Evolution of drug resistance in HIV infected patients remaining on a virologically failing cART regimen

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BACKGROUND

HIV treatment guidelines recommend that after confirmed virological failure a new regimen containing ≥3 mutations compared to HXB2 should be used. However, in everyday clinical practice, it may happen that patients with limited laboratory resources and a low level virion rebound (for example with a viral load >100,000 copies/ml) are kept on a virologically failing regimen probably due to perceived short-term benefit or other personal decisions. This strategy, for example, has the advantage of assuring a good adherence to the regimen as patients have already shown to tolerate the virologically failing regimen while it is uncertain that the new regimen will be accepted the same way. However, there is a main risk associated with this strategy: the accumulation of HIV drug resistance.

OBJECTIVES

- To describe the extent of drug resistance accumulation for a given regimen in patients with persistent viral load rebound or under just and its possible impact on loss of future options.
- To identify the predictors of resistance accumulation

METHODS

Among all patients of EuroSIDA with genotypic data available we studied all 110 people who fulfilled the following: had two genotypic tests performed at a time points (t0 and t1) over a period when viral load was ≥400 copies/ml and the regimen was unchanged (failing regimen containing ≥3 drug). All data were obtained from retrospective sequencing of stored samples. Sequence analysis of HVR-1 and RT reading frames was performed using the Trugene HIV-1 Genotyping Kit and OpenGene DNA Sequencing System (version 8.0) according to the manufacturer’s recommendation.

Assumption: drug resistance mutations (DRM) present at t0 were assumed to be still present at t1. DRM were those listed in the IAS document of April 2005 (www.iavrus.org).

We described the prevalence of DRM at t0 and the incidence of acquired mutations between t0 and t1. We also described mean values (and changes between t0 and t1) in the following parameters:
- Total number of AS-DRM
- Total number of amino-acid differences from HXB2 strain
- Genotypic sensitivity score of failing regimen (GSS_f, giving a score of 0 if drug resistant and intermediate if sensitive)

RESULTS

The main characteristics of the study population at t0 are shown in Table 1. Despite the fact that patients were not heavily pre-treated, on average, 10 only 1.1 drugs in the failing regimen were still active against their virus population according to Rega II. Specifically, at t0, ≥20 patients (18%) had a GSS_f of 0.5-1.5 and 51% had a GSS_f <0.5.

The median time between t0 and t1 was 6 months (range: 2-28). Seventy-five percent of the viral load values measured at t0 or t1 were in the 400-500,000 copies/ml range.

In the majority of patients the failing regimen was a treatment containing more than three drugs belonging to NRTI, NNRTI and PI classes (“other combinations”, Figure 1).

The prevalence of drug resistance at t0 was relatively high: the percentage of people with more than 0.5 resistance was 74.6% (n=83, 76.4% (n=84) with ≥1 major mutations and 51% of people with ≥3 minor PIs mutations).

Seventy-seven percent of patients (85 out of 110) acquired ≥1 mutation over t0-1 that was not already present at t0. 23 acquired >1 mutation: 21 (4.6%) had ≥2 major PIs and 82.7% (n=52) had ≥3 minor PIs mutations.

Mutations acquired from t0 to t1

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>48V</td>
<td>100</td>
</tr>
<tr>
<td>84V</td>
<td>60</td>
</tr>
<tr>
<td>184V</td>
<td>40</td>
</tr>
<tr>
<td>90L</td>
<td>20</td>
</tr>
<tr>
<td>71T</td>
<td>10</td>
</tr>
<tr>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>73S</td>
<td>5</td>
</tr>
<tr>
<td>77I</td>
<td>5</td>
</tr>
<tr>
<td>41L</td>
<td>5</td>
</tr>
<tr>
<td>181T</td>
<td>4</td>
</tr>
</tbody>
</table>

In conclusion, our results are in line with previous studies of patients in virologically failing cART regimens, showing that a large number of amino acid changes from HXB2 can accumulate over a period when viral load is >400 copies/mL and the regimen is unchanged.

Other options for treatment are available.

CONCLUSIONS

In patients kept on the same virologically failing cART regimen (≥400 copies/ml) for a median of 6 months, there was considerable accumulation of DRM. The loss of potential virologically active drugs for future options is likely to be the smallest in people with extensive resistance to the failing regimen and the greatest in those with little resistance.

Interestingly, however, group A (GSS_f >0.5) tended to accumulate the largest number of amino-acid changes from HXB2.

Characteristics of study population at t0 (n=110)

<table>
<thead>
<tr>
<th>Age, (years)</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Mode of HIV transmission</th>
<th>Viral load pre-ART</th>
<th>Viral load t0</th>
<th>Viral load t1</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-44</td>
<td>Male</td>
<td>Caucasian</td>
<td>IDU</td>
<td>0.5-1</td>
<td>0.5-1</td>
<td>0.5-1</td>
</tr>
<tr>
<td>45-54</td>
<td>Male</td>
<td>African</td>
<td>IDU</td>
<td>0.5-1</td>
<td>0.5-1</td>
<td>0.5-1</td>
</tr>
<tr>
<td>55-64</td>
<td>Male</td>
<td>Caucasian</td>
<td>IDU</td>
<td>0.5-1</td>
<td>0.5-1</td>
<td>0.5-1</td>
</tr>
<tr>
<td>65-74</td>
<td>Male</td>
<td>Caucasian</td>
<td>IDU</td>
<td>0.5-1</td>
<td>0.5-1</td>
<td>0.5-1</td>
</tr>
</tbody>
</table>

Number of drugs previously used – median (range) 4 (3-6)

Number of drug classes previously failed (6 months with VL>400) – median (range) 3 (2-3)

Other, n (%) 10 (9.1%)

IDU, n (%) 22 (20.0%)

Homosexual, n (%) 77 (70.0%)

Heterosexual, n (%) 33 (30.0%)

NRTIs, n (%) 87 (87.0%)

PIs, n (%) 37 (34.0%)

Other, n (%) 10 (9.0%)

Months of ART – median (range) 10 (6-58)

Month of cART – median (range) 0 (0-12)

Figure 1

Figure 2

Table 1

Table 2

Table 3

Table 4