New Antiretroviral Data
BHIVA Bournemouth 2019

Dr. Mindy Clarke
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Brighton & Sussex University Hospital NHS Trust
Honorary Senior Clinical Lecturer
Brighton & Sussex Medical School
COMPETING INTERESTS OF FINANCIAL VALUE > £1,000: in last 12 months

• Amanda Clarke: has acted in a consultancy capacity for Gilead Sciences and ViiV Healthcare. She has received personal grants for attending conferences from Gilead Sciences.
What we’ll cover

• Naive– triple & dual
• Switch – triple, dual, injectables
• Failure
• Pipeline
• Guideline changes
Meet Bob, Sam, Izzy & Ray

Bob – been declining Rx, wants new ART, no side effects

Sam – on treatment for years, lots of comorbidities wants to know about switching options

Izzy – fed up of pills, wants to know about injectables

Ray – multidrug resistance, detectable viral load, CD4 declining
Meet Bob, Sam, Izzy & Ray

Bob – been declining Rx, wants new ART, no side effects

Sam – on treatment for years, lots of comorbidities wants to know about switching options

Izzy – fed up of pills, wants to know about injectables

Ray – multidrug resistance, detectable viral load, CD4 declining
Doravirine: treatment naïve – week 96 data
once/day, no food requirements

**Drive Ahead n=728**
- Double blind, RCT, phase III
- Doravirine/3TC/TDF vs EFV/FTC/TDF
- No resistance, VL>1,000 copies/mL
- Week 48 primary endpoint: 84% v 81%

**Drive Forward n=768**
- Double blind RCT, phase III
- Doravirine vs DRV/r + 2NRTIs
- No resistance, VL>1,000 copies/mL
- Week 48 primary endpoint: 84% v 80%

Doravirine Week 96 data
FDA snapshot analyses

Drive Ahead (vs EFV/3TC/TDF)

- Treatment difference: 3.8% (95% CI: -2.4% to 10.0%)

Drive Forward (vs DRV/r & 2NRTIs)

- Treatment Difference: 7.1% (95% CI: 0.5% to 13.7%)

Doravirine Week 96 data
FDA snapshot analyses

### Drive Ahead (vs EFV/3TC/TDF)

- **HIV-1 RNA < 50 copies/mL (%)**
  - DOR/3TC/TDF: 77.5
  - EFV/FTC/TDF: 73.6
  - Treatment difference: 3.8% (95% CI: -2.4% to 10.0%)

DOR/3TC/TDF non-inferior

### Drive Forward (vs DRV/r & 2NRTIs)

- **HIV-1 RNA < 50 copies/mL (%)**
  - DOR + 2 NRTIs: 73.1
  - DRV/RTV + 2 NRTIs: 66.0
  - Treatment Difference: 7.1% (95% CI: 0.5% to 13.7%)

Doravirine higher suppression rates

Doravirine: naïve, week 96
Safety/resistance data

**Drive Ahead (vs EFV/3TC/TDF)**
- Resistance: n=6 (1.6%) DOR vs n=13 (3.8%) EFV arm
- NRTI resistance: 1.4% DOR vs 1.6% EFV
- Drug related AEs: 32% DOR vs 65% EFV
- Fewer neuropsychiatric AEs DOR
- LDL-C & non–HDL cholesterol small decreases DOR cf increases in EFV

**Drive Forward (vs DRV/r & 2NRTIs)**
- Resistance: n=2 (0.5%) DOR vs 1 (0.3%) DRV/r arm
- NRTI resistance: DOR only (FTC)
- Drug related AEs similar
- Favorable lipids profile DOR

Doravirine: treatment naïve – week 96 data

DOR/3TC/TDF
Delstrigo™

Doravirine
Pifeltro™
Bictegravir/FTC/TAF: treatment naïve – week 96 data
no food requirements, single tablet regimen

- **GS-1489** n=629
  - Double blind RCT, phase III
  - BIC/FTC/TAF vs DTG/ABC/3TC
  - VL ≥500, HLA B*5701 neg, eGFR ≥50mL/min
  - Primary endpoint week 48 92.4% vs 93%

- **GS-1490** n=645
  - Double blind RCT, phase III
  - BIC/FTC/TAF vs DTG + F/TAF
  - VL ≥500, eGFR ≥30mL/min
  - Primary endpoint week 48 89% vs 93%

Bictegravir/FTC/TAF: week 96 virological outcomes

- **GS-1489** BIC/F/TAF vs DTG/ABC/3TC

- **GS-1490** BIC/F/TAF vs DTG + F/TAF


Bictegravir/FTC/TAF: week 96 virological outcomes

- **GS-1489** BIC/F/TAF vs DTG/ABC/3TC

- **GS-1490** BIC/F/TAF vs DTG + F/TAF


**Bictegravir/FTC/TAF: treatment naïve – week 96**

**safety/resistance**

<table>
<thead>
<tr>
<th>GS-1489</th>
<th>BIC/F/TAF vs DTG/ABC/3TC</th>
</tr>
</thead>
</table>

No treatment emergent resistance in either arm

Significantly more Rx related AEs in DTG arm (28% vs 40%), mainly nausea

BMD similar

Greater increases total & LDL-C in BIC arm

<table>
<thead>
<tr>
<th>GS-1490</th>
<th>BIC/F/TAF vs DTG + F/TAF</th>
</tr>
</thead>
</table>

Significantly more Rx related AEs in DTG arm (20 vs 28%)

No lipid differences

AMBER: DRV/COBI/FTC/TAF vs DRV/COBI + FTC/TDF in Treatment-Naive Adults at Wk 96

- Multicenter, randomized, double-blind, noninferiority phase III trial[1]

![Diagram](image.png)

- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (noninferiority margin: -10%)[2]
  - DRV/COBI/FTC/TAF vs DRV/COBI + FTC/TDF: 91.4% vs 88.4% (difference: 2.7%; 95% CI: -1.6% to 7.1%; P < .0001)

AMBER (DRV/c/F/TAF vs DRV/c + F/TAF)
Efficacy, resistance & safety at wks 96

Efficacy:
- 88% in the DRV/c/F/TAF arm
- 84% in the DRV/c/F/TDF arm

Resistance:
- 1 patient with M184V/I in each arm
- No emergent DRV, primary PI, or TFV RAMs

Safety:
- Less effects on bone, renal markers with DRV/COBI/FTC/TAF
- No significant change eGFR or cases of Fanconi/tubulopathy
- Similar lipid changes across arm

Dual therapy

OR
Dual therapy
Dual therapy
DTG + 3TC vs DTG + TDF/FTC in Treatment-Naive Patients
GEMINI-1 and -2

- Parallel, international, randomized, double-blind phase III noninferiority studies

ART-naive adults with HIV-1 RNA 1000-500,000 copies/mL, no major resistance associated mutation, no HBV infection (N = 1433)

Primary endpoint: HIV-1 RNA < 50 copies/mL at Week 48 by FDA Snapshot analysis

68% White; 15% women; 10% >50yrs
20% VL>100,000 copies/mL; 8-9% CD4 <200 cells/mL

GEMINI-1 and -2: Virologic Response at Wk 48

Virologic Outcomes by FDA Snapshot Analysis

<table>
<thead>
<tr>
<th></th>
<th>ITT-E</th>
<th>PP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Virologic Success</strong></td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td><strong>Virologic Nonresponse</strong></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>No Virologic Data</strong></td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Adjusted Treatment Difference, † % (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>DTG + TDF/FTC</th>
<th>DTG + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT-E</td>
<td>-4.4</td>
<td>1.1</td>
</tr>
<tr>
<td>PP*</td>
<td>-3.9</td>
<td>1.2</td>
</tr>
</tbody>
</table>

GEMINI-1 and -2: Virologic Response at Wk 48

Virologic Outcomes by FDA Snapshot Analysis

- **HIV-1 RNA < 50 copies/mL (%)**
  - **Virologic Success**
    - DTG + 3TC (n = 716): 91.93%
    - DTG + TDF/FTC (n = 717): 93.94%
  - **Virologic Nonresponse**
    - DTG + 3TC (n = 694): 5%
    - DTG + TDF/FTC (n = 693): 5%
  - **No Virologic Data**
    - DTG + 3TC: 5
    - DTG + TDF/FTC: 4

Adjusted Treatment Difference, †% (95% CI)

- **ITT-E**
  - DTG + TDF/FTC: -4.4
  - DTG + 3TC: 1.1

- **PP**
  - DTG + TDF/FTC: -3.9
  - DTG + 3TC: 1.2

### GEMINI-1 and -2: Virologic Response at Wk 48 by Baseline HIV-1 RNA and CD4+ Cell Count

**Virologic Outcomes by FDA Snapshot Analysis**

<table>
<thead>
<tr>
<th>Baseline HIV-1 RNA, c/mL</th>
<th>Baseline CD4+ Cell Count, cells/mm$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100,000</td>
<td>&gt; 100,000</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>≤ 200</td>
</tr>
<tr>
<td>Patients With</td>
<td>(%)</td>
</tr>
<tr>
<td>DTG + 3TC</td>
<td>DTG + TDF/FTC</td>
</tr>
<tr>
<td>n/N</td>
<td></td>
</tr>
<tr>
<td>526/576</td>
<td>91</td>
</tr>
<tr>
<td>531/564</td>
<td>94</td>
</tr>
<tr>
<td>129/140</td>
<td>92</td>
</tr>
<tr>
<td>138/153</td>
<td>90</td>
</tr>
<tr>
<td>605/653</td>
<td>93</td>
</tr>
<tr>
<td>618/662</td>
<td>93</td>
</tr>
<tr>
<td>50/63</td>
<td>79</td>
</tr>
<tr>
<td>51/55</td>
<td>93</td>
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</tbody>
</table>

**Virologic Outcomes by TRDF Analysis**

<table>
<thead>
<tr>
<th>Baseline HIV-1 RNA, c/mL</th>
<th>Baseline CD4+ Cell Count, cells/mm$^3$</th>
<th>Patients Without TRDF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100,000</td>
<td>&gt; 100,000</td>
<td></td>
</tr>
<tr>
<td>&gt; 200</td>
<td>≤ 200</td>
<td></td>
</tr>
<tr>
<td>Patients Without</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>DTG + 3TC</td>
<td>DTG + TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>n/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>566/576</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>553/564</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>138/140</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>149/153</td>
<td>97</td>
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<tr>
<td>642/653</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>647/662</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>62/63</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>55/55</td>
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</tr>
</tbody>
</table>

- TRDF includes confirmed virologic withdrawal, withdrawal for lack of efficacy or treatment-related AEs, and participants meeting protocol-defined stopping criteria

Details of Nonresponse to DTG + 3TC Among 13 Patients With Baseline CD4+ Cell Count ≤ 200 cells/mm³

<table>
<thead>
<tr>
<th>Participant[1]</th>
<th>Wk 48 Snapshot Outcome</th>
<th>Clinical Reason for Study D/c</th>
<th>Last Study VL, c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VL ≥ 50 c/mL</td>
<td>NA, continued in study</td>
<td>≥ 50 (Wk 60)</td>
</tr>
<tr>
<td>2</td>
<td>VL ≥ 50 c/mL</td>
<td>NA, continued in study</td>
<td>&lt; 50 (Wk 60)</td>
</tr>
<tr>
<td>3</td>
<td>VL ≥ 50 c/mL</td>
<td>NA, continued in study</td>
<td>&lt; 50 (Wk 60)</td>
</tr>
<tr>
<td>4</td>
<td>VL ≥ 50 c/mL</td>
<td>Protocol-defined virologic withdrawal</td>
<td>362 (d/c Day 205)</td>
</tr>
<tr>
<td>5</td>
<td>No virologic data</td>
<td>AE, pulmonary TB</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>6</td>
<td>No virologic data</td>
<td>AE, cerebral chagoma</td>
<td>507,564 (d/c ART before study d/c)</td>
</tr>
<tr>
<td>7</td>
<td>No virologic data</td>
<td>Treatment for HCV infection</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>8</td>
<td>No virologic data</td>
<td>Withdraw consent</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>9</td>
<td>VL ≥ 50 c/mL</td>
<td>NA, unplanned change in ART</td>
<td>≥ 50 (Wk 60)</td>
</tr>
<tr>
<td>10</td>
<td>VL ≥ 50 c/mL</td>
<td>Protocol violation, randomized in error</td>
<td>102 (d/c Day 15)</td>
</tr>
<tr>
<td>12</td>
<td>VL ≥ 50 c/mL</td>
<td>Lost to follow-up</td>
<td>64,366 (d/c Day 356)</td>
</tr>
<tr>
<td>13</td>
<td>No virologic data</td>
<td>Lost to follow-up</td>
<td>&lt; 50</td>
</tr>
</tbody>
</table>
### GEMINI-1 and -2: Safety and Resistance at Wk 48

<table>
<thead>
<tr>
<th>Safety Event, n (%)</th>
<th>DTG + 3TC (n = 716)</th>
<th>DTG + TDF/FTC (n = 717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>543 (76)</td>
<td>579 (81)</td>
</tr>
<tr>
<td>AE in ≥ 5% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>71 (10)</td>
<td>75 (10)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>68 (9)</td>
<td>77 (11)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>55 (8)</td>
<td>78 (11)</td>
</tr>
<tr>
<td>Upper RTI</td>
<td>56 (8)</td>
<td>44 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>27 (4)</td>
<td>53 (7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27 (4)</td>
<td>45 (6)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>36 (5)</td>
<td>32 (4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>35 (5)</td>
<td>31 (4)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>126 (18)</td>
<td>169 (24)</td>
</tr>
<tr>
<td>AE leading to withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>15 (2)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>50 (7)</td>
<td>55 (8)</td>
</tr>
</tbody>
</table>

Confirmed VF: dual = 6; triple = 4

No treatment-emergent INSTI or NRTI mutations in patients with VF in either arm

Significant benefit in renal parameters in dual arm

Significant benefit in bone parameters in dual arm

GEMINI-1 and -2: Viral response & Target Not Detected (TND) analyses

Snapshot analysis of % with HIV RNA <50 c/mL ITT

- Similar proportions in dual/triple arms had TND at snapshot analysis

- No difference in TND rates VL ≤100,000c/mL but numerically higher in DTG/3TC in ≥100,000c (and quicker)

Cahn, Lancet 2018, 393,10167;143-155
Underwood. CROI 2019. P490
EACS 9.1 Oct 2018 Naive

**BIC/F/TAF** *(Biktarvy™)*

**DRV/c/F/TAF** *(Symtuza™)*

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**Initial Combination Regimen for ART-naive Adult HIV-positive Persons**

Out of the recommended regimens in persons starting ART, we recommend the use of an INSTI as preferred third agent, tailoring antiretroviral regimens for each individual is essential as other classes of third agents (e.g. boosted PI) might be indicated in the presence of resistance or risk of poor adherence.

A) Recommended regimens (one of the following to be selected)*

1. Only drugs currently licensed for initiation of therapy by the EMA are taken into consideration (in alphabetical order).
2. *Genomic HIV drugs are becoming more available and can lead to large cost savings. They can be used as long as they replace the same drug and do not break previously recommended fixed-dose combinations.*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
<th>Caution</th>
<th>Food requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 NNRTIs + NRTI</td>
<td>TAF/FTC/DRV</td>
<td>TAF/FTC 250/200 mg, 2 tablet qd + RAL 400 mg, 2 tablet bid</td>
<td>Co-administration of artides containing A/ or M not recommended. Co-administration of RAL 1200 mg qd with Ca containing artides or with Ca, Mg, Fe supplements is not recommended. Use RAL 400 mg bid instead. RAL 400 or 800 mg bid with rifampicin.</td>
</tr>
<tr>
<td>2 NNRTIs + NRTI</td>
<td>TAF/FTC/DRV</td>
<td>TAF/FTC 250/200 mg, 2 tablet qd + RAL 400 mg, 2 tablet bid</td>
<td>None</td>
</tr>
</tbody>
</table>

*EACS 9.1	
  Oct	
  2018	
  Naive

**EACS 9.1 Oct 2018 Naive**

### Other combinations

| [DTG\(^{(x)}\) + 3TC]\(^{(ii, xiii)}\) | DTG 50 mg, 1 tablet qd + 3TC 300 mg, 1 tablet qd |

DTG+3TC = alternative

**Box 2. Selected Recommendations for Initial ART Regimens**

**Generally Recommended Initial Regimens (Listed in Alphabetic Order by InSTI Component)**

- Bictegravir/TAF/emtricitabine (evidence rating Alα)\(^b\)
- Dolutegravir/abacavir/lamivudine (evidence rating Alα)\(^c\)
- Dolutegravir plus TAF/emtricitabine (evidence rating Alα)\(^e\)

**Recommended Initial Regimens for Individuals for Whom Generally Recommended Regimens Are Not Available or Not an Option (Listed in Alphabetic Order by First Component)**

- Darunavir/cobicistat plus TAF (or TDF)/emtricitabine (evidence rating Alα)\(^e\)
- Darunavir boosted with ritonavir plus TAF (or TDF)/emtricitabine (evidence rating Alα)\(^e\)
- Efavirenz/TDF/emtricitabine (evidence rating Alα)
- Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine (evidence rating Alα)\(^e\)
- Raltegravir plus TAF (or TDF)/emtricitabine (evidence rating Alα for TDF)\(^e\)
- Rilpivirine/TAF (or TDF)/emtricitabine (if pretreatment HIV RNA level is <100,000 copies/mL and CD4 cell count is >200/µL) (evidence rating Alα)\(^e\)

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**IAS-USA July 2018 NAIVE**

**BIC/F/TAF**
Initial 2-drug regimens are only recommended in the rare situations in which a patient cannot take abacavir, TAF, or TDF (evidence rating B1a).

Dual therapy – only if ABC/TDF/TAF not an option (DRV/r + Ral; DRV/r + 3TC ...await Gemini studies...)

DHHS May 2018 - naive

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC (AI)
- DTG/ABC/3TC<sup>a</sup> (AI)—if HLA-B*5701 negative
- DTG plus tenofovir<sup>b</sup>/FTC<sup>a</sup> (AI for both TAF/FTC and TDF/FTC)
- RAL<sup>c</sup> plus tenofovir<sup>b</sup>/FTC<sup>a</sup> (BI for TDF/FTC, BII for TAF/FTC)

BIC/F/TAF

### Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

**INSTI plus 2 NRTIs:**  
**Note:** For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/tenofovir\(^3\)/FTC (BI for both TAF/FTC and TDF/FTC)
- RAL\(^5\) plus ABC/3TC\(^3\) (CII)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL

**Boosted PI plus 2 NRTIs:** (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) plus tenofovir\(^3\)/FTC\(^3\) (AI)
- (ATV/c or ATV/r) plus tenofovir\(^3\)/FTC\(^3\) (BI)
- (DRV/c or DRV/r) plus ABC/3TC\(^3\) —if HLA-B*5701 negative (BII)

**NNRTI plus 2 NRTIs:**

- DOR/TDF\(^3\)/3TC (BI) or DOR plus TAF\(^3\)/FTC (BII)  
- EFV plus TDF\(^3\)/FTC\(^3\) (BI for EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC, BII for EFV 600 mg plus TAF/FTC)  
- RPV/tenofovir\(^3\)/FTC\(^3\) (BI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm\(^3\)

**Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:**

- DTG plus 3TC (BI)  
- DRV/r plus RAL BID (CI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm\(^3\)  
- DRV/r once daily plus 3TC\(^3\) (CI)

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**DHHS May 2018 – naïve alternatives**

- **DOR/TDF/3TC**  
  *(Delstrigo™)*

- **DTG+3TC**

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Meet Bob, Sam, Izzy & Ray

Bob – been declining Rx, wants new ART, no side effects

Sam – on treatment for years, lots of comorbidities wants to know about switching options

Izzy – fed up of pills, wants to know about injectables

Ray – multidrug resistance, detectable viral load, CD4 declining
Switch to DOR/3TC/TDF vs Continuation of Baseline ART in Virologically Suppressed Adults - DRIVE-SHIFT Wk 48 results

- **Primary endpoint**: HIV-1 RNA < 50 copies/mL (FDA Snapshot)

**Adults with HIV-1 RNA < 40 copies/mL, stable ART for ≥ 6 mos with no prior virologic failure or resistance to study drugs, and eGFR ≥ 50 mL/min (N = 670)**

<table>
<thead>
<tr>
<th></th>
<th>Wk 24</th>
<th>Wk 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR/3TC/TDF*</td>
<td>(n = 447)</td>
<td>DOR/3TC/TDF*</td>
</tr>
<tr>
<td>Baseline ART†</td>
<td>(n = 223)</td>
<td>DOR/3TC/TDF*</td>
</tr>
</tbody>
</table>

†2 NRTIs + RTV- or COBI-boosted PI (ATV, DRV, LPV), EVG/COBI, or NNRTI (EFV, NVP, RPV).

Switch to DOR/3TC/TDF vs Continuation of Baseline ART

DRIVE-SHIFT: Wk 48 virological/resistance/safety results

No treatment emergent resistance in DOR arm

More TRAEs in DOR (20 vs 2%)

7 (1.6%) d/c due to DOR TRAEs

Significant decreases LDL-C & non-HDL-C in DOR

Switch to DOR/3TC/TDF vs Continuation of Baseline ART

DRIVE-SHIFT: Wk 48 virological/resistance/safety results

- No treatment emergent resistance in DOR arm
- More TRAEs in DOR (20 vs 2%)
- 7 (1.6%) d/c due to DOR TRAEs
- Significant decreases LDL-C & non-HDL-C in DOR

Switch to DTG + RPV vs Continuation of Baseline ART in Virologically Suppressed Adults: SWORD-1 and -2

**Early Switch Phase**

- **Primary Endpoint:** HIV-1 RNA < 50 copies/mL at Wk 48 (noninferiority margin: -8%)[^3]
- **Wk 100:** 1% confirmed virologic withdrawal; emergent NNRTI resistance in 3/10, all early switch arm[^2]

**Late Switch Phase**

- Wk 148 (HIV-1 RNA < 50 copies/mL at Wk 100)[^2]
- 89%
- 93%

---

**Adults on stable ART (INSTI, NNRTI, or PI + 2 NRTIs*) with HIV-1 RNA < 50 copies/mL for ≥ 6 mos at screening; no previous VF or current HBV infection (N = 1024)**

---

Switch to DTG + RPV vs Continuation of Baseline ART: SWORD-1 and -2 Wk 100 results

- Target not Detected (TND) data:
  - 3/10 failures had NNRTI resistance; no INSTI resistance
  - TRAEs: Headache/nausea (2% each)
  - Reduction in markers of bone turnover & renal tubular function
  - No affect on lipids or inflammation markers

EMERALD: Switch From Suppressive Boosted PI + FTC/TDF to DRV/COBI/FTC/TAF at Wk 96

Adults with HIV-1 RNA < 50 c/mL while receiving boosted PI* + FTC/TDF; no prior VF on DRV; no DRV RAMs if historical genotype known (N = 1141)

- Primary endpoint: cumulative virologic rebound at Wk 48 (ITT)
  - Switch to DRV/COBI/FTC/TAF vs continue Boosted PI + FTC/TDF: 2.5% vs 2.1%

EMERALD: Virologic Outcomes & safety in DRV/COBI/FTC/TAF Immediate Switch Arm Through Wk 96 (ITT)

No resistance mutations
Improvement in bone parameters
Small eGFR decrease to Wk 96; other renal markers improved
Lipids – small but significant increase (8% patients requiring Rx at wk 96 cf 3% at wk48)

Eron. IDWeek 2018. Abstr 1768
EACS 9.1 Oct 2018 Stable switch

Dual therapies as class sparing strategies
– DTG + RPV

In patients without a history of treatment failure, data support switching from regimens containing TDF to single-tablet regimens including dolutegravir/abacavir/lamivudine, \(^{46,49}\) dolutegravir/rilpivirine, \(^{31}\) elvitegravir/cobicistat/emtricitabine/TAF, \(^{1}\) rilpivirine/emtricitabine/TAF, \(^{50}\) darunavir/cobicistat/emtricitabine/TAF, \(^{51}\) and bictegravir/emtricitabine/TAF. \(^{20}\) The switch to TAF-
Switching from 3-drug regimens to certain 2-drug regimens in the setting of viral suppression, using dolutegravir/rilpivirine (evidence rating Ala), a boosted PI with lamivudine (evidence rating Alla), or dolutegravir with lamivudine (evidence rating Alla) can be used in patients with no prior virologic failure or transmitted drug resistance. (Longer-term follow-up is needed to confirm the durability of these strategies.)

Dual therapy option in switching:
- DTG/RPV
- DTG/3TC

Meet Bob, Sam, Izzy & Ray

Bob – been declining Rx, wants new ART, no side effects

Sam – on treatment for years, lots of comorbidities wants to know about switching options

Izzy – fed up of pills, wants to know about injectables

Ray – multidrug resistance, detectable viral load, CD4 declining
FLAIR Study Design: Randomized, Multicenter, International, Open-Label, Noninferiority Study in ART-Naïve Adults Week 48

**Screening Phase**
- N=809
- ART-naïve
- HIV-1 RNA ≥1000
- Any CD4 count
- HBsAg-negative
- NNRTI RAMs excluded*

**Induction Phase**
- N=629
- DTG/ABC/3TC single-tablet regimen for 20 weeks†

**Maintenance Phase**
- DTG/ABC/3TC Oral daily n=283
- Oral CAB + RPV n=283

**Extension Phase**
- CAB LA (400 mg) + RPV LA (600 mg)‡ IM monthly n=278

**Study Week**
- −20
- −4
- Day 1
- 4§
- 48
- 96 100

- Confirm HIV-1 RNA <50 copies/mL
- Randomization (1:1)
- Primary Endpoint

FLAIR Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints

**Virologic Outcomes**

- **Virologic nonresponse (≥50 c/mL)**: 2.1% CAB LA + RPV LA, 2.5% DTG/ABC/3TC
- **Virologic success (<50 c/mL)**: 93.6% CAB LA + RPV LA, 93.3% DTG/ABC/3TC
- **No virologic data**: 4.2% CAB LA + RPV LA, 4.2% DTG/ABC/3TC

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

- **Primary endpoint**: LA noninferior to DTG/ABC/3TC (≥50 c/mL) at Week 48
  - 6% NI margin
  - Difference (%): CAB LA + RPV LA vs DTG/ABC/3TC
  - CAB LA + RPV LA: -0.4, DTG/ABC/3TC: 2.1

- **Key secondary endpoint**: LA noninferior to DTG/ABC/3TC (<50 c/mL) at Week 48
  - -10% NI margin
  - Difference (%): CAB LA + RPV LA vs DTG/ABC/3TC
  - CAB LA + RPV LA: -3.7, DTG/ABC/3TC: 4.5

- **3 VF in LA arm**: all A1, L74I at baseline; maintained susceptibility DTG
- **3 VF DTG/TDF/3TC arm**, no resistance

*Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

FLAIR Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints

**Virologic Outcomes**

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

<table>
<thead>
<tr>
<th>Proportion of Participants (%)</th>
<th>Virologic nonresponse (≥50 c/mL)</th>
<th>Virologic success (&lt;50 c/mL)</th>
<th>No virologic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB LA + RPV LA</td>
<td>2.1</td>
<td>93.6</td>
<td>4.2</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>2.5</td>
<td>93.3</td>
<td>4.2</td>
</tr>
</tbody>
</table>

**Primary endpoint:**
LA noninferior to DTG/ABC/3TC (≥50 c/mL) at Week 48

**Key secondary endpoint:**
LA noninferior to DTG/ABC/3TC (<50 c/mL) at Week 48

- **3 VF in LA arm:** all A1, L74I at baseline; maintained susceptibility DTG
- **3 VF DTG/TDF/3TC arm,** no resistance

*Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

ATLAS Study Design: Randomized, Multicenter, International, Open-Label, Noninferiority Study in Adults with Virologic Suppression - week 48

Screening Phase

- PI-, NNRTI-, or INSTI-based regimen with 2 NRTI backbone* N=705

Randomization

1:1

Maintenance Phase

- PI, NNRTI or INSTI†
- Current daily oral ART n=308

- Oral CAB + RPV n=308

Extension Phase‡

- CAB LA (400 mg) + RPV LA (600 mg)§
- IM monthly n=303

- Extension Phase or transition to the ATLAS-2M study

Primary Endpoint

Week 48

Day 1 Baseline

Week 4

Week 96

Week 52

33% Women; 26% > 50yrs; median time on ART 4 yrs (1-21)

*INSTI-based regimen capped at 40% of enrollment; Triumeq excluded from study;

ATLAS Virologic Snapshot Outcomes at Week 48 for ITT-E: Primary and Secondary Endpoints

### Virologic Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>CAB LA + RPV LA (n=308)</th>
<th>CAR (n=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic nonresponse (≥50 c/mL)</td>
<td>1.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Virologic success (&lt;50 c/mL)</td>
<td>92.5</td>
<td>95.5</td>
</tr>
<tr>
<td>No virologic data</td>
<td>5.8</td>
<td>3.6</td>
</tr>
</tbody>
</table>

### Adjusted Treatment Difference (95% CI)*

- **Primary endpoint:**
  - LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48
  - Difference (%): -1.2, 2.5
  - 6% NI margin

- **Key secondary endpoint:**
  - LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48
  - Difference (%): -6.7, 0.7
  - ~10% NI margin

*Adjusted for sex and baseline third agent class.

ATLAS Virologic Snapshot Outcomes at Week 48 for ITT-E: Primary and Secondary Endpoints

**Virologic Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CAB LA + RPV LA (n=308)</th>
<th>CAR (n=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic nonresponse (≥50 c/mL)</td>
<td>1.6%</td>
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<td>92.5%</td>
<td>95.5%</td>
</tr>
<tr>
<td>No virologic data</td>
<td>5.8%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

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

- **Primary endpoint:** LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48
  - Difference (%): -1.2 to 2.5
  - Adjusted for sex and baseline third agent class.

- **Key secondary endpoint:** LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48
  - Difference (%): -6.7 to 0.7

*Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.*
ATLAS: Safety (excluding ISRs) & resistance

- CAB + RPV LA arm 29% TRAES (cf 3% CAR). Nausea, headache, fatigue & pyrexia 4%, mostly (95%) grade 1-2.

- 10 (3%) AEs CAB + RPV LA cf 8 (2%) CAR arm led to withdrawal

- 3 VF in LA arm: all subtype A variety - A/A1 or AG.
  - CAB/RPV resistance in 1
  - RPV only resistance in 2.

- No cases of drug-related SAEs, drug hypersensitivity, or drug-induced liver injury observed on CAB LA + RPV LA arm

The majority (99%, 1439/1460) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days.

4 withdrawals due to ISR

Bars represent incidence of onset ISRs relative to the most recent IM injection visit.

LATTE-2: CAB + RPV LA vs oral CAB + ABC/3TC

ART- Naïve, CD4≥200 cells/mm³, no resistance N=309

Primary endpoints: HIV-1 RNA < 50 copies/mL (FDA Snapshot), PDVF, safety at maintenance Wk 32\[2]\n
94% in Q4W arm (difference vs oral treatment: 2.8%; 95% CI: -5.8% to 11.5%), 95% in Q8W arm (difference vs oral treatment: 3.7%; 95% CI: -4.8% to 12.2%), 91% in oral treatment arm

PDVF in 1% by Wk 96; ISRs mild (84%) or moderate (15%), led to d/c in < 1% of patients

Margolis et al. HIV Glasgow; Glasgow, UK. Poster 118.
Latte-2 Outcomes Randomized and Nonrandomized Switch Arms: Week 160 HIV-1 RNA <50 c/mL (ITT-ME)

Virologic outcomes

PDVF in 2 patients (1%) by wk 48; no PDVF after week 48

ISRs mild (84%) or moderate (15%), led to d/c in < 1% of patients

TRAEs:
Randomized arms: pyrexia (5%), headache (3%), fatigue (3%)
Optimized arms: (all 2%) asthenia, fatigue, palpitations

Margolis et al. HIV Glasgow; Glasgow, UK. Poster 118.
Meet Bob, Sam, Izzy & Ray

Bob – been declining Rx, wants new ART, no side effects

Sam – on treatment for years, lots of comorbidities wants to know about switching options

Izzy –fed up of pills, wants to know about injectables

Ray – multidrug resistance, detectable viral load, CD4 declining
DTG or LPV/RTV + 2NRTIs as Second-line ART: DAWNING

- International, randomized, open-label phase IIIb noninferiority study

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

Patients with HIV infection and VF (2 instances of HIV-1 RNA ≥ 400 copies/mL) on first-line NNRTI + 2 NRTIs; receiving first-line regimen ≥ 6 mos; no primary resistance to INSTIs or PIs (N = 624)

Primary Endpoint
- Wk 48
- Wk 52

DTG + 2 NRTIs* (n = 312)
LPV/RTV + 2 NRTIs*† (n = 312)

*Investigator-selected NRTIs; included ≥ 1 fully active NRTI according to HIV genotypic resistance testing at screening.

Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by FDA Snapshot algorithm with noninferiority margin of 12%

DAWNING: Virologic Response & resistance data at Wk 48

Virologic Outcomes

- **ITT-E**
  - **DTG + 2 NRTIs**: 84%
  - **LPV/RTV + 2 NRTIs**: 70%
  - **n/N** = 261/312

- **PP**
  - **DTG + 2 NRTIs**: 87%
  - **LPV/RTV + 2 NRTIs**: 74%
  - **n/N** = 246/283

DAWNING: Virologic Response & resistance data at Wk 48

Post-hoc analysis

HIV-1 RNA < 50 copies/mL at Wk 48:

- In patients with BL M184V/I ± other NRTI RAMs receiving 3TC or FTC: 85%
- In patients with K65R receiving TDF: 86%
- In patients with ≥ 1 TAM receiving ZDV: 86%

BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults at Wk 48

Randomised Cohort §:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:
• 1 or 2 ARV classes remaining & ≥1 fully active & available agent per class
• Unable to construct viable regimen from remaining agents

Non-randomised Cohort §:
HTE participants, failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:
• 0 ARV classes remaining and no remaining fully active approved agents‡

Randomised 3:1

Blinded FTR 600 mg BID + failing regimen

Open Label FTR 600 mg BID + OBT

Day 1
Day 9 – Open Label FTR + OBT
Week 24
Week 48* Week 96*
End of Study†

Blinded placebo + failing regimen

Day 1
Week 24*
Week 48*
Week 96*
End of Study†

Aberg et al. HIV Glasgow 2018; Glasgow, UK. Oral 334A.
BRIGHTE: fostemsavir efficacy & safety at Wk 48

Median CD4 increase:
127 cells/mm³ randomised arm
35 cells/mm³ non-randomised

Generally well tolerated

35%/44% had SAE

Treatment related SAEs 3%

IBALIZUMAB
Long acting monoclonal antibody
CD4 directed post attachment HIV-1 inhibitor

n=40; inclusion: 3 drug resistance, HIV RNA >1,000c/mL

IBA IV every 2 weeks + OBR (=incl 1 active drug)

9/10 VF/rebound had decreased susceptibility IBA

Most common AE diarrhea

Wk 25 (1o endpoint) – 43% HIV RNA <40 ITT

Wk 48: All 15 with HIV RNA <50c/ml at wk 25 maintained

Wk 96 : Safety & efficacy of IBA maintained

Licensed USA 2018

Emu, NEJM 2018 379;645-654
Cohen, Glasgow 2018 Abs O345
Emu, CROI 2019 Abs 485.
### In case of demonstrated resistance mutations

#### General recommendations:

Use at least 2 and preferably 3 active drugs in the new regimen (including active drugs from previously used classes) based on resistance mutations present in current and earlier genotypic analyses.

Any regimen should use at least 1 fully active boosted PI (e.g. DRV/r) plus 1 drug from a class not used previously e.g. INSTI, FI, or CCR5 antagonist (if tropism test shows R5 virus only), or 1 NNRTI (e.g. ETV), assessed by genotypic testing.

Alternatively, a regimen can be constructed with DTG (when fully active) plus 2 NRTIs, of which at least 1 NRTI is fully active.

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DTG + 2NRTIs
(if ≥1 NRTI active)
alternative to
DRV/r

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**EACS 9.1 Oct 2018 Resistance**

DTG & 2NRTIs: option if NNRTI failure (if ≥ active NRTI)

- Dolutegravir, plus 2 NRTIs (with at least 1 active by genotype) is recommended after initial treatment failure with an NNRTI (evidence rating A1a).
- A boosted PI plus 2 NRTIs (with at least 1 active NRTI) are recommended for initial treatment failure of an InSTI-containing regimen (evidence rating A1I).
- Dolutegravir plus at least 1 fully active other agent may be effective in the setting of raltegravir or elvitegravir resistance. Dolutegravir should be dosed twice daily in this setting (evidence rating B1II).

Ibalizumab, an anti-CD4 monoclonal antibody that inhibits HIV cell entry via CD4 binding, is active against CCR5- and C-X-C chemokine receptor 4 (CXCR4)-tropic HIV isolates and may be useful as a fully active agent for patients with multiclass-resistant virus (evidence rating BII). Almost 50% of adults with virologic failure from multidrug-resistant HIV achieved undetectable HIV RNA levels at 24 weeks after receipt of biweekly intravenous ibalizumab (800 mg) with at least 1 other active drug. 


Ibalizumab in multiclass resistance with 1 other active drug
Pipeline

- **Leronlimab (PRO 140):** (CROI poster 486)
  - Phase IIb/III, weekly subcut, single agent maintenance
- **GSK 2838232 maturation inhibitor (CROI oral abs 142)**
  - Phase IIa, oral daily with COBI
- **GS-6207 Capsid inhibitor (CROI oral abs 141)**
  - Phase I, subcut
- **PGT 121 mAB (CROI oral abs 145)**
  - Phase I IV/Subcut. Resistance in all rebounds

http://www.croiwebcasts.org/y/2019/7?link=nav&linkc=date
Bob, Sam, Izzy & Ray

Bob – BIC/F/TAF or DOR/TDF/3TC....DTG/3TC?

Sam – DOR/TDF/3TC or DRV/c/F/TAF or dual DTG/RPV

Izzy—...CAB/RPV 2020?

Ray – DTG +2NRTIs or Ibalizumab or Fostemsavir?
Thanks for listening

Questions?

Thanks to Yvonne Gilleece
BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)

Introduction

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of adults with HIV infection on antiretroviral therapy (ART).

The scope includes: (i) guidance on the initiation of ART in those previously naïve to therapy; (ii) support of people living with HIV (PLWH) on treatment; (iii) management of individuals experiencing virological failure; and (iv) recommendations in specific populations where other factors need to be taken into consideration.

The guidelines are aimed at clinical professionals directly involved with and responsible for the care of adults with HIV infection, and at community advocates responsible for promoting the best interests and care of HIV-positive adults. They should be read in conjunction with other published BHIVA guidelines.

The 2016 interim update to the 2015 BHIVA antiretroviral guidelines has been published online to include tenofovir-disoproxil fumarate (TDF) in place for famotidine. Changes have been made to update the recommendations for the treatment of HIV-1 infection.

https://www.bhiva.org/HIV-1-treatment-guidelines

Accessed 13.3.19