



New PrEP products (and some old ones)

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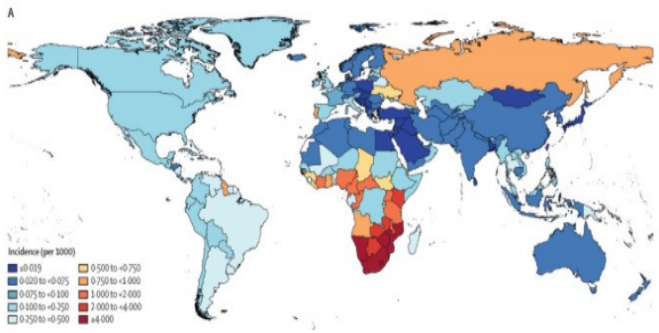
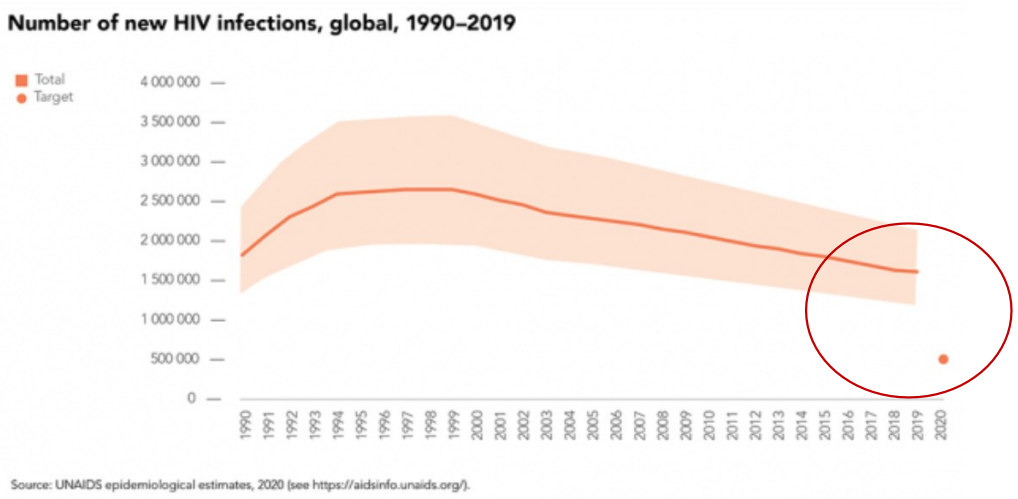
Namibian Clinicians Society Conference Oct 2021

HIV



75 million people infected with HIV since beginning of HIV epidemic
32 million have died
38 million people are currently living with HIV
13 million person treatment gap



In 2020:

- **1.7 million** new cases of HIV
- **690 000** AIDS-related deaths

Each week:

- **5500** new HIV cases among young women aged 15–24 years

In Southern Africa:

- **5 in 6** new HIV cases among youth aged 15–19 years are among girls
- **3 in 5** new HIV cases are among women & girls

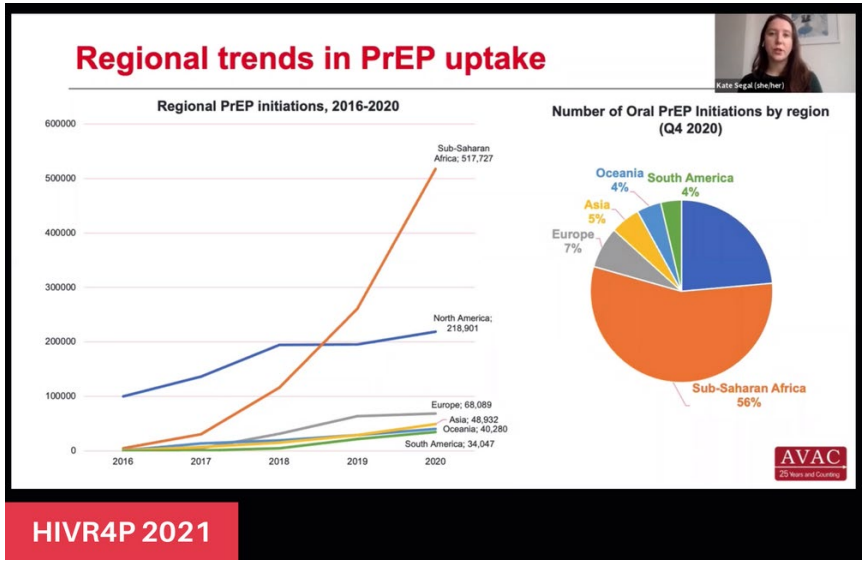
Frank TD et al., *Lancet HIV*, Volume 6, Issue 12, 2019, Pages e831-e859; UNAIDS epidemiological estimates, 2020 https://aidsinfo.unaids.org

A full decade ago now we learnt that….

Antiretroviral based Pre Exposure Prophylaxis (PrEP) provides robust protection against HIV in all populations and routes of infection.

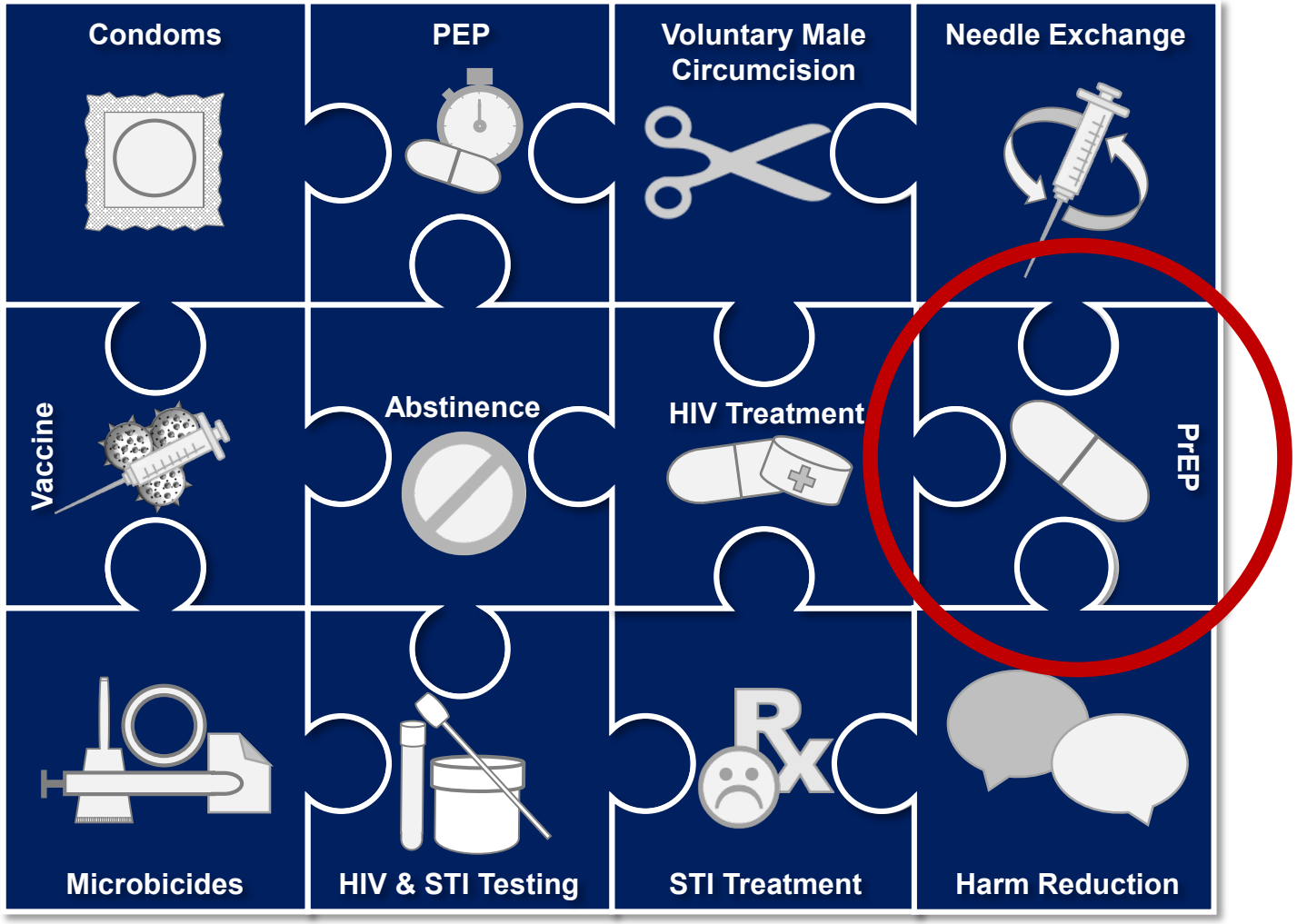
Today almost 1 million people have accessed this prevention.

In more than 70 countries



Nam: Kate Segal presenting to HIVR4P 2021.

1.7 Million new HIV infections in 2020 – 3x higher than the UNAIDS 2020 targets. HIV prevention must remain a key focus.



Q4 2020:

928,750 global PrEP initiations (approx. 1/3 of UNAIDS target & mostly USA)

6x increase 2016-2020

But growth is slowing– only an 18% increase (2019-2020), down from 104% increase in 2017-2018

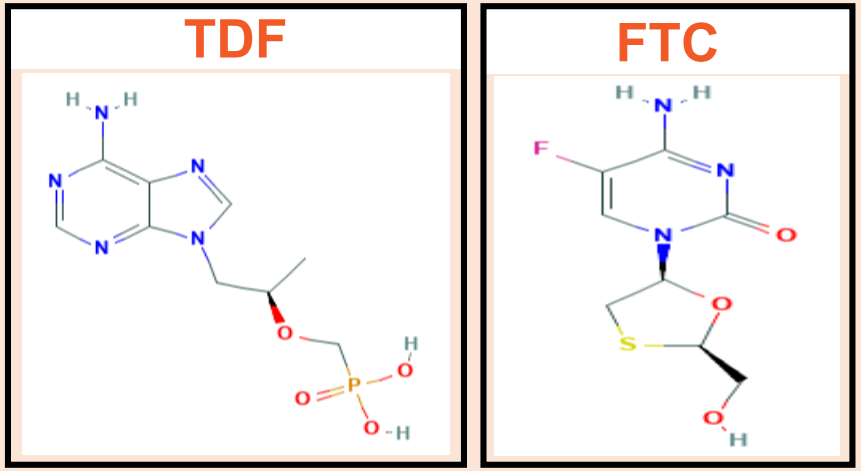
Successful settings had

- Early adoption
- National commitment to scale-up
- Tailored programming

Segal et al., 2021, IAS R4P

TDF/FTC: Daily oral HIV prevention pills

Agent class:
TDF: Tenofovir and FTC: Emtricitabine are nucleoside reverse transcriptase inhibitors (NRTI's)
Safety of TDF/FTC as PrEP – paramount consideration for medication prescribed to healthy individuals



Dosing Strategy: Daily oral PrEP

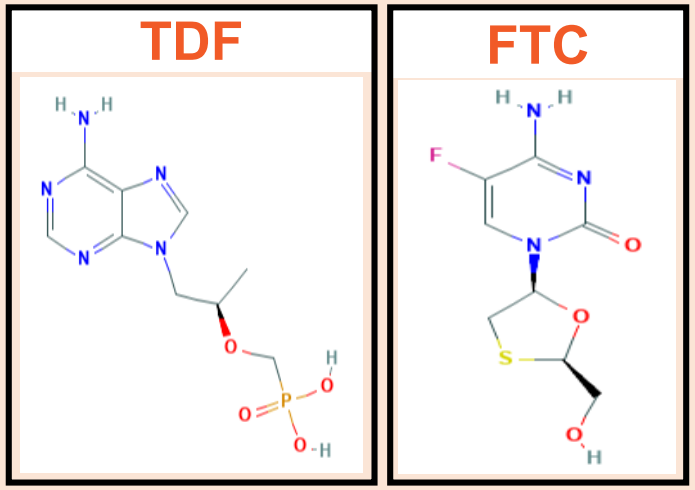
Direct correlation between adherence and protection
When adherence is high, HIV protection is consistent and high

	% of blood samples with tenofovir detected	HIV protection efficacy in randomized comparison	**HIV protection estimate with high adherence**
Partners PrEP TDF/FTC arm	81%	75%	90% (tenofovir in blood)
TDF2	79%	62%	78% (prescription refill)
BTS	67%	49%	70% - 84% (tenofovir in blood / pill count)
iPrEx	51%	44%	92% (tenofovir in blood)
FEM-PrEP & VOICE	<30%	No HIV protection	N/A

Baeten et al N Engl J Med 2012; Thigpen et al N Engl J Med 2012; Choopanya et al Lancet 2013; Grant et al N Engl J Med 2010; Van Damme et al N Engl J Med 2012; Marrazzo et al CROI 2013

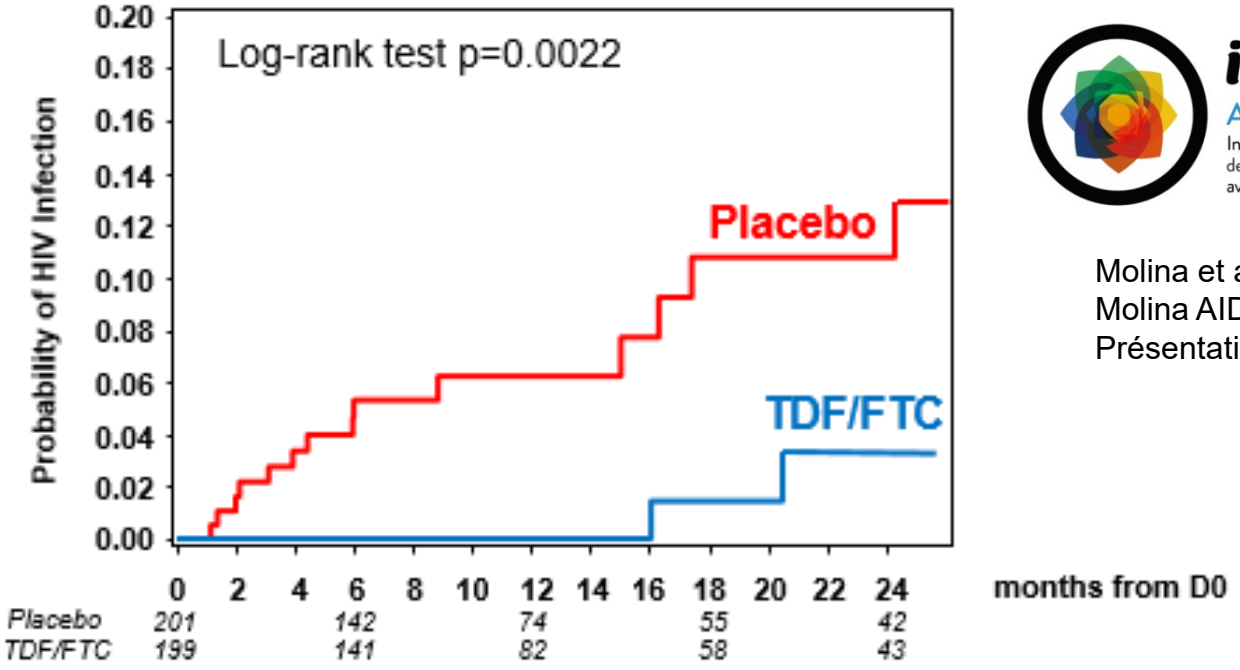
TDF/FTC: Oral HIV prevention – On Demand!

Agent class:
TDF: Tenofovir and FTC: Emtricitabine are nucleotide reverse transcriptase inhibitors



Dosing Strategy:
Oral PrEP, On demand 2-1-1: two tablets 2-24 hours before engaging in sex, a single tablet 24 hours after the first two, and another tablet 24 hours after that.

Randomized Double-Blinded vs. Placebo then Open-Label Extension among MSM (TDF/FTC on demand vs placebo on demand)



ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

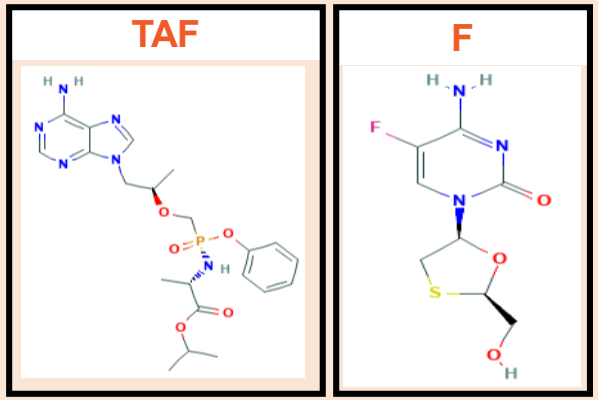
Molina et al NEJM 2015;
Molina AIDS 2016
Présentation

Median follow-up of 9.3 months: 16 subjects infected
14 in placebo arm (incidence: 6.60 /100 PY) and **2 in TDF/FTC arm** (0.91 /100PY)

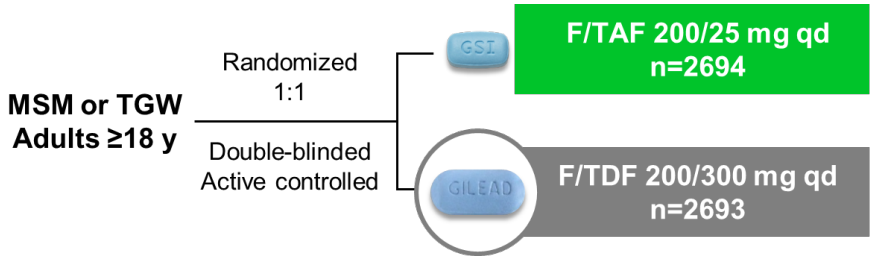
86% relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)
NNT to avert one HIV-infection: 18 (95% CI: 11-50)

DESCOVY F/TAF: Oral pills for HIV prevention (compared to TDF/FTC)

Agent class:
F/TAF = Emtricitabine/ Tenofovir Alafenamide are nucleotide reverse transcriptase inhibitors



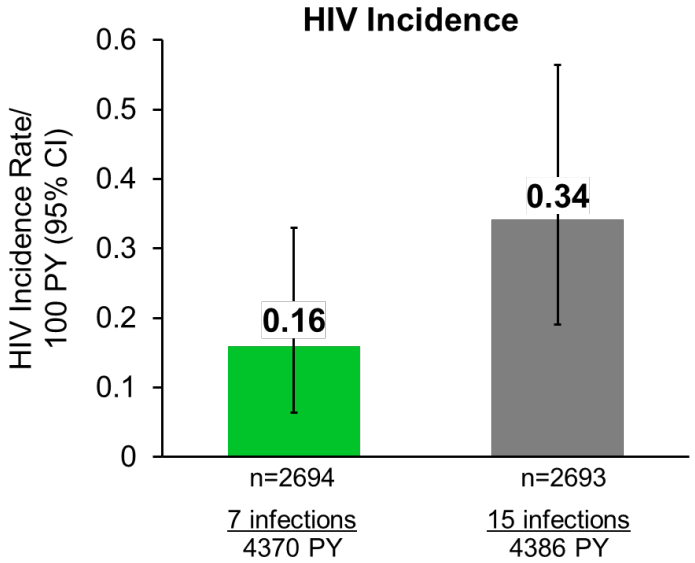
Dosing Strategy: Daily oral PrEP
Advantages: Smaller pill size
Less bone demineralization
Subclinical renal toxicity

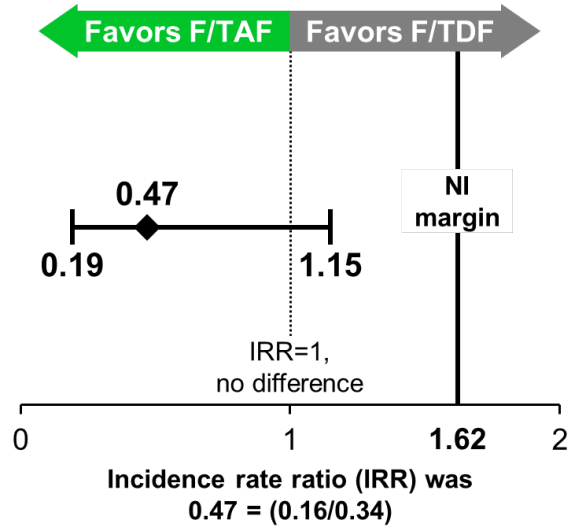


Primary analysis:
HIV incidence/100 PY when 100% complete Week 48 & 50% complete Week 96

Non-inferiority was achieved:

- 22 HIV infections in 8756 PY of follow up
- Confirmed in a sensitivity analysis





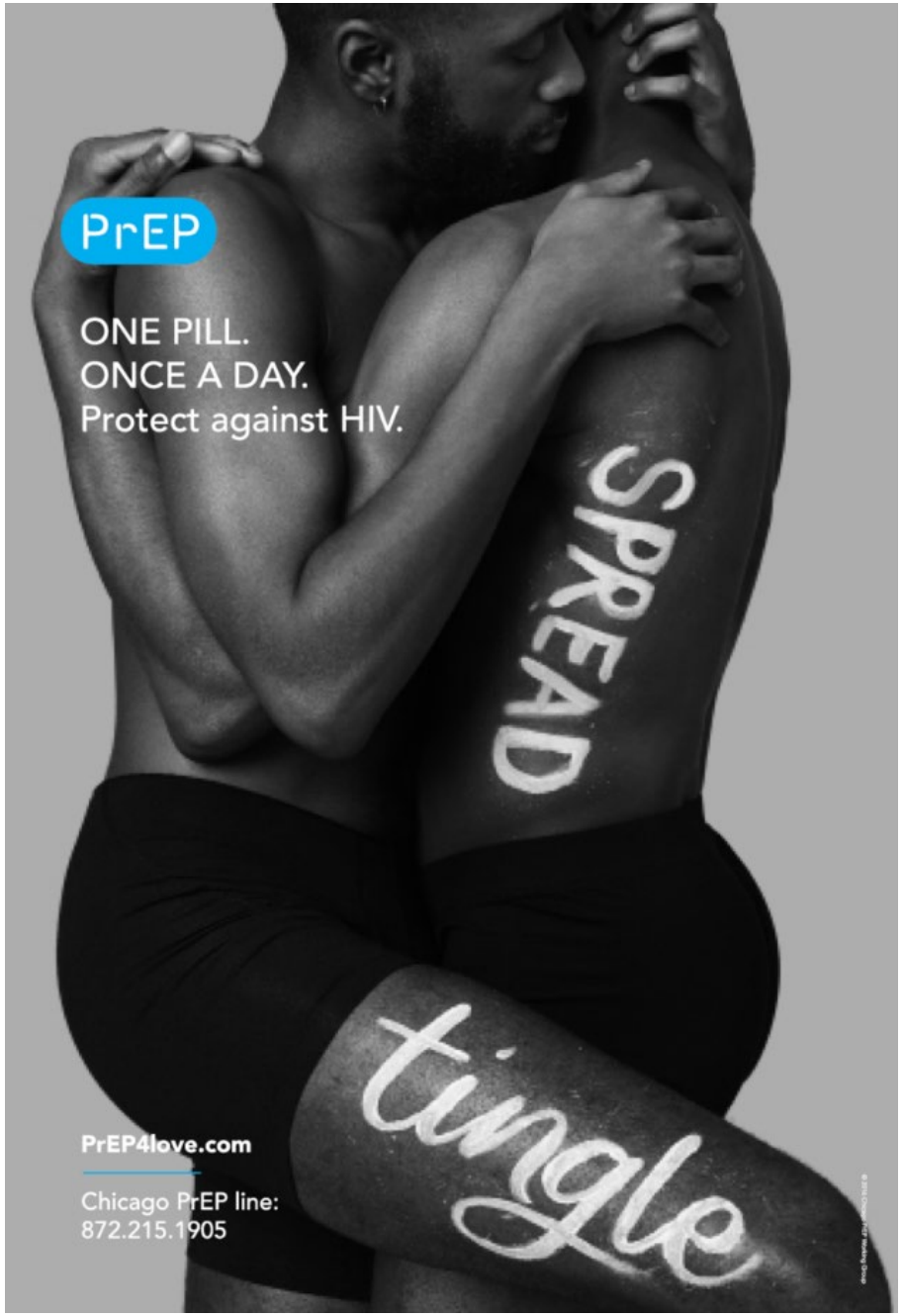
*Under evaluation for on demand

Spinner et al., IAS 2019 Mexico, Oral Abstract

PrEP impacts lives ……

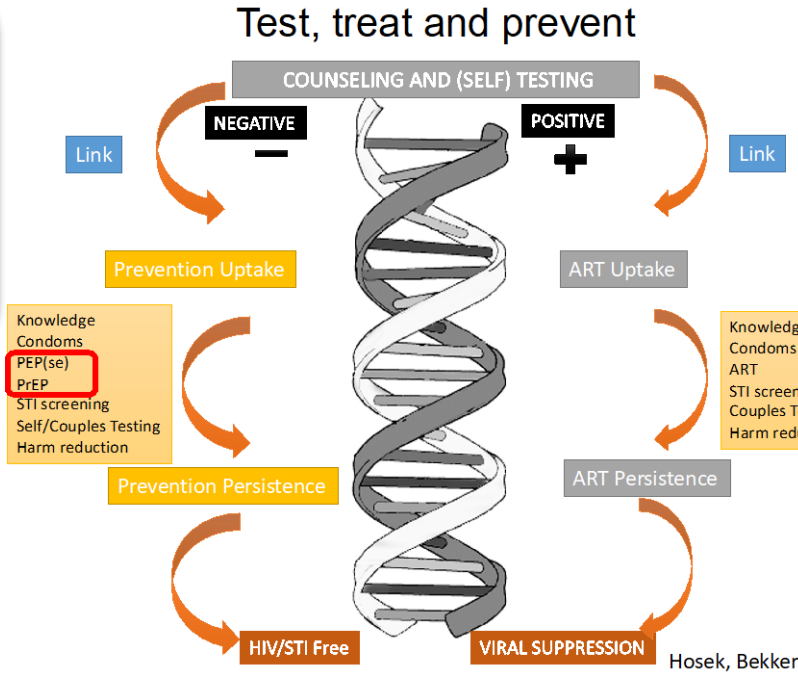
“I just feel PrEP is really helping, so I am not afraid of HIV…PrEP has made me feel so comfortable with my partner”.

- Oral PrEP user 19 yo



Impact so far: Scaling Up PrEP Access in Major Cities Has Resulted in Population-Level Reductions in HIV Risk, among PrEP Users and Non-Users Combined

San Francisco
↓51%
(2012-2016)



London
↓42%
(2016)

Seattle
↓42%
(2010-2017

Sydney
↓32%
(2017)

Key point: Simplify PrEP delivery
Same day start
Lab testing done in parallel with initiation

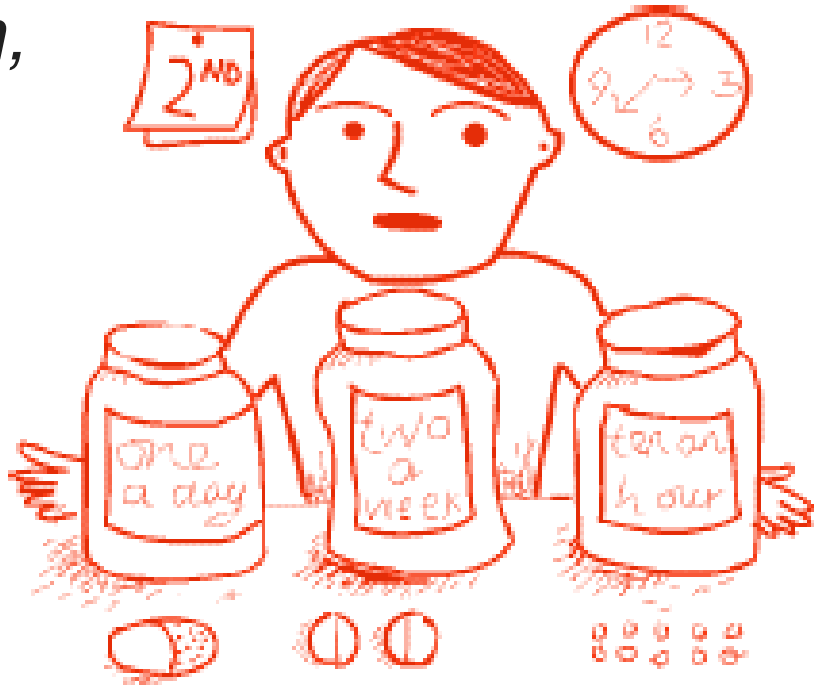
Buchbinder SP, et al. 25th CROI. Boston, 2018. Abstract 87.; Seattle & King County and the Infectious Disease Assessment Unit. HIV/AIDS; Epidemiology Report 2017, Volume 86.; Nwokolo N, et al. *Lancet HIV*. 2017;4:e482-e483; Grulich A, et al. *Lancet HIV*. 2018;5:e629-e637.

Daily oral prep isn't feasible for everyone

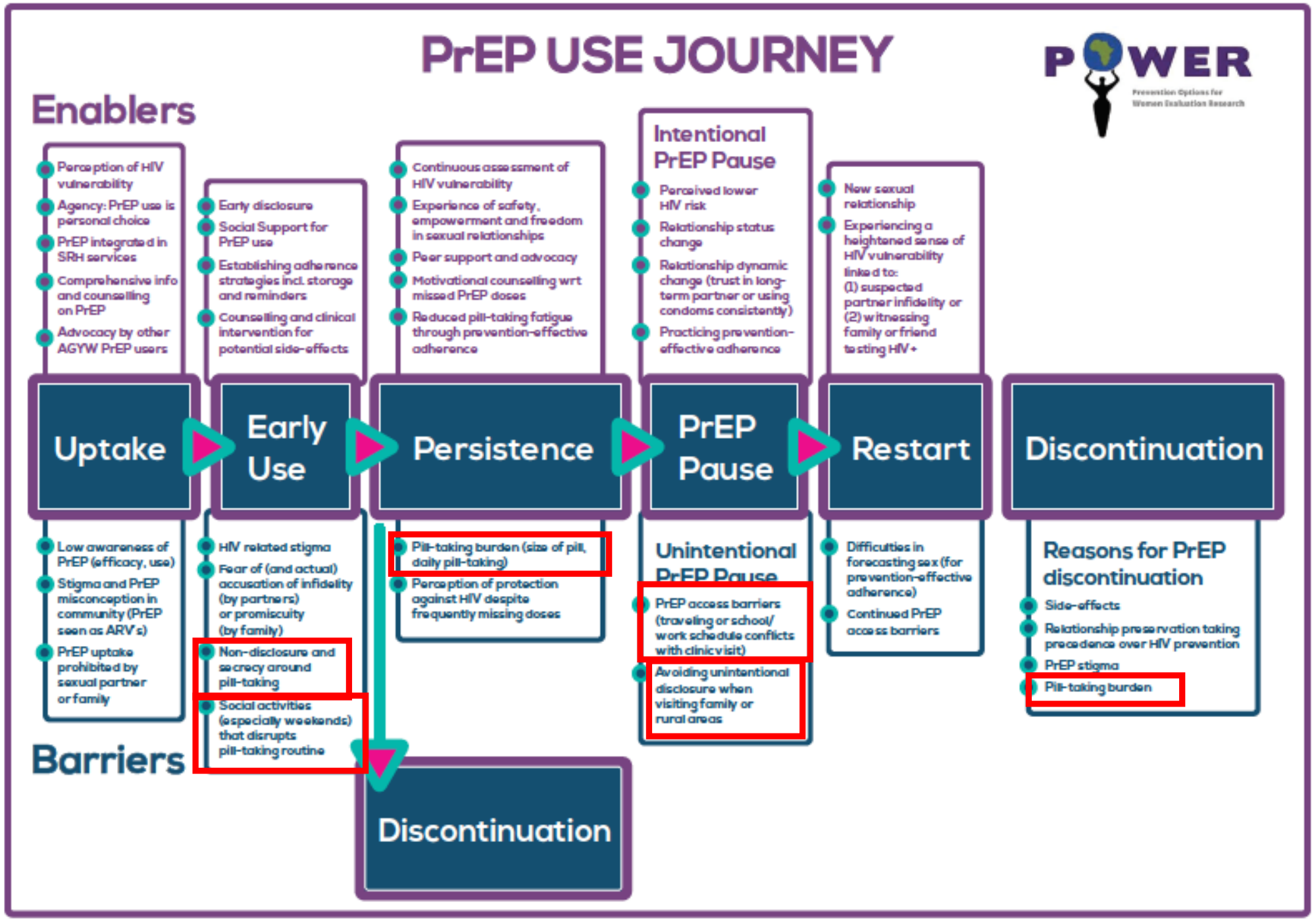
…I have hidden them [PrEP pills], so no one knows about them, so if I forget to take them, there won't be anyone to remind me…

(TGW, 28 years, inconsistently adherent).

Kimani et al., 2021, Plos One



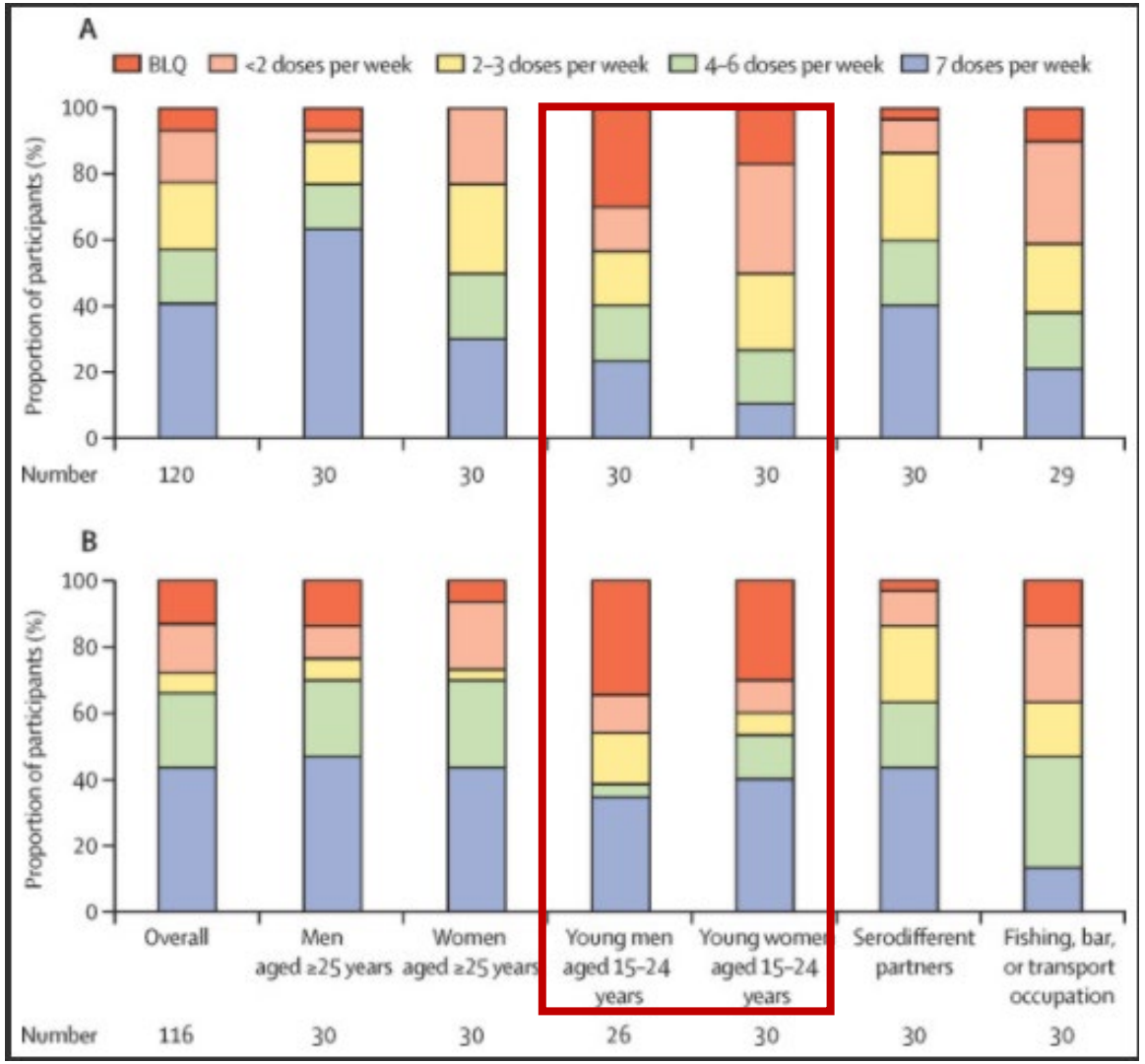
"Sometimes I just forget to take PrEP, I don't know why… maybe because there will be no pain that will remind me that actually, it's paining now, go and drink these tablets and stuff."


PrEP USE JOURNEY
POWER
Prevention Options for Women Evaluation Research
Enablers
Perception of HIV vulnerability
Agency: PrEP use is personal choice
PrEP integrated in SRH services
Comprehensive info and counselling on PrEP
Advocacy by other AGYW PrEP users
Early disclosure
Social Support for PrEP use
Establishing adherence strategies incl. storage and reminders
Counselling and clinical intervention for potential side-effects
Continuous assessment of HIV vulnerability
Experience of safety, empowerment and freedom in sexual relationships
Peer support and advocacy
Motivational counselling wrt missed PrEP doses
Reduced pill-taking fatigue through prevention-effective adherence
Intentional PrEP Pause
Perceived lower HIV risk
Relationship status change
Relationship dynamic change (trust in long-term partner or using condoms consistently)
Practicing prevention-effective adherence
New sexual relationship
Experiencing a heightened sense of HIV vulnerability linked to:
(1) suspected partner infidelity or
(2) witnessing family or friend testing HIV+
Uptake
Early Use
Persistence
PrEP Pause
Restart
Discontinuation
Barriers
Low awareness of PrEP (efficacy, use)
Stigma and PrEP misconception in community (PrEP seen as ARV's)
PrEP uptake prohibited by sexual partner or family
HIV related stigma
Fear of (and actual) accusation of infidelity (by partners) or promiscuity (by family)
Non-disclosure and secrecy around pill-taking
Social activities (especially weekends) that disrupts pill-taking routine
Pill-taking burden (size of pill, daily pill-taking)
Perception of protection against HIV despite frequently missing doses
Unintentional PrEP Pause
PrEP access barriers (traveling or school/ work schedule conflicts with clinic visit)
Avoiding unintentional disclosure when visiting family or rural areas
Difficulties in forecasting sex (for prevention-effective adherence)
Continued PrEP access barriers
Reasons for PrEP discontinuation
Side-effects
Relationship preservation taking precedence over HIV prevention
PrEP stigma
Pill-taking burden
Discontinuation

Challenge of Adherence

POPULATION	ADHERENCE
Young MSM (12-22 yrs), US Hosek et al., 2017, JAIDS	FTV-DP levels consistent with >4 pills/week • Wk 4: 56% • Wk 48: 34%
TGW & MSM, Sub-Saharan Africa Kimani et al., 2021, Plos One	Any FTV-DP detected at 24 wks (6 months) • TGW: 62.5% (5/8) • MSM: 14.7% (5/34)
Population assessment in rural Uganda & Kenya (SEARCH Study) Koss et al., 2020	• 1/3 had drug concentrations consistent with poor adherence • Young people & women showed lower odds of [PrEP] consistent with daily dosing
HPTN 083 – TGW & MSM (subset of participants – 372) *Landovitz RJ et al. AIDS 2020, #OAXLB01*	Overall: 76.1% showed TFV-DP levels consistent with > 4 doses/week Plasma TFV levels • 87% >10 ng/ml • 75% >40 ng/ml

Adherence to PrEP estimated from the concentration of tenofovir in hair samples in the Search Study



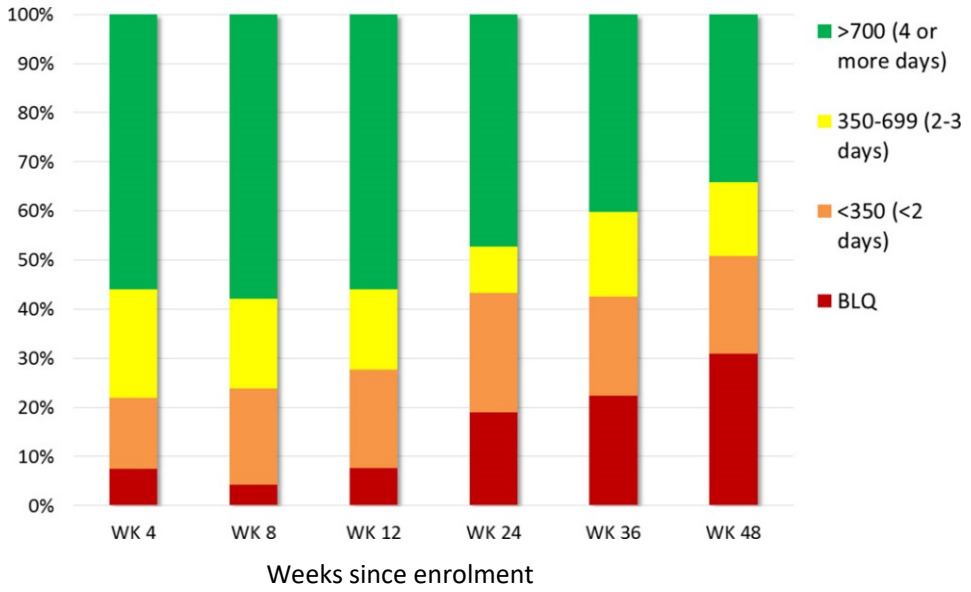
Koss et al., 2020

Particularly in the young and the restless….

400 young MSM (12-22 years) in 12 US cities

- Monthly visits until wk 12 and then quarterly visits until wk 48
- As visit frequency decreased, so did adherence

56% had FTV-DP levels consistent with >4 pills/week in week 4 – dropping to only 34% in week 48

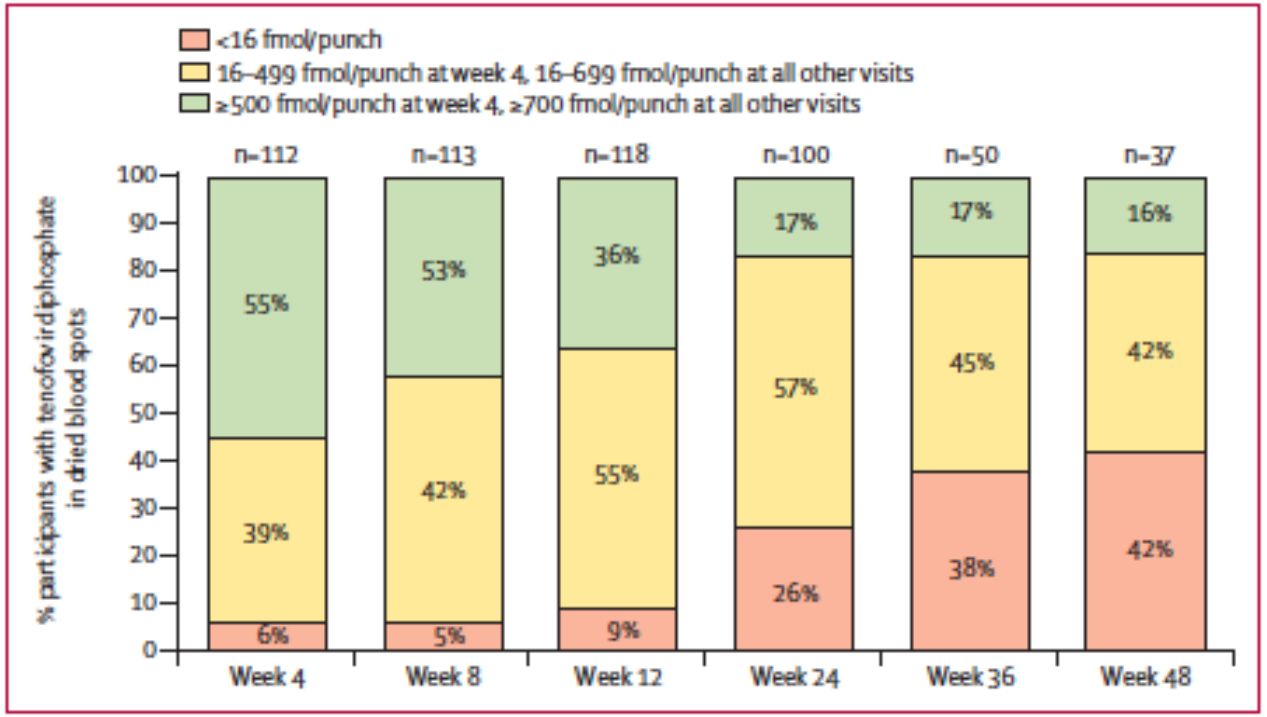


Hosek et al., 2017, JAIDS

148 adolescents (15-19 years) in 2 RSA cities

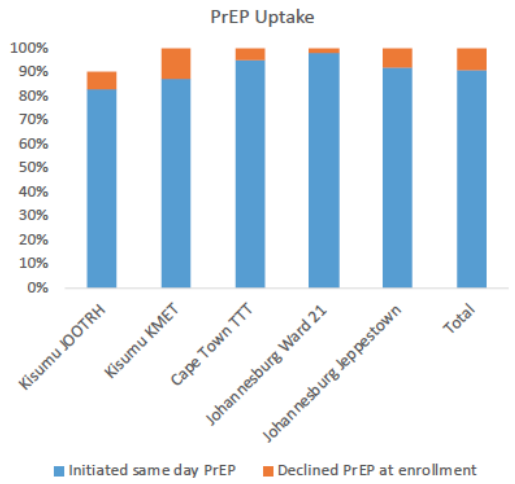
- Monthly visits until wk 12 and then quarterly visits until wk 48
- As visit frequency decreased, so did adherence

55% had FTV-DP levels consistent with >4 pills/week in week 4 – dropping to only 16% in week 48



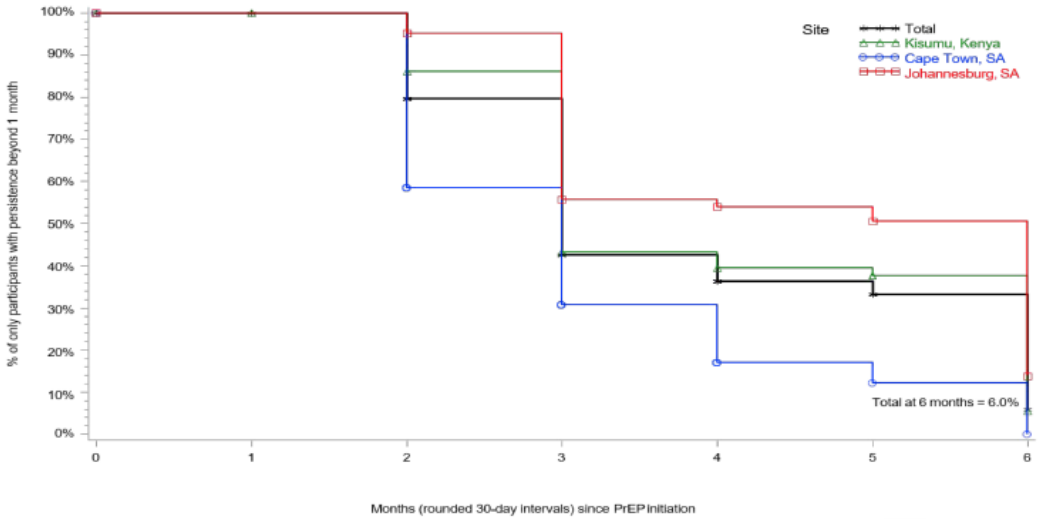
Gill K, et al Lancetchildadol 2020

Oral PrEP: Challenge of persistence



POWER
Prevention Options for Women Evaluation Research:

C Celum, et al R4P 2021



53 transgender women and MSM (SSA)

- By month 6, 20.7% of participants were LTFU or had stopped PrEP
- Any FTV-DP was detected in **62.5% (5/8) of TGW** vs. **14.7% of MSM (5/34, p=0.01)**
- Motives for PrEP discontinuation included negative partner reactions and stigmitising healthcare services

Characteristic		MSM n = 11	%	TGW n = 8	%	Total n = 19	%	p-value
In follow up and on PrEP	Yes	9	81.8	7	87.5	16	84.2	1.00
	No	2	18.2	1	12.5	3	15.8	
Adherence at Month 6 based on self-report	Consistent^	2	22.2	6	85.7	8	50.0	**0.04**
	Inconsitent^	7	77.8	1	14.3	8	50.0	
TFV-DP level~	Detectable	2	22.2	5	71.4	7	43.8	0.13
	Undetectable	7	77.8	2	28.6	9	56.3	
Approximate pills/week	4–6 pills	0	0	3	42.8	3	18.8	0.07
	2–3 pills	0	0	1	14.3	1	6.3	
	<2 pills	2	22.2	1	14.3	3	18.8	
	No pills	7	77.8	2	28.6	9	56.3	

~ TFV-DP -Tenofovir-diphosphate not known at the time of conducting interviews.
^ Defined as consistently and inconsistently adherent if days between the last date PrEP was taken and the month 6 clinic visit date was < 3 days or ≥ 3 days, respectively.

https://doi.org/10.1371/journal.pone.0244226.t002

Kimani et al., 2021, Plos One

Oral PrEP: lack of Persistence

or simply cycling on and off….

- 37-62% of PrEP initiators discontinue within 6 months
- Higher rates of discontinuation among youth and black MSM in the US (Scott et al., 2019; Chan et al., 2016, Rusie et al., 2018, Sullivan et al., 2018)

SEARCH Study: PrEP stopping and restarting was common (1/2 of those that stopped restarted by week 72) (Koss et al., 2020)

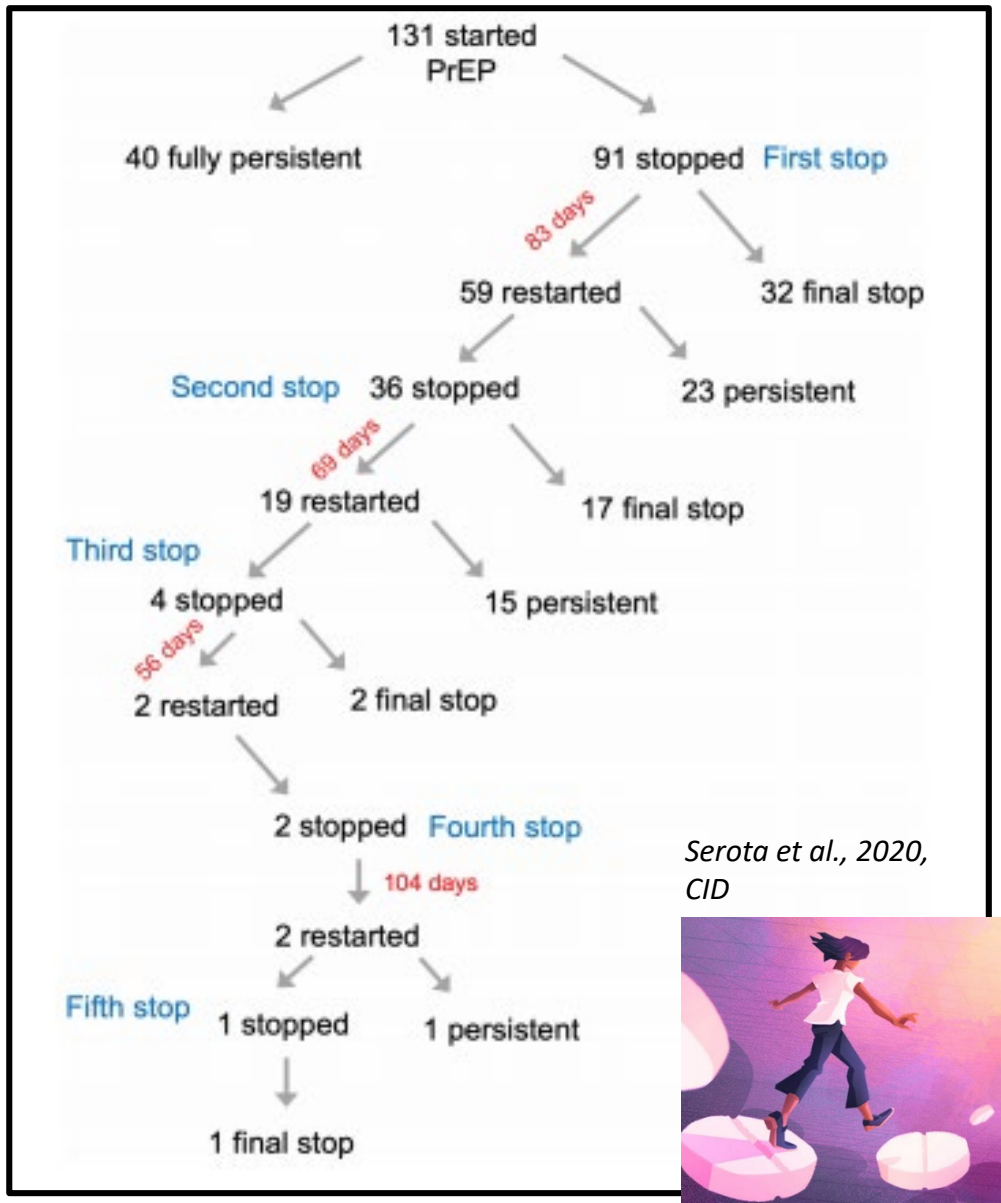
YBMSM in a US city (Serota et al. 2020)

- 44% initiated PrEP through the study
- 69% had a first discontinuation; 40% had a final discontinuation
- **Drivers of persistence:** **s**elf efficacy, STI diagnosis, Condom-less anal intercourse

Reasons for discontinuation:

Reason	N = 52 (%)
Positive HIV test	4 (8)
Not currently at risk for HIV	16 (31)
Dislike taking pills	2 (4)
Side effects intolerable	5 (10)
Logistical problems attending appointments or getting pre-exposure prophylaxis[a]	7 (13)
No reason given[b]	18 (35)

Patterns of PrEP initiation and discontinuation among young, black MSM in the US



Serota et al., 2020, CID

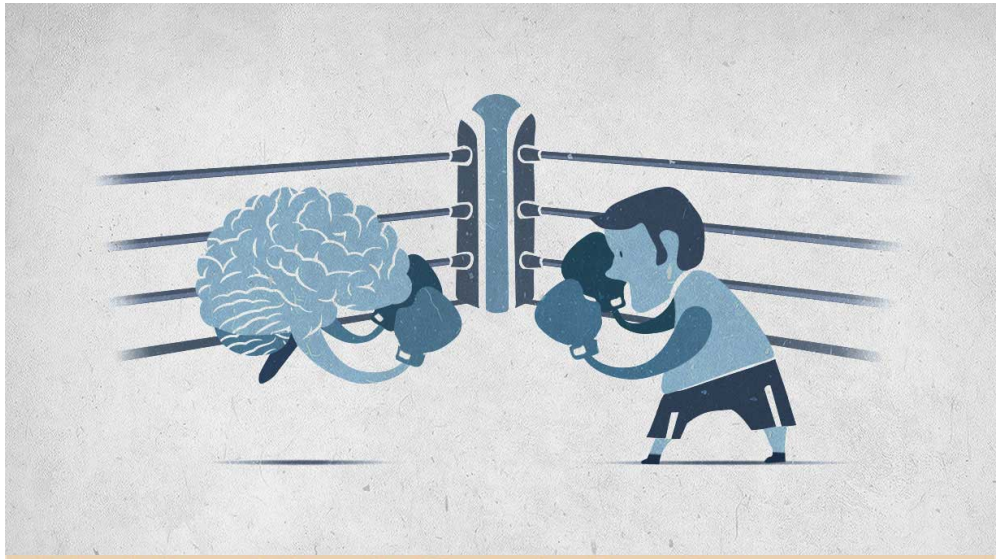
Why can’t we stick to “daily” things?

- We are not rational beings – we’re social and emotional
- We know what is good for us – but we struggle to stick to those decisions
- Medication compliance for chronic diseases **~50% (WHO, 2003)**

Motivation ≠ Action

Behavioural Biases occur when trying to stick to decisions – **more opportunity for these to arise when you have to take actions daily!**

- **Status quo bias**: researchers tend to sit in the same seats at conferences people tend to stick with TV programs as they don’t want to change channel
- **Overconfidence:** people do not take precautions to guard them against their own behavior
- **Myopia:** people give in to temptations at the expense of long-term goals
- **Loss aversion**: prefer to avoid loosing what we have than take a risk in order to gain

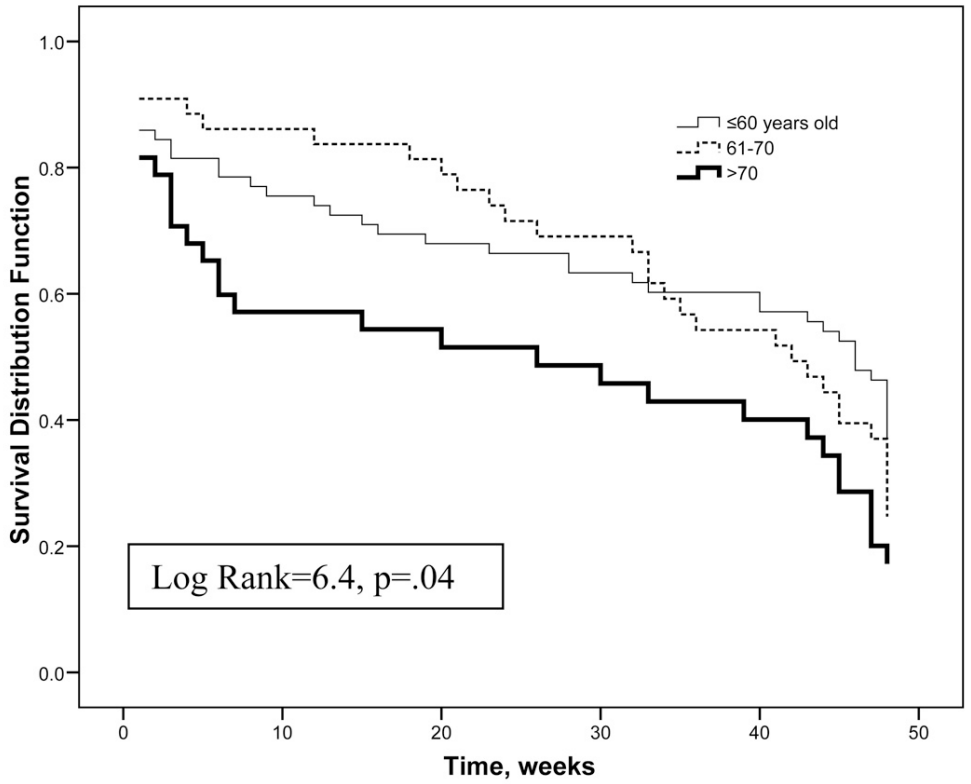


Phil Smith: Thesis 2020

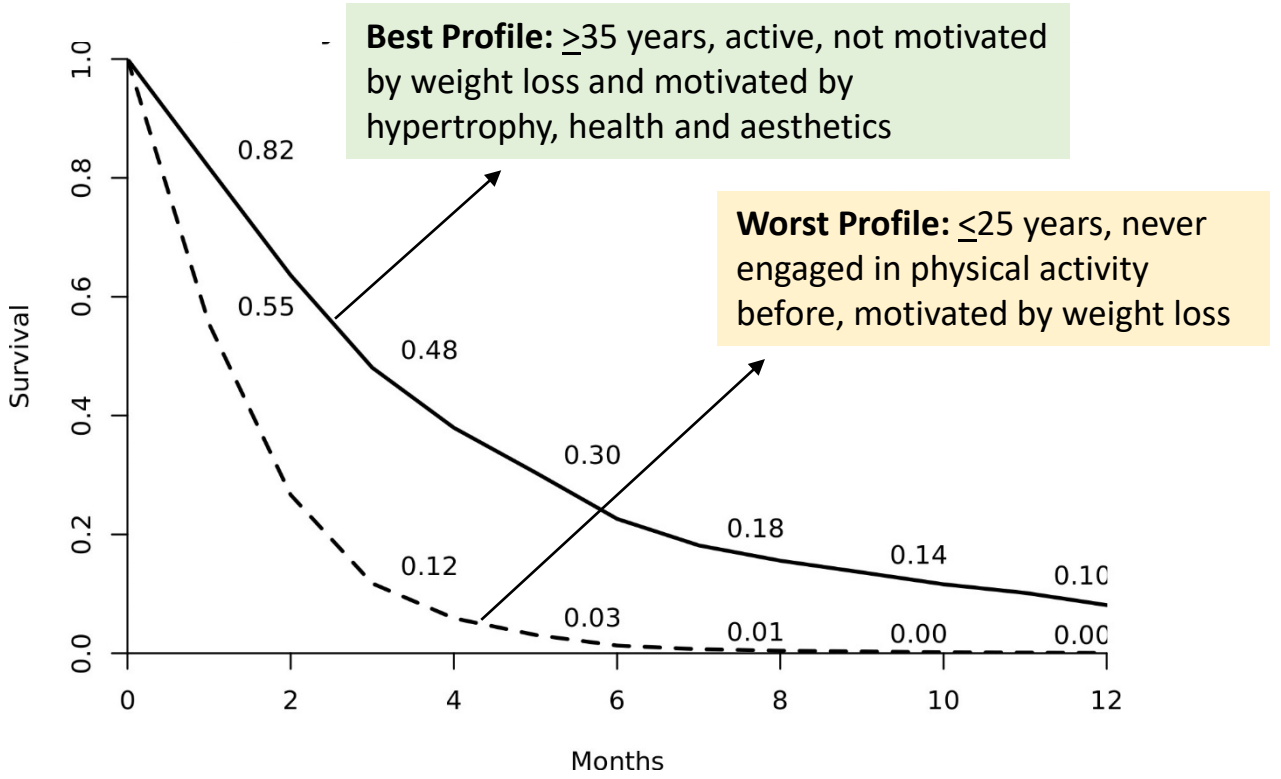
Take Exercise for example.....

- 74% of new users of health apps, stop using them within two weeks. (Endeavour Partners, 2014)
- Approx. 50% of individuals who start an aerobic exercise programme will stop within 6 months (Robinson & Rogers, 2012)

Time to discontinuation of exercise at 3 times a week by age group amongst men following a Cardiac Event (*Dolanskey et al., Res Gerontol Nurs. 2010)*



Probability to stay in the gym according to best and worst profiles (Data from 5240 members of the fitness center in Brazil) (Sperandei et al., 2016)



People make best decisions when:

- **Good feedback** about results of healthy behaviour – social feedback from family, friends, and partners

- Benefits of an **action easy to observe** - benefits of HIV prevention are generally largely invisible

- Decision is **easy to make** (simple decisions) – prevention options need to be available, affordable, simple to administer, EASY to adhere to

Oral PrEP relies on **DAILY** good decision making (like condoms, like masks) = difficult for some populations, especially youth!

Thanks Phil Smith

One solution: Less frequent and alternative dosing

Longer-acting agents in different formulations

I would create a PrEP that lasts longer. I would want a pill that can be taken like once a month or even better make an injection. This takes away all the stigma of need to carry pills around

(TGW, 22 years, consistently adherent, IDI 014).

Kimani et al., 2021, Plos One

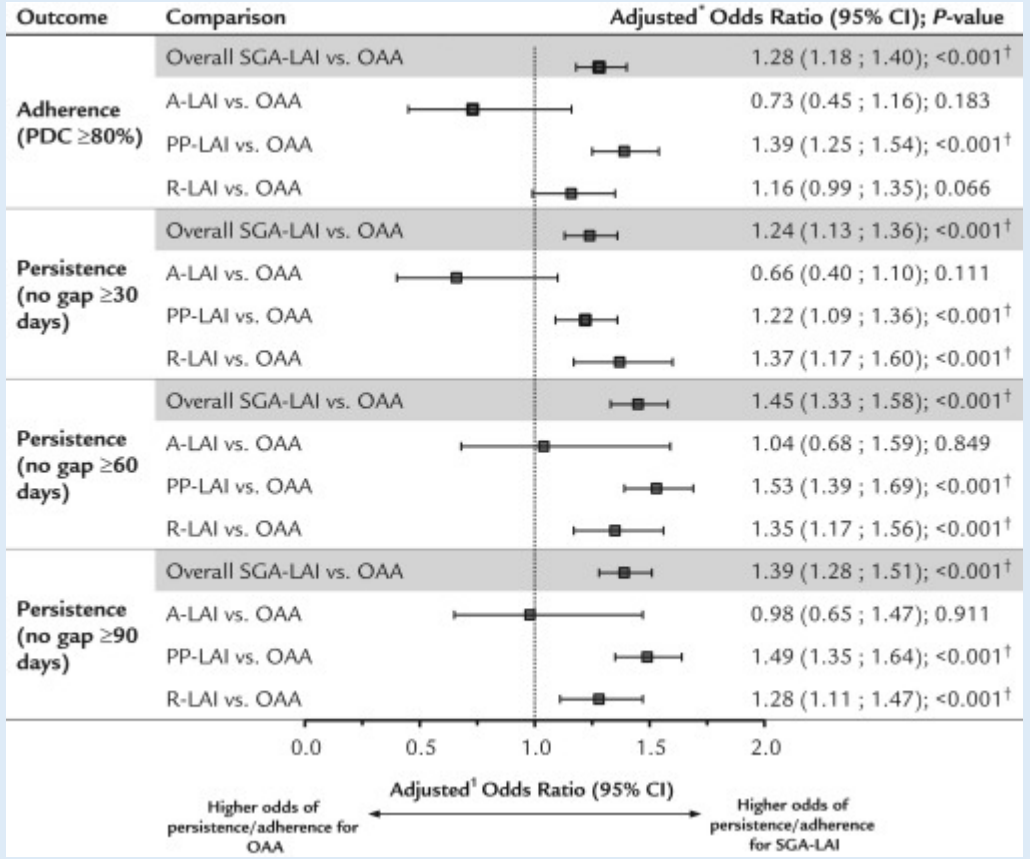
Lessons from Psychiatry……

- Both oral and long-acting injectable formulations of anti-psychotics medications are available
- LAI-APs are considered an effective treatment strategy for improving adherence (Fernández-Miranda et al., 2021; Carpenter and Buchanan, 2015; Correll et al., 2016; Nasrallah, 2018).
- **Early detection** of non-adherence, whereas oral non-adherence can often go undetected until a major problem develops (Fernández-Miranda et al., 2021; Greene et al., 2018; Ljungdalh, 2017; Park et al., 2018).

Adherence and persistence among adult patients (≥18 years) who either began receiving an LAI (no prior LAI therapy) or changed to a different oral antipsychotic (monotherapy).
(Greene et al., 2018, Psychiatry)

	Adherence	Persistence
Schizophrenic patients (N=5638)	5% higher	20% less likely to discontinue
Bipolar disorder patients (N = 11,344)	5% higher	19% less likely to discontinue

Adjusted comparison of adherence and persistence with Oral vs different LA Antipsychotic therapies over 12 months
(Pilon et al., 2017, Clinical therapeutics)



- OAA - oral atypical antipsychotics
- A-LAI = aripiprazole long-acting injectable therapy;
- PDC = proportion of days covered;
- PP-LAI = paliperidone palmitate long-acting injectable therapy;
- R-LAI = risperidone long-acting injectable therapy; SGA-LAI = second-generation long-acting injectable therapy.

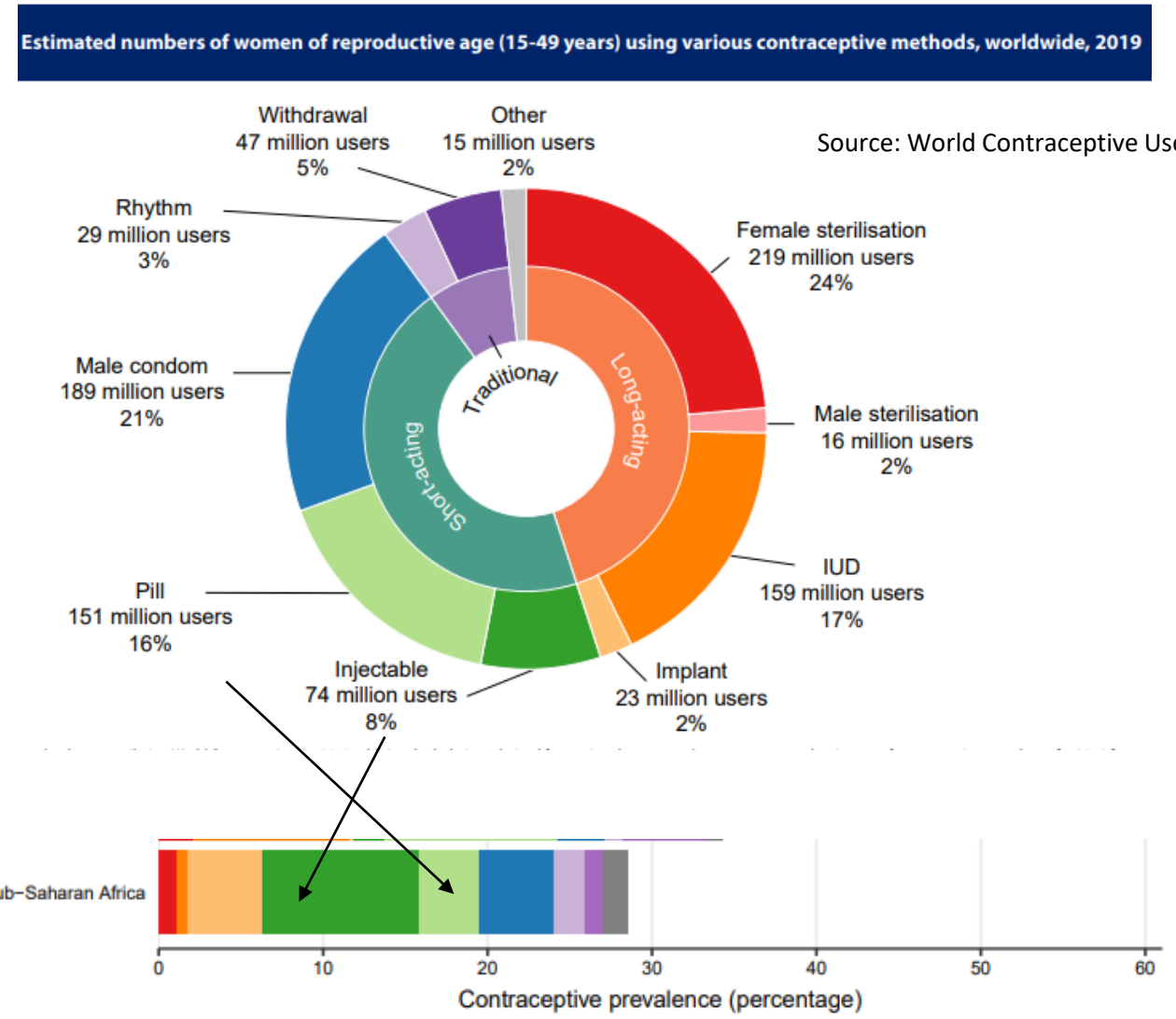
Lessons from reproductive health: LARCs

Similar adherence issues – 5% of unintended pregnancies occur amongst consistent contraception users, but **41% occur due to inconsistent use**.

- Requires no user adherence
- Gained popularity in recent years
- Lower side effects
- Greater effectiveness

Shown to have broader acceptability among different populations of women - higher amongst older women **but rapidly increasing amongst younger populations**

Sonfield, Hasstedt, & Gold, 2014
Strasser at al, 2016



In SSA, injectable contraceptives are largely more used than the Pill

Effectiveness of long-acting reversible contraception

Winner B, eta al. NEJM 2012

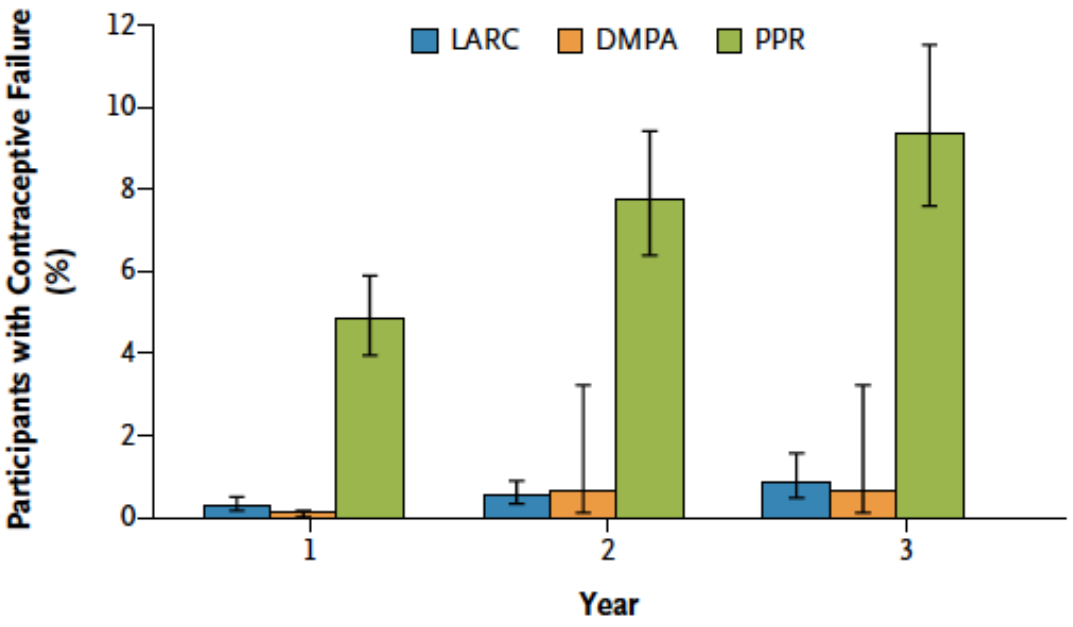


Figure 1. Cumulative Percentage of Participants Who Had a Contraceptive Failure at 1, 2, or 3 Years, According to Contraceptive Method.

Bars depict the cumulative percentage of participants who had a contraceptive failure with long-acting reversible contraception (LARC), depot medroxyprogesterone acetate (DMPA), or pill, patch, or ring (PPR) at 1, 2, or 3 years. Participants using PPR had significantly more unintended pregnancies than those using LARC (P<0.001) or DMPA (P<0.001).

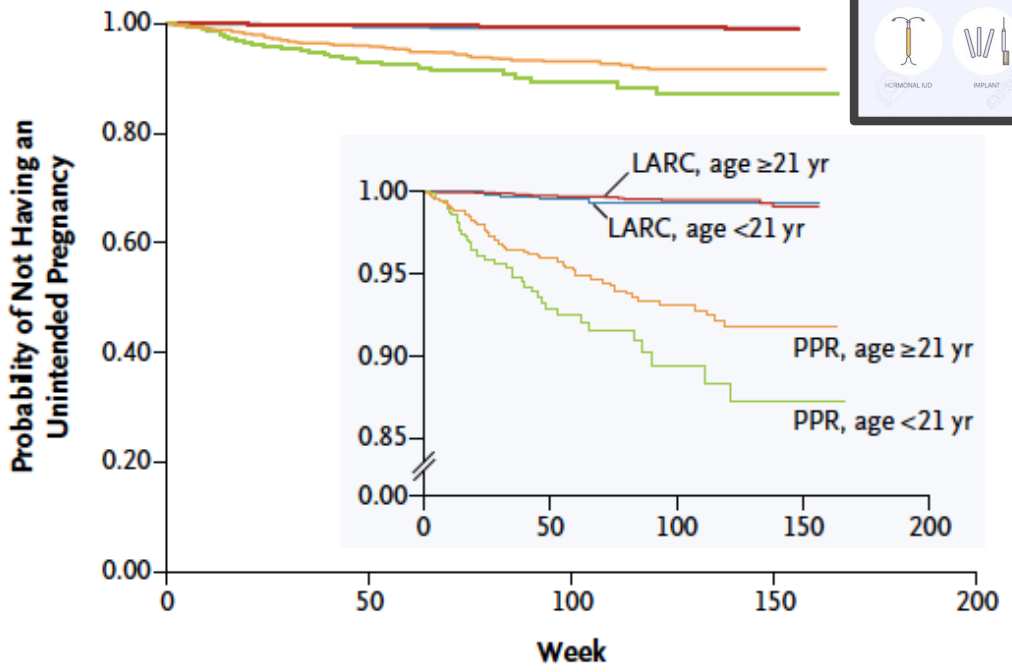


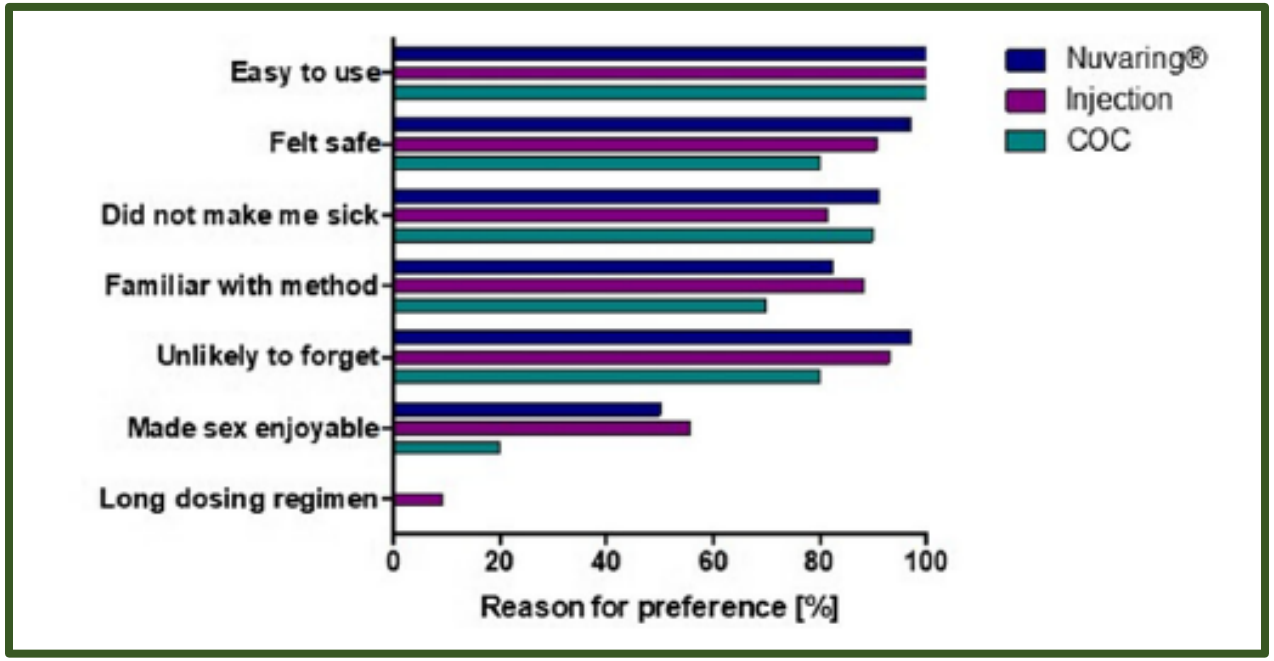
Figure 2. Probability of Not Having an Unintended Pregnancy, According to Contraceptive Method and Age.

Survival curves show the probability of not having an unintended pregnancy, stratified according to age group. LARC methods were the most effective, and failure rates did not vary according to age (P=0.49). PPR methods were less effective, and failure rates in participants younger than 21 years old were twice as great as in women 21 years of age or older (P=0.02).

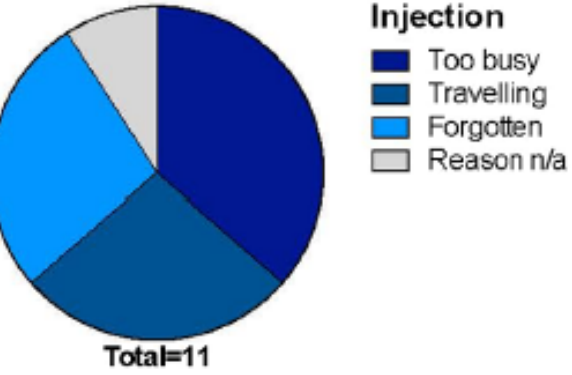
UChoose: An open-label, randomized crossover study to evaluate the acceptability and preference for contraceptive options in female adolescents (15 to 19 yo) in Cape Town, as a proxy for HIV prevention methods.

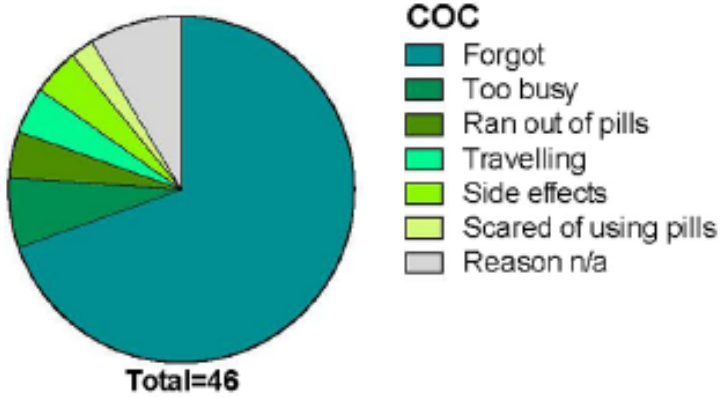
- 180 participants randomised to receive:
  - Monthly vaginal Nuvaring
  - Daily combined oral contraceptive (COC)
  - Bi-monthly injectable contraceptive
- At 16 weeks, participants crossed-over to another modality (all tried the Nuvaring – least familiar contraceptive)

Reasons For



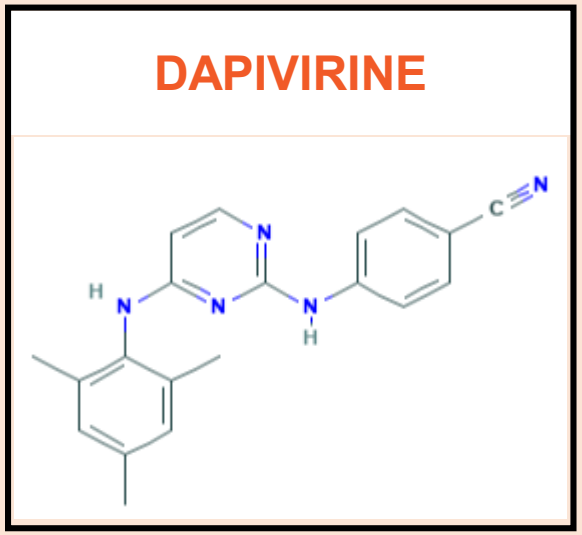
Reasons Against





Dapivirine Ring: Use of a vaginal ring for LA HIV prevention

Agent class:
Non-nucleoside reverse transcriptase inhibitors (NNRTI)

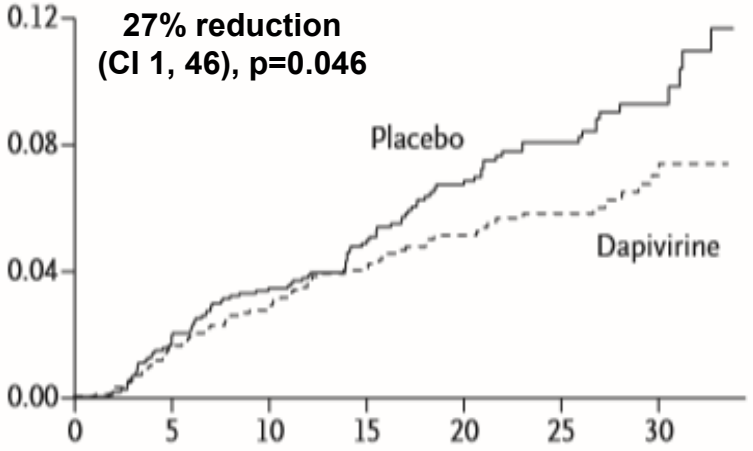


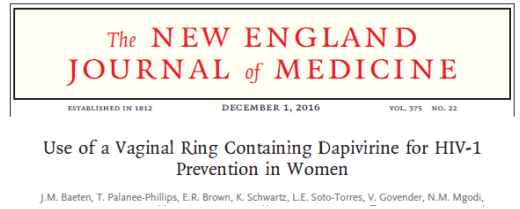
Dosing Strategy:
monthly dapivirine ring

2016

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

Trial sites in South Africa, Uganda, Zambia, Zimbabwe, Malawi



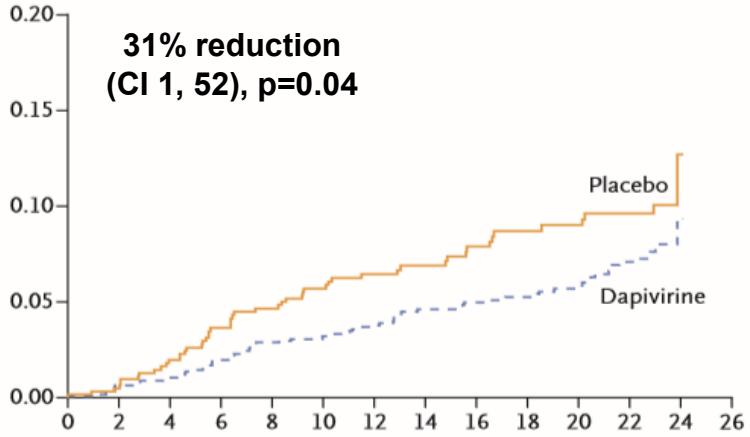

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 1, 2016 VOL. 375 NO. 22

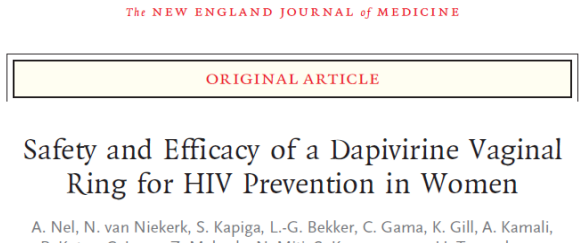
Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women

J.M. Baeten, T. Palanee-Phillips, E.R. Brown, K. Schwartz, L.E. Soto-Torres, V. Govender, N.M. Mgodi,

THE RING STUDY
Developing HIV Prevention for Women

Trial sites in South Africa, Uganda




The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women

A. Nel, N. van Niekerk, S. Kapiga, L.-G. Bekker, C. Gama, K. Gill, A. Kamali,

In both studies: Open label extension improved effectiveness - RR 0.50
EMA approved for section 58: (1) WHO recommendations, (2) Women in LMIC ; Second line to PrEP.

Overall Regulatory Strategy: Dapivirine ring

European Medicines Agency (EMA) Art 58 Positive Opinion

- Scientific opinion on use of a product in developing countries (via Article 58 procedure)
- Positive opinion adopted July 2020

World Health Organization (WHO)

- WHO participates in EMA Article 58 procedure
- Facilitates abbreviated WHO prequalification (PQ) and Collaborative Registration Procedure (CRP)

Amendment of HIV Guidelines

Expression of Interest (EOI)

WHO Prequalification (PQ) and Recommendation

- PQ Nov 2020; Recommendation* granted Q1 2020

IPM request to WHO, NMRAs and EMA to use SRA CRP

IPM submits dossiers via CRP

Submissions Q4 2020 onward

African National Medicines Regulatory Authorities (NMRAs) decisions

US Food and Drug Administration (FDA) decision

- Submitted Q4 2020

In January 2021, the WHO recommended that the dapivirine vaginal ring may be offered as an additional prevention of choice for women at substantial risk of HIV infection as part of combination prevention approaches

Costing and Supply Chain

Ring Costing

- Cost to produce the ring and prepare it for procurement brings the price per ring to ~$12-13 for donors/multilateral agencies and other partners. Further costs might be incurred for country shipping and logistics
- IPM working on 5 X scale up – reduce costs further

Supply Chain

- Global Distributor being appointed
- IPM Registered office – Woodlands Office Park, Gauteng – Responsible Pharmacist

Follow-on Rings

Building on monthly ring, longer-acting rings could:

- Increase convenience to women
- Lower annual costs

3-month dapivirine ring

- Phase I results: Superior dapivirine release achieved at all timepoints over 90 days
- Next steps: Phase II bridging trial
- Timeline: First approvals in 2025

3-month dapivirine-levonorgestrel ring

- HIV prevention and contraception
- Phase I results: well-tolerated, encouraging drug levels seen in blood and vaginal fluid
- Next steps: Clinical evaluation of optimized formulation; Demonstration of contraceptive efficacy
- Timeline: First approvals in 2027

When given a choice between the ring and the Pill....

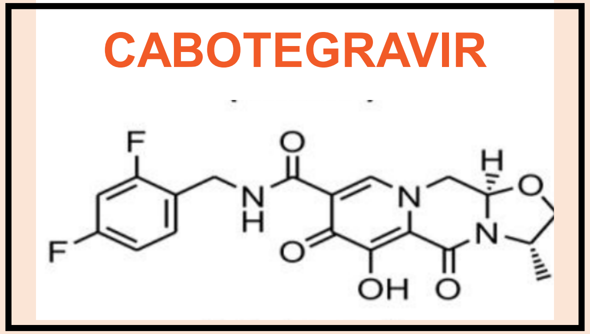
R:*I saw that the ring is easier to use than the pills that I thought that "No, let me take the ring". I thought of taking the pills, but then I thought that it is hard work. What if I go to school and come back stressed and I forget it? So, I was like, "No; let me just take the ring".*

Add sound

Cabotegravir LA: Long-acting suspension for delivery via IM injection

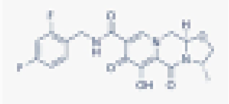
Agent class:
Strand-transfer integrase inhibitor

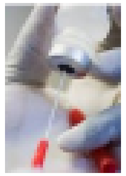
Trials:
HPTN 084 & 083



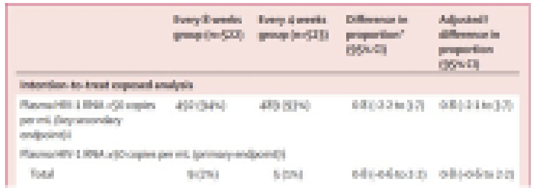
Half-life:
Oral: 40 hours
Injectable: 40-65 days

Dosing Strategy:
Single injection every 8 weeks





- Long-acting nanoformulated injectable integrase strand transfer inhibitor (potent, active vs HIV-1 and 2)
- CAB LA single IM injection protected macaques against sexual acquisition of SHIV, with plasma CAB concentrations that can be readily attained in humans[6-8]
- CAB LA 600 mg IM Q8W maintained plasma CAB concentrations at >1× and >4× in vitro PA-IC_{90} PK efficacy targets in all participants in the phase II HPTN 077 study[9]
- CAB LA demonstrated **virologic efficacy in combination with long-acting rilpivirine** in maintaining HIV-1 suppression[1-3]



ATLAS, ATLAS 2M (2020)

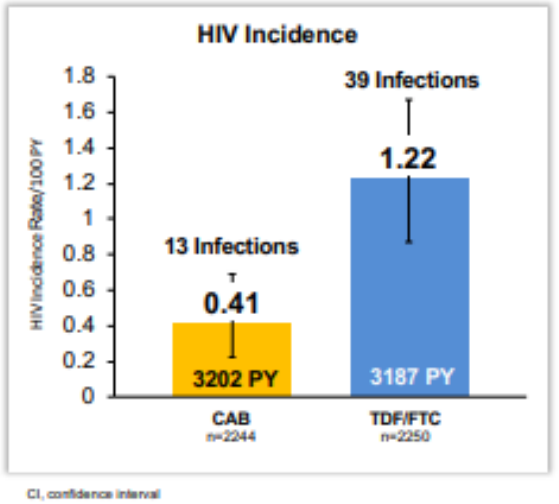
IM, intramuscular; LA, long acting; PA-IC_{90}, protein-adjusted 90% maximal inhibitory capacity; PrEP, preexposure prophylaxis; SHIV, simian/human immunodeficiency virus.

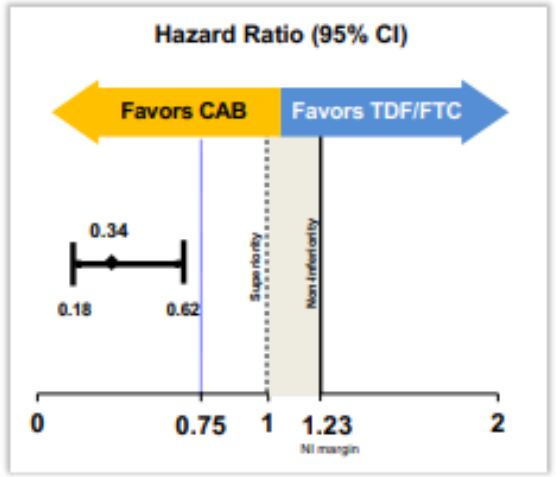
1. Swindells et al. N Engl J Med. 2020;382:1112-1123. 2. Orkin et al. N Engl J Med. 2020;382:1124-1135. 3. Overton ET et al., Lancet Dec 9, 2020. (396) 10267: 1994-2005. 4. Landovitz et al. AIDS 2020: Virtual. Slides OAXLB01. 5. ViiV Healthcare. [illegible] Accessed November 24, 2020. 6. Andrews et al. Science. 2014;343:1151-1154. 7. Andrews et al. [illegible] 8. Spreen et al. CROI 2015. Seattle, WA. Poster [illegible] 9. Landovitz et al. PLoS Med. 2018;[illegible] 10. UNAIDS. UNAIDS data 2020. [illegible] 11. Clement, Meredith E. et al., Long-acting injectable cabotegravir for the prevention of HIV infection. Current Opinion in HIV and AIDS: January 2020 - Volume 15 - Issue 1 - p 19-26

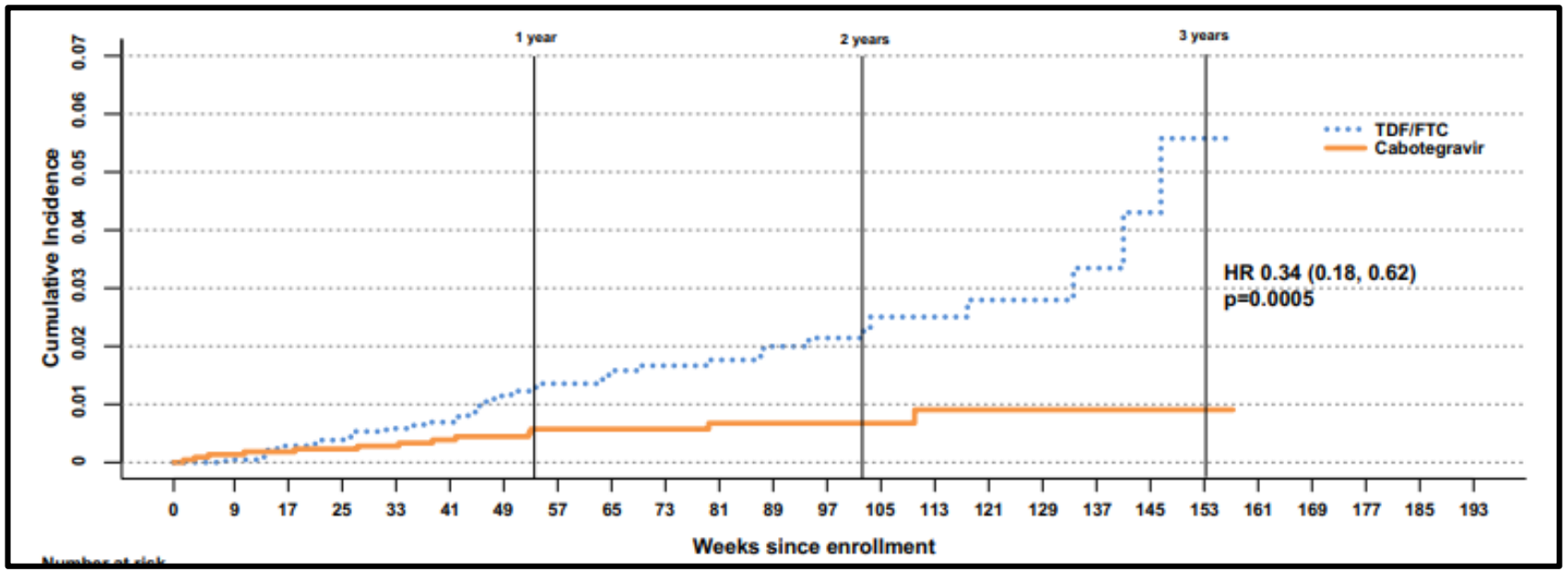
HPTN 083: Superiority of CAB to oral TDF/FTC

Provided evidence of superiority of CAB LA injected once every 8 weeks over daily oral TDF/FTC for HIV prevention among cisgender men and transgender women who have sex with men. The Study found a 68% reduction in risk of HIV infection with CAB compared to TDF/FTC

- 52 HIV infections in 6389 person-years of follow up
- Pooled incidence 0.81 (95% CI o.61-1.07) per 100 PY.





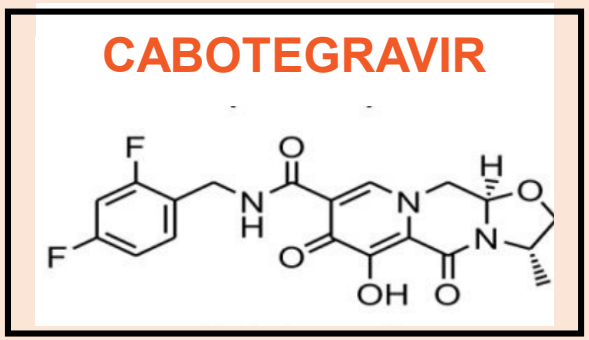


Landovitz, 2020, AIDS 2020 Virtual

Cabotegravir LA: Long-acting suspension for delivery via IM injection

Agent class:
Strand-transfer integrase inhibitor

Trials:
HPTN 084 & 083

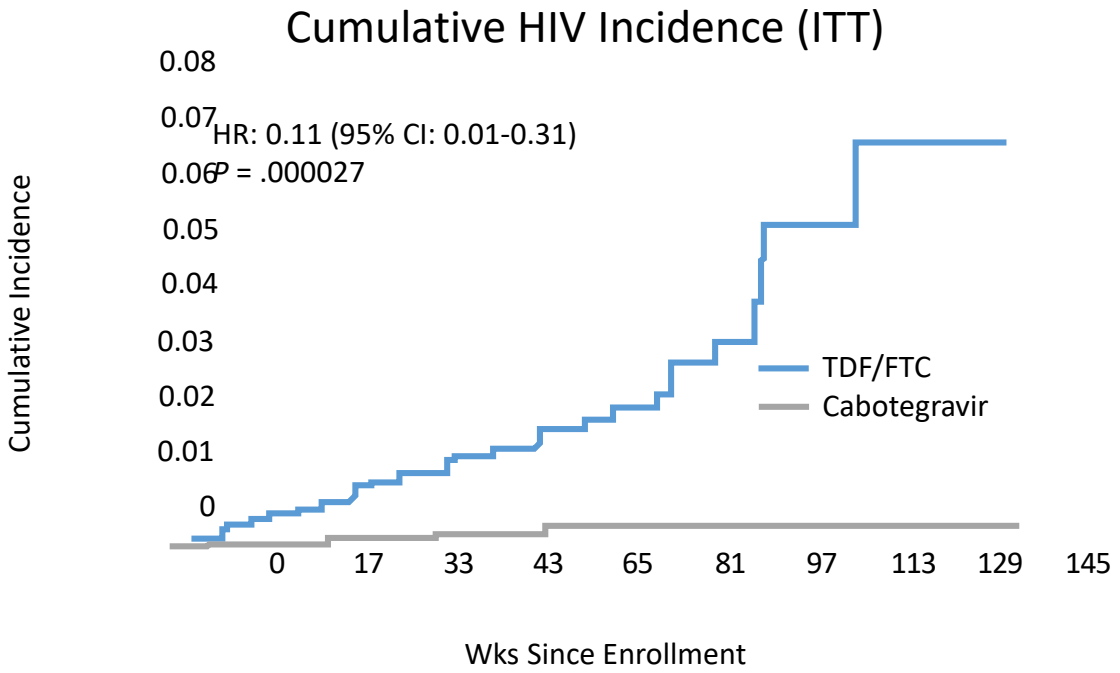


Half-life:
Oral: 40 hours
Injectable: 40-65 days

Dosing Strategy:
Single injection every 8 weeks

HPTN 084

- Women in cabotegravir arm had 89% lower risk of HIV infection vs TDF/FTC



HPTN 084: Final results (reported at IAS R4P 2021) show LA CAB is safe and superior to TDF/FTC amongst cisgender African women

4 infections in CAB arm vs. 36 incident infections in PrEP arm
Post hoc analysis showed one participant was infected prior to study start – risk of becoming infected was 92% lower in CAB arm

Delany-Moretlwe et al., 2021, IAS R4P

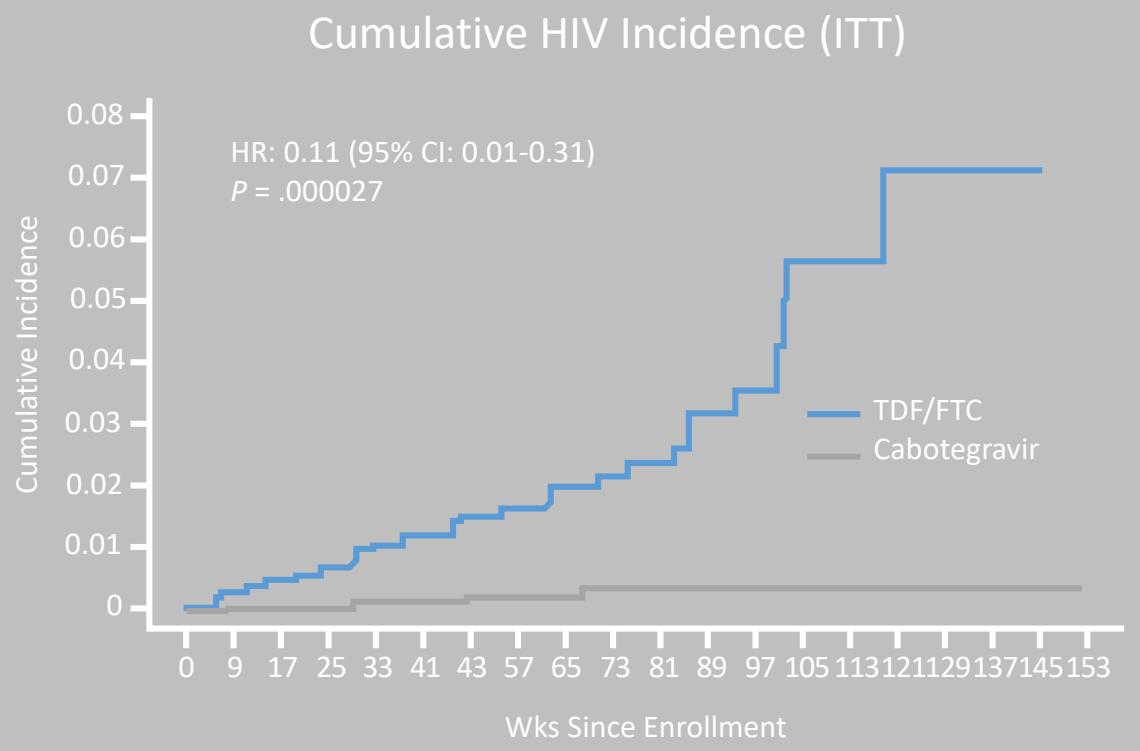
HPTN 084 Interim Analysis: HIV Incidence

Pooled HIV incidence of 1.03 (95% CI: 0.73-1.4) per 100 PY suggests both agents highly effective in reducing HIV acquisition in study population

> No differences in treatment effects between prespecified subgroups, including age, BMI, contraceptive use

Incidence	CAB (n = 1953 PY)	TDF/FTC (n = 1939 PY)
No. HIV infections	4	36
HIV incidence per 100 PY (95%)	0.2 (0.06-0.52)	1.86 (1.30-2.57)

Women in cabotegravir arm had 89% lower risk of HIV infection vs TDF/FTC



Delany-Moretlwe. HIVR4P 2021. Abstr HY01.02.

Slide credit: clinicaloptions.com

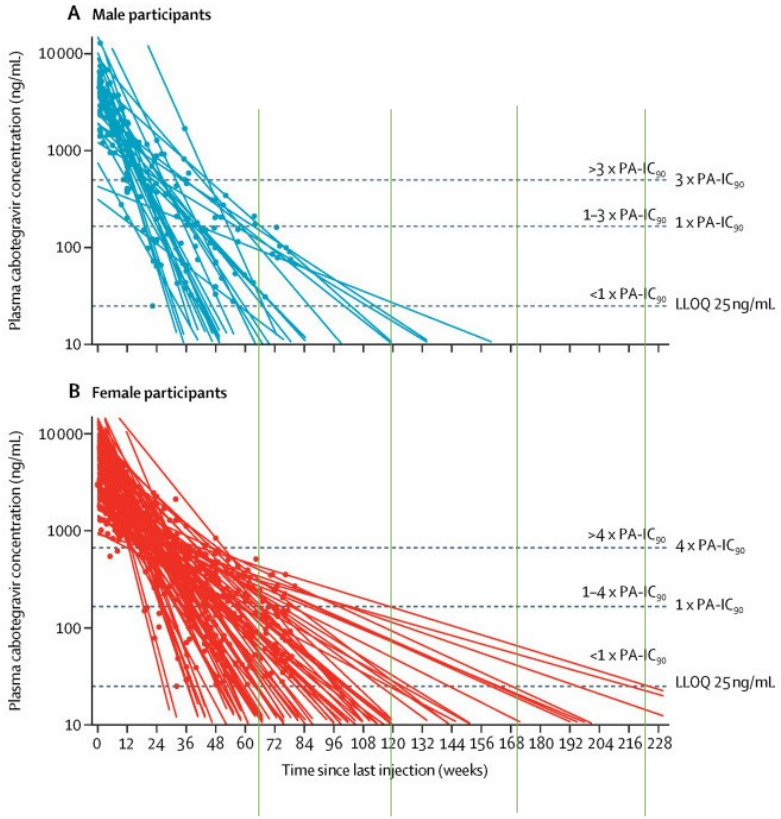
HPTN 084: Further evidence of CAB efficacy & safety

HPTN 084: Final results (reported at IAS R4P 2021) show LA CAB is safe and superior to TDF/FTC amongst cisgender African women = the first safe and effective HIV prevention agent for cisgender women has arrived!

- Women in the CAB group had an **89% lower risk of HIV infection** compared to the TDF/FTC group
  - 9 x incident HIV infections in the TDF/FTC arm compared to the LA CAB arm
  - Adherence advantage!
- As safe and well-tolerated as TDF/FTC
  - Injection site reactions higher in the CAB group but generally mild
  - Immediate increase in body weight (~0,4kg) in CAB arm considered small compared to weight gain seen in both arms (+2.4 kg / year in the CAB arm; +2.2 kg / year in the TDF/FTC arm)
- Pregnancy incidence in the study was 1.5 per 100 person-years in the CAB group, with **no congenital abnormities** reported
- STI incidence (CT and NG) was similar in both arms

Delany-Moretlwe et al., 2021, IAS R4P

HPTN 077 Tail Phase: What did we learn?



♂ $T_{½}$= 45.3 days

♀ $T_{½}$= 60.4 days

Landovitz RJ et al, *Lancet HIV*, 2020-07-01, Volume 7, Issue 7, Pages e472-e481

The clinical significance of the long pharmacokinetic tail of cabotegravir observed in female participants compared with male participants, and those with higher BMI compared with a lower BMI, need to be addressed in future trials.

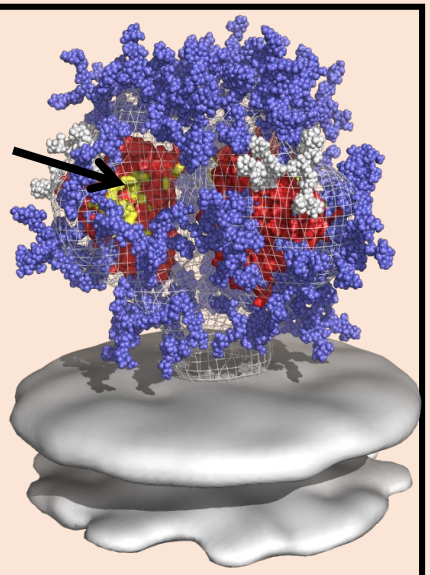
Okay. I would like it to be an injection so that everybody that is both men and young women can use it. If you notice the ring ends with girls. The injection can be used by everyone. It can be accessible from the clinic of one's choice. I would want it to stay for a year. Do you know that if it is to be injected every 3 months they will get tired of going to the clinic to refill. If it is a year a person becomes cool in the mind [stress free] and say to himself, 'Look I know I will only go next year the same date I got it'

Add sound

BNABs: Broad-neutralizing antibodies, VRC01

Agent class:
Broad-neutralizing antibodies

CD4 binding site 1b12, VRC01, VRC02, VRC03, VRC-PG04, HJ16, CH30-CH34, N6

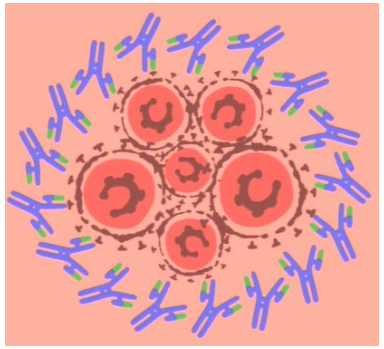


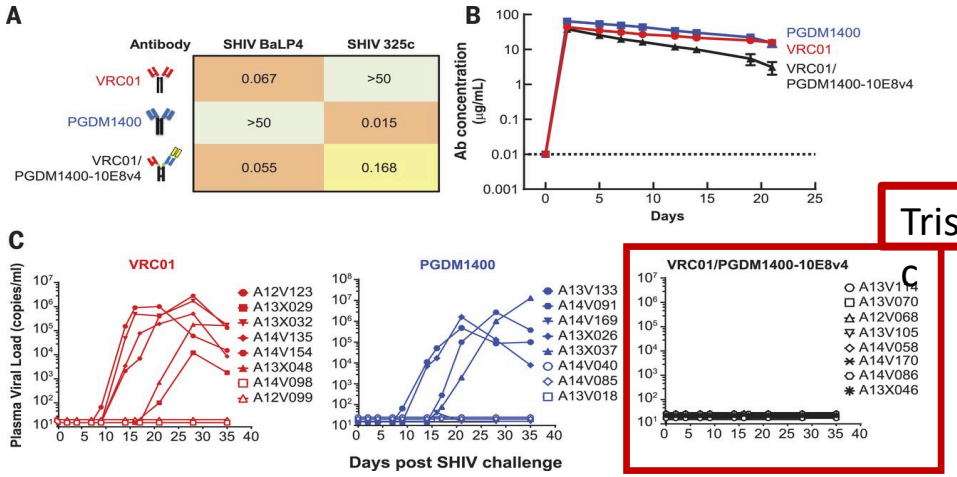
Dosing Strategy (AMP Trial)
VRC01 mAb (IV), given on 8 weekly schedule

Neutralizing antibodies which neutralize multiple HIV-1 strains
First BNAB identified in 1990
VRCO1 attaches to CD4 binding site

2021: proof-of-concept for BnAbs: VRC01 achieved **75% protection** over the 20- month study period (Sheena McCormack, HIV R4P 2021, HY01)

- HIV incidence was 0.2/100 py vs. 0.86 in in VRC01 recipients control recipients (P<0.001)
- The VRC01 antibody did produce a 75% reduction in the number of infections in the type of viruses that were most sensitive to this particular bNAb. As these represent less than a third of circulating viral varieties, VRC01 cannot be used as a solo prevention drug.
- Next generation BNAB's will have longer half lives and be delivered in combination and will target different places on the virus



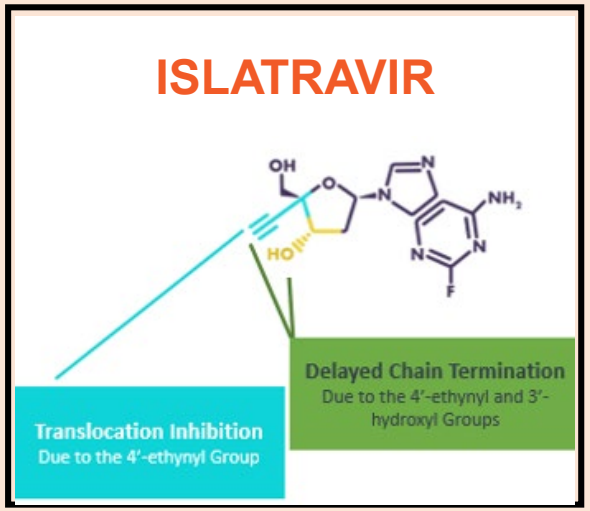


Trispecifi

AMP
ANTIBODY · MEDIATED · PREVENTION
STUDY

Islatravir (ISL, MK-8591): Monthly pill for HIV prevention (and treatment)

Agent class:
Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)



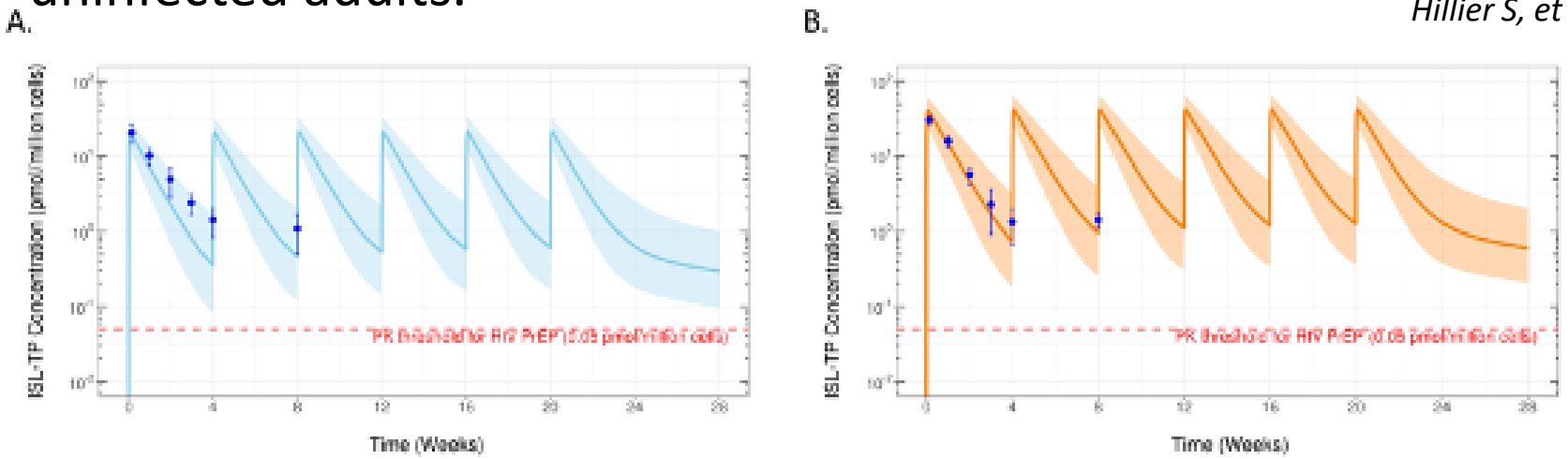
Novel mechanism of action, being developed for both treatment and prevention and as a monthly pill and an implant for prevention

Demographics, blinded safety and pharmacokinetics (PK) data from a phase 2a trial of Islatravir once monthly (QM) for HIV pre-exposure prophylaxis (PrEP)

HIV VIRTUAL AN IAS CONFERENCE

Half-life in PBMCs approximately 190 hrs after oral dose in uninfected adults.

Hillier S, et al

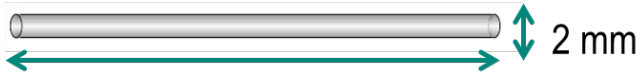


Shaded area represent 95% Prediction Interval (N=1000 simulations); Solid lines represent the pop PK model predicted median concentration; Blue filled circles represent mean of P016 interim observed data; Blue error bars represent standard deviation of P016 interim observed data

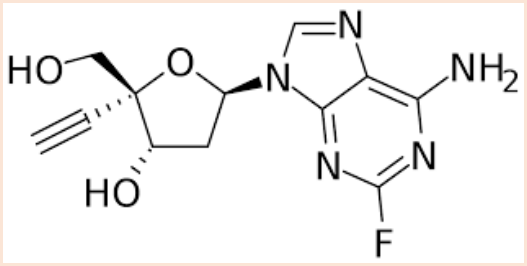
This interim analysis suggests that monthly doses of ISL 60 mg and 120 mg achieved the pre-specified efficacious PrEP PK threshold. Blinded safety data indicate that ISL was well tolerated.

Islatravir (ISL, MK-8591): Long-acting implants for HIV prevention (and treatment)

Agent class:
Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)

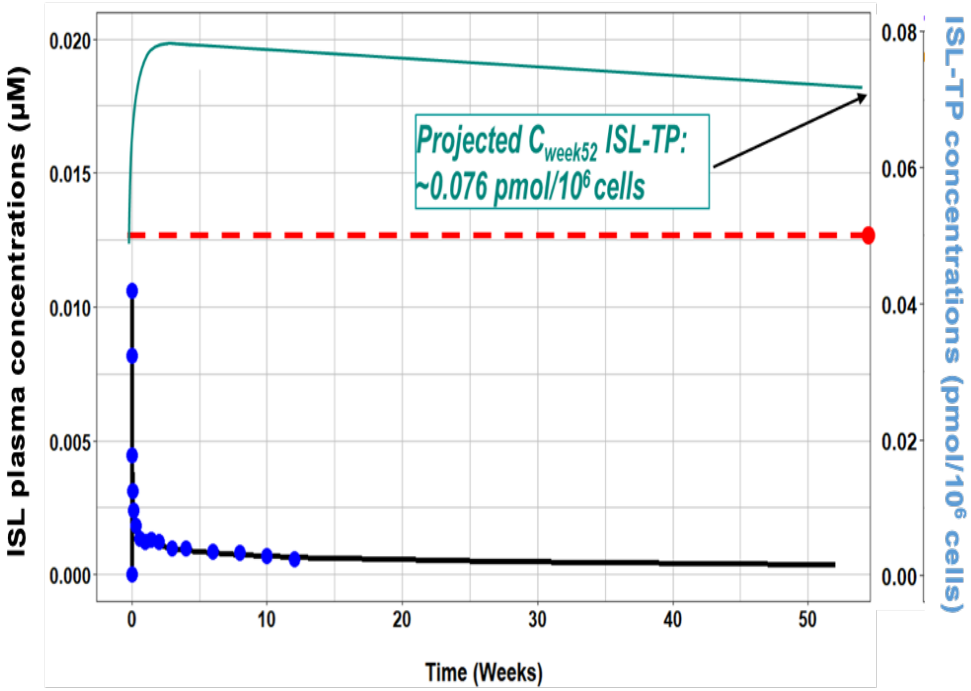


ISL implant based on Implanon®/Nexplanon®
- Uses same polymer
- Removable (not bioerodible)



First in human trial results presented at IAS 2019 (Mexico): Double-blind, placebo-controlled trial in healthy individuals

- Well tolerated (no discontinuations due to AEs and no severe implant-related Aes)
- 62mg implant releases through 52 wks
- Lower threshold ISL-TP = 0.05pmol/10^6 cells. Projected at 12 months = 0.076pmol/10^6 cells
- Projected time to fall below threshold: 68-70 wks (~16 months)
- Supports potential of ISL implant as a once-yearly PrEP option.



Dosing Strategy:
Removable implant (52 or 62mg)

Benefits of Implants
- Reversible with removal
- Long-acting (months to years)
- Potential for Multi-purpose

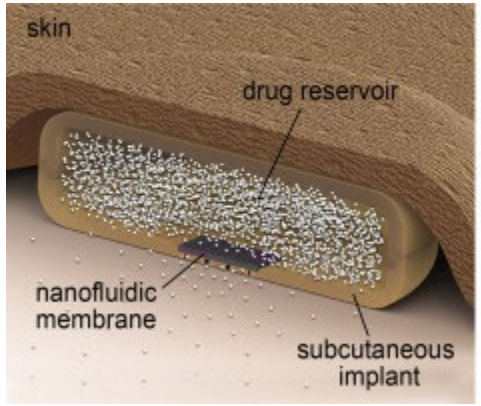
Schlesinger, et al, Pharm Res 2016; Gunawardana, et al., AAC 2015; Matthews, IAS 2019 Mexico, Oral Abstract

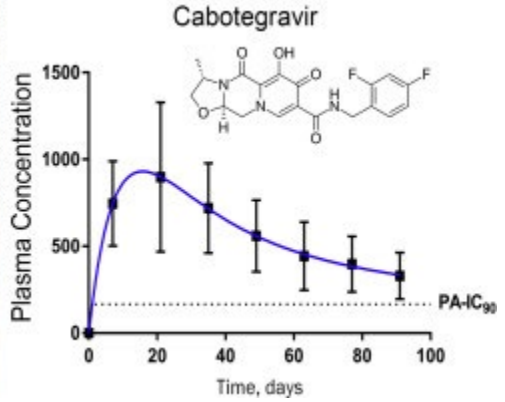
Other implant development underway….

TAF Implant for Prevention of SHIV Infection:

- All 6 macaques with TAF implants (0.7 mg/day) were completely protected against vaginal SHIV infection after 12 challenges and 4-mo follow-up (Wilcoxon *P* = .0037 vs controls)
- Local skin reactions evaluated weekly
- Histology of biopsies collected at time of implant removal assessed with H&E
  - 8/12 skin biopsies exhibited marked deep dermal necrosis (Wk 7)

Cabotegravir Implant





ISL QM oral PrEP – ongoing clinical development program

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

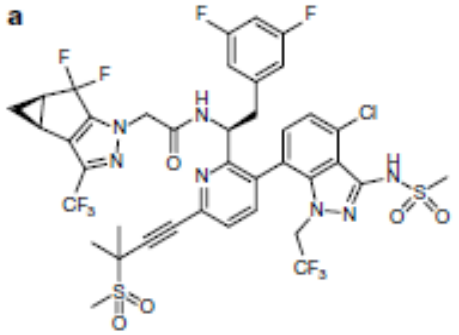
IMPOWER 022 will be done in collaboration with the Bill & Melinda Gates Foundation which intends to provide grant funding to the International Clinical Research Center (ICRC) at the University of Washington Department of Global Health who will be working together with MSD to conduct the trial

FTC, emtricitabine; ISL, islatravir; PrEP, pre-exposure prophylaxis; QM, once monthly; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Lenacapavir (GS-6207): LAs for HIV treatment

Agent class:
HIV-1 capsid inhibitor

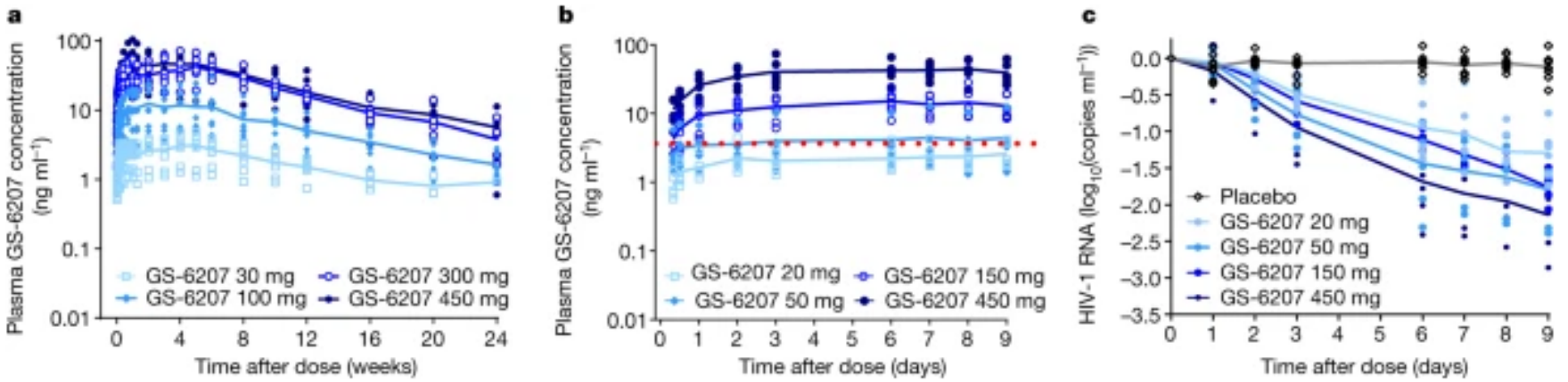
LENACAPAVIR



Dosing Strategy: One injection every 6 months **(ARVs that you only need to take twice a year!)**

Early stages of development

- Single injection shown to reduce HIV-1 viral load in PLHIV with multidrug resistant HIV-1 infection.
- **88%** experienced at least a 0.5 log10 reduction in HIV-1 viral load over 14 days compared to 17% of those in the control arm

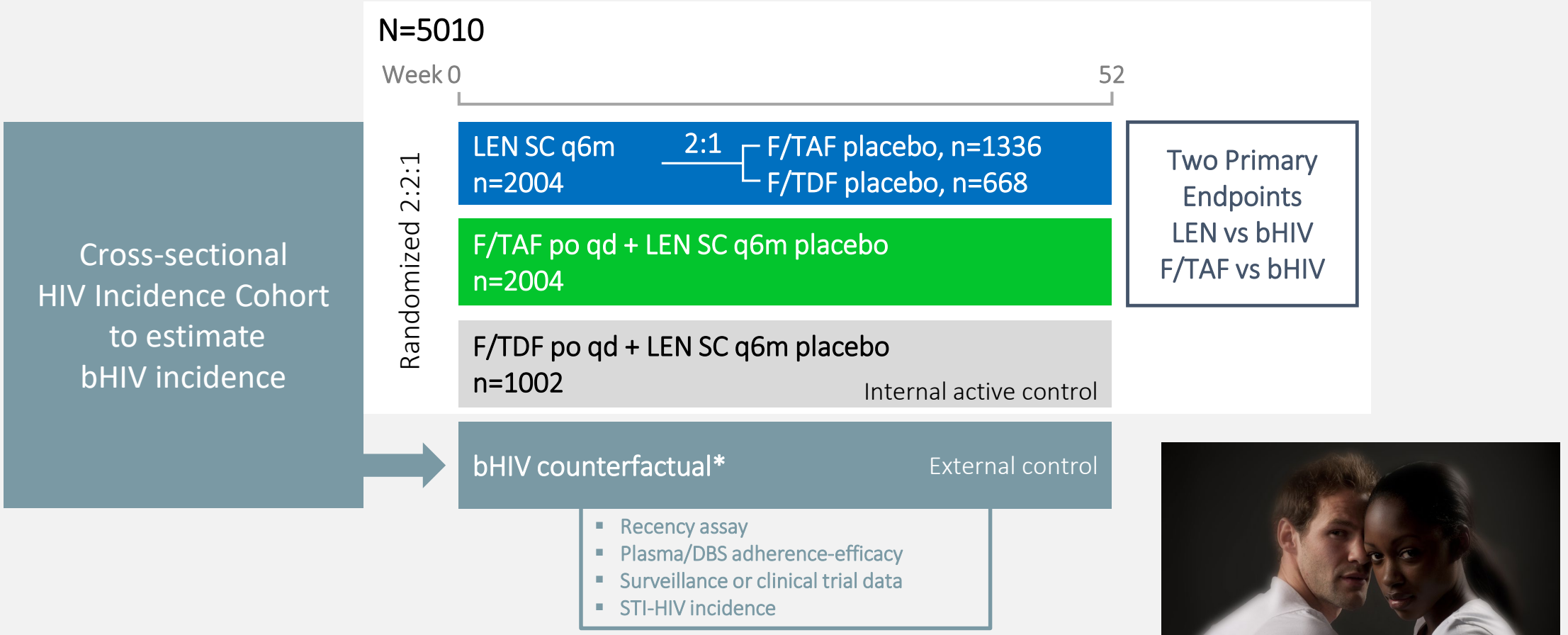


Mean plasma concentration-time profiles of Lenacapavir after a single injection to individuals uninfected with HIV (**Graph A, n=8**) and individuals living with HIV (**Graph B, n=6**).

Graph C: Mean log10 transformed change in plasma HIV-1 RNA in individuals with untreated HIV-1 infection (drug, n = 6 and placebo, n=2)

Link et al., 2020, Nature

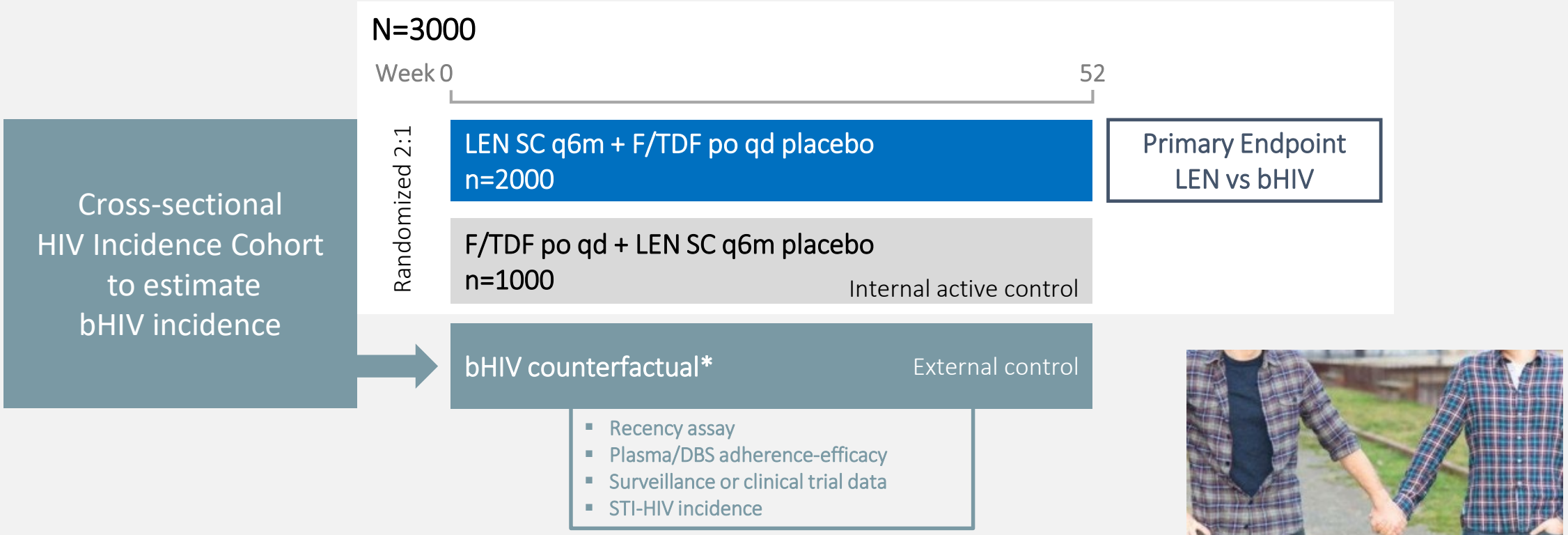
Design to evaluate efficacy & safety of LEN and F/TAF for PrEP in Adolescent Girls and Young Women



Will be conducted in the South Africa and Uganda
Participants may get pregnant and lactate (after reconsent)

bHIV, background HIV incidence; DBS, dried blood spot. AGYW: adolescent girls and young women

Design to evaluate efficacy & safety of LEN and F/TDF for PrEP in Cisgender Men, Transgender Women, Transgender Men, and Gender Non-Binary Individuals

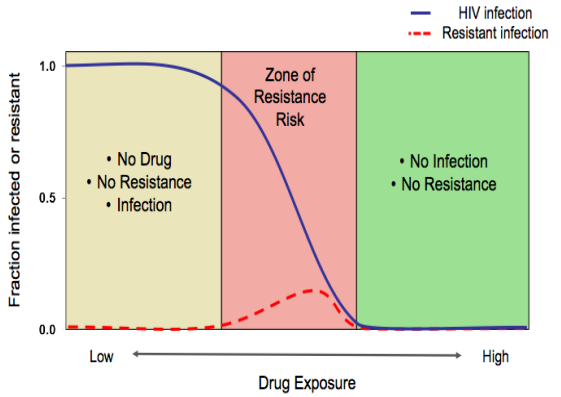


Will be conducted in the U.S.(including Puerto Rico), Brazil, Peru, and South Africa
Will have key recruitment goals on Race, Ethnicity, Age, and Gender

- CGMSM, cisgender men who have sex with men; GNB, gender nonbinary individuals; TGM, transgender men.

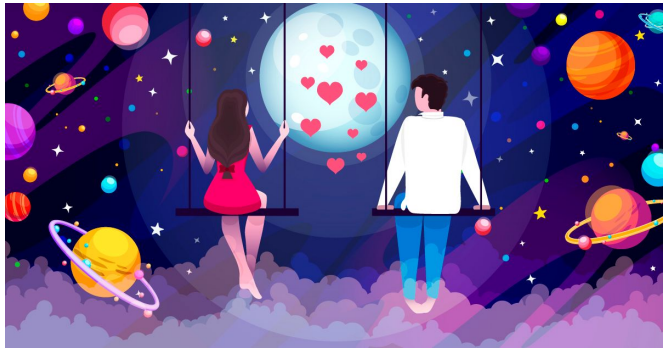
Long Acting PrEP: Pros and Cons

YES!	More thought needed
Improved adherence	Understanding the “long tail” implications
Less frequent reminding	Ongoing persistence challenges- Long periods of forgetting and travel
Fewer healthcare visits	Accredited administrators – can’t be given out by peers
Discreet – easier to keep private than pills	Still need to consider intimacy & other SRH needs, eg timing with LARC



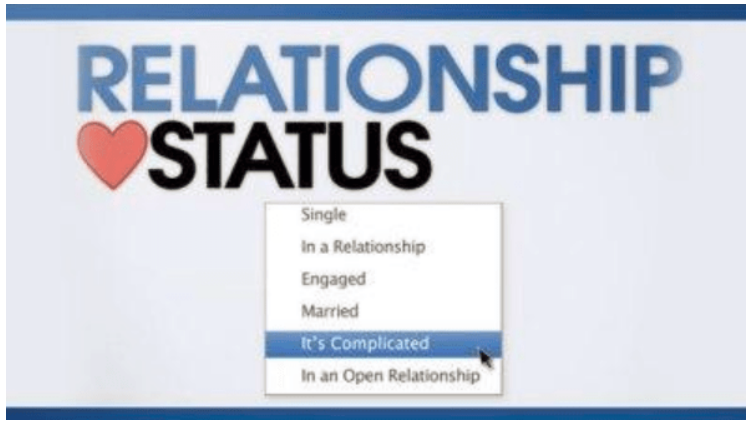
PrEP Preferences

Career Changes



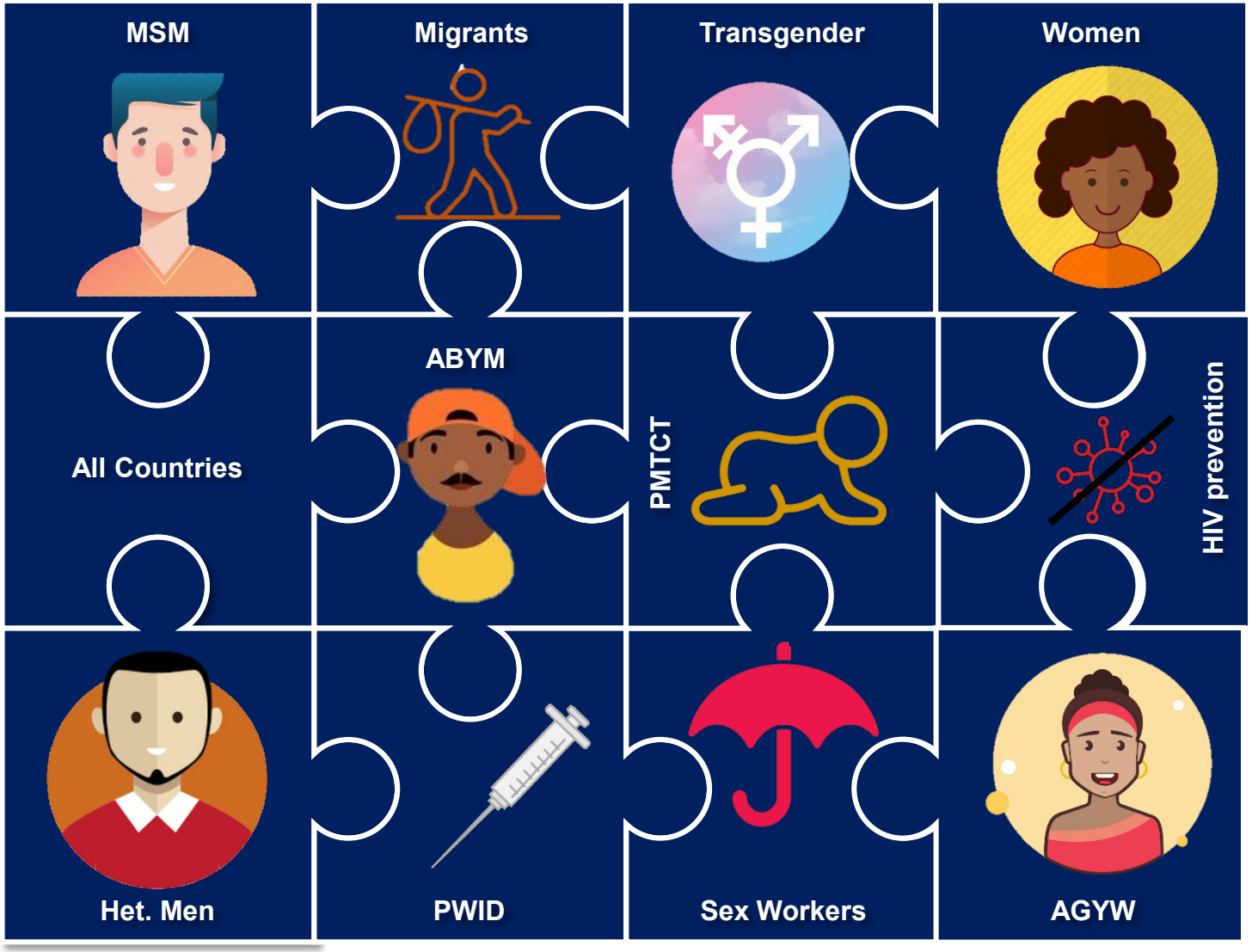
New relationships

Change in relationship status

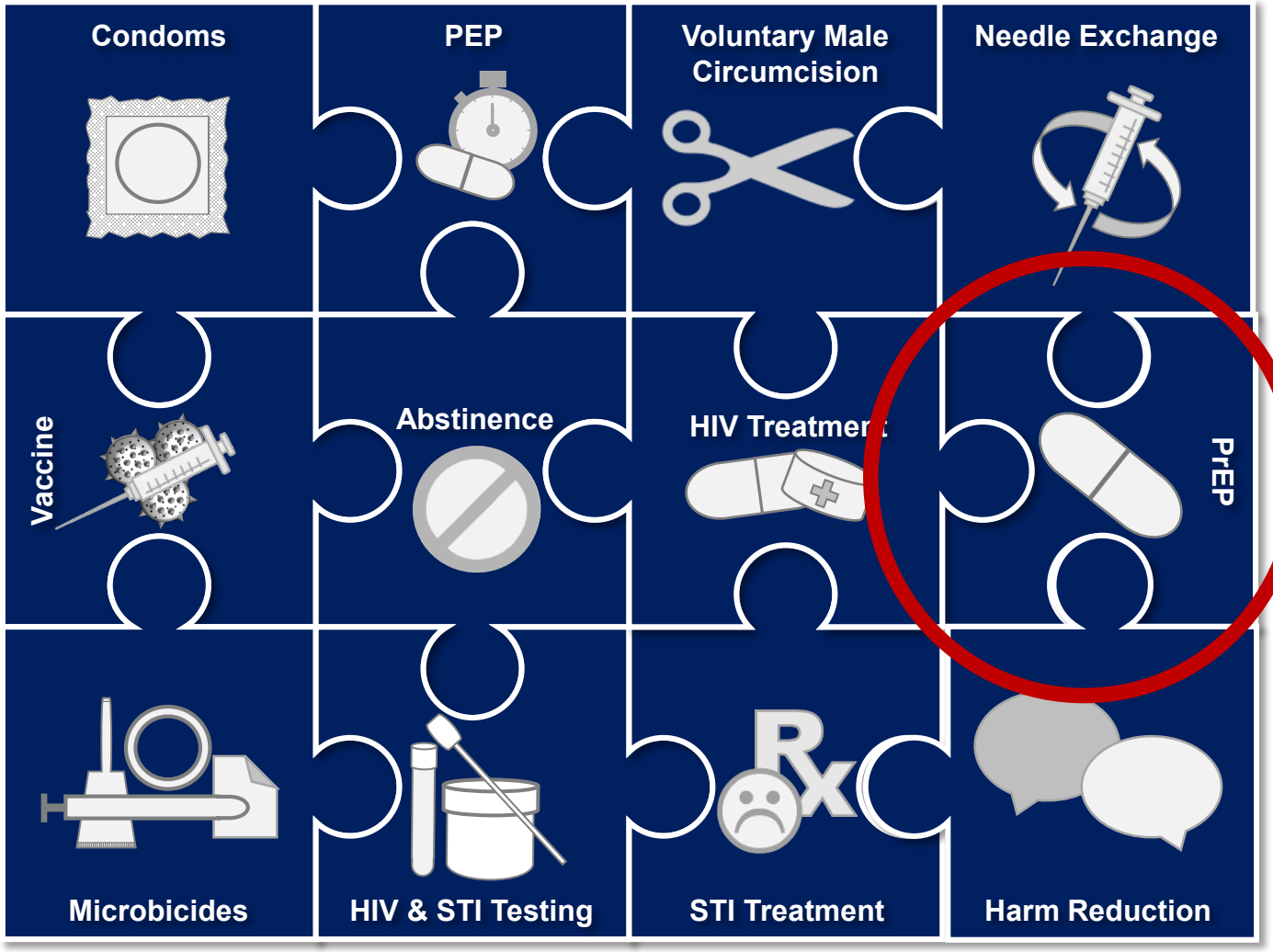


Living circumstances

Travel



Humanity Comes in many Shapes and Forms…



Prevention Should too…

Then we may expect better coverage of <u>all people</u> and better coverage of <u>all exposures</u>!

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