Co-Receptor Tropism Determined by Genotypic Assay in HIV-1 non B subtypes Circulating in Cuba. Implications for Pathogenesis and Maraviro Resistance.

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Introduction

- The V3 loop of the HIV-1 envelope gene is involved in binding to the chemokine receptors CCR5 and CXCR4, thus determining viral tropism.
- R5-tropic viruses predominate at the time of initial HIV-1 infection and a switch to X4-tropic occurs in about 50% of patients in late-stage disease.
- Changes in V3 have been specifically associated with changes in susceptibility to entry inhibitors (Maraviroc, MVC).
- Despite the low prevalence rate of Cuban Epidemic (0.2%), it has been described an extremely high genetic diversity.
- Cuban recombinant CRF19_cpx has been associated to rapid progression to AIDS, CCRX4 co-receptor use, higher viral load and high levels of RANTES.

Aims

To determine the co-receptor use in different variants of Cuban HIV-1 strains and analyze the implication for the use of co-receptor inhibitors and pathogenesis.

Methods

Cross sectional study

Samples: 115 plasma samples received at IPK between January 2014-July 2016

Viral extraction

QIAamp viral RNA Mini Kit

RT-PCR

Nested-PCR

Sequencing

Con-trace co-receptor tropism

GenoType

GPA

Results

Figure 1. Phylogenetic Trees of the C2V3C3 region of 115 HIV-1 strains studied. (Evolutionary history was inferred using Maximum Likelihood method based on Tamura 3 parameters model of program Mega 6).

<table>
<thead>
<tr>
<th>HIV-1 Subtype</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>CRF20–23–24_BG</td>
<td>35 (30.4)</td>
</tr>
<tr>
<td>B</td>
<td>33 (28.7)</td>
</tr>
<tr>
<td>CRF18_cpx</td>
<td>10 (8.7)</td>
</tr>
<tr>
<td>CRF19_cpx</td>
<td>30 (26.1)</td>
</tr>
<tr>
<td>OTHERS</td>
<td>7 (6.1)</td>
</tr>
<tr>
<td>Total</td>
<td>115 (100.0)</td>
</tr>
</tbody>
</table>

Figure 2. Distribution of co-receptor use according to the HIV-1 subtypes.

- Overall, 60% of the viruses exhibited R5 phenotype, 14.8% were R5X4 and 25.2% were X4.
- CRF19_cpx virus was associated with phenotype X4 (46.7%, p=0.0047, OR: 3.96, CI: 1.59-9.84), with infection in young individuals (39.1%, between 15-30 years old. p=0.025, OR:3.548, CI:1.136-11.08).

Figure 3. Comparison of Viral Load and CD4 count according to prediction of viral phenotype

- Higher levels of viral load and lower CD4 counts among the virus R5X4/X4

Figure 4. Comparison of Viral Load according to the HIV-1 subtype detected in C2V3C3 region of env (A) and pol gene (B).

- Higher levels of Viral Load among the CRF19_cpx compared with other subtypes

Figure 5. Alignment of aminocaid sequence of gp120-V3 loop of HIV-1 and prediction of viral tropism for the different Cuban subtypes analyzed.

The comparison of the amino acid sequences of the V3 loop showed differences between the B and non-B subtypes (p=0.0001).

Figure 6. HIV-1 mutations associated to tropism change or Maraviro resistance

Mutations reported to be associated with Maraviro resistance were detected in 75.7% of the samples, in positions 11 (6.1%), 13 (49.6%), 25 (6.1%), 316 (7.0%), 323 (11.3%) and 319 (3.5%) of gp120, particularly in the recombinant forms CRF19_cpx and CRF_BGs.

Figure 7. Comparison of epidemiological and clinical characteristics of patients studied with prediction of phenotype.

Conclusions

The results support the hypothesis previously stated that CRF19_cpx viruses could be more pathogenics and would have limitations for the use of MVC. The high rate of mutations associated to MVC among non-B Cuban subtypes should be further studied.