In chronically HIV-1-infected patients long-term antiretroviral therapy initiated above 500 CD4/mm^3 achieves better HIV-1 reservoirs' depletion and T-cell count restoration

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IAS 2013 Towards an HIV Cure Symposium

Background (1)

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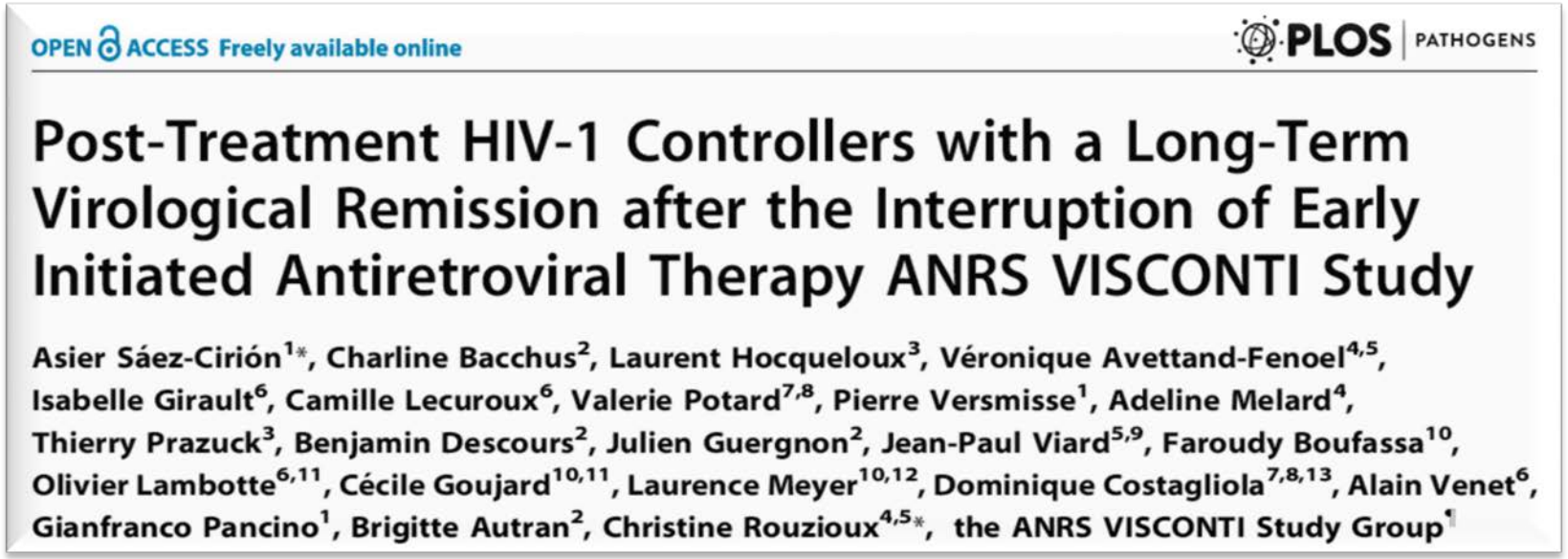

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PLOS | PATHOGENS

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión[1*], Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5*], the ANRS VISCONTI Study Group[¶]

- PTC are characterized by[1,2]:
  - Early cART, within primary-infection (PHI)
  - Weak viral reservoir (HIV-DNA <2.3 log/10^6 PBMC)
  - High immune restoration (CD4 ≈ 900/mm^3, CD4/CD8 >1)

- 900-1000 CD4/mm^3 is the median count in HIV-uninfected people[3]

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[1] Saez-Cirion, PLoS Pathogens 2013
[2] ANRS Symposium – IAS 2013
[3] Le, NEJM 2013

Background (2)

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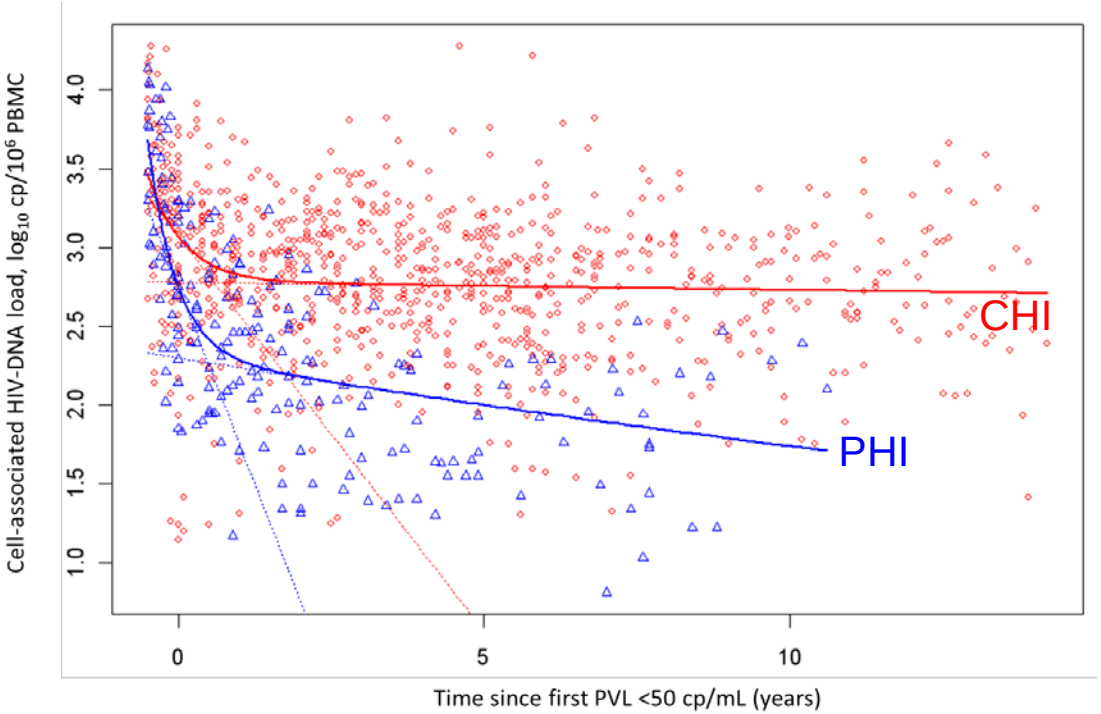
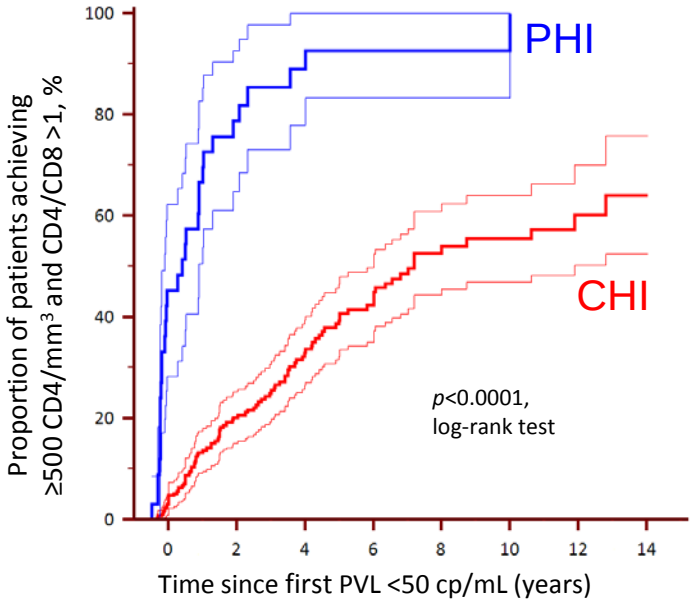
- Our group also has shown that cART started at PHI induces[1]:
  - Deep depletion of the viral reservoir
  - Better CD4 (>500) and CD4/CD8 (>1) restoration





- It is uncertain how long after PHI such viro-immunologic benefit remains possible
  - What about chronically-infected patients (CHI) with CD4 nadir ≥ 500/mm^3 ?

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[1] Hocqueloux, JAC 2013

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 (≥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 ≥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)

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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

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Median or %	≥500 (n=30)	200-499 (n=155)	<200 (n=124)	P-value
Age, y	34	39	40	0.047
Sex M, %	73%	52%	56%	0.11
White ethnicity, %	60%	54%	54%	0.8
MSM, %	40%	34%	27%	0.3
AIDS-related illnesses, %	10%*	7%	36%	<0.0001
Nadir CD4 count, per mm^3	577	292	101	<0.0001
Highest VL, Log cp/mL	4.6	5.0	5.3	0.0004
Time from diagn. to cART, y	0.9	1.5	0.2	0.02
Current cART, PI-based, %	47%	47%	44%	0.9

* Tuberculosis

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Results (3)

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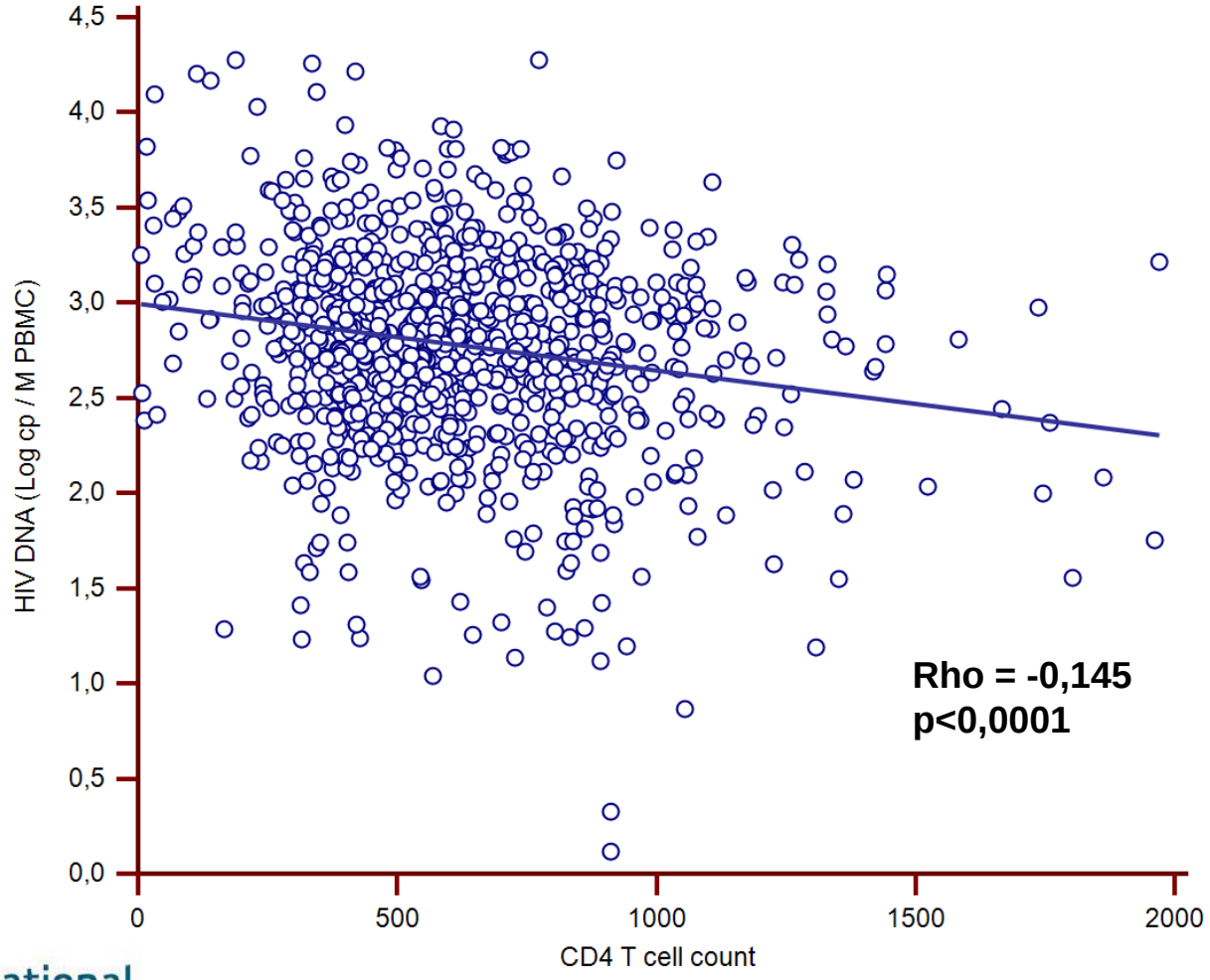
- Overall, HIV-DNA correlated negatively with CD4 count during suppressive cART



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Immuno-virologic parameters at last visit

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Median (IQR) or %	≥500 (n=30)	200-499 (n=155)	<200 (n=124)	P-value
VL<50 cp/mL, y	2.0 (0.5-4.6)	3.3 (1.4-6.2)	4.6 (2.1-8.1)	0.003
Last CD4/mm^3	1011	662	515	<0.0001
Last CD4/CD8	1.25	0.88	0.66	<0.0001
HIV-DNA, Log cp/10^6 PBMC	2.51 (1.9-2.8)	2.78 (2.4-3.1)	2.91 (2.6-3.1)	0.0009

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Last CD4/mm^3	1011	662	515	<0.0001
% with CD4 ≥900	67%	12%	6%	<0.0001
% with CD4 ≥500	100%	76%	50%	<0.0001
Last CD4/CD8	1.25	0.88	0.66	<0.0001
% with CD4/CD8 >1	73%	36%	16%	<0.0001
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% with HIV-DNA <2.3	39%	21%	11%	0.001

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% with HIV-DNA <2.3	39%	21%	11%	0.001
% with all 3 objectives (CD4 ≥900)	**30%**	**3%**	**0%**	**<0.0001**
% with all 3 objectives (CD4 ≥500)	30%	7%	2%	0.0001

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Results (5) : predictive factor

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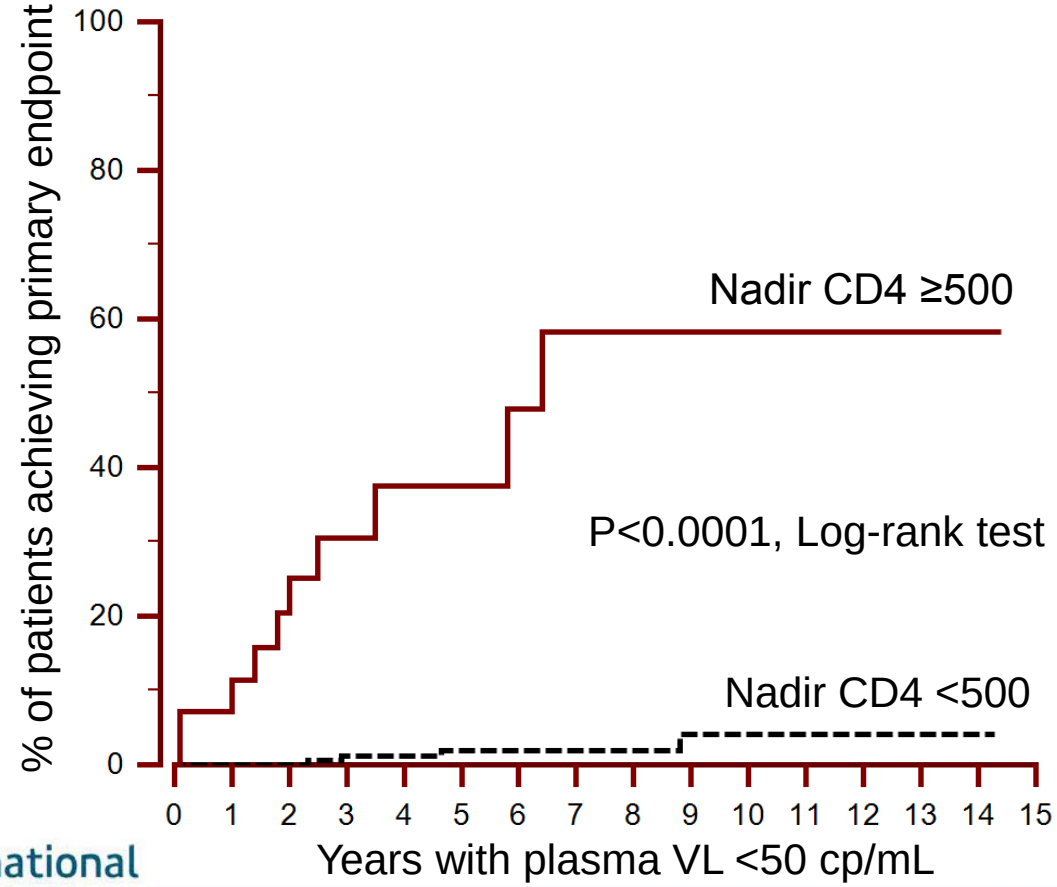
- **In a Cox model, nadir CD4 count ≥500/mm³ was the only predictor of achieving the primary endpoint: HR = 56 (95%CI:15-209), p<0.0001**

Kaplan-Meier estimates of the probability of achieving PEP according to the nadir CD4 stratification



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Results (6)

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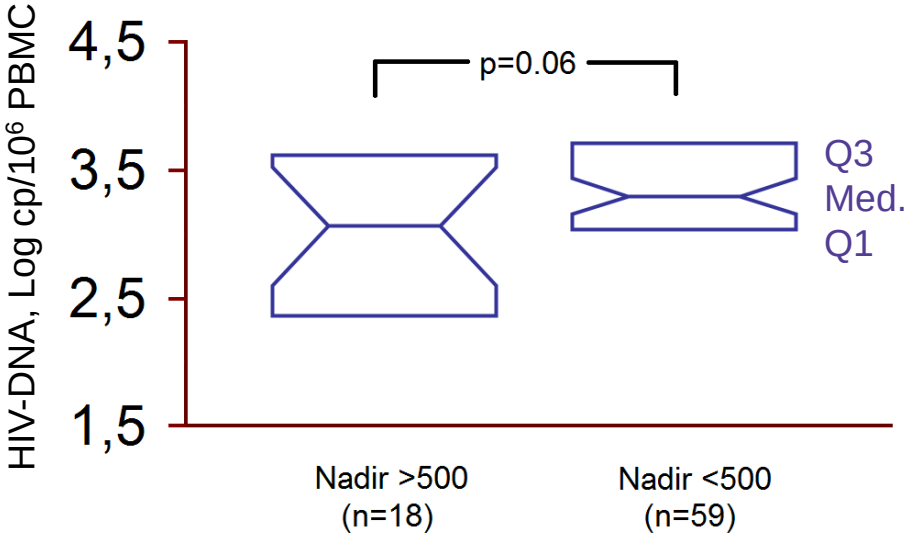
- In the sub-group (n=77) where HIV-DNA was determined before cART initiation:

  - Nadir CD4 ≥500 was associated with slightly lower HIV-DNA level before cART initiation



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Results (6)

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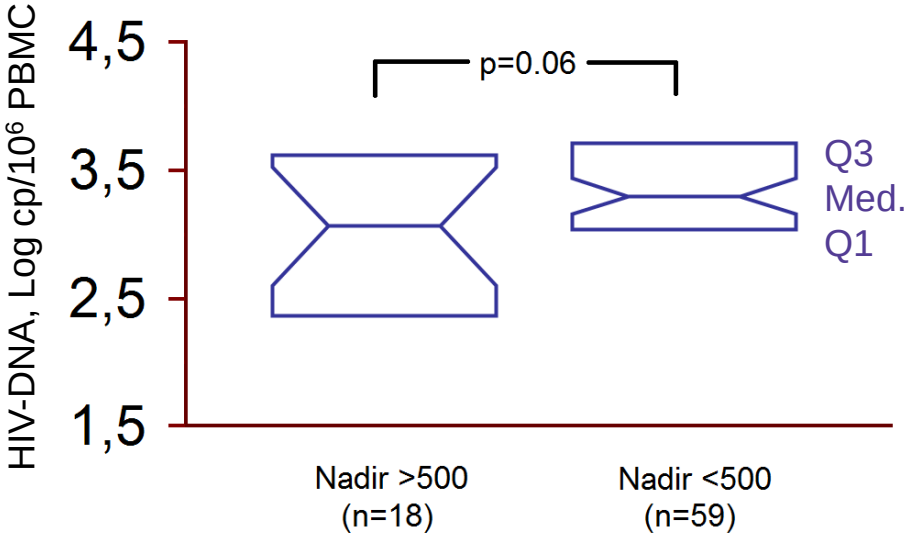
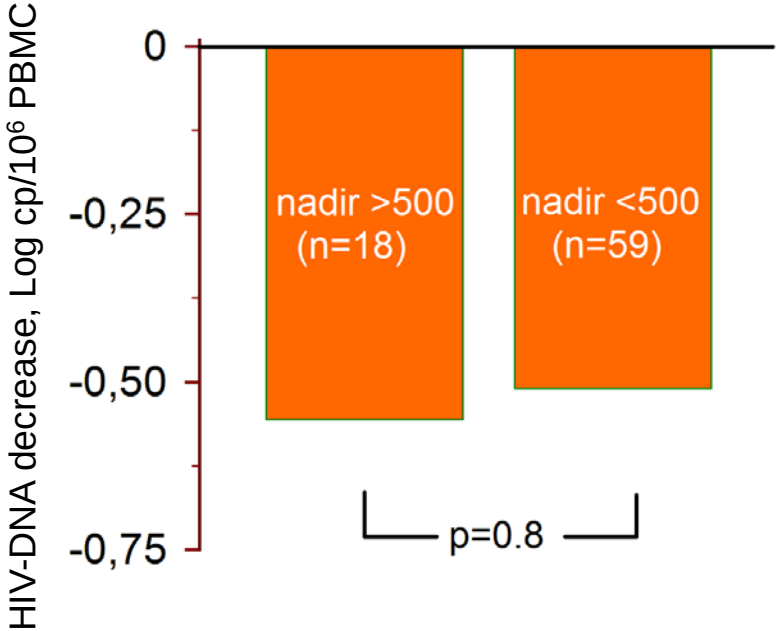


  - Whereas median HIV-DNA decrease was similar after one year of viral suppression under cART



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Limits

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

Discussion - Conclusions

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- 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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Acknowledgments

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- A. Mélard

ANRS AC32 Group

AND ALL PATIENTS FROM ORLEANS !

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