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Review of LAI CAB/RPV and Real-World Experience

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ATLAS/FLAIR week 48 results

Figure 3. Virologic Snapshot Outcomes at Week 48 for ITT-E Noninferiority Achieved for Primary and Secondary Endpoints

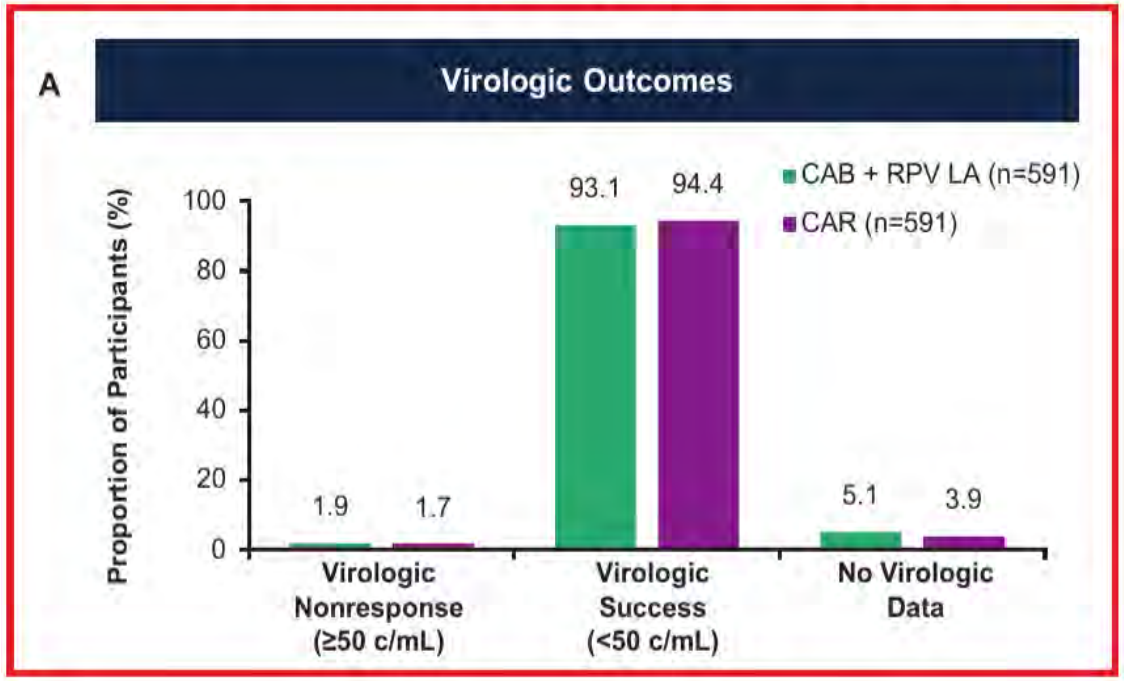
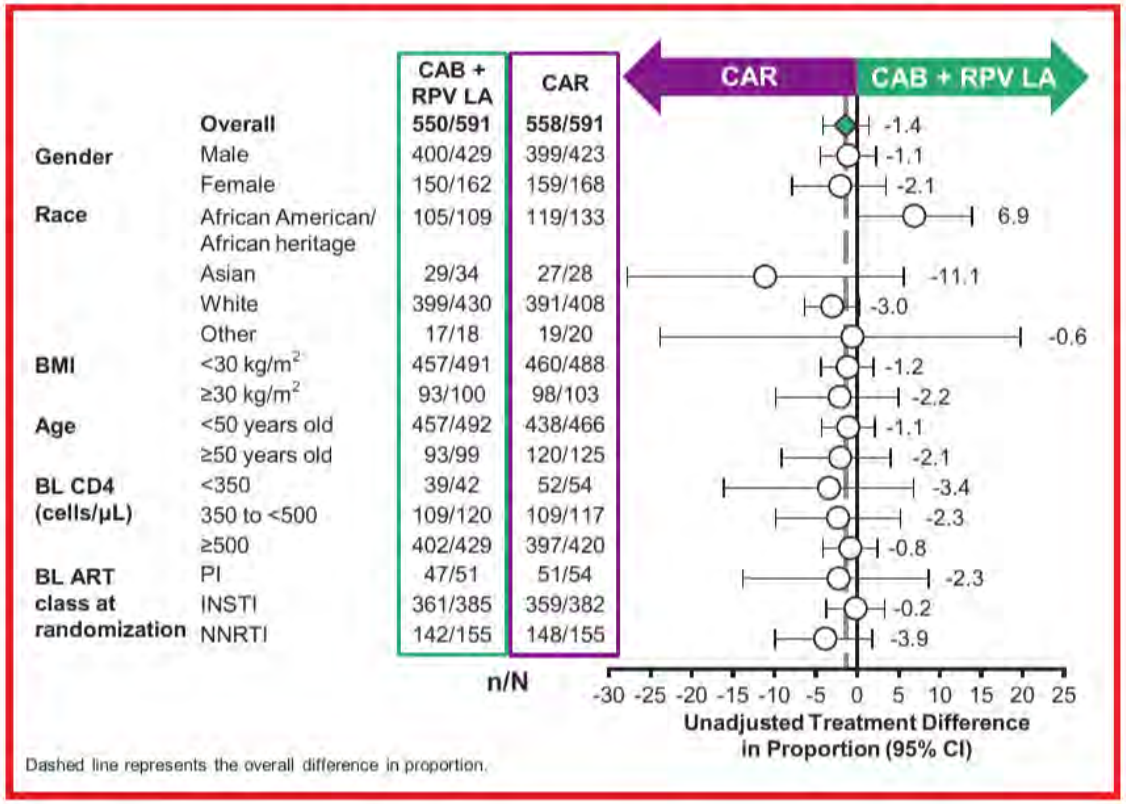


Figure 4. Treatment Difference in Proportion (95% CI) Snapshot HIV-1 RNA <50 c/mL at Week 48 by Subgroup



Rizzardi et al.*JAIDS*.2020;85:498-506.

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ATLAS 2M results

Table 3. Virologic Response* by FDA Snapshot Algorithm from ATLAS-2M at Week 48 (ITT-E)[2]

	Every 8 Week Arm n=522	Every 4 Week Arm n=523
HIV-1 RNA ≥50 copies/mL	9 (1.7)	5 (1.0)
Adjusted* Treatment Difference [% (95% CI)]	0.8 (-0.6 to 2.2)	
Data in window not <50 copies/mL	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	6 (1.1)	2 (0.4)
Discontinued for other reasons while not <50 copies/mL	0	1 (0.2)
HIV-1 RNA <50 copies/mL	492 (94.3)	489 (93.5)
No virologic data	21 (4.0)	29 (5.5)
Discontinued for AE or death	9 (1.7)†	13 (2.5)‡
Discontinued for other reasons	12 (2.3)§	16 (3.1)‖

*adjusted for prior exposure to CAB + RPV

†Discontinuations for AEs (event level) include Q8W: Injection site pain (n=2), injection site abscess, injection site discomfort, skin lesion, fatigue, acute hepatitis B, asthenia, presyncope, pancreatitis acute, headache, rash maculo-papular (all n=1).

‡Q4W: injection site pain (n=11), abnormal dreams (n=2), injection site swelling (n=2), hyperhidrosis (n=2), fatigue (n=2), injection site nodule, influenza, headache, acute hepatitis B, dizziness, glioblastoma, allergic reaction, transaminase increase, depression, chills, insomnia, myalgia, nausea, presyncope, pyrexia, sleep disorder, disturbance in attention (all n=1).

§Q8W: Withdrawal by participant (n=4), investigator decision (n=4), lost to follow-up (n=2), protocol deviation (n=1), lack of efficacy (n=1).

‖Q4W: Withdrawal by participant (n=12), protocol-specified withdrawal criteria met (pregnancy) (n=3), protocol deviation (n=1).

ITT-E = intent-to-treat-exposed; AE = adverse event

- 8 (1.5%) confirmed virologic failures in the 8 week arm and 2 (0.4%) in the 4 week arm at week 48
- Week 152 presented at CROI 2022, with 87.4% in the q8week and 85.9% in the q4week arm maintaining suppression
  - 3 additional failures in the q8week arm since week 48

Overton et al. 2020.

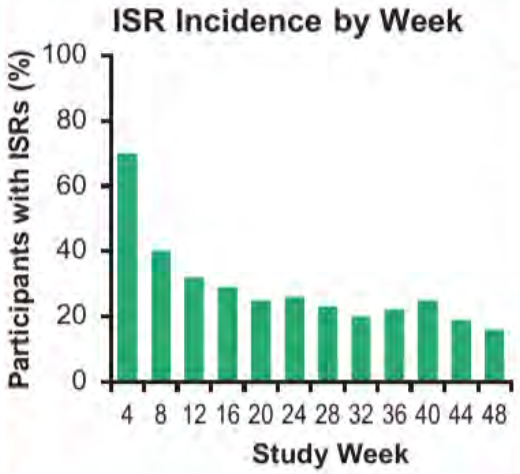
ATLAS/FLAIR side effects

Table 3. Safety Overview, Excluding ISRs, Through Week 48 in Maintenance Phase

	CAB + RPV LA N=591	CAR N=591
Any AE	506 (86%)	444 (75%)
Any Grade 3/4/5 AE*	44 (7%)	35 (6%)
Any drug-related AE	165 (28%)	35 (6%)
Any Grade 3/4/5 drug-related AE*	8 (1%)	1 (<1%)
Any AEs leading to withdrawal	17 (3%)	9 (2%)
Any serious AE	24 (4%)	25 (4%)
Serious AEs related to study treatment†	1 (<1%)	1 (<1%)
Common AEs (≥5%)		
Nasopharyngitis	108 (18%)	90 (15%)
Headache	73 (12%)	38 (6%)
Upper respiratory tract infection	70 (12%)	53 (9%)
Diarrhea	54 (9%)	40 (7%)
Back pain	43 (7%)	23 (4%)
Influenza	42 (7%)	34 (6%)
Pyrexia	43 (7%)	13 (2%)
AEs of special interest		
Anxiety	27 (5%)	20 (3%)
Depression	16 (3%)	14 (2%)
Suicidal ideation/behavior	4 (<1%)	5 (<1%)

*There was only one (<1%) participant with Grade 5 AE in the CAR arm; †Serious AEs related to study treatment: LA arm – arthritis; CAR arm – suicidal ideation.

Figure 5. Pooled Injection Site Reactions



Event	CAB + RPV LA N=591
Participants receiving injections, n	581
Injections given, n	14682
ISR events, n (%)	3663 (24.9)
Pain	3087 (21.0)
Nodule	140 (1.0)
Induration	136 (0.9)
Swelling	86 (0.6)
Grade 3 ISR pain	32 (0.2)
Median duration of ISRs, days	3
Participants with ISR leading to withdrawal, n (%)	6 (1)

Bars represent incidence of onset ISRs relative to the most recent IM injection visit.

- The majority (99%, 3628/3663) of ISRs were Grade 1–2 and most (88%) resolved within ≤7 days

Rizzardini et al. 2020

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Indication and dosing

- Indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (<50cpm) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir (CAB) or rilpivirine (RPV)
- Prior to initiating treatment oral lead-in dosing should be used for approximately one month to assess tolerability
- Every 1 month dosing
  - Initiate injections (600mg CAB + 900mg RPV) on the last day of oral lead-in and continue with 400mg CAB + 600mg RPV every month thereafter
- Every 2 month dosing
  - Initiate injections (600mg CAB + 900mg RPV) on the last day of oral lead-in. Injections should be administered at month 2, month 3, and every 2 months thereafter

ATLAS/FLAIR Resistance

Table 4. ATLAS and FLAIR Confirmed Virologic Failures*: CAB + RPV LA Arm

Study	Sex, Country, HIV-1 Subtype	Previous CAR	Baseline RAMs†		Viral Load at SVF / CVF (c/mL)	SVF Timepoint RAMs		Drug Sensitivity at SVF (Fold Change)§
			RT	INSTI		RT	INSTI‡	
ATLAS	F, Russia, A/A1	3TC, AZT, LPV/r	E138E/A	None	79,166 / 25,745	E138A	None	**RPV (2.4)** CAB (0.8) DTG (0.9)
	F, France, AG	3TC, AZT, NVP to 3TC, ABC, NVP	V108V/I E138K	None	695 / 258	V108I E138K	None	**RPV (3.7)** CAB (1.2) DTG (1.0)
	M, Russia, A/A1	FTC, RAL, TDF to ABC, EFV, 3TC	None	None	544 / 1841	E138E/K	N155H	**RPV (6.5)** **CAB (2.7)** DTG (1.2)
FLAIR¶	F, Russia, A1	–	None	None	373 / 456	E138E/A/K/T	Q148R	**RPV (7.1)** **CAB (5.2)** DTG (1.0)
	M, Russia, A1	–	None	None	287 / 299	K101E	G140R	**RPV (2.6)** **CAB (6.7)** DTG (2.2)
	F, Russia, A1	–	None	None	488 / 440	E138K	Q148R	RPV (1.0) **CAB (9.4)** DTG (1.1)

***In the CAR arm, there were seven CVFs. In ATLAS, there were 4 CVFs in the CAR arm, where RT mutations M184I, M184V+G190S, and M230M/I were detected in HIV-1 RNA samples from one participant each, and one had no mutations. In FLAIR, there were 3/4 CVFs in the CAR arm without treatment-emergent resistance mutations or phenotypic changes.**

†Baseline RAMs were determined using DNA for ATLAS and RNA for FLAIR; ‡L74I was present at baseline in 5/6 subjects and is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity; §Monogram biological cutoffs are: RPV=2.0, CAB=2.5, and the Monogram clinical cutoff for DTG=4.0; ¶FLAIR had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon re-initiation of oral therapy, had suspected VF that was confirmed.

Overton E, et al. 10th IAS Conference on HIV Science. July 21-24, 2019. Poster MOPEB257.

ATLAS 2M Failures

Table 4. Confirmed Virologic Failures in the CAB + RPV LA Arms of ATLAS-2M Through Week 48[2,3]

Study Arm	Country / Gender	HIV Subtype	Prior Duration of CAB + RPV LA	BMI	SVF Timepoint	HIV-1 RNA at SVF / CVF (copies per mL)	Pro-Viral DNA Baseline Major RAMs* (day 1)		On-Treatment RAMs		Drug Susceptibility (FC) at SVF†
							NNRTI	IN	NNRTI	IN	
Every 8 Week Arm	S. Africa / Female	C	1-24 weeks	>30	8	267 / 2355	Y181Y/C H221H/Y	None	None	None	**RPV (2.4)** CAB (1.07)
	Spain / Male	B	None	<30	16	737,830 / 259	None	None	None	None	RPV (1.43) CAB (0.63)
	S. Africa / Female	C	None	>30	16	938 / 2374	Y188Y/F/H/L	G140G/R	Y188L	Q148Q/R N155N/H	**RPV (6.8)** **CAB (2.63)**
	Russia / Female	A1	None	>30	16	141,132 / 19,099	None	None	K101E	Q148R	**RPV (4.7)** **CAB (9.1)**
	Canada / Female	A1	None	>30	24	16,205 / 874	Y188L	None	Y188L	Assay Failed	**RPV (15)** CAB (NA)
	US / Male	B	None	>30	24	5687 / 1928	E138A	None	E138A	N155H	**RPV (7.2)** CAB (1.8)
	Russia / Female	A	1-24 weeks	<30	24	211,639 / 38,015	E138E/A	None	K101E E138A	N155H	**RPV (2.6)** **CAB (6.98)**
	Russia / Male	A/A1	1-24 weeks	<30	48	296 / 303	None	None	E138E/K	N155N/H	**RPV (4.2)** CAB (NA)
Every 4 Week Arm	France / Male	B	None	<30	16	121,233 / 173,421	None	None	None	N155N/H	**RPV (>119.2)** CAB (1.8)
	US / Male	B	None	<30	32	9627 / 2234	None	None	K101E M230L	Q148R E138E/K	**RPV (17)** **CAB (4.6)**

*Post-hoc analysis of peripheral blood mononuclear cell (PBMC) HIV-1 DNA

†Bolding indicates fold change above the biologic or clinical cutoff for the antiretroviral agent. Biologic cutoffs: rilpivirine (2.0), cabotegravir (2.5). Fold Change = IC_{50} patient / IC_{50} reference. Reduced susceptibility was determined from the clinical cut-offs or biological cutoffs used in PhenoSense GT or PhenoSense Integrase assays by Monogram Biosciences

SVF = suspected virologic failure; RAM = resistance-associated mutation; NNRTI = non-nucleoside reverse transcriptase inhibitor; IN = integrase; RPV = rilpivirine; CAB = cabotegravir; FC = fold-change in IC50 compared to wild-type virus

Overton E, et al. CROI 2020. March 8-11, 2020

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CAB/RPV Failures

Parameter	Final Model OR (95% CI), p-value*
RPV RAM(s) at baseline†	37.24 (8.44–>99), p<0.001
Log_2 of *post hoc* Week 8 RPV trough concentration	4.17 (1.59–11.11), p=0.004
Baseline HIV-1 subtype A6/A1	6.59 (1.82–25.26), p=0.005
BMI (kg/m^2) at baseline	1.13 (1.03–1.25), p=0.014
Pre-specified INSTI mutation (excluding L74I non-M mixture) at baseline‡	0.11 (0.01–0.83), p=0.029
Log_2 of *post hoc* Week 8 CAB trough concentration	Not significant
Female at birth	Not significant
Q8W regimen	Not significant
L74I (non-M mixture) INSTI polymorphism at baseline	Not significant
NNRTI RAM(s) (excluding RPV RAMs) at baseline‡	Not significant

Margolis D, et al. HIV Drug Therapy Glasgow. October 5-8, 2020.

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CAB/RPV Failures

Factor	CVF, n (%)	HIV-1 RNA <50 copies/mL, n (%)
No baseline factors	3/732 (0.41)	694/732 (95)
Any one baseline factor	1/272 (0.37)	261/272 (96)
Two or more baseline factors	**9/35 (26)**	**25/35 (71)**
TOTAL [95% CI]	13/1039 (1.3) [0.67–2.13]	980/1039 (94) [92.74–95.65]

- Sensitivity and specificity of at least two baseline factors is optimal

	PPV	NPV	Sensitivity	Specificity
Two or more factors	26%	99.6%	69%	97.5%
Any one factor	<1%	98%	8%	74%

Margolis D, et al. 2020.

Logistics/challenges

- Patient selection
- DDI during oral lead in
- Reimbursement/Acquisition/Billing
- EMR/Tracking Injections
- Resources to administer injections
- Viral load monitoring
- Patient outreach/missed doses
- Oral bridge
- Hospitalizations
- Transition from every 1 month to every 2 month

Reimbursement

- Pharmacy Benefit - Medi-cal, ADAP, Medicare
  - Filled at outpatient pharmacy and supplied to clinic-administered as patient supplied medication
  - Limited Distribution drug
    - Can request access from ViiV
  - Copay resolved using copay card
    - www.cabenuvacopayprogram.com
- Medical benefit – most commercial payors
  - Buy and bill-clinic purchases and bills to insurance
  - Patient responsibility
    - 10-20%, deductibles, out of pocket maximums
    - PAI vs. copay program vs. reimbursement

Owen Clinic Process

- Patient expresses interest in LAI CAB/RPV
- Eligibility reviewed by PMD and clinical pharmacy team
  - Necessary resistance work up completed
- Insurance coverage investigation
  - Includes researching patient responsibility
- Patient contacted to review oral lead-in
  - Delivery set up to patient home or clinic
- Patient contacts clinic when oral lead-in received to schedule first injection visit
  - Treatment plan entered in epic
- Medication obtained from outpatient pharmacy or purchased by clinic one week prior to injection visit
  - Tracking sheet
- Reminder call to all patients day before each injection
- First injection visit with clinical pharmacy team and nurse visit
  - Review and sign counseling sheet
- Viral load monitoring performed at loading dose injection, first maintenance injection, then every 3 months
- Subsequent visits scheduled as nurse visit
- Tracking sheet updated

Owen Clinic Outcomes

- Reviewed first 270 patients referred who had definitive decision to start/not start CAB/RPV
- 131 (48.5%) initiated CAB/RPV
- Baseline genotype available in 110 (41%) of patients
- Prior archive/genotype other than baseline available in 68 (25.2%) of patients
- Archive genotype performed in 89 (33%) of patients
- LAI CAB/RPV added to ADAP formulary in 10/2021

	Total (n=270)	Initiated CAB/RPV (n=131)	Did not start CAB/RPV (n=139)	p-value
Median age (IQR)	44 (35-53)	44 (34-52)	44 (37-54)	0.10
Race (%)				
White	135 (50.0)	57 (43.5)	78 (56.1)	
Black	41 (15.2)	25 (19.1)	16 (11.5)	0.15
Asian	9 (3.3)	4 (3.1)	5 (3.6)	
AI/AN	4 (1.5)	3 (2.3)	1 (0.7)	
Other/mixed race	74 (27.4)	40 (30.5)	34 (24.5)	
Unknown	7 (2.6)	2 (1.5)	5 (3.6)	
Ethnicity (%)				
Hispanic	101 (37.4)	52 (39.7)	49 (35.3)	0.51
Non-Hispanic	166 (61.5)	78 (59.5)	88 (63.3)	
Other/Unknown	3 (1.1)	1 (0.8)	2 (1.4)	
SAB				
Female (%)	34 (12.6)	19 (14.5)	15 (10.8)	0.36
Gender Identity				
Male	234 (86.7)	112 (85.5)	122 (87.8)	0.86
Female	34 (12.6)	18 (13.7)	16 (11.5)	
Non-binary	2 (0.7)	1 (0.8)	1 (0.7)	
Baseline ARV regimen (%)				
2nd Gen INSTI+2 NRTI	170 (63.0)	76 (58.0)	94 (67.6)	
1st Gen INSTI+2 NRTI	24 (8.9)	12 (9.2)	12 (8.6)	**0.001**
NNRTI+2 NRTI	16 (5.9)	10 (7.6)	6 (4.3)	
PI+2 NRTI	11 (4.1)	3 (2.3)	8 (5.6)	
2 drug regimen	29 (10.7)	24 (18.3)	5 (3.6)	
Multi-class	20 (7.4)	6 (4.6)	14 (10.1)	
Primary Insurance*				
Medicaid	113 (41.9)	65 (49.6)	48 (34.5)	
Medicare/Medicaid	31 (11.5)	15 (11.5)	16 (11.5)	0.09
Medicare only	8 (3.0)	2 (1.5)	6 (4.3)	
Ryan White/ADAP	19 (7.0)	7 (5.3)	12 (8.6)	
Commercial	99 (36.7)	42 (32.1)	57 (41.0)	
HBV status				
Negative	191 (70.7)	98 (74.8)	93 (66.9)	
CoreAb+, SAg-, SAb+	65 (24.1)	28 (21.4)	37 (26.6)	0.16
CoreAb+, SAg-, SAb-	10 (3.7)	5 (3.8)	5 (3.6)	
SAg+	4 (1.5)	0 (0.0)	4 (2.9)	
On PPI at baseline	25 (12.4)	14 (10.7)	20 (14.4)	0.36

<u>Owen Clinic</u>
Median age: 53
<u>Race:</u>
White: 53.4%
Black: 12.4%
Asian: 3.7%
AI/AN: 1.3%
Other/unknown: 29.1%
<u>Ethnicity</u>
Hispanic: 32.4%
<u>SAB</u>
Female SAB: 9.8%

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Reasons for not initiating CAB/RPV (n=139)

Reason	N (%)
Previously identified CAB/RPV resistance	28 (20.1)
Inconsistent clinic attendance/not easily reached	20 (14.4)
Patient choice	19 (13.7)
CAB or RPV resistance found on archive genotype	18 (12.9)
Not suppressed	13 (9.4)
Failure to complete resistance work-up	11 (7.9)
Uncertain coverage of out-of-pocket costs	10 (7.2)
Not yet covered	8 (4.8)
Active hepatitis B	4 (2.9)
Insurance contracted with outside pharmacy	3 (2.2)
Drug interaction	1 (0.7)
Other	4 (2.9)

Resistance issues

Previously known resistance (n=28)

Resistance mutation	# patients	Resistance
Y181C	5	RPV
Y188L	3	RPV
G190	1	RPV
K101E/H/G190A	4	RPV
Phenotypic NNRTI res.	2	RPV
A98G	1	RPV
V179L	1	RPV
E138G/A/K	4	RPV
H221Y	2	RPV
K238T	1	RPV
T66I	1	CAB
S230R	1	CAB
T97A/E157Q	1	CAB
G140A	1	CAB

Resistance found on archive (n=18)

Resistance mutation	# patients	Resistance
Y181C	3	RPV
E138G	2	RPV
E138A/K	5	RPV
G190S	1	RPV
H221Y	1	RPV
K238T	1	RPV
K101E	2	RPV
Y143H	1	CAB
L74I+Q148H	1	CAB
T97A+K103N	1	Concern for additional NNRTI resistance

Of those that had an archive genotype performed, 20.2% had a mutation identified that may have resulted in lack of efficacy of CAB/RPV

Other outcomes

- 9/134 patients have discontinued treatment
  - 4 did not like receiving IM injections
  - Unrelated facial swelling
  - Four HBV reactivations?
    - All with high CD4 counts, 2 isolated Core+, 2 with high HBV SAb
  - Decided monthly visit was too burdensome
  - One pregnancy-transitioned to oral therapy
  - One patient with significant weight gain-decided to continue
- One patient currently one week late for his injection, one patient out of the country used 2 month oral bridge
- One hospitalization during due date for injection-discharged 2 days after injection was due
- 97% have transitioned to 2 month dosing
  - 2 chose to stay with every one month, 2 unable to change due to insurance