Reporting relevant data presented at

CROI 2022

David Alain Wohl, MD
Institute of Global Health and Infectious Diseases
The University of North Carolina at Chapel Hill

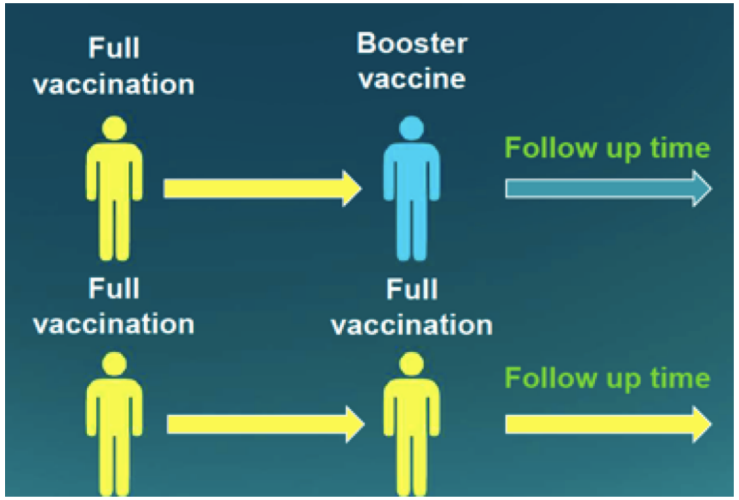
UNC | SCHOOL OF MEDICINE

Let’s Talk About:

- COVID-19
  - Prevention
  - Treatment
- HIV
  - PrEP
  - Treatment
  - Successful Living

COVID-19 Prevention

- Effectiveness of booster C19 vaccination in N3C database in immunocompetent and compromised people
  - Pooled data from 60 US clinical sites
  - >748K fully vaccinated, 174K boosted

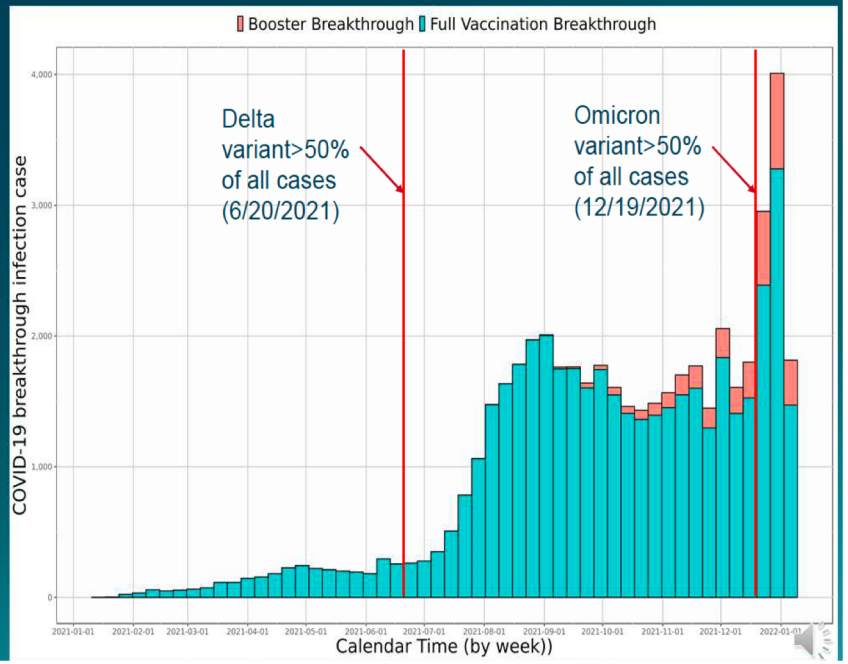


PATIENT CHARACTERSTICS

Variables	Overall cohort (N = 784,555)	Full vaccination (N=614,750)	Full vaccination with booster (N=174,042)
Age, median (IQR)	50 (33, 65)	49 (31, 64)	57 (41, 69)
Female sex, N (%)	450,202 (57%)	350,219 (57%)	99,983 (57%)
Race and ethnicity, N (%)			
Non-Hispanic White	433,374 (55%)	323,156 (53%)	110,218 (63%)
Non-Hispanic Black	85,710 (11%)	71,896 (12%)	13,814 (7.9%)
Hispanic	138,124 (18%)	113,986 (19%)	24,138 (14%)
AAPI	37,918 (4.8%)	27,861 (4.6%)	10,057 (5.8%)
Others	67,834 (8.6%)	55,535 (9.1%)	12,299 (7.1%)
Number of comorbidities, N (%)			
0	413,616 (53%)	334,127 (55%)	79,489 (46%)
1	182,638 (23%)	139,303 (23%)	43,335 (25%)
2	87,827 (11%)	64510 (11%)	23,317 (13%)
≥3	100,474 (13%)	72,573 (12%)	27,901 (16%)
Vaccine manufacturer, N (%)			
Pfizer BioNTech	553,227 (71%)	427,628 (70%)	12,5599 (72%)
Moderna	193,304 (25%)	149,179 (24%)	44,125 (25%)
Janssen	37,998 (4.8%)	33,685 (5.5%)	4,313 (2.5%)

RESULTS

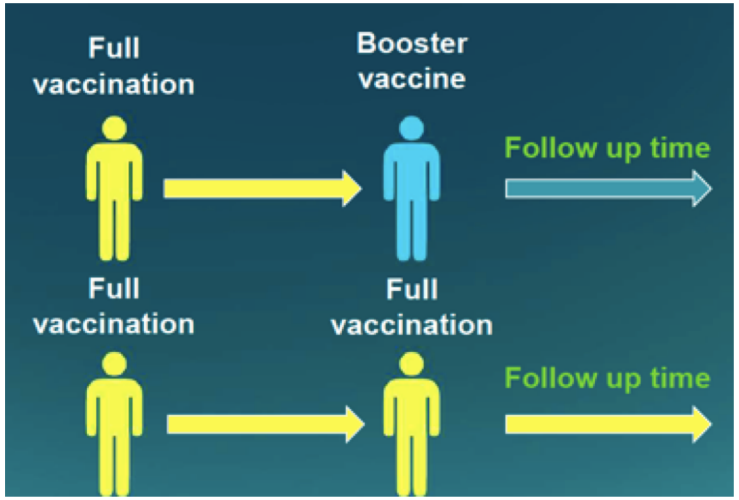
- Total breakthrough infection cases: 48,893
- Weekly breakthrough infection cases increased after Delta and Omicron strains became the dominant strains of infection



Sun J, et al. CROI, February 12-16 and 22-24, 2022.

COVID-19 Prevention

- Effectiveness of booster C19 vaccination in N3C database in immunocompetent and compromised people
  - Pooled data from 60 US clinical sites
  - >748K fully vaccinated, 174K boosted



RESULTS—Booster Effectiveness in Patients without Immune Dysfunction

Months since full vaccination	Breakthrough events during follow-up		Sample size in boosted or non-boosted group*	Hazard Ratio (95% CI)	P-value	Booster vaccine efficacy
	Boosted group	Non-boosted group				
≤5	26	88	2006	0.33 (0.22, 0.52)	<0.001	70.5%
6	34	129	3166	0.27 (0.19, 0.40)	<0.001	73.6%
7	184	815	27148	0.23 (0.19, 0.27)	<0.001	77.4%
8	413	1102	40383	0.36 (0.32, 0.41)	<0.001	62.5%
9	389	812	28952	0.45 (0.40, 0.51)	<0.001	52.1%

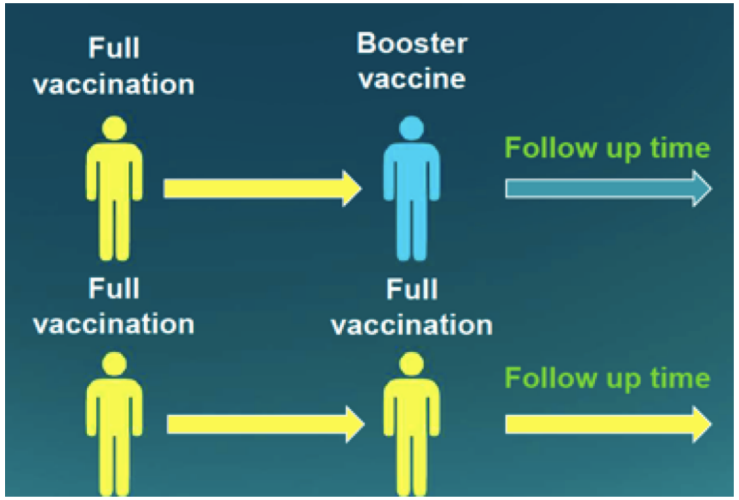
RESULTS—Booster Effectiveness in Patients with Immune Dysfunction

Months since full vaccination	Breakthrough events during follow-up		Sample size in boosted or non-boosted group*	Hazard Ratio (95% CI)	P-value	Booster vaccine efficacy
	Boosted group	Non-boosted group				
≤5	141	201	4418	0.84 (0.67, 1.04)	0.11	29.9%
6	110	185	4587	0.60 (0.47, 0.75)	<0.001	40.5%
7	157	394	12210	0.39 (0.32, 0.47)	<0.001	60.2%
8	150	376	14600	0.38 (0.31, 0.46)	<0.001	60.1%
9	75	124	8423	0.56 (0.42, 0.75)	<0.001	39.5%

Sun J, et al. CROI, February 12-16 and 22-24, 2022.

COVID-19 Prevention

- Effectiveness of booster C19 vaccination in N3C database in immunocompetent and compromised people
  - Pooled data from 60 US clinical sites
  - >748K fully vaccinated, 174K boosted



RESULTS—Risk of COVID-19 Related Outcomes by Booster Vaccine Status

	Patients without immune dysfunction		Patients with immune dysfunction	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Hospitalization	0.13 (0.12, 0.15)	<0.001	0.21 (0.19, 0.23)	<0.001
Invasive ventilation	0.09 (0.05, 0.19)	<0.001	0.25 (0.18, 0.34)	<0.001
Death	0.13 (0.06, 0.30)	<0.001	0.17 (0.11, 0.27)	<0.001

Models controlled for demographics, geographic region, comorbidities, prior COVID-19 infection, and time of full vaccination.

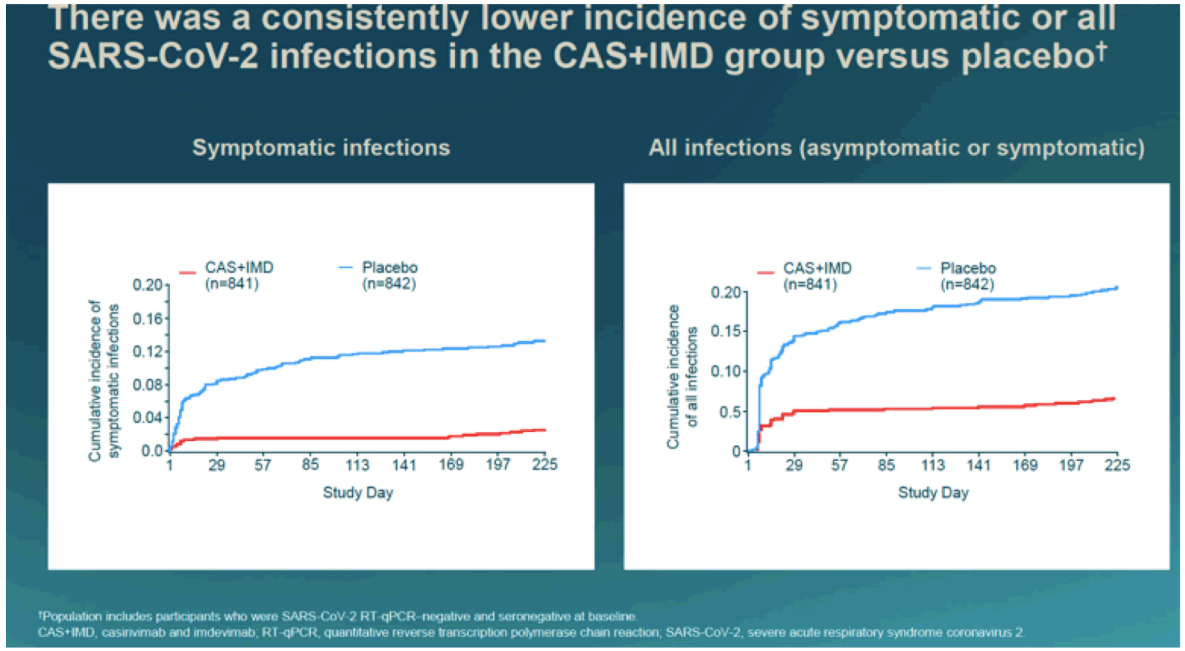
Boosters are:

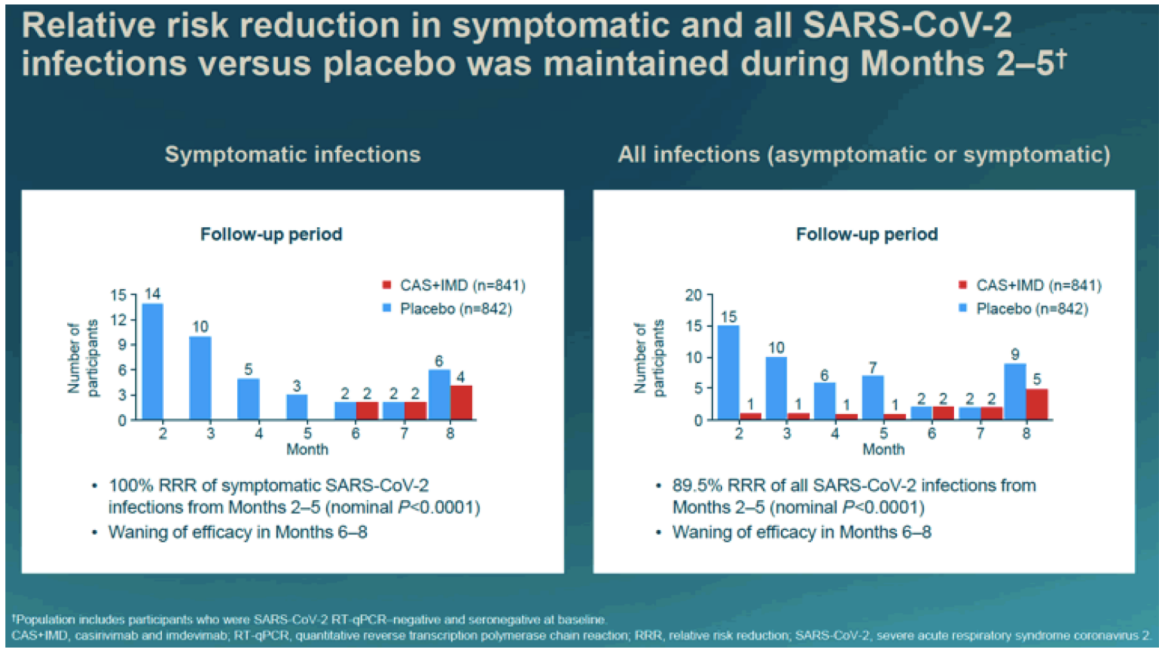
- Effective in preventing *infection* but this protection wanes over time
- Relatively less but still effective in immunocompromised
- Highly effective in preventing hospitalization, need for ventilation, and death for all

Sun J, et al. CROI, February 12-16 and 22-24, 2022.

COVID-19 Prevention

- PrEP with monoclonal antibody (mAb) Regen-CoV (Casi/Imde)
  - Placebo-controlled trial of 1200 mg Casi/Imde subQ to household contacts (N= 1683) within 96 hours of C19 case testing positive
  - Study conducted while Delta surged and before Omicron
  - Previously reported 81% reduction in symptomatic SARS-CoV-2 infections over 28 days (NEJM 2021)
  - At CROI, 7 month follow-up





A single subQ dose of Casi/Imde provided protection from infection for ~5 months.

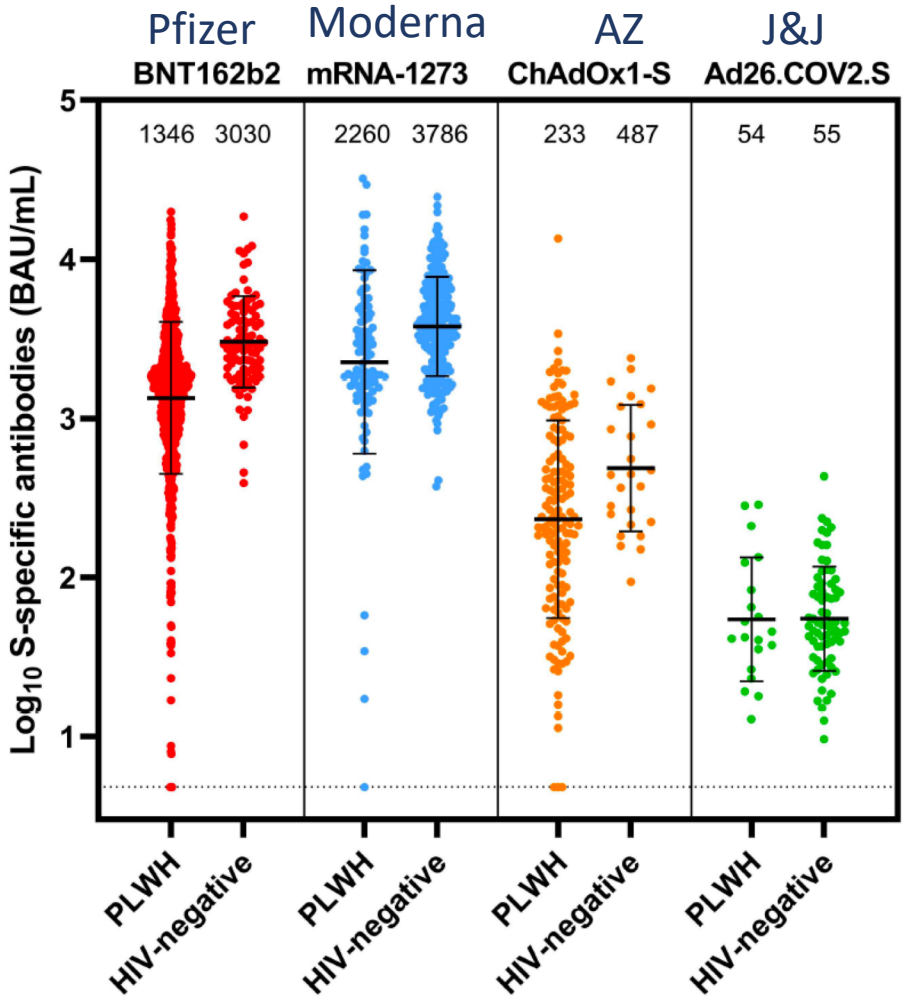
Casi/Imde not active against Omicron but proves concept

O'Brien MP, et al. CROI, February 12-16 and 22-24, 2022.

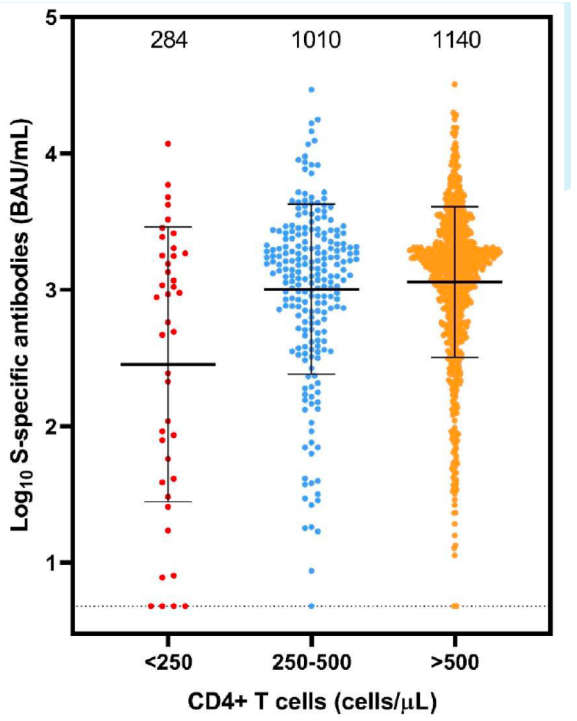
COVID-19 Prevention

- Antibody levels following COVID-19 vaccination in people with and without HIV infection
  - 22 centers in the Netherlands
  - 1154 HIV-pos
  - 440 HIV-neg

		HC (N=440)	PLWH (N=1154)
Vaccine	BNT162b2	94 (21.4%)	884 (76.6%)
	mRNA-1273	247 (56.1%)	100 (8.7%)
	ChAdOx1-S	26 (5.9%)	150 (13.0%)
	Ad26.COV2.S	73 (16.6%)	20 (1.7%)
Sex assigned at birth	Male	126 (28.6%)	987 (85.5%)
	Female	314 (71.4%)	167 (14.5%)
Age category	18-55	352 (80.0%)	703 (60.9%)
	56-65	74 (16.8)	291 (25.2%)
	65+	14 (3.2%)	160 (13.9%)
On cART	Yes	NA	1142 (99.0%)
	No	NA	12 (1.0%)
HIV viral load (copies/ml)	<50	NA	1127 (97.7%)
	≥50	NA	26 (2.3%)
CD4+ T cell count (cells/µL)	<250	NA	41 (3.6%)
	250-500	NA	224 (19.4%)
	>500	NA	889 (77.0%)
CD4 T-cell count nadir † (cells/µL)	<250	NA	443 (38.4%)
	250-500	NA	376 (32.6%)
	>500	NA	152 (13.2%)



Only PLWH who got an mRNA vax



Spike Ab levels after mRNA vax lower in PLWH especially those over age 65 or with viral load over 50.

PLWH with higher CD4 cell counts had higher Ab levels.

Hensley KS, et al. CROI, February 12-16 and 22-24, 2022.

COVID-19 Prevention

- Effect of C19 vaccination on HIV RNA levels
  - COVAC HIV Study - Switzerland

METHODS

Population's sample

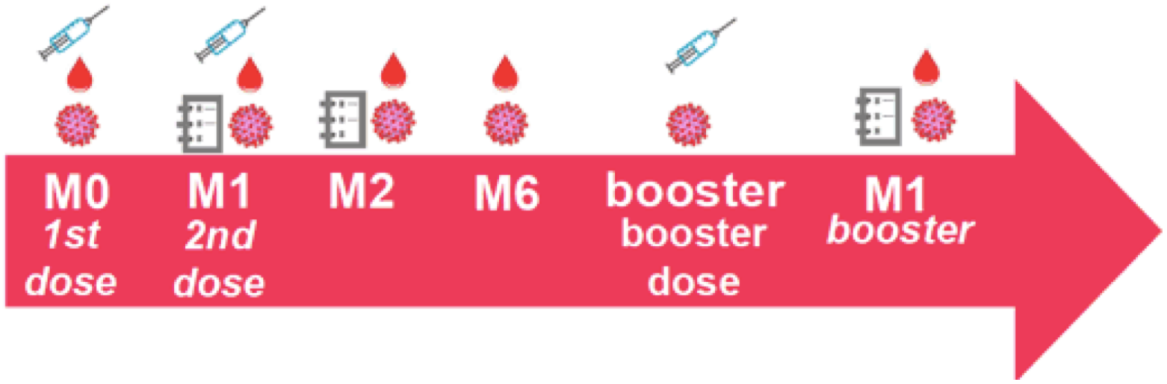
131 PLWH

49 healthy volunteers

Type of vaccine

	PLWH	healthy V
BNT 162b2	40.5%	
mRNA 1273	59.5%	100%

Protocol timeline



BASELINE CHARACTERISTICS

131 PLWH

54 years old (median)
70.2% male

Baseline CD4 (median):
602 cells/µl – 35%

Nadir CD4 (median)
223 cells/µl – 21%

49 healthy volunteers

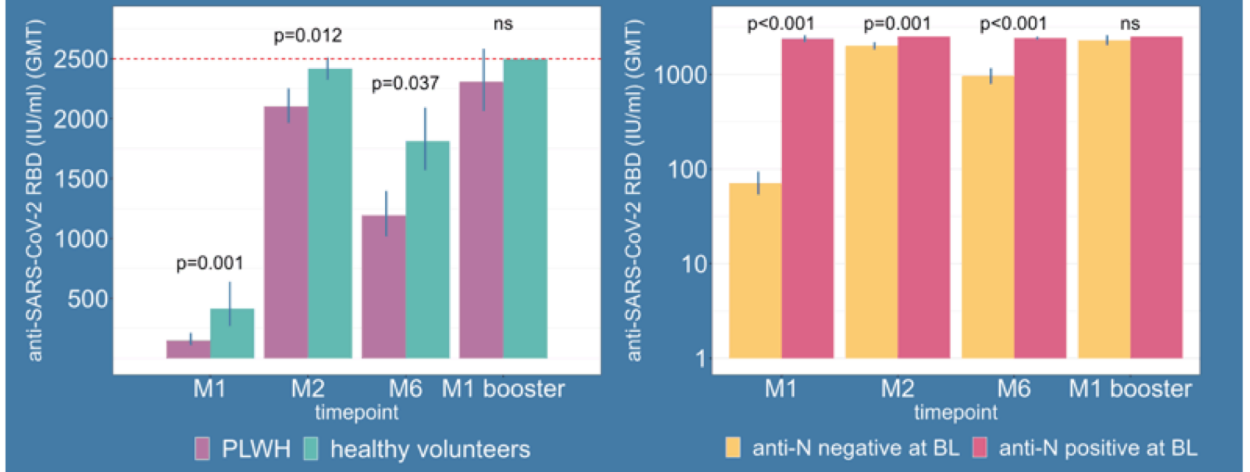
30% years old (median)
60.2% male

Calmy A, et al. CROI, February 12-16 and 22-24, 2022.

COVID-19 Prevention

RESULTS

Quantification of anti-RBD Ig (GMT) at each time point

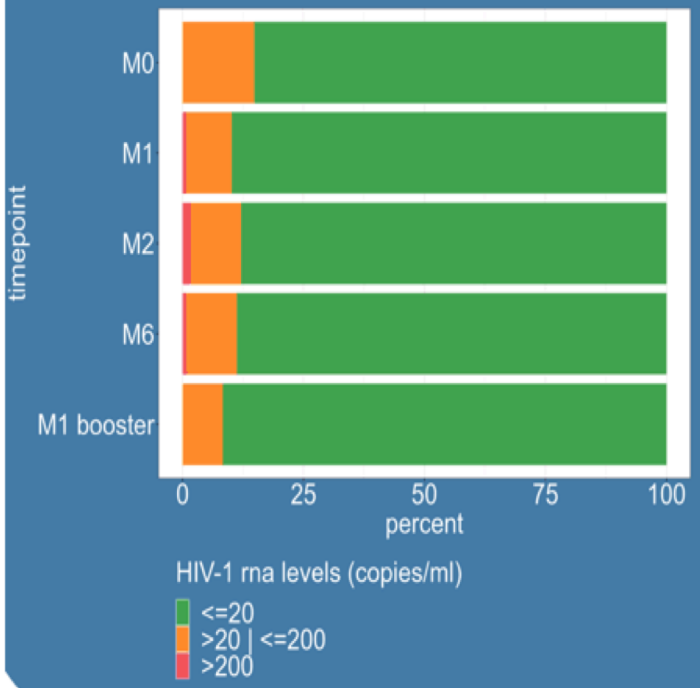


Satisfactory anti-RBD antibodies titers up to 6 months after two doses of SARS-CoV-2 mRNA vaccine in PLWH.

Higher antibodies titers in healthy volunteers.

GMT were significantly higher in patients (PLWH) with positive anti-N at baseline

HIV-RNA at each time point (various cut-off)



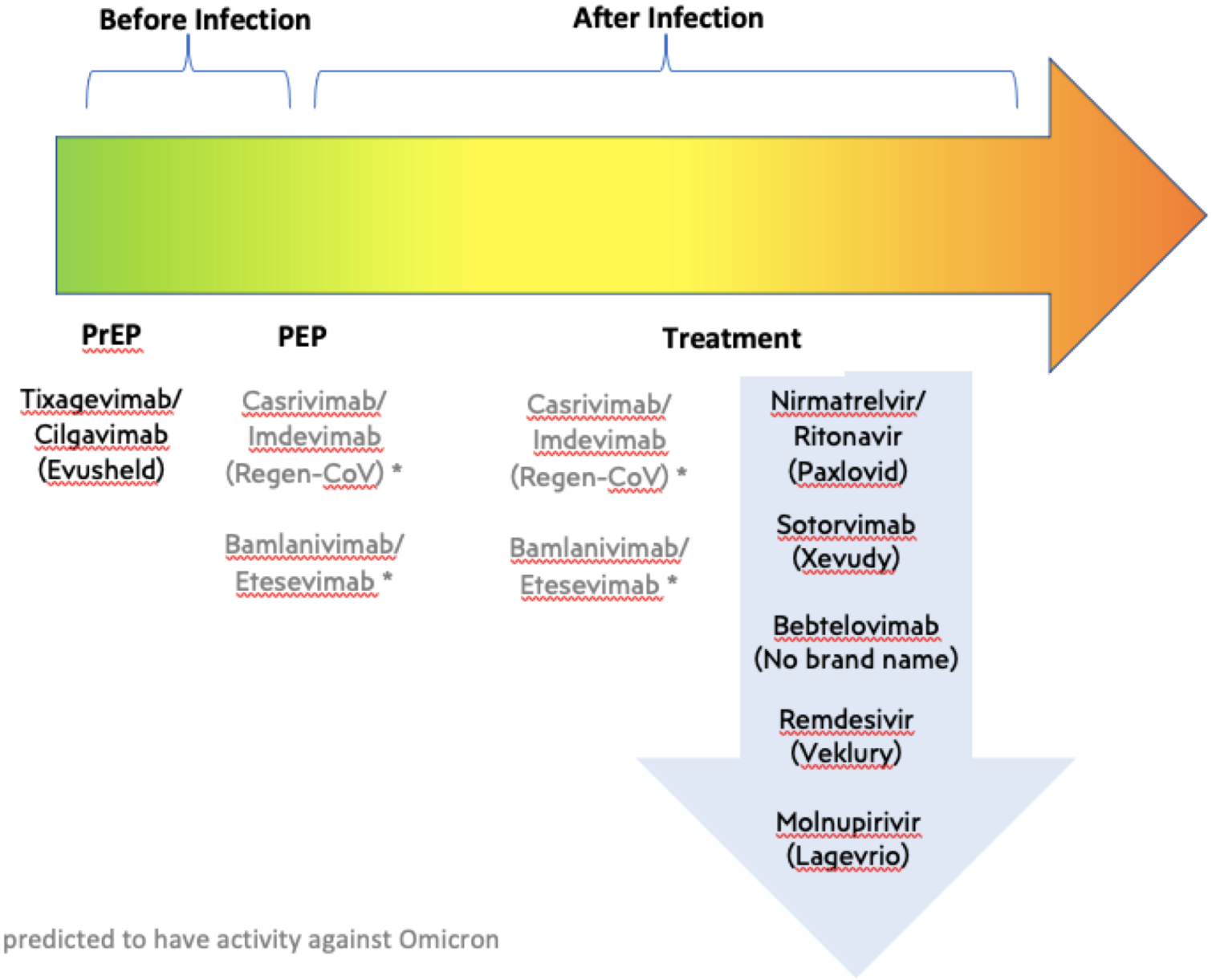
No significant changes in HIV RNA before and after SARS COV-2 vaccine administration (mRNA platform).

Spike Ab levels after mRNA vax lower in PLWH.

Vaccination did not impact suppression of HIV RNA

Calmy A, et al. CROI, February 12-16 and 22-24, 2022.

COVID-19: Treatment



*Not predicted to have activity against Omicron

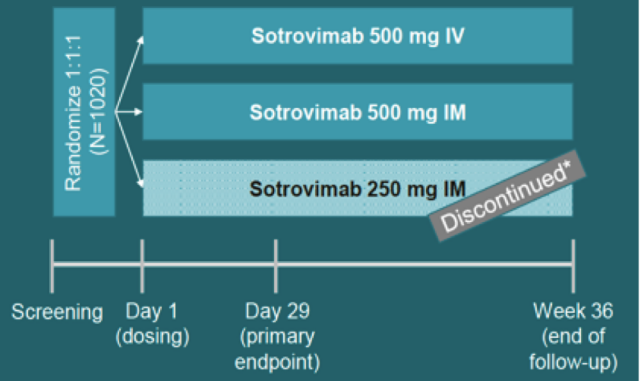
COVID-19 Treatment

- COMET-TAIL Trial
  - IM vs IV
  - Acute COVID-19
  - Enrolled during Delta surge

Study Design

Patient population:

- COVID-19+ with symptoms ≤7 days
- Age ≥12 years and at high risk of progression
  - ≥55 years old
  - Diabetes, obesity, CKD, sickle-cell disease, congenital heart disease, neurodevelopmental disorders, chronic lung disease, immunosuppression or chronic liver disease



Primary endpoint, Day 29: Hospitalization >24 hours for acute management of illness or death, **due to any cause**

Non-inferiority study with a 3.5% NI margin on absolute scale (per feedback from the FDA)

Enrollment occurred from June to August 2021, coinciding with a surge of the Delta variant

*Ongoing safety review led to early discontinuation of the 250 mg IM arm due to an increased rate of hospitalizations compared with the 500 mg arms.

Primary Efficacy Endpoint

Hospitalization >24 hours or death through Day 29, due to any cause

	Sotrovimab 500 mg IV (N=382)	Sotrovimab 500 mg IM (N=379)
Key inclusion/exclusion criteria violations,* n (%)	4 (1)	3 (<1)
Progression status, n (%)		
n	378	376
Hospitalized >24 hours and/or death	5 (1.3)	10 (2.7)
Hospitalized >24 hours	5 (1.3)	10 (2.7)
Death	0	2 (0.5)
Alive and not hospitalized >24 hours	365 (96.6)	356 (94.7)
Missing†	8 (2.1)	10 (2.7)
Sotrovimab 500 mg IM vs 500 mg IV: Hospitalization >24 hours and/or death		
Risk difference (%)‡	1.07	
95% CI	(–1.25, 3.39)	

*Fully vaccinated, immunocompetent participants who were randomized in violation of amendment 2 (IV, n=4; IM, n=1) and 2 participants in the IM arm who did not have a positive SARS-CoV-2 result.
†Missing progression status = participants who were randomized but not dosed (n=6) or withdrew prior to Day 29 (n=12) and had not had a progression event.
‡Analysis performed using binomial regression model with identity link function and with treatment (500 mg IV, 500 mg IM), age (<65, ≥65 years), and sex (male, female) as covariates.

In the 250 mg IM group, 10/183 (5.5%) of participants were hospitalized >24 hours through Day 29.

Day 29 analysis DCO: October 28, 2021.

Sotro 500 mg IM was non-inferior to 500 mg IV for preventing hospitalization/death in modestly high-risk patients with acute COVID-19.

Shapiro AE, et al. CROI, February 12-16 and 22-24, 2022. Abstract 102.

COVID-19 Treatment

- MOVe-OUT Phase 3 blinded trial of Molnupirivir for early C19 found efficacy at preventing combined endpoint hospitalization/death of ~30% (NEJM 2022)
- Randomized Open-Label Trial of Molnupirivir in early C19 in India
  - Test results within prior 2 days, symptoms <5 days
  - 18-60 years of age
  - MOL + SOC versus SOC
  - 14-day hospitalization
  - 1,218 participants

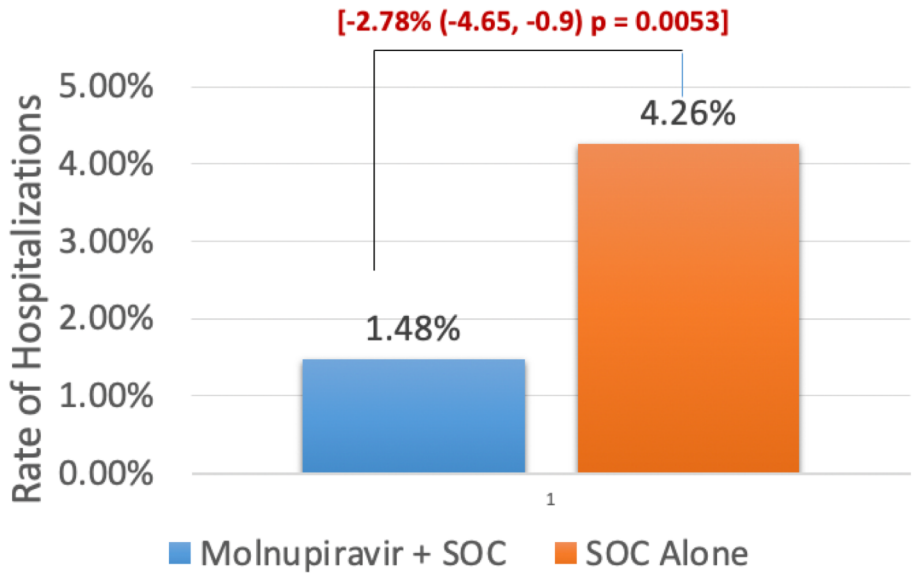
Patient Demographics and Baseline Characteristics

Characteristics	Molnupiravir (N=608) n (%)	Standard of Care (N=610) n (%)
Gender		
Male	408 (67.11)	425 (69.67)
Female	200 (32.89)	185 (30.33)
Race		
Indian	608 (100)	610 (100)
Age (years, Mean ± SD)	35.2 ± 10.8	34.8 ± 10.8
Height (cm, Mean ± SD)	165.6 ±9.5	165.4 ±9.4
Weight (kg, (Mean ± SD)	65.0 ±9.1	64.2 ±7.9
BMI (kg/m2, (Mean ± SD)	23.5 ±2.6	23.4 ±2.6
Comorbidities		
Obesity (BMI > 30)	19 (3.12)	17 (2.78)
Diabetes Mellitus	2 (0.32)	2 (0.32)
Hypertension	3 (0.49)	7 (1.14)
Time Since Symptom Onset		
<3 days	327 (53.7)	335 (54.9)
3 – 5 days	281 (46.3)	275 (25.1)
SARS CoV-2 RT-PCR Test		
Positive <48 hours	608 (100)	610 (100)
Cycle Threshold Value (Mean ± SD)	25.9 (3.8)	25.9 (3.8)
Standard of Care Provided		
Multivitamins, antipyretics and Antihistamines	478 (78.6)	472 (77.4)
Ivermectin	296 (48.68)	472 (77.38)
Inhalation Budesonide	10 (1.6)	10 (1.6)

Kumarasamy N, et al. CROI, February 12-16 and 22-24, 2022. Abstract 102.

COVID-19 Treatment

Primary Endpoint
Rate of hospitalization from randomization up to Day 14



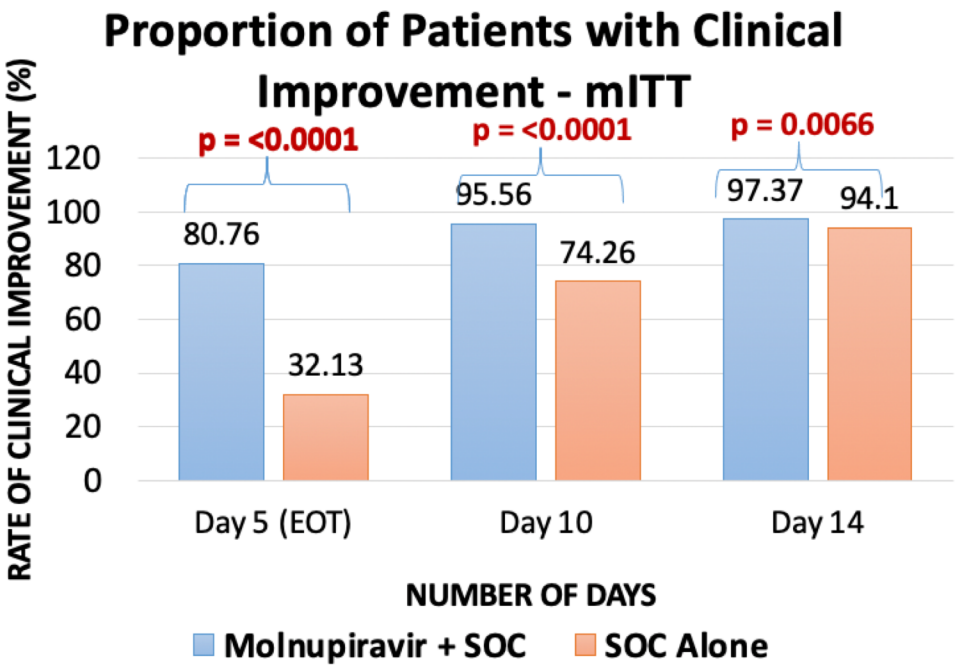
- **The difference in rate of hospitalizations between Molnupiravir and SOC was statistically significant at the end of Day 14 with Molnupiravir 800 mg showing superiority over SOC alone in patients with Mild COVID-19 disease in rate of hospitalizations post treatment up to day 14.**

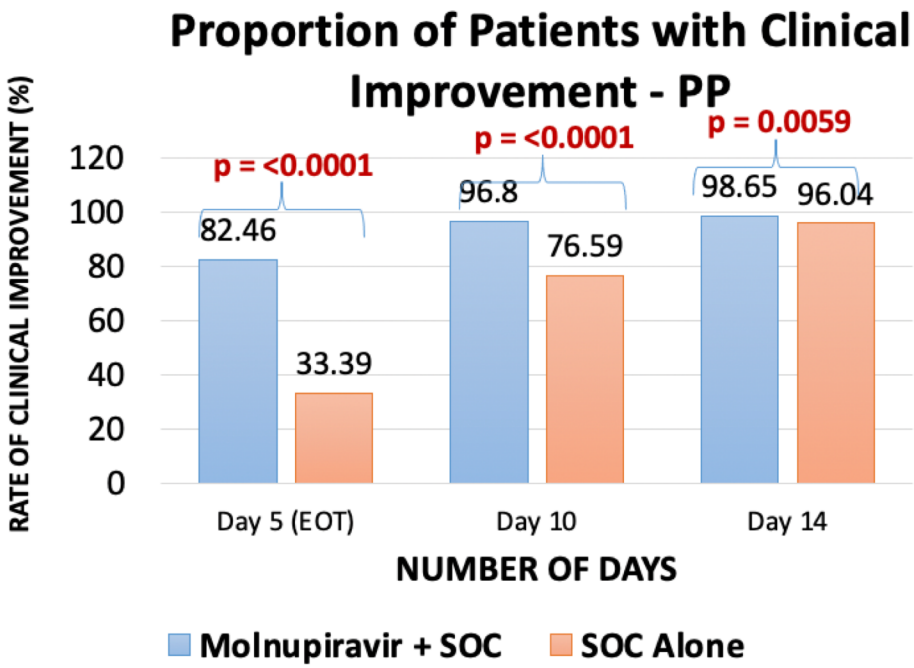
Parameter	Molnupiravir N=608 n (%)	Standard of Care N=610 n (%)	Proportion Difference	95% Confidence Interval	Molnupiravir Vs Standard of Care (p-values**)
Patients Hospitalized	9 (1.48)	26 (4.26)	-2.78	[-4.65, -0.9]	0.0053
**p-values were obtained using Fisher test					

Kumarasamy N, et al. CROI, February 12-16 and 22-24, 2022. Abstract 102.

COVID-19 Treatment

Secondary Endpoint
Proportion of patients with clinical improvement



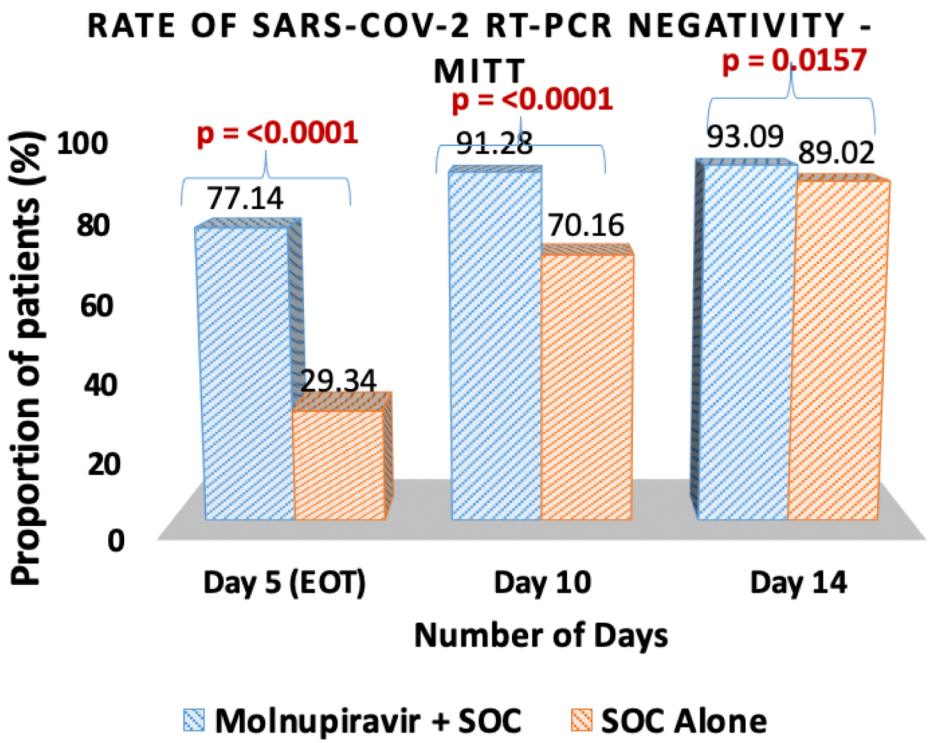


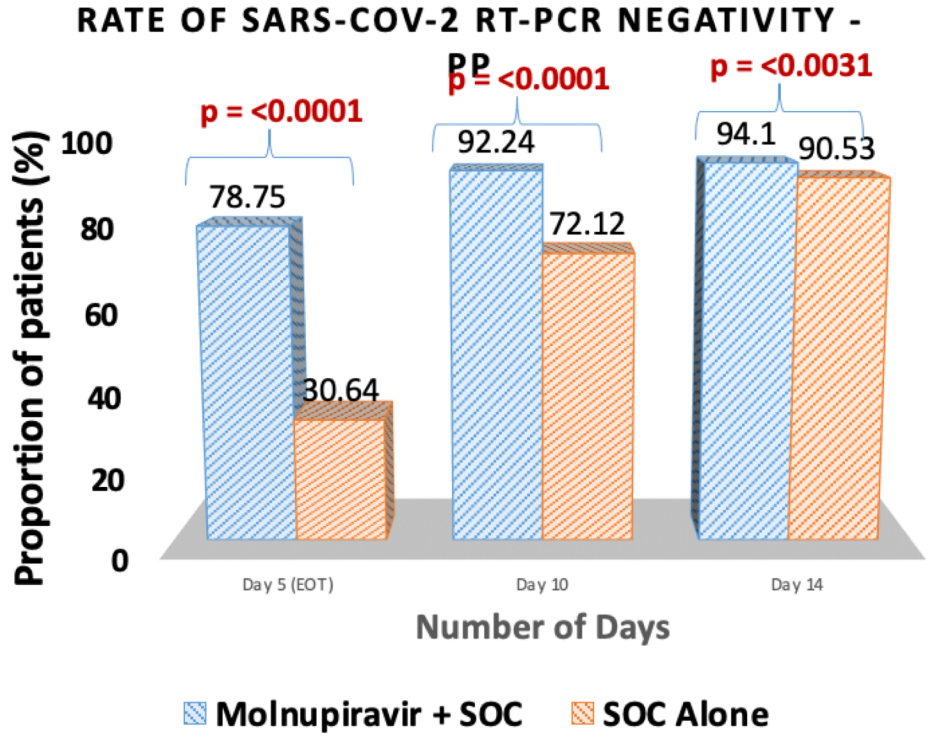
- **The difference in proportion of patients with clinical improvement between Molnupiravir group and SOC alone group were statistically significant at end of treatment, day 10 and end of day 14 with a comparatively early and superior improvement in Molnupiravir group compared to SOC alone group.**

Kumarasamy N, et al. CROI, February 12-16 and 22-24, 2022. Abstract 102.

COVID-19 Treatment

Rate of SARS-CoV2 RT-PCR negativity





- The difference in rate of SARS-CoV-2 RT PCR negativity between Molnupiravir and SOC alone is statistically significant at end of treatment , end of day 10 and end of day 14 with early and superior negativity observed in Molnupiravir compared to SOC alone.

Kumarasamy N, et al. CROI, February 12-16 and 22-24, 2022. Abstract 102.

COVID-19 Treatment

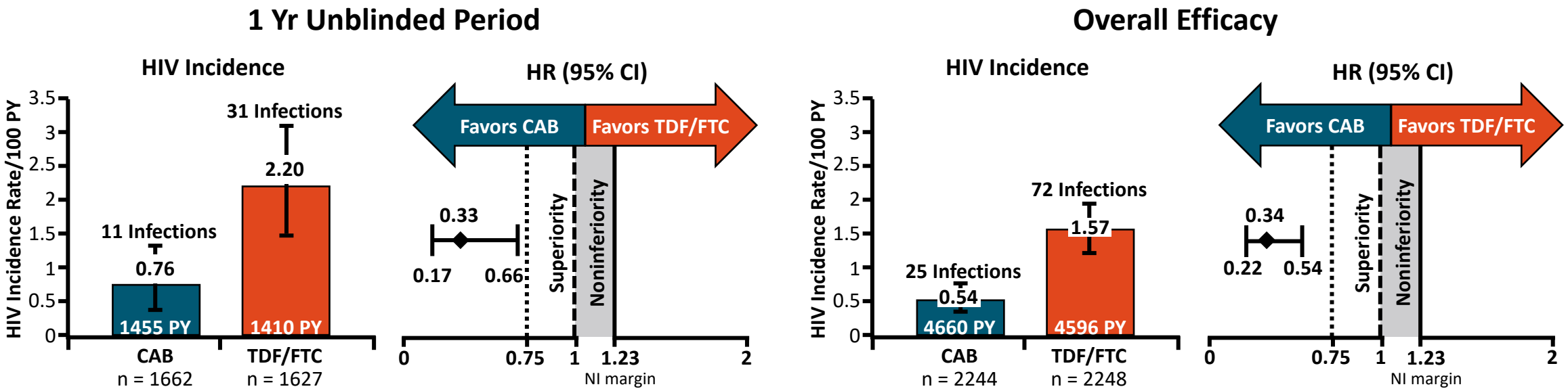
"…issued an EUA for emergency use of…molnupiravir…for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in ***adults with positive results of direct SARS-CoV-2 viral testing*** *who are at* ***high risk for progressing to severe COVID-19,*** *including hospitalization or death,* ***and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate****."*

Molnupiravir. EUA Fact Sheet for Healthcare Providers. Last updated December 23, 2021.

COVID-19 Prevention Treatment

- Vaccine boosters work, especially to protect against severe disease
- People living with HIV may have lower levels of antibodies following vaccination, particularly if older, have lower CD4 cell counts, and/or have detectable viral loads
- COVID-19 vaccination does not lead to loss of virologic suppression of HIV
- Molnupirivir may be more effective than MOVe-Out trial suggests but likely less than other authorized therapies

HPTN 083: 1-Yr Follow-Up After Unblinding

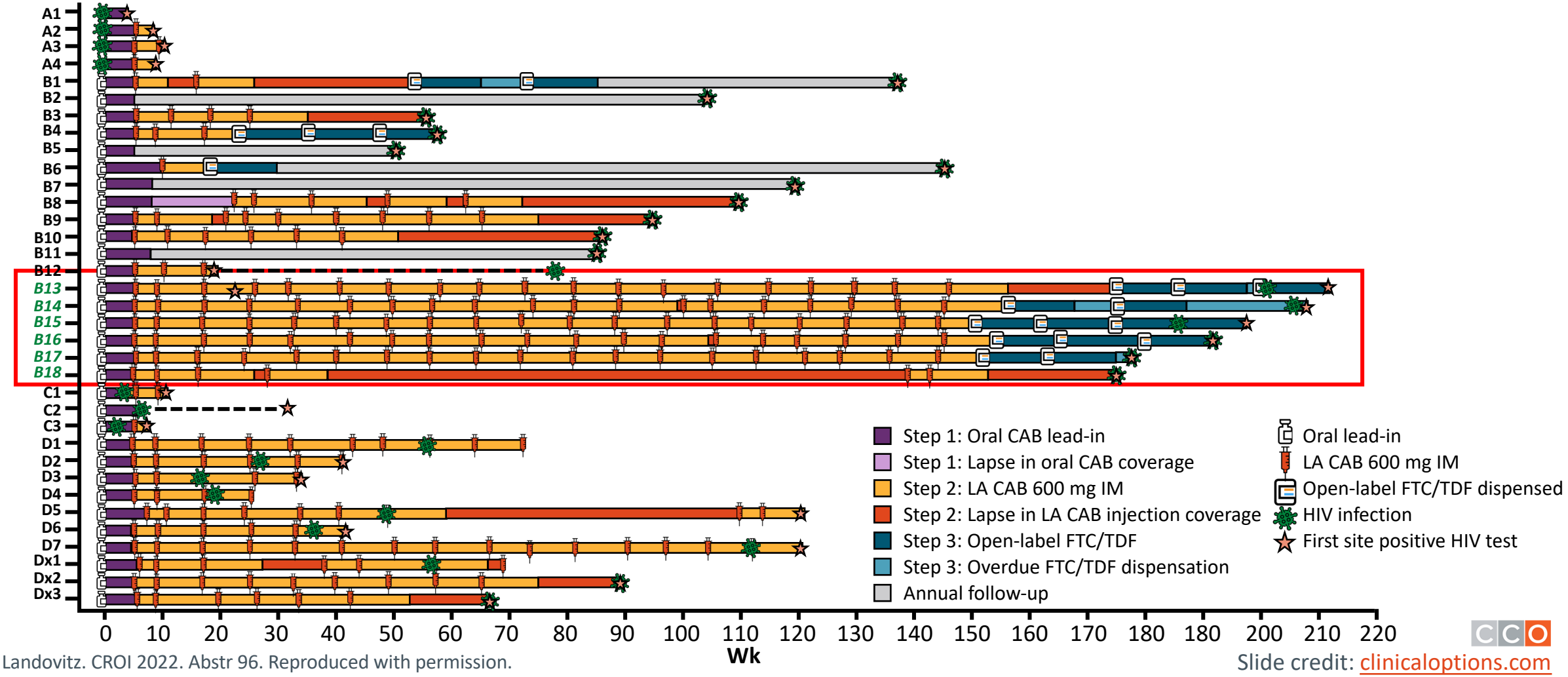


- 13 additional infections identified on CAB
  - 2 newly identified CAB infections during the blinded period, both with on-time injections
  - 11 during the unblinded period (1 with on-time injections, 3 with delayed injections, 7 with ≥6 mo after CAB)
- Total of 7 breakthrough infections on CAB despite on-time dosing to date

Landovitz. CROI 2022. Abstr 96.

HPTN 083: HIV Infections in CAB Arm After ≥3 Yr on Study

- 6 additional HIV infections identified (B13-B18) ≥3 years on study (all ≥6 months after last CAB exposure)



Landovitz. CROI 2022. Abstr 96. Reproduced with permission.

Slide credit: clinicaloptions.com

HIV PrEP

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.

Slide credit: clinicaloptions.com

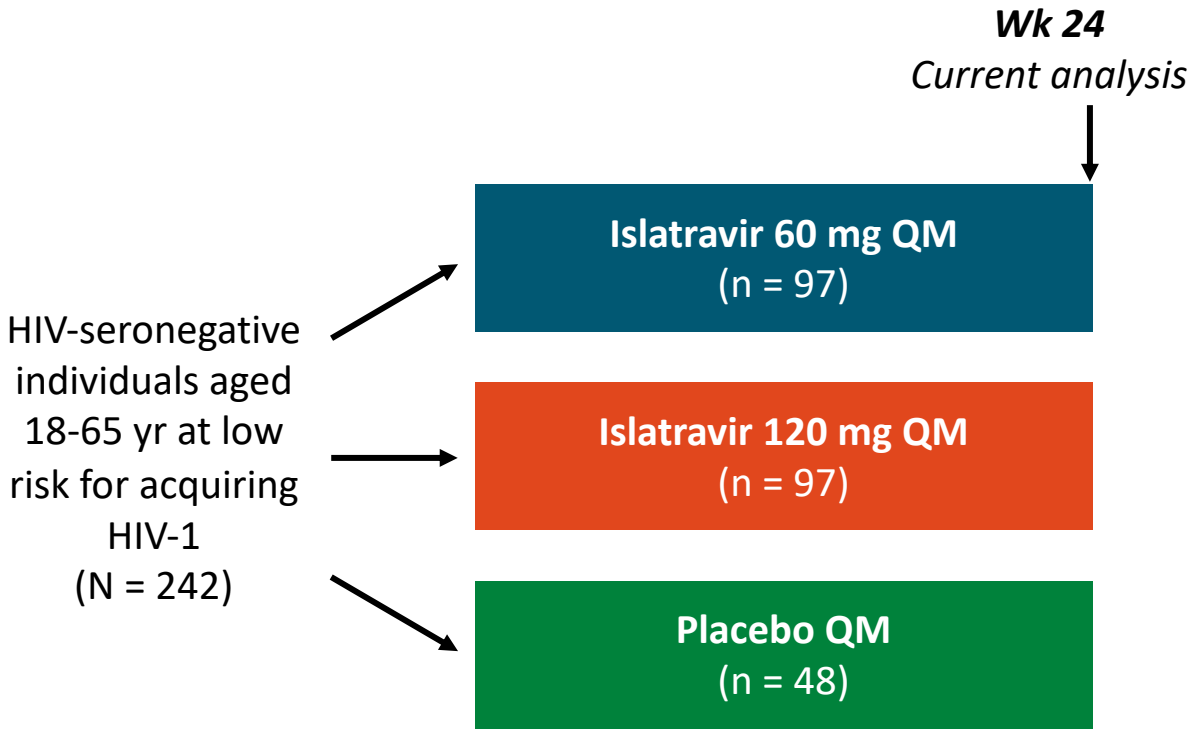
Use of a Single-Genome Sequencing INSTI Genotyping Assay in HPTN 083

- In 6 of 7 participants, major INSTI RAMs were first detected in samples with VL <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 RNA screening is not readily available

Eshleman. CROI 2022. Abstr 95.

MK8591-016 Trial of Islatravir for PrEP

- Multicenter, randomized, double-blind, placebo-controlled phase IIa trial of monthly oral islatravir (NRTTI)



Baseline Characteristic	ISL 60 mg QM (n = 97)	ISL 120 mg QM (n = 97)	Placebo QM (n = 48)
Female at birth, n (%)	66 (68.0)	64 (66.0)	33 (68.8)
Median age, yr (range)	32 (20-58)	31 (18-58)	30 (19-45)
Race ethnicity, n (%)			
▪ White	55 (56.7)	44 (45.4)	29 (60.4)
▪ Black/AA	37 (38.1)	48 (49.5)	16 (33.3)
▪ Hispanic/Latino	19 (19.6)	9 (9.3)	8 (16.7)
▪ Other	5 (5.2)	5 (5.2)	3 (6.3)
Median weight, kg	73.1	72.5	75.1
Median eGFR, mL/min/1.73 m^2	114.4	119.9	118.7

- Key endpoints: safety/tolerability, PK

Macdonald. CROI 2022. Abstr 85.

Slide credit: clinicaloptions.com

HIV PrEP

MK8591-016 Trial of Islatravir for PrEP: Metabolic and Renal Outcomes

Median % Change From Baseline to Wk 24	ISL 60 mg QM (n = 97)	ISL 120 mg QM (n = 97)	Placebo QM (n = 48)
Weight, kg	+0.4	+1.8	+0.2
DEXA parameters			
▪ Body fat			
• Peripheral fat	-0.35 (n = 83)	+2.50 (n = 89)	+0.77 (n = 41)
• Trunk fat	+0.95 (n = 83)	+3.42 (n = 89)	+0.25 (n = 41)
▪ BMD			
• Total hip	+0.22 (n = 83)	-0.09 (n = 87)	+0.10 (n = 42)
• Lumbar spine	+0.53 (n = 82)	0.00 (n = 89)	+0.63 (n = 42)
Renal parameters			
▪ Serum creatinine, mg/dL (IQR)	0.0 (-11.8 to +12.8)	0.0 (-5.8 to +11.1)	0.0 (0.0 to +14.3)
▪ eGFR, mL/min/1.73 m^2 (IQR)	0.0 (-12.9 to +15.6)	0.0 (-11.5 to +7.2)	0.0 (-14.3 to 0.0)

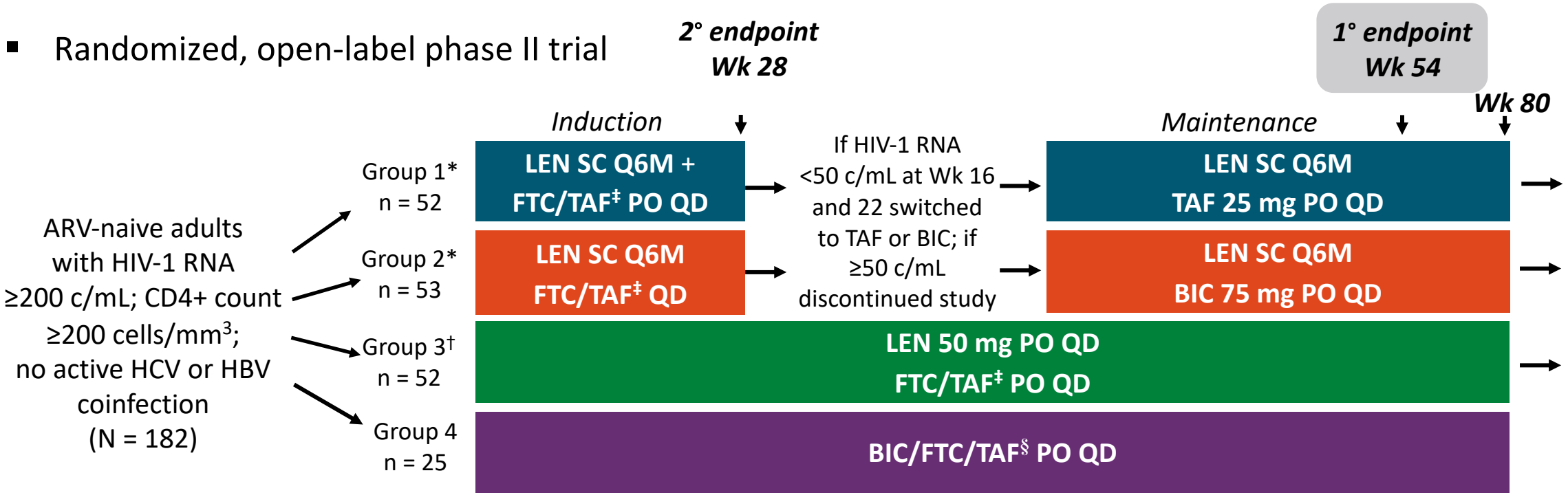
- At Wk 24, no clinically meaningful differences from placebo in metabolic and renal parameters with islatravir 60 mg or 120 mg after 6 QM doses
- **Islatravir PrEP program placed on hold by FDA due to observed changes in lymphocytes in clinical trials**

Macdonald. CROI 2022. Abstr 85.

Slide credit: clinicaloptions.com

CALIBRATE: Lenacapavir in Treatment-Naive PWH

- Randomized, open-label phase II trial

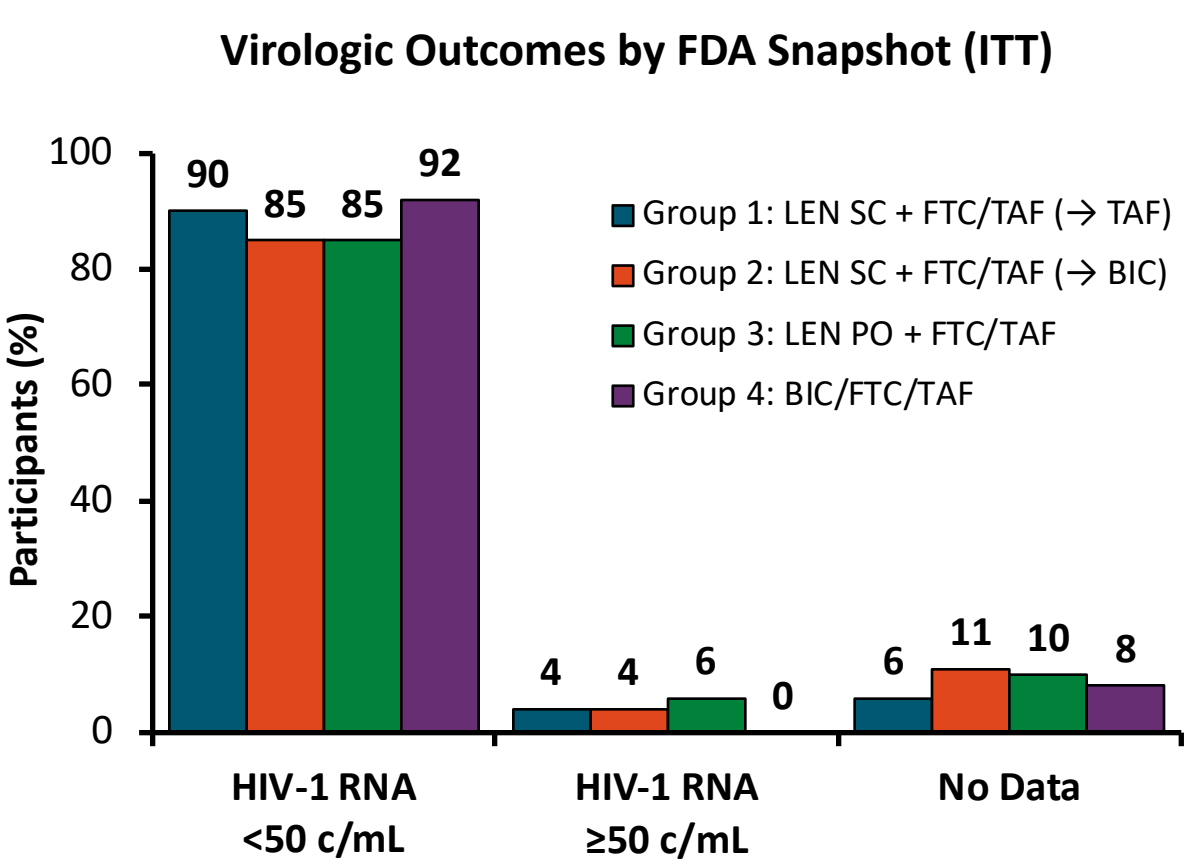


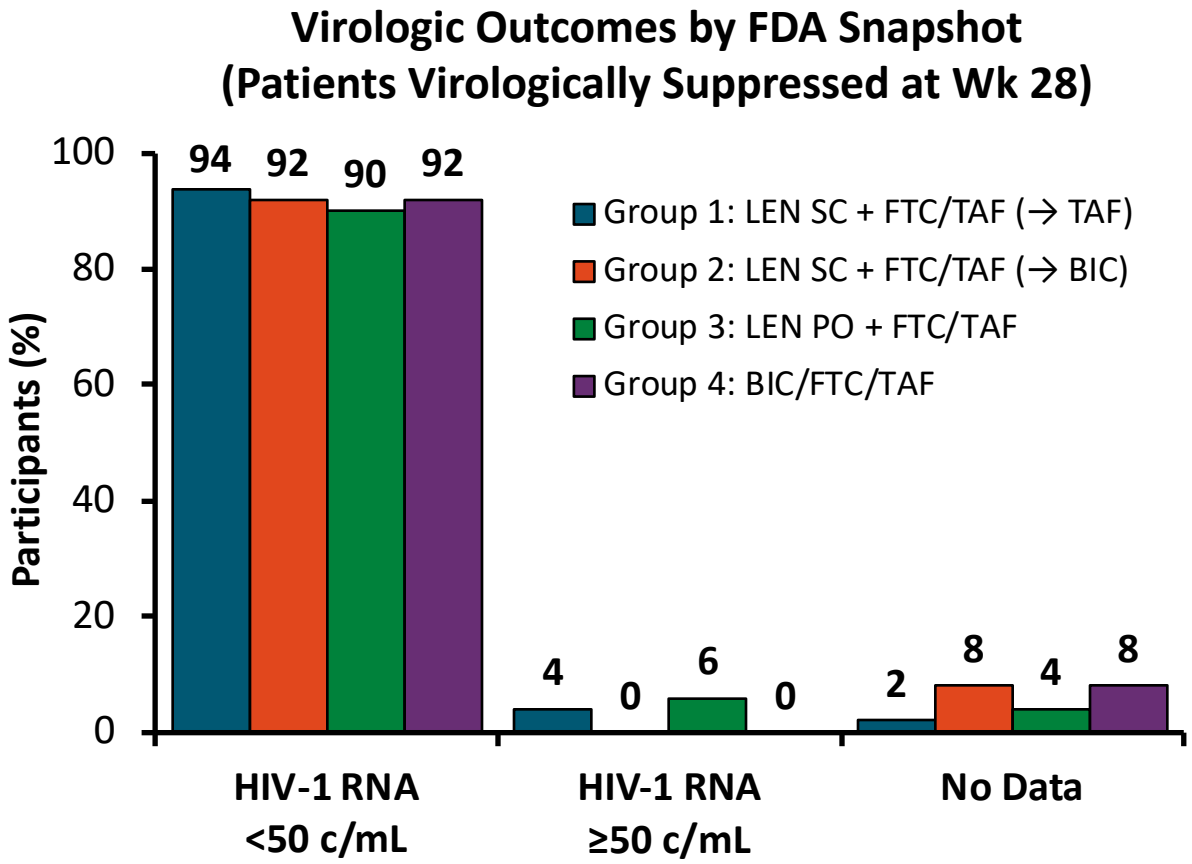
*LEN oral lead-in 600 mg Days 1 and 2, 300 mg Day 8; LEN 927 mg SC Day 15 and then Q6M.
†LEN 600 mg Days 1 and 2, then 50 mg from Day 3. ‡FTC/TAF 200/25 mg. §BIC/FTC/TAF 50/200/25 mg.

- **Primary outcome: proportion with HIV-1 RNA <50 c/mL at Wk 54**
- Secondary outcomes: proportion with HIV-1 RNA <50 c/mL at Wk 28, 38, and 80; change from baseline in log_{10} HIV-1 RNA and CD4+ cell count at Wk 28, 38, 54, and 80

Gupta. CROI 2022. Abstr 138.

CALIBRATE: Wk 54 Virologic Outcomes





Gupta. CROI 2022. Abstr 138.

Slide credit: clinicaloptions.com

CALIBRATE: Resistance and Safety

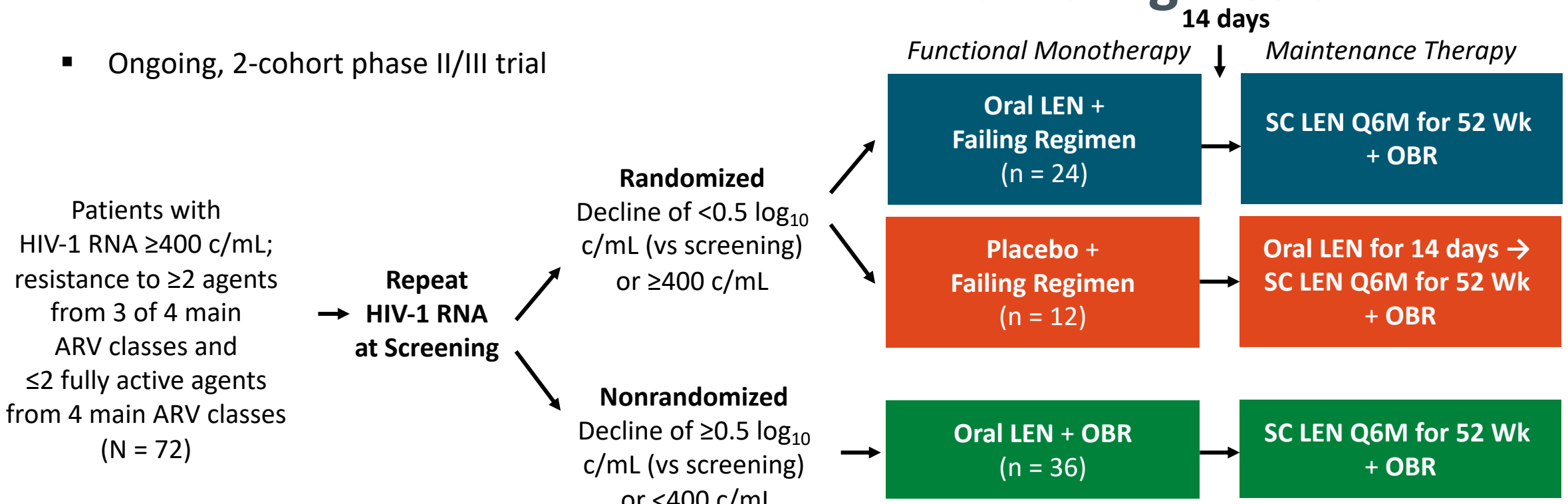
- Emergent LEN resistance observed in 2/157 (1.5%) patients
  - 1 patient receiving **LEN SC + FTC/TAF → BIC** at Wk 10
    - CA: Q67H + K70R (LEN fold change = 20) in CA + M184M/I in RT
    - Pattern suggests incomplete adherence to FTC/TAF
  - 1 patient receiving **LEN PO + FTC/TAF** at Wk 54
    - Q67H (LEN fold change = 7) in CA
    - Nonadherent to FTC/TAF based on pill count, drug levels
- Both later resuppressed on regimen of INSTI + 2 NRTI

- LEN well tolerated with favorable safety profile
  - No SAEs or grade 4 AEs related to study drug
  - Most common AEs: headache and nausea (13% each)
  - GI AEs in SC vs PO LEN
    - Nausea: 14% vs 12%
    - Diarrhea: 7% vs 10%
    - Vomiting: 4% vs 8%
- ISRs mostly grade 1/2; only 1 grade 3 ISR
- 3 discontinuations due to ISRs (due to grade 1 induration or erythema and swelling)

Gupta. CROI 2022. Abstr 138.

CAPELLA: Lenacapavir in People With Multidrug-Resistant HIV

- Ongoing, 2-cohort phase II/III trial



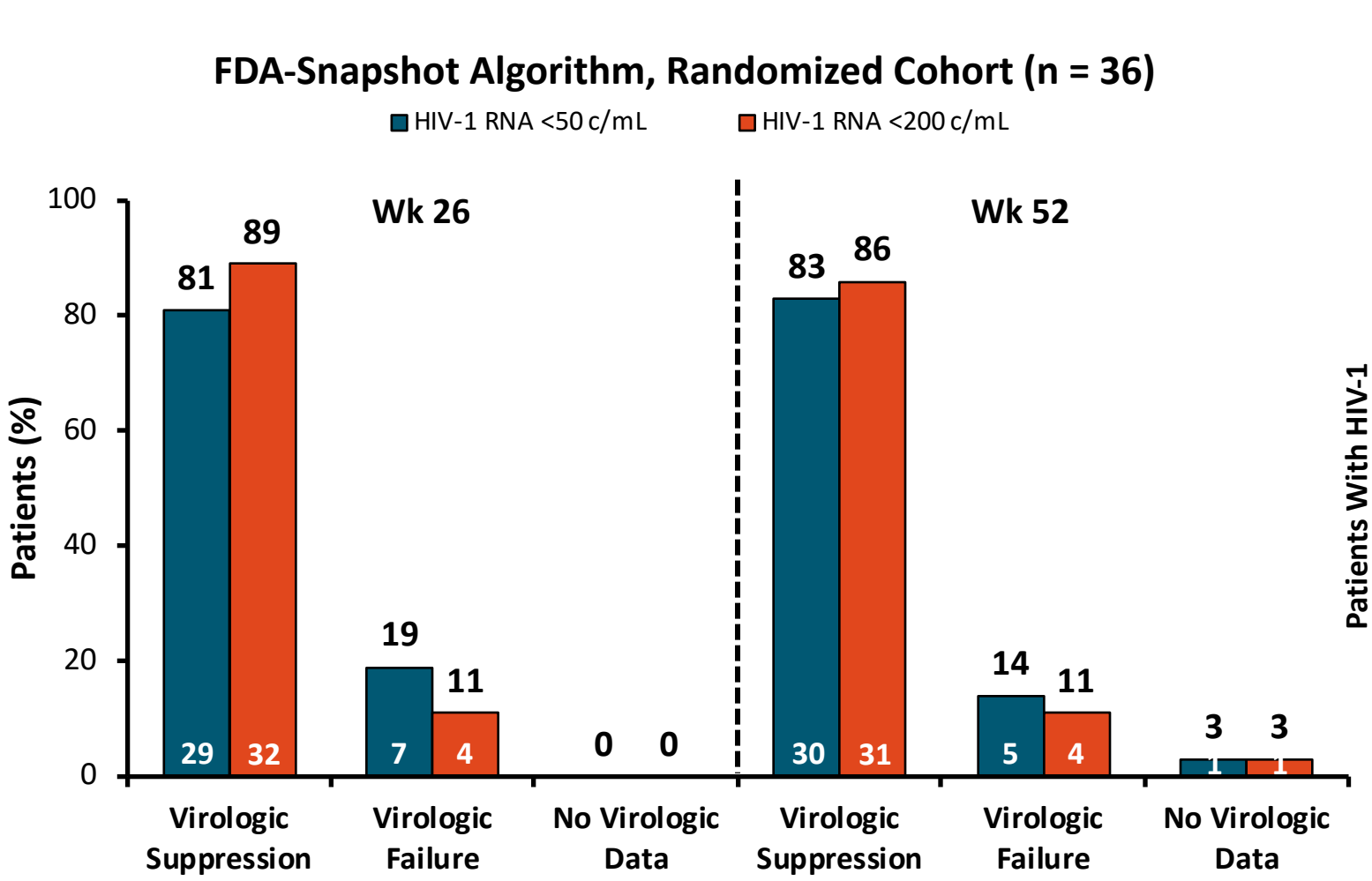
Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

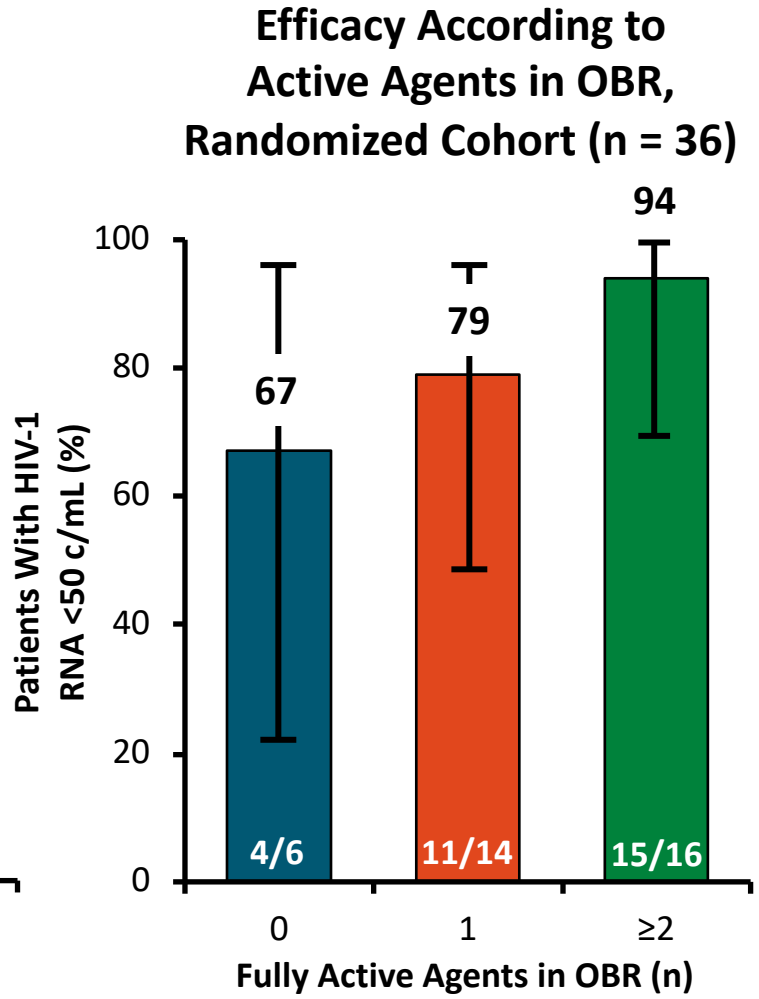
- Primary endpoint achieved in prior analysis: ≥0.5 $\log_{10}$ c/mL decline in HIV-1 RNA at Day 14 in randomized cohort
- Secondary endpoints: HIV-1 RNA <50 c/mL, <200 c/mL at Wk 26 and 52 in randomized cohort

Ogbuagu. CROI 2022. Abstr 491.

Slide credit: clinicaloptions.com

CAPELLA Secondary Endpoints: Lenacapavir Efficacy at Wk 52 in Randomized Cohort





Ogbuagu. CROI 2022. Abstr 491.

Slide credit: clinicaloptions.com

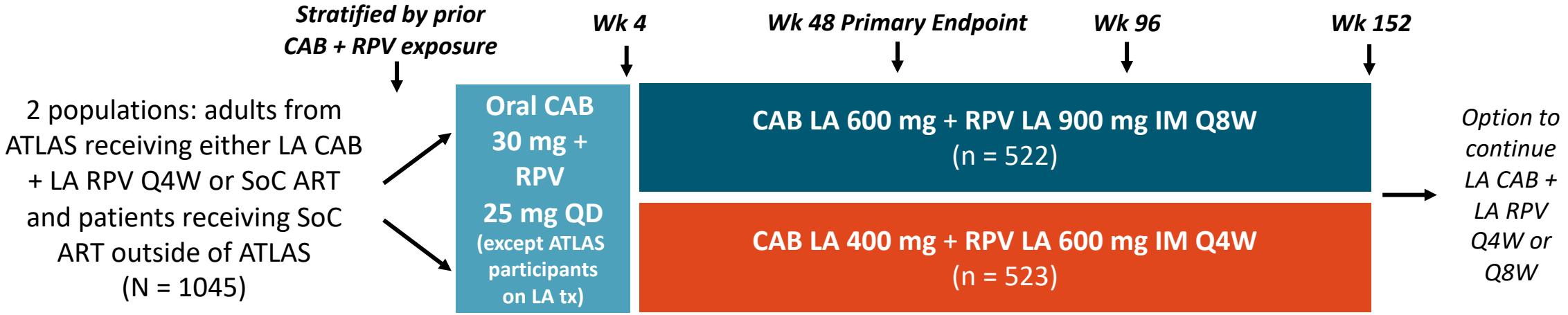
CAPELLA: Other Lenacapavir Efficacy and Safety Outcomes in Randomized Cohort

- **LEN resistance occurred in 4 patients** through Wk 26, but not thereafter
  - All had no fully active drugs in OBR or inadequate adherence to OBR
- Mean change in CD4+ cell count at Wk 52: +83 cells/mm^3
- Incidence of very low CD4+ cell count (<50 cells/mm^3) decreased from 22% (8/36) at baseline to 3% (1/36) at Wk 52
- Incidence of CD4+ cell count ≥200 cells/mm^3 increased from 25% (9/36) at baseline to 60% (21/36) at Wk 52
- ISRs most common AE with SC LEN
  - Most ISRs were grade 1 or 2
  - 2 patients had grade 3 ISRs
  - All nodules were grade 1, except 1 patient with 2 AEs of grade 2 nodules after second and third injections (both resolved in 3 days)
- 1 patient discontinued LEN at Wk 52 due to ISR (nodule; grade 1)
- **LEN clinical trials currently on hold due to concerns about the compatibility with the borosilicate vials**

Ogbuagu. CROI 2022. Abstr 491.

ATLAS-2M: Wk 152 Results of Switch to LA CAB + RPV

- Multicenter, randomized, open-label phase IIIb noninferiority trial



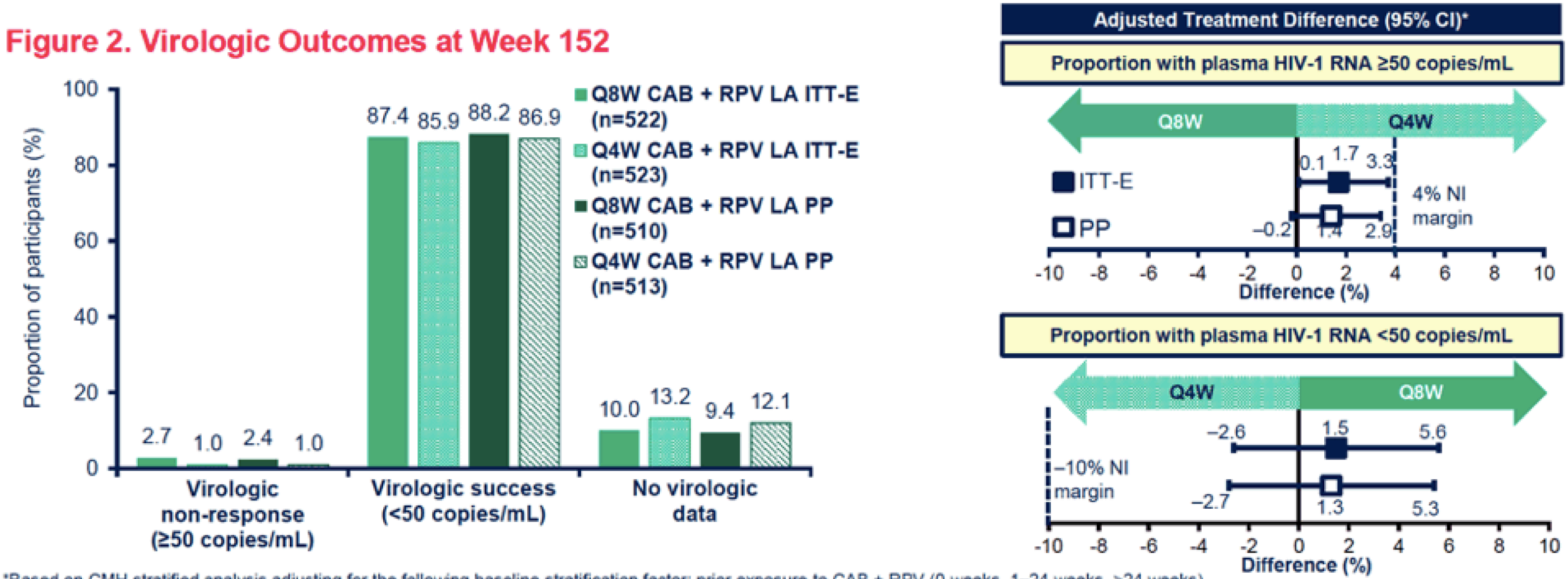
- Primary endpoint: HIV-1 RNA ≥50 c/mL at Wk 48 by FDA snapshot in ITT-E
- Secondary/other Wk 152 endpoints: plasma HIV-1 RNA ≥50 or <50 c/mL at Wk 152 by FDA snapshot in ITT-E, CVF incidence, viral resistance in patients with CVF, safety and tolerability, treatment satisfaction

Overton. Lancet. 2021;396:1994. Overton. CROI 2022. Abstr 479. NCT03299049.

ATLAS-2M: Wk 152 Virologic Outcomes

- 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.

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.

Overton. CROI 2022. Abstr 479.

ATLAS-2M: Wk 152 Virologic Outcomes

- 2 additional participants (both male at birth, BMI <30 kg/m^2) in Q8W arm met CVF criteria between Wk 96 and 152 (Wk 112, 120)
  - At BL, neither had RAMs; participant with A6 subtype had L74I integrase polymorphism
- **Through Wk 152, 13 participants had CVF:**
  - **Q8W, n = 11 (2%); Q4W, n = 2 (<1%)**
  - None with injection >7 days late

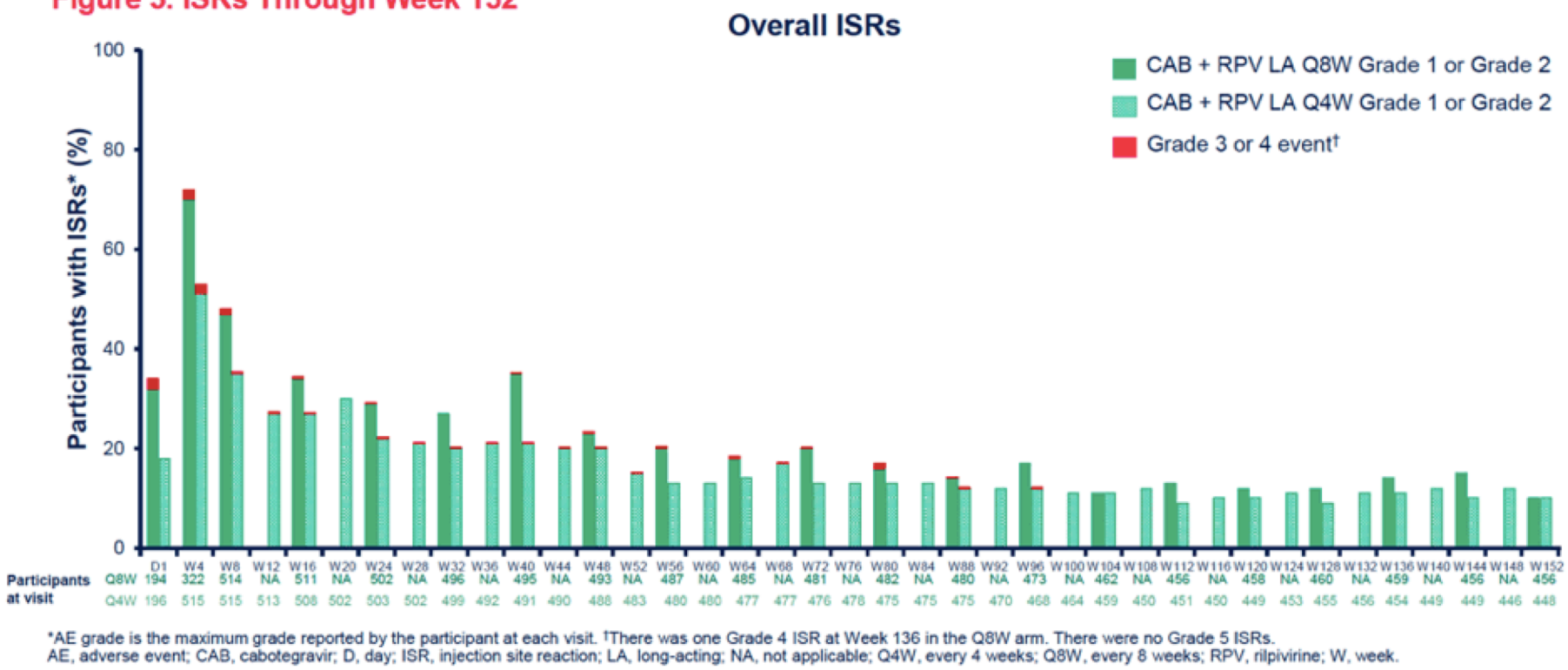
Country	Baseline	At Failure		
	HIV-1 Subtype	HIV-1 RNA (c/mL)	RPV RAMs	INI RAMs
Germany	B	24,221	E138A+ M230M/L	Q148R
Russia	A6*	59,467	E138A+ Y181Y/C	Q148R

*Originally classified as A1; later reclassified as A6 upon reanalysis

Overton. CROI 2022. Abstr 479.

ATLAS-2M: ISRs and Treatment Satisfaction Through Wk 152

Figure 3. ISRs Through Week 152



*AE grade is the maximum grade reported by the participant at each visit. †There was one Grade 4 ISR at Week 136 in the Q8W arm. There were no Grade 5 ISRs.
AE, adverse event; CAB, cabotegravir; D, day; ISR, injection site reaction; LA, long-acting; NA, not applicable; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; W, week.

- HIV treatment satisfaction questionnaire scores from participants without prior CAB
  - Total mean scores significantly improved from BL to Wk 152 for both groups
  - Adjusted mean change from BL significantly favored Q8W dosing at Wk 24, 48, and 152

Overton. CROI 2022. Abstr 479.

HIV Treatment

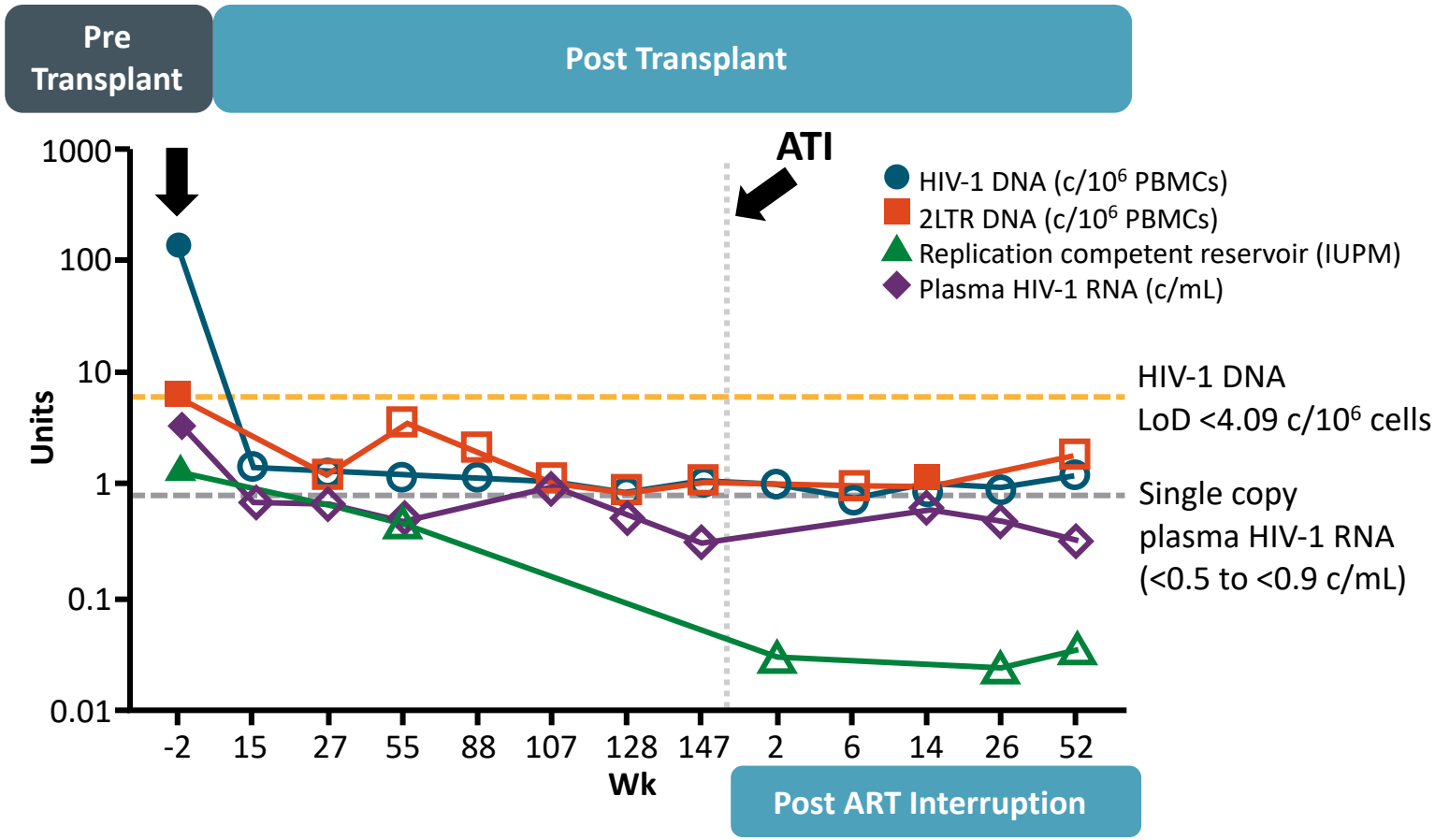
- HAILO Study – In 394 PWH who had neuropsych assessments before and after switch to INSTI scores *improved* over time (years) [O'Halloran JA, et al]. Similar findings of improved cognition from an Italian cohort study [Mastrosa I, et al].
- Phase I bNAbs – Cocktail of bNAbs were able to reduce viral load but unable to keep suppressed. Resistance to some detected with rebound. [Juleg B, et al]
- BFTAF at 5 years – High rates of viral suppression and no failure with resistance. Weight gain of ~6 kg with ~50% seen in first year of starting [Wohl et al].

IMPAACT P1107: Case Report of HIV-1 Remission With CCR5Δ32/Δ32 Haploidentical/Cord Transplant

- 59-yr-old female of “mixed race”
  - Diagnosed with HIV-1 in 2013
  - Diagnosed with high-risk AML in 2017
- Underwent CCR5Δ32/Δ32 cord/haploidentical transplant (5/8 HLA match CBU + PBMCs from relative) in 2017
  - Induction chemotherapy = fludarabine/melphalan/ATG + TBI with 400 cGy
  - 100% sustained engraftment of cord blood by Day 100 post transplant
  - Durable AML remission 4 yr, 6 mo post transplant
- ART stopped 37 mo post transplant

Hsu. CROI 2022. Abstr 65.

IMPAACT P1107: HIV-1 Persistence Post Transplant



- Engrafted cells show:
  - Ex vivo resistance to CCR5- and CXCR4-tropic HIV-1 infection
  - Ex vivo resistance to autologous latent reservoir isolates (CCR5 clade B virus)
- Loss of HIV-1–specific antibody responses observed at Wk 55 post transplant, maintained through 52 wk post ATI

- 14 mo off ART with no viral rebound (no ARVs in plasma)

Hsu. CROI 2022. Abstr 65.

HIV Successful Living

- POPPY Study of Aging in UK
  - Assessment of anticholinergic medications (ACM) and falls

Results

Demographics of PWH ≥ 50

Variable	N=699
Age (median (IQR)), years	57 (53-62)
Male, n (%)	612 (88)
White, n (%)	603 (86)
Unemployed, n (%)	99 (14)
High education, n (%)	479 (69)
Rec drugs last 6 months, n (%)	177 (25)

Prevalence of outcome

9% (63/673) reported recurrent falls

32% (126/609) met frailty criteria

Number of ACM prescribed

ACM number	Frequency n (%)
0	507 (73)
1	129 (18)
≥2 (maximum 9)	63 (9)

ACM1

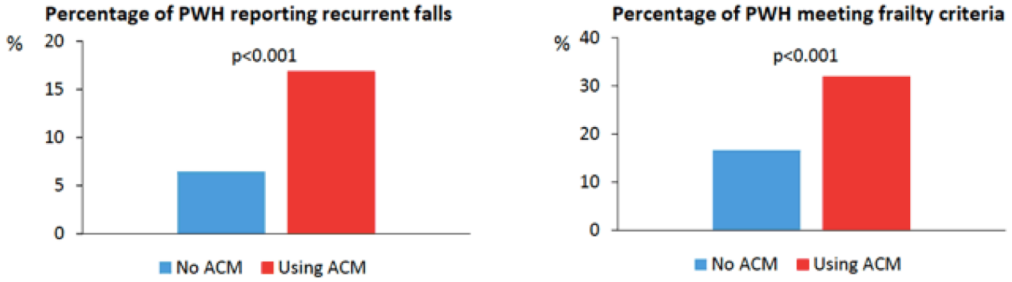
ACM2

ACM3

Commonest ACM prescribed

ACM	Frequency n (%)
Codeine	36 (12)
Citalopram	34 (12)
Loperamide	25 (9)
Amitriptyline	21 (7)
Diazepam	17 (6)
Cetirizine	16 (5)

Association between any ACM use and outcomes

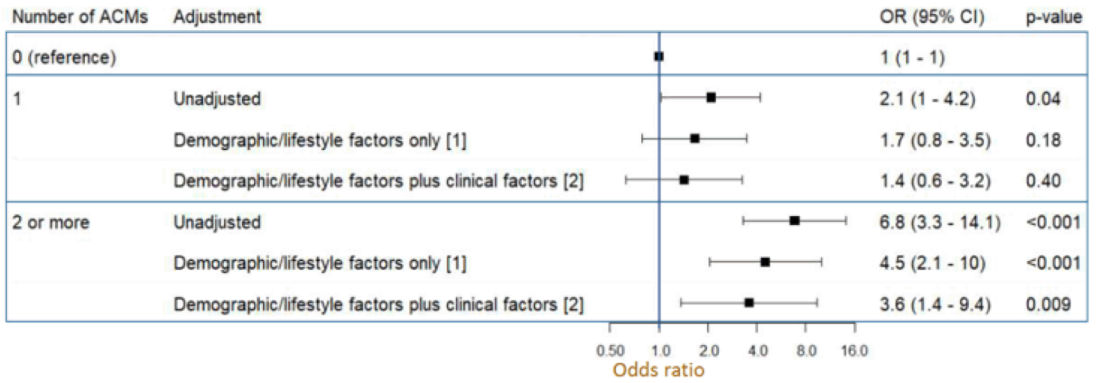


Final regression model of the association of using any ACM with recurrent falls and frailty

Adjustment	ACM	Recurrent falls			Frailty		
		OR	CI	P value	OR	CI	P value
Unadjusted	none	1	n/a		1	n/a	
	Any	3.3	1.9 - 5.9	<0.001	2.3	1.5 - 3.6	<0.001
Demographic/lifestyle	Any	2.5	1.3 - 4.6	0.004	1.8	1.1 – 3.0	0.02
Demographic/lifestyle and clinical factors	Any	1.9	0.9 - 4.0	0.08	1.7	0.9 – 3.0	0.08

Is there a dose relationship?

Association between number of ACM and recurrent falls



[1] age, work, marital status and recent recreational drug use
[2] additionally adjusted for number of non ACM co-medications, number of comorbidities and PHQ-9 score

Anticholinergic medications are commonly prescribed to PWH and are associated with risk of falls and frailty.

Doctor J, et al. CROI, February 12-16 and 22-24, 2022.

HIV Successful Living

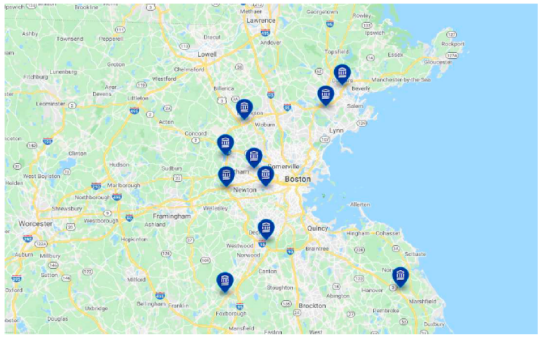
- Kaiser Permanente and Mass Gen Partners Cohorts
  - Compare rates of MI in PWH and PWoH 2005-2020
  - Propensity score matching

Kaiser Permanente Northern California (KPNC)

Integrated healthcare delivery system serving San Francisco Bay Area

4.5 million current members, with ~30,000 cumulative members with HIV

Mass General Brigham (Partners)

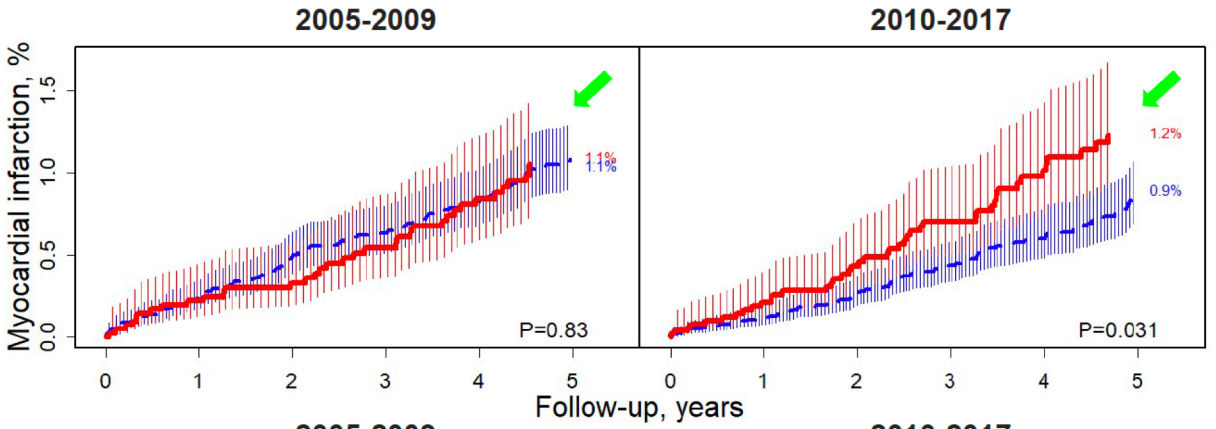


Integrated health care system serving Boston, MA and surrounding regions

Brigham and Women's and Massachusetts General Hospitals and affiliated outpatient centers

1.5 million served annually; ~7,000 cumulative with HIV

Cumulative incidence of MI similar by HIV status in 2005-2009 but higher for PWH compared with PWoH in 2010-2017



2005-2009

	KPNC		Partners		Overall	
HIV Status	PWH	PWoH	PWH	PWoH	PWH	PWoH
N	3,584	10,740	696	3,319	4,280	14,059
MI events	33	105	2	12	35	117
MI rate*	0.24	0.25	0.08	0.10	0.21	0.22

* per 100 person-years

2010-2017

	KPNC		Partners		Overall	
HIV Status	PWH	PWoH	PWH	PWoH	PWH	PWoH
N	4,615	13,857	506	1,502	5,121	15,359
MI events	39	81	4	6	43	87
MI rate*	0.25	0.17	0.22	0.12	0.25	0.16

* per 100 person-years

Adjusted* HRs for MI by HIV Status (PWoH reference), and stratified by Calendar era and Cohort

	KPNC		Partners		Overall	
Era	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
2005-2009	1.0 (0.7, 1.5)	0.90	1.2 (0.3, 5.8)	0.82	1.1 (0.8, 1.5)	0.61
2010-2017	1.6 (1.1, 2.4)	0.02	2.1 (0.6, 7.5)	0.28	1.6 (1.1, 2.4)	0.007

*Stepwise adjusted models considering demographics and Framingham risk score components.

P-interaction (Era*HIV)=0.12

Sensitivity analyses:

(1) evaluate events over 10 years: similar inferences

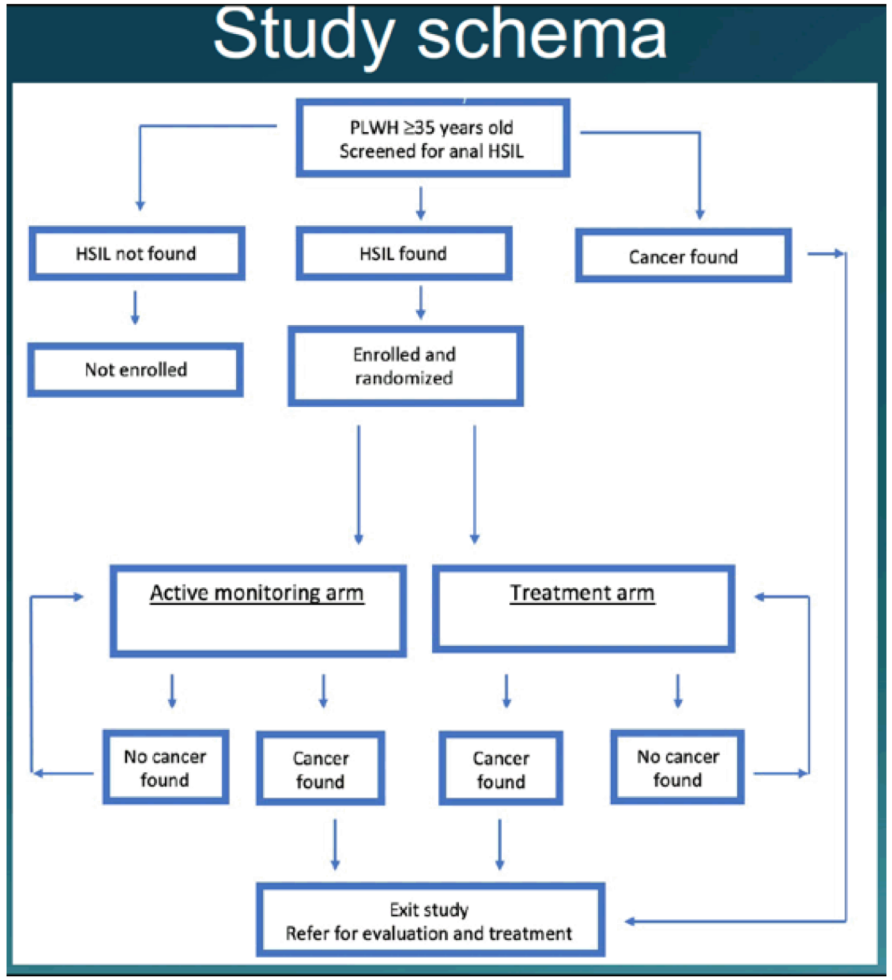
(2) stratify by sex: similar inferences with reduced precision for women

(3) alternative calendar era strata: Evaluated only in KPNC, with similar inferences

Silverberg M, et al. CROI, February 12-16 and 22-24, 2022.

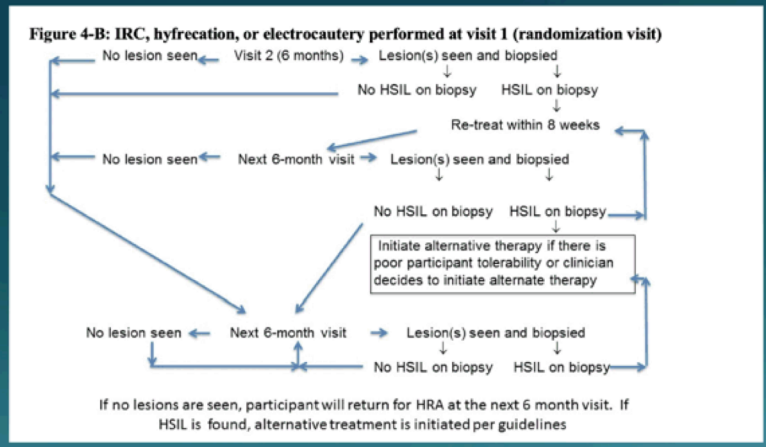
HIV Successful Living

- ANCHOR Study of Anal Cancer Prevention
  - Randomized trial of efficacy and tolerability of treatment of high-grade anal lesions to prevent anal cancer in PLWH



Treatment arm

- Treated immediately- hyfrecation, IRC, 5-FU, imiquimod



the ANCHOR study

Treatment arm

- Followed according to treatment algorithm
- Biopsied if suspicion for HSIL
- Anal cytology, swabs, HRA, blood every 6 months after HSIL cleared
- Every 3 months if concern for cancer
- Biopsied at any visit if concern for cancer

Active monitoring arm

- Anal cytology, swabs, HRA, blood every 6 months
- Biopsied annually to confirm persistent HSIL
- Every 3 months if concern for cancer
- Biopsied at any visit if concern for cancer

Palefsky J, et al. CROI 2022.

HIV Successful Living

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

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

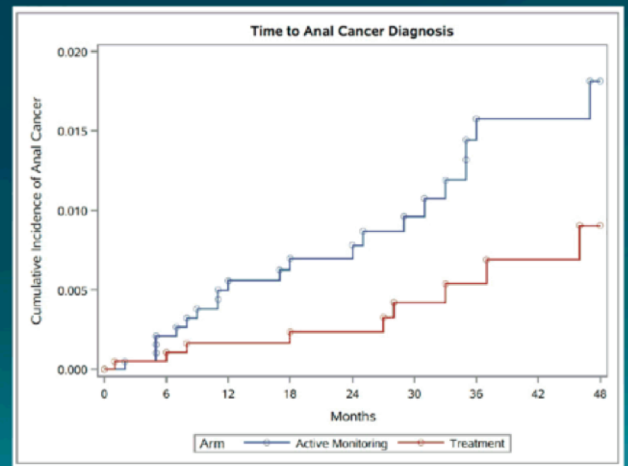
Results

- 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

Results

- DSMB recommended stopping the study for efficacy
- Recommendation made to treat all individuals in the monitoring arm
- We will continue to follow all individuals who wish to be treated and/or followed

Kaplan-Meier curve of time-to-confirmed cancer cases



the ANCHOR study

Questions?