BHIVA ‘Best of CROI’ Feedback Meetings

London | Birmingham
Haydock | Newcastle
Cardiff | Wakefield
Edinburgh
New drugs

Dr David Asboe
Chelsea and Westminster Hospital, London
• New drugs – phase 2/3
• ART strategies
• Early ART data
• Pharmacokinetics
• ART plus
Agents for HIV-1

- **Integrate Inhibitors**
  - Dolutegravir
  - Cabotegravir (III)
  - GS-9883 (Phase III)

- **N(t)RTI**
  - TAF
  - EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine)(Phase I-II)

- **NNRTI**
  - Doravirine (Phase III)

- **Maturation Inhibitors**
  - BMS 955176 (Phase II)

- **Attachment inhibitors**
  - BMS 663068 -> 626529 (Phase III)

- **Broadly neutralizing monoclonal antibodies (I)**

New Targets: e.g. LEDGF, combination entry, additional maturation sites, HIV-1 RNA processing
Cabotegravir + Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 32 Results

Induction period

Maintenance period

- CAB 30 mg + ABC/3TC for 20 weeks (N=309)
- Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period.
- Subjects can elect to enter LA Extension Phase beyond Week 96.

Inclusion criteria
- >18 years old
- Naive to antiretroviral therapy
- CD4+ >200 cells/mm³

Exclusion criteria
- Positive for hepatitis B
- ALT ≥5 × ULN
- Creatinine clearance <50 mL/min

Qualification for maintenance
- HIV-1 RNA <50 c/mL between Week -4 and Day 1

Week 32
- Primary analysis
- Dosing regimen selection

Week 48
- Analysis
- Dosing regimen confirmation

Week 96b

- ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; ULN, upper limit of normal.
- Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period.
- Subjects can elect to enter LA Extension Phase beyond Week 96.

References
- Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
LATTE-2 Study Design

**Induction period**

- CAB 30 mg + ABC/3TC for 20 weeks

**Maintenance period**

- CAB 400 mg IM + RPV 600 mg IM Q4W (n=115)
- CAB 600 mg IM + RPV 900 mg IM Q8W (n=115)
- CAB 30 mg + ABC/3TC PO QD (n=56)

- CAB loading dose at Day 1
- CAB loading doses at Day 1 and Week 4

**Day 1 Randomization 2:2:1**

**Week 32 Primary analysis**

- Dosing regimen selection

**Week 48 Analysis**

- Dosing regimen confirmation

**Week 96**

ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; ULN, upper limit of normal. aSubjects who withdrew after at least 1 IM dose entered the long-term follow-up period. bSubjects can elect to enter LA Extension Phase beyond Week 96.

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
## Baseline Characteristics: ITT-ME Population

<table>
<thead>
<tr>
<th></th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>Oral CAB (n=56)</th>
<th>Total (N=286)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years</strong></td>
<td>35.0</td>
<td>36.0</td>
<td>35.0</td>
<td>35.0</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>8 (7)</td>
<td>6 (5)</td>
<td>10 (18)</td>
<td>24 (8)</td>
</tr>
<tr>
<td><strong>African American/African heritage, n (%)</strong></td>
<td>17 (15)</td>
<td>12 (10)</td>
<td>15 (27)</td>
<td>44 (15)</td>
</tr>
<tr>
<td><strong>CDC class C, n (%)</strong></td>
<td>1 (&lt;1)</td>
<td>2 (2)</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>Median HIV-1 RNA, log_{10} c/mL</strong></td>
<td>4.419</td>
<td>4.455</td>
<td>4.289</td>
<td>4.393</td>
</tr>
<tr>
<td><strong>≥100,000, n (%)</strong></td>
<td>16 (14)</td>
<td>28 (24)</td>
<td>7 (12)</td>
<td>51 (18)</td>
</tr>
<tr>
<td><strong>Median CD4+, cells/mm^3</strong></td>
<td>449.0</td>
<td>499.0</td>
<td>517.5</td>
<td>489.0</td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention; ITT-ME, intent-to-treat maintenance exposed.

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
LATTE-2 Week 32 Results: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

**Induction period**

- BL to D1: 100% virological suppression

**Maintenance period**

- Q4W: 99%
- Q8W: 95%
- Oral CAB: 98%

**Snapshot success:** D1
## Snapshot Outcomes: HIV-1 RNA <50 c/mL at Week 32 (ITT-ME)

<table>
<thead>
<tr>
<th>Week 32 outcome</th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>Oral CAB (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virologic success</strong></td>
<td>109 (95%)</td>
<td>108 (94%)</td>
<td>51 (91%)</td>
</tr>
<tr>
<td><strong>Virologic non-response</strong></td>
<td>5 (4%)</td>
<td>1 (&lt;1%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td><strong>Data in window not &lt;50 c/mL</strong></td>
<td>3 (3%)</td>
<td>1 (&lt;1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Discontinued for lack of efficacy</strong></td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Discontinued for other reason while not &lt;50 c/mL</strong></td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>No virologic data in window</strong></td>
<td>1 (&lt;1%)</td>
<td>6 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td><strong>Discontinued due to adverse event or death</strong>b</td>
<td>0</td>
<td>4 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Discontinued for other reasons</strong>c</td>
<td>1 (&lt;1%)</td>
<td>2 (2%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

- a Week 32 HIV-1 RNA Q8W: 53 c/mL, 70 c/mL, 91 c/mL; Q4W: 70 c/mL; oral CAB: 243 c/mL. All 5 are still in the study.
- b Q4W: hepatitis C, rash, depression, and psychosis; oral CAB: hepatitis C. *Q8W: ISR; Q4W: pregnancy and prohibited medication; oral CAB: lost to follow-up, relocation.
- c Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
### Protocol-Defined Virologic Failure (PDVF): Genotype

<table>
<thead>
<tr>
<th>Maintenance period</th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>Oral CAB (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with PDVF(^a)</td>
<td>1(^b) (1%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>INI-r mutations</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NRTI-r mutations</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NNRTI-r mutations</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)One additional PDVF occurred during oral Induction Period due to oral medication non-adherence. \(^b\)PDVF at Week 4; no detectable RPV at Week 4 and Week 8, suggesting maladministration.

- No INI, NNRTI, or NRTI mutations were detected through Induction or Maintenance

- PDVF: <1.0 log\(_{10}\) c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 log\(_{10}\) c/mL increase from nadir HIV-1 RNA value ≥200 c/mL.

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
**Adverse Events and Labs—Maintenance Period**

<table>
<thead>
<tr>
<th>ITT-ME population, n (%)</th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>Oral CAB (n=56)</th>
<th>IM subtotal (N=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related AEs, excluding ISRs (≥3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (3)</td>
<td>5 (4)</td>
<td>0</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (2)</td>
<td>4 (3)</td>
<td>1 (2)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>0</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Grade 3 and 4 AEs, excluding ISRs</td>
<td>10 (9)</td>
<td>12 (10)</td>
<td>1 (2)</td>
<td>22 (10)</td>
</tr>
<tr>
<td>Drug-related Grade 3/4 AEs(^a), excluding ISRs</td>
<td>3 (3)</td>
<td>4 (3)</td>
<td>0</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Serious AEs(^b)</td>
<td>7 (6)</td>
<td>6 (5)</td>
<td>3 (5)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>AEs leading to withdrawal(^c)</td>
<td>2 (2)</td>
<td>6 (5)</td>
<td>1 (2)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Grade 3 and 4 labs(^d)</td>
<td>17 (15)</td>
<td>20 (17)</td>
<td>8 (14)</td>
<td>37 (16)</td>
</tr>
</tbody>
</table>

\(^a\)Q8W: influenza-like illness, chills and pain, and lipase; Q4W: influenza-like illness, rash, depression, and psychosis. \(^b\)None drug related; one death (epilepsy) evaluated as not likely related to study drug. \(^c\)Q8W: ISR × 2; Q4W: Churg Strauss vasculitis, hepatitis C, depression, epilepsy, psychosis, and rash; oral CAB: hepatitis C. \(^d\)Maintenance emergent. AE, adverse event; ISR, injection-site reaction.

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Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
Summary of Injection Site Reactions (ISRs)

<table>
<thead>
<tr>
<th></th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>IM subtotal (N=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of injections</td>
<td>1623</td>
<td>2663</td>
<td>4286</td>
</tr>
<tr>
<td>Number of ISRs</td>
<td>1054 (0.65)</td>
<td>1228 (0.46)</td>
<td>2282 (0.53)</td>
</tr>
<tr>
<td>Grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>839 (80%)</td>
<td>1021 (83%)</td>
<td>1860 (82%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>202 (19%)</td>
<td>197 (16%)</td>
<td>399 (17%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>12 (1%)</td>
<td>10 (&lt;1%)</td>
<td>22 (&lt;1%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7</td>
<td>943 (89%)</td>
<td>1121 (91%)</td>
<td>2064 (90%)</td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

- Most common ISR events overall were pain (67%), swelling (7%), and nodules (6%)
- Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 32)\(^a\)
- 2/230 subjects (1%) withdrew as a result of injection reactions (Q8W)

\(^a\)Represents percent of subjects with a Week 32 visit (n=220).
Patient-Reported Outcomes at Week 32: Maintenance Treatment Compared With Oral Induction Treatment

How satisfied are you with your current treatment?

- Q8W (n=106): 97% More, 96% Neutral, 1% Less
- Q4W (n=100): 98% More, 3% Neutral, 1% Less
- Oral CAB (n=49): 71% More

How satisfied would you be to continue with your present form of treatment?

- Q8W (n=106): 98% More, 2% Neutral, 1% Less
- Q4W (n=100): 98% More, 1% Neutral, 1% Less
- Oral CAB (n=49): 71% More

Note: based on observed case dataset of subjects who completed Week 32 questionnaires.

aHIV Treatment Satisfaction Questionnaire change version (HIVTSQc).

Margolis et al. CROI 2016, Boston, MA. Abstract 31LB.
Pharmacokinetics

- $C_T$, trough concentration; PA-IC90, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.

- Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
ÉCLAIR Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men

**Phase IIa, randomized, multi-site, 2-arm, double-blinded study in men at low risk of acquiring HIV**

**Oral phase**
- CAB 30 mg PO QD
- Placebo PO QD

**Injection phase**
- CAB LA 800 mg IM Q12W
- Saline placebo IM Q12W

**Follow-up phase**
- Follow-up

**D1**        **W2**      **W4**   **W5**              **W17**          **W29**              **W41**           **W53**  **W65**  **W77**  **W81**

*Injection phase*

*Oral phase*

*Follow-up phase*

5:1 Randomization

Note: not all scheduled study visits are shown in this study schematic.

- PO, orally; Q12W, every 12 weeks; QD, once daily.

- Markowitz et al. CROI 2016; Boston, MA. Abstract 106.
## Adverse Events—Injection Phase (Primary Safety Evaluation)

<table>
<thead>
<tr>
<th></th>
<th>PBO  (N=21) n (%)</th>
<th>CAB (N=94) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1-4 adverse events</strong></td>
<td>19 (90)</td>
<td>92 (98)</td>
</tr>
<tr>
<td><strong>Grade 2-4 adverse events (&gt;5% in CAB arm)</strong></td>
<td>10 (48)</td>
<td>75 (80)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (5)</td>
<td>55 (59)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>0</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>0</td>
<td>6 (6)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>1 (5)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

- No laboratory adverse events, including liver laboratory abnormalities, led to discontinuation throughout the injection phase.

- PBO: deep vein thrombosis (drug-related); CAB: appendicitis.

- Markowitz et al. CROI 2016; Boston, MA. Abstract 106.
ISR Symptoms—Injection Phase

<table>
<thead>
<tr>
<th>ISR events by maximum toxicity</th>
<th>PBO (N=21)</th>
<th>CAB (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any ISR event</td>
<td>12 (57)</td>
<td>87 (93)</td>
</tr>
<tr>
<td>Total number of injections</td>
<td>62</td>
<td>272</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ISR events by maximum toxicity</th>
<th>Number of events (%)</th>
<th>Mean duration (days)</th>
<th>Number of events (%)</th>
<th>Mean duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>16 (26)</td>
<td>2.0</td>
<td>122 (45)</td>
<td>5.4</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (2)</td>
<td>122 (45)</td>
<td>101 (37)</td>
<td>5.4</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>122 (45)</td>
<td>27 (10)</td>
<td>5.4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (6)</td>
<td>1.8</td>
<td>26 (10)</td>
<td>2.5</td>
</tr>
<tr>
<td>Swelling</td>
<td>0</td>
<td>22 (8)</td>
<td>26 (10)</td>
<td>2.5</td>
</tr>
<tr>
<td>Nodule/Bump</td>
<td>0</td>
<td>22 (8)</td>
<td>26 (10)</td>
<td>2.5</td>
</tr>
<tr>
<td>Warm to touch</td>
<td>0</td>
<td>22 (8)</td>
<td>26 (10)</td>
<td>2.5</td>
</tr>
<tr>
<td>Bruising</td>
<td>1 (2)</td>
<td>2.0</td>
<td>16 (6)</td>
<td>3.3</td>
</tr>
<tr>
<td>Induration</td>
<td>0</td>
<td>22 (8)</td>
<td>15 (6)</td>
<td>4.3</td>
</tr>
</tbody>
</table>

- No subjects discontinued due to AEs during the injection phase; 4 subjects who withdrew consent cited injection tolerability as a reason.

*Percentages are out of total number of injections. With the exception of Grade 3 pain, all ISRs listed were Grade 1-2. Subject was misdosed with CAB on third injection.
Switching to F/TAF (Tenofovir Alafenamide) from F/TDF (Tenofovir DF) based Regimen Study 311-1089: 48-Week Data

- Randomized, double-blind, double-dummy, active-controlled study

Virologically Suppressed (< 50 c/mL)
  - F/TDF + Third Agent
  - eGFR ≥50 mL/min

F/TAF (200/10 or 200/25 mg)* QD
  - F/TDF Placebo QD
  - Continue Third Agent

F/TDF (200/300 mg) QD
  - F/TAF* Placebo QD
  - Continue Third Agent

- **F/TAF Dose:**
  - 200/10 mg with boosted PIs
  - 200/25 mg with unboosted third agents

Primary Endpoint
HIV-1 RNA <50 c/mL

Secondary Endpoint

Gallant J et al Abstract 29
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>F/TAF n=333</th>
<th>F/TDF n=330</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>48 (22, 78)</td>
<td>49 (22, 79)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>48 (14)</td>
<td>54 (16)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>244 (73)</td>
<td>253 (77)</td>
</tr>
<tr>
<td>Black or African descent</td>
<td>69 (21)</td>
<td>67 (20)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (6)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Hispanic/Latino ethnicity, n (%)</td>
<td>48 (14)</td>
<td>78 (24)</td>
</tr>
<tr>
<td>Median CD4 count, cells/mm³</td>
<td>663</td>
<td>624</td>
</tr>
<tr>
<td>&lt;200 cells/mm³, n (%)</td>
<td>5 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Median eGFR*, mL/min</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Use of third agent, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boosted PI</td>
<td>155 (47)</td>
<td>150 (45)</td>
</tr>
<tr>
<td>Unboosted third agents</td>
<td>178 (53)</td>
<td>180 (55)</td>
</tr>
</tbody>
</table>

*eGFR calculated with Cockcroft-Gault equation

Gallant J et al Abstract 29
Efficacy at Week 48 (Snapshot)

**Virologic Outcome**

- **F/TAF (n=333)**
- **F/TDF (n=330)**

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt;50 c/mL, %</th>
<th>0.3</th>
<th>1.5</th>
<th>5.4</th>
<th>5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>94.3</td>
<td>93.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-success</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment Difference (95% CI)**

- F/TDF: -2.5 to 5.1
- F/TAF: 1.3

Gallant J et al Abstract 29
Virologic Success by Third Agent

HIV-1 RNA <50 c/mL, %

- **F/TAF (n=333)**
  - Boosted PI: 142%
  - Unboosted Third Agents: 172%

- **F/TDF (n=330)**
  - Boosted PI: 151%
  - Unboosted Third Agents: 167%

Gallant J et al Abstract 29
### Adverse Events Leading to Discontinuation

<table>
<thead>
<tr>
<th>n (%)</th>
<th>F/TAF n=333</th>
<th>F/TDF n=330</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>7 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Insomnia / Mood altered</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Overdose</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rectal tenesmus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Feeling abnormal / Headache</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- No reported cases of proximal renal tubulopathy or Fanconi syndrome in either group

Gallant J et al Abstract 29
Changes in eGFR

- eGFR calculated with Cockcroft-Gault equation

Gallant J et al Abstract 29
Change in Renal Biomarkers at Week 48

All differences between treatments statistically significant (p < 0.001)

- RBP, retinol-binding protein; β2M, β2-microglobulin.

Gallant J et al Abstract 29
Change in Bone Mineral Density through Week 48

≥ 3% BMD increase at Week 48

<table>
<thead>
<tr>
<th></th>
<th>F/TAF</th>
<th>F/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % change (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>-0.2</td>
<td>-0.2</td>
</tr>
<tr>
<td>24</td>
<td>1.5</td>
<td>0.9</td>
</tr>
<tr>
<td>48</td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>p &lt;0.001</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td>Hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>-0.2</td>
<td>-0.2</td>
</tr>
<tr>
<td>24</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>48</td>
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<td>1.1</td>
</tr>
<tr>
<td></td>
<td>p &lt;0.001</td>
<td>p &lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>F/TAF</th>
<th>F/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30%</td>
<td>14%</td>
</tr>
<tr>
<td>p</td>
<td>p &lt;0.001</td>
<td>p =0.003</td>
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</table>

Gallant J et al Abstract 29
Fasting Lipid Results

<table>
<thead>
<tr>
<th></th>
<th>Total Cholesterol</th>
<th>LDL</th>
<th>HDL</th>
<th>Triglycerides</th>
<th>TC: HDL Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>200 (187, 183)</td>
<td>128 (112, 115)</td>
<td>52 (49, 50)</td>
<td>115 (110, 112)</td>
<td>3.7 (3.6, 3.6)</td>
</tr>
<tr>
<td>Week 48</td>
<td>187 (182)</td>
<td>112 (110)</td>
<td>49 (50)</td>
<td>118 (112)</td>
<td>3.6 (3.6)</td>
</tr>
</tbody>
</table>

**F/TAF** vs **F/TDF**
- **Total Cholesterol**: p < 0.001
- **LDL**: p < 0.001
- **HDL**: p = 0.12
- **Triglycerides**: p = 0.004
- **TC: HDL Ratio**: p = 0.069

Patients initiating lipid-lowering agents: 4% F/TAF, 4% F/TDF

Gallant J et al Abstract 29
Doravirine 100 mg QD vs Efavirenz + TDF/FTC in ART-Naive HIV+ Patients: Week 48 Results MK1439-007

**Part 1 Dose Ranging Phase (N=210)**

- DOR 25 mg
- DOR 50 mg
- DOR 100 mg (n=42)
- DOR 200 mg
- EFV 600 mg (n=43)

**Part 1 Extension Phase**

- DOR 100 mg
- Continue EFV

**Part 2: Additional Patients, DOR Selected Dose vs EFV (N=132)**

- DOR 100 mg (n=66)
- EFV 600 mg (n=66)

Patients:
- HIV-1+ ART-naive
- RNA ≥1,000 c/mL
- CD4 ≥100 cells/µL
- Stratified by screening RNA (≤/> 100K c/mL)

Part 2 began after dose selection based on Part 1 week 24 results.

Gatell J. CROI 2016 abstract 470
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DOR 100 mg</th>
<th>EFV 600 mg</th>
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</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>N=108</td>
<td>N=108</td>
</tr>
<tr>
<td>% Male</td>
<td>91.7</td>
<td>93.5</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>35 (19 – 67)</td>
<td>34 (20 – 57)</td>
</tr>
<tr>
<td>% White</td>
<td>79.6</td>
<td>79.6</td>
</tr>
<tr>
<td>% with AIDS</td>
<td>3.7</td>
<td>6.5</td>
</tr>
<tr>
<td>HIV RNA (log_{10} c/mL), median (range)</td>
<td>4.6 (2.6 – 6.5)</td>
<td>4.6 (3.0 – 6.7)</td>
</tr>
<tr>
<td>% with HIV RNA &gt;100,000 c/mL, at screening</td>
<td>35.2</td>
<td>37.0</td>
</tr>
<tr>
<td>CD4 Count (cells/µL), median (range)</td>
<td>402 (92 – 1110)</td>
<td>430 (118 – 1121)</td>
</tr>
<tr>
<td>% with CD4 count ≤ 200 cells/µL</td>
<td>6.5</td>
<td>9.3</td>
</tr>
<tr>
<td>% with Clade B viral subtype</td>
<td>69.4</td>
<td>79.6</td>
</tr>
</tbody>
</table>

All patients also received TDF/FTC.
HIV RNA <40 copies/mL (NC=F Approach)

Week 48 | n/N (%) | Difference (95% CI)
---|---|---
DOR | 84/108 (77.8) | -1.1 (-12.2, 10.0)
EFV | 85/108 (78.7) | 

Gatell J. CROI 2016 abstract 470
Virologic Response by Screening RNA
Week 48 (OF Approach*)

*Excludes patients who (1) discontinued due to AE, (2) discontinued due to non-treatment related reasons and had last RNA <40 c/mL, or (3) were on-study but missing data in week 48 window.

Gatell J. CROI 2016 Abstract#470
## Clinical Adverse Events (%)

<table>
<thead>
<tr>
<th></th>
<th>DOR 100 mg (N=108)</th>
<th>EFV 600 mg (N=108)</th>
<th>Difference [DOR – EFV] (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more adverse events (AE)</td>
<td>87.0</td>
<td>88.9</td>
<td>-1.9 (-10.9, 7.1)</td>
</tr>
<tr>
<td>Serious AE†</td>
<td>6.5</td>
<td>8.3</td>
<td>-1.9 (-9.5, 5.6)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>2.8</td>
<td>5.6</td>
<td>-2.8 (-9.2, 3.0)</td>
</tr>
<tr>
<td>Drug-related‡ AE</td>
<td>31.5</td>
<td>56.5</td>
<td>-25.0 (-37.3, -11.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.9</td>
<td>6.5</td>
<td>---</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.4</td>
<td>5.6</td>
<td>---</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.5</td>
<td>25.9</td>
<td>---</td>
</tr>
<tr>
<td>Headache</td>
<td>2.8</td>
<td>5.6</td>
<td>---</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>5.6</td>
<td>14.8</td>
<td>---</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6.5</td>
<td>2.8</td>
<td>---</td>
</tr>
<tr>
<td>Nightmares</td>
<td>5.6</td>
<td>8.3</td>
<td>---</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>4.6</td>
<td>6.5</td>
<td>---</td>
</tr>
</tbody>
</table>

All patients also received TDF/FTC.

† Two serious AEs in the EFV group were considered drug-related: depression (1) and dizziness (1).

‡ Determined by investigator to be related to study therapy; specific AEs with >5% incidence are listed.

Specific AEs causing discontinuation (n): DOR – hallucination (1), B-cell lymphoma (1), Hodgkin’s disease (1); EFV – dysaesthesia (1), hallucinations (2), drug eruption (1), dizziness (1), disturbance in attention (1).

Gatell J. CROI 2016 Abstract#470
ART strategies
Impact of Transmitted Thymidine Analogue Mutations on Responses to First-Line ART

Anna Maria Geretti Abstract 482

![Graph showing proportion suppressed over time since ART initiation.]

### Number at risk

<table>
<thead>
<tr>
<th>Time since ART initiation (weeks)</th>
<th>1 - No resistance, NNRTI</th>
<th>2 - No resistance, bPI</th>
<th>3 - Isolated TAMs, NNRTI</th>
<th>4 - Isolated TAMs, bPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>8</td>
<td>4749</td>
<td>1581</td>
<td>140</td>
<td>129</td>
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<tr>
<td>16</td>
<td>3557</td>
<td>857</td>
<td>114</td>
<td>114</td>
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<tr>
<td>24</td>
<td>2030</td>
<td>504</td>
<td>65</td>
<td>82</td>
</tr>
<tr>
<td>32</td>
<td>1082</td>
<td>315</td>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td>40</td>
<td>562</td>
<td>219</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>48</td>
<td>356</td>
<td>157</td>
<td>4</td>
<td>16</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>
START Trial: Impact on Cancer

- Results: Immediate vs. deferred ART initiation and the risk of any type cancer, infection-related and infection-unrelated cancers in the START study

<table>
<thead>
<tr>
<th></th>
<th>Any type cancer (n=53)</th>
<th>Infection-related cancer (n=53)</th>
<th>Infection-unrelated cancer (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model D</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A: univariable, estimated in a Cox proportional hazards model with a single treatment indicator

B: adjusted for baseline covariates; age, gender, race, geographical region, smoking, BMI, hepatitis B/C, CD4 cell count and baseline log_{10} HIV RNA

C: adjusted for latest HIV RNA, modelled as <200 copies/mL vs HIV RNA >200 copies/mL

D: adjusted for latest CD4 cell count and latest HIV RNA (<200 copies/mL)

74% reduction in risk of infection related cancers (KS, HL & NHL, HPV)
Factors associated with ↑ risk of Infection-related cancers
- Age
- Baseline HIV-RNA
  ↓ risk:
- high income country

Rap-IT trial -Starting Treatment Isn’t Easy!

- HIV test; result positive
- Give blood sample for CD4 count
- Complete TB symptom screen
- Provide sputum sample if symptomatic

- Provide CD4 count results; treatment eligible
- Provide TB test results and initiate TB treatment if required

- Individual counseling session (education/adherence)

- Group counseling session (education/adherence)

- Provide results of other blood tests
- Treatment buddy session

- Conduct physical examination
- Dispense ARVs

Rosen S et al CROI 2016 abstract 1091

I am exhausted...
Major Programmatic Outcome: ART Initiation ≤ 90 Days

377 ART eligible patients enrolled

190 standard patients
- 54 did not initiate ≤ 90 days (28%)
- 2 initiated ≤ 180 days
- 52 did not initiate

136 initiated ≤ 90 days (72%)

187 rapid patients
- 5 did not initiate ≤ 90 days (3%)
- 1 initiated ≤ 180 days
- 4 did not initiate (all lost during TB workup)

182 initiated ≤ 90 days (97%)

Risk difference 25% (95% CI 19 to 33%)
Crude relative risk 1.36 (95% CI 1.24 to 1.49)

Rosen S et al CROI 2016 abstract 1091
Primary Protocol Outcome: Initiated, Retained, and Suppressed ≤ 10 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard arm</th>
<th>Rapid arm</th>
<th>Crude risk difference [95% CI]</th>
<th>Crude relative risk* [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiated ≤ 90 days</td>
<td>136 (72%)</td>
<td>182 (97%)</td>
<td>25% (19-33%)</td>
<td>1.36 (1.24-1.49)</td>
</tr>
<tr>
<td>Initiated ≤ 90 days and retained and suppressed by 10 months</td>
<td>96 (51%)</td>
<td>119 (64%)</td>
<td>13% (3-23%)</td>
<td>1.26 (1.05-1.50)</td>
</tr>
</tbody>
</table>

Of those not initiated ≤ 90 days and suppressed by 10 months:

| Not initiated | 54 (28%) | 5 (3%) |
| Initiated but not suppressed or with no viral load reported | 40 (21%) | 63 (34%) |
| Initiated ≤ 90 days and retained at 10 months | 121 (64%) | 151 (81%) | 17% (5-23%) | 1.27 (1.12-1.44) |

Of those not initiated ≤ 90 days and retained at 10 months:

| Not initiated | 54 (28%) | 5 (3%) |
| Initiated but not retained | 15 (8%) | 31 (17%) |
How Long Did It Take?

Median time in clinic between study enrollment and ARV dispensing in rapid group: 2.4 hours (IQR 2.1-2.8 hours)

Rosen S et al CROI 2016 abstract 1091
ACTG 5273 Randomized Trial of Second-line ART Supports WHO Guidance

Phase III, open-label, randomized, non-inferiority study
15 sites in 9 low-middle income countries
3 continents

Planned N=600
Failing on NRTIs + NNRTI as initial regimen with VF: confirmed >1,000 cps/mL

LPV/r + RAL (n = 300)
LPV/r + best available NRTIs (n = 300)

48 weeks Primary endpoint
96 weeks f/u for each participant

1:1

• **Primary objective**: To determine whether the efficacy of RAL arm is non-inferior to that of NRTI arm by 48 weeks
• **Primary endpoint**: Time to VF= confirmed VL>400 cps/mL at ≥ 24 wks
• **N adjusted** to 480 after results of SECOND LINE, EARNEST and A5234:
  ➢ Power >90% and 10% non-inferiority margin maintained
  ➢ Follow up shortened to 52 weeks after the last enrollment

La Rosa A et al CROI 2016 abstract 30
Results: Primary Endpoint

Time to virologic failure (confirmed VL>400 c/mL at/after 24 weeks)
Difference in failure probability by week 48
RAL - NRTI: **-3.4%** (95% CI -8.4, 2.5)

Upper bound of CI <10% (non-inferiority boundary)
**RAL non-inferior**

Upper bound of CI > zero
**RAL not superior**

La Rosa A et al CROI 2016 abstract 30
Effect of Prescribed NRTI GSS on primary endpoint of time to VF

NRTI GSS <1 vs ≥1
week 48 difference -8.4%
95% CI: -16.6%, -0.3%
p = 0.04

La Rosa A et al CROI 2016 abstract 30
Associations of other NRTI Resistance Characteristics at Entry with the risk of Virologic Failure (VF) – Both arms included

K65R, ≥3 TAMs, Q151M or 69 ins/del
- No
- Yes

IAS NRTI mutations
- <3
- ≥3

K65R and/or M184V/I
- no M184V/I
- no K65R but M184V/I
- K65R and M184V/I

No difference by arm
Results consistent when adjusted for entry HIV-1 RNA, week 4 self-report adherence, prior exposure to TDF, and country

La Rosa A et al CROI 2016 abstract 30
New ART, phase I-II
4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA)

- EFdA (MK-8591) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Sub-nanomolar potency in vitro\(^1\) and prolonged suppression of SIV in macaque model\(^2\)
- Prolonged persistence of triphosphate form in PBMC and macrophage
- On dose allowed a VL drop of 1.78 log ut to Day 10
- Potential for once weekly dosing (Friedman et al Abstract 437LB)
- Long-acting formulations under development (Grobler et al Abstract 98)

\(^1\)Michailidis et al J Biol Chem 284: 35681-91; 2009  
\(^2\)Murphey-Corb et al AAC 56:4707-12; 2012
HIV-1 Combinectin: BMS-986197-mouse model

- BMS-986197 contains 2 $\alpha$-HIV-1 Adnectins and a peptide fusion inhibitor

Krystal et al Abstract 97

- long-acting (weekly dose) biologic molecule containing 3 individual inhibitors of HIV-1
Pharmacokinetics

- Dolutegravir in pregnancy
- Dabigatrin and cobicistat
IMPAACT P1026

Maternal drug exposure

- Pregnant women (N=21)
- DTG 50mg qd
- Age 31.8 (21.6 – 42.3)

Mothers
- Differences in exposure (NS; low N)
- 2 pre-eclampsia
- 1 ↑ALT
- 100% suppressed

Infants
- DTG T½ 35h vs ~11h in mum
- 9 uninfected, 9 pending
- 4 Infants hypoglycaemia
- 4 congenital anomalies:
  - Total anomalous pulmonary venous return
  - Polycystic kidney and cystic fibrosis
  - Congenital chin tremor
  - Fibrum terminale fibrolipoma & sacral dimple

Mulligan et al CROI 2016; Abstr 438
Oral Anticoagulants

Anticoagulants
- Generally narrow therapeutic index
- Inhibitors – bleeding can be prolonged – consider reversibility
- Inducers – adverse consequences on discontinuation

**Novel Oral Anticoagulants**
- Rivaroxaban & Apixaban – CYP3A4 and PgP substrate
- Dabigatran – PgP substrate
- Dabigatran and cobicistat (CROI 2016, Abstr 430) – prolonged TT
- Caution. Anti-factor Xa useful?

<table>
<thead>
<tr>
<th>DTG</th>
<th>EVGc</th>
<th>RAL</th>
<th>EFV</th>
<th>RPV</th>
<th>DRV cr</th>
<th>ATV cr</th>
<th>TDF</th>
<th>ABC</th>
<th>(X)TC</th>
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ART ‘Plus’

- Antibodies for HIV-1 prevention and treatment
  (Mascola plenary, abstract 15)
Combined Antibodies: Improved Potency and Breadth

Fraction of HIV-1 strains neutralized

IC$_{50}$ cut-off (µg/ml)

2 mAbs > 98% coverage

- VRC07
- PG9
- PGT128
- 10E8
- 2 mAb Combinations
- 3 mAb Combinations
- 4 mAb Combination

Broadly Neutralizing Antibodies as Therapy

• Can they be used successfully as therapy with ART?
  • Single antibodies lack needed breadth\textsuperscript{refs}
  • Combinations of antibodies with differing targets
    • Anti-CD4 binding plus anti-V3 or V2 plus others?
    • Modifiable to increase half-life
    • In combination with long-acting antiretrovirals?

• But…
  • Cumbersome delivery, increasing potency = decreasing dose
  • Virus escape – frequency of monitoring
  • Anti-idiotype or other inhibitory antibodies

Caskey et al Nature 2015;
Lynch et al Sci Transl Med 2015; Bar et al Abstract 32LB; Chun et al Abstract 311LB
ART

- New drugs and new classes continue in development
- New formulations, new routes for delivery
- Implementing universal treatment
- Sustaining long term treatment
- Managing resistance
- New treatment goals?

- Dr Jasmini Alagaratnam
- Prof Brian Angus
- Dr David Asboe
- Dr Sanjay Bhagani
- Dr Daniel Bradshaw
- Dr Kate Childs
- Dr Duncan Churchill
- Dr Amanda Clarke
- Dr Paul Collini
- Mr Simon Collins
- Prof Satyajit Das
- Dr Annemiek de Ruiter
- Prof David Dockrell
- Prof Lucy Dorrell
- Dr Ellen Dwyer
- Dr Sarah Fidler
- Dr Julie Fox
- Dr Andrew Freedman
- Dr David Hawkins
- Prof Saye Khoo
- Prof Clifford Leen
- Prof Derek Macallan
- Dr Achyuta Nori
- Dr Ed Ong
- Dr Chloe Orkin
- Dr Adrian Palfreeman
- Dr Brendan Payne
- Dr Frank Post
- Dr Iain Reeves
- Dr Jonathan Underwood
- Dr Jaime Vera
- Dr Ed Wilkins