CROI 2023 Update
Treatment Innovations and ACTG Studies

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Disclosures

Dr. Bender Ignacio received research funding through her institutions from Novartis, Enanta, and Astentage for COVID-19 research.

Consulting for Resverlogix and SeaGen, unrelated to this presentation.

All risks have been mitigated.

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Disclaimer

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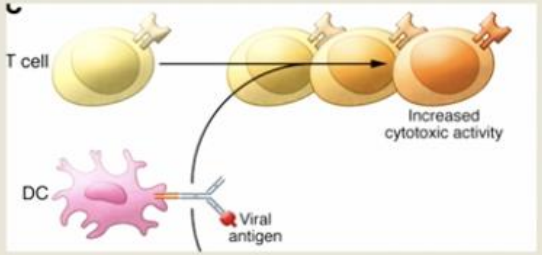
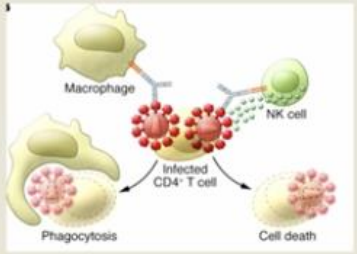
Impact of 3BNC117, 10-1074 + Lefitolimod on HIV Persistence: TITAN trial

Hypotheses

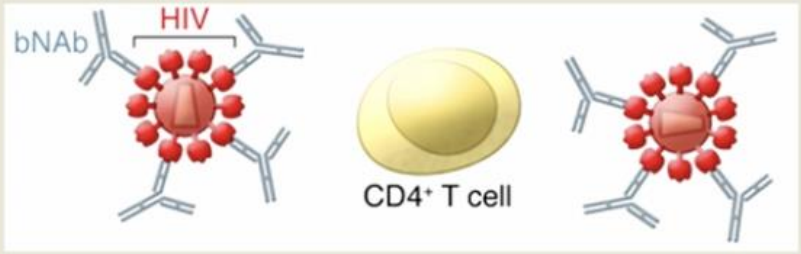
- **TLR9 agonist** prime innate and adaptive immune cells prior to antigen exposure
  - Increase antigen pDC cross-presentation to CD8+ T cells
    - -> boost HIV-specific CTL-mediated immunity
  - Enhance antibody-dependent effector functions

- **bNAbs** mediate slow/controlled release of antigen (HIV) to allow for development of potent adaptive immune responses





Lefitolimod (TLR9a)



3BNC117 and 10-1074 (bNAbs)

Vibholm et al. CID 2017, Vibholm et al. AIDS 2019, Halper-Stromberg and Nussenzweig JCI 2016; Nishimura et al Nature 2017

30th CROI 2023

CROI 2023 Abstract 136, Sogaard

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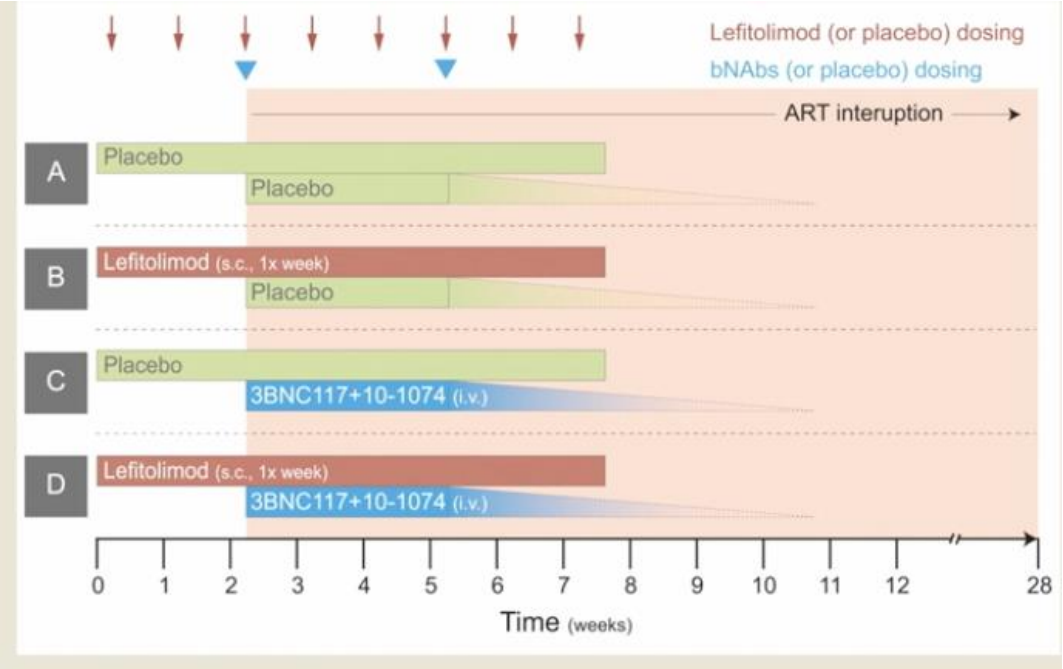
TITAN study design



Population:
Mainly White or Multiracial men (few women)
Denmark, Norway, Australia
Age 40s-50s
On ART for median 11 years

Could have started ART in early or chronic HIV

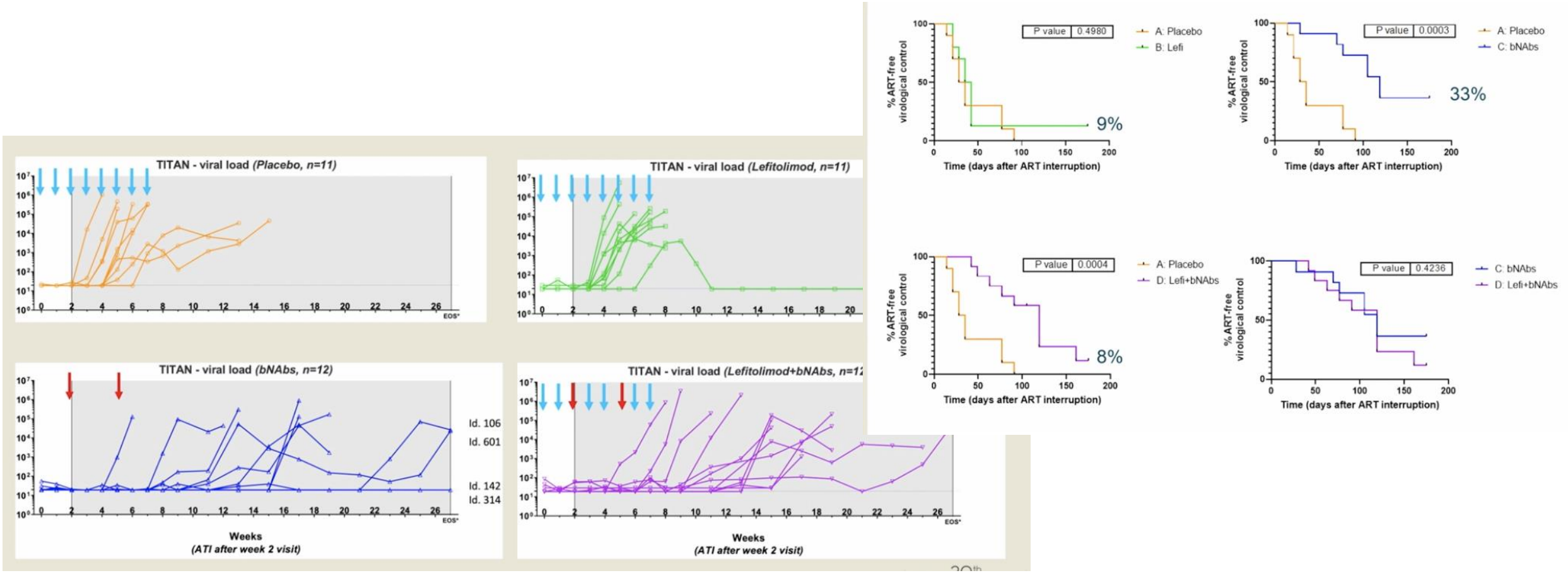
CD4 > 500 and VL <50 copies for 15+ months

All were screened for virus sensitive by phenosense to be sensitive to the 2 bNabs

Groups A and B had n=11 and C and D n=12

CROI 2023 Abstract 136, Sogaard

TITAN TLR-9 agonist and bNAb results



Time to viral rebound >1000 copies for 4 weeks or once: 3BNC117, 10-1074 delayed rebound. No impact of lefitolimod.

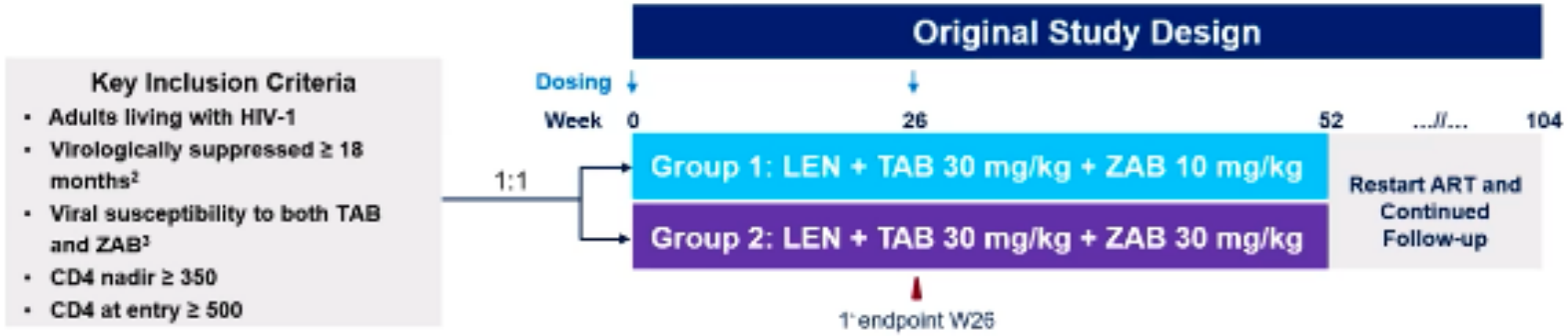
CROI 2023 Abstract 136, Sogaard

Lenacapavir with 2 bNAbs GS-5423 and GS2872

- Teropavimab (TAB; 3BNC117-LS) bNAb against CD4 binding site of gp120
- Zinlirvimab (ZAB; 10-1074-LS) non-overlapping epitope on V3 glycan of Env
  - Both modified to extend half lives and administer q6 month dosing

- Lenacapavir (LEN) a small molecule capsid inhibitor, also dosed q6 monthly

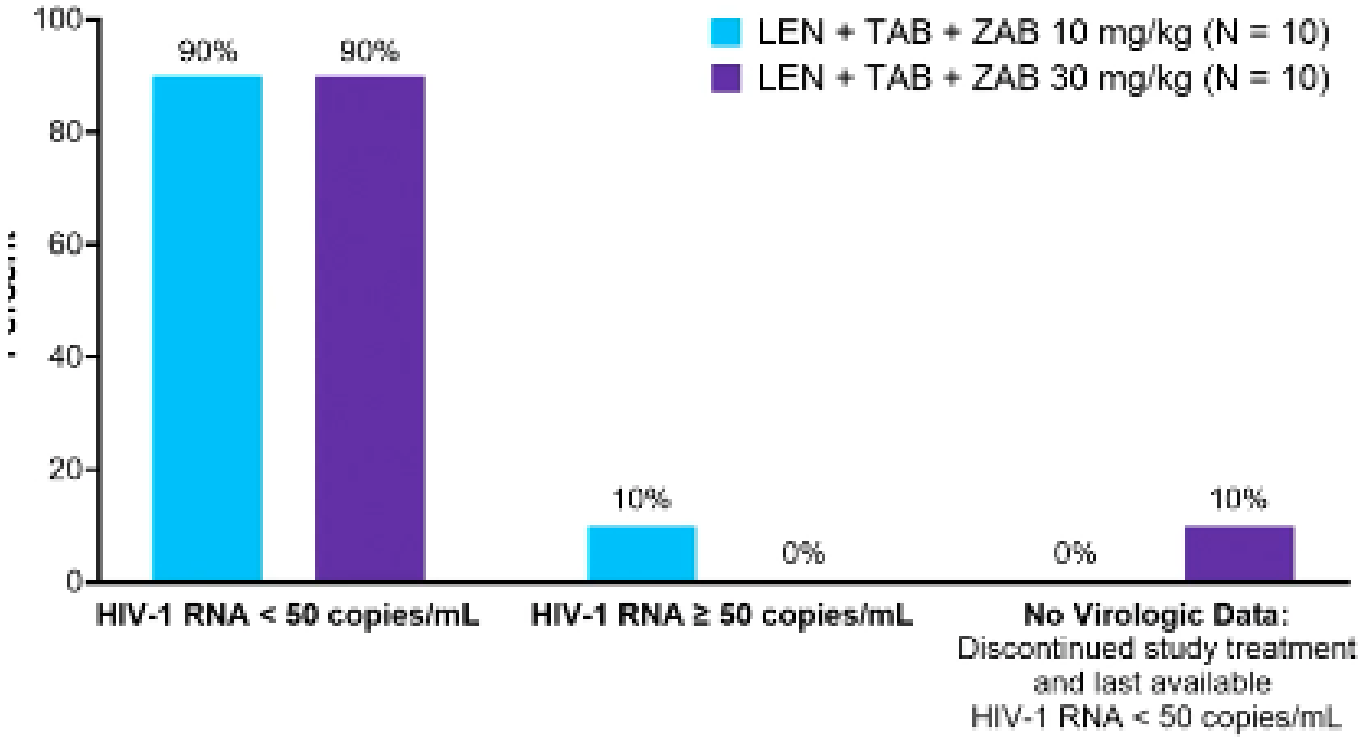
• Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses.[1] (NCT04811040)



HIV RNA measured at least every 4 weeks until Week 52.

CROI 2023 abstract #193, Eron

Week 26 viral efficacy (LEN + TAB + ZAB)



- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

No serious adverse events- 2 Grade 3 injection site reactions, other mild infusion reactions
No meaningful change in CD4 or CD4 ratio

CROI 2023 abstract #193, Eron

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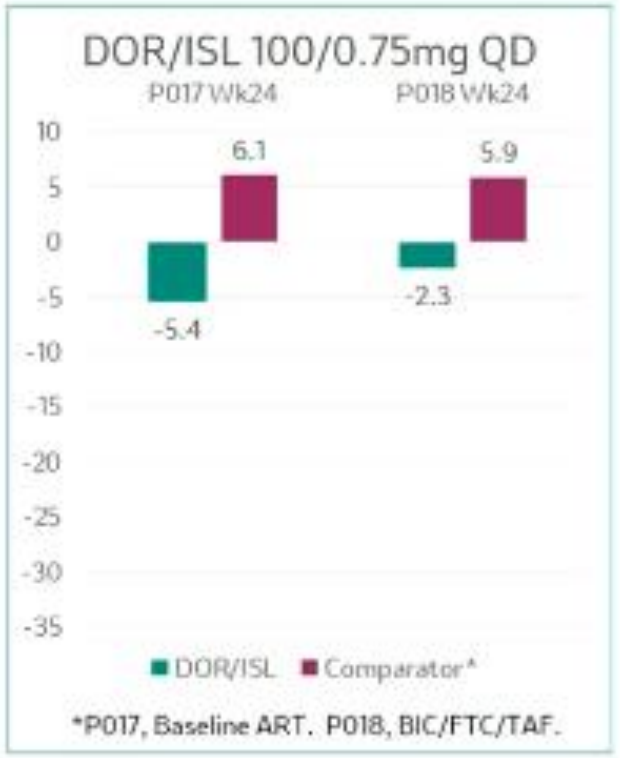
LEN + TAB + ZAB conclusions

- 2 bNAbs in combination with LEN can sustain virologic suppression x 6 months
- Minimal safety issues, well tolerated
- LEN + TAB + ZAB could be considered for a 2x yearly regimen
- This was a very small study
  - Phase 2 study underway (NCT05729568)

- This treatment will be limited by susceptibility of virus to TAB + ZAB
  - Study was in Clade B virus (US)
  - Of 124 screened for study, only 55 met susceptibility criteria

Islatravir effect on Lymphocytes

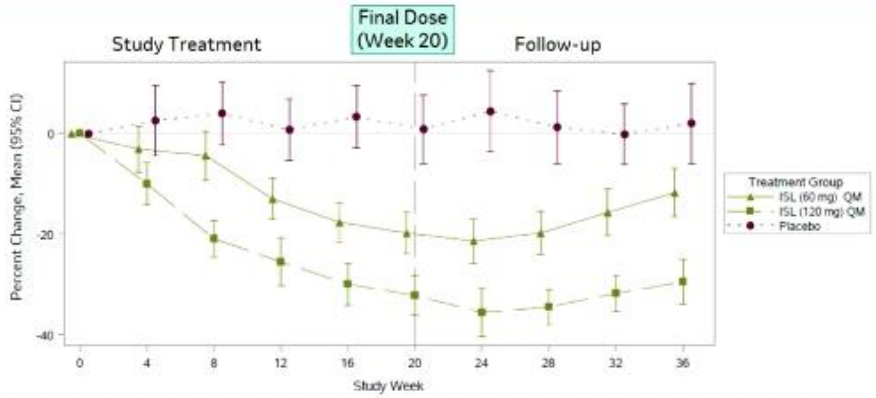
- Islatravir= NRTTI (nucleoside reverse transcriptase translocation inhibitor)
- ISL development paused Dec 2021 by the FDA due to reduced lymphocytes in several studies
- ISL-TP preferentially accumulates in lymphocytes, not mitochondrial toxicity



CROI 2023 abstract #192, Squires (Merck)

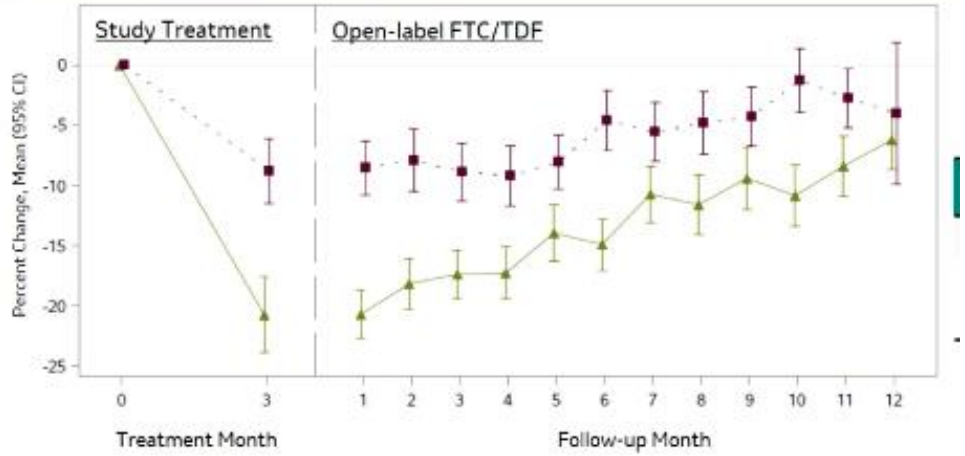
Drop in lymphocytes in HIV prevention trials

Phase 2 ISL Dose-Ranging Study in HIV-1 Low-Risk (MK8591-016)
Total Lymphocyte Count

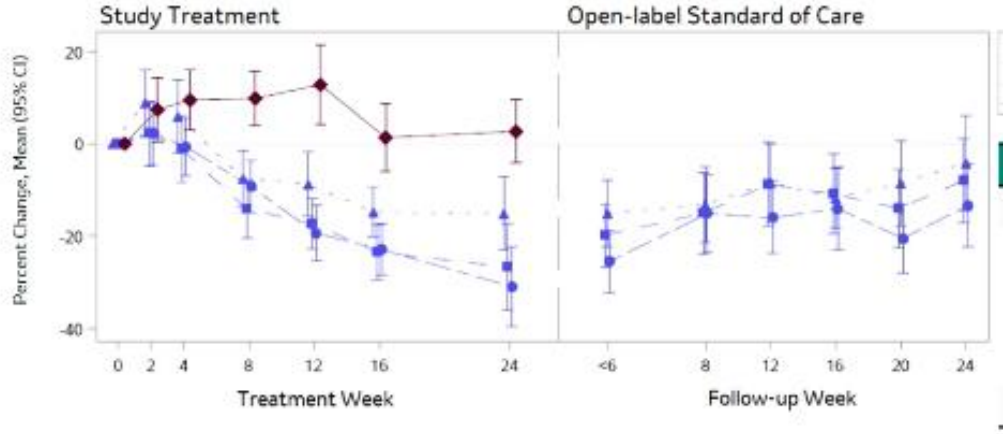


- 95% of participants in the combined ISL arms maintained total lymphocyte counts in the DAIDS Grade 0 category (>650 cells/mm^3)

Phase 3 ISL 60 mg QM PrEP Trial in Women (MK8591-
Total Lymphocyte Count



Phase 2b ISL 20 mg QW in HIV-1 Switch (MK8591-013)
Total Lymphocyte Count



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Future of Islatravir

- ISL resulted in dose-dependent decreases from baseline in total lymphocyte count and CD4+ T cells with higher Qmonth and Qweekly doses > daily
- ISL q monthly for PrEP discontinued indefinitely
- ISL daily and weekly for HIV-1 treatment ongoing at lower doses
- No evidence of association with increased infections
- A dose level that results in ISL-TP levels has been selected for ongoing clinical trials for treatment:
  - ISL 0.25mg (from 0.75mg)+ doravirine 100mg daily
  - ISL 2mg (from 20mg) + lenacapravir 300mg orally once weekly

CROI 2023 abstract #192, Squires (Merck)

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DORAVIRINE + ISLATRAVIR: 2 SWITCH STUDIES (DOR + ISL) "ILLUMINATE SWITCH A and B"

SWITCH TO DOR/ISL (100/0.75MG) QD: WEEK 48 RESULTS FROM AN OPEN-LABEL PHASE 3 TRIAL

Merck study 017
15 countries
Europe, North America
Latin America
Asia, Africa

SWITCH TO DOR/ISL (100/0.75MG) QD FROM B/F/TAF: WEEK 48 RESULTS FROM A PHASE 3 TRIAL

Merck study 018
Predominately
North America and Europe

CROI 2023 Abstracts # 196 (Molina) and #197 (Mills)

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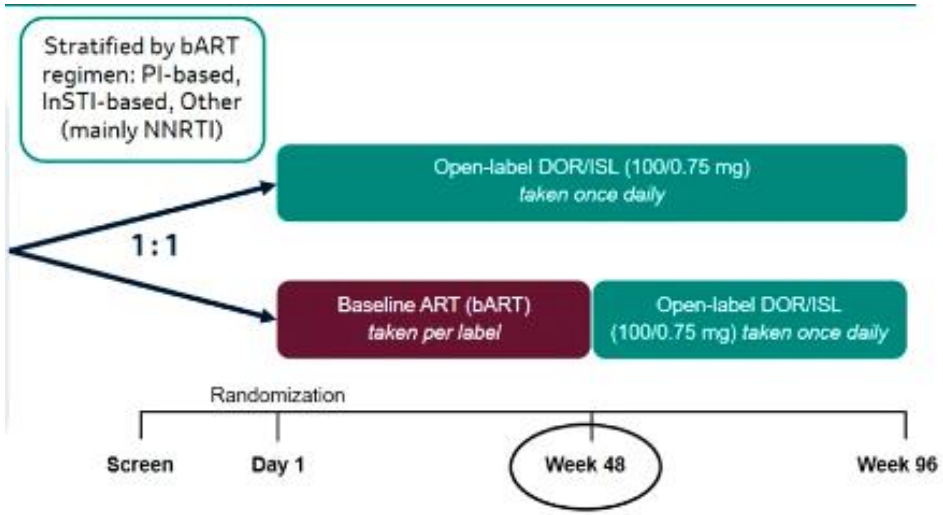
DOR + ISL Switch: both 100/0.75mg daily



Primary Efficacy Endpoint: HIV-1 RNA ≥50 copies/mL at Week 48 (FDA snapshot approach), non-inferiority margin 4%

vs Baseline ART (bART)
N=672

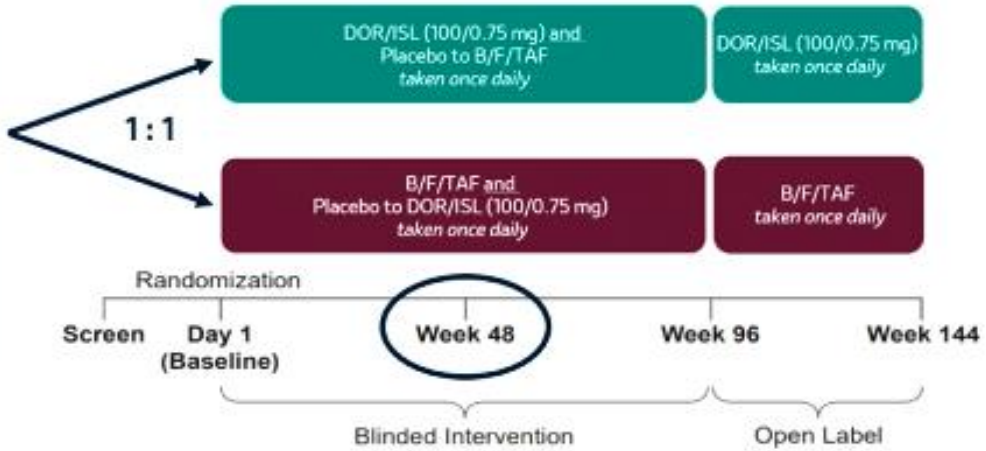
NNRTI (34.5%)
PI (13.7%)
INSTI (51.8%) regimens

Eligibility criteria symmetric except Baseline ART regimen

vs BIC/FTC/TAF
N=641

Population
- PLWH ≥18 years of age
- Virologically suppressed (plasma RNA <50 copies/mL) for ≥3 months on B/F/TAF
- Documented HIV-1 RNA <50 copies/mL at screening
- No history of treatment failure on any regimen
- No known resistance to DOR*
- No active HBV infection

*V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L or Y318F



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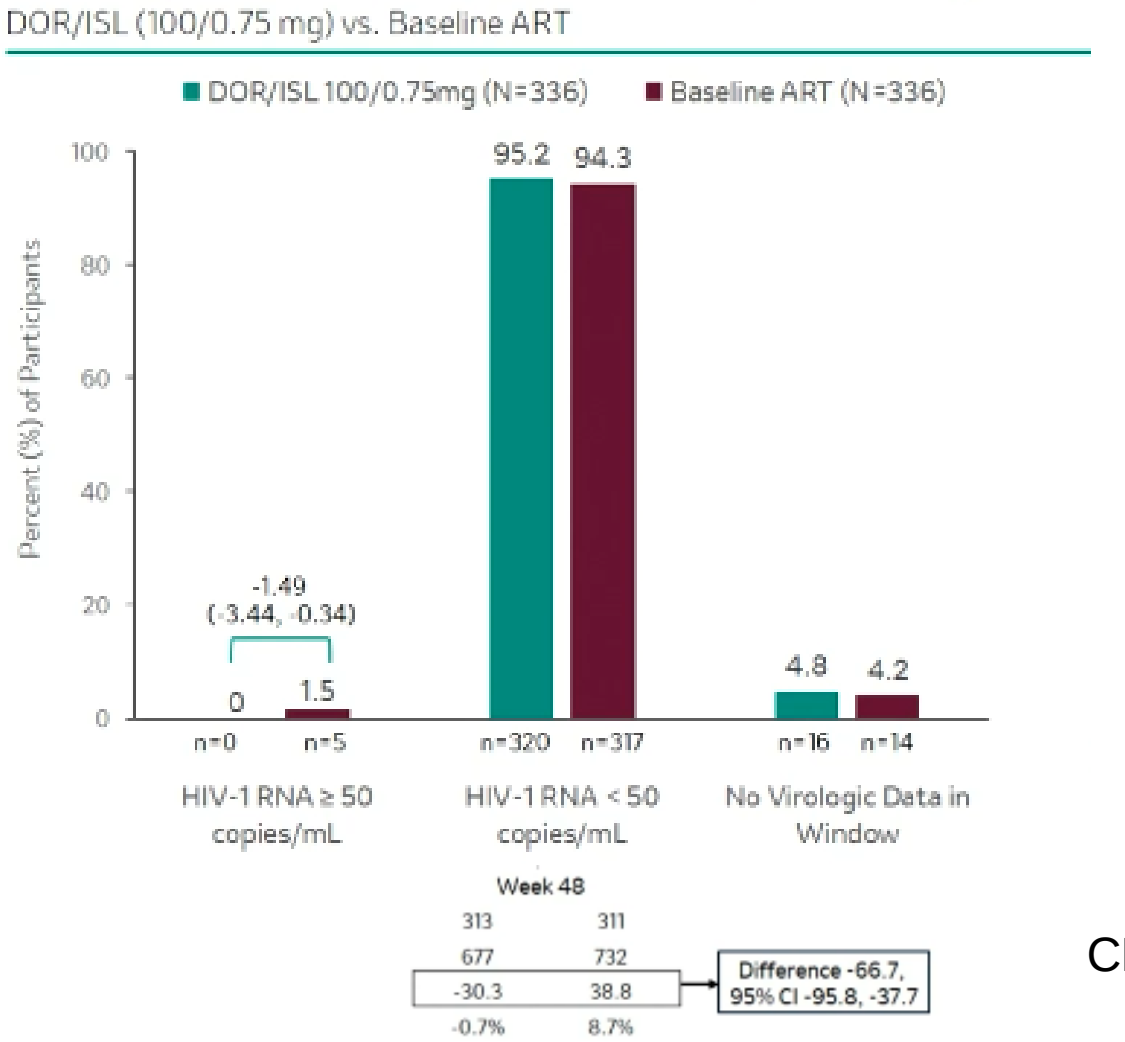
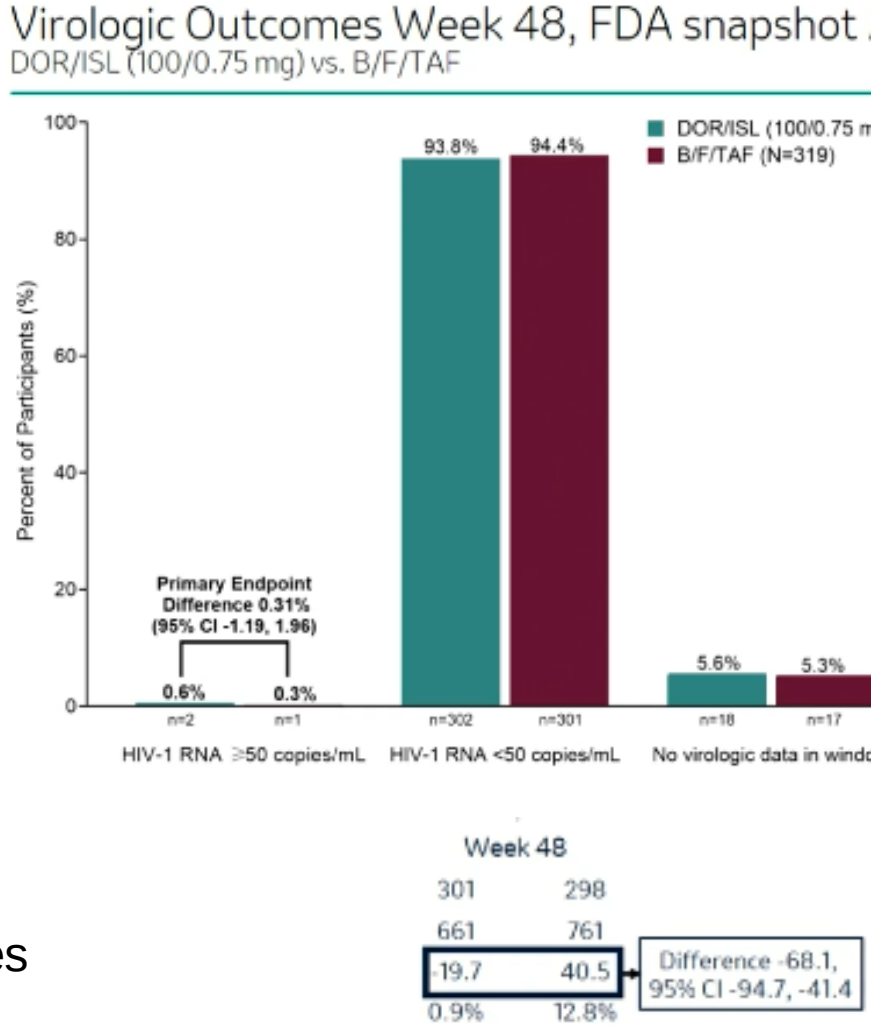
Virologic and CD4 outcomes for DOR/ISL switch





CD4 changes

CROI 2023 Abstracts # 196 (Molina) and #197 (Mills)

DOR + ISL Switch Conclusions

- DOR + ISL (100/0.75mg) non-inferior to bART or B/F/TAF
- Similarly tolerated
  - 10% more drug-related adverse events in switch bART study, no difference in serious
    - Headaches, insomnia, nausea, weight gain (<2%)
  - No differences, except mild nausea from B/F/TAF switch
    - NB: Switch studies always have more adverse events in the switch arm
- Previously described CD4 and total lymphocyte drops- modest
- Phase 3 clinical development continues with 0.25mg daily (3x decrease)

CROI 2023 Abstracts # 196 (Molina) and #197 (Mills)

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29 ACTG Presentations at CROI 2023

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ACTG Long-term HIV/ART outcomes:

- SLOWING OR REVERSAL OF DECAY OF INTACT HIV-1 PROVIRUSES OVER TWO DECADES OF ART (Gandhi, A5321)
- PERICORONARY ADIPOSE TISSUE DENSITY IS ASSOCIATED WITH SUBCLINICAL CORONARY ARTERY DISEASE IN HIV (AND DISPROPORTIONATE IN PWH) (Foldyna, REPRIEVE)
- MUSCLE QUALITY IS ASSOCIATED WITH CORONARY ARTERY PLAQUE & PHYSICAL FUNCTION IN PWH (Erlandson, REPRIEVE)
- CORONARY ARTERY PLAQUE COMPOSITION AND SEVERITY RELATES TO THE INFLAMMASOME IN HIV (Schnittman, REPRIEVE)
- CHANGES IN BODY MASS INDEX WITH INTEGRASE INHIBITOR USE IN REPRIEVE- mainly seen in initial 2 years of use, women, and Black participants (Kileel, REPRIEVE)
- LOW CD4 NADIR AT HIV DIAGNOSIS ASSOCIATES WITH INCREASED RISK OF CLONAL HEMATOPOIESIS (Bhattacharya, REPRIEVE)

ACTG COVID-19 studies

CHARACTERIZATION OF SINGLE VERSUS DUAL ACTIVE MONOCLONAL ANTIBODIES AGAINST SARS-COV-2 (ACTG 5340; Oral Presentation: Tuesday, February 21, 10:21 am PT, Flex C – Level 2) *Manish C. Choudhary, et al.*
This study evaluated the viral kinetics and resistance emergence in individuals with COVID-19 treated with mono versus dual-active anti-SARS-CoV-2 monoclonal antibodies.

SAFETY AND EFFICACY OF INHALED INTERFERON-β1A (SNG001) IN OUTPATIENTS WITH COVID-19 (ACTG 5401; Oral Presentation: Tuesday, February 21, 10:29 am PT, Flex C – Level 2) *Prasanna Jagannathan, et al.*
This study evaluated the safety and efficacy of orally inhaled nebulized interferon-β1a (SNG001) in a phase 2 randomized controlled trial on the ACTIV-2/A5401 platform.

SYMPTOM AND VIRAL REBOUND IN UNTREATED COVID-19 INFECTION (ACTG 5401; Oral Presentation: Tuesday, February 21, 11:08 am PT, Flex C – Level 2) *Rinki Deo, et al.*
Because the natural course of viral and symptom trajectories during COVID-19 have not been well described, this study evaluated the incidence of viral rebound and symptom relapse in untreated individuals with mild-to-moderate COVID-19.

POST-ACUTE COVID OUTCOMES: AMUBARVIMAB+ROMLUSEVIMAB VS PLACEBO IN THE ACTIV-2 TRIAL (ACTG5401; Poster Presentation: Monday, February 20, 2:30 – 4:00 pm PT, Poster Session N1 PASC) *Teresa H. Evering, et al.*
This study assessed the impact of the SARS-CoV-2 monoclonal antibodies amubarvimab+ romlusevimab (which were highly effective in reducing 28-day hospitalizations and deaths among high-risk adults with mild-to-moderate COVID-19) on late outcomes, including Long COVID.

IMPACT OF COVID-19 AND HOST FACTORS ON THE HUMORAL IMMUNE REPERTOIRE IN TREATED HIV (ACTG 5332; Poster Presentation: Monday, February 20, 2:30 – 4:00 pm PT, Poster Session D6) *Samuel R. Schnittman, et al.*
This study sought to elucidate the mechanisms (including the effects of COVID-19 and host factors on the humoral immune repertoire) that seem to increase the risk for worse COVID-19 outcomes among people living with HIV who are on ART.

PLASMA ANTIBODY AND N ANTIGEN STATUS PREDICT OUTCOMES IN OUTPATIENTS WITH COVID-19 (NWCS 540; Poster Presentation: Tuesday, February 21, 2:30 – 4:00 pm PT, Poster Session B7) *Nikolaus Jilg, et al.*
In response to the critical need for reliable biomarkers of COVID-19 severity and outcomes, this study evaluated associations between anti-Spike IgG and SARS-COV-2 nucleocapsid antigen in plasma with clinical outcomes from outpatients with COVID-19.

IMMUNE STATUS AND SARS-COV-2 VIRAL DYNAMICS (ACTG5401; Poster Presentation: Tuesday, February 21, 2:30 – 4:00 pm PT, Poster Session N2) *Yijia Li, et al.*
People who are immunocompromised are disproportionately affected by severe SARS-CoV-2, but immune compromise is heterogenous, which may impact viral dynamics. This study evaluated the relationship between degrees of compromised immunity, viral shedding, and viral clearance in the absence of COVID-19 therapeutics.

TIXAGEVIMAB/CILGAVIMAB IM AND IV IN SYMPTOMATIC COVID-19: A RANDOMIZED CONTROLLED ACTIV-2 TRIAL (ACTG5401; Poster Presentation: Wednesday, February 22, 2:30 – 4:00 pm PT, Poster Session H8) *Rachel Bender Ignacio, et al.*
This study evaluated the safety and efficacy of tixagevimab/cilgavimab, an anti-SARS-CoV-2 monoclonal antibody combination, among outpatients with COVID-19 through both intravenous and intramuscular administration.

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Acknowledgment

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