CROI feedback

UK-CAB: 30 April 2020

Simon Collins

www.i-Base.info

Declarations/conflict of interest

No personal financial conflicts of interest.

CROI 2020

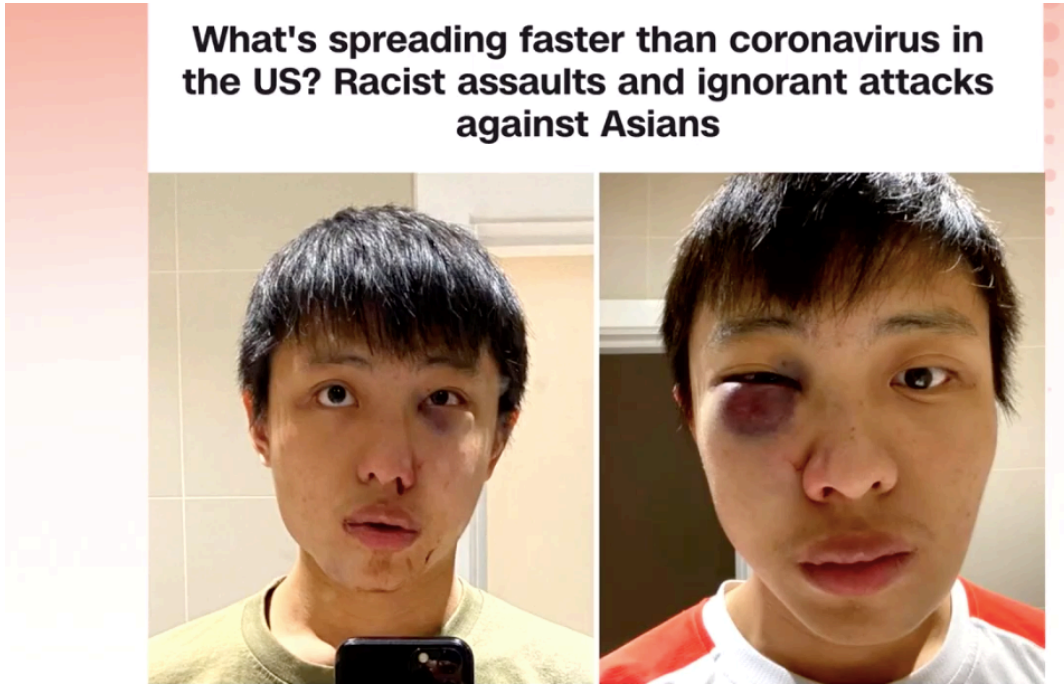
- COVID-19 and move to virtual meeting
- New drugs – pipeline for treatment and prevention
- PrEP and PEP studies and new formulations
- Side effects: weight gain and diabetes

Move to virtual CROI

- Monday drip…
- Friday cancelled…
- Biogen - 100/180 participants.
- Concern for local health services, quarantine for >4000 infectious disease delegates and onward transmission.
- Nearly all the meeting was saved and became virtual.
- Abstracts, webcasts and posters are all online. www.croiconference.org

CROI 2020 move to virtual meeting

Referenced racism linked to COVID-19 using HIV response as a example.



New drugs for treatment

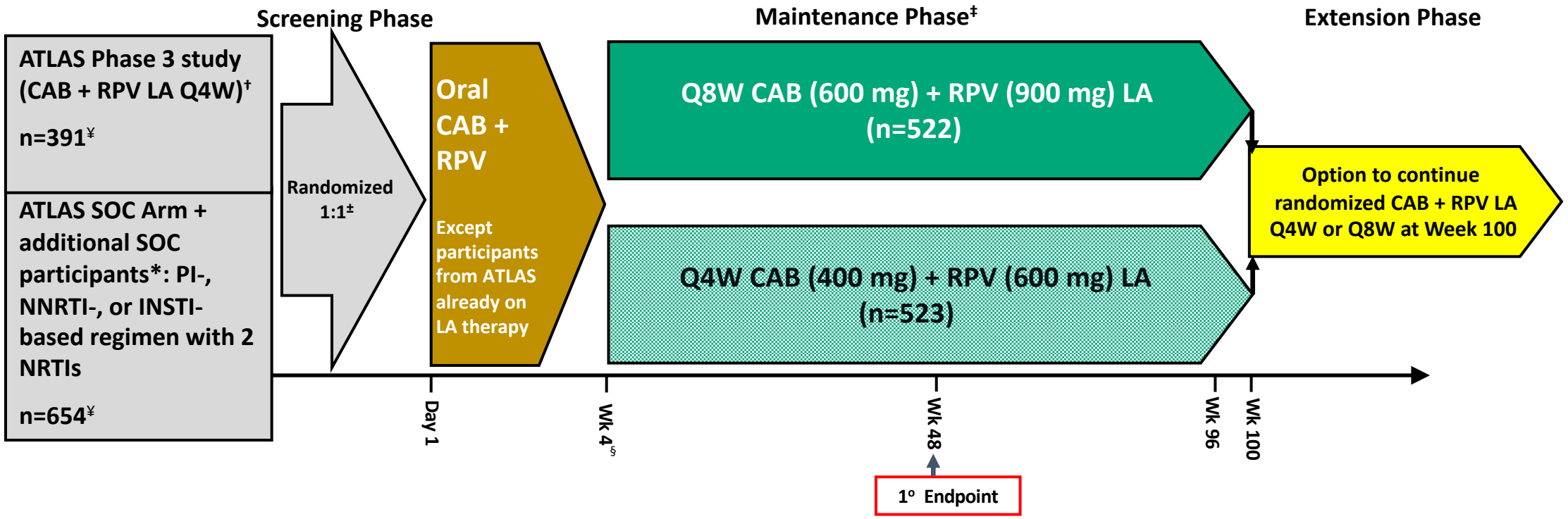
- CAB/RPV-LA: ATLAS 2M – injectable ART…
- Islatravir – monthly pill for PrEP and PEP
- GS-6207 – capsid inhibitor
- GS-9722 - bNAb elipovimab

ATLAS-2M - Cabanuva

- Randomised open label study comparing CAB/RPV LA every month vs every two months.
- Results very similar (ie non inferior)
- Slightly more virological failures in 2M group
- However, these included baseline resistance
- Some comments were that this was a concern.

ATLAS-2M Study Design

Phase 3, randomized, multicenter, parallel-group, noninferiority, open-label study



†Participants transitioning from ATLAS must have been on CAB + RPV LA Q4W or a current ART regimen through at least Week 52 of the ATLAS study and had plasma HIV-1 RNA <50 c/mL at screening.
*SOC participants not transitioning from ATLAS study were to be on uninterrupted current regimen (either the initial or second combined ART regimen) for at least 6 months prior to screening. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to screening: one within the 6- to 12-month window, and one within 6 months prior to screening, was required. Participants were excluded if they had a history of virologic failure; evidence of viral resistance based on the presence of any resistance-associated major INSTI or NNRTI mutation (except K103N) from prior genotype assay results. ¥Intent-to-treat exposed population. ±1149 participants were screened, and 1049 participants were randomized. 4 participants did not receive study drug and therefore were not part of the ITT-E population. ‡Participants who withdraw from the IM regimen must go into 52-week long-term follow-up if randomized regimen is not yet locally approved and commercially available. §Participants on oral lead-in treatment attended a Week 4 visit to assess tolerability. In participants in the Q4W arm who had an oral lead-in, the first LA dose was CAB 600 mg + RPV 900 mg.

ART, antiretroviral therapy; CAB, cabotegravir; INSTI, integrase strand transfer inhibitor; LA, long-acting; NRTI, nucleoside reverse transcriptase inhibitor NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, 4-week dosing interval; Q8W, 8-week dosing interval; RPV, rilpivirine; SOC, standard of care; Wk, week.

Overton et al. CROI 2020; Boston, MA. Presentation 3334.

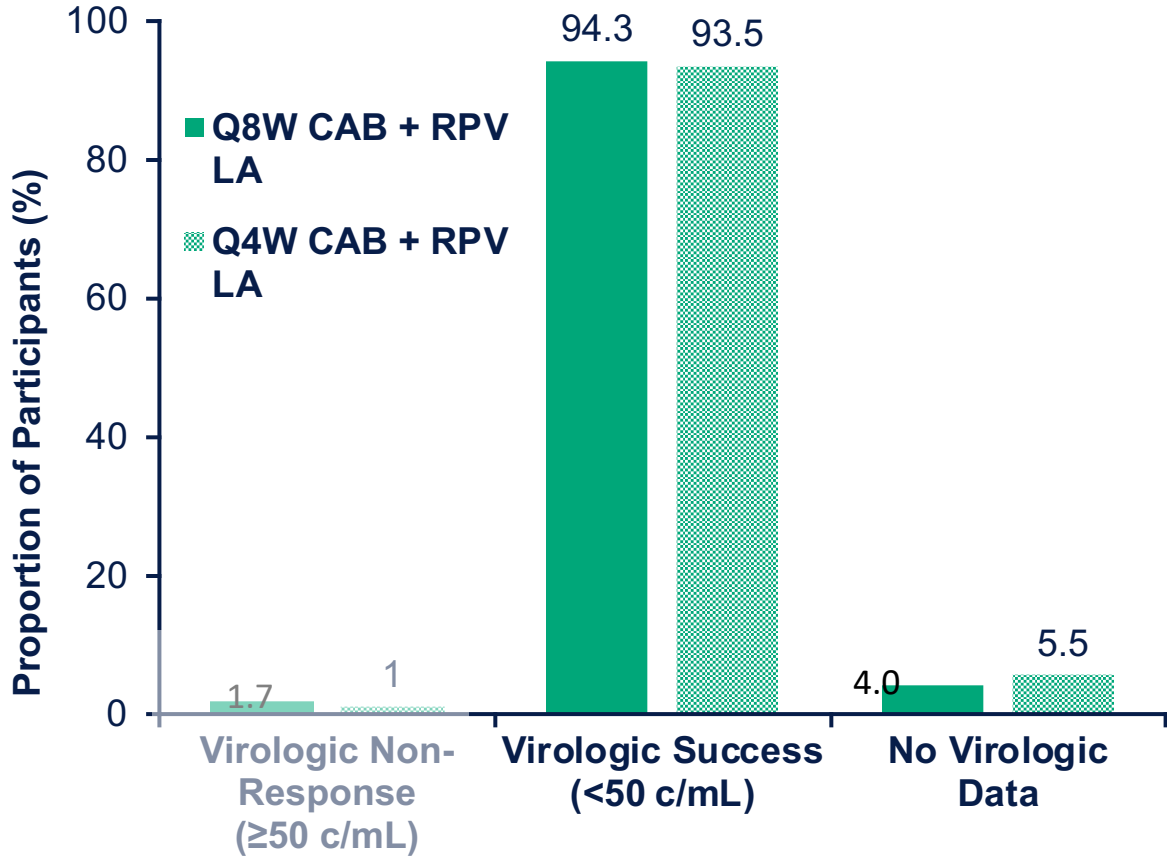
ATLAS-2M 48-Week Endpoints

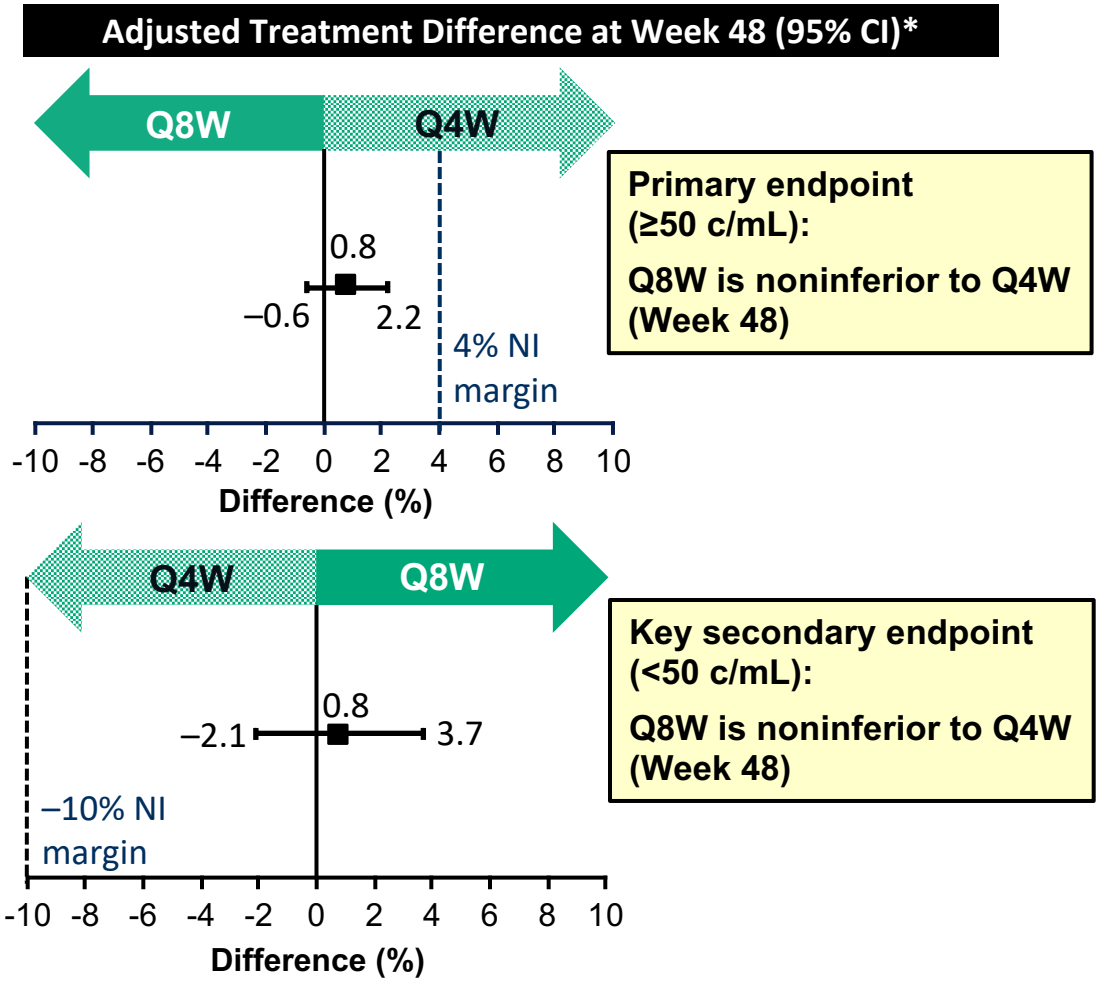
- **Primary endpoint**
  - Proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E)
    - Noninferiority margin of 4%
- **Key secondary endpoint**
  - Proportion of participants with HIV-1 RNA <50 c/mL at Week 48 (Snapshot, ITT-E)
- **Additional secondary endpoints**
  - Safety and tolerability
  - Incidence of confirmed virologic failure
  - Incidences of viral resistance in participants experiencing CVF
  - Participants' treatment preference for long acting regimen
- **Randomization was stratified by prior CAB + RPV exposure**

AE, adverse event; CAB, cabotegravir; CVF, confirmed-virologic failure; ITT-E, intent-to-treat-exposed; RPV, rilpivirine.

Overton et al. CROI 2020; Boston, MA. Presentation 3334.

ATLAS-2M Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints





CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; LA, long-acting; NI, noninferiority; RPV, rilpivirine; Q4W, 4-week dosing interval; Q8W, 8-week dosing interval.

*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).

Overton et al. CROI 2020; Boston, MA. Presentation 3334.

ATLAS-2M: Summary of Confirmed Virologic Failures

	n	CVFs n (%)	CVFs with RPV RAMs	Treatment-emergent RPV RAMs	CVFs with INSTI RAMs	Treatment-emergent INSTI RAMs
Q8W	522	8 (1.5)	6/8*	K101E, E138E/K, E138A, Y188L	5/8*	Q148R[+], N155H[+]
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K,Q148R, N155N/H,

[+]Or mixture

- *Post-hoc baseline PBMC HIV-1 DNA testing (Q8W arm):
  - 5/8 CVFs had pre-existing major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L)
  - 1/8 CVFs had pre-existing major INI RAM (G140G/R)
  - 5/8 CVFs had L74I polymorphism (3 subtype A or A1, 1 subtype C, 1 complex subtype)

- 9/10 CVFs re-suppressed on fully active oral HAART (1/10 non-compliance on PI-based ART)
  - All CVFs retained phenotypic sensitivity to dolutegravir

- Factors contributing to CVF (e.g. baseline resistance and drug concentrations) are being further evaluate
    - PBMC HIV-1 DNA analysis underway across Phase 3 program

CVF definition – 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL

ART, antiretroviral therapy; CVF, confirmed virologic failure; HAART, highly active antiretroviral therapy; INSTI, integrase strand transfer inhibitor; PBMC, peripheral blood mononuclear cell; PI, protease inhibitor; Q4W, 4-week dosing interval; Q8W, 8-week dosing interval; RAMs, resistance-associated mutations; RPV, rilpivirine.

ATLAS-2M Safety and Tolerability Was Similar Between Q8W and Q4W Dosing Arms: AEs Excluding ISRs

	Q8W (n=522) n (%)	Q4W (n=523) n (%)
Any AE	403 (77)	441 (84)
Drug-related AEs	109 (21)	125 (24)
Any Grade ≥3	29 (6)	30 (6)
Drug-related Grade ≥3	4 (<1)	5 (<1)
AEs leading to withdrawal	8 (2)	10 (2)
Drug-related AEs leading to withdrawal	5 (<1)	8 (2)
Any SAE	26 (5)	19 (4)
Drug-related SAEs†	2 (<1)	1 (<1)
Fatal SAEs‡	1 (<1)	0
Drug-related fatal SAEs	0	0

†Drug-related SAEs were presyncope and acute pancreatitis in the Q8W group and allergic reaction in the Q4W group. ‡The fatal SAE was sepsis. The death was not considered related to study drug. A further participant died during screening (did not receive study drug).

- AEs were similar between the Q8W and Q4W dosing arms
- Overall, 96% of drug-related AEs were Grade 1–2
- Drug-related AEs led to withdrawal in 5 participants in the Q8W arm and 8 in the Q4W arm

AE, adverse event; ISR, injection site reaction; Q4W, 4-week dosing interval; Q8W, 8-week dosing interval; SAE, serious adverse event.

Overton et al. CROI 2020; Boston, MA. Presentation 3334.

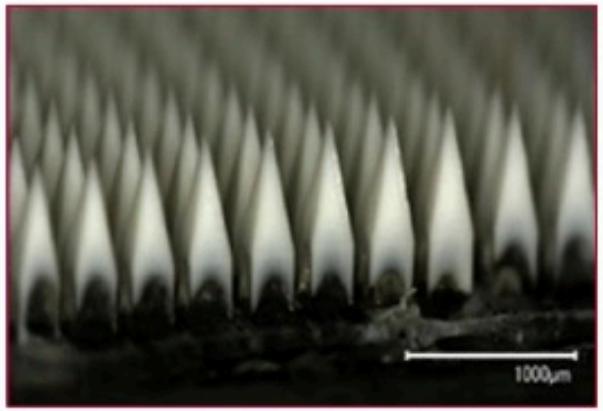
FDA Complete Response Letter

- The reasons given in the CRL relate to Chemistry Manufacturing and Controls (CMC) for Cabenuva (CBV LA/RPV LA)
- No safety issues related to CMC and there is no change to the safety profile of the products used in clinical trials to date.
- ViiV Healthcare will work closely with the FDA to determine the appropriate next steps for this New Drug Application.

- UK access – price?

Other CAB Long Acting Programs

- Microarray Patch (MAP) for Long-Acting HIV PrEP



Light microscopic image (x25) of MAP

PATH

USAID
FROM THE AMERICAN PEOPLE

PEPFAR

- CAB LA Reformulation: double-strength concentration (400mg/mL)

- ViiV HC/GSK internal program

- CAB Implant: non-biodegradable, retrievable

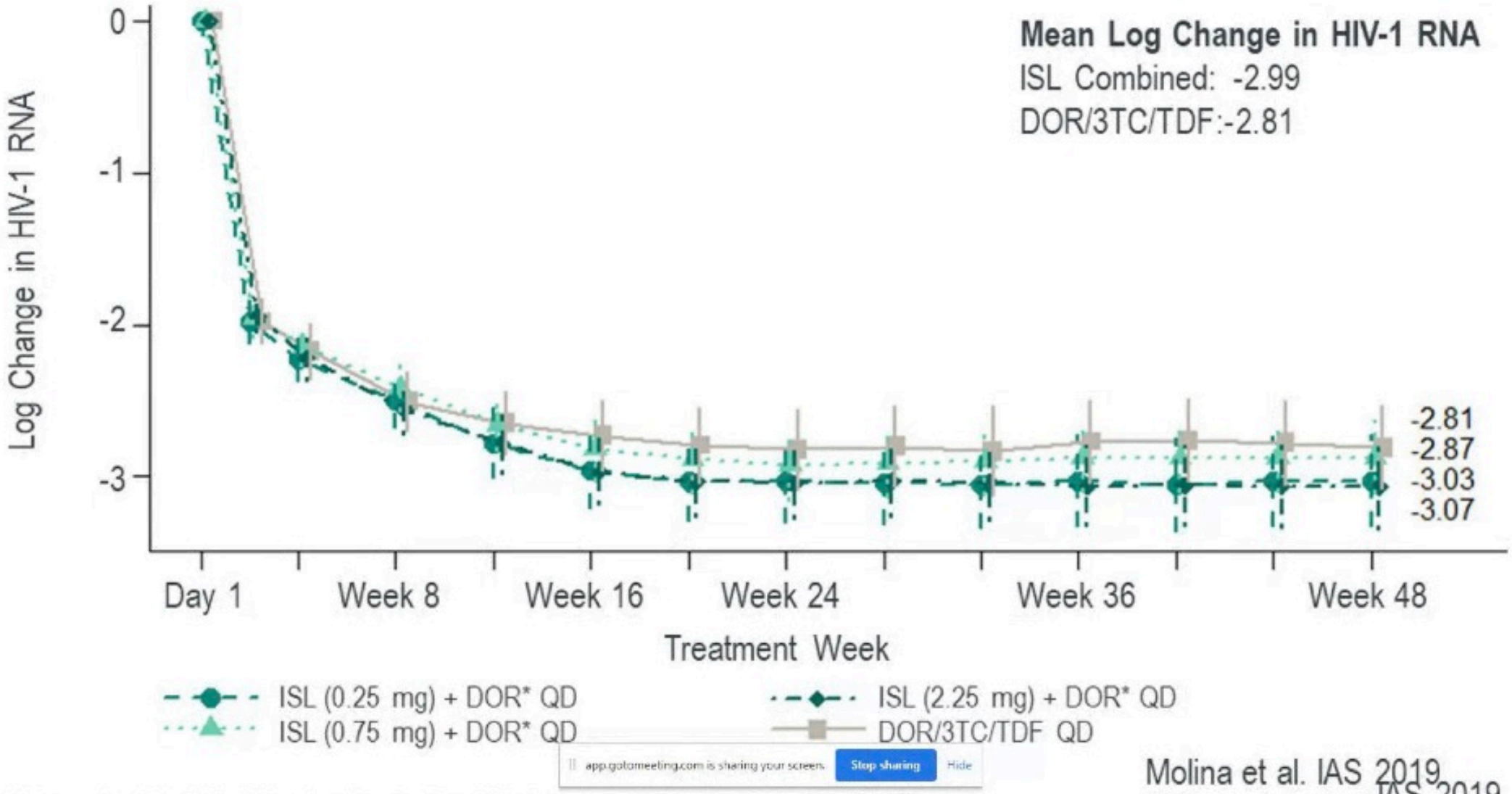
- ViiV/GSK internal program

Rein-Weston, ID Week Oct 2019
https://doi.org/10.1093/ofid/ofz415.2491

Islatravir (MK-8591, EFdA)

- Long acting nuke (NRTTI)
- Dual therapy switch: doravirine + islatravir
- Formulations include daily and weekly pill
- Also an annual implant
- Macaque study: once-monthly pill for PrEP and PEP
- Potential to completely change PrEP and PEP in practice.

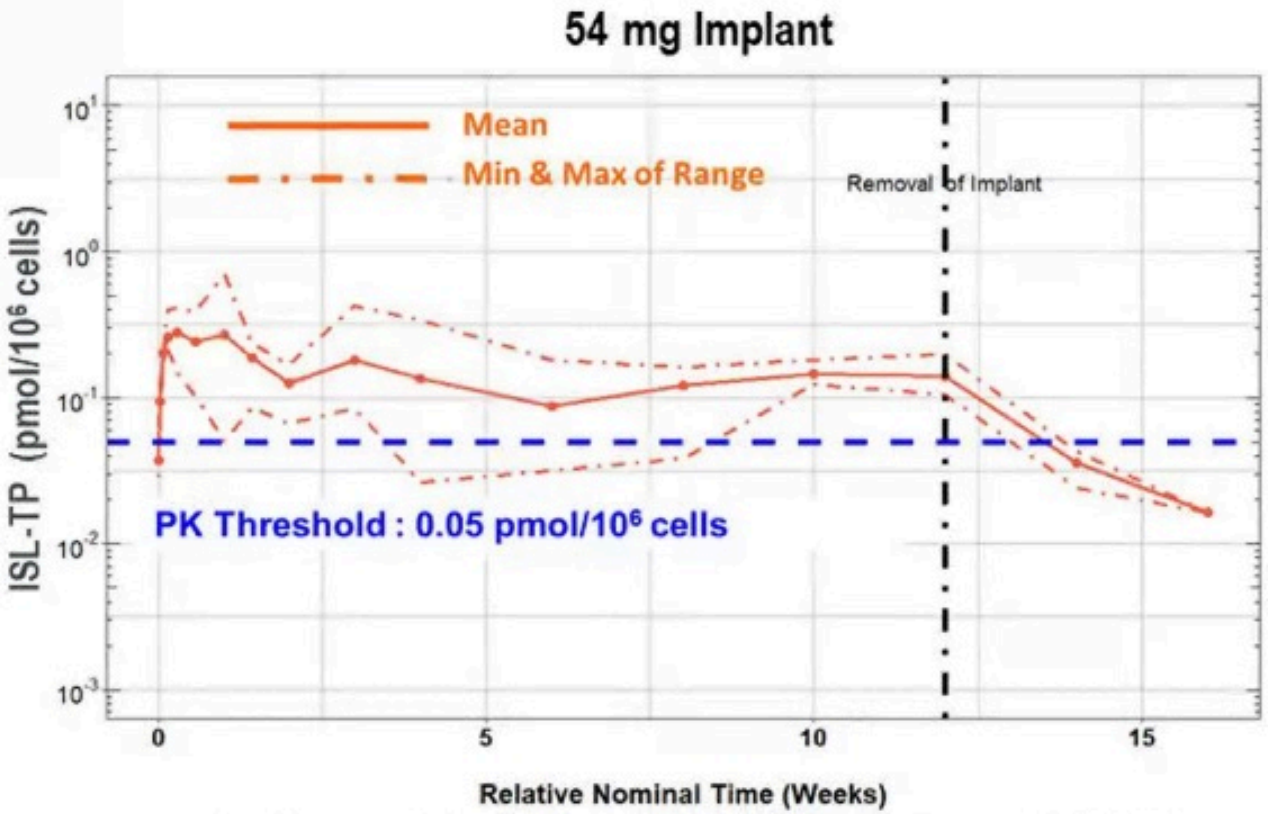
Mean Log Change in HIV-1 RNA (95% CI) Over Time

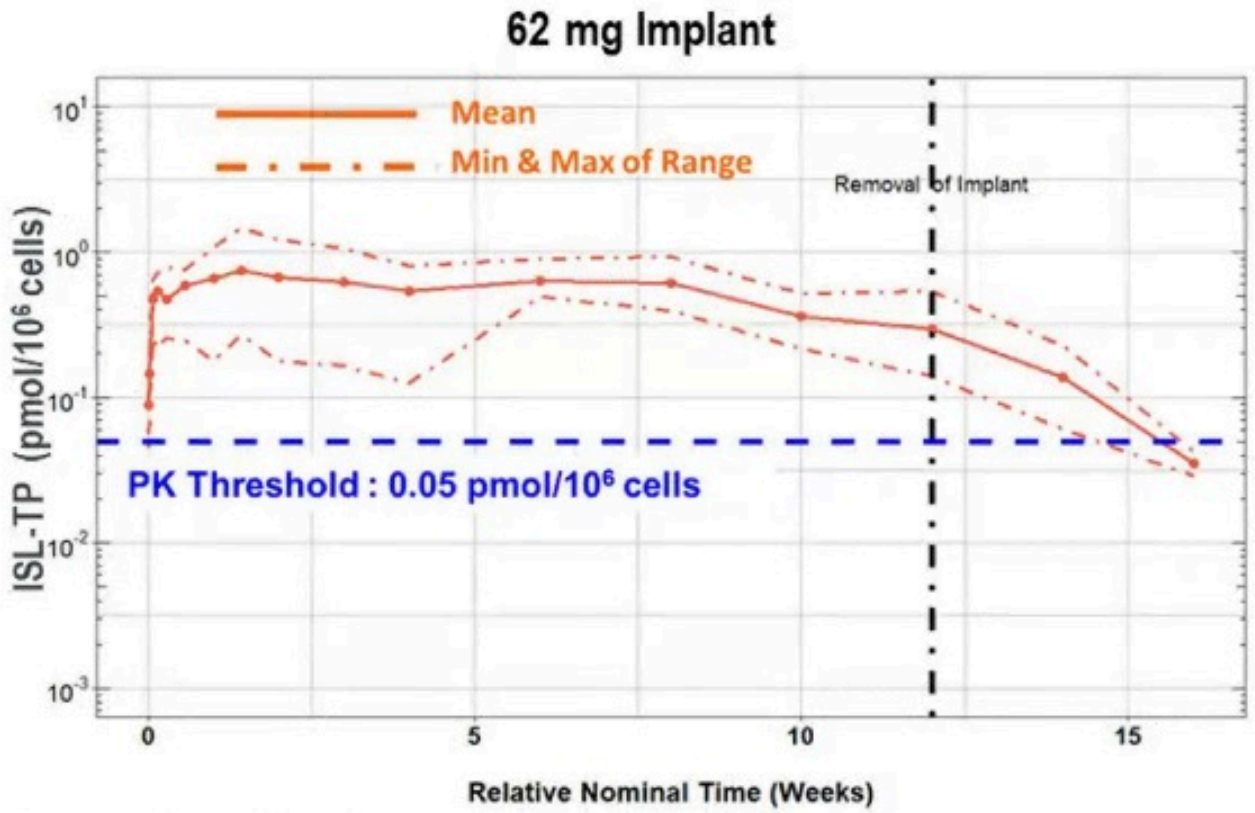


Molina et al. IAS 2019

*Participants initially received ISL+DOR+3TC and switched to ISL+ DOR during the week 24-48 period of the study.

Intracellular ISL-TP PK Threshold of 0.05 pmol/10^6 Cells Maintained Throughout Placement for Both Doses

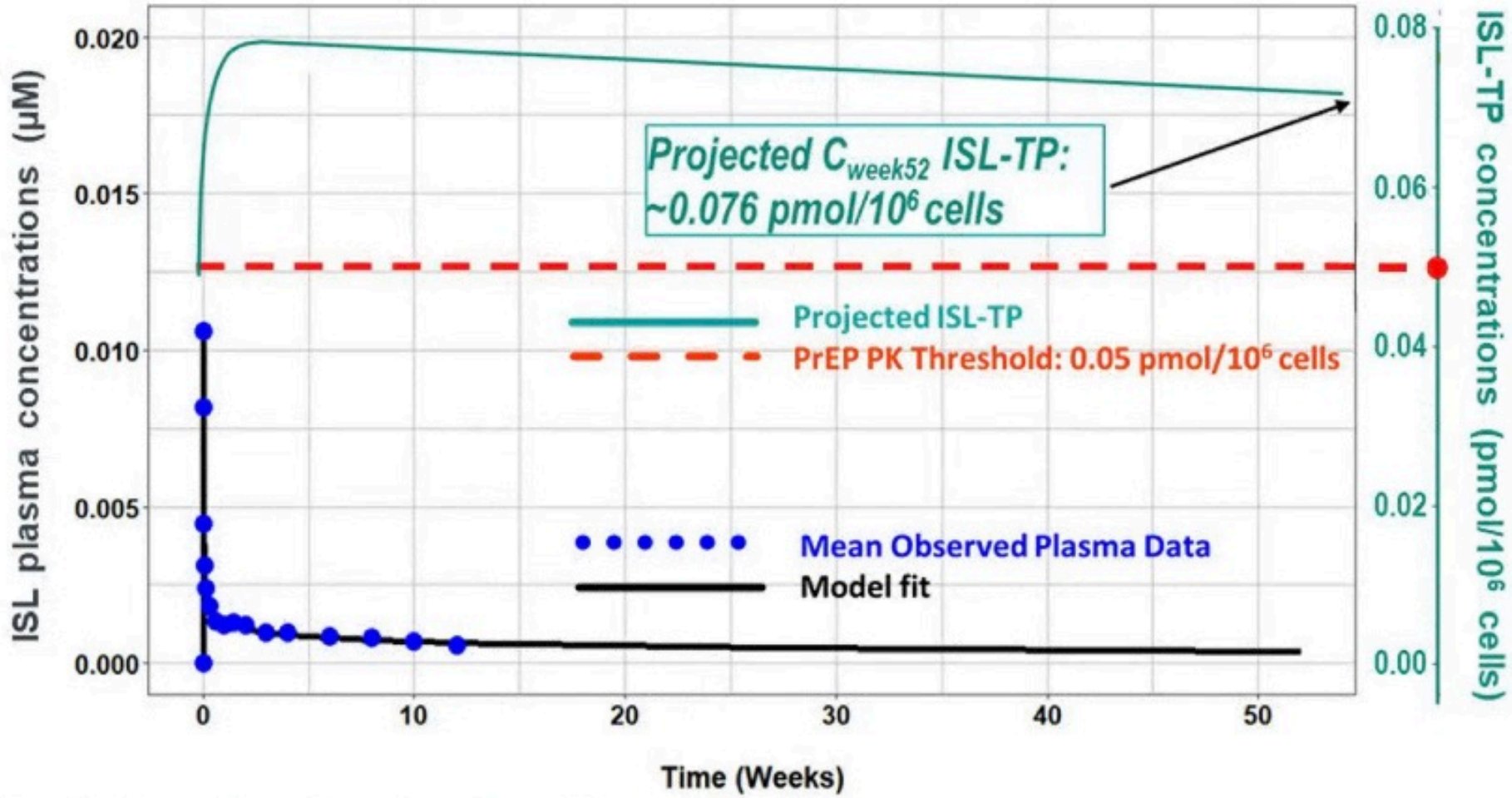




- Ratio of TP/plasma remains fairly constant at ~1000:1 – consistent with oral dosing
- Half-life after removal of implant similar to half-life of orally dosed ISL

Matthews et al. IAS 2019

62 mg Implant Projected to Lead to Concentrations Above Threshold for at Least 12 Months



- 62 mg implant will continue to release through 52 weeks
- ISL-TP should be above threshold (0.05 pmol/10^6 cells) for >12 months
  - Projected concentration at 12 months: **0.07**

Matthews et al. IAS 2019

WEEKLY ORAL ISLATRAVIR PROVIDES EFFECTIVE PEP AGAINST IV CHALLENGE WITH SIVmac$_{251}$

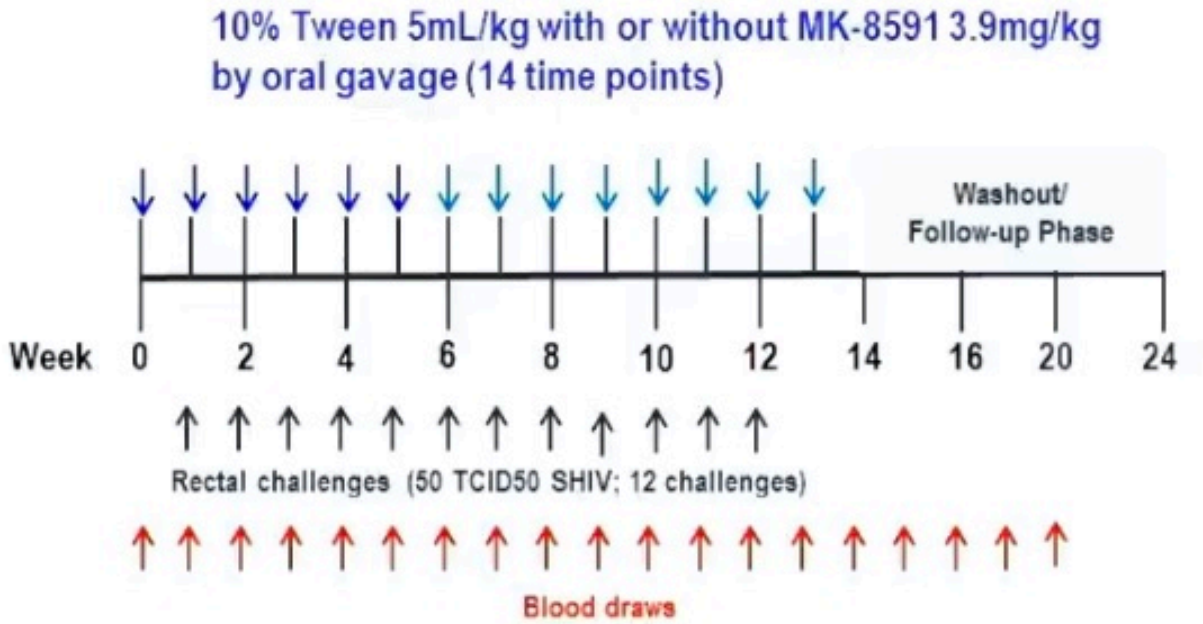
Martin Markowitz[1]; Agegnehu Gettie[1]; Leslie St. Bernard[1]; James Blanchard[2]; Brooke Grasperge[2]; Kerry Fillgrove[3]; Lingling Xue[3]; Neal Dube[3]; Daria Hazuda[3]; **Jay A. Grobler[3]**

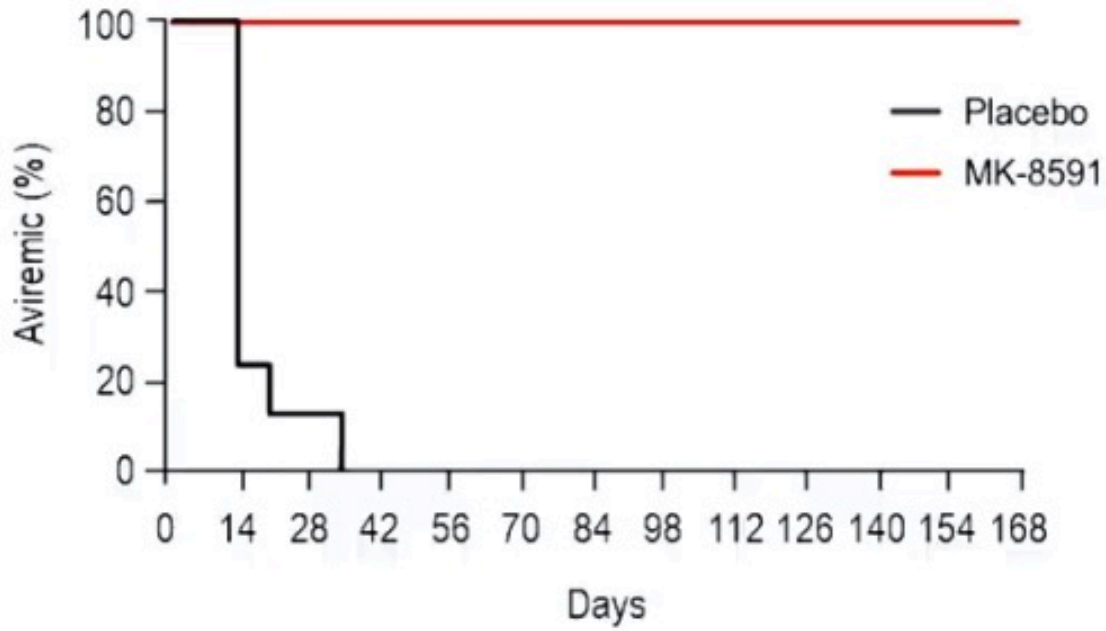
Aaron Diamond AIDS Research Center, New York, NY, USA; Tulane National Primate Research Center, Covington, LA, USA; [3]Merck & Co., Inc., Kenilworth, NJ, USA

10-March-2020

CROI 2020

Islatravir Protects Against SHIV Infection When Dosed Weekly in a Low-Dose Rectal Challenge Rhesus Macaque Model



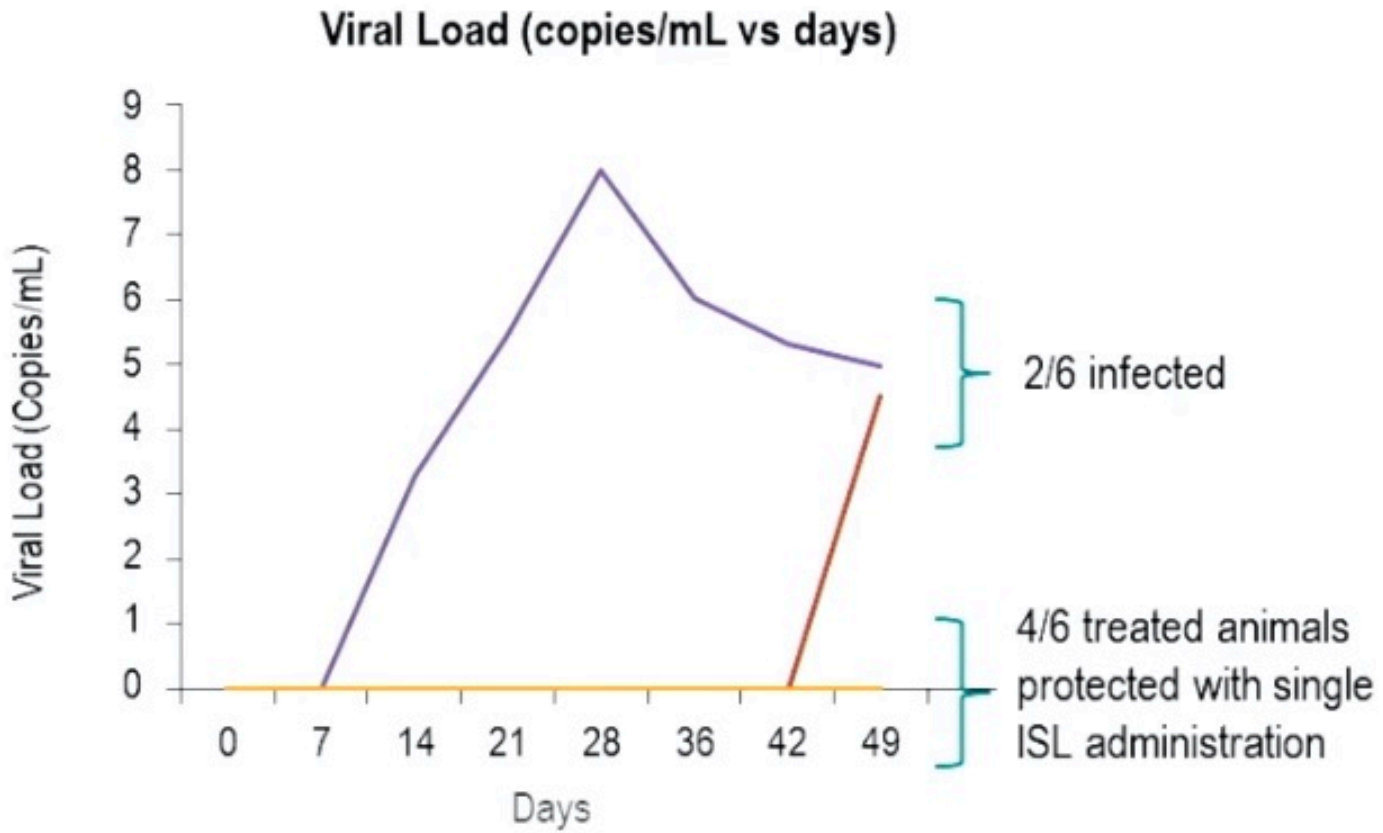


- ISL was completely protective at dose levels ≥0.43 mg/kg and highly protective at doses as low as 0.1 mg/kg in the rhesus macaque/IR SHIV109CP3 challenge model
- ISL-triphosphate (ISL-TP) levels that are protective in this model are achievable in humans with 0.25-mg weekly or 0.01-mg daily dosing, suggesting MK-8591 utility in extended-duration prophylaxis against HIV infection

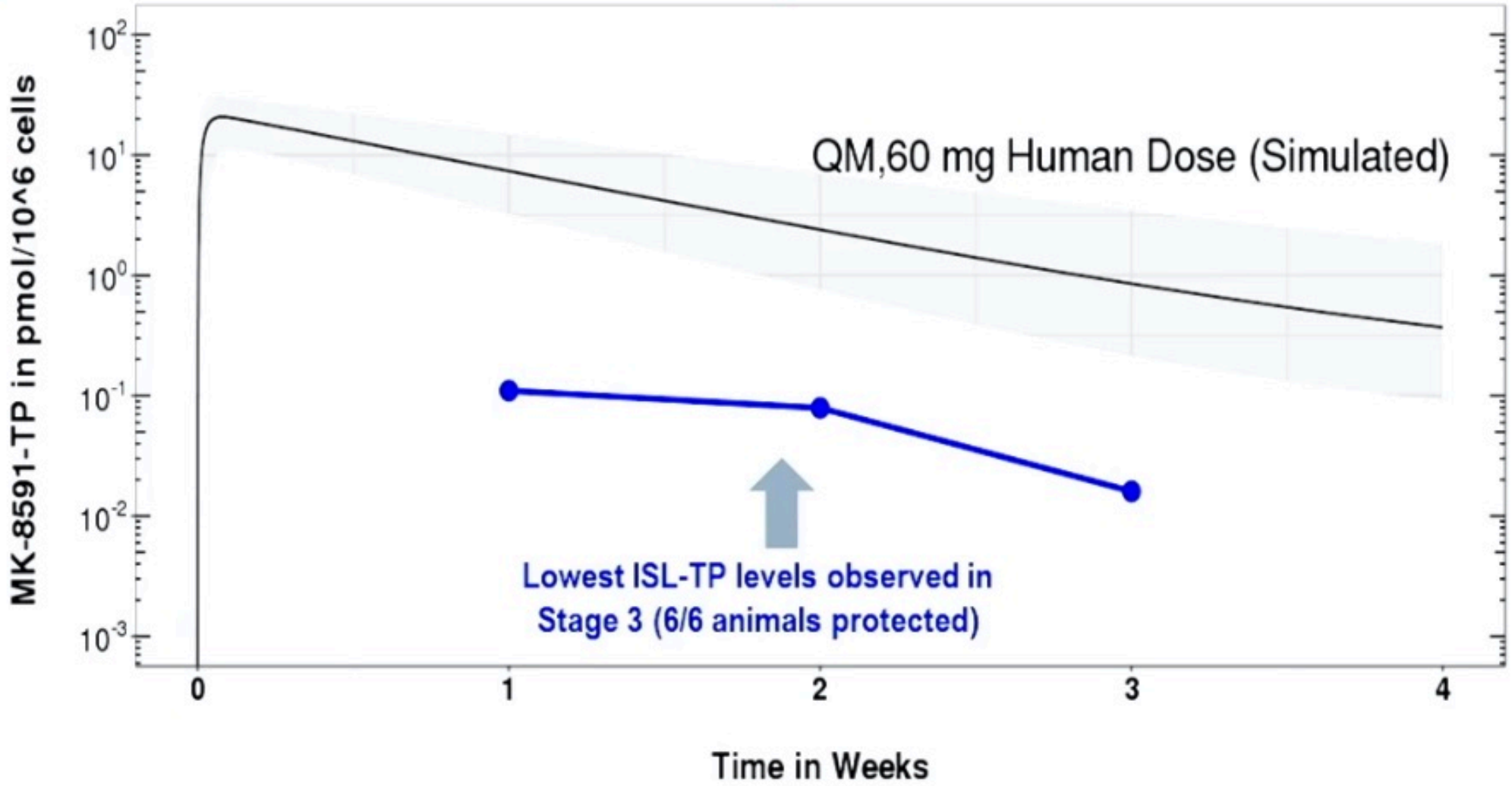
Markowitz M, et al. Once-weekly oral dosing of MK-8591 protects male rhesus macaques from intrarectal SHIV109CP3 challenge. *J Infect Dis*. (2019)

ISL Administered Once 24 Hours After Challenge Is Effective in Reducing Infection

- When ISL was administered only once 24 hours after challenge, two of six animals became viremic with M184M $SIVmac_{251}$ (viremia detected at Day 14 and Day 49)



Single Oral Doses of ISL Given Within 24 Hours of Infection May Provide an Effective PEP Option in Humans



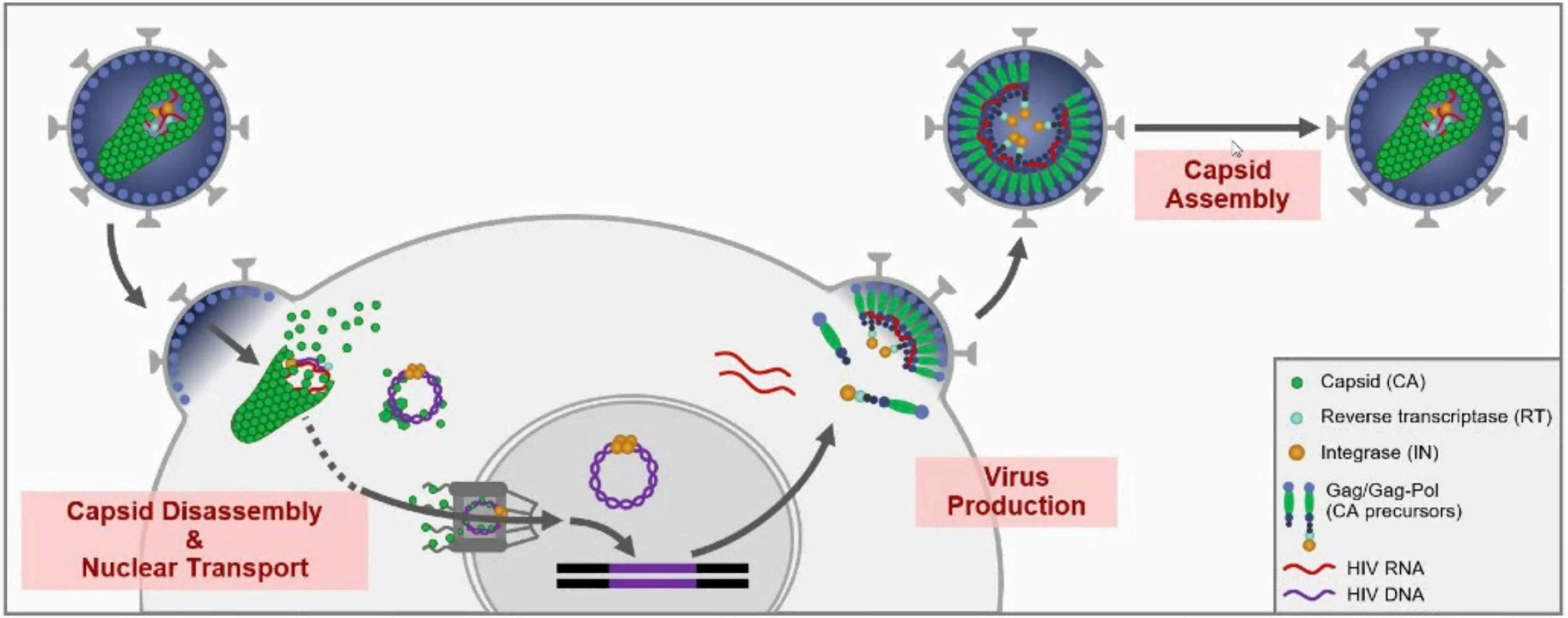
Conclusions

- As few as two weekly oral doses of ISL at 3.9 mg/kg given 24 hours after $SIVmac_{251}$ challenge completely prevented infection of rhesus macaques
- A single ISL dose 24 hours after challenge prevented infection in four of six monkeys
- Extrapolation to human pharmacokinetics suggests that a single oral dose given within 24 hours of HIV exposure in humans may provide effective PEP
- Results support the potential utility of ISL as a simplified PEP agent in humans, though the feasibility of clinical trials is challenging

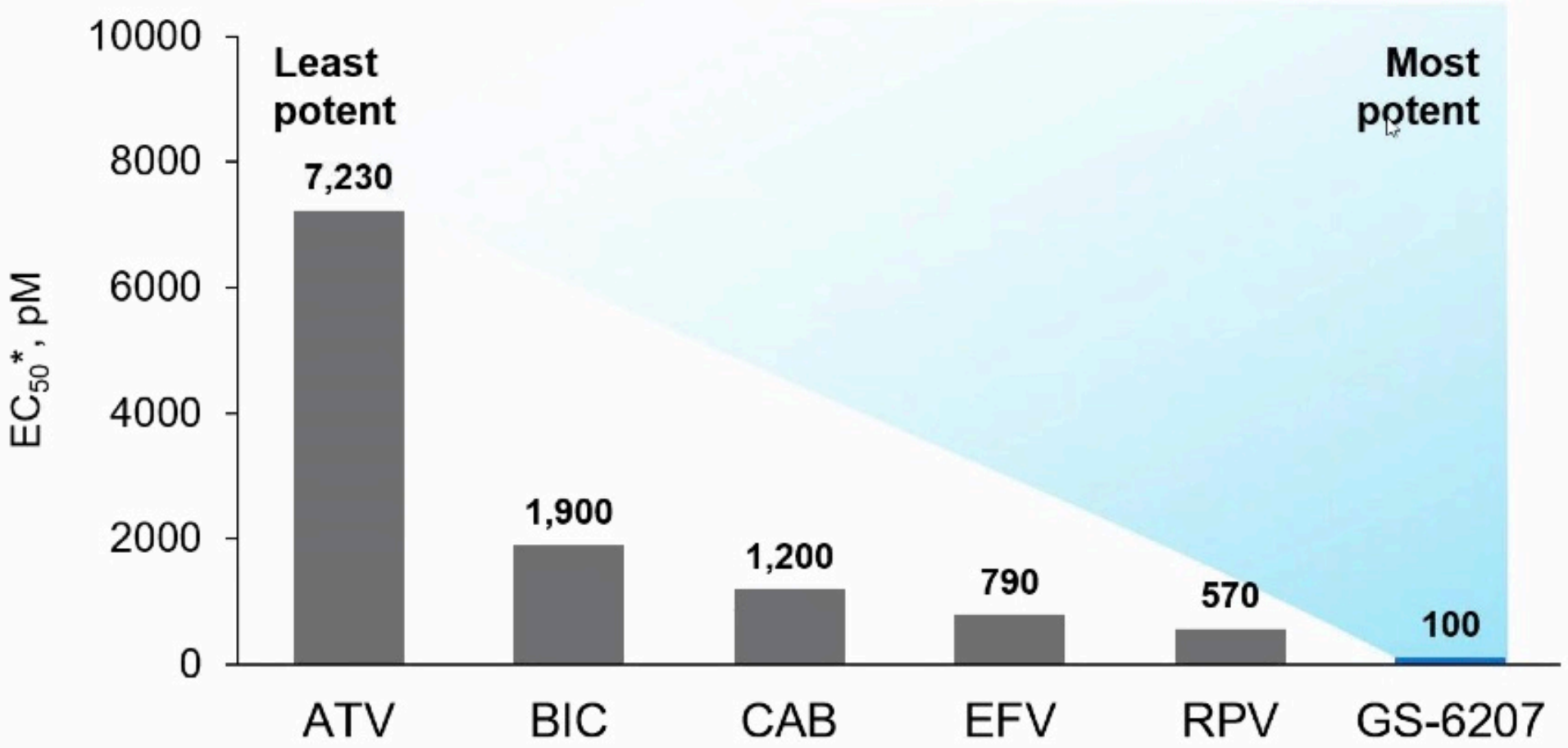
GS-6207 – capsid inhibitor

- New drug in new class
- Potential to work in several parts of lifecycle
- Related research reported that capsid uncoating might occur directly into the nucleus
- long acting formulation - every 6 months
- Studies in people who are treatment experienced and multi-drug resistant

GS-6207: First-in-Class HIV Capsid Inhibitor

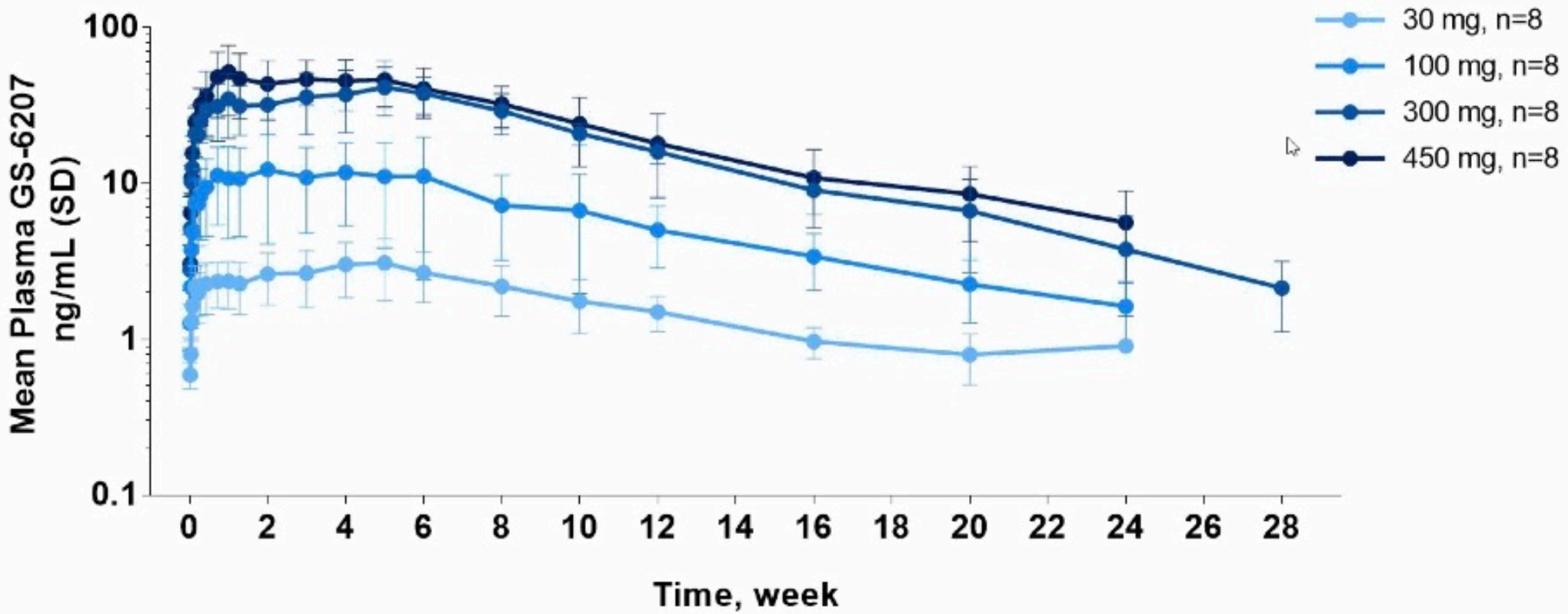


GS-6207 is Highly Potent against HIV-1



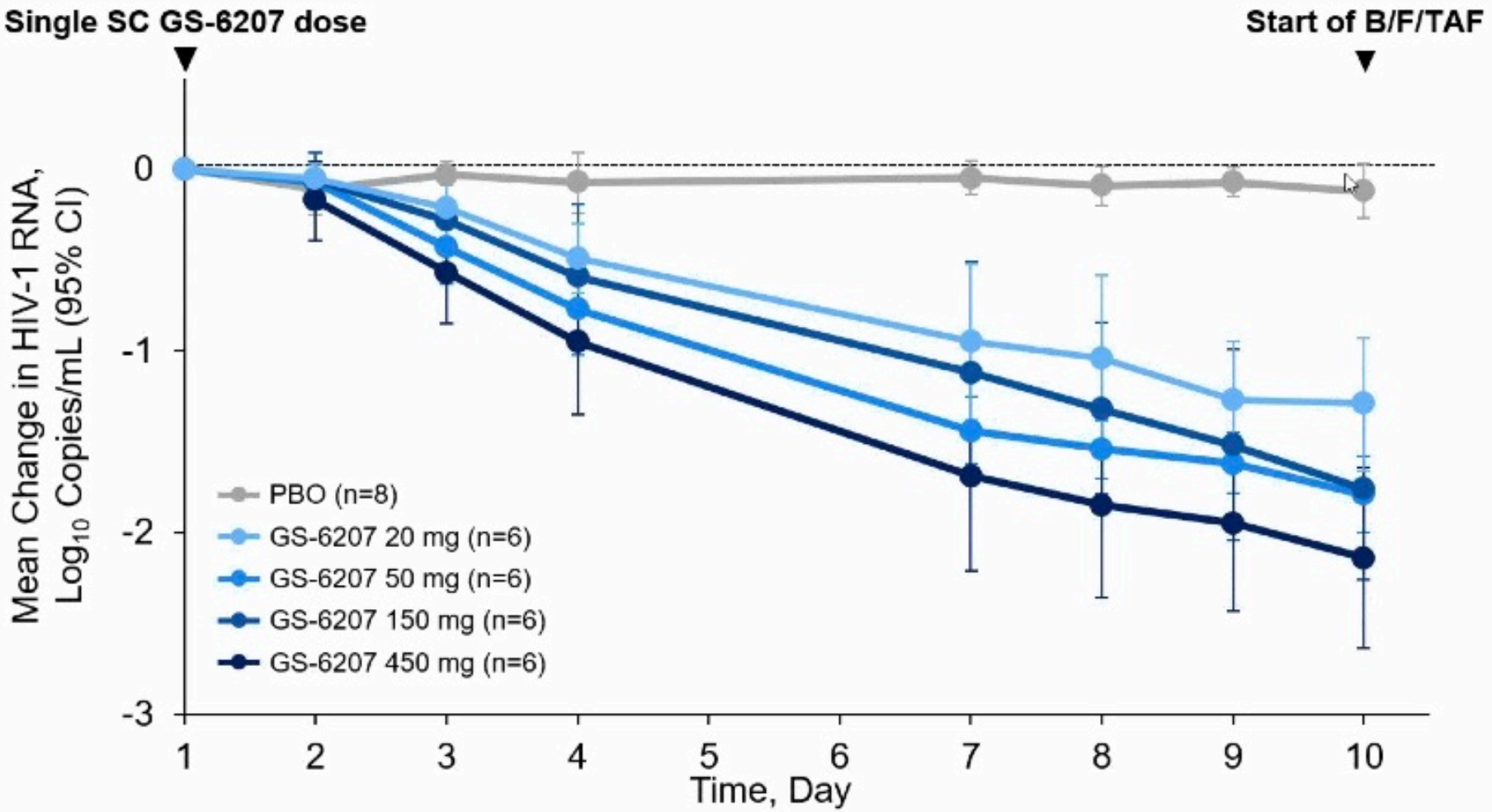
*MT-4 cell line ± infection with HIV-1 (IIIb strain).

Sustained GS-6207 Exposure Following Subcutaneous Injection



- Prolonged exposure, with measurable concentrations for at least 24 weeks

Subcutaneous GS-6207: Antiviral Activity

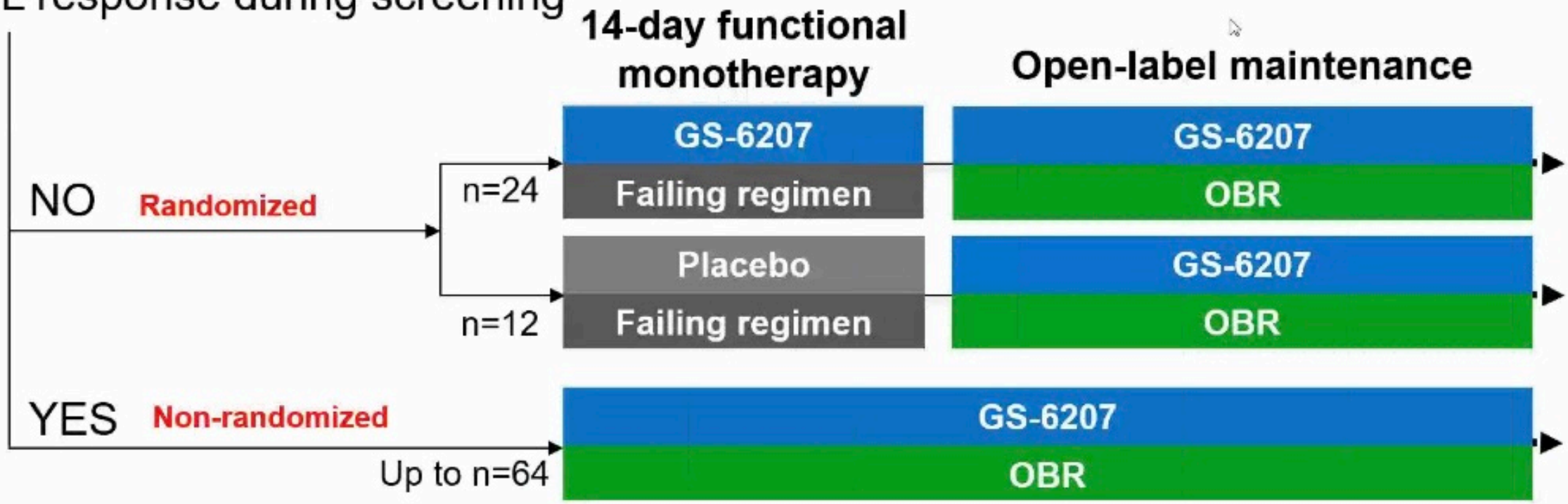


CAPELLA: Phase 2/3 in Heavily Treatment-experienced PLWH

VL > 400 copies/mL with multi-drug resistance

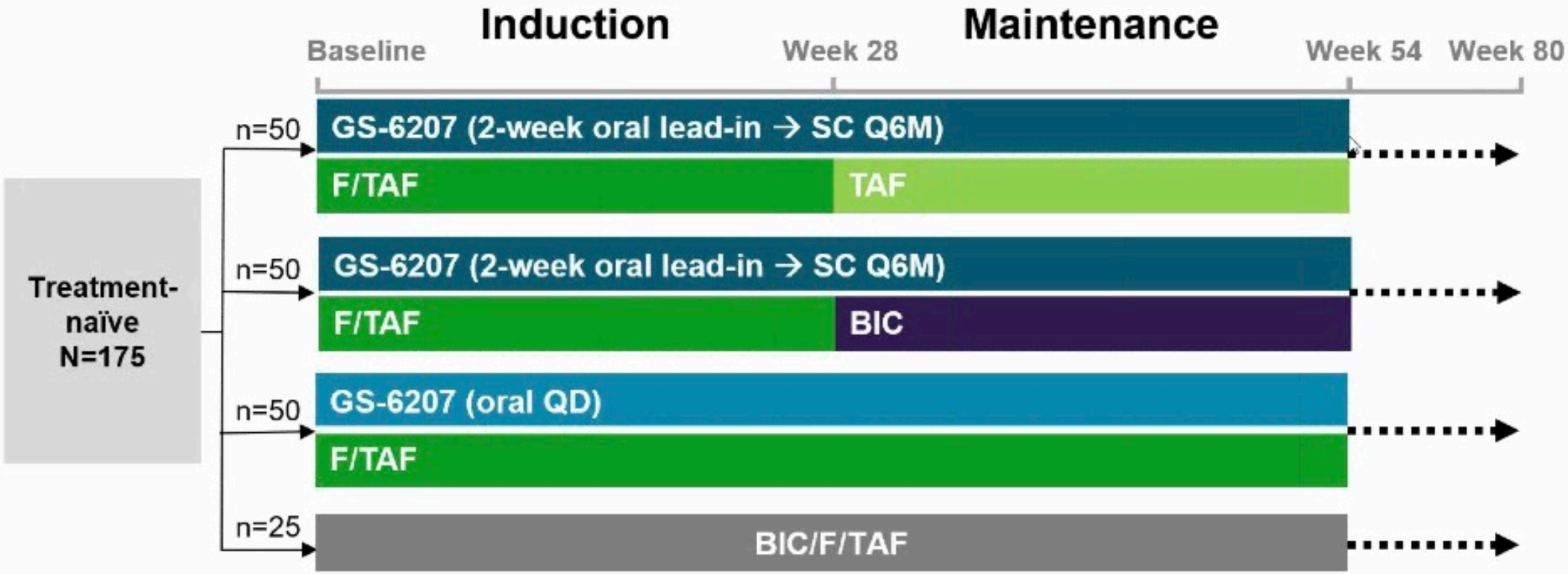
↓

VL response during screening



GS-6207: Oral lead-in (D1 600 mg, D2, 600 mg, and D8 300 mg), followed by D15 SC 900 mg (2 x 1.5 mL)

CALIBRATE: Phase 2 in Treatment-naïve PLWH



- F/TAF, TAF, and BIC are administered as oral QD

Conclusions

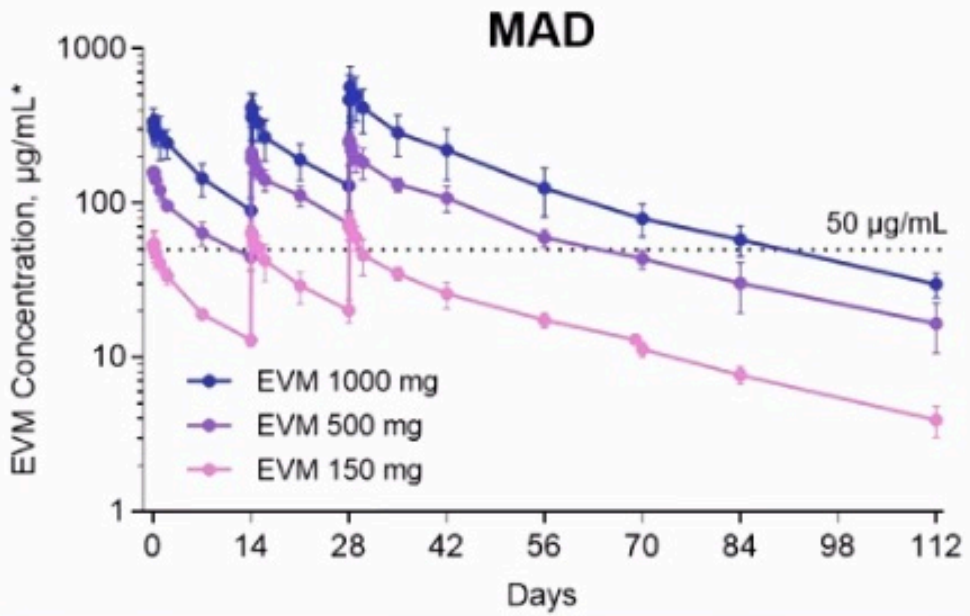
- GS-6207 is a first-in-class HIV capsid inhibitor with:
  - High in vitro potency (EC_{50}=50 pM)
  - No overlapping resistance with existing ARV agents
- In clinical studies to date, GS-6207 demonstrated:
  - A potential as a subcutaneous long acting agent
  - Clinically significant decline in HIV-1 RNA in people living with HIV
- Based on these data, 2 clinical trials are ongoing, with Q6M dosing interval
  - In treatment-naïve PLWH (NCT04143594)
  - In heavily treatment-experienced PLWH (NCT04150068)
- Planning activity is ongoing to develop GS-6207 for PrEP

bNAb elipovimab (GS-9722)

- bNAb – dosing every two weeks.

PK Summary

- EVM PK was linear and dose proportional over the evaluated range
- Half-life of ~26 days supports QOW dosing
- 9 of 37 (24%) participants had antidrug antibodies detected
- The presence of antidrug antibodies did not impact EVM PK in any participant
- Target C_{min} ≥50 µg/mL (~3x the IC_{95} cutoff used to determine in vitro breadth)



	SAD (Day 1)			MAD (Day 29; 3rd dose)		
PK Parameter†	**EVM 150 mg n=6**	**EVM 500 mg n=6**	**EVM 1500 mg n=6**	**EVM 150 mg n=7**	**EVM 500 mg n=6**	**EVM 1000 mg n=6**
AUC, h·µg/mL‡	18,000 (15.0)	56,000 (11.5)	200,000 (14.7)	12,600 (13.4)	48,600 (15.5)	106,000 (31.0)
C_{max}, µg/mL	49.7 (19.4)	164 (11.7)	553 (6.9)	77.6 (12.8)	261 (12.8)	567 (35.2)
C_{14d}, µg/mL	NC	NC	NC	25.8 (19.9)	108 (18.9)	221 (36.7)
$t_{1/2}$, d	24.7 (23.4, 26.8)	26.4 (21.5, 26.8)	25.9 (22.4, 28.5)	28.4 (26.0, 29.0)	23.4 (21.5, 42.0)	29.9 (23.3, 34.6)

*Data are mean (standard deviation [SD]); †PK parameters are presented to 3 significant figures as mean (%coefficient of variation [CV]), except $t_{1/2}$ (median [quartile (Q)1, Q3]); ‡Area under curve from time 0 to infinity (AUC_{inf}) for SAD and AUC over 14 d of dosing interval ($AUC_{0\text{-}14d}$) for MAD. C_{14d}, concentration on Day 14; C_{max}, maximal concentration; C_{min}, minimum concentration; IC_{95}, 95% inhibitory concentration; NC, not calculated.

AAV-delivered bNAbs

- Proof of principle study to deliver bNAbs using a vaccine
- Showed this was possible in a 3/8 people in a small stuy
- Only small quantities of Ab produced
- But a single macaque has been reported to keep antibody levels high for over six years.

Other PrEP studies

- DISCOVER: TAF/FTC vs TDF/FTC
- Islatravir – monthly pill for PrEP and PEP (see above)
- BIC/F/TAF – PEP in monkeys
- MB66 vaginal film against HIV and HSV-2
- TAF/elvitegravir vaginal inserts

Longer Term Efficacy and Safety of F/TAF and F/TDF For HIV PrEP: DISCOVER Trial Week 96 Results

Onyema Ogbuagu[1], Daniel Podzamczer[2], Laura C. Salazar[3], Keith Henry[4], David M. Asmuth[5], David Wohl[6], Richard Gilson[7], Yongwu Shao[8], Ramin Ebrahimi[8], Christoph Carter[8], Moupali Das[8], Scott McCallister[8], Jason M. Brunetta[9], Gitte Kronborg[10], Christoph D. Spinner[3]

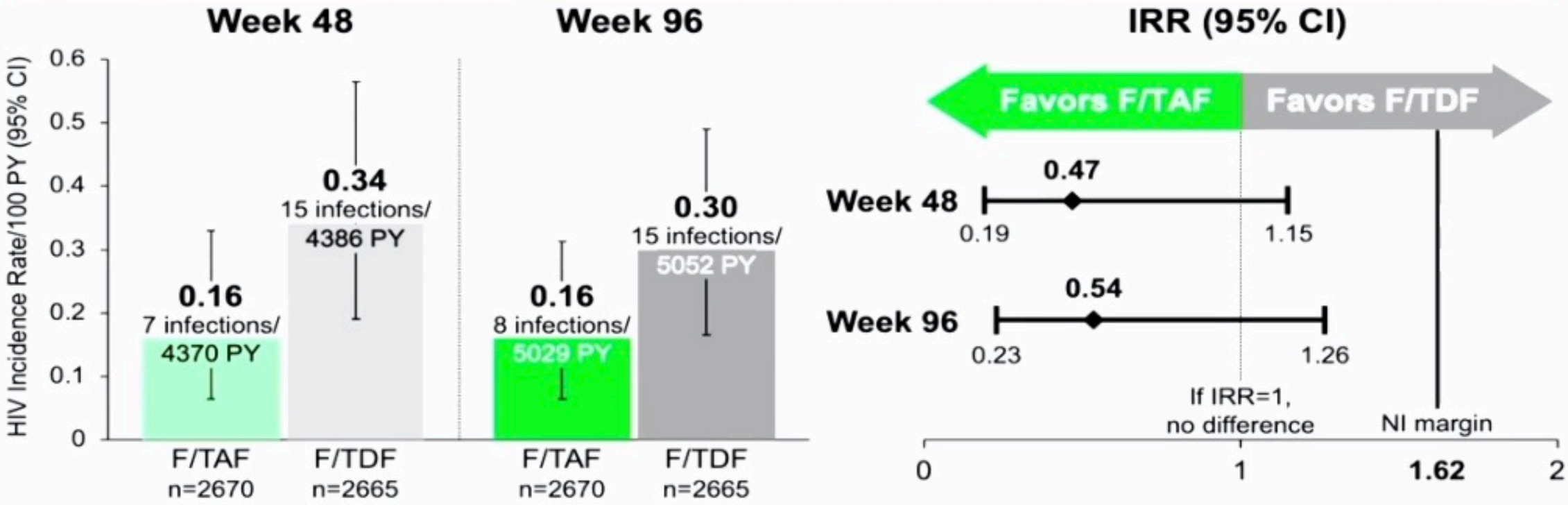
[1]Yale University, New Haven, CT; [2]Hospital Universitario de Bellvitge, Barcelona, Spain; [3]Technical University Munich, Munich, Germany; [4]Hennepin Healthcare Research Institute, Minneapolis, MN; [5]University of California Davis, Davis, CA; [6]University of North Carolina at Chapel Hill, Chapel Hill, NC; [7]University College London, London, UK; [8]Gilead Sciences, Inc., Foster City, CA; [9]Maple Leaf Medical Clinic, Toronto, ON, Canada; [10]Hvidovre Hospital, Hvidovre, Denmark

Study Design

- **Eligibility:** high sexual risk of HIV
  - 2+ episodes of condomless anal sex in the past 12 wk or rectal gonorrhea/chlamydia or syphilis in past 24 wk
  - HIV and hepatitis B virus negative, and $eGFR_{CG}$ ≥60 mL/min
  - Prior use of PrEP allowed
- **Study conducted in Europe and North America in cities/sites with high HIV incidence**
- **Safety assessments**
  - Renal: AEs and renal biomarkers
  - Bone: fracture events and BMD
  - Metabolic: fasting lipids, glucose, and body weight

BMD, bone mineral density; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault.

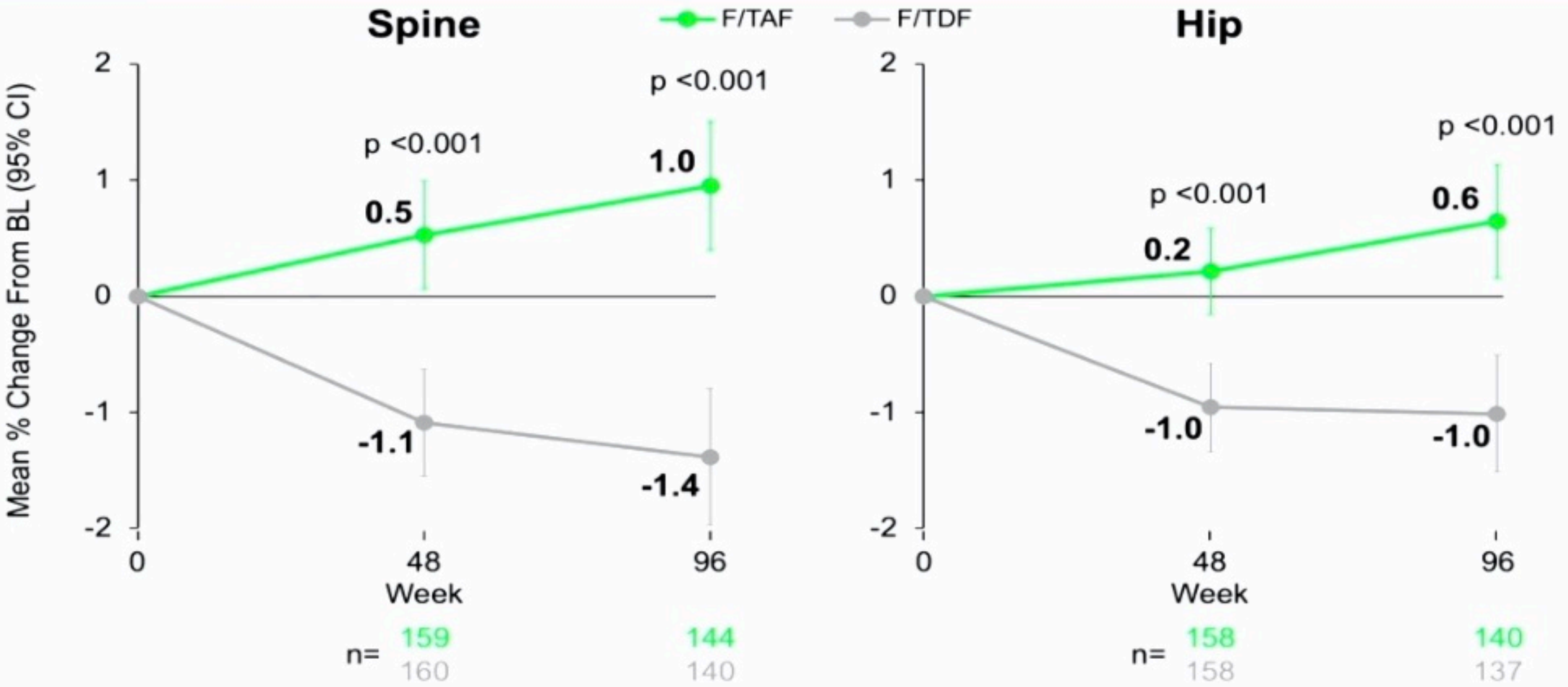
Primary Endpoint Analysis: HIV Incidence



- Primary analysis: 22 HIV infections in 8756 PY of follow-up
- Week-96 analysis: 23 HIV infections in 10,081 PY of follow-up
- F/TAF was noninferior to F/TDF for HIV prevention as the upper bound of IRR 95% CI was <1.62

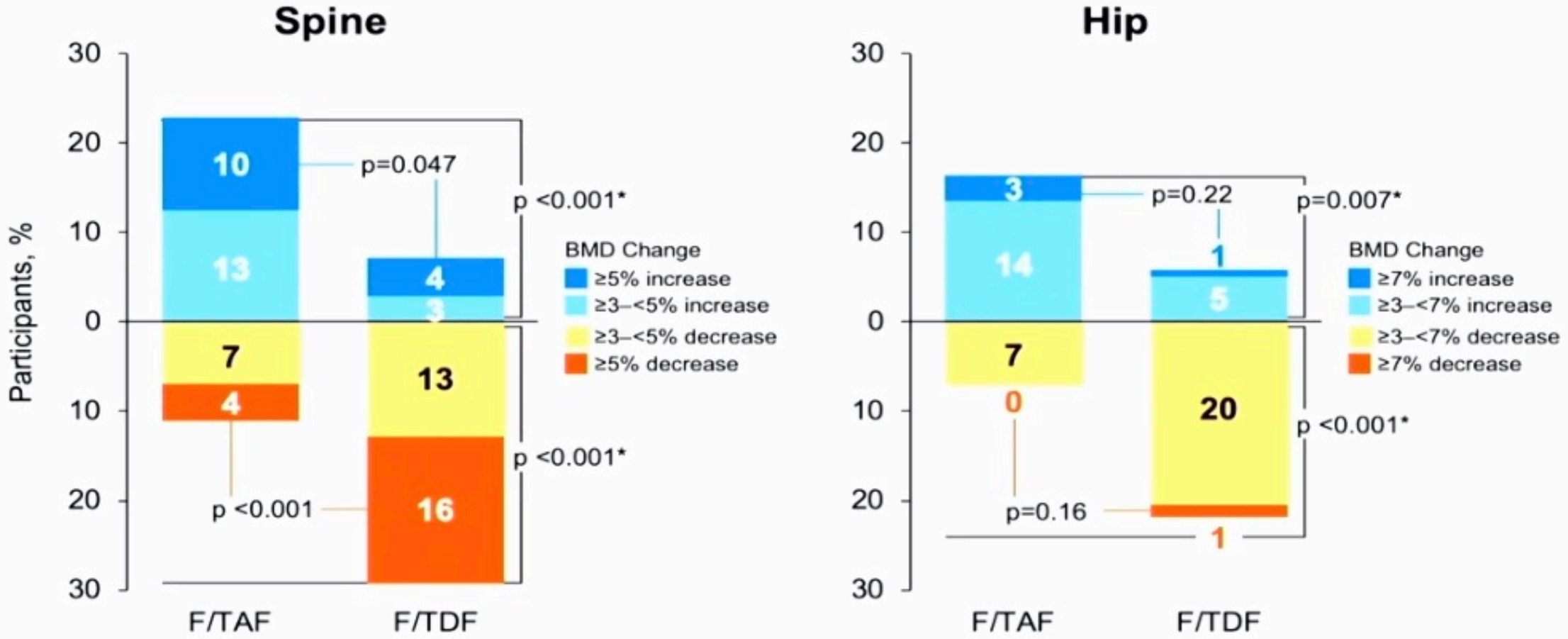
CI, confidence interval; IRR, incidence rate ratio; NI, noninferiority; PY, person-year.

Bone Safety: BMD Substudy (n=375)*



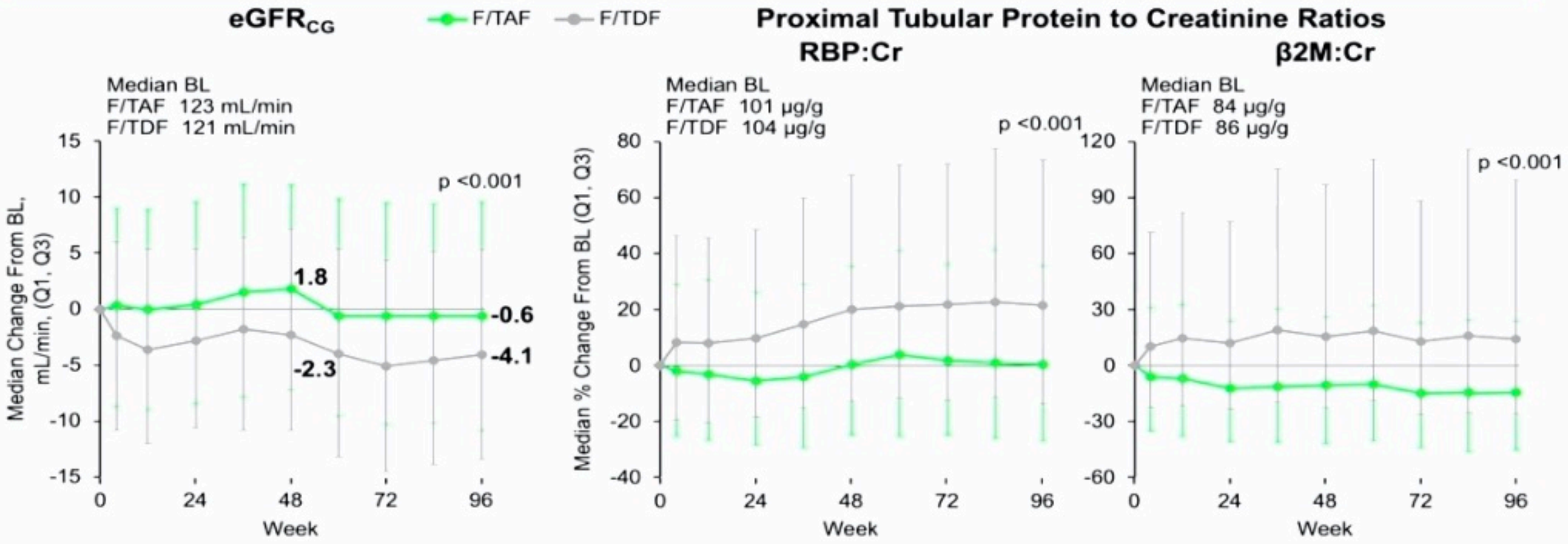
*p-values from analysis of variance model with BL F/TDF for PrEP and study arm as fixed effects. Reported fracture events: F/TAF, n=65; F/TDF, n=64.

Categorical BMD Changes (By Percent Change) at Week 96



*p-values for ≥3% change include ≥5% change. All p-values based on dichotomized response from Cochran-Mantel-Haenszel test for nominal data (general association statistic) adjusting for BL F/TDF for PrEP.

Renal Safety



- Renal discontinuations: F/TAF, n=2; F/TDF, n=6
- Fanconi syndrome: F/TAF, n=0; F/TDF, n=1

*p-values from Van Elteren test stratified by BL F/TDF for PrEP to compare 2 study arms.
β2M, β2-microglobulin; Cr, creatinine; Q, quartile; RBP, retinol-binding protein.

Conclusions

- F/TAF remained noninferior to F/TDF for HIV PrEP through 96 weeks
- DISCOVER provides the largest, single variable comparison of bone and renal safety parameters between TAF and TDF in the absence of underlying HIV or third antiretroviral agents:
  - Differences in BMD between F/TAF and F/TDF increased at week 96; BMD declines of ≥3% were more common in participants taking F/TDF, with more pronounced differences in younger participants
  - Renal biomarker changes remained more favorable in participants taking F/TAF, particularly among older participants and those with reduced eGFR
- F/TDF was associated with greater declines in both LDL and HDL but total cholesterol: HDL ratios or fasting glucose remained similar across both study arms at 96 weeks.
- Weight gain was observed in both arms at 96 weeks, and was approximately 1kg greater in participants taking F/TAF. The weight gain in F/TAF arm was similar to that observed in the placebo arm of iPrEx PrEP trial and the general population[1,2]
- F/TAF is a safe, longer term option for PrEP

1. Glidden DV, et al. Clin Infect Dis 2018;67:411-9. 2. Hill JO, et al. Science 2003;299:853-5.

FTC/TAF + BIC Postexposure Prophylaxis Protects Macaques Against Rectal SHIV Infection

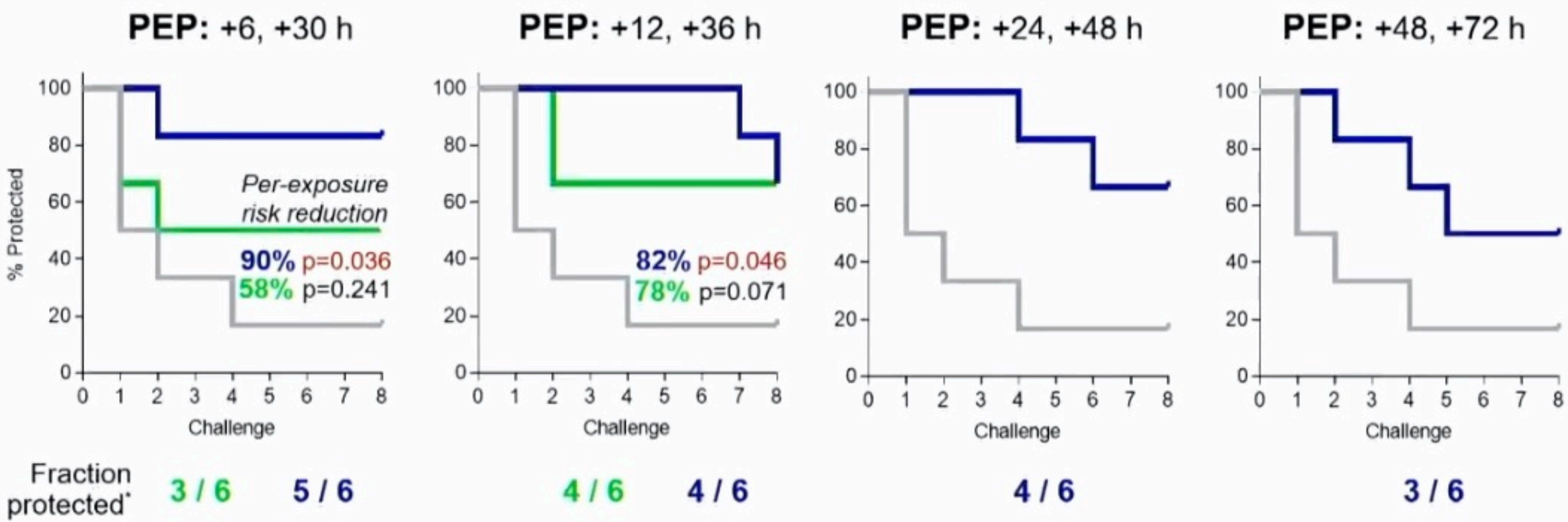
Elena Bekerman, Stephanie Cox, Scott McCallister, Tomas Cihlar, Christian Callebaut

Gilead Sciences, Inc., Foster City, CA

Disclosures:

- *Employed by and stockholder of Gilead Sciences, Inc.*
- *This study was funded by Gilead Sciences, Inc.*

Study 2: 100-mg BIC Extends Postexposure Protective Window

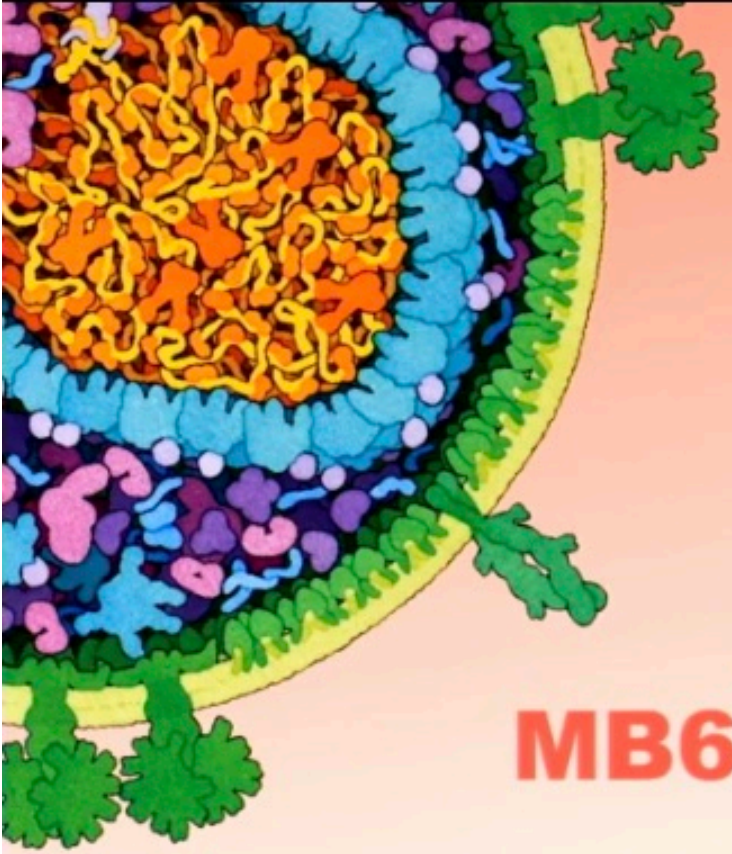


- Significant† protection with FTC/TAF + BIC 100 mg up to 12 h postexposure
- Greater protection with BIC 100 mg (Study 2) vs 25 mg (Study 1)

*5/6 placebo-treated macaques infected; †Cox proportional hazard model.

NHP Study Conclusions and Future Directions

- Simplified 2-dose schedules can protect macaques against SHIV acquisition
- FTC/TAF alone: protective only as PrEP at -2, +24 h relative to exposure
- FTC/TAF + BIC 100 mg: protective as PrEP or PEP
  - PrEP: initiated 2 h pre-exposure
  - PEP: initiated up to 12 h postexposure
- Plan to further define optimal pre/postexposure schedules in rectal and vaginal challenge models



ORAL ABSTRACT: OL-08

Tuesday, March 10, 2020

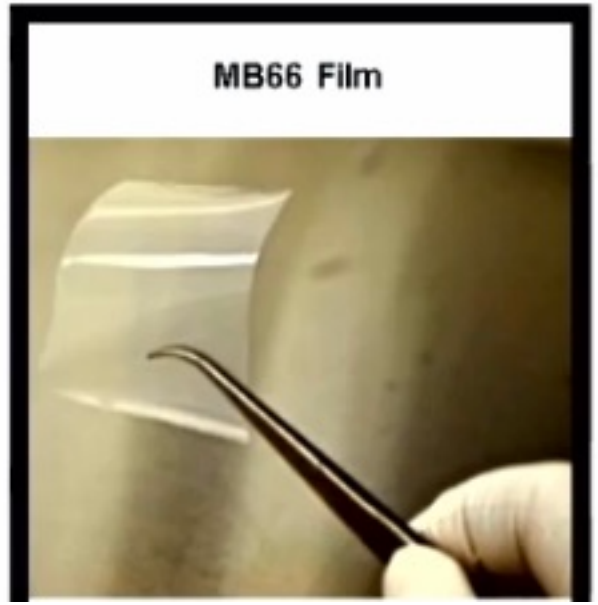
PHASE I PLACEBO-CONTROLED SAFETY, PK, AND PD STUDY OF MB66 ANTI-HIV AND ANTI-HSV FILM

Susan Cu-Uvin

The MIriam Hospital
Providence, RI, USA

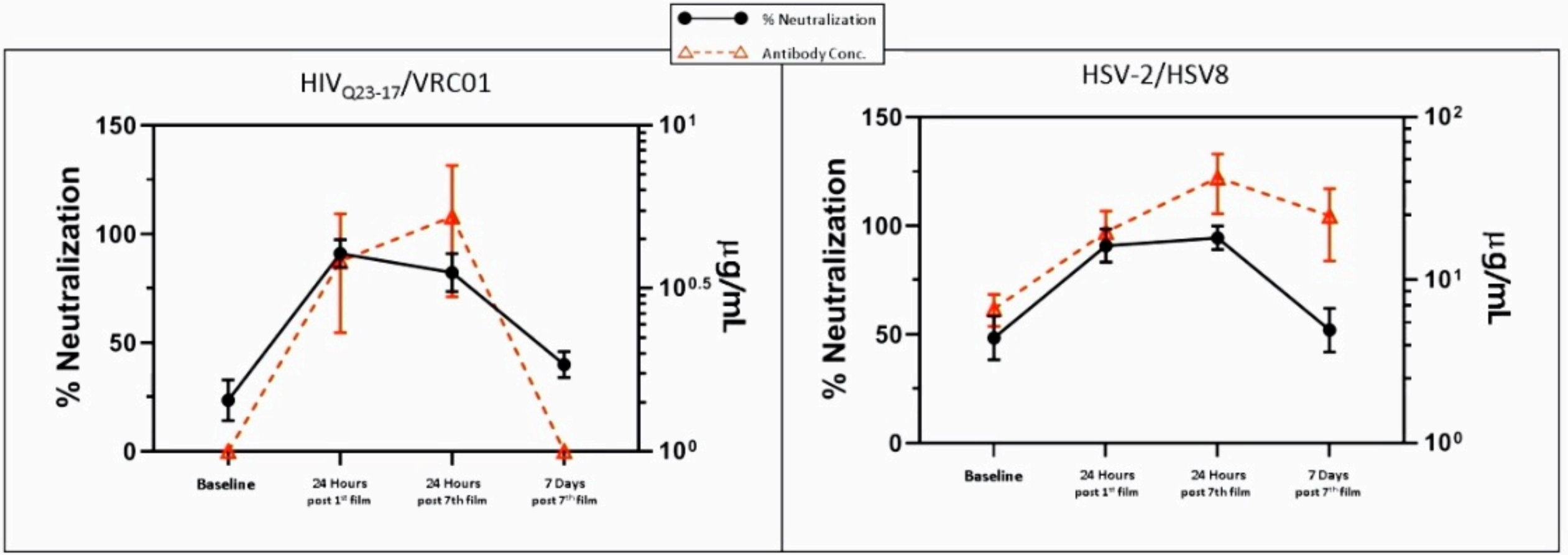
CROI 2020

MB-66: microbicide film

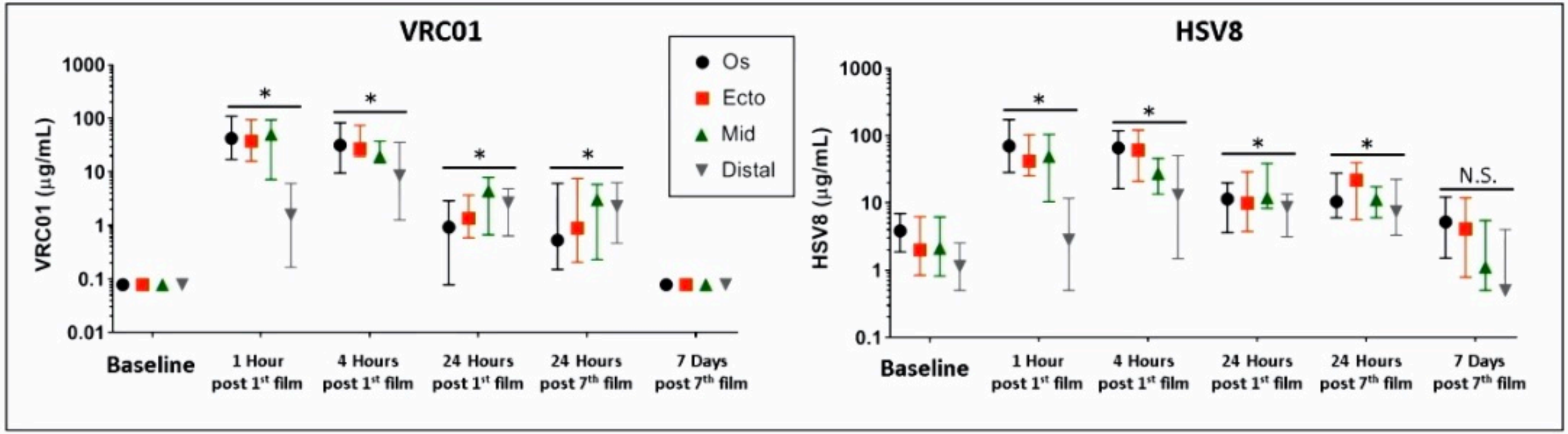


- Active against HIV and HSV-2 (herpes)
- repeat dose of two mAbs as vaginal film
- small phase 1 study – n=29
- dissolved easily, no >2 grade side effects, vaginal PK ok

Viral Neutralization and Antibody PK Data (CVLs)



VRC01 and HSV8 Concentrations in Vaginal TearFlo Samples



Conclusions:

- Repeated dose vaginal application of MB66 film was safe and well tolerated
- Significant film dissolution after one hour
- Vaginal pH and Nugent scores did not significantly change
- No significant increases in proinflammatory cytokine concentrations following film insertion
- Concentrations of VRCO1 and HSV8 mAbs increased significantly in vaginal secretions following insertion of active film, peaking at one hour and remaining elevated at 24 hours post film insertion
- *Ex vivo* efficacy: Significant neutralization of all 3 HIV strains and HSV-2 24 hours after multiple film insertion
- These data indicate that MB66 is a safe and promising MPT product to protect women against HIV-1 and HSV

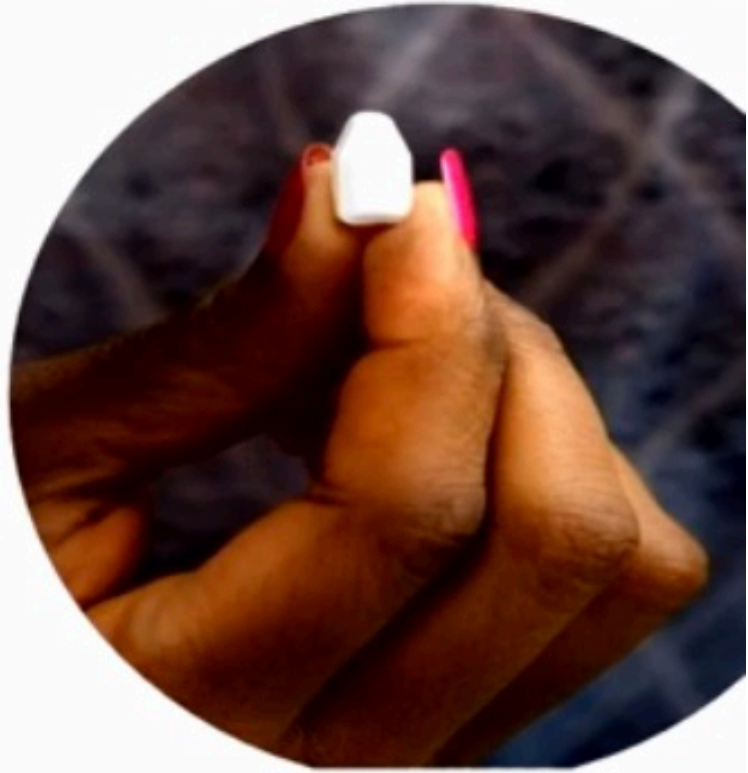
Rationale for selecting TAF + EVG for inserts

❑ Tenofovir alafenamide (TAF)

- ✓ More potent than TFV and TDF
- ✓ Increased TFV-DP concentrations in HIV target cells
- ✓ Favorable safety profile with oral dosing
- ✓ Active against HIV and HSV

❑ Elvitegravir (EVG)

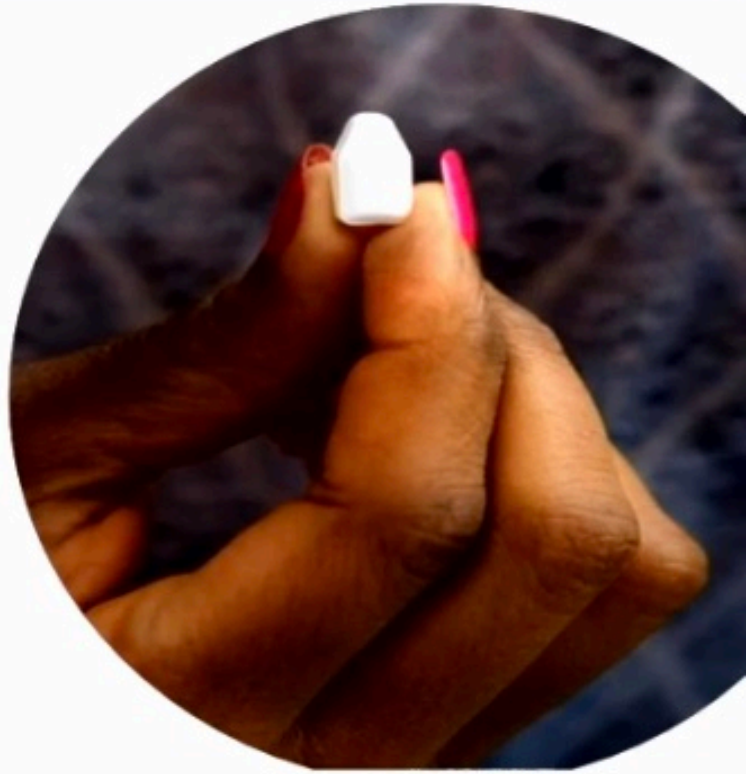
- ✓ Blocks viral integration (~8h after post viral entry)
- ✓ Potential for more flexible dosing regimen (PrEP/PEP)
- ✓ Demonstrated post-exposure protection with Raltegravir gel (up to 3h) in vaginal challenge macaque model[1]



1-Dobard et al, Science Translational Medicine 2014

Rapidly-dissolving inserts for on-demand topical prophylaxis

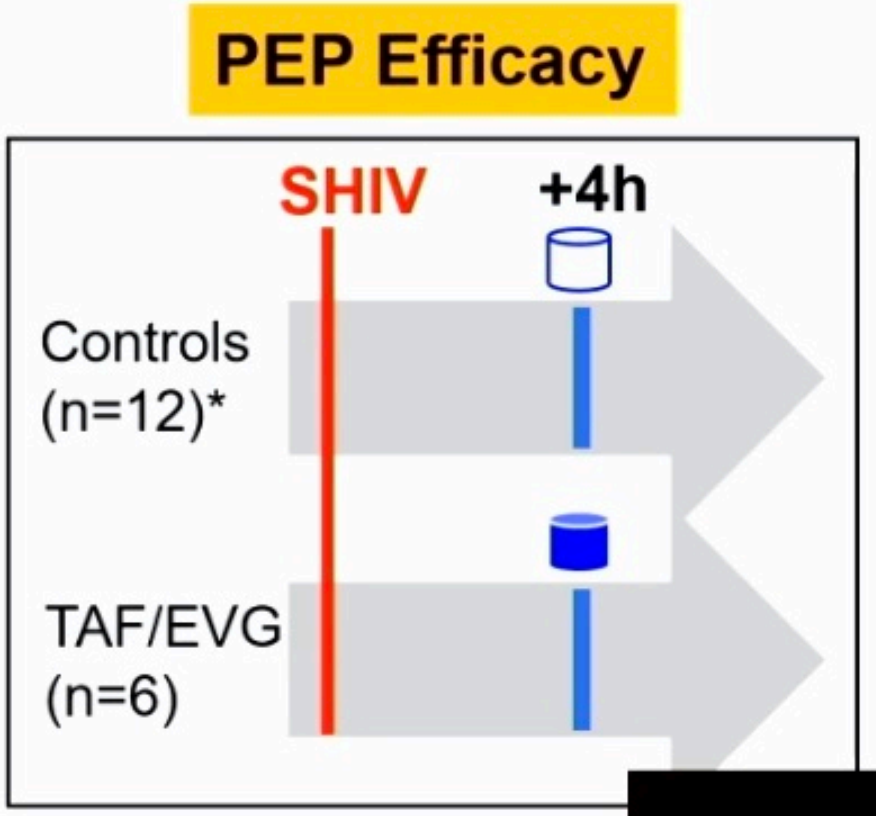
- **On-demand topical prophylaxis**
  - Event-driven drug delivery- right place/right time
- **User-friendly**
  - Small, discreet, easy to carry
  - Self-administered; no applicator
  - Minimal leakage
  - Dual use; vaginal or rectal
- **Favorable safety profile**
  - Low systemic drug exposure/less toxicity
- **Potential for drug combinations**
  - More flexible dosing options (before or after sex)



PEP challenge design

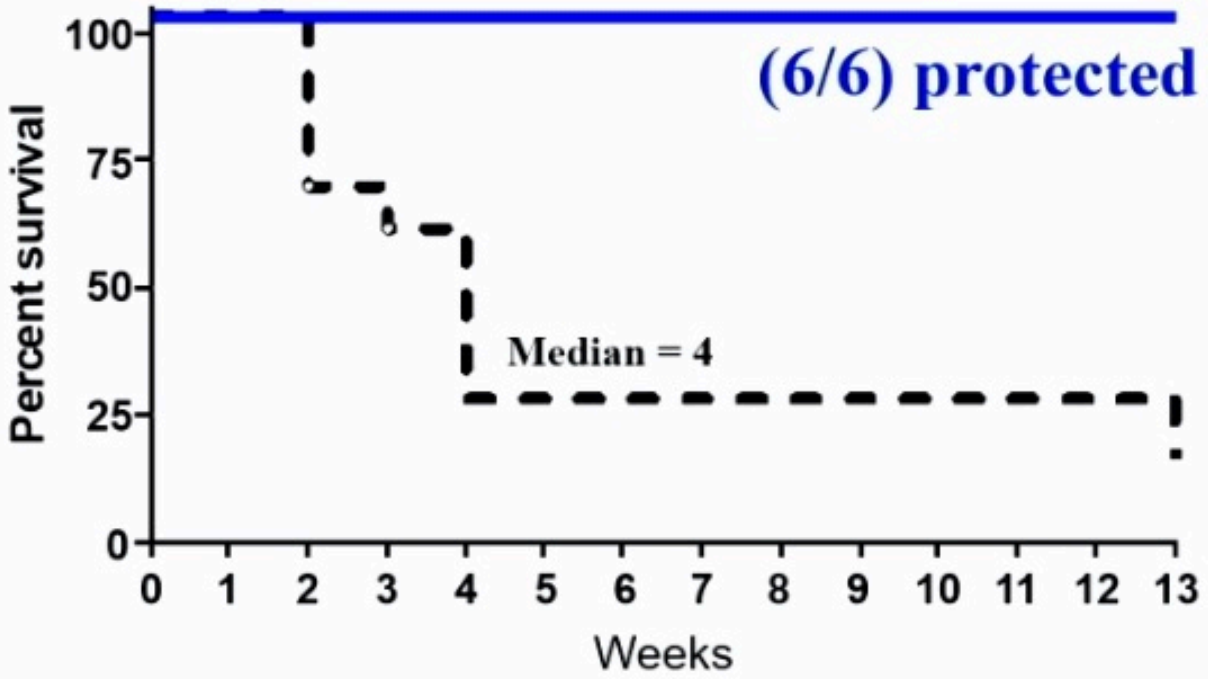
Study Design:

- Pigtailed macaques with regular menstrual cycles
- Vaginal SHIV challenges once per week for up to 13 weeks
- Inserts administered **4 hours after** SHIV challenge
- Blood collected prior to each SHIV inoculation to monitor for SHIV infection and drug concentrations



*5 real-time and 7 historical

PEP efficacy of TAF/EVG inserts administered 4h after SHIV exposure

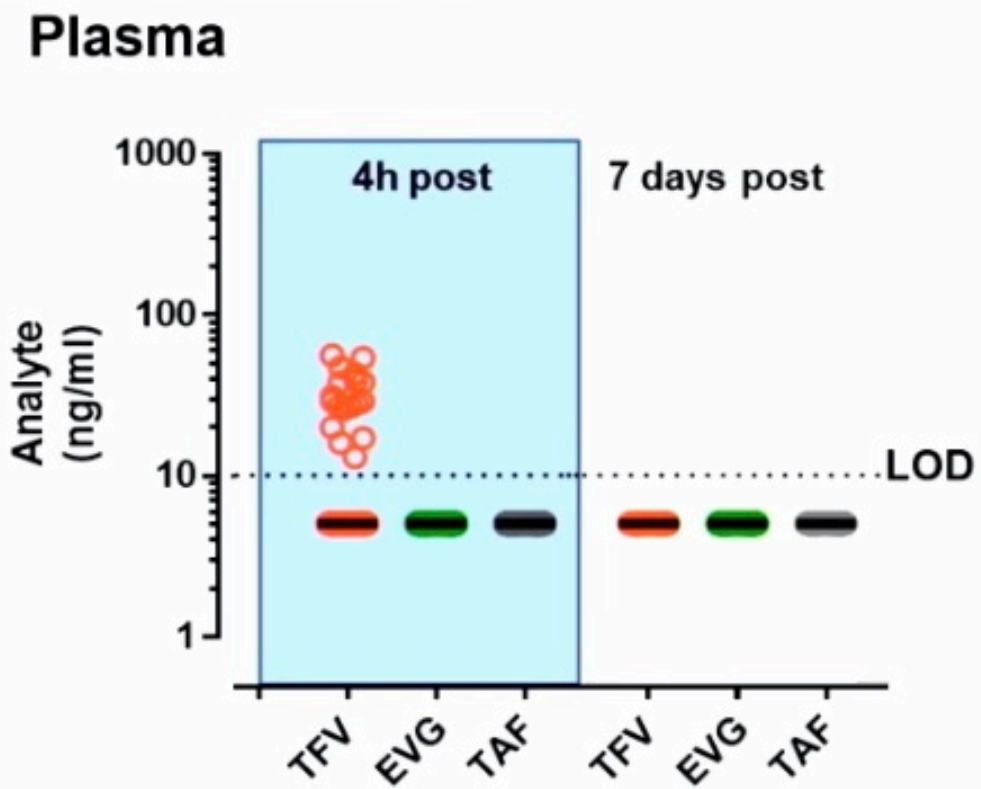


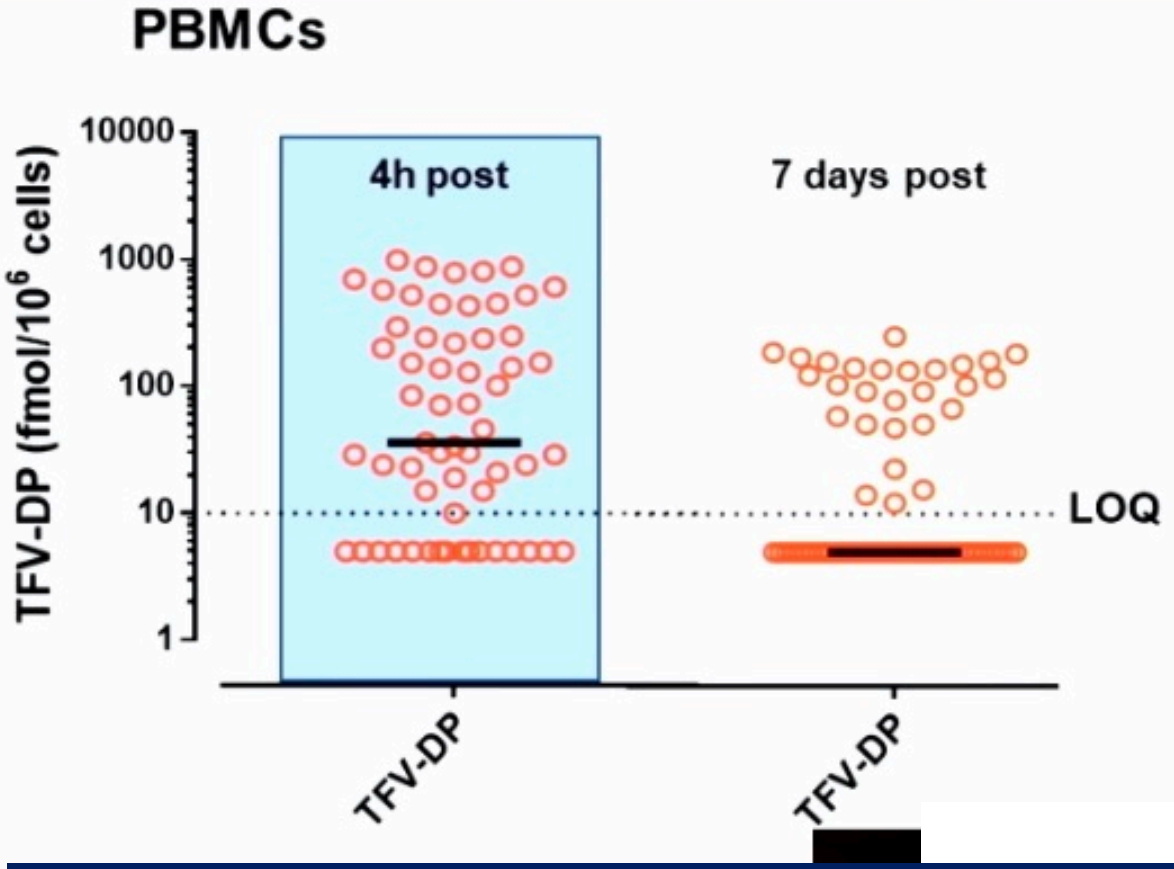
Combined controls (n=12)

4h PEP (n=6)

100% Efficacy (p= 0.009; log-rank test)

Drug exposures in plasma and PBMCs following vaginal dosing with TAF/EVG inserts





- Low drug exposure in plasma

- Median TFV-DP @4h = 36 fmol/106 cells
- Median TFV-DP @ 7d = <LOQ

CONRAD 146 First in-human (Phase 1) clinical studies to assess safety
And PK of TAF/EVG (20/16mg) inserts; reporting mid 2020

Summary

- ❑ Vaginal administration of TAF/EVG (20/16mg) inserts provided high protection against vaginal SHIV infection when administered within a 4-hour window either before or after viral exposure
- ❑ High TFV-DP loading in PBMCs from topical delivery of TAF is unique; unclear role in protection
- ❑ Findings show proof of concept for vaginal TAF/EVG inserts for "on demand" topical **PrEP** or **PEP** and support clinical advancement
- ❑ First-in-human (Phase I) clinical studies to assess safety and PK of TAF/EVG (20/16mg) inserts:
  - ❑ CONRAD 146 (vaginal use) – study completed; results to be available mid-2020
  - ❑ MTN-039 (rectal use) – study ongoing

ADVANCE study

Large randomised study in South Africa

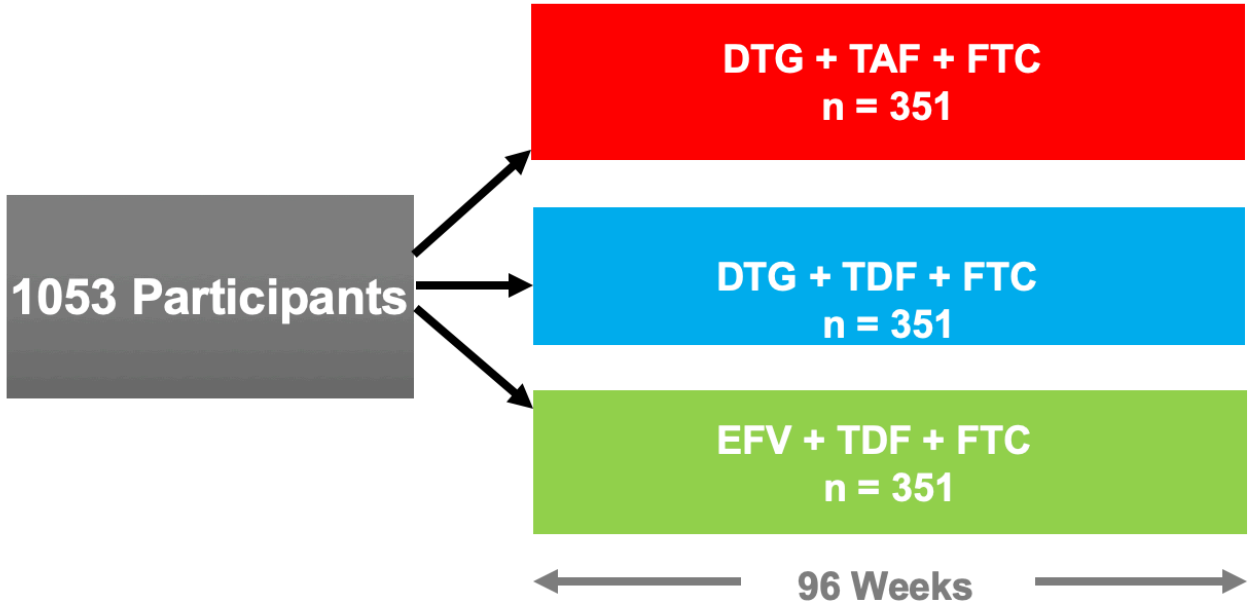
- DTG/TDF/FTC vs DTG/TAF/FTC vs EFV/TED/FTC
- Unexpectedly reported significant weight gains links to DTG and TAF at IAS 2019.
- ~100% black, 60% women
- ~20% VL >100K and CD4 <200 cells/mm3
- BMI higher in women>men ~ 25% overweight
- Looked at changes for risk of heart disease and diabetes

Predicted 10-year risks of diabetes and cardiovascular disease in the ADVANCE trial

ADVANCE study: Trial design

Inclusion criteria:

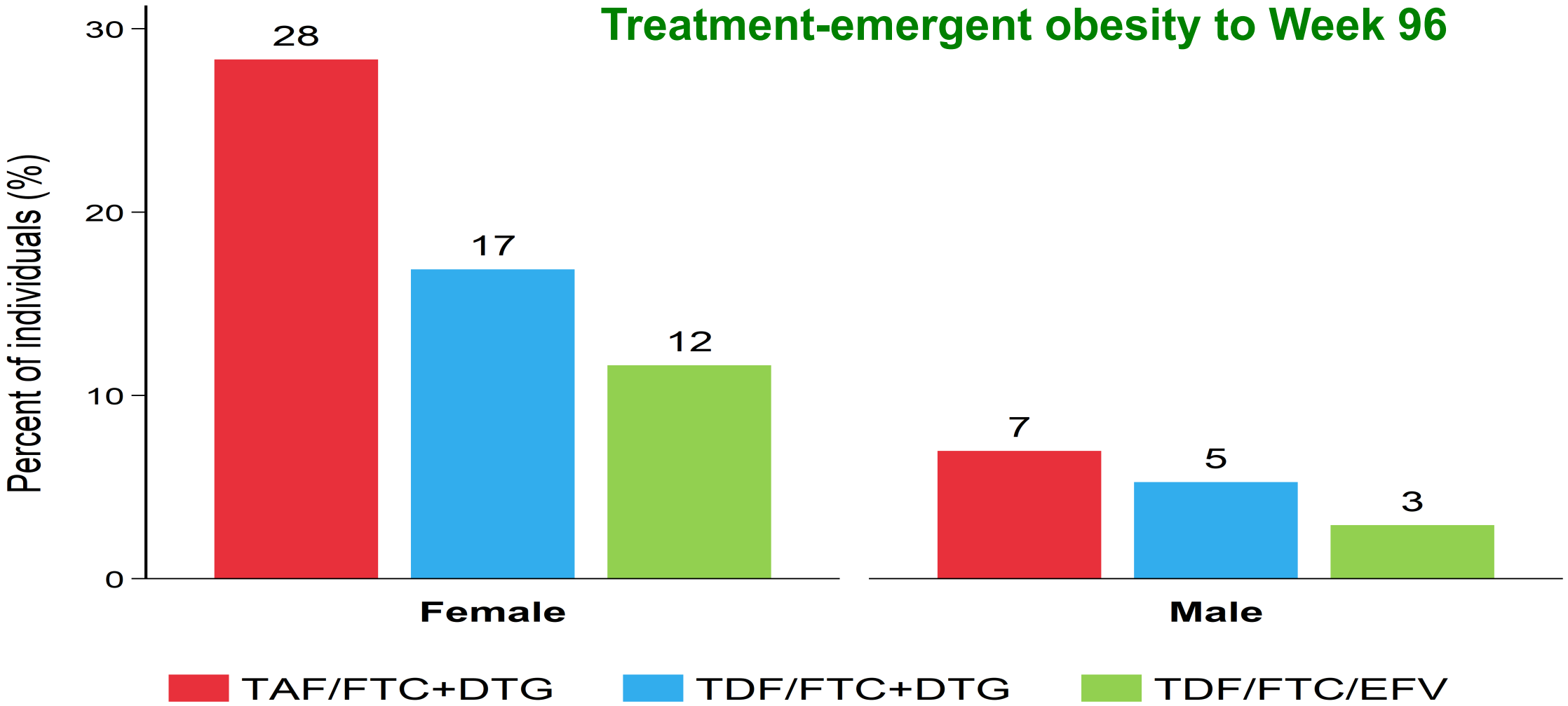
- Treatment-naïve, HIV-1 RNA level >500 copies/mL in the last 60 days



Open-label, 96-week study in Johannesburg, South Africa
Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84 and 96

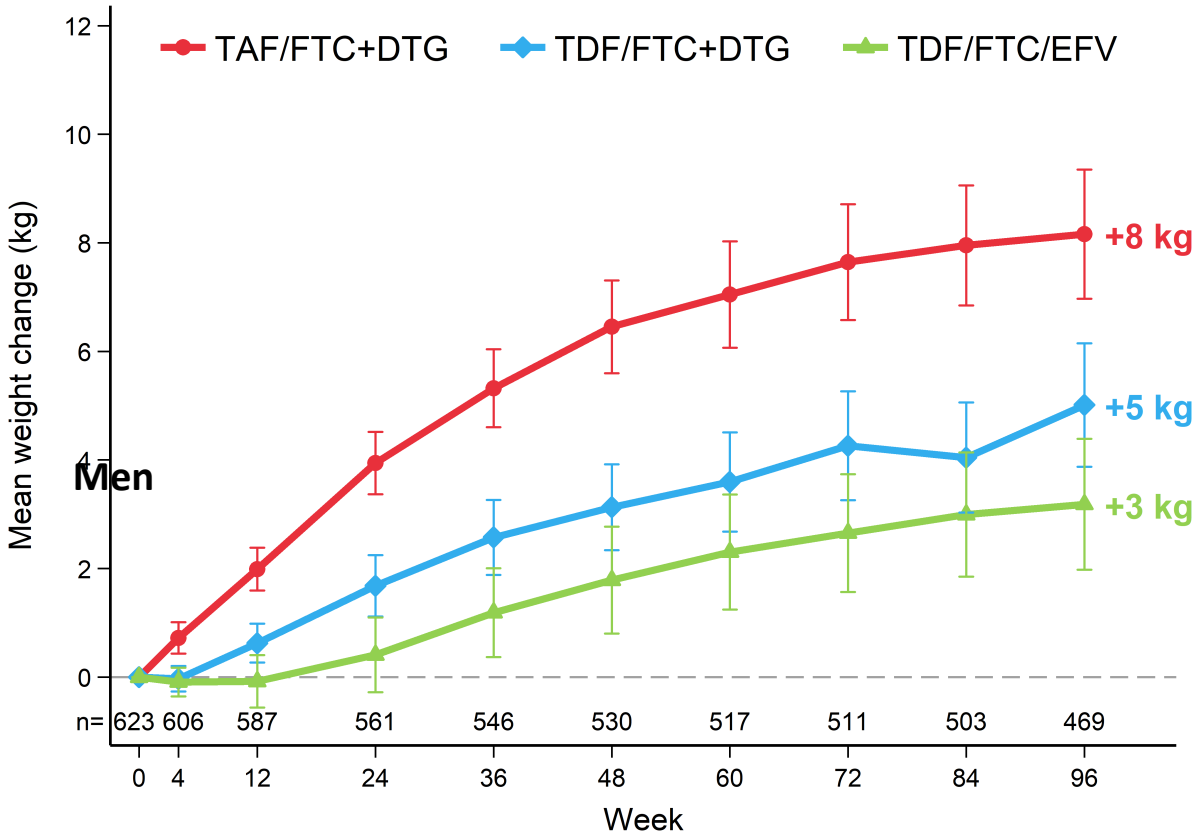
Andrew Hill[1], Kaitlyn McCann[2], Bryony Simmons[2] ,Victoria Pilkington[2], Michelle Moorhouse[3], Godspower Akopmiemie[3], Simiso Sokhela[3], Celicia Serenata[3], Alinda Vos[4], Francois Venter[3]

ADVANCE trial - Mean change in weight (kg) to Week 96

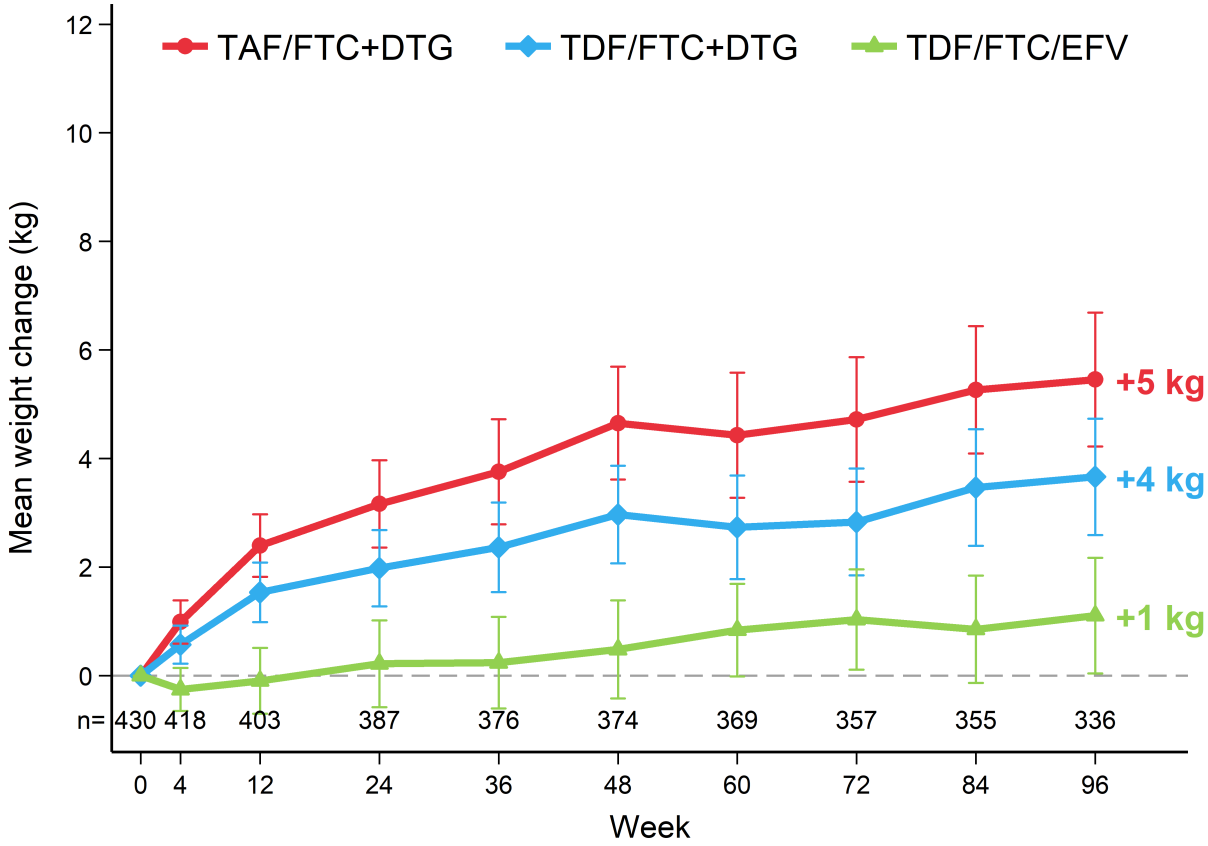


ADVANCE trial - Mean change in weight (kg) to Week 96

Women

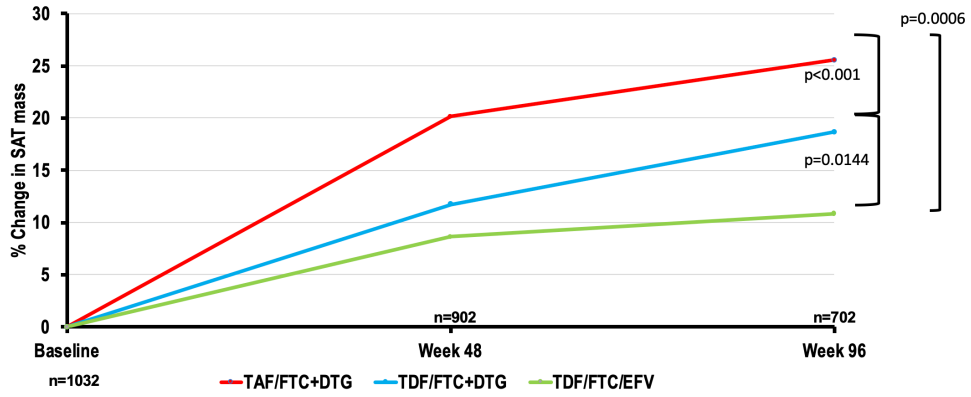


Men

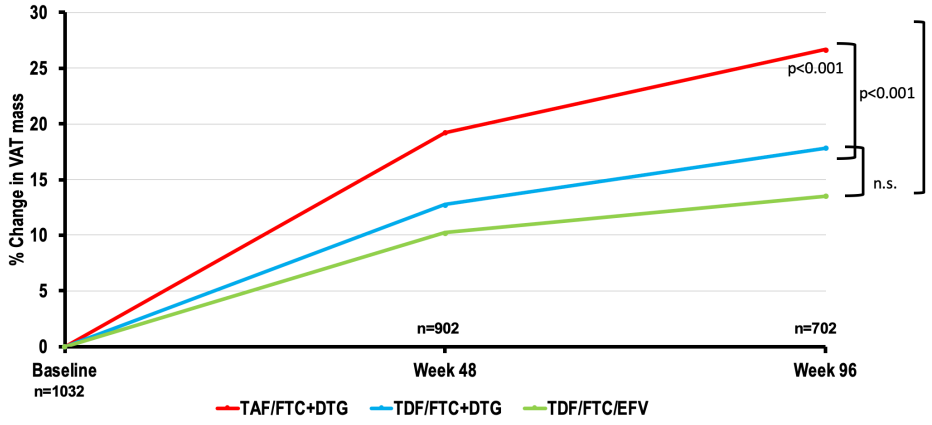


ADVANCE trial – Changes in SAT and VAT, metabolic syndrome & diabetes risk

Median % change in Subcutaneous Adipose Tissue (SAT) to week 96 (DXA)



Median % change in Visceral Adipose Tissue (VAT) from baseline to week 96 (DXA)



Metabolic syndrome at Week 96

	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
Baseline prevalence	16/351 (5%)	21/351 (6%)	14/351 (4%)
Treatment-emergent metabolic syndrome			
Week 96	20/259 (8%)	15/258 (6%)	8/242 (3%)

Statistically significant differences between TAF/FTC+DTG and TDF/FTC/EFV at Week 96 (p=0.031).

QDIABETES Equation results:

Predicted results over time:

Treatment arm / 10-year risk	Baseline	Median change to: Wk 48	Wk 96
TAF/FTC+DTG:	0.30%	+0.70%*	+0.90%*
TDF/FTC+DTG:	0.40%	+0.40%	+0.50%
TDF/FTC/EFV:	0.30%	+0.60%**	+0.70%**

*TAF/FTC+DTG risk significantly higher than TDF/FTC+DTG at Week 48 (p=0.008) and Week 96 (p=0.004)

**TDF/FTC/EFV risk significantly higher than TDF/FTC+DTG at Week 48 (p=0.047) and Week 96 (p=0.005)

No significant differences between TAF/FTC/DTG and TDF/FTC/EFV at Weeks 48 or 96

ADVANCE trial – Changes in SAT and VAT, metabolic syndrome & diabetes risk

Metabolic syndrome at Week 96

	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
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ADVANCE trial – Changes in SAT and VAT, metabolic syndrome & diabetes risk

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TDF/FTC+DTG:	0.40%	+0.40%	+0.50%
TDF/FTC/EFV:	0.30%	+0.60%**	+0.70%**

*TAF/FTC+DTG risk significantly higher than TDF/FTC+DTG at Week 48 (p=0.008) and Week 96 (p=0.004)

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No significant differences between TAF/FTC/DTG and TDF/FTC/EFV at Weeks 48 or 96

ADVANCE trial

Conclusions

In the ADVANCE Trial, TAF/FTC+DTG was associated with a significantly higher risk of:

- **Clinical obesity**
- **Metabolic syndrome**
- **Rises in VAT and SAT**
- **Predicted risk of diabetes**

The predicted risk of MI from these changes is not significant. However, there is a predicted increase in the risk of diabetes – 4 cases per 1000 people treated with TAF/FTC+DTG versus TDF/FTC+DTG. Additional risks for TDF/FTC/EFV as well.

These analyses should be repeated for other studies evaluating TAF/FTC and integrase inhibitors in other patient populations and lines of treatment.

IeDE study

Retrospective analysis – switching from NNRTI to integrase (n=343) or to PI (n=527)

~ 80% white and 60% men

- greater weight increases with INSTI:
  highest on women, black race, older age
- shows not just effect from first-line ART
- differences by race and gender.

Greater weight gain after switch to INSTI-based regimen from NNRTI vs PI regimens

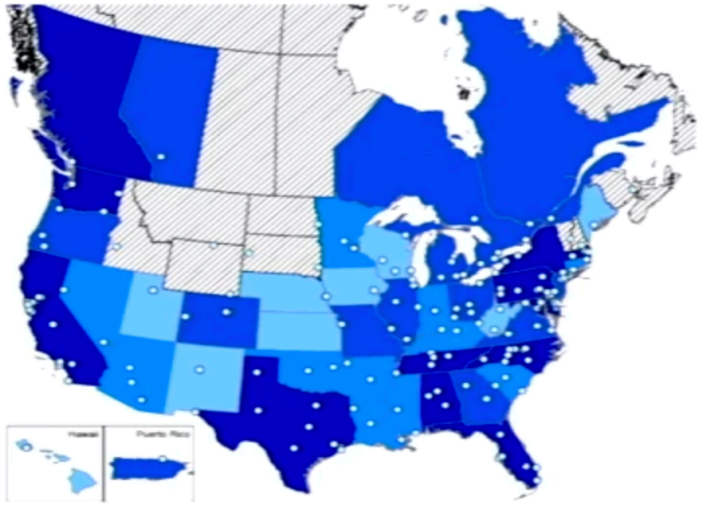
NA-ACCORD @NAACCORD IeDEA @iedeaglobal

Results

VANDERBILT UNIVERSITY MEDICAL CENTER

Source Population:

17 contributing cohorts from NA-ACCORD



Study Population:

870 persons meeting viral suppression criteria

83% Male

59% White

Median age 50 years

Median CD4 620 cells/μl

Median BMI 26 kg/m²

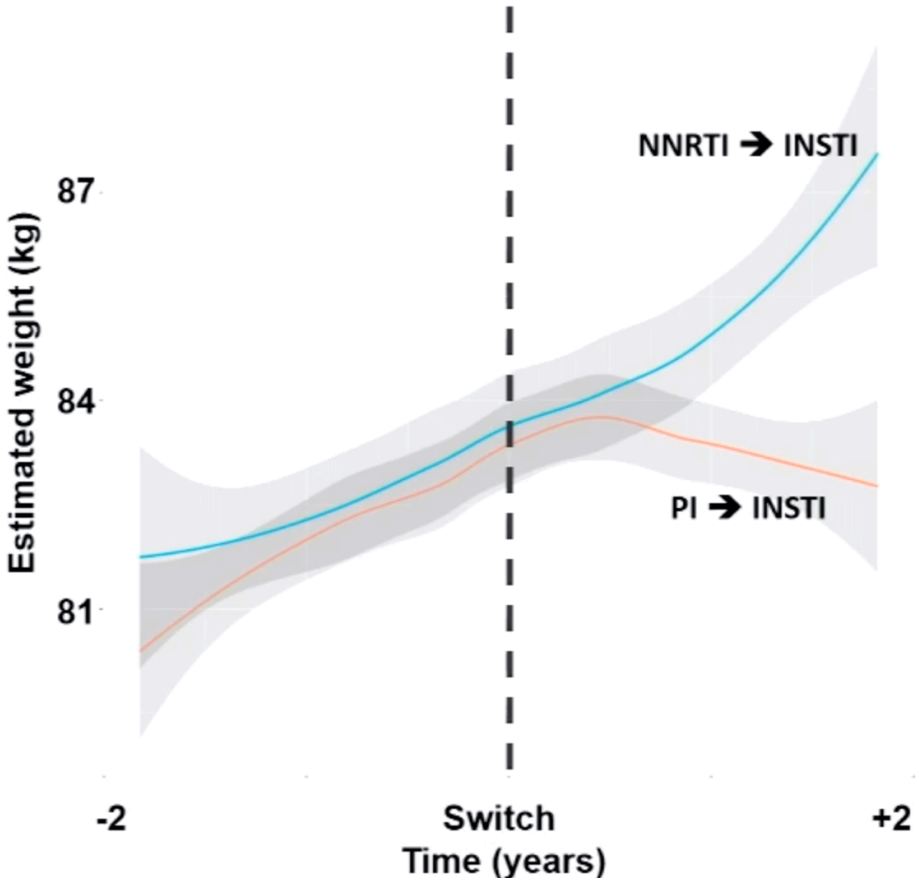
Regimen Switch

343 NNRTI → INSTI	527 PI → INSTI
146 NNRTI → RAL	285 PI → RAL
81 NNRTI → DTG	95 PI → DTG
117 NNRTI → EVG	146 PI → EVG

John Koethe, NA-ACCORD abstract 668

Greater weight gain after switch to INSTI-based regimen from NNRTI vs PI regimens

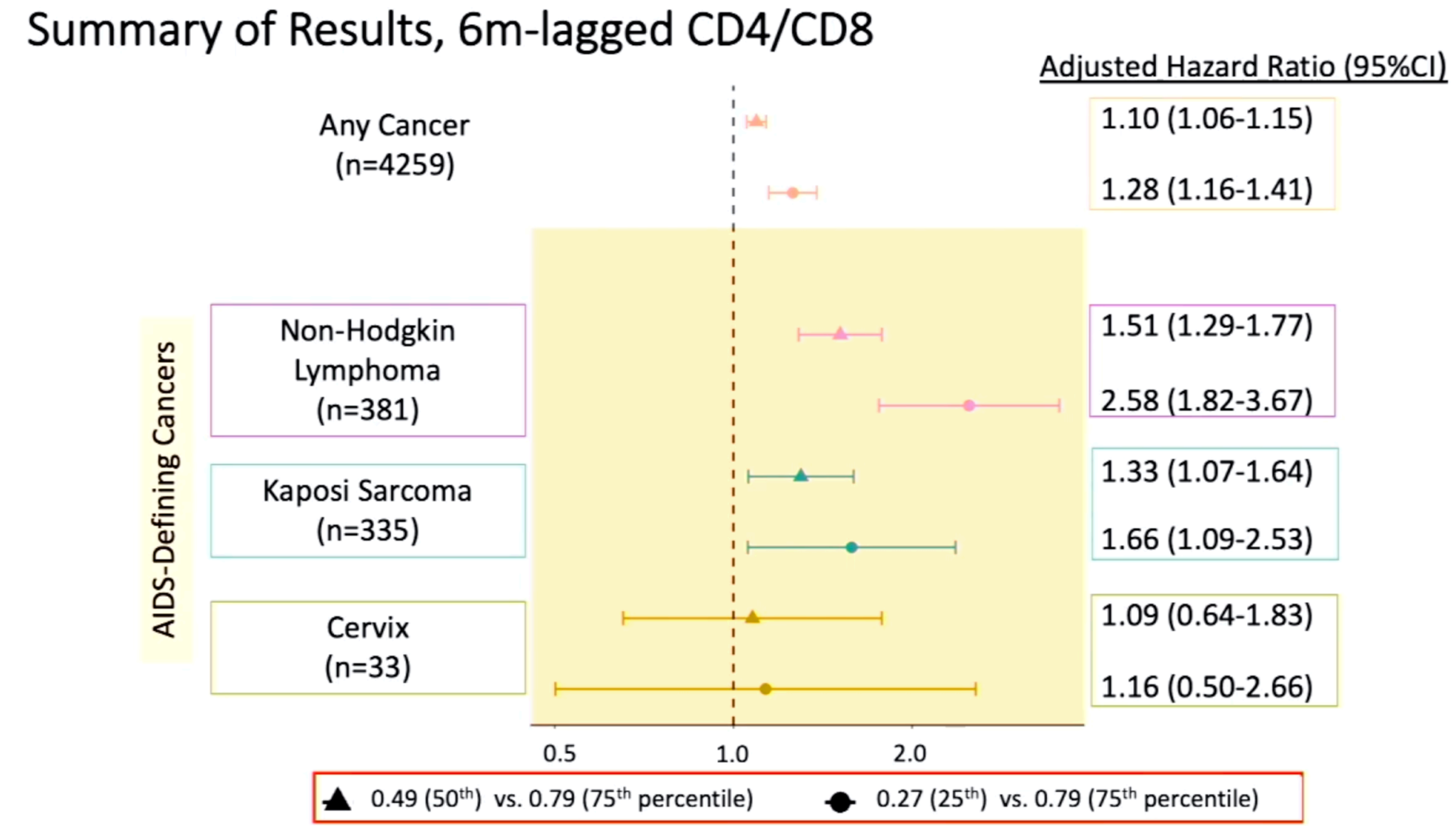
Results



Regimen switch	Pre-switch weight slope (kg/year)	Post-switch weight slope (kg/year)	P-value for slope change
NNRTI → INSTI	**0.63**	**1.13**	**<0.001**
NNRTI → DTG	0.84	1.73	<0.001
NNRTI → RAL	0.74	0.97	0.21
NNRTI → EVG	0.56	1.00	0.07
PI → INSTI	**0.80**	**0.34**	**<0.001**
PI → DTG	0.84	-0.04	<0.001
PI → RAL	0.74	0.17	<0.001
PI → EVG	0.56	0.89	0.11

John Koethe, NA-ACCORD abstract 668

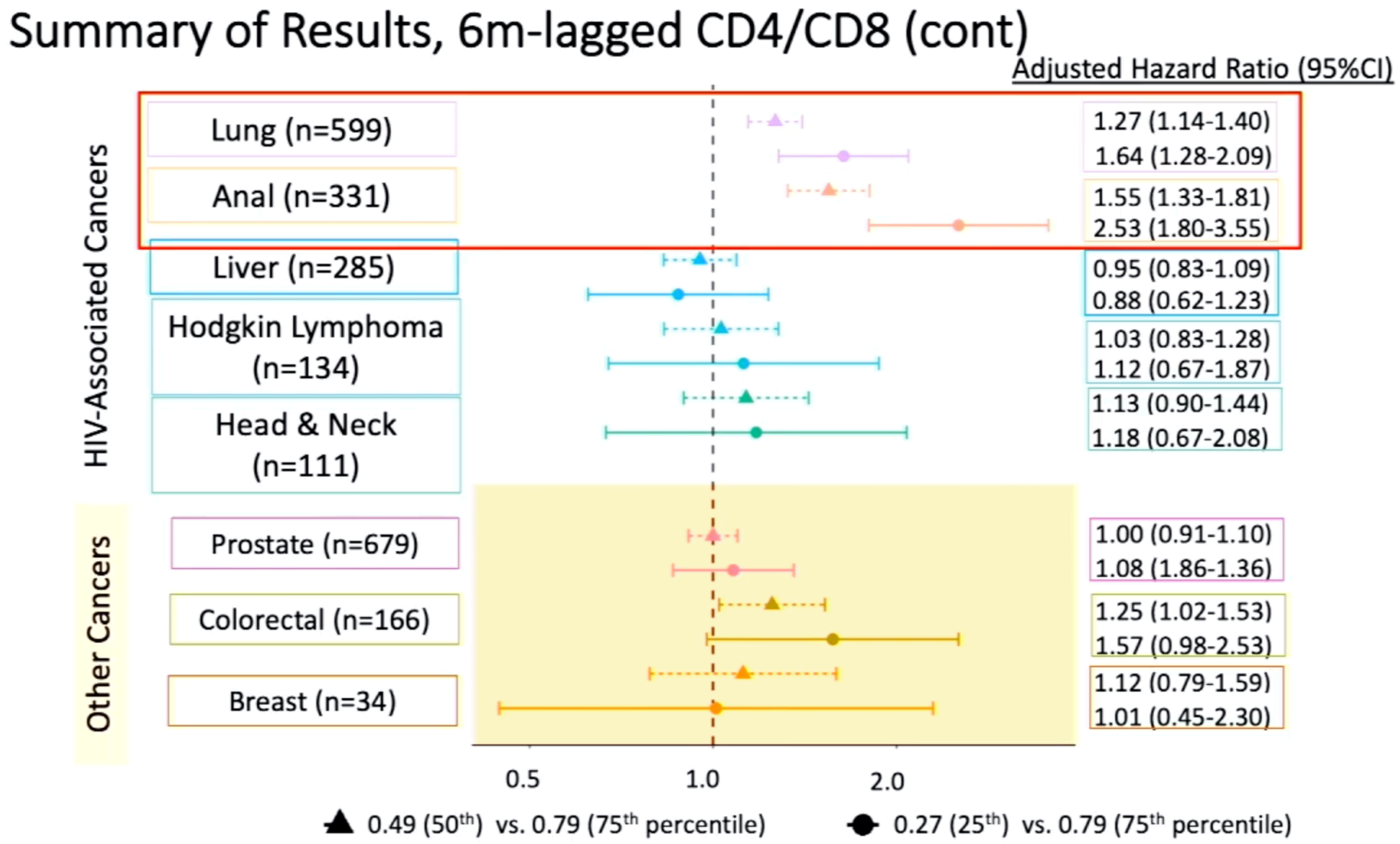
Increased cancer risk with lower CD4/CD8 among adults with HIV in NA-ACCORD



Multivariable models adjusting for: age, sex, race, HCV, time-varying CD4, time-varying HIV RNA, time-varying OI

Jessica Castilho *et al* NA-ACCORD, Abstract 71

Increased cancer risk with lower CD4/CD8 among adults with HIV in NA-ACCORD



Multivariable models adjusting for: age, sex, race, HCV, time-varying CD4, time-varying HIV RNA, time-varying OI

Jessica Castilho *et al* NA-ACCORD, Abstract 71

Increased cancer risk with lower CD4/CD8 among adults with HIV in NA-ACCORD

Conclusions

- Low CD4/CD8 ratio was associated with increased risk of incident cancers overall.
- Low CD4/CD8 ratio and increased cancer risk was observed for a number of ADCs and NADCs.
- Low CD4/CD8 ratio did not predict cancer risk for all virus-associated cancers and the association varied by timing of exposure for others.
- Further investigation of clinical use of CD4/CD8 ratio to inform cancer prevention and screening practices for people with HIV is needed.

Jessica Castilho *et al* NA-ACCORD, Abstract 71

Thanks – and Questions

BHIVA CROI working group for help with slides