

La PrEP d'aujourd'hui et de demain

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Global HIV Epidemic

2020
Globally

37.7 million

People living with HIV

1.5 million

People newly infected



- 31%

New infections annually
relative to 2010



- 47%

Deaths annually
relative to 2010



+ 49% New diagnoses annually relative to 2010 in the WHO European Region

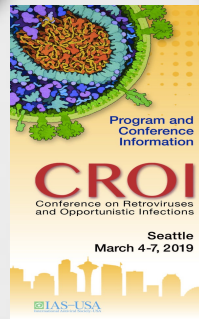
The Fundamental Scientific and Clinical Basis for the Plan to End the HIV Epidemic in the United States



Treatment
as Prevention
(TasP)



Pre-Exposure
Prophylaxis
(PrEP)



A Revolution in HIV Prevention



US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE

A CLINICAL PRACTICE GUIDELINE



JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2020 Recommendations of the International Antiviral Society-USA Panel

Michael S. Saag, MD; Rajesh T. Gandhi, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Melanie A. Thompson, MD; Paul E. Sax, MD; Davey M. Smith, MD; Constance A. Benson, MD; Susan P. Buchbinder, MD; Carlos del Rio, MD; Joseph J. Eron Jr, MD; Gerd Fätkenheuer, MD; Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

Supplemental content

IMPORTANCE Data on the use of antiretroviral drugs, including new drugs and formulations, for the treatment and prevention of HIV infection continue to guide optimal practices.

OBJECTIVE To evaluate new data and incorporate them into current recommendations for initiating HIV therapy, monitoring individuals starting on therapy, changing regimens, preventing HIV infection for those at risk, and special considerations for older people with HIV.

SYNTHESE

Réponses rapides dans le cadre de la COVID-19 - Prophylaxie du VIH par ténofovir disoproxil / emtricitabine dans le cadre de l'urgence sanitaire

Validée par le Collège le 15 avril 2021



PrEP Initiations by Country, 2022

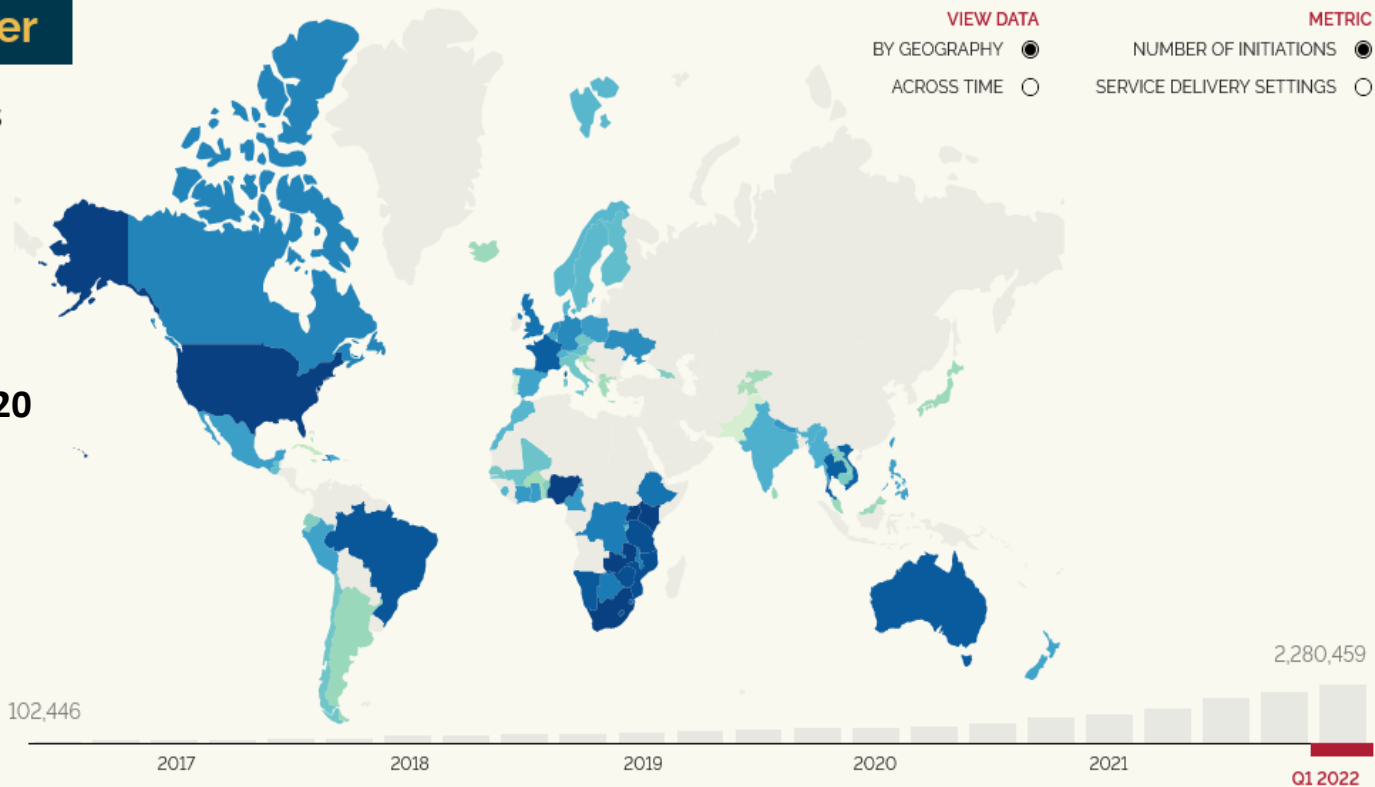
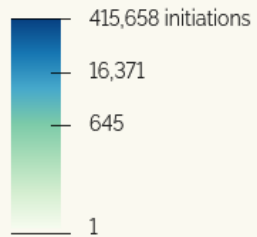
The Global PrEP Tracker

Number of PrEP Initiations

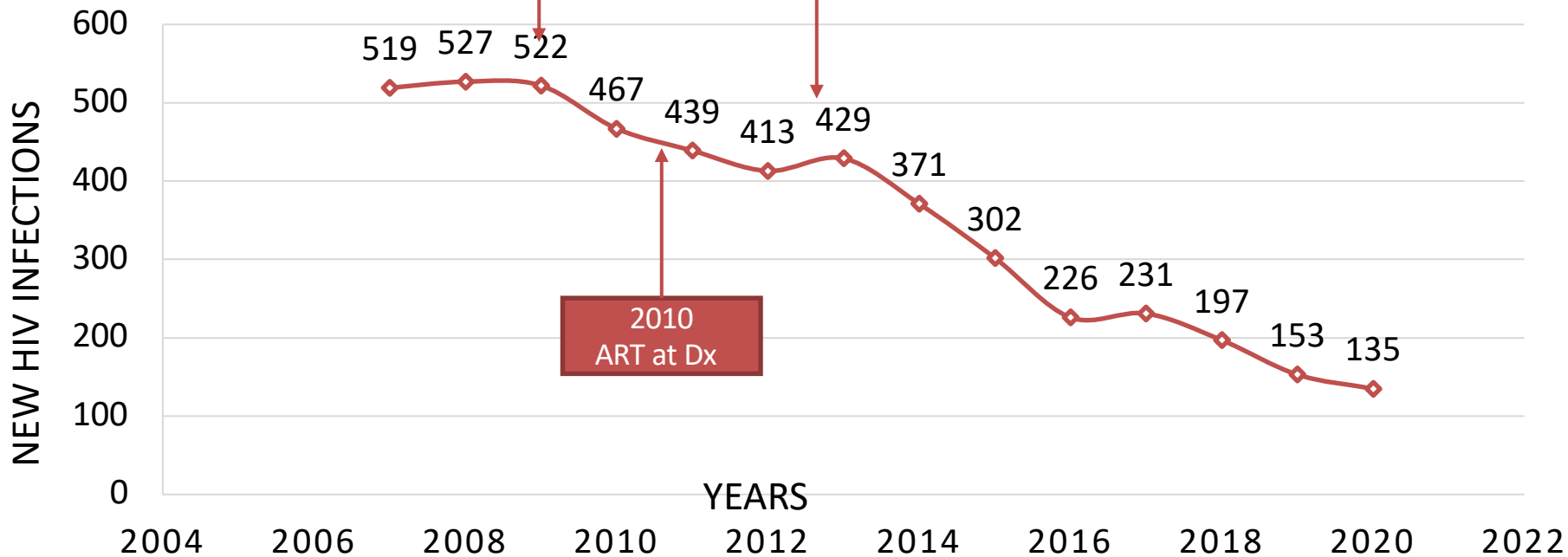
Q1 2022

2,280,459 total

2016 UN Commitment
3M people on PrEP in 2020



HIV Epidemic Trends in San Francisco



PrEP Regimens Approved

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





Effectiveness of Daily PrEP with TDF/FTC 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

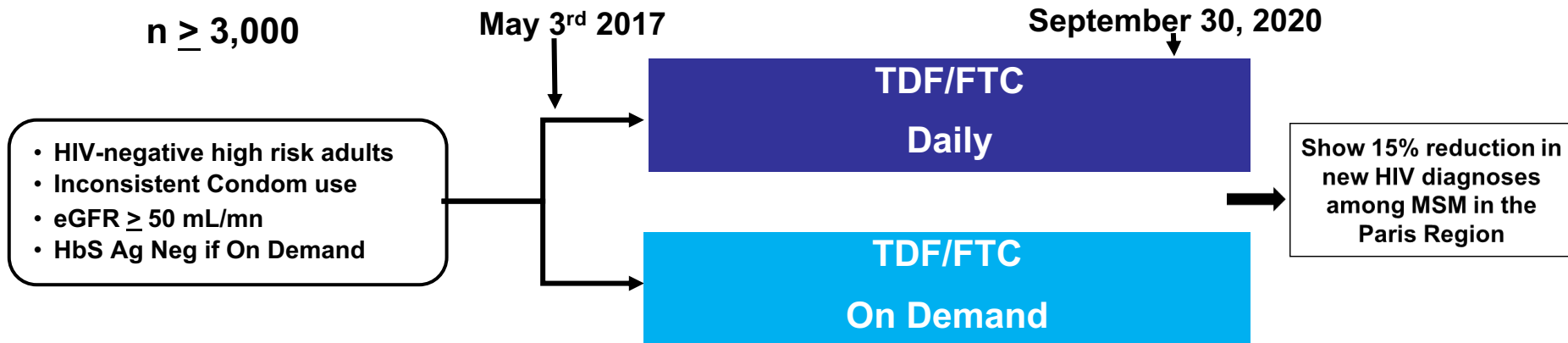
Effectiveness of On Demand PrEP with TDF/FTC in MSM in France and Canada

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
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

PrEP with Daily or On Demand TDF/FTC among MSM

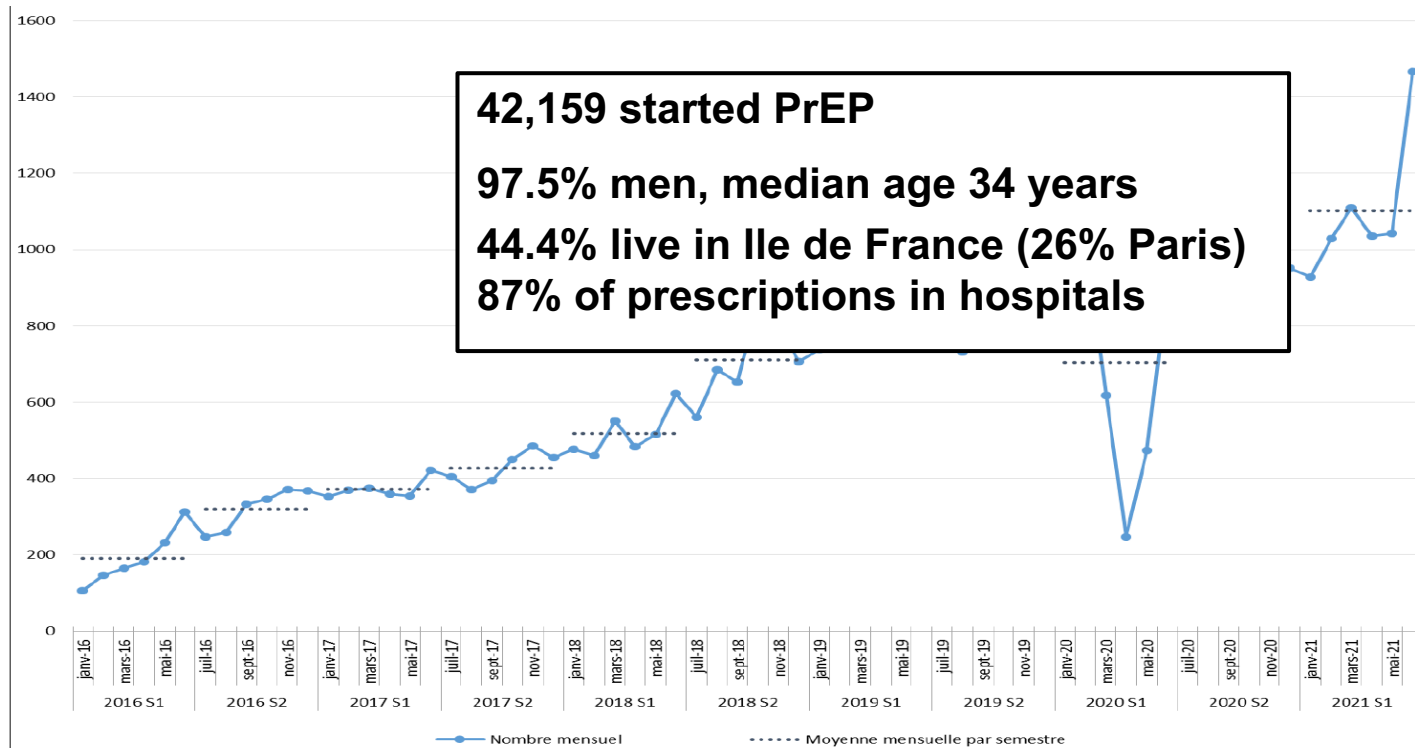
Global HIV Incidence: 0.11/100 PY (95% CI: 0.04-0.23) (6 cases)

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

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)	IRR (95%CI)
TDF/FTC Daily	2583.25	0.12 (0.02 – 0.34)	0.99 (0.13-7.38)
TDF/FTC On Demand	2553.68	0.12 (0.02 – 0.34)	



Number of People Who Initiated PrEP with TDF/FTC in France (2016-2021)



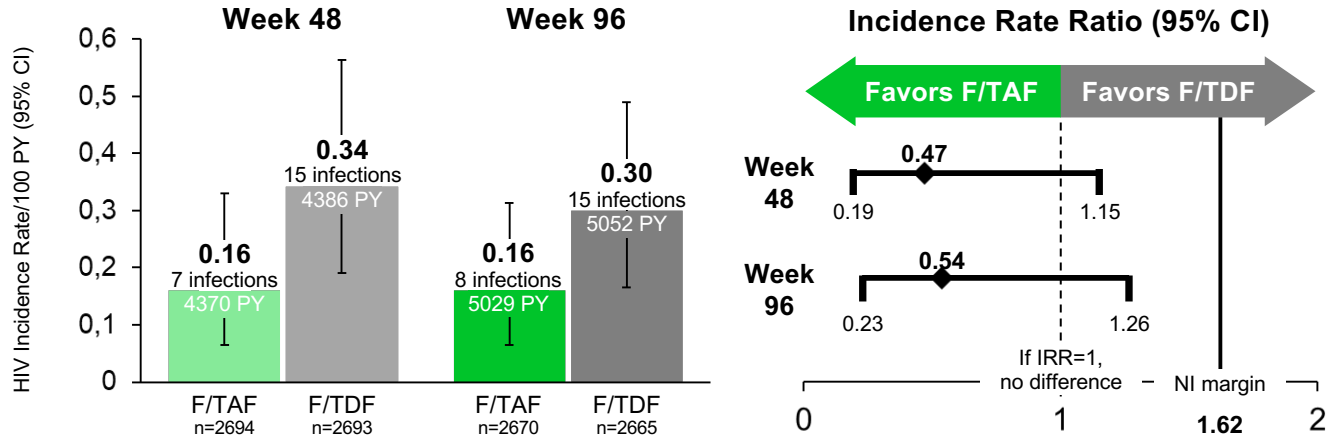
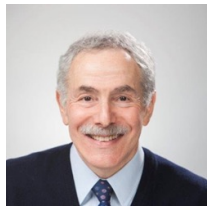
PrEP Effectiveness in Men at high risk of HIV-infection in France (2016-2020)



	Cases	Controls*	Adjusted OR (95% CI)	PrEP Effectiveness (95% CI)
PrEP non consumers	183 (71%)	622 (51%)	Ref	Ref
PrEP consumers				
All	73 (29%)	591 (49%)	0.40 (0.29-0.54)	60% (46, 71)
< 50% follow-up	57 (22%)	239 (20%)	0,82 (0.57-1.18)	18% (-18; 43)
50-74% follow-up	11 (4%)	117 (10%)	0.31 (0.16-0.59)	69% (41, 84)
> 75% follow-up	5 (2%)	235 (19%)	0.07 (0,03-0.16)	93% (84, 97)
Excluding Periods of PrEP Discontinuation	21 (10%)	417 (43%)	0.14 (0,08-0.22)	86% (78, 92)

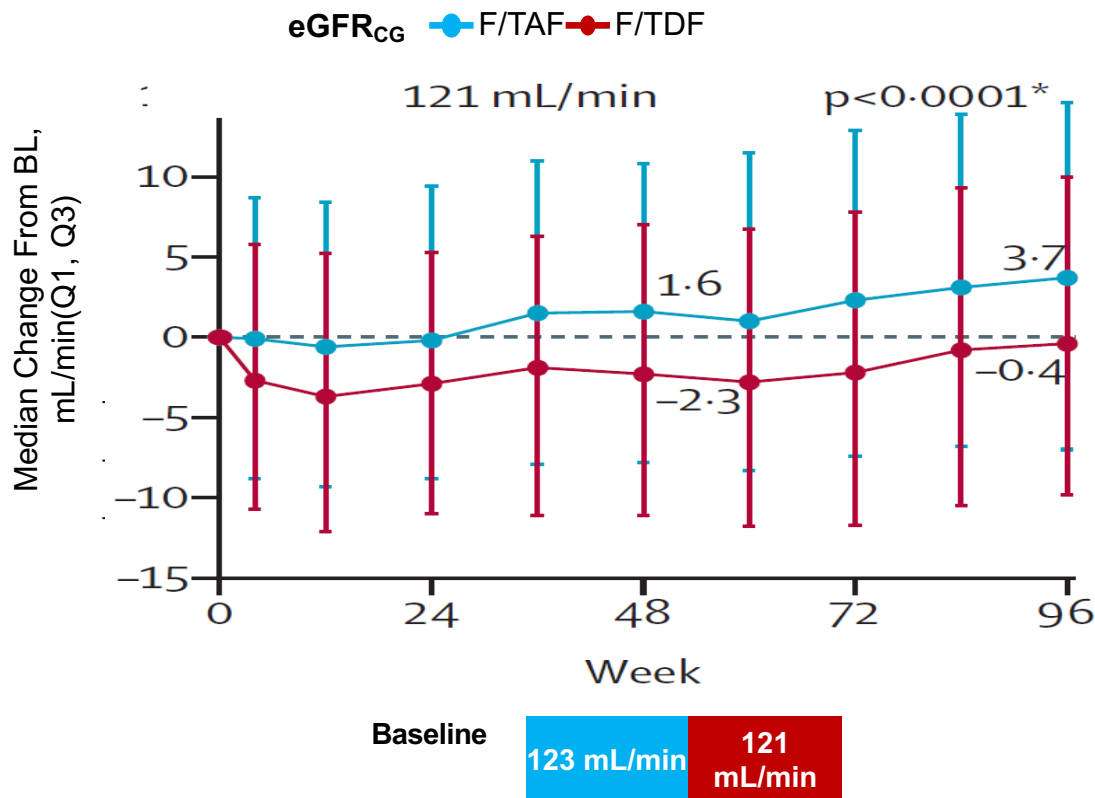
*Men, 18-65 y, living in mainland France using PrEP or with ≥ 4 HIV tests with 1 STI

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



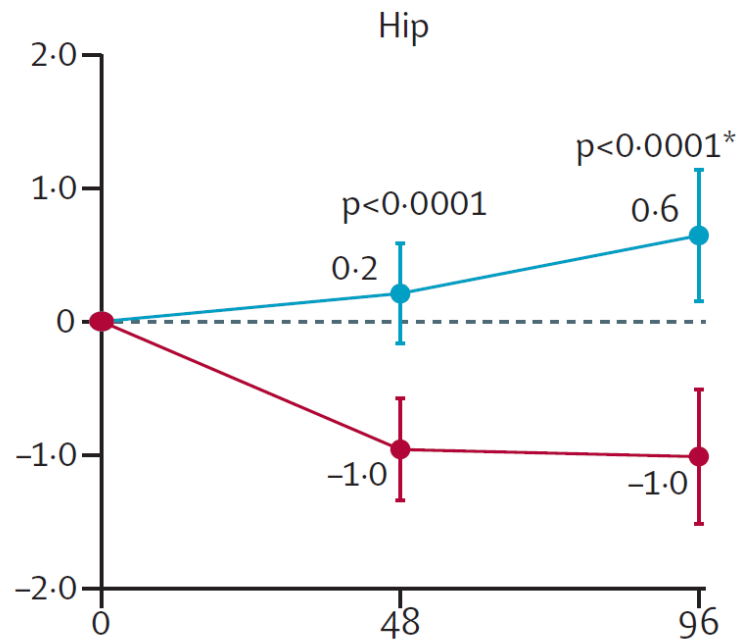
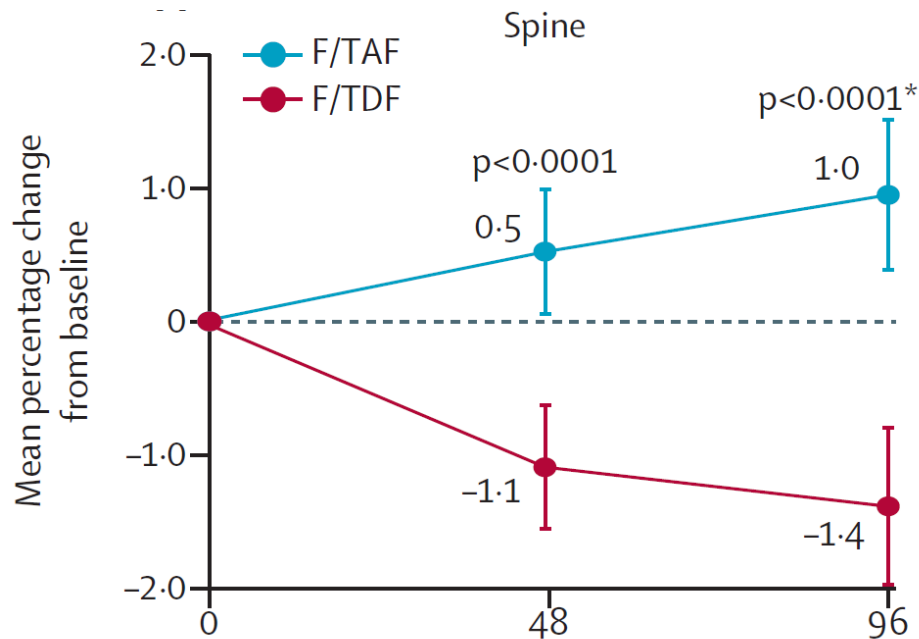
- F/TAF is noninferior to F/TDF for HIV prevention (upper bound of the IRR 95% CI: <1.62)

DISCOVER: eGFR changes at Week 96



- 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-yr old man with no comorbidities)

DISCOVER BMD Sub-study at Week 96



n	Week	
F/TAF	159	144
F/TDF	160	140

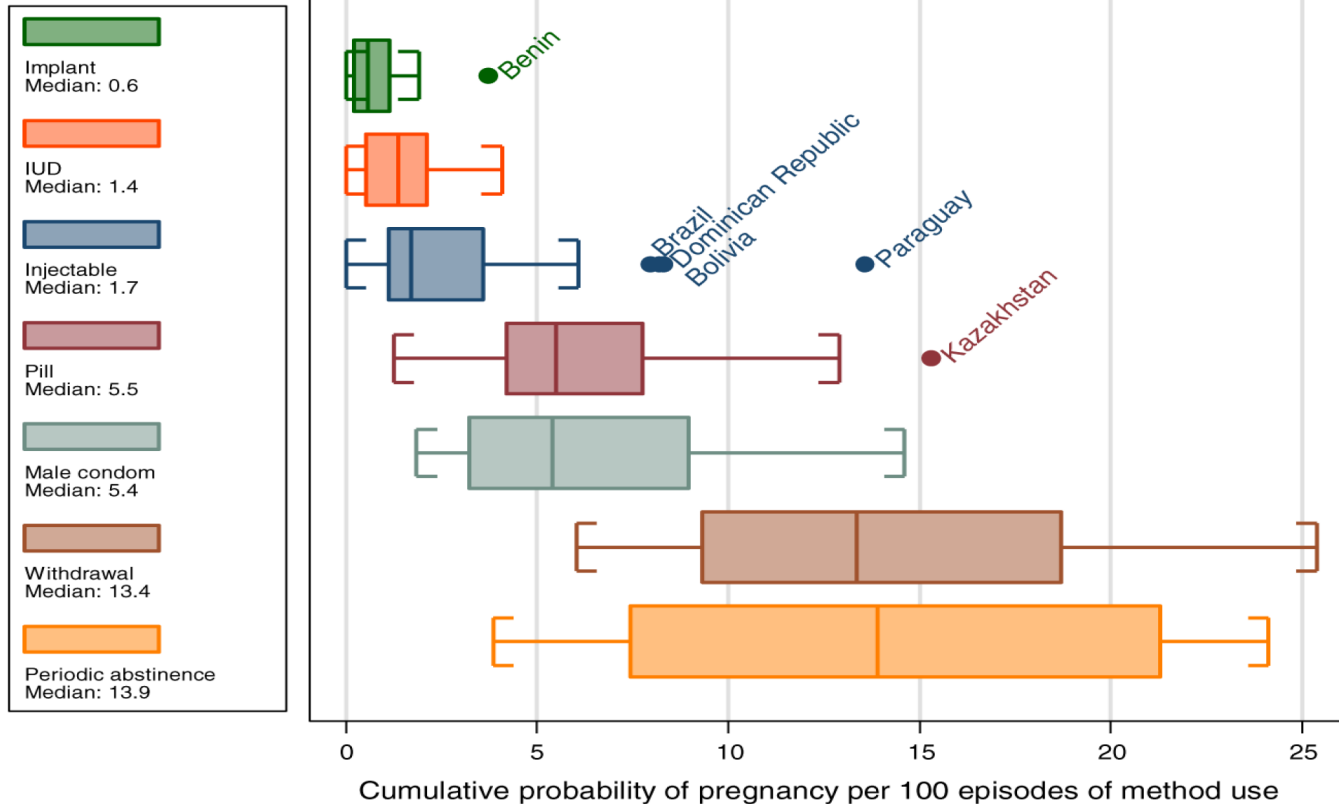
Week	
158	140
158	137

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

Limitations of Oral PrEP

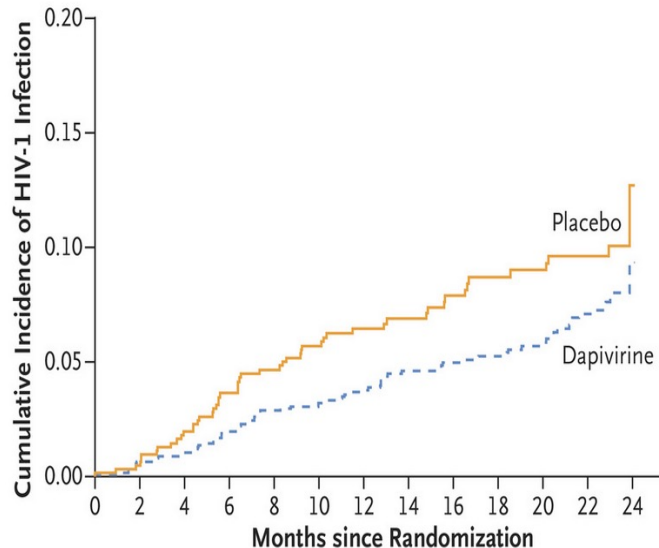
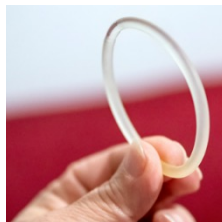
- Stigma associated with pill intake
- Gastro-intestinal AEs (nausea, diarrhea)
- No data yet with TAF/FTC in women and with on demand use
- Cost of TAF/FTC (300 Euros/month) vs generic TDF/FTC
- **Long-term adherence to pills: daily or on demand regimen**

Failure Rate of Different Contraceptives Methods in 43 Countries





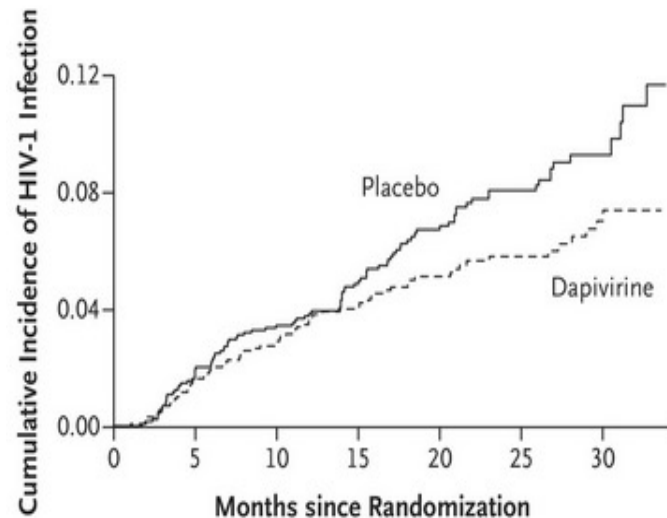
Dapivirine Vaginal Ring



- . 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:

Nel et al. NEJM 2016; Lancet HIV 2021

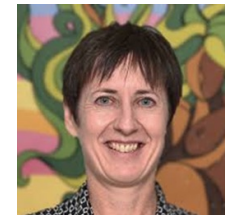


2629 women, mean age 27 years in Sub-Saharan Africa
Reduction in HIV incidence : **27%** (95% CI: 1-46, p=0.046)
39% reduction (95% CI: 14-65) in HIV-incidence in HOPE:

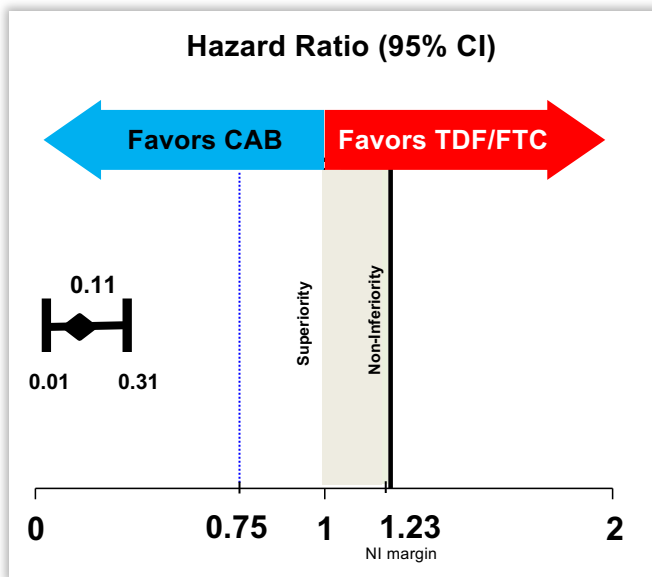
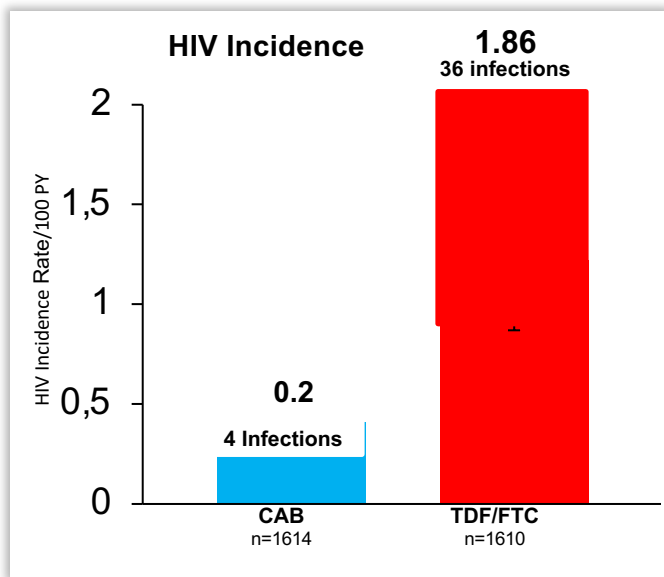
Baeten et al. NEJM 2016; Lancet HIV 2021



PrEP with LA Injectable Cabotegravir Highly Effective for Women



38 HIV infections in 3223 women, median age 26 years
Botswana, Eswatini, Kenya, Malawi, Uganda, Zimbabwe

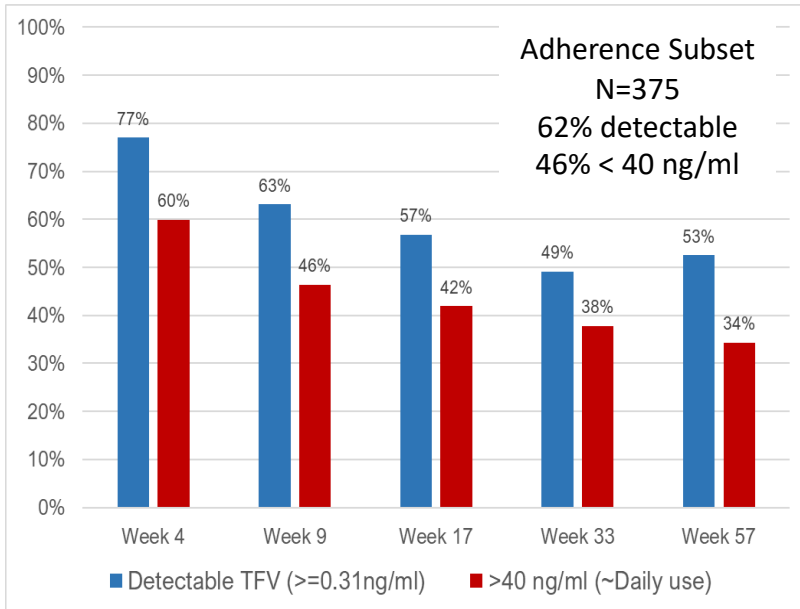


CI, confidence interval

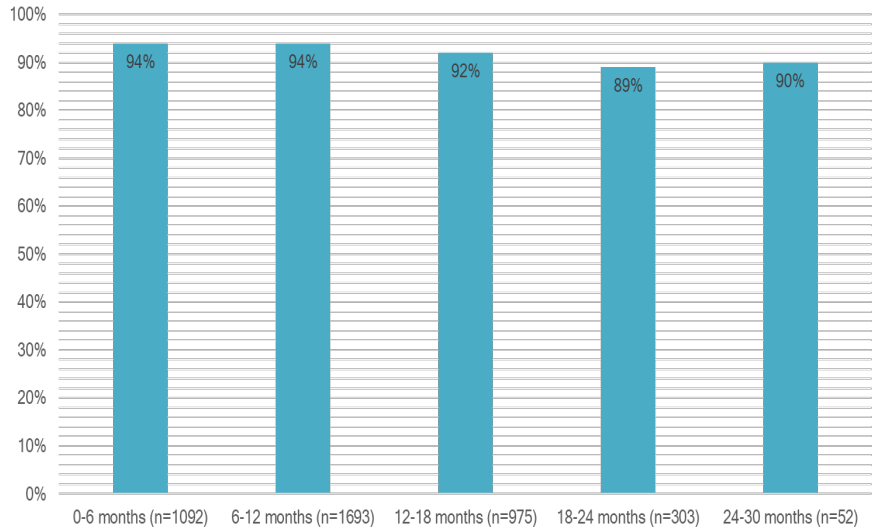


Adherence to Pill and Injections

TFV Plasma Concentrations



Cabotegravir Injections Coverage

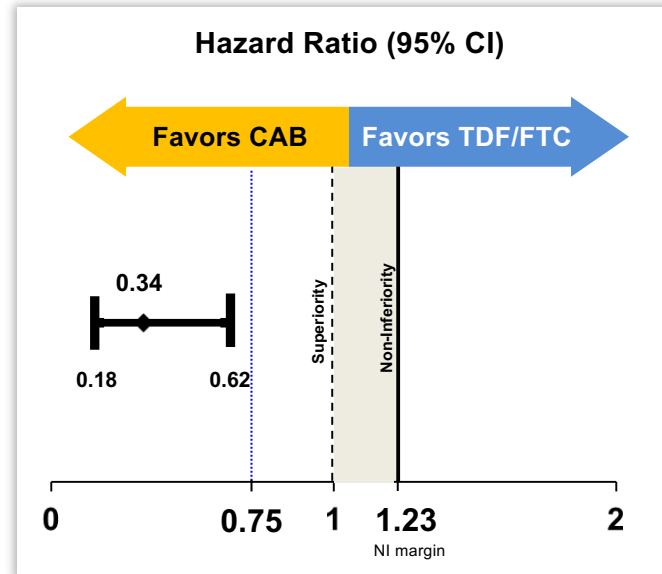
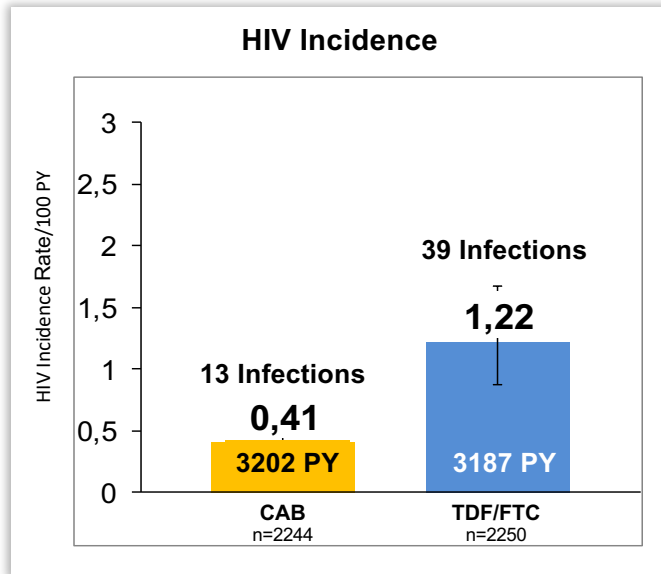


- Both products safe and well tolerated
- No discontinuation due to injection site reaction
- Similar pregnancy outcomes

PrEP with LA Injectable Cabotegravir Highly Effective for MSM and TGW



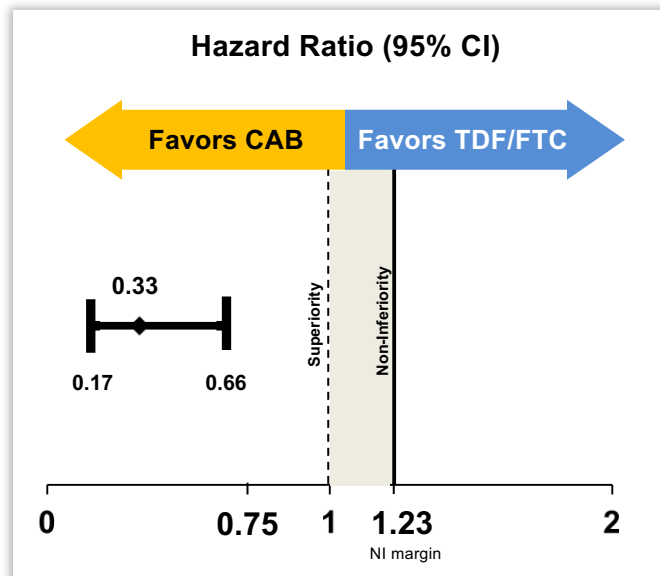
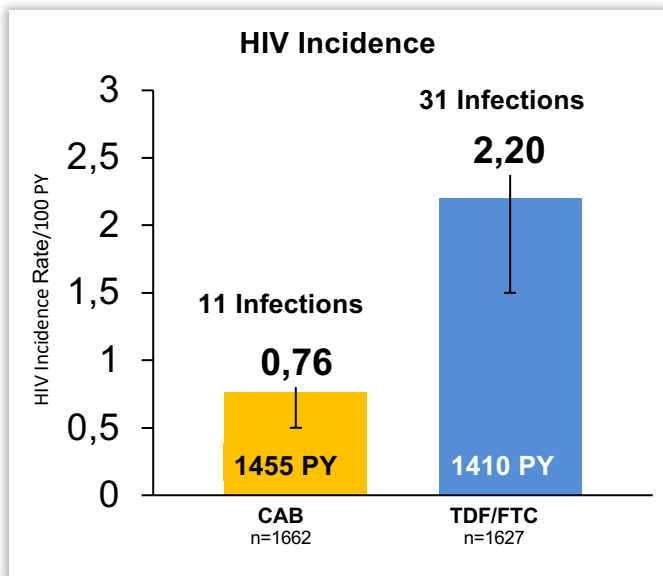
52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up



CI, confidence interval

LA Cabotegravir Remains Highly Effective in the Open Label Phase (1y)

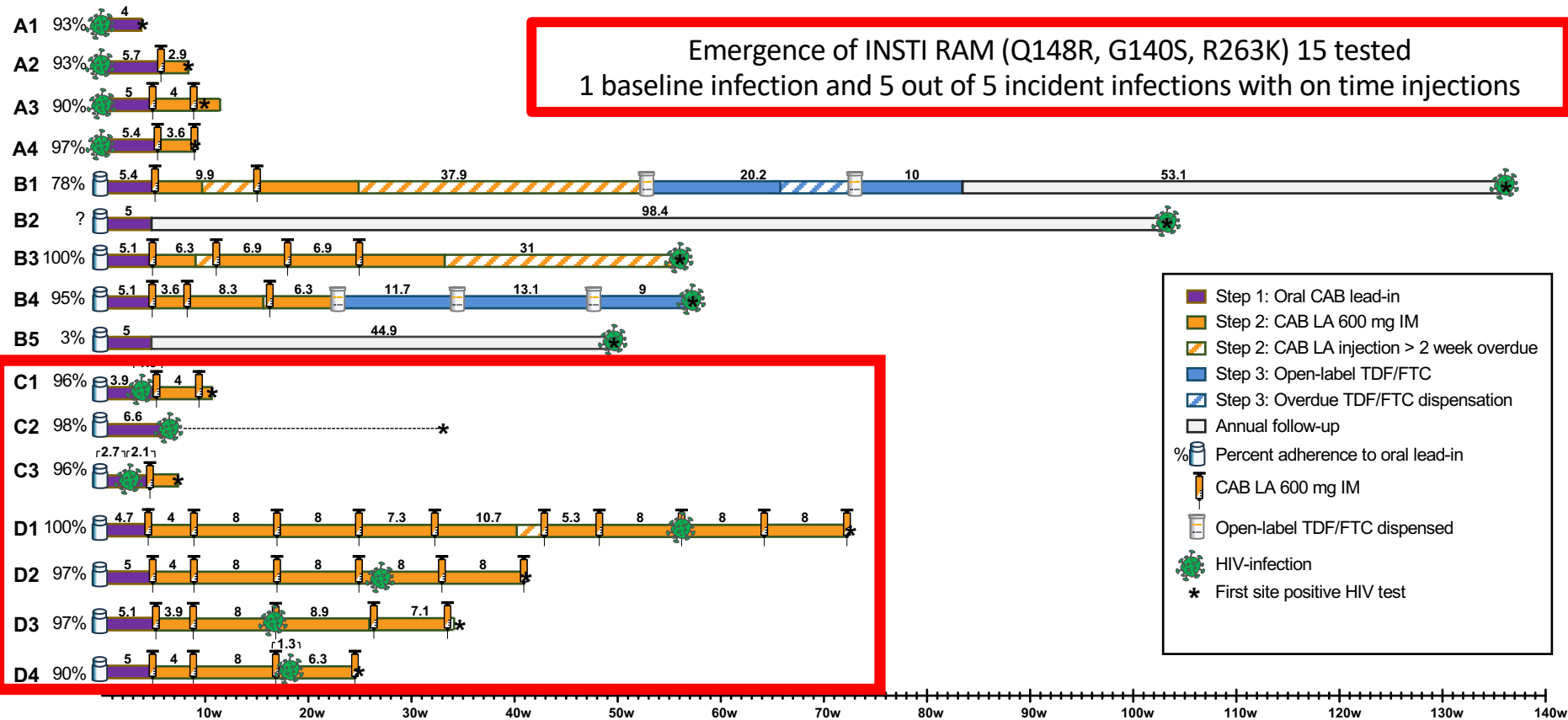
42 incident HIV infections in 2865 PY of follow-up
10.4 months median per-participant follow-up



CI, confidence interval

Incident HIV Infections Despite On Time Cabotegravir Use

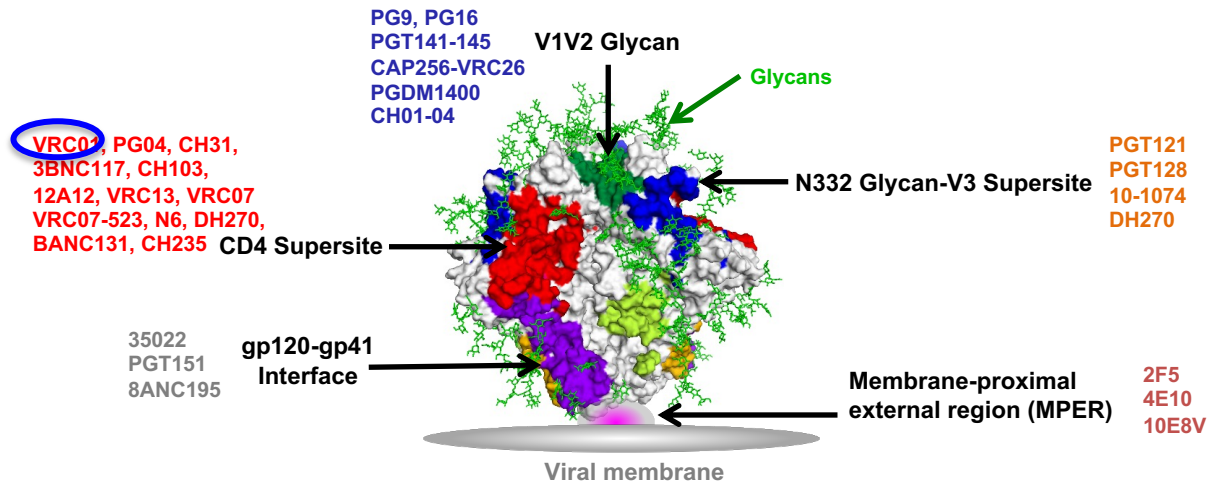
Emergence of INSTI RAM (Q148R, G140S, R263K) 15 tested
 1 baseline infection and 5 out of 5 incident infections with on time injections



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 and forgiveness
- Injection site reactions
- Emergence of INSTI-R with potential cross-resistance to DTG
- Dissemination of INSTI- Resistance
- Cost of drug (450 Euros/month) and implementation
- **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



Prevention Efficacy of bNabs



- Pooled analysis of 2 AMP trials in 4623 MSM and young Women
- Overall non significant reduction in HIV-1 incidence with VRCO1:

Reduction in HIV incidence of 8.8% in Women, 26.6% in MSM ($P > 0.10$)

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)



HIV VACCINE
TRIALS NETWORK

AMP Studies Summary



- Proof of concept that long-term bNabs can prevent HIV-acquisition
- In vitro HIV-1 susceptibility to VRCO1 influences preventive efficacy (only 30% of the circulating HIV-1 strains exhibited $IC_{80} < 1 \mu\text{g/ml}$)
- A neutralization titer or Ab concentration in serum established as a biomarker of protection
- Multiple bNabs will be needed for optimal prevention

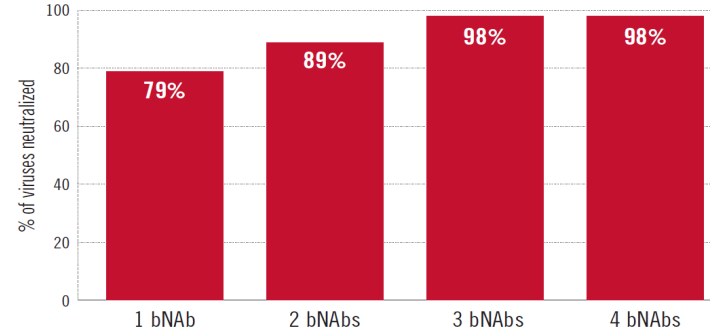
Broadly Neutralizing Antibody Combinations in Development

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

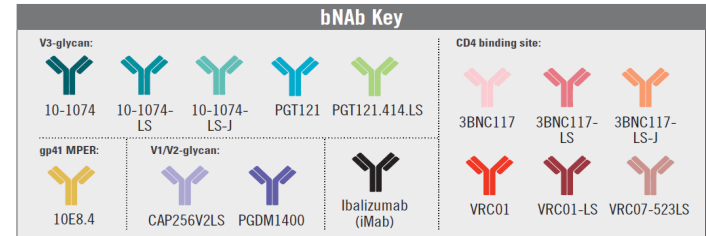
Multispecific: Parts of two or more antibodies on a single antibody				
Regimen	Status	Route	Research Institution	Trial Name
SAR441236	Phase I, Planned	IV	Sanofi, NIAID	HVTN 129/ HPTN 088
	Phase I, Ongoing	IV, SC	ADARC	AAAS1239

Combining bNAb to broaden neutralization*

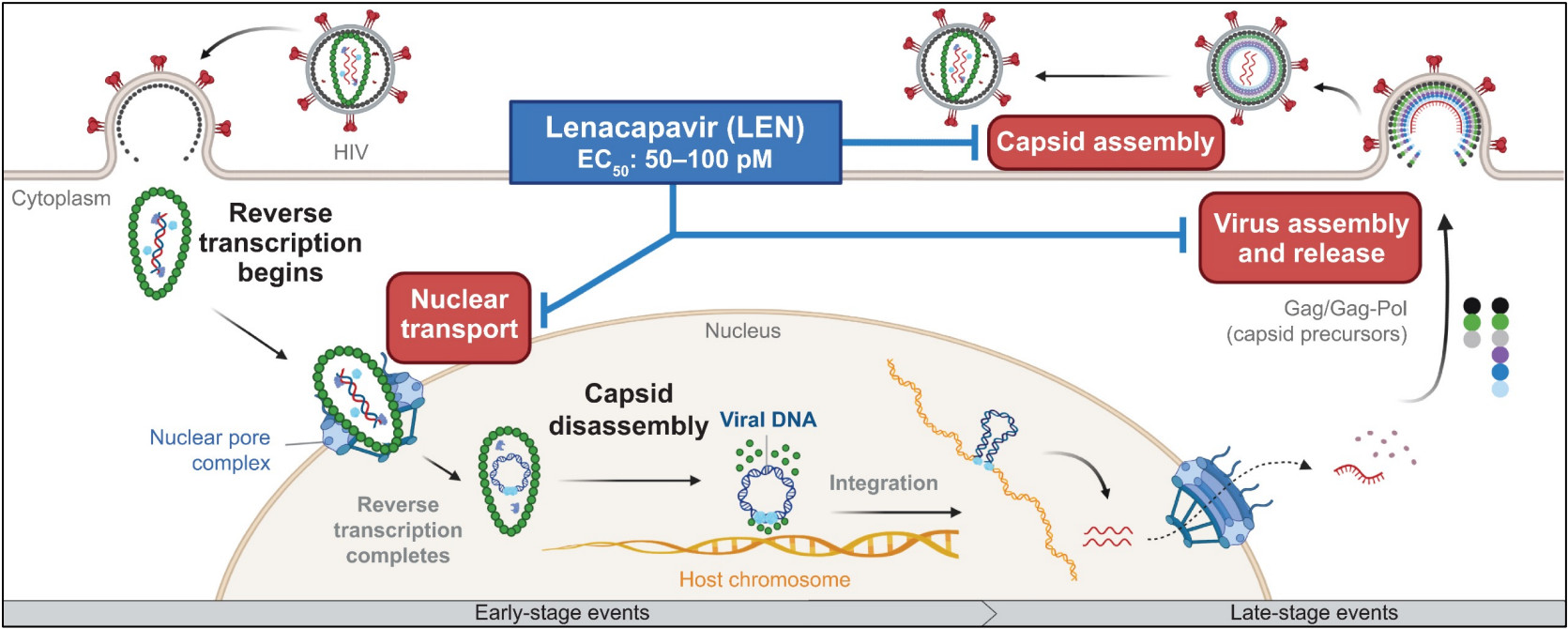


Different antibodies have different neutralizing activities. Modeling and preclinical studies suggest that combining bNAb may lead to broader neutralization compared to giving bNAb alone, and multispecific antibodies might perform better than combinations. Clinical trials will validate whether these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

*Data: Kong et al., 2015



Lenacapavir Targets Multiple Stages of HIV Replication Cycle

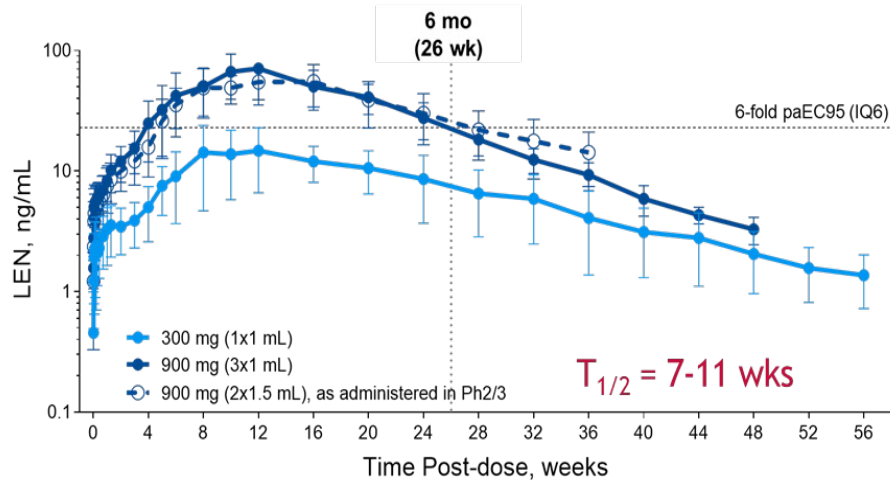


EC₅₀, half-maximal effective concentration; Gag, group antigens; Pol, polyprotein.

LEN Can Be Administered Both Subcutaneously and Orally

Single dose s.c. formulation

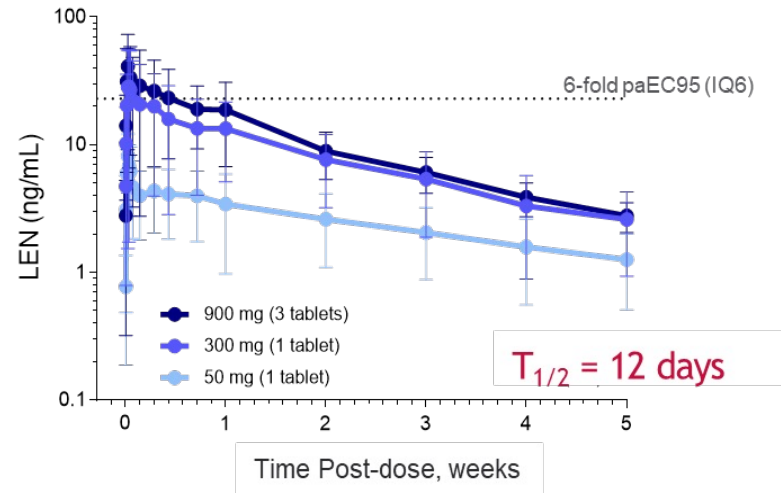
Begley R, et al., AIDS 2020



- Adjustable dosing frequency
- **Once every 6 months dosing feasible**

Single dose oral formulation

Begley R, et al., CROI 2020

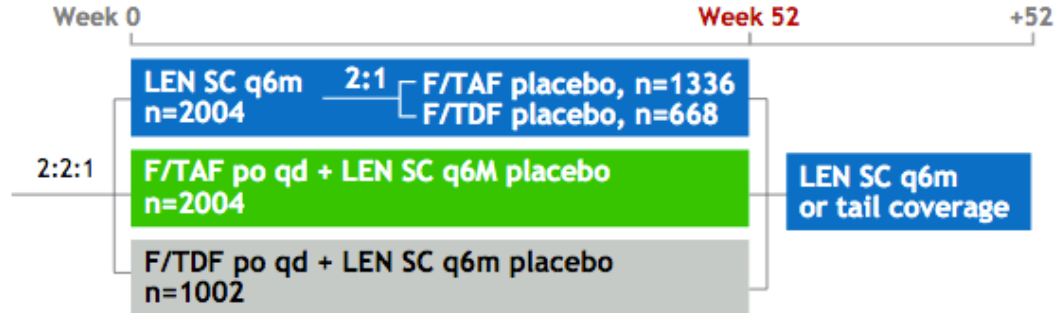


- Accumulation with repeated oral dosing
- Minimal food effect
- **Once-weekly dosing feasible**

Lenacapavir Prevention Trial in Women

Two Primary Endpoints:
 1. LEN vs bHIV
 2. F/TAF vs bHIV

Women's HIV Prevention Study
 Cisgender women and adolescent girls ≥ 35 kg at risk for HIV
 N = ~5000



- Sites in South Africa, Kenya, and Uganda with bHIV $\geq 3.5/100$ PY
- External controls:

Non-PrEP background HIV (bHIV)	Active
<ul style="list-style-type: none"> ▪ Recency assay ▪ bHIV historical HIV incidence 	<ul style="list-style-type: none"> ▪ D4P F/TAF ▪ D4P F/TDF

Other trials planned in MSM and TGW vs daily TDF/FTC in 3,000 in USA and South Africa and in IV drug users

Summary

- The ideal PrEP agent is not yet available
- Oral PrEP is highly cost-effective
- CAB LA for people unlikely to adhere to oral regimen
- More choices = More people on PrEP
- **The most effective PrEP agent is the one people use !**

Acknowledgments

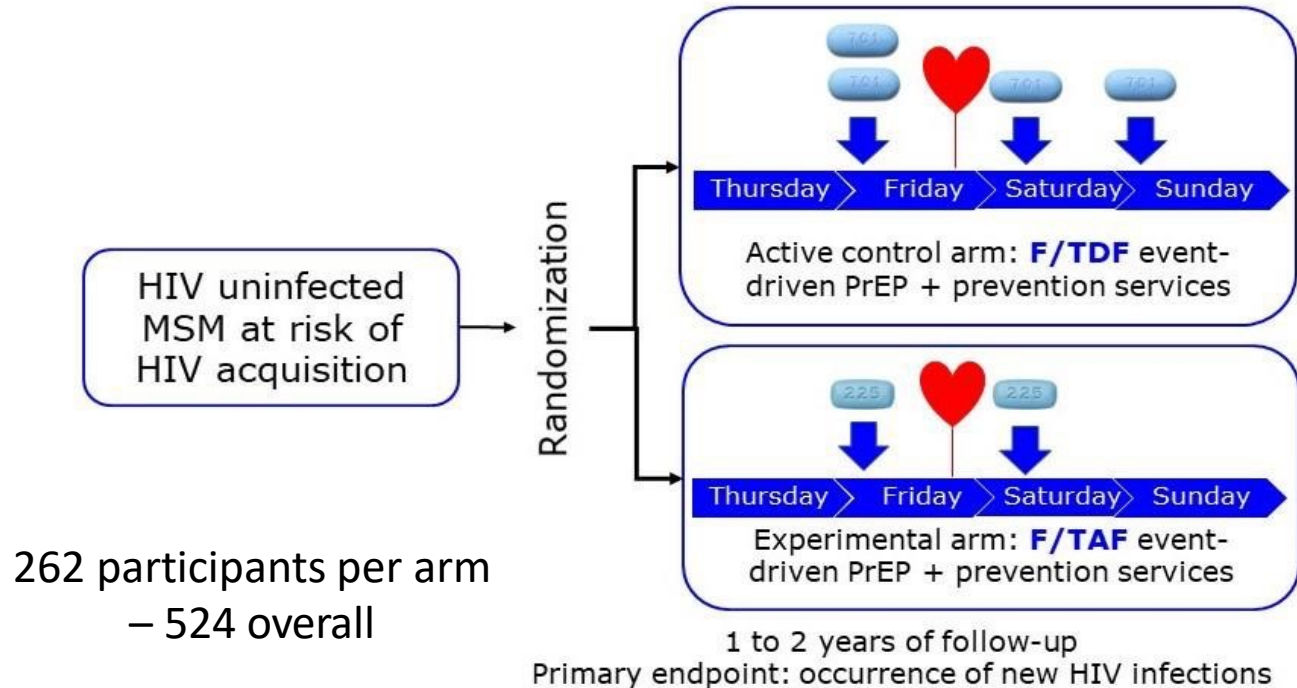


BILL & MELINDA
GATES foundation

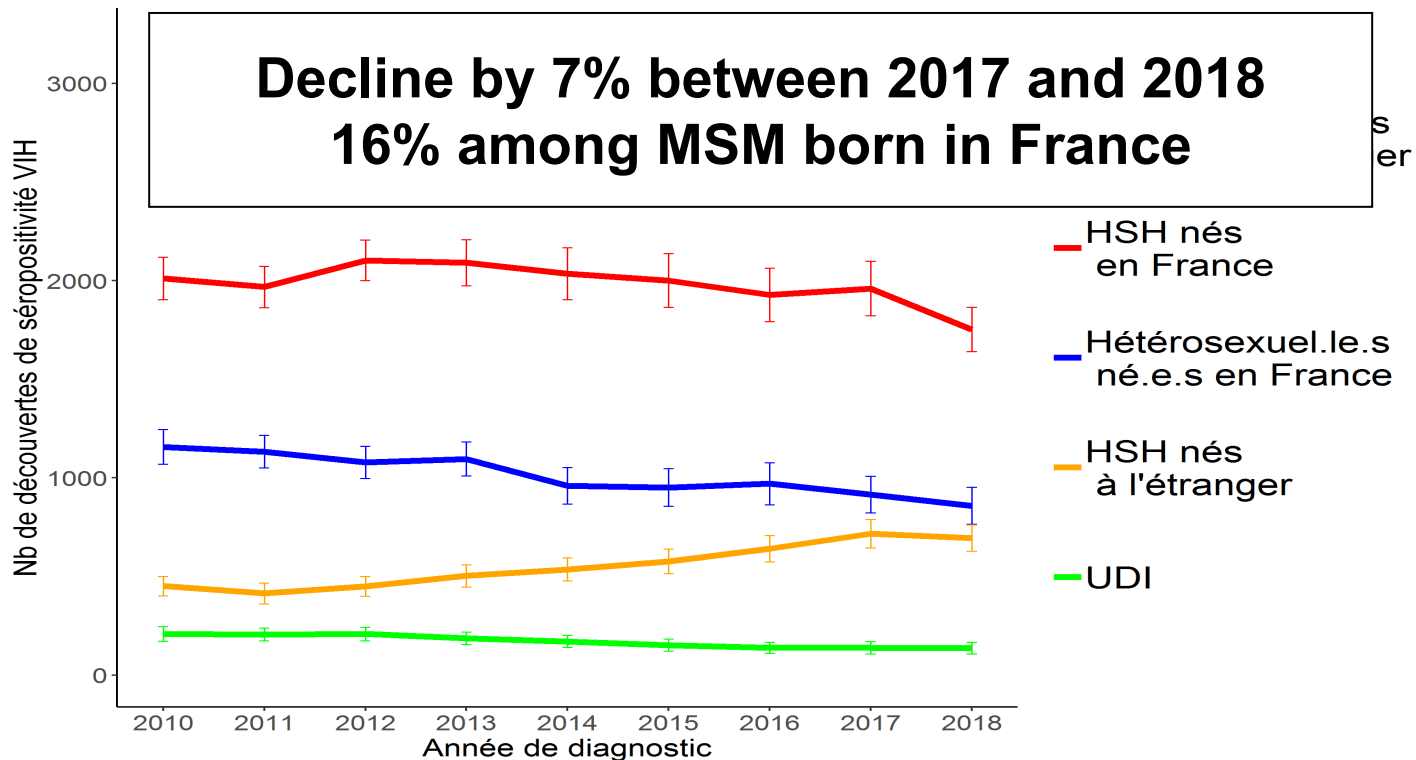


Simplify On Demand PrEP with TAF/FTC

A phase III, multicenter, open-label, randomized, controlled trial in MSM with condomless anal sex twice a month or less and able to plan their sexual activity.

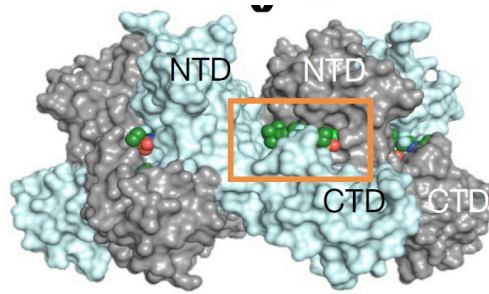
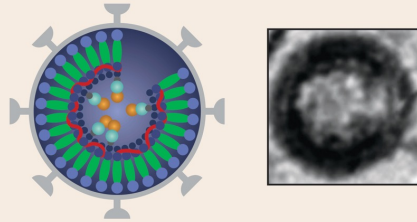


New HIV Diagnoses in France (2010 – 2018)

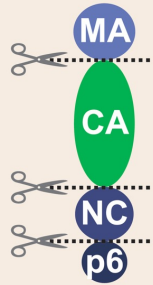
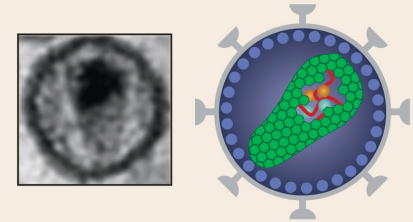


HIV-1 Capsid Core Formation and Lenacapavir MoA

Immature Virion



Mature Virion



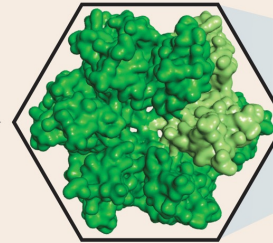
gag
(p55)

Protease

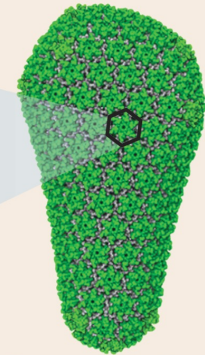
CA



Capsid Protein
(CA; p24; monomer)



Capsid Hexamer



Capsid Core