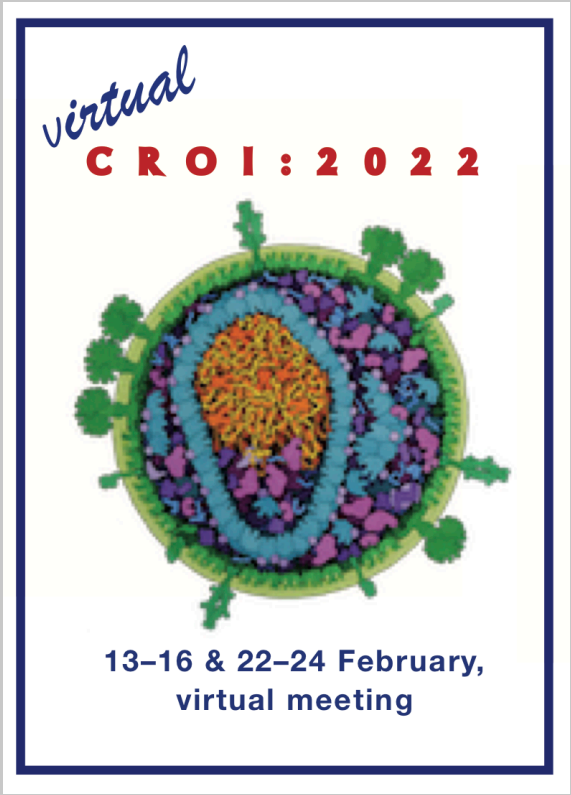
UK-CAB:
CROI 2022 feedback
23 April 2022



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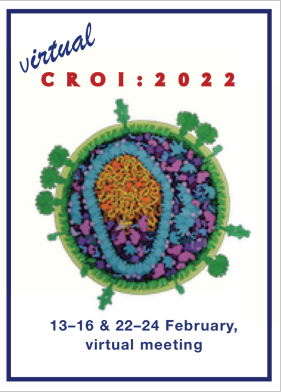
Disclosure

No personal financial conflict of interest

CROI 2022



- Virtual conference

https://www.croiconference.org

http://www.croiwebcasts.org

Roughly 900 abstracts, webcasts, poster PDFs etc are now online and open access.

Special populations included: adolescents (48), 48 MSM (94), People Who Inject Drugs(39), Transgender (37) and Women (130).

Introduction

- What did you hear and how did you access CROI?
- Breakthrough news and views…

Headlines.1 - ART and PrEP

- New HIV meds: lenacapravir and islatravir.
- Recently approved meds: Injectable long-acting cabotegravir and rilpivirine.
- Long-acting cabotegravir PrEP.
- Islatravir characteristics for PrEP (on hold).
- PEP starter packs.

Headlines.2 - cure-related

- Cure research: 4th stem cell cure. First woman, different donor technique.
- bNAbs - used in wide range of settings: prevention and cure - in children and adults. Strategies instead of daily oral ART.

Headlines.3 - complications

- ANCHOR study
- Diabetes in the UK
- NAFLD
- Long-COVID

Links

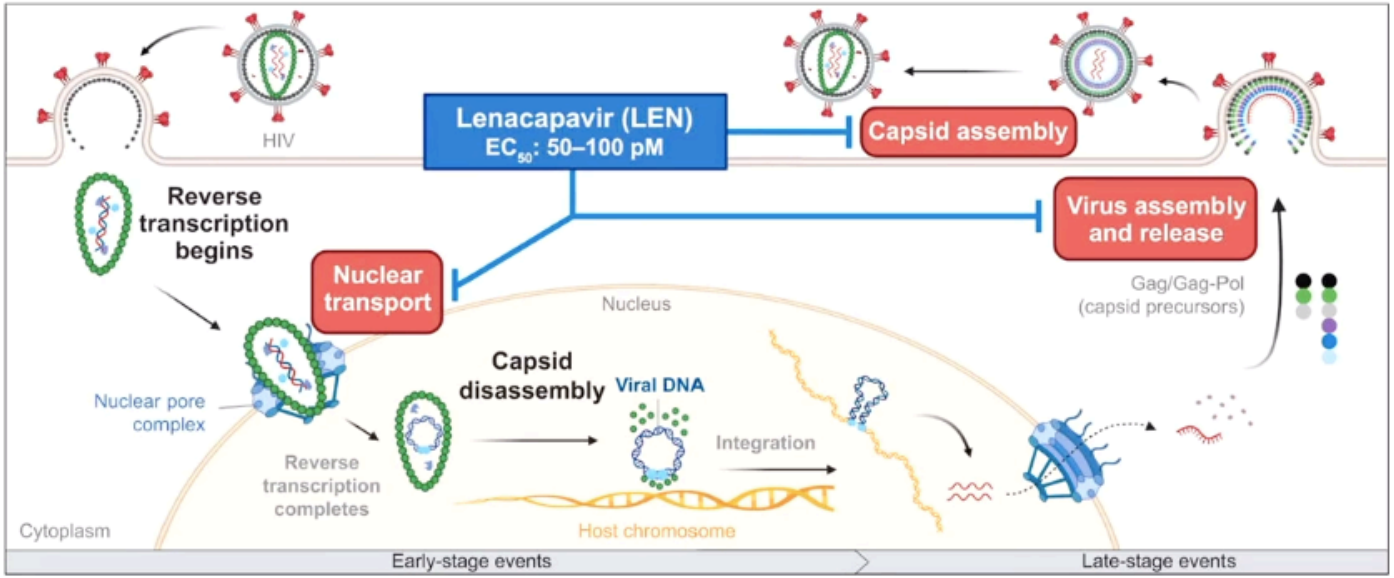
- Pick a webcast from CROI

http://www.croiwebcasts.org

- BHIVA feedback

https://www.bhiva.org/BestofCROI2022

LEN Targets Multiple Stages of HIV Replication Cycle



EC_{50}, half-maximal effective concentration.
Link JO, et al. Nature 2020;584:614-8; Bester SM, et al. Science 2020;370:360-4.

Study Design

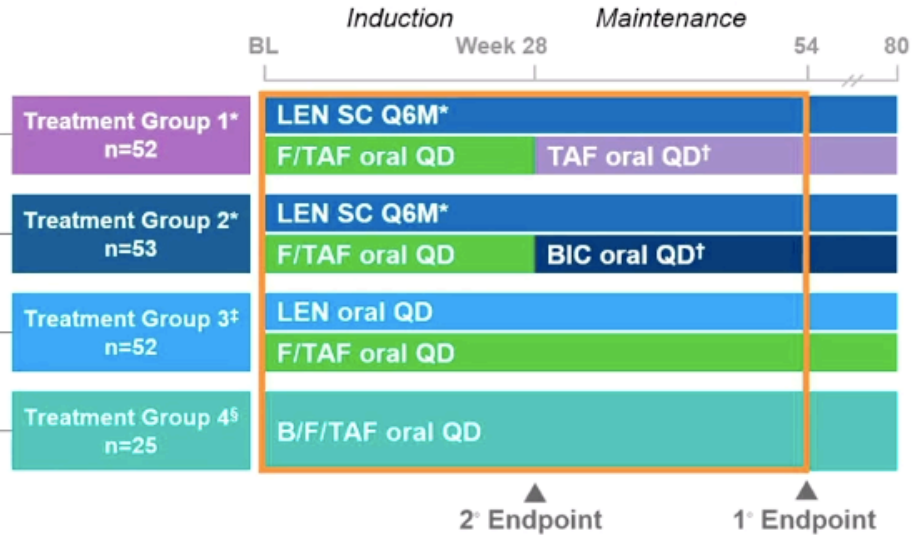
Calibrate

Treatment naïve
N=182

Key eligibility criteria:

- ARV naïve
- HIV-1 RNA ≥200 copies/mL
- CD4+ cell count ≥200 cells/µL

Open label
Randomized



*LEN oral lead-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN SC 927 mg on Day 15; F/TAF 200/25 mg; †Participants in TG 1 and 2 will need HIV-1 RNA results <50 copies/mL at Weeks 16 and 22 to initiate either TAF 25 mg or BIC 75 mg at Week 28; those with HIV-1 RNA ≥50 copies/mL will discontinue study at Week 28; ‡LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; §B/F/TAF 50/200/25 mg.
ARV, antiretroviral; BIC, B, bictegravir; BL, baseline; QD, once daily; Q6M, every 6 months; SC, subcutaneous; TG, treatment group.

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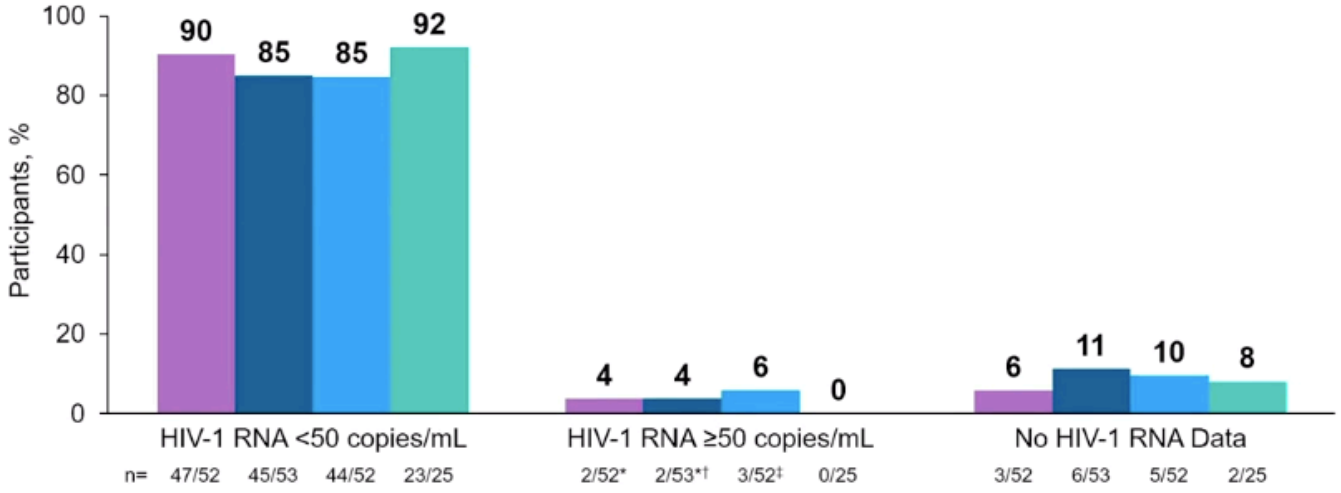
Efficacy at Week 54 (FDA Snapshot)

Calibrate

TG 1: LEN SC + F/TAF to LEN SC + TAF
TG 2: LEN SC + F/TAF to LEN SC + BIC
TG 3: LEN QD + F/TAF
TG 4: B/F/TAF



- In the pooled SC LEN group (TG 1+2: initially in combination with F/TAF, then with TAF or BIC), 88% (92/105) achieved and maintained virologic suppression at Week 54

*3 participants (2 in TG 1 and 1 in TG 2) discontinued due to not meeting the protocol criteria of having HIV-1 RNA <50 copies/mL prior to Week 28;
†1 participant discontinued on Day 2; ‡2 of the 3 participants with HIV-1 RNA ≥50 copies/mL at Week 54 were suppressed in subsequent visit.

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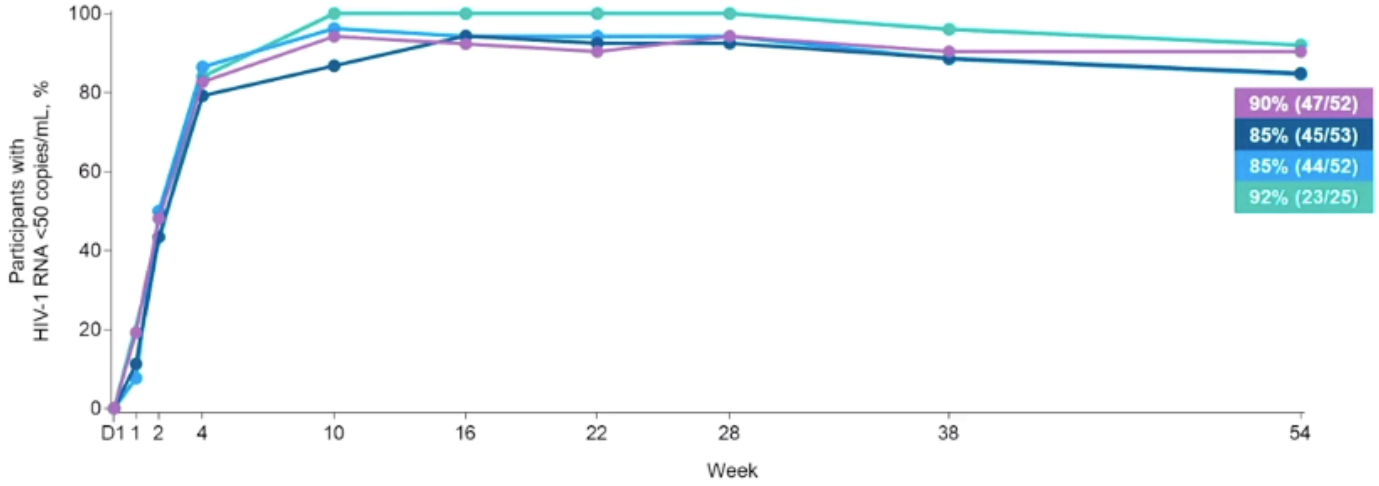
Participants with HIV-1 RNA <50 copies/mL by Visit

Missing = Failure (On Treatment)

Calibrate

TG 1: LEN SC + F/TAF to LEN SC + TAF
TG 2: LEN SC + F/TAF to LEN SC + BIC
TG 3: LEN QD + F/TAF
TG 4: B/F/TAF



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Resistance Analysis*

Calibrate

TG 1: LEN SC + F/TAF to LEN SC + TAF
TG 2: LEN SC + F/TAF to LEN SC + BIC
TG 3: LEN QD + F/TAF
TG 4: B/F/TAF

Participants, n	TG 1 n=52	TG 2 n=53	TG 3 n=52	TG 4 n=25
Participants meeting the resistance testing criteria	1	1	3	1
Emergent LEN resistance	0	1	1	0

- Emergent LEN resistance in 2/157 (1.5%) participants
  - One participant in TG 2 developed Q67H+K70R (LEN fold change=20) in CA at Week 10, preceded by M184M/I in RT (IDWeek 2021)†
    - Pattern of mutation emergence suggests incomplete adherence to F/TAF
  - One participant in TG 3 developed Q67H (LEN fold change=7) in CA at Week 54
    - Nonadherence to F/TAF as assessed by pill count and drug levels
  - Both participants later re-suppressed on a regimen of INSTI + 2 NRTI

*Genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥50 copies/mL and <1 $\log_{10}$ HIV-1 RNA reduction from Day 1 at the Week 10 visit, at any visit after achieving HIV-1 RNA <50 copies/mL and a rebound to ≥50 copies/mL, and at any visit, with >1 $\log_{10}$ increase from the nadir; †Previously presented (Gupta SK, et al. IAS 2021, abstr OALB0302, VanderVeen L, et al. IDWeek 2021, oral 73).
CA, HIV capsid; INSTI, integrase strand transfer inhibitor; NRTI, nucleotide reverse transcriptase; RT, reverse transcriptase.

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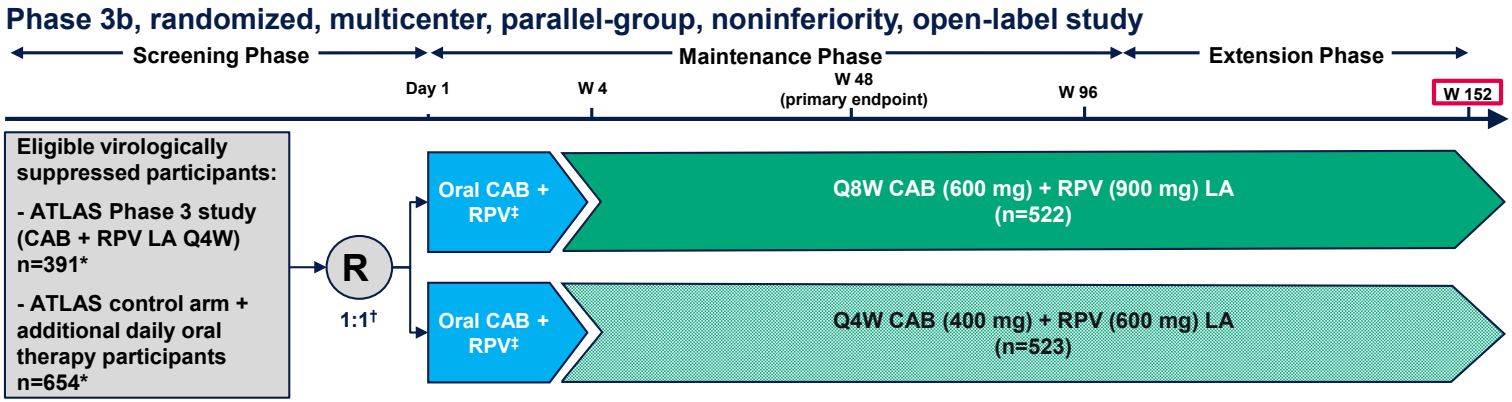
Figure 1. ATLAS-2M Study Design



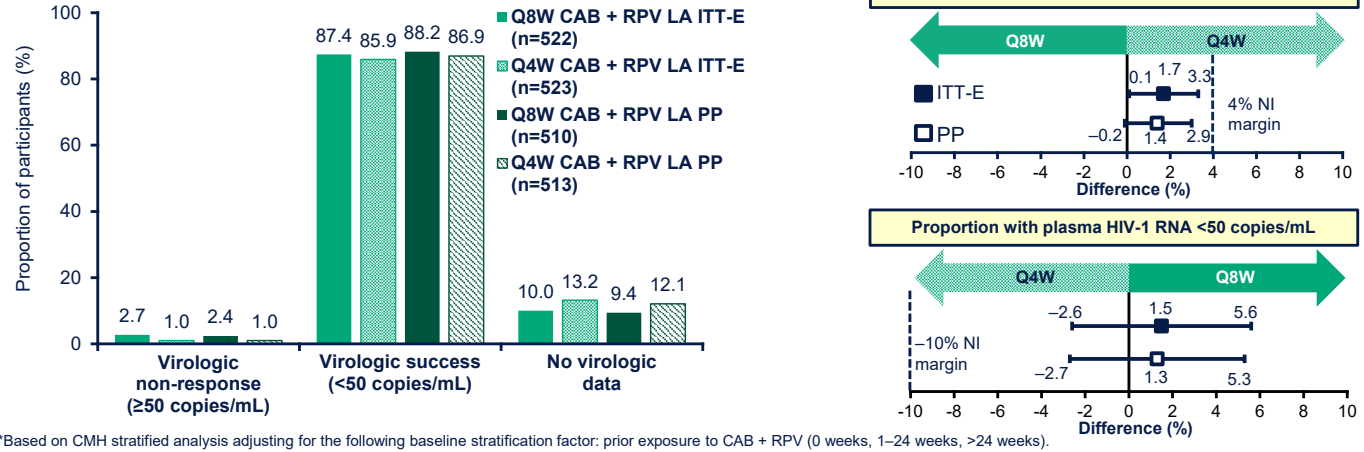
*ITT-E population. †Randomization was stratified by prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). ‡Excluding participants with prior CAB + RPV exposure in ATLAS (n=391). For further study design details, please see Overton ET, et al. *Lancet*. 2020;396(10267):1994–2005. CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; W, week.

- The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (FDA Snapshot, ITT-E) (**Figure 1**).
- Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 copies/mL at Week 152 (FDA Snapshot, ITT-E).
  - Per-protocol analyses were carried out at specific time points, including Week 48, Week 96, and Week 152.
- Other endpoints assessed at Week 152 included the incidence of confirmed virologic failure (CVF; two consecutive plasma HIV-1 RNA levels ≥200 copies/mL), incidence of viral resistance in participants with CVF, safety and tolerability, and treatment satisfaction.

Results

- Baseline characteristics were similar between arms; 27% (n=280) of participants were female at birth, median (range) age was 42 (19–83), 20% (n=211) had a BMI ≥30 kg/m^2, and 37% (n=391) had prior CAB + RPV exposure.[3]

Figure 2. Virologic Outcomes at Week 152



*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).
CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; PP, per protocol; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- Noninferiority between Q8W and Q4W was confirmed for pre-specified analyses of HIV-1 RNA ≥50 and <50 copies/mL (**Figure 2**).
- Results for the pre-specified per-protocol population were consistent with those for the ITT-E population.

Table 3. Participants With CVF Since the Week 96 Analysis

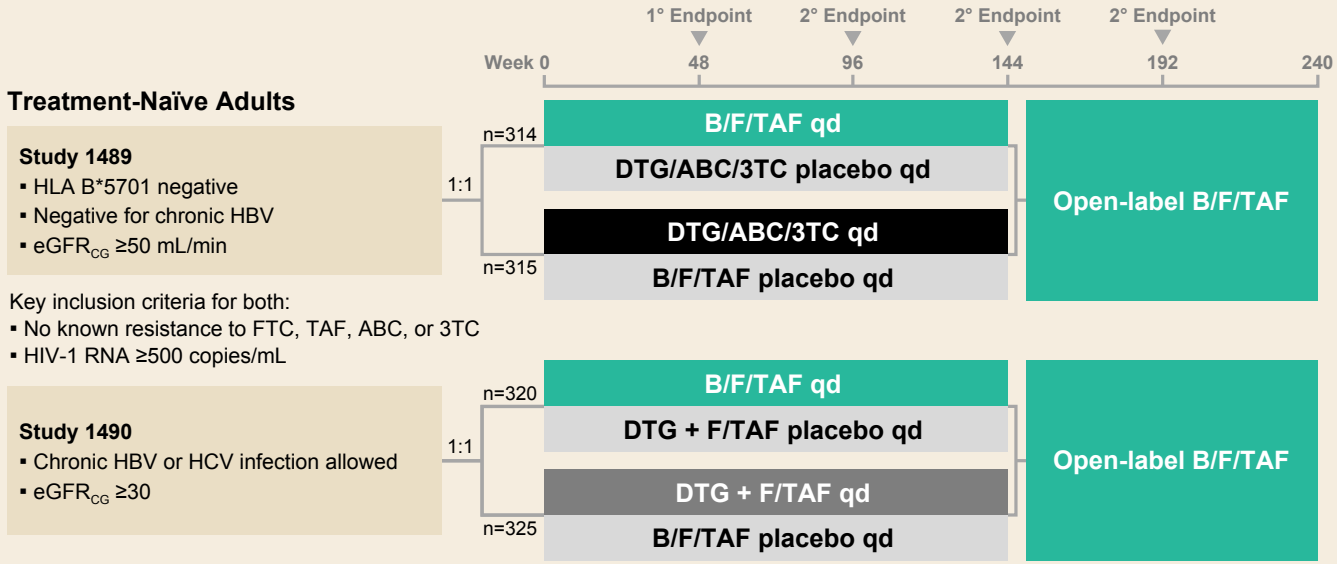
Participants With CVF Since Week 96					
#, arm	Sex at birth, BMI (kg/m^2), country	HIV-1 subtype at baseline	Viral load at failure (copies/mL)	RPV RAMs observed at failure	INI RAMs observed at failure
1, Q8W	Male, <30, Germany	B	24,221	E138A+M230M/L	Q148R
2, Q8W	Male, <30, Russia	A6*	59,467	E138A+Y181Y/C	Q148R

*This participant was originally classified as subtype A1 but, upon reanalysis, was later reclassified as subtype A6.
BMI, body mass index; CVF, confirmed virologic failure; INI, integrase inhibitor; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

- The characteristics of the two participants (Q8W arm) who met the CVF criterion between Week 96 and 152 (Week 112 and Week 120) are shown in **Table 3**.
  - Neither had RAMs at baseline; however, the participant with subtype A6 had L74I integrase (IN) polymorphism at baseline.
  - Both had treatment-emergent RAMs to CAB (Q148R) and RPV (E138A+Y181Y/C; E138A+M230M/L).
- In total, through Week 152, 13 participants had CVF (Q8W, n=11 [2%]; Q4W, n=2 [<1%]).

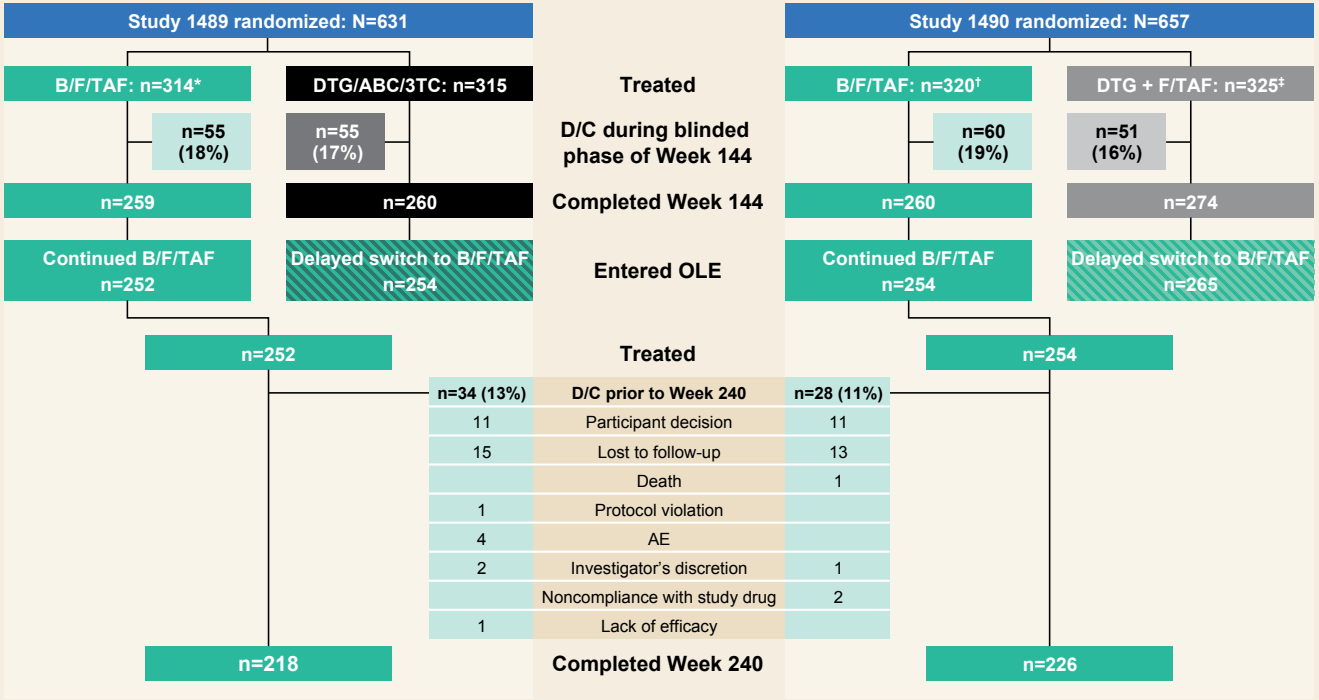
Methods

Study Designs: Randomized, Double Blind, Active Controlled



3TC, lamivudine; ABC, abacavir; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; HBV, hepatitis B virus; HCV, hepatitis C virus; HLA, human leukocyte antigen.

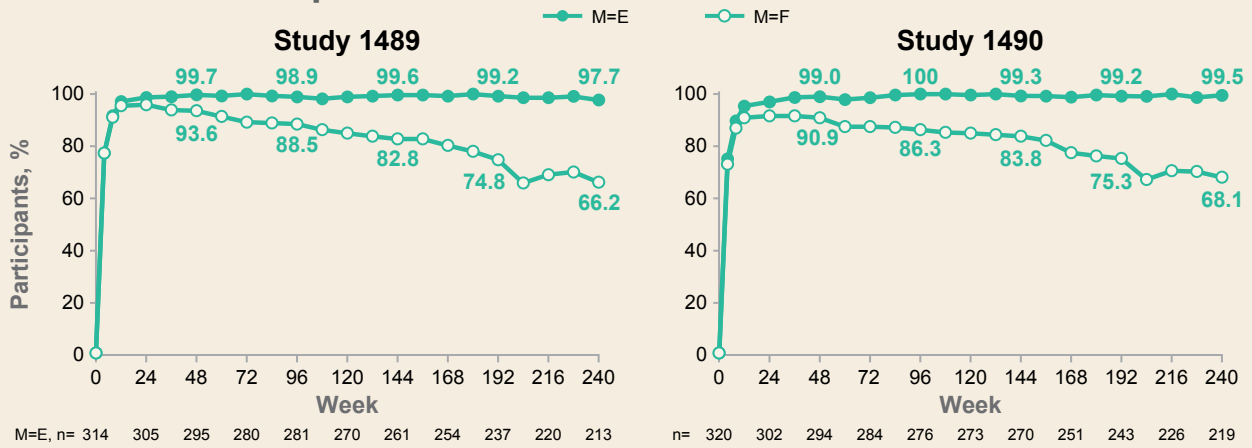
Participant Disposition From Baseline to Week 240



*2 participants randomized and not treated; †7 randomized and not treated; ‡5 randomized and not treated. AE, adverse event; D/C, premature discontinuation.

Virologic Outcomes Through Week 240

HIV-1 RNA <50 Copies/mL*



*Calculated using US FDA Snapshot algorithm; includes only participants initially randomized to B/F/TAF. M=E, missing = excluded; M=F, missing = failure.

- Efficacy was ≥98% (M=E) after Week 48 at each study visit through Week 240 in both studies for all participants
  - Among those with baseline CD4 <200 cells/μL from the pooled studies, 98% (49/50) had HIV-1 RNA <50 copies/mL at Week 240
- Median CD4 changes from B/F/TAF start to Week 240, cells/μL (IQR): Study 1489: +313 (179, 475); Study 1490: +331 (215, 467)

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IMPAACT P1107: Conclusions

- **First US woman of mixed race** living with HIV-1 successfully transplanted with CCR5Δ32/Δ32 haplo-cord SCT with 100% sustained engraftment of cord blood and in HIV-1 remission
- Durable remission of AML 4 years 6 months post SCT
- **14 months off ART; no viral rebound (no ARV's in plasma)**
- **No detectable replication-competent latent reservoir** (74.5 million CD4+ T cells analyzed)
- **Undetectable HIV-1-specific cellular immune** responses and **HIV antibody negative; *in-vitro* resistance to lab & autologous virus**
- Negative-(transient trace) HIV-1 DNA by ddPCR
- Remains clinically well with **NO GVHD**

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

bNAbs

- Broadly neutralising monoclonal antibodies.
- Derived from HIV positive people found to have a strong immune response to HIV.
- Developed into treatment, including long-acting formulations.
- Two actions: antiviral and vaccine-like immune boosters?

bNAb examples

- 3BNC117 and romidepsin given with early ART, then stop ART a year later. One person off ART for 3.7 years. Gunst et al. Abs 62.
- VRC01-LS and 10-1074 given to 28 children (median 3.6 years (range: 2.4 to 5.6) who started ART after birth and who had undetectable viral load for at least the previous 6 months. 11/24 remained undetrectable. Shapiro et al. Abs 32.
- VRC07-523-LS: PrEP in 22 newborn infants in the US and South Africa, supports 3-monthly dosing. Cuningham et al. Abs 732.
- VL stayed undetectable in 2/6 people given 3BNC117 and 10-1074 given to people off-ART. Caskey et al. Abs 140.

bNAb cautions

- Need sensitivity screening at baseline.
- Only in research.
- Still difficult to produce and usually expensive.
- AMP 1 and 2 studies using VRC01 as PrEP included >4000 participants including in southern African countries - unsuccessful though due to sensitivity,

CROI 2022

Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer

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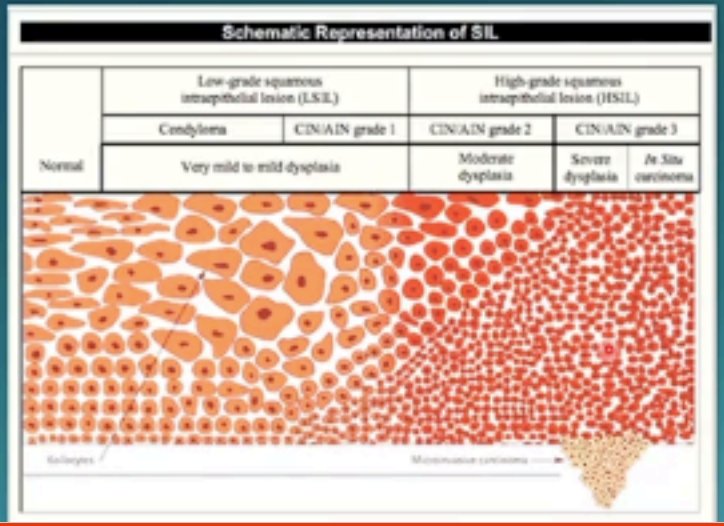
Disclosure:

Consultant: Merck and Co, Vir Biotechnology, Virion Therapeutics, Antiva Biosciences

Speaker's honorarium: Merck and Co.

The cervical model

- Anal and anal cancer are very similar diseases
- Cervical cancer and anal cancer are preceded by high grade squamous intraepithelial lesions (HSIL)



the ANCHOR study

Study schema

Screening

- 10,723 PLWH from 9/24/2014 to 8/5/2021
  - 52.2% had biopsy-proven anal HSIL
    - 53.3% of men
    - 45.8% of women
    - 62.5% of transgender individuals
- 17 individuals (0.16%, 160/100,000) were diagnosed with anal cancer

the ANCHOR study

Demographics of randomized population (1)

	Randomized population N=4,446		P value
	Treatment arm	Active monitoring arm	
	N=2,227	N= 2,219	
Median age at randomization (years, IQR)	51.0 (44.0-57.0)	51.0 (44.0-57.0)	0.79
Median years at randomization since HIV diagnosis (years, IQR)	17.0 (10.0-24.0)	17.0 (10.0-25.0)	0.96
Months of follow-up (median, IQR)	25.3 (11.7 – 42.0)	27.2 (12.0 – 42.1)	0.77
Gender identity N (%)			0.30[2]
Male	1793 (80.5)	1782 (80.3)	
Female	346 (15.5)	365 (16.5)	
Transgender	85 (3.8)	68 (3.1)	
Neither male nor female	2 (0.1)	2 (0.1)	
Decline to answer	1 (0.0)	2(0.1)	

Results

- For the participants in the treatment arm, the initial treatment
  - office-based electrocautery ablation (92.9%)
  - infrared coagulation (5.6%)
  - TUA (4.6%)
  - topical 5-fuorouracil cream (7%)
  - topical imiquimod (1.2%)

- Over the course of the study:
  - 1921 (86.0%) with therapeutic modality
  - 233 (10.4%) with two modalities
  - 33 (1.5%) with three modalities
  - 1 (<0.1%) with four modalities

the ANCHOR study

Results

- DSMB notified when 32 cancers diagnosed
  - final analysis based on 30 cases
- 9 participants were diagnosed with invasive anal cancer in the treatment arm and 21 in the AM arm
- Median follow-up of 25.8 months, 57% reduction in anal cancer (95% CI 6% to 80%, chi-squared = 4.74, P=.029)
- Cancer incidence in the treatment arm was 173/100,000 PY of follow-up, compared with 402/100,000 PY in the AM arm

the ANCHOR study

Additional slides

Thank you

Questions?

www.i-Base.info