New antiretroviral drugs and trials

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Consultant in infectious diseases, North Manchester General Hospital

DipHIVMed revision day, Manchester, January 2020
36. The examination will include questions that relate to relevant UK guidelines (e.g. British HIV Association (www.bhiva.org), British Association of Sexual Health and HIV (www.bashh.org)) and European AIDS Clinical Society (EACS)). The most current, completed (i.e. final) guidelines, position statements and standards that are available (either on-line or published) at the time of closing date for applications to the examination will be the guideline version referred to. Questions relating to important, well-publicised studies and presented to major HIV academic conferences prior to the closing date for applications to the exam may also be included.

Closing date for February 2020 exam was 27th November 2019 and for September 2020 is 16th June.
So what’s new since the last BHIVA ART guidelines?

• Quick look at current ART guidelines
• Two-drug regimens (2DR)
  • DTG/3TC
  • DTG/RPV
  • (DTG monotherapy)
  • DRV/3TC
• Bictegravir
• Doravirine
• Long acting injectables
• Fostemsavir
• Ibalizumab
BHIVA guidelines: ART

Last updated 2015.
Interim update 2016.

We recommend that therapy-naive PLWH start ART containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the following: ritonavir-boosted protease inhibitor (PI/r), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI) (1A).

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI backbone</td>
<td>Tenofovir-DF and emtricitabine</td>
</tr>
<tr>
<td>Tenofovir-AF and emtricitabine</td>
<td></td>
</tr>
<tr>
<td>Third agent (alphabetical order)</td>
<td>Atazanavir/r</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/c&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Abacavir is contraindicated if an individual is HLA-B*57:01 positive

<sup>b</sup> Use recommended only if baseline viral load is ≥100,000 copies/mL except when initiated in combination with dolutegravir in which case abacavir/lamivudine can be used at any baseline viral load.

<sup>c</sup> Tenofovir-DF/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in individuals with creatinine clearance <70 mL/min; tenufovir-AF/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in patients with estimated CrCl <30 mL/min

<sup>d</sup> Use recommended only if baseline viral load is ≥100,000 copies/mL

NB. The viral load advice for abacavir/lamivudine and rilpivirine applies only to initiating these agents in individuals with a detectable viral load – when these agents are used as a switch option in the context of viral load suppression the baseline viral load can be disregarded.
EACS guidelines: ART

Really sensible advice:

Wide range of combinations:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Main requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 NRTIs + INSTI (PREFERRED)</strong></td>
<td></td>
</tr>
<tr>
<td>ABC/3TC + DTG</td>
<td>HLA-B*57:01 negative</td>
</tr>
<tr>
<td>ABC/3TC/DTG</td>
<td>HBsAg negative</td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + DTG</td>
<td></td>
</tr>
<tr>
<td>TAF/FTC/3TC</td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or lx</td>
<td></td>
</tr>
<tr>
<td><strong>1 NRTI + INSTI</strong></td>
<td></td>
</tr>
<tr>
<td>DTG + 3TC</td>
<td>HBsAg negative</td>
</tr>
<tr>
<td></td>
<td>HIV-1 VL &lt; 500,000 copies/mL</td>
</tr>
<tr>
<td></td>
<td>CD4 count &gt; 200 cells/μL</td>
</tr>
<tr>
<td><strong>2 NRTIs + NNRTI</strong></td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + DOR</td>
<td></td>
</tr>
<tr>
<td>TDF/3TC/3TC</td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + RPV</td>
<td>TDF/3TC/3TC/3TC</td>
</tr>
<tr>
<td>TAF/FTC/3TC</td>
<td>CD4 count &gt; 200 cells/μL</td>
</tr>
<tr>
<td></td>
<td>HIV-1 VL &lt; 100,000 copies/mL</td>
</tr>
<tr>
<td></td>
<td>Not on proton pump inhibitor</td>
</tr>
<tr>
<td></td>
<td>With food</td>
</tr>
<tr>
<td><strong>2 NRTIs + PIs or P7iC</strong></td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + DRV+c or DRV/VR</td>
<td>With food</td>
</tr>
<tr>
<td>TAF/FTC/3TC</td>
<td></td>
</tr>
</tbody>
</table>
### EACS: Wide Range of Combinations: Including 2DR

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Main requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended regimens</strong></td>
<td></td>
</tr>
<tr>
<td><strong>2 NRTIs + INSTI (PREFERRED)</strong></td>
<td></td>
</tr>
<tr>
<td>ABC/3TC + DTG</td>
<td>HLA-B*57:01 negative HBsAg negative</td>
</tr>
<tr>
<td>ABC/3TC/DTG</td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + DTG</td>
<td></td>
</tr>
<tr>
<td>TAF/FTC/3TC</td>
<td></td>
</tr>
<tr>
<td><strong>1 NRTI + INSTI</strong></td>
<td></td>
</tr>
<tr>
<td>DTG + 3TC</td>
<td>HBsAg negative HIV-VL &lt; 50,000 copies/mL CD4 count = 200 cells/μL</td>
</tr>
<tr>
<td><strong>2 NRTIs + NNRTI</strong></td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + DOR TDF/3TC/DOR</td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + RPV TAF/FTC/RPV TDF/FTC/RPV</td>
<td></td>
</tr>
<tr>
<td><strong>2 NRTIs + PI/r or PI/c</strong></td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + DRV/r or DRV/r TAF/FTC/DRV/r</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Main requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alternative regimens</strong></td>
<td></td>
</tr>
<tr>
<td><strong>2 NRTIs + INSTI</strong></td>
<td></td>
</tr>
<tr>
<td>ABC/3TC + RAL qd or bid</td>
<td>HLA-B*57:01 negative HBsAg negative</td>
</tr>
<tr>
<td>TDF/FTC/EVG/c TAF/FTC/EVG/c</td>
<td></td>
</tr>
<tr>
<td><strong>2 NRTIs + NNRTI</strong></td>
<td></td>
</tr>
<tr>
<td>ABC/3TC +EFV</td>
<td>HLA-B*57:01 negative HBsAg negative HIV-VL &lt; 100,000 copies/mL At bedtime or 2 hours before dinner</td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + EFV TDF/FTC/EV</td>
<td></td>
</tr>
<tr>
<td><strong>2 NRTIs + PI/r or PI/c</strong></td>
<td></td>
</tr>
<tr>
<td>ABC/3TC + ATV/c or ATV/r</td>
<td>HLA-B*57:01 negative HBsAg negative HIV-VL &lt; 100,000 copies/mL Not on proton pump inhibitor With food</td>
</tr>
<tr>
<td>ABC/3TC + DRV/c or DRV/r</td>
<td></td>
</tr>
<tr>
<td><strong>Other combinations</strong></td>
<td></td>
</tr>
<tr>
<td>TAF/FTC or TDF/FTC or TDF/3TC + ATV/c or ATV/r</td>
<td>HLA-B*57:01 negative HBsAg negative HIV-VL &lt; 100,000 copies/mL CD4 &gt; 200 cells/μL With food</td>
</tr>
<tr>
<td>RAL 400 mg bid + DRV/c or DRV/r TAF/FTC/DRV/c</td>
<td></td>
</tr>
</tbody>
</table>
BHIVA current recommendations on dual therapy ("2DR")

• Current 2DR recommendation = DRV/r + RAL in naïves, with CD4 >200, VL <100,000 if ABC, TDF, TAF unsuitable
• Recommend against use of PI-based dual ART with single NNRTI, NRTI, CCR5 antagonist for naïves
• Suggest boosted PI plus 3TC as alternative to 3DR in virologically suppressed (switch) patients

PI/r + 3TC based on 2 switch studies:

1. LPR/r + 3TC vs LPR/r + XTC + another NRTI (OLÉ, published 2015); 2DR non-inferior to 3DR
2. ATZ/r + 3TC vs ATZ/r + 2NRTI (SALT, published 2015); 2DR non-inferior to 3DR
BHIVA interim position statement on dual therapy ("2DR")

**DTG + 3TC** is an option for:
- no hepatitis B (and ideally immune)
- no resistance
- VL<500,000 and CD4 >200
- "Special populations"

"Dovato" = DTG/3TC combined tablet
18.5 x 9.5mm
OR – use separate DTG 50mg, 3TC 300mg

DTG + 3TC recommendation based on GEMINI naïve studies, with results now (IAS, July 2019) to 96 weeks and TANGO switch study, with results now to 48 weeks (next slide)
GEMINI studies: DTG/3TC to 96 weeks in naïves

“Late breaker” at IAS July 2019
Watch the podcast here: Cahn et al [http://programme.ias2019.org/Abstract/Abstract/4767]

Identically designed, randomised, double-blind, parallel-group, multicentre, non-inferiority studies

Screening (28 days) 1:1

DTG + 3TC (N=716)
DTG + TDF/FTC (N=717)

Day 1 Week 24 Week 48 Week 96 Week 144

• ART-naive adults

Eligibility criteria
• VL 1000-500,000 c/mL at screening
• ≤10 days of prior ART
• No major RT or PI resistance mutation
• No HBV infection or need for HCV therapy

Primary endpoint at Week 48:
participants with
HIV-1 RNA <50 c/mL
(ITT-E Snapshot)*

ITT-E = intention to treat, exposed
GEMINI studies: DTG/3TC to 96 weeks in naïves

No "treatment emergent" resistance at virological failure
Renal, bone, lipid markers favoured 2DR (clinical relevance?)

TRDF = treatment related discontinuation = failure (stricter criteria for failure, so fewer individuals defined as having experienced treatment failure)
TANGO studies: DTG/3TC to 48 weeks in switch

Randomized, open-label, multicenter, parallel-group, non-inferiority study

- Adults, virologically suppressed (HIV-1 RNA <50 c/mL) for >6 months
- Stable TAF-based regimen

Primary endpoint: participants with virologic failure per FDA Snapshot (ITT-E)

Eligibility criteria:
- ≥2 documented HIV-1 RNA measurements <50 c/mL
- No HBV infection or need for HCV therapy
- No prior VF and no documented NRTI or INSTI resistance
- TAF/FTC + PI or INI or NNRTI as initial regimen

Countries:
- Australia, Belgium, Canada, France, Germany, Japan, Netherlands, Spain, United Kingdom, United States
TANGO studies: DTG/3TC to 48 weeks in switch

No "treatment emergent" resistance at virological failure
Renal, bone, lipid markers favoured 2DR (clinical relevance?)
**TANGO studies: DTG/3TC to 48 weeks in switch**

**Virologic Response by Pro-viral M184V/I Status:**
*Post-hoc analysis of stored baseline samples*

<table>
<thead>
<tr>
<th>Participants, n (%)</th>
<th>DTG/3TC (N=318)</th>
<th>TAF-based regimen (N=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pro-viral M184V/I at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt;50 c/mL at Week 48</td>
<td>4 (100)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥50 c/mL at Week 48</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>No pro-viral M184V/I at baseline</strong></td>
<td>314 (99)</td>
<td>305 (99)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;50 c/mL at Week 48</td>
<td>314 (100)</td>
<td>303 (99)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥50 c/mL at Week 48</td>
<td>0</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

- All participants in the DTG/3TC group with pro-viral M184V/I at baseline maintained HIV-1 RNA <50 c/mL at Week 48
DTG/RPV 2DR: SWORD studies

• Switch studies: compared with continuing baseline ART (1\textsuperscript{st} or 2\textsuperscript{nd} regimen)
• Two identical licensing studies

“Juluca” = DTG/RPV combined tablet
14 x 7mm
OR – use separate DTG 50mg, RPV 25mg
SWORD 1 & 2: Switch to DTG + RPV dual therapy

Method: Study Design

Screening
- VL <50 c/mL on INI, NNRTI, or PI + 2 NRTIs
- 1:1
- Early-switch phase
  - DTG+RPV (n=513)
  - CAR (n=511)
- Late-switch phase
  - DTG+RPV
- Continuation phase
  - DTG+RPV

Inclusion criteria
- On stable CAR ≥6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA ≤50 c/mL during the 12 months before screening
- HBV negative

Primary endpoint at 48 weeks: participants with VL <50 c/mL (ITT-E snapshot)

70% to 73% receiving TDF at baseline

CAR = current antiretroviral regimen
SWORD 1 & 2: Switch to DTG + RPV dual therapy from suppressive ART non-inferior to continued baseline ART at week 48

- 2 pts met criteria for virological withdrawal. One, at week 36 in DTG + RPV arm, had K101K/E
  - Documented non-adherence at virological failure
  - Resuppressed with continued DTG + RPV
  - No INSTI resistance

Llibre et al, Lancet 2018
SWORD 1 & 2: Switch to DTG + RPV dual therapy

Bone turnover biomarkers (low = “good”)

70% to 73% receiving TDF at baseline

Llibre et al, Lancet 2018
**DTG monotherapy vs triple ART in virologically suppressed patients**

- **MONCAY**: randomised, open-label study comparing switch to DTG monotherapy vs continuing DTG/ABC/3TC in virologically suppressed chronic infection (N = 158)[1]
  - HIV-1 RNA < 50 copies/mL at Wk 24:
    - DTG monotherapy, 94%; triple ART, 96%
      - **Virological failure with DTG monotherapy**:
        - Week 24, n = 2; Week 48, n = 7
          - \( P = .005 \) vs triple ART
        - Emergent INSTI mutations in 2/7 at failure
        - Low CD4+ cell count, detectable but not quantifiable HIV-1 RNA at screening predicted virological failure in multivariate analysis
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    - DTG monotherapy, 94%; triple ART, 96%
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- Similar results in **DOMONO** trial of DTG maintenance monotherapy:
  - Non-inferior virologic suppression at Wk 24, unacceptable VF afterwards[2]
    - **11 of 122 people who switched to DTG monotherapy experienced virological failure**
      - 9 of 11 had genotypic INSTI resistance at failure
      - INSTI resistance pathways varied:
        - 92Q/155H (n = 1); 97A/155H (n = 1); 155H/148R (n = 1); 118R (n = 2); 148K (n = 1); 148H (n = 2); 148R (n = 1)

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Slide credit: clinicaloptions.com
DTG monotherapy vs triple ART in virologically suppressed patients

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- HIV-1 RNA < 50 copies/mL at Wk 24: DTG monotherapy, 94%; triple ART, 96%
  - **Virological failure with DTG monotherapy**: Week 24, n = 2; Week 48, n = 7 (%P = .005 vs triple ART)
  - Emergent INSTI mutations in 3/7 at failure

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Slide credit: clinicaloptions.com
DRV/r + 3TC as dual therapy: ANDES study at week 48

- Used fixed dose combination DRV/r 800/100 available in Argentina
- Enrolled ART-naïve individuals
- 48 week results presented as poster; CROI 2018
ANDES: 3TC/DRV/r + \textbf{vs} TDF/3TC/DRV/r in naïves at week 48

- Open-label, randomised phase IV study
  - Primary endpoint: HIV-1 RNA < 50 c/mL at week 48 (FDA snapshot)

\begin{itemize}
  \item ART-naïve people with HIV-1 RNA > 1000 copies/mL, no NRTI or PI resistance, and HBsAg negative (N = 145)
  \item Stratified by HIV-1 RNA (≤ or > 100,000 copies/mL)
  \item 24 Wks: Interim Analysis
  \item 48 Wks: Primary Endpoint
  \item DRV/RTV + 3TC* (n = 75)
  \item DRV/RTV + 3TC/TDF† (n = 70)
\end{itemize}

\*DRV/RTV 800/100 mg QD + 3TC 300 mg QD.
†DRV/RTV 800/100 mg QD + 3TC/TDF 300/300 mg QD.

**ANDES: 3TC/DRV/r + vs TDF/3TC/DRV/r**

**Efficacy and safety at week 48**

*HIV-1 RNA < 50 copies/mL at Wk 48 (ITT)*

- Treatment difference (HIV-1 RNA < 50 c/mL; ITT snapshot):
  - All pts: -1.0% (95% CI: -7.5% to 5.6%)
  - Pts with high BL HIV-1 RNA: -1.4 (95% CI: -17.2 to 14.4)
- No significant difference in AEs leading to discontinuation, serious AEs, or deaths between arms
- TC change from BL significantly greater with dual ART vs triple ART (19% vs 4%; \( P = .01 \)); LDL-C and TG trended toward greater increases with dual ART

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**Pts (%):**

- **All Pts**
  - DRV/r + 3TC: 93
  - DRV/r + 3TC/TDF: 94

- **Pts With BL HIV-1 RNA > 100,000 c/mL (n = 35)**
  - DRV/r + 3TC: 91
  - DRV/r + 3TC/TDF: 92

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Figueroa MI, et al. CROI 2018. Abstract 489.  **AE = adverse event**  **ITT = intention to treat**

Slide credit: clinicaloptions.com
**ANDES: 3TC/DRV/r + vs TDF/3TC/DRV/r**

Efficacy and safety at week 48

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**Figueroa MI, et al. CROI 2018. Abstract 489.**  
**AE = adverse event  ITT = intention to treat**

- Lipids a bit better in triple therapy arm (ie with TDF)
Bictegravir: a new INSTI that’s a bit like DTG

- It only comes in the single-tablet regimen “Biktarvy”
  - Bictegravir 50mg, FTC 200mg, TAF 25mg
  - 15 x 8mm
  - For those with creatinine clearance ≥30ml/min

- Signature toxicity: nothing more than DTG in studies
  - But wait for post-marketing surveillance re: CNS side effects and weight gain

- Studies are:
  - GS-1489: naïves, vs ABC/3TC/DTG; to 96 weeks (Lancet 2019)
  - GS-1490: naïves, vs TAF/FTC/DTG; to 96 weeks (Lancet 2019)
  - 380-1844: switch, vs continuing ABC/3TC/DTG (Lancet HIV 2018)
  - 380-1878: switch, vs continuing PI-based triple therapy (Lancet HIV 2018)

INSTI = integrase strand transfer inhibitor; or integrase inhibitor
Bictegravir studies: vs DTG in naïves (1489 with ABC; 1490 both with TAF)
**GS-1489: BIC/F/TAF vs DTG/ABC/3TC in naïves; week 96**

- Multicenter, randomized, double-blind, active-controlled noninferiority phase III trial\(^1\)

Stratified by HIV-1 RNA (≤ 100,000 or > 100,000 to ≤ 400,000 or > 400,000 copies/mL), CD4+ cell count (< 50 or 50-199 or ≥ 200 cells/mm\(^3\)), geographic region (US or ex-US)

- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (noninferiority margin: -12\%)\(^2\)
  - **BIC/FTC/TAF** vs **DTG/ABC/3TC**: 92.4\% vs 93.0\% (difference: -0.6\%; 95\% CI: -4.8\% to 3.6\%; \(P = .78\))
  - Nausea less frequent with **BIC/FTC/TAF** vs **DTG/ABC/3TC** (10\% vs 23\%; \(P < .0001\))

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**Slide credit:** clinicaloptions.com
GS-1489: Virological outcomes at week 96

- No treatment-emergent resistance detected in any patient through Wk 96


Slide credit: clinicaloptions.com
GS-1489: Safety outcomes to week 96

<table>
<thead>
<tr>
<th>Drug-Related AEs Differing by Treatment, n (%)</th>
<th>BIC/FTC/TAF (n = 314)</th>
<th>DTG/ABC/3TC (n = 315)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug-related AE</td>
<td>28</td>
<td>40</td>
<td>.002</td>
</tr>
<tr>
<td>- Nausea</td>
<td>6</td>
<td>17</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

- BMD changes similar in both arms
- Greater increases in fasting total and LDL cholesterol with BIC/FTC/TAF vs DTG/ABC/3TC
- No cases of proximal tubulopathy or d/c for renal AEs in BIC/FTC/TAF arm

GS-1490: BIC/F/TAF vs DTG + F/TAF in naïves; week 96

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

Stratified by HIV-1 RNA (≤ 100,000 or > 100,000 to ≤ 400,000 or > 400,000 copies/mL), CD4+ cell count (< 50 or 50-199 or ≥ 200 cells/mm³), geographic region (US or ex-US)

Primary Analysis
- Wk 48

Current Analysis
- Wk 96
  - BIC/FTC/TAF QD + DTG + FTC/TAF Placebo QD
    - (n = 320)
- Wk 144
  - DTG + FTC/TAF QD + BIC/FTC/TAF Placebo QD
    - (n = 325)

- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (noninferiority margin: -12%)[2]
  - BIC/FTC/TAF vs DTG + FTC/TAF: 89% vs 93.0% (difference: -3.5%; 95% CI: -7.9% to 1.0%; P = .12)
  - No treatment-emergent resistance in either treatment arm


Slide credit: clinicaloptions.com
GS-1490: Virological outcomes at week 96

- HIV-1 RNA < 50 copies/mL (PP analysis): **100% BIC/FTC/TAF** vs **98% DTG + FTC/TAF**
- No treatment-emergent resistance detected in any patient through Wk 96
- Very few differences in adverse events; renal and lipids the same
Bictegravir: a new INSTI that’s a bit like DTG

- It only comes in the single-tablet regimen “Biktarvy”
  - Bictegravir 50mg, FTC 200mg, TAF 25mg
  - 15 x 8mm
  - For those with creatinine clearance ≥30ml/min

- Signature toxicity: nothing more than DTG in studies
  - But wait for post-marketing surveillance re: CNS side effects and weight gain

- Studies are:
  - GS-1489: naïves, vs ABC/3TC/DTG; to 96 weeks (Lancet 2019)
  - GS-1490: naïves, vs TAF/FTC/DTG; to 96 weeks (Lancet 2019)
  - 380-1844: switch, vs continuing ABC/3TC/DTG (Lancet HIV 2018)
  - 380-1878: switch, vs continuing PI-based triple therapy (Lancet HIV 2018)
380-1844: TAF/FTC/BIC as switch vs continuing ABC/3TC/DTG

Results:
HIV RNA >50 in 3/282 (BIC) vs 1/281 (DTG)
HIV RNA <50 in 264/282 (93.6%) (BIC) vs 267/281 (85.0%) (DTG)

Primary endpoint: Wk 48 HIV-1 RNA ≥ 50 c/mL (FDA snapshot; noninferiority margin: 4%)
380-1878: TAF/FTC/BIC as switch vs continuing boosted PI

• Open-label, randomised phase III trial

• No treatment-emergent resistance in switch arm
• Lipids improved in switch arm, compared with continued bPI
• Non-inferior at week 48

Daar ES, et al. IDWeek 2017. Abstract LB-4
## Bictegravir in women

Analysis of TAF/FTC/BIC in women, in phase II – III trials

### BIC/FTC/TAF in Women and Girls: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Virologically Suppressed</th>
<th>ART Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-17 Yrs (n = 59)</td>
<td>18-49 Yrs (n = 191)</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Black</td>
<td>78</td>
<td>38</td>
</tr>
<tr>
<td>▪ White</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>▪ Asian</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Median HIV-1 RNA, log$_{10}$ c/mL</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Median CD4+ cell count, cells/mm$^3$</td>
<td>848</td>
<td>666</td>
</tr>
<tr>
<td>Median eGFR, mL/min*</td>
<td>147</td>
<td>101</td>
</tr>
</tbody>
</table>

*Calculated with Schwartz formula for pediatrics (mL/min/1.72 m$^2$) and Cockcroft-Gault for adults.

Bictegravir in women

Analysis of TAF/FTC/BIC in women, in phase II – III trials

- No emergence of resistance detected in BIC/FTC/TAF recipients; efficacy profile consistent with overall analyses in both sexes
Doravirine studies: “DRIVE”

Doravirine is a new NNRTI – with activity against virus with common first-generation NNRTI mutations

- K103N
- Y181C
- G190A

Made alone as doravirine or DOR 100mg (“Pifeltro”)
Or as single tablet regimen “Delstrigo” – with TDF/3TC

Studies are:

**DRIVE-AHEAD**\(^1\): TDF/3TC/DOR vs TDF/FTC/EFV in naïves

**DRIVE-FORWARD**\(^2\): 2NRTIs/DOR vs 2NRTIs/DRV/r in naïves (now to 96 weeks)

**DRIVE-SHIFT**\(^3\): TDF/3TC/DOR vs triple therapy (PI or ETG or NNRTI-based) as switch
Doravirine studies: “DRIVE-AHEAD”: TDF/3TC/DOR vs TDF/FTC/EFV in naïves (to 48 weeks)

Inclusion criteria:

- VL >1000 copies/mL
- ART-naïve, no known resistance to study drugs
- Randomised double-blind, non-inferiority trial, at 126 sites

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>DOR/3TC/TDF (N=364)</th>
<th>EFV/FTC/TDF (N=364)</th>
<th>Total (N=728)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Median (range)</td>
<td>32.0 (18, 70)</td>
<td>36.0 (18, 69)</td>
<td>31.0 (18, 70)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>305 (84%)</td>
<td>311 (85%)</td>
<td>616 (85%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>177 (49%)</td>
<td>170 (47%)</td>
<td>347 (48%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>67 (19%)</td>
<td>68 (19%)</td>
<td>135 (19%)</td>
</tr>
<tr>
<td>Asian</td>
<td>59 (16%)</td>
<td>55 (15%)</td>
<td>114 (17%)</td>
</tr>
<tr>
<td>Other*</td>
<td>61 (17%)</td>
<td>61 (17%)</td>
<td>122 (17%)</td>
</tr>
<tr>
<td>Hispanic or Latino Ethnicity</td>
<td>126 (35%)</td>
<td>120 (32%)</td>
<td>246 (34%)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>37 (10%)</td>
<td>27 (7%)</td>
<td>64 (9%)</td>
</tr>
<tr>
<td>Asia/Pacific</td>
<td>59 (16%)</td>
<td>82 (17%)</td>
<td>141 (17%)</td>
</tr>
<tr>
<td>Europe</td>
<td>88 (24%)</td>
<td>94 (26%)</td>
<td>182 (25%)</td>
</tr>
<tr>
<td>Latin America</td>
<td>89 (24%)</td>
<td>87 (24%)</td>
<td>176 (24%)</td>
</tr>
<tr>
<td>North America</td>
<td>91 (25%)</td>
<td>94 (25%)</td>
<td>185 (25%)</td>
</tr>
<tr>
<td>CD4+ T Cell Count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), cells/mm³</td>
<td>414 (19, 1359)</td>
<td>388 (19, 1452)</td>
<td>397 (19, 1452)</td>
</tr>
<tr>
<td>&lt;200 cells/mm³, n (%)</td>
<td>44 (12%)</td>
<td>46 (13%)</td>
<td>90 (12%)</td>
</tr>
<tr>
<td>&gt;200 cells/mm³, n (%)</td>
<td>320 (88%)</td>
<td>318 (87%)</td>
<td>638 (88%)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), log₁₀ copies/mL</td>
<td>4.4 (2.4, 6.1)</td>
<td>4.5 (2.6, 6.4)</td>
<td>4.4 (2.4, 6.4)</td>
</tr>
<tr>
<td>&lt;100 000 copies/mL, n (%)</td>
<td>291 (80%)</td>
<td>292 (77%)</td>
<td>573 (79%)</td>
</tr>
<tr>
<td>&gt;100 000 copies/mL, n (%)</td>
<td>73 (20%)</td>
<td>82 (23%)</td>
<td>155 (21%)</td>
</tr>
</tbody>
</table>

Doravirine studies: “DRIVE-AHEAD”: TDF/3TC/DOR vs TDF/FTC/EFV in naïves (to 48 weeks)

Rashes: 5% vs 12%
Long-acting injectables

LATTE studies: 1 and 2

(Long-Acting antireTroviral Treatment Enabling)

Phase II studies

ATLAS and FLAIR

Phase III studies

• “Depot” ART: cabotegravir and rilpivirine as intramuscular injection
  • 4 or 8 weekly
  • Half life im CAB 40 days; im RPV 90 days
  • For those struggling with burden of daily oral therapy

BUT

• Adherence to visits/injections is still key – so not for the poorly adherent or chaotic
  • Needs oral lead-in ideally of 4 weeks
  • Can’t stop it easily….. need to know no impending drug-drug-interactions or tolerability issues
**LATTE-2**: long-acting cabotegravir/rilpivirine to week 160

- **Induction Phase**
  - CAB 30 mg PO QD + ABC/3TC

- **Maintenance Phase**
  - 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 PO + ABC/3TC PO QD (n = 56)

- **Extension Phase**
  - CAB + RPV 400/600 IM Q4W (n = 101)
  - CAB + RPV 600/900 IM Q8W (n = 107)
  - CAB + RPV 600/900 IM Q4W (n = 10) or Q8W (n = 34)

**Primary endpoints:** HIV-1 RNA < 50 copies/mL (FDA Snapshot), PDVF, safety at maintenance Wk 32

- 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

---


PDVF = protocol-defined virological failure  
Q4W = every 4 weeks; Q8W = every 8 weeks
ATLAS: Open label, non-inferiority study of long acting CAB/RPV (switch) vs ongoing oral triple regimen

Screening Phase

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

Randomization 1:1

Day 1 Baseline

Maintenance Phase

- PI, NNRTI or INSTI
- Current daily oral ART n=308
- Oral CAB + RPV n=308
- CAB LA (400 mg) + RPV LA (600 mg)
- IM monthly n=303

Extension Phase

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

Primary Endpoint

- Week 48
- Week 52
- Week 96

ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral; IM, intramuscular; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside RTI, PI, protease inhibitor; RPV, rilpivirine; VL, viral load.

*Uninterrupted ART 6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months; †INSTI-based regimen capped at 40% of enrollment; Triumeq excluded from study; ‡Optional switch to CAB LA + RPV LA at Week 52 for those on CAR; §Participants who withdraw/complete IM CAB LA + RPV LA must complete 52 weeks of follow-up; †‡Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks.

**ATLAS**: Open label, non-inferiority study of long acting CAB/RPV (switch) vs ongoing oral triple regimen (“CAR”)

ATLAS 2M update August 2019
Has now reported primary endpoint
8 weekly im CAB/RPV vs 4 weekly = non-inferior at week 48
**ATLAS:** Open label, non-inferiority study of long acting CAB/RPV (switch) vs ongoing oral triple regimen (“CAR”)

**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 (≥250 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
- Key secondary endpoint: LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

CAB: cabotegravir; CAR: current antiretroviral; CI: confidence interval; ITT-E: intention-to-expose; LA: long-acting; NI: noninferiority; RPV: rilpivirine.

*Adjusted for sex and baseline third agent class.

ATLAS: Open label, non-inferiority study of long acting CAB/RPV (switch) vs ongoing oral triple regimen

Injection-site reactions were the main adverse event

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

Participant satisfaction very high

“It might be painful, but it’s better than pills” (Qualitative study; Kerrigan et al, PloS One 2018)
FLAIR: Open-label, non-inferiority study of long-acting CAB/RPV vs ABC/3TC/DTG in “the recently naïve”

- **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**: Oral CAB + RPV n=283, CAB LA (400 mg) + RPV LA (600 mg)
  - IM monthly n=278.
- **Extension Phase**: DTG/ABC/3TC Oral daily n=283.
FLAIR: Open-label, non-inferiority study of long-acting CAB/RPV vs ABC/3TC/DTG in “the recently naïve”

Virologic Outcomes

<table>
<thead>
<tr>
<th>Proportion of Participants (%)</th>
<th>CAB LA + RPV LA (n=283)</th>
<th>DTG/ABC/3TC (n=283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic nonresponse (≥50 c/mL)</td>
<td>2.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Virologic success (&lt;50 c/mL)</td>
<td>93.6</td>
<td>93.3</td>
</tr>
<tr>
<td>No virologic data</td>
<td>4.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>

ISR Incidence by Week

- The majority (99%, 2189/2203) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days.

## ATLAS & FLAIR: virological failures

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype</th>
<th>Previous CAR</th>
<th>SVF Timepoint</th>
<th>Viral Load at SVF/CVF (c/mL)</th>
<th>SVF Timepoint RAMs (HIV-1 RNA)</th>
<th>Drug Sensitivity at SVF (Fold Change)</th>
<th>Baseline RAMs (PBMC/HIV-1 DNA; Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A/A1</td>
<td>3TC, AZT, LPV/r</td>
<td>Week 8</td>
<td>79,166 / 25,745</td>
<td>E138A</td>
<td>RPV (2.4) CAB (0.8) DTG (0.9)</td>
<td>E138E/A L74I</td>
</tr>
<tr>
<td>F, France, AG</td>
<td>3TC, AZT, NVP to 3TC, ABC, NVP</td>
<td>Week 12</td>
<td>695 / 258</td>
<td>V108I E138K</td>
<td>RPV (3.7) CAB (1.2) DTG (1.0)</td>
<td>V108V/I E138K</td>
</tr>
<tr>
<td>M, Russia, A/A1</td>
<td>FTC, RAL, TDF to ABC, EFV, 3TC</td>
<td>Week 20</td>
<td>544 / 1841</td>
<td>E138E/K N155H L74I</td>
<td>RPV (6.5) CAB (2.7) DTG (1.2)</td>
<td>None L74I</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype, Virologic Load (Baseline)</th>
<th>Baseline RAMs (HIV-1 RNA)</th>
<th>SVF Timepoint</th>
<th>Viral Load at SVF/CVF (c/mL)</th>
<th>SVF Timepoint RAMs (HIV-1 RNA)</th>
<th>Drug Sensitivity at SVF (Fold Change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A1, 54K</td>
<td>None</td>
<td>L74I</td>
<td>Week 20</td>
<td>373 / 456</td>
<td>E138E/A/K/T RPV (7.1) CAB (5.2) DTG (1.0)</td>
</tr>
<tr>
<td>M, Russia, A1, 23K</td>
<td>None</td>
<td>L74I</td>
<td>Week 28</td>
<td>287 / 299</td>
<td>K101E L74I RPV (2.6) CAB (6.7) DTG (2.2)</td>
</tr>
<tr>
<td>F, Russia, A1, 20K</td>
<td>None</td>
<td>L74I</td>
<td>Week 48</td>
<td>488 / 440</td>
<td>E138K L74I RPV (1.0) CAB (9.4) DTG (1.1)</td>
</tr>
</tbody>
</table>

FDA Declines to Approve Cabotegravir/Rilpivirine

DEC 21, 2019 | MICHAELA FLEMING

VIIIV Healthcare has announced the receipt of a complete response letter (CRL) from the US Food and Drug Administration (FDA) for its new drug application for cabotegravir and rilpivirine long-acting injectable to treat HIV-1 in virologically suppressed adults.

Cabotegravir is an integrase strand transfer inhibitor developed by VIIIV Healthcare and rilpivirine is a non-nucleoside reverse transcriptase inhibitor developed by Janssen Sciences. The cabotegravir and rilpivirine long-acting regimen is investigational and is not approved anywhere in the world.

According to the company, the reasons given in the CRL relate to chemistry manufacturing and controls. However, VIIIV reports that there have been no reported safety issues related to chemistry manufacturing and controls and that there is no change to the safety profile of the products used in clinical trials to date.

In April, the FDA accepted the new drug application for the product.

The submission was based on the global ATLAS (Antiretroviral Therapy as Long-Acting Suppression) and FLAIR (First Long-Acting Injectable Regimen) phase 3 studies. Combined, the studies included more than 1,100 patients from 16 countries and demonstrated that when injected monthly, cabotegravir/rilpivirine was as effective as a standard of care, daily, oral 3-drug regimen in maintaining viral suppression throughout the 48-week study period. These results were presented in March at the 2018 Conference on Retroviruses and Opportunistic Infections.

In the ATLAS study, 308 patients were enrolled in the treatment arm and received oral cabotegravir 30 mg + rilpivirine 25 mg once daily for 4 weeks for safety monitoring. Then, the participants went on to receive single 3 mL loading doses of cabotegravir long-acting (LA) 600 mg (200 mg/mL) and rilpivirine long-acting 900 mg (300 mg/mL) via intramuscular injection, followed by 2 mL intramuscular injections every 4+1 weeks of cabotegravir LA 400 mg and rilpivirine long-acting 600 mg.
**Fostemsavir**: new drug for “salvage” therapy

- Entry inhibitor, or gp120 attachment inhibitor
- Prodrug of temsavir
- Temsavir binds to gp120 (on virus), near CD4 binding site
- Prevents conformational change to gp120 needed for virus to attach to cell
- Virus accumulates in extracellular space and is removed by host
- Phase 3 study = **BRIGHTE** study
- 1st in class, so no cross-resistance
**Fostemsavir**: BRIGHTE study in heavily treatment-experienced adults with multi drug-resistant HIV, on failing ART regimen

BRIGHTE is an ongoing Phase 3 randomized, placebo-controlled, double-blind trial

**Randomized Cohort**: HTE participants failing current regimen with confirmed HIV-1 RNA $\geq 400$ c/mL and:
- 1 or 2 ARV classes remaining with $\geq 1$ fully active† approved agent per class
- Unable to construct viable regimen from remaining agents

**Non-randomized Cohort**: HTE participants failing current regimen with confirmed HIV-1 RNA $\geq 400$ c/mL and:
- 0 ARV classes remaining and no remaining fully active† approved agents‡

OBT = optimised background therapy  HTE = highly treatment experienced

Lataillade et al. IAS 2013; Mexico City, Mexico. Sides MCAB0102
**Fostemsavir: BRIGHTE study baseline characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo BID (N=69)</th>
<th>Randomized Cohort</th>
<th>Total randomized (N=272)</th>
<th>Non-randomized Cohort (N=99)</th>
<th>Total treated participants (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, median (range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years, n (%)</td>
<td>45 (19–66)</td>
<td>48 (18–73)</td>
<td>48 (18–73)</td>
<td>50 (17–72)</td>
<td>49 (17–73)</td>
</tr>
<tr>
<td></td>
<td>46 (67)</td>
<td>116 (57)</td>
<td>162 (60)</td>
<td>44 (44)</td>
<td>206 (56)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (17)</td>
<td>60 (30)</td>
<td>72 (26)</td>
<td>10 (10)</td>
<td>82 (22)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>48 (70)</td>
<td>137 (67)</td>
<td>185 (68)</td>
<td>74 (75)</td>
<td>259 (70)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>18 (26)</td>
<td>42 (21)</td>
<td>60 (22)</td>
<td>23 (23)</td>
<td>83 (22)</td>
</tr>
<tr>
<td><strong>HIV-1 RNA log_{10} c/mL, median (IQR)</strong></td>
<td>4.5 (3.6–5.2)</td>
<td>4.7 (4.0–5.1)</td>
<td>4.7 (3.9–5.1)</td>
<td>4.3 (3.6–4.8)</td>
<td>4.6 (3.9–5.0)</td>
</tr>
<tr>
<td><strong>HIV-1 RNA c/mL, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400</td>
<td>7 (10)</td>
<td>14 (7)</td>
<td>21 (8)</td>
<td>5 (5)</td>
<td>26 (7)</td>
</tr>
<tr>
<td>400 to &lt;1000</td>
<td>3 (4)</td>
<td>7 (3)</td>
<td>10 (4)</td>
<td>4 (4)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>1000 to &lt;100,000</td>
<td>35 (51)</td>
<td>126 (62)</td>
<td>161 (59)</td>
<td>75 (76)</td>
<td>236 (64)</td>
</tr>
<tr>
<td>≥100,000</td>
<td>24 (35)</td>
<td>56 (28)</td>
<td>80 (29)</td>
<td>15 (15)</td>
<td>95 (26)</td>
</tr>
<tr>
<td><strong>CD4+ T cells/μL, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 (23–244)</td>
<td>99 (15–203)</td>
<td>99 (15–203)</td>
<td>41 (6–161)</td>
<td></td>
<td>80 (11–202)</td>
</tr>
<tr>
<td><strong>CD4+ T cells/μL, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>17 (25)</td>
<td>55 (27)</td>
<td>72 (26)</td>
<td>40 (40)</td>
<td>112 (30)</td>
</tr>
<tr>
<td>20 to &lt;50</td>
<td>6 (9)</td>
<td>19 (9)</td>
<td>25 (9)</td>
<td>14 (14)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>50 to &lt;200</td>
<td>26 (38)</td>
<td>76 (37)</td>
<td>102 (37)</td>
<td>25 (25)</td>
<td>127 (34)</td>
</tr>
<tr>
<td>200 to &lt;500</td>
<td>16 (23)</td>
<td>42 (21)</td>
<td>58 (21)</td>
<td>18 (18)</td>
<td>78 (20)</td>
</tr>
<tr>
<td>≥500</td>
<td>4 (6)</td>
<td>11 (5)</td>
<td>15 (6)</td>
<td>2 (2)</td>
<td>17 (5)</td>
</tr>
<tr>
<td><em><em>AIDS history,</em> n (%)</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>320 (86)</td>
</tr>
</tbody>
</table>
Fostemsavir: BRIGHT study baseline characteristics

Most common ARV agents in initial OBT

Randomized Cohort (N=272)

<table>
<thead>
<tr>
<th>ARV</th>
<th>Fully active</th>
<th>Not fully active</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV (74% BID)</td>
<td>40</td>
<td>49</td>
</tr>
<tr>
<td>TFV (96% BID)</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>ETR</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>MVC</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>ENF</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

Non-randomized Cohort (N=99)

<table>
<thead>
<tr>
<th>ARV</th>
<th>Fully active</th>
<th>Not fully active</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV (92% BID)</td>
<td>75</td>
<td>24</td>
</tr>
<tr>
<td>TFV (96% TDF)</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>ETR</td>
<td>21</td>
<td>77</td>
</tr>
<tr>
<td>MVC</td>
<td>8</td>
<td>91</td>
</tr>
<tr>
<td>ENF</td>
<td>11</td>
<td>88</td>
</tr>
<tr>
<td>IBA</td>
<td>15</td>
<td>85</td>
</tr>
</tbody>
</table>

DRV, darunavir; DTG, dolutegravir; ENF, enfuvirtide; ETR, etravirine; IBA, ibalizumab; MVC, maraviroc; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102
Fostemsavir: BRIGHTE study results: % with VL <40

- Among randomized participants with CD4+ T-cell count <50 cells/μL at baseline (n=71), 56% had ≥200 cells/μL at Week 96.

- Adverse events: nausea, diarrhoea, headache, IRIS.

- Discontinuation in 14/272 randomised and 12/99 non-randomised, including for abdominal pain, QT prolongation, non-cardiac chest pain and hepatic failure.
The mAb

- Humanised IgG4 monoclonal Ab, blocking viral entry into CD4 cells ("postattachment inhibitor"). Tropism irrelevant.

- Single-arm study, n=40 with viral load >1000, resistance to ≥1 drug in ≥3 classes

- Loading dose 2000mg, then 800mg infusion every 2 weeks

- Plus… “OBR” or “OBT” (=optimised background regimen/therapy)

- Primary endpoint = proportion with decrease in VL at day 14
Ibalizumab: results of single-arm study

Emu, NEJM 2018
So what’s new?

- Quick look at current ART guidelines
- Two-drug regimens (2DR)
  - DTG/3TC
  - DTG/RPV
  - (DTG monotherapy)
  - DRV/3TC
- Bictegravir
- Doravirine
- Long acting injectables
- Fostemsavir
- Ibalizumab
So what’s new since the last BHIVA ART guidelines?

• Quick look at current ART guidelines
• Two-drug regimens (2DR)
  • DTG/3TC
  • DTG/RPV
  • (DTG monotherapy)
  • DRV/3TC
• Bictegravir
• Doravirine
• Long acting injectables
• Fostemsavir
• Ibalizumab

And things that there wasn’t enough time for.....

• Investigational NRTTI (islatravir... with DOR as 2DR?)
• RAL 1200mg od vs 400mg bd (ONCEMRK)
• D/C/F/TAF studies (AMBER, EMERALD)
• DAWNING – DTG vs LPV/r as second line, in low/middle income settings (DTG superior)
New antiretroviral drugs and trials

Clare van Halsema
Consultant in infectious diseases, North Manchester General Hospital

DipHIVMed revision day, Manchester, January 2020

Good luck!