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

Alternative Formulation Development
Current Status: Alternative Formulations

• “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

• 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  – Rilpivirine (withdrawn from PrEP development)

• 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)

• 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

- Upper Target (safety)
- Lower Target (efficacy)
- SC or IM Injection
- Implantable & IVR
- Oral Dosing

Plasma Concentration vs. Day

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%)
  - 2º 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 2º transportation, cost

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

Cohort 1 Injection every 3 months

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

Cohort 2 Injection every 2 months

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

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

**Blinded Injections & Safety Visits**

- **Arm A**
  - CAB LA 600 mg IM at Weeks 5, 9, and Q8 Weeks thereafter Plus Daily Oral Placebo for TDF/FTC
  - Step 1: Oral Phase

- **Arm B**
  - Daily Oral TDF/FTC Plus Placebo for CAB LA IM at Weeks 5, 9, and Q8 Weeks thereafter
  - Step 2: Injection/Oral Phase

- **Open Label Follow Up**

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

Injections: Every 8 weeks
Safety visits: Two weeks after each injection

Weeks: 0, 12, 24, 36, 48, 72, 108, 144, 180, 216, 252

= Week 187
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  - 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, $C_{\text{trough}}$

  ![Diagram showing concentration comparisons between Tenofovir and Cabotegravir-LA in different compartments (Blood, Colorectal Tissue, Colorectal Lumen) for Rectal, Oral, and IM administration.]

- **Colorectal active conc’n:** $\text{CAB } 40x < \text{ oral TDF } & \text{ 1,000x } < \text{ rectal TFV}$
Tenofovir vs. Cabotegravir-LA: RVI

• Active ARV Concentrations Compared
  – Reference for comparison (1x): treatment dose blood (or PBMC) concentration, $C_{\text{trough}}$

$$\begin{align*}
\text{Tenofovir} & \quad \text{Cabotegravir} \\
\text{Vaginal} & \quad 0.1x \quad 1x \\
\text{Oral} & \quad 1x \quad 0.6x \\
\text{IM} & \quad 1x \quad 0.2x
\end{align*}$$

• Cervicovaginal active conc’n: $\text{CAB 3x < oral TDV} \quad \& \quad 500x < \text{vaginal TFV}$
• 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

- 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

> 500 fmol/10^6 cells (first 35 days)

Daily Oral peak concentration TFV plasma

Gunawardana et al., AAC, 2015.
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

**Formulated drug core**

**Thin-film polymer membrane**

**Dissolved drug** (saturated)

**Biological fluid in**

**Dissolved drug out**

Compatibility with Existing Trocars

- Implanon
- Jadelle

Courtesy Ariane van der Straten
TAF TFPD: In vitro & Rabbit Studies

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

Durham PG, et al. CROI 2017 Abstract 420

- 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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