French National Agency for Research on AIDS and Viral Hepatitis
An autonomous agency at Inserm

International AIDS Society
Stronger Together Against HIV

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

A. Chéret, G. Nembot, V. Avettand-Fenoë, A.Mélard, I.Ravaux, B.Hoen, C. Lascoux-Combe, Chaix ML, C. Tamalet, P.Yeni, F.Raffi, L.Slama, Katlama C, Venet A, B. Autran, A.Saez-Cirion, L. Meyer, C. Rouzioux, and the **OPTIPRIM ANRS Study Group**.

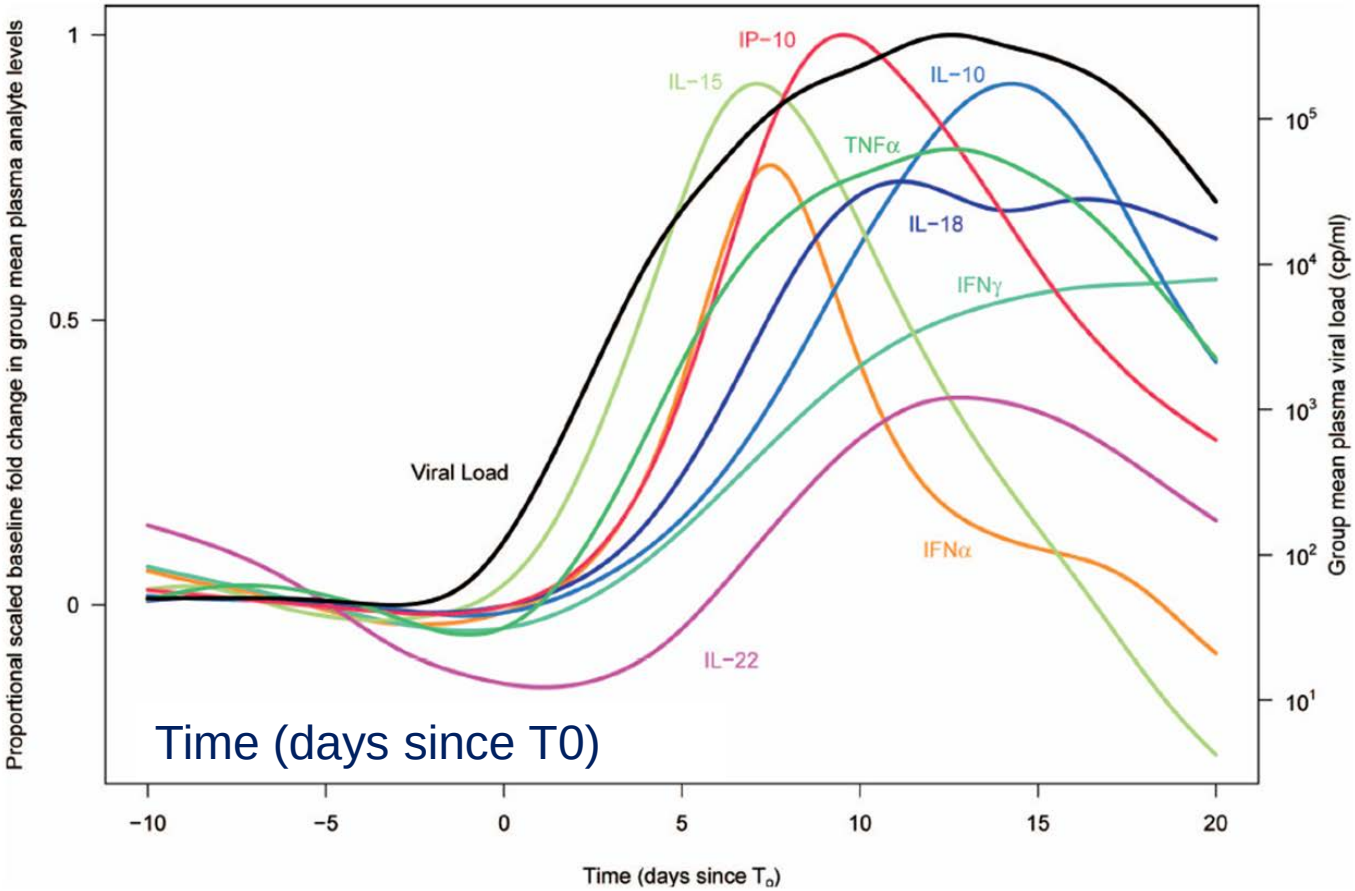
Université Paris Descartes
Université Paris Sud

IAS 2013 Towards an HIV Cure Symposium

towards an HIV cure
people focused science driven

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

towards an HIV cure
people focused science driven



Primary infection : immune homeostasis is skewed with a cytokin storm

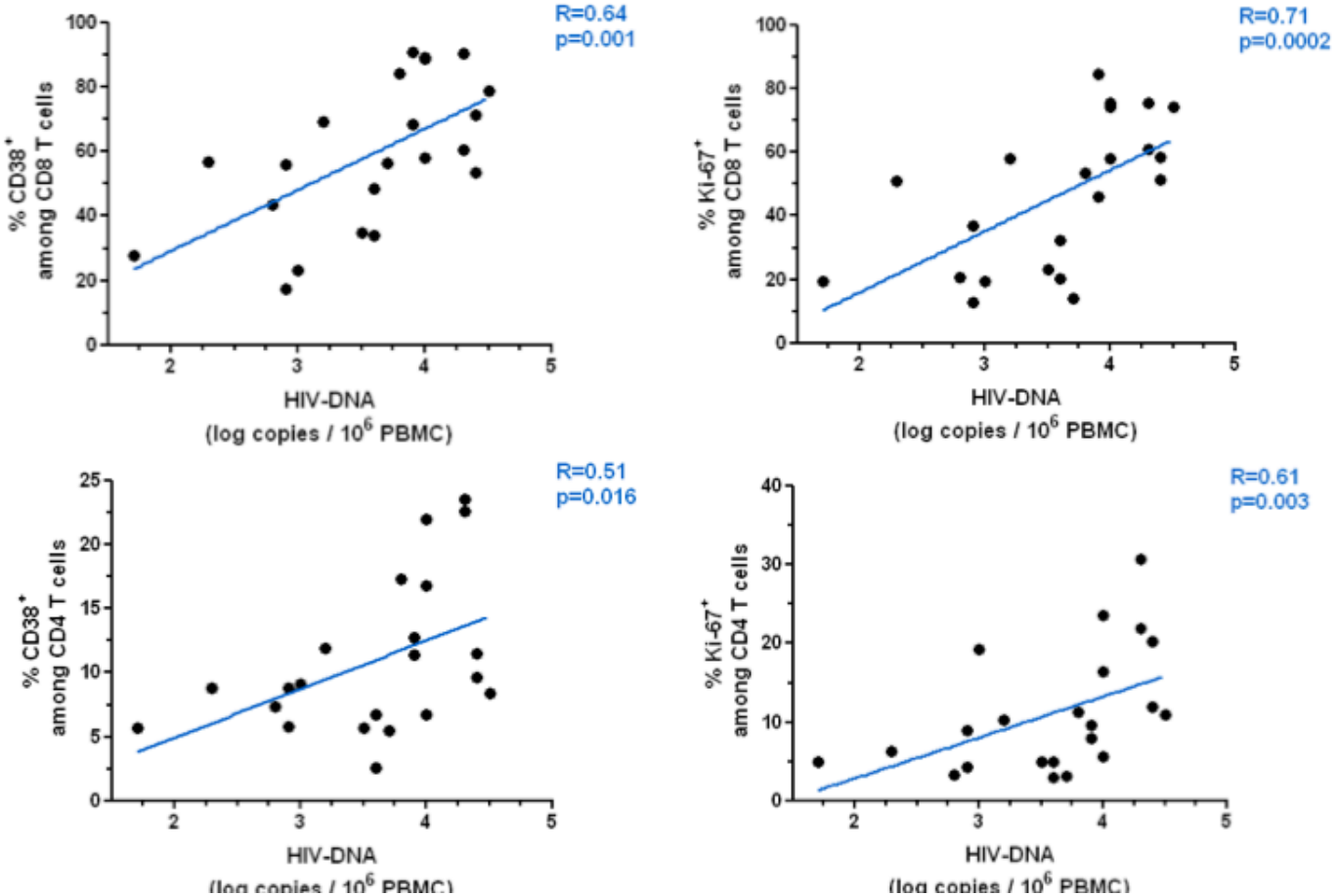
Stacey R; J.Virol, 2008

International AIDS Society
Stronger Together Against HIV

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

towards an HIV cure
people focused science driven

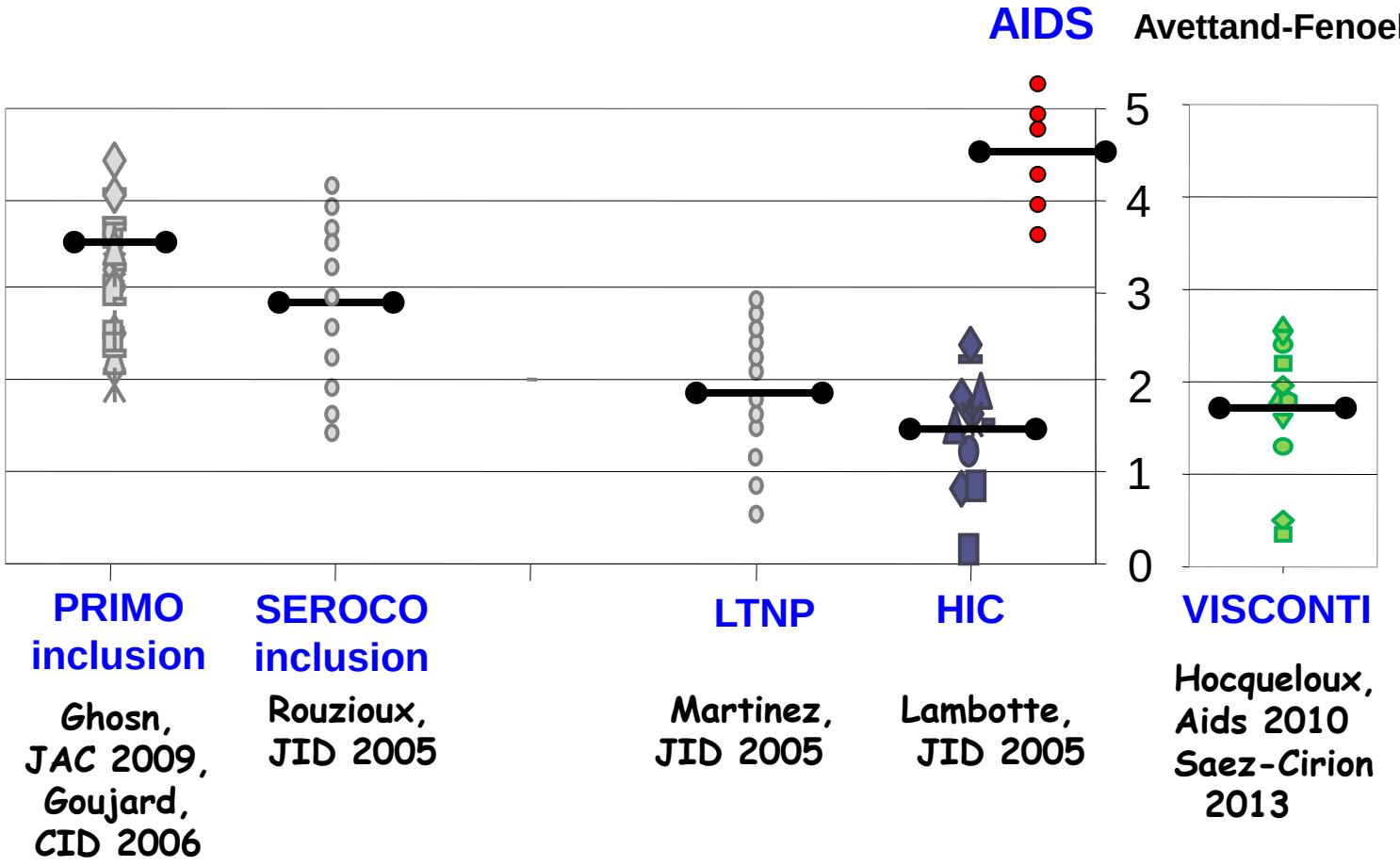
Figure 2 HIV-DNA in PBMCs is associated with CD8 and CD4 T-cell activation in PHI patients



Immune activation is correlated with HIV-DNA level

Laurence weiss (Towards an HIV cure, July 2013)

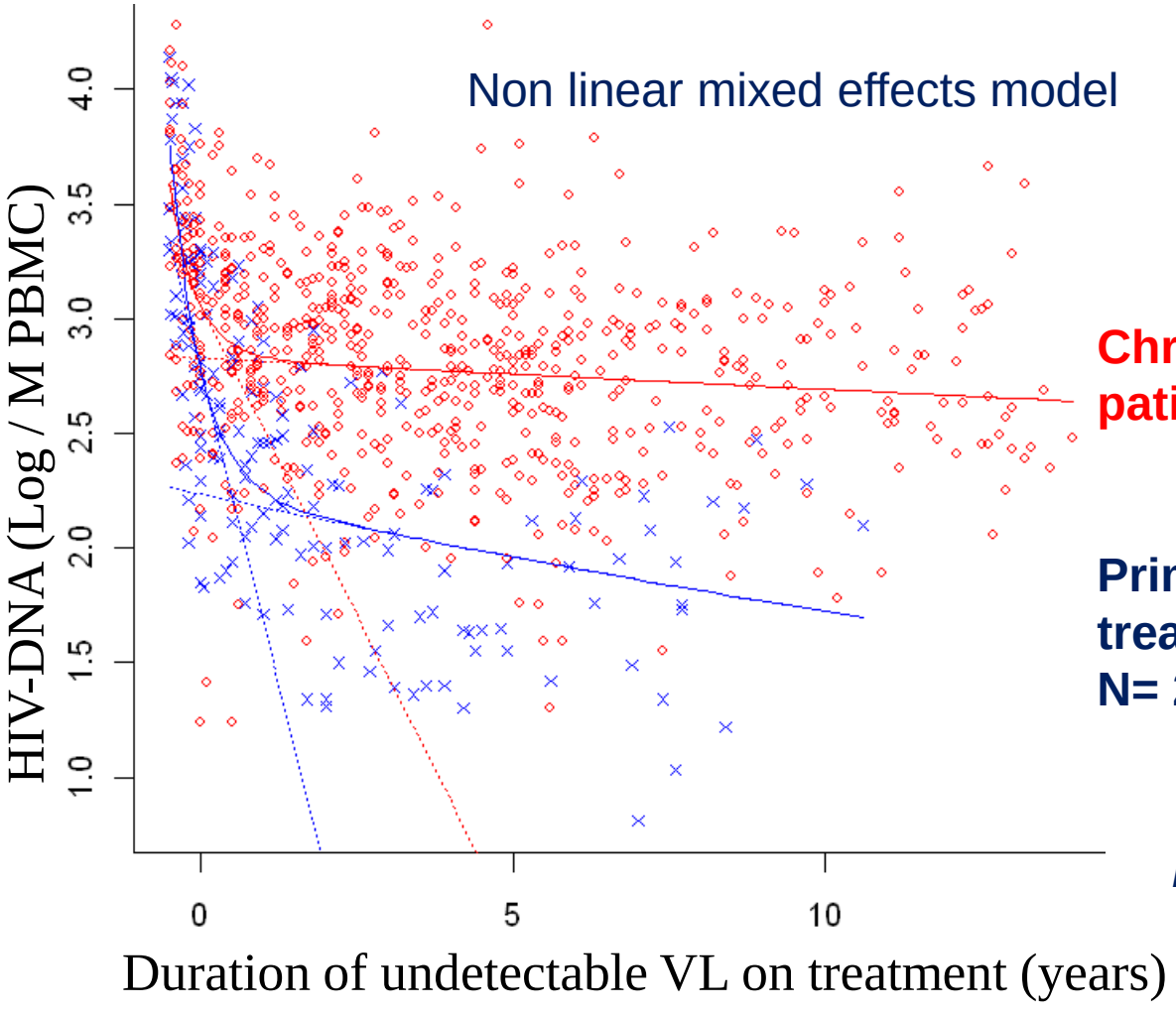
HIV-DNA in PBMC : Natural history of HIV infection (ANRS cohort studies)



- 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

towards an HIV cure
people focused science driven



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
4-Ananworanich et al. PLoS One. 2012;7(3):e33948

International AIDS Society
Stronger Together Against HIV

ANRS 147 OPTIPRIM : Rational

towards an HIV cure
people focused science driven

- **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 (log10/106 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

International AIDS Society
Stronger Together Against HIV

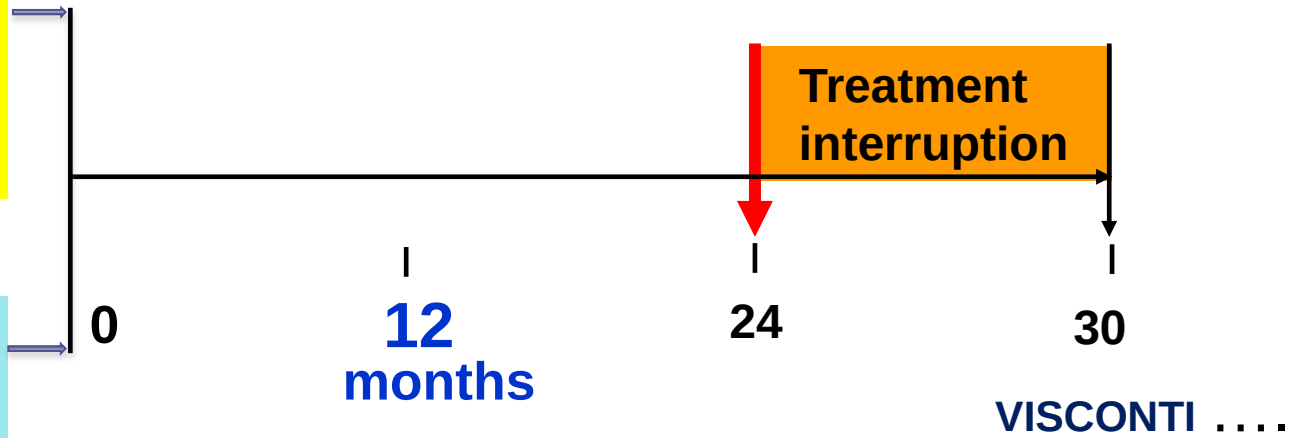
ANRS 147 OPTIPRIM : Study design

towards an HIV cure
people focused science driven

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

International AIDS Society
Stronger Together Against HIV

Baseline characteristics

towards an HIV cure
people focused science driven

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

[a](in the previous 7 days)

International AIDS Society
Stronger Together Against HIV

Patient disposition - Month 12

- 90 patients randomized

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

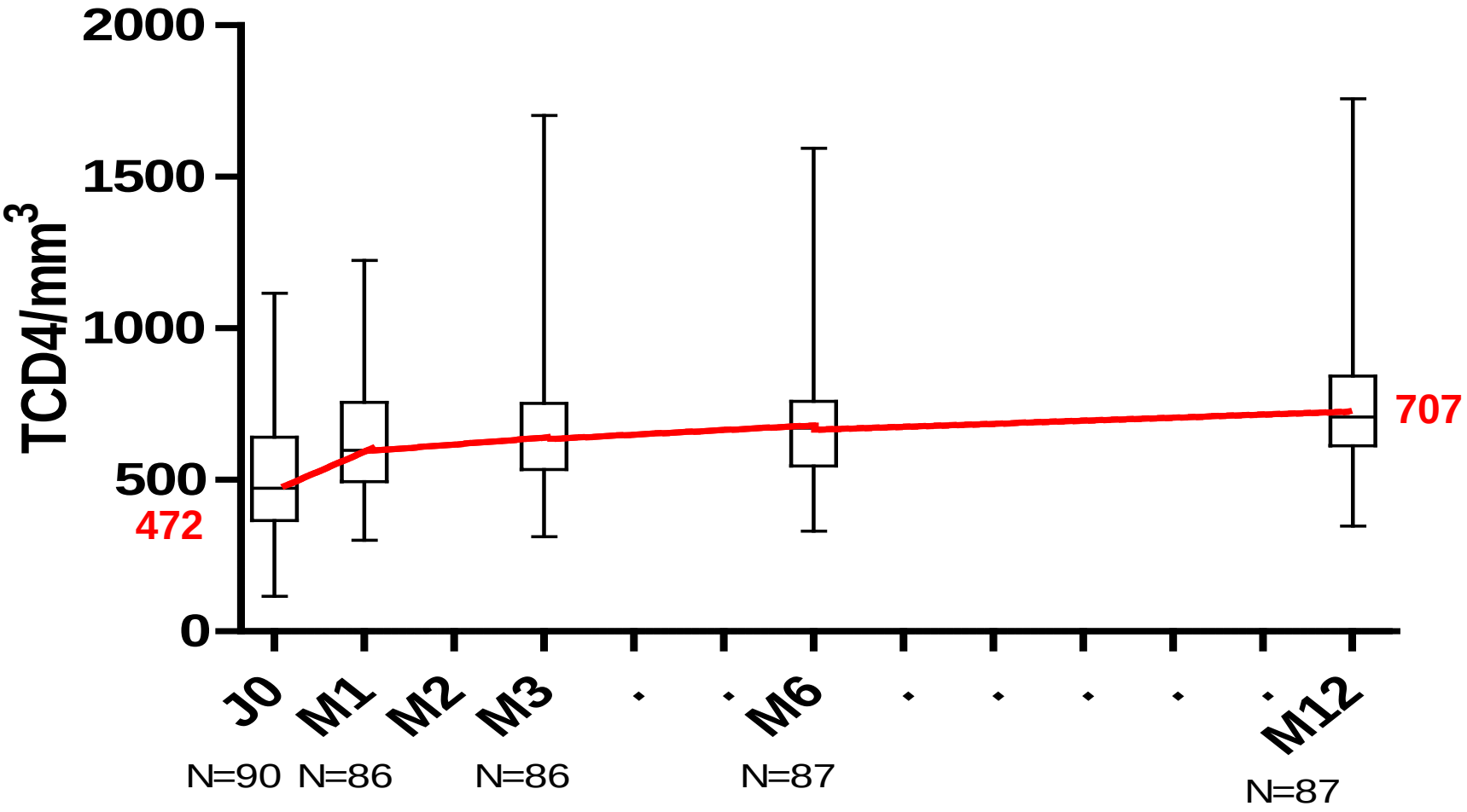
- Tolerance :
  - well tolerated (survey adherence)
  - 2 serious adverse side effects

    (both in the 3 drugs arm)
    - 1 lipodystrophy (20 kgs within a year)
    - 1 moderate acute pancreatitis

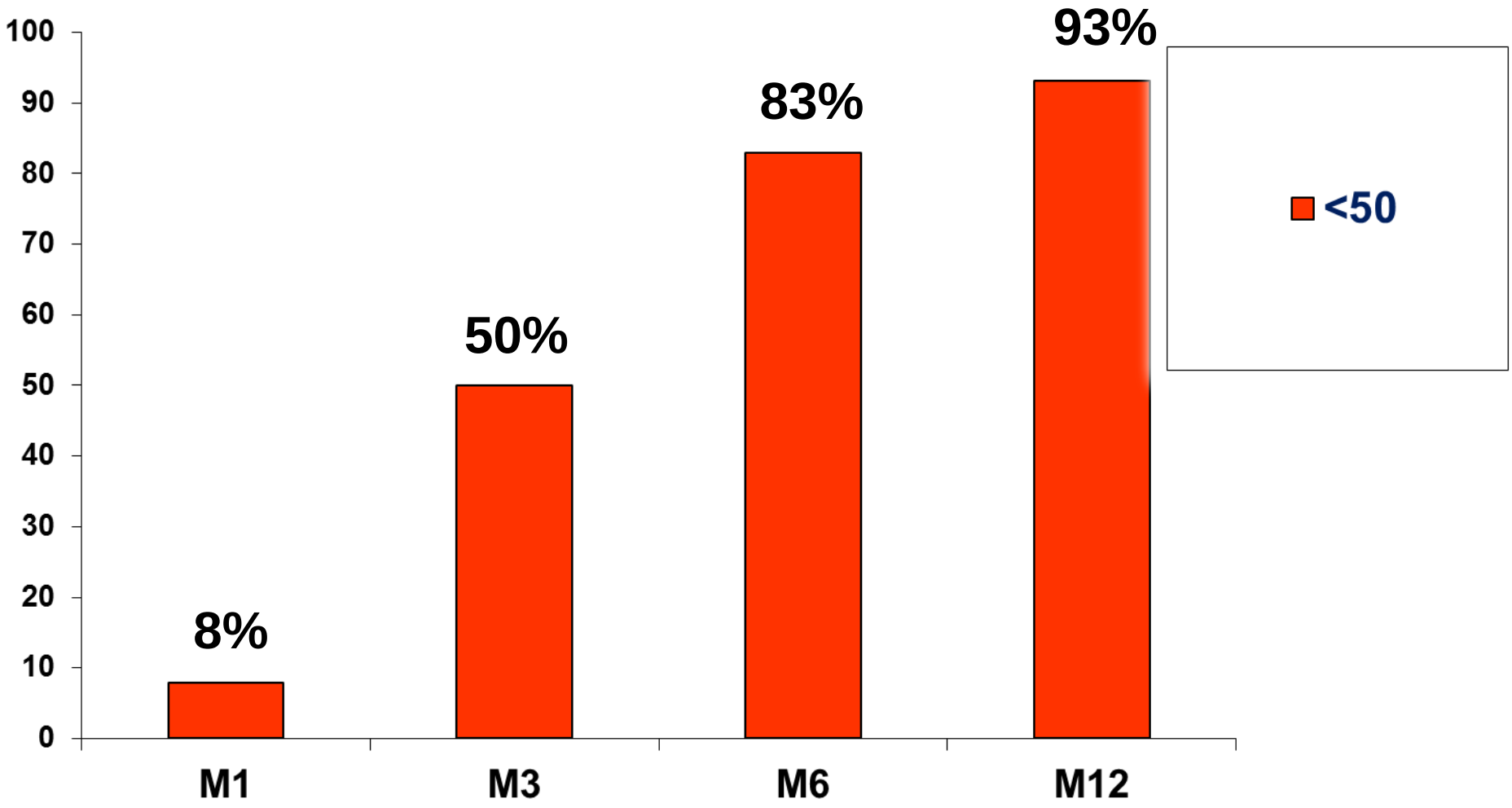
Immunology : CD4+ T cells kinetic

towards an HIV cure
people focused science driven

Median TCD4 gain : + 235/mm³ [119-378.5]
Median CD4/CD8 : 1,13 [0.87-1.38]

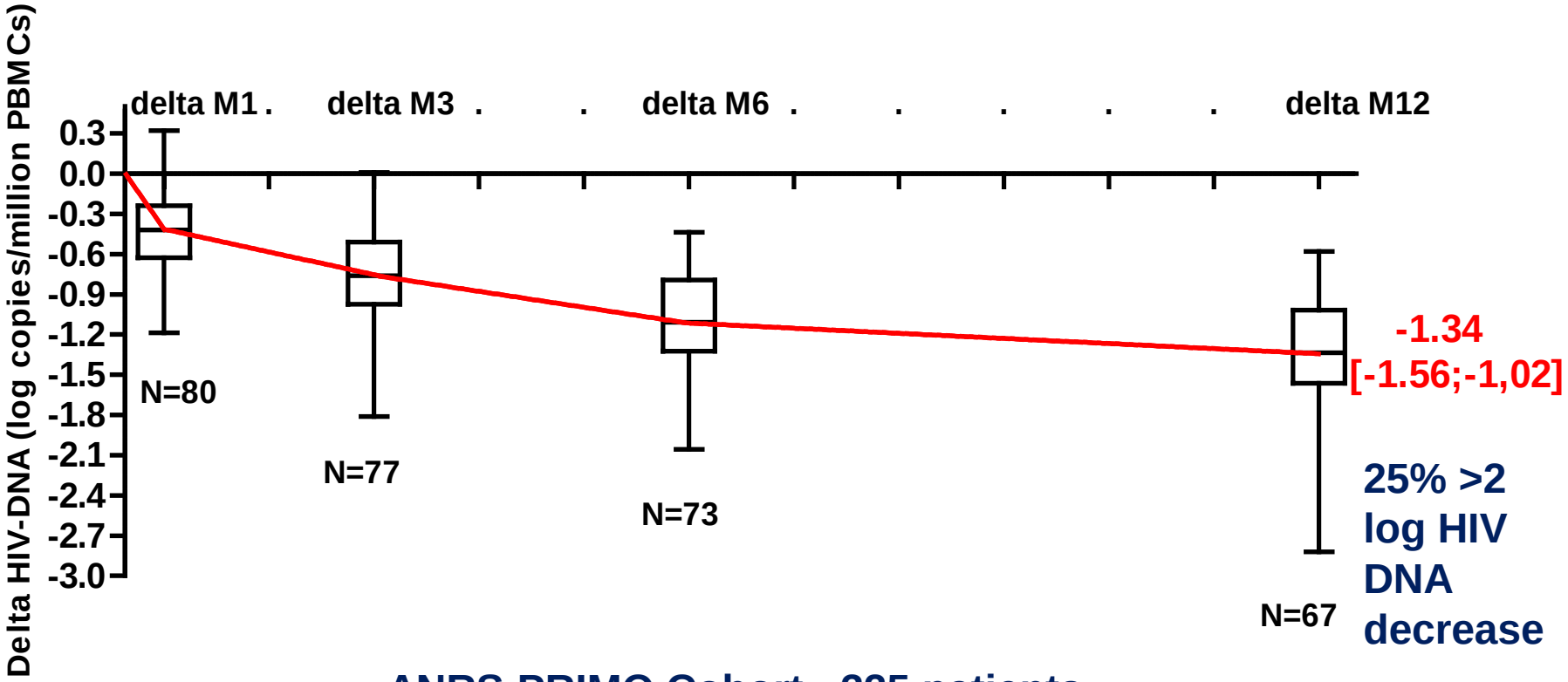


Virology: HIV-RNA < 50 copies/mL



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

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

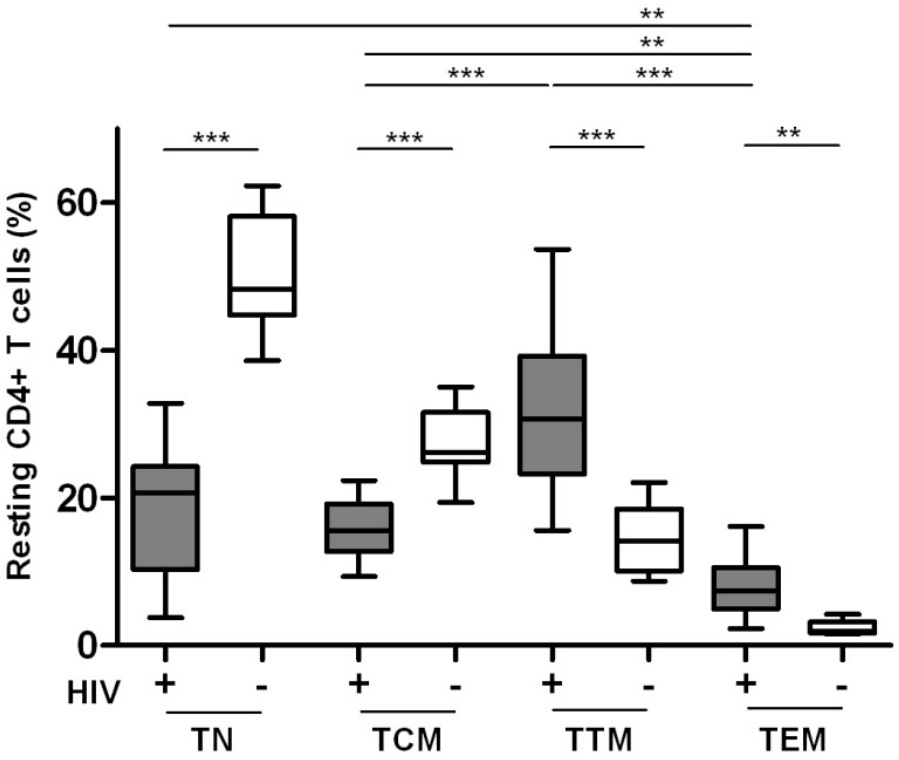
Median delta HIV-DNA M12 : **- 1.1[-1.6;-0.8]**

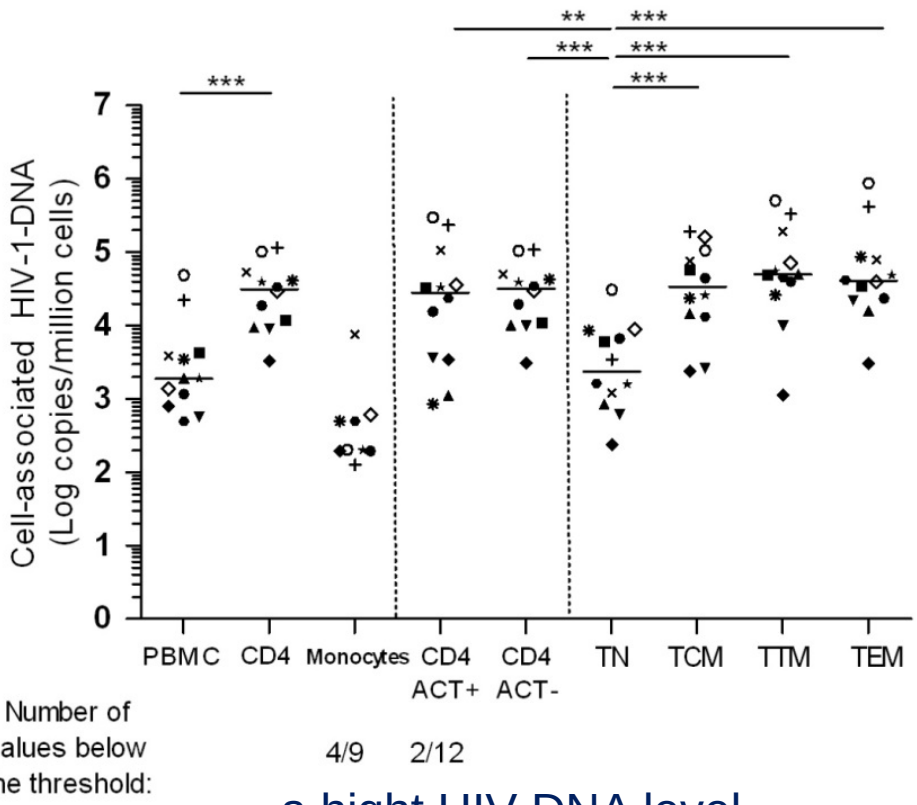
(B.Hoen, CID 2007)

Factors associated with HIV-DNA decrease at Month 12

Baseline characteristics (N=67)	Delta HIV-DNA at Month 12 (r corrélation coefficient)	P value
Time from PIS	0.15	0.26
CD4 cell count	0.0003	0.99
log HIV-RNA (cop/ml)	-0.37	**0.002**
LogHIV-DNA (cop/million PBMCs)	-0.31	**0.01**

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 hight HIV-DNA level.

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

CONCLUSION

- 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 condionned 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

Principal Investigators	MEC / co-investigators	Hospital	Town
PHILIBERT Patrick		Ambroise Paré	Marseille
GREDER BELAN Alix	THERBY Audrey	André Mignot	Le Chesnay
GOUJARD Cécile	AMRI Imane, FOURN Erwann, SEGUIN Valérie	Bicêtre	Le Kremlin Bicetre
YENI Patrick	PHUNG Bao-Chan, GUIROY Frédérique, RIOUX Christophe, PAPOT Emmanuelle	Bichat	Paris
MAY Thierry	BRIAUD Amandine, ANDRE Marie, LETRANCHANT Lorraine	Brabois	Vandoeuvre les Nancy
GRAS Guillaume	DAILLOUX Jean-François	Bretonneau	Tours
ALLEGRE Thierry		Centre Hospitalier du Pays d'Aix	Aix en Provence
DUVIVIER Claudine	SHOAI Michka, CONSIGNY Paul-Henri, CESSOT Gilles	Centre Médical de l'Institut Pasteur	Paris
DEBAB Yasmine		Charles Nicolle	Rouen
SALMON Dominique	CHAKVETADZE Catherine, TAN Boun Kim	Cochin	Paris
RAVAUX Isabelle		Conception	Marseille
MIAILHES Patrick	KOFFI Joseph, SCHLIENGER Isabelle, PAILHES Sophie, PERPOINT Thomas, BIRON François, SENECHAL Agathe	Croix Rousse	Lyon
LIVROZET Jean-Michel	MAKHLOUFI Djamila	Edouard Herriot	Lyon
LAFEUILLADE Alain	HITTINGER Gilles	Font Pré	Toulon
REYNES Jacques	JACQUET Jean-Marc, MAKINSON Alain, ATOUI Nadine, FAUCHERE Vincent	Gui de Chauliac	Montpellier
CHERET Antoine	HULEUX Thomas, BIEKRE Raphael, AISSI Emmanuelle	Gustave Dron	Tourcoing
LEVY Yves	LASCAUX Anne-Sophie	Henri Mondor	Créteil
CHENNEBAULT Jean-Marie	FIALAIRE Pascale	Hôtel Dieu	Angers
RAFFI François	BRUNET FRANCOIS Cécile, BOUCHEZ Sabelline, ALLAVENA Clothilde, FEUILLEBOIS Nicolas, BONNET Bénédicte, RELIQUET Véronique, BILLAUD Eric,	Hôtel Dieu	Angers
PREVOTEAU DU CLARY François		La Grave	Toulouse
NAQVI Alissa		l'Archet 1	Nice
RAMI Agathe	DUREL Aurélie	Lariboisière	Paris
RAGNAUD Jean-Marie	Didier NEAU	Pellegrin	Bordeaux
ABEL Sylvie	Sandrine PIERRE-FRANCOIS	Pierre Zobda Quitman	Fort De France
KATLAMA Christine	SCHNEIDER Luminita, SEANG Sophie, TUBIANA Roland, STITOU Hind	Pitié-Salpétrière	Paris
SIMON Anne	PICHON Francois	Pitié-Salpétrière	Paris
SOUALA Faouzi	RATAJCZAK Maja	Pontchaillou	Rennes
CUZIN Lise	CHAUVEAU Marie	Purpan	Toulouse
MORLAT Philippe	VANDENHENDE Marie-Anne	Saint André	Bordeaux
HOEN Bruno	HAFFNER-MAUVAIS Cécile	Saint Jacques	Besançon
LASCOUX COMBE Caroline	Claire PINTADO	Saint Louis	Paris
MOLINA Jean-Michel	COLIN DE VERDIERE Nathalie, DE LASTOURS Victoire, PAVIE Juliette, PONSCARME Diane, GALIEN Sebastien	Saint Louis	Paris
SLAMA Laurence	CHAS Julie, L'YAVANC Thomas	Tenon	Paris

towards an HIV cure
people focused science driven

Scientific commitee
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

Trial conducted with the support of MSD,Jansen, ViiV Healthcare and Gilead