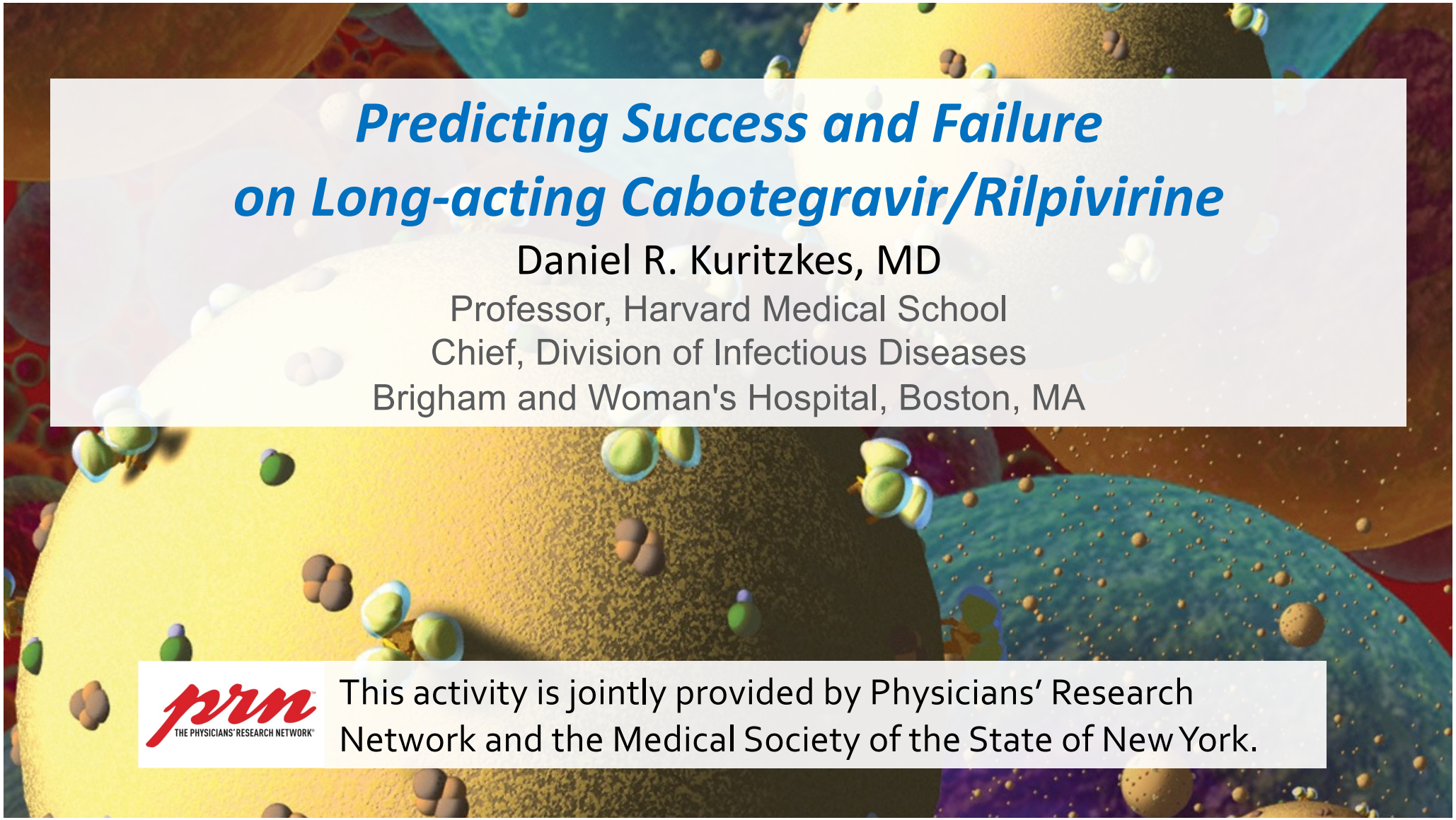


Predicting Success and Failure on Long-acting Cabotegravir/Rilpivirine

Daniel R. Kuritzkes, MD
Professor, Harvard Medical School
Chief, Division of Infectious Diseases
Brigham and Woman's Hospital, Boston, MA

This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

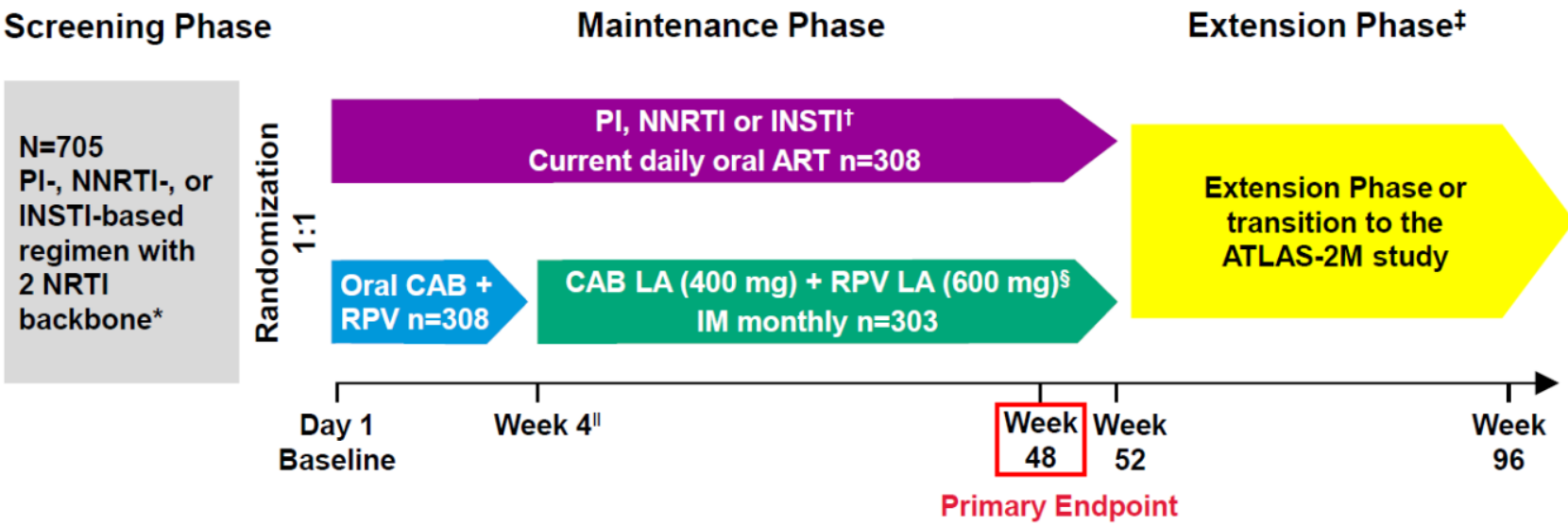
Predicting Success and Failure on Long-acting Cabotegravir/Riplivirine

Daniel R. Kuritzkes, M.D.
Division of Infectious Diseases
Brigham and Women's Hospital
Harvard Medical School

Disclosures

- **The speaker is a consultant and/or has received speaking honoraria and/or grant support from the following companies relevant to this talk:**
  - AbbVie
  - Gilead
  - GlaxoSmithKline
  - Janssen
  - Merck
  - Roche
  - ViiV

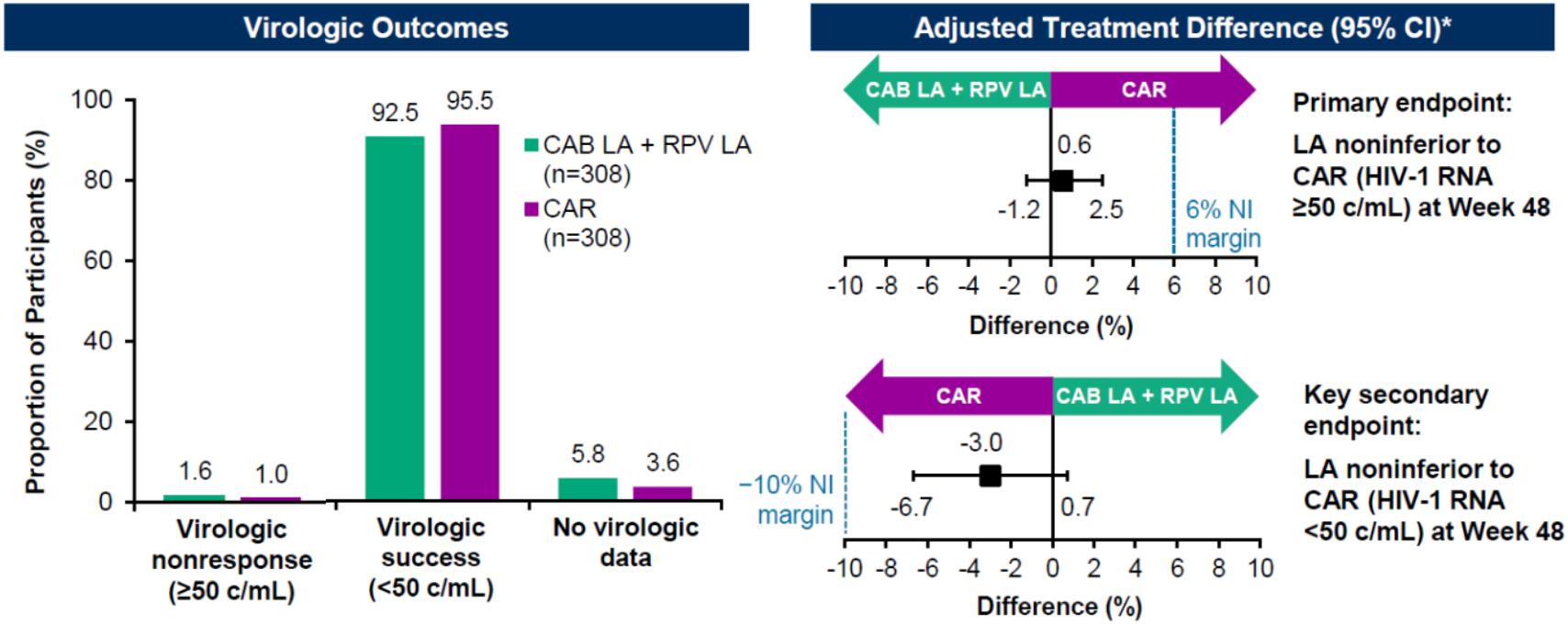
ATLAS study design



*Participants must have been virologically suppressed on the same regimen for at least 6 months with at least 2 VL determinations <50 copies/mL within the previous 12 months.

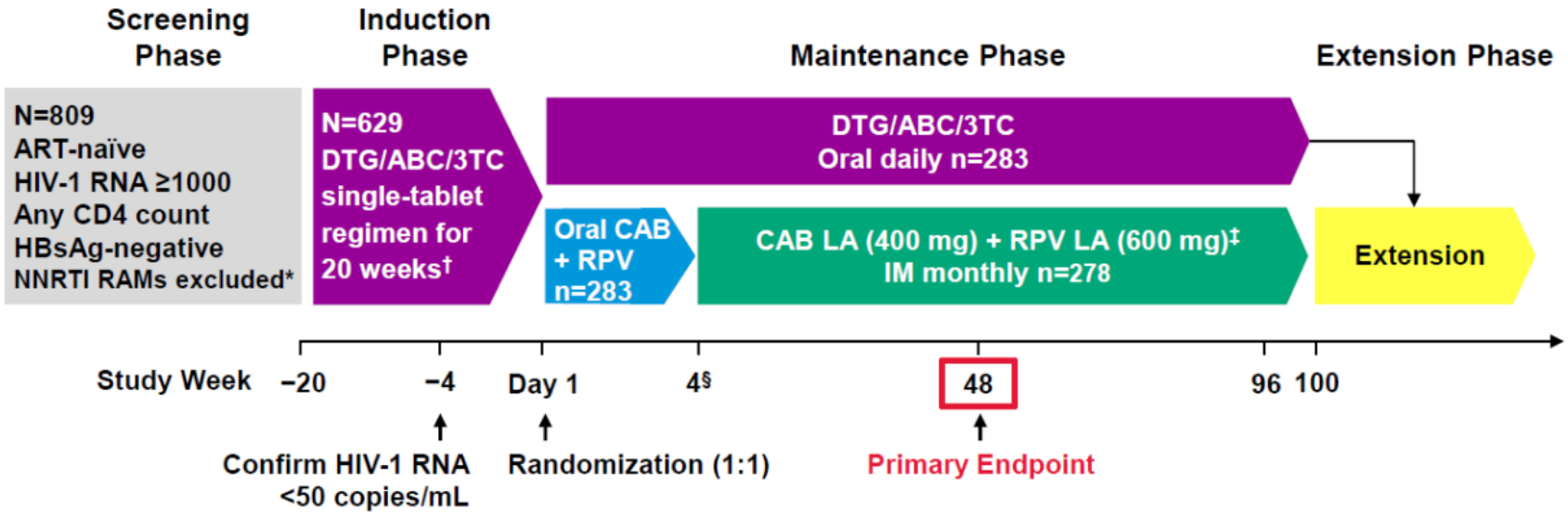
Swindells S et al 26th CROI, Boston, 2019; N Engl J Med 2021

ATLAS—Primary and Secondary Endpoints



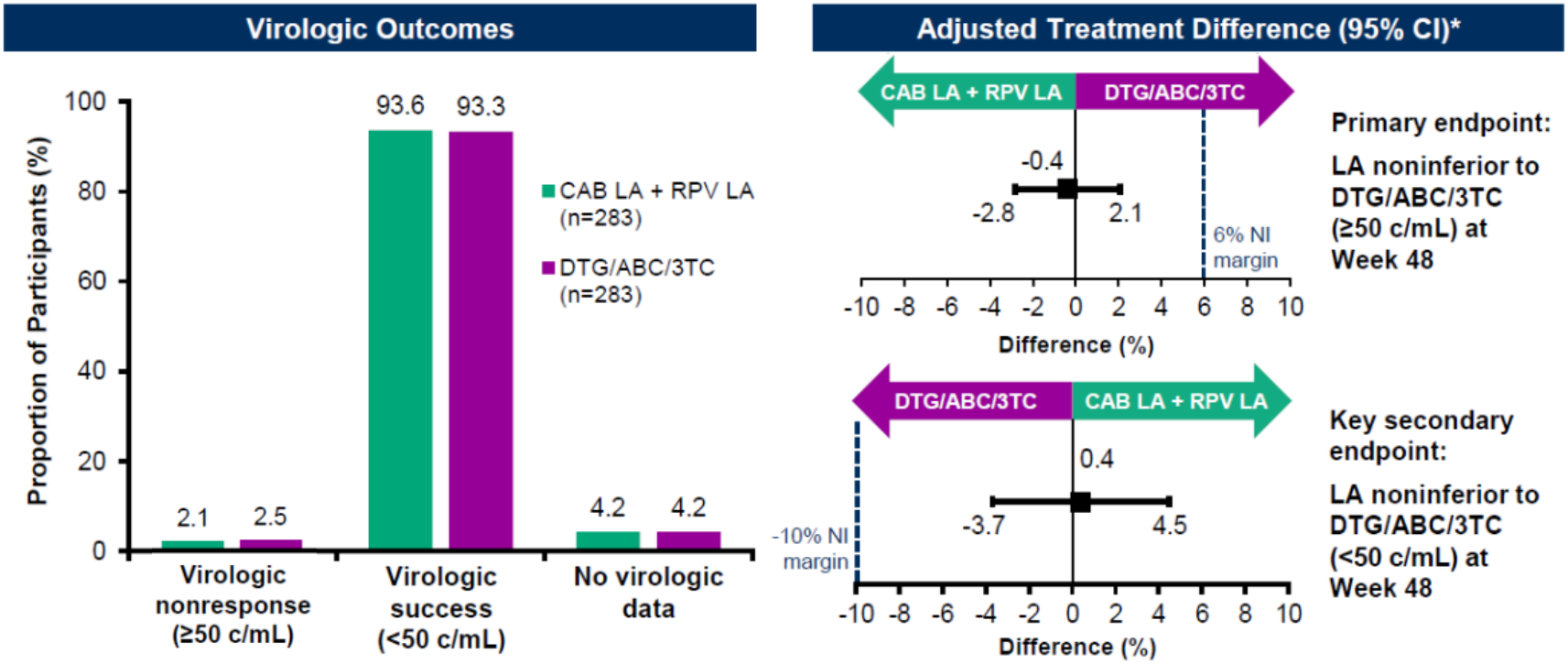
Swindells S et al 26th CROI, Boston, 2019; N Engl J Med 2021

FLAIR—study design



Orkin C et al 26th CROI, Boston, 2019; N Engl J Med 2021

FLAIR—Primary and Secondary Endpoints



Orkin C et al 26th CROI, Boston, 2019; N Engl J Med 2021

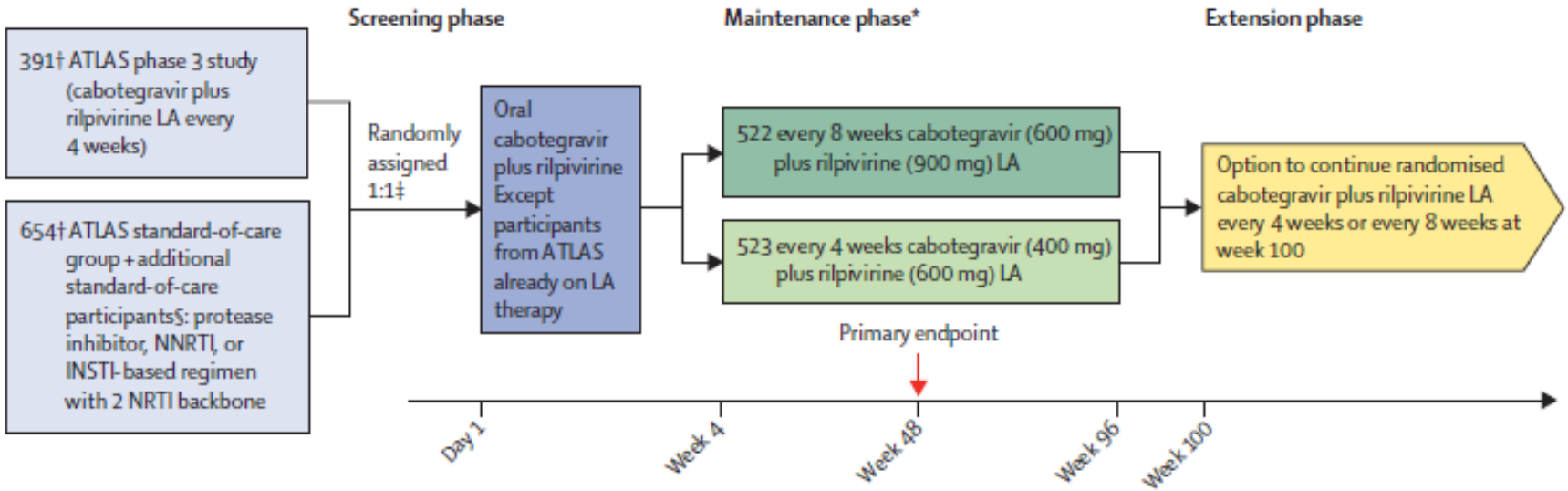
Resistance data from ATLAS and FLAIR

TABLE 3. Subtypes and Mutations in ATLAS and FLAIR*

Study	Sex at Birth, Country, HIV-1 Subtype (Day 1/SVF)	Baseline RAMs†		Viral Load at SVF/CVF (Copies/mL)	SVF Timepoint RAMs		Drug Sensitivity at SVF (Fold Change)§
		NNRTI	INSTI‡		NNRTI	INSTI‡	
ATLAS	W, Russia, A1/A	E138E/A	None	79,166/25,745	E138A	None	RPV (2.4) CAB (0.8) DTG (0.9)
	W, France, AG/AG	V108V/I, E138K	None	695/258	V108I, E138K	None	RPV (3.7) CAB (1.2) DTG (1.0)
	M, Russia, A/A1	None	None	544/1841	E138E/K	N155H	RPV (6.5) CAB (2.7) DTG (1.2)
FLAIR‖	W, Russia, A1/A1	None	None	373/456	E138E/A/K/T	Q148R	RPV (7.1) CAB (5.2) DTG (1.0)
	M, Russia, A1/A1¶	None	None	287/299	K101E	G140R	RPV (2.6) CAB (6.>7) DTG (2.2)
	W, Russia, A1/A	None	None	488/440	E138K	Q148R	RPV (1.0) CAB (9.4) DTG (1.1)

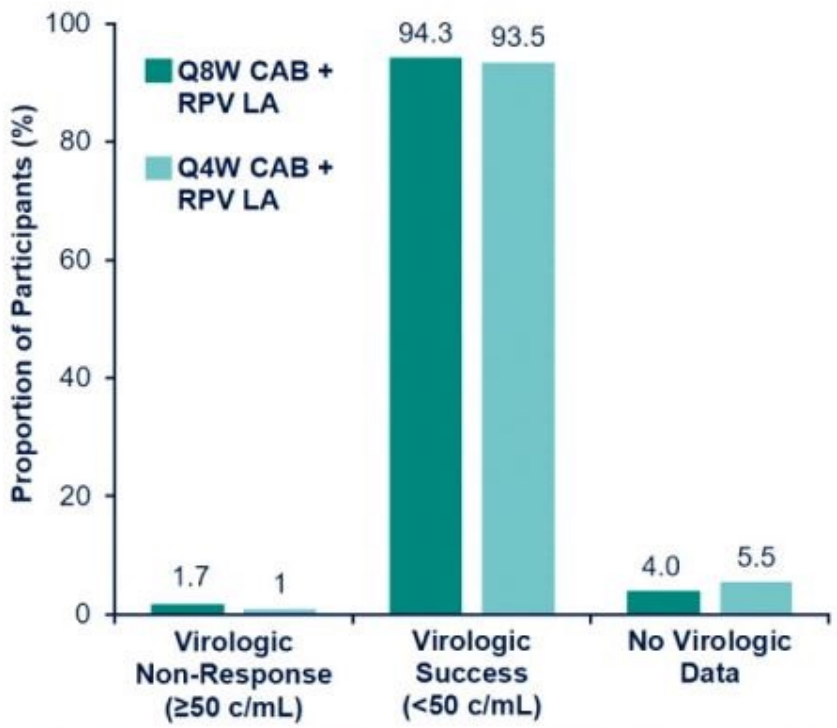
Rizzardini G et al JAIDS 2020

ATLAS-2M Study Design

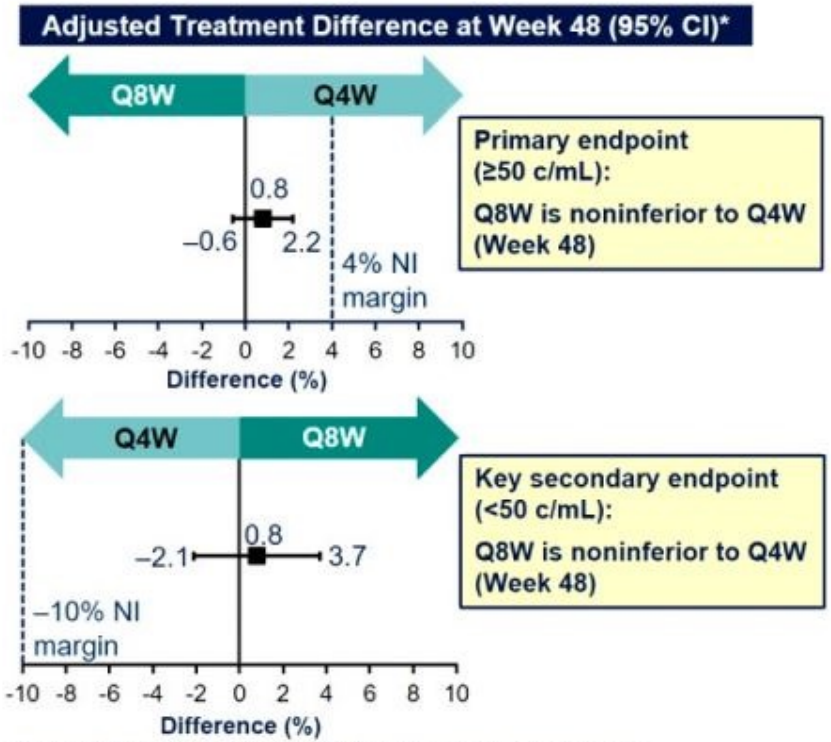


Overton T et al Lancet 2021

ATLAS-2M Week 48 Snapshot Outcomes



CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; LA, long-acting; NI, noninferiority; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks.



*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).

Overton T et al CROI 2020; Lancet 2021

Injection site reactions in ATLAS-2M

	Every 8 weeks group (n=522)	Every 4 weeks group (n=523)
(Continued from previous column)		
Participants who received ≥1 injection of study drug	(n=516)	(n=517)
Participants with ISR event	392 (76%)	390 (75%)
Maximum grade or intensity		
Mild or grade 1	364 (71%)	362 (70%)
Moderate or grade 2	140 (27%)	143 (28%)
Severe or grade ≥3†	14 (3%)	21 (4%)
Serious ISR	1 (<1%)	0
Discontinuations owing to injection-related reasons‡	6 (1%)	11 (2%)
Participants with ISRs (≥5% as reported)		
Pain	371 (72%)	363 (70%)
Nodule	54 (10%)	89 (17%)
Induration	41 (8%)	39 (8%)
Discomfort	36 (7%)	41 (8%)
Swelling	32 (6%)	27 (5%)
Pruritus	27 (5%)	25 (5%)

Overton T et al Lancet 2021

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

Amy G. Cutrell, Jonathan M. Schapiro, Carlo F. Perno, Daniel R. Kuritzkes, Romina Quercia, Parul Patel, Joseph W. Polli, David Dorey, Yongwei Wang, Sterling Wu, Veerle Van Eygen, Herta Crauwels, Susan L. Ford, Mark Baker, Christine L. Talarico, Marty St Clair, Jerry Jeffrey, C. Thomas White, Simon Vanveggel, Kati Vandermeulen, David A. Margolis, Michael Aboud, William R. Spreen and Jan van Lunzen

Cutrell AG et al AIDS 2021

Baseline and multivariable analysis of factors influencing treatment outcome on LA-CAB/RPV

- Understanding predictors of response is important for selecting patients for whom a LA-CAB/RPV regimen is appropriate
- A post-hoc analysis pooled data from the three studies to explore potential factors associated with virologic outcome at Week 48

Cutrell AG et al AIDS 2021

Methods

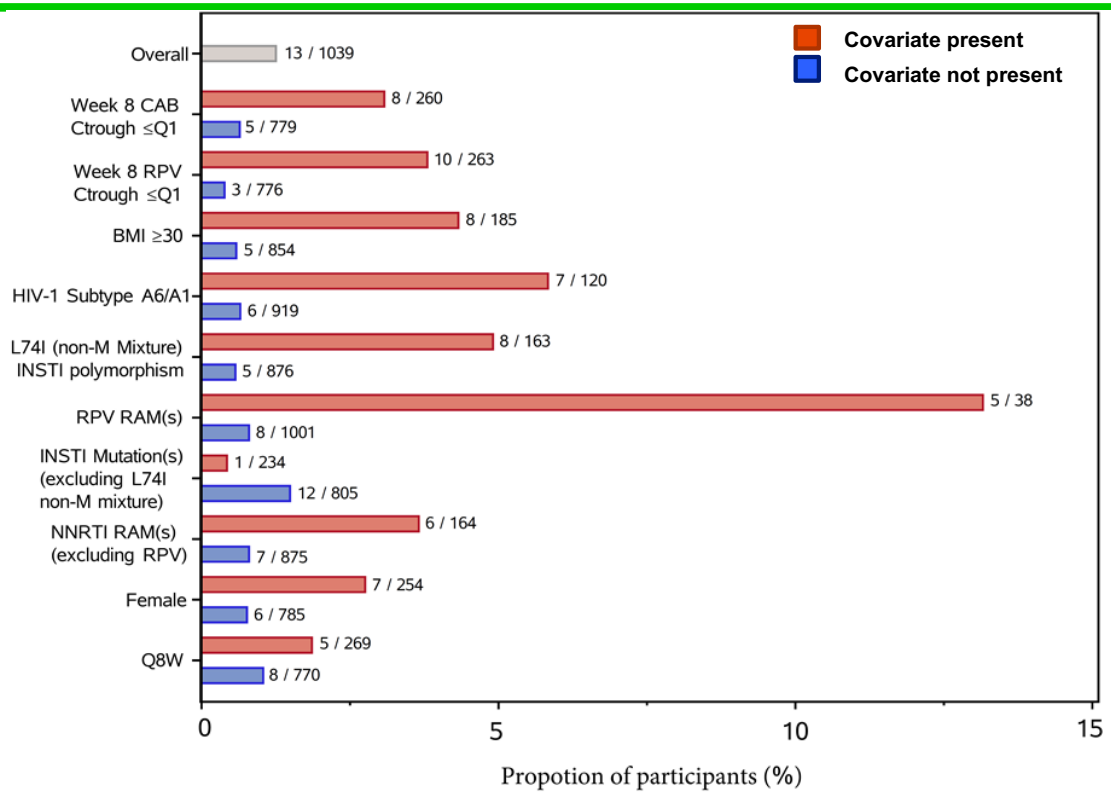
- **1039 adults from the ATLAS, FLAIR and ATLAS-2M Phase 3 studies who were naïve to CAB+RPV LA at study entry were included in this pooled multivariable analysis**
- **Of the 308 ATLAS, 283 FLAIR, and 654 ATLAS-2M participants (excluding those who received CAB+RPV in ATLAS*), 10 participants who discontinued treatment prior to receiving CAB+RPV LA injections, and 196 participants with missing covariates were excluded**
- **A logistic regression model was used to examine the influence of 10 covariates known or suspected to contribute to virologic outcomes, including factors impacting drug exposure, key virus characteristics and dosing interval (Q8W vs. Q4W), on the occurrence of CVF**
  - Final model obtained using a backwards variable selection procedure:
  - Initial model fitted with all 10 selected covariates
  - Removed the covariate with the largest p-value (among all with p>0.20) and refit the model
  - Repeated until no covariate yielded a p-value >0.2
- **Covariates found to be significant and present at baseline were further evaluated to determine if a specific combination of covariates were more or less likely to contribute to CVF compared when present alone using Youden's J statistic**

Cutrell AG et al AIDS 2021

Summary of covariates per participant

Study	ID[a]	CAB PK[b] ≤Q1	RPV PK[b] ≤Q1	HIV-1 subtype A6/A1	Baseline IN L74I[c]	Baseline INSTI mutation[d]	Baseline Proviral RPV RAM[e]	Baseline NNRTI RAM[f]	Female sex at birth[g]	BMI ≥30 kg/m^2	Q8W
ATLAS-2M	1	✓			✓	✓	✓	✓	✓	✓	✓
ATLAS-2M	2	✓	✓	✓	✓				✓	✓	✓
ATLAS	3	✓	✓	✓	✓		✓		✓		
ATLAS	4	✓	✓				✓	✓	✓	✓	
FLAIR	5	✓	✓	✓	✓			✓		✓	
FLAIR	6	✓	✓	✓	✓				✓	✓	
FLAIR	7	✓	✓	✓	✓				✓	✓	
ATLAS-2M	8			✓	✓		✓	✓	✓	✓	✓
ATLAS-2M	9	✓	✓								
ATLAS	10		✓	✓	✓						
ATLAS-2M	11						✓	✓		✓	✓
ATLAS-2M	12		✓								✓
ATLAS-2M	13							✓			

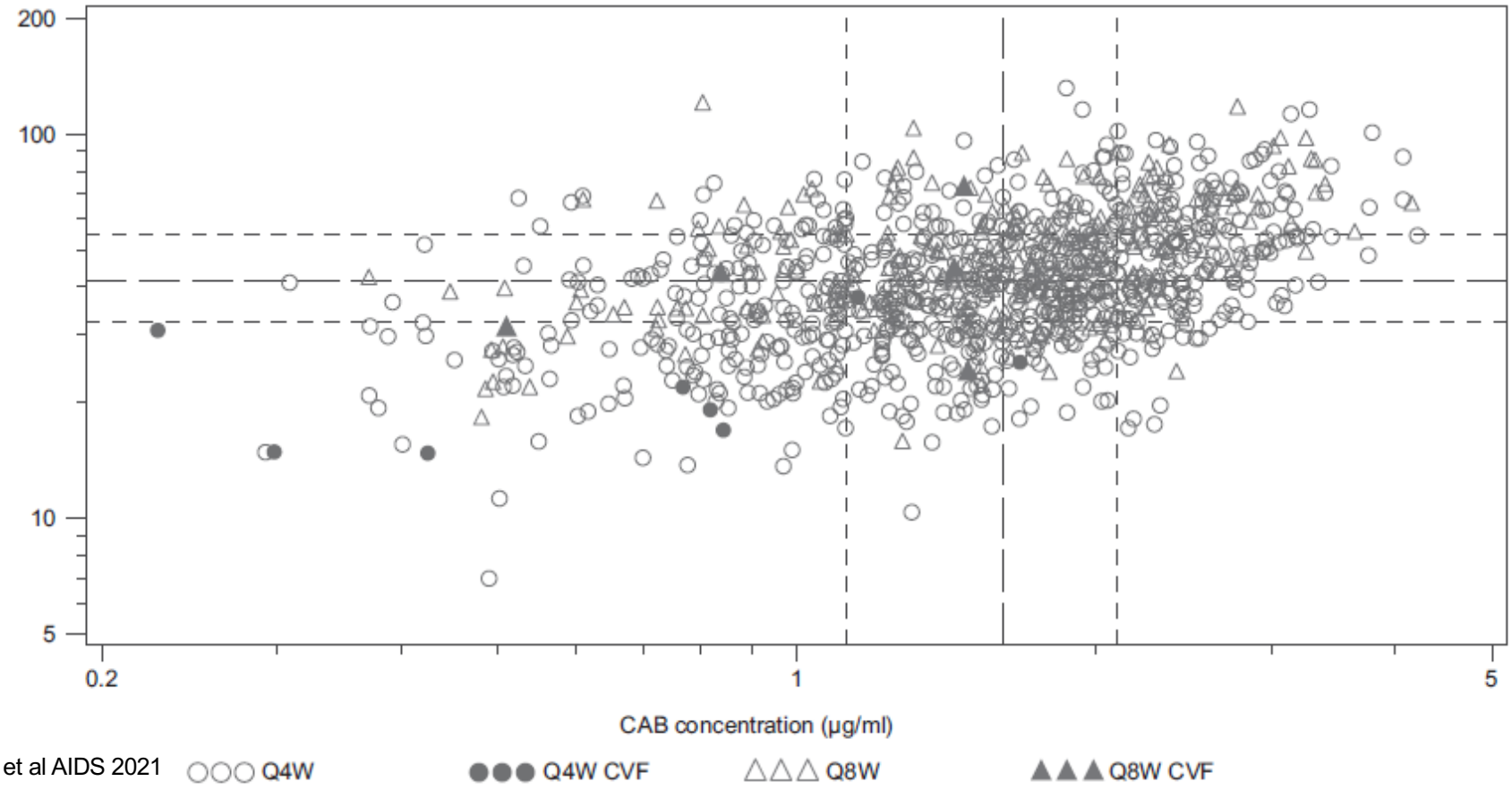
Univariate analysis of CVF outcome by 10 pre-specified factors



IAS–USA major mutations associated with resistance to RPV:
L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L

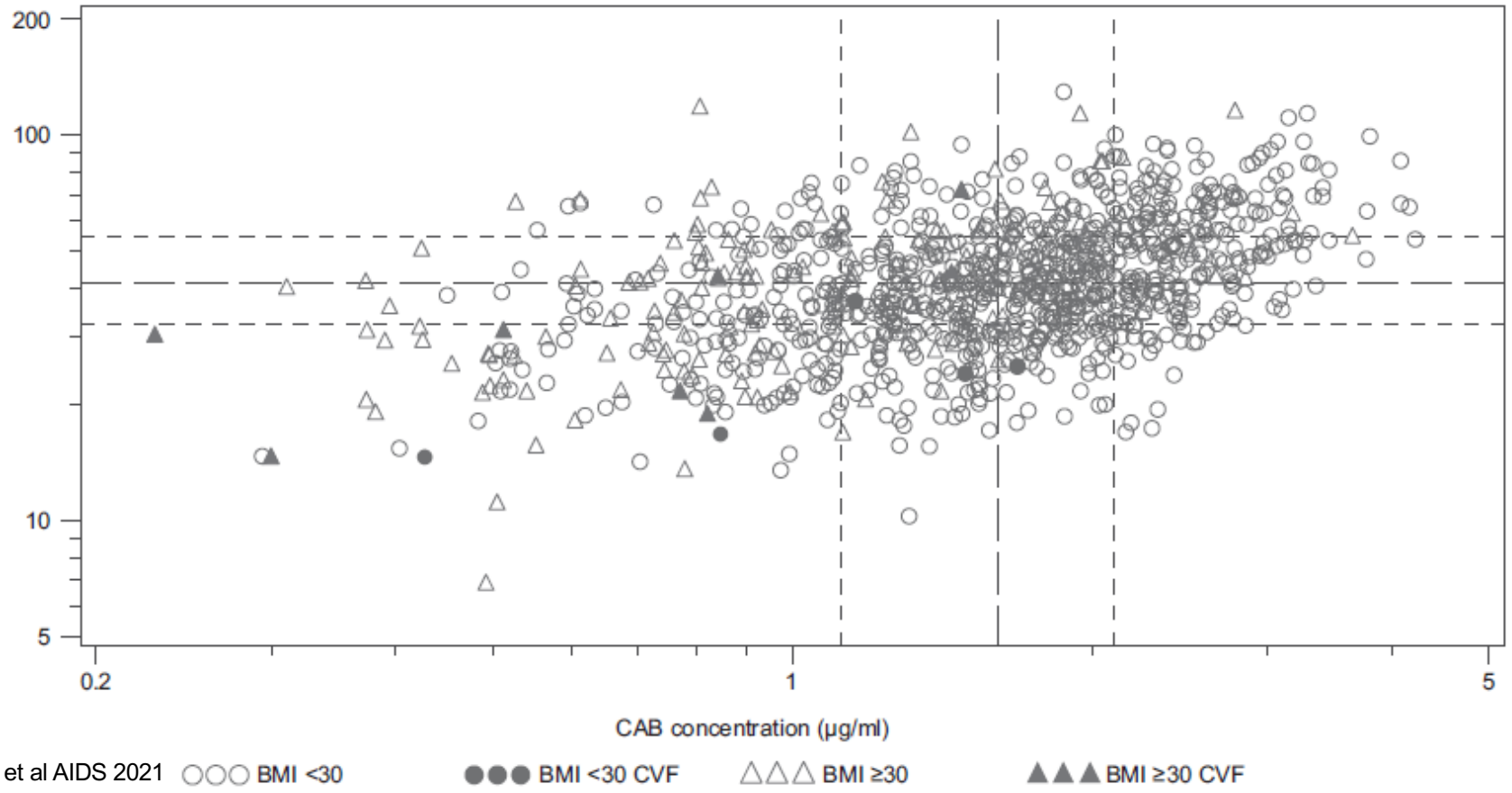
Cutrell AG et al AIDS 2021

Cabotegravir and rilpivirine trough concentrations at Week 8 (by regimen)



Cutrell AG et al AIDS 2021

Cabotegravir and rilpivirine trough concentrations at Week 8 (by baseline BMI)



Cutrell AG et al AIDS 2021

Multivariable regression analysis of CVF (week 48)

N	Parameter	Full model OR (95% CI), *P*[a]	Backwards elimination model OR (95% CI), *P*[a]
1039	RPV RAM(s) at baseline	30.23 (6.25–>99), <0.001	40.36 (8.81–>99), <0.001
	Log_2 of *post hoc* Week 8 RPV trough concentration	3.85 (1.15–14.29)[b], 0.029	5.00 (1.79–16.67)[b], 0.002
	Baseline HIV-1 subtype A6/A1	2.37 (0.34–22.14), 0.394	5.92 (1.62–22.89), 0.008
	BMI (kg/m^2) at baseline	1.08 (0.96–1.22), 0.192	1.13 (1.02–1.24), 0.020
	Prespecified INSTI polymorphism (excluding L74I [excluding mixtures with L74M]) at baseline	0.16 (0.01–1.05), 0.057	0.14 (0.01–0.91), 0.038
	NNRTI RAM(s) (excluding RPV RAMs) at baseline	2.64 (0.72–9.21), 0.137	2.78 (0.78–9.63), 0.111
	Q8W regimen	2.76 (0.65–11.68), 0.164	2.77 (0.67–11.38), 0.156
	L74I (excluding mixtures with L74M) INSTI polymorphism at baseline	2.51 (0.33–13.85), 0.347	Eliminated from model
	Female (sex at birth)	1.09 (0.26–4.36), 0.899	Eliminated from model
	Log_2 of *post hoc* Week 8 CAB trough concentration	0.66 (0.25–1.74), 0.395	Eliminated from model

CAB, cabotegravir; CI, confidence interval; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

[a]95% penalized profile confidence intervals and penalized likelihood ratio *P* values are provided. Backwards elimination used a significance threshold of alpha = 0.2. CAB and RPV pharmacokinetic parameters were log_2-transformed; therefore, the corresponding odds ratios are per halving of each variable.

[b]Results are reciprocal of these so that all ORs are in same direction.

Cutrell AG et al AIDS 2021

Baseline factor analysis (RPV RAMs, subtype A6/A1, BMI ≥30 kg/m^2)

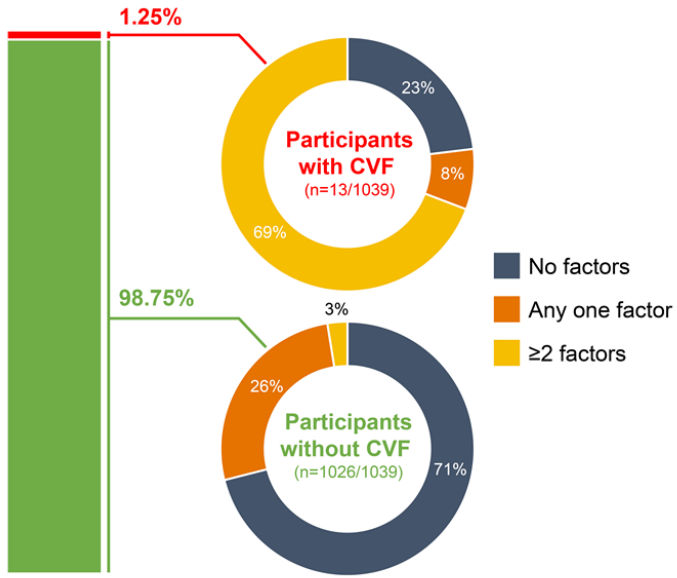
Baseline factors	Virologic success[a] *n* (%)	CVF[b] *n* (%)
None of the three factors	694/732 (94.8)	3/732 (0.41)
Any one of the three baseline factors	261/272 (96.0)	1/272 (0.37)
HIV-1 subtype A6/A1 alone	90/95 (94.7)	1/95 (1.1)
BMI ≥30 kg/m^2 alone	147/153 (96.1)	0/153 (0)
RPV RAM(s) alone	24/24 (100)	0/24 (0)
At least two of the three baseline factors	25/35 (71.4)	9/35 (25.7)
RPV RAM(s) + HIV-1 subtype A6/A1	2/3 (66.7)	1/3 (33.3)
RPV RAM(s) + BMI ≥30 kg/m^2	7/10 (70.0)	3/10 (30.0)
HIV-1 subtype A6/A1 + BMI ≥30 kg/m^2	16/21 (76.2)	4/21 (19.0)
All three baseline factors	0/1 (0)	1/1 (100)
TOTAL	980/1039 (94.3)	13/1039 (1.25)
[95% CI (exact method)]	(92.74–95.65)	(0.67–2.13)

CI, confidence interval; CVF, confirmed virologic failure; RAM, resistance-associated mutation; RPV, rilpivirine.
[a]Based on the FDA Snapshot algorithm of HIV-1 RNA <50 copies/ml.
[b]Defined as two consecutive measurements of HIV-1 RNA ≥200 copies/ml.

	PPV	NPV	sensitivity	specificity
At least 2 factors	26%	99.6%	69%	97.5%
Any 1 factor	<1%	98%	8%	74%

Cutrell AG et al AIDS 2021

Week 48 CVF outcome by presence of key baseline factors (RPV RAMs, HIV-1 subtype A6/A1, and BMI ≥30 kg/m^2)



BMI, body mass index; CVF, confirmed virologic failure; RAM, resistance-associated mutation; RPV, rilpivirine

Cutrell AG et al AIDS 2021

Conclusions

- **Confirmed virologic failure occurred with a rate of ~1% in the LA arms across ATLAS, FLAIR and ATLAS-2M**
- **Presence of 2 or more factors associated with increased CVF risk:**
  - BMI ≥30 kg/m^2
  - A6/A1 subtype
  - Presence of 2 or more RPV RAMs in proviral DNA
  - (Low RPV trough concentrations at week 8)

Cutrell AG et al AIDS 2021

Effect of the L74I polymorphism on fitness of HIV-1 subtype A6 resistant to cabotegravir

ZX Hu, T Cordwell, JL Jeffrey and DR Kuritzkes

Subtype A6 and L74I in Integrase

- Subtype A6 is the predominant HIV-1 subtype circulating in Russia and Eastern Europe
- 5 of 6 participants with confirmed virologic failure in ATLAS and FLAIR had HIV-1 A6
- Presence of A6 (A1) virus identified as independent risk factor for virologic failure in ATLAS, FLAIR, ATLAS-2M
- The L74I polymorphism in IN is characteristic of HIV-1 A6

Cutrell AG et al AIDS 2021
Hu ZX et al CROI 2022

Prevalence of L74I in IN of different HIV-1 subtypes

Subtype	A	B	C	D	F	G	CRF01_AE	CRF02_AG
Number of sequences of this subtype	1034	644	2517	335	244	203	1824	843
Prevalence of L74I among this subtype	21%	4%	6%	2%	4%	12%	1%	16%

Stanford database

Subtype	A	A1	A6
Number of sequences of this subtype	57	266	338
Prevalence of L74I among this subtype	12.3%	9.5%	91.9%

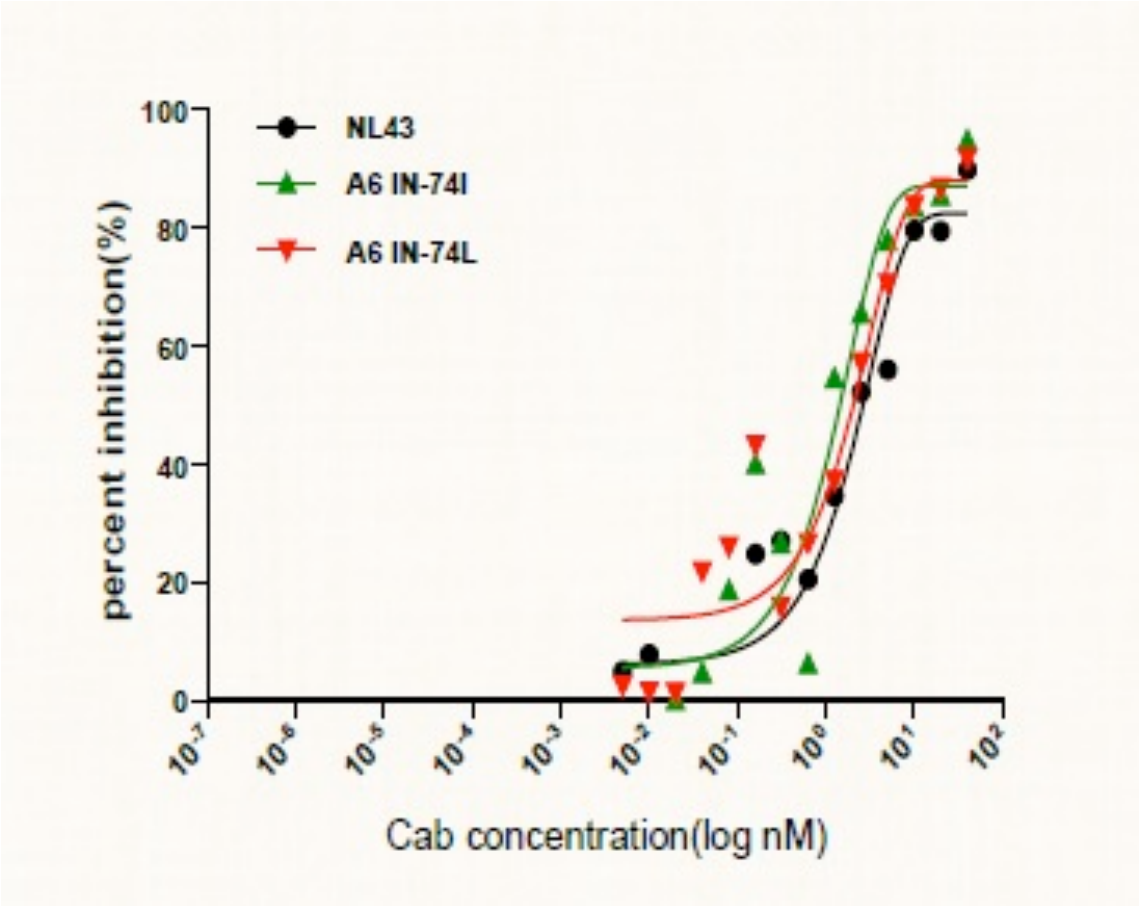
Los-Alamos database

Kirichenko A et al 17th European Meeting on HIV and Hepatitis, 2017, Rome, Italy.

Methods

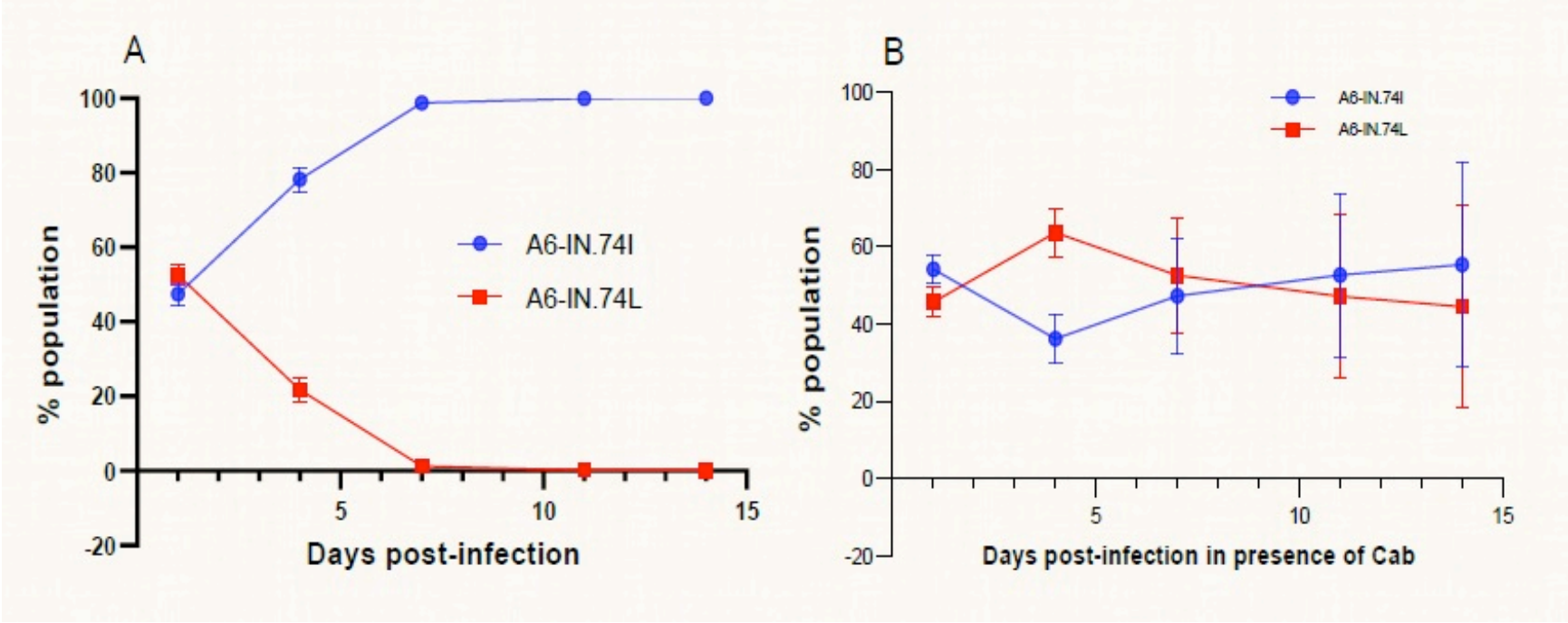
- An HIV-1 IN gene based on the A6 consensus sequence (A6.IN) was synthesized used to construct a plasmid containing HIV-1NL4-3 pol in which the IN-coding region was replaced by A6.IN.
- Major CAB resistance mutations in the A6.IN backbone were introduced by site-directed mutagenesis.
- Infectious recombinant viruses carrying the IN gene of interest were generated by co-transfection with a plasmid carrying an HIV-1NL4-3 backbone deleted in IN together with the PCR-amplified IN into 293T cells.
- Replication capacity (RC) in the absence or presence of 2 nM CAB was determined in TZM-bl and MT-2.
- Viral fitness of recombinants carrying A6.IN.74I or A6.IN.74L were compared by growth competition assays

The L74I polymorphism does not affect susceptibility to CAB



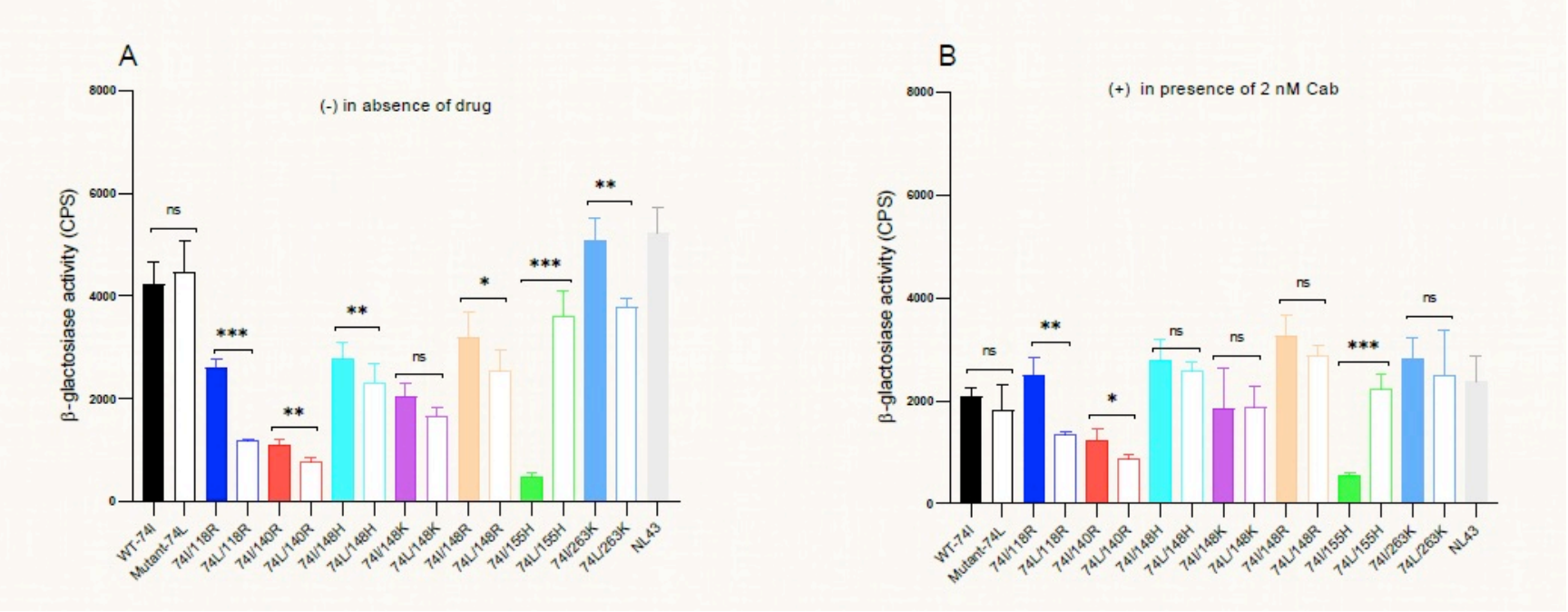
Hu ZX et al CROI 2022

Growth competition of HIV-1 A6 IN 74I vs 74L



Hu ZX et al CROI 2022

Replication capacity of HIV-1 A6 IN mutants in presence of 74L or 74I



Hu ZX et al CROI 2022

Conclusions

- **Susceptibility to CAB of recombinant HIV-1 expressing the subtype A6 IN was similar whether L or I was present at position 74.**
  - The 74L or 74I variants showed similar replication capacity on TZM-bl and MT-2 cells in the absence and presence of 2 nM CAB.
  - In the absence of CAB, viruses carrying 74I outcompeted 74L variants in growth competition assays, suggesting greater fitness of L74I in an A6 IN context.
- **Presence of the L74I polymorphism conferred greater replication capacity to recombinant viruses expressing HIV-1 A6 IN when present together with INSTI resistance mutations at positions 118, 140, 148 and 263.**
  - This finding may explain, in part, the association of HIV-1 subtype A6 and virologic failure observed in clinical trials of CAB-LA in combination with RPV-LA.
- **Surprisingly, the opposite effect was observed with respect to N155H mutant, in which case the 74L variant showed greater replication capacity than 74I.**
  - Further analysis and clinical correlation are needed to understand the significance of this finding.


Thank You for Your Attendance!
Please visit us at:
www.prn.org