Faut-il traiter la Primo-Infection ?

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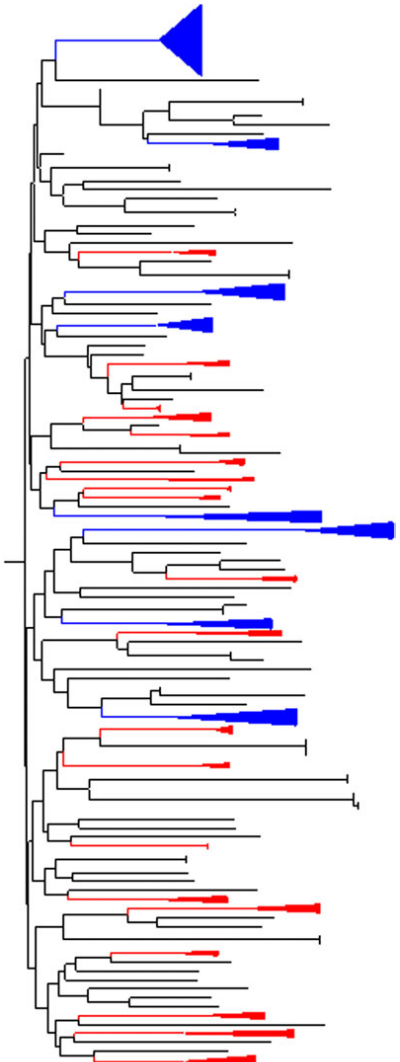
Brief but Efficient: Acute HIV Infection and the Sexual Transmission of HIV

Christopher D. Pilcher,[1] Hsiao Chuan Tien,[2] Joseph J. Eron, Jr.,[1] Pietro L. Vernazza,[3] Szu-Yun Leu,[2] Paul W. Stewart,[2] Li-Ean Goh,[4] and Myron S. Cohen,[1] for the Quest Study and the Duke-UNC-Emory Acute HIV Consortium[a]

Departments of [1]Medicine and [2]Biostatistics, University of North Carolina at Chapel Hill; [3]University Hospital, St. Gallen, Switzerland; [4]Clinical

Lancet infectious disease, 2004



- Transmission est proportionnelle à la charge virale plasmatique et génitale
- En primo-infection les charges virales plasmatiques et génitales sont élevées avec un risque de transmission élevé jusqu'à 26 fois /phase chronique
- Clusters de transmissions

1-Powers KA, rethinking the heterosexual infectivity of HIV-1: a systematic review and metaanlysis. Lancet infectious disease, 2008

2-Hollingsworth TD, HIV-1 transmission, by stage of infection. J Infect Dis. 2008; 198(5):687-92

3-Brenner BG, High rate of forward transmission events after acute/early HIV-1 infection. J Infect Dis. 2007;195(7):951-9

4-Deirdre Hollingsworth, High Infectivity of Acute HIV Infection amongst Men Who Have Sex with Men: San Francisco, Croi 2012 poster 552

5-Miller WC, Role of Acute and early HIV infection in the sexual transmissionof Hiv. Current Opin HIV AIDS 2010;5:277-82

6-Hamlyn E, Antiretroviral treatment of Primary Infection to reduce onward transmission, Curr Opin HIV AIDS 5:283-290

7-Frange P, Recent HIV-1 infection contributes to the viral diffusion over the French territory with a recent increasing frequency. PLoS One. 2012;7(2)

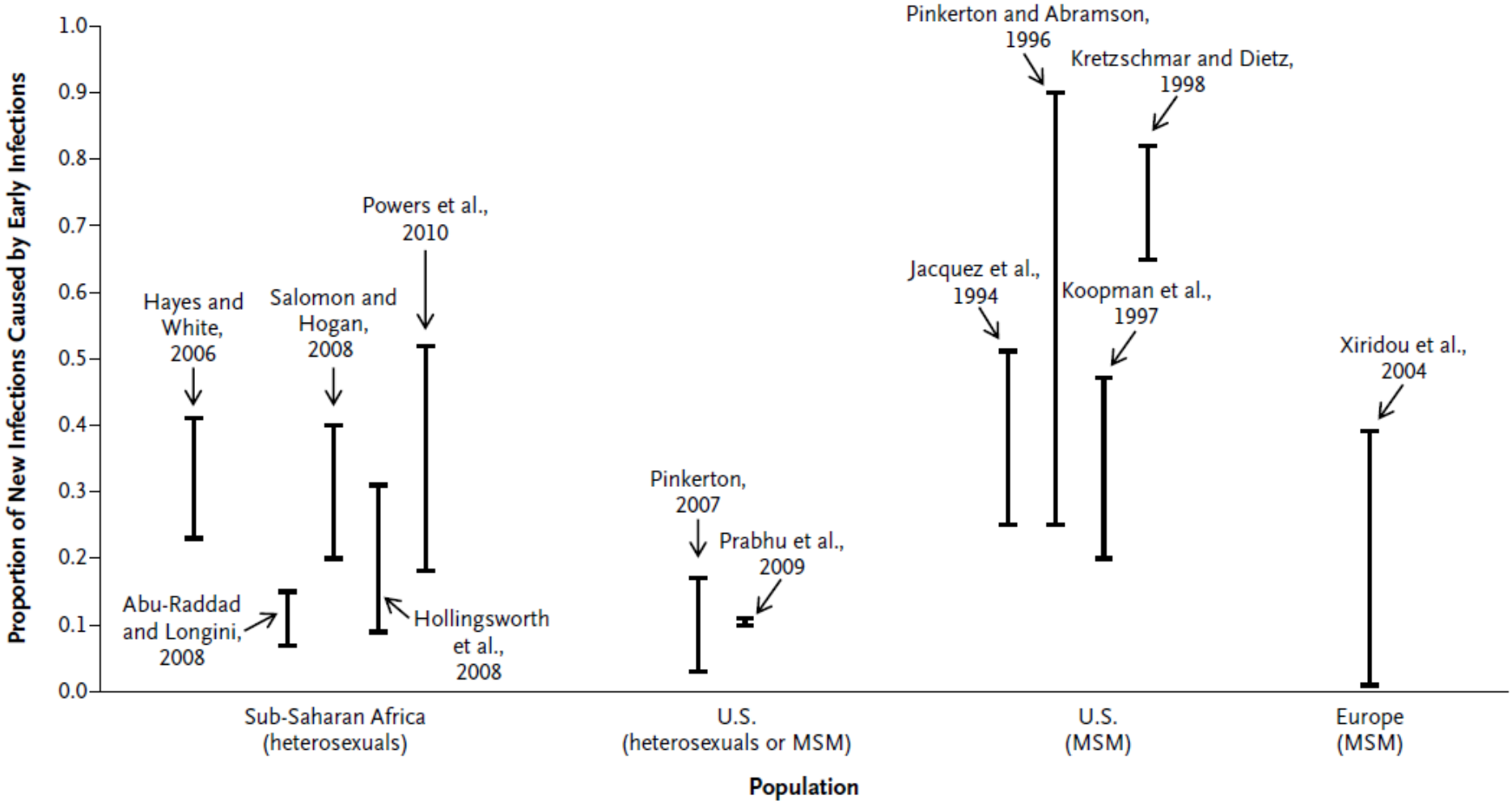


Figure 4. Role of Acute and Early HIV-1 Infection in the Spread of HIV-1, According to Population Studies in Sub-Saharan Africa, the United States, and Europe.

Myron S. Cohen, Acute HIV-1 Infection, New England Journal of Medecine, May 19, 2011

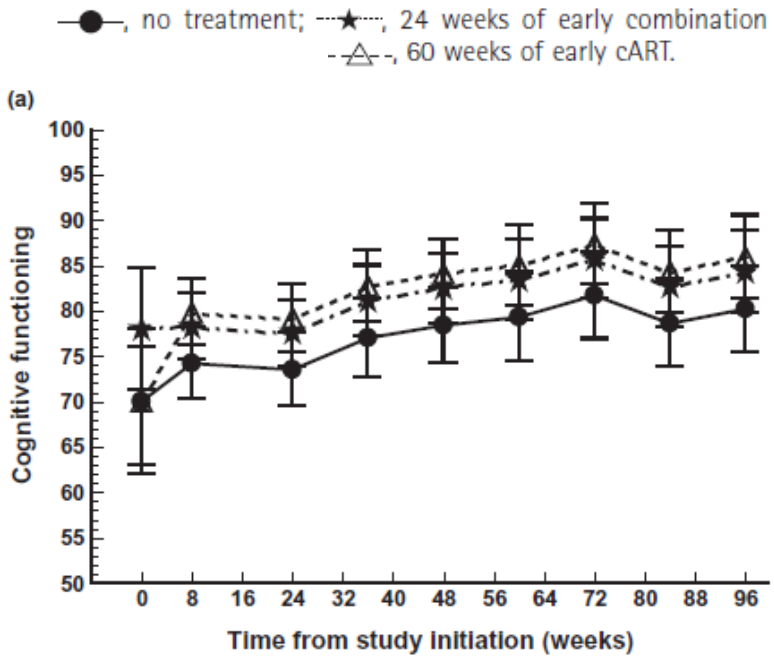
Bénéfices cliniques

-Réduction des symptômes liés au syndrome viral

1-Kassuto S, Longitudinal analysis of clinical markers following antiretroviral therapy iniated during acute or early HIV type 1 infection. Clin Infect Dis 2006, 42:1042-1043

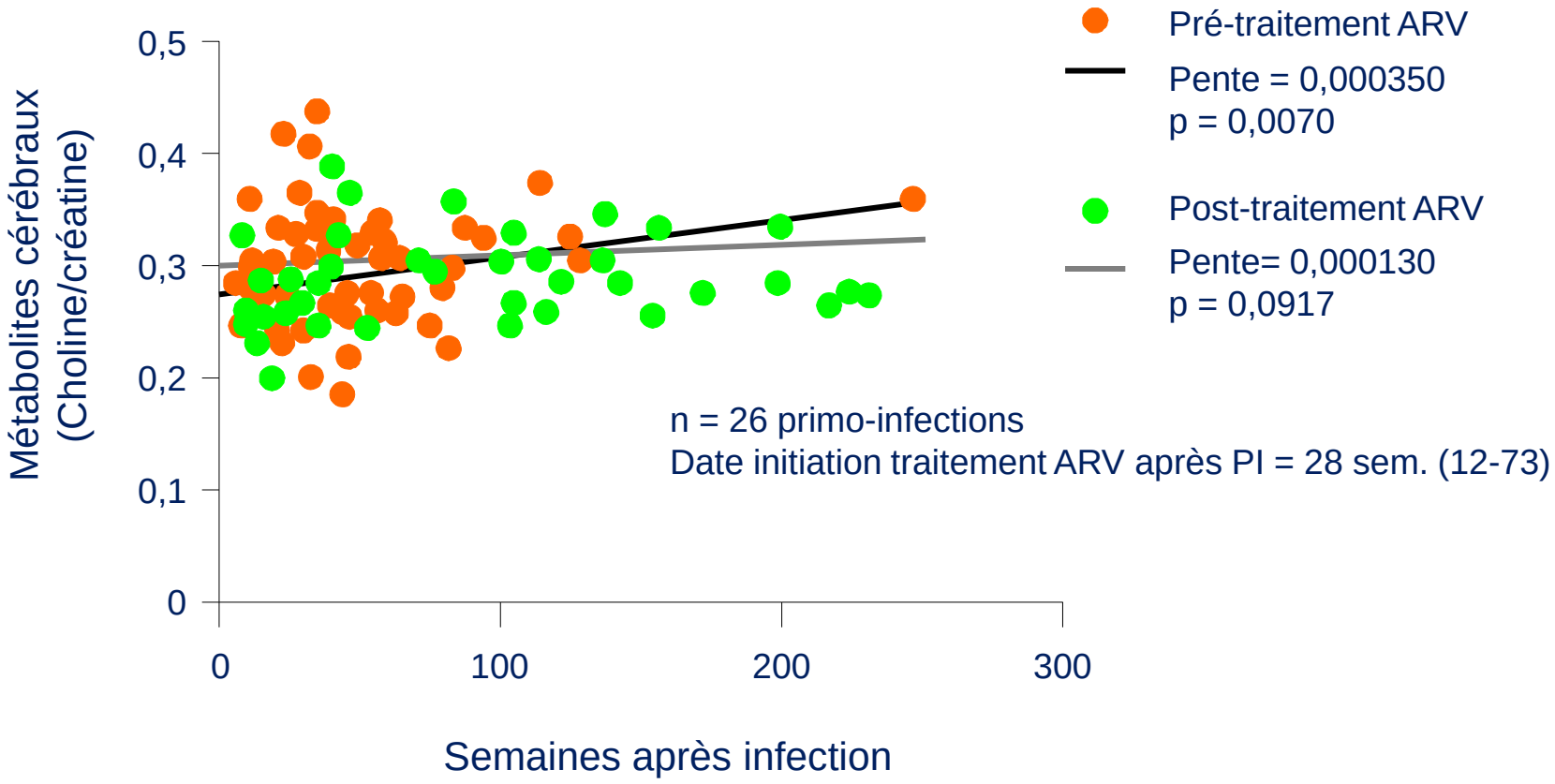
Impact sur les troubles neurocognitifs

2- julia Peterson, changes in Neurocognitive performance from early HIV-1 infection to initiation of ART, Oral abstract 80, Cro
3- T Marcotte, Ealier initiation of ART results in better neurocognitive functionning, Poster 485, Croi 2012
4-Grijsen ML, HIV Medecine 2012, 13, 630-635



L'inflammation précoce du SNC au cours de la primo- infection est atténuée par le traitement ARV

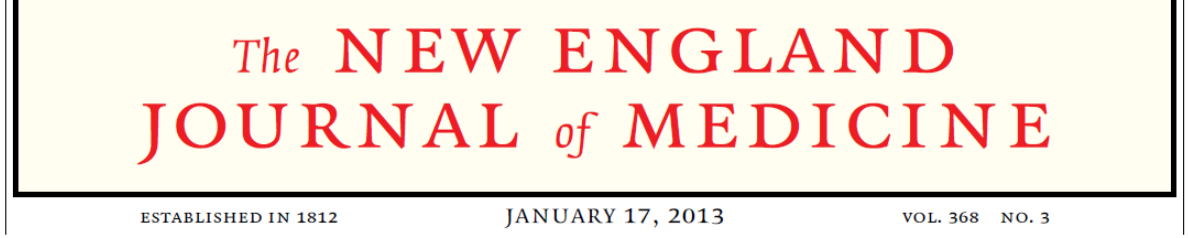
Etude en spectroscopie par résonance magnétique du proton



Young A., CROI 2012, Abs. 79; 1- N Sailasutra, Brain tCho/Cr is elevated in Acute HIV within the first Month of Infection, Poster 456, Croi 2012

Table 1 Summary of clinical trials of treatment of acute HIV with ART

Study	Time to ART from diagnosis	Duration of ART	Outcome, as compared to untreated
Kinloch-De Loes (1995) [34] Placebo-controlled RCT AZT monotherapy	25 days	24 weeks	Less opportunistic infections during treatment
Niu (1995) [35] Placebo-controlled RCT AZT monotherapy	18 days	24 weeks	Improved CD4+ T cell counts at 1 year after treatment interruption (TI) but no difference in viral load (VL) or clinical events
Hogan, SETPOINT (2011) [36••] RCT 3-drug ART	Within 6 months	36 weeks	Delayed time to CD4+ T cell counts ≤ 350 cells/mm^3 after TI
Streeck (2006) [39] Observational prospective 3-drug ART	25 days	24 weeks	Improved HIV-specific CD8+ T cell responses, no improved VL for 6 months after TI
Hecht (2006) [40] Observational prospective 3-drug ART	14 days	12 weeks	Decreased VL, improved CD4+ T cell count for 72 weeks after TI
Fidler (2007) [41] Retrospective 3-drug ART	"During primary infection"	12 weeks	Slower CD4+ T-cell decline after TI
Von Wyl (2011) [42] Observational prospective 3-drug ART	16 weeks	18 months	Decreased VL for 1 y but not 3 y after TI
Grijsen (2011) [37] Randomized 3-arm 3-drug ART	"During primary infection"	24 or 60 weeks	Decreased VL and decreased time to start ART 36 wk after TI
Fidler, SPARTAC (2011) [41] RCT 3-drug ART	Within 6 months	12 or 48 weeks	Delayed time to CD4 T-cell count < 350 cells/mm^3 after TI
Hoen, QUEST (2007) [43] Observational prospective	"During primary infection"	48 weeks	During treatment, improved CD4+ T-cell counts, decreased markers of immune



Short-Course Antiretroviral Therapy in Primary HIV Infection

The SPARTAC Trial Investigators*

- Definition of PHI
  - Laboratory evidence of infection within 6 months of a previous negative test, <3 bands WB, RITA incident, antibody negative PCR+
- Randomisation to one of three arms (1:1:1):
  - 48-week short course ART (ART-48)
  - 12-week short course ART (ART-12)
  - No therapy (Standard of Care SOC)
- Primary end point
  - **Time to CD4 <350 cells/mm^3 or long-term ART initiation**
- Sample size
  - 360 patients, 8 countries
  - Median CD4 :559 (435-700)

Hamlyn E, et al. PLoS One. 2012;7(8):e43754
Fidler et al. IAS, 2011

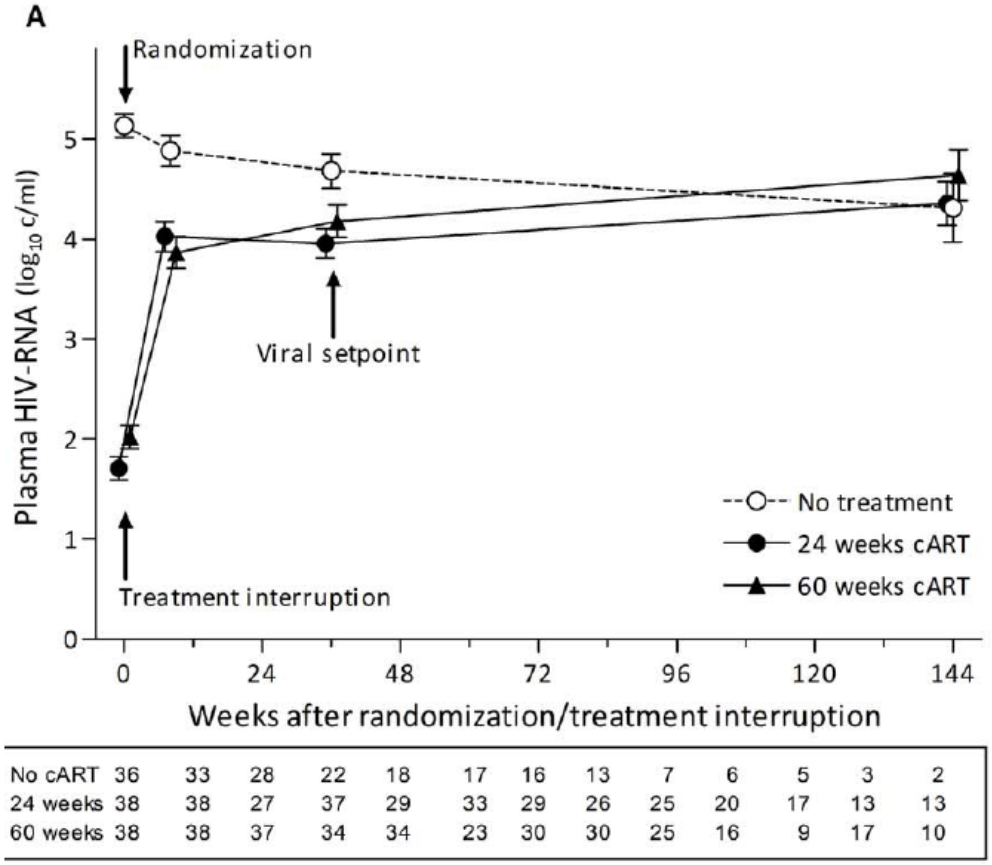
Time to primary endpoint

Time to primary endpoint	SOC	ART12	ART48
Median, weeks (95% CI)	157 (114,213)	184 (140,214)	222 (189,270)
Difference vs. SOC	-	27 (-25,79)	**65 (17,114)**
Difference vs. ART12	-	-	38 (-3,79)

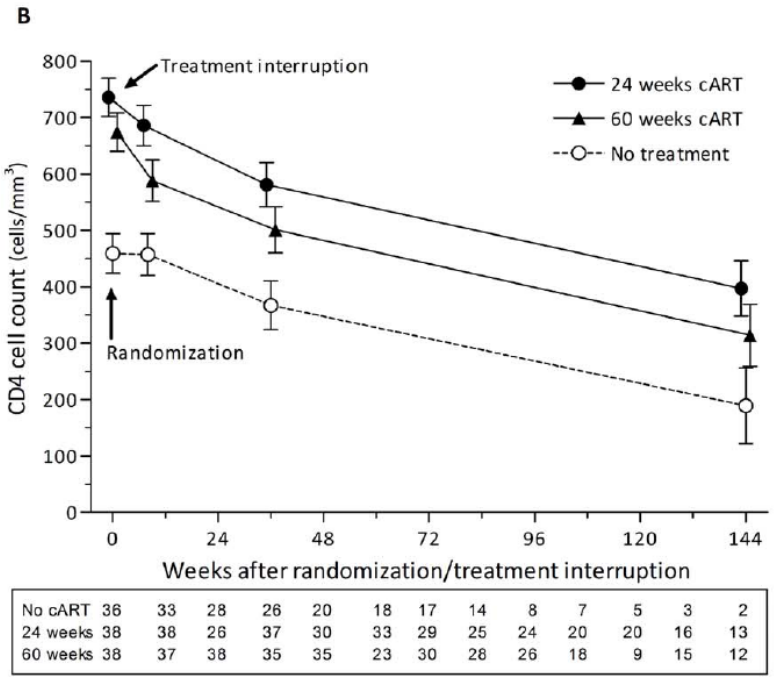
	Hazard ratio	95% CI	p
ART12 vs. SOC	0.93	0.67 - 1.29	0.67
ART48 vs. SOC	0.63	0.45 - 0.90	0.01
ART48 vs. ART12	0.68	0.48 - 0.96	0.03

Hamlyn E, *et al. PLoS One.* 2012;7(8):e43754
Fidler *et al*. IAS, 2011

Essai Primo-SHM : 0, 24 ou 60 semaines de traitement ARV en primo-infection VIH



No cART	36	33	28	22	18	17	16	13	7	6	5	3	2
24 weeks	38	38	27	37	29	33	29	26	25	20	17	13	13
60 weeks	38	38	37	34	34	23	30	30	25	16	9	17	10



No cART	36	33	28	26	20	18	17	14	8	7	5	3	2
24 weeks	38	38	26	37	30	33	29	25	24	20	20	16	13
60 weeks	38	37	38	35	35	23	30	28	26	18	9	15	12

Grinjsen, Plos Medicine

Essai Primo-SHM : 0, 24 ou 60 semaines de traitement ARV en primo-infection VIH

Facteurs prédictifs de la (ré)initiation d'un traitement ARV (modèle de Cox multivarié ajusté sur âge, CD4, résistance et tropisme à baseline)

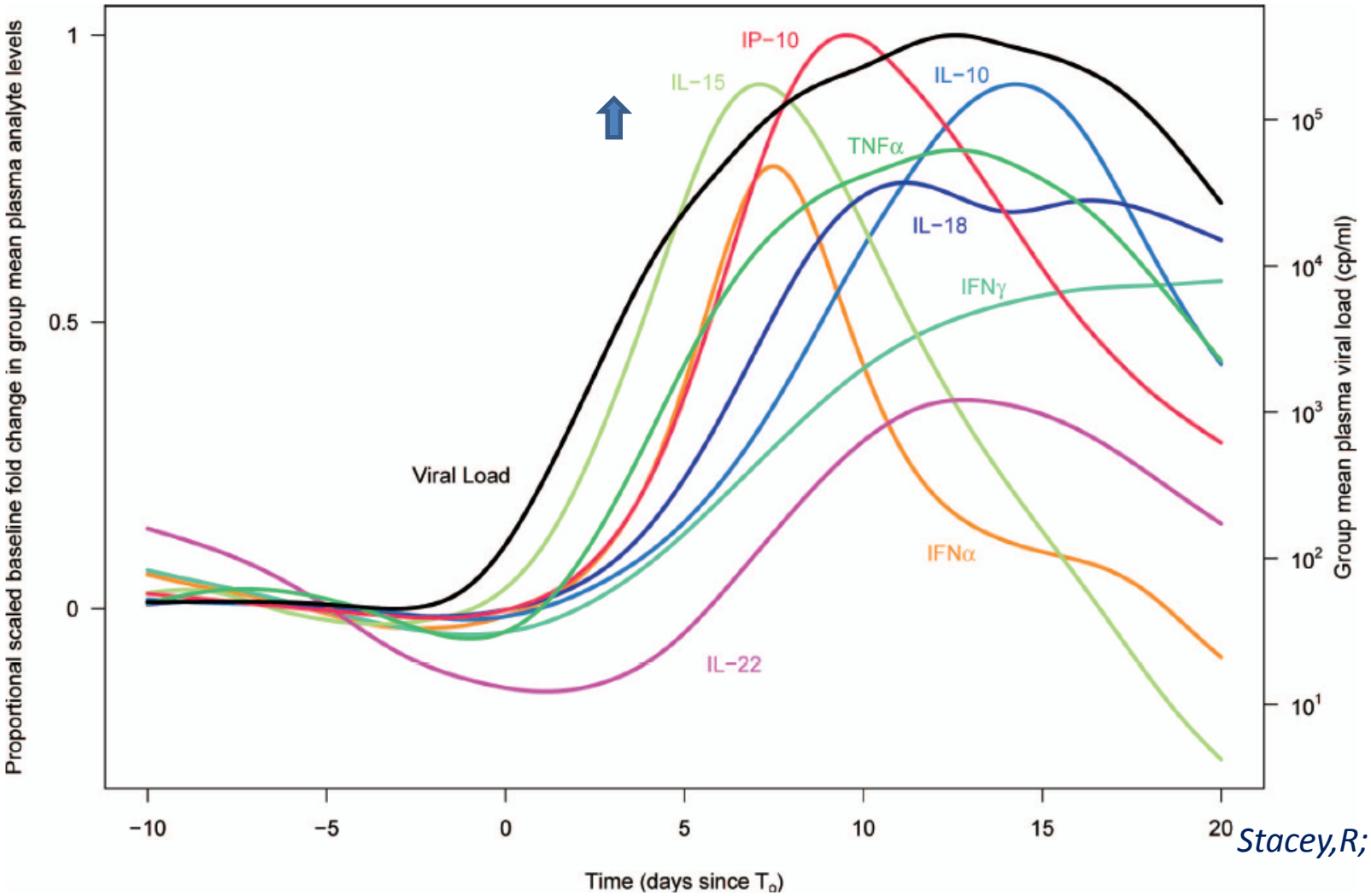
	HR (IC 95%)	P
CV au setpoint(log10cop/ml)	1,69 (1,08-2,65)	0,02
CD4 au setpoint (log10 CD4/mm3)	0,002 (0,0-0,03)	< 0,001
HAART Précoce	**0,36 (0,19_0,7)**	**0,003**

Le traitement précoce augmente le temps passé sans traitement et réduit le setpoint virologique

Pas de différence entre 24 semaines et 60 semaines de traitement

Grinjsen, Plos Medicine

Physiopathologie et cytokines



Stacey,R; J.Virol, 2008

1-Formes graves : cytokines (grippe) *(Yu, XPLoS One 6:e28680)*

2-Cytokines prédictives du set point viral *(Roberts,L Aids 24:819-831)*

3-Suractivation lymphocytaire favorise la réplication virale et intervient en favorisant des mécanismes immunopathologiques délètèrent à terme pour les patients

Grande diversité immuno-virologique en Primo-infection

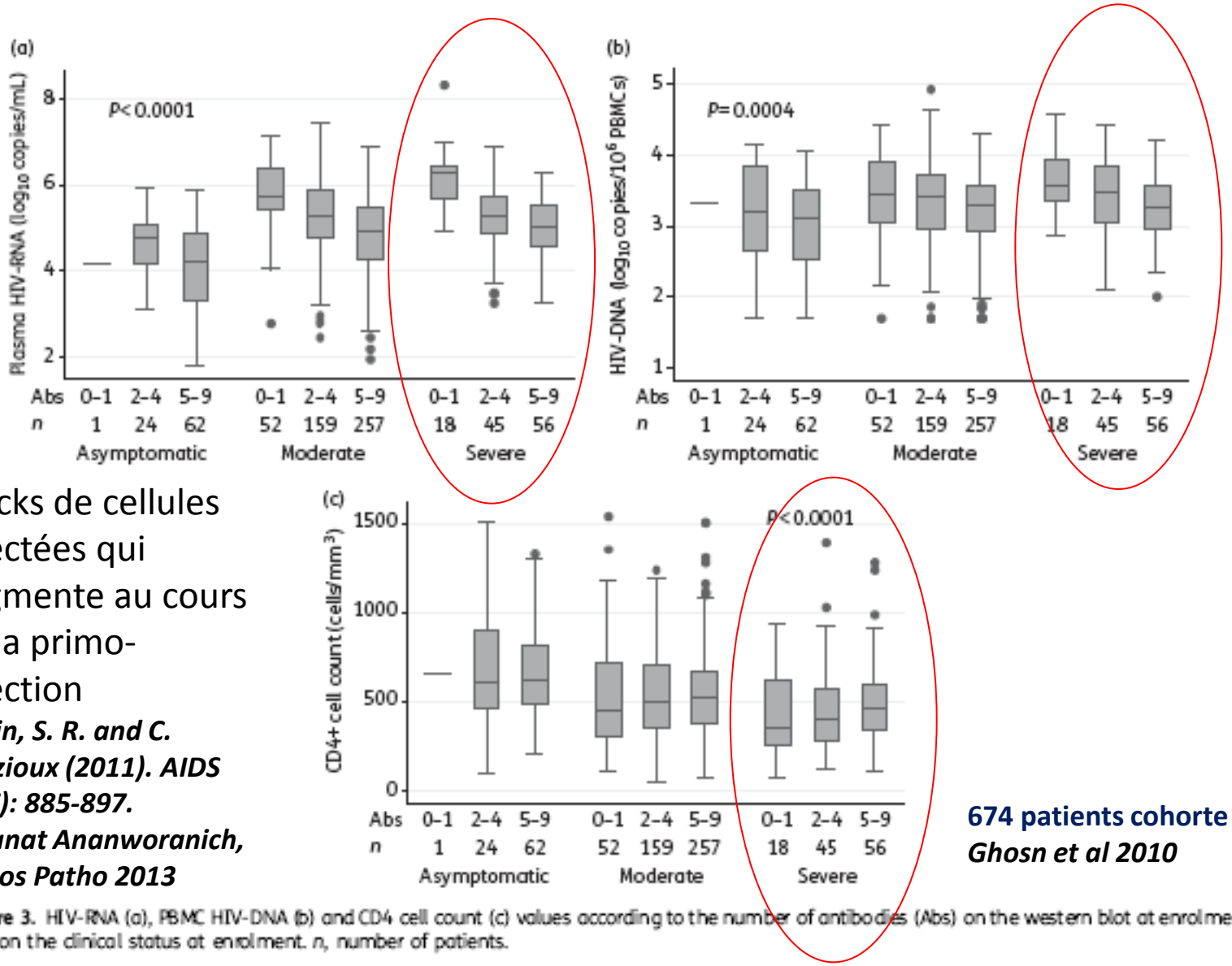


Figure 3. HIV-RNA (a), PBMC HIV-DNA (b) and CD4 cell count (c) values according to the number of antibodies (Abs) on the western blot at enrolment and on the clinical status at enrolment. *n*, number of patients.

Stocks de cellules infectées qui augmente au cours de la primo-infection

Lewin, S. R. and C. Rouzioux (2011). AIDS 25(7): 885-897.

Jintanat Ananworanich, C. Plos Patho 2013

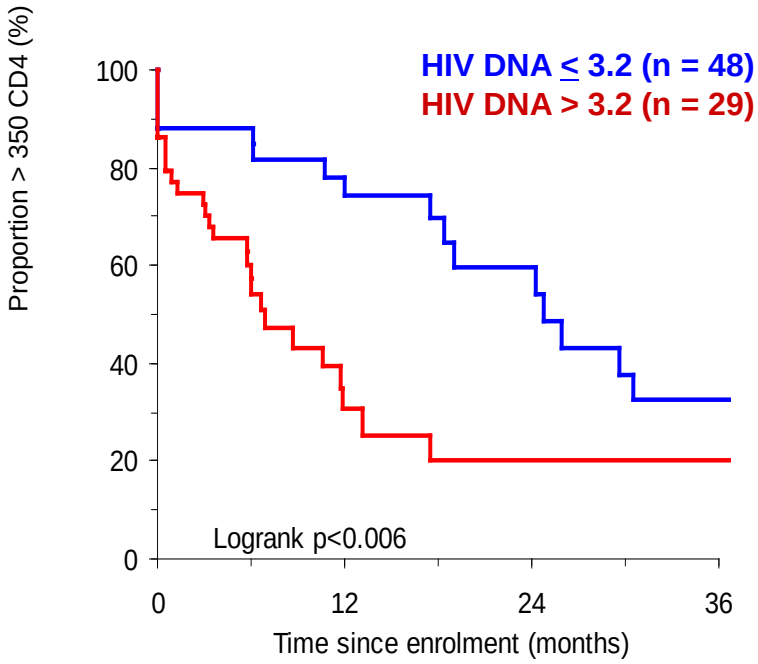
674 patients cohorte primo

Ghosn et al 2010

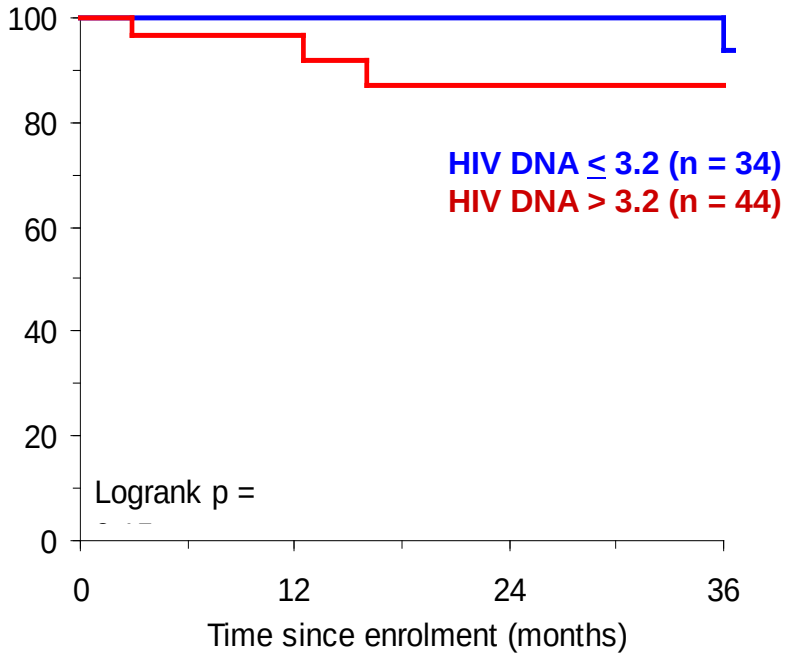
Progression-free survival according to the baseline HIV DNA level : ANRS Primo Cohort

155 patients, ne recevant pas de TT 36 mois après la primo-infection

A : CD4 à J0 < 628/mm³



B: CD4 à J0 ≥ 628/mm³

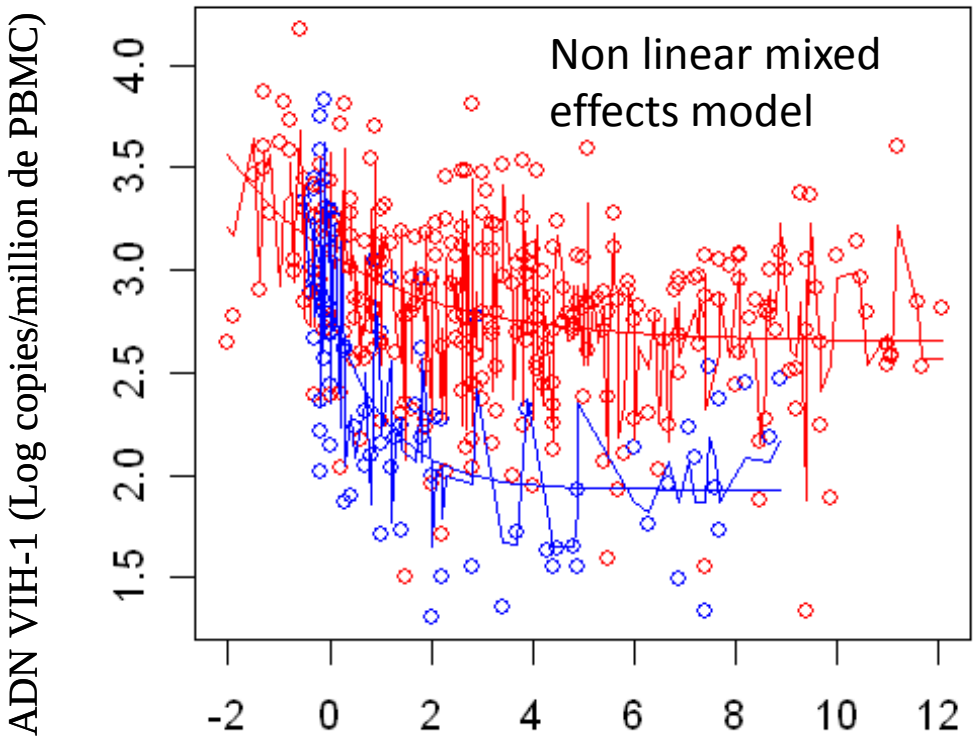


Stratification for the median baseline CD4 cell count of 628/mm³, Kaplan-Meier estimates were made for patients with low CD4 cell counts (A) and high CD4 cell count (B).

Goujard et al, CID 2006

Modélisation des Réservoirs VIH sous traitement en primo-Infection et en phase chronique

CHR ORLEANS



135 Pts Chroniques
22 Pts Primo-Inf.

Hoqueloux et al JAC 2013

Cinétique de l'ADN VIH

- à18 mois -0.68 versus - 0.43
- de 18 mois à 4 ans -0.22 versus -0.08
- suit un plateau dans les deux groupes

1- S.Yerly, AIDS 2000

2-Gianella sara, effect of early antiretroviral therapy during primary HIV-1 infection on cell-associated HIV-1 DNA and plasma HIV-1 RNA,Antiviral Therapy 2011;16:535-545

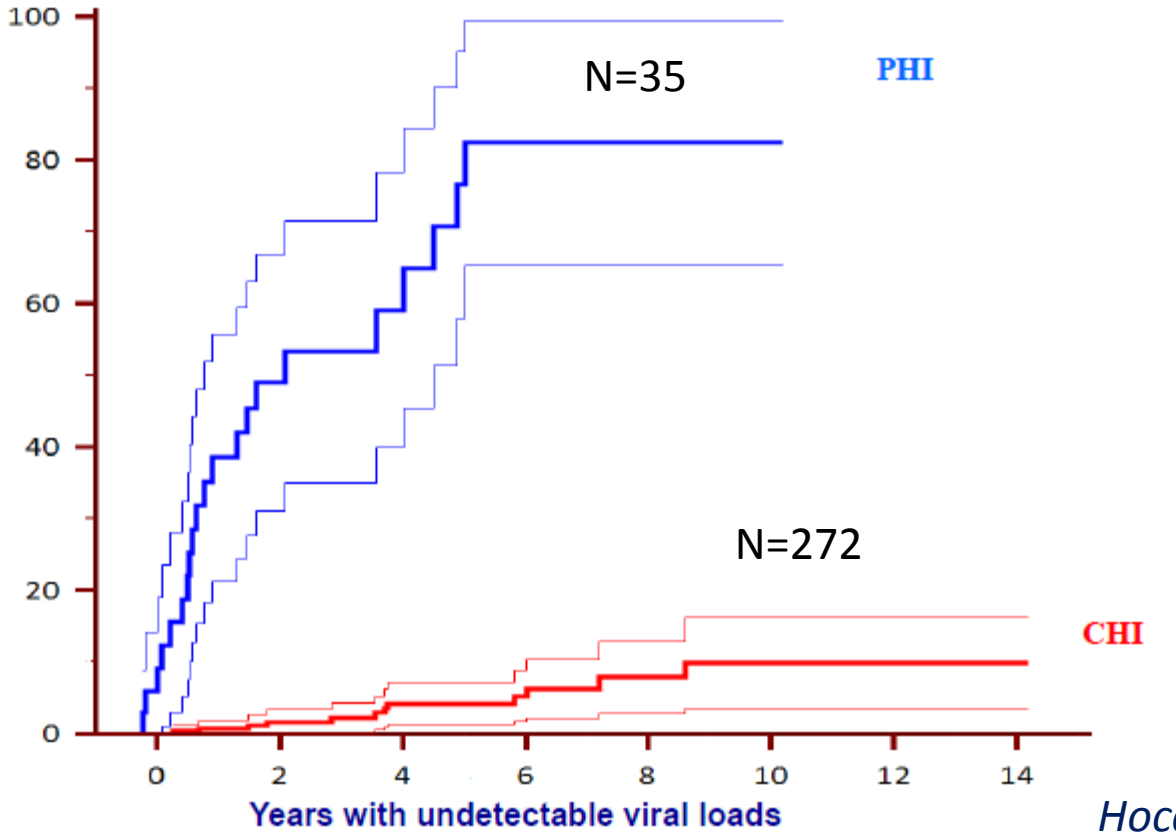
3-Strain, M. C., S. J. Little, et al. (2005). Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. Journal of infectious diseases 191(9): 1410-1418.

4-Victor von Wyl early antiretroviral therapy during primary HIV-1 infection results in a transient reduction of the viral setpoint upon treatment interruption, plosone, november 2011

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

PRIMO ART enhances the probability to achieve both low cell-associated HIV-DNA level and normal T cells count

Probability to achieve both low cell-associated HIV-DNA level and normal T cells count



Hocqueloux, JAC 2013

Baseline characteristics :OPTIPRIM

	N=90
% Men	92.2
% MSM	75.6
Age[a]	35.5 (28 - 44)
% Symptomatic	97
Acute stage	43%
HIV-1 RNA log copies/ml[a] (abbot roche)	5.4 (4.9 - 5.8)
HIV-1 DNA log cp/million PBMC [a] (technique ANRS comercialize by Biocentric)	3.6 (3.4 - 4.1)
CD4+ T cell (count /mm^3)[a]	472 (368 - 640)

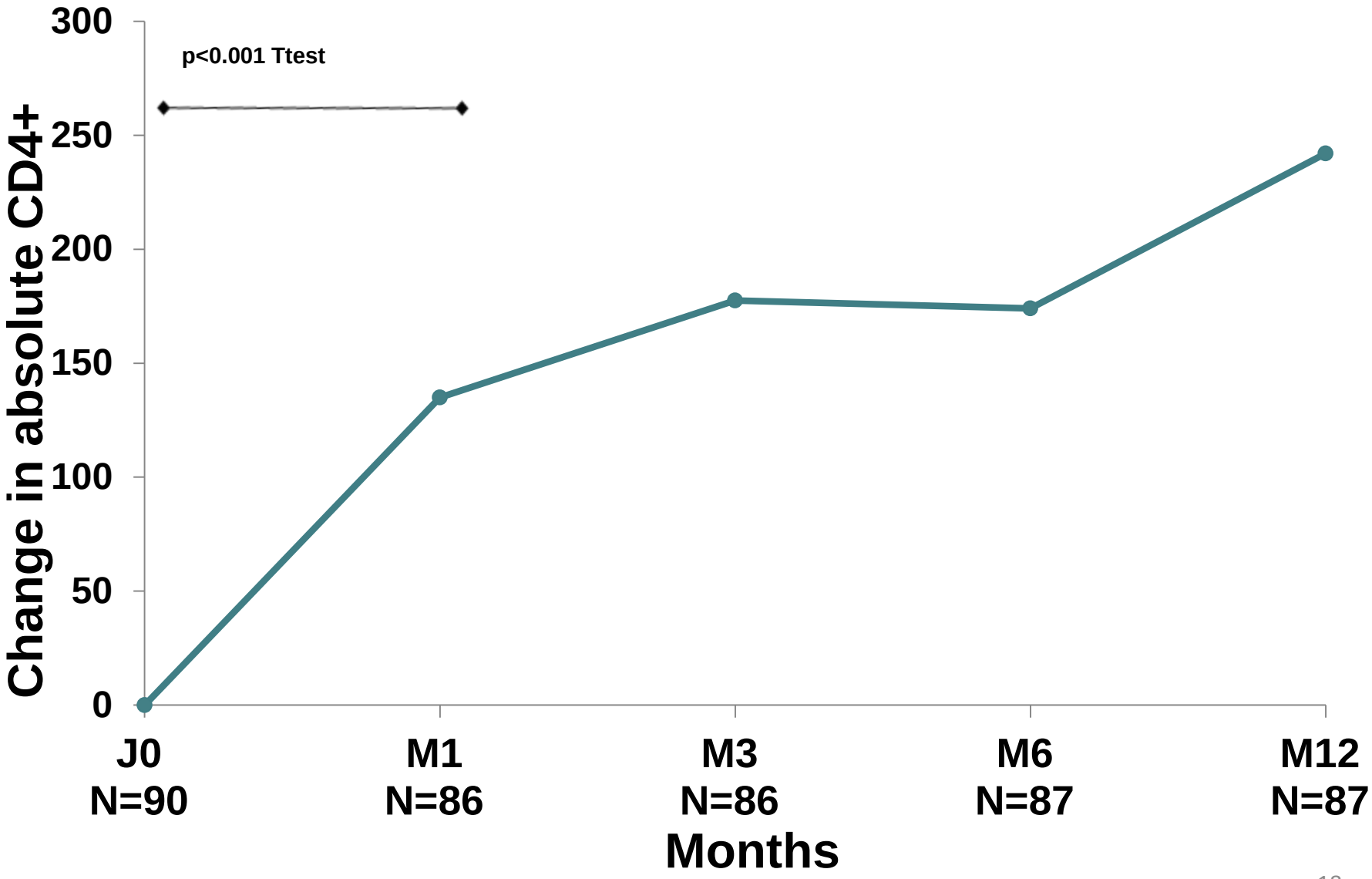
[a]Median, IQR

[b](0 - 1 Ab on western blot at enrolment)

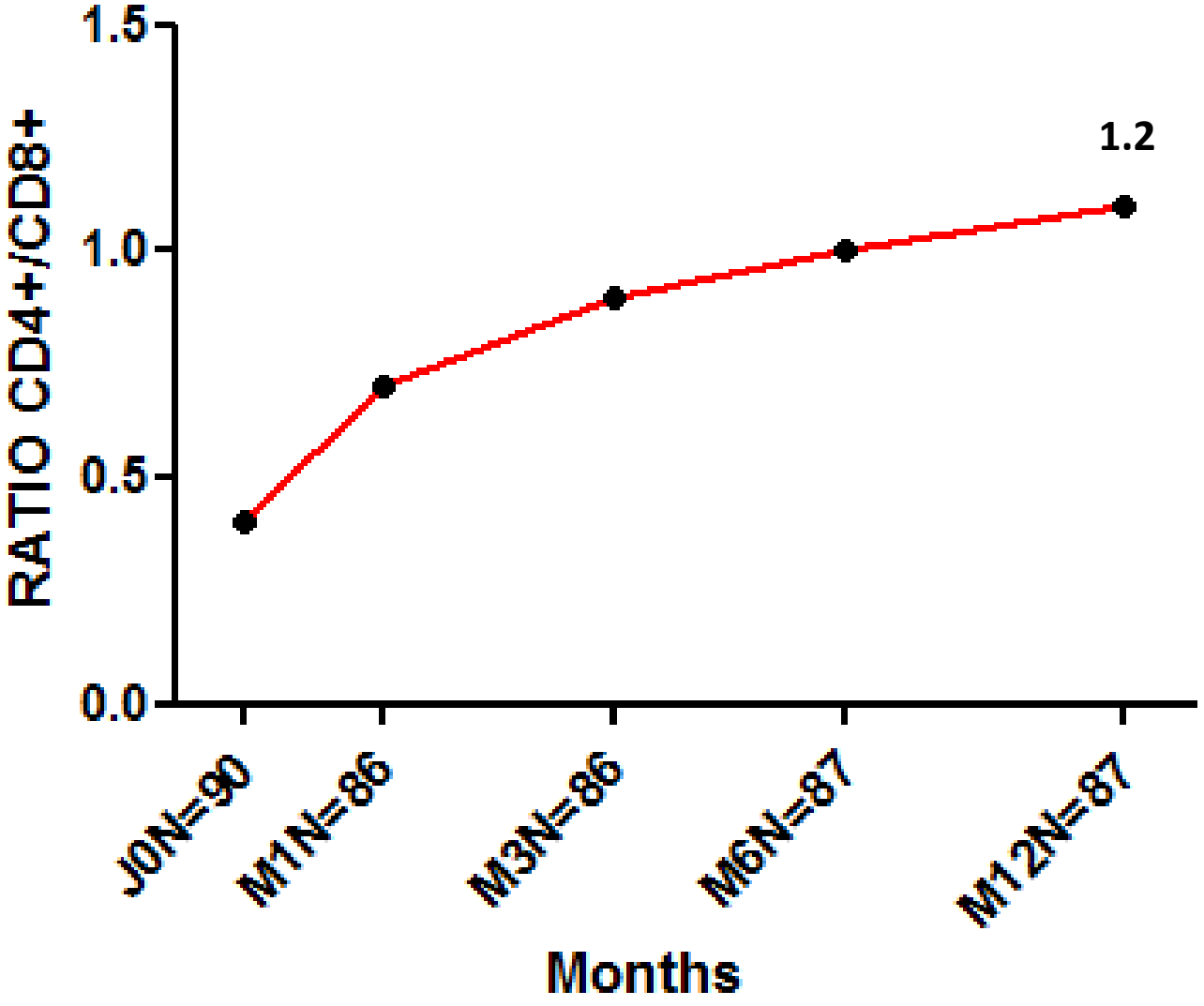
Patient disposition - Month 12

- 90 patients randomized and included
- 2 patients drop out (pregnancy, patient decision)
- **Tolerance :**
  - well tolerated
  - 2 Serious adverse effects (both in 3 drugs arm)
    - 1 lipodystrophy
    - 1 acute pancreatitis

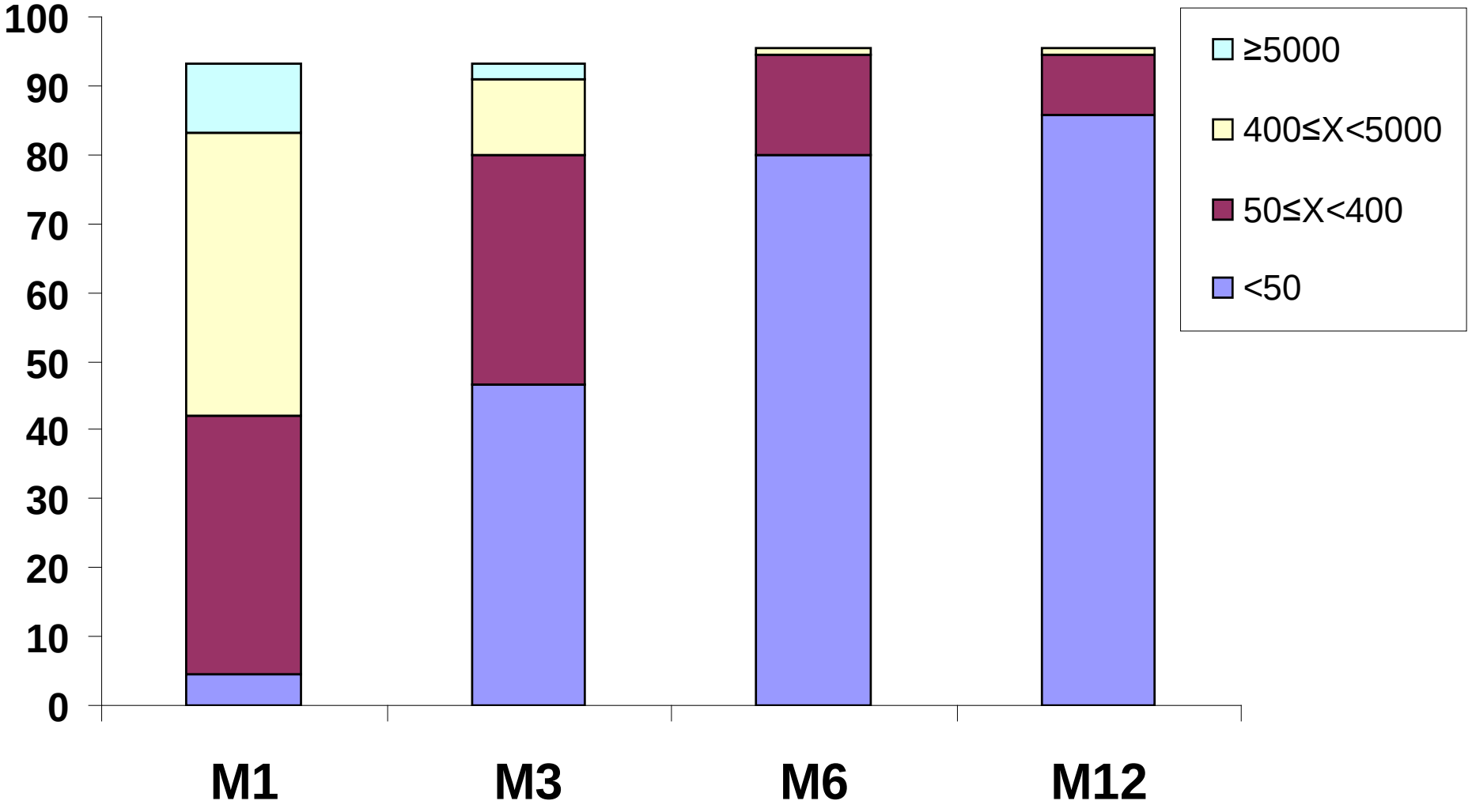
Immunology: Median change in absolute CD4+ T cells (/mm3)



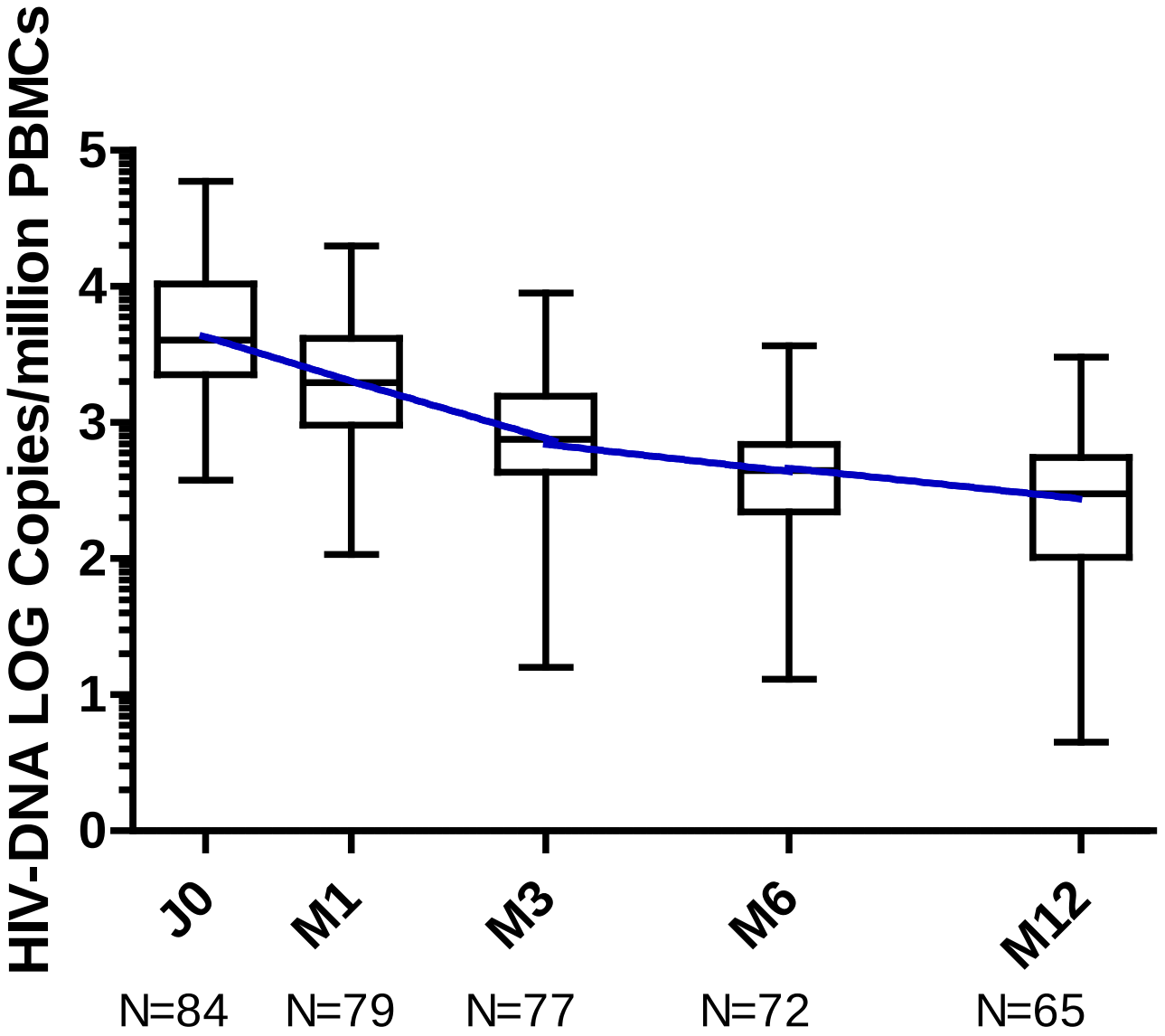
Immunology: Ratio CD4/CD8 Increase



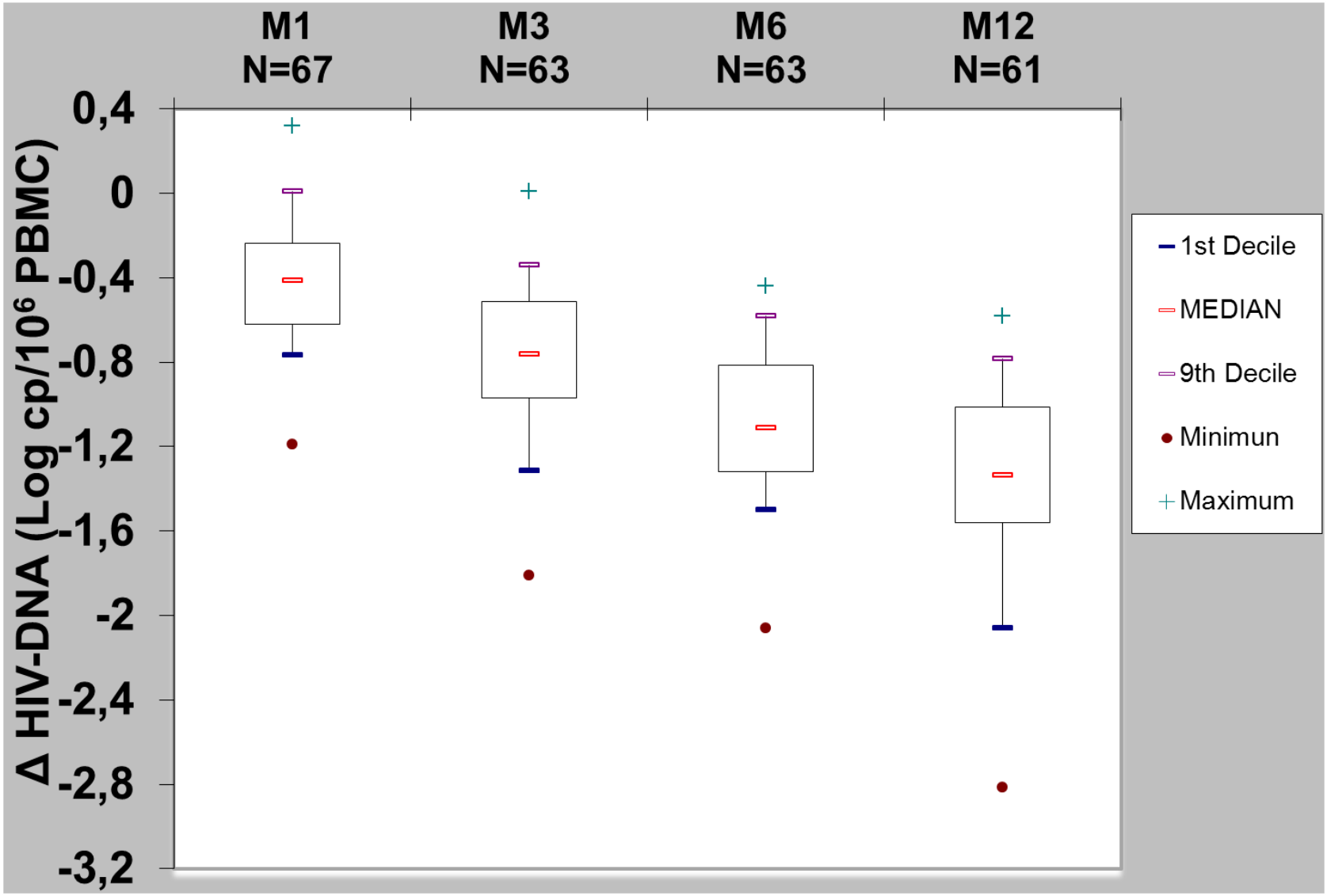
ARN-VIH1 : OPTIPRIM



ADN-VIH : OPTIPRIM

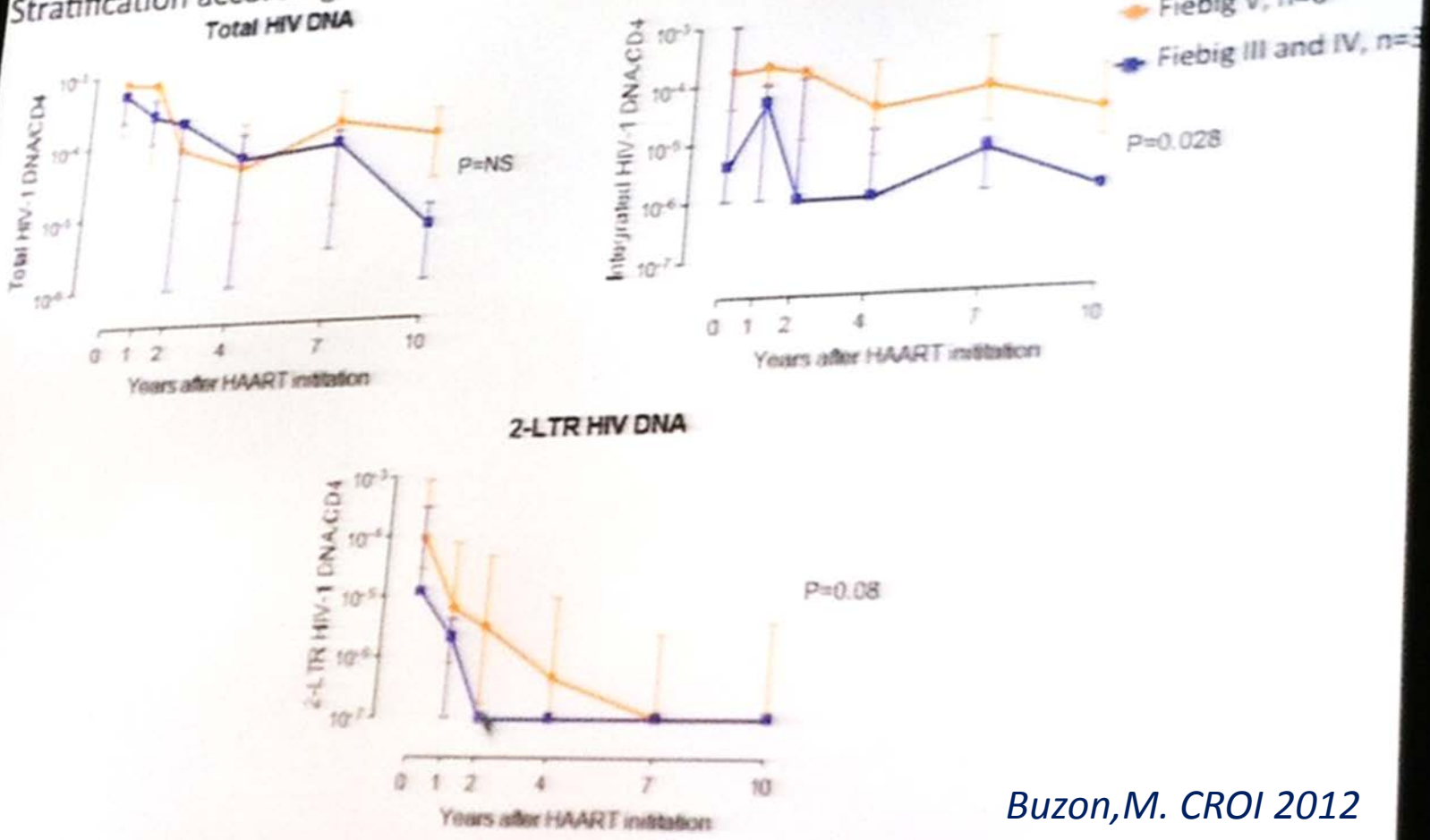


Delta ADN-VIH



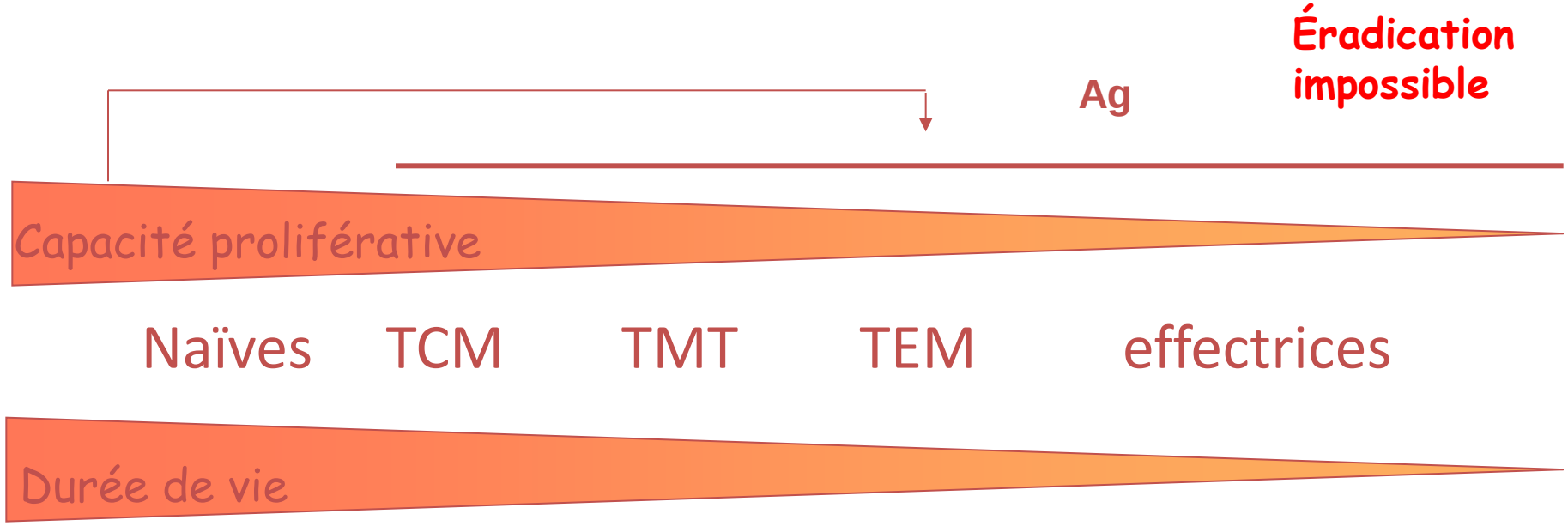
HAART initiation at Fiebig III and IV results in better depletion of integrated and 2LTR HIV DNA

Stratification according to Fiebig Stage



Buzon,M. CROI 2012

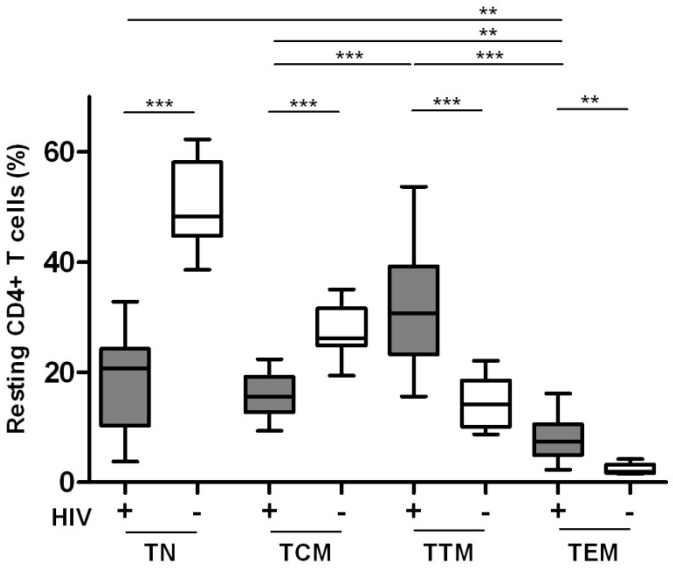
Capacité proliférative et demi-vie des sous-populations lymphocytaires T CD4

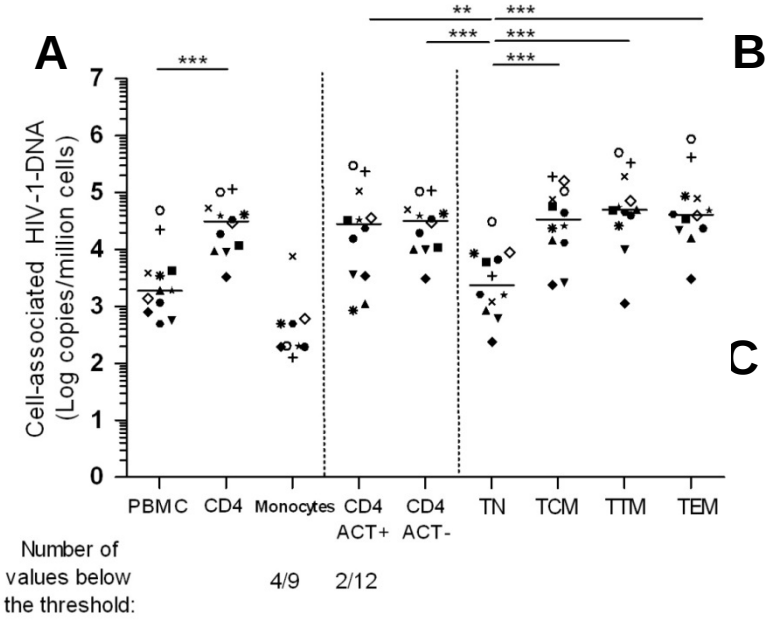


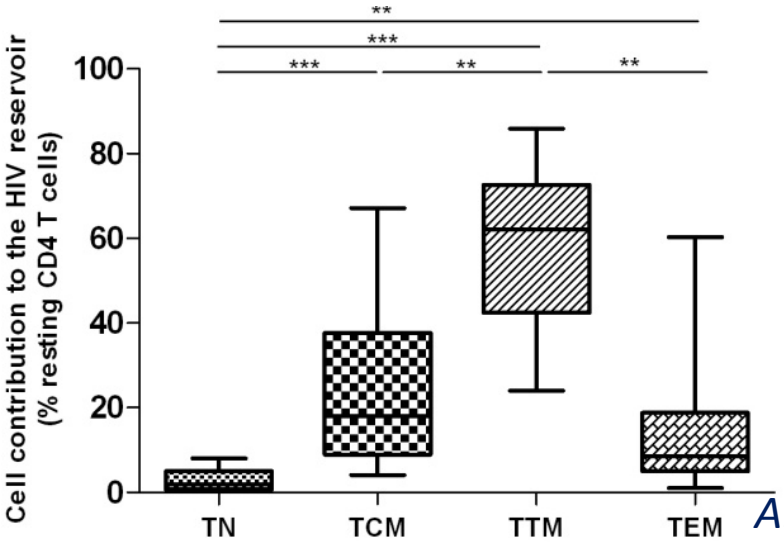
Durée de vie	10 ANS	6-12 mois	3-6 mois	0,6–3 mois	8-15 jours
CXCR4	+	+	+	+	+
CCR5	+ faible	+	++	++	+++

Victor Appay et al Cytometry, 2008

Réservoir VIH-1 en primo-infection





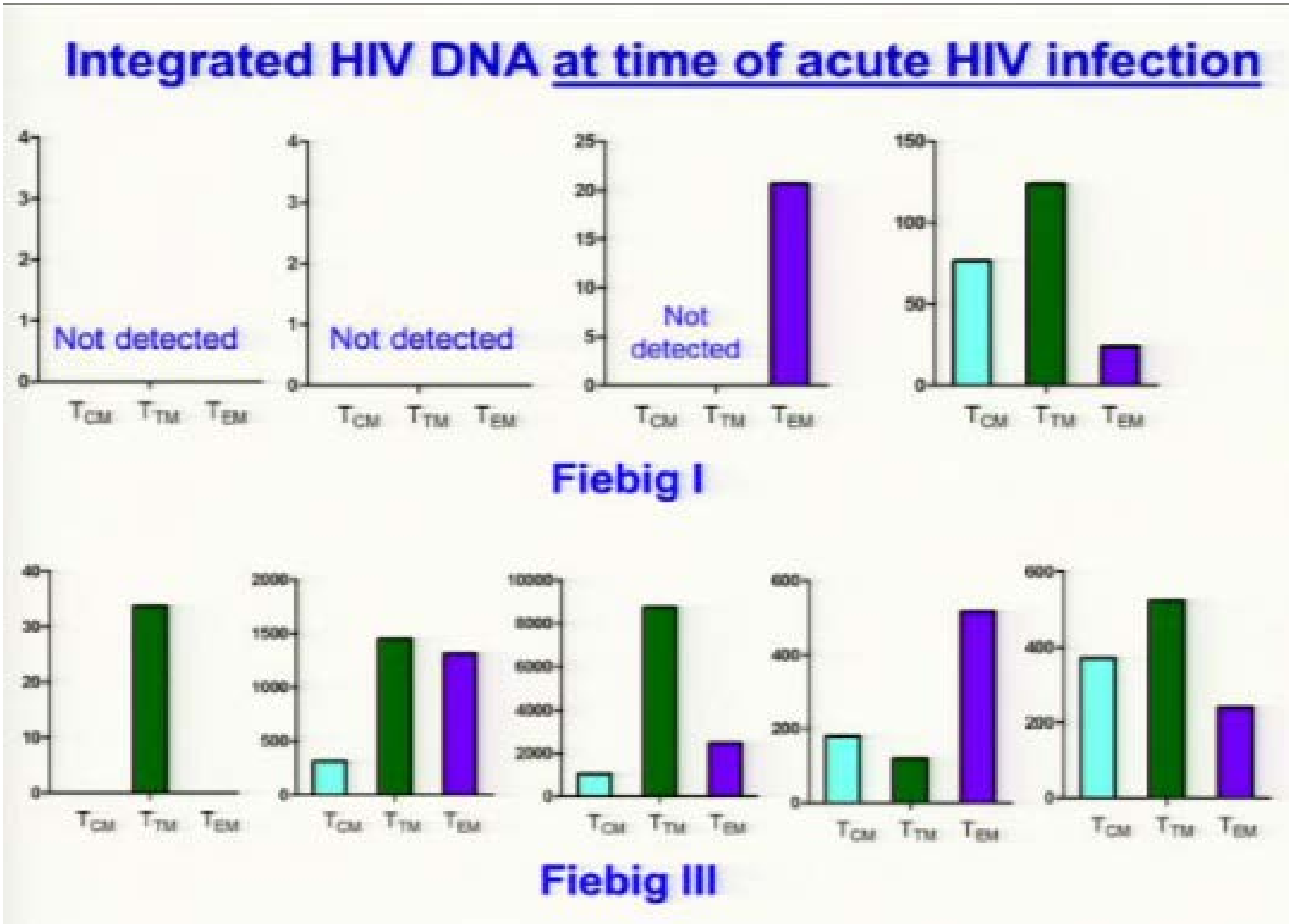


- **Rôle majeur des TCM :**

✓ *HIV Contrôleurs bas niveau de réservoir, Saez-Cirion blood 2011*

✓ *Capacité de renouvellement Okoye AA J exp Med April 2012*

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



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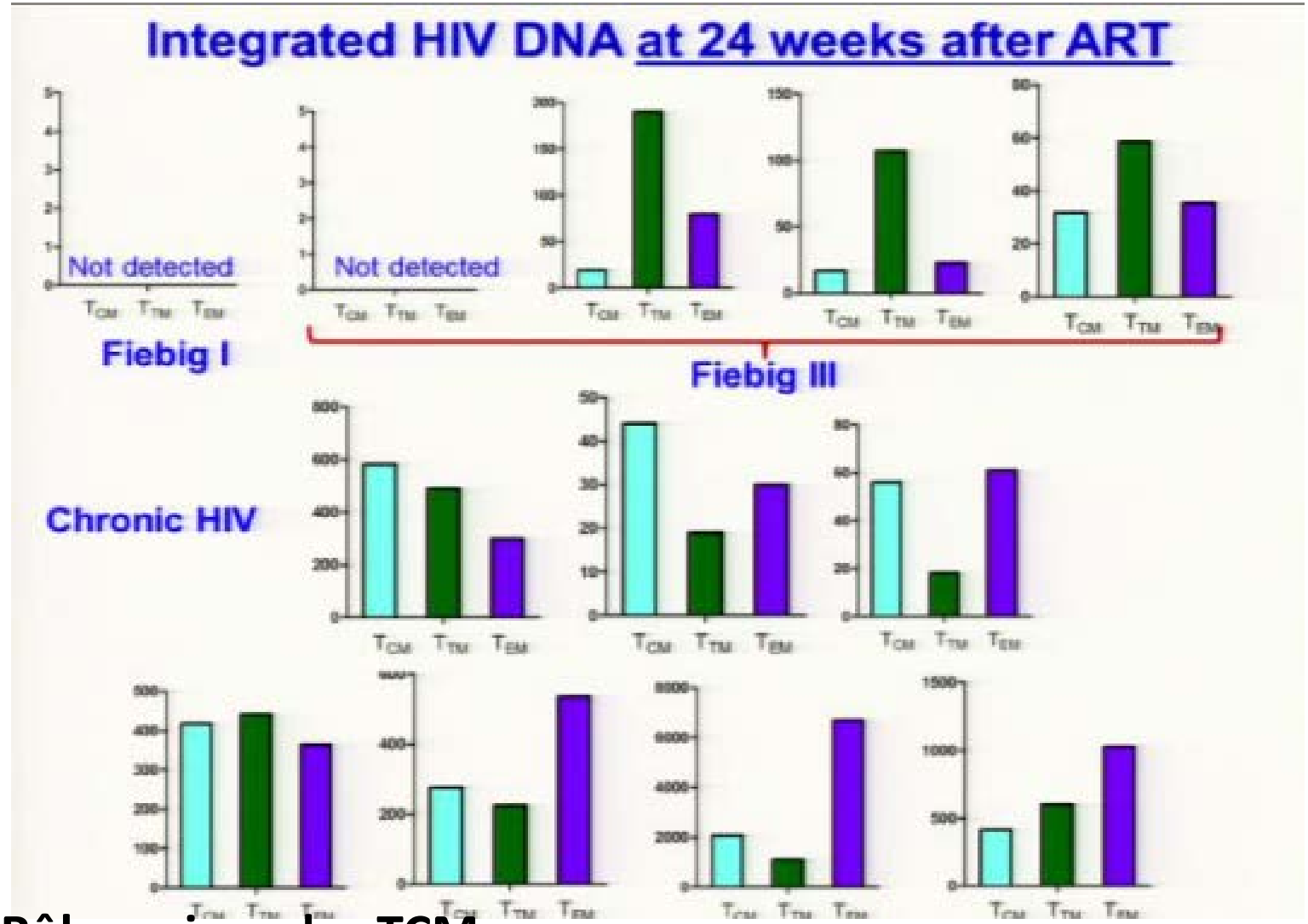

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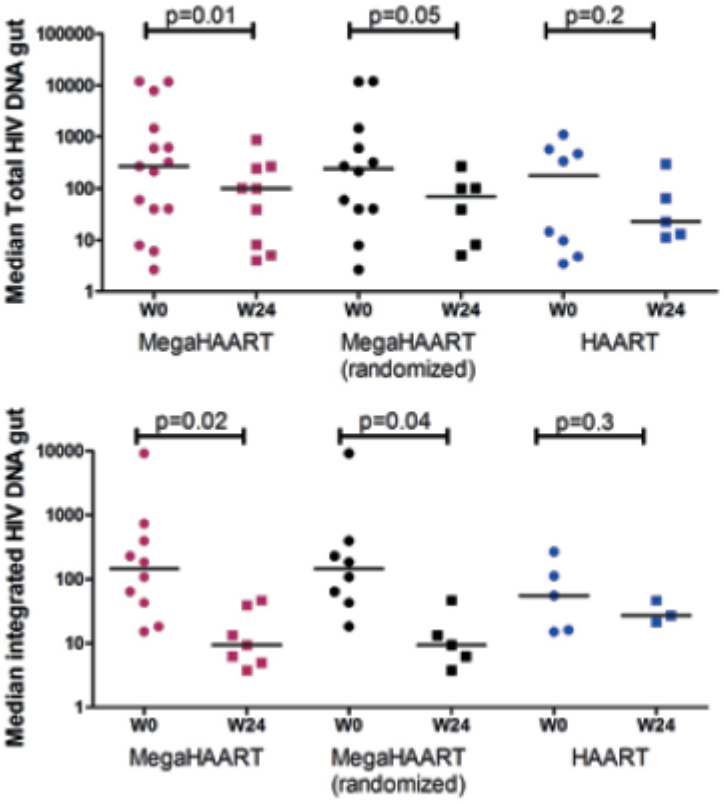
Jintanat Anaworanich, oral abstract 46, CROI 2013

95 % du réservoir est dans le GUT !

Figure 6: Total and integrated HIV DNA in sigmoid colon declined significantly after megaHAART

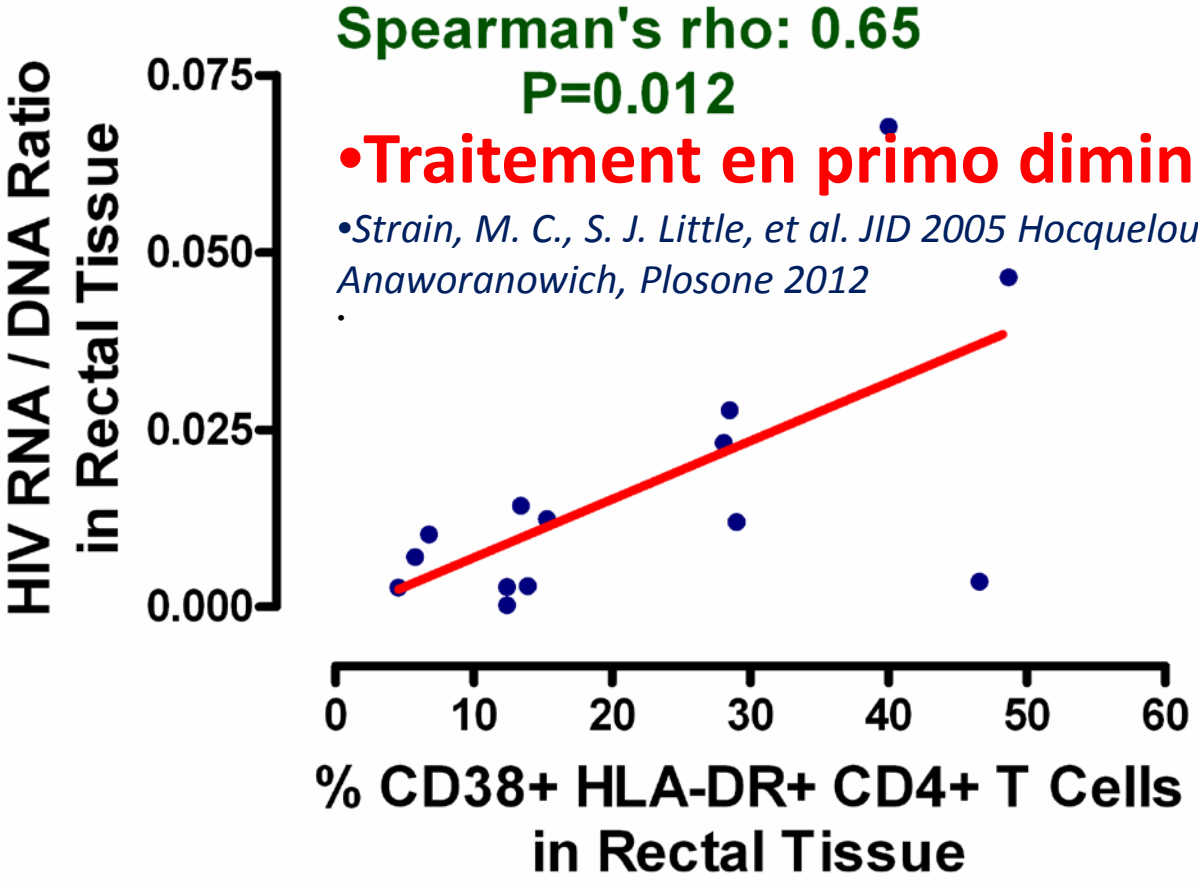


Total HIV DNA
Wk 24:
Undetectable in 35%

Integrated HIV DNA
Wk 24:
Undetectable in 78%

Jintanat Anaworanich, oral abstract 46, CROI 2013

Persistance de l'activation immunitaire chez des patients traités en fonction du niveau de réservoir



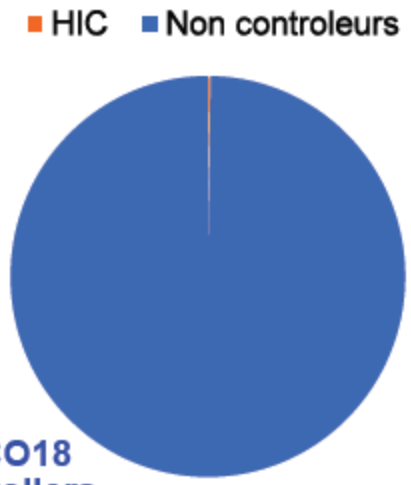
- **Traitement en primo diminue activation**
- *Strain, M. C., S. J. Little, et al. JID 2005 Hocqueloux L, et al Aids 2010 Jun, Anaworanowich, Plosone 2012*

Hatano, Hunt, Yukl and Wong (IAS 2011, JID 2013)

1.Yukle, JID 2010
2.Altfeld M, cellular immune responses and viral diversity in individuals treated during acute and early HIV-1 infection. J Exp Med; 2001;193:169-180
3.Dalod M, Weak anti-HIV CD8(+) T-cell effector activity in Hiv primary infection. J Virol.2003;77:6867-6878
4.Lacabaratz-Porret c,impact of antiretroviral therapy and changes in virus load on human immunodeficiency virus (HIV)-specific T cell responses in primary HIV infection. J Infect Dis. 2003;187:748-757
5.Rosenberg ES, Immune control of HIV-1 after early treatment of acute infection. Nature. 2000;407:523-526
6.Bouscarat F,Changes in blood CD8+ lymphocyte activation status and plasma HIV RNA levels during antiretroviral therapy. Aids. 1998;12:1267-1273
7. Hogan C, DeGruttola V, Daar E et al. A finite course of ART during early HIV-1 infection modestly delays need for subsequent ART initiation : ACTG A5217, the SETPOINT Study. 17th Conference on Retroviruses and Opportunistic Infections. San Francisco USA, Feb 2010. Abstract 134.

A long-term treatment initiated during primary infection seems to increase the chances to control viremia

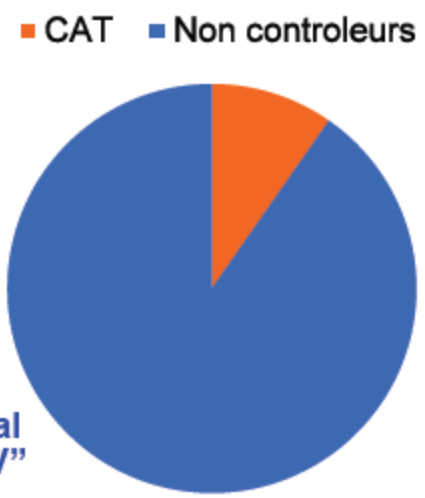
<1 % spontaneous controllers



ANRS CO18
HIV controllers

Grabar et al. AIDS 2009
Boufassa et al. PLoS One 2011

~10% controllers after interruption of early treatment
22/232 patients identified in France

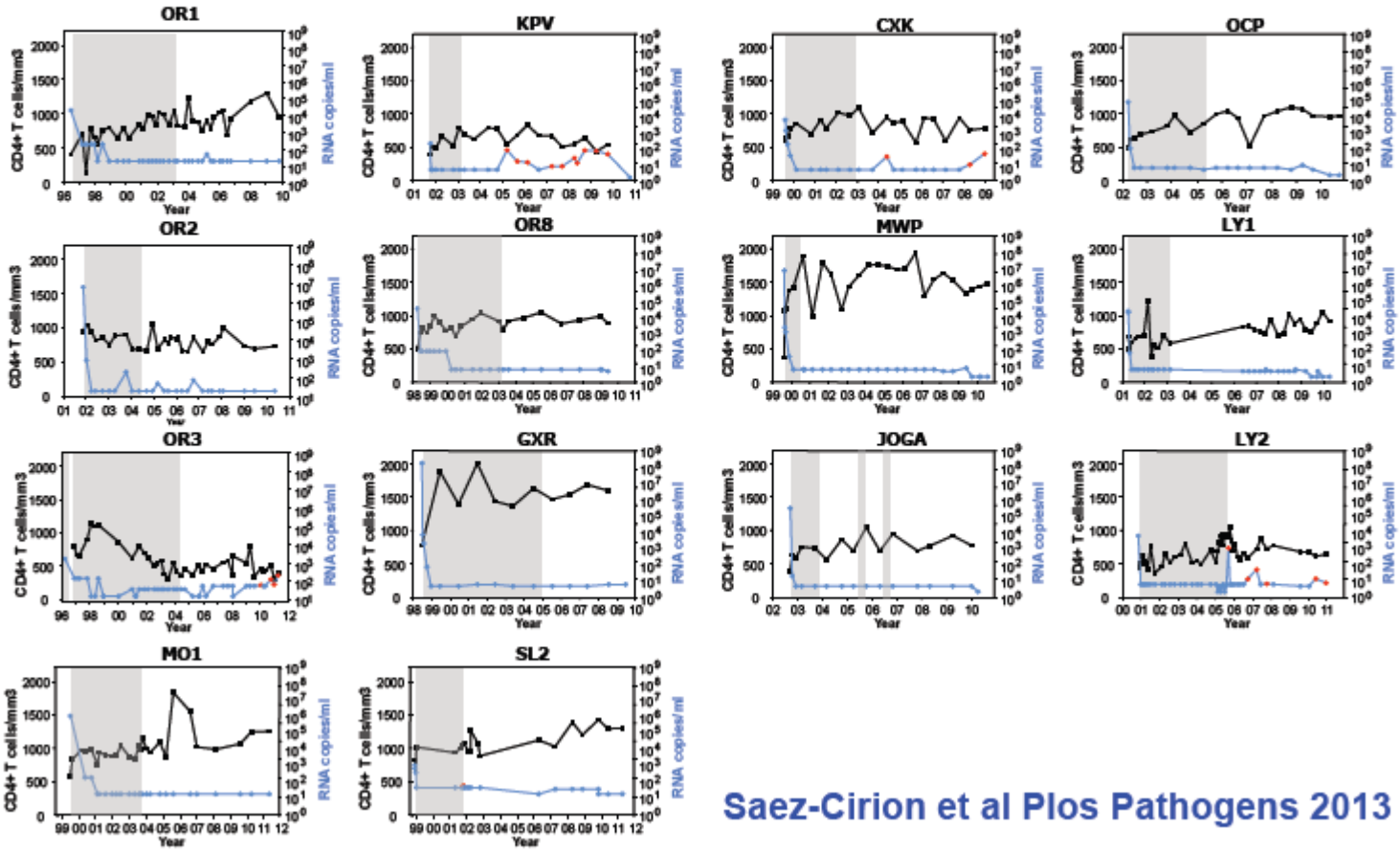


FHDH
"French Hospital Database on HIV"

Hocqueloux et al. AIDS 2010
Goujard et al. AntTher 2012
Costagliola (unpublished data)

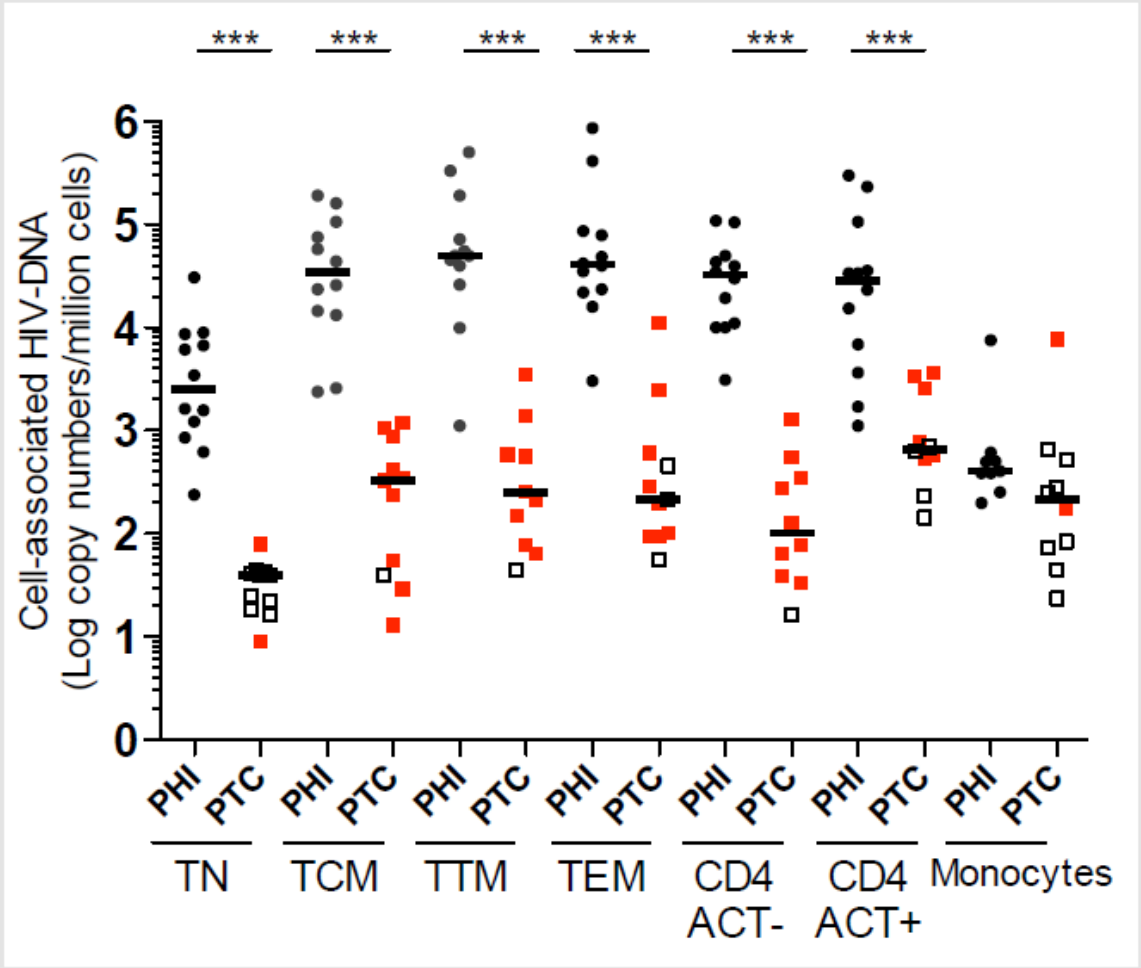
Etude VISCONTI : ANRS EP 047

14 patients en rémission

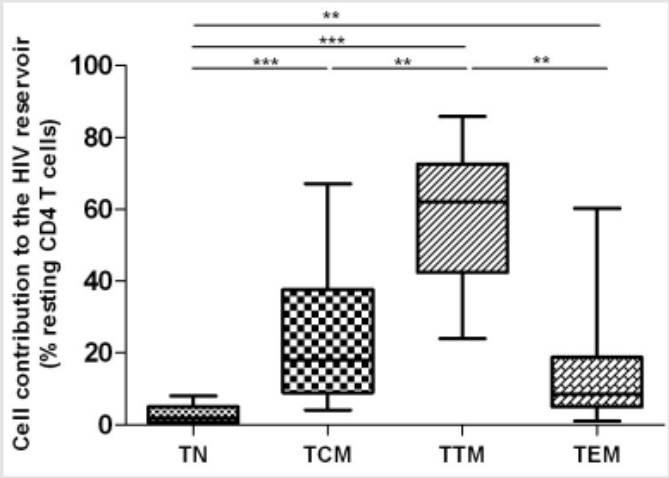


Saez-Cirion et al Plos Pathogens 2013

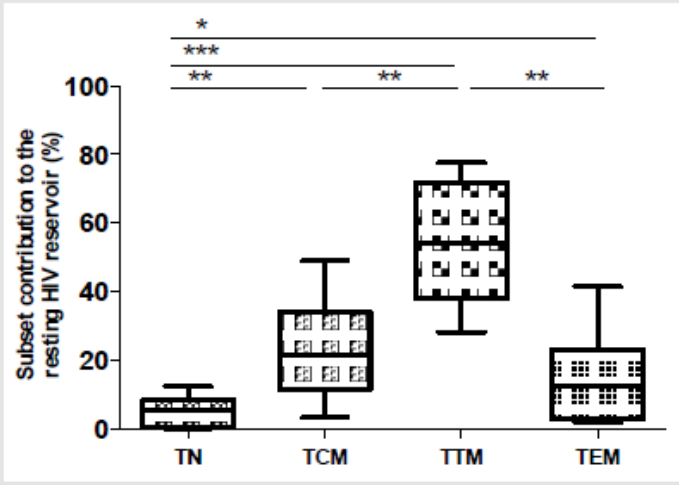
Primary infection vs PTC patients



PHI



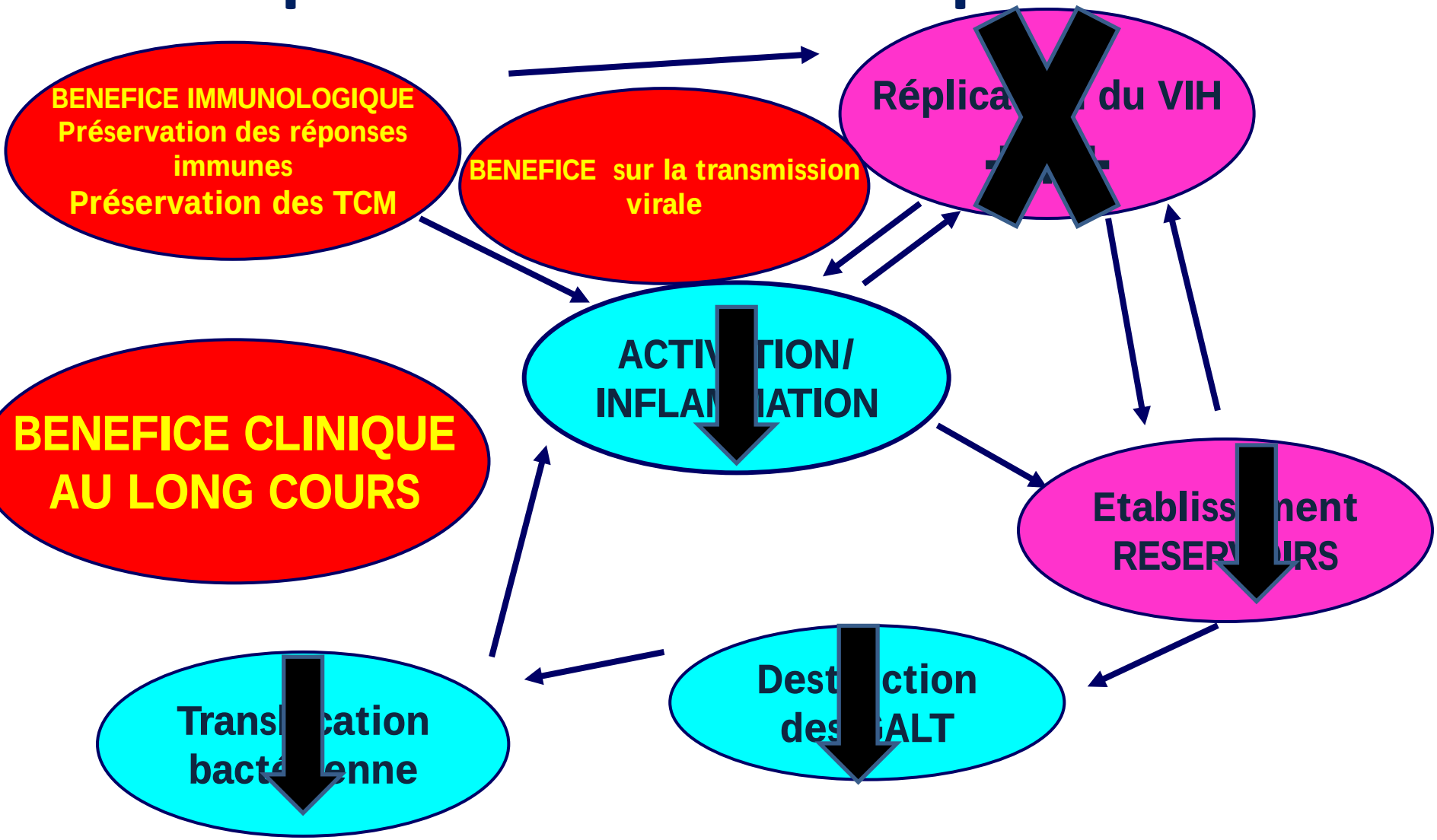
PTC



Cheret, et al ICAAC 2012

Influence du traitement précoce et long sur l'homéostasie lymphocytaire et l'homéostasie du réservoir ?

OPTIPRIM ANRS047 : un réservoir bas pour une immunité préservée



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