In chronically HIV-1-infected patients long-term antiretroviral therapy initiated above 500 CD4/mm³ achieves better HIV-1 reservoirs' depletion and T-cell count restoration

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PTC are characterized by\textsuperscript{1,2}:

- Early cART, within primary-infection (PHI)
- Weak viral reservoir (HIV-DNA <2.3 log/10^6 PBMC)
- High immune restoration (CD4 \approx 900/mm^3, CD4/CD8 >1)

900-1000 CD4/mm^3 is the median count in HIV-uninfected people\textsuperscript{3}

\textsuperscript{1} Saez-Cirion, PLoS Pathogens 2013
\textsuperscript{2} ANRS Symposium – IAS 2013
\textsuperscript{3} Le, NEJM 2013
Our group also has shown that cART started at PHI induces:
- Deep depletion of the viral reservoir
- Better CD4 (>500) and CD4/CD8 (>1) restoration

It is uncertain how long after PHI such viro-immunologic benefit remains possible
- What about chronically-infected patients (CHI) with CD4 nadir ≥ 500/mm³?
Objectives

- We designed a composite primary endpoint (PEP): the proportion of chronically-infected patients (i.e. Fiebig VI) under efficient cART achieving
  - a normal CD4+ T cell count ($\geq 900$/mm$^3$)
  - AND a normal CD4/CD8 ratio ($>1$)
  - AND a low HIV-DNA level ($<2.3$ Log cp/$10^6$ PBMC) according to their CD4 nadir

- Secondary endpoint:
  - % achieving the same status with CD4+ T cell count $\geq 500$/mm$^3$

- Factors leading to the primary endpoint were determined (Cox proportional-hazards regression)
Patients and methods

- Monocentric, longitudinal study in a prospective French cohort (Orléans)
- Including HIV-1-infected adults
  - treated at the chronic phase (Fiebig VI)
  - whatever the nadir CD4 count (≥500, 200-499, <200)
  - whose VL became/remained <50 cp/mL under cART
  - ‘blip’ accepted between 50-200 cp/mL

- Data collected
  - Demographic data, contam. modal, CDC stage, hepatitis co-infection
  - CD4 nadir and highest plasma VL
  - CD4, CD8 and plasma VL (every 3-4 months)
  - Total cell-associated HIV-DNA in the PBMC (Biocentric, Bandol, France)
    (before treatment, when possible, then at least once a year)
  - HLA B*, activation markers (CD38, HLA-DR)

- Individual CD4 count, CD4/CD8 ratio and HIV-DNA curves over time were modeled to avoid fluctuations around the values of interest
Results (1)

From 2005 to 2012:

- 309 patients with sustained undetectable VL were included in the study
- Follow-up with undetectable VL:
  - Overall: 1407 patient-years
  - Median: 3.7y (IQR:1.5-6.8)
  - Mean: 4.6y ± 3.9 (SD)
- Overall measurements:
  - CD4, CD4/CD8 and plasma VL (n=4900)
  - HIV-DNA (n=1500)
    - In 77/309 patients (25%) HIV-DNA was determined before cART initiation
- No patient met primary/secondary endpoint before cART initiation
## Results (2) : patients characteristics

<table>
<thead>
<tr>
<th>Median or %</th>
<th>≥500 (n=30)</th>
<th>200-499 (n=155)</th>
<th>&lt;200 (n=124)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34</td>
<td>39</td>
<td>40</td>
<td>0.047</td>
</tr>
<tr>
<td>Sex M, %</td>
<td>73%</td>
<td>52%</td>
<td>56%</td>
<td>0.11</td>
</tr>
<tr>
<td>White ethnicity, %</td>
<td>60%</td>
<td>54%</td>
<td>54%</td>
<td>0.8</td>
</tr>
<tr>
<td>MSM, %</td>
<td>40%</td>
<td>34%</td>
<td>27%</td>
<td>0.3</td>
</tr>
<tr>
<td>AIDS-related illnesses, %</td>
<td>10%*</td>
<td>7%</td>
<td>36%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nadir CD4 count, per mm(^3)</td>
<td>577</td>
<td>292</td>
<td>101</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Highest VL, Log cp/mL</td>
<td>4.6</td>
<td>5.0</td>
<td>5.3</td>
<td>0.0004</td>
</tr>
<tr>
<td>Time from diagn. to cART, y</td>
<td>0.9</td>
<td>1.5</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Current cART, PI-based, %</td>
<td>47%</td>
<td>47%</td>
<td>44%</td>
<td>0.9</td>
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* Tuberculosis
Overall, HIV-DNA correlated negatively with CD4 count during suppressive cART
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<td>2.0 (0.5-4.6)</td>
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<td>Last CD4/mm³</td>
<td>1011</td>
<td>662</td>
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<td>Last CD4/CD8</td>
<td>1.25</td>
<td>0.88</td>
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<td>HIV-DNA, Log cp/10^6 PBMC</td>
<td>2.51 (1.9-2.8)</td>
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<td>% with all 3 objectives (CD4 ≥900)</td>
<td>30%</td>
<td>3%</td>
<td>0%</td>
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<tr>
<td>% with all 3 objectives (CD4 ≥500)</td>
<td>30%</td>
<td>7%</td>
<td>2%</td>
<td>0.0001</td>
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Results (5) : predictive factor

- In a Cox model, nadir CD4 count ≥500/mm$^3$ was the only predictor of achieving the primary endpoint: HR = 56 (95%CI: 15-209), p<0.0001

Kaplan-Meier estimates of the probability of achieving PEP according to the nadir CD4 stratification
In the sub-group (n=77) where HIV-DNA was determined before cART initiation:

- Nadir CD4 ≥500 was associated with slightly lower HIV-DNA level before cART initiation.
Results (6)

- In the sub-group (n=77) where HIV-DNA was determined before cART initiation:
  - Nadir CD4 ≥500 was associated with slightly lower HIV-DNA level before cART initiation.
  - Whereas median HIV-DNA decrease was similar after one year of viral suppression under cART.
Limits

- Cohort study
- Short follow-up for the upper stratum (CHI$_{>500}$)
- Needs to be validated in other cohorts / trials
Discussion - Conclusions

- Our results support early treatment, even in patients with high CD4 count

- One third of CHI_{>500} achieved a ‘normal’ T cell count (CD4 ≥900/mm^3 and CD4/CD8 >1) together with a low viral reservoir
  - no less than those treated at PHI (unpublished personal data)
  - as seen in most of PTC
  - whereas CHI-infected pts treated <500 CD4 are unlikely to achieve it

- In CHI_{>500}, a lower pre-therapeutic HIV-DNA level is likely to explain part of this good viro-immunologic outcome

- CHI_{>500} may be better candidates to benefit from a therapeutic vaccine and / or drugs emptying viral reservoirs
  (and thus to achieve a functional cure?)
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ANRS AC32 Group

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