CROI Update on Bio-Behavioral HIV Prevention
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Disclosures

Gilead Sciences – Research grants, scientific advisory committee
Merck – Research grants, scientific advisory committee
Janssen – HIV vaccine studies
HIV tests determine the next prevention step, PrEP or HIV treatment.

86% of people with HIV know they have it. TARGET: 95%

PREVENT
People without HIV, but at risk for it, can take PrEP as prescribed to prevent getting HIV.

HAVE PREP PRESCRIPTION
18% 18%
TARGET 50%

TREAT
People who know they have HIV should take medicine daily to control the virus.

HAVE HIV UNDER CONTROL
63% 63%
TARGET 95%
Rapid Start in Young People With HIV in New Orleans

- Rapid ART initiation improves linkage to care and viral suppression\(^{1-3}\); younger PWH have lower rates of both than older people with HIV\(^4\)

- Current study compared viral suppression and retention in care in newly diagnosed young vs adult people with HIV initiating rapid ART at Rapid ART initiation in adults (≥ 25 yrs) and young persons (18-24 yrs) within 72 hrs of diagnosis at CrescentCare, a CHC in New Orleans\(^5\)

- 97.6% of patients achieved viral suppression, which was rapid in both age groups
  - Median time to suppression in adults: 28 days
  - Median time to suppression in young persons: 29 days

PrEP and AHI screening at the TRC Anonymous Clinic

TRC PrEP-15 clients: cumulative number

RV254/SEARCH010
Acute infection cohort with early ART

Real-time screening of 371,994 samples in Thailand

Acute HIV infection (n=632 enrolled/809 detected)

Immediate ART (n=632)

Through 31-December-2019

Pooled Qual. HIV RNA (Aptima) on all HIV Ab NR samples
Starting PrEP during AHI and risk for HIV resistance at the TRCAC

• ~ 1/350 PrEP users have AHI at PrEP initiation
• Screening for AHI with pooled qualitative HIV RNA tests can detect most, but not all AHI prior to starting PrEP
• The risk for development of new drug resistance mutations increases with time on PrEP
  – <= 15 days has a low risk for DRM
  – >4 weeks has a high risk for DRM
• The most common DRM: M184I/V
• There is a low risk for resistance to TDF when PrEP is taken for < 5 weeks
DISCOVER: Study Design

- International, randomized, double-blind, active-controlled phase III trial

- Prevention services (eg, risk reduction, condoms/lubricant) and adherence counseling provided at entry and every 12 wks

- Endpoints of current analysis: safety, including renal AEs and biomarkers, bone fractures, BMD, and metabolic parameters at Wk 96

HIV and HBV-negative cis-MSM and transgender women at high risk of HIV* with eGFR ≥ 60 mL/min; previous PrEP use permitted (N = 5387)

*Condomless anal sex ≥ 2 times with ≥ 2 unique partners in past 12 wks or rectal gonorrhea, rectal chlamydia, or syphilis in past 24 wks.


Slide credit: clinicaloptions.com
Discover: Conclusions at 96 weeks

- FTC/TAF noninferior to FTC/TDF for preventing HIV infection in cis-MSM and transgender women at high risk of HIV acquisition through 96 wks
  - Wk 96 HIV incidence: 0.16/100 PY vs 0.30/100 PY (IRR: 0.54; 95% CI: 0.23-1.26)
- Both regimens well tolerated with low rates of discontinuation for AEs (1% to 2%)
- FTC/TAF associated with significantly more favorable renal and bone safety outcomes vs FTC/TDF
  - More favorable hip and spine BMD changes through Wk 96 ($P < .001$)
  - More favorable eGFR_{CG} changes in overall population, participants aged $\geq 50$ yrs, and participants with BL CrCl 60 to $\leq 90$ mL/min ($P < .001$ for PrEP regimen comparison in each group)
- Impact on lipids differed between arms, with greater decrease in total, LDL, HDL cholesterol, and triglycerides with FTC/TDF ($P < .001$)
- Weight gain and BMI increases significantly higher with FTC/TAF ($P < .001$)

Conclusions: Black and Latinx Pts (N=1831), 9% Black, 25% Latinx

- The HIV incidence rate was low in Black and H/Lx participants on PrEP in DISCOVER, and was similar in the F/TAF and F/TDF arms.
- Adherence to study drug was high in all groups; however, more Black participants had medium or low adherence vs non-Black participants.
- Study drug-related TEAEs were similar between groups.
- eGFR changes were more favorable in the F/TAF arm, including Black and H/Lx participants.
- Black and H/Lx participants taking F/TAF had either increases or less declines in BMD than those taking F/TDF.
- Black and H/Lx participants taking F/TAF had stable LDL and HDL cholesterol, whereas those taking F/TDF had proportional declines in LDL and HDL.
- Weight increases occurred in Black and H/Lx participants in both arms, and were 0.8–1.1 kg greater in those taking F/TAF.
Conclusions: Transgender women (N=54)

- The majority of transwomen in DISCOVER were taking gender-affirming hormones
- No transwomen in DISCOVER acquired HIV infection
- Safety outcomes in transwomen taking F/TDF and F/TAF were similar to those observed in MSM
- Intracellular PBMC concentrations of TFV-DP were higher in transwomen receiving F/TAF vs those receiving F/TDF
- Intracellular PBMC concentrations of TFV-DP and FTC-TP were similar between transwomen taking gender-affirming hormones and MSM
<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Favors</th>
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</thead>
<tbody>
<tr>
<td>Pre-existing renal or bone disease/risk factors</td>
<td>TAF/FTC</td>
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<tr>
<td>Patient is MSM or transgender women without a vagina</td>
<td>TDF/FTC or TAF/FTC</td>
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<td>Patient has receptive vaginal sex*</td>
<td>TDF/FTC</td>
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<tr>
<td>Patient has hyperlipidemia and/or is obese</td>
<td>TDF/FTC</td>
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*efficacy trial in African cisgender women underway
PrEP Pricing

• Currently, both meds cost the same (20K/year)
• Generic TDF/FTC should be available from one manufacturer in Sept, 2020→modest ↓ cost
• 6 months later, any generic manufacturer can produce TDF/FTC, which should lower costs substantially
• Questions include:
  - impact on drug assistance programs
  - 340B pricing
Urine Monitoring of Tenofovir

• Sensitivity, specificity, and accuracy of a novel urine point-of-care adherence test all 98-100% vs. laboratory-based assay in diverse populations

• Assay ready for field testing

• Literature on drug-level targeted adherence interventions: real-time information is most acceptable/effective\textsuperscript{1-3}

• Adherence information can be used to implement interventions: i.e. mHealth, motivational interviewing, action planning, incentives

Spinelli/Gandhi, CROI 2020
Results

- Overall 684 samples from 324 participants comparing LFA to ELISA (comparator)
- Sensitivity: 505/505 = 100% (97.5% CI: 99.3)
- Specificity: 176/179 = 98.3% (95% CI: 95.2%-99.7%)
- Accuracy: 681/684 = 99.6% (95% CI: 98.7%-99.9%)
Discussion about the use of the urine test

- **Limitations:**
  - Recent adherence information is susceptible to “white-coat effects” (although not seen so far in PrEP\(^1,2\))
  - Will need to test interventions using urine test with cumulative adherence metric as outcome (drug levels in dried blood spots or hair)

- **Future directions:**
  - Testing targeted adherence interventions in young Kenyan Women (PUMA study NCT03935464) and U.S. Young MSM (PrEP2-BAY study K23MH122286)

1. Landovitz JAIDS 2017 2. Koss CID 2018
Discussion: Useful in PrEP but Real-Time Adherence Information could also inform ART

<table>
<thead>
<tr>
<th>HIV Viral Load</th>
<th>ART Adherence Measure</th>
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<tbody>
<tr>
<td></td>
<td>High</td>
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<tr>
<td>Suppression</td>
<td>Expected outcome</td>
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<td></td>
<td>POSITIVE FEEDBACK</td>
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<td>Viremia</td>
<td>Test for Resistance</td>
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<tr>
<td></td>
<td>Low</td>
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<tr>
<td></td>
<td>Impending Problem</td>
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<td></td>
<td>COUNSEL</td>
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<td>Adherence Challenge</td>
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<td>IDENTIFY BARRIER</td>
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Adherence information enhances interpretation of viral load

<table>
<thead>
<tr>
<th>Efficacy Trial</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
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<tbody>
<tr>
<td><strong>Vaginal Ring Dapivirine Ring</strong></td>
<td>HOPE (MTN 025) Open-label trial of the once-monthly slow-release dapivirine vaginal ring, ongoing in 2,500 women in Malawi, South Africa, Uganda, Zimbabwe</td>
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<td>DREAM (IPM 032) Open-label trial of the once-monthly slow-release dapivirine vaginal ring, ongoing in 1,400 women in South Africa and Uganda</td>
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<td><strong>Antibody VRC01</strong></td>
<td>AMP (HVTN 704/ HPTN 085) Randomized controlled trial of the VRC01 antibody infused every two months, ongoing in 2,700 MSM and transgender men &amp; women in Brazil, Peru, Switzerland and US</td>
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<td></td>
<td>AMP (HVTN 703/ HPTN 081) Randomized controlled trial of the VRC01 antibody infused every two months, ongoing in 1,500 women in Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe</td>
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<tr>
<td><strong>Oral PrEP F/TAF</strong></td>
<td>DISCOVER Randomized controlled trial of once-daily F/TAF as PrEP, ongoing in 5,000 MSM and transgender women at approximately 90 sites in Europe and the Americas</td>
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<td><strong>Long-Acting Injectable</strong> Cabotegravir</td>
<td>HPTN 083 Randomized controlled trial of injectable cabotegravir every two months, ongoing in 4500 MSM and transgender women in Argentina, Brazil, India, Peru, South Africa, Thailand, US, Vietnam</td>
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<td></td>
<td>HPTN 084 Randomized controlled trial of injectable cabotegravir every two months, planned for 3,200 women in southern and East Africa</td>
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<tr>
<td><strong>Preventive HIV Vaccine</strong></td>
<td>ALVAC/gp120 w/MF59 Randomized controlled trial of ALVAC/gp120 prime-boost with MF59 adjuvant, five doses over 12 months, ongoing in 5,400 men and women in South Africa</td>
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<tr>
<td></td>
<td>HVPTN 702 Randomized controlled trial of Alvac/gp120 prime-boost with gp140 boost, planned for women in southern Africa</td>
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Antiretroviral Approaches in HIV Prevention

HIV Exposure

Day 1

Daily Pre-exposure Prophylaxis (PrEP)
FTC/TDF or FTC/TAF

Postexposure Prophylaxis (PEP)
FTC/TDF + INSTI* or + PI†

Event-Driven Prophylaxis
IPERGAY: FTC/TDF (2:1:1)

*Raltegravir (or dolutegravir); †Darunavir + ritonavir. FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; IPERGAY, Intervention Préventive de l’Exposition aux Risques avec et pour les Gays; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
NHP Efficacy Study 1 Design

Objective: assess protective efficacy of FTC/TAF ± 25 mg BIC

<table>
<thead>
<tr>
<th>SHIV Exposure</th>
<th>-2</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72h</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>n=6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PrEP -2,+24 h</td>
<td>n=6</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PrEP +24,+48 h</td>
<td>n=6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEP +48,+72 h</td>
<td>n=5</td>
<td></td>
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FTC 200 mg/ TAF 25 mg
FTC 200 mg/ TAF 25 mg + BIC 25 mg
NHP Study Conclusions and Future Directions

- Simplified 2-dose schedules can protect macaques against SHIV acquisition
- FTC/TAF alone: protective only as PrEP at -2, +24 h relative to exposure
- FTC/TAF + BIC 100 mg: protective as PrEP or PEP
  - PrEP: initiated 2 h pre-exposure
  - PEP: initiated up to 12 h postexposure
- Plan to further define optimal pre/postexposure schedules in rectal and vaginal challenge models
This was the first evaluation of single tablet combination of BIC and TAF/FTC for PEP in humans.

This regimen was safe and well-tolerated when used as PEP, with occasional mild gastrointestinal side effects and fatigue, and limited, reversible lab abnormalities.

Daily BIC/FTC/TAF for PEP compares very favorably with historical regimens, including other integrase strand transfer inhibitors.

The excellent safety profile and the high completion rates suggest that BIC/FTC/TAF should be considered for use as PEP.
BACKGROUND

Islatravir (ISL, MK-8591), a First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI), Has Multiple Mechanisms of Action (MOAs)

- Multiple mechanisms contribute to the high potency of ISL against HIV-1 and drug-resistant variants and their high barrier to resistance

Translocation Inhibition
Due to the 4’-ethynyl Group

- Prevents nucleotide binding and incorporation to the DNA chain, resulting in immediate chain termination

Delayed Chain Termination
Due to the 4’-ethynyl and 3’-hydroxyl Groups

- Prevents nucleotide incorporation even in the event of translocation
- ISL is no longer susceptible to resistance-conferring mutations once out of the active site

Subcutaneous PrEP Implants

- Several strategies in animal studies
- Simple insertion AND removal
- Long-acting (months to years)
- PrEP + contraception?
- Current development: TAF, CAB, EfDA
- Low doses of EfDA confer high level of protection for monkeys challenged with SHIV (CROI 2018: Markowitz et al)

ISL Provides Complete Protection Against Infection When Administered 24 Hours After Challenge With Two or More Weekly Doses

Viral Load (copies/mL vs days)

- 6/6 untreated controls infected upon challenge
- 6/6 treated animals protected with 4, 3, or 2 weekly doses
Single Oral Doses of ISL Given Within 24 Hours of Infection May Provide an Effective PEP Option in Humans
B66: Background and Objectives:

• HIV-1 and HSV-2 are associated with significant morbidity, HSV-2 increases the risk of HIV-1 acquisition

• Monoclonal antibodies (mAbs) show promise as microbicides because of their specificity, flexibility, and safe profile

• Two pilot Phase I clinical trials conducted in Europe of vaginally applied HIV antibodies were shown to be safe for women

• We report the first-in-human Phase I clinical trial of a repeated dose antibody-based multipurpose prevention technology (MPT) vaginal film against HIV and HSV

Objectives: To assess the safety, pharmacokinetics (PK) and ex vivo efficacy of repeated doses of MB66 film delivered vaginally to women
B66 Conclusions:

• Repeated vaginal application of MB66 film was safe and well tolerated
• Significant film dissolution after one hour
• Vaginal pH and Nugent scores did not significantly change
• No significant increases in proinflammatory cytokine concentrations following film insertion
• Concentrations of VRCO1 and HSV8 mAbs increased significantly in vaginal secretions following insertion of active film, peaking at one hour and remaining elevated at 24 hours post film insertion
• *Ex vivo* efficacy: Significant neutralization of 3 HIV strains and HSV-2 24 hours after multiple film insertions
• These data indicate that MB66 is safe and is a potential MPT product that could protect women against HIV-1 and HSV
UK: Evidence of a decline in HIV transmission

CD4 Back-calculation of new HIV diagnoses among gay, bisexual and other men who have sex with men, **England**

Source: Public Health England
Test & Treat

Proportion of people diagnosed receiving antiretroviral treatment (ART):
United Kingdom, 2018

<table>
<thead>
<tr>
<th>Gender</th>
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<tbody>
<tr>
<td>Men</td>
<td>97%</td>
</tr>
<tr>
<td>Women</td>
<td>97%</td>
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<table>
<thead>
<tr>
<th>Age-group</th>
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<tbody>
<tr>
<td>15-24</td>
<td>95%</td>
</tr>
<tr>
<td>25-34</td>
<td>96%</td>
</tr>
<tr>
<td>35-49</td>
<td>97%</td>
</tr>
<tr>
<td>50-64</td>
<td>98%</td>
</tr>
<tr>
<td>≥65</td>
<td>98%</td>
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<table>
<thead>
<tr>
<th>Ethnicity</th>
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<tbody>
<tr>
<td>White</td>
<td>97%</td>
</tr>
<tr>
<td>Black African</td>
<td>97%</td>
</tr>
<tr>
<td>Other</td>
<td>97%</td>
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<table>
<thead>
<tr>
<th>Exposure-group</th>
<th></th>
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<tbody>
<tr>
<td>Sex between men</td>
<td>98%</td>
</tr>
<tr>
<td>Heterosexual contact - men</td>
<td>97%</td>
</tr>
<tr>
<td>Heterosexual contact - women</td>
<td>97%</td>
</tr>
<tr>
<td>Injected drug use</td>
<td>96%</td>
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<table>
<thead>
<tr>
<th>Region</th>
<th></th>
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<tbody>
<tr>
<td>London</td>
<td>98%</td>
</tr>
<tr>
<td>Outside London</td>
<td>96%</td>
</tr>
<tr>
<td>Total</td>
<td>97%</td>
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</table>
Data Source: Public Health England

- Walk-in slots to ensure short time to treatment – same/next day
- Stat dose where possible – it’s done
- No sex – or at least no condomless sex – until completed treatment/tested for cure
- Health Advisors undertake partner notification directly or using contact slips
- Epidemiological treatment of partners at other GU clinics notified back to 56 Dean Street
Introduction: Impact of PrEP on Ending the HIV Epidemic: A Plan for America
48 Highest Burden Counties, 7 States, and Washington, DC

Priority US counties, Washington, DC, and San Juan, Puerto Rico
Priority states
Over this 6-y analysis, the US rate of HIV diagnoses in the 48-EHE locations decreased at a rate of 7.1%/y (95% CI -6.9%, -7.3%)
HIV viral suppression (proportion suppressed) increased by 1.4%/y (95% CI 1.1%, 1.7%) during the same time among people being treated for HIV.
PrEP use in people with a CDC-defined PrEP indication increased 9.9-fold in the same locations from a mean 1.31/100 individuals (95% CI 0.3, 2.3) in 2012 to 13.1/100 (12.1, 14.1) in 2017.
Conclusions

- From 2012 to 2017, HIV diagnoses declined significantly in the 48 counties and localities selected for intervention where PrEP use was the highest.
- The effect of PrEP use was significantly associated with this decline and was independent of TasP.
- Improvements in PrEP and TasP coverage in these localities would result in important declines in the rate of new HIV diagnoses.
PrEP Cascade in Urban US MSM (HPTN 078)
(Boston, Baltimore, Atlanta, Birmingham)

- 72.5% heard of PrEP
- 16.1% had used it in the past year
- Less than half who used it had protective drug levels

Mayer et al, CROI 2020
PrEP Demonstration in California Cisgender Women

- Poor retention; 61% at 48 wks, 48% at 60 wks
- Only 18.4% met adherence target of $\geq 6-7$ doses/wk at 48 wks
- Main reasons for non-persistence:
  - concerns about side/long term effects (13.6%)
  - change in risk behavior (5.8%)
  - medical issues (2.9%)
  - concern that medication would be stolen (2.2%)
- Few adverse events; Low HIV and STI incidence rates
- US PrEP programs may need to consider offering alternatives for women who discontinue or struggle with adherence
- Need to identify ways to optimize adherence and retention

Blumenthal, CROI 2020
HIV among MSM: A Syndemic Theory (Stall et al)
Need to Address more than HAART & PrEP

Interventions to Increase HIV and STI Testing

- Test
  - HIV negative
  - HIV positive
    - Positive prevention
    - Linkage to care
      - Enroll in care
        - ART initiation
          - Retain
            - Adherence to ART
          - Maintain viral suppression

Risk assessment PrEP, adherence counseling

Address concomitant concerns:
depression, substance use, relationship dynamics, structural/social issues, STI

Decrease in HIV and BSTI transmission