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Disclosures

ViiV/GSK funded clinical trial managed through JHU
Outline

- What’s needed to improve PREP products for women?
  - Long vs. short acting & systemic vs. topical
- What female specific innovations are in development?
  - Inserts, films, combination rings,
- What about rectal protection for men & women?
  - On demand, behaviorally-congruent lubricants & douches
  - Informative for vaginal lubes & douches?
- What systemic products are in the pipeline?
  - Injectable, implantable, infusion
Why Variable PrEP Outcomes in Women?

- Poor adherence major, but doesn’t explain all underperformance
- Active drug (TFV-DP) far lower in cervicovaginal than colon tissue
  - Increases impact of poor adherence
- RAI – certain, but variable magnitude of impact on vaginal products
  - If 1/20 HIV exposures is anal & 20x anal HIV risk, then max RRR is 50%
- Vaginal dysbiosis may reduce vaginally dosed TFV with BV
- FGT and colorectal ARV tissue conc’n may not be enough

*Variables indicate needed product improvements*
PrEP ARV Underperformance in Women

- **TFV Vaginal Gel**
  - CAPRISA 004: 39% RRR**
  - VOICE gel: 0% RRR
  - FACTS 001: 0% RRR

- **Dapivirine IVR**
  - ASPIRE: 27% RRR
  - The Ring Study: 31% RRR

- **TDF/FTC Oral**
  - VOICE: 0% RRR
  - iPrEx: 42% RRR
  - Partners: 75% RRR
  - CDC TDF2: 62% RRR

* mITT, modified intent to treat analysis; **RRR = relative risk reduction in HIV infection

- 40-88% with post hoc adherence adjustments
- 60-75% with post hoc adherence adjustments
- No post hoc adherence boost
- 90-100% with post hoc adherence adjustments
Better Formulations for More Women

Challenges of *Oral & Vaginal* PrEP

- Long-Acting Formulation
- On Demand + Behaviorally Congruent

Alternative Formulation Development
PrEP Product Profile Wish List

- High level of protection
- Low adherence burden
- Behaviorally-congruent (piggy-back onto existing sex product use); no behavior change required
- RVI & RAI coverage
- Minutes or hours to protection
- Short pharmacokinetic tail
- Minimal systemic toxicity
- Minimal local toxicity
- Low healthcare system cost (product, administration, monitoring)
# HIV PrEP Pipeline by Formulation

<table>
<thead>
<tr>
<th></th>
<th>Systemic</th>
<th>Topical - Vaginal</th>
<th>Topical – Rectal</th>
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<tbody>
<tr>
<td><strong>Short-Acting</strong></td>
<td>Tablet</td>
<td>Vaginal Gel</td>
<td>Rectal Gel*</td>
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<tr>
<td></td>
<td>• Oral TDF/FTC daily • Oral TDF/FTC 2/1/1 (MSM/TGW)</td>
<td>• TFV BAT24 (mITT &amp; post hoc) • TFV daily (post hoc) • Giffithsin/carageenan • PC-1005 Fast-dissolving film • TFV film • Dapivirine film Fast-dissolving insert • TFV/FTC insert • TFV/EVG insert pre-clinical</td>
<td>• TFV • MVC • DPV • IQP-0528 • PC-1005 • Giffithsin/carageenan • *potential as lubricant Douche • TFV Fast-dissolving Insert • TFV/EVG</td>
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<tr>
<td><strong>Long-Acting</strong></td>
<td>Injectable IM</td>
<td>Intravaginal ring (IVR)</td>
<td></td>
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<tr>
<td></td>
<td>• CAB-LA q2m</td>
<td>• Dapivirine • TFV • TDF • MVC • DPV/MVC • Pod-IVR TFV/FTC/MVC • IVR TFV/LNG</td>
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<tr>
<td></td>
<td>Implantable SC</td>
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<td></td>
<td>• TAF q12m</td>
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<td>• CAB</td>
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<td>Infusion IV</td>
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<td></td>
<td>• bnAb q2m</td>
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**Key**
- Clinical efficacy established
- Clinical trial ongoing/complete
- Clinical trial pending
- Pre-clinical testing
## PrEP Formulation Pros & Cons

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Topical - Vaginal</th>
<th>Topical - Rectal</th>
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</thead>
<tbody>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
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<tr>
<td><em>Superior efficacy (44-100%)</em></td>
<td><em>Modest VM efficacy (39-60%)</em></td>
<td><em>Untested RM efficacy</em></td>
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<tr>
<td>High adherence burden</td>
<td>Reduced adherence burden</td>
<td>Reduced adherence burden</td>
</tr>
<tr>
<td>New behaviors</td>
<td>New behaviors</td>
<td>New behaviors</td>
</tr>
<tr>
<td>RVI &amp; RAI coverage</td>
<td>Site specific coverage</td>
<td>Site specific coverage (MSM/TGW)</td>
</tr>
<tr>
<td>Days to protection</td>
<td>Hours to protection</td>
<td>Hour to 1 dose protection</td>
</tr>
<tr>
<td>Short PK tail</td>
<td>Short PK tail</td>
<td>Short PK tail</td>
</tr>
<tr>
<td>Systemic toxicity</td>
<td>Reduced systemic toxicity</td>
<td>Reduced systemic toxicity</td>
</tr>
<tr>
<td>Minimal local toxicity</td>
<td>Local toxicity inapparent?*</td>
<td>Better sex/No toxicity</td>
</tr>
<tr>
<td>Modest system burden</td>
<td>Low HCS burden</td>
<td>Low HCS burden</td>
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<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
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</tr>
<tr>
<td><em>Untested efficacy</em></td>
<td>Modest VM efficacy (27-75%)</td>
<td></td>
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<tr>
<td>Reduced adherence burden</td>
<td>Reduced adherence burden</td>
<td>Reduced adherence burden</td>
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<td>New behaviors</td>
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<td>New behaviors</td>
</tr>
<tr>
<td>RVI &amp; RAI coverage</td>
<td>Site specific coverage</td>
<td>Site specific coverage</td>
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<tr>
<td>Days to protection (ex. bnAbs)</td>
<td>Days to protection</td>
<td>Days to protection</td>
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<tr>
<td>Long PK tail</td>
<td>Short PK tail</td>
<td>Short PK tail</td>
</tr>
<tr>
<td>Systemic toxicity</td>
<td>Reduced systemic toxicity</td>
<td>Reduced systemic toxicity</td>
</tr>
<tr>
<td>Incision/injection site reaction</td>
<td>Local toxicity inapparent</td>
<td>Local toxicity inapparent</td>
</tr>
<tr>
<td>Increased HCS burden (IM/IV, AEs)</td>
<td>Low HCS burden</td>
<td>Low HCS burden</td>
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</tbody>
</table>

**Key**
- Pros
- Intermed/Conditional
- Cons

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Keller M, et al. CROI 1059LB
Vaginal Microbicide Formulations
Pod-IVR Design

- Up to 10 Polymer-coated drug “pods”
- Un-medicated ring holds the pods
- Channels control release rate
- Flexible drug combinations unlike matrix or reservoir rings
- Phase I TDF-FTC-MVC Pod-IVR
  - Well-tolerated
  - No toxicity
  - PK targets achieved
  - *rectal fluid FTC & MVC > in vitro IC₅₀
- Contraceptive/ARV MPT pre-clinical

IP/CP-HTM U19 Oakcrest Institute of Science; *Vincent K, PLOS Med, PLOS One 2018
Fast-Dissolve Vaginal Film

- **Dapivirine Film**
  - Acceptable
  - Low AE profile
  - Explant protection \((ss > \text{single dose})\)

- **Tenofovir Film**
  - Acceptable
  - Low AE profile
  - Explant protection \((ss > \text{single dose})\)
  - 5 hr tissue TFV-DP > Css oral TDF

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**Cervical Tissue Homogenate**

**Ex vivo HIV Tissue Challenge**

- FAME U19: Bunge JAIDS 2016, Bunge (in review), Robinson ARHR 2016, Robinson ARHR 2018
Fast-Dissolving Vaginal Inserts (Tablets)

- In Development by CONRAD & MTN
- Small and easy to store
- On demand, though not behaviorally-congruent
- Inexpensive
- APIs: TFV, FTC, elvitegravir
- Preclinical animal testing
  - TFV & FTC prototype in rabbits similar PK compared to gel formulation
  - No safety issues identified
- Vaginal & rectal clinical trials of TFV/elvitegravir insert 2018
Multipurpose Prevention Technologies

- HIV & Other STI* +/or Contraception
- Complicated design, development, & partnerships
- Balances
  - limiting attributes of each optimized single drug platform
  - Improved adherence with one device, two purposes
- Product pipeline (22 products)
  - Intravaginal ring – 4 pregnancy, 5 STI
  - Vaginal Gels – 3 pregnancy, 4 STI
  - Vaginal films – 2 STI
  - Fast dissolve insert – 3 STI
  - Barrier - 1 pregnancy/STI

*Most STIs are HIV in combination with HSV-2 +/or HPV, 2 products also cover chlamydia
Rectal Microbicide Formulations
Tenofovir Microbicide Development

**Methods/Vehicle Development**
- "HIV" surrogate distribution?
- Tissue pharmacology?
- Luminal distribution?
- Vaginal product optimization?
- PD Surrogate: Explant, BLT, NHP?

**Drug Product Development**
- Vaginal Formulation (VF)
  - 3,111 mOsm/kg
  - TFV 1%

**Phase I**
- HPTN 050
  - PK blood
  - AEs, culposcopy

**Phase II**
- HPTN 059
  - PK blood
  - AEs

**Phase III**
- CAPRISA 004 BAT 24
- VOICE QD
- FACTS 001 BAT 24

"HIV" surrogate distribution?
# Tenofovir Microbicide Development

## Methods/Vehicle Development

<table>
<thead>
<tr>
<th>Method/Vehicle Development</th>
<th>Development</th>
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<tbody>
<tr>
<td>JHU</td>
<td>“HIV” surrogate distribution</td>
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<tr>
<td>JHU</td>
<td>Tissue pharmacology</td>
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<tr>
<td>CDC/NIH</td>
<td>Luminal PK-D imaging</td>
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<tr>
<td>NIH</td>
<td>PD Surrogates: Explant, BLT, NHP</td>
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<tr>
<td>MDP 2/2b</td>
<td>RF vehicle development</td>
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<tr>
<td>MDP 1</td>
<td>Enema vehicle development</td>
</tr>
<tr>
<td>JHU</td>
<td>Lube dosing feasibility</td>
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</tbody>
</table>

## Drug Product Development

### Vaginal Formulation (VF)
- **Composition**: 3,111 mOsm/kg, TFV 1%
- **Phase I**: HPTN 050 PK blood, AEs, culposcopy
- **Phase II**: HPTN 059 PK blood AEs
- **Phase III**: CAPRISA 004 BAT 24, VOICE QD, FACTS 001 BAT 24

### Reduced Glycerin (RGVF)
- **Composition**: 836 mOsm/kg, TFV 1%
- **Phase I**: RMP-02/MTN-006 PK blood/tissue, AEs, flow, histology
- **Phase II**: MTN-007 AE, flow, ‘omics no PK
- **Phase III**: MTN-017 Safety, Adherence PK Acceptability

### Rectal Formulation (RF)
- **Composition**: 479 mOsm/kg, TFV 1%
- **Phase I**: CHARM 01/02 VF, RGVF, RF PK blood/tissue, imaging, SURAI ex vivo PD, microbiome AE, histology, flow, permeability Acceptability
- **Phase II**: MTN-007 Safety, Adherence PK Acceptability
- **Phase III**: No Phase III • Applicator • (Safety)

### Enema Formulation (EF)
- **Dose escalation**: Iso- or hypo-osmolar
- **Phase I**: DREAM 01/02 Dose escalation PK blood/tissue, imaging, SURAI AE, histology, ‘omics ex vivo PD Acceptability
- **Phase II**: No Phase II • Safety
- **Phase III**: No Phase III • Applicator • (Safety)

## Future RCT?
- **On Demand Lube**: Phase II ? TFV 10% RF Lube PK, Safety, Accept
- **On Demand Douche**: Phase II ? TFV Douche Safety/Accept
Is Formulation as Lube or Douche Feasible?

- **Douche**: Saline-like 125 mL
- **Applicator Gel**: HEC 10 mL
- **Manual Lube Application**: Wet™ 10 mL

- How much product is delivered?
- Where is the gel distributed?
Is Formulation as Lube or Douche Feasible?

- **Douche**
  - Saline-like 125 mL
  - Intraluminal
  - Retention: 60%
  - Distribution: 60 cm

- **Applicator Gel**
  - HEC 10 mL
  - Intraluminal
  - 95%
  - 5.9–7.4 cm

- **Manual Lube Application**
  - Wet™ 10 mL
  - Intraluminal
  - Extracorporeal
  - 10% (of 3.5 mL gel)
  - 4.4–15.3 cm
**DREAM Program**

**On Demand, Behaviorally-Congruent TFV Douche**

- **Grindr Survey 4,751 took survey (2017)**
  - 78% RAI last 3 months; 80% douche before RAI
  - Likelihood of using effective douche: currently douche 98%; not currently douche 94%; tops supportive of partner douching 95%

- **Pre-clinical comparison of prodrugs not superior to TFV**

- **Clinical single ascending dose study**
  - 18 MSM, 3 products, 6-fold dose range
  - No symptoms or histologic toxicity
  - Highly acceptable including take home doses
  - Douche 100-1,000x greater colon cell TFV-DP in 1-3hrs vs. steady-state daily TDF
  - Prevents ex vivo HIV challenge of colon tissue
  - Same tissue concentrations as macaque

- **Macaque Rectal SHIV challenge**
  - Oral TDF vs. Rectal TFV douche: Surprising results (Villinger CROI 1060LB)
# Rectal Product Role & Timeline

<table>
<thead>
<tr>
<th>Active Drug</th>
<th>Gel w/ Applicator</th>
<th>Gel as Lube</th>
<th>Douche</th>
<th>Insert</th>
<th>Suppository</th>
<th>All Complete By 2019</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓ MTN-035</td>
<td>MTN-035</td>
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<td>✓ ✓</td>
<td>DREAM-01</td>
<td>MTN-035</td>
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<td>Behaviorally-Congruent</td>
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<td>Dapivirine</td>
<td>MTN-026 12/18</td>
<td>MTN-033 01/19</td>
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<tr>
<td>Maraviroc</td>
<td>✓</td>
<td>✓ ✓</td>
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<tr>
<td>MIV-150/Zn/CG</td>
<td>**MTN-037 09/19</td>
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<td>Vaginal &amp; Rectal</td>
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<td>Elvitegravir</td>
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<td>✓ ✓</td>
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<td>MTN-039 08/19</td>
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<td>IQP-0528</td>
<td>ImQuest 02 12/18</td>
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<td>Multi-Purpose STI &amp; HIV</td>
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<tr>
<td>Griffithsin</td>
<td>**PREVENT 2019</td>
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*McGowan CROI Abstract 481; **Also vaginal development
Vaginal Lube & Douche Feasibility?

- Product attribute preferences & Sex-related Product Use Survey
- Female Sex workers in Northern Mexico (Ciudad Juarez, Tijuana)
- Product attribute assessment using conjoint analysis
  - Site specific preferences for pills vs. balanced pills & gels
  - Gels preferred at site with greater vaginal lube use
  - Monthly products preferred
- Peri-sexual Product Use
  - Vaginal washing 56% and 22% of participants
  - Vaginal lubrication 64% and 45% of participants
- Conclusions
  - Oral and behaviorally-congruent vaginal PrEP products may facilitate uptake and ensure sufficient coverage among FSWs
  - MPT lube & douche (hygiene, lubrication, HIV prevention) may be acceptable in this FSW population, but also vary regionally

Pines H, et al. UCSD (In review)
Long-Acting Formulations
Cabotegravir-LA

- **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 PrEP one month lead-in to rule out toxicity
- Long period of low drug concentrations ("PK Tail")
  - Below [protective] for one year or more (longer in women)
  - Oral PrEP one year to protect from resistance if HIV infection
HPTN 077 Cabotegravir PK

Cohort 1 Injection 800 mg CAB-LA every 3 months

- 8x PA-IC$_{90}$
- 4x PA-IC$_{90}$
- 1x PA-IC$_{90}$

Cohort 2 Injection 600 mg CAB-LA every 2 months

- 8x PA-IC$_{90}$
- 4x PA-IC$_{90}$
- 1x PA-IC$_{90}$
HPTN 077 Injection Site Reactions (ISR)

ISR
- 60-80% any grade
- 20-40% mod-severe
HPTN 083 & 084 Study Schema

Blinded Injections & Safety Visits

- CAB LA 600 mg IM at Weeks 5, 9, and Q8 Weeks thereafter Plus Daily Oral Placebo for TDF/FTC
- Daily Oral TDF/FTC Plus Placebo for CAB LA IM at Weeks 5, 9, and Q8 Weeks thereafter

Key:
- Cabotegravir oral
- TDF/FTC oral
- Cabotegravir injection
- TDF/FTC placebo
- Cabotegravir placebo injection

Enrollment
Screening
Arm A
Arm B

Step 1: Oral Phase
Step 2: Injection/Oral Phase
Step 3: Open Label Follow Up
Subdermal Implant Designs

- Oak Crest (removable)
- RTI (biodegradable)
- SLAP-HIV (removable)

Courtesy Marc M. Baum, Oak Crest Institute of Science; Gunawardana et al., AAC, 2015; Ariane van der Straten LEAP 2018; Thomas Hope SLAP-HIV.
Broadly Neutralizing Monoclonal Antibodies

- Neutralize virus & recruit effector cells to kill HIV infected cells
- Rare “elite” neutralizers: evolve nAbs broadly neutralize across clades
- Engineering improvements – increase coverage, potency, and half-life
  - Passive immunoglobulin low potency, narrow breadth
  - Early bnMAbs (from elite neutralizers) increase potency & breadth
  - Combinations broadens coverage
  - FcRn substitution increases half-life
  - Increased potency = SC vs. IV infusion
- Transiently reduces VL (VRC01)
- Prevention
  - SHIV vaginal/rectal protection NHP
  - AMP Clinical Trials

Sok D. Immunity 2016;45(5):958-960 (Figure 1)
Antibody Mediated Prevention (AMP) Study

- Phase 2b (not 3) safety & efficacy of VRC01 IV infusion q8w
- Goals:
  - Bridge to other types of bnAbs and other bnAb delivery systems
  - Identify antibody concentration-response thresholds for future development
- Design
  - Double-blind, randomized: 10 mg/kg VRC01: 30 mg/kg VRC01: placebo x 24m
  - High dose trough (10ug/mL) between 72% to 90% strain coverage
  - TDF/FTC PrEP available (by referral, not prescribed, not required)
- Subjects
  - HVTN704/HPTN085 – 2,700 HIV- MSM and TG (W&M), sex with men or TG
  - HVTN703/HPTN081 – 1,500 HIV- heterosexual women
- Statistics
  - 90% power to detect 60% prevention efficacy
  - assumes 3% placebo background HIV incidence (including PrEP use)
Topical & Long-Acting PrEP Formulations

- **Vaginal Microbicides**
  - Vaginal gel & IVR underperformed in RCT
  - Novel formulations enhance adherence (?) – MPT IVR, film, insert, lube, douche
  - Uncertain role anal sex, CV conc’n targets, systemic concentration, microbiome
  - Commercial partners?

- **Rectal Microbicides**
  - 6 ARVs, 4 formulations currently in development
  - Behaviorally-congruent strategies - lube feasible?, douche widely acceptable?
  - Uncertain rectal tissue concentration target,
  - Commercial partners?

- **Long-Acting**
  - Injectables – in clinical trials, limitations AEs, oral lead-in, long tail
  - Infusion bnMAbs – similar dosing to injectables, less AEs, less resistance issue, COST
  - Implantables – less frequent dosing, some retrievable, pre-clinical development
Acknowledgements

- Funders - NIH/DAIDS (MTN, HPTN, IP/CP-HTM), CDC, USAID, Gates
- Drug Development Unit, JHU
- Clinical Pharmacology Analytical Laboratory, JHU
- Peter Anton, UCLA
- Ian McGowan, University of Pittsburgh
- Raphael Landovitz, UCLA
- Bill Spreen & Parul Patel, ViiV/GSK
- Ariane van der Straten, Research Triangle Institute
- Marc Baum, Oak Crest Institute of Science
- Thomas Hope & Pat Kiser, Northwestern University
Thank You
Formulation PK Profiles Compared

- Upper Target (safety)
- Lower Target (efficacy)
- SC or IM Injection
- Implantable & IVR
- Oral intermittent
- On demand topical

Modified, Courtesy Ariane van der Straten