
Advanced
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EACS
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AIDS
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# HIV pathogenesis

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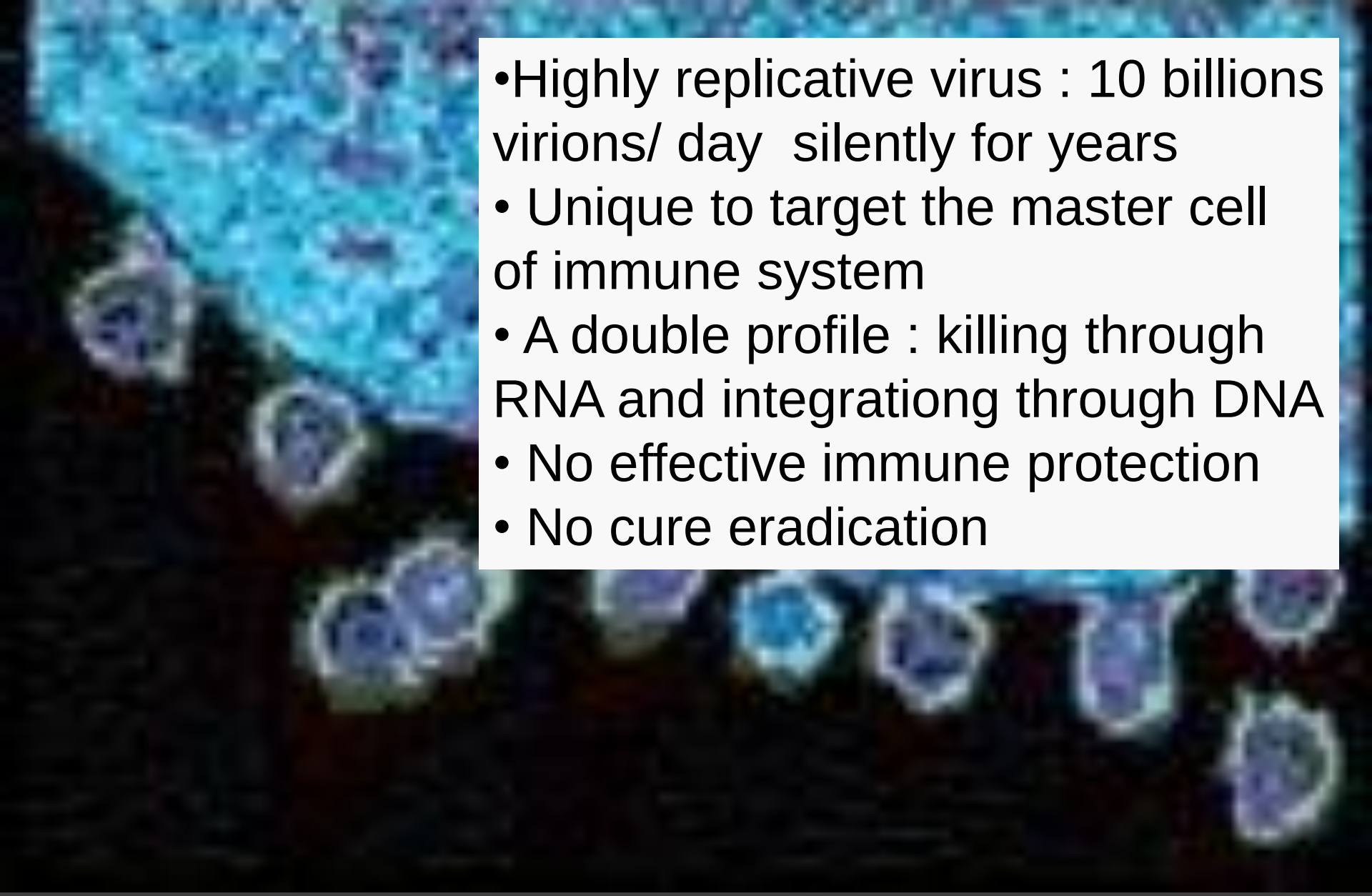
# HIV Pathogenesis

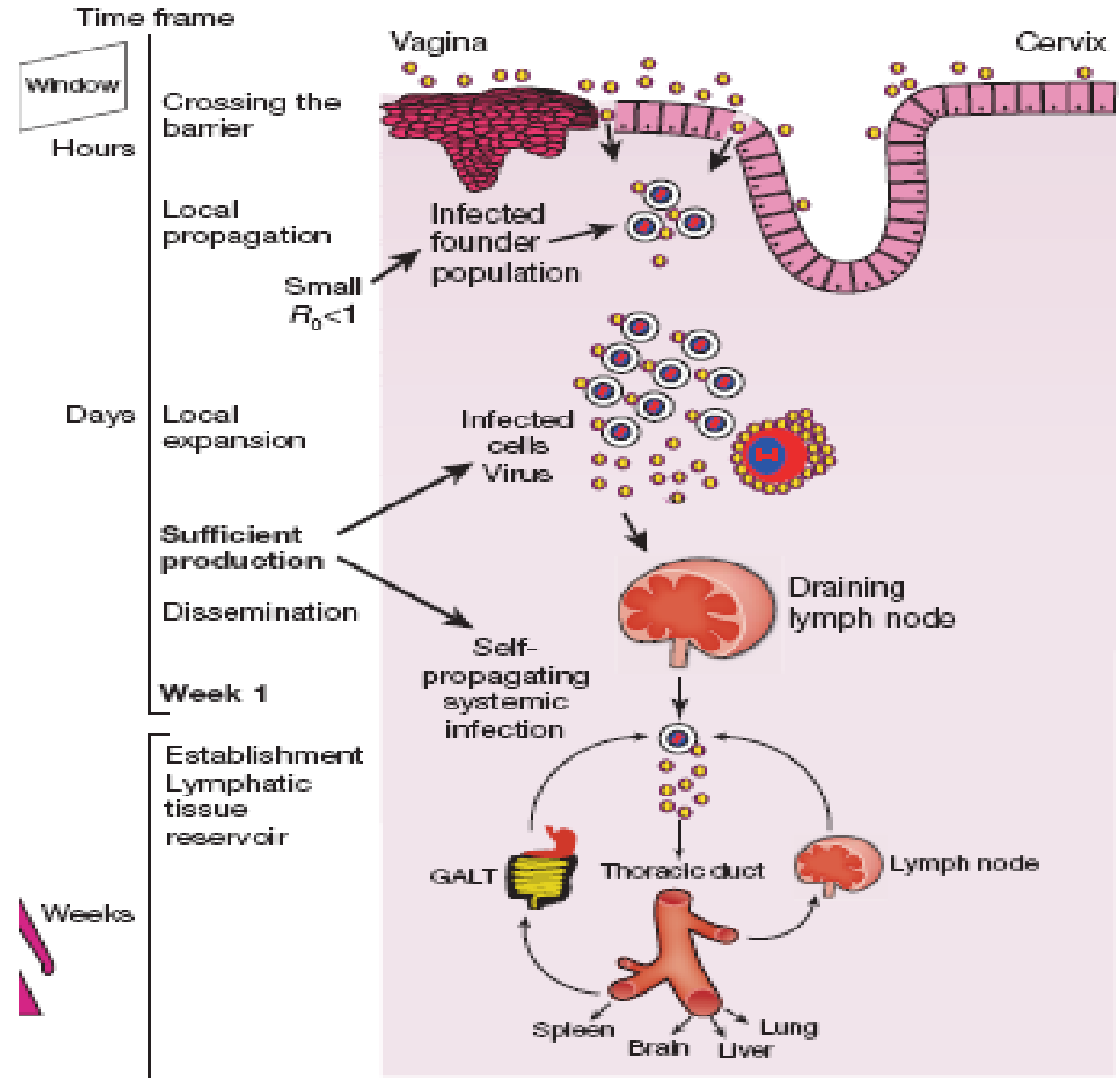
- HIV primary infection : a viro-immunological tsunami
- Establishement of HIV reservoirs
- HIV induced immune suppression
- HIV immune activation and inflammation
- Immune reconstitution
- HIV cure
- HIV immune protection

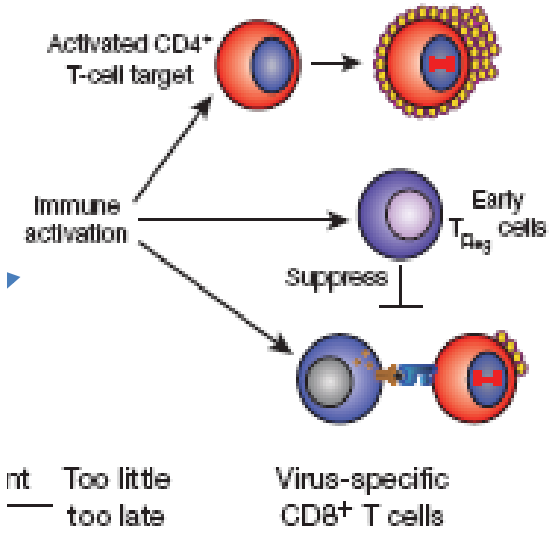


- Highly replicative virus : 10 billions virions/ day  silently for years
- Unique to target the master cell of immune system
- A double profile : killing through RNA and integrationg through DNA
- No effective immune protection
- No cure eradication

# VIH: a smart predator

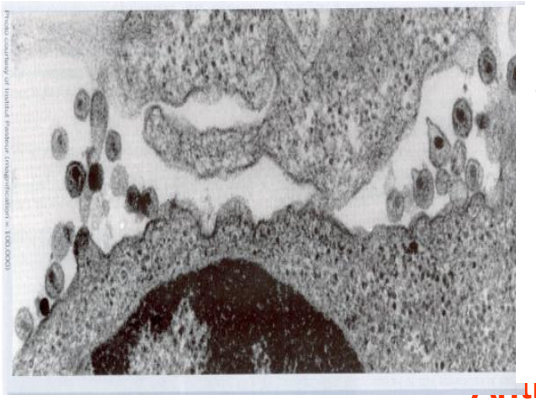
# Primary Infection :
# A defeated immune system in a viral tsunami



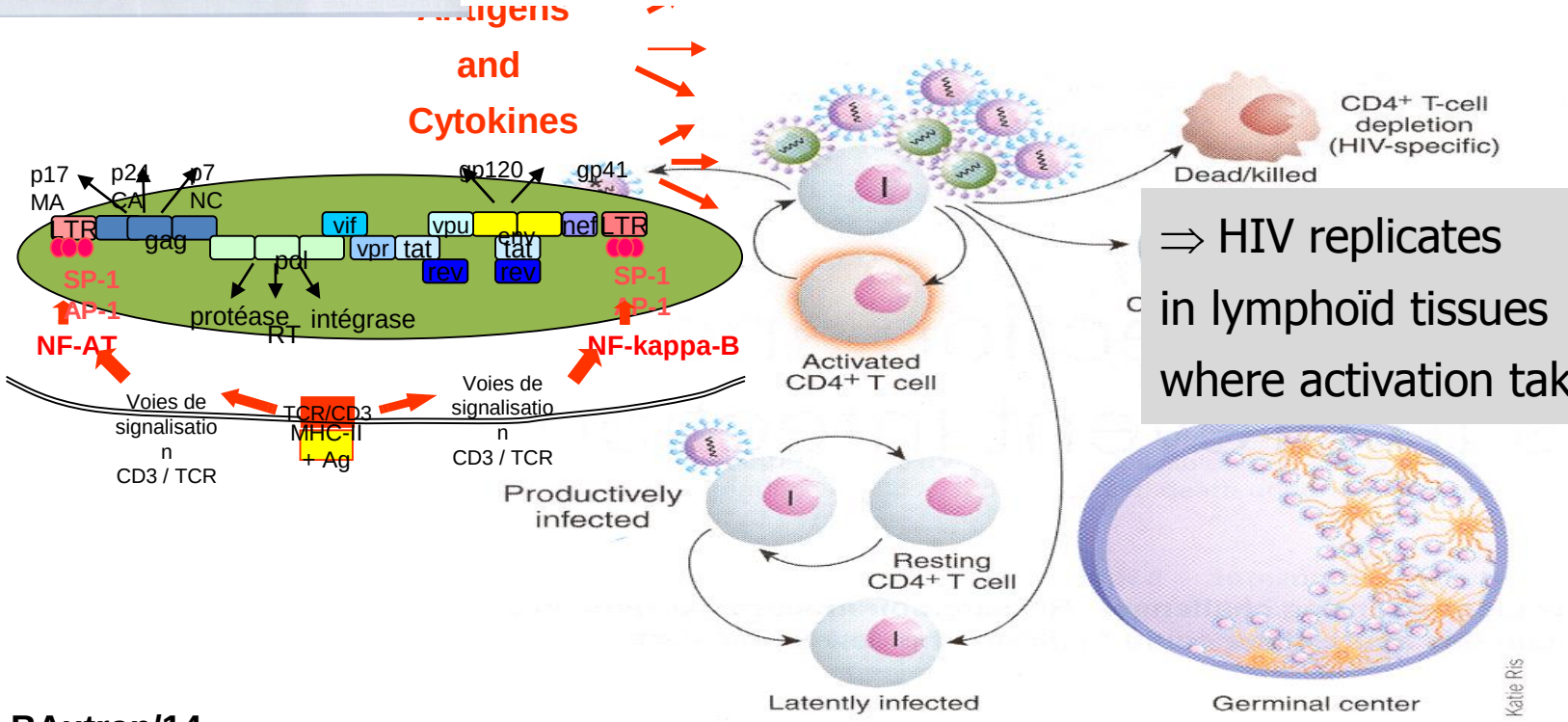

*From A Haase et al. 2008*

# HIV depends upon immune activation to replicate



*F Barré-Sinoussi et al.*
*Science,*
*May 1983,*

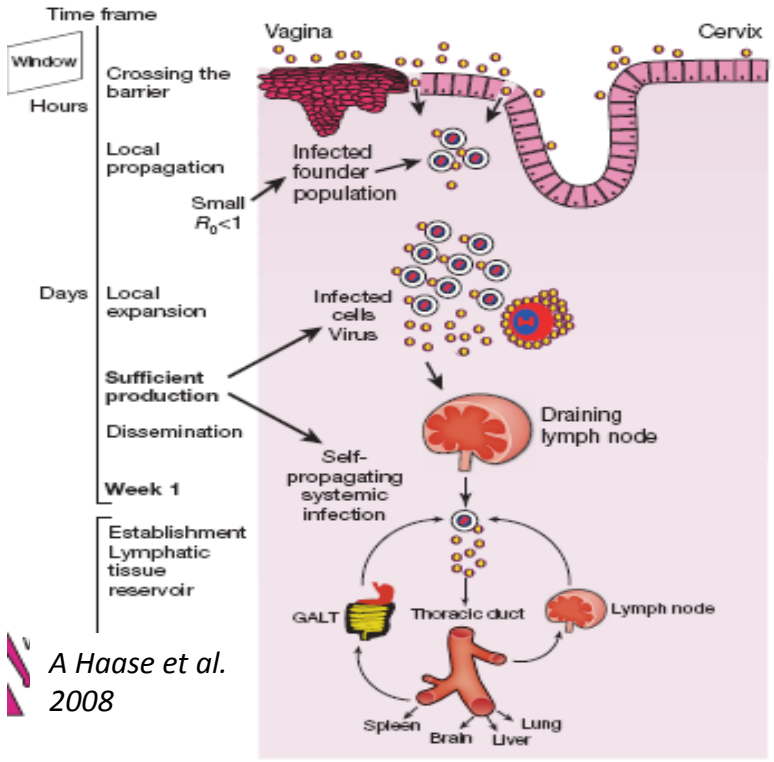
HIV was discovered in lymphoïd tissues where the massive antigen stimulation of CD4 T cells favors HIV replication




⇒ HIV replicates in lymphoïd tissues where activation takes place

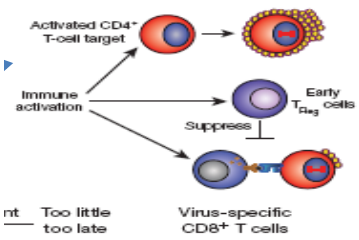
**BAutran/14**

# Early establishement of durable HIV reservoirs




*A Haase et al. 2008*

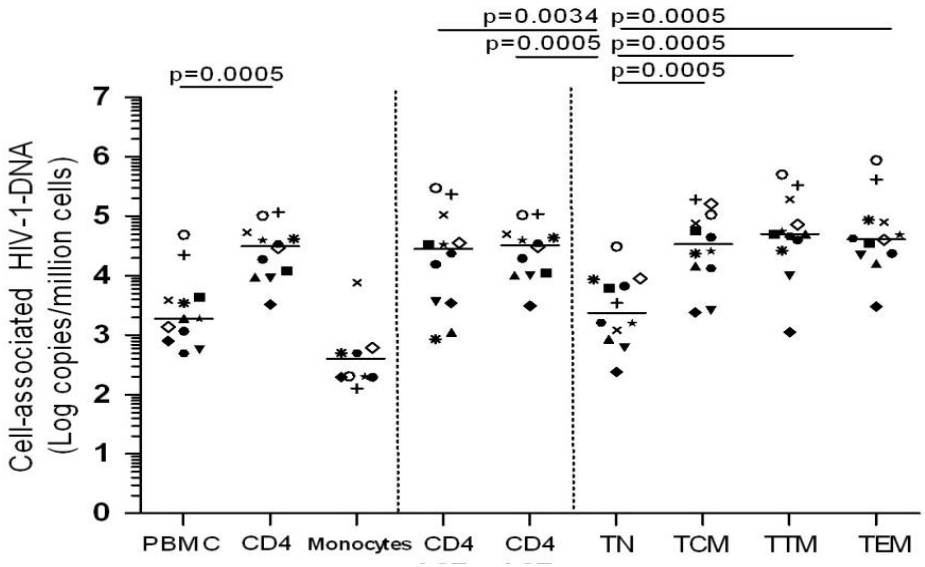
Immune responses to HIV: too little, too late




High level of infection in short-and long-lived CD4+ cells
Massive depletion of gut CD4

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

Early establishment of the HIV Reservoirs in CD4 cells




*Bacchus&Cheret et al Plos One 2013*

# Target cells for HIV

## Various CD4+ target cells

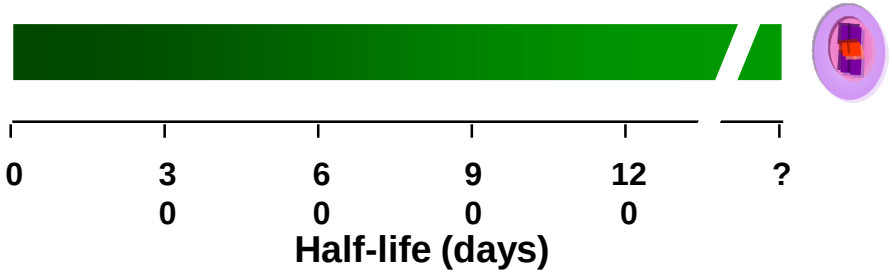
Free Virions

Infected activated CD4 T cells producing HIV

Resting CD4+ T cells harboring HIV DNA

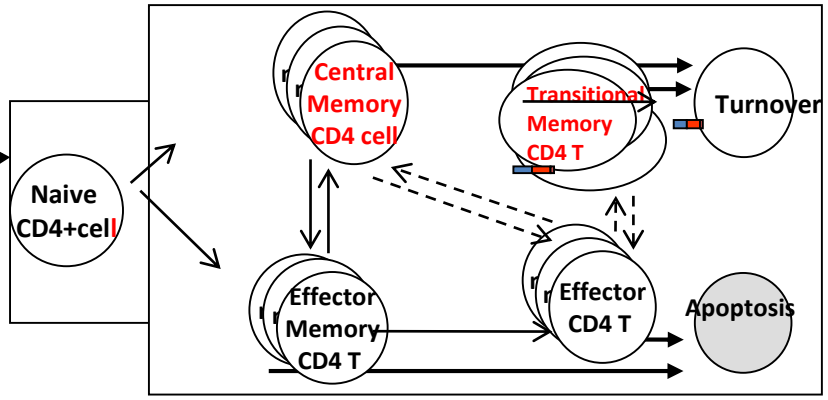
Free Virions on follicular dendritic cells (lymphoid tissues)

Infected Macrophages (all tissues and sanctuaries)



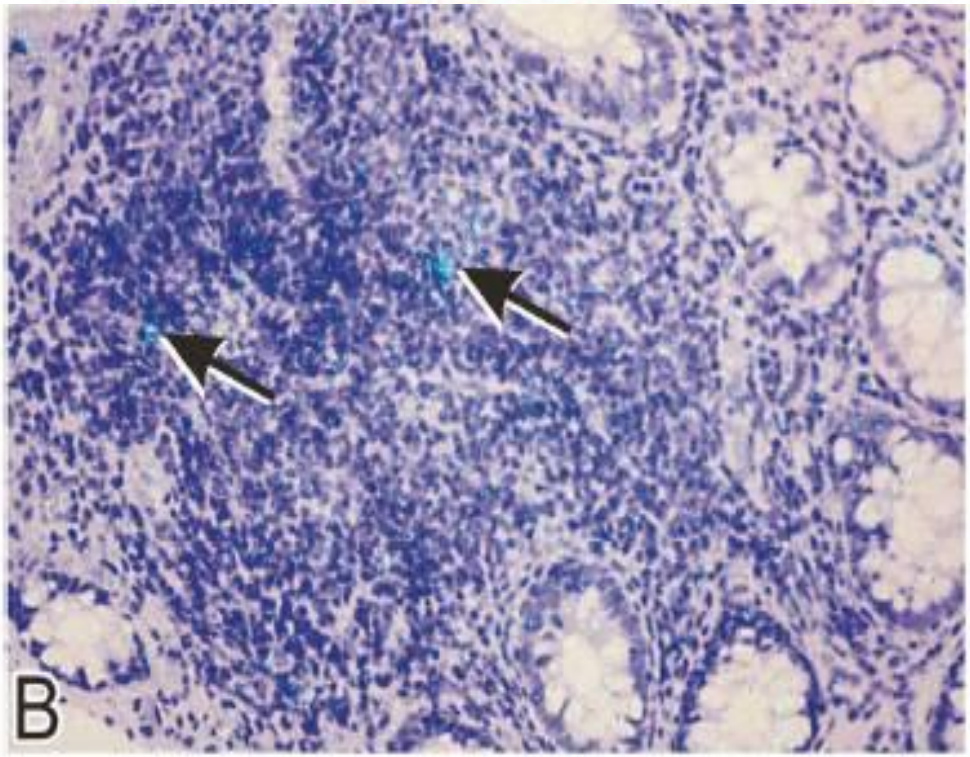

*From Siciliano, AIDS 1999, 13 Suppl A : S49-58*

## Heterogeneous CD4 T cells with a wide range of Half-lives and reproductive capacities

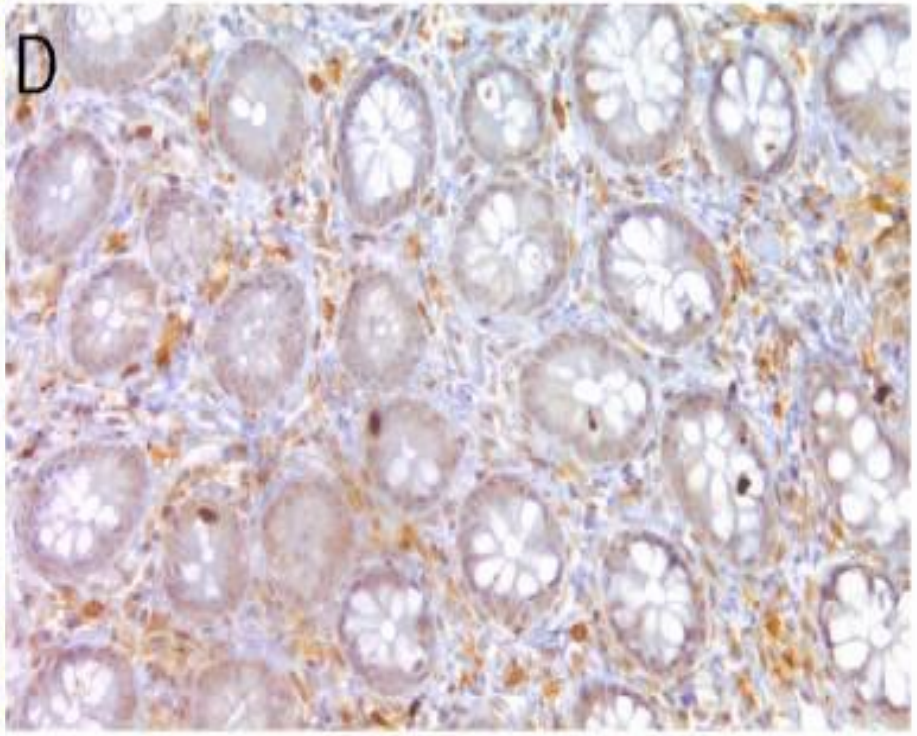



**TN Years** **TCM Months** **TTM** **TEM Weeks** **Effectors Days**

# HIV-1 Infection is massively located in the Gastrointestinal Tract with massive depletion of CD4 T Lymphocytes and durable tissue alterations




*S Mehandru,…….P Racz, and M Markowitz, J Exp. Med. 2004*




*JM. Brenchley, ..AT. Haase,and DC. Douek J Exp. Med. 2004*

GI tract represents half the immune system

# Primary infection and HIV reservoir dynamics

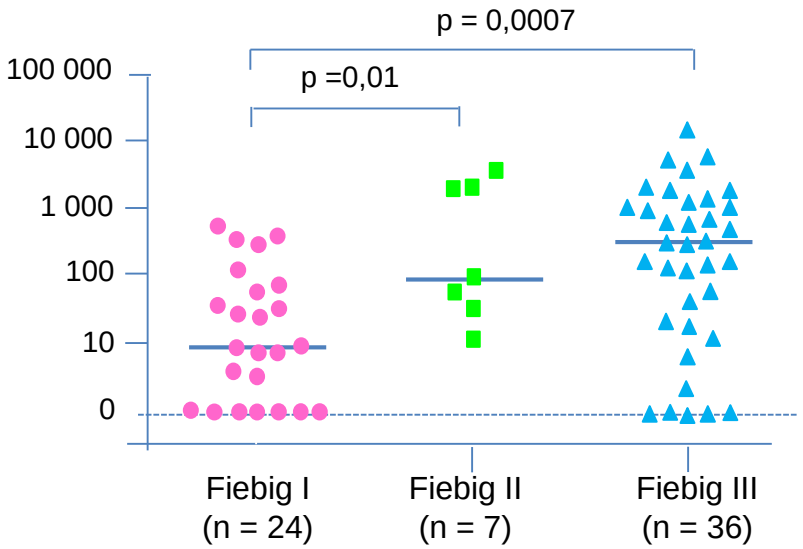
- 68 patients starting ART within 2-3 days after contamination Avant tout traitement :

**Total HIV DNA lower in Fiebig I**

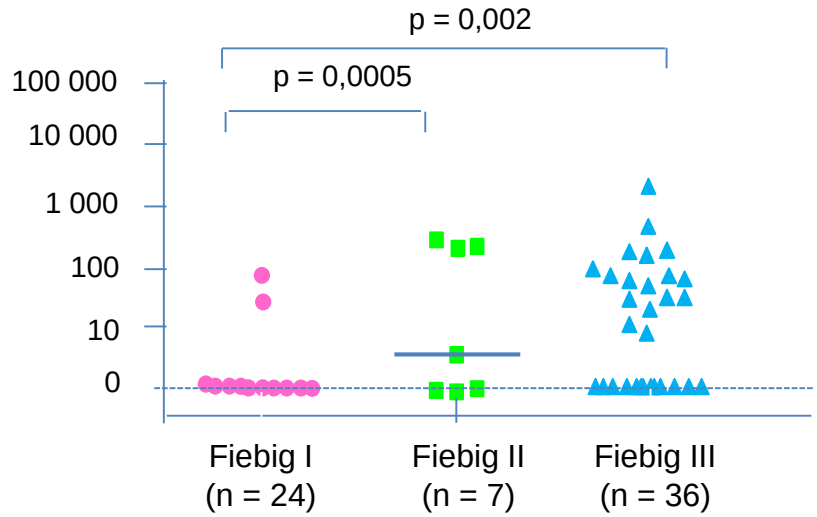
**Unintegrated DNA not detected in détecté chez 22/24 (92 %) Fiebig I**

- Fiebig I: RNA+, p24-, 3°G ELISA neg
- Fiebig II: RNA+, p24+, 3G ELISA neg
- Fiebig III: 3rd-gen ELISA+, WB neg

**Total HIV DNA (c/$10^6$ PBMC)**




**Integrated HIV DNA (c/$10^6$ PBMC)**

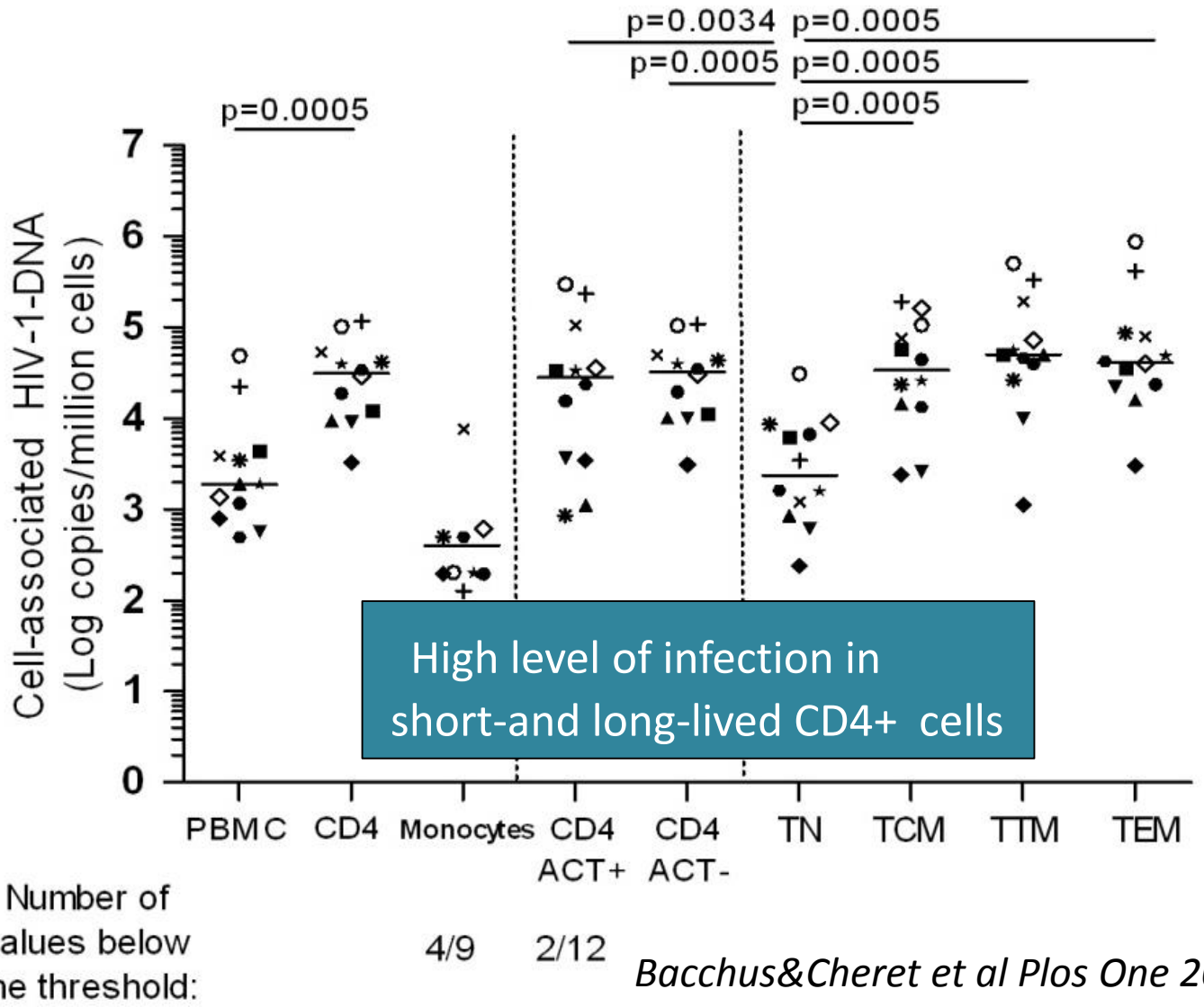



| | Fiebig I (n = 24) | Fiebig II (n = 7) | Fiebig III (n = 36) |
|---|---|---|---|
| **Non détecté** | **92 %** | **29 %** | **53 %** |

*Ananworanich J, CROI 2013, Abs. 47*

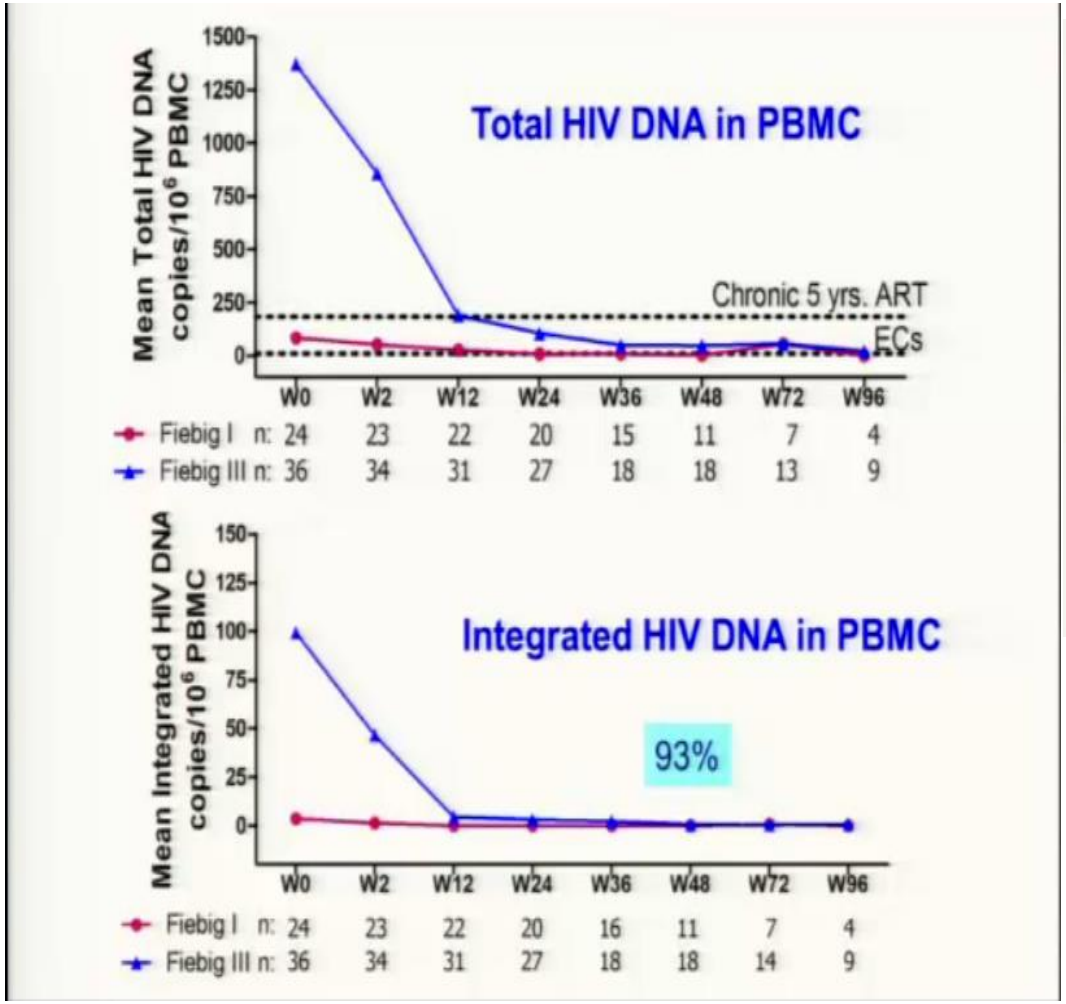
# Early establishement of durable HIV reservoirs OPTIPRIM study in primary infection

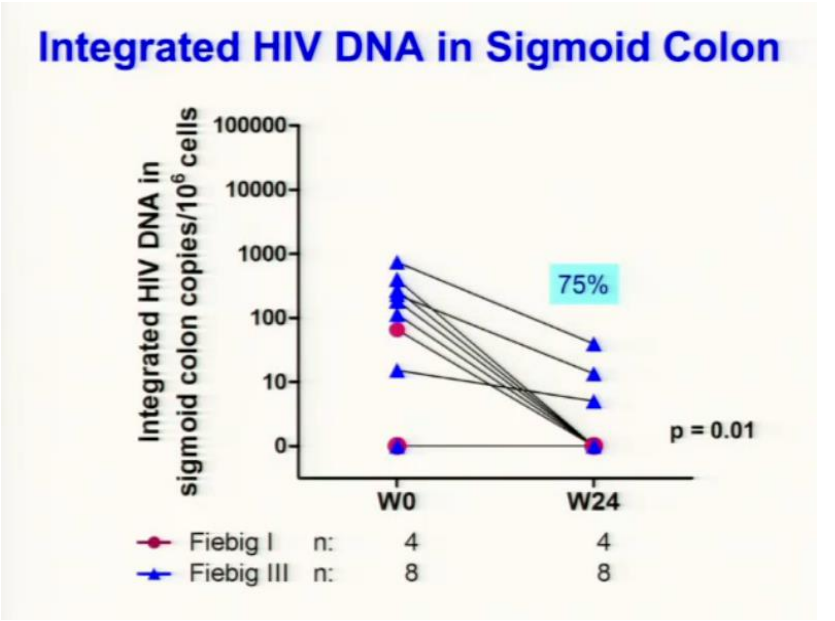
**The Optiprim Study: at Fiebig III (D30) post-infection**



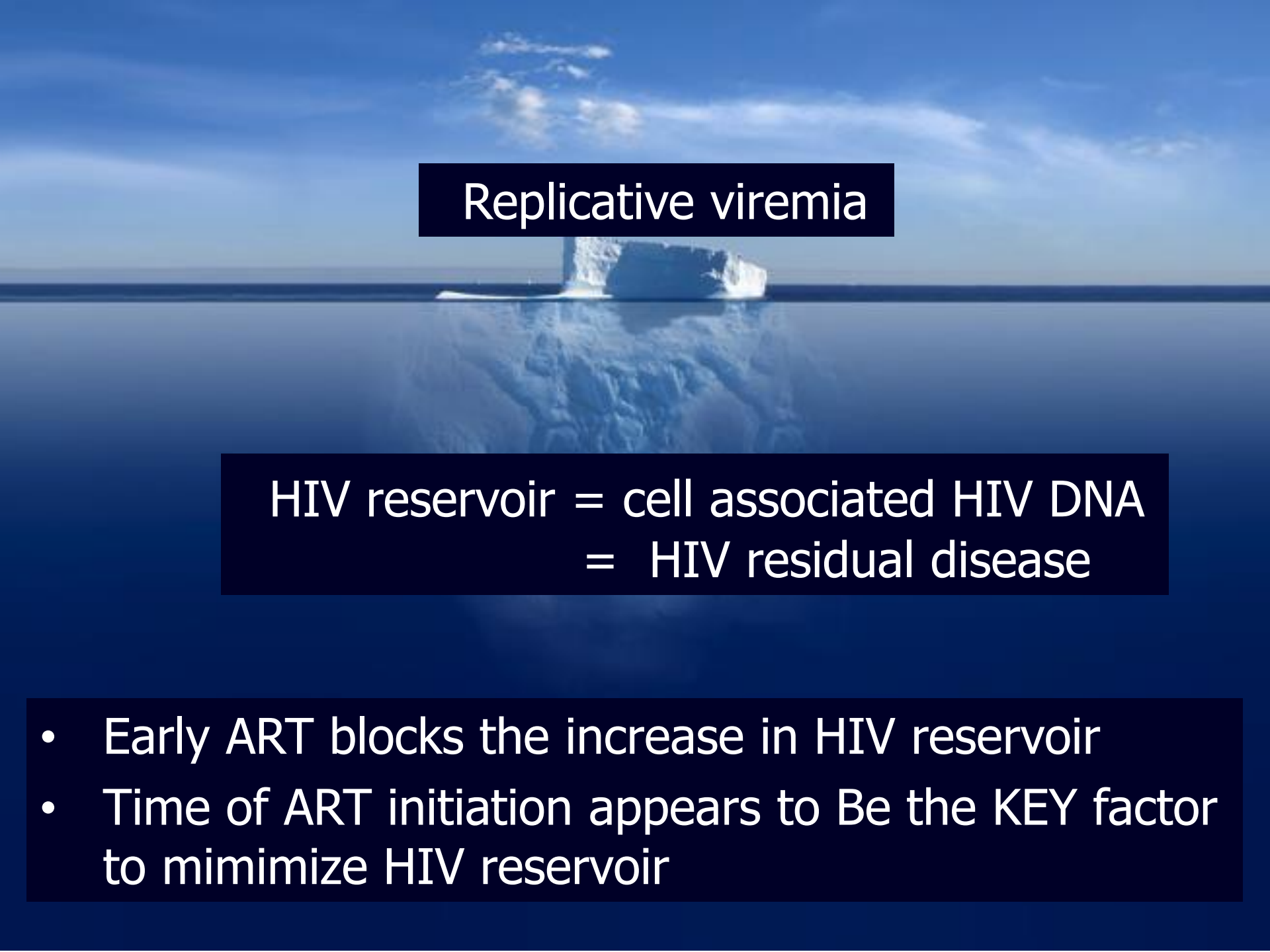

*Bacchus&Cheret et al Plos One 2013*

# Early ART at primary infection massively reduces the size of HIV reservoir



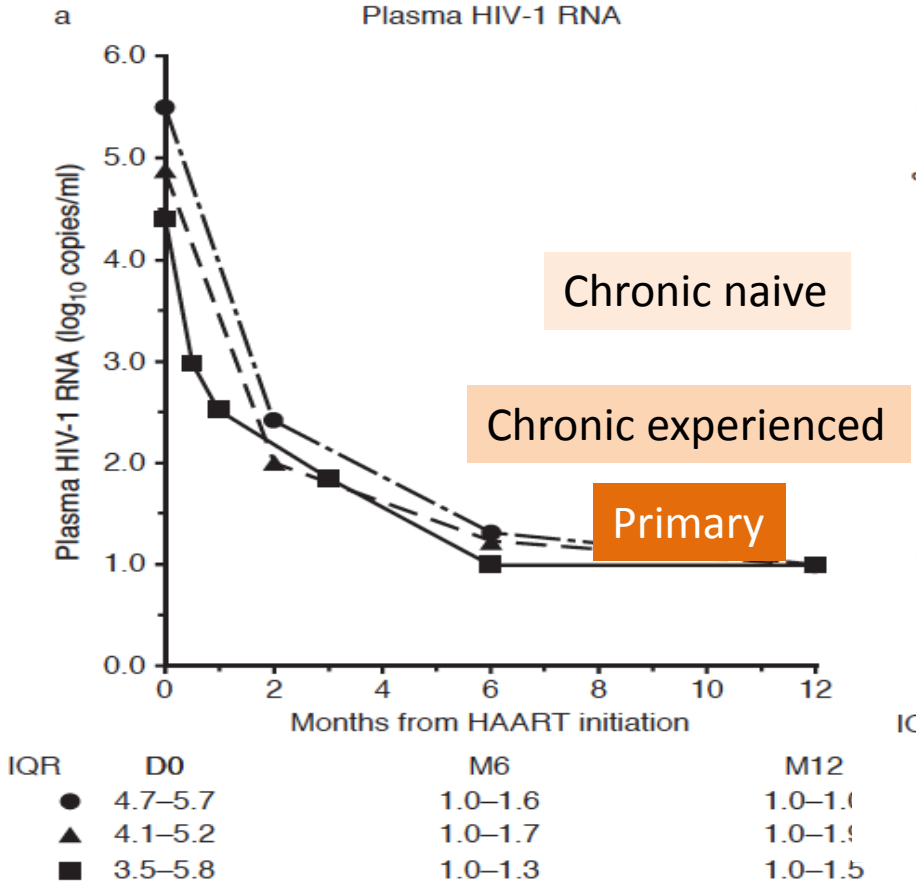



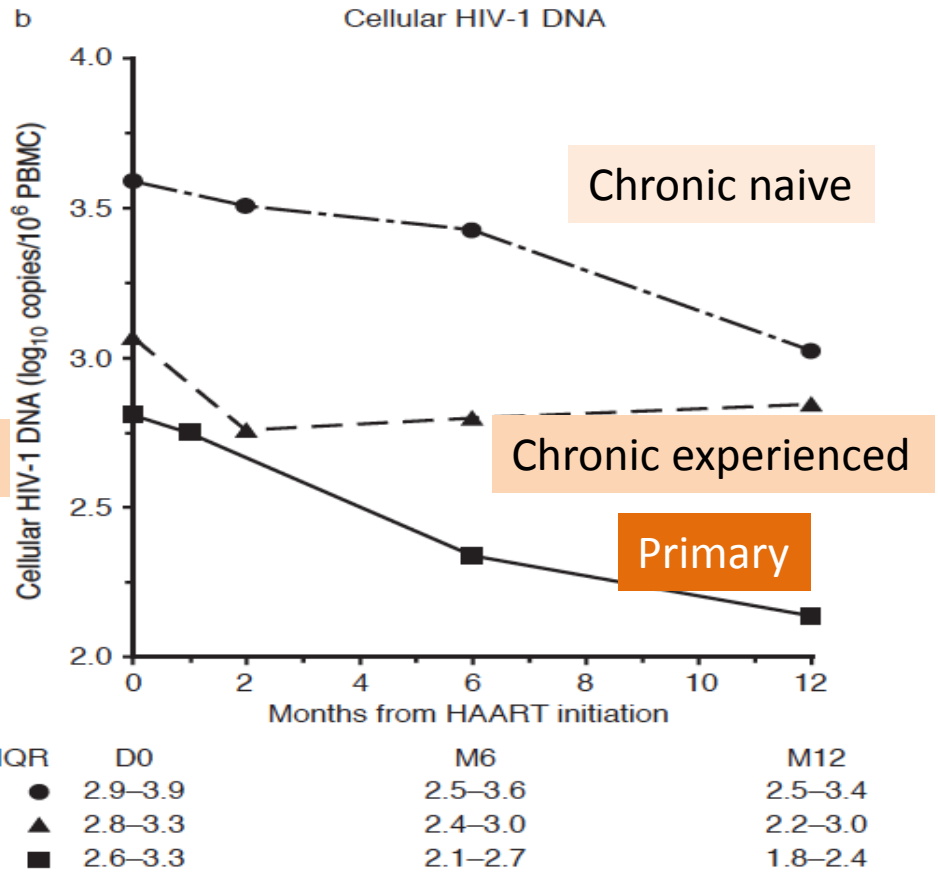

*Ananworanich J, et al. CROI 2013. Abstract 47.*




- Early ART blocks the increase in HIV reservoir
- Time of ART initiation appears to Be the KEY factor to mimimize HIV reservoir

# Evolution of HIV RNA and HIV DNA in patients following ART initiation




*Ngo-Giang-Huong et al. AIDS. 15(6):665-673, April 13, 2001.*

HIV
induced Immune suppression

ART
leads to immune restoration

# Mechanisms of the CD4 lymphopenia

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

## 1- Destruction of CD4+ cells

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

## 2- Defaults of cell regeneration

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

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

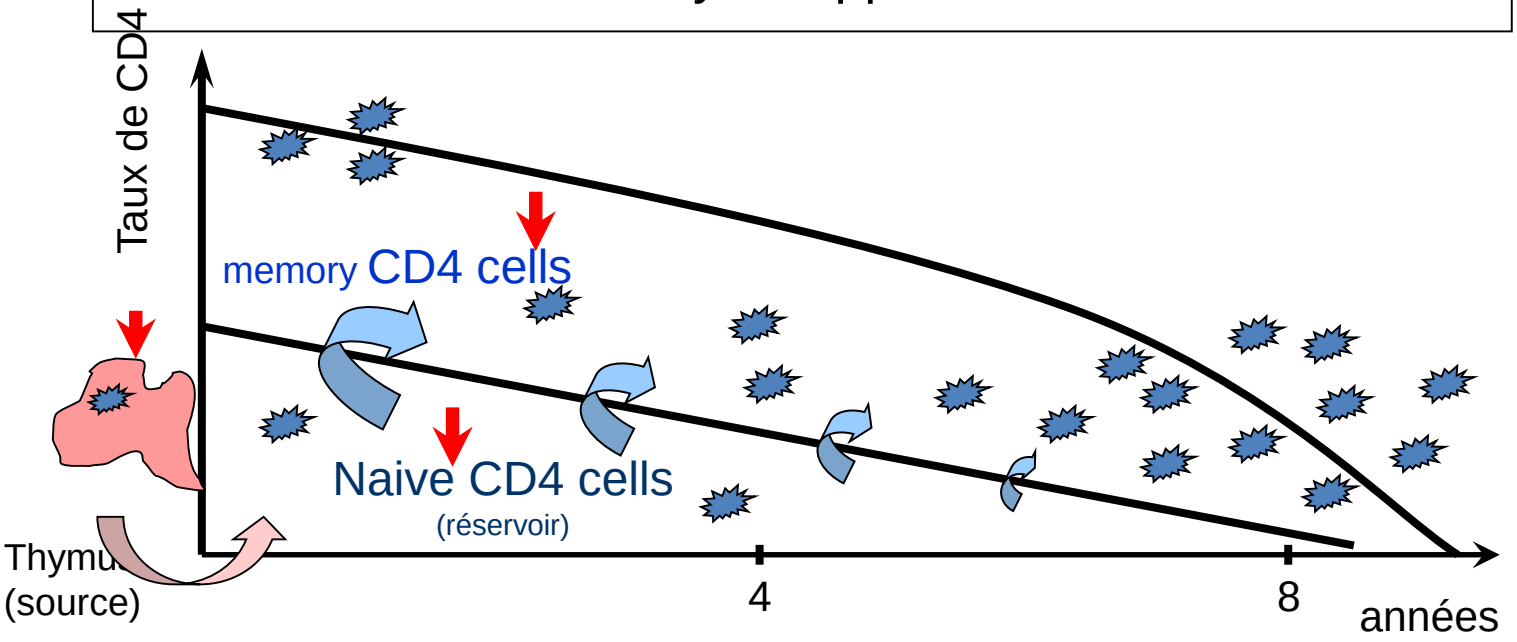
- Rapid loss in naive CD4 cells

  => accelerated conversion towards memory cells

- Infection/Anergy of Memory CD4 T cells

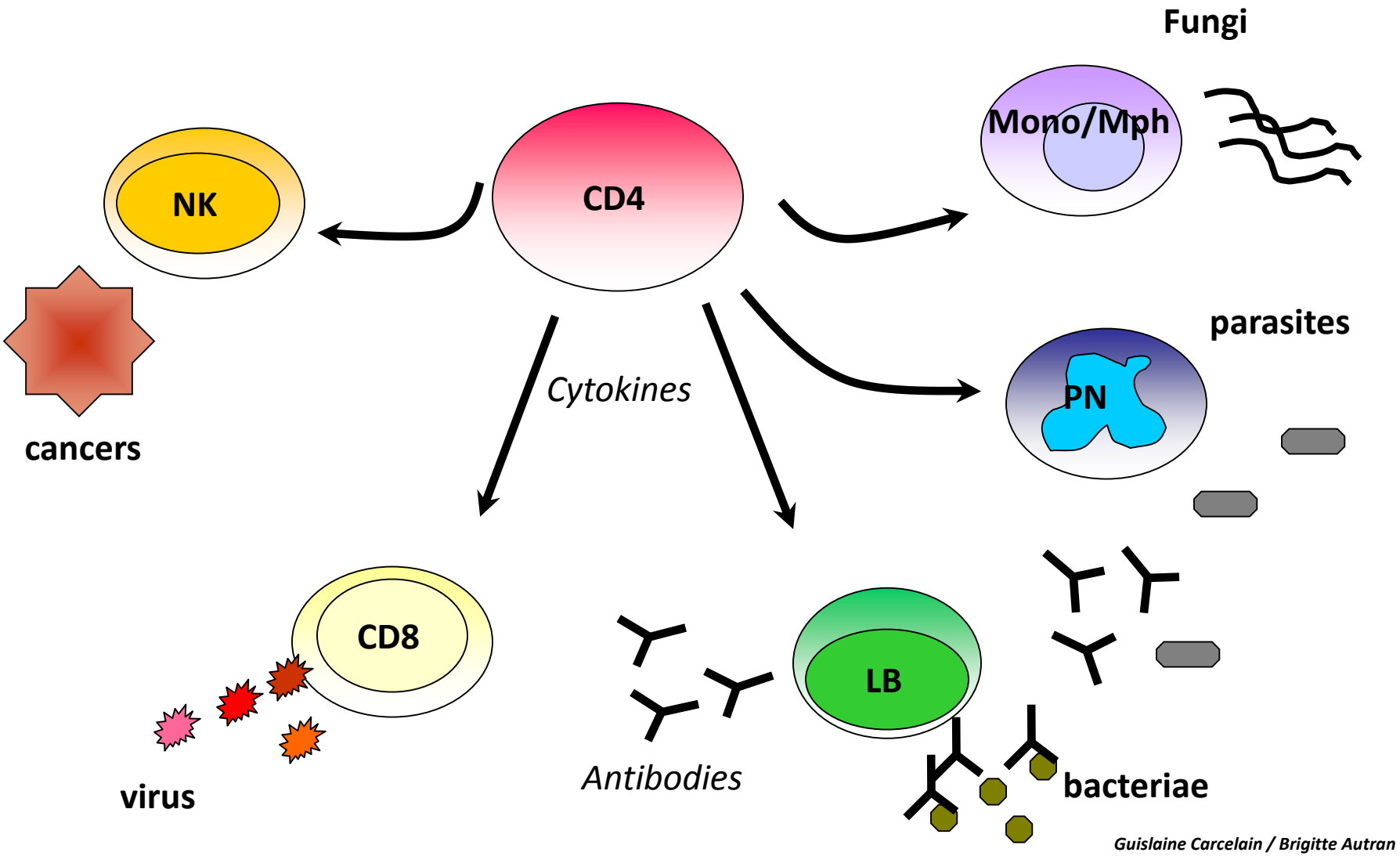
  ⇒ cell destruction

  ⇒ Loss of Memory to Opportunistic infections



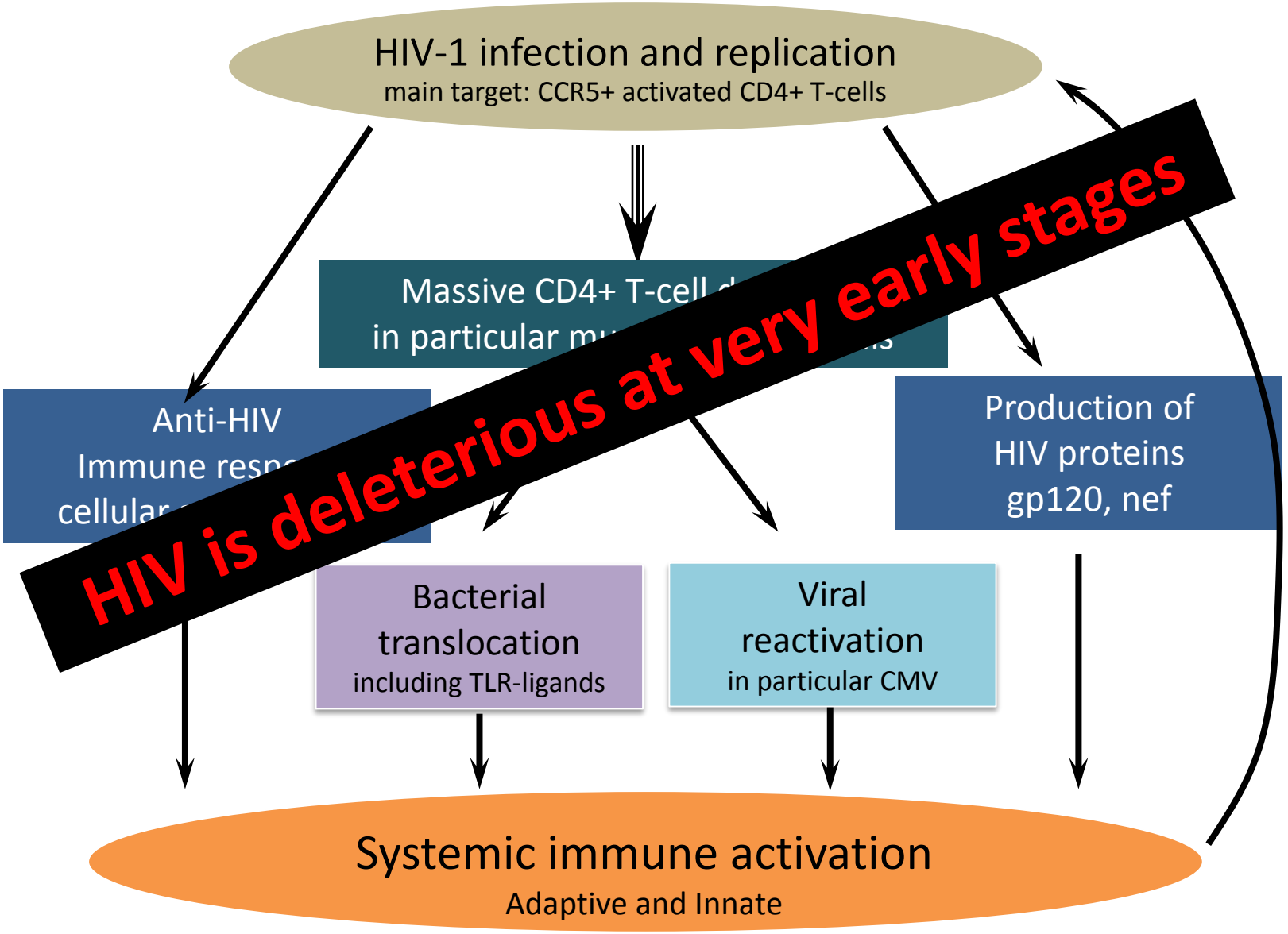

*BAutran*

# Lymphocyte CD4 : the key driver of immune response



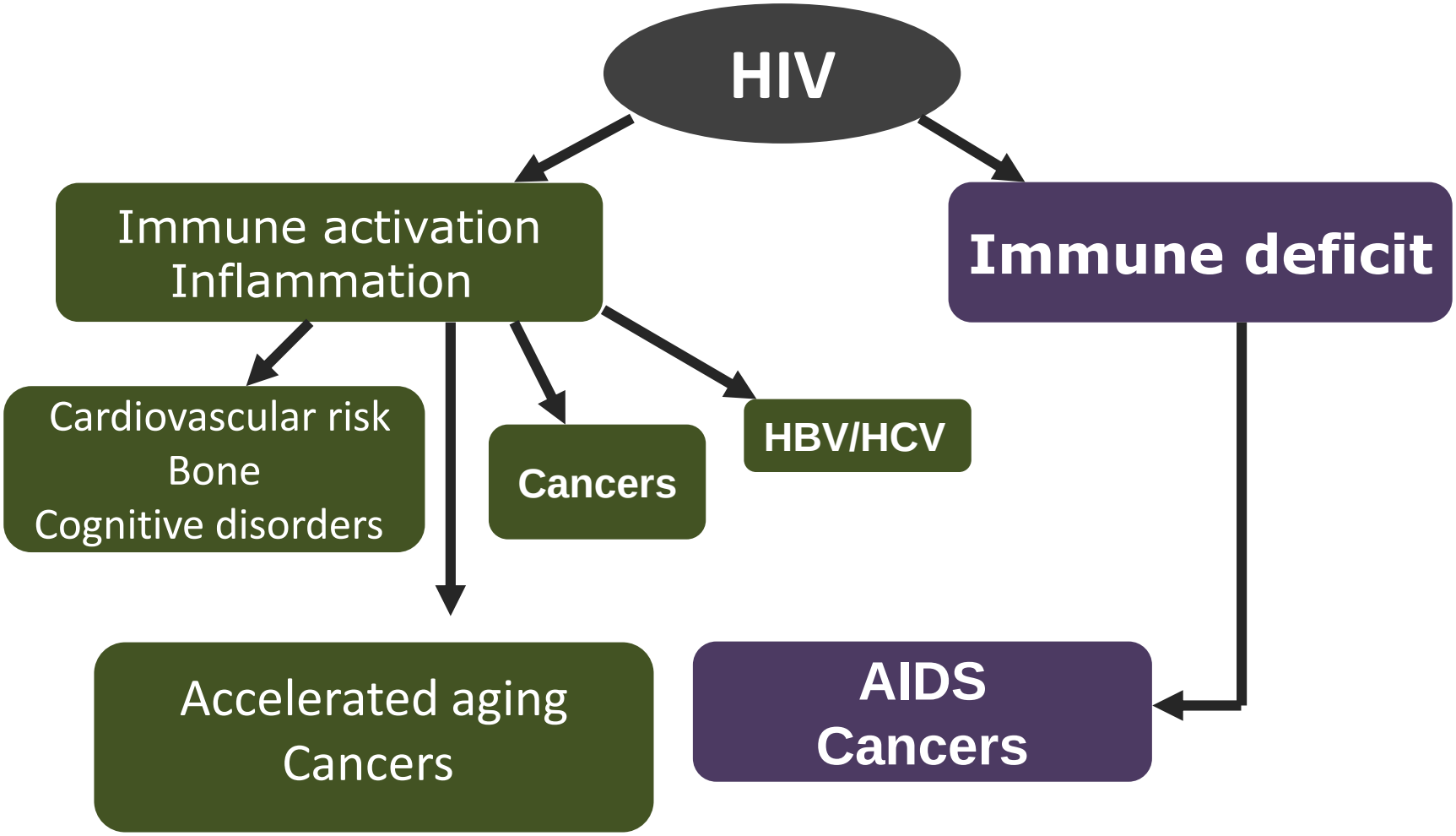

*Guislaine Carcelain / Brigitte Autran*

# Immune activation and HIV replication




*Appay et al, J Pathol 08*

# Pathogenesis of HIV




HIV is deleterious through a slow immune deficit ( AIDS)
and a chronic inflammation/activation ( comomorbidities )


ART
leads to immune restoration

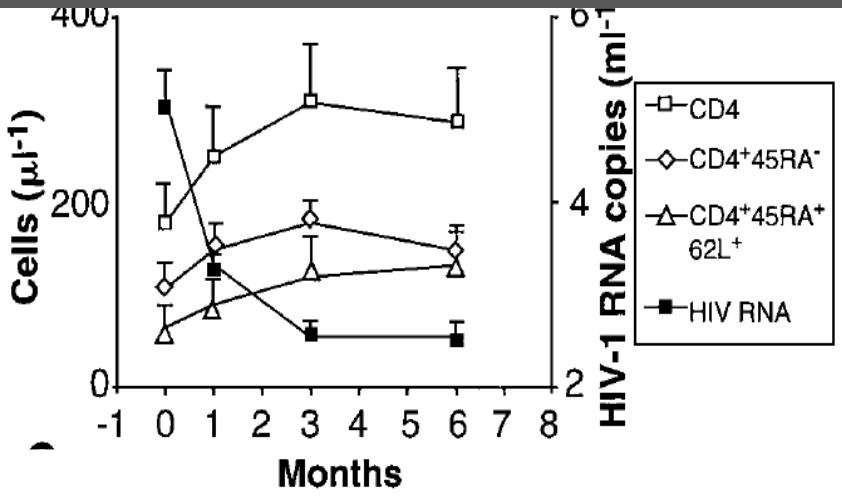
# Immune restoration following ART

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

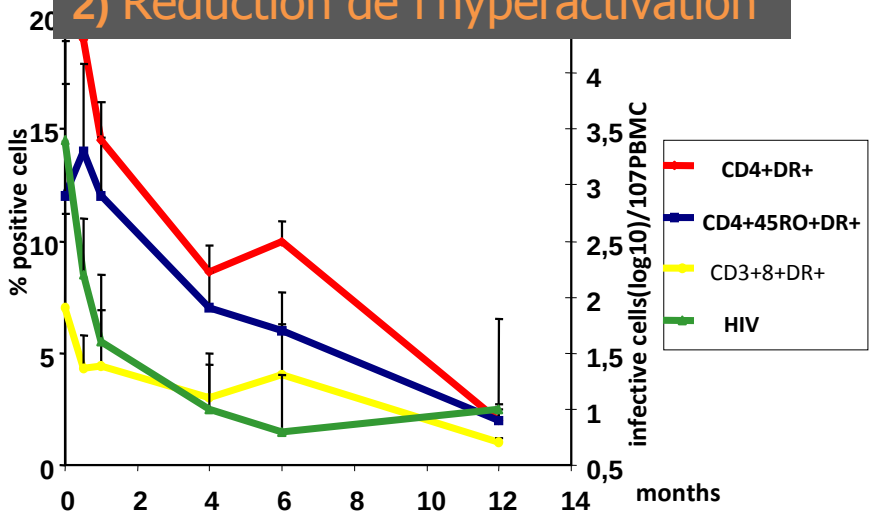
B. Autran,* G. Carcelain, T. S. Li,† C. Blanc,† D. Mathez, R. Tubiana, C. Katlama, P. Debré, J. Leibowitch

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

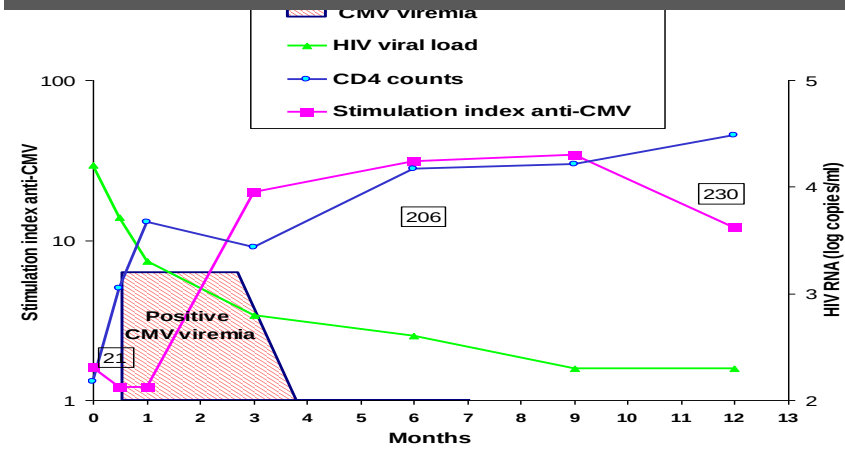
## 1) Restoration of CD4 counts, naive & memory




## 2) Réduction de l'hyperactivation

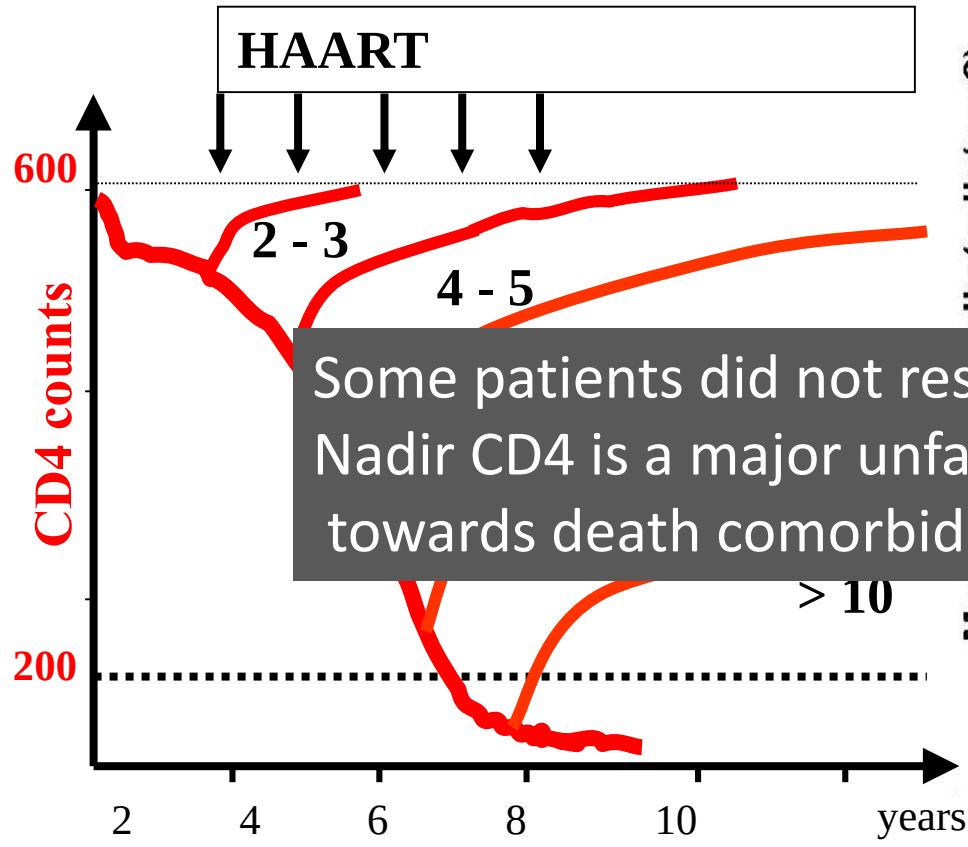



## 3) Restauration fonctionnelle des Ly CD4



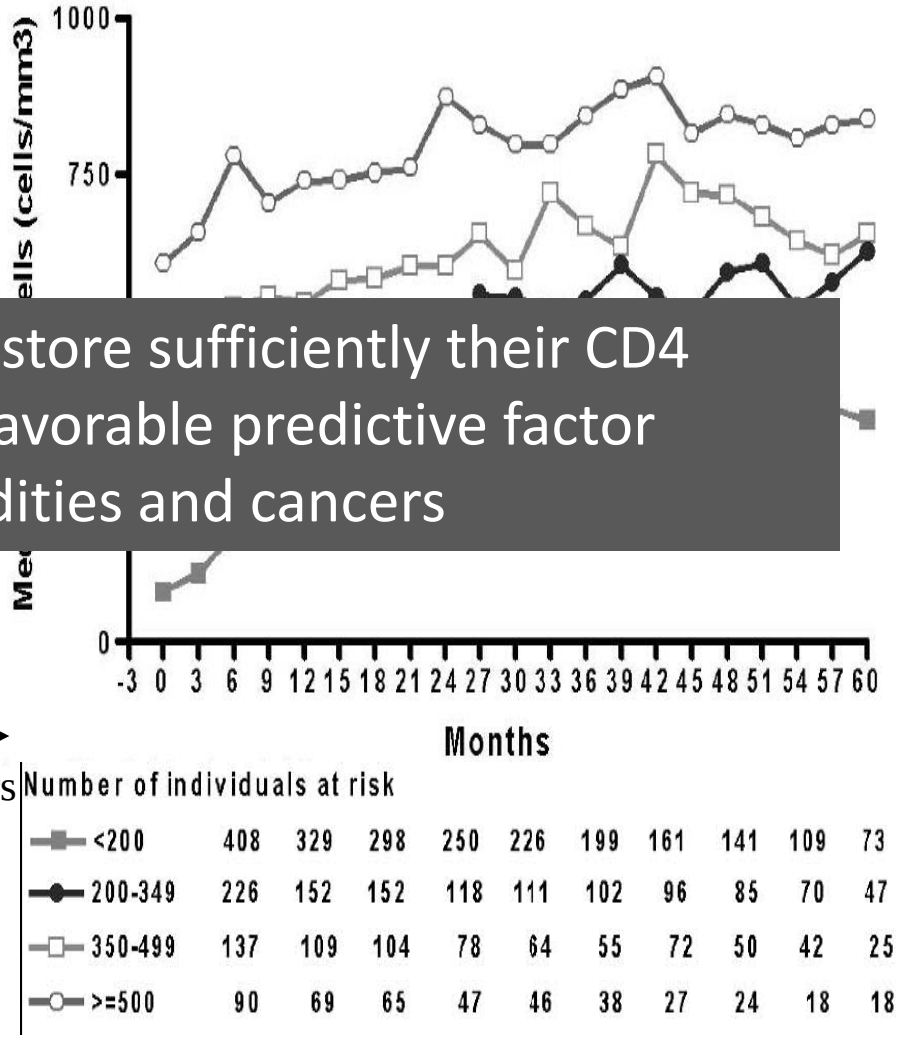
# Long term CD4 cell reconstitution with ART

As Predicted




B Autran et al. 1998

As Observed



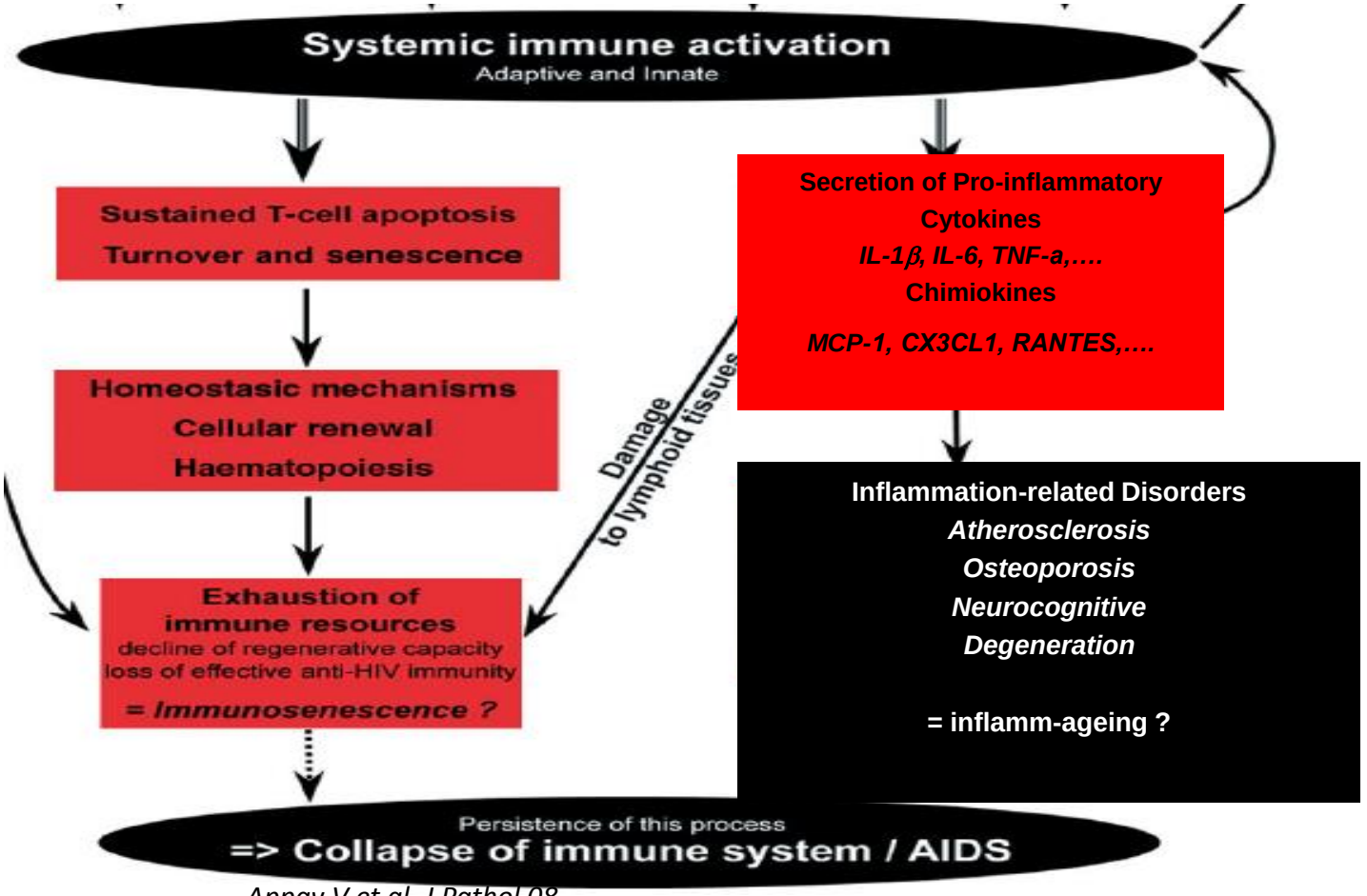

Garcia, J AIDS 2004

Some patients did not restore sufficiently their CD4
Nadir CD4 is a major unfavorable predictive factor
towards death comorbidities and cancers


HIV induced
activation and inflammation

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

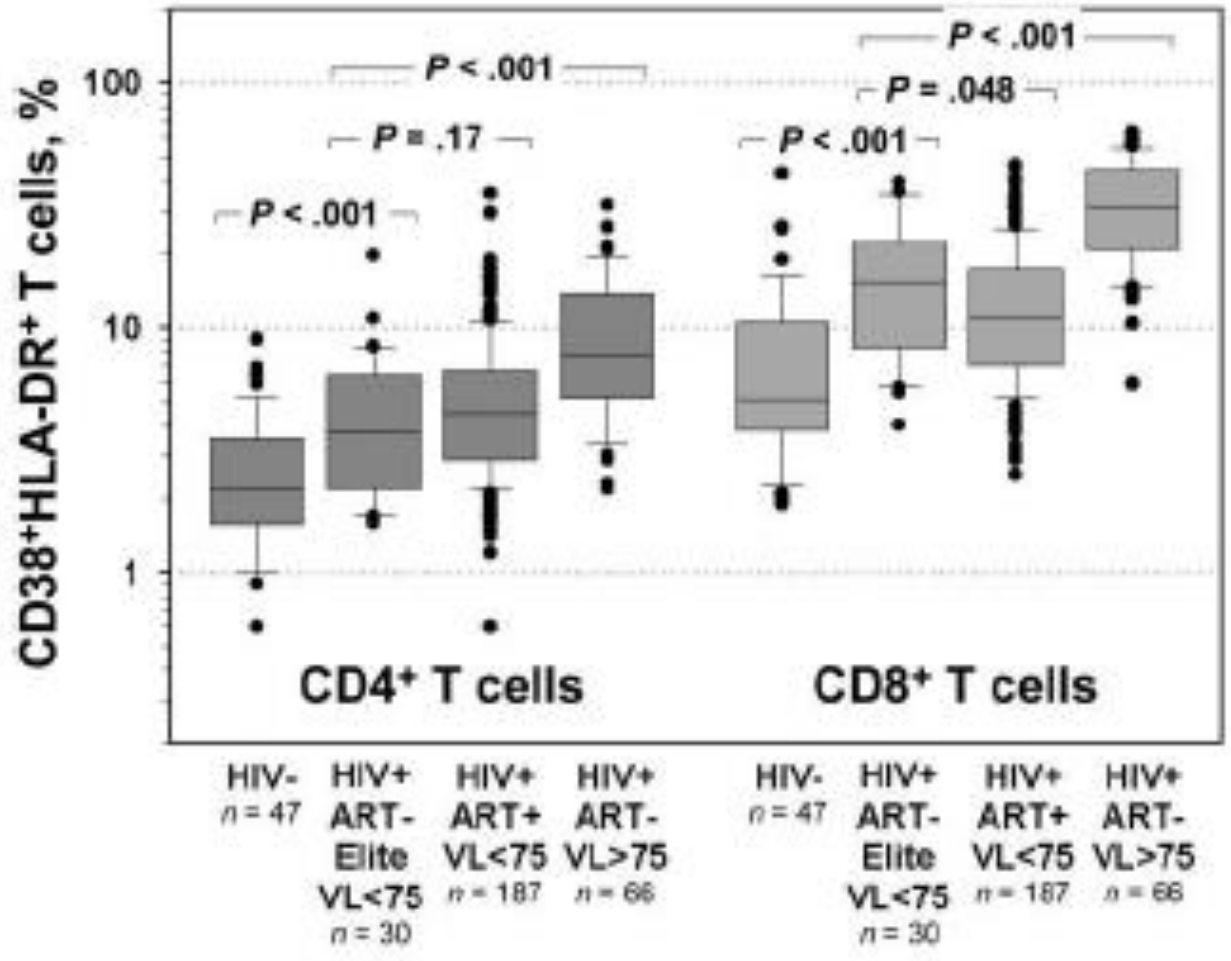
## Induction of Immune defects and Co-morbidities




*Appay V et al, J Pathol 08*

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

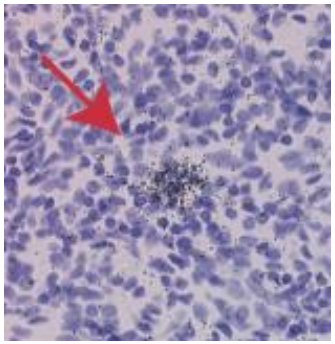
# T-cell activation persists under ART despite apparently optimal viral suppression



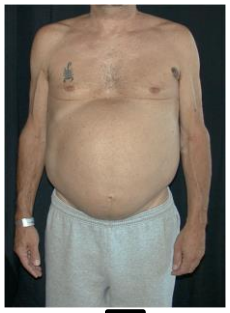

*Hunt, JID 2008*

# Persistence of Inflammation despite viral suppression

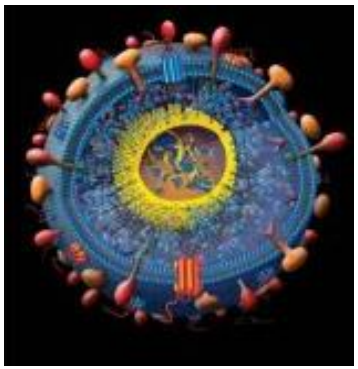
**HIV production**



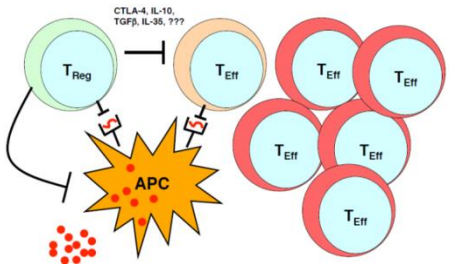
**HIV-associated fat**
**Metabolic syndrome**



**Excess pathogens**
**CMV HBV HCV**

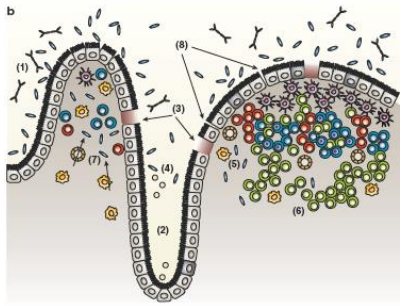


**Loss of regulatory cells**




**Inflammation**
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

**Microbial translocation**




**Co-morbidities**
**Aging**

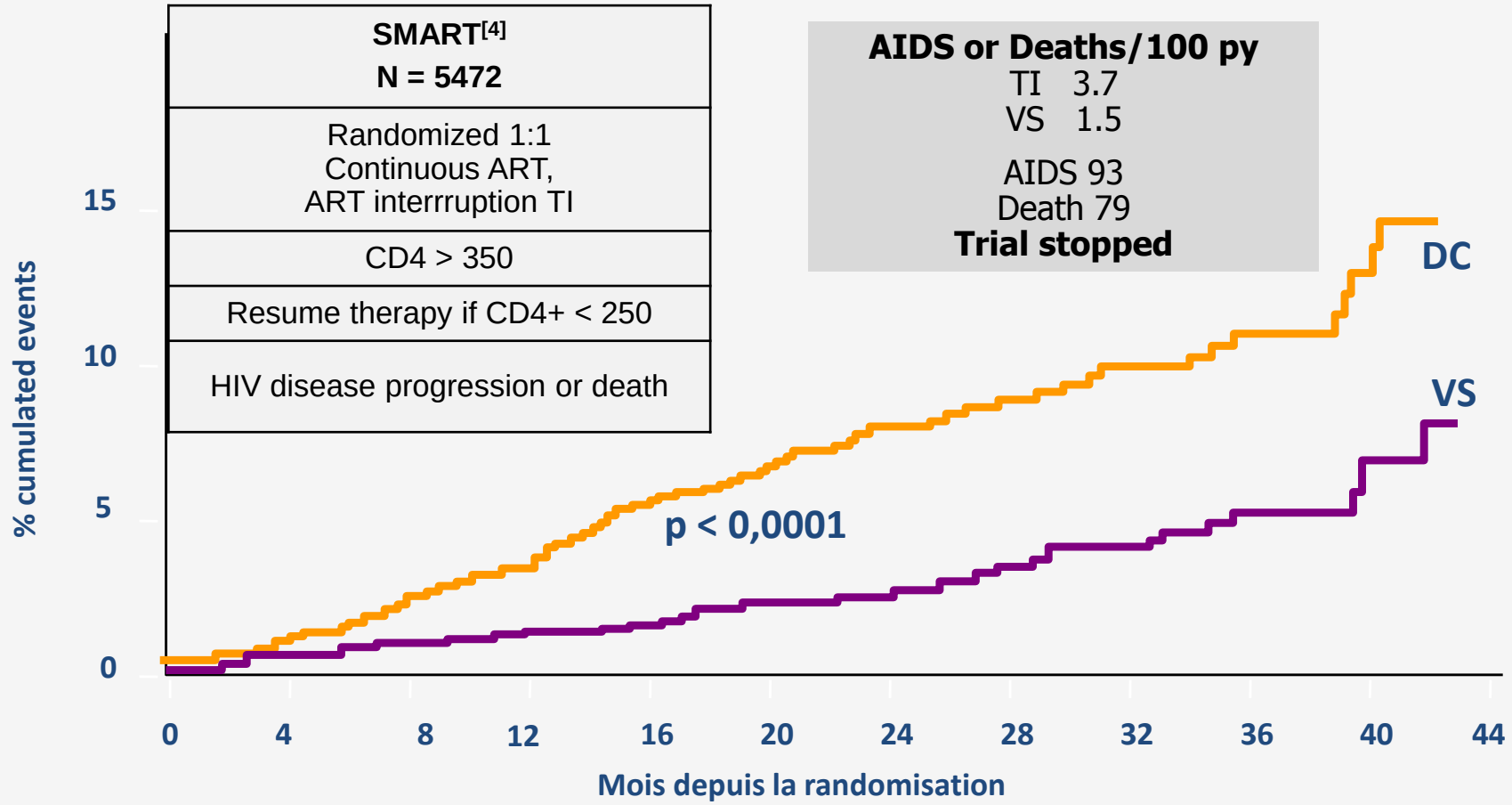
*From S Deeks 2013*


# Inflammation predicts disease in treated HIV infection, as it does in the general population

- Mortality (Kuller, PLoS Med, 2008, Sandler JID 2011, Tien JAIDS 2011)
- Cardiovascular Disease (Baker, CROI 2013)
- Lymphoma (Breen, Cancer Epi Bio Prev, 2010)
- Venous Thromboembolism (Musselwhite, AIDS, 2011)
- Type II Diabetes (Brown, Diabetes Care, 2010)
- Cognitive Dysfunction (Burdo AIDS 2012)
- Frailty (Erlandson, JID 2013)

# 2006 SMART

## Replication of HIV is associated to an excess of morbi/mortality




TI associated with significantly greater disease progression or death, compared with CT: RR: 2.5 (95% CI: 1.8-3.6; *P* < .001)

*El-Sadr W.,NEJM 2006,*

# SMART : Increase morbidity / mortality is associated with imflamation and coagulation markers

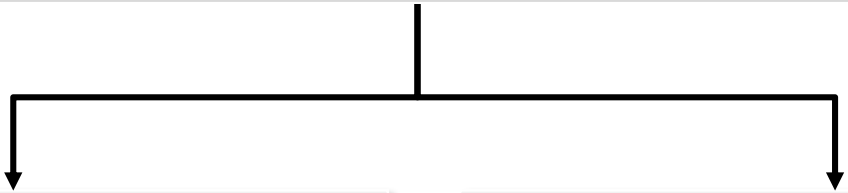
| Marker | Un-adjusted | | Adjusted | |
|---|---|---|---|---|
| | OR ($4^{th}/1^{st}$) | P-Value | OR ($4^{th}/1^{st}$) | P-Value |
| Hs-CRP | 2.0 | 0.05 | 2.8 | 0.03 |
| Amyloid A | 2.2 | 0.07 | 2.6 | 0.09 |
| Amyloid P | 0.7 | 0.39 | 1.1 | 0.84 |
| **IL-6** | **8.3** | **<0.0001** | **11.8** | **<0.0001** |
| **D-Dimer** | **12.4** | **<0.0001** | **26.5** | **<0.0001** |
| F1.2 | 1.0 | 0.92 | 1.2 | 0.66 |

*Adjusted for age, race, ART, VL, BMI, Cholesterol, Smoking, Hepatitis, Statins, BP med's

Kuller LH, et al. PLoS Med. 2008;5:e203.doi;10.1371/journal.pmed.0050203

# START: when to start ART ?

HIV-infected individuals who are ART-naïve with CD4>500 cells/mm$^3$



## Immediate ART Group

Initiate ART immediately following randomization

**N=2,326**

## Deferred ART Group

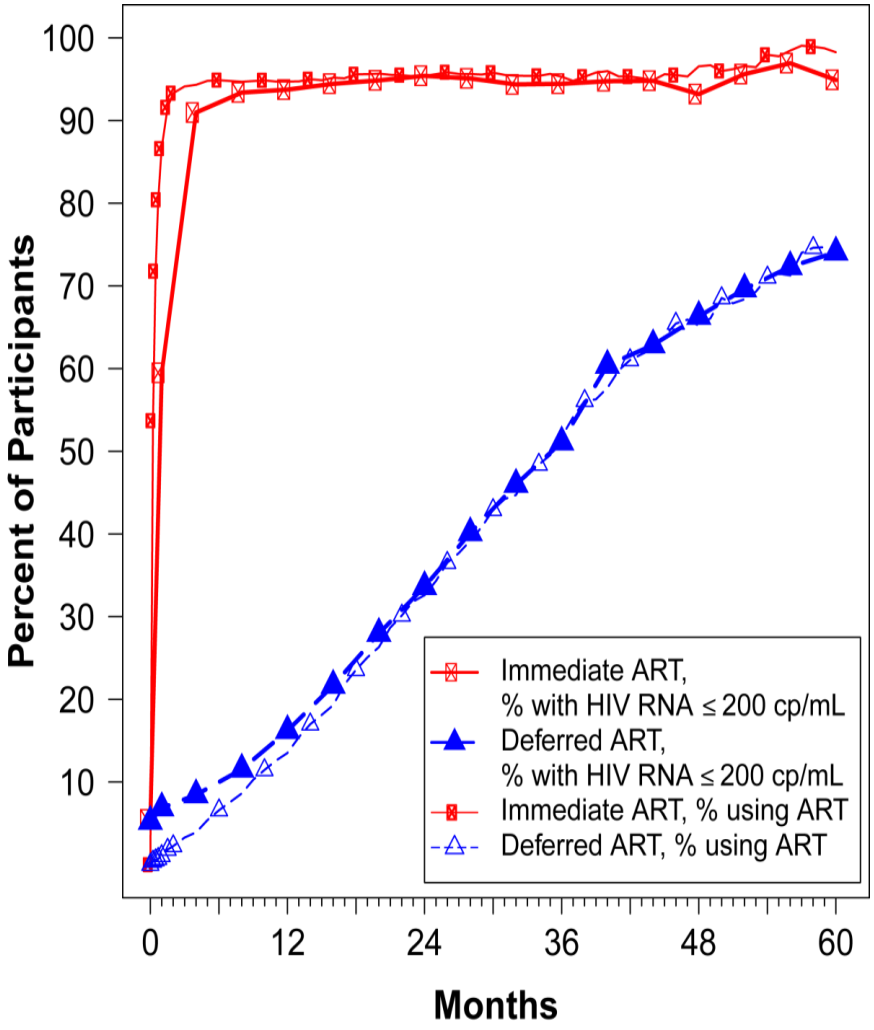
Defer ART until the CD4+ count declines to <350 cells/mm$^3$ or AIDS develops

**N=2,359**

**Primary composite endpoint, target = 213**

- Serious AIDS or death from AIDS
- Serious Non-AIDS Events and death not attributable to AIDS CVD, ESRD, decompensated liver disease, & non-AIDS defining cancers

# START Proportion of patients on ART with with HIV-RNA ≤200 copies/mL




| | % of Follow-up on ART |
|---|---|
| Immediate | 94 |
| Deferred | 28 |

**Deferred Arm:**
**Median time to ART 3 years** (IQR 1.6–4.8) (projected 4 years)

# START Types of Serious Events

| AIDS events | Imm. ART | Def. ART |
|---|---|---|
| TB, pulm or extrapulm.* | 6 | 20 |
| Lymphoma, HL or NHL | 3 | 10 |
| Kaposi's sarcoma | 1 | 11 |
| PCP | 1 | 5 |
| Herpes zoster, diss. | 0 | 3 |
| Other** | 3 | 1 |
| Any Serious AIDS | 14 | 50 |

| Non-AIDS events | Imm. ART | Def. ART |
|---|---|---|
| Cancer, non-AIDS* | 9 | 18 |
| Cardiovascular disease* | 12 | 14 |
| Liver or renal disease | 1 | 2 |
| Death, other | 7 | 13 |
| Any Serious Non-AIDS | 29 | 47 |

* Participants from Africa: 16/26 (62%) of TB cases

** Cervical carcinoma, extra-pulm. cryptococcosis, CMV, recurrent bacterial pneumonia

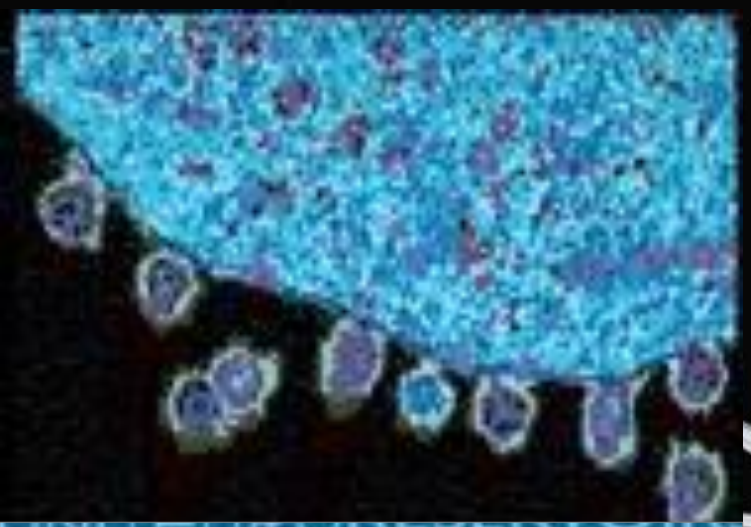
# Even Moderate Immune deficit increases risk of non AIDS related cancers

| | Hodgkin<br>RR (95% CI) | Lung<br>RR (95% CI) | Liver<br>RR (95% CI) |
|---|---|---|---|
| Last CD4 | | | |
| >500 | 1,0 | 1,0 | 1,0 |
| 350-500 | 1,2 (0,7-2,2) | 2,2 (1,3-3,6) | 2,0 (0,9-4,5) |
| 200-350 | 2,2 (1,3-3,8) | 3,4 (2,1-5,5) | 4,1 (2,0-8,2) |
| 100-200 | 4,8 (2,8-8,3) | 4,8 (2,8-8,0) | 7,3 (3,5-15,3) |
| 50 -100 | 7,7 (3,9-15,2) | 4,9 (2,3-10,2) | 6,6 (2,4-17,6) |
| <50 | 5,4 (2,4-12,1) | 8,5 (4,3-16,7) | 7,6 (2,7-20,8) |

*Guiguet et al Lancet Oncology 2012*

# Early control of HIV replication is the best way to preserve future

- Nadir of CD4 is a predictor for ART failure - death , comorbidities , cancer .
- High CD4 > 500/mm3 and normal CD4/CD8 ratio is the optimal way to preserve clinical future
- ART at primary infection :
  - Suppresses immune activation
  - Reservoir size limitation
- Optimize retention in care

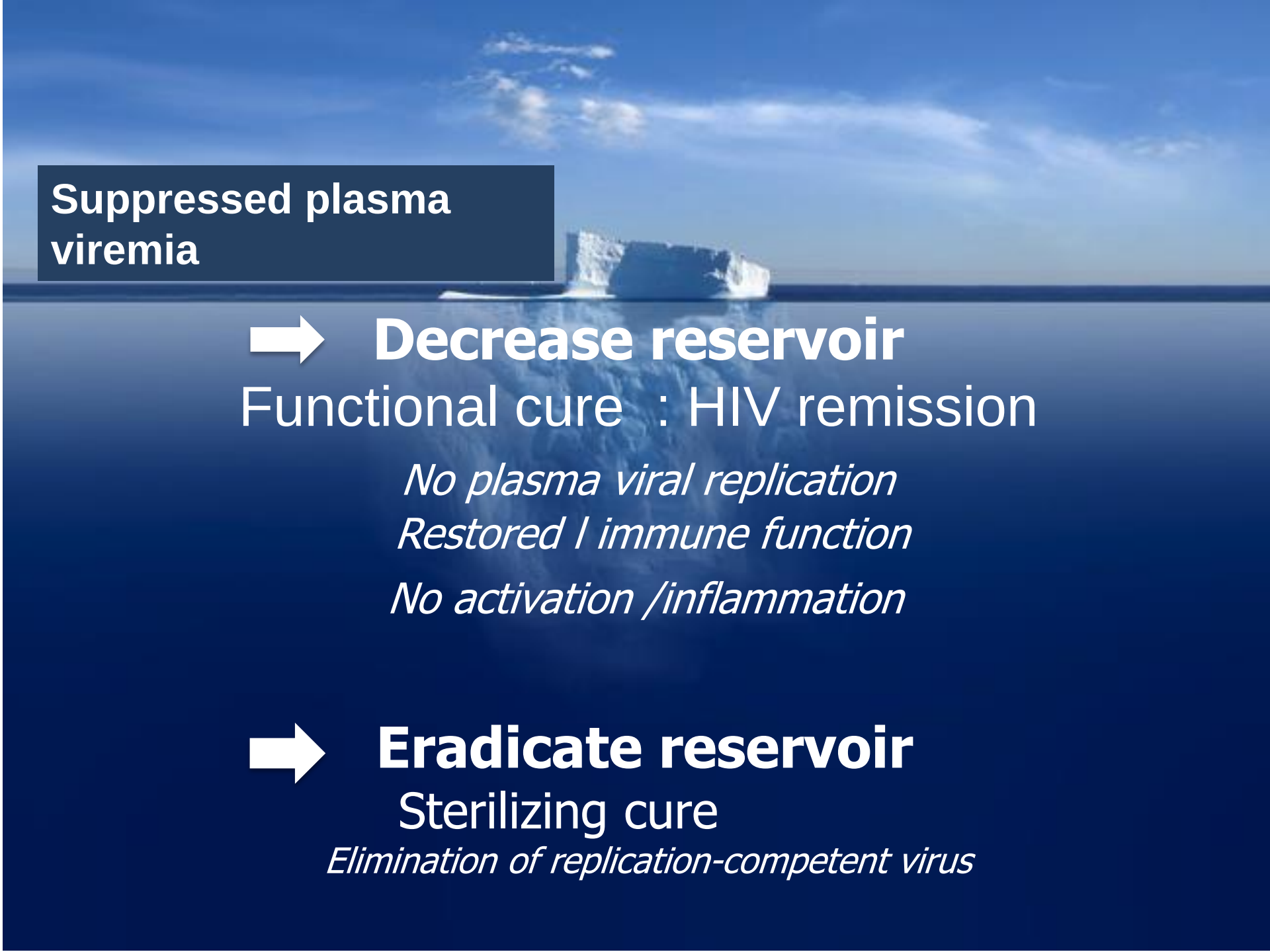


# Is HIV cure achievable ?

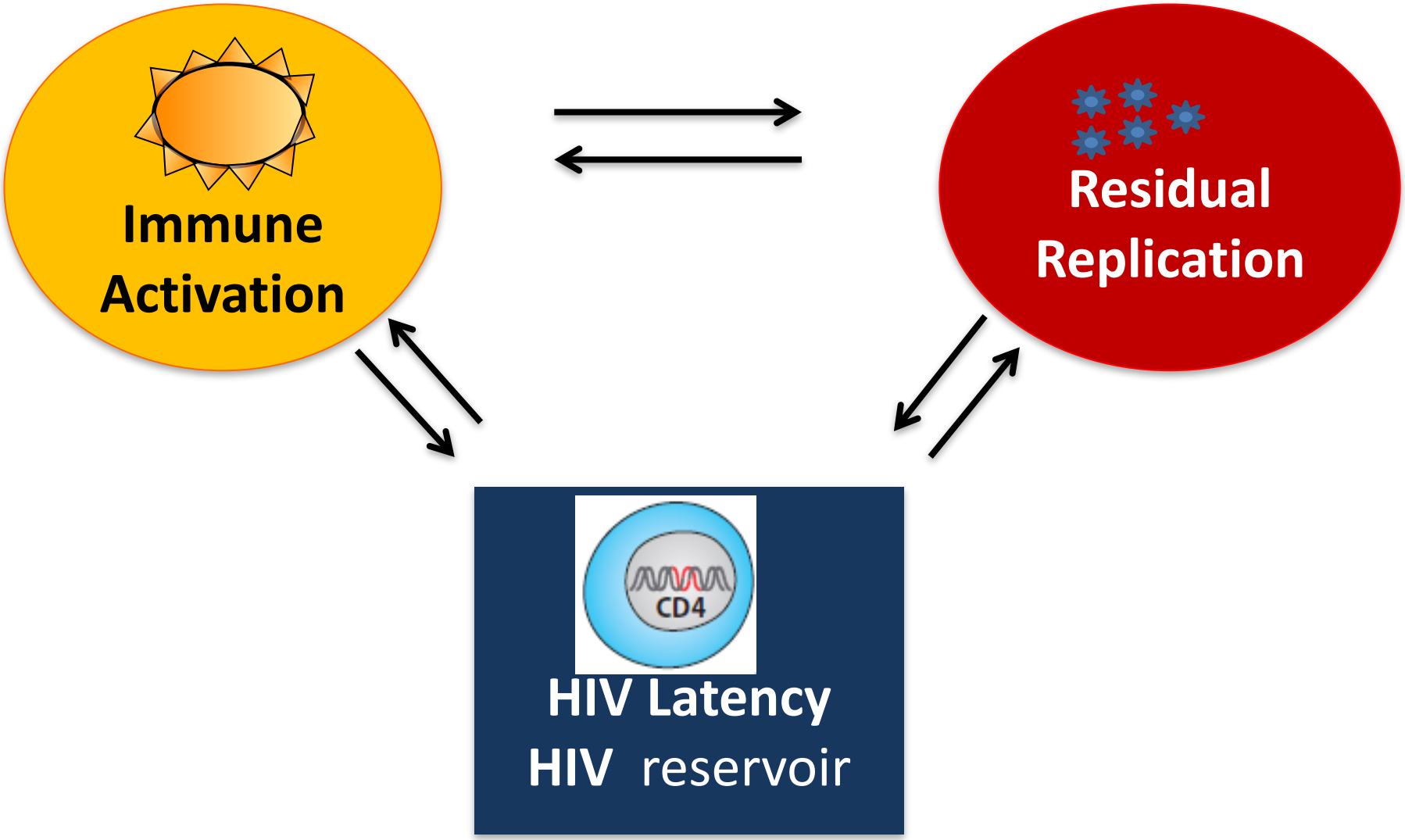
towards an HIV cure

people focused science driven

Abstract Book


Suppressed plasma viremia
Decrease reservoir
Functional cure : HIV remission
No plasma viral replication
Restored l immune function
No activation /inflammation
Eradicate reservoir
Sterilizing cure
Elimination of replication-competent virus

# Obstacles to Eradication of the HIV Reservoirs



# Is HIV cure /remission achievable

- Spontaneous control of HIV replication

**French Hospital Data Base (FHDH):** *Grabar.. D Costagliola, AIDS 2009*

On 46,880 HIV+ patients:

- LTNP = 0.4%
- Elite LTNP = 0.05%
- HIV Controlers = 0.22%
- Elite Controllers = 0.15%

- **Elite Controllers and LTNPs**

  Infected for 10-30 years, No ART

  **Genetic Background**;

  Strong CD4 and CD8 response/HIV

  Preserved CD4 TCM cells

  Low immune activation

- **Post-Treatment Controllers** (Visconti)

  Control HIV without ARV for 3.5 y.

  ARV for 5 years started at PHI

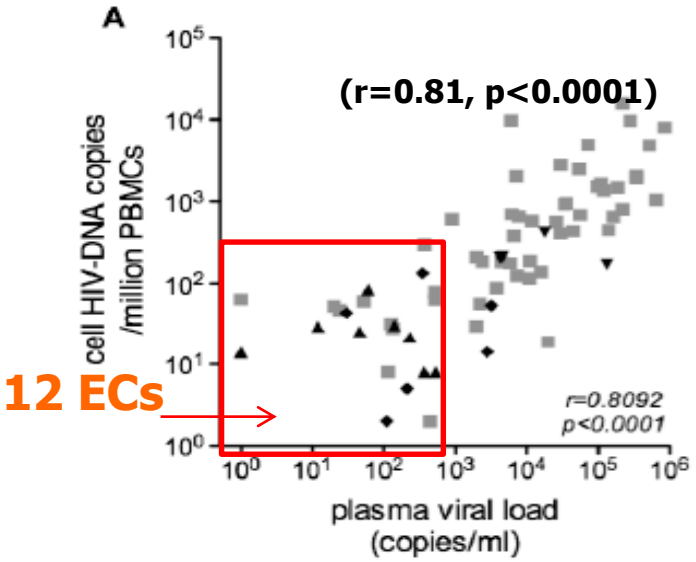
  No genetic background

  Low Immune activation

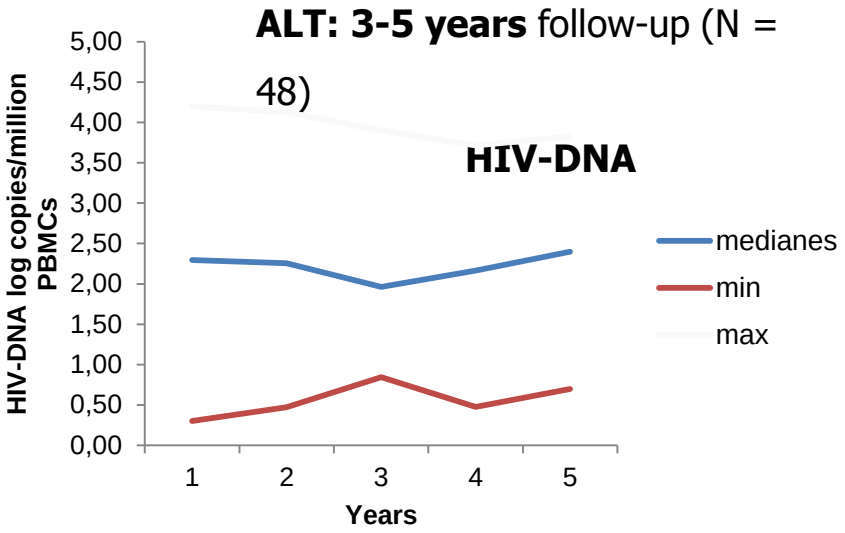
# Elite Controlers as a model of Functional Cure
## ALT Cohort (ANRS CO-15)

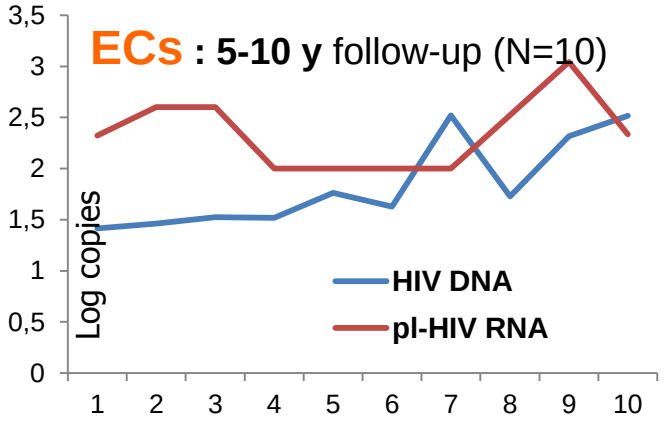
**Baseline**

| BL Characteristics | Total (n=71) |
|---|---|
| **CD4** count (/mm$^3$) | **639** (489—751) |
| **HIV-DNA** (log cp10$^6$ PBMCs) | **2.29** (1.53—2.89) |
| **plasma HIV-RNA** (log cp/ml) | **3.78** (2.57—4.56) |




**Follow-up**



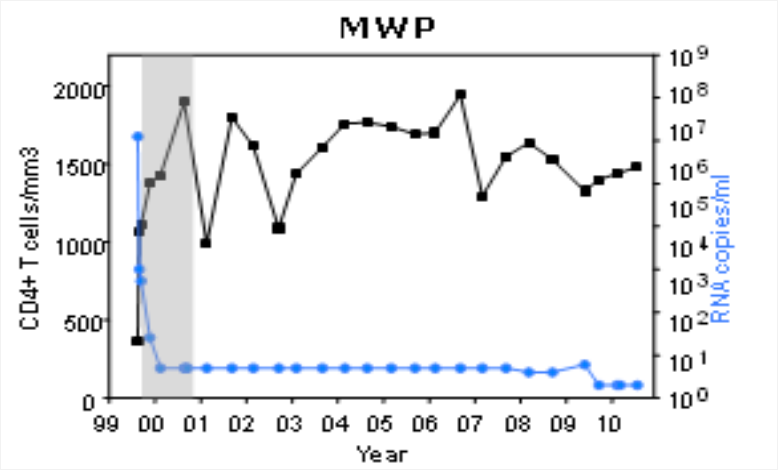

**Correlation between HIV reservoirs and Virus production**

# Post Treatment Controllers(PTC) Visconti Patients

- **14 patients** treated in primary infection
  ART duration (med ) : 35 mois
  Duration off ART : 5 years
- **CD4 count**
  - pre ART : 489 ( 371-955)
  - at stop : 931 (354-1639
  - last value : 837( 388-1598
- **HIV RNA**
  - pre ART : 5.0 log ( 3 - 7.3)
  - last value : 1.7 log ( 1.7 -2.4)

- **After > 6 years without ART**
  Median RNA = <20 copies/mL
  Median DNA = 83 copies/M PBMC

- No protective HLA profile
- **Low DNA**
- **Low CD8 response**
- Reservoir less localized in central memory cells




*Saez Cirion et al Plos Path 2013*

# SALTO ANRS 116
# Treatment interruption in patients treated at CD4 > 350 et VL < 50 000 cp/ml

## 95 patients

Age 40 years (IQR: 36–45)

**Pre-cART values**

- CD4 : **454** /mL (392–576)
- VL : **4.3** $\log_{10}$ cp/ml (3.9 – 4.5)
- CD4 nadir : **382** /mL (340–492)

**Duration of cART : 5.3 years** (4.0–6.0)-

**Baseline values**

- CD4 count : **813** cells/mL (695–988),
- DNA : **206** copies/$10^6$ PBMCs
- (IQR : 53–556)

## 12 months post TI

7 /95 patients still had a VL<400 cp/ml

- KP: 7.5%, CI: 3.7-14.6)

4 kept a VL<400 copies/mL up to 36 months;

- All had CD4 cell >500/$mm^3$

**HIV DNA was the only significant predictor** of maintaining VL < 400 cp/ml med value : < 10 vs 233 cp / $10^6$PBMCs p < 0.001

Piketty et al, J Med Virol, 2010;82:1020-3 Assoumou et al, CROI 2013

# Immune Characteristics in Models of Functional Cure

| | Frequency | Genetic Traits | Reservoir and distribution | HIV specific Immunity | Immune activation | Transcriptional profiling |
|---|---|---|---|---|---|---|
| Elite Controlers | 0.15-0.4% | YES: MHC | Low<br><br>Low in TCM | Strong CD4, CD8 and Abs | Low | Strong TCR<br>Low IFN-alpha signatures |
| Post-Treatment Controlers | 12-15% | ?<br>No MHC | Low<br><br>Low in TCM | ? | Low | ? |

Lessons for therapeutic strategies towards a functional Cure of HIV ?

Early ART might control the HIV reservoirs in Visconti PTC

as efficiently as the « genetically-driven immune control of ECs

# Who controls viral replication without ART ?

- Elite controllers
- Bone marrow transplant
- Patients - baby or adults treated at primary infection
- Few chronic early treated patients

All these patients are characterized by

- Early ART or no ART
- low HIV DNA
- high CD4, High CD4/CD8


# ULTRASTOP: a pilot study

- Can HIV remission off ARTwith HIV RNA < 400 cp/ML be achieved in chronic patients with early start of ART :
  - Total DNA < 100 cp/$10^6$ PBMC
  - CD4 > 500/ $mm^3$
  - CD4/CD8 > 0.9
  - Jamais de sida
  - CV < 50 cp/mL for at least 2 years

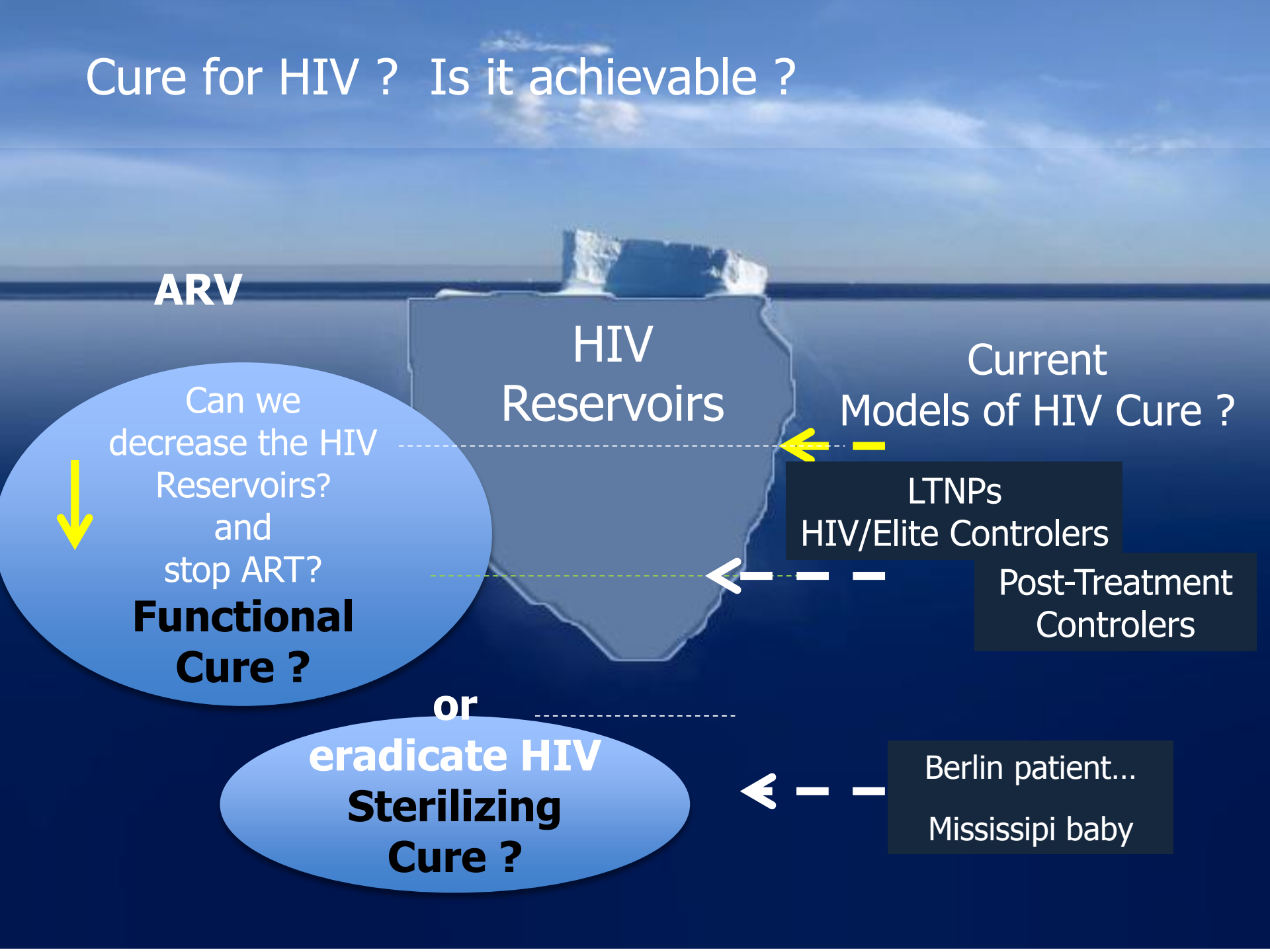
  - A pilot study with 3 cohorts of 5 patients successively enrolled if at least one success in the previous cohort


# ULTRASTOP: a pilot study

- Can HIV remission off ARTwith HIV RNA < 400 cp/ML be achieved in chronic patients with early start of ART :
  - CV < 50 cp/mL depuis 2 ans

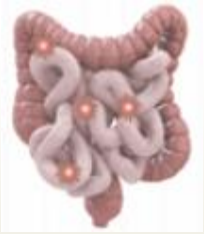
10 patients in 2 cohorts
DNA ultralow < 100 cp
CD4 > 500
5 years of viral suppression
One patient in remission ( 16 months)
9/10 rebounded within 4 weeks

- A pilot study with 3 cohorts of 5 patients successively enrolled if at least one success in the previous cohort

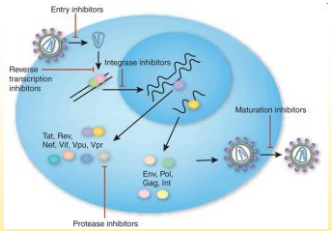

Cure for HIV ? Is it achievable ?
ARV
HIV Reservoirs
Current Models of HIV Cure ?
Can we decrease the HIV Reservoirs? and stop ART?
Functional Cure ?
LTNPs
HIV/Elite Controlers
Post-Treatment Controlers
or
eradicate HIV
Sterilizing Cure ?
Berlin patient…
Mississipi baby

# Potential strategies to reduce HIV reservoirs

Maraviroc
Anti-inflammatory drugs
- Statins
- OH-Chlorochin



Massive CD4 T-cell depletion
Bacterial translocation




ARV Intervention
- Intensification
- Nevirapine


Cellular Immunity
Immune Intervention
- Anti-HIV vaccine
- IL7

Systemic Inflammation

Pre-Probiotics

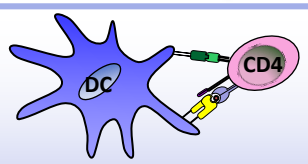
Viral Co-Infections

Antiviral drugs

Immune Activation

Residual Replication

Gene therapy



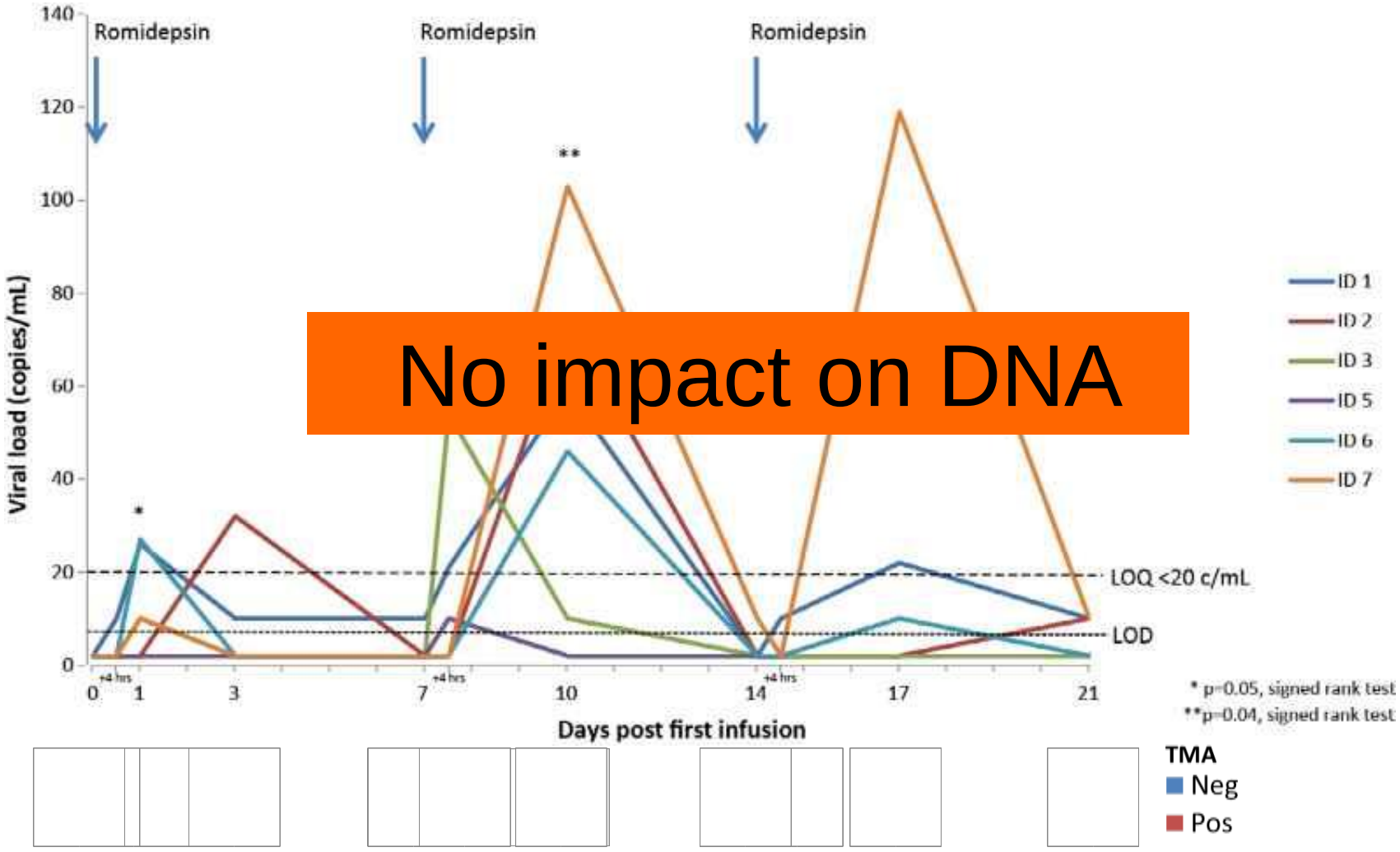

Anti-co-stimulatory molecules
- anti PD1 / anti PDL1
- anti-CTLA4
- anti-CD137

HIV Reservoirs Latency

Quiescent T cells activation
- IL7

Pre/post-transcriptional factors disruption
- HDACi
- HMBA

# Romidepsin : Impact on Plasma HIV-1 RNA




No impact on DNA

Viral load: COBAS® TaqMan® HIV-1 Test, v2.0
TMA: Qualitative NAT screening system (PROCLEIX ULTRIO Plus, Genprobe)

# Why hav'nt we an HIV vaccine yet?

- **A failure but not a lack of researches**
- **Obstacles against HIV vaccines : HIV escape**
  - **Immediate and definitive HIV Integration in host genome**

  **= Trojan Horse**
  - **HIV Variability in Antibody** and T cell **epitopes** (Enveloppe, Tat, Nef, Gag)
  - **Weak neutralizing antibodies**

***Difficulties are illustrated by***
***the lack of cure or spontaneous recovery from the HIV infection***

# The search for an immune protection HIV vaccine:

## Time for Hope or for Despair?

**T cell-based vaccines in Humans: The Prime-boost approach**

**Phase IIb studies of Recombinant Live vectors alone or combined to DNA**

- **AdenoVirus:** Strong T cell immunogenicity but anti-vector pre-existing Abs
  - **Ad5-HIV**-(Gag, Pol, Nef) clade B vaccines (no Env) *(Merck)*

    => 2005: A large Phase IIb trial in N &S americas, Australia, South-Afr.

    = The STEP trial
- **Pox-virus**
  - **Canary-poxV** *(sanofi-pasteur)*: T cell immunogenicity in Humans but weak

    => 2004: A large Phase IIb trial with Clade B vaccines:

    HIV-rec vCP(Env, Gag, Pol Nef) + gp120

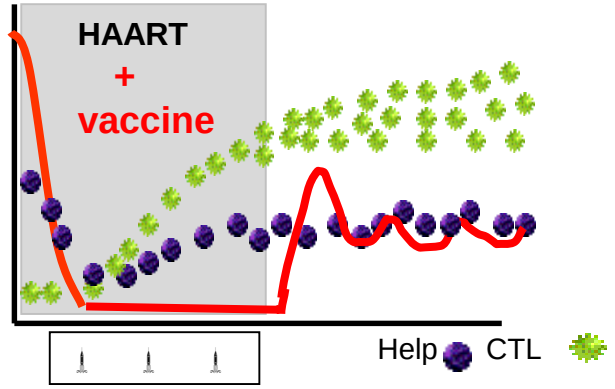
    = The Thaï Trial (with US gov.)
- **Broad neutralizing antibodies**

# Therapeutic vaccines against HIV : Changes in paradigms

## The 2000s years :

- **to limit : - time on therapy and**
  **- disease progression when « off ART »**

*Autran et al NRI 2003, Science 2004, Exp.Rev.Vaccine2004, Immunol.Rev.2013*




- **vCP** : *Tubiana (Vaccine 2005) (Autran 2008, Papagno 2009)*
  + gp160: *Markowitz( J Inf Dis, 2002)*
  + Remune: *Kinloch (J Inf Dis, 2002)*
  + Lipopept.+IL2: *Levy (Aids 2005, 06), Goujard (J Inf Dis 2007)*
  +/- IL2: *M Kilby et al. (J Inf Dis, 2006)*
  - **Safety, Immunogenicity** for CD4 T cells, CD8?
  - **Modest impact** on **HIV or *Enhancement !***
- **Dendritic cells** loaded in vitro **:**
  + Inactivated HIV: *Garcia. (JID 2011, Science Trans.Med. 2013)*
  - **Transient reduction in Virus Load**

towards an HIV cure
people focused science driven

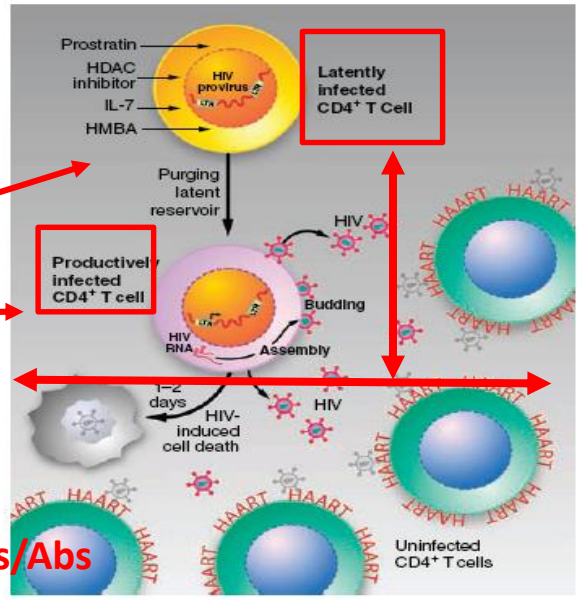
## The 2010s years :

- **in synergy with anti-latency agents**
- **to : - reduce or purge the HIV reservoirs**
  **- allow functional cure of HIV**

- Anti-latency agents

**Purging the HIV reservoirs ?**

**+**




*D Richmann et al. Science 2009*

**+ Vaccine**

⇒ **CTLs/Abs**

- to kill residual cells producing HIV
- to block cell to cell HIV spread

*Murphy et al. Science 2009; Trono D. et al Nat.Med. 2010; the IAS Working Scientific group on HIV Cure, NRI 2012 Katlama C. et al.Lancet 2013 Carcelain&Autran, Immunol. Rev. 2013*

# HIV pathogenesis : key messages

- HIV invades immune system within days with forever scars .
- HIV reservoirs establishes very early
- HIV induces a massive activation /inflammation
- HIV is deleterious from early stages of disease
- CD4 nadir and CD4/CD8 are major prognostic factor
- Activation/inflammation perists even in a context of viral suppression
- Early , maximal and permanent viral control is the best way to preserve future

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L Schneider

Virology V . Calvez
AG marcellin
Immunology : B. Autran
G . Carcelain

Methodology D. Costagliola

**ANRS INSERM UPMC ORVACS**

*From Edward Hopper*