ASHM ART guidelines session

Why HIV integrase inhibitors (InSTIs) are first-line agents of choice

ASHM Conference Brisbane 2015

Mark Boyd MD, FRACP
Senior NHMRC Research Fellow
The Kirby Institute
for infection and immunity in society
UNSW Australia

Why InSTIs are first-line agents of choice

Declarations

- AbbVie
- Bristol-Myers Squibb
- Boehringer Ingelheim
- Gilead
- Janssen-Cilag
- Merck
- ViiV Healthcare

Why InSTIs are first-line agents of choice

Outline

- Pivotal (blinded, placebo-controlled) InSTI studies
- Open label studies

Why InSTIs first-line agents of choice

Pivotal (blinded, placebo-controlled) InSTI studies

- STARTMRK: RAL versus EFV
  Phase III, non-inferiority trial, n=643

- GS-US-236-0102/0103: EVG versus EFV and ATV/r

- SINGLE: DTG versus EFV
  Randomised, double-blind trial, n=403

- SPRING-2: DTG versus RAL
  Saag MS et al. Lancet 2013;381:735-743
  Randomised, double-blind, active controlled, non-inferiority trial, n=822
**SPRING-2: virological response by baseline viral load and N(t)RTI backbone at week 96**

- Overall: 126/242 (52%), 106/242 (44%), 16/242 (7%)
- Mono 500 mg SD (≤ 100,000 c/mL): 18/67 (27%), 14/67 (21%), 6/67 (9%)
- Mono 500 mg SD (> 100,000 c/mL): 15/75 (20%), 12/75 (16%), 3/75 (4%)
- 3TC/FTC (both FDC): 18/39 (46%), 16/39 (41%), 5/39 (13%)
- 3TC/FTC (both FDC): 15/44 (34%), 12/44 (27%), 3/44 (7%)

- Proportion of DTG subjects achieving HIV-1 RNA <50 c/mL more pronounced in subjects with high baseline viral load, and in subjects receiving TDF/FTC.
- Subject numbers were small and confidence intervals wide and overlapping.

**Primary endpoints:**
- Virological success: HIV-1 RNA <50 c/mL
- Analysis of Week 48

**Outline**

- Pivotal (blinded, placebo-controlled) InSTI studies
- Open label studies

**Why InSTIs are first-line agents of choice**

- Open-label ART (N=1809)
- In favor of DTG
- In favor of DRV
- In favor of RAL

**ACTG 5257: study design**

- Treatment-naive
- HIV-1 RNA <1000 copies/mL
- Randomized by HIV-1 RNA (≤ 100,000 copies/mL) participation in metabolic substudy.

- Primary endpoint:
  - VF: time to HIV-1 RNA >1000 copies/mL (at Week 16 or before Week 24) or >200 copies/mL (at or after Week 24)
  - Tolerance failure: time to discontinuation of randomized component for toxicity
  - Composite endpoint: the washer occurrence of either VF or tolerability failure in a given participant
  - Switch of regimen allowed for tolerability

**FLAMINGO: efficacy snapshot at W48 & W96**

- Primary endpoint: HIV-1 RNA <50 copies/mL at Week 48

- Week 48 Virological success: 90/93 (97%), 68/71 (96%), 47/60 (79%)
- Week 98 Virological success: 83/83 (100%), 68/70 (97%), 47/60 (79%)

**FLAMINGO: phase III trial in ART-naïve PLH**

- Primary endpoint: HIV-1 RNA <50 copies/mL at Week 96
- MDMF algorithm
- Randomised phase (Day 1)
- Analysis: Week 96

**Why InSTIs are first-line agents of choice**

- Open label ATV/r versus DRV/r versus RAL as first-line ART (N=1809)

- ATV/r 300/100 mg OD plus TDF/FTC (n=811)
- RAL 400 mg BID plus TDF/FTC (n=811)
- DRV/r 800/100 mg QD plus TDF/FTC (n=811)

- Week 48 after last patients enrolled

---

**References**

ACTG 5257: primary endpoint analyses at W96

**VF**
- Regimens equivalent in time to VF

**Tolerability failure**
- Significantly greater incidence of treatment failure with ATV/r vs RAL or DRV/r in part due to high proportion of patients with hyperbilirubinemia

**Composite endpoint**
- RAL superior to either boosted PI
- DRV/r superior to ATV/r

**ACTG 5257: primary endpoint analyses at W96**

**Emergent resistance in Phase 3 trials in ART naive**

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Study</th>
<th>Resistance analysis population, n (%)</th>
<th>INSTI mutations</th>
<th>NRTI/RTI Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
<td>STARTMRK (n=279)</td>
<td>9 (3.2)</td>
<td>4 (1.4)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td></td>
<td>GDMRK (n=389)</td>
<td>16 (4.1)</td>
<td>2 (0.5)</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>EVG</td>
<td>102 (n=350)</td>
<td>14 (4)</td>
<td>2 (0.5)</td>
<td>7 (2)</td>
</tr>
<tr>
<td></td>
<td>103 (n=353)</td>
<td>12 (3.4)</td>
<td>4 (1.1)</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>DTG</td>
<td>SPRING-2 (n=411)</td>
<td>20 (4.9)</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>SINGLE (n=414)</td>
<td>18 (4.3)</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>FLAMINGO (n=234)</td>
<td>2 (0.8)</td>
<td>0 (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Selected DDIs of INSTIs**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potential DDIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
<td>- metabolized by UGT1A</td>
</tr>
<tr>
<td></td>
<td>- ATV increases RAL concentrations; dose adjustment not recommended</td>
</tr>
<tr>
<td></td>
<td>- avoid aluminum- and/or magnesium-containing antacids</td>
</tr>
<tr>
<td></td>
<td>- rifampin decreases RAL level; double RAL dose if co-administered with rifampin</td>
</tr>
<tr>
<td>EVG/Cobi</td>
<td>- metabolized by CYP3A, CYP2D6</td>
</tr>
<tr>
<td></td>
<td>- cobicistat increases levels of drugs metabolized by CYP3A</td>
</tr>
<tr>
<td></td>
<td>- separate dosing with aluminum- and/or magnesium-containing antacids</td>
</tr>
<tr>
<td></td>
<td>- not recommended for use with rifampin</td>
</tr>
<tr>
<td>DTG</td>
<td>- metabolized by UGT1A, with contribution from CYP3A</td>
</tr>
<tr>
<td></td>
<td>- avoid use with etravirine unless co-administered with boosted PI; avoid dosing with nevirapine</td>
</tr>
<tr>
<td></td>
<td>- separate dosing with aluminum- and/or magnesium-containing antacids</td>
</tr>
<tr>
<td></td>
<td>- DTG may increase metformin concentrations; metformin dose adjustment may be needed; monitor clinically when starting/stopping DTG</td>
</tr>
</tbody>
</table>