Inflammation et activation : quelles implications en pratique clinique ?

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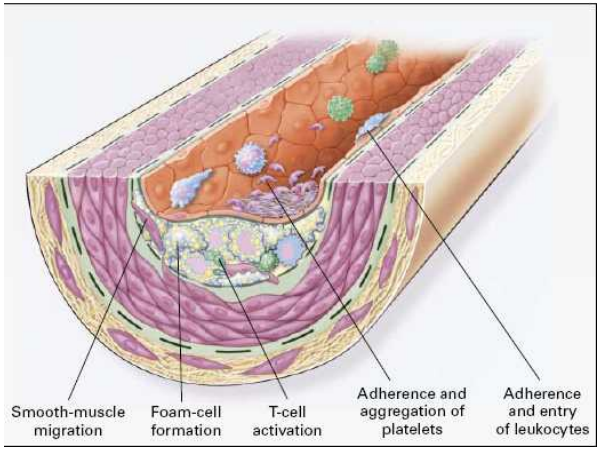
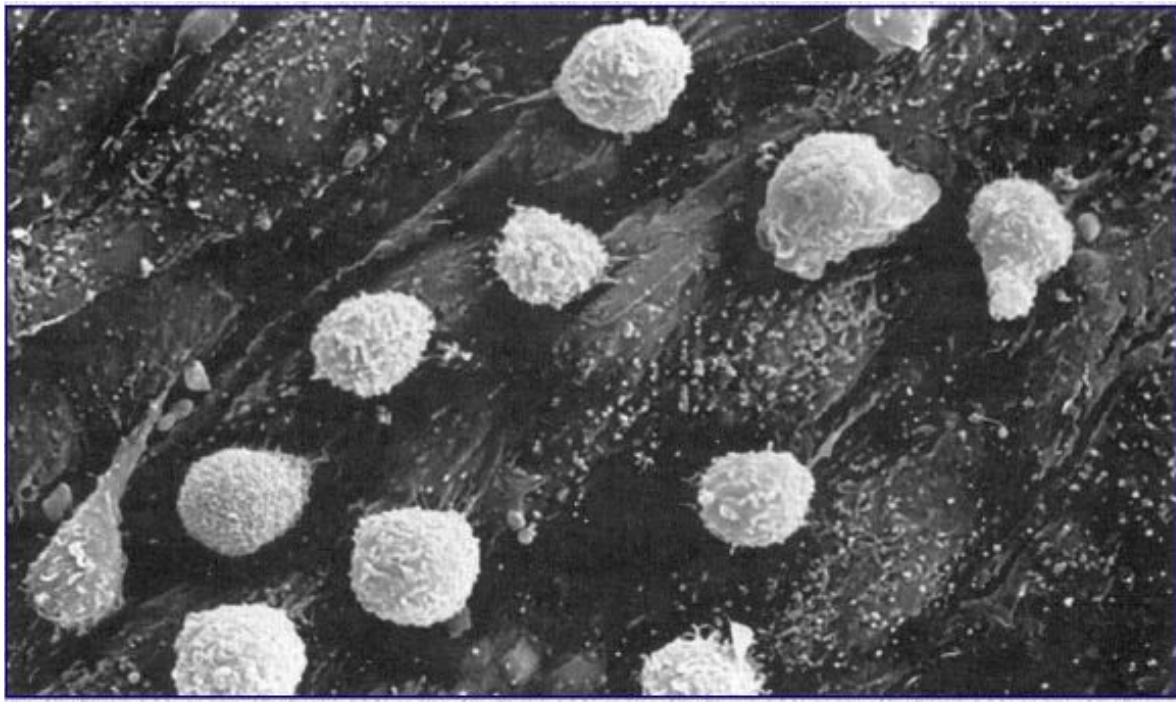
Régulation des Infections Rétrovirales

“L’athérosclérose est une maladie inflammatoire”



Russell Ross, NEJM 1999

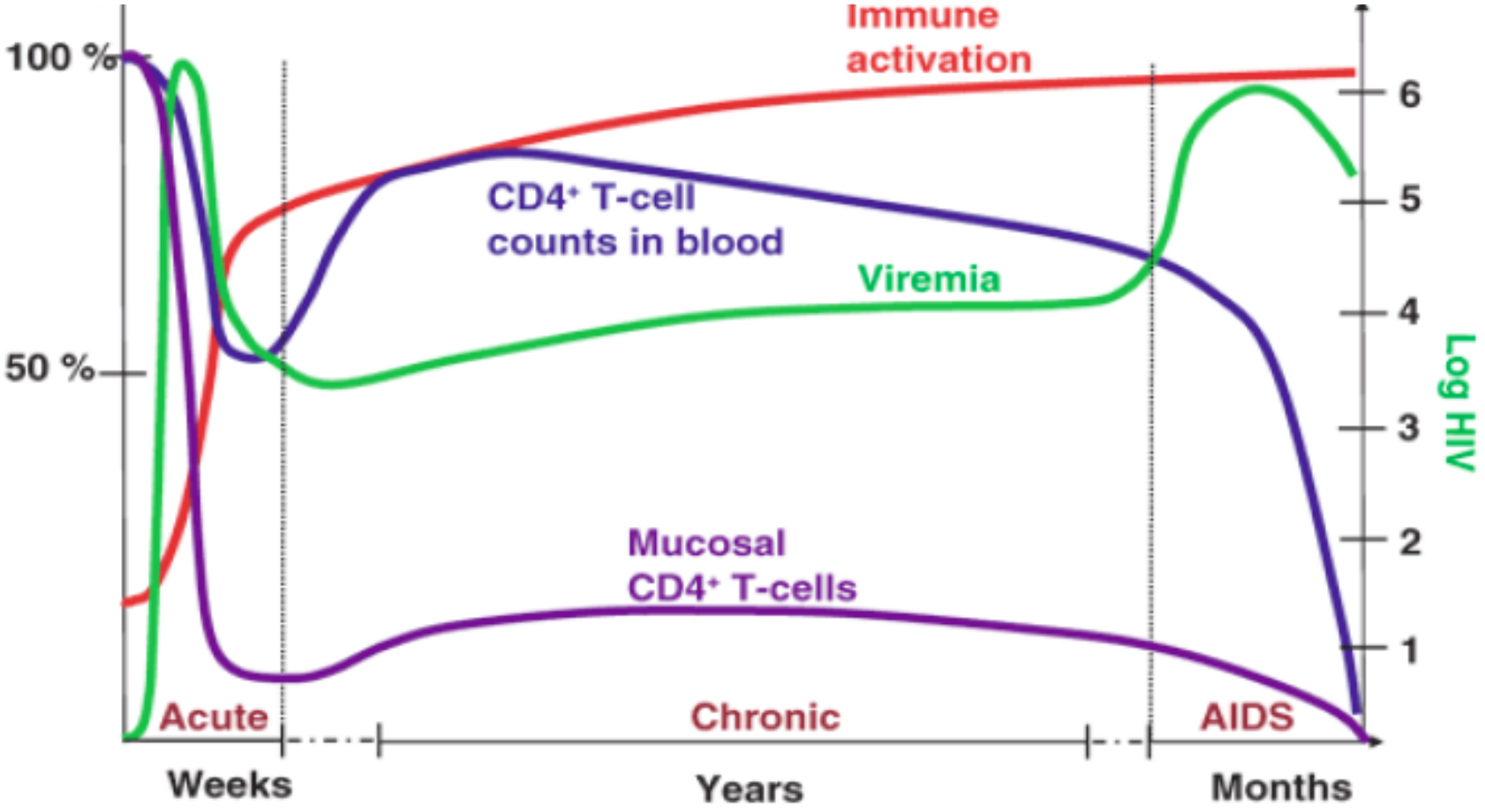


A. Tedgui, Congrès Complications Avignon 2008

Activation du système immunitaire-Inflammation

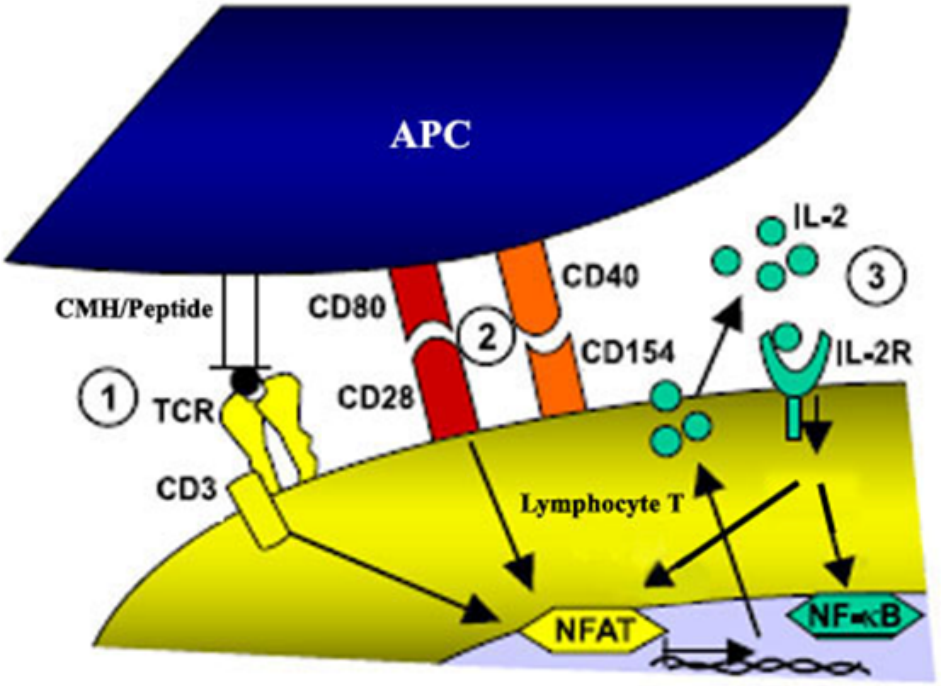
- **Réponse inflammatoire aigüe**
  - Après stimulation par un pathogène
  - Dure quelques jours
  - Eradication du stimulus (par ex: pathogène)
  - Retour à un stade quiescent des cellules du système immunitaire
  - **Réponse protectrice - Bénéfique pour l'hôte**
- **Réponse inflammatoire chronique**
  - **Prolongée**: plusieurs semaines ou mois
  - Persistance du stimulus (pathogène, cancer, auto-antigènes)
  - **Délétère** pour l'hôte

Histoire naturelle de l'infection VIH



Picker, Nat.Med. 2006

Activation du système immunitaire au cours de l'infection VIH

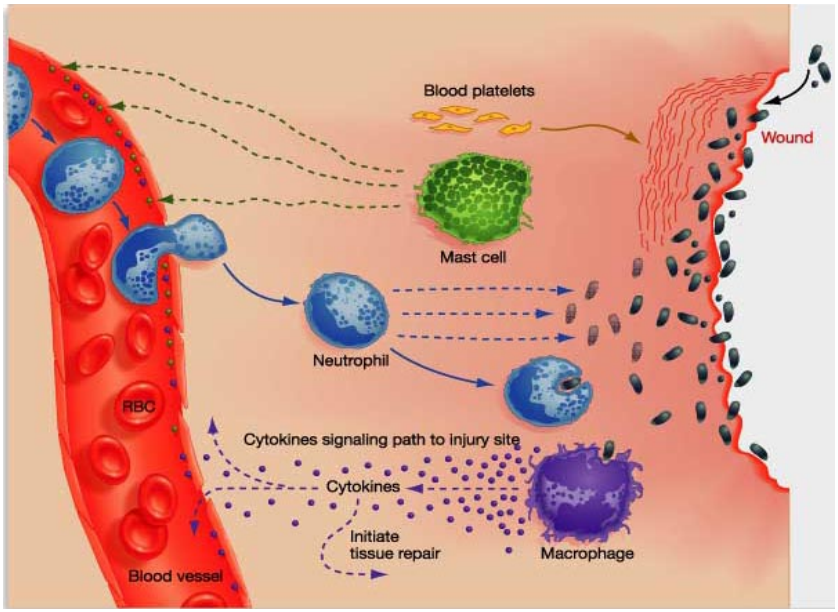


Activation chronique

- Monocytes/macrophages
- Lymphocytes T CD4+ et CD8+
- Lymphocytes B ⇒ hypergammaglobulinémie polyclonale ou oligoclonale

Première étape de la réponse immune :
réponse innée et création d'un foyer inflammatoire

Première ligne de défense par les macrophages



Production de médiateurs inflammatoires

- **Reconnaissance** de structures conservées sur un gd nbre de pathogènes (PAMPs: **pathogen-associated molecular pattern**) par des PPR (pattern recognition receptors) par les PNn et les macrophages, les cellules dendritiques …

- **Ingestion par phagocytose et destruction** par burst oxydatif

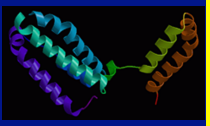
- **Activation des Macrophages** : production médiateurs inflammatoires : **Cytokines, chimiokines**, protéines phase aigue, complément…

→ Recrutement des leucocytes, limitation du foyer infectieux, transition vers ls ʻmmunité adaptative, réparation tissulaire

Immunité
Innée

Inflammation

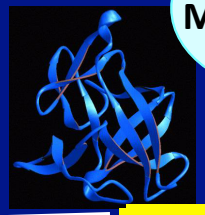
CYTOKINES INHIBITRICES



IL-4
IL-10
IL-13
TGFβ
IFNα

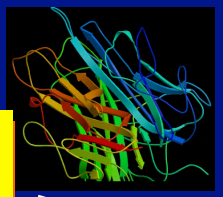
SIGNAUX D'ACTIVATION

Macrophage



CYTOKINES AMPLIFICATRICES

IFNγ
IL-3
GM-CSF



IL-1 TNF

IL-6
IL-11
LIF
TGFβ

SYSTÈME NERVEUX CENTRAL

ACTH

Fièvre
Sommeil
anorexie

SURRENALES

Glucocorticoïdes

HEPATOCYTES

protéines phase aiguë

CELLULES CIBLES

Protéases

PAF

radicaux libres

eicosanoïdes

TISSUS

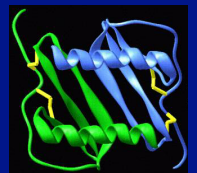
- catabolisme
- dégradation
- nécrose
- protéolyse

CELLULES ENDOTHELIALES

- activité procoagulante
- permeabilité vasculaire
- adhérence

IL-8 / MCP-1

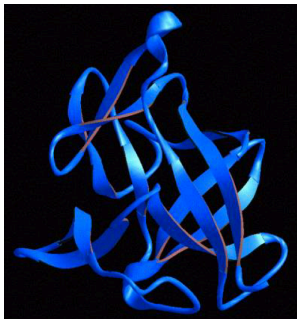
Chimiotactisme



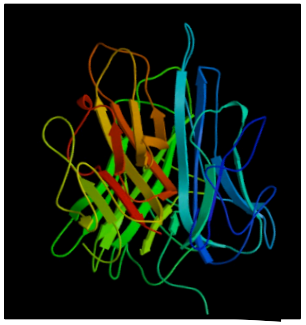
INFLAMMATION

PRO-INFLAMMATORY CYTOKINES

INTERLEUKIN-1
IL-1



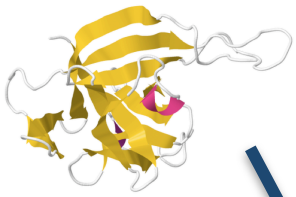
TUMOR NECROSIS FACTOR
TNF



IL-1 FAMILY MEMBERS

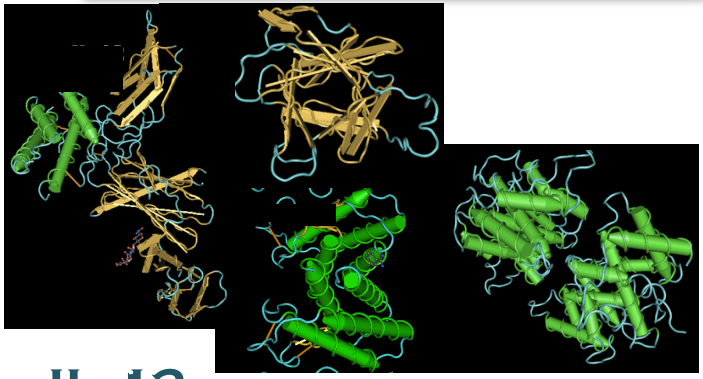
IL-18

IL-33



IL-36

IFNγ AND PARTNERS



IL-12

IL-15

IFNγ

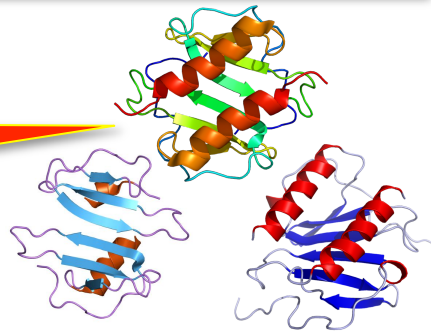
IL-17 AXIS

Th17

IL-17
IL-22

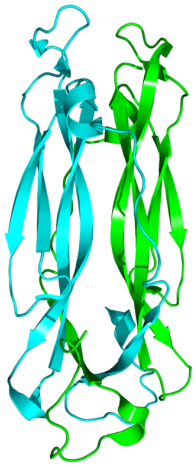
IL-23

CHEMOKINES



INFLAMMATION

IL-17 Axis



TGFβ
IL-6
IL-21
IL-23

Th0 → Th17

IL-27
IFNγ

IL-17

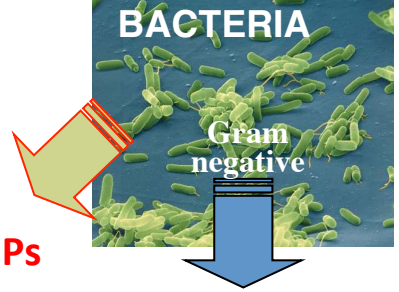
MØ Dendritic ¢	IL-1, TNF IL-6,	INFLAMMATION
Endothelial ¢	IL-6, MMP Coagulation	VASCULAR ACTIVATION
Fibroblast	IL-6, MMP Chemokines Growth fact.	MATRIX DEGRADATION
Osteoclast	RANKL MMP	BONE DEGRADATION
Chondrocyte	MMP	CARTILAGE DEGRADATION

NB There are six IL-17:

IL-17A; IL-17B; IL-17C; IL-17D; IL-17E (IL-25); IL-17F

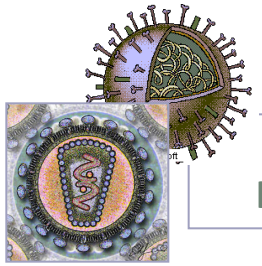
SYNERGY

Adib-Conquy M, Cavaillon JM.
FEBS Lett. 2007; 581: 3723-33



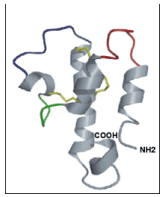
Other PAMPs
(Lipoprotein, peptidoglycan, DNA…)

ENDOTOXINS

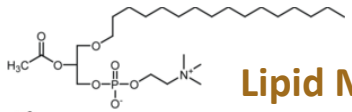


OTHER INFECTIONS

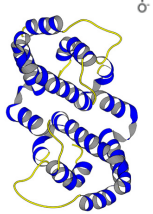
INFECTIOUS PROCESS



Complement activation (C5a)



Lipid Mediators



Cytokines

Neuromediators

Coagulation factors

Glucose

Necrotic cells

OTHER PATHO-PHYSIOLOGICAL EVENTS

Hypoxia

Ischemia / reperfusion

macrophage

IATROGENIC EVENTS

Mechanical ventilation

IL-12 IL-6 IL-1 TNF IL-18

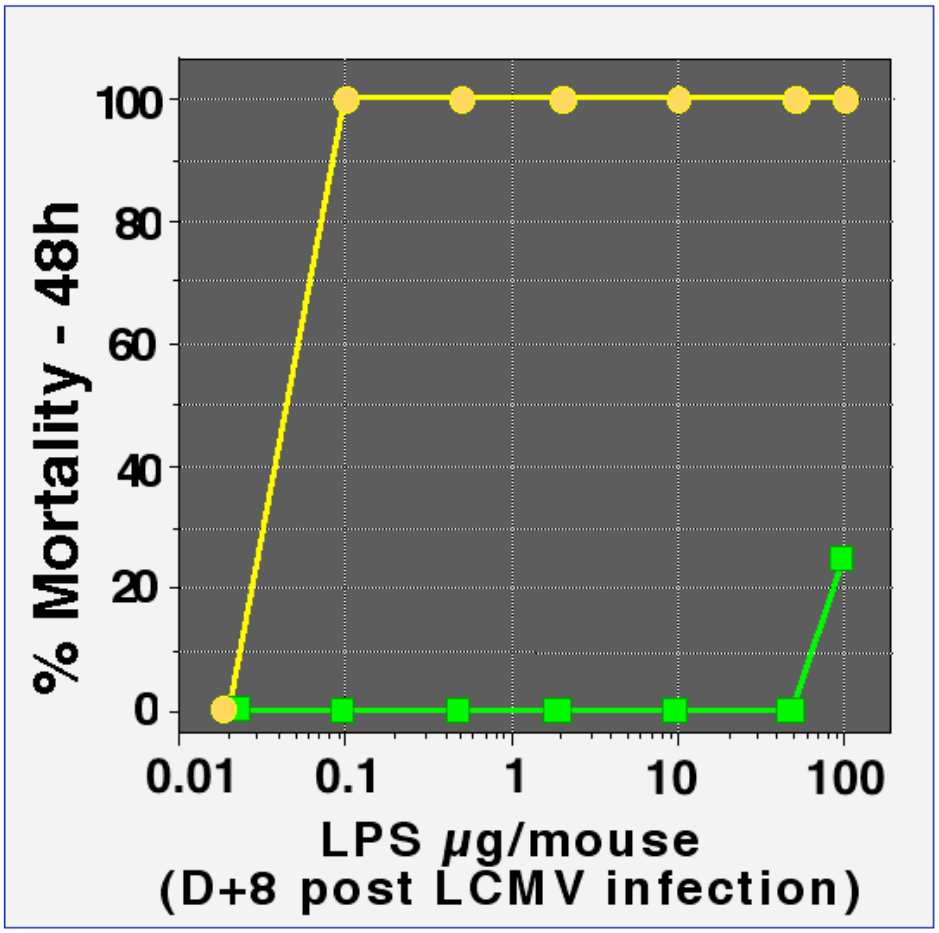
CCL MIF HMGB1 CXCL

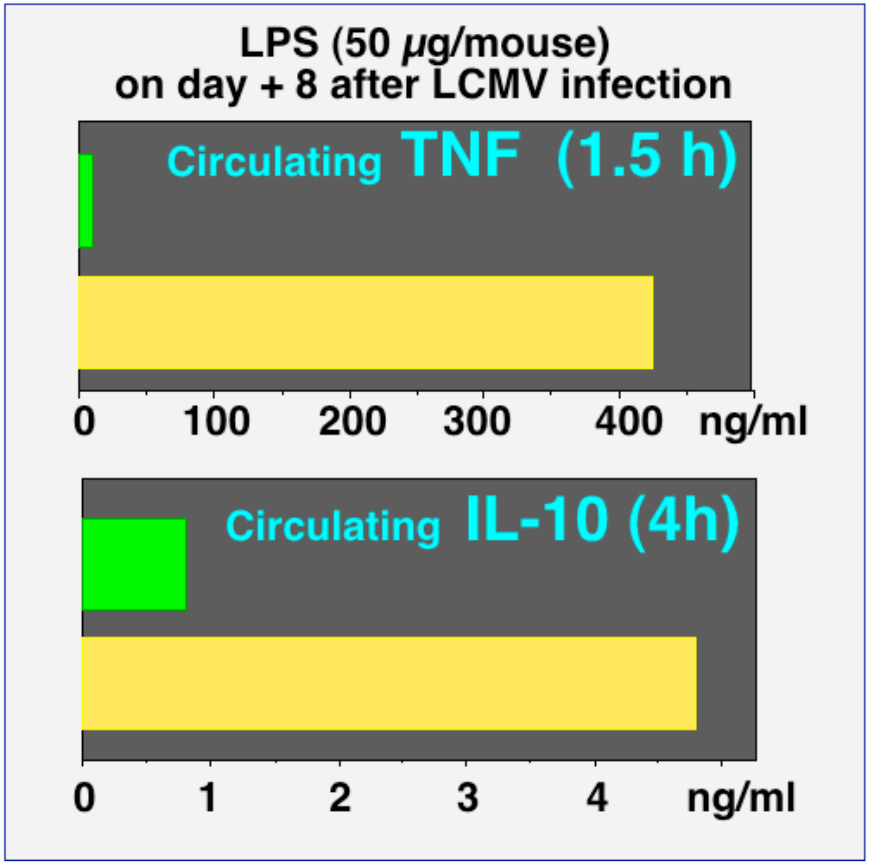
Synergy

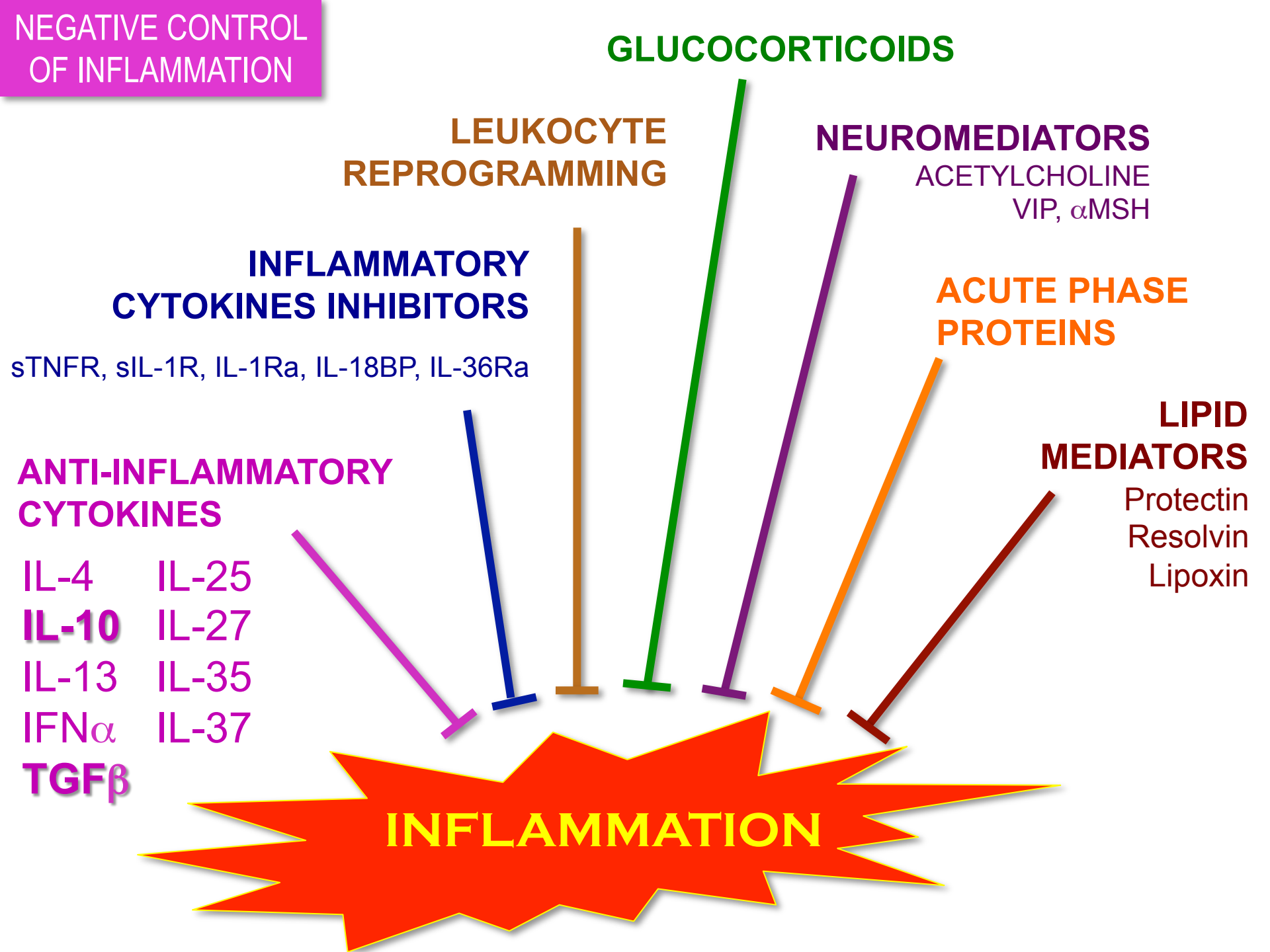
SENSITIZATION TO LPS IN MICE WITH ASYMPTOMATIC VIRAL INFECTION

Role of T-cell dependent production of Interferon-γ

Nansen et al. J. Infect. Dis. 1997, 176, 151



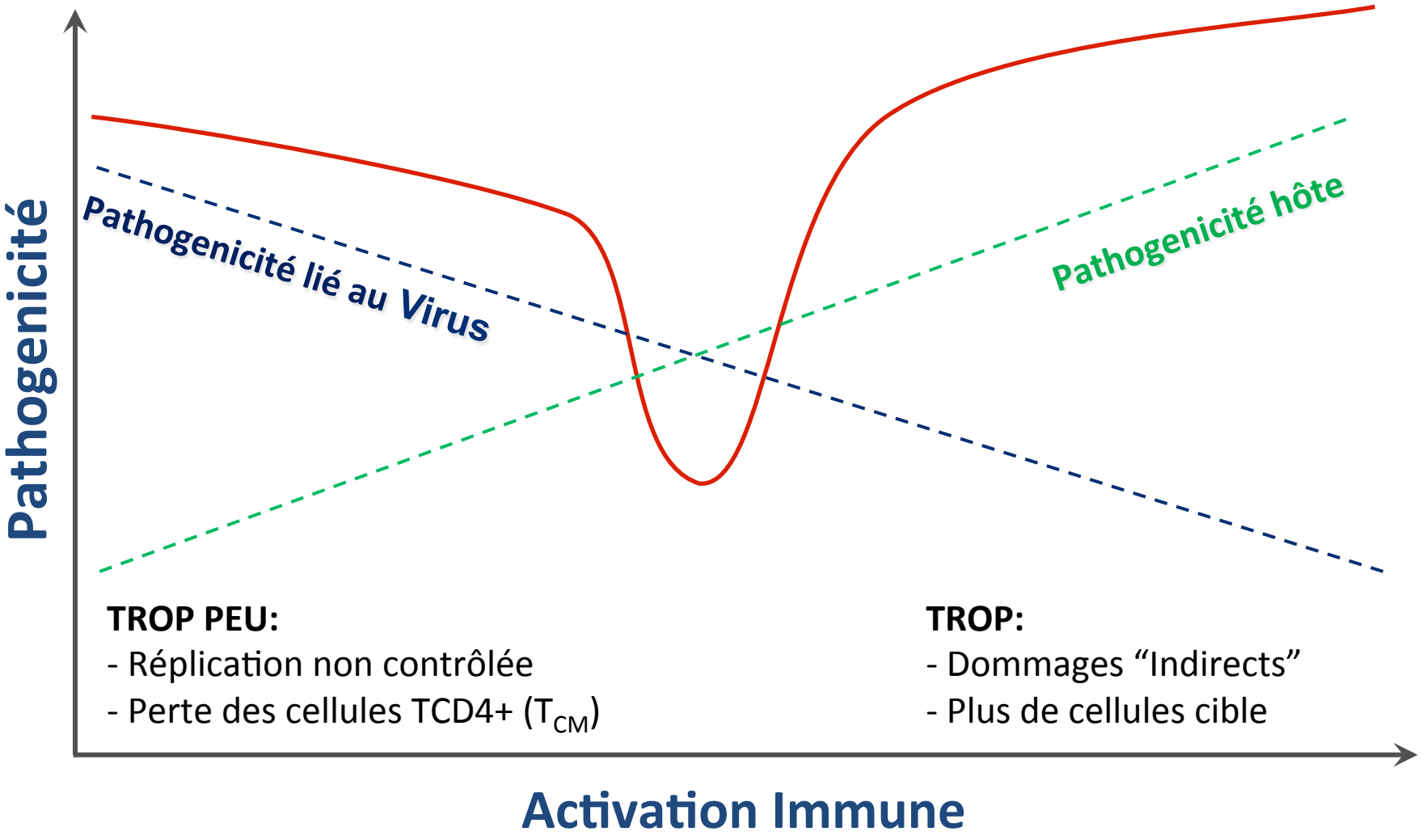



NEGATIVE CONTROL OF INFLAMMATION
GLUCOCORTICOIDS
LEUKOCYTE REPROGRAMMING
NEUROMEDIATORS
ACETYLCHOLINE
VIP, αMSH
INFLAMMATORY CYTOKINES INHIBITORS
sTNFR, sIL-1R, IL-1Ra, IL-18BP, IL-36Ra
ACUTE PHASE PROTEINS
LIPID MEDIATORS
Protectin
Resolvin
Lipoxin
ANTI-INFLAMMATORY CYTOKINES
IL-4
IL-10
IL-13
IFNα
TGFβ
IL-25
IL-27
IL-35
IL-37
INFLAMMATION

Inflammation – Activation chronique du système immunitaire

- **Situations cliniques associées à une activation chronique**
  - **Infection par le VIH**
  - **Autres infections chroniques**
  - **Maladies auto-immunes et/ou maladies inflammatoires chroniques**
  - **Cancers**
- **L'activation chronique est délétère**
- Conséquences de l'activation chronique
  - Athérosclérose accélérée
  - Risque accru de cancer

Activation Immune : un “diable nécessaire “ ?



adapted from G. Silvestri

Les marqueurs d'activation:

Marqueurs cellulaires et marqueurs solubles

Marqueurs d'activation (1): Marqueurs cellulaires

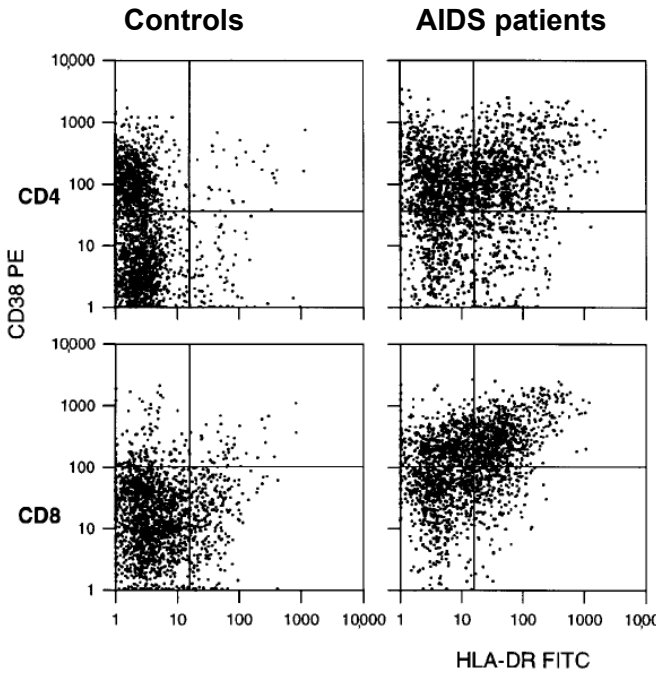
Cellules T activées:

- expression à leur membrane des marqueurs d'activation

HLA-DR (HLA de classe II), CD38, CD25, CD70, NKp44L

- Entrent en cycle cellulaire et expriment le marqueur intranucléaire Ki-67

- ont une apoptose accrue



Giorgi, JID 99

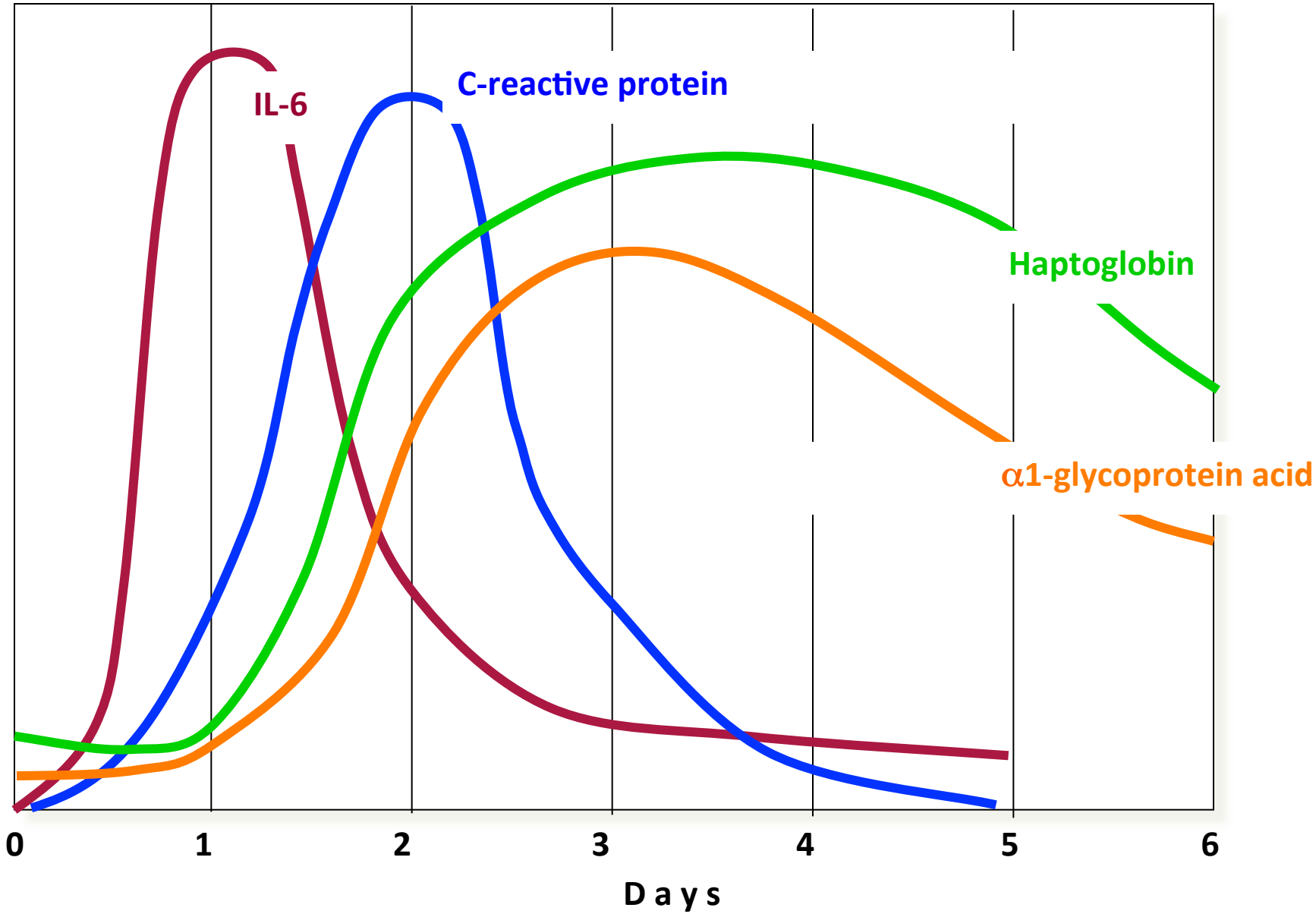
Marqueurs d'activation (2): Marqueurs solubles

- β2- microglobuline
- **CRP** (hs CRP): protéine de la phase aigüe
- **Cytokines: IL-6, IL-1ra**
- **D dimères** (marqueur d'une activité pro-coagulante)
- Molécules d'adhésion ICAM, VCAM (endothélium)
- **CD14s** (« translocation microbienne »; activation des monocytes)
- **CD163s** (relargué par les monocytes/macrophages activés)

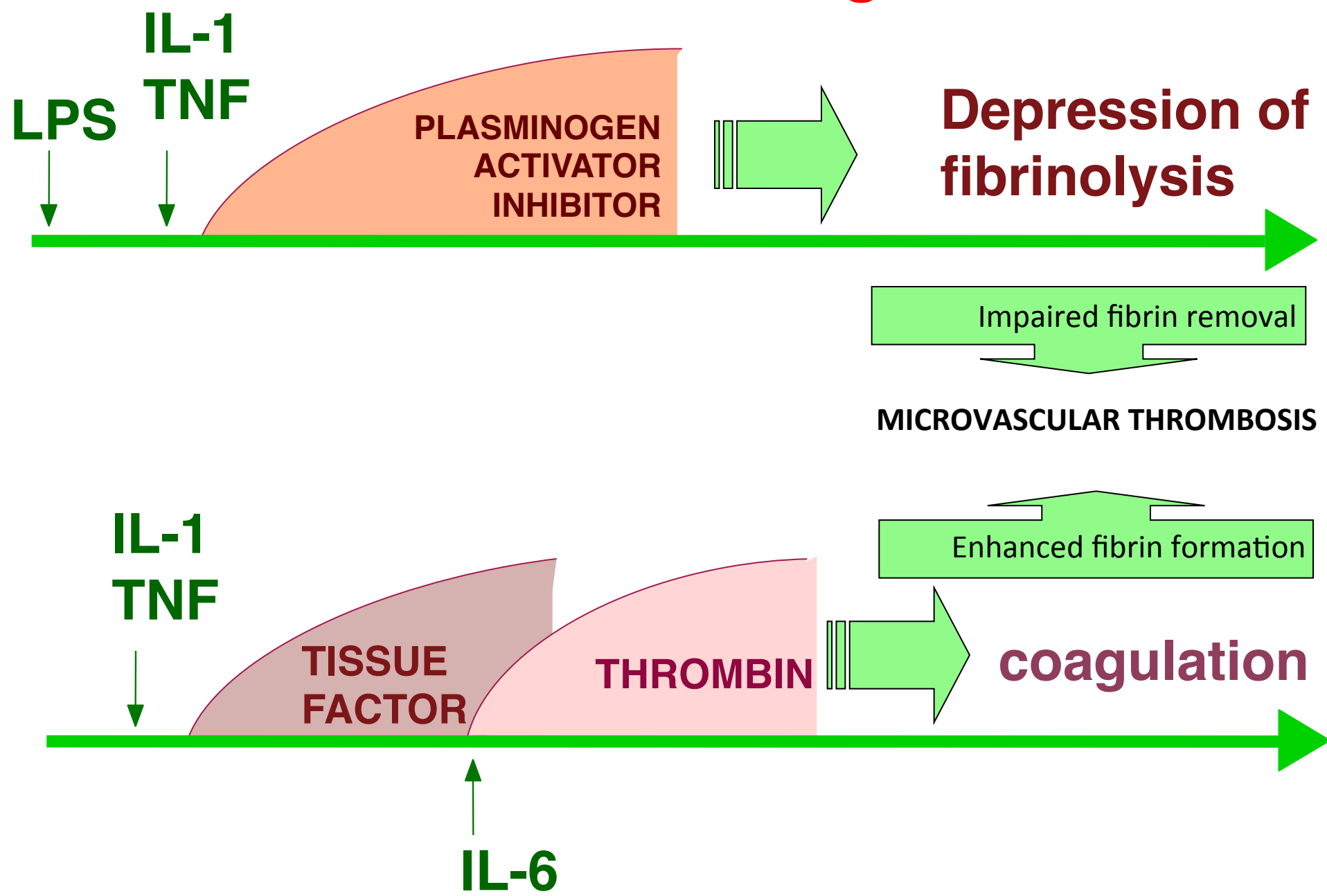
Kuller, PloS Med 2008, Sandler, JID 2011, Burdo, JID 2011

KINETICS OF IL-6 AND MAIN ACUTE PHASE PROTEINS

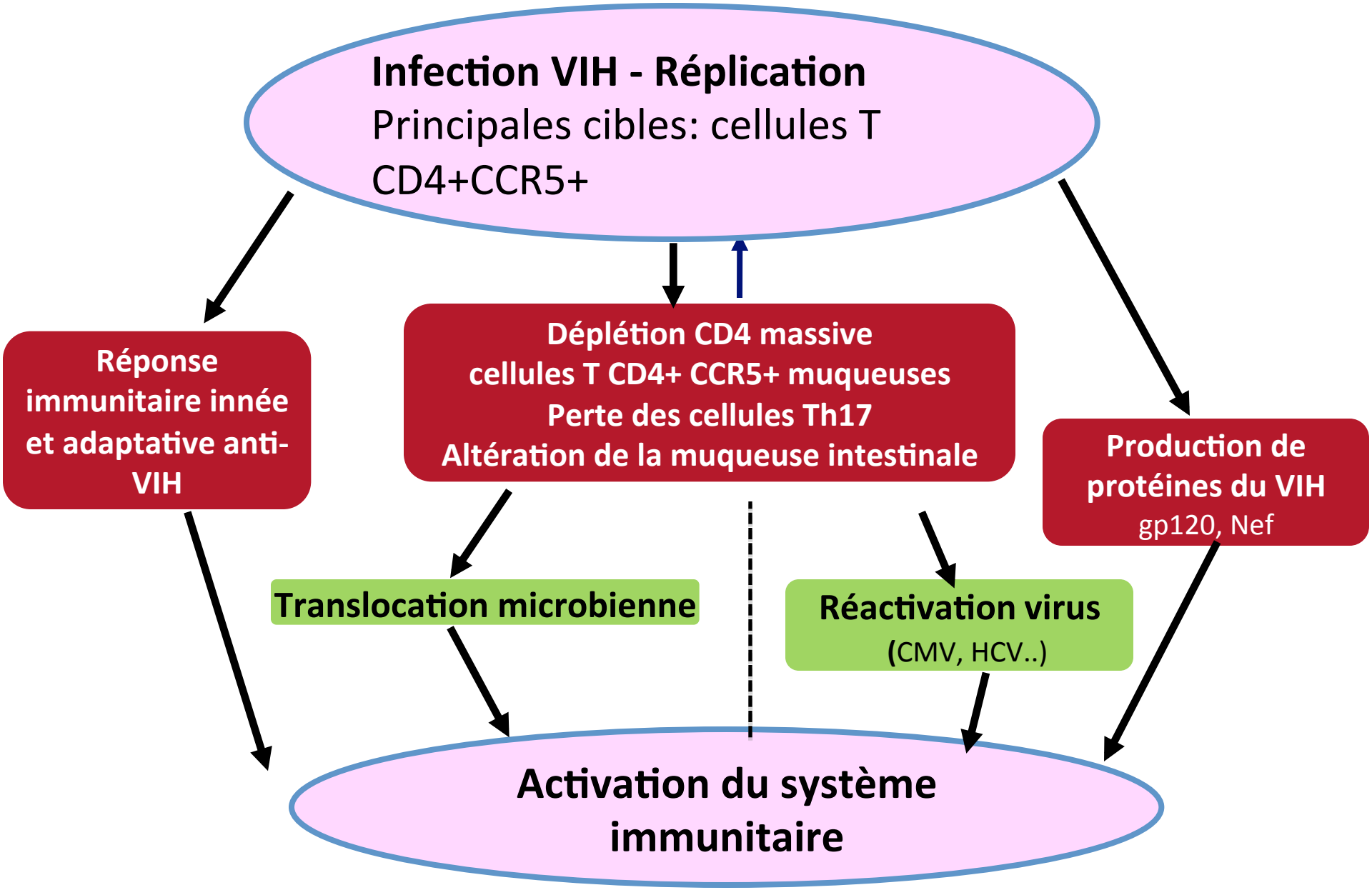
After an inflammatory insult on day 0



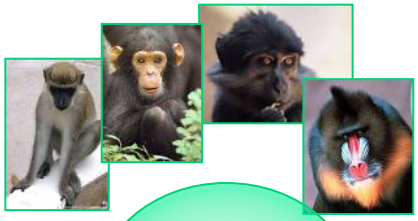
Inflammation et Coagulation



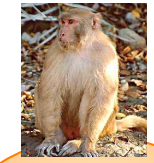
Mécanismes à l'origine de l'activation immunitaire



Adapted from Appay, J Pathol 2008



PNH
Chimpanzees
SM
AGM



PNH
Macaques

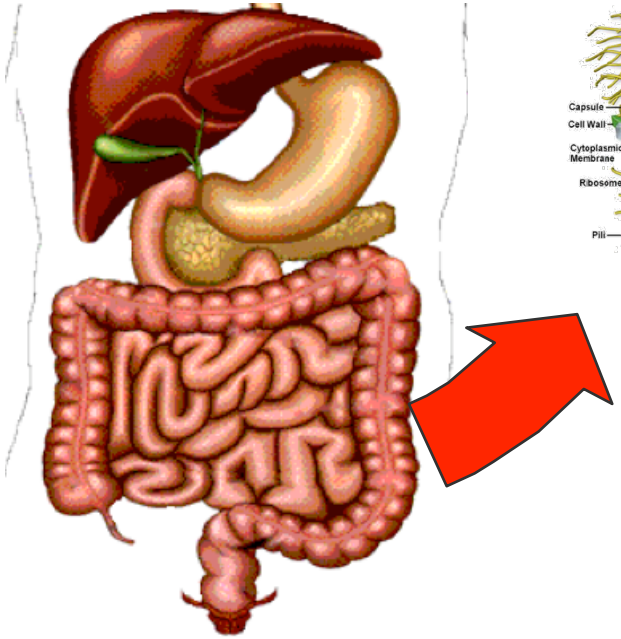
HUMAINS

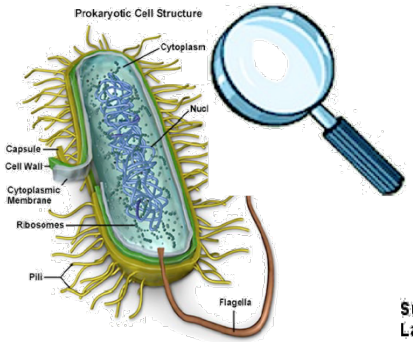
ASYMPTOMATIQUES

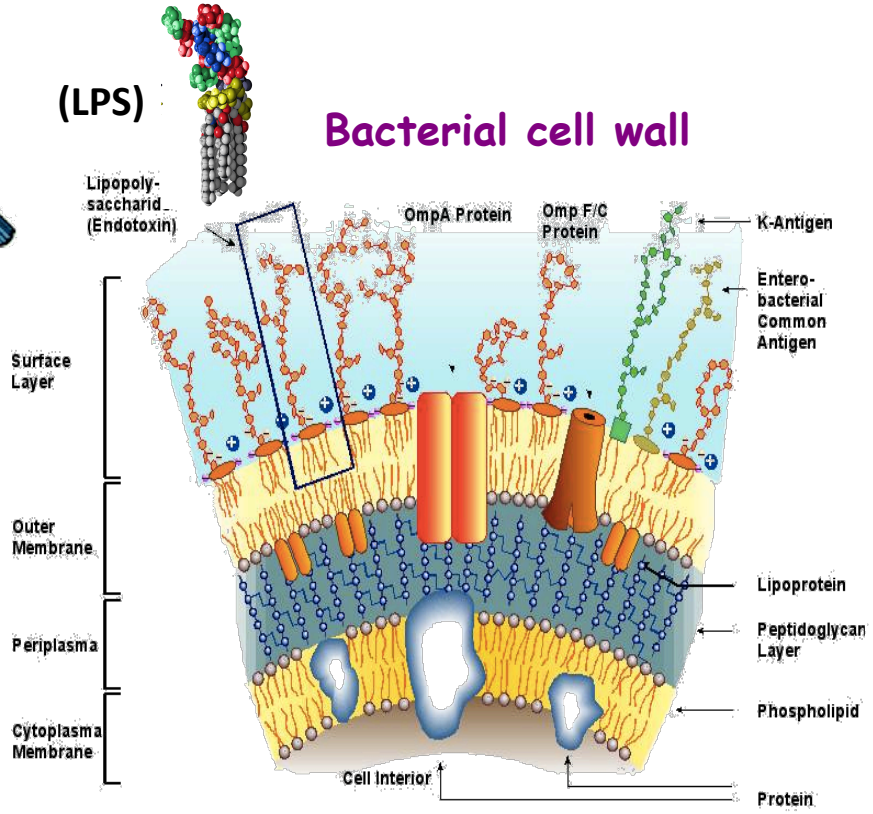
SIDA

Paramètre	Modèle non-pathogène SIV-AGM	Modèle pathogène HIV/SIV mac
Charge virale Sang, intestin	+++	+++
Activation chronique du système immunitaire	+	+++
Translocation microbienne	-	++

DETECTION OF ENDOTOXIN IN PLASMA AS A TESTIMONY OF BACTERIAL TRANSLOCATION







Sepsis **Successful cardiopulmonary resuscitation after cardiac arrest**

Cardiopulmonary bypass surgery **Abdominal aortic surgery**

Hemorrhagic shock **Liver transplantation** **Cirrhosis** **Thermal injury**

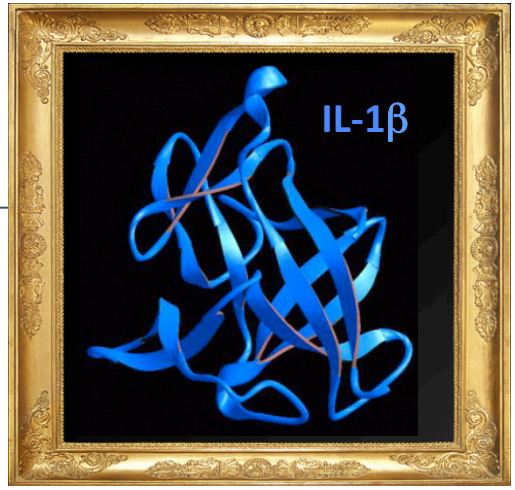
Pancreatitis **ARDS** **Lethal irradiation and bone marrow transplant**

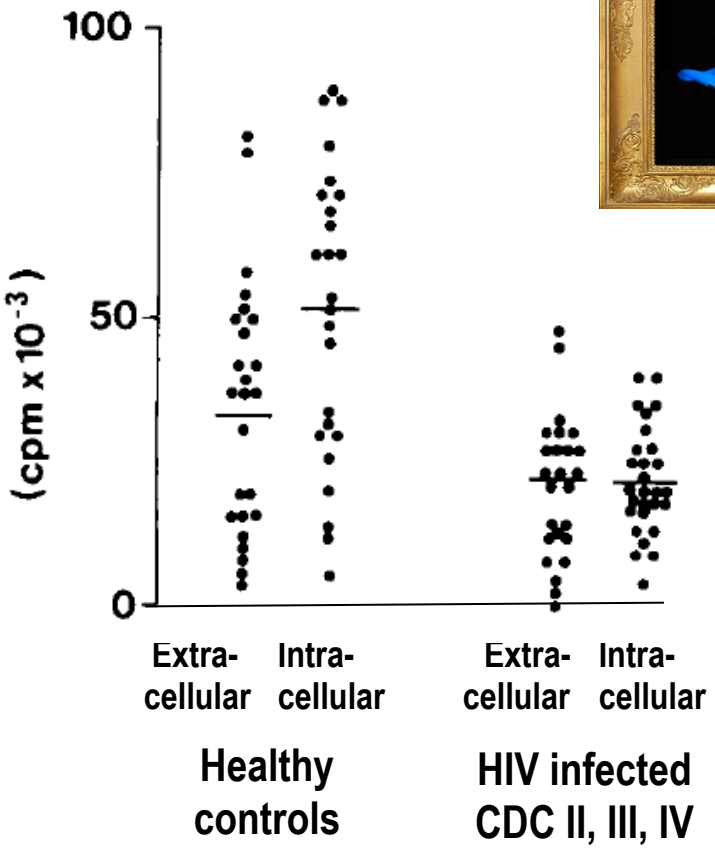
Inflammatory bowel disease **Chronic heart failure** **Traumatic brain injury**

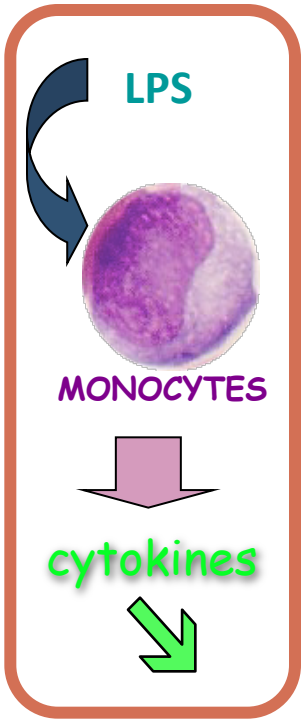
HIV

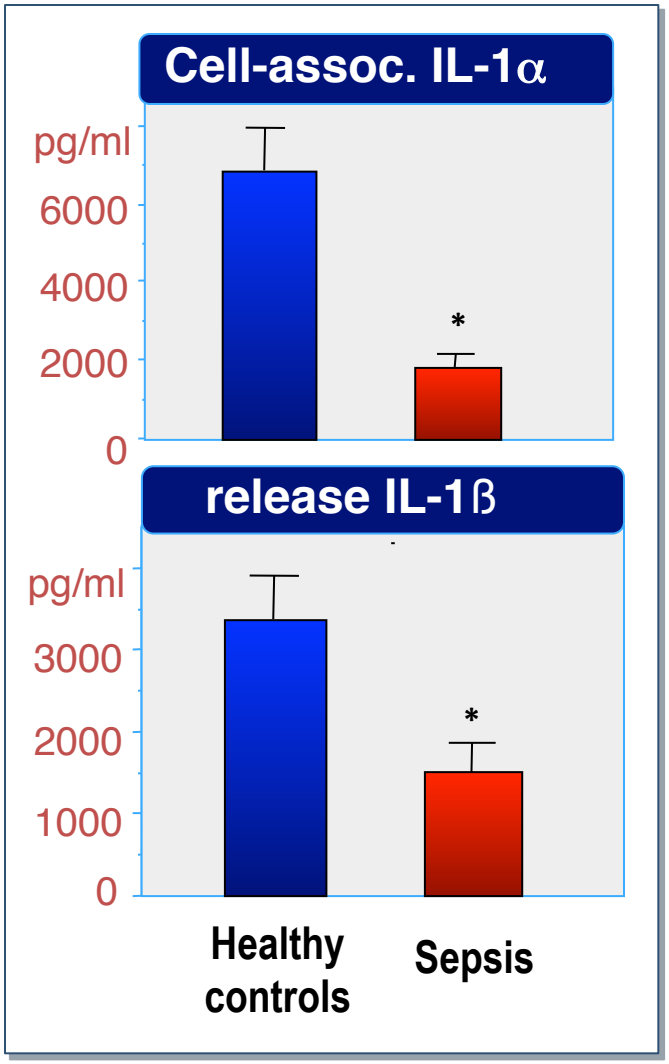
HIV

Sepsis





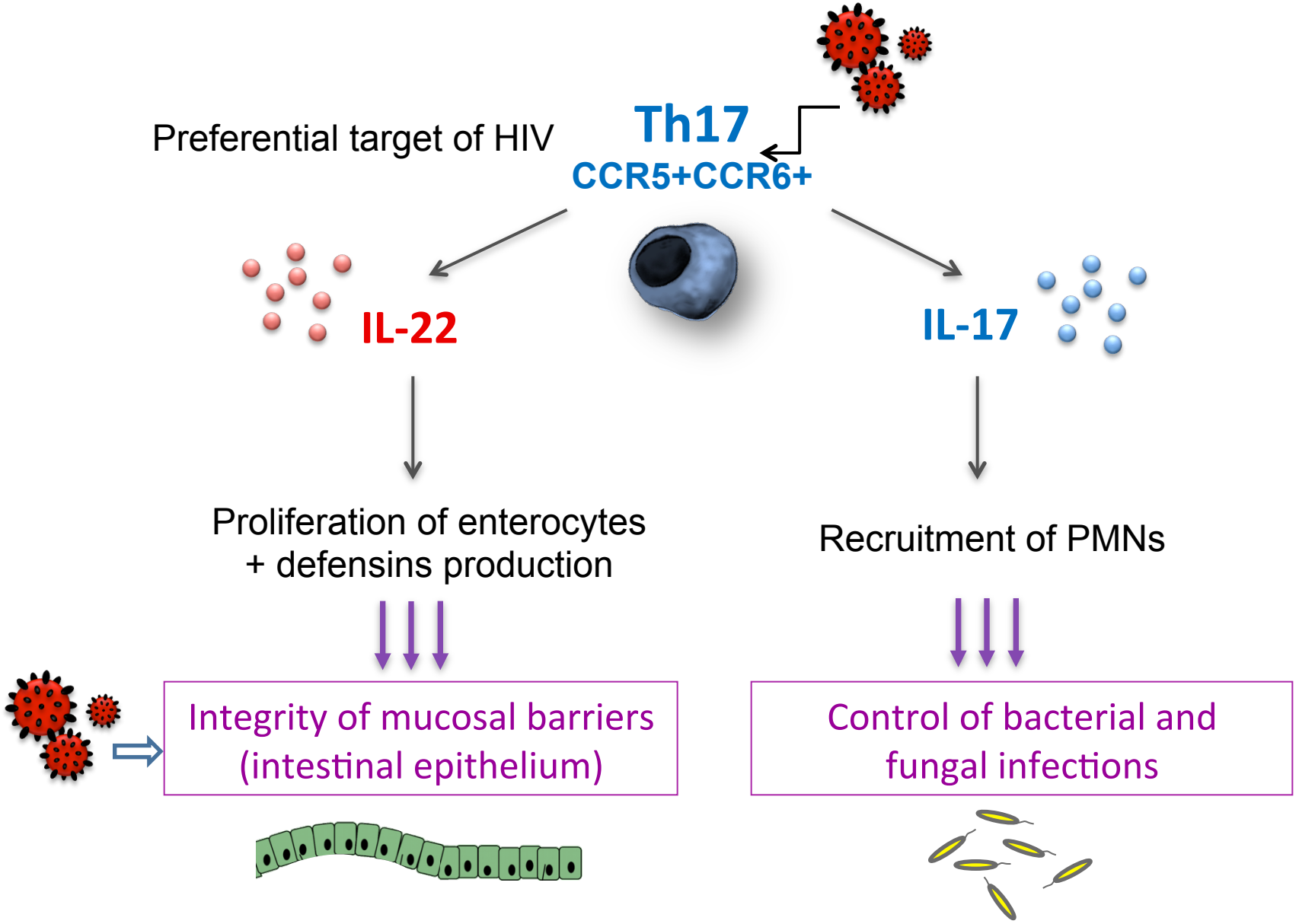




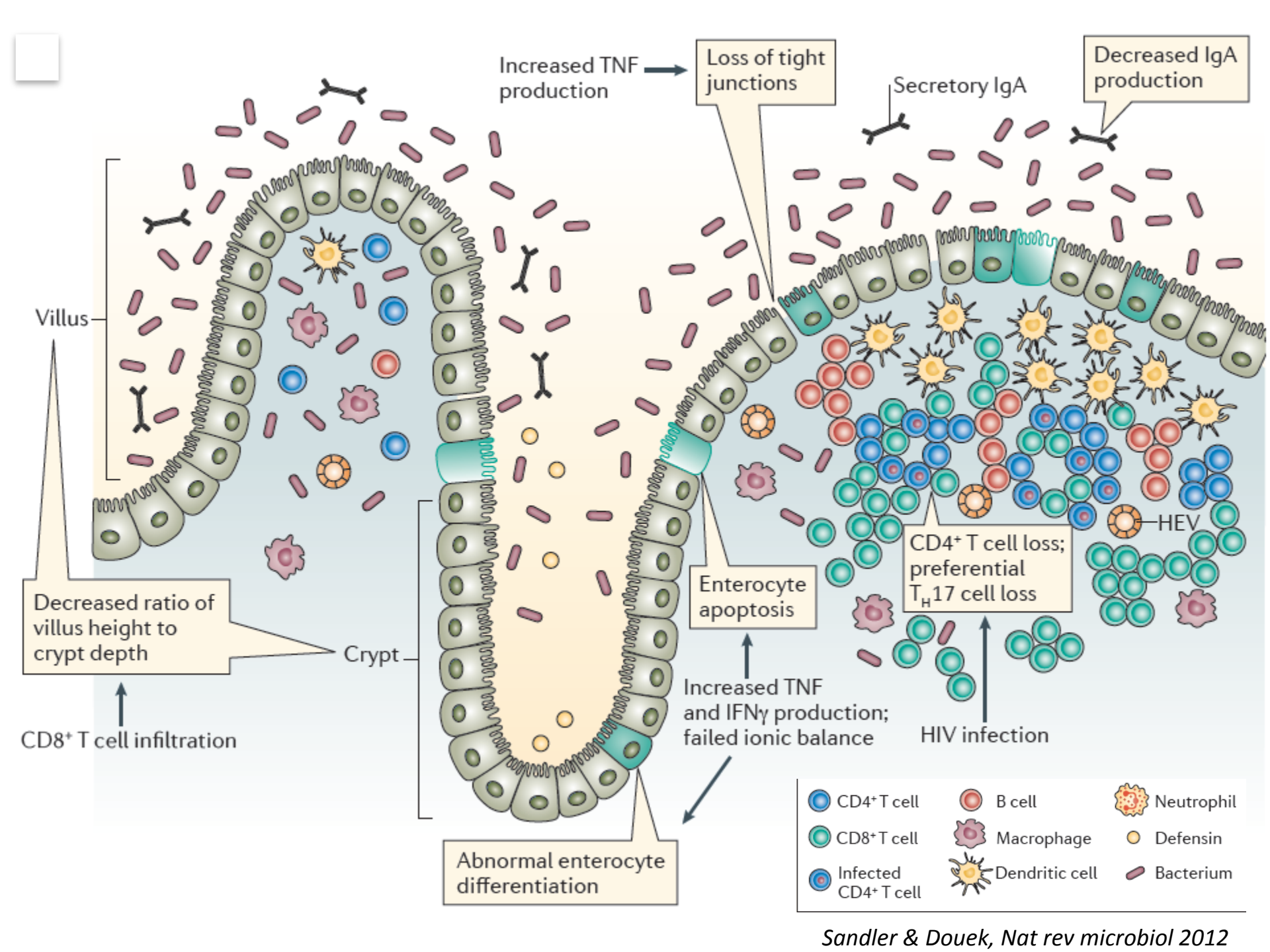
Weiss et al. *AIDS.* ***1989****; 3: 695-9.*

Muñoz et al. *J Clin Invest 1991,* ***88****: 1747*

Th17 cells: HIV and microbial translocation

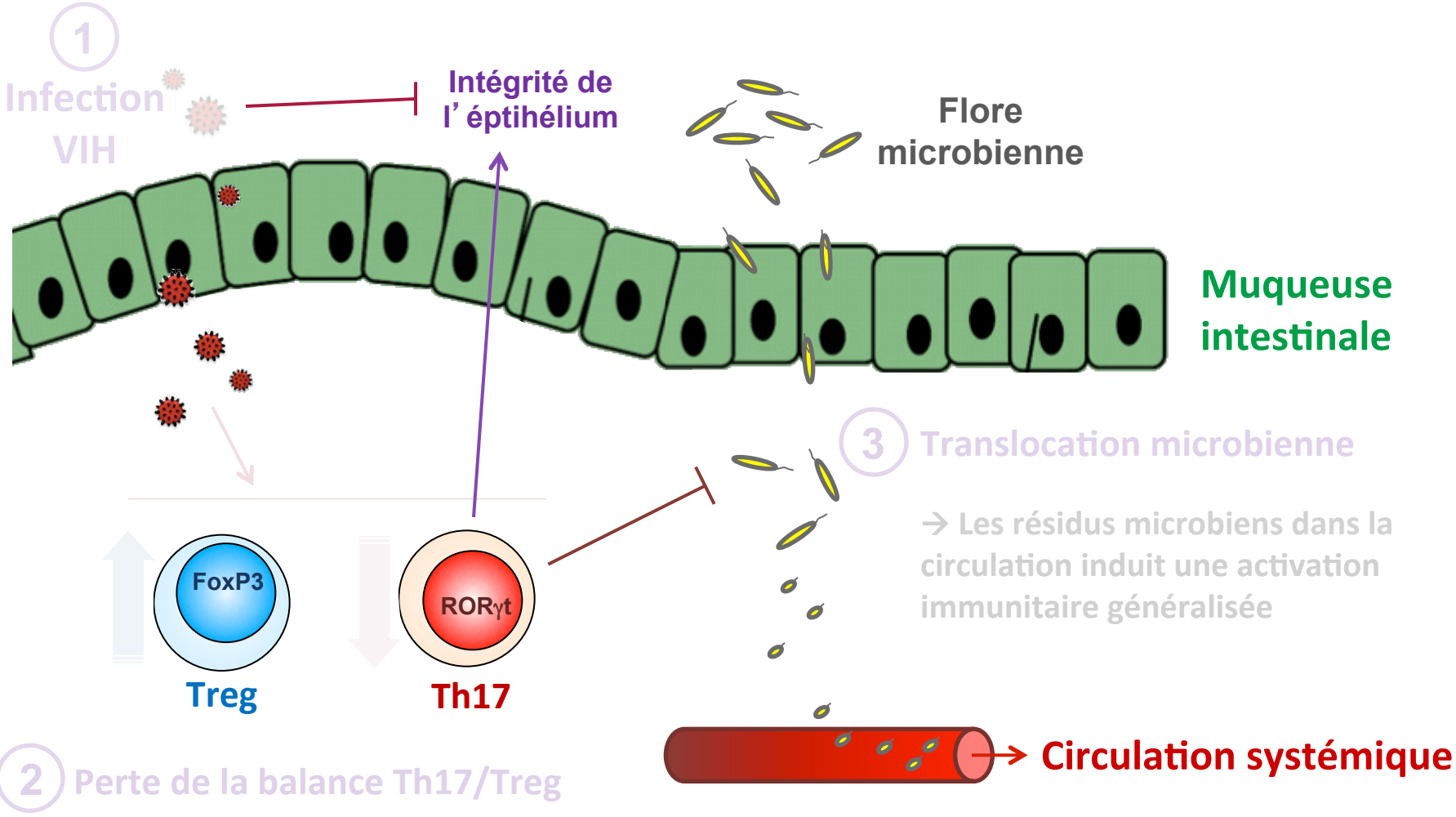


Epple, Gastroenterology 2010; Brenchley, Blood 2008; Cecchinato,Mucosal Immunol 2008; El Hed, JID 2010

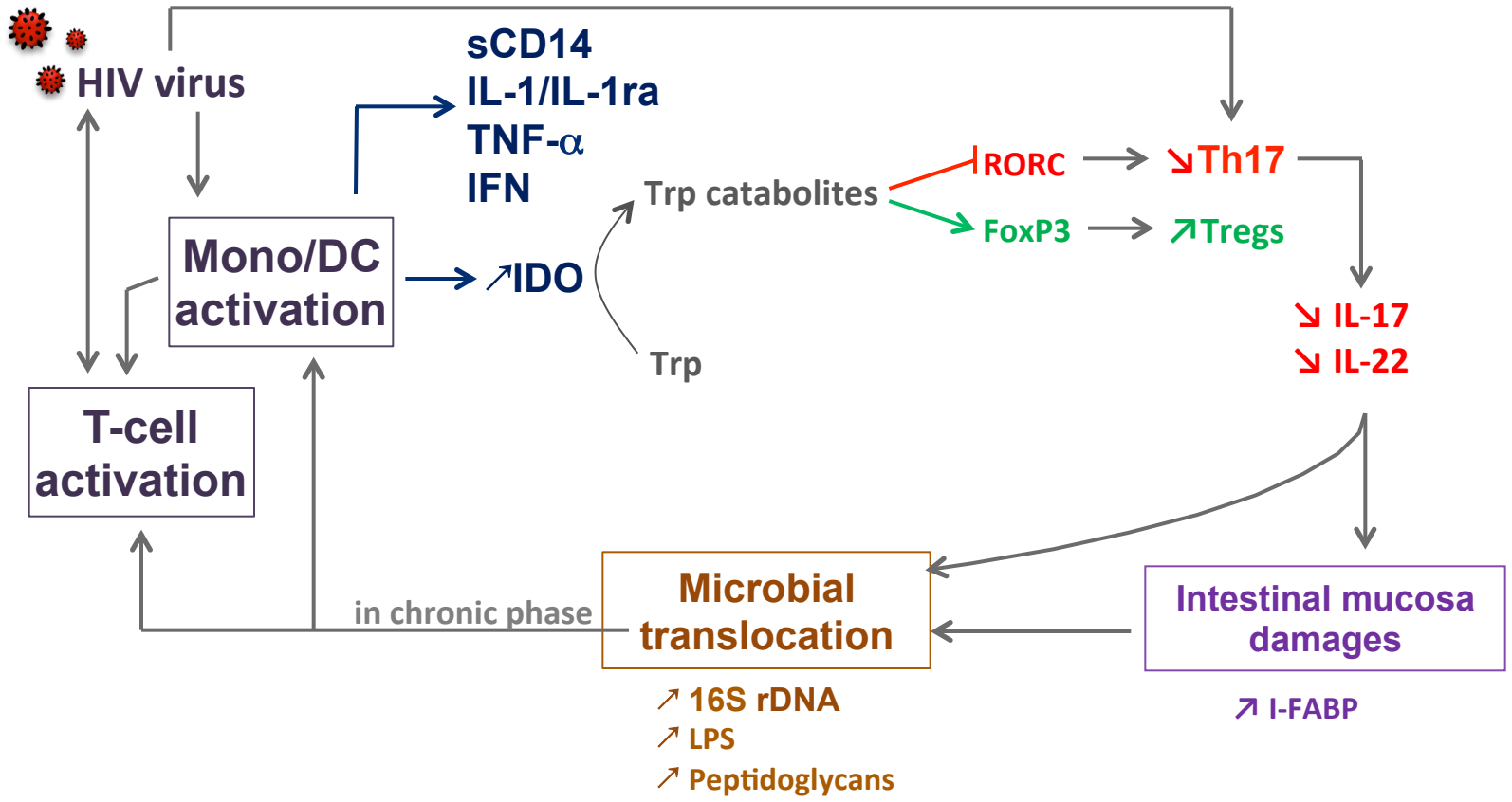


Sandler & Douek, Nat rev microbiol 2012

Th17 et translocation

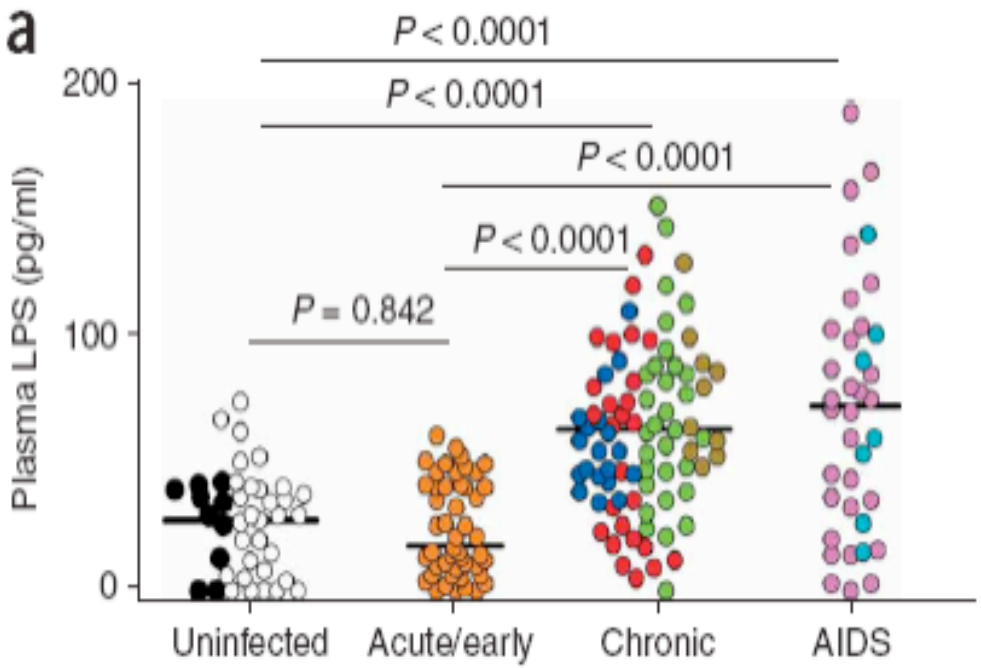


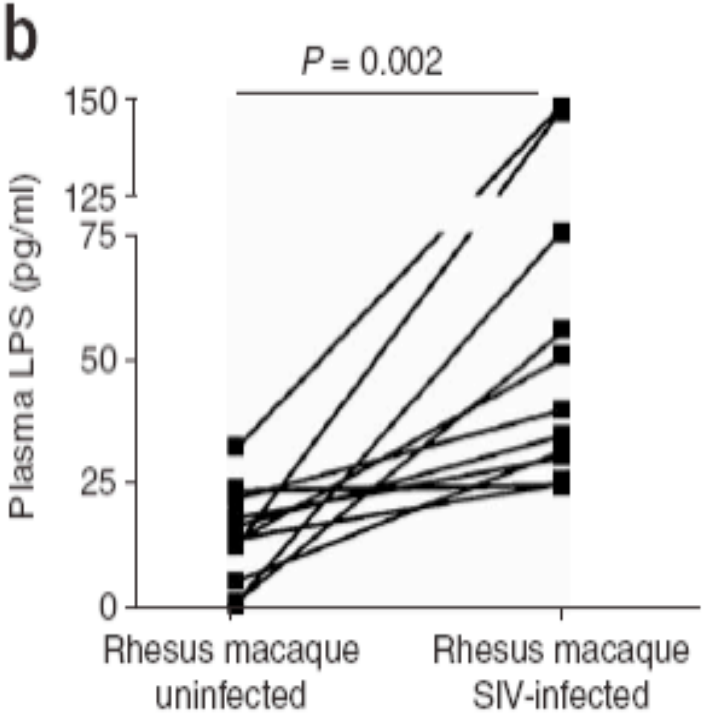
What is driving immune activation ?
A proposed model



Translocation microbienne au cours de l'infection HIV/SIV pathogène

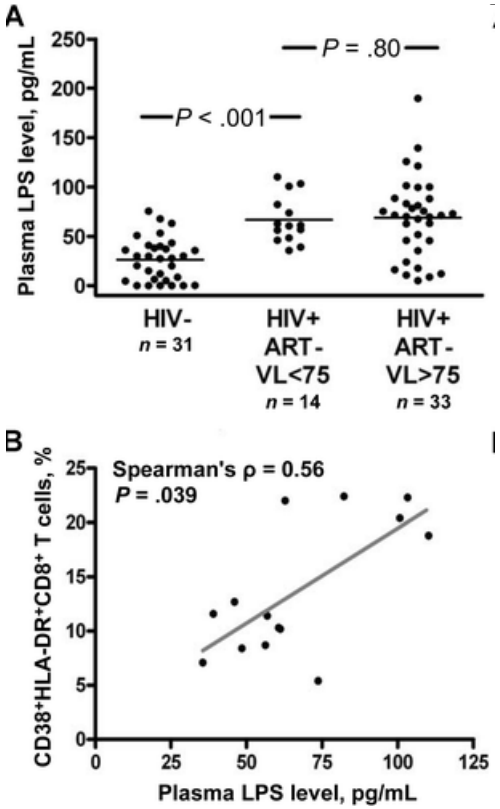
pathogène





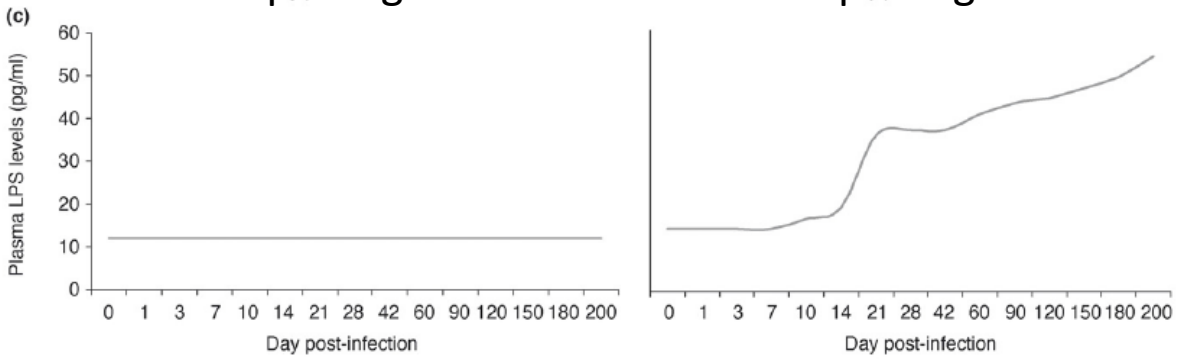
Brenchley et al, *Nat Med* **2006**

Relation translocation microbienne (LPS circulant) et activation lymphocytaire



non pathogènes

pathogène

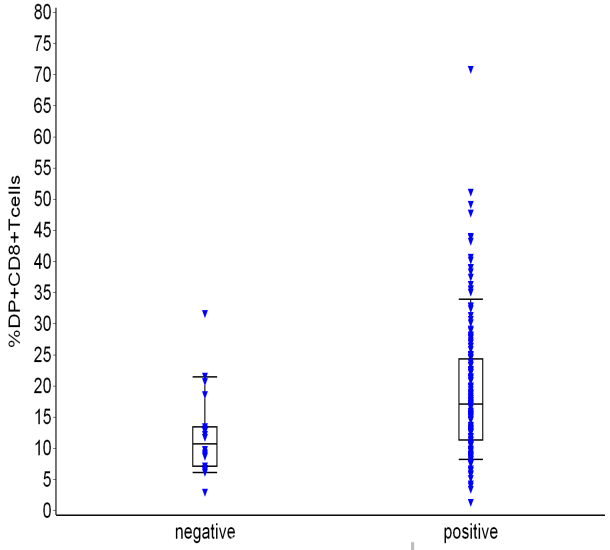


Pandrea et al, Trends in Immunology, 2008

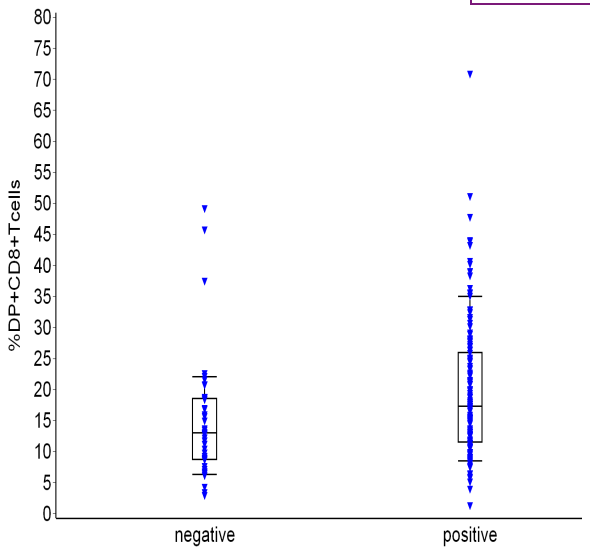
Hunt et al, JID, 2008

Rôle des réponses T anti-CMV dans l'activation immunitaire persistante sous ART ?

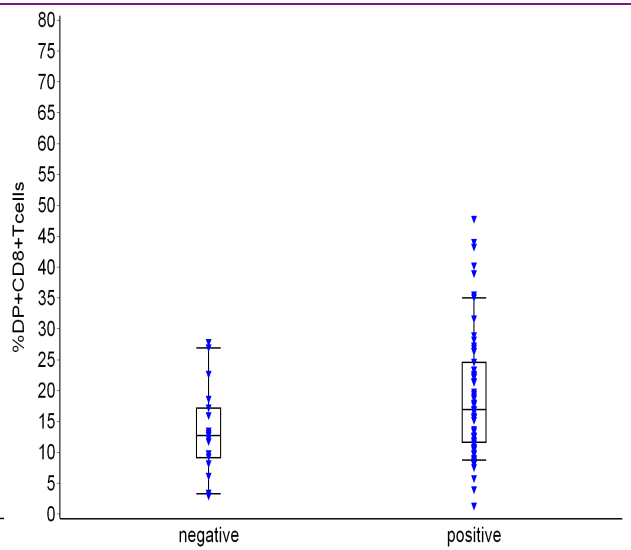
QuantiFeron-CMV positive (if > 0.2 IU/mL)	148	(77.5)
CMV-Tetramers *pp65 positive*	64	(78.0)
Elispot-CMV *pp65 positive*	170	(89.0)



ELISPOT



QF-CMV



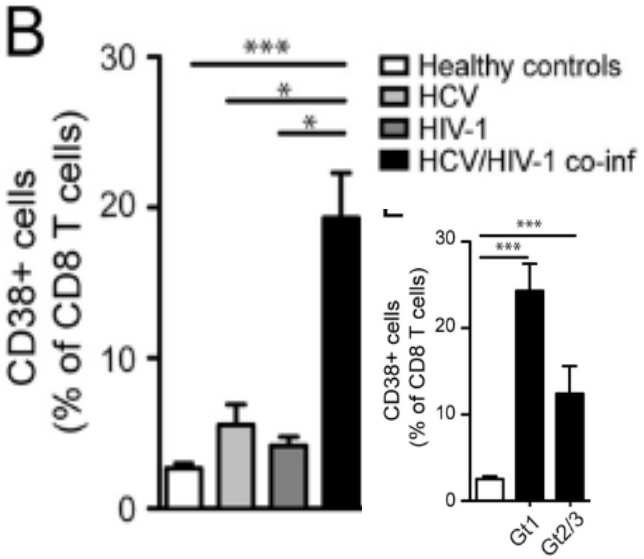
Tetramères pp65

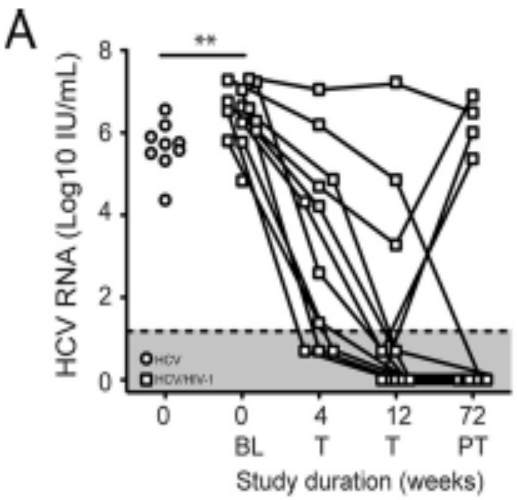
- **Patients indétectables >5 ans, CD4+>500/µl, nadir CD4+ =200/µl**
- **Réponse immunitaire spécifique du CMV significativement associée à l'activation LT mesurée par % of DP+HLA-DRCD38+ T cells**

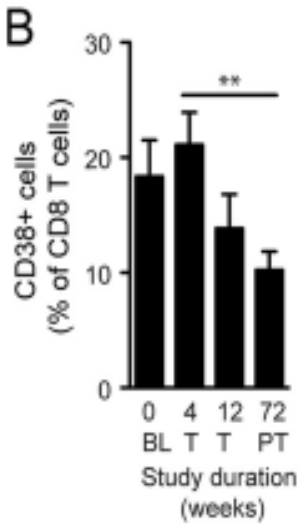
  *indépendamment de l'âge, CD4 cell count, Treg and 16SrDNA

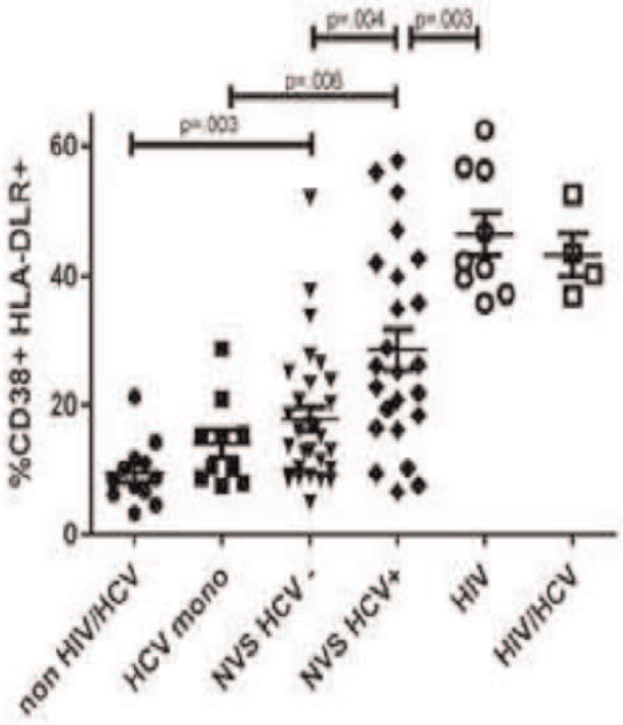
Wittkop L, Pellegrin I., CROI 2012, JID in press

Rôle du VHC









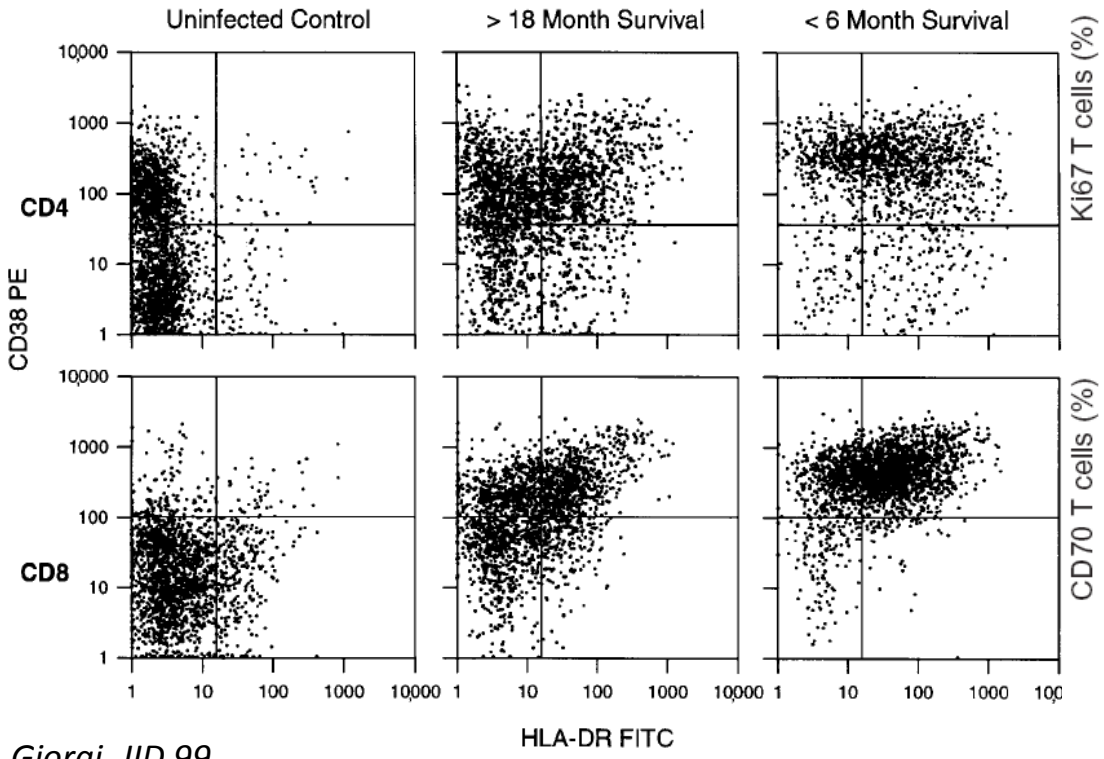
Sajadi, AIDS 2012

Gonzalez VD, JVirol 2009
Massanella, Antiviral Therapy 2010

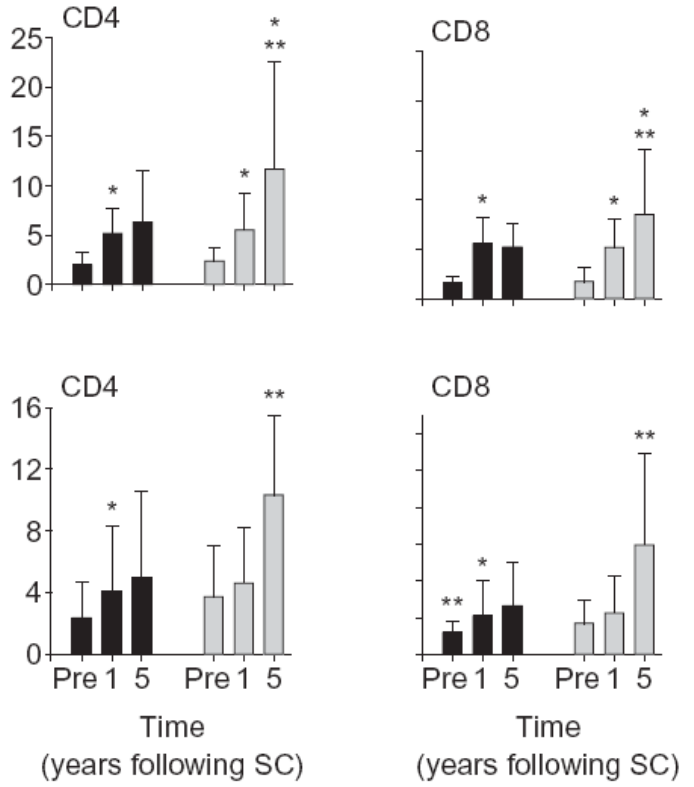
Conséquences de l'activation/ inflammation chronique (1)

Activation & Progression

Activation Lymphocytaire T CD4 et CD8 et progression/survie



Giorgi, JID 99



Le niveau d'activation lymphocytaire T CD8 est un des meilleurs marqueurs de progression vers le SIDA, indépendant de la charge virale

Slow progressors
Rapid progressors

Hatzenberg et al, AIDS 2003

Plasma Levels of Soluble CD14 Independently Predict Mortality in HIV Infection

Netanya G. Sandler,[1] Handan Wand,[10] Annelys Roque,[1] Matthew Law,[10] Martha C. Nason,[3] Daniel E. Nixon,[5] Court Pedersen,[8] Kiat Ruxrungtham,[9] Sharon R. Lewin,[11,12,13] Sean Emery,[10] James D. Neaton,[6] Jason M. Brenchley,[2] Steven G. Deeks,[7] Irini Sereti,[4] and Daniel C. Douek,[1] for the INSIGHT SMART Study Group

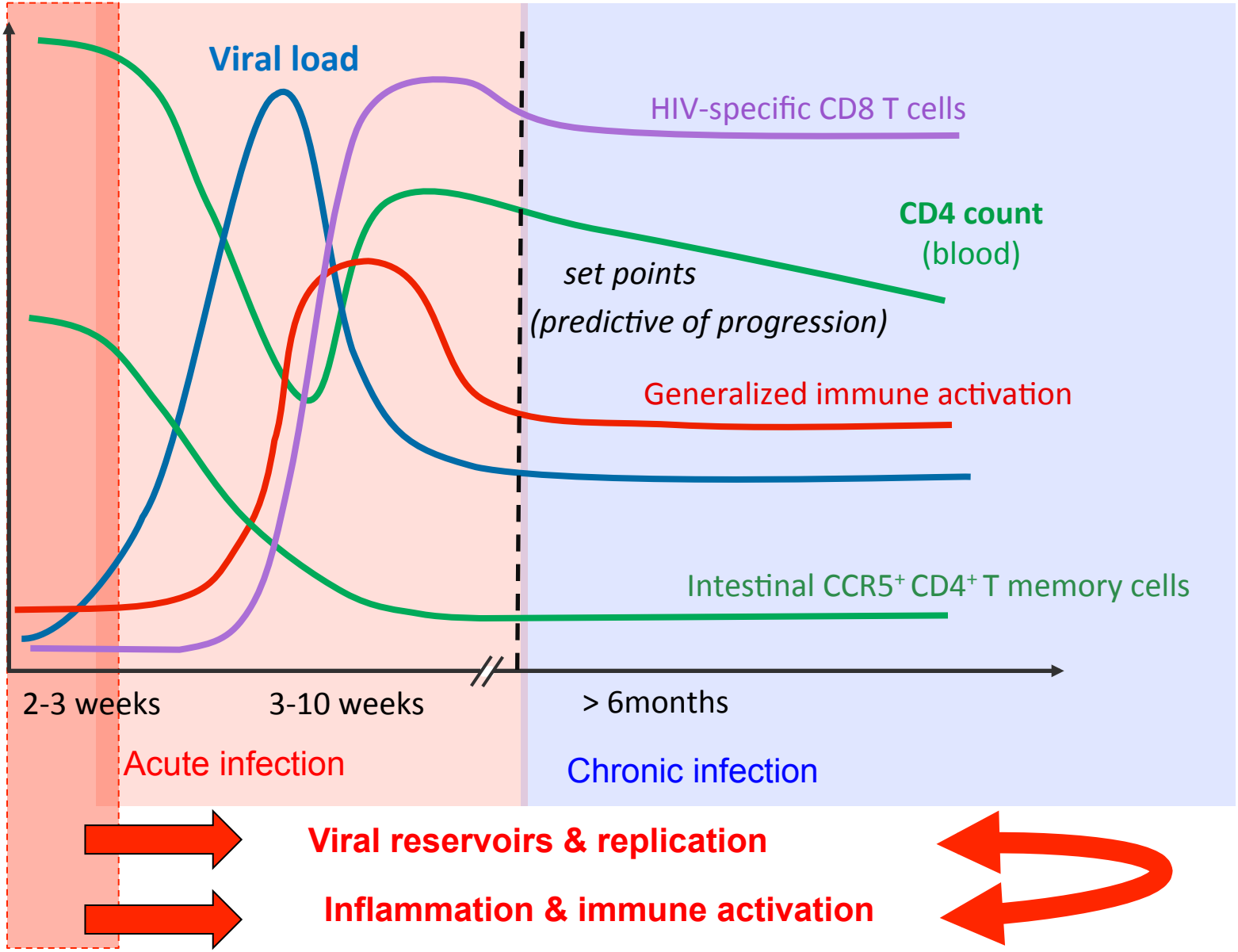
The Journal of Infectious Diseases 2011;203:780–790

Biomarker	<25th Percentile(Reference)	25th – 49th Percentile OR (95% CI)	*P*	50th – 74th Percentile OR (95% CI)	*P*	≥74th Percentile OR (95% CI)	*P*
sCD14 (×10^6 pg/mL)							
N (case patients/control subjects)	10/46	16/39		21/35		27/28	
Univariate	1.0	2.1 (0.8–5.7)	.12	3.3 (1.3– 8.6)	.01	6.0 (2.2–16.1)	<.001
Adjusted—risk factors[a]	1.0	2.8 (0.8–10.0)	.10	2.7 (.8–9.0)	.11	8.0 (2.0–31.9)	.003
Adjusted—inflammation[b]	1.0	2.3 (0.7–8.1)	.18	2.9 (.9–9.4)	.07	4.1 (1.2–13.9)	.02

Table 3. The Increased Risk for Mortality Conferred by Higher sCD14 Levels Does Not Differ between Treatment Arms

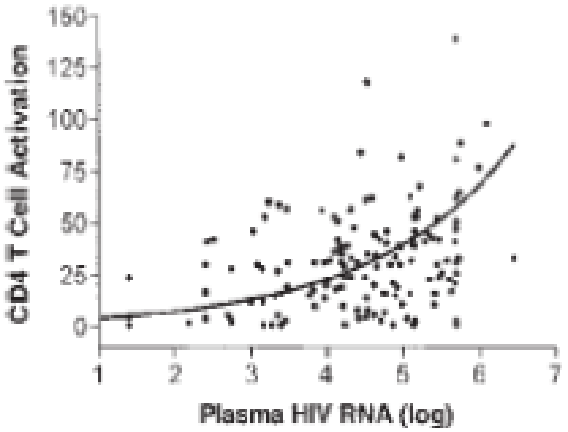
Biomarker	Drug conservation arm OR (95% CI)[a]	*P*	Viral suppression arm OR (95% CI)	*P*	*P* for interaction
sCD14 level, ×10^6 pg/mL	3.5 (1.5–8.3)	.004	2.0 (0.8–5.4)	.15	.43
LPS, pg/mL	1.0 (0.6–1.7)	.96	0.7 (0.3–1.7)	.40	.63
I-FABP, pg/mL	0.9 (0.4–2.1)	.84	2.3 (0.6–8.8)	.19	.58
16S rDNA, copies/μL	0.9 (0.4–2.2)	.90	0.5 (0.2–1.4)	.21	.26
EndoCAb, MMU/mL	1.1 (0.8–1.6)	.49	0.9 (0.6–1.4)	.66	.57

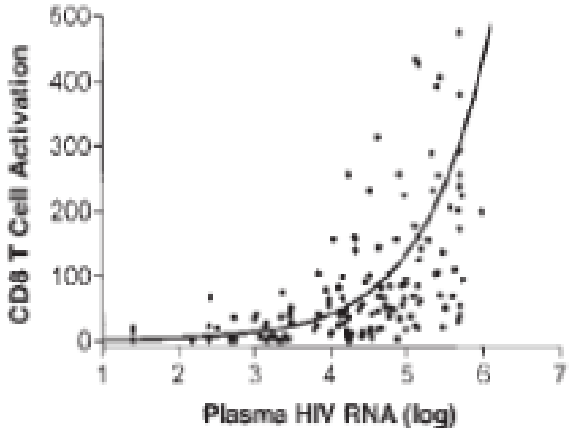
Evénements précoces post-primo-infection



Deeks et al Blood 2004

Le set point immunologique en post-primo-infection prédit la déplétion lymphocytaire T CD4





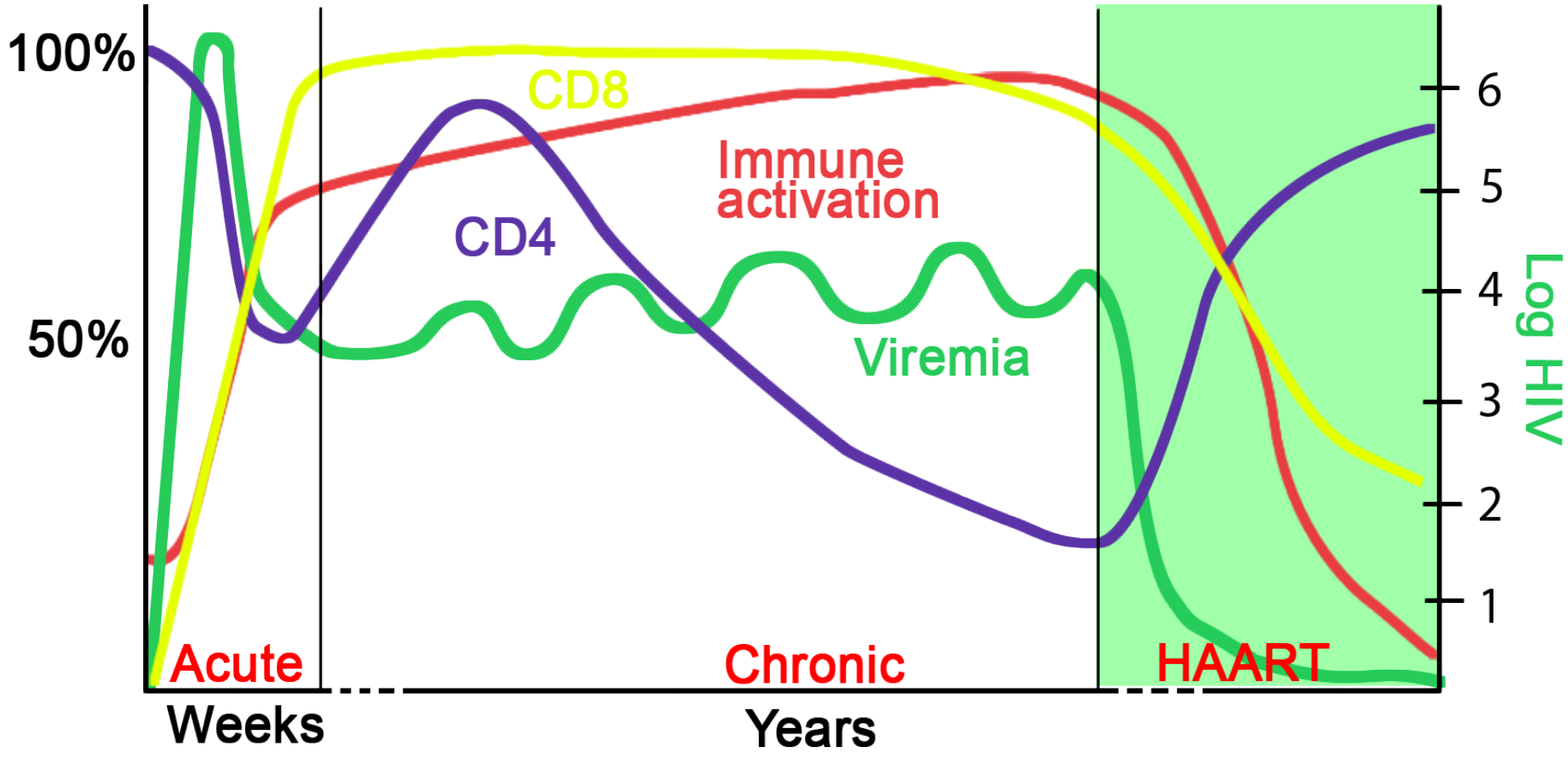
Parameter	Estimate	Standard error	*P*
Univariate model			
Plasma HIV RNA level, log_{10}	−0.032	0.007	< .001
$CD8^+$ T-cell activation, log_{10}	−0.049	0.014	< .001
$CD4^+$ T-cell activation, log_{10}	−0.039	0.017	.021
Multivariate model			
Intercept	2.921	0.042	< .001
Plasma HIV RNA level, log_{10}	−0.026	0.009	.005
$CD8^+$ T-cell activation, log_{10}	−0.033	0.015	.027
$CD4^+$ T-cell activation, log_{10}	−0.013	0.019	.474

Deeks Blood 2004

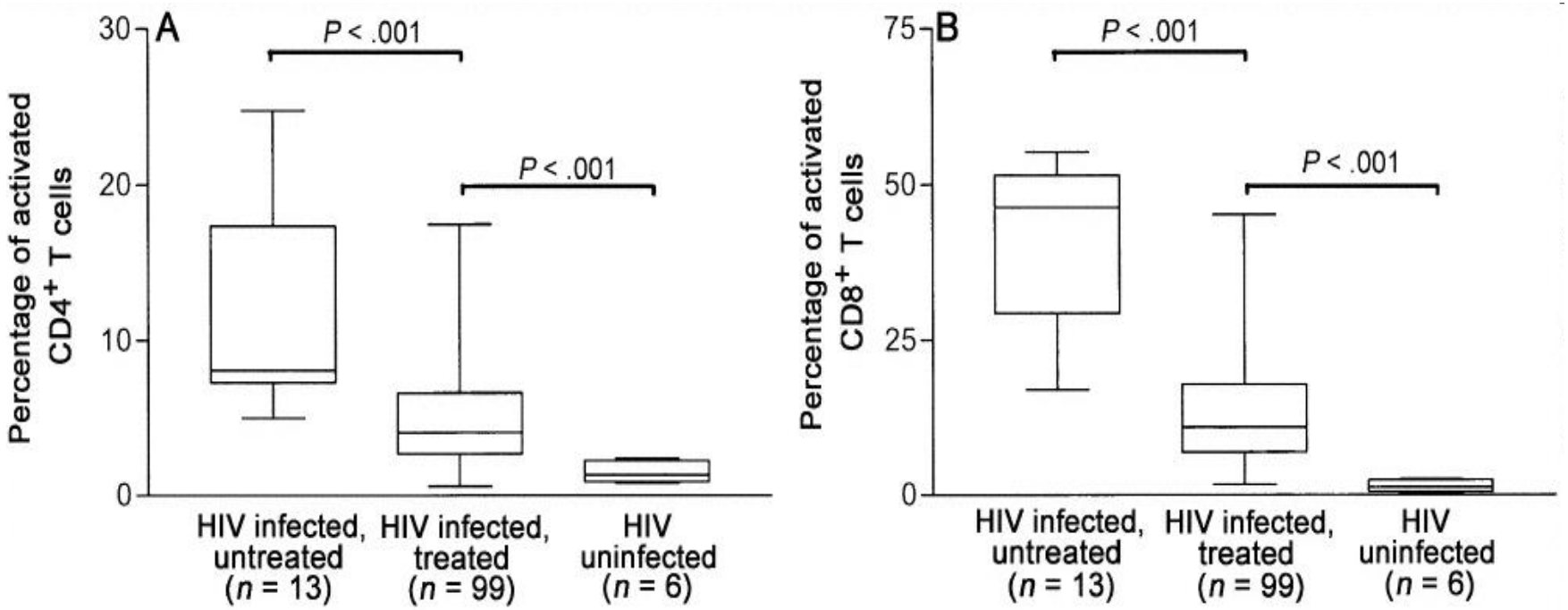
Conséquences de l'activation/ inflammation chronique (2)

Patients à charge virale contrôlée

Impact du traitement ARV sur l'histoire naturelle de l'infection VIH

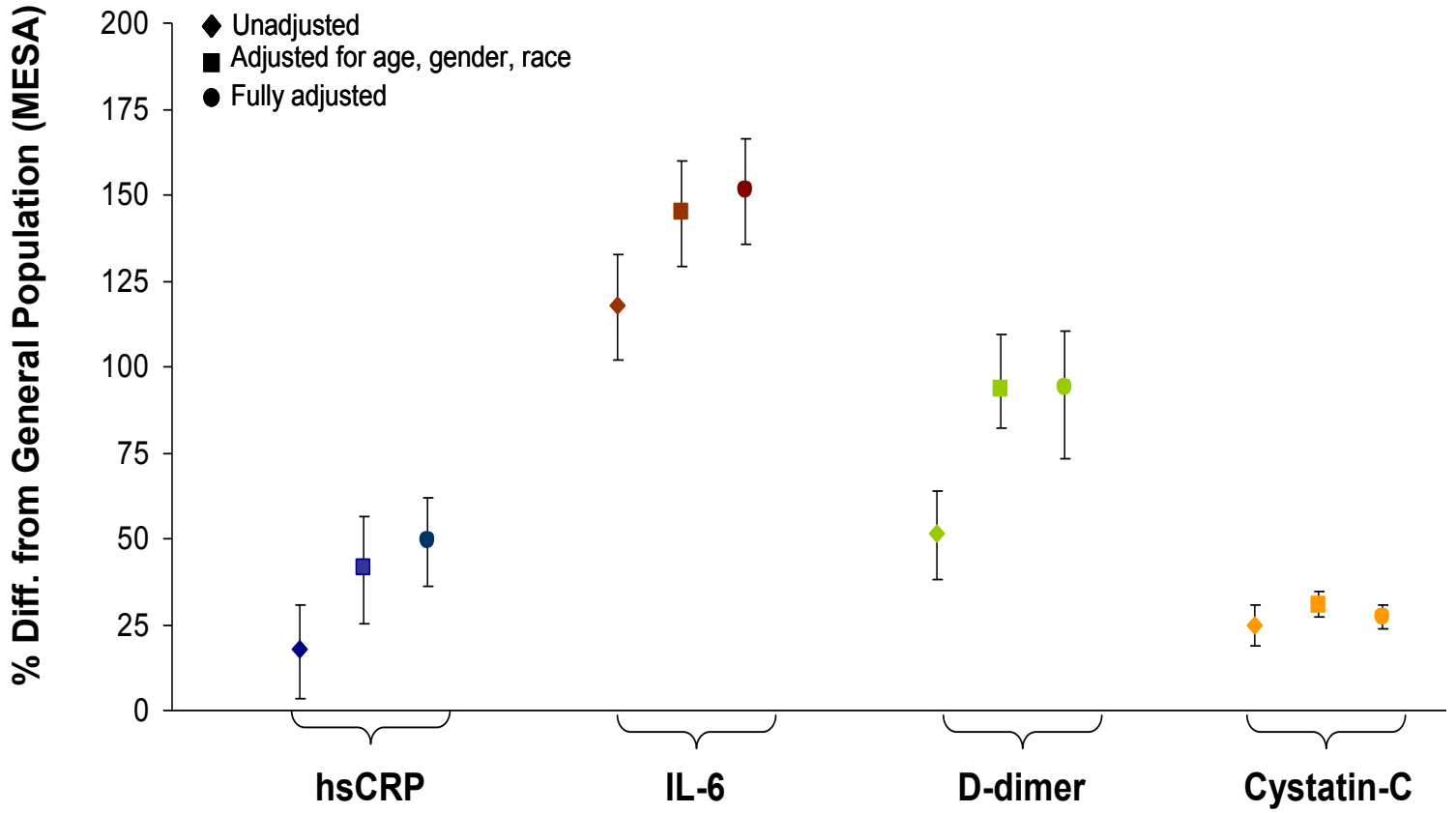


Persistance d'une activation résiduelle sous traitement ARV



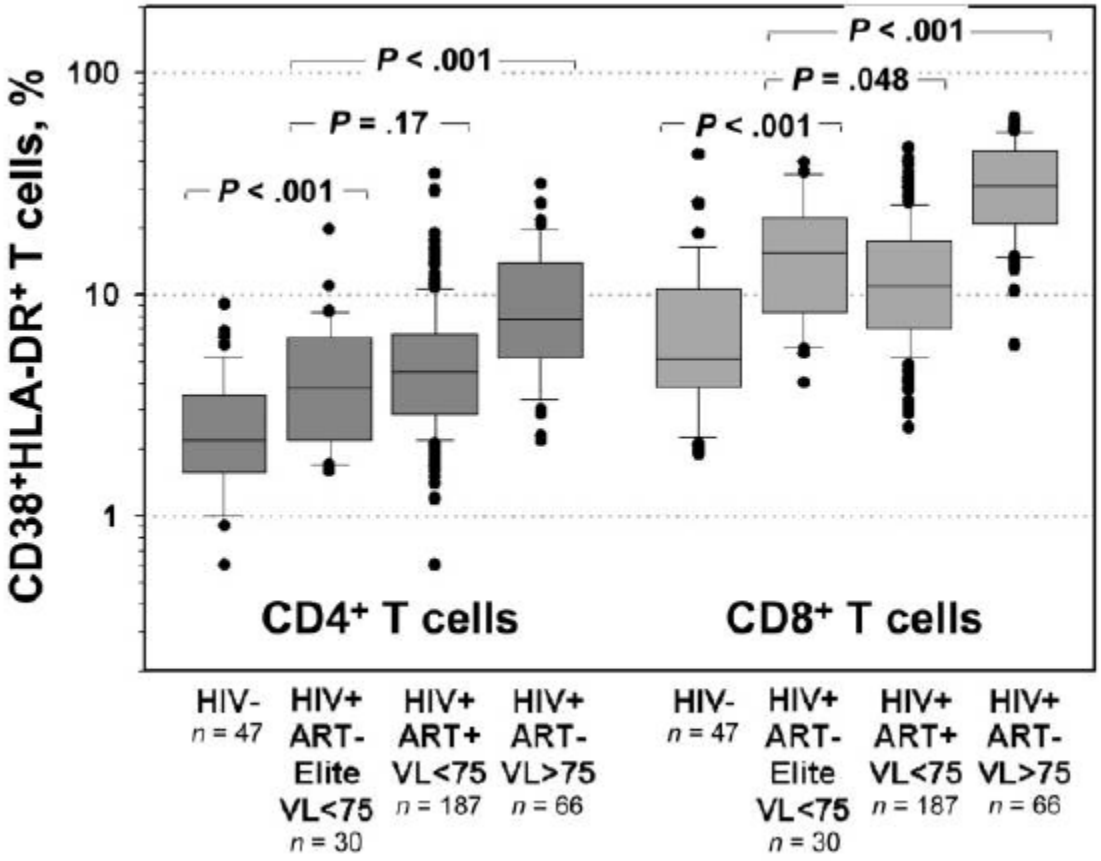
Hunt et al, JID, 2003

Malgré un traitement ARV actif sur le long-terme, les marqueurs inflammatoires solubles demeurent élevés



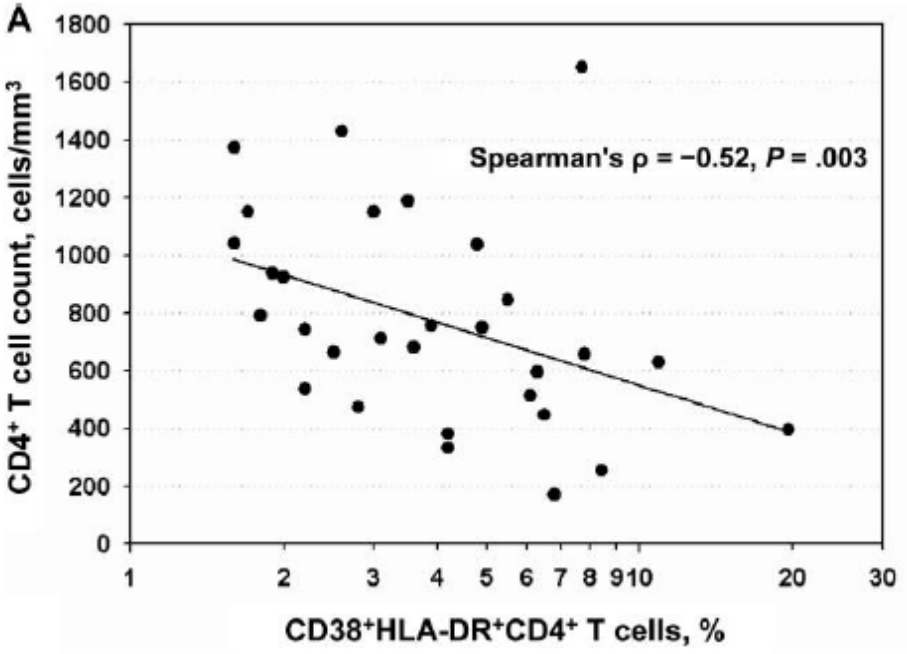
Neuhaus et al JID 2010; 201(12): 1788, Folsom et al Am J Hematol 2009; 84(6):349, Harris et al Am J Med 1999; 106:506, and unpublished data (SMART adjusted ORs in table)

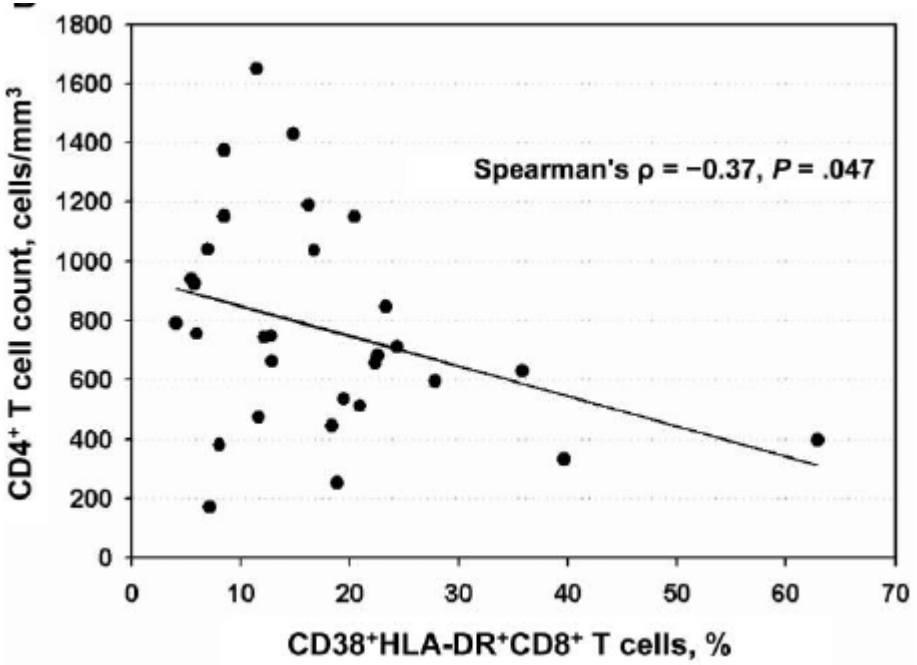
Activation chronique du système immunitaire chez les HIV contrôleurs



Hunt, JID 2008

Relation activation lymphocytaire T et LT CD4 circulants





n = 30 HIV+ avec CV < 75 c/mL

Hunt, JID 2008

CANCER

CHRONIC VIRAL INFECTIONS HIV

Inflammation

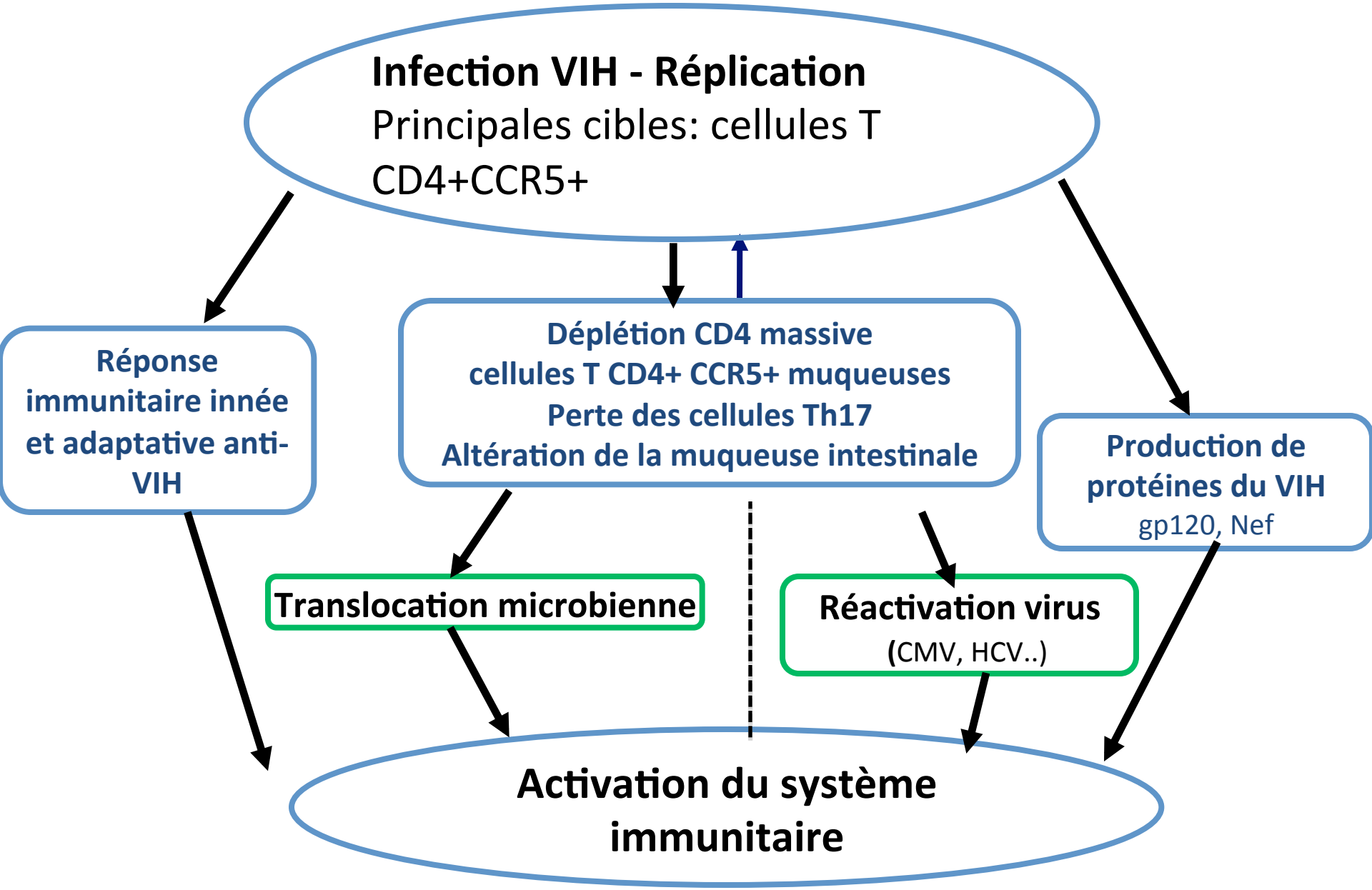
Cardio-Vascular Diseases

CHRONIC INFLAMMATORY DISEASES

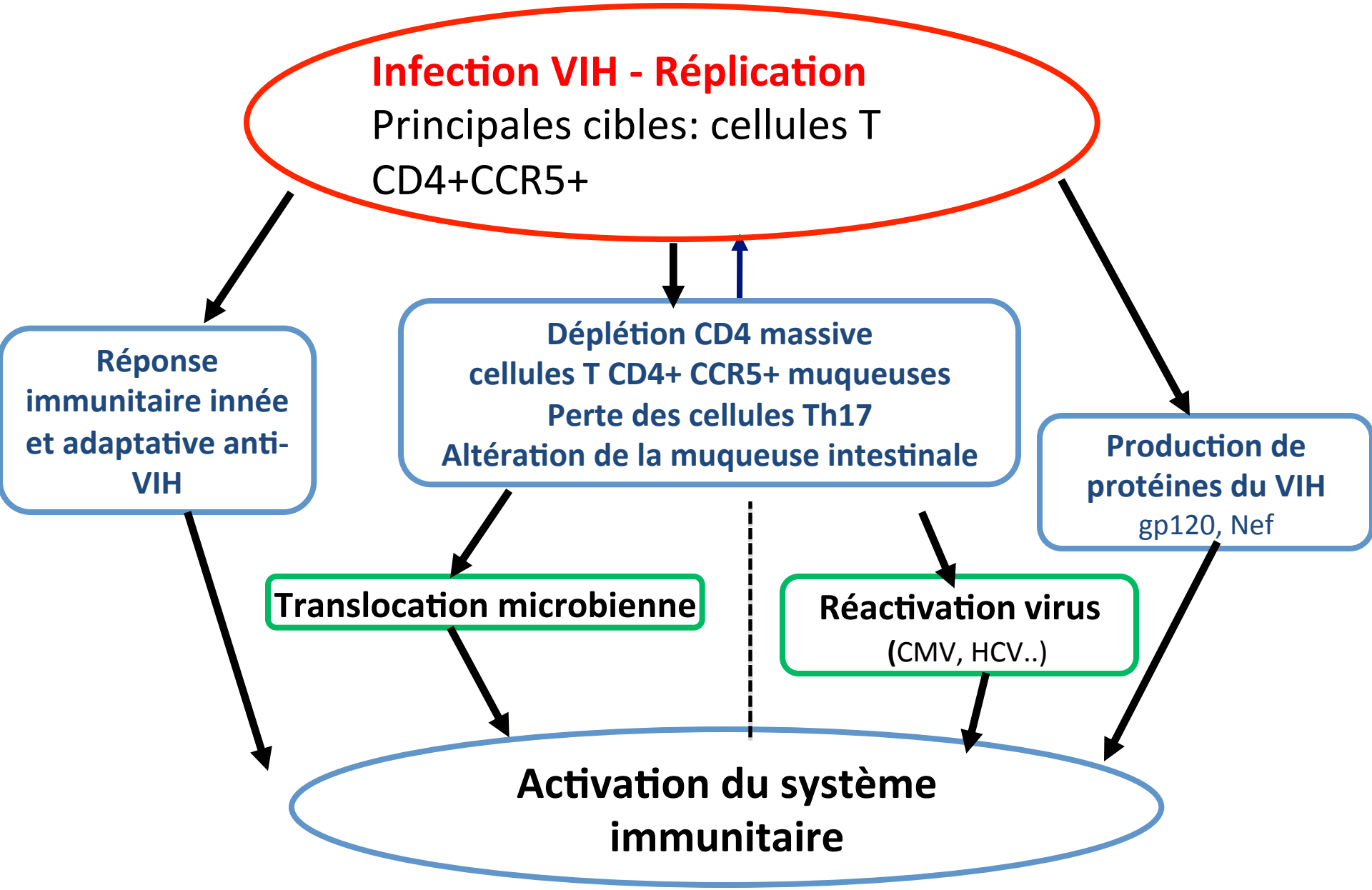
AUTO-IMMUNE DISEASES

Neuro-degeneratives

Quelles interventions possibles pour cibler l'activation ??



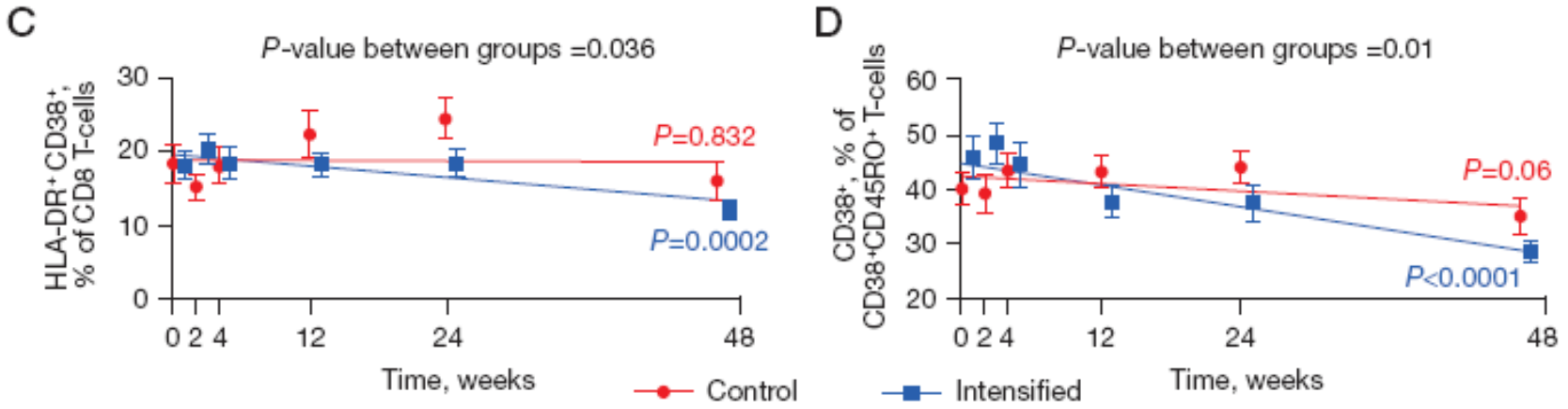
Adapted from Appay, J Pathol 2008



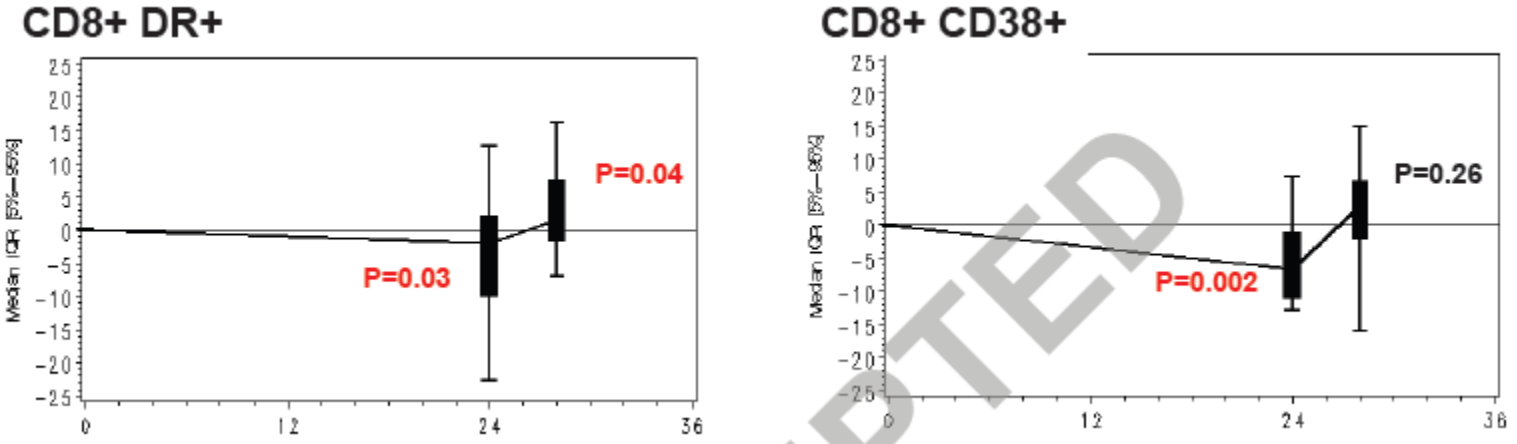
Adapted from Appay, J Pathol 2008

Essais d'intensification ARV pour diminuer la réplication résiduelle

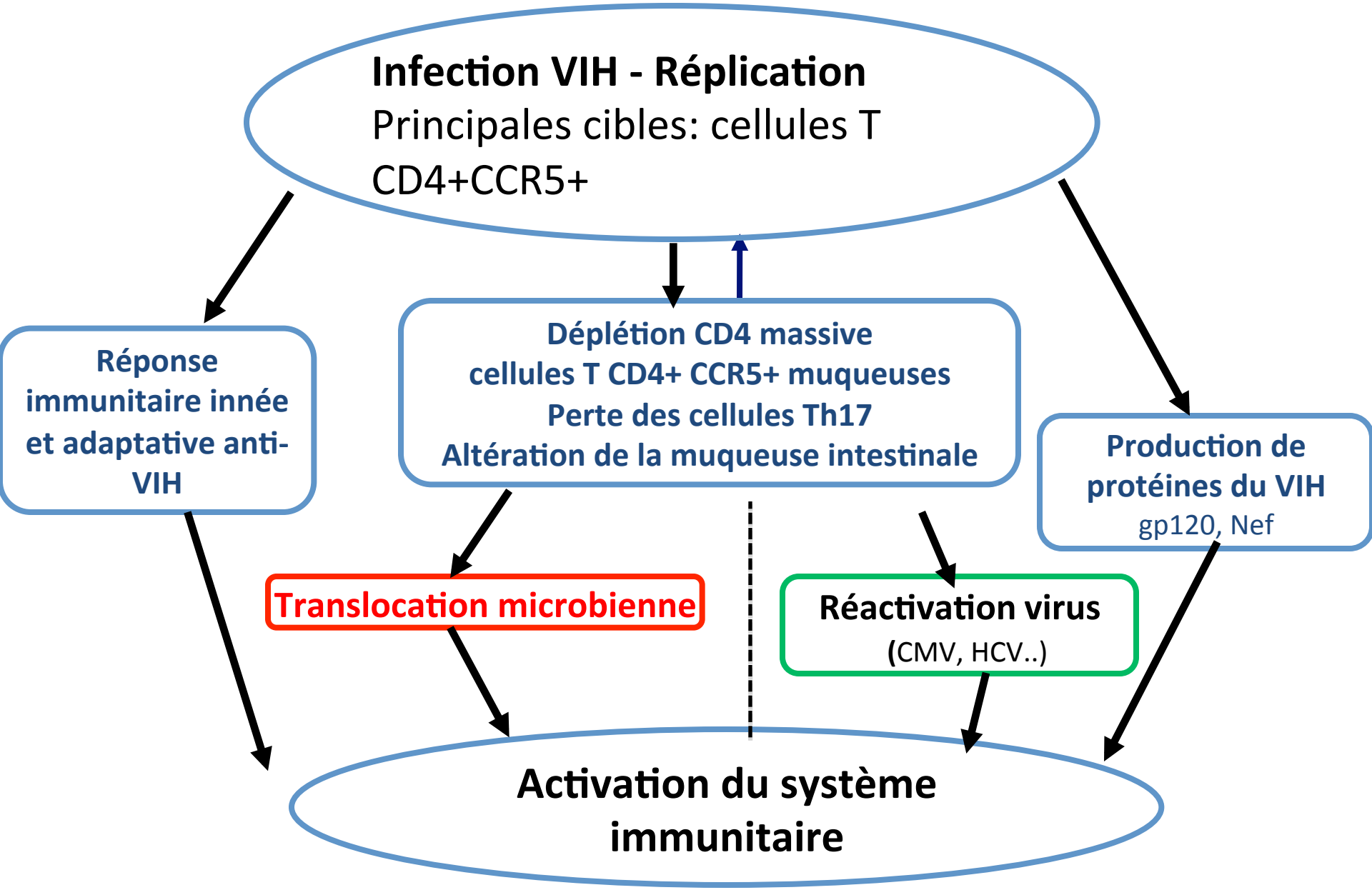
Pas ou peu d'effet sur la réplication résiduelle *(Yukl, AIDS 2012; Buzon, Nat Med 2012; Dinoso, PNAS 2009; Ghandi, Plos Med 2010; McMahon, CID 2010, Hatano JID 2011)*



Intensification Ralté (RCT) *Llibre, Antiviral ther 2012*



Intensification Maraviroc *Cuzin, JAIDS 2012*



Adapted from Appay, J Pathol 2008

Translocation microbienne: cause ou conséquence ??

- Les études observationnelles ne peuvent pas prouver la causalité
- Activation des DCs et des MΦ induisent IDO, une ↘ Th17 et une TM
- Etudes en cours ou à venir pour bloquer la TM
  - A Pilot Study of Rifaximin as a Modulator of Gut Microbial Translocation and Systemic Immune Activation in HIV-Infected Individuals With Incomplete CD4+ T-cell Recovery on Antiretroviral Therapy (ACTG)
  - Sevalamer

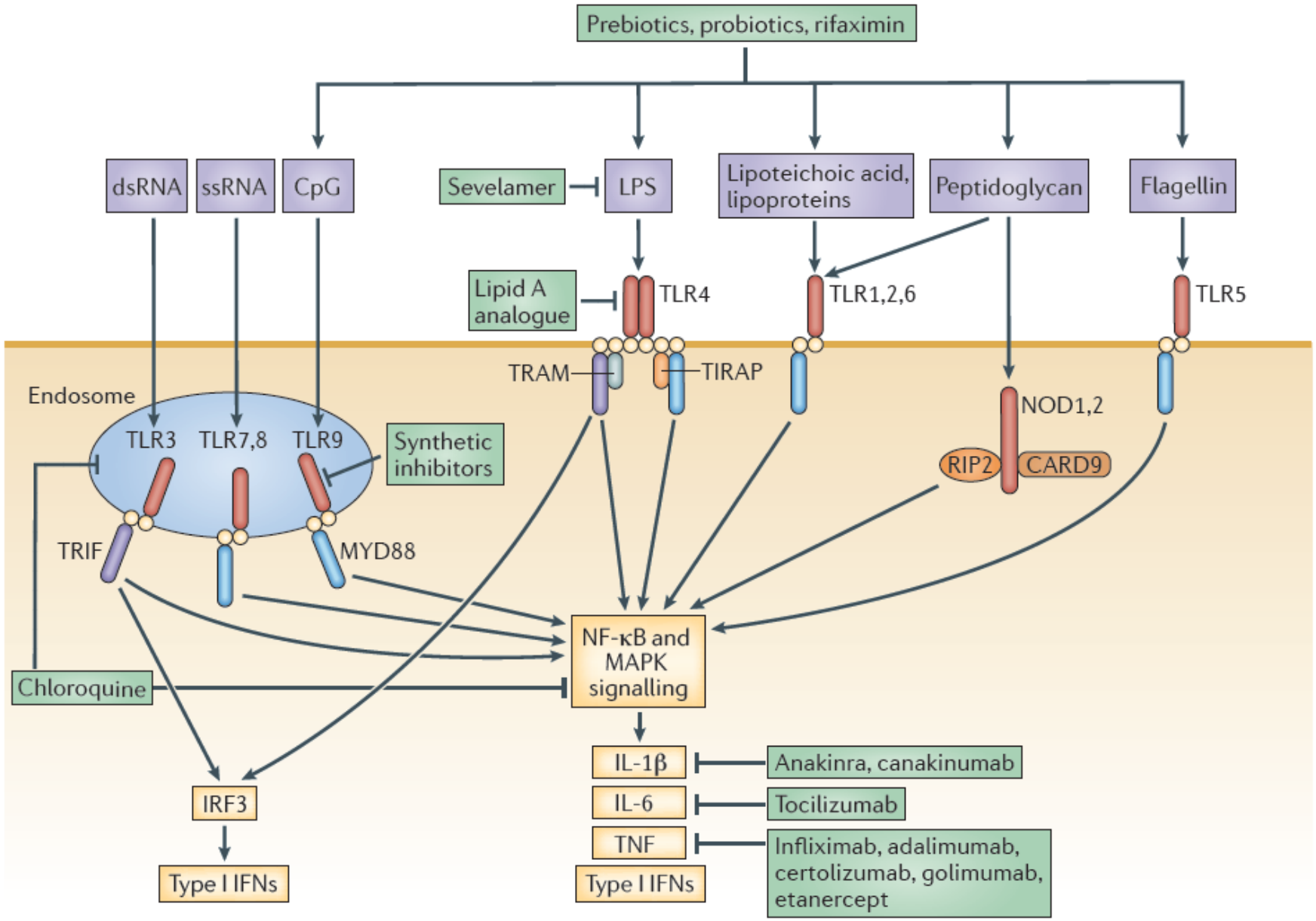


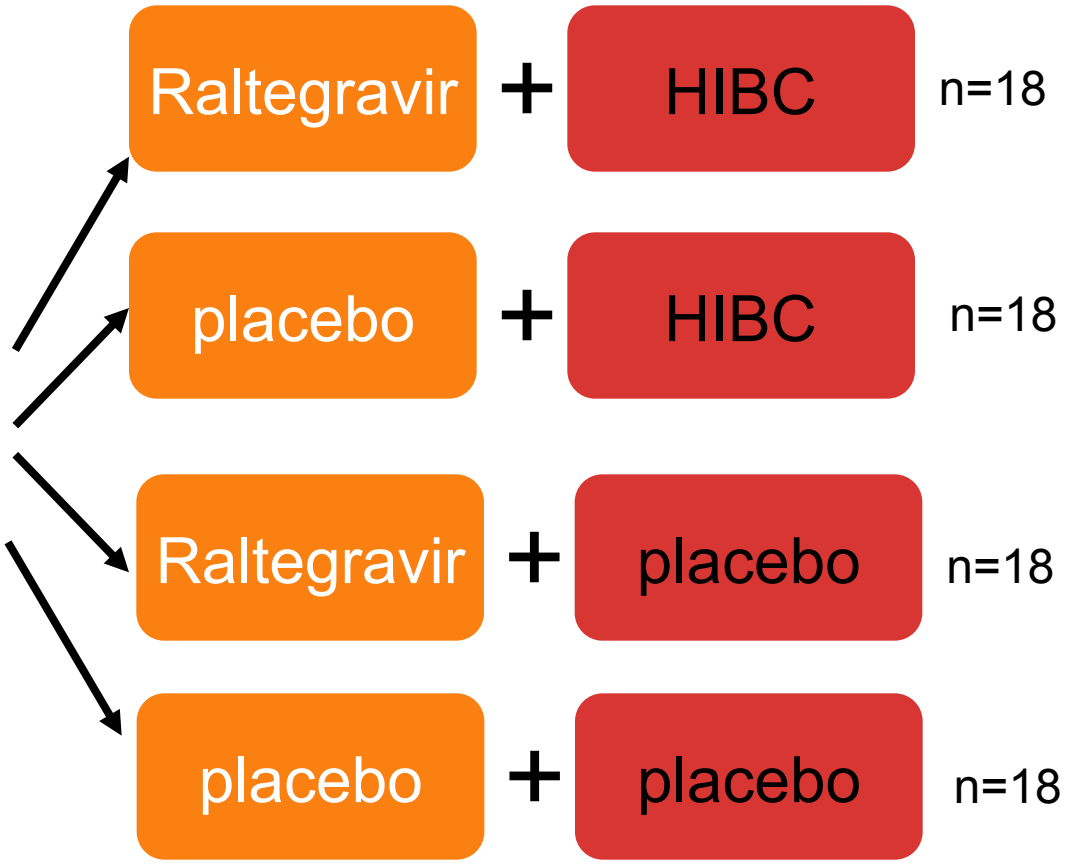
Figure 3 | **Therapeutic interventions to attenuate microbial translocation-induced immune activation.**

Sandler & Douek, Nat rev microbiol 2012

Anti-LPS antibodies have no effect on CD4 recovery: CORAL

HIBC= hyperimmune bovine colostrum
Enriched in anti-LPS antibodies

HIV+
On cART
CD4<350 cells/ul
ΔCD4<50 past 12 months



RESULTS
No effect on CD4 recovery
No effect on LPS, sCD14, T cell activation

Bykawaga *et al, J Infect Dis* 2011

Slide courtesy of Sharon Lewin

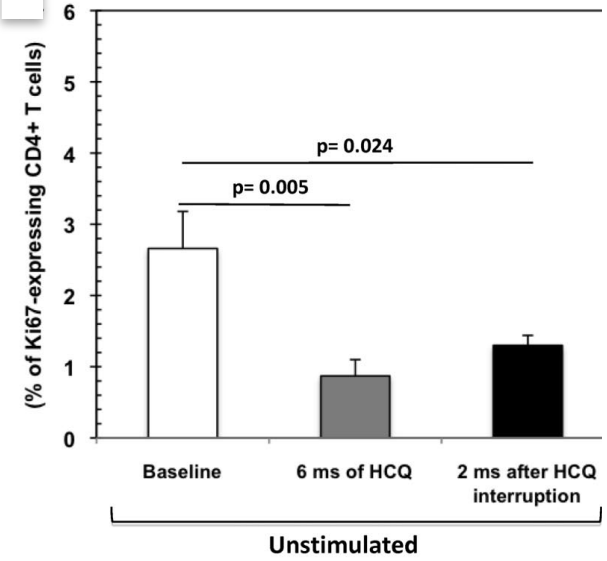
Hydroxychloroquine (1)

- Effets immunomodulateurs
- utilisée dans les MAI (LED)

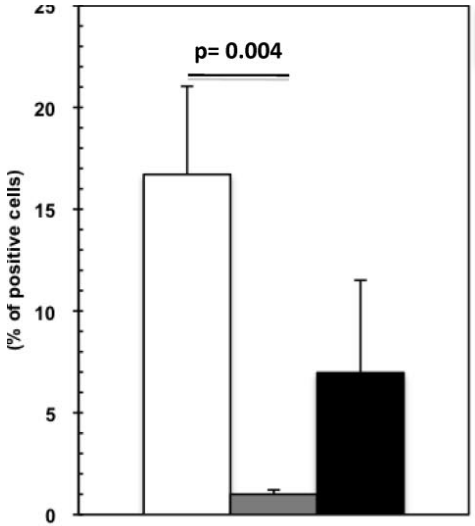
- ⇘ cytokines proinflammatoires

- ⇘ expression des TLR 4 et 9

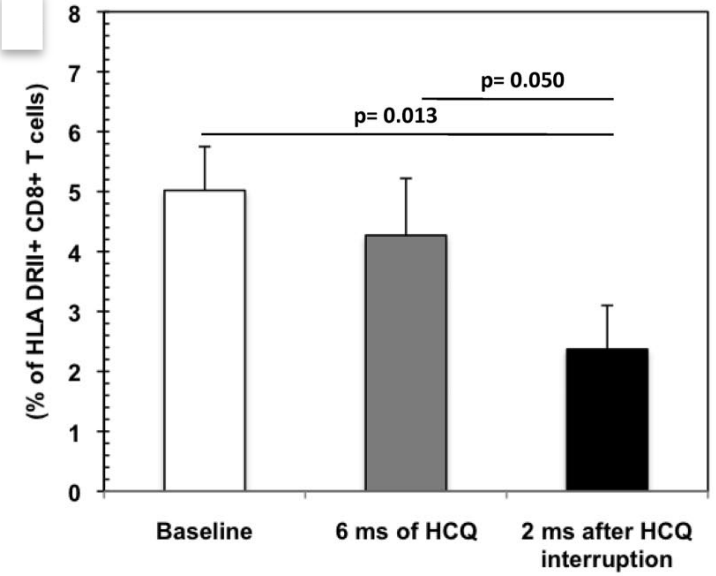
- **Etude propective**
- **N= 20** patients INR (CD4 <200 ou ⇗ CD4 < 5% la dernière année
- HCQ 400 mg/j pendant 6 mois
- Patients: median CD4= 143; nadir CD4= 55; CV indécelable < 20



CD4+Ki67+



CD14+TLR4+



CD8+HLA-DR+

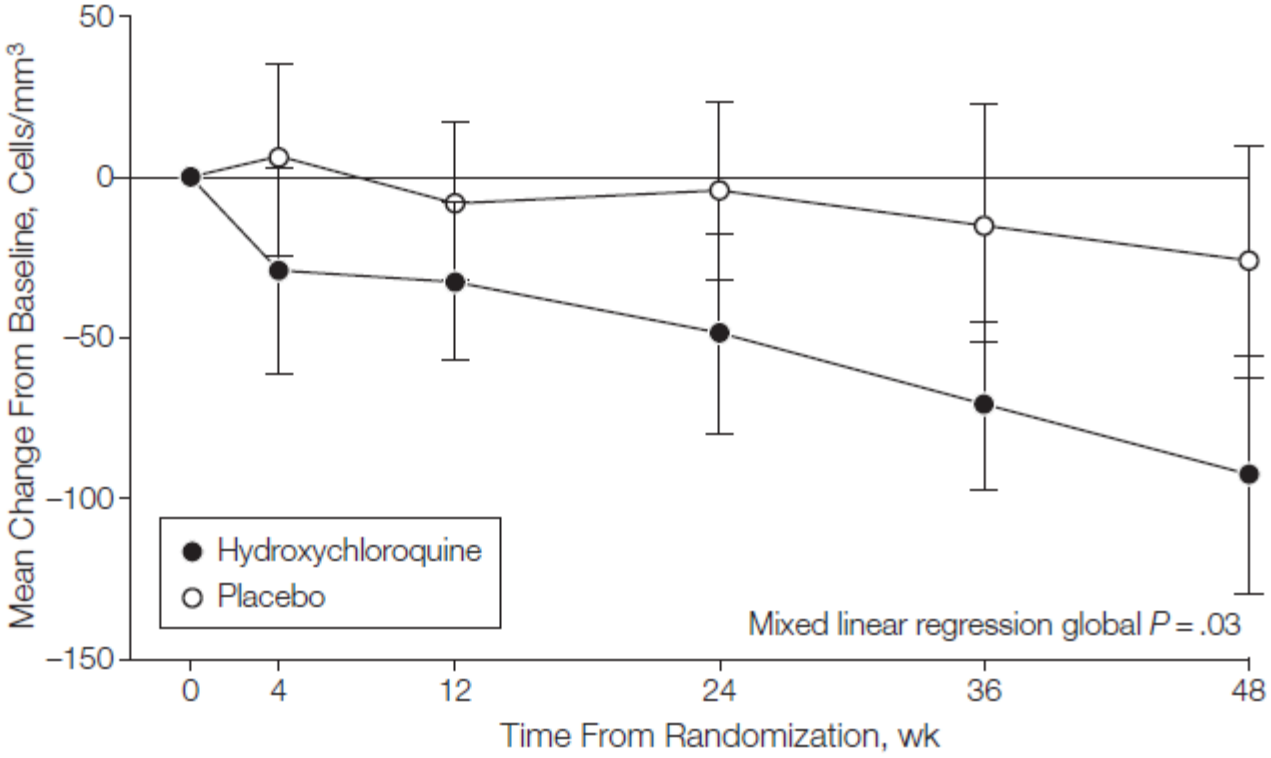
⇘ LPS circulant; ⇘ IL-6

Piconi, Blood 2011

Hydroxychloroquine (2)

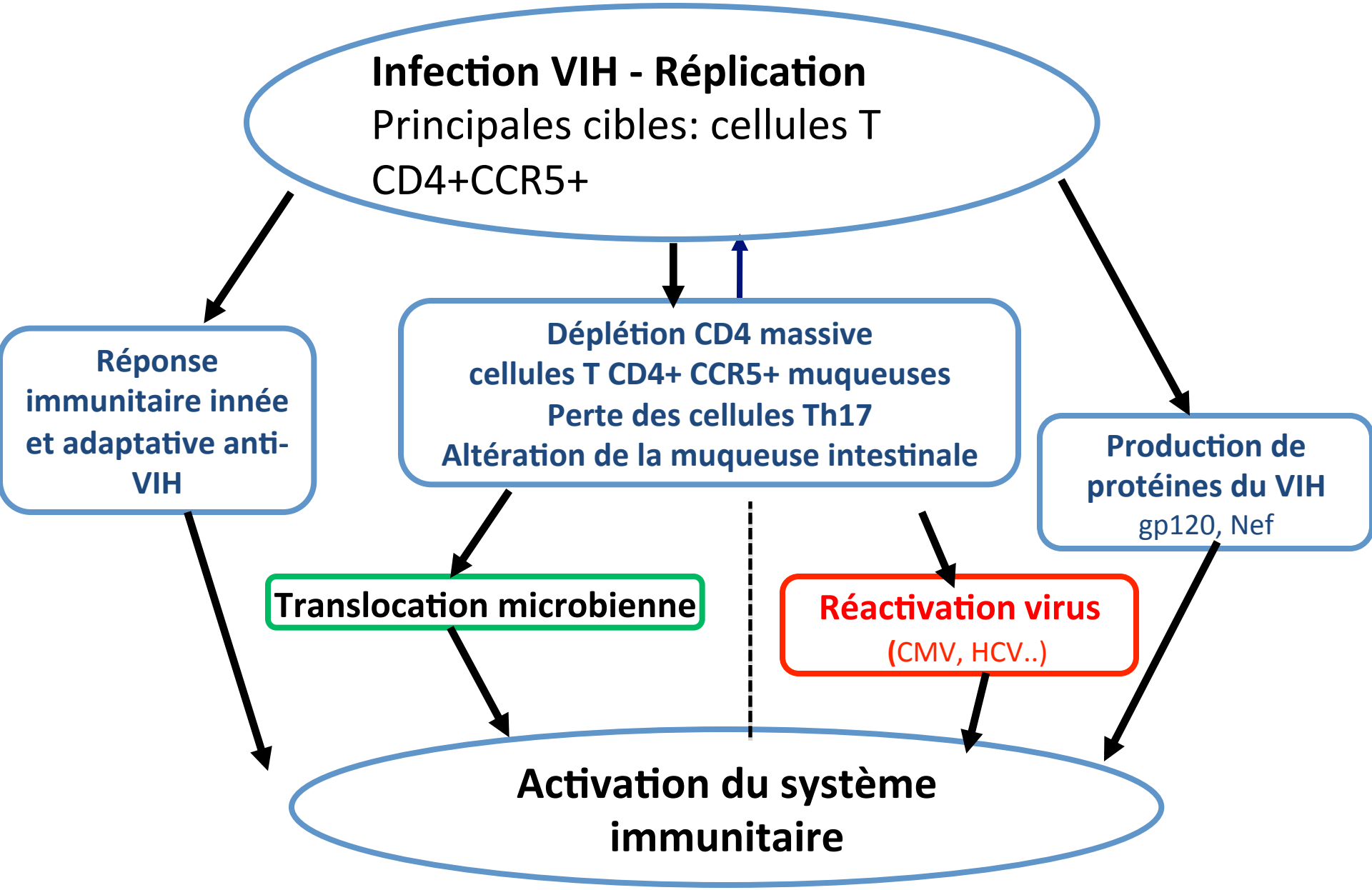
N= 83 patients
Naïfs d'ARV
CD4 > 400
HCQ (400 mg/j) vs PCB
48 semaines

CD4 change during the trial by treatment group



No. of observed values						
Hydroxychloroquine	42	42	38	33	29	27
Placebo	41	36	40	38	33	35

Paton 2012



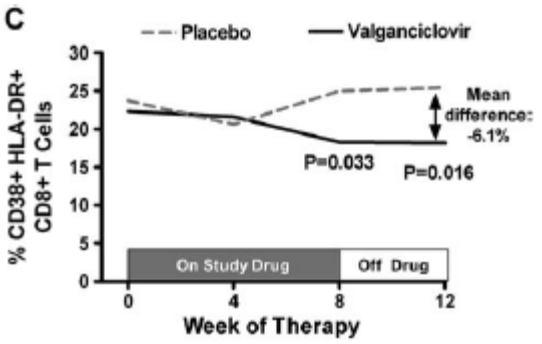
Adapted from Appay, J Pathol 2008

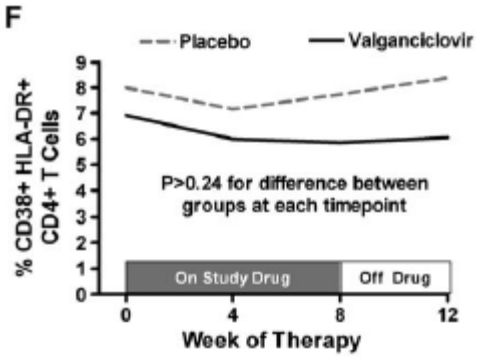
Valganciclovir Reduces T Cell Activation in HIV-Infected Individuals With Incomplete $CD4^+$ T Cell Recovery on Antiretroviral Therapy

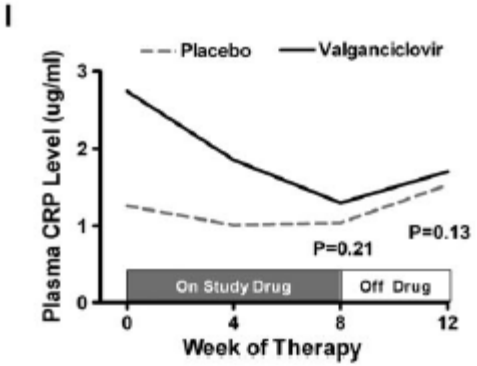
Peter W. Hunt,[1] Jeffrey N. Martin,[1] Elizabeth Sinclair,[1] Lorrie Epling,[1] Juli Teague,[1] Mark A. Jacobson,[1] Russell P. Tracy,[2] Lawrence Corey,[3] and Steven G. Deeks[1]

JID 2011

- N= 30 patients
- **Valganciclovir: 900 mg/j ou placebo**
- **8 semaines** de traitement + suivi S8-S12
- Médiane CD4 190
- 70% patients CV < 75
- 40% AND-CMV >0 dans la salive, le plasma ou le sperme







Effet anti-inflammatoire des statines

En population générale: JUPITER

17,802 personnes sans ATCD CV
avec LDL <3.4 et CRP >2

Level	12 Mo	
	Rosuvastatin	Placebo
High-sensitivity C-reactive protein (mg/liter)		
Median	2.2	3.5
Interquartile range	1.2–4.4	2.0–6.2

CRP US ↓ de 37%

↓ Significative des événements CV dans le groupe Rosuvastatine

combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

Ridker, NEJM 2008

Chez les pts infectés par le VIH

ANRS 126 Vihstatine

N= 58 patients (29 rosu et 29 prava)

âge 47 ans, 77 % hommes

74 % avec CRPus > 2 mg/L

CRPus moyenne : 3,6 ± 2,6 mg/L

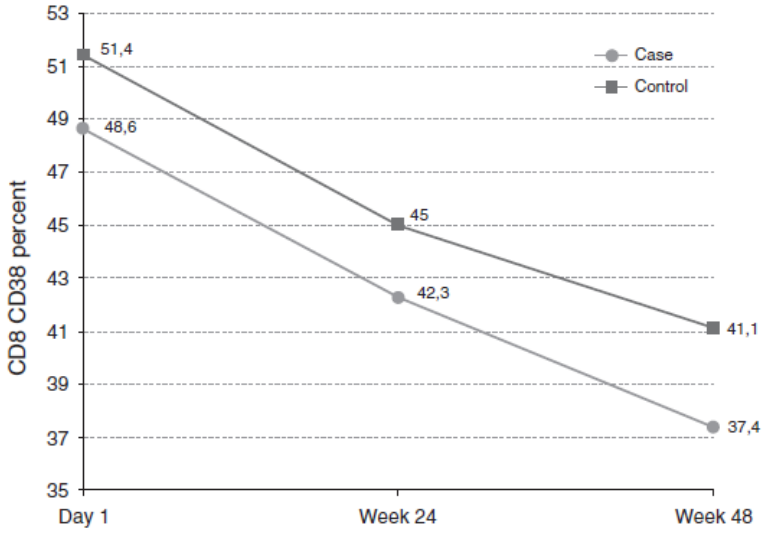
21 % de réduction sous statine à J45 ($p < 0.001$)

pas de différence entre rosuvastatine et pravastatine

à J45 - 0,76 ± 1,75 mg/L ($p<0.01$)

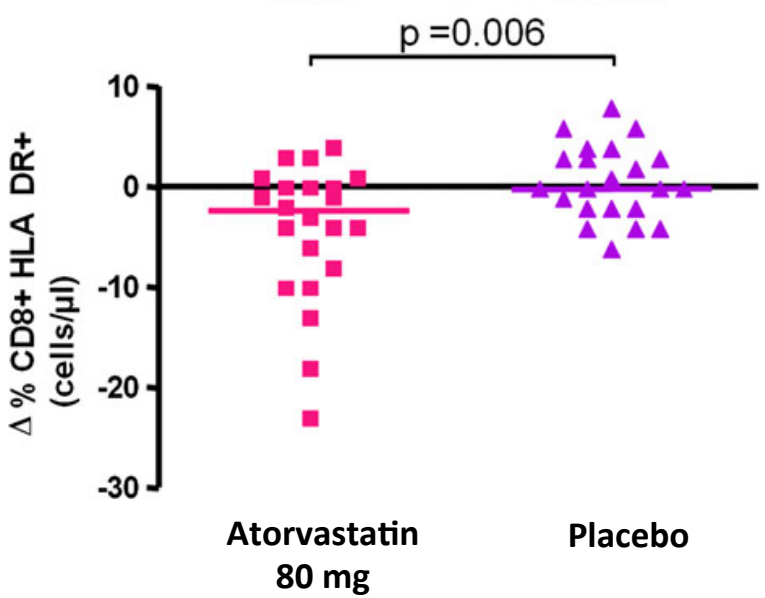
Aslangul, AIDS 2011

Statines et activation LT



Etude cas-contrôles
N= 133 cas; N= 266 contrôles
Cas= patients exposés à l'atorvastatin pdt au moins 48 sem avec CV< 50 copies pdt au moins 6 mois

De Wit, AIDS 2011

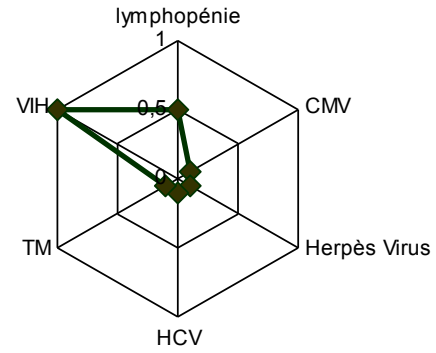


Patients non traités
N= 24
Design: étude cross over (8 sem avec 4-6 sem de washout)
Critère principal: CV: pas d'effet

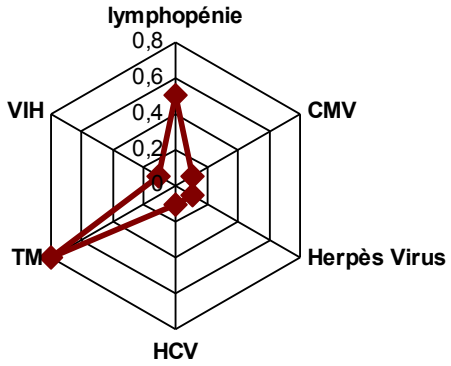
Ganessan, JID 2011

Etudes prospectives en cours chez les patients contrôlés au plan virologique

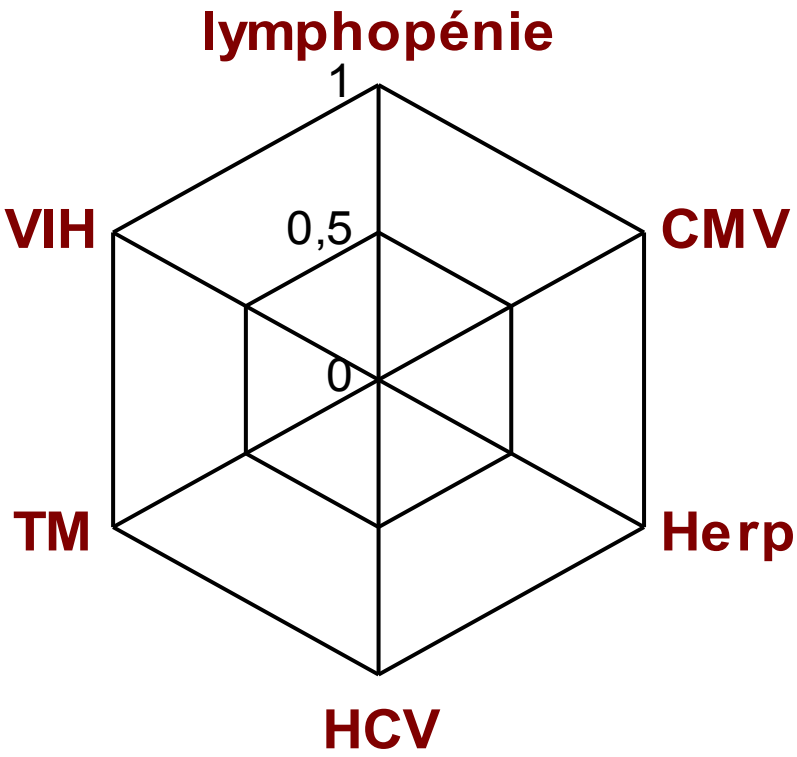
Individualisation de la prise en charge selon l'étiologie de la CIA?



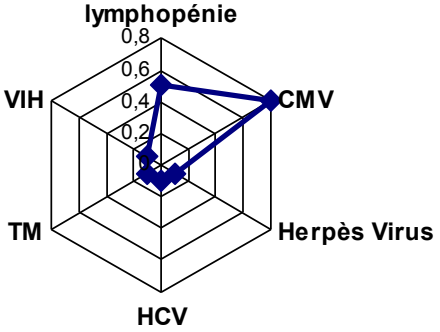
Intensification par ART
Si réplication résiduelle



Traitement
« symptomatique »
Chloroquine, statines



Bi/Tri- thérapie
anti VHC



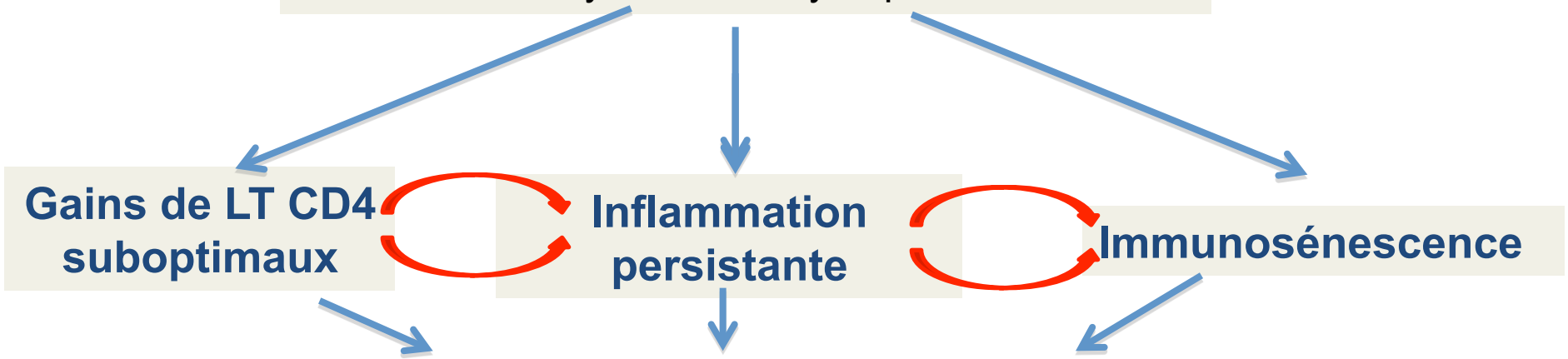
Intensification par
Aciclovir

Intensification par
Valganciclovir

Adapted from I. Pellegrin

Déterminants et conséquences de l'activation/ inflammation persistante

Réplication virale (résiduelle)
Expression (persistante) du VIH (ganglions)
Lymphopénie CD4
Perte de la balance Th17/Tregs
Translocation microbienne
Dépôt de collagène
Co-infections (CMV, VHC)
Dysfonction thymique



Comorbidités (CV, cancers, troubles neurocognitifs, maladie rénale chronique, ostéoporose), ↗ réservoir VIH
risque accru de mortalité,

Adapté de Volberding & Deeks, Lancet 2010

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