HIV A1 OR B DO NOT DIFFERENTIALLY IMPACT CABOTEGRAVIR IN VITRO POTENCY OR DURABILITY

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Background

- The Phase 3 FLAIR study evaluated monthly administration of long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) as maintenance therapy in suppressed HIV-1–infected adults over 48 weeks and demonstrated non-inferiority to 3-drug daily oral ART. A total of 3/283 (1%) participants (PTS) who received CAB + RPV LA had confirmed virologic failure (CVF). All 3 CVF PTS were among the 8 PTS in the study with subtype A1 virus and all 3 had the baseline integrase (IN) substitution L74I, as did 2/5 PTS who maintained viral suppression. All 8 PTS with subtype A1 virus in the study were sensitive to CAB at baseline. 174/283 (61%) PTS in the LA arm had subtype B, 7% with L74I without CVF
- Given the apparent clustering of CVF among A1 and presence of L74I, we sought to determine the impact of L74I and subtype A1 compared to subtype B IN on CAB sensitivity and durability

Table 1. Summary of FLAIR CVFs Through Week 48[1]

CVF case	Baseline IN genotype	IN genotype at CVF	CAB FC IC_{50}
1	L74I	L74I, Q148R	5.2
2	L74I	L74I, G140R	6.7
3	L74I	L74I, Q148R	9.4

FC, fold change to reference virus.
CAB FC for each case at baseline was 0.95, 0.67, and 0.69, respectively.
Monogram Biosciences biological cutoff for CAB = 2.5.

Methods

- FLAIR CVF genotypes and phenotypes were generated at Monogram Biosciences Inc (Table 1 only)
  - Subtype A1 assignment is based on Monogram algorithm which does not include reference sequences for A6, a predominant subtype in Russia. Further in-house analysis suggests that the subtype for all 3 CVFs is A6
- A consensus A1 based integrase sequence was generated from the integrase sequences of the CVFs
- Site-directed integrase (SDM) mutants were created in a replication defective NL4-3 based proviral vector (subtype B) or a chimeric proviral vector containing the consensus A1 integrase (ConA1) to measure CAB IC_{50}s
- CAB Breakthrough Experiment:
  - Replication competent vectors were created in a NL4-3 proviral plasmid containing +/- L74I or the conA1 integrase chimeras +/- L74I
  - Virus growth was measured in MT2 cells for each virus to ensure similar replication kinetics prior to the breakthrough experiment
  - The ability of CAB to suppress viral replication in a bulk infected culture was assessed at multiple CAB concentrations (0, 1, 5, 410nM=1xPAEC90)

Results

Table 2. Summary of CAB In Vitro IC_{50}

Virus description & (subtype)		SDM	CAB FC IC_{50}
NL4-3 (B)	Standard lab strain	L74I	1.2
		L74I, G140R	0.6
		L74I, Q148R	4.4
ConA1 (A1)	Derived from consensus CVF integrase	I74L	0.8
		I74, G140R	0.9*
		I74, Q148R	4.1

SDM, site-directed mutant.
FC, fold change to parent virus (n=3 independent experiments).
*FC discrepancy relative to FLAIR CVF case 2 is being explored.

Figure 1. Summary of CAB Breakthrough Experiments

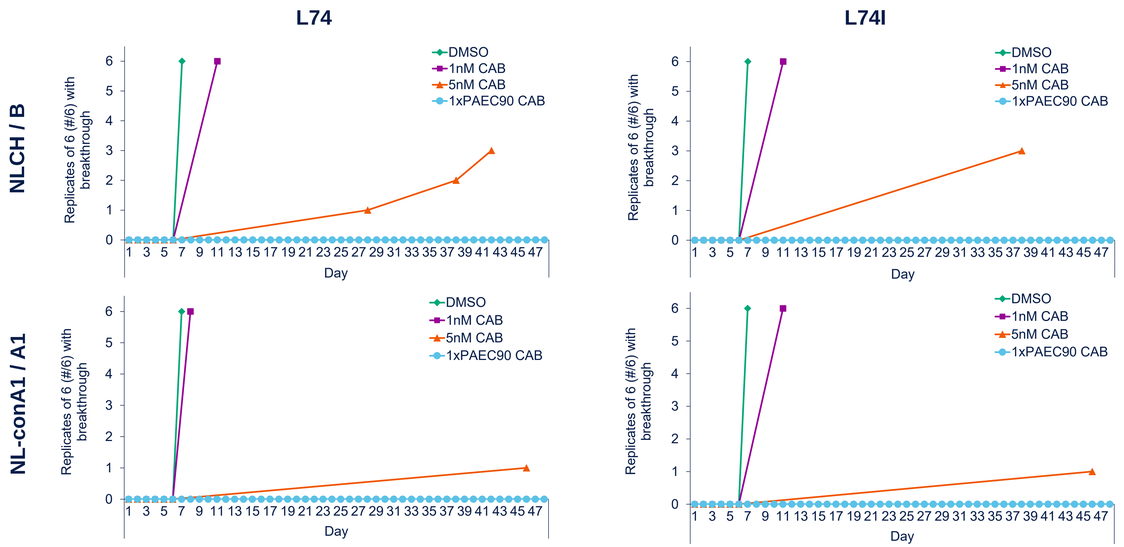
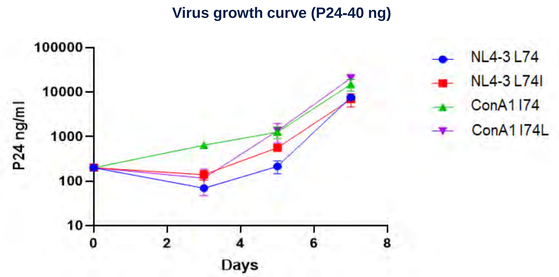


Table 3. Summary of Resistance in Breakthrough Experiment

Virus subtype	Position 74	No drug	1nM	5nM	1xPAEC90 (410nM)
		# with resistance / # breakthroughs			
NL4-3 B	L74	0/6	0/6	0/3	0/0
	L74I	0/6	0/6	1/3*	0/0
ConA1 A1	L74	0/6	0/6	0/1	0/0
	L74I	0/6	0/6	0/1	0/0

*Q148R emerged in 1/3 breakthrough viruses.

Figure 2. Viral Replication Kinetics for Subtype A1 & B Viruses



Conclusions

- FLAIR demonstrated CAB + RPV long-acting was non-inferior to oral ART at Week 48[1]
- Integrase from subtype A1 did not differentially impact CAB potency in vitro compared to subtype B
- Integrase +/- L74I did not impact CAB potency in vitro for either subtype A1 or subtype B
- The integrase mutant L74I/Q148R conferred resistance to CAB and did not differentiate in subtype A1 compared to subtype B
- The in vitro replication kinetics did not differ between subtype B, subtype A +/- L74I
- Subtype A1 integrase at baseline did not pre-dispose the virus to generate CAB resistance in vitro
- The emergence of Q148R in 1 of 3 subtype B L74I viruses is being further explored
- Other factors besides subtype A1 or the presence of L74I at baseline may contribute to virologic failure to CAB + RPV long-acting and require further investigation

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Reference: 1. Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir + rilpivirine for HIV maintenance: FLAIR Week 48 results. Presented at: Conference on Retroviruses and Opportunistic Infections; March 4-7, 2019; Seattle, WA. Slides O-13.