

Pre-Exposure Prophylaxis (PrEP) for HIV Prevention: HPTN 083 Injectable Cabotegravir for PrEP

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9/9/2020

Disclosures

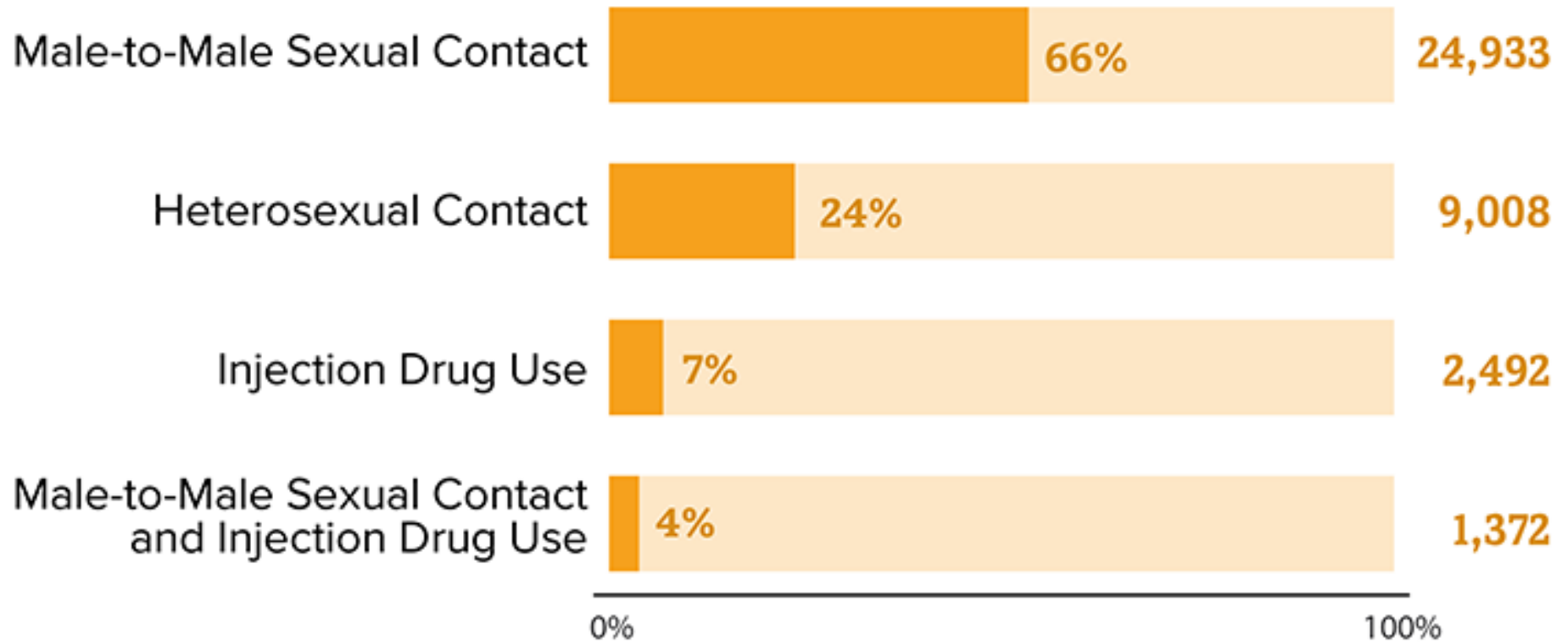
- I will discuss research studies on agents that are not FDA approved
- We are NIH funded to conduct clinical trials research on HIV prevention and treatment
- Most of these slides are from Dr. Raphael Landowitz' talk at IAS this past summer

HIV in the U.S.

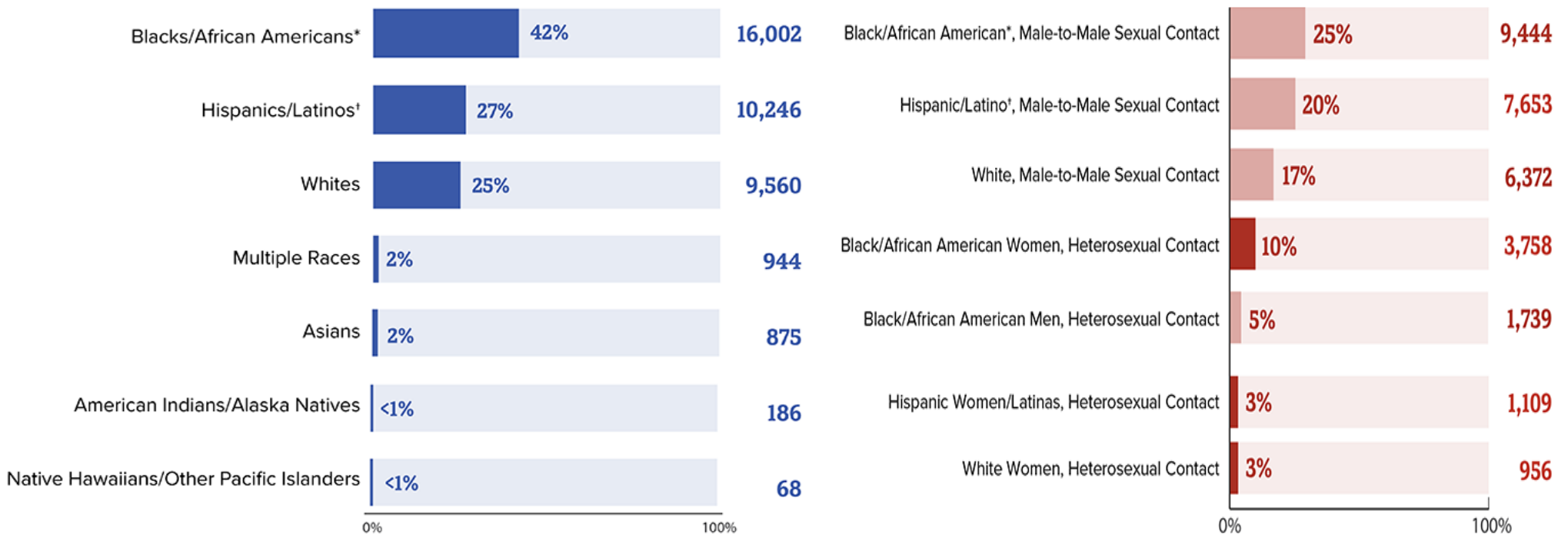
- 1.2 million people currently living with HIV
 - 38,500 new cases per year
- Men who have sex with men (MSM)
 - 60% of new HIV infections in US
- 1 in 6 people unaware of their infection



HIV infections by risk factor



HIV infections by race and risk factor



HIV transmission risk

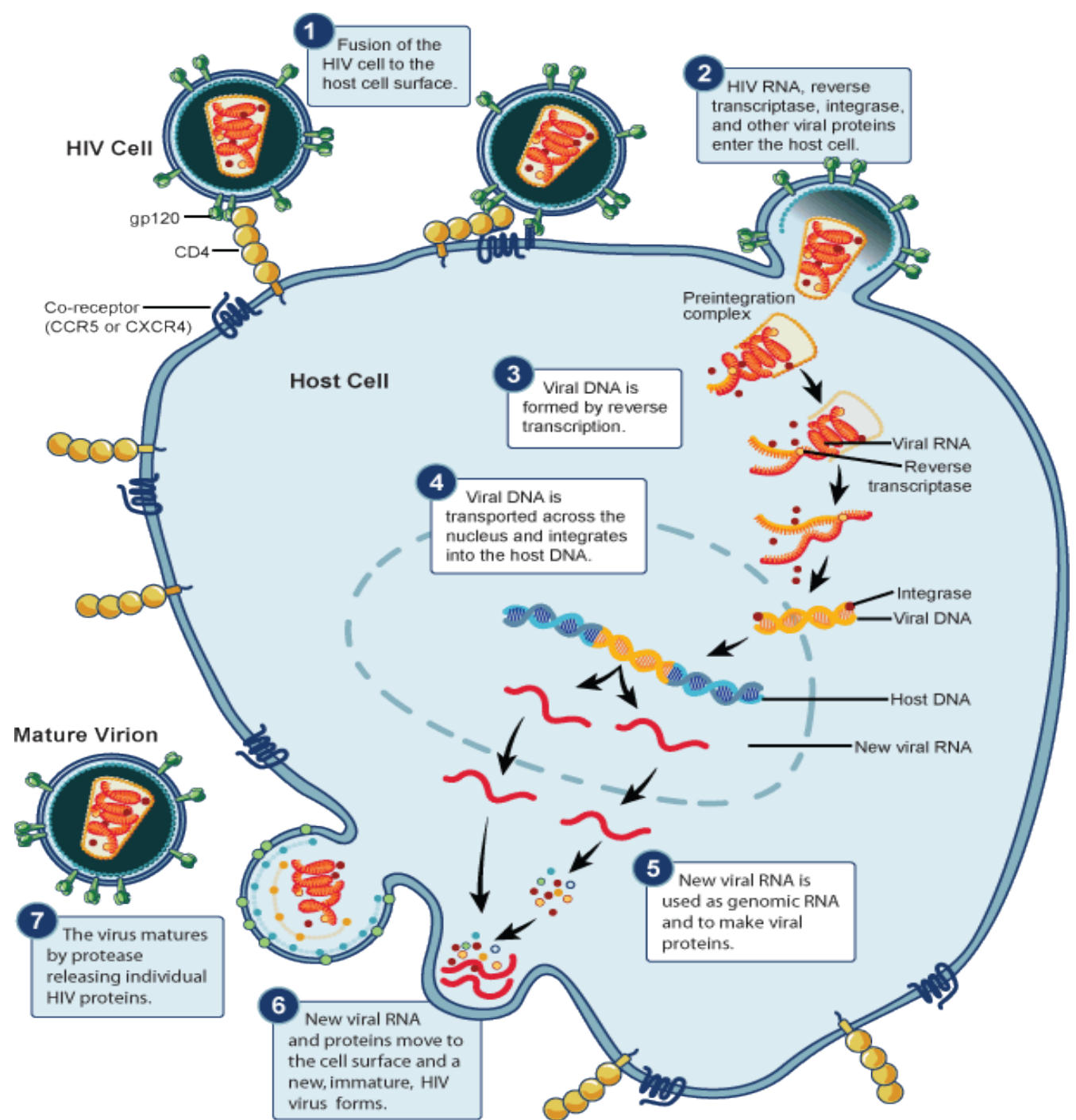
Exposure	HIV Transmission Risk per 10,000 exposures
Blood transfusion	9,000
Needle-sharing injection-drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Receptive oral intercourse	1
Insertive oral intercourse	0.1

Adapted from “Antiretroviral postexposure prophylaxis after sexual, inject-drug use, or other nonoccupational exposure to HIV in the United States. Recommendations from the U.S. Department of Health and Human Services” by DK Smith, LA Grohskopf, et al. 2005. *MMWR Recomm Rep.* p. 7.

Assessing risk: hivrisk.cdc.gov

The screenshot displays the HIV Risk Reduction Tool website. At the top, the browser's address bar shows the URL `hivrisk.cdc.gov`. The page header includes the CDC logo and the text "Centers for Disease Control and Prevention" with the tagline "CDC 24/7: Saving Lives, Protecting People™". A search bar is located in the top right corner, and a link to the "A-Z Index" is visible. The main content area features a dark blue banner with the "HIV Risk Reduction Tool" logo and social media icons for Facebook, Twitter, and YouTube. Below the banner, a large image of a smiling couple is overlaid with the text "Welcome to the HIV Risk Reduction Tool". Underneath this text, a grey box contains the instruction: "Use this tool to access tailored information about your risk of getting or transmitting HIV, and how you can reduce your risk". Two call-to-action buttons are positioned below the instruction: "Find Answers to Your Questions" (with a question mark icon) and "Estimate the HIV Risk from Sex" (with a calculator icon). The bottom of the screenshot shows the Windows taskbar with various open applications and the system clock displaying "11:17 AM 8/4/2020".

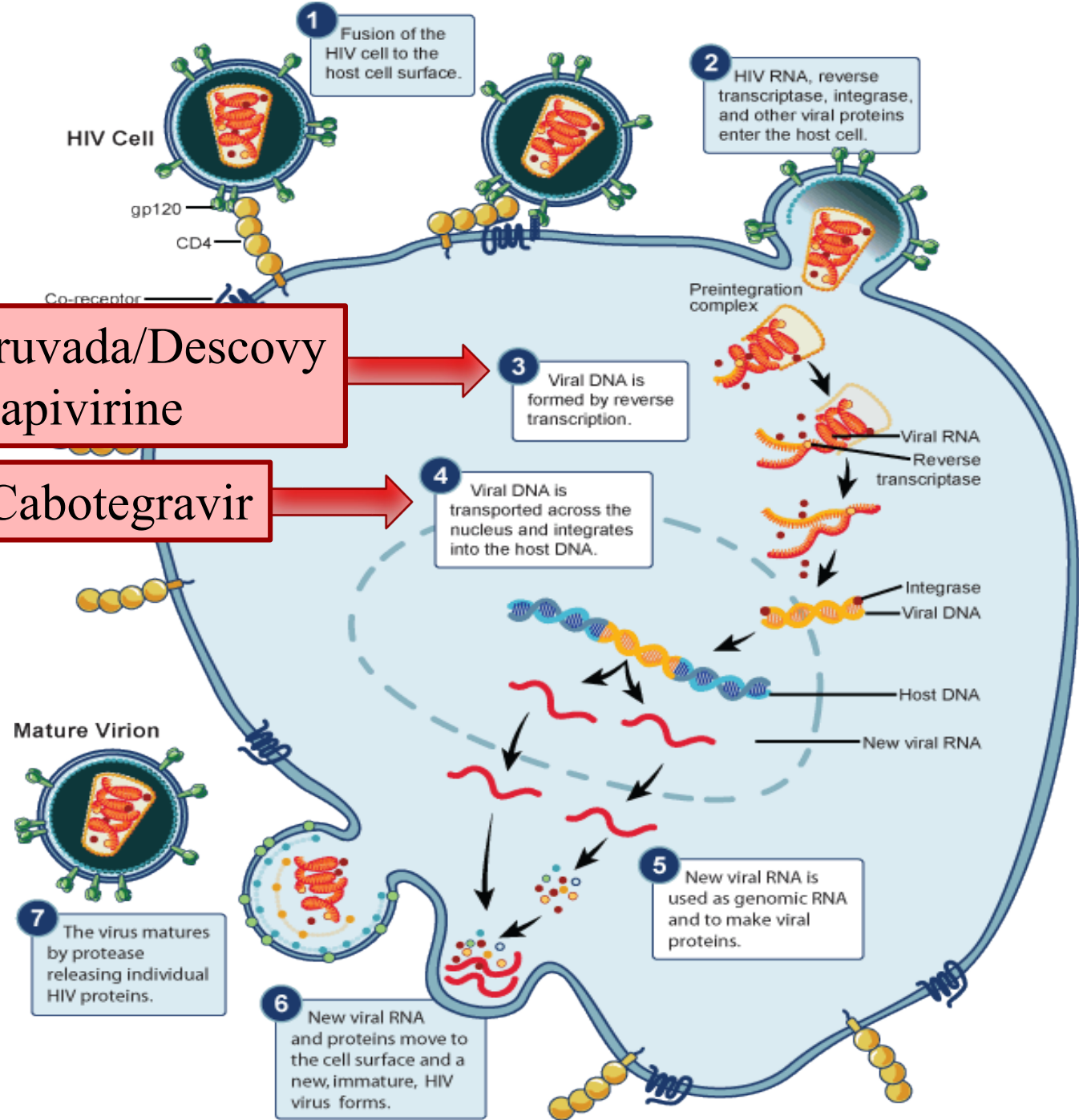
HIV replication



HIV replication: drugs for PrEP

Truvada/Descovy
Dapivirine

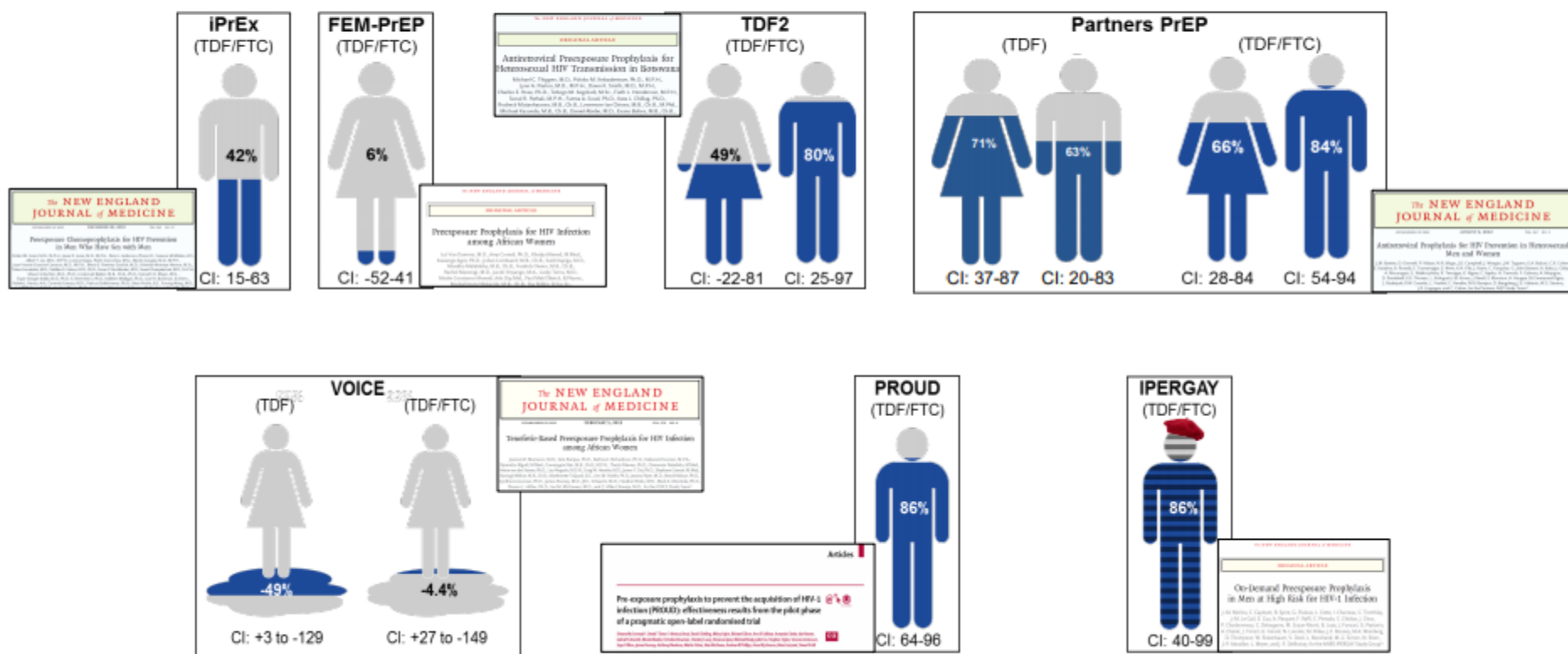
Cabotegravir



Clinical trials showing PrEP effectiveness

- iPrEX Study (2010)
 - 44% reduction in HIV acquisition (MSM)
- TDF2 Study (2012)
 - 62% reduction in HIV acquisition (heterosexuals)
- Partners PrEP Study (2012)
 - 75% reduction in HIV infection (heterosexuals)
- Bangkok Tenofovir Study (2013)
 - 49% reduction in HIV infection (IDU)

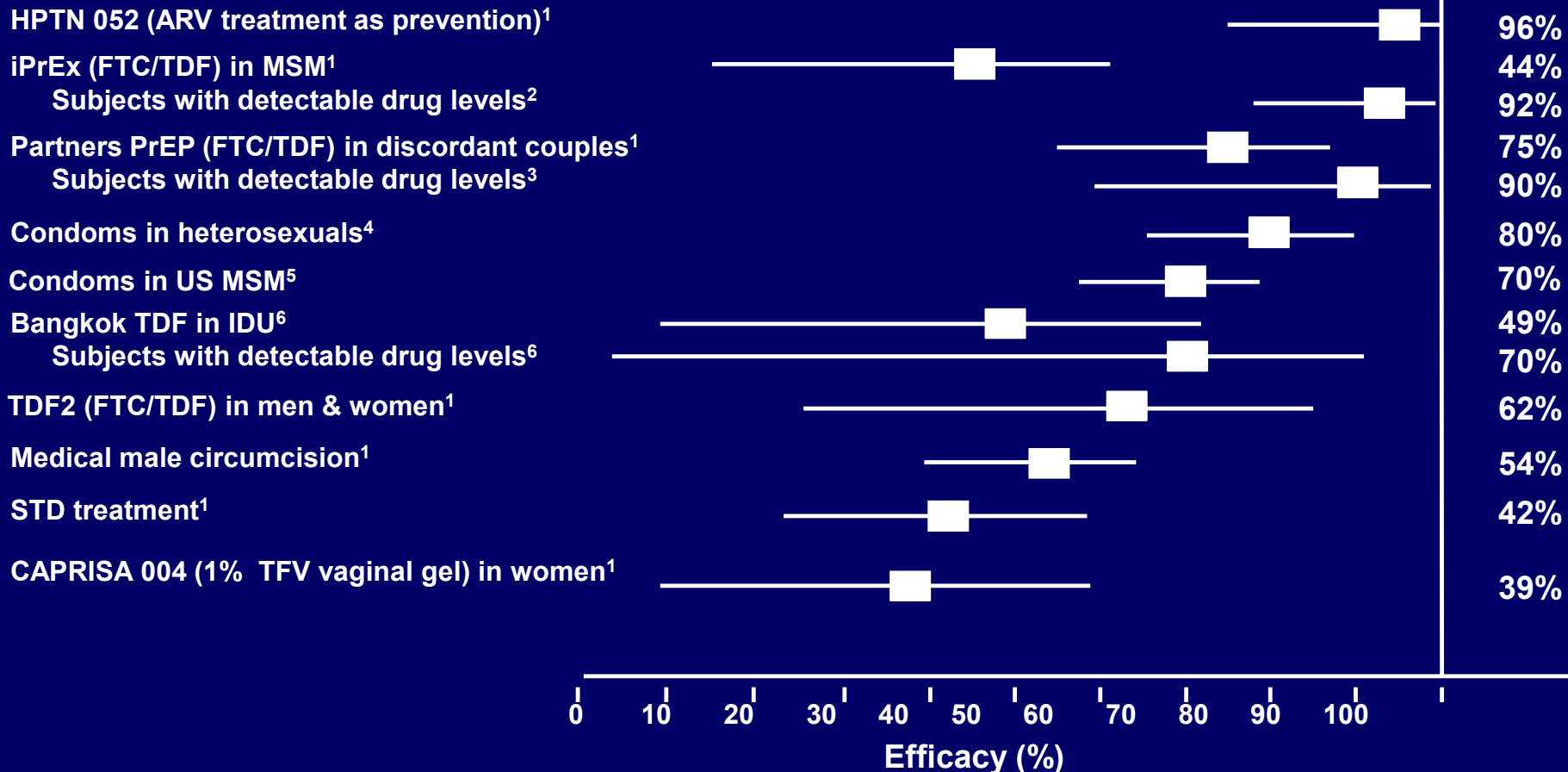
Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials



Relative Efficacy of HIV Prevention Strategies

Study

Reduction in HIV Transmission



1. Adapted from Abdool Karim S and QA. Lancet 2011;S0140-6736:1136-7

2. Amico R, et al. IAC 2012. Washington DC. #TUPE310

3. Baeten J, et al. NEJM 2012;367:399-410

4. Weller S, et al. Cochrane Database Syst Rev 2002:CD003255

5. Smith DK, et al. CROI 2013; Atlanta, GA. Oral #32

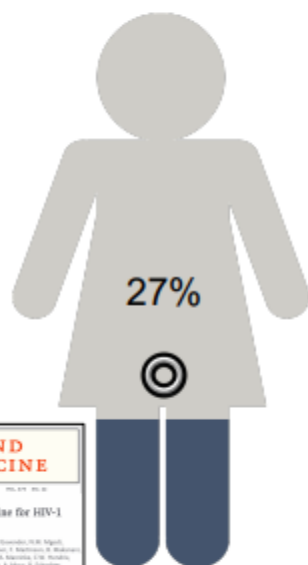
6. Choopanya K, et al. IAS 2013; Kuala Lumpur, Malaysia. Oral #WELBCO5

CDC position on PrEP

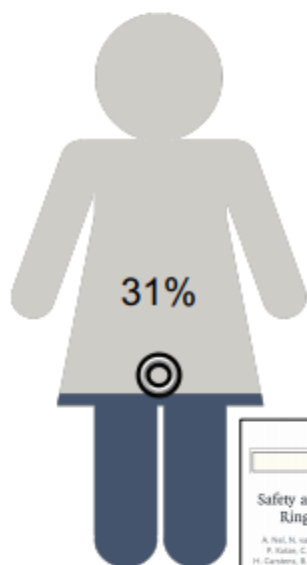
- “When used consistently, PrEP has been shown to be effective in men who have sex with men and heterosexually active men and women”
- Should be coupled with:
 - Regular monitoring of HIV status
 - Ongoing risk reduction counseling
 - PrEP medication adherence counseling

“PrEP 2.0”: Trials of Novel PrEP Agents

ASPIRE (Dapivirine)



Ring (Dapivirine)



DISCOVER

(TDF/FTC)

(TAF/FTC)



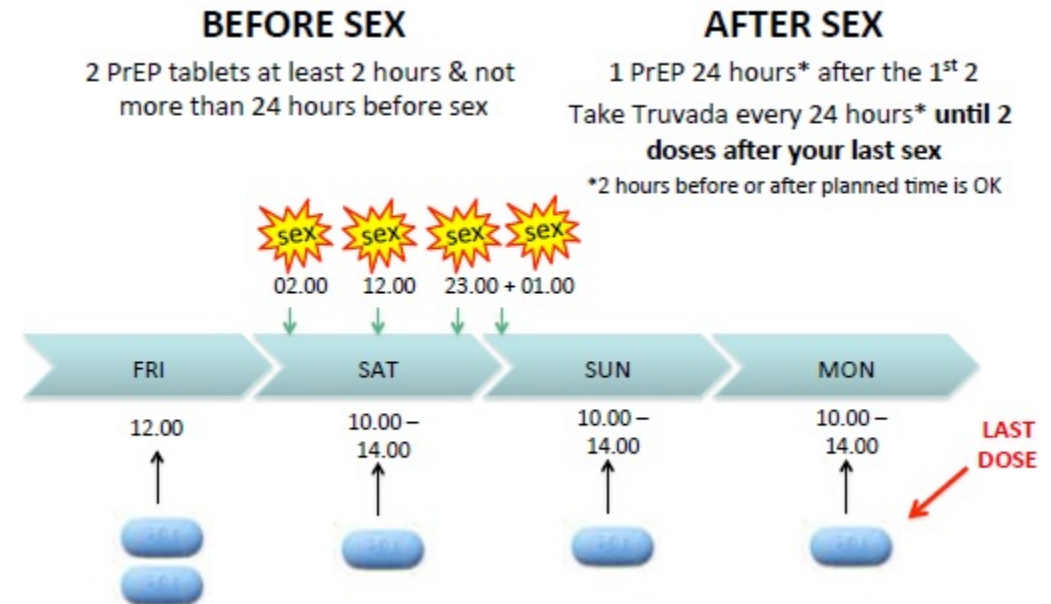
CI: 1 – 46



CI: 1 – 51

Dosing options: daily vs PrEP on demand

- Dosing around individual sexual exposures
- Still under investigation, but appears to work equivalently to daily dosing in several studies



TDF vs TAF

- Initial study was comparing two HIV regimens: FTC/TDF/ELV/cobi vs FTC/TAF/ELV/cobi in naïve PLWH
- Similar effect on virologic suppression and virologic failure
- Side effects: “well-tolerated”, same between both: diarrhea, nausea, headache, fatigue, vomiting, dizziness – all mild
- Kidneys: Creatinine higher in TDF than TAF, also other urine proteins
- Bone mineral density: everyone got thinner bones: 1-2% for TAF vs 3% for TDF. Measured by DEXA. Fractures occurred, but all due to violence/accidents
- Lipids: higher in TAF than TDF. 4% of people on TAF had to start anti-cholesterol drugs; 3% of people on TDF.

Which medication should I prescribe for daily PrEP?

TDF/FTC (Truvada)



EFFECTIVENESS

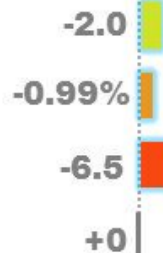
- ✓ for multiple populations

SAFETY

- Small ↓ in eGFR and BMD

COST

- \$1,845/month in 2019
- Generic in 2020



100

0

EFFECTIVENESS

MSM & TRANSWOMEN

HETEROSEXUALS

PWID

SAFETY / 48 WKS

eGFR (mL/min)

HIP BMD

LDL (mg/dL)

BODY WEIGHT (kg)



TAF/FTC (Descovy)



EFFECTIVENESS

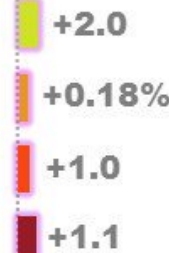
- ✓ for MSM and transwomen
- ? for other populations

SAFETY

- Small ↑ in LDL and weight

COST

- \$1,845/month in 2019



0

100

Figure 1. Dapivirine Vaginal Ring



- Off-white, flexible
- Platinum-catalyzed, silicone elastomer matrix ring (25 mg dapivirine)
- 56 mm outer diameter; 7.7 mm cross-sectional diameter
- Intended for monthly use

July 2020, EU regulatory agency gave favorable opinion. Pending approval by FDA and African regulatory agencies.

ASPIRE and The Ring Study Results – A Snapshot

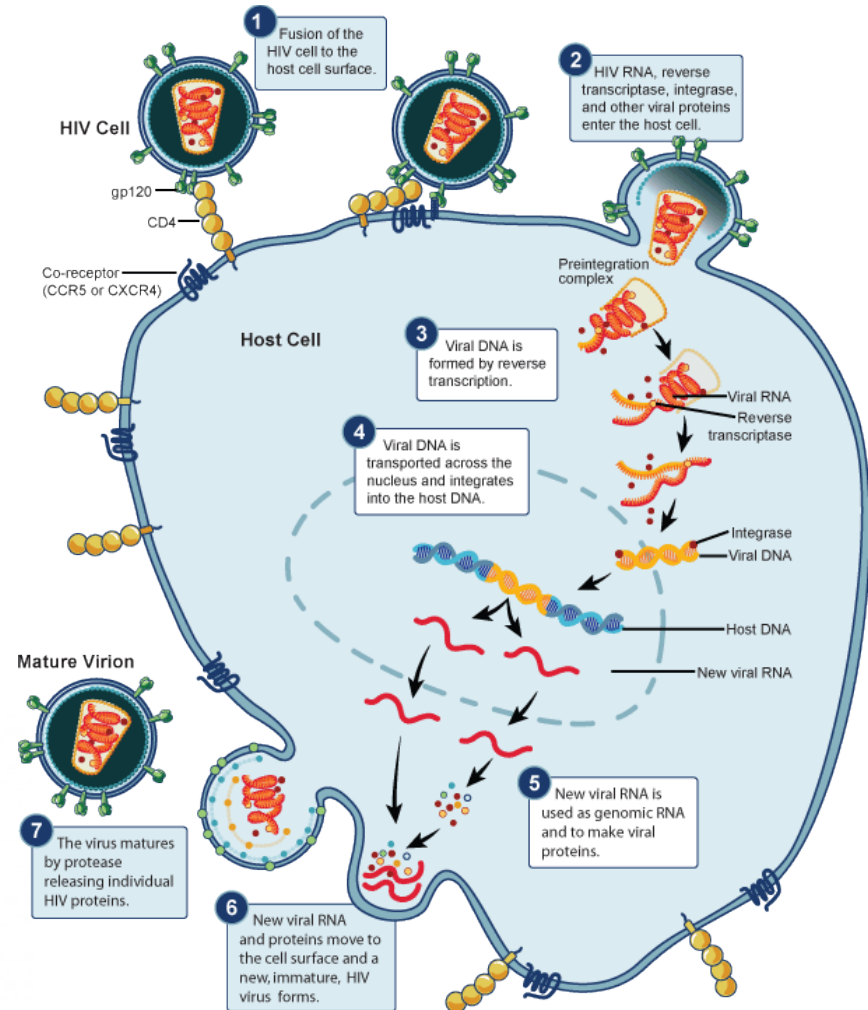
Study	The Ring Study (IPM 027) International Partnership for Microbicides	ASPIRE (MTN 020) Microbicide Trials Network
Study design and enrollment		
Objectives	Long term safety and effectiveness	Safety and effectiveness
Study design	Double blind randomized placebo controlled with 2:1 randomization (active: placebo)	Double blind randomized placebo controlled with 1:1 randomization (active: placebo)
Enrollment	Total: 1959 women, ages 18-45 Active arm: ~1300	Total: 2629 women, ages 18-45 Active arm: ~1325
Regulatory requirement	3000 women on dapivirine ring for at least 1 year follow-up 1500 women on dapivirine ring for 2 year follow-up	
Participant follow-up	2 years + 6 weeks following ring discontinuation	Minimum 1 year + 4 weeks following ring discontinuation
Research sites	7 IPM research center partners in South Africa and Uganda	15 MTN research centers in Malawi, South Africa, Uganda, Zimbabwe
Results		
Overall results	31% effective, confidence interval 1-51	27% effective, confidence interval 1-46
Secondary analysis that excluded data from 2 sites with lower retention and adherence		37% effective, confidence interval 12-56
Results by age stratification (post hoc analysis)		
Women over 21 years of age	37% effective, confidence interval 3.5-59	56% effective, confidence interval 31-71
Women 18-21 years of age	No statistically significant effect	No statistically significant effect
HIV incidence		
Overall	4.1% among women in active arm 6.1% among women in placebo arm	3.3% among women in active arm 4.5% among women in placebo arm

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Study drugs

- Truvada (standard PrEP)
- Injectable cabotegravir
 - **Integrase inhibitor** for HIV
 - Injected into the buttocks
 - Very long half life



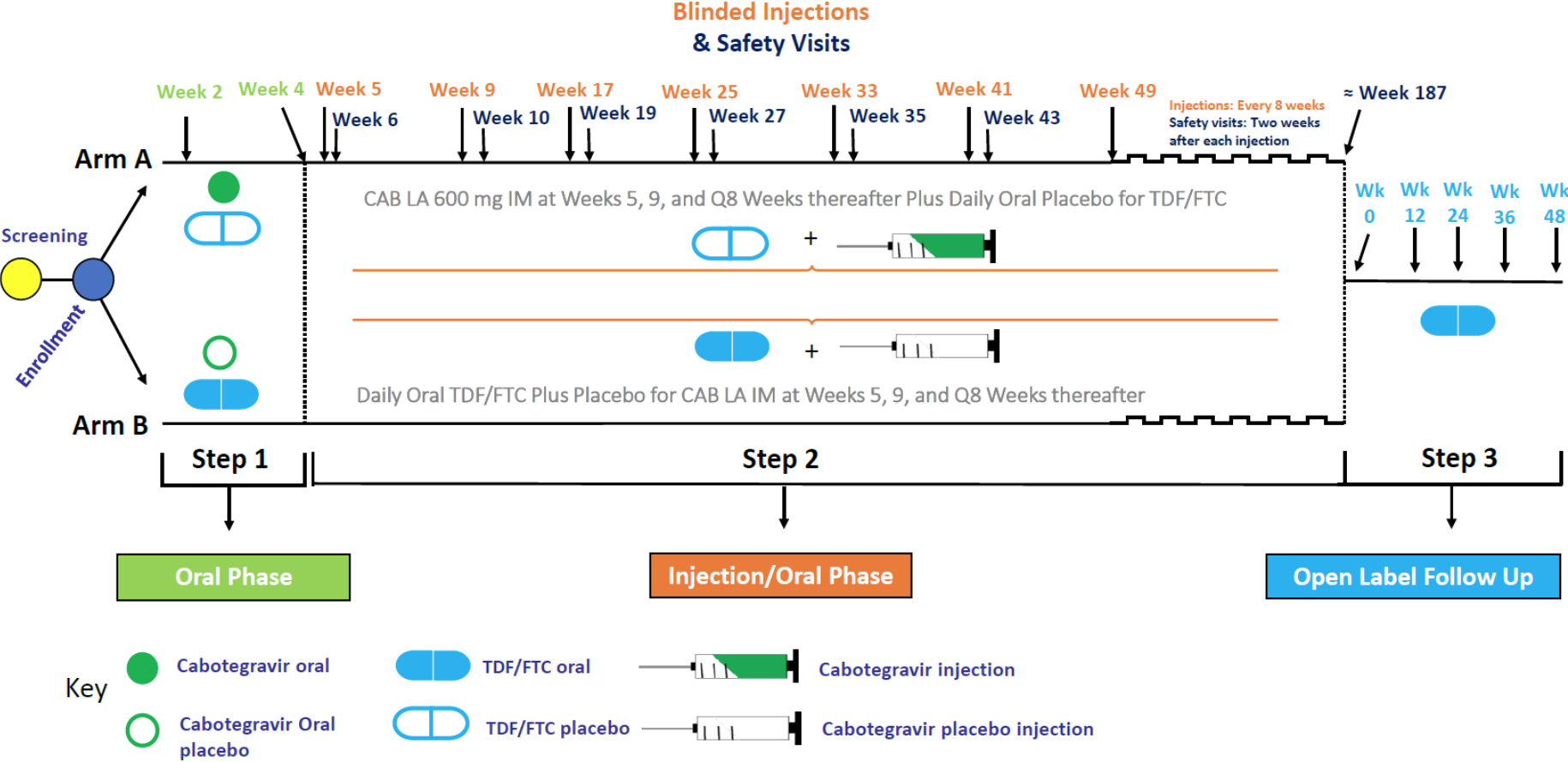


HPTN 083 Study Design

- **Phase 2b/3 randomized, double-blind, double-dummy @ 43 sites globally**
 - **MSM/TGW age 18+**
 - **Risk: any nCRAI, >5 partners, stimulant drug use, incident rectal or urethral STI (or incident syphilis) in past 6 months; or SexPro Score ≤ 16 (US only)**
 - **Generally good health**
 - **No HBV or HCV**
 - **No contraindication to gluteal injections, seizures, gluteal tattoos/skin conditions**
- **Planned enrollment 5000**
 - **$\geq 50\%$ under age 30**
 - **$\geq 10\%$ TGW**
 - **$\geq 50\%$ of US enrollment Black**
- **Primary efficacy endpoint: Incident HIV infections during blinded comparison**
- **Primary safety endpoint: G2 or higher clinical and laboratory AEs**

Please see Grinsztejn B. et al,
Abstract #OACLB0101

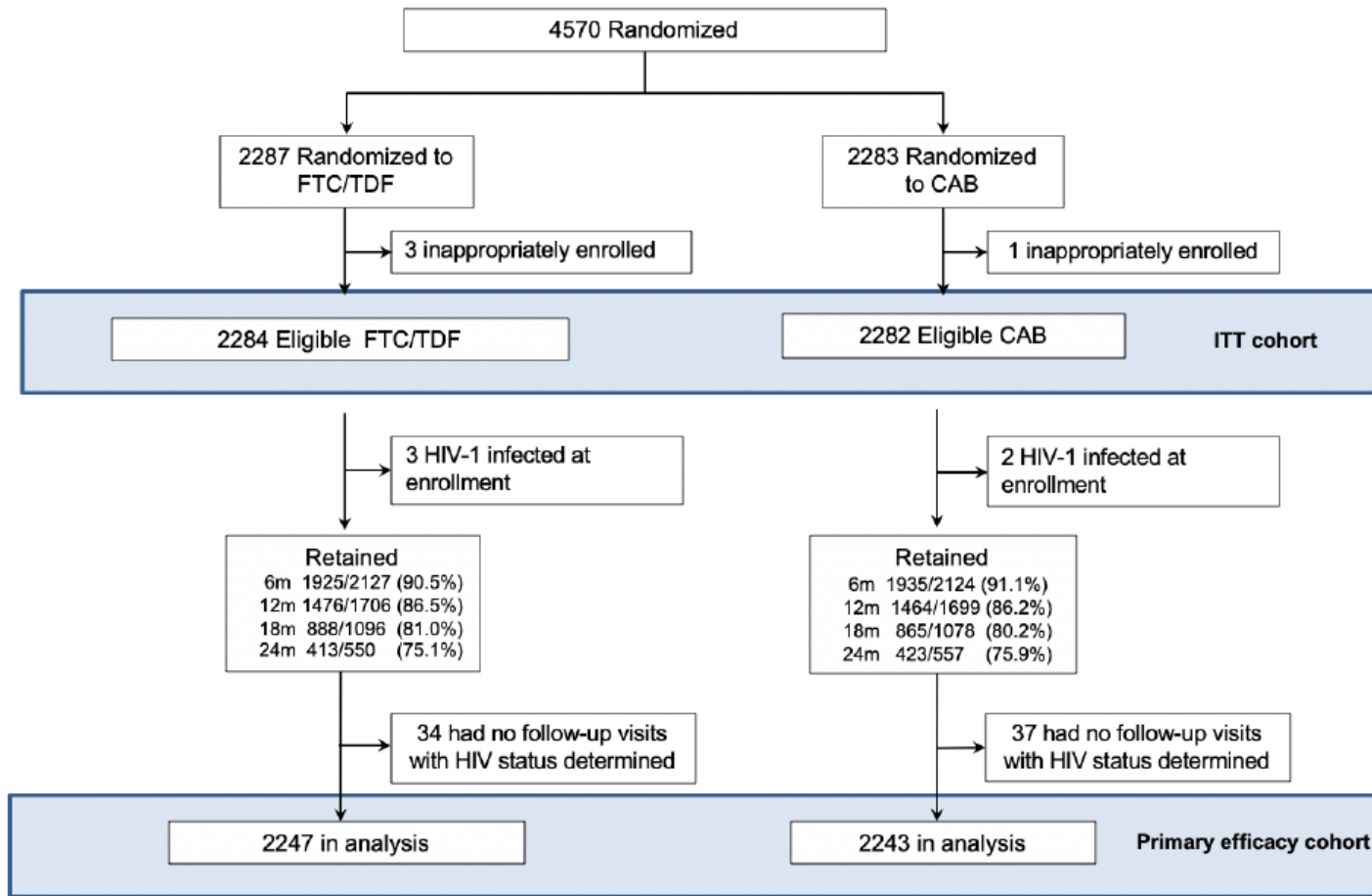
HPTN 083: Study Visit Schema



Statistical Design: Efficacy

- **Non-inferiority design**
 - **Non-inferiority margin 1.23**
 - **Alternative hypothesis of HR 0.75**
 - **Target background HIV Incidence ~4.5%**
 - **Anticipated TDF/FTC adherence by TFV plasma detectable ~67%**
- **Endpoint-driven (172 events) with pre-specified interim analyses at 25%, 50%, and 75% of endpoints**
 - **O'Brien-Fleming stopping boundaries for interim data analysis used to determine early stopping metrics**
- **DSMB recommended termination of blinded study after interim analysis on May 14, 2020 (25% endpoints accrued) for crossing pre-specified stopping bound**
- **Results include events occurring through May 14, 2020; participants unblinded, continuing on study**
 - **All to be offered CAB as soon as available at sites**

Participant Disposition



Controversies during HPTN083

- Approval of Descovy for PrEP
 - Not provided by study
 - Discussion with participants
 - Talk to CAB about advantages/disadvantages of TDF vs TAF
 - If on open label Truvada, discussed PCP change to Descovy
- Cabotegravir and pregnancy
 - Concern for neural tube defects in pregnant women receiving dolutegravir
 - Required hold and revision of HPTN 084
- Cabotegravir and weight gain

Study Population

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Gender Identity, n (%)			
MSM	3995 (87.5)	1981 (86.7)	2014 (88.3)
TGW	567 (12.4)	302 (13.2)	265 (11.6)
Age, median (IQR)			
	26 (22, 32)	26 (22, 32)	26 (22, 32)
Age, n (%)			
18-29	3079 (67.4)	1508 (66.0)	1571 (68.8)
30-39	1049 (23)	550 (24.1)	499 (21.9)
40-49	315 (6.9)	170 (7.4)	145 (6.4)
50-59	110 (2.4)	50 (2.2)	60 (2.6)
≥60	13 (0.3)	6 (0.3)	7 (0.3)
Region, n (%)			
United States	1698 (37.2%)	849 (37.2%)	849 (37.2%)
Latin America	1964 (43.0%)	984 (43.2%)	980 (42.9%)
Asia	752 (16.5%)	377 (16.5%)	375 (16.5%)
Africa	152 (3.3%)	74 (3.2%)	78 (3.4%)
Education, n (%)			
Post-Secondary (YES)	3477 (76.1)	1715 (75.1)	1762 (77.2)
Relationship Status, n (%)			
Single (YES)	3750 (82.1)	1863 (81.6)	1887 (82.7)

Study Population

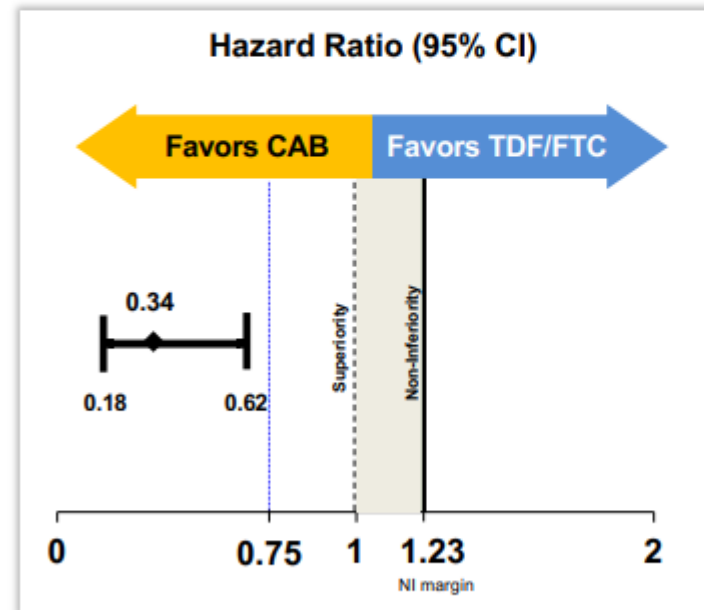
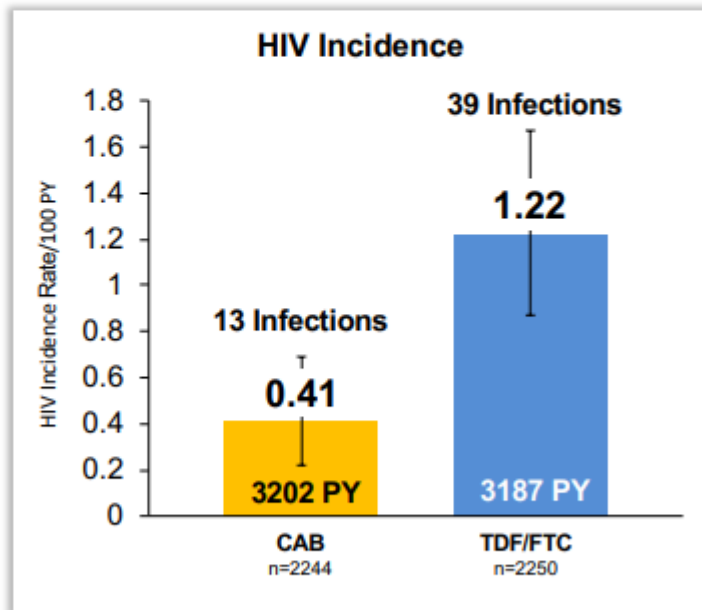
	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Race, n (%)			
United States			
Black/African American	844 (49.7)	433 (51.0)	411 (48.9)
White/Asian/Native/Other	854 (50.4)	416 (49.0)	438 (51.1)
Latin America			
Black/Afro-Caribbean	395 (20.1)	196 (19.9)	199 (20.3)
Native	858 (43.7)	425 (43.2)	433 (44.2)
White/Asian/Other	711 (59.6)	363 (36.8)	348 (35.5)
Asia			
Asian	749 (99.6)	375 (99.5)	374 (99.7)
Other	3 (0.4)	2 (0.5)	1 (0.3)
Africa			
Black	119 (78.3)	57 (77.0)	62 (79.5)
Other	5 (3.3)	3 (4.1)	2 (2.6)
Ethnicity, n (%)			
United States: Latinx	303 (17.8)	154 (18.1)	149 (17.6)
Latin America: Latinx	1805 (91.9)	912 (92.7)	893 (91.1)



HIV Incidence

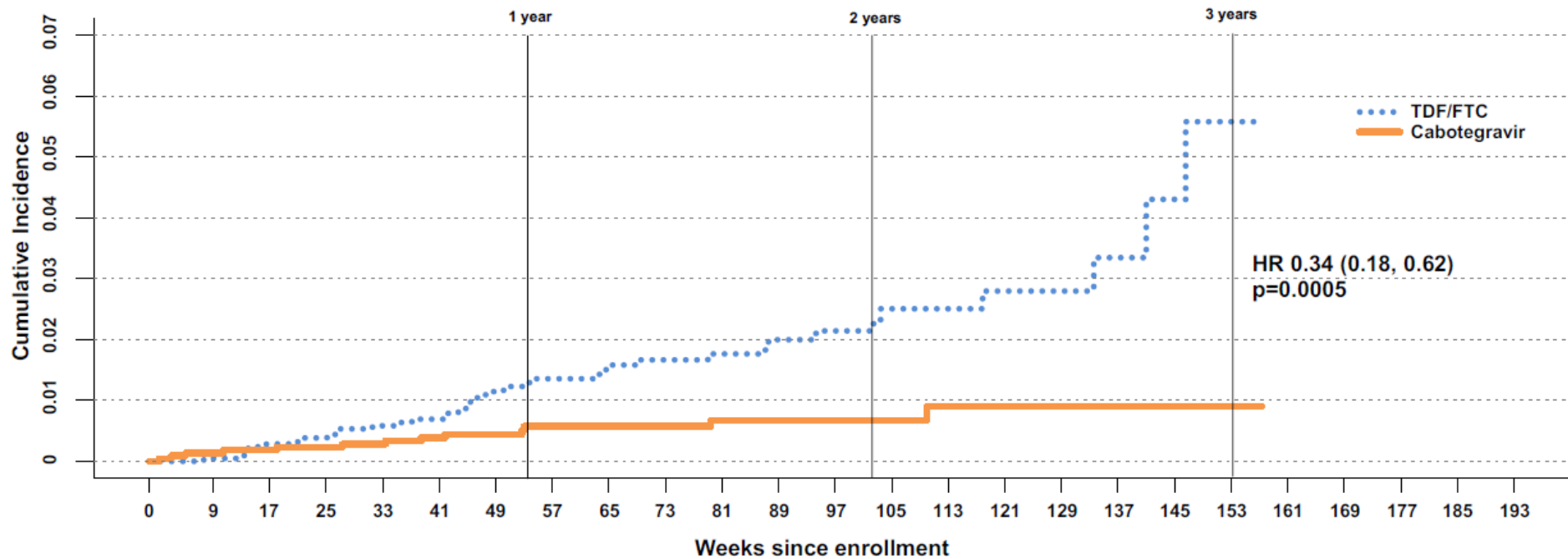
CAB vs. TDF/FTC

52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY



CI, confidence interval

HIV Incidence – ITT



Number at risk

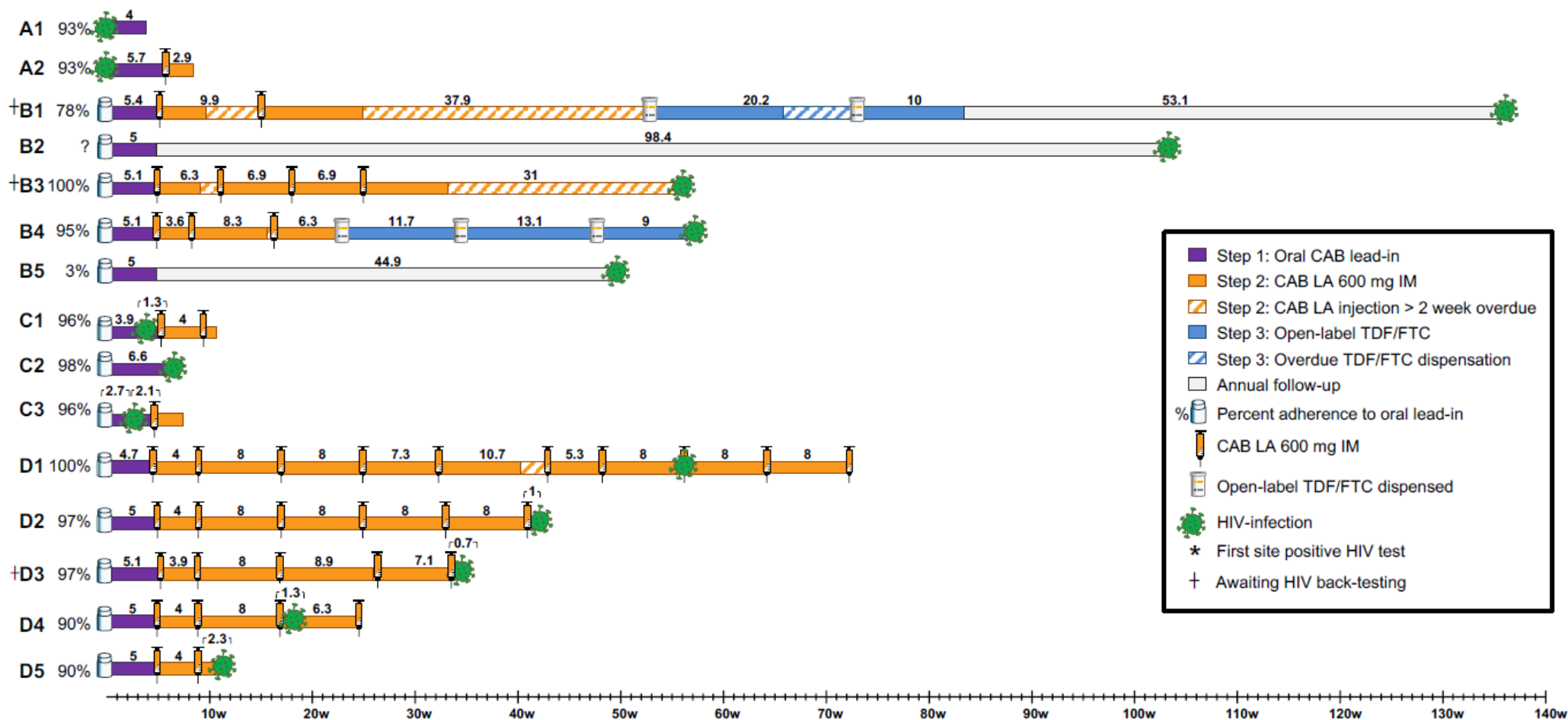
TDF/FTC	2247	2133	2081	2019	1913	1764	1624	1494	1294	1132	965	816	643	516	400	310	230	149	85	33	0	0	0	0	0
Cabotegravir	2243	2138	2092	2032	1921	1776	1632	1488	1312	1119	957	795	644	503	401	318	243	172	111	42	0	0	0	0	0

Cumulative number of events

TDF/FTC	0	1	6	8	12	14	22	25	27	29	30	32	33	35	35	36	36	37	38	39	0	0	0	0	0
Cabotegravir	0	3	4	5	6	8	9	11	11	11	12	12	12	12	13	13	13	13	13	13	0	0	0	0	0

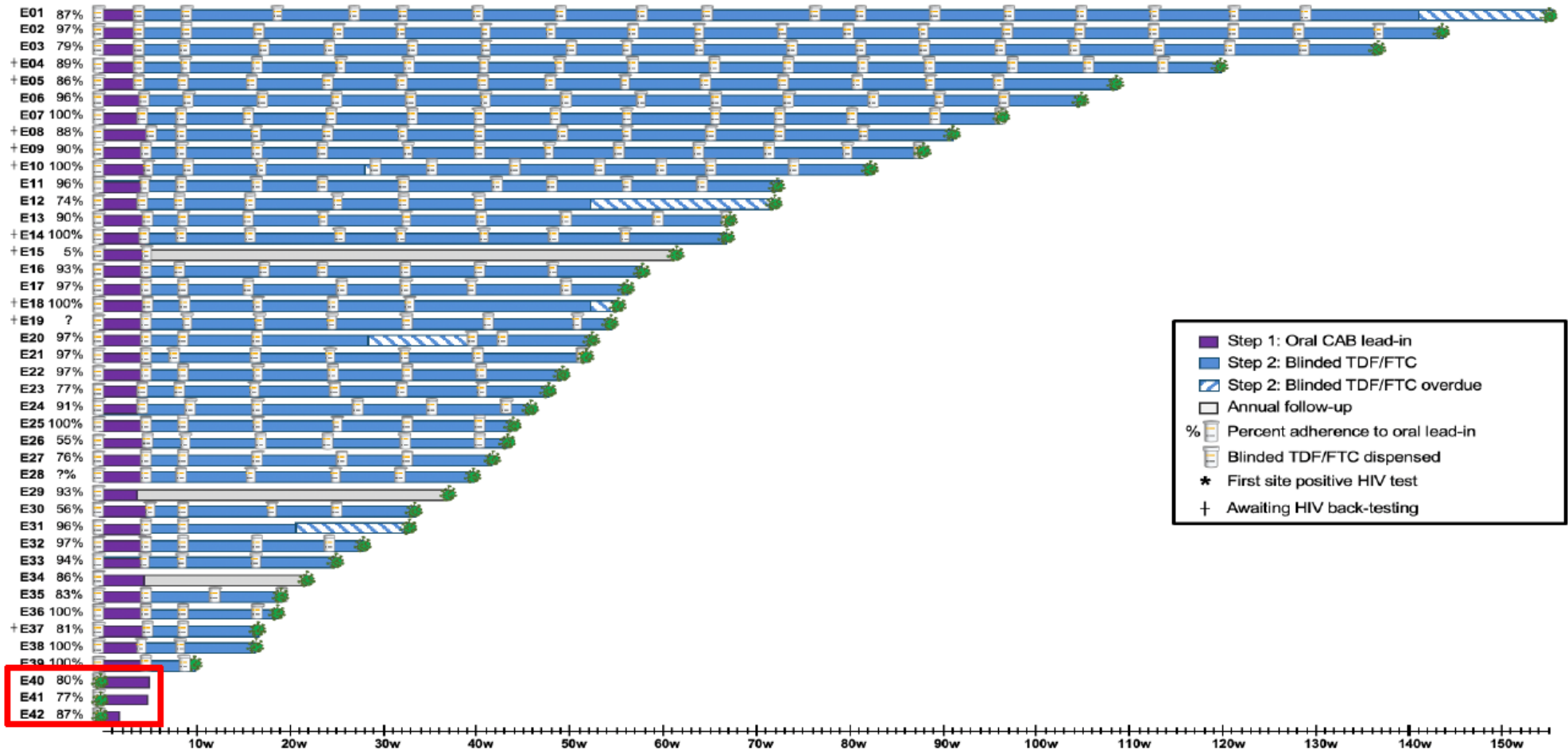
13 Incident HIV Infections

Cabotegravir





39 Incident HIV Infections TDF/FTC

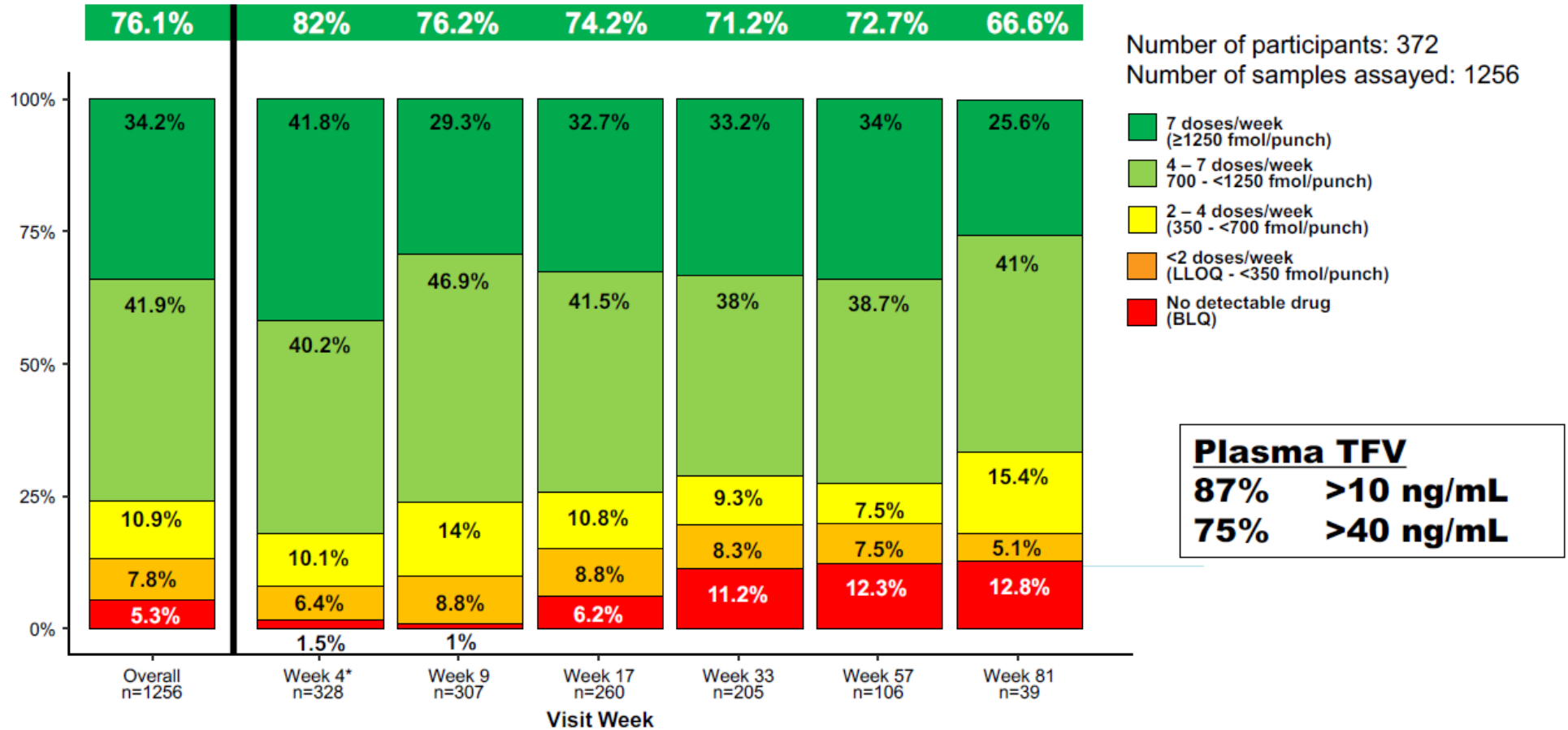


Prevalent and Incident STIs

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Prevalent at baseline, n (%)			
Syphilis	241 (5.3)	115 (5.1)	126 (5.5)
Gonorrhea _{urine}	29 (0.6)	17 (5.1)	12 (0.5)
Gonorrhea _{rectal}	297 (6.5)	150 (6.6)	147 (6.5)
Chlamydia _{urine}	122 (2.7)	57 (2.5)	65 (2.9)
Chlamydia _{rectal}	502 (11)	255 (11.2)	247 (10.9)
Incidence, n (rate per 100 py)			
Syphilis	908 (16.5)	451 (16.4)	457 (16.5)
Gonorrhea _{urine}	128 (2.4)	57 (2.1)	71 (2.6)
Gonorrhea _{rectal}	592 (10.9)	295 (10.9)	297 (11)
Chlamydia _{urine}	241(4.4)	124 (4.6)	117 (4.3)
Chlamydia _{rectal}	906 (16.7)	481 (17.8)	425 (15.7)

DBS TFV-DP

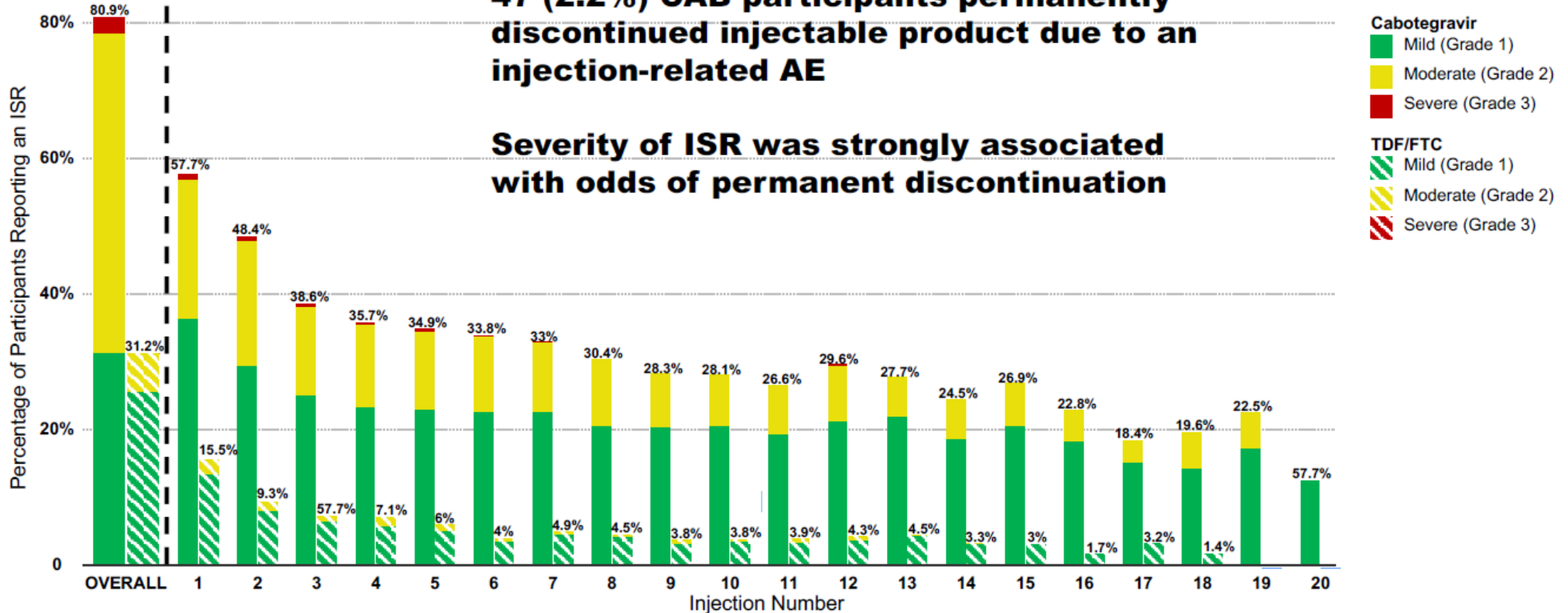
Randomly selected “adherence” subset



Injection Site Reactions

47 (2.2%) CAB participants permanently discontinued injectable product due to an injection-related AE

Severity of ISR was strongly associated with odds of permanent discontinuation



Cabotegravir, n	2117	2117	2037	1938	1872	1761	1620	1464	1360	1200	1034	877	744	604	465	372	298	234	168	111	8
TDF/FTC, n	2081	2081	2014	1940	1869	1760	1606	1463	1355	1193	1037	903	760	596	482	370	288	220	146	89	6

Grade 2+ Adverse Events Reported in $\geq 5\%$

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)	p-value
Participants with grade 2+ AEs, n (%)	4202 (92.1%)	2106 (92.3%)	2096 (91.9%)	
Creatinine clearance decreased	3204 (70.2%)	1642 (72.0%)	1562 (68.5%)	0.01
CPK increased	937 (20.5%)	460 (20.2%)	477 (20.9%)	0.52
Nasopharyngitis	828 (18.1%)	388 (17.0%)	440 (19.3%)	0.04
Creatinine increased	775 (17.0%)	412 (18.1%)	363 (15.9%)	0.06
Upper Respiratory Infection	510 (11.2%)	255 (11.2%)	255 (11.2%)	0.99
Musculoskeletal discomfort	507 (11.1%)	253 (11.1%)	254 (11.1%)	0.95
Lipase increased	495 (10.9%)	252 (11.0%)	243 (10.7%)	0.68
Headache	448 (9.8%)	216 (9.5%)	232 (10.2%)	0.42
AST/SGOT increased	382 (8.4%)	197 (8.6%)	185 (8.1%)	0.53
ALT/SGPT increased	347 (7.6%)	191 (8.4%)	156 (6.8%)	0.05
Blood glucose increased	323 (7.1%)	117 (5.1%)	206 (9.0%)	<0.001
Amylase increased	316 (6.9%)	166 (7.3%)	150 (6.6%)	0.36
Diarrhoea	306 (6.7%)	158 (6.9%)	148 (6.5%)	0.56
Rash	253 (5.5%)	139 (6.1%)	114 (5.0%)	0.11
Hypoglycaemia	241 (5.3%)	123 (5.4%)	118 (5.2%)	0.75
Pyrexia*	181 (4.0%)	60 (2.6%)	121 (5.4%)	<0.001

*70% of pyrexia events in CAB were within 7 days of an injection (event probability 0.65%)
16% of pyrexia events in TDF/FTC were within 7 days of an injection (event probability 0.05%)



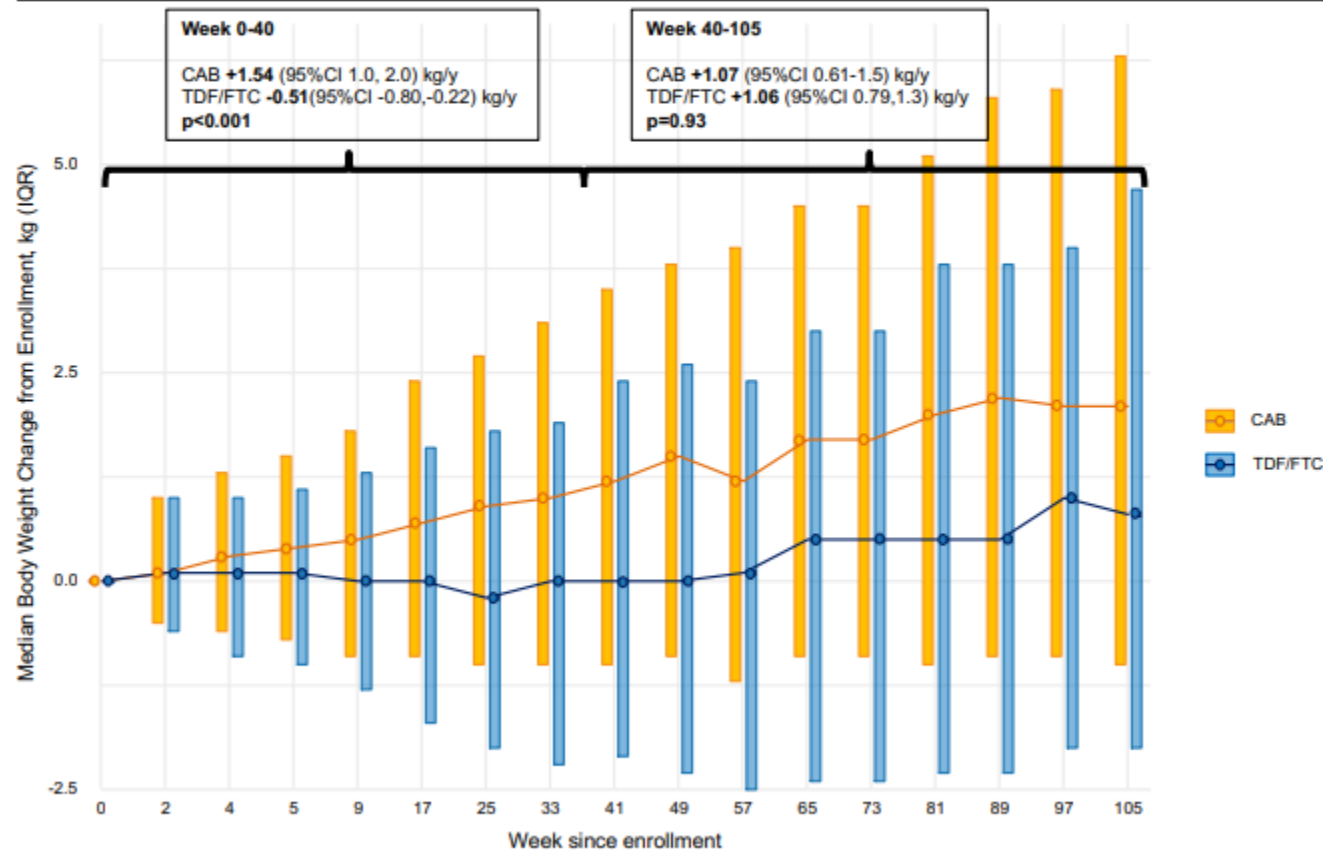
Adverse Events: Grade 3+ Reported in $\geq 2\%$

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)	p-value
Participants with grade 3+ AEs, n (%)	1490 (32.7%)	766/2282 (33.6%)	724/2280 (31.8%)	
CPK increased	633 (13.9%)	309 (13.5%)	324 (14.2%)	0.51
Creatinine clearance decreased	348 (7.6%)	190 (8.3%)	158 (6.9%)	0.08
Lipase increased	152 (3.3%)	76 (3.3%)	76 (3.3%)	0.99
Creatinine increased	152 (3.3%)	75 (3.3%)	77 (3.4%)	0.87
AST/SGOT increased	122 (2.7%)	69 (3.0%)	53 (2.3%)	0.14
Participants with EAEs and SAEs, n (%)	240 (5.3%)	122 (5.4%)	118 (5.2%)	
Participant deaths, n (%)	11 (0.24%)	7 (0.3%)	4 (0.2%)	



Changes in Weight

Median of changes from baseline



Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus-uninfected Individuals in HPTN 077

Raphael J Landovitz¹, Sahar Z Zangeneh², Gordon Chau², Beatriz Grinsztejn³, Joseph J Eron⁴, Halima Dawood⁵, Marya Magnus⁶, Albert Y Liu⁷, Ravindra Panchara⁸, Mina C Hosseini⁹, Ryan Kotron¹, David A Margolis¹⁰, Alex Rinehart¹⁰, Adeola Adeyeye¹¹, David Burns¹¹, Marybeth McCauley¹², Myron S Cohen⁴, Judith S Currier¹

HPTN 077: Over 41 weeks

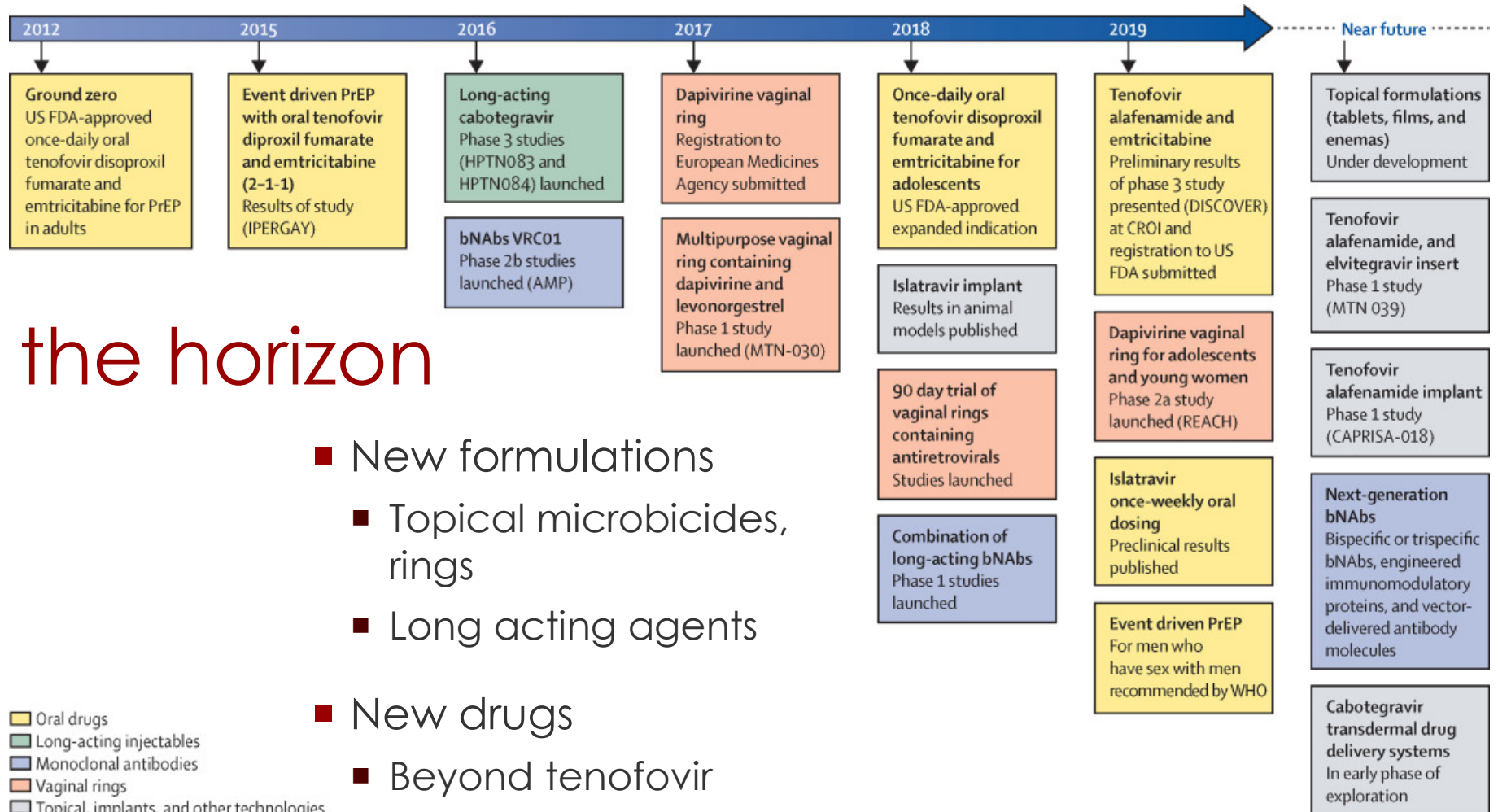
CAB +1.48 (95%CI 0.15, 2.8) kg/y
PBO +1.57 (95%CI -1.35, 4.49) kg/y
p=0.95

Landovitz RJ et al. CID 2019.



Conclusions

- **Both agents were highly effective for HIV prevention**
- **The PrEP regimen containing CAB-LA was superior to a daily oral regimen of TDF/FTC in HPTN 083, with a 66% reduction in risk of HIV infection observed in participants receiving CAB compared to TDF/FTC**
- **CAB-LA was well tolerated despite injection site reactions**
- **Peri-infection drug concentrations and detailed resistance profiles are needed to fully understand and contextualize results**
- **CAB is the first long-acting injectable agent to demonstrate robust HIV prevention efficacy in MSM/TGW**
- **Awaiting results for cisgender women (HPTN 084)**



On the horizon

- New formulations
 - Topical microbicides, rings
 - Long acting agents
- New drugs
 - Beyond tenofovir
 - Maraviroc, cabotegravir

Key points on PrEP

- **Adherence is key**
 - more effective if you actually take the medication
- **Getting the right population access**
- **Key pillar in the strategy to end the HIV epidemic**

- Long-term effects in HIV-negative persons unknown
- “Off-label” use
 - non-Truvada regimens
 - intermittent dosing (i.e. just before sex)
 - sharing meds among friends
- Cost
 - Insurance coverage
 - Public health benefit
- Medication scarcity

ENDING THE HIV EPIDEMIC: A PLAN FOR AMERICA



Diagnose HIV as early as possible



Treat HIV quickly and effectively



Protect people at risk



Respond quickly to clusters of new cases

Ending the HIV Epidemic: A Plan for America

HHS is proposing a once-in-a-generation opportunity to eliminate new HIV infections in our nation. The multi-year program will infuse 48 counties, Washington, D.C., San Juan, Puerto Rico, as well as 7 states that have a substantial rural HIV burden with the additional expertise, technology, and resources needed to end the HIV epidemic in the United States. Our four strategies – diagnose, treat, protect, and respond – will be implemented across the entire U.S. within 10 years.

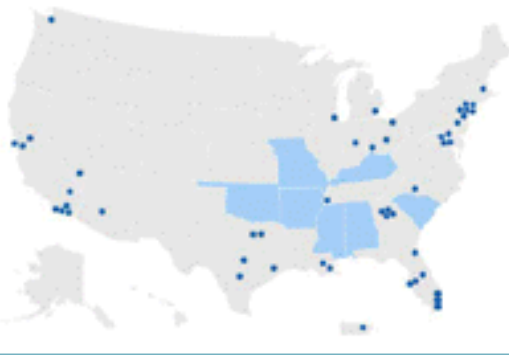
GOAL:

75% reduction in new HIV infections in 5 years and at least 90% reduction in 10 years.

HHS will work with each community to establish local teams on the ground to tailor and implement strategies to:

- Diagnose** all people with HIV as early as possible.
- Treat** the infection rapidly and effectively to achieve sustained viral suppression.
- Prevent** new HIV transmissions by using proven interventions, including pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs).
- Respond** quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.

The Initiative will target our resources to the 48 highest burden counties, Washington, D.C., San Juan, Puerto Rico, and 7 states with a substantial rural HIV burden.



Geographical Selection:

Data on burden of HIV in the US shows areas where HIV transmission occurs more frequently. More than 50% of new HIV diagnoses* occurred in only 48 counties, Washington, D.C., and San Juan, Puerto Rico. In addition, 7 states have a substantial rural burden – with over 75 cases and 10% or more of their diagnoses in rural areas.

Ending the HIV Epidemic

www.HIV.gov

*2016-2017 data

Ending the HIV Epidemic: Jurisdictional Plans

An increasing number of cities, counties, and states are developing plans to "End the Epidemic" in their jurisdictions.

