CMV VIREMIA AND DISEASE IN PATIENTS WITH ADVANCED HIV INFECTION: A PROSPECTIVE STUDY

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BACKGROUND
- The prevalence of CMV viremia is about 30% in patients with HIV infection with ≤100 CD4 T-lymphocytes.
- CMV viremia is known to be a risk factor for developing CMV end-organ disease (EOD). However, the efficacy of CMV-specific treatment in patients with CMV viremia without evidence of EOD has not been fully demonstrated.
- Lack of anti-CMV immune function may be associated with the development of CMV disease in patients with advanced HIV.
- We hypothesize that antiretroviral treatment (HAART) that ensures a correct immune recovery, rather than anti-CMV specific treatment, is the best strategy to clear CMV viremia in patients without EOD.

AIM OF THE STUDY
- To evaluate the dynamics of CMV replication in patients with advanced CMV infection after HAART initiation.
- To study the recovery of specific immune response against CMV and its correlation with CMV-EOD development.

RESULTS
- Here we present the results of a pre-planned interim analysis to check the safety of this strategy.
- Patients disposition: on February 15, 2018 forty-nine patients were included. One patient was excluded due to CMV-EOD diagnosis (esophagitis) at baseline. They were 29 (60.4%) men and 19 (39.6%) women with mean (SD) age 43.2 (10.6) years. Twenty-four patients had completed the study period at the moment of interim analysis.
- Baseline characteristics:
  - Risk factor for HIV infection: heterosexual transmission 23 (47.9%), MSM 13 (27%), IDU 12 (25%).
  - Median (IQR) CD4 lymphocytes: 30.0 (17.5-60.0) cel/mm3, median HIV-VL: 486,000.0 (179,750.0-1,322,500.0) copies/mL.
  - Co-morbidities: 2 patients had Diabetes mellitus, 2 had had an stroke and 1 was receiving chemotherapy.
  - They were 17 naïve patients, 19 had previously received HAART but had abandoned treatment and 2 had persistently less than 100 CD4 cel/mm3 despite undetectable HIV-VL.
- Clinical evaluation: Two patients were lost to follow-up whereas 5 patients died, none of them related to CMV infection.

### Table 1

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Week 0 (n=48)</th>
<th>Week 4 (n=44)</th>
<th>Week 12 (n=36)</th>
<th>Week 24 (n=30)</th>
<th>Week 48 (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV INFECTION</td>
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<tr>
<td>CD4 T cell count (cell/mm3) [Median (IQR)]</td>
<td>30.0 (17.5-60.0)</td>
<td>120.0* (60.0-200.0)</td>
<td>135.0 (80.0-207.5)</td>
<td>140.0 (100.0-262.5)</td>
<td>170.0 (127.5-325.0)</td>
</tr>
<tr>
<td>HIV RNA (copies/mL)* [Median (IQR)]</td>
<td>486,000.0 (179,750.0-1,322,500.0)</td>
<td>394.0 (125.2-2,070.0)</td>
<td>187.0 (14.0-688.2)</td>
<td>72.0 (24.0-393.0)</td>
<td>36.5 (24.0-121.2)</td>
</tr>
<tr>
<td>Undetectable viral load (&lt;50 copies/mL [n (%)]</td>
<td>2 (4.2)</td>
<td>5 (11.4)</td>
<td>10 (27.8)</td>
<td>12 (40.0)</td>
<td>13 (54.2)</td>
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<tr>
<td>CMV infection</td>
<td></td>
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<tr>
<td>Positive CMV PCR [n (%)]</td>
<td>16 (33.3)</td>
<td>15 (34.1)</td>
<td>2 (5.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PCR CMV+ (cop/ml) [Median (IQR)]</td>
<td>15.218 (3,582-61,627)</td>
<td>1,956 (937-37,514)</td>
<td>51,088 (-)</td>
<td>(-)</td>
<td>(-)</td>
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<tr>
<td>CMV-Specific Immunological Response (QuantiFERON CMV®)</td>
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<tr>
<td>Reactive (Cut-Off &gt;0.2 IU/ml [n (%)]</td>
<td>39 (72.9)</td>
<td>13 (78.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>CMV-specific IFN-γ response [median (IQR)]</td>
<td>3.210 (1.115-6.730)</td>
<td>5.000 (1.790-8.025)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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</tbody>
</table>

PATIENTS AND METHODS
- Design: Prospective, observational on-going study of all adult patients (≥18 years old) with HIV infection and ≤100 (or ≤10%) CD4 T-lymphocytes at baseline.
- The recruitment period started in September 2015 and is still on-going.
- Sample size: we have planned to include 80 patients in order to have a complete follow-up of 70 patients (15% estimated loss to follow-up).
- Variables: HIV viral load (VL), CD4 T lymphocytes and CMV VL were determined at baseline, 4,12,24 and 48 weeks.
- The specific immune response against CMV was determined at baseline and at 48 weeks with QuantiFERON-CMV QuantiFERON® kit.
- Patients with CMV viremia with EOD at baseline were excluded from the study.
- Therapeutic strategy: Antiretroviral therapy was initiated in all patients. CMV specific therapy was initiated only in patients who developed CMV-EOD during the study period.
- Statistical analysis: Wilcoxon signed-rank sum was used to assess the evolution over time of CMV-specific immune response.

CONCLUSIONS
- Dynamics of CMV replication (table 3): twenty-one (41.6%) patients had detectable CMV viremia within the first 4 weeks of inclusion.
- At 12 weeks after TAR initiation only 2 (5.6%) patients had detectable CMV viremia. At 24 and 48 weeks the CMV VL was negative in all patients. We only registered 1 case of CMV-EOD (stomatitis) during the follow-up.
- CMV specific immune response (table 1): Thirty-five out of 48 (72.9%) patients had a positive CMV-specific immune response at baseline and 19 out of 24 (79.2%) patients at the end of the study. Four patients had an indeterminate QuantiFERON-CMV result at baseline. We observe a significant increase in the amount of CMV-specific IFN-γ response among the 24 patients who have already completed the study (p=0.007).
- We represent in figure 1 the CD4 lymphocytes cell count, HIV-VL, CMV VL and CMV-specific immune response evolution of the 24 patients who completed the study.

The prevalence of CMV viremia in patients with advanced HIV infection is high. However, the incidence of CMV-EOD is low due to the presence of specific immunological response to CMV, which quantitatively improves after starting HAART. These findings suggest that CMV specific treatment might not be necessary in these patients.