A Big Year for New HIV Prevention Choices

Craig W. Hendrix, MD
Wellcome Professor and Director, Division of Clinical Pharmacology
Departments of Medicine and Pharmacology
Johns Hopkins University, Baltimore, MD

This activity is jointly provided by Physicians’ Research Network and the Medical Society of the State of New York.
Disclosures

- **Research grants**: Gates, ViiV/GSK, Merck, & Gilead managed by JHU
- **Advisory Board**: Population Council, RTI, PREVENT Program, Gilead, Merck, ViiV/GSK, Orion Biopharma
- **Founding Partner** Priönde Biopharma, LLC
- **US Patent** 10,092,509 microbicide formulations
HIV Prevention Milestones in One Year!

- FDA approves oral F/TAF for MSM/TGW
  - Gilead commits to F/TAF PrEP RCT for cisgender women

- Cabotegravir long-acting injectable formulation
  - HPTN 083 DSMB stopped early for non-inferiority
  - Full analysis CAB-LA demonstrates superiority over oral daily F/TDF

- Dapivirine vaginal ring
  - EMA “positive scientific opinion” public health
  - Opens the door for rapid regulatory approval in LMIC

- HIV Vaccine (RV144 Clade C modification)
  - HVTN 702 DSMB stopped early for futility
Objectives

- Describe the limitations to PrEP impact
- Describe the benefits of choice to PrEP products
- Discuss ongoing development of long-acting PrEP
- Discuss ongoing development of on demand PrEP
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### HIV Prevention Need

- **New HIV infections continue each year (~40K US)**
  - Globally 2.7 million - US ~40 thousand

![Bar Chart](chart.png)

- Receptive partner lacks prevention control
- Treatment expensive, not curative
- Vaccine prevention distant
- **Condoms**
  - Effective, but not often used
  - Receptive partners lack control
  - Require behavioral change
HIV Prevention Strategies

DECREASE SOURCE OF INFECTION
(TasP, treatment as prevention)

DECREASE HOST SUSCEPTIBILITY
(PrEP, pre-exposure prophylaxis; Vaccine)

ALTER RISK-TAKING BEHAVIOR
(Most challenging, least understood)
**TDF + FTC* is Effective for HIV PrEP**

- **Partners**
  - Discordant Heterosexual Couples: N= 4,758

- **CDC Bangkok**
  - PWID: N=2,413

- **iPrEx**
  - MSM & TGW: N=2,499

- **CDC TDF2**
  - Heterosexual Cis Men & Women: N=1,219

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*TDF tenofovir disoproxil fumarate, FTC Emtricitabine, RRR relative risk reduction, PWID persons who inject drugs

Clockwise from upper left: Baeten NEJM 2012; Grant NEJM 2010; Thigpen NEJM 2012; Choopanya Lancet 2013
“Substantial” or “High Risk” of HIV infection

- FDA - combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk (Truvada™ Package insert 2012)

- CDC - one prevention option for sexually-active adults & IDU at substantial risk of HIV acquisition (IA, USPHS Clinical Practice Guidelines – 2014)

<table>
<thead>
<tr>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
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<tr>
<td>Detecting substantial risk of acquiring HIV infection</td>
<td>HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work</td>
<td>HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work In high-prevalence area or network</td>
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<tr>
<td>HIV-positive injecting partner Sharing injection equipment Recent drug treatment (but currently injecting)</td>
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<td></td>
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</table>

- WHO - additional prevention choice for people at substantial risk (>3/100 py) of HIV infection as part of combination HIV prevention approaches
### MSM PrEP Effectiveness Models

#### Clinical Effectiveness (number needed to treat)

<table>
<thead>
<tr>
<th>HIV Prevalence</th>
<th>0.05</th>
<th>0.1</th>
<th>0.15</th>
<th>0.19</th>
<th>0.25</th>
<th>0.3</th>
<th>0.35</th>
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<th>0.45</th>
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<td>5</td>
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</table>

*Figure 2c: High PrEP adherence/efficacy: 92% relative risk reduction*

#### Cost-Effectiveness (thousands $US per QALY gained)

<table>
<thead>
<tr>
<th>HIV Prevalence</th>
<th>0.05</th>
<th>0.1</th>
<th>0.15</th>
<th>0.19</th>
<th>0.25</th>
<th>0.3</th>
<th>0.35</th>
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<td>Cost Saving</td>
<td>Cost Saving</td>
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<td>400</td>
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<td>Cost Saving</td>
<td>Cost Saving</td>
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<td>140</td>
<td>48</td>
<td>9</td>
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*Figure 2f: High PrEP adherence/efficacy: 92% relative risk reduction*

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Dowdy, et al. PLOS One 2014
<table>
<thead>
<tr>
<th>NNT</th>
<th>Drug</th>
<th>Condition/Duration</th>
<th>Outcome prevented</th>
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<td>Rhogam</td>
<td>Rh incompatibility</td>
<td>Prevent future pregnancy alloimmunization</td>
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<tr>
<td>8</td>
<td>Antibiotics</td>
<td>COPD exacerbation</td>
<td>Death</td>
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<tr>
<td>39</td>
<td>Statin</td>
<td>Known heart disease/5 yr</td>
<td>Stroke</td>
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<td>67</td>
<td>HTN meds</td>
<td>HTN/5 yr</td>
<td>MI</td>
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<td>77</td>
<td>Clopidogrel</td>
<td>MI or stroke history/1 yr</td>
<td>MI</td>
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<td>83</td>
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<td>HTN meds</td>
<td>HTN/5 yr</td>
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<td>MI</td>
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<td>200</td>
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<td>MI or stroke history/1 yr</td>
<td>Stroke</td>
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<td>333</td>
<td>Clopidogrel</td>
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<td>2000</td>
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<td>MI</td>
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<tr>
<td>3000</td>
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<td>No MI/Stroke history/1 yr</td>
<td>Death</td>
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</table>

NB, none benefitted. Source: [http://www.thennt.com](http://www.thennt.com)

HIV prevalence NNT with high adherence from Dowdy, et al. PLOS One 2014
POPULATION-LEVEL IMPACT

- New South Wales, Australia (*FIGURE*): PrEP associated with a 25% decrease in new HIV diagnoses among MSM

- United States: Diagnosis rate decreased by 1.3% for increase in PrEP coverage of 1 per 100 persons

- King County, WA: Reduced HIV incidence by 84% among MSM & transgender persons with STIs

Grulich et al. 2018; Smith et al. 2020; Pagkas-Bather et al. 2020

PrEP UPTAKE IN THE US

Global PrEP Uptake 2020


AVAC Global PrEP Initiation Tracker; avac.org. accessed September 2020
PrEP in Women

Sources of PrEP Failure

- Poor Adherence
  - Young, especially women
  - Repeatedly seen in demonstration projects
  - Complex risk perception, stigma, power, etc. …
  - Fear of systemic drug
  - Desire for multiple PrEP options

- Vaginal TFV (CAPRISA 004, VOICE, FACTS 001)
  - Dysbiotic flora degrades TFV
  - Vaginal ring & gel don’t protect anal sex

Marrazzo NEJM 2015; van Damme NEJM 2012; Klatt Science 2017; Justman JAIDS 2018;
## Impact of Adherence (PK-defined)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Variable</th>
<th>Method</th>
<th>iPrEx F/T Oral</th>
<th>Partners F/T Oral</th>
<th>CAPRISA TFV Gel</th>
<th>VOICE TFV Gel</th>
<th>ASPIRE DPV Ring</th>
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<td>Baeten Ruberman</td>
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<td>mITT</td>
<td>TMLE</td>
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<td>39 73</td>
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<td>15 70 55 64</td>
<td>6 8 29 2 44</td>
<td>1 51</td>
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<td>Upper 95%</td>
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<td>63 99 87 94</td>
<td>60 92 -31 84 100</td>
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<td>High Adherer PK Criterion</td>
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<td>NA 7/wk &gt;LLOQ</td>
<td>&gt;LLOQ CVF &gt;LLOQ All &gt;LLOQ</td>
<td>&gt;4 Residual</td>
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</tbody>
</table>
Oral F/TDF PrEP in Women

**Pregnant Women**
- HIV risk increased 2-4 times
- PrEP discontinued in RCTs during pregnancy (so, understudied)
- Partners Demo. Project (N=37) found 2x TFV conc’n reduction

**Transgender Women (TGW)**
- Two prospective DDI studies
  - F/TDF + gender affirming hormones (GAHT)
  - GAHT includes estrogen & anti-androgen
- Results
  - No effect of F/TDF on GAHT
  - 17-32% plasma TFV reduction by GAHT
  - 17-24% plasma FTC reduction by GAHT
- Impact
  - Concern for short “on demand” 2+1+1 regimen (proven effective in MSM)

<table>
<thead>
<tr>
<th>Population</th>
<th>% Below Protective Threshold</th>
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<tbody>
<tr>
<td></td>
<td>Standard Dose TDF/FTC</td>
</tr>
<tr>
<td>Non-pregnant</td>
<td>3.7%</td>
</tr>
<tr>
<td>1st Trimester</td>
<td>31.5%</td>
</tr>
<tr>
<td>2nd Trimester</td>
<td>47.2%</td>
</tr>
<tr>
<td>3rd Trimester</td>
<td>62.6%</td>
</tr>
</tbody>
</table>

DISCOVER: F/TAF vs. F/TDF

- **Efficacy**
  - F/TAF *non-inferior* to F/TDF
  - All failures w/ DBS <2/wk adherence
  - Few TGW (N=74, 1%, no failures)

- **Toxicity (Wk48 minor differences)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>TDF-FTC</th>
<th>TAF-FTC</th>
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</thead>
<tbody>
<tr>
<td>Mean estimated glomerular filtration rate, mL/min/1.73 m²</td>
<td>−2.0</td>
<td>+2.0</td>
</tr>
<tr>
<td>Mean hip bone mineral density, %</td>
<td>−1.0</td>
<td>+0.2</td>
</tr>
<tr>
<td>Median fasting low-density lipoprotein cholesterol level mmol/L</td>
<td>−0.17</td>
<td>+0.03</td>
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<tr>
<td></td>
<td>−6.5</td>
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</tr>
<tr>
<td>Mean body weight, kg</td>
<td>0</td>
<td>+1.1</td>
</tr>
</tbody>
</table>

**Cost**

- Average wholesale price per month, $ 2110 2110
- Year in which generic version will be available 2020 2022 to 2025

Wholesale acquisition cost 30-day supply: Teva $1,455, Gilead $1,600-$1,800

Mayer Lancet 2020; Krakower AIM 2020; FDA Briefing Document (AVAC F/TAF) August 19, 2019
Oral F/TDF PrEP in Cisgender Women

- **8/2019 FDA Advisory Committee**
  - FDA Brief: ...important to compare TFV-DP concentrations in the same mucosal tissues if bridging of efficacy between F/TDF and F/TAF is being proposed. Bridging of efficacy results from men to cisgender women based on mucosal tissue concentrations, however, is not possible because the effective drug concentrations could be different for rectal and vaginal HIV exposures.
  - Recommends F/TAF approval for MSM/TGW, not GCW

- **10/2019 FDA**
  - Post-marketing commitment in F/TAF PrEP approval

- **12/2019 Gilead**
  - Commitment to Phase 3 F/TAF PrEP RCT in women
  - Not listed yet in clinicaltrials.gov
Barriers to PrEP Uptake/Persistence/Impact

- Awareness of PrEP
- HIV Risk Perception
- Stigma
- Provider bias
- Healthcare System Distrust
- Access to Medical Care
- Lack of Access to Financial Assistance
- Side Effects
- Daily tablet dissatisfaction

Objectives

- Describe the limitations to PrEP impact
- Describe the benefits of choice to PrEP products
- Discuss ongoing development of long-acting PrEP
- Discuss ongoing development of on demand PrEP
CHOICE: Proven Benefit in Contraception

- WHO Systematic Review (231 articles)

- CHOICE associated with better:
  - Contraceptive *Uptake*
  - Contraceptive *Persistence*
  - Health outcomes (↓ pregnancies, ↓ STIs)

- CHOICE, as with needs, vary over a lifetime

- Why should PrEP be different?

- EACH add’l product option yields 12% increase in contraceptive use

- How much will it be for PrEP?

Gray AL, et al. WHO RHBU 2006

Jain AK, et al. Stud Fam Plan 1989
Many Factors Influence Choice

- **Effectiveness** does not drive all decision-making

- **Safety** similarly important

- **Convenience, other health benefits, control, privacy, etc.**, important, too
Womens’ PrEP Desires

VOICE-D (MTN-003-D): Luecke, JIAS 2016
Women’s Choice Matters

- Discrete Choice Study of Vaginal PrEP Products

Preference varies **Geographically**

![Bar chart showing preferences for different vaginal PrEP products in South Africa and Zimbabwe.]

- South Africa: Ring 28%, Insert 35%, Film 13%, Gel 25%
- Zimbabwe: Ring 29%, Insert 18%, Film 45%, Gel 8%

*Significantly different, p<0.05

Preference varies with **Experience**

![Graph showing average rank changes over time (Pre-Video, Post-Video, Post-Crossover).]

Most Preferred: Ring (N=51), Insert (N=47), Film (N=53), Gel (N=29)

Least Preferred: Gel, Ring, Insert, Film

Quatro: Elizabeth Montgomery OA05.04 HIVR4P 2018
Grindr Survey

Especially with sex product, Essential to build around user experience

- 4,751 Took Grindr Survey
  - 78% RAI last 3 months
    - 80% douche before RAI
    - 27% douche after RAI

Likely use microbicide douche (currently do not douche) 94%
Likely use microbicide douche (currently do not douche) 98%
Insertive partner supportive of RM douching partner 96%

Definitely Yes
Probably Yes
Supportive
Opposed

Generally much higher than similar survey research for vaginal products
Likely use stats replicated in Latin America & Africa

Alex Carballo-Dieguez, et al. AIDS Behav 2019 Jun;23(6):1484-1493; Giguere CROI 2020
More Formulation CHOICE, Better Adherence

Uptake/Persistence Challenges Motivate Alternative Formulation Development

Long-Acting Formulations
- Parenteral
- Oral
- Topical

Infrequent dosing to minimize need for adherence
Trade-off increased exposure for improved adherence

On Demand + Behaviorally Congruent
- Oral
- Topical

Reduced systemic exposure & minor behavior change
Objectives

- Describe the limitations to PrEP impact
- Describe the benefits of choice to PrEP products
- Discuss ongoing development of long-acting PrEP
- Discuss ongoing development of on demand PrEP
HIV Vaccine Setbacks

RV144: **31% RRR Low**

- Intention-to-Treat Analysis
  - No. at Risk:
    - Placebo: 8200, 7775, 7643, 7441, 7325
    - Vaccine: 8200, 7797, 7660, 7471, 7347
  - Cumulative No. of Infections:
    - Placebo: 32, 52, 67, 76
    - Vaccine: 17, 37, 50, 56

- Prime–Boost Vector + Protein
  - 4 priming recombinant canarypox vector (ALVAC-HIV)
  - 2 boosters of recombinant gp120 subunit vaccine (AIDSVAX B/E)

HVTN 502: **Enhancement**

- Enrollment: > 5400 across 14 sites
- 6 injections over 18 months
- Trial stopped FEB 2020 for futility
- No safety concerns

- Vector + Protein
  - MRKAd5 HIV-1 gag/pol/nef
  - 0, 1, 6 month schedule

HVTN 702: **Futility**

- Prime-Boost Vector + Protein
  - Recombinant canarypox vector ALVAC-HIV & 2-component gp120 protein subunit vaccine (for Clade C) with adjuvant (adjuvant & proteins modified from RV144)

---

Referenced:
- Buchbinder Lancet 2008 (HVTN 502)
- NIAID News Release Feb 3, 2020 (HVTN 702)
Long-Acting Dapivirine Vaginal Ring

- Vaginal Ring Design
  - Silicone matrix ring, 25 mg of dapivirine (NNRTI)
  - Monthly replacement, trivial systemic exposure

- Two phase III placebo-controlled trials
  - Well tolerated
  - Reduced HIV incidence ~30%
  - Greater protection (up to 85%) with high adherence

- OLEs High uptake, better adherence

- 90-day Ring in Development

- EMA favorable scientific review

Baeten, et al., ASPIRE & Nel, et al., The Ring Study (IPM) NEJM 2016; International Partnership for Microbicides (IPM)
Impact: Persistence - Adherence - Protection

1,2 Based on 12 month data; adherence > mod-high; 3 protection associated with mod adherence

Impact of Choice

Commentary

HIV Prevention: The Need for Methods Women Can Use

Zena A. Stein, MA, MB, BCCh

“...a less efficacious [method], frequently used, might serve the public health as well or better than a more efficacious, but less frequently used [method], and...play an important role in preventing transmission at the population level.”

(Am J Pub Health, 1990)
Dapvirine Ring Regulatory Status

- **IPM & MTN:**
  - Release The Ring Study & ASPIRE positive results (FEB 2016)
- **IPM: initiates Article 58 procedure (JUN 2017)**
  - EMA (with WHO) provides scientific opinion on safety, efficacy & quality of medicines marketed exclusively in LMIC for diseases of major public health interest
- **EMA:**
  - Announced a “positive benefit-risk opinion” (JUL 2020)
- **WHO:**
  - Guideline development & prequalification review
- **African Countries:**
  - parallel regulatory review
  - EMA’s Article 58 opinion recognized by many countries in Africa
  - IPM submitting to those countries through WHO-coordinated process
  - First submissions where ring studies took place
- **FDA NDA submission (late 2020)**
Pod-IVR: Flexible MPT Capability

- ≤10 Polymer-coated drug “pods”
- An un-medicated, torus-shaped elastomeric support holds the pods
- Release rate controlled through delivery channels size
- Flexible drug combinations unlike matrix of single reservoir rings
- MPT (contraception/ARV) pre-clinical
- Clinical studies one month IVRs

Marc Baum & John Moss, Oakcrest Institute of Science
Multipurpose Prevention Technologies (MPT)

- **Concept:**
  - Many women at risk of HIV also want family planning
  - Why not combine HIV prevention with contraception?
  - Improve adherence with single product

- **MPT IVRs – phase I / early phase II**
  - Tenofovir / levonorgestrol ring (CONRAD)
  - Dapivirine / levonorgestrol ring (IPM, MTN044/IPM-053/CCN019)
  - Pod-IVRs ARVs / contraceptive / α-STI (Oak Crest Institute of Science)

- **Development trade-offs:**
  - Combination requires compromise, e.g., duration
Cabotegravir-LA Nanosuspension PrEP

- **Goal:** Provide *alternative to oral daily PrEP*

- HIV InSTI
  - Similar to Dolutegravir (proven effective HIV treatment)
  - 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 one year* to protect from resistance if HIV infection
HPTN 083 Study Design

**STEP 1**
- Group A: Every day for 5 weeks - CAB
- Group B: CAB

**STEP 2**
- Weeks 5 and 9: TDF/FTC
  - (Every day)

**STEP 3**
- Every day for 1 year: TDF/FTC

Landovitz RJ et al. AIDS 2020, #OAXLB0101
Long PK Tail CAB-LA (HPTN 077)

Median time to <1x PAIC_{90}: Men ~36 weeks, Women ~44 weeks
Median time to < LLOQ: Men ~68 weeks, Women ~76 weeks:

HIV Incidence

52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY

HIV Incidence

<table>
<thead>
<tr>
<th></th>
<th>CAB</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2244</td>
<td>2250</td>
</tr>
<tr>
<td>13 Infections</td>
<td>3202 PY</td>
<td>3187 PY</td>
</tr>
<tr>
<td>39 Infections</td>
<td>1.22</td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Favors CAB</th>
<th>Favors TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>0.34</td>
<td>0.18</td>
</tr>
<tr>
<td>Superiority</td>
<td>1.4 (IQR 0.8-1.9) years median per-participant follow-up</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval

Landovitz RJ et al. AIDS 2020, #OAXLB0101
Injection Site Reactions

- **Significantly more frequent & increased severity vs. placebo injection**
- **ISR severity & discontinuation strongly associated**
- **Few CAB ppts. (2.2%) permanently discontinued due to injection-related AE**

Landovitz RJ et al. AIDS 2020, #OAXLB0101
## Grade 2+ Adverse Events (≥5%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>TOTAL (n=4566)</th>
<th>TDF-FTC (n=2284)</th>
<th>CAB (n=2282)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with grade 2+ AEs, n (%)</td>
<td>4202 (92.1%)</td>
<td>2106 (92.3%)</td>
<td>2096 (91.9%)</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance decreased</td>
<td>3204 (70.2%)</td>
<td>1642 (72.0%)</td>
<td>1562 (68.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>CPK increased</td>
<td>937 (20.5%)</td>
<td>460 (20.2%)</td>
<td>477 (20.9%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>828 (18.1%)</td>
<td>388 (17.0%)</td>
<td>440 (19.3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>775 (17.0%)</td>
<td>412 (18.1%)</td>
<td>363 (15.9%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>510 (11.2%)</td>
<td>255 (11.2%)</td>
<td>255 (11.2%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Musculoskeletal discomfort</td>
<td>507 (11.1%)</td>
<td>253 (11.1%)</td>
<td>254 (11.1%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>495 (10.9%)</td>
<td>252 (11.0%)</td>
<td>243 (10.7%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Headache</td>
<td>448 (9.8%)</td>
<td>216 (9.5%)</td>
<td>232 (10.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>AST/SGOT increased</td>
<td>382 (8.4%)</td>
<td>197 (8.6%)</td>
<td>185 (8.1%)</td>
<td>0.53</td>
</tr>
<tr>
<td>ALT/SGPT increased</td>
<td>347 (7.6%)</td>
<td>191 (8.4%)</td>
<td>156 (6.8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>323 (7.1%)</td>
<td>117 (5.1%)</td>
<td>206 (9.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>316 (6.9%)</td>
<td>166 (7.3%)</td>
<td>150 (6.6%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>306 (6.7%)</td>
<td>158 (6.9%)</td>
<td>148 (6.5%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Rash</td>
<td>253 (5.5%)</td>
<td>139 (6.1%)</td>
<td>114 (5.0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>241 (5.3%)</td>
<td>123 (5.4%)</td>
<td>118 (5.2%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>181 (4.0%)</td>
<td>60 (2.6%)</td>
<td>121 (5.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*70% of pyrexia events in CAB were within 7 days of an injection (event probability 0.65%)
16% of pyrexia events in TDF/FTC were within 7 days of an injection (event probability 0.05%)

Landovitz RJ et al. AIDS 2020, #OAXLB0101
Implantable ARV-Eluting Devices

- Sustained release of PrEP drugs with constant release over time
- User-independent, subcutaneous implant
- Biodegradable
- Compatible with existing contraceptive implant trocar applicators

Compatibility with Existing Trocars

- Implanon
- Jadelle

Courtesy Marc Baum & Ariane van der Straten
**Islatravir Oral & Implantable Formulations**

- Multiple mechanisms of action
- Good safety profile oral & implantable
- Pharmacokinetics
  - PBMC ISL-TP $t_{1/2}$ 120-177 hr
  - ISL-TP rectal & vaginal tissue similar to PBMC
- Pharmacodynamics
  - Monotherapy antiviral effect NHP & clinical
  - Target 0.05 pmol/10^6 cells (NHP & clinical Rx)
  - In vitro WT IC$_{50}$ ~0.01 pmol/10^6 cells
  - 0.05 pmol/10^6 cells > in vitro IC$_{50}$ M184I/V
  - *Likely monthly oral (& yearly implantable)*

Matthews R, et al. IAS 2019; data courtesy Merck (R. Matthews)
Objectives

- Describe the limitations to PrEP impact
- Describe the benefits of choice to PrEP products
- Discuss ongoing development of long-acting PrEP
- Discuss ongoing development of on demand PrEP
On Demand Oral

- **Ipergay – Effective**
  - RCT On demand 2+1+1
    - 2 TDF-FTC 2 - 24 hours before sex
    - 3rd 24 hours after the first dose
    - 4th 24 hours after the 3rd
  - 40% < weekly dosing

- **Prevenir – Popular**
  - Open label
  - Ppts select on demand (54%) or daily (45%)
  - Acquisition Risk 0 (95%CI 0.0, 0.7) & 0 (0.0, 0.8), no infections in 506 & 443 PY, respectively

- Molina NEJM 2015; Molina IAS 2018
On Demand Topical

- CAPRISA 004 TFV Vaginal Gel – Highly effective when used

mITT Analysis

PK-Adjusted Log Reg – 73% RRR

On Demand & Behaviorally-Congruent PrEP

- Behaviorally-congruent medicates product already in common use
- Common health fortification of existing products
  - Fluoridated water & toothpaste; vitamin fortified bread & milk
- PrEP-medicated Sexual Lubricants
  - Very high levels (>85%) of sexual lubricant use among MSM
  - Modest levels among women, but higher among FSW (>60%)
- PrEP-medicated Douches
  - High levels of anal douching among MSM (>80%)
  - Not well studied among women, but modest to high among FSW (22-56%)
- On Demand Advantages
  - Do not require learning an entirely new PrEP taking behavior
  - Very high local tissue & very low systemic levels of ARVs
Anal Lube or Douche as Microbicide

- **Douche**
  - Saline-like 125 mL

- **Gel - Applicator**
  - HEC 10 mL

- **Lube**
  - Wet™ 10 mL

- How much product is delivered?
- Where is the gel distributed?
Anal Lube or Douche as Microbicide

**Douche**
Saline-like 125 mL

**Gel - Applicator**
HEC 10 mL

**Lube**
Wet™ 10 mL

- Retention: 60%
- Distribution: 60 cm
- Retention: 95%
  Distribution: 5.9–7.4 cm
- Retention: 10% (3.5 mL gel)
  Distribution: 4.4–15.3 cm
  (requires 10x [API] increase)
Rectal Douche as Microbicide

**Human: Colon Cell TFV-DP**
- High dose exceeds **Target** >30x @ 1h, >100x @ 3h
- High dose exceeds target x 4 days (~Ipergay 2+1+1)
- Plasma $C_{max}$ 5x < daily oral $C_{tau}$

**Macaque: Rectal SHIV Challenge**

Daily Oral F/TDF vs. Single Douche 1 hr before SHIV

- High dose douche superior to daily oral F/TDF

Objectives

- Describe the limitations to PrEP impact
- Describe the benefits of choice to PrEP products
- Discuss ongoing development of long-acting PrEP
- Discuss ongoing development of on demand PrEP
Questions?
Thank You for Your Attendance!

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