Le VIH, *pirate*
de la cabine de pilotage du système immunitaire

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Le VIH, *pirate*
de la cabine de pilotage du système immunitaire

1. Cellules cibles du VIH et réponses immunitaires contre le VIH
2. Histoire naturelle de l'infection et déterminants de la pathogénicité:

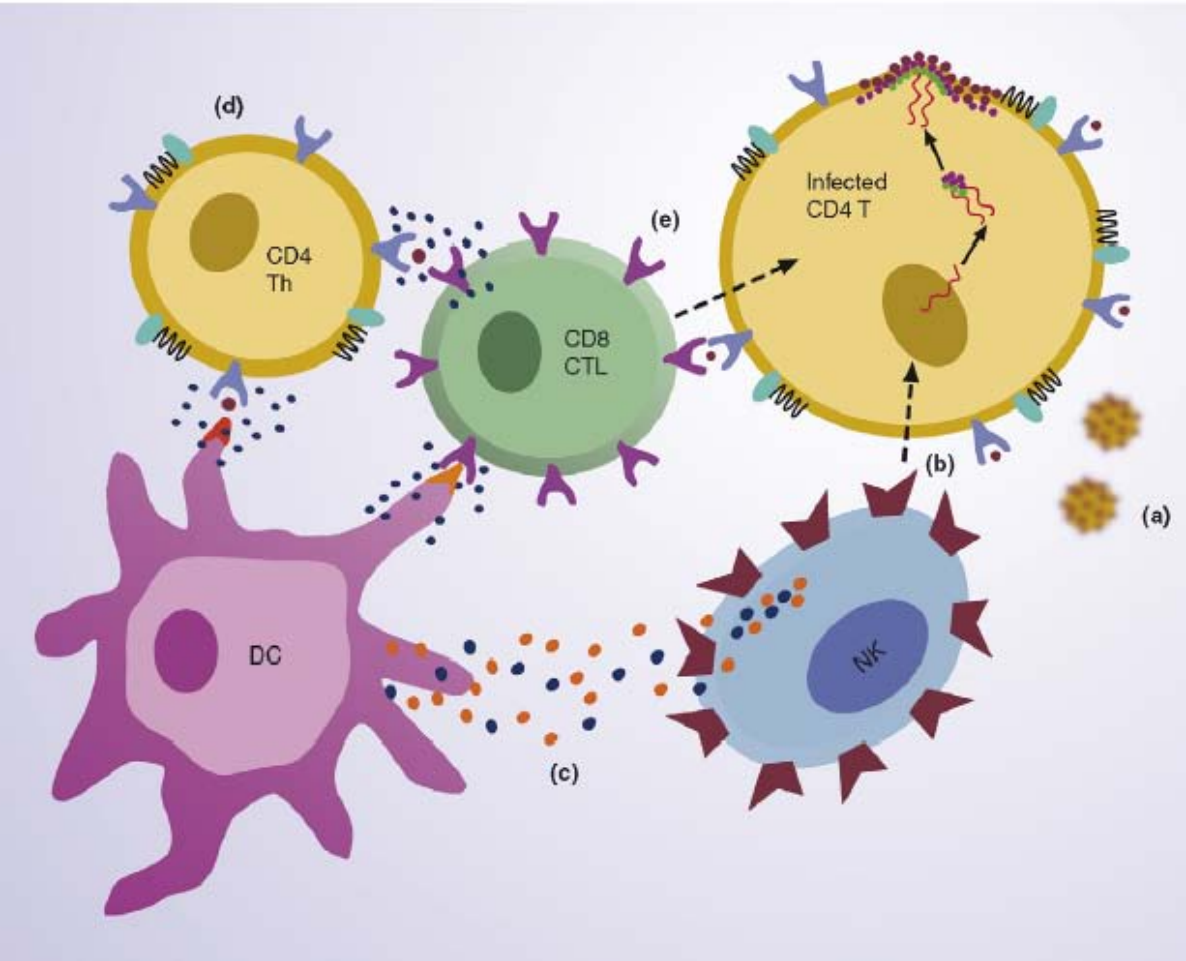
   comment reprendre le contrôle de l'avion?

Réponses immunes cellulaires anti-VIH

T auxiliaires CD4+++

T cytotoxiques CD8 +++

Cellules NK



Saez-Cirion, Pancino, Sinet, Venet,Lambotte, ANRS EP36 HIV controller study group, Trends Immunol 2007; 28:532

Les cellules dendritiques sont indispensables à la défense contre le VIH

Rôle crucial des lymphocytes T CD8+ et CD4+ T lymphocytes

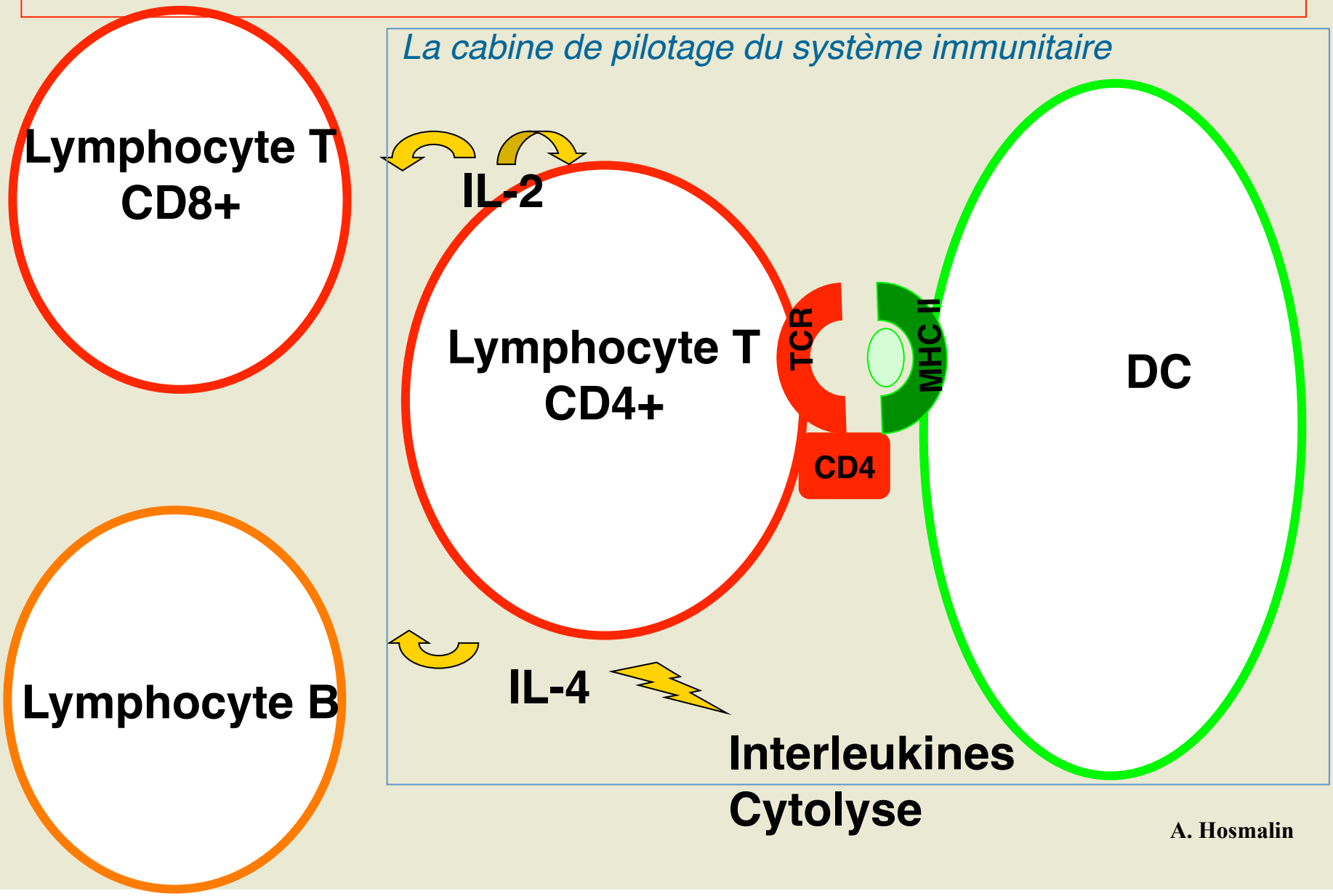
dans le contrôle de la réplication virale

-> Rôle crucial des DC,

qui sont nécessaires pour initier les réponses des lymphocytes T naïfs :

- **Vaccination**
- **Infection primaire**
- **Réponses après mutation d'échappement des épitopes**
- **Stimulation des lymphocytes Naïfs spécifiques du VIH**

Le VIH infecte les lymphocytes T CD4+ Classe II-restreints: Auxiliaires et effecteurs de la réponse immune spécifique



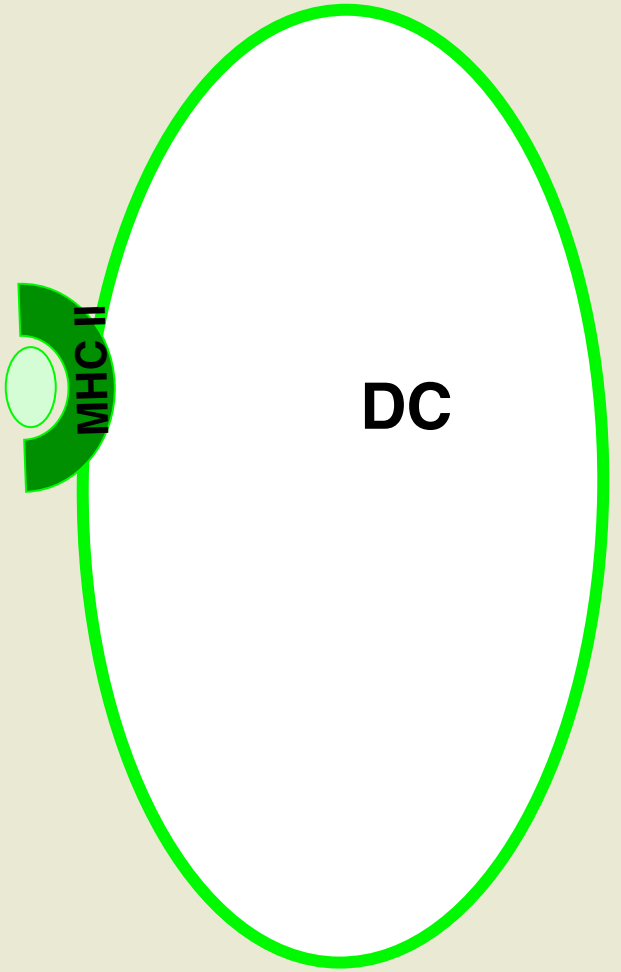
A. Hosmalin

Le VIH infecte les lymphocytes T CD4+ Classe II-restreints: Auxiliaires et effecteurs de la réponse immune spécifique

Lymphocyte T CD8+

Lymphocyte B

Déficit en lymphocytes T CD4+:
déficit immunitaire profond contre les pathogènes intracellulaires
-> infections opportunistes



A. Hosmalin

Aspects dynamiques de la réplication du VIH in vivo

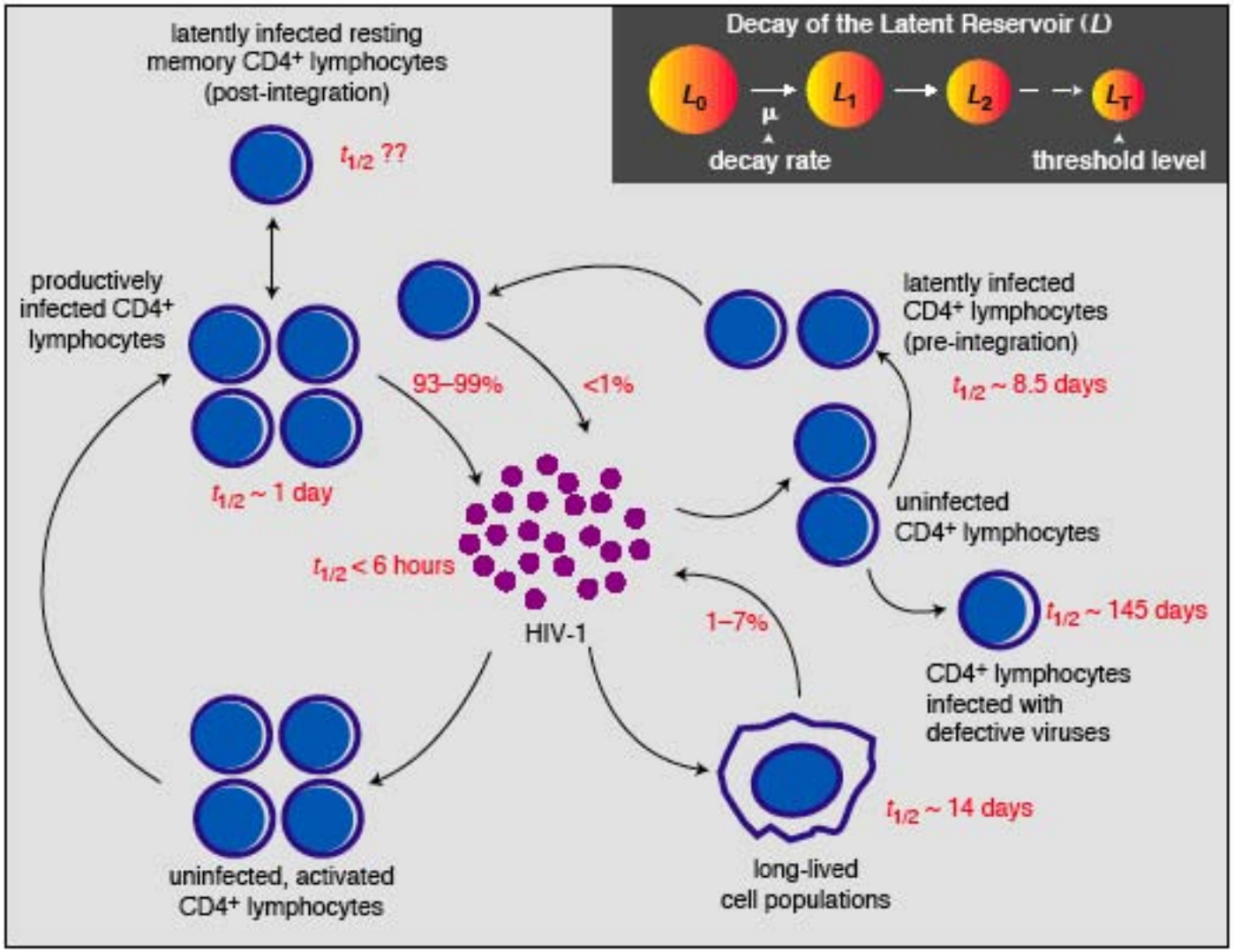


Fig. 1. A schematic representation of the dynamics of HIV-1 replication in vivo [adapted from (3)]. The latent reservoir *L* is shown at the top left, and its decay is hypothetically depicted in the insert.

Ho 1998 www.sciencemag.org • SCIENCE • VOL. 280 • 19 JUN

Les lymphocytes T CD4+, cible principale de l'infection par le VIH, disparaissent tôt, notamment au niveau de l'intestin

Brenchley Douek et al
Nat Med 2006,
Nat immunol 2006

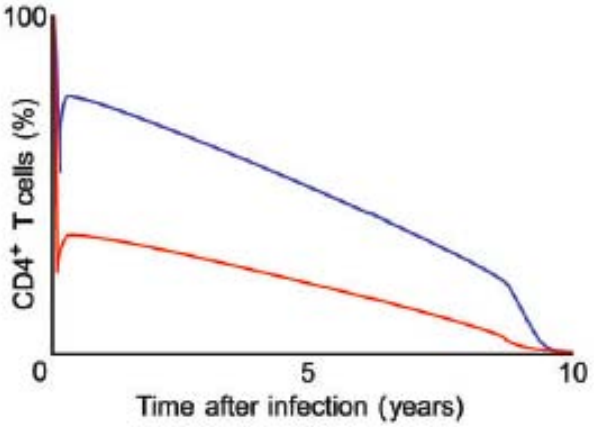


Figure 3 Decrease in total-body CD4+ T cells. Depletion of peripheral blood (blue) and whole-body reservoirs (red) of CD4+ T cells, based on percentage of T cells that express CD4, after infection with HIV.

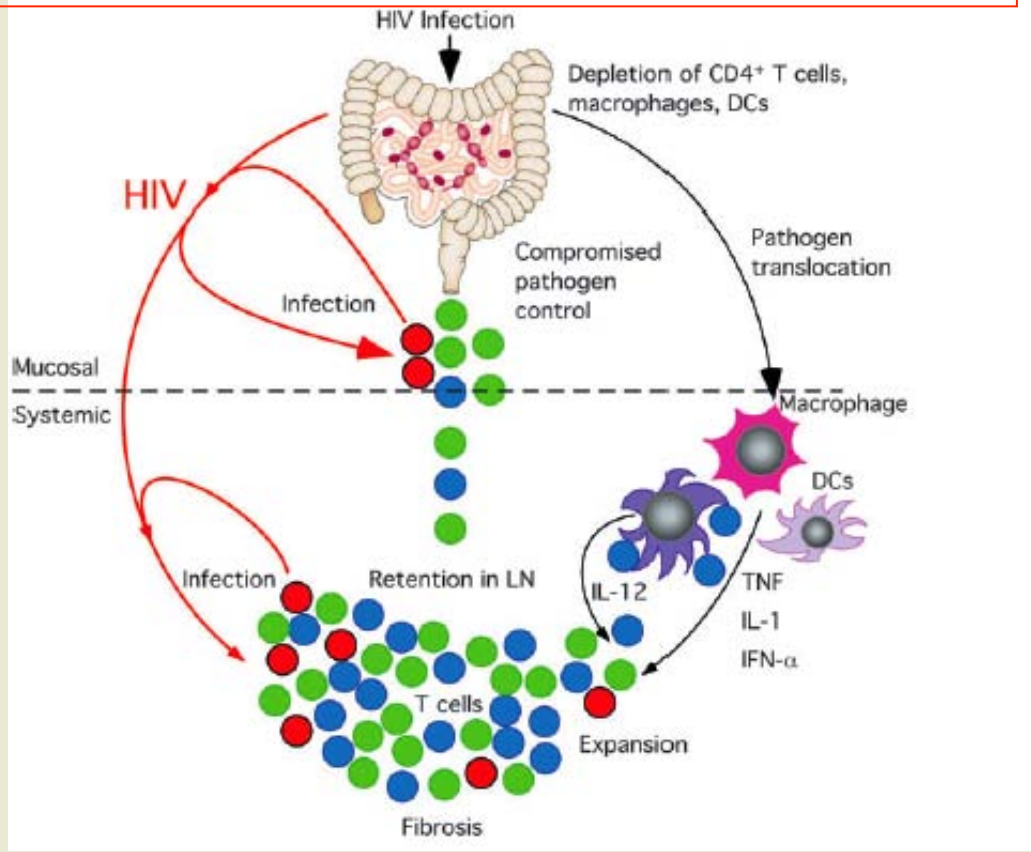
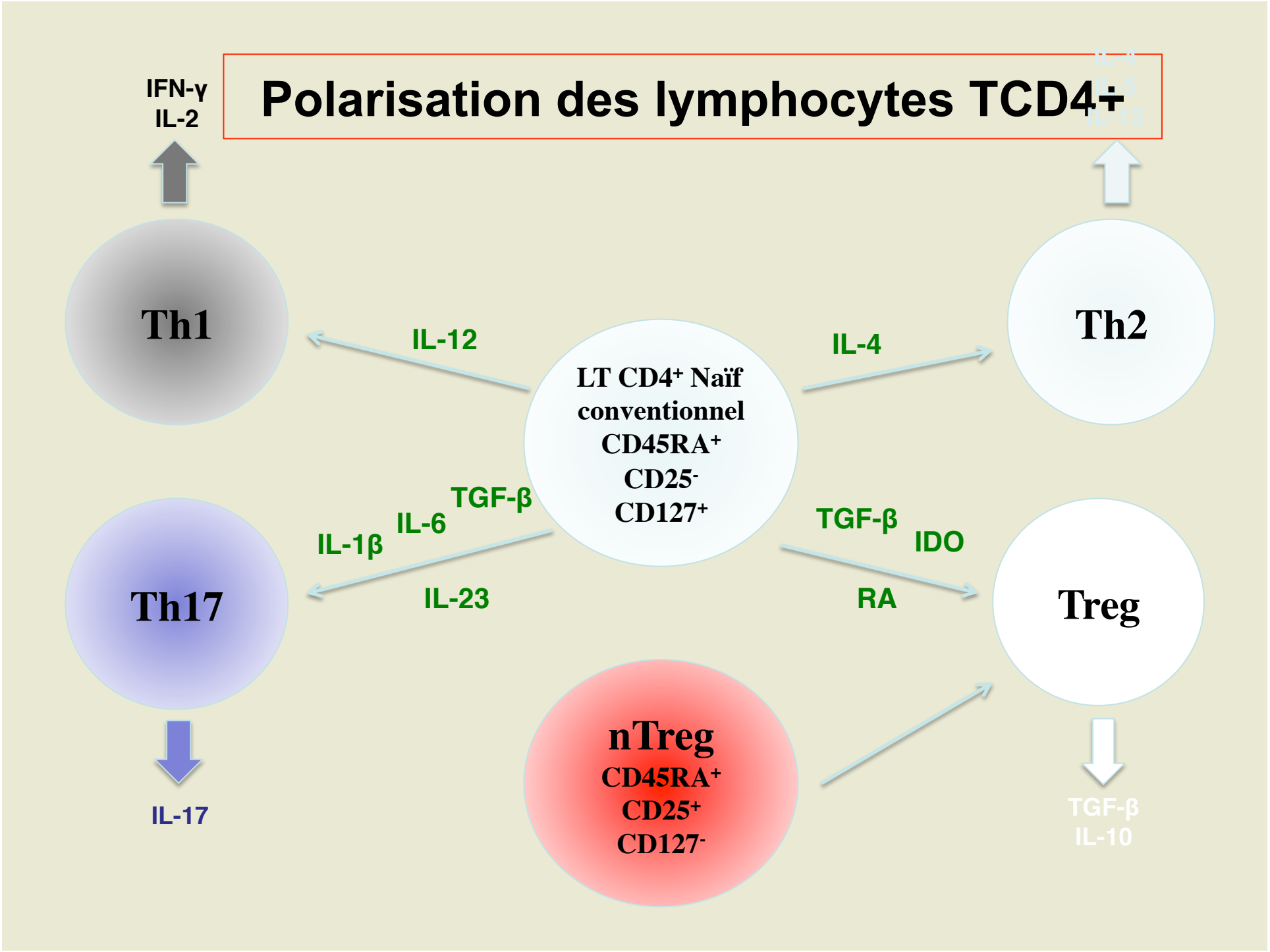


Figure 2 Cycle of HIV disease pathogenesis: a hypothesis. Acute HIV infection depletes the mucosa of CD4+ T cells, which compromises the integrity of the mucosal barrier and leads to increased translocation of bacteria from the intestinal lumen. Bacteria and bacterial components stimulate innate immune cells systemically, creating the proinflammatory milieu associated with chronic HIV infection. Immune activation results in the stimulation and expansion of both CD4+ (blue) and CD8+ (green) T cell populations, thus creating more targets for direct infection of CD4+ T cells (red) and resulting in lymph node fibrosis. The fibrotic process leads to architectural damage that limits the ability of lymph nodes to support healthy lymphocyte homeostasis; together with T cell retention in lymph nodes, this acts to limit the regenerative capacity and delivery of CD4+ T cells to mucosal surfaces. CD4+ T cells that do migrate to mucosal sites or proliferate therein become targets for direct infection at all stages of disease progression, thus fueling the cycle. DCs, dendritic cells; LN, lymph node; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon.


Polarisation des lymphocytes TCD4+
IFN-γ
IL-2
Th1
IL-12
LT CD4+ Naïf
conventionnel
CD45RA+
CD25-
CD127+
IL-4
Th2
TGF-β
IL-6
IL-1β
IL-23
TGF-β
IDO
RA
Th17
Treg
IL-17
nTreg
CD45RA+
CD25+
CD127-
TGF-β
IL-10

Les T CD4+ productrices de Th17, importantes dans la défense antibactérienne, disparaissent rapidement de l'intestin lors de l'infection pathogène par HIV ou SIV: induction de translocation bactérienne

- *Blood. 2008 Oct 1;112(7):2826-35.*
  Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. Brenchley JM, … Silvestri G, Douek DC.

- *PLoS Pathog. 2009 Feb;5(2):e1000295.*
  Critical loss of the balance between Th17 and T regulatory cell populations in pathogenic SIV infection. Favre D, …, McCune JM.

- *Nat Med . 2008*
  SIV-induced mucosal Th17 depletion promotes salmonella dissemination from the gut. Raffatellu et al.

- *J Immunol. 2010 Jan 15;184(2):984-92.*
  AIDS progression is associated with the emergence of IL-17-producing cells early after simian immunodeficiency virus infection. Campillo-Gimenez L, … Estaquier J

Etablissement et maintien des réservoirs T CD4+ latents

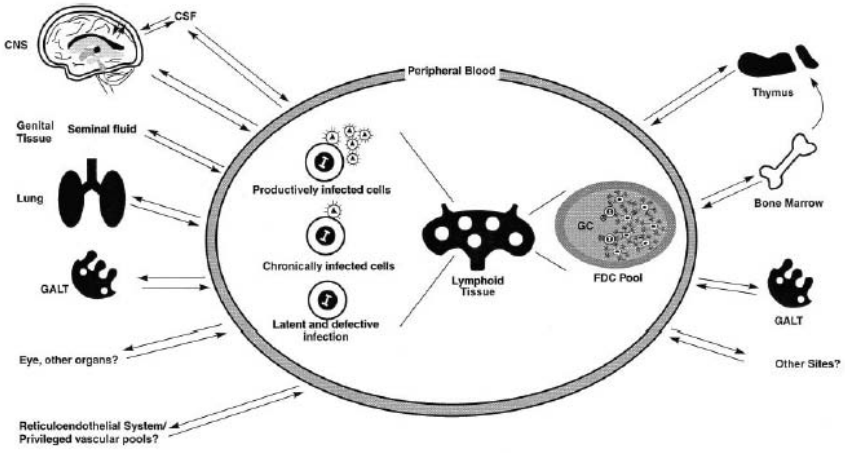


Fig. 1. Cellular and systemic reservoirs of HIV-1 infection and immune reconstitution. HIV-1 is produced and stored in immune complexes bound to follicular dendritic cells (FDCs) in LT. These tissues and others shown in the figure, such as the CNS, are also sites where virus may persist in long-lived latently or chronically infected cells. Most memory or naïve CD4+ T cells generated by thymopoiesis or other renewal mechanisms reside in LT as well. The correspondence between viral and T cell populations in tissues and the more accessible tissue fluids such as peripheral blood is inexact. A bank of tissues from lymphoid and other organs would provide a better opportunity to address issues of viral eradication and immune reconstitution. GALT, gut-associated lymphoid tissue.

Cavert Haase

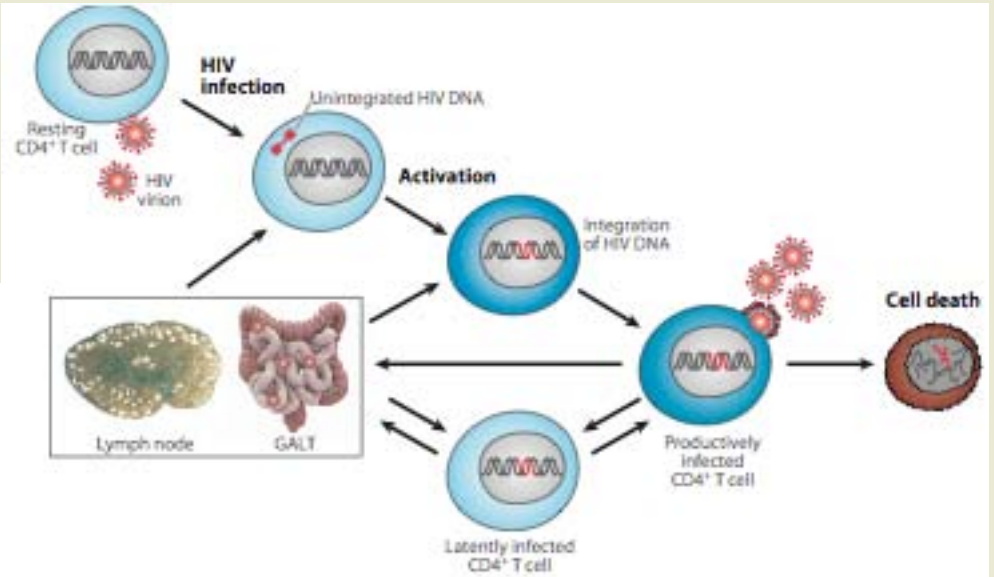


Figure 5

Establishment and maintenance of the resting CD4+ T cell reservoir in human immunodeficiency virus (HIV)-infected individuals. HIV infects resting CD4+ T cells and completes reverse transcription. In the absence of cellular activation and prior to the integration of a provirus into the nuclear DNA of the cell, infected resting CD4+ T cells "cure" themselves of virus as a result of the short half-life of the HIV preintegration complex. Following activation of the infected cells, the vast majority of these cells die from HIV-induced cytopathic effects and the host immune response. However, a very small fraction of productively infected cells revert to a resting memory state. In the presence of effective antiretroviral therapy, these latently infected, resting CD4+ T cells can persist for prolonged periods of time in infected individuals. Some of these cells reactivate in lymphoid tissues and may further contribute to the persistence of viral reservoirs in infected individuals by cell-to-cell spread of virus, even in the absence of detectable viremia. Abbreviation: GALT, gut-associated lymphoid tissue.

Moir… Fauci Ann Rev Path 2011

Lymphocytes T effecteurs ou régulateurs dans l'infection par le VIH: induction par les cellules dendritiques

Protection de l'hôte contre l'immunopathologie / diminution des défenses anti-infectieuses

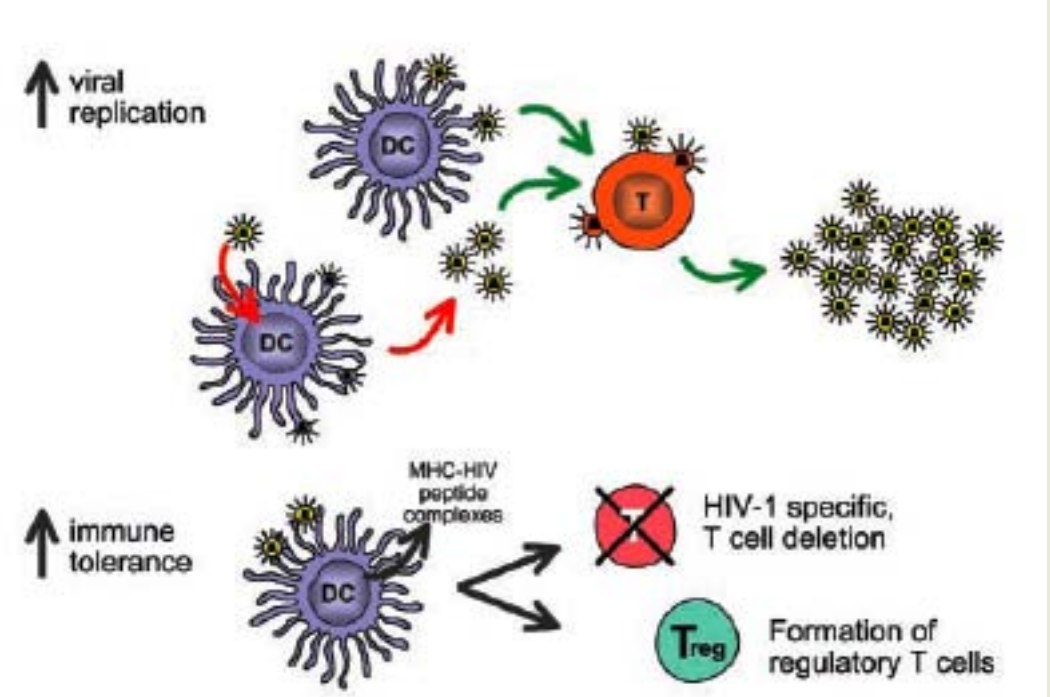


Fig. 4. Potential sites for involvement of DCs in HIV pathogenesis. In the virologic pathway (*Upper*), emphasized in the past, DCs catalyze HIV replication in T cells. In the immunologic pathway (*Lower*) proposed here, immature DCs continually capture and even replicate HIV virions, which induces peripheral tolerance, including regulatory T cells, thereby blocking the effector or protective limbs of the immune response.

Steinman Nussenzweig PNAS 2002: avoiding horror autotoxicus: the importance of DC in peripheral T cell tolerance
Rouse JI 2004 Regulatory cells and infectious agents: detente cordiale and contraire

Lymphocytes T régulateurs dans l'infection par le VIH

Inhibition des réponses T spécifiques, corrélation avec la charge virale: un rôle délétère

Weiss…Lévy Blood 2003
Aandahl J Virol 2004
Andersson…Chougnet JI 2005 **ganglions**
Haase 2006 **SIV vs CMV, ganglions**
Karlsson 2007

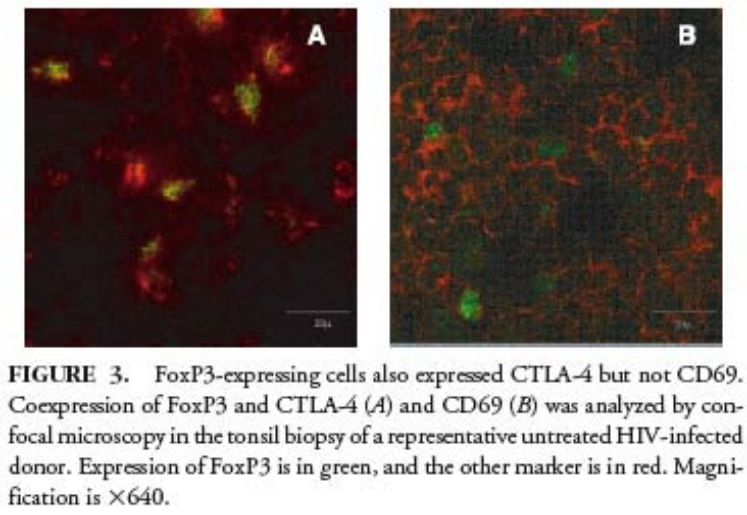
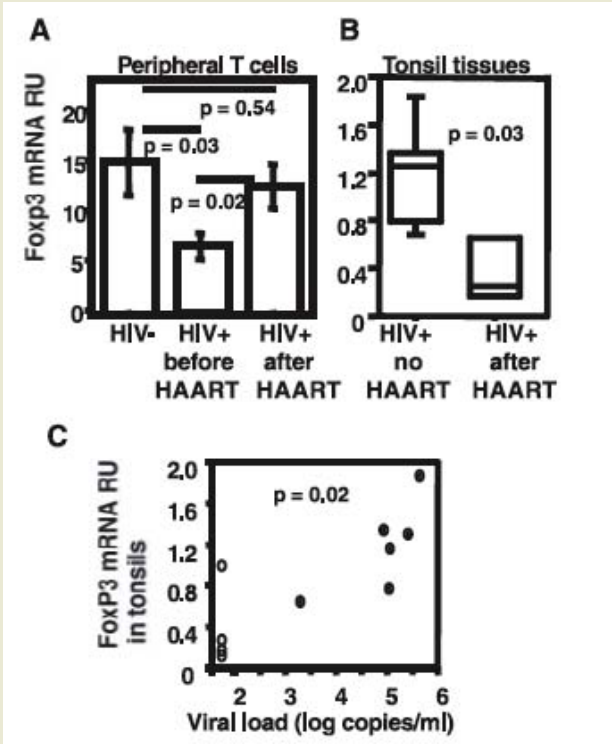


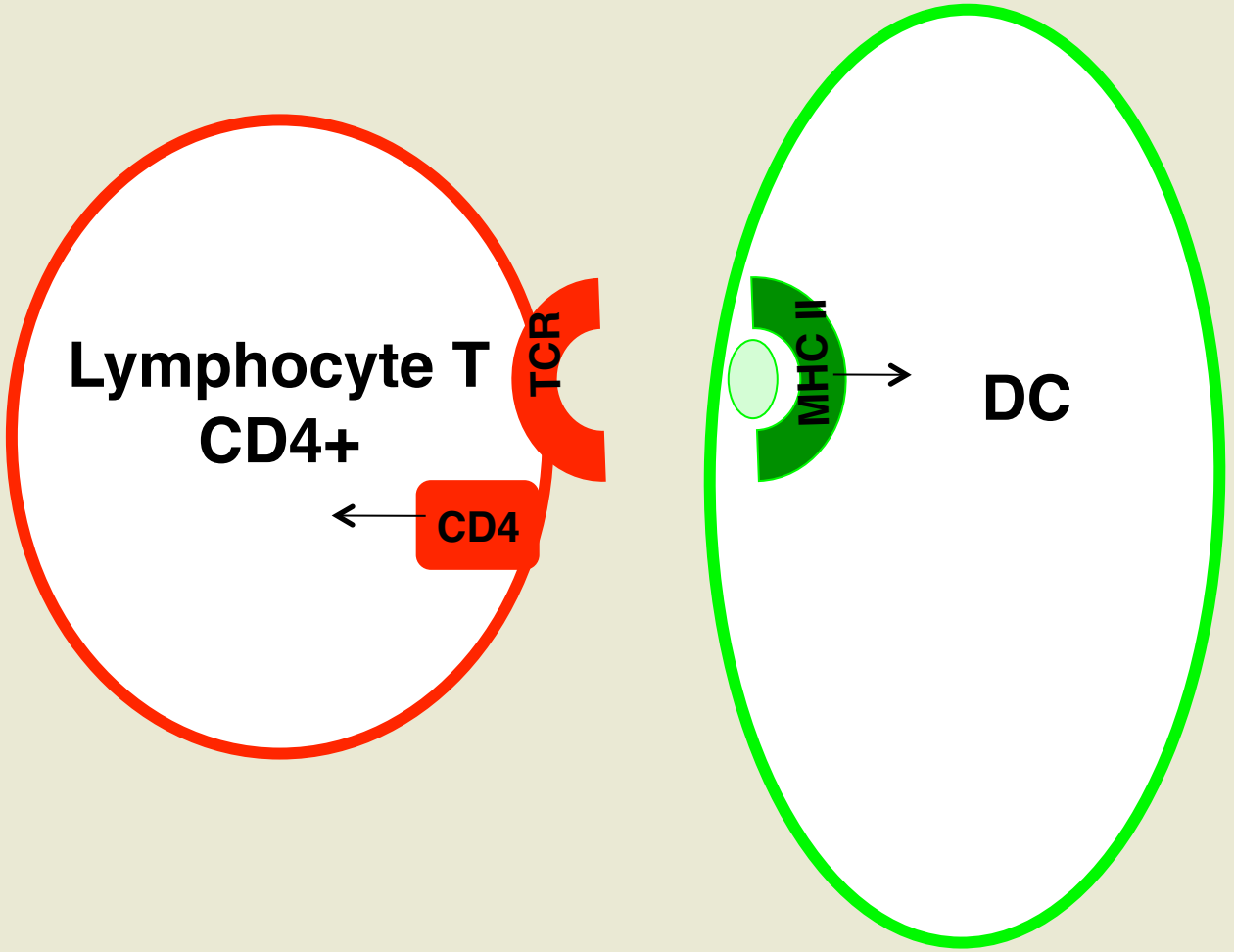
FIGURE 3. FoxP3-expressing cells also expressed CTLA-4 but not CD69. Coexpression of FoxP3 and CTLA-4 (*A*) and CD69 (*B*) was analyzed by confocal microscopy in the tonsil biopsy of a representative untreated HIV-infected donor. Expression of FoxP3 is in green, and the other marker is in red. Magnification is ×640.



Corrélation inverse: effet protecteur au début de l'infection? ?

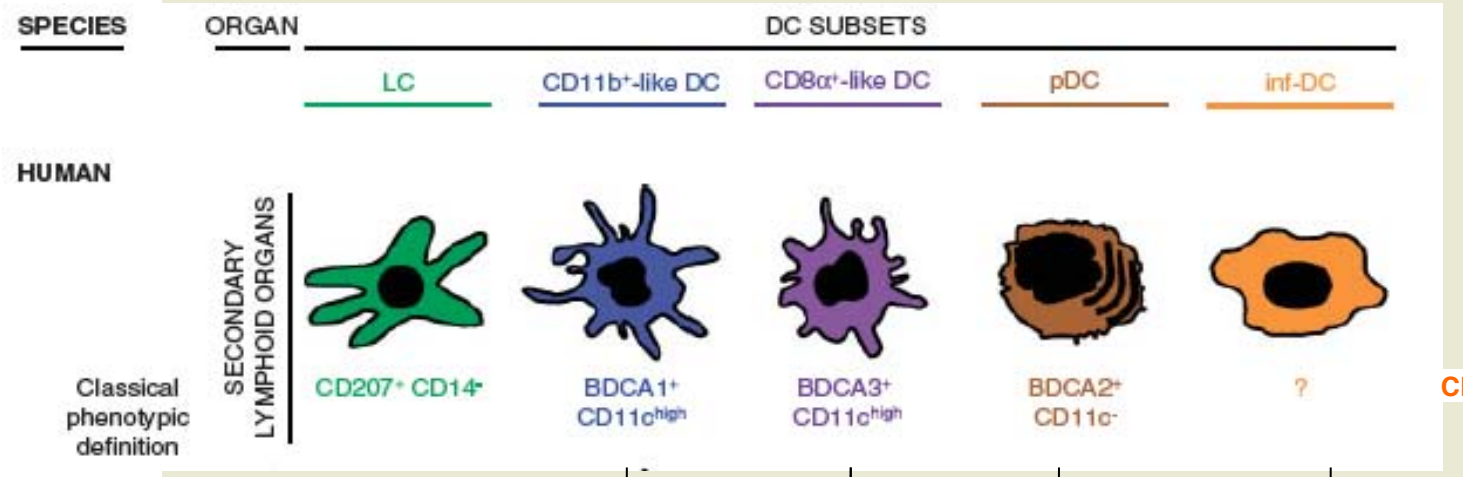
Kinter J Exp Med 2004
Kornfeld JCI 2005
Estes…Haase JID 06
Ploquin Retrovirol 2006

La protéine Nef du VIH réduit le recyclage à la surface des molécules d'histocompatibilité de classe I et II, ainsi que l'expression de CD4



O Schwartz, P Benaroch, S Benichou, J Sodroski….

Cellules dendritiques humaines et monocytes humains, porteurs du récepteur CD4 et des co-récepteurs CCR5 (et CXCR4) du VIH



MONOCYTES

Classiques

CD14faible CD16++

CD14+++ CD16-

mDC BDCA-1+

Production IL-12, IL-23
Polarisation Th1 ou Th17 des réponses antivirales

mDC BDCA-3+

Equivalents des DC CD8-α
Souris spécialisées présentation croisée
Crozat JEM 2010:
sensibilisation contre les antigènes du VIH

pDC BDCA-2+

Production IFN Type I (α , β): Antiviraux

Production TNF α , IL-12 Inflammation

Production IL-12, IL-23 Phagocytose

D'après Guilliams Dalod Malissen EJI 2010

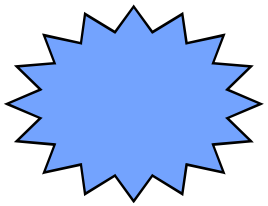
Cellules dendritiques:

les seules cellules présentatrices capables de stimuler

les lymphocytes T naïfs

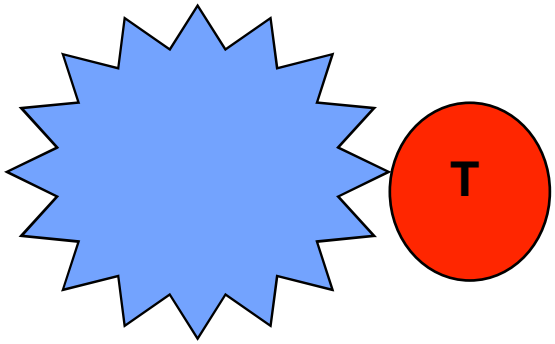
DC immatures: sentinelles

Capture, apprêtement de l'antigène



DC matures:

Présentation de l'antigène aux lymphocytes T naïfs et mémoire



Cellules de Langerhans

epithelia pluristratifiés

DC interstitielles

autres organes

Migration

DC interdigitées

régions T des ganglions

Récepteurs: lectines-mannose, DC-SIGN, Langerine- RFc, R-hsp ...

Macropinocytose constitutive

CMH Classe II +++ en surface

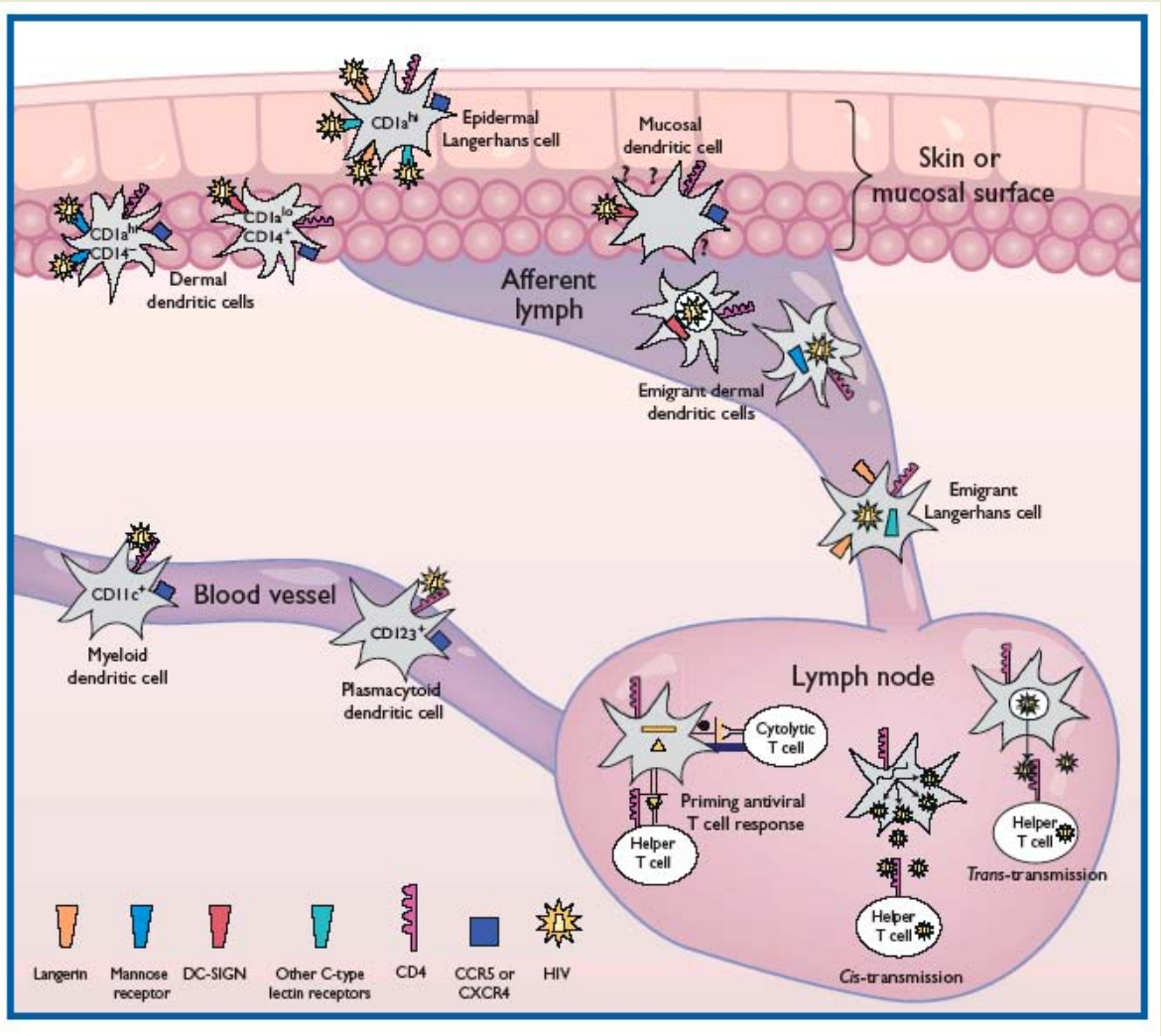
Adhésion

Costimulation

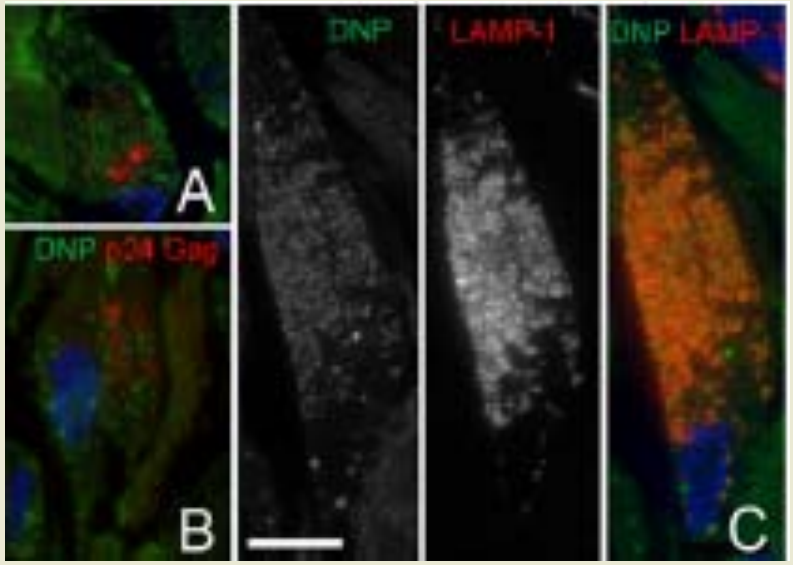
Populations de DC et récepteurs responsables de l'entrée muqueuse et de la migration du VIH

Patterson, Reece, Zaitseva, Schmitt, 1998

Turville, Cunningham 2001, 2003



Le VIH s'accumule dans des compartiments non acides des macrophages, ce qui évite sa destruction ou sa présentation au système immunitaire,
et inhibe leur fonction de phagocytose via Nef



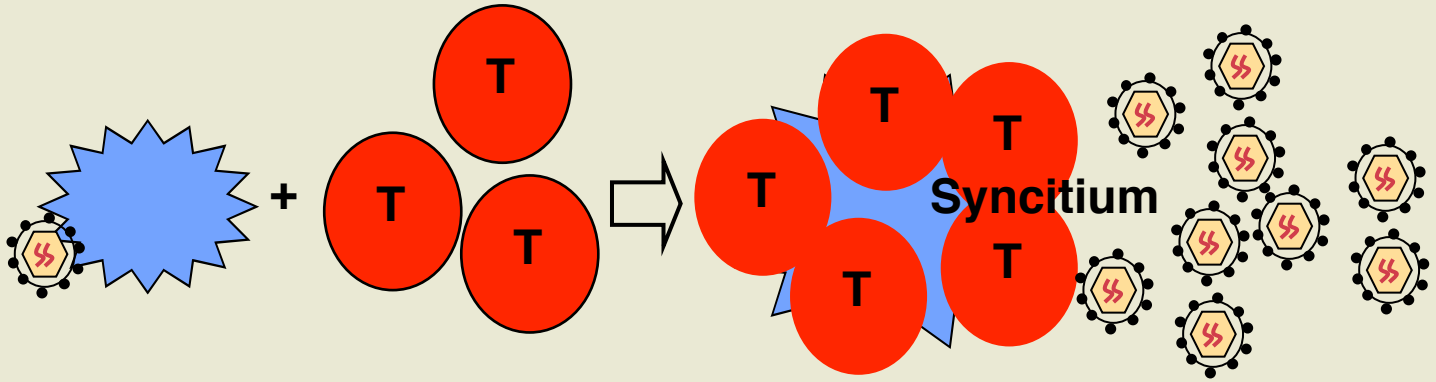
Jouve…Benaroch Cell Host and microbe 2007; 2:105

Le Roux… Niedergang 2010

Susceptibilité des DC myéloïdes et plasmacytoïdes à l'infection par VIH *in vitro*

S Patterson, E Engleman, M Kapsenberg &Berkhout, Yonezawa &Kadowaki…

Potentialisation de la réplication *in vitro* de VIH/SIV par le contact DC/T



Forte production virale dans les syncitia

P Cameron, M Pope, S Frankel , A Granelli-Piperno, A Blauvelt, D Weissmann, O Schwartz, Loré , Koup…

MDDC
mDC sang, peau, amygdales …
pDC
Explants cutanés, LC

Role de Nef: expression augmentée et clustering de DC-SIGN et diffusion du virus

Lymphocytes T CD4⁺ infectés préferentiellement par contact avec des DC infectées
Lymphocytes T CD4⁺ VIH-spécifiques préférentiellement infectés

DC et cellules de Langerhans sont infectées *in vivo* par le VIH, mais rarement

Cellules de Langerhans infectées : Dezutter, Cimarelli, Zanetti, Kanitakis
(plus dans le derme)
Tenner-Racz, Racz, Miller
Syncitia p24 p55+ amygdales: Frankel

Cellules productrices d'IFN infectées et syncitia amygdales: Fong, Engleman

S. Macatonia, S. Knight 1990 — **3 to 31%**

P. Cameron, R Steinman 1992
Karhumäki 1993 — **non infectées**

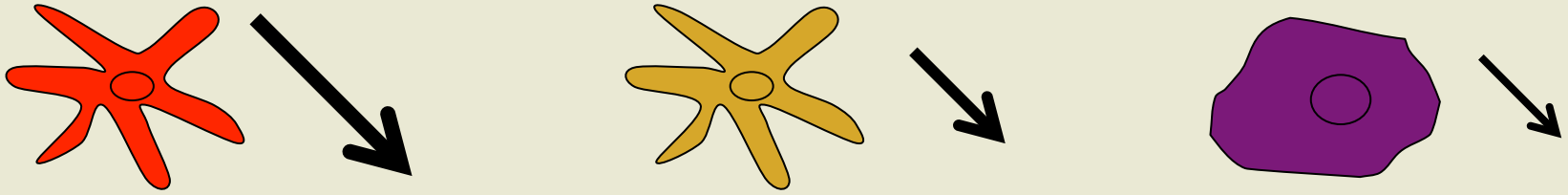
D McIlroy, A Hosmalin, J Virol 1995 — **1/3000 DC vs. 1/60 CD4+ T**
1/50000 monocytes CD14++
Purification DC spléniques, HIV env DNA PCR, analyse en dilution limite

Impact de l'infection par VIH-1 sur la numération des cellules dendritiques et des monocytes

DC myéloïdes BDCA-3^{+}

DC myéloïdes BDCA-1^{+}

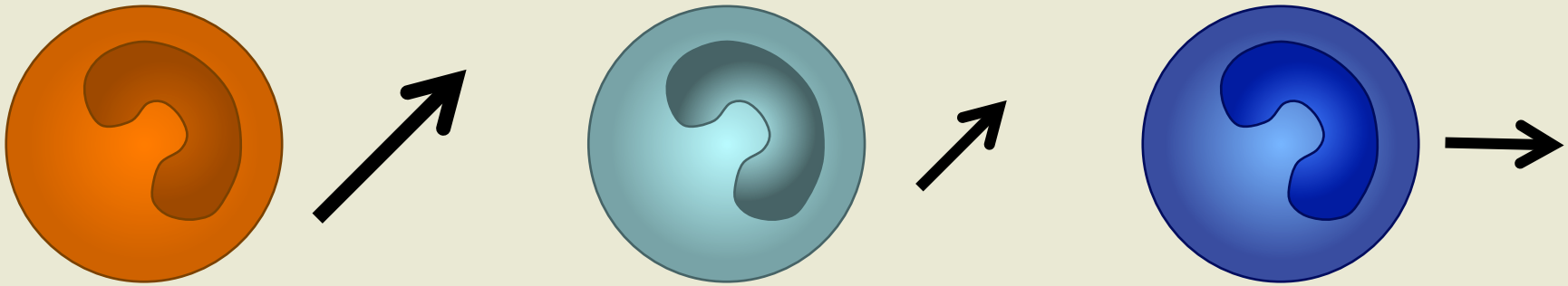
DC plasmacytoïdes, pDC



monocytes CD14$^{+/-}$CD16^{++}

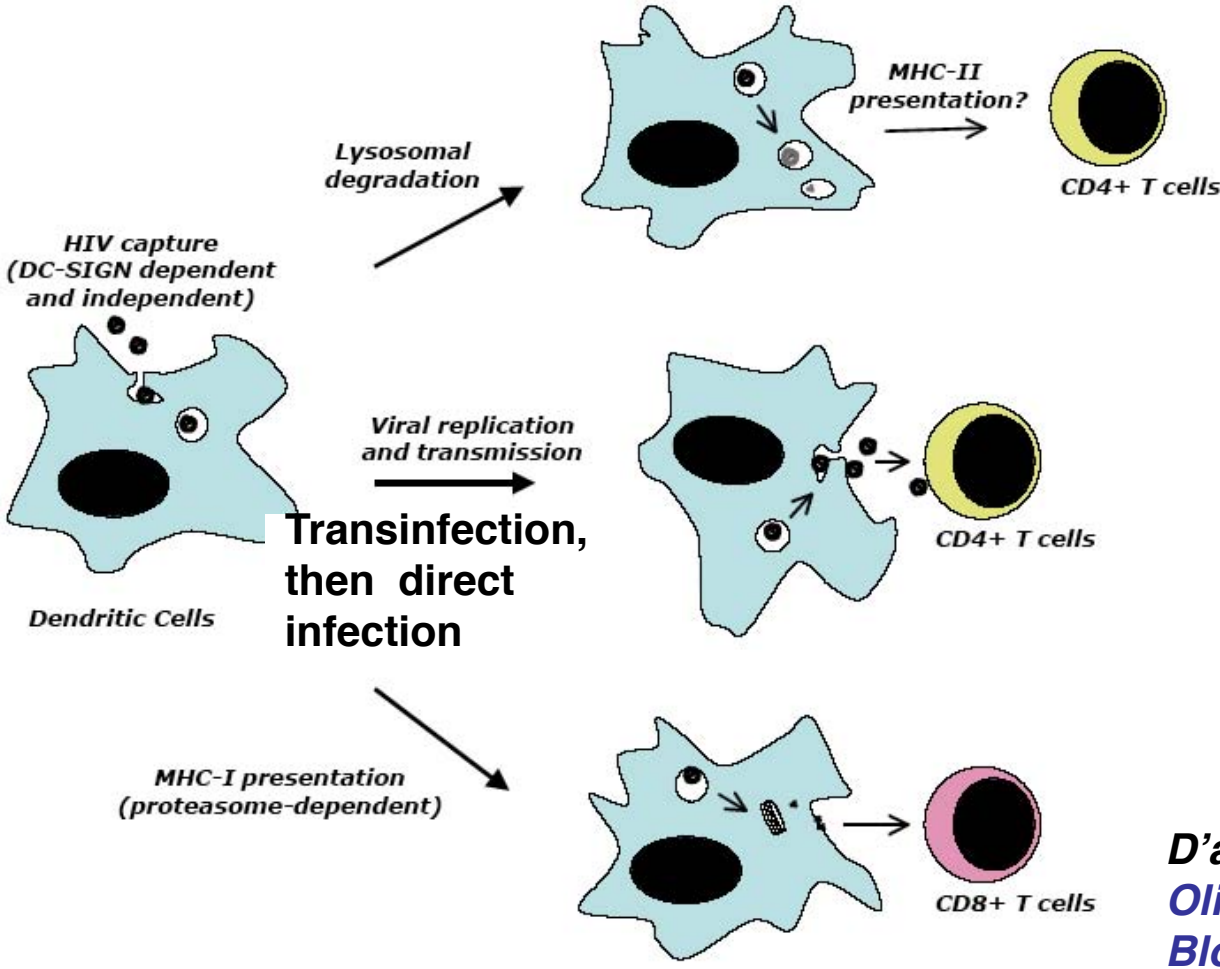
monocytes intermédiaires CD14^{+}CD16^{+}

monocytes classiques CD14^{++}CD16^{-}



Thieblemont 1995, Ancuta 2000, Pulliam 1999, Dutertre, submitted

Infection des DC par VIH : transmission aux lymphocytes T CD4+ ou présentation de l'antigène



Kwon & Littman
Trumpfheller & Pope
Van Kooyk
Cameron
Amara
Romani

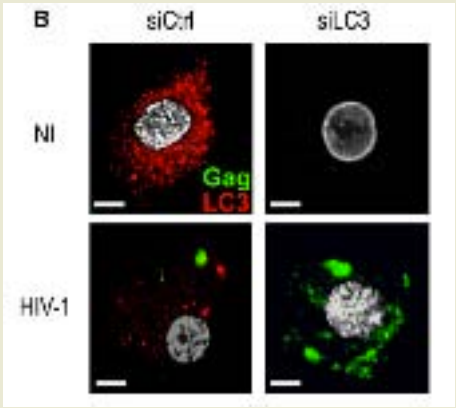
D'après
Olivier Schwartz
Blood 2003, 2004

Maturation partielle seulement des mDC lors de l'infection par le VIH et réduction de l'autophagie

CD80
CD86
CD83

Déficit de production IL-12

Bhardwaj, Wilson, Blauvelt, Chougnet, Shearer, Gessani, Montaner, Vanham, Lore, Andersson, Granelli-Piperno, etc…



Maturation partielle dûe à Env, Vpr

Diminution par Env de l'autophagie et des immunoamphisomes (LC3+ autophagosomal-like structures that are able to intersect with HIV-1 endocytosis)***: diminution de la dégradation et de la présentation du virus, augmentation de la transmission aux T CD4+***

Schwartz Immunity 10

Déséquilibre des réponses IL-12/IL-23 à la stimulation par LPS in vitro

LPS
LPS+ IFN-γ
SAC

+

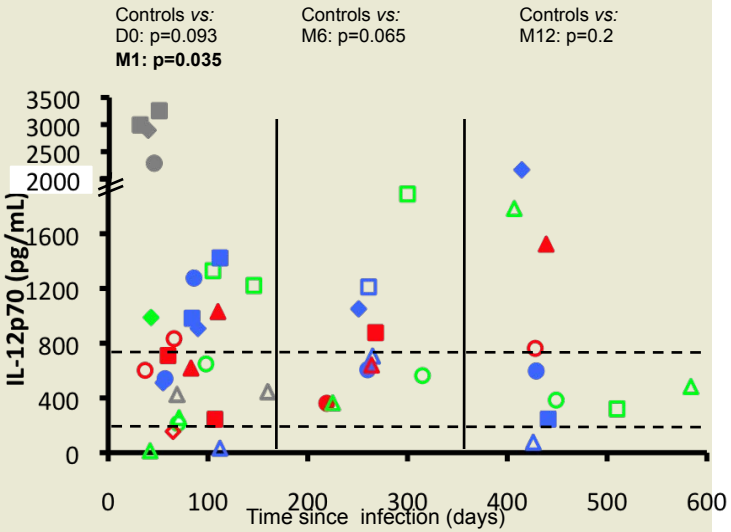
PBMC

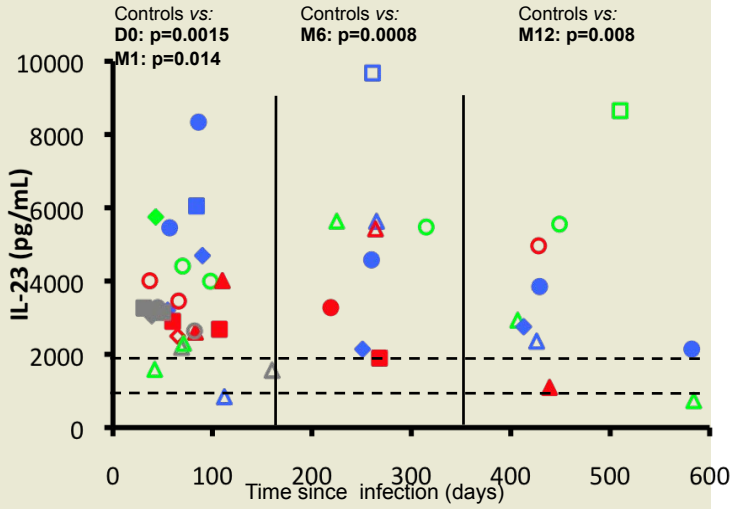
→ IL-12 p40 + p35 = p70
IL23 p40 + p19

- *C. Chougnet, G. Shearer JCI 1996:*
- *Meyaard, Miedema, Blood 1997*
- *Marshall, Trinchieri, Blood 1999*
- *Vanham, Blood 2000*

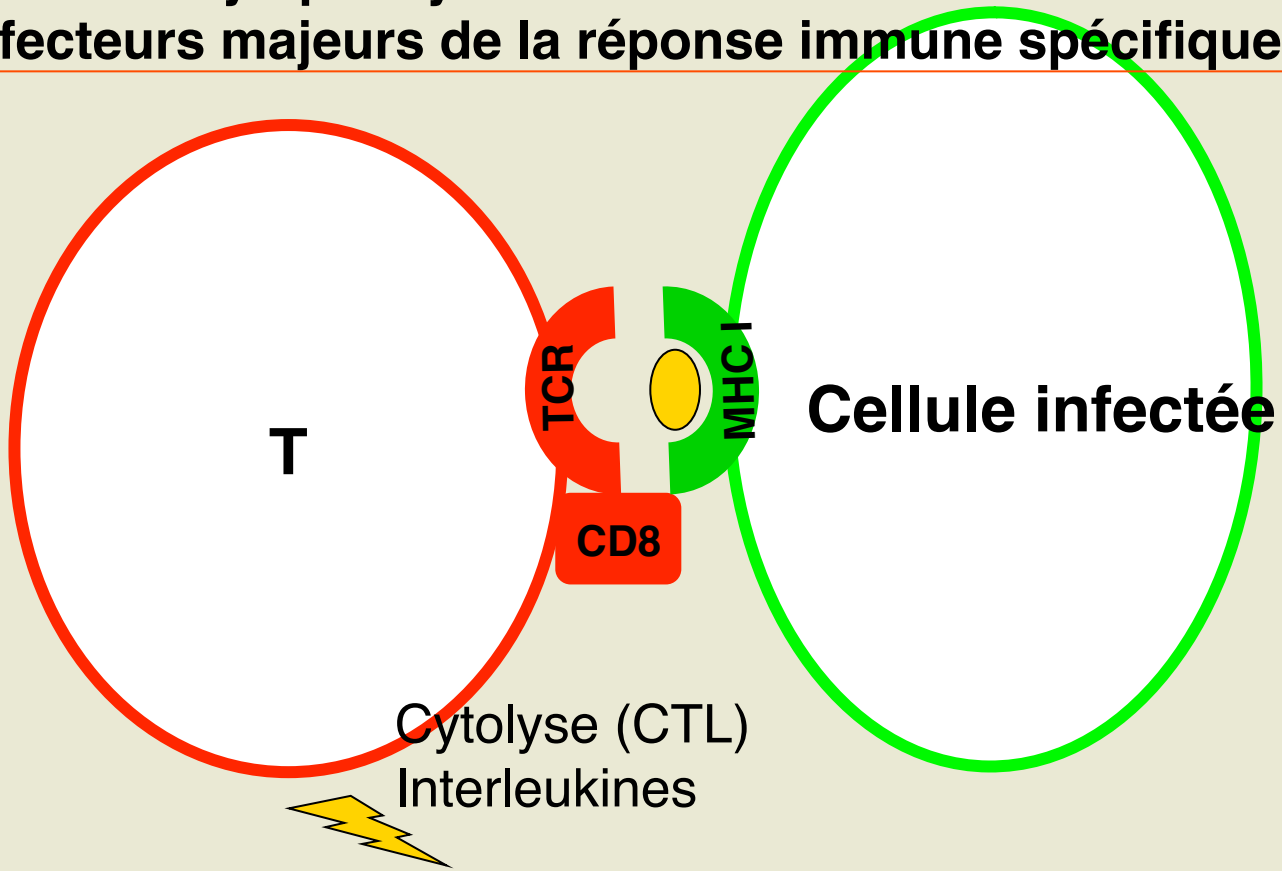
- *Bocchino AIDS 2001*
- *Martinson Cell immunol 2007*
- *Byrnes J Leuko Bio 2008*

- *Louis J Leuko Bio 2010*





Lymphocytes T CD8+ classe I-restreints: Effecteurs majeurs de la réponse immune spécifique du VIH



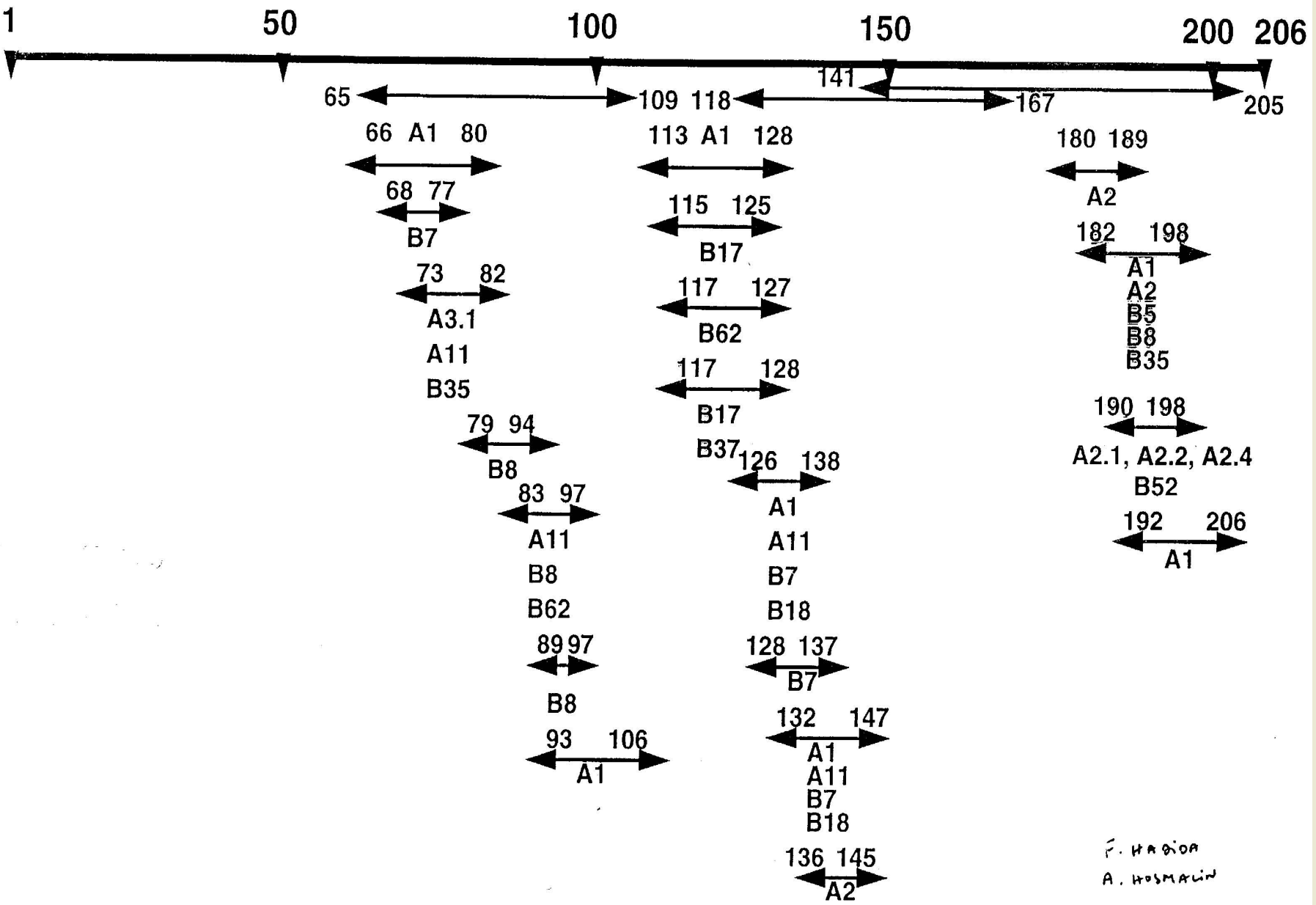
Correlation entre plateau de charge virale à la fin de la primo-infection et le pronostic ***Mellors 1996***

Correlation entre des réponses fortes et diverses, diminution charge virale et pronostic ***Rinaldo 1995, Musey 1997, Ogg 1998***

Déplétion cellules CD8⁺ : flambée de la réplication virale ***Matano 1998, Jin 1999, Schmitz 1999***

Sujets exposés non infectés ***Rowland Jones 1996***

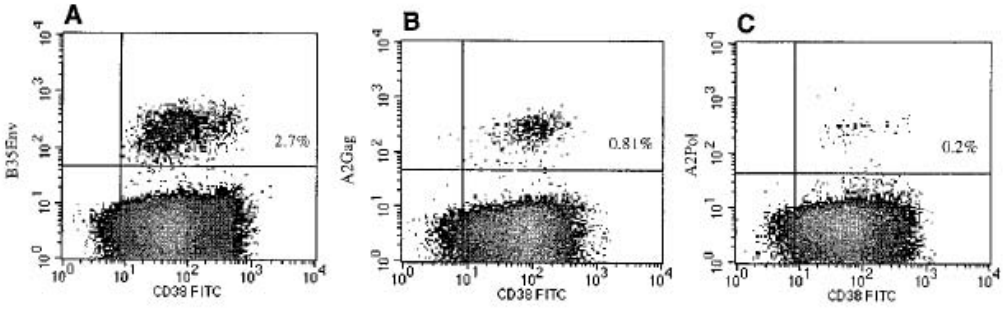
CARTE DES ÉPITOPES CTL DE NEF HIV-1



Correlation entre réponses T CD8+ spécifiques et charge virale plasmatique

Ogg McMichael

Science 1998



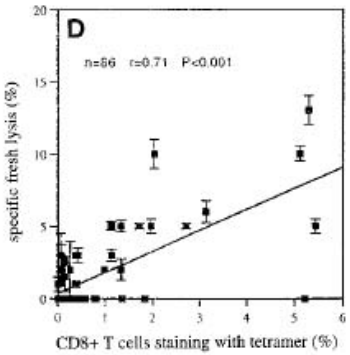
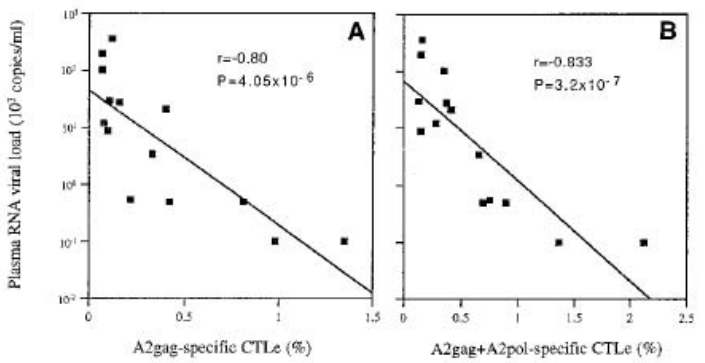


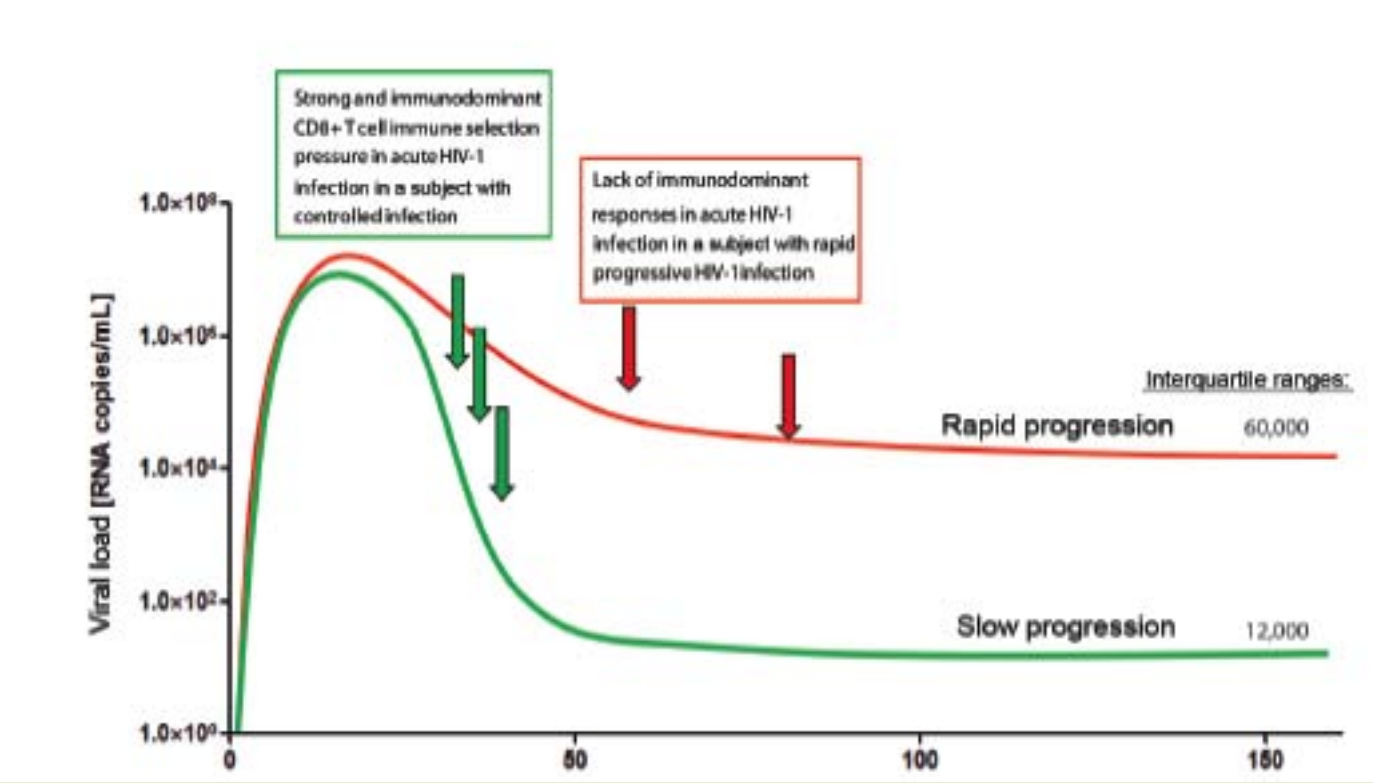
Fig. 1. Analysis of PBMCs for the expression of cell surface markers with a FACS Calibur (Becton Dickinson) and CellQuest software (Becton Dickinson). Antibody to CD38 (anti-CD38)–fluorescein isothiocyanate (Dako) and anti-CD8–Tricolour (Caltag) were used according to standard protocols. Briefly, 10^6 PBMCs were centrifuged at 300*g* for 5 min and resuspended in 50 μl of cold phosphate-buffered saline. Tri-color analysis was performed with tetramer-phycoerythrin, anti-CD8–Tricolor, and anti-CD38. The cells were incubated with tetramer and antibodies on ice for 30 to 60 min and then washed twice before formaldehyde fixation. Gates were applied to contain >99.98% of control samples. Controls for the tetramers included both A*0201-negative individuals and A*0201-positive HIV-1–uninfected donors. (**A** to **C**) $CD8^+$ T cells from three HIV-1–infected individuals with staining for CD38 along the *x* axes and for B*3501-Env tetrameric complex, A*0201-Gag, and A*0201-Pol along the *y* axes, respectively. The tetramer-positive cells make up 0.2 to 2.7% of all $CD8^+$ cells (values are indicated in each plot) and are all $CD38^+$. (**D**) Comparison of the percentage of $CD8^+$ cells staining with tetramer and the uncultured peptide-specific cytolytic activity of PBMCs. Each experiment was performed in triplicate. Donors were all HLA A*0201–positive and were either untreated or treated with combination antiretroviral therapy. Responses to three epitopes were measured [A2Gag, A2Pol, A2EBV BMLF1 280-8 GLCTLVAML (*27*)] and were all included in the data. Subgroup analyses gave identical results, namely, a significant positive correlation (Pearson correlation coefficient) between percentage peptide-specific lysis and percentage of $CD8^+$ T cells staining with each tetramer. By multiple stainings on single samples, we have found tetramer binding to be highly reproducible with variation of less than 5% between stains.

Fig. 2. Association between plasma RNA viral load and the percentage of $CD8^+$ cells staining with (**A**) A2Gag tetramer alone and (**B**) A2Gag and A2Pol tetramers.



Association entre les réponses T CD8+ immuno-dominantes pendant l'infection primaire et le niveau de réplication virale à la fin de cette infection, « viral set point » prédictif du pronostic

Streeck & Nixon J Inf Dis 2010

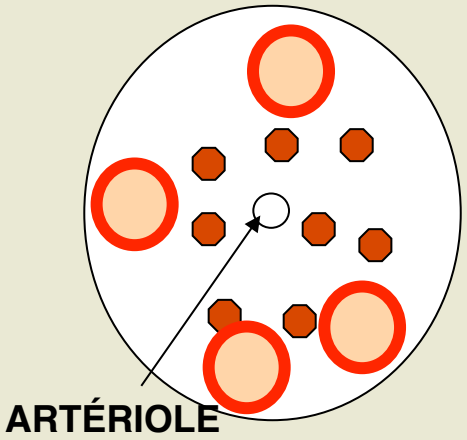


Compartimentalisation de la réponse effectrice CTL dans les pulpes blanches de la rate des patients VIH+

-Réplication majeure du VIH localement dans les organes lymphoïdes secondaires, incluant pulpes blanches de la rate,
mais limitation

-Rôle des T CD8+ dans contrôle réplication

-Infiltration par T CD8+



Mise en évidence fonction effectrice CTL anti-VIH ex vivo dans les pulpes blanches

COLOCALISATION avec

Réplication virale

(ARN splicé env VIH)

Hosmalin, Wain Hobson, Cheynier Blood 2001

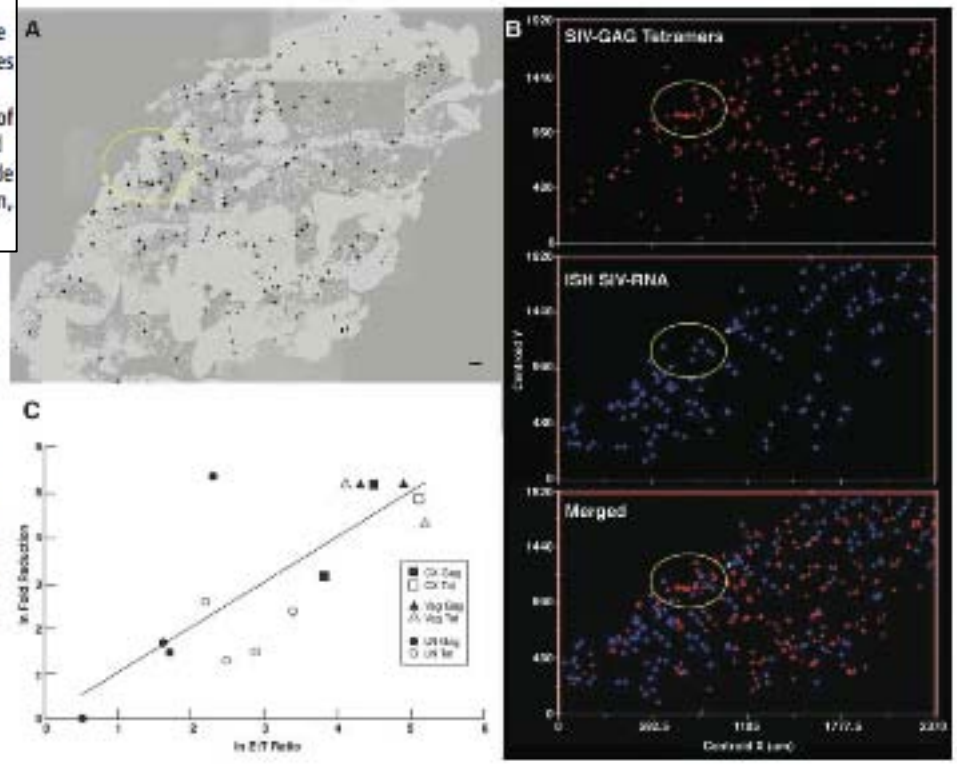
La rapidité et l'amplitude de la réponse effectrice CTL dans les ganglions corrèlent avec le contrôle de la réplication du SIV

Visualizing Antigen-Specific and Infected Cells in Situ Predicts Outcomes in Early Viral Infection

Qingsheng Li,[1] Pamela J. Skinner,[2] Sang-Jun Ha,[3] Lijie Duan,[1] Teresa L. Mattila,[2] Aaron Hage,[2] Cara White,[2] Daniel L. Barber,[4] Leigh O'Mara,[3] Peter J. Southern,[1] Cavan S. Reilly,[5] John V. Carlis,[6] Christopher J. Miller,[7] Rafi Ahmed,[3] Ashley T. Haase[1]*

In the early stages of viral infection, outcomes depend on a race between expansion of infection and the immune response generated to contain it. We combined in situ tetramer staining with in situ hybridization to visualize, map, and quantify relationships between immune effector cells and their targets in tissues. In simian immunodeficiency virus infections in macaques and lymphocytic choriomeningitis virus infections in mice, the magnitude and timing of the establishment of an excess of effector cells versus targets were found to correlate with the extent of control and the infection outcome (i.e., control and clearance versus partial or poor control and persistent infection). This method highlights the importance of the location, timing, and magnitude of the immune response needed for a vaccine to be effective against agents of persistent infection, such as HIV-1.

Li … Haase Science 2009



(centroids) onto a two-dimensional grid measured from a fixed starting position (0,0). Upper panel, Gag-tetramer$^+$ cells; middle panel, SIV RNA$^+$ cells; lower panel, superimposition of upper and middle panels revealing the close spatial proximity of the virus-specific tetramer$^+$ cells with SIV RNA$^+$ throughout the lymph node. The white crosses and encircled areas in the panels are included as points of reference. (C) E:T ratio correlates with reduction in viral load in cervical vaginal and lymphatic tissues. Natural log–transformed viral load fold reductions are plotted against E:T ratios for Gag- and Tat-tetramer$^+$ cells in cervical (CX) and vaginal (Vag) tissues and lymph nodes (LN) from five animals at 20 to 28 dpi. E:T ratios were determined by ISH as described (*13*).

Echappement aux CTL par mutations du VIH et du SIV

Impaired Cytotoxic T Lymphocyte Recognition Due to Genetic Variations in the Main Immunogenic Region of the Human Immunodeficiency Virus 1 NEF Protein

By Isabelle Couillin,*§ Béatrice Culmann-Penciolelli,‡§ Elisabeth Gomard,‡§ Jeannine Choppin,‡§ Jean-Paul Levy,§ Jean-Gérard Guillet,‡§ and Sentob Saragosti*§

J Exp Med 1994

DONOR	VIRAL CLONES	73													82	84								92	94
				2											10			2						9	
	LAI	T	P	Q	V	P	L	R	P	M	T	Y	K	A	A	V	D	L	S	H	F	L	K	E	K
W8	8-1	R	-	-	-	-	-	-	-	-	-	F	-	G	-	L	-	-	-	-	-	-	-	-	-
	8-2	K	-	-	-	-	-	-	-	-	-	-	-	G	-	L	-	-	-	-	-	-	-	-	-
	8-3	K	-	-	-	-	-	-	-	-	-	-	-	G	-	L	-	-	-	-	-	-	-	-	-
	8-4	K	-	-	-	-	-	-	-	-	-	-	-	G	-	L	-	-	-	-	-	-	-	-	-
	8-5	K	-	-	-	-	-	-	-	-	-	-	-	G	-	L	-	-	-	-	-	-	-	-	-
	8-6	K	-	-	-	-	-	-	-	-	-	-	-	G	-	L	-	-	-	-	-	-	-	-	-
	8-7	K	-	-	-	-	-	-	-	-	-	-	-	G	-	L	-	-	-	-	-	-	-	-	-
	8-8	K	-	-	-	-	-	-	-	-	-	-	-	G	-	L	-	-	-	-	-	-	-	-	-
	8-9	K	-	-	-	-	-	-	-	-	-	-	-	G	-	L	-	-	-	-	-	-	-	-	-
	LAI	T	P	Q	V	P	L	R	P	M	T	Y	K	A	A	V	D	L	S	H	F	L	K	E	K
W24	24-1	R	-	-	-	-	-	-	-	-	-	S	R	-	-	R	-	-	-	-	-	-	-	-	-
	24-2	R	-	-	-	-	-	-	-	-	-	-	-	-	-	F	-	-	-	-	-	-	R	-	-
	24-3	R	-	-	-	-	-	-	-	-	-	S	R	-	-	R	-	-	-	-	-	-	-	-	-
	24-4	R	-	-	-	-	-	-	-	-	-	S	R	-	-	R	-	-	-	-	-	-	-	-	-

Figure 2. Mutations in the putative anchorage residues (in italic and bold type) or in flanking residues of two HLA-A11–restricted NEF epitopes from different isolates from HIV-infected donors W8 and W24. The LAI peptides recognized by CTL from these donors (see Fig. 1) are shown in gray boxes.

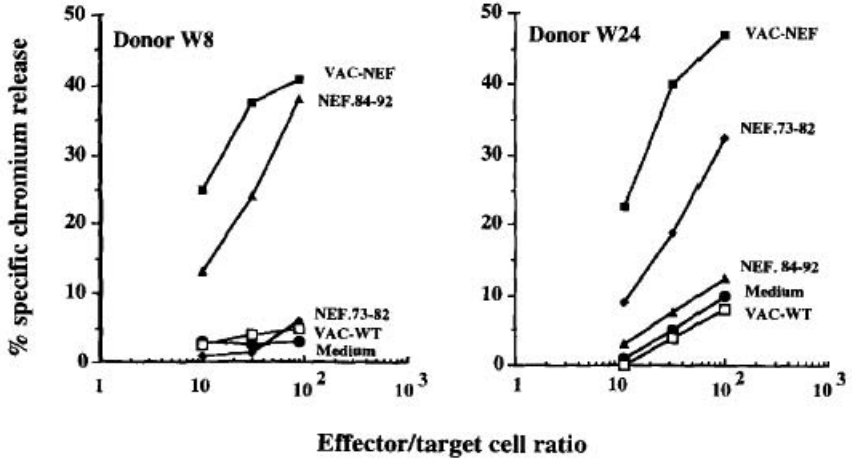
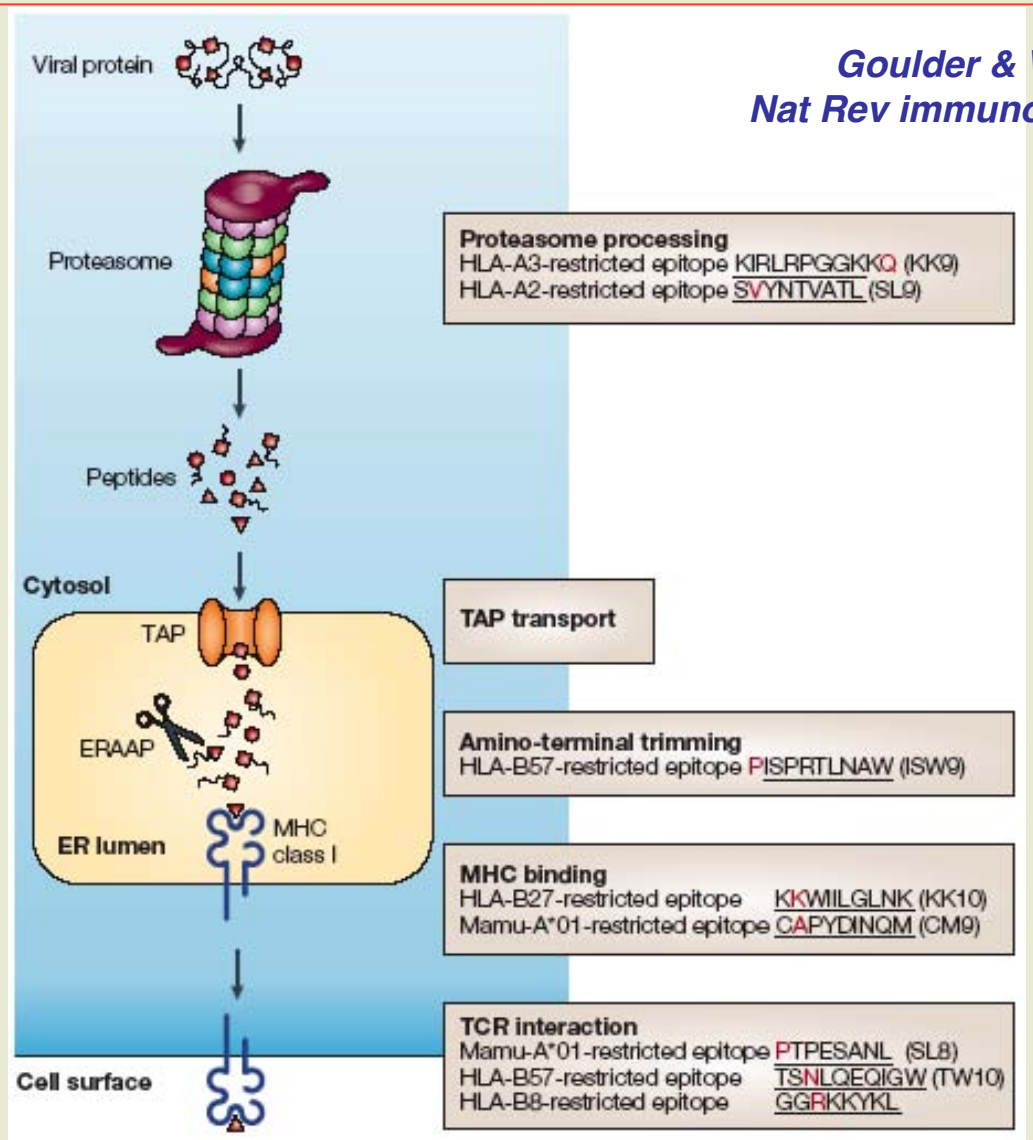


Figure 1. Cytotoxic activity of CTL prepared from the PBMC of W8 and W24 HLA-A11 donors against two HLA-A11–restricted epitopes in the central region of NEF protein. Effector cells were prepared as described in Materials and Methods. Target cells shared only the HLA-A11 molecule with effector cells, and were either infected with VAC-WT or VAC-NEF, or incubated with synthetic peptides NEF 73-82 and NEF 84-92.

Mécanismes d'échappement par mutations du VIH et du SIV



Goulder & Watkins
Nat Rev immunol 2004;4:630

Equilibre entre les facteurs contribuant à l'échappement du VIH et du SIV

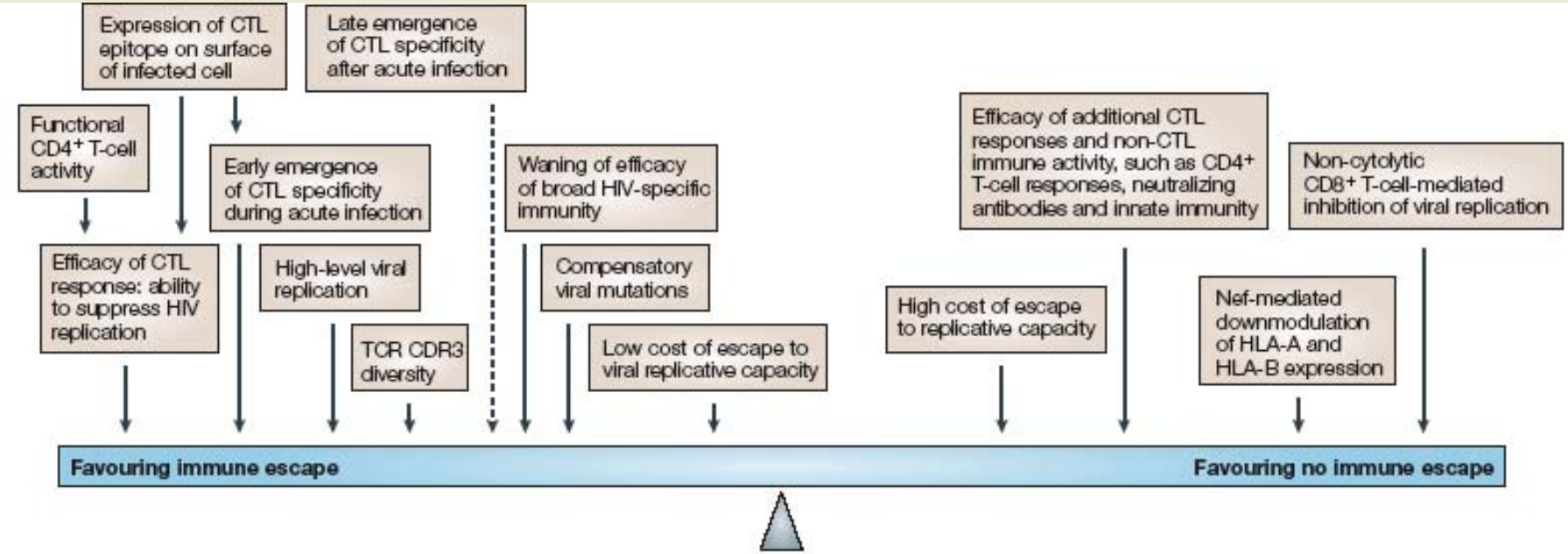


Figure 5 | **The dynamic balance between the factors that contribute to the occurrence of escape.** In general, the factors that favour immune escape oppose those that favour optimal viral replicative capacity. The main selection forces in operation are described in the text. The fine balance between these opposing selection forces is crucially altered throughout the course of infection: as viral load is brought rapidly under control following acute infection, as functional CD4+ T-cell activity is lost, as broadly based HIV-specific immunity wanes and as compensatory mutations arise that reduce the fitness cost to the virus of cytotoxic T-lymphocyte (CTL) escape mutants. Dashed arrow indicates weaker selection pressure. CDR, complementarity-determining region; Nef, negative factor; TCR, T-cell receptor.

Goulder & Watkins
Nat rev immunol 2004;4:630

De la naïveté à la mémoire

NAIVES	MEMOIRE	MEMOIRE EFFECTRICES
CCR7+ CD62L+ CD45 RA+ CD27+ CD28+	CCR7+ CD62L+ CD45 RA - CD27+ CD28+ PERFORINE -	CCR7- CD62L- CD45 RA- CD27- CD28- PERFORINE +
	CTL ANTI CMV	CTL ANTI CMV
	CTL ANTI VIH	Déficit parmi les T spécifiques du VIH

Lanzavecchia 2000
Appay 2000
Champagne 2001

« Epuisement » fonctionnel des lymphocytes T CD8+ lors des infections virales chroniques

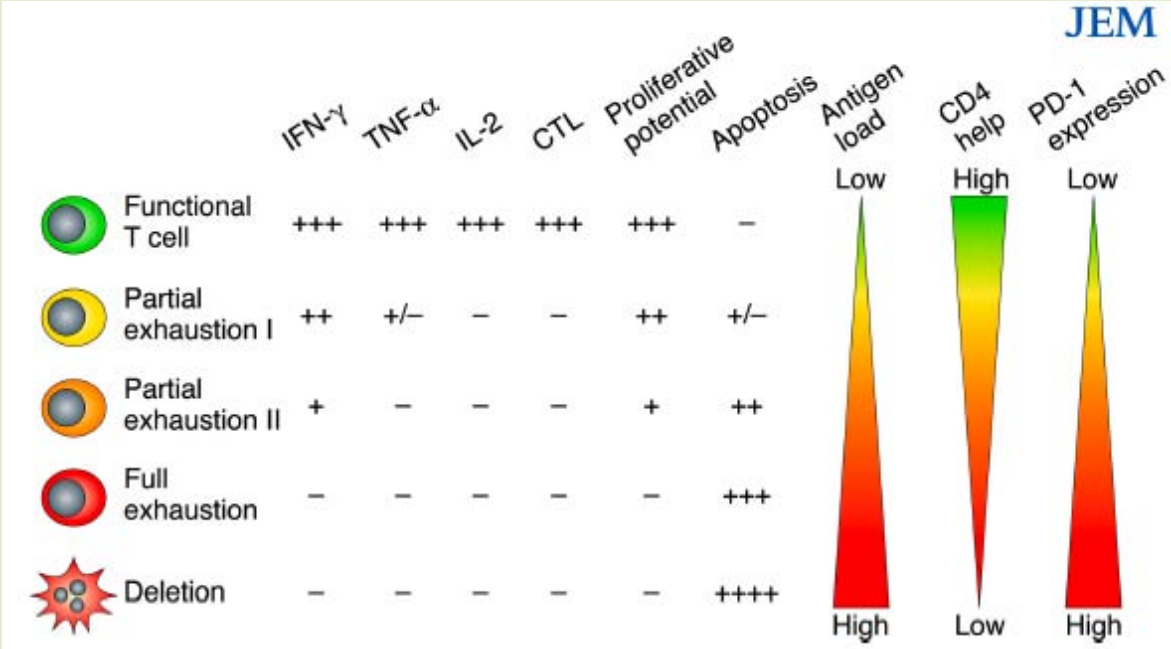
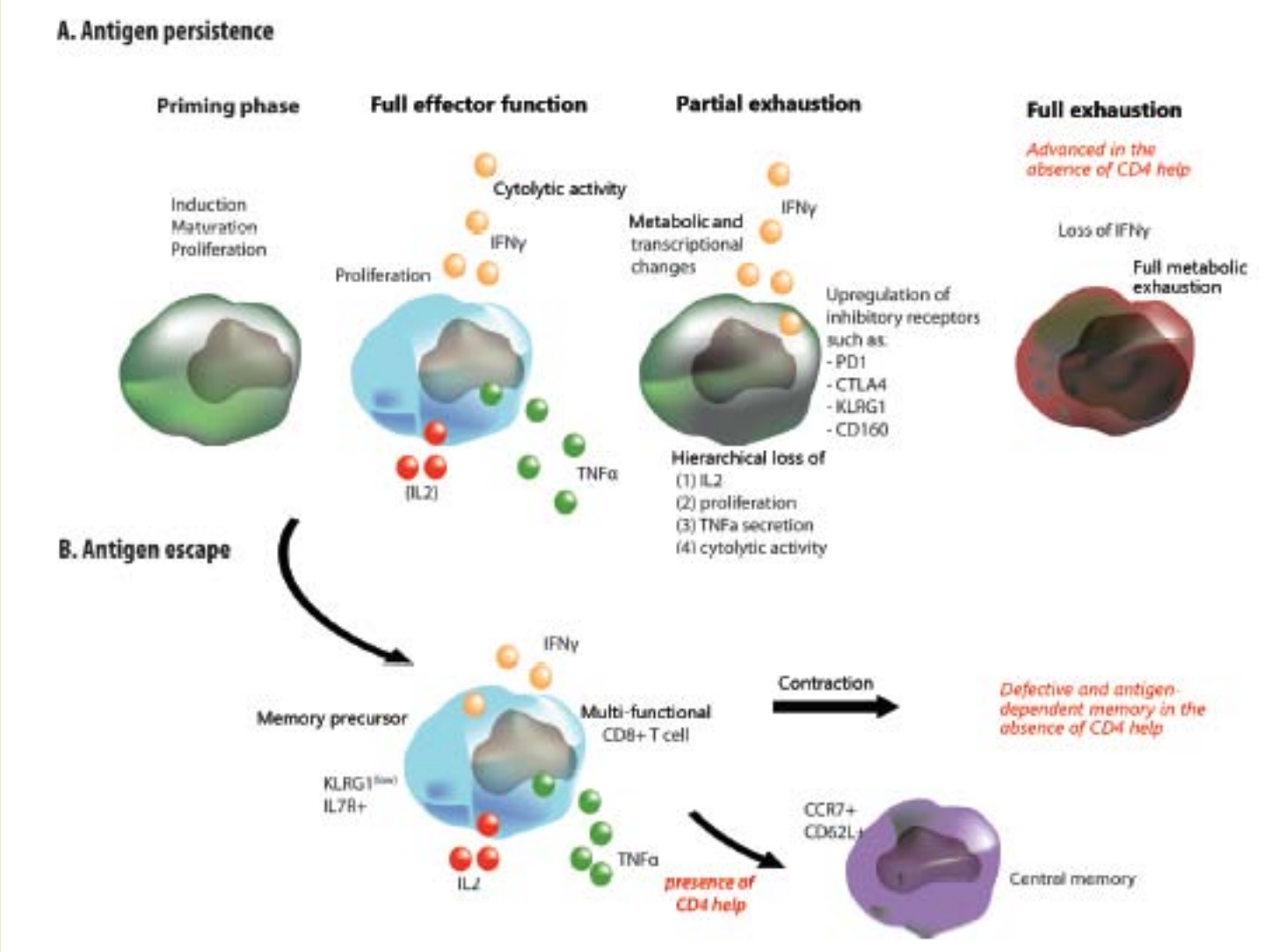


Figure 1. T cell exhaustion during chronic viral infections. Virus-specific CD8 T cells posses multiple functions including production of IFN-γ, TNF-α, IL-2, cytotoxicity, antigen-driven proliferation, and resistance to apoptosis. During chronic infections, functions can be exhausted. Exhaustion represents a spectrum from mild (Partial exhaustion I: little IL-2 and poor TNF-α and cytotoxicity) to moderate (Partial exhaustion II: modestly defective IFN-γ, cytotoxicity, and little IL-2 or TNF-α) to severe (Full exhaustion: lack of IFN-γ, TNF-α, IL-2, and cytotoxicity). Finally, physical deletion (apoptosis) of T cells occurs. Proliferative potential decreases concomitantly with the loss of other functions while apoptosis increases. Antigen and CD4 help strongly influence exhaustion; as antigen increases and/or CD4 help decreases, virus-specific T cells become more exhausted. Recent studies now identify the PD-1–PD-L pathway as a key regulator of exhaustion. Increased expression of PD-1 by virus-specific T cells, and PD-L1 by APCs, leads to more severe exhaustion during chronic viral infection.

From
Freeman, Sharpe, J Exp Med 2006

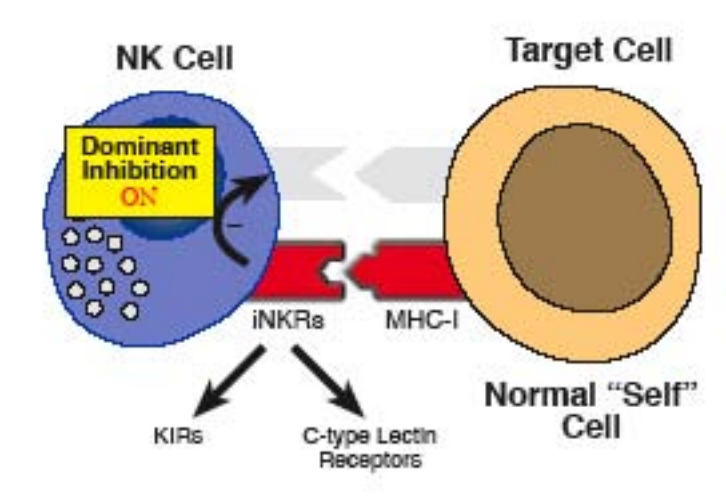
Modèle schématique du développement de la mémoire et de l'épuisement progressif des lymphocytes T CD8+ lors de l'infection par le VIH

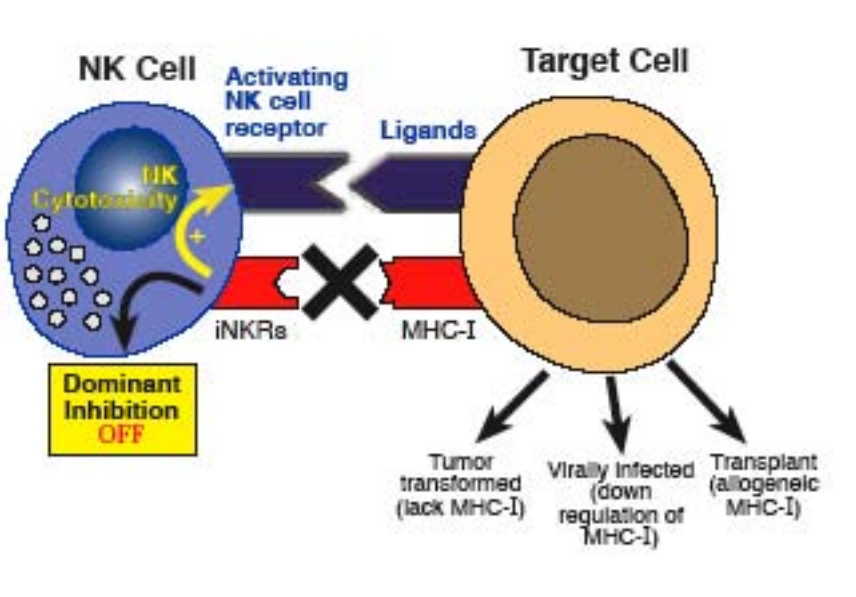
Streeck & Nixon J Inf Dis 2010



Cellules NK

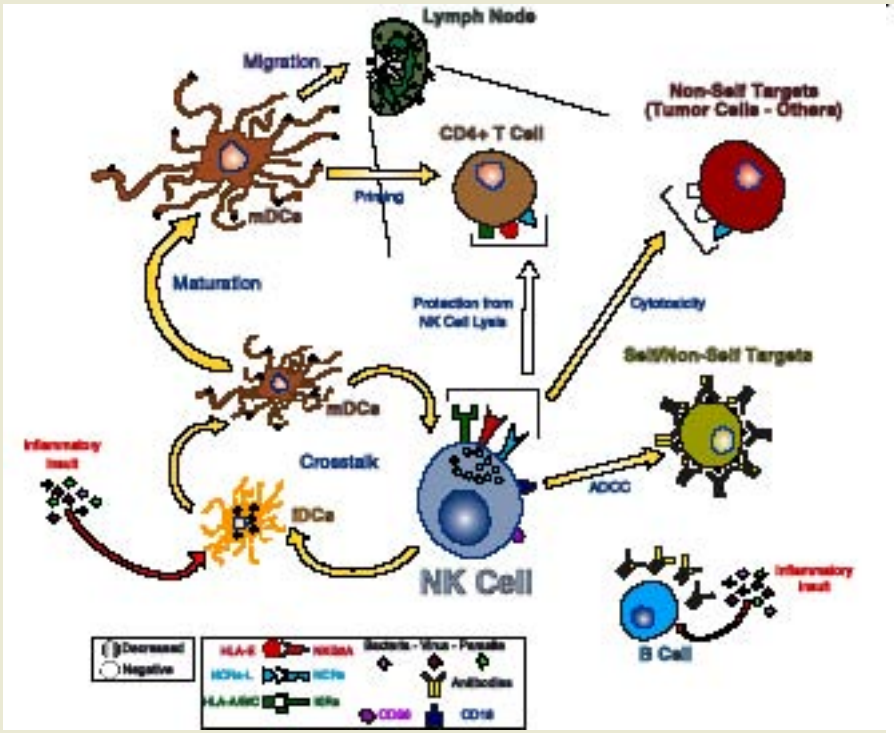
Mavilio et al, Springer 2010

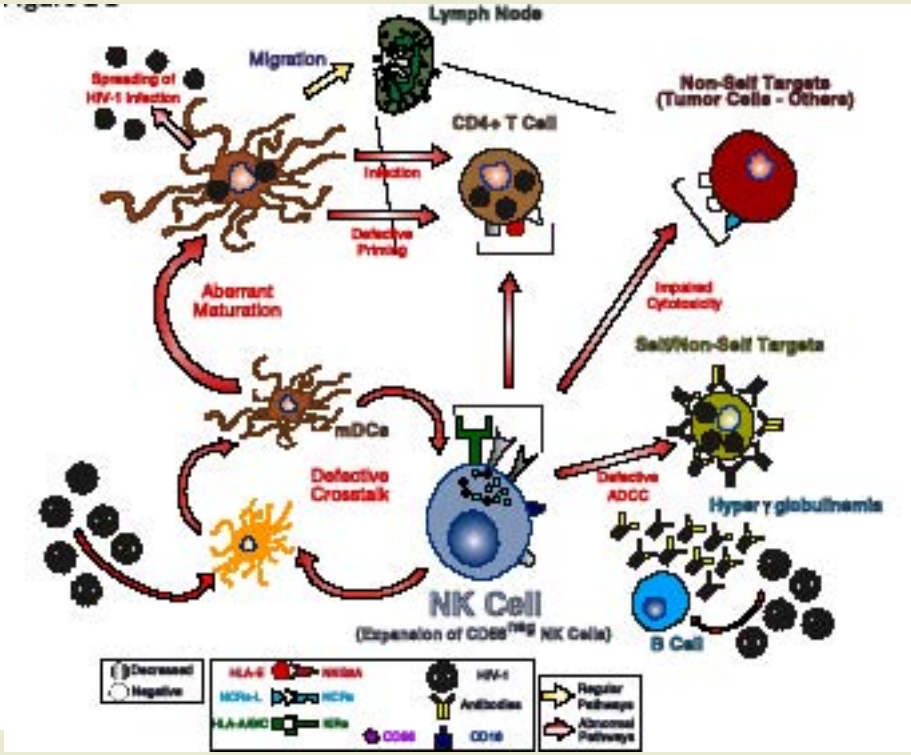




CELLULES NK ET VIH

Mavilio et al, Springer 2010





Neutralisation du VIH par les anticorps

-Les Ac neutralisants préviennent la contamination de mère à enfant

-Le virus passe principalement de cellule à cellule

-La fenêtre d'opportunité des Ac neutralisants: au moment de la contamination, au site de l'infection: IgA (et IgG) au niveau des muqueuses

Burton

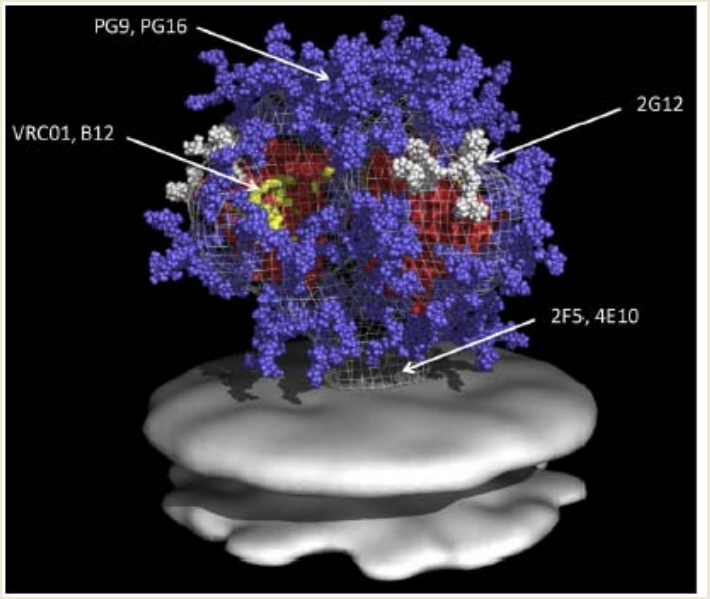
Poignard

Sattentau

Moore

Bomsel

etc



McElrath, Haynes J Inf Dis 2010

Echappement du VIH aux réponses anticorps

-Erreurs de la réverse transcriptase, mutations très fréquentes, Enorme diversité des protéines et notamment les enveloppes témoignant d'une sélection par les Ac

-Masquage des épitopes B par la glycosylation: très peu de sites accessibles, très peu d'Ac neutralisants reconnus

Diversité du VIH:
Résultat de la sélection par les réponses immunes

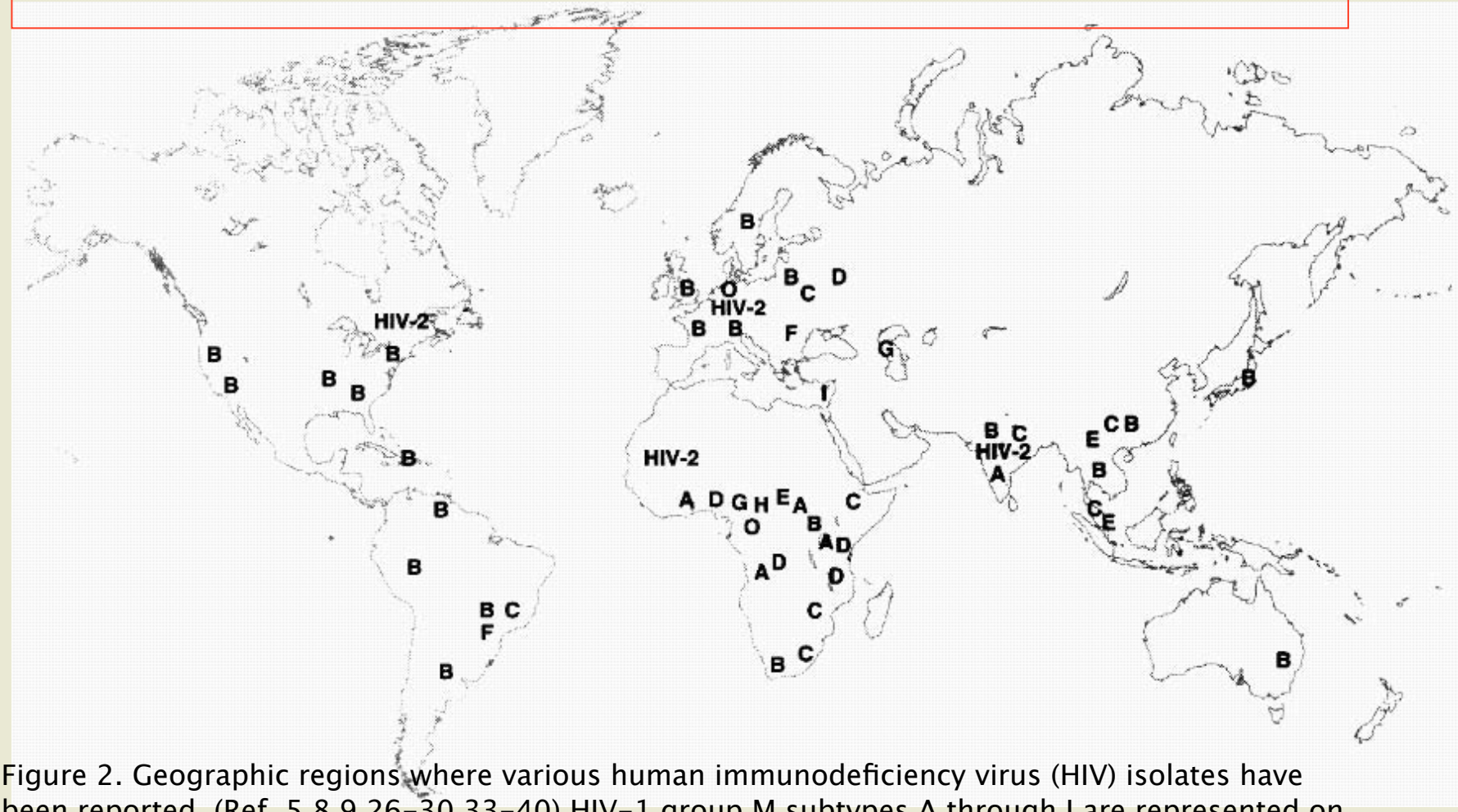
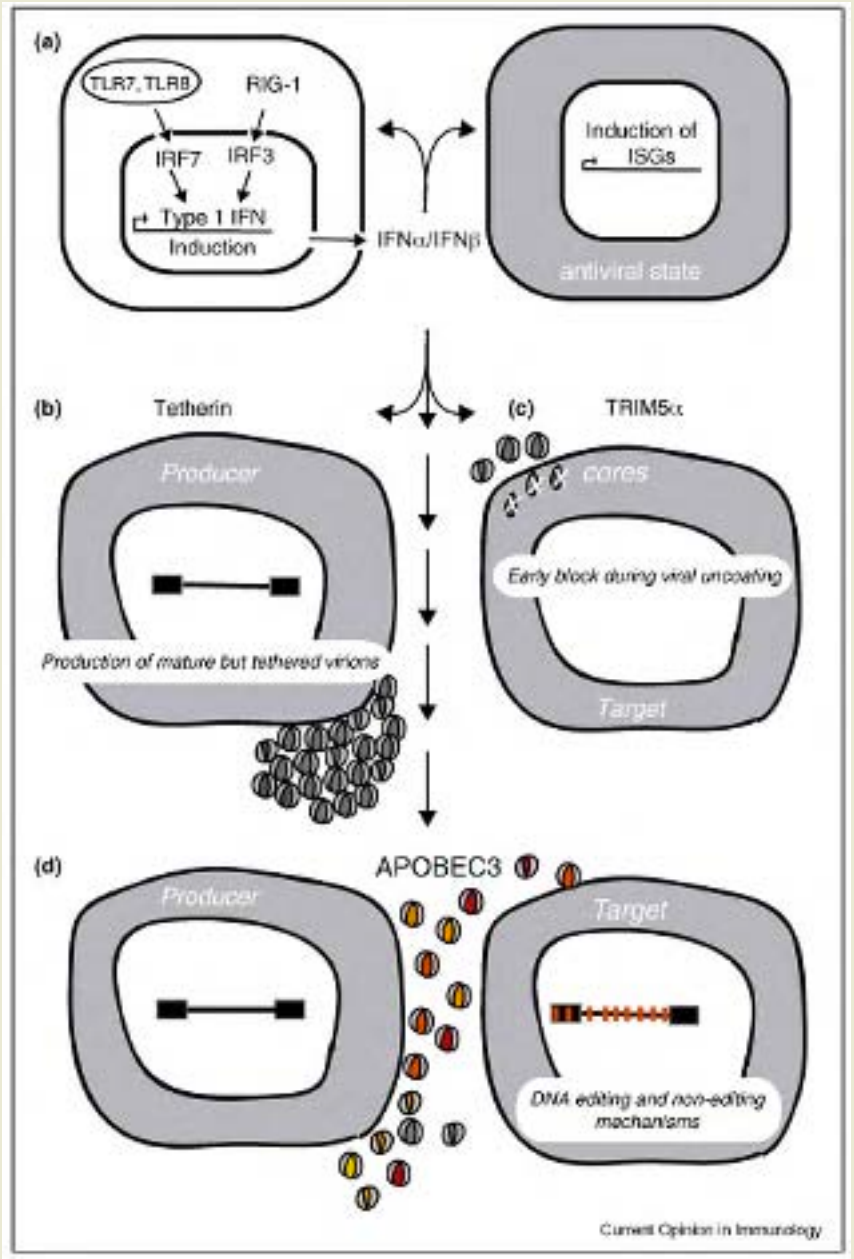


Figure 2. Geographic regions where various human immunodeficiency virus (HIV) isolates have been reported. (Ref. 5,8,9,26–30,33–40) HIV–1 group M subtypes A through I are represented on the map by letters A through I, while HIV–1 group O is represented by the letter O. The points on the map represent the approximate locations where persons infected with certain HIV strains have been reported and does not imply the actual distribution of HIV strains (which is currently unknown). This map does not represent an exhaustive list of all reported subtypes and does not include isolated reports of single cases or recently imported cases.



Facteurs de restriction

Innate immune mechanisms that may contribute to HIV control. (a) Virus recognition by TLR7/8 and RIG-I activates IRF7 and IRF3, respectively, leading to IFN transcription. IFN is secreted and sets off signaling cascades resulting in up-regulation of >100 INF stimulated genes (ISG), creating an 'antiviral state' (symbolized by grey color). TLR7/8 are located in endosomal compartments of DC while RIG-1 is found in the cytoplasm of many cells. TLR7/8 sense predominantly single-stranded RNA and cellular mRNA while the substrates for RIG-I are double-stranded RNA or RNA with 50-triphosphate. HIV virions and HIV-infected cells preferentially trigger TLR7/8. Intrinsic restriction factors are intracellular molecules that inhibit HIV. They are constitutively expressed but also inducible by IFN. Their mode of action in the absence of viral counterstrategies is depicted. Grey color symbolizes the antiviral state of the cell. (b) Tetherin reduces virion release by tethering mature virions to the plasma membrane or/and to each other. Viral counterstrategy: HIV-1 accessory protein Vpu. (c) TRIM5a interferes with the uncoating step early in the viral life cycle. The known TRIM5a variants have little activity against HIV-1 but restrict multiple other retroviruses including SIVmac. Viral counterstrategy: TRIM5a-insensitive HIV-1 capsid protein. (d) The APOBEC3 family comprises seven distinct cytidine deaminases, which differ both in their antiviral activity and their susceptibility to HIV-1 Vif-mediated proteosomal degradation. APOBEC3 activity becomes only apparent in the next cycle of infection when, during reverse transcription, virion-encapsidated APOBEC3 molecules lead to proviral mutagenesis. The red color in the core of the mature virions represents incorporated APOBEC3 molecules. Viral counterstrategy: HIV-1 accessory protein Vif induces APOBEC3G/3F degradation.

Le facteur de restriction Bst2 ou tetherine

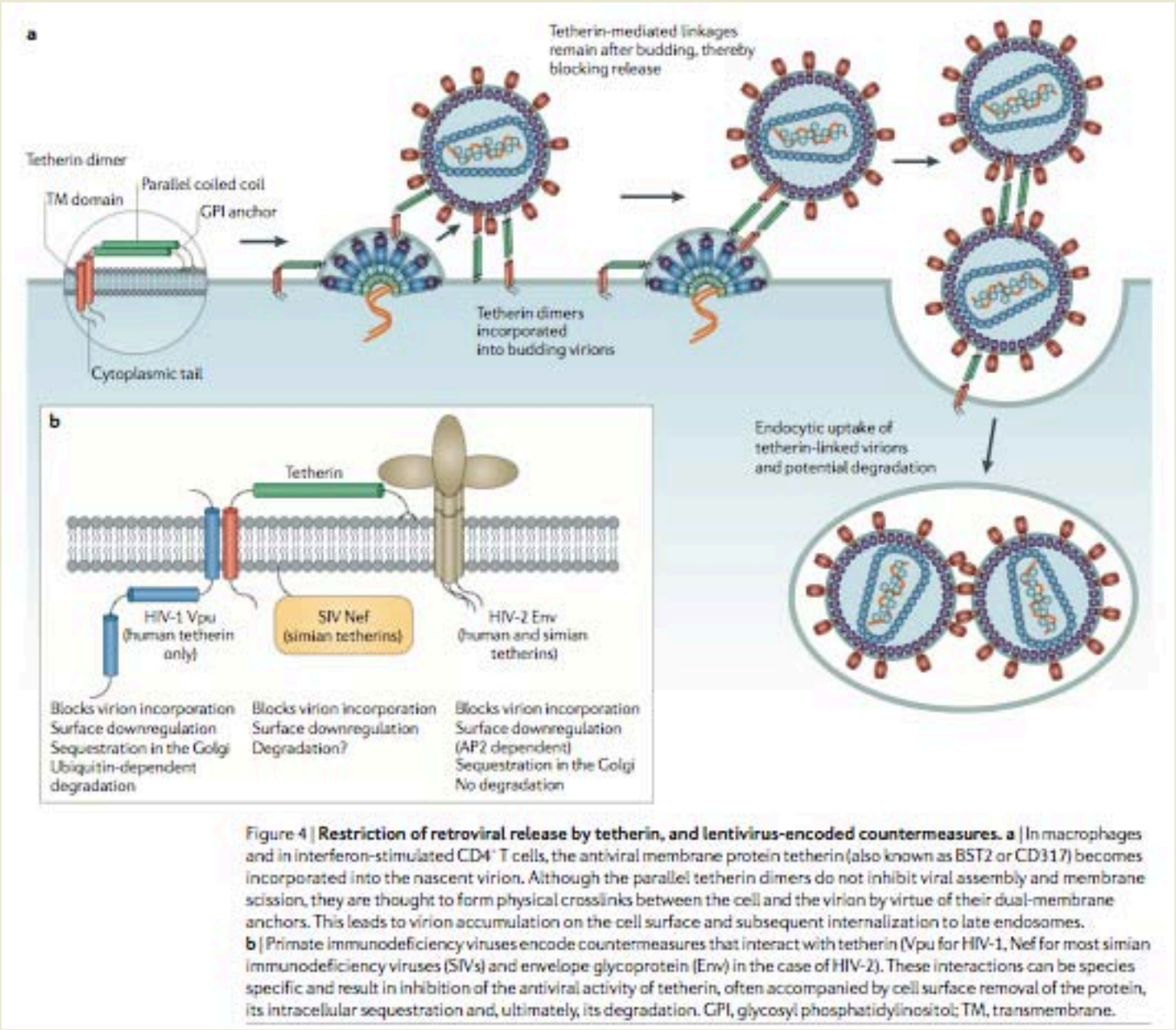
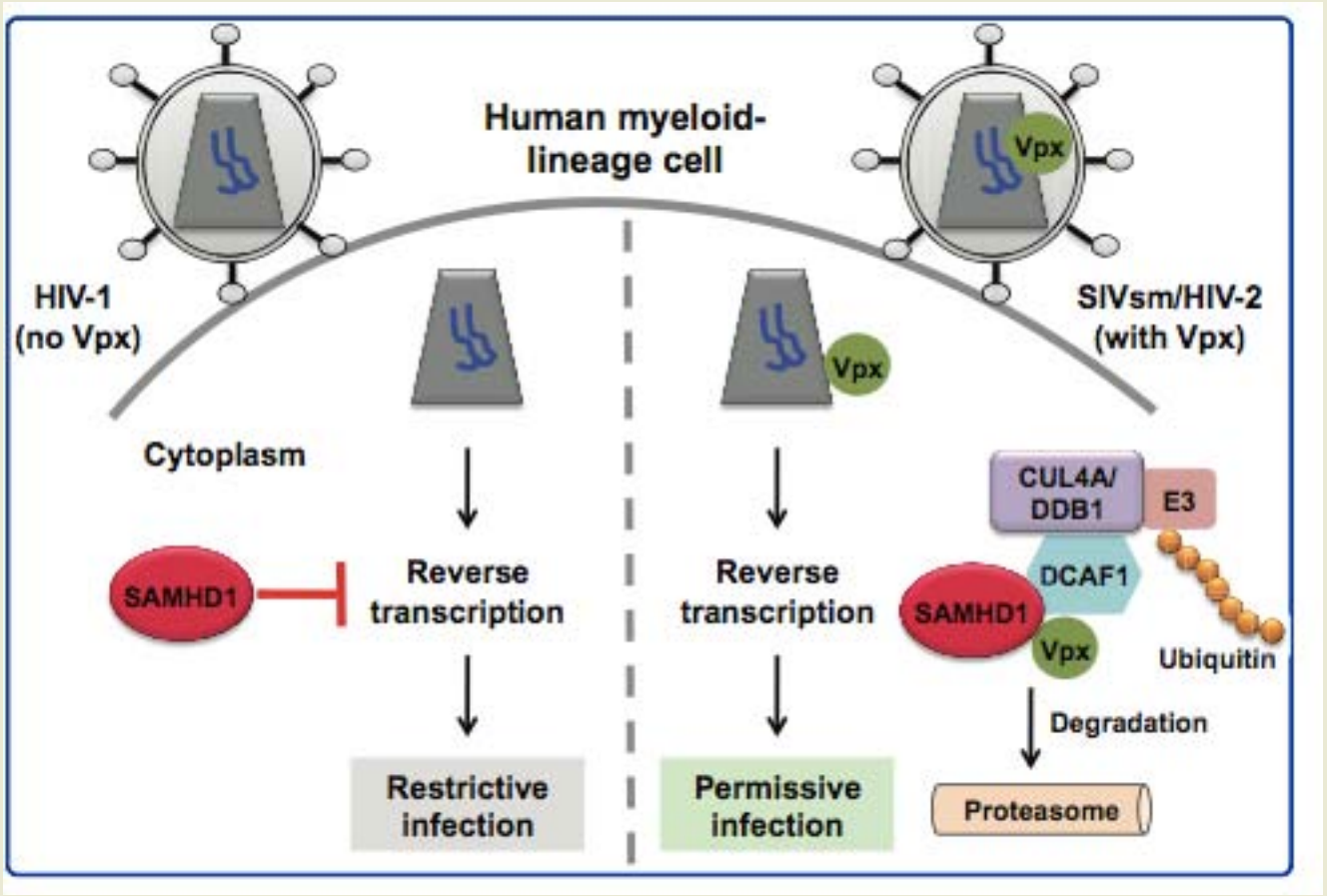


Figure 4 | **Restriction of retroviral release by tetherin, and lentivirus-encoded countermeasures. a** | In macrophages and in interferon-stimulated CD4$^+$ T cells, the antiviral membrane protein tetherin (also known as BST2 or CD317) becomes incorporated into the nascent virion. Although the parallel tetherin dimers do not inhibit viral assembly and membrane scission, they are thought to form physical crosslinks between the cell and the virion by virtue of their dual-membrane anchors. This leads to virion accumulation on the cell surface and subsequent internalization to late endosomes. **b** | Primate immunodeficiency viruses encode countermeasures that interact with tetherin (Vpu for HIV-1, Nef for most simian immunodeficiency viruses (SIVs) and envelope glycoprotein (Env) in the case of HIV-2). These interactions can be species specific and result in inhibition of the antiviral activity of tetherin, often accompanied by cell surface removal of the protein, its intracellular sequestration and, ultimately, its degradation. GPI, glycosyl phosphatidylinositol; TM, transmembrane.

St Martin-Serrano & Neil, Nature Rev Microbiology 2011

Le facteur de restriction SamHD1



Vpx interacts with the E3 ubiquitin ligase complex to target the restriction factor SAMHD1 for proteasomal degradation. Human myeloid-lineage cells that are non-permissive to HIV-1 infection express high levels of SAMHD1, which appears to act early in infection at the reverse transcription step. HIV-1 has not evolved a viral antagonist to counter this restriction; however, SIVsm/SIVmac and HIV-2 express Vpx to circumvent this restriction. Vpx targets SAMHD1 using the host cell E3 ubiquitin ligase complex, in which Vpx interacts with the DCAF1 subunit of the CUL4A/DDB1 ubiquitin ligase to degrade SAMHD1 via the proteasome. This allows HIV-1 reverse transcription to occur and viral replication to complete.

St Gelais & Wu, Retrovirol 2100 about Laguette Nature 2011 and Hrecka Nature 2011

Le VIH, *pirate*
de la cabine de pilotage du système immunitaire

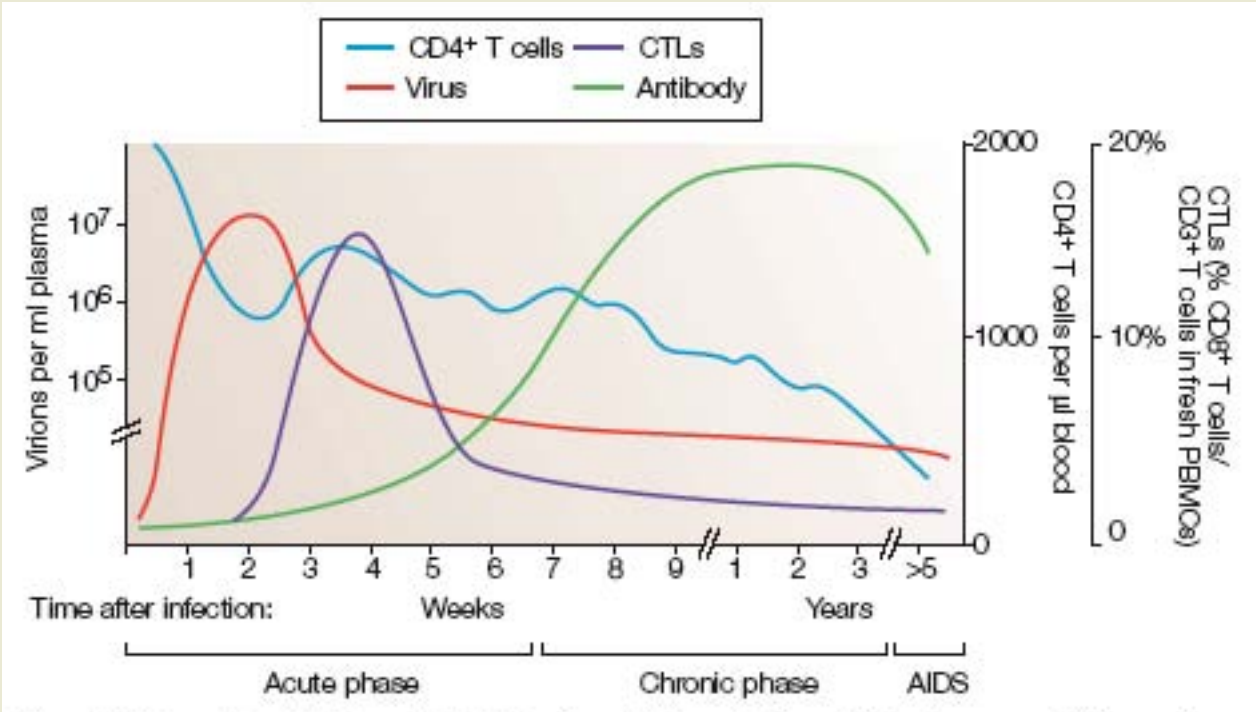
1. Cellules cibles du VIH et réponses immunitaires contre le VIH
2. Histoire naturelle de l'infection et déterminants de la pathogénicité:

   comment reprendre le contrôle de l'avion?

Histoire naturelle de l'infection par le VIH

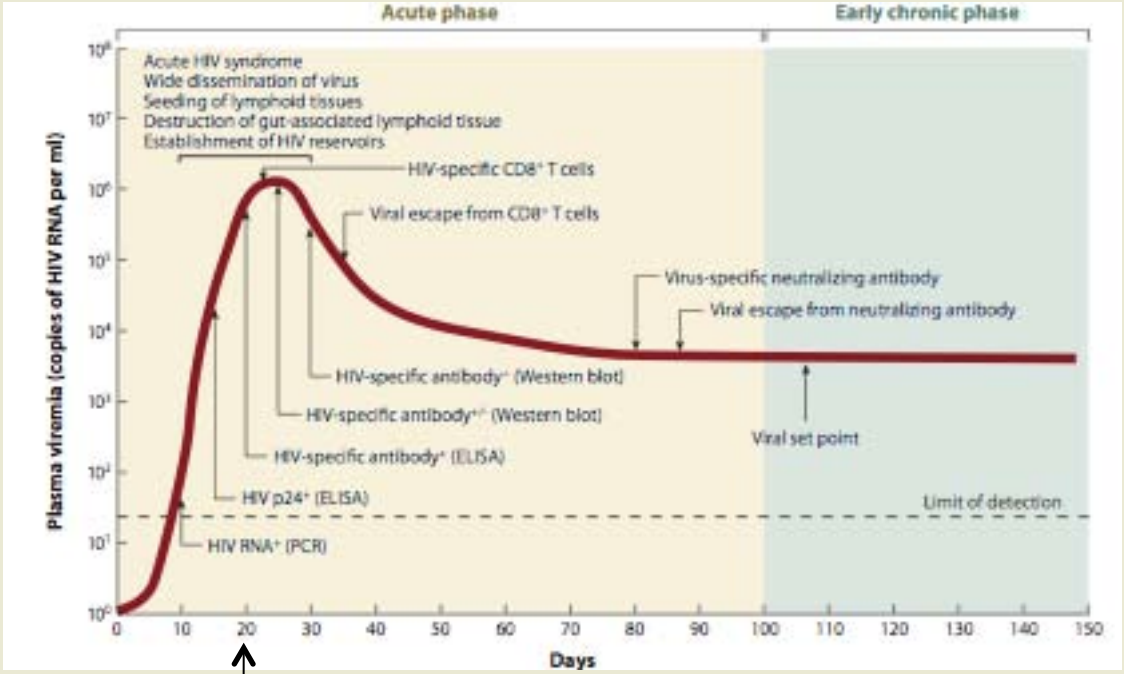
R5

X4



Goulder & Watkins Nat Rev immunol 2004;4:630

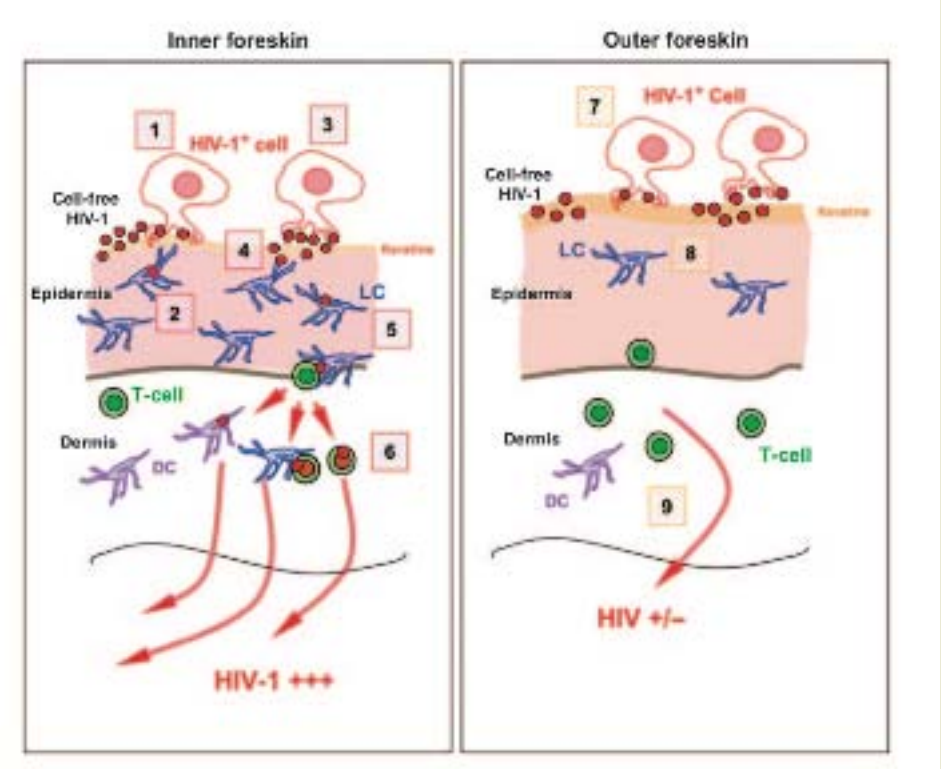
Importance de la phase aigüe (souvent inaperçue) de l'infection par le VIH



Fenêtre d'opportunité thérapeutique?

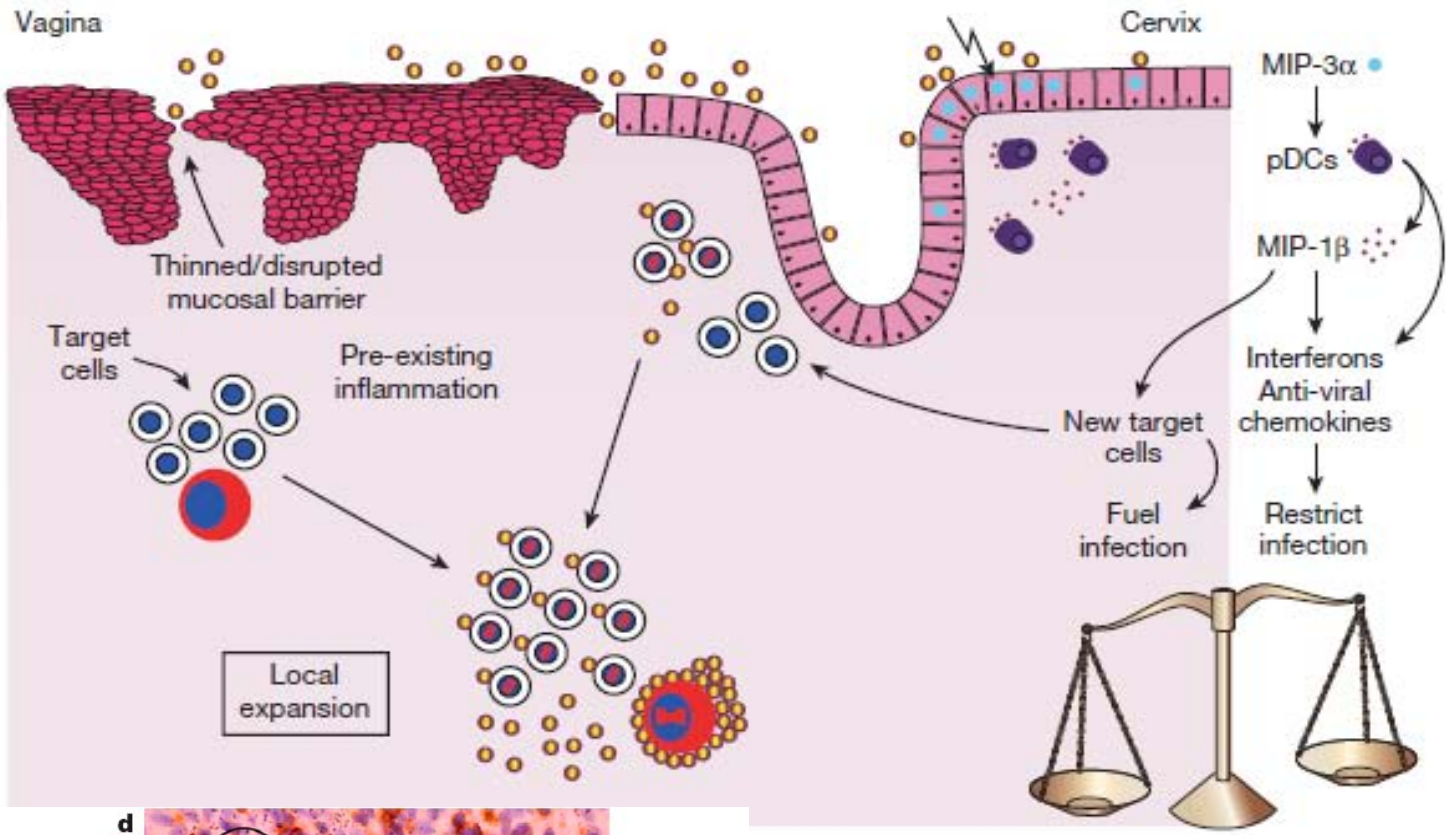
Moir… Fauci Ann Rev Path 2011
McMichael Nat Rev Immunol 2010

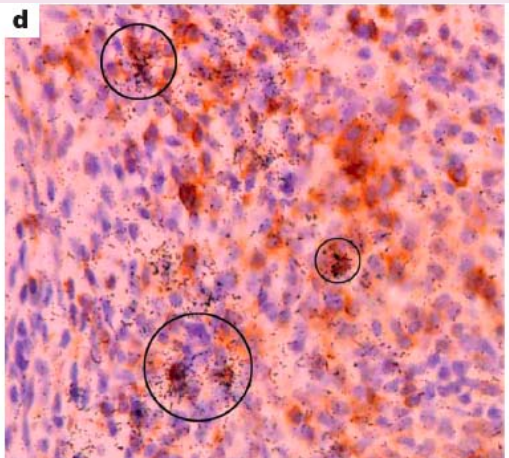
En 1 heure, HIV-1 utilise les synapses virales pour entrer efficacement dans la muqueuse du prépuce externe, mais pas interne, et provoque des conjugués entre cellules de Langerhans et lymphocytes T CD4+



Bomsel, Mucosal Immunol 2010

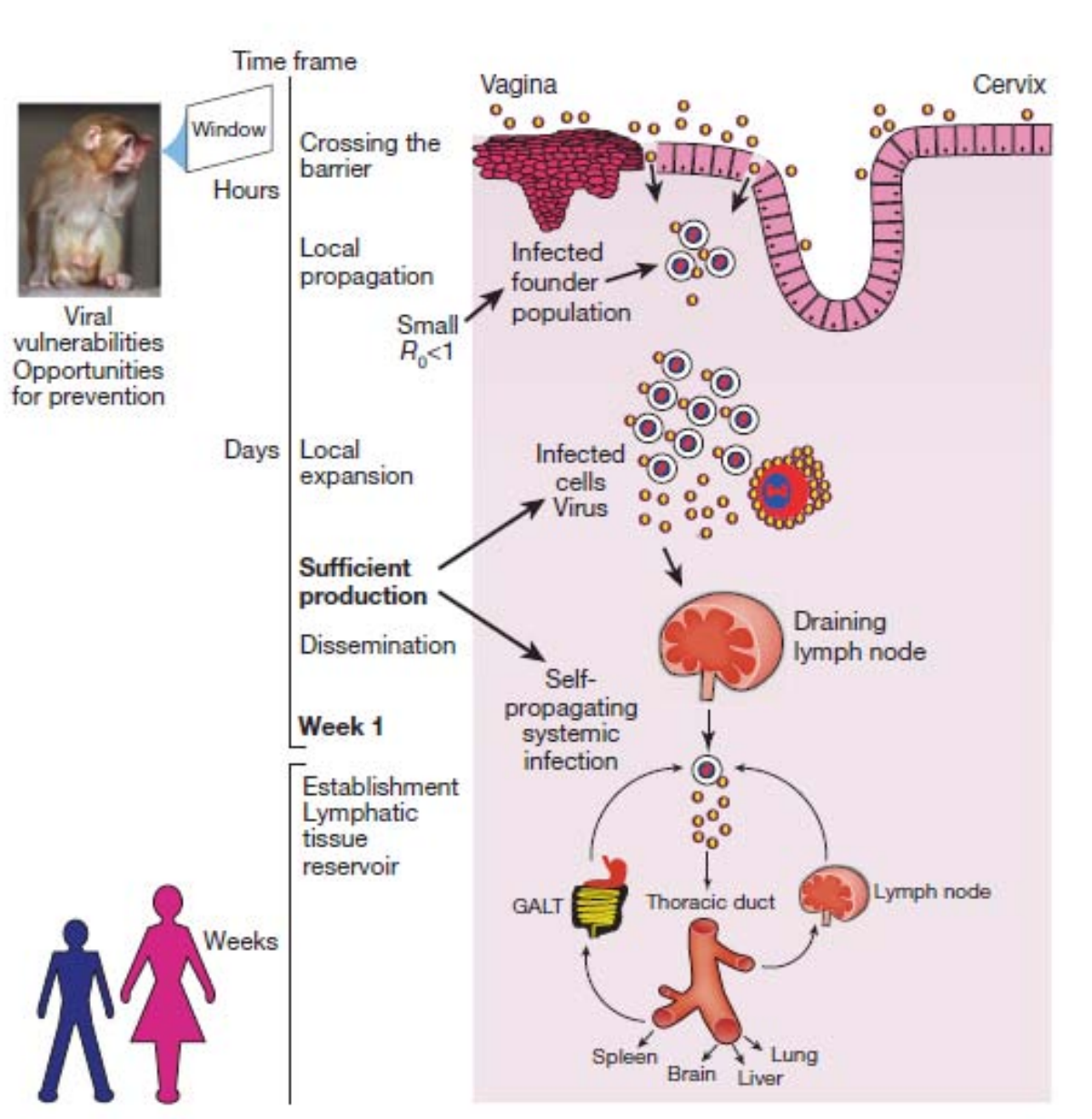
Les pDC domicilieraient rapidement à la muqueuse endo-cervicale après contact avec de fortes doses de SIV, favorisant l'infection des lymphocytes T CD4+





D'après Haase Nature 2010

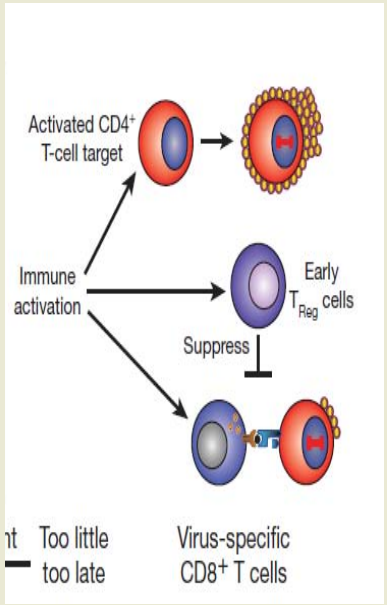
Une fenêtre d'opportunité pour l'intervention très étroite!



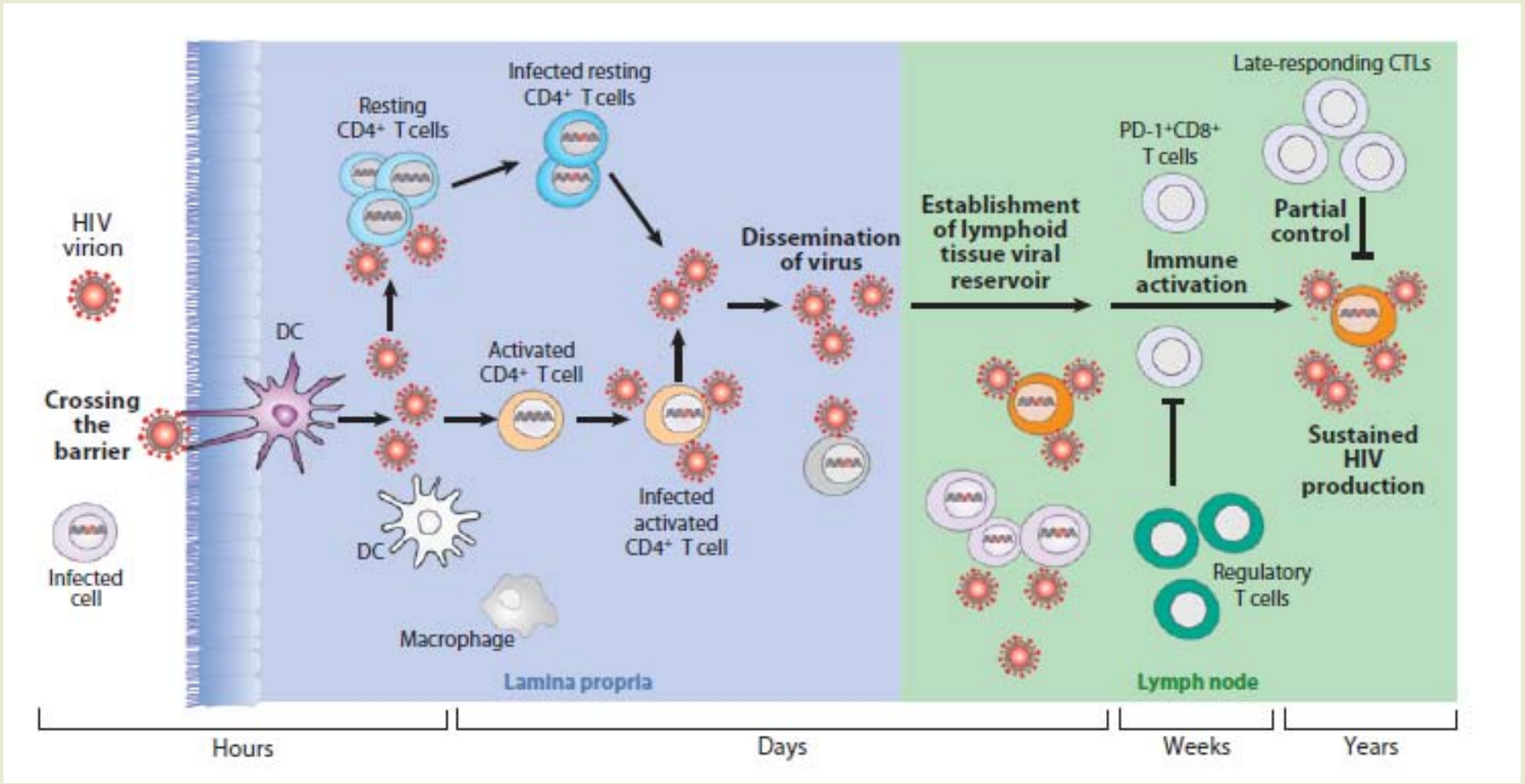
D'après Haase Nature 2010

Heures

Jours



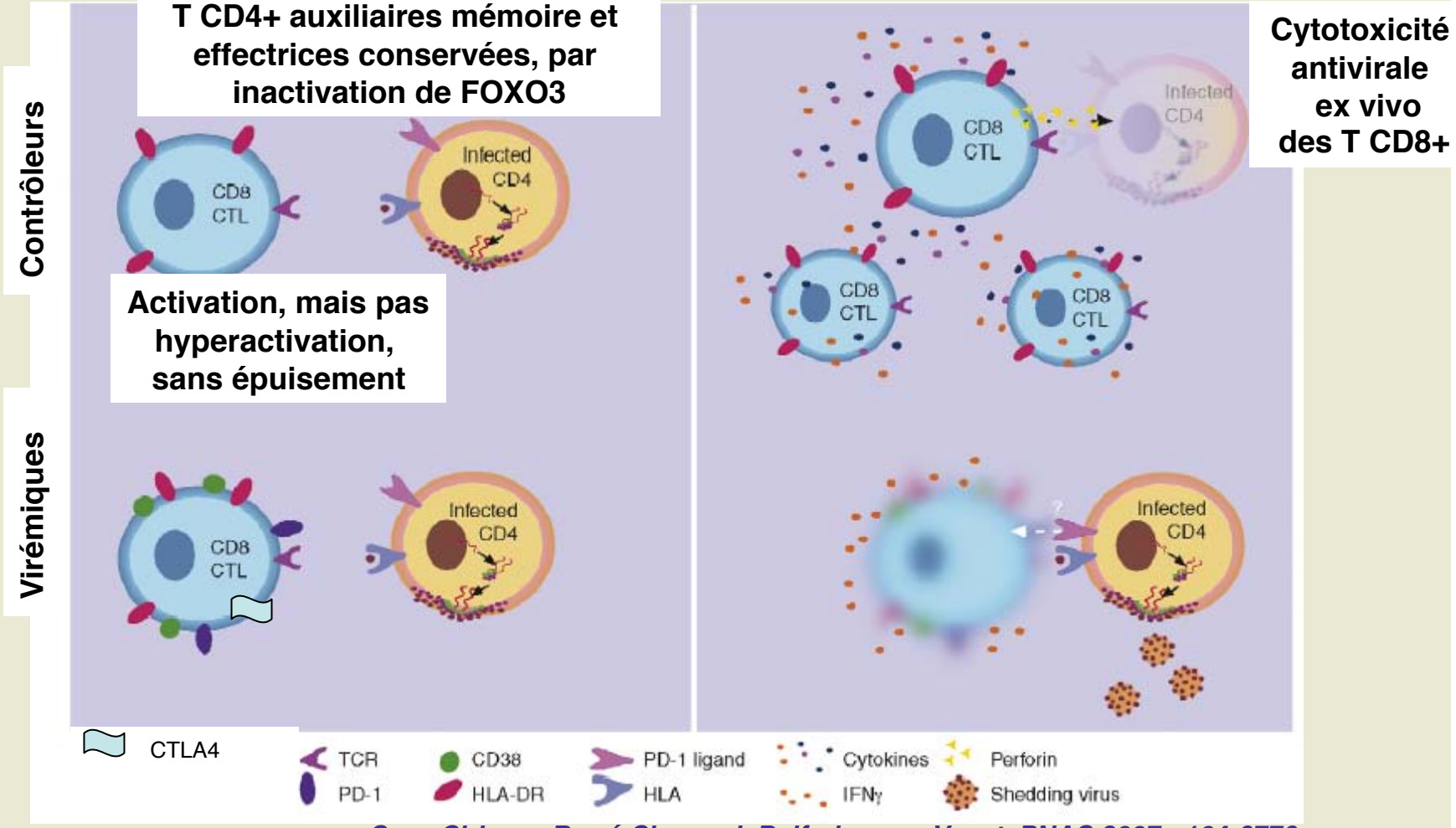
Une fenêtre d'opportunité pour l'intervention très étroite… mais que faire après!



D'après Moir Fauci Annu Rev Med 2011

Les patients «contrôleurs » ont des réponses immunes plus efficaces que les patients virémiques

Que peut-on apprendre d'eux afin de conférer leurs propriétés aux autres patients?



Cohorte de l'ANRS
-infectés depuis plus de 10 ans
-Contrôle spontané de la charge virale
-Virus infectieux
-moins de 1% des patients

Saez-Cirion… Barré-Sinoussi, Delfraissy, … Venet, PNAS 2007 ; 104:6776
Saez-Cirion, Pancino, Sinet, Venet,Lambotte, ANRS EP36 HIV controller study group, Trends Immunol 2007; 28:532
Van Grevenynghe.. Sekaly, Nature Medicine 2008; 14:266
Kaufmann…Walker Nature Immunol 2007;8:1246

nature medicine

Comparaison des modèles d'infection pathogène ou non pathogène

Toward an AIDS vaccine: lessons from natural simian immunodeficiency virus infections of African nonhuman primate hosts

Sodora Nat Med 2009

Review

Trends in Microbiology Vol.16 No.12

de Silva, Cotten, Rowland-Jones Trends Microbiol 2008

Table 1. Comparison of HIV-1, HIV-2 and SIV_{sm}

	HIV-1 in humans	HIV-2 in humans	SIV in sooty mangabeys
Clinical illness	Majority develop AIDS; <2% behave as LTNPs	~20–25% develop AIDS; remainder behave as LTNPs	No significant clinical illness
Plasma viral load	High in acute illness and during disease progression (10^5–10^7 RNA copies per ml); could be undetectable in asymptomatic phase	High in progressors (10^3–10^4 RNA copies per ml); undetectable in majority.	High (10^5–10^7 RNA copies per ml)
$CD4^+$ count	Decreases during acute infection and rarely returns to normal levels, followed by steady decline over time	Normal in LTNPs; reduced $CD4^+$ count in progressors	Normal, preserved T-cell subsets
$CD4^+$ depletion in gut associated-lymphoid tissue	Massive depletion	Not known	Yes
Vertical transmission	Up to 40% in breast-feeding mothers	<4%	Not known
Immune activation	Elevated, even in subjects with undetectable VL	Not elevated in LTNPs; increased in progressors and predicts disease progression	Not elevated
T cell proliferation	Increased turnover of both $CD4^+$ and $CD8^+$ T cells	Not known	Normal
Thymopoiesis	Reduced	Enhanced	Normal
T cell apoptosis	Increased	Lower than HIV-1	Not increased
Virus-specific $CD8^+$ T cell response	Vigorous, Gag-specific responses correlated with lower VL	Vigorous; magnitude and Gag peptide specificity show inverse correlation with VL	Present but modest; no relationship with VL
Selection of cytotoxic T lymphocyte escape variants	Occurs frequently and might be associated with clinical decline	Not known	Reported
Virus-specific $CD4^+$ T cell responses	Interferon-gamma (IFNγ) responses present throughout infection but IL-2 secretion and proliferation correlate with LTNP status	IFNγ responses present in most subjects but IL-2 secretion and proliferation correlate with LTNP status	Modest IFNγ responses in most animals but IL-2 secretion is uncommon

Reduced CCR5 coreceptor and CD4 receptor expression on T cells
Brenchley, Silvestri, Douek J Inf Dis 2010

Hyperactivation du système immunitaire -> immunodeficience

- **Hyperactivation du système immunitaire infection pathogène HIV, SIV :**

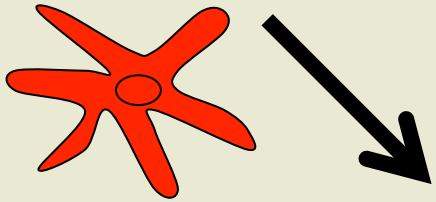
  Infection CD4+ T lymphocytes activées
  Activation dans Muqueuse digestive
  Lésions muqueuses
  Destruction lymphocytes T CD4+ Th1 Th17
  Translocation produits bactériens
  Brenchley 2009

- **Stimulation experimentale chronique -> immunodeficience**

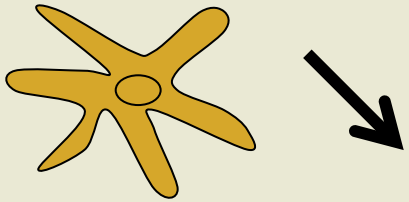
  CD27-CD70 ***Tesselaar… Van Lier Nat Imm 2002***
  TLR9 Heikenwalder 2004; TLR7 Benziger Blood 2009

Impact de l'infection par VIH-1 sur la numération des DC et des monocytes

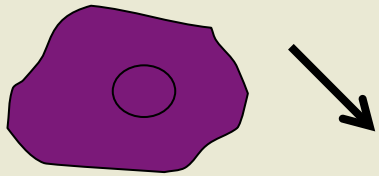
DC myéloïdes BDCA-3^{+}



DC myéloïdes BDCA-1^{+}

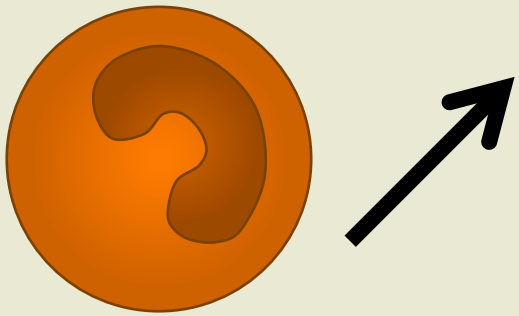


DC plasmacytoïdes, pDC

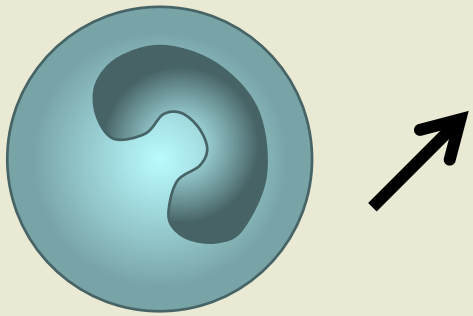


Correlation avec production *in vitro* IFN type I basse, mauvais contrôle charge virale, déficit immunitaire

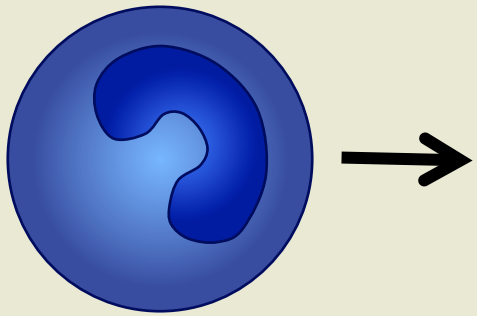
monocytes CD14$^{+/-}$CD16^{++}



monocytes intermédiaires CD14^{+}CD16^{+}



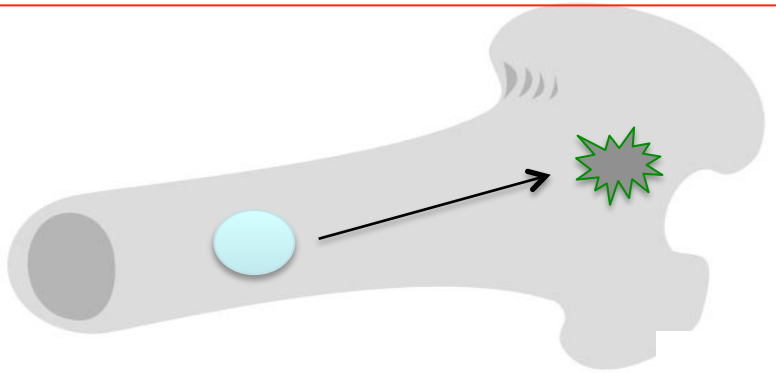
monocytes classiques CD14^{++}CD16^{-}



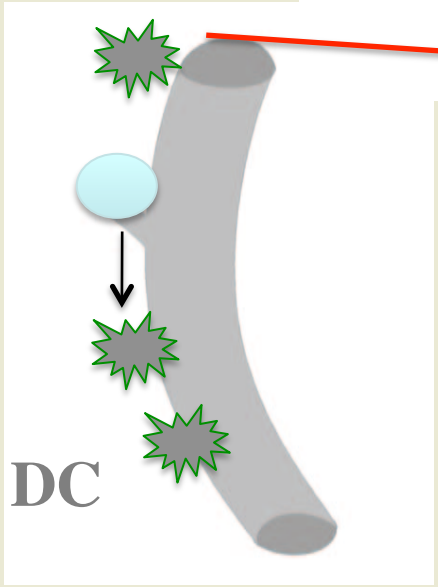
Thieblemont 1995, Ancuta 2000, Pulliam 1999, Dutertre, submitted

Hosmalin, Patterson, Gotch, Levy, Soumelis, Liu, Rinaldo, Barratt-Boyes, Siegal, Fistgerald-Bocarsly, Wilson, Chehimi, Montaner, Anthony, De Sousa, Bhardwaj

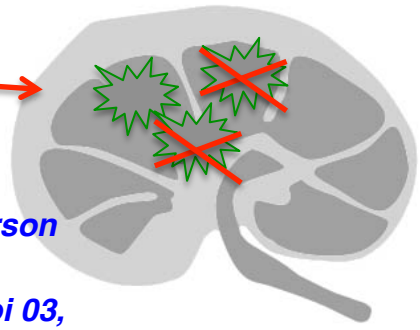
La domiciliation dans les organes lymphoïdes, suivie d'apoptose, rendent compte au moins en partie de la déplétion des pDC circulantes lors de l'infection par le VIH



Moëlle osseuse (central)



Sang



Organe Lymphoide

Domiciliation

Foussat Emilie 01, Loré Anderson 02, Dillon 08

Zimmer Barratt-Boyes 02, Choi 03, Reeves 07 Brown 07 & 09

Diop 08

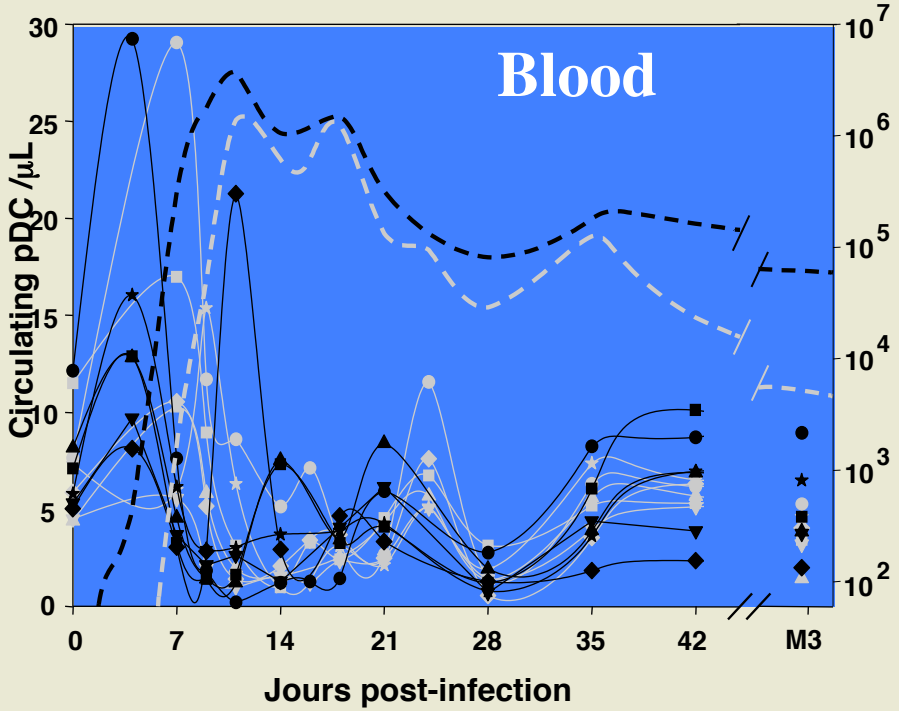
Malleret 08

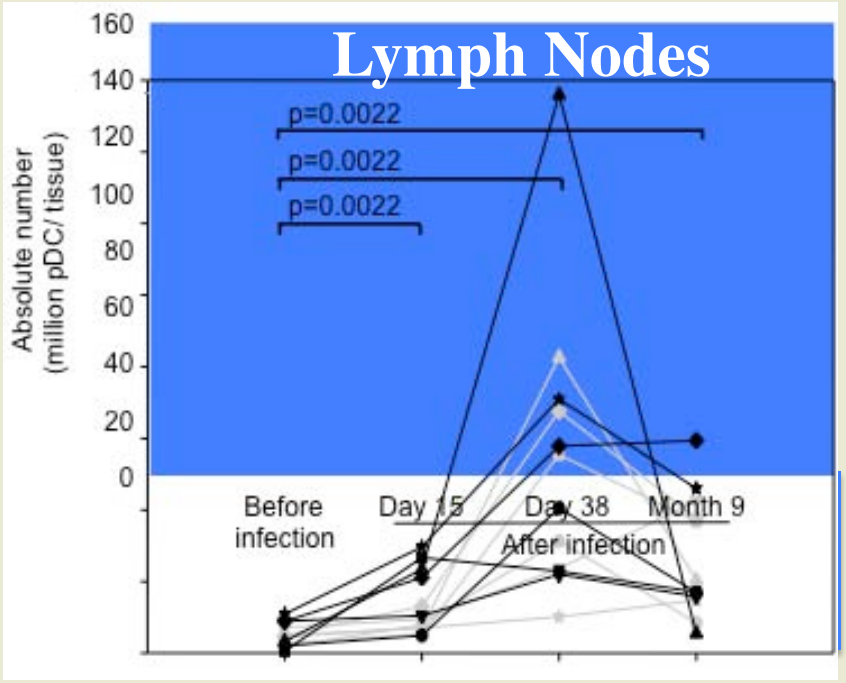
Nascimbeni, Perié et al 09

Apoptose

Brown Barratt-Boyes 09

SIV Infection pathogène chez le macaque cynomolgus : Domiciliation spécifique des DC plasmacytoïdes





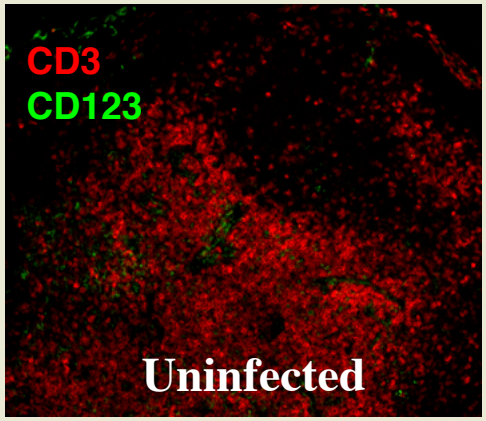
Malleret, Vaslin, Le Grand et al Blood 2008

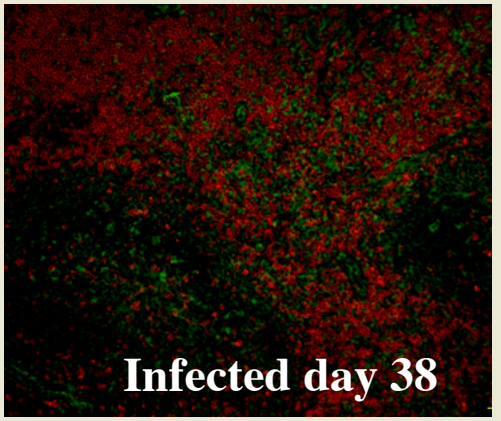
Singes verts africains: domiciliation transitoire

Diop, Mueller-Trutwin et al J Virol 2008

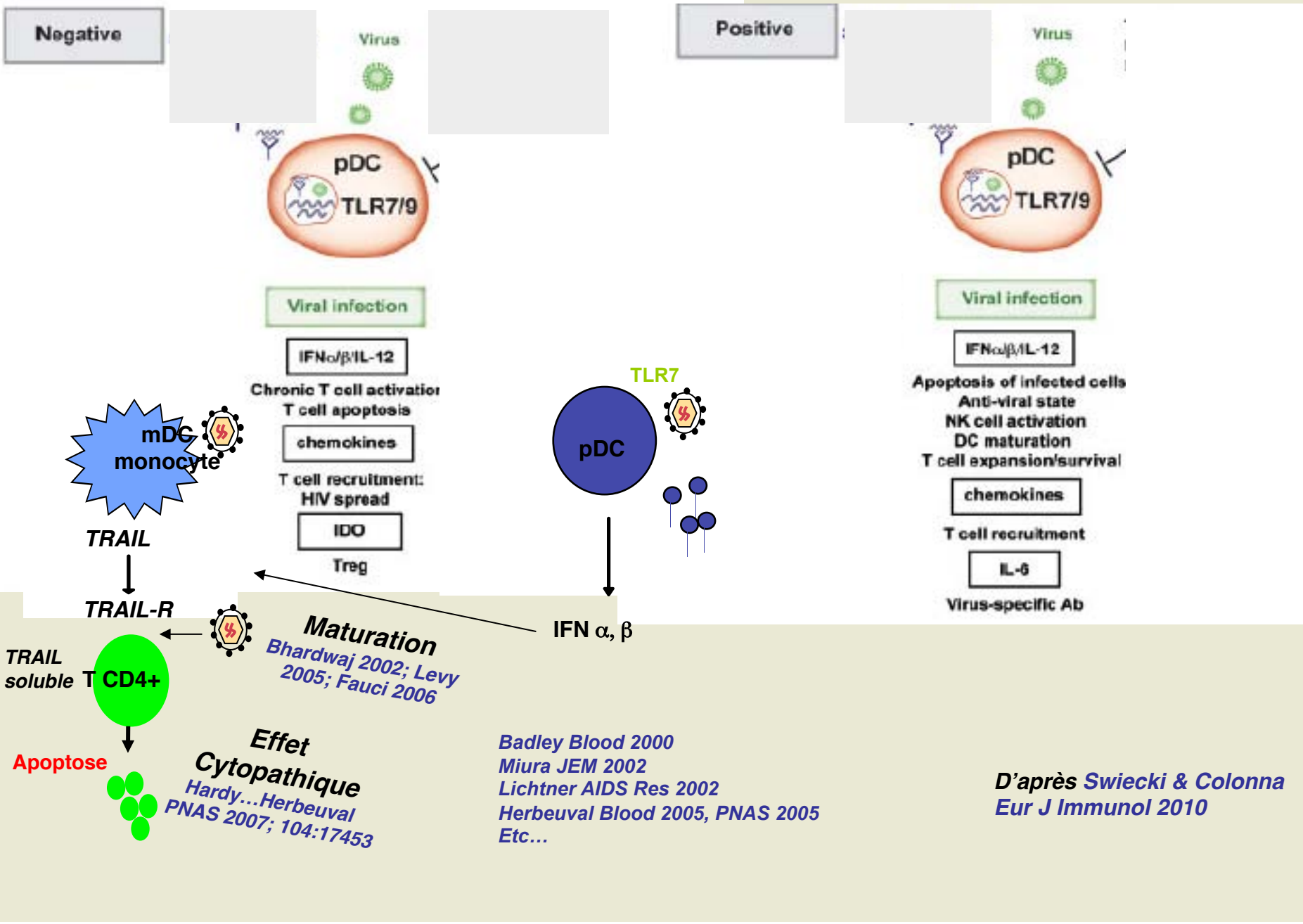
Patients infectés par le VIH: Accumulation lymphoïde corrélée à charge provirale

Nascimbeni, Perie et al Blood 2009





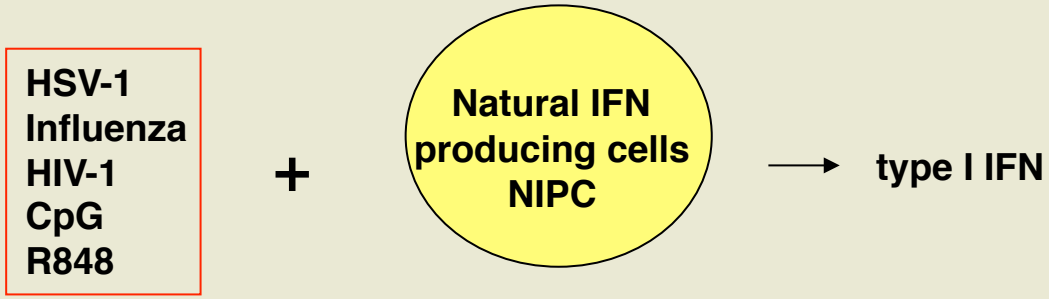
Conséquences potentielles de l'accumulation des pDC



Badley Blood 2000
Miura JEM 2002
Lichtner AIDS Res 2002
Herbeuval Blood 2005, PNAS 2005
Etc…

D'après Swiecki & Colonna
Eur J Immunol 2010

Evolution de la capacité de production d'IFN de Type I après stimulation *in vitro* au cours de l' infection par HIV ou SIV



AVANT INFECTION

- **Sooty mangabeys , singes verts africains: < macaques humains**
  Mandl … Feinberg 2008; Diop J Virol 2008

INFECTION PRIMAIRE

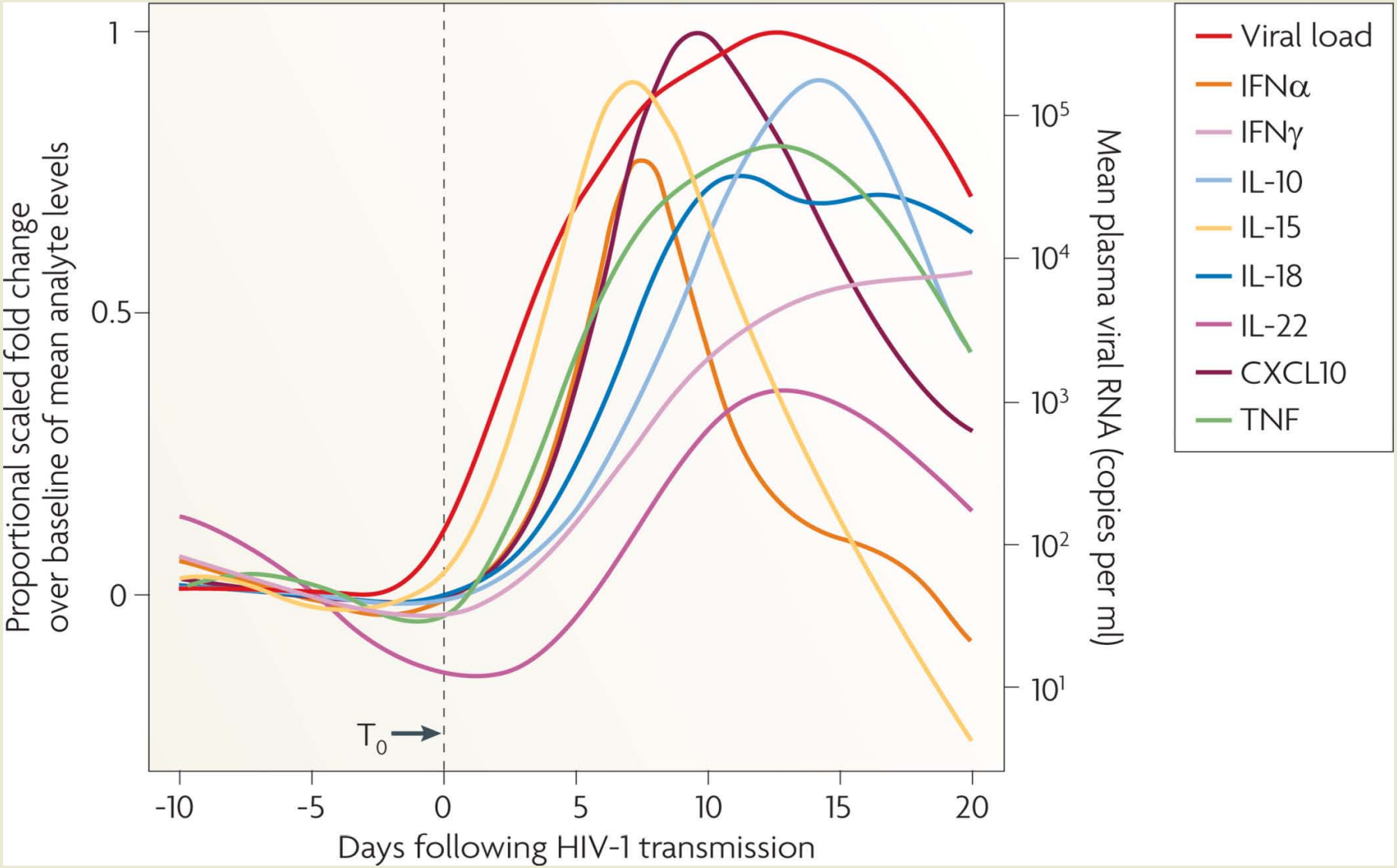
- **Diminution: dès le début infection primaire**
  - **patients** ***Kamga 2005; Bhardwaj 2010***
  - **macaques** ***Malleret Blood 2008***

- **Augmentation:**
  - **Completion Western Blot (Fiebig V-VI)** ***Bhardwaj 2010***
  - **African green monkeys** ***Diop J Virol 2008***

INFECTION CHRONIQUE

- **Perte progressive , restaurée par cART, préservation si asymptomatiques à long terme**
  Lopez 1983, Siegal, Fitzgerald-Bocarsly JCI 1986; Rinaldo, Ferbas 95; Siegal 2001
- **Désensibilisation**
  Hardy Blood 2009 Martinson

Réponses IFN et autres cytokines très précoces



Stacey… Borrow J Virol 2010

Comparaison des modèles d'infection pathogène ou non pathogène: rôle de la persistance de la réponse IFN

- Fort pic charge virale 10j post-infection
  - Macaques african green monkeys *Chakrabarti 1994*
  - patients at onset of infection *Stacey…. Borrow 2009*

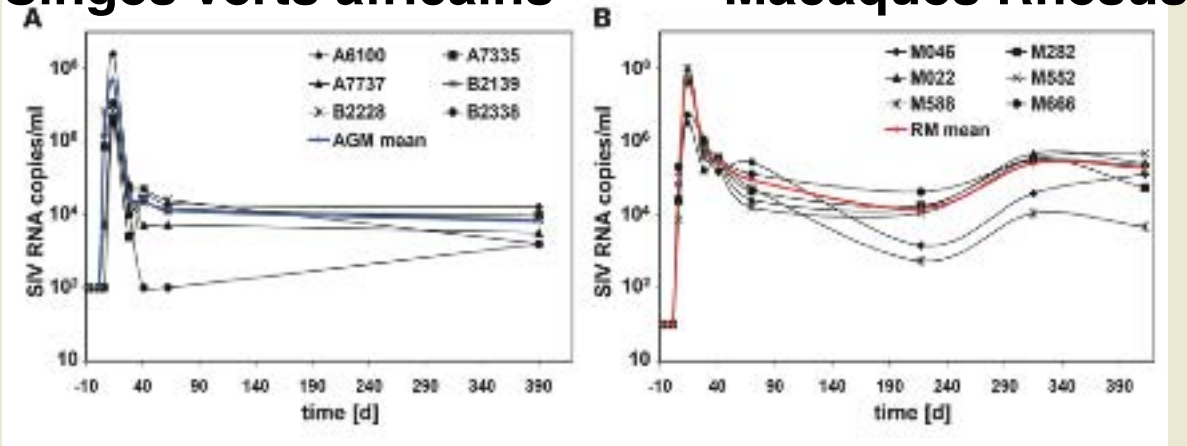
- Fort pic IFN type I concomittant

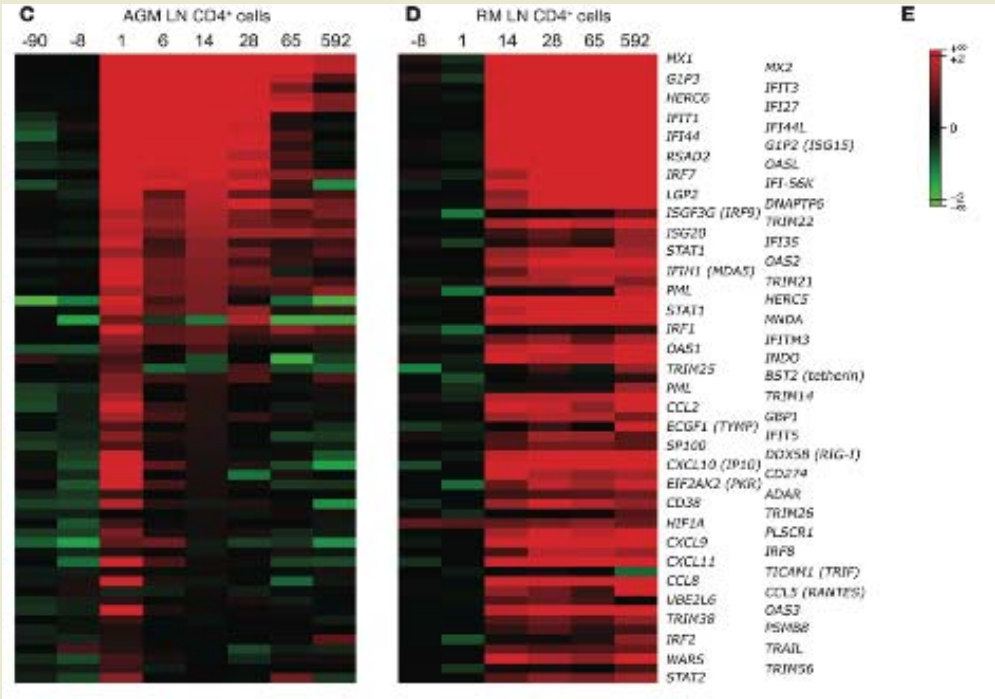
- activation précoce IFN et IFN-stimulable genes durant infection primaire,

- qui ne reste élevée que dans les infections chroniques pathogènes+++

Singes verts africains

Macaques Rhesus





Jacquelin, J Clin invest 2009; Harris 2010

IFN Type I *in vivo* pendant infection HIV ou SIV

- **Perte IFN sur les pDC in vivo chez patients**

Herbeuval Shearer PNAS 2006 Nascimbeni Blood 2009

  - **Mais pas chez les singes *Harris J Virol 10***
  - **Production par autres cellules dans modèles infection virale murins**

Oehnen 95, Dalod 02, Kumagai 07, Johansson 07, Stockinger 09

- **Hypothèse: pDC désensibilisées, remplacées par d'autres?**

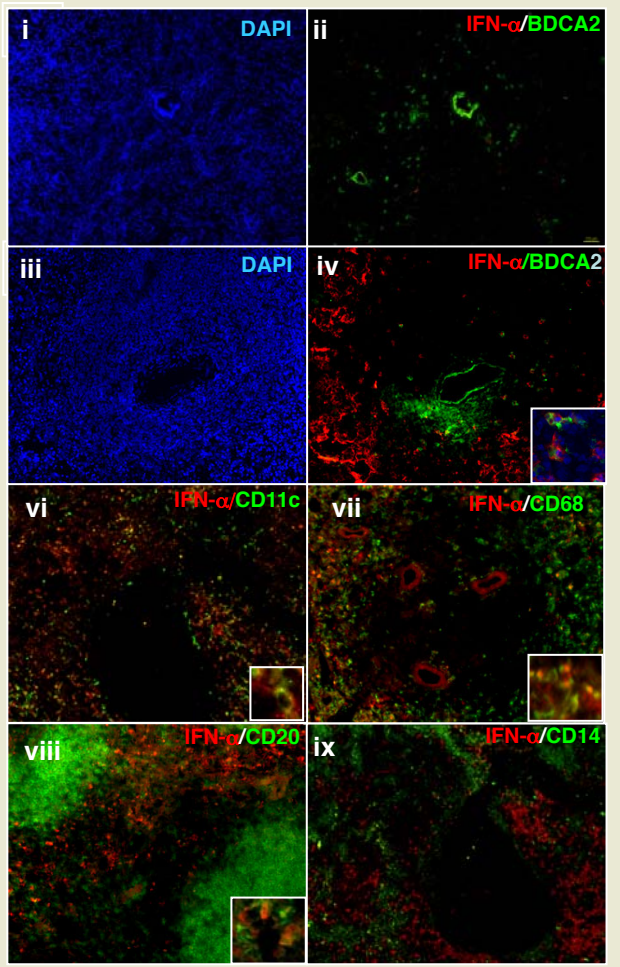
Martinelli PNAS 2008, Fonteneau Blood 2005

LCMV *Zuniga Cell Host Micr*

Ex vivo, IFN+ producing cells *Tilton Connors J Virol 2008*

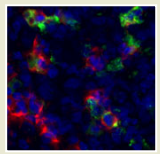
Ex vivo, lymph nodes from patients during chronic infection, low pDC numbers in blood but normal in LN, high IFN+ and MxA+ mRNA in blood pDC correlates with stage of disease, normal or low in stage A in LN

Lehmann Gallo JAIDS 2008



HIV-

HIV+



Perspectives thérapeutiques

Devrait-on inhiber la production d'IFN-α pour diminuer l'hyperactivation du système immunitaire?

Guiducci… Barrat J Exp Med 2006, J Intern Med 2009

Ou au contraire, traiter par IFN-α ou induire sa production, pour combattre la réplication virale?

Adalid-Peralta et al J Leuko Bio 2008

Ongoing studies during chronic infection

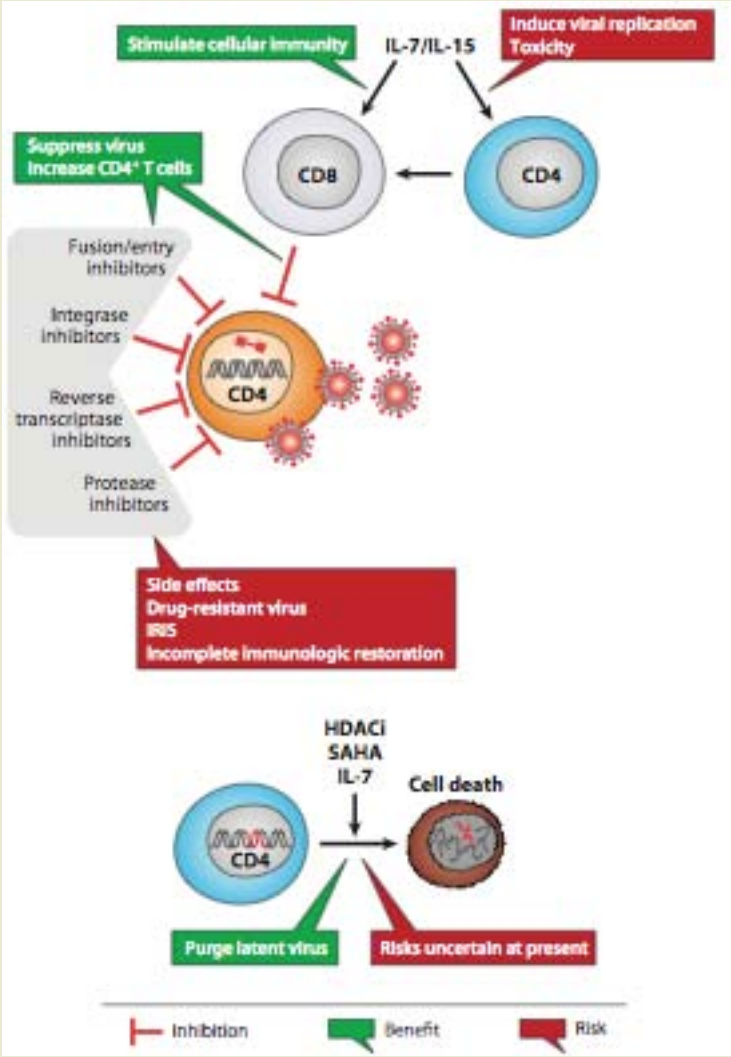
Ou réduire l'acidification des endosomes pour éviter l'activation des voies des récepteurs aux pathogènes?

Murray et al choloroquine

Ou utiliser des variants structuraux des IFN de type I avec une action plus antivirale et moins toxique?

Vazquez… Wahl Blood 11

Perspectives thérapeutiques



Moir… Fauci Ann Rev Path 2011

Targets for mucosal vaccination against HIV

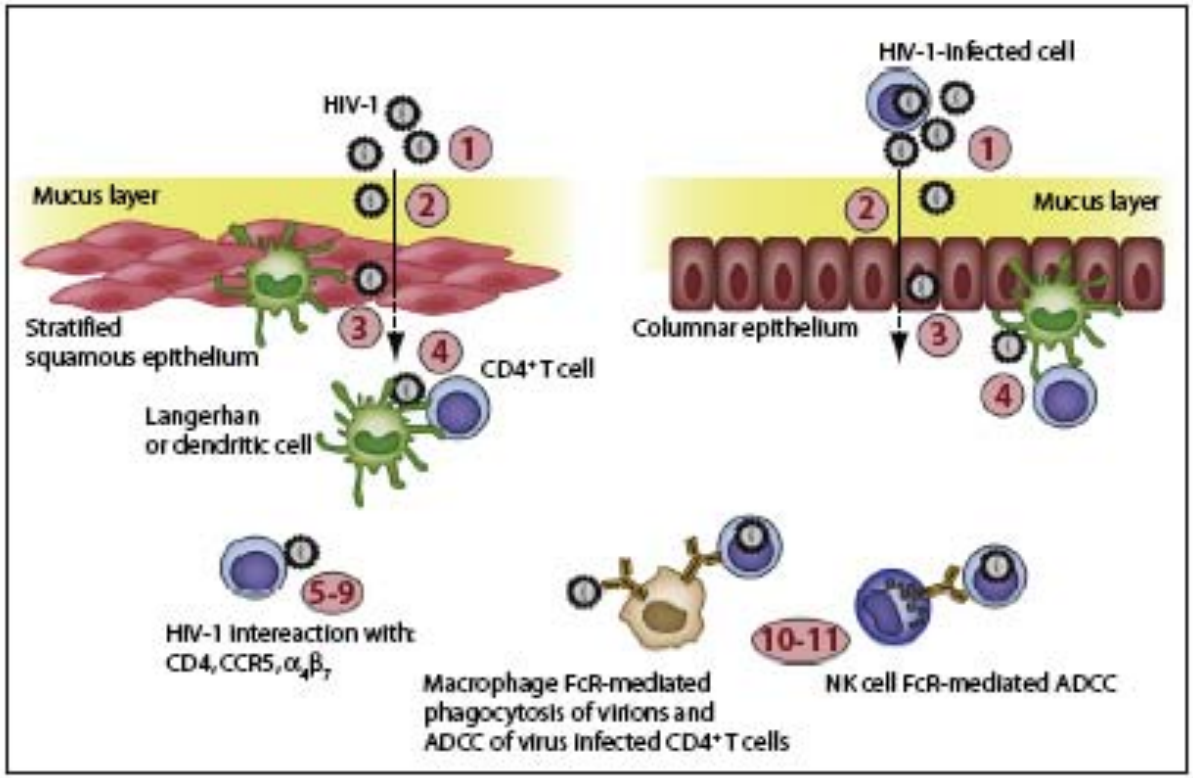


Figure 2. Steps in Mucosal HIV-1 Transmission Potentially Amenable to Intervention by Vaccination

Steps are keyed to assays listed in Table S1. Antibodies that score positive in in vitro assays and protect against SHIV acquisition in in vivo passive protection trials in nonhuman primates are candidates for correlates of protective immunity in the RV144 vaccine trial. Free virions or virions from infected cells can be aggregated by antibodies (1) and their movement through the mucus layer inhibited (2). Possible sites of transmission are female vagina and cervix (squamous epithelium), endocervix, and rectum (columnar epithelium), as well as male rectum (columnar epithelium and forskin (squamous epithelium). Transcytosis through either squamous or columnar epithelium may be blocked by antibodies (3), as can the transfer of DC-bound virions to $CD4^+$ T cells (4). Various assays measure the ability of antibody to block $CD4^+$ T cell and monocyte-macrophage (not shown) infection such as inhibition of gp120 binding to $\alpha 4\beta 7$ (5), pseudovirus infection inhibition (not shown) (6), PBMC infection inhibition (not shown) (7), syncytium inhibition (not shown) (8), and cell-to-cell infection inhibition (4 and implied in 9). ADCVI and ADCC, as well as phagocytosis assays of opsonized virions, can measure Fc receptor-mediated anti-HIV activities. Antibody and/or immune complexes bound to IgG FcR-bearing immune cells such as NK cells and/or monocyte macrophages can also release anti-HIV-1 chemokines and other factors.

McElrath, Haynes J Inf Dis 2010

***Antibody responses**: Broliden, Wahren, Lopalco, Bomsel, Moog et al*

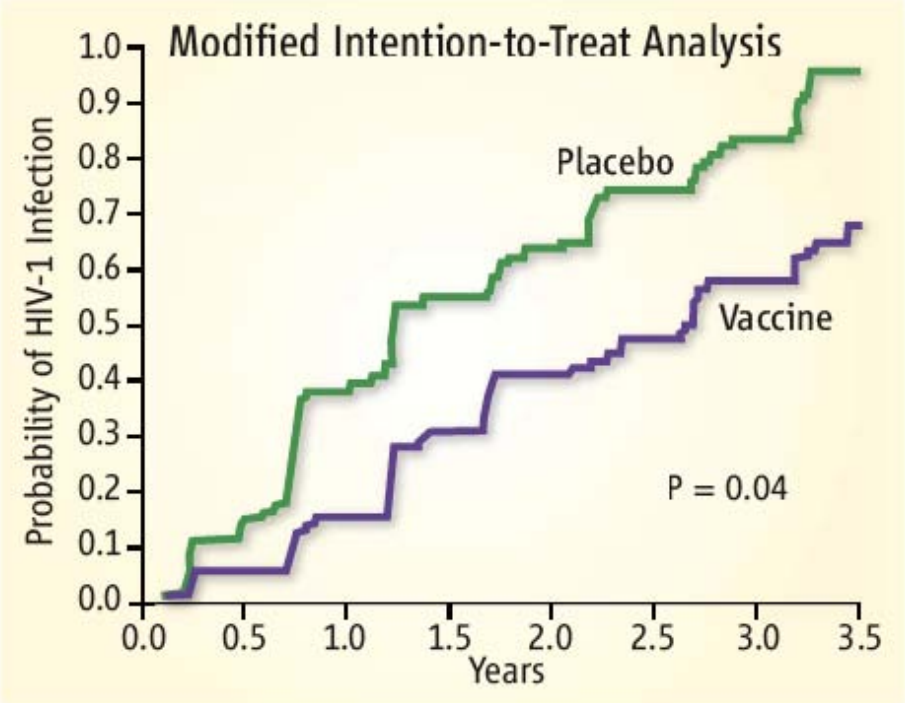
***T cell responses**:*
Belyakov, Berzofsky, 2004 transcutaneous, CT or LT or CpG, HIV long peptides
Anjuère Czerkinsky oral CTB-OVA, CD8 responses in intestinal draining lymph nodes 2003
Rosenthal J Inf Dis 2004 Remune, CpG, PolyIC
Arnzen PNAS 2004 Tomato, CTB -gp41 P1

First significant, but partial protection induced by vaccination in a phase III trial

N Engl J Med. 2009 Dec 3;361(23):2209-20. Epub 2009 Oct 20.

Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand.

Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Premsri N, Namwat C, de Souza M, Adams E, Benenson M, Gurunathan S, Tartaglia J, McNeil JG, Francis DP, Stablein D, Birx DL, Chunsuttiwat S, Khamboonruang C, Thongcharoen P, Robb ML, Michael NL, Kunasol P, Kim JH; MOPH-TAVEG Investigators.



Graphic difference. In this statistically significant analysis, infection rates climb more steeply in the placebo group but then become similar.

Cohen Science 326:653

Un agent qui inhibe l'inflammation dans la muqueuse inhibe l'afflux des pDC et des CD4 activées et limite l'infection par SIV

Haase Nature 2010

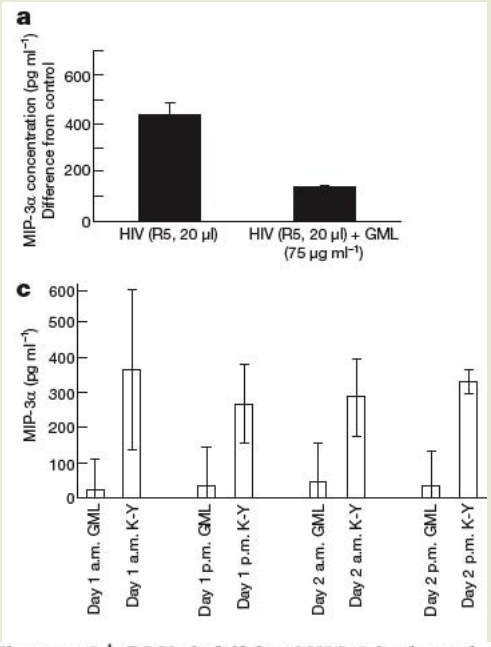


Figure 4 | GML inhibits HIV-1 induced expression of MIP-3α and IL-8 in HVECs and in cervical and vaginal fluids. **a**, **b**, R5 isolate of HIV-1 added to HVECs in the amounts indicated ± GML. MIP-3α (**a**) and IL-8 (**b**) release from HVECs was measured and expressed as the difference from control. **c**, **d**, At the end of a 6-month safety study, cervical and vaginal fluids were collected with a swab that reproducibly adsorbed 0.1 ml of fluid from animals that received GML or K-Y warming gel in the a.m. and p.m. of two successive days. MIP-3α (**c**) and IL-8 (**d**) were measured by ELISA. Bars indicate s.e.m.

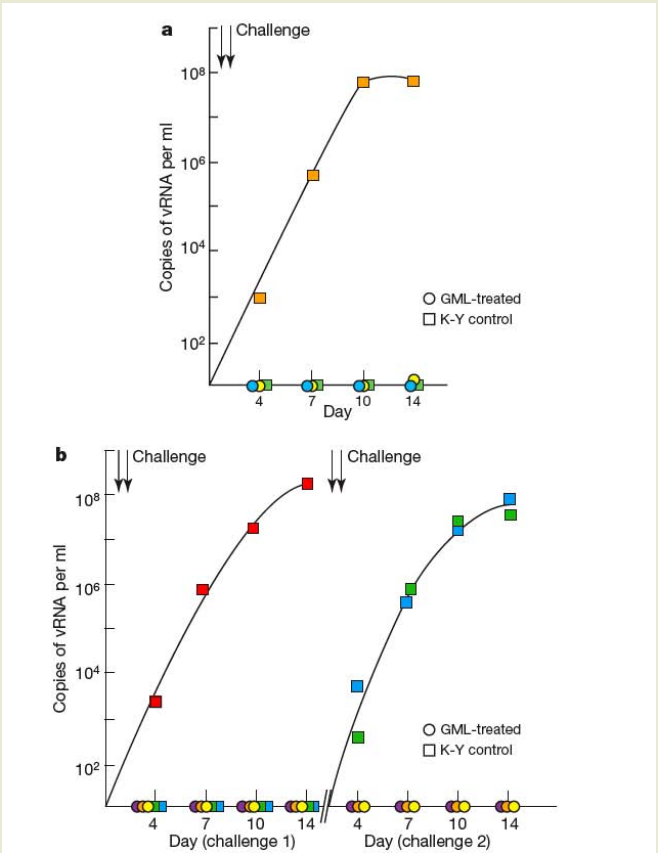


Figure 5 | GML prevents mucosal transmission and acute infection. **a**, Pilot experiment continuation of daily dosing safety study. Two animals treated with GML in K-Y warming gel (circles) and two treated with gel only (squares) were challenged twice (two arrows), 1 h after treatment, with 10^5 $TCID_{50}$ of SIV. Colours indicate individual animals. SIV RNA in plasma was measured to peak viremia, 14 d.p.i. **b**, Three animals treated with GML and three given K-Y warming gel were challenged as described in **a**. The animals that were not infected were treated and challenged again 4 weeks later, shown at the right.