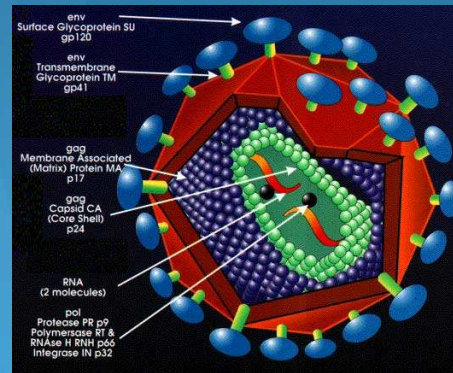


Vieillesse immunitaire prématurée chez les patients VIH+



Delphine Sauce

Infection & Immunity, INSERM U1135, Hôpital Pitié-Salpêtrière, Paris

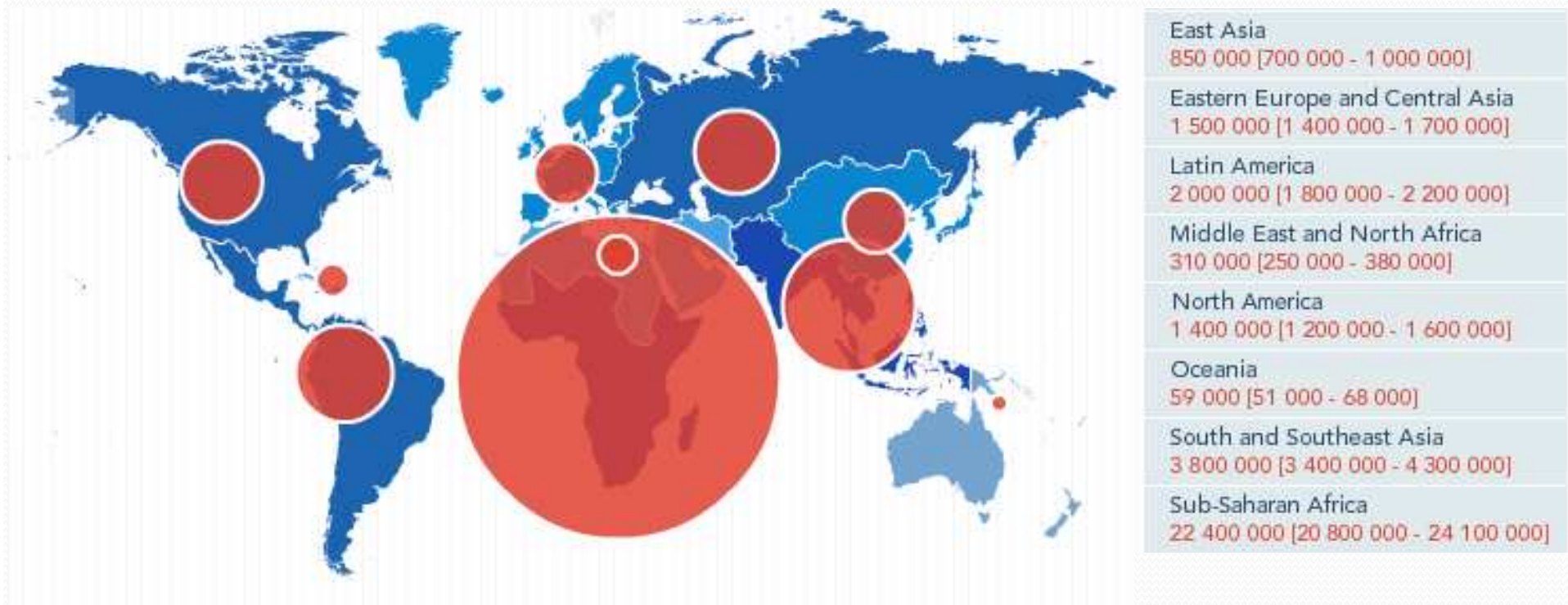


1 ère Partie:

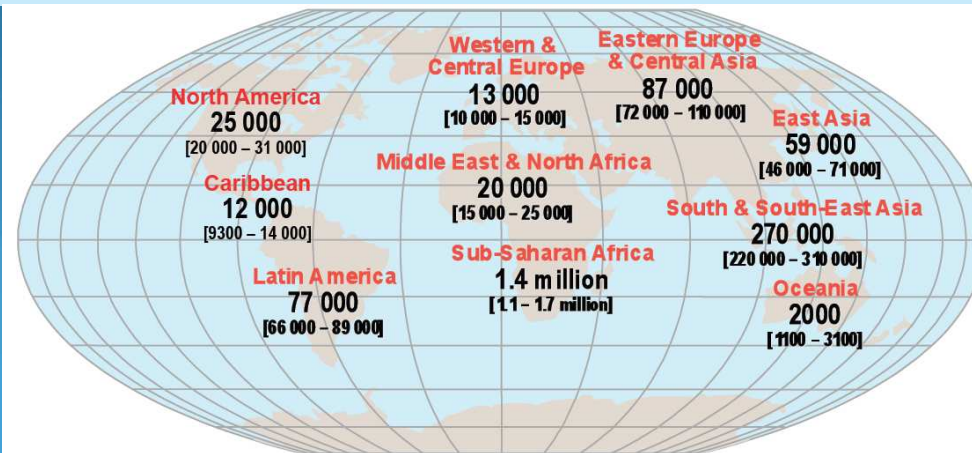
Petits rappels

- Infection VIH**
- Réponse immunitaire**

Adults and children estimated to be living with HIV/AIDS as of end 2014 (UNAIDS) 36,9 millions

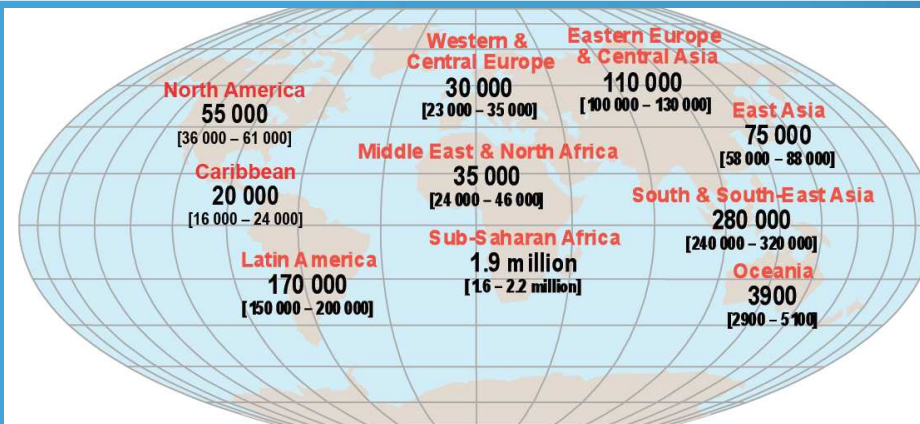


Estimated adult and child deaths from AIDS, 2013



Total: 2.0 million (1.7 – 2.4 million)

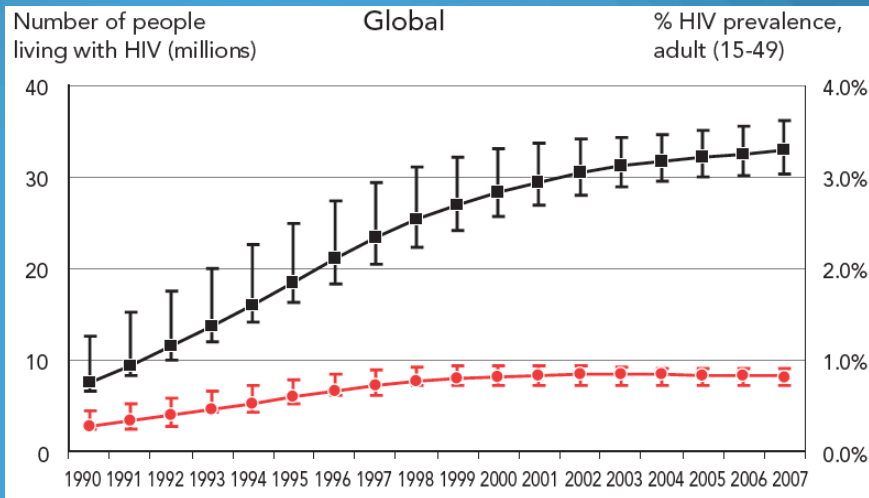
Estimated number of adults and children newly infected with HIV, 2013



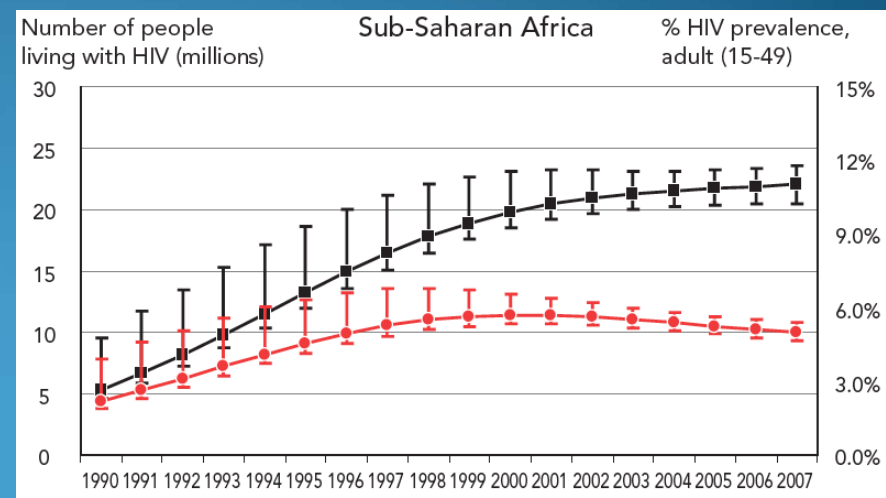
Total: 2.7 million (2.4 – 3.0 million)

Estimated number of people living with HIV and adult HIV prevalence

Global HIV epidemic, 1990–2007

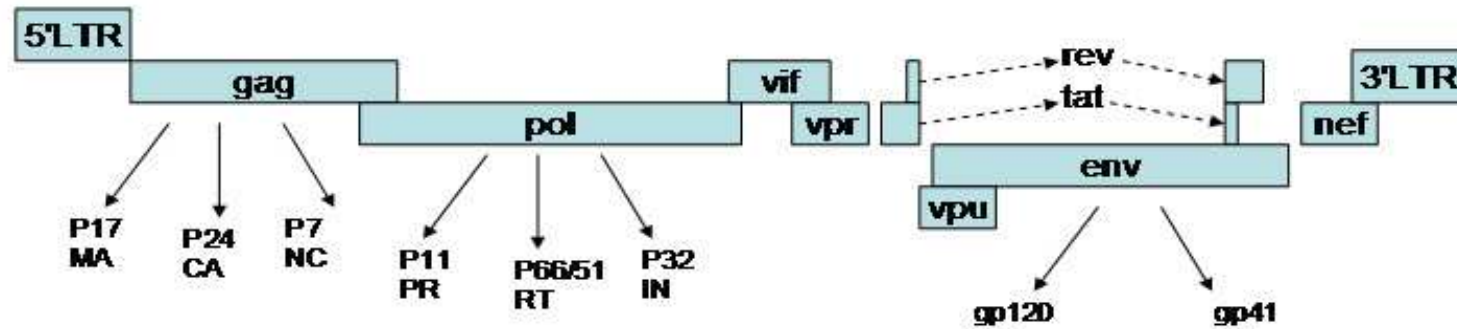


HIV epidemic in sub-Saharan Africa, 1990–2007

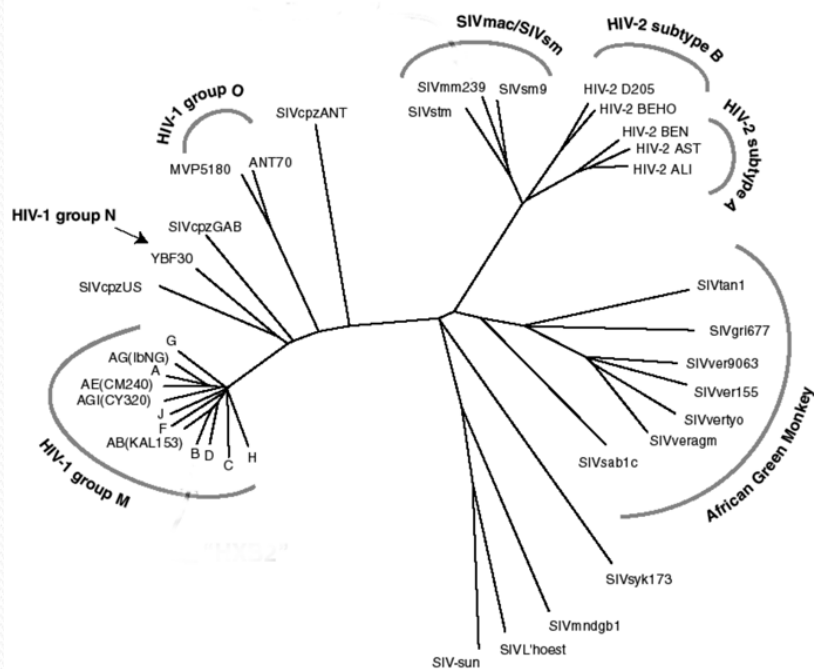


- Number of people living with HIV
- % HIV prevalence, adult (15-49)

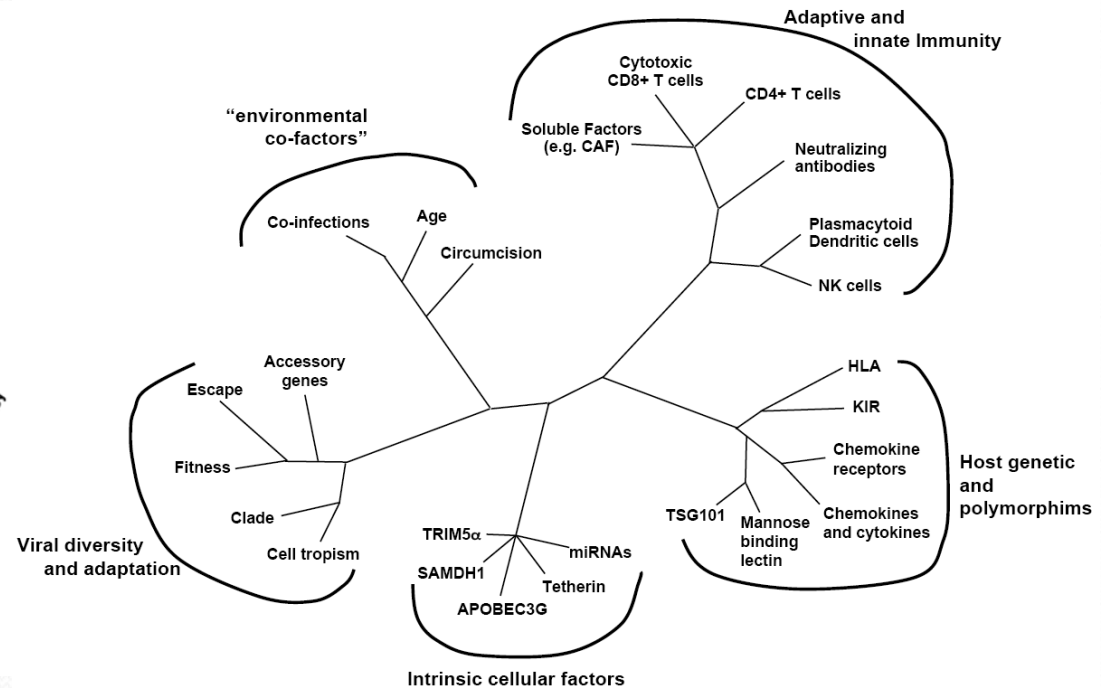
HIV pathogenesis



HIV is small but ...

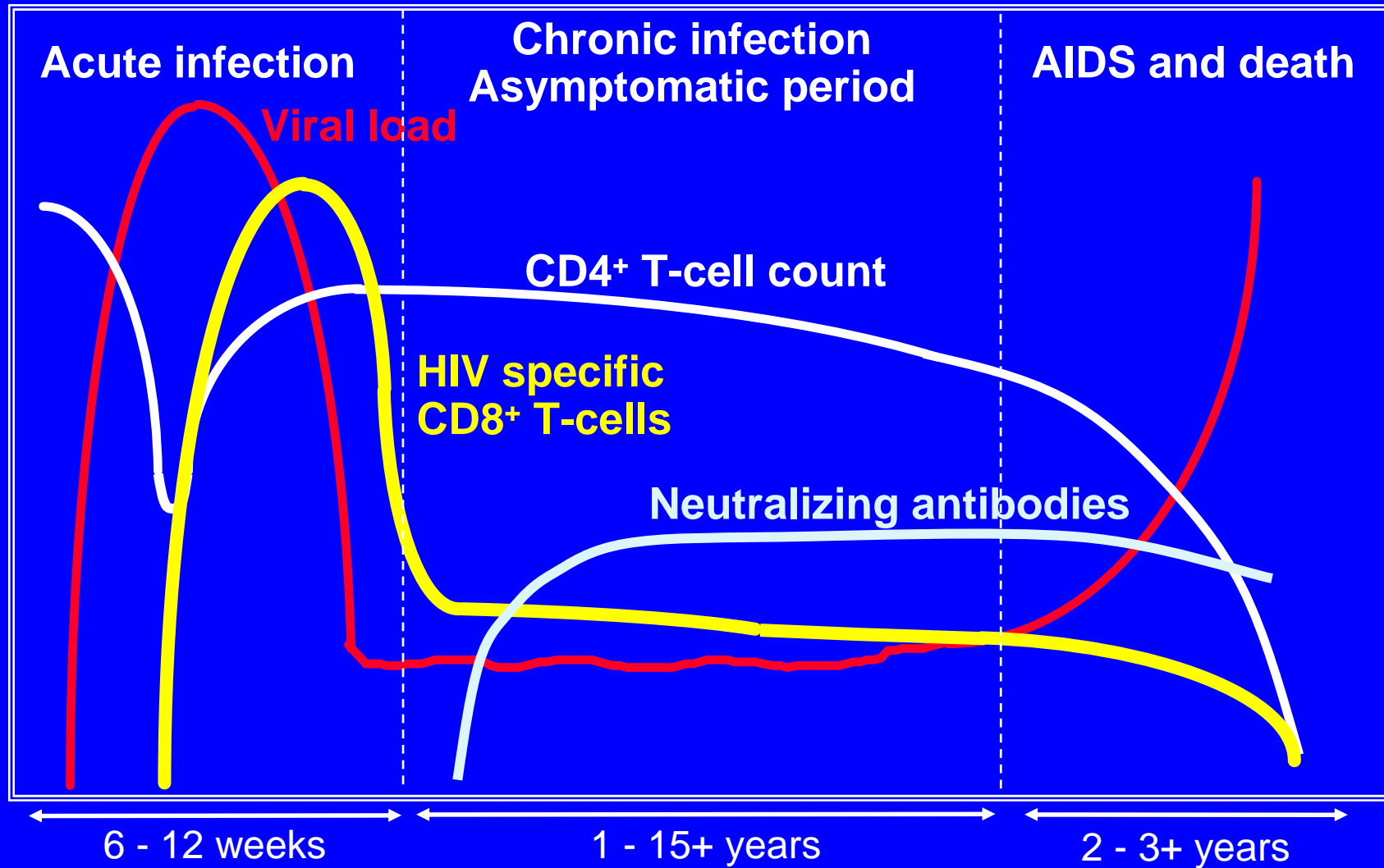


High viral diversity



Complex pathogenesis

Course of HIV infection



CD8+ T cell attributes of efficacy?

Immune activation and progression towards AIDS

HIV infection and replication

Main target: activated CCR5+ CD4+ T lymphocytes

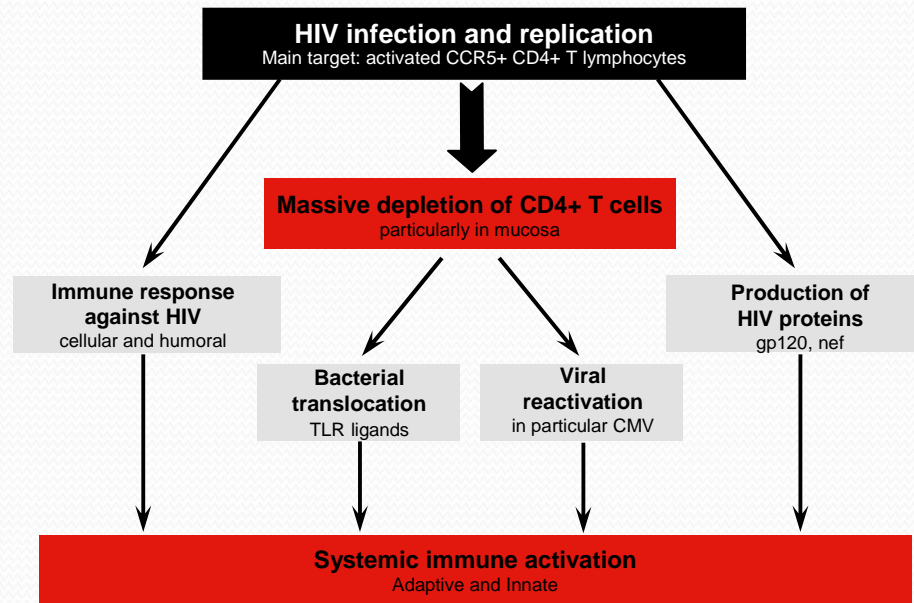
Systemic immune activation

Adaptive and Innate

Persistence of this process participates to
Collapse of the immune system / AIDS

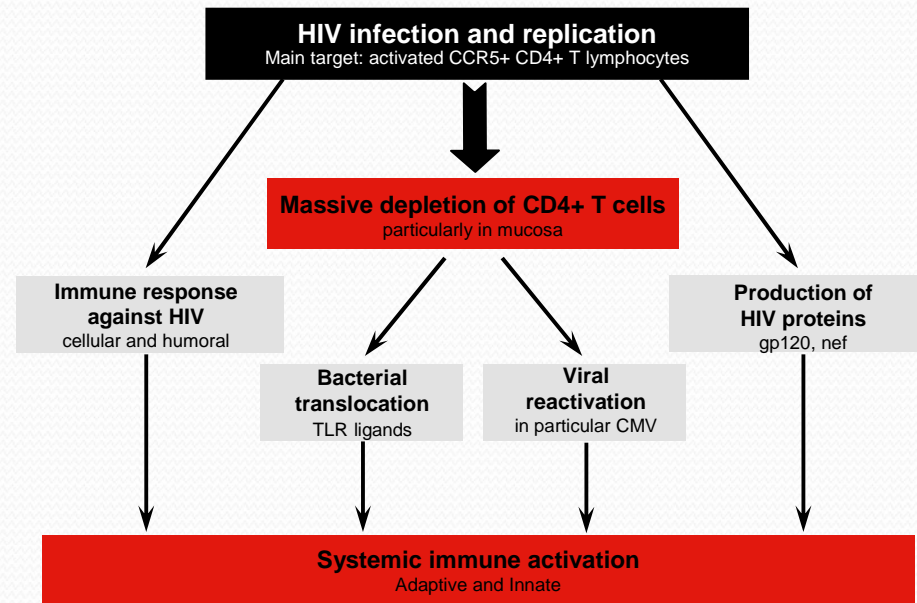
Immune activation and progression towards AIDS

Causes



Immune activation and progression towards AIDS

Causes

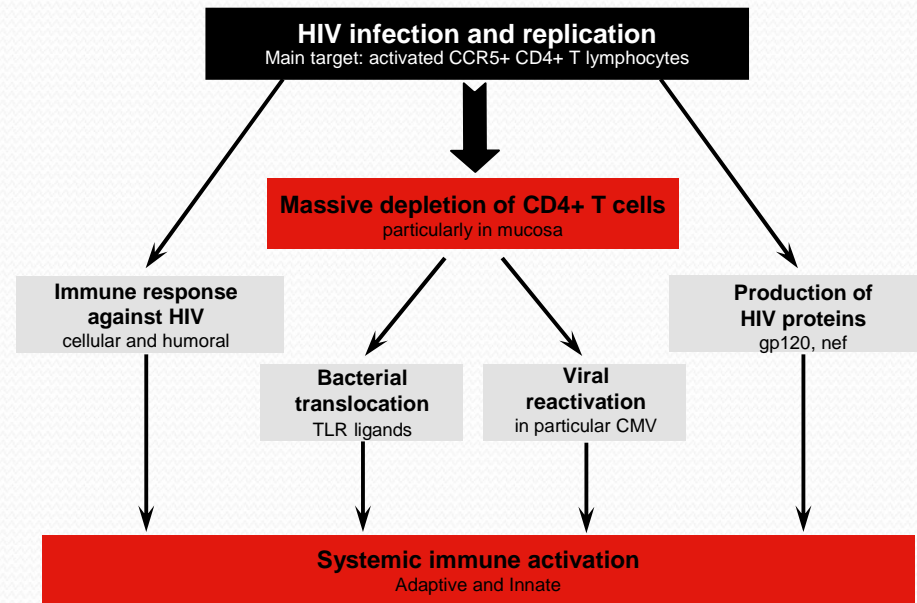


Consequences

??

Immune activation and progression towards AIDS

Causes



Consequences

??

Immunosenescence?

What is immunosenescence?

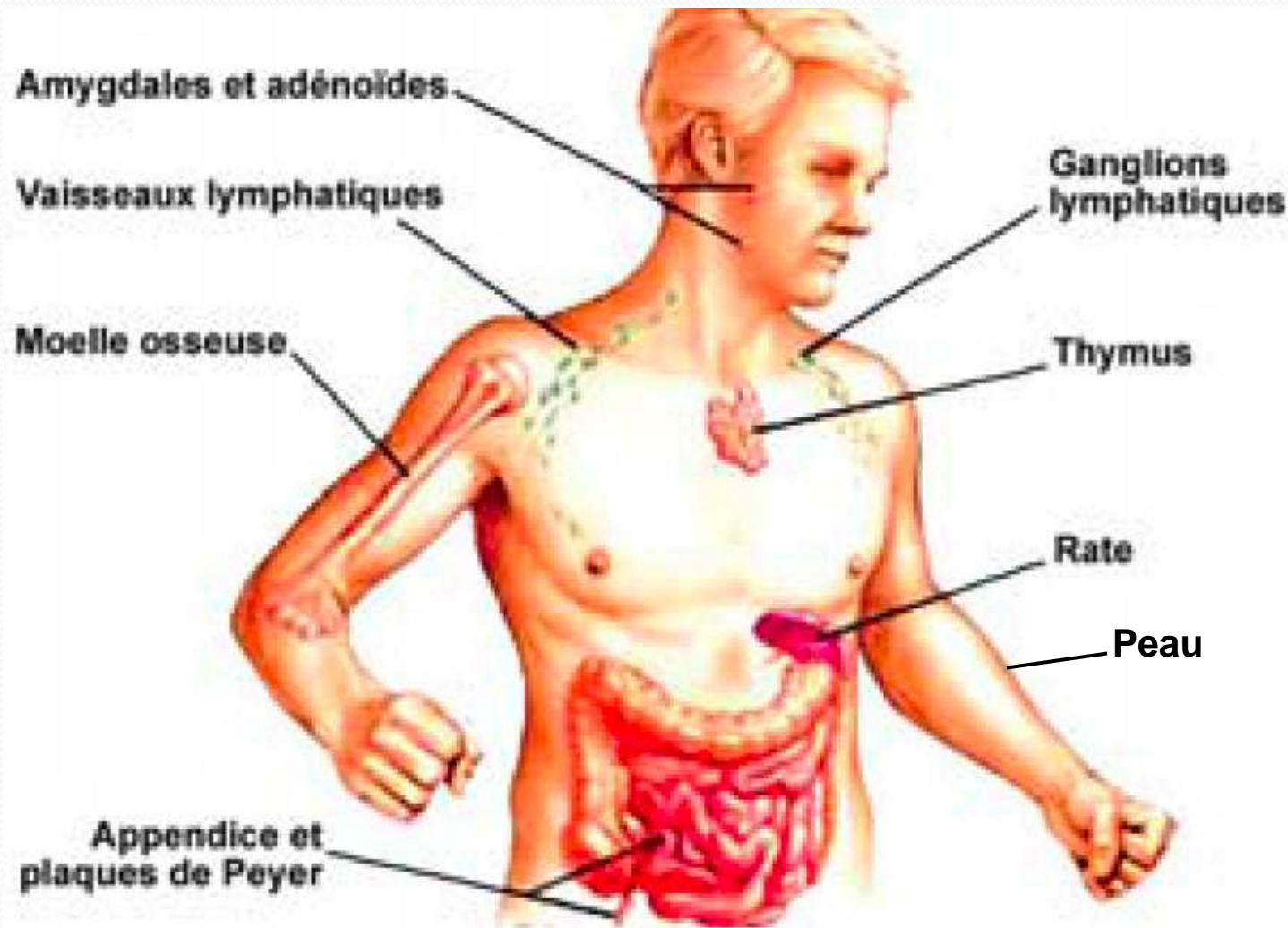
Immunosenescence:

Deterioration of the immune system with time / age

=> Increased susceptibility and severity of old people to infectious, auto-immune and cancer diseases

=> Alterations of phenotype and function of cells and organs of the immune system associated to advanced age (in particular adaptive immunity)

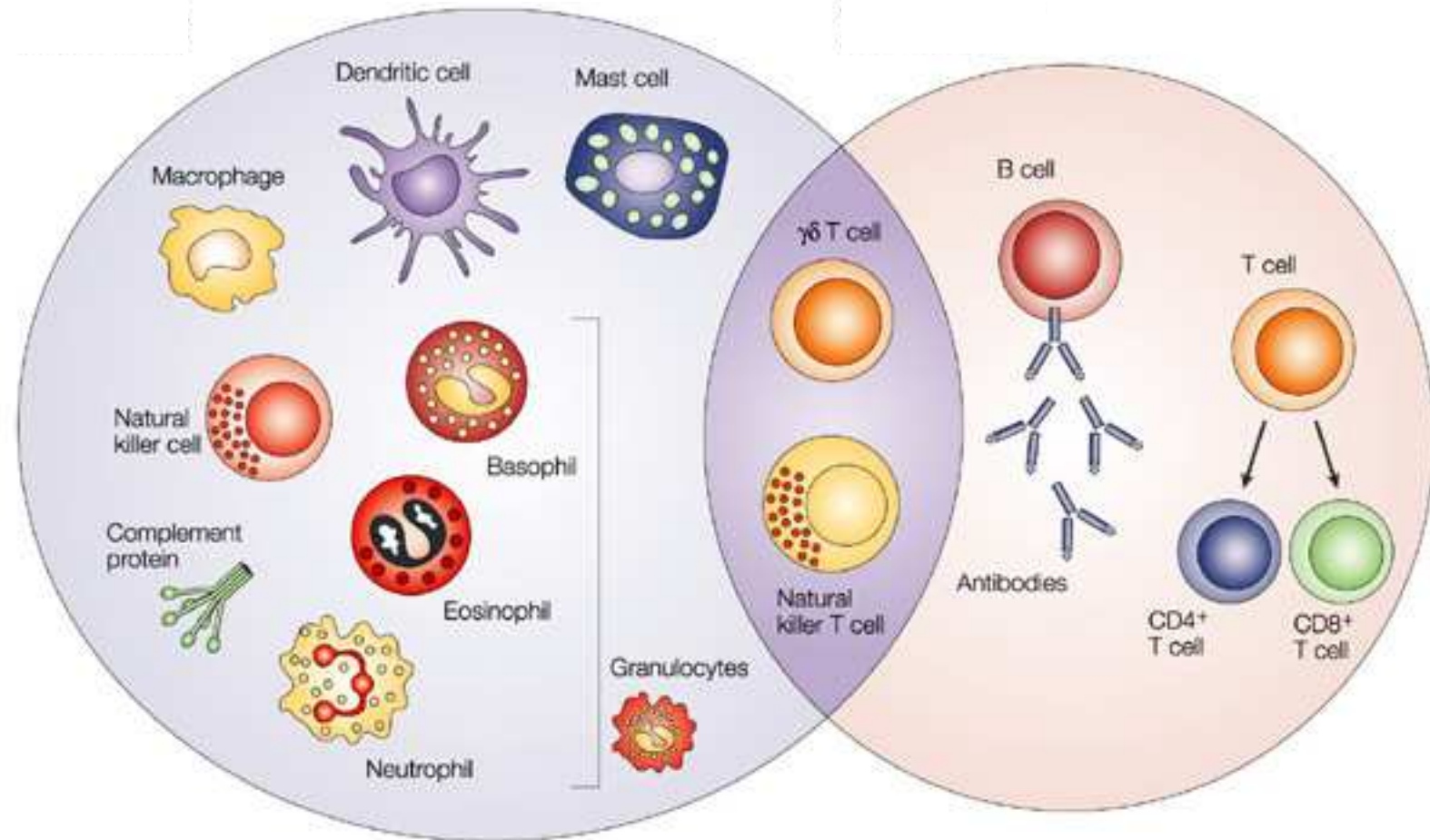
The different organs of the immune system



Immune response / immunocompetent cells

NON SPECIFIC IMMUNITY

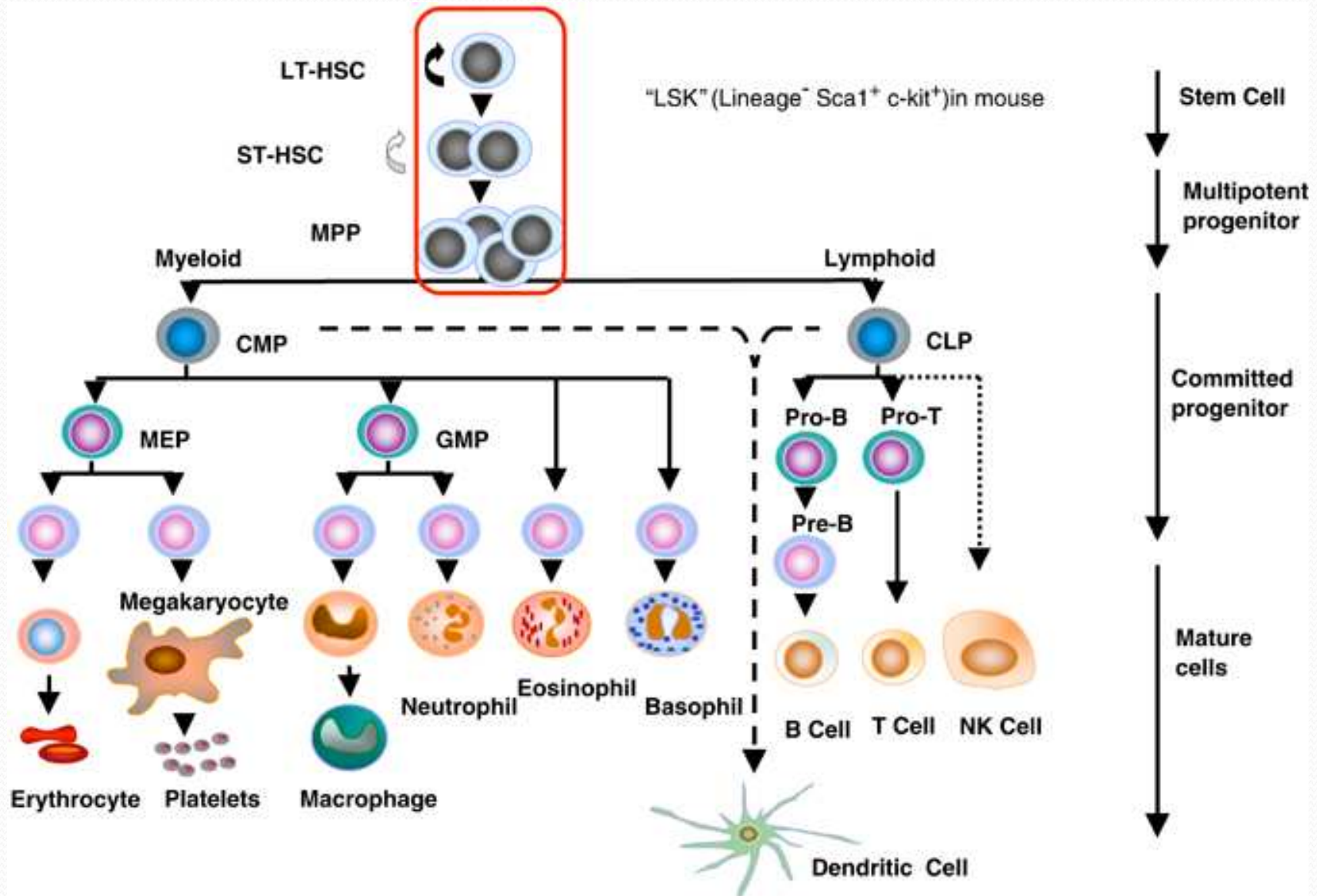
SPECIFIC IMMUNITY



IMMEDIATE ACTION

DELAYED ACTION, **MEMORY**

The development of immune system cells



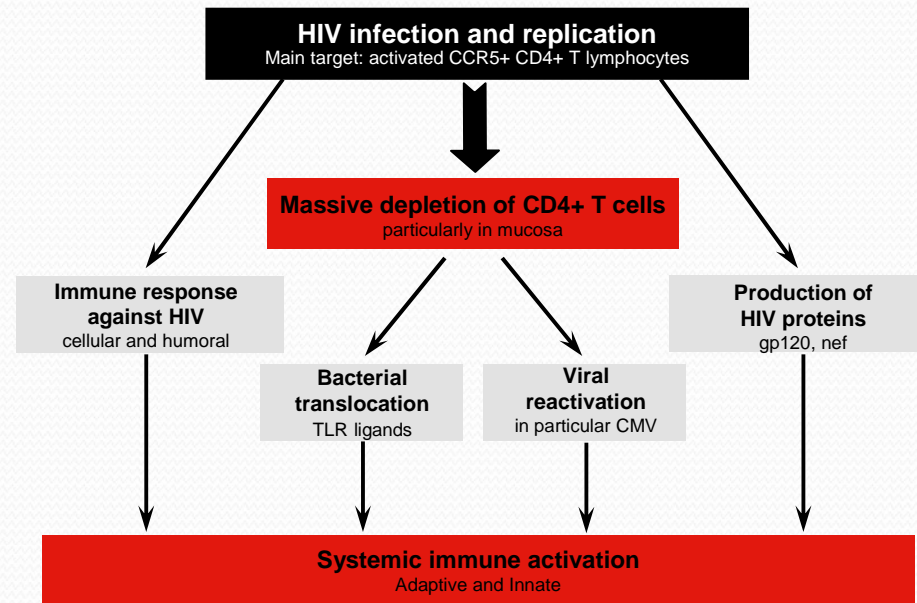


2 ème Partie:

Infection VIH et vieillissement immunitaire prématuré

Immune activation and progression towards AIDS

Causes



Consequences

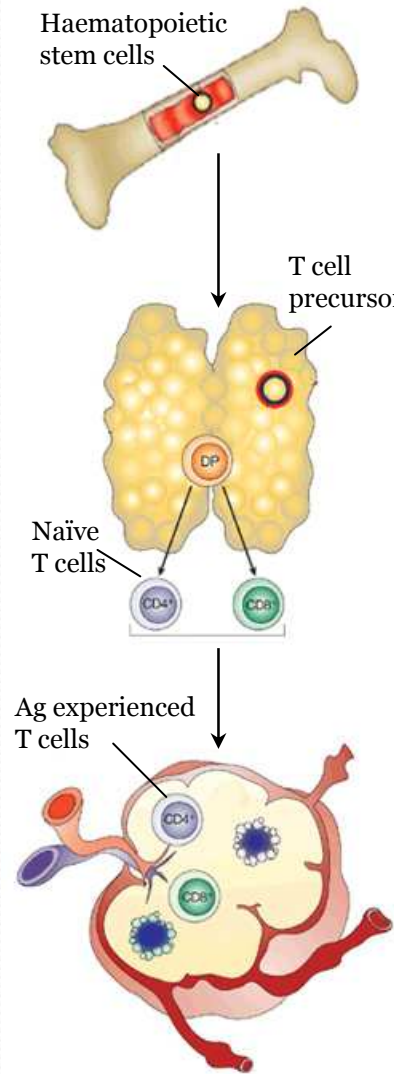
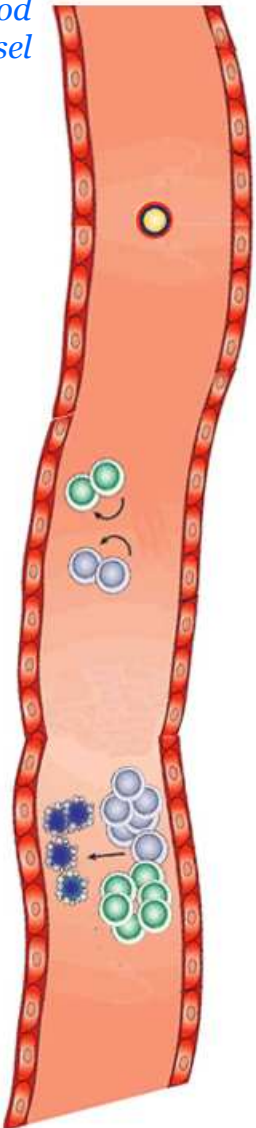
??

Immunosenescence?

Comparative study of immunological parameters:
Age vs HIV infection

→ Multiparametric study of immune phenotype & functions

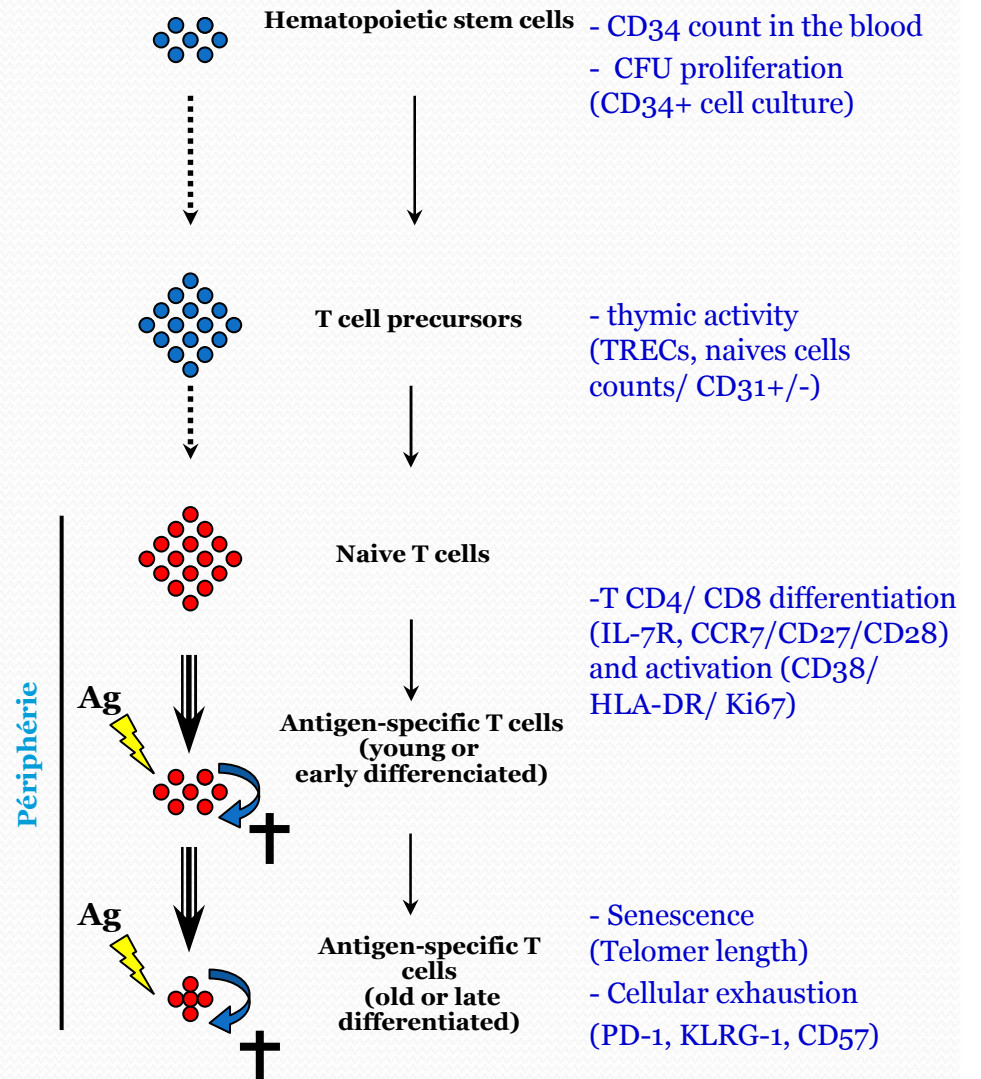
Blood vessel



Bone marrow

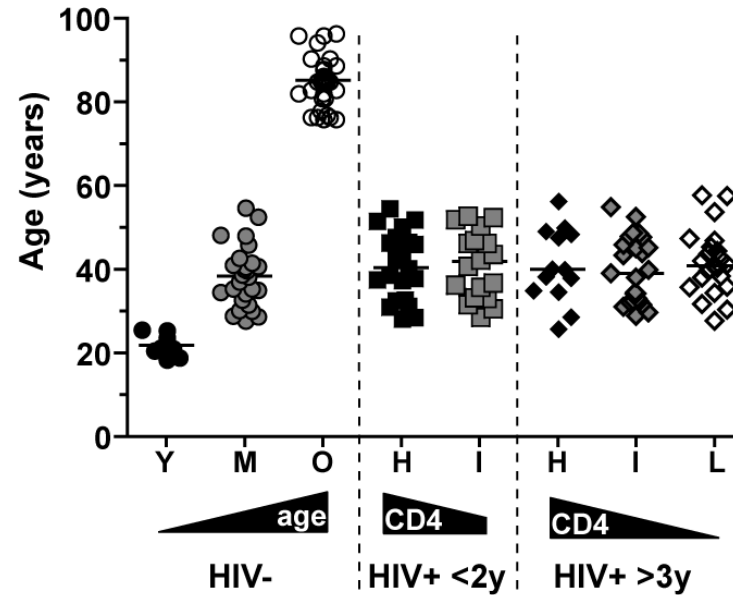
Thymus

Lymph node



Cross sectional study of ART naïve patients

Patients groups



Treatment naïve HIV-1 infected patients

H: above 500 CD4⁺ T cells/ μ l

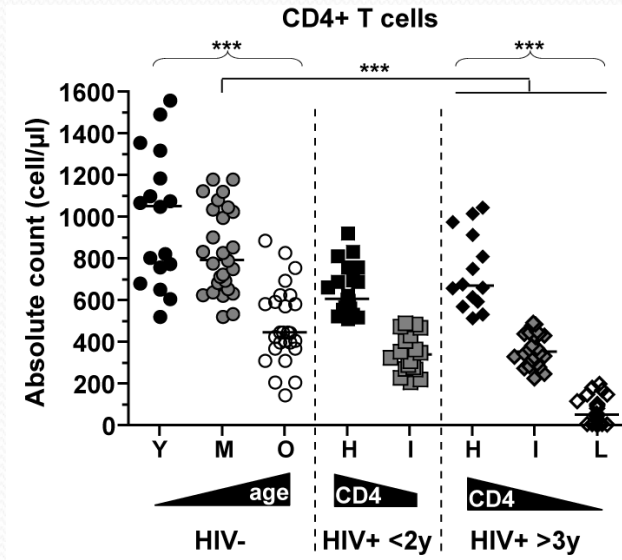
I: between 200 and 500 CD4⁺ T cells/ μ l

L: below 200 CD4⁺ T cells/ μ l

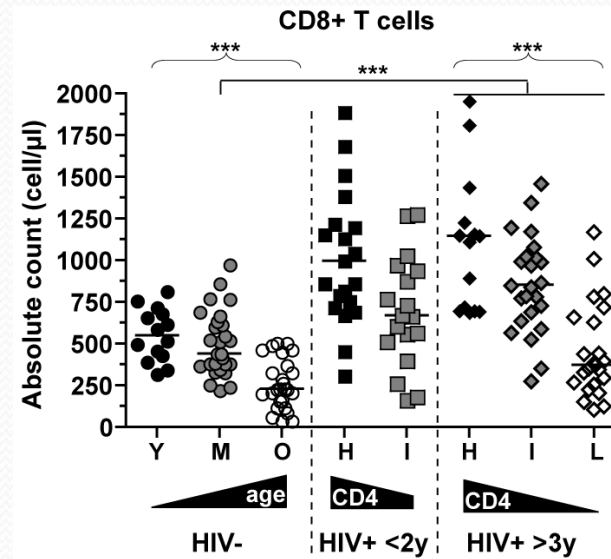
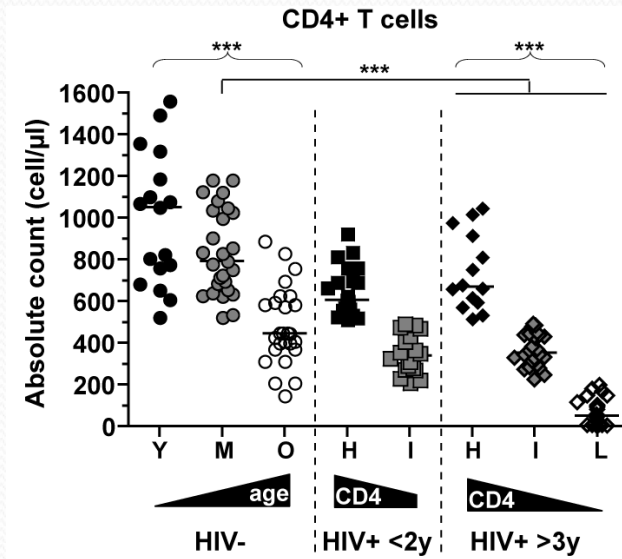
Healthy donors

young (Y), middle aged (M) or old (O) adults,

Number of T lymphocytes



Number of T lymphocytes



T lymphocyte subsets....

Use of cell surface molecules to characterise T-cells

CD45R isoforms

- A transmembrane phosphatase that regulates signalling through the T-cell receptor (TCR)–CD3 complex⁷⁸.
- Distinct isoforms are generated by alternative splicing of amino-terminal A, B and C exons. The high-molecular-weight protein (CD45RA) contains A and B and/or C exons, whereas the low-molecular-weight form (CD45RO) does not contain any of the variable exons⁷⁹.
- T-cell activation induces a shift from expression of CD45RA to CD45RO^{80,81}.
- The transition from expression of CD45RA to CD45RO is reversible³¹.
- CD45RO might be more efficient in supporting TCR–CD3 signalling⁸².

CD62 ligand (CD62L)

- A member of the selectin family of cellular adhesion molecules⁸³.
- Involved in homing to high-endothelial venules through the binding of 6-sulpho-Lewis X⁸⁴.
- Expressed by naive T cells, but is rapidly lost after activation¹².
- CD62L might be re-expressed by primed T cells *in vivo* when central memory cells are formed²³.

CD28

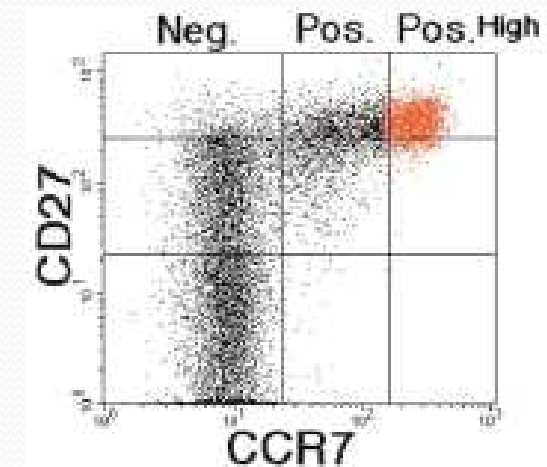
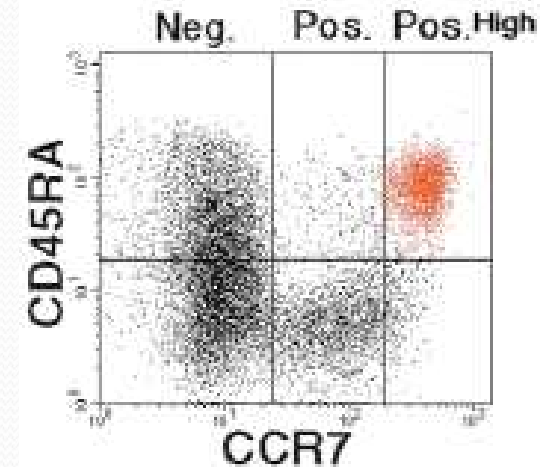
- An immunoglobulin-superfamily protein that binds to both CD80 and CD86 expressed by antigen-presenting cells⁸⁵.
- A potent transducer of co-stimulatory signals that influence proliferation, interleukin-2 secretion, survival and acquisition of effector functions⁸⁶.
- Prolonged stimulation might result in the loss of CD28 expression from both CD4⁺ and CD8⁺ T cells⁸⁷.
- T-cell activation can induce re-expression of CD28 on the cell surface of CD28⁻ T-cell clones³⁶.

CD27

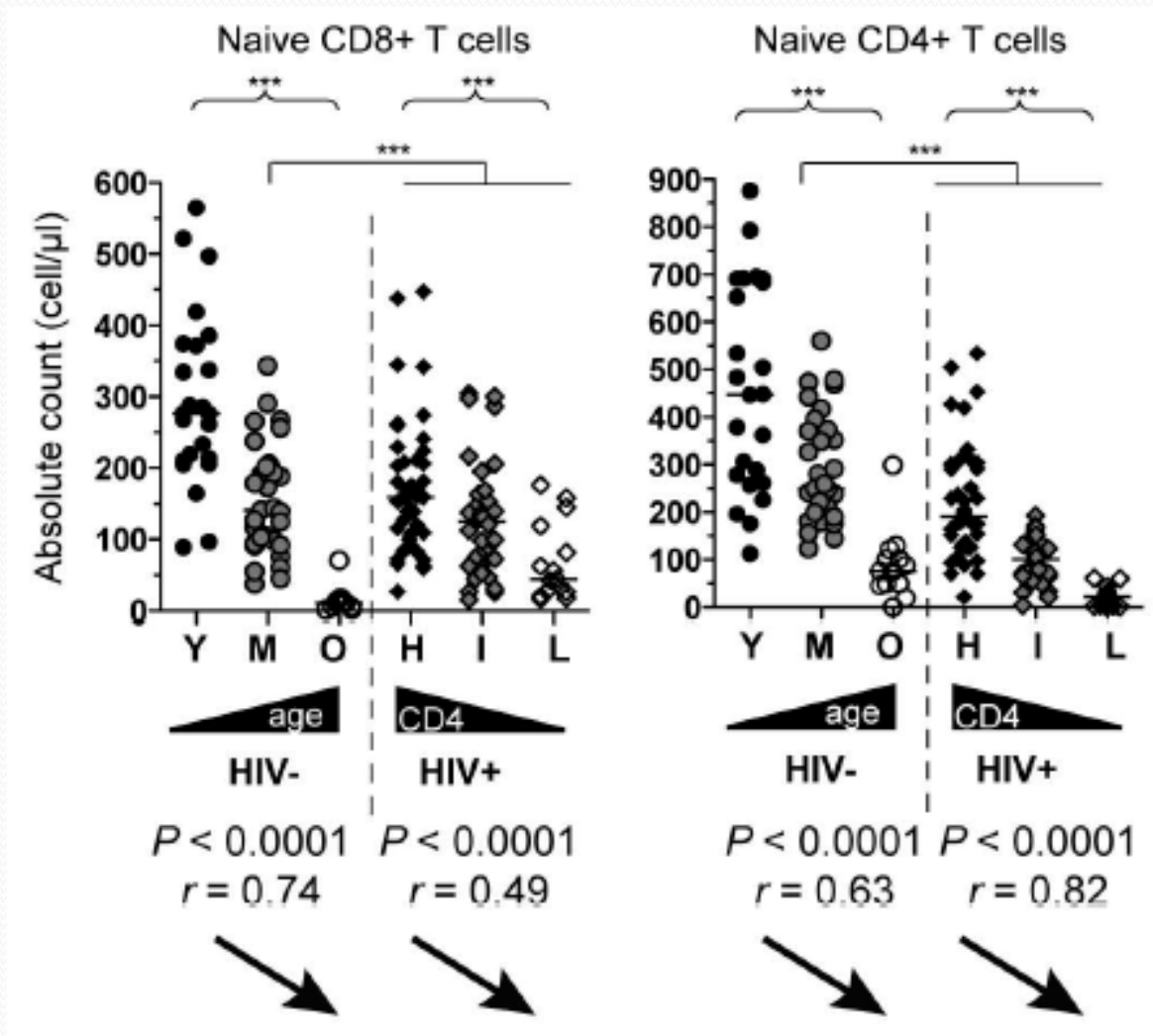
- A tumour-necrosis factor (TNF)-superfamily protein that binds to CD70 expressed by activated lymphocytes and dendritic cells^{88,89}.
- Promotes the formation of effector and memory T cells and the acquisition of effector functions^{64,65,88}.
- The interaction between CD27 and CD70 induces the loss of cell-surface expression of CD27 (REFS 65,66).
- Prolonged stimulation might result in the loss of CD27 expression by both CD4⁺ and CD8⁺ T cells⁹⁰.
- T-cell activation does not induce re-expression of CD27 at either the messenger RNA or protein level⁶⁶.

CCR7

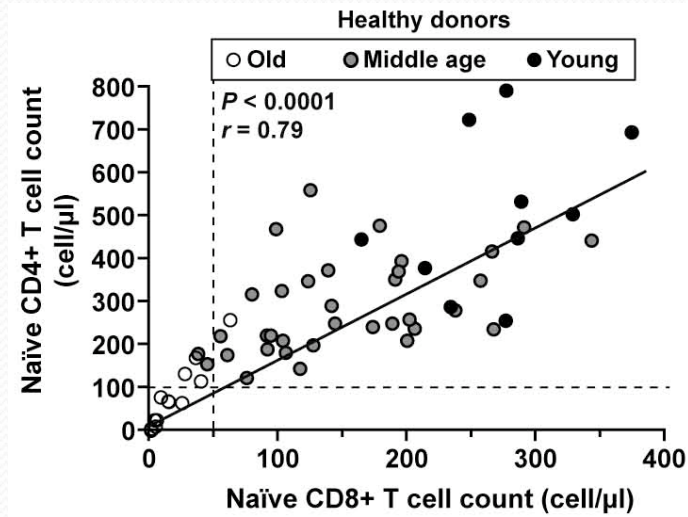
- A chemokine receptor that binds both CC-chemokine ligand 19 (CCL19) and CCL21 (REF. 91).
- Directs the migration of lymphocytes to lymph nodes⁹².
- Activation of naive T cells leads to the downregulation of expression of CCR7 (REF. 15).
- CCR7 is re-expressed by CCR7⁻ T cells after stimulation^{35,60}.



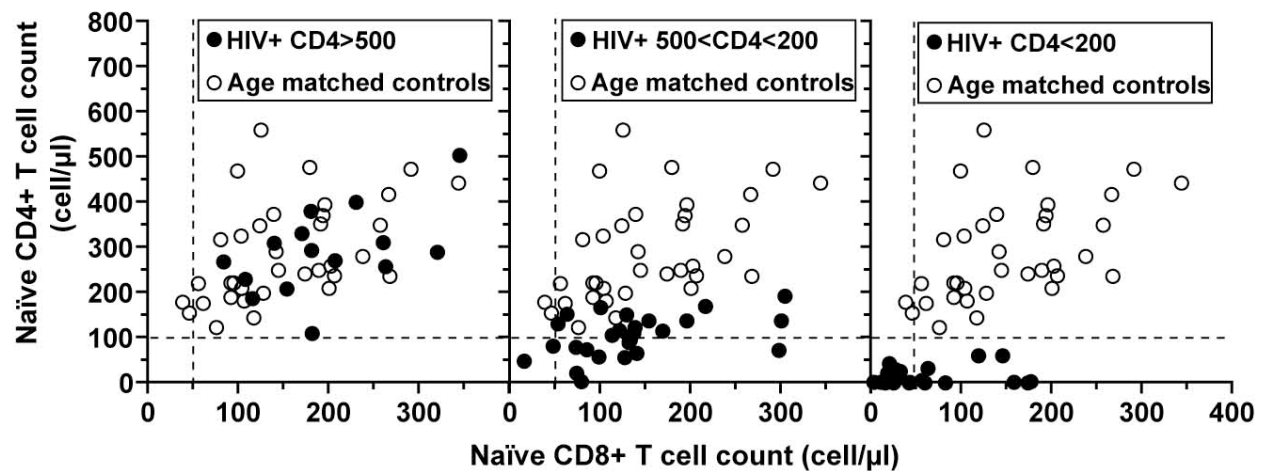
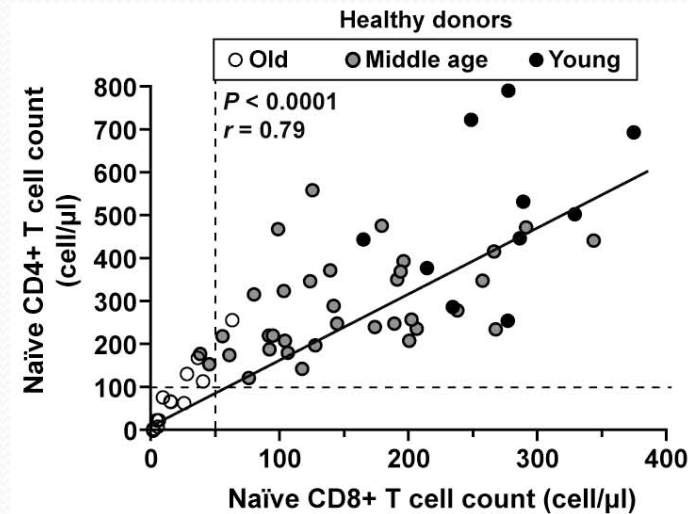
Naive T cell frequencies with HIV infection and aging



HIV infection and premature immune aging



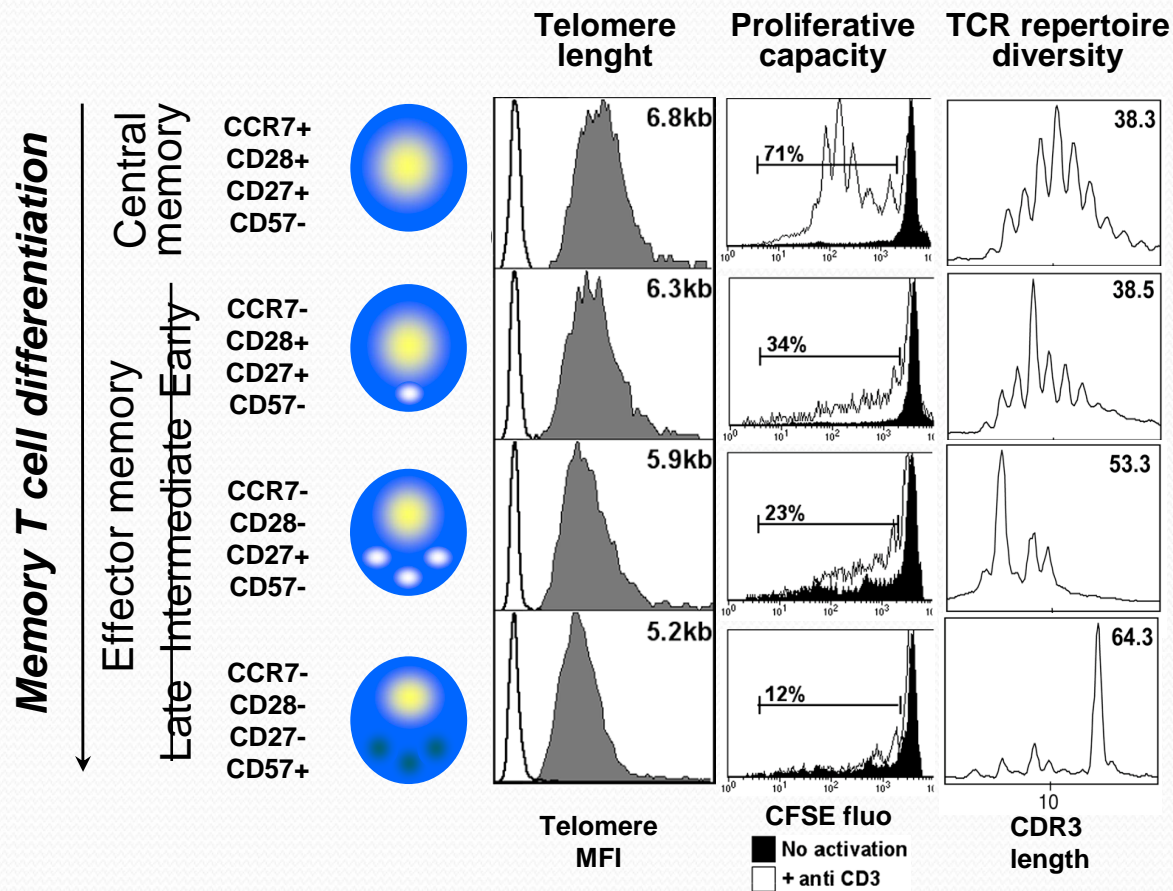
HIV infection and premature immune aging



➔ **40y old AIDS patient = 80y old uninfected donor**
(criteria = naïve T cell frequency)

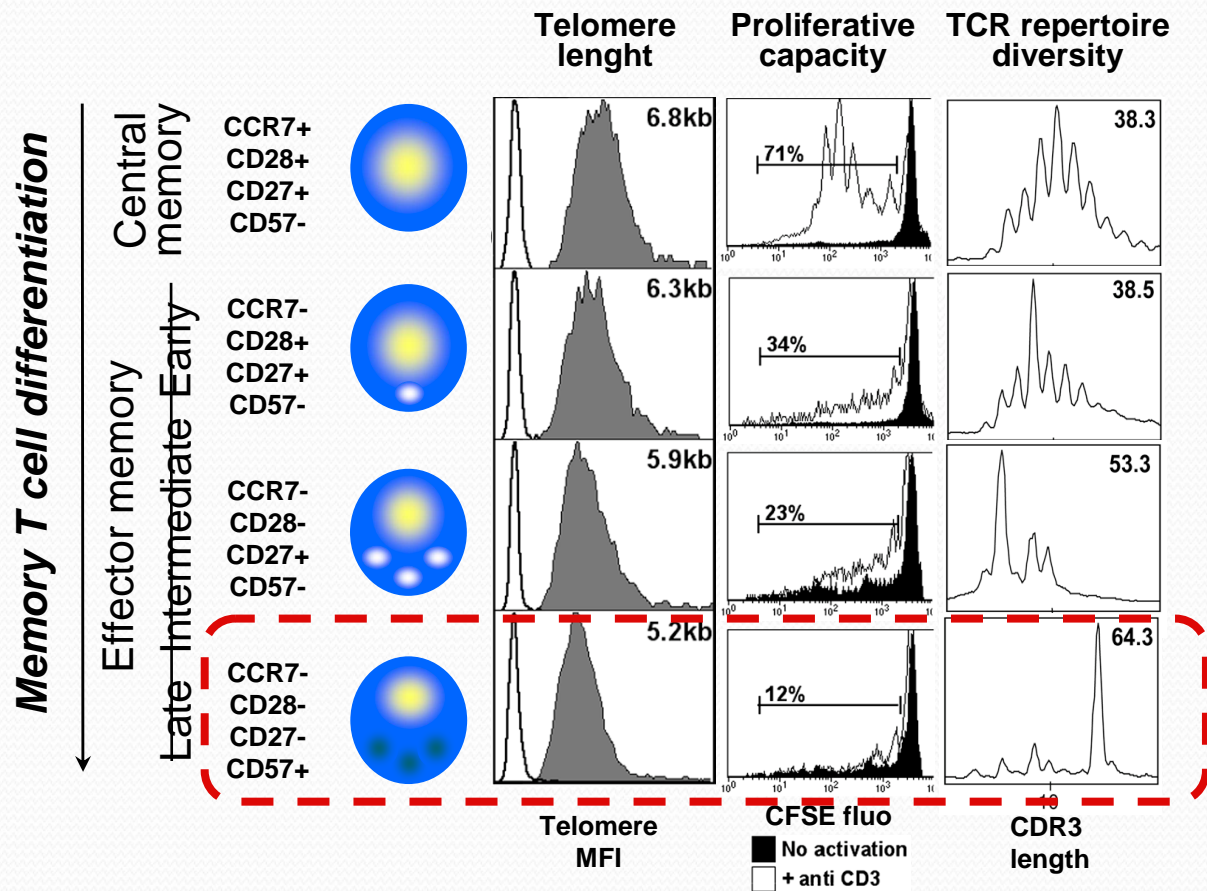
Accumulation of end stage memory T lymphocytes with age or HIV infection

Memory T cell subsets



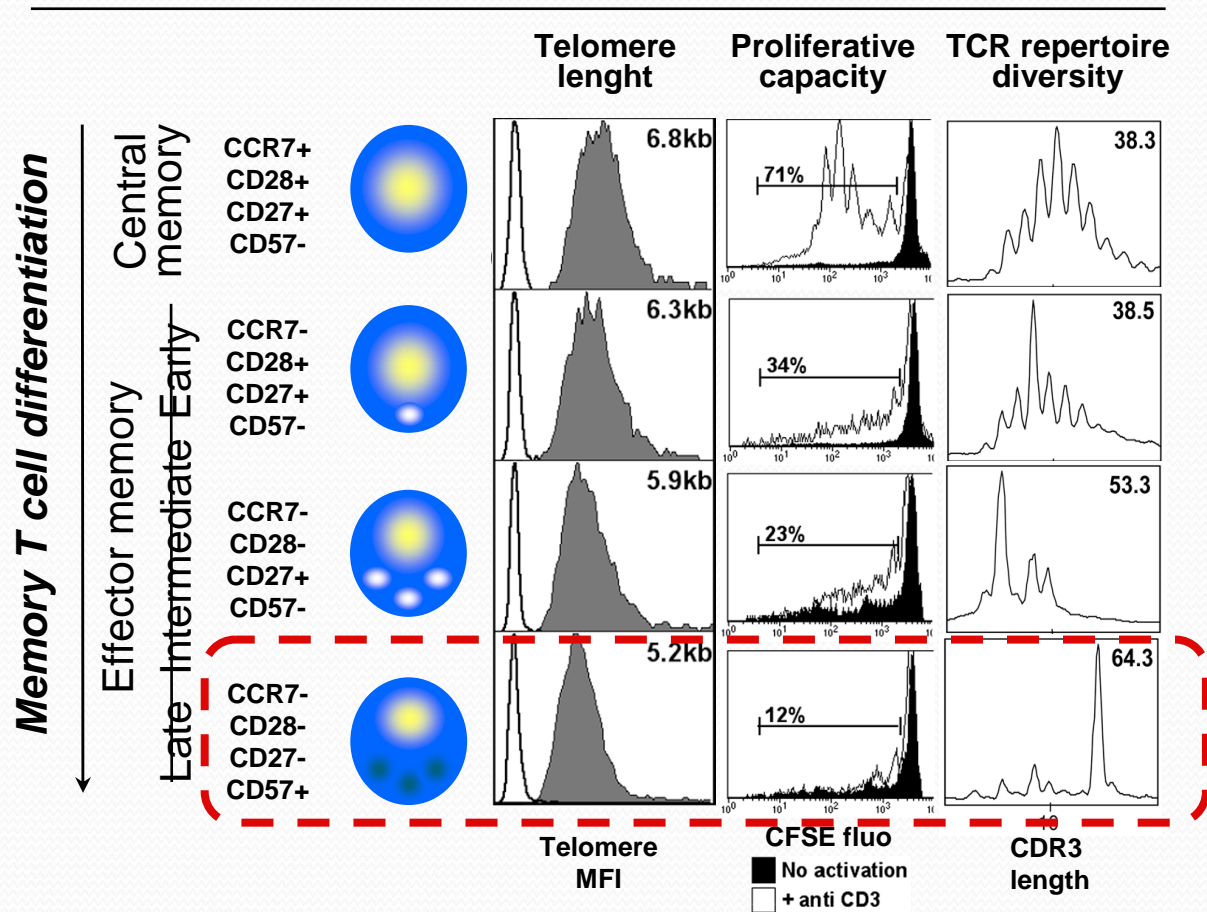
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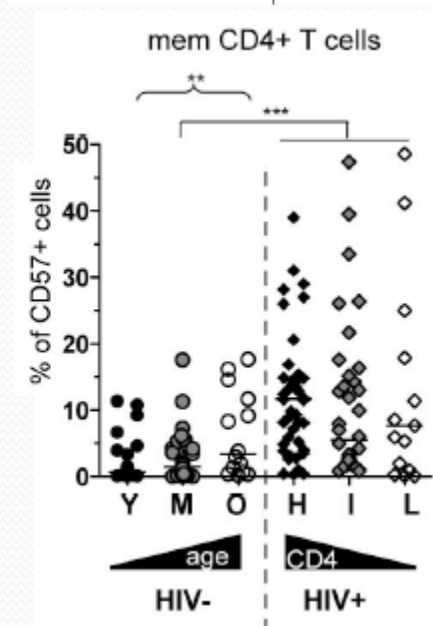
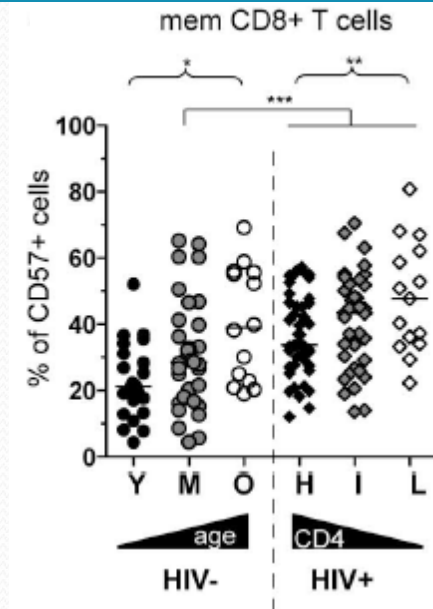


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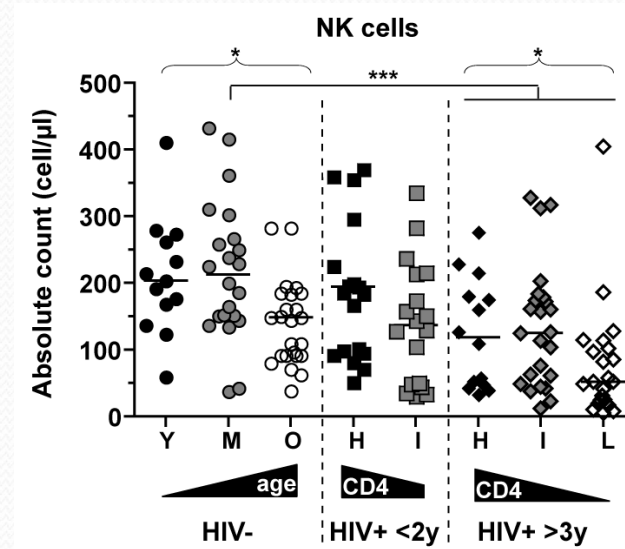
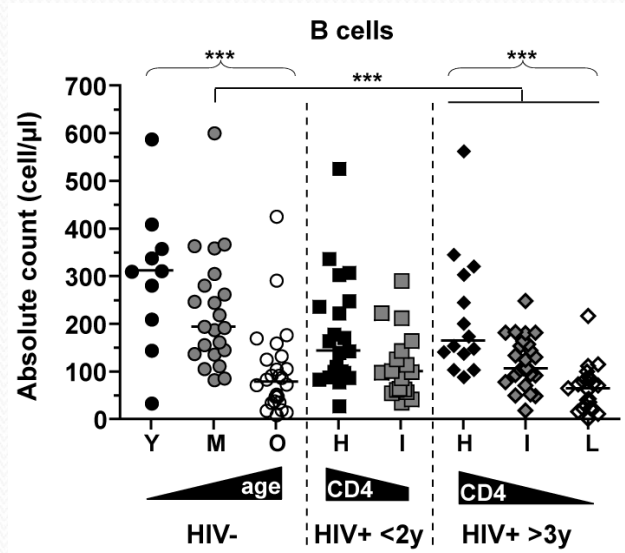
Memory T cell subsets



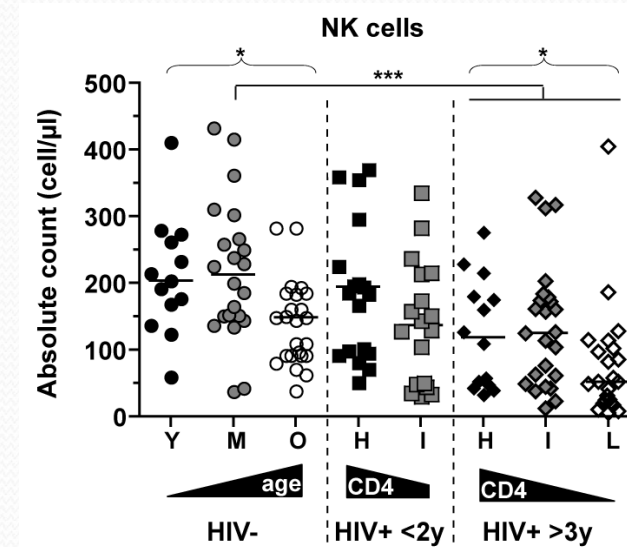
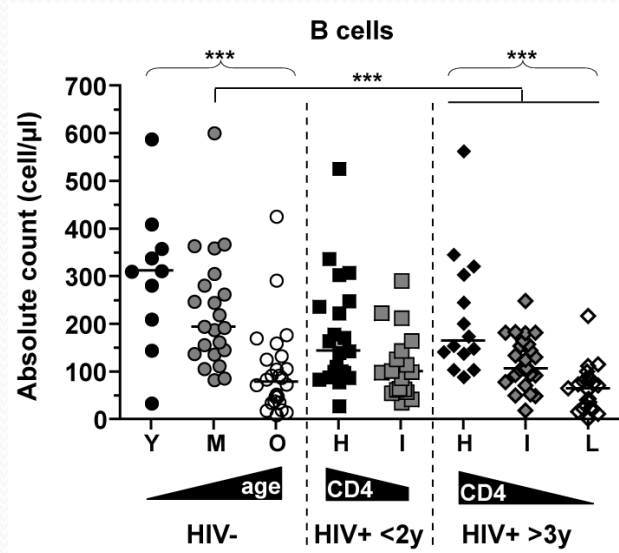
↗↗ with age and HIV-1 infection



Number of other lymphocytes: B and NK cells



Number of other lymphocytes: B and NK cells

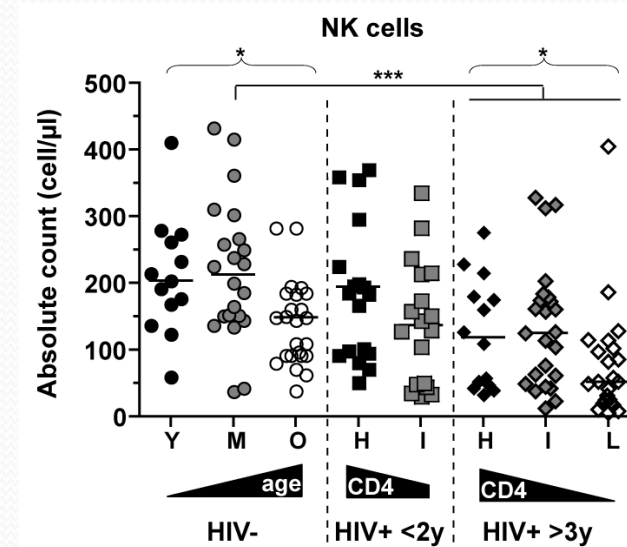
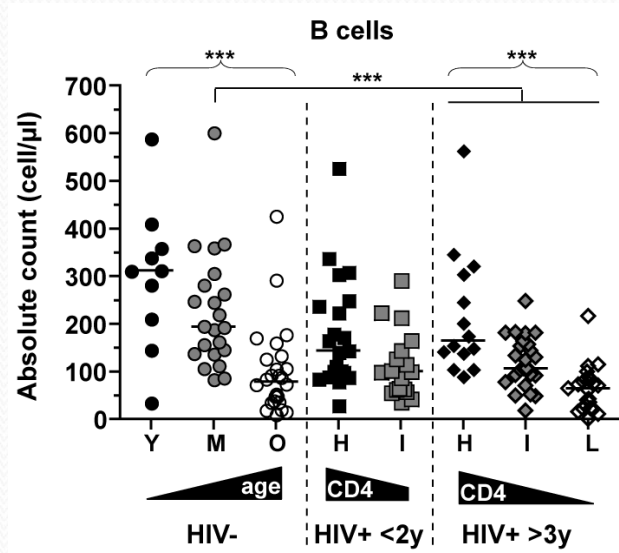


Subsets....

Accumulation of
“exhausted / highly differentiated”
memory B cells (IgD- / CD27-)
Decreased Ig / BCR diversity
 Moir and Fauci, NRI, 2009
 Siegrist and Aspinall, NRI, 2009

Accumulation of
“Dysfunctional / highly differentiated”
NK cells (CD16+ / CD56-)
Shorter telomere length
 Goodier et al, Isheid, 2010
 Romagnani C et al, JI, 2007
 Chan et al, JI, 2007

Number of other lymphocytes: B and NK cells



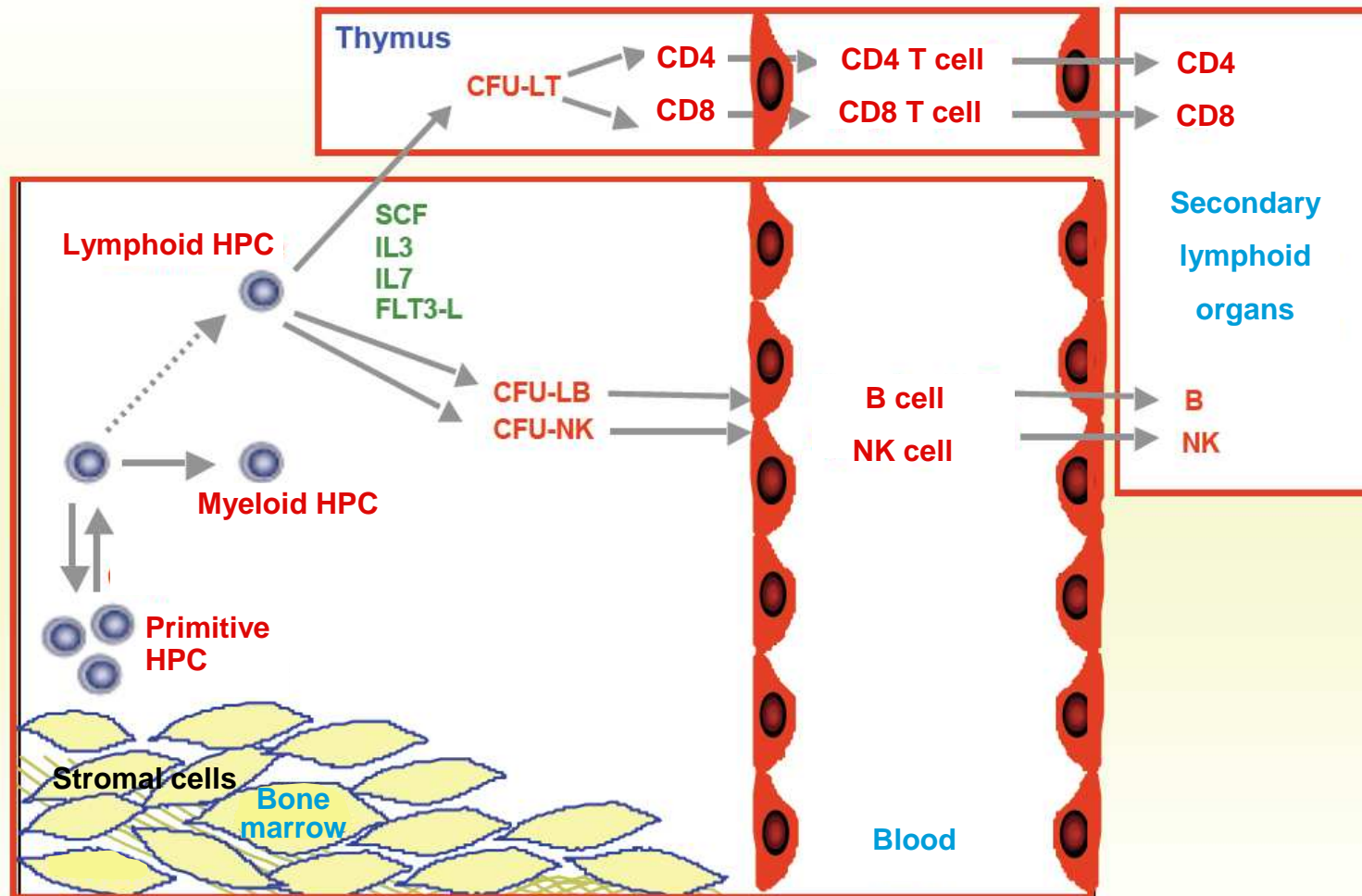
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➔ **Reduced capacity to produce**
all lymphocyte subpopulations with age or HIV disease progression

Development of lymphocytes: Hematopoietic progenitors



Hematopoietic progenitors and HIV infection...

Impaired HPC function: Yes! (reviewed in Moses et al, Blood, 1998)

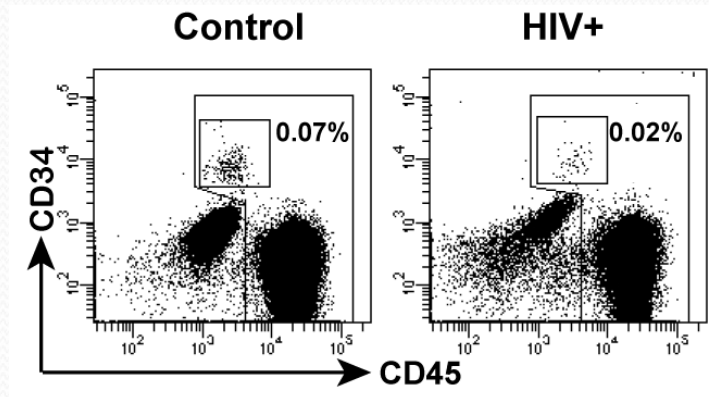
But relevance in HIV pathogenesis?

Study of hematopoietic progenitors

CD34+ cells: quantitative aspects

Analyse HPC in the blood to generate large data set

1. Numbers of circulating CD34+ (lin-) cells

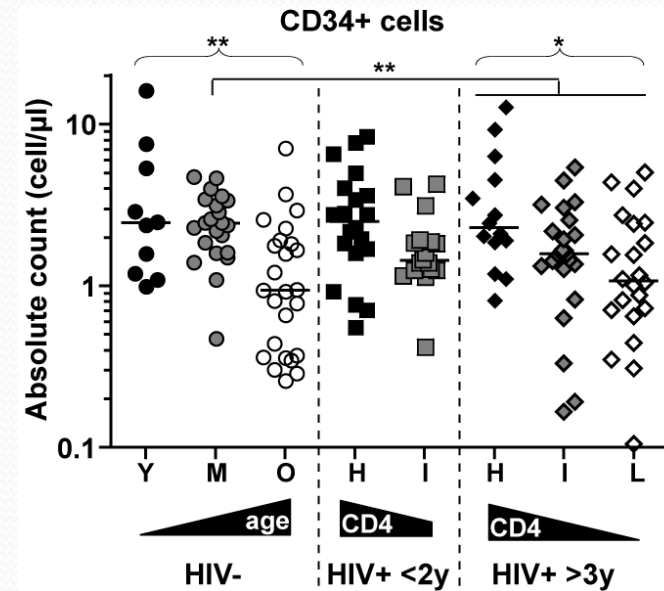
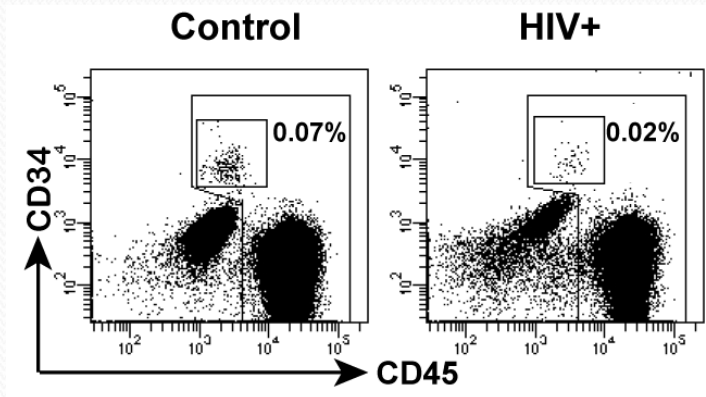


Study of hematopoietic progenitors

CD34+ cells: quantitative aspects

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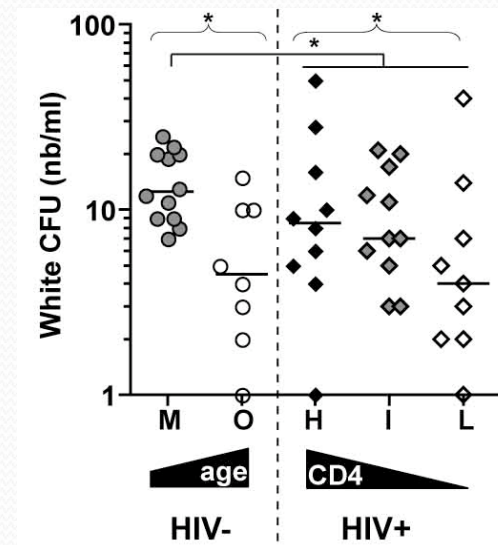
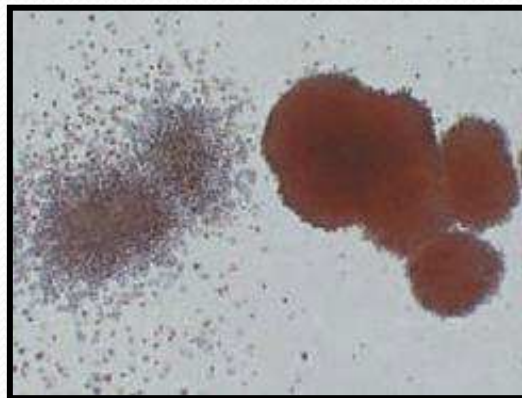


→ Diminution of CD34+ cell number with HIV disease progression or age

Study of hematopoietic progenitors

CD34+ cells: qualitative aspects

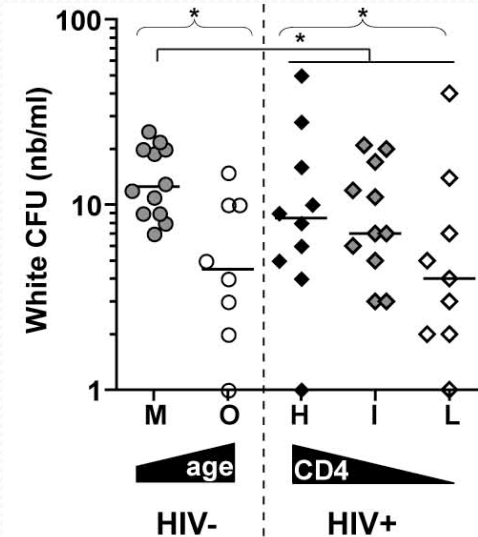
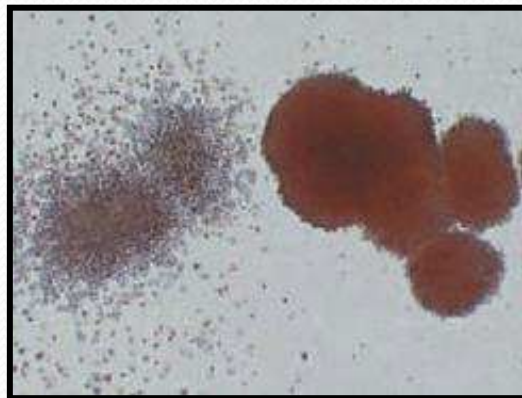
2. Clonogenic potential (CFU assay)



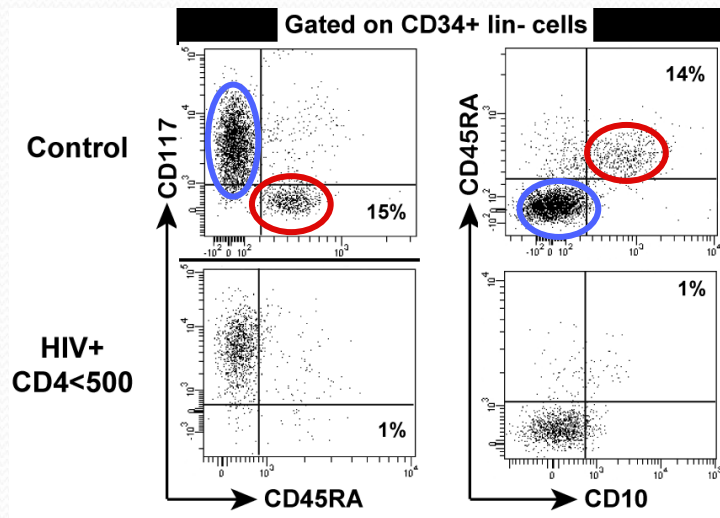
Study of hematopoietic progenitors

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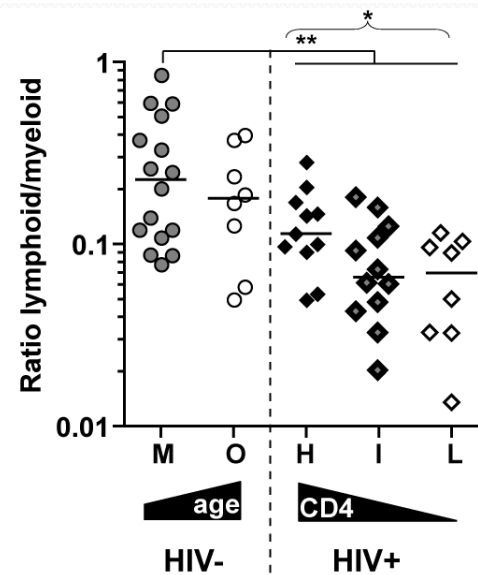


3. Lymphoid vs myeloid potential (phenotype)



lymphoide

myeloide



➔ Alteration of both quantitative and qualitative attributes

***=> HIV disease progression
and impaired lymphopoiesis***

***=> Basis of immune parallel
between HIV infection & aging***

***Cause of impaired lymphopoiesis
in HIV-1 infection?***

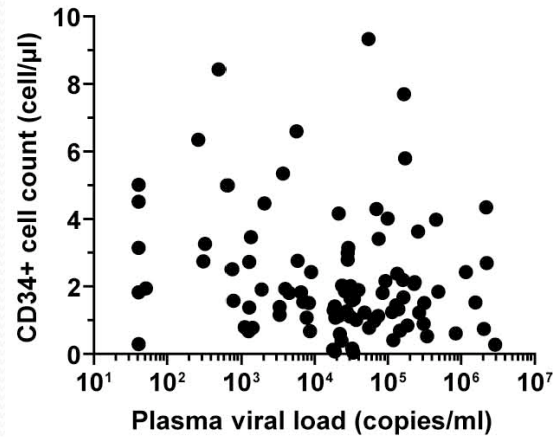
Cause of impaired lymphopoiesis ?

I. Infection of CD34+ cells by HIV?

Cause of impaired lymphopoiesis ?

I. Infection of CD34+ cells by HIV?

No correlation
HIV load vs CD34+ cells

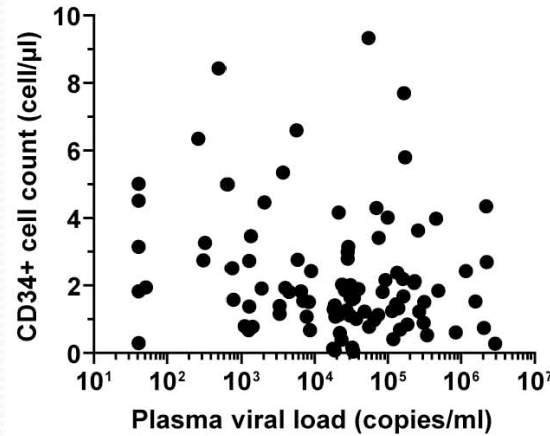


=> No direct effect of HIV
on CD34+ cell
compartment

Cause of impaired lymphopoiesis ?

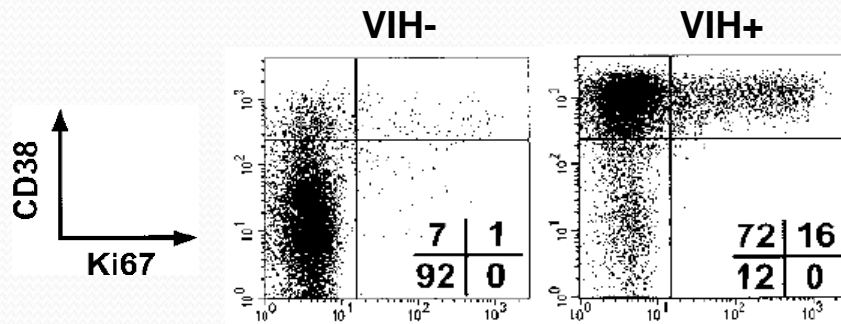
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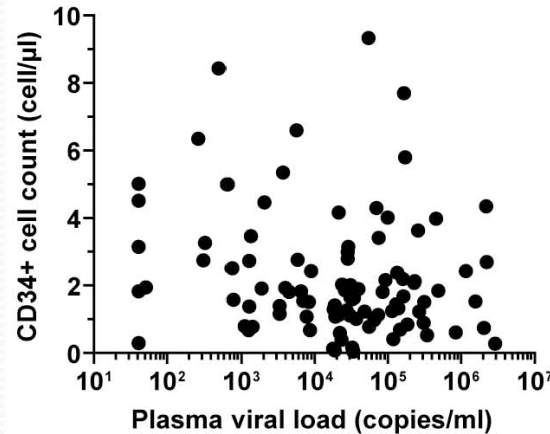
II. Effect of immune activation?



Cause of impaired lymphopoiesis ?

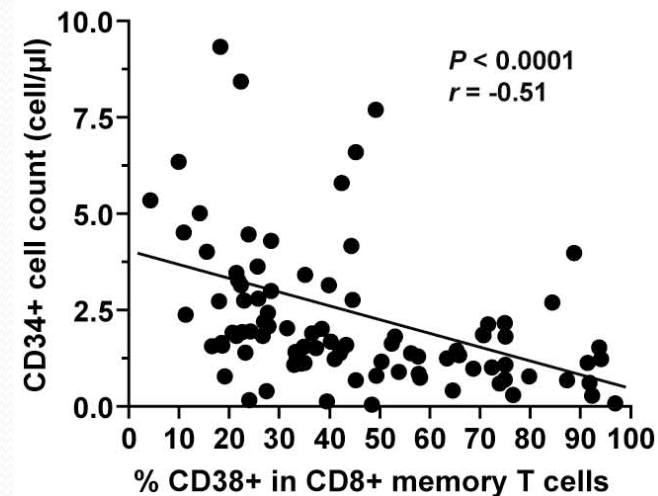
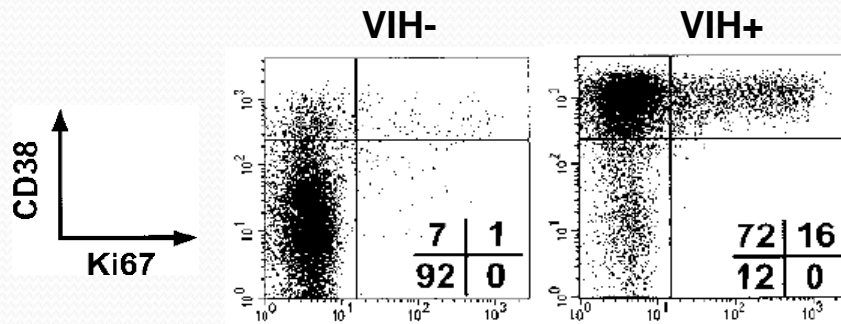
I. Infection of CD34+ cells by HIV?

No correlation
HIV load vs CD34+ cells



=> No direct effect of HIV
on CD34+ cell
compartment

II. Effect of immune activation?



➔ Inverse correlation between CD34+ cell frequency and immune activation

Immune activation and hematopoietic factors

SDF-1 α

(Aiuti et al, JEM, 1997)

IP-10

(Sarris et al, JEM, 1993)

MIG

(Schwartz et al, JI, 1997)

**=> Mobilisation of
Hematopoietic
progenitors**
(migration & proliferation)

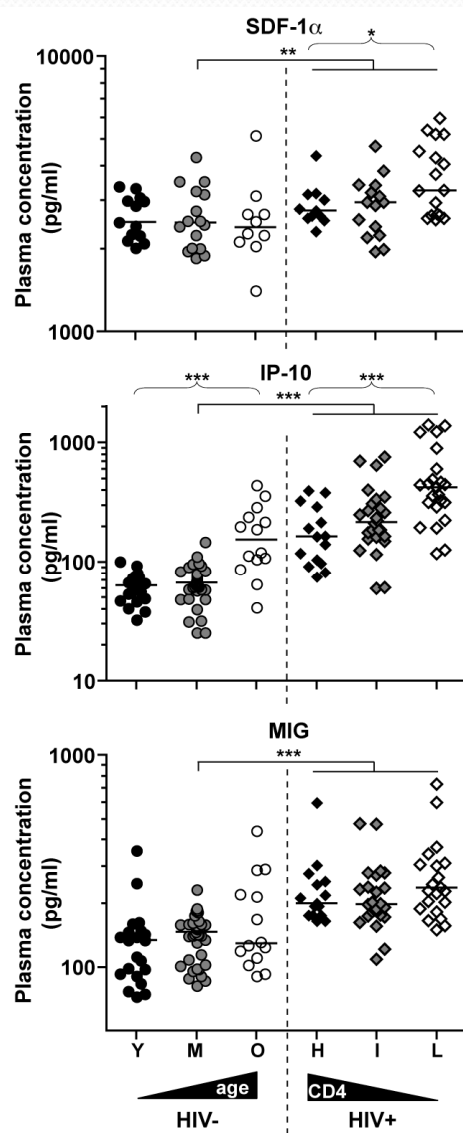
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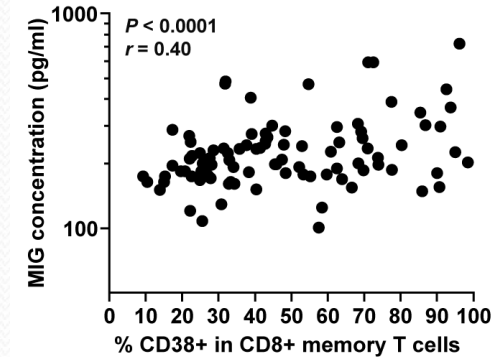
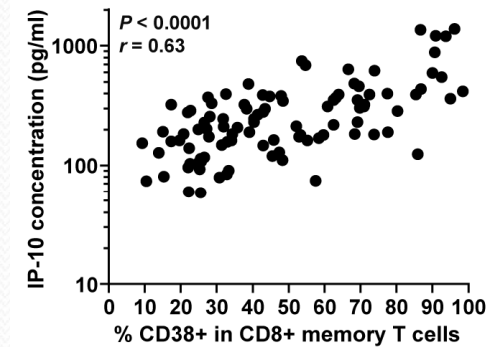
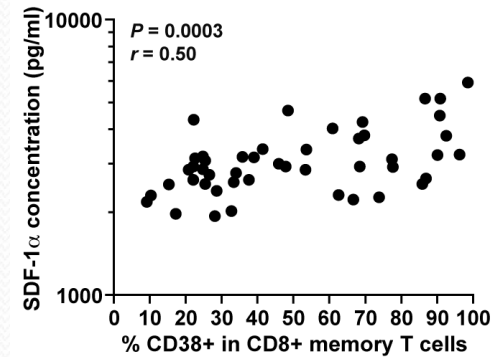
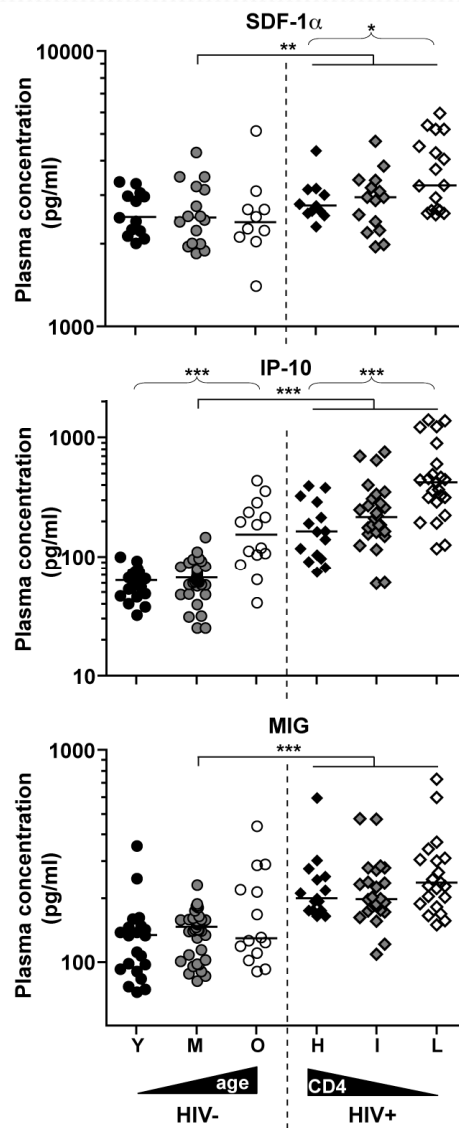
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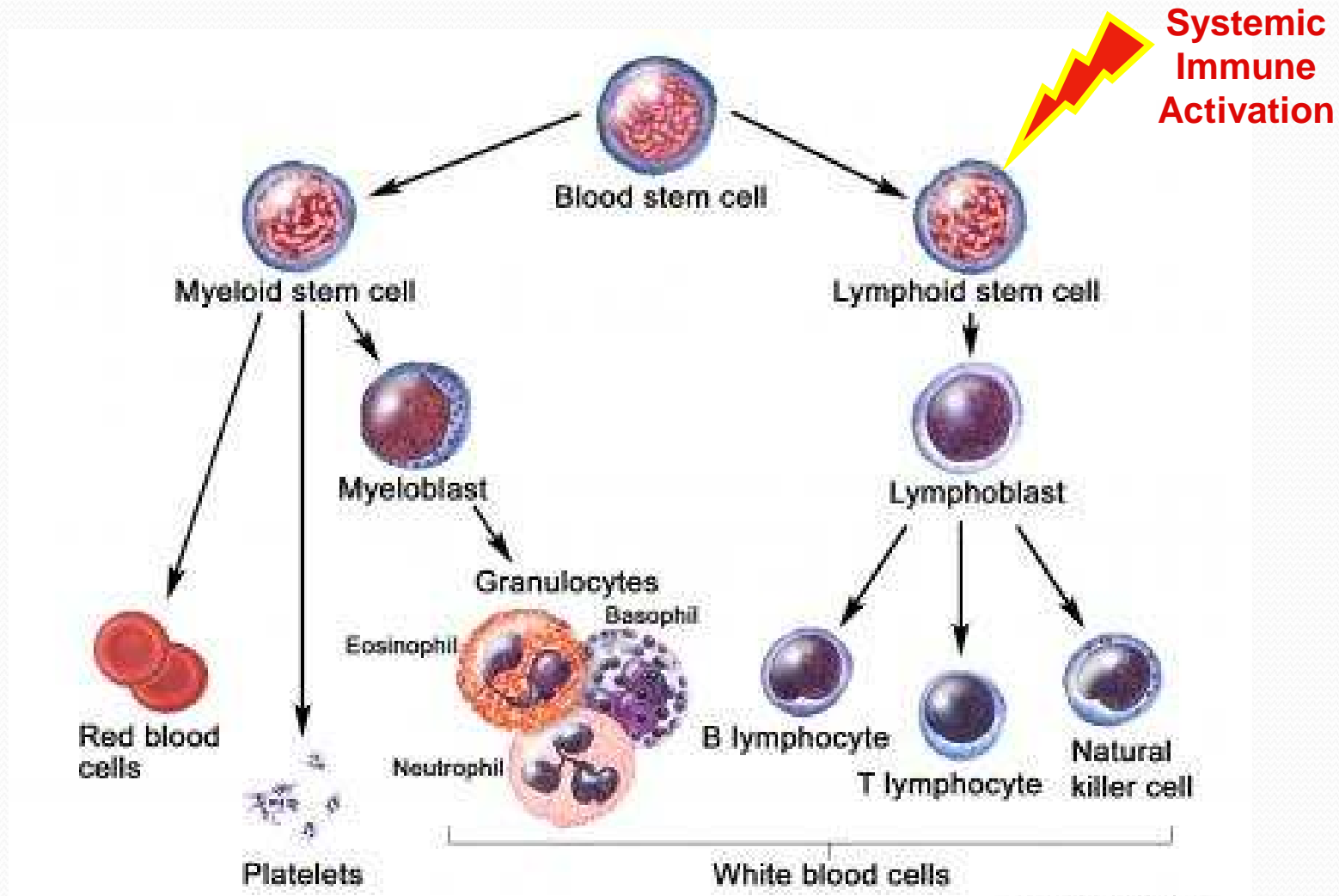
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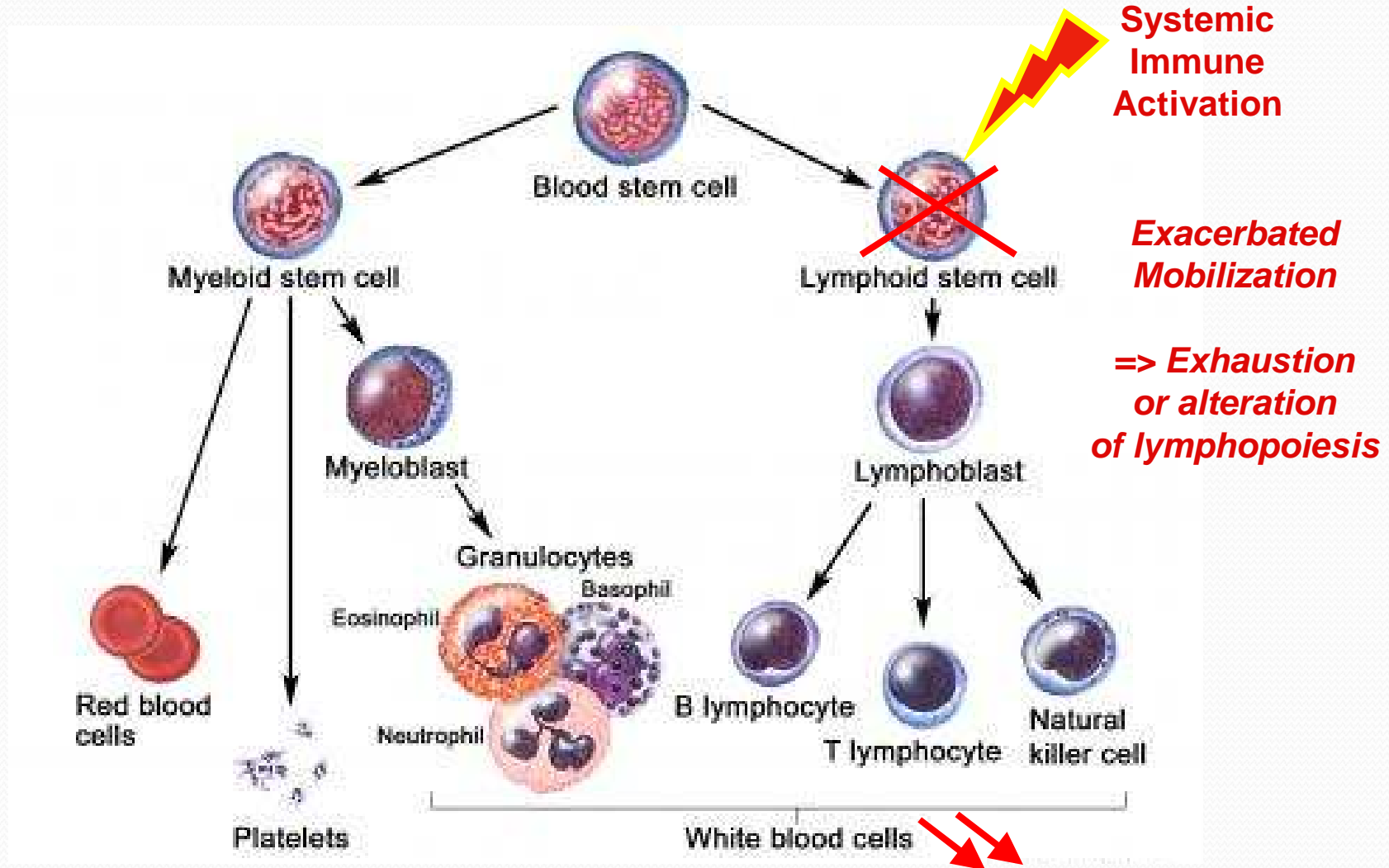


→ Alteration of hematopoietic system in HIV infection related to immune activation

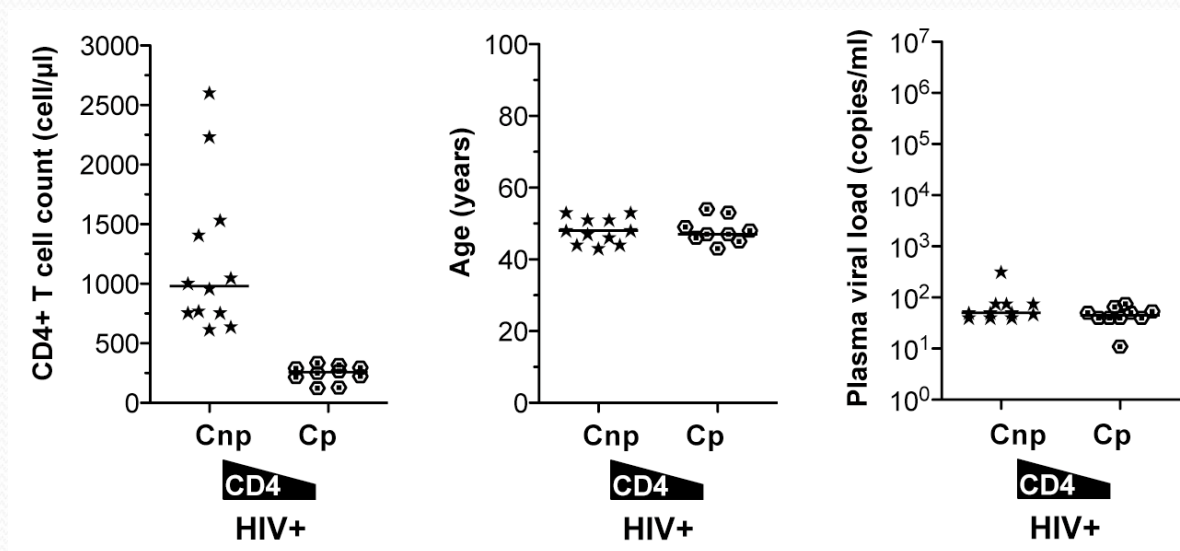
Immune activation and altered lymphopoiesis



Immune activation and altered lymphopoiesis



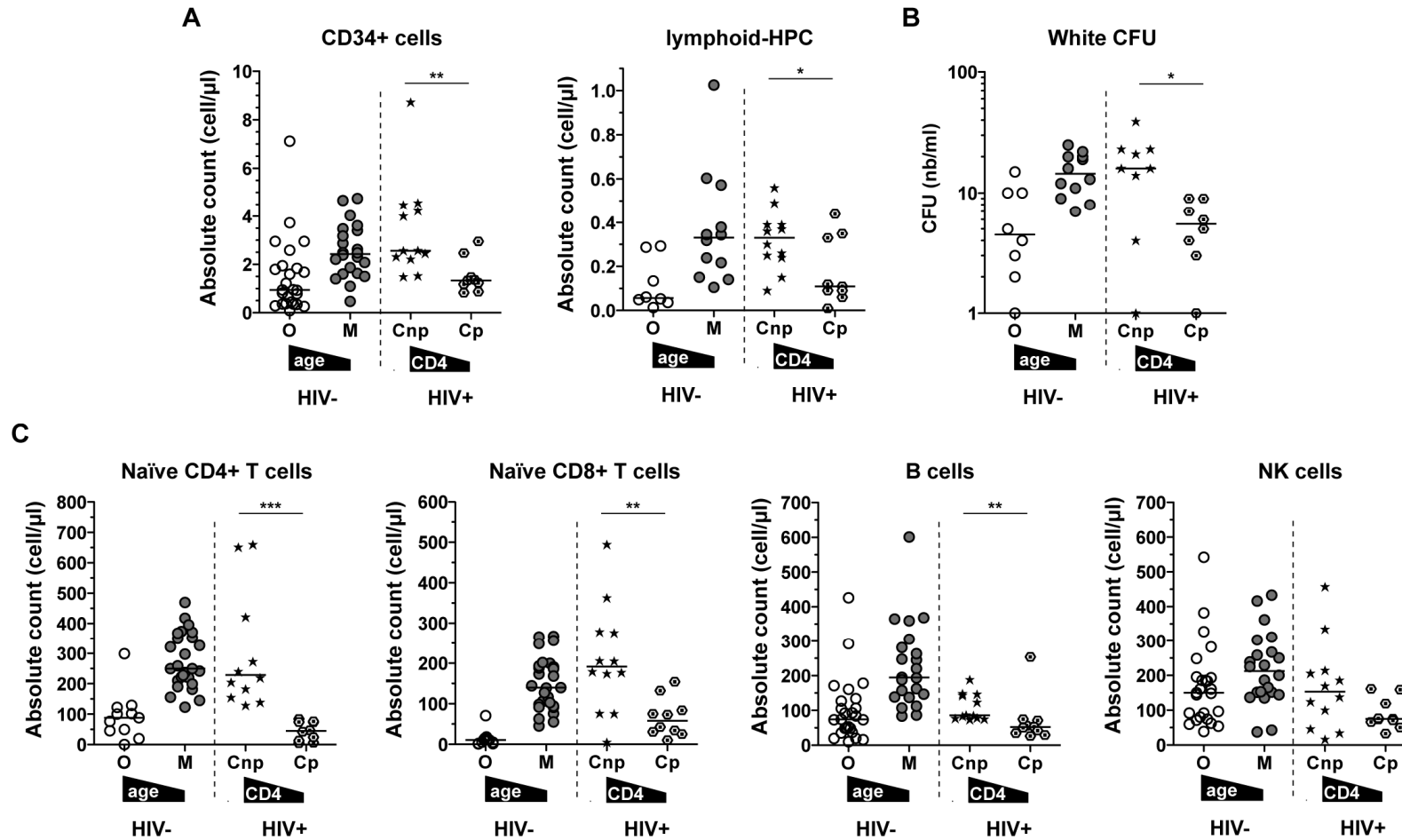
Disease progression despite elite control of HIV replication



Cnp = HIV elite Controller non progressors
Cp = HIV elite Controller progressors

But, elevated immune activation levels - Hunt et al, JID 2008

Disease progression despite elite control of HIV replication



... is associated with exhausted lymphopoiesis



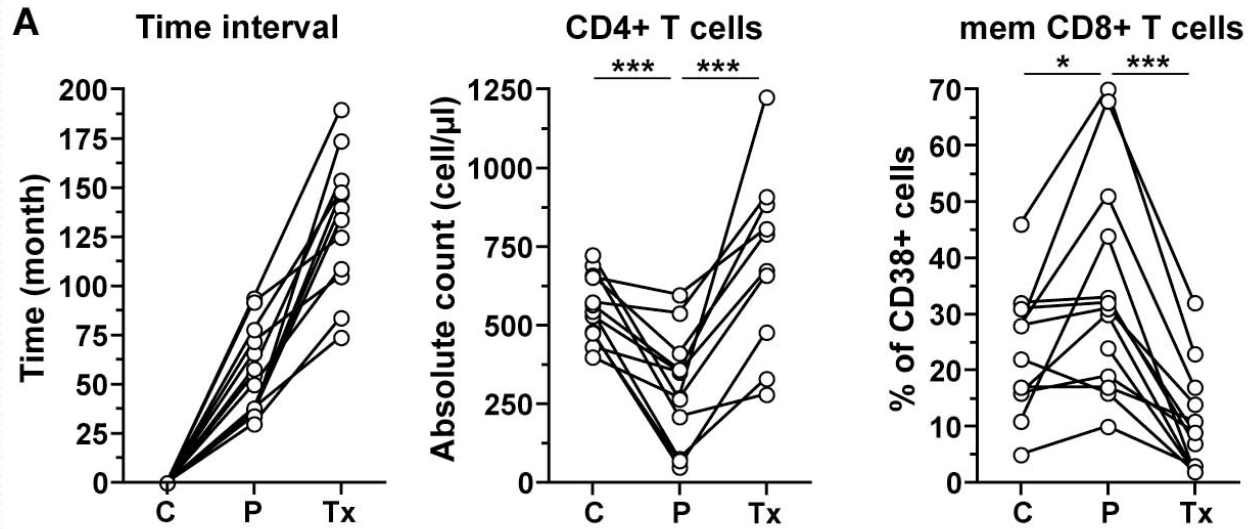
Part III: Resources & reconstitution in ART- treated HIV seropositive patients



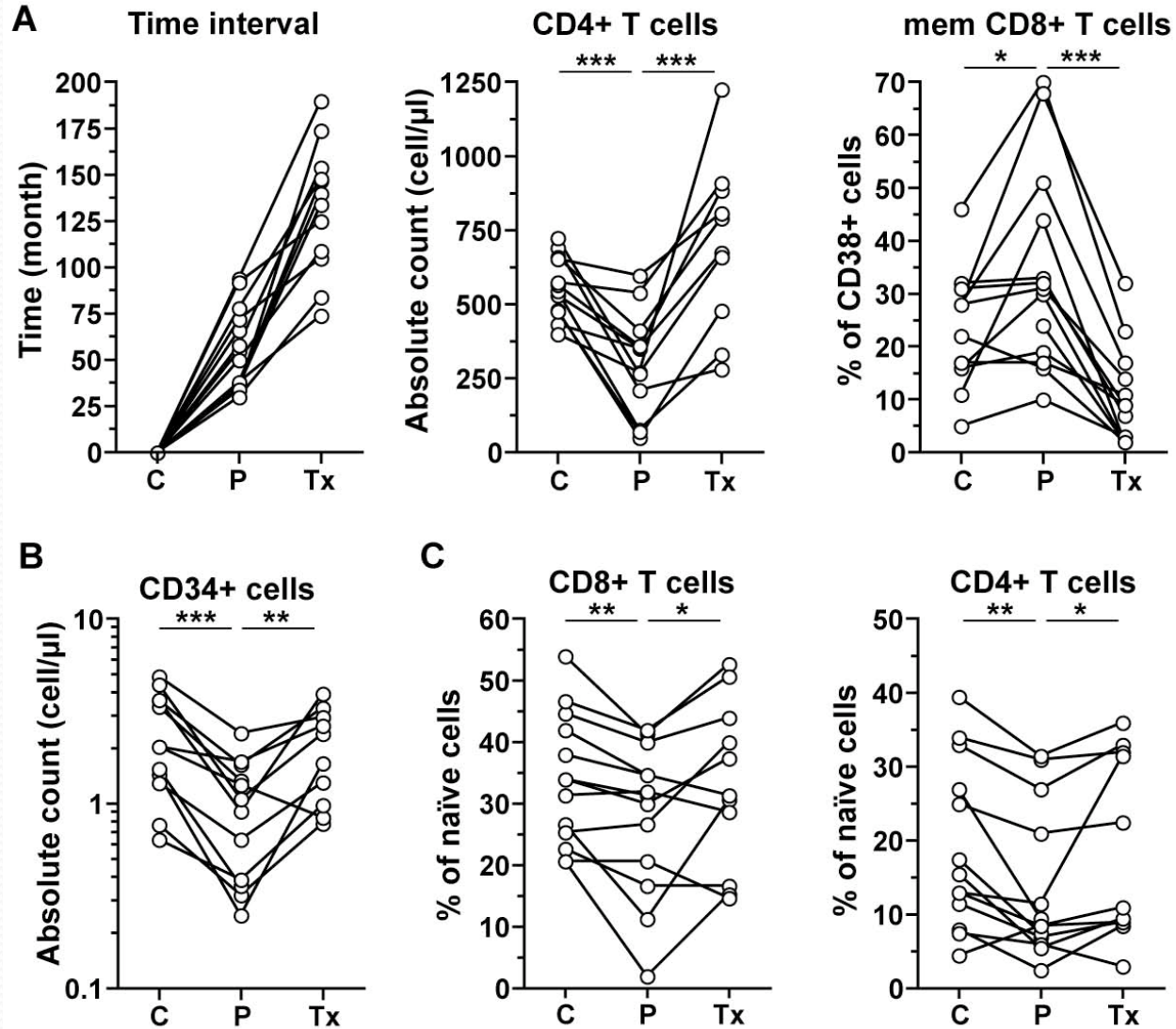
***=> Impaired lymphopoiesis:
consequence of immune activation***

Effect of anti-retroviral therapy?

Longitudinal study of treated patients

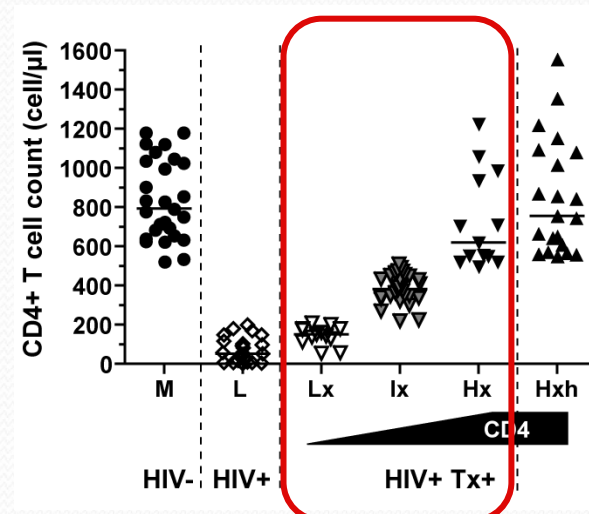
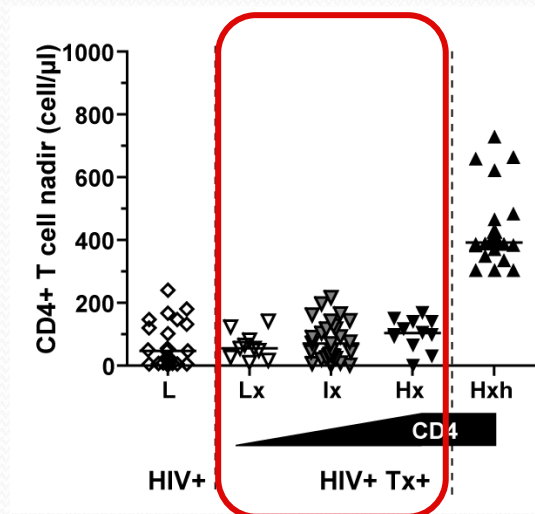
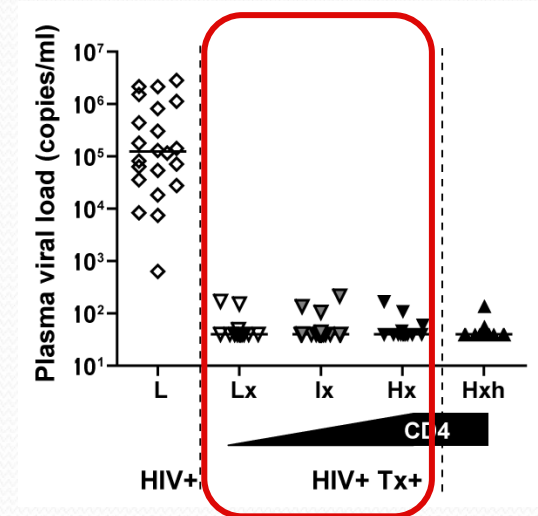
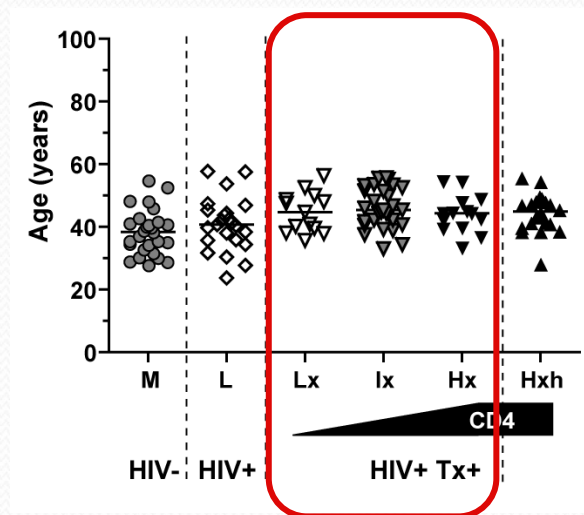


Longitudinal study of treated patients

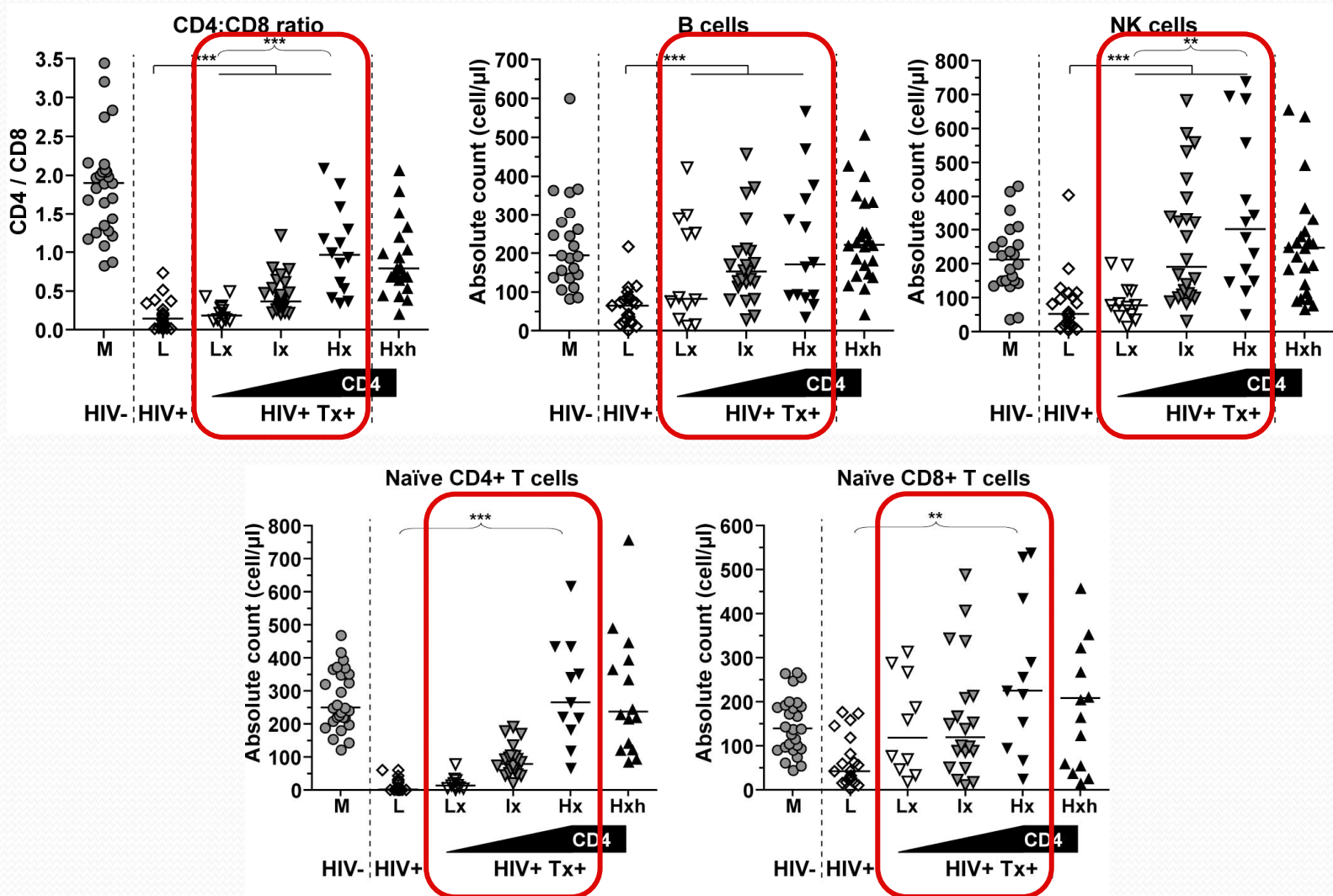


Cross sectional study of treated patients

Patients groups

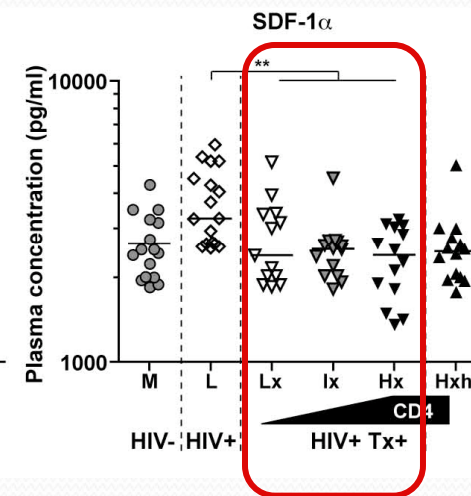
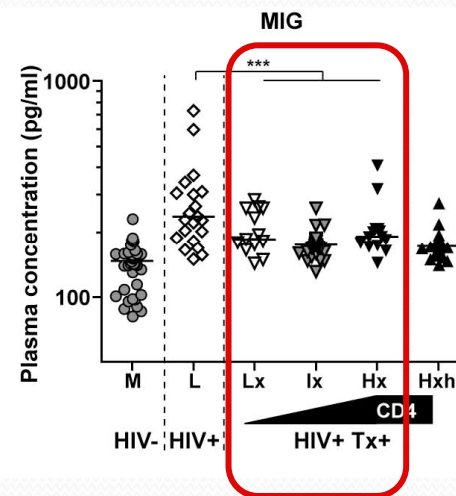
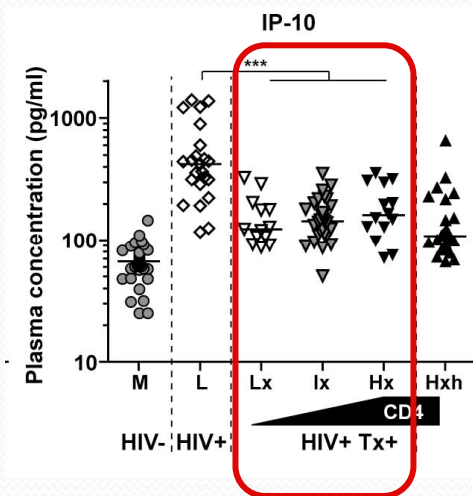
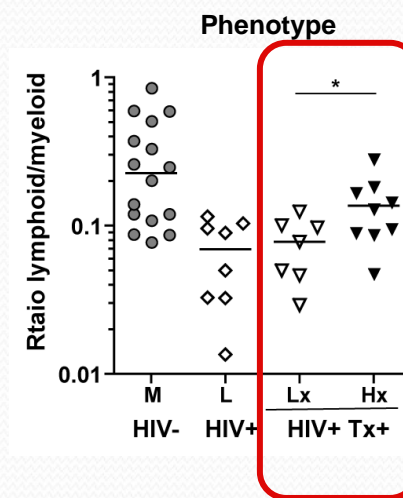
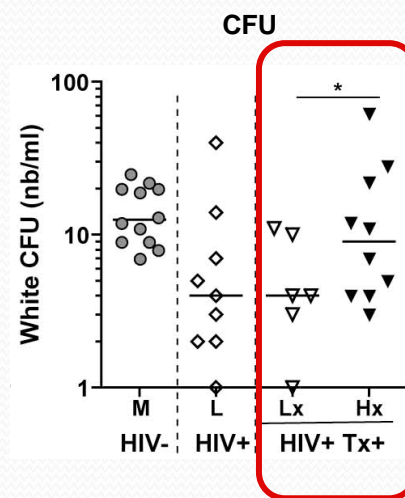
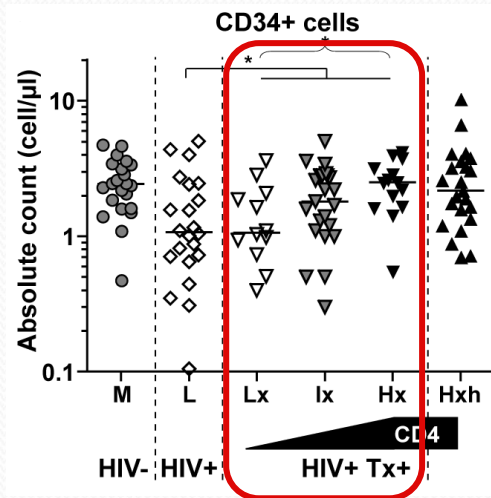


ART and lymphocyte reconstitution



⇒ It is all linked

Lymphopoiesis attributes



=> Association reconstitution of CD4 compartment and lymphopoiesis normalization

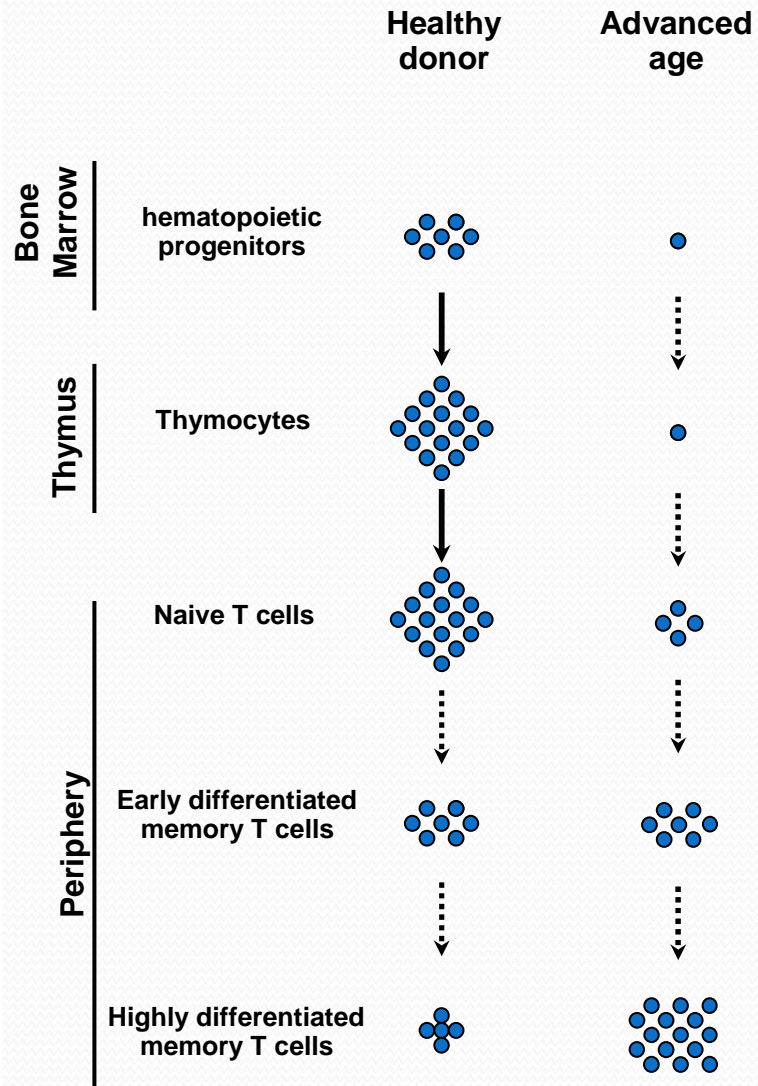


Conclusions:

Accelerated immune senescence in HIV-1 infection

- I. HIV disease progression => development of premature immunosenescence phenotype**
Basis = altered lymphopoiesis
- II. Altered lymphopoiesis => likely consequence of immune activation / inflammation levels**
(= mechanism in HIV pathogenesis... and immune aging...?)
- III. CD4 reconstitution with ART is associated with re-established lymphopoiesis**
(immunologic failure = persistent damage to hematopoietic system)

Exhaustion of lymphopoiesis with HIV disease progression



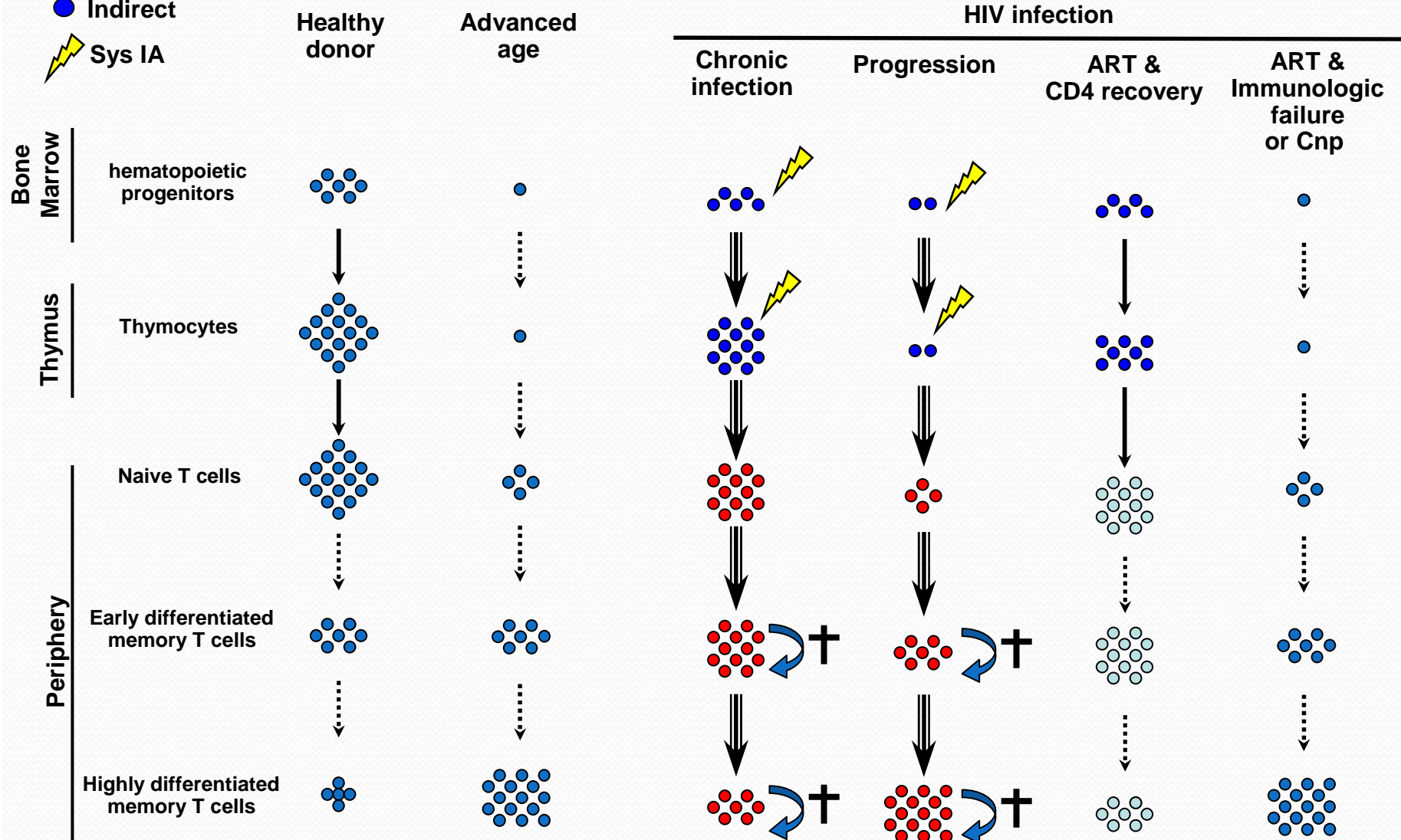
Exhaustion of lymphopoiesis with HIV disease progression

Activation/Mobilization

● Antigenic

● Indirect

⚡ Sys IA



Differences Aging and HIV infection

- Profound CD4 T-lymphopenia
- Infection of the thymus
- HIV protein mediated effects
- Susceptibility to opportunistic pathogens

=> HIV infection leads to severe immunodeficiency

Autres parallèles?

Infection VIH et vieillissement

- **Inflammation accrue**

Niveaux élevés de cytokines proinflammatoires (ex TNF- α , IL-6) dans le serum

- **Atteintes cardio-vasculaires (athérome)**

Taux élevé d'infarctus du myocarde, épaisseur intima-media carotidienne élevée

- **Biologie de l'os altérée (ostéoporose)**

Contenu mineral et capacité régénatrice des os diminués

- **Symptomes associés avec des altérations neurocognitives**

Perte de mémoire, capacité mentale réduite, démence

- **Développement prématuré de la fragilité**

Altérations physiologiques associées avec un âge avancé (perte de poids, sensation d'épuisement, faiblesse, marche ralentie et faible activité physique)

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