Long Acting HIV Drugs for Prevention: Data and Potential implementation

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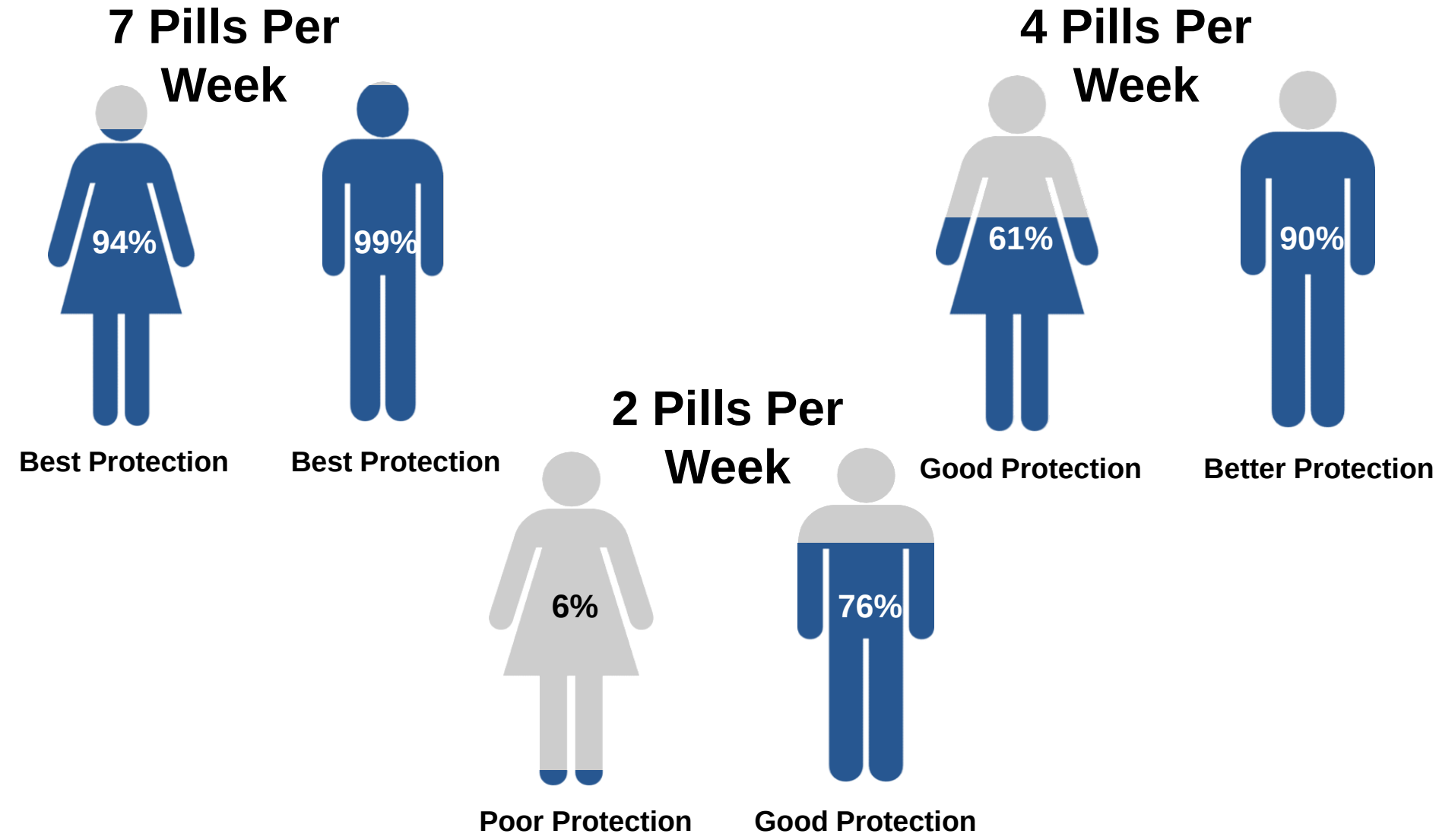
Content

- **Importance of adherence for PrEP**
- **Vaginal rings**
- **Injectables**
- **The future**
  - Broadly neutralising antibodies
  - Implants
  - Microneedles

ADHERENCE

Adherence *really* matters: PrEP



Adapted from Delany-Moretlwe S. IAS 2018, Amsterdam: Hanscom, JAIDS 2016; Fonner, AIDS 2016

PrEP adherence in trials

- **Daily oral tablets**
  - Adherence to visits may not = adherence to medication
  - Several PrEP trials show reports >> reality
- **Injectables (so far)**
  - Visit = injection = adherence
- **Vaginal rings….**

VAGINAL RINGS

Dapivirine most advanced: two phase 3 RCTs of monthly ring vs placebo

- **ASPIRE[1] (n=2629)**
  - 27% reduction in new HIV in active arm (56% if restricted to >21s with better adherence, no significant reduction in women <21)
  - Similar adverse vents and HIV resistance in both arms
- **RING[2] (n=1959)**
  - HIV incidence 31% lower in dapivirine group arm (HR 0.69; P=0.04)
  - NNRTI RAMs: 18.2% dapivirine arm vs 16.1%
  - Serious adverse events more common on dapivirine (2.9% vs 0.9%) with no clear pattern

1. Baeten JM at al. N Engl J Med. 2016 Dec 1;375(22):2121-2132;
2. Nel A et al. N Engl J Med 2016; 375:2133-2143

ASPIRE: adherence is not just a pill issue

- **Analysis of 1211 women on active product**
- **Plasma & ring concentrations vs self-report**
  - Correlation between PK & self-report BUT….
  - PK non-adherence more frequent than self-report, particularly for 18-21 year olds vs older women
  - 11% 18–21 year olds and 7% of 22+ year olds who rated their ability to keep the ring inserted as **good, very good or excellent** were **non-adherent** by PK measures

Mensch BS et al. AIDS Behav. 2019 Feb;23(2):504-512.

Two open-label studies at CROI 2018

- **DREAM (RING rollover)**
  - Lower dapivirine concentrations in rings then in RING study & estimated 96% (vs 83% in RING) had used ring for at least some of the preceding 4 weeks
  - HIV incidence 59% lower than predicted
- **HOPE (ASPIRE rollover)**
  - 1299/1407 (92%) eligible accepted the ring rollover
  - HIV incidence 1.9/100PY vs anticipated 4.1/100PY
- **Both completed early 2019, final results awaited**

https://www.ipmglobal.org/our-work/our-products/dapivirine-ring accessed May 2019

Tenofovir ring studies

- **Animal studies promising**
  - Good PK, *slight-moderate increase inflammatory infiltrates*
- **Phase 1 TDF intra-vaginal ring vs placebo trial *stopped early* when 17/40 women recruited:**
  - 8/12 women in TDF arm experienced **grade 1 vaginal ulceration** near the ring at average 32 days into ring use
  - No ulceration in placebo arm (n=5)
  - Higher inflammatory markers in TDF vs placebo arm
- **MTN-038**
  - Phase 1, 90-day study of TDF vs placebo ring; results 2020

Keller MJ et al. CROI 2019; March 4–7, 2018 | Boston, Massachusetts. Abstract 1059LB
Johnson TJ et al. AAC 2012; 56(12): 6272-83

Vaginal flora: impact on PK & efficacy

- **TOPICAL: FAME studies[3]**
  - **TFV gel: vaginal & plasma concentrations & efficacy reduced by dysbiosis**
  - **Dapivirine film/gel: concentrations not affected**
- **ORAL: PARTNERS-PREP[1]**
  - **No impact of vaginal dysbiosis** on oral PrEP efficacy
- **DAPIVIRINE VAGINAL RING: ASPIRE trial[2]**
  - **No impact of flora on vaginal or plasma concentrations**
  - **No difference in efficacy by vaginal flora**

1. Heffron R et al. CROI 2017 abstract 85; 2. Hillier S et al, IAS 2017
2. Baeten JM at al. N Engl J Med. 2016 Dec 1;375(22):2121-2132;
3. Hillier S et al. 9th IAS Conference on HIV Science (IAS 2017), July 23-26, 2017, Paris. TUAC0104

Combined ring preparations

- **Combined TDF + FTC ring**
  - Protective in macaques
  - MTN-038: phase 1, results 2020
- **Phase 2a 90 day safety study in Kenya:**
  - TFV vs TFV/LNG vs placebo
  - Estimated completion July 2019
- **Will TDF concentrations from vaginal ring be impacted by vaginal flora?**
- **Nuvaring promotes lactobacilli-dominated vaginal flora in a population with high BV prevalence**

Srinivasan P et al. PLOS ONE 11(6): e0157061.
https://clinicaltrials.gov/ct2/show/NCT03762382
Crucitti T et al PLOS ONE 13(7): e0201003.

Practical challenges

- **Too early to know?**
- **Adherence**
- **Safety**
- **Impact of vaginal flora on NRTI rings**
- **Impact of topical PrEP on genital tract immunity**
  - Dapivirine hydrogel impairs some markers of vaginal innate immunity more than dapivirine film…..
- **(AT LEAST) THREE CRUCIAL FACTORS:**
  - ARV + route + vaginal flora

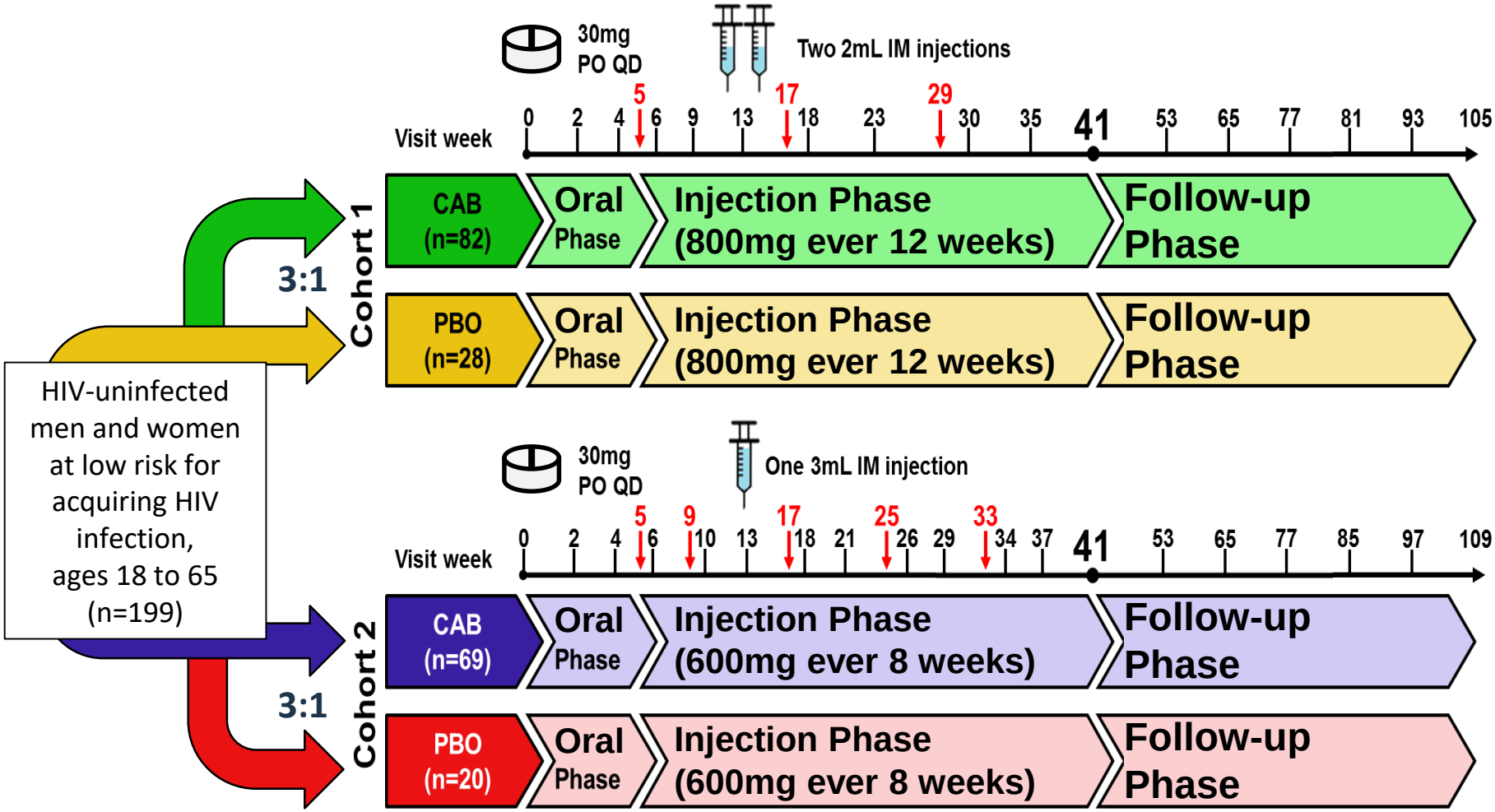
Koppolu S et al. ACS Infect Dis. 2018 Nov 9;4(11):1613-1622.

INJECTABLES

PK & efficacy for injectable HIV PrEP

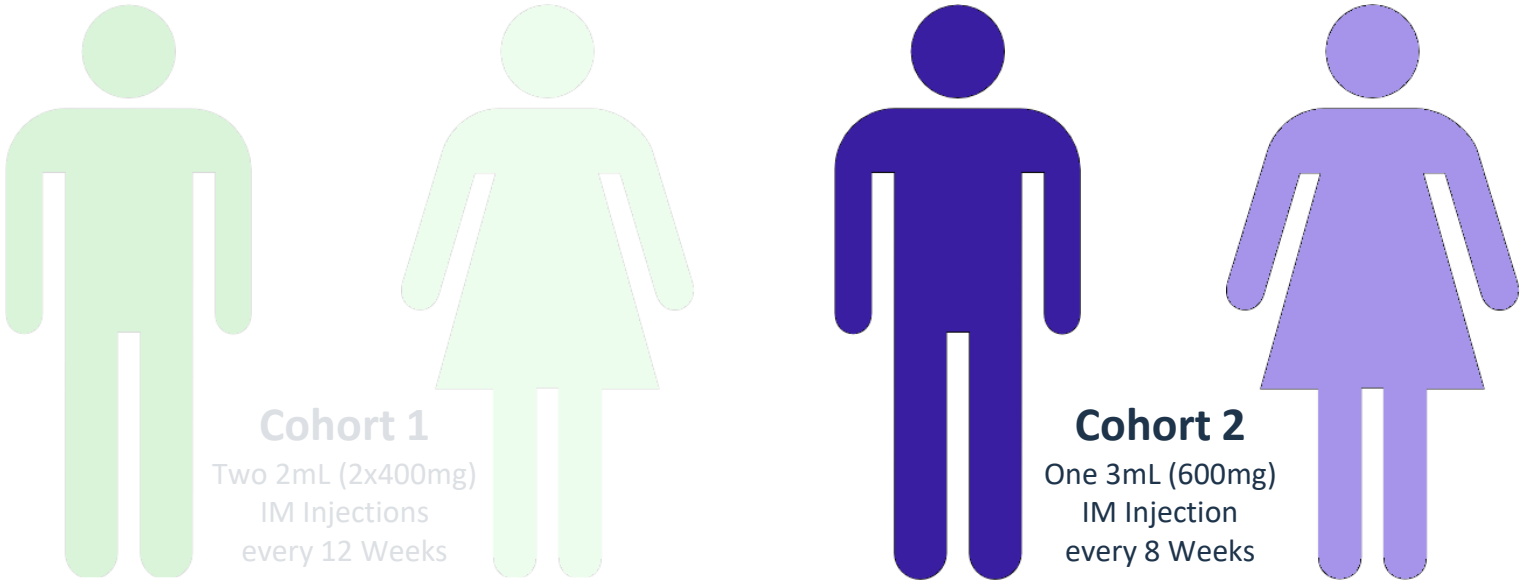
- **IM RPV discontinued in 2017**
  - Inadequate female genital tract PK & explant suppression
- **IM CAB phase 2**
  - **ECLAIR**: MSM & TGW
  - **HPTN 077**: men & women
- **IM CAB phase 3**
  - **HPTN 083**: MSM & TGW
  - **HPTN 084**: cis-women

PrEP: HPTN 077



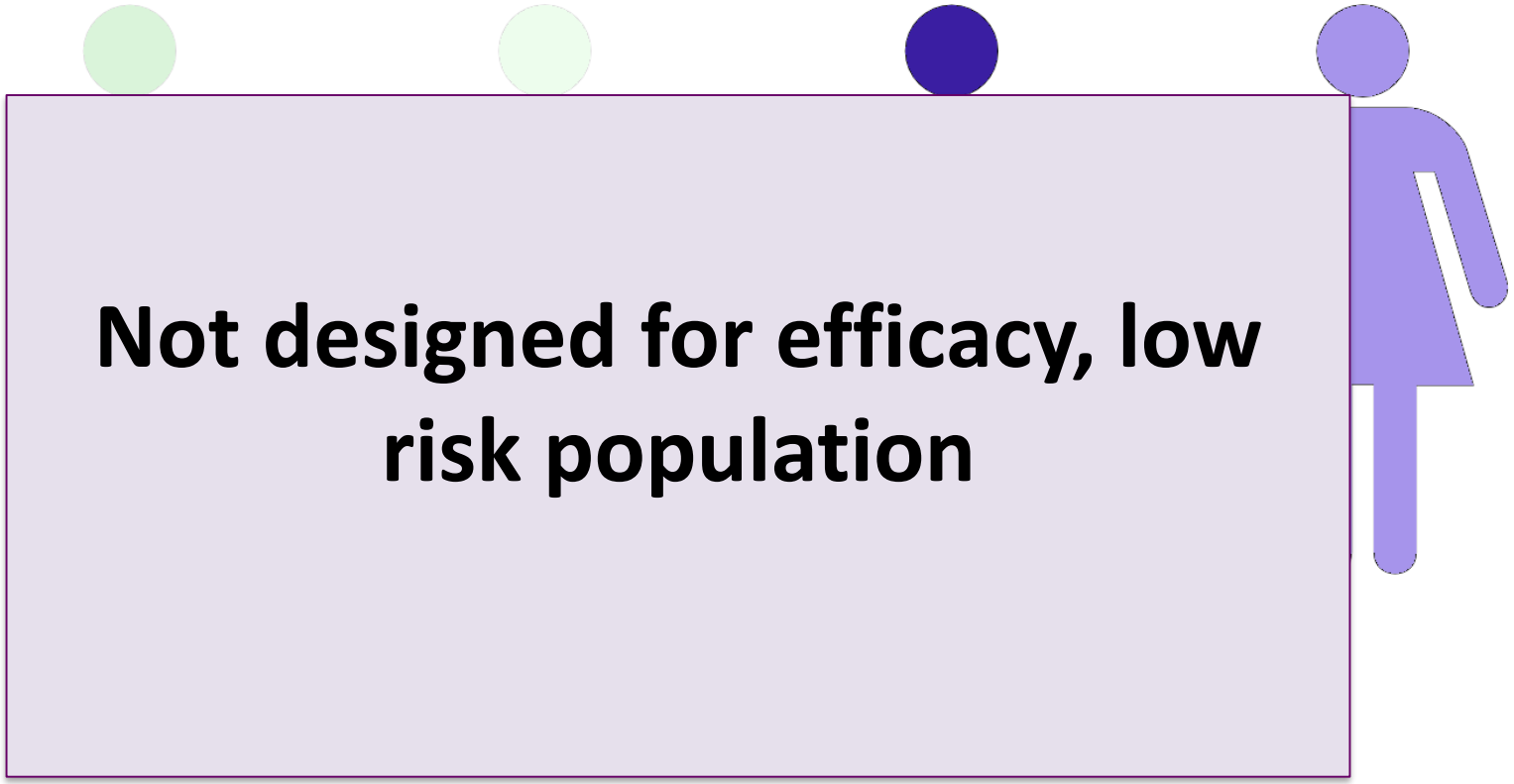
Landowitz R et al. PLoS Med. 2018 Nov; 15(11): e1002690.

HPTN 077: cohort 2 met PK targets for male & female participants



Median Steady State Trough:	~1.35 ug/mL
% > 1X PA-IC90:	≥95%
% > 4X PA-IC90:	≥80%

HPTN 077: cohort 2 met PK targets for male & female participants



Median Steady State Trough:	~1.35 ug/mL
% > 1X PA-IC90:	≥95%
% > 4X PA-IC90:	≥80%

ECLAIR

- **12-weekly 5:1 CAB vs placebo after oral lead-in phase (n=127 men at low risk of HIV)**
- **Injection site reactions common**
- **PK suboptimal**
  - Despite modelling data predicting adequate trough
- **2 new HIV diagnoses**
  - 1 in placebo arm
  - 1 in CAB arm 24 weeks after last injection when plasma CAB concentrations undetectable

Markowitz M et al. Lancet HIV. 2017 Aug;4(8):e331-e340.

HPTN 083: CAB LA 600mg

To Prevent HIV Acquisition in MSM and TGW

Landovitz and Grinsztejn, *Protocol Chairs*

Step 1	**Daily oral CAB and TDF/FTC placebo**	**TDF/FTC and oral CAB placebo**
Step 2	**CAB LA at two time points 4 weeks apart and every 8 weeks thereafter and TDF/FTC placebo**	**TDF/FTC and injectable placebo at two time points 4 weeks apart and every 8 weeks thereafter**
Step 3	**Open-label TDF/FTC to cover the PK tail**	**Open-label TDF/FTC to Cover the PK tail**

Primary Objective: Reduce HIV Incidence (non-inferiority, double blind, double dummy design)

N=4500; Study duration: Enrollment 24-30 months; follow-up ~ 4.5 years

Enrollment goals:

- *Minimum* 50% of US enrollment Black MSM (~ 950)
- Overall minimum 10% TGW (~ 450)
- Overall > 50% under age 30

HPTN 084: CAB LA 600mg

To Prevent HIV Acquisition in Women

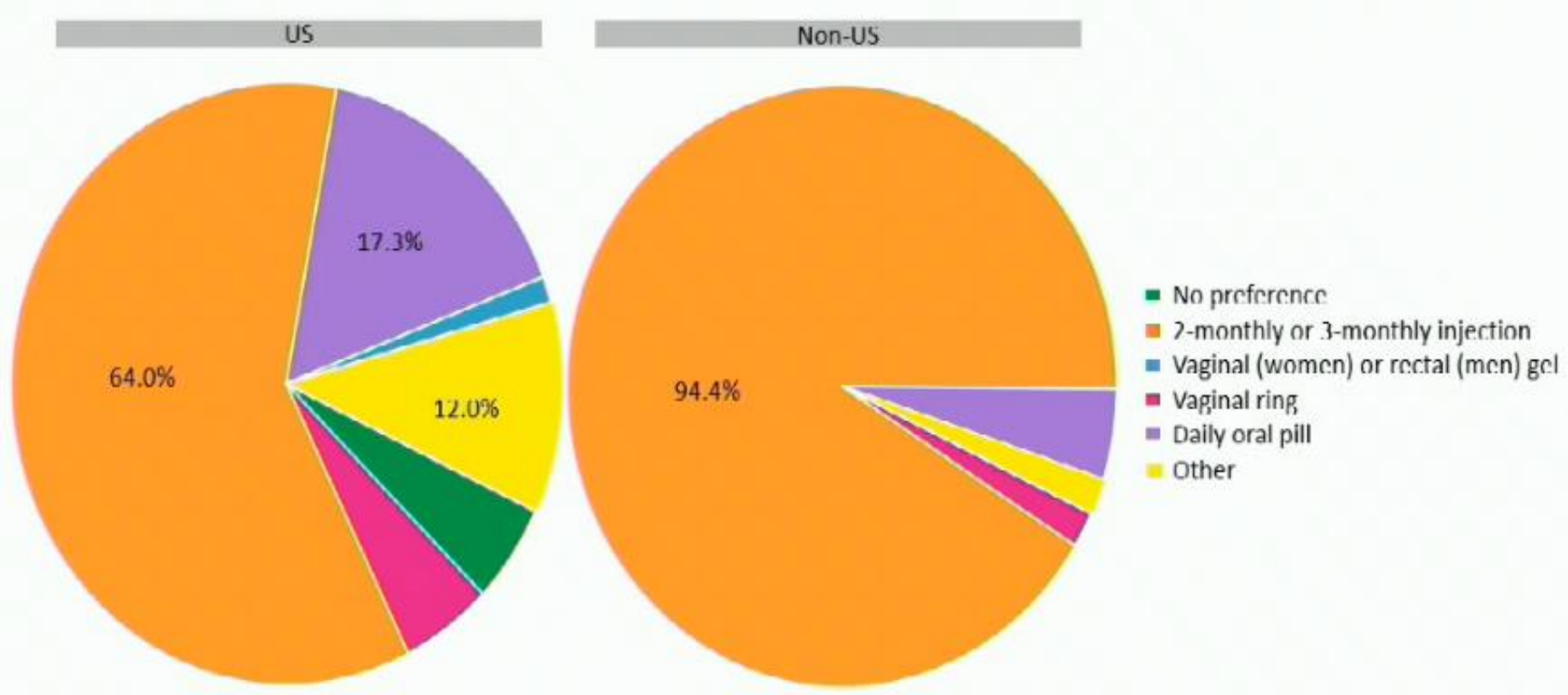
Delaney-Moretlwe and Hosseinipour, *Protocol Chairs*

Step 1	**Daily oral CAB and TDF/FTC placebo**	**Oral TDF/FTC and oral CAB placebo**
Step 2	**CAB LA and oral TDF/FTC placebo at two time points 4 weeks apart and every 8 weeks thereafter**	**Oral TDF/FTC and injectable placebo at two time points 4 weeks apart and every 8 weeks thereafter**
Step 3	**Open-label oral TDF/FTC to cover the PK tail**	**Open-label oral TDF/FTC to cover the PK tail**

Primary Objective: Reduce HIV Incidence (superiority, double blind, double dummy design)

Study duration: Enrollment 24 months; follow-up up to 4.5 years, N=3200

Patients prefer injectable in ART trials, what about PrEP? HPTN 077



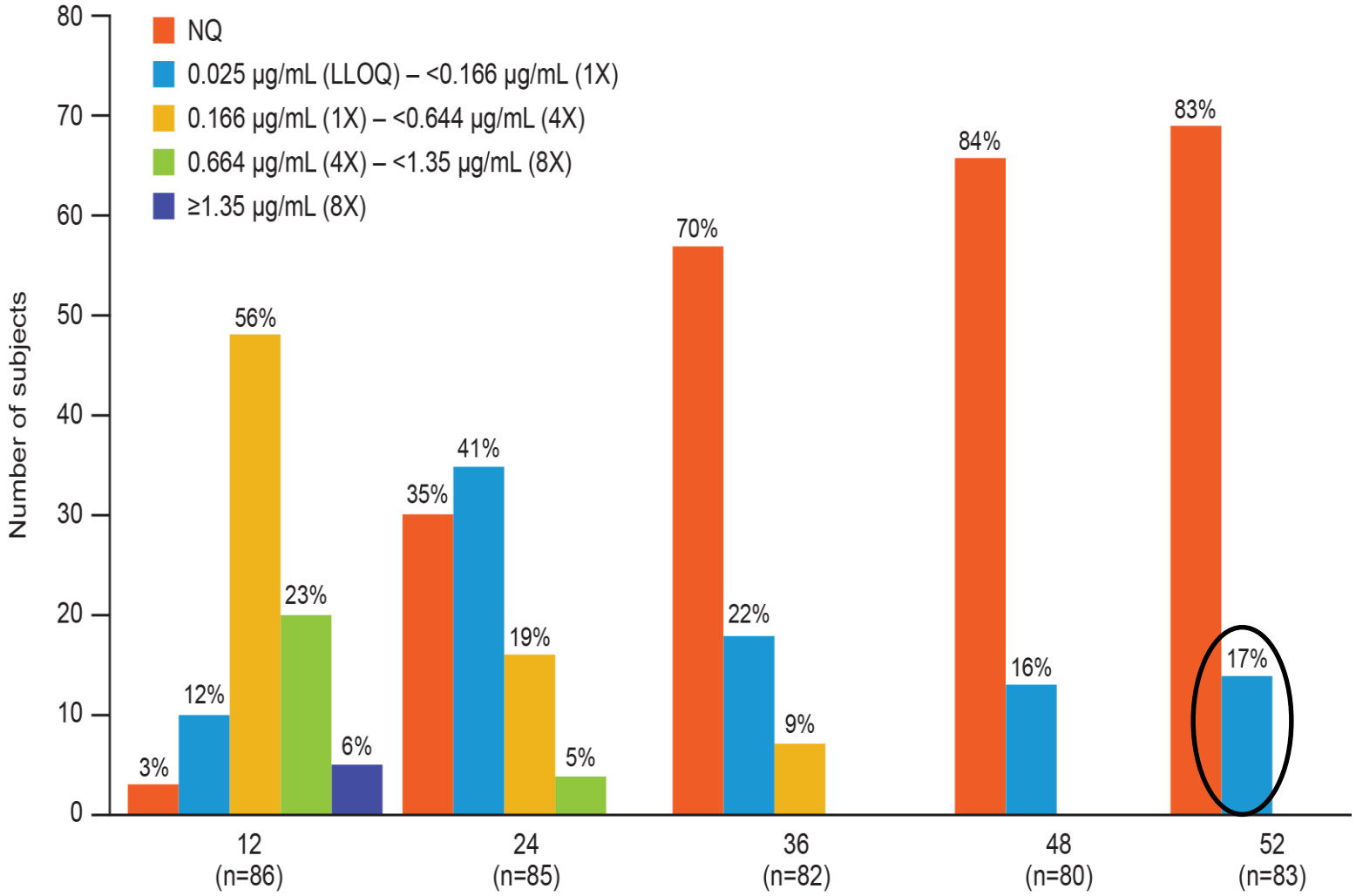
Landovitz RJ et al. HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid. Abstract OA15.06.

Patient preferences

- **Discrete choice studies: efficacy most important**
- **Non-oral options largely preferred**
  - Particularly injectables, rings if multi-purpose
- **Questions are based real & estimated attributes**
- **TRIO: 277 women randomised to placebo PrEP:**
  - Monthly ring, monthly IM injection, daily tablet for 1 month then choice of product for 2 months
  - 85% preferred PrEP over condoms
  - 64% chose injections for phase 2
  - Adherence highest for injections

Straten Avd et al. Journal of the International AIDS Society 2018, 21:e25094

ECLAIR: CAB persists in a minority 52W after last injection



C_T Injection 3.

14 subjects had detectable CAB 52 weeks after injection 3

Ford et al. HIVR4P 2016; Chicago, IL. Abstract OA12.06LB.

Unanswered questions

- **What will happen with delayed or missed doses?**
- **Covering the PK tail?**
  - How long? TDM guided?
  - What with?
- **Acceptability of long-term IM injections**
- **Impact of BMI**
- **Impact of additional IM injections**
- **Practicalities & costs of service delivery**

THE FUTURE

Journal of Controlled Release

- Rilpivirine dissolving microarray patches
- ‘Self-limiting’ but what will the tail be?
- Will the patch size be practical?

McCrudden MTC et al. J Control Release. 2018 Dec 28; 292: 119–129

Implants

- **Lots of preclinical work**
  - TAF
  - Cabotegravir
  - Multipurpose implants possible
- **Macaque studies of TAF/FTC implant:**
  - Sustained delivery 83 days, preventative tenofovir levels within 3 days, refillable transcutaneously

https://www.contagionlive.com/publications/contagion/2018/june/implants-for-delivery-of-antiretroviral-drugs-for-hiv-preexposure-prophylaxis
Chua CYX et al. J Control Release. 2018 Sep 28;286:315-325.

Skepticism

AIDS Patient Care and STDs, Vol. 33, No. 4 | Clinical and Epidemiologic Research

Design of an Implant for Long-Acting HIV Pre-Exposure Prophylaxis: Input from South African Health Care Providers

Emily A. Krogstad, Elizabeth T. Montgomery, Millicent Atujuna, Alexandra M. Minnis, Shannon O'Rourke, Khatija Ahmed, Linda-Gail Bekker, and Ariane van der Straten

Broadly neutralising antibodies

- **Promising PrEP efficacy in animal studies**
  - Rectal, vaginal & penile exposure
- **Risk of resistance with 'monotherapy'**
  - Combinations crucial

https://www.iasociety.org/The-latest/Blog/ArticleID/222/A-week-in-review-CROI-2019 accessed May 2019

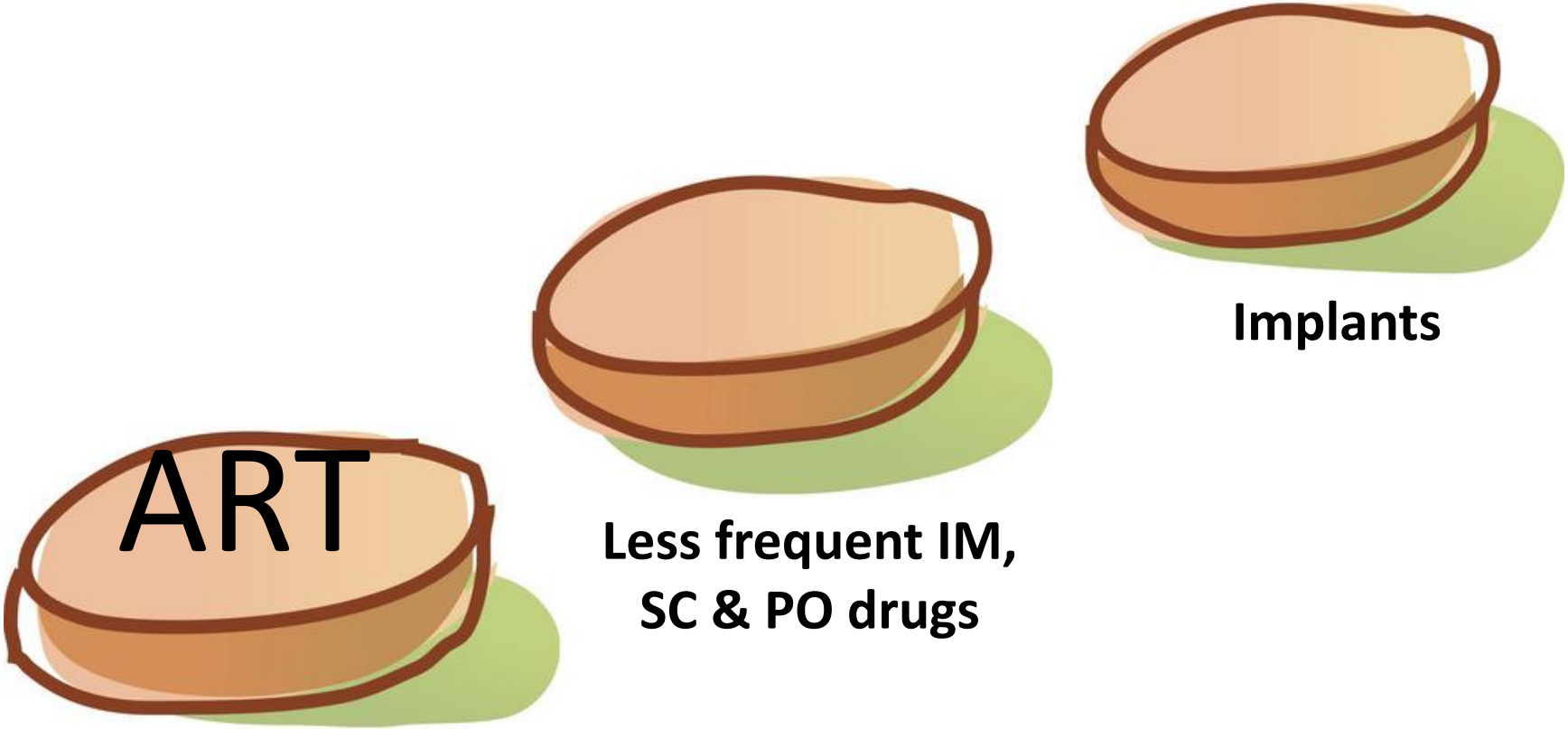
CONCLUSIONS

Concerns: a non-exhaustive list

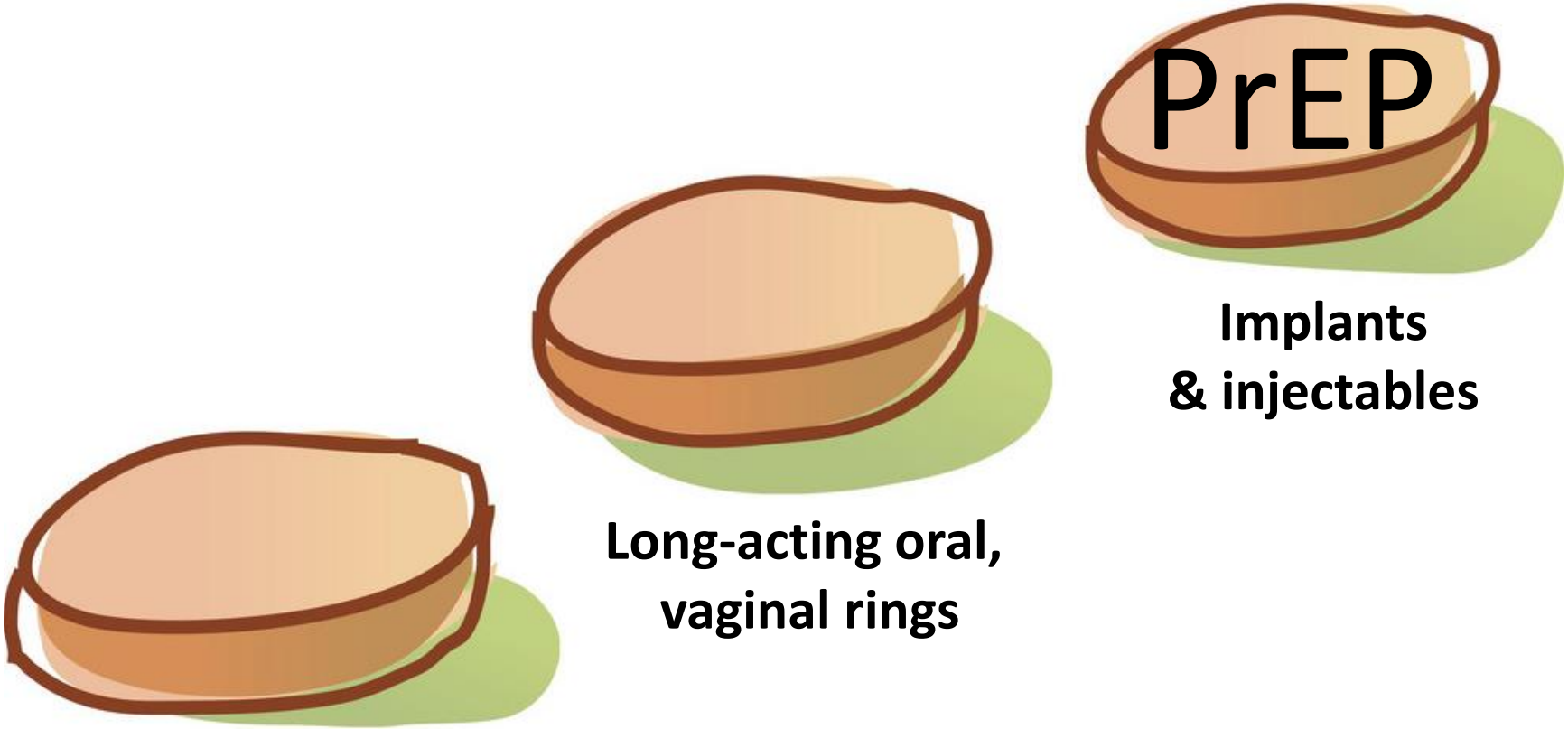
1. **Safety in pregnancy**
   - e.g. CAB signal in animal studies
2. **Drug-drug interactions**
   - e.g. modelled impact of rifampicin + LA CAB at CROI 2019
3. **Systemic exposure with topical methods**
   - e.g. low concentrations of dapivirine in breast milk & low plasma concentrations of tenofovir following enema
4. **Impact of topical methods on mucosa**
   - Nonoxynol-9, lubricants

Noguchi LM et al. Antimicrob Agents Chemother. 2019 Feb 26;63(3).

Long-acting ART: it's a journey



Long-acting PrEP:
are we heading in the wrong direction?



Why?!

- **For *some* immediate short acting PrEP preferable?:**
  - Risk is not continuous
  - Event-based methods may limit toxicity
  - Short-acting methods may limit resistance
- **Link PrEP with higher risk sexual practices?**
  - Lubricant
  - Rectal douches: men reporting RAI in last 3/12 80% douched before, 27% after, 98% reported high likelihood of using an HIV-prevention douche: PrEP dissolvable in tap water with rapid onset of action ideal??
  - **IS THIS A DREAM?!**

Carballo-Dieguez A et al. AIDS Behav. 2018 Nov 10. doi: 10.1007/s10461-018-2336-6.

Development of rectal enema as microbicide (DREAM)

- **DREAM: TDF enema murine studies**
  - Vehicle characteristics crucial (e.g. osmolality)
- **DREAM 01: single pre-sex TDF rectal douche**
  - 98% currently douching & 94% not currently douching would definitely or probably try a microbicide douche
  - Significantly lower plasma exposure than oral
  - Similar colon TFV-DP levels after 1 dose to 7 days consecutive rectal tenofovir gel
  - From 1 to 24 hours after dosing, median colon cell TFV-DP concentrations exceeded target inhibitory concentrations
  - Effective in ex vivo replication analyses

DREAM: Hoang T et al. Eur J Pharm Biopharm. 2019 May;138:23-29.
DREAM 01: Weld E,et al. HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid. Abstract OA20.03.

My dream future

- **Non-treatment agents**
  - Vaginal ring delivery HIV CCR5 inhibitor 5P12-RANTES in sheep (could this be combined with contraception?)
- **Intelligent implants**
  - Drug release adjusted to plasma concentrations
  - Option for immediate shut down without removal
  - Individualised concomitant medication
    - Depot contraception
    - STI treatment (in-built RPR monitoring?!

McBride JW et al J Control Release. 2019 Mar 28; 298: 1–11.

Thank you!

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