Dr Chloe Orkin
Barts Health NHS Trust, London
<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Chloe Orkin</td>
<td>Dr Orkin acts in a Consultancy capacity and as a speaker at company-sponsored events for Gilead, MSD, Viiv, Jannsen, Abbvie and BMS. She has received personal grants to attend conferences from Gilead, Viiv, Jannsen, BMS, BI and MSD and has received research grants from the same companies</td>
</tr>
<tr>
<td>Date</td>
<td>October 2014</td>
</tr>
</tbody>
</table>
FIRST-LINE ART: WHERE TO NOW?

Dr Chloe Orkin
Consultant and Honorary Reader in HIV Medicine
What’s new since BHIVA 2013?

✧ Guidelines
✧ Backbone
✧ 3rd Agent
✧ Tolerability
✧ Robustness
✧ Durability
✧ STR
✧ Horizon scanning
Life expectancy of HIV-positive persons vs general population

Danish HIV Cohort Study

Population controls
HIV patients – risk (n=871)

HIV patients + risk (n=704)

HIV patients + co-morb. (n=379)

HIV patients + abuse (n=313)


HIV patients n=2267; population controls n=9068
NRTI BACKBONE IN HIV TREATMENT: WILL IT REMAIN RELEVANT?

Drugs 2012 Nov 12;72(16):2051-62
DAD data 2014: Association between current ABC use and MI risk

Overall

Pre-March 2008

Post-March 2008

Not currently on ABC

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Pre-March 2008</th>
<th>Post-March 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/PYRS</td>
<td>600/295642</td>
<td>425/169417</td>
<td>175/126225</td>
</tr>
<tr>
<td>Rate (95% CI)/100PYRS</td>
<td>0.2 (0.19, 0.22)</td>
<td>0.25 (0.23, 0.28)</td>
<td>0.14 (0.12, 0.16)</td>
</tr>
</tbody>
</table>

Currently on ABC

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<th>Pre-March 2008</th>
<th>Post-March 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/ PYRS</td>
<td>341/71917</td>
<td>247/40833</td>
<td>94/31084</td>
</tr>
<tr>
<td>Rate (95% CI)/100 PYRS</td>
<td>0.47 (0.42, 0.52)</td>
<td>0.61 (0.53, 0.68)</td>
<td>0.30 (0.24, 0.36)</td>
</tr>
</tbody>
</table>

Adapted from: CA Sabin et al DAD study CROI Boston 2014
Conflicting evidence on risk of MI/CV event associated with ABC treatment

NB. Data compared either MI risk associated with ABC or CV event risk associated with ABC – no consistent outcome measured across all studies

KEY:
- Observational studies
- Randomised control trials
- Meta-analyses

Time

Association of MI/CV events with ABC

Yes

No

SMART 2 2008

D.A.D 2008

D.A.D 3 2009

Quebec 2009

STEAL 4 2009

VA * 6 2009

FHDH** 7 2010

ALLRT 9 2009

GSK analysis1 2009

HEAT 10 2009

ARIES 12 2010

BICOMBO 13 2010

ASSERT 15 2010

ACTG 5202 16 2010

Cruciani 17 2011

FDA 14 2011

D.A.D 8 2014

*Although initial analysis identified an association between ABC and increased risk of MI, further analyses showed no association after adjustment for traditional CV risk factors and renal dysfunction.

**Sensitivity/supportive analysis censoring cocaine or IV drug use

BHIVA GUIDELINES 2013 (BEING RE-WRITTEN)

### PREFERRED

<table>
<thead>
<tr>
<th>NRTI</th>
<th>3rd agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF and FTC</td>
<td>ATV/r</td>
</tr>
<tr>
<td></td>
<td>DRV/r</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
</tr>
<tr>
<td></td>
<td>EVG/cobi</td>
</tr>
</tbody>
</table>

### ALTERNATIVE

<table>
<thead>
<tr>
<th>NRTI</th>
<th>3rd agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC*‡ and 3TC</td>
<td>RPV‡</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
</tr>
<tr>
<td></td>
<td>FPV/r</td>
</tr>
<tr>
<td></td>
<td>NVP‡</td>
</tr>
</tbody>
</table>

*ABC is contraindicated if HLA-B*5701 positive
†NVP is contraindicated if baseline CD4 cell count is greater than 250/400 cells/mL in women/men
‡Use recommended only if baseline VL <100 000 copies/mL: RPV as a third agent, ABC/3TC as NRTI backbone
# DHHS, IAS-USA, EACS on NRTI Backbone for ART-Naïve Patients

<table>
<thead>
<tr>
<th>DHHS¹ (Dept. of Health and Human Services)</th>
<th>IAS-USA² (International Antiviral Society USA Panel)</th>
<th>EACS³ (European AIDS Clinical Society)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI-based therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV/TDF/FTC</td>
<td>EFV + TDF/FTC or ABC/3TC*</td>
<td>EFV or RPV** + TDF/FTC or ABC/3TC*** NVP‡ + TDF/FTC</td>
</tr>
<tr>
<td><strong>Ritonavir-boosted PI-based therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP/r or DRV/r + TDF/FTC</td>
<td>ATP/r + TDF/FTC or ABC/3TC*</td>
<td>ATP/r, DRV/r, or LPV/r + TDF/FTC or ABC/3TC**</td>
</tr>
<tr>
<td><strong>INI-based therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL + TDF/FTC EVG/cobi/TDF/FTC DTG + ABC/3TC or TDF/FTC</td>
<td>RAL + TDF/FTC</td>
<td>RAL + TDF/FTC</td>
</tr>
</tbody>
</table>

*ABC/3TC only to be used in HLA-B*5701 negative patients with baseline plasma HIV-1 RNA <100,000 c/mL
**RPV: only if VL <100 000 c/mL; PPI contraindicated, H₂ antagonists to be taken 12h before or 4h after RPV
***ABC contra-indicated if HLA-B*5701 positive. Even if HLA-B*5701 negative, counselling on HSR risk still mandatory.
ABC should be used with caution in patients with a high CVD risk and/or patients with a VL > than 100,000 c/mL
‡NVP only if benefits outweigh risk

CVD, cardiovascular disease; HSR, hypersensitivity reaction
PPI, proton pump inhibitors; VL, viral load

1. DHHS Guidelines February 2013 and October 2013
3. EACS Guidelines Version 7.0, October 2013
NRTI-free regimes:

- MODERN
- ACTG5262
- SPARTAN
- RADAR
- A4001078
- GARDEL
- NEAT 001
- PROGRESS

Mascolini M RADAR IAS June 2013, Malaysia.
NEAT 001/ANRS 143 study design

- Phase III, randomised, open-label, multicentre, parallel-group, non-inferiority, strategic trial
- 78 sites, 15 countries*

**ART-naïve**
- ≥ 18 years
- HIV-1 RNA > 1000 c/ml
- CD4 ≤ 500/mm³
- HBs Ag negative
- No major IAS-USA mutations

Randomisation 1:1

- Composite virological and clinical primary endpoint (6 components)
- Non-inferiority margin: absolute difference up to 9% for failure rate RAL vs. TDF/FTC by W96

* Austria, Belgium, Denmark, France, Germany, Great Britain, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden

Adapted from Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014; Clinicaltrials.gov identifier: NCT01066962
Primary analysis:
Time from randomisation to primary endpoint

### Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>401</td>
<td>404</td>
</tr>
<tr>
<td>N with primary endpoint</td>
<td>76 (19%)</td>
<td>61 (15%)</td>
</tr>
</tbody>
</table>

**V1. Regimen change for insufficient response**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 log_{10} c/ml HIV RNA reduction W18*</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HIV RNA ≥ 400 c/ml W24*</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**V2. HIV RNA ≥ 50 c/ml at W32**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA ≥ 50 c/ml at W32*</td>
<td>27</td>
<td>28</td>
</tr>
</tbody>
</table>

**V3. HIV RNA ≥ 50 c/ml after W32**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA ≥ 50 c/ml after W32*</td>
<td>32</td>
<td>22</td>
</tr>
</tbody>
</table>

**C1. Death**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**C2. AIDS event**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS event</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

**C3. SNAIDS event**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAIDS event</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

* confirmed by a subsequent measurement

**Estimated proportion reaching primary endpoint at W96**

- **RAL:** 17.4%
- **TDF/FTC:** 13.7%

**Adjusted difference:** 3.7% (95% CI: -1.1, 8.6%)

Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014
Primary endpoint at W96 by baseline characteristics

Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r

Overall
- n = 805
- RAL + DRV/r: 17.4%
- TDF/FTC + DRV/r: 13.7%
- Difference: 3.7% (95% CI: -1.1 to 8.6)

Baseline HIV-1 RNA
- < 100,000 c/ml
  - n = 530
  - RAL + DRV/r: 7%
  - TDF/FTC + DRV/r: 7%
  - Difference: 0% (95% CI: -3.9 to 3.5)
  - p = 0.09*
- ≥ 100,000 c/ml
  - n = 275
  - RAL + DRV/r: 36%
  - TDF/FTC + DRV/r: 27%
  - Difference: 9.3% (95% CI: -0.05 to 19.3)

Baseline CD4+
- < 200/mm³
  - n = 123
  - RAL + DRV/r: 39.0%
  - TDF/FTC + DRV/r: 21.3%
  - Difference: 17.7% (95% CI: 4.7 to 30.8)
  - p = 0.02*
- ≥ 200/mm³
  - n = 682
  - RAL + DRV/r: 13.6%
  - TDF/FTC + DRV/r: 12.2%
  - Difference: 1.4% (95% CI: -3.4 to 6.3)

* Test for homogeneity

Adapted from Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014
### Virological failure and resistance data

<table>
<thead>
<tr>
<th></th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol-defined virological failure (PDVF), n</td>
<td>66</td>
<td>52</td>
</tr>
<tr>
<td>Number of PDVF who met criteria for genotype testing (HIV RNA &gt; 500 copies/ml at or after W32)</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>Number of patients with single unconfirmed value of HIV RNA &gt; 500 copies/ml at or after W32 (meeting criteria for genotype testing)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Genotype done, n</td>
<td>28/36</td>
<td>13/15</td>
</tr>
<tr>
<td>Major resistance mutations, n</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NRTI</td>
<td>1 (K65R)</td>
<td>0</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>INI</td>
<td>5 (N155H)*</td>
<td>-</td>
</tr>
</tbody>
</table>

* 1 additional patient with T97A

Protocol-defined virological failure change of any component of the initial randomised regimen before W32 because of confirmed insufficient virological response, defined as HIV-1 RNA reduction $< 1 \log_{10}$ copies/ml by W18 or HIV-1 RNA $\geq$ 400 copies/ml at W24; failure to achieve virological response by W32 (confirmed HIV-1 RNA $\geq$ 50 copies/ml at W32); confirmed HIV-1 RNA $\geq$ 50 copies/ml at any time after W32.

According to the protocol, genotypic testing was carried out by local laboratories when patients had a single VL $> 500$ copies/ml at or after W32.

Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014
NRTI’s remain

Success depends on your backbone, not your wishbone
A GOOD 3\textsuperscript{RD} AGENT?

- Robustness
- Forgiveness
- Od dosing
- Few DDI’s
- Resistance profile
- Efficacy
- Durability

ART
Primary endpoints

- **VF**: time to HIV-1 RNA > 1000 c/mL (at Wk 16 or before Wk 24) or > 200 c/mL (at or after Wk 24)
- **TF**: time to discontinuation of randomized component for toxicity

**Composite endpoint**: the earlier occurrence of either **VF** or **TF** in a given participant

**Switch of regimens** allowed for tolerability

---

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=1809)</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ATV/r (N=605)</td>
</tr>
<tr>
<td>Sex</td>
<td>435 (24%)</td>
<td>144 (24%)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean 37</td>
<td>38</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Non-His.</td>
<td>615 (34%)</td>
<td>212 (35%)</td>
</tr>
<tr>
<td>Black Non-His.</td>
<td>757 (42%)</td>
<td>252 (42%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>390 (22%)</td>
<td>125 (21%)</td>
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## Baseline Characteristics

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<td>38</td>
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<tr>
<td>Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA (log_{10} c/ml) (copies/ml)</td>
<td>4.6 (4.1-5.1)</td>
<td>4.6 (4.1-5.2)</td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>70%</td>
<td>68%</td>
</tr>
<tr>
<td>100,000-500,000</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;500,000</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>
# Baseline Characteristics

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<td>68%</td>
</tr>
<tr>
<td>100,000-500,000</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;500,000</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>CD4+ cells (cells/mm³)</td>
<td>308 (170-425)</td>
<td>309 (176-422)</td>
</tr>
<tr>
<td>%</td>
<td>30%</td>
<td>29%</td>
</tr>
</tbody>
</table>
ACTG 5257: Virologic Efficacy

- In ITT analysis ART changes allowed (per protocol), Wk 96 through Wk 144

- In ITT analysis (change = failure) (Snapshot), RAL superior to both bPI’s at Wk 96. DRV/RTV superior to ATV/RTV at Wks 96 and 144

# Toxicity-Associated Discontinuation of randomized ART *

<table>
<thead>
<tr>
<th>Toxicity Category</th>
<th>ATV/r (N=605)</th>
<th>RAL (N=603)</th>
<th>DRV/r (N=601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any toxicity discontinuation</td>
<td>95 (16%)</td>
<td>8 (1%)</td>
<td>32 (5%)</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>25</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Jaundice/Hyperbilirubinaemia</td>
<td>47</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other hepatic toxicity</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Metabolic toxicity</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Renal toxicity (all nephrolithiasis)</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal chem/haem (excl. LFTs)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other toxicity</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Participants allowed to switch therapy for intolerable toxicity

Resistance to Study Agents

1809 Participants

295 Virologic Failures

- **ATV/r**
  - 75/94 VF
  - Available
  - 9 Any Resistance (1.5% of ATV/r)
  - 5 isolated M184V
  - 1 integrase mutation
  - 2 T69D/T215AIT
  - 1 K70N + M184V

- **RAL**
  - 65/85 VF
  - Available
  - 18 Any Resistance (3% of RAL)
  - 1 isolated integrase mutation
  - 7 M184V
  - 7 integrase + M184V
  - 3 integrase + M184V + K65R

- **DRV/r**
  - 99/115 VF
  - Available
  - 4 Any Resistance (<1% of DRV/r)
  - 3 M184V
  - 1 integrase mutation

1 Baseline Missing
56 VF Failed to Amplify

ACTG 5257: Primary Endpoint Analyses at Wk 96

**Virologic Failure**
- Regimens equivalent in time to VF endpoint

**Tolerability Failure**
- Significantly greater treatment failure with ATV/RTV vs RAL or DRV/RTV
  - In part due to high proportion of pts with hyperbilirubinaemia

**Composite Endpoint**
- Considering both efficacy and tolerability, RAL superior to either b PI
- DRV/RTV superior to ATV/RTV

### Difference in 96-Wk Cumulative Incidence (97.5% CI)

- **Favours RAL**
  - ATV/RTV vs RAL: 3.4% (-0.7 to 7.4)
  - DRV/RTV vs RAL: 5.6% (1.3-9.9)
  - ATV/RTV vs DRV/RTV: -2.2% (-6.7 to 2.3)

- **Favours RAL**
  - ATV/RTV vs RAL: 13% (9.4-16.0)
  - DRV/RTV vs RAL: 3.6% (1.4-5.8)
  - ATV/RTV vs DRV/RTV: 9.2% (5.5-13.0)

- **Favours RAL**
  - ATV/RTV vs RAL: 15% (10-20)
  - DRV/RTV vs RAL: 7.5% (3.2-12.0)
  - ATV/RTV vs DRV/RTV: 7.5% (2.3-13.0)

Dolutegravir vs RAL, EFV, DRV/r

- Randomized, non-inferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48

**SPRING-2**[1] (active controlled)
- ART-naive pts
- VL ≥ 1000 c/mL
- (N = 822)
- DTG 50 mg QD + 2 NRTIs*
  - (n = 411)
- RAL 400 mg BID + 2 NRTIs*
  - (n = 411)

**SINGLE**[2] (placebo controlled)
- ART-naive pts
- VL ≥ 1000 c/mL
- HLA-B*5701-neg
- CrCL > 50 mL/min
- (N = 833)
- DTG 50 mg QD + ABC/3TC QD
  - (n = 414)
- EFV/TDF/FTC QD
  - (n = 419)

**FLAMINGO**[3] (open label)
- ART-naive pts
- VL ≥ 1000 c/mL
- (N = 484)
- DTG 50 mg QD + 2 NRTIs*
  - (n = 242)
- DRV/RTV 800/100 mg QD + 2 NRTIs*
  - (n = 242)

*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=833)</th>
<th>Total (N=822)</th>
<th>Total (N=484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>35</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>Female, %</td>
<td>16</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>African-American/African heritage, %</td>
<td>24</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (log10 c/mL)</td>
<td>4.68</td>
<td>4.55</td>
<td>4.49</td>
</tr>
<tr>
<td>&gt;100,000 c/mL, %</td>
<td>32</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Median CD4 cell count, cells/mm(^3)</td>
<td>338</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>&lt;200, %</td>
<td></td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

Feinberg J, et al. ICAAC 2013. Abstract H1464a
Tolerability

- DTG vs RAL\(^{[1,2]}\)
  - Adverse events similar between arms

- DTG vs EFV\(^{[3]}\)
  - CNS events and rash more common with EFV; insomnia more frequent with DTG

- DTG vs DRV/RTV\(^{[4]}\)
  - More diarrhea with DRV/RTV; more headache with DTG

- DTG associated with small, rapid increase in serum creatinine in first 4 wks: remained stable through Wk 48 (mean change from baseline: +0.11 mg/dL; range: -0.60 to 0.62 mg/dL)\(^{[5]}\)
  - Rise in creatinine related to inhibition of tubular secretion of creatinine by DTG
  - No drug-related discontinuations due to renal adverse events

SPRING-2: DTG vs RAL + 2 NRTIs Wk 48 & 96

- DTG non-inferior to RAL at Wk 48\(^1\) and Wk 96\(^2\)
- 2% treatment-related study d/c: in each arm (Wk 96)
- VF at Wk 96\(^2\): 5% DTG vs 7% RAL arm
- Similar CD4+ cell count increase at Wk 96

SINGLE: DTG + ABC/3TC vs EFV/TDF/FTC Wk 48 data

- DTG superior to EFV at Wk 48
- Treatment-related study d/c: 2% DTG vs 10% EFV
- VF at Wk 48: 4% DTG and 4% EFV arm
- CD4+ cell count increase at Wk 48 greater with DTG:
  - +267 cells/mm$^3$ (DTG) vs +208 cells/mm$^3$ (EFV) ($P < .001$)

FLAMINGO: DTG vs DRV/r + 2 NRTIs at Wk 48

- DTG superior to DRV/RTV at Wk 48
- Treatment-related study d/c: 2% DTG vs 4% DRV/r
- VF at Wk 48: < 1% (n = 2) in each arm
- Similar CD4+ cell count increase at Wk 48

Resistance Summary

- **DTG vs RAL**\(^{[1,2]}\)
  - 0 pts with resistance in DTG arm
  - 1 pt with INSTI-R and 4 pts with NRTI-R with RAL at Wk 48; no additional resistance by Wk 96

- **DTG vs EFV**\(^{[3]}\)
  - 0 pts with resistance in DTG arm
  - 1 pt with NRTI and 4 with NNRTI resistance in EFV arm

- **DTG vs DRV/RTV**\(^{[4]}\)
  - No pts with resistance in either arm

---

Who are our study subjects?

- Rilpivirine
- ECHO/THRIVE
- DTG
- Single/Flamingo/Sailing
- RAL/DRV/r
- NEAT 001
- TDF/FTC/ELVI/c
- 0102/3

CD4 >250

VL <100K

ACTG 5257
Robustness:
High Baseline VL > 100,000c/ml affects performance of all drug classes

- **NRTI:** Abacavir - ACTG 5202
- **NNRTI:** Rilpivirine - ECHO/THRIVE
- **PI:** Lopinavir/r - Artemis
- **INSTI:** Raltegravir - QD MRK

DHHS Guidelines May 2014

<table>
<thead>
<tr>
<th></th>
<th>For All Pts, Regardless of BL VL or CD4+ Count</th>
<th>Only for Pts With Pre-ART VL &lt; 100,000 c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>▪ EFV/TDF/FTC</td>
<td>▪ EFV + ABC/3TC*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ RPV/TDF/FTC†</td>
</tr>
<tr>
<td>Boosted PI</td>
<td>▪ ATV/RTV + TDF/FTC</td>
<td>▪ ATV/RTV + ABC/3TC*</td>
</tr>
<tr>
<td></td>
<td>▪ DRV/RTV + TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>INSTI</td>
<td>▪ RAL + TDF/FTC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ EVG/COBI/TDF/FTC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ DTG + ABC/3TC*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ DTG + TDF/FTC</td>
<td></td>
</tr>
</tbody>
</table>

*Only for pts who are HLA-B*5701 negative. †Only for those with CD4+ cell counts > 200 cells/mm³.

- If initiating ART in a pt with acute/early HIV before resistance test results are available, use a boosted PI plus NRTIs due to slow emergence of PI resistance and uncommon transmitted resistance.

DHHS Guidelines. May 2014.
STARTMRK:
EFV vs RAL through 240 weeks (NC=F)

48-week difference
estimate 4.2%,
95% CI: –1.9–10.3

192-week difference
estimate 9.0%,
95% CI: 1.6–16.4

240-week difference
estimate 9.5%,
95% CI: 1.7–17.3

DC due to AEs (%)

<table>
<thead>
<tr>
<th></th>
<th>RAL (n=281)</th>
<th>EFV (n=282)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>

No. of virologic failures with resistance data

<table>
<thead>
<tr>
<th></th>
<th>RAL or EFV resistance alone</th>
<th>RAL or EFV resistance + NRTI resistance</th>
<th>NRTI resistance alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL (n=23)</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>EFV (n=20)</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

NC=F: non-completer=failure; *HIV-RNA <50 copies/mL

Durability:
EVG/COBI/TDF/FTC Non-inferior Through Week 144

**vs EFV**

<table>
<thead>
<tr>
<th>EVG/COBI/TDF/FTC (n = 348)</th>
<th>EFV/TDF/FTC (n = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 48</td>
<td>Wk 96</td>
</tr>
<tr>
<td>△: 3.6%</td>
<td>△: 2.7%</td>
</tr>
<tr>
<td>(-1.6 to 8.8)</td>
<td>(-2.9 to 8.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 50 copies/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVG/COBI/TDF/FTC</td>
</tr>
<tr>
<td>88</td>
</tr>
<tr>
<td>84</td>
</tr>
<tr>
<td>84</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>75</td>
</tr>
</tbody>
</table>

**vs ATV/r**

<table>
<thead>
<tr>
<th>EVG/COBI/TDF/FTC (n = 353)</th>
<th>ATV/RTV + TDF/FTC (n = 355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 48</td>
<td>Wk 96</td>
</tr>
<tr>
<td>△: 3.0%</td>
<td>△: 1.1%</td>
</tr>
<tr>
<td>(-1.9 to 7.8)</td>
<td>(-4.5 to 6.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 50 copies/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVG/COBI/TDF/FTC</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>87</td>
</tr>
<tr>
<td>83</td>
</tr>
<tr>
<td>82</td>
</tr>
<tr>
<td>78</td>
</tr>
</tbody>
</table>

STR (single tablet regimen)
Potential Benefits and Limitations of an STR

### Benefits

- **Approved STRs combine components of preferred or alternative ARVs**
  - High virologic response rates especially in adherent patients
- **Avoids risk of partial regimen adherence**
  - Pharmacy dispensing error
  - Pt preference to miss select pills
- **US Medicaid data set has reported better adherence**
- **Patients prefer the simplicity**

### Limitations

- **Friction between costs for medications vs. generic components**
- **Cannot dose adjust ARV components**
  - e.g. pts with renal dysfunction
- **No PI inhibitor based regimen available yet in the UK**
  - PI has highest barrier to resistance of all initial regimens
- **No randomized study of any STR vs. multi-tablet regimen to assess actual benefits**
- **Patients who need three or more pills a day may feel less prepared to take these regimes**

---

Juday T, et al. AIDS Care 2011;23(9):1154-62

Cohen C, et al. ICAAC 2012; San Francisco, CA. #H-211
Horizon Scanning

New compounds:
TAF, GSK744 (CAB)

Co-formulations:
TRII; TAF/E/C/F; ATZ/c; DRV/c

Induction Maintenance
NRTI sparing:
Latte; injectables
We need more studies enrolling...

- CD4 < 250
- VL > 100K
- Sick people

5164 like studies
Waves: TAF QUAD
RAL/DRV/r NEAT 001
ACTG 5257
ARIA: DTG
GS-292-102: TAF vs. TDF as E/C/F/TAF STR component

Phase II, Randomized, double-blind, 48-week study

ART-naive adults
HIV-1 RNA ≥5000 c/mL
CD4 >50 cells/mm³
N=170 (2:1 randomization)

Stratification by HIV RNA >100,000

EVG/COBI/FTC/TAF (E/C/F/TAF)
plus Placebo

EVG/COBI/FTC/TDF
plus Placebo

Primary objective
- To evaluate the efficacy of the E/C/F/TAF single-tablet regimen vs. EVG/COBI/FTC/TDF
  - Primary endpoint: HIV-1 RNA <50 c/mL at Week 24

TAF Phase II: GS-292-102

Week 24 Results – Efficacy and GFR

Virological suppression at 24 weeks

- No renal AEs or discontinuation occurred
- No cases of proximal renal tubulopathy seen

Median Estimated GFR Change from Baseline (Cockcroft-Gault)

Adapted from: Zolopa A, et al. CROI 2013; Atlanta, GA. Oral #99LB
ATV/COBI + TDF/FTC vs ATV/RTV + TDF/FTC Wk 48: non-inferior

- Randomized, double-blind, phase III trial in ART-naive patients
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48


- Coformulation of ATV and COBI being considered for approval by FDA

*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm
†Discontinued for AE, death, or missing data.
Ongoing Studies of COBI-Boosted DRV Plus 2 NRTIs

- Phase IIIb study in tx-naive tx-exp’d pts with no DRV RAMs\[^1\]
  - Primary endpoint: grade 3 or grade 4 AEs by Wk 24
  - Secondary endpoints: HIV-1 RNA at Wk 24 and Wk 48

- Randomized, double-blind phase II trial\[^2\]
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24

Pts with HIV-1 RNA $\geq$ 500; naive or on stable ART for 12 wks and sensitive to 2 NRTIs with no DRV RAMS (N = 300)

\[\text{DRV + COBI + 2 NRTIs}\]

\[\text{Wk 24} \quad \text{Wk 48}\]

ART-naive pts, HIV-1 RNA $\geq$ 5000 c/mL, eGFR $\geq$ 70 mL/min (N = 150)

- DRV/COBI/TAF/FTC QD (n = 75)
- DRV/COBI + TDF/FTC (n = 75)

Coformulation of DRV and COBI being considered for approval by FDA

LATTE: GSK1265744 ART for Naive Pts: Results of 24-Wk Induction

- GSK1265744 (744), DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48

Stratified by HIV-1 RNA (≤ vs > 100,000 c/mL) and NRTI

**Induction Phase**

<table>
<thead>
<tr>
<th>ART-naive pts, HIV-1 RNA &gt; 1000 c/mL (N = 243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>744 10 mg QD + 2 NRTIs† (n = 60)</td>
</tr>
<tr>
<td>744 30 mg QD + 2 NRTIs† (n = 60)</td>
</tr>
<tr>
<td>744 60 mg QD + 2 NRTIs† (n = 61)</td>
</tr>
<tr>
<td>EFV 600 mg QD + 2 NRTIs QD (n = 62)</td>
</tr>
</tbody>
</table>

**Maintenance Phase**

| 744 10 mg QD + RPV 25 mg QD                     |
| 744 30 mg QD + RPV 25 mg QD                     |
| 744 60 mg QD + RPV 25 mg QD                     |

*Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
†TDF/FTC or ABC/3TC.

LATTE: GSK1265744 ART for Naive Pts: Results of 24-Wk Induction
Virologic Success During Induction and Maintenance Phases

- 2 pts with PDVF during maintenance; both with INSTI mutations at BL

LATTE-2: Study Design – Induction

265 subjects enrolled
HIV RNA ≥ 1000
CD4 ≥ 200
ART naïve

Week - 20
Week - 16
Week - 12
Week - 8
Week - 4
Day 1

GSK744 30 mg + ABC/3TC
Orally Once Daily

Add RPV 25 mg once daily

Randomization is 2:2:1 and stratified by HIV-1 RNA prior to Week (-8) (<50 c/mL, yes or no)

IM Q4W Regimen
IM Q8W Regimen
Cont Oral Regimen

IM Qualification Visit
For Maintenance and Addition of RPV 25 mg for All Subjects

Day 1 – Start of Maintenance and Randomization Visit

Week -4 Qualification Visit
LATTE-2: Study Design – Maintenance and Extension

**Maintenance Period**
- **GSK744 LA 400 mg IM + TMC278 LA 600 mg IM Every 4 Weeks (Q4W)**
  - Continue From Induction
  - Loading Doses at Day 1 and Week 4
- **GSK744 LA 600 mg IM + TMC278 LA 900 mg IM Every 8 Weeks (Q8W)**
  - Continue on or Switch to either Q4W or Q8W

**Extension Period**
- **Add RPV 25 mg**

**Key Study Events**
- **Day 1 Randomization**
- **Week 32 Primary Analysis**
- **Week 48 Analysis**
- **Dosing Regimen Selection**
- **Dosing Regimen Confirmation**

**Weeks**
- W96
- W102*
- W104

*Subject who WD after at least 1 IM dose enter Long Term Follow Up Period
*If eligible
Generics & new drugs/formulations: An evolving competitive landscape

New drugs

Dolutegravir
GSK744
Cobicistat
TAF

EU patent expiration (approx.)

www.clinicaltrials.gov and:
Universal Testing for HIV, Hepatitis B and Hepatitis C

13th -20th October 2014

9 Emergency Department sites across England

Barts Health NHS Trust

Public Health England

The Hepatitis Trust
Thank you!
Back-up slides
**EVG/COBI/TDF/FTC Resistance Through Week 144**

- EVG/COBI vs EFV [1-3]

<table>
<thead>
<tr>
<th>Wk</th>
<th>EVG/COBI (n = 348)</th>
<th>EFV (n = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>96</td>
<td>+2</td>
<td>+2</td>
</tr>
<tr>
<td>144</td>
<td>+0</td>
<td>+4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wk</th>
<th>EVG/COBI (n = 353)</th>
<th>ATV/RTV (n = 355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>96</td>
<td>+1</td>
<td>+0</td>
</tr>
<tr>
<td>144</td>
<td>+2</td>
<td>+2</td>
</tr>
</tbody>
</table>

- EVG/COBI vs ATV/ [4-6]

<table>
<thead>
<tr>
<th>Wk</th>
<th>EVG/COBI (n = 353)</th>
<th>ATV/RTV (n = 355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>96</td>
<td>+1</td>
<td>+0</td>
</tr>
<tr>
<td>144</td>
<td>+2</td>
<td>+2</td>
</tr>
</tbody>
</table>

SPRING-2 and FLAMINGO: Virologic response by NRTI backbone at Week 48

1. Adapted from Raffi F et al. Lancet 2013;381:735–43

2. Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
DAD Results 2014: Use of ABC in cohort over time

Presentation of D:A:D ABC findings

% of those with given CVD risk receiving ABC

Total cohort

CA Sabin et al DAD study CROI Boston 2014
## Association between 10-year CVD risk and ABC initiation

<table>
<thead>
<tr>
<th>10-year CVD risk</th>
<th>ABC initiations/ Total ART initiations</th>
<th>% (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-March 2008</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/unknown</td>
<td>1251/9213</td>
<td>13.6 (12.8, 14.3)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate/high</td>
<td>111/648</td>
<td>17.1 (13.9, 20.3)</td>
<td>1.14 (0.90, 1.44)</td>
</tr>
<tr>
<td><strong>Post-March 2008</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/unknown</td>
<td>326/4282</td>
<td>7.6 (6.8, 8.4)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate/high</td>
<td>33/622</td>
<td>5.3 (3.5, 7.1)</td>
<td>0.74 (0.48, 1.13)</td>
</tr>
</tbody>
</table>

Interaction P-value 0.007
Association between 10-year CVD risk and ABC discontinuation

<table>
<thead>
<tr>
<th>10-year CVD risk</th>
<th>Discounts/ PYRS</th>
<th>Rate (95% CI) /100 PYRS</th>
<th>aRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suppressed/low viral load</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-March 2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/unknown</td>
<td>2045/16506</td>
<td>12.4 (11.9, 12.9)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate/high</td>
<td>562/5465</td>
<td>10.3 (9.4, 11.1)</td>
<td>1.04 (0.93, 1.16)</td>
</tr>
<tr>
<td>Post-March 2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/unknown</td>
<td>1403/13950</td>
<td>10.1 (9.5, 10.6)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate/high</td>
<td>880/6560</td>
<td>13.4 (12.5, 14.3)</td>
<td>1.49 (1.34, 1.65)</td>
</tr>
</tbody>
</table>

Interaction *P*-value 0.0001
Association between 10-year CVD risk and ABC discontinuation

<table>
<thead>
<tr>
<th>10-year CVD risk</th>
<th>Discounts/ PYRS</th>
<th>Rate (95% CI) /100 PYRS</th>
<th>aRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-suppressed viral load</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-March 2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/unknown</td>
<td>2966/7766</td>
<td>38.2 (36.8, 39.6)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate/high</td>
<td>662/2041</td>
<td>32.4 (29.9, 34.9)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>Post-March 2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/unknown</td>
<td>622/2297</td>
<td>27.1 (25.0, 29.2)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate/high</td>
<td>236/921</td>
<td>25.6 (22.4, 28.9)</td>
<td>1.23 (1.02, 1.48)</td>
</tr>
<tr>
<td><strong>Interaction P-value</strong></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
</tbody>
</table>
Association between current ABC use and MI risk

• 941 MI events, rate 0.26 [95% CI 0.24-0.27] /100 PYRS

• Current ABC use associated with a 98% increase in MI rate (aRR 1.98 [1.72-2.29])
Association between current ABC use and MI risk

• 941 MI events, rate 0.26 [95% CI 0.24-0.27] /100 PYRS

• Current ABC use associated with a 98% increase in MI rate (aRR 1.98 [1.72-2.29])

<table>
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<tr>
<th></th>
<th>Pre-March 2008</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>672</td>
<td>269</td>
</tr>
<tr>
<td>PYRS</td>
<td>210,250</td>
<td>157,309</td>
</tr>
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<td>Rate (95% CI)</td>
<td>0.32 (0.30, 0.34)</td>
<td>0.17 (0.15, 0.19)</td>
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Association between current ABC use and MI risk

- 941 MI events, rate 0.26 [95% CI 0.24-0.27] /100 PYRS
- Current ABC use was associated with a 98% increase in MI rate (aRR 1.98 [1.72-2.29])

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<td>Rate (95% CI)</td>
<td>0.32 (0.30, 0.34)</td>
<td>0.17 (0.15, 0.19)</td>
</tr>
<tr>
<td>RR (current ABC vs. no ABC)</td>
<td>1.97</td>
<td>1.97</td>
</tr>
<tr>
<td>95% CI</td>
<td>(1.68, 2.33)</td>
<td>(1.43, 2.72)</td>
</tr>
<tr>
<td>P-value for interaction</td>
<td></td>
<td>0.74</td>
</tr>
</tbody>
</table>
Association between current ABC use and MI risk

Overall          Pre-March 2008          Post-March 2008
Conclusions

• Clear that there has been some channelling of ABC away from those at higher CVD risk since 2008

• Despite this, we continue to see a strong association between current ABC use and MI risk

• Whilst confounding can never be ruled out in any cohort study, any channelling bias would now be expected to be much weaker (or even to act in the opposite direction)

• Thus, our findings continue to argue against channelling bias as an explanation for our findings
NRTI-free regimes:

- **MODERN Study Stopped: An NRTI-Sparing, Two-Drug Initial Regimen Disappoints Again**
- And for the record, here’s a list of NRTI-sparing studies that gave “meh” results at best:
  - **ACTG 5142 — LPV/r + EFV vs NRTIs + EFV vs NRTIs vs LPV/r.**
    LPV/r + EFV had high rates of hyperlipidemia; regimen was also cumbersome with lots of GI side effects.
  - **SPARTAN — ATV + RAL vs ATV/r + TDF/FTC.**
    More treatment failure, more jaundice in the ATV + RAL arm.
  - **PROGRESS — LPV/r + RAL vs. LPV/r + TDF/FTC.**
    Comparable success rates, but baseline HIV RNA low in the study population; 3 pill, twice-daily regimen.
  - **ACTG 5262 — Single-arm study of DRV/r + RAL.**
    Unexpectedly high rates of virologic failure (with resistance), especially among those with HIV RNA > 100k at baseline.
  - **A4001078 — ATV/r + MVC vs ATV/r + TDF/FTC**
    Only 75% virologic suppression rate in ATV/r + MVC arm, with more hyperbilirubinemia than the control group; study not fully powered.
  - **RADAR — DRV/r + RAL vs. DRV/r + TDF/FTC.**
    63% suppression rate in the RAL arm, vs 84% for TDF/FTC; study not fully powered.
- Regardless, HIV clinicians and researchers eagerly await the result of two completed but not yet presented clinical trials — the fully-powered NEAT study comparing RAL to TDF/FTC (both with DRV/r), and the GARDEL study, comparing 3TC to NRTI/3TC (both with LPV/r).

### CVS debate 2014

#### Study or Subgroup

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC</th>
<th>ABC/3TC</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td><strong>1.2.1 48 weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post 2010 (ASSERT)</td>
<td>2</td>
<td>193</td>
<td>6</td>
<td>192</td>
</tr>
<tr>
<td>Sax 2011 (ACTG5202)</td>
<td>88</td>
<td>929</td>
<td>131</td>
<td>928</td>
</tr>
<tr>
<td>Smith 2009 (HEAT)</td>
<td>48</td>
<td>345</td>
<td>49</td>
<td>343</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1467</td>
<td>1463</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>138</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 1.2.2 96 weeks

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC</th>
<th>ABC/3TC</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Daar 2011 (ACTG5202)</td>
<td>114</td>
<td>925</td>
<td>155</td>
<td>923</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>925</td>
<td>923</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>114</td>
<td>155</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from BHIVA APPENDIX 3 Grade tables; www.bhiva.org; accessed November 2012
## Systematic reviews/meta-analyses

<table>
<thead>
<tr>
<th>Study name</th>
<th>n</th>
<th>Increased risk of CV Events and abacavir?</th>
<th>Results (study methodologies and primary endpoints varied)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 5001/ALLRT</td>
<td>3,207</td>
<td>No</td>
<td>Retrospective review of five ACTG trials identified a total of 36 MIs and 56 serious CV events. There was no association between recent abacavir use and an increased risk of CV events. Adj HR = 1.0 CI 95% 0.4 - 2.9, p = 0.98.</td>
</tr>
<tr>
<td>GSK analysis</td>
<td>14,174</td>
<td>No</td>
<td>Retrospective review of 52 clinical trials identified 23 coronary artery disorders in adults receiving abacavir compared with 20 in those not receiving abacavir; there were 11 MIs in those who received abacavir compared with 7 in those who did not. There was no association between abacavir use and an increased risk of CV events RR 0.81 CI 95% 0.38 - 1.75.</td>
</tr>
<tr>
<td>Cruciani meta-analysis</td>
<td>9,233</td>
<td>No</td>
<td>No increased risk for MI in abacavir-containing cART (risk ratio [RR] 0.73 [95%CI 0.39–1.35]) when compared to non-abacavir-containing cART.</td>
</tr>
<tr>
<td>FDA meta-analysis</td>
<td>9,868</td>
<td>No</td>
<td>Retrospective review of 26 studies identified MI in 24/5,028 patients receiving abacavir compared with 22/4,840 receiving non-abacavir-containing therapy. There was no association between recent abacavir use and an increased risk of CV events. No significant difference in risk of MI detected between the 2 groups (difference 0.008%, 95% CI -0.26, 0.27)</td>
</tr>
</tbody>
</table>

### Randomised Controlled Trial Data

<table>
<thead>
<tr>
<th>Study name</th>
<th>n</th>
<th>Increased risk of CV Events and abacavir?</th>
<th>Results (study methodologies and primary endpoints varied)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEAL</td>
<td>357</td>
<td>Yes</td>
<td>Randomised 96 week trial comparing viral suppression with Kivexa and TDF/FTC reported nine serious CV events, one in the TDF/FTC arm and eight in the Kivexa arm. HR (TDF/ABC) 0.13 CI 95% 0.02 - 0.98, p = 0.046.</td>
</tr>
<tr>
<td>HEAT</td>
<td>688</td>
<td>No</td>
<td>Randomised 96 week trial comparing markers of inflammation and endothelial activation after initiation of Kivexa and TDF/FTC reported six CV-related events, four in the TDF/FTC arm and two in the Kivexa arm. Analysis unavailable</td>
</tr>
<tr>
<td>ARIES</td>
<td>515</td>
<td>No</td>
<td>Phase IIIb, randomised open-label non-inferiority study in naive patients comparing the efficacy of Kivexa and atazanavir with or without ritonavir.</td>
</tr>
<tr>
<td>ASSERT</td>
<td>380</td>
<td>No</td>
<td>Open-label randomised controlled trial comparing the eGFR in patients receiving Truvada and Kivexa.</td>
</tr>
<tr>
<td>BiCombo</td>
<td>80</td>
<td>No</td>
<td>Retrospective sub-study of BICOMBO RCT, using stored plasma. ABC/3TC did not lead to significant changes in markers of inflammation, endothelial dysfunction, insulin resistance or hypercoagulability vs TDF/FTC.</td>
</tr>
<tr>
<td>ACTG5202</td>
<td>1,857</td>
<td>No</td>
<td>Rate of Vascular Events (coronary artery disease, infarct, ischemia, angina, cerebrovascular accident, transient ischemic attack or peripheral vascular disease)/1000 Patient-Years was 1.4 and 2.5 in the ABC/3TC and TDF/FTC arms, respectively</td>
</tr>
</tbody>
</table>

The D:A:D study initially suggested a potential association between recent ABC use and an increased risk of MI. Studies such as the VA, FHDH and Partners (John Hopkins) which controlled for additional risk factors such as chronic kidney disease and illicit drug use, did not find the same association.

<table>
<thead>
<tr>
<th>Cohort/study</th>
<th>Design</th>
<th>MI Event ascertainment</th>
<th>Subjects in cohort/study, n</th>
<th>Events associated with ABC, n</th>
<th>Association with ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>D:A:D</td>
<td>Prospective observational cohort</td>
<td>Prospective, pre-defined MI</td>
<td>33,347</td>
<td>192</td>
<td>Yes</td>
</tr>
<tr>
<td>SMART</td>
<td>RCT observational</td>
<td>Prospective, pre-defined MI</td>
<td>2,752</td>
<td>19</td>
<td>Yes</td>
</tr>
<tr>
<td>US VA clinical case registry</td>
<td>Retrospective observational cohort</td>
<td>Retrospective, MI identified via ICD-9</td>
<td>19,424</td>
<td>23</td>
<td>No*</td>
</tr>
<tr>
<td>Quebec Public Health Insurance Database(RAMQ)</td>
<td>Case control in observational cohort</td>
<td>Retrospective, MI identified via ICD-9</td>
<td>N/A</td>
<td>45</td>
<td>Yes</td>
</tr>
<tr>
<td>Danish HIV cohort study</td>
<td>Prospective observational cohort</td>
<td>Prospective, MI hospitalisation identified via ICD-8/10</td>
<td>2,952</td>
<td>36</td>
<td>Yes</td>
</tr>
<tr>
<td>FHDH</td>
<td>Case control in observational study</td>
<td>Prospectively reported MI, retrospectively validated via ICD-10</td>
<td>N/A</td>
<td>127</td>
<td>No**</td>
</tr>
<tr>
<td>&quot;Partners HealthCare System&quot; clinical care data registry</td>
<td>Retrospective observational registry-based cohort</td>
<td>Retrospective, MI identified via ICD-9- CM codes</td>
<td>6,517</td>
<td>–†</td>
<td>No‡</td>
</tr>
</tbody>
</table>

* After adjustment for traditional CV risk factors and renal dysfunction
** Sensitivity/supportive analysis censoring cocaine or IV drug use
¶ After adjustment for renal dysfunction and CD4 cell count
† Information not available

* Recent analysis of VA cohort demonstrated an association between ABC and increased risk of atherosclerotic events

Largest observational cohort demonstrating an association between ABC and MI risk: D:A:D

In an update from the D:A:D Study group, ATV was not associated with an increased risk of MI or stroke.

*Not shown (low number of patients currently on ddC)

1. Adapted from Lundgren J, et al. CROI 2009, abstract 44
2. d’Arminio Monforte A et al. CROI 2012, poster 823
Is There Continued Evidence for an Association Between Abacavir and Myocardial Infarction Risk?

C.A. Sabin,¹ P. Reiss,² L. Ryom,³ S. de Wit,⁴ O. Kirk,³ R. Weber,⁵ C. Pradier,⁶ F. Dabis,⁷ A.N. Phillips,¹ J.D. Lundgren,³ for the D:A:D study group

Adapted from Sabin et al. CROI 2014; Boston, MA. Poster 747LB.
FDA meta-analysis of RCTs did not show an association between ABC and MI

BHIVA guidelines
Cardiovascular Disease

• No RCT has been powered to assess the CVD risk associated with the use of individual ARVs and a history of CVD may be an exclusion criteria.
• Avoid abacavir (2C), fosamprenavir/ritonavir (2C) and lopinavir/ritonavir( 2C) in patients with a high CVD risk, if acceptable alternative antiretroviral drugs are available
• Modifiable risk factors should be addressed in all patients with high CVD risk
• A meta-analysis of all RCTs where ABC was assigned randomly found no association with MI, but the event rate in the population was low; the extent to which these findings can be extrapolated to a population with high CVD risk is unknown
Boosted PIs: efficacy across the board

KLEAN\(^1\) (ITT-E, TLOVR)
Noninferiority

GEMINI\(^2\) (ITT, M=NR)
Noninferiority
p<0.0119

ARTEMIS\(^3\) (ITT, TLOVR)
Noninferiority

M05-730\(^4\) (ITT, NC=F)
Noninferiority

CASTLE\(^5\) (ITT, NC=F)
Noninferiority

Data in figures are from different studies and cannot be compared directly
ITT-E, intent-to-treat exposed
LATTE: GSK1265744 ART for Naive Pts: Results of 24-Wk Induction

- GSK1265744 (744), DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48

**Induction Phase**

<table>
<thead>
<tr>
<th>ART-naive pts, HIV-1 RNA &gt; 1000 c/mL (N = 243)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wk 24</strong></td>
</tr>
<tr>
<td>744 10 mg QD + 2 NRTIs† (n = 60)</td>
</tr>
<tr>
<td>744 30 mg QD + 2 NRTIs† (n = 60)</td>
</tr>
<tr>
<td>744 60 mg QD + 2 NRTIs† (n = 61)</td>
</tr>
<tr>
<td>EFV 600 mg QD + 2 NRTIs QD (n = 62)</td>
</tr>
</tbody>
</table>

**Maintenance Phase**

- 744 10 mg QD + RPV 25 mg QD
- 744 30 mg QD + RPV 25 mg QD
- 744 60 mg QD + RPV 25 mg QD

Stratified by HIV-1 RNA (≤ vs > 100,000 c/mL) and NRTI

*Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
†TDF/FTC or ABC/3TC.

LATTE-2: Study Design – Induction

265 subjects enrolled
HIV RNA ≥ 1000
CD4 ≥ 200
ART naïve

Week - 20
Week - 16
Week - 12
Week - 8
Week - 4
Day 1

Induction Period

GSK744 30 mg + ABC/3TC
Orally Once Daily

Add RPV 25 mg once daily

Randomization is 2:2:1
and stratified by HIV-1 RNA prior to Week (-8)
(<50 c/mL, yes or no)

IM Q4W Regimen
IM Q8W Regimen
Cont Oral Regimen

Week -4 Qualification Visit
For Maintenance and Addition of RPV 25 mg for All Subjects

Day 1 – Start of Maintenance and Randomization Visit
New benchmark comparator: Durability vs EFV?

- **STARTMRK: RAL vs EFV in naïve patients – 5-year outcomes**

  
  Proportion of patients with HIV RNA <50 copies/mL (ITT, NC=F)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Proportion (%) RAL</th>
<th>Proportion (%) EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>24</td>
<td>81</td>
<td>79</td>
</tr>
<tr>
<td>48</td>
<td>81</td>
<td>79</td>
</tr>
<tr>
<td>72</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>96</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>120</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>144</td>
<td>76</td>
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<td>168</td>
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<td>192</td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td>216</td>
<td>67</td>
<td>61</td>
</tr>
<tr>
<td>240</td>
<td>61</td>
<td>61</td>
</tr>
</tbody>
</table>

  Difference at Week 240 (95% CI): 9.5 (1.7–17.3)*
  
  p value (non-inferiority): <0.001

- Number of contributing patients
  - RAL 400 mg BID: 281 278 279 280 281 281 277 280 281 281 277 279
  - EFV 600 mg at night: 282 282 282 281 282 282 282 282 282 279

  - Week 240 CD4 count (cells/mm³) change: RAL +374 vs EFV +312
  - Difference (95% CI): 62 (22–102)

Potential clinical benefits for smoking cessation in HIV patients

- >27,500 HIV-positive patients in the D:A:D study
- Rates of CVD before and after smoking cessation

Adapted from Petoumenos K, et al. 17th CROI; 2010 Feb 16–19; San Francisco, USA. Oral abstract paper 124.
Benchmark for efficacy? Cross-study comparison of treatment-naïve trials

HIV RNA <50 copies/mL at Week 48

*GS-103 QUAD (n=353)12
*GS-102 QUAD (n=348)11
*GS-103 ATV/r (n=355)12
STARTMRK RAL (n=281)8
*GS-102 Atripla (n=352)11
ARTEMIS DRV+RTV (n=343)7
ECHO/THRIVE RPV (n=578)10
ECHO/THRIVE EFV (n=561)10
STARTMRK EFV (n=282)8
GS 934 EFV (n=255)4
ARTEMIS LPV/r (n=346)7
CASTLE ATV+RTV (n=438)6
ABT 730 LPV/r qd (n=333)5
CASTLE LPV/r (n=440)6
ABT 730 LPV/r bid (n=331)5
GS-903 EFV (n=299)9
ASSERT EFV (n=193)1
GS 934 EFV (n=254)4
MERIT ES MVC (n=360)3
MERIT ES EFV (n=361)3
HEAT LPV/r (n=343)2
HEAT LPV/r (n=345)2
ASSERT EFV (n=192)1

This slide depicts data from multiple studies published from 2004 to 2012 and cannot be compared directly.
*Studies involve investigational drugs not approved for use in the UK.

Primary endpoint: Sensitivity/secondary analysis

**Sensitivity analysis**: Time to virological failure as measured by virological components in primary endpoint

**Secondary analysis**: Time to primary endpoint with the addition of discontinuation of any component of randomised regimen for any reason as an endpoint

![Graph showing time to virological failure and estimated proportions for primary and secondary endpoints.](image)

**Estimated proportion reaching endpoint at W96**
- RAL: 15.4% vs TDF/FTC: 11.8%
- Adjusted difference: 3.6% (95% CI: -0.8, 8.1%)

**Estimated proportion reaching endpoint at W96**
- RAL: 22.8% vs TDF/FTC: 19.5%
- Adjusted difference: 3.3% (95% CI: -1.9, 8.4%)

Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014
Virologic Suppression at Wk 48 by Baseline HIV-1 RNA

Similar Efficacy of INSTIs (RAL or DTG) + ABC/3TC or TDF/FTC, Even for High BL VL

- In SPRING-2, similar efficacy with ABC/3TC or TDF/FTC + RAL or DTG, including with high BL HIV-1 RNA*

*Pooled data from both INSTIs.

Resistance Summary

• DTG vs RAL\textsuperscript{[1,2]}
  • 0 pts with resistance in DTG arm
  • 1 pt with INSTI-R and 4 pts with NRTI-R with RAL at Wk 48; no additional resistance by Wk 96

• DTG vs EFV\textsuperscript{[3]}
  • 0 pts with resistance in DTG arm
  • 1 pt with NRTI and 4 with NNRTI resistance in EFV arm

• DTG vs DRV/RTV\textsuperscript{[4]}
  • 0 pts with resistance in DTG arm

EVG/COBI/TDF/FTC Noninferior to EFV/TDF/FTC Through Wk 144

- EVG/COBI arm noninferior to EFV arm at Wk 48 primary endpoint\(^1\) and through Wk 144\(^2,3\)
  - Results consistent across subgroups: BL HIV-1 RNA, CD4+ cell count, age, sex, race
  - Treatment-related study d/c: 6% in EVG/COBI arm vs 7% in EFV arm at Wk 144
- VF: 7% in EVG/COBI arm and 10% in EFV arm at Wk 144
- Similar CD4+ cell count increase at Wk 144:
  - +321 cells/mm\(^3\) (EVG/COBI) vs +300 cells/mm\(^3\) (EFV)

EVG/COBI/TDF/FTC Noninferior to ATV/RTV + TDF/FTC Through Wk 144

• EVG/COBI arm noninferior to ATV/RTV arm at Wk 48 primary endpoint[1] and through Wk 144[2,3]
  – Results consistent across subgroups: BL HIV-1 RNA, CD4+ count, adherence, age, sex, race
• Treatment-related study d/c: 6% in EVG/COBI arm vs 9% in ATV/RTV arm at Wk 144
• VF: 8% in EVG/COBI arm vs 7% in ATV/RTV arm at Wk 144
• Similar CD4+ cell count increase at Wk 144: +280 cells/mm³ (EVG/COBI) vs +293 cells/mm³ (ATV/RTV)

ARTEMIS: DRV/RTV vs LPV/RTV in Naive Pts Through 96 Weeks

- DRV/RTV noninferior to LPV/RTV at Wk 48; superior at Wk 96
  - Efficacy results better in DRV/RTV arm among those with BL VL > 100K ($P = .023$) c/mL and CD4+ < 200 ($P = .009$)
- VF in 1% of DRV/RTV arm vs 2% of LPV/RTV by Wk 96
  - No major PI mutations in either arm at Wk 96; NRTI mutations in 2 pts in DRV/RTV arm vs 5 in LPV/RTV arm
- Treatment-related study d/c: 4% in DRV/RTV arm vs 9% in LPV/RTV arm at Wk 96
- CD4+ count increase at Wk 96: +171 (DRV/RTV) vs +188 (LPV/RTV)
- Significantly smaller mean change in TC and TG at Wk 48 with DRV/RTV

ACTG 5257: Mean Change From BL in Fasting Lipids

PI Resistance Rare at VF in First-line Studies of Boosted PIs

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PI</th>
<th>Wk</th>
<th>Genotypes</th>
<th>Major PI Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASTLE[1]</td>
<td>440</td>
<td>ATV/RTV</td>
<td>96</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>443</td>
<td>LPV/RTV</td>
<td>96</td>
<td>26</td>
<td>0</td>
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<tr>
<td>ACTG 5202[2]</td>
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<td>ATV/RTV</td>
<td>96</td>
<td>83</td>
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</tr>
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<td>Study 103[3]</td>
<td>355</td>
<td>ATV/RTV</td>
<td>144</td>
<td>NR</td>
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<tr>
<td>ARTEMIS[4]</td>
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<td>DRV/RTV</td>
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<td>31</td>
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<td>346</td>
<td>LPV/RTV</td>
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<td>46</td>
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</tr>
<tr>
<td>FLAMINGO[5]</td>
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<td>DRV/RTV</td>
<td>48</td>
<td>NR</td>
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<td>ACTG 5257[6]</td>
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<td>ATV/RTV</td>
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<td>75</td>
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<tr>
<td></td>
<td>601</td>
<td>DRV/RTV</td>
<td>96</td>
<td>99</td>
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</table>

- Among 4303 pts in these trials, only 2 pts developed major PI mutations at initial VF

A5257 Study Design: 96 week F/U*

HIV-infected ARV naïve patients, ≥18 yr, VL ≥ 1000 c/mL (N=1809)

Randomized 1:1:1 to Open Label Therapy
Stratified by HIV-1 VL (≥ vs < 100,000 c/mL)

- ATV 300 mg QD + RTV 100mg QD + FTC/TDF 200/300 mg QD (N=605)
  - ATV/r 605 (5 never started ART)
  - 556 (92%) Completed 96 Weeks

- RAL 400 mg BID + FTC/TDF 200/300 mg QD (N=603)
  - RAL 603 (4 never started ART)
  - 560 (93%) Completed 96 Weeks

- DRV 800 mg QD + RTV 100 mg QD + FTC/TDF 200/300 mg QD (N=601)
  - DRV/r 601 (4 never started ART)
  - 546 (91%) Completed 96 Weeks

*With the exception of RTV, all ART drugs were provided by the study
Adapted from Landowitz et al*
Study Design

• Hypothesis
  • FTC/TDF with ATV/r, RAL, or DRV/r will be equivalent in terms of virologic efficacy and tolerability over 96 weeks

• Primary Endpoints*
  • Time to HIV-1 RNA >1000 c/mL wk 16 to before wk 24, or >200 c/mL at or after wk 24 (VF)
  • Time to discontinuation of randomized component for toxicity (TF)

• Pre-planned Composite Endpoint
  • The earlier occurrence of either VF or TF in a given participant

* Time measured from date of study entry/randomization
Cumulative Incidence of Virologic Failure

Difference in 96 wk cumulative incidence (97.5% CI)

- **ATV/r vs RAL**: 3.4% (-0.7%, 7.4%)
- **DRV/r vs RAL**: 5.6% (1.3%, 9.9%)
- **ATV/r vs DRV/r**: -2.2% (-6.7%, 2.3%)
Cumulative Incidence of Tolerability Failure

Difference in 96 wk cumulative incidence (97.5% CI)

- **ATV/r vs RAL**: 13% (9.4%, 16%)
- **DRV/r vs RAL**: 3.6% (1.4%, 5.8%)
- **ATV/r vs DRV/r**: 9.2% (5.5%, 13%)
Cumulative Incidence of Virologic or Tolerability Failure

Difference in 96 wk cumulative incidence (97.5% CI)

- ATV/r vs RAL: 15% (10%, 20%)
- DRV/r vs RAL: 7.5% (3.2%, 12%)
- ATV/r vs DRV/r: 7.5% (2.3%, 13%)
Proportion VL ≤50 copies/mL

ITT, regardless of ART change

<table>
<thead>
<tr>
<th>Study week</th>
<th>ATV/r</th>
<th>RAL</th>
<th>DRV/r</th>
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<tr>
<td>24</td>
<td>83%</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>48</td>
<td>90%</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>96</td>
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<td>89%</td>
</tr>
<tr>
<td>144</td>
<td>90%</td>
<td>94%</td>
<td>90%</td>
</tr>
</tbody>
</table>

ITT, off-ART=failure (SNAPSHOT)

<table>
<thead>
<tr>
<th>Study week</th>
<th>ATV/r</th>
<th>RAL</th>
<th>DRV/r</th>
</tr>
</thead>
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<tr>
<td>24</td>
<td>70%</td>
<td>84%</td>
<td>77%</td>
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<td>73%</td>
</tr>
<tr>
<td>144</td>
<td>62%</td>
<td>76%</td>
<td>71%</td>
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</tbody>
</table>
DRV/COBI FDC Bioequivalent to DRV + RTV and to DRV + COBI

- PK analyses in healthy subjects

** DRV Concentration When Administered as DRV + RTV or as DRV/COBI Coformulation[^1]**

- DRV/RTV 800/100 mg QD as single agents (n = 32)
- DRV/COBI 800/150 mg QD as FDC (n = 33)

** DRV Concentration When Administered as Single Agents or as Coformulation[^2]**

- Single agents; fed (n = 38)
- FDC; fed (n = 40)
- Single agents; fasted (n = 72)
- FDC; fasted (n = 74)

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ACTG 5257: Loss of BMD With First-line Boosted PI vs RAL

• All arms associated with significant loss of BMD through Wk 96 (P < .001)

• At hip and spine, similar loss of BMD in the PI arms
  – Significantly greater loss in the combined PI arms than in the RAL arm

Horizon Scanning

- New compounds: TAF MSD? Gilead
- More co-formulation Single-tablet regimens: TRII; TAF QUAD; ATV/COBI; DRV/COBI; DRV/COBI/TAF/FTC
- Initiation/ maintenance: NRTI-sparing combinations: INSTI+NNRTI or INSTI+NNRTI
- Injectable preps: Rilpivirine containing; gold-based preparations