Impact of 12 month HAART on cell associated HIV-DNA in acute primary HIV-1 infection: The OPTIPRIM-ANRS 147 trial

HIV-DNA and immunity at the time of primary HIV infection

Primary infection: immune homeostasis is skewed with a cytokin storm

Stacey R; J.Virol, 2008
Immune activation is correlated with HIV-DNA level

Laurence weiss (Towards an HIV cure, July 2013)
HIV-DNA level varies according to the stage of HIV infection

- The highest level are found during primary HIV infection and AIDS patient.

**HIV-DNA in PBMC: Natural history of HIV infection**

(ANRS cohort studies)

- Rouzioux, *JID* 2005
- Martinez, *JID* 2005
- Lambotte, *JID* 2005
- PRIMO inclusion
- SEROCO inclusion
- LTNP
- HIC
- VISCONTI

**AIDS** Avettand-Fenoel 2010

**VISCONTI**

Hocqueloux, *Aids* 2010

Saez-Cirion 2013

- HIV-DNA level varies according to the stage of HIV infection
- The highest level are found during primary HIV infection and AIDS patient.
HIV Reservoirs and ARV Treatment

Non linear mixed effects model

Chronic HIV treated patients N= 135

Primary HIV infection treated patients N= 22

Hoqueloux et al JAC 2013

1- S.Yerly, AIDS 2000
2- Gianella sara, Antiviral Therapy 2011;16:535-545
**Very early intervention** with potent and well tolerated 5 drugs regimen may have

- a greater impact on cell-associated HIV-DNA levels than standard 3 drugs PI based ART
- a greater impact on immune restoration and decrease of activation/inflammation

**Primary Endpoint**

- Level comparison of cell-associated HIV-DNA (log10/10^6 PBMC) at M24 between the 2 treatment arms

**Inclusion Criteria : (Randomization 1:1)**

**Subjects with acute or early HIV-1 infection :**

- HIV-1 Western Blot ≤ 4 antibodies
- HIV-RNA >50copies/ml
- symptomatic PHI
- asymptomatic PHI if CD4<500 /mm3
ANRS 147 OPTIPRIM: Study design

**Arm 1 (N=45):**
- Darunavir/R: 800/100 mg QD
- Tenofovir/emtricitabine: 245/200 mg QD
- Raltegravir: 400 mg BID
- Maraviroc: 150 mg BID

**Arm 2 (N=45):**
- Darunavir/R: 800/100 mg QD
- Tenofovir/emtricitabine: 245/200 mg QD

**Primary end-point:** July 2013
HIV-DNA level at M24

**Secondary Endpoints**
- **Virologic:** HIV-DNA and HIV-RNA kinetics
- **Immunologic:** CD4 and CD4/CD8 changes
- **Tolerance:** 5 drugs or 3 drugs
- **Physiopathological studies:** for example
  - HIV-RNA in semen and Rectal HIV-DNA biopsy
  - innate and HIV specific immunity
## Baseline characteristics

<table>
<thead>
<tr>
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<th>N=90</th>
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<tbody>
<tr>
<td>Men</td>
<td>92.2%</td>
</tr>
<tr>
<td>MSM</td>
<td>75.6%</td>
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<tr>
<td>Age, Median,[IQR]</td>
<td>35.5 [28 – 44] years</td>
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<tr>
<td>Symptomatic PHI</td>
<td>97%</td>
</tr>
<tr>
<td>Acute: 0 - 1 Ab on HIV-1 Western Blot(a)</td>
<td>43%</td>
</tr>
<tr>
<td>HIV-RNA log copies/ml (Abbott, Roche)</td>
<td>5.4 [4.9 - 5.8]</td>
</tr>
<tr>
<td>HIV-DNA log cp/million PBMC (technique ANRS comercialized by Biocentric)</td>
<td>3.6 [3.4 - 4.1]</td>
</tr>
<tr>
<td>CD4+ T cell /mm(^3)</td>
<td>472 [368 – 640]</td>
</tr>
</tbody>
</table>

\(a\)(in the previous 7 days)
90 patients randomized

2 patients drop out, soon after enrolment (pregnancy, patient decision)

Tolerance:

- well tolerated (survey adherence)
- 2 serious adverse side effects (both in the 3 drugs arm)
  - 1 lipodystrophy (20 kgs within a year)
  - 1 moderate acute pancreatitis
Immunology: CD4+ T cells kinetic

Median TCD4 gain: +235/mm³ [119-378.5]
Median CD4/CD8: 1.13 [0.87-1.38]
Virology: HIV-RNA < 50 copies/mL

Percentage of patients with HIV-RNA <50 copies/mL

- M1: 8%
- M3: 50%
- M6: 83%
- M12: 93%
HIV-DNA Decrease over time

ANRS PRIMO Cohort: 325 patients
Median delta HIV-DNA M12: -0.81[-1.14;-0.51]
(data not published)

Quest Cohort: 56 patients
Median delta HIV-DNA M12: -1.1[-1.6;-0.8]
(B.Hoen, CID 2007)
Factors associated with HIV-DNA decrease at Month 12

<table>
<thead>
<tr>
<th>Baseline characteristics (N=67)</th>
<th>Delta HIV-DNA at Month 12 (r corrélation coefficient)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Time from PIS</td>
<td>0.15</td>
<td>0.26</td>
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<tr>
<td>CD4 cell count</td>
<td>0.0003</td>
<td>0.99</td>
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<tr>
<td>log HIV-RNA (cop/ml)</td>
<td>-0.37</td>
<td>0.002</td>
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<tr>
<td>LogHIV-DNA (cop/million PBMCs)</td>
<td>-0.31</td>
<td>0.01</td>
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HIV-1 Reservoir in T CD4 subsets

- skewed CD4 subsets distribution, loss of TN, TCM for the benefit of the more differentiated TTM and TEM

A.chéret, C.Bacchus, C.Rouzioux Plosone 2013 Mai

a high HIV-DNA level.
This is the first randomized study targeting reservoir in the early phase of PHI.

Despite a virological and immunological storm, administrated early treatment is effective as soon as the first three months.

The effectiveness of this therapeutic approach on the reservoir and the immune system is:

- clearly higher than that observed in chronic treated patients at M12.
- related to the excellent tolerance and adherence whatever the treatment arm.
- probably conditioned by the early protection of cells with a long half-life (TN, TCM). Responses in few months with the final results.
CONCLUSION

- We are definitely convinced that treating at the time of primary infection might prepare patients as good candidates for treatment aiming at reducing reservoirs.
- This might be one the first steps for an HIV CURE or an HIV functional CURE.
## Acknowledgements

<table>
<thead>
<tr>
<th>Principal Investigators</th>
<th>MEC / co-investigators</th>
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<td>Centre Hospitalier du Pays d'Aix</td>
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<td>CHAS Julie, L'YAVANC Thomas</td>
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<td>Paris</td>
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**Scientific committee**

- Christine ROUZIOUX
- Laurence MEYER
- Caroline LASCOUX-COMBE
- Annie LE PALEC
- Alain VENET
- Antoine CHERET
- Brigitte AUTRAN
- Cécile GOUJARD
- Gianfranco PANCINO
- Yann MAZENS
- Isabelle RAVAUX
- Georges NEMBOT
- Daniel OLIVE
- Alain LAFEUILLADE
- Philippe HALFON
- Bruno HOEN
- Catherine TAMALET
- Bruno SPIRE
- Jean-Marc TRELUYER
- Sandrine COUFFIN CADIERGUES
- Juliette SAILLARD

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