Infection à VIH :
une rémission possible

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Viral reservoirs persist in HIV-infected individuals receiving cART

Finzi et al. Cells 1997
Viral replication resumes as soon as therapy is interrupted
Targeting viral reservoirs

Draining ➔ Eradication

Limiting ➔ Remission
HIV controllers (HIC): infected individuals spontaneously controlling HIV-1 infection

- Optimal T response
- Preserved immune functions
- Repression of viral reservoir
- Reduced dynamics of viral replication
- Attenuated virus
- Cell restriction
- Innate responses (NK/pDC)

Pancino and Saez-Cirion. Immunological Reviews. 2013
Favorable genetic background and Efficient CD8 T cell responses are associated with control

- Greater and faster upregulation of cytotoxic mediators
- MHC and TCR plasticity—Chen et al Nat Immunol 2012; Pereyra et al Science 2010; Bailey et al JEM 2006
Is it possible to induce a HIV controller-like status?

VISCONTI Study
Virological and Immunological Studies in CONtrollers after Treatment Interruption
ANRS VISCONTI: Post-Treatment Controllers (PTC)

Therapy started within 10 weeks following Primary Infection
Therapy started 39 days p.i.

3 years on therapy followed by 7.5 years of control off therapy

Saez-Cirion et al PLoS Path 2013
Post-treatment controllers have a tougher primary infection than HIV controllers

Saez-Cirion et al PLoS Path 2013
Post-treatment controllers don’t have a favorable MHC background
Post-treatment controllers have weak HIV-specific CD8+ T cell responses

Saez-Cirion et al PLoS Path 2013
Post-treatment controllers have weak levels of T cell activation
Post-treatment controllers have low levels of HIV-1 DNA in PBMC, which further decreased after treatment interruption in some cases.

Saez-Cirion et al PLoS Path 2013
Skewed CD4 subsets distribution in PTC impacts the subsets contribution to the HIV reservoir

Resting CD4 Cell Subsets Contribution to the HIV reservoir

- A contribution to the HIV reservoir:
  - Major for TTM subset
  - Low for the TN and TCM subsets

Saez-Cirion et al PLoS Path 2013
A long-term treatment initiated during primary infection seems to increase the chances to control viremia

Natural control of infection: 81 HIC from 34 317 patients followed-up: 0.24%

Early treatment induced control of infection:
Hocqueloux et al AIDS 2010: N=32 patients, 15.6% VL<50 at M24
Goujard et al Antivir Ther 2013: N=164 patients, 8.5% VL<50 at M24

3538 patients included in the FHDH within 6 months of primary infection 1997-2011

756 patients treated within 6 months and at least for a year

74 patients with a viral load below <50 RNA copies/ml who stop

Probability to keep controlling infection at 24M (loss of control: 2VL>50 RNA copies/ml or 1VL>50 RNA copies/ml +cART) : 15.7% [6.5-28.5]

Saez-Cirion et al PLoS Path 2013
<table>
<thead>
<tr>
<th>HIV controllers (HIC)</th>
<th>Post-Treatment Controllers (PTC)</th>
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</thead>
<tbody>
<tr>
<td><strong>Asymptomatic</strong> primary infection, <strong>low viral loads</strong> and <strong>high CD4 T cell counts</strong> in PHI</td>
<td><strong>Symptomatic</strong> primary infection, <strong>high viral loads</strong> and <strong>low CD4 T cell counts</strong> in PHI</td>
</tr>
<tr>
<td>80% HIC carry one <strong>protective HLA-class I allele</strong></td>
<td>57% PTC carry one <strong>HLA-class I allele</strong> associated with <strong>high viral loads</strong></td>
</tr>
<tr>
<td>Generally <strong>strong</strong> HIV-specific T cell responses with strong capacity to eliminate infected cells</td>
<td>Generally very <strong>weak</strong> HIV-specific T cell responses with poor capacity to eliminate infected cells</td>
</tr>
<tr>
<td>Abnormal <strong>high</strong> levels of <strong>T cell activation</strong></td>
<td><strong>Low</strong> levels of <strong>T cell activation</strong></td>
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<tr>
<td>Estimated <strong>frequency</strong>: 0.5% of HIV infected patients</td>
<td>Estimated <strong>frequency</strong>: 5-15% of HIV infected patients interrupting a &gt;12 months-length treatment initiated in primary infection</td>
</tr>
</tbody>
</table>
Conclusions from the VISCONTI study

We have identified a group of HIV patients in virological remission, who are able to maintain a durable control of viral replication after treatment interruption.

Overall, these patients have a different HLA profile, lower frequency and quality of HIV-specific CD8+ T cell responses, and lower CD8+ T cell activation than “natural” HIV controllers.

Post-treatment controllers have a weak HIV reservoir in which there is a minor contribution of long-lived cells.

Post-treatment control Patients in the VISCONTI study was likely achieved through early and long-lasting therapeutic intervention.
cART initiation during primary infection deeply impacts on HIV reservoirs

Hocqueloux et al, JAC 2013
However, a weak HIV reservoir is not enough

Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication

Tae-Wook Chun, J. Shawn Justement, Danielle Murray, Claire W. Hallahan, Janine Maenza, Ann C. Collier, Prameet M. Sheth, Rupert Kaul, Mario Ostrowski, Susan Moir, Colin Kovacs and Anthony S. Fauci

![Graph showing rebound of plasma viremia after discontinuation of ARV therapy.](image-url)
**EARLY TREATMENT**

Limiting the establishment of the viral reservoir
- Limiting viral diversity
- Reducing immune activation
- Preserving and cooperating with immune responses

Limiting the dynamics of viral replication in acute infection may be crucial for spontaneous control of infection
HIV remission in a 28-month old Perinatally-infected child (Mississippi Toddler)

![Graph showing HIV-1 RNA levels over time and drug regimens.]

- **HIV-1 RNA (copies/ml)**
  - 19,812 c/ml (4.3 log)
  - 2,617 c/ml (3.4 log)
  - 516 c/ml (2.7 log)
  - 265 c/ml (2.4 log)
  - <48 c/ml (<1.68 log)

- **Age (days)**
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100

- **Months of Life**
  - 0
  - 20
  - 25
  - 30

**Closed symbols = Detectable**
**Open Symbols = Undetectable Viral Load**

**Off ART:**
Plasma HIV RNA undetectable
HIV ELISA Negative
HIV-DNA PCR Negative

**Regimen #1:** AZT/3TC/NVP (31 hours - 7 days of life)
**Regimen #2:** AZT/3TC/LPV/ritonavir (7 days - 18 months of life)

Persaud et al, CROI 2013
World-wide observations of post-treatment controllers

Remember: treatment interruption is not recommended outside structured protocols!!!
OBJECTIVES

• To build an international cohort of Post Treatment Controllers in order to:
  – Uncover mechanisms underlying viral control, i.e. HIV remission
  – Identify predictive markers associated with viral control after treatment interruption

• Main Outcome:
  To identify patients in whom HAART could be safely interrupted

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Patients and clinicians who participate in the studies

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