Antiretroviral Therapy for HIV Infection 2017

Novel and Investigational Strategies

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Current Status: 90-90-90 Targets

Global (2016)

- Number of People Living With HIV (Millions)
  - People With HIV Who Know Their Status: 18.5
  - People With HIV on Treatment: 50
  - People With HIV Who Are Virally Suppressed: 100

- Percent: 70% 53% 44%

Western and Central Europe and North America (2015)

- Number of People Living With HIV (Thousands)
  - People With HIV Who Know Their Status: 2000
  - People With HIV on Treatment: 1500
  - People With HIV Who Are Virally Suppressed: 200

- Percent: 85% 76% 64%

Eastern and Southern Africa (2016)

- Number of People Living With HIV (Millions)
  - People With HIV Who Know Their Status: 37
  - People With HIV on Treatment: 75
  - People With HIV Who Are Virally Suppressed: 25

- Percent: 76% 60% 50%

When to Start ART: Global Consensus

<table>
<thead>
<tr>
<th>AIDS or HIV-Related Symptoms</th>
<th>CD4 Count (cells/mm³)</th>
<th>&lt;200</th>
<th>200-350</th>
<th>350-500</th>
<th>&gt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States DHHS (2016)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IAS-USA (2016)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>British HIV Association (2016)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>European AIDS Clinical Society (2016)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO (2015)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

HOPS Cohort: ART Initiation and Achieving CD4 Normalization

- CD4 trajectories in the HOPS Cohort after >3 years of ART (n=1327) (1996-2012)
  - CD4 normalization (>750 cells/mm³)

- After 7.9 years of follow-up, progressively higher CD4 at ART initiation was associated with
  - Greater gains in CD4
  - Greater likelihood of CD4 normalization (baseline CD4 and hazard ratio for achieving CD4 normalization with ART)
    - 500-750 cells/mm³: 12.78 (P<0.001)
    - 350-499 cells/mm³: 7.02 (P<0.001)
    - 200-349 cells/mm³: 3.16 (P<0.001)
    - Reference: 0-49 cells/mm³: 1.0
  - Increased survival rates

Narrowing the Gap in Life Expectancy Between HIV-Positive and Uninfected Persons (1996-2011)

Kaiser Permanente Northern California (1996 to 2011): HIV-positive (n=25,768) and matched non-HIV-infected adults (n=257,600). Males (91%) and MSM (75%).

### DHHS Guidelines: Recommended Regimens

**Regardless of Baseline HIV RNA Level or CD4 Count**

#### INSTI
- Raltegravir + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF
- Elvitegravir/cobicistat/emtricitabine/tenofovir AF*
- Elvitegravir/cobicistat/emtricitabine/tenofovir DF*
- Dolutegravir/abacavir/lamivudine*
- Dolutegravir + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF

#### PI
- Darunavir + ritonavir (qd) + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF

*Available as a once-daily, single-tablet regimen.

**Notes:**
- Lamivudine may be substituted for emtricitabine or vice versa (if non-fixed dose NRTI combination is desired).
- The evidence supporting the use of emtricitabine/TAF with dolutegravir or raltegravir is based on relative bioavailability data plus data from randomized, controlled switch trials demonstrating the safety/efficacy of TAF-containing regimens.
- Tenofovir DF: use with caution in patients with renal insufficiency.
- Elvitegravir/cobicistat/emtricitabine/tenofovir AF: only for patients with pre-ART creatinine clearance ≥30 mL/min.
- Elvitegravir/cobicistat/emtricitabine/tenofovir DF: only for patients with pre-ART creatinine clearance ≥70 mL/min.
- Dolutegravir/abacavir/lamivudine: only for patients who are HLA-B*5701 negative.

DHHS Guidelines:
Alternative Regimens

May Be the Preferred Regimen for Some Patients

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Efavirenz/emtricitabine/tenofovir DF*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efavirenz + emtricitabine/tenofovir AF</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine/emtricitabine/tenofovir DF*</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine/emtricitabine/tenofovir AF*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI</th>
<th>Atazanavir/cobicistat + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atazanavir + ritonavir + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</td>
</tr>
<tr>
<td></td>
<td>Darunavir/cobicistat + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</td>
</tr>
<tr>
<td></td>
<td>Darunavir/cobicistat or darunavir/ritonavir + abacavir/lamivudine</td>
</tr>
</tbody>
</table>

*Available as a once-daily, single-tablet regimen.

Notes:
- Lamivudine may be substituted for emtricitabine or vice versa (if non-fixed dose NRTI combination is desired).
- The evidence supporting the use of emtricitabine/TAF with efavirenz, rilpivirine, atazanavir, or darunavir is based on relative bioavailability data plus data from randomized, controlled switch trials demonstrating the safety/efficacy of TAF-containing regimens.
- Efavirenz: avoid use in women trying to conceive or are sexually active and not using contraception.
- Tenofovir DF: use with caution in patients with renal insufficiency.
- Rilpivirine/emtricitabine/tenofovir DF: only for patients with pre-ART HIV RNA <100K copies/mL and CD4 >200 cells/mm³.
- Atazanavir/cobicistat or darunavir/cobicistat + emtricitabine/tenofovir DF: only for patients with pre-ART creatinine clearance ≥70 mL/min.
- Atazanavir + RTV: absorption depends on food and low gastric pH.
- Atazanavir + RTV: absorption depends on food and low gastric pH.

### IAS-USA Guidelines: Recommended Regimens

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elvitegravir/cobicistat/emtricitabine/tenofovir AF*</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir/abacavir/lamivudine†</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir + emtricitabine/tenofovir AF*</td>
</tr>
<tr>
<td></td>
<td>Raltegravir + emtricitabine/tenofovir AF*</td>
</tr>
</tbody>
</table>

* Tenofovir DF may be substituted for tenofovir AF if tenofovir AF is not available.
† HLA-B*5701-negative patients.

**Notes:**
- Tenofovir DF is not recommended for individuals with creatinine clearance <50 mL/min or at high risk of kidney or bone disease (e.g., osteopenia/osteoporosis).
- Abacavir should be used with caution in patients who have or are at high risk of cardiovascular disease.
- Tenofovir AF is not recommended in patients with creatinine clearance <30 mL/min.

**IAS-USA Guidelines: Alternative Regimens in Whom an INSTI is not an Option**

| PI                                | Darunavir/cobicistat + emtricitabine/tenofovir AF  
|                                   | Darunavir + ritonavir + emtricitabine/tenofovir DF |
| NNRTI                             | Rilpivirine/emtricitabine/tenofovir AF             
|                                   | Rilpivirine/emtricitabine/tenofovir DF             
|                                   | Efavirenz/emtricitabine/tenofovir DF               |

**Notes:**

- Tenofovir DF is not recommended for individuals with or at high risk of kidney or bone disease (osteopenia or osteoporosis).
- Tenofovir AF is not recommended in patients with a creatinine clearance <30 mL/min.

Registrational Treatment-Naive Clinical Trials: Cross-Study Comparison*

HIV RNA <50 c/mL at Week 48

*This slide depicts data from multiple studies published from 2004-2012. Not all regimens have been compared head-to-head in a clinical trial.
Current Status of INSTI Resistance in the United States

- Transmitted INSTI resistance remains rare and rates of on-treatment INSTI resistance continue to be low \cite{1-3}

- **CDC National HIV Surveillance System** \cite{1}:
  - Prevalence of INSTI resistance for HIV diagnoses through 2014: 65/14,468 (0.4%)
  - Pre-ART prevalence of INSTI resistance (ie, transmitted): 2/4631 (0.04%)

- **UNC CFAR HIV Clinical Cohort** \cite{2}:
  - 2015 INSTI resistance prevalence in 685 pts who began ART in 2007 or later: 1%

- **In modeling study assuming 0.1% rate of transmitted INSTI resistance and $250 cost per test: pre-ART INSTI resistance testing correlated with worse outcomes, higher costs vs no test** \cite{3}

Investigational ART Regimens
Bictegravir/FTC/TAF vs Dolutegravir-Containing Regimens for Treatment-Naive Pts

- **Bictegravir**: novel QD unboosted INSTI coformulated with FTC/TAF
- **GS-1489**: randomized, double-blind, active-controlled phase III trial[1]
  
  ART-naive, HLA-B*5701–negative pts with eGFR_{CG} ≥ 50 mL/min (N = 629)

  - Bictegravir/FTC/TAF* (n = 314)
  - Dolutegravir/ABC/3TC† (n = 315)

  ART-naive, HLA-B*5701–negative pts with eGFR_{CG} ≥ 30 mL/min (N = 645)

  - Bictegravir/FTC/TAF* (n = 320)
  - Dolutegravir + FTC/TAF‡ (n = 325)

Wk 48

All pts also received placebo tablets for comparator regimen (eg, pts in GS-1489 who received BIC/FTC/TAF also received DTG/ABC/3TC placebo). *BIC/FTC/TAF, 50/200/25 mg PO QD. †DTG/ABC/3TC, 50/600/300 mg PO QD. ‡DTG + FTC/TAF, 50 + 200/25 mg PO QD

### BIC/FTC/TAF vs DTG-Containing Regimens: Selected Baseline Characteristics

<table>
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</thead>
<tbody>
<tr>
<td></td>
<td>BIC/FTC/TAF (n = 314)</td>
<td>DTG/ABC/3TC (n = 315)</td>
<td>BIC/FTC/TAF (n = 320)</td>
<td>DTG + FTC/TAF (n = 325)</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>31 (18-71)</td>
<td>32 (18-68)</td>
<td>33 (18-71)</td>
<td>34 (18-77)</td>
</tr>
<tr>
<td>Male, %</td>
<td>91</td>
<td>90</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Median HIV-1 RNA, log_{10} copies/mL (IQR)</td>
<td>4.42 (4.03-4.87)</td>
<td>4.51 (4.04-4.87)</td>
<td>4.43 (3.95-4.90)</td>
<td>4.45 (4.03-4.84)</td>
</tr>
<tr>
<td>HIV-1 RNA &gt; 100,000 copies/mL, %</td>
<td>17</td>
<td>16</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Median CD4+ cell count, cells/mm³ (IQR)</td>
<td>443 (299-590)</td>
<td>450 (324-608)</td>
<td>440 (289-591)</td>
<td>441 (297-597)</td>
</tr>
<tr>
<td>CD4+ cell count &lt; 200 cells/mm³, %</td>
<td>11</td>
<td>10</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

BIC/FTC/TAF vs DTG-Containing Regimens: Key Efficacy Findings

- No resistance for any regimen components detected for either group

# BIC/FTC/TAF vs DTG-Containing Regimens: Key Safety Findings

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BIC/FTC/TAF (n = 314)</td>
<td>DTG/ABC/3TC (n = 315)</td>
</tr>
<tr>
<td>Diarrhea, %</td>
<td>12.7</td>
<td>13.0</td>
</tr>
<tr>
<td>Headache, %</td>
<td>11.5</td>
<td>13.7</td>
</tr>
<tr>
<td>Nausea, %</td>
<td><strong>10.2</strong></td>
<td>22.9*</td>
</tr>
<tr>
<td>Upper respiratory tract infection, %</td>
<td>6.4</td>
<td>10.8</td>
</tr>
<tr>
<td>Median eGFR_CG (\Delta) from BL, mL/min</td>
<td>-10.5</td>
<td>-10.8†</td>
</tr>
<tr>
<td>Mean BMD (\Delta) from BL, % spine/hip</td>
<td>-0.83/-0.78</td>
<td>-0.60/-1.02†</td>
</tr>
<tr>
<td>D/c for AE, n (%)</td>
<td>0</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>

*[^P < .001. †^P = NS. ‡^P = .02.]

- GS-1489: similar changes in lipids and proteinuria between groups; some pt-reported neuropsychiatric (eg, anxiety, depression) and sleep-related symptoms (eg, disturbance) more frequent with DTG/ABC/3TC
- No d/c for renal AEs and no proximal tubulopathy for any regimen

**DRIVE-AHEAD: Doravirine/3TC/TDF vs EFV/FTC/TDF for Treatment-Naive Pts**

- **Doravirine**: NNRTI with unique resistance profile, low drug–drug interaction potential; doravirine + 2 NRTIs noninferior to DRV/RTV + 2 NRTIs with improved lipid profile in phase III DRIVE-FORWARD[1]

- DRIVE-AHEAD: randomized, double-blind, active-controlled phase III trial[1]

**ART-naive pts with HIV-1 RNA ≥ 1000 copies/mL within 45 days of Day 1; no resistance to study drugs (N = 734)**

- Baseline: male, 84% to 85%; mean CD4+ cell count, 416-435 cells/mm³ (12% to 13% ≤ 200 cells/mm³)

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**DRIVE-AHEAD: Key Efficacy Findings**

### Wk 48 Virologic Efficacy

- **Treatment difference:** 3.5% (95% CI: -2.0% to 9.0%)

### Outcome at Wk 48, n (%)

<table>
<thead>
<tr>
<th></th>
<th>DOR/3TC/TDF (n = 364)</th>
<th>EFV/FTC/TDF (n = 364)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDVF</td>
<td>22 (6.0)</td>
<td>14 (3.8)</td>
</tr>
<tr>
<td>Genotyped</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Primary NNRTI* resistance</td>
<td>6 (1.6)</td>
<td>12 (3.3)</td>
</tr>
<tr>
<td>Primary NRTI* resistance</td>
<td>5 (1.4)</td>
<td>5 (1.4)</td>
</tr>
</tbody>
</table>

*See slidenotes for specific mutations.

- No unanticipated mutations observed

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**DRIVE-AHEAD: Key Safety Findings**

### Neuropsychiatric Outcomes, Wk 48

- **Dizziness**: DOR/3TC/TDF (8.8%) vs. EFV/FTC/TDF (37.1%)
- **Sleep Disorders and Disturbances**: DOR/3TC/TDF (12.1%) vs. EFV/FTC/TDF (25.5%)
- **Altered Sensorium**: DOR/3TC/TDF (4.4%) vs. EFV/FTC/TDF (8.2%)
- **Depression and Suicide/Self-injury**: DOR/3TC/TDF (4.1%) vs. EFV/FTC/TDF (6.6%)
- **Psychosis and Psychotic Disorders**: DOR/3TC/TDF (0.3%) vs. EFV/FTC/TDF (1.1%)

### Drug-related AE, %
- DOR/3TC/TDF (31%)
- EFV/FTC/TDF (63%)

### D/c for AEs, %
- DOR/3TC/TDF (3%)
- EFV/FTC/TDF (7%)

### Lipid ∆ From BL at Wk 48, mg/dL

<table>
<thead>
<tr>
<th>Lipid</th>
<th>DOR/3TC/TDF</th>
<th>EFV/FTC/TDF</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-1.6</td>
<td>8.7</td>
<td>-10.3 (-13.7, -6.8)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>-3.8</td>
<td>13.3</td>
<td>-17.1 (-20.6, -13.6)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-2.0</td>
<td>21.8</td>
<td>-23.8 (-27.4, -19.2)</td>
<td>NR</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-12.4</td>
<td>22.0</td>
<td>-34.4 (-37.9, -30.8)</td>
<td>NR</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.9</td>
<td>8.5</td>
<td>-6.6 (-9.1, -4.1)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Doravirine or Darunavir + RTV Both With FTC/TDF or ABC/3TC in Treatment-Naive Pts

- Doravirine: next-gen NNRTI, unique resistance profile, low DDI potential
- Multicenter, randomized, double-blind phase III trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48

Efficacy similar in both arms regardless of baseline HIV-1 RNA or CD4+ cell count.

No drug resistance detected in pts with PDVF through Wk 48 in either arm.

- n = 1 pt with noncompliance discontinued at Wk 24, developed DOR and FTC resistance.

### Doravirine vs DRV + RTV in Combination With FTC/TDF or ABC/3TC: Safety

<table>
<thead>
<tr>
<th>AE, %</th>
<th>DOR (n = 383)</th>
<th>DRV + RTV (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 AE</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Serious AE</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Discontinuation for AE</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>AEs of clinical interest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Rash*</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>▪ Neuropsychiatric†</td>
<td>11</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fasting Lipid Δ From BL to Wk 48, mg/dL</th>
<th>DOR (n = 383)</th>
<th>DRV + RTV (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-c*</td>
<td>-4.51</td>
<td>9.92</td>
</tr>
<tr>
<td>Non-HDL-c*</td>
<td>-5.3</td>
<td>13.75</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-1.37</td>
<td>17.9</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>-3.14</td>
<td>21.97</td>
</tr>
<tr>
<td>HDL-c</td>
<td>3.94</td>
<td>4.15</td>
</tr>
</tbody>
</table>

*Discontinued due to rash: n = 2 in DOR arm; n = 1 in DRV + RTV arm.
†No discontinuation for neuropsychiatric conditions.

\* P < .0001 for DOR vs DRV + RTV.
Dual-Therapy Regimens for Initial ART

- **ANDES**: randomized phase IV study of DRV/RTV + 3TC vs DRV/RTV + TDF/3TC in ART-naive pts (N = 145)\(^1\)
  - Baseline: 24% HIV-1 RNA > 100,000 c/mL

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 400 c/mL (ITT) at Wk 24, n/N (%)</th>
<th>DRV/RTV + 3TC</th>
<th>DRV/RTV + TDF/3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>71/75 (95)</td>
<td>68/70 (97)</td>
</tr>
<tr>
<td>BL HIV-1 RNA &gt; 100,000 c/mL</td>
<td>20/20 (100)</td>
<td>15/15 (100)</td>
</tr>
</tbody>
</table>

- 1 virologic failure with DRV/RTV + TDF/3TC

- **ACTG A5353**: single-arm phase II study of DTG + 3TC in ART-naive pts (N = 120)\(^2\)
  - Baseline: 31% HIV-1 RNA > 100,000 c/mL

<table>
<thead>
<tr>
<th>Virologic Outcome at Wk 24, n (%)</th>
<th>Baseline HIV-1 RNA, c/mL</th>
<th>Total (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 100,000 (n = 37)</td>
<td>≤ 100,000 (n = 83)</td>
</tr>
<tr>
<td>Success*</td>
<td>33 (89)</td>
<td>75 (90)</td>
</tr>
<tr>
<td>Nonsuccess</td>
<td>3 (8)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>No data</td>
<td>1 (3)</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

*HIV-1 RNA < 50 copies/mL.
- n = 3 with PDVF; n = 1 with emergent M184V and R263R/K mixture
- **GEMINI 1/2** randomized phase III trials of DTG + 3TC ongoing\(^3,4\)

Switch/Simplification
SWORD 1 & 2: Switch FromSuppressive ART to DTG + RPV Dual Therapy

- Randomized, open-label, multicenter phase III trials
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-E snapshot)

HIV-infected pts with HIV-1 RNA < 50 c/mL for ≥ 12 mos while receiving first-line or second-line ART with 2 NRTIs + INSTI, NNRTI, or PI; no previous VF; HBV negative (N = 1024)

- 70% to 73% of pts receiving TDF at baseline

Llibre JM, et al. CROI 2017. Abstract 44LB.
Switch From Suppressive ART to DTG + RPV 
Noninferior to Continued Baseline ART at Wk 48

- 1 pt with confirmed criteria for virologic withdrawal at Wk 36 in DTG + RPV arm had K101K/E
  - Documented nonadherence at VF
  - Resuppressed with continued DTG + RPV
  - No INSTI resistance

Switch From Suppressive ART to DTG + RPV: Safety Outcomes

- AE rates generally similar between treatment arms through Wk 52
  - Numerically higher rate of drug-related grade 1/2 AEs with switch: 17% vs 2%
  - Numerically higher rate of withdrawal for AEs with switch: 4% vs < 1%

- No notable change in serum lipid values from baseline to Wk 48 in either treatment arm
SWORD 1 & 2 Substudy: BMD Impact of Switch From TDF-Based ART to DTG + RPV

- Randomized, open-label, multicenter phase III trials demonstrated that switch to DTG + RPV noninferior to remaining on baseline ART at Wk 48 in virologically suppressed pts[1]

- Current analysis assessed BMD in pts who continued on TDF-containing triple ART regimen or switched from TDF-containing triple ART to DTG + RPV (N = 102)[2]


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### Change From BL in BMD at Wk 48

**Primary endpoint.**

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<tr>
<th></th>
<th>DTG + RPV (n = 46)</th>
<th>Continued TDF-based ART (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Hip</strong></td>
<td>P = .014</td>
<td></td>
</tr>
<tr>
<td>Mean Adjusted Change in BMD From BL (%)</td>
<td>1.34 ± 0.05</td>
<td>0.05 ± 0.15</td>
</tr>
<tr>
<td>BL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 Wks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DTG + RPV (n = 46)</th>
<th>Continued TDF-based ART (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumbar Spine</strong></td>
<td>P = .039</td>
<td></td>
</tr>
<tr>
<td>Mean Adjusted Change in BMD From BL (%)</td>
<td>1.46 ± 0.15</td>
<td>0.15 ± 0.05</td>
</tr>
<tr>
<td>BL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 Wks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ANRS 167 LAMIDOL: Switch to DTG + 3TC in Virologically Suppressed Pts on Triple ART

- Noncomparative, open-label, single-arm multicenter trial
  - Primary endpoint: therapeutic success at Wk 56 (ie, after 48 wks of dual therapy)
  - Therapeutic failure: HIV-1 RNA > 50 copies/mL, interruption, lost to f/u, death

HIV-infected pts with HIV-1 RNA ≤ 50 copies/mL for ≥ 2 yrs on first-line ART;
≤ 2 ART modifications allowed, except within 6 mos of study start; CD4+ cell count > 200 cells/mm³
(N = 110)

Phase I

Wk 8*

DTG 50 mg QD + 2 NRTI†

Phase II

Wk 56

DTG 50 mg QD + 3TC 300 mg QD
(n = 104)

*Pts with HIV-1 RNA ≤ 50 copies/mL proceeded to phase II.
†In phase I, third agent in regimen replaced with DTG; baseline NRTI backbone maintained.

LAMIDOL Interim Analysis: Switch to DTG + 3TC Effective in Maintaining Viral Suppression

- 97% (101/104) pts maintained therapeutic success through 40 wks of dual therapy (study Wk 48)[1]
  - No INSTI resistance in 3 pts with virologic failure
  - 7 pts with serious AEs, only 2 related to dual therapy

- DTG + 3TC dual therapy currently under phase III evaluation as both initial ART[2,3] and as a switch strategy for virologically suppressed pts[4]

<table>
<thead>
<tr>
<th>Therapeutic Success, n/N* (%)</th>
<th>DTG + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 0 (entry; on BL triple therapy)</td>
<td>110/110 (100)</td>
</tr>
<tr>
<td>Wk 8 (end of phase I, start of phase II)</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>Wk 12</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>Wk 16</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Wk 24</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Wk 32</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Wk 40</td>
<td>102/104 (98)</td>
</tr>
<tr>
<td>Wk 48</td>
<td>101/104 (97)</td>
</tr>
</tbody>
</table>

*Pts enrolled in phase I, N = 110; pts enrolled in phase II, N = 104.

DOMONO: Switch to DTG Monotherapy in Virologically Suppressed Pts Not Sufficient

- Randomized comparison of switch to DTG 50 mg QD monotherapy vs continued baseline ART for 24 wks in virologically suppressed pts with no previous VF\(^2\)

- At Wk 24, DTG monotherapy noninferior to continued baseline ART for maintained HIV-1 RNA < 200 c/mL
  - After 24 wks, all pts allowed to switch to DTG QD monotherapy

- Study d/c early because of high VF rate after 48 wks of DTG monotherapy
  - VF in 8/77 pts with DTG monotherapy vs 3/152 pts on combination ART in concurrent control group \((P = .03)\)
  - Among 6 VF cases with resistance data in DTG monotherapy group, 3 developed INSTI resistance

Emergent INSTI Resistance After Switch to DTG Monotherapy

- International, multicenter retrospective study evaluated virologically suppressed pts who were switched from combination ART to DTG 50 mg QD monotherapy
  - Pts with history of VF on INSTI and INSTI resistance excluded
- 11 of 122 pts switched to DTG monotherapy experienced VF
  - 9 of 11 had genotypic INSTI resistance at VF
  - INSTI resistance pathways varied: 92Q/155H (n = 1); 97A/155H (n = 1); 155H/148R (n = 1); 118R (n = 2); 148K (n = 1); 148H (n = 2); 148R (n = 1)
**LATTE-2: 96-Wk Results for Cabotegravir IM + Rilpivirine IM as Long-Acting Maintenance ART**

- **Cabotegravir**: INSTI formulated as PO tablet and for long-acting IM injection
- LATTE-2: phase IIb study in which pts randomized to CAB 400 mg + RPV 600 mg IM Q4W, CAB 600 mg + RPV 900 mg IM Q8W, or CAB 30 mg + ABC/3TC 600/300 mg PO QD after induction/virologic suppression with oral CAB + ABC/3TC (N = 309)

**Wk 96 Virologic Efficacy**

- At 96 wks, ~ 30% pts receiving IM injection experienced ISR
  - 99% of ISRs mild/moderate
- AEs leading to withdrawal
  - Pooled Q4W/Q8W IM arms, 4%; PO arm, 2%
- Withdrawals between Wks 48 and 96: CAB IM arms, n = 4 (n = 1 for AE, n = 3 withdrew consent); CAB PO arm, n = 3 (all withdrew consent)
- No additional PDVFs after Wk 48 in any arm
- ~ 88% of pts receiving IM CAB very satisfied to continue present treatment vs 43% receiving PO CAB

**Virologic Success**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM CAB + RPV Q4W (n = 115)</td>
<td>87</td>
</tr>
<tr>
<td>IM CAB + RPV Q8W (n = 115)</td>
<td>94</td>
</tr>
<tr>
<td>PO CAB + ABC/3TC (n = 56)</td>
<td>84</td>
</tr>
</tbody>
</table>

**Treatment difference (vs CAB PO):**
- CAB IM Q4W: 3.0% (95% CI: -8.4% to 14.4%)
- CAB IM Q8W: 10.0% (95% CI: -0.6% to 20.5%)

**Virologic Nonresponse**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM CAB + RPV Q4W (n = 115)</td>
<td>0</td>
</tr>
<tr>
<td>IM CAB + RPV Q8W (n = 115)</td>
<td>4</td>
</tr>
<tr>
<td>PO CAB + ABC/3TC (n = 56)</td>
<td>2</td>
</tr>
</tbody>
</table>

**No Virologic Data**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM CAB + RPV Q4W (n = 115)</td>
<td>13</td>
</tr>
<tr>
<td>IM CAB + RPV Q8W (n = 115)</td>
<td>2</td>
</tr>
<tr>
<td>PO CAB + ABC/3TC (n = 56)</td>
<td>14</td>
</tr>
</tbody>
</table>

*HIV-1 RNA < 50 copies/mL.


Slide credit: clinicaloptions.com
NEAT 022: Switch From Boosted PI to DTG in Suppressed Pts With High CV Risk

- International, randomized, open-label phase IV study
  - Primary endpoints at Wk 48: proportion with HIV RNA < 50 copies/mL (ITT), change in total plasma cholesterol

Pts with stable HIV-1 RNA < 50 c/mL on PI/RTV + 2 NRTIs, high CV risk,* no resistance mutations, no VF (N = 415)

Immediate switch to DTG + 2 NRTIs† (n = 205)

Continue PI/RTV + 2 NRTIs‡ (n = 210)

Deferred switch to DTG + 2 NRTIs‡

Wk 48
Wk 96

* > 50 yrs of age and/or Framingham risk score > 10% at 10 yrs. †NRTIs to remain the same throughout study.

- Baseline NRTI backbones: FTC/TDF, 64.8%; ABC/3TC, 31.3%


Slide credit: clinicaloptions.com
NEAT 022: Key Findings

- Switching to DTG noninferior to continuing boosted PI through Wk 48

- Switching to DTG associated with improved lipid profile vs continuing boosted PI through Wk 48

- No emergent resistance in pts with VF

- No significant differences in grade 3/4 AEs, serious AEs, AE-related d/c

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Slide credit: clinicaloptions.com
DAWNING: Second-line DTG vs LPV/RTV + 2 NRTIs in Pts With Virologic Failure

- Interim results of an international, randomized, open-label phase IIIb study (N = 627)
  - Most frequent enrolment sites: South Africa (27%), Peru, Ukraine, Brazil, Thailand, China (8% to 10% each)

**Stratified by HIV-1 RNA (≤ vs > 100,000 c/mL), fully active investigator-selected NRTIs (2 vs < 2)**

- Interim analysis
  - Wk 24

- Primary analysis
  - Wk 48
  - Wk 52

Pts on first-line NNRTI + 2 NRTIs ≥ 6 mos with VF*, no primary resistance to INSTIs or PIs (N = 627)

- DTG + 2 NRTIs
  - (n = 312)

- LPV/RTV + 2 NRTIs†
  - (n = 312)

**HIV-1 RNA ≥ 400 copies/mL on 2 occasions. †After preplanned analysis (all Wk 24 and subsets of Wks 36/48 data), it was recommended that LPV/RTV be discontinued due to differences in virologic nonresponse and PDVF favoring DTG arm. Protocol amendment allowed pts on LPV/RTV to switch to DTG.**

- Baseline characteristics (DTG vs LPV/RTV): female, 37% vs 33%; African heritage, 42% vs 36%; HIV-1 RNA > 100,000 copies/mL, 22% vs 20%

### DAWNING: Key Findings

<table>
<thead>
<tr>
<th>Virologic Outcome at Wk 24, n (%)</th>
<th>DTG + 2 NRTIs (n = 312)</th>
<th>LPV/RTV + 2 NRTIs (n = 312)</th>
<th>Treatment Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success*</td>
<td>257 (82)</td>
<td>215 (69)</td>
<td>13.8 (7.3-20.3; P &lt; .001)</td>
</tr>
<tr>
<td>Nonresponse</td>
<td>37 (12)</td>
<td>77 (25)</td>
<td>NR</td>
</tr>
<tr>
<td>No data</td>
<td>18 (6)</td>
<td>20 (6)</td>
<td>NR</td>
</tr>
</tbody>
</table>

**ITT-E population. *HIV-1 RNA < 50 copies/mL.**

- **Virologic withdrawal†**: DTG arm, n = 10 (3%); LPV/RTV arm, n = 28 (9%)

- In pts with virologic withdrawal:
  - No pts in DTG arm developed INSTI or NRTI RAMs
  - n = 3 in LPV/RTV arm developed NRTI RAMs

- **AEs, DTG vs LPV/RTV**
  - Drug related, 15% vs 36%
  - Serious/death, 5% vs 6%
  - Leading to withdrawal, 2% vs 5%

†HIV-1 RNA decrease of < 1 log_{10} c/mL by Wk 16, increase to ≥ 400 c/mL after suppression, ≥ 400 c/mL at or after Wk 24.
Efficacy, Safety of Ibalizumab Through 24 Wks

- Non-immunosuppressive monoclonal antibody that binds CD4 and inhibits viral entry
- Able to block both CCR5- and CXCR4 tropic viruses.

Primary endpoint: 83% with ≥ 0.5 log\(_{10}\) HIV-1 RNA decrease at Day 14 vs 3% at end of control period (\(P < .0001\))
  - 60% with ≥ 1.0 log\(_{10}\) HIV-1 RNA decrease
  - Mean decrease by Day 14: 1.1 log\(_{10}\)

9 pts reported 17 serious AEs
  - 1 drug-related serious AE (IRIS) resulted in discontinuation

9 other pts discontinued
  - Death (n = 4; liver failure, Kaposi sarcoma; end-stage AIDS, lymphoma)
  - Consent withdrawal (n = 3)
  - Lost to follow-up (n = 2)

No cases of anti-ibalizumab antibodies

<table>
<thead>
<tr>
<th>Wk 24 Virologic Outcome</th>
<th>Ibalizumab + OBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0 log(_{10}) HIV-1 RNA decrease, %</td>
<td>55</td>
</tr>
<tr>
<td>≥ 2.0 log(_{10}) HIV-1 RNA decrease, %</td>
<td>48</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL, %</td>
<td>43</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 copies/mL, %</td>
<td>50</td>
</tr>
<tr>
<td>Mean HIV-1 RNA decrease from baseline, log(_{10})</td>
<td>1.6</td>
</tr>
</tbody>
</table>
TMB-301: Long-Acting Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Ibalizumab: humanized mAb to conformational epitope on CD4 receptor that blocks postattachment HIV entry into CD4+ T-cells without altering normal cell function
- Single-arm, open-label phase III trial
  - Primary endpoint: $\geq 0.5 \log_{10}$ HIV-1 RNA decrease at Day 14

- 53% with resistance to all drugs from $\geq 3$ classes; 68% with INSTI resistance

CD01 Extension: Long-term, Maintenance PRO 140 Monotherapy Following Initial ART

- PRO 140: humanized IgG4 CCR5 mAb
- Single-arm, open-label phase IIb extension study\(^1\)
  - Maintenance PRO 140 given at 350 mg SC/wk for ≤ 3 yrs in pts stable on initial ART from CD01 study (N = 16)
- Wkly PRO 140 maintenance SC injection generally well tolerated
  - No drug-related severe AEs or d/c for AEs
  - Infrequent, mild, transient administration-site reactions in < 10% of pts
- HIV-1 RNA < 40 copies/mL maintained in majority of pts
  - > 40 wks: 13/16 pts (81.3%)
  - > 2 yrs: 10/16 pts (62.5%)
  - 1 pt d/c due to relocation; 5 pts had VF
- CD4+ cell counts stable through study
- No anti-PRO 140 antibodies detected
- Ongoing phase IIb/III studies of PRO 140 monotherapy\(^2\) and in combination with ART\(^3\)

---

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA or Formulation</th>
<th>Phase</th>
<th>Dosing/Administration</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-CA1[^1]</td>
<td>HIV capsid inhibitor</td>
<td>Pre-clinical</td>
<td>Extended release, suitable for SC of solid depot formulation</td>
<td>Potent ART with orthogonal resistance profile to existing ART; potential for long-acting formulation due to low aqueous solubility, high stability</td>
</tr>
<tr>
<td>GS-9131[^2]</td>
<td>NRTI</td>
<td>Pre-clinical</td>
<td>Potential for once daily dosing</td>
<td>Potent ART active against NRTI RAMs K65R, L74V, M184V alone or in combination; minimal loss of susceptibility with 4 or more TAMs</td>
</tr>
<tr>
<td>MK-8591[^3]</td>
<td>Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)</td>
<td>Pre-clinical</td>
<td>10 mg QW PO; potential for extended duration</td>
<td>Comparable MK-8591 levels in animal rectal, vaginal tissue to TDF levels in tissues of human subjects highlights potential prophylaxis utility</td>
</tr>
<tr>
<td>GS-PI1[^4]</td>
<td>PI</td>
<td>Pre-clinical</td>
<td>Potential for unboosted, once daily dosing</td>
<td>Potent ART with high barrier to resistance, including &lt; 2-fold loss in potency against major PI RAMs, and 10-fold to 40-fold longer in vivo half life vs ATV or DRV</td>
</tr>
<tr>
<td>NANO-EFV, NANO-LPV[^5]</td>
<td>Oral, lower dose SDN</td>
<td>I</td>
<td>nEFV: 50 mg QD, 21 d nLPV/RTV: 200/100 mg BID, 7 d</td>
<td>Enhanced oral bioavailability suggests can reduce EFV, LPV dose by ~ 50% while maintaining PK</td>
</tr>
</tbody>
</table>

### Additional Investigational Agents Reported at CROI 2017: Phase II

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA or Formulation</th>
<th>Phase</th>
<th>Dosing/Administration</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC278 LA[1]</td>
<td>LA injectable RPV (IM)</td>
<td>II</td>
<td>1200 mg IM Q8W</td>
<td>Potential as injectable, long-acting PrEP</td>
</tr>
<tr>
<td>Elsulfavirine[2]</td>
<td>Prodrug of new NNRTI VM1500A</td>
<td>IIb</td>
<td>Combined therapy: 20 mg elsulfavirine + FTC/TDF PO QD</td>
<td>Less toxic alternative to EFV for initial ART</td>
</tr>
<tr>
<td>UB-421[3]</td>
<td>Anti-CD4 receptor mAb</td>
<td>II</td>
<td>10 mg/kg QW IV or 25 mg/kg Q2W IV</td>
<td>Possible ART alternative for maintenance therapy in virologically suppressed pts</td>
</tr>
</tbody>
</table>

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ART and Pregnancy
## Current DHHS Recommendations: Initial ART in Pregnant Women

<table>
<thead>
<tr>
<th>Guideline Status</th>
<th>NRTIs</th>
<th>PIs</th>
<th>INSTIs</th>
<th>NNRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>3TC/ABC</td>
<td>ATV/RTV*</td>
<td>RAL* §</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FTC/TDF</td>
<td>DRV/RTV*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3TC + TDF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative</td>
<td>3TC/ZDV</td>
<td>LPV/RTV*†</td>
<td>EFV*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RPV*‡</td>
<td></td>
</tr>
<tr>
<td>Insufficient data to</td>
<td>FTC/TAF</td>
<td>FPV</td>
<td>DTG</td>
<td>EVG/COBI</td>
</tr>
<tr>
<td>recommend</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In addition to preferred 2-NRTI backbone. †Must be used twice daily in pregnancy. ‡Only if pretreatment HIV-1 RNA ≤ 100,000 copies/mL and CD4+ cell count ≥ 200 cells/mm³. § If adherence concerns or potential for ART discontinuation postpartum, a PI is preferred over INSTI to reduce resistance risk.

Tsepamo: Birth Outcomes When Initiating First-line DTG vs EFV in Pregnancy

- Prospective cohort study in HIV-infected women in Botswana initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF while pregnant (N = 5438)

<table>
<thead>
<tr>
<th>Adverse Birth Outcomes, n (%)</th>
<th>DTG (n = 845)</th>
<th>EFV (n = 4593)</th>
<th>aRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>291 (34.4)</td>
<td>1606 (35.0)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td></td>
<td>92 (10.9)</td>
<td>519 (11.3)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>18 (2.1)</td>
<td>105 (2.3)</td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td>Neonatal death (&lt; 28 d)</td>
<td>11 (1.3)</td>
<td>60 (1.3)</td>
<td>1.0 (0.5-1.9)</td>
</tr>
<tr>
<td>Preterm birth (&lt; 37 wks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm (&lt; 32 wks)</td>
<td>149 (17.8)</td>
<td>844 (18.5)</td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td></td>
<td>35 (4.2)</td>
<td>160 (3.5)</td>
<td>1.2 (0.8-1.7)</td>
</tr>
<tr>
<td>SGA (&lt; 10th percentile weight)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very SGA (&lt; 3rd percentile weight)</td>
<td>156 (18.7)</td>
<td>838 (18.5)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td></td>
<td>51 (6.1)</td>
<td>302 (6.7)</td>
<td>0.9 (0.7-1.2)</td>
</tr>
</tbody>
</table>

*For DTG vs EFV; adjusted for maternal age, education, gravida.

- Few first-trimester ART exposures (DTG, n = 116; EFV, n = 396); most second/third trimester
- Only 1 major congenital abnormality observed (skeletal dysplasia in EFV-exposed group)
- Adverse birth outcome risks similar when initiating first-line DTG vs EFV in pregnancy
Selected Prevention Studies

- **Opposites Attract**: international, prospective cohort study assessing the incidence of linked HIV transmission in MSM serodiscordant couples when HIV-infected partner on ART and virologically suppressed (N = 343 couples; 591 CYFU; 16,889 acts of CLAI)\(^1\)
  - For HIV-infected partner, HIV-1 RNA undetectable for 95% of CYFU
  - **No linked infections; 3 infections occurring during study contracted from outside partners**

- **Pluspills**: open-label demonstration study of FTC/TDF PO QD + support for HIV prevention in uninfected, sexually active adolescents 15-19 yrs of age in South Africa (N = 148)\(^2\)
  - **Adherence decreased over time and with less frequent study visits**; at Wk 12 (monthly visits), 54% had plasma TDF levels of ≥ 10 ng/mL; at Wk 48 (visits every 3 mos), 38% had plasma TDF levels of ≥ 10 ng/mL

- **MTN023/IPM 030**: randomized, double-blind, placebo-controlled phase IIa trial of a dapivirine vaginal ring for HIV prevention in uninfected, sexually active US adolescents 15-17 yrs of age (N = 96)\(^3\)
  - At Wk 24, similar rates of grade ≥ 2 AE between study groups; **87% of plasma samples (taken at 2, 4, 12, 24 wks) showed dapivirine levels suggestive of adherence; 95% of returned rings had residual dapivirine levels suggestive of adherence**

IPERGAY: randomized, double-blind, placebo-controlled study of event-driven FTC/TDF PO PrEP for uninfected, high-risk MSM in France and Canada (N = 400)

- Previous findings: HIV incidence/100 PY, FTC/TDF vs placebo groups 0.91 vs 6.60 ($P = .002$; 86% reduction in HIV incidence with event-driven FTC/TDF); median pills/mo 15[^1]

- Substudy of 269 pts using ≤ 15 pills/mo with reported PrEP use systematically/often during intercourse: HIV incidence/100 PY, FTC/TDF vs placebo groups 0 vs 9.3 ($P = .013$)[^2]

PROUD: randomized, open-label study of immediate vs deferred FTC/TDF PO QD PrEP for uninfected, high-risk MSM in England (N = 544)[^3]

- Current analysis: post deferred phase, in which all pts offered PrEP

<table>
<thead>
<tr>
<th>HIV Incidence/100 PY (Infections/PY)[^4]</th>
<th>Immediate PrEP</th>
<th>Deferred PrEP</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred phase (Yr 1)</td>
<td>1.6 (4/254)</td>
<td>9.4 (21/223)</td>
<td>NR</td>
</tr>
<tr>
<td>Post deferred phase (Yrs 2-4)</td>
<td>1.2 (5/424)</td>
<td>0.3 (1/356)*</td>
<td>.18</td>
</tr>
</tbody>
</table>

[^1]: Significant difference in HIV incidence observed for deferred group pts in deferred vs post deferred phases ($P < .0001$).

HPTN 077: Cabotegravir for PrEP in Low-Risk Persons

- International, randomized, double-blind, placebo-controlled phase IIa study (N = 199)

**Men and women at low risk of HIV infection (N = 199)**

**Cohort 1**
- Oral Phase:
  - CAB 30 mg PO QD (n = 82)
  - Placebo PO QD (n = 28)
- Injection Phase:
  - CAB 800 mg IM Q12W
  - Placebo IM Q12W

**Cohort 2**
- Oral Phase:
  - CAB 30 mg PO QD (n = 69)
  - Placebo PO QD (n = 20)
- Injection Phase:
  - CAB 600 mg IM Q8W*
  - Placebo IM Q8W*

*Pts received 4-wk loading dose.

- Grade ≥ 2 AEs significantly different between CAB and PBO during injection phase: injection-site pain (34% vs 2%; *P* < .0001), headache (15% vs 2%; *P* = .03)
  - Most injection-site reactions mild/moderate; 1 discontinuation due to injection-related AE
- 1 seroconversion (CAB cohort 1): detected 48 wks after final injection; CAB levels undetectable
- Participants in cohort 2 (600 mg IM Q8W) consistently met prespecified PK targets; this dose will be assessed in phase III studies


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HIV Cure Strategies Currently in Human Trials

Minimize Reservoir
Early Treatment to Limit Reservoir
ART
Broadly neutralizing antibodies

Shock
Reactivate Latently Infected Cells
- HDAC inhibition
- Bromodomain and extra-terminal inhibition
- Activate toll-like receptors
- Activate protein kinase

Kill
Viral Clearance by Immune System
- Broadly neutralizing antibodies
- Therapeutic vaccines
- Anti-programmed death (PD) 1
- Anti-PD ligand 1

HIV-Resistant Cells
Transfuse Cells Without CCR5 Gene
- Gene-editing therapy
- Bone marrow or cord blood transplantation
Timing of ART Initiation in Primary Infection and HIV Reservoirs: Key Lessons

- **HIV persistence**
  - Established early in primary HIV infection in long-lived memory CD4+ T cells and not eliminated by immune surveillance or ART

- **ART initiated during primary HIV infection**
  - Can reduce the HIV reservoir size to a greater extent than when treatment is given in chronic HIV
  - However, infection persists in memory CD4+ T cells in most early treated individuals

- **Treatment initiated in the earliest primary HIV infection stage (Fiebig I)**
  - May protect central memory CD4+ T cells from infection and skew the distribution of latently infected cells to the shorter-lived memory CD4+ T cells (eg, elite controllers and post-treatment controllers)

- **Containing HIV reservoir seeding with ART in primary HIV infection (before use of other interventions aimed at eliminating all latently infected cells)**
  - May be a first critical step in achieving HIV remission