The HLA-B*53 / HLA-C*04 Haplotype is Strongly Associated with DRESS Syndrome during Treatment with Raltegravir.

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**Background**

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, potentially life-threatening, T lymphocyte-mediated, hypersensitivity reaction that may occur during treatment with various drugs. Raltegravir-induced DRESS syndrome has previously been reported in four patients of African ethnicity and one patient of Hispanic ethnicity. We have recently cared for a further patient, of African ethnicity, with raltegravir-associated DRESS syndrome.

**Method**

We performed HLA testing in four patients who had developed DRESS syndrome during treatment with raltegravir. We then determined the potential site of binding of raltegravir within the HLA-B*53:01 peptide binding groove.

**Table: Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ Gender Ethnicity</th>
<th>Therapy at onset of DRESS syndrome (weeks of treatment)</th>
<th>Main clinical features of DRESS syndrome</th>
<th>Peak Creatinine (µmol/L)</th>
<th>ALT (U/L)</th>
<th>Eosinophil count (cells X10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44/ M African</td>
<td>Raltegravir (4)</td>
<td>Generalised rash, malaise, diarrhoea, no fever</td>
<td>149</td>
<td>295</td>
<td>1.9</td>
</tr>
<tr>
<td>2</td>
<td>64/ F African</td>
<td>Raltegravir (6)</td>
<td>Generalised rash, facial oedema, lymphadenopathy, no fever</td>
<td>520</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>46/ F African</td>
<td>Raltegravir (8)</td>
<td>Generalised rash, abdominal pain, lymphadenopathy, fever</td>
<td>65</td>
<td>N</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>55/ F African</td>
<td>Raltegravir (4)</td>
<td>Generalised rash, malaise, fever</td>
<td>617</td>
<td>N</td>
<td>1.3</td>
</tr>
<tr>
<td>5</td>
<td>39/ M African</td>
<td>Raltegravir (4)</td>
<td>Rash, oral ulcers, fever</td>
<td>147</td>
<td>N</td>
<td>1.3</td>
</tr>
<tr>
<td>6</td>
<td>18/ F Hispanic</td>
<td>Raltegravir (5)</td>
<td>Generalised rash, oedema of facehands and feet, lymphadenopathy, fever</td>
<td>153</td>
<td>N</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Raltegravir is shown within the peptide binding groove of HLA-B*53:01. The four polymorphic differences between HLA-B*53:01 and HLA-B*35:01, in the C-terminal end of the α1 helix are shown in blue cyan and green. The cyan oval indicates the 4-fluorobenzyl group of raltegravir which is predicted to bind to Asn77, the green amino acid present in the risk allele HLA-B*53:01 but not present in the closely related and apparently non-risk allele HLA-B*35:01.

The prevalence of the HLA-B*53:01 allele is approximately 10-20% in many African populations, approximately 6% in American Hispanics, and approximately 0.8% in American Caucasians. Therefore the probability of finding the HLA B*53 allele in three African patients and one Hispanic patient with DRESS syndrome is < 0.0005.

**Conclusions**

Patients with the HLA-B*53:01 allele are at risk of developing DRESS syndrome when treated with raltegravir. This allele is common (10-30% prevalence) in people of African ethnicity but rare (<1% prevalence) in people of European ethnicity. Computer modelling suggests that raltegravir may bind within the peptide binding groove of the HLA-B*53:01 molecule and alter the repertoire of peptides that are presented to CD8 lymphocytes, thus initiating a delayed hypersensitivity response.