State-of-the-Art Cases on Antiretroviral Therapy

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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Gandhi has no relevant financial affiliations to disclose. (Updated 11/04/21)

Slide 2

Case #1

52 yo man diagnosed with HIV 30 years ago

- AZT/3TC then AZT/3TC/nevirapine then TDF/FTC + efavirenz in 2002 (and single pill combination in 2007)
- Had off-and-on problems with adherence and viral load detectability over time with emergence of K65R, M184V, K103N, D67N
- Switched to RAL/ETR/DRV/r BID in 2008, then DTG/DOR/DRV/cobi once daily in 2018
- Low-grade viremia from variable adherence (current VL 830 copies/mL), no new mutations from above,
- Wants a change from 3 pills a day ("I can't do this anymore"), housed, food secure

ARS: What is the regimen you would choose for this patient?

1. BIC/TAF/FTC
2. DRV/cobi/DTG
3. DTG/RPV
4. CAB/RPV IM
5. DRV/cobi/TAF/FTC

Genotype shows K65R, M184V, D67N, K103N in the RT gene

Case #1 continued

- The patient started by your colleague on BIC/TAF/FTC who said "you can't get INSTI mutations on bictegravir"

ARS: In rare cases, which of the following is an emerging signature mutation for bictegravir?

1. N155H
2. E92Q
3. Q148H
4. L74I
5. R263K

Serial passage experiments in cell culture with increasing amounts of drug -not *in vivo*

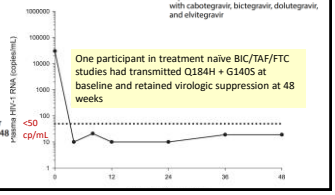
Drug	Week 8	Week 16	Week 24-30	Week 43-46
		Acquisition of resistance mutations		
DTG	wt	wt	wt	H51HY
DTG	wt	R263K	R263K	R263K
BIC	wt	S153Y	S153Y	S153Y
BIC	wt	E157K	E157K, S153FS	~~E157KK, S153FS~~
CAB	S153FS	Q148K	T97AT, G140S, S147GS , Q148K	L74M, G140S, S147G, Q148K
CAB	R263KR	R263KR, Q148R, E138EK	L74LM, R263K, Q148R, E138K	L74LM, R263K, Q148R, E138K
EVG	wt	wt	R263K, S153A	R263K, S153A
EVG	T66I	T66I, S147G, G163GR	T66I, S147G, G163GR	T66I, Q146R, S147G, Q95R

BIC resistance didn't emerge in naïve or switch studies (genotypes –not proviral DNA- WT)

Selective resistance profiles emerging in patient-derived clinical isolates with cabotegravir, bictegravir, dolutegravir, and elvitegravir

Antimicrobial Agents and Chemotherapy

Resistance Analysis of Bictegravir-Emtricitabine-Tenofovir Alafenamide in HIV-1 Treatment-Naive Patients through 48 Weeks



One participant in treatment naïve BIC/TAF/FTC studies had transmitted Q184H + G140S at baseline and retained virologic suppression at 48 weeks

- NGS performed in advance of BIC/FTC/TAF initiation in 48-yr-old woman hospitalized at MHH medical center in Hannover, Germany; R263K with BIC high-level resistance (and M184V) emerged

	Apr 2019	June 2019	Aug 2019	Oct 2019	Jan 2020	Apr 2020	July 2020
ART	Diagnosis	BIC/FTC/TAF			DRV/COBI/FTC/TAF		
HIV-1 RNA	2 x 10^6 c/mL		200 c/mL	700 c/mL	1000 c/mL	4000 c/mL	5000 c/mL
CD4+ cell count	75 cells/mm³		400 cells/mm³	300 cells/mm³			
Health Status		PML. Patient not able to speak	Quick PML symptom improvement	Worsened, palliative care, enteric adhesions	Treatment failure occurs	Lives at home, somatotrop targets ART	
High Level Resistance							

4 case reports of BIC failure: R263K may be "signature" mutation

Case 1: 48 year old woman in Germany presented at HIV Glasgow (Braun et al.) with high viral load on diagnosis (2 million), low CD4 (75), no resistance at baseline on BIC/TAF/FTC poor adherence 2 PML, **developed M184V, R263K and failed BIC**

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Failure to bictegravir and development of resistance mutations in an antiretroviral-experienced patient

Case 2: Antiretroviral experienced patient with poor adherence. BIC/TAF/FTC started with 1 million viral load; Cerebral toxo developed; After 2 months, **rebound on BIC with M184V, R263K**

Case Report: Emergent Resistance in a Treatment-Naive Person With Human Immunodeficiency Virus Under Bictegravir-Based Therapy

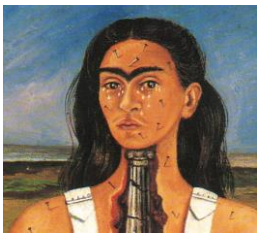
Open Forum Infectious Diseases

Case 3: 51 yo M, newly dx'd with HIV (CD4 16, VL 3.7M), Cryptococcal Meningitis L74I mutation on diagnosis. Poor adherence on BIC/TAF/FTC, developed M184 then R263K

Case 4: 54 yo man at Ward 86 with poor adherence to BIC/TAF/FTC, first evolved **M184V, then R263K** with high-level virologic failure

Case #1 continued

- The patient quickly switched off BIC/TAF/FTC and on to DTG/RPV
- Called 2 weeks later and patient said he likes it better but taking at his usual adherence pattern of 1-2 missed doses a week



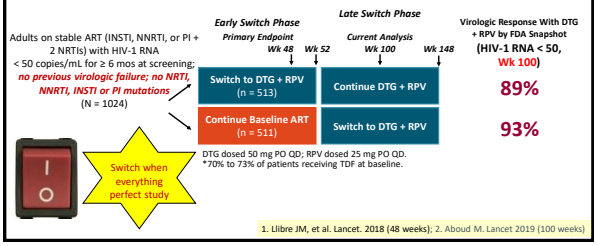
ARS: The SWORD trials (DTG/RPV) excluded participants with prior virologic failure or any mutations, but do you use DTG/RPV with NRTI mutations?

1. No, I adhere to the inclusion criteria in my decisions
2. Yes, NRTI mutations will not affect this regimen
3. Yes, but I assess adherence first
4. I have not, but this question is getting me thinking..

Spotty adherence; Genotype shows K65R, M184V, D67N, K103N in the RT gene

SWORD-1 and -2: Switch to DTG + RPV vs Continuation of Baseline ART in Virologically Suppressed Adults (100 wks)

- Parallel, randomized, open-label, multicenter phase III noninferiority studies[1,2]



1. Llibre JM, et al. Lancet. 2018 (48 weeks); 2. Aboud M. Lancet 2019 (100 weeks)

Case #1 continued

- Although you are increasingly using DTG/RPV single pill combination in patients with NRTI or PI or K103N mutations if they are now adherent, patient misses 1-2 doses a week
- You switch to DRV/cobi/TAF/FTC single pill combination

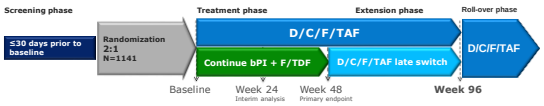
DRV/COBI/TAF/FTC

- **FDA approved on July 17, 2018:** Complete regimen in adults who are *either* ART naive *or* virologically suppressed on stable ART for ≥ 6 mos with no known resistance substitutions to DRV or TFV[1]

PROS	CONS
▪ DRV has the highest genetic barrier to resistance of ARVs[2] ▪ First PI-based STR[3] ▪ 10 mg of TAF so no more 25 mg TAF with DRV/COBI[1] ▪ Works against NRTI-resistant virus (EMERALD)[4,5]	▪ PI-based and has COBI booster[1] ▪ DRV trough with DRV/COBI lower than with DRV/RTV[6] ▪ Use a PI when you need a PI only, not first line[7]

1. DRV/COBI/TAF/FTC PI. 2. Tang. Drugs. 2012;72:e1. 3. Sax. NEJM Journal Watch. July 22, 2018. 4. Orkin. Lancet HIV. 2018;5:e23. 5. Eron. CROI 2018. Abstr 502. 6. Kakuda. J Clin Pharmacol. 2017;54:949. 7. DHHS Guidelines. October 2018.

EMERALD: Phase 3, Randomized, Open-label, Multicenter Trial



Primary objective: Assess efficacy (non-inferiority) and safety of switching to D/C/F/TAF vs continuing bPI + F/TDF regimens in virologically suppressed adults until Week 48

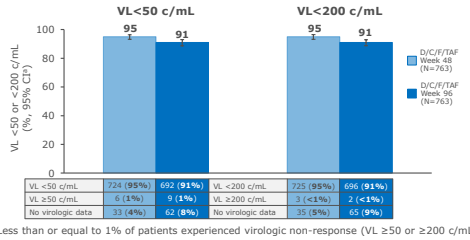
Secondary objectives to evaluate long-term safety, resistance and efficacy of D/C/F/TAF (**until Week 96 and beyond**)

Key inclusion criteria:

- On a stable bPI + F/TDF regimen for ≥6 months
- VL <50 c/mL for ≥2 months before screening; one 50≤VL<200 c/mL within 12 months prior to screening allowed
- Previous ART VF allowed (no history of VF on DRV-based regimens), and if historical genotypes were available, absence of DRV RAMs[1]; no restriction on FTC or tenofovir RAMs

[1]Eron. AntiViral Research 2019

FDA Snapshot at Weeks 48 and 96 in D/C/F/TAF arm (ITT)



VL <50 c/mL	724 (95%)	692 (91%)	VL <200 c/mL	725 (95%)	696 (91%)
VL ≥50 c/mL	6 (1%)	9 (1%)	VL ≥200 c/mL	3 (<1%)	2 (<1%)
No virologic data	33 (4%)	62 (8%)	No virologic data	35 (5%)	65 (9%)

- Less than or equal to 1% of patients experienced virologic non-response (VL ≥50 or ≥200 c/mL)
- **No discontinuations for efficacy reasons**

Resistance Analysis Through Week 96 in EMERALD

- Post-baseline genotyping performed in those with VL ≥400 c/mL at failure, 11 rebounders, no DRV-associated mutations but 1 M184V
- In participants with prior VF and genoarchive data (*N* = 140; 98 D/C/F/TAF and 42 control),
  - 4% had viruses with darunavir RAMs
  - 38% with emtricitabine RAMs, mainly at position 184 (41% not fully susceptible to emtricitabine)
  - 4% with tenofovir RAMs
  - 21% ≥ 3 thymidine analog-associated mutations (24% not fully susceptible to tenofovir) detected at screening.
- **All achieved VL <50 copies/mL**

Lathouwers J. Med Virol. 2021

ARS: Was there ever a trial performed of DTG plus boosted DRV as 2-drug therapy?

1. No, but it makes sense this would work
2. Yes, the DUO trial
3. Yes, the FOXTROT study
4. Yes, the DUALIS study
5. Yes, the Doppelgänger study

DUALIS study

Open Forum Infectious Diseases

MAJOR ARTICLE

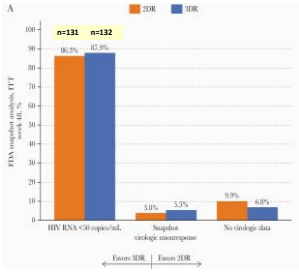
IDSA hivma

Efficacy and Safety of Switching to Dolutegravir With Boosted Darunavir in Virologically Suppressed Adults With HIV-1: A Randomized, Open-Label, Multicenter, Phase 3, Noninferiority Trial: The DUALIS Study

Published August 13, 2020

DUALIS study

- Phase 2b study of switching to DTG + DRV/r from 3-drug regimen with 2 NRTIs + DRV/r
- Participants had to be virologically suppressed x 6 months, no h/o DRV-associated mutations or INSTI mutations
- Study had to be terminated early due to low enrollment since DRV/r regimens less used (~130 in each arm)
- Equal rates of VS in each arm out to 48 weeks; lipids better with tenofovir



Case #1 continued

- You tried to put patient on DTG/DRV/cobi, but he points out to you doesn't feel "that different" from DTG/DRV/cobi/DOR and he wants one pill once a day
- So you try DTG/RPV

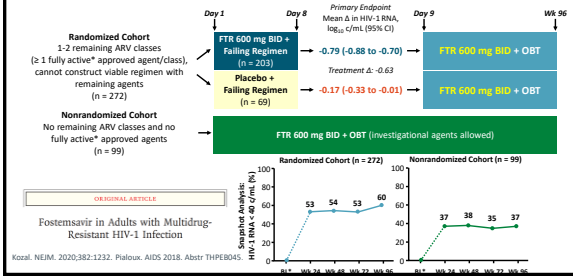
Case 1 continued

- Pt does fine for 2 months on DTG/RPV with virologic suppression despite K65R, K103N, M184V, D67N
- But viral load 830 by 3rd month
- New genotype shows emergence of E138K mutation (RPV RAM) and Q148H/N155H (INSTI mutations)
- Pt now has resistance to RPV, INSTIs, NRTIs

ARS: What regimen would you use next?

1. Fostemsavir + DRV/cobi + doravirine
2. Doravirine + DRV/cobi
3. Fostemsavir + DRV/cobi
4. Fostemsavir + DOR
5. Fostemsavir + Ibaluzimab

Fostemsavir (attachment inhibitor) approved July 2, 2020 for heavily treatment experienced patients



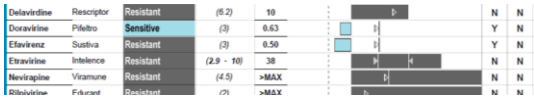
ORIGINAL ARTICLE

Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection

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

Case #1 continued

- Phenotype confirms persistent doravirine susceptibility with the K103N, E138K mutations so you change to DRV/cobi + DOR
- Pt now on one less drug than before (DTG) but with INSTI resistance; fostemsavir BID so you will maintain on two drugs but stress importance of adherence



ARS: Have you started a patient on injectables yet?

1. Yes
2. No
3. Still figuring it out
4. Waiting for even longer-acting ART

Case 2

- 49 yo MSM with h/o HIV since 2003
- Was started on EFV/TDF/FTC at time (SPC In 2006) but developed viral load to 2400 copies/mL, K103N mutation in 2008
- Switched to RAL/TDF/FTC at that time
- Changed to ELV/cobi/TDF/FTC in 2012 and then DTG/ABC/3TC in 2014
- Has maintained virologic suppression since
- Now comes to you saying – give me the shots, read about them, but I want them as infrequently as possible, very busy
- No other PMH, no other meds, married and husband HIV-negative not on PrEP

ARS: Would you give this patient injectable CAB/RPV?

1. No, has history of K103N mutation (NNRTI)
2. Yes, every 4 weeks
3. Yes, every 8 weeks
4. Yes, every 4 weeks for a while, then I would be comfortable switching to 8 weeks
5. Have great bedside manner and say "how hard is it to take one pill once a day, for Pete's sake?"

Implementation challenges for long-acting antivirals as treatment

2015

Diane Havlir and Monica Gandhi

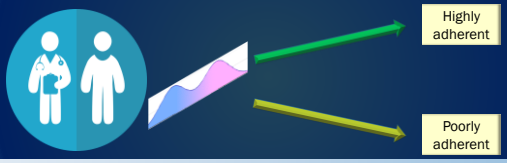
Oral ART has been revolutionary for HIV but challenges persist, including

- Difficulties in patients linking to or staying in care
- Maintaining adherence to daily medications
  - Youth, marginal housing, mental illness, cognitive impairment, food insecurity, substance use, adverse effects, etc.
- Pill fatigue
- Cost constraints and lack of political will to ensure even access to ART
- Stigma of daily pill
- **Reminder that "I have HIV"**

1987

1998

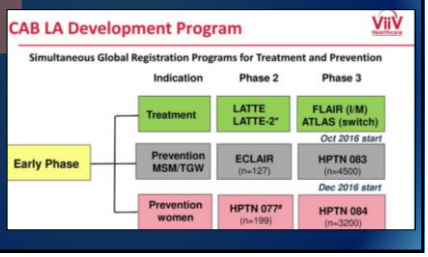
Bimodal population wanting/needing long-acting ART often invoked prior to approval



Barriers for "highly adherent" may be circumvented by shot clinics (in and out), pharmacies or mobile vans administering the shots, constant supply of oral CAB/RPV at home for bridges, training to do home injections

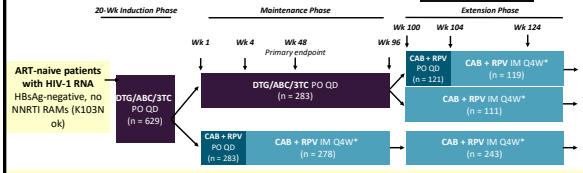
Let's remind ourselves of the inclusion criteria of the pivotal studies for long-acting CAB/RPV

ÉCLAIR showed us q12 weeks in low-risk population had too low of levels (some HIV infections)



FLAIR
Naïve study: "Flair for new things"

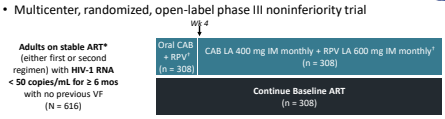
- Multicenter, randomized, open-label, phase III noninferiority study



- Naïve patients, only K103N okay, suppressed on DTG/ABC/3TC x 20 weeks
- Then oral "lead in" of CAB 30mg/RPV 25mg x 28 days (111 went straight to LA)
- Then CAB 600mg IM/RPV 900mg IM x 1 (load), then CAB 400mg/RPV 600mg every 4 weeks

ATLAS
Switch study: "Ah, you have traveled before"

- Multicenter, randomized, open-label phase III noninferiority trial



- 1st or 2nd regimen, no VF in past, no known INSTI or NNRTI mutations (K103N okay), suppressed x 6 months <50 copies/mL
- Then oral "lead in" of CAB 30mg/RPV 25mg x 28 days then initiation dose (CAB 600mg IM/RPV 900mg IM), then maintenance every 4 weeks (400/600)

ARS: So, your patient fits the inclusion criteria of the ATLAS study. How would you give the shots now?

1. Every 4 weeks
2. Every 8 weeks
3. Every 4 weeks for a while, then I would be comfortable switching to 8 weeks
4. Can we discuss CAB resistance seen at 8 weeks (even in the prevention trials) to make sure we are comfortable?

Let's look at 3 major trials to assess resistance on CAB/RPV

FLAIR

- Now have data out to 124 weeks

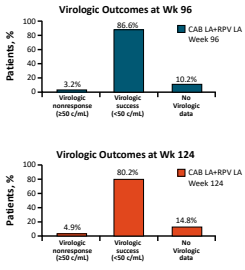
ATLAS and ATLAS 2M

- We now have data on ATLAS and from the ATLAS 2M trial that changed from every 4 weeks to every 8 weeks

HPTN 083

- Yes, the resistance data from Cabotegravir given every 8 weeks for prevention will have relevance here

FLAIR: Viral Suppression Through Week 124



THE LANCET

Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study

- 4 failures up to week 96; 1 additional failure between 96-124 weeks (at 108 weeks – male, BMI 24.7, ended up being treated with EFV/TDF/FTC after and suppressed)
- Of the 14.8% "without virologic data", most discontinued with AEs

IAS 2021 18 - 21 July

Orkin. IAS 2021. Abstr OAB0302.

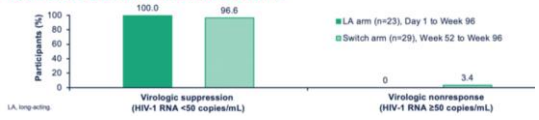
Study	INSTI mutations	Baseline mutations	Time of virologic failure	Drug Sensitivity at failure (fold change)
FLAIR	G140R	L74I	Week 28	CAB(6.7)
FLAIR	Q148R	L74I	Week 20	CAB (5.2)
FLAIR	Q148R	L74I	Week 48	CAB(9.4)
FLAIR (on orals only, never on inj)	None	None		
FLAIR	N155H, R263K	None	Week 108	CAB (2.7)

ATLAS: 96 week data

- CAB LA + RPV LA was non-inferior to continuing 3 drug ART
- In CAB + RPV arm, 3 failures (2 of 3 had baseline NNRTI RAMs)

HIV Drug Therapy GLASGOW 2020

Figure 2. ATLAS Week 96 Virologic Outcomes



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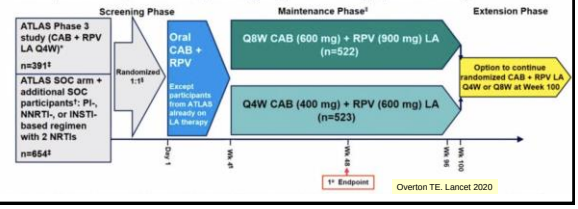
FLAIR (on orals only, never on inj)	None	None		
FLAIR	N155H, R263K	None	Week 108	CAB (2.7)
ATLAS	None	L74I	Week 8	
ATLAS	N155H	E138K, L74I	Week 20	CAB(2.7)
ATLAS	None	V108V/I E138K	Week 12	

Cabotegravir and Rilpivirine LA every 8 weeks

- ATLAS 2M – after q4 weeks, tried q8 weeks vs q4 weeks (ATLAS 2M)

Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study

Phase 3, randomized, multicenter, parallel-group, noninferiority, open-label study

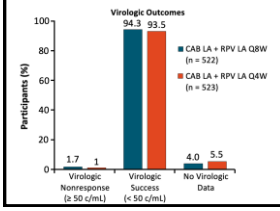


Overton TE. Lancet 2020

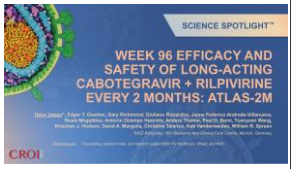
THE LANCET

48 weeks

Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study



96 weeks



ATLAS-2M: By Week 96, 11 confirmed virologic failures

CVFs Through Wk 96	n	CVFs (%)	CVFs With RPV RAMs	RPV RAMs Observed at Failure	CVFs With IN RAMs[†]	Integrase RAMs at Failure
Q8W	522	9 (1.7)	7/9	K101E, E138E/K, E138A, Y188L, Y181C	5/9	Q148R,[‡] N155H[‡]
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

- In Q4W arm, 2 virologic failures
- In Q8W arm: 8 virologic failures until week 48, one additional failure at week 88
- Phenotypic susceptibility to DTG retained in all virologic failures

Jaeger. CROI 2021. Abstr 401.

Study	INSTI mutations(n)	Baseline mutations(n), NNRTI	Time of virologic failure	Drug Sensitivity at failure (fold change)
FLAIR	G140R	L74I	Week 28	CAB(6.7)
FLAIR	Q148R	L74I	Week 20	CAB (5.2)
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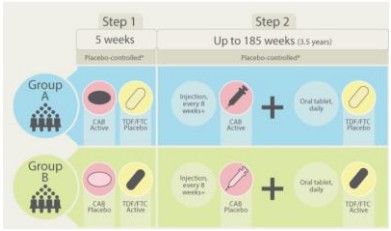
FLAIR (on orals only, never on inj)	None	None		
FLAIR	N155H, R263K	None	Week 108	CAB (2.7)
ATLAS	None	L74I	Week 8	
ATLAS	N155H	E138E/A ,L74I	Week 20	CAB(2.7)
ATLAS	None	V108V/I E138K	Week 12	
ATLAS 2M (8wk) 9 failures	5/9 with INSTI mutations: Q148R(3),N155H(3), T97A(2),G140R(1)	**NNRTI:**Y181C plus H221Y(1); Y188Y/F/H/L(1); Y188L(1); E138A(2) **INSTI:**G140R(1) L74I (6)	7: before week 24 1: week 24-48 1: week 88	
ATLAS 2M(4wk) 2 failures	N155N/H(1),E138E/K +Q148R(1)	None	Before week 24	

ARS: What do you think the ranking is for genetic barrier to resistance for the INSTIs (lowest to highest)?

1. Elvitegravir < Raltegravir < Cabotegravir < BIC/DTG
2. Raltegravir < Elvitegravir < Cabotegravir < BIC/DTG
3. Raltegravir/Elvitegravir < CAB/BIC/DTG
4. Raltegravir/Elvitegravir < DTG/BIC < CAB
5. On CAB- I don't like this 8 week burst of resistance in the treatment trials

HPTN 083 and 084 Study Design

- Phase 2b/3 randomized, double-blind, double-dummy
  - Oral lead in phase with PO (placebo v CAB) 5 weeks
  - Transition to Q8w injections (placebo v CAB)



ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

HIV infections in HPTN 083 trial of CAB LA PrEP among MSM, transwomen			
Timing or category of infection	**N**	**No. with INSTI mutations after study product exposure**	
Undetected HIV infection at baseline	4	1	1) E138K, Q148K
No recent CAB exposure	5	0	
Infected during oral lead-in	3	2	1) L74I, E138E/K, G140G/S, Q148R 2) E138A, Q148R
Infected despite on-time injections	4	2	1) R263K 2) G140A, Q148R
Total	**16**	**5 (31%)**	

5 out of 16 failures in HPTN083 (q8 weeks) evolved INSTI resistance - concerning for treatment too

Final CAB resistance table: look at that 8 week data

Study	INSTI mutations(n)	Baseline mutations(n)	Time of virologic failure
FLAIR (5 failures of which 1 never started injectables)	G140R (1), Q148R(2), N155H (1), R263K(1)	L74I (3)	Week 20,28,48, 108
ATLAS (3 failures)	N155H(1)	L74I(2), E138E/A, E138K, V108V/I	Week 8, 12,20
ATLAS 2M (8 weeks) (9 failures)	5/9 with INSTI mutations: Q148R(3),N155H(3),T97A(2), G140R(1)	**NNRTI:**Y181C plus H221Y(1); Y188Y/F/H/L(1); Y188L(1); E138A(2) **INSTI:**G140R(1) L74I (6)	7: before week 24 1: week 24-48 1: week 88
ATLAS 2M (4 weeks) (2 failures)	N155N/H(1),E138E/K+Q148R (1)	None	Before week 24
HPTN083 (8 weeks) (16 failures)	E138K(1), Q148K(1),Q148R(3), R263K(1),G140G/S(1), G140A(1),L74I(1)		

INSTI mutations that emerged (but usually never alone): Q148R/K, N155H, E138A/K, G140R/S, R263K

Case 1 (continued)

- You go over all of this data with the patient and discuss giving the injection every 4 weeks with some hesitation to give every 8 weeks
- He then says: "okay, doc, tell me since I really want to eventually get the shots every 8 weeks: any risk factors more associated with all of this resistance you are trying to scare me about?"

ARS: What are the risk factors for the development of CAB resistance in the combined phase 3 treatment trials?

1. Being late for injections
2. Proviral rilpivirine resistance mutations
3. HIV-1 clade B
4. HIV-1 A1/A6
5. Body mass index > 30 kg/m^2
6. Answers 1, 2, 5
7. Answers 2, 4, 5

Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

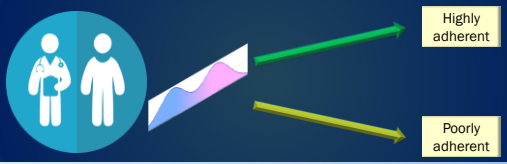
AIDS: July 15, 2021 - Volume 35 - Issue 9 - p 1333-1342

Conclusion: CVF is an infrequent multifactorial event, with a rate of approximately 1% in the long-acting CAB+RPV arms across Phase 3 studies (FLAIR, ATLAS and ATLAS-2M) through Week 48. Presence of at least two of proviral RPV RAMs, HIV-1 subtype A6/A1 and/or BMI at least 30 kg/m^2 was associated with increased CVF risk. These findings support the use of long-acting CAB+RPV in routine clinical practice.

Case 1 (continued)

- Your patient's BMI is 24 kg/m^2 and decision made to start IM CAB/RPV every 4 weeks with re-evaluation with patient as more data evolves when feel comfortable going to every 8 weeks
- He agrees but states he wants the every 8 week injection re-evaluated soon and also tells you your clinic needs to figure out an in-and-out shot clinic

Bimodal population wanting/needing long-acting ART often invoked prior to approval



Barriers for "highly adherent" may be circumvented by shot clinics (in and out), pharmacies or mobile vans administering the shots, constant supply of oral CAB/RPV at home for bridges, training to do home injections

Case 2:

- 39 yo MSM with HIV I met in an Uber
- Diagnosed with acute HIV in 2009 on pooled testing at City Clinic, VL 500K, CD4 491 (hives, pharyngitis, fever)
- Started on TDF/FTC/ATV/r but never suppressed, former MD left so fell out of care and then moved to Florida when put on ELV/cobi/TDF/FTC in 2014
- Moved back to SF in 2015, Uber ride 2016, had difficulty with adherence due to methamphetamine use (frequent)
- On 10/22/16, HIV viral load 12K, CD4 153, genotype showed M184V and N155H mutations
- Put on DRV/cobi + TDF/FTC and then DRV/cobi/TAF/FTC in 2018 but patient could not take ART, off and on adherence

Case 2 (continued)

- Patient then went back to Florida due to ailing mother, could not find non-stigmatizing care there so no meds
- Came back to this provider in 2021 – CD4 now 18 and viral load >500K
- Absolutely cannot take oral meds: states it is very stigmatizing
- Continues to work as Uber driver, sex 3-4 times a week with different partners (no condoms); yes, still has that N155H and M184V
- Worked up for various OIs (CMV optho exam as blurry vision; HA so LP; but only diagnosis syphilis); very fatigued
- BMI 27; no exposure to NNRTIs; this provider is at end of rope

ARS: Would you put this patient on long-acting CAB/RPV?

1. Yes! Perfect candidate- high viral load, low CD4 count, one INSTI mutation, long history of non-adherence
2. Um….are you crazy?
3. Ibaluzimab and something else non-oral?
4. Nuance is key to decision-making…this patient has no other options; won't take oral; young and in grave health position

Case 2 (continued)

- Started on loading dose of IM CAB 900mg and IM RPV 600mg on June 8, 2021
- Came in for 2nd dose on July 6, 2021
- Drew pre-2nd dose viral load and then gave dose

ARS: What do you think the viral load was before 2nd dose (started with VL 516,258)

1. 492,000
2. 49,000
3. 4,900
4. 49
5. <30 copies/mL

Case 2 (continued)

- HIV viral load <30 after 1st loading dose
- Patient is now on 6th dose of IM CAB/RPV (received yesterday) and has had three HIV viral loads <30
- CD4 78 from 18 cells/mm^3
- Patient called mother from clinic on day of first viral load result and hugged provider
- Fatigue much improved- back to Uber

Ward 86 pilot program for long-acting ART for poorly-adherent ONLY WHEN NO OTHER OPTION

Inclusion criteria of trials:

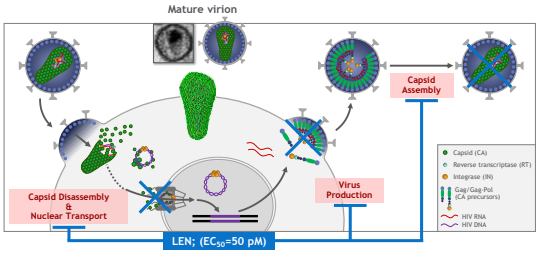
- Virologically suppressed x at least 16 weeks on oral regimen first
- No history of virologic failure
- Only K103N or INSTI mutations
- Oral CAB/RPV x 28 days but direct-to-inject data

Inclusion criteria of Ward 86

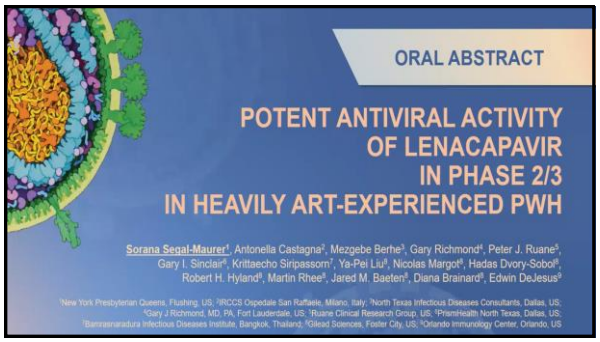
- Does not need to be virologically suppressed or take orals before
- Can go direct to inject
- No RPV mutations, allow 1 (only) INSTI mutation non-defining of CAB-R
- **Must require STRICT demonstration of every 4 week coming to clinic**
- Biweekly review of all patients

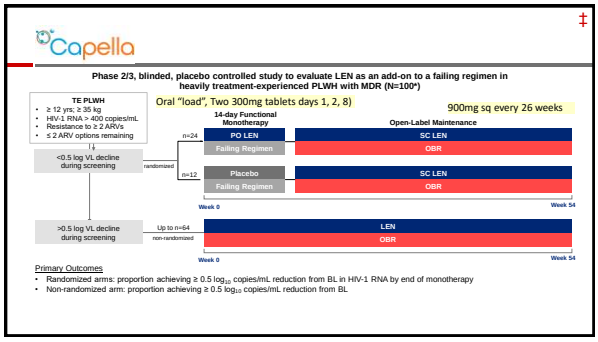
33 referrals to date; 13 started- all doing well so far, but early in program & only 4 out of 13 non-suppressed prior to starting (**EXCEPTION NOT THE RULE**)

Lenacapavir (LEN; GS-6207): Novel HIV Capsid Inhibitor

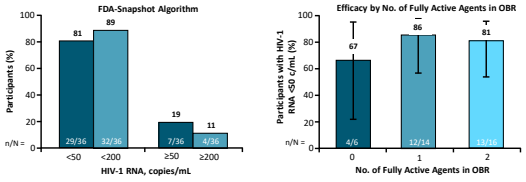


Yant S et al. CROI 2019, Poster 480. EC_{50}=half-maximal effective concentration.





CAPELLA Secondary Endpoints: Wk 26 Efficacy in Randomized Cohort

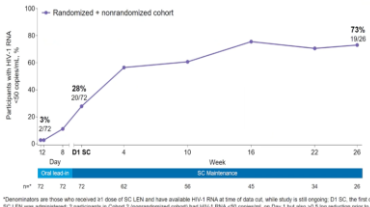


- **Mean change in CD4+ cell count: +81 cells/mm³**
- Proportion of participants with very low CD4+ cell count (< 50 cells/mm³) **decreased from 22% (8 of 36) at baseline** to **0% (0 of 34) at Wk 26**

Molina. IAS 2021. Abstr OALX01L802.

Slide credit: clinicaloptions.com

Results: HIV-1 RNA <50 copies/mL at week 26

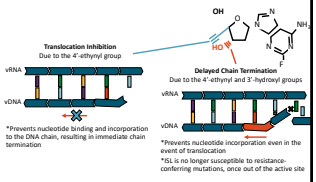


2 of 72 patients had emergent capsid mutations conferring high level LEN resistance:

- 1) M66I and N74D at Wk 10 2) M66 at Wk 26.
- Both re-suppressed (1 with and 1 without OBR* change), but M66I substantially impairs viral replication

Islatravir (MK-8591, ISL): Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)

- First-in-class NRTTI
  - High potency; half-life up to 128 hours, once per year dosing feasible



Multiple mechanisms may contribute to high potency, use in drug-resistant virus, and high genetic barrier to resistance

Press Releases

March 15, 2021

Gilead and Merck Announce Agreement to Jointly Develop and Commercialize Long-Acting, Investigational Treatment Combinations of Lenacapavir and Islatravir in HIV

– *Collaboration to Focus on Oral and Injectable Formulations of Lenacapavir and Islatravir* –

– *Agreement Brings Together Potentially Complementary Medicines in Late-Stage Development with the Goal to Provide Innovative, Long-Acting Treatments in HIV* –

FOSTER CITY, Calif. & KENILWORTH, N.J.–(BUSINESS WIRE)-- Gilead Sciences, Inc. (Nasdaq: GILD) and Merck (NYSE: MRK), known as MSD

Question-and-Answer Session

Changes

- Replaced original title slide with IAS-USA formatted slide
- Added Financial Disclosure slide

Slide 67 of X