ULTRASTOP: Is remission achievable in chronically HIV-1 infected patients with low HIV DNA reservoir? 
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BACKGROUND: Viral remission is observed in elite controllers and post early-treatment controllers (PTCs). We show a good immune status and extremely low blood total cell-associated HIV DNA levels. ULTRASTOP investigates whether HIV remission after ART discontinuation can be achieved in long-term chronically infected patients with good immunological status and low HIV DNA levels.

METHODS: The proof-of-concept study was designed to involve 1 cohort of 5 patients (pts) with HIV-1 RNA <100 copies/mL (c/mL) as per Euro01 study, CD4≥500 cells/mm3, ≤424 CD4/CD8, nadir ≥400 c/mL, and no important organ damage or HIV-DNA ≥100 copies/106 PBMCs at ART discontinuation (ATI). Treatment was rescheduled in case of HIV RNA >100 c/mL or in ART-related clinical event. The primary endpoint was the percentage of patients who did not reach HIV data criteria at ART re-intervention. In cohort 2, testing was performed at 8 weeks post ATI.

RESULTS: Ten patients were enrolled in cohort 1, then 2, with median (min-max) duration of ART 5.3 years (3.0-15.5), viral suppression 4.9 years (2.9-8.3), CD4 nadir 495/mm3 (330-739), HIV-DNA levels 744 copies/106 PBMCs, <100 c/mL and no important organ damage or HIV-DNA ≥100 copies/106 PBMCs at ART discontinuation. In cohort 2, testing was performed at 8 weeks post ATI. None were virus viremic at cohort 2 time, with median (max-min) duration of ART 5.2 years (3.0-11.5), viral suppression 5.0 years (3.0-13.6), CD4 nadir 497/mm3 (330-739), HIV-DNA levels 744 copies/106 PBMCs, <100 c/mL and no important organ damage or HIV-DNA ≥100 copies/106 PBMCs at ART discontinuation.

CONCLUSIONS: Despite excellent immunological characteristics and low plasma HIV RNA levels, the occurrence of HIV RNA rebound was confirmed in 9/10 patients (90.0%) within 1 month post ATI. All patients quickly returned to baseline immune and virological parameters after prompt treatment resumption (TxR).

Objectives
- Primary objectives
  - To evaluate the proportion of patients with HIV RNA <400 c/mL 24 weeks after interruption of antiretroviral therapy
  - Failure is defined as:
    - A plasma HIV-1 RNA > 400 copies/mL confirmed by two successive tests between 2-4 weeks apart
    - Or a CD4 cell count < 400 cells/mm3
    - Or the occurrence of HIV-related (grade B or C of the CDC classification) failure
- Secondary objectives
  - To evaluate During ART interruption
    - Time to viral rebound
    - Changes in HIV DNA
  - After ART resumption
    - Time to viral suppression
    - CD4, CD8, changes
    - Clinical evolution

Study Design
- Cohort 1
  - n = 5
  - Completed
- Cohort 2
  - n = 5
  - Completed
- Cohort 3
  - n = 5
  - Suspended

Baseline Patients Characteristics
- n = 10
  - Age, year, median (IQR) 45.1 (37.0 – 48.0)
  - Male sex – n (%) 7 (70.0)
  - Duration of suppressed HIV viremia, years, median (IQR) 4.9 (3.3 – 7.0)
  - Duration of antiretroviral treatment, years, median (IQR) 5.3 (3.4 – 12.8)
  - Nadir CD4 cells /mm3, median (IQR) 495 (366 – 572)
  - Pre-HAART pVL, log10 copies/mL, median (IQR) 4.0 (3.6 – 4.4)
  - US pVL at inclusion cp/mL, median (IQR) 100% < 1 (1-1)
  - HLA B57 and/or B27 – n (%)
  - No AIDS history – n (%)

Dynamics of HIV RNA, DNA, and CD4 count following Treatment Interruption

<table>
<thead>
<tr>
<th>1/ 10 patient controlled pVL (&lt;400 cp/mL) at 48 weeks post ATI</th>
<th>HIV status</th>
<th>US HIV pVL cp/mL</th>
<th>HIV DNA copies/106 PBMC</th>
<th>CD4/mm3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt</td>
<td>cART at BL</td>
<td>Duration undetectable HIV pVL (years)</td>
<td>Pre-HAART pVL (log10 cp/mL)</td>
<td>Nadir CD4/mm3</td>
</tr>
<tr>
<td>1</td>
<td>TDF+FTC+RPV</td>
<td>3.5</td>
<td>4.4</td>
<td>572</td>
</tr>
<tr>
<td>2</td>
<td>ETR+RAL</td>
<td>7.0</td>
<td>3.6</td>
<td>343</td>
</tr>
<tr>
<td>3</td>
<td>TDF+FTC</td>
<td>7.0</td>
<td>4.2</td>
<td>366</td>
</tr>
<tr>
<td>4</td>
<td>DRV/r</td>
<td>6.9</td>
<td>5.0</td>
<td>547</td>
</tr>
<tr>
<td>5</td>
<td>TDF+FTC+RAL</td>
<td>2.9</td>
<td>4.5</td>
<td>442</td>
</tr>
<tr>
<td>6</td>
<td>TDF+FTC+MVC</td>
<td>3.3</td>
<td>2.3</td>
<td>566</td>
</tr>
<tr>
<td>7</td>
<td>TDF+FTC+DRV/r</td>
<td>3.0</td>
<td>4.2</td>
<td>330</td>
</tr>
<tr>
<td>8</td>
<td>TDF+FTC</td>
<td>8.3</td>
<td>3.0</td>
<td>377</td>
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<tr>
<td>9</td>
<td>DTG</td>
<td>3.8</td>
<td>3.6</td>
<td>739</td>
</tr>
<tr>
<td>10</td>
<td>ABC+STC+ATV</td>
<td>5.9</td>
<td>3.7</td>
<td>640</td>
</tr>
</tbody>
</table>

BL: baseline; VR: viral rebound; TR: Treatment resumption; LV: last visit

Conclusion
- In this pilot study of HIV chronically infected patients with baseline ultralow HIV cell-associated reservoir and excellent immune parameters:
  - 1/10 patient controlled pVL (<400 cp/mL) at 48 weeks post ATI
  - 9/10 patients rapidly reboanded within 1 month post ATI
- Low HIV DNA and high immune status are not sufficient for ART-free remission
- All patients quickly returned to baseline immune and virological parameters after prompt treatment resumption.