Primary resistance to integrase strand transfer inhibitors in patients infected with diverse HIV-1 subtypes in sub-Saharan Africa

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Introduction

• WHO since 2016 recommends the use of dolutegravir INSTI as an alternative first-line regimen for use in LMIC’s (WHO 2016 consolidated HIV treatment guidelines)

• Due to a rise in pre-treatment drug resistance (PDR), WHO provisional guidelines recommends use of dolutegravir as preferred first-line in countries with PDR ≥10% (WHO 2017 guidelines on response to pre-treatment HIV drug resistance)

• There is however limited information on primary INSTI resistance for non-B subtypes

• Studies also suggest subtype influence in the pattern of DTG resistance (Quashie PK et al, JVI 2012)
  – R263K mainly observed in subtype B
  – G118R observed in non-B subtypes and influenced by codon usage
Methods

**Aim:** To assess the prevalence of major and accessory INSTI resistance mutations, across diverse HIV-1 subtypes in sub-Saharan Africa

- Secondary aim: To assess codon usage at position G118 influencing occurrence of DTG resistance in non-B subtypes
• Prospective cohort study 2007-2016
• 6 Countries, 13 clinic sites
• 2733 patients initiating on first-line

6 countries, 13 clinical sites
Methods

- Study design: Baseline analysis of samples from 489 patients selected in a case-control, PASER sub-study to assess impact of minority variants
  - Cases - viral-load (VL) >400 cps/ml @ 12 months
  - 2 Controls matched on baseline Viral-load, CD4 counts, age and country
Methods

• Sequencing by Illumina Miseq NGS

• Sequence analysis: PASeq- automated HIVDR pipeline (IRSICaixa, Barcelona https://paseq.org

• Resistance classified by
  • Major DRM-IAS 2017 mutation list
  • Accessory DRM-IAS 2017 mutation list and with Stanford HIVdb ≥10 resistance penalty score
  • Resistance detection thresholds (≥20%, ≥10%, ≥5%, ≥2%, ≥1%)

• HIV subtyping by REGA v3.0
Results

• 425 (87%) of 489 samples successfully genotyped

• Uganda (25.2%), Zambia (23.5%), South Africa (22.8%), Kenya (21.2) and Nigeria (7.3%)

• Subtype C (48.7%), A (28.5%), D (10.1%), recombinants forms (9.9%) and G (2.8%)
  • AD (3.3%) CRF_02AG (2.1%), AC (1.4%) AG (0.9%), AG complex recombinants (1.4%) CD (0.5%), DG (0.2%)
Prevalence of primary INSTI resistance across major subtypes in sub-Saharan Africa

Major DRM ≥20% = 0%
≥1% = 2.8%
Access DRM ≥20% = 15.1%
≥1% = 23.5%

Any IAS major DRM
Any Accessory mutation

Subtypes:
- All
- A
- C
- D
- G
- Recombinants

Resistance:
- <2%
- 2-4%
- 5-10%
- 10-20%
- ≥20%
Patterns of major DRM to INSTI regimens

<table>
<thead>
<tr>
<th>Resistance Threshold(^a)</th>
<th>Raltegravir/Eviltegravir</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>0.7 0.5 - 0.7 0.2 0.7 0.2</td>
<td>0.7 0.2 0.2</td>
</tr>
<tr>
<td>92</td>
<td>0.2 - 0.2 - 0.2</td>
<td>0.2 0.2 0.2</td>
</tr>
<tr>
<td>121</td>
<td>0.2 - - - 0.2</td>
<td>0.2 - -</td>
</tr>
<tr>
<td>143</td>
<td>- - - - - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>147</td>
<td>- - - - - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>148</td>
<td>- - - - - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>155</td>
<td>- - - - - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>148</td>
<td>≥1%</td>
<td>0.2 0.2 0.2</td>
</tr>
<tr>
<td>155</td>
<td>≥2%</td>
<td>0.2 0.2 0.2</td>
</tr>
<tr>
<td>263</td>
<td>≥5%</td>
<td>0.2 - -</td>
</tr>
<tr>
<td>155</td>
<td>≥10%</td>
<td>- - - -</td>
</tr>
<tr>
<td>263</td>
<td>≥20%</td>
<td>- - - -</td>
</tr>
</tbody>
</table>

\(^a\)Cumulative resistance thresholds
## Variations of primary INSTI DRMs by subtype

<table>
<thead>
<tr>
<th>Variation</th>
<th>All (n=425)</th>
<th>A (n=121)</th>
<th>C (n=207)</th>
<th>D (n=43)</th>
<th>G (n=12)</th>
<th>Recombinants (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any major mut</td>
<td>2.8</td>
<td>2.5</td>
<td>3.4</td>
<td>-</td>
<td>8.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Any access mut</td>
<td>23.5</td>
<td>35.5</td>
<td>15.5</td>
<td>18.6</td>
<td>25.0</td>
<td>33.3</td>
</tr>
<tr>
<td>L</td>
<td>10.4</td>
<td>14.0</td>
<td>7.7</td>
<td>7.0</td>
<td>16.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Q</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.8</td>
</tr>
<tr>
<td>T</td>
<td>4.0</td>
<td>9.1</td>
<td>1.0</td>
<td>2.3</td>
<td>8.3</td>
<td>4.8</td>
</tr>
<tr>
<td>E</td>
<td>0.7</td>
<td>-</td>
<td>0.5</td>
<td>2.3</td>
<td>-</td>
<td>2.4</td>
</tr>
<tr>
<td>G</td>
<td>0.7</td>
<td>1.7</td>
<td>-</td>
<td>2.3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*≥1%*
## Codon usage for G118 polymorphisms by subtype

<table>
<thead>
<tr>
<th>Subtype (n)</th>
<th>GGA</th>
<th>GGG</th>
<th>GGC</th>
<th>GGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (425)</td>
<td>4 (17)</td>
<td>2.1 (9)</td>
<td>83.1 (353)</td>
<td>10.8 (46)</td>
</tr>
<tr>
<td>A (121)</td>
<td><strong>6.6 (8)</strong></td>
<td><strong>1.7 (2)</strong></td>
<td><strong>85.1 (103)</strong></td>
<td>6.6 (8)</td>
</tr>
<tr>
<td>C (207)</td>
<td>3.4 (7)</td>
<td>1.4 (3)</td>
<td>79.2 (164)</td>
<td>15.9 (33)</td>
</tr>
<tr>
<td>D (43)</td>
<td>2.3 (1)</td>
<td>-</td>
<td>97.7 (42)</td>
<td>-</td>
</tr>
<tr>
<td>G</td>
<td>-</td>
<td>-</td>
<td>91.7 (11)</td>
<td>8.3 (1)</td>
</tr>
<tr>
<td>Recombinants (42)</td>
<td><strong>2.4 (1)</strong></td>
<td><strong>9.5 (4)</strong></td>
<td><strong>78.6 (33)</strong></td>
<td><strong>9.5 (4)</strong></td>
</tr>
<tr>
<td>Subtype B (5128)</td>
<td><strong>1.4 (69)</strong></td>
<td><strong>0.2 (10)</strong></td>
<td><strong>91.8 (4707)</strong></td>
<td><strong>6.0 (307)</strong></td>
</tr>
</tbody>
</table>

GGA and GGG have low genetic barrier, single nucleotide transition from glycine to Arginine

- **GGA→AGA**, **GGG→AGG**

Compared to transversion or two step transition for GGC and GGT

- **GGC→AGA**, **GGT→AGA** or **GGC→CGC**, **GGT→CGT**

*Data source:* Brenner BG et al JAC 2016
Conclusion and recommendation

• Low prevalence of major INSTI resistance present only at <20% threshold, gives some assurance for DTG efficacy
  – Real-life data is still required due to limited knowledge on DRM patterns in non-subtype B viruses
  – Need to determine the role and frequency threshold at which the pre-existing minority INSTI variants are likely to be clinically relevant

• High frequency of G118 polymorphisms with low genetic barrier to resistance
  – Suggest need for resistance monitoring with DTG rollout due to risk of novel resistance patterns previously unobserved in subtype B strains
Acknowledgements

Special thanks to all study participants, study doctors, laboratory staff, study coordinators and data team

The PASER network
IrsiCaixa Barcelona
AIGHD Amsterdam & Kampala
PharmAccess Foundation
Academic Medical Centre, Amsterdam