Advances in HIV Prevention and Management 2021

IDAC Symposium

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Outline

• Prevention
  • Treatment as prevention
  • Current PrEP
  • Future PrEP

• HIV antiretroviral therapy
  • When to start
  • What to start
  • Switching in those suppressed
  • Managing virologic failure
HPTN 052: Treatment as Prevention

Linked HIV Transmission

<table>
<thead>
<tr>
<th>Year</th>
<th>Delayed ART</th>
<th>Early ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>2005-2011</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>2011-2014</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

### PARTNER2: HIV Transmission

- PARTNER2: 2014-2018 (MSM only) with 783 discordant couples and 1596 CYFU
- No linked transmissions documented in ~ 77,000 condomless sex acts when HIV-positive MSM partner suppressed to HIV-1 RNA < 200 copies/mL
- Unlinked transmissions occurred in 15 initially HIV-negative MSM partners

<table>
<thead>
<tr>
<th>Sexual Behavior Reported by HIV-Negative Partner</th>
<th>Linked Transmissions, n</th>
<th>Upper 95% CI*</th>
<th>Condomless Sex Acts, n</th>
<th>CYFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sex</td>
<td>0</td>
<td>0.23†</td>
<td>76991</td>
<td>1596</td>
</tr>
<tr>
<td>Anal sex</td>
<td>0</td>
<td>0.24</td>
<td>70743</td>
<td>1546</td>
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<tr>
<td>Insertive anal sex</td>
<td>0</td>
<td>0.27</td>
<td>52572</td>
<td>1345</td>
</tr>
<tr>
<td>Receptive anal sex without ejaculation</td>
<td>0</td>
<td>0.43</td>
<td>23153</td>
<td>867</td>
</tr>
<tr>
<td>Receptive anal sex with ejaculation</td>
<td>0</td>
<td>0.57</td>
<td>20770</td>
<td>652</td>
</tr>
<tr>
<td>Any sex with an STI</td>
<td>0</td>
<td>2.74</td>
<td>6301</td>
<td>135</td>
</tr>
</tbody>
</table>

*For rate of within-couple HIV transmission per 100 CYFU. †Compared with 0.84 for MSM and 0.46 for heterosexuals in PARTNER1.

HIV Undetectable equals Untransmittable
iPrEx: TDF/FTC PrEP in MSM

Grant R. et al. NEJM 2010.
DISCOVER Trial: HIV Incidence at Week 96 With Daily F/TAF or F/TDF for HIV PrEP in MSM/TGW

- F/TAF was non-inferior to F/TDF for HIV prevention at both week 48 and 96
- HIV infections: 23 in 10,081 person-years of follow-up
  - F/TAF (n=8): suspected baseline infection (n=1), low TFV-DP levels (n=6), medium TFV-DP levels (n=1)
    - No FTC or TAF resistance
  - F/TDF (n=15): suspected baseline infection (n=4), low TFV-DP levels (n=10), high TFV-DP levels (n=1)
    - FTC resistance: 4/13 genotyped

2 tablets 2-24 hours before sex
1 tablet 24 hours later
1 tablet 48 hours after first intake

4 pills of TDF/FTC taken over 3 days to cover one sexual intercourse

Molina JM, et al. NEJM 2016
ANRS Prévenir Study

Ongoing, open-label, prospective study (Paris region)

HIV negative, high-risk adults
Inconsistent condom use
Creatinine clearance (≥50 mL/min)
HBsAg negative (on-demand arm)

Primary outcome
≥15% reduction in new HIV diagnoses in Paris region at year 3

Participants may choose either daily or on-demand PrEP and could switch regimens during trial

Current Analysis
Data up to 9/30/20

HIV infections (n=6)
- 3/group over a follow-up of 22.1 months

Overall HIV incidence
- 0.11 per 100 patient-years

High incidence of bacterial/viral STIs

Safety
- No discontinuations due to adverse events

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**Results (9/30/20)**

<table>
<thead>
<tr>
<th></th>
<th>Daily PrEP (n=1544)</th>
<th>On-Demand PrEP (n=1515)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (patient-years)</td>
<td>2583</td>
<td>2554</td>
</tr>
<tr>
<td>HIV incidence per 100 patient-years (95% CI)</td>
<td>0.12 (0.02-0.34)</td>
<td>0.12 (0.02-0.34)</td>
</tr>
<tr>
<td>At last sexual intercourse (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct PrEP use</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>Condom use</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>All viral hepatitis (per 100 patient-years)</td>
<td>0.9 (0.5-1.7)</td>
<td>1.2 (0.6-2.0)</td>
</tr>
<tr>
<td>Creatinine clearance 50-70 mL/min per 100 patient-years (95% CI)</td>
<td>9.8 (8.7-11.1)</td>
<td>11.0 (9.8-12.4)</td>
</tr>
</tbody>
</table>
**HPTN 083: LA CAB vs. TDF/FTC**

- Phase 2b/3 (43 sites globally)
- Double-blind, double-dummy
- HIV-negative MSM and transgender women at risk for HIV
- No HBV or HCV
- No contraindication to gluteal injections, seizures, gluteal, tattoos/skin conditions

<table>
<thead>
<tr>
<th>Step 1 (5 Weeks)</th>
<th>Step 2 (5 Weeks)</th>
<th>Step 3 (1 Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily, Oral Cabotegravir</td>
<td>Cabotegravir Injection (q2 months for ~3 years) (n=2282)</td>
<td>Daily, Oral F/TDF</td>
</tr>
<tr>
<td>Daily, Oral F/TDF</td>
<td>Daily, Oral F/TDF (n=2284)</td>
<td>Daily, Oral F/TDF</td>
</tr>
</tbody>
</table>

DSMB recommended early termination May 14, 2020
(52 Incident HIV Infections over a median follow-up of 1.4 years)

Both agents were highly effective for HIV prevention
Long-acting injectable cabotegravir was superior to daily, oral F/TDF

Extended LC testing identified and reclassified 1 incident infection to a baseline infection in the cabotegravir arm

- Both agents were highly effective for HIV prevention

Long-acting cabotegravir arm

- 4 incident infections occurred despite target plasma concentrations (evaluation is ongoing)
- INSTI resistance
  - Seen when viremic “escape” occurs at higher cabotegravir concentrations

Multicenter, randomized, double-blind phase IIb/III trial in participants without HIV

Primary endpoints: incident HIV infections in Steps 1 and 2, grade ≥ 2 AEs

Secondary endpoints: incident HIV infection during follow-up, safety

Sexually active cisgender women age 18-45 yrs without HIV and at high risk of HIV infection (N = 3224)

Step 1

- CAB 30 mg PO QD + PBO QD (n = 1614)
- PBO QD + TDF/FTC QD (n = 1610)

Wk 5

Step 2 (Up to 185 Wks)

- CAB LA 600 mg IM Q8W* + PBO QD
- PBO IM Q8W* + TDF/FTC QD

Step 3

- TDF/FTC QD†
- TDF/FTC QD†

*First 2 doses given 4 wks apart then every 8 wks thereafter.
†Open-label TDF/FTC initiated maximum 8 wks after last injection for up to 48 wks.

HPTN 084: LA CAB vs. TDF/FTC in Women

89% lower risk of HIV infection for women in CAB group vs TDF/FTC group ($P = .000027$)

4 incident HIV infections in CAB arm
- 2 observed despite CAB injections
- 2 observed in the absence of CAB exposure

Any ISR (21%); Grade >1 ISR 4%; no discontinuations due to ISRs

50 pregnancies without increased risk congenital abnormalities

Islatravir Implant

- Phase 1, Double-blind, placebo-controlled
- Persons at low-risk for HIV
- Implant removed after 12 weeks, with
  - follow-up 8-weeks post-removal

- 48-mg implant (n=8)
- 52-mg implant (n=8)
- 62-mg implant (n=8)
- Placebo implant (n=8)
All 3 doses had concentrations above the pharmacokinetic threshold at 12 weeks
- 56-mg implant projected to be above pharmacokinetic threshold at 12 months

Overall, islatravir implants were well tolerated
- No discontinuations due to adverse events
- No severe implant-related adverse events
- Local tolerability adverse events (61%): generally mild and did not appear to be dose-dependent

Results support the continued development of islatravir implants for PrEP
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  • What to start
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  • Managing virologic failure
Improved Clinical Outcomes With Rapid ART Initiation

- Systematic review of rapid ART initiation (including 4 RCTs)
  - In the 4 RCTs, compared with standard care, same day ART increased likelihood of ART initiation in first 90 days, patient retention and viral suppression at 12 mos.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART start within 90 days</td>
<td>1.35 (1.13-1.62)</td>
</tr>
<tr>
<td>Retained in care at 12 mos</td>
<td>1.11 (0.99-1.26)</td>
</tr>
<tr>
<td>Viral suppression at 12 mos</td>
<td>1.17 (1.07-1.27)</td>
</tr>
<tr>
<td>LTFU at 12 mos</td>
<td>0.66 (0.42-1.04)</td>
</tr>
<tr>
<td>Died by 12 mos</td>
<td>0.53 (0.28-1.00)</td>
</tr>
</tbody>
</table>


Patients With HIV-1 RNA < 200 c/mL (%)

Ever achieving HIV RNA < 200 c/mL at 1 yr after ART start

HIV RNA < 200 c/mL at last recorded assessment

Yearly percentages:
- 0-0.25 yrs: 95.8%
- 0.25-0.50 yrs: 91.2%
- 0.50-0.75 yrs: 91.2%
- 0.75-1.00 yrs: 91.2%
- 1.00-1.25 yrs: 91.2%
- 1.25-1.50 yrs: 91.2%
- 1.50-1.75 yrs: 91.2%
- 1.75-2.00 yrs: 91.2%
- 2.00-2.25 yrs: 91.2%
- 2.25-2.50 yrs: 91.2%
- 2.50-2.75 yrs: 91.2%
- 2.75-3.00 yrs: 91.2%

Coffey. AIDS. 2018;[Epub].
Recommendations for Rapid Start

- **DHHS:** ART should be started immediately or as soon as possible following diagnosis
  - Should not include an NNRTI, ABC, or DTG/3TC

- **IAS-USA:** Recommended for all ambulatory patients committed to starting ART as soon as possible after diagnosis
  - Caveats in setting of possible opportunistic infection
  - Should not include an NNRTI or ABC

Rapid ART, or starting ART immediately or as soon as possible following diagnosis, can be started without labs or resistance testing.

DHHS, Department of Health and Human Services; IAS, International Antiviral Society; NNRTI, nonnucleoside reverse transcriptase inhibitor.
## Recommended ART regimens

**DHHS and IAS-USA**

### Recommended initial regimens for most people with HIV
- BIC/TAF/FTC\(^1,2\)
- DTG/ABC/3TC\(^1,2\)
- DTG+(TDF or TAF)+(FTC or 3TC)\(^1,2\)
- RAL+(TDF or TAF)+(FTC or 3TC)\(^1\)
- DTG/3TC\(^1,2\)
  - Need HIV RNA <500,000 copies/mL, no HBV coinfection, real-time genotypic resistance testing

### Recommended rapid ART regimens
- BIC/TAF/FTC\(^1,2\)
- DTG+(TDF or TAF)+(FTC or 3TC)\(^1,2\)
- (DRV/r or DRV/c)+(TAF or TDF)+(FTC or 3TC)\(^1\)

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GEMINI-1/2: DTG + 3TC in ART-Naive Adults

ART-naive adults with HIV-1 RNA 1000-500,000 copies/mL*, ≤ 10 days on previous ART; no major resistance associated mutation; no HBV infection or HCV infection requiring therapy (N = 1433)

Screening within 28 days of study start; studies double-blinded until Wk 96, open-label until Wk 144.

*In each arm, 2% of patients had BL HIV-1 RNA > 500,000 copies/mL and were incorporated into the ITT-E analysis.

GEMINI-1 and -2: Virologic Response at Wk 96

- DTG + 3TC met Snapshot criteria for **noninferior efficacy** vs DTG + FTC/TDF at Wk 96

*Adjusted for baseline HIV-1 RNA, baseline CD4+ cell count, and study.
†Accounts for CVW, withdrawal for lack of efficacy or treatment-related AE, and participants meeting protocol-defined stopping criteria.

HIV-1 RNA < 50 copies/mL by Snapshot, % (95% CI)

Cahn. IAS 2019. Abstr WEAB0404LB.
## Latest on DTG and NTDs in Women With HIV

### Effect of DTG on NTD in Tsepamo Study in Botswana

<table>
<thead>
<tr>
<th>Category</th>
<th>NTD/ Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG at conception</td>
<td>7/3591</td>
</tr>
<tr>
<td>Non-DTG ART at conception</td>
<td>21/19,361</td>
</tr>
<tr>
<td>EFV at conception</td>
<td>8/10,958</td>
</tr>
<tr>
<td>DTG started during pregnancy</td>
<td>2/4581</td>
</tr>
<tr>
<td>HIV negative</td>
<td>87/119,630</td>
</tr>
</tbody>
</table>

*P*<0.05.

IMPAACT 2010: Maternal Virologic Response

Key Eligibility Criteria
- Pregnant WLHIV 14-28 weeks gestation
- ART-naïve (up to 14 days ART in current pregnancy allowed)

Participants were enrolled at 22 sites in 9 countries
Total enrollment 643 women and 617 live births

IMPAACT 2010: Maternal Virologic Response

Maternal HIV-1 RNA < 200 Copies/mL at Postpartum Wk 50

Per ITT analysis

- Combined DTG Arms: 96.3%
- EFV/FTC/TDF: 96.4%

$P = .97$

Maternal Virologic Failure* at ≥ 24 Wks on Study

Post hoc comparisons

- DTG+FTC/TAF: 4.1%
- DTG+FTC/TDF: 5.1%
- EFV/FTC/TDF: 10.4%

$P = .012$

*2 successive HIV-1 RNA ≥ 200 copies/mL

IMPAACT 2010: Maternal Virologic Response

- **Major congenital anomalies** occurred among 4 infants:
  - 2 in DTG+FTC/TAF arm:
    - Atrial septal defect
    - Talipes equinovarus in the right foot
  - 2 in EFV/FTC/TDF arm:
    - Duodenal atresia/ileal stenosis
    - Subgaleal cyst

- % women/infants with AE:
  - Maternal Grade ≥3 AE: 25.1% (DTG+FTC/TAF), 30.8% (DTG+FTC/TDF), 27.9% (DTG+FTC/TAF), 30.9% (DTG+FTC/TDF)
  - Infant Grade ≥3 AE: 25.3% (DTG+FTC/TAF), 28.6% (DTG+FTC/TDF)
  - Infant Deaths: 1.0% (DTG+FTC/TAF), 2.0% (DTG+FTC/TDF), 6.9% (EFV/FTC/TDF)
  - Stillbirth or Infant Deaths*: 4.6% (DTG+FTC/TAF), 7.0% (DTG+FTC/TDF), 8.5% (EFV/FTC/TDF)

*Post hoc analysis
ADVANCE: Phase III Trial of First-line DTG + FTC/(TAF or TDF) vs EFV/FTC/TDF in South Africa

- Multicenter, randomized, open-label phase III trial conducted in South Africa

- Primary efficacy endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by ITT (M=F) analysis
  - DTG + FTC/TAF and DTG + FTC/TDF noninferior to EFV/FTC/TDF at Wk 48: 84% vs 85% vs 79%

- Secondary endpoints: safety, weight gain

Significantly greater weight increase* with DTG vs EFV, with TAF vs TDF; plateauing in weight gain after Wk 48 observed in men but not in women.
Multivariate Analysis of Weight Gain Following ART Initiation

- Pooled analysis of weight gain across 8 randomized phase III clinical trials of first-line ART initiation occurring in 2003-2015 (N = 5680)

*Color-coded to match respective comparators, denoting $P \leq .05$ vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).
The Why and How of Switching in Virologically Suppressed Patients

**Why**
- Simplify regimen (# and frequency)
- Tolerability
- Co-morbidity
- Drug-drug, drug-food interactions
- Pregnancy
- Cost

**How**
- Maintain viral suppression to avoid resistance
- Need to consider
  - Previous ART
  - Previous resistance
  - Likelihood of adherence
  - Drug-drug or drug-food
  - Comorbid conditions

SWORD Studies: DTG + RPV maintenance for those on stable regimen with no history of failure

TANGO: Continue TAF-based Regimen or Switch to DTG/3TC

Virologic outcomes (Snapshot analysis)

Adjusted treatment difference (95% CI)

- Superiority was demonstrated in the per-protocol analysis: 0/348 participants in the DTG/3TC group and 4/351 in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 96 (adjusted difference, -1.1%; 95% CI, -2.3% to -0.0%; P=0.044)
- In the DTG/3TC group, there were no cases of confirmed virologic withdrawal through Week 96 and 3 cases in the TAF-based regimen group; no resistance mutations were observed

*Sensitivity analysis excluding 16 and 28 participants in the DTG/3TC and TAF-based regimen groups, respectively, because of no Week 96 HIV-1 RNA data due to effects of the COVID-19 pandemic. *Primary endpoint (Snapshot virologic non-response, ITT-E). Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC – TAF-based regimen) adjusting for baseline third agent class.
ATLAS and FLAIR: LA CAB + RPV Q4 weeks vs. Baseline ART

- Multicenter, randomized, open-label phase III noninferiority trials

**ATLAS**

- Adults on stable ART (either first or second regimen) with HIV-1 RNA < 50 copies/mL for ≥ 6 mos with no previous VF (N = 616)

**FLAIR**

- ART-naive patients with HIV-1 RNA ≥ 1000 copies/mL, HBsAg negative, no NNRTI RAMs but K103N permitted (N = 629)

- Primary endpoint for both trials: HIV-1 RNA ≥ 50 copies/mL at Wk 48 by FDA Snapshot in ITT-E

ATLAS and FLAIR: LA CAB + RPV Q4 weeks vs. Baseline ART

ATLAS Virologic Outcomes at Wk 48

- **LA CAB + LA RPV** (n = 308)
- **Continued BL ART** (n = 308)

<table>
<thead>
<tr>
<th>Virologic Nonresponse (≥ 50 c/mL)</th>
<th>Virologic Success (&lt; 50 c/mL)</th>
<th>No Virologic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6</td>
<td>92.5</td>
<td>5.8</td>
</tr>
<tr>
<td>1.0</td>
<td>95.5</td>
<td>3.6</td>
</tr>
</tbody>
</table>

FLAIR Virologic Outcomes at Wk 48

- **LA CAB + LA RPV** (n = 283)
- **DTG/ABC/3TC** (n = 283)

<table>
<thead>
<tr>
<th>Virologic Nonresponse (≥ 50 c/mL)</th>
<th>Virologic Success (&lt; 50 c/mL)</th>
<th>No Virologic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>93.6</td>
<td>4.2</td>
</tr>
<tr>
<td>2.5</td>
<td>93.3</td>
<td>4.2</td>
</tr>
</tbody>
</table>

- Noninferiority also observed at Wk 96
- No additional CVF during Wk 48 to 96 in CAB+RPV arm

Swindells. NEJM. 2020;382:1112.
ATLAS-2M: LA CAB + RPV Q4 vs. Q8 weeks

Phase 3b, randomized, multicenter, parallel-group, noninferiority, open-label study

- The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E)
- Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 c/mL at Week 96 (Snapshot, ITT-E)
- Other endpoints assessed at Week 96 included the incidence of CVF (two consecutive plasma HIV-1 RNA levels ≥200 c/mL), incidence of viral resistance in participants with CVF, and safety and tolerability

*ITT-E population. †Randomization was stratified by prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). ‡Excluding participants with prior CAB + RPV exposure in ATLAS.

For further study design details, please see Overton et al. CROI 2020; Boston, MA. Presentation 3334.

CAB, cabazitavir; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; SoC, standard of care; W, week.


Conference on Retroviruses and Opportunistic Infections; March 6–10, 2021; Virtual

Jaeger et al. CROI 2021; Virtual: Science Spotlight 1753.
ACTG 5459: LA CAB + RPV in Nonadherent Patients

**STEP 1: 24 wks**
- **SoC** (3 ARVs at least 2 active)
  - SoC R

**STEP 2: 52 wks**
- IM CAB LA (600 mg LD → 400 mg maint) + IM RPV LA (900 mg LD → 600 mg maint) (Q4W)
- RPV 25mg + CAB 30mg (QD)

**STEP 3: 52 wks**
- 48 wks of IM CAB-LA + RPV-LA
- NOT randomized

**STEP 4: up to 52 wks SoC “tail” for anyone receiving at least one dose of LA ARV**

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**Study entry wk**

<table>
<thead>
<tr>
<th>Step 1, Wk</th>
<th>Milestone</th>
<th>Incentive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Completed visit</td>
<td>$75</td>
</tr>
<tr>
<td>4</td>
<td>HIV-1 RNA &gt; 1 log_{10} drop</td>
<td>$75</td>
</tr>
<tr>
<td>8</td>
<td>HIV-1 RNA &gt; 2 log_{10} drop</td>
<td>$75</td>
</tr>
<tr>
<td>12</td>
<td>HIV-1 RNA &lt; 200 copies/mL</td>
<td>$150</td>
</tr>
<tr>
<td>16</td>
<td>HIV-1 RNA &lt; 200 copies/mL</td>
<td>$150</td>
</tr>
<tr>
<td>20</td>
<td>HIV-1 RNA &lt; 50 copies/mL</td>
<td>$150</td>
</tr>
</tbody>
</table>
SWITCHMRK: A Cautionary Tale if Underlying Resistance

- Randomized, double-blind trials in which virologically suppressed patients continued LPV/RTV-based regimen or switched to RAL-based regimen (N = 702)

- Underlying resistance matters: % with HIV-1 RNA < 50 c/mL for RAL vs LPV/RTV by investigator report of previous virologic failure: no, 89% vs 90%; yes, 77% vs 92%

*Prespecified noninferiority margin: -12%.

Patients with viral suppression on stable triple DTG-based ART switched to BIC/FTC/TAF or continued DTG-based ART; documented or suspected NRTI, NNRTI, or PI resistance permitted

- Preexisting NRTI resistance: 25% in BIC/FTC/TAF arm and 24% in DTG-based ART arm

**Virologic Outcomes (FDA Snapshot)**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>HIV-1 RNA ≥ 50 c/mL</th>
<th>HIV-1 RNA &lt; 50 c/mL</th>
<th>No Virologic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC/FTC/TAF</td>
<td>93/284</td>
<td>265/284</td>
<td>18/284</td>
</tr>
<tr>
<td>DTG + FTC/TAF</td>
<td>91/281</td>
<td>256/281</td>
<td>22/281</td>
</tr>
</tbody>
</table>

**Treatment Difference, % (95% CI)**

Favors BIC/FTC/TAF: -2.8 (95% CI: -2.8 to 1.0)

Favors DTG + FTC/TAF: 1.0

**HIV-1 RNA ≥ 50 copies/mL**

Study 380-4030: Switch to BIC/FTC/TAF from DTG + FTC/TAF (or TDF)

- HIV-1 RNA $\geq 50$ c/mL not observed in any patient with preexisting NRTI resistance

Virologic Outcomes at Wk 48 (FDA Snapshot)

Data suggest switching 1 high-resistance barrier drug for another may be effective in patients with viral suppression, even in the setting of underlying resistance

BRAAVE 2020: Continue Current Regimen or Switch to BIC/FTC/TAF in Black PLWH

- 2:1 randomized, open-label, active-controlled phase III study
- Evaluated switch from BL regimen (2 NRTIs + third agent) to BIC/FTC/TAF in virologically suppressed black PLWH (N = 495)

Switch to BIC/FTC/TAF noninferior to remaining on BL regimen at Wk 24
  - Wk 24 was primary efficacy endpoint
- Patients with BL NRTI resistance remained suppressed at Wk 24

<table>
<thead>
<tr>
<th>BL ARV Resistance, %</th>
<th>BIC/FTC/TAF (n = 330)</th>
<th>Continue BL Regimen (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M184V/I</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>NNRTI</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>PI</td>
<td>11</td>
<td>15</td>
</tr>
</tbody>
</table>

Wk 24 Virologic Outcomes

- HIV-1 RNA < 50 c/mL (%)

<table>
<thead>
<tr>
<th>NRTI Resistance</th>
<th>M184V or M184I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>98 96</td>
</tr>
<tr>
<td>No</td>
<td>44 26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NRTI Resistance</th>
<th>M184V or M184I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>96 95</td>
</tr>
<tr>
<td>No</td>
<td>269 132</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NRTI Resistance</th>
<th>M184V or M184I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>97 95</td>
</tr>
<tr>
<td>No</td>
<td>31 20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NRTI Resistance</th>
<th>M184V or M184I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>96 95</td>
</tr>
<tr>
<td>No</td>
<td>282 138</td>
</tr>
</tbody>
</table>

**EARNEST: First-line NNRTI Failure**

- **Randomized, open-label, multicenter trial in sub-Saharan Africa**
  - Primary endpoint: good HIV disease control at Wk 96

  - HIV-infected pts with confirmed VF on NNRTI + 2 NRTIs with no previous PI use (N = 1277)

  - LPV/RTV + RAL (n = 433)

  - LPV/RTV + 2-3 NRTIs* (n = 426)

  - LPV/RTV Monotherapy (n = 418)

  *NRTIs chosen WITHOUT genotype by clinician.

Pts stratified by center, CD4+ cell count (< 200 or ≥ 200 c/mm³). LPV/RTV and RAL dosed BID.

ERNEST: NRTIs Maintain Activity Even With Extensive Resistance

- Second-line therapy after failure of 2 NRTIs plus NNRTI-based regimen (N = 1277)
- Recycled “inactive” NRTIs plus boosted PI more active than PI monotherapy

DAWNING: DTG vs. LPV/r for NNRTI Failures

- Patients with VF on first-line NNRTI + 2 NRTIs switched to DTG or LPV/RPV + 2 NRTIs (≥ 1 fully active NRTI per GT resistance testing at screening); no primary resistance to INSTIs or PIs

- Emergent INSTI and INSTI + NRTI resistance at CVW with DTG: n = 2[^2]

- Emergent NRTI resistance but no PI resistance at CVW with LPV/RTV: n = 3[^2]

*Did not confer resistance to either NRTI taken during trial.

[^1]: *P < .001 for superiority.

DAWNING: Virologic Response by Presence of M184V/I and Use of 3TC or FTC at Wk 48

Virologic Outcomes (ITT-E)

<table>
<thead>
<tr>
<th>Use of 3TC or FTC</th>
<th>DTG + 2 NRTIs</th>
<th>No use of 3TC or FTC</th>
<th>No M184V/I</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 50 c/mL (%)</td>
<td>12.6</td>
<td>9.1</td>
<td>9.1</td>
</tr>
<tr>
<td>n/N =</td>
<td>187/220</td>
<td>152/210</td>
<td>41/51</td>
</tr>
</tbody>
</table>

Use of 3TC or FTC
No use of 3TC or FTC
No M184V/I

Eligible patients:
On TDF+3TC/FTC+NNRTI regimen for ≥ 6m with treatment failure defined as:
VL ≥ 1000 copies/ml at screening AND
EITHER: VL ≥ 1000 copies/ml on test taken < 6m (& ≥4wks) prior to screening
OR: VL ≥ 1000 copies/ml on confirmatory test taken ≥4wks after screening

2 X 2 factorial randomisation

RANDOMISATION 1

DTG

DRV/r (900mg/100mg od)

RANDOMISATION 2

TDF + ZDV

TDF + 3TC

ZDV + 3TC

TDF + 3TC

Follow up for 96 weeks

Primary outcome: Viral load < 400 copies/ml at week 48
### NADIA Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dolutegravir group (N=235)</th>
<th>Darunavir group (N=229)</th>
<th>Tenofovir group (N=233)</th>
<th>Zidovudine group (N=231)</th>
<th>Overall (N=464)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex – no (%)</td>
<td>140 (59.5)</td>
<td>142 (62.0)</td>
<td>140 (60.1)</td>
<td>142 (61.5)</td>
<td>282 (60.8)</td>
</tr>
<tr>
<td>Median age (IQR) – yr</td>
<td>33 (28-40)</td>
<td>35 (28-42)</td>
<td>34 (28-43)</td>
<td>35 (28-40)</td>
<td>34 (28-41)</td>
</tr>
<tr>
<td>CD4+ lymphocyte count, Median (IQR) – per mm³</td>
<td>189 (58-388)</td>
<td>202 (84-357)</td>
<td>200 (77-388)</td>
<td>191 (58-340)</td>
<td>194 (68-367)</td>
</tr>
<tr>
<td>&lt; 50 per mm³ – no (%)</td>
<td>54 (23.0)</td>
<td>39 (17.0)</td>
<td>45 (19.3)</td>
<td>48 (20.8)</td>
<td>93 (20.0)</td>
</tr>
<tr>
<td>50-199 per mm³ – no (%)</td>
<td>71 (30.2)</td>
<td>74 (32.3)</td>
<td>70 (30.0)</td>
<td>75 (32.5)</td>
<td>145 (31.3)</td>
</tr>
<tr>
<td>200-349 per mm³ – no (%)</td>
<td>43 (18.3)</td>
<td>56 (24.5)</td>
<td>47 (20.2)</td>
<td>52 (22.5)</td>
<td>99 (21.3)</td>
</tr>
<tr>
<td>&gt; 350 per mm³ – no (%)</td>
<td>67 (28.5)</td>
<td>60 (26.2)</td>
<td>71 (30.5)</td>
<td>56 (24.2)</td>
<td>127 (27.4)</td>
</tr>
<tr>
<td>HIV-1 viral load, Median (IQR) – log₁₀ copies/ml</td>
<td>4.5 (3.9-5.1)</td>
<td>4.4 (3.8-5.1)</td>
<td>4.4 (3.9-5.1)</td>
<td>4.4 (3.9-5.1)</td>
<td>4.4 (3.9-5.1)</td>
</tr>
<tr>
<td>K65R/N present at baseline – no (%)</td>
<td>120 (52.9)</td>
<td>107 (47.6)</td>
<td>126 (50.7)</td>
<td>111 (49.8)</td>
<td>227 (50.2)</td>
</tr>
<tr>
<td>M184V/I present at baseline – no (%)</td>
<td>196 (86.3)</td>
<td>195 (86.7)</td>
<td>201 (87.8)</td>
<td>190 (85.2)</td>
<td>391 (86.5)</td>
</tr>
<tr>
<td>Int/high TDF resistance – no (%)</td>
<td>139 (61.2)</td>
<td>125 (55.9)</td>
<td>132 (57.9)</td>
<td>132 (59.2)</td>
<td>264 (58.5)</td>
</tr>
<tr>
<td>Int/high ZDV resistance – no (%)</td>
<td>45 (19.8)</td>
<td>38 (17.0)</td>
<td>41 (18.0)</td>
<td>42 (18.8)</td>
<td>83 (18.4)</td>
</tr>
<tr>
<td>Int/high 3TC resistance – no (%)</td>
<td>213 (93.8)</td>
<td>202 (90.2)</td>
<td>212 (93.0)</td>
<td>203 (91.0)</td>
<td>415 (92.0)</td>
</tr>
</tbody>
</table>
### NADIA Outcomes by Third Drug

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dolutegravir Group (N=235)</th>
<th>Darunavir Group (N=229)</th>
<th>Difference (95% CI) %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV-1 RNA level (primary outcome) – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 400 copies/ml (ITT)</td>
<td>212 (90.2)</td>
<td>210 (91.7)</td>
<td>-1.49 (-6.7 to 3.7)</td>
<td>0.576</td>
</tr>
<tr>
<td>≥ 400 copies/ml</td>
<td>20 (8.5)</td>
<td>16 (7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No virological data</td>
<td>3 (1.3)</td>
<td>3 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Withdrew because of AE/death</td>
<td>2 (0.9)</td>
<td>3 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Withdrew for other reasons</td>
<td>1 (0.4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV-1 RNA level (sensitivity analyses, secondary, other outcomes) – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 400 copies/ml (adjusted)</td>
<td>88.2</td>
<td>89.8</td>
<td>-1.6 (-6.9 to 3.6)</td>
<td>0.541</td>
</tr>
<tr>
<td>VL &lt; 400 copies (per protocol)</td>
<td>205 (92.3)</td>
<td>204 (93.2)</td>
<td>-0.8 (-5.6 to 4.0)</td>
<td>0.744</td>
</tr>
<tr>
<td>VL &lt; 1000 c/ml (ITT)</td>
<td>217 (92.3)</td>
<td>213 (93.0)</td>
<td>-0.7 (-5.4 to 4.1)</td>
<td>0.781</td>
</tr>
<tr>
<td>VL&lt; 50 c/ml (ITT)</td>
<td>190 (80.9)</td>
<td>182 (79.5)</td>
<td>1.4 (-5.9 to 8.6)</td>
<td>0.710</td>
</tr>
<tr>
<td><strong>Rebound (secondary outcome) – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VL rebound ≥ 1000 c/ml, confirmed (ITT)</td>
<td>14 (6.0)</td>
<td>13 (5.7)</td>
<td>0.3 (-4.0 to 4.5)</td>
<td>0.897</td>
</tr>
<tr>
<td>VL rebound ≥ 1000 c/ml, confirmed with</td>
<td>4*</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 major RM to DTG or DRV*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


≥1 major DRV mutation: 0
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenofovir Group (N= 233)</th>
<th>Zidovudine Group (N= 231)</th>
<th>Difference (95% CI) %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA level (primary outcome) – no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 400 copies/ml (ITT)</td>
<td>215 (92.3)</td>
<td>207 (89.6)</td>
<td>2.7 (-2.6 to 7.9)</td>
<td>0.317</td>
</tr>
<tr>
<td>≥ 400 copies/ml</td>
<td>15 (6.4)</td>
<td>21 (9.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No virological data</td>
<td>3 (1.3)</td>
<td>3 (1.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Withdrew because of AE/death</td>
<td>3 (1.3)</td>
<td>2 (0.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Withdrew for other reasons</td>
<td>0</td>
<td>1 (0.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HIV-1 RNA level (sensitivity analyses, secondary, other outcomes) – no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 400 copies/ml (adjusted)</td>
<td>88.2</td>
<td>85.4</td>
<td>2.8 (-2.5 to 8.0)</td>
<td>0.304</td>
</tr>
<tr>
<td>VL &lt; 400 copies (per protocol)</td>
<td>209 (93.7)</td>
<td>200 (91.7)</td>
<td>2.0 (-2.9 to 6.8)</td>
<td>0.423</td>
</tr>
<tr>
<td>VL &lt; 1000 c/ml (ITT)</td>
<td>219 (94.0)</td>
<td>211 (91.3)</td>
<td>2.6 (-2.1 to 7.4)</td>
<td>0.274</td>
</tr>
<tr>
<td>VL &lt; 50 c/ml (ITT)</td>
<td>188 (80.7)</td>
<td>184 (79.7)</td>
<td>1.0 (-6.2 to 8.3)</td>
<td>0.780</td>
</tr>
<tr>
<td>Rebound (secondary outcome) – no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VL rebound ≥ 1000 c/ml, confirmed (ITT)</td>
<td>11 (4.7)</td>
<td>16 (6.9)</td>
<td>-2.2 (-6.5 to 2.1)</td>
<td>0.310</td>
</tr>
<tr>
<td>VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* ≥1 major DTG mutation: 4
≥1 major DRV mutation: 0
Prevalence of Heavily Treatment–Experienced Patients With Multiclass Resistance

- CNICS cohort of > 26,000 ART-experienced people with HIV receiving care in the US
- Limited treatment options defined as ≤ 2 available classes with ≤ 2 active drugs per class by resistance testing

BENCHMRK: Management of Treatment-Experienced

HIV RNA < 50 Copies/mL (Wk 48)

- OBT + RAL 400 mg BID
- OBT + placebo

TMB-301: Ibalizumab in Pretreated Patients Infected With Multidrug-Resistant HIV

- Single-arm, open-label phase III trial in patients with virologic failure
  - Primary endpoint: HIV-1 RNA decrease $\geq 0.5 \log_{10}$ copies/mL from baseline to Day 14

- 53% with resistance to all drugs from $\geq 3$ classes; 68% with INSTI resistance
- Mean BL VL $4.5 \log_{10}$ copies/mL; mean BL CD4+ cell count: 150 cells/mm³

Emu. NEJM. 2018;379:645.
TMB-301/-311: Virologic Outcomes Through 96 Wks

- TMB-311: patients enrolled in US and Puerto Rico who completed 25 wks in TMB-301 continued ibalizumab 800 mg Q2W for up to 96 wks

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.5 log(_{10}) HIV-1 RNA decrease, %</td>
<td>83*[^†]</td>
<td>63</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>≥ 1.0 log(_{10}) HIV-1 RNA decrease, %</td>
<td>60</td>
<td>55</td>
<td>67</td>
<td>NR</td>
</tr>
<tr>
<td>Mean log(_{10}) HIV-1 RNA decrease</td>
<td>1.1</td>
<td>1.6</td>
<td>2.1</td>
<td>NR</td>
</tr>
<tr>
<td>Median log(_{10}) HIV-1 RNA decrease</td>
<td>NR</td>
<td>2.5</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL, %</td>
<td>NR</td>
<td>43</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 copies/mL, %</td>
<td>NR</td>
<td>50</td>
<td>63</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Primary endpoint; P < .0001 vs 3% at end of control period. †3 patients without ≥ 0.5 log\(_{10}\) HIV-1 RNA decrease at Day 14 later reached HIV-1 RNA < 50 copies/mL with ibalizumab + OBR.[^5]

[^1]: Emu. NEJM. 2018;379:645.
BRIGHTE: Fostemsavir in Heavily Treatment-Experienced Adults With Multidrug-Resistant HIV

Randomized Cohort
1-2 remaining ARV classes
(≥ 1 fully active* approved agent/class), cannot construct viable regimen with remaining agents
(n = 272)

Nonrandomized Cohort
No remaining ARV classes and no fully active* approved agents
(n = 99)

Primary Endpoint
Mean Δ in HIV-1 RNA, log_{10} c/mL (95% CI)
-0.79 (-0.88 to -0.70)
-0.17 (-0.33 to -0.01)

Day 1
FTR 600 mg BID + Failing Regimen
(n = 203)
Placebo + Failing Regimen
(n = 69)

Day 8
FTR 600 mg BID + OBT
FTR 600 mg BID + OBT

Day 9
FTR 600 mg BID + OBT
FTR 600 mg BID + OBT

Wk 96

*No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV.

BRIGHTE: Virologic and Safety Outcomes Through 96 Wks

**Outcome at Wk 96, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Randomized (n = 272)</th>
<th>Nonrandomized (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 40 c/mL</td>
<td>163 (60)</td>
<td>37 (37)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥ 40 c/mL</td>
<td>81 (30)</td>
<td>43 (43)</td>
</tr>
<tr>
<td>No virologic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ D/c due to AE or death</td>
<td>28 (10)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>▪ D/c due to AE or death</td>
<td>15 (6)</td>
<td>14 (14)</td>
</tr>
</tbody>
</table>

*Snapshot analysis excluded BL data; 1 patient had BL HIV-1 RNA < 40 c/mL.

Lenacapavir in Heavily Treatment Experienced Patients

- 2 of 72 patients had emergent capsid mutations conferring high level LEN resistance: M66I and N74D at Wk 10; M66I at Wk 26
  - Both pts resuppressed (1 with, 1 without OBR change), but M66I significantly impairs viral replication

*600 mg QD on Days 1 and 2; 300 mg QD on Day 8. Administered as 927 mg SC in abdomen on Day 15, followed by OBR selected by investigator.

Lenacapavir in Heavily ART-Experienced PWH: Interim Data From SC Maintenance Phase

Proportion of Participants With Viral Suppression by Week 26

*Patient denominators are participants at each time period who received ≥ 1 dose of LEN SC and had an HIV-1 RNA result at time of data cut in Feb 2021 (study ongoing). *2 patients in open-label cohort had HIV-1 RNA < 50 copies/mL by Day 2 of oral lead-in phase, presumed to be due to improved adherence.

Management of ARV Failure: Second Line and Beyond

- Boosted PI and/or DTG susceptible
  - Yes
    - DTG† + 2 NRTIs‡
    - Boosted PI + 2 NRTIs‡
    - Boosted PI + active INSTI
  - Neither*
    - DTG only
      - PI only
        - Boosted PI + 2 NRTIs‡
      - 2 and preferably 3 fully active drugs
  - DTG only
    - 2 and preferably 3 fully active drugs

*Rare in patients never exposed to unboosted PIs (eg, NFV, DHHS alternative since 2003 and not recommended since 2008).
†If INSTI naive or in patients with no INSTI resistance (limited data in patients with resistance to RAL or EVG but susceptibility to DTG).
‡At least 1 fully active NRTI.

Adapted from DHHS ART Guidelines. December 2019.
Thank You!!