Highlights from the Virtual IAS Conference on HIV Science 2021

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Educational Objectives:

• Discuss new clinically relevant advances in antiretroviral therapy and prevention strategies for HIV

• Recognize emerging metabolic effects associated with antiretrovirals used for treatment and prevention of HIV

• Explore the interface between the co-occurring HIV and COVID-19 pandemics
Overview

• COVID-19 and HIV
• Epidemiologic trends and engagement in care
• HIV prevention
• ART trials
• New agents
PISCIS: COVID-19 Risk and Outcomes Among PWH

- Analysis of data from PISCIS, a population-based cohort study of PWH (n=13,142) conducted in Catalonia, Spain (16 collaborating hospitals, collected between January 1998- December 2020) matched with data from PADRIS (Public Health Records in Catalonia).
  All COVID-19 diagnoses confirmed by + RNA, +Ag or +Ab.
  - PWH: COVID-19 positive (n=749), hospitalization (n=103), deaths (n=13)

- Factors associated with increased risk of COVID-19 diagnosis in PWH
  - MSM transmission (aHR 1.42; P<0.01), immigrant (aHR 1.55; P<0.01), ≥4 comorbidities (aHR 1.46; P<0.01)
  - PWID transmission associated with decreased risk of COVID-19 diagnosis (aHR 0.66; P<0.04)

- Factors associated with increased risk of severe COVID-19 outcomes in PWH
  - Detectable HIV RNA levels, age ≥75 years, increasing number of comorbidities (neuropsychiatric, autoimmune, respiratory, metabolic), and immigrant origin
  - Of note, lower CD4+ T cell counts were a risk factor for severe COVID-19 outcome only among those with detectable HIV RNA levels

Real-World Utilization of PrEP During the COVID-19 Pandemic

- Real-world pharmacy claims database (~80% of US retail pharmacies) of persons initiating PrEP (12/2019 to 12/2020; n=123,983); PrEP use by validated algorithm
  - Prevalent PrEP users in 12/2020 (n=130,102)
    - 26 to 44 years of age: 58%; males: 94%
  - Progressive decline in PrEP initiation was observed from 2/2020 to 4/2020; then slow progressive increase after 4/20
    - Overall number of PrEP users showed decrease 4/2020 to 5/2020 with slight increase after 6/2020
  - Most pronounced decreases were in white persons > other races/ethnicities and those living in the Southern US
  - Findings show how real-world pharmacy data can track PrEP use during the COVID-19 pandemic


- TDF/FTC has been shown to have *in vitro* activity against SARS-Cov-2 RdRp.
- Substudy of Prevenvir (daily or on-demand TDF/FTC PrEP users) matched with participants in the SAPRIS-Sero Registry in Paris (non-TDF/FTC users) studies (n=1688)
  - Cohorts matched on:
    - Characteristics: age (+/- 5 yrs), socio-occupational category and date of sampling (+/- 1 month)
      - Prevenir participants younger than SAPRIS-Sero; 60%-70% -executive occupation
      - When tested for anti-SARS-CoV-2 Abs (users-non-users): May-June (16%-18%), July August (34%-61%), September-October (49%-20%), November-January 2021 (<1%)
- COVID-19 positive (TDF/FTC versus non-TDF/FTC users)
  - Overall 9.2% versus 10.3% (OR 1.1 95% CI 0.82-1.5)
  - No difference between daily, oral and on-demand F/TDF users
- Conclusion: TDF/FTC has no role in reducing SARS-CoV-2 acquisition

Impact of HIV on Hospital Mortality, Cardiac/Critical Care AEs, Among PWH in the US

- Data analysis from American Heart Association’s COVID-19 Cardiovascular Disease Registry (March – December 2020; 107 U.S. hospitals; n=21,528 persons hospitalized for COVID-19; largest to date)

- Primary outcome was in-hospital mortality; secondary outcomes included major adverse cardiac event (MACE), severity of illness including ICU admission & mechanical ventilation, length of stay, and clinical trial enrollment
  - 220 persons with HIV matched 3:1 with 21,308 HIV-negative persons
  - Rigorous clinical outcome adjudication

- HIV and hospitalization (adjusted odds ratios)
  - In-hospital mortality: 1.14 (95% CI 0.78-1.68); MACE: 0.99 (95% CI 0.69-1.44); ICU: 0.90 (95% CI 0.65-1.23); Mechanical ventilation: 1.00 (0.71-1.40); Length of stay: 1.02 (0.98-1.07)

- No significant adverse associations between + HIV status and in-hospital COVID-19-related outcomes

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Cardiovascular Risk Factors and Disease in PWH in the U.K.

- Data analysis from The Health Improvement Network (THIN)-retrospective, matched to HIV–negative cohort study in the UK (2000-2020; n=44,954); Persons living with HIV = 9233
  - Baseline characteristics: age (41 years), male (66%), white/black/Asian/other-missing (43%/8%/2%/44%), BMI under-normal weight/overweight/obese/missing (36%/26%/15%/23%)

- PWH were at higher risk for:
  - Composite CVD (stroke, PVD, ischemic HD, MI, HF) overall
  - Stroke, hypertension, lipid-lowering drug use, chronic kidney disease, and all-cause mortality (HR 2.68, 95% CI 2.32, 3.10)
  - CVD risk remained significant across sub-groups of gender, age, smoking status and index year
  - Younger PWH (≤40 years) had the highest risk of CVD (HR 2.01) and all-cause mortality (HR 6.09)

- Results support current CVD guidelines for regular screening of CVD risk factors and disease

Hazard Ratio for Outcome in Person With Versus Without HIV

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD risk</td>
<td></td>
</tr>
<tr>
<td>Composite CVD</td>
<td>1.54 (1.30, 1.83)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.49 (1.11, 2.00)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.59 (1.25, 2.02)</td>
</tr>
<tr>
<td>CVD risk factors and all-cause mortality</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.37 (1.22, 1.55)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>1.96 (1.78, 2.16)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1.28 (1.07, 1.52)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2.68 (2.32, 3.1)</td>
</tr>
</tbody>
</table>

No significant differences for peripheral vascular disease, heart failure, MI, atrial fibrillation.

ACCESS Cohort: Impact of Opioid Agonist Therapy for PWH on Linkage and Progression of HIV Care Cascade

- Ongoing prospective cohort study - Vancouver, BC (2005-2017; n=639)
  - PWH using at least daily unregulated opioids
    - Baseline characteristics: age (42 years), male (59%), homelessness (32%), on OAT (70%)
- Outcome
  - Cumulative progression through the HIV care cascade stratified by OAT engagement
- Proportion accessing OAT during the study ranged from 73% to 90%
- While OAT was not associated with linkage to HIV care, it was positively associated with progression through some of the steps of HIV care

HIV Cascade of Care

- Engaged in HIV Care
- On ART
- Adherent to ART
- HIV RNA <50 Copies/mL

ACCESS: AIDS Care Cohort to Evaluate Exposure to Survival Services.
OAT: opioid agonist therapy.
ANRS-CO21 CODEX Cohort: ART in HIV Controllers

- Retrospective analysis of HIV controllers (n=301; 90 on ART)
  - u-HIV controller: strictly undetectable viral load (7/73 on ART)
  - b-HIV controller: with viral blips (83/228 on ART)

- Indications for ART initiation (n=90)
  - Immunologic/virologic progression (30%/14%), non-AIDS defining events (13%), suspected virologic/immunologic progression (12%/7%), combined reasons (11%), other (11%)

- Impact of ART
  - u-HIV controller: reduced activated CD4+ & CD8+ T lymphocytes and total CD8+ T cells, increased CD4/CD8 ratio but did not significantly increase total CD4+ T cells.
  - b-HIV controller: did not increase nor reduce CD4+ T cells, CD8+ T cells, CD4/CD8 ratio, proportion of activated CD4+or CD8+ lymphocytes

- Results indicate that HIV controller status is stable and underscores the importance of patient-centered treatment decision

C-FREE Study: Community HCV Test-and-Treat in PWH Who Use Drugs and Their Partners

- Prospective cohort study of people screened every 3 months for HIV, HBV, HCV (n=1322)
  - Nested cohort of those with chronic HCV (n=754)
    - Excluded: prior failure of sofosbuvir-based regimen, decompensated cirrhosis, HCC, eGFR <30 min/mL, pregnancy
- Started sofosbuvir/velpatasvir for 12 weeks (n=667)
- Interim analysis (per protocol) SVR12: 96%
  - Majority of participants in the process of completing treatment or awaiting SVR visit
- Serious adverse events leading to treatment discontinuation (n=2) and deaths (n=2)
- Interim results indicate sofosbuvir/velpatasvir was safe and effective in the community-based setting of this study population

Baseline characteristics of C-FREE cohort:
Age (42 years), MSM (13%), female (15%), current IDU/alcohol use (36%/36%), history of incarceration (44%).
HIV (38%: 94% on ART and 75% HIV RNA <40 copies/mL), chronic HCV (83%), coinfections: HIV/HCV (71%), HIV/HBV (2%) HBsAg positive (5%).

Global Systematic Review and Meta-Analysis: HCV Reinfection Among PWH

- Systematic review and meta-analysis of 37 studies (13,009 person-years of follow-up)
  - Clinical trial/prospective/retrospective observational trial (n=12/24/43)
  - DAA/IFN-based/mixed regimen (n=22/8/7)
  - Reinfection: recurrent viremia (n=9), different HCV strain via sequencing (n=5), genotype/subtype change (n=4), mix (n=19)

- Rates of HCV reinfection
  - Higher rates in studies with higher proportion of MSM (OR 2.6) or those with recent HCV infection (OR 2.2)
  - Lower rates in studies with longer duration of follow-up (OR 0.98)

- Implications
  - Continuous education and harm reduction services to reduce reinfection risk (particularly HIV-positive MSM)
  - Regular post-treatment reinfection HCV assessment (particularly in those with recent HCV infection)

<table>
<thead>
<tr>
<th>HCV Reинфекtion Rates</th>
<th>Rate (per 100 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.85</td>
</tr>
<tr>
<td>MSM</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>5.89</td>
</tr>
<tr>
<td>Never injection drug use</td>
<td>4.75</td>
</tr>
<tr>
<td>Ever injection drug use</td>
<td>4.13</td>
</tr>
<tr>
<td>PWID</td>
<td></td>
</tr>
<tr>
<td>Ever injection drug use</td>
<td>3.29</td>
</tr>
<tr>
<td>Recent injection drug use</td>
<td>5.48</td>
</tr>
</tbody>
</table>

Overview

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HIV prevention
• ART trials
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DISCOVER Trial:
Outcomes in Persons Switching From F/TDF to F/TAF for PrEP

Phase 3, non-inferiority study

Double-blind
HIV negative MSM and transgender women at risk for HIV
eGFR: ≥60 mL/min

- F/TAF qd (n=2670)
- F/TDF qd (n=2665)

Week 0  96  +48

Current Analysis

**Efficacy Analysis: HIV Incidence Rate**

**OL Week 48**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline to Week 48</th>
<th>Baseline to Week 96</th>
<th>OL Day 1 to OL Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/TAF</td>
<td>0.16</td>
<td>0.16</td>
<td>0.09*</td>
</tr>
<tr>
<td>F/TDF</td>
<td>0.34</td>
<td>0.30</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

- 7 infections/4370 PY
  - 15 infections/4386 PY
- 8 infections/5029 PY
  - 15 infections/5052 PY
- 2 infections/2139 PY
  - 1 infections/2152 PY

*During the OL phase, one additional participant in each group had a positive quantitative HIV nucleic acid amplification test subsequent to a presumptive positive.*

CI: confidence interval; PY: person-years.
## DISCOVER Trial: Safety Outcomes During 48 Week Open-Label Extension

<table>
<thead>
<tr>
<th></th>
<th>Stay on F/TAF</th>
<th>F/TDF→F/TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td>Week 48 change</td>
<td>+1.2</td>
<td>+2.0</td>
</tr>
<tr>
<td><strong>eGFR (mL/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>119</td>
<td>114</td>
</tr>
<tr>
<td>Week 48 change</td>
<td>-2.8</td>
<td>+0.3</td>
</tr>
<tr>
<td><strong>BMD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip/Spine</td>
<td>1.14/1.03</td>
<td>1.12/1.00</td>
</tr>
<tr>
<td>Baseline (g/cm²)</td>
<td>+0.20/-0.06</td>
<td>+1.2*/+0.9*</td>
</tr>
<tr>
<td>Week 48 change (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>Week 48 change</td>
<td>+7</td>
<td>+13*</td>
</tr>
<tr>
<td><strong>HDL-C (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>Week 48 change</td>
<td>0</td>
<td>+3*</td>
</tr>
</tbody>
</table>

*P<0.05 versus stay on F/TAF. Baseline values are from open-label baseline.

Global Evaluation of Microbiocide Evaluation (GEMS): Background

- Monitoring for HIV resistance in patients taking TDF-based oral PrEP is essential
  - ART resistance from PrEP breakthrough infections may lead to virologic failure
  - Transmitted resistance from failing ART may lead to PrEP breakthrough infections
- GEMS Project Team monitors HIV drug resistance in PrEP rollout programs in Sub-Saharan Africa
  - More than 104,000 persons on PrEP across >36 partner groups were monitored for HIV drug resistance
- Current report analyzed drug resistance mutations and adherence for persons diagnosed with HIV in TDF-based PrEP rollout programs in Kenya, Zimbabwe, Eswatini, and South Africa
GEMS: Study Design

- Observational cross-sectional study
- Blood samples (whole blood for plasma or dried blood spots) collected from participants diagnosed with HIV on PrEP
- Demographics and self-reported adherence obtained through a questionnaire
- HIV drug resistance mutations revealed by Sanger sequencing of reverse transcriptase and analyzed using Stanford HIVdb v9.0
- Tenofovir-diphosphate levels measured by liquid chromatography–mass spectrometry
GEMS: Characteristics of Patients Who Seroconverted on PrEP

- 229 reported seroconversions on PrEP between December 2017 and June 2021
- 208 (91%) patients provided a sample
  - South Africa: 79 (38%)
  - Kenya: 65 (31%)
  - Zimbabwe: 36 (17%)
  - Eswatini: 28 (13%)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>155 (75)</td>
</tr>
<tr>
<td>Age category at seroconversion, n (%)</td>
<td></td>
</tr>
<tr>
<td>▪ 16-24</td>
<td>108 (52)</td>
</tr>
<tr>
<td>▪ ≥25</td>
<td>95 (46)</td>
</tr>
<tr>
<td>▪ Unknown</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Population, n (%)</td>
<td></td>
</tr>
<tr>
<td>▪ Adolescent girl/young woman</td>
<td>87 (42)</td>
</tr>
<tr>
<td>▪ Serodifferent couple</td>
<td>50 (23)</td>
</tr>
<tr>
<td>▪ Female sex worker</td>
<td>20 (10)</td>
</tr>
<tr>
<td>▪ Men who have sex with men</td>
<td>15 (7)</td>
</tr>
<tr>
<td>▪ Transgender woman</td>
<td>12 (6)</td>
</tr>
<tr>
<td>▪ Pregnant or lactating</td>
<td>8 (4)</td>
</tr>
<tr>
<td>▪ Incarcerated</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

**GEMS: Analysis of Resistance and Adherence Level**

- **118/208** samples (57%) successfully sequenced
  - Insufficient HIV-1 RNA (30% of samples) most common reason for no result

<table>
<thead>
<tr>
<th>Resistance Mutations</th>
<th>Adherence</th>
<th>Resistance</th>
<th>Adherence</th>
<th>Resistance</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Resistance Mutations</strong></td>
<td>65/118 (55%)</td>
<td><strong>Low</strong>*</td>
<td>34/41 (82%)</td>
<td>Moderate†</td>
<td>1/41 (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>High‡</strong></td>
<td></td>
<td></td>
<td>6/41 (15%)</td>
</tr>
<tr>
<td><strong>Resistance Mutations Not Associated With PrEP</strong></td>
<td>26/118 (22%)</td>
<td><strong>Low</strong>*</td>
<td>12/20 (60%)</td>
<td>Moderate†</td>
<td>1/20 (5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>High‡</strong></td>
<td></td>
<td></td>
<td>7/20 (35%)</td>
</tr>
<tr>
<td><strong>Resistance Mutations Associated With PrEP</strong> (K65R, K70E, M184IV)</td>
<td>27/118 (23%)</td>
<td><strong>Low</strong>*</td>
<td>2/18 (11%)</td>
<td>Moderate†</td>
<td>2/18 (11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>High‡</strong></td>
<td></td>
<td></td>
<td>14/18 (78%)</td>
</tr>
</tbody>
</table>

* <350 fmol/punch, <2 doses/week.
† 350-699 fmol/punch, 2-3 doses/week.
‡ ≥700 fmol/punch, 4-7 doses per week.

GEMS: Conclusions

- Number of reported HIV infections in patients on PrEP in Sub-Saharan Africa extremely small (229 out of >104,000 estimated to be on PrEP), but ART resistance frequency in these patients with breakthrough infections was high.

- Of the 118 patients with breakthrough infections and successfully sequenced samples:
  - 22% had NNRTI mutations only, signifying background transmitted resistance.
  - 23% had PrEP-associated mutations, the majority of which had TFV-DP levels that correlated with high rates of adherence.

- Authors conclude that accurately diagnosing acute HIV infection prior to PrEP initiation, and monitoring for HIV drug resistance on PrEP, is essential to preserve ART options for treatment and prevention.

Projeto PrEPParadas Substudy: Impact of TDF/FTC and Estradiol Exposure in TGW on PrEP

- Drug-drug interaction study from a demonstration project in Rio de Janeiro) (2017-2020; n=24)
  - TGW on daily F/TDF for PrEP and feminizing hormone therapy (estradiol valerate 2-4 mg plus spironolactone 100-200 mg)
  - Baseline characteristics: age (26 years), BMI (23 kg/m²), creatinine clearance (132 mL/min)

- Design
  - FHT washout, FHT (15 days), baseline FHT PK then 12 weeks of FHT + F/TDF, week 12 FHT + F/TDF PK

- Results
  - Oral, daily F/TDF and estradiol valerate may be used concomitantly
  - Data from this substudy adds to data on the potential impact of oral PrEP on FHT among TGW

<table>
<thead>
<tr>
<th>Estradiol (divided by dose)</th>
<th>Baseline</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC/D (h·pg/mL/mg)</td>
<td>596 (387-757)</td>
<td>511 (367-707)</td>
</tr>
<tr>
<td>Cmax/D (pg/mL)</td>
<td>36 (24-48)</td>
<td>28 (22-43)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spironolactone (divided by dose)</th>
<th>Baseline</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC/D (h·pg/mL/mg)</td>
<td>3.0 (2.1-5.1)</td>
<td>2.8* (1.5-3.5)</td>
</tr>
<tr>
<td>Cmax/D (ng/mL)</td>
<td>0.9 (0.7-1.3)</td>
<td>0.8 (0.7-1.2)</td>
</tr>
</tbody>
</table>

*P=0.008 versus baseline.

FHT: feminizing hormone therapy.

American Men’s Internet Survey: Perceived Facilitators or and Barriers to Long-Acting Injectable PrEP

- Internet-based survey of HIV-negative MSM to identify preferred implementation profiles of long-acting injectable PrEP (n=2441)
  - Online recruitment in the 2019 American Men’s Internet Survey
- Discrete-choice design; respondents ranked 27 scenarios containing 5 different attributes and 3 conditions
  - Side effects (low, medium, high)
  - Treatment frequency (every 6, 3, or 2 months)
  - Out-of-pocket expenses ($0, $25, $100)
  - Location of services (private doctor’s office, sexual health clinic, pharmacy)
  - Stigma (high, medium, low)
- Participants: <30 years of age (64%), white (63%), 2+ male partners (84%), past/current oral PrEP use (28%)
- Potential side effects and cost were the 2 most important concerns for using long-acting injectable PrEP

Survey Results

<table>
<thead>
<tr>
<th>Very or somewhat likely to use long-acting injectable PrEP (%)</th>
<th>Participants (n=2241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative importance of attributes (%)</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>52</td>
</tr>
<tr>
<td>Treatment burden</td>
<td>11</td>
</tr>
<tr>
<td>Cost</td>
<td>30</td>
</tr>
<tr>
<td>Location of services</td>
<td>2</td>
</tr>
<tr>
<td>Stigma</td>
<td>5</td>
</tr>
<tr>
<td>Willingness to pay (US$)</td>
<td></td>
</tr>
<tr>
<td>Reduce side effect severity</td>
<td>84</td>
</tr>
<tr>
<td>Avoid stigma</td>
<td>8.75</td>
</tr>
<tr>
<td>Delay injection frequency by 1 month</td>
<td>6.60</td>
</tr>
<tr>
<td>Increase location privacy</td>
<td>0.37</td>
</tr>
</tbody>
</table>

CAP016 Study: PreP Use in Pregnant and Lactating Women in South Africa

Phase 2b
Open-label
Pregnant women (≥18 years of age)
HIV-negative
High-risk for HIV infection

Randomization 1:1

Immediate F/TDF (n=250)
(during pregnancy)

Delayed F/TDF (n=247)
(after cessation of breastfeeding)

Primary Outcomes
Pregnancy outcomes
Neonatal outcomes

Baseline characteristics:
Age: 23 years.
Education: 22% (primary-secondary), 50% (matriculation), 11% (tertiary).
Gravidity: 1.8.
Previous pregnancies (n=278):
  Complications: 6%.
  Term births (≥37 weeks): 92%.
  Preterm births: 4%.
  Stillbirths: 14%.
  Spontaneous abortions/neonatal deaths: 2%.
  Gestational age at enrollment: 17 weeks.

Difference between immediate start versus delayed PrEP arms were minimal

- Preterm births: (9.2% vs 8.9); live births: (96% vs 96.4%); still births: (3.9% vs 2.8%)
- Mean birth weight: (3.14kg vs 3.08kg); low-birth weight <1.5kg: (0.84% vs 0.84%); <2.5kg: (8.4% vs 5.9%)
- Appropriate for gestational age (AGA): (89% vs 94%))
- Neonatal deaths: (0 vs 3)
- Maternal AEs (mild increases in headache, vomiting, nausea) and lab toxicities (similar renal and liver)

HIV incidence: Immediate versus delayed PrEP: 3.3 versus 1.1 per 100 person-years

Early stopping of accrual due to change in the national PrEP policy led to a smaller sample size with resulting loss of power to conclude equivalence between PreP and Standard-of-care arms formally
Overview

- COVID-19 and HIV
- Epidemiologic trends and engagement in care
- HIV prevention
- **ART trials**
- New agents
SALSA Trial: Switch to Dolutegravir/3TC in Treatment-Experienced Patients

Phase 3 (17 countries)

Open-label
Treatment-experienced
Stable ART of 2 NRTIs + either INSTI, NNRTI, or bPI (HIV RNA <50 copies/mL)
No HBV
No prior virologic failure or NRTI or INSTI resistance

Randomization 1:1

Continue Stable ART (n=247)
Switch to Dolutegravir/3TC (n=246)

Week 0 48 96 144

Primary Endpoint
Virologic Failure
(5% non-inferiority margin)

Virologic failure: includes changing background therapy component, discontinued due to lack of efficacy, or HIV RNA ≥50 copies/mL by week 48.

Baseline characteristics:
Age: 45 years.
Male: 60%.
White/black/Asian: 60%/19%/9%.
CD4: 668-675 cells/mm³.
Third agent: INSTI/NNRTI/bPI: 40%/50%/10%.
Weight: 73-75 kg.
BMI: 26 kg/m².

SALSA Trial: Outcomes With Switch to Dolutegravir/3TC at Week 48

- Switching to dolutegravir/3TC was non-inferior to continuing baseline stable ART
  - Virologic failure (5% margin)
  - HIV RNA <50 copies/mL (12% margin)
- No confirmed virologic withdrawals in either arms
- Both treatment arms were well-tolerated (switching to dolutegravir/3TC versus continuing stable ART)
  - Discontinuations due to drug-related adverse events: 2% versus <1%
  - Any serious adverse events: 3% versus 6% (none were treatment-related)
  - Weight increase: 6% versus 0%
  - Changes in proximal tubular renal function and bone formation biomarkers favored dolutegravir/3TC

BRAAVE 2020: Switch to Bictegravir/F/TAF in African American With HIV

Phase 3 study
Open-label
Black
On stable ART (2 NRTIs + 3rd agent)
HIV RNA <50 copies/mL
eGFR: ≥50 mL/min

Primary outcome: HIV RNA ≥50 copies/mL at week 24.
Non-inferiority margin: 6% (FDA snapshot algorithm).
Baseline demographics:
  Male: 68%.
  Age: 49 years.
  Hispanic/Latinx: 4%.
  CD4: 747-758 cells/µL.
  HBV infection: 4%.
  eGFR: 107-110 mL/min.
  NRTI backbone: F/TAF (67%), F/TDF (19%), ABC/3TC (14%).
  3rd agent: INSTI (59%), NNRTI (29%), bPI (6%), other (6%).
  Resistance:
    NRTI (14%), NNRTI (20%), PI (12%).
BRAAVE 2020: Switch to Bictegravir/F/TAF in African Americans With HIV

- Switching to bictegravir/F/TAF was highly effective with no treatment-emergent resistance
- Switching to bictegravir/F/TAF was safe and well tolerated
  - Discontinuations due to adverse events: 2%
  - Small reductions in total cholesterol and triglycerides following the switch
  - Weight gain was similar between the 2 arms at week 24 and stable from weeks 24 to 72
    - Week 24 change (bictegravir/F/TAF versus baseline ART): +0.9 versus +0.2 kg; $P=0.09$
- Adherence to therapy remained high despite the COVID-19 pandemic

**HIV RNA <50 Copies/mL at Week 72**

Switch to bictegravir/F/TAF:

- **Immediate**
  - Overall (n=328/163): 98%
  - Yes (n=43/25): 100%
  - No (n=269/131): 99%

- **Delayed**
  - Overall (n=328/163): 98%
  - Yes (n=43/25): 100%
  - No (n=269/131): 99%

(100% of patients were included for analysis. Patients with missing data for HIV RNA were excluded.)

STAT Study: Dolutegravir/3TC in a Test-and-Treat Setting

- Open-label, phase 3b study of ART-naïve patients
  - Start dolutegravir/3TC within 14 days of receiving an HIV diagnosis
  - Laboratory results not available at baseline
- Dolutegravir/3TC treatment was adjusted if the results from baseline testing showed
  - HBV co-infection
  - Genotypic resistance to dolutegravir or 3TC
  - Creatinine clearance <30 mL/min
- Key outcomes at week 48
  - Proportion with HIV RNA <50 copies/mL (observed, ITT-E, and FDA snapshot analyses)

<table>
<thead>
<tr>
<th>Baseline Characteristics (ITT-E Population)</th>
<th>Patients (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>31</td>
</tr>
<tr>
<td>Male (%)</td>
<td>92</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
</tr>
<tr>
<td>White/black</td>
<td>50</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>47</td>
</tr>
<tr>
<td>Median time from HIV diagnosis (days)</td>
<td>5</td>
</tr>
<tr>
<td>Median HIV RNA (copies/mL)</td>
<td>63K</td>
</tr>
<tr>
<td>&lt;100K/100 to 500K copies/mL (%)</td>
<td>60</td>
</tr>
<tr>
<td>≥500K copies/mL (%)</td>
<td>24</td>
</tr>
<tr>
<td>Median CD4 (cells/mm³)</td>
<td>389</td>
</tr>
<tr>
<td>&lt;200 cells/mm³ (%)</td>
<td>28</td>
</tr>
<tr>
<td>HBV co-infection (%)</td>
<td>5</td>
</tr>
<tr>
<td>M184V (%)</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

STAT Study: Dolutegravir/3TC in a Test-and-Treat Setting

- Rapid dolutegravir/3TC initiation resulted in high virologic suppression rates
  - Rates by baseline HIV RNA level (copies/mL)
    - >1 million (n=10) and >100K (n=51): 90% and 82%
  - Required adjustment to regimen (n=10: baseline HBV [n=5] and M184V [n=1]; decision by proxy [n=1], rash [n=1], pregnancy [n=1])
    - All remained on study at week 48 and had HIV RNA <50 copies/mL
- Dolutegravir/3TC was safe and well-tolerated
  - Change in weight (6% increase) and BMI (+1.6 kg/m²)
- Results demonstrate the feasibility of rapid initiation in a test-and-treat setting

TANGO Study: Metabolic Parameters in Treatment-Experienced Patients Switching to Dolutegravir/3TC

Phase 3
Open-label
Treatment-experienced
Stable TAF-based ART
(HIV RNA <50 copies/mL)
No HBV
No prior virologic failure or NRTI or INSTI resistance

Randomization 1:1

Switch to Dolutegravir/3TC (n=369)
Continue TAF-Based ART (n=372)

Week 0 48 96 144

Current Analysis
Weight gain
Metabolic health parameters
Change in lipids, BMI

Baseline characteristics:
3rd ART class: INSTI (79%), NNRTI (13%), boosted PI (8%).
Baseline resistance:
No major RAMs: 74%
Major RAMs:
NRTI (7%), NNRTI (14%), PI (7%), INSTI: 1%.
Mean weight: 82 kg.
Mean BMI: 27 kg/m².
Metabolic syndrome: 11%.
Fasting insulin: 72 pmol/L.
HOMA-IR: 2.7.

TANGO Study: Metabolic Parameters in Treatment-Experienced Patients Switching to Dolutegravir/3TC

- Weight changes were similar between both arms and comparable to what would be expected in the general population (0.5 to 1.0 kg/year)
- Changes in lipids generally favored the dolutegravir/3TC group
- Changes in other metabolic health parameters were generally similar between the 2 arms

<table>
<thead>
<tr>
<th>Main Outcomes at Week 144</th>
<th>Switch to DTG/3TC</th>
<th>Continue TAF-Based Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in weight (kg)</td>
<td>2.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Change in lipids (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-3.3</td>
<td>4.2</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-3.0</td>
<td>4.6</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-2.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-9.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Change in fasting glucose (mmol/L)</td>
<td>0.0</td>
<td>-0.1</td>
</tr>
<tr>
<td>Change in HOMA-IR (%)</td>
<td>11.2</td>
<td>11.0</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>

FLAIR Study: Long-Acting Injectable Cabotegravir + Rilpivirine as Maintenance Therapy

Phase 3 (ongoing)

Open-label, non-inferiority

Induction phase:
- Treatment-naive
- HIV RNA >1000 copies/mL
- Any CD4 count
- No HBV infection
- No NNRTIs RAMs

Start of maintenance phase:
- HIV RNA <50 copies/mL

Primary endpoint: HIV RNA ≥50 copies/mL (non-inferiority margin: 6%).

Cabotegravir dosing:
- Week 0-4: oral cabotegravir 30 mg + rilpivirine 25 mg qd.
- At week 4: initial loading dose of cabotegravir LA 600 mg + rilpivirine LA 900 mg IM.
- Week 4 onwards: cabotegravir LA 400 mg + rilpivirine LA 900 mg IM every 4 weeks.

FLAIR Study: Long-Acting Injectable Cabotegravir + Rilpivirine as Maintenance Therapy

- Most patients with no virologic data at week 124 were due to adverse events or other non-virologic reasons
- From week 96 to 124:
  - HIV RNA ≥50 copies/mL: 5 additional patients
  - Confirmed virologic failure: 1 additional patient
    - Emergent INSTI RAMs: N155H and R263K
- Safety and tolerability profile was consistent with week 48 and 96 analyses

Virologic Outcomes With Cabotegravir + Rilpivirine

Baseline Virologic Factors Associated With Risk of Virologic Failure With Cabotegravir + Rilpivirine in Treatment-Naïve Patients

- Cohort study conducted in Paris hospitals (2010-2020)
  - RT and INSTI sequences (ANRS algorithm and the IAS-USA list) (from 4212 treatment-naïve patients)
  - HIV subtype B: 39%
  - A6/A1 subtype: 5%
- Prevalence of virologic risk factors for virologic failure to cabotegravir + rilpivirine
  - 1 baseline risk factor: 10.1%
  - 2 baseline risk factors (E138A + L74I polymorphisms): 0.4%
  - A1/A6 sequences resistant to rilpivirine: 0.4%
    - 2 baseline risk factors: <0.5%
- Results underscore importance of checking cumulative genotypic resistance profile and viral subtype prior to initiating cabotegravir + rilpivirine

## INSTI and RT Mutations

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Excluding L74I</th>
<th>Non-B versus B subtype</th>
<th>Resistant to cabotegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabotegravir RAMs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>16</td>
<td>3</td>
<td>22 versus 8*</td>
<td>0.7</td>
</tr>
<tr>
<td>Rilpivirine RAMs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistant to rilpivirine</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-B versus B subtype</td>
<td>7</td>
<td>versus 4*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.0001.
Resistance interpretation using ANRS algorithm.

CUSTOMIZE Study: Implementation of Long-Acting Injectable Cabotegravir + Rilpivirine in US Healthcare Settings

- Phase 3b, hybrid III implementation-effectiveness study
  - 5 clinic types* across 8 cities (Sacramento, Kansas City, Dallas, Detroit, Atlanta, Jackson, Jacksonville, Miami)
- Long-acting cabotegravir + rilpivirine
  - Healthcare staff found it acceptable (91%-96%), appropriate (95%), feasible (80% to 100%), and sustainable
    - Most felt optimal implementation was achieved in 1 to 3 months (78%)
  - Healthcare staff found perceived barriers decreased from baseline by month 12
    - Initial concerns: ability of patients to keep monthly appointments, obtain transportation, and flag missed visits
    - Concerns were mitigated with minor process adjustments that varied by clinic type

Changes Made Through Month 12

<table>
<thead>
<tr>
<th>Infrastructure Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Extended clinical hours</td>
</tr>
<tr>
<td>- Increased coordination with other department</td>
</tr>
<tr>
<td>- Purchased new refrigerators</td>
</tr>
<tr>
<td>- Found available room space</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Attitude Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Implementation ease mitigated concerns regarding leadership support</td>
</tr>
<tr>
<td>- Good tracking/reminder system addressed concerns about patients keeping appointments</td>
</tr>
<tr>
<td>- Short wait times and increased patient-provider touchpoints eased concerns regarding length of injection visits</td>
</tr>
<tr>
<td>- Patients’ zealous acceptance of treatment was a great surprise</td>
</tr>
</tbody>
</table>

*Clinic types: federally qualified health centers, university practices, private practices, AIDS healthcare foundation, health maintenance organizations.

Overview

• COVID-19 and HIV
• Epidemiologic trends and engagement in care
• HIV prevention
• ART trials
• New agents
Phase 3

Treatment-naive
HIV RNA ≥200 copies/mL
CD4 >200 cells/µL

Induction

<table>
<thead>
<tr>
<th>LCV po 600mg x2, 800mg x1</th>
<th>LCV sc 927mg q6 months (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC oral qd</td>
<td>TAF/FTC oral qd</td>
</tr>
</tbody>
</table>

Maintenance

<table>
<thead>
<tr>
<th>LCV po 600mg x2, 800mg x1</th>
<th>LCV sc 927mg q6 months (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC oral qd</td>
<td>Bictegravir oral qd</td>
</tr>
<tr>
<td>LCV oral qd + F/TAF oral qd (n=52)</td>
<td></td>
</tr>
<tr>
<td>Bictegravir/F/TAF oral qd (n=25)</td>
<td></td>
</tr>
</tbody>
</table>

Week 0 28 54 80

Current Analysis
HIV RNA <50 copies/mL
(secondary endpoint)

Lenacapavir sc arms: oral lead-in (600 mg for days 1 and 2 and 300 mg day 8) followed by 927 mg sc on day 15.

Baseline demographics (overall):
- Male: 93%.
- Age: 29 years.
- Black: 52%.
- HIV RNA level:
  - Median: 4.4 log_{10} copies/mL.
  - >100K copies/mL: 15%.
- CD4 count:
  - Median: 437 cells/µL.

CALIBRATE Study: Outcomes at Week 28 With Lenacapavir-Based ART in Treatment-Naïve Patients

- All treatment arms lead to high rates of virologic suppression (94% to 100%)
  - >80% were suppressed by week 4
- Treatment emergent resistance at week 10 (n=1)
  - Lenacapavir sc + F/TAF
    - Lenacapavir concentrations consistently in target range
    - Capsid: Q67H + K70R (lenacapavir 20-fold change)
    - RT: M184M/I
- Lenacapavir was safe and well-tolerated
  - Injection site reactions (39%): majority were grade 1 and resolved within a few days
- Results support ongoing evaluation of lenacapavir in treatment-naïve patients

CAPELLA Study: Lenacapavir in Heavily ART-Experienced Patients

Phase 2/3
Treatment-experienced on failing regimen
HIV RNA ≥400 copies/mL
Resistance to ≥2 agents from
3 of 4 main ARV classes
≤2 fully active agents

Non-randomized cohort
Pre-randomization repeat HIV RNA
Decline of ≥0.5 log₁₀ copies/mL
<400 copies/mL

Baseline demographics (overall):
Male: 75%.
Age: 52 years.
Black: 38%.
HIV RNA level:
Mean: 4.5 log₁₀ copies/mL.
≥75K copies/mL: 28%.
CD4 count:
Mean: 150 cells/µL.
≤200 cells/µL: 64%.
Number of prior ARV agents: 11
Resistance (NRTI/NNRTI/PI/INSTI): 96%/90%/89%/90%.

CAPELLA Study (Randomized Cohort): Outcomes With Lenacapavir + OBR at Week 26

- HIV RNA by number of active agents in OBR
  - 0 (n=6)/1 (n=14)/≥2 (n=16): 67%/86%/81%

- CD4 increase: 81 cells/μL

- Emergent lenacapavir resistance (n=4)
  - Re-suppressed (1 with and 2 without OBR change)
  - 1 never re-suppressed (no fully active agents)

- No emergent resistance to agents in the OBR

- Overall well-tolerated (no serious adverse events and no discontinuations due to adverse events)
  - Injection-site reactions: 56% (most grade 1: 70%) and resolved within days

- Results support ongoing evaluation of lenacapavir in heavily ART-experienced patients

FDA Snapshot: Virologic Outcomes (n=36)

Study P016: Islatravir Once-Monthly Oral Tablet for PrEP

Phase 2a
Double-blind
HIV negative (18-65 years of age)
Low risk for HIV acquisition

Baseline demographics:
Female: 67%.
Age: 31 years.
White/black/other: 53%/42%/5%.

Study P016: Outcomes After 24 Weeks of Islatravir Once Monthly Oral Tablet for PrEP

- Islatravir once-monthly was well-tolerated
  - Discontinued due to adverse events: <1%
- Most adverse events were mild (73%)
  - Most common: headache (9%), diarrhea (6%), nausea (6%)
  - Drug-related: <3%
- Incidence of grade 3/4 laboratory changes were similar in both arms
  - Decreased creatinine clearance: 6%
  - Elevated lipase: 2%
- Islatravir-TP trough concentrations
  - Remained above the pre-specified threshold for HIV prevention (0.05 pmol/10⁶ PBMCs) for at least 8 weeks after the last dose

**Study 011: Safety and Metabolic Results at Week 96 With Islatravir + Doravirine in Treatment-Naïve Patients**

**Phase 2b study**

Open-label, dose-ranging Study
Treatment-naïve Study
HIV RNA ≥1000 copies/mL Study
No ART resistance Study
No HCV or HBV Study

**Baseline demographics (median values):**
- Male: 93%
- Age: 28 years
- HIV RNA: 4.6 log_{10} copies/mL
- CD4 count: 456 cells/mm$^3$
- Weight: 74-80 kg
- BMI: 23-26 kg/m$^2$
- Hip/spine BMD: 1.0-1.1/1.1-1.2 g/cm$^2$
- Peripheral fat: 7.2-9.3 kg
- Trunk fat: 9.7-12.7 kg

ISL: islatravir; DOR: doravirine.

Switch Allowed if HIV RNA <50 Copies/mL

Study 011: Safety and Metabolic Results at Week 96 With Islatravir + Doravirine in Treatment-Naïve Patients

• Safety
  – Headaches more common with islatravir + doravirine versus doravirine/3TC/TDF (11% versus 7%)
  – Diarrhea more common with doravirine/3TC/TDF versus islatravir + doravirine (19% versus 8%)

• Metabolic
  – Weight change was comparable between islatravir + doravirine and doravirine/3TC/TDF arms
  – Changes in hip and spine BMD were 3.2- and 2.7-fold lower, respectively, with islatravir + doravirine
  – Increases in HDL-C and LDL-C were numerically higher in the islatravir + doravirine groups versus doravirine/3TC/TDF

<table>
<thead>
<tr>
<th></th>
<th>Islatravir 0.25 mg + Doravirine (n=24)</th>
<th>Islatravir 0.75 mg + Doravirine (n=22)</th>
<th>Islatravir 2.25 mg + Doravirine (n=20)</th>
<th>Doravirine + 3TC + TDF (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in BMD (%)</td>
<td>0.7</td>
<td>0.7</td>
<td>-1.7</td>
<td>-3.4</td>
</tr>
<tr>
<td>Hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>+0.7</td>
<td>-0.3</td>
<td>-0.8</td>
<td>-2.2</td>
</tr>
<tr>
<td>Mean change in fat (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>+11</td>
<td>-0.9</td>
<td>+86</td>
<td>+8</td>
</tr>
<tr>
<td>Trunk</td>
<td>+19</td>
<td>+9.0</td>
<td>+19</td>
<td>+13</td>
</tr>
</tbody>
</table>
Next Generation Hybrid CAR-T Cells: Proof-of-Concept
*In Vitro* Study

- Primary CD8+ cells (derived from healthy donors): lentivirally transduced to express anti-HIV CAR and bNAb
  - Coculture of Hybrid CAR-T cells with autologous, HIV-infected CD4+ T cells
- Results
  - Hybrid CAR-T cells efficiently killed HIV-infected, autologous CD4+ T cells with complete inhibition of viral replication
  - Secreted antibodies alone reduced infectivity of HIV (dual, synergistic functionality of the Hybrid CAR)
- These data provide proof-of-concept for the Hybrid CAR platform
  - Show successful secretion of anti-HIV antibodies from primary T cells
  - Retained killing function mediated by simultaneously expressed CAR
  - Antibodies secreted by transfected cells initiated NK T cell degranulation
  - Ongoing experiments are being performed

CAR: chimeric antigen receptor; bNAb: broadly neutralizing antibodies.
REACH (MTN-034): Interim Results on Adherence to PrEP in Adolescent Girls and Young Women in Africa

- Randomized, open-label, cross-over study (2019-2021; n=247)
  - Non-pregnant, HIV negative (Cape Town, Harare, Johannesburg, Kampala)
  - Baseline characteristics: age (18 years), ever been pregnant (40%), not married (87%), ≥1 STI (35%), having a primary sex partner (89%), aware of HIV status of primary partner (75%), average number of sex partners in last 3 months (2.5)

- 6 months of dapivirine ring or F/TDF, then crossover for 6 months
  - At end of crossovers, participants chooses which PrEP option they prefer to continue for another 6 months

- Interim outcomes
  - HIV incidence: 0.5 per 100 woman years (1/247)
  - Adherence to the ring was higher than anticipated
  - Both PrEP options were well-tolerated
  - Adherence to both PrEP options can be achieved with tailored adherence support

### Interim Results

<table>
<thead>
<tr>
<th></th>
<th>Dapivirine Ring</th>
<th>F/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product-related adverse events ≥1 (%)</td>
<td>33</td>
<td>53</td>
</tr>
<tr>
<td>Average number</td>
<td>2.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Adherence (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Some use</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>High use</td>
<td>50</td>
<td>59</td>
</tr>
<tr>
<td>Full compliant use (%)</td>
<td>50</td>
<td>78</td>
</tr>
<tr>
<td>Product acceptability (%)</td>
<td>89</td>
<td>64</td>
</tr>
</tbody>
</table>

REACH: Reversing the Epidemic in Africa with Choices in HIV prevention.
GS-CA1: Long-Acting HIV Capsid Inhibitor as PrEP Against Vaginal SHIV Transmission in Macaques

- GS-CA1 (lenacapavir analog)
  - PBMC EC\textsubscript{50} SHIV: 0.748 nM
- Female pigtail and rhesus macaque vaginal SHIV challenge model (n=6 per group)
  - Single subcutaneous injection: GS-CA1 150 or 300 mg/kg, or placebo
  - 10 weekly escalating titer SHIV challenges starting 1-week post dosing
- All placebo controls acquired SHIV
  - Median time to infection: 4 weeks
- Complete protection against all 10 SHIV challenges with 300 mg/kg
  - Median time to infection (150 and 300 mg/kg): 14 weeks and not reached, respectively ($P<0.001$ for both)
- Results from this proof-of-concept study with GS-CA1 support clinical development of lenacapavir for HIV prevention in both males and females