CROI 2024 Report Back: Treatment Updates

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Disclosures

No conflicts of interest or relationships to disclose.

Outline

- LA CAB-RPV Updates
- Lenacapavir Updates

LA CAB-RPV Updates

Key LA CAB-RPV Abstracts

1. CARES Study
2. LATITUDE Interim Data
3. Real world experiences
    a. Ward 86 Week 48 Data
    b. Virologic Failures at a Chicago Clinic

Background: LA CAB-RPV

- ATLAS, FLAIR, and ATLAS-2M studies demonstrated efficacy of LAI CAB-RPV and led to FDA approval for those with viral suppression[1,2]
  - Virologic failures in ATLAS-2M have occurred at a rate of 2.3% q8w vs 0.4% q4w[2]

- Clinical trials to date had not included persons with adherence challenges[3]

- Clinical trials to date had little representation from Africa[4], among people who are
  - mostly Black African women
  - have different subtypes of HIV-1
  - have high exposure to NNRTI and pre-treatment resistance and
  - have varied treatment strategies with infrequent lab monitoring

1-Orkin C et al, NEJM, 2020. 2-Overton ET et al, CID, 2023. 3-Rana AI et al, CROI 2024 #212. 4-Kityo CM et al, CROI 2024 #122.

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CARES: Study Design

- Phase 3b, Randomized, Open-Label, Active-Controlled, Non-Inferiority Study

- ≥ 18 years of age
- On stable oral TDF + XTC + DTG or NVP or EFV
- HIV-1 RNA < 50 copies/mL at ≥4-12 prior to and at screening
- No history of renal failure
- No HBV infection

→ Oral ART Standard of Care (SOC)
n = 256

→ CAB-RPV q 8 weeks +/- 4-week oral lead-in
n = 256

- HIV-1 RNA checked every 24 weeks
- Resistance analysis performed at 48 weeks due to their public health approach to enrollment, so proviral DNA was performed for archived resistance on stored PBMCs
- Study sites in Uganda, Kenya, and Tanzania

Kityo CM et al, CROI 2024 #122.

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CARES: Baseline Characteristics

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

Kityo CM et al, CROI 2024 #122.

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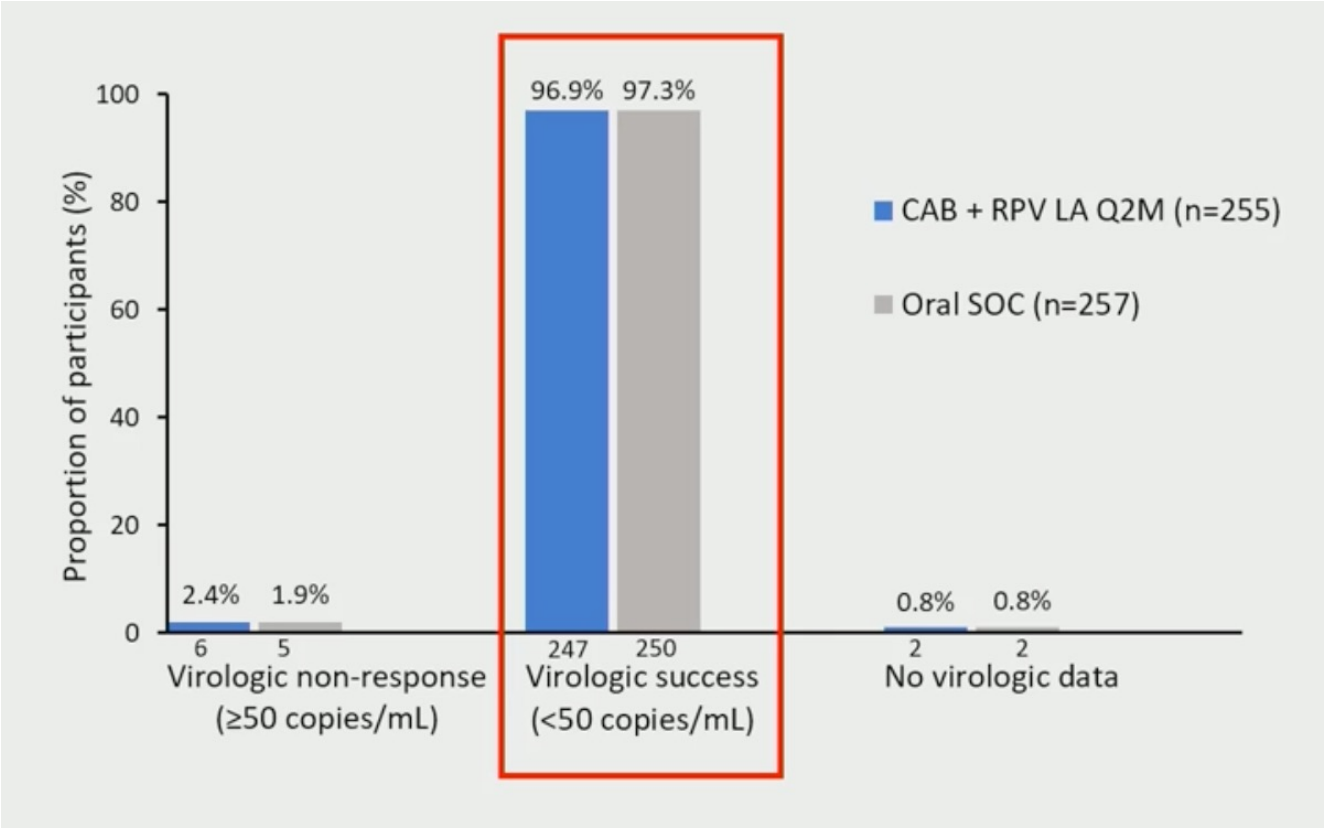
CARES: Week 48 Results

- LA CAB-RPV demonstrated noninferior virologic efficacy as compared to oral standard of care ART
- 73% had an injection site reaction (ISR)
- Satisfaction increased for those who switched to LA CAB-RPV
- 96% of scheduled injections occurred within the 7-day target injection date
- 2 cases of virologic failure (0.4%)



Kityo CM et al, CROI 2024 #122.

CARES: Virologic Failures at Week 48

Outcome	LA CAB + RPV (n = 255)	Oral ART (SoC) (n = 257)	Difference (95% CI)
Confirmed virologic failure, n (%)	1 (0.4)*	0	0.4 (-0.4 to 1.2)

*1 additional virologic failure (unconfirmed) in LA CAB + RPV arm.

Confirmed Virologic Failure: Patient Characteristics

- HIV-1 RNA 8608 copies/mL
- No delayed injections
- Sex and location: female from Uganda
- Baseline BMI 25.9 kg/m^2
- Subtype A1
  - Resistance mutations at baseline: no NNRTI or INSTI
  - Failure mutations: V108I, E138K, V179L (RPV high); E92E/V, N155H, L74M (CAB intermediate; DTG nil)
- Resuppressed on TDF/3TC/DTG once daily

Unconfirmed Virologic Failure: Patient Characteristics

- HIV-1 RNA 44,984 copies/mL
- No delayed injections
- Sex and location: male from Uganda
- Baseline BMI 22.0 kg/m^2
- Subtype D
  - Resistance mutations at baseline: K103N/S, E138A (RPV low); no INSTI mutations
  - Failure mutations: K103N/S, V106V/A, E138A (RPV low), G118R (CAB high; DTG intermediate)

Slide credit: clinicaloptions.com

Kityo CM et al, CROI 2024 #122.

CARES: Conclusions

- At Week 48, LA CAB-RPV q 8 weeks administered in sub-Saharan Africa in public health settings was non-inferior in virologic efficacy to oral standard of care, had a good safety profile, and was well tolerated

- Only 2 cases of VF occurred in the LA CAB-RPV arm, both with emergence of INSTI and NNRTI resistance

- In demonstrating safety and efficacy of LA CAB-RPV in sub-Saharan Africa using their public health approach, CARES 48-week results are a key first step in implementation in this patient population

Kityo CM et al, CROI 2024 #122.

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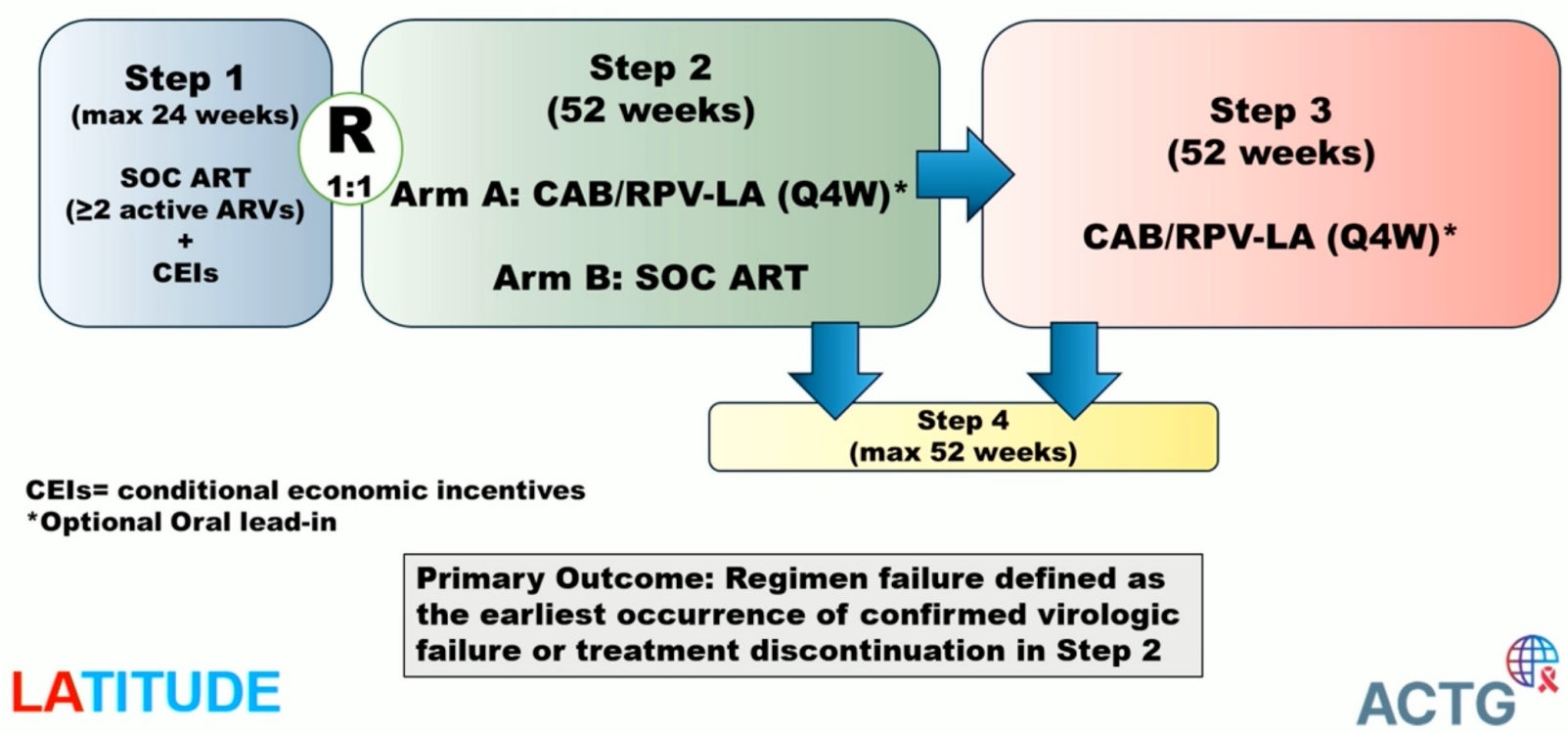
LATITUDE: Study Design

- Phase 3 prospective, randomized, open-label trial

- PWH who have barriers to adherence:
  - Poor viral response despite oral ART for ≥ 6m
  - Loss to follow up with ART non-adherence ≥ 6m
- No Hepatitis B
- No INSTI or RPV RAM historically or by screening



LATITUDE: Baseline Characteristics

Study population (Step 1 and Step 2)

Characteristic		Total (N=434)
Age, years	Median (Q1, Q3)	40 (32, 51)
	≤30	88(20%)
	31-50	232(53%)
	51+	114 (26%)
Sex at birth	Female	129 (30%)
Gender Identity	Transgender Spectrum	21 (5%)
Race	Black/African American	277 (64%)
	White	117 (27%)
	Other/multiple/unknown	40 (9%)
Ethnicity	Hispanic/Latino	75 (17%)
History of IDU	Currently + Previous	61 (14%)
Non-Adherence criteria	Lost to follow-up	87 (20%)
	Poor response	283 (65%)
	Both	64 (15%)
Time since HIV Dx, years	Median (Q1, Q3)	13 (7, 21)

Characteristic		Step 1 Total (N=434)
Baseline HIV-1 RNA (c/mL)	<200	141 (32%)
	201-10,000	110 (25%)
	10,001-100,000	121 (28%)
	>100,000	62 (14%)
Baseline CD4⁺ T (cells/mm³)	Median (Q1, Q3)	270 (116, 498)

Characteristic		Step 2 Treatment Arm: CAB/RPV-LA (n=146)	Step 2 Treatment Arm: SOC (n=148)
Step 2 Baseline HIV-1 RNA (c/ml)	>200*	24 (17%)	10 (7%)
Baseline CD4+ T (cells/mm3)	Median (Q1, Q3)	417 (198, 688)	374 (198, 605)

* including 8 participants with HIV-1 RNA >10,000 c/ml in the CAB/RPV-LA arm

LATITUDE

ACTG

Rana AI et al, CROI 2024 #212.

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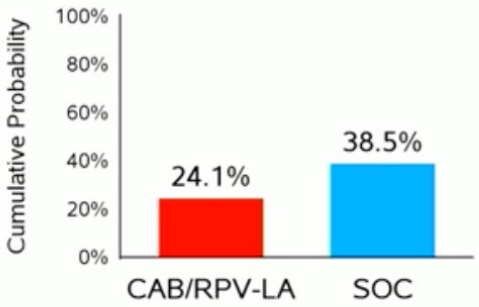
LATITUDE: Interim Data

Primary Outcome

Regimen Failure

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



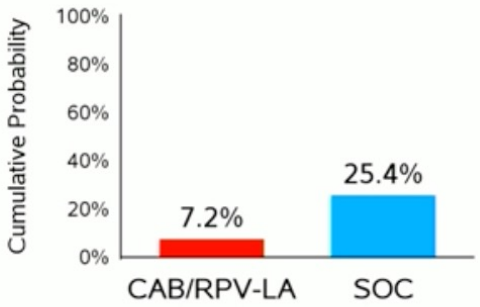
Number of participants

Regimen Failure	28	47
VF	6	28
TRT-DISC	23	19

Secondary Outcomes

Virologic Failure

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

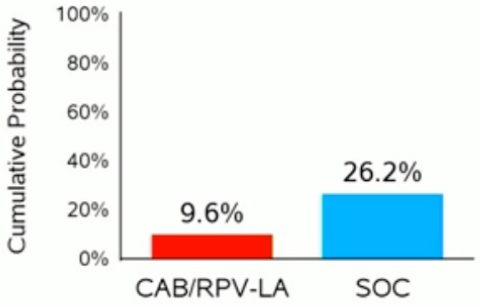


Number of participants

Virologic Failure	6	28

Treatment-related Failure

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

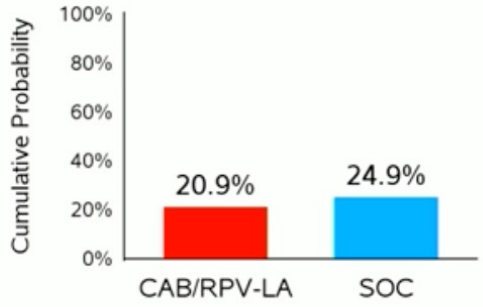


Number of participants

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

Permanent Treatment Discontinuation

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



Number of participants

Permanent TRT-DISC	25	30

LATITUDE

ACTG

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Rana AI et al, CROI 2024 #212.

LATITUDE: Interim Data

- Injection Site Reactions
  - Occurred in 57% of individuals

- Timing
  - 93% on time (21 to <36 days)
  - 3% missed

Patient	Week	LA CAB-RPV RAMs
1	18	E138K, G140GS, Q148K, K103R
2	49	E138K, Q148K, K20R, M230L

- Confirmed Virologic Failures
  - 6 in LA CAB-RPV arm: 2 with RAMs
  - 28 in SOC arm: 2 with RAMs

Rana AI et al, CROI 2024 #212.

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LATITUDE: Conclusions

- In PWH with adherence challenges, LA CAB-RPV q4w showed superior efficacy to oral SOC in secondary outcomes; there were fewer:
  - Virologic failures
  - Treatment-related failures

- On February 12, 2024, given these key secondary endpoints met stringent stoppage criteria, DSMB recommended halting randomization and offering all eligible participants switch to CAB/RPV

- Data supports the use of LA CAB-RPV in populations with adherence challenges

Rana AI et al, CROI 2024 #212.

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Ward 86 LA CAB-RPV: Week 48 Results

- CROI 2023: 55/57 without VS achieved VS at median of 33 days[1]
  - VF rate of 1.5% with INSTI RAMs
- At Ward 86, 286 patients on LA CAB-RPV[2]
  - 101 with baseline VL ≥ 50 copies/mL
  - 185 with VL < 50 copies/mL
- 59 included in Week 48 analysis
  - Viral suppression
    - 81% (48/59) remained on LA-CAB-RPV and were VS
    - 93% (55/59) VS on LA-CAB-RPV + alternative ART
  - Virologic failure
    - 3 with VF (5%)
      - 2 within 8 weeks of initiation despite on-time injections
      - 1 following self-discontinuation of ART

Patient	Pretreatment VL and mutations	Treatment-emergent RAMs
1	137K; T97A	E138K (NNRTI) R263K
2	215K; V179I, N348I	L100I, Y181I
3	67K; none	K101E, E138K, Y181FIN, M230L

1-Gandhi M et al, CROI 2023, #OA518. 2-Hickey MD et al, CROI 2024, #628.

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Virologic Failures at a Chicago HIV Clinic

- 75 virally suppressed PWH switched to LA CAB-RPV
  - 10 received at independent infusion center
  - 65 received at clinic
- 3 VFs occurred (4%)
  - 2 at infusion center, 1 at clinic
  - VF occurred at 8, 10, and 16 months
  - All used a 1.5-inch needle
  - All 3 switched to a PI-based regimen and achieved VS

Demographics		Patient 1	Patient 2	Patient 3
Age at VF		24	44	47
Gender		F	M	M
Race/ethnicity		Other/Latinx	African American/Non Latinx	African American/Non Latinx
Years since HIV diagnosis		23	18	1
No. of prior ART regimens		>3	2	1
Smoker		N	N	N
BMI		27	35	28
Injection delivery site				
	Clinic	Y		
	Infusion center		Y	Y
UD on INI at time of switch		Y	Y	Y
Prior Rilpivirine exposure		Y	N	N
Prior known resistance mutations		M184V	K103N	N/A
Resistance mutations at VF		L74L/M, T97T/A, **G140S, Q148H** **K101P, E138K,** I178L, Q207E	L74I, T97T/A, S147S/G, **N155H**	**G140G/S, Q148Q/R**

Shankaran S et al, CROI 2024 #686.

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Lenacapavir Updates

Background: Lenacapavir

- Lenacapavir (LEN) is a capsid inhibitor administered subcutaneously every 6 months
- FDA approved in December 2022 for MDR HIV, informed by the CAPELLA Study
- CAPELLA: When combined with an optimized background regimen (OBR) in individuals with MDR HIV, LEN every 6 months led to viral suppression at week 104 in 82% of PWH by missing=excluded analysis
- LEN has a low barrier to resistance with M66I as the signature capsid mutation
  - LEN-R is associated with inadequate OBR adherence and OBRs lacking fully active agents

Segal-Maurer S et al, NEJM, 2022.

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LEN efficacy with no fully active agents in OBR

- Aim: Assess LEN efficacy through week 104 in CAPELLA participants whose OBR had no fully active ARVs
- Calculated OBR overall susceptibility score (OSS)
  - 12 of 72 had no fully active ARVs
    - 5/12 had an OSS of zero
    - 6/12 had an OSS of 0.5
    - 1/12 had an OSS of 1 (two partially active ARVs)
  - Note: CAPELLA median OSS was 2.0
- Heavily treatment experienced cohort
  - Median of 4 agents in the OBR
  - Baseline mean HIV-1 RNA 4.02 $\log_{10}$ copies/mL
  - Baseline mean CD4 175 cells/mm^3

Ogbuagu O et al, CROI 2024 #630.

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LEN efficacy with no fully active agents in OBR

Table 2. Resistance Mutations at Baseline

Participant	Baseline Resistance Mutations			
	INSTIs	NNRTIs	NRTIs	PIs
1	M50I, T97A, S119R, E138K, G140S, Q148H	Y181I, Y188L	M41M/L, M184V, T215F	V32I, I54M, Q58E, I84V, L90M
2	L74I/M, S119P, E138E/K, S147S/G, S153S/A/C/G, N155H, E157E/Q	V106M, V108I, Y181V	D67N, K70R, M184V, T215F, K219E	V32I, M46I, I54L, L76V, I84V, L90M
3	M50I, T97A, S119P, E138K, G140S, Q148H	L100I/V, G190Q	M41L, D67N, L74I/V, M184V, L210W, T215Y, K219R	V32I, M46I, I47V, I54L, I84V
4	T97A, E138K, G140S, Q148H	L100I, K103N, V108V/I	M41L, D67N, L74I, M184V, L210W, T215Y, K219N	M46I, I47V, I50V, L76V, V82T
5	E138K, G140A, S147G, Q148R, E157Q	K101H, Y181C, G190A	M41L, D67N, K70K/R, M184V, T215F, K219Q	V32I, M46L, I54L, N83D, I84V
6	M50I/T, L74M, T97A, S119T, Y143C, S147G, N155H, E157Q	L100I/M, K103S, H221Y	T69(del), V75I, F77L, Y115F, F116Y, Q151M, M184V, K219Q	V32I, M46L, I54L, T74P, V82T, I84V, L90M
7	N155N/H	K101E, Y181I	M41L, M184V, T215F	V32V/I, I47I/V, I54I/M, Q58Q/E, I84I/V, L90M
8	M50M/I, T97A, S119R, S147G, N155H, E157Q	L100I, K103N	M41L, D67N, L74V, L210W, K219D/N	V32I, M46I, Q58E, I84V, L90M
9	M50I, G140S, Q148H, N155H	E138Q, Y181V, H221Y, M230L	M41L, M184V, T215F	V32I, M46I, I47V, I54L, Q58E, I84V, L90M
10	E138A, G140A, S147G, Q148R, N155H, E157Q	V106I/M, Y181C	M41L, V75I, F77L, F116Y, Q151M	V32I, I54L, Q58E, T74P, V82L, I84V, L90M
11	E138E/A, G140A, Q148R	K103N, E138Q	K70R, T215F, K219E	V32I, M46I, I54L, L76V, I84V
12	G140S, Q148H	K103N	M41L, D67N, L210W, T215Y, K219R	V32I, M46L, I54V, T74P, V82A, I84V, L90M

Ogbuagu O et al, CROI 2024 #630.

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Results: LEN efficacy with no fully active agents in OBR

- 8/12 suppressed at all 3 visits; of the 4 not suppressed at all 3 visits:
  - 3/4 developed an M66I/M at weeks 4, 4, and 10, respectively
  - 1/4 never achieved viral suppression
  - Lack of viral suppression prompted changes to their OBR
- Mean increase in CD4 cell count was 105 cells/mm^3
- None developed treatment emergent resistance to their OBR through week 104
- When considering LEN use, I recommend looking at Tables 1-3 and Figure 2

Ogbuagu O et al, CROI 2024 #630.

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Lenacapavir + LA Cabotegravir

- Case series of 34 patients from 4 clinics using off-label LEN and CAB with or without RPV for selected patients with adherence challenges
  - UCSF Ward 96, UCSD Owen Clinic, MetroHealth's HIV Clinic, UPenn Clinic
- Patient Characteristics
  - 76% male, 24% cis/trans female; 41% Black, 38% Latino/a
  - 29% and 71% on CAB every 4 or 8 weeks, respectively
- Reasons for using LEN + LA CAB with or without LA RPV
  - Documented or suspected NNRTI-R (59%), INSTI-RAMs (15%), high VL (18%) or continued viremia on CAB-RPV alone (12%)
  - Look at their table for patient details!
- Results
  - ISR in 44% of patients
  - 94% viral suppression (median 8w after starting LEN), up from 47% suppressed at baseline

Gandhi M et al, CROI 2024, #629.

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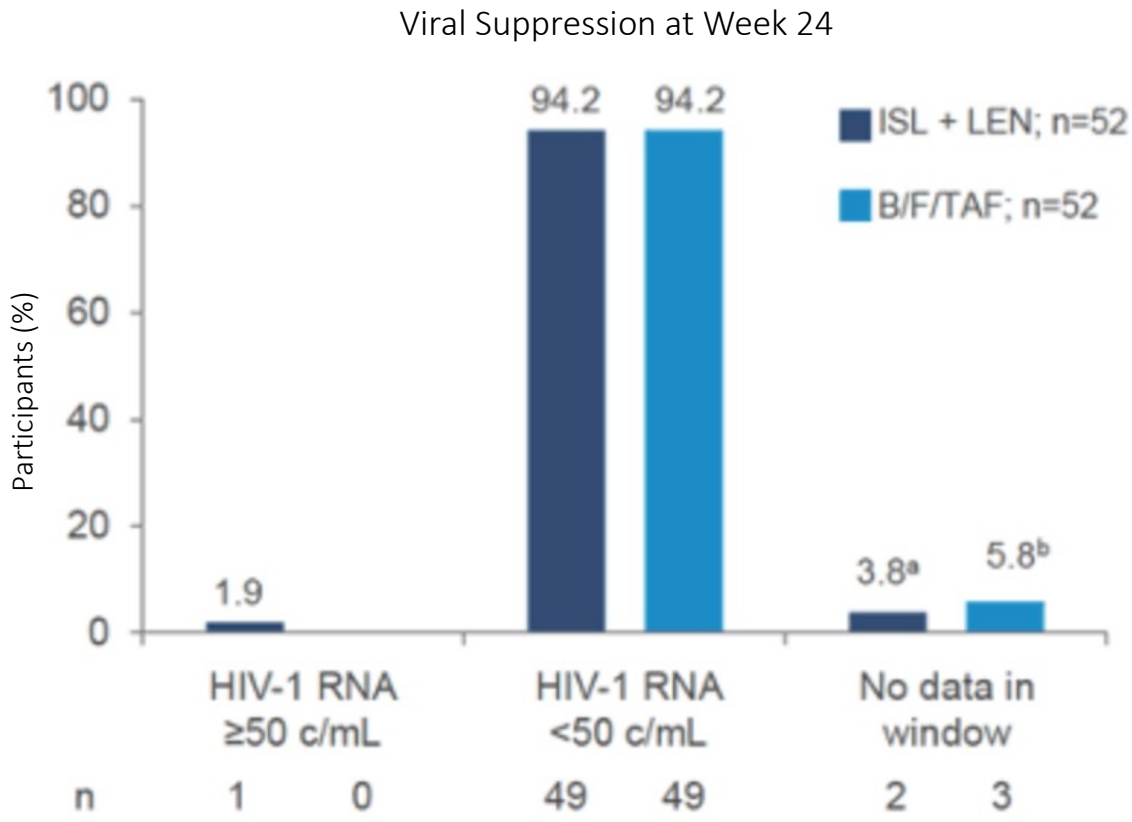
Weekly Oral Islatravir + Lenacapavir

- Phase II trial of once weekly oral Islatravir 2mg (NRTTI) + oral Lenacapavir 300mg compared to BIC/TAF/FTC in PWH who are virologically suppressed
- Viral suppression was achieved in 94% of participants at 24 weeks and was well tolerated
- No significant differences in changes in CD4 cell count or absolute lymphocyte count with ISL + LEN vs BIC/TAF/FTC



Colson A et al, CROI 2024 #208.

Conclusions

1. Week 48 CARES data demonstrated that LA CAB-RPV was non-inferior to oral SOC in sub-Saharan Africa.
2. LA CAB-RPV is superior to oral SOC in key secondary outcomes in the LATITUDE study, leading the DSMB to stop randomization and offer CAB-RPV to all eligible participants.
3. LA CAB-RPV appears durable, but real world virologic failures are ~4-5%.
4. Lenacapavir, even when combined with no fully active agents in the OBR, was efficacious in 8/12 participants from the CAPELLA study.
5. The combination of LEN + LA CAB +/- LA RPV proved efficacious in 34 patients, and we will likely see more data about this in the coming years.
6. Still in phase II, weekly oral islatravir plus lenacapavir has the potential to become a long-acting option for PWH.

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CROI Update: Prevention

March 2024

Julie Dombrowski, MD, MPH
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Deputy Director, HIV/STI/HCV Program
Public Health – Seattle & King County

Last Updated: 3/18/2024

Disclosures

I have conducted research with supplies donated by Hologic and Mayne Pharmaceuticals

Prevention

DOXY-PEP

HIV PREP

Doxy-PEP: Final results of clinical trials, impact of use in clinical practice, & preliminary AMR data

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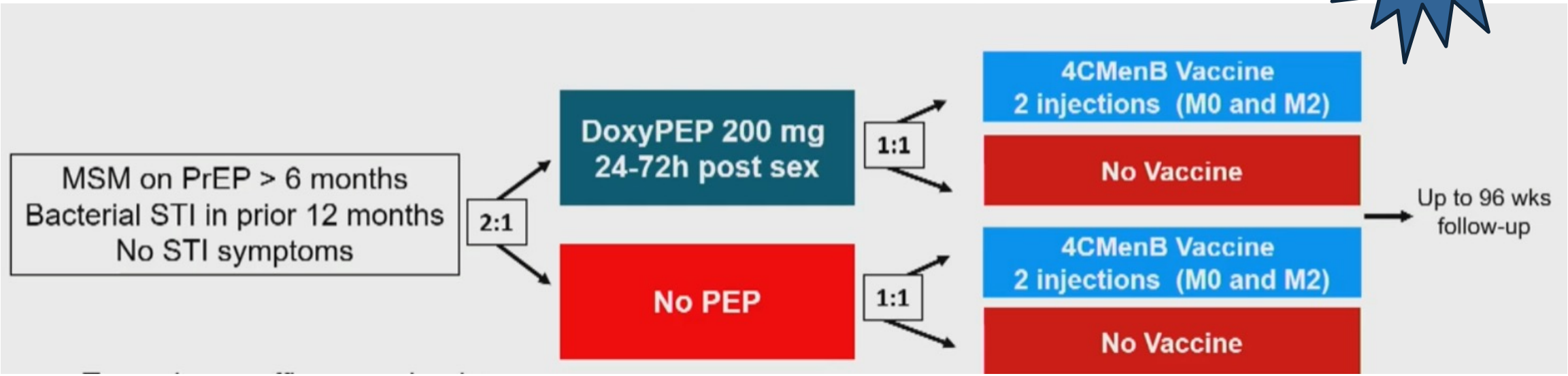
Final Results of ANRS 174 DOXYVAC: A Randomized Trial to Prevent STI in MSM on PrEP

Molina, J-M G, et al. Abstract #124

- Multicenter, 2 x 2 factorial randomized, open-label trial
- Primary efficacy endpoints:
  - Impact of Doxy-PEP on time to first episode of syphilis or chlamydia
  - **Impact of 4CMenB vaccine on time to first episode of gonorrhea**

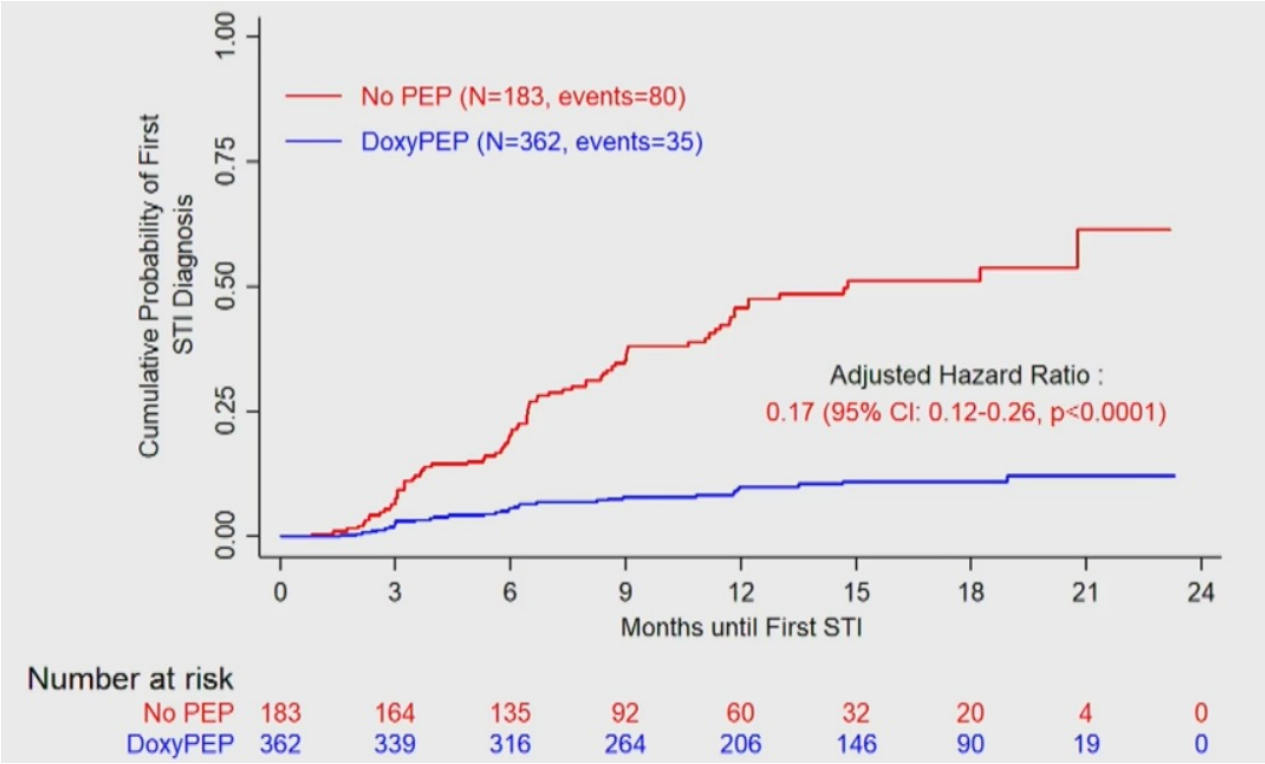
Change after audit



Final Results of ANRS 174 DOXYVAC: A Randomized Trial to Prevent STI in MSM on PrEP

Molina, J-M G, et al. Abstract #124

Time to first episode of syphilis or chlamydia



Time to first GC

Intervention	Adjusted Hazard Ratio & p-value
Doxy-PEP	0.67 (95% CI: 0.52 – 0.87), p=0.003
4CMenB	0.78 (95% CI: 0.60 – 1.01), p=0.061

High-level TCN-resistant GC

- 12.5% no doxy-PEP (N=40)
- 35.5% doxy-PEP (N=31)
- P-value for difference: 0.043

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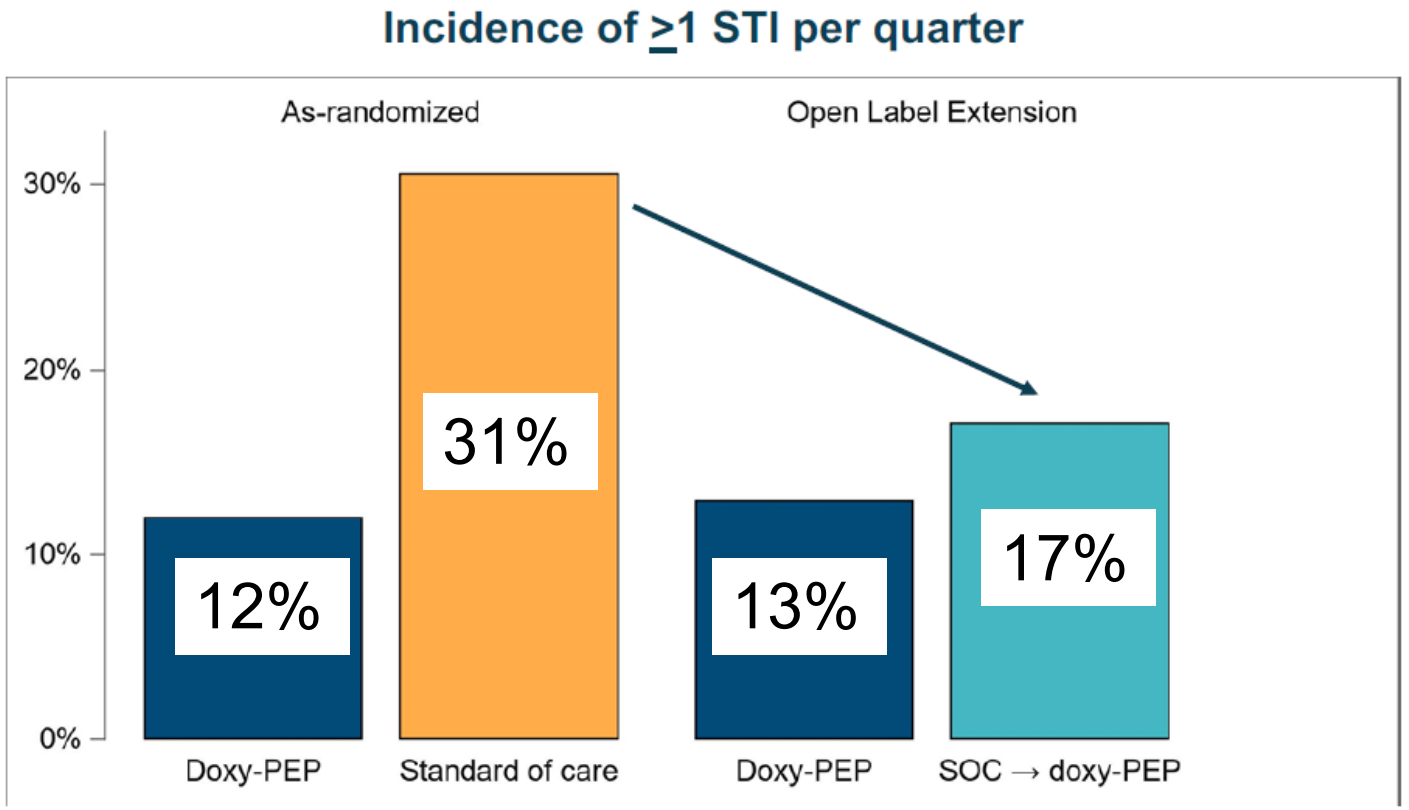
Sustained Reduction of Bacterial STIs during the DoxyPEP Study Open-Label Extension

Luetkemeyer A, et al. Abstract #125

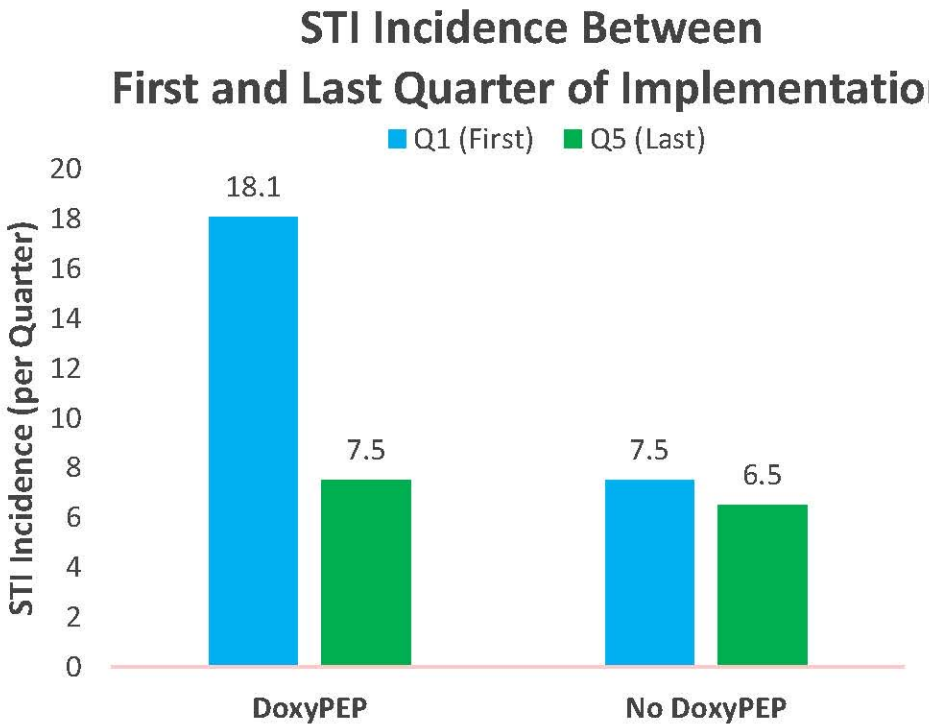
- Doxy-PEP study: 65%↓ in quarterly STI rates among MSM & transgender women (TGW)
- May 2022 DSMB: Enrollment stopped & participants notified of results
- Doxy-PEP offered to standard-of-care group (all but 1 accepted; N=82 in open label extension)
- Sustained decreased incidence in STI, comparable to RCT results



Doxycycline Post-Exposure Prophylaxis (DoxyPEP): High Uptake & Significant Decline in STIs after Clinical Implementation

Scott H, et al. Abstract #1151

- Magnet Clinic @ Strut – San Francisco AIDS Foundation
- Interrupted time series analysis of quarterly STI incidence in patients taking PrEP



	IRR	95% CI	p-value
Any STI	0.42	0.24 - 0.74	0.003
Chlamydia	0.33	0.23 - 0.46	<0.001
Syphilis	0.22	0.09 - 0.54	0.001
Gonorrhea	0.89	0.69 - 1.15	0.383

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Doxy-PEP Effectiveness in Men Who Have Sex with Men (MSM) and Transgender Women (TGW) on HIV PrEP

Bacon O, et al. Abstract #1151

- San Francisco City Clinic, Pre- (11/2021 – 11/2022) & Post- (11/2022 – 11/2023) Doxy PEP implementation
- Compared STI test positivity among doxy-PEP users vs. non-users
- Analysis: difference in differences

Figure 1: Chlamydia Positivity

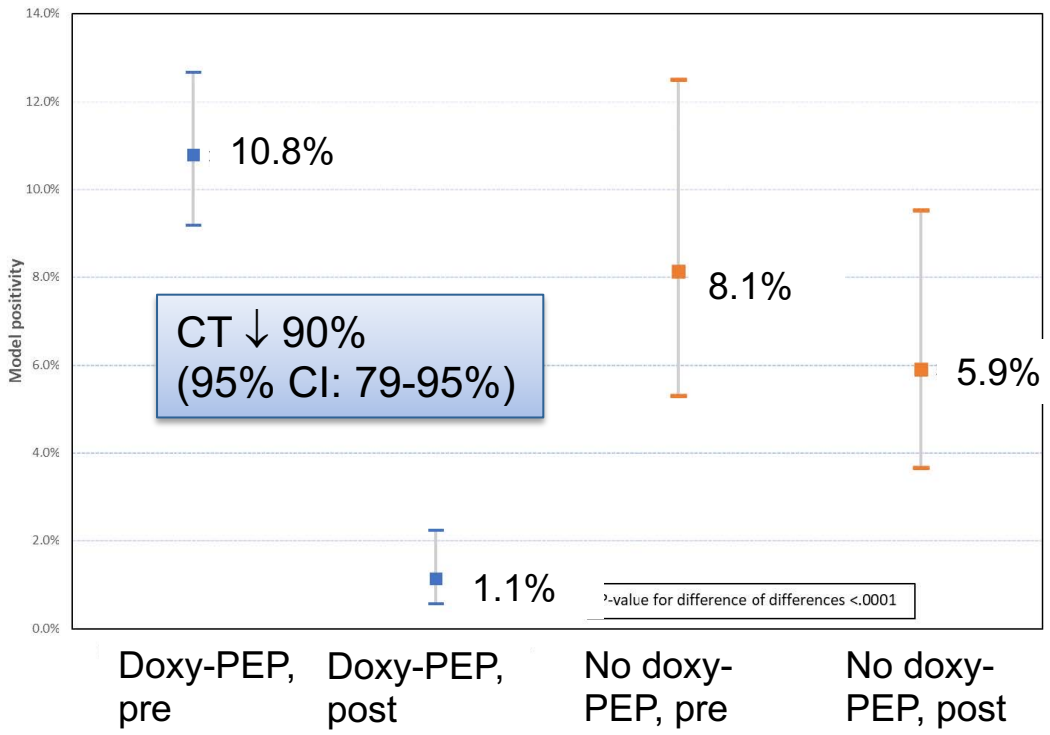
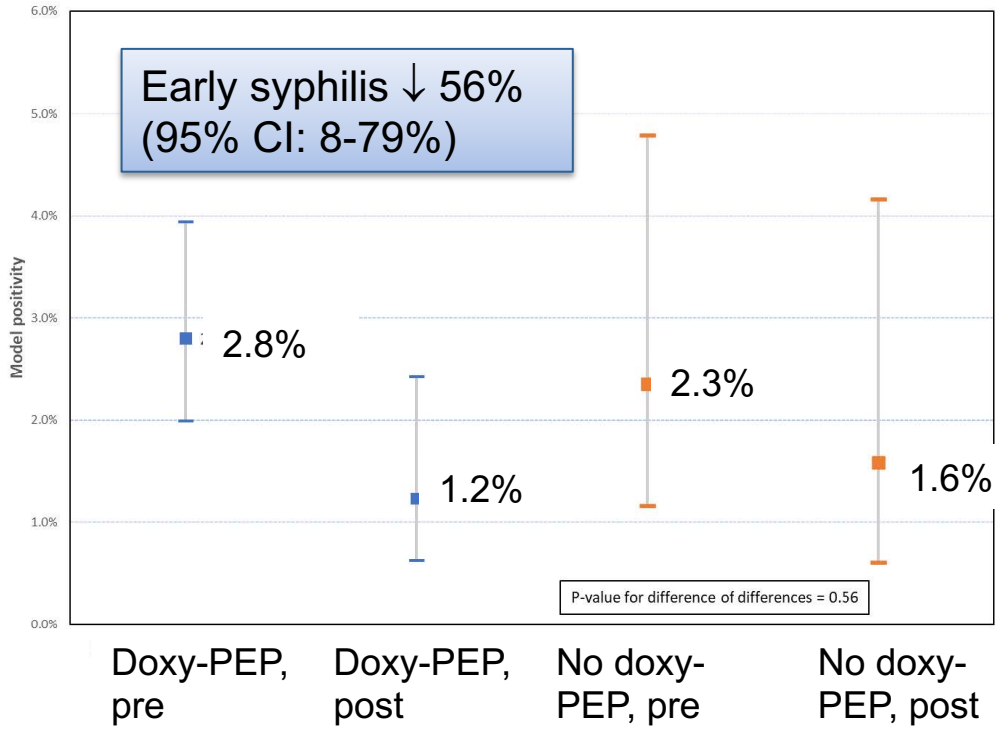


Figure 2: Early Syphilis Positivity

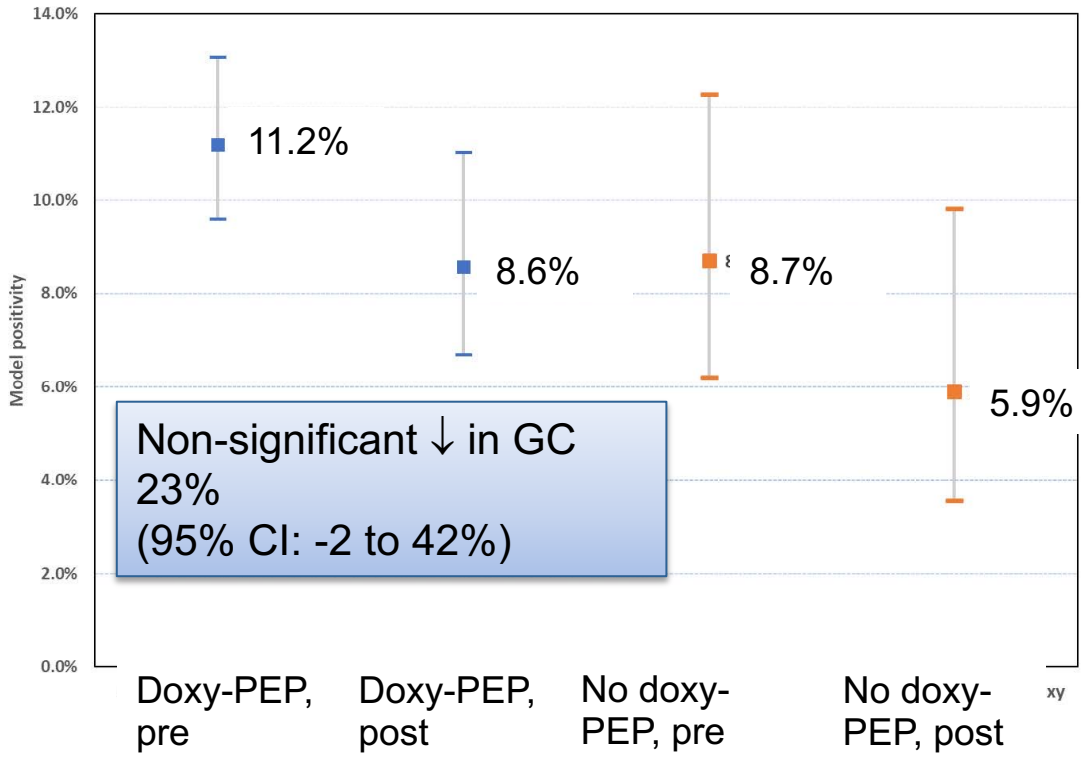


Doxy-PEP Effectiveness in Men Who Have Sex with Men (MSM) and Transgender Women (TGW) on HIV PrEP

Bacon O, et al. Abstract #126

- San Francisco City Clinic, Pre- (11/2021 – 11/2022) & Post- (11/2022 – 11/2023) Doxy PEP implementation
- Compared STI test positivity among doxy-PEP users vs. non-users

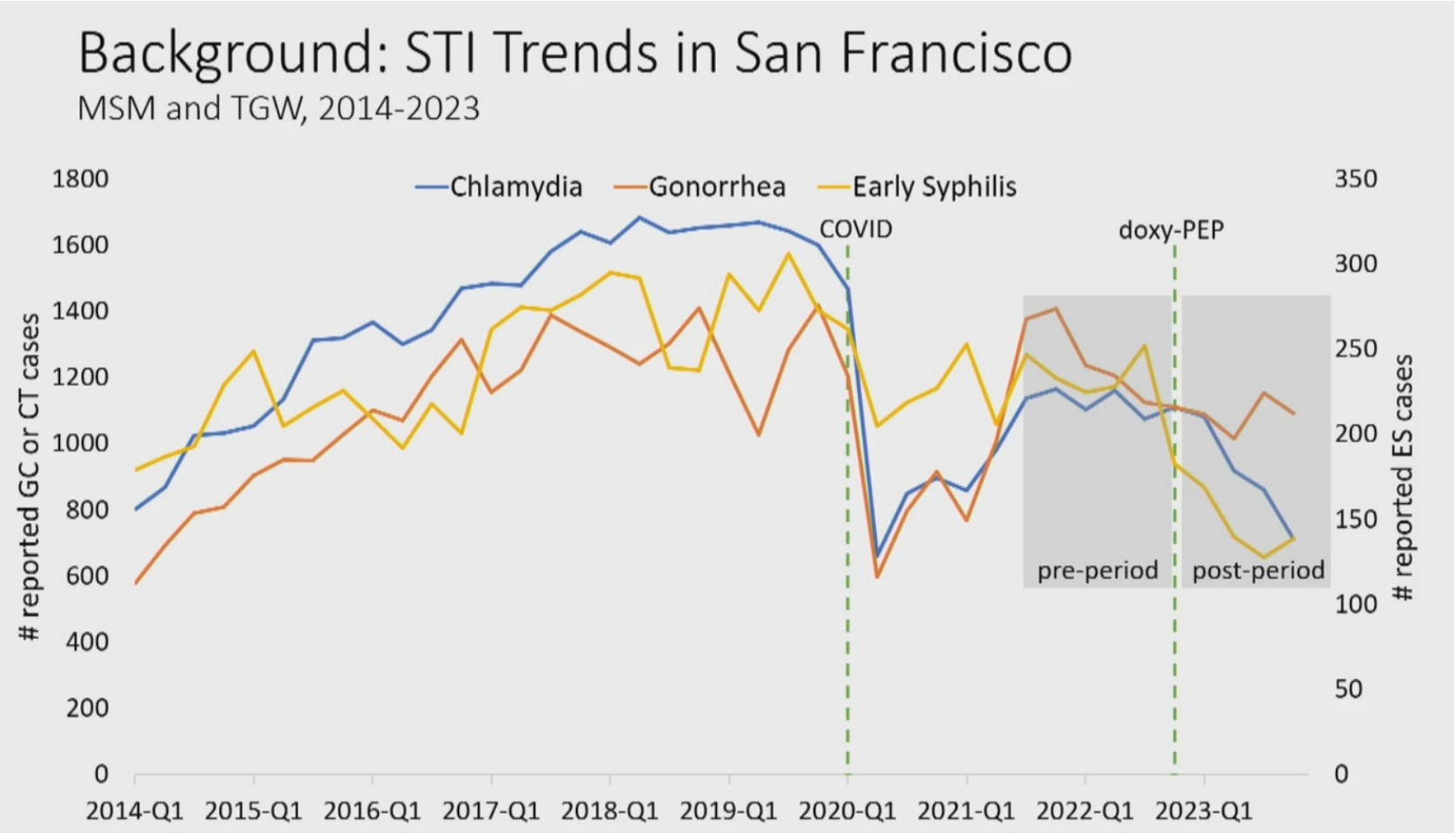
Figure 3: Gonorrhea Positivity



Doxy-PEP Associated with Declines in Chlamydia and Syphilis in MSM and Trans Women in San Francisco

Sankaran M, et al. Abstract #127

- Population level: San Francisco citywide surveillance data
- Ecological analysis
- Before & after doxy-PEP guidelines, focus on "post-COVID" era
- Interrupted time series
- Estimated >3700 people on doxy-PEP, ~20% of MSM & TGW

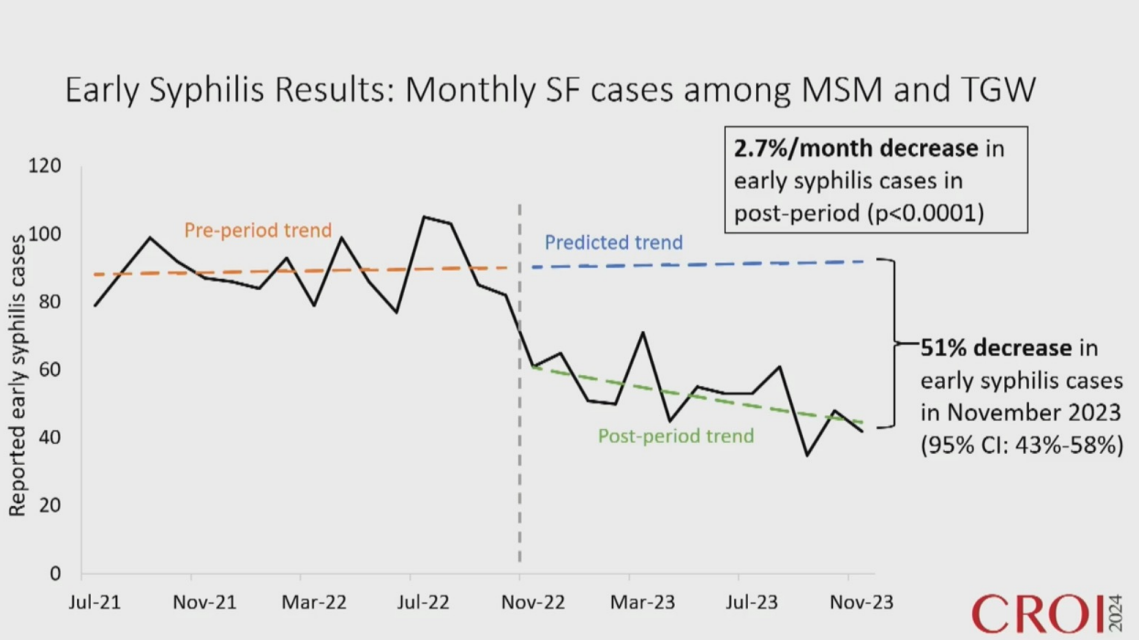


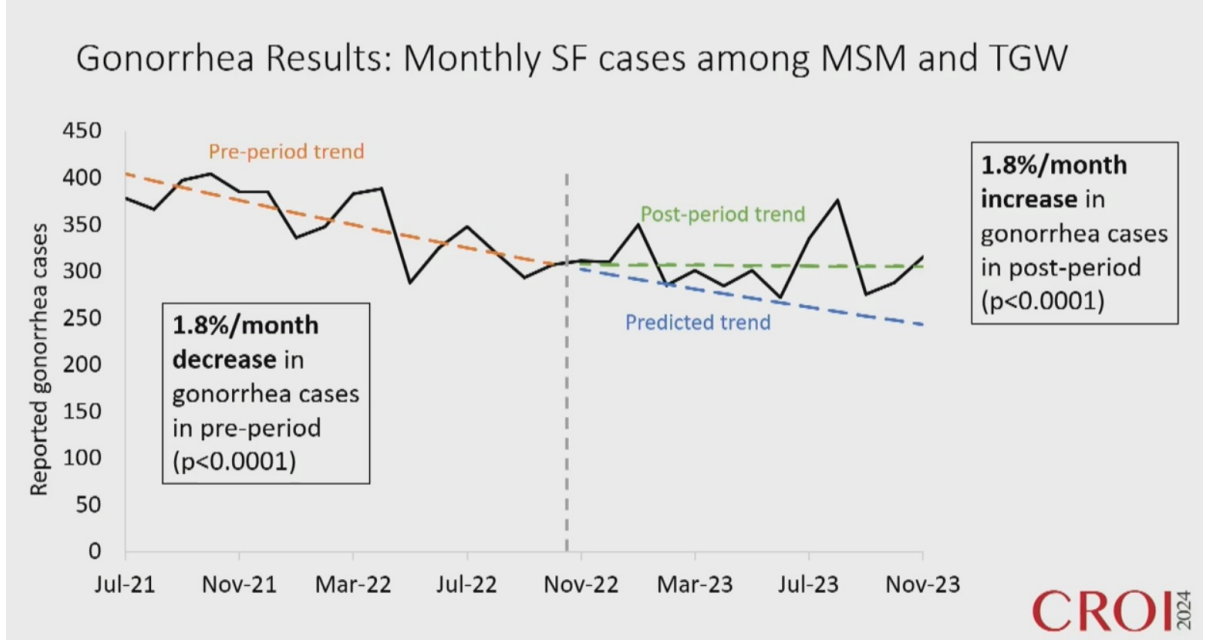
Doxy-PEP Associated with Declines in Chlamydia and Syphilis in MSM and Trans Women in San Francisco

Sankaran M, et al. Abstract #127

50% decrease in chlamydia (p<0.001)*
51% decrease in early syphilis (p<0.001)

1.8% per month <u>increase</u> in gonorrhea (p<0.001)





*no change in CT cases among cisgender women in the same time period

MWAETC

Impact of Doxycycline as STI Postexposure Prophylaxis on the Gut Microbiome and Antimicrobial Resistance Gene Expression

Chu V, et al. Abstract #1154

- DoxyPEP study collected rectal swabs at enrollment & 6 months
- DNA and RNA metagenomic sequencing of samples from participants with the highest reported doxy-PEP use vs. standard-of-care

Microbiome (not shown)

Bacterial diversity & total bacterial abundance **did not differ** between doxy-PEP and SOC or over time by arm

Tetracycline ARG expression

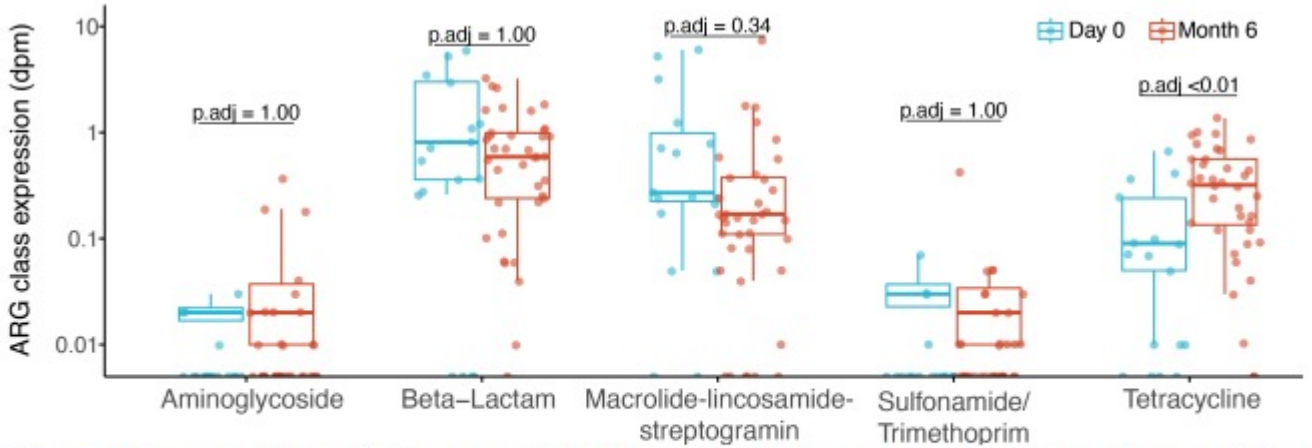


Figure 2. Impact of doxy-PEP use on ARG class expression, normalized by reads per million sequenced and gene length (depth per million, dpm) in the doxy-PEP RNA-seq samples (n=55). Tetracycline ARG expression significantly increased between Day 0 and Month 6, while no difference was observed among non-tetracycline ARG classes.

Impact of Doxycycline as STI Postexposure Prophylaxis on the Gut Microbiome and Antimicrobial Resistance Gene Expression

Chu V, et al. Abstract #1154

- Doxy-PEP was associated with a dose-dependent increase in tetracycline antimicrobial resistance gene abundance.

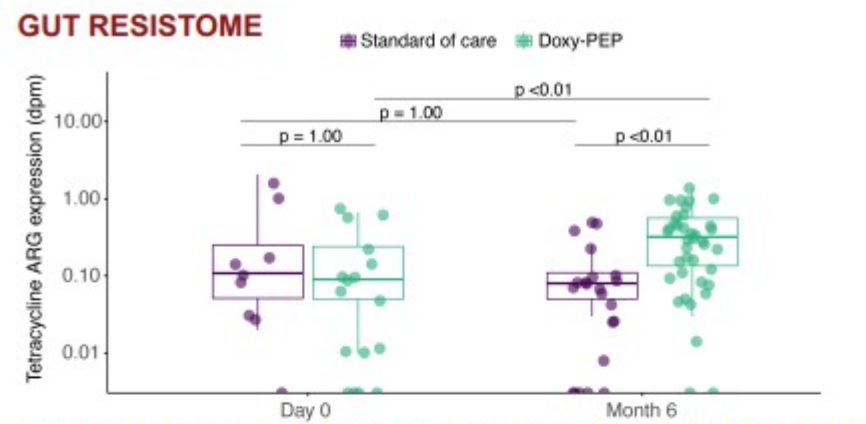


Figure 3. Tetracycline ARG expression by study arm and visit in the RNA-seq samples (n=86). Tetracycline ARG expression increased in the doxy-PEP Month 6 group compared with the SOC Month 6 and the doxy-PEP Day 0 groups.

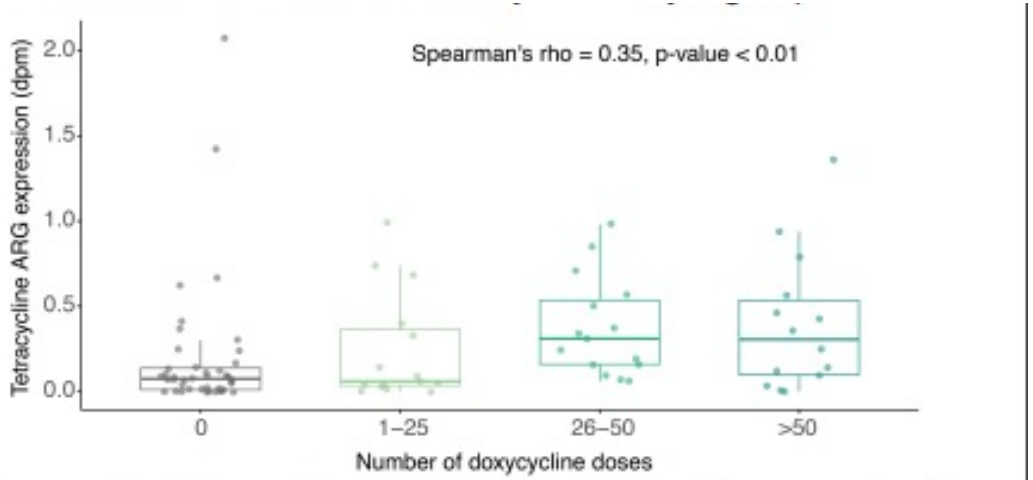


Figure 4. Tetracycline ARG expression increased with number of doxycycline doses since enrollment in the RNA-seq samples (n=86).

Doxy-PEP Section Summary

- Doxy-PEP decreases STI rates in MSM and transgender women
  - Clear impact on chlamydia and syphilis in both clinical trial & practice data
  - Decreased gonorrhea risk in clinical trials but no clear impact in practice
- Scale-up occurred quickly in San Francisco (high interest in the intervention)
- Doxy-PEP use does not appear to impact gut bacterial diversity over 6 months, but is associated with a dose-dependent increase in tetracycline AMR genes in the gut
  - Clinical significance & impact of longer term use unknown

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PrEP: Novel formulations, public health impact & encouraging data in cisgender women

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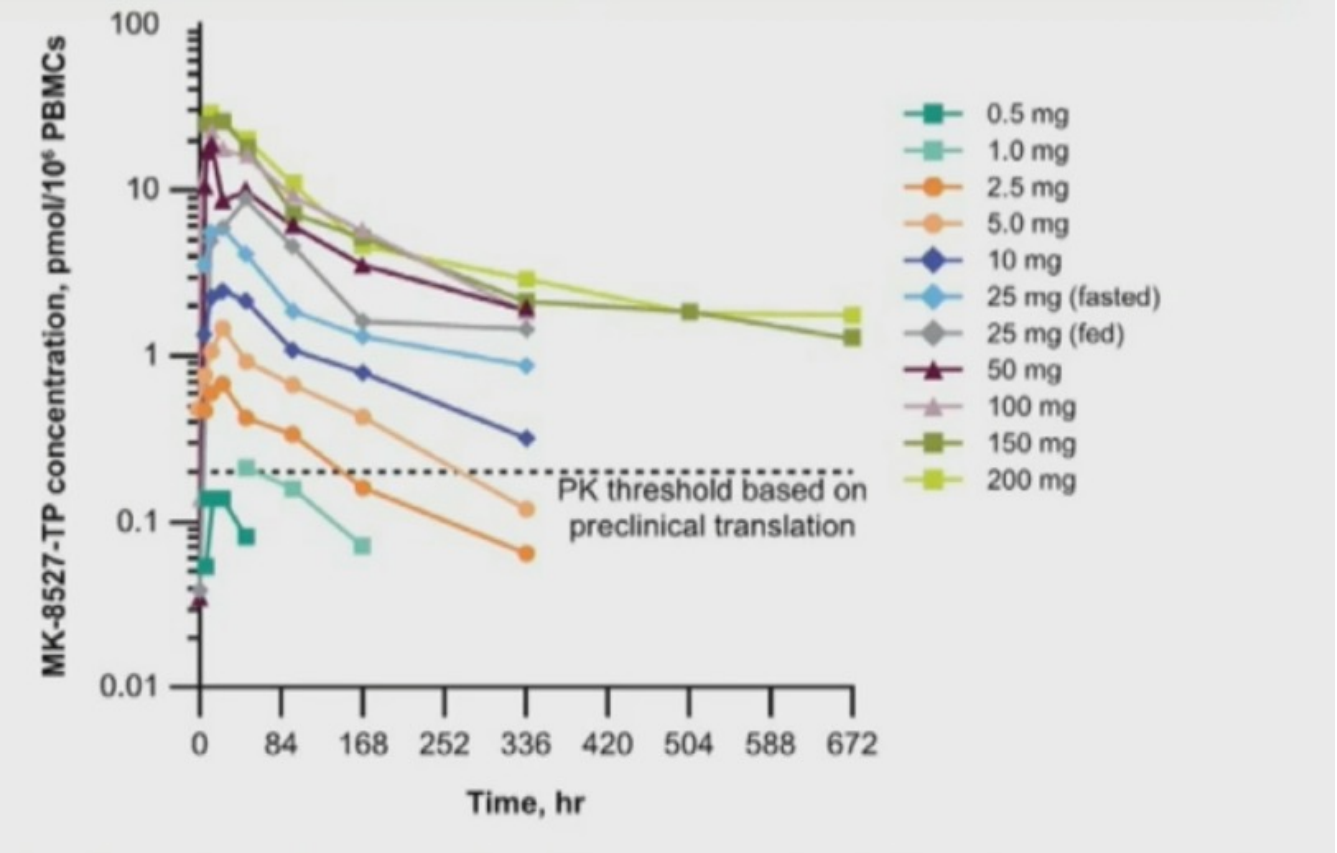
PrEP: What's in the pipeline?

- **Weekly oral medication**
- Novel oral nucleoside reverse transcriptase translocation inhibitor (NRTTI) – MK-8527
- Phase 1 study
- Safe & well-tolerated
- PK profile supports weekly (or less frequent dosing)

Mean MK-8527 concentration following a single dose



Gillespie G et al, Abstract #129

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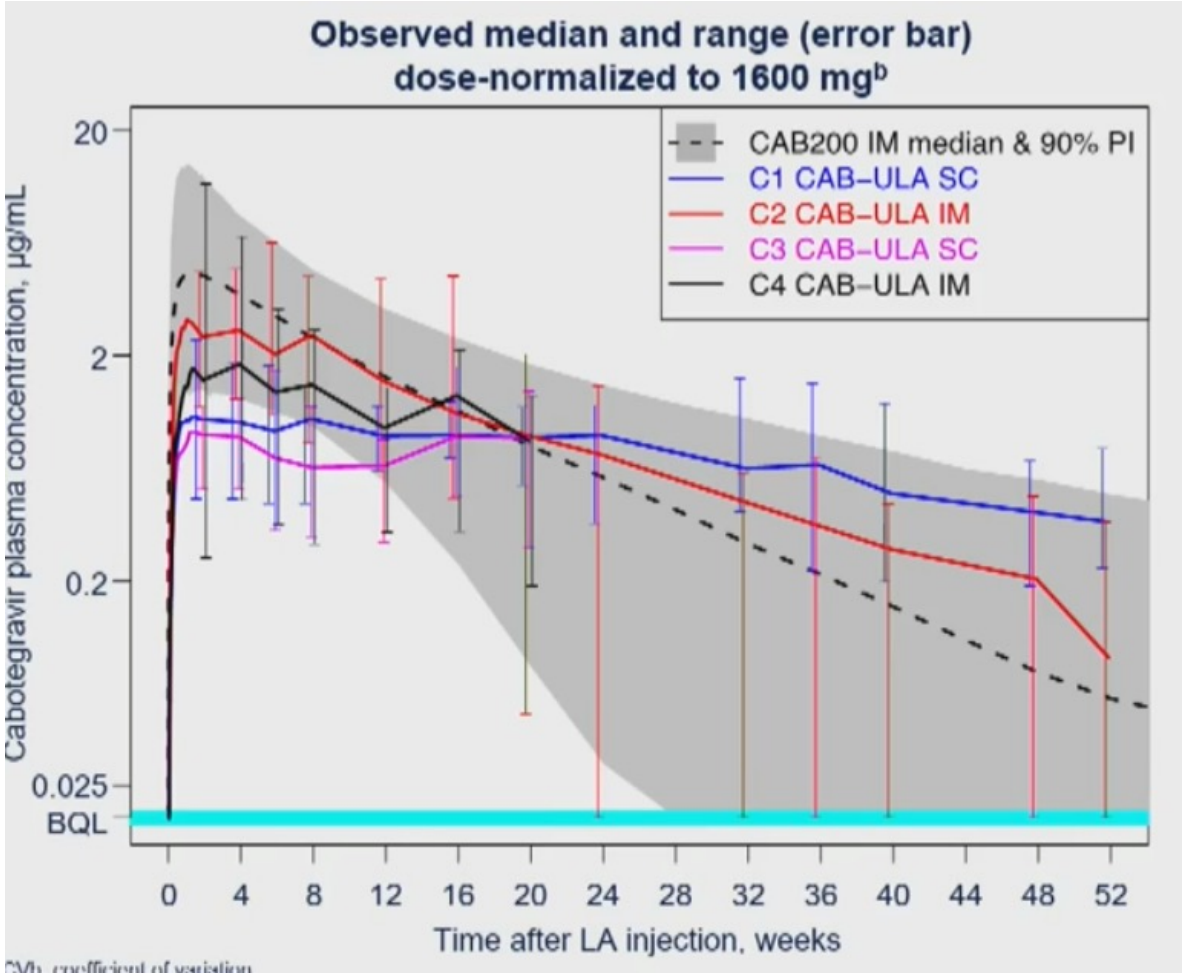
PrEP: What's in the pipeline?

- **Longer acting injectable**
- Approved cabotegravir formulation + recombinant human hyaluronidase
- A new ultra-long-acting CAB formulation
- Phase 1 study
- IM version of ultra-long acting well-tolerated
- Dosing interval ≥ 4 months



Han K et al, Abstract #130

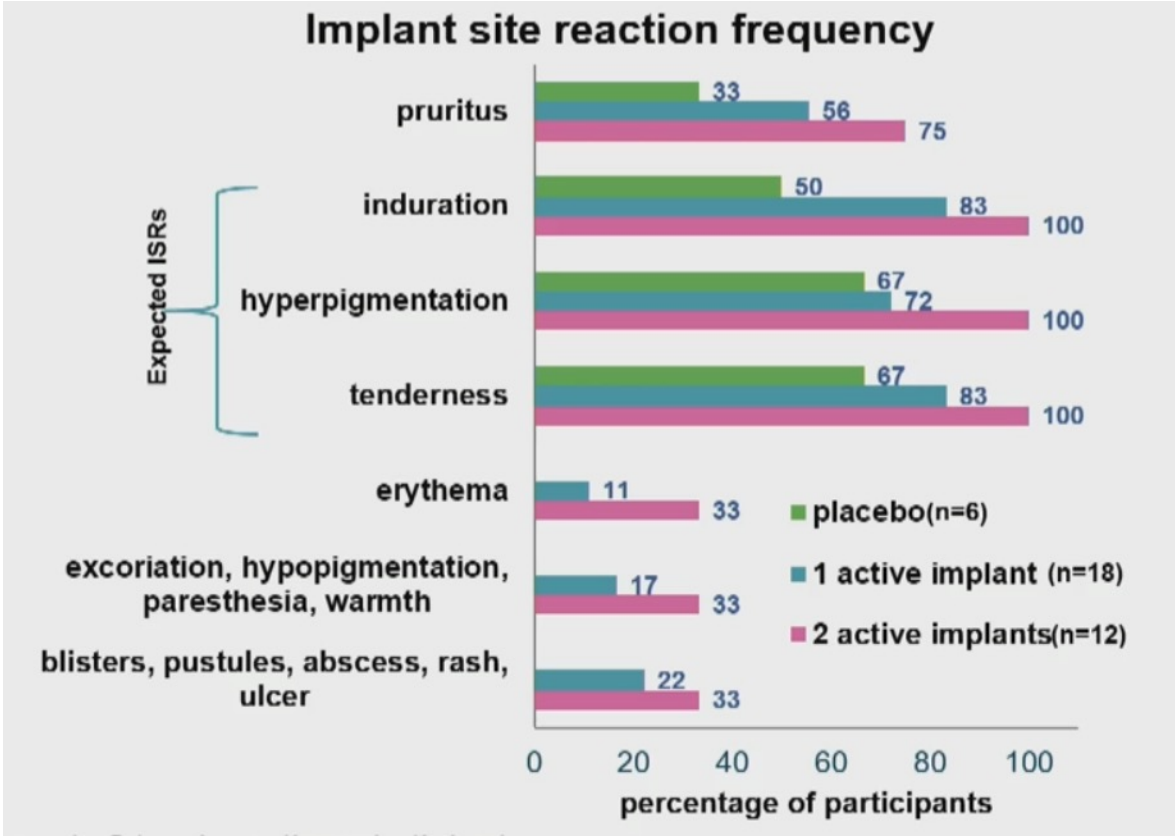
PrEP: What's in the pipeline?

- Annual TAF implant

First in-human Phase 1 Study: 48 weeks

31% removed early, median 19 weeks

Lower than planned drug release



Gengiah et al, Abstract #123

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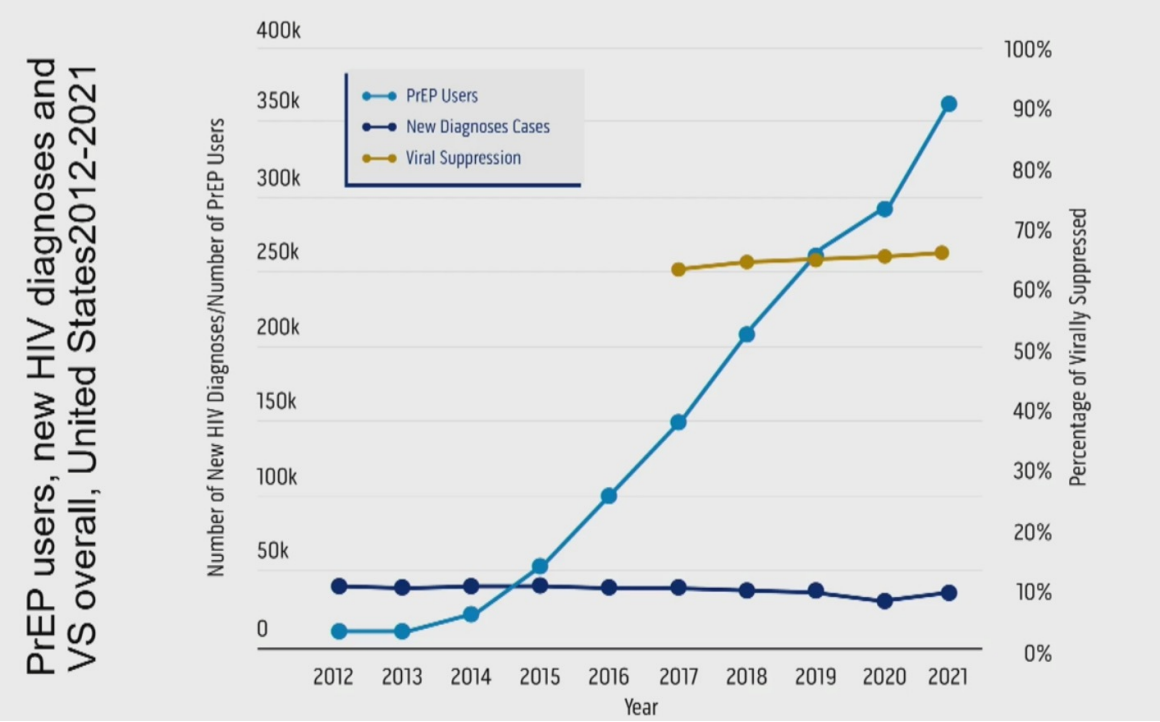
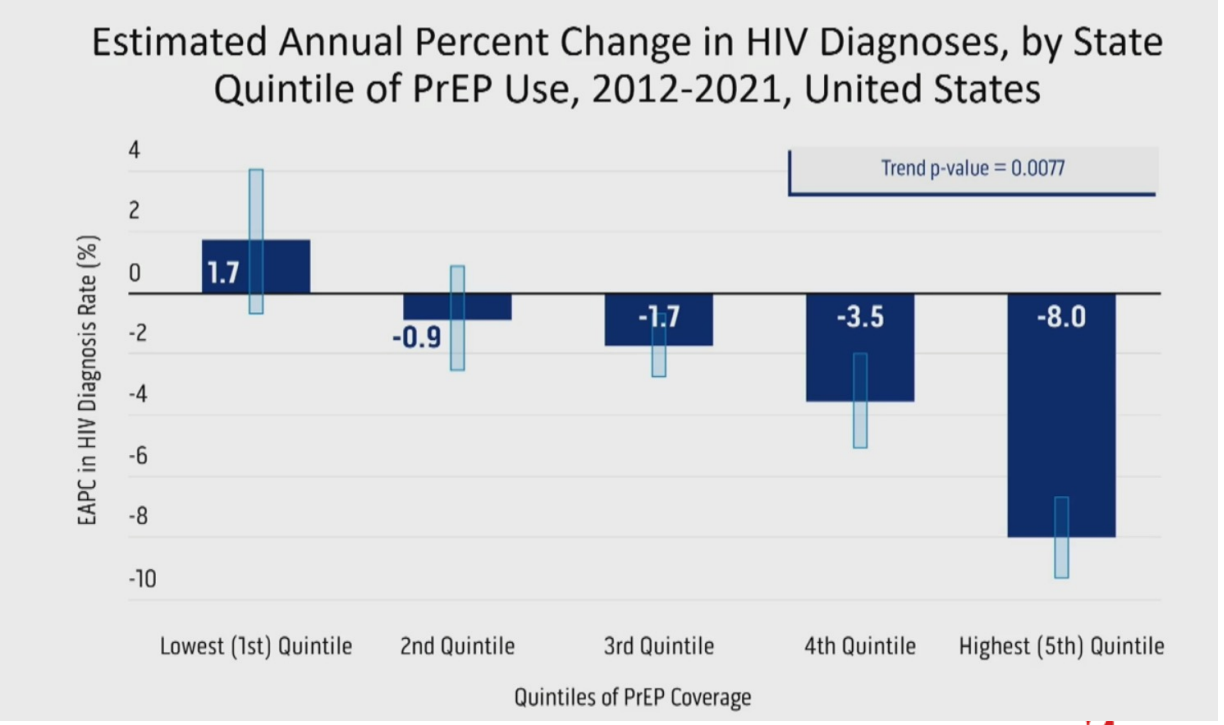
Association of State-Level PrEP Coverage and State-Level HIV Diagnoses, US, 2012-2021

Sullivan P et al., Abstract #165

- Ecological study of association between PrEP coverage & new diagnoses
- PrEP use: commercial data sets
- PrEP coverage: # of PrEP users/100 persons with indications (CDC & AIDSVu data)





Adherence Benchmarks for TFV-DP in DBS and PBMCS for African Women using FTC/TDF PrEP

Mugwanya et al., Abstract #165

- Background: PrEP adherence-response defined for MSM, but not cisgender women
- Goal: establish expected concentrations of TDF in dried blood spots and peripheral blood mononuclear cells in women taking directly observed meds

Observed TFV-DP concentrations in PBMCs (fmol/10^6): Week 4

	Non-pregnant 2 Doses/week	Non-pregnant 4 Doses/week	Non-pregnant 7 Doses/week	Pregnant 7 Doses/week
Sample size	N=17	N=17	N=18	N=18
Range	2–48	10–43	21–121	11–71
Mean±SD	13 ± 11	28 ± 10	52 ± 24	47 ± 17
Median (IQR)	9 (7–19)	28 (21–34)	49 (36–63)	50 (35–58)
% Difference; p-value (Wilcoxon exact)	82%; <0.001	43%; <0.001	—ref—	2%; 0.71

Similar concentrations in pregnant & non-pregnant women and similar to previous US-based observations

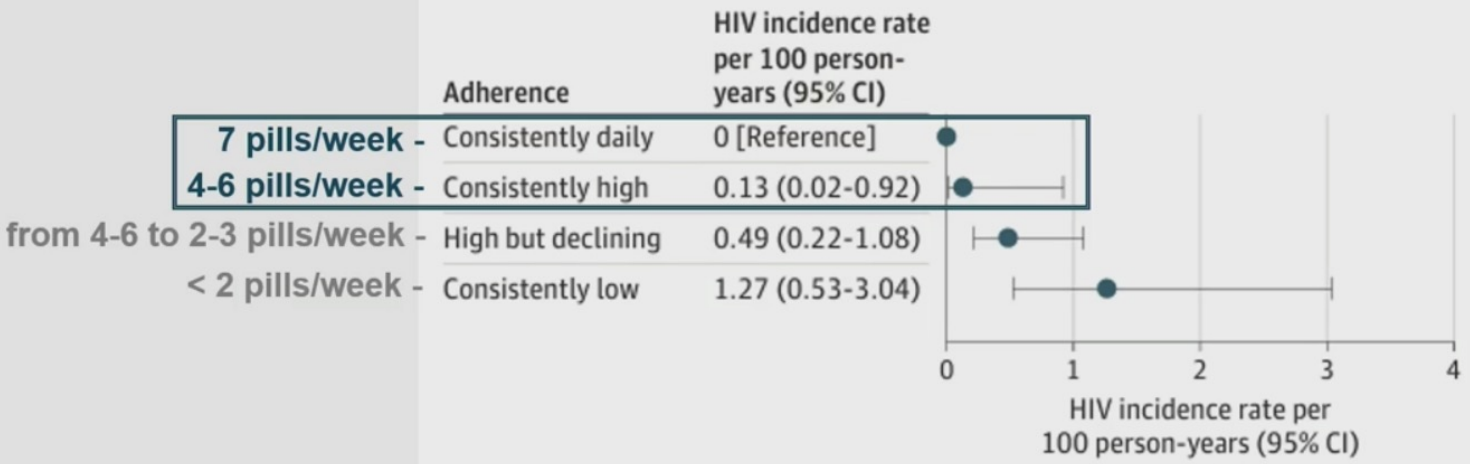
MWAETC

Challenging the Dogma of Event-Driven PrEP

Stewart, J. Abstract #50

Do vaginas demand perfection?

Figure 4. HIV Incidence Rates Among Cisgender Women by Adherence Trajectory (n = 2954)



Pooled data from 11 F/TDF PrEP studies among cisgender women in 6 countries [2012 to 2020]

CROI 2024

Marrazzo et al, JAMA, March 1, 2024

"These data suggest that women can be just as imperfect as we've been allowing men to be."
-Jenell Stewart

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Thank you!

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CROI 2024 Updates: Co-Occurring Conditions

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University of Washington

Last Updated: 3/18/24

Disclosures

No conflicts of interests or relationships to disclose

CROI Updates: Co-Occurring Conditions

- Updates in anal cancer screening strategies

- Review updates in metabolic complications of HIV
  - Use of semaglutide

- Updates in HBV vaccination
  - BEe-HIVe Arm A results

Anal Dysplasia Screening

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Anal Cancer in PWH

- Incidence of anal cancer high among PWH; men who have sex with men (MSM) with HIV have the highest risk of anal cancer

- ANCHOR: Treating anal HSIL reduces incidence of anal cancer (57% reduction)
  - Risk highest with greater: lesion size, smoking, no. of years from HIV diagnosis

- HRA (high resolution anoscopy) is gold standard for HSIL detection….
  - **…..but availability is limited**

- Need practical strategies to approach anal cancer screening in PWH
  - Prioritization of referrals by demographics, low CD4 nadir, cytology/high risk HPV (HR-HPV)

Palefsky et al. NEJM 2022; Martin-Iguacel et al, CROI 2024 (poster)

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Evaluation of Performance of Different HRA Triage Strategies in MSM LWH

Determine “best” strategy for HRA triage in MSM living with HIV (LWH) to efficiently allocate HRA resources

	Median (±SE)
Age (years)	47 (±10.7)
CD4 nadir (cells/uL)	350 (±241)
Current CD4 (cells/uL)	800 (±272)
CD4/CD8	1.03 (±0.39)
HIV RNA (copies/mL)	<37

180 MSM LWH had anal cytology, anal HPV, and HRA collected on same day

Results	Percent
Cytology	
NILM	10%
ASC-US	14%
LSIL	69%
ASC-H	5%
HSIL	2%
HR-HPV*	75%
HRA	43% HSIL

*Of HR-HPV, 54% HPV-16

Cavallari et al. CROI 2024

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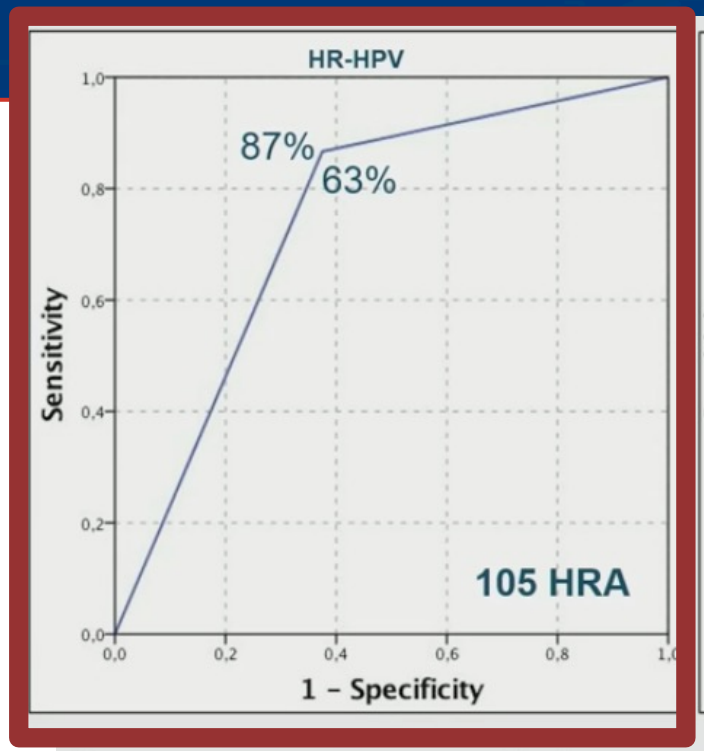
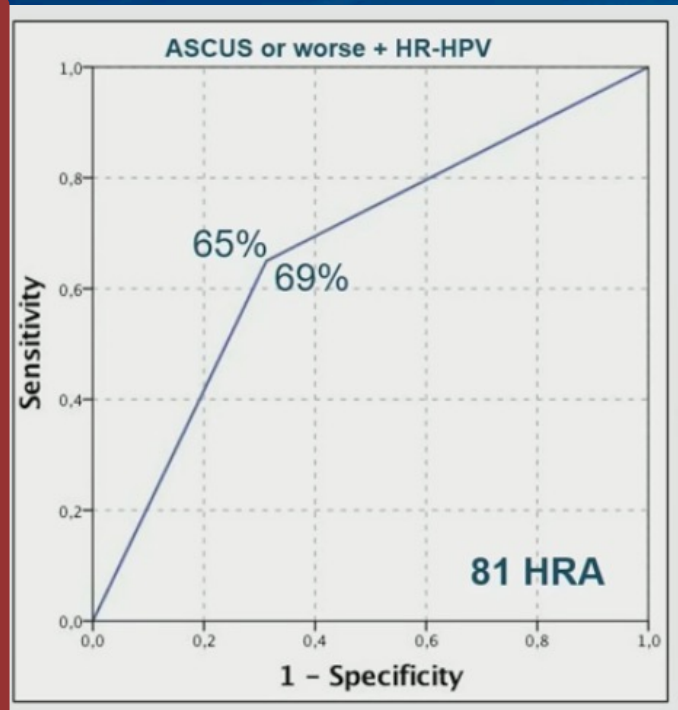
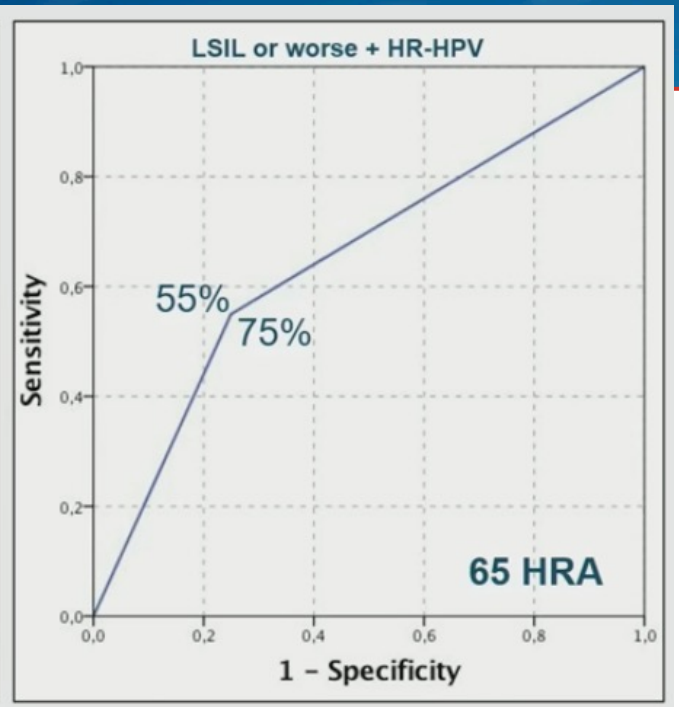
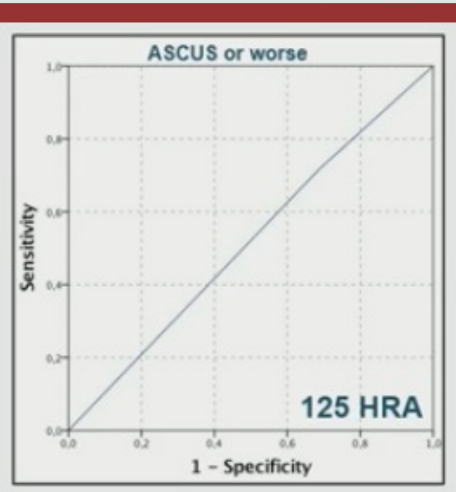
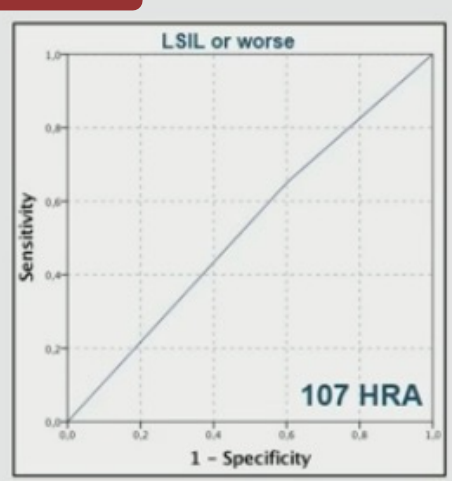
Results

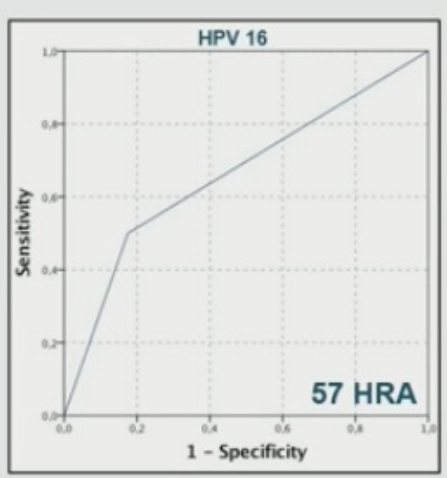


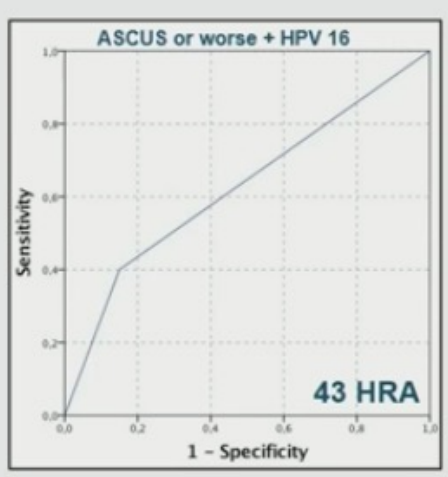












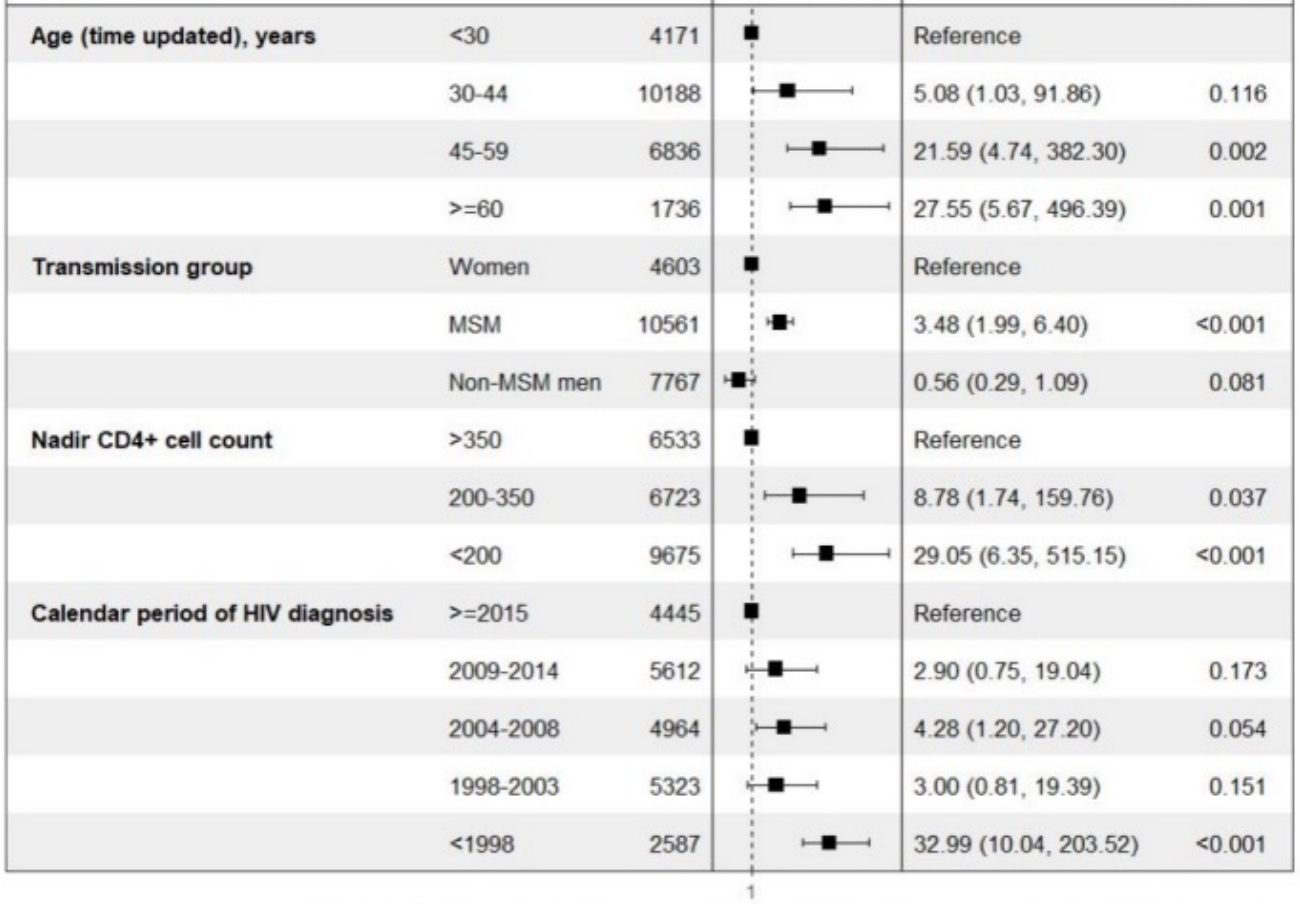
Cavallari et al. CROI 2024

CD4 Nadir and anal cancer risk

- PWH with nadir CD4 <200 had highest anal cancer risk (aIRR 29 v nadir > 350)
- PWH with nadir CD4 > 350 with similar risk as compared to general population
- Age, MSM, and nadir CD4 count strongest association w/anal cancer risk in PWH

Figure 2. Risk factors for anal cancer in the multivariable model.

Variable		N	Adjusted IRR	p-value
Age (time updated), years	<30	4171	Reference	
	30-44	10188	5.08 (1.03, 91.86)	0.116
	45-59	6836	21.59 (4.74, 382.30)	0.002
	>=60	1736	27.55 (5.67, 496.39)	0.001
Transmission group	Women	4603	Reference	
	MSM	10561	3.48 (1.99, 6.40)	<0.001
	Non-MSM men	7767	0.56 (0.29, 1.09)	0.081
Nadir CD4+ cell count	>350	6533	Reference	
	200-350	6723	8.78 (1.74, 159.76)	0.037
	<200	9675	29.05 (6.35, 515.15)	<0.001
Calendar period of HIV diagnosis	>=2015	4445	Reference	
	2009-2014	5612	2.90 (0.75, 19.04)	0.173
	2004-2008	4964	4.28 (1.20, 27.20)	0.054
	1998-2003	5323	3.00 (0.81, 19.39)	0.151
	<1998	2587	32.99 (10.04, 203.52)	<0.001



IRR adjusted for calendar time, age (time-updated), risk group and nadir CD4⁺ cell count

Martin-Iguacel et al. CROI 2024

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Anal Self Sampling for HR-HPV Detection

- Access to HRA, cytology limited in certain settings (such as sub-Saharan Africa)

- Evaluation of anal self-sampling (ASS) for HR-HPV detection as compared to anal swab by practitioner (ASP) in 188 MSM (67% with HIV) in Togo
  - Practitioner conducted anal exam and anal cytology post self sampling

- Acceptability: 99% found ASS procedurally easy; 60% would prefer ASS to ASP (19% with no preference)

- Performance: 6% v 4% of ASS samples uninterpretable

Charpentier et al. CROI 2024

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Anal Self Sampling for HR-HPV Detection

- Substantial agreement between methodologies for HR-HPV (89.7%, k = 0.66) and HPV16 (90.3%, k =0.75)
- At least one HR-HPV detected in 83% of ASS and 77% of ASP samples
- HPV16 detected in 28% of ASS and 26% of ASP

High concordance between two sampling methods and high acceptability and ease of self-sampling

Self-sampling (ASS) may help achieve anal cancer screening targets, especially in LMIC

Charpentier et al. CROI 2024

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Takeaways

- In discussion of how to develop guidance for HRA referral, consider:
  - HPV testing (HR-HPV types 16 and 18), inclusive of self sampling
  - Anal cytology in combination
  - Nadir CD4

Metabolic Complications

GLP-1 Receptor Agonists

- Mechanism: Promote insulin release and suppress hepatic glucose output
  - Many off target effects

- Semaglutide
  - DM: 2% decrease in A1c, 6.4 kg weight loss, 26% decrease in MACE events
  - Without DM: 3-4 kg weight loss, 20% decrease in MACE events

- Semaglutide in PWH?

Marso et al. NEJM 2016
Lincoff et al. NEJM 2023

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SLIM LIVER

- Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is common among people with HIV
  - GLP-1 (semaglutide) associated with metabolic improvements including improved hepatic steatosis

- Semaglutide for MASLD in HIV:
  - **ACTG A5361 (SLIM LIVER)**: single arm, open label, phase IIb study of **effects of semaglutide on hepatic steatosis**
    - MRI proton density fat fraction (MRI-PDFF) quantified intrahepatic trigylceride content (IHTG)

- 49 PWH suppressed on ART w/ elevated minimum waist circumference, insulin resistance, and ≥ 5% IHTG on MRI-PDFF

- Initiated on semaglutide, uptitrated over 24 weeks: 0.25 mg sc weekly --> 0.5 mg --> 1.0 mg)
  - MRI-PDFF performed again at week 24

Lake et al. CROI 2024

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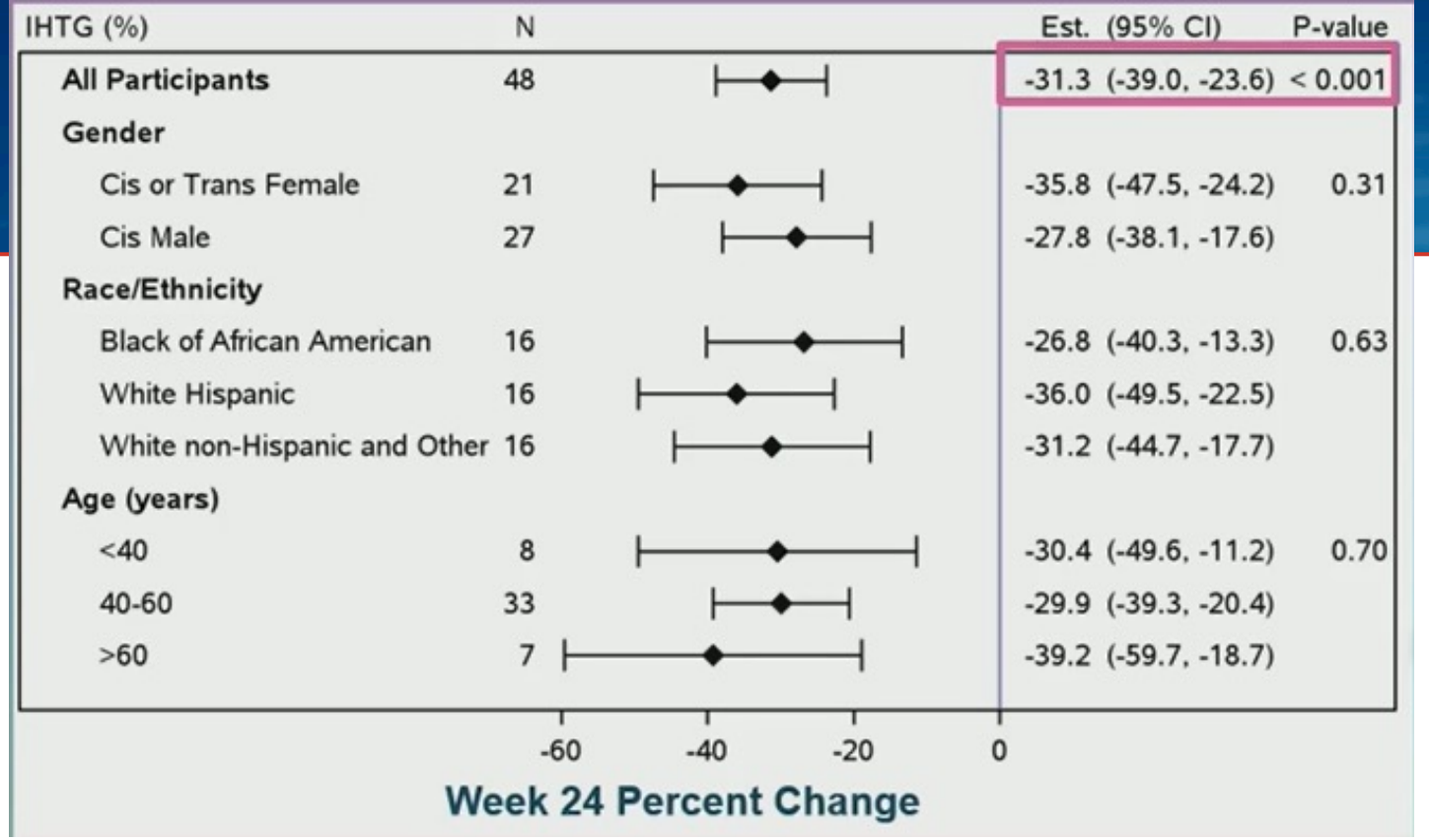
SLIM LIVER

Demographics:

- 37% cis-women, 6% transwomen, 57% cis-men
- 27% white non-Hispanic, 33% Black or African American, 39% Hispanic
- Median BMI 35 kg/m2, Median waist circumference 114 cm
- Median CD4 701 (IQR 586,869)
- 82% on INSTI, 22% on NNRTI, 4% on PI



Overall clinically significant reductions in IHTG

- 1/3 of participants with complete MASLD resolution
- IHTG improvements correlated with weight loss (mean 7.8 kg loss over 24 weeks) along with weight circumference, fasting plasma glucose, A1c, and serum triglycerides

Lake et al. CROI 2024

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Semaglutide in HIV

- Effects of Semaglutide on Muscle Structure and Function in the SLIM Liver Study (Ditzenberger et al.)
  - Use of semaglutide associated with loss of psoas muscle volume (without change in physical function) but no change in muscle fat among SLIM Liver participants

- Impact of Semaglutide on Weight Change Among People with HIV: A Stratified Analysis by Baseline BMI (Crane et al.)
  - Among PWH, semaglutide a/w significant weight loss (6.5 kg, 5.7% of body weight)
  - Sensitivity analysis: weight loss was the same regardless of INSTI use

Ditzengerger et al CROI 2024
Crane et al CROI 2024

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Takeaways

- Use of semaglutide in PWH:
  - Associated with significant weight loss
  - Can be used for successful treatment of MASLD
  - May impact muscle volume without impact in physical function (in short term)

- Needs:
  - Longer term data
  - Access to medication!

Hepatitis B Vaccination in PWH

Background

- HBV vaccine seroprotection rates (SPR) in persons with HIV (PWH) are lower (range 18-71%) than in adults without HIV (range 60-80%) with conventional HBV vaccine (HepB-alum)[1]

- ACTG 5379 (BEe-HIVe):

Arm B (vaccine naïve)[2]

  - 100% of PWH receiving 3-dose series HepB-CpG (Heplisav-B) vaccine achieved seroprotection response (SPR, HBsAb ≥ 10 mIU/mL), 84% HBsAb ≥ 1000 mIU/mL
  - 98.5% achieved SPR after two doses, though at lower titers (28% HBsAb ≥ 1000 mIU/mL)

[1] Kim NH, et al. Int J STD AIDS. 2009
[2] Marks KM, et al. Clin Infect Dis 2023

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B-Enhancement of HBV Vaccination in Persons Living With HIV (BEe-HIVe): Study Design

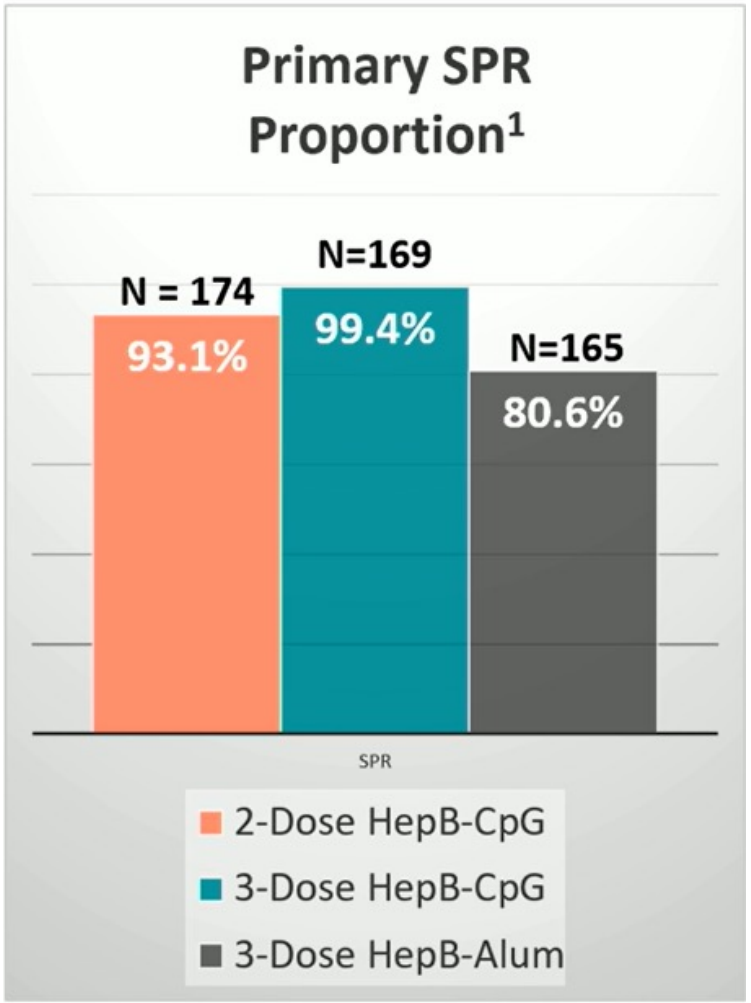
- **Entry Criteria Arm A and B**
  - PWH and age 18-70 years
  - On ART & HIV-1 RNA <1,000 copies/mL
  - CD4 >100 cells/mm^3
  - Negative HBV surface Ab (sAb)
  - No history of hepatitis B
  - Not pregnant
- **Arm A (Vaccine Non-Responders)**
  - Serum Hep B sAb <10 mIU/mL
  - HBV vaccination (>168 days prior)
- **Arm B (Vaccine Naïve)**
  - Hep B sAb negative (<45 days)

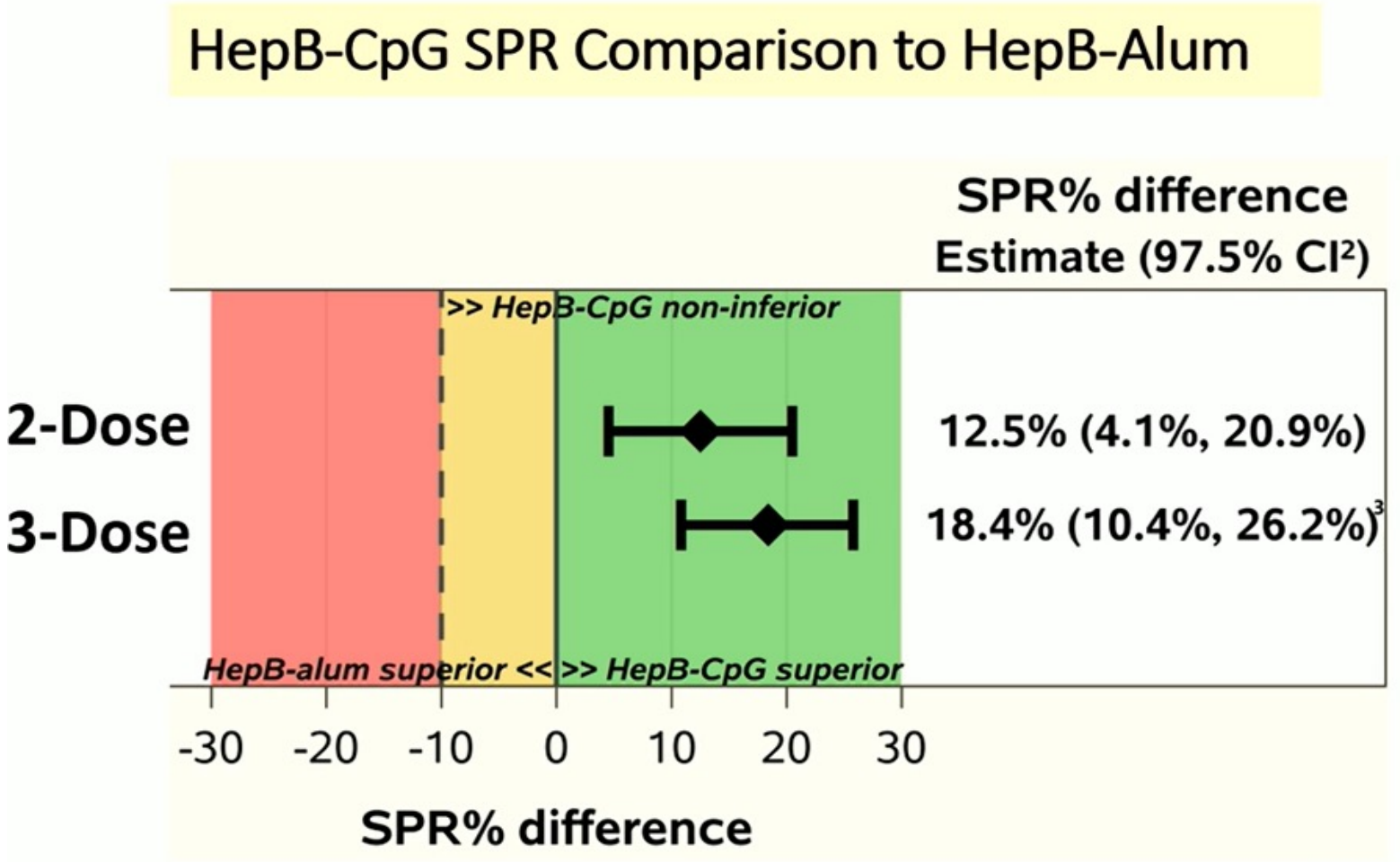
Arm A: HBV Vaccine Non-Responders	
HepB (CpG)	2 doses: 0, 4 weeks
HepB (CpG)	3 doses: 0, 4, and 24 weeks
HepB (Eng-B)	3 doses: 0, 4, and 24 weeks

Arm B: HBV Vaccine Naive	
HepB (CpG)	3 doses: 0, 4, and 24 weeks

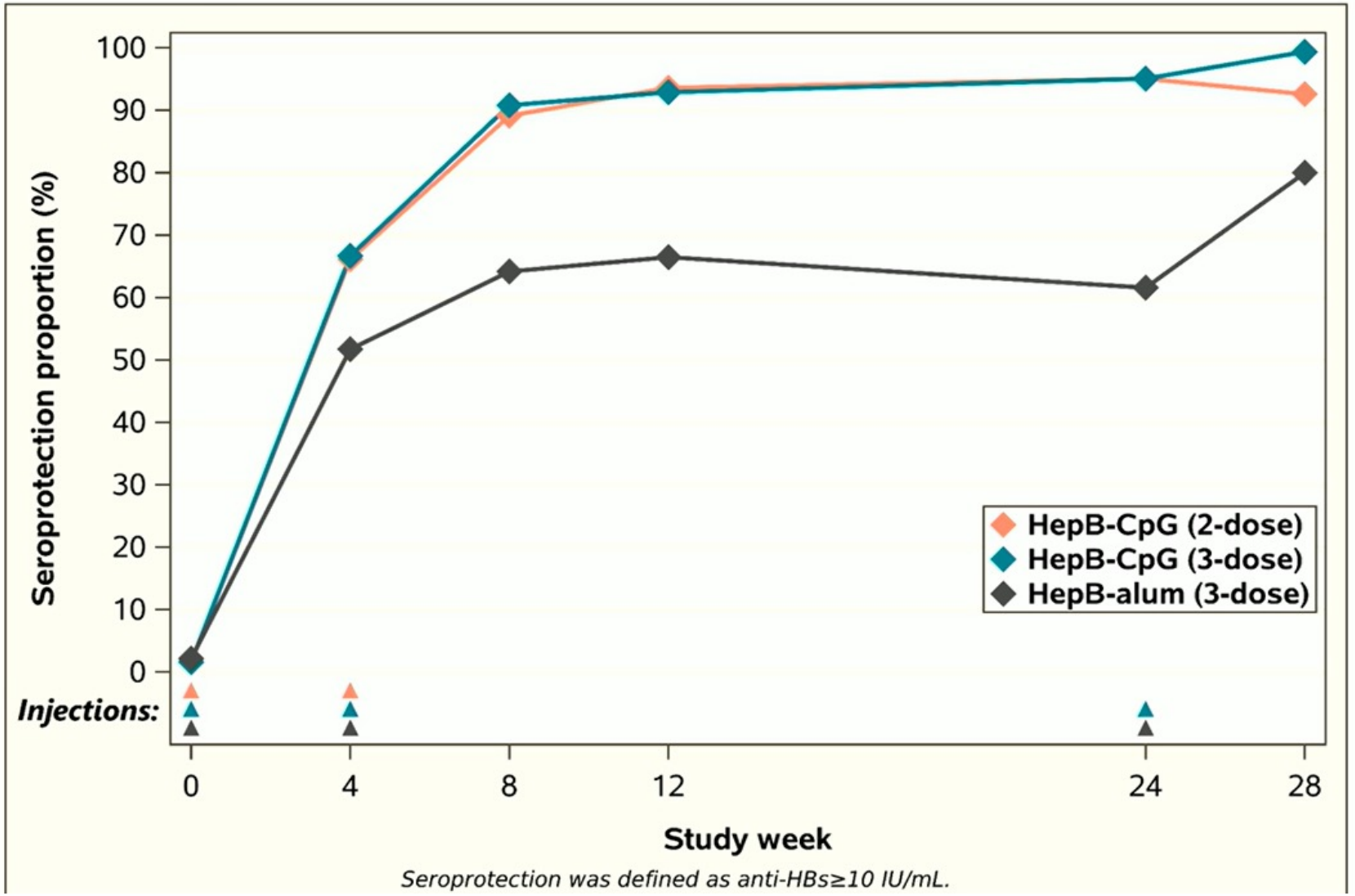
Source: Marks K, et al. ID Week. October 19-23, 2022; Washington, D.C. Poster LB749.; National HIV Curriculum

National HIV Curriculum

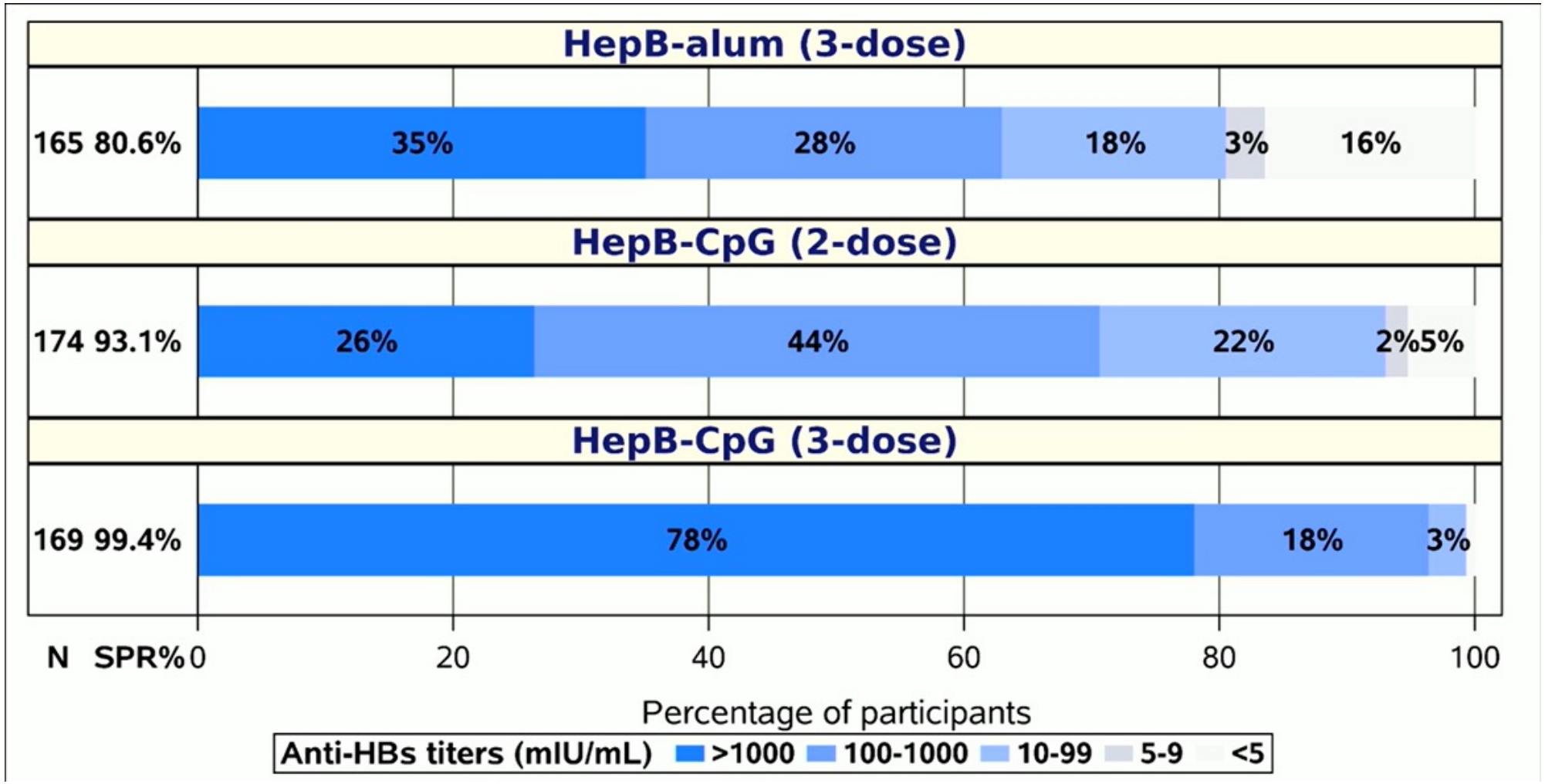

Primary SPR Proportion[1]
N = 174
93.1%
N=169
99.4%
N=165
80.6%
SPR
2-Dose HepB-CpG
3-Dose HepB-CpG
3-Dose HepB-Alum


HepB-CpG SPR Comparison to HepB-Alum
SPR% difference
Estimate (97.5% CI[2])
>> HepB-CpG non-inferior
2-Dose
12.5% (4.1%, 20.9%)
3-Dose
18.4% (10.4%, 26.2%)[3]
HepB-alum superior << >> HepB-CpG superior
-30
-20
-10
0
10
20
30
SPR% difference

SPR Proportions at Study Visits



Distribution of Anti-HBs titers at respective endpoints



Takeaways

- PWH with non-response to conventional HBV vaccine achieved superior SPR as compared to 3 doses of HepB-alum

- Three doses of HepB-CpG achieved high proportion of SPR with HBsAb titers > 1000 mIU/mL (78%)
  - Do we need titers this high?
  - Underrepresentation of factors associated with poor response (low CD4 cell count, HIV viremia, HCV, older age)

- No unexpected safety issues or deaths

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Co-Occuring Conditions: Take Home Points

- A triaged referral process including CD4 nadir, age, MSM, and HR-HPV (including self testing), for anal cancer screening in PWH may help tailor population who will benefit most
- Semaglutide leads to significant weight loss and improvement of MASLD in PWH
- HepB-CpG (Heplisav-B) is superior to conventional HBV vaccination in PWH who are prior vaccine non-responders

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Questions?

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Disclaimer

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