Influence du traitement précoce sur les réservoirs.

Dr Laurent HOCQUELOUX
CHR d'Orléans – La Source

JNI – Tours 15 juin 2012

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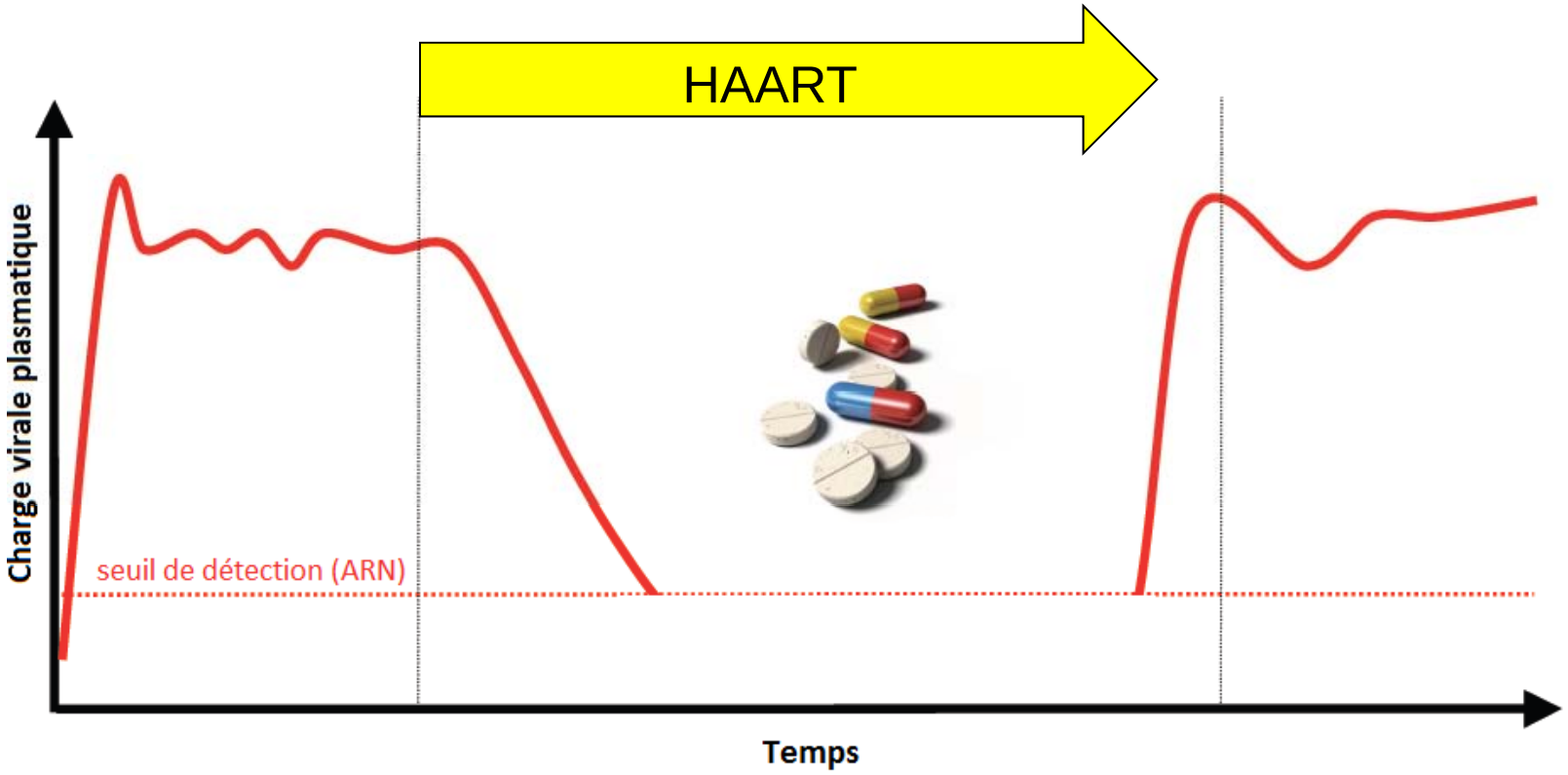
1. Rappel sur les réservoirs
2. Moteurs de l'infection VIH
3. Impact du traitement précoce

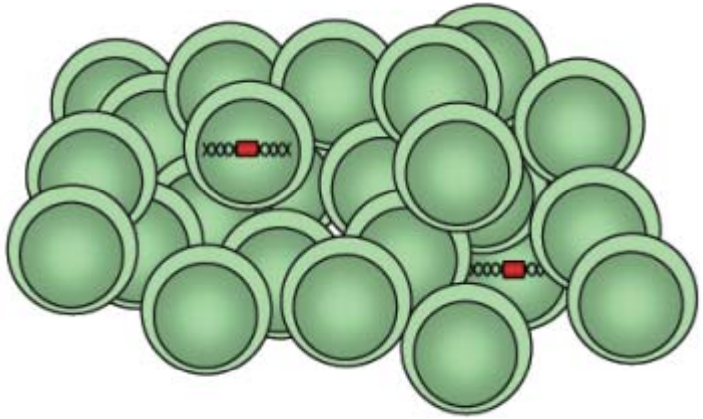
   (vs. en phase chronique)
4. Conclusions / perspectives

Réservoirs = rechute sans traitement



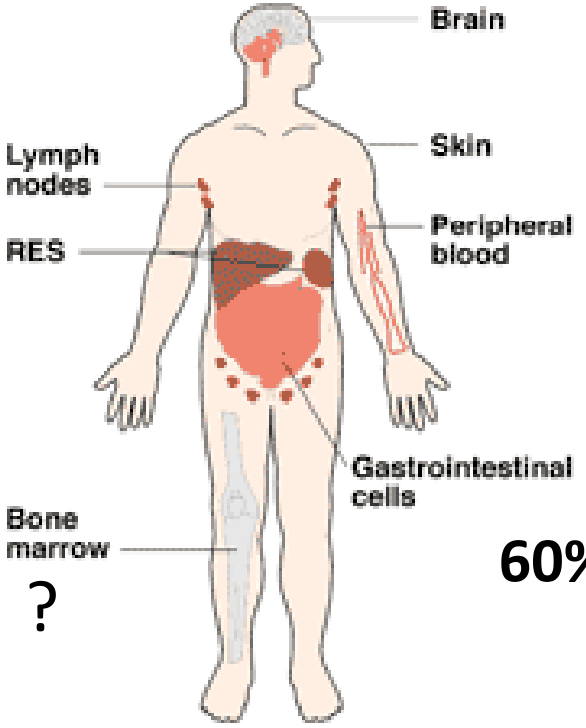
Que / où sont les réservoirs ?

Cellulaires



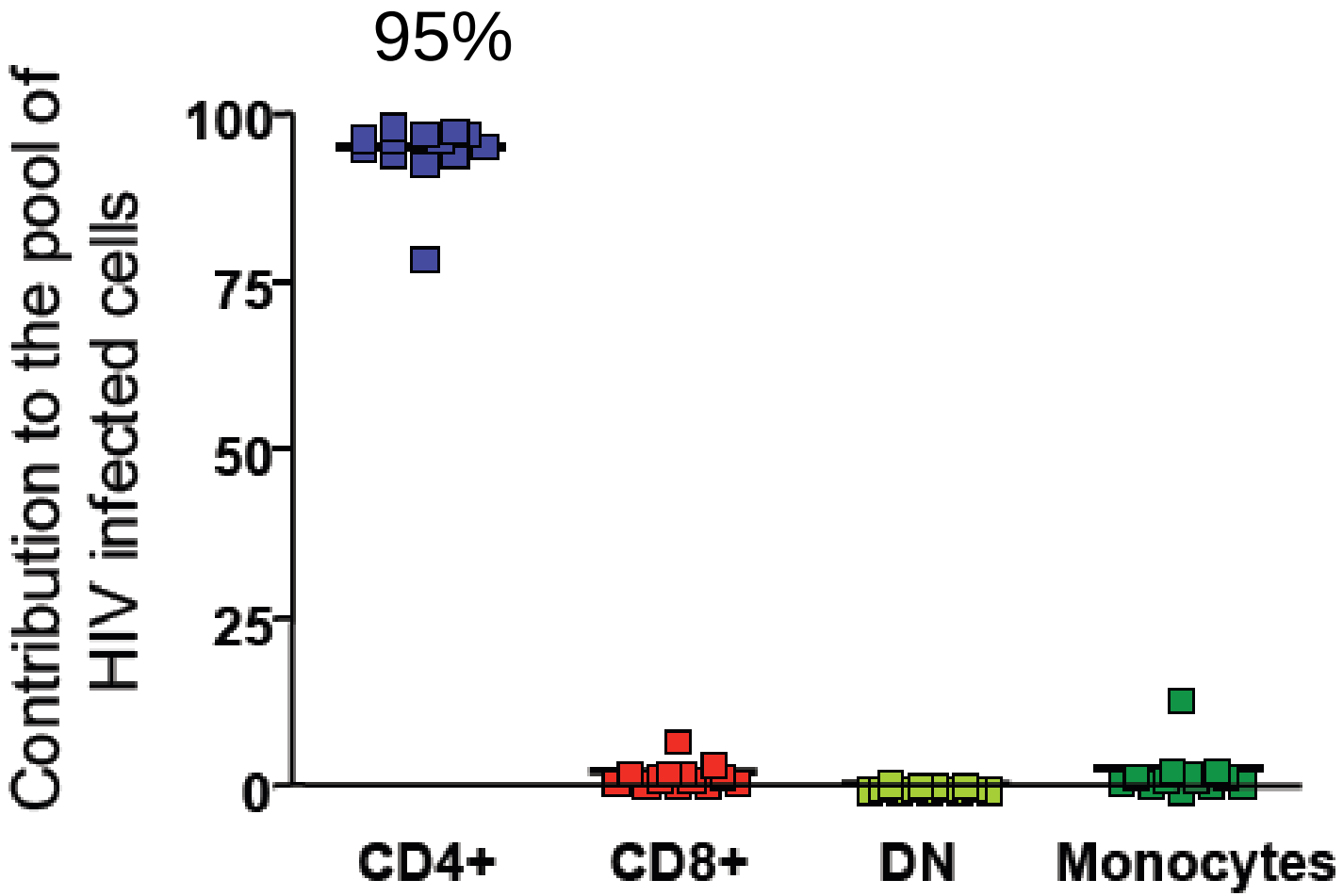
Lymphocytes
Monocytes-macrophages

Anatomiques



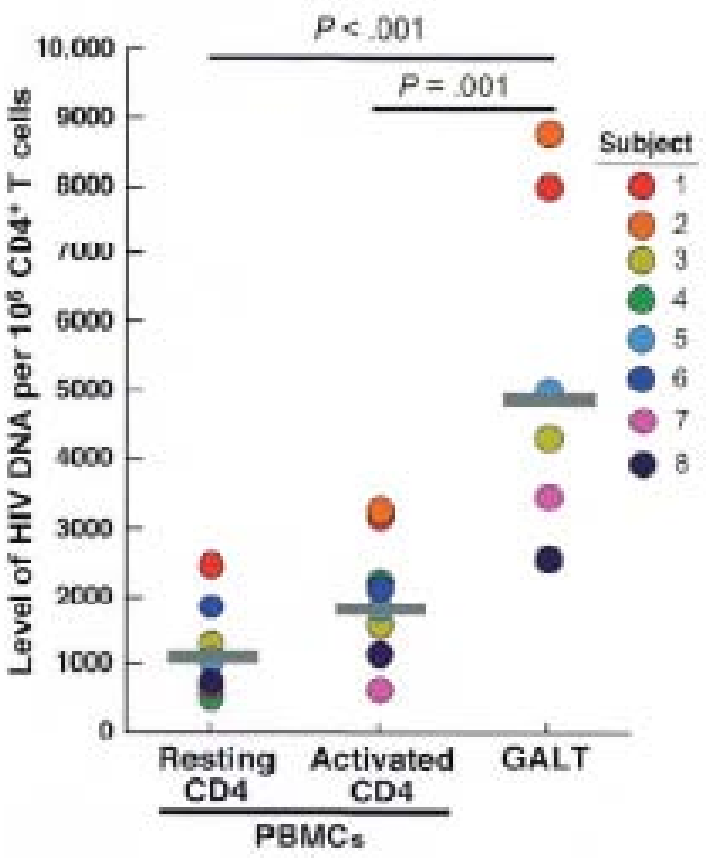
?

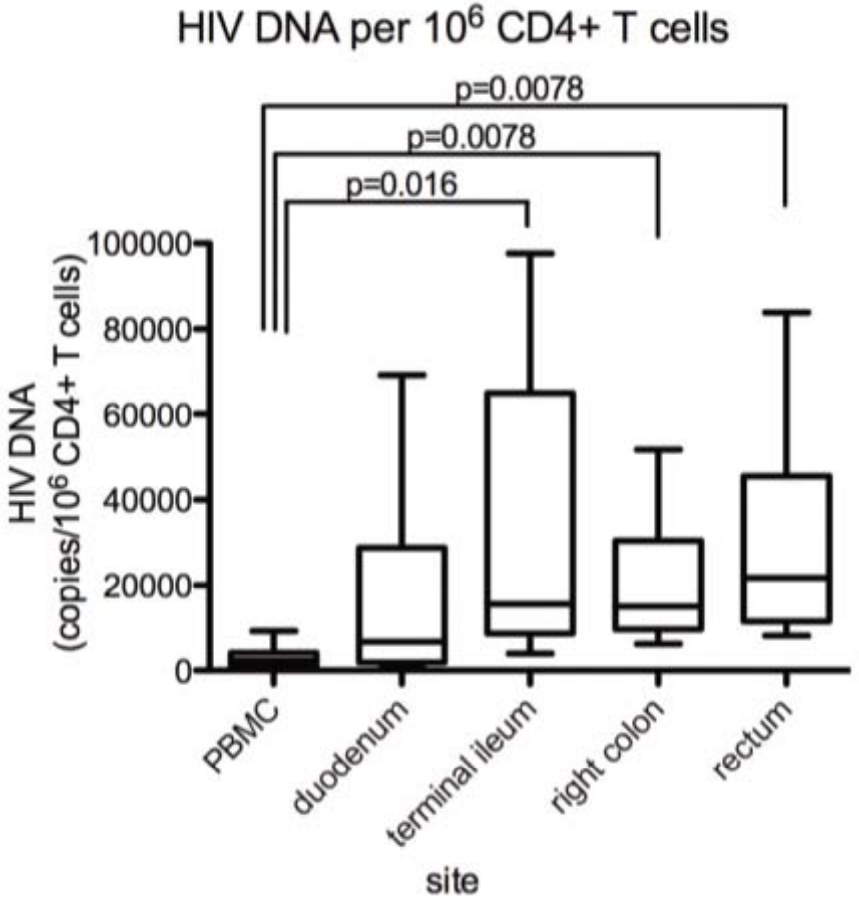
60%



Chomont N et al. *Nat Med* 2009;15:893-900.

Importance du GALT

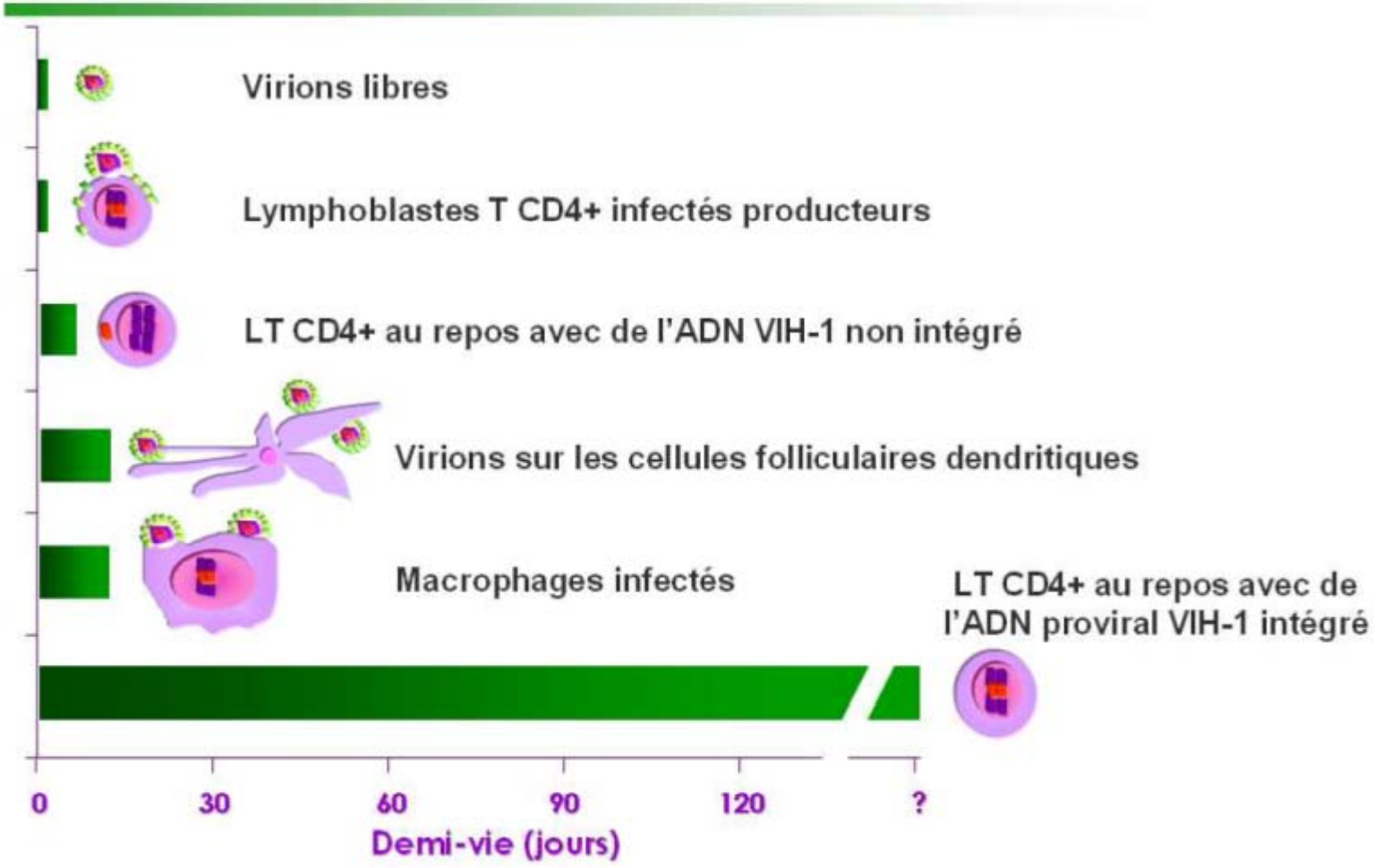


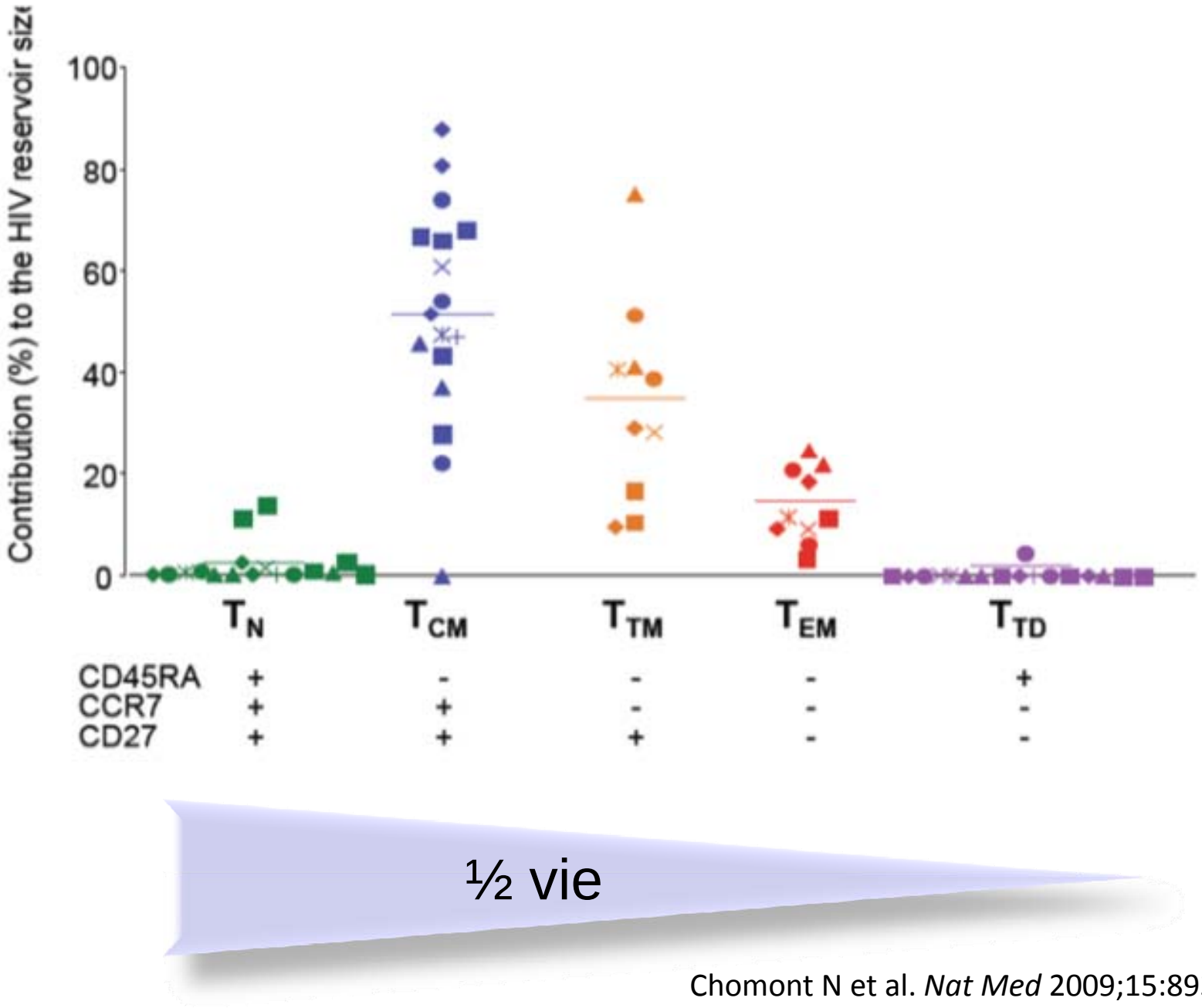


Chun TW et al. J Infecti Dis 2008

Yukl S et al. J Infecti Dis 2010;202:1553-61.

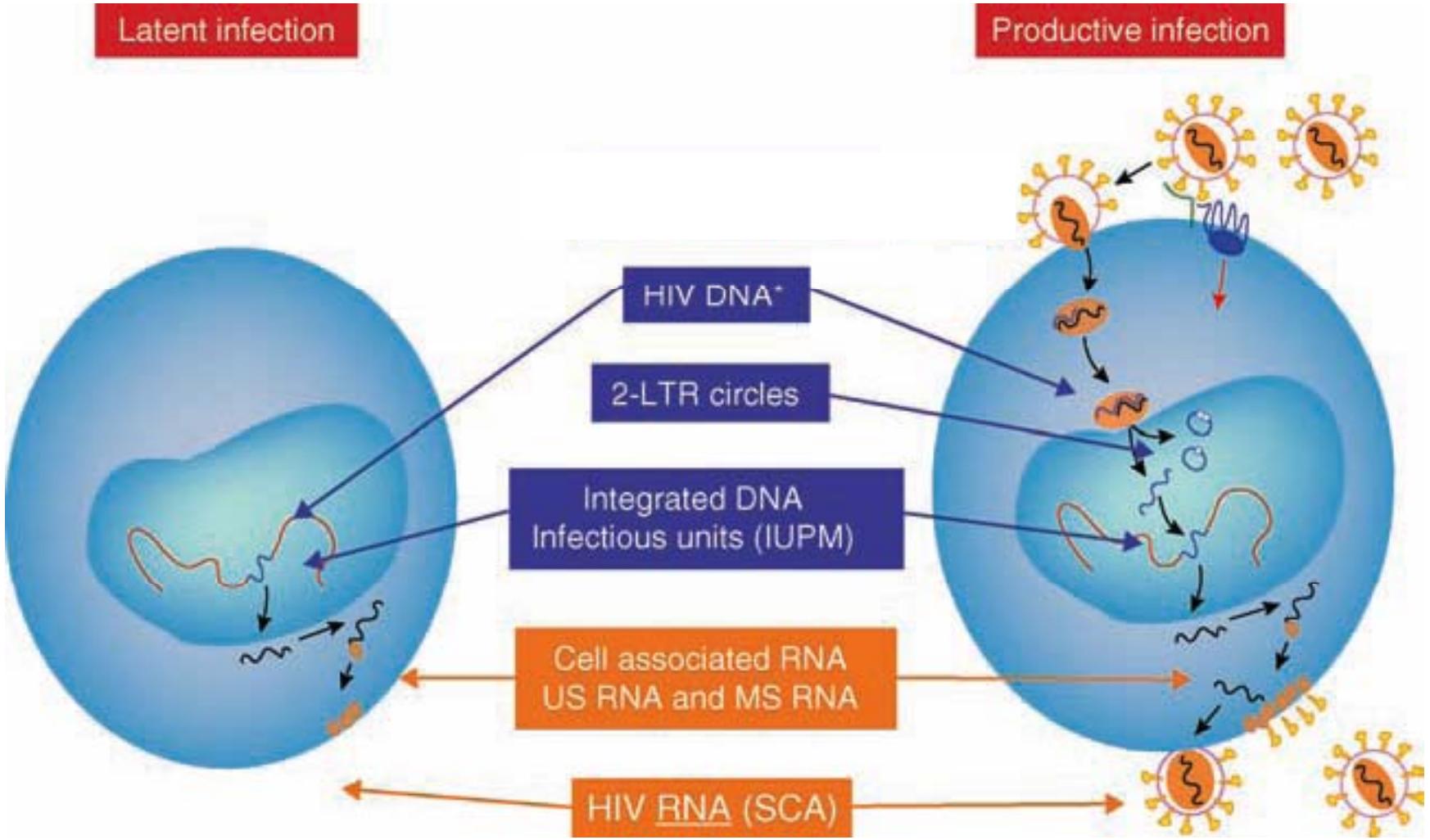
Demi-vies estimées des différentes formes du VIH





Chomont N et al. *Nat Med* 2009;15:893-900.

Comment mesurer les réservoirs ?



Lewin S, Rouzioux C. AIDS 2011; 25: 885-897.

recherche

Methods	Objective	Advantages	Disadvantages
IUPM	Measures capacity of the cell to produce infectious virus	Gold standard to identify latently infected resting $CD4^+$ T cells	Labour-intensive technique Large volume of fresh blood needed Unable to perform on tissue
Integrated HIV DNA	Measures integrated provirus	Marker of latency in sorted resting $CD4^+$ T cells Can be performed on small volumes of frozen samples	Quantifies both replication competent and incompetent integrated virus Labour-intensive technique Multiple methods used in different studies Reproducibility across multiple labs unknown
2-LTR circles	Measures a labile byproduct of HIV integration	Marker of recent cycles of replication Can be performed on small volumes of frozen samples	Reproducibility across multiple labs unknown
Total cell-associated HIV DNA	Measures unintegrated, integrated linear DNA and 2-LTR circles	Good correlation with integrated DNA Can be performed on small volumes of frozen samples including blood and tissue Standardized International quality controls available	Includes quantification of replication competent and incompetent virus

Lewin S, Rouzioux C. AIDS 2011; 25: 885-897.

routine

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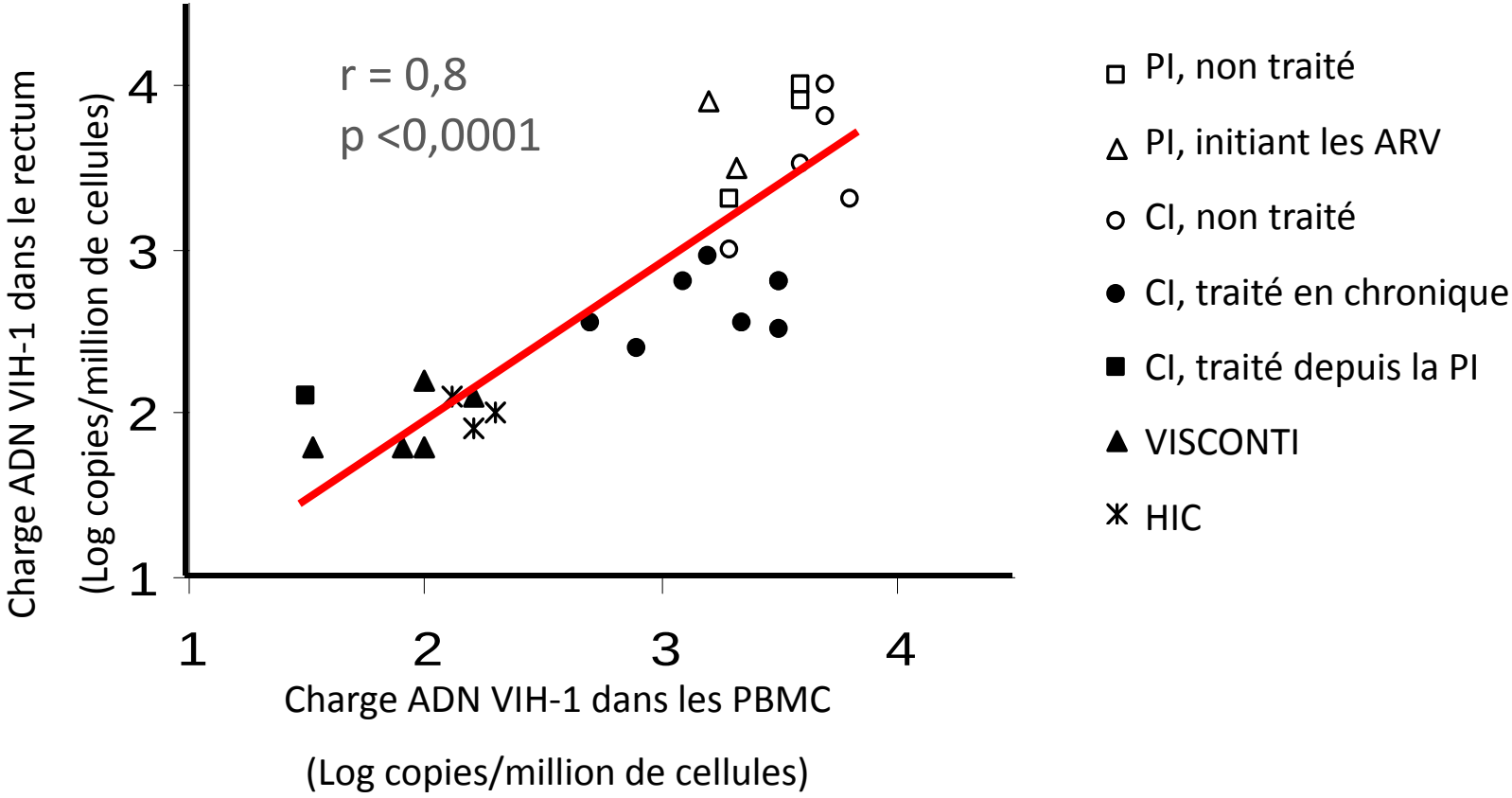
Lewin S, Rouzioux C. AIDS 2011; 25: 885-897.

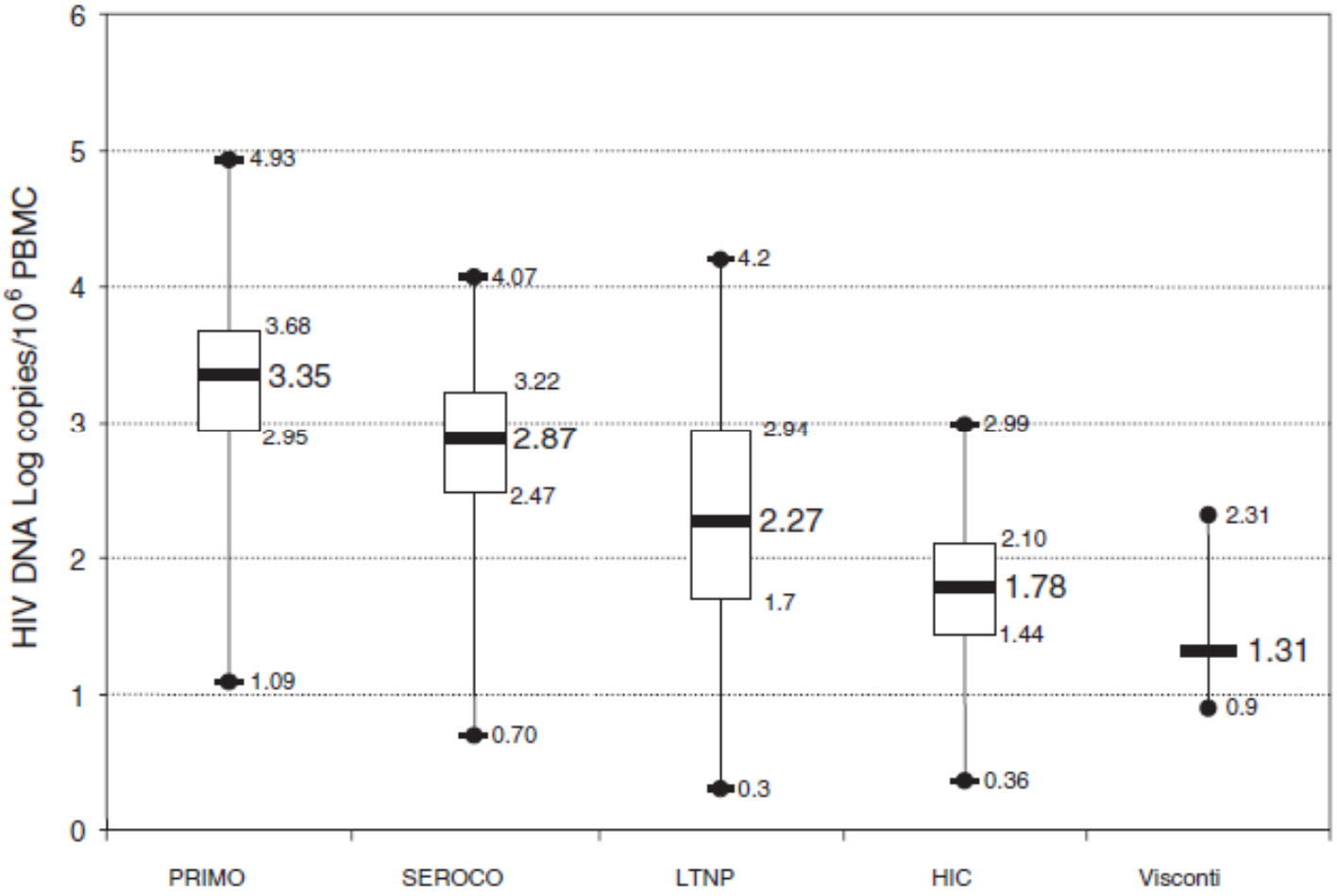
L'ADN-VIH dans les PBMC est un très bon reflet des réservoirs digestifs



Avettand-Fènoël V et al. AIDS 2008

Quelles significations ont-ils ?

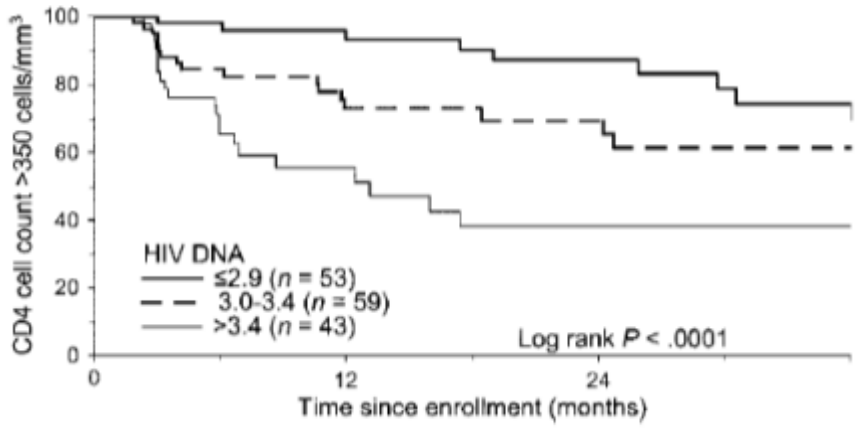
Marqueur d'évolution (sans traitement)



Lewin S, Rouzioux C. AIDS 2011; 25: 885-897.

CD4 Cell Count and HIV DNA Level Are Independent Predictors of Disease Progression after Primary HIV Type 1 Infection in Untreated Patients

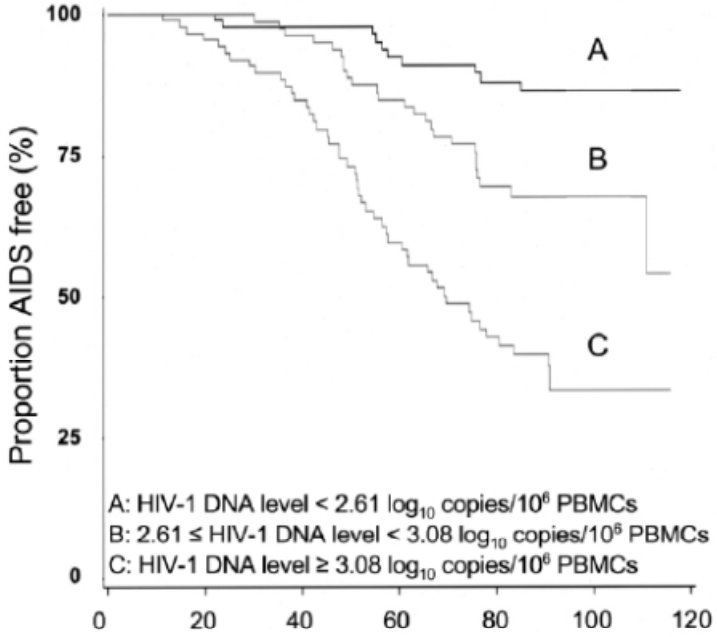
Cécile Goujard,[1,3] Mojgan Bonarek,[5] Laurence Meyer,[2] Fabrice Bonnet,[5] Marie-Laure Chaix,[6] Christiane Deveau,[2] Martine Sinet,[3] Julie Galimand,[4] Jean-François Delfraissy,[1,3] Alain Venet,[3] Christine Rouzioux,[4] Philippe Morlat,[5] and the Agence Nationale de Recherche sur le Sida PRIMO Study Group*



Clinical Infectious Diseases 2006; 42:709–15

Early Levels of HIV-1 DNA in Peripheral Blood Mononuclear Cells Are Predictive of Disease Progression Independently of HIV-1 RNA Levels and CD4+ T Cell Counts

Christine Rouzioux,[1] Jean-Baptiste Hubert,[5] Marianne Burgard,[1] Christiane Deveau,[5] Cécile Goujard,[4] Marc Bary,[3] Daniel Séréni,[4] Jean-Paul Viard,[2] Jean-François Delfraissy,[6] and Laurence Meyer,[5] for the SEROCO Cohort Study Group*



JID 2005:192 (1 July) • Rouzioux et al.

Sous traitement, marqueur prédictif :

- de la réplication résiduelle
- du risque d'échec virologique
- de rebond à l'arrêt du traitement

Havlir D et al. *J Infect Dis* 2005; **191**:1164–1168.
Hocqueloux L et al. *AIDS* 2010; **24**:1598–1601.
Yerly S et al. *AIDS* 2004; **18**:1951–1953.
Piketty C et al. *J Med Virol* 2010; **82**:1819–1828.
Masquelier B et al. *J Antimicrob Chemother* 2011; **66**:1582–1589.

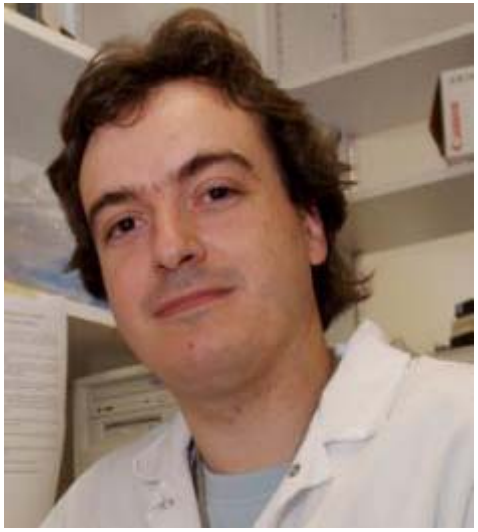
En l’absence de réservoir (fonctionnel)

Eradication

- « Berlin patient »

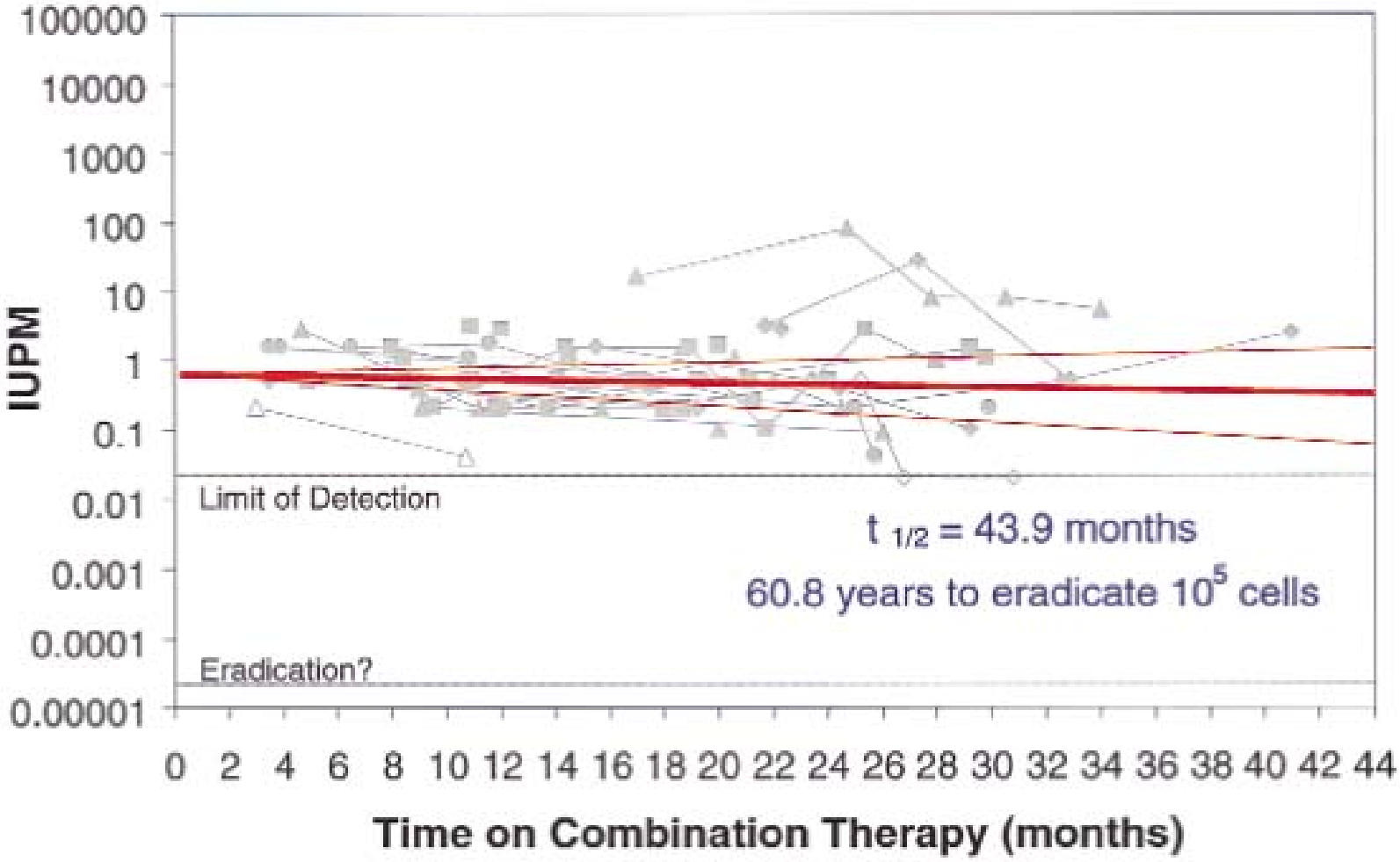
Cure fonctionnelle

- Visconti (PTC)



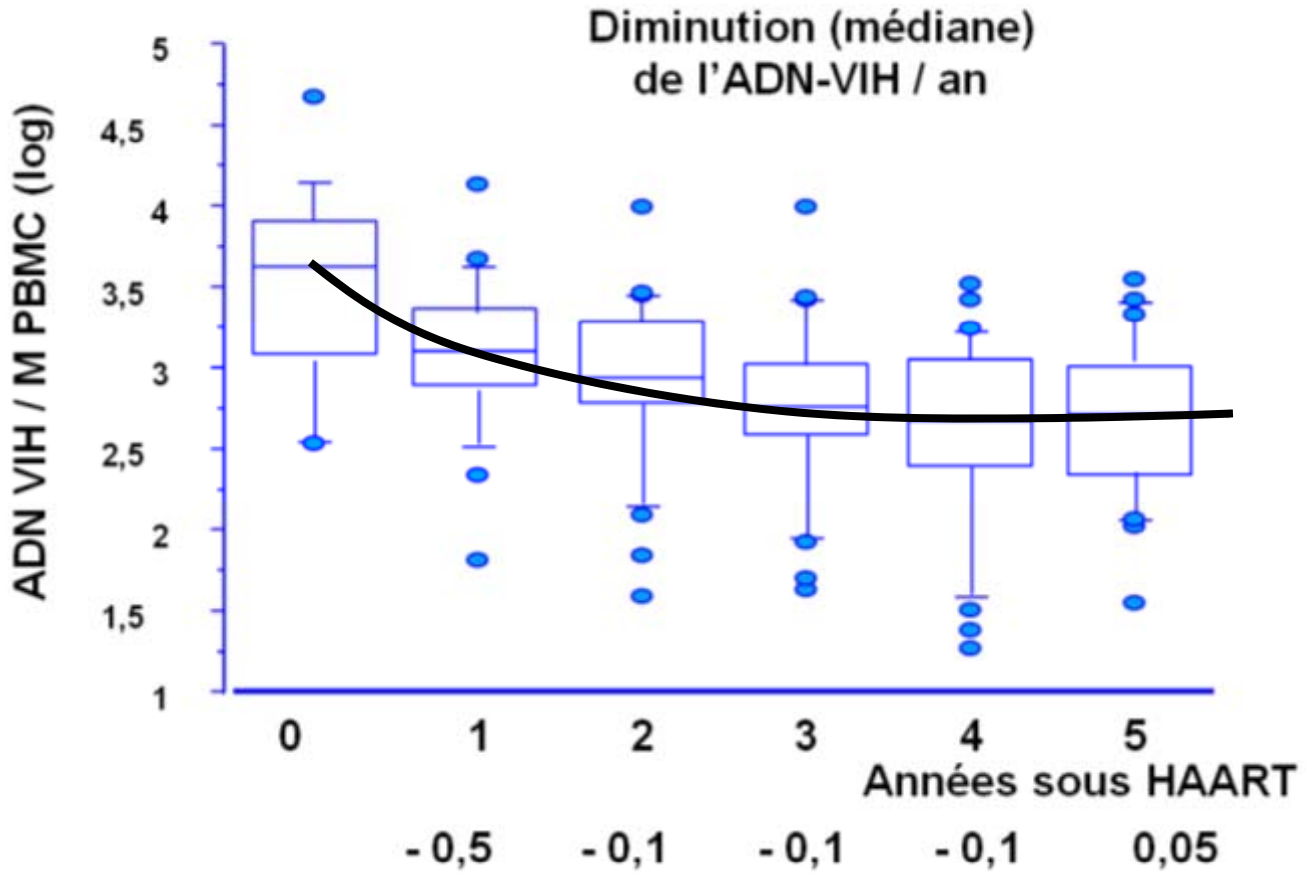
Les antirétroviraux peuvent-ils purger les réservoirs ?

Impact modeste en phase chronique



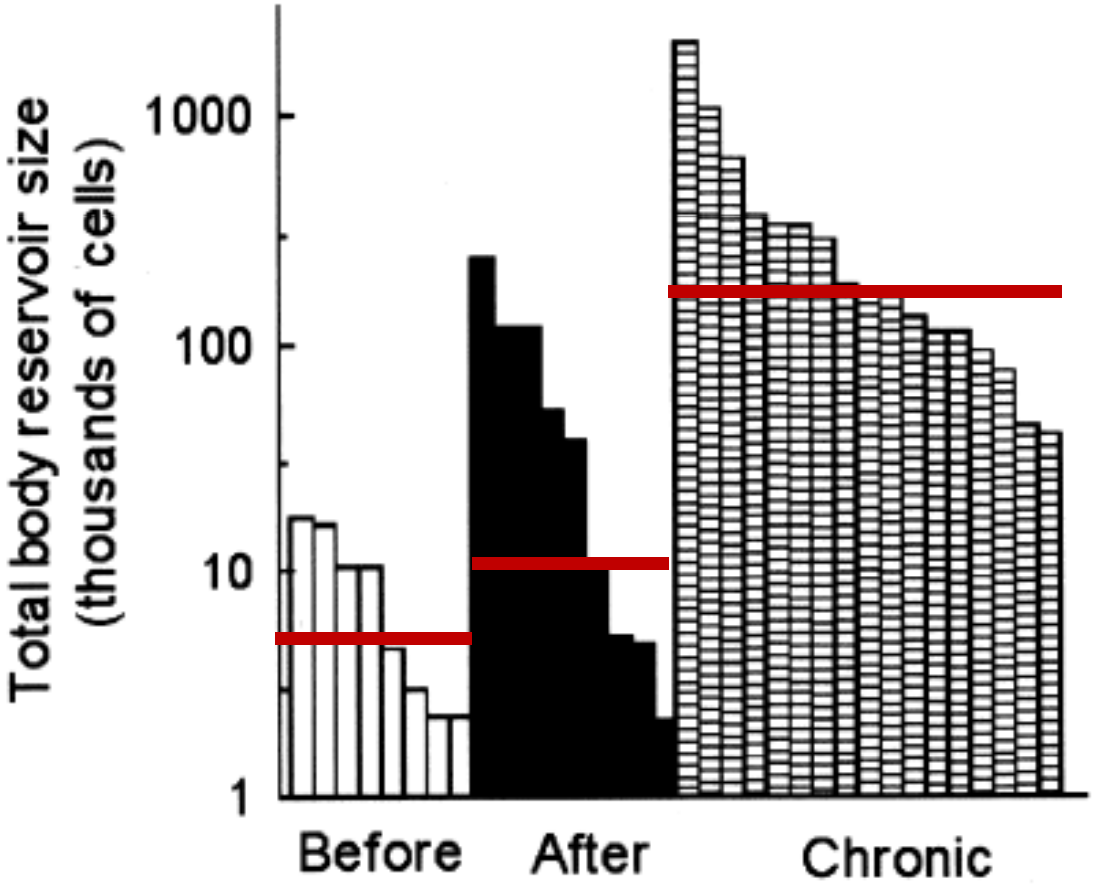
Finzi et al. *Nat Med* 1999; 5: 512-517.

Impact modeste en phase chronique



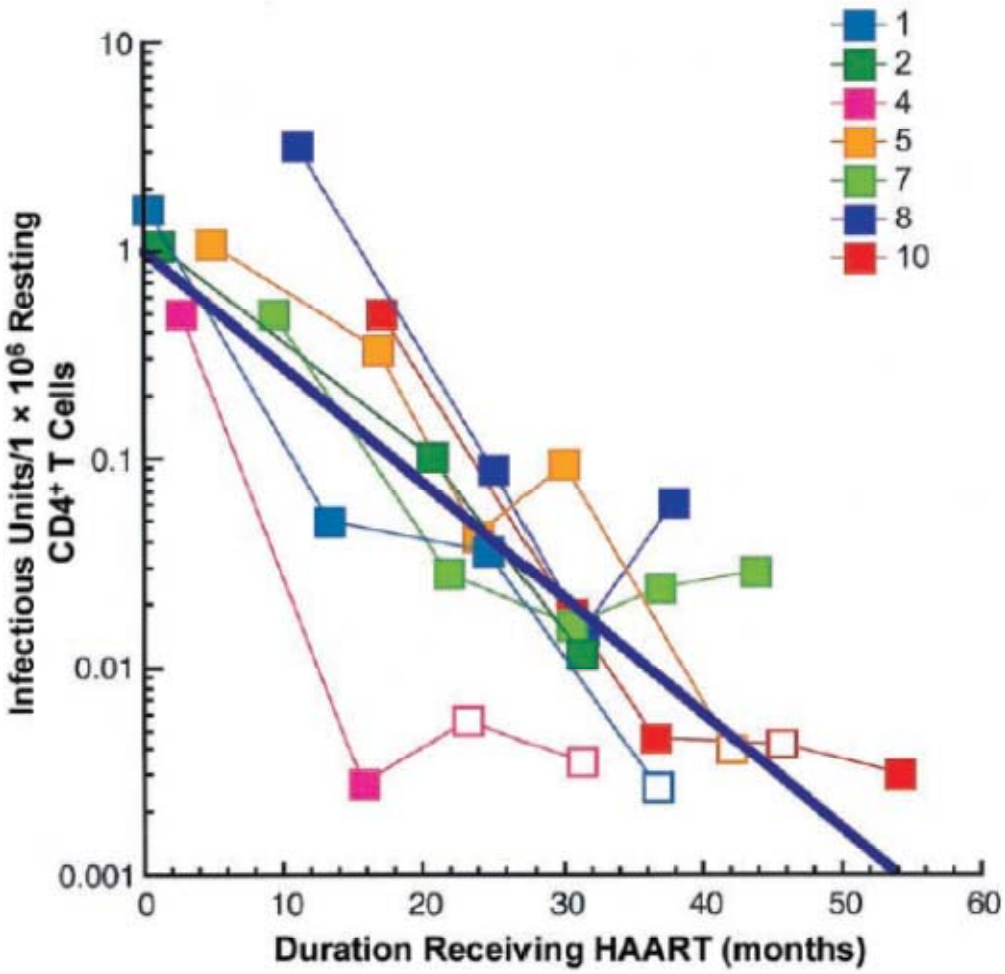
Viard JP et al. AIDS 2004, 18:45–49.

Impact en phase aiguë (vs. chronique)



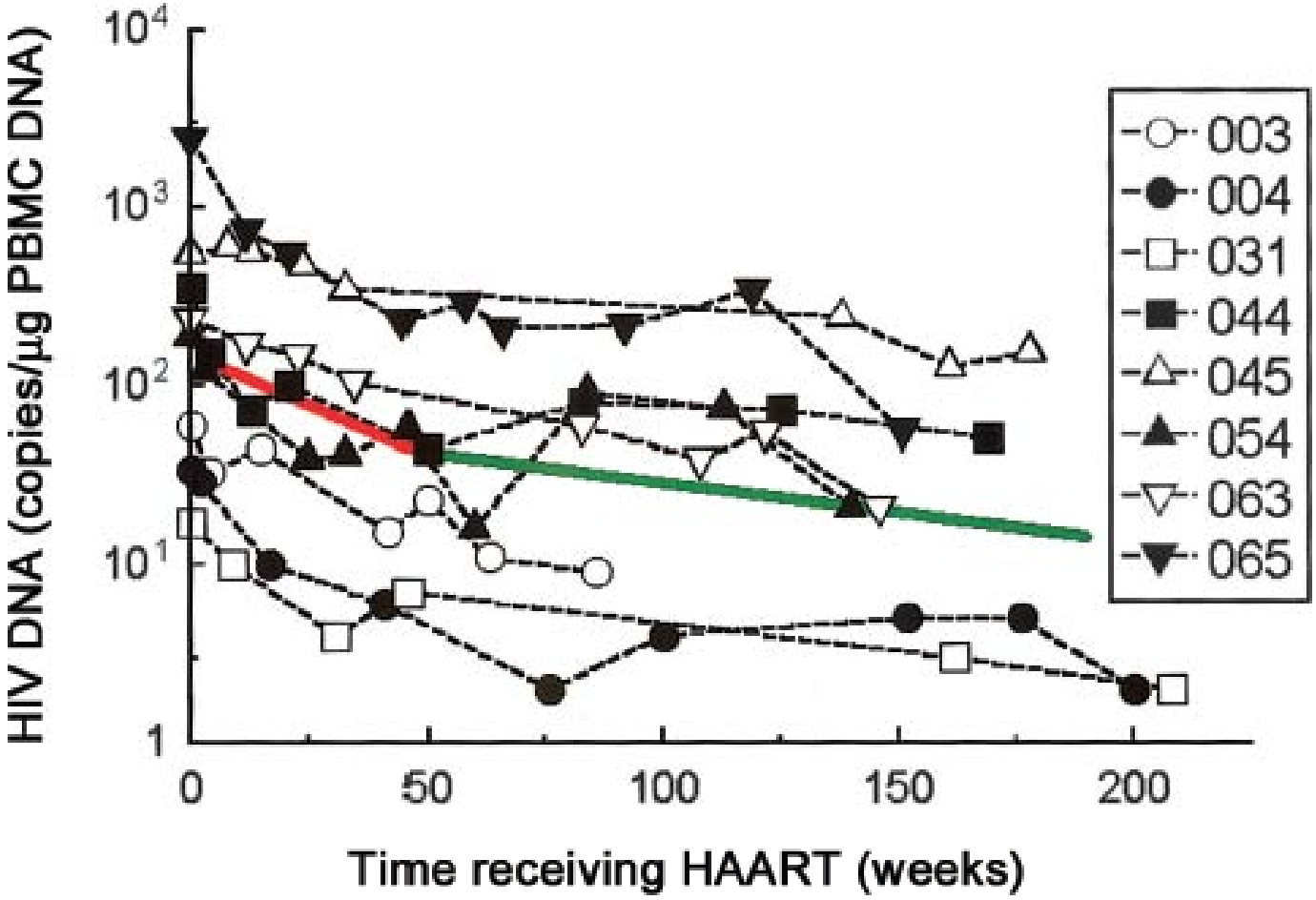
Strain M et al. J Infect Dis 2005; 191: 1410-8.

Clairance des réservoirs en phase aiguë



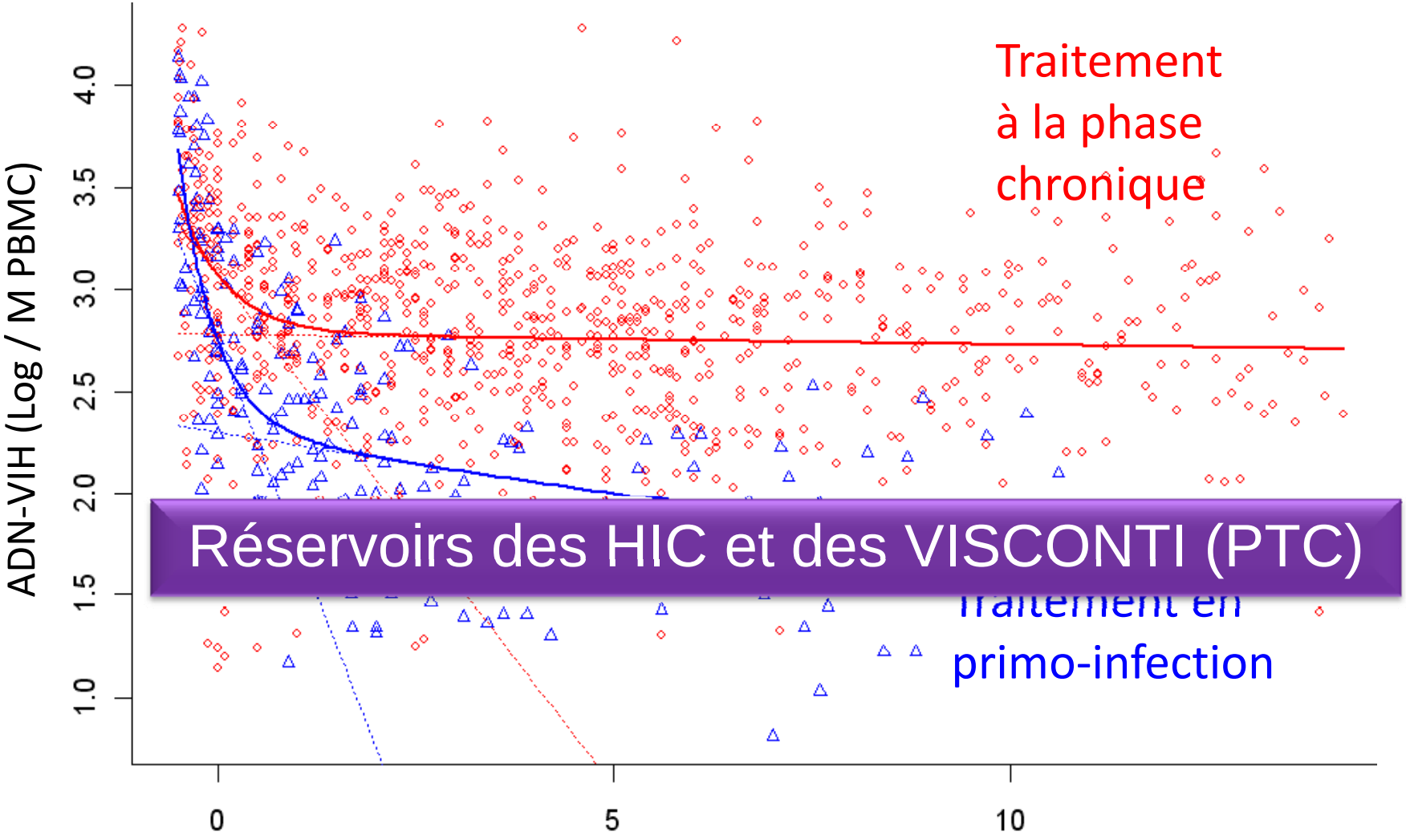
8 ans

Chun TW et al. J Infect Dis 2007; 195: 1762-4.



Strain M et al. J Infect Dis 2005; 191: 1410-8.

Modélisation de la décroissance de l'ADN-VIH



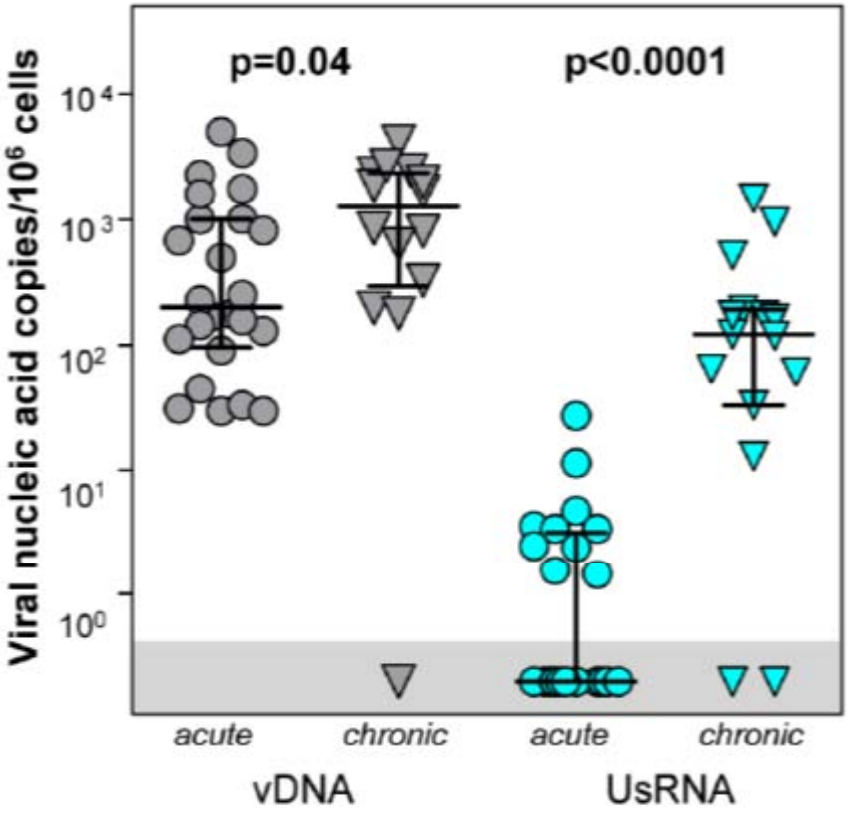
Hocqueloux L et al. IAS 2011

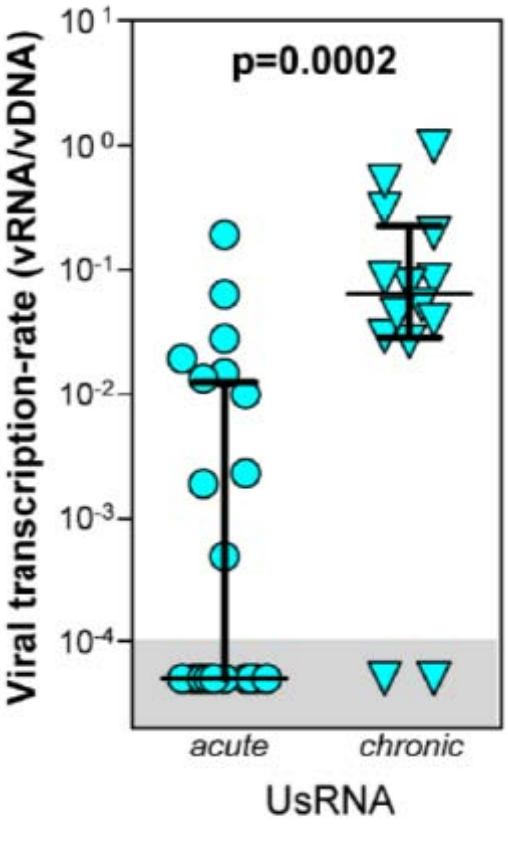
OPEN ACCESS Freely available online

PLoS one

Profound Depletion of HIV-1 Transcription in Patients Initiating Antiretroviral Therapy during Acute Infection

Adrian Schmid[¶], Sara Gianella[¶], Viktor von Wyl, Karin J. Metzner, Alexandra U. Scherrer, Barbara Niederöst, Claudia F. Althaus, Philip Rieder, Christina Grube, Beda Joos, Rainer Weber, Marek Fischer*[¶], Huldrych F. Günthard*[¶]





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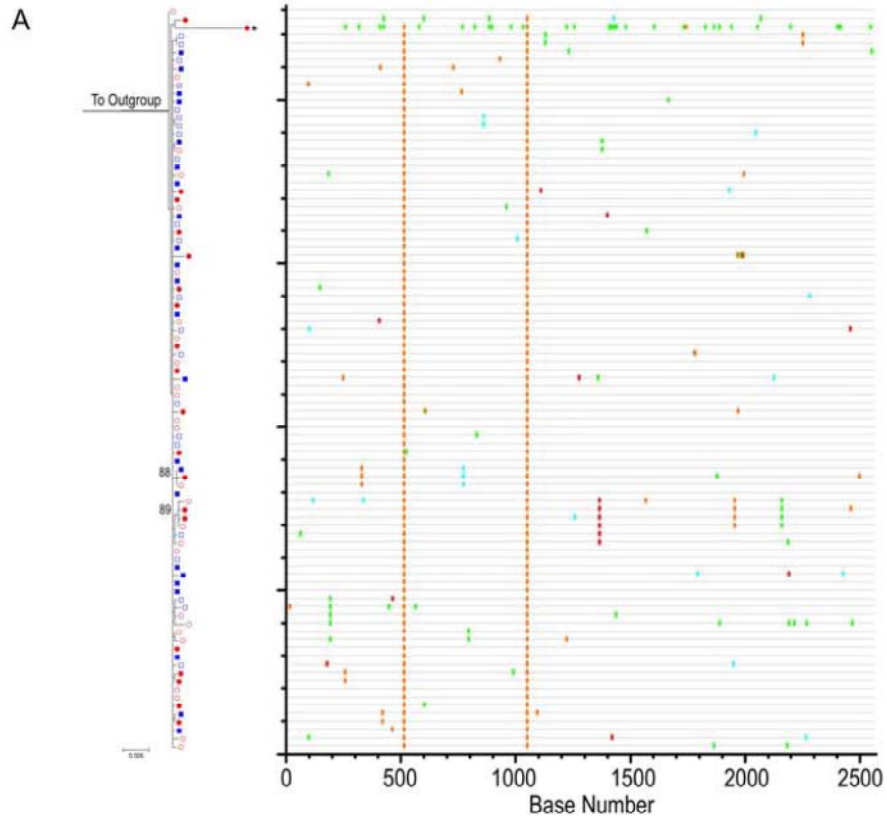
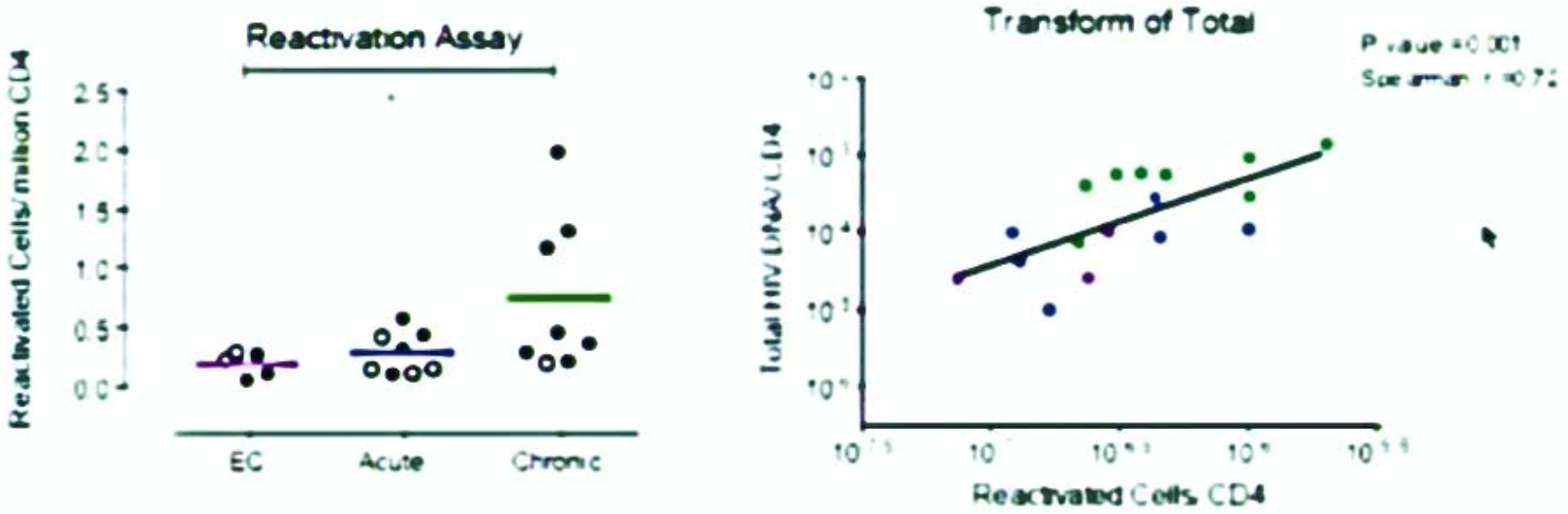
PLoS PATHOGENS

Absence of HIV-1 Evolution in the Gut-Associated Lymphoid Tissue from Patients on Combination Antiviral Therapy Initiated during Primary Infection

Teresa H. Evering[1], Saurabh Mehandru[1¤], Paul Racz[2], Klara Tenner-Racz[2], Michael A. Poles[3], Amir Figueroa[1], Hiroshi Mohri[1], Martin Markowitz[1]*



Higher functional reservoir in patients treated during chronic infection

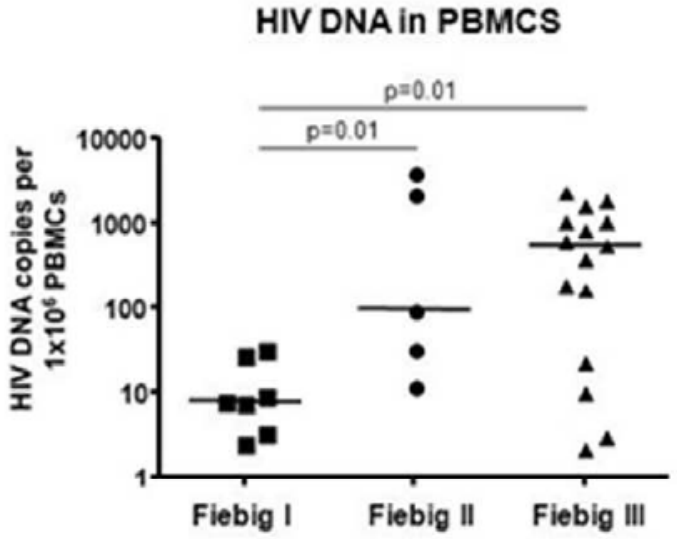


Early treatment reduce the functional reservoir to those levels observed in EC

Buzon M et al. CROI 2012, oral communication

Jusqu'à quand le traitement est-il « précoce » (très efficace) ?

- Pas d'évidence d'une plus grande déplétion du réservoir chez des patients traités aux différents stades Fiebig (c'est-à-dire jusqu'à 3-4 mois après l'infection aigüe)
- Toutefois…



Ananworanich J et al. PLoS One 2012;7:e33968.

Trithérapie vs pentathérapie pour l'infection VIH aiguë ou récente : résultats à S48 d'un essai randomisé

- 40 patients avec infection aiguë ou récente
  Randomisation (1:2)
  - trithérapie TDF/FTC + ATV/r ou DRV/r qd
  - pentathérapie avec en plus RAL 400 mg bid + MVC 150 mg bid
- 34 patients analysables (3 arrêts prématurés dans chaque bras)

	3 ARV (n = 11)	**5 ARV** (n = 23)	**p**
Facteurs de risque	HSH 10/1 H hétérosexuel	HSH 100 %	-
Symptomatique (%)	100	91	-
Durée moyenne estimée de l'infection, jours	48 (27-77)	54 (19-155)	-
CV moyenne, log_{10} c/ml	6,3 (4,8-7,0)	5,6 (3,1-6,4)	0,17
CD4/mm^3, moyenne	405 (305-524)	539 (230-1 066)	0,15

Critère principal : indétectabilité à S48 (test Roche Amplicor/TaqMan 1.0 [limite détection : 50 c/ml] et test ultrasensible à 1 c/ml)

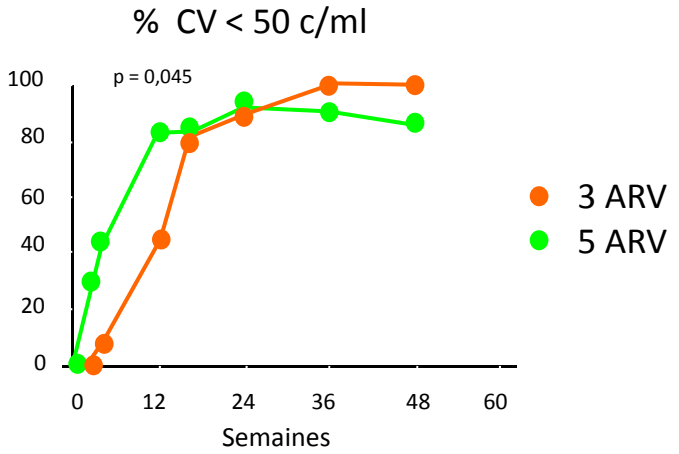
Markowitz M, CROI 2011, Abs. 148LB

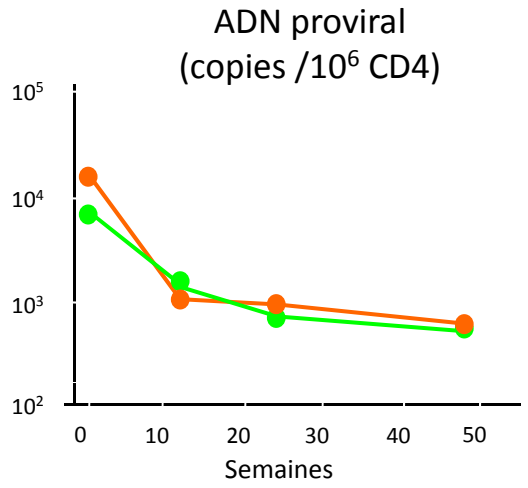
Trithérapie vs pentathérapie pour l'infection VIH aiguë ou récente : résultats à S48 d'un essai randomisé

Résultats virologiques

Résultats à S48	3 ARV (n = 11)	5 ARV (n = 23)	p
CV < 48/50 c/ml	11/11 (100 %)	20/23* (87 %)	0,53
CV < 1 c/ml	3/11 (27 %)	9/21 (43 %)	0,46

* 3 échecs virologiques dans le bras 5 ARV : 2 CV toujours détectables à S36, 1 CV indétectable à S12 mais rebond à bas niveau à S48





- Au total : pas de différence à S48 sur ARN plasmatique, ADN proviral et ARN cellulaire
- Evaluation en cours des taux résiduels de virus infectieux dans les cellules CD4 latentes à S96

Markowitz M, CROI 2011, Abs. 148LB

OPEN ACCESS Freely available online

PLoS one

Early and Prolonged Antiretroviral Therapy Is Associated with an HIV-1-Specific T-Cell Profile Comparable to That of Long-Term Non-Progressors

Cristina Cellerai[1], Alexandre Harari[1,2], Hans Stauss[3], Sabine Yerly[4], Anna-Maria Geretti[5], Anne Carroll[6], Thynn Yee[7], Jonathan Ainsworth[8], Ian Williams[9], John Sweeney[10], Andrew Freedman[11], Margaret Johnson[6], Giuseppe Pantaleo[1,2], Sabine Kinloch-de Loes[3,6]*

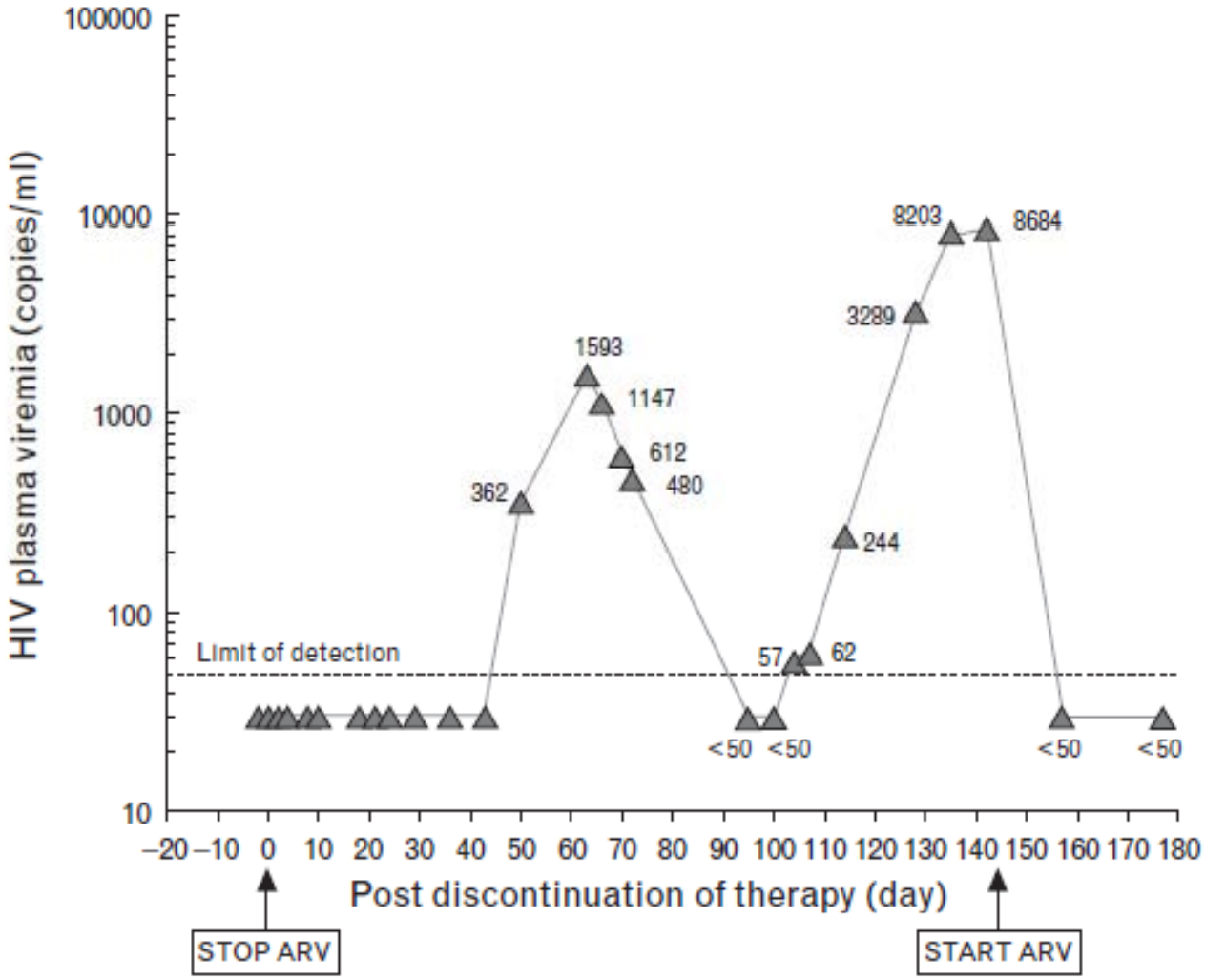
Abstract

Background: Intervention with antiretroviral treatment (ART) and control of viral replication at the time of HIV-1 seroconversion may curtail cumulative immunological damage. We have therefore hypothesized that ART maintenance over a very prolonged period in HIV-1 seroconverters could induce an immuno-virological status similar to that of HIV-1 long-term non-progressors (LTNPs).

Methodology/Principal Findings: We have investigated a cohort of 20 HIV-1 seroconverters on long-term ART (LTTS) and compared it to one of 15 LTNPs. Residual viral replication and reservoirs in peripheral blood, as measured by cell-associated HIV-1 RNA and DNA, respectively, were demonstrated to be similarly low in both cohorts. These two virologically matched cohorts were then comprehensively analysed by polychromatic flow cytometry for HIV-1-specific $CD4^+$ and $CD8^+$ T-cell functional profile in terms of cytokine production and cytotoxic capacity using IFN-γ, IL-2, TNF-α production and perforin expression, respectively. Comparable levels of highly polyfunctional HIV-1-specific $CD4^+$ and $CD8^+$ T-cells were found in LTTS and LTNPs, with low perforin expression on HIV-1-specific $CD8^+$ T-cells, consistent with a polyfunctional/non-cytotoxic profile in a context of low viral burden.

Conclusions: Our results indicate that prolonged ART initiated at the time of HIV-1 seroconversion is associated with immuno-virological features which resemble those of LTNPs, strengthening the recent emphasis on the positive impact of early treatment initiation and paving the way for further interventions to promote virological control after treatment interruption.

Bémol : le réservoir ne fait pas tout…



Chun TW et al. *AIDS* 2010;24:2803-8.

Conclusions

- La persistance de cellules infectées latentes est l'obstacle majeur à l'éradication du VIH
- Le traitement initié précocement (en PHI) est le plus efficace :
  - pour diminuer ces réservoirs (quantitativement et qualitativement)
  - Et pour préserver / restaurer l'immunité

→ Ces conditions font le lit d'une cure fonctionnelle

Remerciements

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Laboratoire de Virologie

Christine Rouzioux

Véronique Avettand-Fenoel

Université d'Orléans

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