Immunopathogenesis of HIV

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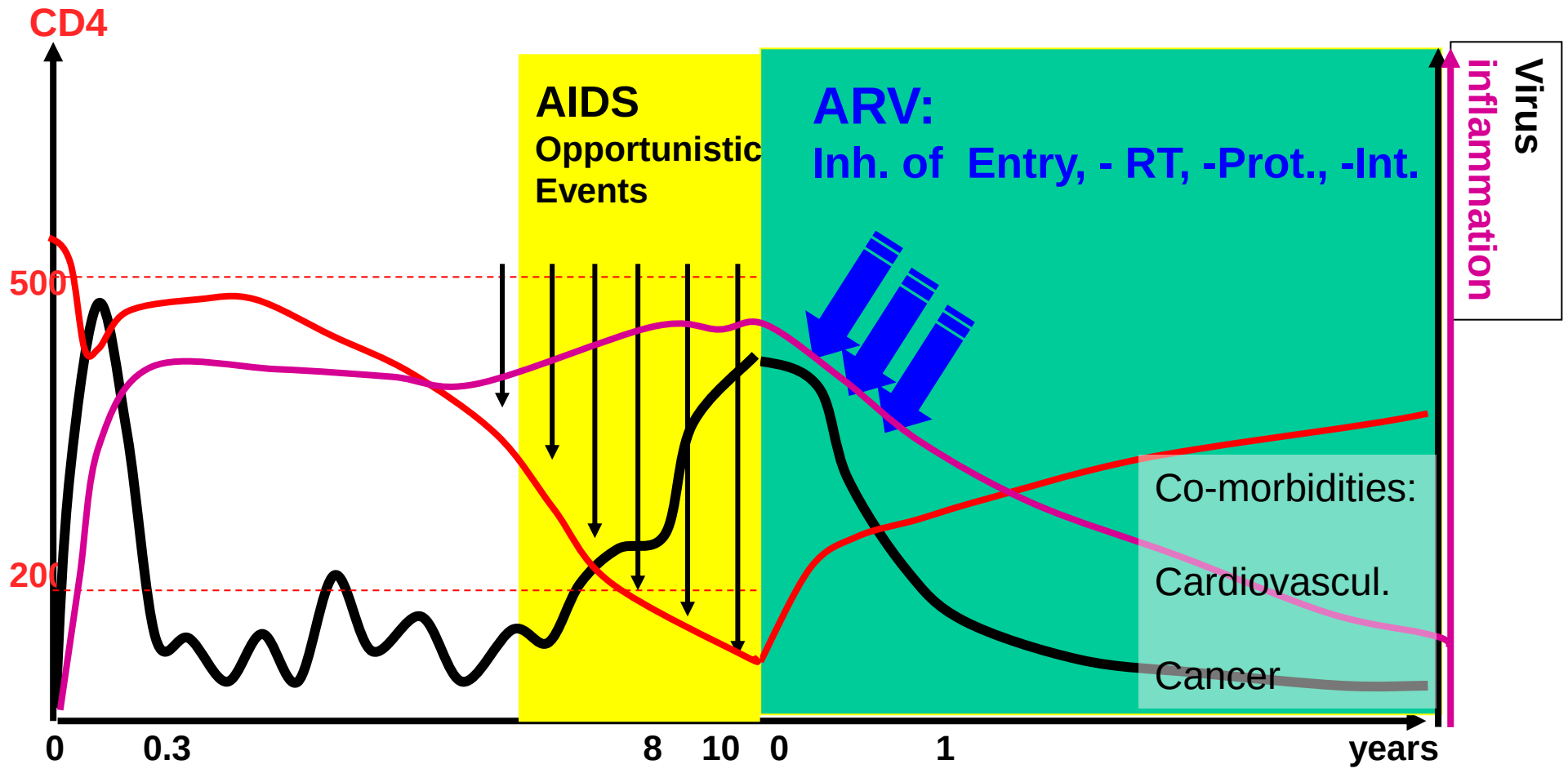
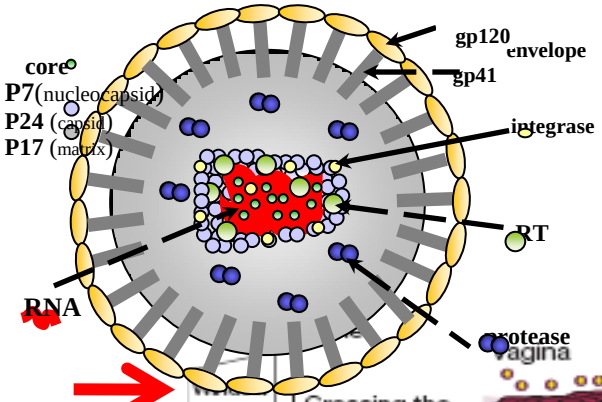
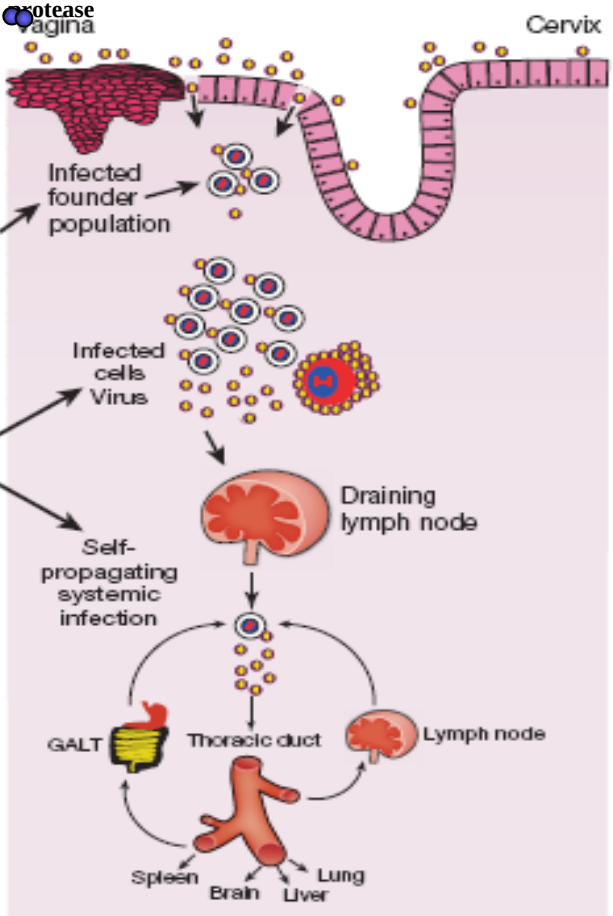
HIV infection: a slow immune disease with 2 pathogenic effects:

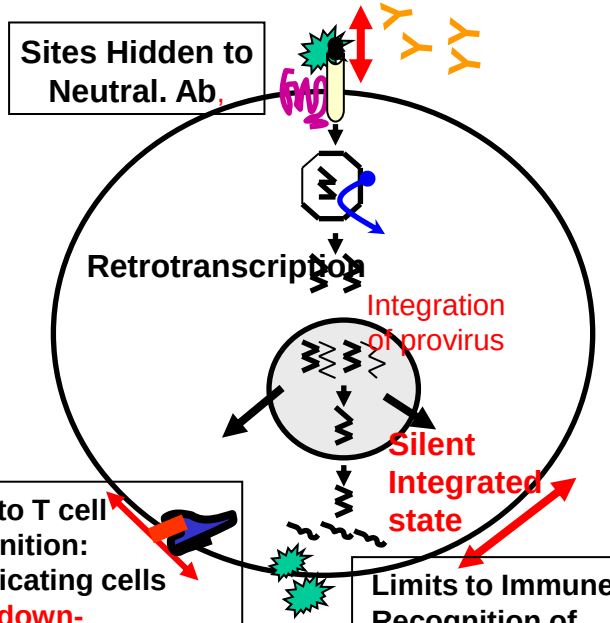
1) a lethal immune deficiency causing AIDS
2) a systemic inflammation with co-morbidities

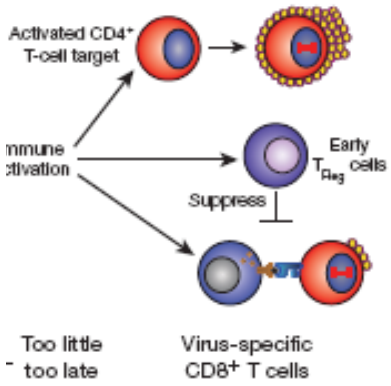


HIV: The Trojan Horse , its Kinetics of early infection and dissemination, its mechanisms of immune escape



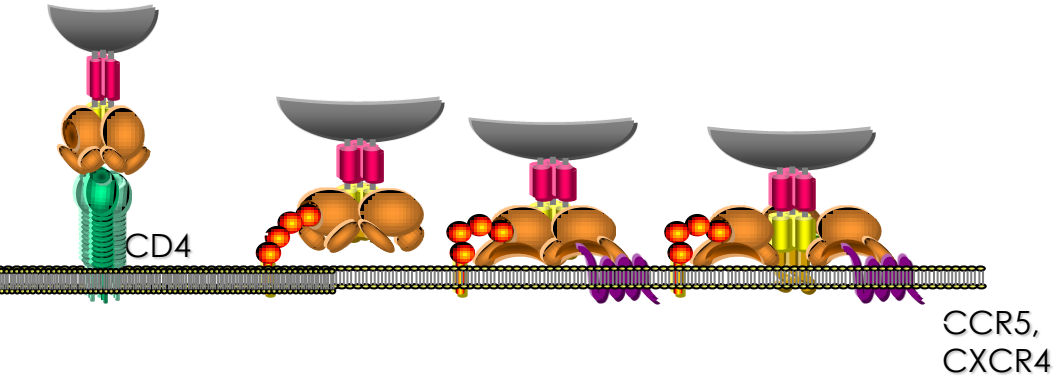


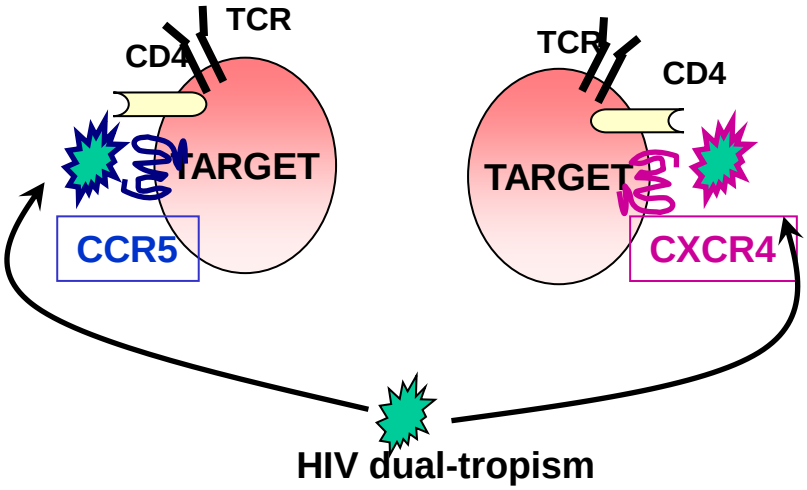




A Haase, NatRev Immunol 2010

Receptors for HIV : a 10 years long quest





CD4

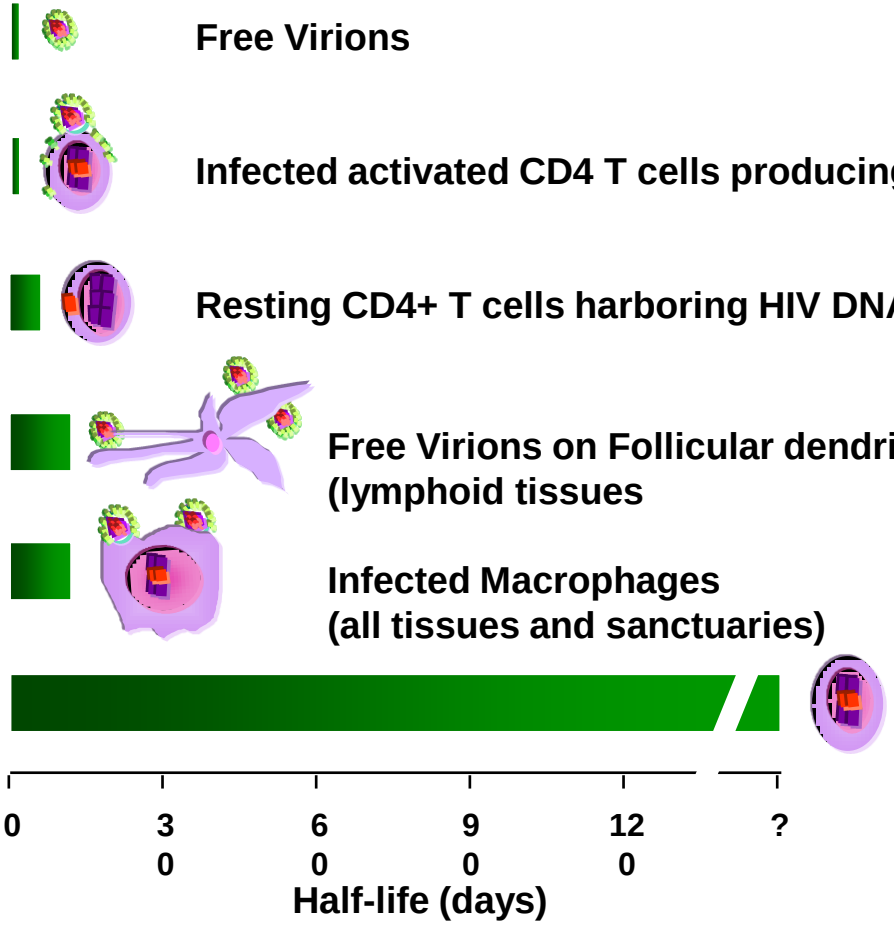
Klatzmann D, Barre-Sinoussi F, Nugeyre MT,et al..
Science. 1984
Dalgleish AG, Beverley PC, Clapham PR, et al... Nature. 1984

Co-Receptors

Cocchi F, DeVico AL, Garzino-Demo A, Arya SK, Gallo RC, Lusso P.
Science. 1995
Oberlin E, Amara A, Bachelerie F, Bessia C, Virelizier JL et al
Nature. 1996

Target cells for HIV

Various CD4+ target cells

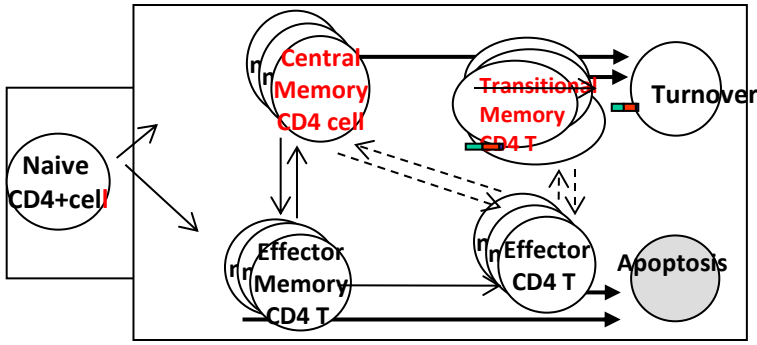


From Siciliano, AIDS 1999, 13 Suppl A : S49-58

Heterogeneous CD4 T cells

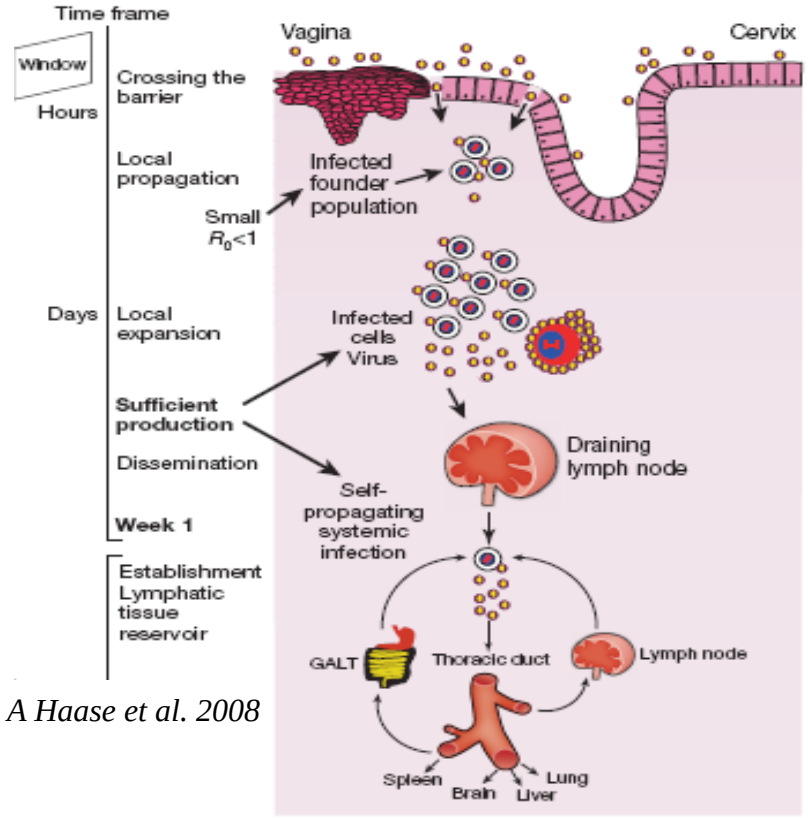
with a wide range of

Half-lives and reproductive capacities

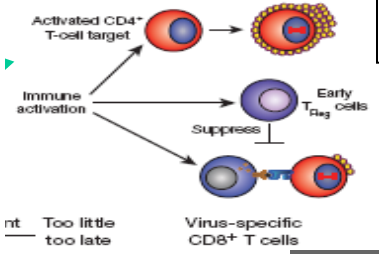


TN Years | TCM TTM Months | TEM Weeks | Effectors Days

Very early kinetics of Constitution of durable HIV Reservoirs



A Haase et al. 2008



Immune Responses to HIV:

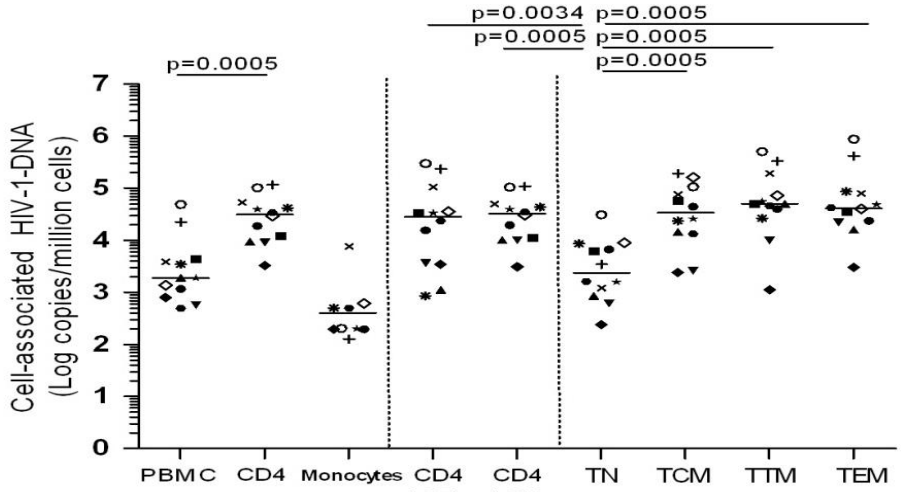
- Too little, too late

Huge level of infection in short-and long-lived CD4+ cells

The Optiprim Study: at Fiebig III (D30) post-infection

Bacchus&Cheret et al Plos One 2013

Early Establishment of the HIV Reservoirs in CD4 cells



HIV depends upon immune activation to replicate

HIV was discovered and replicates in lymphoïd tissues

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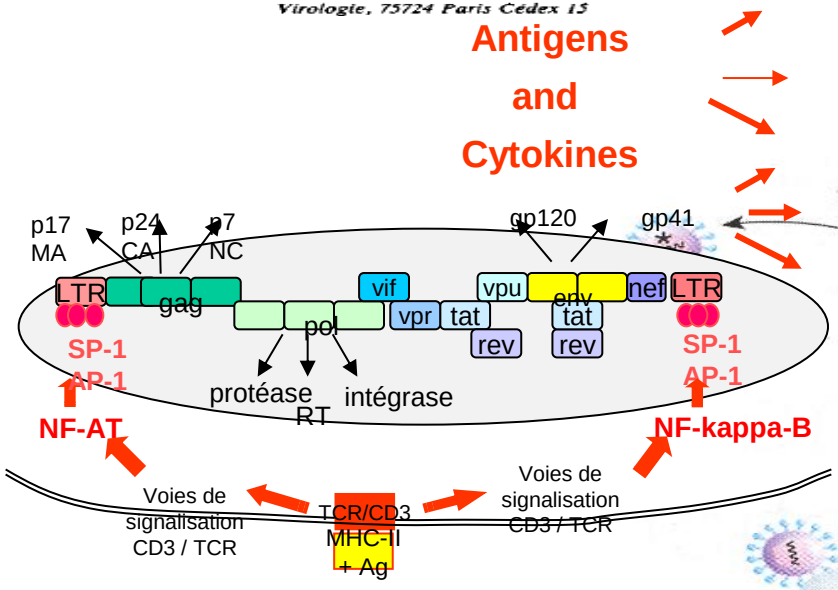
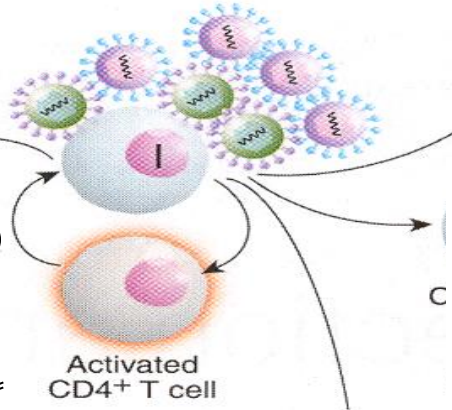
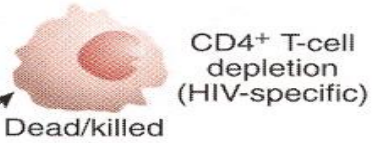
Virologie, 75724 Paris Cédex 15

ussi et al.

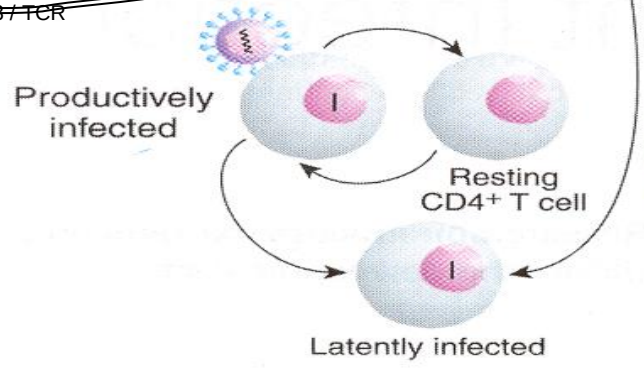
because HIV requires immune activation to replicate in activated CD4 T cells

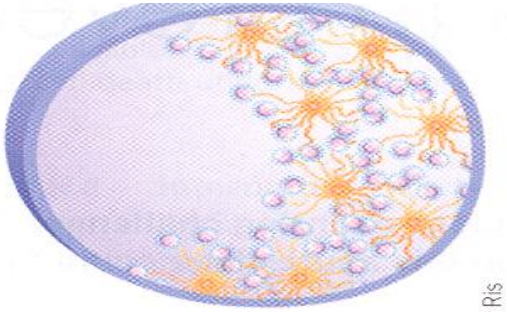






=> HIV replicates In lymphoïd tissues where Activation takes place

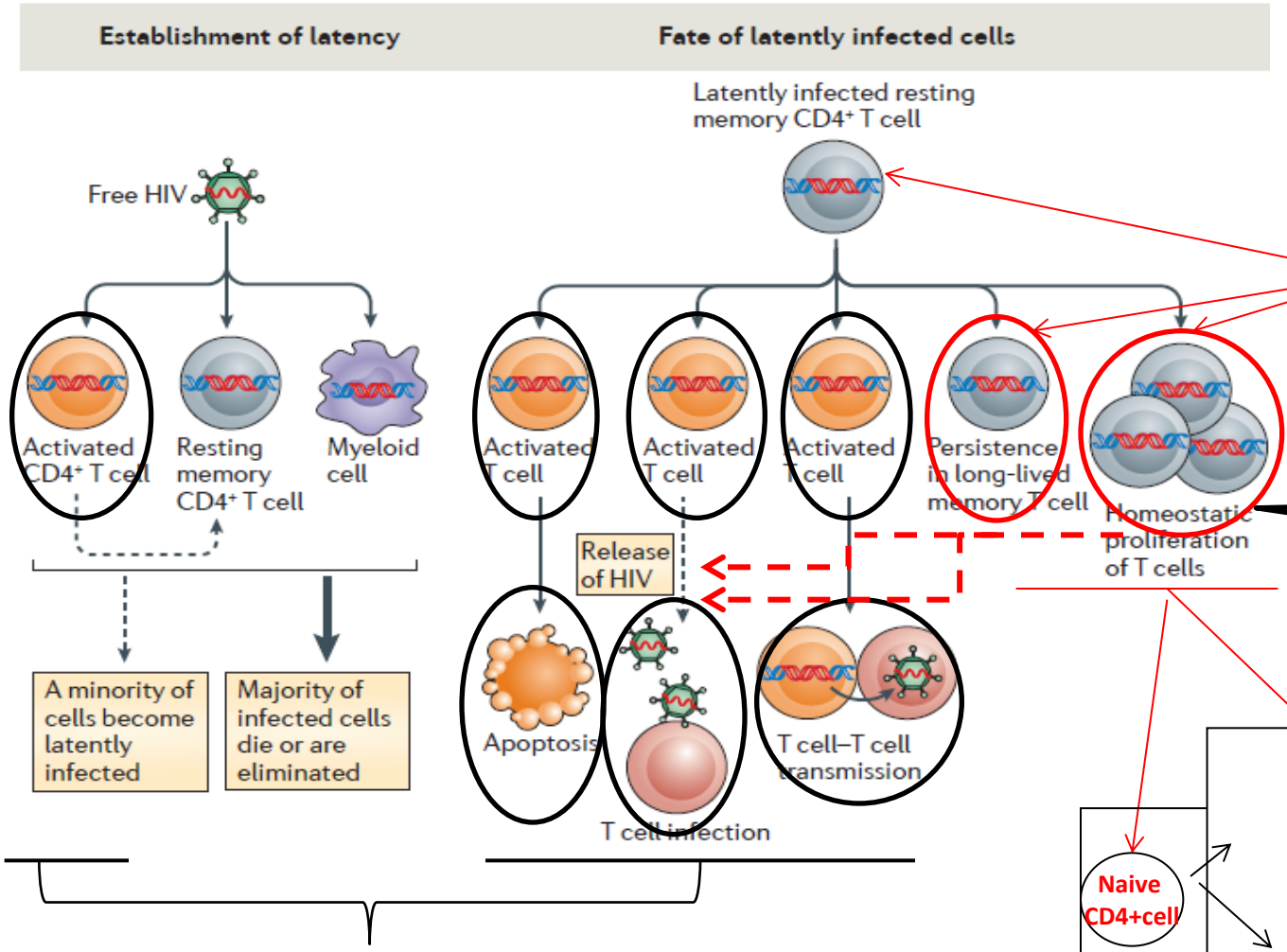




BAutran/14

Towards an HIV cure:
a global scientific strategy
The International AIDS Society Scientific Working Group on HIV Cure
NATURE REVIEWS | IMMUNOLOGY VOLUME 12 | AUGUST 2012 | 607

HIV reservoirs among highly heterogeneous CD4+ cells

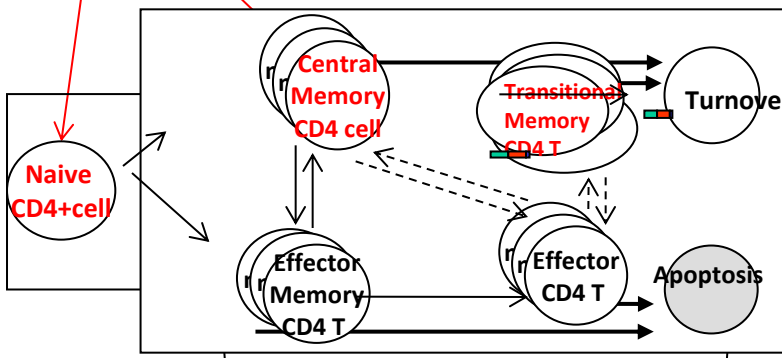


Immune activation:

The Sleeping Beauty

&

The Trojan Horse

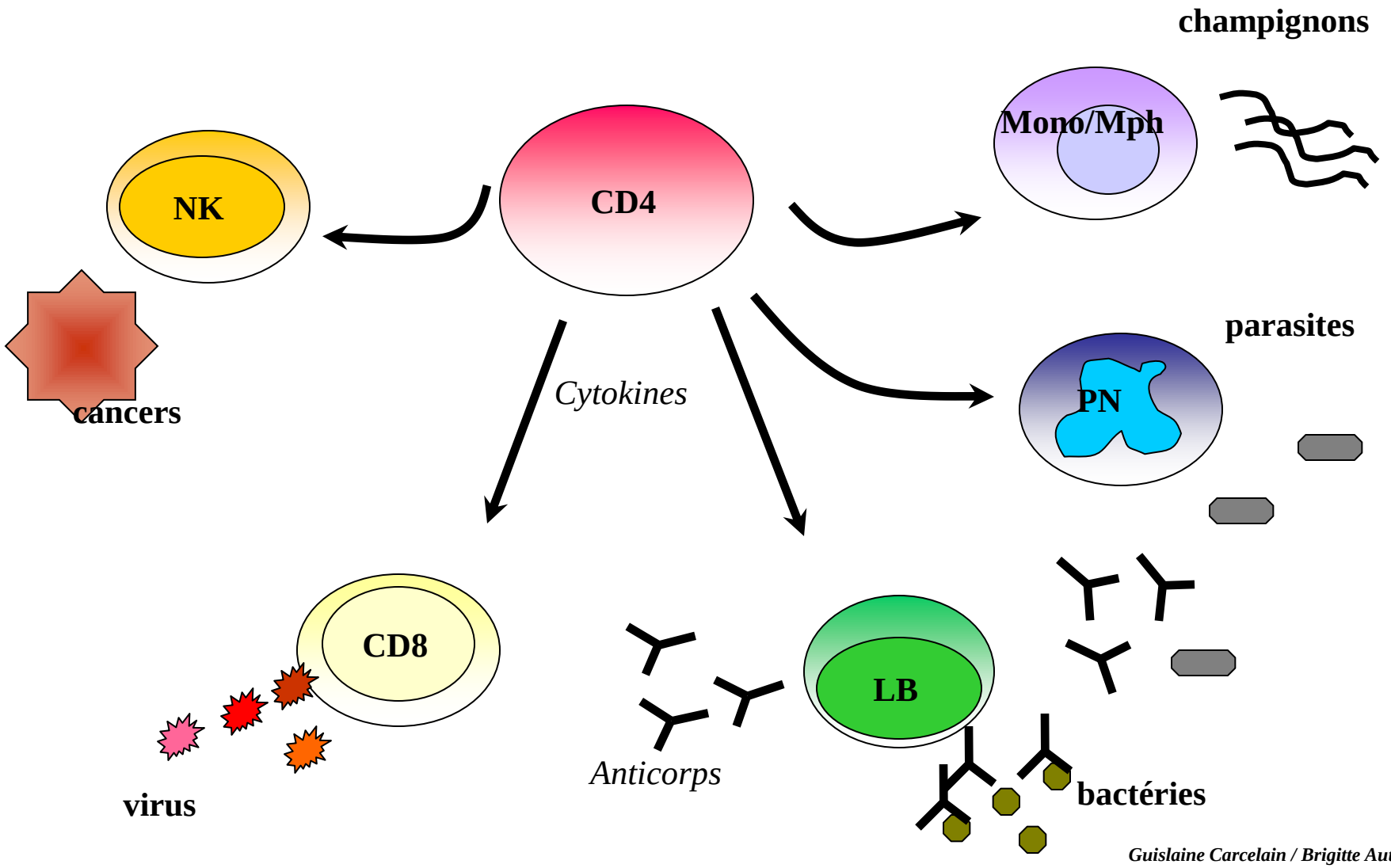


Targeted by ARV

anti-HIV CTLs

Abs

Le lymphocyte CD4 : chef d'orchestre de la réponse immunitaire



Guislaine Carcelain / Brigitte Autran

Mechanisms of the CD4 LYMPHOPENIA

Mean losses = 50 CD4/mm3/j ➔ 10^9 /j
1/2 life infected CD4 cells = 1,2 j *(Perelson et al. 96)*

1- Destruction of CD4+ cells:

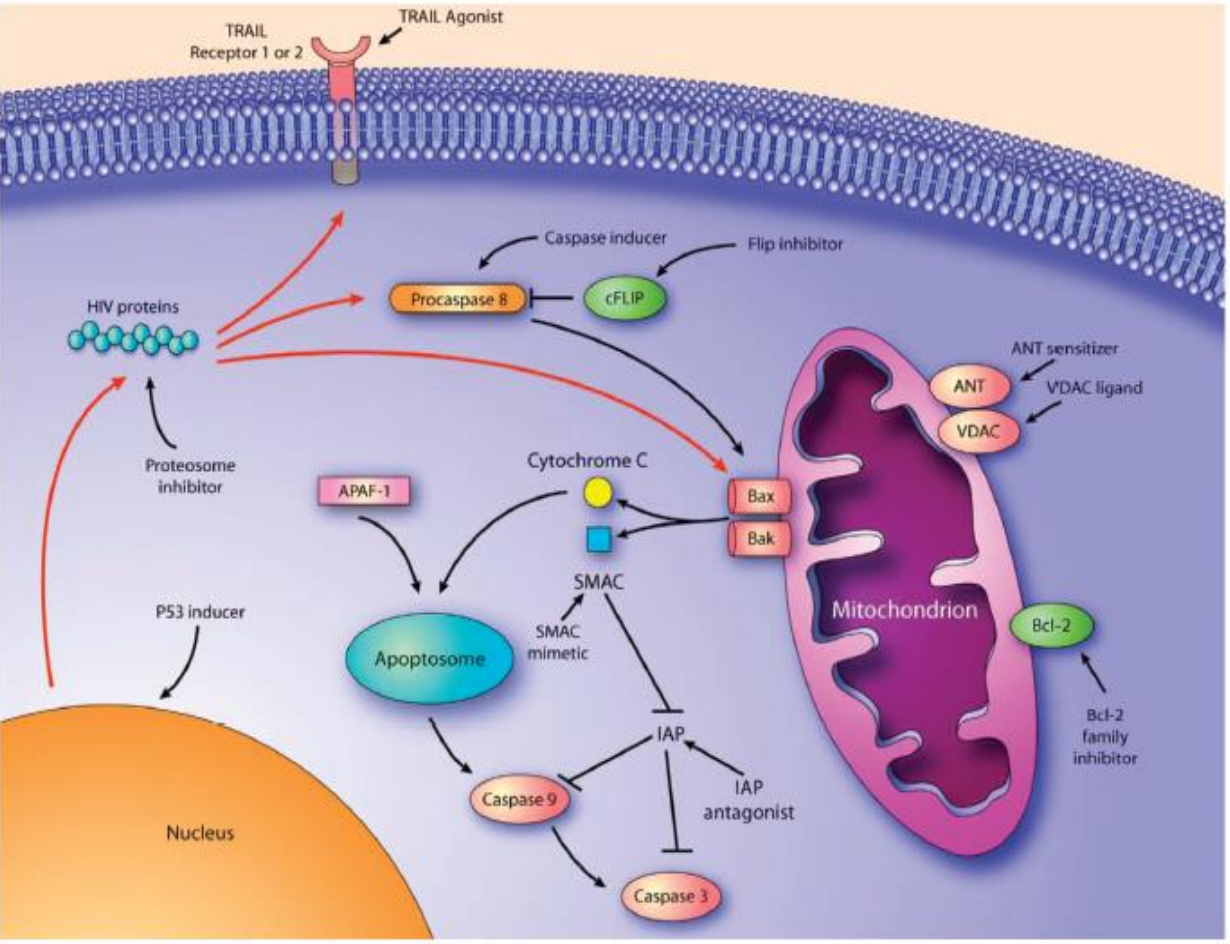
- **HIV-infected:**
  - Infection + replication HIV = **cytopathogenicity** (syncitia : X4)
  - Destruction by anti-HIV immune responses
- **Non-infected:**
  - Apoptosis as a consequence of **Chronic activation and AICD** :

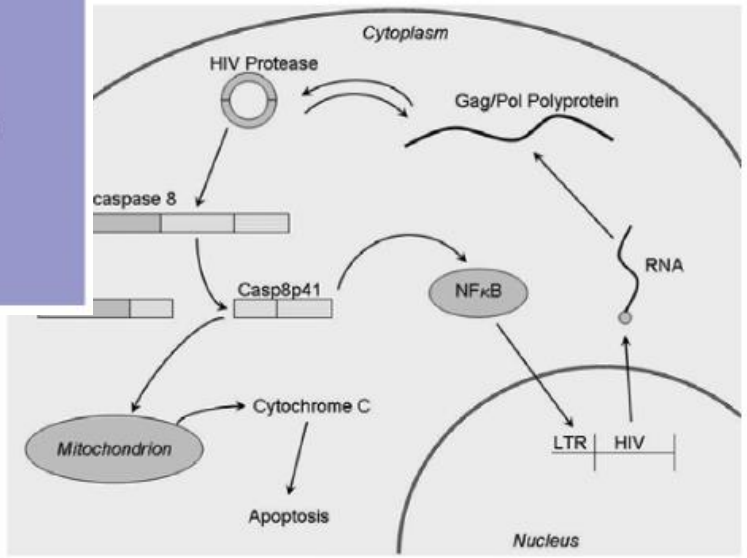
2- Defaults of cell regeneration :

- **Central**: Thymus : limiting production of **naive** CD4+ T cells
- **Peripheral** : Anergy (loss of IL-2 production and proliferative capacity):

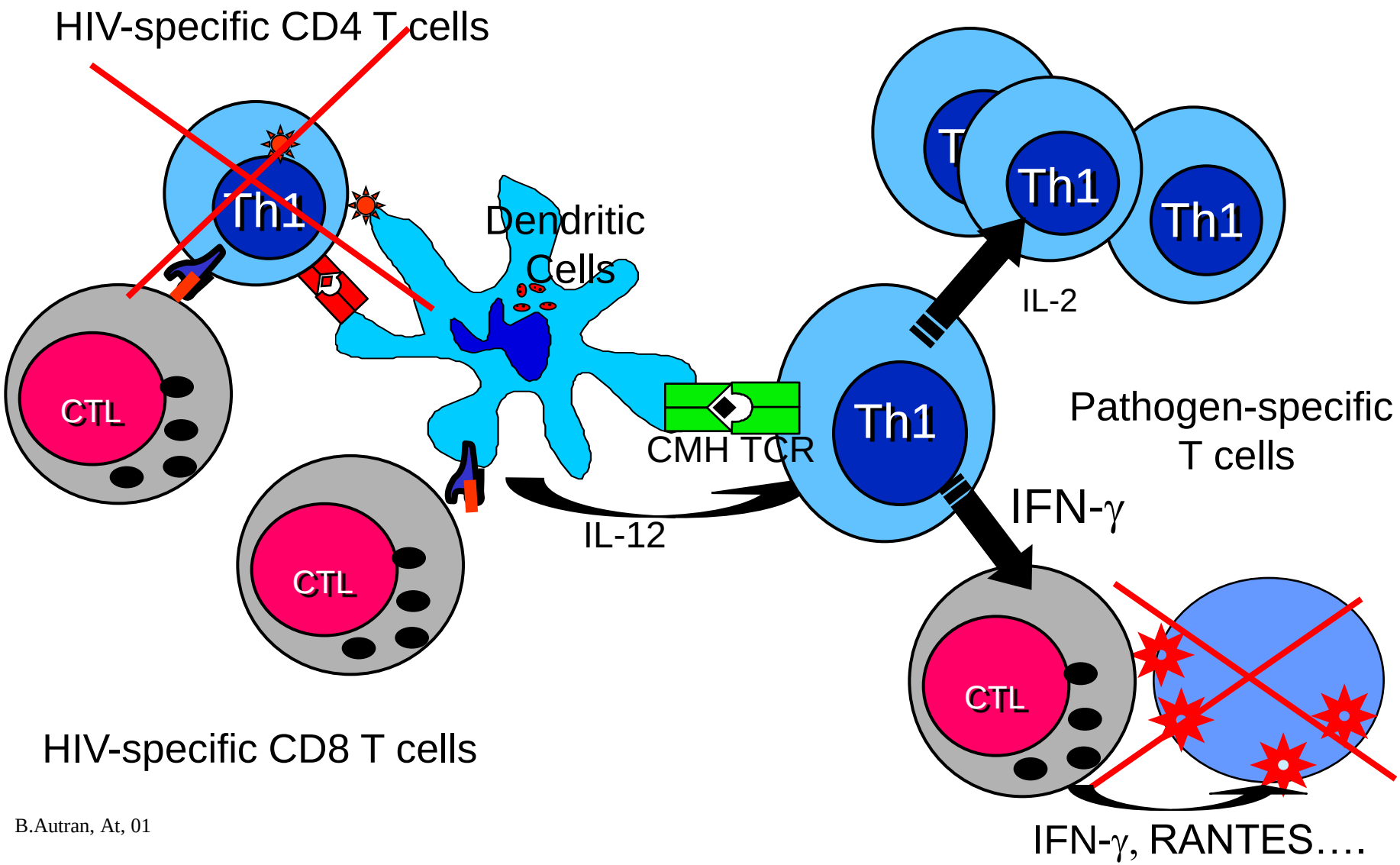
  limiting **central-memory** T cells

HIV Cytopathogenicity: Interactions between HIV proteins and the intra-cellular Apoptosis regulatory network





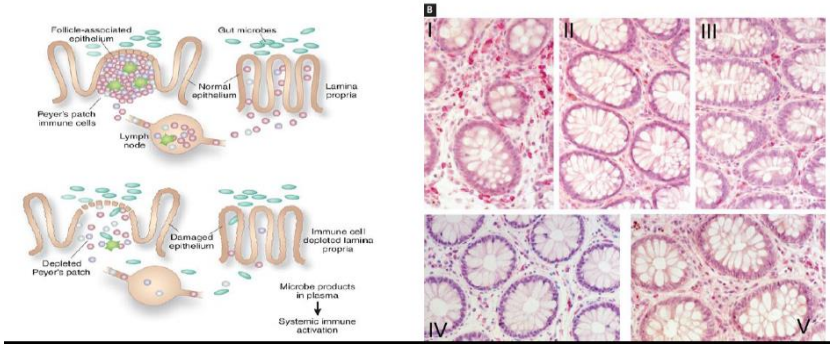
Preferential infection and destruction of HIV-specific CD4 Th cells *(Douek, Nature, 2001)*



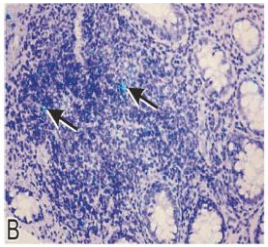
HIV-related death in gut mucosal epithelia and systemic immune activation

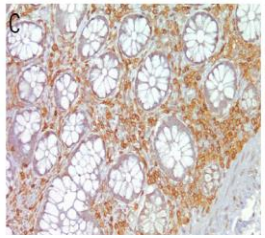
HIV replication and CD4 cell death in lymphoid tissues

Sites of replication : gut

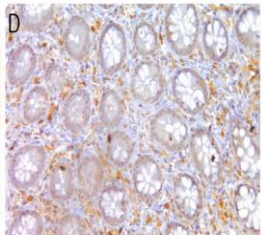


JM. Brenchley, ….AT. Haase,and DC. Douek Nat Med 2006





Subject	HIV status	Infection duration	CD4	VL	Collagen deposition
1421	HIV⁻	NA	1,497	0	2.6

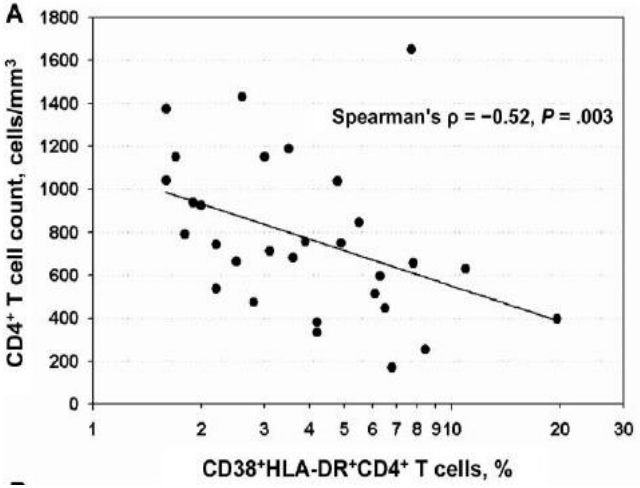


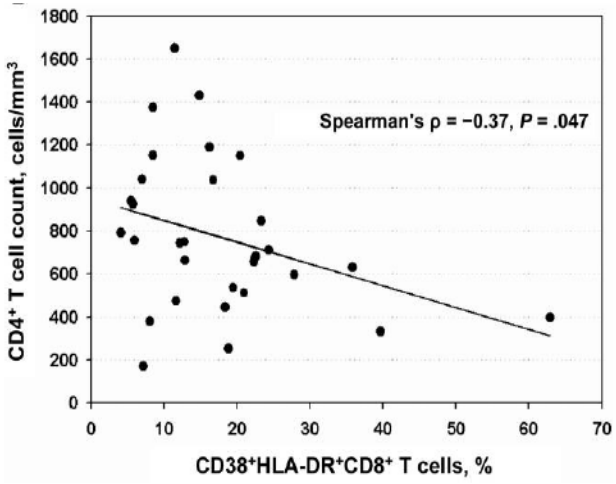
Subject	HIV status	Infection duration	CD4	VL	Collagen deposition
1329	Acute	<1 mo	370	484,694	5.4

HIV-related systemic T cell immune activation

Giorgi et al. 1994

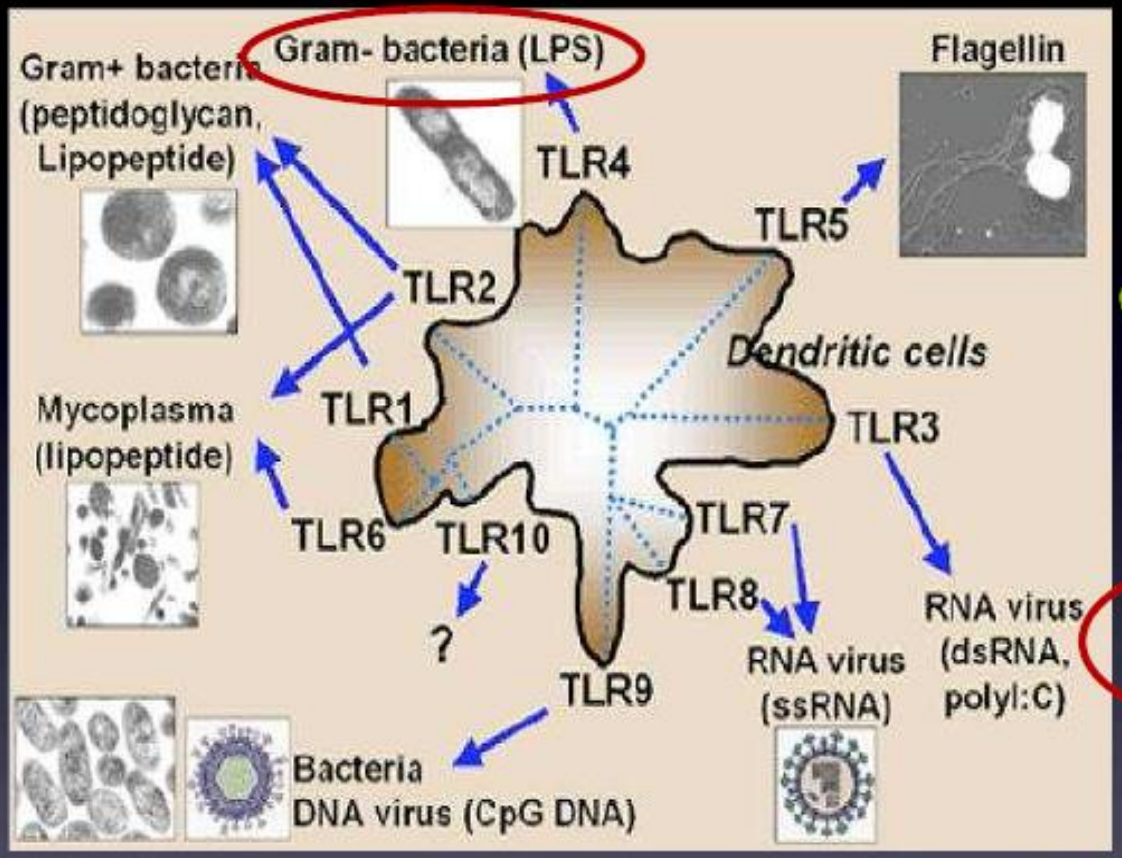
²Hunt, JID 2008





Inflammation and HIV

antigène
signal danger



CMV (TLR9)
VIH (TLR3/7)
➔ IFN α

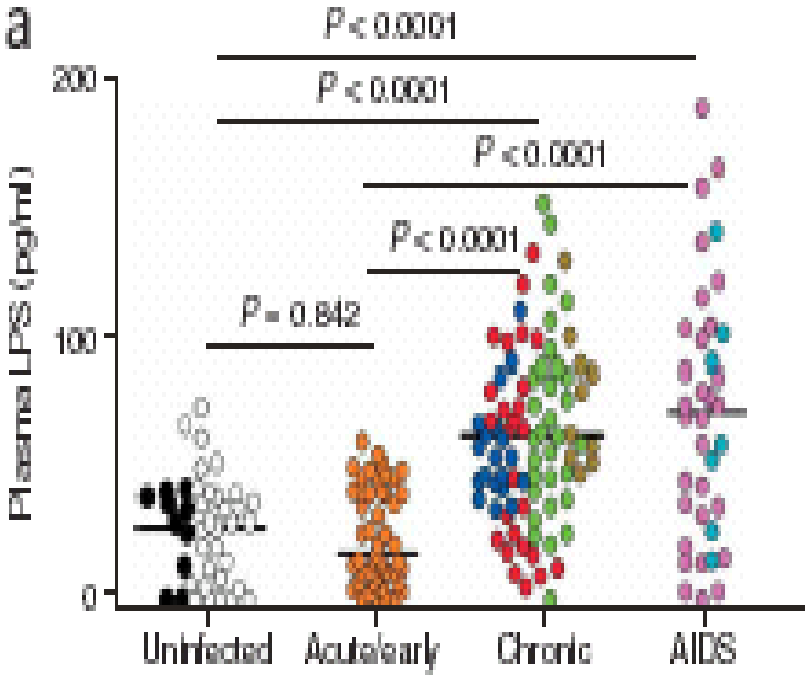
PAMP ← PRR (TLR, …)

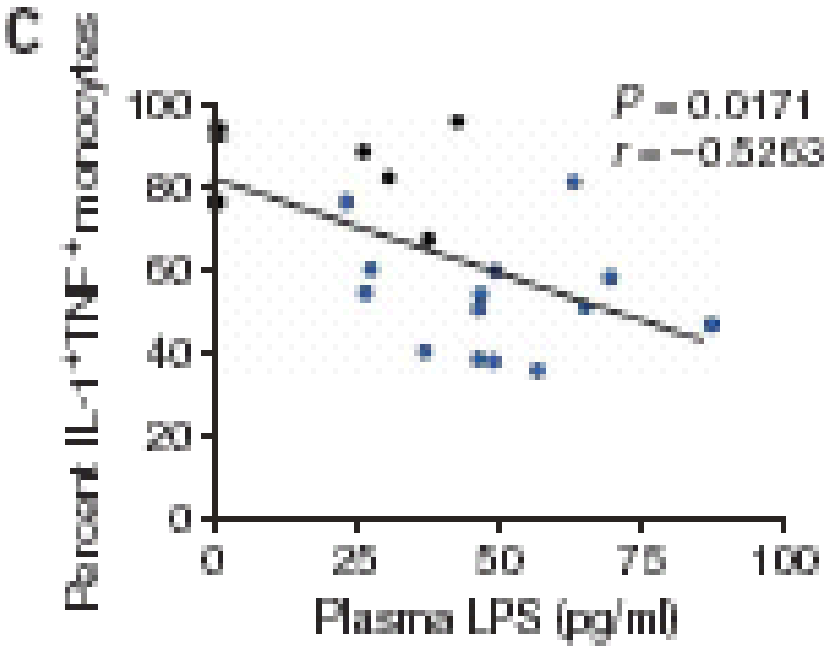
CK PRO-INFL
IL-1
IL-6
TNFα
IL8
IL-12

HIV-related apoptosis of the gut mucosal epithelia induces microbial translocation eliciting systemic immune activation

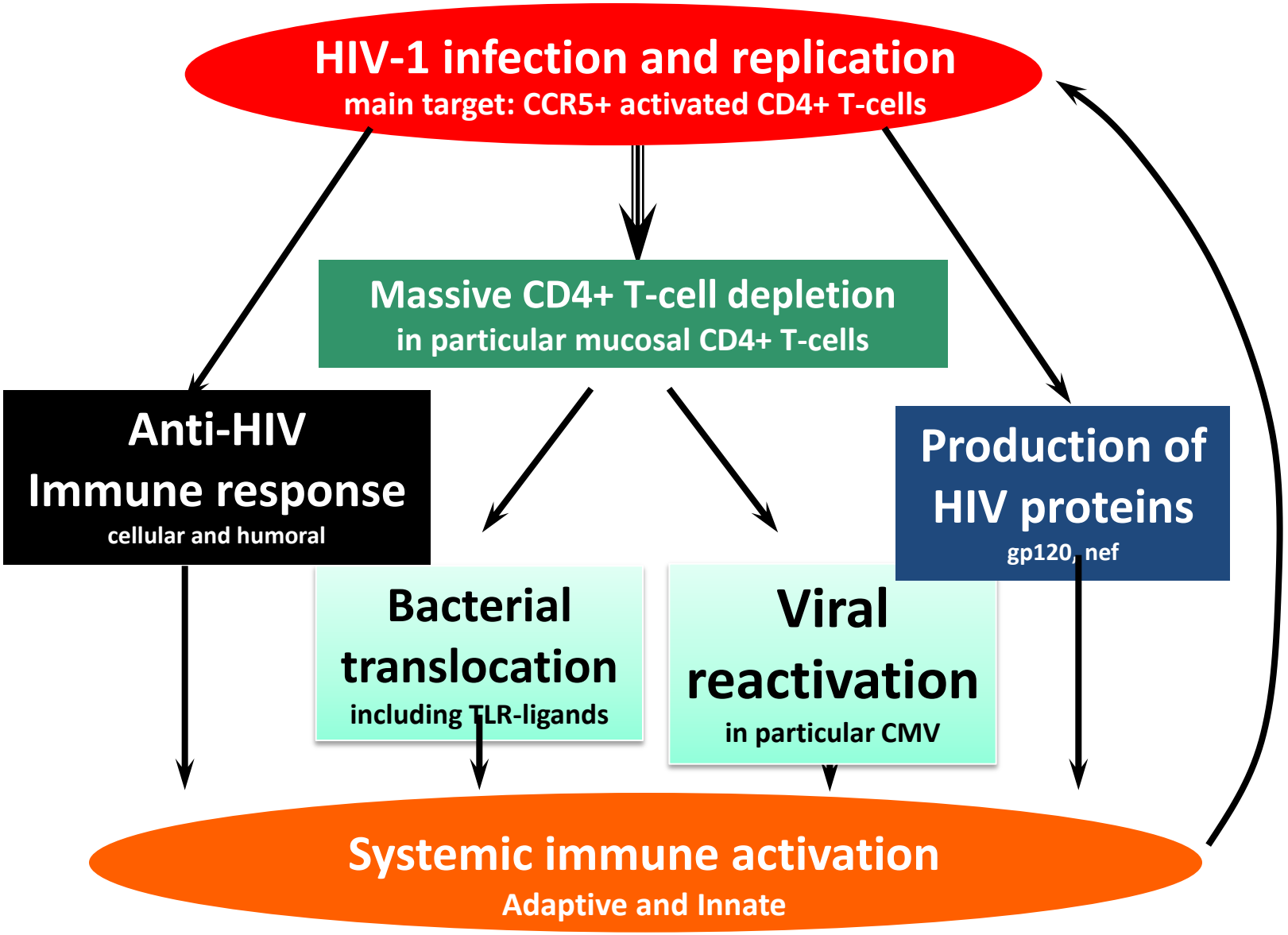
Systemic LPS from translocated bacteria correlates with disease progression

Systemic LPS binds Monocytic receptors (CD14) and elicits release of pro-inflammatory cytokines





Immune activation and HIV replication



Appay et al, J Pathol 08

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Mean losses = 50 CD4/mm3/j ➔ 10^9 /j
1/2 life infected CD4 cells = 1,2 j *(Perelson et al. 96)*

1- Destruction of HIV-infected CD4 :

- Infection + replication HIV
  = cytopathogenicity (syncitia : X4)
- Destruction by CD8 Ly mediated immune response)
- Apoptosis of non infected CD4 cells: Chronic activation and AICD

•**Defaults of cell regeneration :**

- Central: (thymus)
- Peripheral : Anergy (loss of IL-2 production)

MECHANISMS of CD4 LYMPHOPENIA
Progressive loss of Immune ressources and memory to pathogens

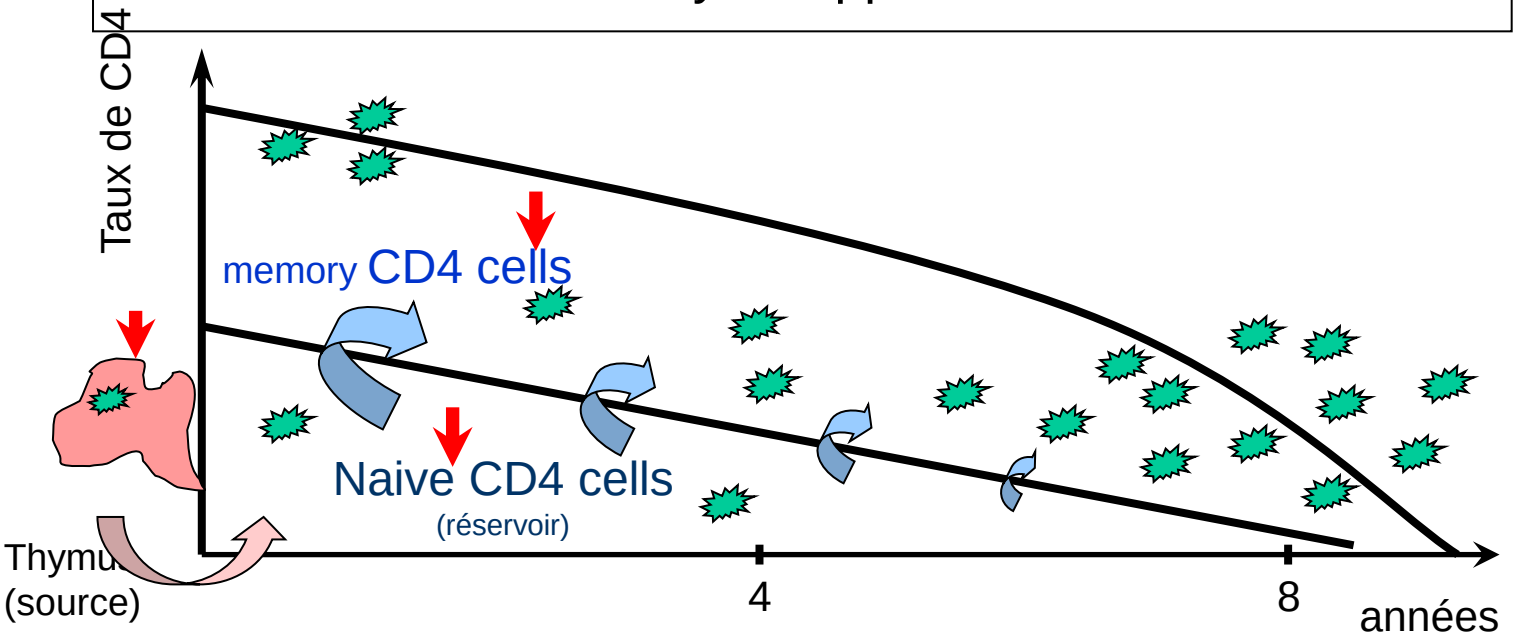
- Rapid loss in naive CD4 cells

  => accelerated conversion towards memory cells

- Infection/Anergy of Memory CD4 T cells

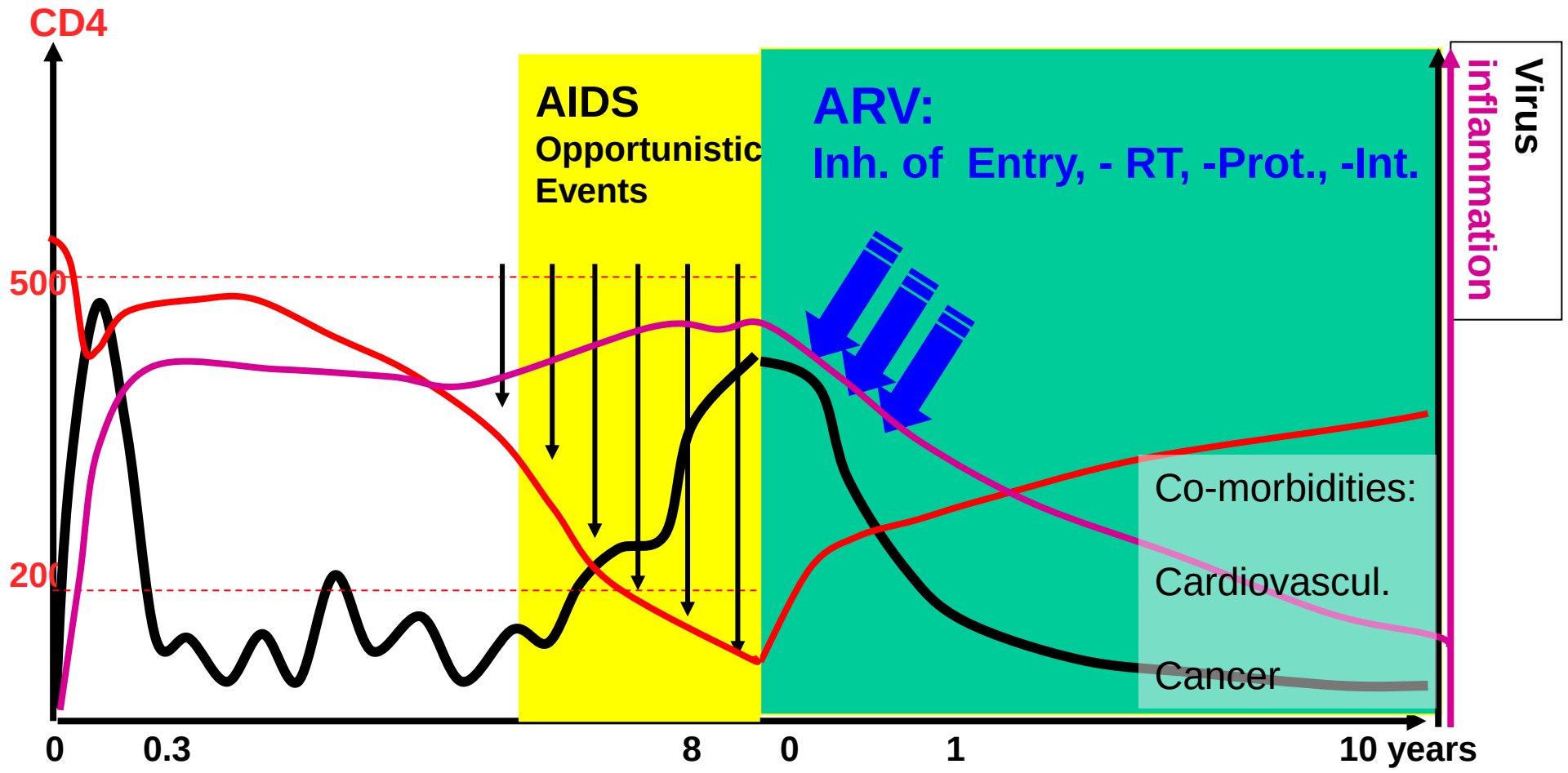
  ⇒ cell destruction

  ⇒ Loss of Memory to Opportunistic infections



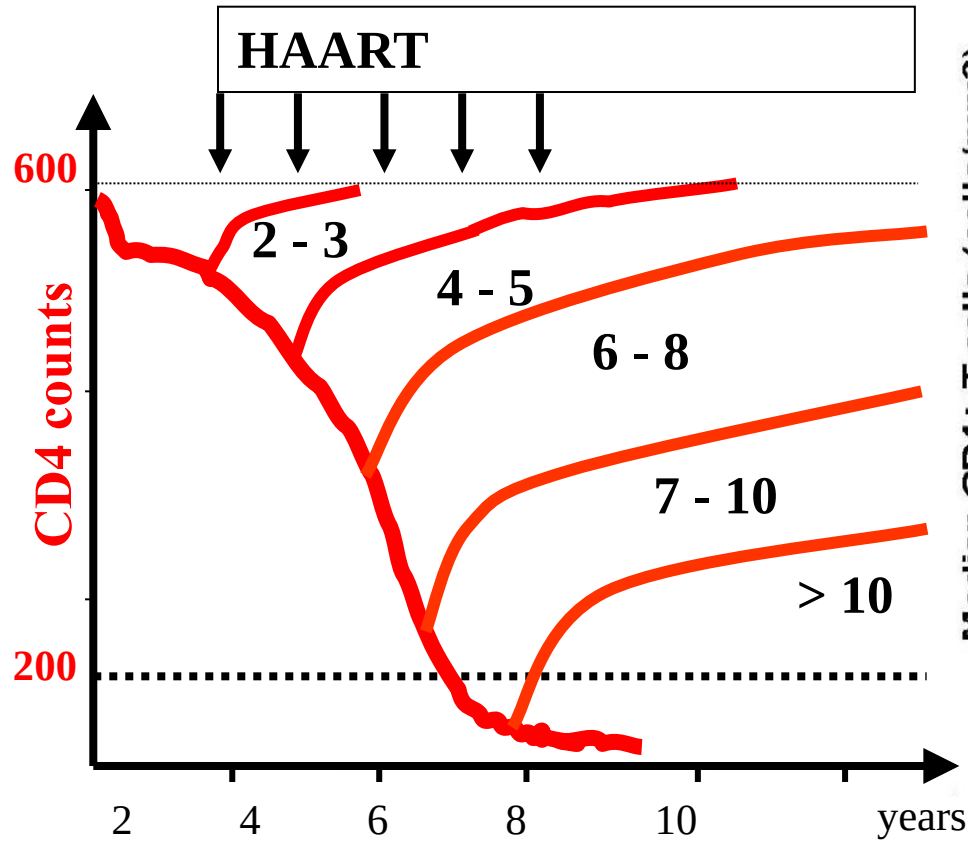
BAutran

HIV infection: a slow but lethal systemic immune disease: from immune deficiency and AIDS to inflammation and co-morbidities



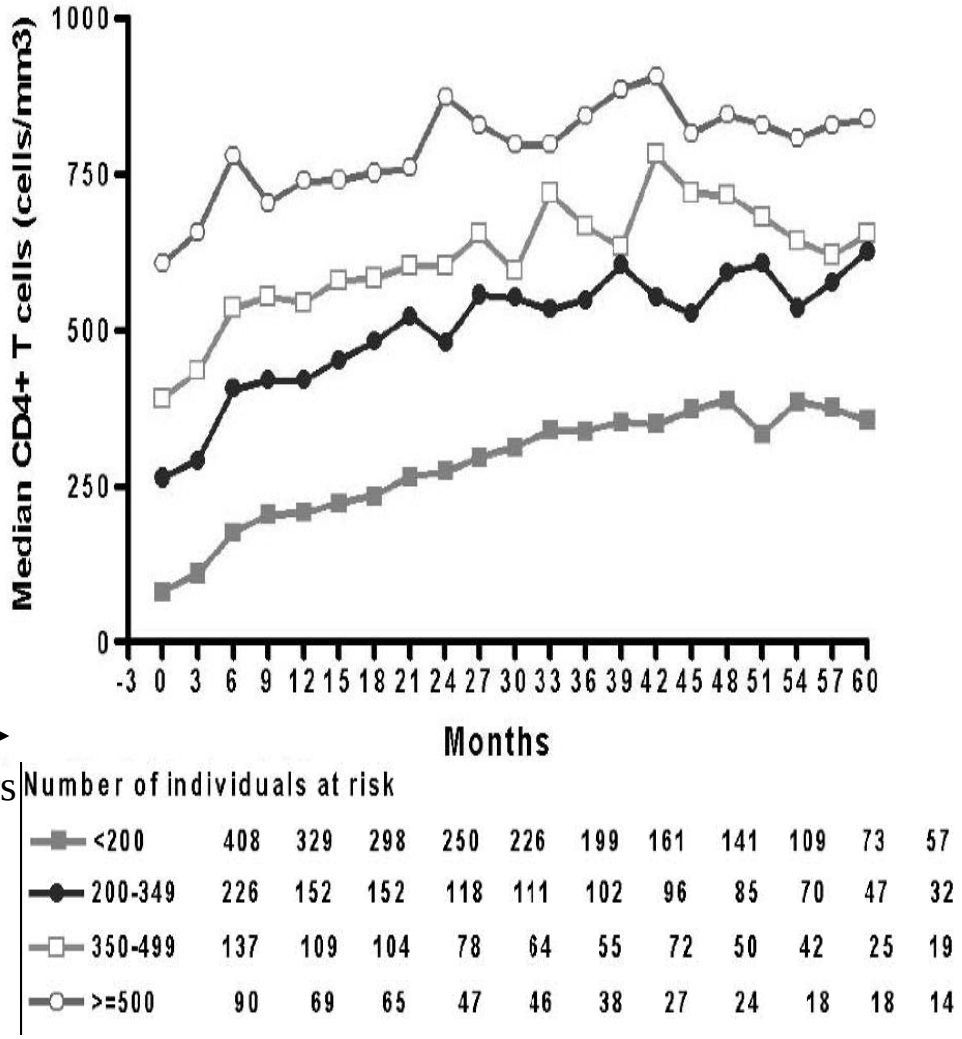
Long term CD4 cell reconstitution with ART

As Predicted



B Autran et al. 1998

As Observed



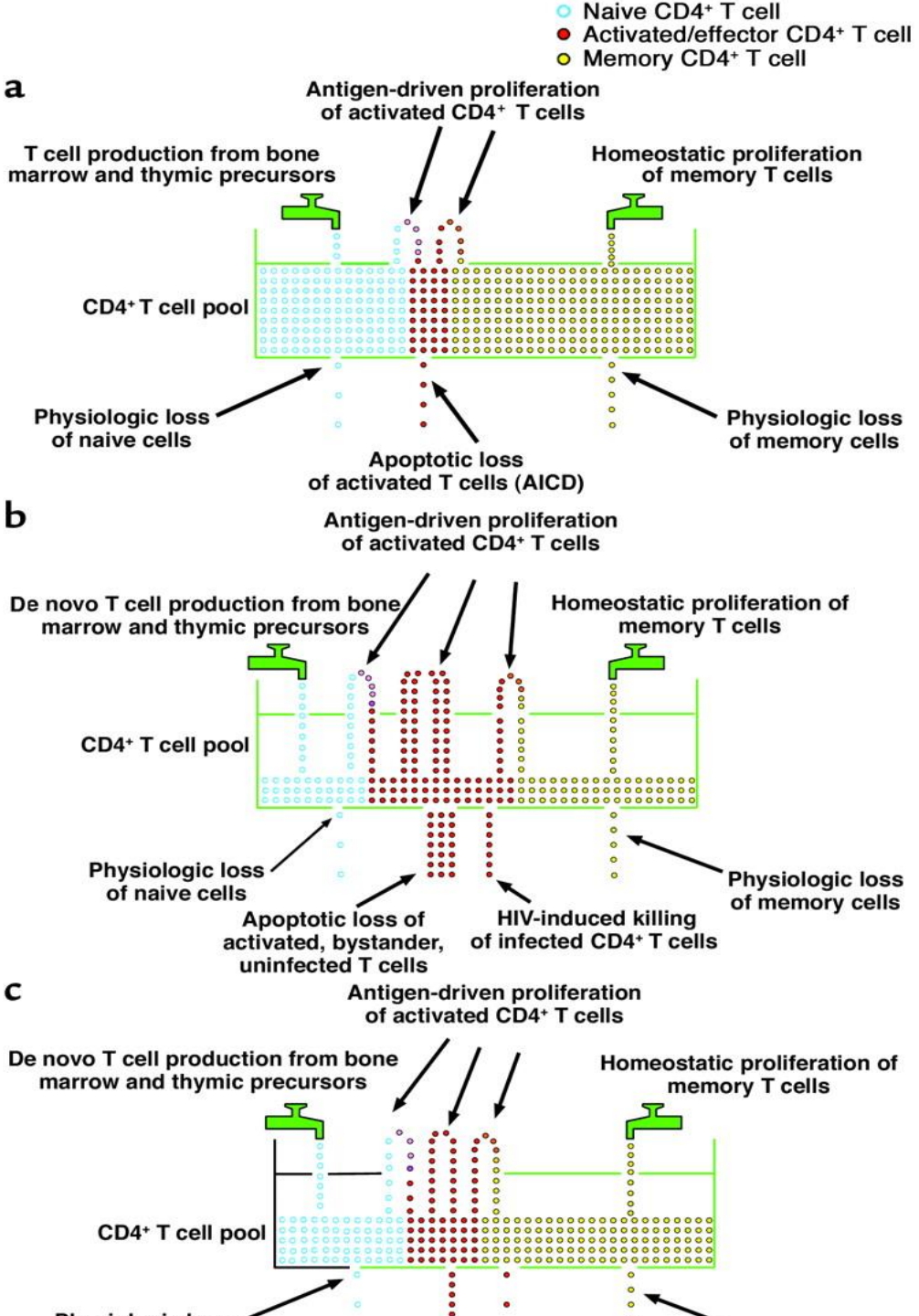
Garcia, J AIDS 2004

The Tap and Drain phenomenon

reflecting the turnover of CD4+ T cell subsets

(naive versus central memory versus effector memory)

Silvestri, G. et al. J. Clin. Invest. 2003;112:821-824



Immune restoration with antiretroviral therapy (HAART): Quantitative, qualitative and functional

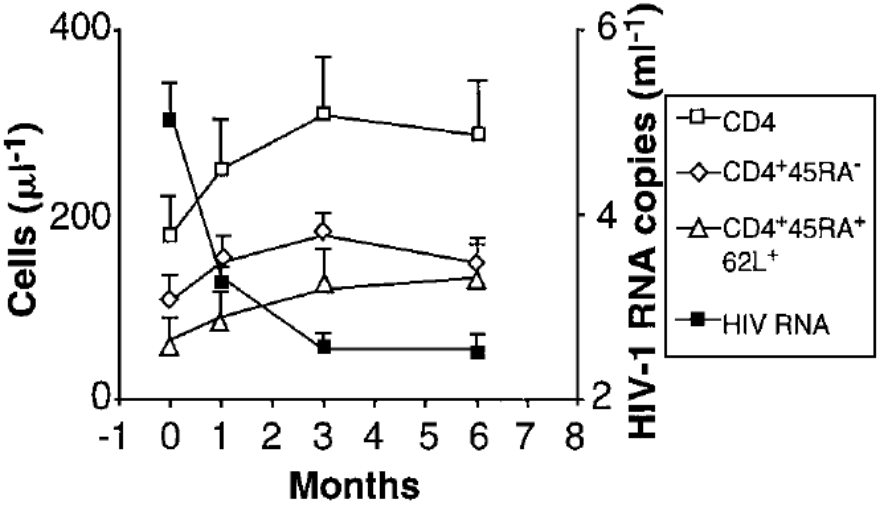
Positive Effects of Combined Antiretroviral Therapy on CD4⁺ T Cell Homeostasis and Function in Advanced HIV Disease

B. Autran,* G. Carcelain, T. S. Li,† C. Blanc,† D. Mathez, R. Tubiana, C. Katlama, P. Debré, J. Leibowitch

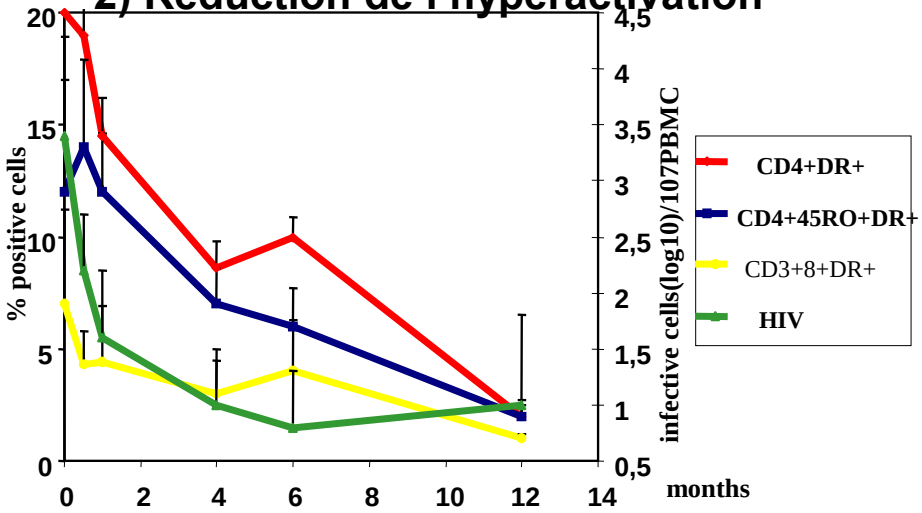
Science 4 July 1997,

…. Li TS et al. Lancet, 1998; AIDS Res. Retrov. 1999, .

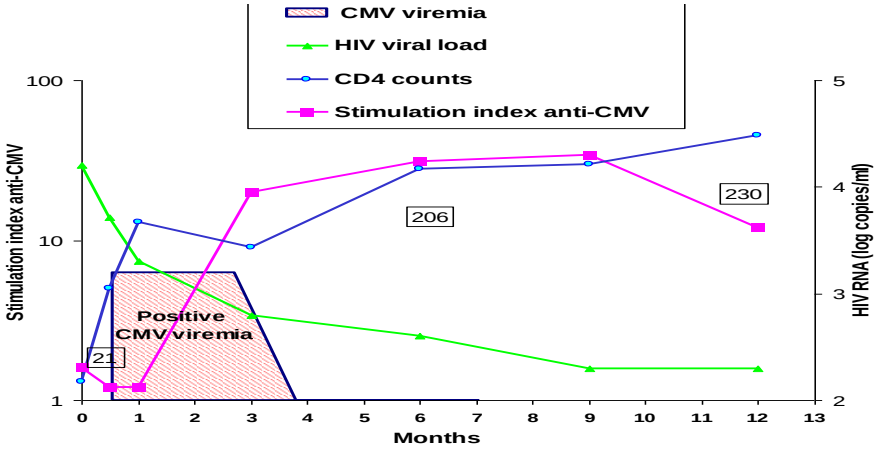
1) Restoration of CD4 counts, Naive & Memory



2) Réduction de l'hyperactivation



3) Restauration fonctionnelle des Ly CD4



Cancers classants SIDA

		Kaposi RR (95%CI)	LNH RR (95%CI)
Dernier CD4 (>500, ref)	350-500	1.9 (1.3-2.7)	1.3 (0.9-2.0)
	200-350	3.3 (2.3-4.6)	3.3 (2.3-4.6)
	100-200	6.2 (4.2-9.0)	4.9 (3.3-7.2)
	50-100	14.1 (9.4-21.3)	11.6 (7.7-17.6)
	<50	25.2 (17.1-37.0)	14.8 (9.7-22.6)
Dernière CV (<500, ref)	500-4 log	1.0 (0.7-1.4)	1.6 (1.2-2.2)
	4-5 log	1.4 (1.1-1.9)	1.5 (1.1-2.0)
	>5log	3.1 (2.3-4.2)	2.9 (2.1-3.9)
cART	Oui (>6 mois)	0.3 (0.2-0.4)	0.8 (0.6-1.0)

HIV
A disease of immune activation and inflammation

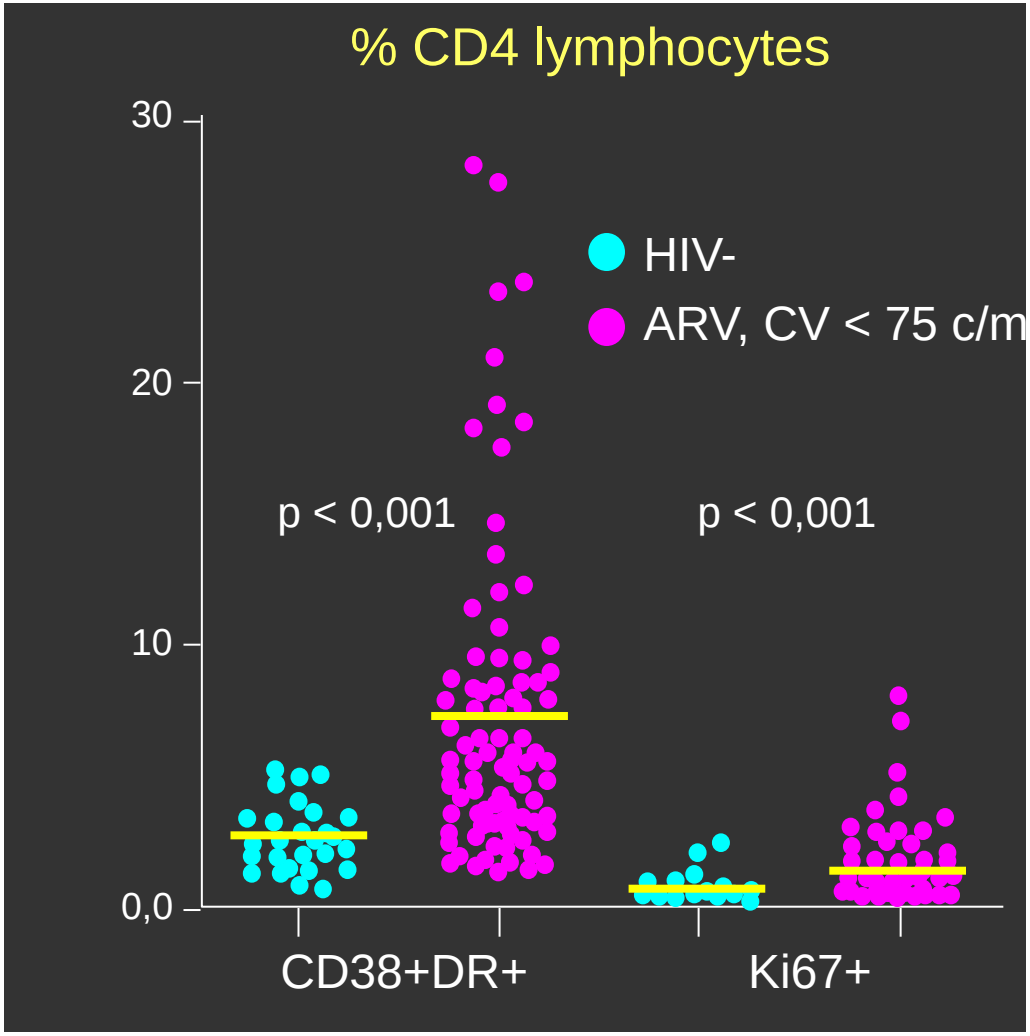
Immune activation

1. persists desite antiretroviral therapy
2. is associated to residual viremia
3. is associated to comorbidities

Persistence of immune activation despite suppressed viremia
associated with lack of immune restoration

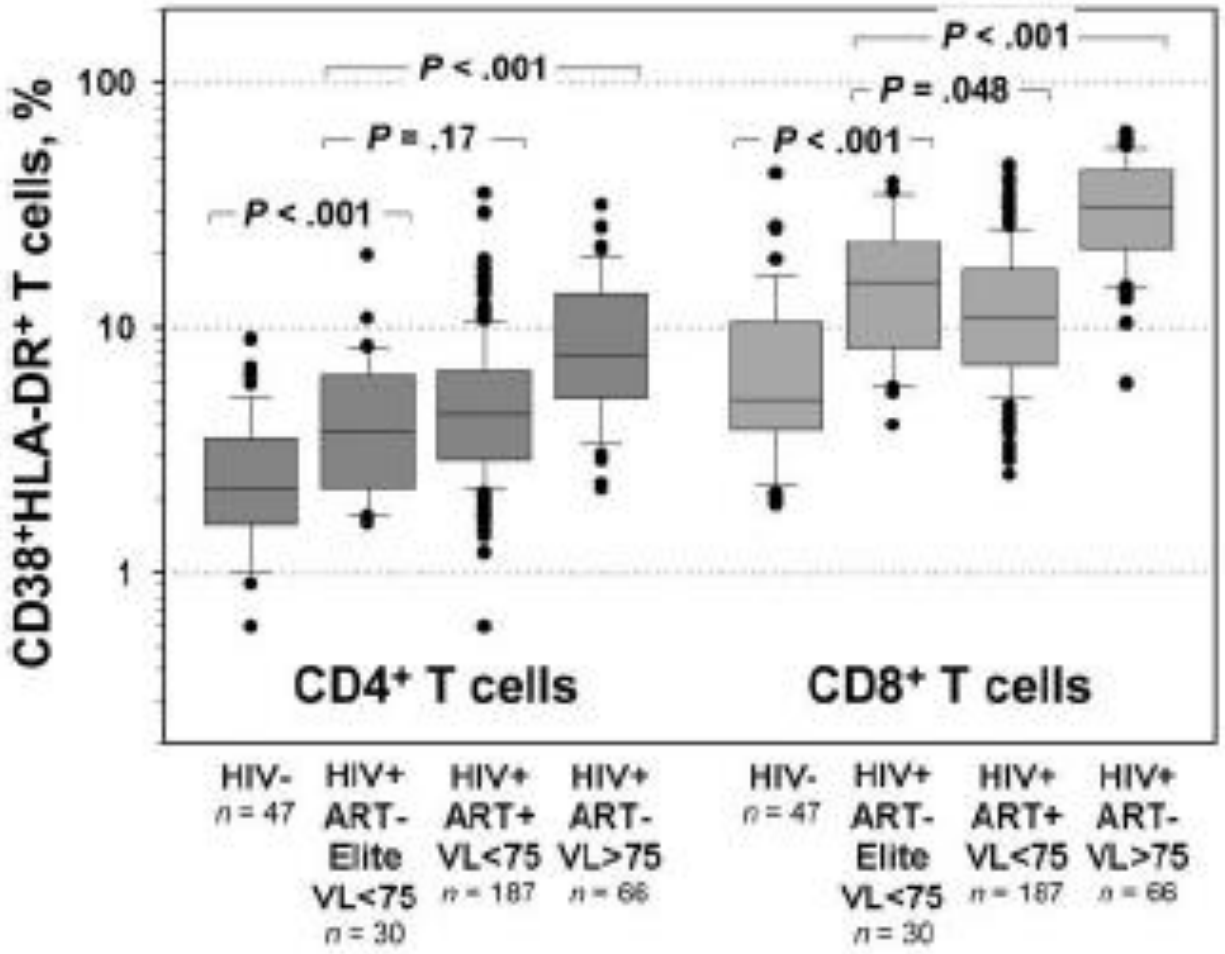
- 87 HIV+patients on ART , with VL < 50 c/ml since median 22 months
- 30 HIV- controls
- Determination of activation of CD4 et CD8 T cells

  (CD38, HLA DR and Ki67)



Hunt P, 2010,

T-cell activation persists under ART despite apparently optimal viral suppression



Hunt, JID 2008

Inflammation caused by HIV

the STACCATO Study Group

HIV increases markers of cardiovascular risk: results from a randomized, treatment interruption trial

Alexandra Calmy[a], Angèle Gayet-Ageron[a], Fabrizio Montecucco[b], et al. *AIDS* 2009, **23**:000–000

Uni- and multi-variate analysis of soluble markers of inflammation:

under ARV (CT)and during thérapeutic Interruption (STI)

Inflammation markers	STI (off cART) ($n=97$)	CT (on cART) ($n=48$)	r^b (P)	Adjusted r (P)
s-VCAM-1 (ng/ml)	2322.1	2054.9*	0.270 (0.001)	0.271 (0.001)
Adiponectin (mg/ml)	3.7	4.7*	−0.199 (0.02)	−0.248 (0.002)
CCL2 (pg/ml)	15.6	15.6*	0.239 (0.005)	0.238 (0.005)
CCL3 (pg/ml)	8.0	14.7	−0.144 (0.08)	−0.153 (0.07)
P-selectin (ng/ml)	87.1	65.1*	0.065 (0.44)	0.080 (0.36)
Leptin (ng/ml)	7.2	7.6	−0.007 (0.93)	−0.008 (0.90)
CRP (mg/l)	0.6	0.8	−0.128 (0.13)	−0.126 (0.14)
D-dimer (ng/ml)	270.9	247.9	−0.016 (0.87)	0.018 (0.85)
	Below the limit of detection (%)		Unadjusted OR (95% CI)	Adjusted OR (95% CI, P)
GM-CSF (≤31.25 pg/ml)	99.0	95.7	0.79 (0.29–2.16)	0.97 (0.34–2.81, 0.96)
IL-6 (≤0.156 pg/ml)	92.7	100	1.08 (0.60–1.93)	1.27 (0.65–2.47, 0.49)
IL-10 (≤0.78 pg/ml)	89.4	63.0	0.67 (0.46–0.99)	0.64 (0.43–0.96, 0.03)

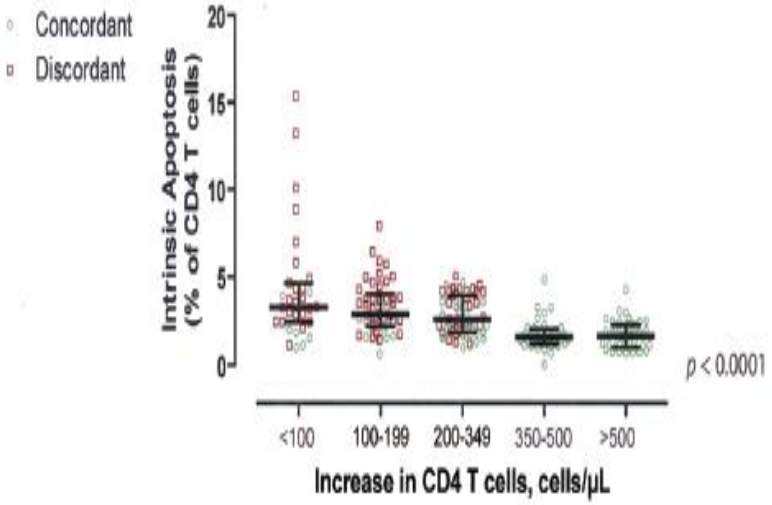
cART, combination antiretroviral therapy; CCL, chemokine ligand; CI, confidence interval; CRP, C-reactive protein; CT, continued cART; GM-CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; OR, odds ratio; STI, ; s-VCAM, soluble vascular cell adhesion molecule.
[a]All results are presented in median.

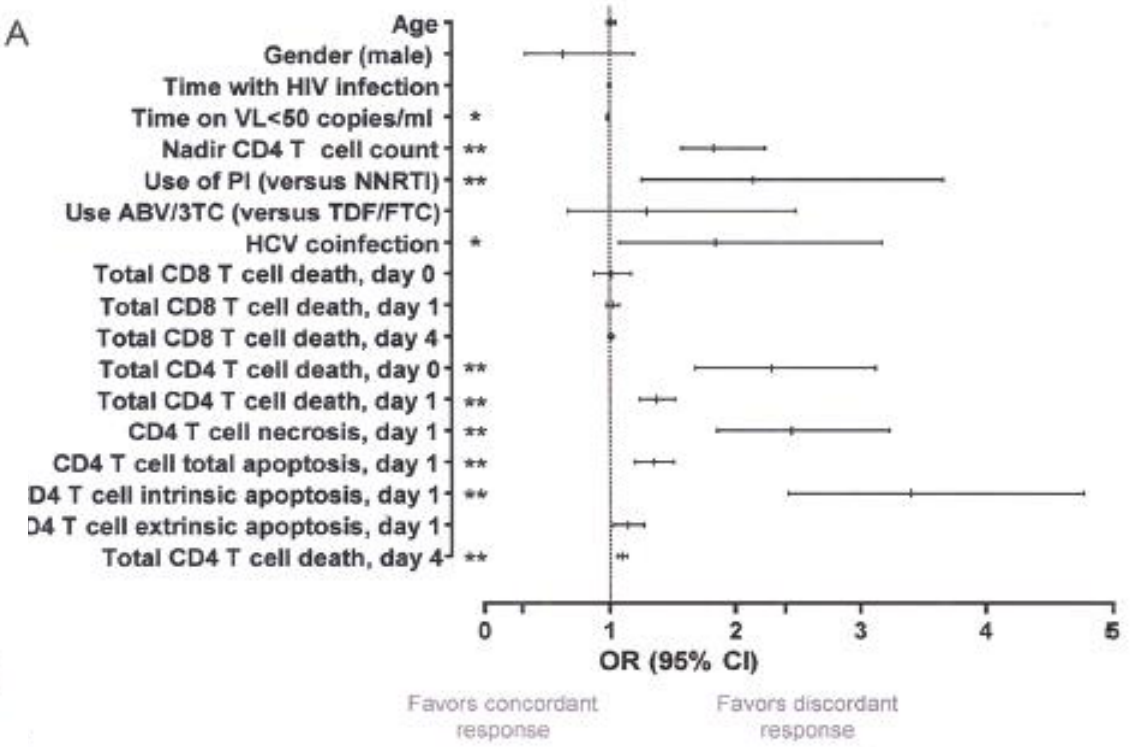
Immune Non Responders to ART

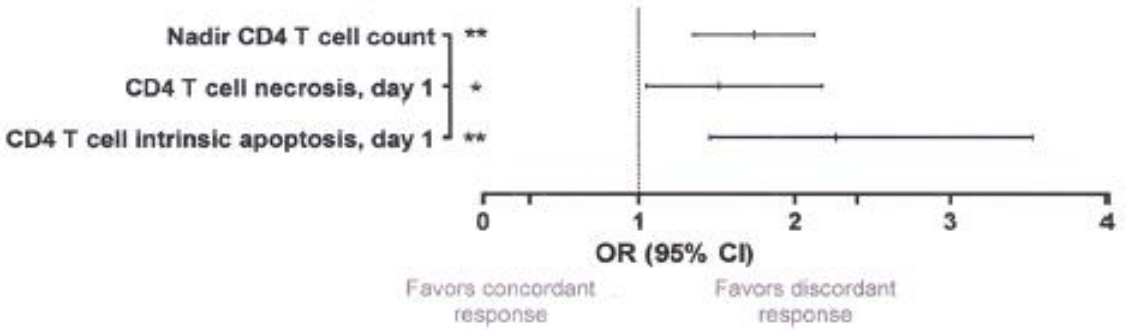
Nadir CD4 T Cell Count as Predictor and High CD4 T Cell Intrinsic Apoptosis as Final Mechanism of Poor CD4 T Cell Recovery in Virologically Suppressed HIV-Infected Patients: Clinical Implications

Eugènia Negredo,[1,a] Marta Massanella,[2,a] Jordi Puig,[1] Núria Pérez-Álvarez,[1,3] José Miguel Gallego-Escuredo,[4,5] Joan Villarroya,[4,5] Francesc Villarroya,[4,5] José Moltó,[1] José Ramón Santos,[1] Bonaventura Clotet,[1,2] and Julià Blanco[2]

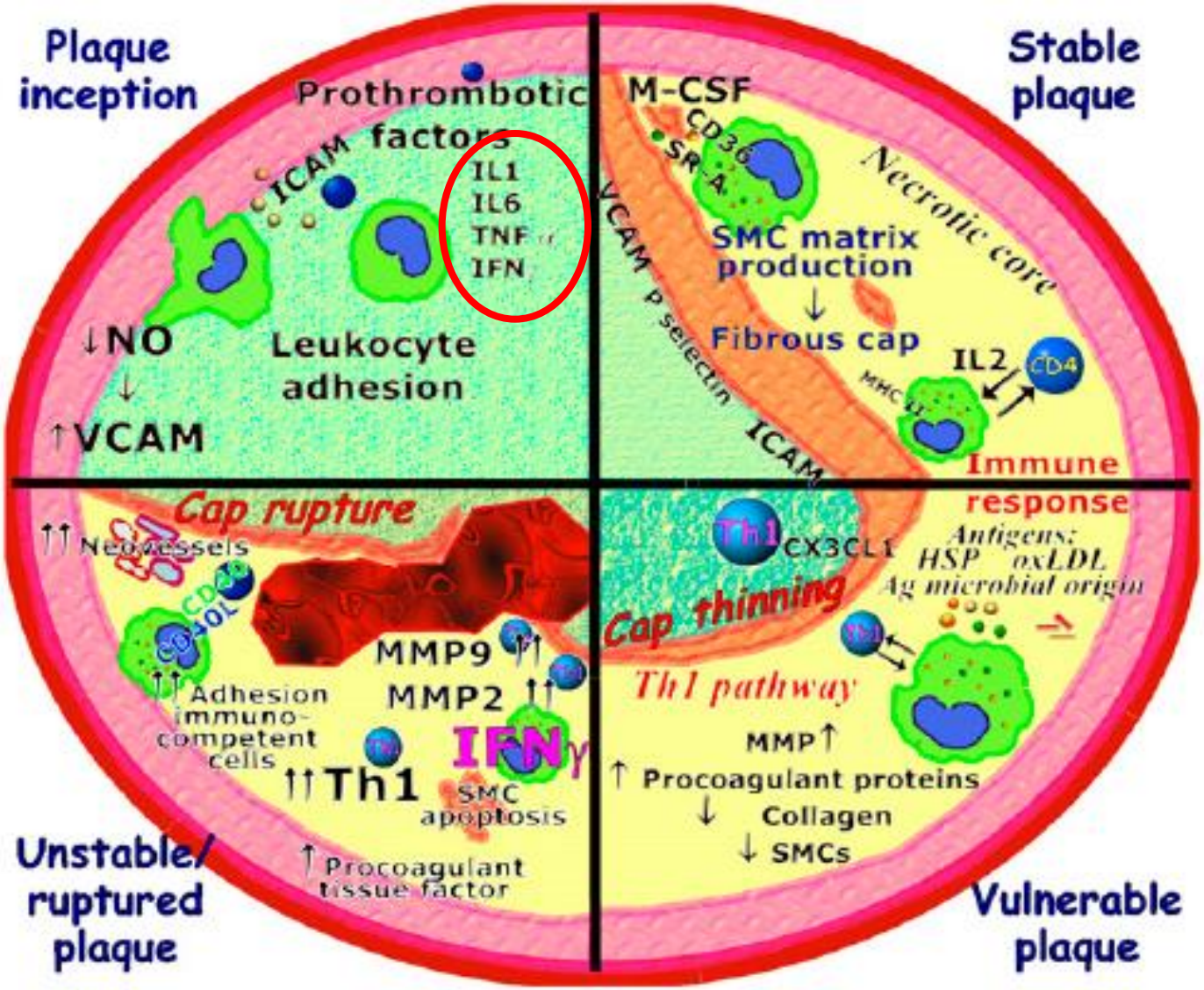
CID 2010







How can HIV induce atherosclerosis? Through Inflammation and activation of macrophages



ROLE OF INFECTION DURATION, ANTIRETROVIRAL THERAPY AND INFLAMMATORY IMBALANCE IN INCREASED ATHEROSCLEROSIS AMONG HIV-INFECTED NEVER-SMOKERS

Moise Desvarieux, Franck Boccara, Jean-Luc Meynard, Jean-Philippe Bastard, Ziad Mallat, Beny Charbit, Ryan T Demmer, Nabila haddour, Soraya Fellahi, Alain Tedgui, Ariel A Cohen, Jacqueline Capeau, Anders boyd, and Pierre-Marie Girard

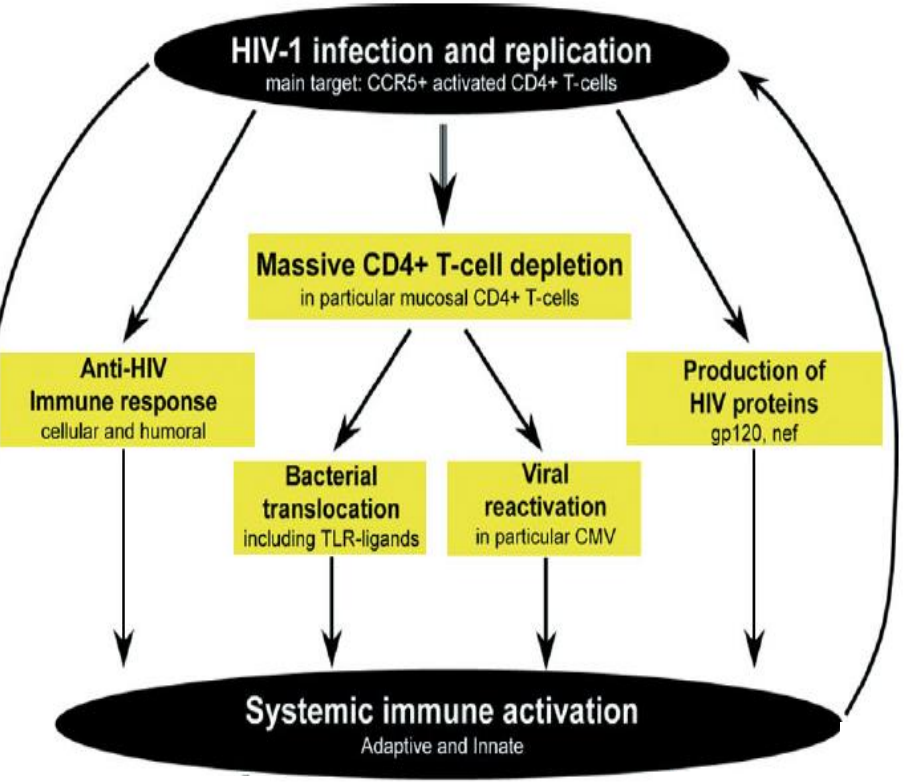
The CHIC Study (Circulation, 2012)

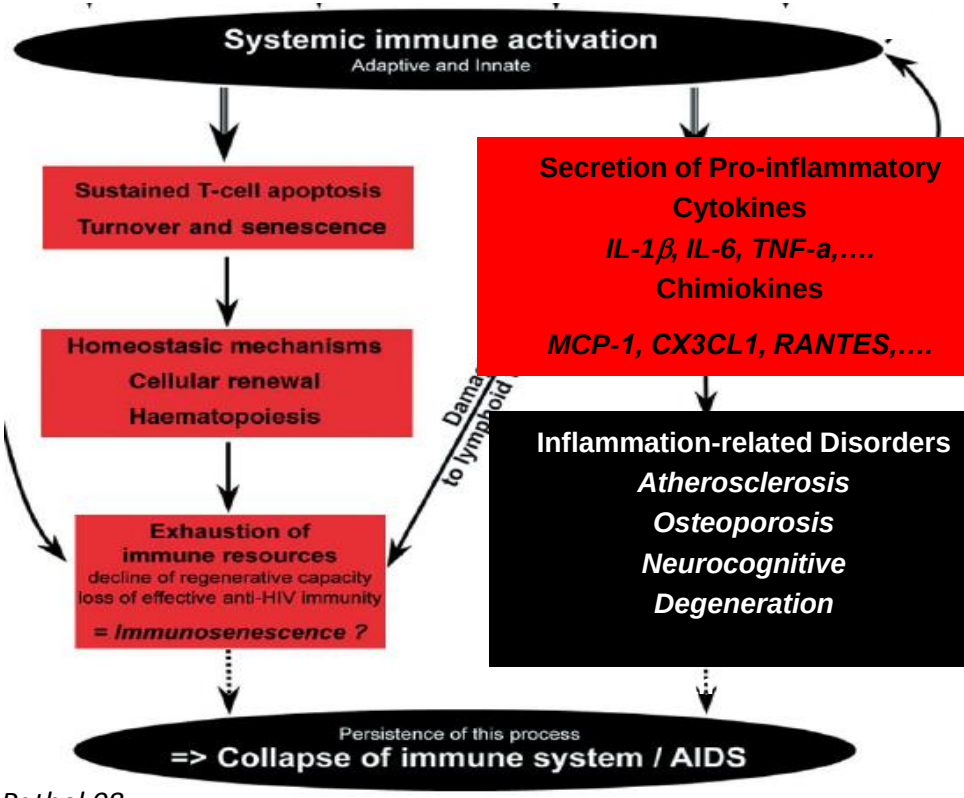
Metabolic and Pro- and anti-inflammatory markers

	HIV+		HIV-	
	Treated ≥4 years with cART	Never treated		$p^{\dagger}$
*Median (25-75th%tile)**	(*n*=50)	(*n*=50)	(*n*=50)	
Metabolic parameters				
Total cholesterol *mmol/L*	4.83 (4.22-5.72)	4.43 (3.87-4.80)	4.75 (4.31-5.36)	*ns*
HDL cholesterol *mmol/L*	1.12 (0.97-1.27)	1.07 (0.92-1.29)	1.23 (1.06-1.62)	*ns*
LDL cholesterol *mmol/L*	3.05 (2.63-3.72)	2.82 (2.41-3.17)	3.05 (2.50-3.42)	*ns*
Triglycerides *mmol/L*	1.33 (0.80-2.09)	0.87 (0.67-1.11)	0.86 (0.69-1.28)	*1, 2*
Pro-inflammatory markers				
hs-CRP *mg/l*	2.74 (0.72-5.32)	2.09 (0.60-4.21)	1.21 (0.43-3.15)	*2*
Resistin *ng/ml*	6.51 (4.42-8.98)	6.66 (4.85-8.32)	7.04 (5.12-9.37)	*ns*
IL-6‡ *pg/mL*	1.01 (0.31-1.39)	0.94 (0.23-2.63)	0.65 (0.22-1.16)	*ns*
IL-18‡ *pg/mL*	129.3 (7.2-206.4)	117.8 (7.2-261.9)	10.0 (7.2-99.7)	*2, 3*
Anti-inflammatory markers				
Total adiponectin *µg/ml*	2.70 (1.56-3.98)	3.10 (2.07-5.25)	3.72 (2.48-5.22)	*ns*
HMW adiponectin *µg/ml*	0.90 (0.69-1.71)	1.26 (0.89-2.00)	1.37 (0.89-2.16)	*1, 2*
IL-27‡ *pg/mL*	894 (523-2480)	1040 (336-1739)	1225 (615-3846)	*ns*
IL-10‡ *pg/mL*	0.77 (0.53-1.04)	1.39 (0.68-2.42)	0.68 (0.47-0.96)	*1, 3*

Chronic Inflammation/activation plays a key role in immunopathology of HIV:

Induction of Immune defects and Co-morbidities





Appay V et al, J Pathol 08

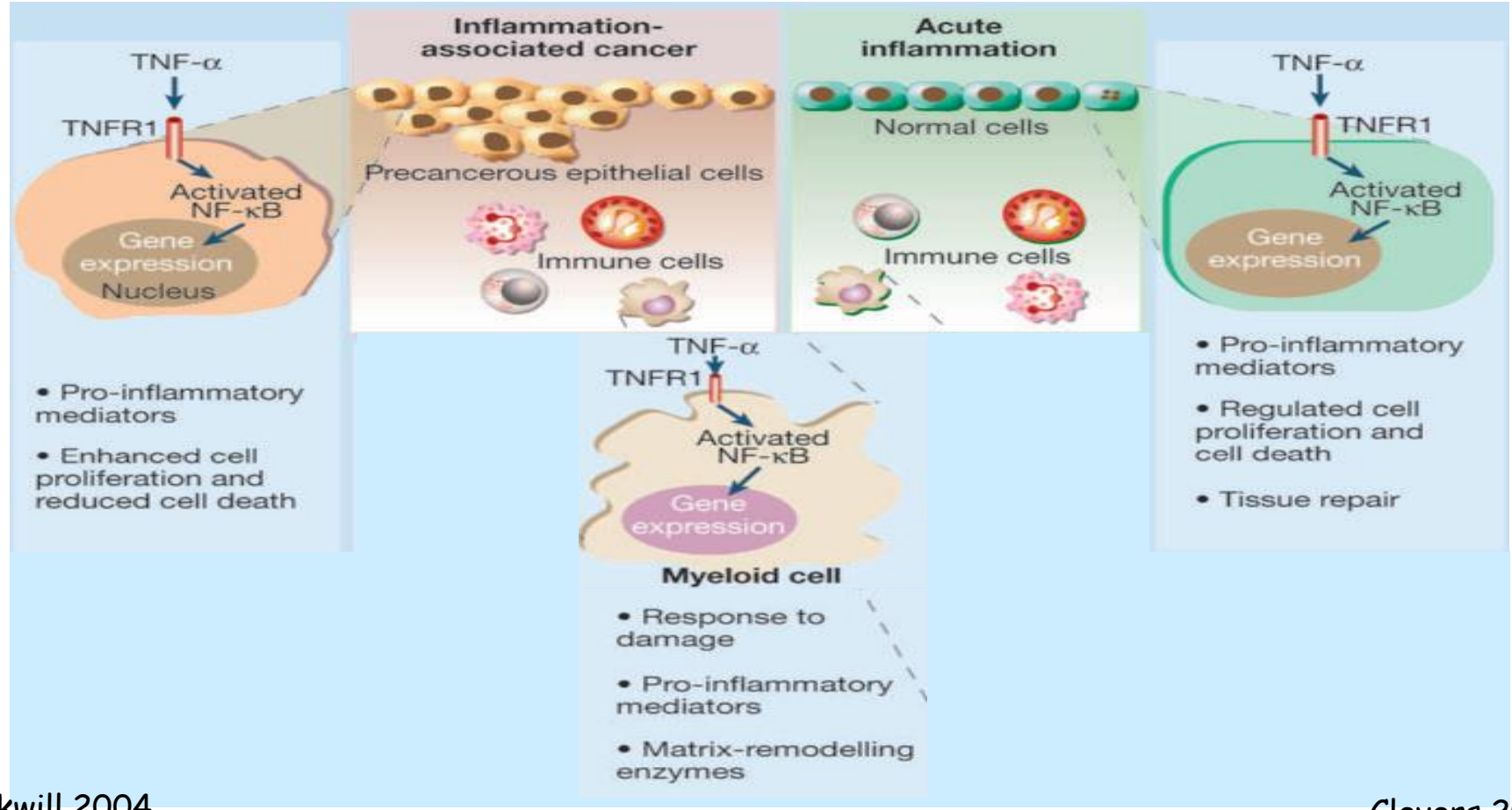
- Cellular Markers of Immune Hyperactivation : Ly CD4 and CD8 *(Ki67,DR, CD38)*
  B *(hypergammaglobulinemie, CD23s…)*
  Monocytes: CD14s, CD163s…
- Seric levels of Markers of Inflammation: pro-inflammatory Cytokines *(IL-6, TNF, MCP-1, IP-10, IFN-alpha*

Immunodépression et risque de cancer non classant SIDA

	Hodgkin RR (IC à 95 %)	Poumon RR (IC à 95 %)	Foie RR (IC à 95 %)
dernier CD4			
>500	1.0	1.0	1.0
350-500	1.2 (0.7-2.2)	2.2 (1.3-3.6)	2.0 (0.9-4.5)
200-350	2.2 (1.3-3.8)	3.4 (2.1-5.5)	4.1 (2.0-8.2)
100-200	4.8 (2.8-8.3)	4.8 (2.8-8.0)	7.3 (3.5-15.3)
50 -100	7.7 (3.9-15.2)	4.9 (2.3-10.2)	6.6 (2.4-17.6)
<50	5.4 (2.4-12.1)	8.5 (4.3-16.7)	7.6 (2.7-20.8)

Role of inflammation in tumor progression

Inflammation: Stimulation chronique de la voie de signalisation NF-KB



Balkwill 2004

Clevers 2004

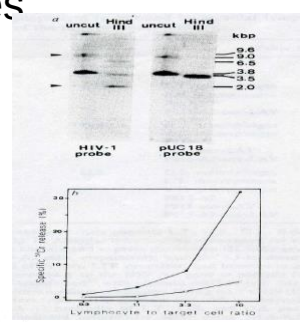
Cytokines, Chimiokines, Facteurs de l'angiogénèse …

→ Croissance / progression tumorale

Poor Immune Correlates of protection against HIV

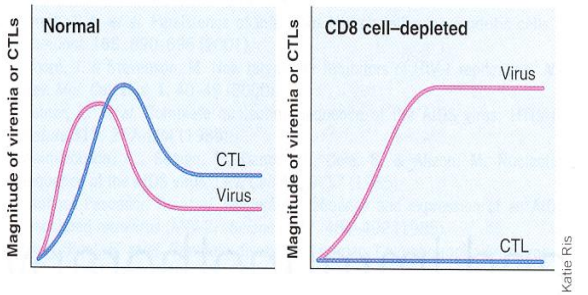
- **Antibodies against HIV?**
  - ✓ **No significant relationship** between **neutralizing Ab** and **viral control**
  - ✓ **BUT Control of SHIV/HIV** after transfers of anti-Env Monoclonal Abs *(Mascola, 98. Trkola 2000..).*

- **CD8 T Lymphocytes (CTLs or killer cells) specific for HIV:**
  - ✓ **Inverse relationship between viral load and HIV-specific CTL** frequencies during acute *(Koup, 93…)* or chronic infection *(Ogg,98, Kiepela 2009…)* and in LTNP/Elite Controlers *(Klein, 95, Kalams 99, Martinez 2005, Saez-Cirion 2008…)*



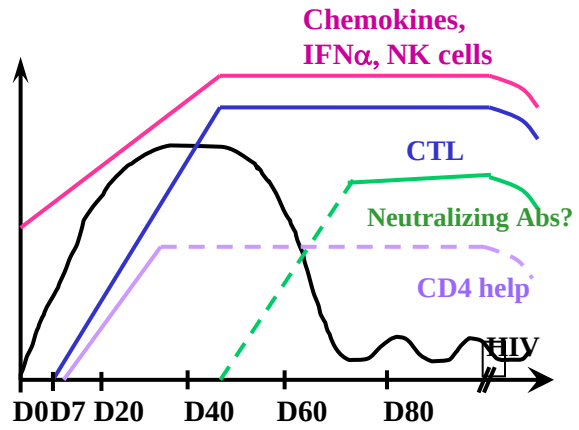
  - ✓ **Tissue infiltration of HIV-specific CTLs** *(Plata et al. Nature 1987, Hadida et al. J.C.I. 1992, Cheynier et al. Cell 1994)….*

  - ✓ **Loss of SIV control after CD8 cell depletion in Macaques** *(Schmitz, Zhang, 99)*

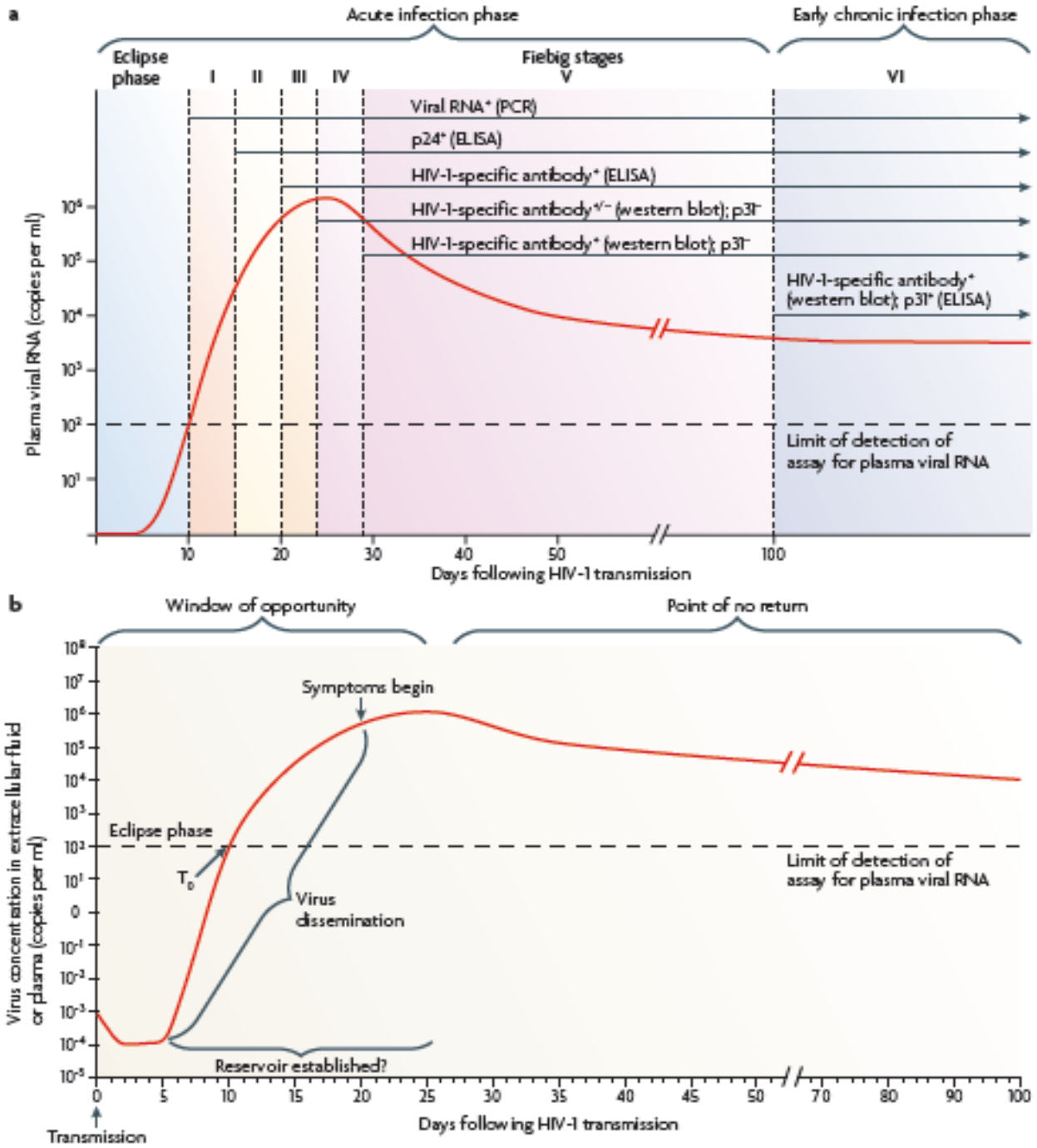


- **CD4 Thelper-1 Lymphocytes specific for HIV :**
  - ✓ Required for generation and maintenance of HIV-specific CTL and Ab
  - ✓ **Inverse relationship between viral load and HIV-specific CD4 Th1cells** during primary infection and in LTNP *(Rosenberg, 97, 2000, Martinez 2005…)*

against HIV: early Kinetics of innate and adaptive responses



A McMichael et al.
NRI, 2010



Poor efficacy of Neutralizing Abs against HIV:

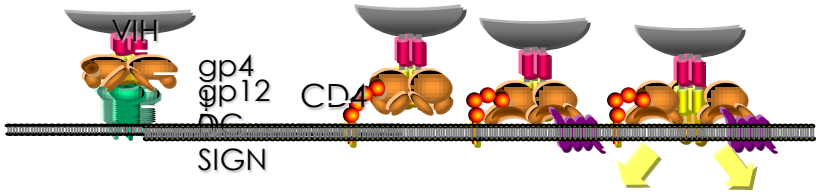
Poor accessibility of the conserved Antigenic targets favors immune escape

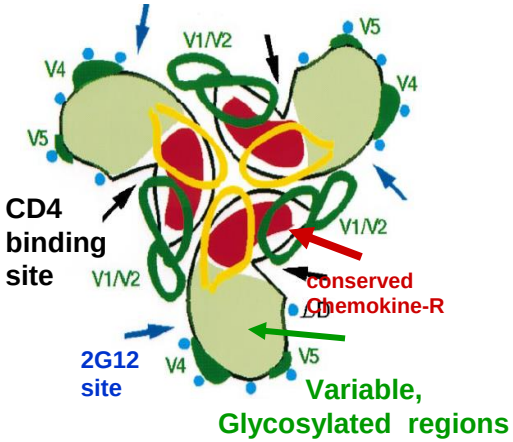
Neut. Ab binding sites :

1- **Hidden CD4 binding site** with conformational changes post CD4 binding,

2- **CD4-induced epitopes**

3- **surface 2G12 bs**





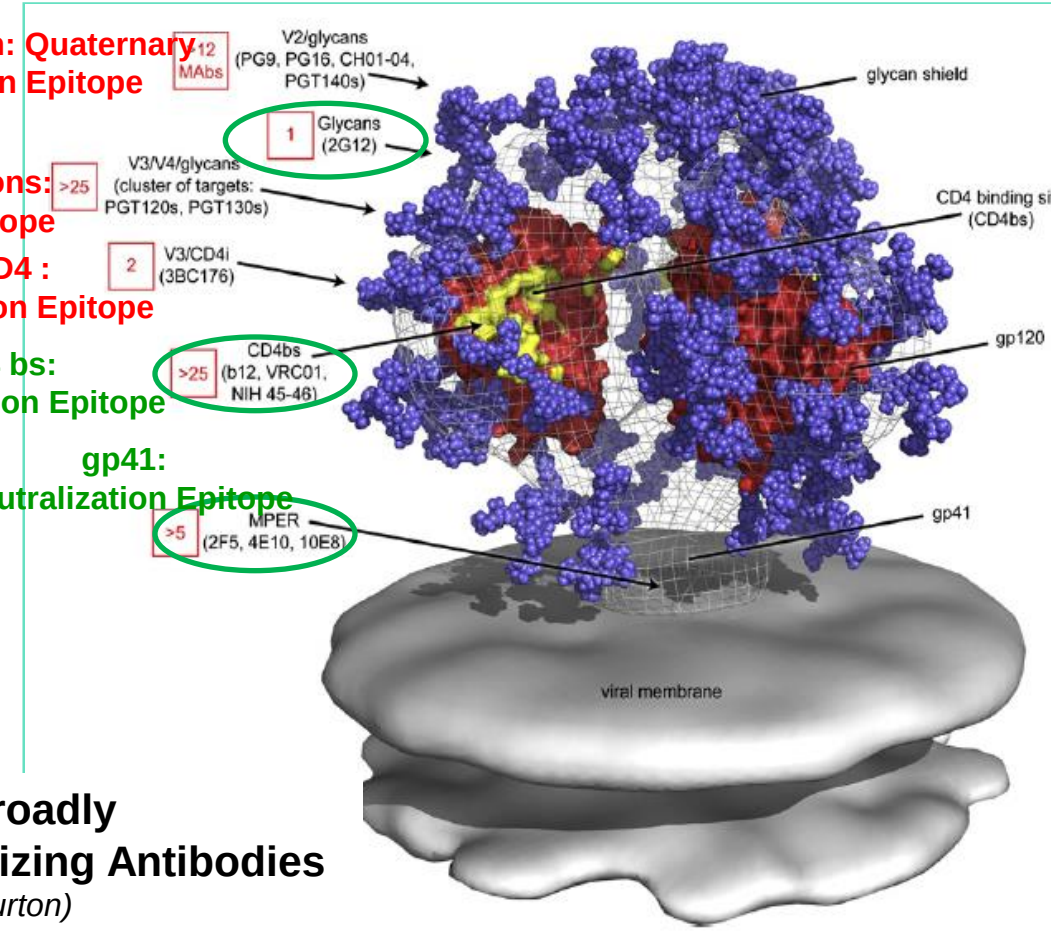
V2/Glycan region: Quaternary Neutralization Epitope

V3/V4 glycan regions: Neutralization Epitope

V3/CD4 : Neutralization Epitope

CD4 bs: Neutralization Epitope

gp41: Neutralization Epitope



Rare Broadly Neutralizing Antibodies

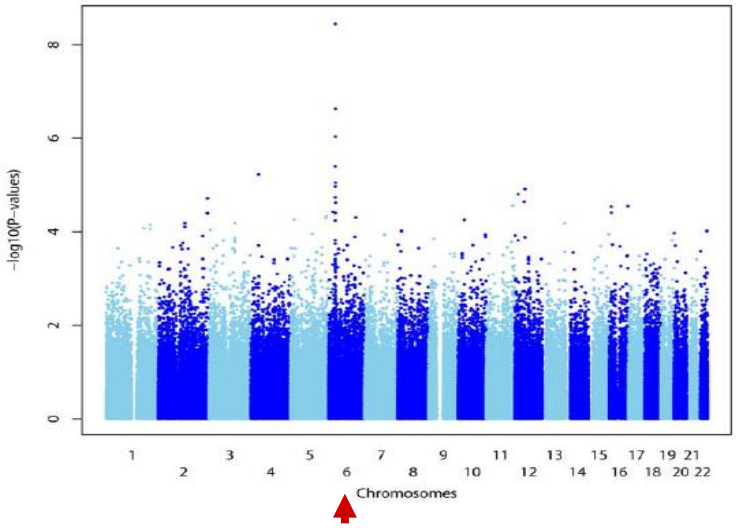
(from D Burton)

Molecular signature of an Immunogenetics control of the HIV Reservoir

Genome-wide analysis in Elite Controllers and LTNP

➢ **The MHC locus: the strongest genetic marker :**

- **HIV controlers** *(Dalmasso et al.: 2009)*
- **Elite Controlers** *(Pereyra et al. 2010)*
- **LTNP** (GISHEAL: French & Italian) *(Guergnon et al:2011)*



3 MHC regions linked to NP:

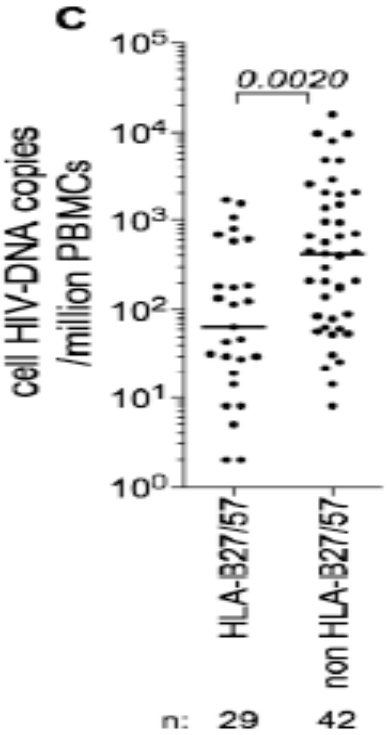
- MHC **class I**,
- **C4** Complement locus
- **MIC** region.

(Dalmasso, Guergnon)

➢ **MHC class I:**

HLA-B 57 : 66% vs 3%
HLA-B 27 : **25%** vs 3%
HLA-B14, B51….
HLA Cw8

Antoni et al. 2013



Lower Reservoir (HIV-DNA) in B27+/57+ vs negatives

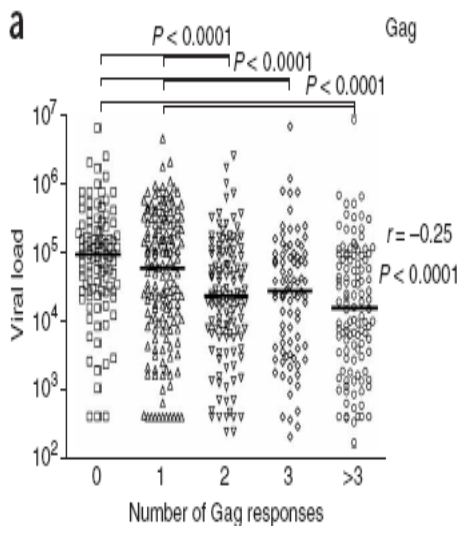
B Descours et al. Clin. Inf. Dis 2011

Immune Correlates of protection against HIV disease progression ?

HIV-Gag specific CD8 responses

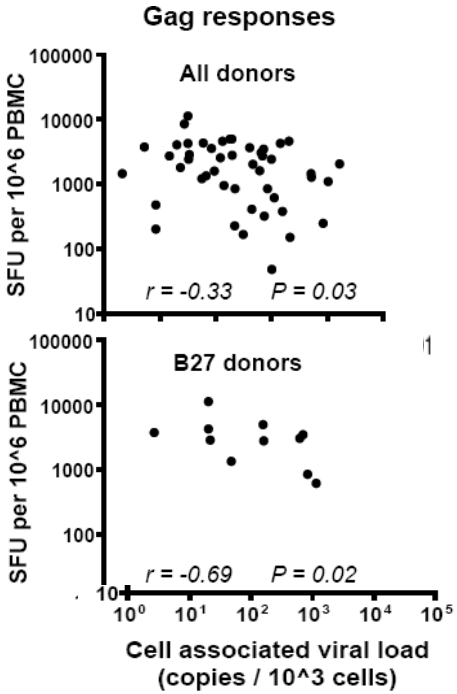
1. Magnitude

- **Against plasma VL in large cohorts of Standard infection**



Photini Kiepiela[1], NATURE MEDICINE 2006

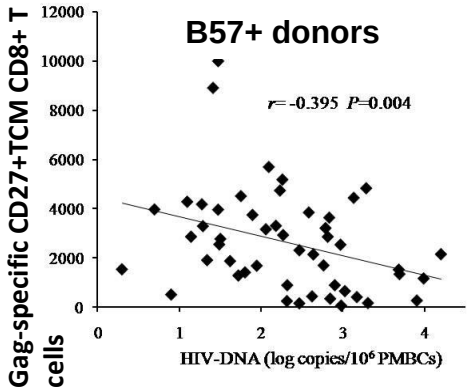
- **Against Reservoirs in cohort of LTNPs**



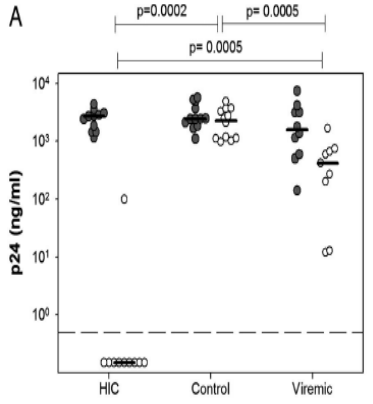
Martinez V et al. J.I.D. 2005;
Almeida et al. J Exp Med 2007,

2. Quality: in LTNPs, Elite Controlers, HIC

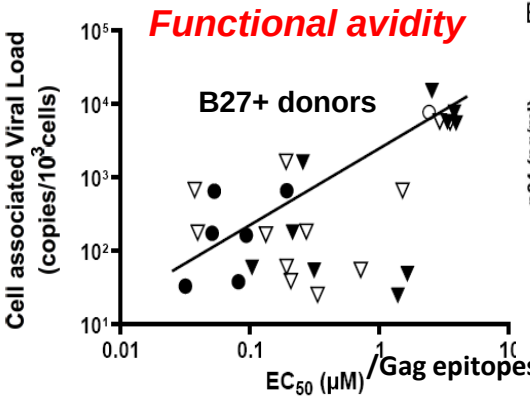
Differentiation

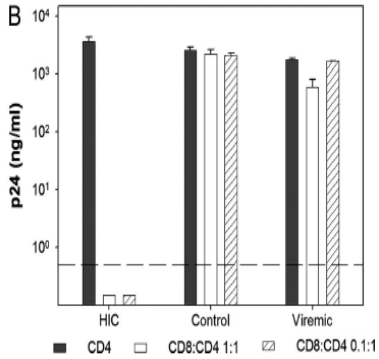


Anti-viral activity



Functional avidity





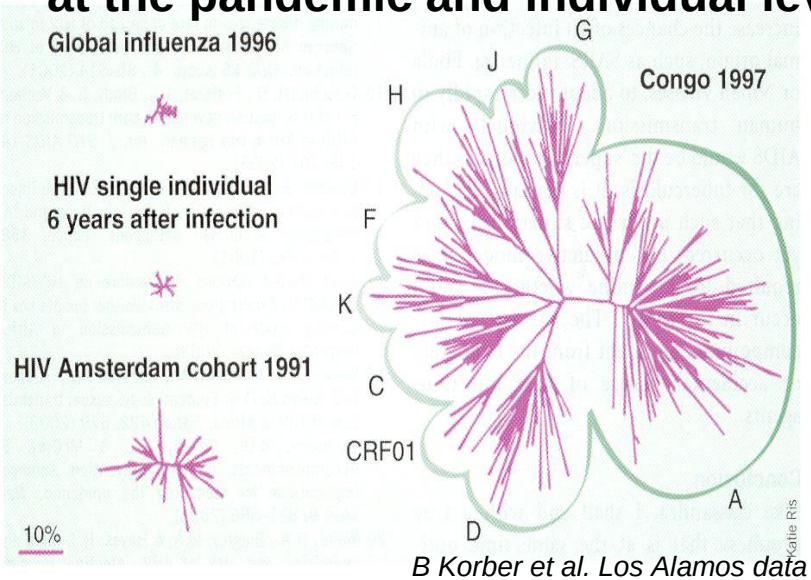
Almeida et al. Blood 2009; X Jie et al. AIDS 2010; *Saez-Cirion et al., 2009 PNAS*

HIV Variability: Immune escape and Obstacle to HIV Vaccines

Worldwide Distribution of HIV Clades

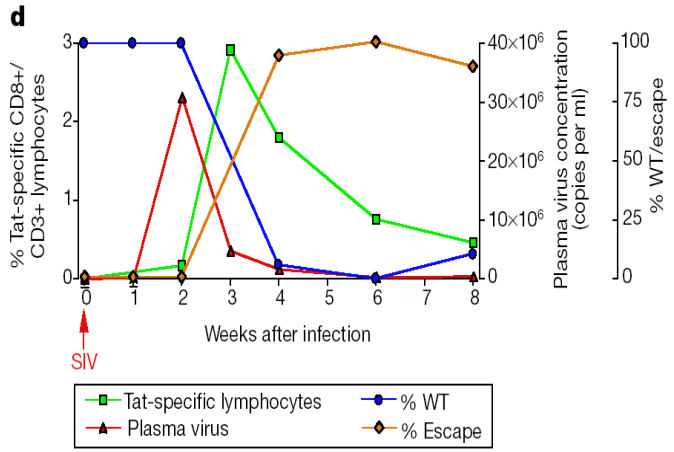
David A Garber, Guido Silvestri, and Mark B Feinberg
THE LANCET Infectious Diseases Vol 4 July 2004

HIV sequence Variability at the pandemic and individual levels



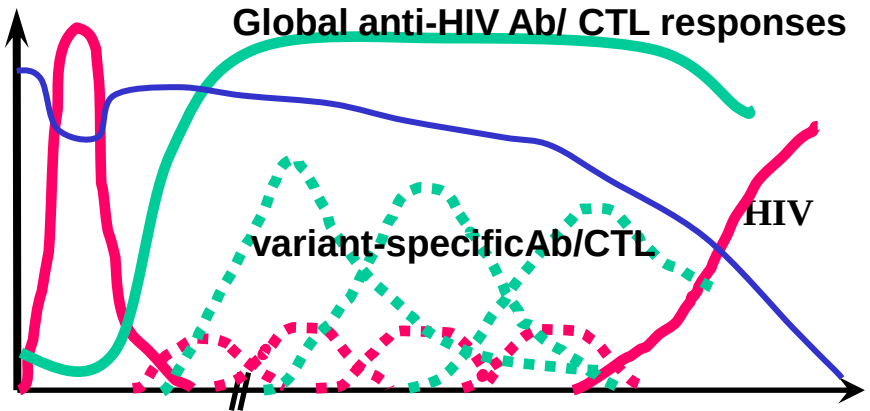
B Korber et al. Los Alamos data bank

Immune Escape to T cells



T.Allen et al. Nature 2000

A permanent predator/prey chase



« Towards an HIV CURE »

F Barré-Sinoussi

AIDS 2010
XVIII INTERNATIONAL AIDS CONFERENCE
JULY | 18-23 | 2010 | VIENNA AUSTRIA
Rights Here, Right Now

Workshop on towards a cure → Connecting researchers together

WHAT ELSE?

INTERNATIONAL SCIENTIFIC WORKING GROUP ⟷ **INTERNATIONAL ADVISORY BOARD**

Development

INTERNATIONAL CONSULTATIONS

Implementation

Clinical Trials

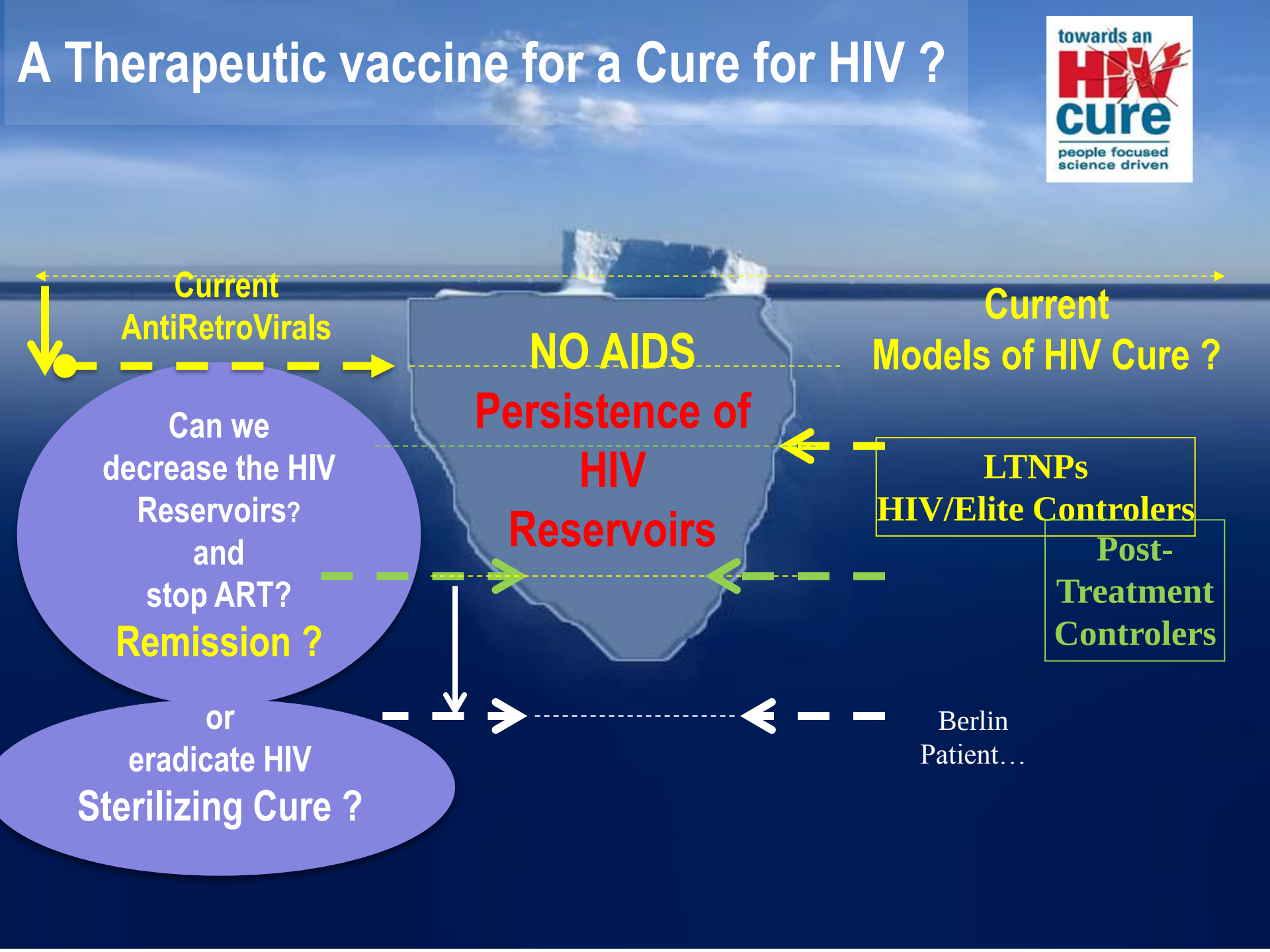
Basic Science

Launch

A global scientific strategy defining research priorities

AIDS 2012 | XIX INTERNATIONAL AIDS CONFERENCE JULY 22 - 27 WASHINGTON DC USA

A Therapeutic vaccine for a Cure for HIV ?



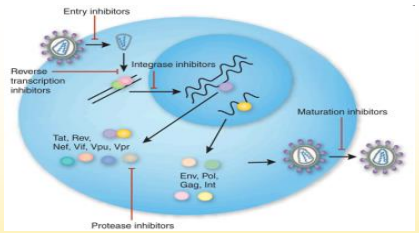
Lessons from Controlers for strategies to reduce HIV reservoirs

Anti-inflammatory drugs

Systemic Inflammation

Viral Co-Infections

Immune Activation



ARV

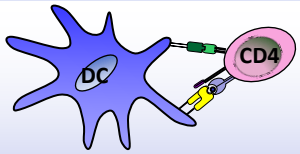
- Acute vs Chronic ???
- Intensification
- Nevirapine

Cellular Immunity Immune Intervention

- Anti-HIV vaccine

Residual Replication

Gene therapy



Anti-co-stimulatory molecules

HIV Reservoirs Latency

Quiescent T cells : activation Pre/post-transcriptional factors mofulation

from C Katlama et al. Lancet 2013