What happened at CROI 2023

(that you should know about)

NATAP NATIONAL AIDS TREATMENT ADVOCACY PROJECT
EDUCATING COMMUNITIES ABOUT HIV AND HEPATITIS

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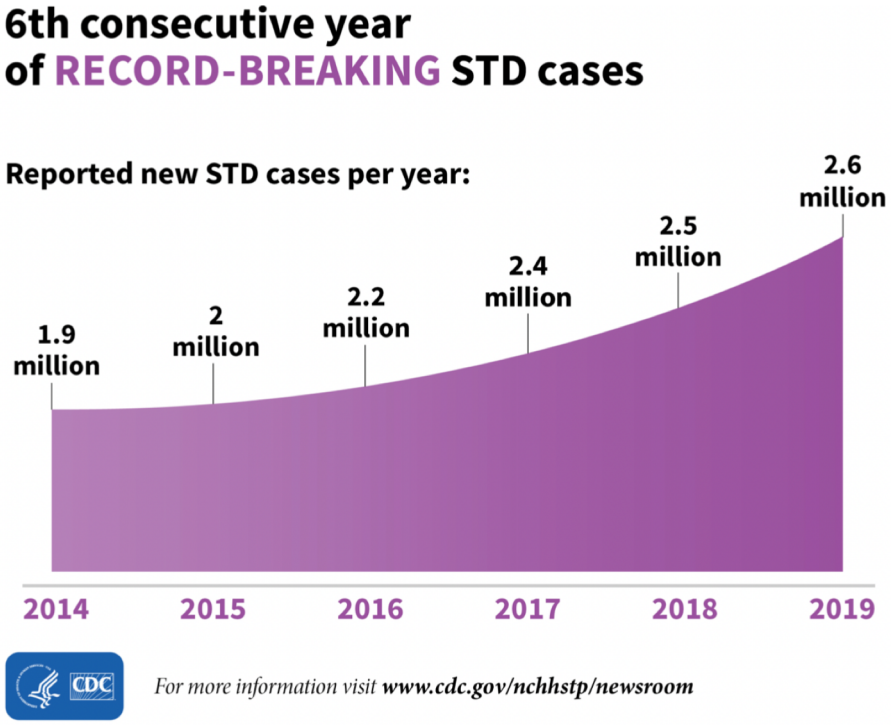
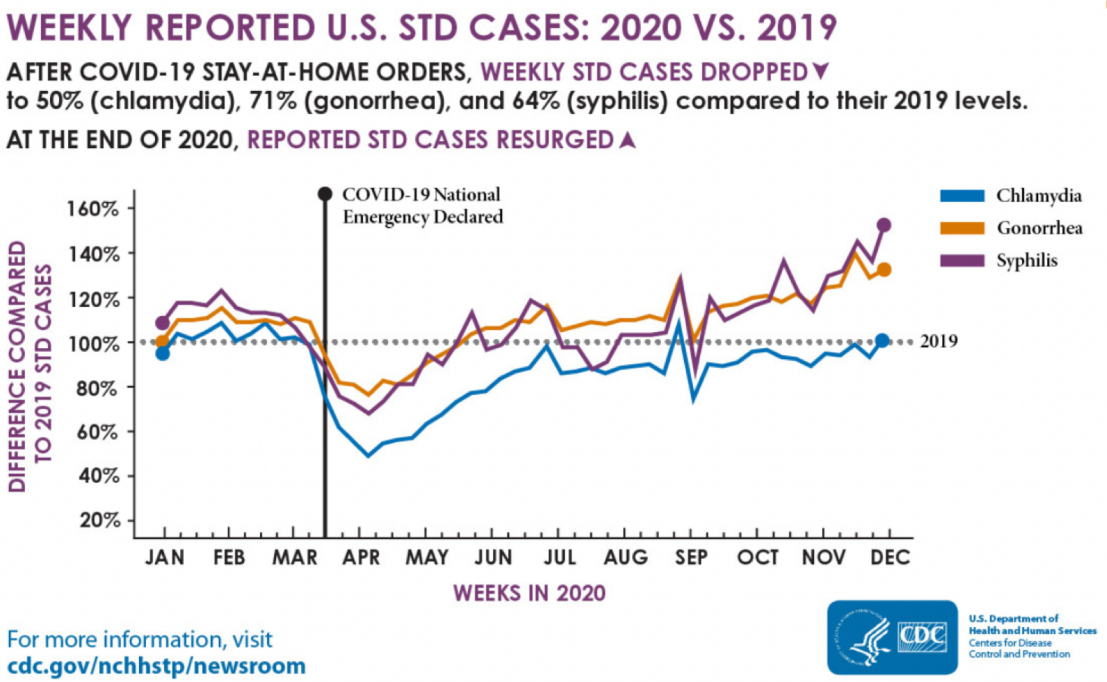
University of North Carolina

DOXY PEP

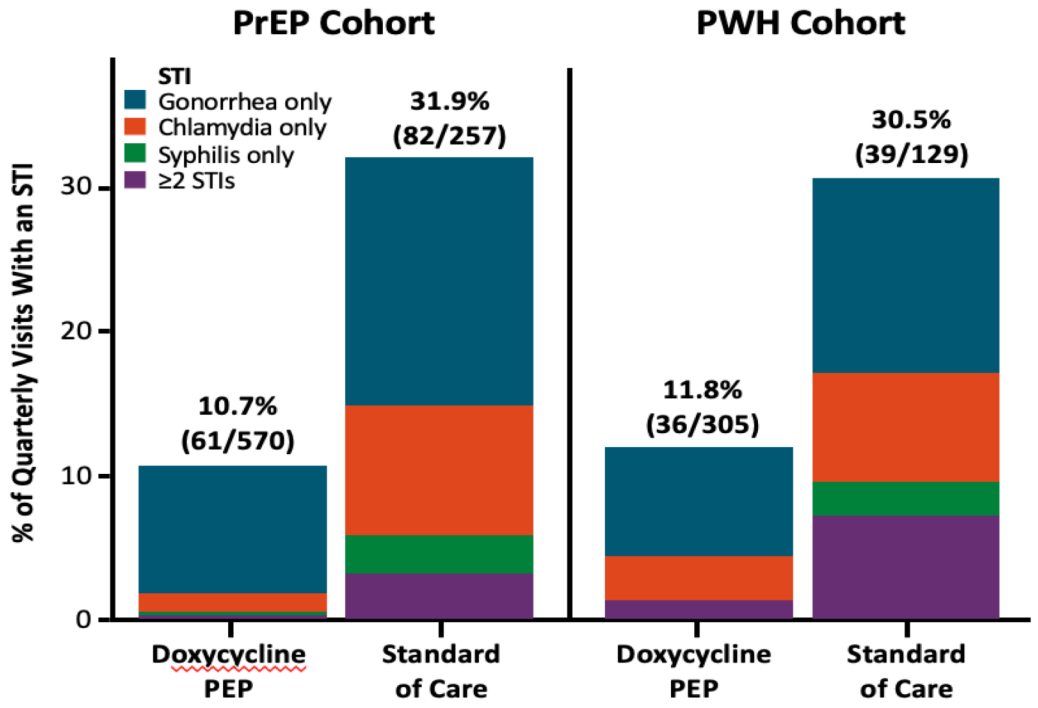
- Rates of STIs (gonorrhea, chlamydia, syphilis) in US are high
  - Rising pre-COVID-19
  - After dip, rising again
  - Compared to white people, rates are higher for people of color
- Doxycycline has activity against all three bacteria, although gonorrhea resistance not uncommon





DOXY PEP

- ANRS iPERGAY: Doxycycline PEP (within 24h) reduced occurrence of initial bacterial STI in MSM at high risk for STIs[1]
  - 70% and 63% reduction in chlamydia and syphilis, respectively, but no prevention efficacy observed for gonorrhea
- DOXYPEP (SF & Seattle): Doxy PEP (within 72h)
  - 65% reduction in STIs per quarter – 55% drop in gonorrhea[2]



Risk Reduction in STI Incidence per Quarter (95% CI)	Doxy PEP*
PrEP	0.34 (0.24-0.46)
PWH	0.38 (0.24-0.60)
Total	0.35 (0.27-0.46)

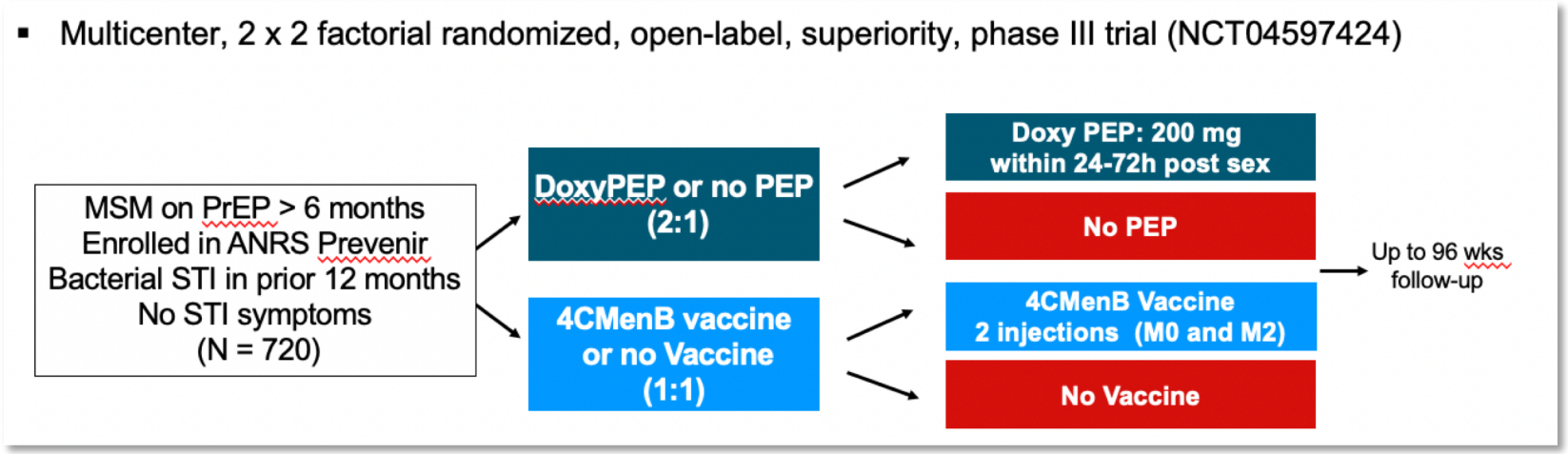
*All *P* <.0001

Risk Reduction per Quarter (95% CI)	PrEP	PWH
Gonorrhea	0.45 (0.32-0.65) *P* <.0001	0.43 (0.26-0.71) *P* = .001
Chlamydia	0.12 (0.05-0.25) *P* <.0001	0.26 (0.12-0.57) *P* = .0007
Syphilis	0.13 (0.03-0.59) *P* = .0084	0.23 (0.04-1.29) *P* = .095

1. Molina. Lancet Infect Dis. 2018;18:308. 2. Luetkemeyer. AIDS 2022. Abstr OALBX0103

DOXY PEP at CROI 2023

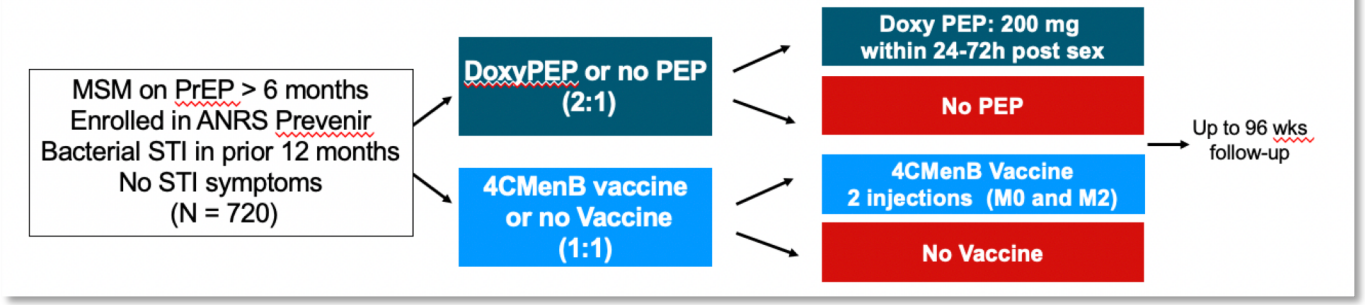
- **DOXYPEP (SF & Seattle):**[1] Gonorrhea resistance detected during the trial but was thought likely to represent infection with doxy-resistant organisms. In subset with culture data:
  - Rates of resistant gonorrhea in those taking and not taking doxy little different than rate at baseline.
  - Staph aureus detect was reduced with doxy PEP with small increase in rate of doxy-resistant Staph aureus.
  - Low rates of MRSA detection and no different between arms
- **ANRS DOXYVAC Study:**[2]
  - Meningococcal B vaccination associated with a 26-46% reduction in gonorrhea incidence.

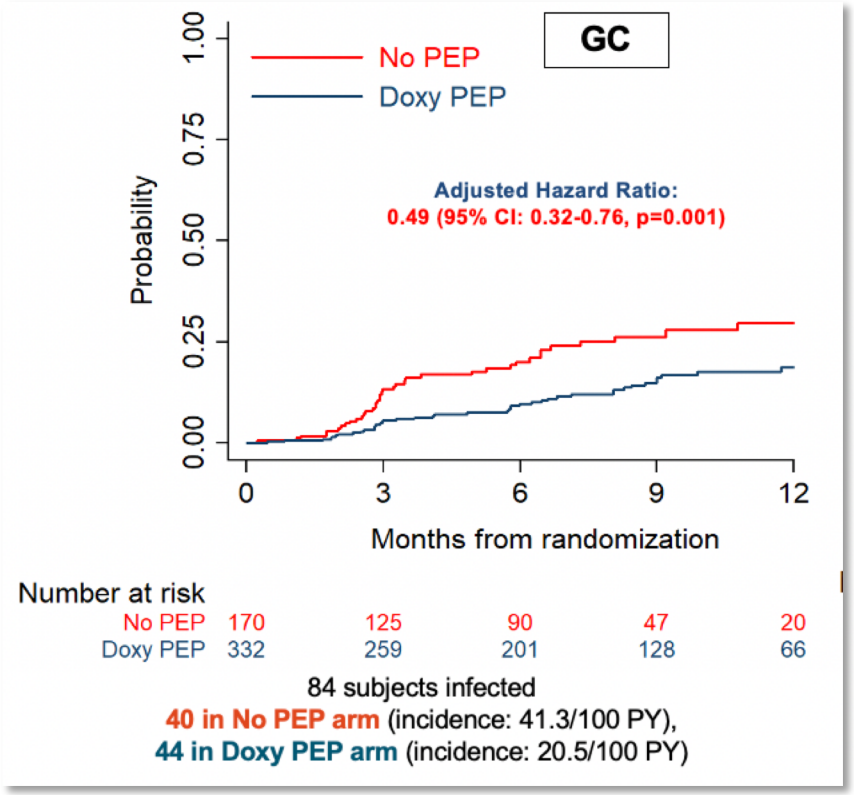


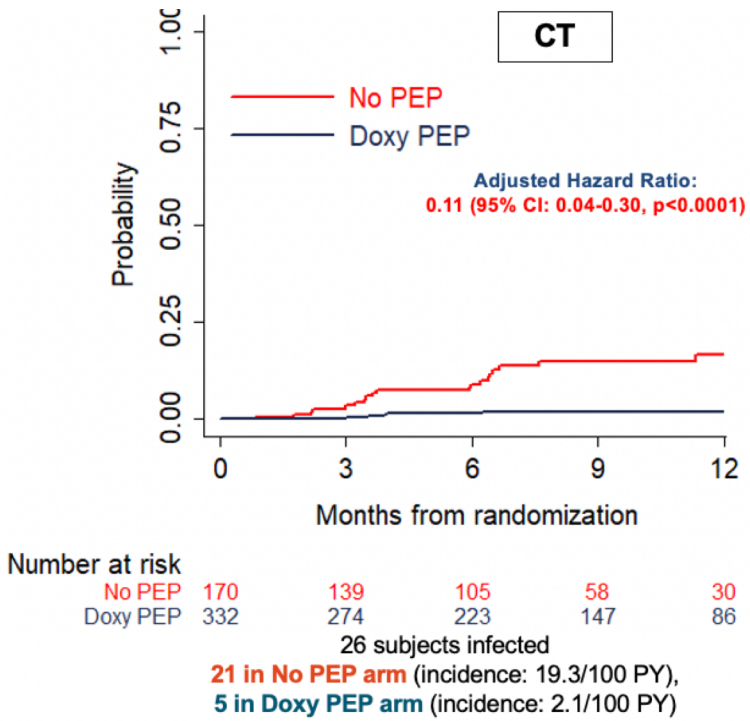
1. Luetkemeyer. CROI 2023. 2. Molina. CROI 2023

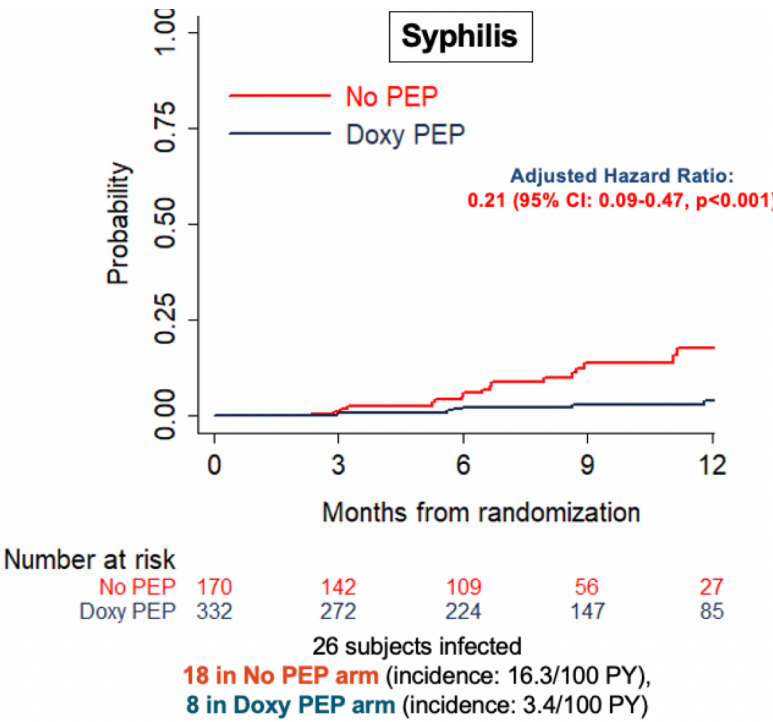
DOXY PEP at CROI 2023

- Multicenter, 2 x 2 factorial randomized, open-label, superiority, phase III trial (NCT04597424)









Molina. CROI 2023

DOXY PEP at CROI 2023

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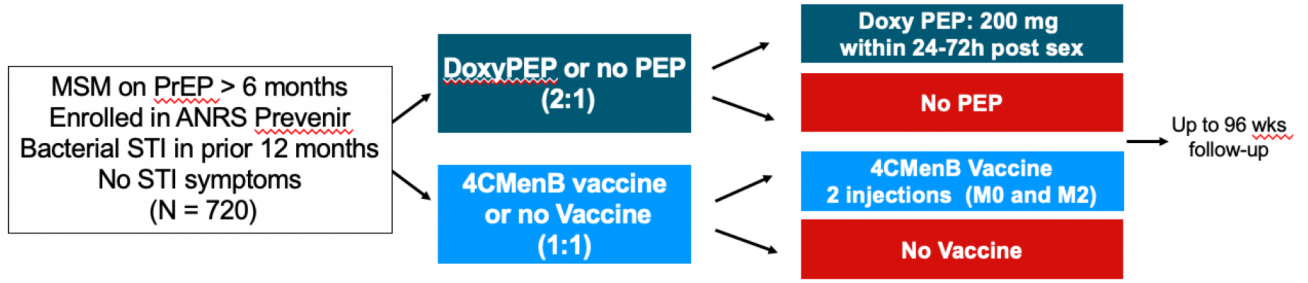
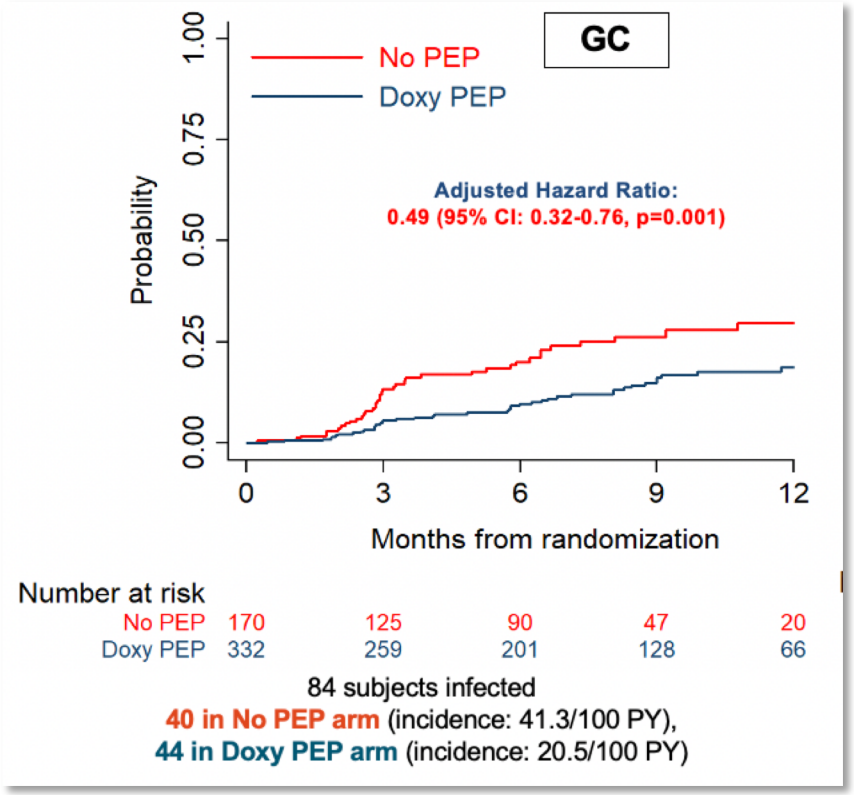




Number at risk

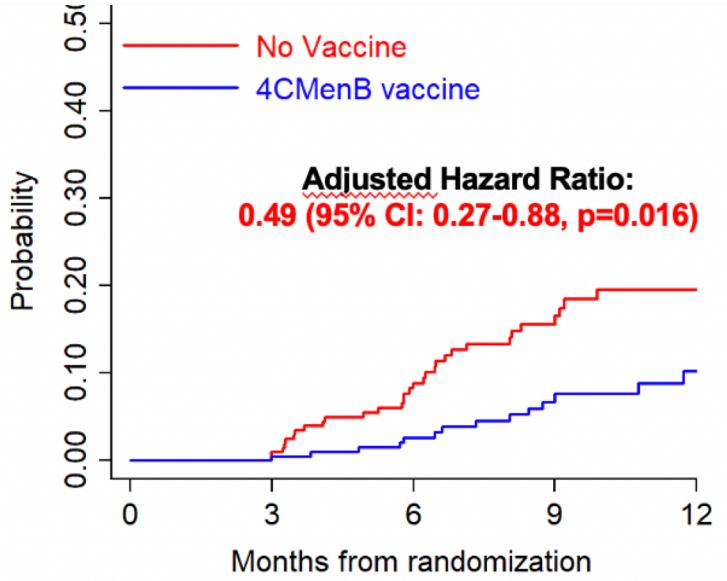
No PEP	170	125	90	47	20
Doxy PEP	332	259	201	128	66

84 subjects infected
40 in No PEP arm (incidence: 41.3/100 PY),
44 in Doxy PEP arm (incidence: 20.5/100 PY)

No interaction between Doxy PEP and 4CMenB vaccine (p=0.41)

49 subjects infected
32 in No Vaccine arm
(incidence: 19.7/100 PY),
17 in 4CMenB vaccine arm
(incidence: 9.8/100 PY)

GC infections were considered from M3 visit (1 month after 2nd vaccine dose)



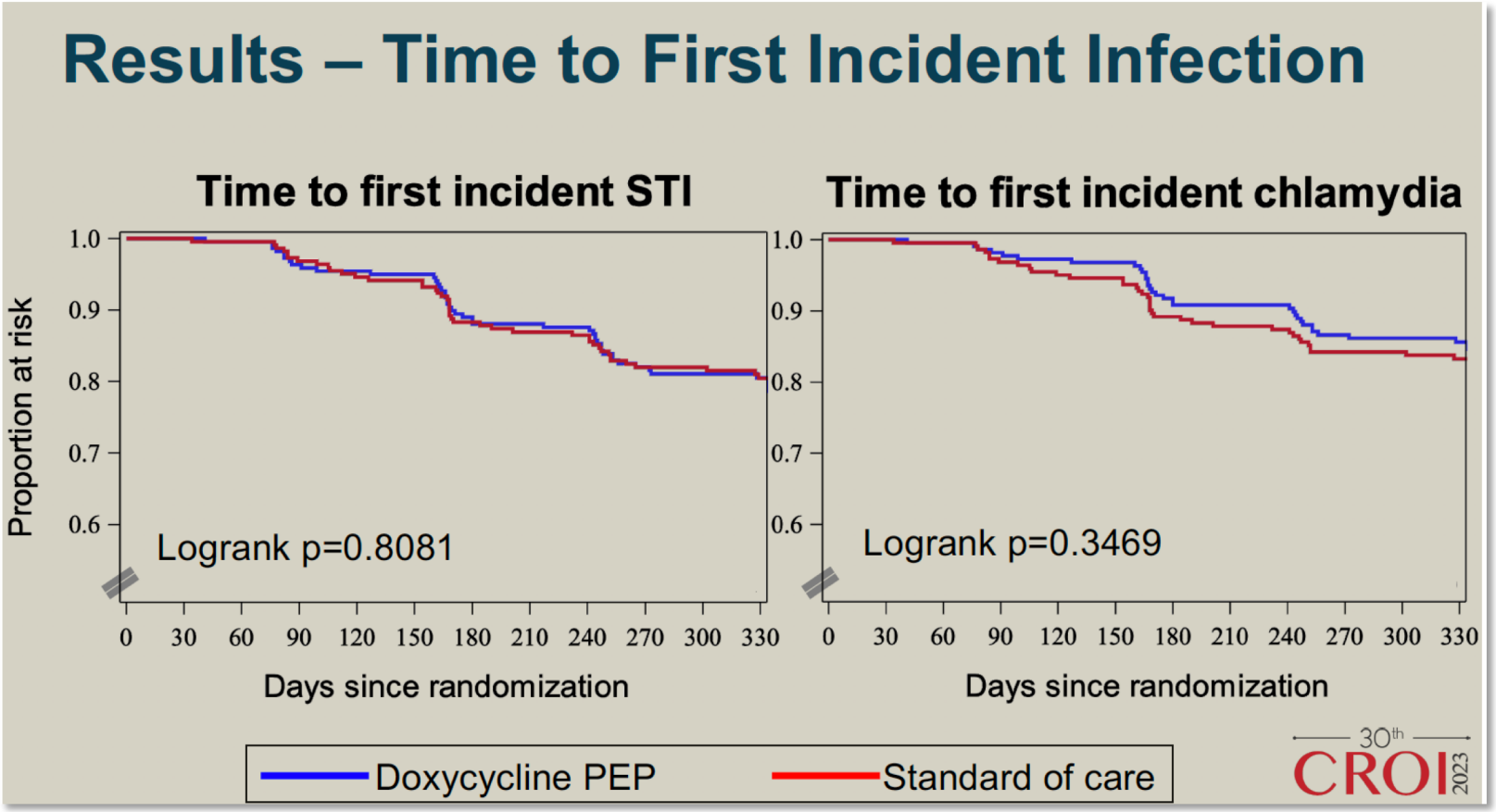
Number at risk

No Vaccine	245	208	150	91	49
4CMenB vaccine	257	208	170	102	49

Molina. CROI 2023

DOXY PEP at CROI 2023

- **dPEP Kenya Study:**[1] Open label RCT of doxy PEP (within 72h) among 499 cis-women (18-30 years) in prescribed HIV PrEP in Kisumu, Kenya.



Why?

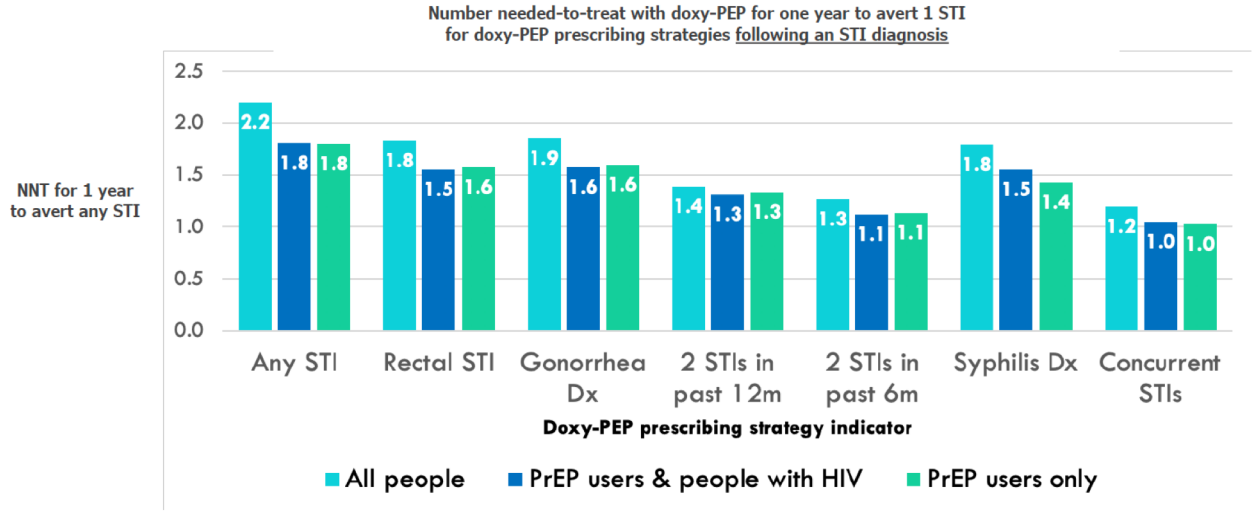
- Anatomical
- Pharmacological/Tissue concentration
- Adherence
- **IMO: It is premature to conclude doxy PEP does not work for cis-women given the limitations of this trial**

Stewart. CROI 2023

DOXY PEP at CROI 2023

- Several well designed, placebo-controlled trials of DOXY-PEP in MSM with and without HIV have demonstrated effectiveness and minimal adverse effects.
- Antibiotic resistance has not been demonstrated to be an issue with intermittent doxycycline exposure.
- Given these data, use of DOXY PEP is reasonable for select patients (i.e., following any STI):

Results *Restricting doxy-PEP to PrEP users & people with HIV*



STI-based prescribing strategies had a similar NNT across subgroups

DOXY PEP at CROI 2023

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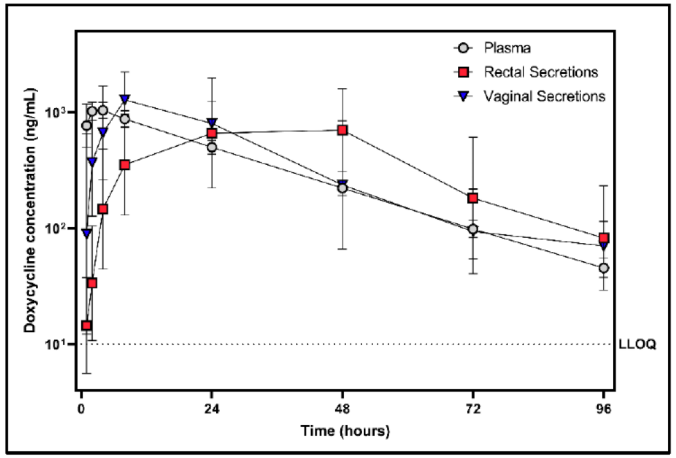
- Antibiotic resistance has not been demonstrated to be an issue with intermittent doxycycline exposure.
- Given these data, use of DOXY PEP is reasonable for select patients (i.e., following any STI):

- The limitations of dPEP-Kenya trial preclude the conclusion that DOXY-PEP is ineffective in cis-women.

- Well designed trials with objective measures of adherence and tissue concentrations are needed to determine ability to protect against STI via vaginal sex.

Mucosal Doxycycline Concentrations



	C_{max} (ng/mL) [95% CI]	T_{max}	$AUC_{0\text{-}96h}$ (ng*h/mL) [95% CI]	AUC Ratio (S:P)
Plasma	1042 [889 – 1222]	4 hr	33,951 [29,632 – 38,899]	
Rectal Secretions	704 [311 – 1596]	48 hr	73,511 [34,332 – 156,487]	2.17
Vaginal Secretions	1284 [742 – 2223]	8 hr	58,562 [32,719 – 104,816]	1.72

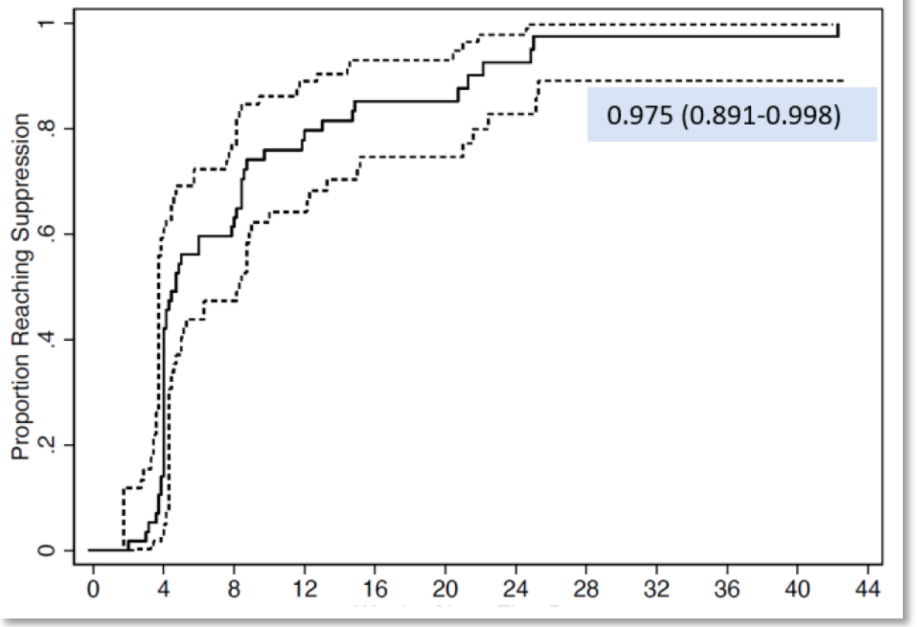
- Doxycycline concentrations peak later in rectal secretions than plasma
- Rectal and vaginal doxycycline exposure greater in mucosa than plasma

Long Acting CAB+RPV at CROI 2023

- Cabotegravir (CAB) and Rilpivirine (RPV) injectable ART is indicated in those with suppressed plasma HIV RNA
- UCSF long acting injectable program has reported starting CAB+RPV in people with viremia.[1,2]
- Follow-up of prior experience presented

- Between June 2021-November 2022, 133 diverse PWH started on LA-ART, 76 (57%) suppressed on oral ART, 57 (43%) with viremia
- Median CD4 count in those with viremia lower in suppressed
- 74% (66-81%) on-time injections
- In those with suppression, 100% (95% CI 94%-100%) remained so
- Among viremic PWH, all suppressed but 2 with early virologic failure.
- Current cohort virologic failure rate 1.5% similar to that across clinical trials (1.4%) by 48 weeks (68% by 24 weeks)

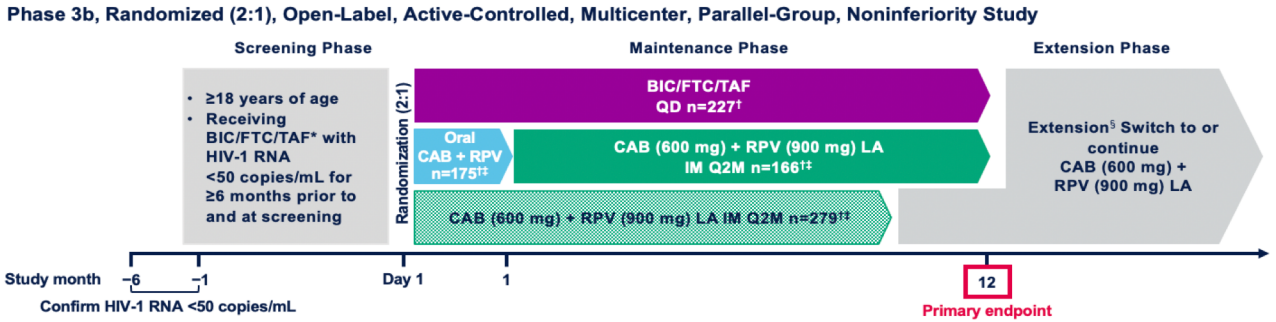
Figure: KM curve of probability of reaching virologic suppression (VL <30) on LA ART (n=57); dotted lines 95% CI



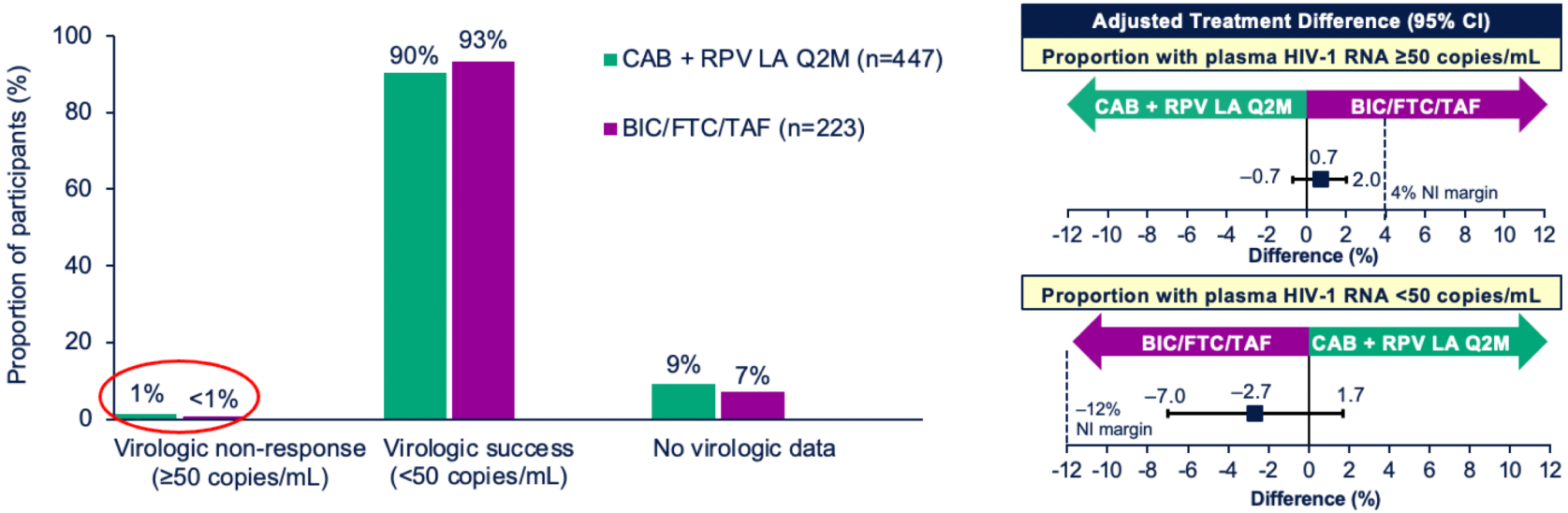
1. Christopoulos. AIDS 2022. Abstr EPB286. 2. Christopoulos. Clin Infect Dis. 2022;ciac631. 3. Gandhi. CROI 2023

Long Acting CAB+RPV at CROI 2023

SOLAR Study Design



Virologic Outcomes at Month 12 (mITT-E Population)



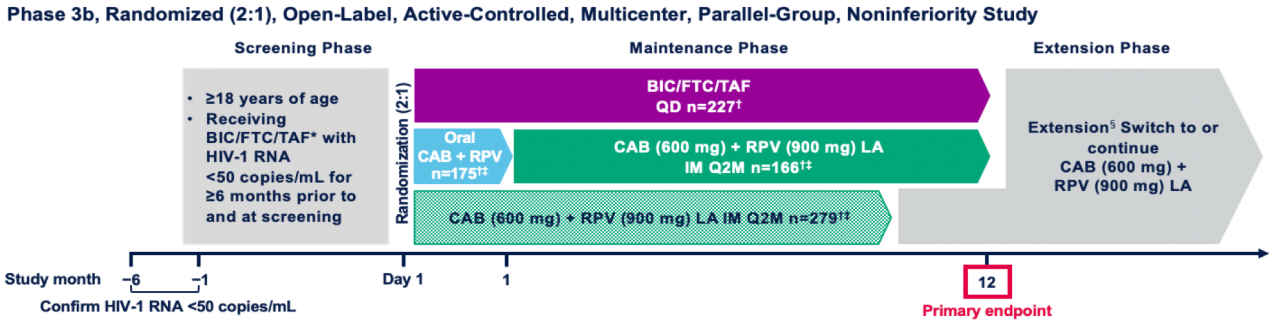
- At Month 12, CAB + RPV LA demonstrated noninferior efficacy compared with BIC/FTC/TAF for the proportion of participants with HIV-1 RNA ≥50 copies/mL and <50 copies/mL in the mITT-E, ITT-E, and per-protocol populations*

*In the ITT-E population, 89% (n=406/454) and 93% (n=211/227) of participants receiving LA and BIC/FTC/TAF demonstrated virologic success (HIV-1 RNA <50 copies/mL; adjusted treatment difference [95% CI], –3.5% [–7.9, 0.9]), 1% (n=6/454) and <1% (n=1/227) of participants receiving LA and BIC/FTC/TAF demonstrated virologic non-response (HIV-1 RNA ≥50 copies/mL; adjusted treatment difference [95% CI], 0.9% [–0.5, 2.2]), and 9% (n=42/454) and 7% (n=15/227) of participants receiving LA and BIC/FTC/TAF had no virologic data, respectively. In the per protocol population, 91% (n=394/433) and 93% (n=203/218) of participants receiving LA and BIC/FTC/TAF demonstrated virologic success (HIV-1 RNA <50 copies/mL; adjusted treatment difference [95% CI], –2.1% [–6.4, 2.2]), <1% (n=4/433) and <1% (n=1/218) of participants receiving LA and BIC/FTC/TAF demonstrated virologic non-response (HIV ≥50 copies/mL; adjusted treatment difference [95% CI], 0.5 [–0.8, 1.7]). ITT-E, intention-to-treat exposed; mITT-E, modified intention-to-treat exposed; NI, noninferiority.

Ramgopal. CROI 2023.

Long Acting CAB+RPV at CROI 2023

SOLAR Study Design



Participants With Confirmed Virologic Failure (CVF)

Participants With CVF in the mITT-E Population									
Sex at birth, country	Baseline BMI (kg/m²)	HIV-1 subtype at baseline	Viral load at SVF/CVF (copies/mL)	RPV RAMs observed at baseline (proviral DNA)	INI RAMs observed at baseline (proviral DNA)	RPV RAMs observed at failure (viral RNA)	INI RAMs observed at failure (viral RNA)	Phenotypic resistance (fold-change) to RPV/CAB	SVF timepoint (month)
Male, Italy*	21.5	B	1327/1409	None	None	M230L	Q148R	3.2/3.1	6
Male, Spain†	22.9	AE	6348/419	None	G140G/R	K101E	G118R	1.9/8.4	11
Participant With CVF in the ITT-E Population‡									
Male, United States	30.5	C§	3797/928	Assay failed	Assay failed	E138E/K + Y181Y/C	None	4.2/assay failed	3

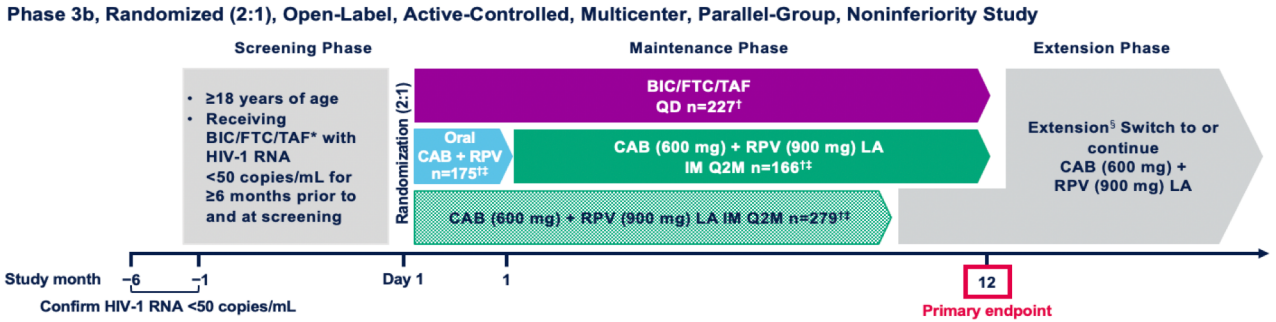
- Two (0.4%) participants receiving CAB + RPV LA in the mITT-E population, and one additional participant receiving CAB + RPV LA in the ITT-E population, met the CVF criterion through Month 12
  - Two of the participants had on-treatment RPV and/or INI RAMs (genotyping for third participant failed at baseline)
- No participants in the BIC/FTC/TAF arm met the CVF criterion through Month 12

*Prior to enrolling in the study, the participant received BIC/FTC/TAF, and after discontinuation re-suppressed on darunavir/cobicistat/emtricitabine/tenofovir alafenamide during long-term follow-up. †Prior to enrolling in the study, the participant had received abacavir/dolutegravir/lamivudine and BIC/FTC/TAF; they re-suppressed on BIC/FTC/TAF and darunavir/cobicistat/emtricitabine/tenofovir alafenamide during long-term follow-up. The participant did not continue in the long-term follow-up phase. ‡Prior to enrolling in the study, the participant had received prohibited prior ART with at least three prior INI regimens; they re-suppressed on BIC/FTC/TAF during long-term follow-up. This participant was excluded from the mITT-E population due to significant and persistent non-compliance to protocol entry requirements at the study site. §Participant had HIV-1 subtype C at Month 3. Baseline analysis failed.
ITT-E, intention-to-treat exposed; LA, long-acting; mITT-E, modified intention-to-treat exposed; NA, not available; RAM, resistance-associated mutation; SVF, suspected virologic failure.

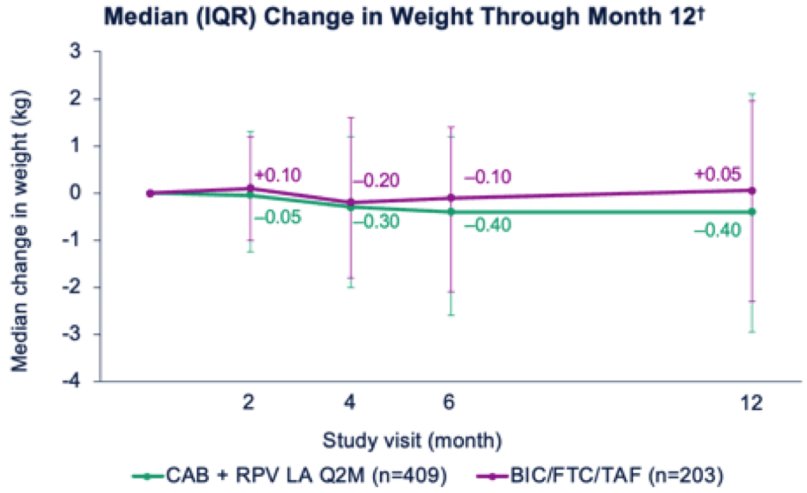
Ramgopal. CROI 2023.

Long Acting CAB+RPV at CROI 2023

SOLAR Study Design

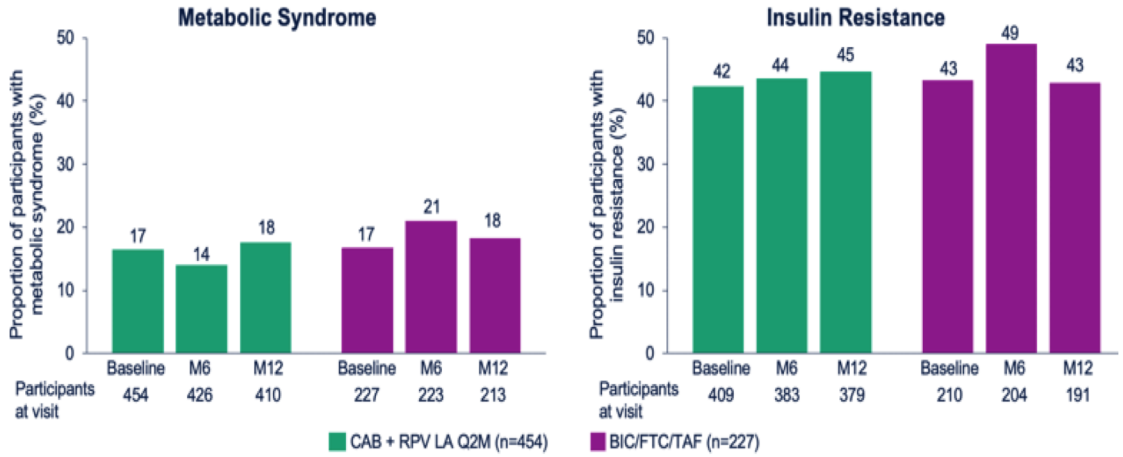


Change in Weight Through Month 12 by Treatment Regimen*



- At Month 12, median (IQR) change in weight in the CAB + RPV LA group was -0.40 (-2.95, +2.10) kg and +0.05 (-2.30, +1.95) kg in the BIC/FTC/TAF group

Metabolic Syndrome* and Insulin Resistance† Through Month 12 by Treatment Regimen



- There were no clinically relevant changes from baseline to Month 12 in the proportion of participants with metabolic syndrome or insulin resistance in either arm

Darnell. CROI 2023.

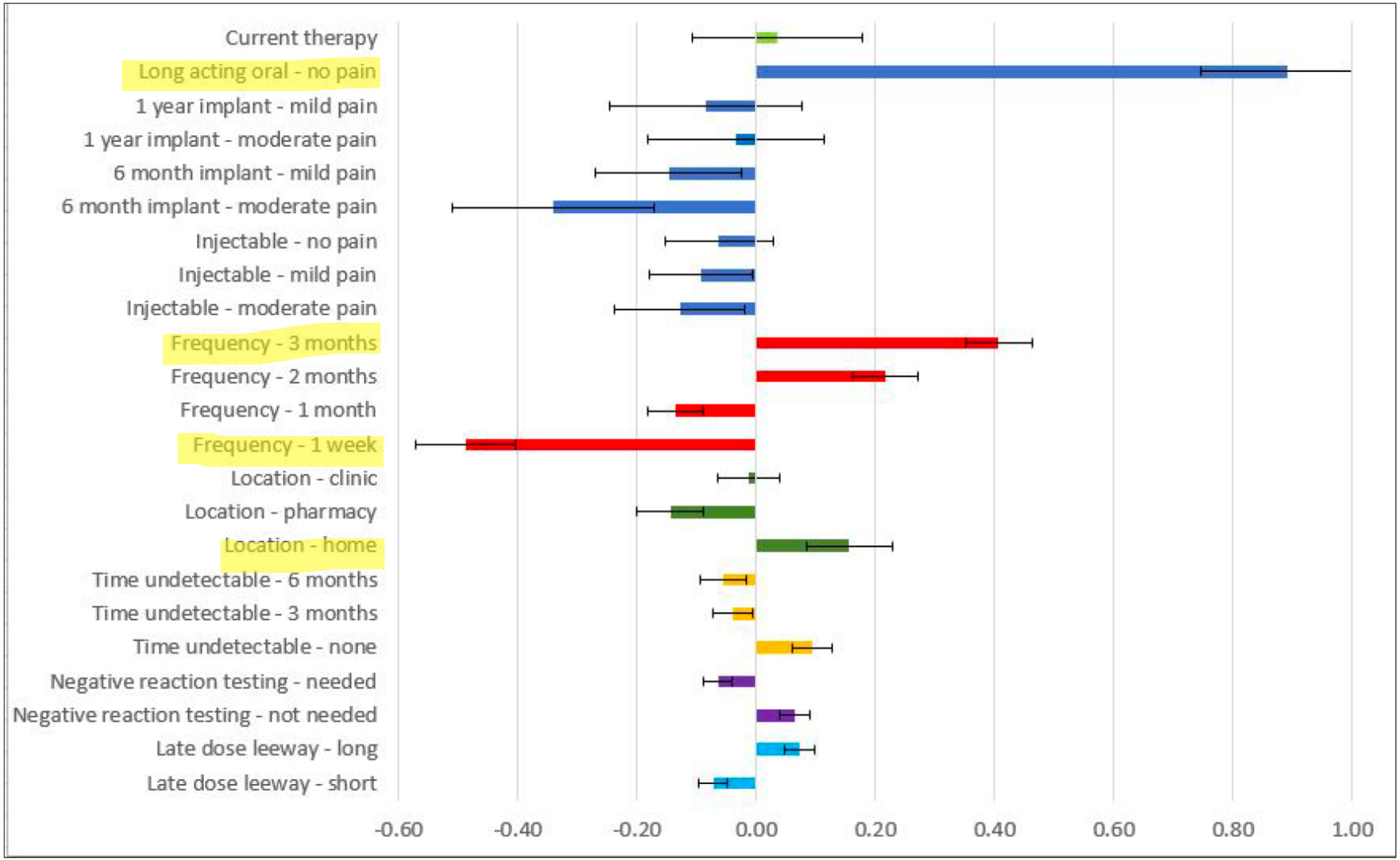
Long Acting CAB+RPV at CROI 2023

- What do people want?
- Discrete choice experiment among 700 PWH on ART in Washington state and Atlanta, Georgia
  - 70% male, 24% female, 6% non-binary/missing

Figure 1. Example Choice Set	Option A	Option B	Option C - your current HIV regimen
Treatment type - How do I take this treatment?	Long-acting oral pills 	Injections under the skin 	
Location - Where would I get this treatment?	Home	Local chemist	
Frequency - How often would I get this treatment?	Once a week	Once a month	
Pain - How much pain would I feel?	None	Mild	
Which do you prefer?	○	○	○

Graham. CROI 2023.

Figure 2. Preference Weights, Both Sites Combined



Graham. CROI 2023.

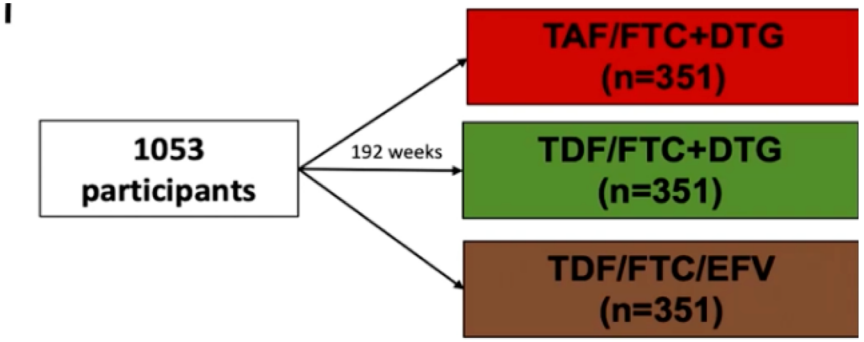
Long Acting CAB + RPV at CROI 2023

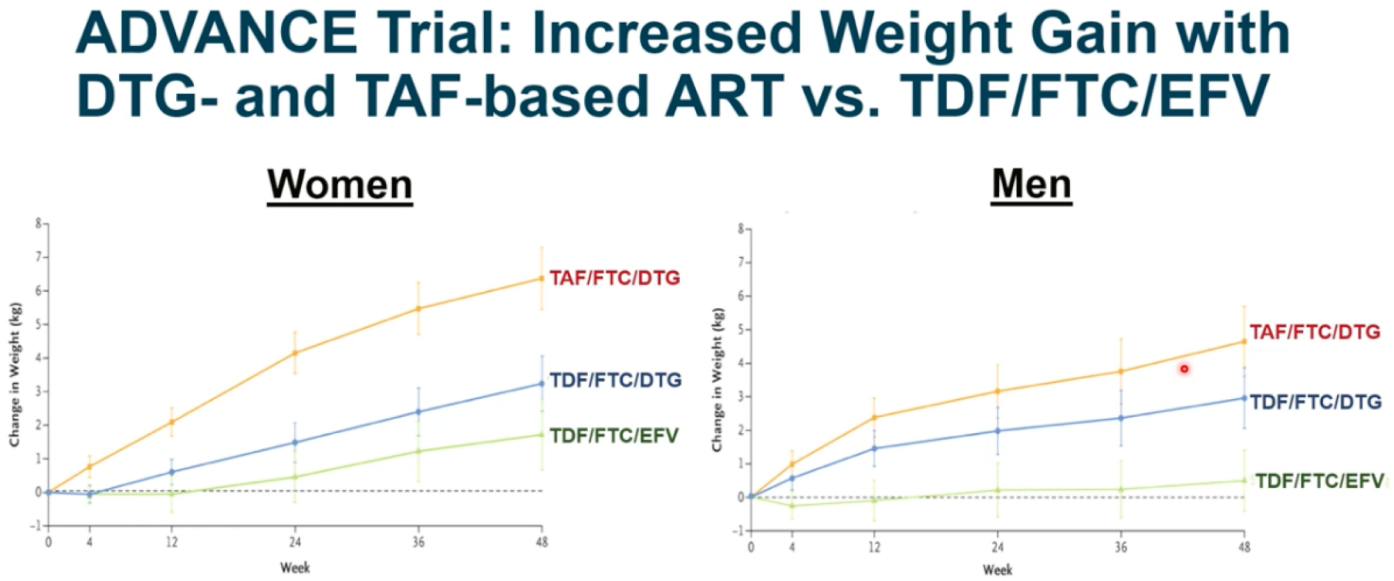
- Role for injectable ART in those with challenges to taking oral HIV therapy.
  - Requires support to ensure attendance to injection visits (or novel approaches to administration).
  - Harm reduction model.

- Switch from BIC/F/TAF to CAB + RPV was non-inferior to remaining on the oral regimen.
  - Failure including with resistance was rare but not zero with switch
  - Weight and metabolic parameters not significantly altered by switch
  - People motivated to be in the trial, favored the injections

Integrase Inhibitors & Weight

- SOLAR Trial ✓
- ADVANCE Trial extension -> CHARACTERISE
- ATHENA Cohort
- REPRIEVE Cohort





Venter. NEJM 2019.

Integrase Inhibitors & Weight

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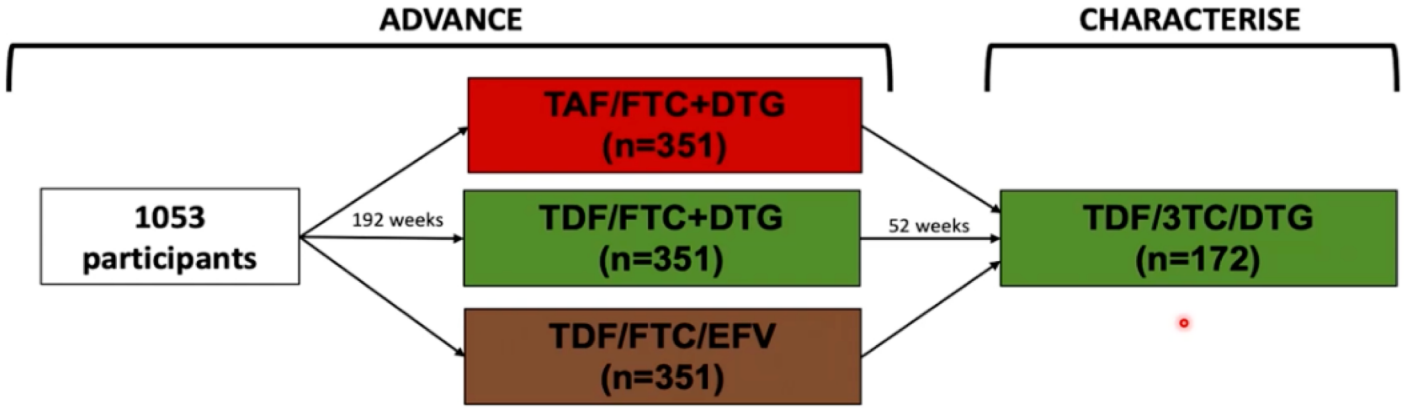
ADVANCE and CHARACTERISE trials



- At follow up, participants were assessed for weight, lipids, fasting glucose, HBA1C and HIV RNA

- Changes in weight and laboratory parameters during the first 192 weeks of randomized treatment and then after the switch to TDF/3TC/DTG were evaluated in each treatment arm using paired non-parametric tests

Bosch. CROI 2023.

Integrase Inhibitors & Weight

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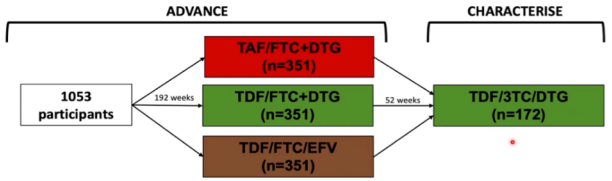
Change in weight after switch to TDF/3TC/DTG – Females and Males

ADVANCE and CHARACTERISE trials



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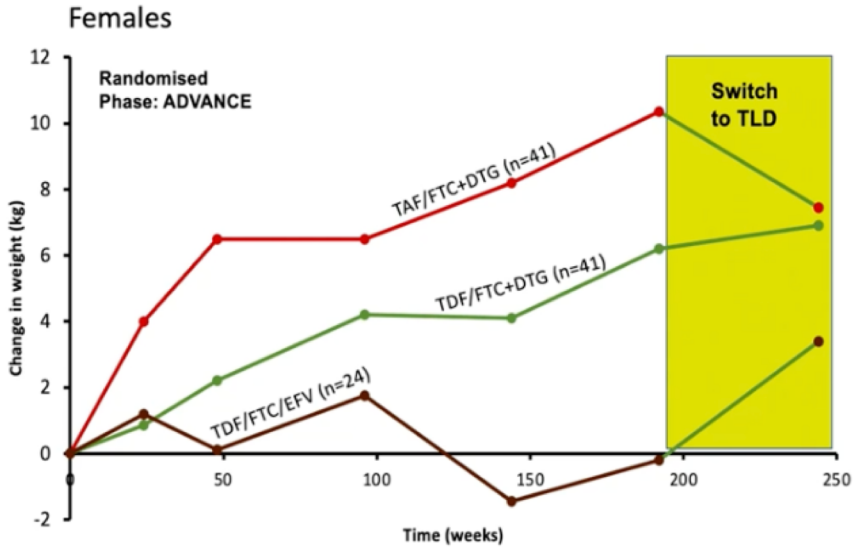

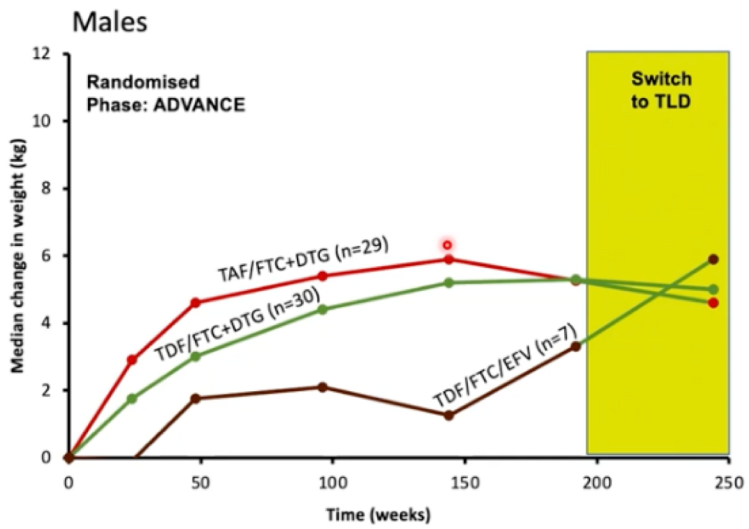

Bosch. CROI 2023.

Integrase Inhibitors & Weight

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AMPATH Program – Kenya

- Switch from standard of care NNRTI-based regimens to DTG
- N = 23,131
  - ~30% on EFV
  - ~30% on NVP

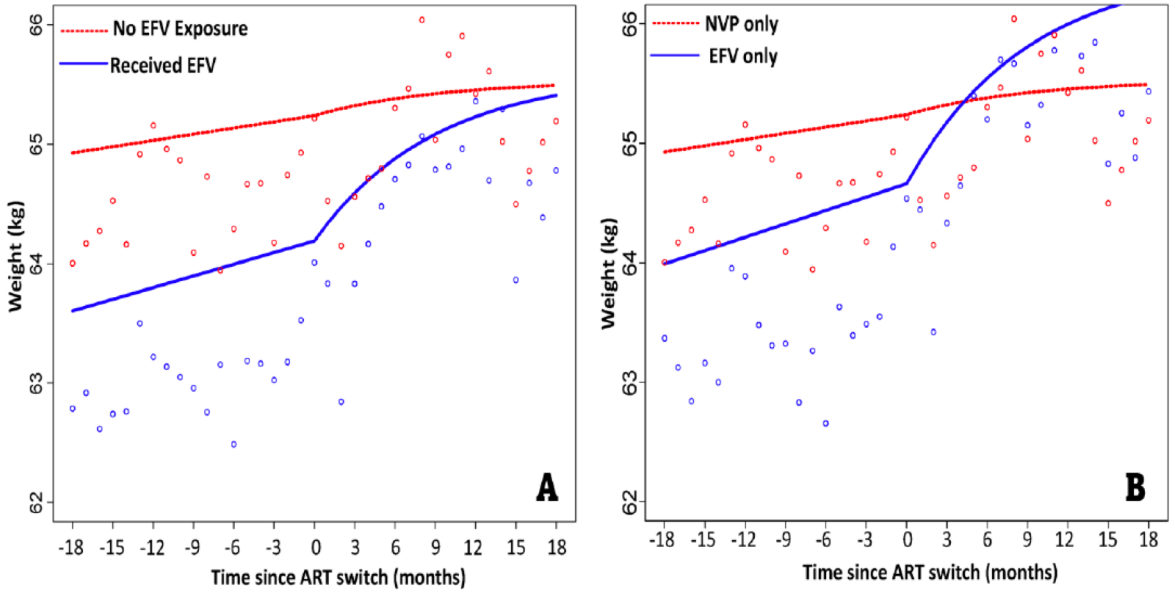

Figure 2. Changes in the rate of weight gain after ART switch by baseline NNRTI drug. In **A** EFV group includes participants exposed to EFV in 2 years pre-switch (EFV only + Both). In **B** compares participants who were on EFV only vs. NVP only.
Rate of weight gain for EFV-exposed participants**: 0.39 kg/year (pre-switch)** vs. **0.94 kg/year (post-switch).** Rate of weight gain for EFV-only participants: **0.44 kg/year (pre-switch)** vs. **1.2 kg/year (post-switch).** Rate of weight gain for NVP-only participants: **0.20 kg/year (pre-switch)** vs. **0.19 kg/year (post-switch)**

Bourgi. CROI 2023.

Integrase Inhibitors & Weight

- SOLAR Trial ✓
- ADVANCE Trial extension -> CHARACTERISE ✓
- ATHENA Cohort
- REPRIEVE Cohort

AMPATH Program – Kenya

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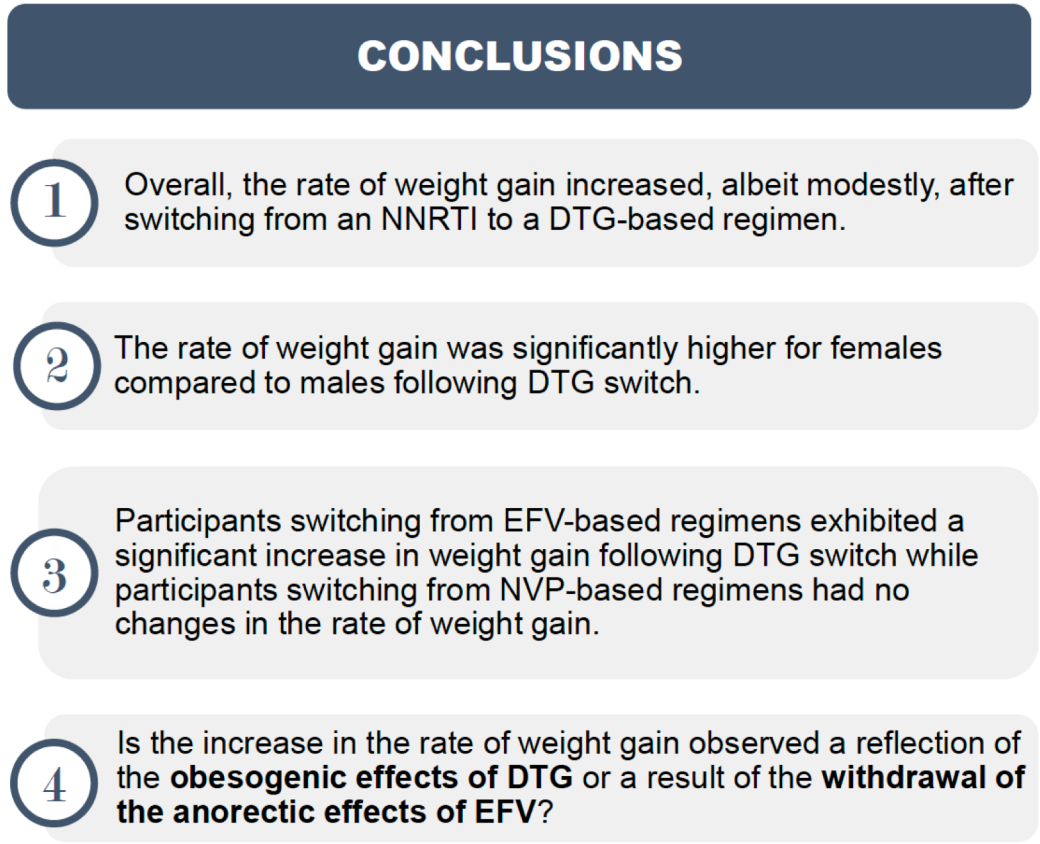
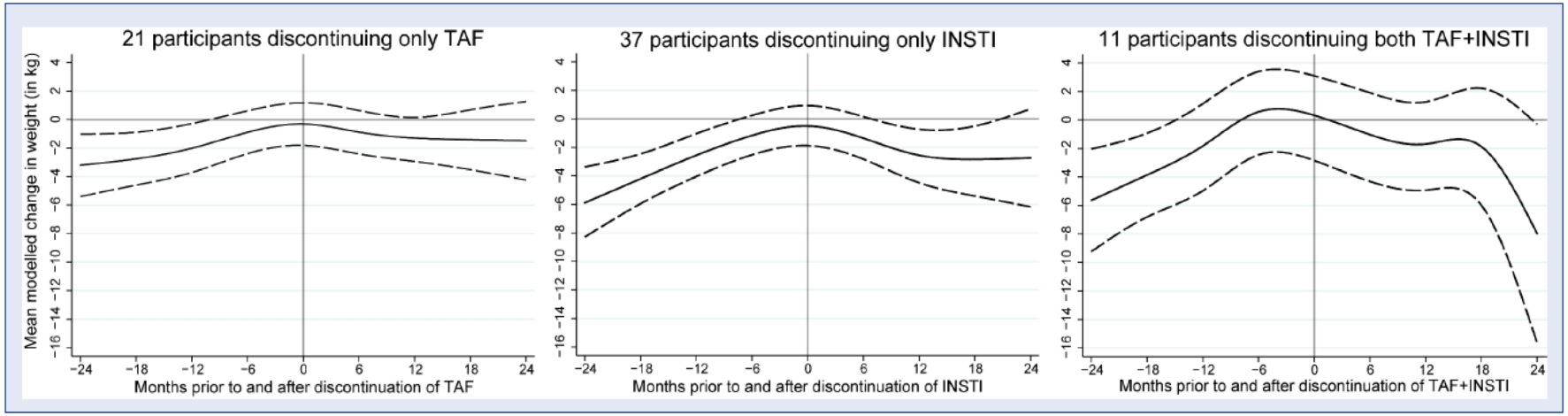


Bourgi. CROI 2023.

Integrase Inhibitors & Weight

- **ATHENA Cohort**
  - Examined people with:
  - 7+% weight gain within 2 years of switch to TAF alone, INSTI alone, or TAF+INSTI
  - Switched off of TAF alone, INSTI alone, or TAF+INSTI
  - Comparators: 7+% weight gain within 2 years of switch to TAF alone, INSTI alone, or TAF+INSTI who stayed on their regimens

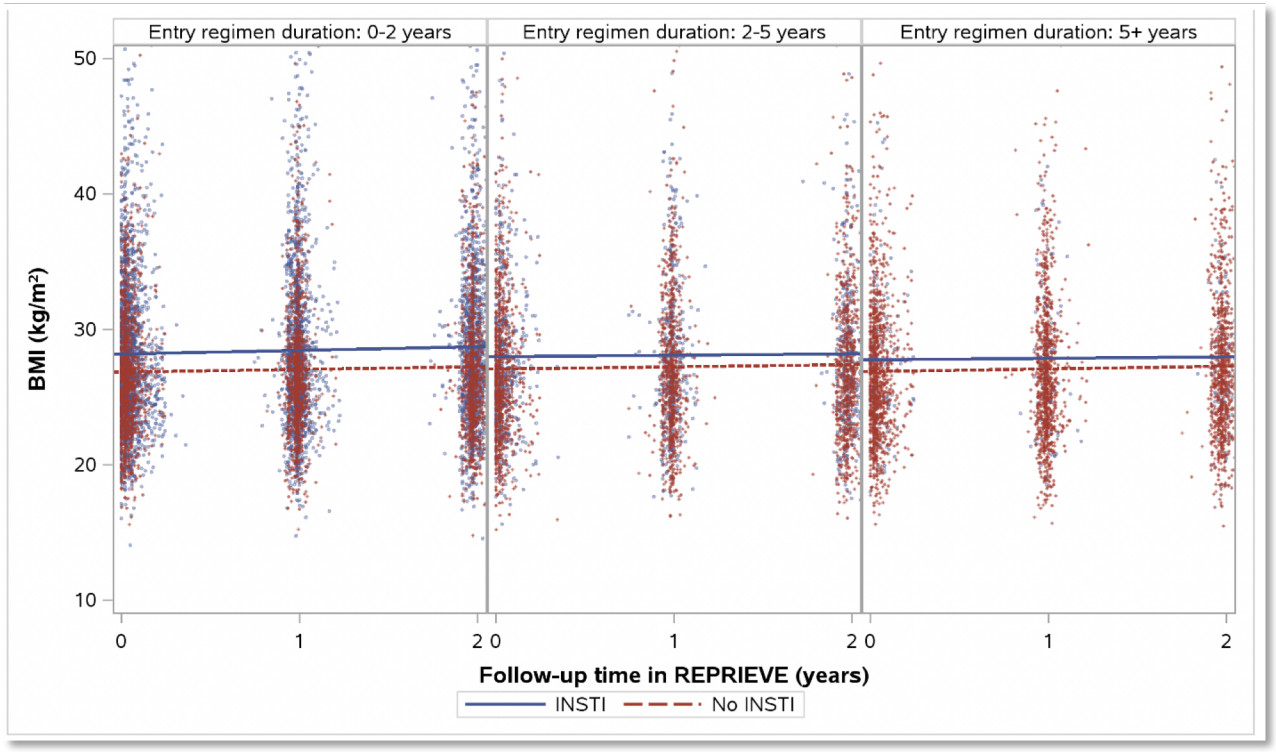
- 6,245 eligible participants:
  - Of those, 1,440 participants gained ≥7% weight within 24 months after switch to TAF and/or INSTI.
    - Of those, 165 discontinued TAF and/or INSTI.
      - Of those, **69** with available follow-up weight were included: 21 discontinuing only TAF, 37 only INSTI and 11 both TAF+INSTI.
    - 998 (of the 1,440) participants continued using TAF and/or INSTI, of whom **800** with available follow-up weight were included.



Verburgh. CROI 2023.

Integrase Inhibitors & Weight

- **REPRIEVE Cohort**
  - RCT of pitavastatin in PWH 40-75 on stable ART
  - Change in BMI by INSTI status among 5,475 participants (2,493 INSTI users)



CONCLUSIONS

- Among a multi-national cohort of over 5000 PWH, the average rate of change in BMI attributable to INSTI use was modest over 2 years of observation.
- Even among key subgroups of the population, including female and Black/African American participants, the 2-year change in BMI associated with INSTI use was less than 0.5 kg/m2 overall once participants' entry BMI was accounted for.
- Changes in weight over the 2-year follow-up period among long-term users were modest and related primarily to weight at the time of study entry.
- Lack of significant weight change with longer term INSTI use suggests effects on metabolic endpoints may be minimal, but care should be given to assess such changes in particular groups including female and Black/African American individuals.

Kileel. CROI 2023

Integrase Inhibitors & CVD

- SWISS Cohort
  - Long-term observational study
  - Mostly male, white

Methods

30th CROI 2023

Target Trial

Population	Intervention	Outcome
SHCS cohort participants ART naïve after **05/2008*** **Detectable** HIV-RNA	**INSTI**-based ART **Control** **Other** ART combination	**First cardiovascular disease event** ○ myocardial infarction ○ stroke ○ invasive cardiovascular procedures

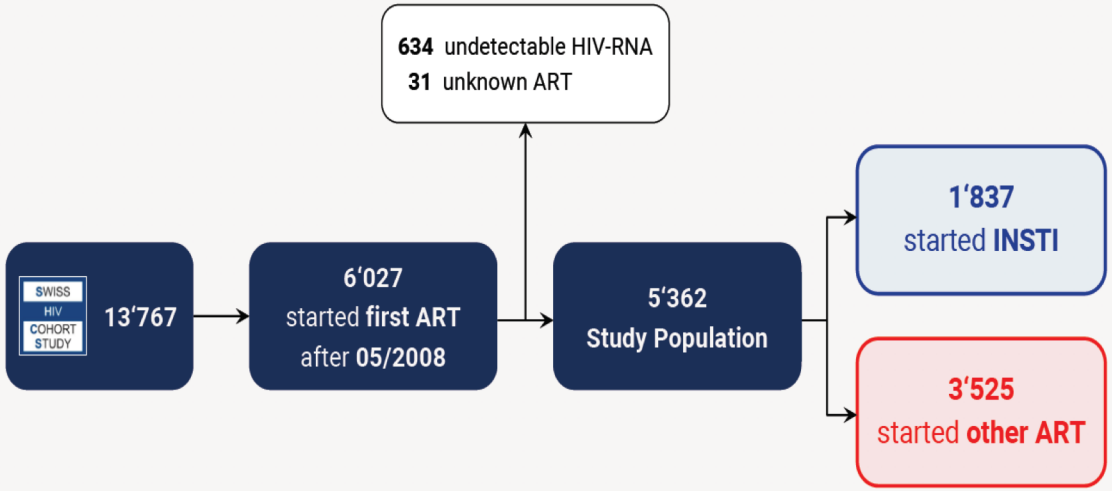
- Individuals who stopped the intended strategy were **artificially censored**
- Pooled logistic regression models
- Adjustments with **inverse probability of treatment and censoring weights**

*Introduction of INSTI in Switzerland

Surial B

Selection of Population

30th CROI 2023



Surial. CROI 2023

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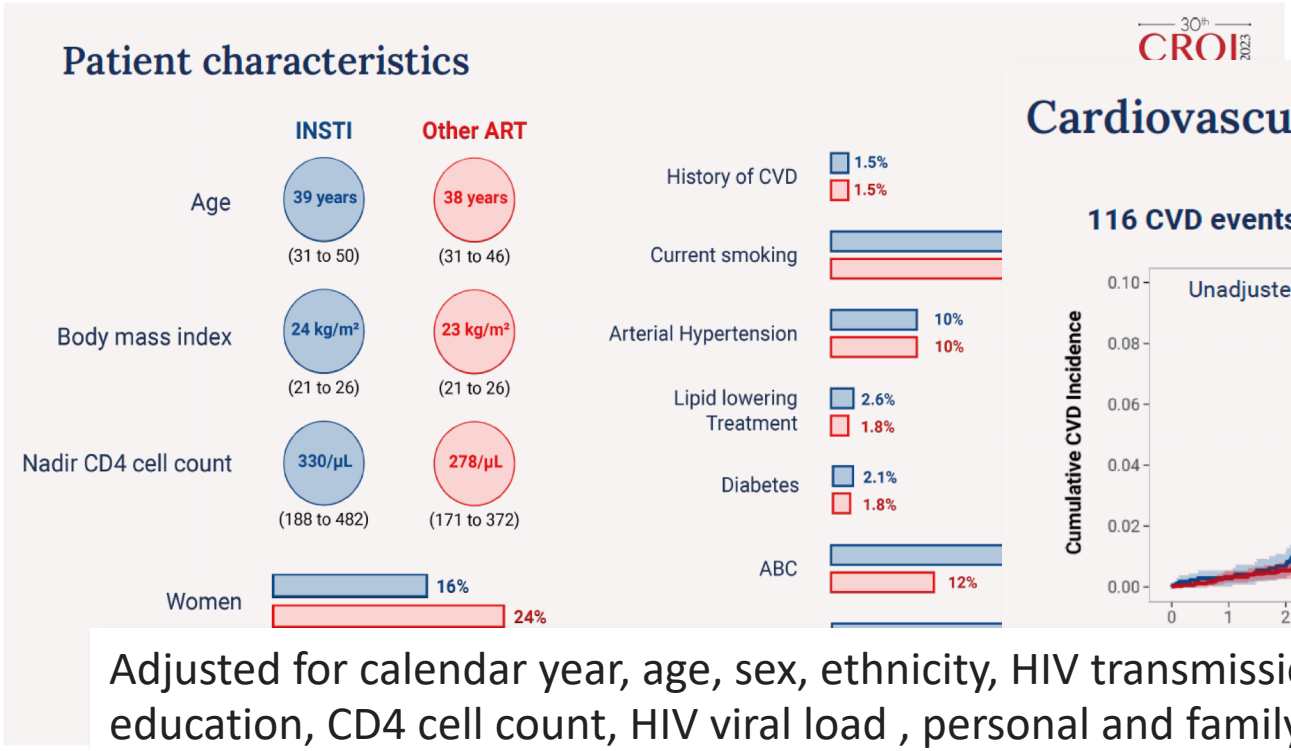
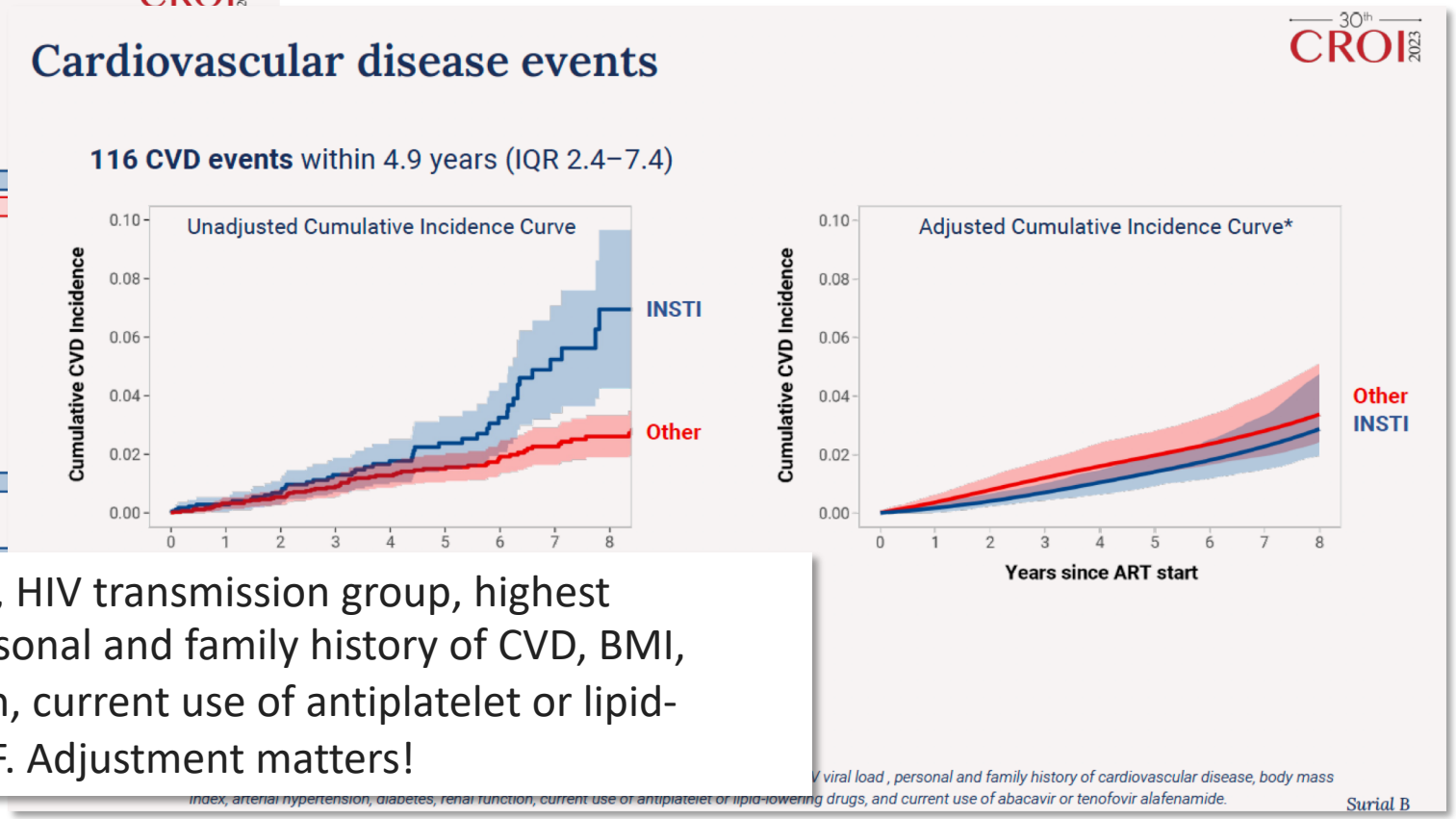




Adjusted for calendar year, age, sex, ethnicity, HIV transmission group, highest education, CD4 cell count, HIV viral load , personal and family history of CVD, BMI, arterial hypertension, diabetes, renal function, current use of antiplatelet or lipid-lowering drugs, and current use of ABC or TAF. Adjustment matters!

Integrase Inhibitors at CROI 2023

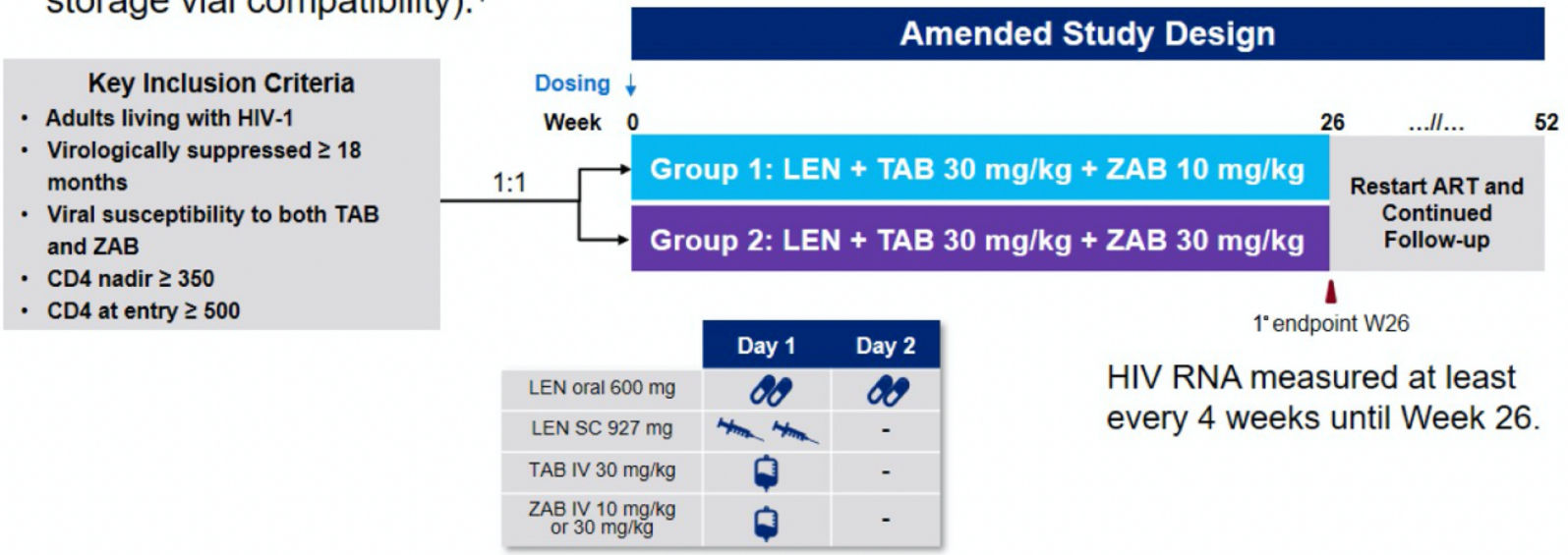
- Weight changes are complicated to study.
  - Clear: TDF and EFV suppress weight
  - Less Clear: Role of INSTI +/- TAF directly on weight change but recent data suggest less impact than commonly perceived
  - Weight changes are reversible

- When controlling for confounders, no association between INSTI and CVD

Lenacapavir at CROI 2023

- Super Long-Acting injectable ART (capsid inhibitor)
- Every 6-month subcutaneous injection
- FDA approved for use in people who are heavily treatment experienced

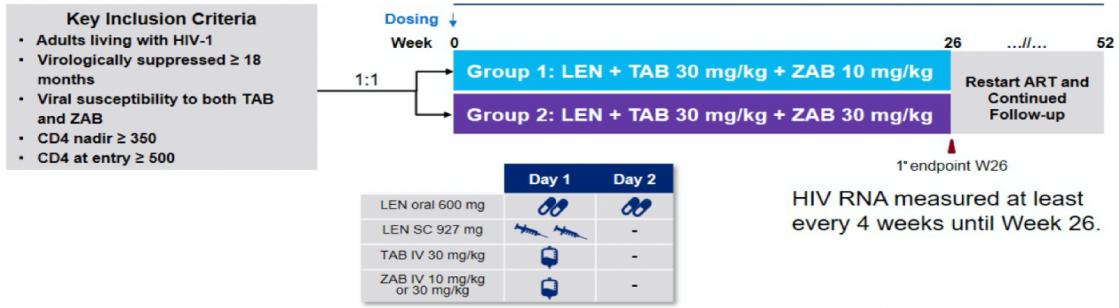
- Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses. (NCT04811040)
- Study design was modified when LEN was unavailable due to temporary clinical hold (for storage vial compatibility).[1]



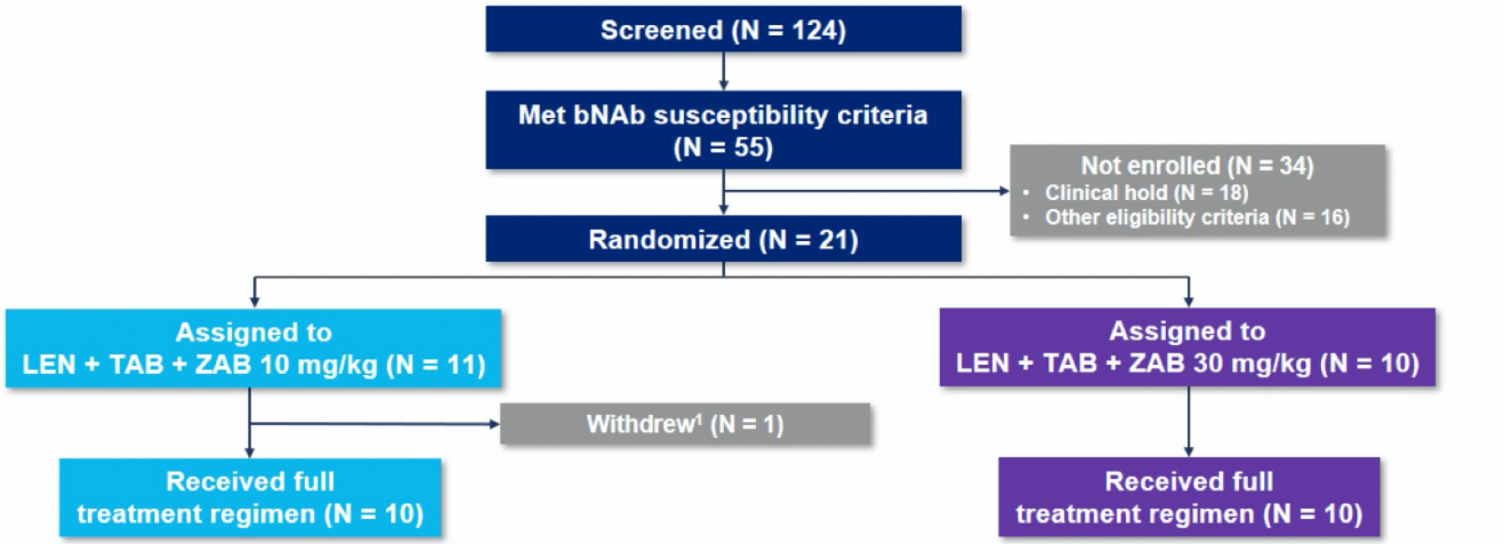
Eron. CROI 2023

[1] FDA lifts clinical hold on investigational lenacapavir for the treatment and prevention of HIV. Press release. May 16, 2022.

Lenacapavir at CROI 2023



Participant Disposition

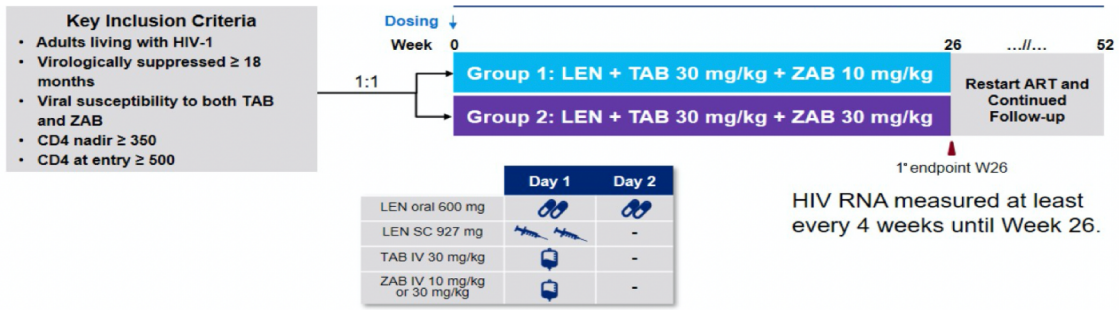


- All randomized participants were included in the safety analysis (N = 21); those who received the complete study regimens (oral LEN, SC LEN, and bNAbs) are included in the efficacy analyses (N = 20).

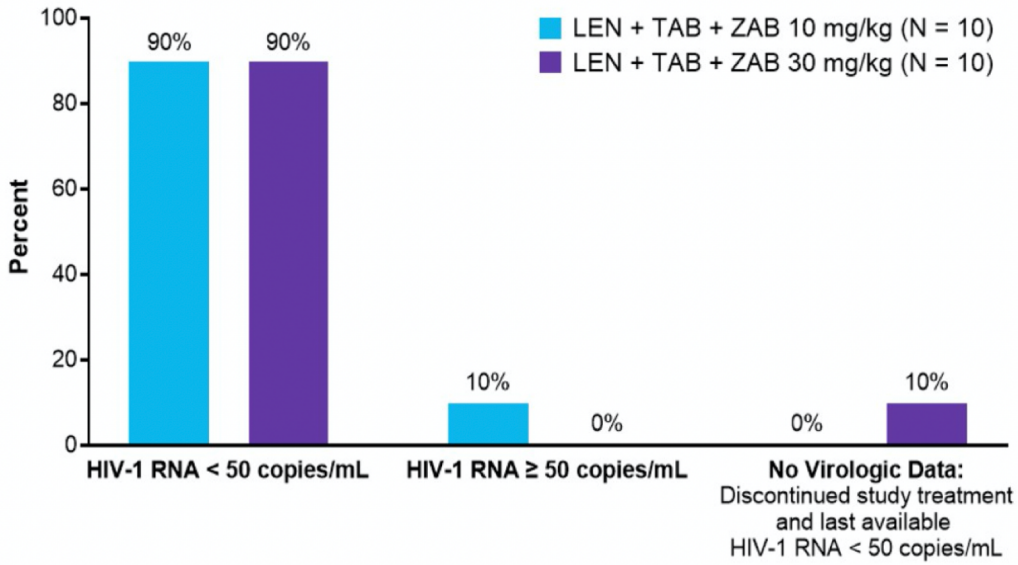
[1] Participant received oral LEN and then withdrew consent prior to injections or infusions; they continued their baseline ART and are included in the safety analyses.

Eron. CROI 2023

Lenacapavir at CROI 2023

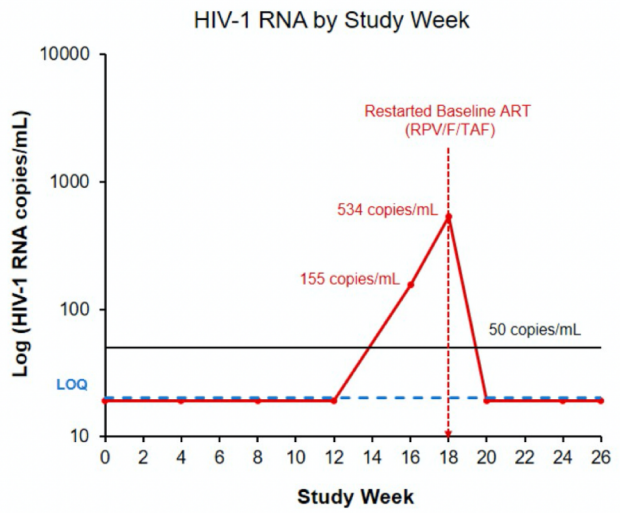


Virologic Efficacy Outcomes at Week 26 by FDA Snapshot Algorithm



- 18 out of 20 part maintained viral suppression on s regimen through
- One participant v at Week 12 with RNA < 50 copies
- One participant h confirmed virolog rebound at Week was resuppresse baseline oral AR

HIV-1 RNA by Study Week in Participant with Viral Rebound



- Rebound participant had baseline phenotypic susceptibility to teropavimab and zinlirvimab, and no pre-existing LEN resistance mutations were detected.
  - Resistance testing of rebound samples resulted in assay failure.
- Participant's CD4 count remained above 500 through Week 26.

The limit of quantification (LOQ) is 20 copies/mL. For the rebound participant, except for Weeks 16 and 18, HIV-1 RNA levels were < 20 copies/mL.

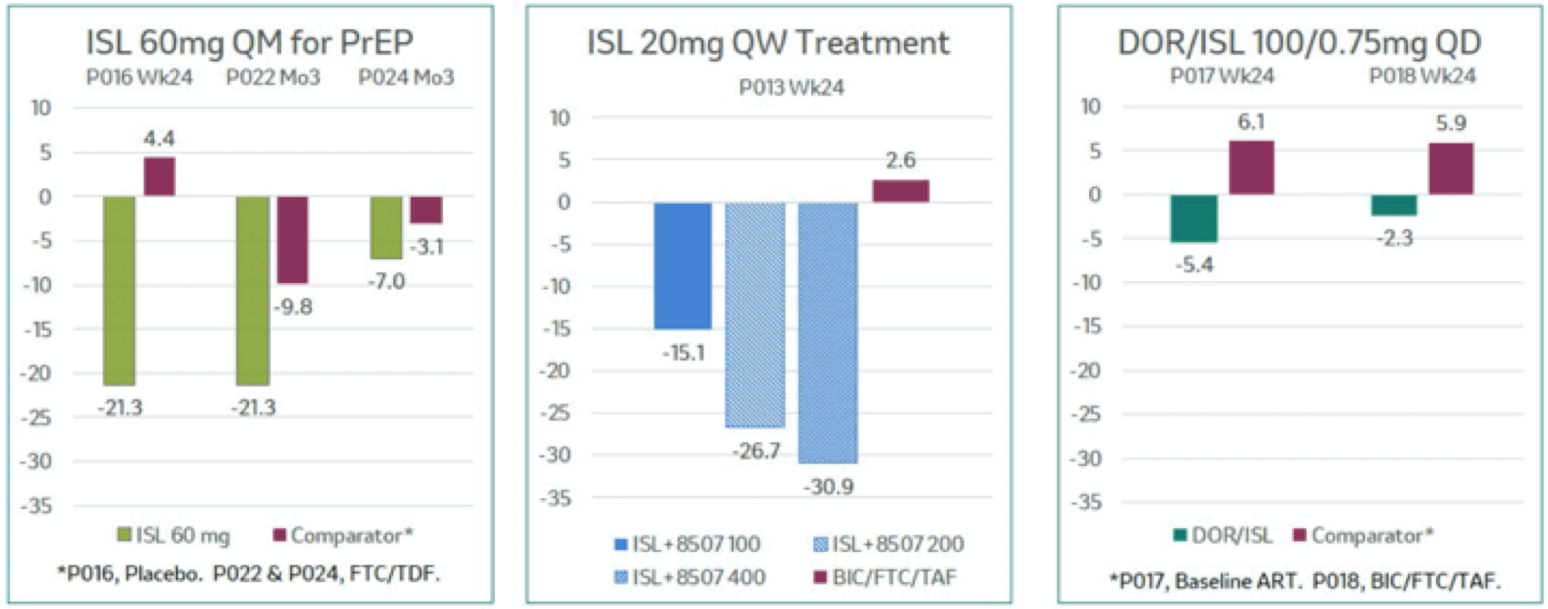
[1] Participant withdrew due to personal decision.

Eron. CROI 2023

Islatravir at CROI 2023

- NRTTI that can be take taken orally
- Long half life -> daily, weekly administration (implant?)
- But, suppression of lymphocytes, including CD4+ cells, observed during later phase study leading to FDA clinical pause

Initial Observations:
Total Lymphocyte Count, Mean % Change from Baseline



Squires. CROI 2023

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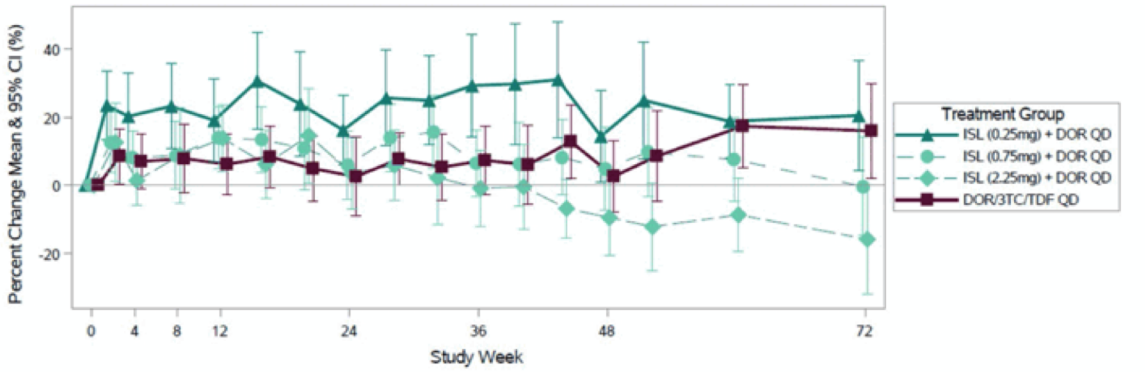
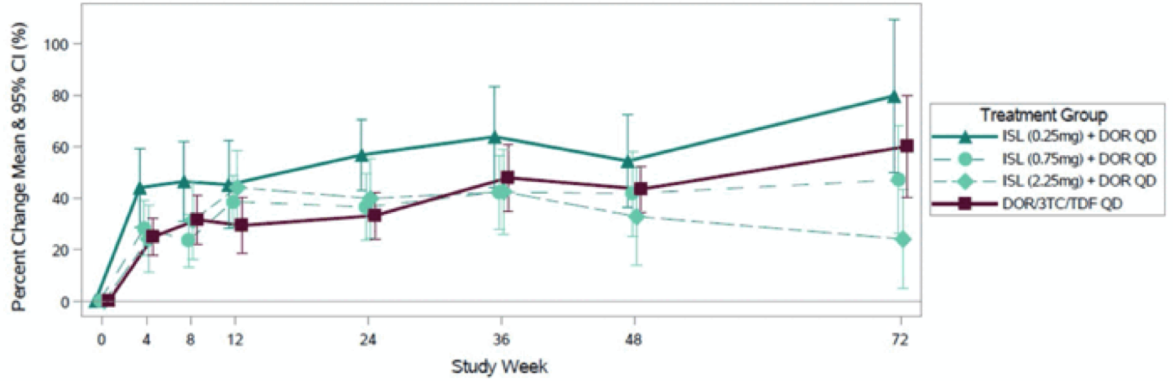
Phase 2b ISL Dose-Ranging Study (MK8591-011)
Total Lymphocyte Count, through Week 72



- Exposure-related decreases in total lymphocyte counts were observed in the ISL 0.75-mg and 2.25-mg groups
- Effects on total lymphocyte counts were comparable for the ISL 0.25-mg group and the DOR/3TC/TDF group

Phase 2b ISL Dose-Ranging Study (MK8591-011)
CD4+ T-Cell Count, through Week 72



- Mean increases from baseline in CD4+ T-cell count were similar for the ISL 0.25-mg and DOR/3TC/TDF groups through Week 72, with smaller mean increases observed for the ISL 0.75- and 2.25-mg groups

Plans:
ISL/Doravirine 0.25/100mg PO daily
ISL 2mg + Lenacaprivir 300 mg PO weekly

Squires. CROI 2023

Lenacapavir and Islatravir at CROI 2023

- LEN:
  - Proof of concept for every 6-month therapy (which is kind of amazing)
  - Longer term follow-up of participants in treatment naïve and heavily experienced trials supportive of early findings. Additional metabolic data needed.
- ISL:
  - Sweet spot for dosing may be the exposure achieved with 0.25mg daily PO.
  - Additional studies now underway.

HIV PrEP at CROI 2023

- Current options in US:
  - Oral TAF/FTC
  - Oral TDF/FTC
  - IM CAB + RPV
- US PrEP use 2013-2022
  - IQVIA database

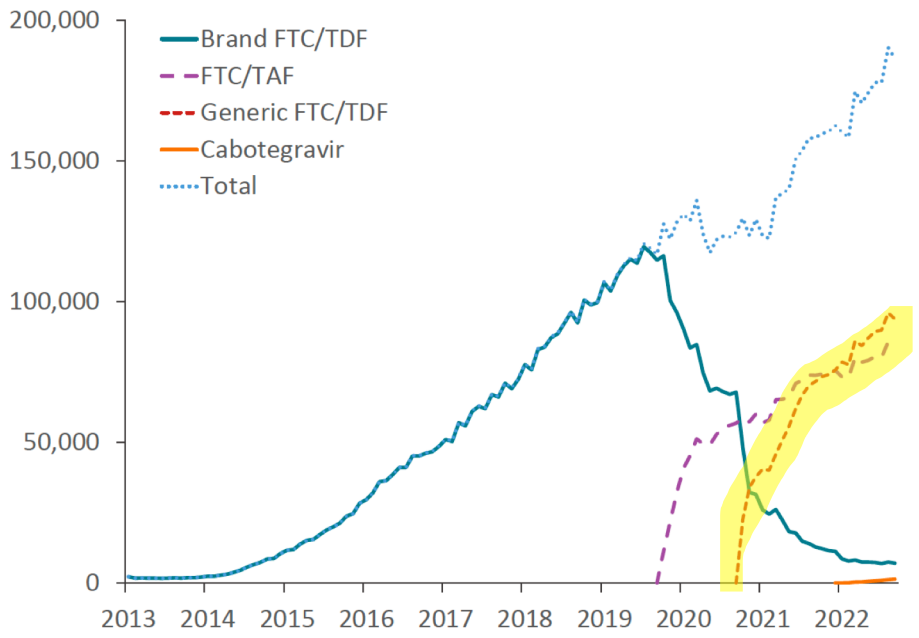


Figure. Persons prescribed PrEP by type of PrEP drug, IQVIA Real-World Data — Longitudinal Prescription Database — United States, January 2013 through September 2022

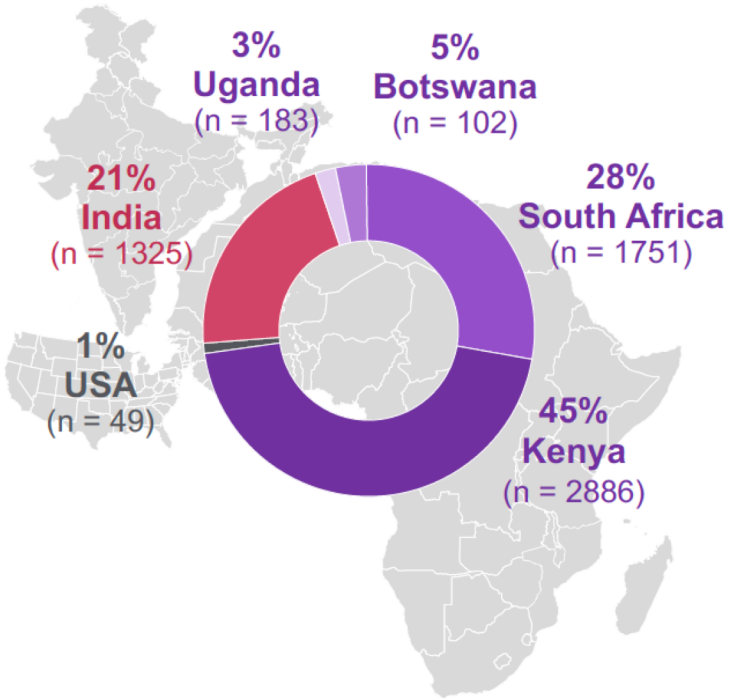
Zhu. CROI 2023

Results

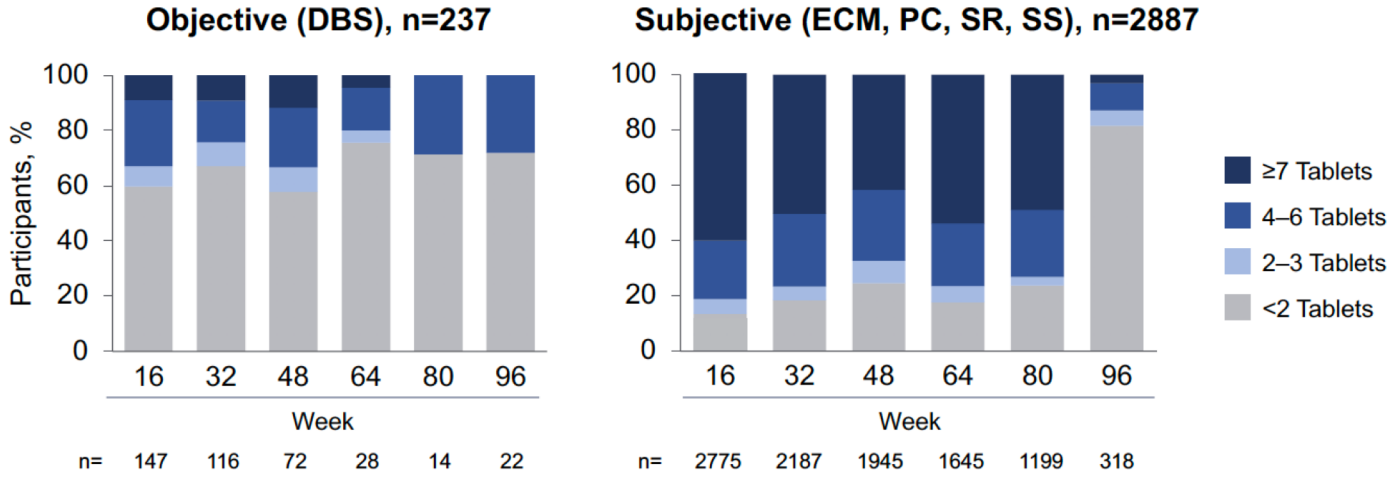
- In September 2022, 186,367 persons were prescribed PrEP
  - Generic FTC/TDF: 93,808 (50.3%)
  - FTC/TAF: 84,141 (45.1%)
  - Brand FTC/TDF: 7,065 (3.8%)
  - CAB-LA: 1,353 (0.5%)
- From January 2022 through August 2022
  - 1,951 persons picked up CAB-LA prescription
  - 1,638 (84.0%) received a prescription for a second dose within one month of the first prescription

HIV PrEP at CROI 2023

- Oral TDF/FTC PrEP Adherence in Cis-Woman
- 8 years of data from 11 demonstration projects
- N = 6,296
  - 2,995 with adherence data
  - Objective: DBS, plasma
  - Subjective: electronic caps, pill count, self-report



Cross-sectional Objective and Subjective Adherence by Visit (n = 2955)



- By both measures, overall adherence declined over time
- Higher adherence reported with subjective vs objective measures

DBS, dried blood spot; ECM, electronic pill cap-monitoring; PC, pill-counts; SR, self-report; SS, study-reported adherence scale.

Marrazzo. CROI 2023

HIV PrEP at CROI 2023

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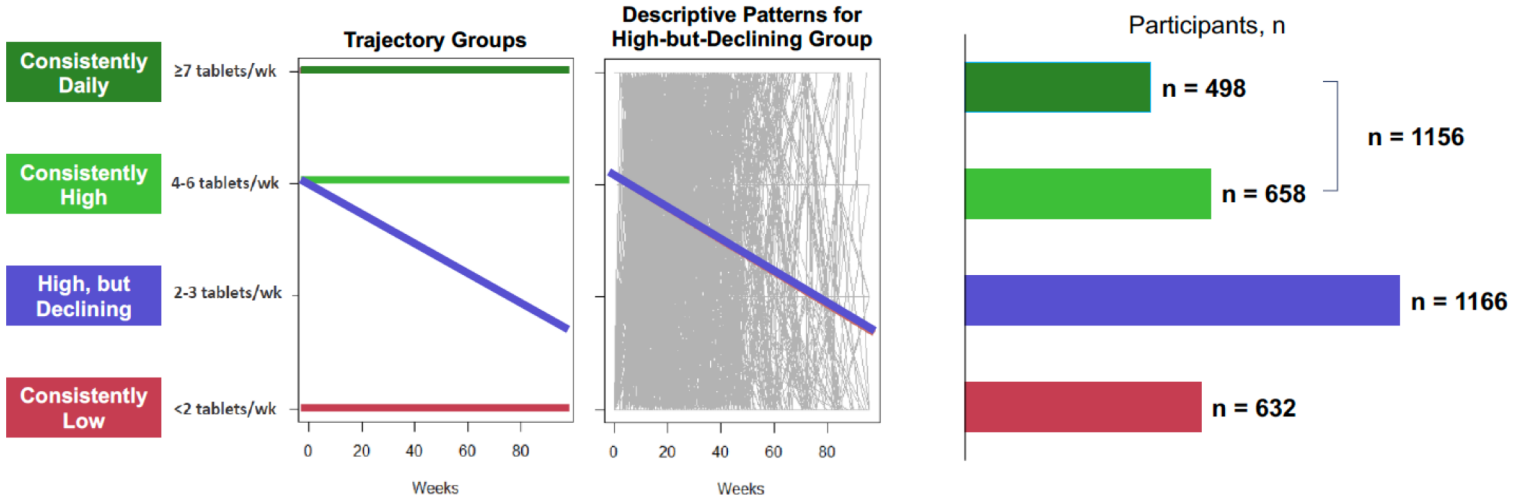
Longitudinal Patterns of Adherence By Group-based Trajectory



- Group-based trajectory modeling shows four groups with distinct patterns of adherence
- Three groups had stable adherence over time, regardless of model used
- One group had dynamic adherence over time – initially high then declined

Marrazzo. CROI 2023

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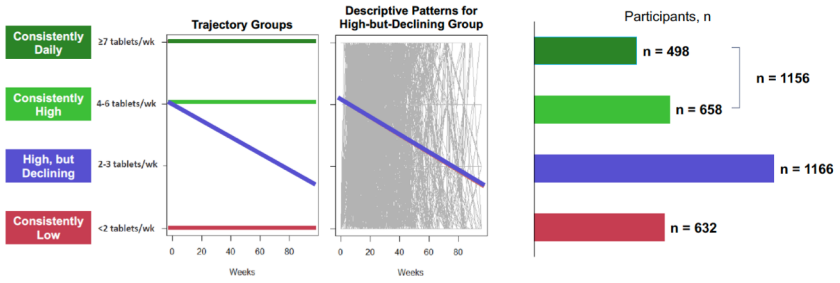

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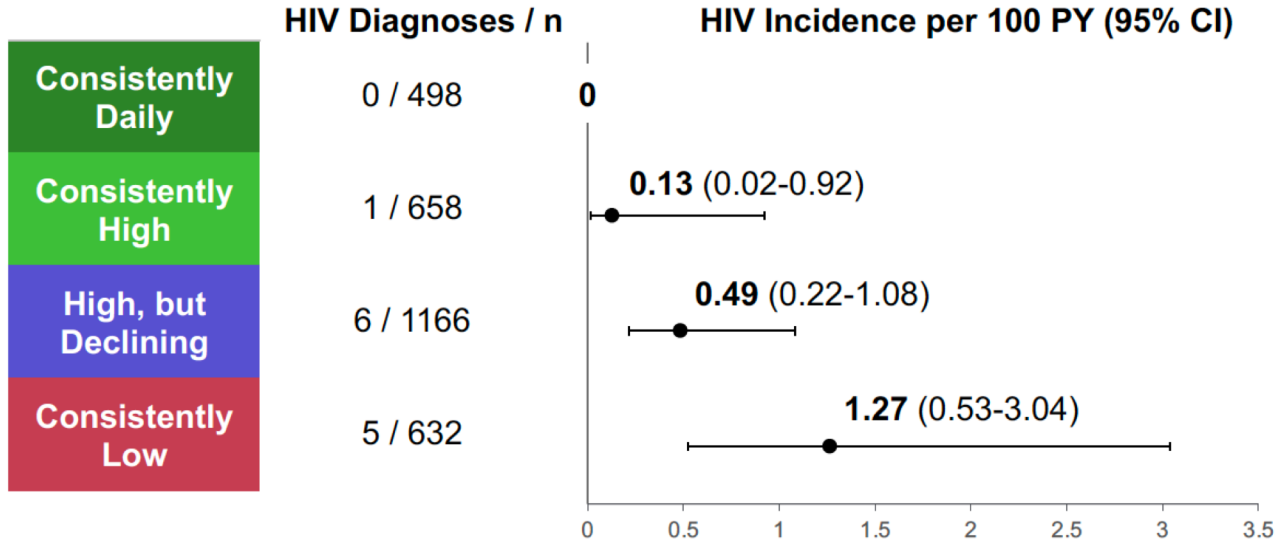
HIV Incidence Rates Among Women with Available Adherence Data (n = 2955)



- Even with low incidence overall, higher patterns of adherence were directly associated with lower risk of HIV acquisition

Calculated by Poisson regression.

Marrazzo. CROI 2023

HIV PrEP at CROI 2023

HPTN 083 Trial of CAB IM vs TDF/FTC PO PrEP in MSM and TGW

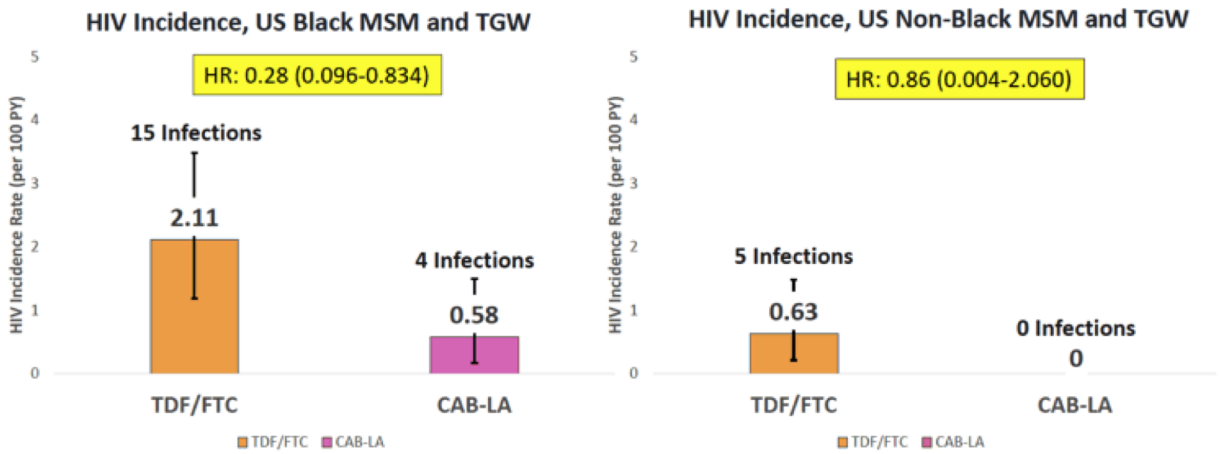
- Examination of efficacy by race in US participants
- N = 1,698
  - 49.7% self identified as Black

Baseline HIV Risk Factors

Behavioral*	Overall N=1,495	US Black N=771	US Non-Black N=722
Sex Partners in past month, median (IQR)	2 (1-4)	2 (1-3)	2 (1-4)
Number of receptive anal acts, median (IQR)	1 (0-3)	1 (0-3)	1 (0-4)
Injected drugs in the past 6 months	18 (1.2%)	10 (1.3%)	8 (1.1%)
Any recreational drugs in the past 6 months	1,006 (67.3%)	481 (62.4%)	524 (72.6%)
AUDIT –C ≥ 4	617 (41.3%)	250 (32.4%)	366 (50.7%)
Prevalent STIs	**Overall N=1,698**	**US Black N=844**	**US Non-Black N=852**
Active Syphilis	50 (3.0%)	38 (4.0%)	16 (1.9%)
Rectal Gonorrhea	77 (4.6%)	48 (5.7%)	29 (3.4%)
Rectal Chlamydia	139 (8.2%)	74 (8.8%)	65 (7.7%)
Urine Gonorrhea	12 (0.7%)	9 (1.1%)	3 (0.4%)
Urine Chlamydia	33 (2.0%)	19 (2.3%)	14 (1.7%)

*Behavioral data includes data from 1,495 completed baseline CASI

HIV Incidence and Efficacy



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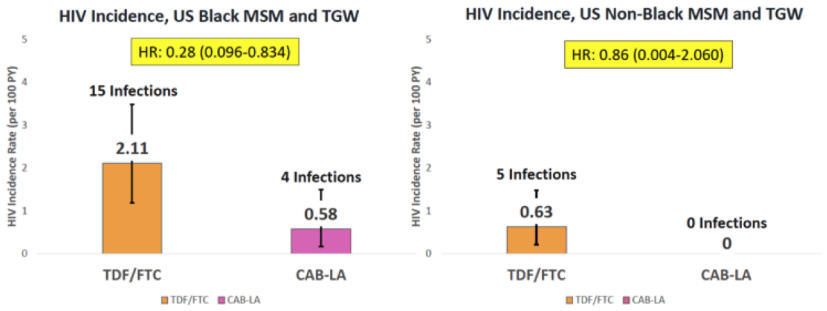
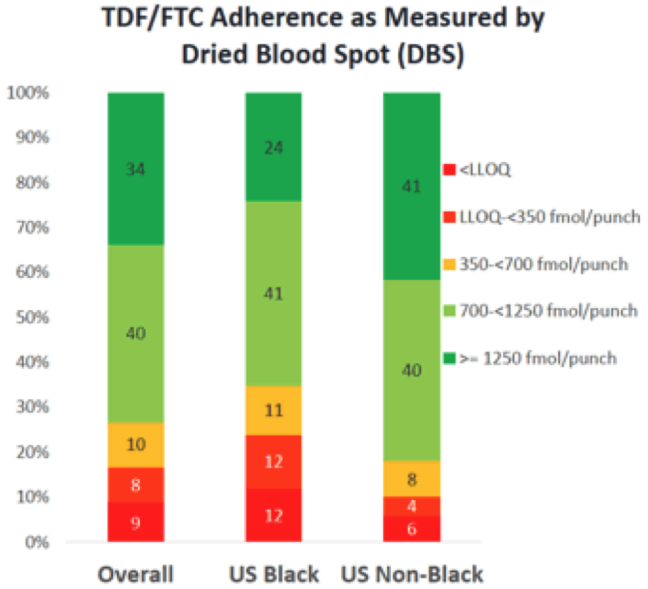
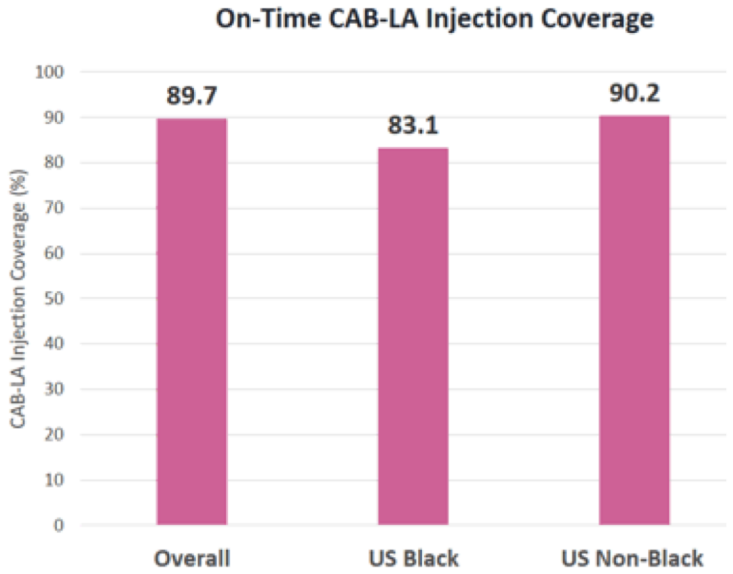


TDF/FTC and CAB-LA Adherence





Hanscom. CROI 2023

Use of a Single-Genome Sequencing INSTI Genotyping Assay in HPTN 083

- Data from HIV infections occurring during HPTN 083 showed CAB suppresses viral replication and delays Ab production[1]
- Failure of Ab/Ag tests to detect infection resulted in:
  - Treatment initiation delay
  - Emergence of INSTI RAMs
- 7 participants in HPTN 083 received LA CAB after HIV infection; 5 had INSTI resistance; 2 had no genotyping results because HIV-1 RNA <500 c/mL at all visits[1]
- A single-genome sequencing of samples in which HIV-1 RNA was detected by a qualitative assay was done in order to determine whether earlier detection of HIV could find evidence of infection prior to the appearance of INSTI RAMS[2]
  - 21 samples from these 7 individuals tested with qualitative RNA assay (LLOD: 30 c/mL)
  - INSTI RAMs assessed with Stanford HIV Resistance Database

1. Marzinke. J Infect Dis. 2021;224:1581. 2. Eshleman. CROI 2022. Abstr 95.

Use of a Single-Genome Sequencing INSTI Genotyping Assay in HPTN 083: Results

- In 6 of 7 participants, major INSTI RAMs were first detected in samples with HIV-1 RNA <500 c/mL
  - **Screening with an HIV-1 RNA assay would have detected infection before a major INSTI RAM (4 cases) or accumulation of additional major INSTI RAMs (2 cases)**
- Investigators conclude that use of a **sensitive RNA assay** for HIV screening in the setting of LA CAB for PrEP could improve earlier detection of infection, earlier ART initiation, and reduce risk of developing INSTI resistance
  - Owing to its high efficacy, LA CAB PrEP should still be considered in settings where HIV-1 RNA screening is not readily available

Eshleman. CROI 2022. Abstr 95.

HIV PrEP at CROI 2023

HPTN 083 Trial of CAB IM vs TDF/FTC PO PrEP in MSM and TGW

- Examination of detection of HIV infection in breakthrough cases
- Long-acting Early Viral Inhibition Syndrome (LEVI)

HPTN 083 – CAB arm HIV infections

6 infections occurred despite on-time injections among 2,282 participants randomized to CAB-LA

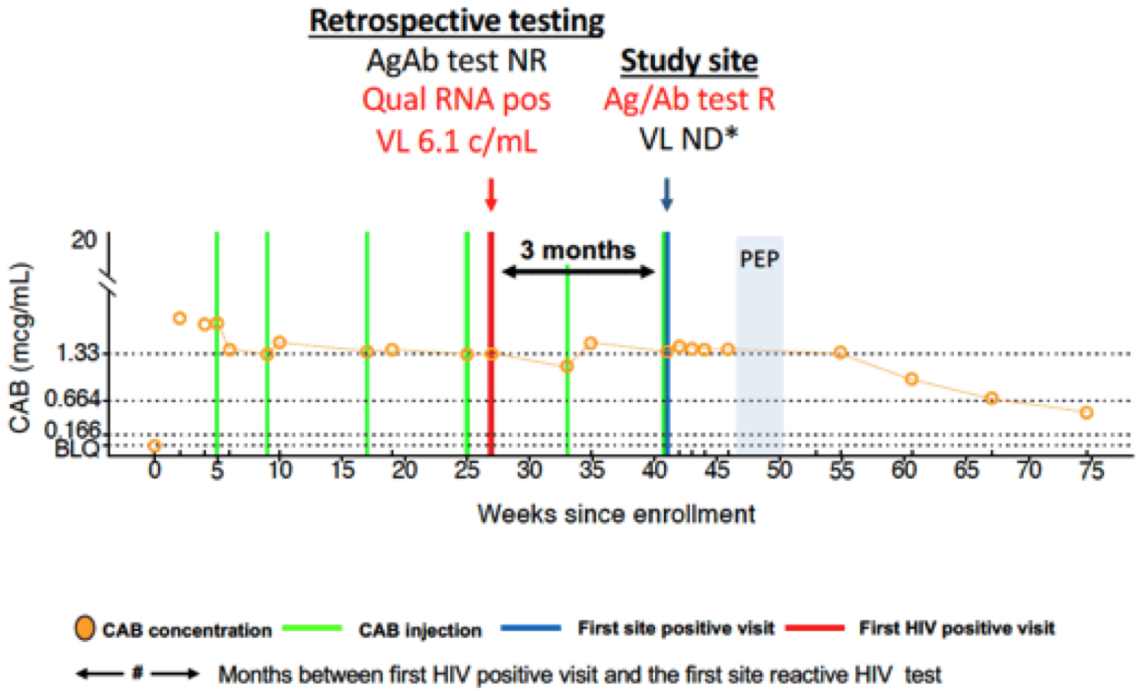
Type of case	# Cases
Infected despite on-time injections	**6**
28 other infections	
No recent CAB exposure (within 6 months)	16
HIV+ at enrollment	4
Infected while receiving oral CAB	3
Infected after ≥ 1 delayed injection	3
Infected near the time of CAB re-initiation	2

Delayed detection of HIV infection

- HIV rapid tests and Ag/Ab tests often fail to detect HIV infection in the setting of CAB-LA PrEP
- Viral suppression and delayed/diminished Ab expression can persist for months after infection, even after injections are discontinued

Delayed detection of HIV infection
→ Unnecessary CAB-LA injections
→ Delayed ART initiation
→ Potential to impact personal health or on-going HIV transmission
→ Emergence of INSTI resistance

- In HPTN 083, detection of infection was delayed in ~½ of the CAB arm infections
- This was rarely observed when infection occurred > 6 months after CAB administration



*LLOQ: 20 c/mL

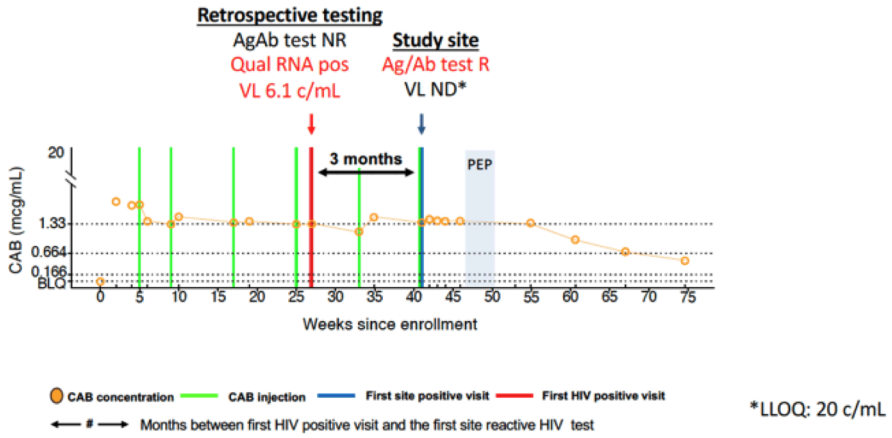
Eshleman. CROI 2023

HIV PrEP at CROI 2023

US Public Health Service

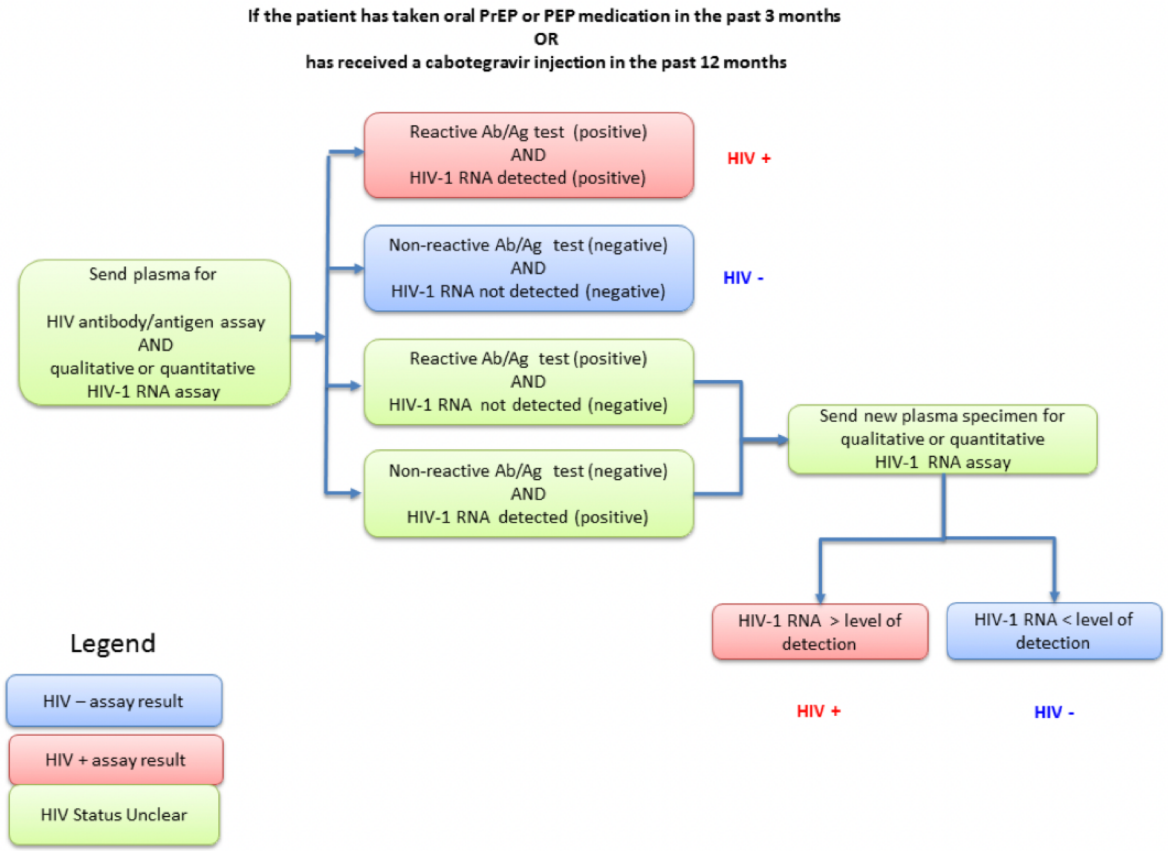
PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE

A CLINICAL PRACTICE GUIDELINE



*LLOQ: 20 c/mL

Eshleman. CROI 2023



COVID at CROI 2023

Who is at risk of getting very sick?

Retrospective cohort study of persons testing positive for SARS-CoV-2 in the UNC Health system, 1 July 2021 - 31 May 2022

Study site	Integrated health care system in North Carolina	• 16 hospitals • >900 clinics
Data source	UNC Health electronic health record system	• SARS-CoV-2 diagnostic test results • Demographic information • ICD-10 diagnosis codes • Vaccinations • Medications • Hospital admission & discharge dates
Study population	UNC Health patients	• ≥18 years of age • Positive SARS-CoV-2 PCR result

Henderson. CROI 2023

COVID at CROI 2023

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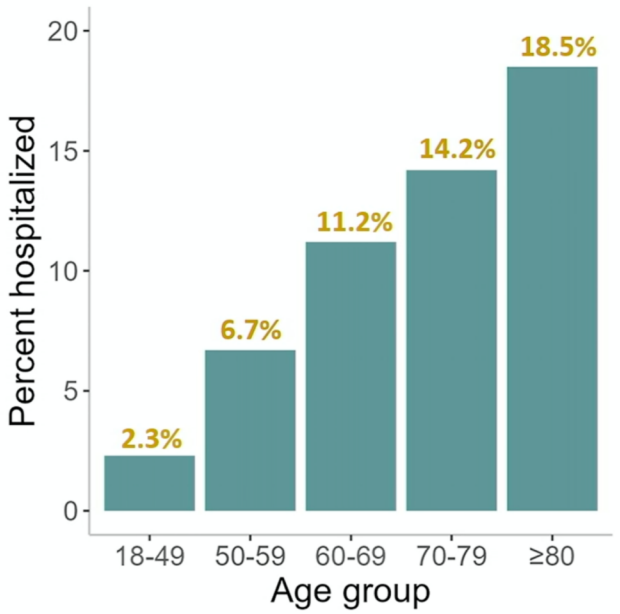
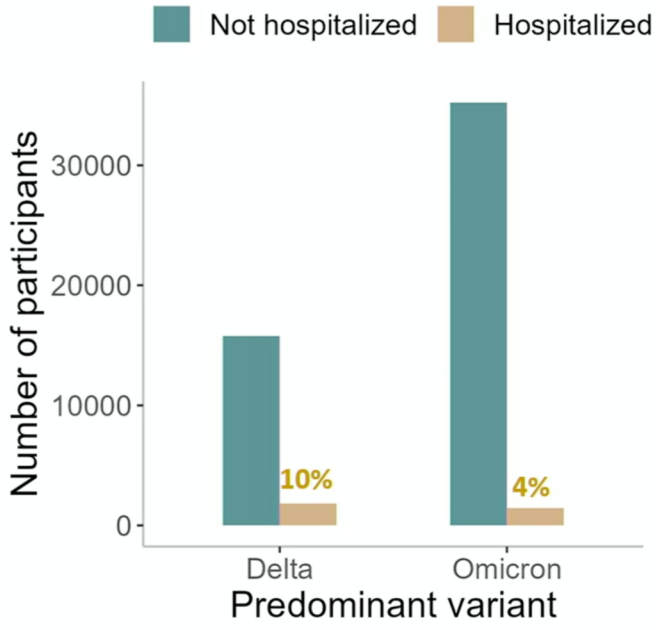
Study population	UNC Health patients	• ≥18 years of age • Positive SARS-CoV-2 PCR result

134

N = 54,256; 41% male
6% were hospitalized with COVID-19 as a primary diagnosis





Henderson. CROI 2023

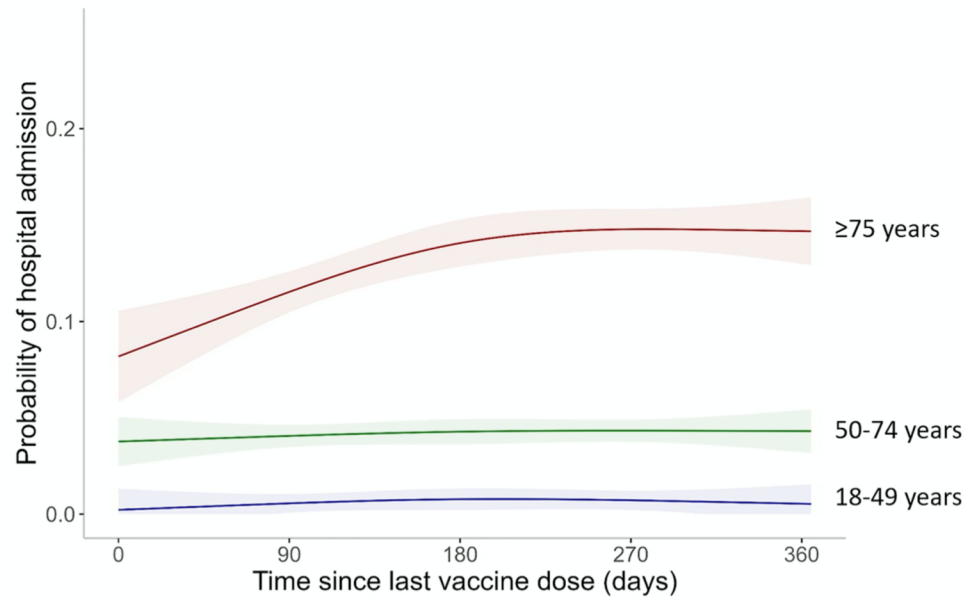
71% relative reduction in risk with ≥3 doses

Vaccine doses	N	Hospitalized (%)	Age-adjusted RR
0	37,289	2,694 (7.2)	1.
1	2,136	72 (3.4)	0.46 (0.36-0.58)
2	10,042	350 (3.5)	0.44 (0.39-0.49)
≥3	4,789	134 (3.0)	0.29 (0.24-0.34)

28% relative increase in risk after 180 days since the last vaccine dose

Days since last dose	N	Hospitalized (%)	Age-adjusted RR
≤90	3,904	115 (2.9)	1.
91-180	4,878	151 (3.1)	1.14 (0.90-1.46)
181-270	4,581	149 (3.3)	1.28 (1.00-1.63)
>270	3,604	150 (4.2)	1.24 (0.98-1.59)

Risk increased with time since last vaccine in older participants



Henderson. CROI 2023

70% relative risk reduction with casirivimab/imdevimab & 98% reduction with nirmatrelvir/ritonavir

12% of participants received outpatient therapy

Outpatient therapy	N	Hospitalized (%)	Age-adjusted RR
None	47,783	3,130 (6.6)	1.
Bamlanivimab-etesevimab	417	10 (2.4)	0.25 (0.13-0.44)
Bebtelovimab	226	2 (0.9)	0.07 (0.01-0.20)
Casirivimab/imdevimab	3,524	100 (2.8)	0.30 (0.25-0.37)
Molnupiravir	327	4 (1.2)	0.12 (0.04-0.27)
Nirmatrelvir/ritonavir	1,307	2 (0.2)	0.02 (0.004-0.05)
Remdesivir	78	1 (1.3)	0.14 (0.01-0.61)
Sotrovimab	642	10 (1.6)	0.13 (0.06-0.23)

144

Outpatient therapy	N	Hospitalized (%)	Age-adjusted RR
Casirivimab/imdevimab	3,524	100 (2.8)	0.30 (0.25-0.37)
Nirmatrelvir/ritonavir	1,307	2 (0.2)	0.02 (0.004-0.05)

Casirivimab/imdevimab in use from beginning of study until 11 Jan 2022
Nirmatrelvir/ritonavir in use from 1 Jan 2022 until end of study period

Henderson. CROI 2023

COVID at CROI 2023

Who benefits from treatment?

US data, N=699,848, April-September 2022, ≥50 years or ≥18 with underlying condition, 69% 2+ mRNA vaccine doses

% prescribed NMV/r	Adjusted hazard ratio (95% C) for COVID hospitalization within 30 days of diagnosis by age group		Events per 100,000 person-days	
			Treated	Untreated
28.4%	18-49 yrs		6.99	11.68
			7.90	20.10
		0.53 (0.48-0.58)	29.72	68.80

Most socially vulnerable least likely to be prescribed NMV/r

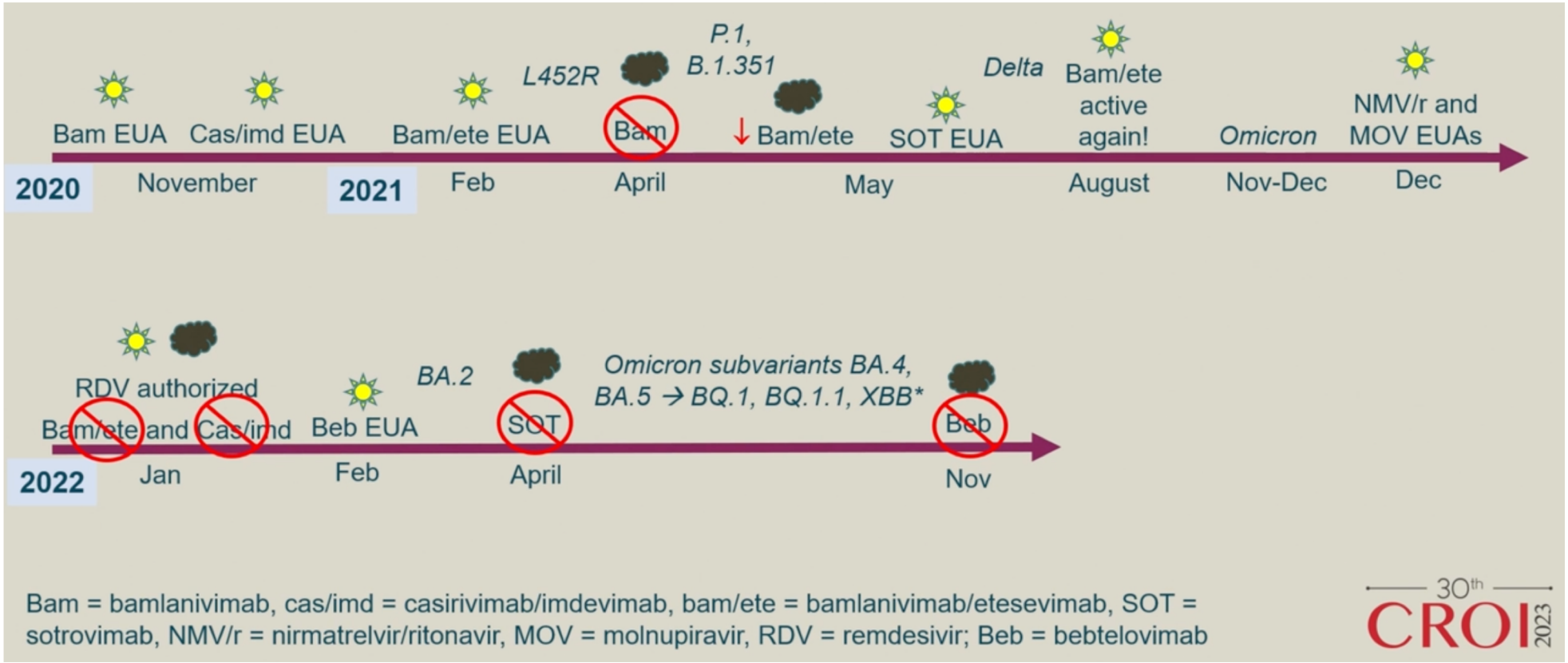
Drive by those with underlying conditions

Treat: Older, younger with multiple comorbidities, unvaccinated/under-vaccinated, immunocompromised. Improve access for the most vulnerable/at risk.

Shaw. MMWR 2022. Chew. CROI 2023

COVID at CROI 2023

The rise and fall of monoclonal antibodies for the treatment of COVID-19



Chew. CROI 2023

Current treatment options in non-hospitalized adults for prevention of hospitalization/death

Recommended	Major limitations	Use in pregnancy
Nirmatrelvir/ritonavir (NMV/r)	Drug-drug interactions, advanced kidney and liver disease, dysgeusia	✓
Remdesivir (RDV)	IV x 3 days, advanced kidney disease	✓

Alternative	Major limitations	Use in pregnancy
Molnupiravir (MOV)	Lower efficacy, concern for mutagenicity, bone and cartilage risk <18	✗

- Placebo-controlled efficacy trials: pre-Omicron, unvaccinated
- Eligible: high risk for progression to severe COVID-19 – *who is high risk today?*
- Positive test no longer required if COVID-19 suspected

K Chew. CROI 2023

Hammond, NEJM 2022; Kuriakose Abstract 515 (NMV/r DDIs); Gottlieb, NEJM 2022; Jayk Bernal, NEJM 2022; NIH COVID-19 Treatment Guidelines, www.covid19treatmentguidelines.nih.gov

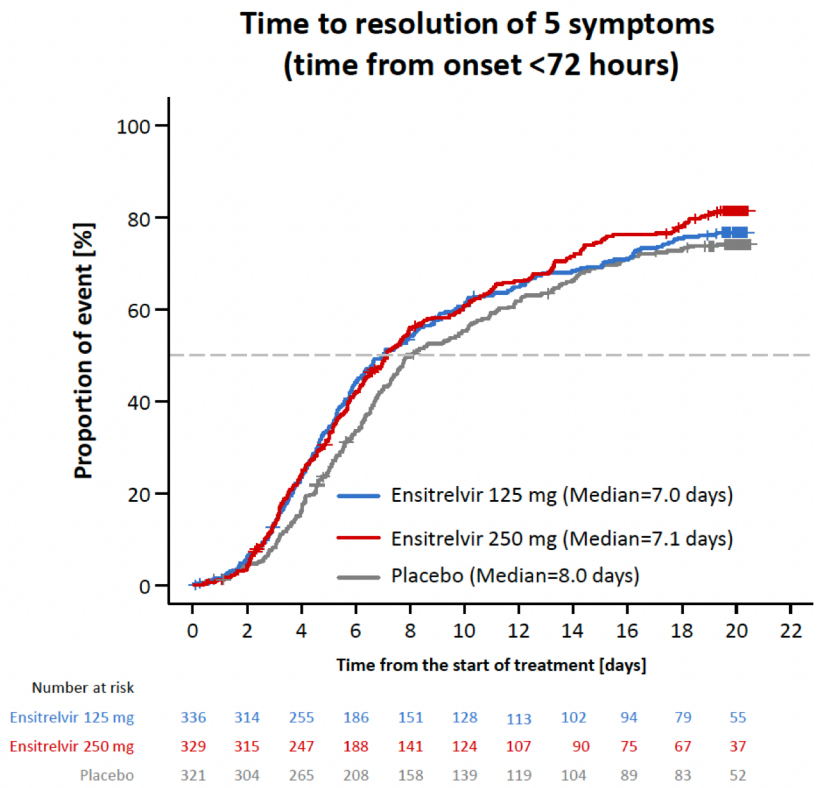
COVID at CROI 2023

Ensitrelvir (SCORPIO-SR)

- SARS-CoV-2 protease inhibitor, no booster, once daily, 42-48h half-life
- Phase 3 RCT, Japan/Asia, Feb-Nov 2022 (early Omicron)
- Mixed risk, >90% vaccinated, within 72h of symptoms (primary)
- Ensitrelvir once daily × 5 days vs blinded placebo

	COVID-19 onset to randomization: <72hr (Primary analysis)		
	Ensitrelvir 125 mg (n=347)	Ensitrelvir 250 mg (n=340)	Placebo group (n=343)
Kaplan-Meier estimator (time)			
Median [95% CI]	167.9 [145.0, 197.6]	171.2 [150.8, 190.3]	192.2 [174.5, 238.3]
Difference from placebo group [95% CI]	**-24.3** [-78.7, 11.7]	-21.0 [-73.8, 7.2]	---
Stratified Peto-Prentice's generalized Wilcoxon test [a]			
p-value (two-tailed)	**0.0407**	0.0203	---

Analysis in the intention-to-treat population (all cases confirmed positive for SARS-CoV-2 viral RNA at baseline) with any of 5 symptoms at baseline
CI = Confidence Interval, 5 Symptoms: stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness
[a] Adjusted for SARS-CoV-2 vaccination with or without vaccination.



Ichihashi. CROI 2023

COVID at CROI 2023

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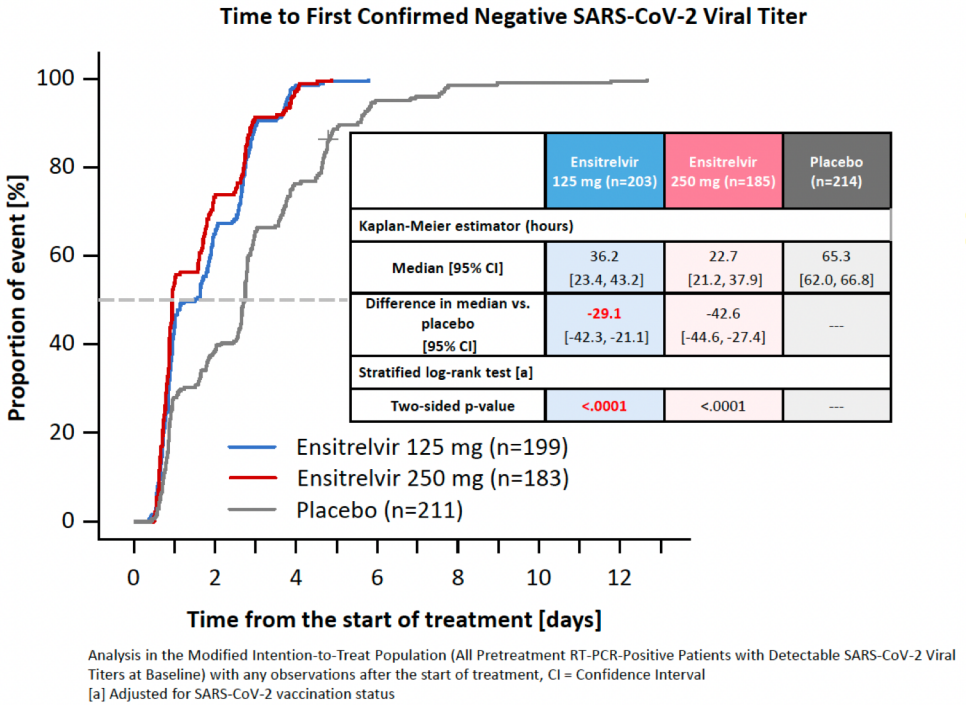
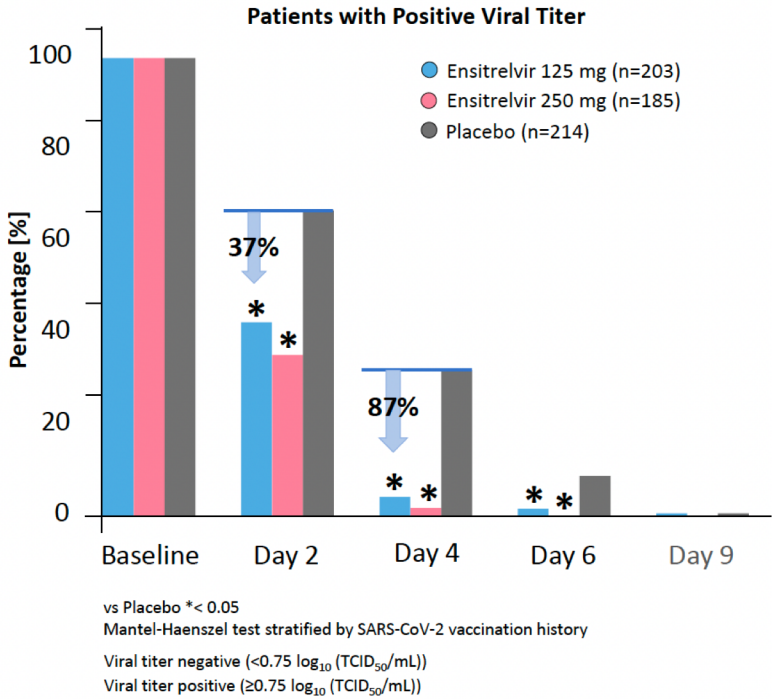
Ensitrelvir 125 mg shorten the time to cessation of SARS-CoV-2 viral shedding by 29 hours (median) compared with placebo.
Ensitrelvir 125mg showed 87% reduction of patient with positive viral titer at Day 4 compared with placebo.



	Ensitrelvir 125 mg (n=203)	Ensitrelvir 250 mg (n=185)	Placebo (n=214)
Kaplan-Meier estimator (hours)			
Median [95% CI]	36.2 [23.4, 43.2]	22.7 [21.2, 37.9]	65.3 [62.0, 66.8]
Difference in median vs. placebo [95% CI]	-29.1 [-42.3, -21.1]	-42.6 [-44.6, -27.4]	---
Stratified log-rank test [a]			
Two-sided p-value	<.0001	<.0001	---

Analysis in the Modified Intention-to-Treat Population (All Pretreatment RT-PCR-Positive Patients with Detectable SARS-CoV-2 Viral Titers at Baseline) with any observations after the start of treatment, CI = Confidence Interval
[a] Adjusted for SARS-CoV-2 vaccination status



vs Placebo *< 0.05
Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history
Viral titer negative (<0.75 $\log_{10}$ ($TCID_{50}$/mL))
Viral titer positive (≥0.75 $\log_{10}$ ($TCID_{50}$/mL))

Ichihashi. CROI 2023

COVID at CROI 2023

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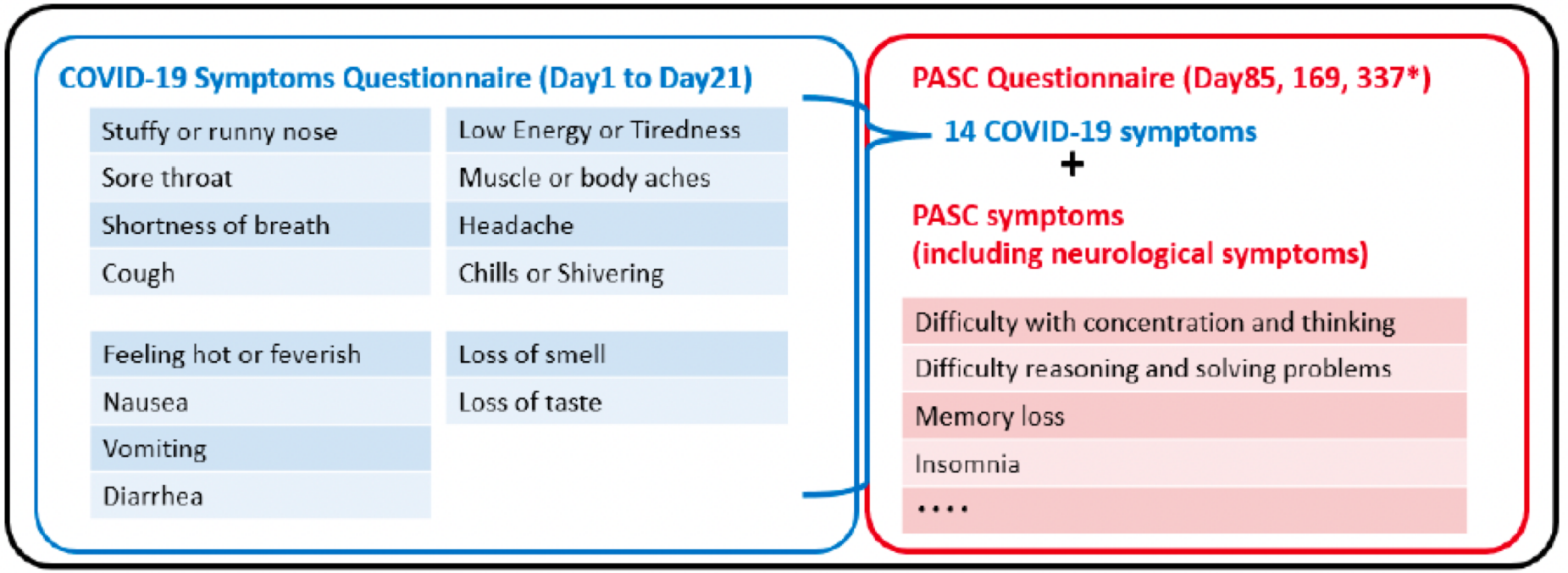
- Mixed risk, >90% vaccinated, within 72h of symptoms (primary)
- Ensitrelvir once daily × 5 days vs blinded placebo

Questionnaire at Day 85, 169 (already data available), Day 337 (data not yet available)



PASC= post-acute sequelae of SARS-CoV-2, *No data at Day 337 is available

Ichihashi. CROI 2023

COVID at CROI 2023

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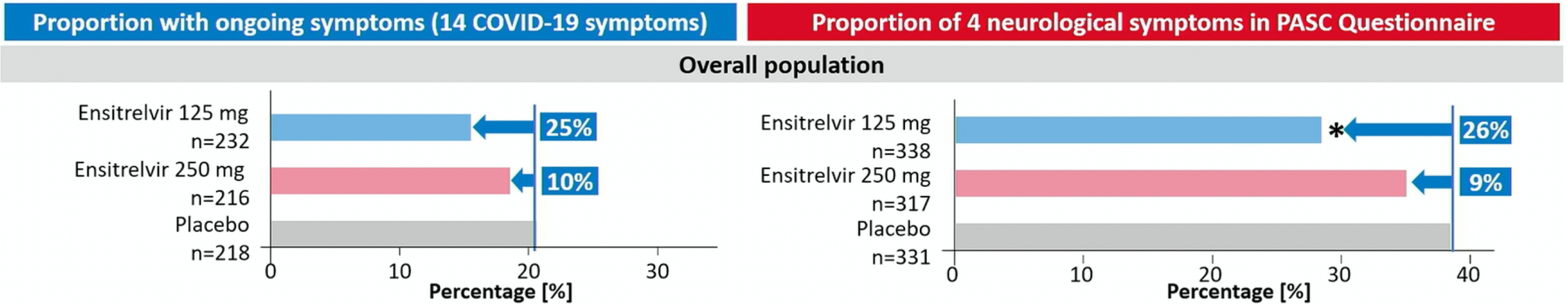
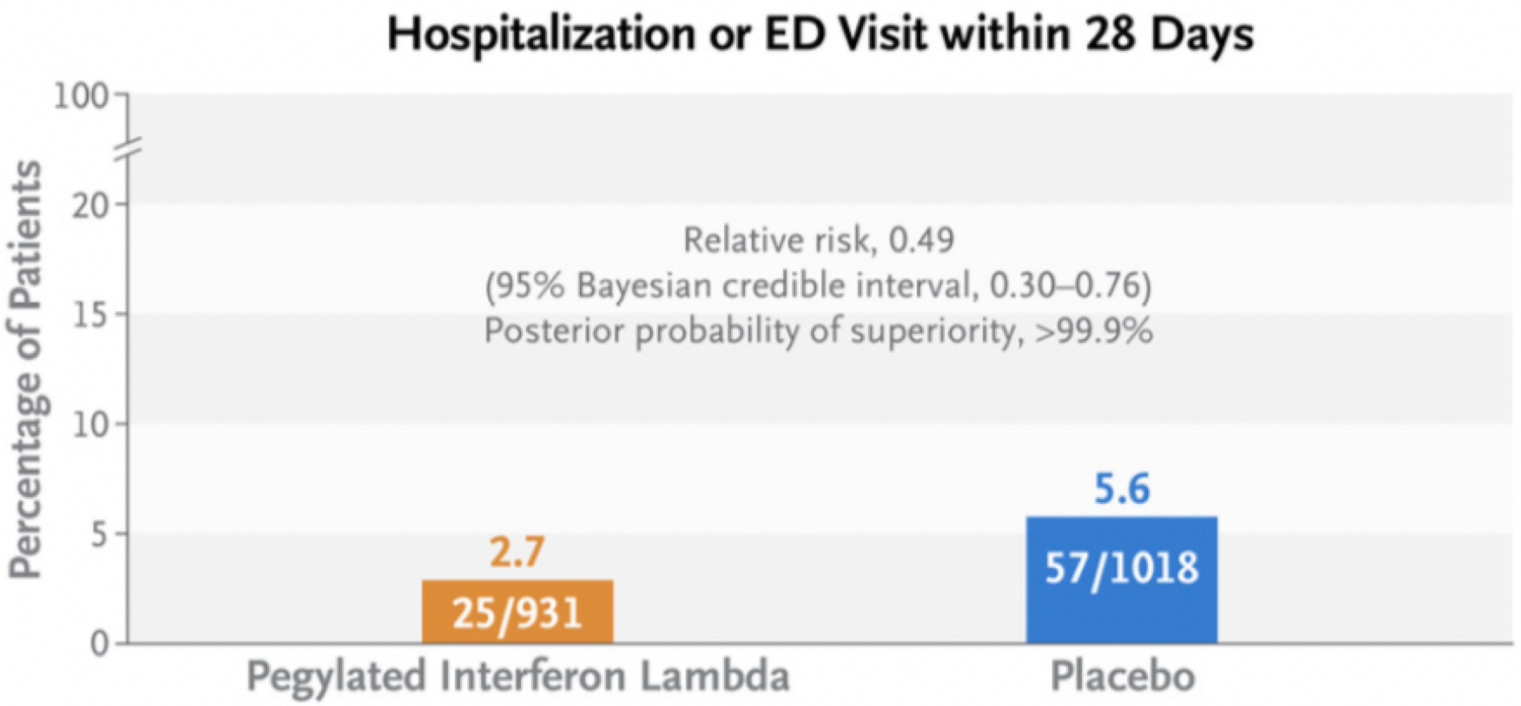


Ichihashi. CROI 2023

COVID at CROI 2023

Pegylated Interferon Lambda

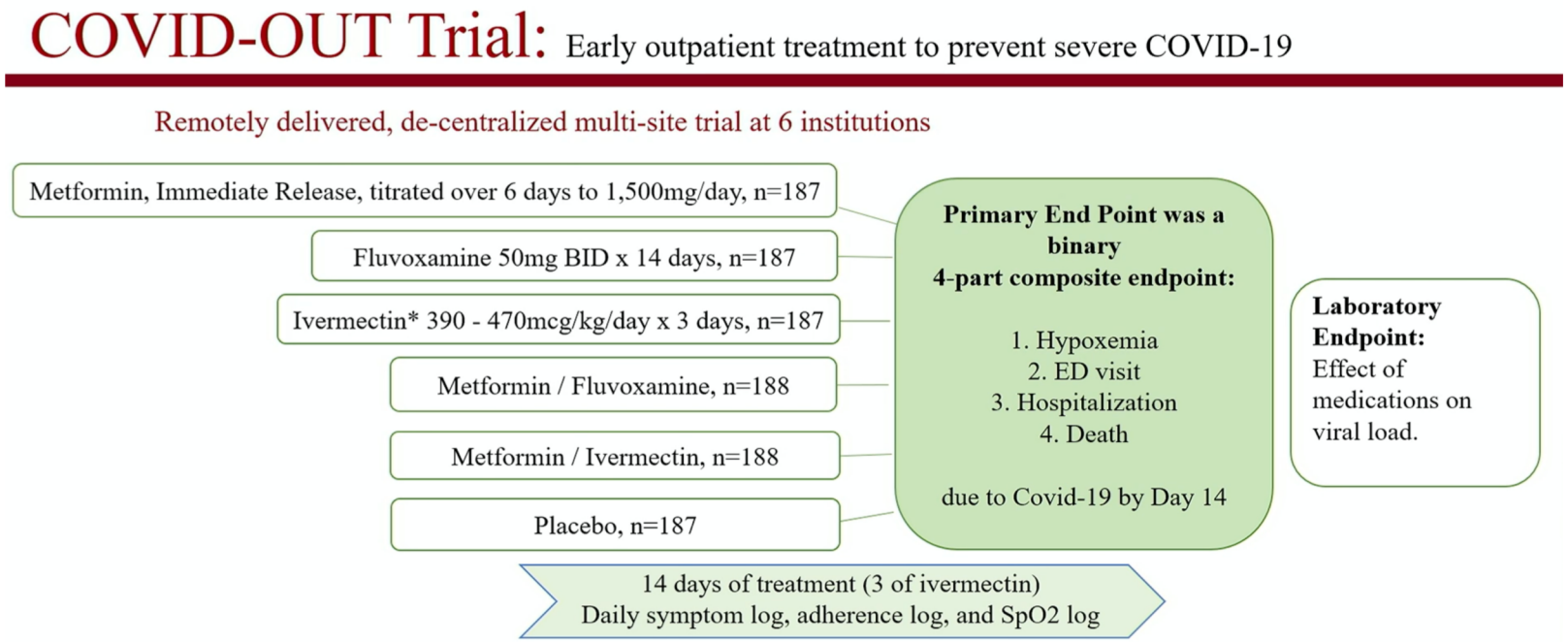
- Phase 3, Brazil and Canada
- June 2021-Feb 2022
- High-risk, within 7 days of symptoms, 83% vaccinated
- Interferon-lambda 180ug SC or blinded placebo
- Primary outcome: hospitalization (or transfer to tertiary hospital or ED visit (observation >6 hours) within 28 days



Reis. CROI 2023

COVID at CROI 2023

COVID-OUT Trial: Metformin



Key Inclusion/Exclusion criteria:

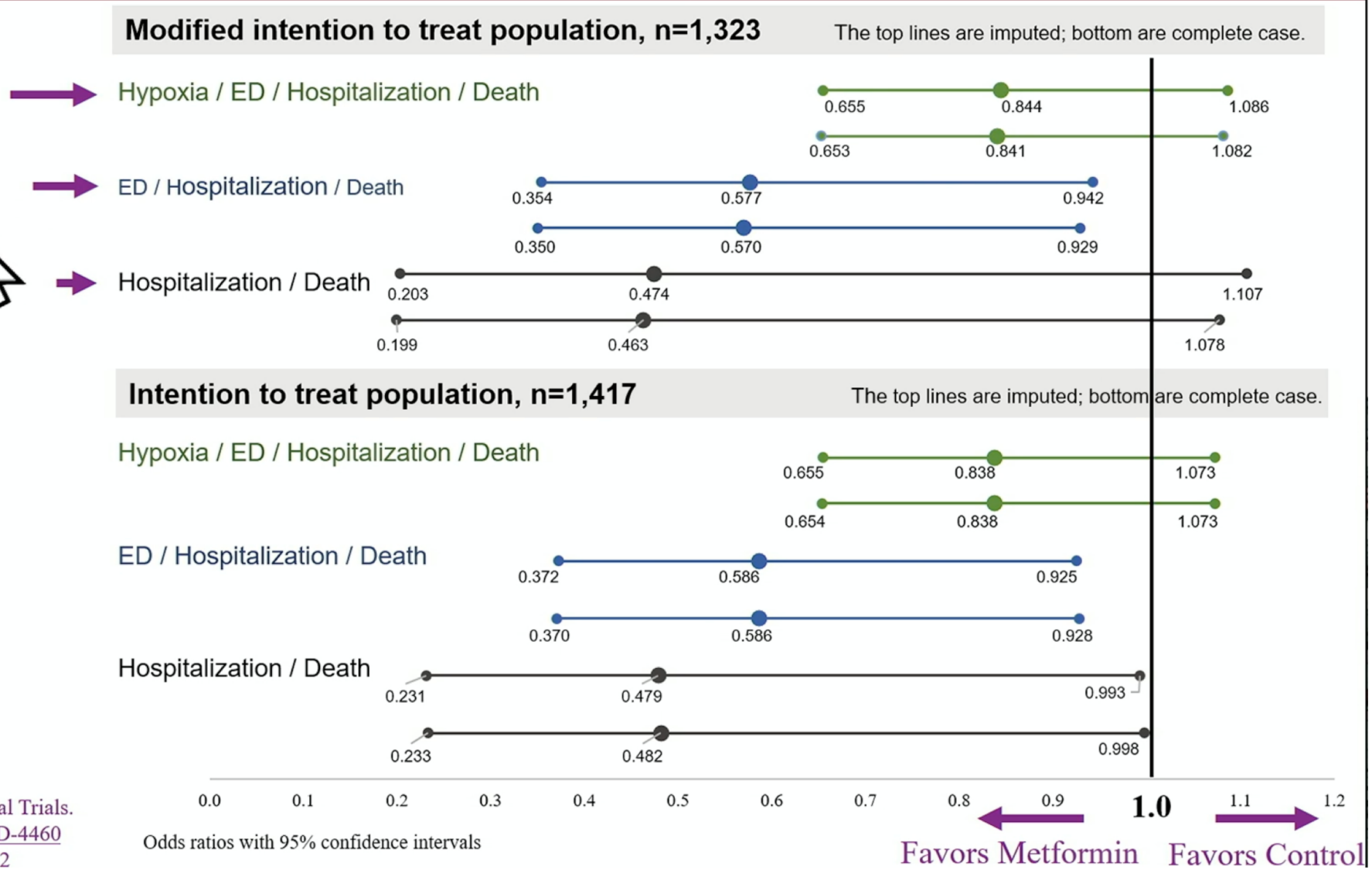
- Adults aged 30 – 85
- Confirmed +SARS-CoV-2 within 3 days, < 7 days of symptoms, No known prior infection with SARS-CoV-2
- Pregnancy not excluded
- Overweight or obesity

*6 weight categories.

Primary Outcome: Prevention of severe Covid-19 by Day 14.

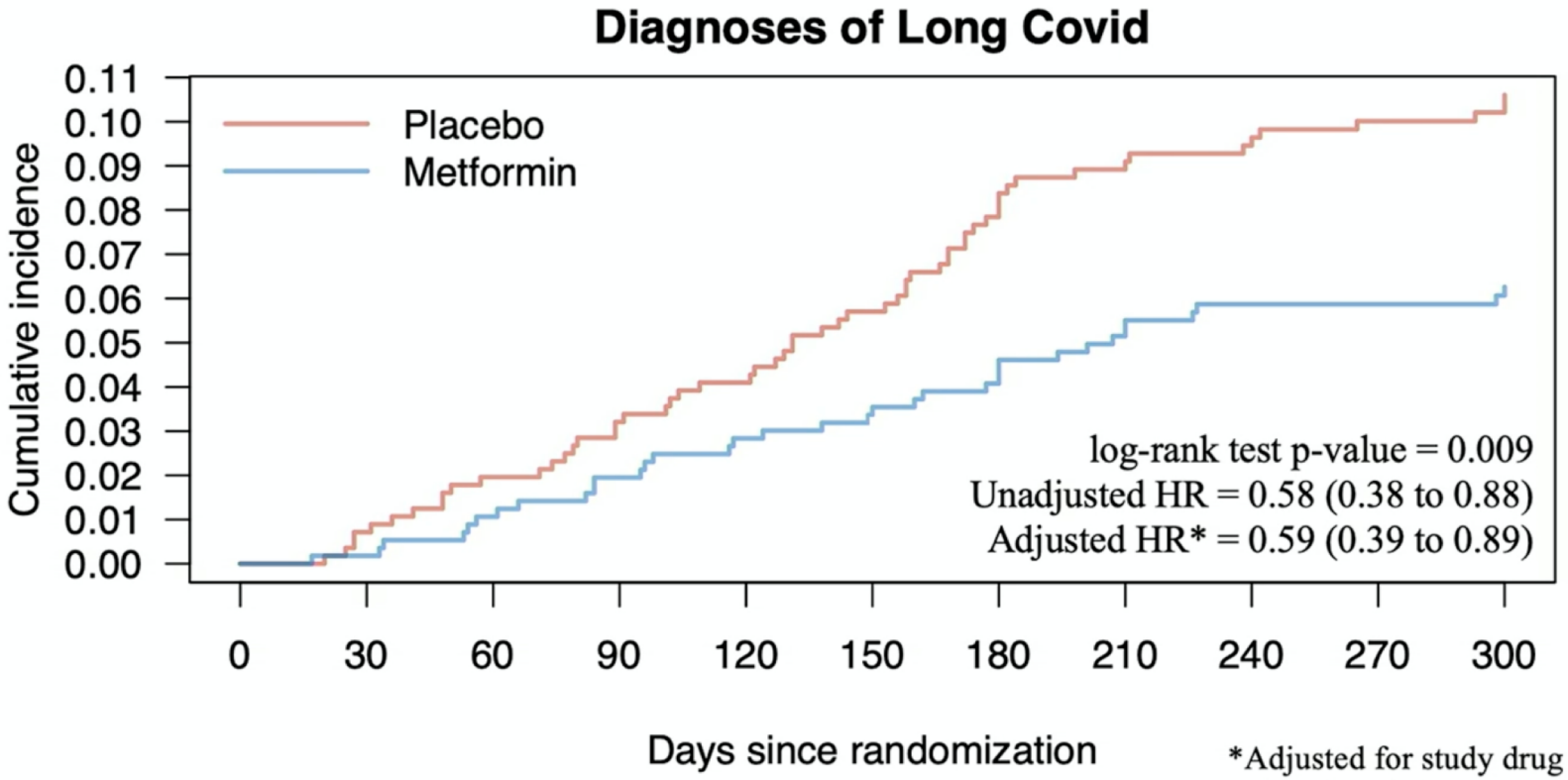
Binary, 4-part composite outcome

Sequentially remove components less associated with severe disease.[1]



1. FDA. Multiple Endpoints in Clinical Trials. 2017; January. Docket FDA-2016-D-4460
2. Bramante et al. *NEJM* Aug 18, 2022

Does metformin during acute Covid prevent Long Covid



*Adjusted for study drug and vaccination at baseline (primary and booster)

Number at risk

Placebo	561	557	550	543	538	529	517	506	497	479	455
Metformin	564	563	558	553	548	545	540	529	517	502	483

Number censored

Placebo	0	0	0	0	0	0	0	5	11	26	49
Metformin	0	0	0	0	0	0	1	6	14	29	47

Bramante et al, medrxiv.org

COVID at CROI 2023

What about rebound?

Popular Latest Newsletters *The Atlantic* Sign In Sub

Inside the Mind of an Anti-Paxxer

Paxlovid can be a lifesaving treatment for COVID. Why do so many patients turn it down?

By Rachel Gutman-Wei

Getty; Zuma Press, Inc. / Alamy; The Atlantic

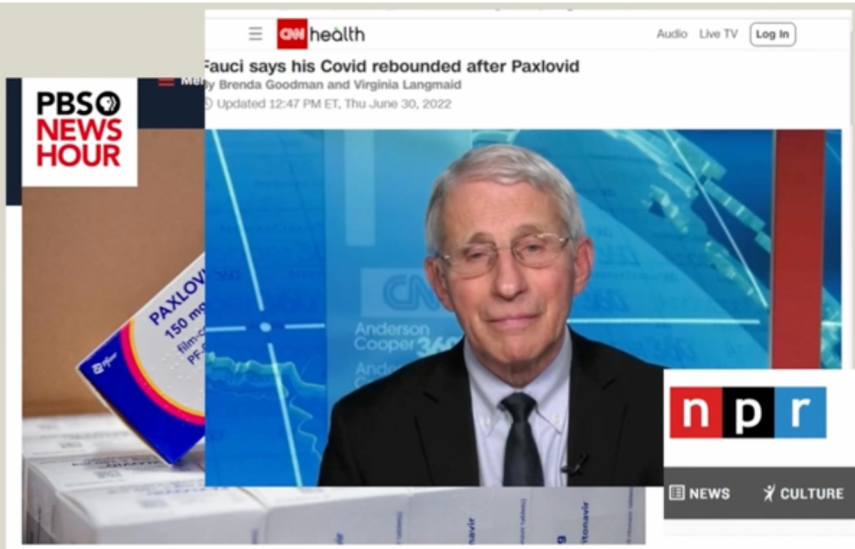
NOVEMBER 22, 2022 SHARE

CNN health Audio Live TV Log In

Fauci says his Covid rebounded after Paxlovid

By Brenda Goodman and Virginia Langmaid

Updated 12:47 PM ET, Thu June 30, 2022



Leave your feedback Share

By Edward Chen, STAT

Physicians say they need clearer guidance on prescribing Paxlovid amid concerns around COVID-19 rebound

As reports of 'Paxlovid rebound' increase, Covid researchers scramble for answers

By Jason Mast May 24, 2022

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POLITICS

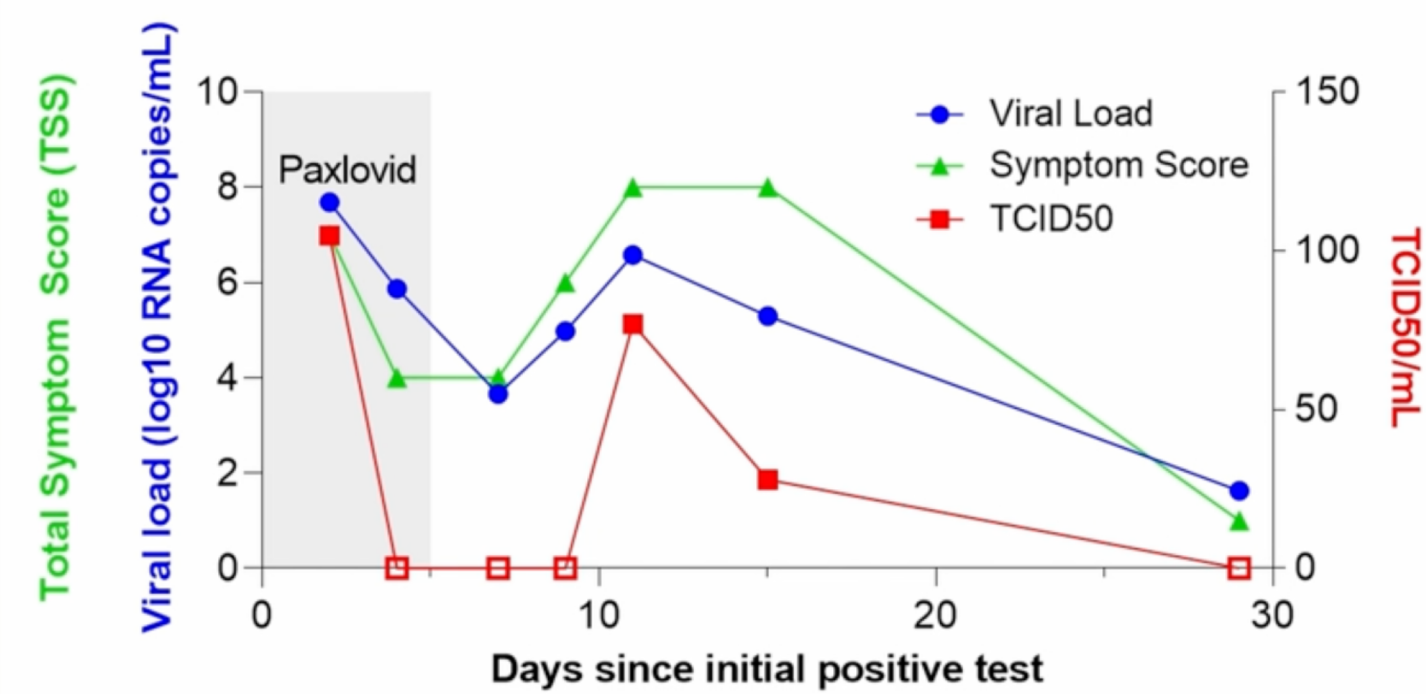
Biden tested positive for COVID again after taking Paxlovid. That was a known risk

Updated July 30, 2022 · 5:31 PM ET

BILL CHAPPELL

COVID at CROI 2023

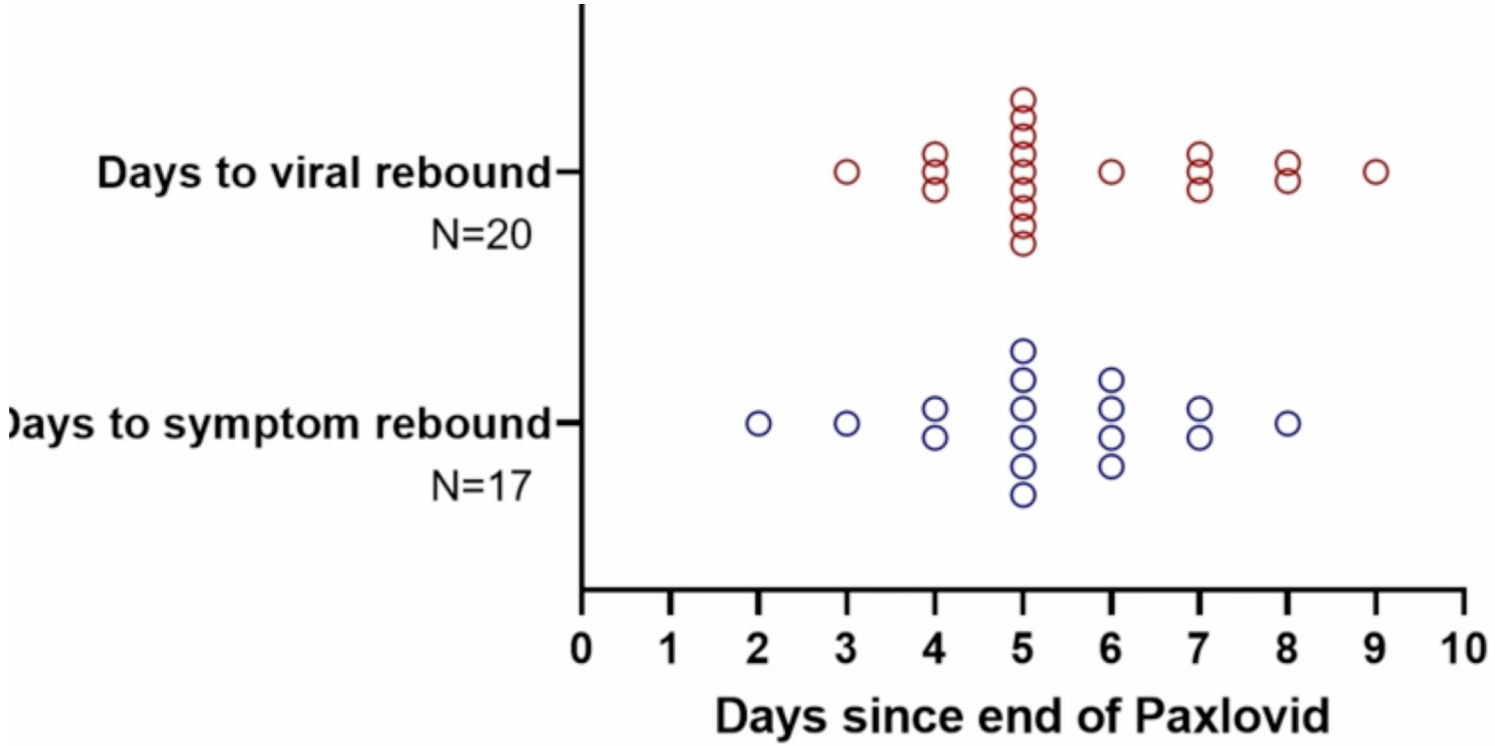
What about rebound?



Li. CROI 2023

COVID at CROI 2023

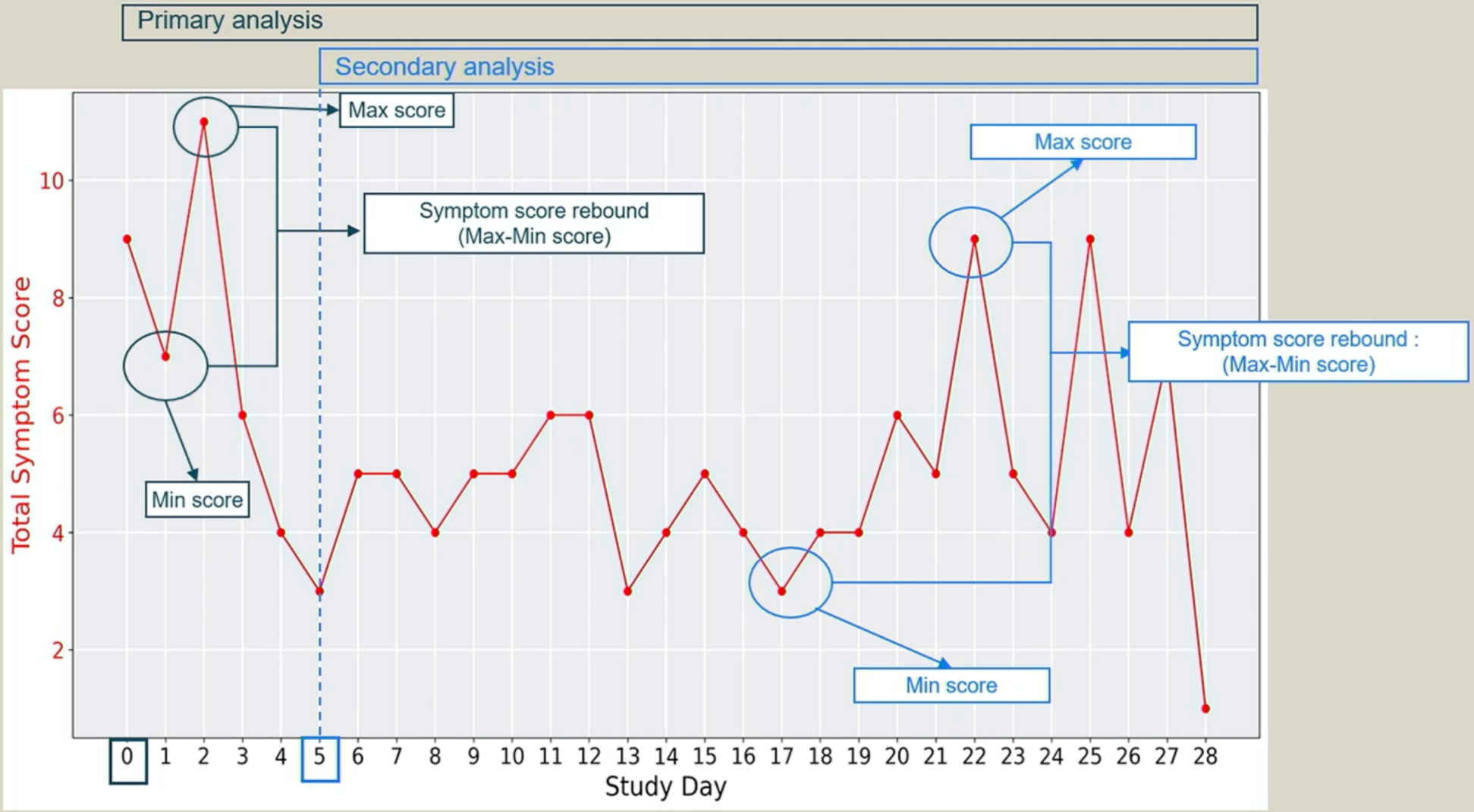
What about rebound?



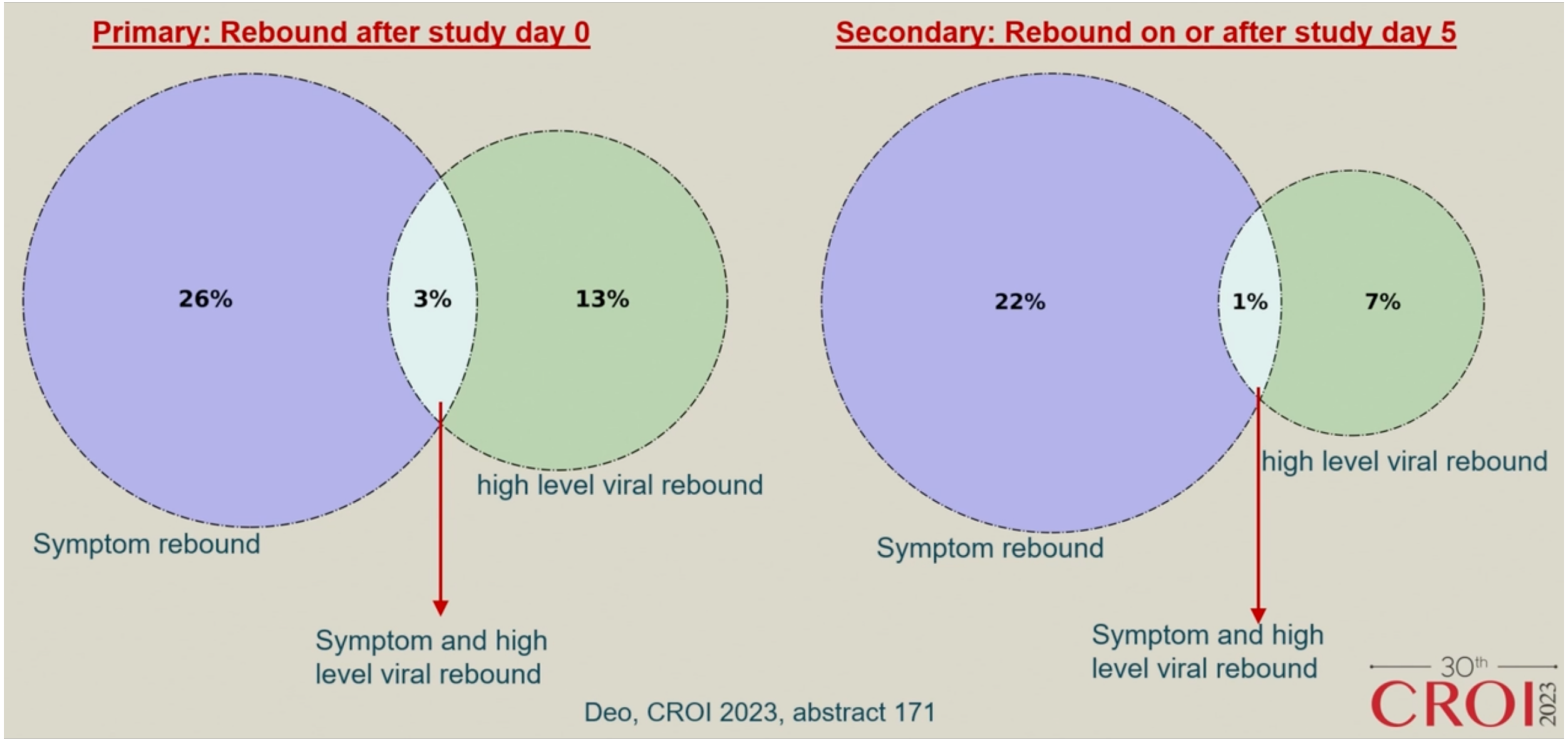
- Boucau/Siedner, 2022; Charness/Ho, 2022

An example of symptom rebound after improvement

≥4 point symptom score rebound



R. Deo, CROI 2023



Deo, CROI 2023

COVID-19 Risks and Treatment

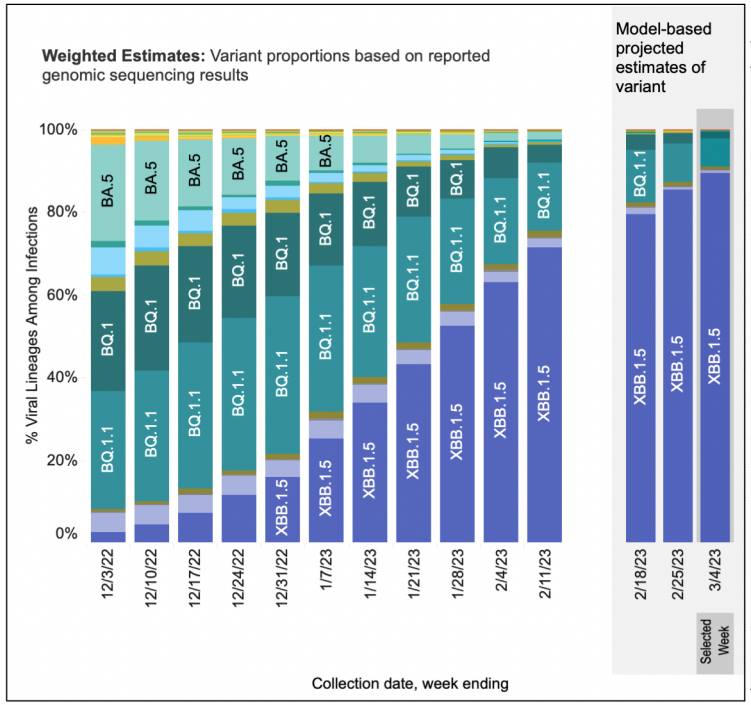
- Most at risk remain the elderly (~70+) and others with predicted less robust immune response.
- People with less access to healthcare and more comorbidities at heightened risk for severe disease regardless of age

- Treatment options are limited but there are interventions that work to prevent disease progression including Paxlovid and Molnupirivir as well as Remdesivir.
  - Clinicians need to be familiar with these medications and not withhold from those at highest risk of severe COVID-19
- Rebound is not specific to Paxlovid and should not be a reason to not treat higher risk patients

COVID at CROI 2023

How good are the bivalent vaccines? (Spoiler alert: *Very* good)

Weighted and Nowcast Estimates in United States for Weeks of 11/27/2022 – 3/4/2023



Nowcast Estimates in United States for 2/26/2023 – 3/4/2023

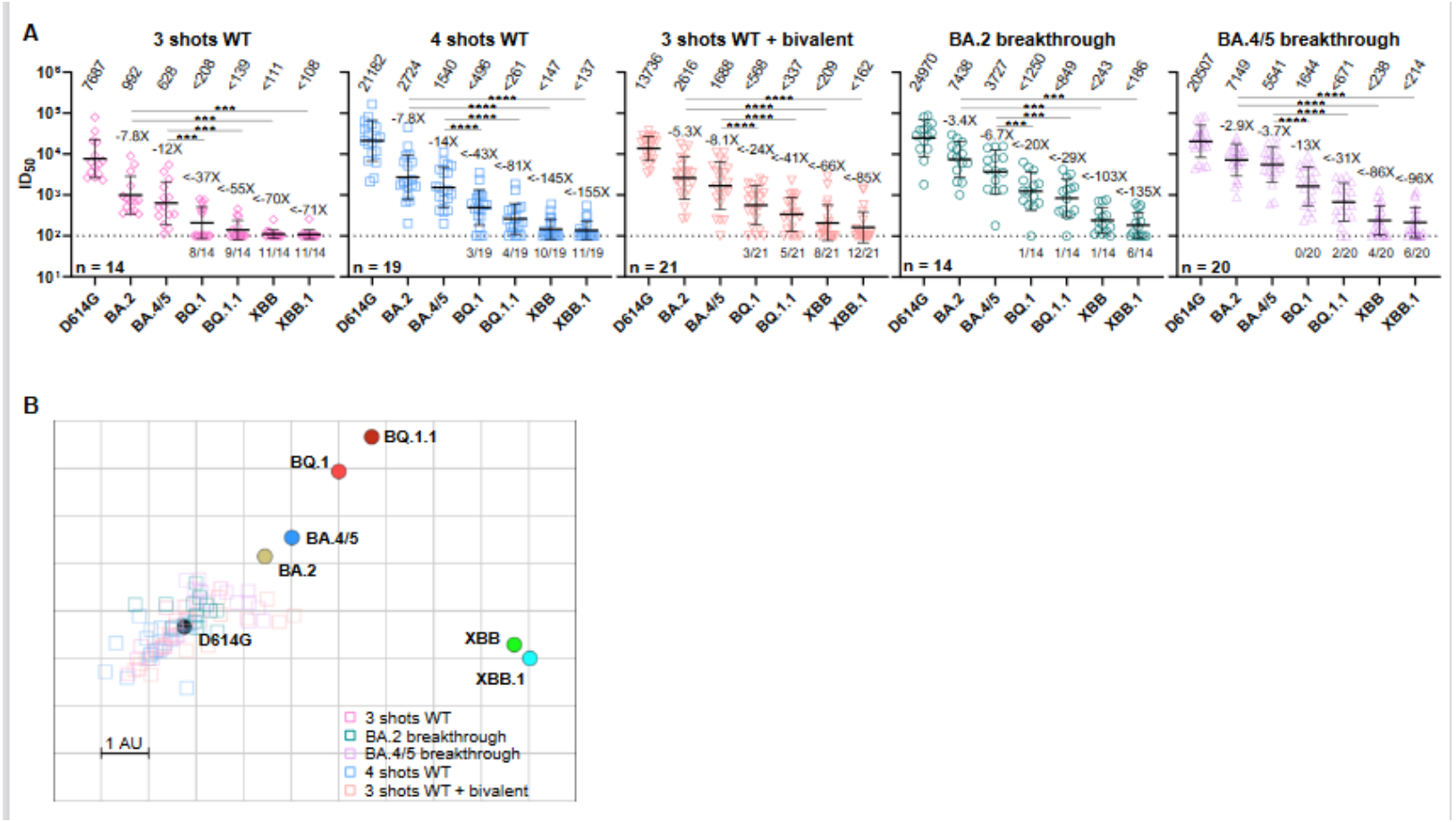
USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	89.6%	85.6-92.6%
	BQ.1.1	VOC	6.7%	4.7-9.4%
	BQ.1	VOC	1.6%	1.1-2.3%
	CH.1.1	VOC	0.8%	0.5-1.1%
	XBB	VOC	0.7%	0.5-1.0%
	BN.1	VOC	0.2%	0.2-0.4%
	BA.5	VOC	0.1%	0.1-0.1%
	BA.2	VOC	0.1%	0.0-0.5%
	BF.7	VOC	0.1%	0.0-0.1%
	BA.5.2.6	VOC	0.0%	0.0-0.0%
	BF.11	VOC	0.0%	0.0-0.0%
	BA.2.75	VOC	0.0%	0.0-0.0%
	BA.2.75.2	VOC	0.0%	0.0-0.0%
	BA.4.6	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.1%	0.0-0.1%

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants

The SARS-CoV-2 Omicron variant continues to evolve, with new BQ and XBB subvariants now rapidly expanding in Europe/US and Asia, respectively. As these new subvariants have additional spike mutations, they may possess altered antibody evasion properties. Here, we report that neutralization of BQ.1, BQ.1.1, XBB, and XBB.1 by sera from vaccinees and infected persons was markedly impaired, including sera from individuals who were boosted with a WA1/BA.5 bivalent mRNA vaccine. Compared to the ancestral strain D614G, serum neutralizing titers against BQ and XBB subvariants were lower by 13-81-fold and 66-155-fold, respectively, far beyond what had been observed to date.



Wang Q, et al. https://www.biorxiv.org/content/10.1101/2022.11.23.517532v1

Neutralization against BA.2.75.2, BQ.1.1, and XBB Bivalent Booster

- Study tested We tested serum samples obtained from participants who had received either one or two monovalent boosters or the bivalent booster to determine the neutralization efficiency of the booster vaccines against wild-type (WA1/2020) virus and primary isolates of omicron subvariants BA.1, BA.5, BA.2.75.2, BQ.1.1, and XBB using an in vitro, live-virus focus reduction neutralization test (FRNT).
- Results: In the cohort that received the BA.5-containing bivalent booster, the neutralizing activity against all the omicron subvariants as compared with that against WA1/2020 was better than in the other two cohorts (Fig. 1C). The FRNT50 GMTs were 2481 against WA1/2020, 618 against BA.1, 576 against BA.5, 201 against BA.2.75.2, 112 against BQ.1.1, and 96 against XBB. The results in this cohort correspond with neutralization titers against BA.1 and BA.5 that were 4 times as low as that against WA1/2020 and neutralization titers against BA.2.75.2, BQ.1.1, and XBB that were 12 to 26 times as low as that against WA1/2020. Persons who received either one or two monovalent Covid-19 vaccine boosters had much lower neutralization activity against omicron subvariants (especially against BA.2.75.2, BQ.1.1, and XBB, which contain the predicted escape mutation R346T) than that against the WA1/2020 strain.

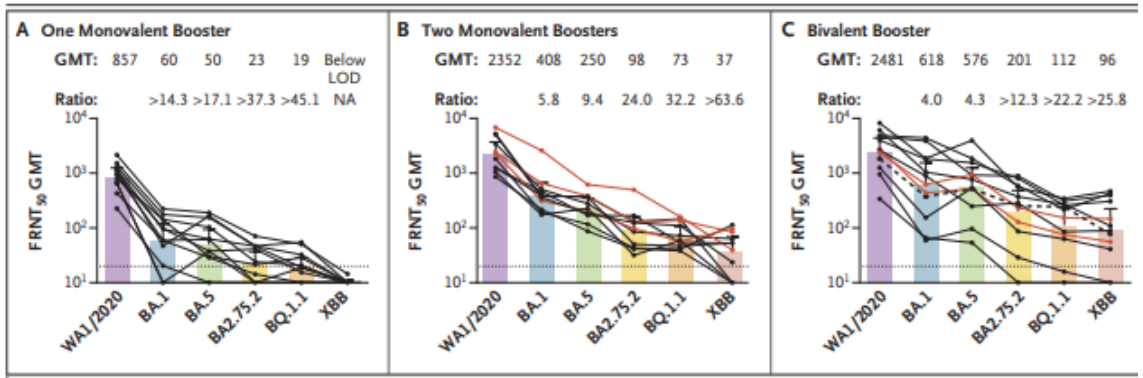


Figure 1. Neutralizing Responses against the WA1/2020 Strain and Omicron Subvariants.

Shown is the neutralization activity against the WA1/2020 strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the omicron subvariants BA.1, BA.5, BA.2.75.2, BQ.1.1, and XBB in 12 participants who received one monovalent booster (Panel A), in 11 participants who received two monovalent boosters (Panel B), and in 12 participants who received the updated bivalent booster (Panel C). The focus reduction neutralization test ($FRNT_{50}$ [the reciprocal dilution of serum that neutralizes 50% of the input virus]) geometric mean titer (GMT) of neutralizing antibodies against the WA1/2020 strain and each omicron subvariant is shown at the top of each panel, along with the ratio of the neutralization GMT against the WA1/2020 strain to that against each omicron subvariant. The connecting lines between the variants represent matched serum samples. The horizontal dotted lines represent the limit of detection of the assay ($FRNT_{50}$ GMT 20). The red lines in Panels B and C indicate the participants who reported previous SARS-CoV-2 infection, and the dashed line in Panel C indicates one participant who received two monovalent boosters before the bivalent booster. The colored bars represent the $FRNT_{50}$ GMT among the participants in the cohort, and the I bars indicate 95% confidence intervals, which were not adjusted for multiplicity and may not be used for hypothesis testing. LOD denotes limit of detection, and NA not applicable.

Davis-Gardner ME, et al. NEJM 2022;22 December

Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated ED or Urgent Care Encounters and Hospitalizations Among Immunocompetent Adults, VISION Network, Nine States, Sept.–Nov. 2022

TABLE 2. Bivalent booster COVID-19 vaccine effectiveness* against laboratory confirmed COVID-19–associated emergency department and urgent care encounters and hospitalizations among immunocompetent adults aged 18 years — nine states,† September–November 2022

mRNA dosage pattern	Total	Negative SARS-CoV-2 test result, no. (%)	Positive SARS-CoV-2 test result, no. (%)	Median interval since last dose, days (IQR)	VE % (95% CI)
ED/UC encounters					
Relative VE					
Only MV doses, last dose 2–4 mos earlier	**5,668**	5,131 (91)	537 (9)	115 (91–134)	Ref
BV booster dose, ≥7 days earlier	**3,905**	3,658 (94)	247 (6)	25 (16–37)	31 (19–41)
Only MV doses, last dose 5–7 mos earlier	**6,891**	6,166 (89)	725 (11)	184 (166–209)	Ref
BV booster dose, ≥7 days earlier	**3,905**	3,658 (94)	247 (6)	25 (16–37)	42 (32–50)
Only MV doses, last dose 8–10 mos earlier	**14,220**	12,543 (88)	1,677 (12)	294 (273–312)	Ref
BV booster dose, ≥7 days earlier	**3,905**	3,658 (94)	247 (6)	25 (16–37)	53 (46–60)
Only MV doses, last dose ≥11 mos earlier	**23,477**	20,694 (88)	2,783 (12)	459 (365–542)	Ref
BV booster dose, ≥7 days earlier	**3,905**	3,658 (94)	247 (6)	25 (16–37)	50 (43–57)
Absolute VE					
Unvaccinated	**24,142**	21,102 (87)	3,040 (13)	NA	Ref
BV booster dose, ≥7 days earlier	**3,905**	3,658 (94)	247 (6)	25 (16–37)	56 (49–62)
Hospitalizations					
Relative VE					
Only MV doses, last dose 2–4 mos earlier	—§	—	—	—	—
BV booster dose, ≥7 days earlier	—	—	—	—	—
Only MV doses, last dose 5–7 mos earlier	**1,819**	1,652 (91)	167 (9)	178 (164–201)	Ref
BV booster dose, ≥7 days earlier	**783**	734 (94)	49 (6)	23 (14–34)	38 (13–56)
Only MV doses, last dose 8–10 mos earlier	**2,655**	2,422 (91)	233 (9)	294 (273–313)	Ref
BV booster dose, ≥7 days earlier	**783**	734 (94)	49 (6)	23 (14–34)	42 (19–58)
Only MV doses, last dose ≥11 mos earlier	**4,595**	4,147 (90)	448 (10)	472 (362–556)	Ref
BV booster dose, ≥7 days earlier	**783**	734 (94)	49 (6)	23 (14–34)	45 (25–60)
Absolute VE					
Unvaccinated	**4,092**	3,658 (89)	434 (11)	NA	Ref
BV booster dose, ≥7 days earlier	**783**	734 (94)	49 (6)	23 (14–34)	57 (41–69)

Tenforde MW, et al. MMWR 2022;71:16 December 2022

Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Hospitalization Among Immunocompetent Adults Aged ≥65 Years, IVY Network, 18 States, September 8–November 30, 2022

What is already known about this topic? - Immunity from monovalent COVID-19 mRNA vaccination wanes over time. A bivalent COVID-19 mRNA booster dose is recommended for all eligible persons; however, little is known about its effectiveness against COVID-19 hospitalization.

What is added by this report? - Among immuno-0competent adults aged ≥65 years hospitalized in the multistate IVY Network, a bivalent booster dose provided 73% additional protection against COVID-19 hospitalization compared with past monovalent mRNA vaccination only.

What are the implications for public health practice? - To maximize protection against severe COVID-19 this winter season, all eligible persons, especially adults aged ≥65 years, should receive a bivalent booster dose and consider additional prevention strategies, including masking in indoor public spaces.

Surie D, et al. MMWR 2022;71:16 December 2022

TABLE 2. Effectiveness of a bivalent COVID-19 mRNA booster dose against COVID-19–associated hospitalization among immunocompetent adults aged ≥65 years — IVY Network, 22 hospitals,* 18 states, September 8, 2022–November 30, 2022

Characteristic	Received BV vaccine dose, by case status, n/N (%)		Median interval† from last vaccine dose to illness onset (IQR), days	Adjusted VE, % (95% CI)§
	Case-patients	Control patients		
Absolute VE (BV booster dose versus no vaccine)				
Unvaccinated (Ref)	—	—	NA	—
BV booster dose¶ ≥7 days before illness onset	20/101 (20)	59/121 (49)	29 (15–45)	84 (64–93)
Relative VE (BV booster dose versus MV-only, by interval since last dose)				
≥2 MV-only mRNA doses, last dose ≥2 mos before illness onset (Ref)	—	—	305 (168–377)	—
BV booster dose ≥7 days before illness onset	20/300 (7)	59/355 (17)	29 (15–45)	73 (52–85)
≥2 MV-only mRNA doses, last dose 2–5 mos before illness onset (Ref)			137 (111–155)	—
BV booster dose ≥7 days before illness onset	20/82 (24)	59/155 (38)	29 (15–45)	—**
≥2 MV-only mRNA doses, last dose 6–11 mos before illness onset (Ref)	—	—	304 (258–333)	—
BV booster dose ≥7 days before illness onset	20/155 (13)	59/176 (34)	29 (15–45)	78 (57–89)
≥2 MV-only mRNA doses, last dose ≥12 mos before illness onset (Ref)	—	—	528 (386–575)	—
BV booster dose ≥7 days before illness onset	20/103 (19)	59/142 (42)	29 (15–45)	83 (63–92)

COVID-19 Incidence and Mortality Among Unvaccinated and Vaccinated Persons Aged ≥12 Years by Receipt of Bivalent Booster Doses and Time Since Vaccination — 24 U.S. Jurisdictions, October 3, 2021–December 24, 2022

FIGURE 1. Age-standardized weekly COVID-19 incidence* and COVID-19–associated mortality rates,† by vaccination status and receipt of a bivalent booster dose§ — 24 U.S. jurisdictions,¶ October 2021–December 2022**

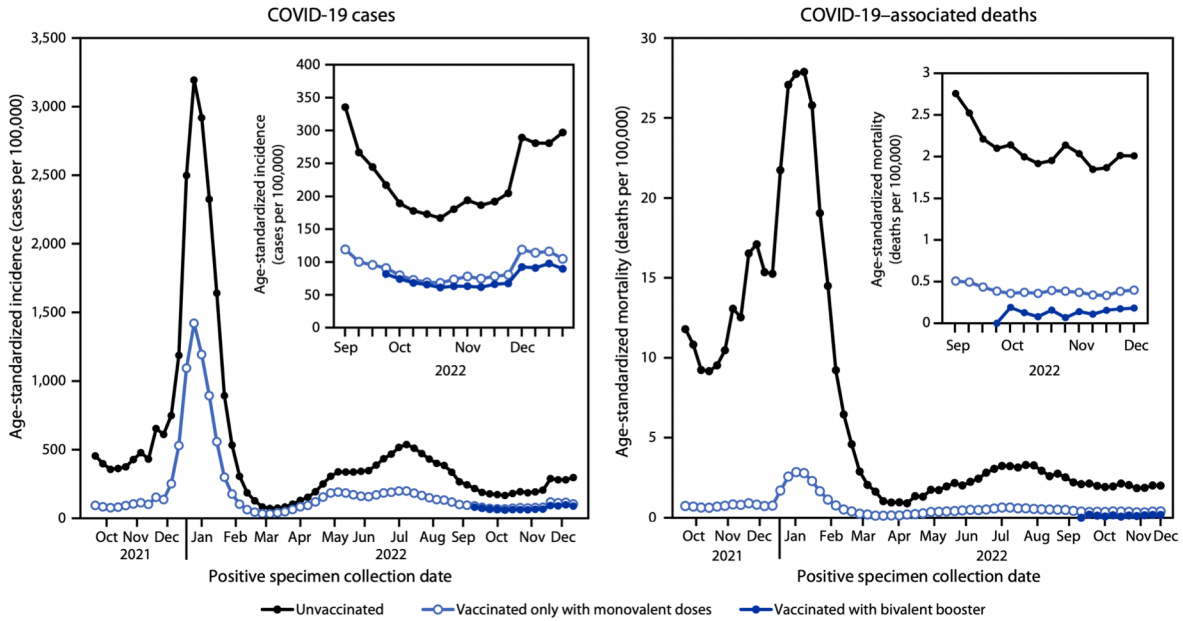
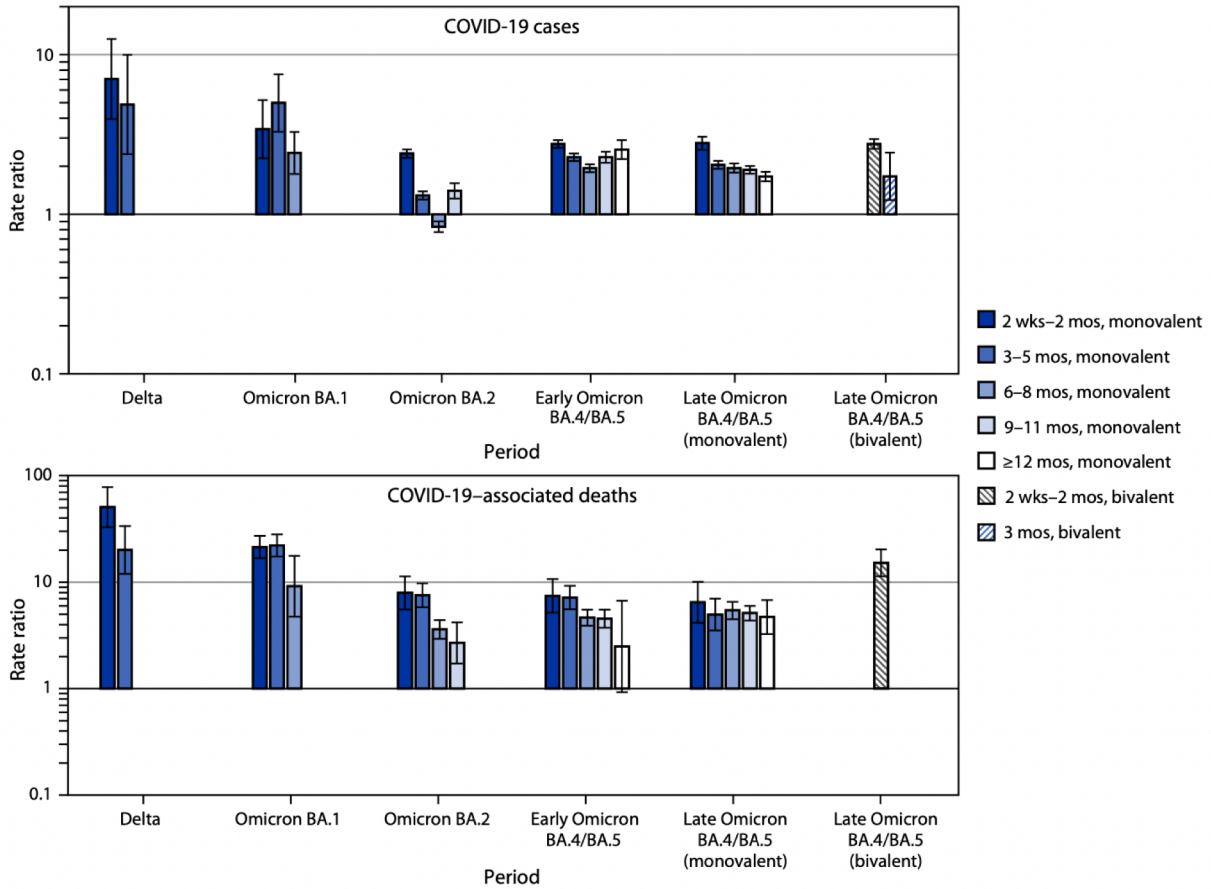


FIGURE 2. Age-standardized average weekly case* and mortality† rate ratios with 95% CIs§ in unvaccinated persons compared with booster dose recipients, by variant period¶ and time since receipt of last booster dose — 23 U.S. jurisdictions,†† October 2021–December 2022§§**



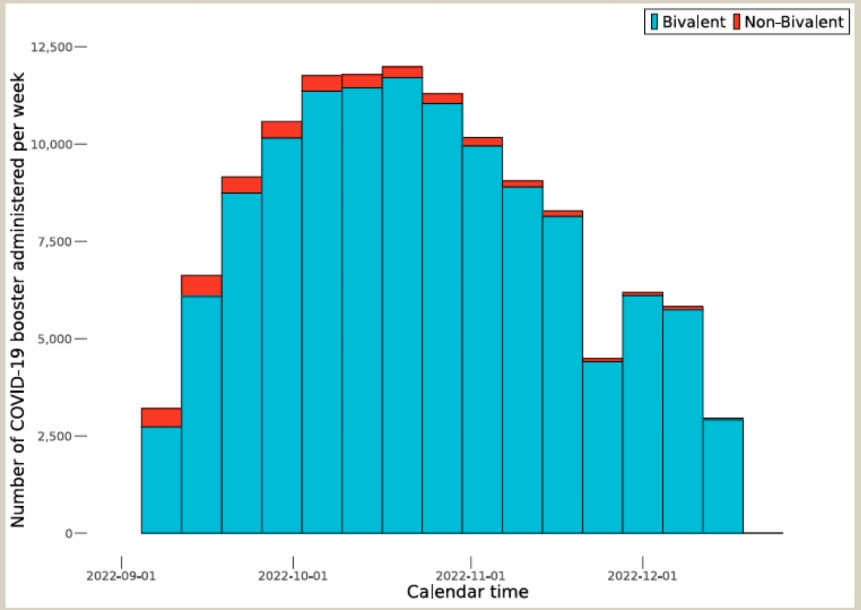
Johnson. MMWR FEB 2023

COVID at CROI 2023

National COVID Cohort Collaborative (N3C)

National COVID Cohort Collaborative

- N3C: NIH funded, rapidly developed, open science community
- N3C Enclave includes patient-level data from >70 clinical centers across the U.S.
- We included 45 clinical sites that have COVID-19 vaccine and bivalent booster data
- Total COVID-19 full vaccination (2 doses of mRNA vaccine) between 9/1/2022-12/15/2022
  - Full mRNA vaccine series: 2,333,624
  - Bivalent booster vaccine: 68,079



30th

COVID at CROI 2023

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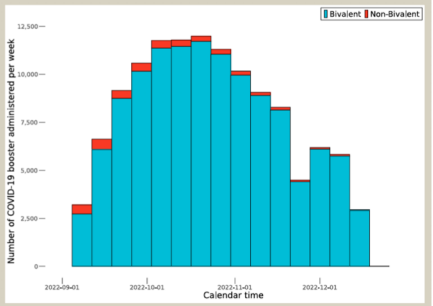

30th

METHODS

- ***Population***
  - Patients completing 2+ doses of mRNA vaccination in N3C by 9/1/2022. Data extracted on 12/15/2022.
  - Patients with immune dysfunction: HIV infection, solid organ or bone marrow transplant, autoimmune disease, and cancer
- ***COVID-19 vaccination***
  - Full vaccination: completed 2 doses of mRNA vaccine
  - COVID-19 bivalent booster: one additional dose of bivalent booster after 9/1/2022
- ***COVID-19 breakthrough infection***
  - RT-PCR, antigen positive, or ICD code at least 14 days after COVID-19 vaccination
- ***COVID-19 related outcomes***
  - Hospitalization, invasive ventilation/ECMO, or death within 28 days after COVID-19 breakthrough infection

COVID at CROI 2023

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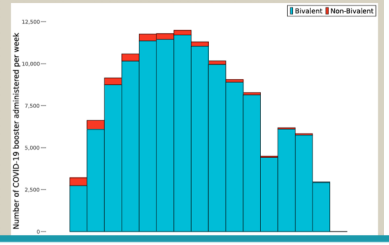

PATIENT CHARACTERISTICS

Variables	Overall cohort (N = 2,401,703)	Full vaccination without bivalent booster (N = 2,333,624)	Full vaccination with bivalent booster (N = 68,079)
Age, median (IQR)	52 (36, 67)	52 (36, 67)	51 (37, 66)
Female sex, N (%)	1,444,150 (60%)	1,401,953 (60%)	42,197 (62%)
Race and ethnicity, N (%)			
Number of comorbidities, N (%)			
0	1,268,870 (53%)	1,243,524 (53%)	25,346 (37%)
1	569,050 (24%)	548,576 (24%)	20,474 (30%)
2	290,344 (12%)	278,884 (12%)	11,460 (17%)
≥3	273,439 (11%)	262,640 (11%)	10,799 (16Any%)
Immune dysfunction*, N (%)	336,954 (14%)	325,466 (14%)	11,488 (17%)
Moderate to severe	53,233 (2.2%)	51,441 (2.2%)	1,792 (2.6%)

*Immune dysfunction conditions included HIV infection, solid organ/bone marrow transplant, autoimmune diseases, and cancer; Severe immune dysfunction included patients with history of leukemia or lymphoma, receipt of a solid organ or bone marrow transplant, people with HIV with CD4<350 cells/ml3 or viral load >50 copies/mL, and patients with rheumatologic diseases on active immunosuppressive therapy as moderate to severe immune dysfunction based on CDC guidelines.

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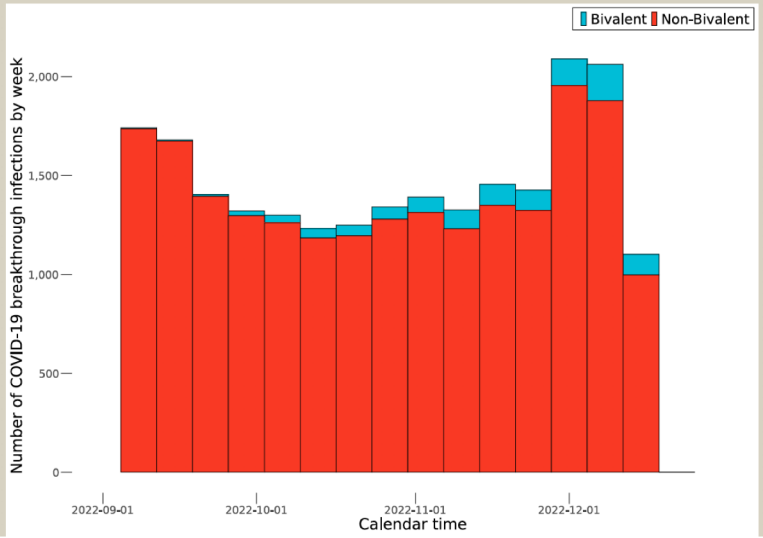
- ***COVID-19 related outcomes***
  - Hospitalization, invasive ventilation/ECMO, or death within 28 days after COVID-19 breakthrough infection

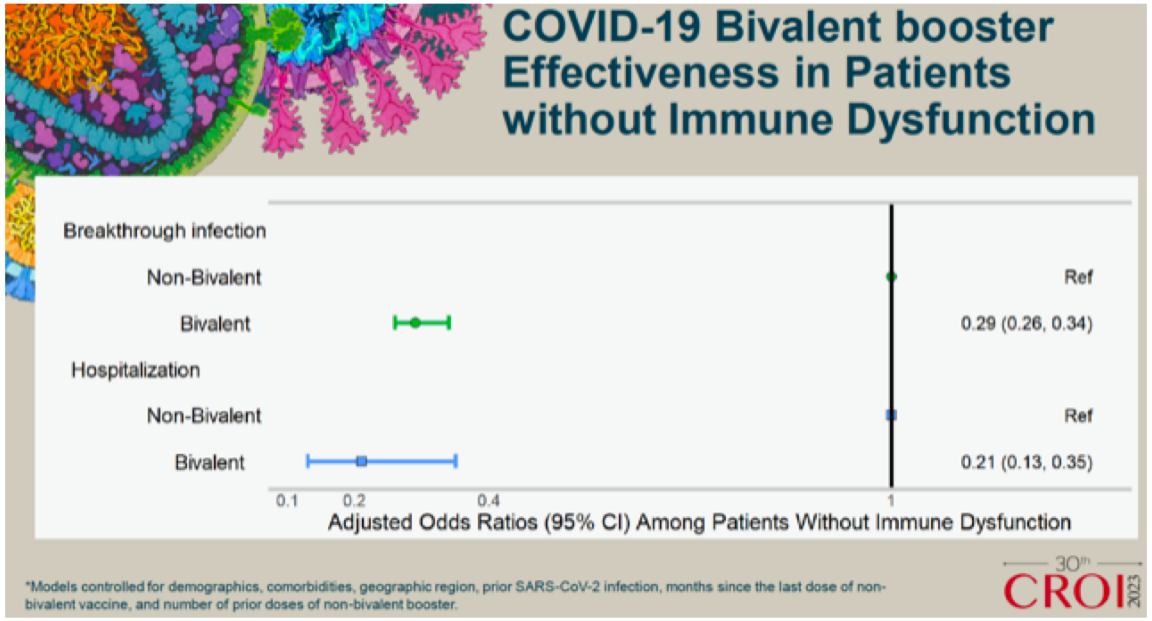
COVID at CROI 2023

National COVID Cohort Collaborative (N3C)

RESULTS

- Total breakthrough cases during the study period: 23,750
- Breakthrough infection by groups:
  - Non-bivalent: 23,452
  - Bivalent: 298





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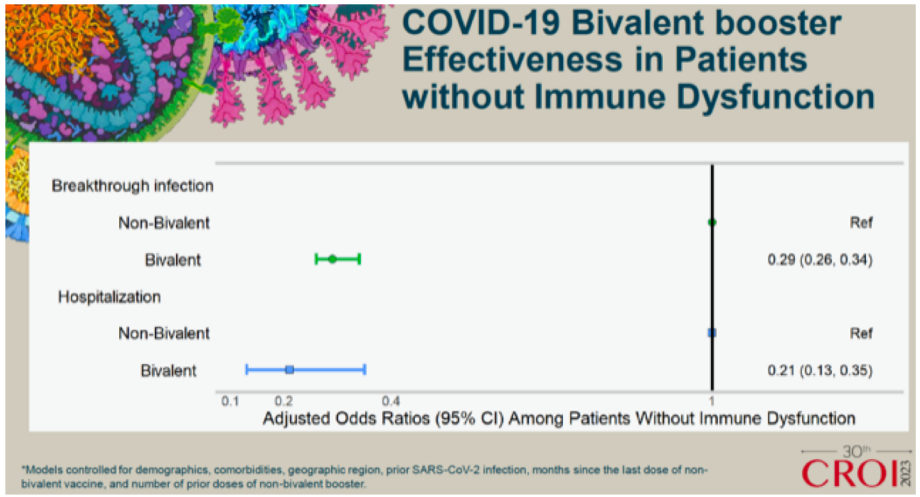
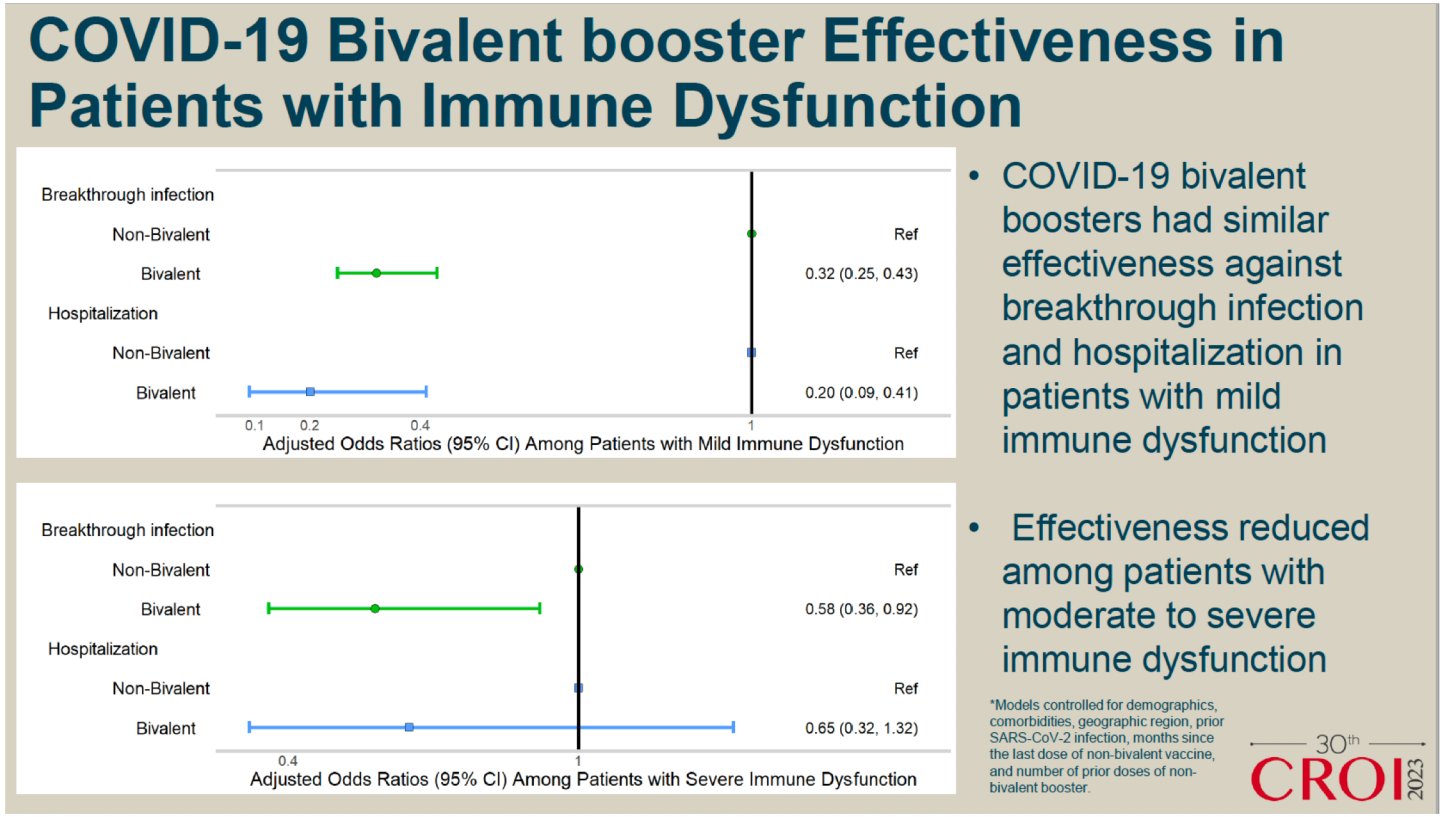
National COVID Cohort Collaborative (N3C)





Sun. CROI 2023

COVID-19 Prevention

- Newest variants are:
  - More transmissible
  - Better evade natural and vaccine induced immunity
- However, vaccination works:
  - Protests from infection
  - Reduces disease severity]
  - Lowers risk of Long COVID
- Bivalent vaccine is just as safe as monovalent and has been found to better protect against hospitalization and death
- There is still a role for infection avoidance including masking in crowds, masking in high-risk settings like clinics and hospitals, use of home tests

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THANK YOU

Questions