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optimising care 2021

Optimising the care of people living with HIV: An update on management of comorbidities to improve patient health

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Recent Advances in PrEP for HIV Prevention

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anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Global HIV Epidemic

2019
Globally

38.0 million
People living with HIV

1.7 million
People newly infected

- 23%
New infections annually relative to 2010

- 39%
Deaths annually relative to 2010

57% of all new diagnoses in Africa

2030 Target: < 200.000 new HIV infections

UNAIDS/WHO estimates, Presented at the IAS 2020 Conference

Approved and Investigational PrEP Agents

- Topical
  - Dapivirine ring
- Oral
  - **TDF/FTC**
  - **TAF/FTC**
  - Islatravir
- Parenteral
  - Cabotegravir LA IM
  - Lenacapavir SC
  - Implants (Islatravir, cabotegravir, TAF)
  - Broadly Neutralizing Antibodies (bNabs)

PrEP Initiations by Country, 2021

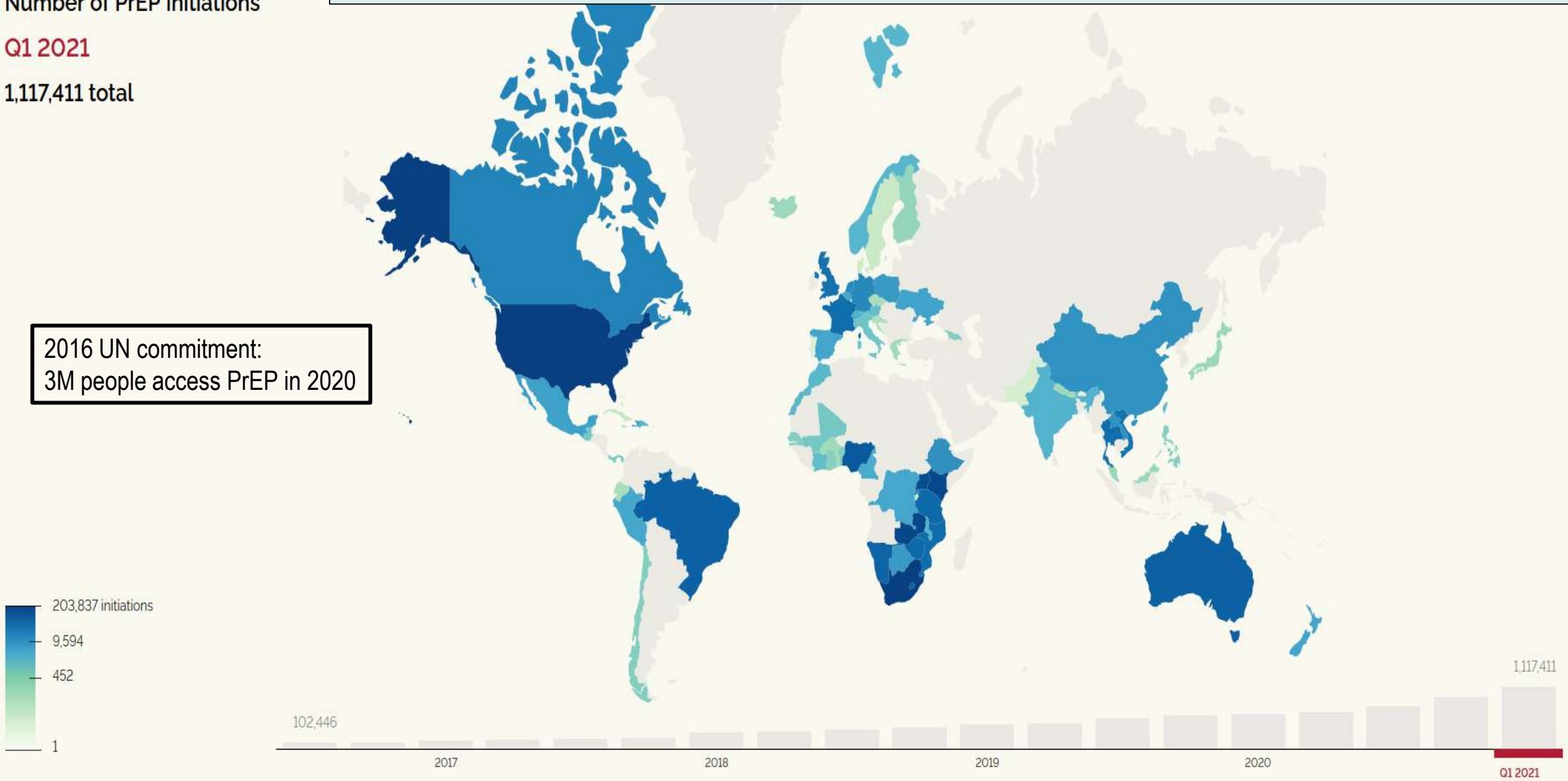
The Global PrEP Tracker

Number of PrEP Initiations

Q1 2021

1,117,411 total

2016 UN commitment:
3M people access PrEP in 2020



THE RING STUDY
Predicting HIV Prevention for Women

DREAM
Dapivirine Ring Extended Access and Monitoring

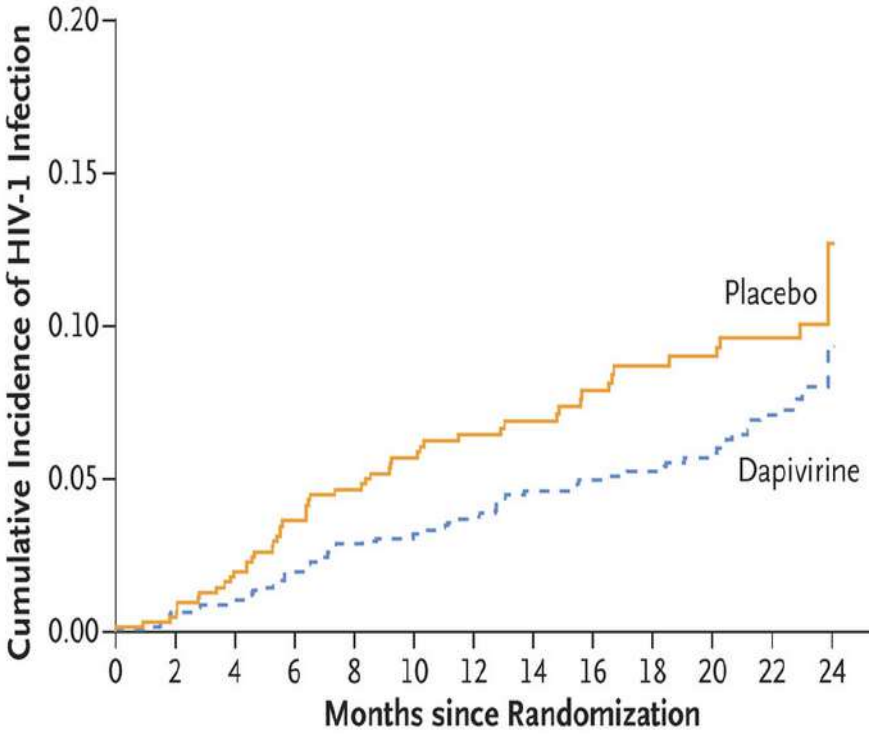
INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Dapivirine Vaginal Ring

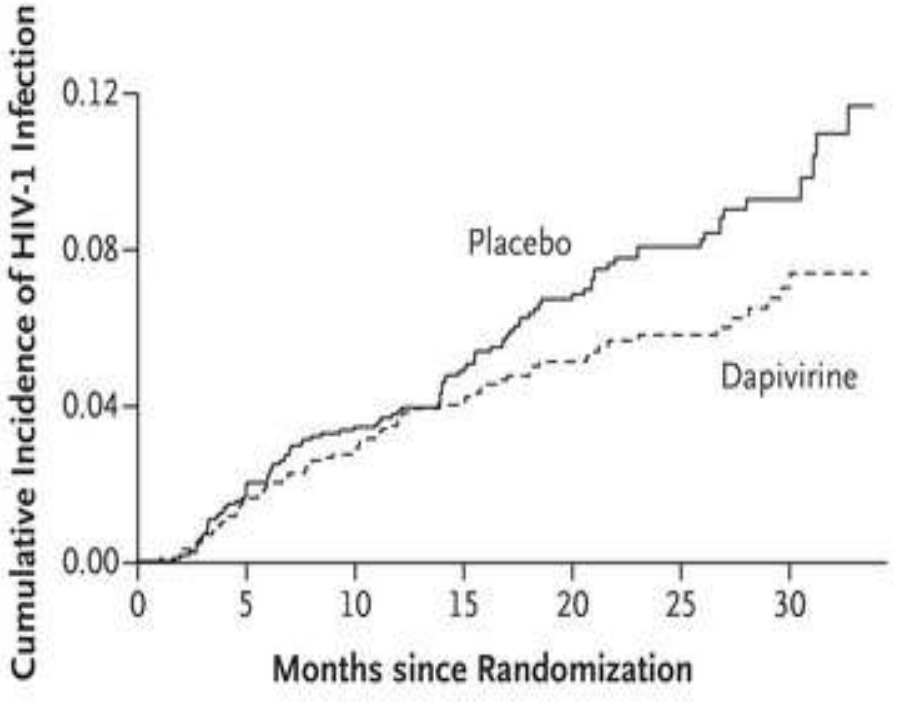
ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

HOPE
HIV Open-label Prevention Extension
Out of ASPIRE, there is HOPE

MTN
microbicide trials network



. Randomized double-blinded study
. Dapivirine vaginal ring vs placebo
. Flexible, silicone matrix
. Ring with 25 mg Dapivirine
. Self-inserted every 4 weeks
. Releases drug into vaginal tissue



1959 young women, median age 25.9 years in South Africa and Uganda
31% reduction in HIV-incidence HR: 0.69 (95% CI: 0.49-0.99; p=0.04)
62% reduction in HIV-incidence in DREAM:
Incidence in DREAM: **1.8/100 PY**

Nel et al. NEJM 2016; Lancet HIV 2021

2629 women, mean age 27 years in Sub-Saharan Africa
Reduction in HIV incidence : **27%** (95% CI:1-46, p=0.046) **37%** without two sites
39% reduction (95% CI: 14-65) in HIV-incidence in HOPE:
Incidence in HOPE**: 2.7/100 PY**

Baeten et al. NEJM 2016; Lancet HIV 2021

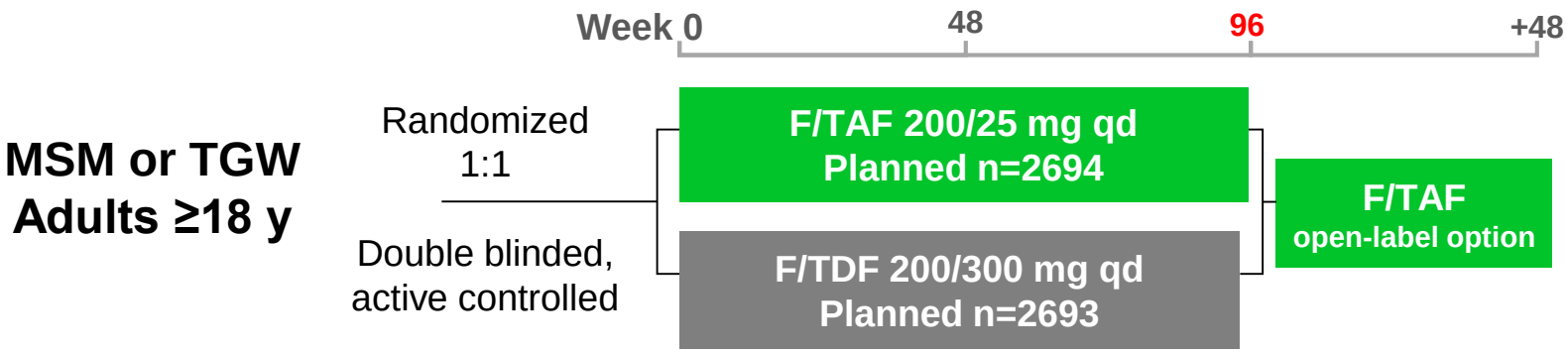
Next Steps with Dapivirine Vaginal Rings

- EMA approval in July 2020 and WHO recommendation in January 2021 for DPV-VR as a new choice for HIV prevention for women

- More studies ongoing in Africa:
  - 300 Adolescent girls and young women: REACH study
  - 750 pregnant women: DELIVER study
  - Breast-feeding women: B-PROTECTED in Africa
  - Extended duration vaginal rings: 3-monthly dapivirine vaginal rings
  - Multipurpose technologies : rings with dapivirine and levonorgestrel

- Limitations
  - Low effectiveness due to topical PrEP
  - Selection of NNRTI resistance
  - Long-term acceptability

DISCOVER Study Design



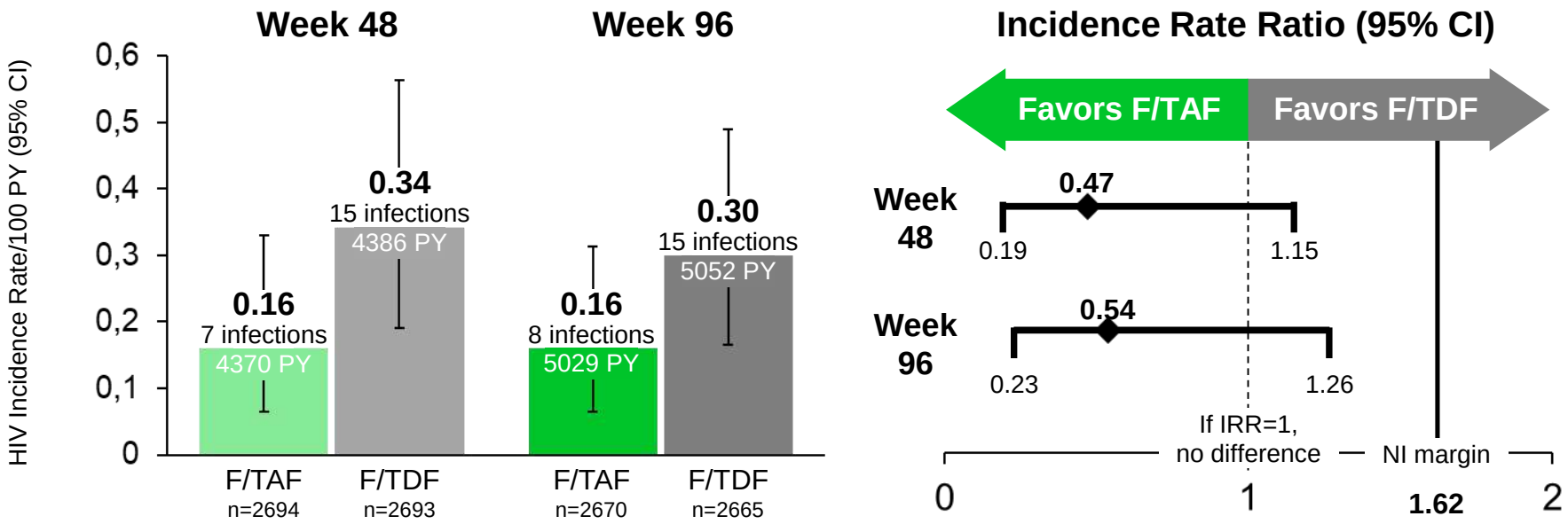
- **Eligibility:** high sexual risk of HIV
  - 2+ episodes condomless anal sex in past 12W **or** rectal gonorrhea/chlamydia, syphilis in past 24W
  - HIV & HBV negative, $eGFR_{CG}$ ≥60 mL/min
  - Prior use of PrEP allowed
- **Study conducted in Europe, North America in cities/sites with high HIV incidence**
- **Assessments**
  - Safety (AEs, AE-related discontinuation, BMD, renal biomarkers)
  - Adherence (self-report, pill counts, drug levels and DBS)
  - HIV lab testing (rapid HIV testing on-site, Central lab)
  - HIV risk behavior (CASI questionnaire, STI testing at every visit)

Mayer K et al. Lancet 2020; Ogbuagu O et al. Lancet HIV 2021

Baseline Demographics and HIV Risk Factors

		F/TAF n=2694	F/TDF n=2693
Demographics	Median age, y (range)	34 (18–76)	34 (18–72)
	Race, n (%)		
	White	**2264 (84)**	**2247 (84)**
	Black	240 (9)	234 (9)
	Asian	113 (4)	120 (5)
	Hispanic or Latinx ethnicity, n (%)	635 (24)	683 (25)
	Proportion TGW, n (%)	**45 (2)**	**29 (1)**
HIV risk factors, %	≥2 condomless anal sex (receptive), past 12W	60	58
	Rectal gonorrhea, past 24W	10	10
	Rectal chlamydia, past 24W	13	12
	Syphilis, past 24W	9	10
	Recreational drug use, past 12W	67	67
	Binge drinking	23	22
	Taking F/TDF for PrEP at baseline	**17**	**16**

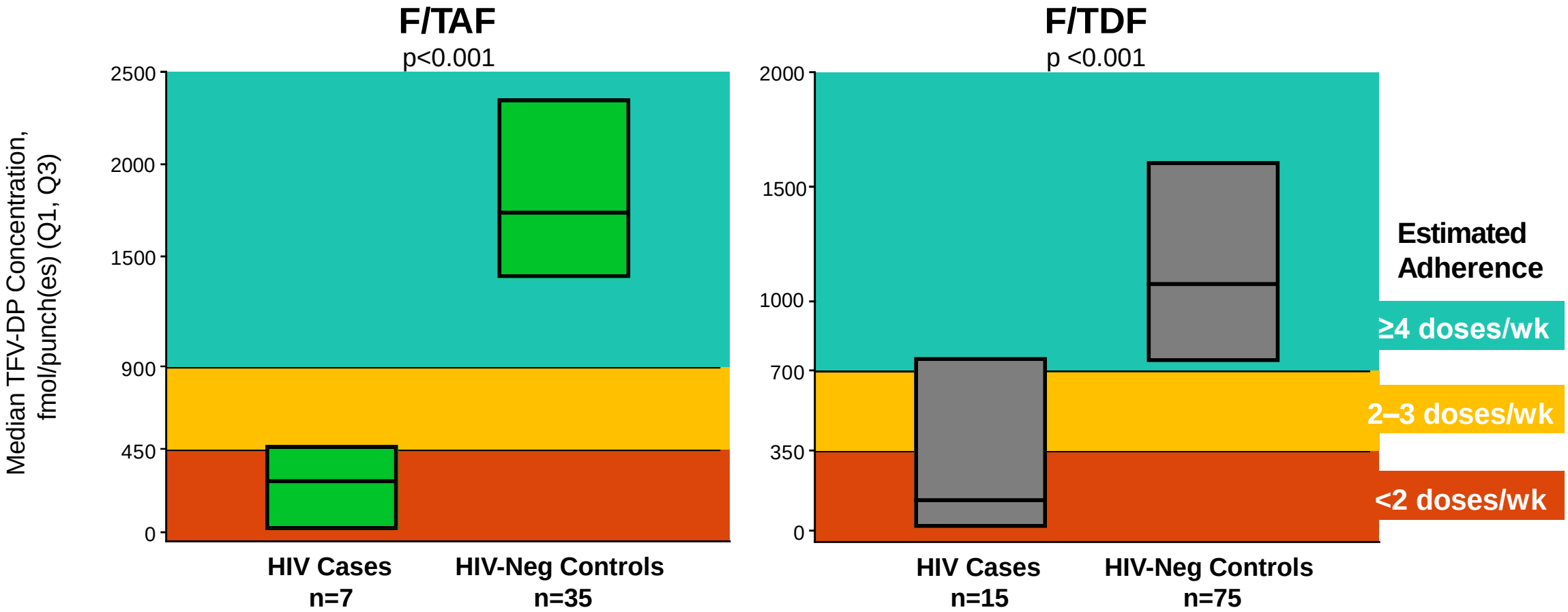
Daily F/TAF is Non-Inferior to Daily TDF/FTC for PrEP among MSM



- F/TAF is noninferior to F/TDF for HIV prevention (upper bound of the IRR 95% CI: <1.62)
- Five participants with suspected HIV-infection before baseline (4 TDF/FTC, 1 TAF/FTC): HR: 0.64 (0.25-1.65)

Mayer K et al. Lancet 2020; Ogbuagu O et al. Lancet HIV 2021

Adherence by DBS at HIV Diagnosis Visit Strongly Associated with HIV acquisition



- Low adherence (adherence <2 doses/week) was independently associated with increased risk of HIV acquisition in both groups (P-value < 10^{-4})
  - Similar results from sensitivity analyses excluding 5 suspected baseline infections

Mayer K. et al. Lancet 2020

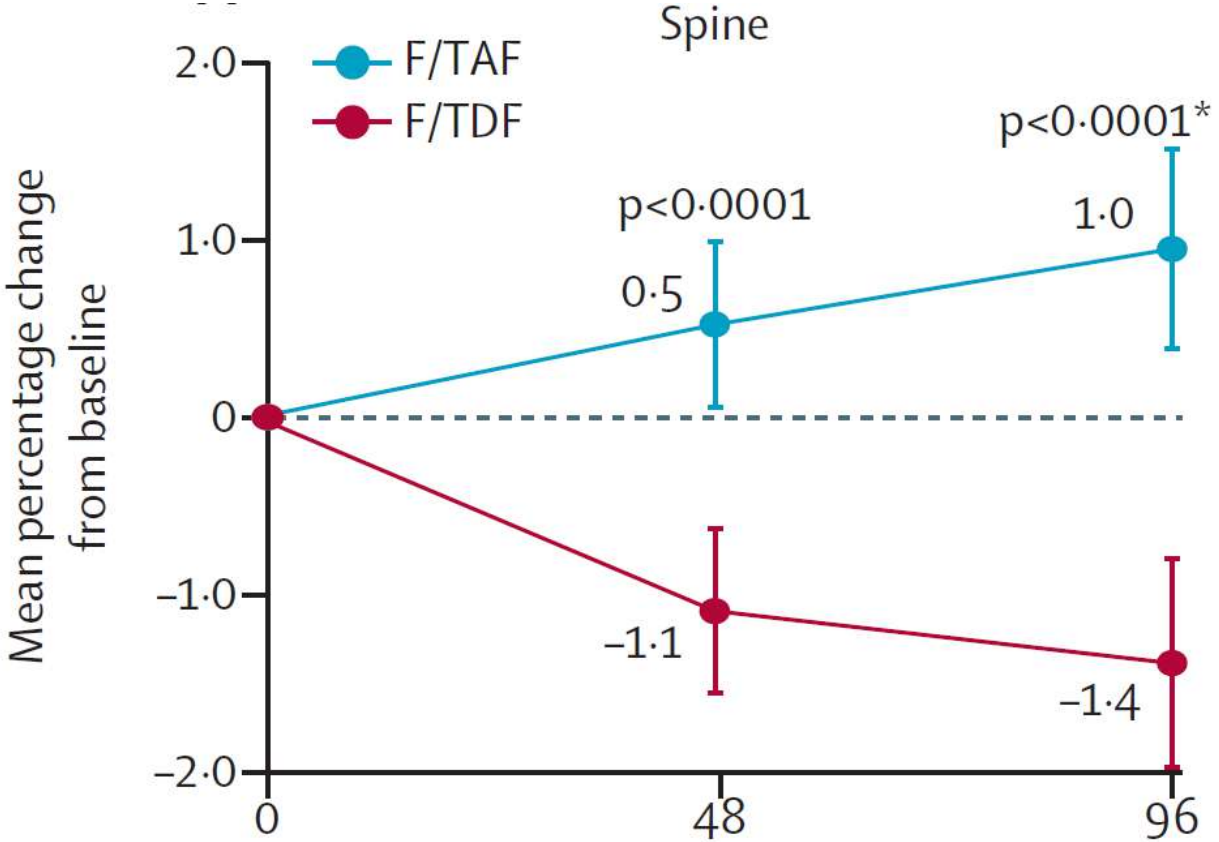
Overall Safety Summary at Week 96 in Discover

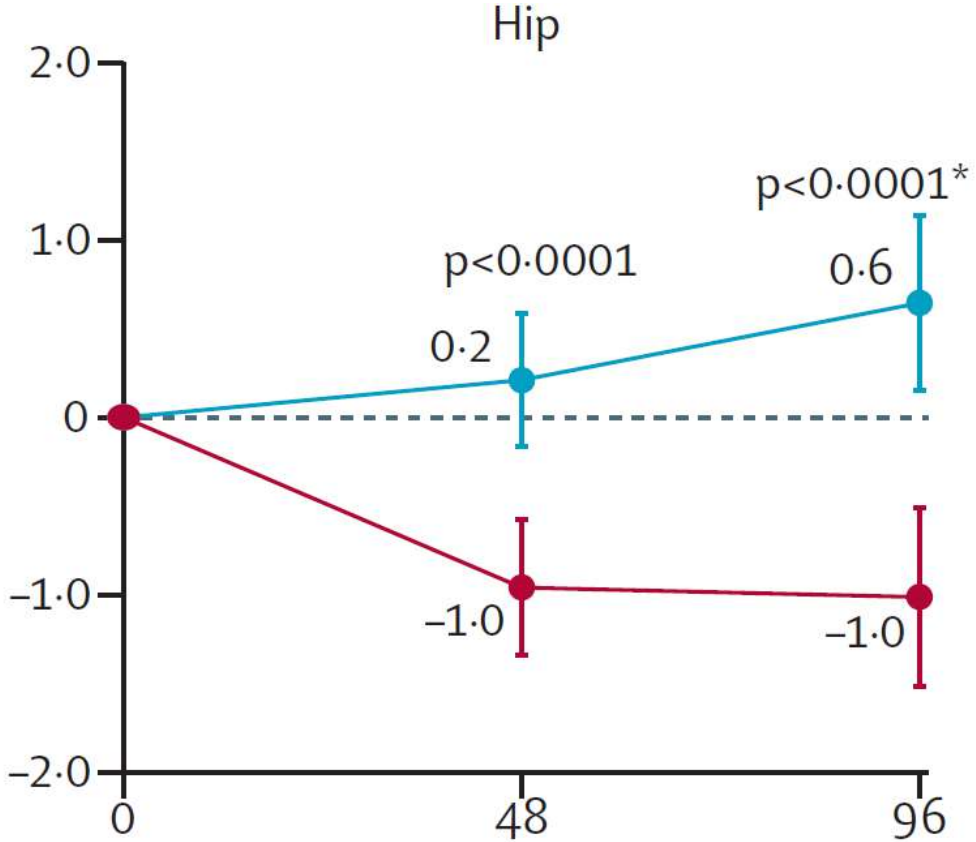
% (n)	F/TAF n=2694	F/TDF n=2693
Any AEs	94	94
Study drug-related AEs	21	24
Grade ≥2 AEs	49	47
Grade ≥3 AEs	7	6
SAEs	7	6
Study drug-related SAEs	0.1 (3)	0.2 (5)
AEs leading to discontinuation	1 (40)	2 (51)
Deaths, n*	0.1 (3)	0.1 (2)

*Reasons: traffic accident, metastatic squamous cell carcinoma, unknown. SAE, serious AE.

Mayer K et al. Lancet 2020; Ogbuagu O et al. Lancet HIV 2021

DISCOVER BMD Sub-study at Week 96



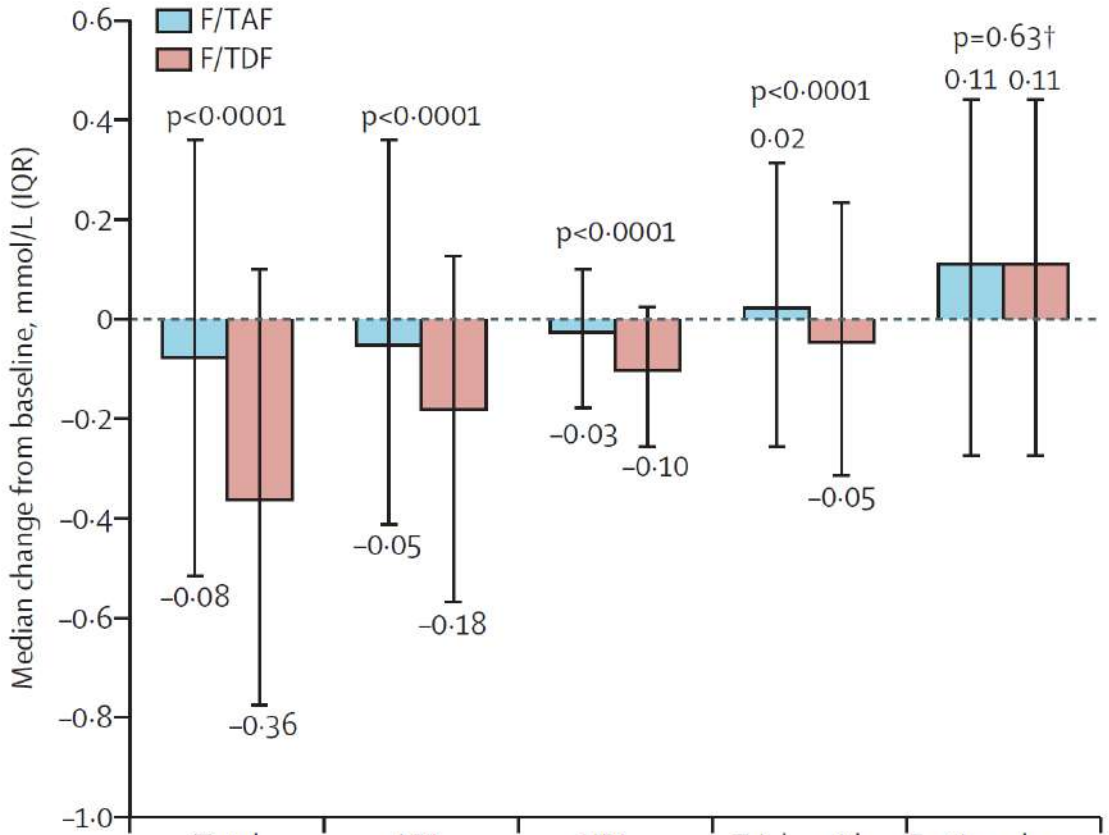


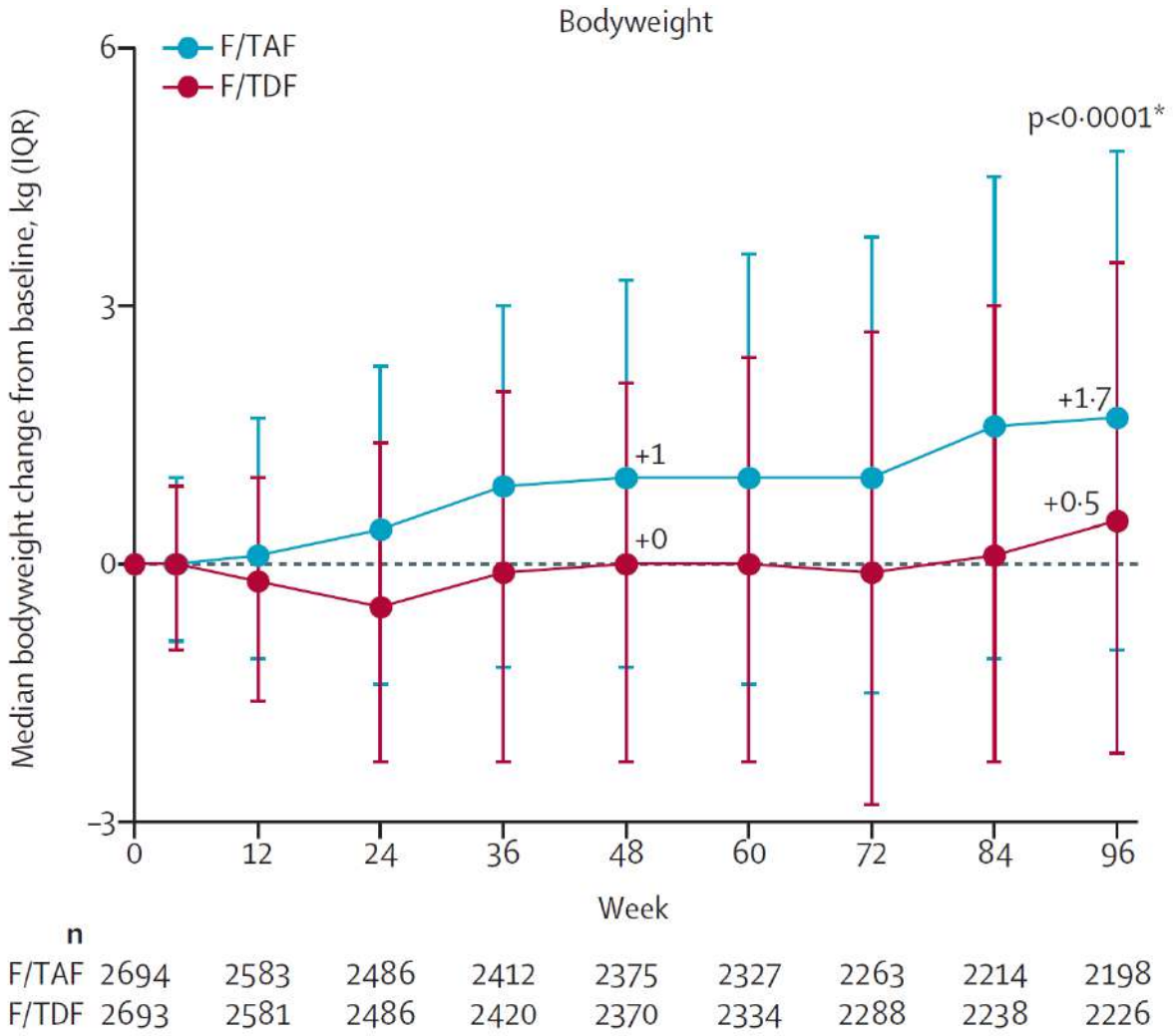
n				
F/TAF	159	144	158	140
F/TDF	160	140	158	137

*p-values from analysis of variance model with baseline F/TDF for PrEP and treatment as fixed effects.

Ogbuagu O et al. Lancet HIV 2021

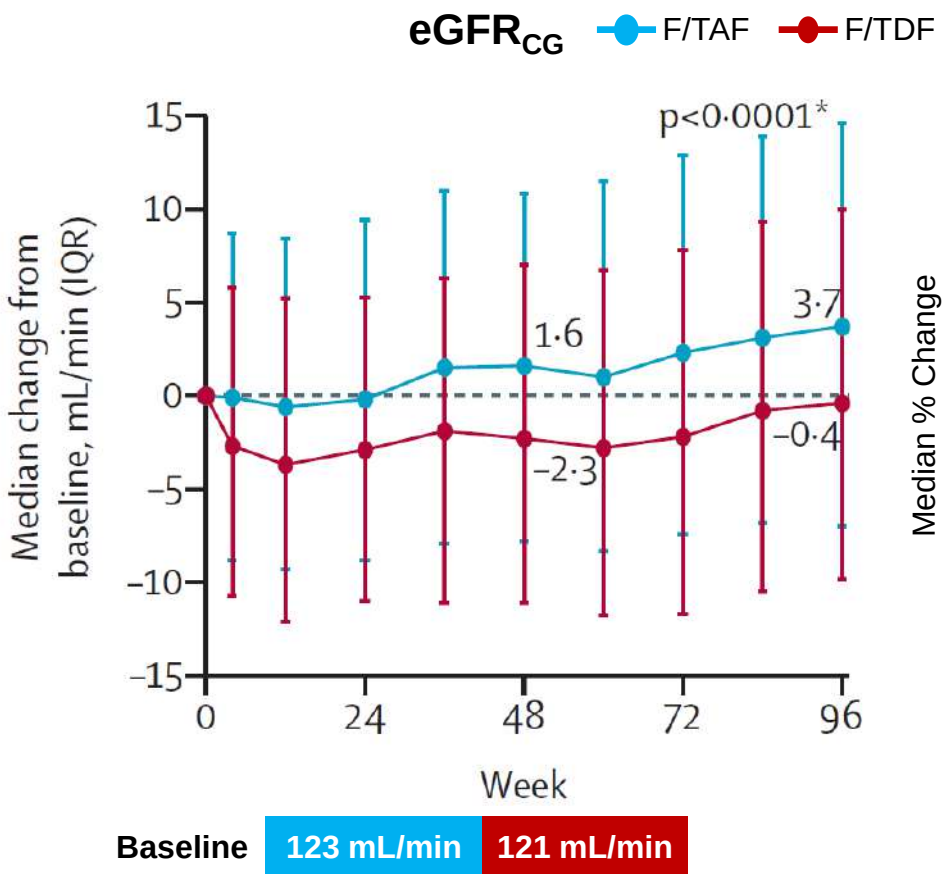
DISCOVER Lipids and Body Weight



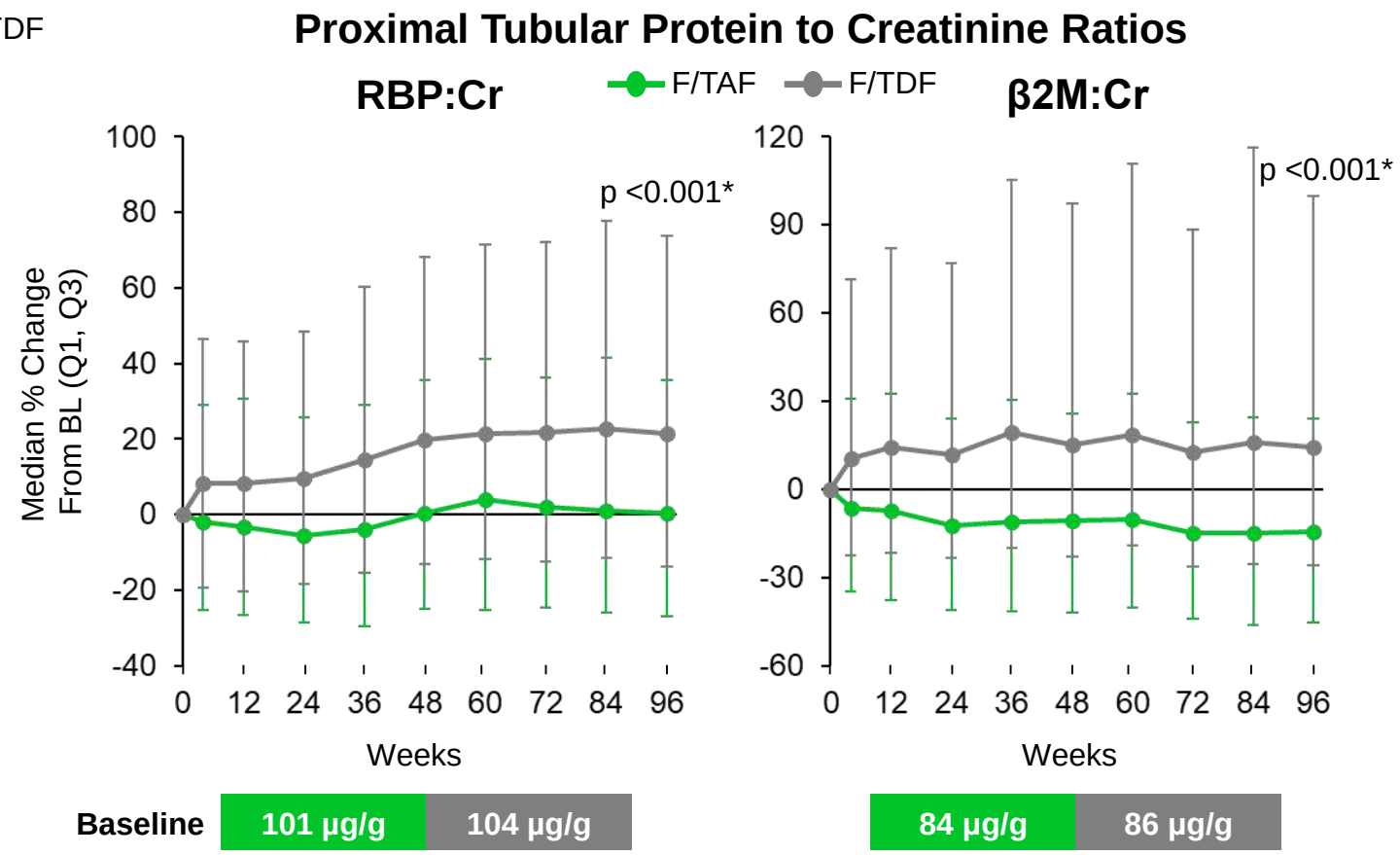


Ogbuagu O et al. Lancet HIV 2021

DISCOVER: Renal Biomarkers at Week 96



Baseline	123 mL/min	121 mL/min



Baseline	101 µg/g	104 µg/g	84 µg/g	86 µg/g

- Renal discontinuations: F/TAF, n=2; F/TDF, n=6
- Fanconi syndrome: F/TAF, n=0; F/TDF, n=1 (at day 421 in a 49 year old man with no comorbidities)

β2M, β2-microglobulin; Cr, creatinine; Q, quartile; RBP, retinol-binding protein.

Ogbuagu O et al. Lancet HIV 2021

Limitations of Oral TAF/FTC for PrEP

- FDA approval for MSM only (exclude those with receptive vaginal intercourse)
  - Additional studies ongoing in women
- Daily use: One pill of 25 mg TAF/200 mg FTC every day
  - No clinical data supporting the use of event-driven PrEP with TAF/FTC
- Improved safety vs. TDF/FTC not demonstrated clinically
  - Clinical correlates of DXA and renal biomarkers unclear
  - Recommended only when eGFR <60 mL/mn or prior history of osteopenia or osteoporosis
- Cost
- **Since approval in 10/2019 in the US, TAF/FTC users increased from 2,637 to 76,000 in 2020**

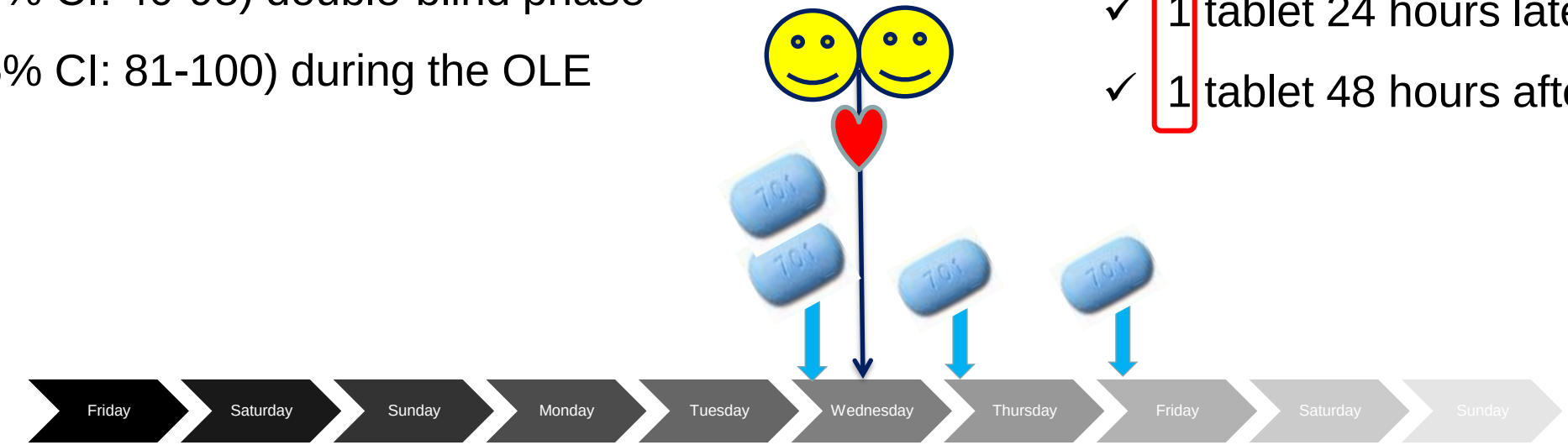
Saag M. et al. IAS-USA guidelines panel JAMA 2020; Hoover KW et al. CROI 2021

IPERGAY : Sex-Driven iPrEP

Relative Reduction in HIV-incidence

- ✓ 86% (95% CI: 40-98) double-blind phase
- ✓ 97% (95% CI: 81-100) during the OLE

- ✓ 2 tablets 2-24 hours before sex
- ✓ 1 tablet 24 hours later
- ✓ 1 tablet 48 hours after first intake



4 pills of TDF/FTC taken over 3 days to cover one sexual intercourse

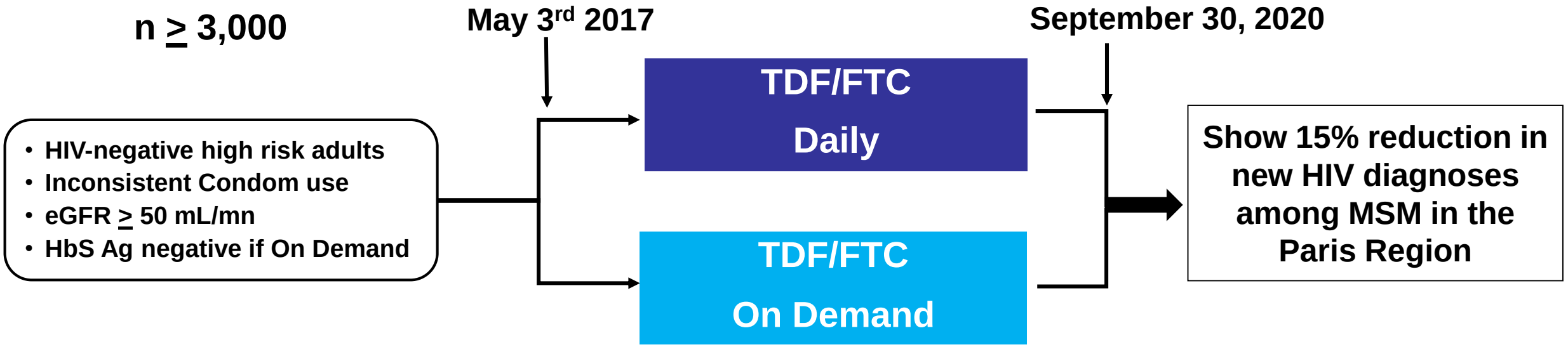
Molina JM et al NEJM 2015, Lancet HIV 2017

Potential Benefits of On Demand PrEP

- Convenient dosing regimen could improve adherence and effectiveness
- Clear guidance on how to start and stop PrEP
- Better safety due to lower drug exposure (kidneys, bones)
- Improved cost-effectiveness
- Easier diagnosis of breakthrough HIV-infection
- Lower risk of selecting drug resistance in case of HIV-infection

PrEP with Daily or On Demand TDF/FTC among MSM

Open-Label Prospective Cohort Study in the Paris Region



- **Participants opted for either Daily or On Demand PrEP and could switch regimen**
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

Molina JM et al CROI 2021

Baseline Characteristics

Characteristics (Median, IQR) or (n, %)	Daily N=1544 (50.5%)	On Demand N=1515 (49.5%)	P-value
Age (years)	35 (28 – 43)	36 (30 – 44)	<.0001
MSM	97.9	99.2	0.0002
Heterosexual men or women	20 (1.3)	11 (0.7)	
Transgender	13 (0.8)	1 (0.1)	
2-year university degree or more	83.8	87.8)	0.0033
Employed	85.2	86.4	0.3620
History of PrEP use	54.6	57.3	0.1333
Use of Chemsex*	14.4	13.4	0.4045
No. condomless sex acts in prior 4 weeks	2 (0 - 6)	2 (0 - 4)	<.0001
No. sexual partners in prior 3 months	12 (6 - 25)	10 (5 - 15)	<.0001

* at last sexual intercourse : cocaine, GHB, MDMA, mephedrone..

Adherence to PrEP using DBS and Pill Intake

Median (IQR)	Daily n = 146	On Demand n = 203	P Value
TFV-DP (fmol/l)	1264* (1003-1600)	691** (359-1039)	<0.0001
% < LOQ (8.7 fmol/punch)	1 (0.7%)	13 (6.4%)	0.010
FTC-TP (pmol/l)	0.25 (0.17-0.34)	<0.1 (<0.1-0.21)	0.57
% < LOQ (0.1 pmol/punch)	14 (9.6%)	111 (54.7%)	<0.0001
Nb pills/week (self-report)*	7 (6-7)	2 (0-5)	<0.0001

* Estimated pill intake: 2-3 doses /week ** 6 doses per week
Correlation between TFV-DP and pill count: r=0.44 (p< 0.0001)

HIV Incidence

Mean Follow-up of 22.1 months and 5633 Person-Years

Rate of study discontinuation: 14.4/100 PY

Global HIV Incidence: 1.1/1000 PY (95% CI: 0.04-0.23) (6 cases)

Dosing Regimen	Follow-Up Pts-years	HIV Incidence per 1000 Prs-years (95% CI)	IRR (95%CI)
TDF/FTC Daily	2583.25	1.2 (0.2 – 3.4)	**0.99** (0.13-7.38)
TDF/FTC On Demand	2553.68	1.2 (0.2 – 3.4)	

Adverse Events

	Daily 2583.25 Prs-years		On Demand 2553.68 Prs-years		Incidence Rate Ratio Daily vs On Demand (95% CI)
	No. Pts	Incidence per 100 PY (95% CI)	No. Pts	Incidence per 100 PY (95% CI)	
Drug-Related AEs	152	5.88	192	7.52	0.78 (0.63-0.97)
Gastrointestinal AEs	113	4.37	149	5.83	0.75 (0.58-0.96)
SAE	92	3.56	77	3.01	1.18 (0.86-1.62)
Death (suicide)	1		0		
Treatment D/C due to Drug-Related AE*	7	0.27	9	0.35	0.77 0.24-2.32)

* Only 3 patients had permanent PrEP discontinuation due to GI AEs (2 daily and 1 on demand).

Lab Abnormalities

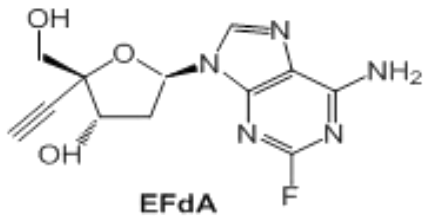
	Daily 2583.25 Prs-years		On Demand 2553.68 Prs-years		IRR Daily vs On Demand (95% CI)
	No. Pts	Incidence per 100 PY (95% CI)	No. Pts	Incidence per 100 PY (95% CI)	
All Grades ALAT	574	22.22	468	18.33	1.21 (1.07-1.37)
Grade 3 or 4	26	1.01	24	0.94	1.07 (0.59-1.95)
Grade 1 Creatinine	194	7.51	176	6.89	1.09 (0.88-1.34)
Creat. Clearance* 50-70 ml/mn	254	9.83	282	11.04	0.89 (0.75-1.06)
<50 ml/mn	14	0.54	14	0.55	0.99 (0.44-2.24)

*4 participants with e-GFR <70 ml/min temporarily discontinued PrEP

Limitations of Event-Driven with TDF/FTC for the Prevention of HIV

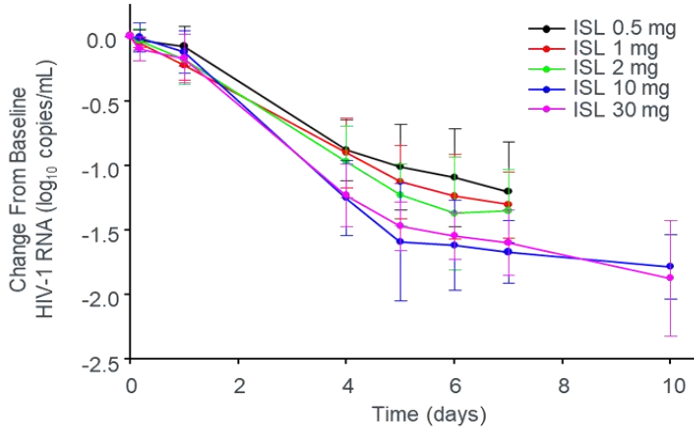
- ANRS Prevenir is not a randomized trial
- More frequent drug-related Gastro-Intestinal AEs
- No data in Heterosexuals men and women
- No data with TAF/FTC yet
- Can we simplify the 2-1-1 dosing regimen ?

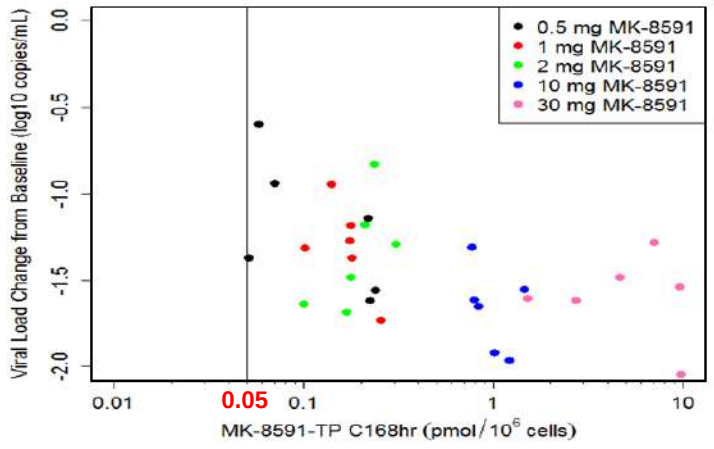
Antoni G. et al Lancet HIV 2020; Liegeon G. et al J Int AIDS Soc 2020; Molina JM et al. IAS 2019 Mexico, Hoornenborg E. et al Lancet HIV 2019; Sewel WC. et al JAIDS 2020



Islatravir: A New Potent and Long-Acting Antiretroviral Agent

- Nucleoside reverse transcriptase translocation inhibitor.
- Potent antiviral activity with low in vitro IC_{50} :1.5 nM and activity against NRTI-resistant HIV-1 strains.
- Single-dose oral ISL associated with reduction in plasma HIV-RNA without emergence of viral resistance.
- Robust viral load decline associated with ISL-TP concentrations as low as **0.05 pmol/10^6 cells.**
- Long ISL-TP half-life ~120 hr in healthy adults.
- ISL-TP concentrations in rectal and vaginal tissue similar to PBMC concentrations at steady state.
- Protects against SHIV infection in a rectal challenge Rhesus macaque model (Markowitz et al. JID 2020).





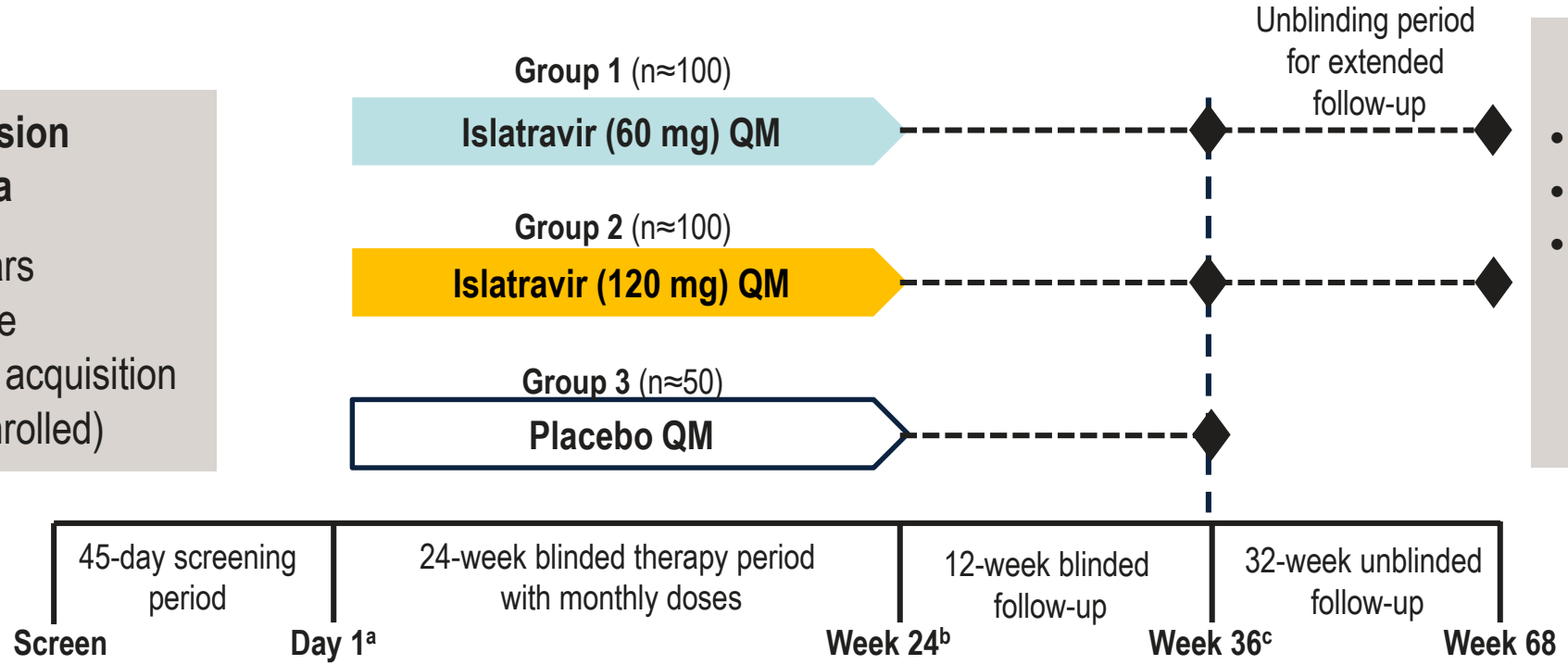
Schurmann D. et al. Lancet HIV 2020;7:e164-72

HIV R4P
HIV RESEARCH FOR PREVENTION
CAPE TOWN, SOUTH AFRICA · 17–21 JANUARY 2021

Blinded Interim Analysis of a Randomized Placebo Controlled Study of Monthly Oral Islatravir for PrEP

Key inclusion criteria

- Aged 18–65 years
- HIV seronegative
- Low risk for HIV acquisition
- N ≈ 250 (192 enrolled)



Outcome measures

- Safety/tolerability
- PK (ISL/ISL-TP)
- Exploratory
  - PBMC PK
  - tissue PK
  - hormonal DDIs

NCT04003103 (P016).

HIV RESEARCH FOR PREVENTION
CAPE TOWN, SOUTH AFRICA · 17–21 JANUARY 2021

Blinded Safety Analysis of a Randomized Placebo Controlled Study of Monthly Oral Islatravir for PrEP

- Most AEs mild or moderate and resolved on treatment
  - **2 discontinuations due to AEs**: sensation of foreign body in the throat (mild), rash, and pruritus (moderate)
- No serious AEs or deaths

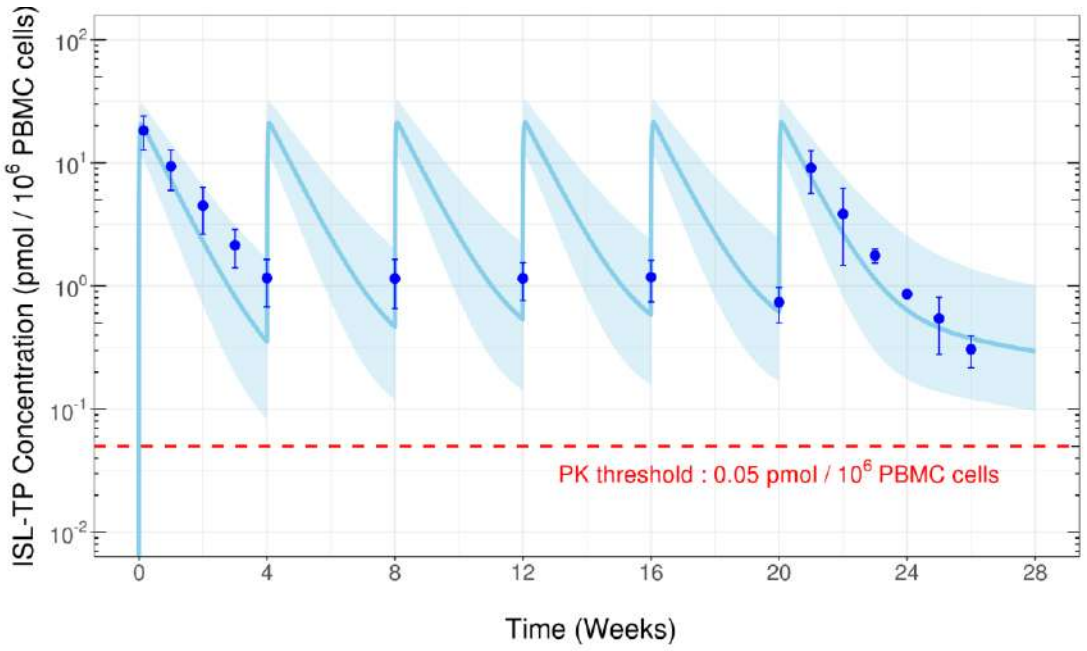
AE, %	Patients (N = 192)
Any	53.1
Headache	7.3
Diarrhea	5.7
Nausea	4.7
Abdominal pain	4.2
Upper respiratory tract infection	4.2
Proteinuria	3.6
Cough	3.1

Hillier S. et al HIV R4P 2021 virtual 01363

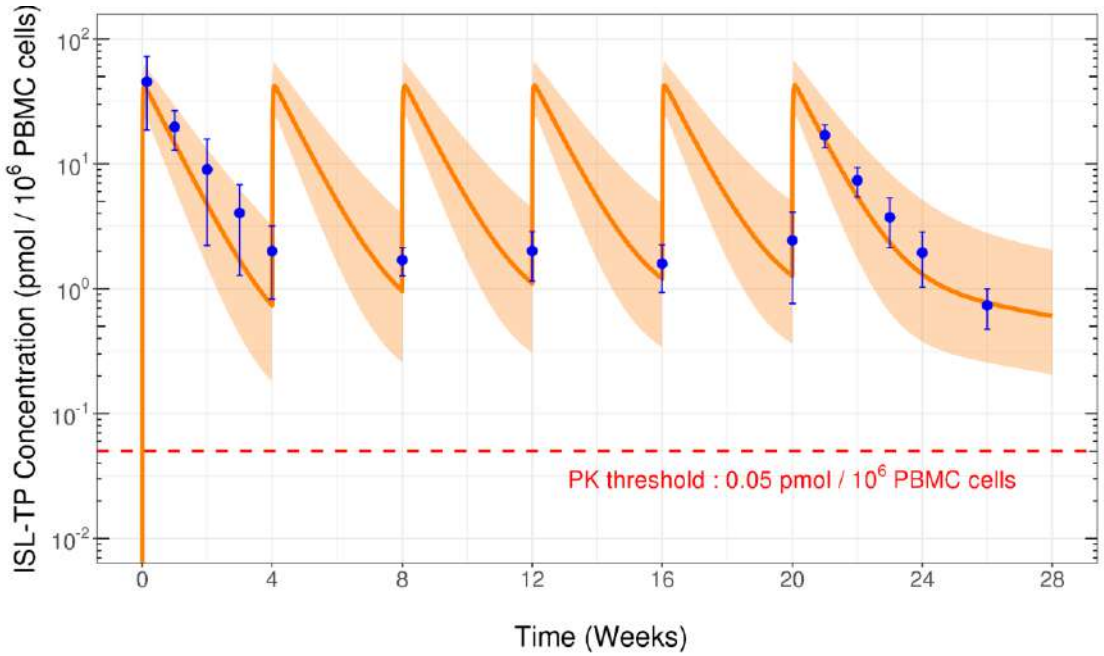
HIV RESEARCH FOR PREVENTION
CAPE TOWN, SOUTH AFRICA · 17–21 JANUARY 2021

Mean ISL-TP concentration in PBMCs overlaid on population PK model simulated median ISL-TP concentrations in PBMCs

ISL 60 mg QM



ISL 120 mg QM



- **PBMC ISL-TP trough concentrations were all above the pre-specified PK threshold of 0.05 pmol/10^6 PBMCs**
- Half-life in PBMCs ~ 190 hrs after oral dose
- Observed concentrations in PBMCs correlate well with population pharmacokinetic simulations for both doses
- Pharmacokinetics show approximately linear dose proportionality and sustained distribution to rectal, cervical, and vaginal tissues

Hillier S. et al HIV R4P 2021 virtual 01363

ISL 60 mg QM Oral PrEP Clinical Development Program

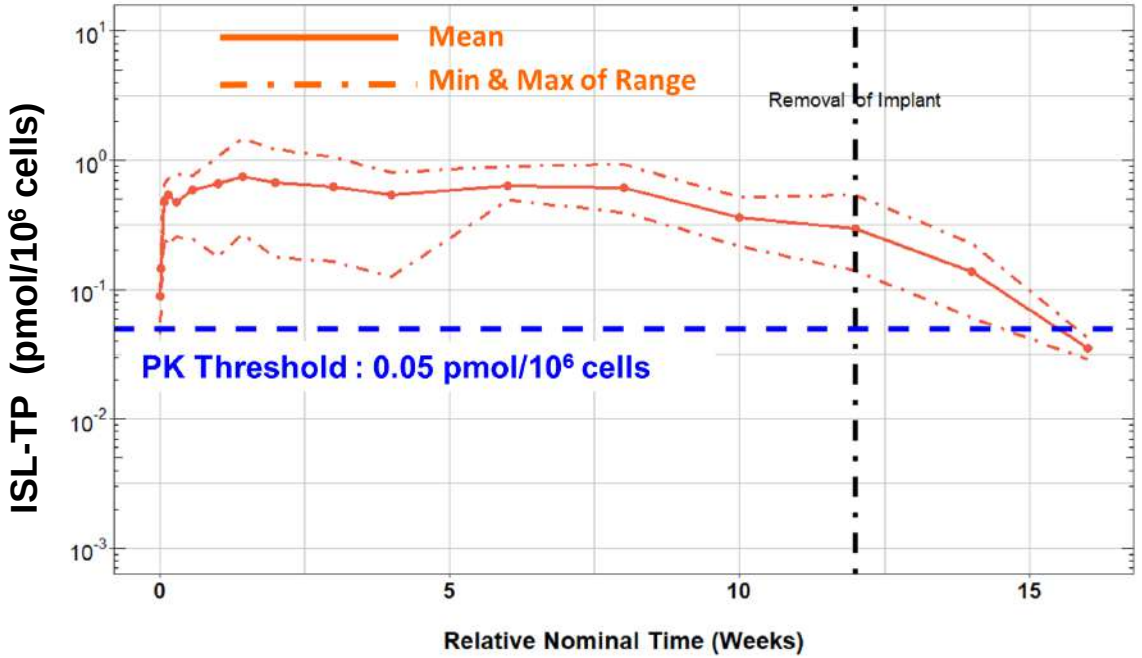
Impower

	Trial name (protocol number)	Population	Active comparator	ClinicalTrials.gov
Phase 3	IMPOWER-022	4,500 Cisgender women and adolescent girls at high risk of HIV-1 infection in Sub-Saharan Africa	FTC/TDF	NCT04644029
	IMPOWER-024	1,500 Men and transgender women who have sex with men and are at high risk for HIV-1 infection	FTC/TDF or FTC/TAF	NCT04652700

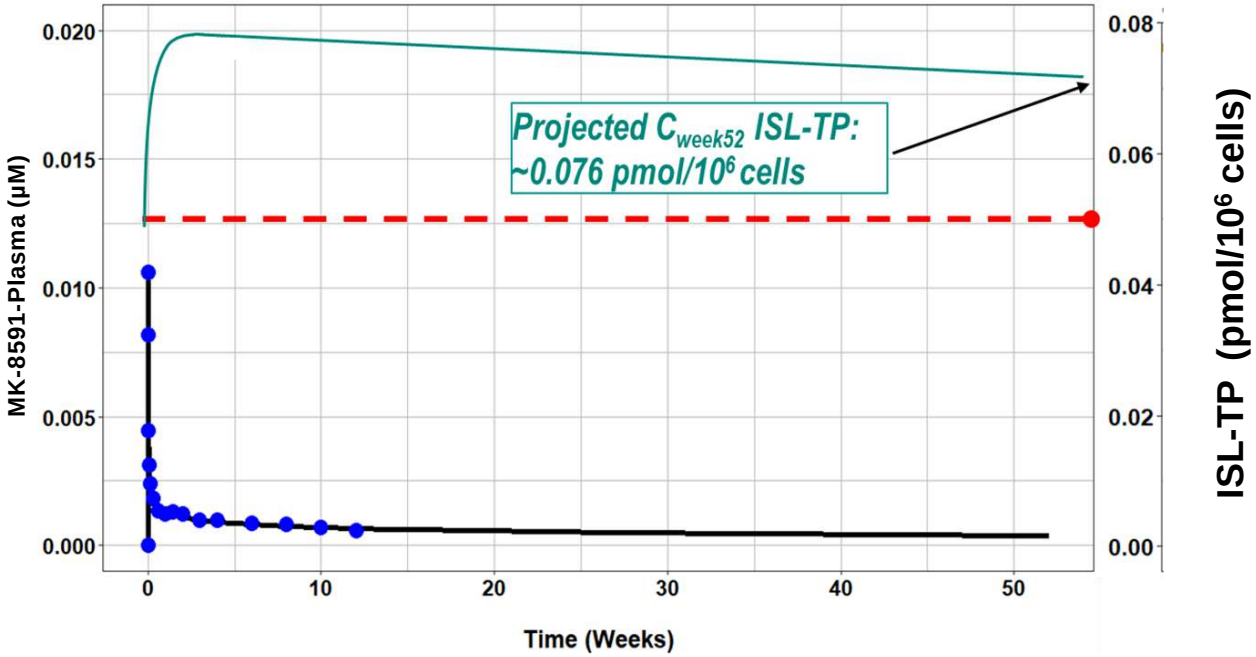
IMPOWER 022 will be done in collaboration with the Bill & Melinda Gates Foundation which intends to provide grant funding to the International Clinical Research Center (ICRC) at the University of Washington Department of Global Health who will be working together with MSD to conduct the trial

Islatravir Implants: Intracellular ISL-TP PK Threshold Maintained for Months

62 mg Implant

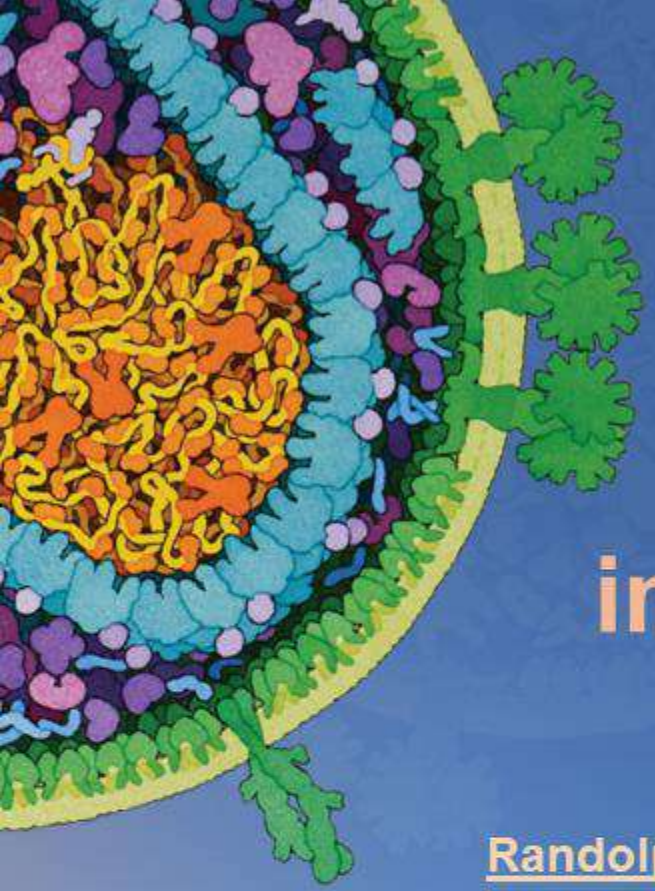


62 mg Implant: Simulations for 1 Year



- 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: **0.076 pmol/10^6 cells**
  - Projected time at which concentration falls below 0.05 pmol/10^6 cells: 68-70 weeks (~**16 months**)
- Implants in development also with TAF, cabotegravir

Barrett SE. et al. Antimicrob Agents Chemother 2018, Matthew R. IAS 2019



ORAL ABSTRACT

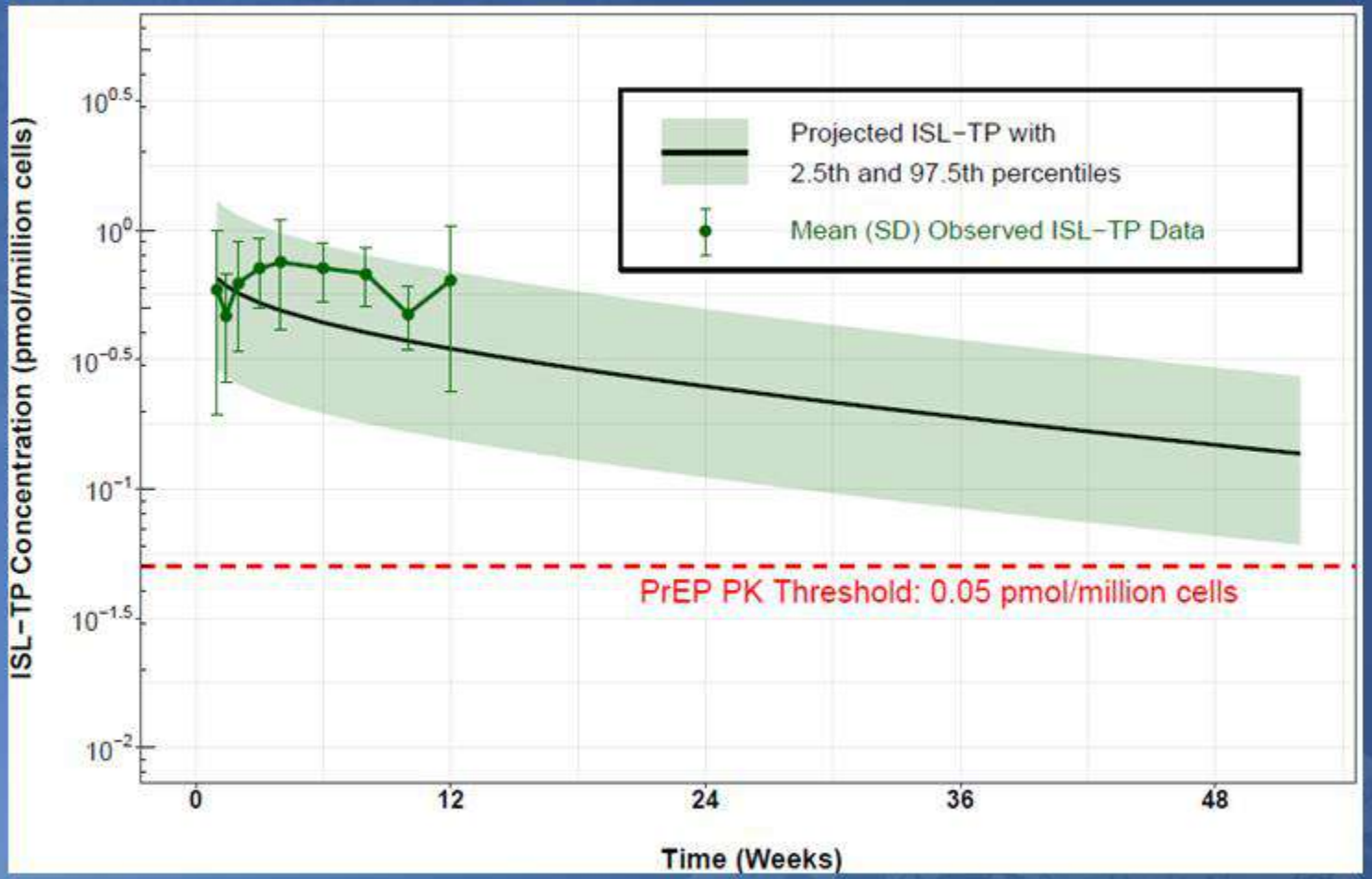
Next generation islatravir-eluting implants projected to provide yearly HIV-1 prophylaxis

Randolph P. Matthews[1], Xiaowei Zang[1], Stephanie E. Barrett[1], Adrian Goodey[1], Tycho Heimbach[1], Vanessa L. Weissler[1], Carlien Leyssens[1], Tom Reynders[1], Yang Liu[1], Sylvie Rottey[2], Robert Schwab[3], Ryan Vargo[1], Michael N. Robertson[1], S. Aubrey Stoch[1], and Marian Iwamoto[1]

[1]Merck & Co., Inc., Kenilworth, NJ, USA; [2]Drug Research Unit Ghent, Belgium; [3]Celerion, Lincoln, NE, USA

Disclosure: [1]These authors are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, which provided the funding for this research.

56 mg implant projected to lead to concentrations above threshold for 52 weeks



- 56 mg implant projected to release adequate ISL-TP (above the PK threshold) for almost all individuals for >52 weeks

Safety Summary
Generally Mild Local Tolerability Effects

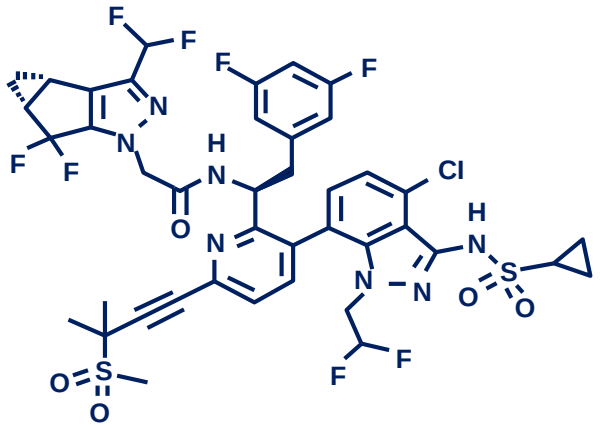
- Review of implant site adverse events (AEs) suggests that implants were generally well tolerated
  - 22/36 (61%) participants reported at least 1 implant site AE (not including hematoma)
  - All AEs were mild or moderate in severity
  - No serious AEs and no discontinuations due to an AE
  - Types of AEs observed consistent with those observed with other implants

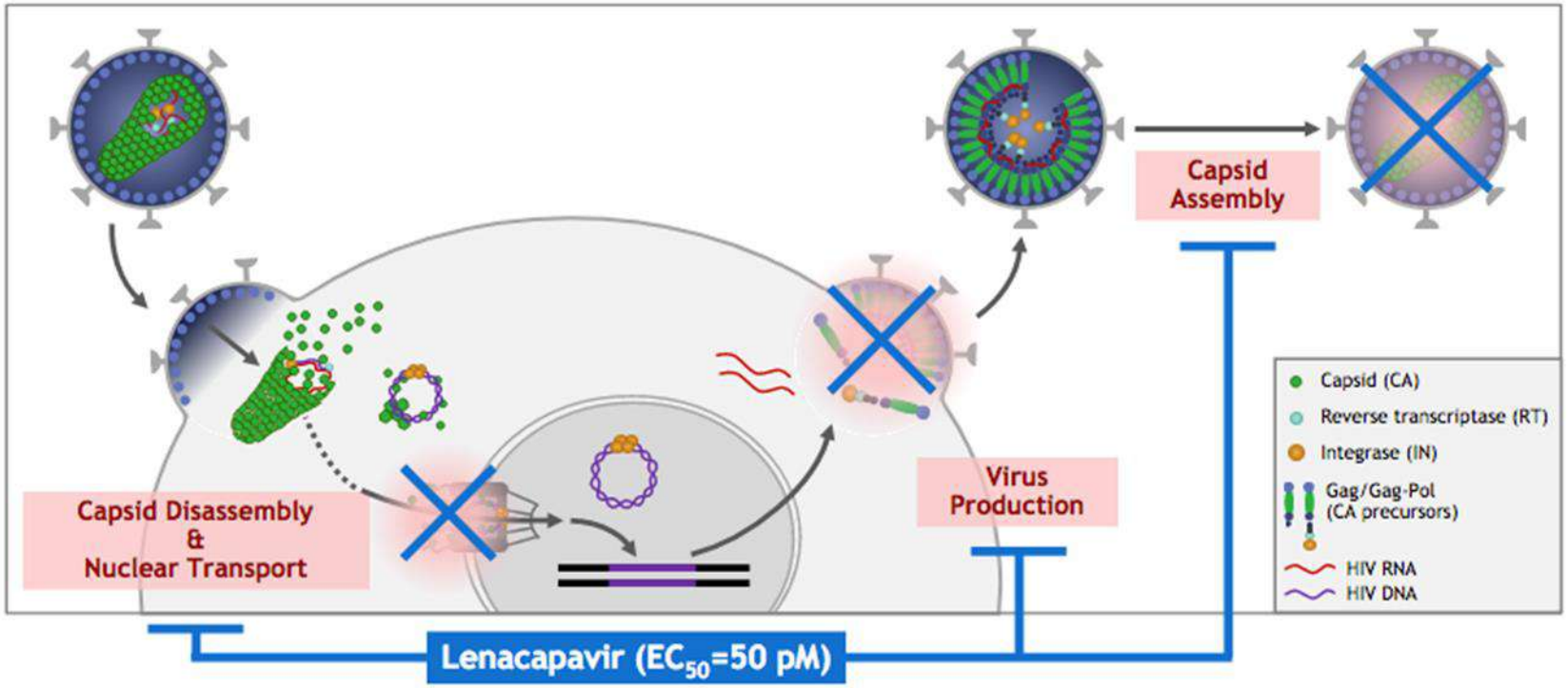
	Number (percent) of individuals reporting AE during study N=8 active/dose, 12 PBO (placebo; mod=moderate)			
	PBO	48 mg	52 mg	56 mg
TOTAL	6 (50)	6 (75)	4 (50)	6 (75)
Erythema	3 (25)	4 (50) 2/4 mod	2 (25)	4 (50) 1/4 mod
Tenderness/pain	4 (33)	2 (25)	4 (50)	4 (50)
Pruritis	3 (25)	5 (63) 1/5 mod	2 (25)	6 (75)
Induration	2 (17)	4 (50)	4 (50)	4 (50)

- No clear relationship between dose and AE frequency/severity
- Most common AE not related to implant was headache, with no clear dose relationship
- No effects on laboratory studies, ECGs, vital signs

Lenacapavir: First in Class Long-Acting HIV Capsid Inhibitor for Treatment and Prevention

Lenacapavir (GS-6207)



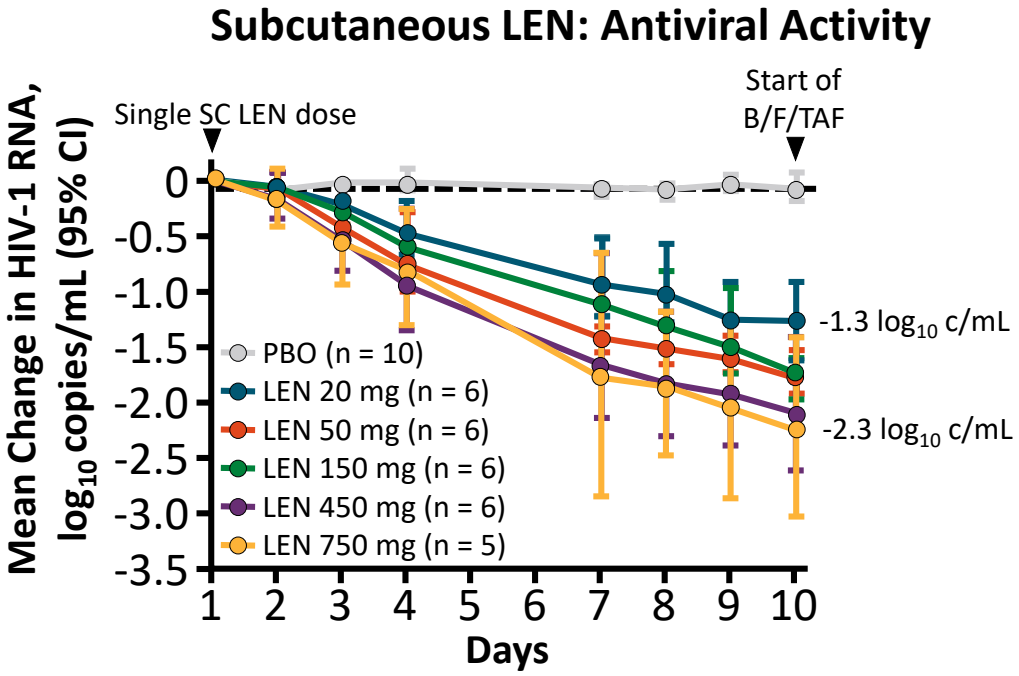


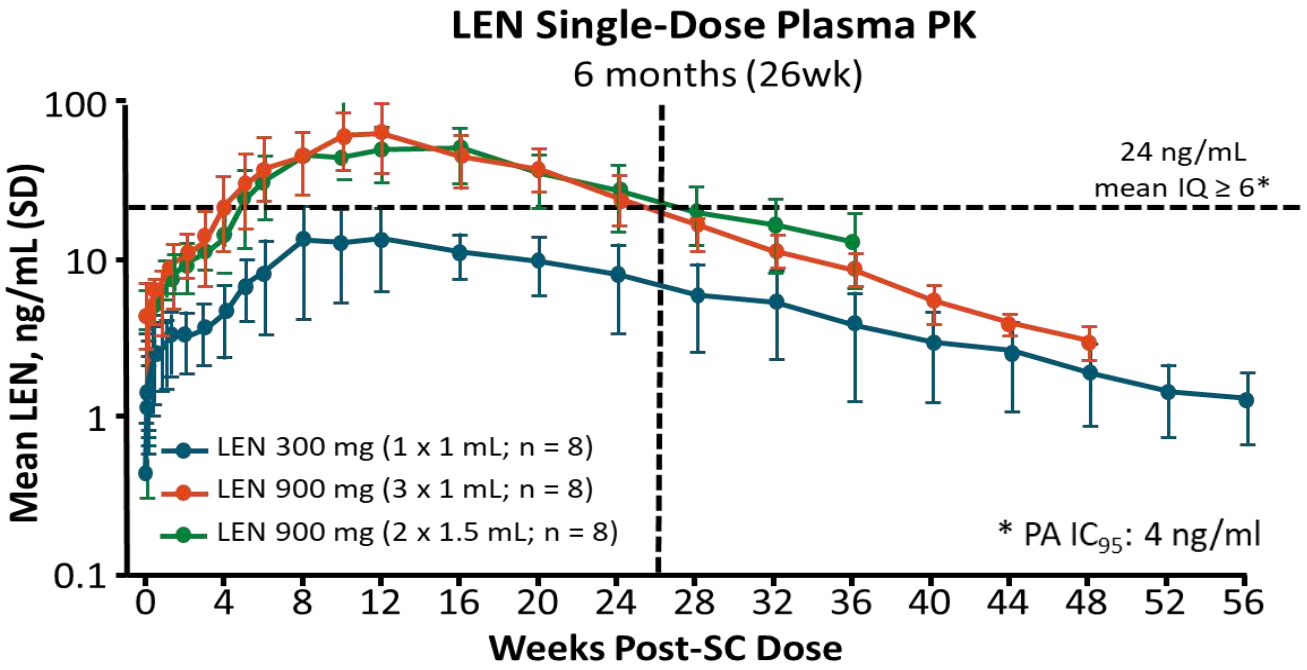
- Small molecule which disrupts the functions of HIV capsid protein
- High potency: Antiviral activity at very low doses (pM) and no cross-resistance with approved drugs
- Low in vivo systemic clearance
- Slow release kinetics from the subcutaneous injection site

Link JO et al. Nature 2020; 584: 614-8

Lenacapavir Antiviral Activity and Pharmacokinetics

- Potent antiviral activity with a single SC injection in HIV-infected untreated patients with maximum HIV-1 RNA reduction seen at mean concentrations ≥ 4.4 ng/mL (IQ > 1.1)
- Lenacapavir 900 mg every 6 months used in phase 3 treatment and prevention trials: half-life > 50 days with target concentrations sustained for > 24 weeks

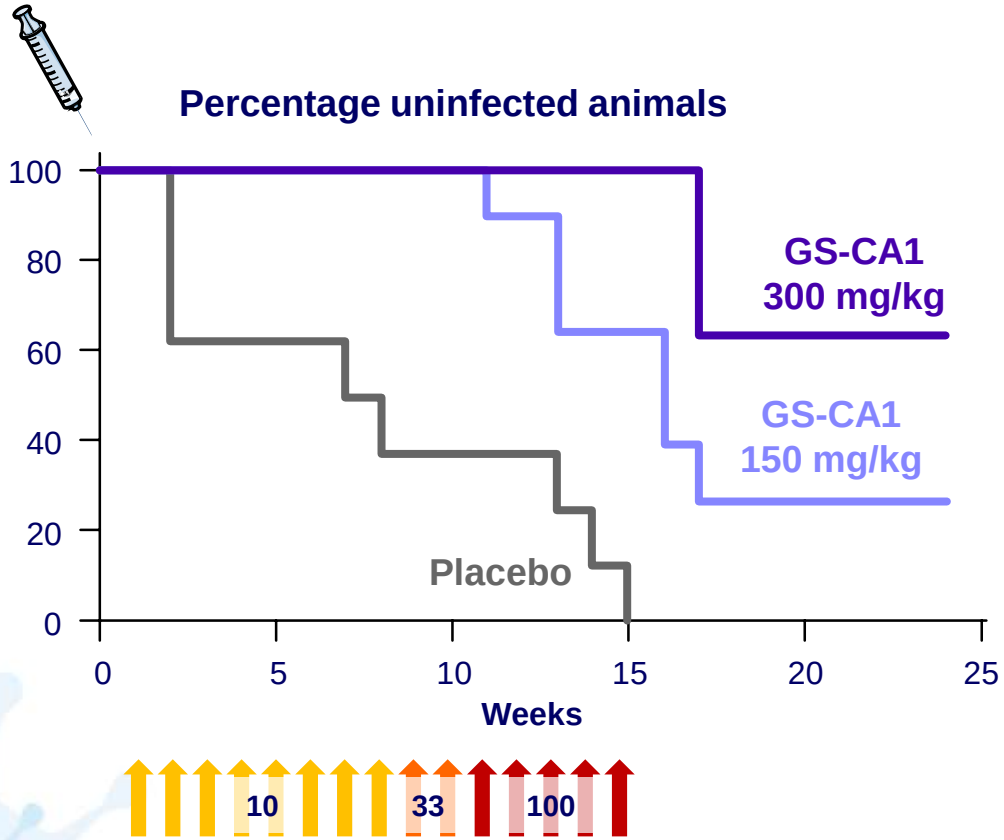




Link JO et al. Nature 2020, 584: 614-8

Begley R. et al AIDS 2020. Abstr PEB0265

Efficacy of a single subcutaneous injection of a Lenacapavir analog (GS-CA1) for PrEP



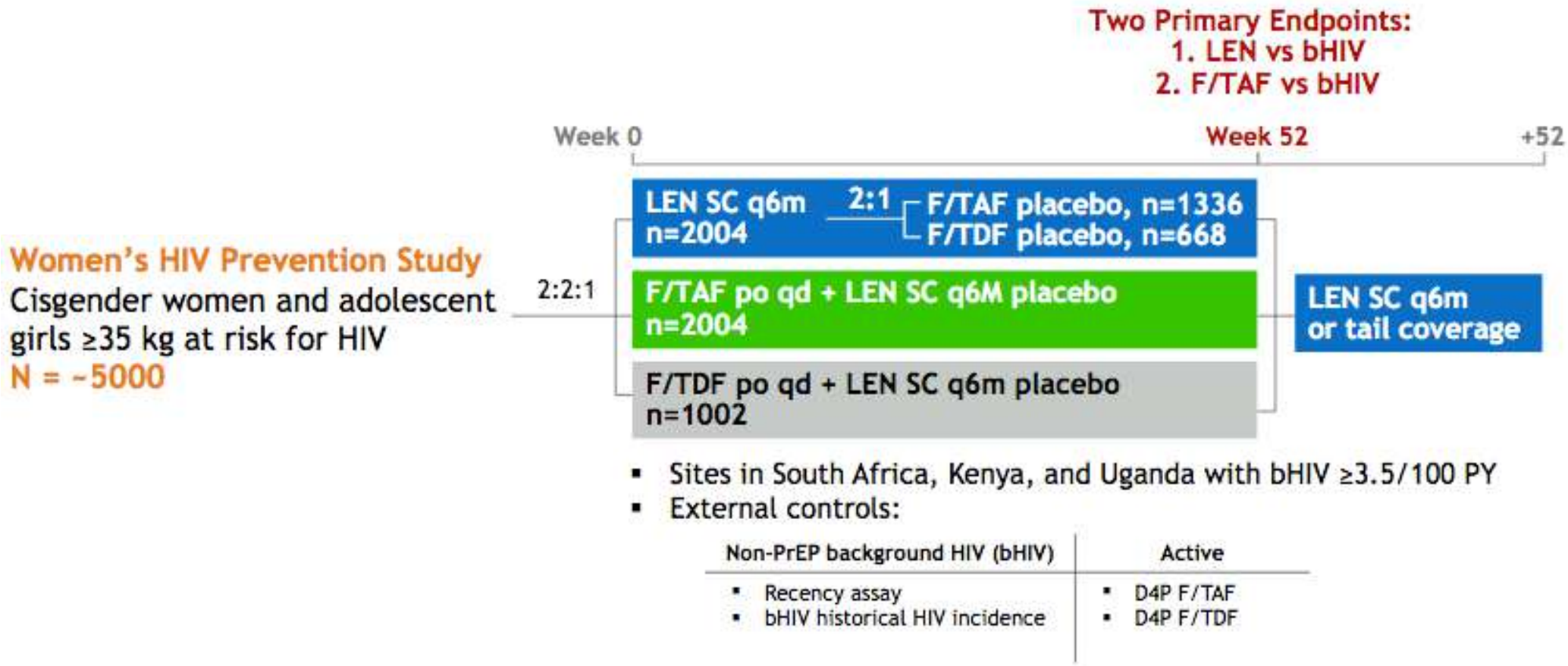
Weekly rectal challenges of SHIV.SF162P3
(10-100 $TCID_{50}$)

	N Protected	Median Time to Infection (weeks)	Hazard ratio	p
GS-CA1 300 mg/kg	5 / 8	Not reached	0.038	0.0002
GS-CA1 150 mg/kg	2 / 8	16	0.141	0.0061
Placebo	0 / 8	7,5	1	

p using a Cox model

Bekerman E et al., CROI 2021, Abs. 717

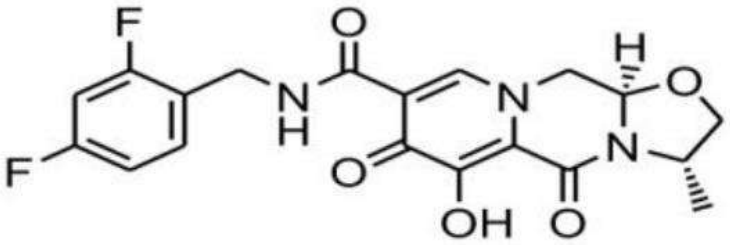
Lenacapavir Prevention Trial in Women



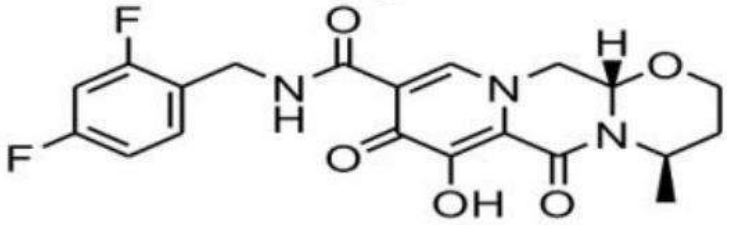
Another trial planned in MSM and TGW vs daily TDF/FTC in 3,000 in USA ans South Africa

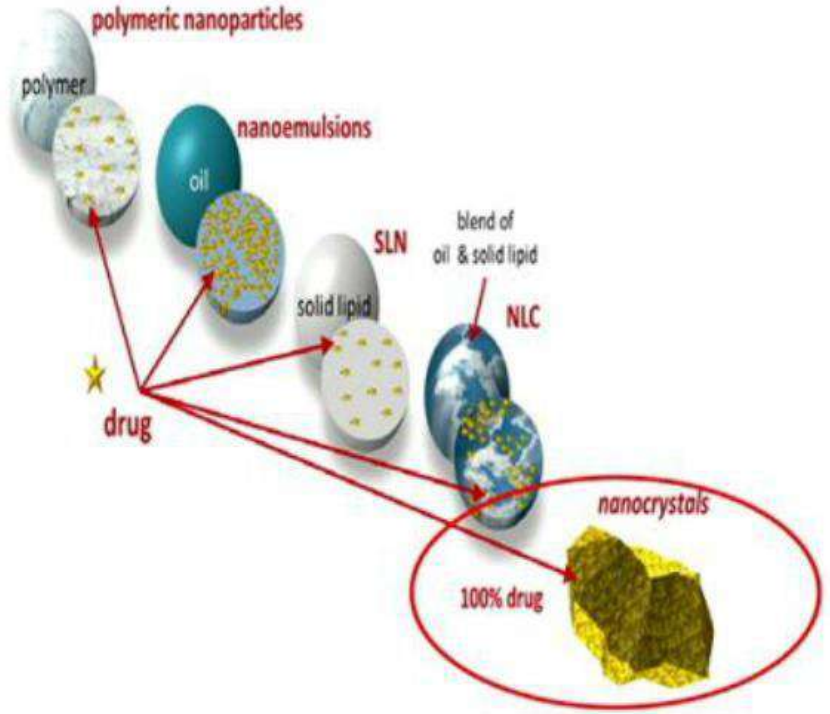
Cabotegravir
GSK126744 Long Acting Integrase Inhibitor

GSK1265744
(GSK744)



Dolutegravir





Favorable attributes for PrEP:

- High genetic barrier to resistance
- PK profile: half life of 21-50 days
- Once-daily oral
- 1-2 months injectable dosing using nanosuspension formulation

Muller *et al*, European Journal of Pharmaceutics and Biopharaceutics,2011
Spreen, 7th IAS, 2013; Min, ICAAC, 2009
Taoda, International Congress on Drug Therapy in HIV Infection, 2012

PrEP with LA Injectable Cabotegravir Highly Effective for Young Women

Study design

HIV, pregnancy testing and safety assessments at each product administration visit; additional post injection safety visits
Real-world adherence counselling support aligned with national guidelines

Delany-Moretllwe S. et al. HIV R4P virtual Jan 2021 LB 1479

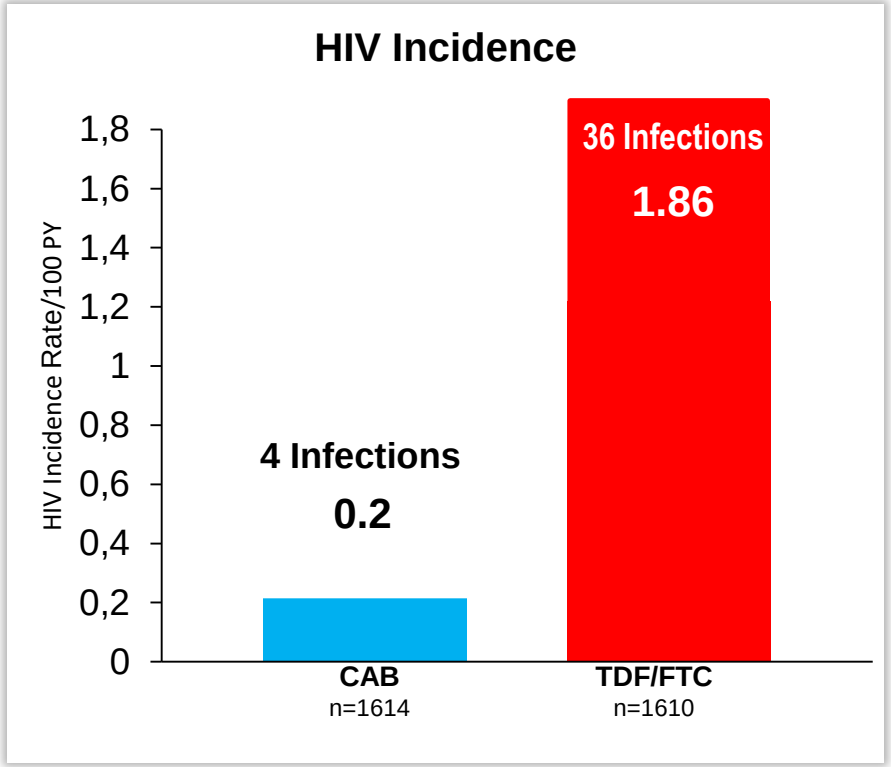
PrEP with LA Injectable Cabotegravir Highly Effective for Women

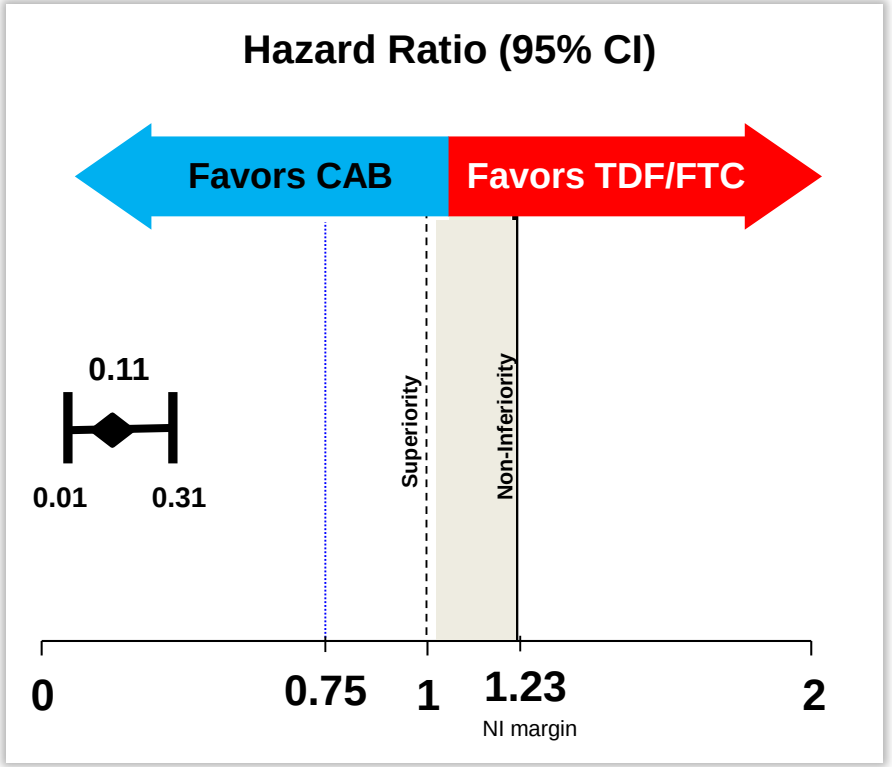
HPTN 084 Long-acting Injectable For the Epidemic

HIV R4P HIV RESEARCH FOR PREVENTION CAPE TOWN, SOUTH AFRICA · 17–21 JANUARY 2021

38 HIV infections in 3223 women, median age 26 years

Botswana, Eswatini, Kenya, Malawi, Uganda, Zimbabwe



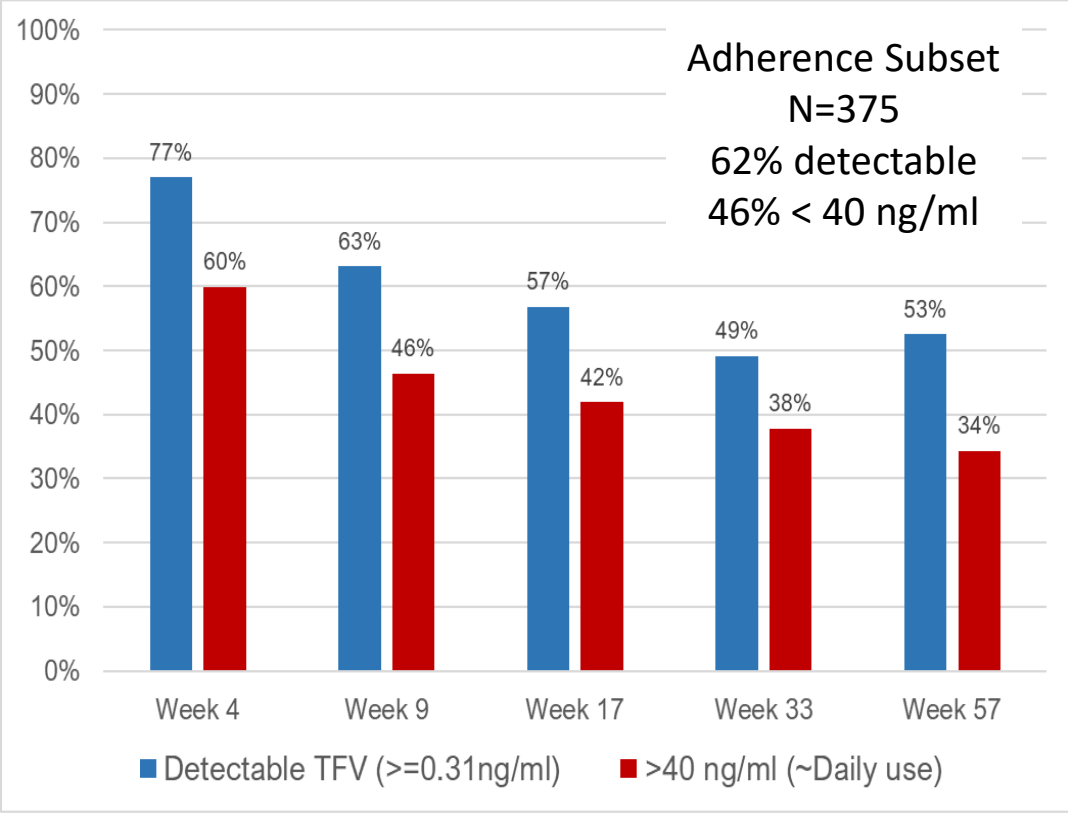


CI, confidence interval

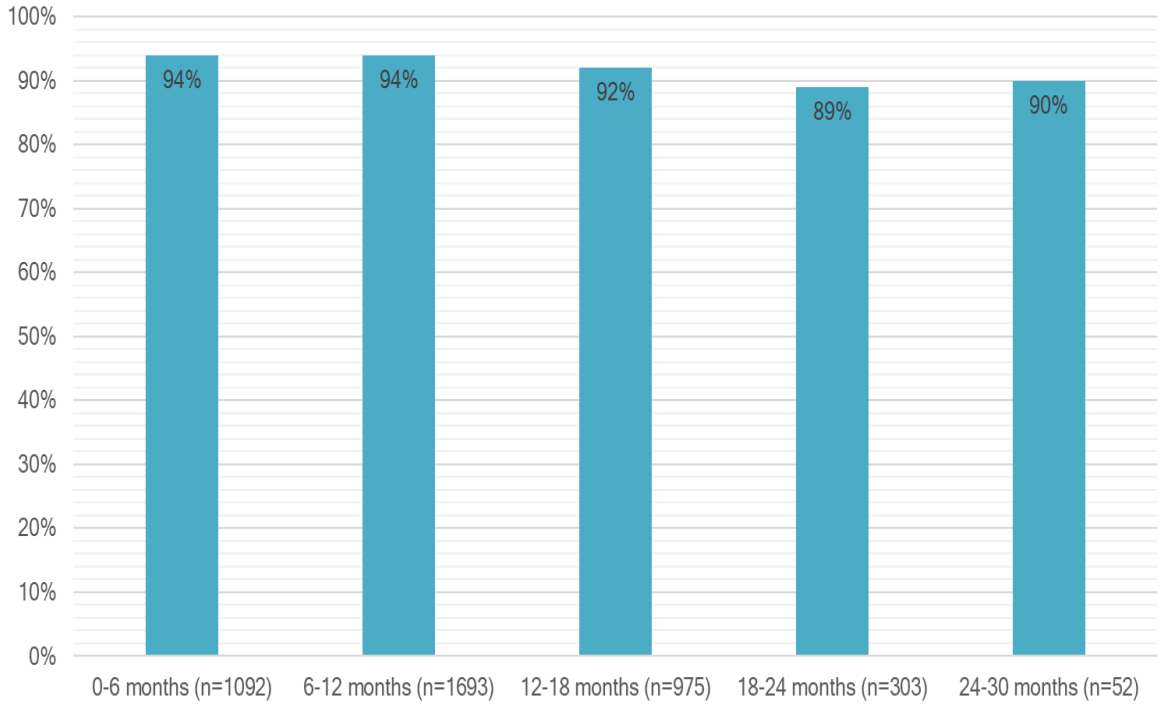
Delany-Moretllwe S. et al. HIV R4P virtual Jan 2021 LB 1479

Adherence to Pill and Injections

TFV Plasma Concentrations



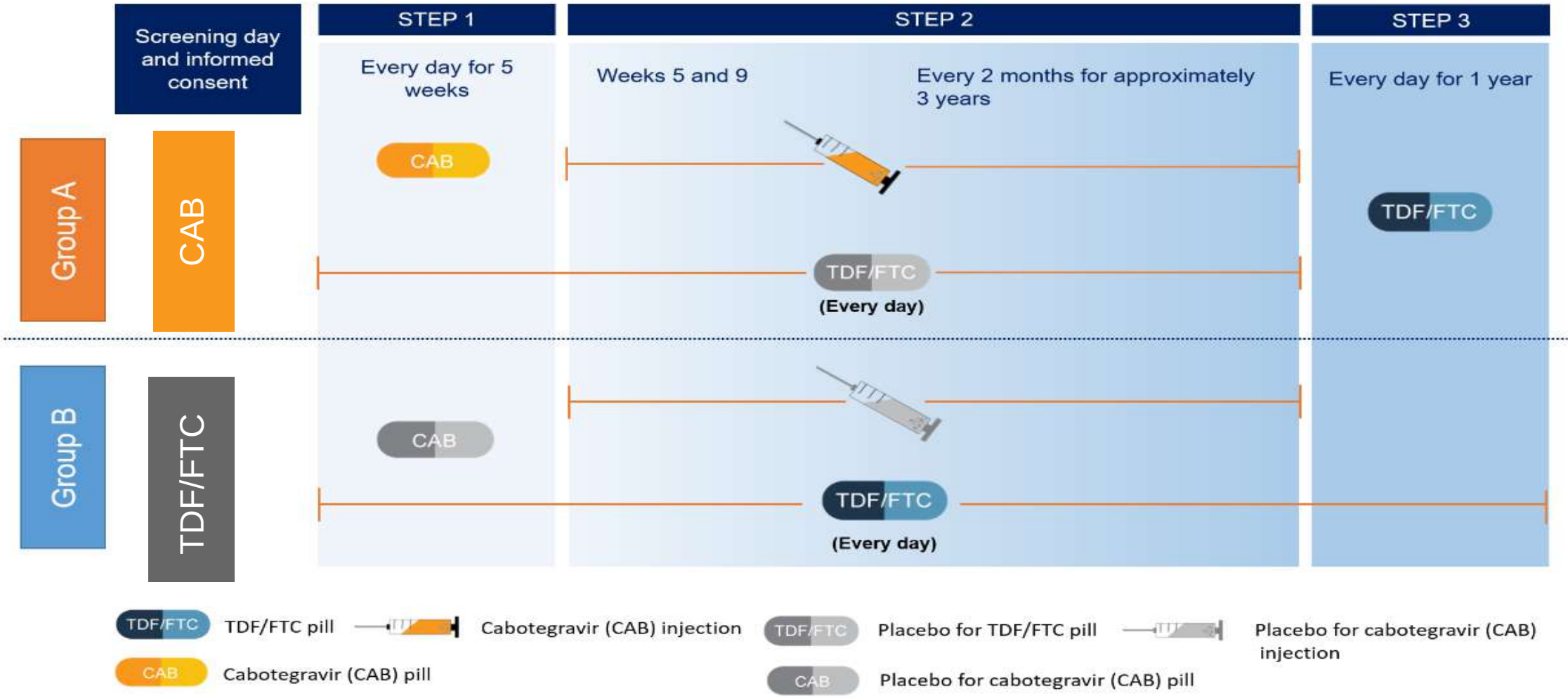
Cabotegravir Injections Coverage



- Both products safe and well tolerated
- No discontinuation due to injection site reaction
- Similar pregnancy outcomes

Delany-Moretllwe S. et al. HIV R4P virtual Jan 2021 LB 1479

Cabotegravir IM vs Oral TDF/FTC for PrEP in MSM and TGW

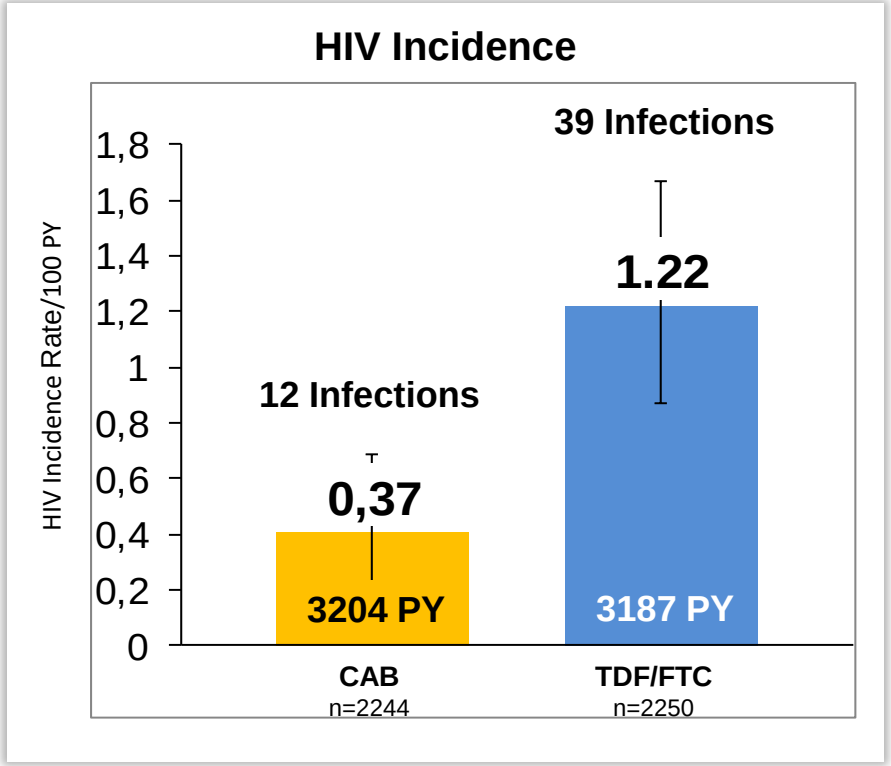


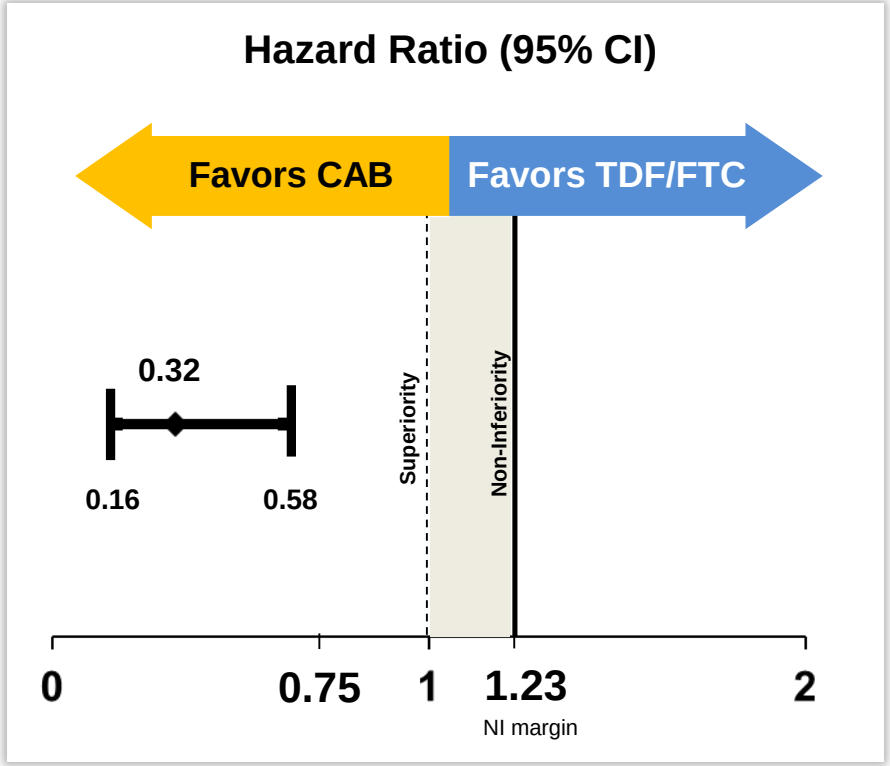
Landovitz RJ et al. AIDS 2020, #OAXLB0101

PrEP with LA Injectable Cabotegravir Highly Effective for MSM and TGW

52 HIV infections in 6389 PY of follow-up

1.4 (IQR 0.8-1.9) years median per-participant follow-up

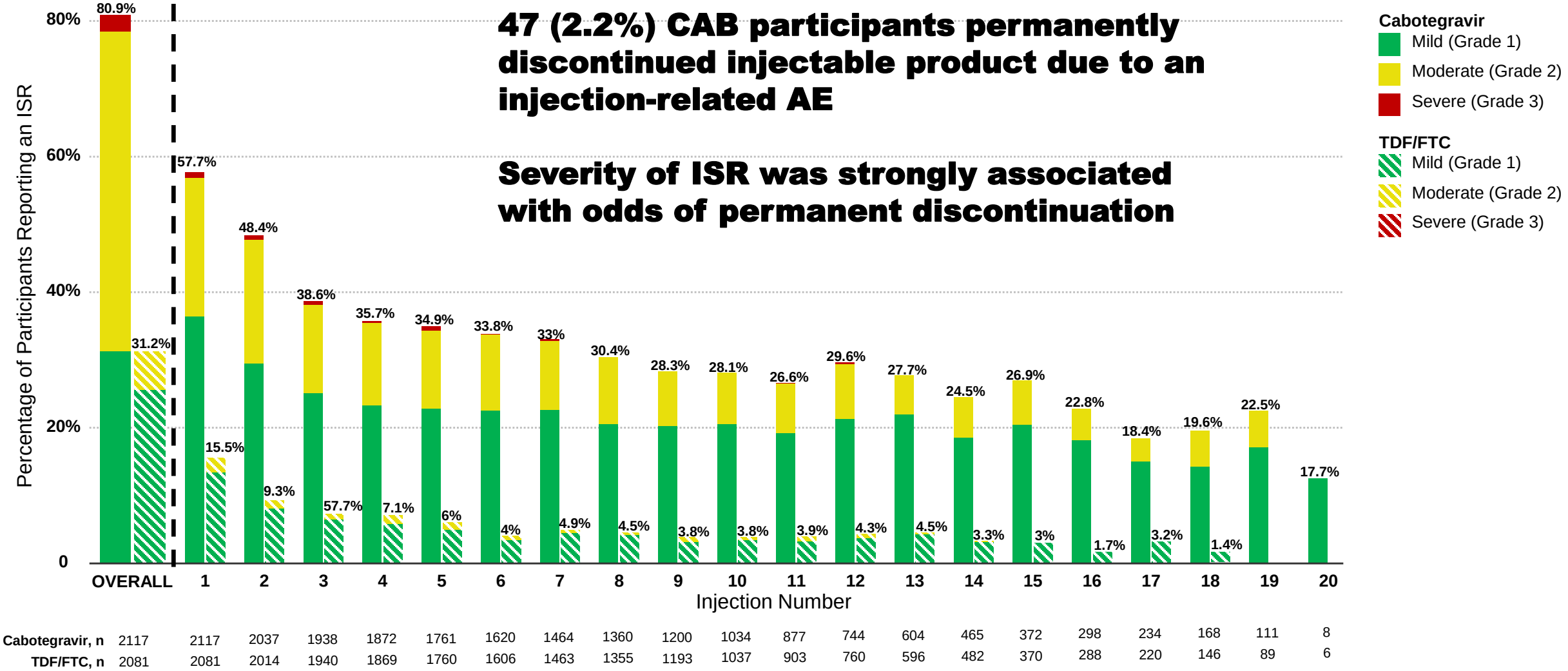




CI, confidence interval

Landovitz RJ et al. AIDS 2020, #OAXLB0101; CROI 2021 LB

Injection Site Reactions

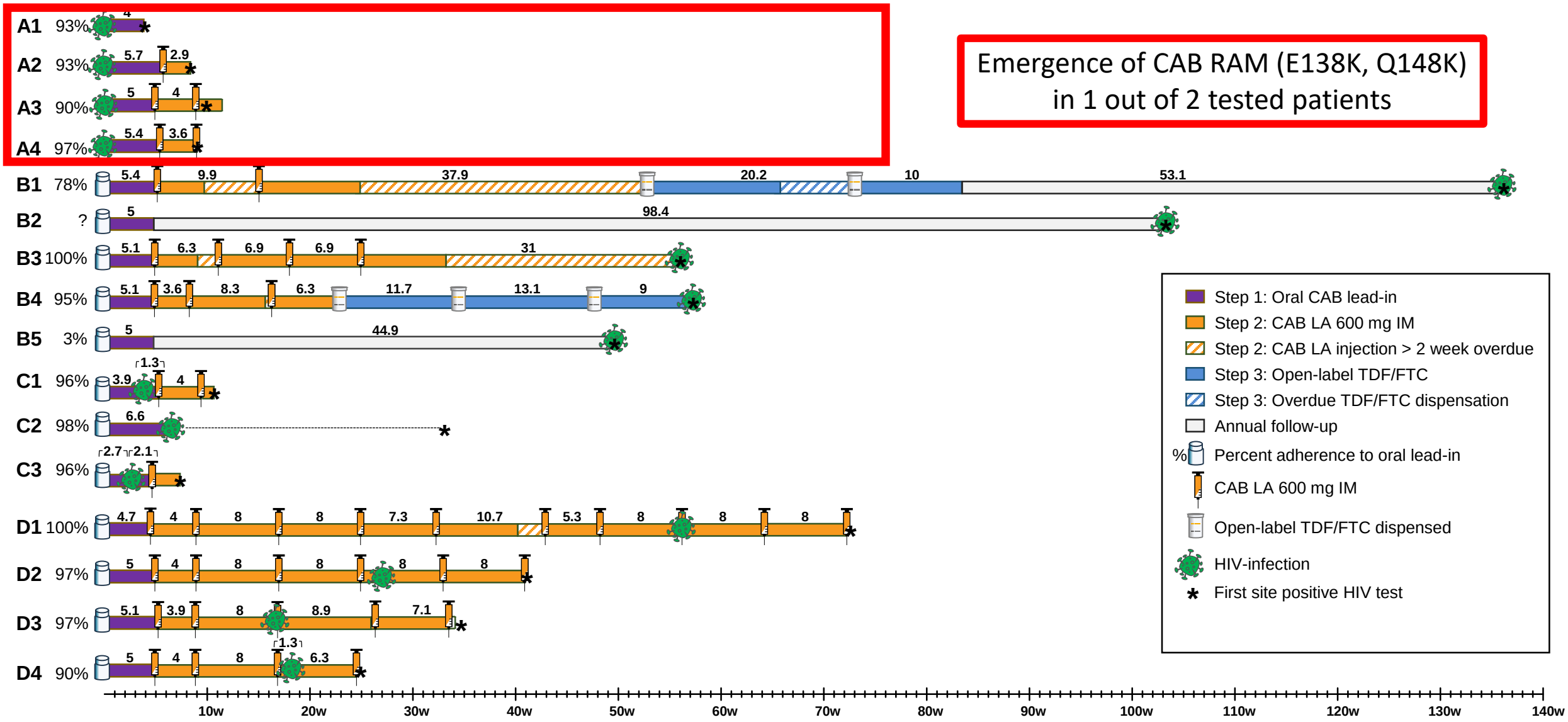


Landovitz RJ et al. AIDS 2020, #OAXLB01

virtual CROI2021
Conference on Retroviruses and Opportunistic Infections
March 6-10, 2021

Prevalent and Incident HIV Infections with Cabotegravir

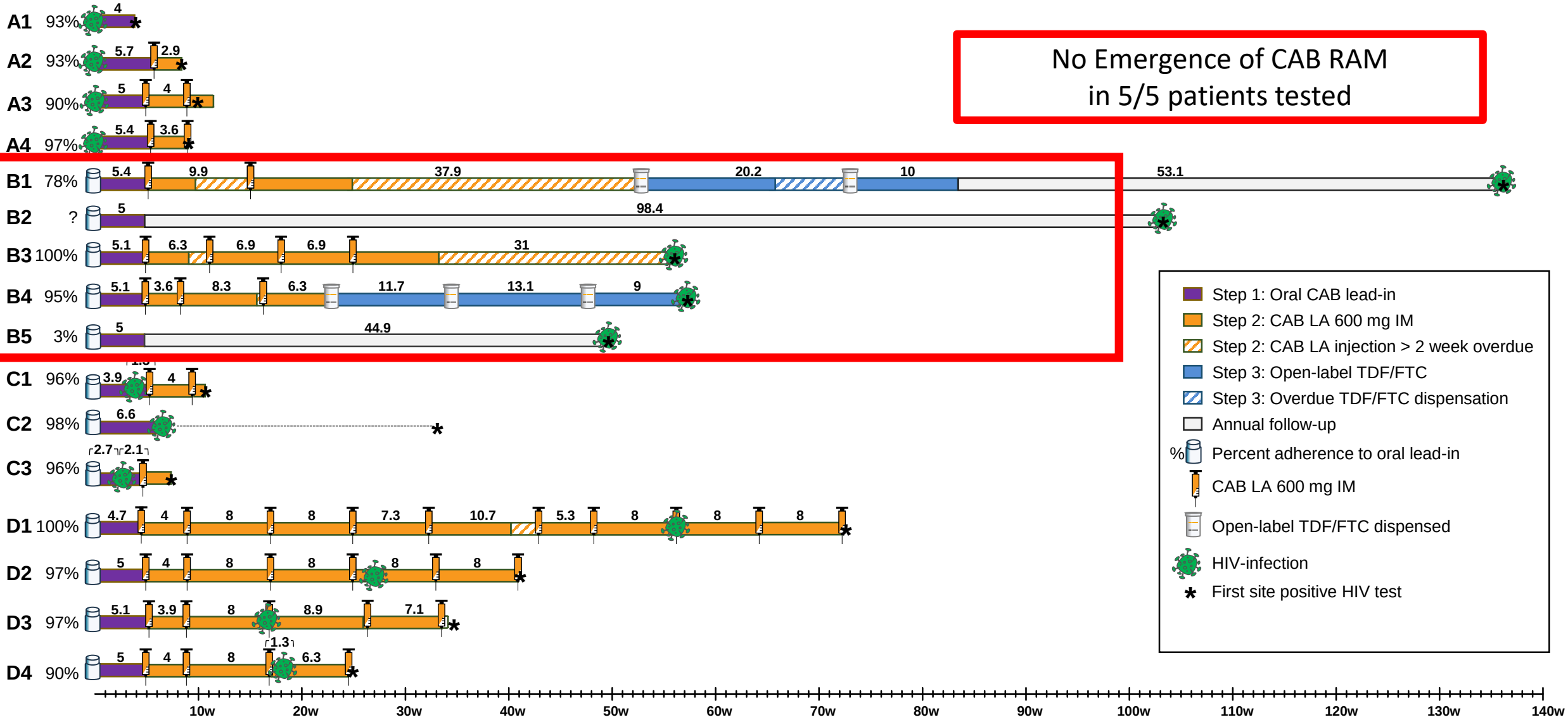
Emergence of CAB RAM (E138K, Q148K) in 1 out of 2 tested patients



virtual CROI2021
Conference on Retroviruses and Opportunistic Infections
March 6-10, 2021

Prevalent and Incident HIV Infections with Cabotegravir

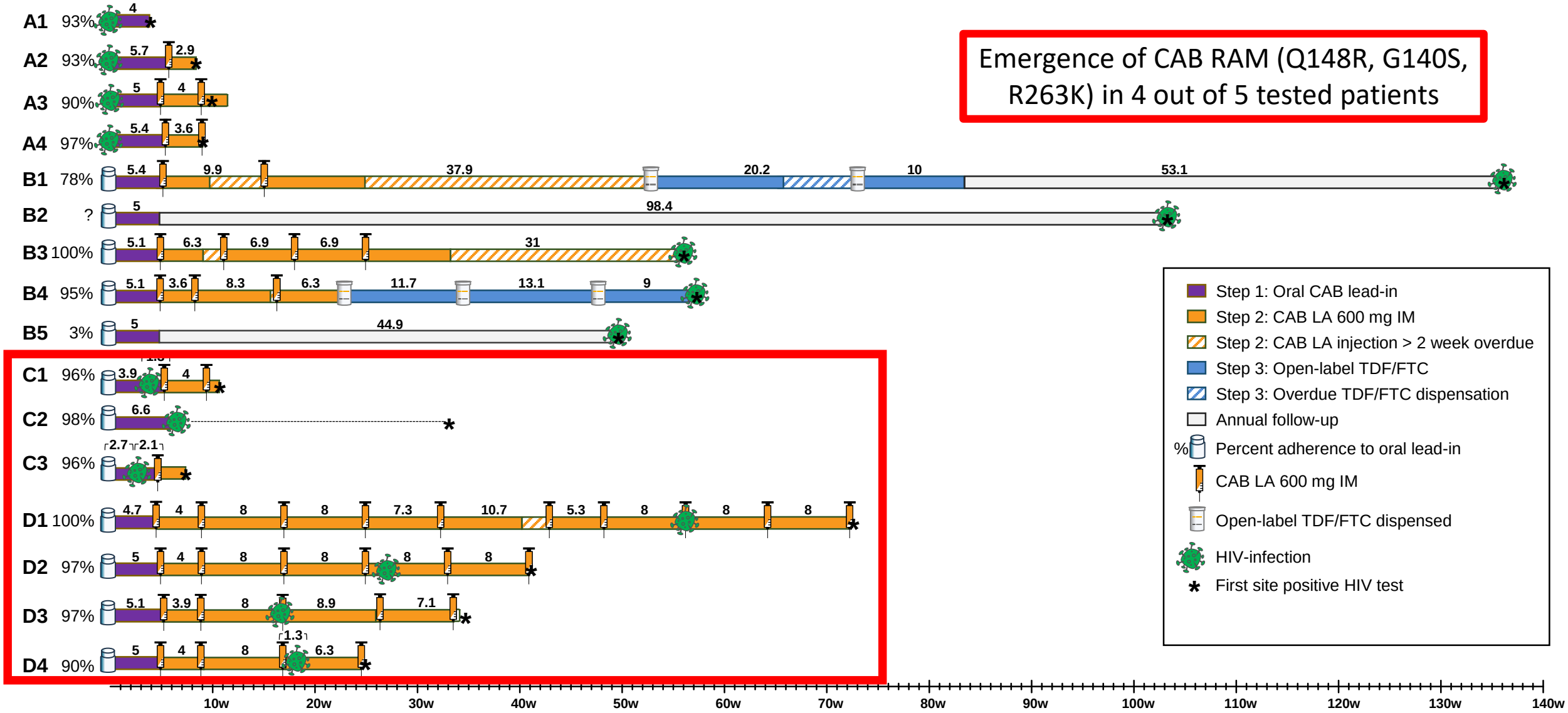
No Emergence of CAB RAM
in 5/5 patients tested



virtual CROI2021
Conference on Retroviruses and Opportunistic Infections
March 6-10, 2021

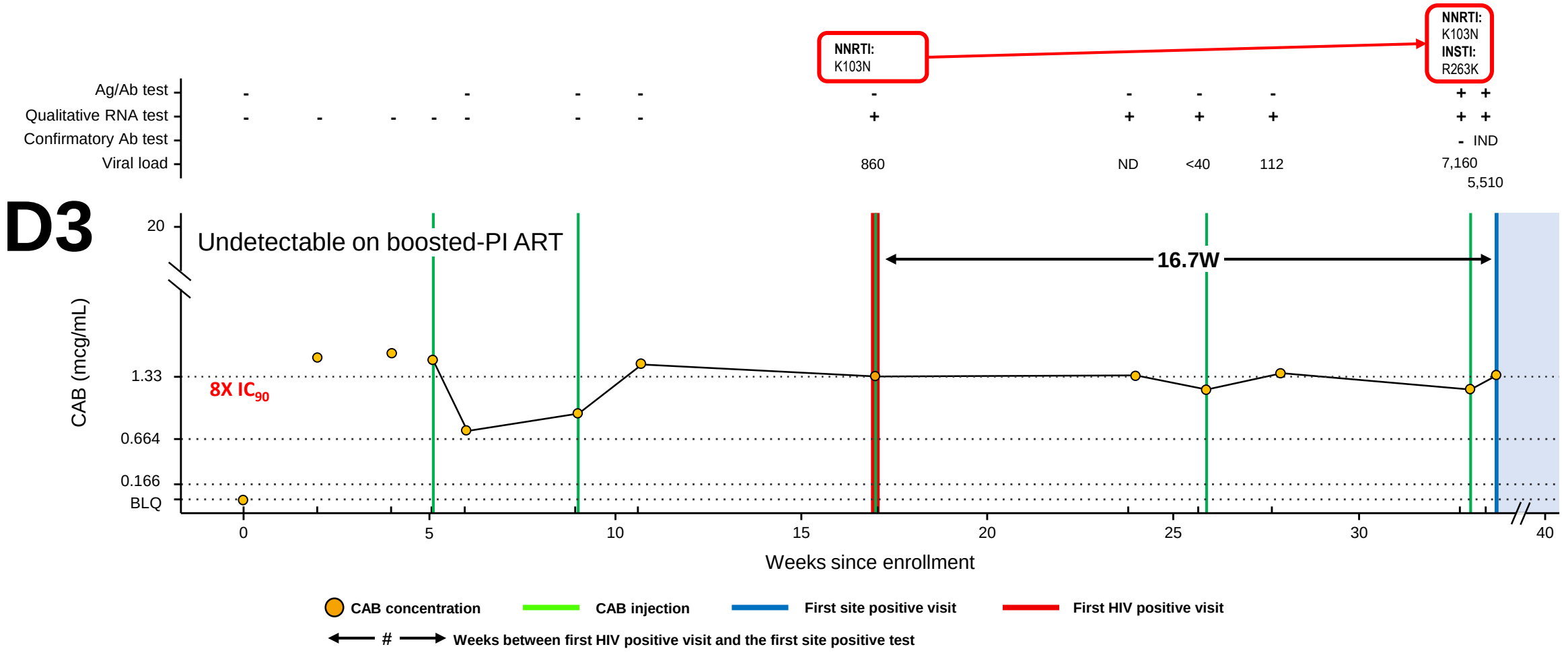
Prevalent and Incident HIV Infections with Cabotegravir

Emergence of CAB RAM (Q148R, G140S, R263K) in 4 out of 5 tested patients



virtual CROI2021
Conference on Retroviruses and Opportunistic Infections
March 6-10, 2021

Delayed Diagnosis of Breakthrough HIV-Infection with Cabotegravir



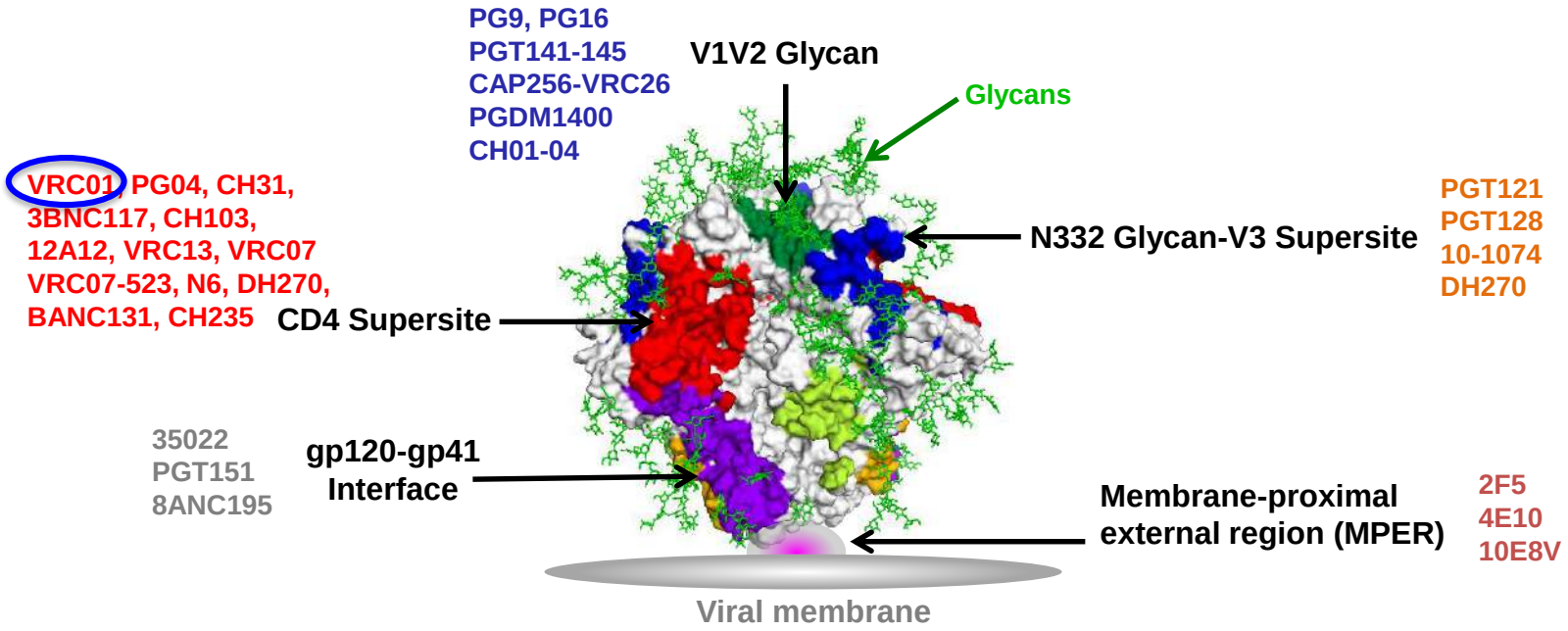
The shaded area represents time on ART.

Marzinke M, Grinsztejn B, Landovitz RJ et al. CROI 2021 LB

Limitations of Cabotegravir LA for the Prevention of HIV

- Burden of two-monthly injections
- Not self-administered
- Lead-in phase and tail coverage
- Unknown time to protection
- Unknown forgiveness
- Injection site reactions
- Emergence of INSTI-R with potential cross-resistance to DTG
- **Breakthrough infections despite correct use with delayed diagnosis**

Broadly Neutralizing mAbs (bNabs) in Development for Treatment and Prevention of HIV-Infection



VRCO1 (IgG1) targets the conserved region of the CD4-binding site of the HIV-1 envelope glycoprotein with broad in vitro neutralization capacity against all major circulating HIV-1 sub-types

VRCO1 can prevent HIV/SHIV transmission in animal models

Wu X. et al. Science 2010; Mascola JR. Et al. Nat Medicine 2000; Gautam R. et al. Nature 2016.

The AMP Studies: Phase 2b Proof of Concept Trials to Test the Efficacy of VRC01 Antibody to Prevent HIV Acquisition

Two harmonized protocols:

- HVTN 704/HPTN 085 (~2,700 MSM and TG in the Americas & Europe)
- HVTN 703/HPTN 081 (~1,900 Women in sub-Saharan Africa)
- Placebo controlled trial of VRC01 mAb (IV), given on q2 month schedule
- Both trials opened in April/May 2016

Study Schema for The AMP STUDY Studies

Regimen	MSM & TG in the Americas	Women in SSA	Total
VRC01 10 mg/kg	899	642	1541
VRC01 30 mg/kg	897	645	1542
Placebo	903	637	1540
Total	2699	1924	4623

10 infusions total
&
Infusions every 8 weeks

Study duration:
~22 months

HIV RESEARCH FOR PREVENTION
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Prevention Efficacy Declines by HIV-1 in vitro IC_{80}

HIV IC_{80} (μg/ml)	Regimen	Nb HIV-infections	Incidence /100 PY	Efficacy (95% CI)
< 1	**Placebo**	**19**	**0.86**	**75.4**
	VRCO1 pooled	**9**	**0.26**	(45;89)
1-3	**Placebo**	**10**	**0.45**	**4.2**
	VRCO1 pooled	**19**	**0.43**	(-108;56)
> 3	**Placebo**	**35**	**1.59**	**3.3**
	VRCO1 pooled	**70**	**1.58**	(-48;37)

Overall non significant reduction in HIV-1 incidence with VRCO1: 8.8% in Women, 26.6% in MSM (P> 0.10)

Corey L. et al. N Engl J Med. 2021 Mar 18;384(11):1003-1014

HIV VACCINE TRIALS NETWORK

AMP Studies Summary

HPTN HIV Prevention Trials Network

- Proof of concept that long-term bNabs can prevent HIV-acquisition
- In vitro HIV-1 susceptibility to VRC01 influences preventive efficacy (only 30% of the circulating HIV-1 strains exhibited $IC_{80} < 1$ μg/ml)
- A neutralization titer or Ab concentration in serum established as a biomarker of protection
- Viruses from VRC01 cases more resistant to VRC01 than viruses from placebo cases (> 2-fold greater IC_{80}): immunologic pressure
- Multiple bNabs will be needed for optimal prevention

Corey L et al. N Engl J Med. 2021 Mar 18;384(11):1003-1014

AVAC
Global Advocacy for HIV Prevention

Broadly Neutralizing Antibody Combinations in Development

bNAb Cocktails: Two or more antibodies in a regimen

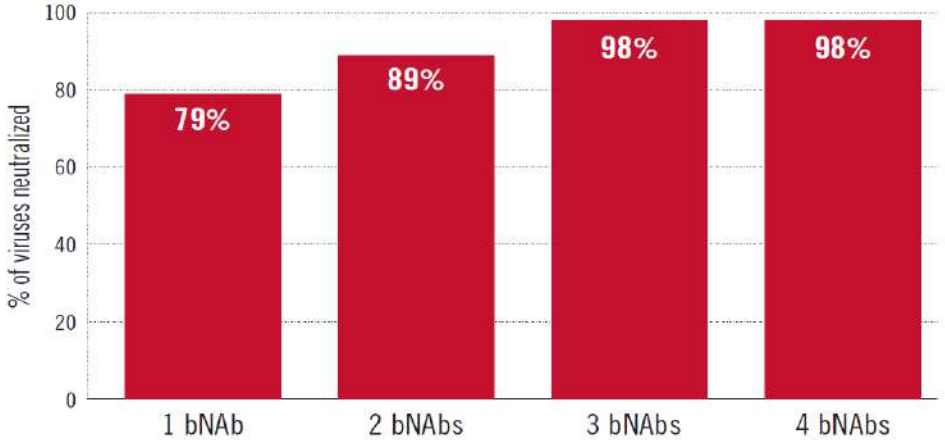
Regimen	Status	Route	Research Institution	Trial Name
	Phase I, Completed	IV	Rockefeller University	YCO-0899
	Phase I, Ongoing	IV, SC	Rockefeller University	YCO-0971
	Phase I/2, Ongoing	IV, SC	IAVI, Rockefeller University, University of Washington	IAVI C100
	Phase I, Completed Phase I/2a, Ongoing	IV	BIDMC, IAVI, NIAID	IAVI T002 IAVI T003
	Phase I, Ongoing	IV	NIAID	HVTN 130/ HPTN 089
	Phase I, Ongoing	IV, SC	NIAID	HVTN 136/ HPTN 092
	Phase I, Ongoing	SC	NIAID	HVTN 138/ HPTN 098
	Phase I, Ongoing	IV, SC	CAPRISA, NIAID	CAPRISA 012B

▭ Trial includes multiple arms, testing up to 3-bNAb combinations

Multispecific: Parts of two or more antibodies on a single antibody

Regimen	Status	Route	Research Institution	Trial Name
SAR441236	Phase I, Planned	IV	Sanofi, NIAID	HVTN 129/ HPTN 088
	Phase I, Ongoing	IV, SC	ADARC	AAAS1239

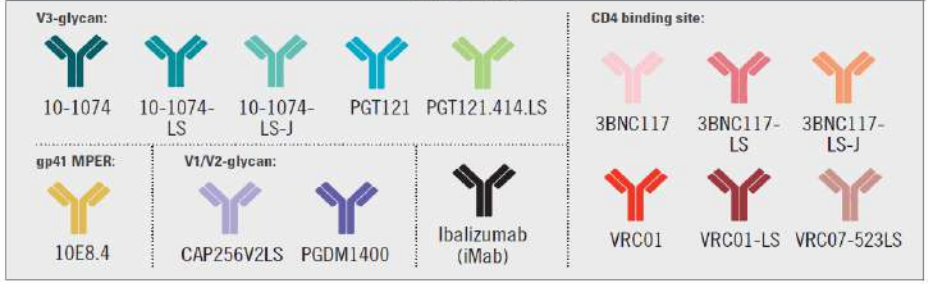
Combining bNAbs to broaden neutralization*



Different antibodies have different neutralizing activities. Modeling and preclinical studies suggest that combining bNAbs may lead to broader neutralization compared to giving bNAbs alone, and multispecific antibodies might perform better than combinations. Clinical trials will validate whether these differences are seen in humans, and guide selection of best antibodies and combinations types.

*Data: Kong et al., 2015

bNAb Key



ADARC: Aaron Diamond AIDS Research Center; **BIDMC**: Beth Israel Deaconess Medical Center; **CAPRISA**: Centre for the AIDS Programme of Research in South Africa; **IAVI**: International AIDS Vaccine Initiative; **NIAID**: National Institute of Allergy and Infectious Diseases; **VRC**: Vaccine Research Center of NIAID; **IV**: Intravenous; **SC**: Subcutaneous

Ideal PrEP Regimen

- **Effectiveness**
  - 100% effectiveness when taken as recommended
  - Work for all populations (MSM, heterosexual men and women, IVDU, adolescents, pregnancy)
- **Adherence**
  - Simple with high forgiveness: long-acting formulations, clear guidance on how to start/stop PrEP
  - Simple assessment of adherence (DBS for TFV-DP)
- **Breakthrough HIV-infection**
  - Rapid and simple diagnosis of breakthrough HIV-infections
  - Low risk for resistance and cross-resistance within class to avoid compromising treatment options
- **Safety and Tolerability**: Almost perfect without need for safety monitoring
- **Implementation**
  - Easy to use and self-administered
  - Affordable cost
  - Multipurpose tools: HIV, contraception, STIs

Acknowledgments

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