Adverse drug reactions associated with integrase strand transfer inhibitors (INSTI) in clinical practice: Post-marketing experience with raltegravir, elvitegravir-cobicistat and dolutegravir.

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Background

• The integrase strand transfer inhibitors (INSTI) have demonstrated safety and efficacy in clinical trials.
• This observational study compares adverse drug reactions (ADRs) reported with raltegravir, elvitegravir-cobicistat (in a fixed dose combination) and dolutegravir during routine clinical use in British Columbia (BC) Canada.

Methods

NOTE: The interim analysis presented in this poster has been updated to include results from the completed enrollment period 01-Jan-2012 to 31-Dec-14 (previously to 31-Aug-14) and interim follow-up period (extended to 30-Apr-15).

Inclusion criteria

• HIV-1-infected persons, either antiretroviral treatment naïve or treatment experienced.
• Age ≥19 years at the time of INSTI initiation.
• Raltegravir, elvitegravir-cobicistat or dolutegravir initiated as a component of the antiretroviral regimen between 01-Jan-2012 and 31-Dec-2014.
• Patients could contribute data for more than one INSTI.

Data sources

• Clinical, demographic and ADR data: BC Centre for Excellence in HIV/AIDS (BC-CIE) Drug Treatment Program and BC-CIE Pharmacovigilance Initiative.

Follow-up

• All patients had 24 months follow-up opportunity until 30-Apr-2015. Planned 212 months follow-up opportunity will continue until 31-Dec-2015.

Primary outcome and data analysis

• Primary outcome was any ADR resulting in INSTI discontinuation, excluding suspected ADRs with causality classification assessed as “unlikely”.
• ADR incidence density rates and 95% confidence intervals (CI95) were estimated by robust Poisson regression (controlled for under-dispersion) and adjusted for covariates.
• Raltegravir was the reference category for adjusted ADR rates.

Results

• Of 1347 INSTI-treated patients, 115/1347 (8.5%) contributed data for ≥2 INSTIs.
• The cohort included 1467 distinct INSTI-patient records: 553 raltegravir, 395 elvitegravir-cobicistat and 519 dolutegravir treated. See Table 1.

Table 1. Baseline patient characteristics at time of INSTI initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Raltegravir</th>
<th>Elvitegravir-Cobicistat</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) years</td>
<td>50 (43,56)</td>
<td>43 (34,50)</td>
<td>48 (40,55)</td>
</tr>
<tr>
<td>Sex, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>450 (81)</td>
<td>293 (74)</td>
<td>419 (81)</td>
</tr>
<tr>
<td>Female</td>
<td>103 (19)</td>
<td>102 (26)</td>
<td>100 (19)</td>
</tr>
<tr>
<td>CD4, median (IQR) cells/μl</td>
<td>440 (330,640)</td>
<td>470 (270,672)</td>
<td>530 (360,748)</td>
</tr>
<tr>
<td>Viral Load &lt;50 copies/mL, n(%)</td>
<td>307 (56)</td>
<td>175 (44)</td>
<td>348 (67)</td>
</tr>
<tr>
<td>Hepatitis C infection, n(%)</td>
<td>251 (45)</td>
<td>147 (37)</td>
<td>138 (27)</td>
</tr>
<tr>
<td>Previous ARV therapy, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment naïve</td>
<td>73 (13)</td>
<td>84 (21)</td>
<td>69 (13)</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>480 (87)</td>
<td>311 (79)</td>
<td>450 (87)</td>
</tr>
</tbody>
</table>

• For each INSTI, treatment duration, ADR rates and proportion of patients experiencing an ADR are summarized in Table 2.
• ADR rates are presented as both unadjusted and adjusted (for sex, antiretroviral treatment experience and hepatitis C co-infection) rates.

Table 2. Incidence of INSTI adverse drug reactions leading to therapy discontinuation

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Median (IQR) yr</th>
<th>Cumulative person-yr</th>
<th>Number (%) persons with ADR</th>
<th>Unadjusted ADR rate/person-year (CI95)</th>
<th>Adjusted ADR rate/person-year (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRV</td>
<td>1.0</td>
<td>86 (4.0,1.3)</td>
<td>36</td>
<td>2.8 (1.8-3.0)</td>
<td>1.9 (1.8-2.0)</td>
</tr>
<tr>
<td>Elv-C</td>
<td>1.0</td>
<td>86 (4.0,1.3)</td>
<td>36</td>
<td>2.8 (1.8-3.0)</td>
<td>1.9 (1.8-2.0)</td>
</tr>
<tr>
<td>Dolte</td>
<td>1.0</td>
<td>86 (4.0,1.3)</td>
<td>36</td>
<td>2.8 (1.8-3.0)</td>
<td>1.9 (1.8-2.0)</td>
</tr>
</tbody>
</table>

• Adjusted ADR relative rates (CI95) were:
  - Raltegravir (reference category) 1.0
  - Elvitegravir-cobicistat 2.8 (1.8-3.0)
  - Dolutegravir 1.9 (1.8-2.0)

• As shown in Figure 1, the most commonly reported ADR symptoms were:
  - O Gastrointestinal tract: Nausea, diarrhea, gastrointestinal discomfort.
  - Central nervous system: Sleep disturbance, nightmares, headache.
  - General: fatigue/malaise.

• No serious ADRs (grade IV severity or leading to hospitalization) were reported.

Conclusion

• All INSTIs were generally well tolerated.
• The newer INSTIs elvitegravir-cobicistat and dolutegravir had shorter follow-up times than raltegravir, but had relatively higher rates of ADRs resulting in therapy discontinuation in this interim analysis.
• The planned 12 month follow-up of this cohort will continue until 31-Dec-2015.