



Session 2 | Clinical Aspects of the Implementation of PrEP

Implementation of PrEP - Efficacy and Resistance Considerations



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Disclosures

Advisory boards: Gilead, Merck, ViiV, Sanofi

Research grants: Gilead

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



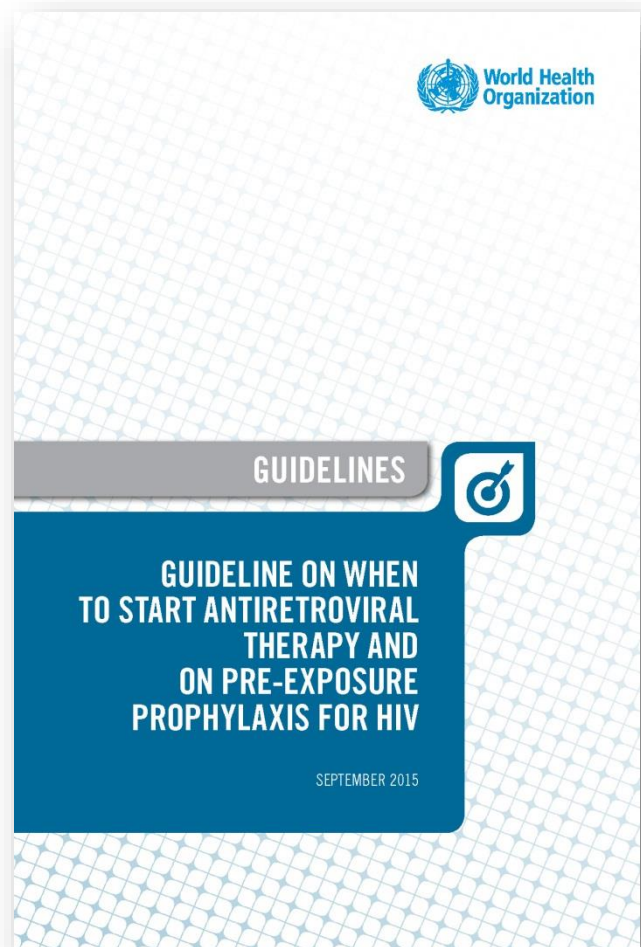
- 39%

Deaths annually
relative to 2010



30% of new diagnoses in Asia reported among MSM and TGW

WHO 2015 Guidelines

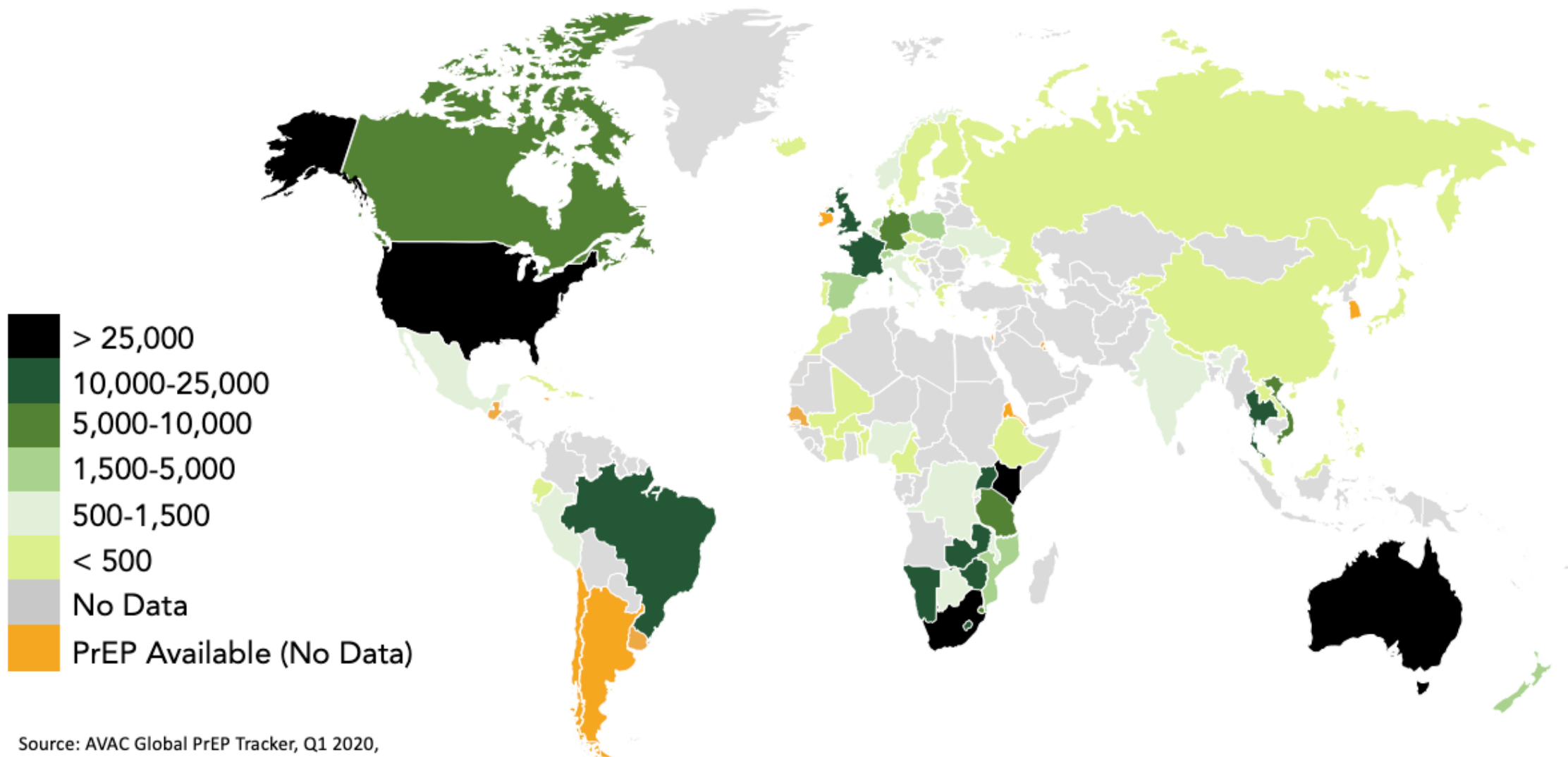


Oral PrEP should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches

Defining “substantial risk”: Substantial risk of HIV infection is provisionally defined as HIV incidence greater than 3 per 100 person–years in the absence of PrEP. HIV incidence greater than 3 per 100 person–years has been identified among some groups of men who have sex with men, transgender women in many settings and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection.

<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/>

PrEP Initiations by Country, April 2020



Source: AVAC Global PrEP Tracker, Q1 2020,
<https://www.prepwatch.org/country-updates/>

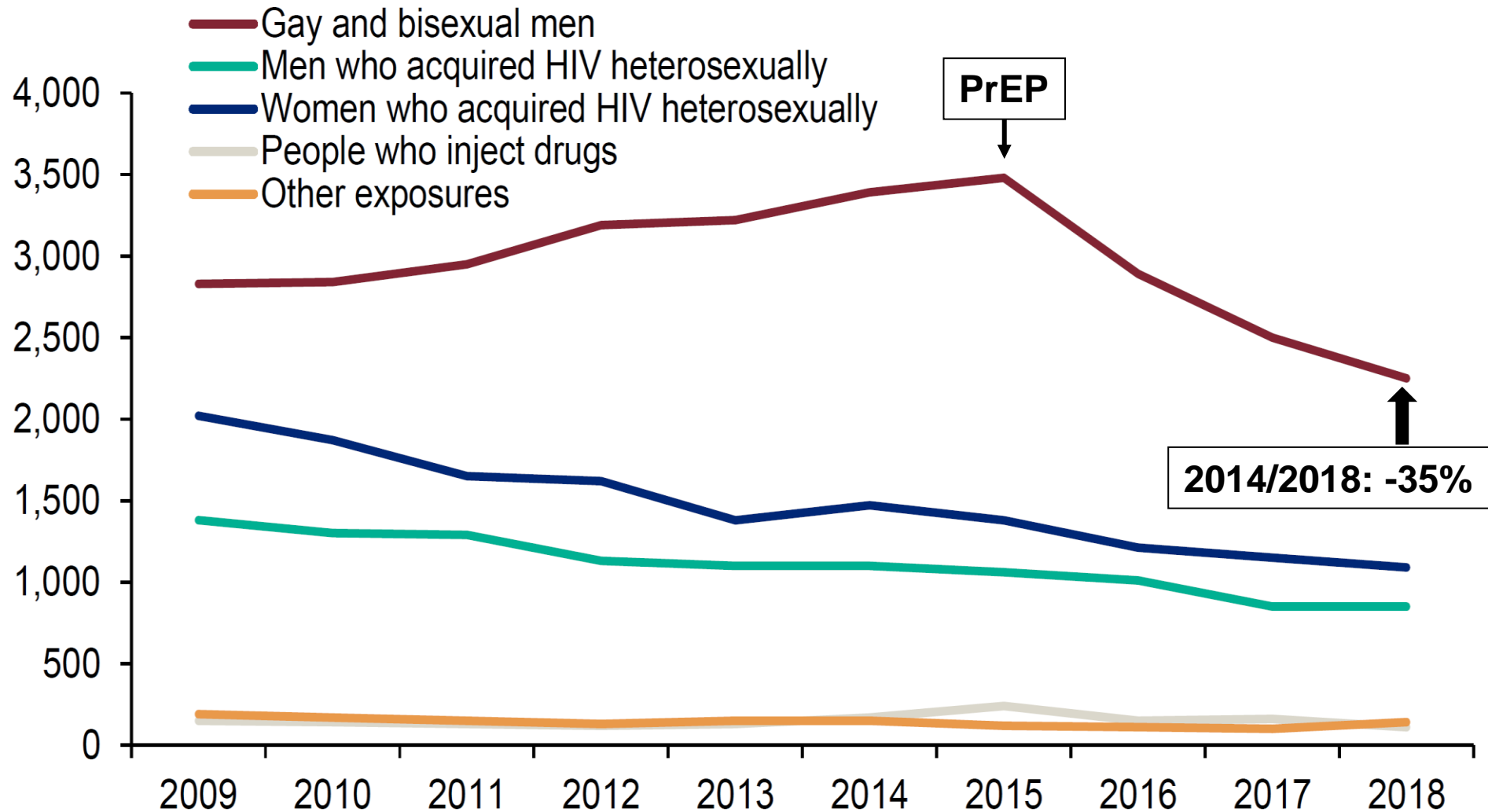
How to Upscale PrEP Implementation ?

- **Increase awareness of this new preventive tool**
- **Integrate PrEP with other health care services**
 - Increase Nb sites delivering PrEP: training, task shifting, rapid appointments, rapid PrEP start
 - Involve GPs
- **Address concerns regarding increases in STIs and cost**
- **Extend PrEP beyond MSM to other high risk groups**
- **Measure the impact of PrEP implementation**

AIDES Advertising Campaign 2018

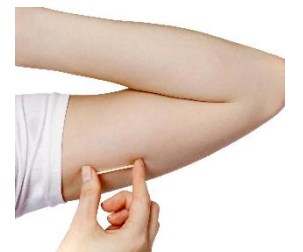


New HIV Diagnoses in the UK



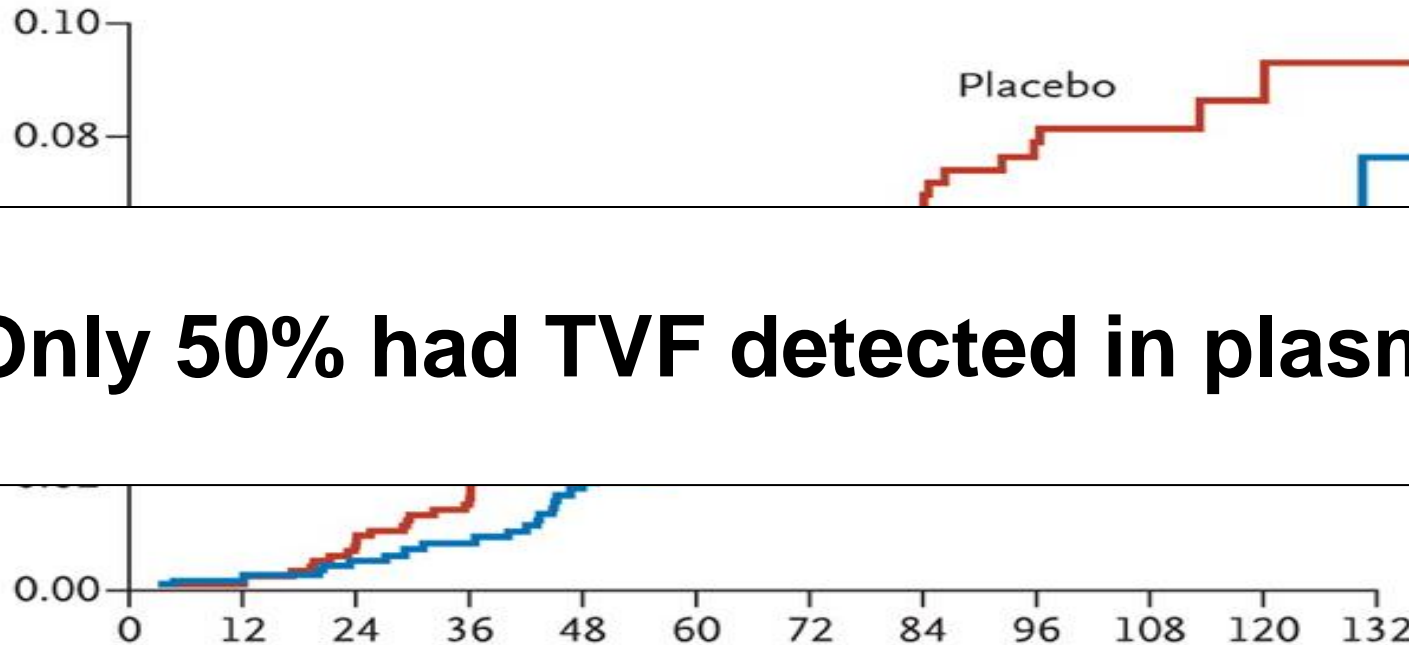
PrEP Regimens

- Oral TDF/FTC
- Oral TAF/FTC
- Dapivirine vaginal ring
- Cabotegravir LA intramuscular injections
- Investigational agents:
 - Neutralizing antibodies
 - LA oral or parenteral agents (Islatravir, Capsid inhibitors)
 - Subcutaneous implants (Islatravir, TAF)





iPrEx : Effectiveness of Daily TDF/FTC in MSM and TGW



Only 50% had TVF detected in plasma

After a median follow-up of 14 months, 100 subjects became infected, 36 in the TDF/FTC arm and 64 in the placebo arm :

44% reduction in the incidence of HIV (95% CI : 15-63, p=0.005)

Effectiveness of Daily PrEP in MSM in the UK

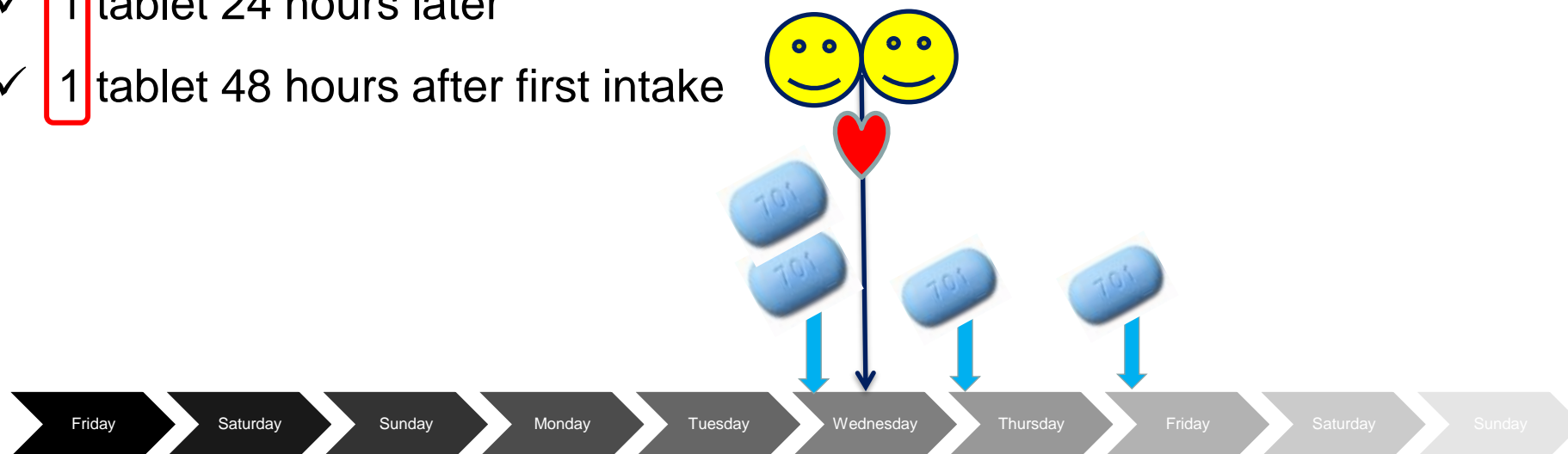


Group	No. of infections	Follow-up (PY)	Incidence (per 100 PY)	90% CI
Overall	23	465	5.0	3.5–6.9
Immediate	3	243	1.2	0.4–2.9
Deferred	20	222	9.0	6.1–12.8

Effectiveness = **86%** (90% CI: 64-96%) P-value = 0.0001

IPIERGAY : Sex-Driven iPrEP

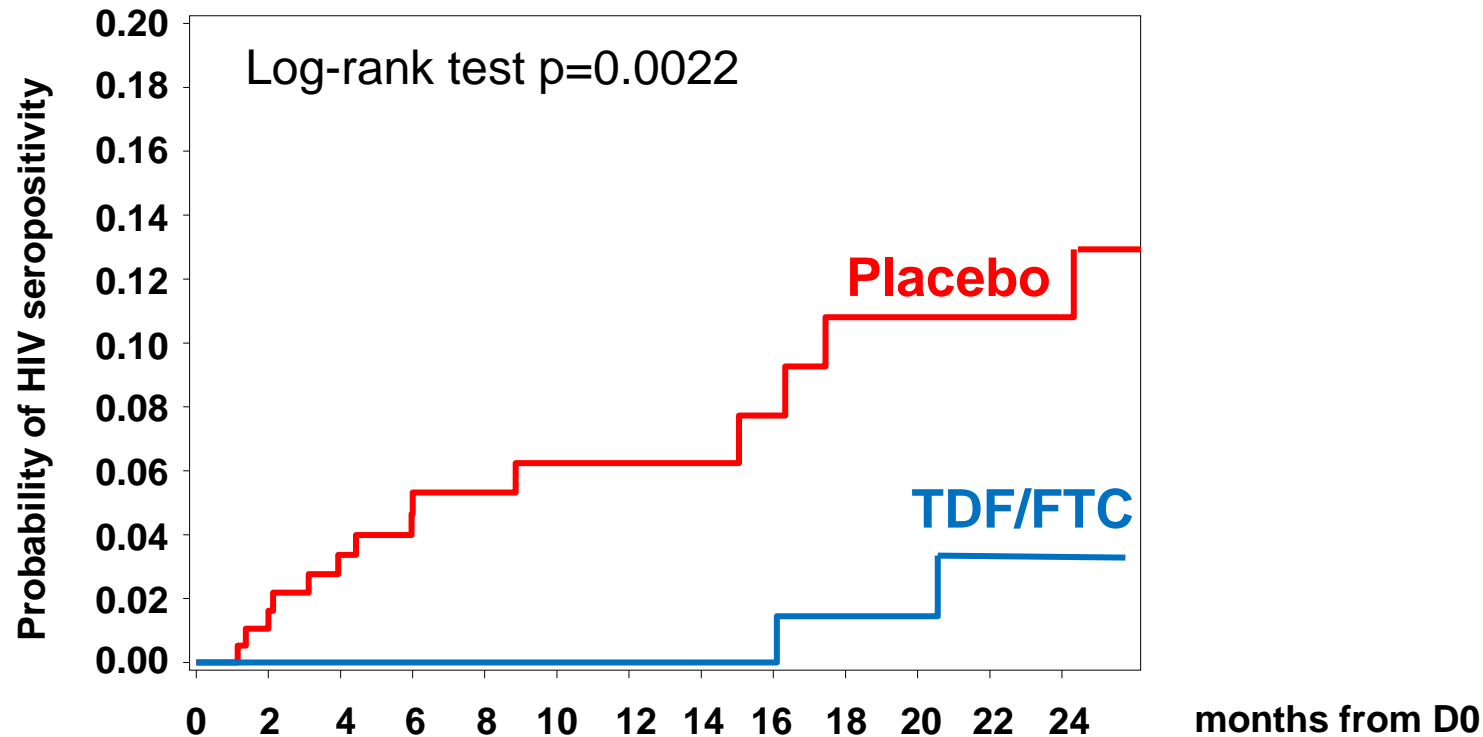
- ✓ 2 tablets 2-24 hours before sex
- ✓ 1 tablet 24 hours later
- ✓ 1 tablet 48 hours after first intake



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

On demand PrEP tells you How to Start and How to Stop PrEP

Effectiveness of On Demand PrEP with TDF/FTC in MSM in France and Canada



Mean follow-up of 12 months: 16 subjects infected (**14 placebo**, **2 in TDF/FTC**)

Incidence : 6.6 /100 PY (9.17 in Paris) placebo and 0.9/100 PY with TDF/FTC

Effectiveness = 86% in relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)

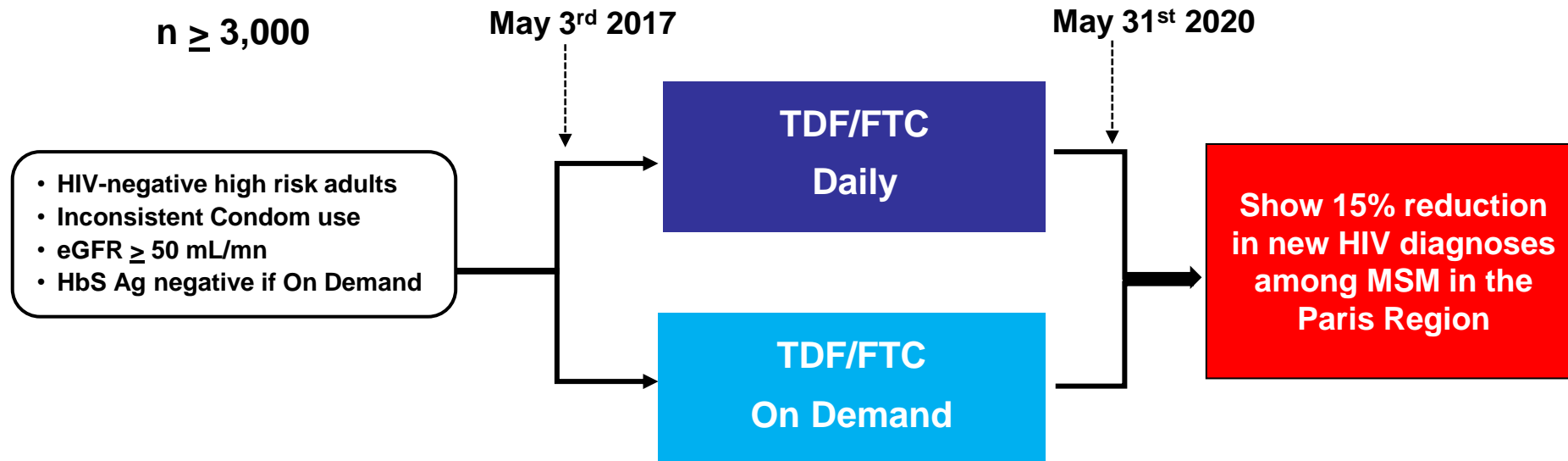
HIV Incidence with On Demand PrEP in MSM

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)
Placebo	212	6.60 (3.60-11.1)
TDF/FTC (double-blind)	219	0.91 (0.11-3.30)
TDF/FTC (open-label)	515	0.19 (0.01-1.08)

Median Follow-up in Open-Label Phase 18.4 months (17.5-19.1)

97% relative reduction vs. placebo

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
- STI screening at physician's discretion (Guidelines recommend every 3 months in MSM)
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

HIV Incidence (mITT Analysis)

Global HIV Incidence: 0.09/100 PY (95% CI: 0.01-0.33) (2 cases)

Mean Follow-up of 8.7 months and 2208 Person-Years

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)	P-value
TDF/FTC (Daily)	1072.9	0.0 (0.0 – 0.3)	0.132
TDF/FTC (On Demand)	1132.7	0.2 (0.0 – 0.6)	

143 HIV-infections averted*

* assuming an incidence of 6.6/100 PY as observed in the Placebo group of the ANRS Ipergay study



**World Health
Organization**

TECHNICAL BRIEF

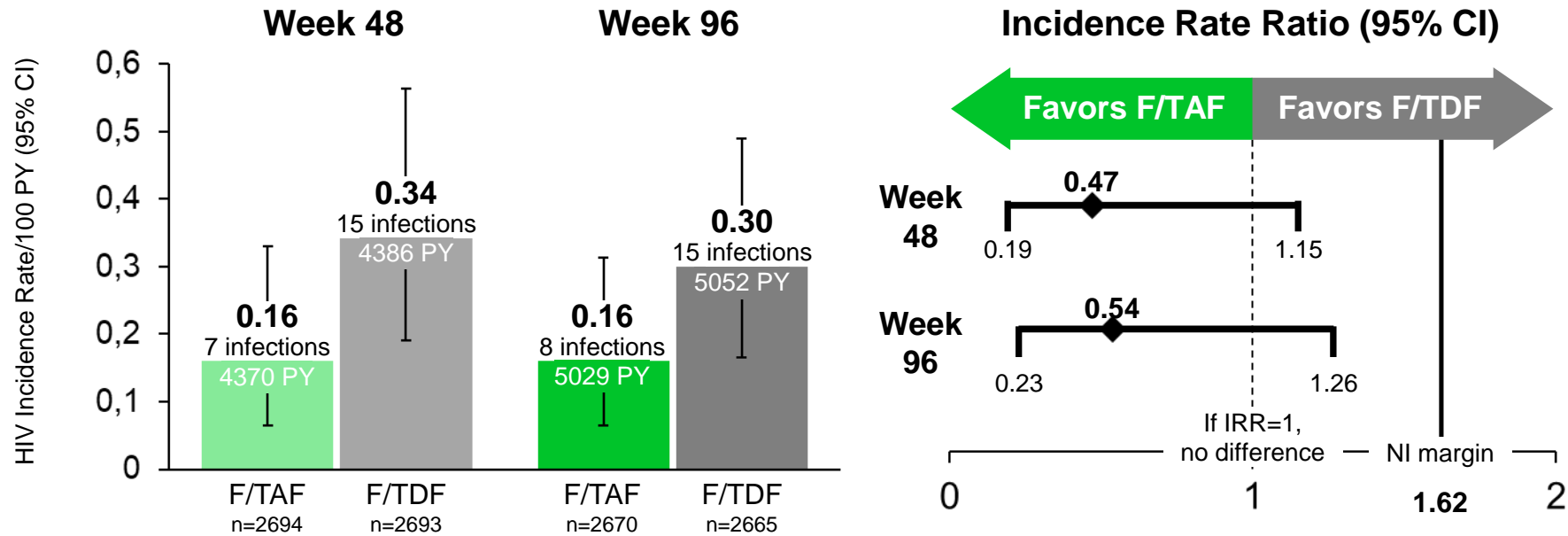
WHAT'S THE 2+1+1?

EVENT-DRIVEN ORAL PRE-EXPOSURE
PROPHYLAXIS TO PREVENT HIV FOR MEN
WHO HAVE SEX WITH MEN: UPDATE TO WHO'S
RECOMMENDATION ON ORAL PREP

JULY 2019



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)

Drug Resistance Selection in Breakthrough HIV-Infection on PrEP with TDF/FTC

- Resistance rare in clinical trials of PrEP
- RAMs assessed: K65R (TDF, FTC), K70E (TDF) or M184V/I (FTC)
- Resistance when seroconverting in the TDF/FTC arm: **M184V/I (1 K65R)**

Trial	N (TDF/FTC)	Undiagnosed Acute Infection At enrolment Nb resistance / total	Seroconverted after enrolment Nb resistance / total
iPrEx	1224	2/2	0/48
Partners PrEP	1579	2/4	0/21
TDF2	611	1/1	0/9
FEM-PrEP	1062	0/1	4/33
VOICE	1003	2/9	1/61
PROUD	275	2/3	0/2
IPERGAY	199	0/2	0/2
DISCOVER (TDF/FTC)	2693	4/4	0/11
DISCOVER (TAF/FTC)	2694	0/1	0/5
TOTAL	11340	13/27 (48%)	5/192 (< 3%)

Acquisition of TDF/FTC Resistant HIV Despite High PrEP Adherence

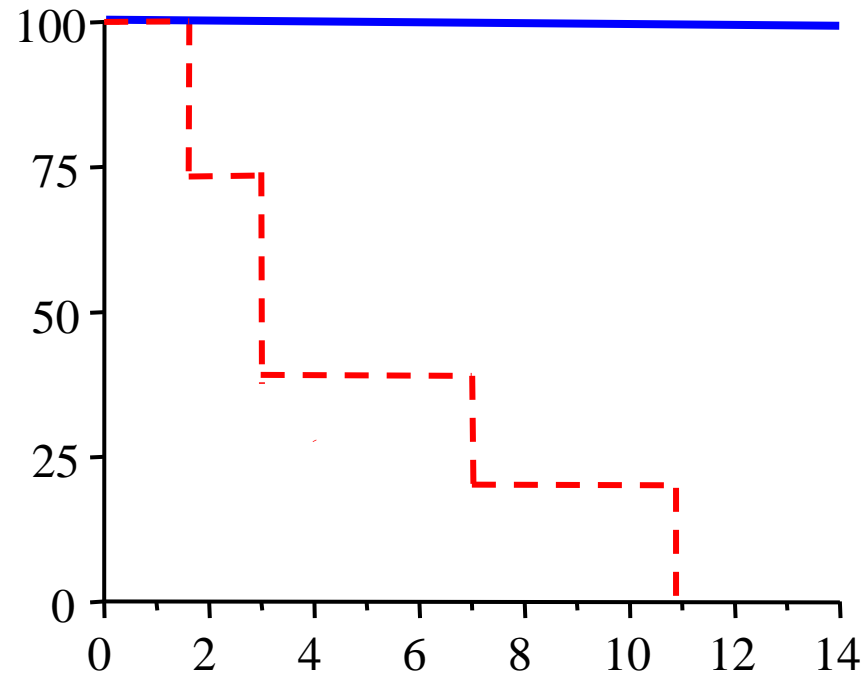
Cases	Time since PrEP Initiation	NRTI RAMs	Drug Concentration*
Knox et al. NEJM 2017	24 months	M184V, K70R, Y215E, M41L	DBS, plasma
Markowitz et al. JAIDS 2017	5 months	M184V, K65R	Hair, DBS
Thaden et al. AIDS 2018	14 months	M184V, K65R, K70T	Hair, plasma
Colby et al. CID 2018	8 weeks	M184V	Hair, plasma
Cohen et al. Lancet HIV 2019	13 months	M184V, L74V	Hair, DBS, plasma

* DBS and hair levels consistent with daily dosing in prior 6 weeks



Effect of TDF/FTC against Rectal Challenges with R-SHIV and **M184V**

% Uninfected Macaques



Oral TDF/FTC (-72h, +2h)
(n = 5)

100% Efficacy

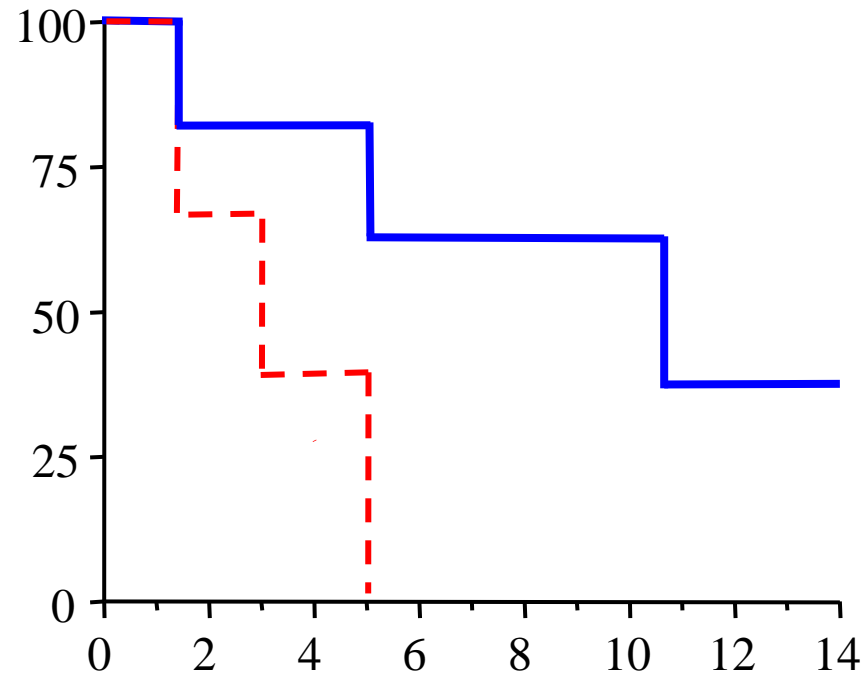
Untreated Controls (n = 5)

Number of weekly rectal SHIV **M184V** exposures



Effect of TDF/FTC against Rectal Challenges with R-SHIV and **K65R**

% Uninfected Macaques



Oral TDF/FTC (-72h, +2h)
(n = 6)

33% Efficacy

Untreated Controls (n = 6)

Number of weekly rectal SHIV **K65R** exposures

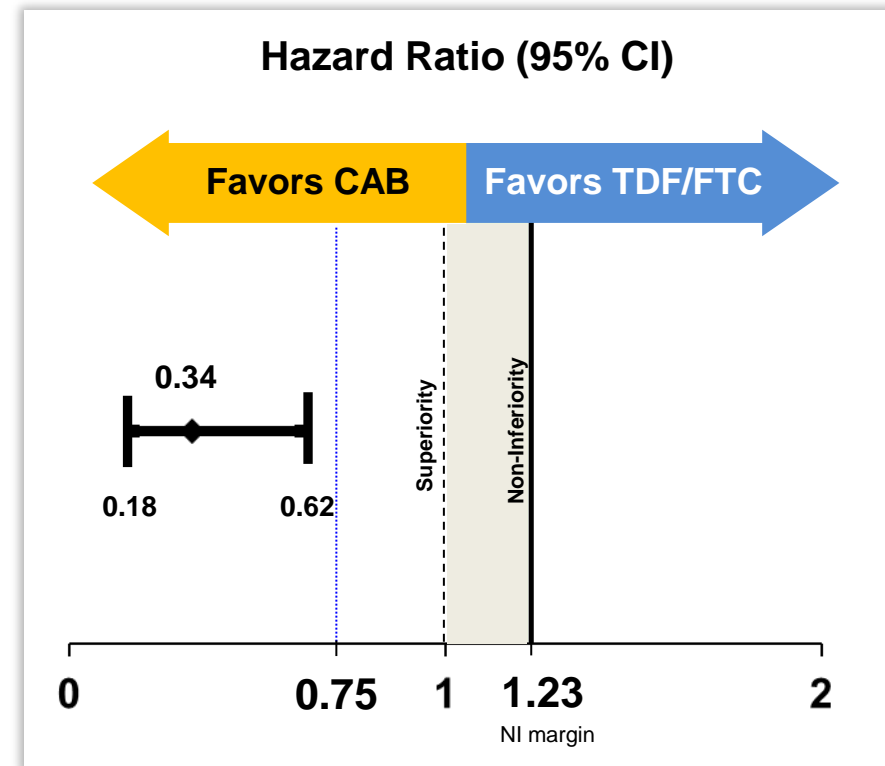
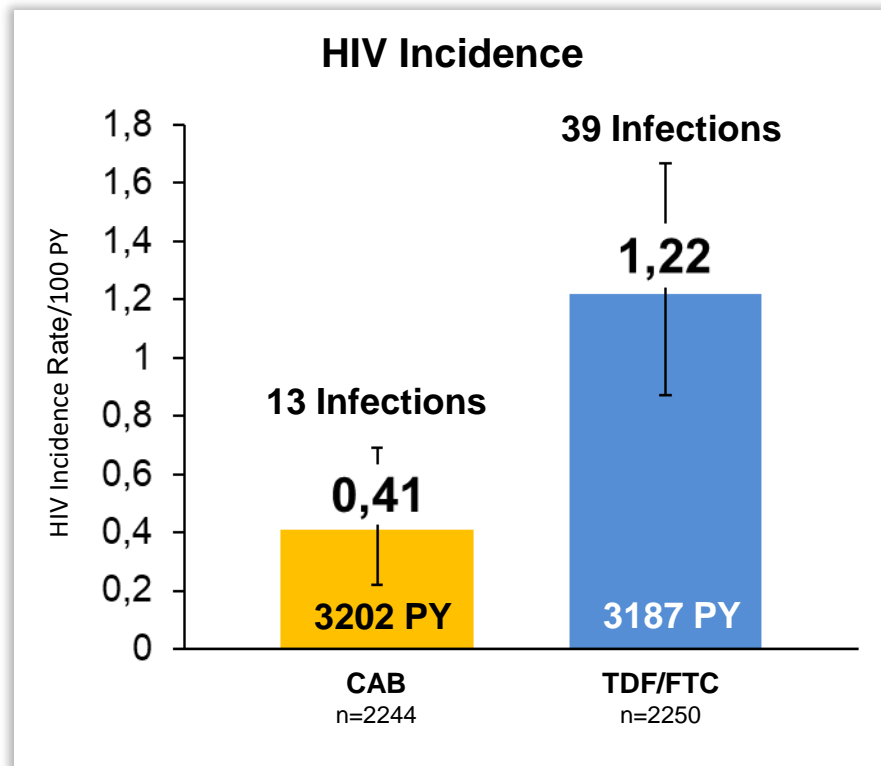
Rates of Transmitted HIV-1 Resistance to TDF/FTC among Treatment Naïve Patients

References	Nb Pts	Years	M184V/I (Nb, %)	K65R (Nb, %)	K70E (Nb, %)
Rhee et al. CID 2019	4,253	2003-2016	20 (0.5%)	2 (0.05%)	0 (0%)
Banez Ocfemia CROI 2014	10,894	2008-2011	44 (0.4%)	3 (0.03%)	4 (0.04%)
Gupta et al. Lancet ID 2017	56,044	2014-2016	292 (0.5%)	(0.1%)	NA
Chan et al. JIAS 2012	19,823	1999-2008	NA	20 (0.1%)	3 (0.015%)
Olson et al. AIDS 2018	4,717	1996-2012	34 (0.7%)	8 (0.2%)	0 (0%)
Visseaux et al. JAC 2020*	1,121	2014-2016	4 (0.4%)	1 (0.1%)	0 (0%)

NA: not available * Primary HIV-infection

PrEP with LA injectable cabotegravir: safe and highly effective for men and transgender women who have sex with men

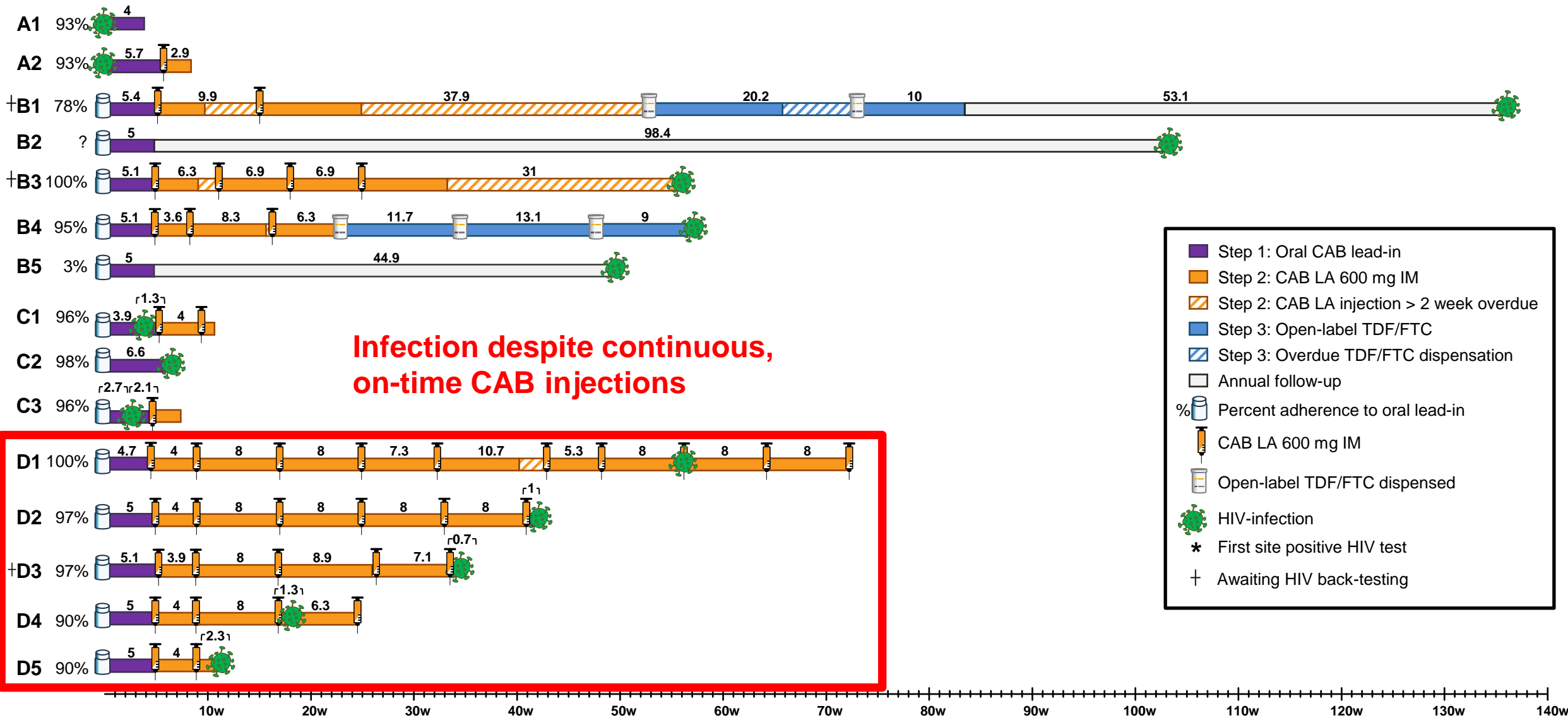
52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY



CI, confidence interval

13 Incident HIV Infections

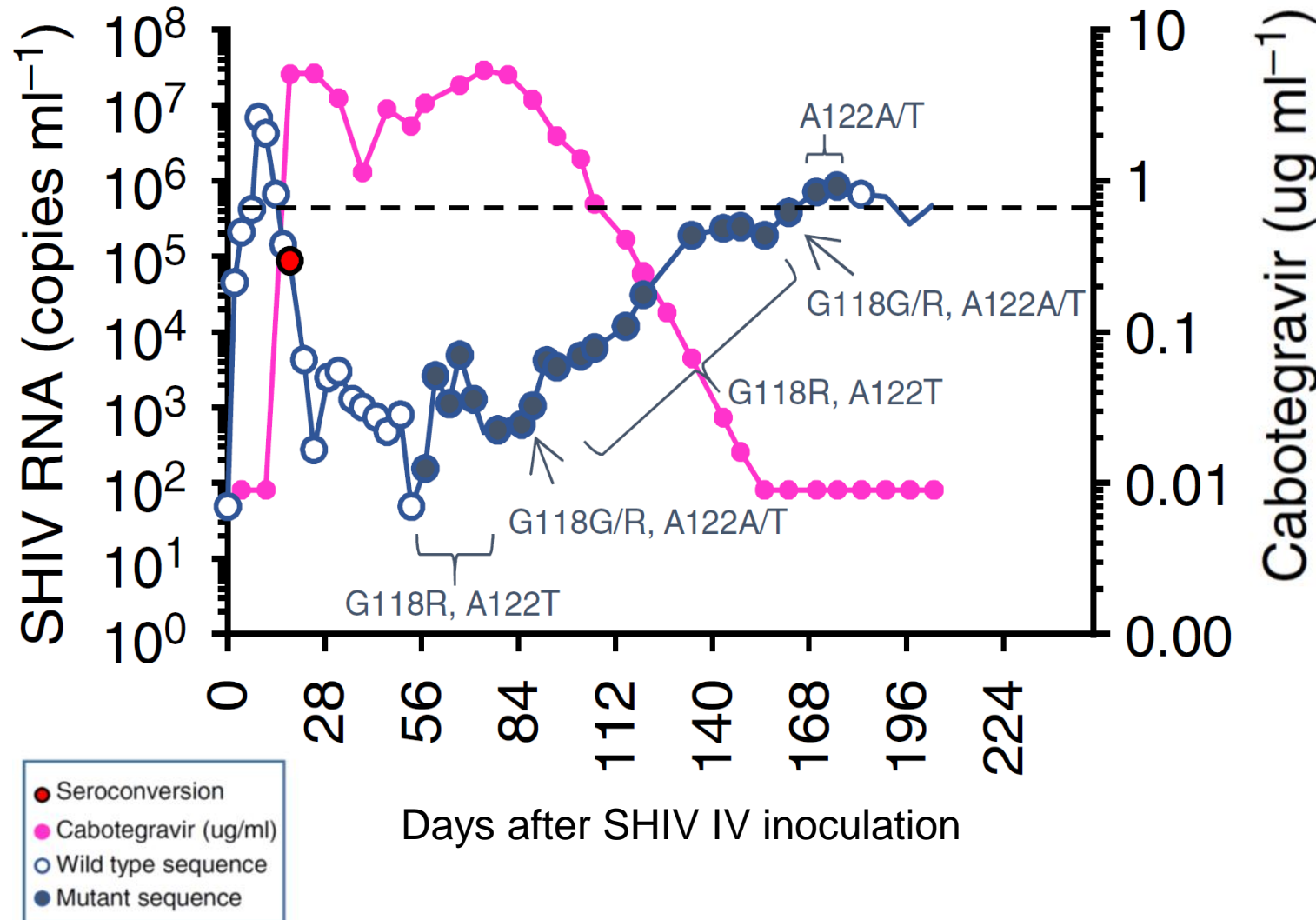
Cabotegravir



Infection despite continuous, on-time CAB injections



Emergence of Integrase Resistance in Macaques Given LA-CAB after Acute SHIV infection



- 6 macaques infected with SIV received CAB-LA before seroconversion
- 3/6 with Integrase RAMs in plasma and vaginal and rectal fluid
- G118R and G140R RAMs confer high level resistance to CAB and cross resistance to all integrase inhibitors
- **Need to exclude HIV-infection before starting CAB-LA**

Summary

- PrEP implementation should be upscaled and key populations should have access to PrEP
- PrEP with oral TDF/FTC is very effective when taken as recommended
- Rule out acute HIV-infection before starting PrEP
- Rare true biomedical failures
- Thorough investigation of biomedical failures

Acknowledgments



Implementation of PrEP Efficacy and Resistance Considerations

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ANRS and INSERM U944, France

Asia Pacific HIV Clinical Forum Meeting

