Using Lenacapavir and Fostemsavir in Practice

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November 7, 2025

Disclosures/Acknowledgements

- Consulting/advisory boards: Gilead, Merck, ViiV
- Research grants/coinvestigator: Gilead, Merck, ViiV

Mr. K

- 70 yo male, HIV+ since 1990, MDR-HIV. Virally suppressed since 2001; on dolutegravir and darunavir/cobicistat

- Comorbidities:
  - stroke, depression, diabetes, hypertension, renal insufficiency (eGFR 40)

- Comedications:
  - citalopram 20 mg
  - diltiazem 180 mg
  - loxapine 10 mg
  - methylphenidate 10 mg BID
  - pantoprazole 40 mg
  - rosuvastatin 20 mg
  - benztropine 1 mg BID
  - ferrous fumarate 300 mg
  - KCl 8 mmol

Mr. K

- Recent admission for falls/upper GI bleed. DOAC changed from edoxaban to apixaban 2.5 mg BID due to renal function.

- Significant interaction between darunavir/cobicistat and apixiban
  - Contraindicated in Canadian monograph
  - US monograph states ok to reduce apixiban by 50% to 2.5 mg BID in normal renal function; avoid if already taking low dose apixaban

- Options to replace darunavir/cobicistat with new ARV?

Lenacapavir vs Fostemsavir

	Lenacapavir	Fostemsavir
Dosing	SC q6 months	PO 600 mg BID
Side effects	nodules	QT (++ doses)
DDIs	Moderate CYP3A4 inhibitor	Inhibits OATP1B1/3, BCRP
Contraindications	Strong CYP3A4 inducers	Strong CYP3A4 inducers
Coverage	Compassionate access	Compassionate access
Other	Still need other ARVs which are dosed more frequently	CD4 boosting effect?

Fostemsavir use in Trio cohort

- N=77 prescribed FTR
  - N=46 (60%) viremic, FTR + new OBT
  - N=31 (40%) suppressed, FTR most commonly added to existing ART (70%)

Figure 1: Virologic Suppression At 6-/12-Months Follow-up on FTR

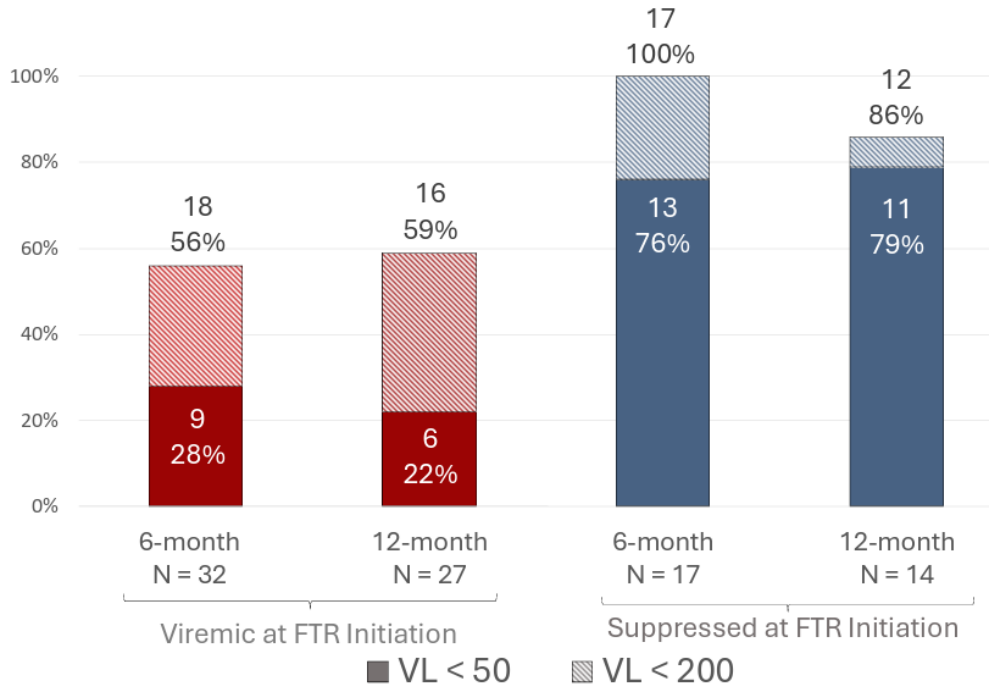
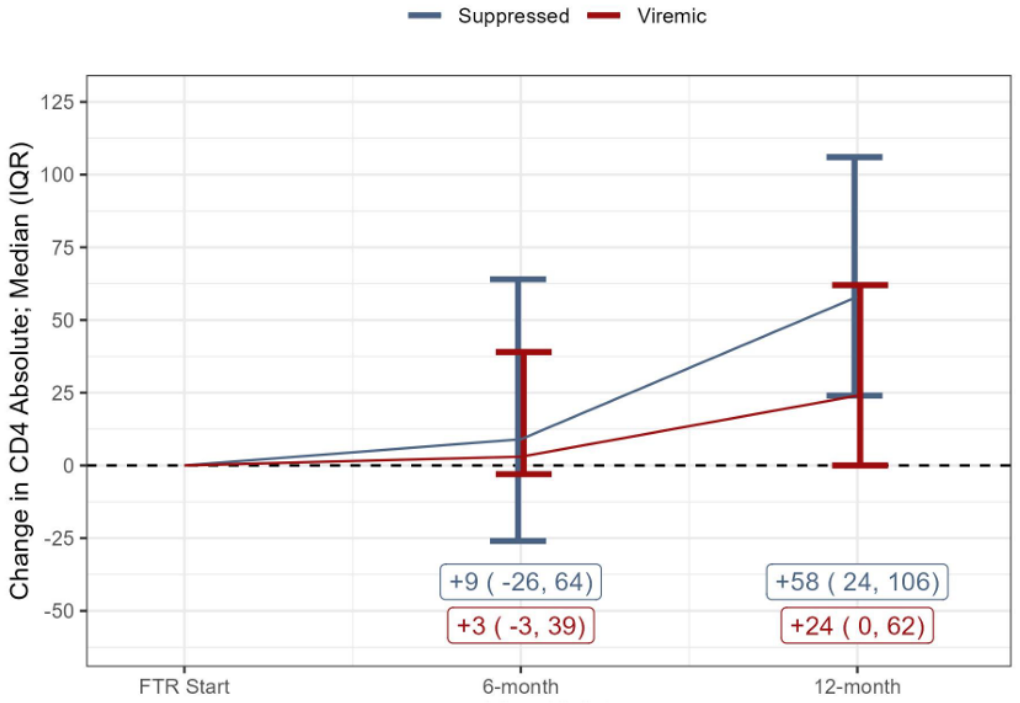


Figure 2: Immunologic Outcomes at 6-/12-months on FTR



- those suppressed at FTR initiation had higher gains in CD4 vs those viremic at start; similar proportions of CD4 recovery observed among those with baseline CD4<350

Ramgopal et al. CROI 2025, #699.

Mr. K – con't

- Switched to fostemsavir 600 mg BID plus dolutegravir 50 mg daily

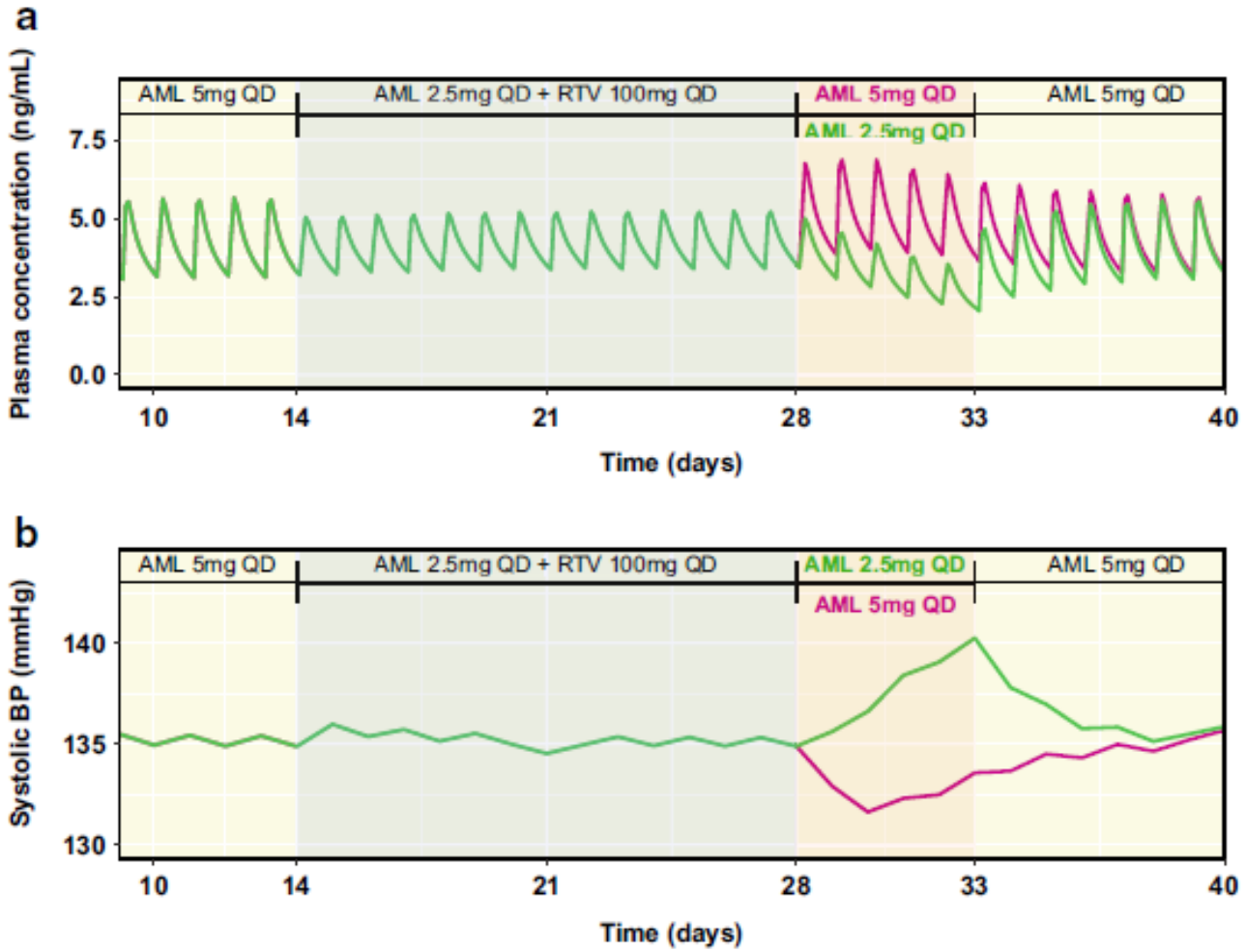
- Two months later, elevated BP (in 200s) noted at nephrology follow-up
- Nephrologist felt it was due to fostemsavir, recommended going back to darunavir/cobicistat

Mr. K – con’t

- Hypertension not mentioned in fostemsavir monograph
- Removal of darunavir/cobicistat likely led to a reduction in diltiazem

After discontinuing ritonavir, amlodipine concentrations drop and blood pressure increases

- Modelling study on dose adjustment of calcium channel blocker (amlodipine) with/without ritonavir



Mukherjee et al. J Pharmacokinet Pharmacodynamics 2018;45:443-56.

Mr. K – con’t

- → explained mechanism of interaction with nephrologist, agreed to go back to fostemsavir
- Titrate diltiazem from 180 mg to 240 mg daily, then 360 mg if needed

Mr. A

- 55 year old male, HIV+ since 1992

Dates	ARV	Response
1992-2003	RTI monotherapy, triple therapy with unboosted PIs	Detectable VL
2003-2013	RTIs + boosted PIs	Virally suppressed, then stopped ARVs
2013-2015	Rilpivirine/F/TDF + darunavir/r	Virally suppressed
2015-2019	Rilpivirine/F/TDF + dolutegravir	Virally suppressed, developed Fanconi's (TDF)
2019-2021	Rilpivirine/dolutegravir	Virally suppressed
2022	"	VL 3,290 copies/mL

Mr A: Genotypes

Date	NRTI	NNRTI	PI	InSTI	Tropism
05/2003	211K		20I, 36I		
02/2005	74V, 184V, 211K	135V	20I, 36I, 46I, 76V		
09/2006	39A, 211K	98wt/S, 135V	13V, 20I, 36I		
01/2007	211K	135V	13V, 20I/V, 36I		
08/2009	335D, 371V	-	13V, 20I, 36I, 64M, 69K, 89M		
07/2012	335D, 371V	98wt/S	13V, 20I, 36I, 64M, 69K, 89M		
10/2013	-	98S	13V, 20I, 36I, 37N, 64M, 69K, 89M		Non-R5
07/2022	-	90I/wt, 101E, 221wt/Y	20I	138K, 148K	

Composite genotype (Stanford)

	Susceptible	Low-level R	Intermediate R	High-level R
PIs	Tipranavir/r	Darunavir/r Atazanavir/r, saquinavir/r (potential)	Indinavir/r, lopinavir/r	Fosamprenavir/r
NNRTIs		Doravirine efavirenz Etravirine	Nevirapine	Rilpivirine
NRTIs	AZT, d4T, tenofovir			Abacavir, Emtricitabine Lamivudine
INSTIs			Bictegravir dolutegravir	Cabotegravir Elvitegravir Raltegravir
CCR5				maraviroc

Mr A: ARV options?

- PI: darunavir/cobicistat (low-level resistance)
- RTI: 3TC (for viral fitness)? Use of TAF (renal safety? Access?) None?
- NNRTI: use etravirine or doravirine? (low-level resistance)
- New drug class: lenacapavir or fostemsavir?

Mr A: Follow-up

- Approved to receive lenacapavir plus darunavir/cobicistat

Date		Viral Load	CD4
Nov/2022	Started lenacapavir + darunavir/cobicistat	6650	435
Dec/2022	1st LEN injection	1530	483
Jan/2023	Tolerating well	265	
Mar/2023	"	<20	745
Jun/2023	2nd LEN injection	<20	543

- Continues to receive on-time LEN injections q6months, adherent to oral ART
- Remains virally suppressed, next LEN (7th!) dose: Nov 2025

Mr. G

- 85 year old male, HIV+ since 1994, MDR-HIV, numerous ADRs.
  - RTI monotherapy, unboosted PIs, mega-HAART

- Virally suppressed since 2006:
  - 2006-2007: TDF, ABC, etravirine, LPV/r, enfuvirtide
  - 2007-2010: ABC/3TC, etravirine, darunavir/r
  - 2010-2012: ABC/3TC, atazanavir/ritonavir BID
  - 2012-2017: atazanavir/ritonavir BID
  - 2017-2021: darunavir/cobicistat

Mr. G

- 2019: started having swallowing challenges, occasional non-adherence
- 2021: stopped taking darunavir/c, VL 152,000 copies/mL
- Restarted darunavir/c (crushed) + dolutegravir, VL <20

- 06/2023: no longer able to tolerate crushed darunavir/c (bitter taste)

Feb/2004: Genotype analysis (Stanford)

		Susceptible	Low-level R	Intermediate R	High-level R
PIs	Other: 20R, 77I	ALL			
NNRTIs	101E, 103N, 190A		Doravirine, etravirine		Efavirenz, nevirapine, rilpivirine
NRTIs	41L, 67N, 70R, 41I, 184V, 215F, 219E			Tenofovir	Abacavir, Emtricitabine Lamivudine, AZT
INSTIs	-	ALL			
CCR5	Non-R5				maraviroc

Mr. G

- Sep/2023: switched to LEN + daily dolutegravir
  - Receiving injections at home

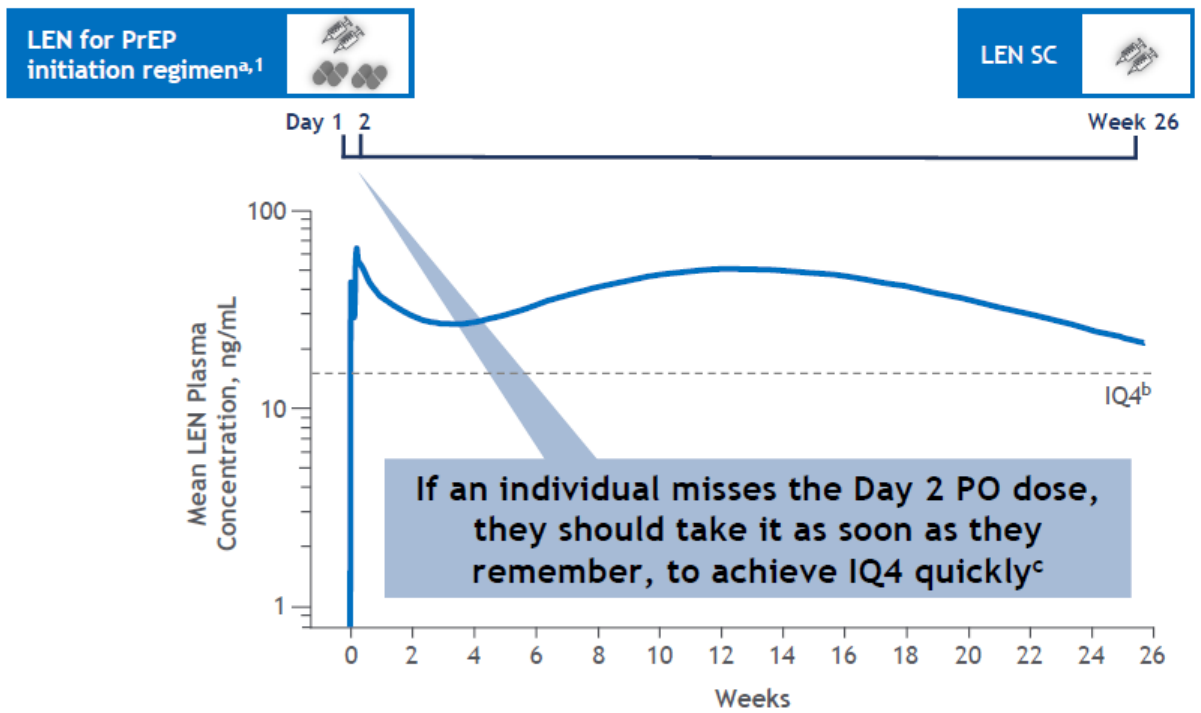
- Sep 2025:
  - Remains on LEN + DTG; still virally suppressed
  - Moved into assisted living facility

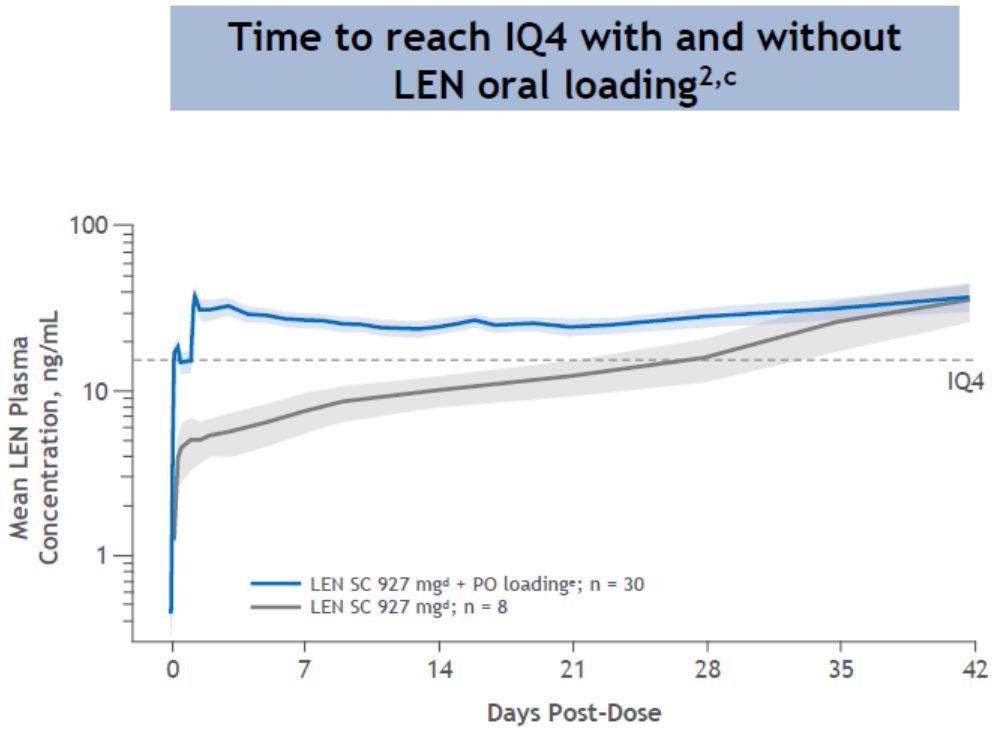
Additional Thoughts

- Able to obtain compassionate access to LEN outside of standard criteria
- Patient could still swallow oral LEN tablets & oral dolutegravir

https://www.askgileadmedical.com/docs/sunlenca/sunlenca-crushing-or-splitting-tablets

LEN Initiation Dosing with Oral Loading Achieves LEN Target Concentrations by Day 2 through Week 26[1]





Omission of LEN oral loading significantly delays achievement of target concentrations

Bekker L-B. IAS 2025.

Sunlenca® (lenacapavir)
Crushing or Splitting of Tablets

Product Labeling[1]

There is no information in the LEN product labeling about the crushing or splitting of LEN and therefore, it is not recommended that LEN be administered as a crushed or split tablet.

LEN is practically insoluble in water.

Available Data on Crushing and Splitting of Tablets

Gilead Data

Crushing LEN tablets and adding into a liquid medium has not been studied and is not recommended. Currently, there are no studies evaluating the pharmacokinetics (eg, oral bioavailability) of a crushed LEN tablet dispersed into a liquid medium (eg, milk, water, juice) compared to a whole tablet.

Similarly, splitting LEN tablets has not been studied and it is not recommended. Currently, there is no study evaluating the pharmacokinetics of a split tablet versus a whole tablet.

https://www.askgileadmedical.com/docs/sunlenca/sunlenca-crushing-or-splitting-tablets

Use of new ARVs at TGH (case series)

	Age	Time on ART (yrs)	VL at switch	Co-morbidities	Comeds	Reasons for switch	OBR	Follow-up/ viral suppression
Fostemsavir (n=6) 5 M/1 F	66	32.5	• N=4 TND/<20 • n=2 @ 60 c/mL	6	7.5	DDI (n=6)	• B/F/TAF, DOR (n=3) • B/F/TAF DTG BID, DOR • DTG, MVC	• 29 months (9-33) • 100%
Lenacapavir (n=4) 3 M/1 F	60	30	• N=1 <20 • 6650-114,000	1.5	3	intolerance (n=1), viremia (n=3)	• DTG • DTG/3TC, DRV/c • DRV/c • CAB	• 18 months (11-32) • 100%

*values provided as medians

Summary

- Both fostemsavir and lenacapavir are effective agents for people with multi-drug resistant virus
- Different PK properties, dosing schedules and DDI profiles which can impact choice