PrEP IN EUROPE

Europe needs PrEP now

PrEP in Europe Summit 2019:

The PrEP needs of cis and trangender women and transgender men

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Introduction

- Why focus on cis and trangender women and transgender men ?
  - High-risk population: MSM, TGW, « vulnerable women »
  - 1.7 million new HIV infection in the world (UNAIDS 2018)
  - 18.8 million **women** (51%) out of 36.2 million PLWH in 2018 (UNAIDS 2018)
  - AIDS-related illness is the second leading cause of death in young women (15-24 years) in Africa (WHO estimate 2016)
  - High-risk sex acts: condomless receptive anal intercourse (RAI); condomless receptive vaginal intercourse
  - TGW: HIV prevalence of 22% ($CI_{95\%}$:19-24) in 5 high-income countries and OR of HIV = 49 ($CI_{95\%}$:21-76) compared to other adults of reproductive age (Baral et al. Lancet HIV 2013)
  - TM : sparse data, TMSM: frequent condomless RAI

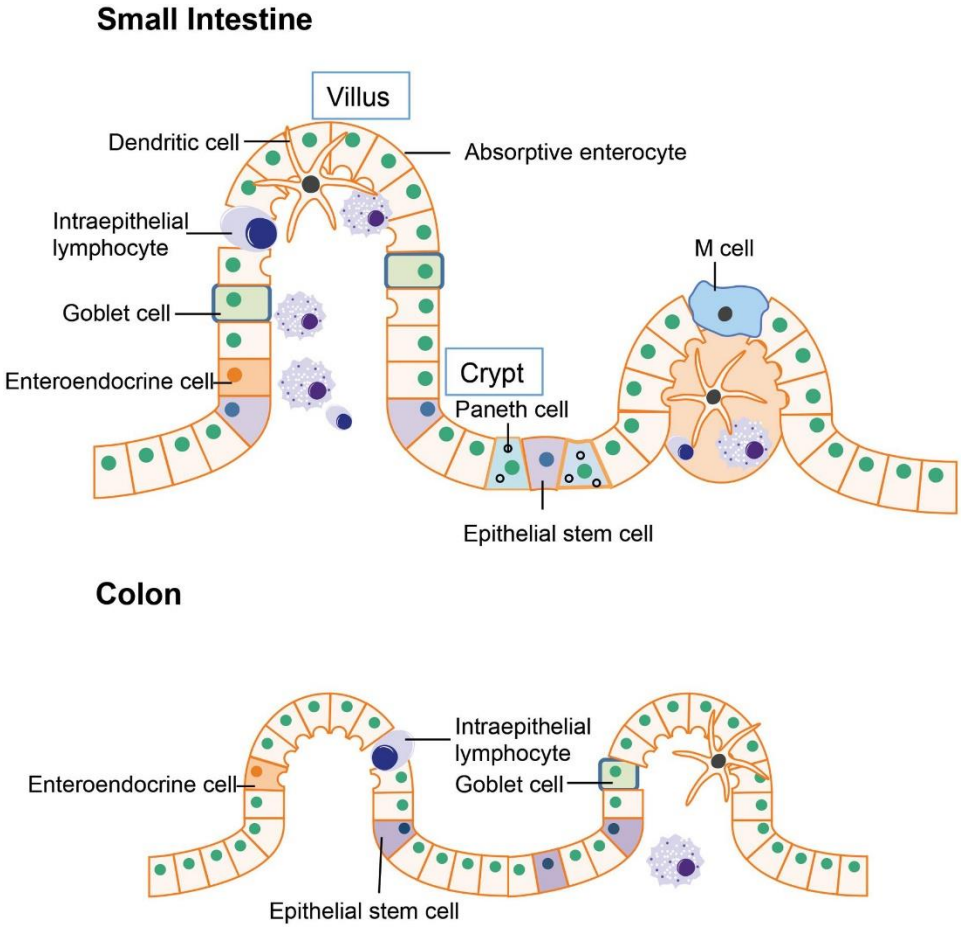
Sex Act	RR
Insertive fellatio†	1
Receptive fellatio†	2
Insertive vaginal[21]	10
Insertive anal[21]	13
Receptive vaginal[21]	20
Receptive anal	100

Patel et al. AIDS 2018

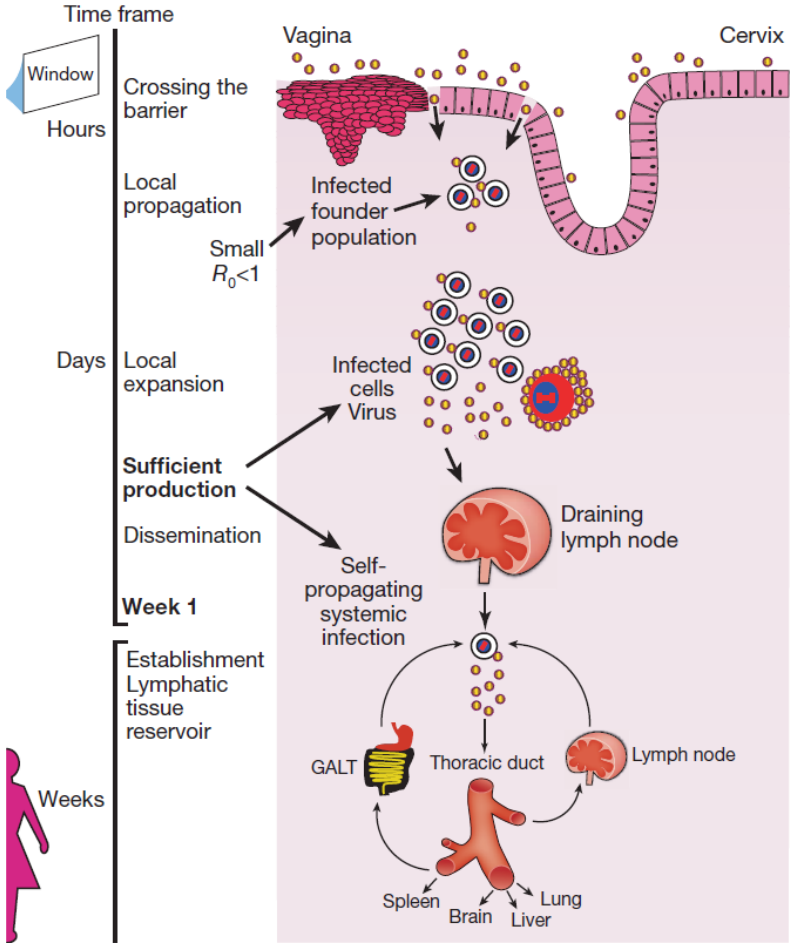
Varghese et al. STD 2002

Genital composition and HIV transmission

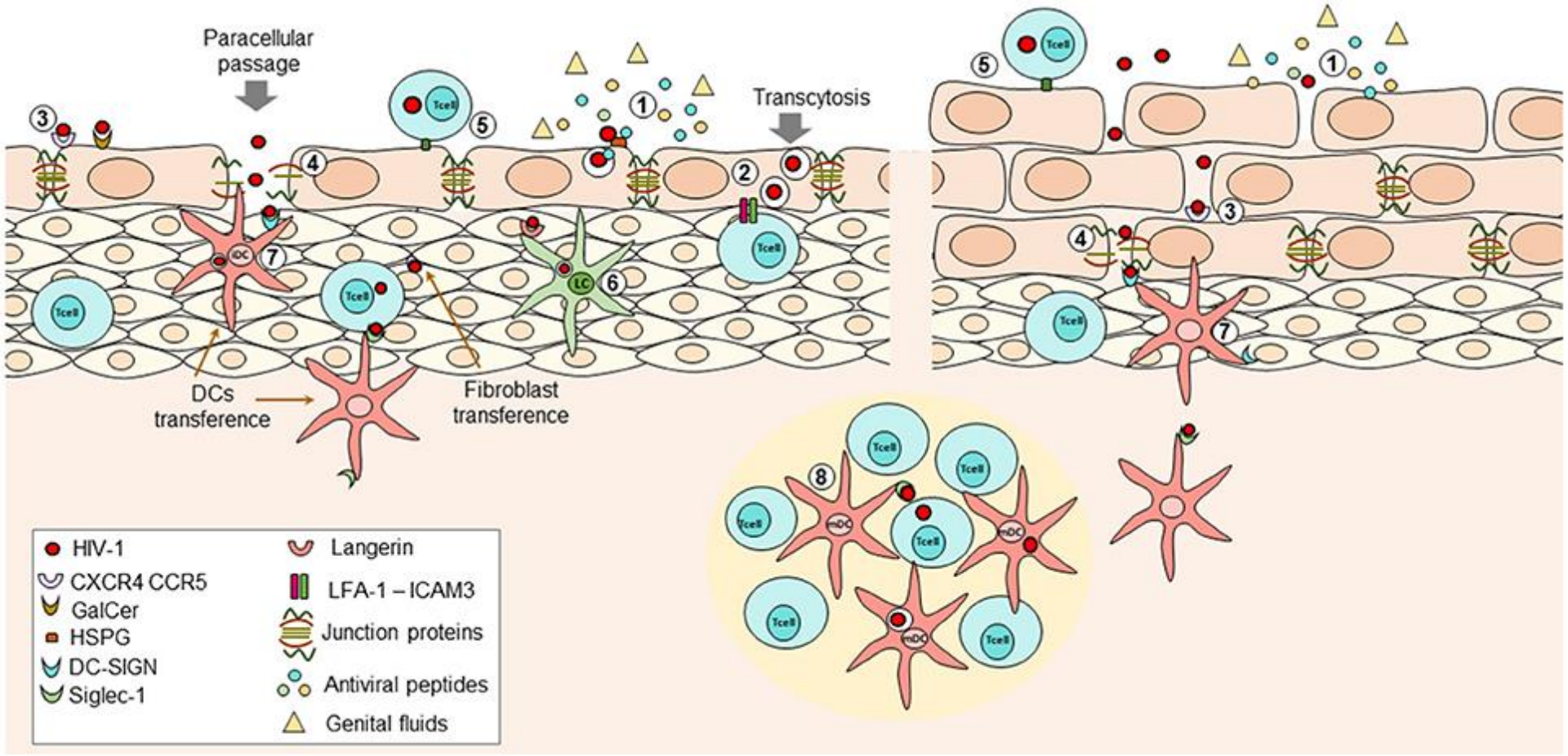
- Difference in HIV transmission due to:
  - Layers of epithelia
  - Microbiota
  - Keratinocytes
  - Submucosal immunological cells
  - Antiviral factors in the genital fluids
  - Effect of hormones



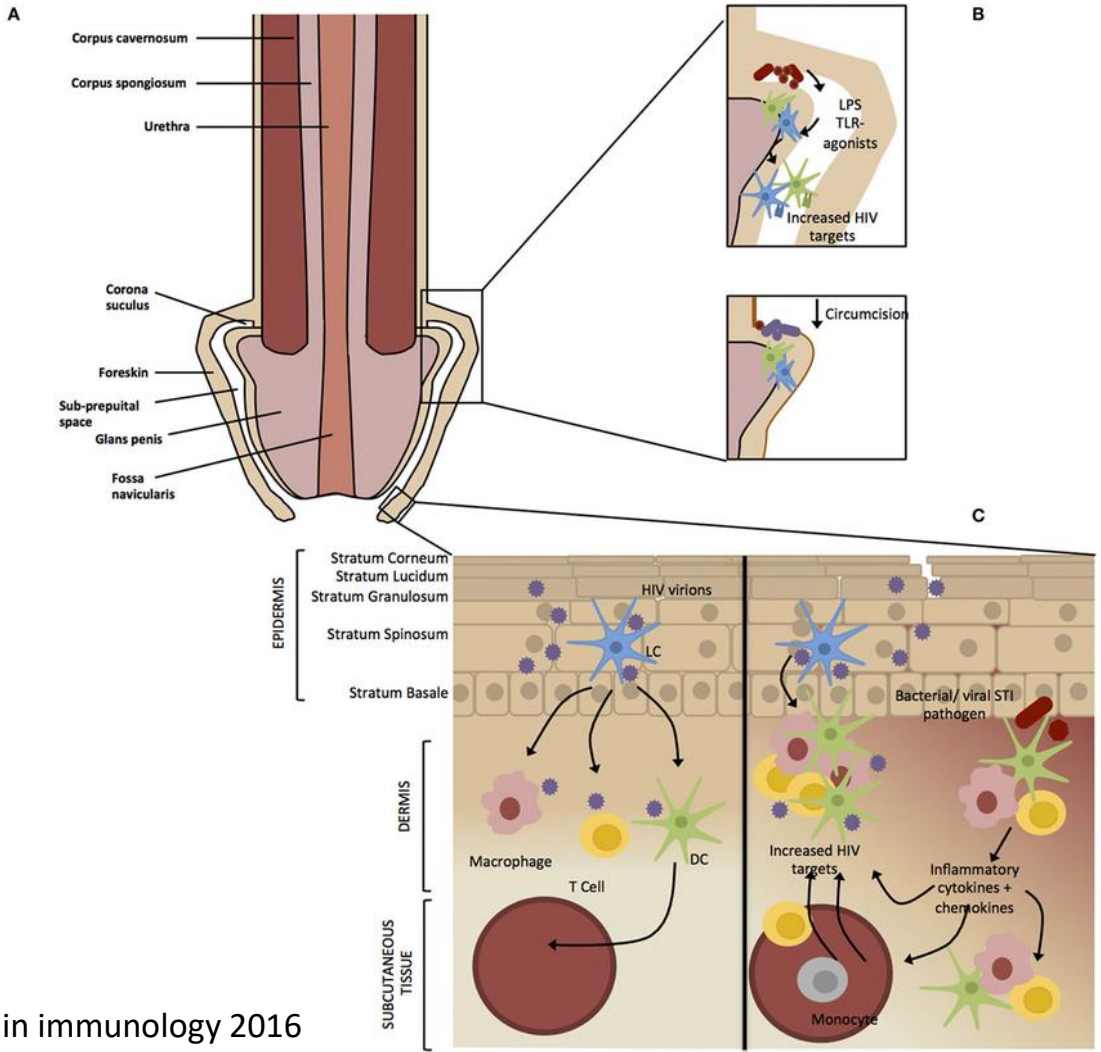
Source : https://www.frontiersin.org/files/Articles/149542/fmicb-06-00643-HTML/image_m/fmicb-06-00643-g001.jpg



Haase Nature 2010



Source: Gonzalez Frontiers in immunology 2019



Source : Esra Frontiers in immunology 2016

Role of hormones

- HIV transmission and hormones

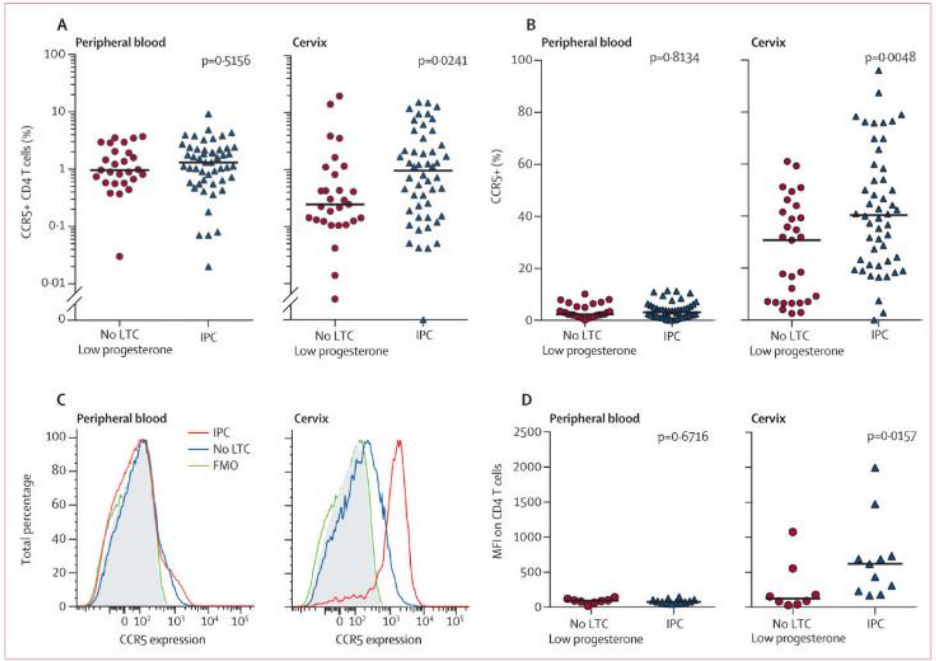


Figure 2. HIV target cells in women using no LTC compared with women using an IPC
CCR5+ CD4 T cells as a percentage of live CD45+ cells in the blood and cervix (A) and CCR5+ expression as a percentage of CD4 T cells in the blood and cervix (B). CCR5 expression levels on CD4 T cells as shown by a representative fluorescence-activated cell sorting histogram (C) and within all patients analysed (D). All participants had a plasma progesterone concentration of 0·3 ng/mL or less. p values were determined by the Mann-Whitney test. LTC=long-term contraception. IPC=injectable progestin-only contraception. FMO=Fluorescence minus one. MFI=Median fluorescence intensity.

Byrne Lancet ID 2016

Role of hormones

- PrEP pharmacology and hormones

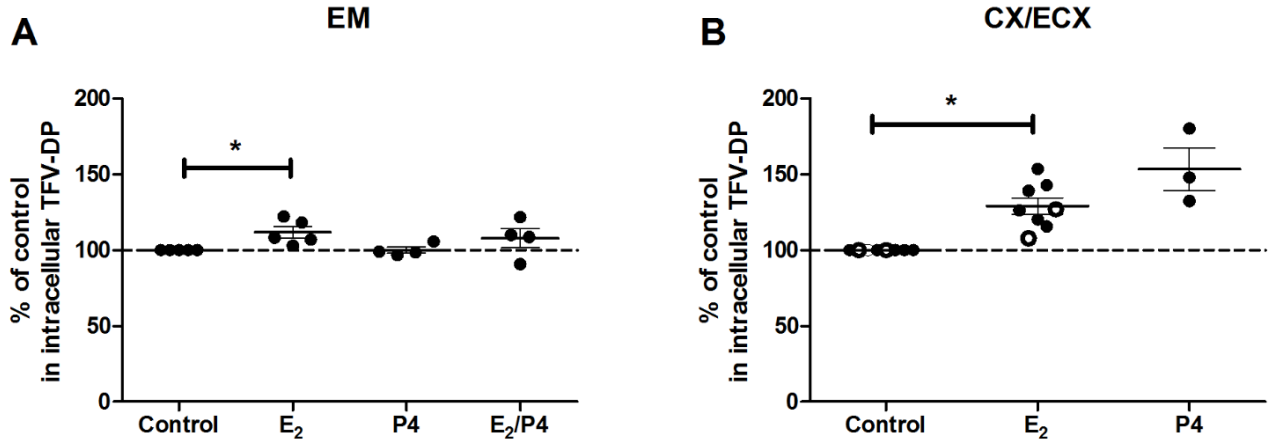


Figure 4. Effect of estradiol and/or progesterone on TFV-DP levels in epithelial cells from endometrium, endocervix and ectocervix. TFV-DP levels were measured by LC-MS/MS in polarized cultures of FRT epithelial cells treated with TFV (1 mg/ml) and estradiol (5×10^{-8} M), progesterone (1×10^{-7} M), either alone or the combination for 24 hr. Data were normalized to % of control values from (A) EM epithelial cells (n = 4–5) and (B) CX/ECX epithelial cells (n = 3–8). Dashed line indicates an assigned value of 100. Each circle represents a different patient. Dark circles indicate (A) EM epithelial cells and (B) CX epithelial cells. Open circles indicate ECX epithelial cells. The mean and SEM are shown. *, $p<0.05$.
doi:10.1371/journal.pone.0100863.g004

Zheng PlosOne 2014

Role of hormones

- PrEP pharmacology and hormones
  - Contraception:

Nicol CID 2019

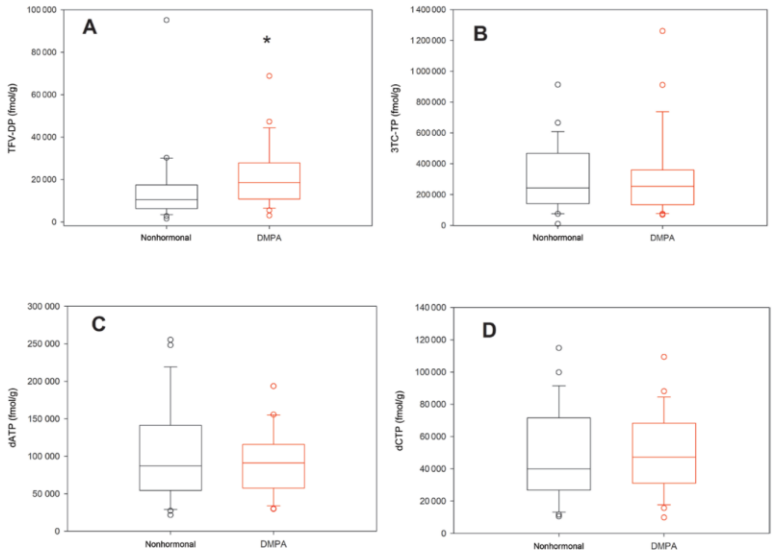


Figure 1. Concentrations of intracellular metabolites and endogenous nucleotides in cervical tissue. *A–D*, Box plots showing distribution of analytes measured in cervical homogenates by contraceptive group: tenofovir diphosphate (*A*), lamivudine triphosphate (*B*), deoxyadenosine triphosphate (*C*), and deoxycytidine triphosphate (*D*). Abbreviations: 3TC-TP, lamivudine triphosphate; dATP, deoxyadenosine triphosphate; dCTP, deoxycytidine triphosphate; DMPA, depot medroxyprogesterone acetate; TFV-DP, tenofovir diphosphate. **P* < .05, Wilcoxon rank-sum test.

Role of hormones

- PrEP pharmacology and hormones
  - Feminizing hormones

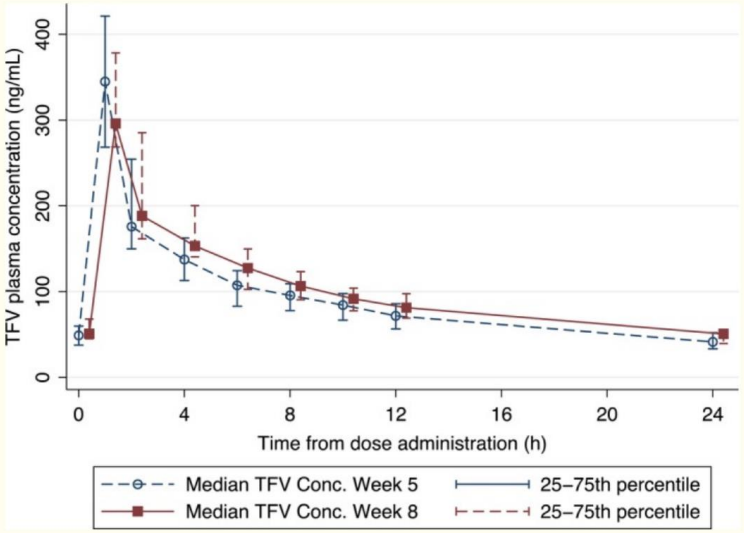


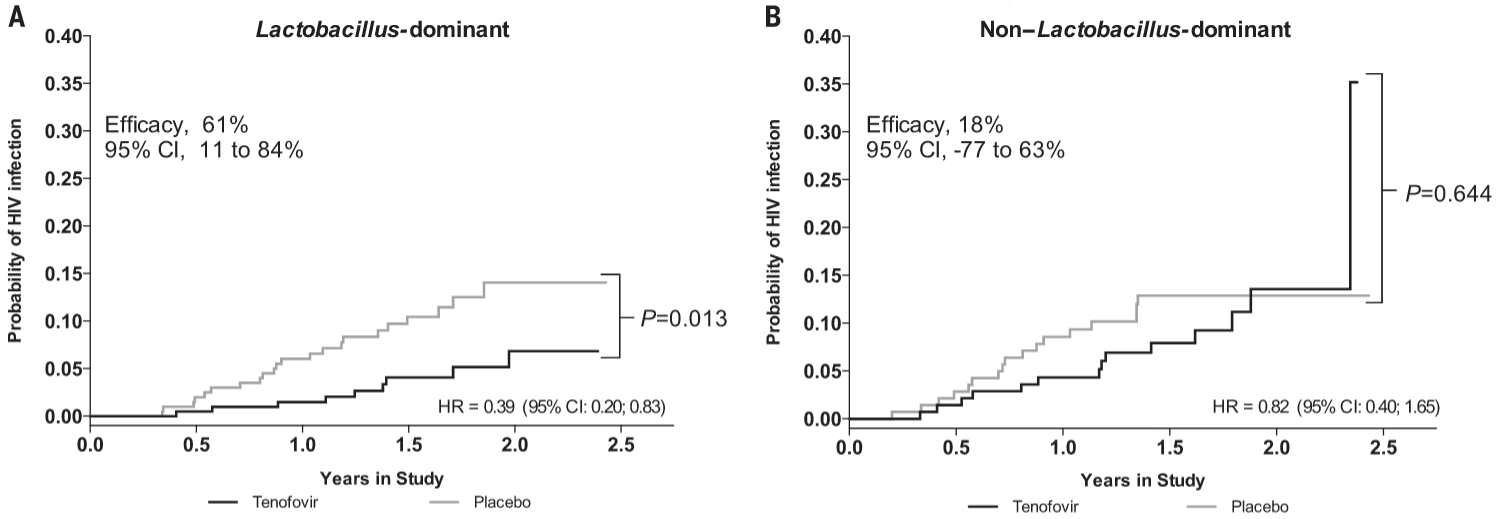
Figure 3

Median tenofovir (TFV) concentration-times curves at week 5 and week 8

Error bars represent the 25th to 75th percentile. Week 8 times have been offset by 0.4 hours to improve readability.

Hiransuthikul JIAS 2019

Vaginal microbiota



***Lactobacillus*-dominant women at risk (Cumulative number of infections)**

Tenofovir	205 (0)	204 (1)	183 (3)	129 (7)	46 (9)	0 (9)
Placebo	202 (0)	196 (4)	173 (12)	123 (19)	51 (22)	0 (22)

Non–*Lactobacillus*-dominant women at risk (Cumulative number of infections)

Tenofovir	140 (0)	137 (2)	123 (6)	87 (10)	32 (13)	0 (14)
Placebo	141 (0)	137 (4)	116 (12)	84 (17)	28 (17)	0 (17)

Fig. 2. Cumulative HIV infection probability by treatment assignment in women with vaginal *Lactobacillus* dominance and non-*Lactobacillus* bacterial dominance. Data for (**A**) *Lactobacillus*-dominant (*Lactobacillus* > 50%) (*n* = 407) and (**B**) non–*Lactobacillus*-dominant (*Lactobacillus* ≤ 50%) (*n* = 281) women. The tables below each panel show the cumulative number of HIV infections in each study arm, corresponding HIV incidence rates, and efficacy of tenofovir gel to prevent HIV acquisition for each additional 6 months of follow-up. The protective efficacy of tenofovir gel was more than threefold higher in women with *Lactobacillus* dominance (A) compared with non-*Lactobacillus* dominance (B). HR, hazard ratio.

Klatt Science 2017

CISGENDER WOMEN

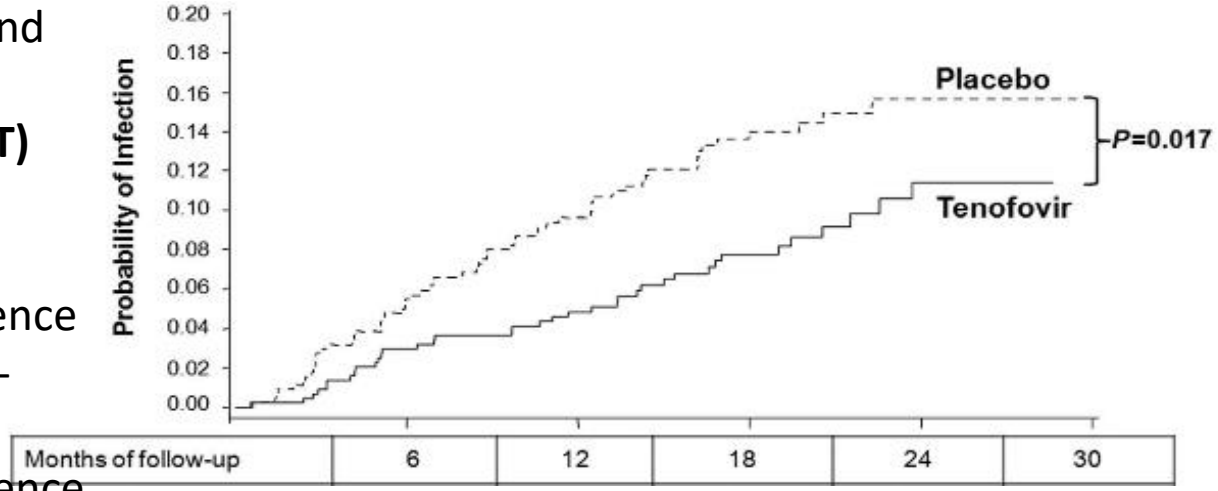
Topical PrEP

- Vaginal gel CAPRISA 004

Double blinded study comparing placebo and 1% TFV gel **B**efore and **A**fter vaginal intercourse and no more than **T**wo doses in 24h **(BAT)**
445 vs 444 cis women
South Africa

➔ 39% $CI_{95\%}$[6-60] relative incidence reduction HR=0.61 $CI_{95\%}$ [0.40-0.94]; p=0.017

➔ 54% $CI_{95\%}$ [4-80] relative incidence reduction in women with high adherence



Abdool Karim et al. Science 2010

Topical PrEP

- Vaginal gel FACTS 001

Double blinded study comparing placebo and 1% TFV gel

BAT

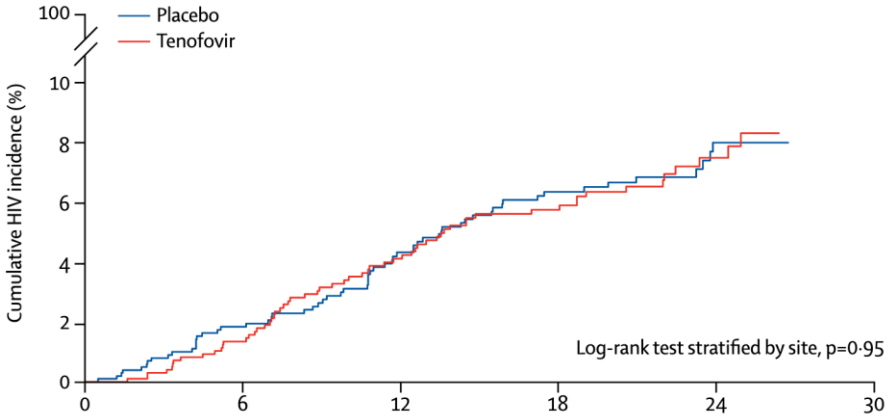
2059 women in South Africa, mean age 23 years, 88% unmarried

HIV infection: 61 in the TFV arm and 62 in the placebo group **(HR: 0.98 $CI_{95\%}$ [0.7-1.4])**

➔ Low adherence overall

➔ Only 20% of participants had an adherence of > 80% of gel use for each intercourse (based on returned used product), in this subgroup, HR for HIV acquisition was HR: 0.52 $CI_{95\%}$ [0.27-0.99];p=0.04 with TDF compared to placebo

➔ And in participants with TFV > 30 ng/mL in cervicovaginal lavage ajusted HR was 0.45 $CI_{95\%}$[0.23–0.89]



Delany et al. Lancet HIV 2018

Topical PrEP: VOICE

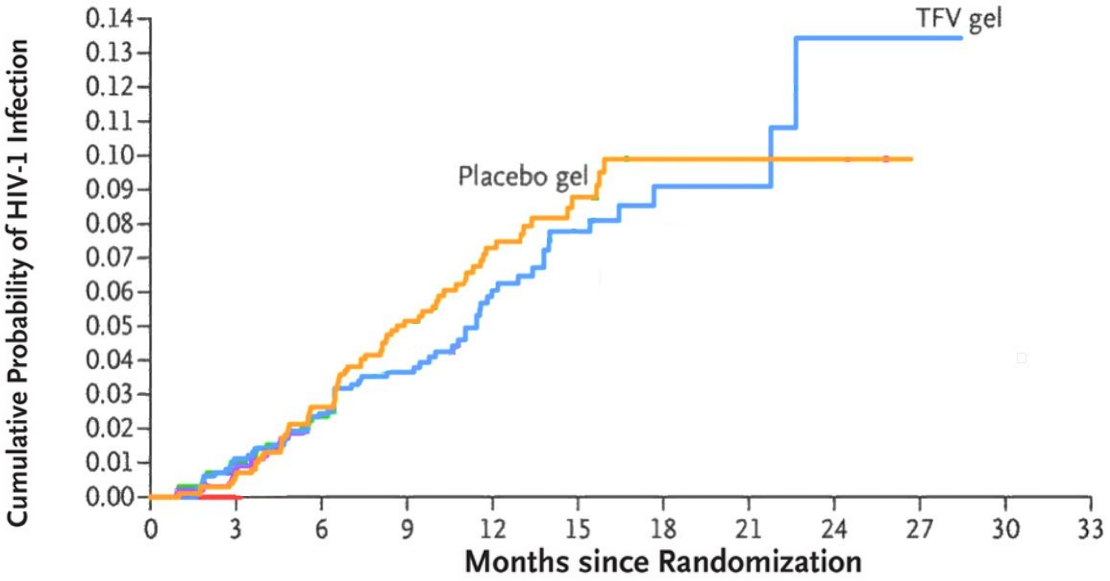
- **Daily** use of 1% TFV gel (vaginal)
- 5029 women in South Africa (15 sites)
  - 18 to 45 years
  - Neither pregnant nor breast-feeding
  - Recent vaginal intercourse and using effective contraception
  - 21% married
  - High prevalence of RAI (17%)
- HIV relative incidence reduction: 14.5%
- HR: 0.85 $CI_{95\%}$[0.61-1.21]

➔ **Low adherence ?**

➔ Proportion of product not returned divided by the number of days since the previous visit = **83%**

➔ A mean of 25% had quarterly detectable TFV level in plasma and 49% detectable in vaginal swab

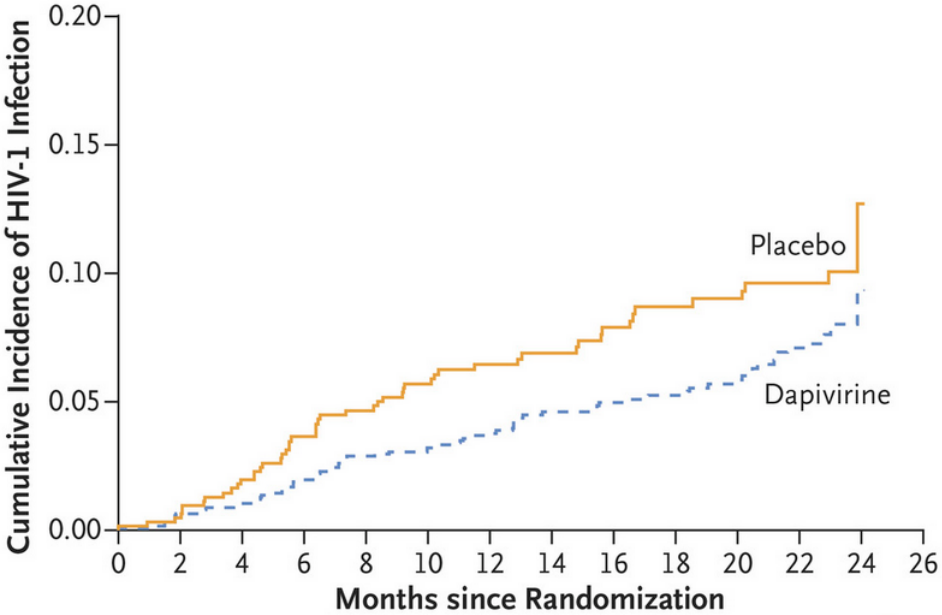
➔ In participants with detectable TFV in plasma HIV acquisition **HR: 0.34** $CI_{95\%}$**[0.13 - 0.87] p=0.02**



Marrazzo et al. NEJM 2015

Topical PrEP

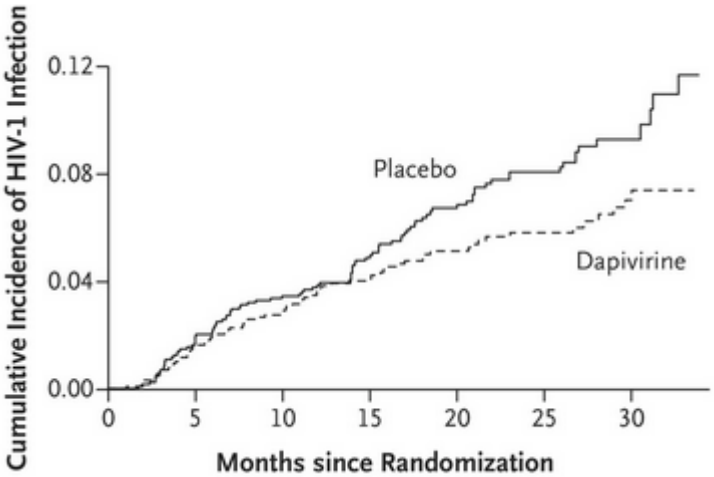
- Ring Study
  - South Africa and Uganda
  - Double blinded study
  - Dapivirine ring vs placebo
    - Once/4weeks, self-inserted
    - Up to 24 months
  - 1959 women, mean age 25.9 years, 89% single
  - 31% HIV relative incidence reduction
  - **HR: 0.69 $CI_{95\%}$[0.49-0.99]; p=0.04**



Nel et al. NEJM 2016

Topical PrEP

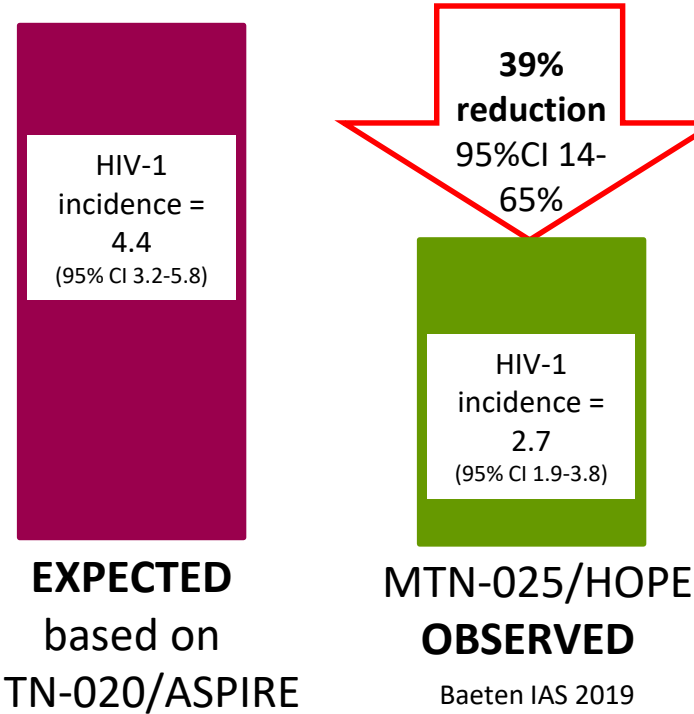
- ASPIRE
  - Randomised controlled double blinded study
  - Dapivirine vaginal ring vs placebo
    - Once a month, self-inserted
  - Africa (Malawi, SA, Uganda and Zimbabwe)
  - 2629 women
  - mean age 27 years, 40% married; 2% of RAI in the past 3 months
  - HIV relative incidence reduction: 27% $CI_{95\%}$ [1-46] p=0.05
  - After exclusion of two sites with reduced retention and adherence, relative incidence reduction: 37% $CI_{95\%}$ [12-56]; p=0.007



Baeten et al. NEJM 2016

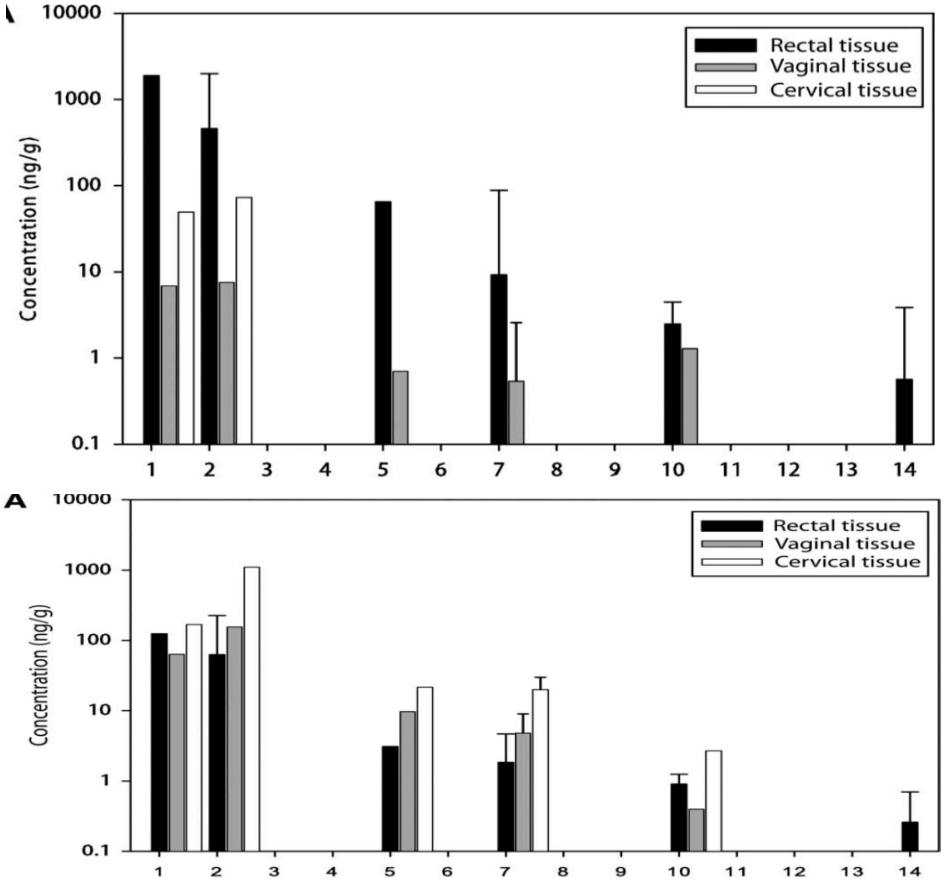
Topical PrEP

- HOPE study
  - Phase IIIB OLE follow up of ASPIRE dapivirine vaginal ring study
  - 1456 women in the same 4 countries
  - Median age 31 y
  - 47% married
  - 90% of at least some use of dapivirine based on residual drug level on the ring



Systemic PrEP

- PK studies:
  - Healthy individuals
    - 8 male
    - 7 female
  - Tissue and fluid samples
  - Single dose of TDF/FTC
  - Measurement of TFV and in tissue at D1,D2, D5, D7, D10 and D14



TFV

FTC

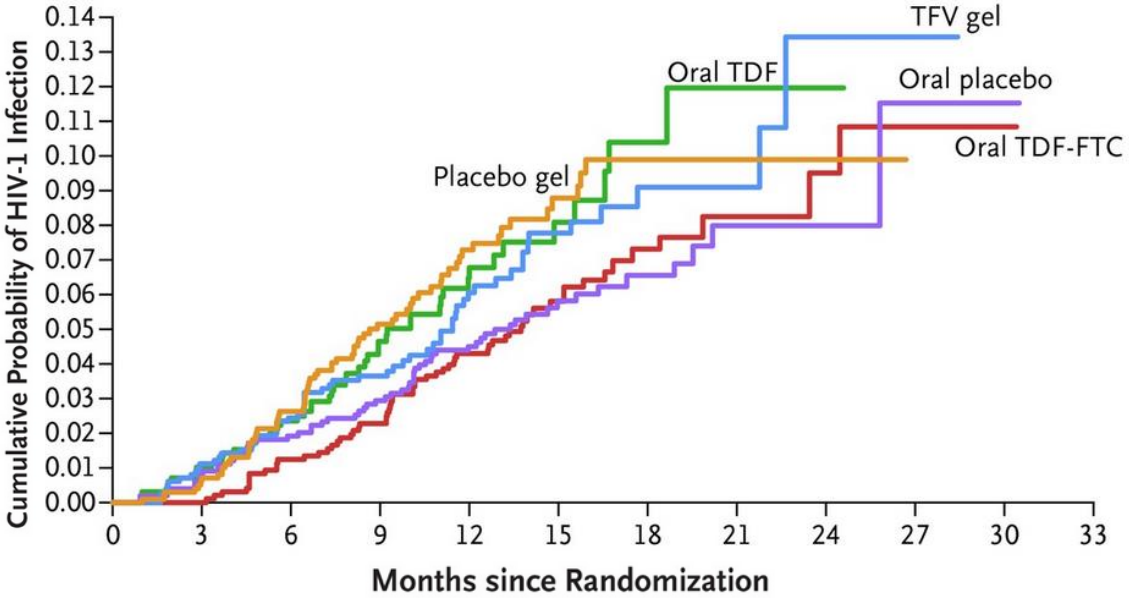
Patterson et al Sci Transl Med 2011

Systemic PrEP: VOICE

- Daily use of TDF pill, TDF/FTC pill or placebo
- HIV acquisition compared to placebo :
  - Oral TDF: HR= 1.49 $CI_{95\%}$[0.97 - 2.29]
  - Oral TDF/FTC: HR= 1.04 $CI_{95\%}$ [0.73 - 1.49]

➔ **Low adherence** estimated by the TFV level in plasma:

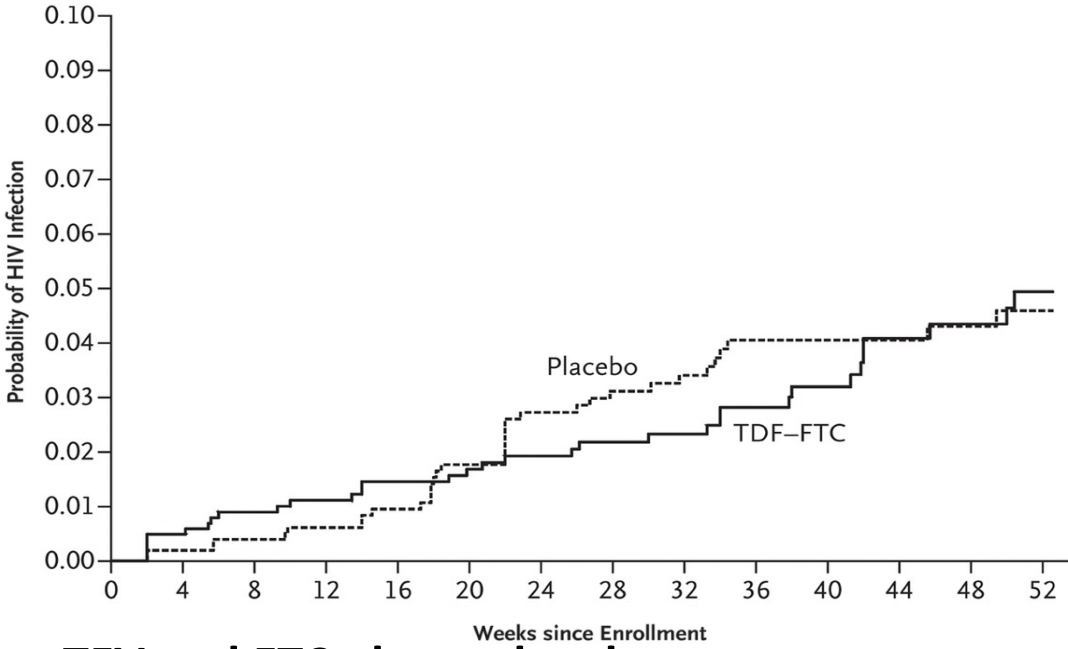
➔ A mean of 30% and 29% of quarterly detectable TFV in plasma for oral TDF and oral TDF/FTC respectively



Marrazzo et al. NEJM 2015

Systemic PrEP: FEM-PREP

- FEM-PREP
  - Randomized double blinded study
  - Daily oral TDF/FTC vs placebo
  - 2120 Women in Africa (Kenya, SA, Tanzania) mean age 24.2 y; 30.9% married; 12.6% of transactional sex in the past 4 months
  - HIV acquisition compared to placebo **HR 0.94 [0.59-1.52] p=0.81**



Adherence lower than 40% based on TFV and FTC plasma levels

Van Damme L et al. NEJM 2012

Systemic PrEP: Partners PrEP

- First phase
  - Randomized Controlled Trial of daily TDF or TDF/FTC vs placebo
  - 4747 serodiscordant couples in Africa (Kenya, Uganda)
  - **Specifically seronegative women**: **n=1785**
    - Reduction of HIV infection of 71% and 66% for TDF and TDF/FTC respectively
- Second phase Open-labelled
  - 1636 women
  - HIV infection : 0.9/100 person-year and 0.88/100 person-year in TDF and TDF/FTC arm respectively
  - Expected: 2/100 person-year

Baeten J et al. NEJM 2012 and Lancet ID 2015

Subgroup	TDF				TDF/FTC				Placebo or expected		
	N	# event	Rate /100py	HR compared to placebo	N	# event	Rate /100py	HR compared to placebo	N	# event	Rate /100py
Female seronegative in phase I	595	8	0.81	0.29 [0.13 0.63]	566	9	0.95	0.34 [0.16-0.72]	619	28	2.91
Female seronegative in phase II	832	15	0.90		804	14	0.88				2.0

Systemic PrEP: Bangkok TDF

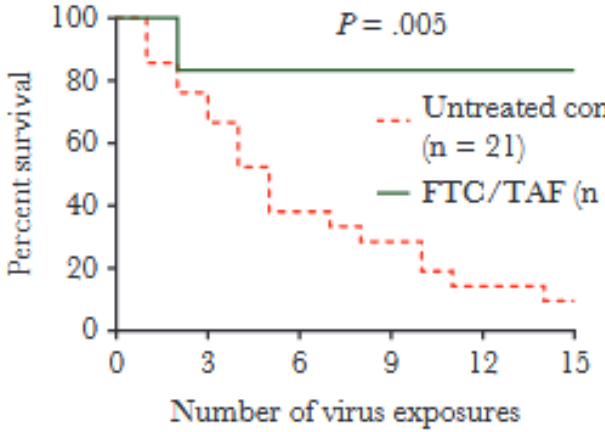
- **IDU and heterosexual cis women:**
  - RCT daily TDF vs placebo
  - n=2413, women: 489
  - Efficacy to prevent HIV transmission 78.6% [16.8-96.7]
  - *No specific data on IV vs sexual route of infection in women*

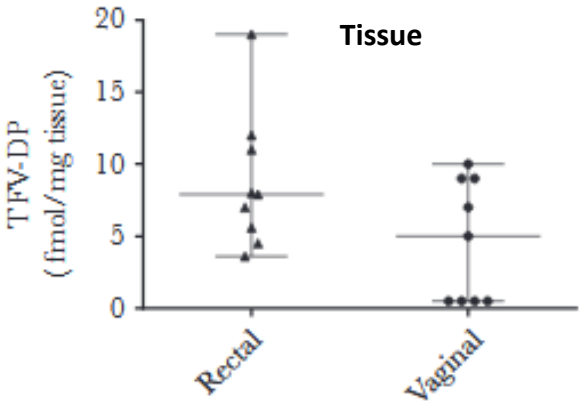
	Tenofovir		Placebo			p value
	Infections/ person-years	Incidence per 100 person-years (95% CI)	Infections/ person-years	Incidence per 100 person-years (95% CI)	Efficacy (95% CI)	
Sex						
Male	15/3836	0·39 (0·22 to 0·65)	24/3840	0·63 (0·54 to 1·26)	37·6 (−17·8 to 67·9)	0·15
Female	2/1007	0·20 (0·02 to 0·72)	9/983	0·92 (0·42 to 1·74)	78·6 (16·8 to 96·7)	0·03

Choopanya et al. Lancet 2013

Focus on TAF

- Vaginal SHIV exposure in macaques with no treatment, TAF or FTC/TAF at 24h and 2h before challenge
  - Efficacy : FTC/TAF 91% (35to99%), TAF 58% ($CI_{95\%}$ −9to84%)





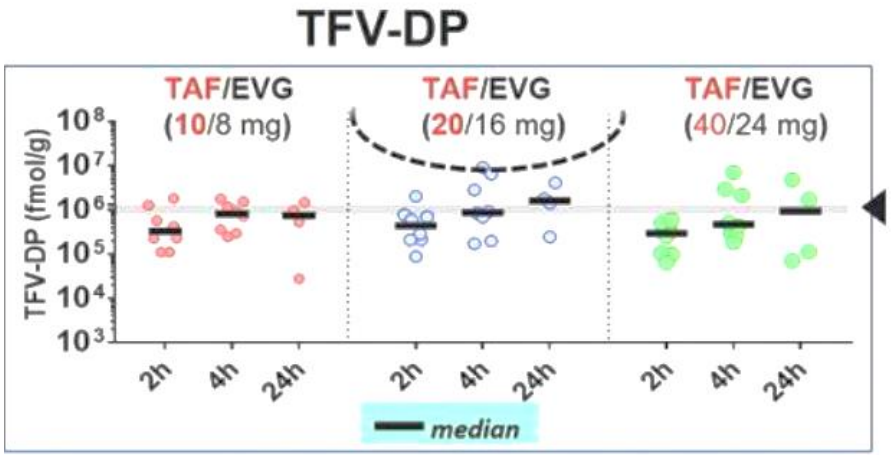
PK/PD of FTC/TAF

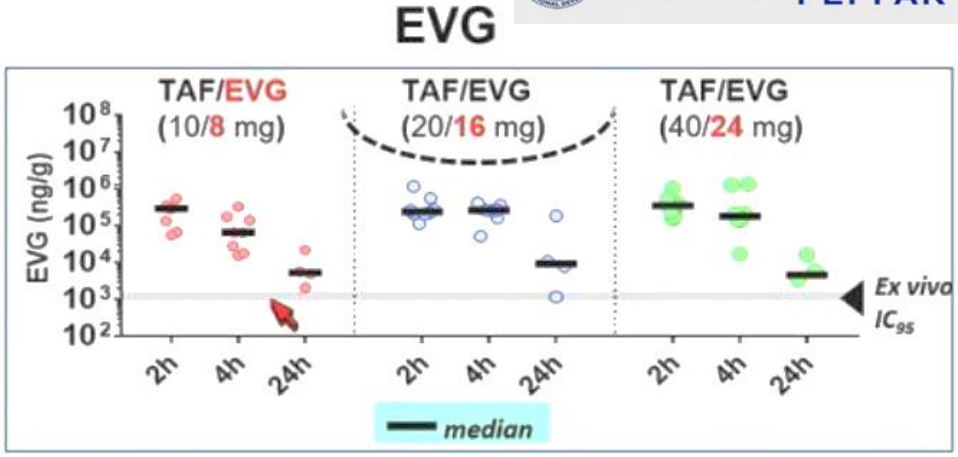
Massud JID 2019

Focus on TAF

- NHP studies
  - Vaginal insert of TAF/EVG « On demand » before SHIV challenge in macaques

USAID FROM THE AMERICAN PEOPLE PEPFAR





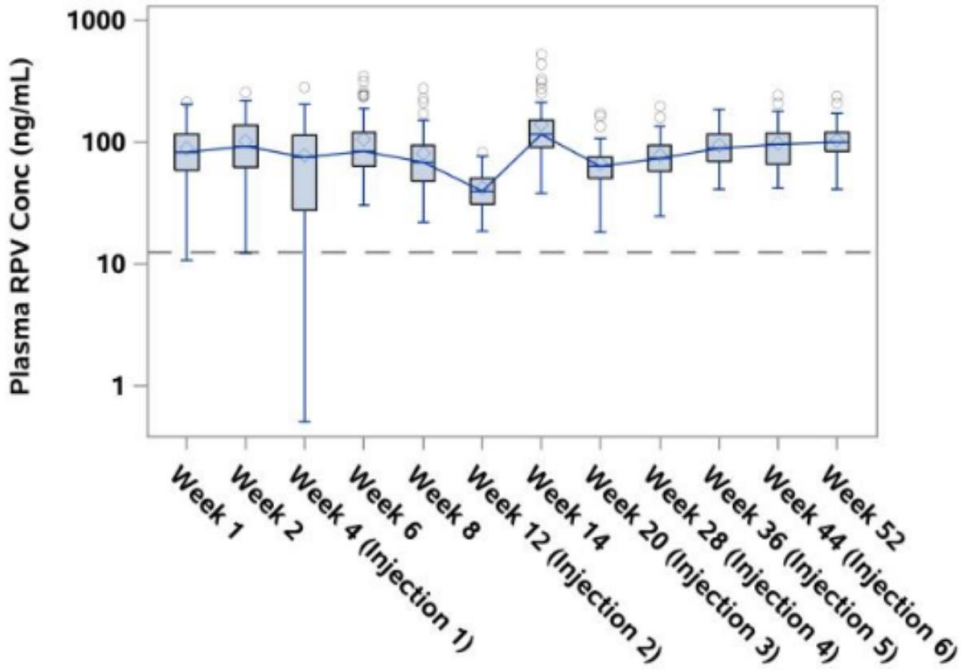
Dobard CROI 2019

Focus on TAF

- DISCOVER study:
  - MSM and TGW
  - Comparing TAF/FTC to TDF/FTC
  - No clinical data on women currently
  - No registered PrEP study in women with TAF on ClinicalTrials.gov
- Study in women with TAF are lacking
- TAF/FTC indication at the moment: excluding vaginal receptive intercourse

Systemic PrEP: HPTN 076

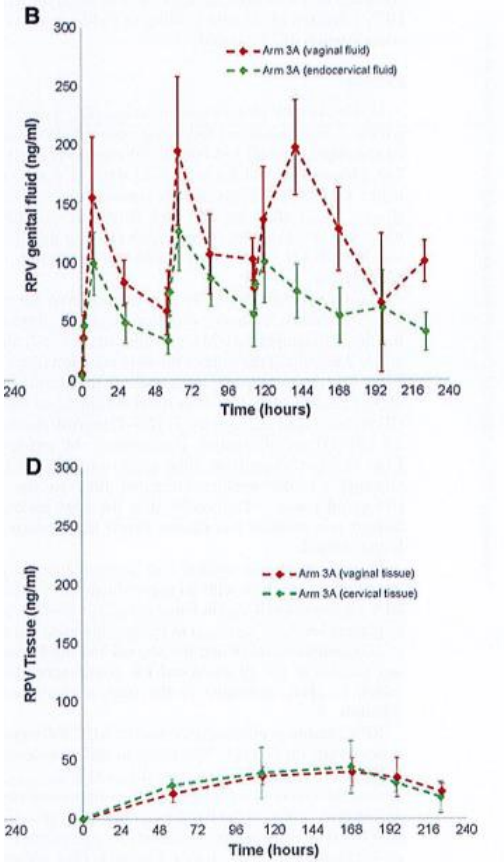
- RILPIVIRINE LA
  - HPTN 076 phase II clinical study
  - 136 HIV-uninfected women with low-HIV risk
  - 4 cities: Cape Town, Harare, Newark and Bronx
  - 67 of the 80 (84%) women who received long-acting rilpivirine injections had side effects.
  - 33 of the 42 (79%) women who received placebo injections had side effects.
  - Most participants preferred injectable PrEP over other route of administration

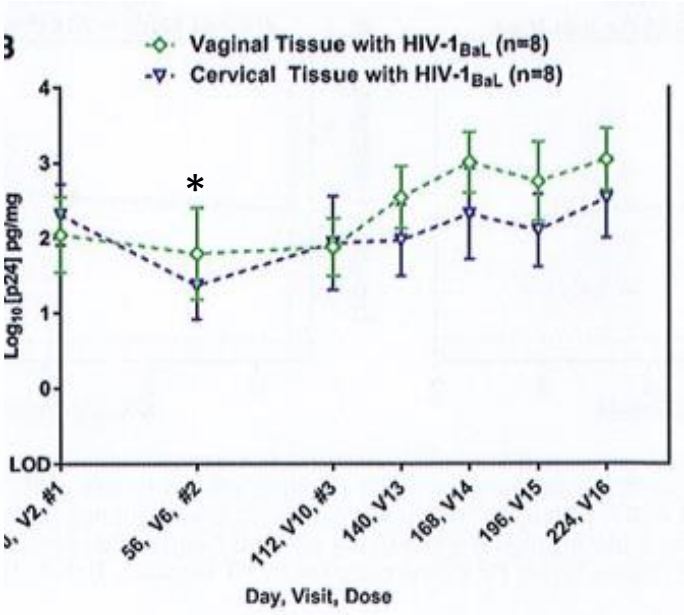


Bekker et al. CROI 2017

Systemic PrEP

- RILPIVIRINE LA
  - MWRI-01 study
  - 3 IM doses of 1200mg RPV LA evry 8 weeks
  - 8 women and 4 men
  - PK assessed in tissue and plasma
  - Pharmacodynamics: *ex vivo* HIV infection challenge
    - Rectal tissue: reduction of infection
    - Cervicovaginal tissue: no reduction

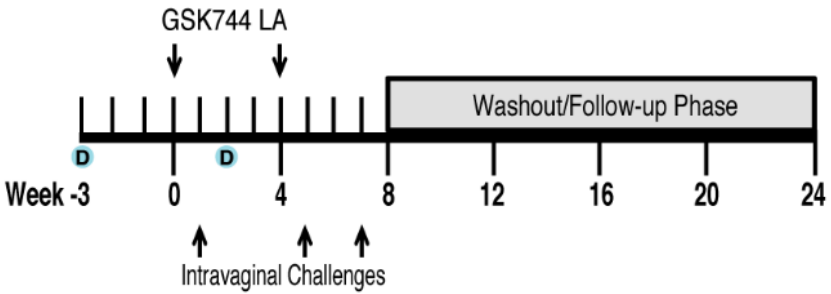


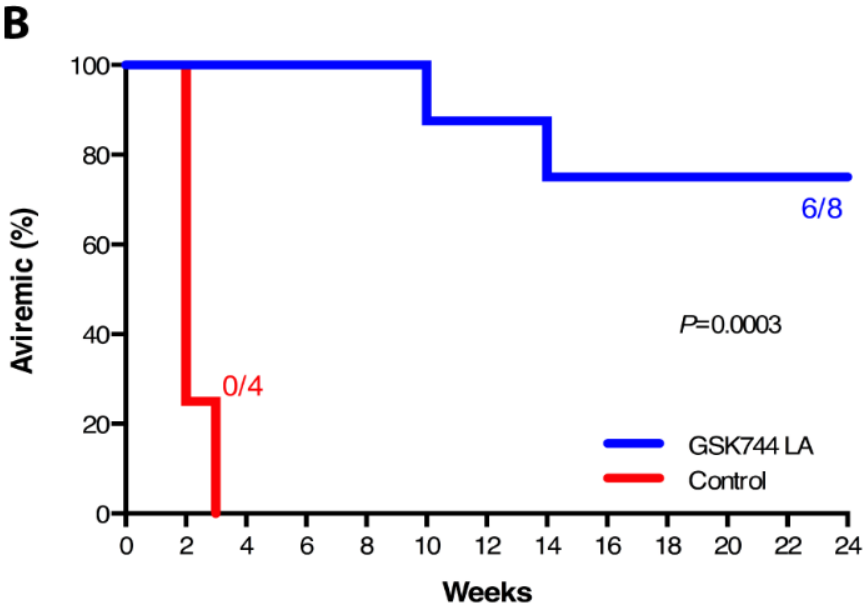


Cranston et al. AIDS Res Hum Retrovir 2019

Systemic PrEP

- Cabotegravir LA: NHP, IntraVaginal exposure to SHIV



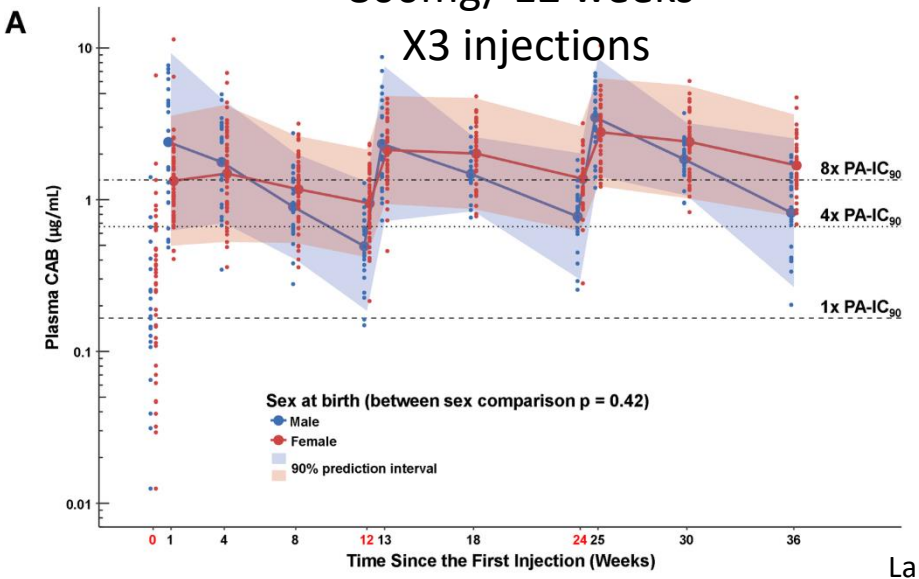


Andrews et al. Sci Transl Med 2015

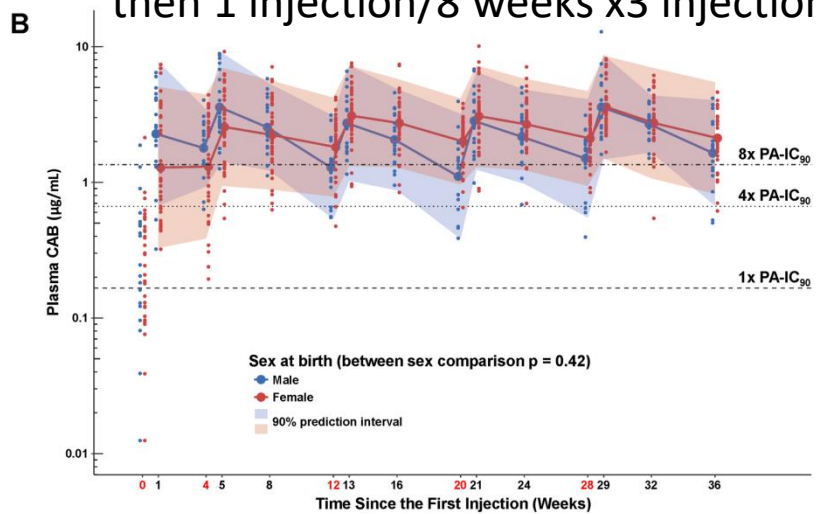
Systemic PrEP

- Cabotegravir IM LA: PK studies in human HPTN 077
  - Low risk individuals (women n= 131/199)
  - First 4 weeks of daily CAB 30mg

800mg/ 12 weeks
X3 injections



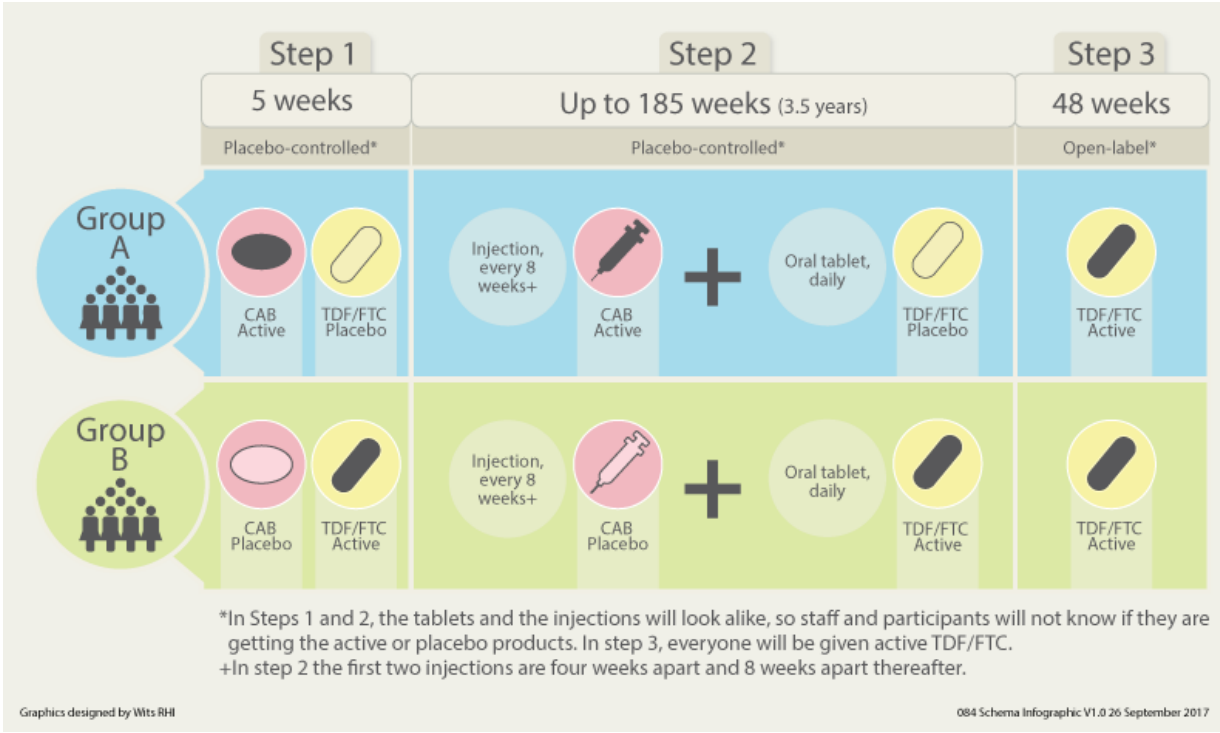
600mg/4 weeks for 2 injections
then 1 injection/8 weeks x3 injections



Landovitz et al. PlosOne 2018

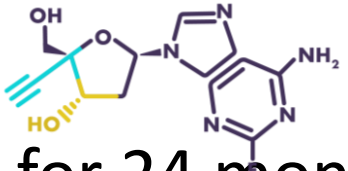
Systemic PrEP

- HPTN 084
- On going
  - Goal 3,200 women
  - 18 to 45 years
  - Sub-Saharan Africa
  - At risk for HIV
  - Using effective contraception
- Superiority study
  - Expected better adherence with injections



Systemic PrEP

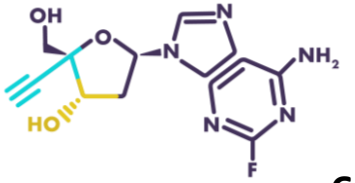
- PK studies: Islatravir



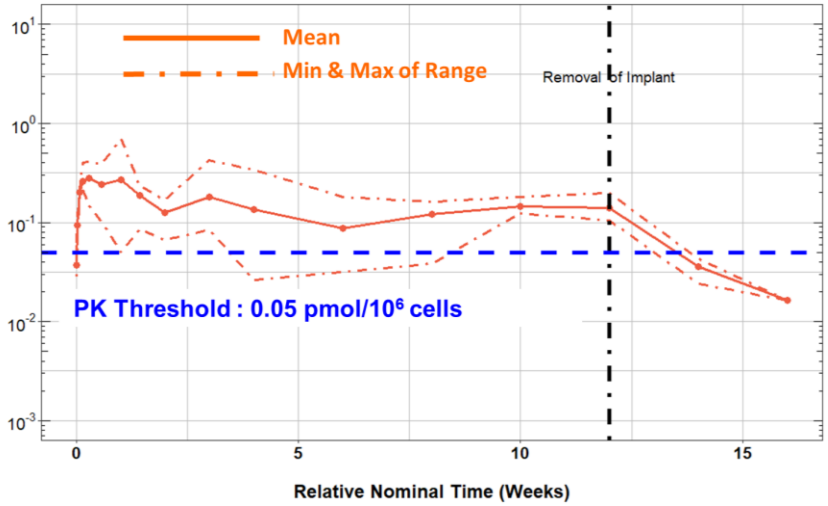
  - Oral pill once monthly for 24 months; 60 and 120 mg dosing
  - On going study
  - Phase II, controlled vs placebo
  - Endpoint: safety, tolerability and PK
  - In low-risk of HIV individuals

Systemic PrEP

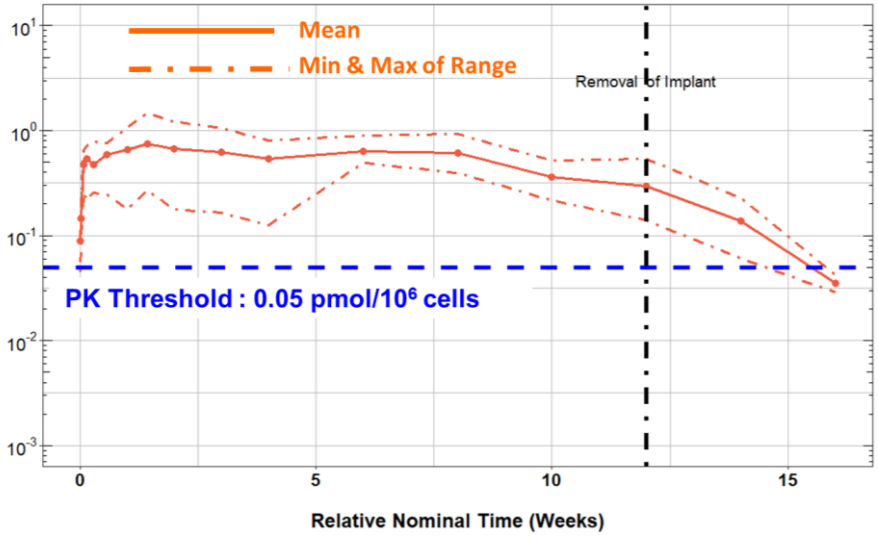
- PK studies: Islatravir



54 mg Implant (n=6)



62 mg Implant (n=6)



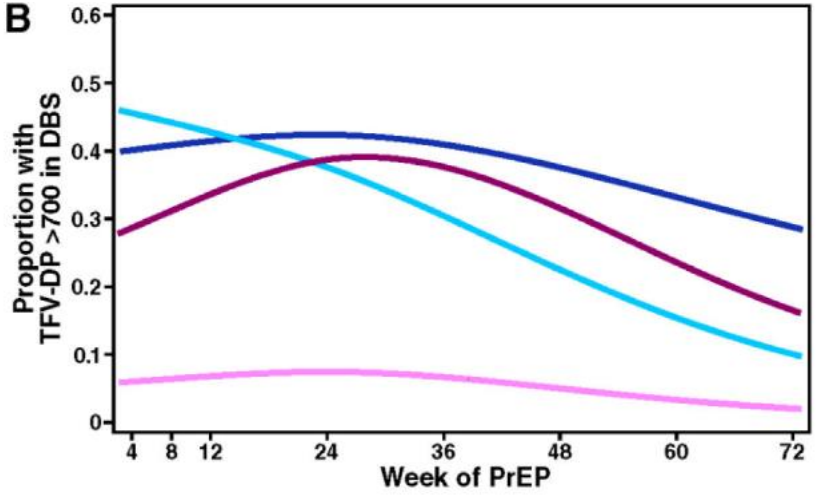
Supports potential of the ISL implant as a once-yearly PrEP option

Matthews IAS 2019

TRANS WOMEN

Systemic PrEP: iPrex

- Study of daily oral FTC/TDF, double blinded study followed by an OLE
- iPrex subgroup of TGW: n= 531
  - 11 vs 10 HIV-infections in the treated and placebo arm respectively
  - 3 infections during the OLE phase (1 taking PrEP)
  - Not effective?
- iPrex subgroup of TGW
- **No infection with detectable drug level**
- Higher HIV risk compared to other MSM



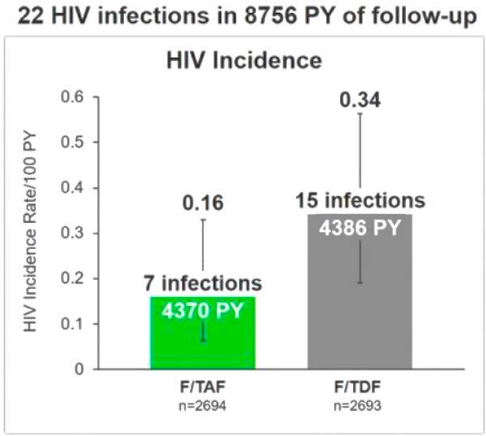
➔Lower use of PrEP at high risk moments

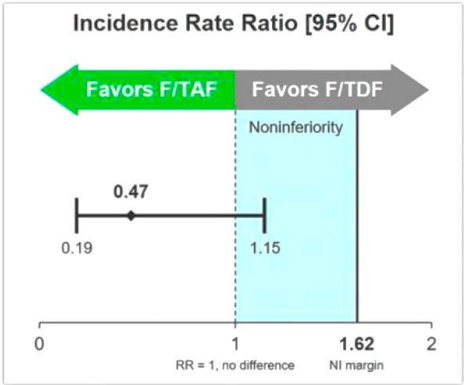
➔No impact of FHT (n=67 ; 20%)

Deutsch Lancet HIV 2015

Focus on TAF

- Clinical studies: DISCOVER
  - MSM and TGW
  - Randomized double blinded daily oral TDF/FTC vs daily oral FTC/TAF
  - USA, EU, Canada
- **TGW** : 1% out of 5387 participants (45 in F/TAF arm and 29 in F/TDF arm)
  - **No HIV-infection amongst TGW**



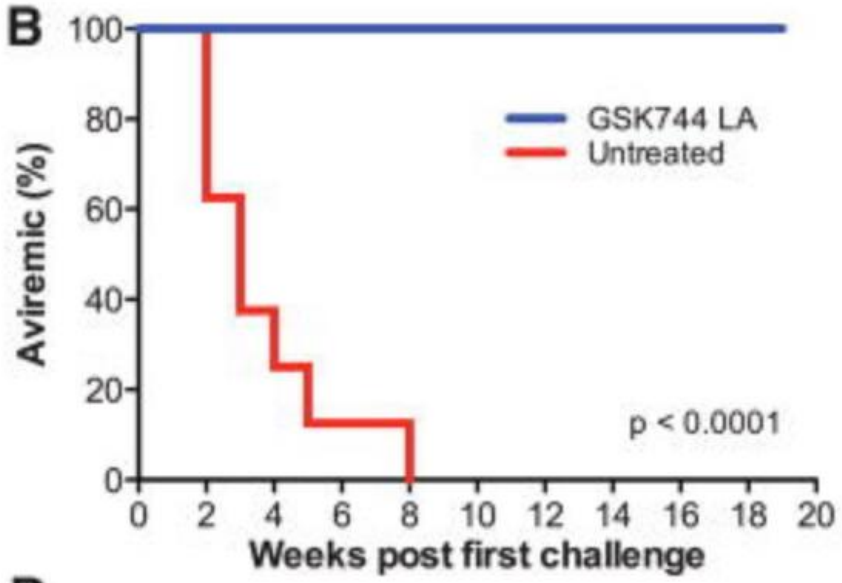


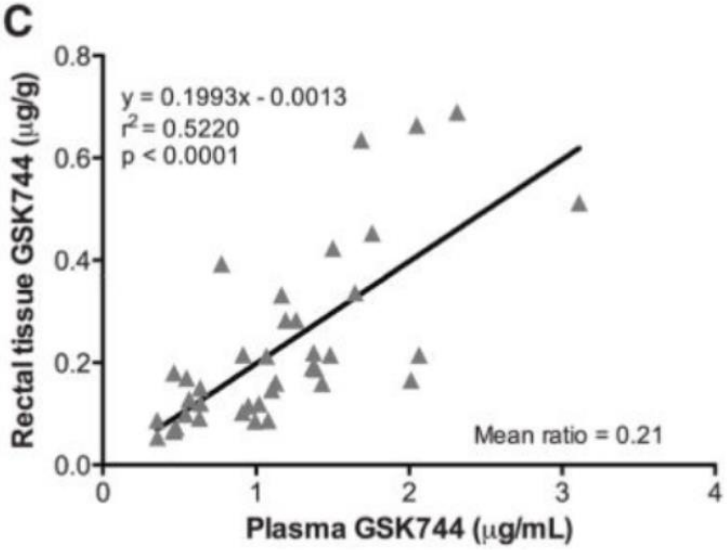
TAF is noninferior to F/TDF for HIV prevention

Hare CROI 2019

Systemic PrEP

- NHP studies: Cabotegravir LA, rectal SHIV exposure

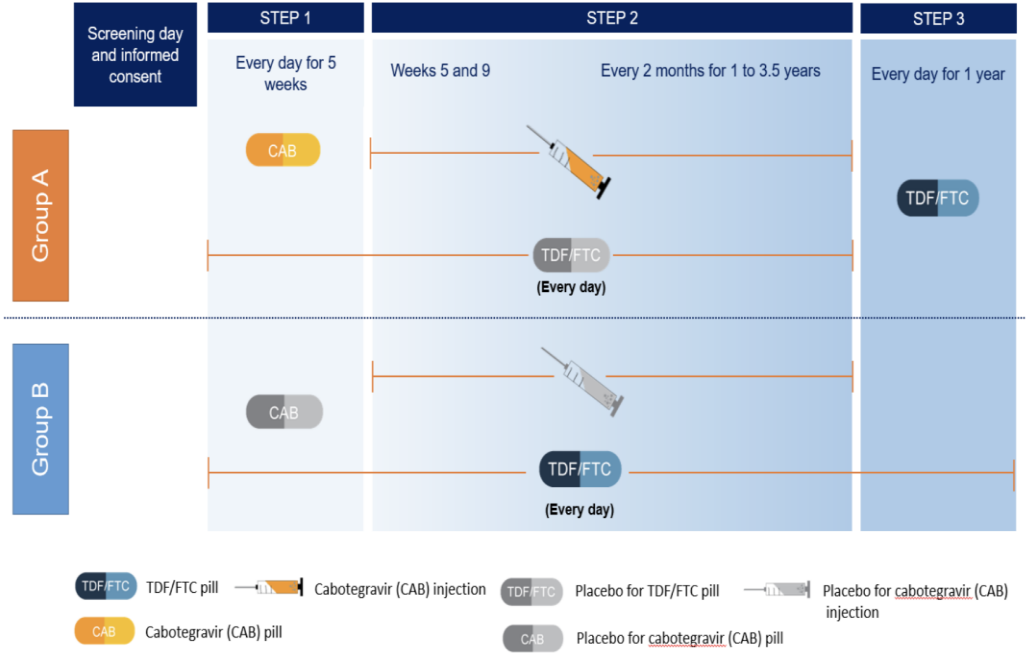




Andrews Science 2014

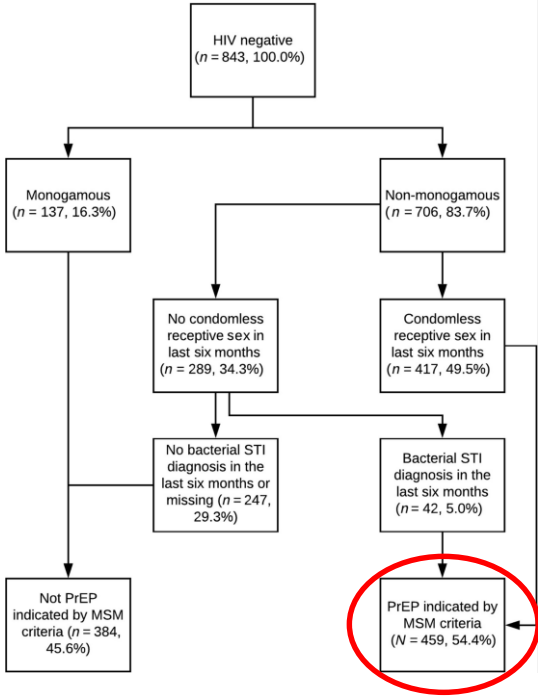
Systemic PrEP

- Cabotegravir LA: Clinical study : HPTN 083
  - MSM and TGW
  - Goal: 4500 individuals
    - 10% of TGW
  - Asia, America (N&S) and South Africa



TRANSGENDENDER MEN

- Little evidence
- One study in 2017 (Reisner et al.) = no TM studied had taken PrEP
- Very recently (JIAS September 2019) the same team published a study to characterize PrEP awareness uptake and indications in TM having sex with men in the U.S.
- Only 33% of PrEP (including 12% not current, but past PrEP use)



Conclusion

- Proven efficacy of oral TDF/FTC daily for all populations
- Most difference between genders can be explained by **adherence**
- Vaginal rings promising for women in high prevalence countries
- New drugs and new mode of administration (injectable, implants) are on the way
- No specific data on TM ➔ RAI is the main risk factor for HIV ➔ reasoning derived from MSM

Thanks

- Pr Jean-Michel MOLINA

- Annabelle PATRICIA, Laurence NIEBIELSKI
- Flavien LORHO, Bénédicte LOZE, Iris BOUCHARD
- Community agents at AIDES who help us every day understand more on the work we have to do
- The very motivated participants to PrEP studies

Supplementary

Number of new HIV infections
Estimates by WHO region

Also available:

– Estimates by country

filter table | reset table
Last updated: 2019-08-07

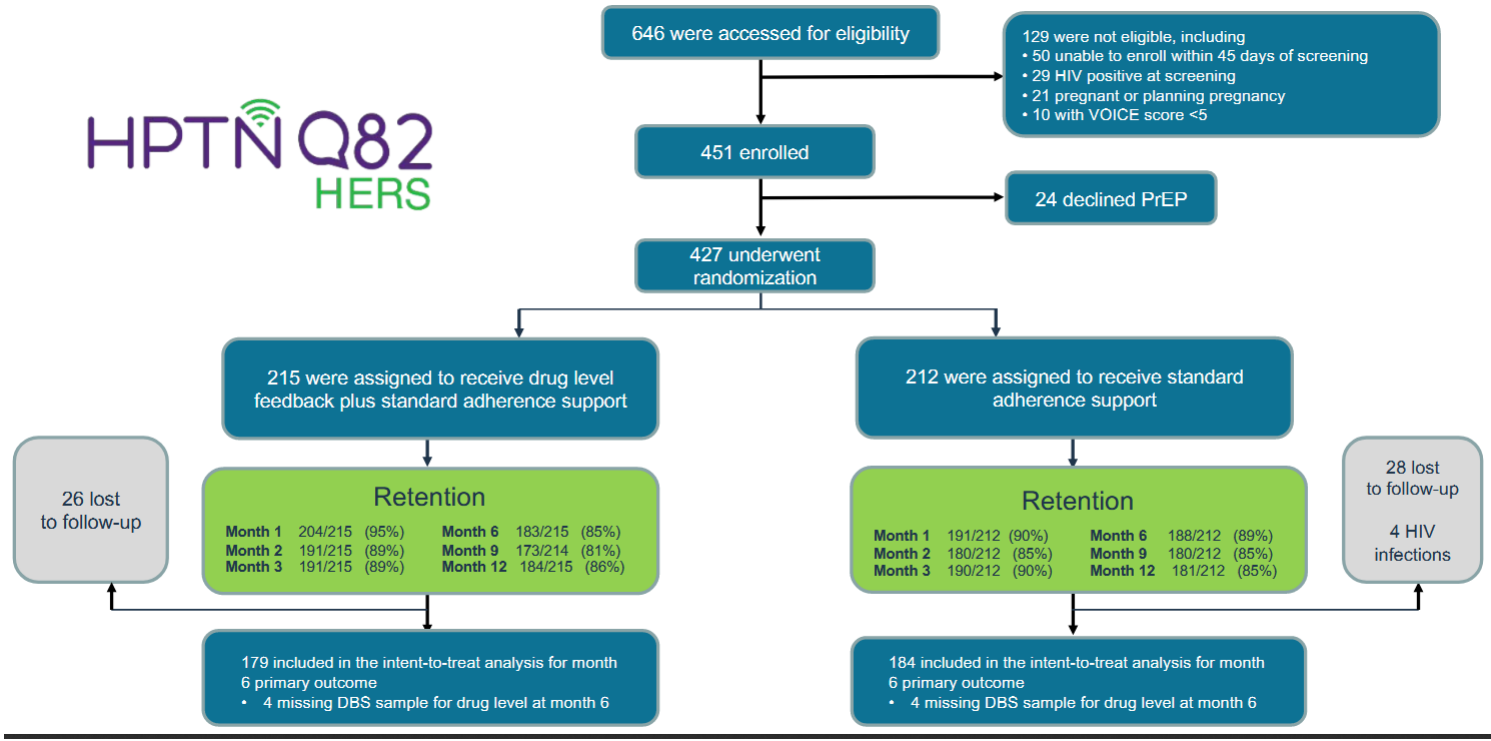
Download filtered data as: CSV table | XML (simple) | JSON (simple)
Download **complete** data set as: CSV table | Excel | CSV list | more...

	Number of new HIV infections[i]	New HIV infections (per 1000 uninfected population)[i]
	2018	2018
WHO region		Both sexes
Africa	1 100 000 [800 000 - 1 500 000]	1.07 [0.79-1.48]
Americas	160 000 [120 000 - 200 000]	0.16 [0.12-0.20]
South-East Asia	170 000 [110 000 - 200 000]	0.09 [0.06-0.10]
Europe	170 000 [150 000 - 190 000]	0.19 [0.17-0.20]
Eastern Mediterranean	41 000 [26 000 - 68 000]	0.07 [0.04-0.11]
Western Pacific	120 000 [110 000 - 140 000]	0.06 [0.06-0.07]
(WHO) Global	1 700 000 [1 400 000 - 2 300 000]	0.24 [0.18-0.31]

Citation	City, State	Population	Sampling Method	Sample Size	Prevalence, % (n) (Incidence in Person-Yrs)	Method of HIV Ascertainment
Mixed Gender or Gender Spectrum Unspecified						
Benotsch et al[34]	Mid-Atlantic	All trans	Clinics, bars, events	TF 104; TM 51	22.6 (n = 35) overall	Self-report
Bradford et al[35,36]	Virginia	All trans	Internet, peer referral	TF 229; TM 121	16 of TF (n = 28)	Self-report
Feldman et al[37]	National	All trans	Internet	TF 697; TM 532	2.0 (n = 14); 0.4 (n = 2)	Self-report
Green et al[38]	San Diego, CA	All trans	HTC program	TF 151; TM 30	2.0 (3); 3.3 (1)	Laboratory
Habarta et al[39]	US, PR, UVI	All trans	HIV testing event* data	TF 13,154; TM 2364	2.7 new; 0.5 new	Laboratory
Leinung et al[40]	Upstate, NY	All trans	Gender clinic chart review	TF 192; TM 50	8.3 of TF (n = 16)	Laboratory
Reisner et al[41]	Boston, MA	All trans	Clinic attendees	31	12.9 (n = 4)	Self-report
Reisner et al[42]	Boston, MA	Sexually active trans youth 14–29	Retrospective EMR review	TF 63; TM 82	7.9 (n = 5); 2.4 (n = 2)	Laboratory
Castel et al[43]	Washington, DC	Trans unspecified	HIV testing campaign	85	10.6 (n = 9) overall	Laboratory
Trans Feminine						
Brennan et al[44]	Chicago and Los Angeles, CA	Youth 15–24 yrs	Clinic, venue based, peer referral	151	15.9 (n = 24)	Self-report
Garofalo et al[45]	Chicago, IL	Youth 16–24 yrs	Active and passive	51	5.9 (n = 3)	Self-report
Rowe et al[46]	San Francisco, CA	Youth 16–24 yrs	Peer referral, social network sites, trans events, CBOs	292	4.5 (n = 13)	Laboratory
Bowers et al[47]	Los Angeles, CA	Adult	HIV prevention program	320	21.9 (n = 70)	Self-report
Fletcher et al[48]	Los Angeles, CA	Adult	HIV prevention program	517	24.2 (n = 125)	Self-report
Nuttbrock et al[33]	New York, NY	Adult	Purposive	591 (baseline); 230 (cohort)	40.1 2.9/100 p-y	Laboratory
Nemoto et al[13]	San Francisco and Oakland, CA	Adult	Purposive, TW with sex work history	538	29.9	Laboratory
Rapues et al[49]	San Francisco, CA	Adult	RDS	314	35.0 (n = 110)	Lab
Reback and Fletcher[50]	Los Angeles	Adult	Street outreach	2136	13.6	Self-report
Reisner et al[51]	San Francisco, CA	Adult	Purposive	191	18.3 (n = 35)	Self-report
Trans Masculine						
Peitzmeier et al[52]	Boston, MA	Adult	Clinic chart review	233	0.9 (n = 2)	Lab
Reisner et al[53]	Boston, MA	Adult	Retrospective chart review + STD screen	23	4.3 (n = 1)	Lab

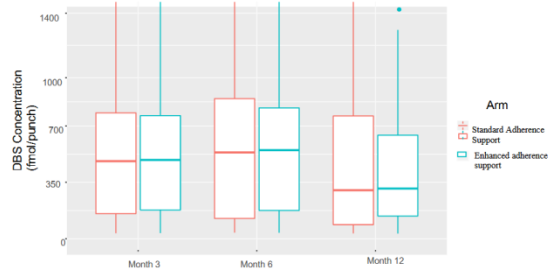
*Data are not deduplicated. Therefore, one person may have had multiple testing events.
TM, trans masculine; TF, trans feminine; RDS, respondent driven sampling; EMR, electronic medical record.

HPTN 082 IAS 2019



HPTN 082 IAS 2019

PrEP adherence & persistence, by arm



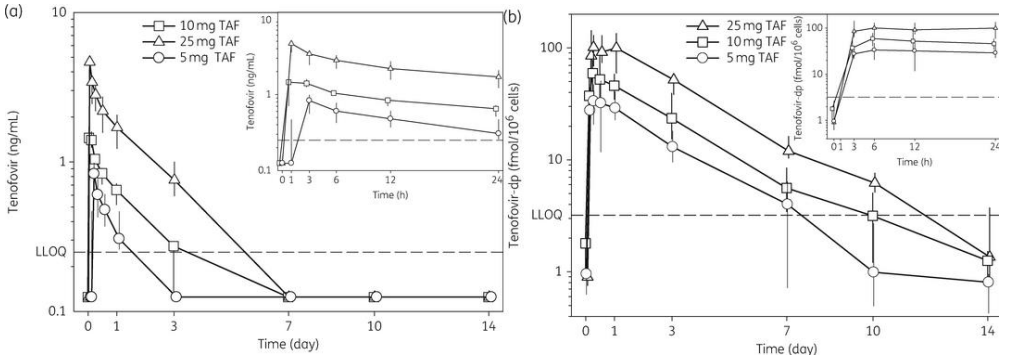
DBS results	N=371	N=363	N=347
Drug hold or stopped PrEP in prior month	N=7	N=21	N= 26
Detectable TFV-DP among those on PrEP	305 (84%)	202 (59%) *	109 (34%)*

*p<0.001 for months 6 and 12 compared to month 3

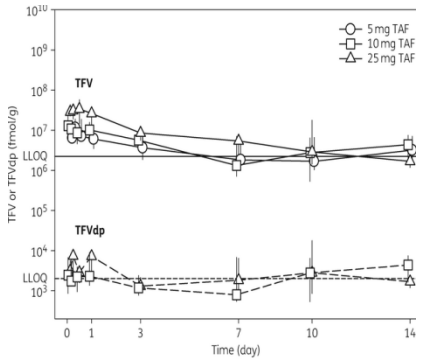
HIV seroconversions

- Four HIV seroconverters (at months 3, 6, and two at 9) observed in 404 person-years of follow-up
- HIV incidence of 1.0/100 person-years (95% CI 0.3-2.5)
- 2 had undetectable DBS TFV-DP concentrations and 2 detectable but low concentrations (74 and 243 fmol/punch) in the visit at or prior to when they were first detected HIV seropositive

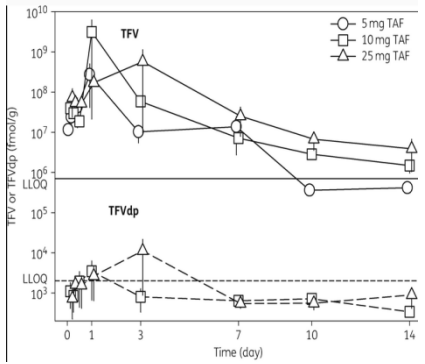
TAF PK in tissue and PBMC



PBMC



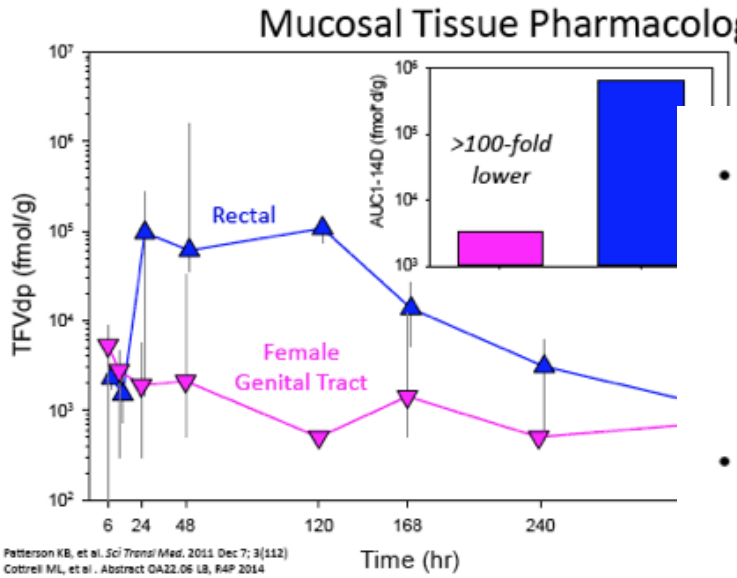
Vaginal



Rectal

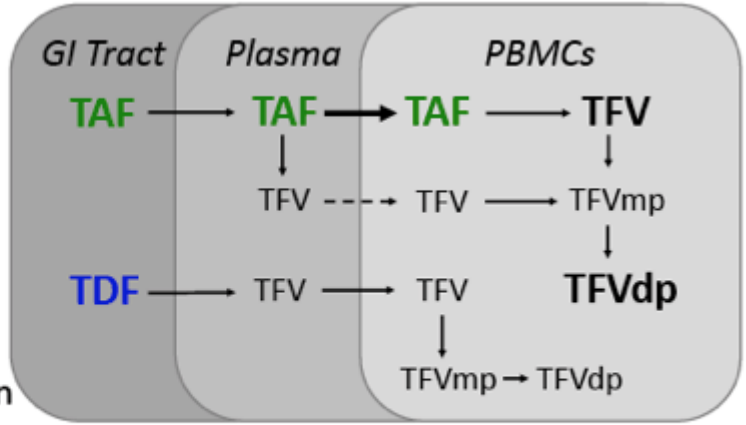
Focus on TAF

- PK studies



Patterson KB, et al. *Sci Transl Med.* 2011 Dec 7; 3(112)
Cottrell ML, et al . Abstract OA22.06 LB, R4P 2014

- Tenofovir Alafenamide 25mg Pharmacokinetics
  - 4-7 fold higher TFVdp in PBMCS than TDF 300mg
  - 7 fold lower TFV in plasma than TDF 300mg
- Mucosal tissue concentrations unknown

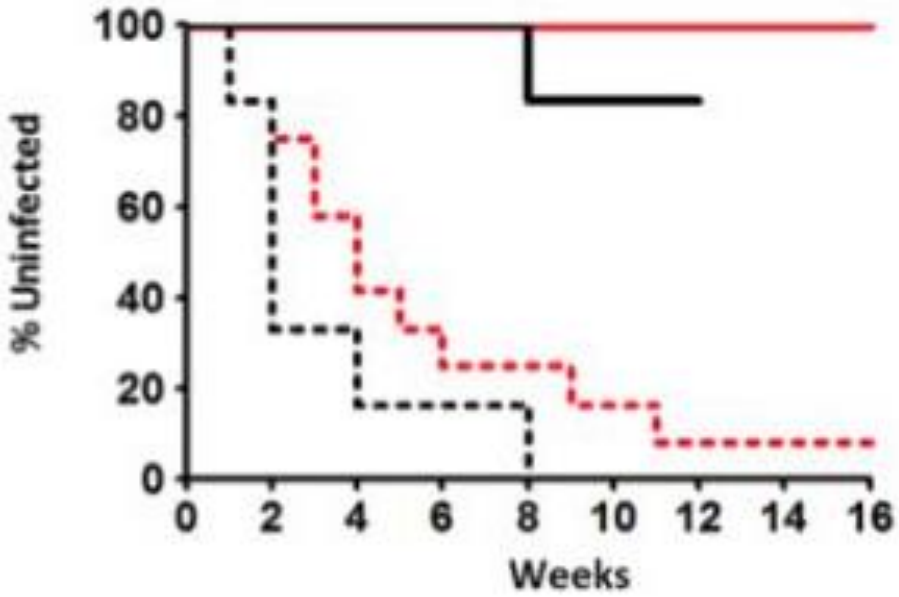


Adapted from Liu Y. Poster Number H-664, ICAAC 2013.

102LB CROI 2016 Garrett, Cottrell, Prince, Sykes, Schauer, Peery, Rooney, McCallister, Gay, Kashuba. UNC-CH, Gilead

Vaginal rings

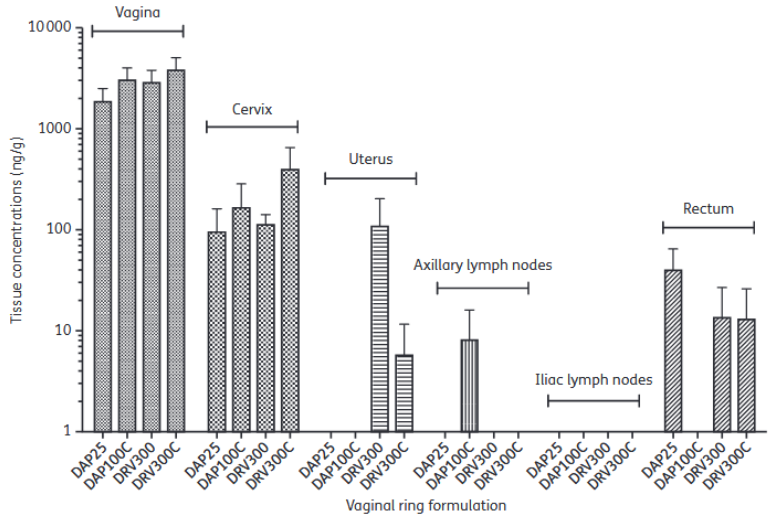
- Pk studies with TDF in NHP



Smith et al. JAIDS 2015

Vaginal rings

- PK studies in NHP: Dapivirine

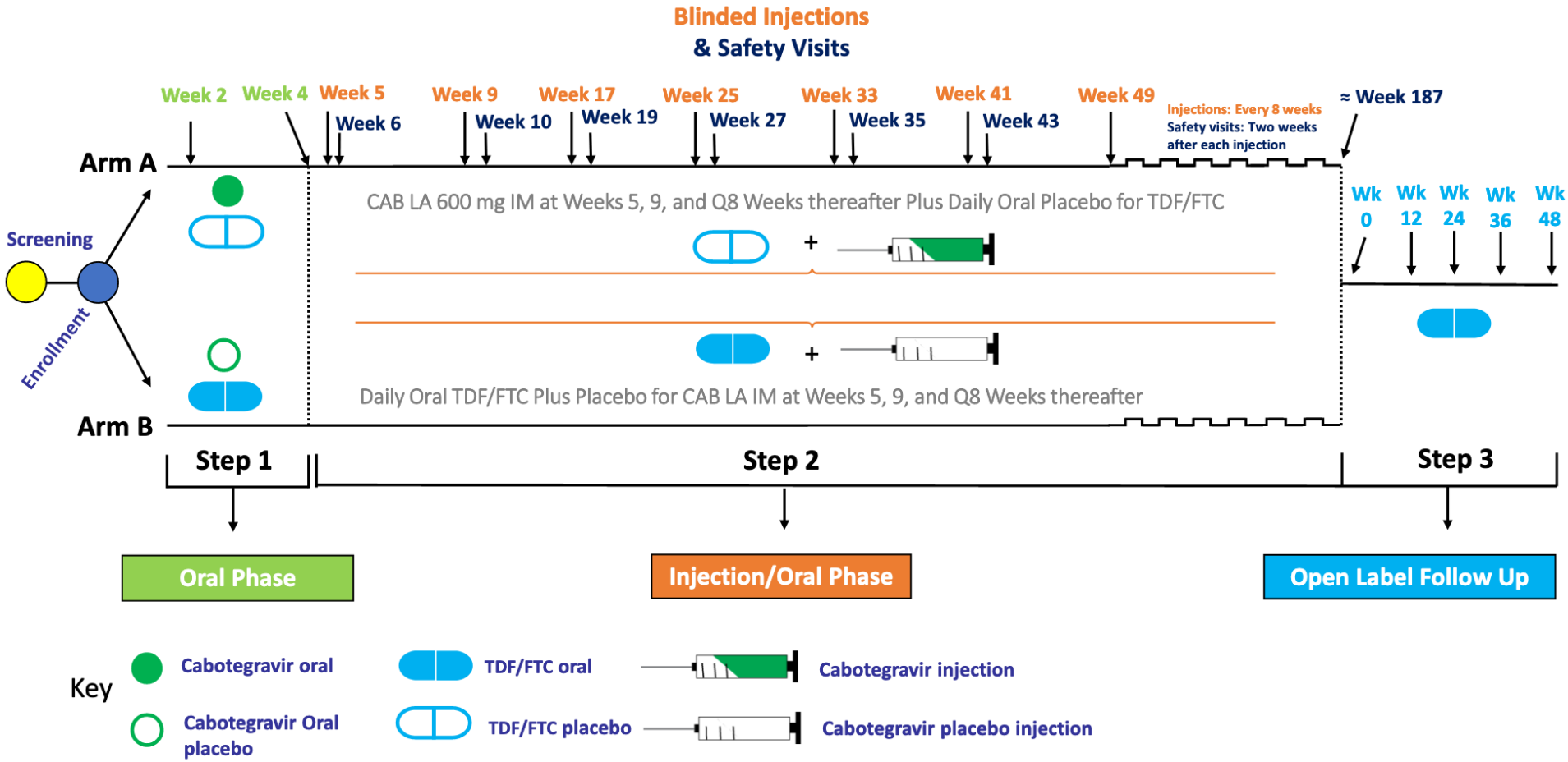


Murphy et al. JAC 2014

DREAM

- Follow up OLE Phase IIIb of Ring study dapirivine ring once monthly
- 900 Women in SA and Uganda
  - Mainly < 30 y, unmarried, 97% main partner
- High adherence based on residual levels of drug in the ring: 96%
- HIV incidence:
  - Modelled placebo group: 3.9 per 100 person-year $CI_{95\%}$ [2.9-4.9]
  - With active treatment: 1.8 per 100 person-year $CI_{95\%}$ [0.9-3.2]

HPTN 083: Study Visit Schema

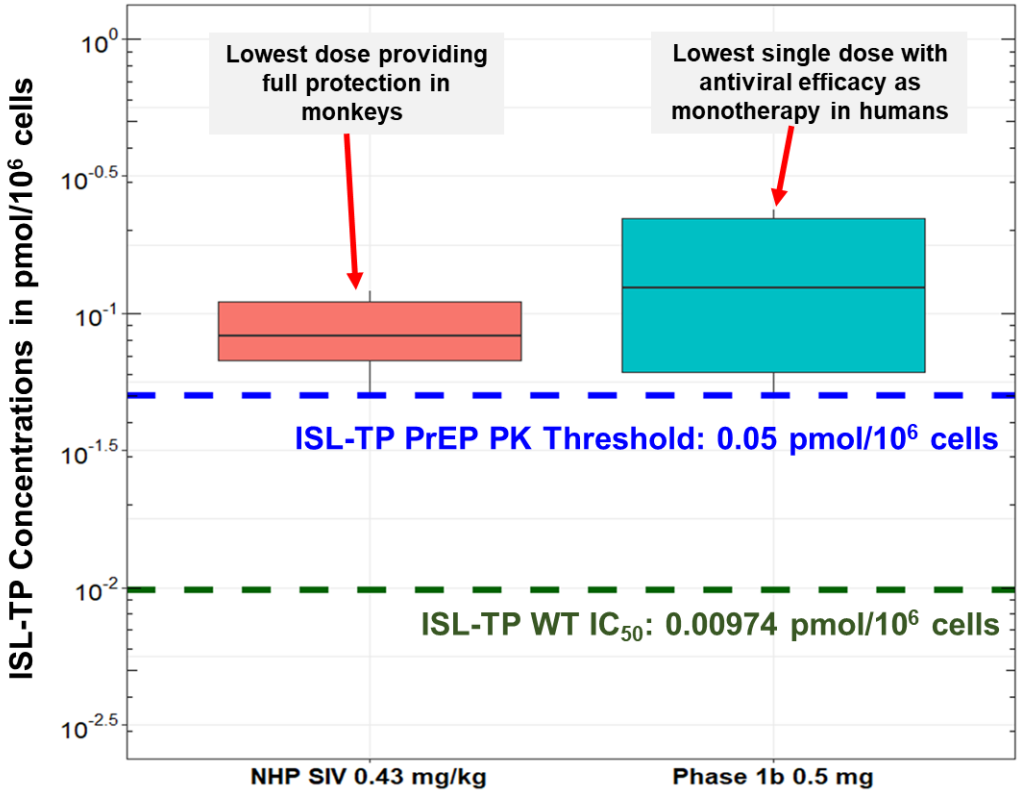


Translational PK/PD Modeling Supports PrEP Exposure Threshold of 0.05 pmol/10⁶ Cells ISL-TP

- Threshold of **0.05 pmol/10^6 cells** supported by:
  - ISL rhesus macaque SIV study
  - Efficacious concentrations at 0.5 mg

- 0.05 pmol/10^6 cells = ~5.0x in vitro IC_{50}
  - In vitro WT IC_{50} of ISL-TP is ~0.01 pmol/10^6 cells
  - 0.05 pmol/10^6 cells ISL-TP also covers in vitro IC_{50} for M184I/V

Goal is to maintain concentrations above 0.05 pmol/10^6 cells for the entire duration of implant placement



TGW : Gels

- Clinical studies: MTN -017 Phase 2
- 19 TGW/195 total
- Gel of 1% TFV vs TDF/FTC oral
- Deemed safe
- Efficacy ?

Implants

- NHP studies

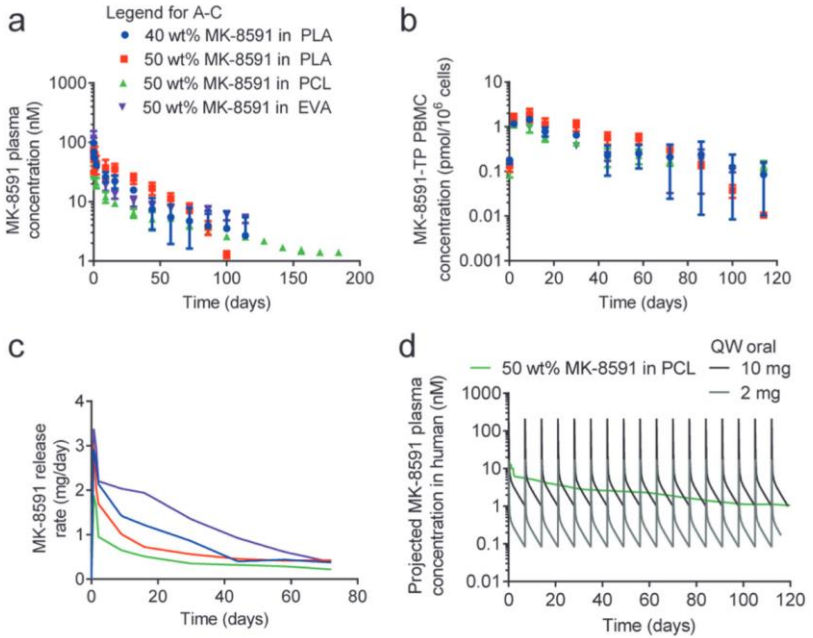
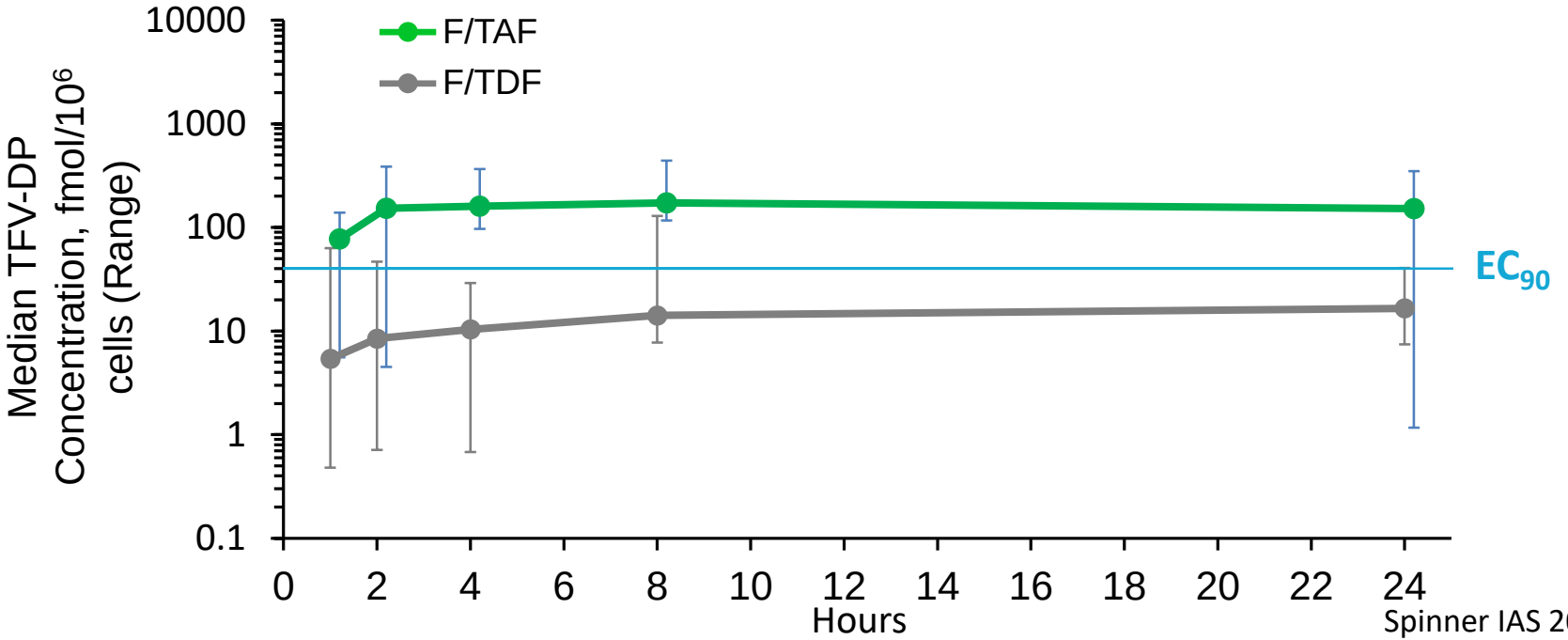


FIG 7 Concentration-versus-time profiles of MK-8591 in plasma (a) and MK-8591-TP in PBMC (b) for 40 wt% or 50 wt% MK-8591 in PLA, 50 wt% MK-8591 in PCL, and 50 wt% MK-8591 in EVA (mean ± SD). (c) MK-8591 release rate from a series of both bioerodible and nonerodible MK-8591-containing implants in nonhuman primates. (d) The projected human MK-8591 plasma profile compared to once-weekly (QW) 2 and 10 mg MK-8591 oral dosing.

Barret et al. ACA 2018

Focus on TAF

- PK: DISCOVER study results



Injectables

- Cabotegravir LA: PK studies : ECLAIR
- Phase 2a study of CABOTEGRAVIR LA 800mg vs PLACEBO in MSM (n= 127) in the U.S.
- No TGW reported
- 2 seroconversion: 1 in placebo arm the other 24 weeks after final injection in the treated arm

Markowitz Lancet HIV 2017

Systemic PrEP

- TDF2
  - Randomized double-blinded study
  - Daily TDF/FTC vs placebo in Bostwana
  - Women: 180 in the treated arm and 277 in the placebo arm
  - Adherence assessed by pill-count

Table S8a - Number of HIV-infected participants and protective efficacy by Gender, Modified Intention-to-Treat Cohort

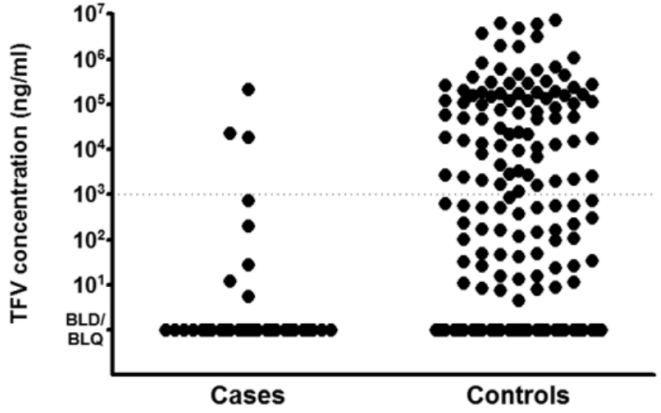
	TDF-FTC group	Placebo group	Efficacy	95% CI	P-value
Female	7	14	49.4	-21.5, 80.8	0.11
Male	2	10	80.1	24.6, 96.9	0.03

Table S8b - Number of HIV-infected participants and protective efficacy by Gender, As-Treated Cohort

	TDF-FTC	Placebo	Efficacy	95% CI	P-value
Female	3	13	75.4	23.7, 94.4	0.02
Male	1	6	82.4	-2.9, 99.1	0.07

Thigpen M et al. NEJM 2012

Cis women



	Cases		Controls
N	34		302
% detected (n)	23.5% (8)	*p=0.076*	39.4% (119)
Median (IQR) TFV (ng/ml) among detectable	476 (20-20674)	*p=0.107*	13821 (300-171920)

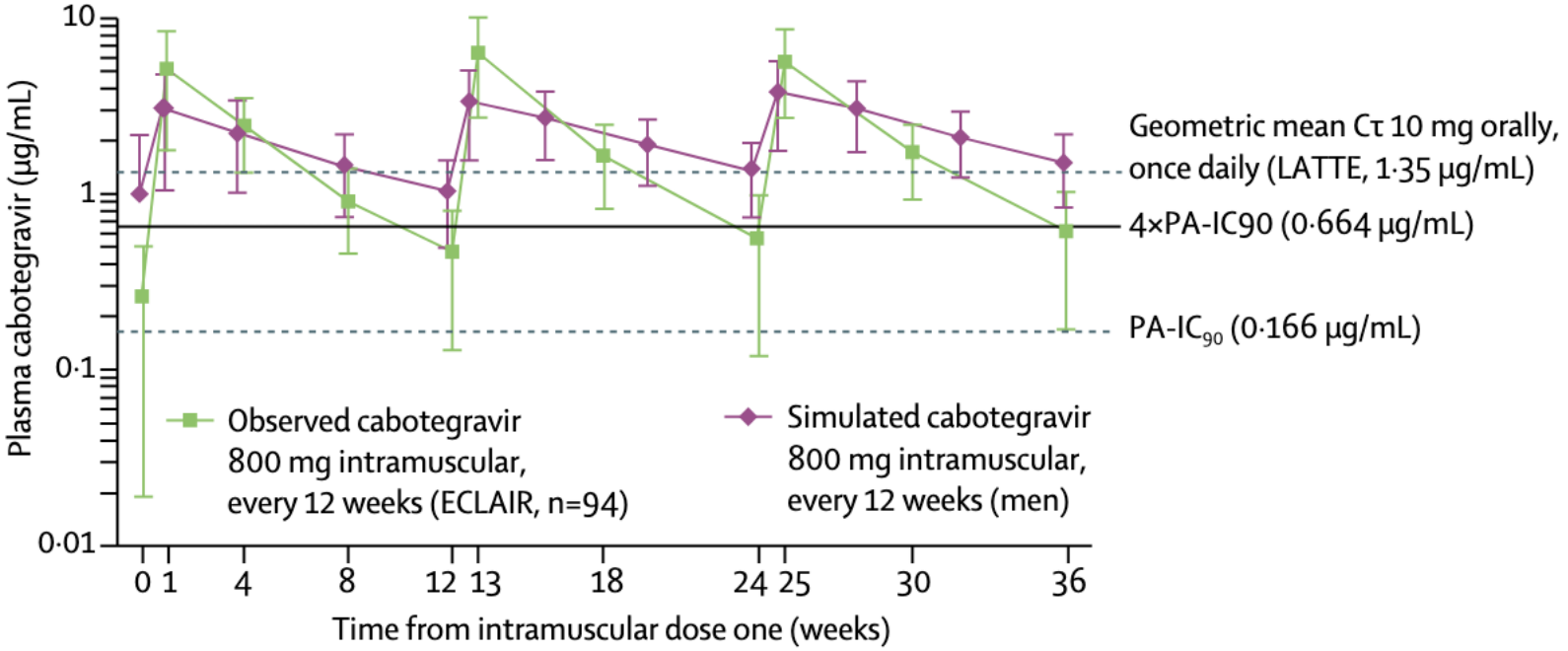
Figure 2. Cervicovaginal tenofovir concentrations for HIV cases and controls

➔ **Adherence is crucial**

CAPRISA 004
Abdool Karim Science 2010

Injectables

- Cabotegravir LA: PK studies : ECLAIR



Markowitz Lancet HIV 2017