Next Generation PrEP?
Injectable & Implantable ARVs

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Objectives

- Describe alternative formulations to improve adherence
- Describe benefits & liabilities of long-acting injectibles
- Describe benefits & liabilities of long-acting implantables

Formulations for Poor Adherence

Challenges of Poor Adherence

Long-Acting Formulation

- Intravaginal ring (topical)
- **Injectable & Implantable**
  - Systemic Exposure
  - Lower mucosal exposure
  - Both RVI & RAI coverage (?)

On Demand ± Behaviorally Congruent

- Film, Douche, Insert, Gel
  - Single dose
  - Low systemic exposure
  - Behaviorally low impact
  - RVI & RAI, but likely 2 doses

Current Status: Alternative Formulations

Phase III/IV

- "On demand" (Periodic Dosing)
  - Periodic oral TDF/FTC dosing 3 days/4 doses, Ipergay
- Long-acting Vaginal Ring 1 month (*3 month in development*)
  - Dapivirine RCTs, IPM & MTN-020, under EMA review

IIB/III

- ***Long-acting Injectable*** bi-monthly
  - Cabotegravir vs. TDF/FTC Phase 2B/3 HPTN 083 (enrolling) & HPTN 084 (start late 2017)
  - Rilpivirine (withdrawn from PrEP development)

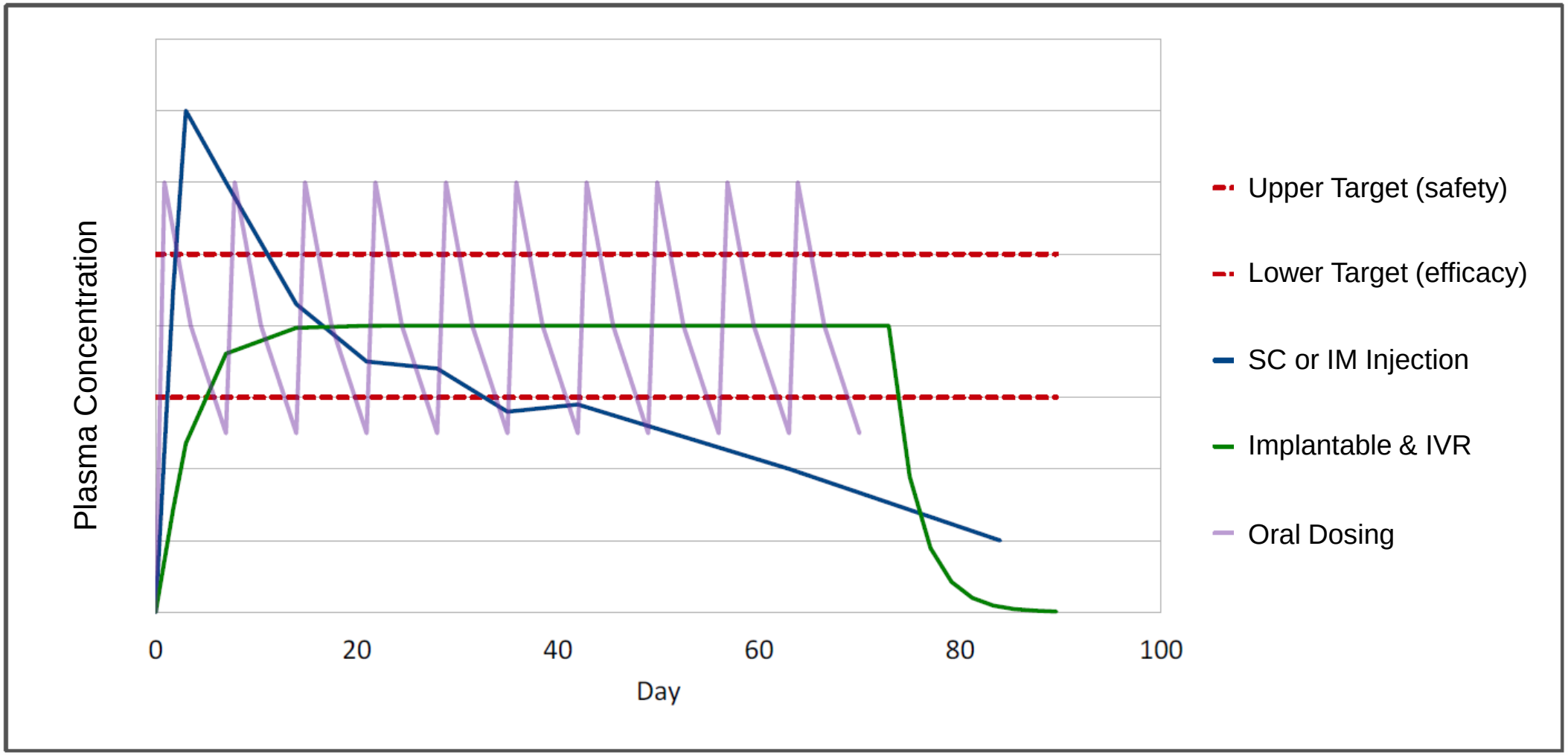
I

- ***On Demand + Behavioral congruence***
  - Gels, films, inserts, suppositories
  - Lubricant - DPV applied as lubricant, MTN-033
  - Douche - TFV/prodrug (TDF, TAF, CMX-157), U19 JHU DREAM 01 (enrolling)

Animal

- ***Longer-acting Implantable***
  - TAF silicone/PVA rod OCIS U19 (beagle)
  - TAF biodegradable implant, RTI (rabbit)
  - Cabotegravir, Rilpivirine,TAF, CMX-157 NU UM1 (rabbit)

Formulation PK Profiles Compared



Courtesy Ariane van der Straten

Learning from Injectable Depo-Provera®

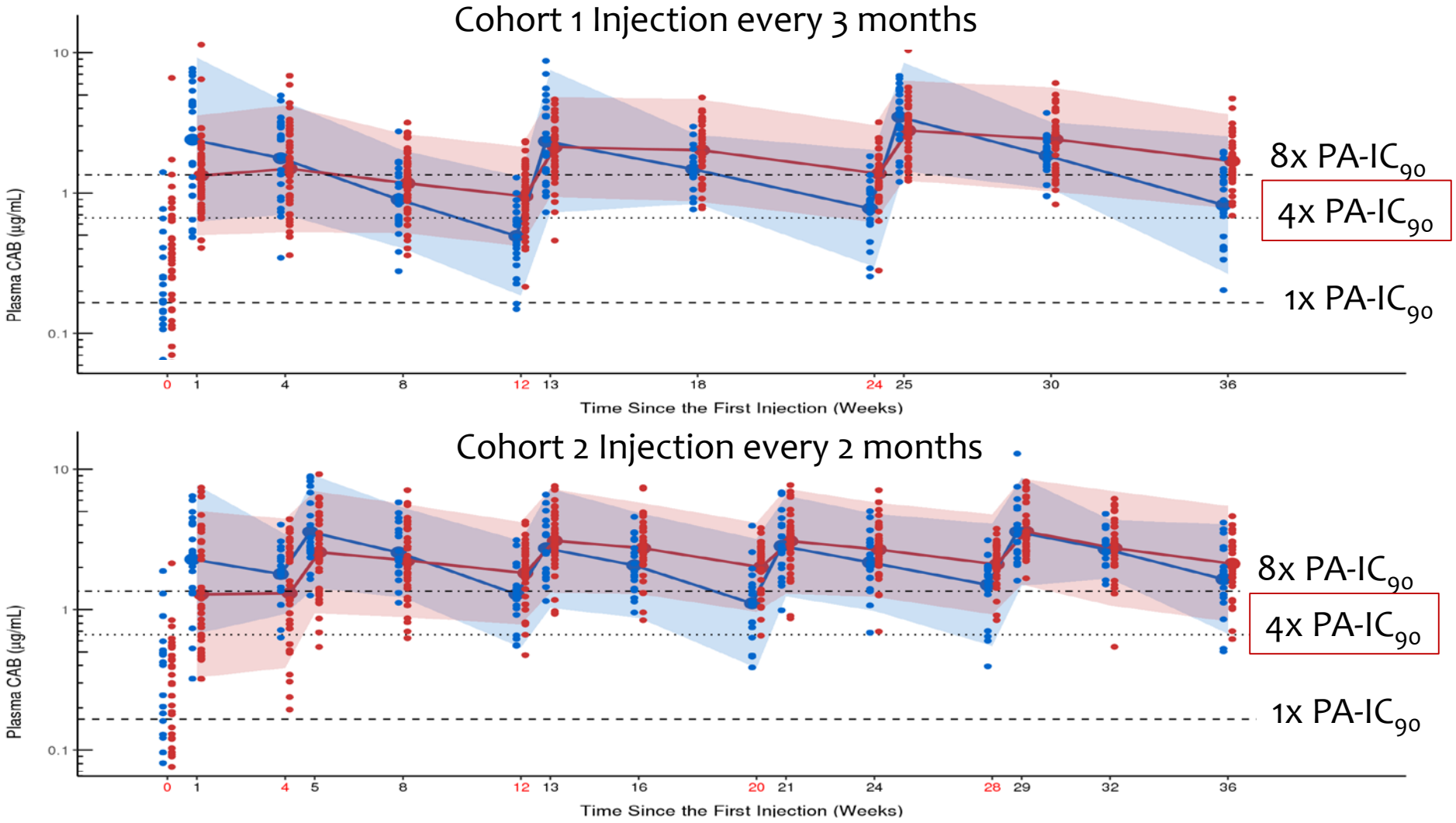
- Valuable precedent for long-acting injectable prevention
- US FDA approved contraception (1992)
- Extensive acceptability work along w/ product development
- Low continuation rates (first year 40-60%)
  - 2° menstrual disruption, limited access, similar to OCP
  - Spurred development of truly long-acting (1 year) IUD & implants
  - Development of SQ administration, successfully piloted
- Challenges with timing of initiation
  - Concern: administer only when certainty of no pregnancy
  - Led to Quick Start: same-day contraception & pregnancy test, no waiting for menses, back-up contraception if recent sex; 4x less pregnancy vs. waiting for menses
- Difficulty ensuring access for vulnerable populations 2° transportation, cost

Myers JE, et al. Curr Opin HIV AIDS 2015, 10:271–277

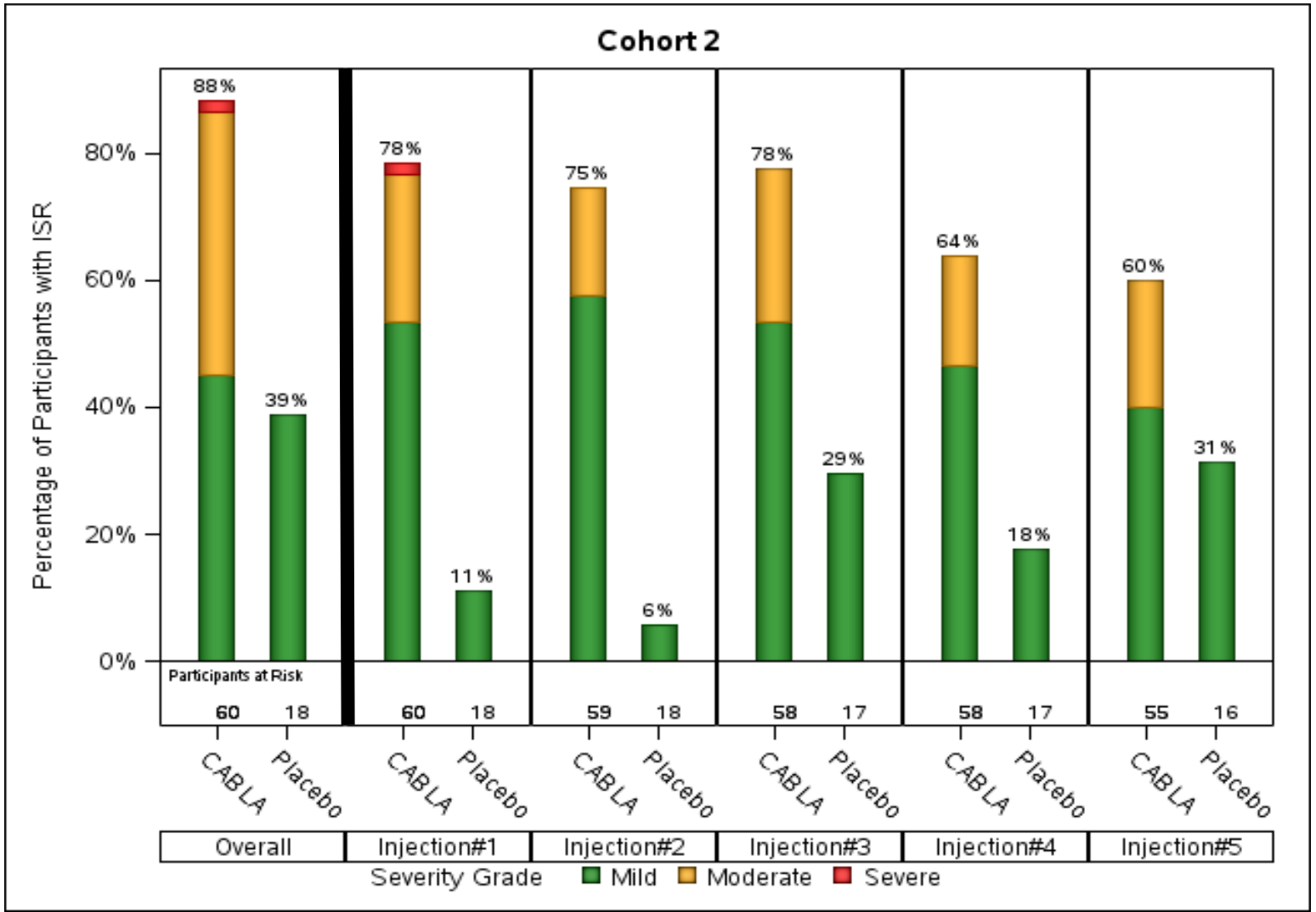
Cabotegravir-LA Nanosuspension PrEP

- *Goal: Provide alternative to oral daily PrEP*
- HIV InSTI
  - Similar to Dolutegravir
  - Proven effective for treatment
- Every 8 week intramuscular injection
- Non-removable, non-dialyzable following injection
  - Oral cabotegravir one month lead-in to rule out toxicity
- Long period of inadequate drug concentrations (“PK Tail”)
  - Below [protective] for months to more than a year (longer in women)
  - Oral PrEP for months to year to protect from resistance if HIV infection

HPTN 077 Cabotegravir PK



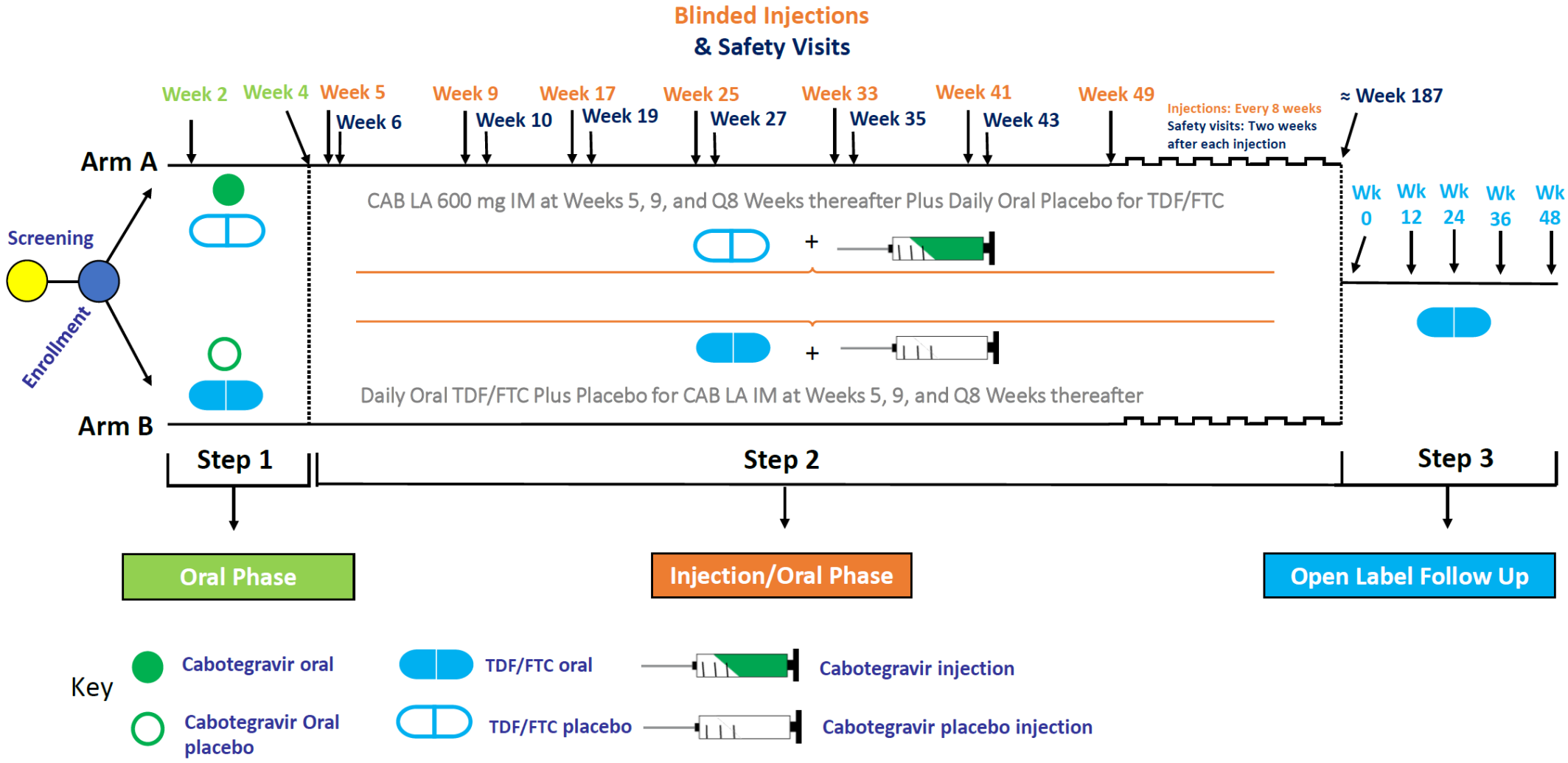
HPTN 077 Injection Site Reactions



Injection Site Reactions

- 60-80% any grade
- 20-40% mod-severe

HPTN 083 Study Schema

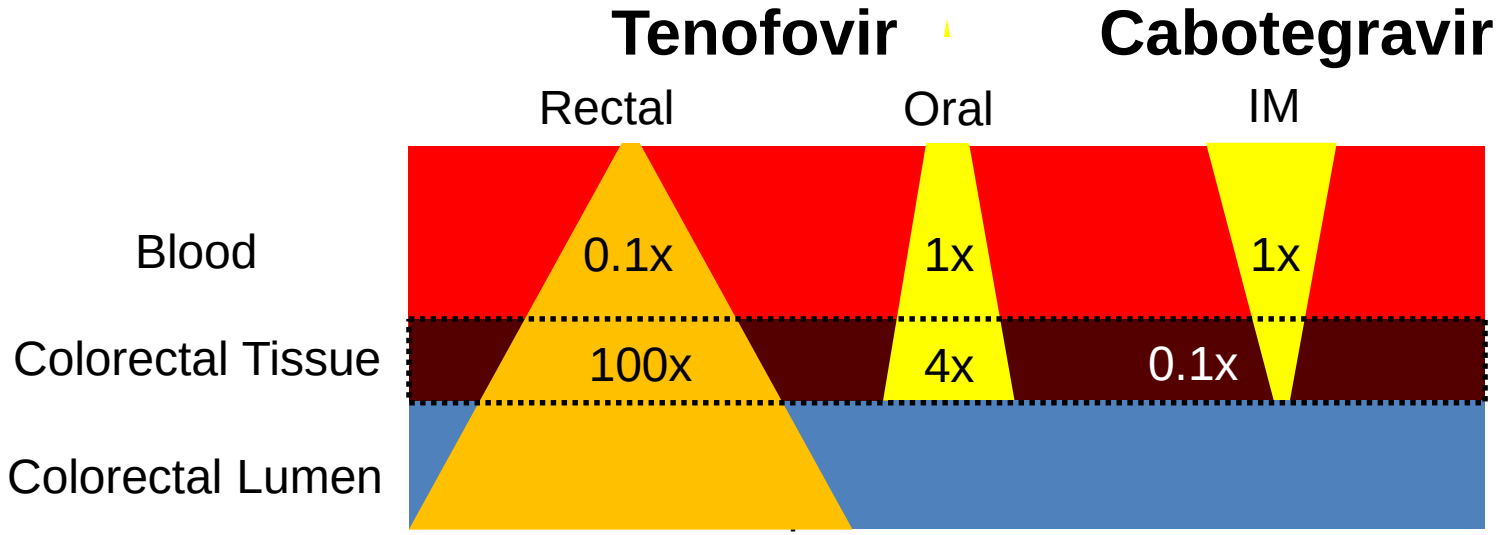


Cabotegravir-LA Nanosuspension PrEP

- *Goal: Provide alternative to oral daily PrEP*
- HIV InSTI
  - Similar to Dolutegravir
  - Proven effective for treatment
- Bi-monthly intramuscular injection
- Non-removable, non-dialyzable following injection
  - *Oral cabotegravir one month* lead-in to rule out toxicity
- Long period of inadequate drug concentrations (“PK Tail”)
  - Below protection for months to more than a year (more in women)
  - *Oral PrEP for months to year* to protect from resistance if HIV infection

Tenofovir vs. Cabotegravir-LA: RAI

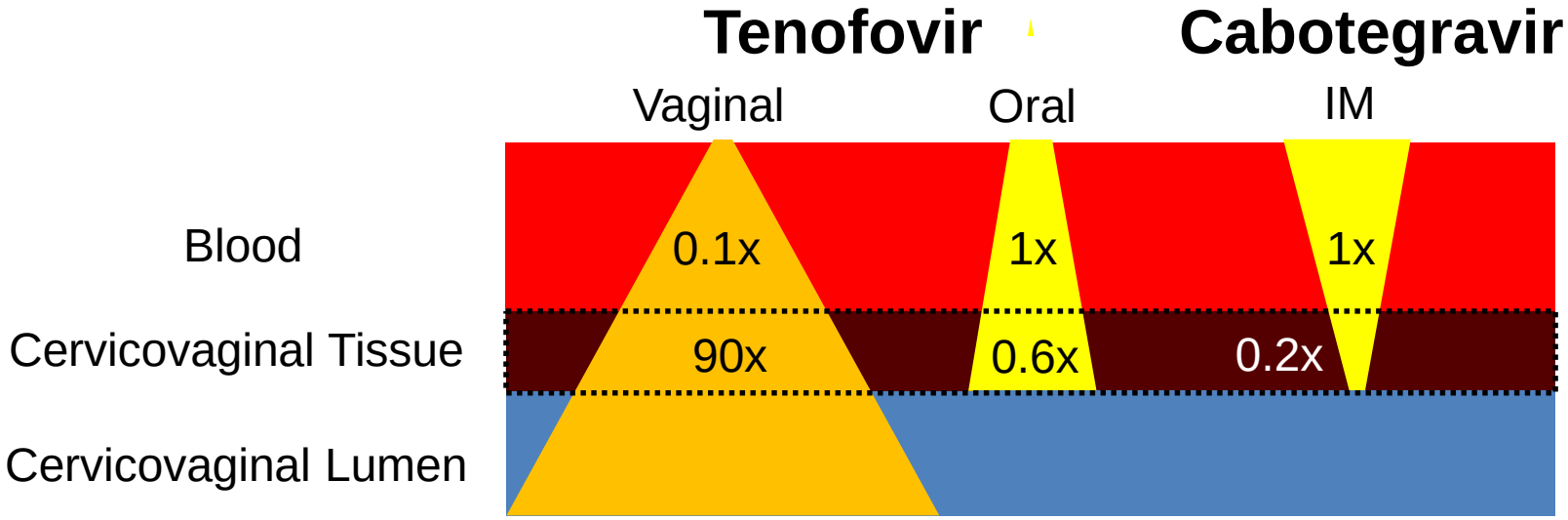
- Active ARV Concentrations Compared
  - Reference for comparison (1x): treatment dose blood (PBMC) concentration, C_{trough}



- Colorectal active conc'n: ***CAB 40x*** < ***oral TDF*** & ***1,000x*** < ***rectal TFV***

Tenofovir vs. Cabotegravir-LA: RVI

- Active ARV Concentrations Compared
  - Reference for comparison (1x): treatment dose blood (or PBMC) concentration, C_{trough}

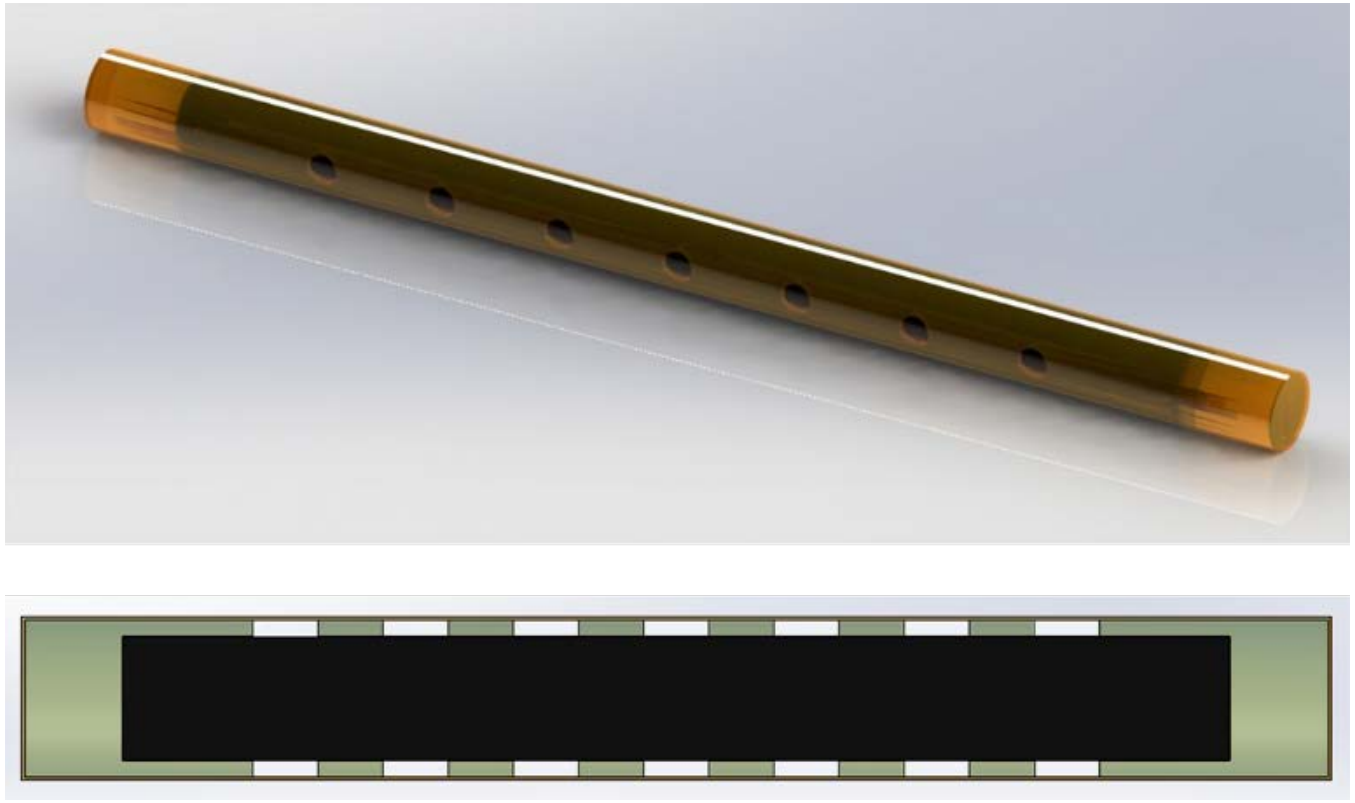


- Cervicovaginal active conc'n: ***CAB 3x*** < ***oral TDV*** & ***500x*** < ***vaginal TFV***
- HPTN 083 & 084 will demonstrate significance of systemic vs. local [ARV]
- Premature to count on CAB-LA as only solution to adherence/choice goals

Injectable Cabotegravir Promise

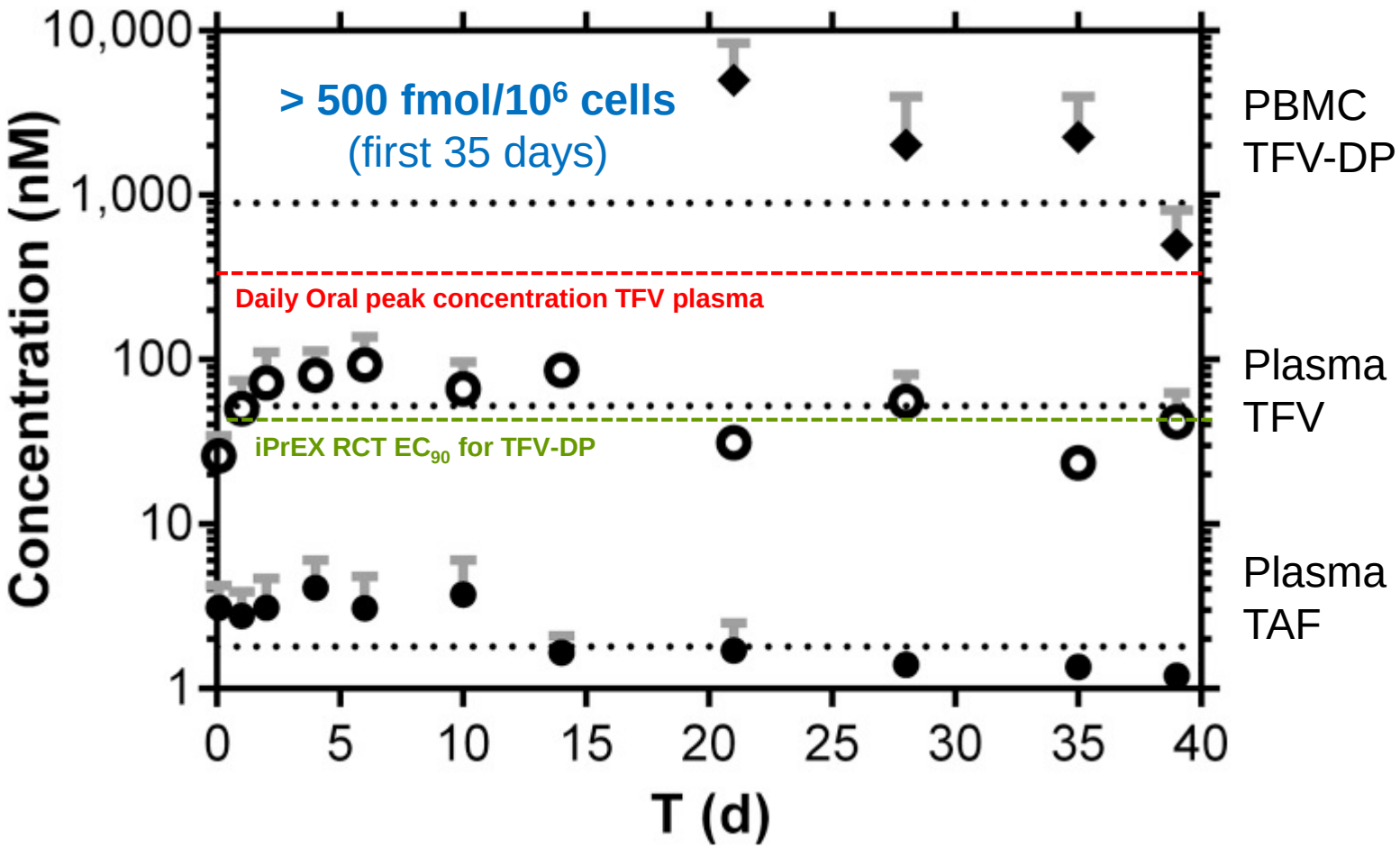
- Promise for PrEP
  - Dolutegravir highly potent, effective orally for HIV treatment
  - Cabotegravir-LA highly effective IM for treatment
  - Protects vaginal & rectal SHIV challenge in macaques
- Liability for PrEP
  - Systemic exposure (fever, fatigue, flu-like illness, headache, rash)
  - Local – ISR 60-80% any, 20-40% moderate to severe
  - Oral lead-in (may be dropped as safety demonstrated)
  - Long tail, potential resistance to most potent oral Rx class
  - Compared to plasma, low conc'n vaginal (16%) and rectal (8%) tissue
    - If [tissue] important, 3x - 40x less suitable vs. oral TFV

Subdermal Implant Design



Courtesy Marc M. Baum, Oak Crest Institute of Science; Gunawardana *et al.*, *AAC*, **2015**.

TAF Implant in Dogs

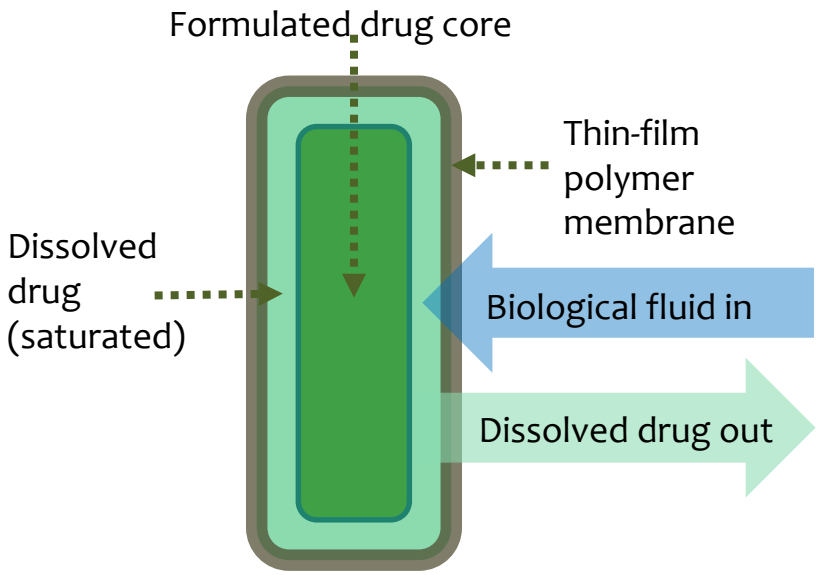


Gunawardana *et al.*, *AAC*, **2015**.

- Subdermal implantation of TAF LA prototype device in beagle dogs (*N* = 4)
- Low systemic TAF & TFV
- PBMC TFV-DP [above target]
- Estimate 1 year clinical coverage (2 rods)
- Clinical Study planned 2018

Implantable Thin Film Polymer Device (TFPD)

- User-independent, ***biodegradable***, subcutaneous implant
- Sustained release of PrEP drugs with constant release over time
- Compatible with existing trocar applicators
- Target TFPD size ranges from 2-2.5mm diameter x 40mm length

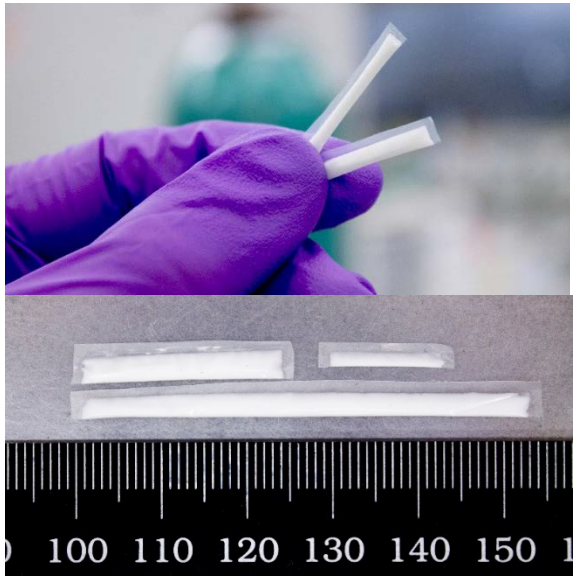


Courtesy Ariane van der Straten

Compatibility with Existing Trocars

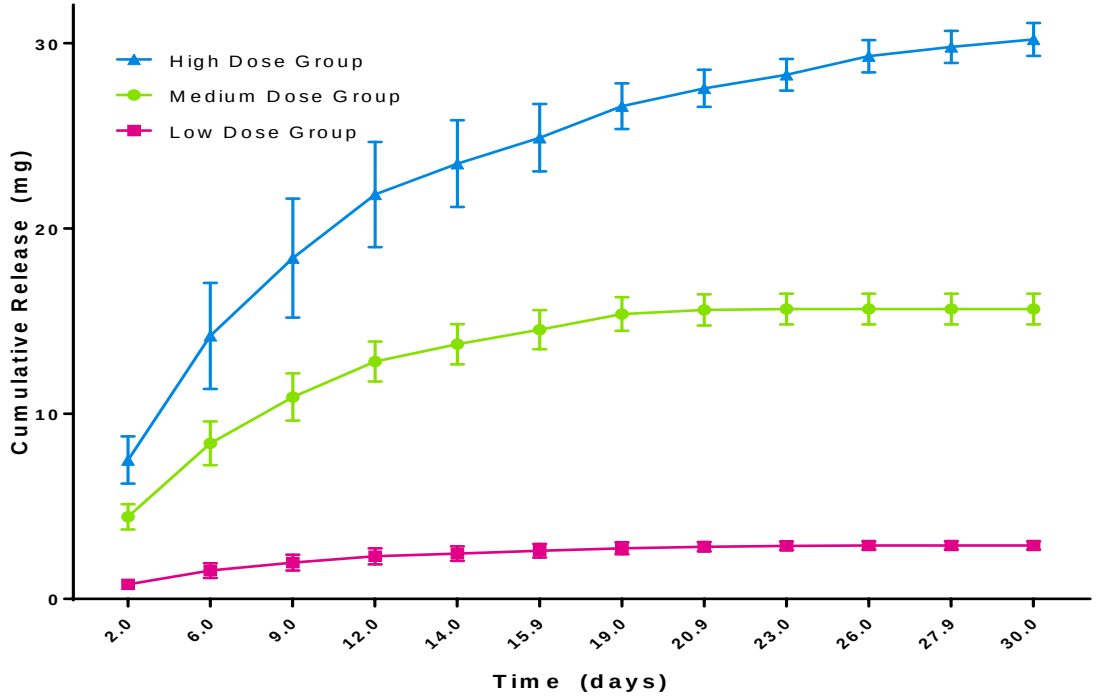
Implanon

Jadelle



TAF TFPD: In vitro & Rabbit Studies

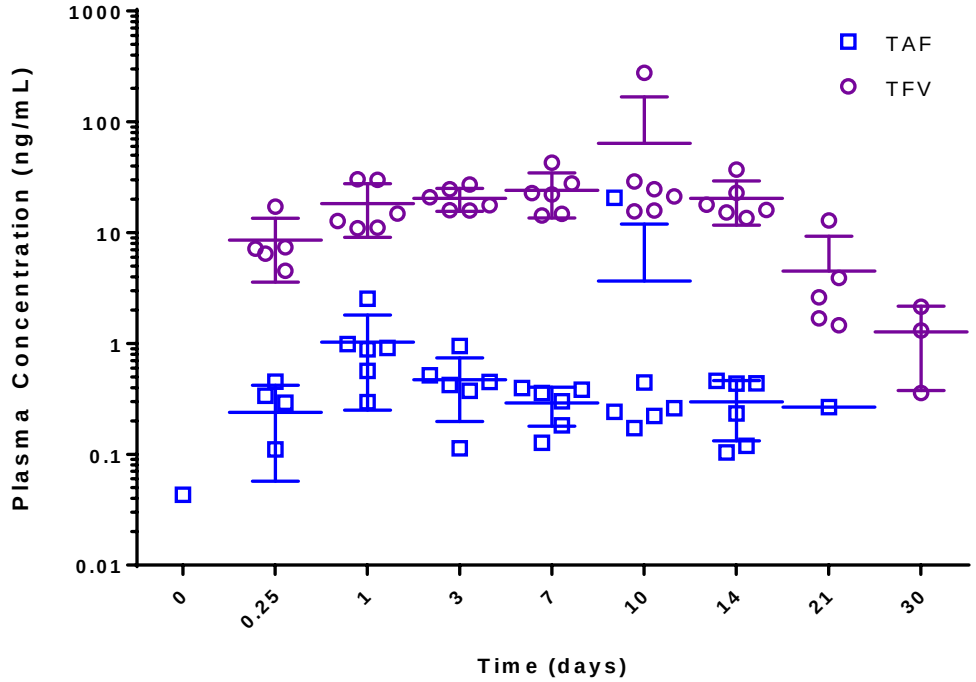
In Vitro TAF Cumulative Release



- Linear release (in PBS)
- TAF release proportional to TFPD size
- Releases 24%-47% faster than targeted

Durham PG, et al. CROI 2017 Abstract 420

In Vivo (Rabbit) TAF & TFV Plasma



- TAF & TFV levels fairly constant x 14d
- Detectable by 6 hrs
- PBMC TFV-DP D21 296 fmol/10^6 cells (target 36)

Possible* LA Formulation (Dis)Advantages

- User independent method improves adherence (*v. oral, topical*)
- Less social & logistical challenges of pills, tablets, & gels (*v. oral, topical*)
- Steady concentration (v. *oral*, *topical*, *injectable*)
- One dose (may) distribute to vagina and rectum (*v. **one** topical dose*)
- Very long term implant protection (*v. injectable*)
- Removable implant allows reversal – toxicity, period of risk (*v. injectable*)
- Removable implant avoids long tail (resistance risk) (*v. injectable*)
- Biodegradable implant avoids removal procedure (*v. non-biodegradable*)
- Clinician administration (increased cost) (v. *oral*, *topical*)
- Sustained systemic exposure (AE's & ISR's) (v. *topical*)

**assumes implantable, injectable efficacy*

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Acknowledgements

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