Agence nationale de recherches sur le sida et les hépatites virales
French National Agency for Research on AIDS and Viral Hepatitis
Agence autonome de l'Inserm
An autonomous agency at Inserm

Cure fonctionnelle ? Quels traitements ?

Laurent HOCQUELOUX
CHR d'Orléans – La Source
Cohorte VISCONTI (ANRS EP47)

XI[ème] rencontres à Saint-Malo – 5 et 6 mars 2015

Liens d’intérêt

- AbbVie
- Actélion
- Bristol-Myers-Squibb 

- Gilead 

- MSD
- Tibotec (Janssen)
- ViiV Healthcare 

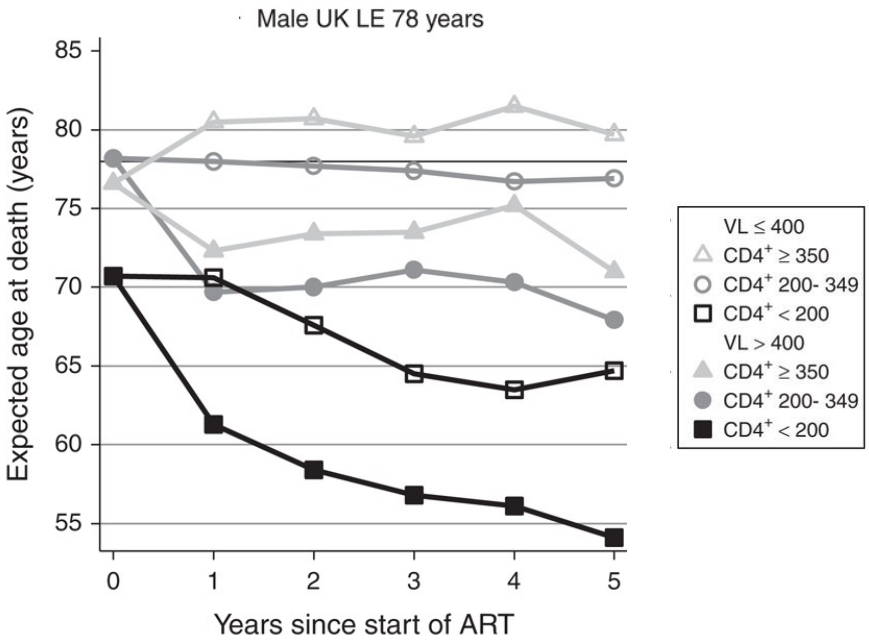
Sommaire

- Cure fonctionnelle = rémission (≠ éradication)
  - Besoins
  - Etat des lieux des connaissances
  - Comment ça marche?
- Quels traitements pour y parvenir ?
  - Diminuer le réservoir
  - Augmenter l'immunité
- Perspectives
  - Nouveaux traitements, nouvelles stratégies
- Conclusions

Une rémission du VIH

Pourquoi ?

Progrès en 36 ans (1979-2015)



Progrès en 36 ans (1979-2015)

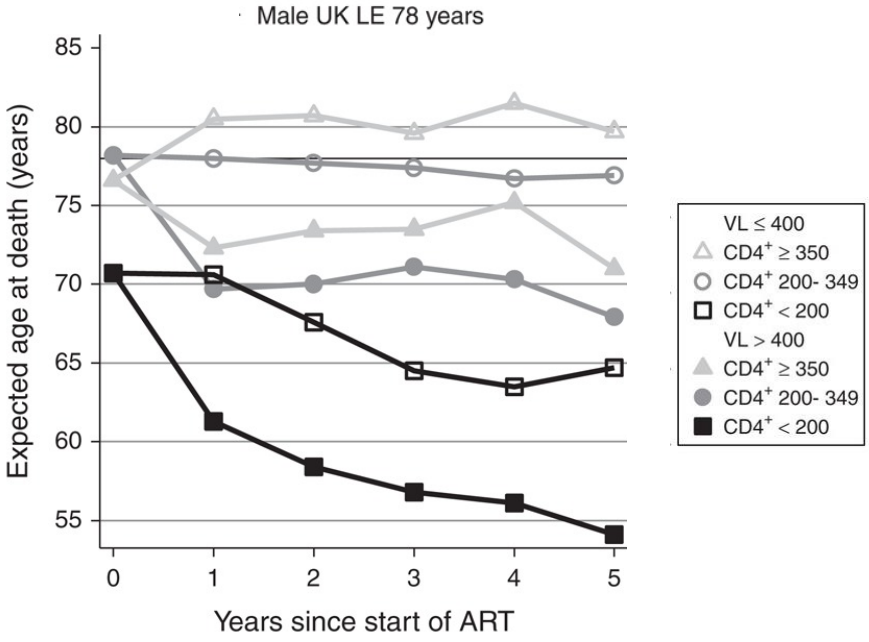
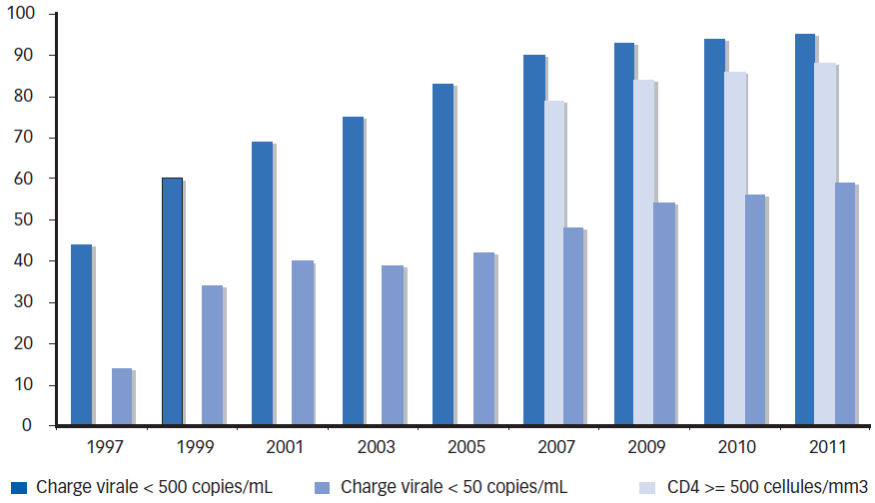


Figure 2. Proportion de patients traités depuis au moins 6 mois ayant une charge virale inférieure à 500 copies/mL ou à 50 copies/mL ou ayant un taux de CD4 supérieur à 500/mm³ dans la cohorte FHDH ANRS C04



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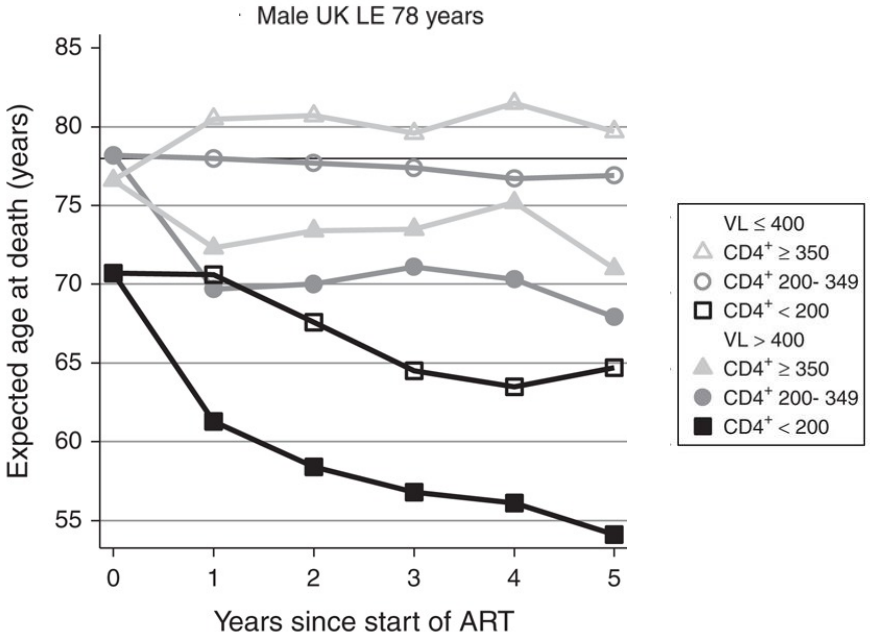
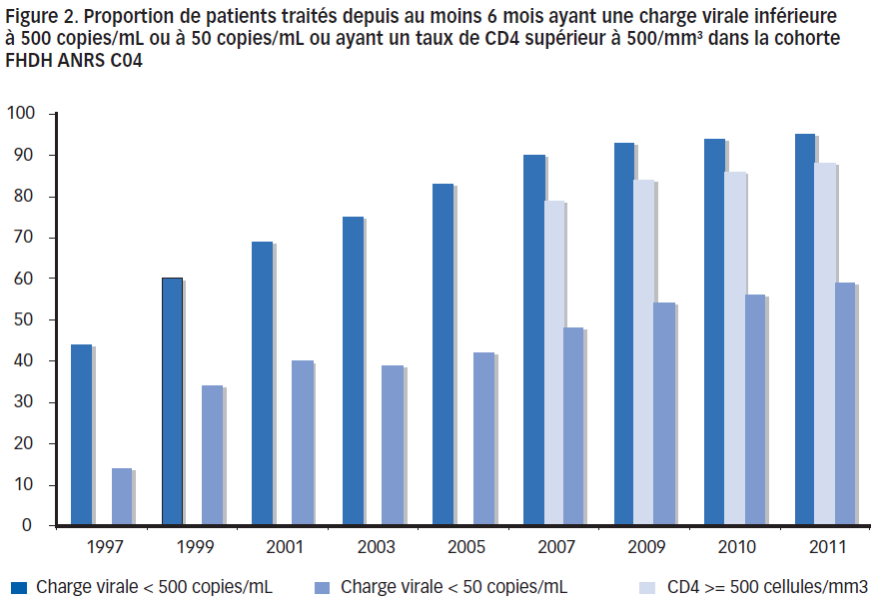
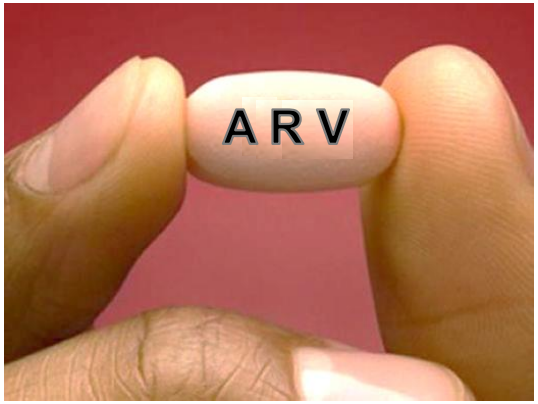






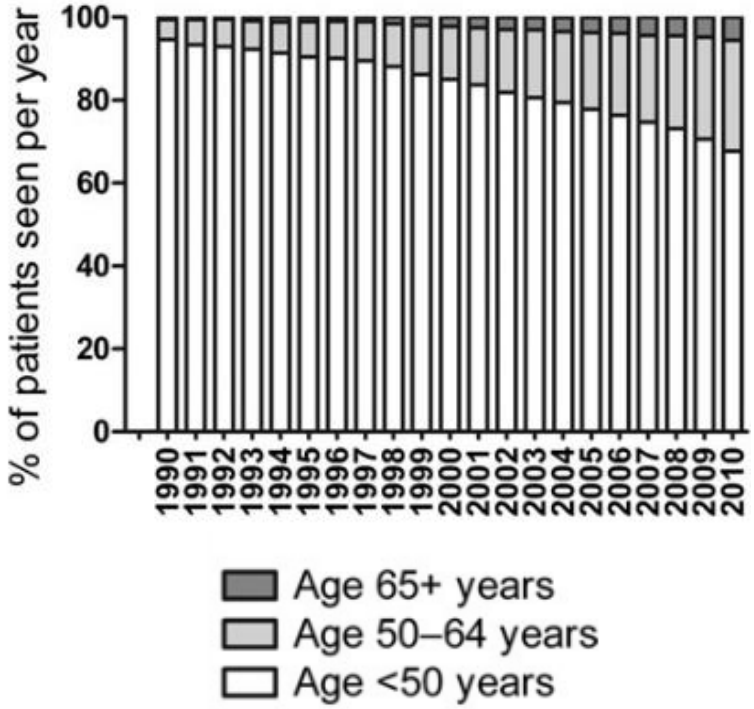
40 ans de trithérapie ?

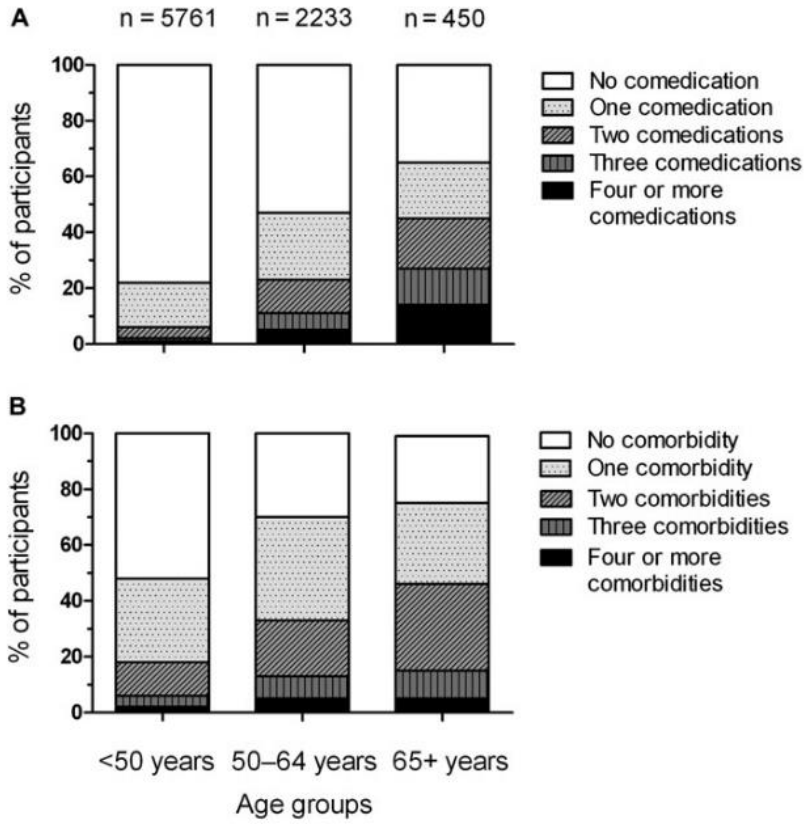
- 7 à 30 kilos de produits actifs ingérés

40 ans de trithérapie ?

Et pas que…

Morbidity and Aging in HIV-Infected Persons: The Swiss HIV Cohort Study

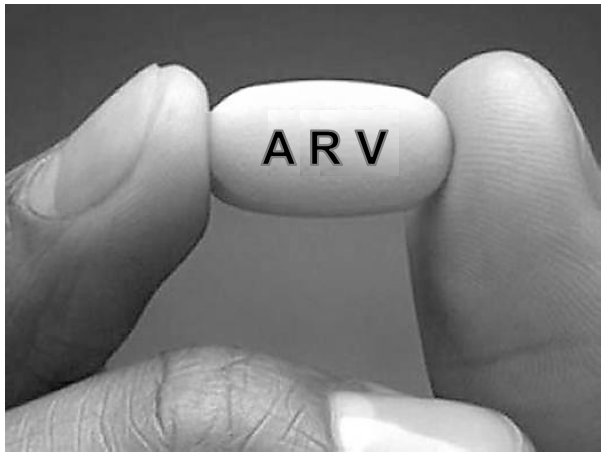


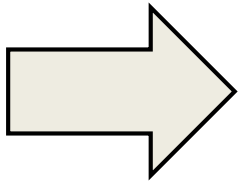


Hasse et al. CID 2011;53:1130-9.

Peut-on franchir la dernière étape ?

- Arrêter les ARV, au moins temporairement
- Sans risque pour le patient, ni pour les autres
- Vivre avec le VIH comme avec d'autres virus (EBV, …)
- Induire une rémission prolongée / définitive

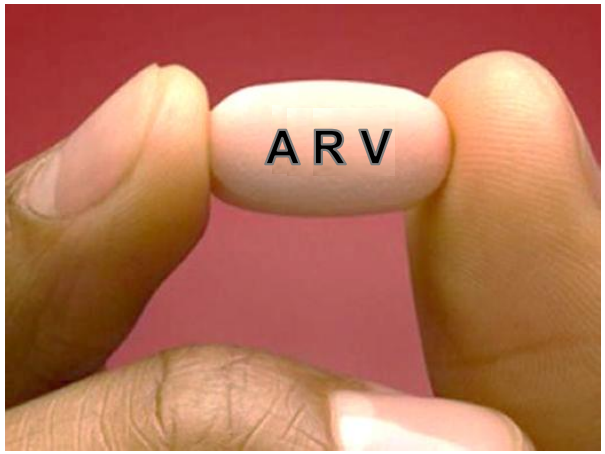




Une rémission du VIH

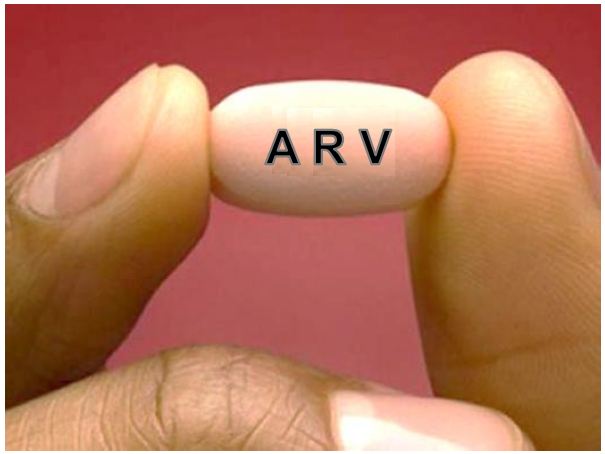
Quels patients ?

Deux voies pour induire une rémission…



… l’une d’entre elles n’est pas raisonnable.

Deux voies pour induire une rémission…



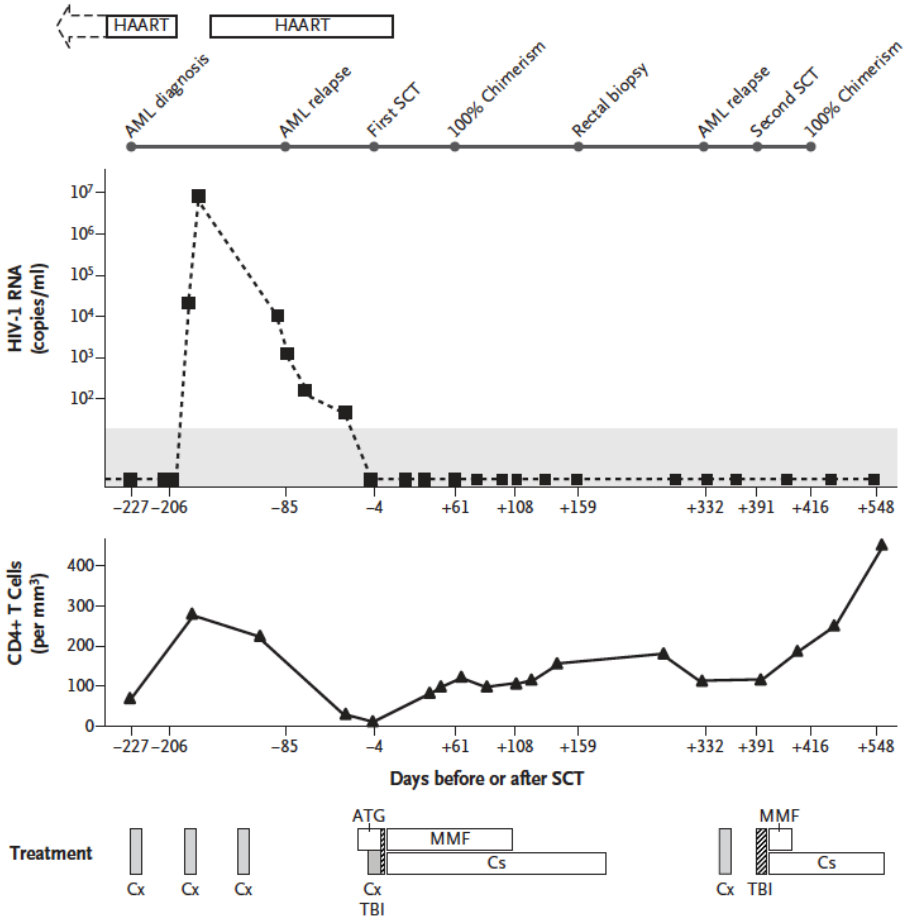
- **Cure fonctionnelle**
  - VISCONTI / PTC
  - Cas sporadiques
  - (Mississippi Baby)
- **Eradication**
  - Le patient de Berlin (n° 2)

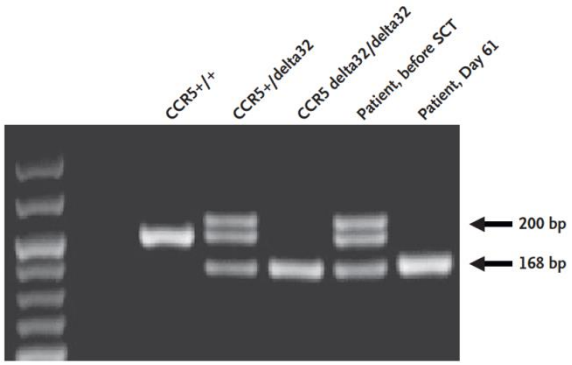
… l'une d'entre elles n'est pas raisonnable.

Un cas unique d'éradication à ce jour

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S.,



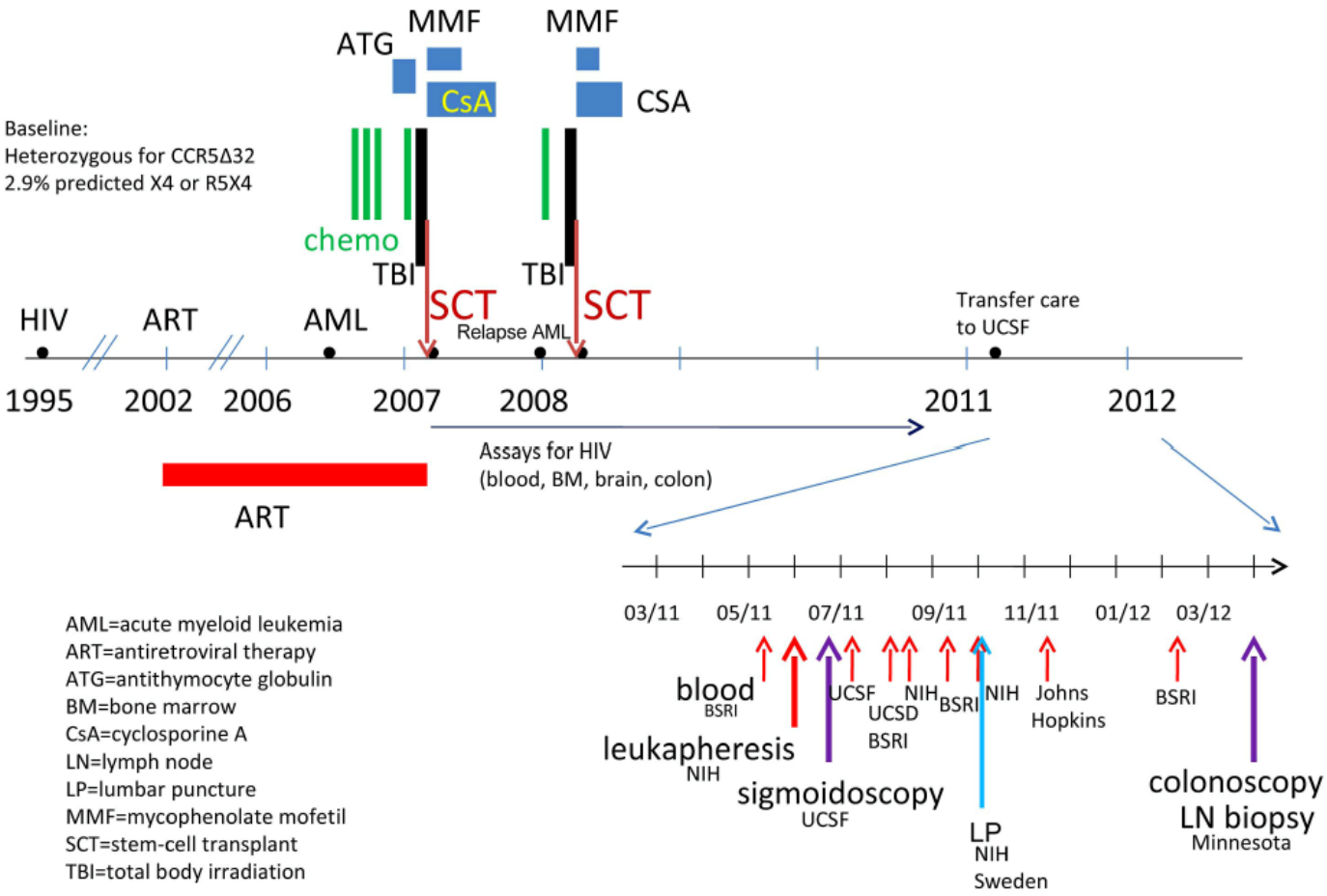


T.R. Brown est guéri (disparition du virus)

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Challenges in Detecting HIV Persistence during Potentially Curative Interventions: A Study of the Berlin Patient



AML=acute myeloid leukemia
ART=antiretroviral therapy
ATG=antithymocyte globulin
BM=bone marrow
CsA=cyclosporine A
LN=lymph node
LP=lumbar puncture
MMF=mycophenolate mofetil
SCT=stem-cell transplant
TBI=total body irradiation

T.R. Brown est guéri (disparition du virus)

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Challenges in Detecting HIV Persistence during Potentially Curative Interventions: A Study of the Berlin Patient

Table 4. Summary of virologic measures.

Sample	Measure	# Labs that tested samples	# Labs with + Test	Consensus	Typical levels in ART-suppressed patient	Fold Difference
Plasma	HIV RNA	4	2 labs (3 samples)	?Intermittent positive, ?<1 copy/ml	1–2 copy/ml	2–20
PBMC	HIV DNA	4	0	Negative (≤1 in 10^{6-7})	751 per 10^6 total PBMC [18]	750–7500
PBMC	HIV RNA	3	0	Negative (≤1 in 10^{6-7})	66 per 10^6 total PBMC [18]	66–660
Sorted cells from blood	HIV DNA	1	0	Negative	Unknown	
Sorted cells from blood	HIV RNA	1	0	Negative	Unknown	
Peripheral CD4+T	IUPM	2	0	Negative (≤1 IU/10^{7-9} cells)	1 per 10^6 CD4+T [8,9,11,12]	10–1000
CSF	HIV RNA	2	0	Negative		
CSF cells	HIV DNA	1	0	Negative		
Lymph node	HIV DNA	1	0	Negative	1–12 copies/100 ng [14]	
Lymph Node	HIV RNA	1	0	Negative	≤4 log10 copies/g (FDC) [14]	
Rectum (biopsy or cells)	HIV DNA	2	1	?Intermittent positive, <1 in 10^6 cells	777 per 10^6 total gut cells [18]	780
Rectum (biopsy or cells)	HIV RNA	3	0	Negative (<1 in 10^{6-7})	21 per 10^6 total gut cells [18]	21–210
Ileum (biopsy or cells)	HIV DNA	1	0	Negative (≤1 in 10^6)	415 per 10^6 total gut cells [18]	415
Ileum (biopsy or cells)	HIV RNA	2	0	Negative (≤1 in 10^6)	37 per 10^6 total gut cells [18]	37

Plus de virus, plus de défenses…

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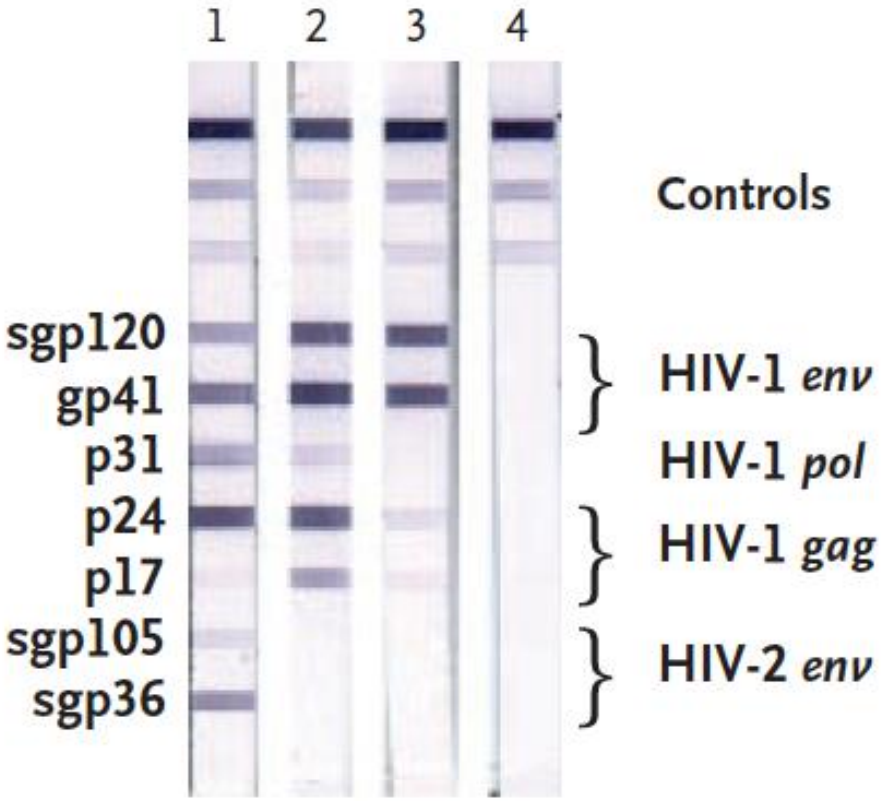
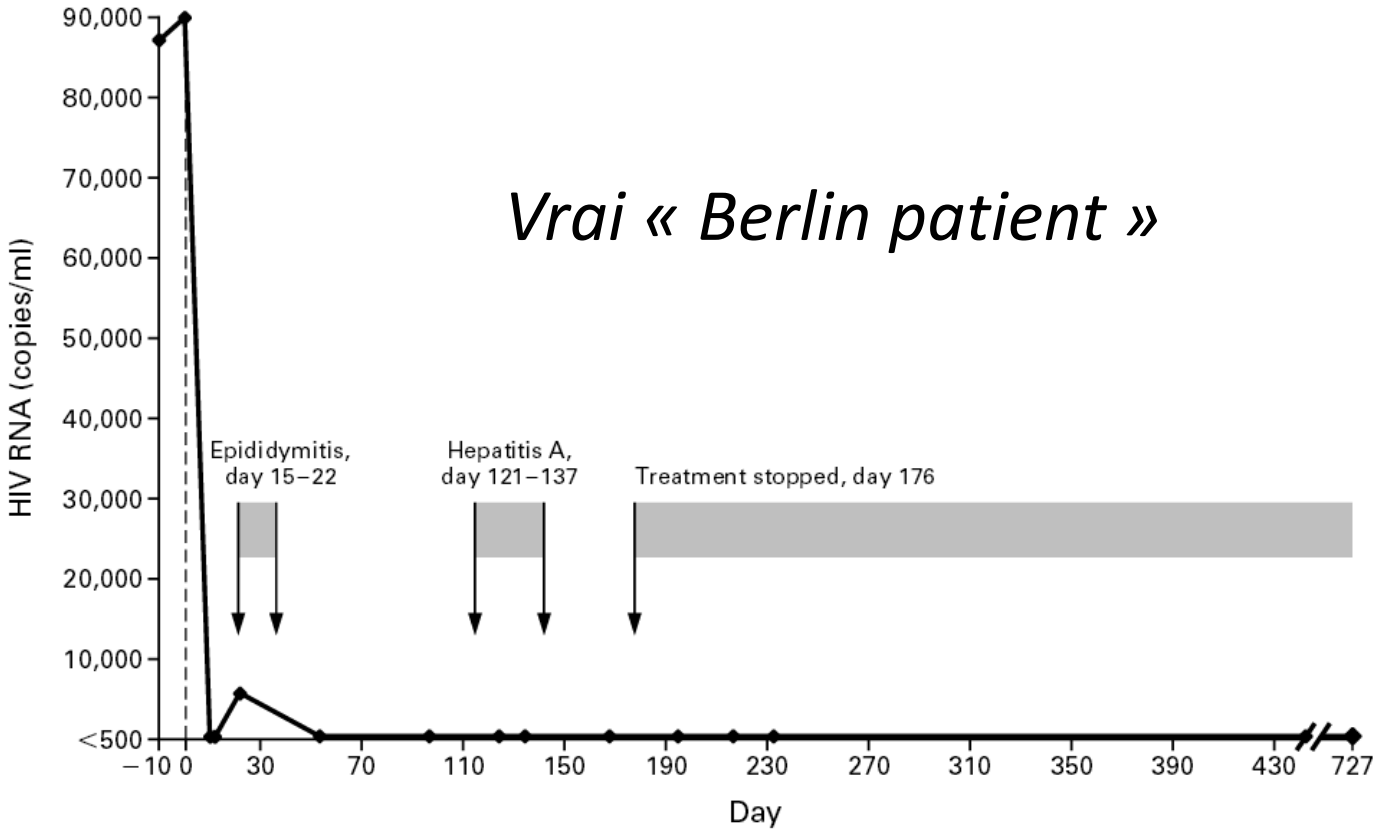
Challenges in Detecting HIV Persistence during Potentially Curative Interventions: A Study of the Berlin Patient



Cure fonctionnelle : connue depuis 1999



Vrai « Berlin patient »

Figure 1. Plasma Levels of HIV RNA in the Patient.

Plasma levels of HIV RNA were measured by a branched-chain DNA assay with a limit of sensitivity of 500 copies per milliliter. Day 0 was the first day of treatment. Shaded areas indicate periods of no treatment.

Lisziewicz J. et al, *NEJM* 1999

Une quarantaine de cas décrits depuis

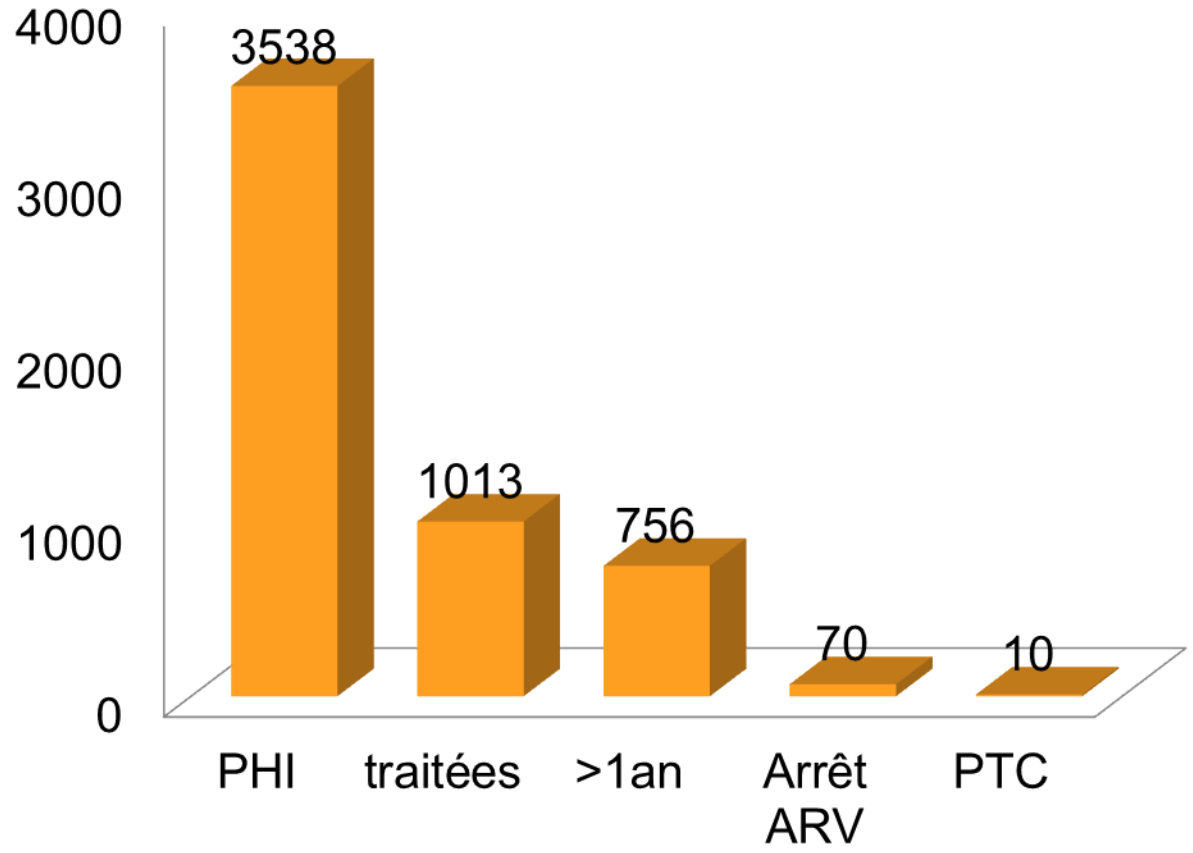
- Lafeuillade A. et al, *J Infect Dis* 2003 N=2
- Steingrover R. et al, *AIDS* 2008 N=2
- Fomsgaard, *ARHR* 2008 N=1
- Hocqueloux L. et al, *AIDS* 2010 N=5
- Salgado M. et al, *Retrovirology* 2011 N=1
- Goujard C. et al, *Antiv Therapy* 2012 N=14
- Lodi S. et al, *Arch Intern Med* 2012 N=11
- Sáez-Cirión A. et al, *PLoS Pathogens* 2013 N=14
- Congrès divers N>3

The ANRS International VISCONTI (i-VISCONTI) Post Treatment Controller (PTC) Cohort

Treatment for more than 12 months and initiated either in primary-infection **or** during the chronic phase.

Control of viral load after treatment interruption <400 copies/mL for at least 12 months (and at inclusion)

Cascade vers le statut de PTC



Données FHDH

Fréquence des PTC

- Steingrover R. et al, *AIDS* 2008 — 8%
- Hocqueloux L. et al, *AIDS* 2010 — 15%
- Goujard C. et al, *Antiv Therapy* 2012 — 8.5%
- Lodi S. et al, *Arch Intern Med* 2012 — 10.5%
- Sáez-Cirión A. et al, *PLoS Pathogens* 2013 — 14%
- Chéret A et al., *Lancet Infect Dis* 2015 — 3%
- Frater J. et al, *CROI* 2015 — 14%

environ 10%

Caractéristiques des Post-Treatment Controllers

- Étude VISCONTI
  - 21 patients identifiés en France
  - PHI symptomatiques (idem à PRIMO)
- Traitement précoce (dans les 10 semaines)
  - Bi / tri / quadrithérapies
  - Molécules anciennes
- Prolongé (plusieurs années)
  - 1 à 7 ans

Evolution à long terme

- Recul médian = 9.3 ans
  (IQR: 8.4-10 – range: 4.5-12.5)
- Age médian = 48 (IQR: 43-53)
- Pas d'évènement SIDA
- Reprise traitement chez 2/21 patient (9,5%)
  - Cancer ORL (n=1), sein (n=1)
  - VL <40 cp/mL avant reprise ARV

Les PTC ont une restauration immunitaire ample et stable dans le temps

	Median	All PTC (n=18)	
At PHI	CD4/mm^3	544	P=0.001
	Ratio		
At TI	CD4/mm^3	915	P=0.5
	Ratio		
At last visit	CD4/mm^3	855	
	Ratio		

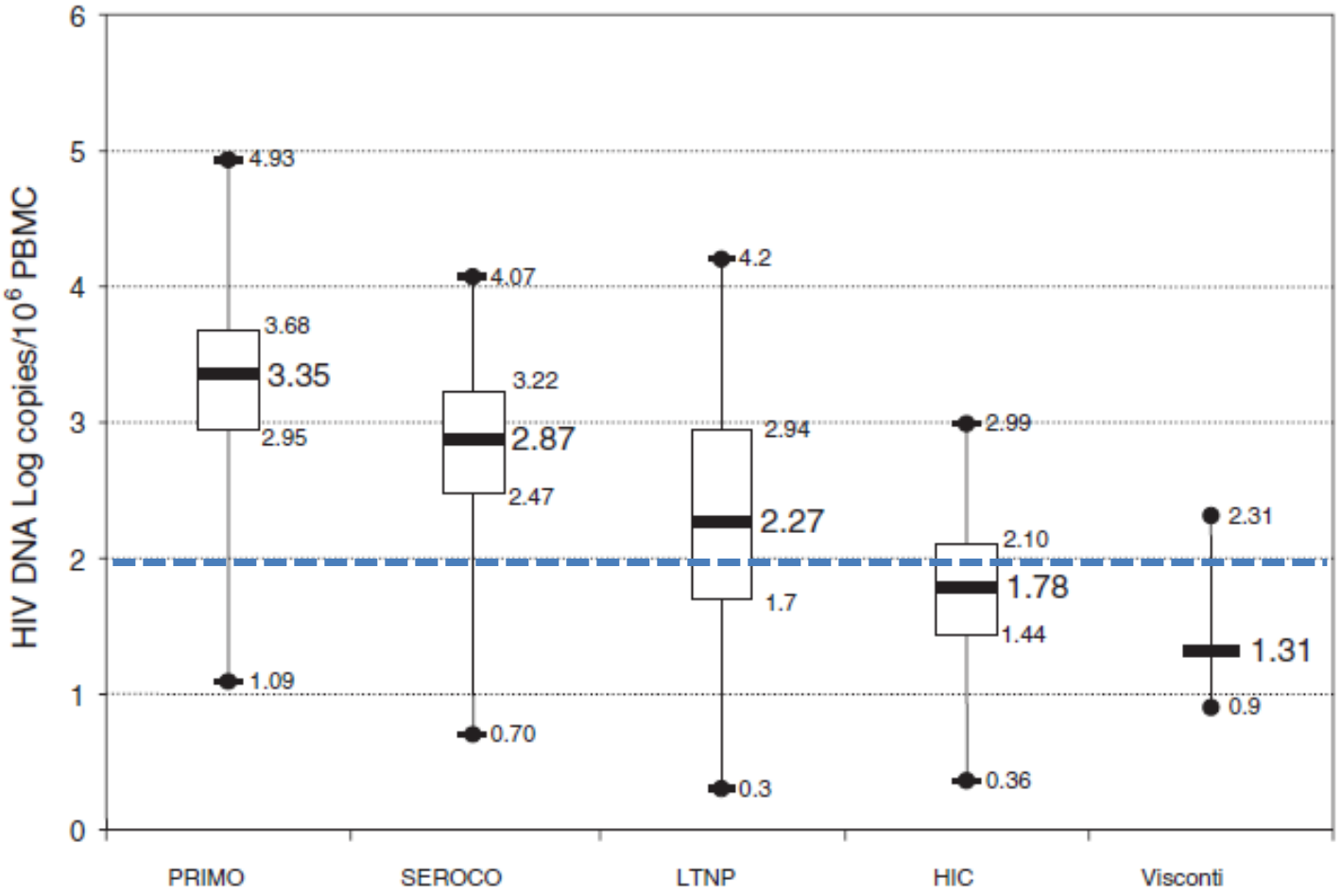
Les PTC ont une restauration immunitaire ample et stable dans le temps

	Median	All PTC (n=18)	
At PHI	CD4/mm^3		
	Ratio	0.80	P=0.003
At TI	CD4/mm^3		
	Ratio	1.51	P=0.8
At last visit	CD4/mm^3		
	Ratio	1.48	

Les PTC ont très faible réplication résiduelle

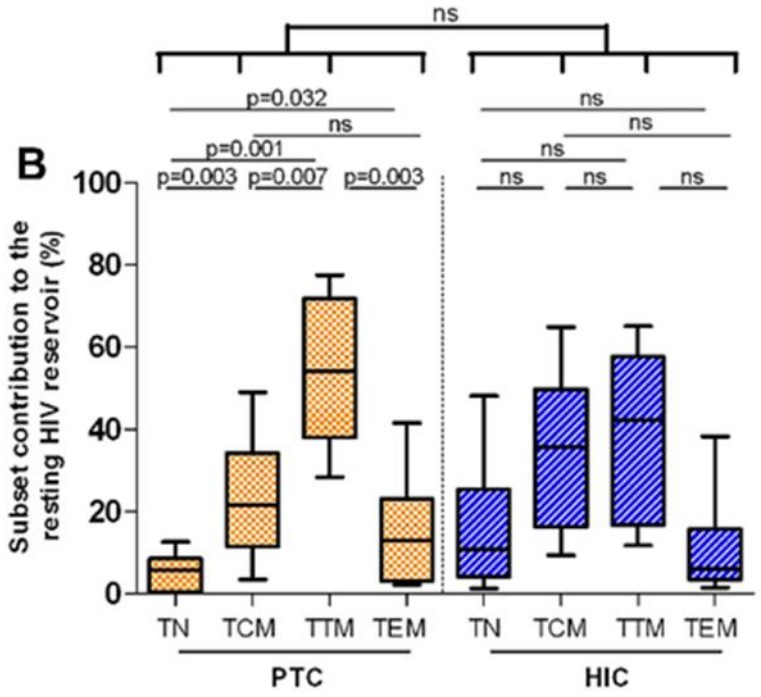
Median (IQR) or %	No residual viremia (n=13)	Residual viremia + (n=5)	P-value
VL before at PHI, cp/mL	5.6 (4.7-6.9)	4.3 (3.3-4.9)	0.04
VL after TI, n (%) <50 cp/mL 50 to 400 cp/mL >400 cp/mL	199 (100%) 197 (99%) 2 (1%) 0 (0%)	139 (100%) 90 (65%) 43 (31%) 6 (4%)	<0.0001
Ultrasensitive VL, cp/mL	5 (3-5)	45 (12-89)	0.014

Les PTC ont très faible réservoir



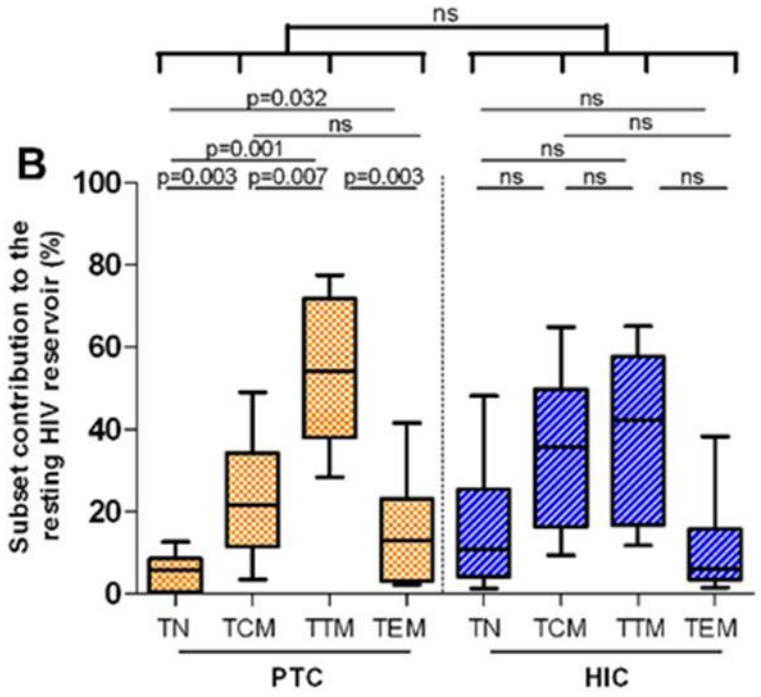
Lewin S, Rouzioux C. *AIDS* 2011; 25: 885-897.

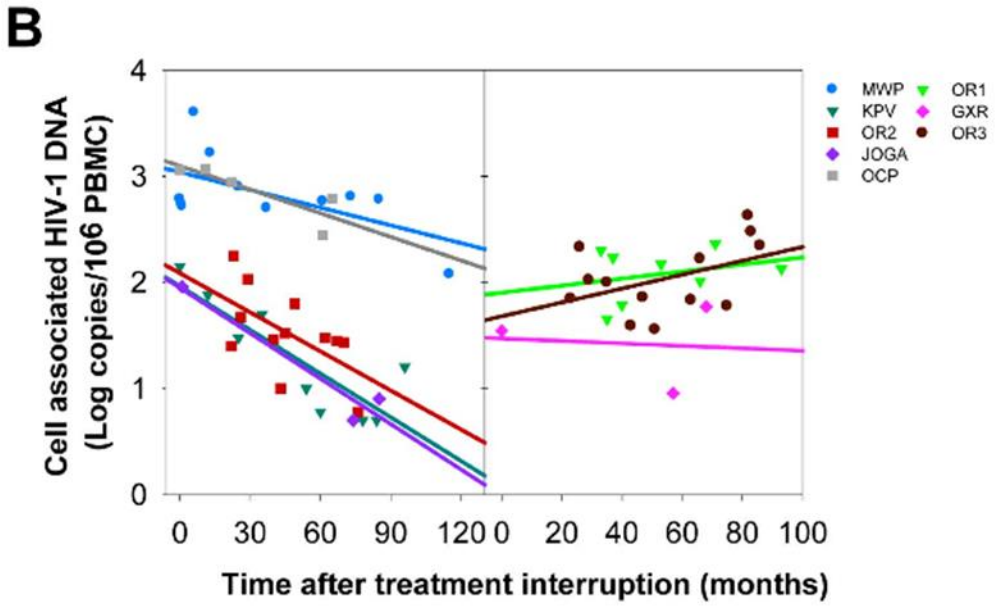
Le traitement précoce a préservé les T_{cm}



Saez-Cirion A, *PLoS Pathogens* 2013
Cheret A. *JAC (en révision)*

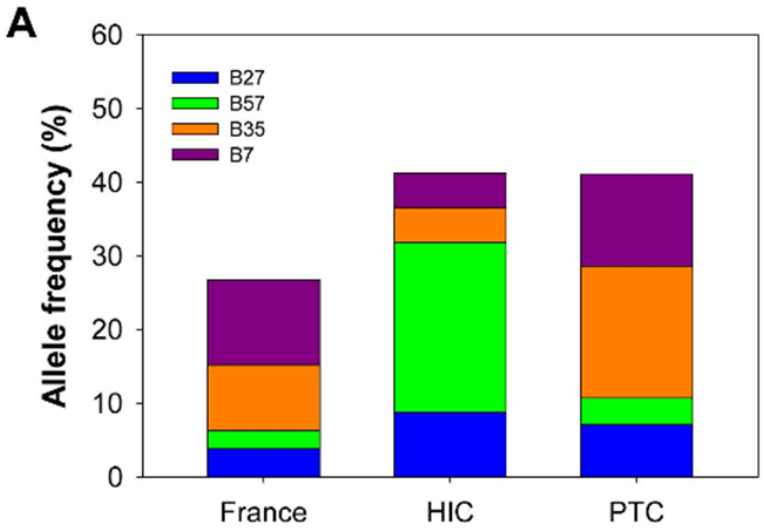
Le traitement précoce a préservé les T_{cm}





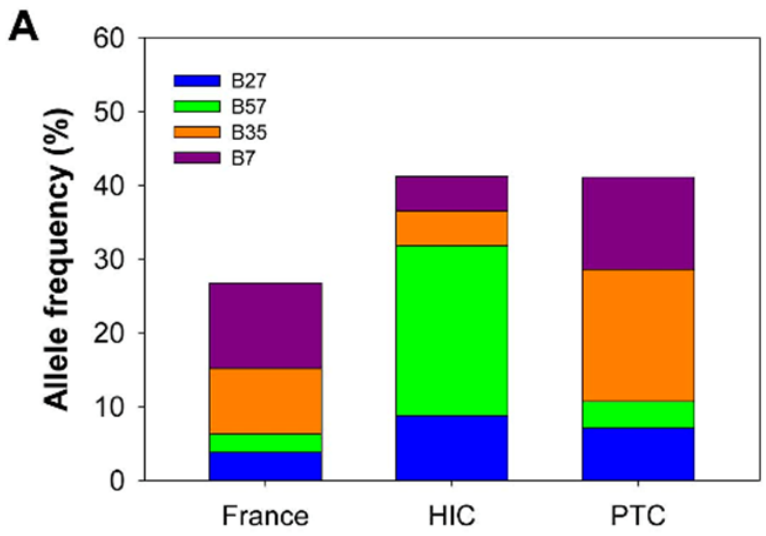
Saez-Cirion A, *PLoS Pathogens* 2013
Cheret A. *JAC (en révision)*

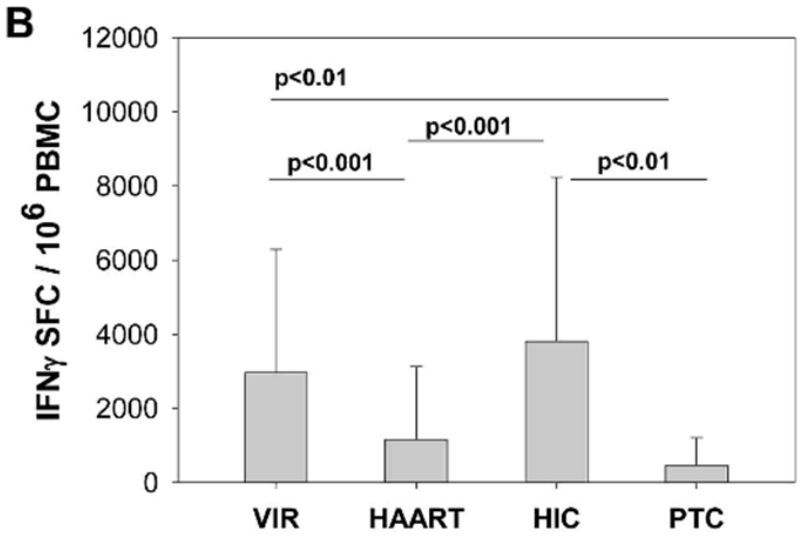
Données génétiques et immunologiques

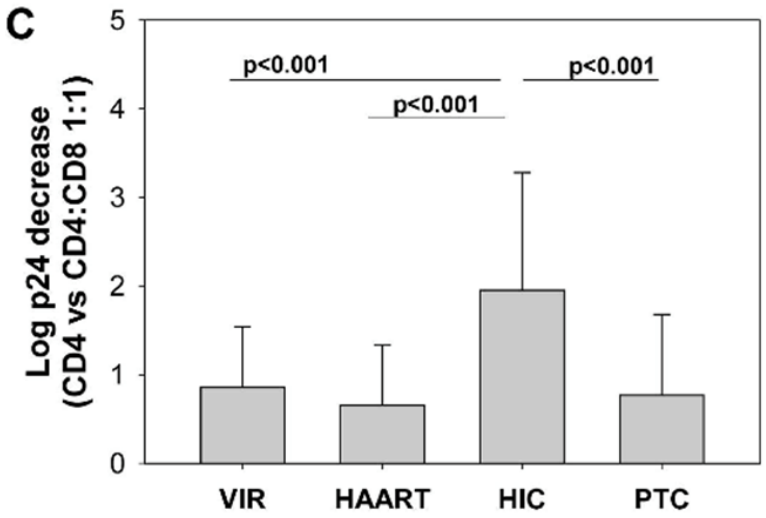


Saez-Cirion A, *PLoS Pathogens* 2013

Données génétiques et immunologiques

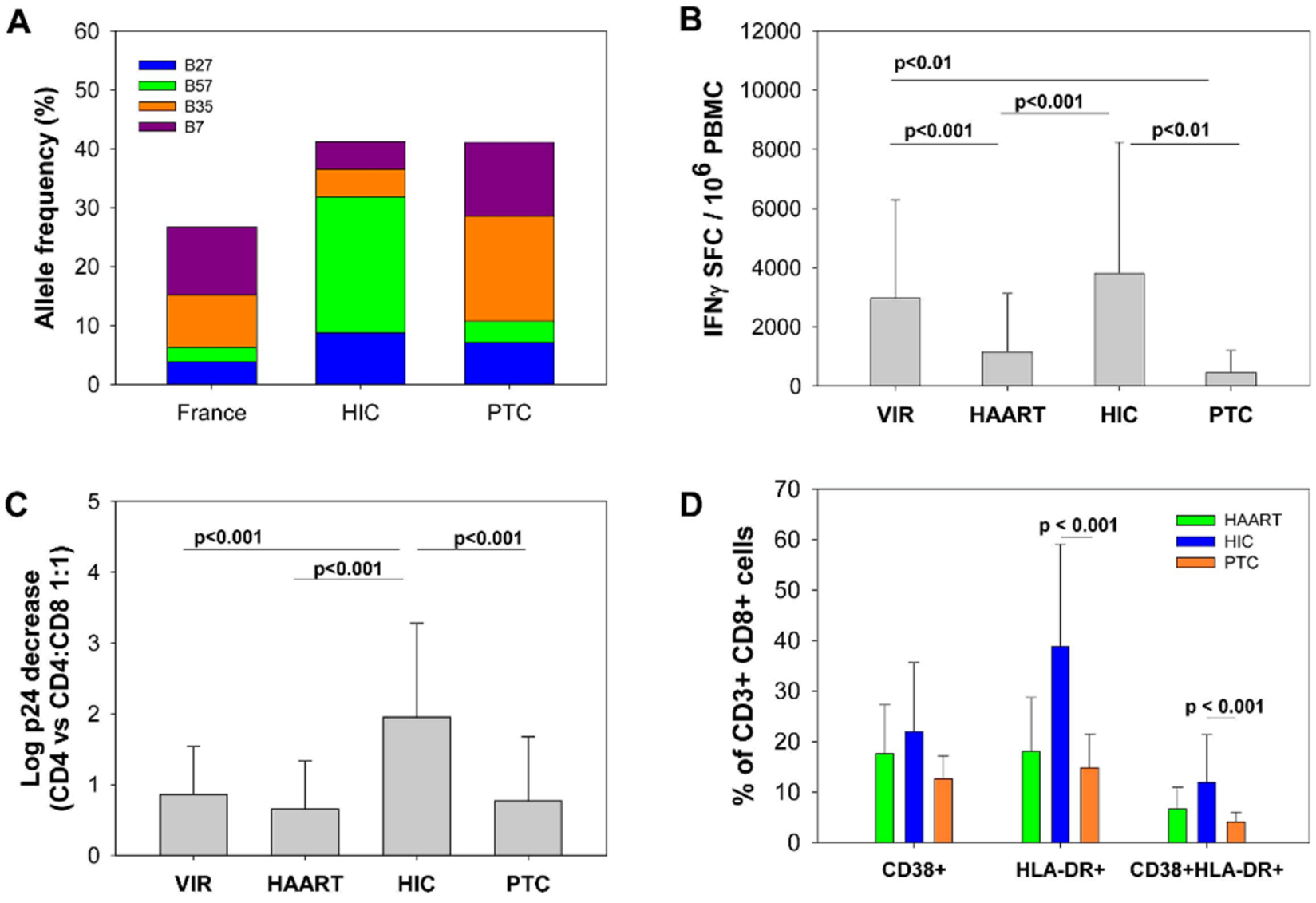






Saez-Cirion A, *PLoS Pathogens* 2013

Données génétiques et immunologiques



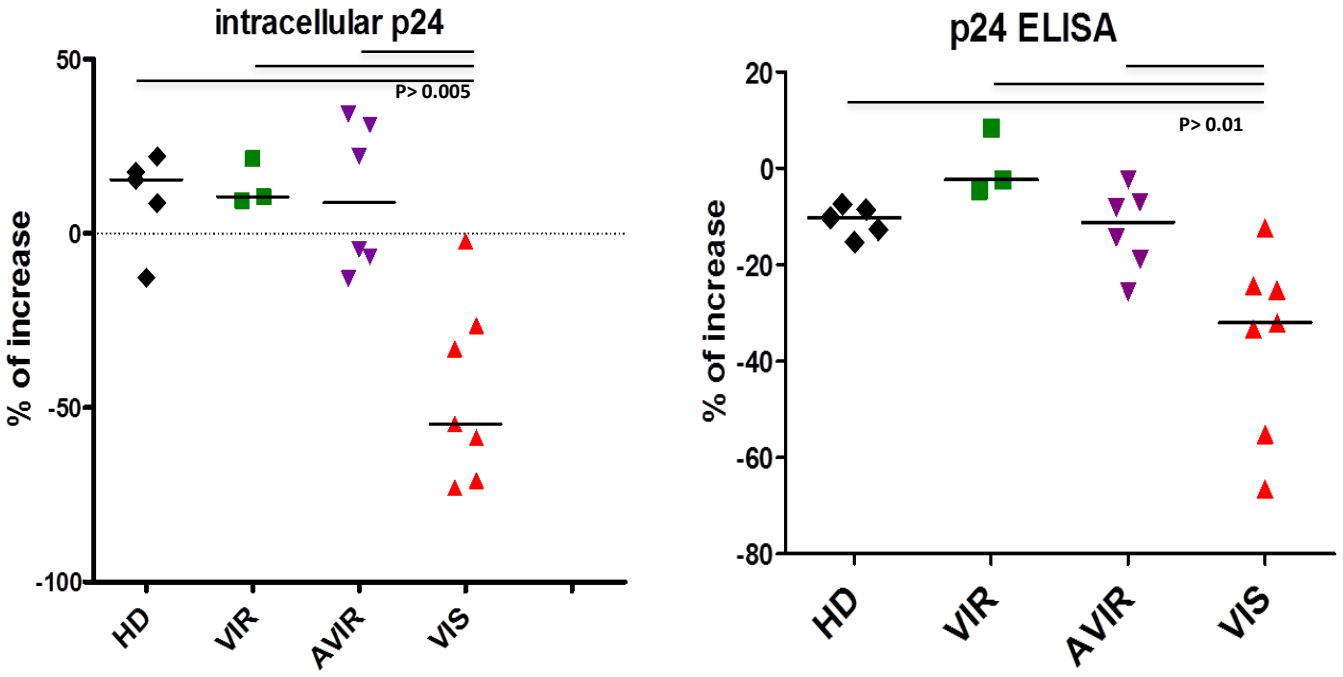
Saez-Cirion A, *PLoS Pathogens* 2013

Comment les PTC contrôlent-ils le virus ?

- Pas de forte suppression des CD8 (≠ HIC)
- Mais en face : faible réservoir et restriction génétique
- Préservation de l'immunité innée / acquise (par le ttmt précoce)
  - Polyfonctionnalité des CD4 et des CD8
  - **Activité NK +++**
- Faible inflammation résiduelle ?
- Répression de la latence ?

Samri A. et al., *CROI* 2014
Scott-Algara D. et al, *CROI* 2015

High capacity to control *in vitro* HIV infection on autologous CD4 T cells in Visconti patients



NK cells from Visconti patients have better capacity to control HIV infection in autologous CD4 T cells as measured by the lower expression of p24

Scott-Algara D et al., *CROI* 2015

Une rémission du VIH

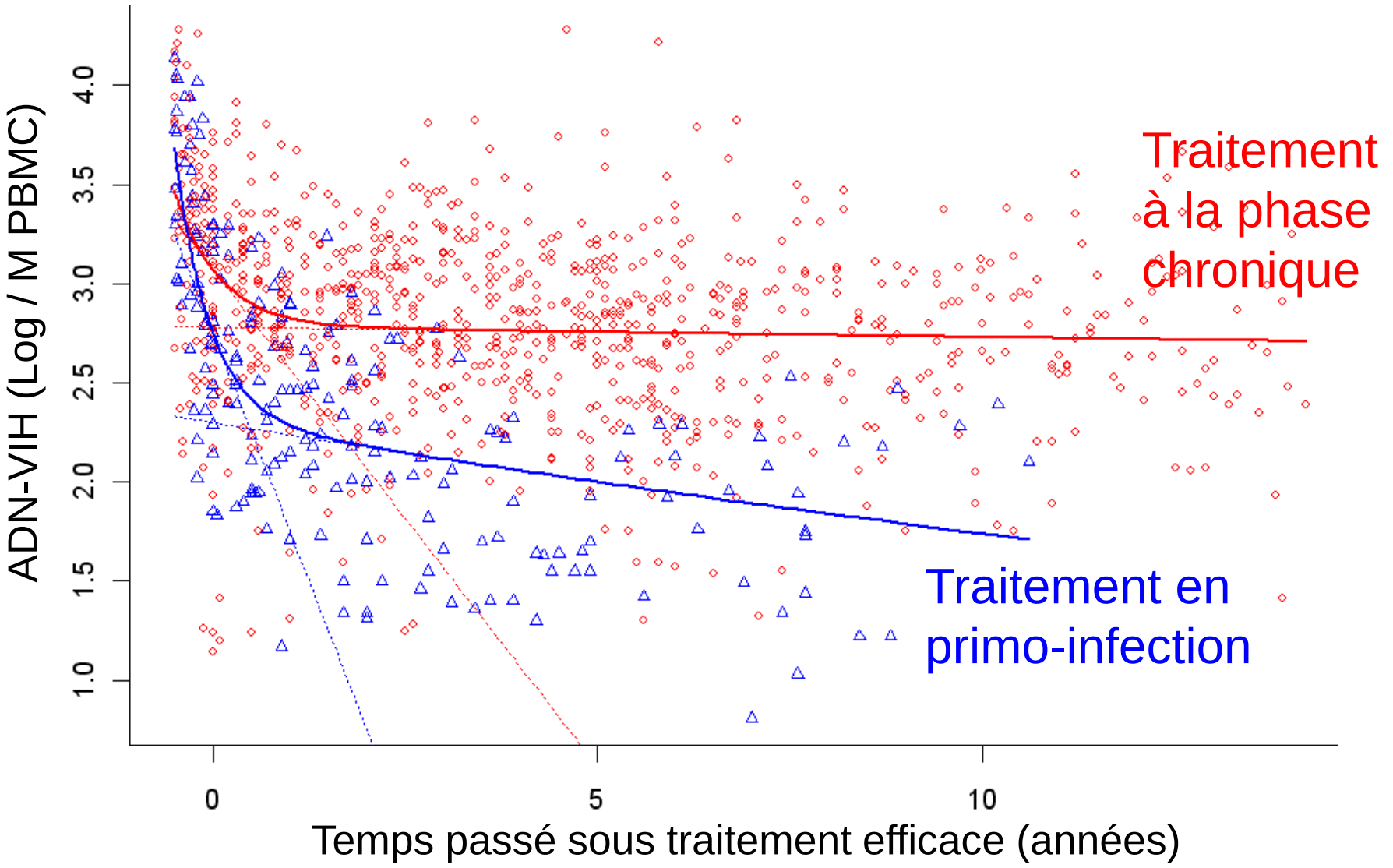
Quels traitements ?

Quels traitements pour une rémission ?

Principales pistes :

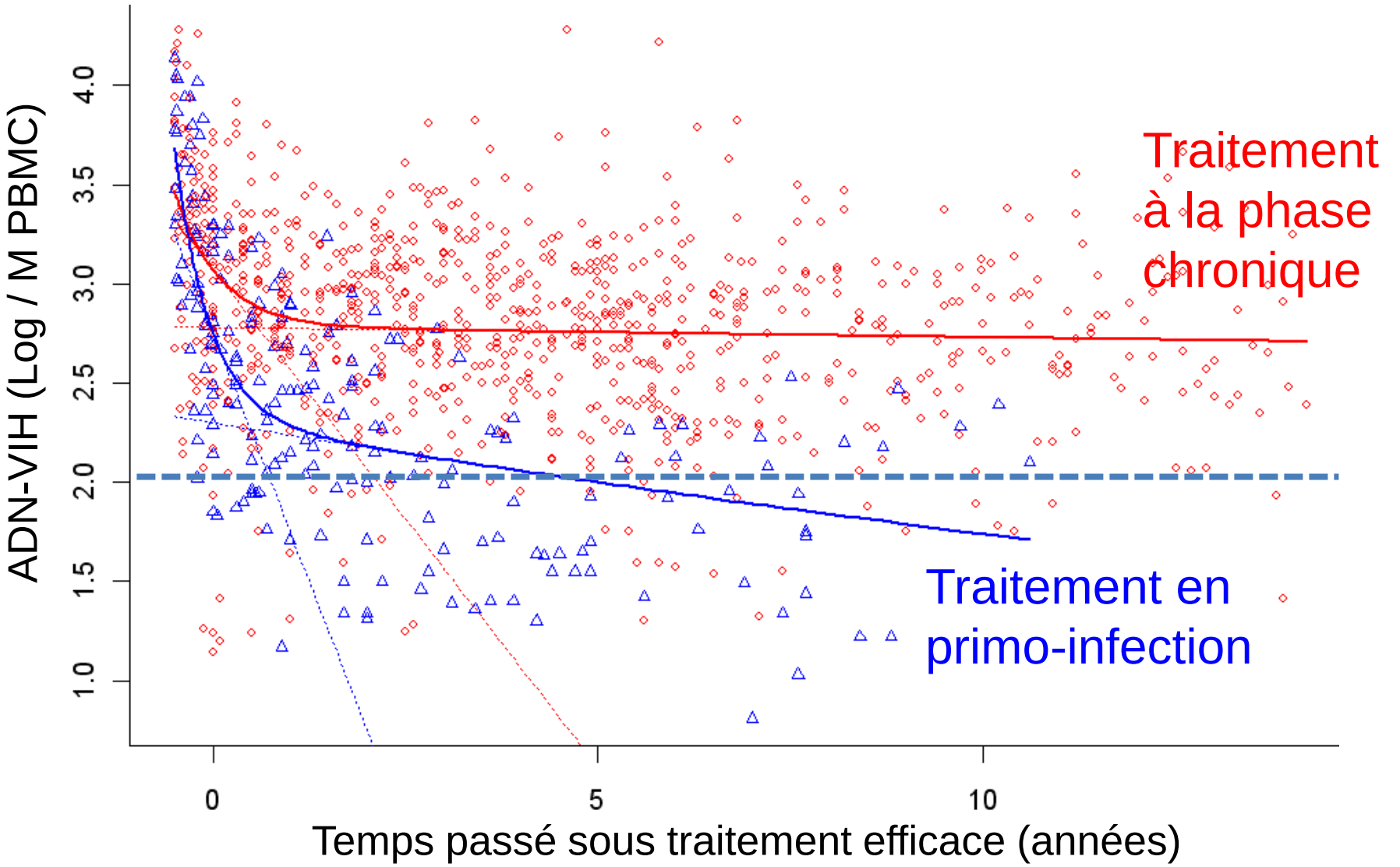
- Diminuer le réservoir de façon drastique
- Conserver / amplifier l'immunité (anti-VIH)
  - Innée (NK)
  - Adaptative (CTL, Ac, etc)
- Moduler la latence virale
  - Mais dans quel sens ?

Le traitement en PHI atteint l'objectif ADN



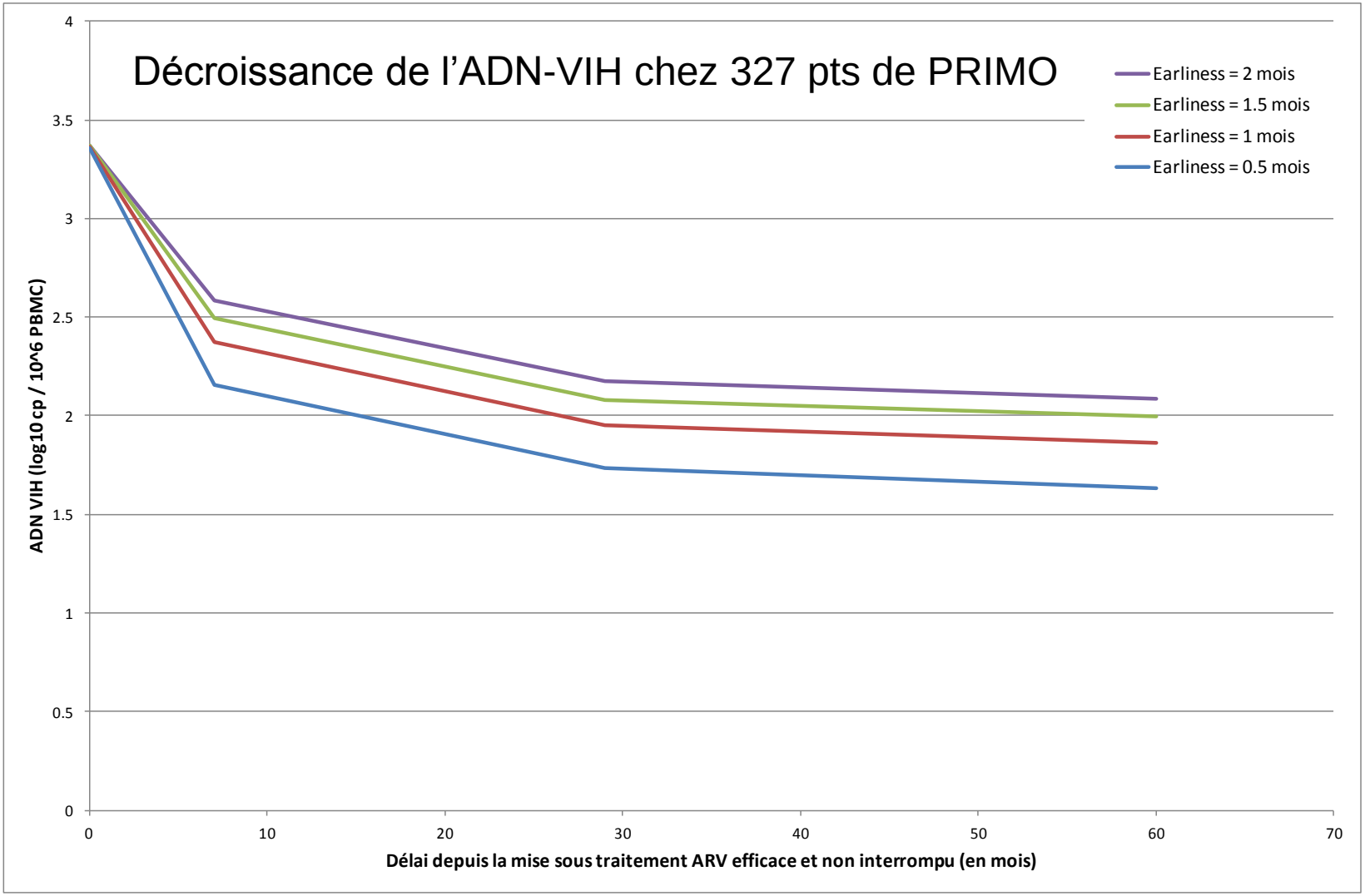
Hocqueloux et al., *JAC* 2013

Le traitement en PHI atteint l'objectif ADN



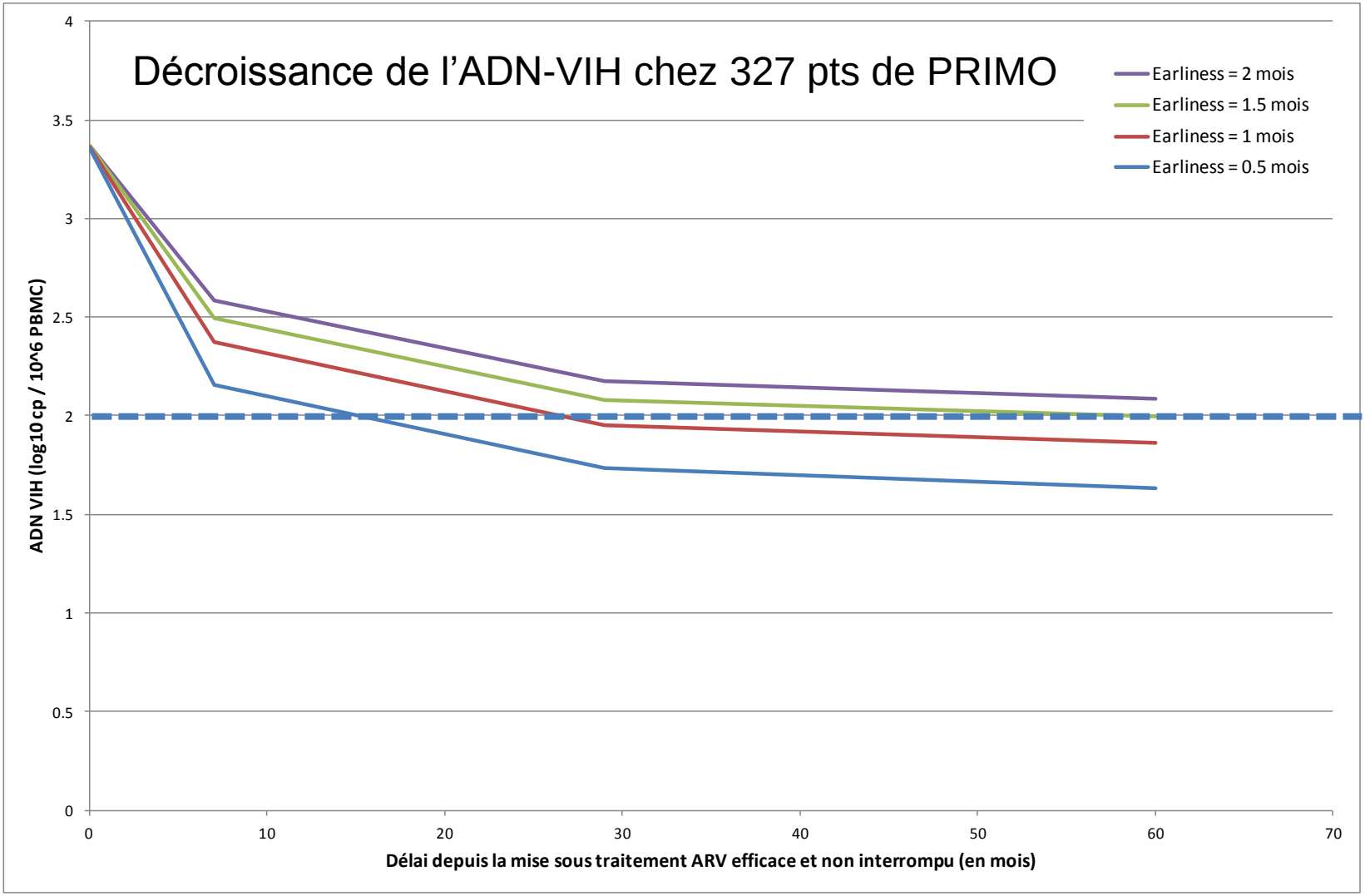
Hocqueloux et al., *JAC* 2013

Le plus tôt étant le mieux…



Laanani M. et al., *CROI* 2015

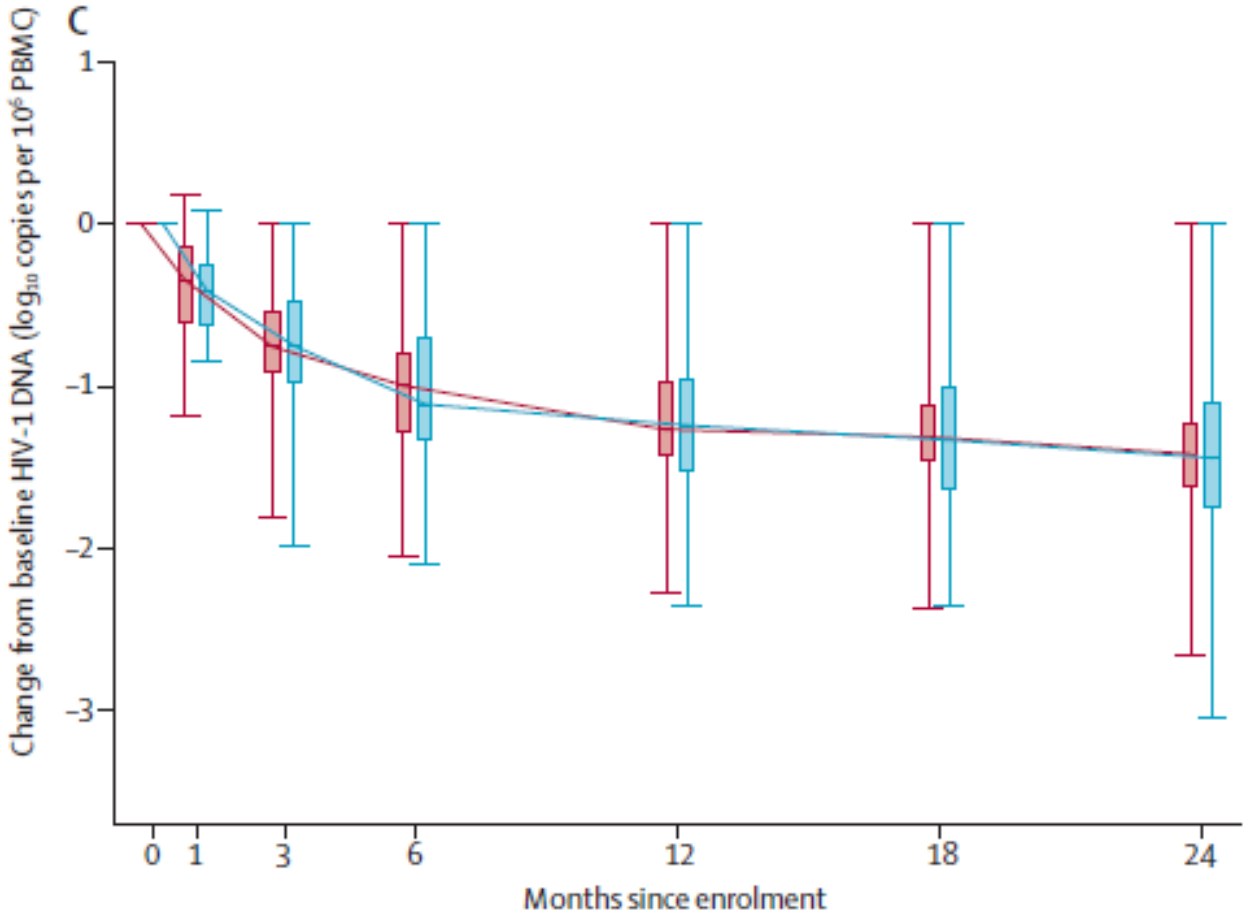
Le plus tôt étant le mieux…



Laanani M. et al., *CROI* 2015

Aucun bénéfice à intensifier en primo

***Figure 2*: Median HIV-DNA load and change from baseline to month 24 in the modified intention-to-treat population**
Boxes show IQR and bars show range. cART=combination antiretroviral therapy. PBMC=peripheral blood mononuclear cells.

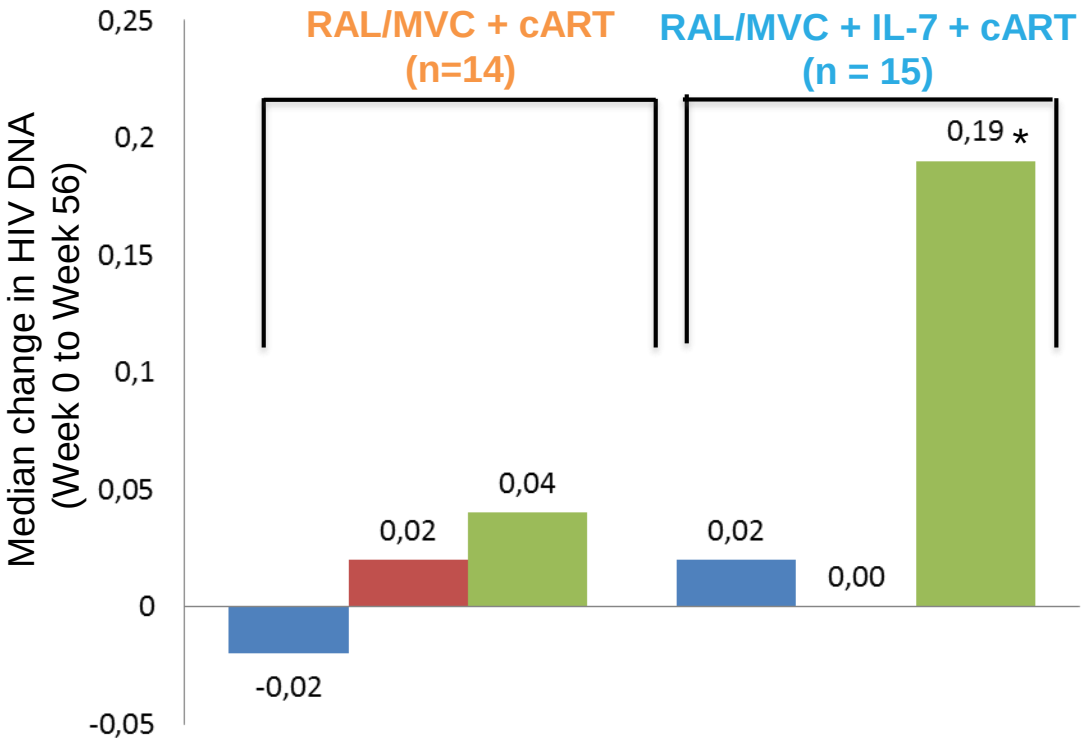


Chéret, et al., *Lancet Inf Dis* 2015

Et encore moins en phase chronique !

EraMUNE-01

Intensification of current cART with the addition of raltegravir (RAL)/maraviroc (MVC), with or without IL-7, failed to significantly reduce the total HIV DNA reservoir in peripheral blood monocytes (PBMCs) after 56 weeks of treatment



HIV DNA $\log_{10}$ copies/million PBMCs

HIV DNA $\log_{10}$ copies/million CD4+ cells

HIV DNA $\log_{10}$ copies/mL whole blood

(*Week 0 to week 56 difference, p = 0.01)

Katlama C, et al. *CROI* 2013. Abstract 170aLB

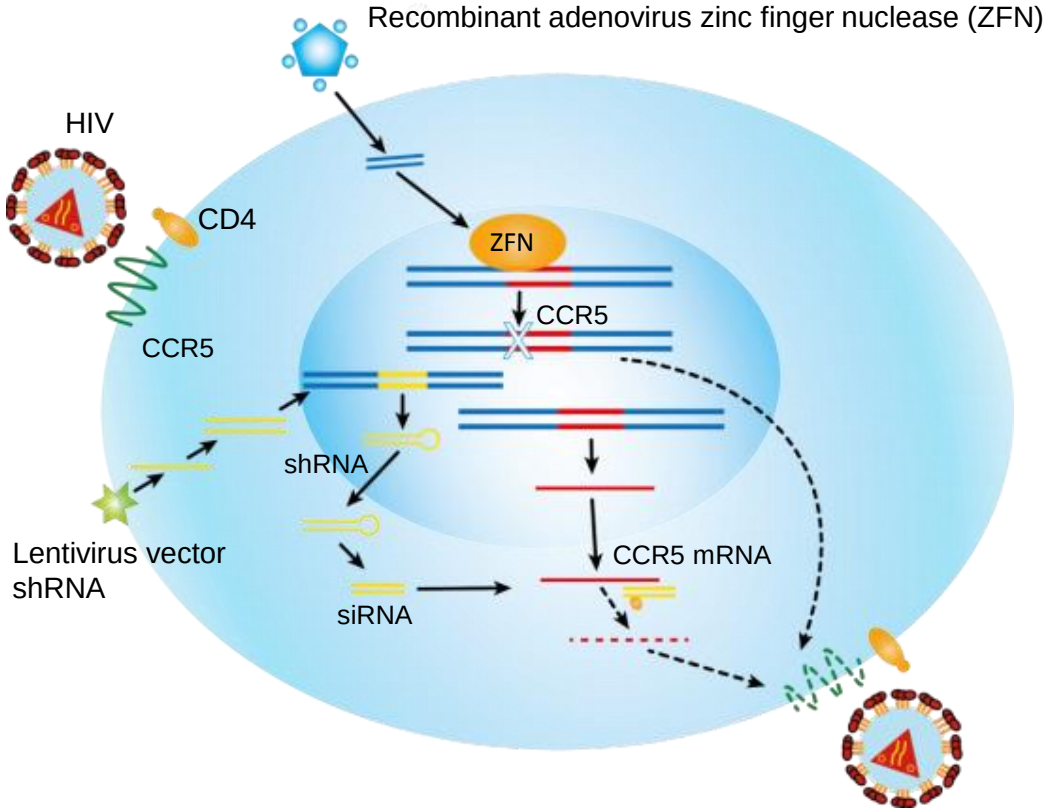
Réduire encore le réservoir : allogreffer ??

- Echec des « patients de Boston »
  - Mini-conditionnement, pas de greffon CCR5 – Δ32
  - Malgré la diminution faramineuse du réservoir
  - Les patients n'avaient plus d'immunité spécifique
  - Rechute rapide avec tableau de PHI

- Echec d'un « nouveau patient de Berlin »
  - Échappement rapide, malgré un greffon Δ32 / Δ32
  - Sélection d'un virus CXCR4

Heinrich TJ et al. , *Ann Intern Med* 2014
Kordelas et al., *NEJM 2014*

Gene therapy: HIV-1 resistant cells can be created with gene therapy



- Zinc finger nucleases are transfected into autologous CD34+ stem cells or CD4 T cells that are re-infused back into the patient
  - Zinc finger permanently modifies *CCR5* within these cells
- Or, CCR5 translation can be stopped using a lentivirus vector containing siRNA, which is incorporated into CD34+ stem cells or CD4 T cells
- Both strategies lead to the creation of a pool of cells permanently resistant to HIV-1

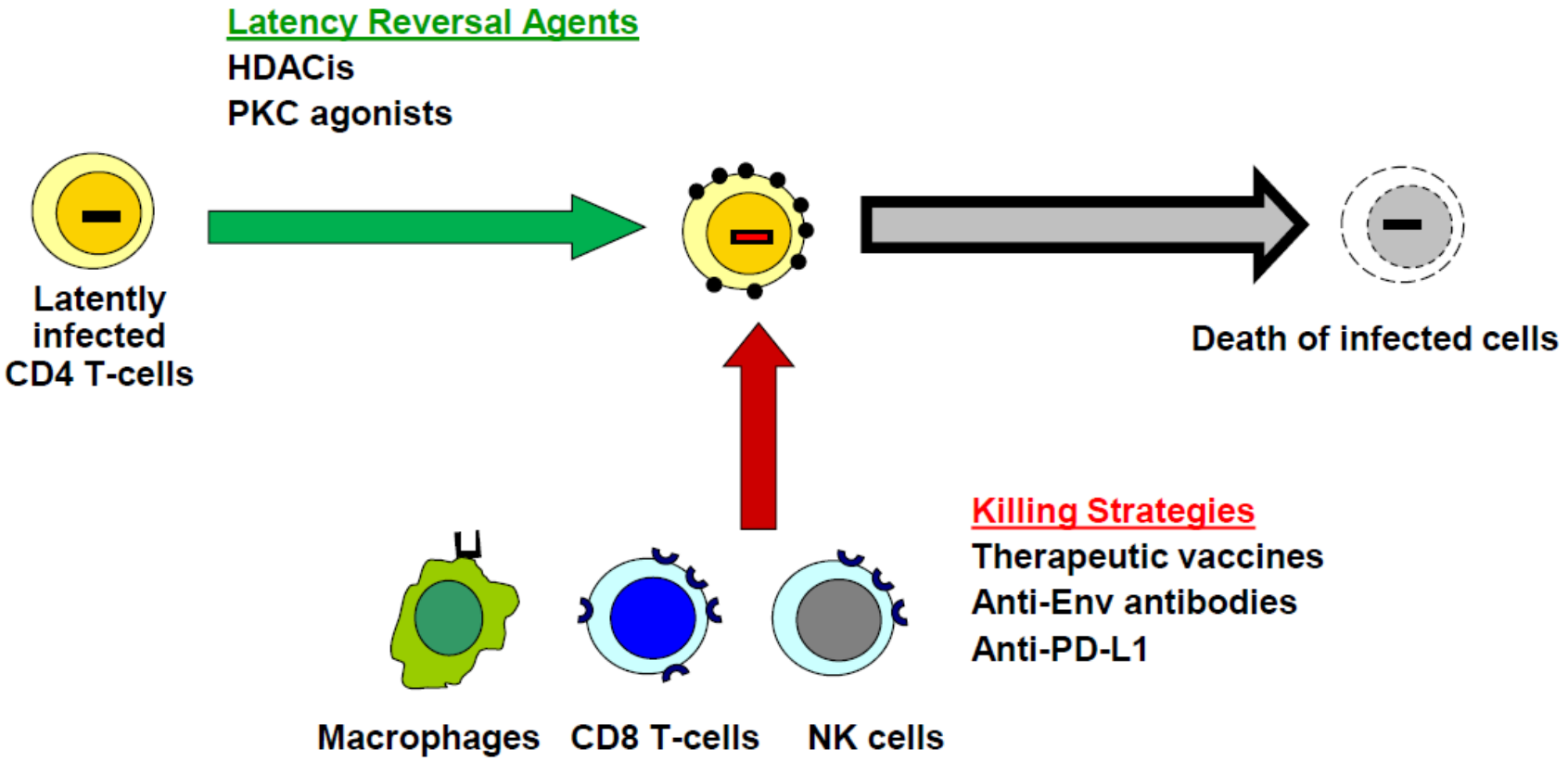
shRNA, short hairpin RNA; siRNA, short interfering RNA.

Adapted from Kent at al. Lancet Infect Dis 2013;13(7):614–21.

Kick and Kill Strategy to Eliminate Reservoirs of Latent HIV

KICK
Activate expression of HIV

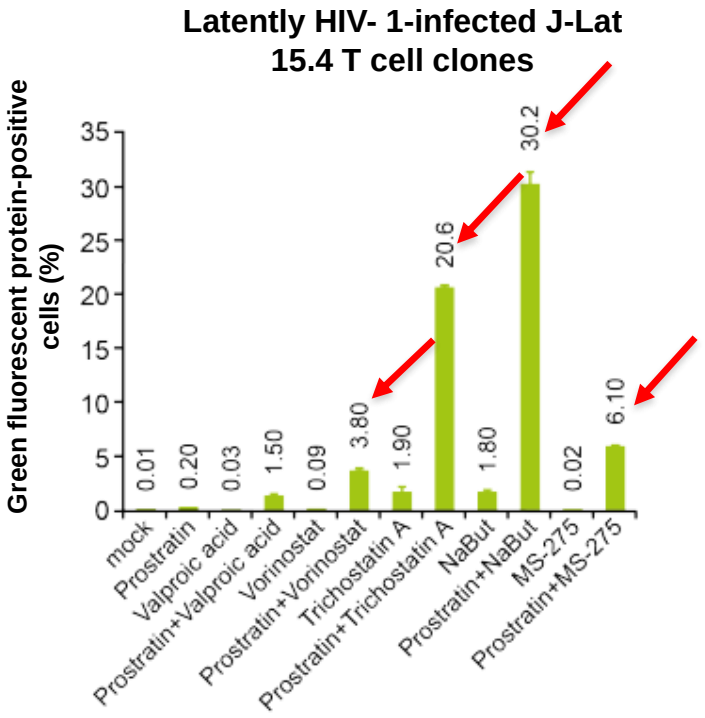
KILL
Kill cells expressing HIV proteins



Whitney et al., *CROI* 2015

Elimination of latent HIV-infected cells will probably need more than one target

- The strongest effects on HIV transcription in latently infected cells have been demonstrated when combinations of drugs are used
  - HDAC inhibitor plus NF-κB inducer or methylation inhibitor



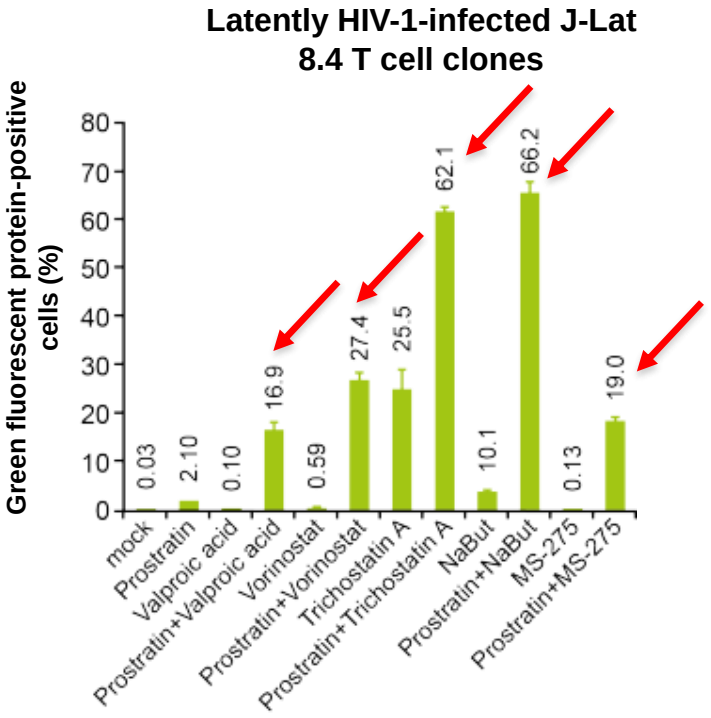
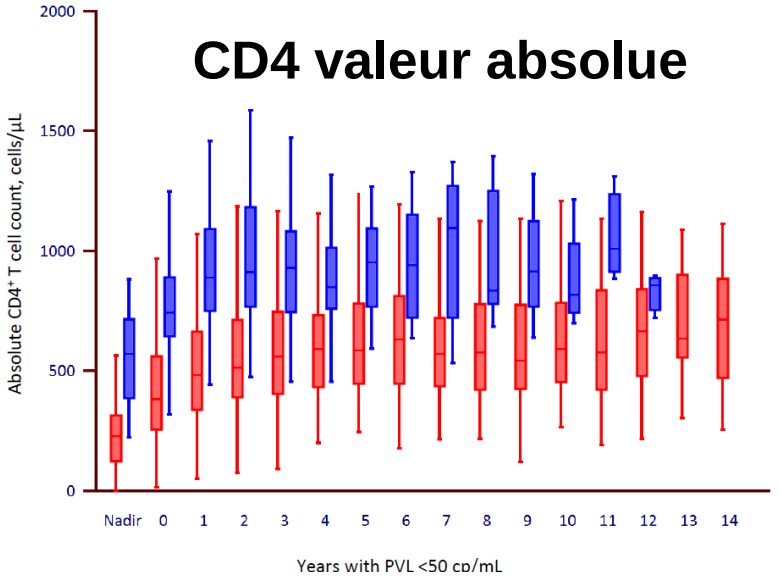
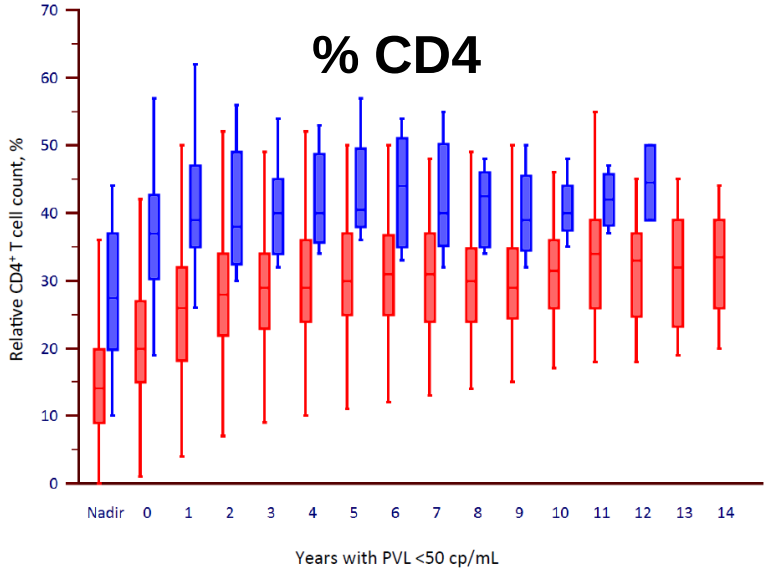


Figure adapted from Reuse S, et al. PLoS One 2009;4:e6093.

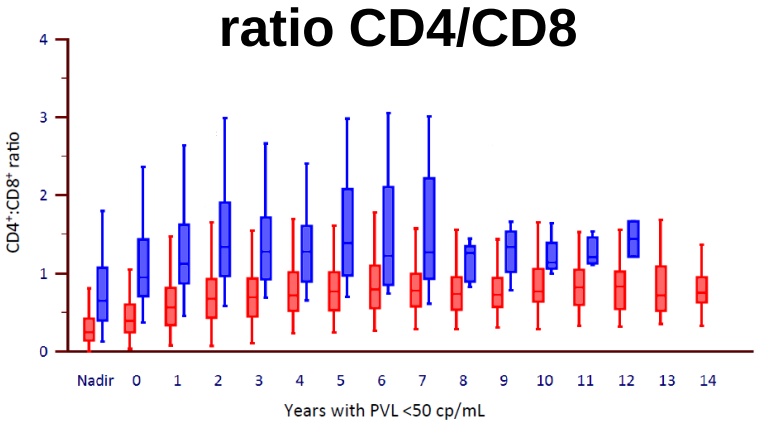
Le traitement en PHI restaure mieux les CD4





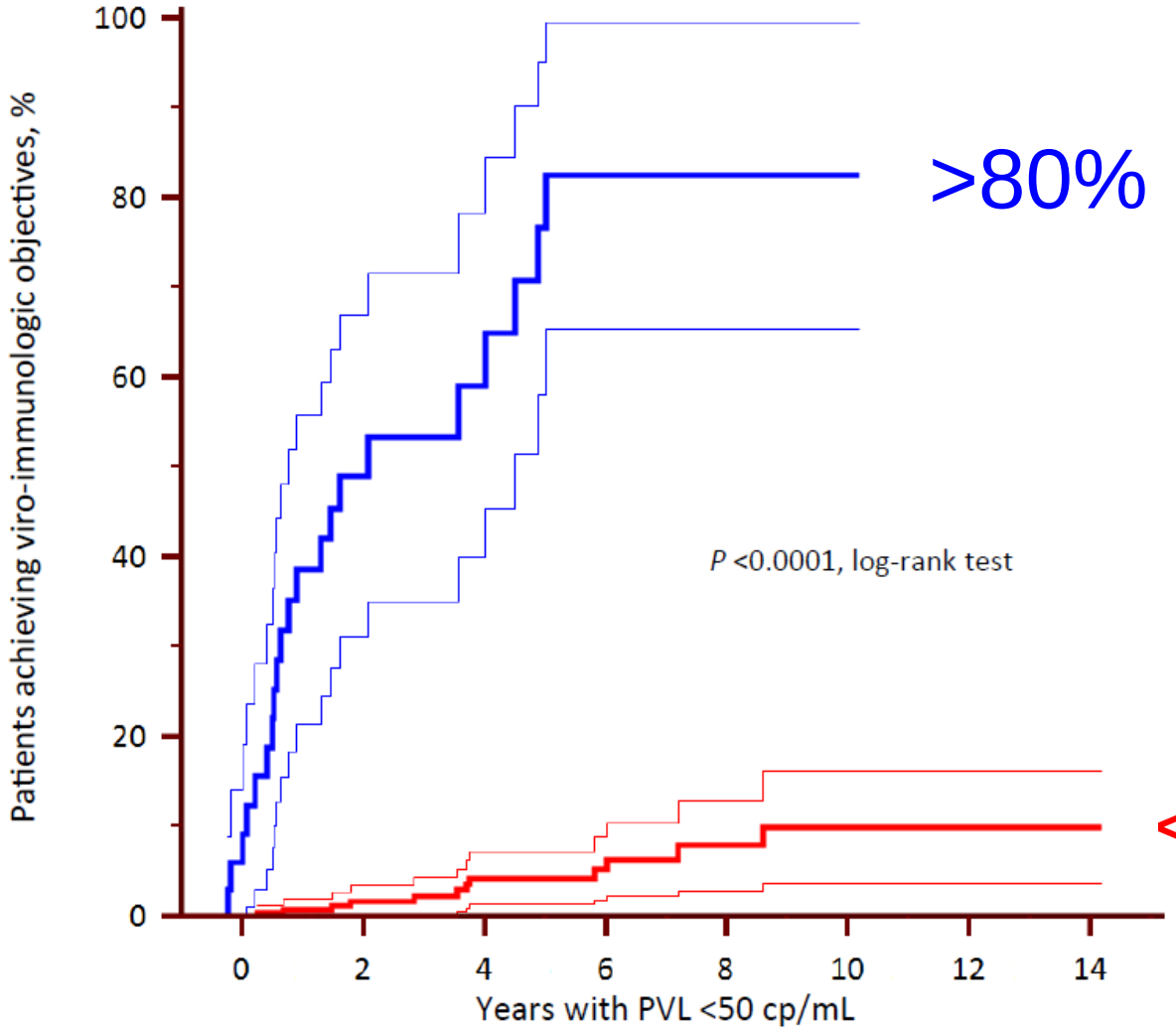
PHI

CHI



Hocqueloux et al. *JAC* 2013

Le traitement en PHI restaure mieux CD4 et ratio



Hocqueloux et al. *JAC* 2013

Inutile d'intensifier le traitement en PHI

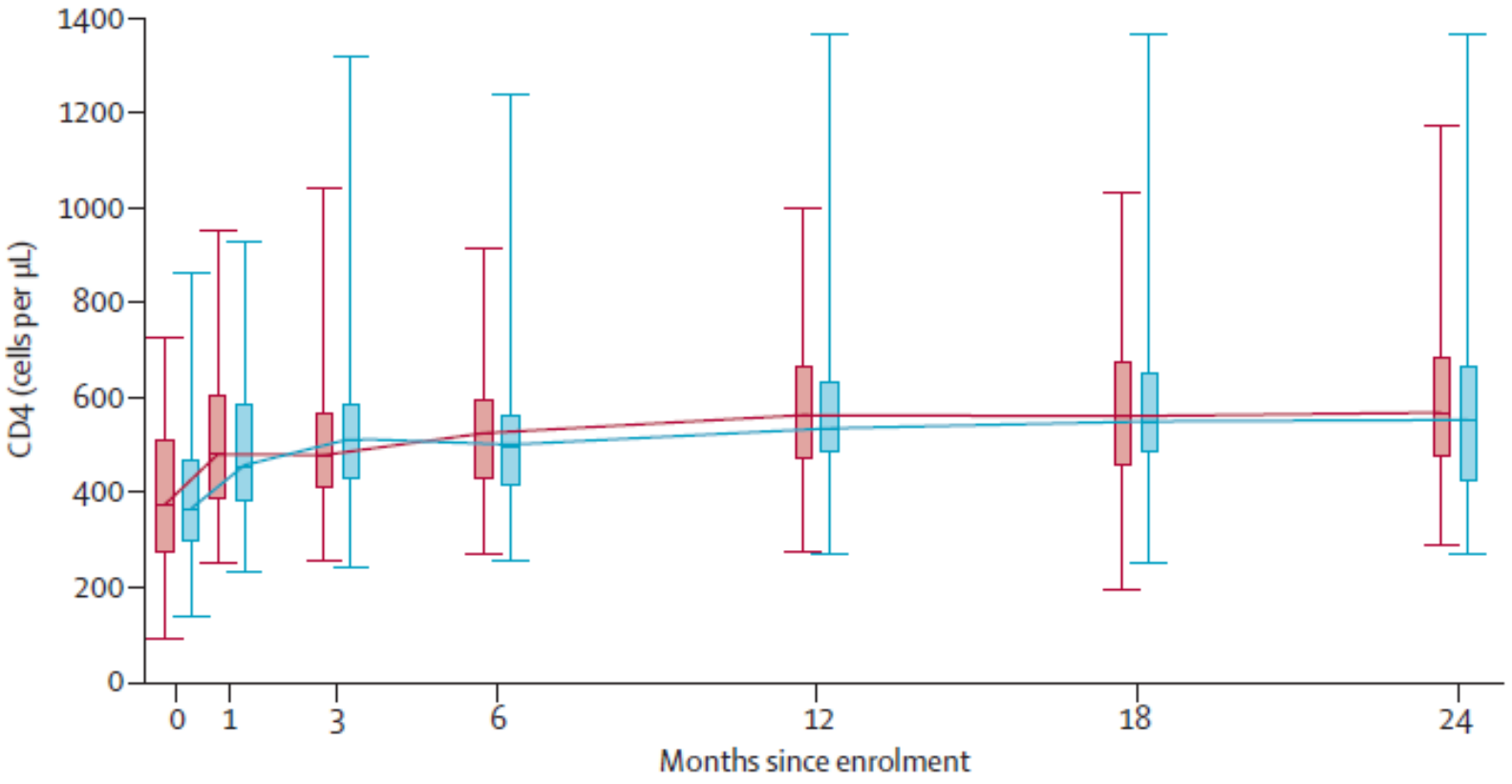


***Figure 3*: Changes in HIV-RNA loads and CD4 cell counts in the modified intention-to-treat population**
Proportion of patients in the intention-to-treat population who had less than 50 HIV-RNA copies per mL (A) and the proportion of those who had less than 400 HIV-RNA copies per mL (B); error bars show 95% CI. (C) Median CD4 cell count; boxes show IQR and bars show range. cART=combination antiretroviral therapy.

Chéret, et al., *Lancet Inf Dis* 2015

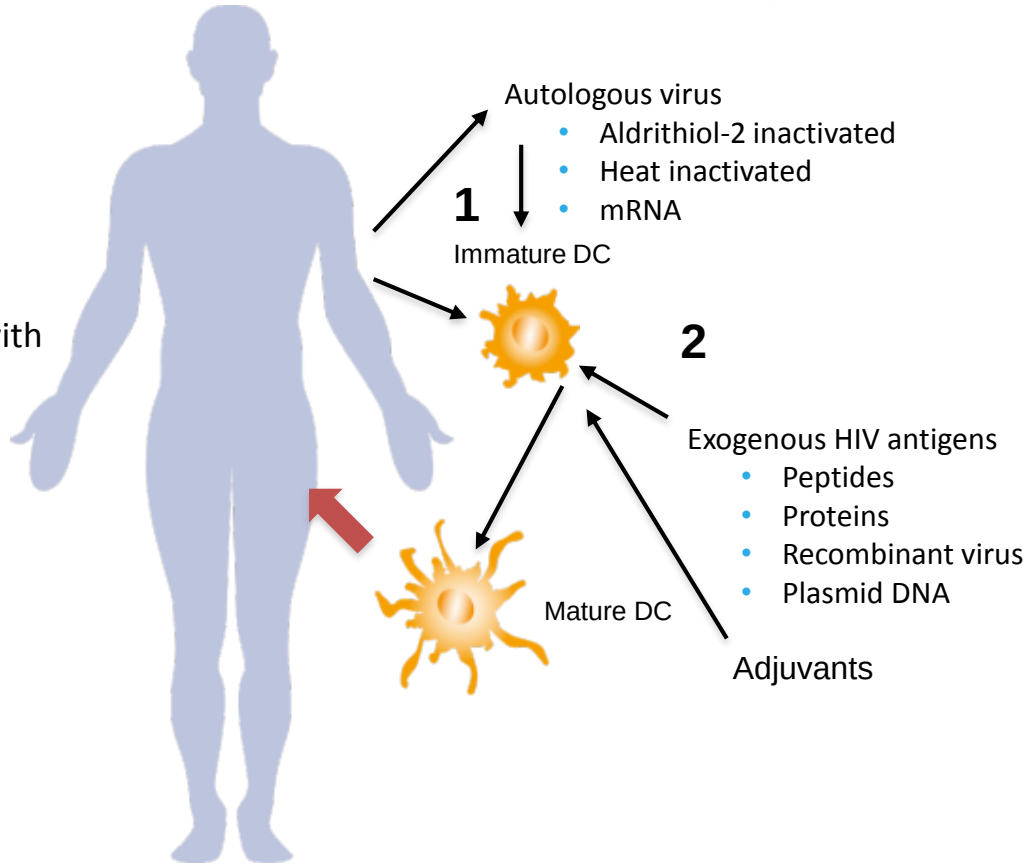
Immune stimulation: restoring immune function with therapeutic vaccines in HIV infection

Direct *in vivo* injection

Non-targeted
- Peptides
- Viral vectors/live viruses
- DNA vaccines

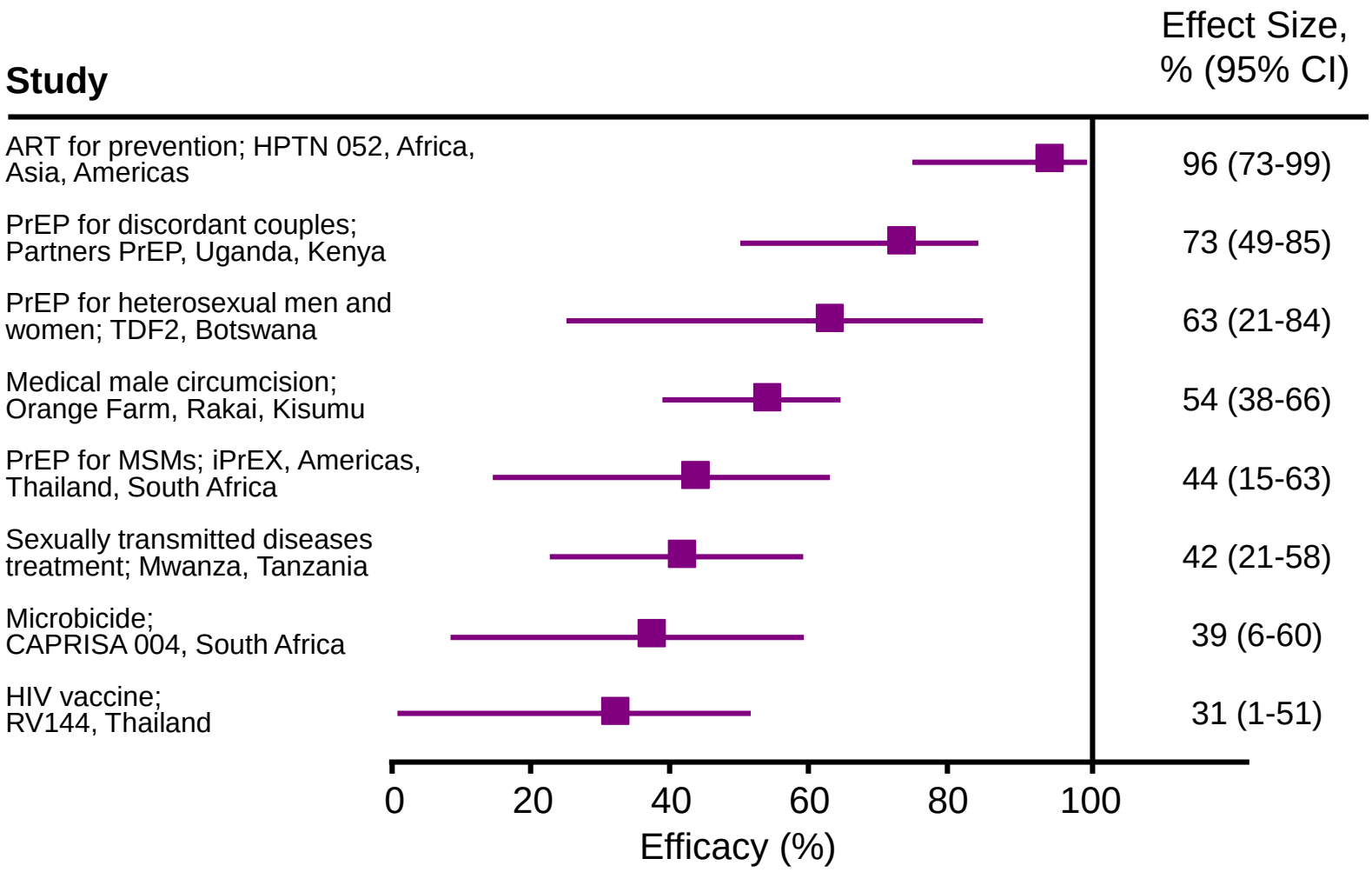
Targeted
- Protein antigens complexed with DC-SIGN or DEC205

Ex vivo loading



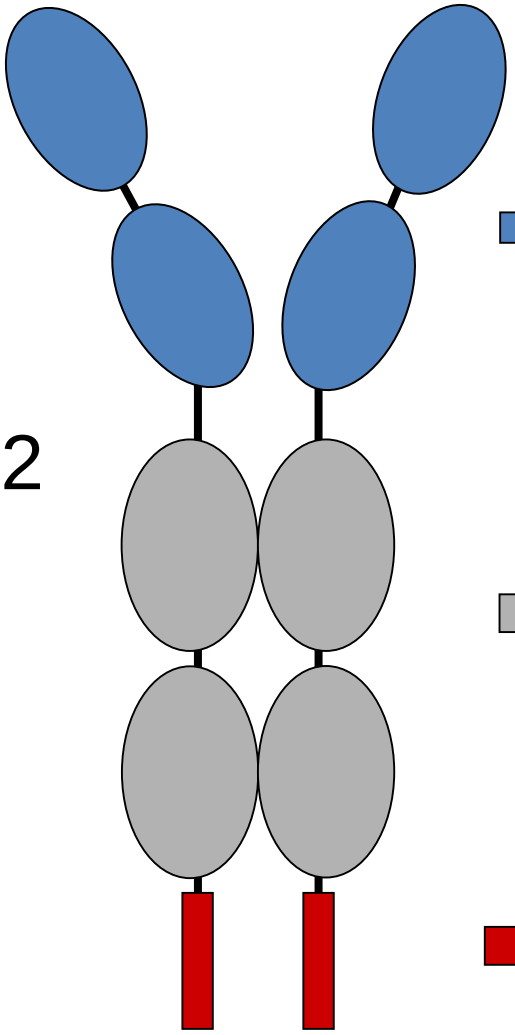
Adapted from Vanham G & Van Gulck E. Retrovirology 2012;9:72.

Vaccins : efficacité proche du placebo…



Abdool Karim SS, et al. *Lancet* 2011

« CD4-Ac-CCR5-like » super-neutralisants !



eCD4-Ig^{mim2}

CD4-like

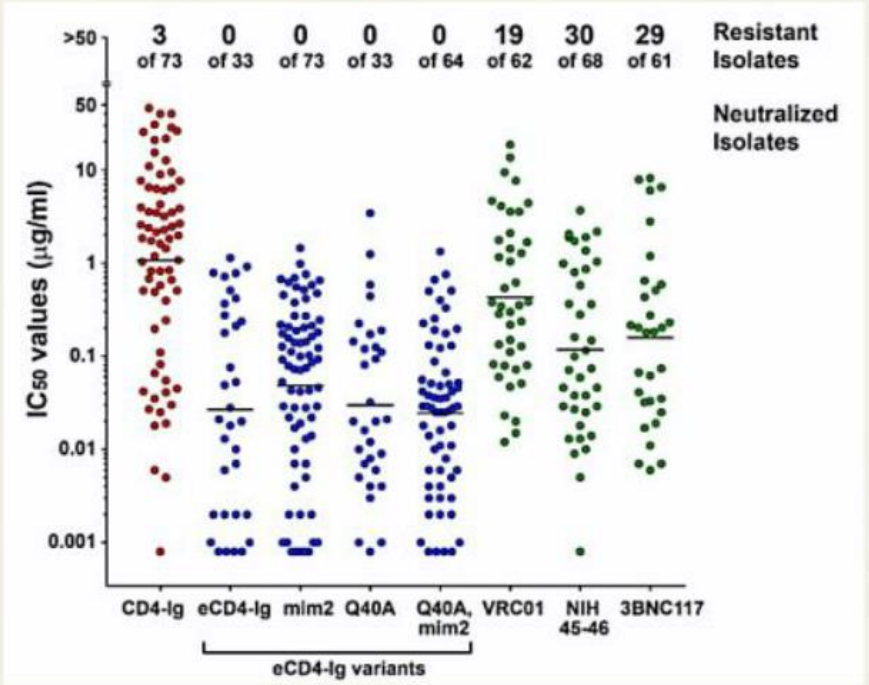
Ig

CCR5-like

Farzan M. et al., *Nature* 2015

« CD4-Ac-CCR5-like » super-neutralisants !

Summary of IC_{50}s from two panels

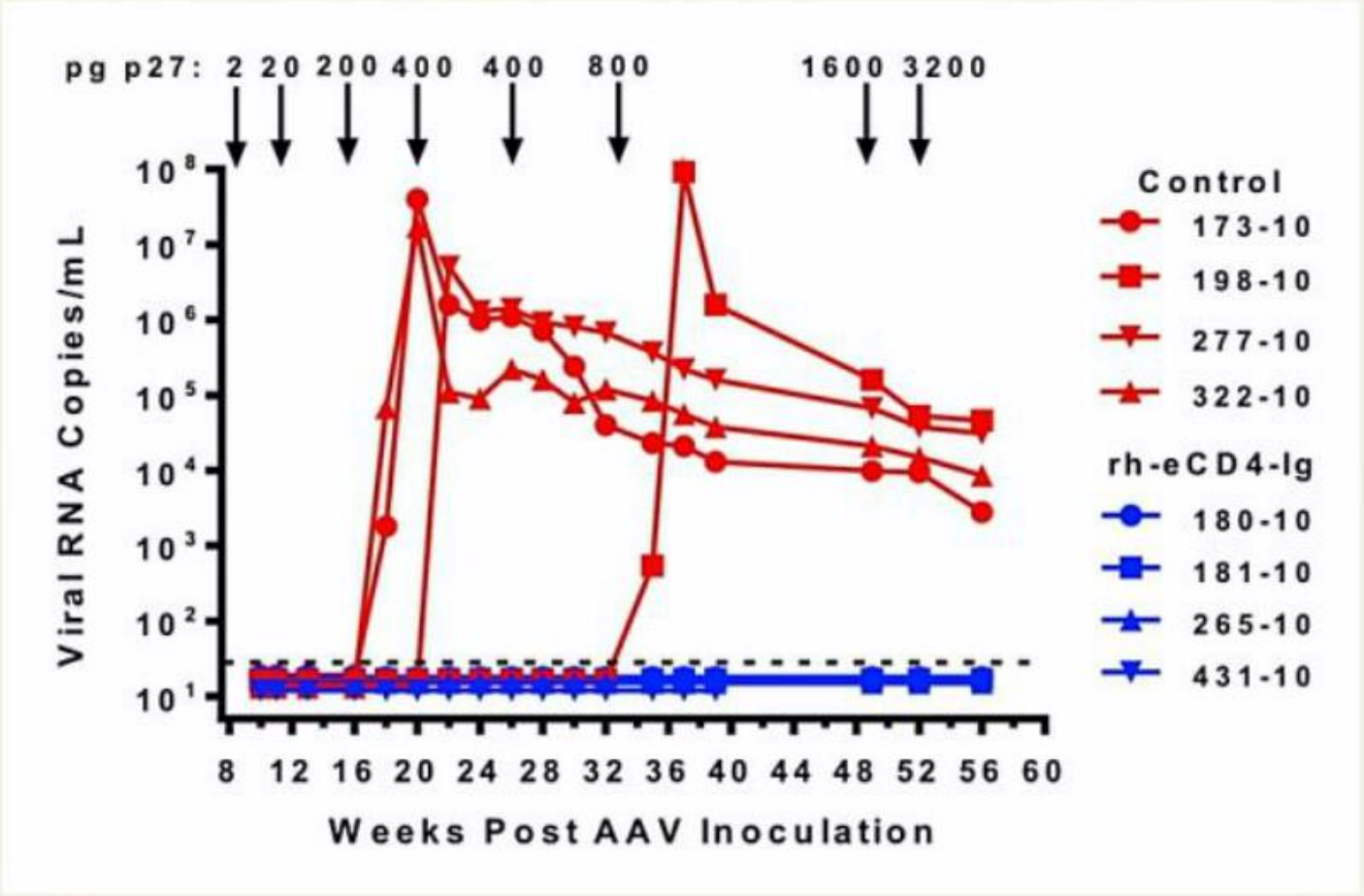


$eCD4\text{-}Ig^{mim2}$ (our lead candidate)

Geometric mean IC_{50} < 0.05 ug/ml (panels biased toward hard-to-neutralize)
All IC_{50}s < 1.2 ug/ml
All IC_{80}s < 5.2 ug/ml
100% isolates neutralized, including SIV and HIV-2 isolates

Farzan M. et al., *Nature* 2015

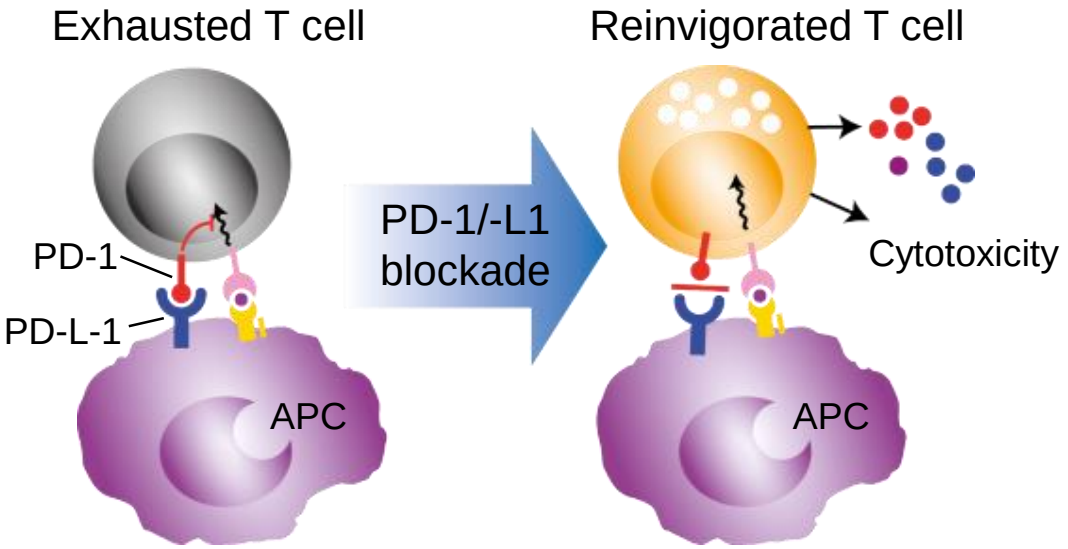
AAV-rh-eCD4-Ig protects from six infectious SHIV-AD8 challenges, the last 16x the AID_{50} at 1 year



Controls	4 of 4 infected	
AAV-eCD4-Ig	0 of 4 infected	(p = 0.0062)

Immune stimulation: PD-1 blockade helps to refresh exhausted T cells

- Persistent antigenaemia leads to T-cell exhaustion
- PD-1 is a key inhibitory receptor affecting T-cell response
  - Increased on virus-specific T cells in chronic HIV
  - CD4+ and CD8+ cells
- Inhibition of PD-1/PD-L1 (murine study)
  - Restores HIV-specific immune function *in vitro* and *ex vivo*
  - Reduces viraemia and prolongs survival *in vivo*



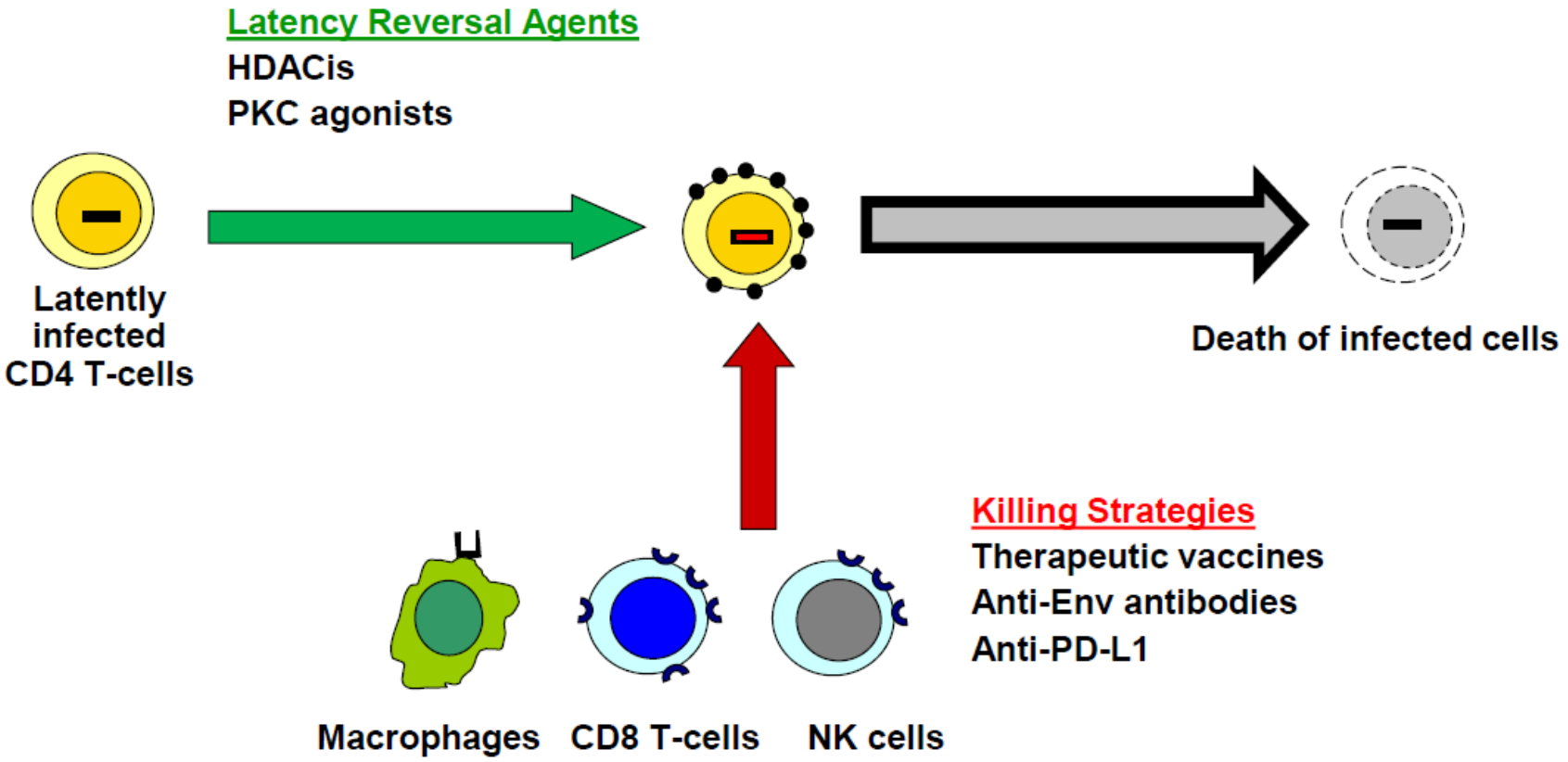
APC, antigen-presenting cell.

Adapted from Freeman G, et.al. J Exp Med 2006;203(10):2223–7. Palmer B et al. J Immunol 2013 ;190(1):2119.

Kick and Kill Strategy to Eliminate Reservoirs of Latent HIV

KICK
Activate expression of HIV

KILL
Kill cells expressing HIV proteins



Whitney et al., *CROI* 2015

TLR7 Background

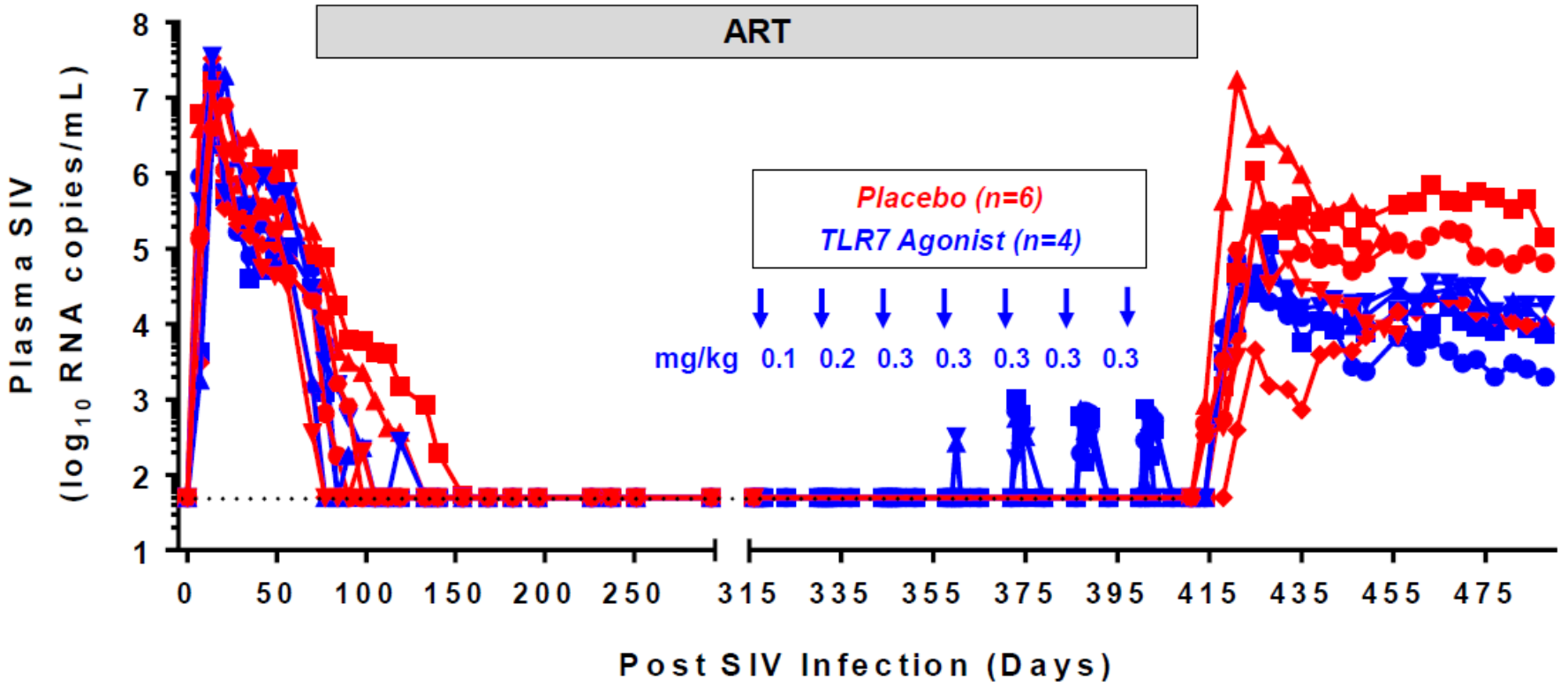
TLR7

- Expressed in plasmacytoid dendritic cells and B lymphocytes
- Part of the innate immune system linked to adaptive immunity
- TLR7 activation leads to
  - increased antigen presentation
  - enhanced NK and CD8+ T cell activation (KILL)
  - activation of CD4+ T cells

GS-9620

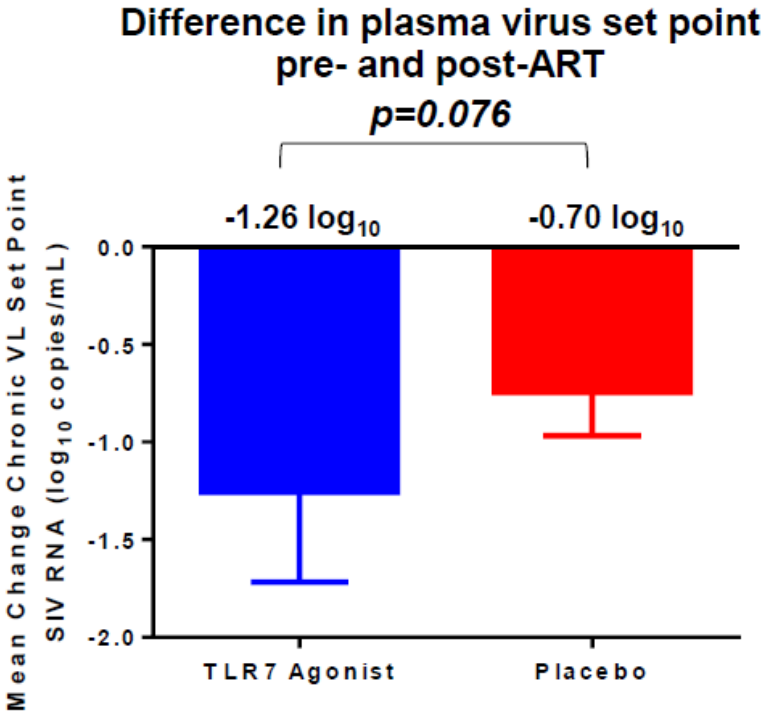
- Potent and selective oral TLR7 agonist
- Demonstrated antiviral activity: reduced sAg and viral DNA in woodchucks (WHV) and chimpanzees (HBV)
- Phase 2 study in HBV subjects ongoing
- Current NHP study uses an analog of GS-9620

Kinetics of Plasma Virus Rebound after Stopping ART



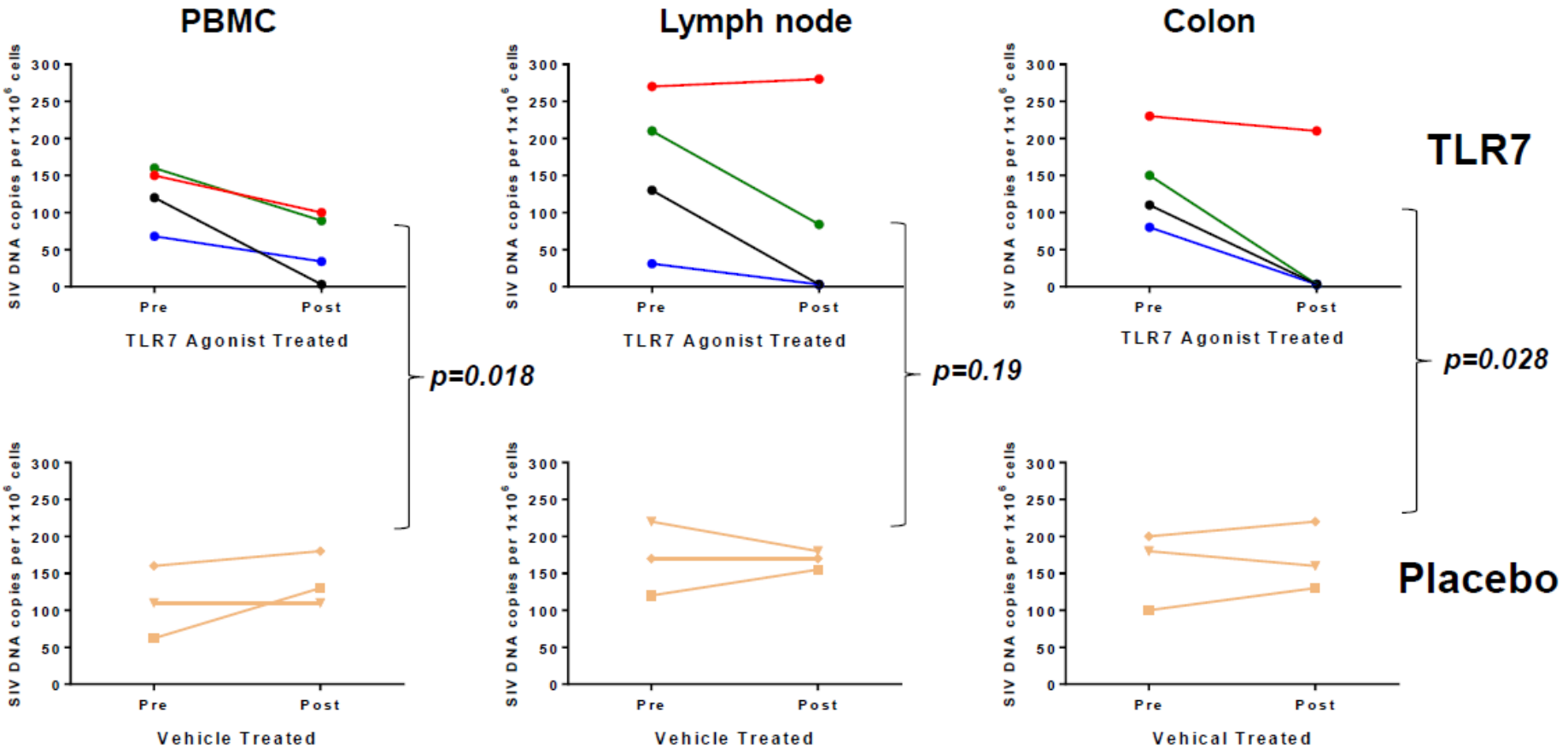
- No apparent difference in plasma virus rebound kinetics after stopping cART in TLR7 agonist vs. placebo groups
- Lower plasma virus set point in TLR7 treated vs. placebo

Treatment with TLR7 Agonist Leads to Lower Plasma Virus Set Points after Stopping ART

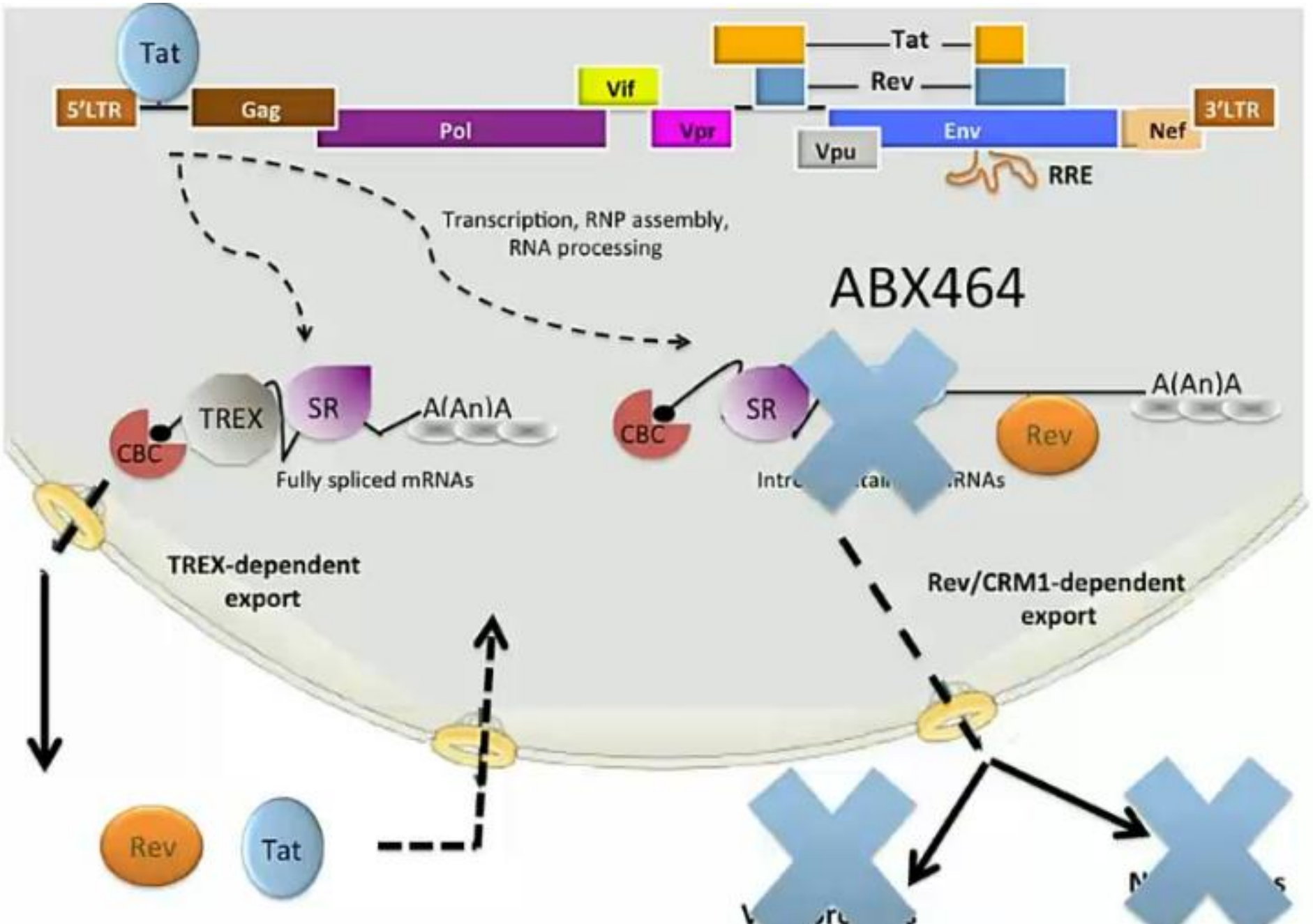


- 1 year ART leads to ~0.7 log_{10} lower plasma virus set point vs. pre-cART
- cART + TLR7 agonist treatment: additional ~0.5 log_{10} reduction in set point

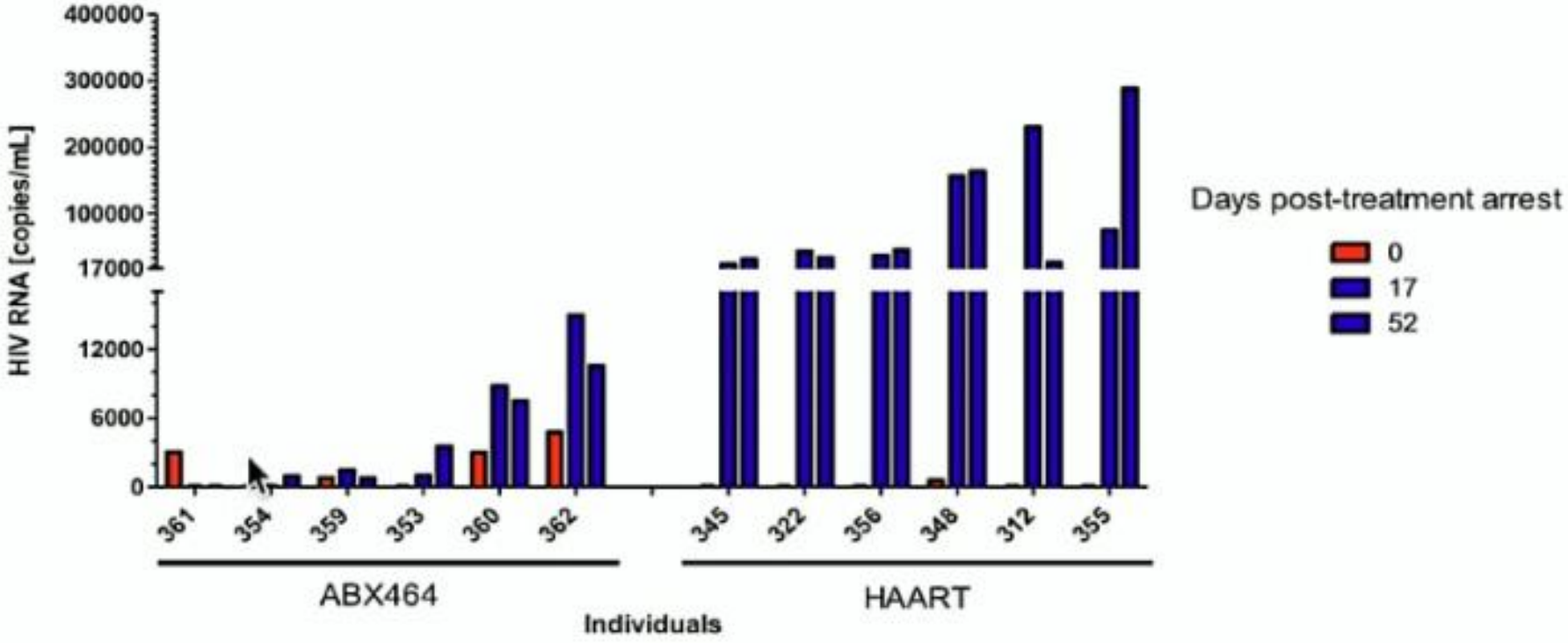
SIV DNA Levels Reduced in TLR7 Agonist Treated Monkeys on cART



- SIV DNA decrease in 3 of 4 animals treated with TLR7 agonist
- No significant SIV DNA change in placebo animals


Tat
5'LTR
Gag
Pol
Vif
Vpr
Tat
Rev
Vpu
Env
Nef
3'LTR
RRE
Transcription, RNP assembly,
RNA processing
ABX464
CBC
TREX
SR
A(An)A
Fully spliced mRNAs
CBC
SR
A(An)A
Rev
TREX-dependent
export
Rev/CRM1-dependent
export
Rev
Tat

ABX464 is an anti-HIV drug able to suppress viral load sustainably after treatment arrest



Perspectives à court terme

- Les patients traités tôt, ayant une bonne restauration immunitaire, un parfait contrôle viral prolongé et un réservoir faible devraient pouvoir bénéficier d'allègement thérapeutique (2 molécules, voire 1)
  - Bithérapies diverses, monothérapies IP/r
  - Observatoire Moncay (JNI 2015?)
  - Essai Trulight (en cours)

Perspectives à moyen/long terme

- Des thérapies allégées pourraient être administrées de manière discontinue
  - Version injectable de l'essai LATTE (cabotegravir LP + rilpivirine LP)

- L'interruption des ARV parait enfin « envisageable » avec des nouvelles cibles thérapeutiques prometteuses
  - Agonistes TLR7, eCD4-Ig^{mim2}, ABX464…

Conclusions

- A ce jour l'éradication ne parait pas raisonnable, mais un traitement précoce et prolongé peut induire une rémission (≈10%)
  - Pour le moment aucun marqueur ne permet de prédire le statut PTC avant l'interruption
  - Le risque de transmission des PTC parait faible mais doit être précisé, et le risque est certain si le patient ne contrôle pas…

Conclusions (suite)

- A défaut de rémission un traitement précoce offre les meilleurs :
  - De contrôler le virus avec un traitement allégé
  - De bénéficier des formes injectables de ces traitements allégés
    (dans un avenir proche)
  - De bénéficier de nouvelles cibles thérapeutiques qui pourraient permettre de stopper les ARV
    (à plus long terme)

Conclusions (suite)

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  - De contrôler le virus avec un traitement allégé
  - De bénéficier des formes injectables de ces traitements allégés
    (dans un avenir proche)
  - De bénéficier de nouvelles cibles thérapeutiques qui pourraient permettre de stopper les ARV
    (à plus long terme)
- Une vie sans traitement « à prendre tous les jours » n'est plus un rêve

Remerciements

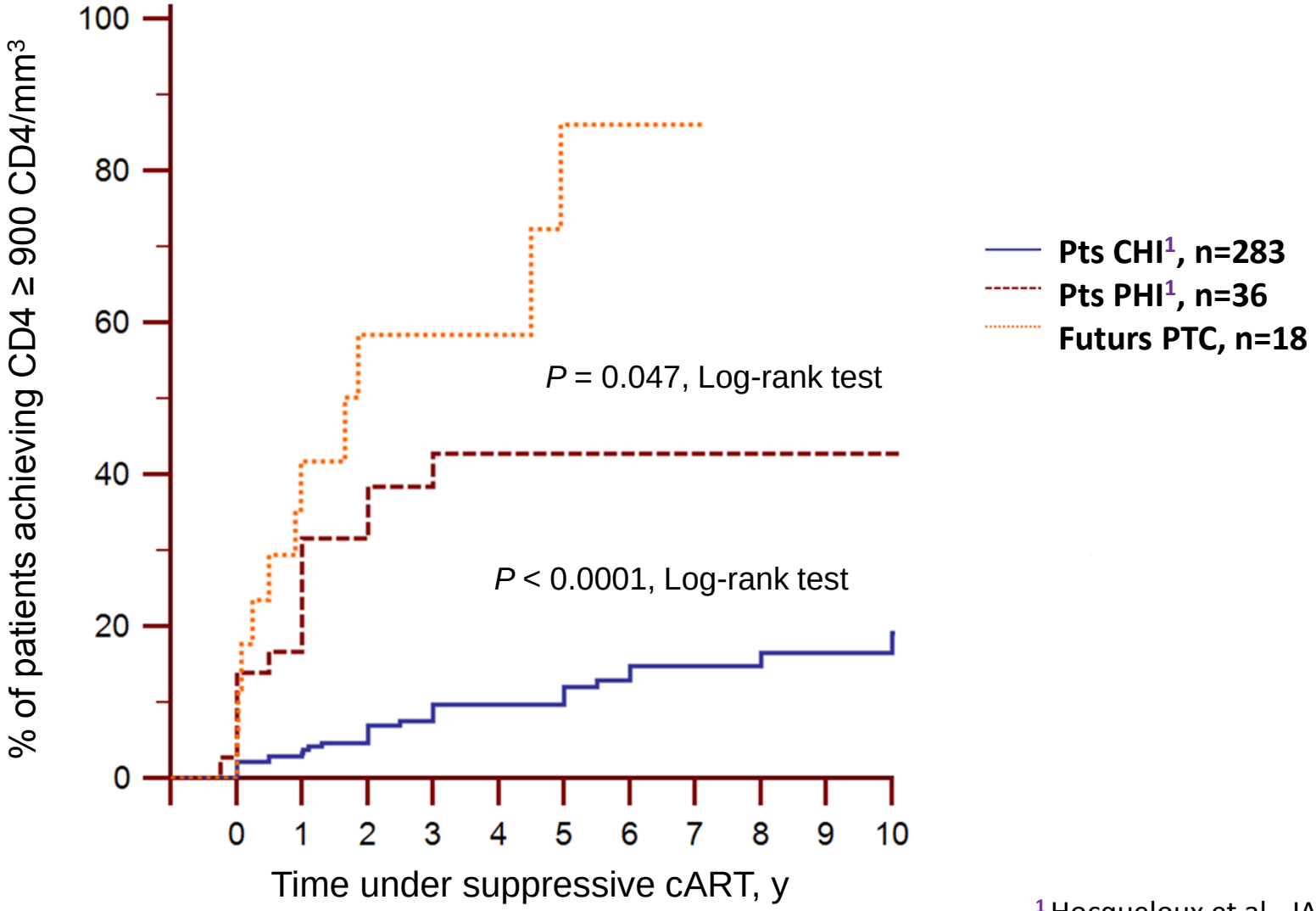
- ANRS AC32
  - **C. Rouzioux**
  - V. Avettand-Fènoël
  - **A. Saez-Cirion**
- Mes collègues CHRO
  - **T. Prazuck**
  - B. De Dieuleveult
- Cohorte VISCONTI
  - **Patients**
  - Investigateurs
- Cohorte CODEX
  - O. Lambotte
  - B. Autran
- VRI / H. Mondor
  - S. Hüe
  - Y. Lévy

Les PTC ne sont pas des EC/HIC traités

Elite controllers (HIC)		Post-treatment controllers
< 1% of HIV-infected patients	Estimated frequency	5–15% of HIV-infected patients interrupting a > 12 months treatment period initiated in primary infection
Asymptomatic: low viral loads and high CD4 T-cell counts	Primary infection	Symptomatic: high viral loads and low CD4 T-cell counts
Lower T-cell activation than cART patients (but higher than uninfected)	T-cell activation	Low levels of T-cell activation
Generally strong HIV-specific T-cell responses with strong capacity to eliminate infected cells	T-cell responses	Generally very weak HIV-specific T-cell responses with poor capacity to eliminate infected cells
Up to 85% carry one protective HLA-class I allele	HLA alleles	57% carry one HLA-class I allele associated with high viral loads

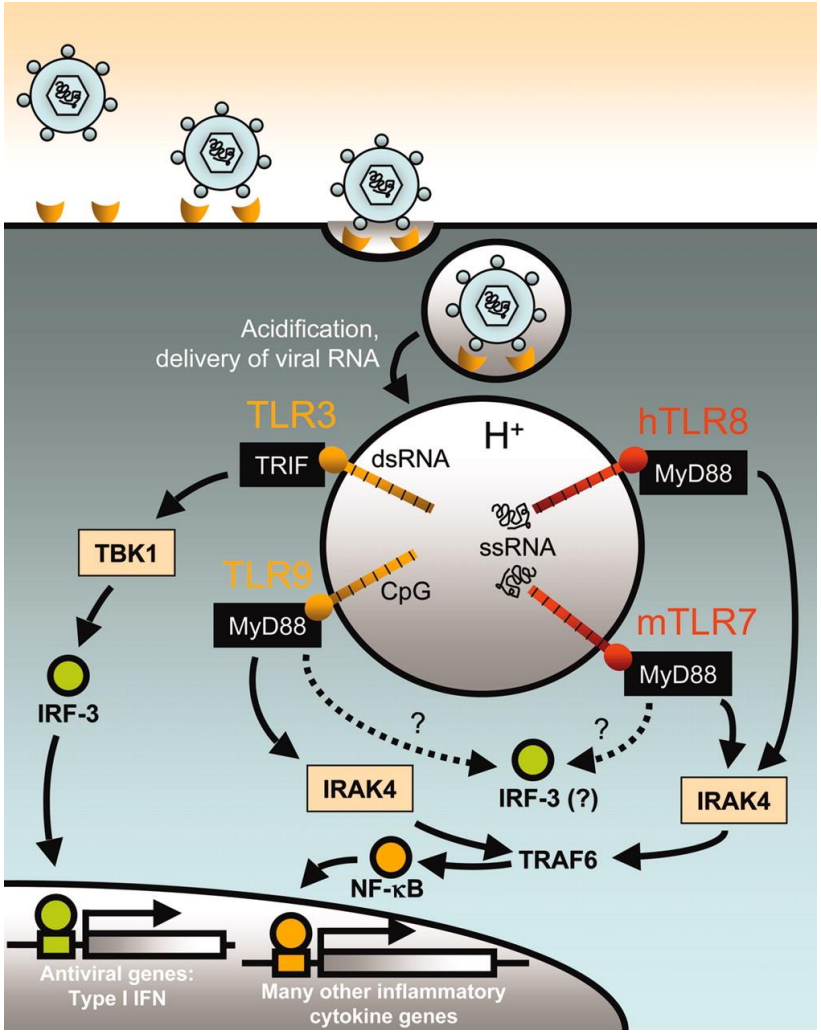
Saez-Cirión A, et al. PLoS Pathog 2013;9:e1003211. Migules SA, et al. PNAS 2000;97(6):2709–14.

Les PTC ont une restauration ample / rapide



[1] Hocqueloux et al., JAC 2013

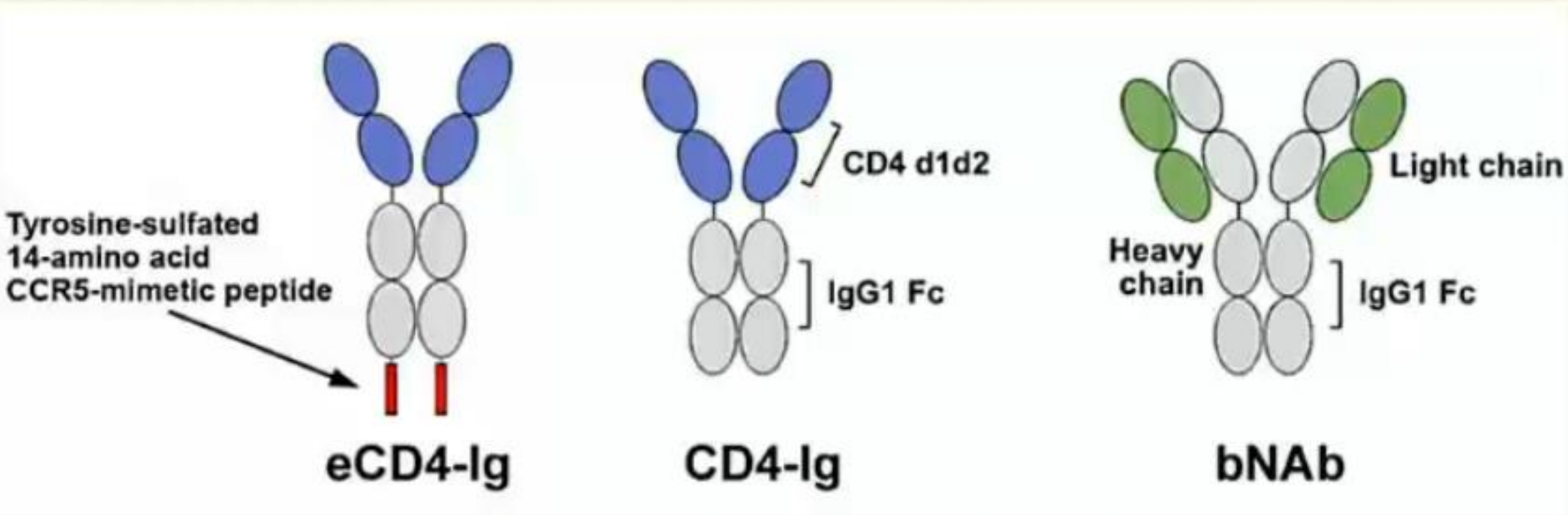
What is the role of mTLR7 in the antiviral response? Many ssRNA viruses (including VSV and influenza viruses) engage host cell receptors that trigger endocytosis.



K. Crozat, and B. Beutler PNAS 2004;101:6835-6836

« Ac-CD4-CCR5-like » super-neutralisants !

AAV-expressed eCD4-Ig provides durable protection from multiple SHIV-AD8 challenges



Mike Farzan, The Scripps Research Institute
CROI, February 27, 2015

Publié dans *Nature* 2015

HIV remission

HIV remission should allow patients to durably discontinue therapeutic intervention, without
(i)developing HIV-associated morbidities,
(ii) showing decline of clinical parameters or progression to disease,
(iii) while maintaining viremia at the lowest levels to avoid risk of transmission of infection.