inhibitors.


(A)
Buprenorphine (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
0
4
8
12
16
20
24
Time (h)
(B)
Norbuprenorphine (pg/mL)
5000
4000
3000
2000
1000
0
0
4
8
12
16
20
24
Time (h)
Buprenorphine/naloxone
Buprenorphine/naloxone + FTR 600 mg ER BID


Time (h)
(C)
Total methadone (ng/mL)
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (h)
Methadone
Methadone + FTR 600 mg ER BID

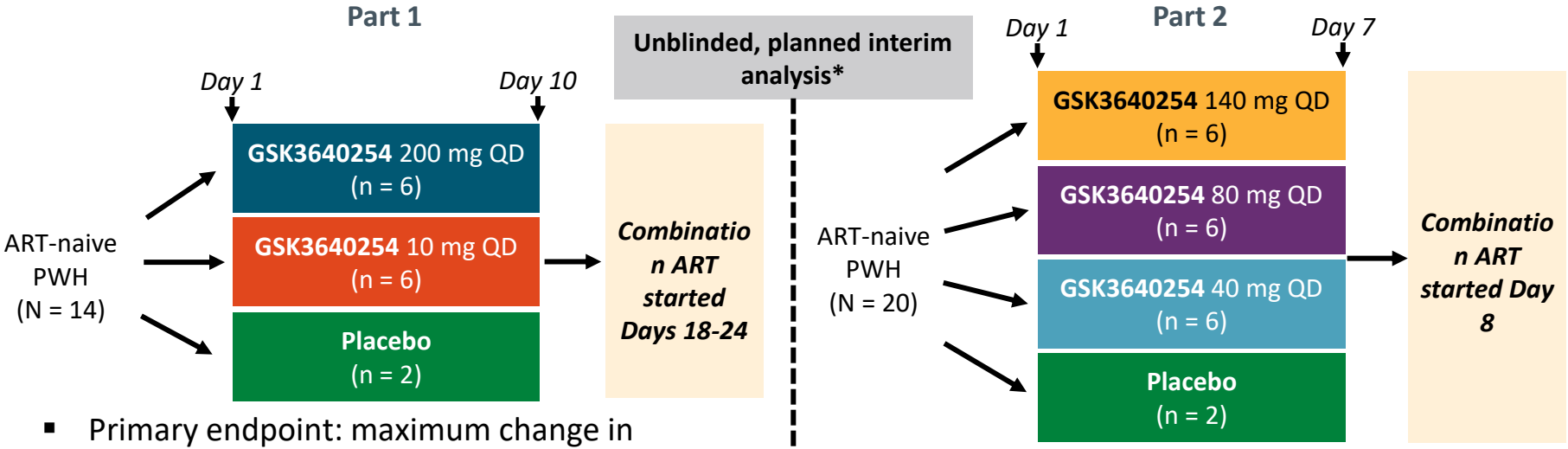
- Potential mechanisms may involve modest increases in bioavailability,given that P-gp is implicated in gut absorption and efflux and MET, BUP, TMR and BMS-930644 are all P-gp substrates.
- Inhibition of hepatic or gut CYP3A4 metabolism by BMS-930644 (IC50 = 9.9 μM) may play a role, although circulating BMS-930644 concentrations are low --> clinically significant interactions unlikely
- FTR can be administered with MET or BUP without dose adjustment.
- MET (R-, S- and total) exposures (plasma C_{trough} , C_{max} and AUC) increased 9–15% and BUP and norBUP exposures increased 24–39%.

Moore K. et al., Br J Clin Pharmacol. 2019;85:1771–1780

GSK3640254

Phase IIa Study of GSK3640254 in Treatment-Naive PWH

- **GSK3640254: investigational HIV-1 maturation inhibitor**
- Multicenter, randomized, double-blind (sponsor-unblinded), placebo-controlled trial



- Primary endpoint: maximum change in HIV-1 RNA vs Day 1 during parts 1 and 2
- Secondary endpoints: resistance, PK, safety

*Detection of resistance mutations at interim analysis resulted in protocol amendment, reducing duration of monotherapy from 10 days to 7 days in Part 2.

Spinner. CROI 2021. Abstr 126.

Slide credit: clinicaloptions.com

A Dose-Range Finding Clinical Trial Study in Human Immunodeficiency Virus (HIV-1) Infected Treatment-Naive Adult (DOMINO)

Interventional Randomized study Phase 2

Recruiting

Estimated enrollment: 150 naive pts

Primary outcome: Proportion of participants with plasma HIV-1 ribonucleic acid (RNA) <50 copies per milliliter (c/mL) at Week 24

Secondary outcome: including PK parameters (AUC over the dosing interval; plasma C_{max}, C_{trough})

Estimated primary outcome measure: Oct 2022

- https://clinicaltrials.gov/ct2/show/NCT04493216

A Clinical Trial of GSK3640254 + Dolutegravir (DTG) in Human Immunodeficiency Virus-1 Infected Treatment-naive Adults (DYNAMIC)

A Phase IIb, Randomized, Double-blind, Parallel-group Study

Assess the Efficacy, Safety, Tolerability, and Resistance Profile of GSK3640254 in Combination With Dolutegravir Compared to Dolutegravir Plus Lamivudine in HIV-1 Infected, Treatment-naïve Adults

Recruiting

Estimated enrollment: 150 naive pts

Estimated primary outcome measure: Nov 2022

https://clinicaltrials.gov/ct2/show/NCT04493684

REAL LIFE SCENARIO

Comedications

DTG

Contraceptives

Phase I evaluation of pharmacokinetics and tolerability of the HIV-1 maturation inhibitor GSK3640254 and dolutegravir in healthy adults

Dumitrescu et al., Brit Jnl Clinical Pharma. 2021;87:3501–3507.

- Phase I, open-label, fixed-sequence, 2-way drug interaction study to investigate the PK interactions and tolerability and safety of GSK3640254 and DTG administered alone and in combination in healthy adults

- GSK3640254 is a mild inhibitor of uridine diphosphate glucuronosyltransferase 1A1 in vitro

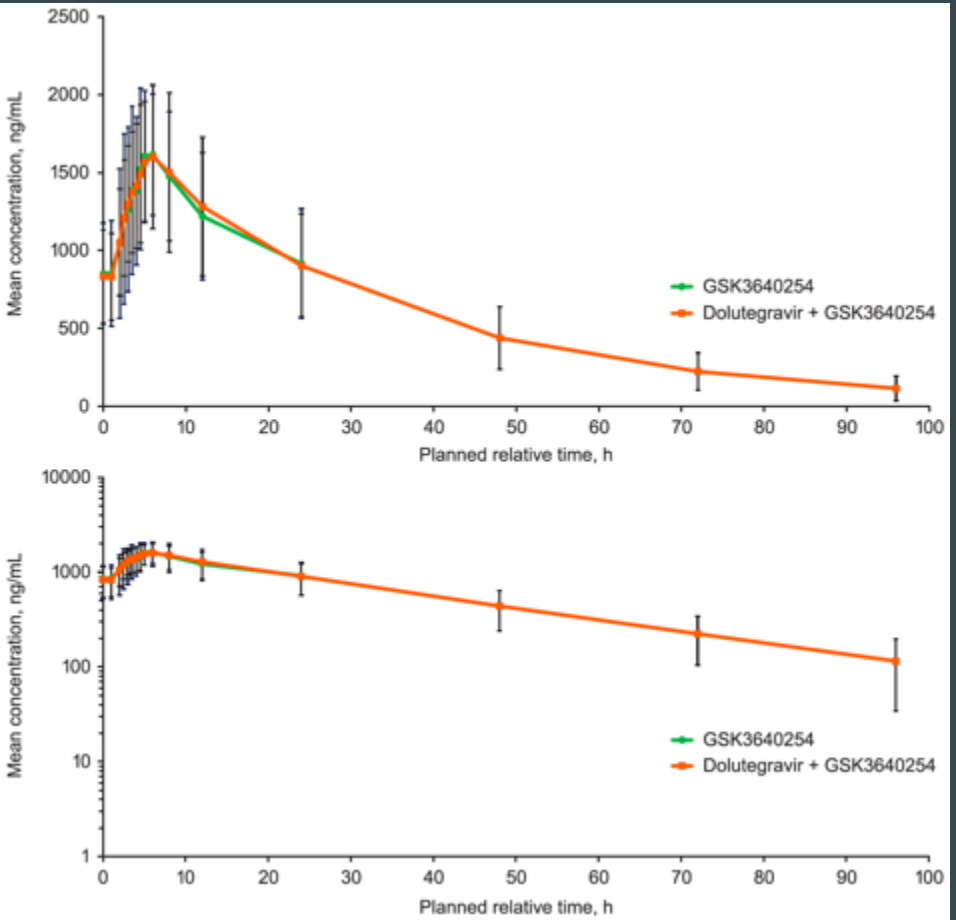
- The slightly increased DTG C_{trough} values plus GSK3640254 could be attributed to mild inhibition of UGT1A1-mediated clearance of dolutegravir
- → not clinically meaningful

TABLE 1 Baseline demographics

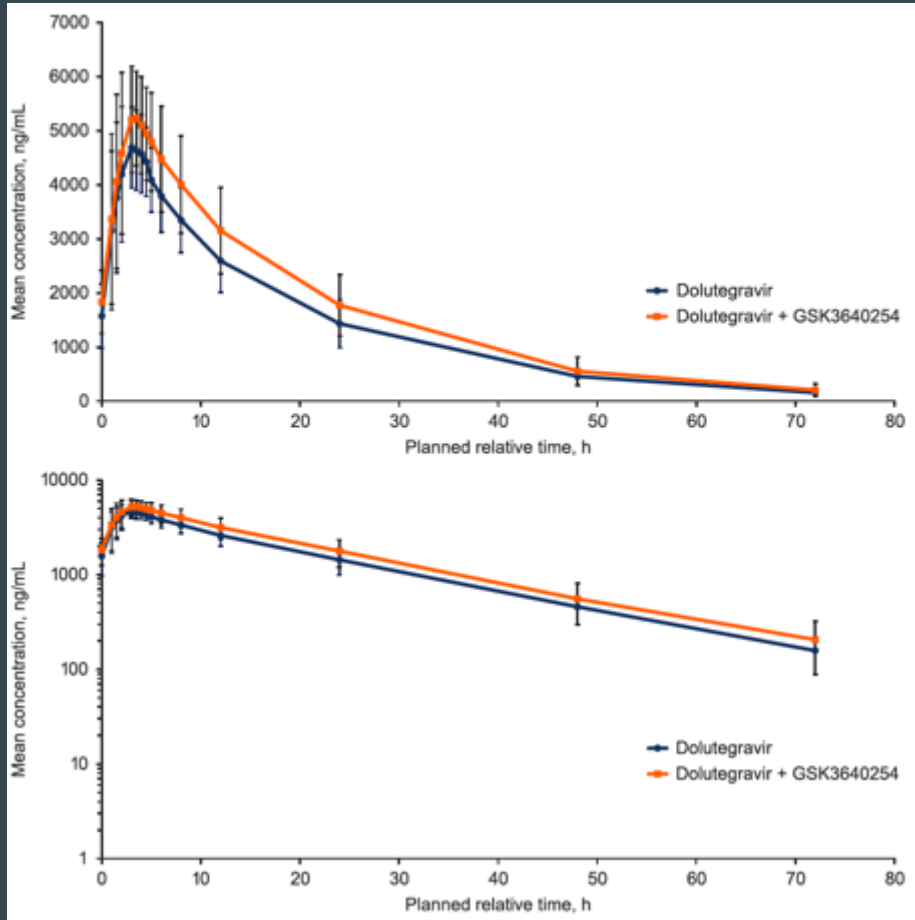
Parameter	Participants (*n* = 16)
Age, mean (SD), y[a]	36.7 (10.7)
Sex, *n* (%)	
Female	1 (6)
Male	15 (94)
Body mass index (SD), kg/m^2	26.8 (2.8)
Height (SD), cm	170.3 (5.6)
Weight (SD), kg	77.9 (9.9)
Ethnicity, *n* (%)	
Hispanic/Latino	9 (56)
Not Hispanic/Latino	7 (44)
Race/Ethnicity, *n* (%)	
Asian heritage	2 (13)
Black/African American	3 (19)
White/Caucasian/European heritage	11 (69)

SD, standard deviation.
[a]Age was imputed if full date of birth was not provided.

GSK3640254 plasma PK



DTG plasma PK

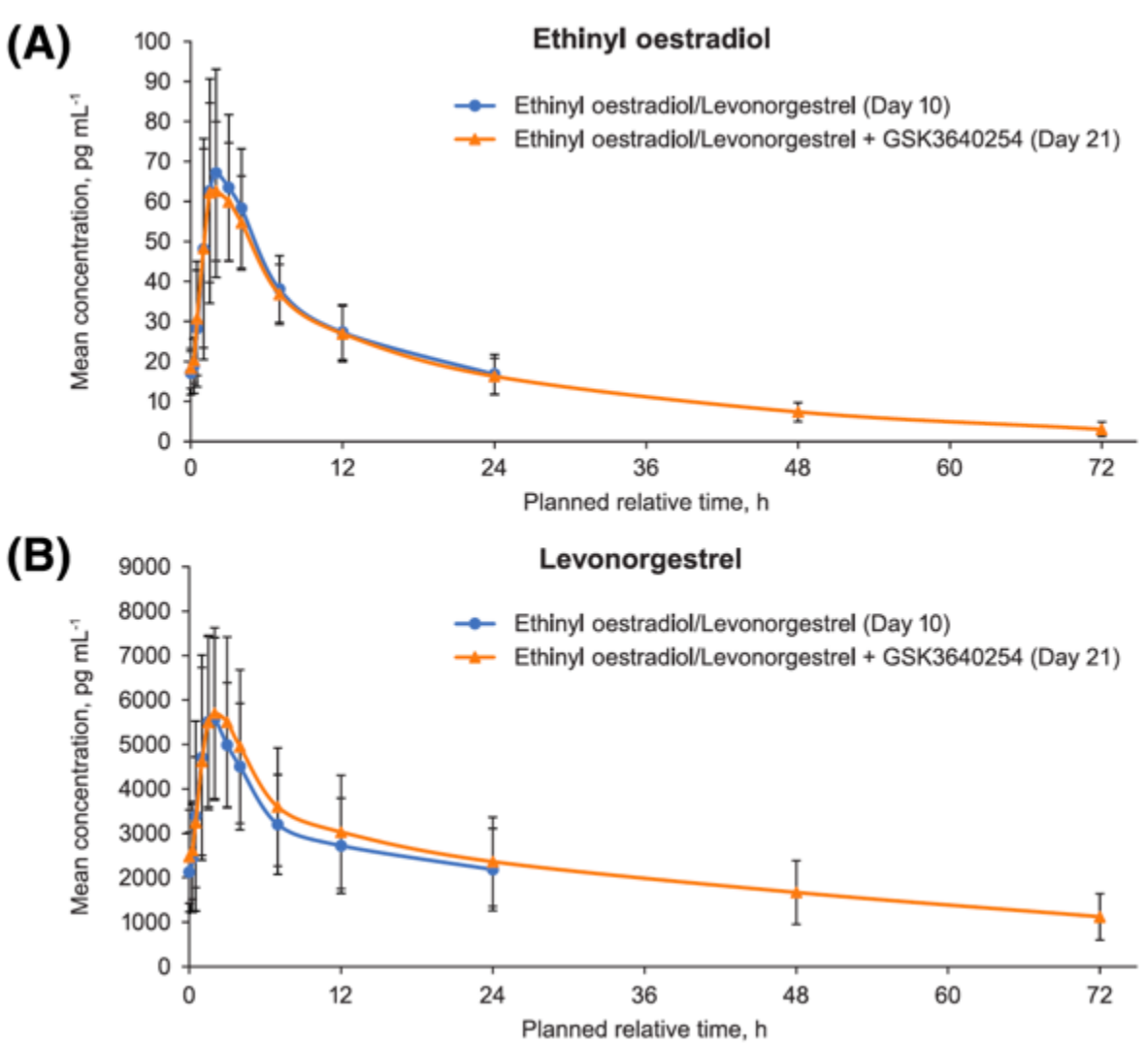


Lack of pharmacokinetic interaction between the HIV-1 maturation inhibitor GSK3640254 and combination oral contraceptives in healthy women

Dumitrescu T. et al, Br J Clin Pharmacol. 2021;1–9

- Phase I, open-label, 1-way study
- 23 enrolled participants, 17 completed the study
- GSK3640254 is a mild inhibitor of uridine diphosphate glucuronosyltransferase 1A1 in vitro and has an unknown impact on sulfotransferases, both of which are enzymes that metabolize ethinyl oestradiol
- Most oestrogens and progestins are metabolized by cytochrome P450 enzymes, which GSK3640254 minimally inhibited or induced in in vitro studies

Parameter	Participants ($n = 23$)
Age, mean (SD), y	34.7 (7.8)
Sex, *n* (%)	
Female	23 (100)
Infertile (of childbearing age)	5 (22)
Childbearing potential	18 (78)
Body mass index, mean (SD), kg m^{-2}	27.4 (2.9)
Height, mean (SD), cm	162.1 (6.6)
Weight, mean (SD), kg	72.2 (10)
Ethnicity, *n* (%)	
Hispanic/Latino	6 (26)
Not Hispanic/Latino	17 (74)
Race/ethnicity, *n* (%)	
Black/African American	12 (52)
White	9 (39)
American Indian/Alaska native	1 (4)
Asian	1 (4)



Islatravir

Compound	Islatravir (ISL or MK-8591)
Mechanism of Action	Nucleoside reverse transcriptase translocation inhibitor (NRTTI) High potency against wild-type and NRTI-resistant mutants Multiple mechanisms of action (translocation and delayed chain termination inhibition)
PK and Metabolism Summary	ISL plasma $t_{1/2}$ 50-60 hrs, converts to active triphosphate (TP) intracellularly ISL-TP $t_{1/2}$ ~190 hrs Eliminated via excretion of parent and metabolism by adenosine deaminase • Not expected to be victim of inhibitors/inducers • Not an inhibitor or inducer of major metabolic enzymes or transporters

Safety and Pharmacokinetics of Once-Daily Multiple-Dose Administration of Islatravir in Adults Without HIV

Matthews RP et al., J Acquir Immune Defic Syndr Nov 2021;88:314–321

Phase 3-panel, randomized, double-blind, placebo controlled, multiple-dose study in 36 adults without HIV

Islatravir plasma concentrations decreased in a biphasic manner, initial rapid phase and a slow terminal

Potential redistribution of the parent drug from the PBMCs back into the plasma

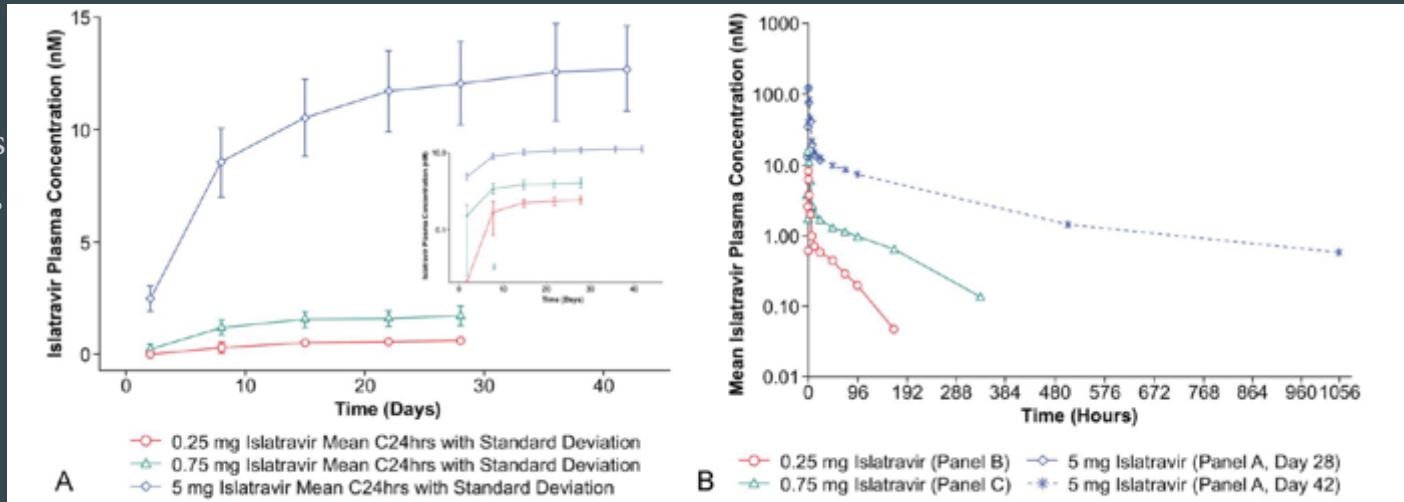


FIGURE 1. Plasma C_{24} concentration–time profiles (semi-log scale) of islatravir in adults without HIV (n = 9 per dose). A, Multiple QD doses of islatravir (through day 28 or 42). B, Final dose (day 28 or day 42) after QD administration.

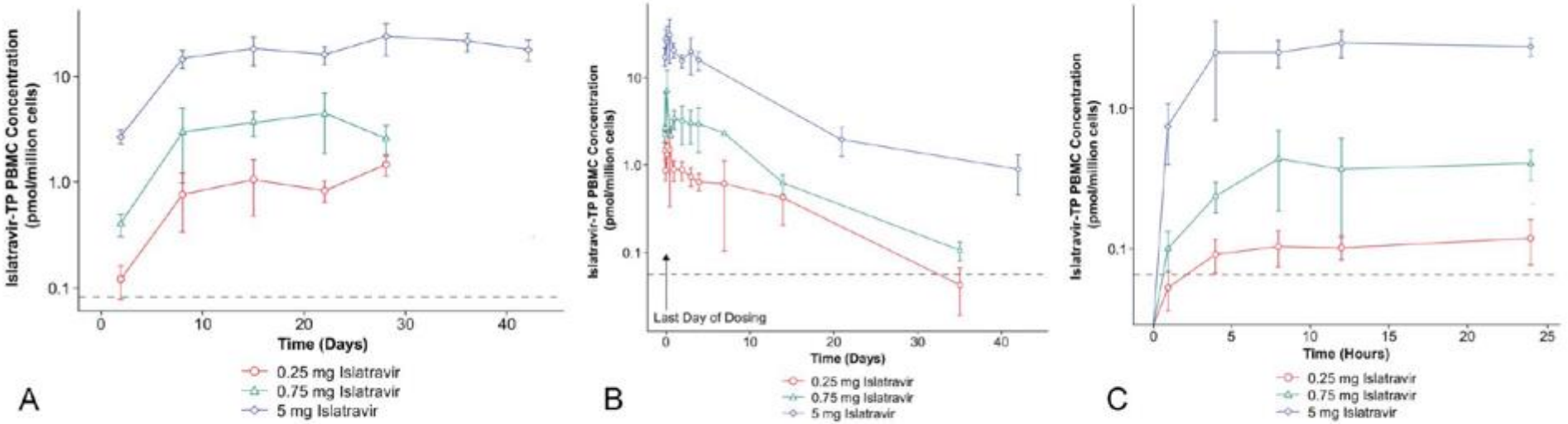


FIGURE 2. PBMC concentration–time profiles (semi-ln scale) of ISL-TP in adults without HIV (n = 9 per dose). A, Multiple QD doses of islatravir (through day 28 or 42)*. B, Final dose (day 28 or day 42) of islatravir after QD administration. C, Single oral dose of islatravir. *Trough concentrations. Error bars indicate SD. Horizontal gray line denotes a PK threshold of 0.05 pmol/10^6.

- Islatravir has a 4-fold lower in vitro intracellular IC50 for wild-type HIV-1 virus than any approved NRTI
- IQs of islatravir for both WT and NRTI-resistant HIV-1 at low dose QD and once weekly doses are substantially higher than those of any NRTIs
- Long intracellular half-life of ISL-TP and IQs :opportunity for multiple low-dosing options both wild-type and NRTI-resistant HIV-1 at low QD

REAL LIFE SCENARIO

Comorbidity

CKD

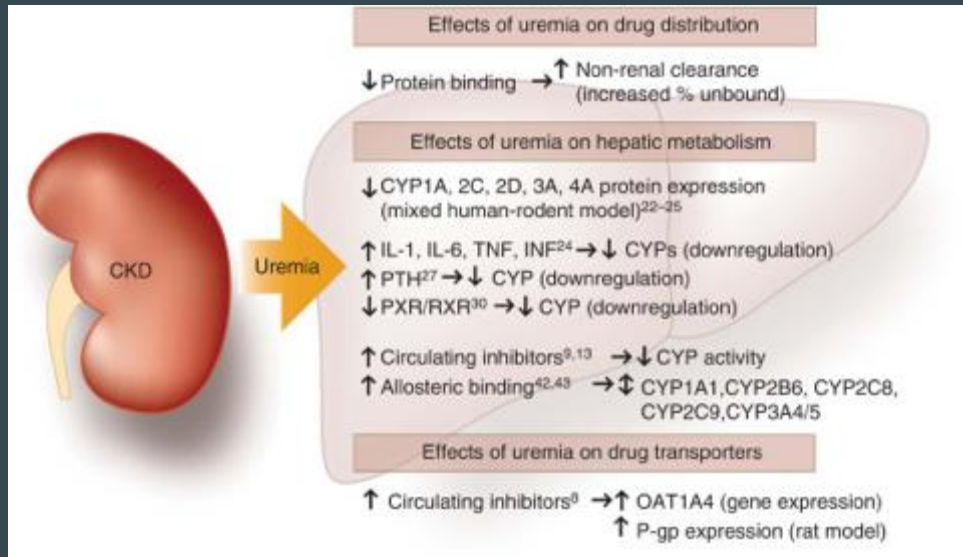
Comedications

Doravirine

Prep

Pharmacokinetics of Islatravir in Participants with Severe renal Impairment (MK-8591-026)

- Open-Label, Single-Dose Study, non-randomized
- Interventional (Clinical Trial), Phase 1
- Completed, first results Oct 2021
- Single dose ISL 60 mg
- 12 participants, 6 each group
- PK results after 168 hrs post dose



https://clinicaltrials.gov/ct2/show/NCT04303156

Area Under the Curve From Time 0 to Last Sampling Time (AUC0-last) of Plasma ISL

Unit of Measure: hr*µM

	Severe Renal Impairment	Healthy
	Participants with severe renal impairment received a single oral dose of 60 mg Islatravir administered in capsule form	Healthy participants received a single oral dose of 60 mg Islatravir administered in capsule form.
	11.0 (9.17 to 13.1)	5.68 (4.06 to 7.94)

Maximum Concentration (Cmax) of Plasma ISL

1.23 (1.06 to 1.42)	1.19 (0.699 to 2.04)

Apparent Clearance (CL/F) of Plasma ISL

14.2 (11.6 to 17.4)	31.3 (22.8 to 42.9)

Apparent Terminal Half-life (t1/2) of Plasma ISL

127 (7.7%)	72.0 (15.5%)

Secondary Outcome

Concentration at 672 Hours Post Dose (C672) of ISL-TP in PBMC

Severe Renal Impairment	Healthy
Participants with severe renal impairment received a single oral dose of 60 mg Islatravir administered in capsule form	Healthy participants received a single oral dose of 60 mg Islatravir administered in capsule form.
1.96 (0.982 to 3.92)	0.730 (0.489 to 1.09)

Concentration at 168 Hours Post Dose (C168) of ISL-TP in PBMC

8.06 (4.69 to 13.9)	4.43 (0.938 to 20.9)

AUC0-inf of ISL Triphosphate (ISL-TP) in Peripheral Blood Mononuclear Cells (PBMC)

5810 (3890 to 8700)	3920 (2830 to 5420)

Effects of islatravir (4′-ethynyl-2-fluoro-2′-deoxyadenosine or EFdA) on renal tubular cells and islatravir's interactions with organic anion transporters

Journal of Pharmacological Sciences, June 2021

Meika Kaneko [a], Yoshie Reien [a], Hanae Morio [a], Tomoko Fukuuchi [b], Kiyoko Kaneko [b], Yuri Hirayama [a], Hirofumi Hashimoto [a], Nobuyo Kuwata [c], Hiroaki Mitsuya [c], Naohiko Anzai [a]

- The cytotoxicity of ISL or TDF to S2 cells increased in a concentration-dependent manner.
- ISL, TDF, and TFV may cause damage to the proximal tubule at high concentrations.
- In the clinical setting, blood levels of ISL would not be high enough to cause kidney damage:
large gap in ISL concentration between the pharmacological dose to proximal tubular cells and the clinical dose.
- ISL is unlikely to be taken up via OAT1, OAT3 or OCT2, and therefore, the mechanism of cytotoxicity caused by ISL remains unknown

A Phase 1 Study to Evaluate the Drug Interaction Between Islatravir (MK-8591) and Doravirine in Adults Without HIV

Matthews RP et al., Clinical Drug Investigation (2021) 41:629–638

Double-blind, placebo-controlled, randomized, fixedsequence, two-period, multiple-dose

- Extensive DDI studies of doravirine demonstrated interaction only with CYP3A4 inhibitors and inducers
- Islatravir is not metabolized by CYP enzymes nor is it a substrate of major transporters
- Elimination of islatravir is expected to be balanced between renal excretion and adenosine deaminase-mediated metabolism
- Doravirine is not anticipated to influence intracellular islatravir-TP levels.
- Uptake of NRTIs occurs by diffusion or by a combination of diffusion and active transport, and the subsequent phosphorylation to the active form is catalyzedby endogenous kinases, with multiple enzymes capable of catalyzing each phosphorylation step

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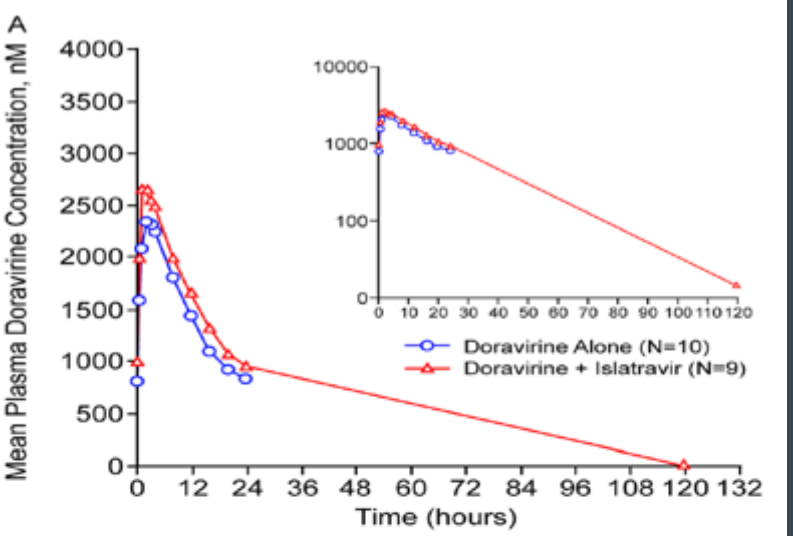
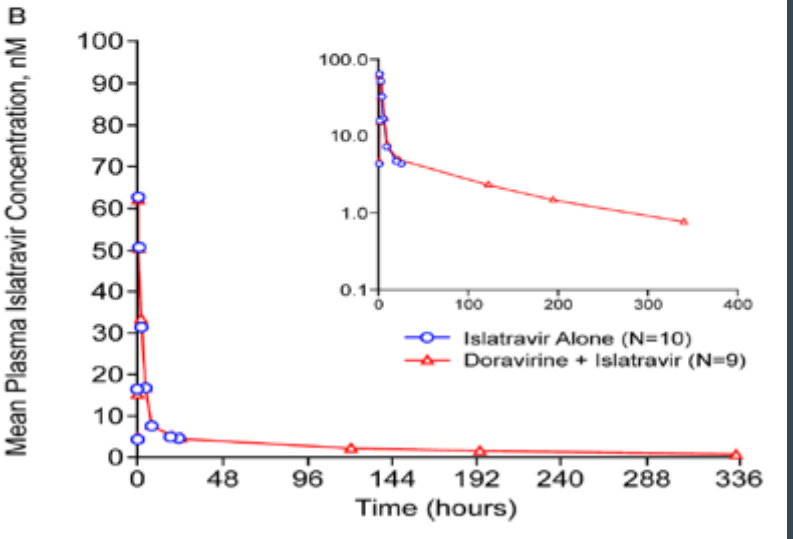
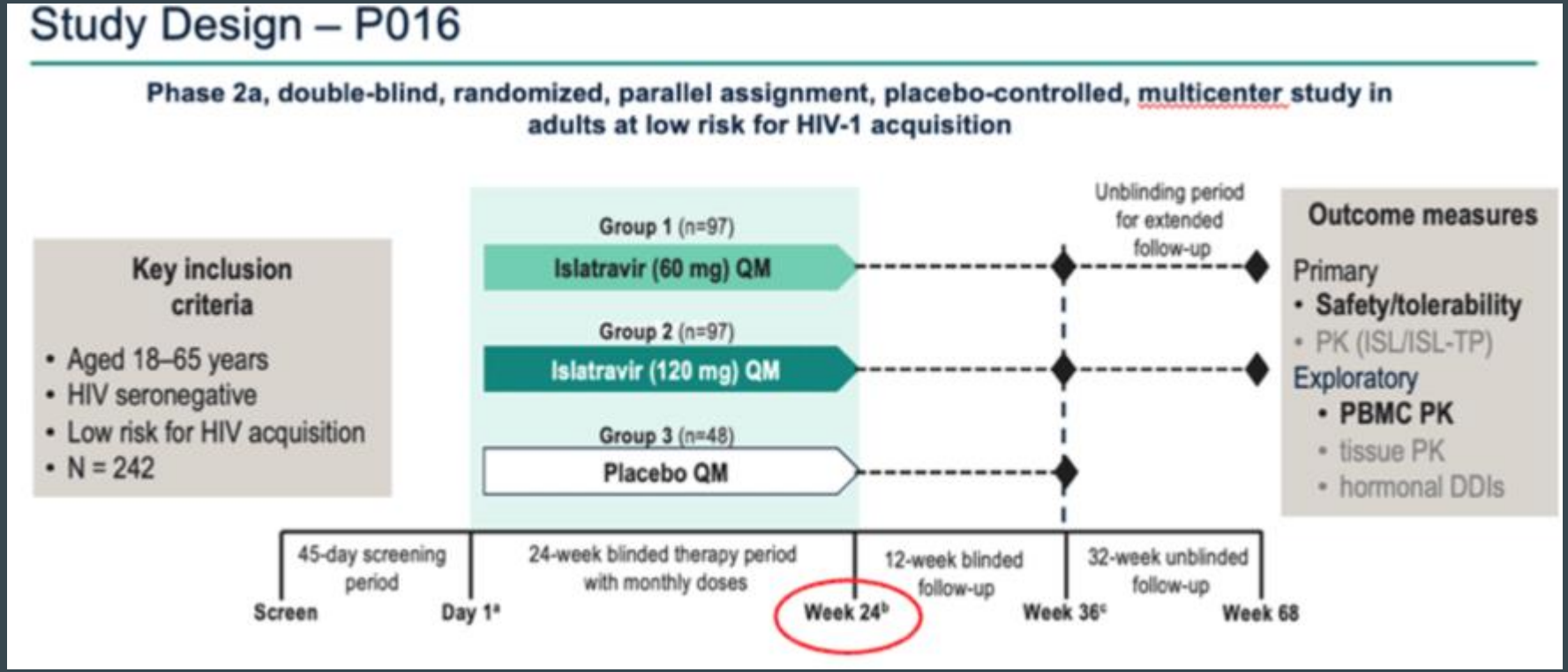
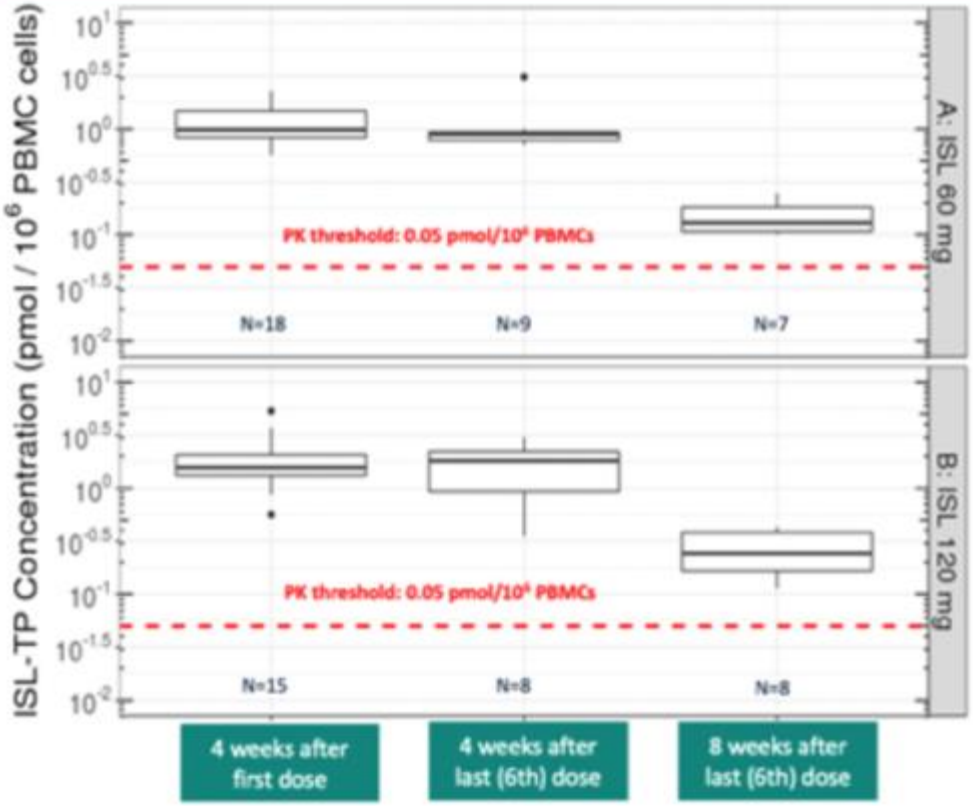

A
Mean Plasma Doravirine Concentration, nM
4000
3500
3000
2500
2000
1500
1000
500
0
0 12 24 36 48 60 72 84 96 108 120 132
Time (hours)
10000
1000
100
0
0 10 20 30 40 50 60 70 80 90 100 110 120
Doravirine Alone (N=10)
Doravirine + Islatravir (N=9)


B
Mean Plasma Islatravir Concentration, nM
100
90
80
70
60
50
40
30
20
10
0
0 48 96 144 192 240 288 336
Time (hours)
100.0
10.0
1.0
0.1
0 100 200 300 400
Islatravir Alone (N=10)
Doravirine + Islatravir (N=9)

Safety and Pharmacokinetics of Oral Islatravir Once Monthly for HIV Pre-exposure Prophylaxis (PrEP): Week 24 Analysis of a Phase 2a Trial poster IAS conference Jul 21



ISL-TP Trough Concentrations in PBMCs (pmol/10^6 PBMCs)



- ISL-TP trough concentrations following 60 mg or 120 mg QM doses were all above the pre-specified PK threshold of 0.05 pmol/10^6 PBMCs (IQ=5)[a]

[a] Patel M et al, Oral Abstract Number 87, CROI 2021; IQ=Inhibitory quotient defined as ratio of active intracellular concentration and intracellular IC50

MERCK

Merck Announces Clinical Holds on Studies Evaluating Islatravir for the Treatment and Prevention of HIV-1 Infection

December 13, 2021 5:00 pm ET

The following studies have been placed on full clinical hold:

- MK-8591-016 – A Phase 2a PrEP study evaluating the safety and pharmacokinetics of oral islatravir once-monthly in participants at low risk of HIV-1 infection
- MK-8591-022 (IMPOWER 22) – A Phase 3 PrEP study evaluating oral islatravir once-monthly in cisgender women at high risk for HIV-1 infection
- MK-8591-024 (IMPOWER 24) – A Phase 3 PrEP study evaluating oral islatravir once-monthly in cisgender men and transgender women who have sex with men, and are at high risk for HIV-1 infection
- MK-8591-034 – A Phase 1 study evaluating injectable islatravir (dosing complete)
- MK-8591-035 – A Phase 2 PrEP study evaluating once-monthly oral islatravir in trans and gender diverse individuals (study had not yet opened enrollment)
- MK-8591-043 – A Phase 2a PrEP study evaluating islatravir implant once-yearly in individuals at low risk for HIV-1 infection (study had not yet opened enrollment)

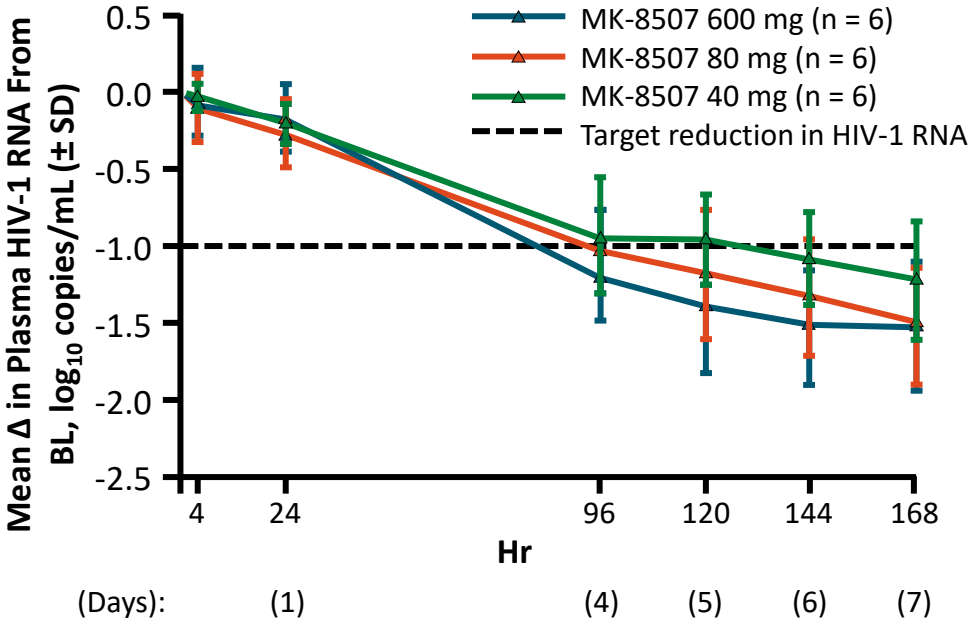
The following studies have been placed on partial clinical hold:

- MK-8591-011 – A Phase 2 dose ranging study of oral DOR/ISL once-daily and lamivudine (3TC) in treatment-naïve adult participants with HIV-1 infection (fully enrolled)
- MK-8591A-017 (ILLUMINATE SWITCH A) – A Phase 3 oral once-daily, open label study evaluating a switch from antiretroviral therapy (ART) to DOR/ISL in adults with HIV-1 who are virologically suppressed (fully enrolled)
- MK-8591A-018 (ILLUMINATE SWITCH B) – A Phase 3 oral once-daily study evaluating a switch from bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) to DOR/ISL in adults with HIV-1 who are virologically suppressed (fully enrolled)
- MK-8591A-019 (ILLUMINATE HTE) – A Phase 3 study evaluating oral islatravir and DOR/ISL once-daily in heavily treatment-experienced (HTE) participants with HIV-1 infection
- MK-8591A-020 (ILLUMINATE NAIVE) – A Phase 3 study evaluating oral islatravir and DOR/ISL once-daily in treatment-naïve participants with HIV-1 infection
- MK-8591A-028 (ILLUMINATE YOUTH) – A Phase 2 open label study evaluating oral DOR/ISL once-daily for the treatment of HIV-1 infection in pediatric participants who are virologically suppressed on ART for ≥3 months or are treatment-naive
- MK-8591A-033 – A Phase 3 open label follow up of adult and pediatric participants with HIV-1 who were treated with oral DOR/ISL once-daily in earlier clinical studies

MK-8705

Single-Dose MK-8507: Antiviral Efficacy

- All doses achieved target HIV-1 RNA reduction by Day 7



HIV-1 RNA Change From BL at Day 7, log_{10} c/mL (95% CI)

-1.53 (-1.84 to -1.23)

-1.50 (-1.80 to -1.19)

-1.22 (-1.52 to -0.91)

Ankrom. HIV Glasgow 2020. Abstr O416.

Slide credit: clinicaloptions.com

Single-Dose MK-8507: Resistance, Pharmacokinetics, Safety

- Viral rebound: 0/14 patients initiating standard ART at Day 7, 1/4 patients initiating standard ART after Day 14
  - F227C detected 10 days post-dose in 1 patient receiving 600-mg dose
- Pharmacokinetic analysis supports once weekly dosing
  - MK-8507 doses >80 mg met selected PK target of $C_{168hr} \geq 6 \times IC_{50}$
  - Mean apparent terminal half-life: ~56-69 hr
- All doses generally well tolerated
  - No clinically meaningful trends in vitals, electrocardiograms, or laboratory tests
- Most common AEs: nasopharyngitis (n = 3), headache (n = 3)
  - Headache only AE considered related to study drug
  - 1 serious AE: diffuse large B-cell lymphoma, not considered related to study drug

Ankrom. HIV Glasgow 2020. Abstr O416.

Slide credit: clinicaloptions.com

Pharmacokinetic and Safety Profile of the Novel HIV Nonnucleoside Reverse Transcriptase Inhibitor MK-8507 in Adults without HIV

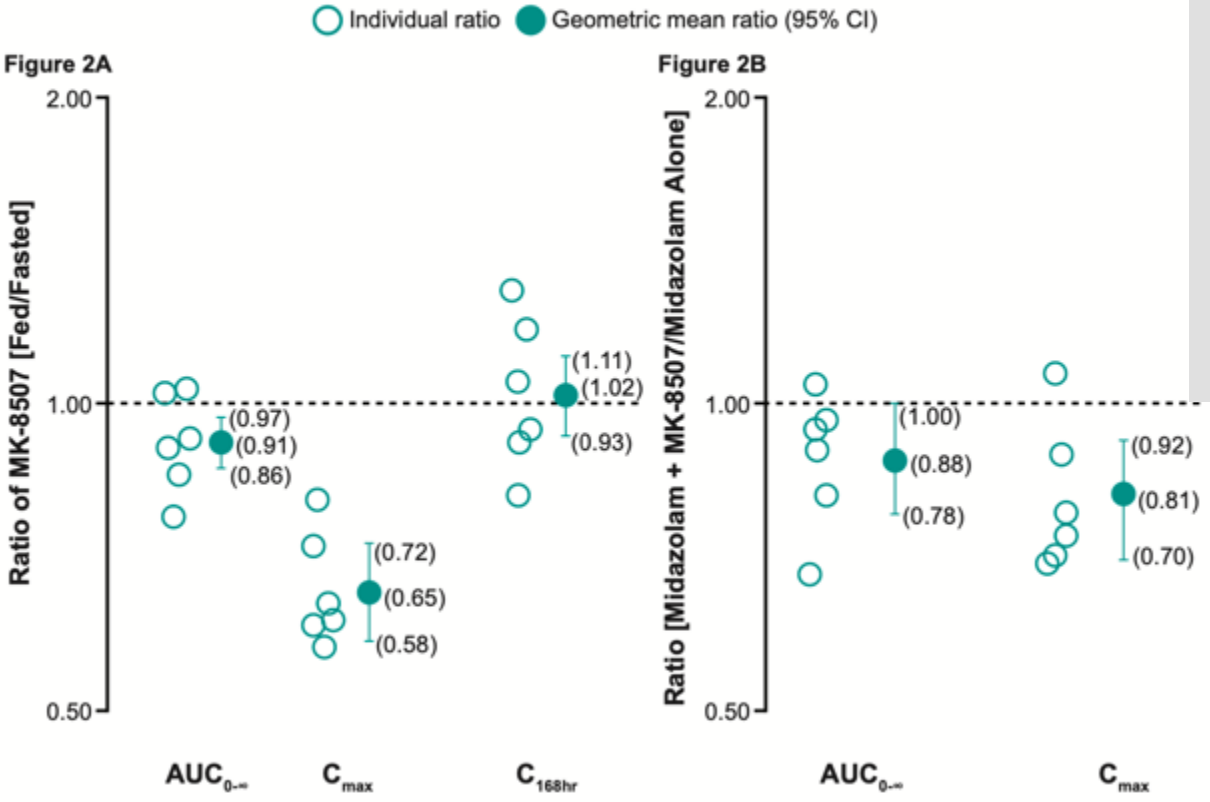
Ankrom et al, HIV Glasgow (Virtual event); 5–8 October 2020, P099; AAC Dec 2021

- Median Tmax : 2–7 hrs (fasted)
- Median T ½ : 70 hrs

- Fed/fasted status on MK-8507 plasma PK ??

- In vitro studies CYP3A4 inducer ?→ Midazolam was selected as a probe substrate: 7-14 days to reach steady state, assessed with the third QW dose.

Figure 2. MK-8507 Plasma PK under Fed and Fasted Conditions (Study 1) (A), and Interactions with Midazolam (Study 2) (B)



AUC0-∞, area under the concentration–time curve from 0 to i
C_{max}, maximum plasma concentration; PK, pharmacokinetics

FED/FASTED-MK-8507

High-fat meal
no clinically meaning effect on
MK-8507 plasma PK

MIDAZOLAM-MK-8507

Small decrease in midazolam plasma concentration was observed with coadministration (12% decrease in AUC and 18% decrease in Cmax)

MK-8507 400mg once-weekly no clinically meaningful interaction with midazolam MK-8507 is not a meaningful inducer of CYP3A4 in vivo.

No pharmacokinetic interaction between novel NNRTI MK-8507 and Islat

W. Ankrom et al, eposter IAS 2021

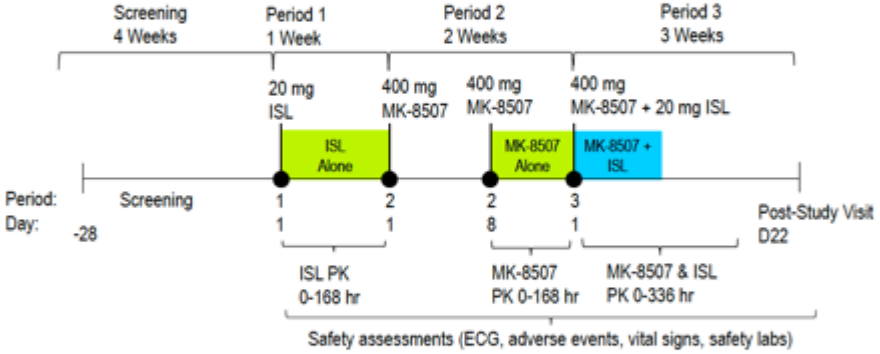
Compound	Islatravir (ISL or MK-8591)	MK-8507
Mechanism of Action	Nucleoside reverse transcriptase translocation inhibitor (NRTTI) High potency against wild-type and NRTI-resistant mutants Multiple mechanisms of action (translocation and delayed chain termination inhibition)	Non-nucleoside reverse transcriptase inhibitor (NNRTI) High antiviral potency and activity against common NNRTI resistance-associated mutations
PK and Metabolism Summary	ISL plasma $t_{1/2}$ 50-60 hrs, converts to active triphosphate (TP) intracellularly ISL-TP $t_{1/2}$ ~190 hrs Eliminated via excretion of parent and metabolism by adenosine deaminase • Not expected to be victim of inhibitors/inducers • Not an inhibitor or inducer of major metabolic enzymes or transporters	$t_{1/2}$ of ~70 hrs Based on nonclinical data, elimination anticipated to be via excretion of parent and metabolism via multiple routes • Clinically meaningful interactions with inhibitors of metabolic enzymes or P-gp not expected • Potential for moderate/strong inducers to affect MK-8507 PK to be evaluated clinically Not expected to cause DDIs via inhibition of major CYP enzymes, OATP1B1/B3 or OAT1/3 at doses ≤ 400 mg • No clinically meaningful effect of MK-8507 on midazolam (CYP3A4 substrate) in DDI study • Potential to inhibit P-gp, to be evaluated clinically

Methods

- Open-label, 3-period, Phase 1 study
- Study was approved by the Midlands Independent Review Board
- All participants provided written informed consent

Study population

- Healthy adult men and women not of childbearing potential
- HIV-1 negative
- Not using prescription or non-prescription medication or herbal remedies



- Enrolled 14, with 13 completers; 1 withdrew for personal reasons

Participant characteristics	
Sex	9 male/5 female
Age	29-59 years
Race	7 Black or African American/7 White
Ethnicity	2 Hispanic or Latino
Mean (standard deviation) BMI	26.3 (2.9) kg/m^2

Table 1. MK-8507 PK results

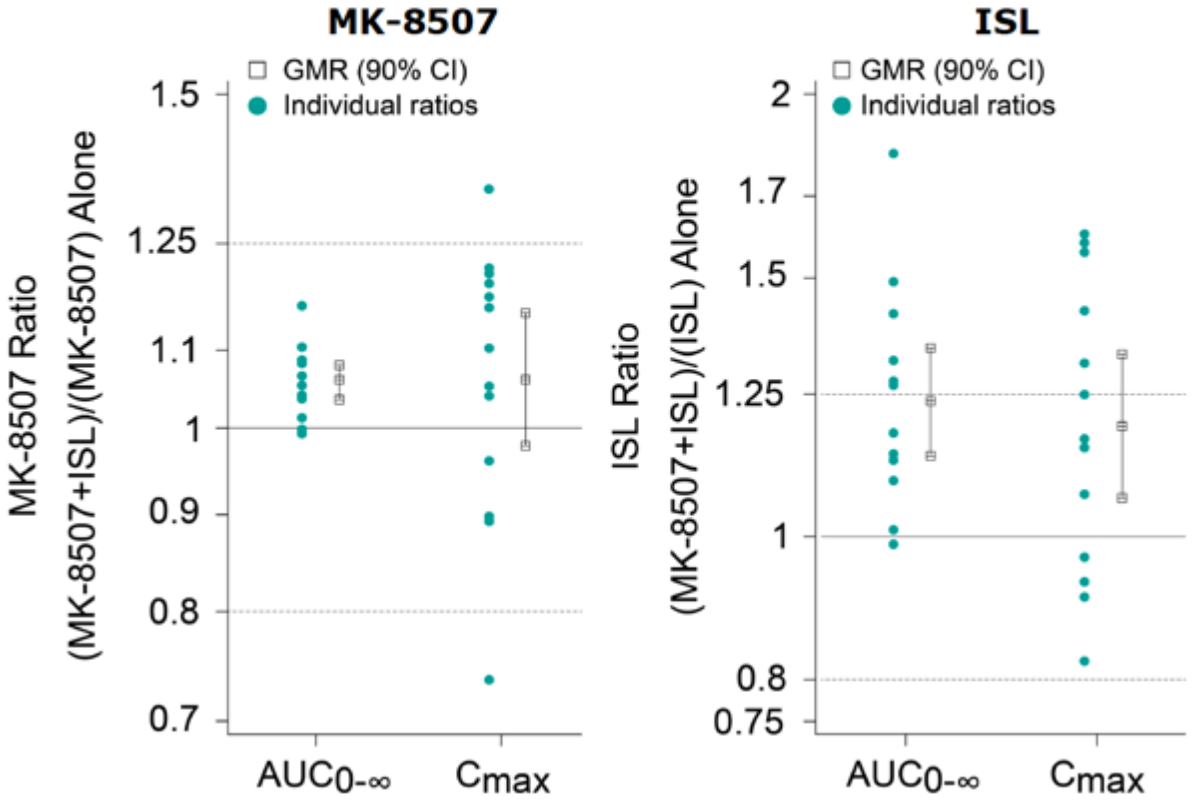
Pharmacokinetic Parameter	MK-8507 + ISL			MK-8507 Alone			MK-8507 + ISL/MK-8507	
	N	GM	95% CI*	N	GM	95% CI*	GMR (90% CI)	% CV
$AUC_{0\text{-}168}$ (hr*µmol/L)	13	750	(685, 821)	13	702	(630, 783)	1.07 (1.04, 1.09)	3.5
C_{max} (µmol/L)	13	11.7	(10.6, 12.8)	13	11.0	(9.34, 12.9)	1.06 (0.98, 1.15)	11.6
C_{168} (µmol/L)	13	2.12	(1.83, 2.45)	13	1.43	(1.25, 1.64)	1.48 (1.41, 1.55)	6.7
T_{max} (hr)	13	4.00	(2.00, 4.03)	13	4.00	(2.00, 6.00)		
Apparent terminal $t_{1/2}$ (hr)	13	85.8	16.9	13	89.9	21.0		

Table 2. Islatravir PK results

Pharmacokinetic Parameter	MK-8507 + ISL			ISL Alone			MK-8507 + ISL/ISL	
	N	GM	95% CI*	N	GM	95% CI*	GMR (90% CI)	% CV
$AUC_{0\text{-}168}$ (hr*nmol/L)	13	2.45	(2.12, 2.83)	14	2.10	(1.84, 2.39)	1.17 (1.07, 1.27)	12.4
$AUC_{0\text{-}\infty}$ (hr*nmol/L)	13	2.91	(2.51, 3.37)	14	2.35	(2.06, 2.69)	1.24 (1.14, 1.34)	11.9
C_{max} (µmol/L)	13	0.490	(0.401, 0.599)	14	0.412	(0.342, 0.496)	1.19 (1.06, 1.33)	16.0
T_{max} (hr)	13	1.00	(0.50, 4.00)	14	1.00	(0.50, 2.00)		
Apparent terminal $t_{1/2}$ (hr)	13	119	6.6	14	88.4	14.7		

Geometric mean ratios and individual ratios of AUC and C_{max} ([coadministered]/[alone]) and 90% confidence intervals

(N=14 for ISL alone, N=13 for MK-8507 alone and MK-8507 + ISL)



- Coadministration of MK-8507 and ISL did not meaningfully affect PK of either compound
- Results support further clinical development of this 2-drug once-weekly regimen

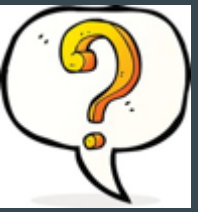
Conclusion

- Optimal PKs characteristics on Cyp metabolism and drug transporters
- Optimal DDI profile with common use drugs or in particular setting
- Novel oral ARVs for Prep

Elderly

HTE

Woman



Lack information on inflammation, inflammaging, tissue penetration and viral reservoirs

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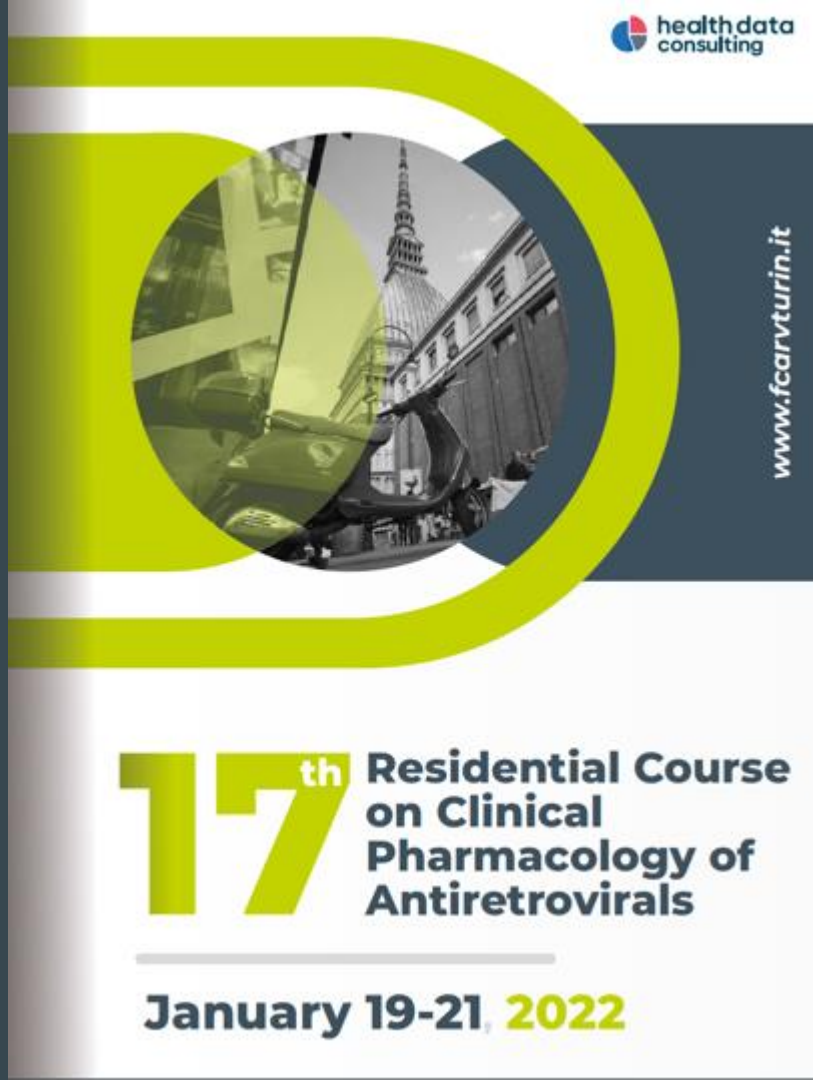
J. Mula

Thank you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January 19-21, 2022