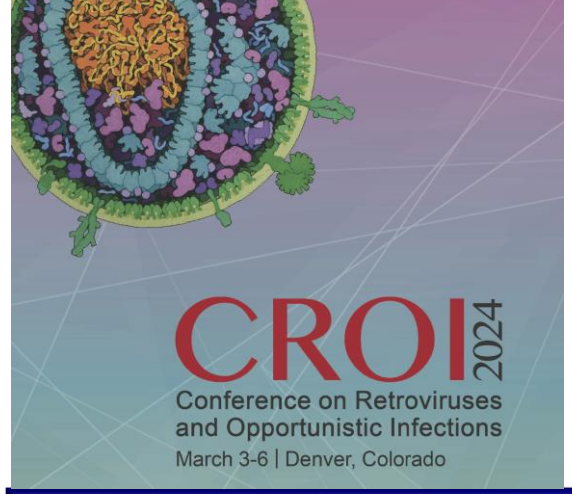

CROI 2024: TAR. Nuevos fármacos y estrategias

Josep M Llibre, MD, PhD

Malalties Infeccioses, Fundació Lluita contra les Infeccions

Hospital Universitari Germans Trias, Badalona, Barcelona

@DrBike7

ScienHub

Summary & Conclusions

CAB + RPV LA

- CAB + RPV Q4W a new possibility in people with adherence challenges, but full support program missed.
- CARES: CAB + RPV LA Q8W high efficacy in Sub-saharan Africa, despite high-risk baseline factors.

New strategies

- BIC + LEN Oral QD Phase 2: safe “strategic simplification” RCT in MTR: Week 24.
- QW oral LEN + ISL: a promising strategy in switch. Week 24.
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- GS-1720, a new QW oral INSTI, Exhibited Potent Antiviral Activity (Phase 1b)
- bNAbs: A lot of interest, but disappointing as ART

New hypothesis

- TDF toxicity on duodenal enterocytes could impact body weight and lipids.

Oral Abstract Session-14 | Special Session: Clinical Late-Breaking Oral Abstracts

12:15 PM - 1:30 PM • Mile High Ballroom 1-2-3

Moderators


Constance A. Benson, *University of California San Diego, La Jolla, CA, USA*

Peter Reiss, *Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands*

Introductions

208 12:20 PM — LB
Efficacy and Safety of Weekly Islatravir Plus Lenacapavir in PWH at 24 Weeks: A Phase II Study
Amy Colson, Gordon Crofoot, Peter J. Ruane, Moti Ramgopal, Alexandra W. Dretler, Ronald G. Nahass, Gary Sinclair, Mezgebe Berhe, Chris Deaton, Angela S. Liu, Eva Mortensen, Martin S. Rhee, Elizabeth G. Rhee, Jared Baeten, Joseph J. Eron

209 12:28 PM — LB
HepB-CpG Vaccine Is Superior to HepB-alum in People With HIV and Prior Vaccine Nonresponse: A5379
Kristen Marks, Minhee Kang, Triin Umbleja, Andrea Cox, Karen J. Vigil, Ngan T. Ta, Ayotunde Omoz-Oarhe, Jennifer Price, Josphat Kosgei, Leolin Katsidzira, Hugo Perazzo, Kevin Knowles, Beverly L. Alston-Smith, Kenneth E. Sherman, for the ACTG 5379 (BEe-HIVe) Study Team

210 12:36 PM — LB
Efficacy, Safety, and Immunogenicity of H56:IC31 Vaccine for Prevention of Recurrent TB
Alvaro Borges, Marisa Russel, Dereck Tait, Elana van Brakel, Andrea Cabibbe, Daniela Cirillo, Elisa Nemes, Thomas Scriba, Gavin Churchyard, Rodney Dawson, Isa Sabi, Andreas H. Diacon, Rasmus Mortensen, Mark Hatherill, for the POR TB Consortium

211 12:44 PM — LB
Efficacy, Safety, and PK of BIC/FTC/TAF in Adults With HIV and Tuberculosis on Rifampicin at Week 24
Anushka Naidoo, Kogieleum Naidoo, Marothi P. Letsoalo, Hylke Waalewijn, Gillian Dorse, Rubeshan Perumal, Mahomed-Yunus S. Moosa, Emmanuella C. Osuala, Resha Boodhram, Dennis Israelski, Paolo Denti, James F. Rooney, Kelly Dooley, for the INSIGHT Trial Team

212 12:52 PM — LB
Long-Acting Injectable CAB/RPV Is Superior to Oral ART in PWH With Adherence Challenges: ACTG A5359
Aadia I. Rana, Yajing Bao, Lu Zheng, Sara Sieczkarski, Jordan E. Lake, Carl J. Fichtenbaum, Tia Morton, Lawrence Fox, Paul Wannamaker, Jose R. Castillo-Mancilla, Kati Vandermeulen, Chanelle Wimbish, Karen T. Tashima, Raphael J. Landovitz, for the ACTG A5359 Team

Questions and Answers

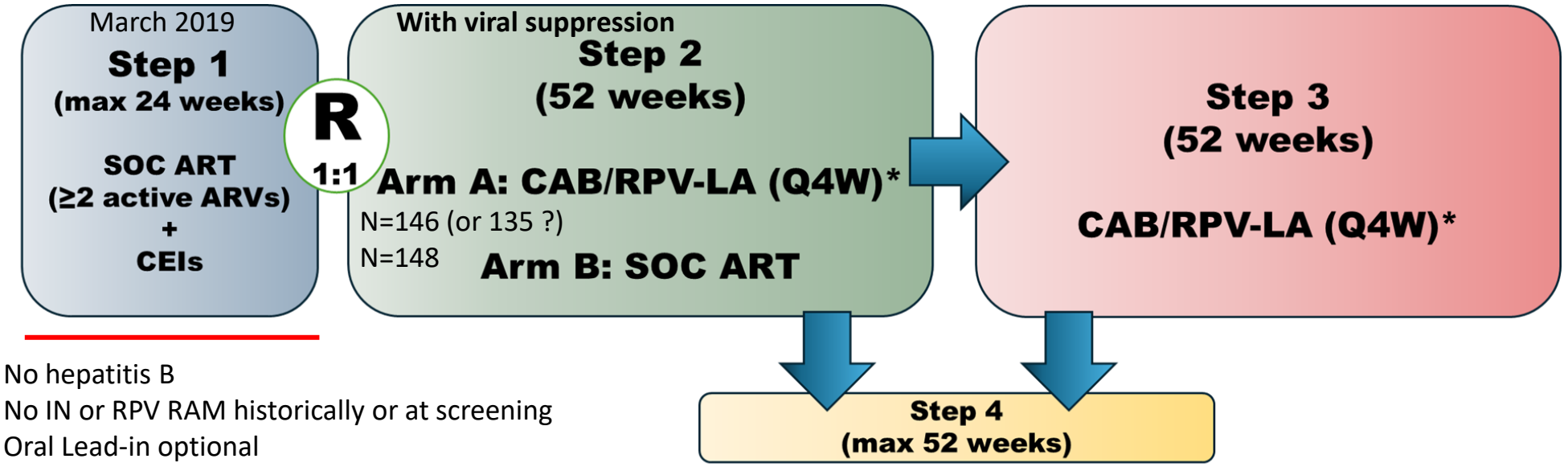
CROI Deadline for LB submission: January 9, 2024

DSMB halts ACTG A5359 study:
Feb 12, 2024 performs interim analysis
Feb 21, 2024 press releases

ACTG A5359: CAB + RPV Q4W open-label RCT in people with adherence challenges*

* a) Poor viral response despite oral ART for ≥6 months.
b) Loss to clinical follow-up with ART non-adherence ≥6 months.

Some $ offered to partially support peer/outreach & transportation worker though noy all sites used.



No hepatitis B
No IN or RPV RAM historically or at screening
Oral Lead-in optional
No exclusion on CD4, HIV-RNA, drug abuse

Primary Outcome: Regimen failure defined as the earliest occurrence of confirmed virologic failure or treatment discontinuation in Step 2

ACTG A5359: CAB + RPV Q4W open-label RCT in people with adherence challenges*

Main study population characteristics:

Median age	40 years (30% female)
Black African American	64%
IVDU (Current/previous)	**14%**
Non-adherence criterion	
Lost to follow-up	**35%**
Time since HIV Dx.	13 years
HIV-RNA >100.000.	14%
Median CD4, cells	**270**
SOC ART ??	

93% injections on time $(\pm 1\ week)$

At step 2:	CAB+RPV / SOC
Median CD4	417 / 374
People with HIV-RNA >200 c/mL	17%. / 7%

(including 8 participants with >10.000 c/mL in CAB+RPV arm)

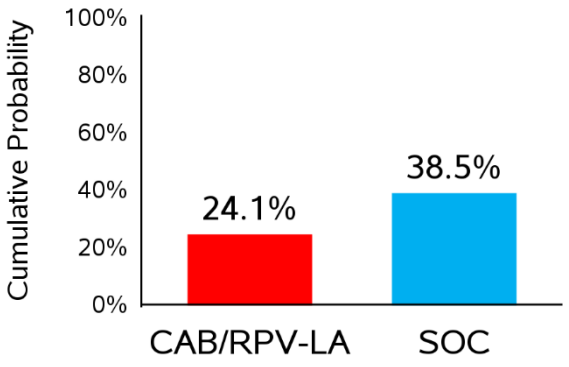
Results-All Outcomes

Feb 12, 2024, DSMB halted the study due to superior efficacy of LA CAB+RPV in secondary endpoints

Primary Outcome

Regimen Failure

Difference	Nominal 98.75% CI
-14.5%	(-29.8%, 0.8%)



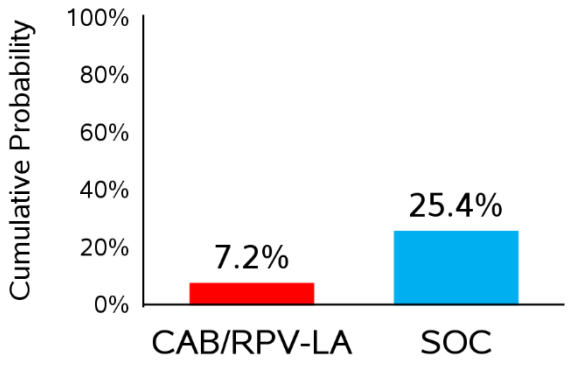
Number of participants

Regimen Failure	28	47
VF	5	28
TRT-DISC	23	19

Secondary Outcomes

Virologic Failure

Difference	Nominal 98.75% CI
-18.2%	**(-31.1%, -5.4%)**

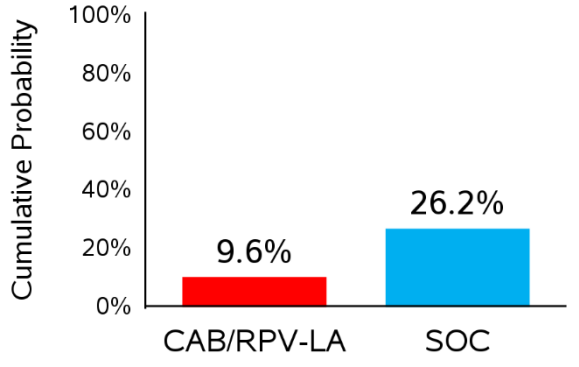


Number of participants

Virologic Failure	6	28

Treatment-related Failure

Difference	Nominal 98.75% CI
-16.6%	**(-29.9%, -3.3%)**

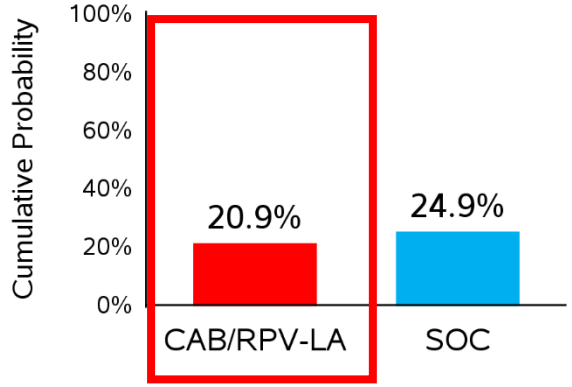


Number of participants

Treatment-related Failure	9	29
VF	6	28
TRT-DISC (AE)	3	1

Permanent Treatment Discontinuation

Difference	Nominal 98.75% CI
-4.1%	(-18.0%, 9.8%)



Number of participants

Permanent TRT-DISC	25	30

LATITUDE

ACTG

Participants with confirmed VF in Step 2

RAM Evaluation	CAB/RPV-LA (n=6; 4.4%)	Oral SOC ART (n=28; 19%)	Total (n=34)
With new RAM, n	2 (1.5%)	2	4
	Week 18 E138EK; G140GS; Q148K; K103R	Week 37 A71V; V77I; V106I	
	Week 49 E138K; Q148K; K20KR; M230ML	Week 48 M184I	
Without new RAM, n	3	19	22
D/c without confirmation sample, n	0	2	2
HIV-1 RNA <400 c/mL, n	1	3	4
Sample not collected, n	0	2	2

COMMENT & RESPONSE

Updated Treatment Recommendation on Use of Cabotegravir and Rilpivirine for People With HIV From the IAS-USA Guidelines Panel

When supported by intensive follow-up and case management services, injectable cabotegravir and rilpivirine (CAB-RPV) may be considered for people with viremia who meet the criteria below when no other treatment options are effective due to a patient's persistent inability to take oral ART (rating AIIa under the conditions described).

- Unable to take oral ART consistently despite extensive efforts and clinical support
- High risk of HIV disease progression (CD4 cell count <200/μL or history of AIDS-defining complications)
- Virus susceptible to both CAB and RPV

If applicable, patients should also be referred for treatment of substance use disorder and/or mental illness.

- CAB + RPV Q4W
- Commitment to continue oral ART for > 6 months if injections D/C

PE Sax. JAMA Published online March 1, 2024

CARES. Phase 3b, Randomized (1:1), Open-Label, Non-inferiority Study in SS-Africa

Kenya, Uganda, South-Africa

Main eligibility criteria

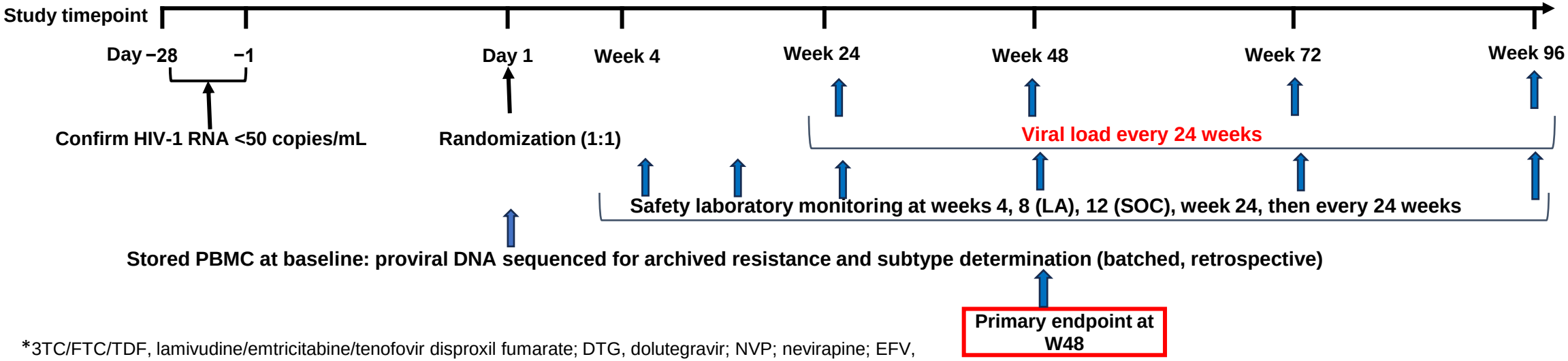
- ≥18 years of age
- On stable oral therapy:
  TDF + 3TC/FTC + DTG/NVP/EFV
- HIV-1 RNA <50 copies/mL at ≥4-12m prior to and at screening
- No history of Rx failure
- No HBV infection

Study treatment

Oral ART (SOC)
TDF + 3TC/FTC + DTG/NVP/EFV
n=256

Optional Oral CAB + RPV

CAB (600 mg) + RPV (900 mg) LA
IM Q8W
n=256



*3TC/FTC/TDF, lamivudine/emtricitabine/tenofovir disproxil fumarate; DTG, dolutegravir; NVP; nevirapine; EFV, efavirenz; CAB, cabotegravir; LA, long-acting; Q8W, every 8 weeks; RPV, rilpivirine; SOC, standard of care

Kityo et al. CROI 2024; Denver, CO. #122

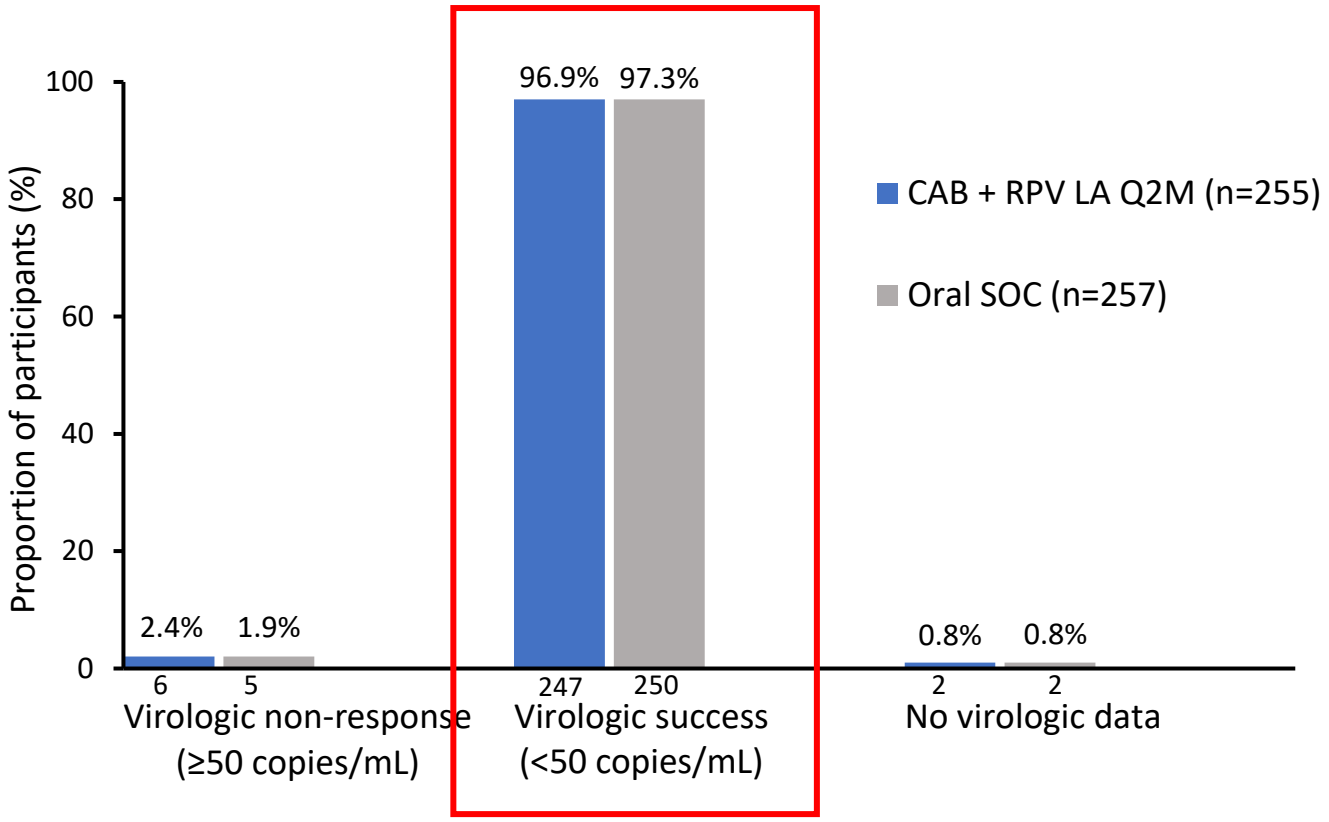
CARES: Baseline Characteristics

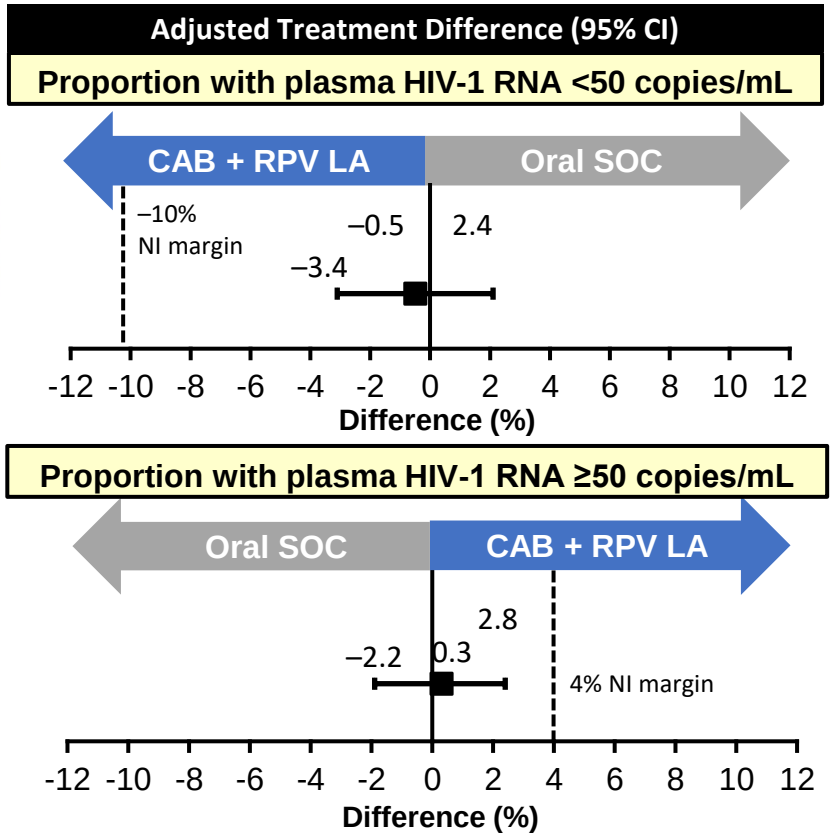
Characteristic	CAB + RPV LA (n=255)	Oral ART (SOC) (n=257)	Overall (N=512)
Female sex, n (%)	146 (57.2)	149 (58.0)	295 (57.6)
Age, median (IQR), years	43 (36-51)	42 (35-49)	42 (35-51)
BMI ≥30 kg/m^2, n (%)	57 (22.4)	51 (19.8)	108 (21.1)
Black race, n (%)	254 (99.6)	256 (99.6)	510 (99.6)
Time on first-line ART, median (IQR), years	8 (4-13)	7 (4-13)	8 (4-13)
Prior exposure to NNRTI, n (%)	189 (73.7)	191 (74.3)	380 (74.2)
INSTI regimen at screening	231 (90.6)	240 (93.4)	471 (92.0)
NNRTI regimen at screening	24 (9.4)	17 (6.6)	41 (8.0)
Archived DNA analysis * †			
***Viral subtype A1**, n/n (%)*	119/213 (55.9)	115/201 (57.2)	234/414 (56.5)
***RPV resistance mutations**, n/n (%)*	25/200 (12.5)	26/177 (14.7)	51/377 (13.5)
***RPV intermediate/high-level resistance**, n/n (%)*	17/200 (8.5)	21/177 (11.9)	38/377 (10.1)
***CAB resistance mutations**, n/n (%)*	15/95 (15.8)	14/85 (16.5)	29/180 (16.1)
***CAB intermediate/high-level resistance**, n/n (%)*	10/95 (10.5)	5/85 (5.9)	15/180 (8.3)

- * Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline
- † Viral subtype, resistance mutations and drug susceptibility were determined using the Los Alamos National Laboratory Panel, and Stanford al gorithm respectively

Kityo et al. CROI 2024; Denver, CO. #122

CARES: Virologic Outcomes at Week 48 (ITT)





2 (0.8%) VF (VL >200), both at week 48 and both BMI <30:

1 confirmed VF: no BL RPV DRMs, subtype A1 with high RPV R and I CAB R.

1 non-confirmed VF (died before re-test, VL 44.984 c/mL), BL RPV DRMs, subtype D, L-L RPV R, high CAB R.

Oral SOC: 0.

Kityo et al. CROI 2024; Denver, CO. #122

Everything so big in US

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- bNAbs: A lot of interest, but disappointing as ART

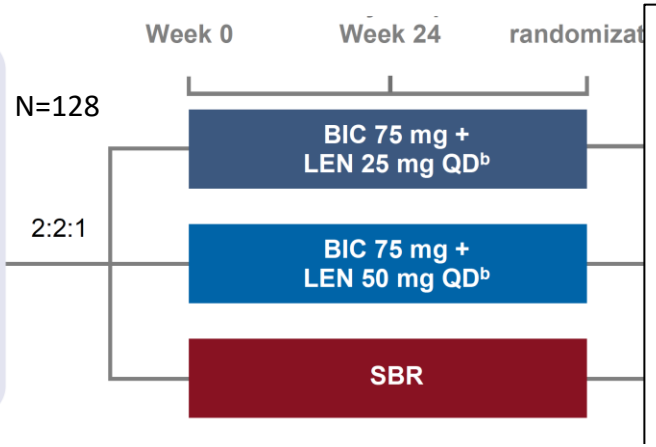
New hypothesis

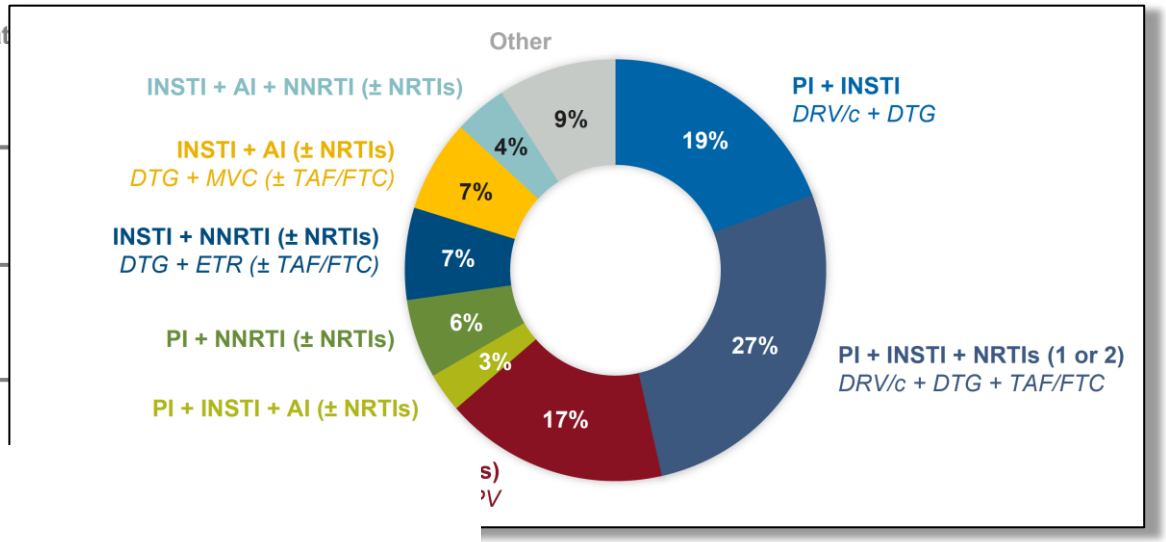
- TDF toxicity on duodenal enterocytes could impact body weight and lipids.

BIC + LEN Oral QD Phase 2 strategic simplification RCT in MTR: Week 24.

Adults ≥ 18 years of age on a complex ART regimen[a] (N = 128)

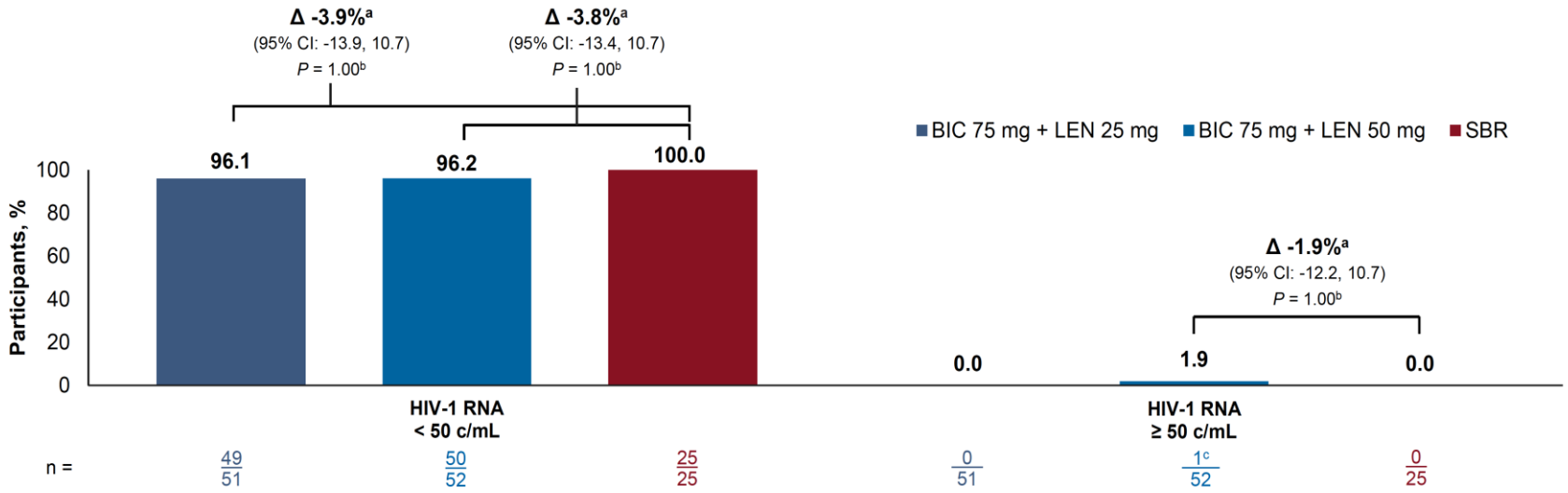
- HIV-1 RNA < 50 c/mL on SBR for ≥ 6 months prior to screening
- No prior exposure to LEN or resistance to BIC
- No history of chronic HBV infection
- eGFR ≥ 15 mL/min; not on renal replacement therapy





, 36% PIs, 64% NRTIs, 52% NNRTIs

Virologic Outcome at Week 24 (FDA Snapshot Algorithm)



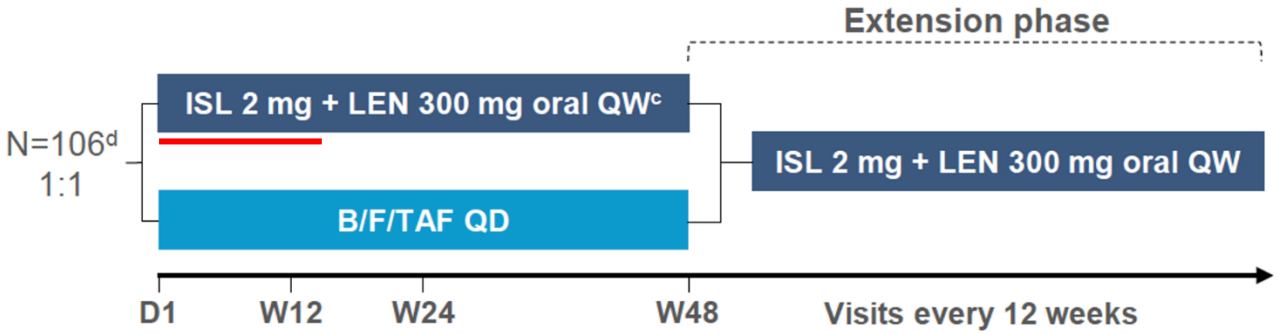
(<200 c/mL, resuppressed)

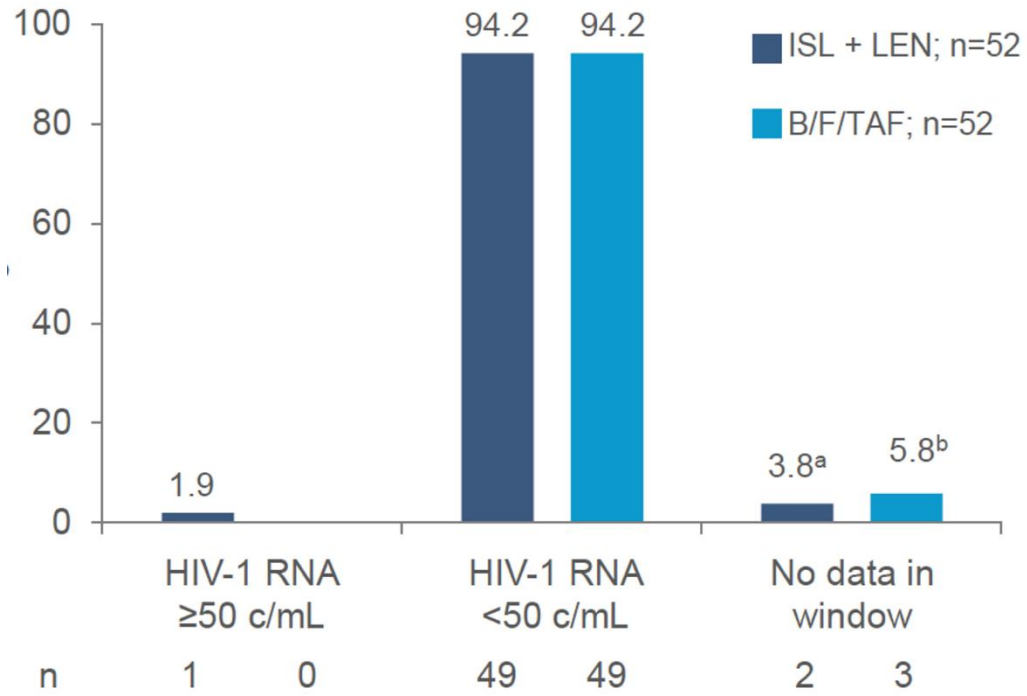
- No resistance emergence
- Similar safety
- Similar CD4 evolution

K Mounzer. ARTISTRY 1. CROI 2024, Denver, CO. #642.

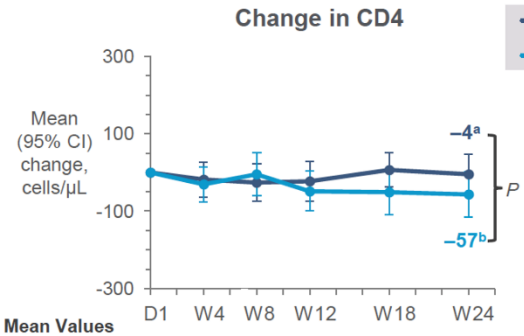
Oral Weekly ISL+LEN in switch from BIC/F/TAF, Phase 2: Week 24 (!).

Inclusion criteria
- Aged ≥18 years
- Viral load <50 c/mL on B/F/TAF[b]
- No history of virologic failure
- CD4 count ≥350 cells/µl
- Lymphocytes ≥900 cells/µl
- No HBV infection

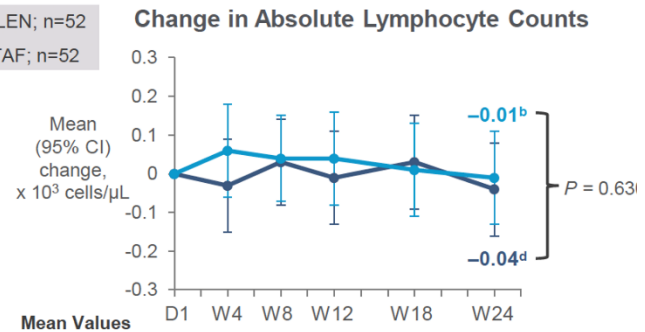




CD4 and Absolute Lymphocyte Count Changes Through Week 24



Mean Values	D1	W4	W8	W12	W18	W24
ISL + LEN	755	738	729	732	766	755
B/F/TAF	818	787	813	758	767	761



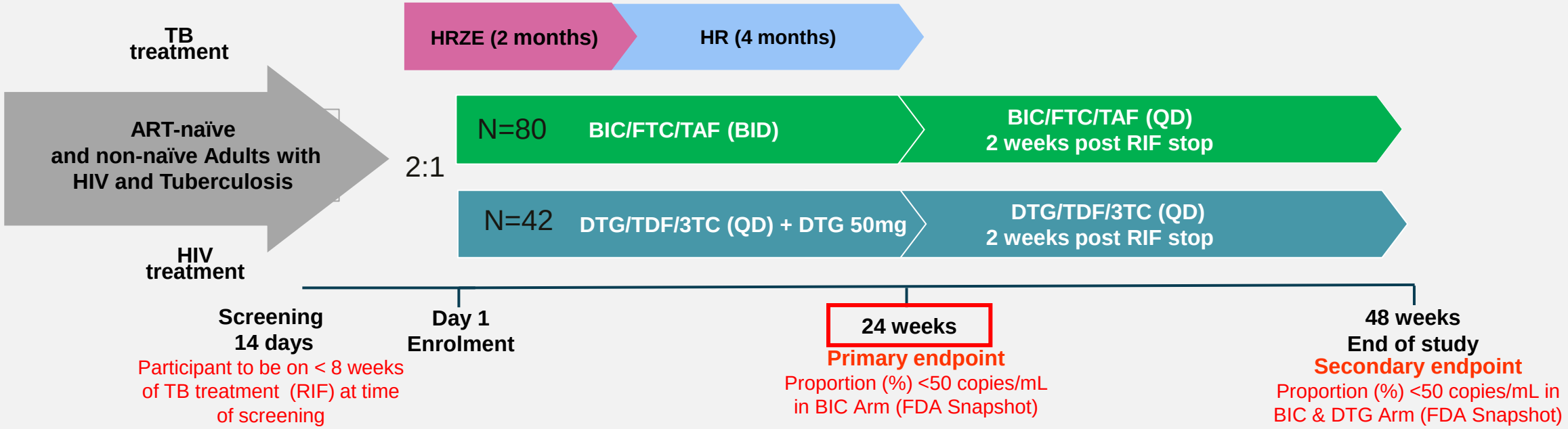
Mean Values	D1	W4	W8	W12	W18	W24
ISL + LEN	1.94	1.93	1.97	1.94	1.98	1.92
B/F/TAF	1.95	1.97	1.99	1.99	1.97	1.96

- No VF, 0 resistance.
- More AEs (open-label switch) but no more D/C due to TRAEs.

Amy E Colson. CROI 2024, Denver, CO. #208.

INSIGHT Study Design, Week 24 data

Phase IIb open-label, non-comparative, randomized-controlled trial



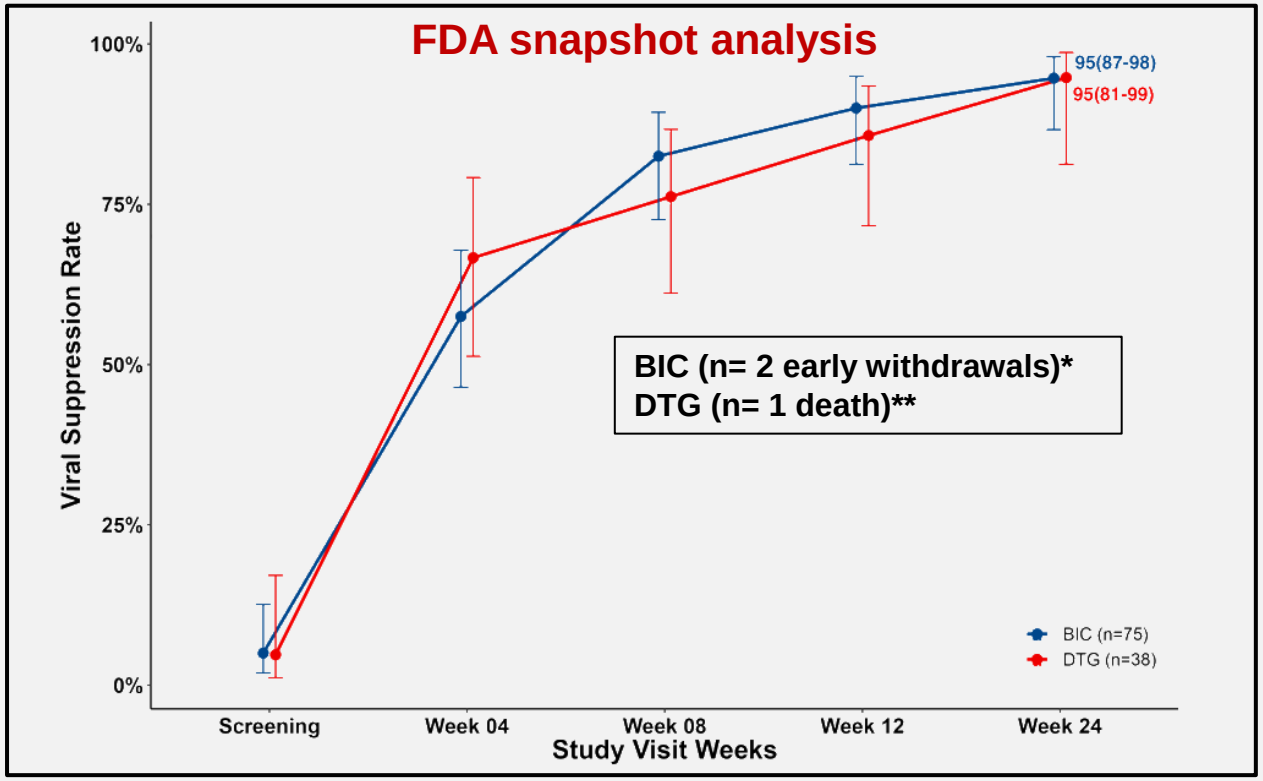
Inclusion criteria

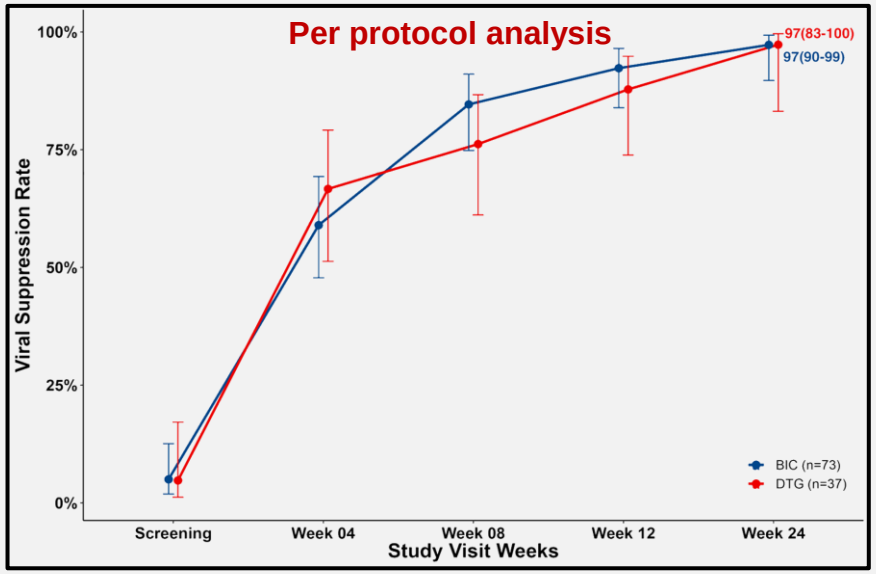
- ART-naïve OR ART non-naïve Adults with HIV (no exposure to ART at least ≥ 3 months at the time of enrolment)
- CD4+ ≥ 50 cells/µl; Females on contraception, HBsAg -ve
- Confirmed RIF-susceptible TB and/or on first-line RIF-based TB treatment (not > 8 weeks at the time of enrolment)
- eGFR ≥ 60 mL/min/1.73m^2, ALT ≤3 ULN, Total bilirubin ≤2.5 ULN
- Hb ≥ 7.0 g/dL/ ♀ ≥6.5g/dL, Platelet ≥ 50,000/mm^3, ANC ≥650/mm^3

- Median CD4: 161 cells (59% <200 CD4 cells)
- HIV-RNA >100.000: 42%

CROI 2024

Primary Endpoint: Viral Suppression at Week 24



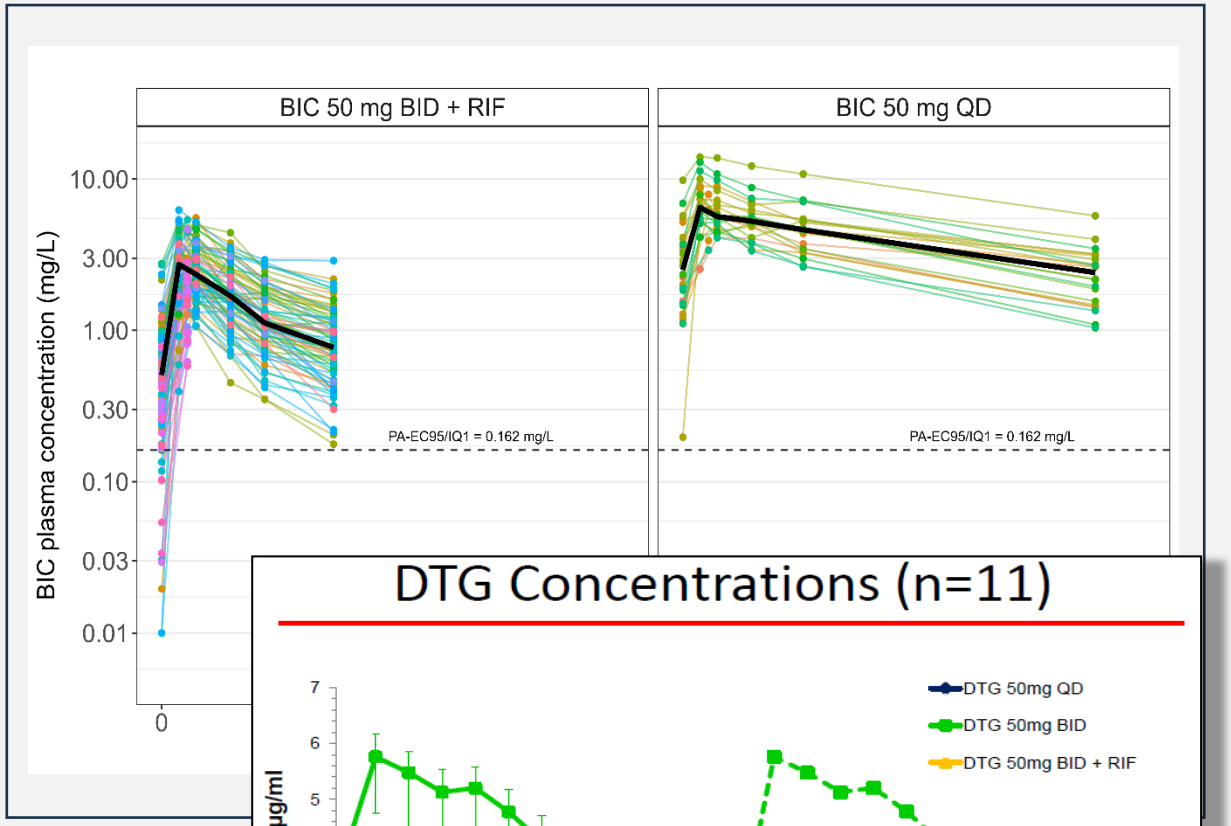


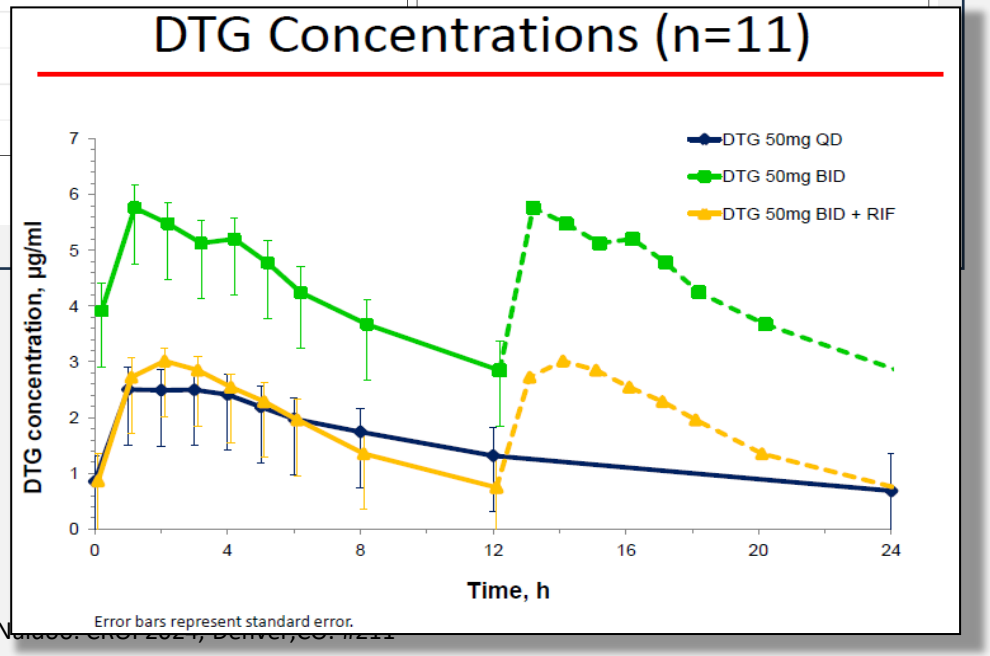
- SAE (11%, 7%)and G3-4 AEs (46%, 50%) BIC and DTG.
- No AE leading to D/C.
- No virologic failures (>400 c/mL), no resistance selection.

- **Median CD4+ cell count** (Q1, Q3) cells/mm^3 at Week 24
  - BIC: 259 (213, 505)
  - DTG: 231 (170, 311)
- **Median change in CD4+ cell count** (Q1, Q3) cells/mm^3 at Week 24
  - BIC: 96 (35, 137)
  - DTG: 69 (27, 122)

**** two relocations; **hemoptysis***

BIC PK data (TAF and FTC coming soon)





***BIC Trough Concentration & AUC during and post-TB treatment**

Trough concentration (Ctau) and AUC 0-24:
BIC 50 mg BID **with RIF**

Time	n	BIC C_{tau} (mg/L) Geometric mean (CV%)	AUC 0-24 (mg*h/L) Geometric mean (CV%)
Weeks 4 and 12	75	**0.397 (73.4%)**	30.9 (42.2%)

Trough concentration (Ctau) and AUC 0-24:
BIC 50 mg QD **without RIF**

Time	n	BIC C_{tau} (mg/L) Geometric mean (CV%)	AUC 0-24 (mg*h/L) Geometric mean (CV%)
Week 32	22	**2.29 (45.1%)**	**94.9 (35.9%)**

Ct (µg/mL):
DTG 50 mg 0.55-0.76
DTG 50 mg BIG + Rif 0.53-0.67
Kelly E Dooley, JAIDS 2014. DOI: 10.1097/QAI.0b013e318276cda9

TAKE OUT & DELIVERY AVAILABLE
7 DAYS

MENUS

ABOUT US

CONTACT

MUSIC

Bison filet, Appaloosa Grill, Denver, CO.

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- CARES: CAB + RPV LA Q8W high efficacy in Sub-saharan Africa, despite high-risk baseline factors.

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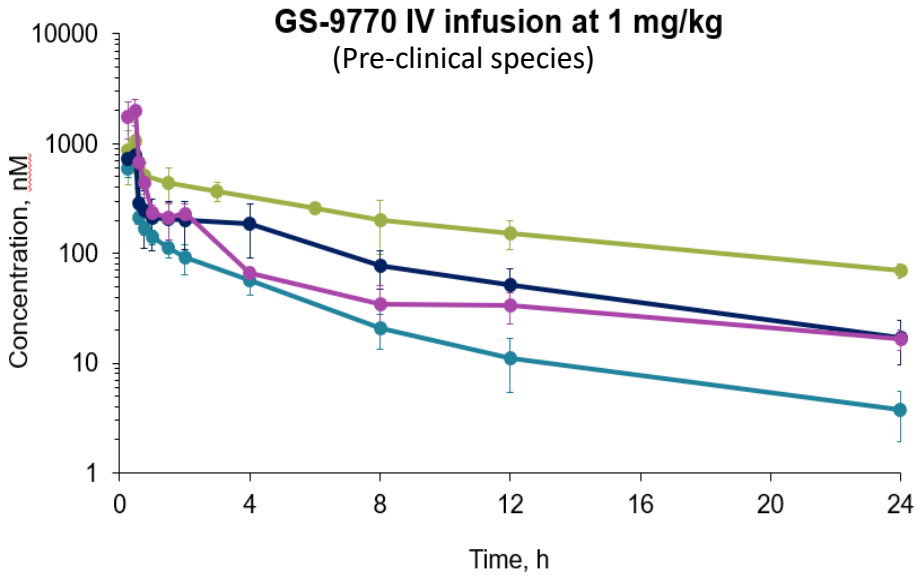
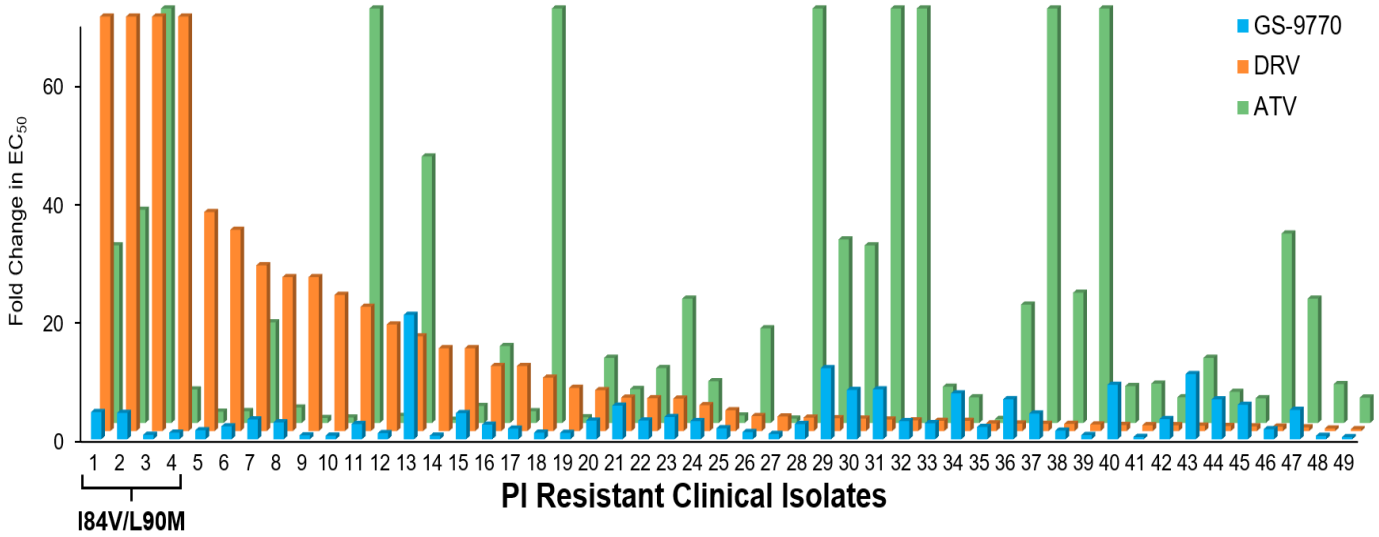
Poster Session-G2 | Novel Antiretrovirals Development: More Than You Think!

2:30 PM - 4:00 PM • Poster Hall C-D

Discovery of GS-9770 –a Novel, Unboosted, Once-Daily Oral PI

- GS-9770, a novel **potent unboosted once daily PI, active against DRV-resistance HIV-1**.
- Step-by-step improvement of all properties.
- Expected **$t_{1/2}$ humans: 18.9 h**



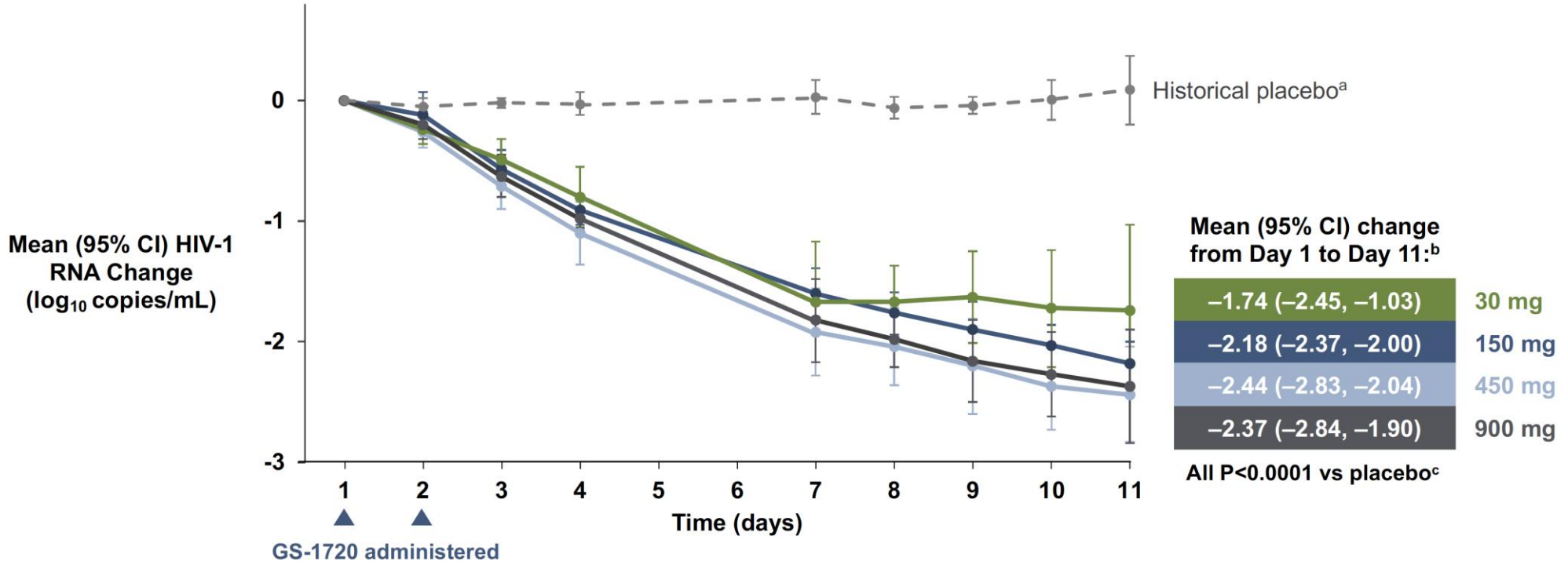


Fold Change in EC_{50}	GS-9770	DRV	ATV
Mean (SD)	3.8 (3.8)	52.8 (154.9)	16.4 (23.2)
Range	0.4–21	0.3–615	0.6–>132
Viruses with >10-fold change in EC_{50}, n/N (%)	3/49 (6)	17/49 (35)	23/49 (47)

Xiaochun Han. CROI 2024, Denver, CO. #636.

Phase 1b: GS-1720, a new QW oral INSTI, Exhibited Potent Antiviral Activity

- Single dose, naives. 7 participants in each cohort
- **No resistance emergence** at day 11 in 150 mg and 450 mg groups (30 mg and 900 mg ongoing).
- **Median $t_{1/2}$: 9.4 days.**
- Safe.
- **Median HIV-RNA decline >2 log_{10} copies/mL** in the highest dose cohorts, ≈ currently approved OD INSTIs.



Carl J. Fichtenbaum. CROI 2024, Denver, C=. #116.

Poster Session-F3 | Long-Acting Injectables, Broadly Neutralizing Antibodies, and New Drugs, Oh My!
2:30 PM - 4:00 PM • Poster Hall C-D

Oral Abstract Session-03 | Clinical Trials of Novel Antiretroviral Therapies
10:00 AM - 12:00 PM • Mile High Ballroom 1-2-3

5 out of 8 studies in the session are about bNAbs.

- **Would you prefer 3 bNAbs or a Tri-specific one?**
- **One bNAb with LEN or one bNAb with CAB?**

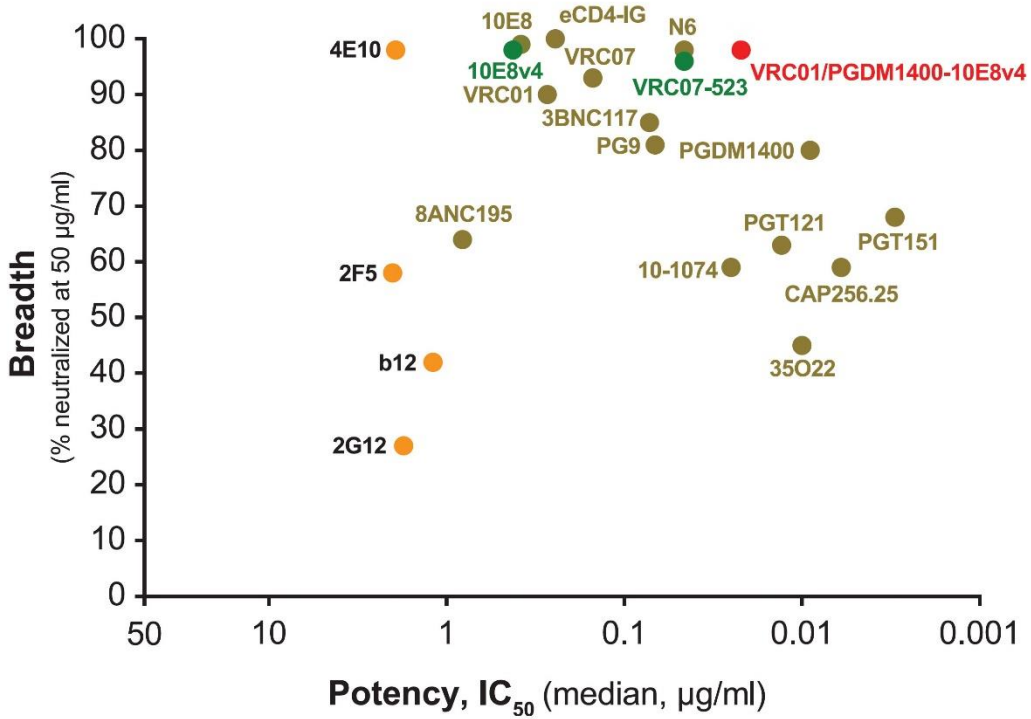
bNAbs: A lot of interest, but disappointing as ART

- Q1M **CAB** + VRC07-523LS (Q8W IV): **11/71 (16%) premature D/C, 5/71 (7.3%) VF and G3 AEs 11/71 (16%)**. #119

- SAR441236 **tri-specific bNAb** (Q3M IV or SC) has **modest effect on pro-viral DNA, frequent ADA and faster clearance PK in viremic (vs aviremic) PWH**. #118

- N6LS BANNER Phase 2. Monotherapy, naives, single-dose. **Needs baseline sensitivity. Lower viral decay with lower doses or SC (vs IV) response**. #117

- **PGT121, PGDM1400 and VRC07-523LS** (V3, V2, CD4; QM IV). 2/12 (17%) **early VF despite high levels, correlated with baseline resistance despite using 3 bNAbs**. #121



CROI 2024, Denver, CO. Oral presentations 117, 118, 119 and 121.

Toxicity of TDF > TAF on duodenal enterocytes: weight and lipids.

- PWH on TDF (11) or TAF (12) without known GI disease. Matched for 3RD ARV agent and age.
- **Duodenal villi were flatter** (p=0.016), **crypts deeper** (p=0.09), and **villus height to crypt depth ratio** (p=0.009) **was lower in TDF** vs TAF group, especially in **proximal duodenum**.
- **I-FABP concentration** was significantly higher in TDF vs. TAF group (p=0.003).
- **TDF group had numerically (NS) lower plasma/serum concentrations of iron, folate, vitamins A, B1, D and E.**
- Both groups showed signs of mitochondrial toxicity in duodenal enterocytes (confirmed by EM).
- **TDF group displayed signs of villous damage especially in proximal duodenum when compared to TAF group. This could impact body weight and lipids.**

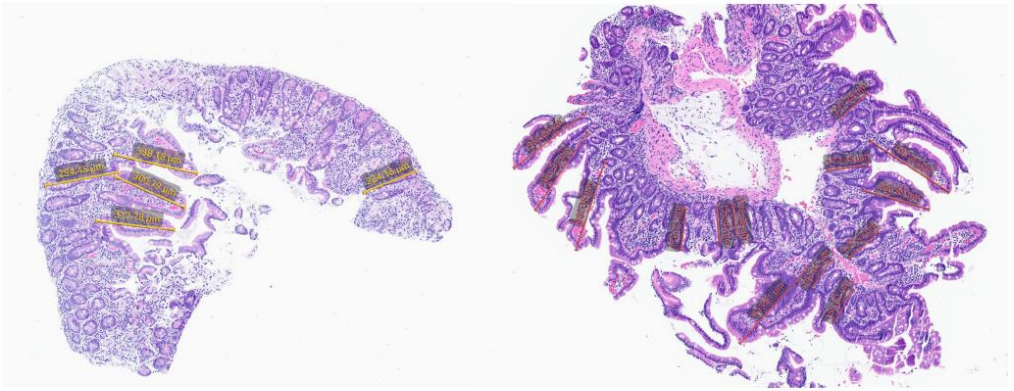


Figure 1. Histological sample of duodenal epithelium of patients receiving TDF (left) or TAF (right).

Kai Juhani Kauppinen. CROI 2024, Denver, CO. #806.

Summary & Conclusions

CAB + RPV LA

- CAB + RPV Q4W a new possibility in people with adherence challenges, but full support program missed.
- CARES: CAB + RPV LA Q8W high efficacy in Sub-saharan Africa, despite high-risk baseline factors.

New strategies

- BIC + LEN Oral QD Phase 2: safe “strategic simplification” RCT in MTR: Week 24.
- QW oral LEN + ISL: a promising strategy in switch. Week 24.
- BIC/F/TAF BID + rifampicin in TB similar to DTG, but lower BIC levels. Week 24.

New drugs in pipeline

- GS-9770 –a Novel, Unboosted, Once-Daily Oral PI
- GS-1720, a new QW oral INSTI, Exhibited Potent Antiviral Activity (Phase 1b)
- bNAbs: A lot of interest, but disappointing as ART

New hypothesis

- TDF toxicity on duodenal enterocytes could impact body weight and lipids.