Immunology of HIV:

What can we learn from

LTNPs / Elite Controlers ?

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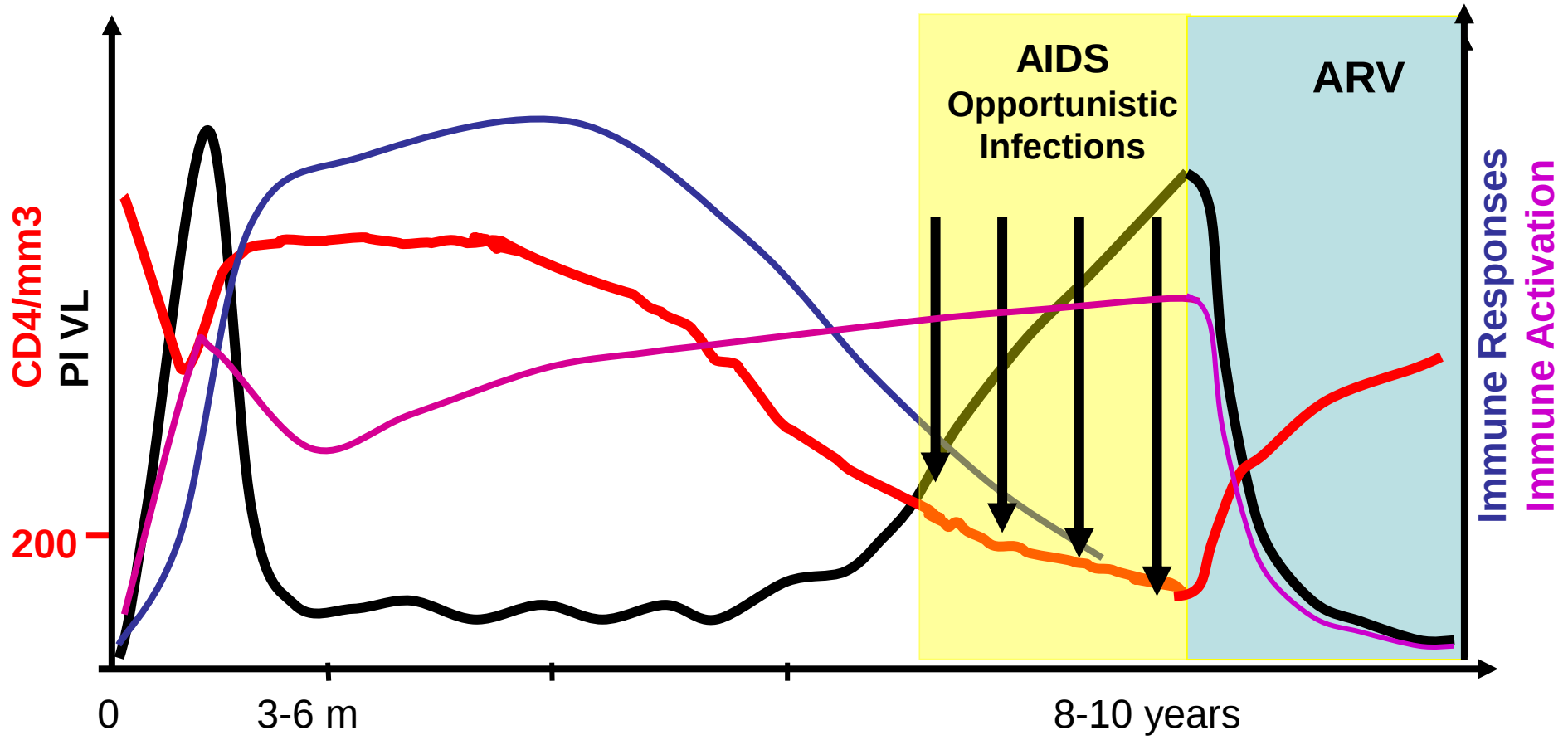
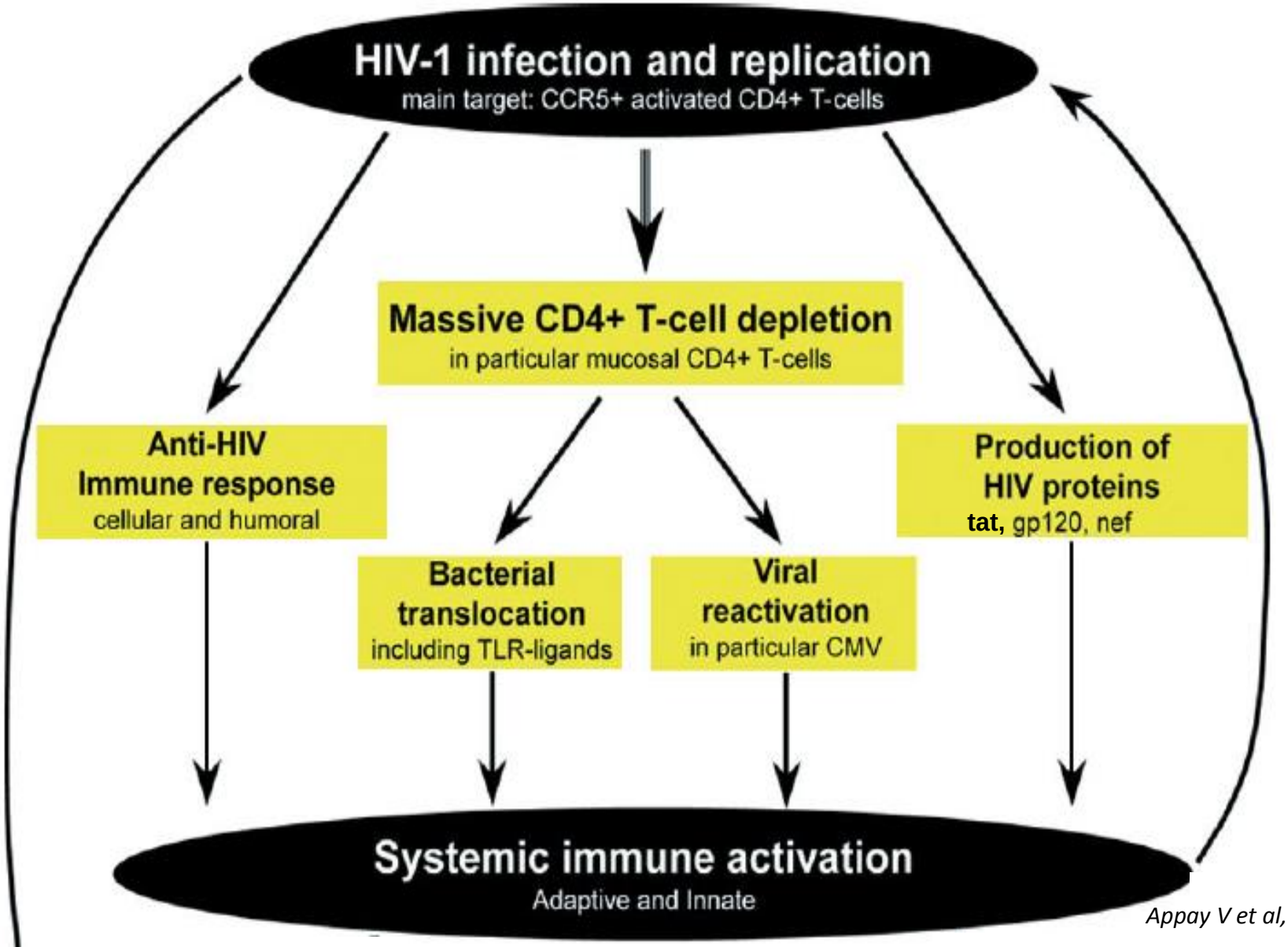
HIV and Immune Deficiencies :

- Are CD4 defects & AIDS the only complication of the HIV infection?
- The collateral damages of Immune activation…



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



Appay V et al, J Pathol 08

LTNPs and HIV / Elite Controllers: Models of functional Cure of HIV?

- **Who are they ?**
  - Definition?
  - Control of CD4 and HIV : is it stable ?
  - Control of Immune Activation ?

- **How do they control the virus ?** : Is it the Virus or the Host ?
  - Which virus characteristics ?
  - Which Immunity ?

- **Are they a model for :**
  - Vaccines ???
  - Cure of HIV ?

Which **definition** for LTNP and HIV / Elite Controllers ?

- **LTNPs:**
  - **1st evidence: 1993: LTS** (Long Term Survivors): SanFrancisco Cohort: *S Buchbinder & J Levy (1994)*
  - **Immuno/Clinical definition: > 1994: LTNPs:**
    - » **Seropositivity > 7-8 years**
    - » **No AIDS,**
    - » **Normal CD4 counts : >500, >600/mm3**
    - » **No Treatment**
    - » **(VL not available)**

- **HIV / Elite Controllers (Suppressors):**
  - **1st evidences: 2000s:** *HIV Controlers: O. Lambotte 2005 / HIV Suppressors: J. Blanke 2005*
    Elite Controllers : S Deeks & B Walker 2007
  - **Virological Definition**:
    - ➢ **Seropositivity > 8-10 years**
    - ➢ **Plasma Viral Load < 400 or 500 cp / mL** over 90% measures +/- undetectability
    - ➢ **No Treatment**
    - ➢ **(AIDS symptoms or CD4 non necessary)**

Which **Epidemiology** for LTNP and HIV / Elite Controllers ?

- **LTNPs:**
  - **1993: LTS** SanFrancisco Cohort: **7%?** *S Buchbinder (1994)*
  - Others *: < 5%, <2%, ….*

- **HIV / Elite Controllers :**
  - **late 90s:** ***HIV / Elite Controlers:*** **??? < 1%**

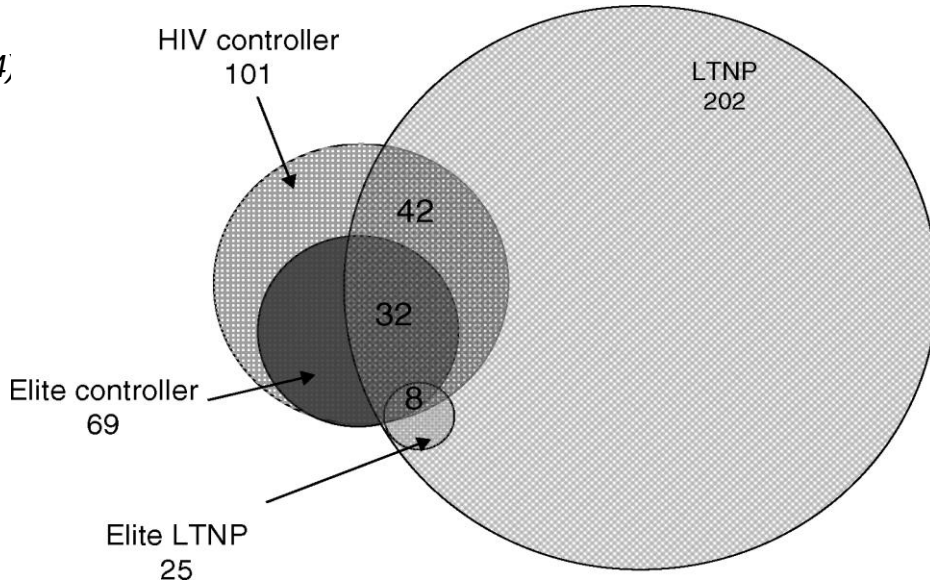
- **French Hospital Data Base (FHDH):**

Grabar.. D Costagliola, AIDS 2009

46,880 HIV+ patients:

- **LTNP: Sero+ >8y , CD4 nadir > 500** **= 0.4%**
- **Elite LTNP: idem + CD4 nadir > 600, CD4 slope+** **= 0.05%**
- **HIV Controlers: >10y , 90% VL<500cp/ml** **= 0.22%**
- **Elite Controllers: idem HIC + last VL<50 cp** **= 0.15%**

Data from FHDH:



- **Elite LTNP:**
  = 40% HIC
  = 32% EC
  = 60% detectable plVL

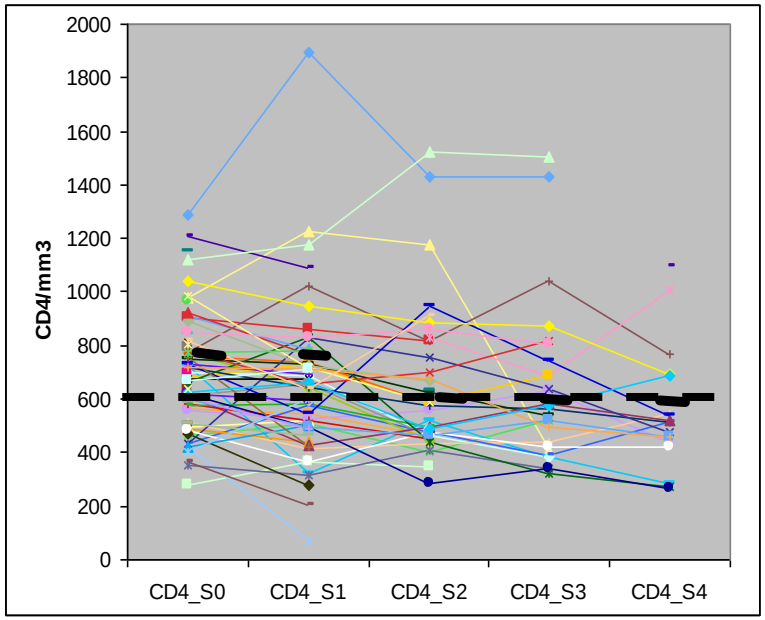
- **Elite Controlers:**
  = 46% LTNP
  = 12% Elite LTNP
  = 25% CD4 < 500/mm3

EACS: B Autran 2013

French Cohort of LTNPs: ALT –ANRS CO15:

- **Recruitment: 1994 – 96** :
  - **Inclusion Criteria** : **Seropositivity known > 8 years**
    CD4>600/mm3 for > 5 years and + CD4 slope
    Lack of HIV-related symptoms
    Lack of ARV
  - **N=71:** **median seropositivity: 9 y**
  - **Evolution: very slow decrease in CD4 over an 18 years Follow-up:**

Years	Number subjects	Nb CD4>600
1	71	46 (65%)
2	61	28 (46%)
3	44	17 (27%)
4	30	12 (40%)
5	24	8 (33%)
2001-12	18	9 (44%)



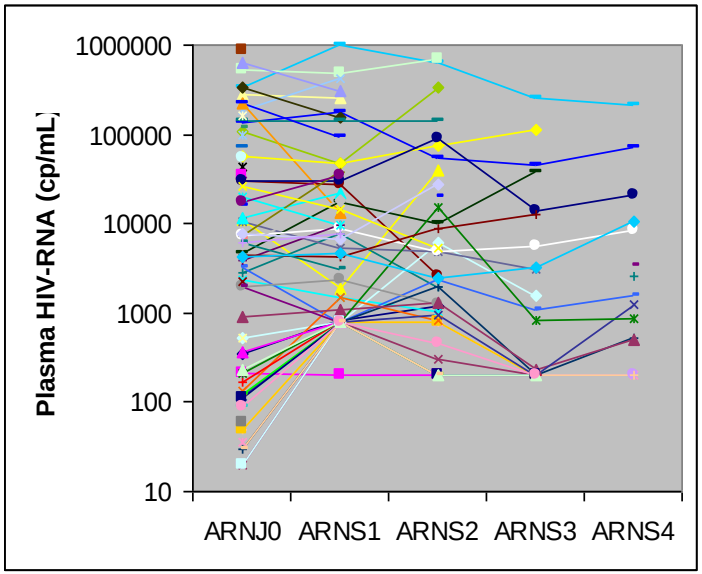
HIV – Elite Controllers, LTNPs

- **The Virus** or the Host?
  - Deletions ?
  - Evolution and escape ?
  - What is the key parameter ?
    - Production or Reservoir ?

ALT-ANRS CO15 cohort: HIV characteristics at entry: It is NOT the Virus !

- **Low but Heterogeneous viral production**:
  - **Median plasma VL =**
    - **10 000 cp/mL at entry** (20-880,000)
    - **Slow increase:**

  Candotti et al. 1999, 2000



- **R5-dependent HIV Type**:

  All isolates: NSI (Candotti J Gen Virology1999)

- **No HIV gene deletion** in:

  env, nef, gag, LTR but a Vif signature *(Candotti, Vigne, J Virol 2000)*

➢ **SIMILAR FINDINGS**

in OTHER LTNP COHORTS

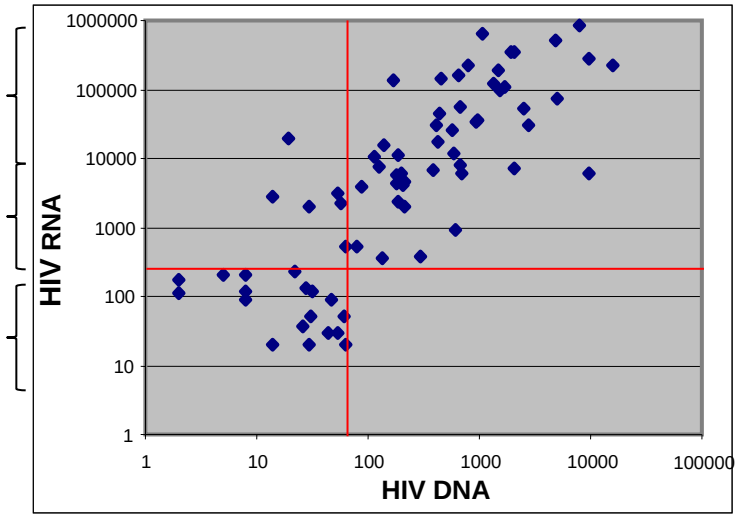
- **Low Reservoir** (cell associated HIV-DNA)

correlated to virus production

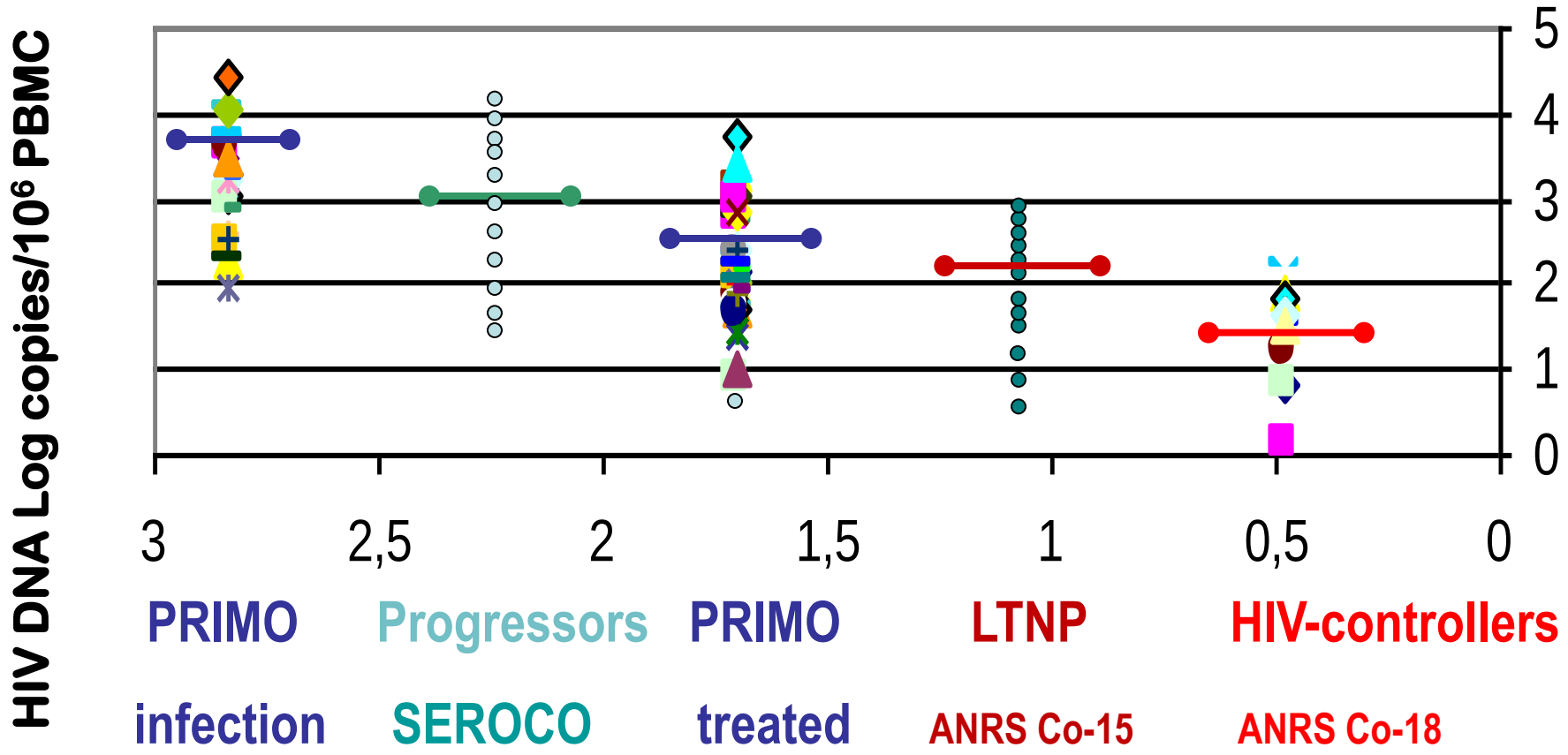
Viremic Slow Progressors

Viremic Controlers

Elite Controlers

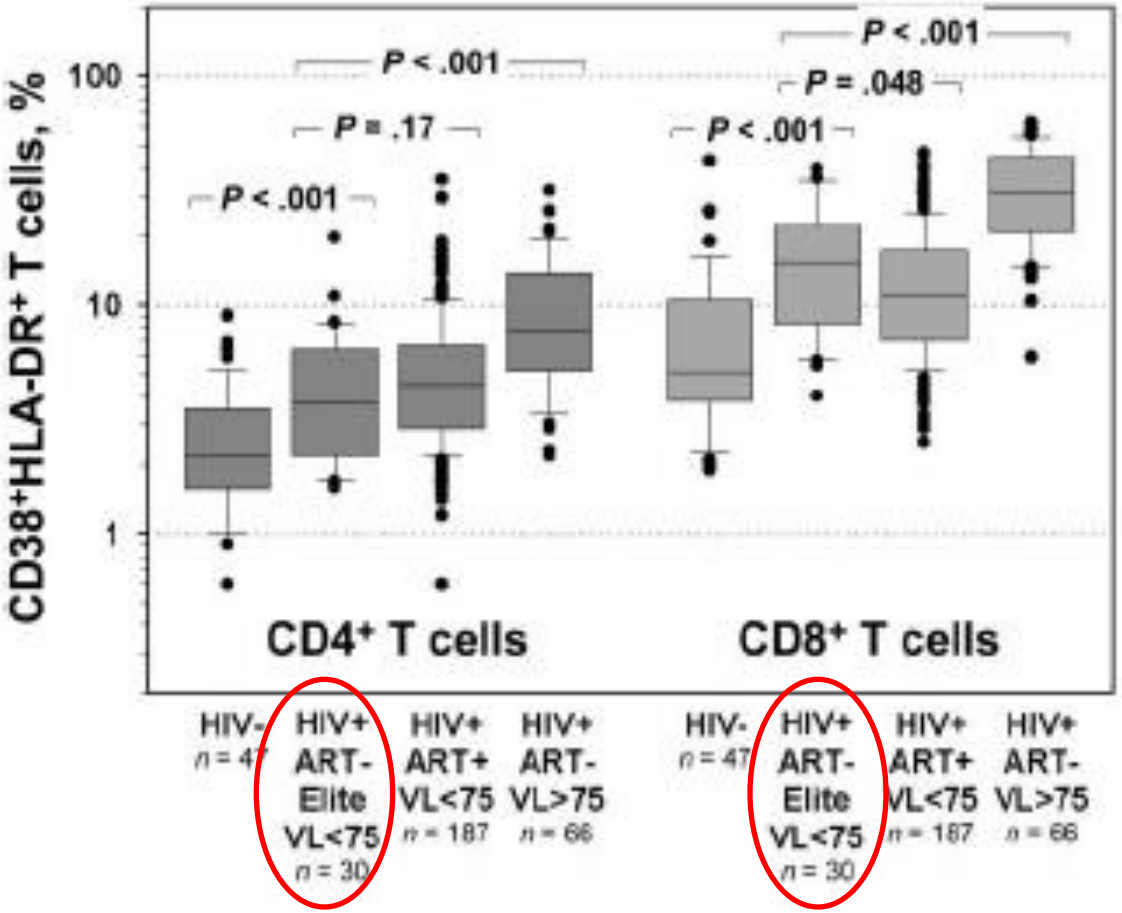


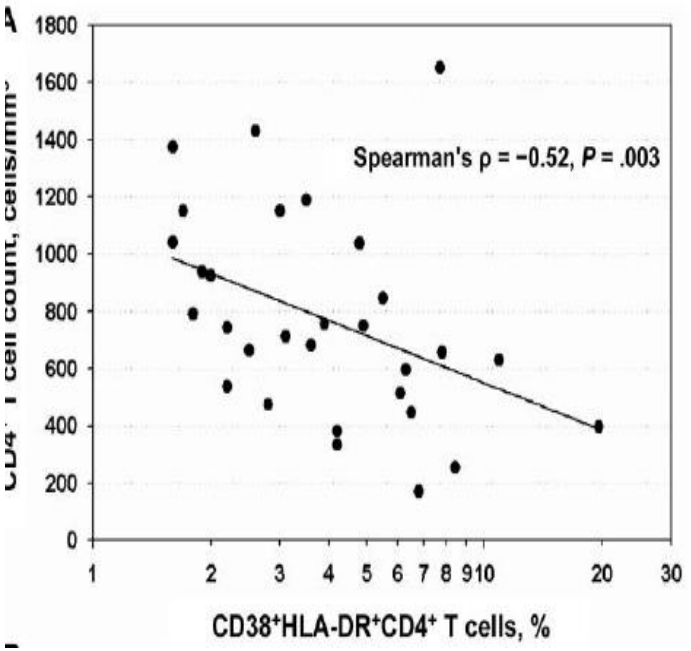
Low HIV Reservoir (HIV-DNA) in PBMC : associated with a low risk of HIV disease progression



S Lewin & C Rouzioux et al. AIDS 2011

HIV / Elite Controllers, LTNPs
Do they control T-cell activation ?





- **Low Immune Activation in Elite Controlers with undetectable plVL:**
  - CD4 activation as low as in ARV-suppressed patients, CD8 activation higher

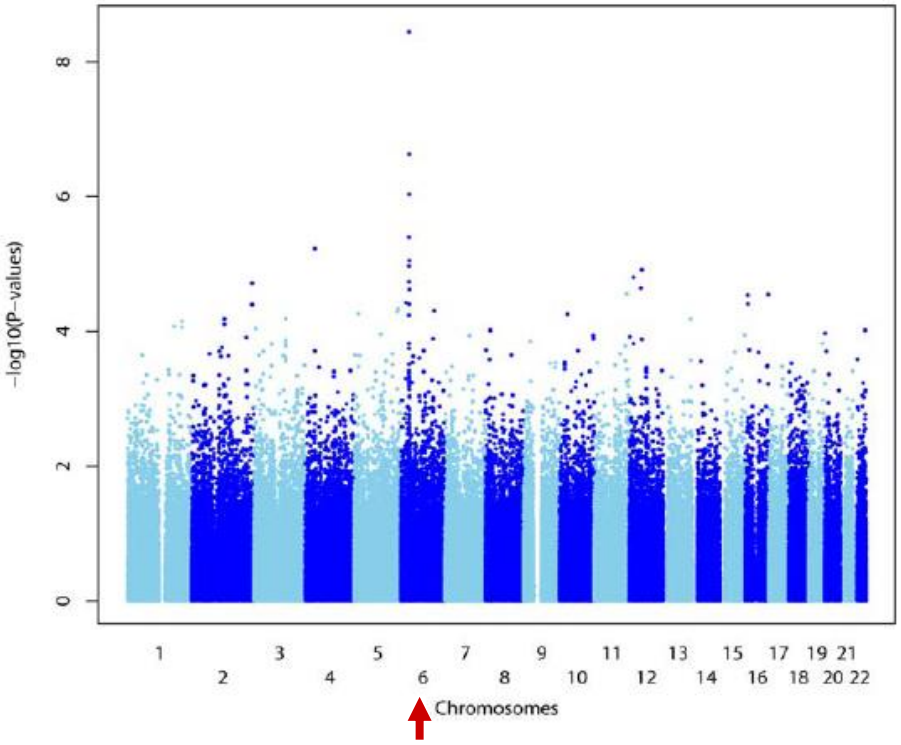
Hunt, JID 2008

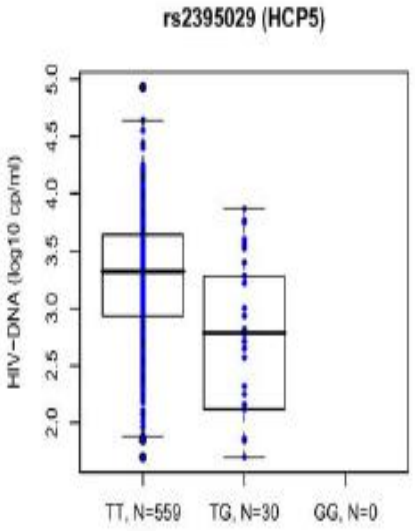
HIV – Elite Controllers, LTNPs

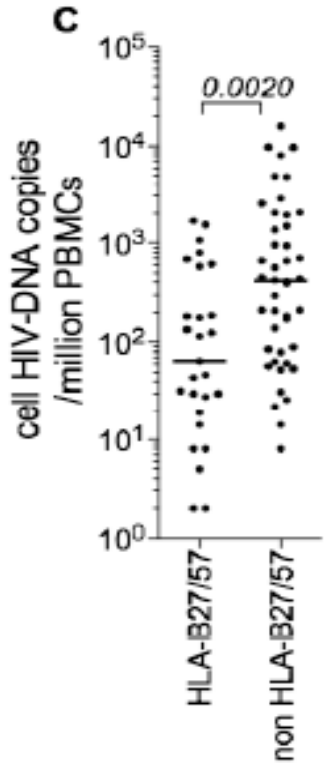
- **The Virus or the Host?**
  - **Is it all in the Genes ?**
    - **Immune Response genes**
      - **Adaptive Immunity**
      - **Innate Immunity**
  - **Is it the anti-HIV Immunity ?**

ImmuneGenetics and control of the HIV Reservoirs:

Genome-wide analysis in Elite Controllers and LTNP







➢ **HLA-B57 (HCP5) is the strongest Marker for low HIV reservoirs**

(Dalmasso et al.)

➢ **The HLA locus in Chromosome 6 is the strongest genetic marker for:**

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

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

B Descours et al. Clin. Inf. Dis 2011

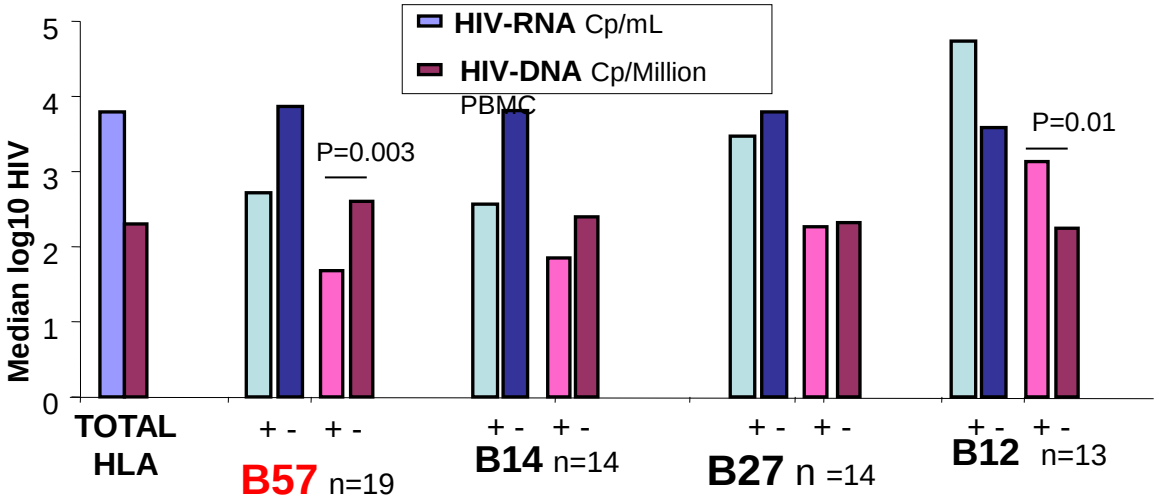
ANRS-CO15 (ALT) cohort: Immune Genetics of LTNPs : It is the HOST !

- **A composite of HLA + chemokine /chemoreceptors gene mutations**

  CCR5 Δ32(hzg) + SDF-1 wt + HLA-B27^{+}, DR6^{-}+ 3 of the HLA-A3, B14, B57 + DR7

  Significantly predicts 80% of LTNP vs Progressors *(Magierowska et al.Blood, 2000)*

- **Association HLA-B57 and low pl VL:**



- **Protective HLA**

  enriched during Follow-up:

  59% at Year0 vs 75% at year5

- **Distinct influences**:

  HLA-B57 and B14 associated to HIV control

  HLA-B27 associated to LTNPs

  Antoni G, AIDS 2013

- **SIMILAR FINDINGS for HLA-B57 in all LTNP / HIC & EC cohorts**

  (M Carrington, 1999, Deeks & Walker, 2007, ….)

- **Other genetic parameters???** Mutations of the KIRDL1 gene (M Carrington 2005), CX3CR1gene *(Faure 2001)* No gene polymorphisms in TRIM-5, APOBEC3G, FcγR

- **Genome Wide Association Studies (GWAS)**

HIV – Elite Controllers, LTNPs

- **The Virus or the Host?**
  - **Is it Immunity ?**
    - **T cell adaptive Immunity:**

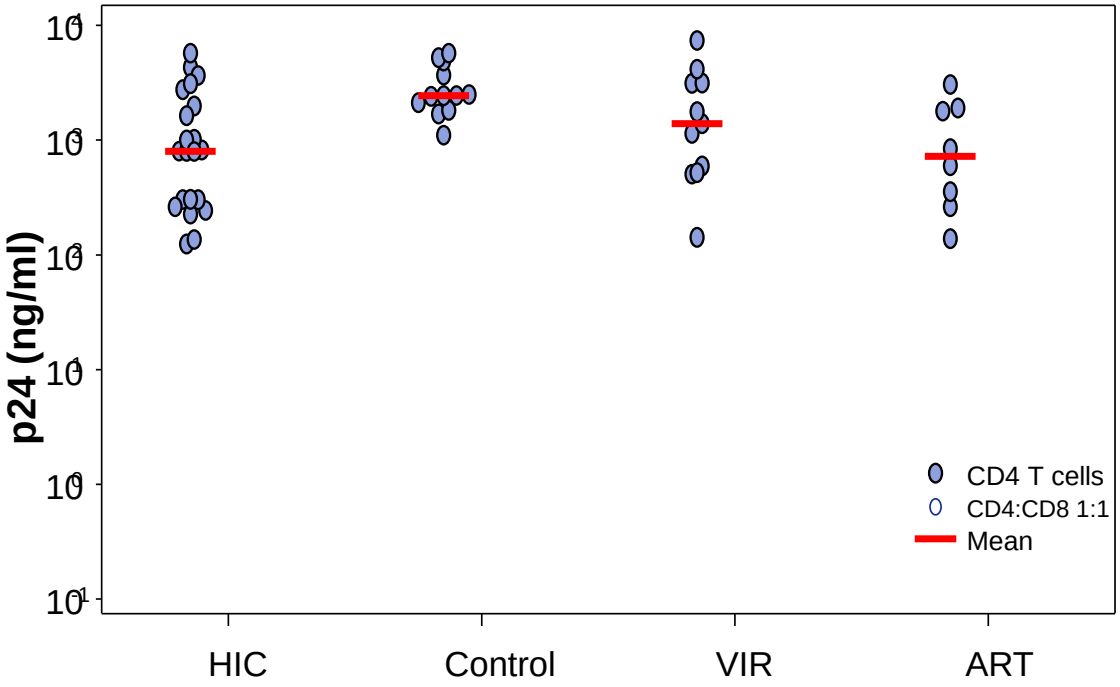
- **CD8 T cells ?**
  Specificity ?
  Function ?
  Gene associations ?

- **CD4 T cells ?**
  Function ?
  Other parameters ?

Correlates of protection ?

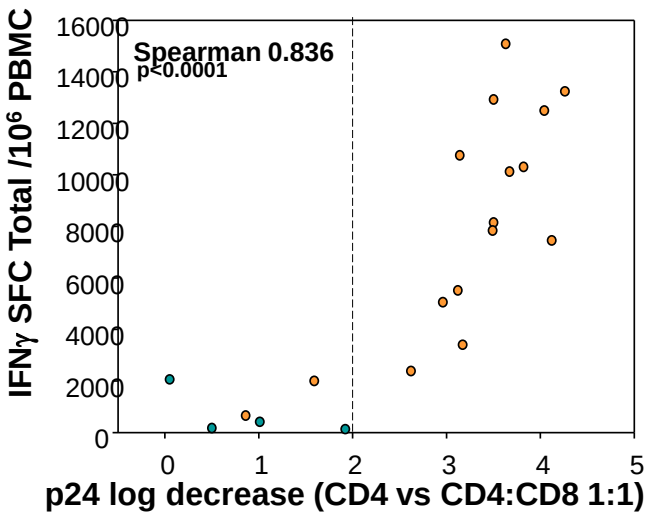
Is it the hen or the egg ???

The ANRS Co-18 Cohort of HIV Controllers: CD8 T cells mediate a strong anti-viral activity



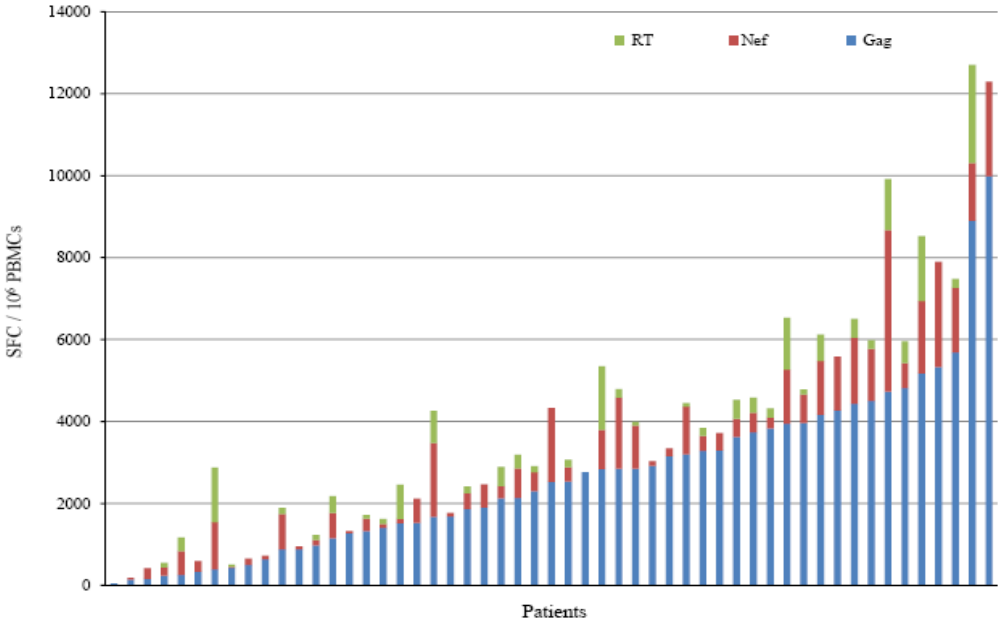
- CD8 T cells from HIC inhibit HIV production
  Saez-Cirion, PNAS 2008

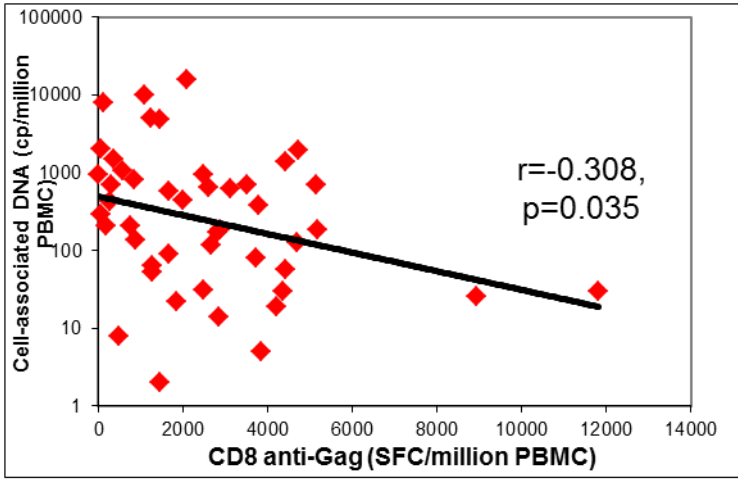
- Some correlation between anti-viral functions of CD8 T cells from HIC HIV inhibition and IFN-g production
  Saez-Cirion, JI 2009

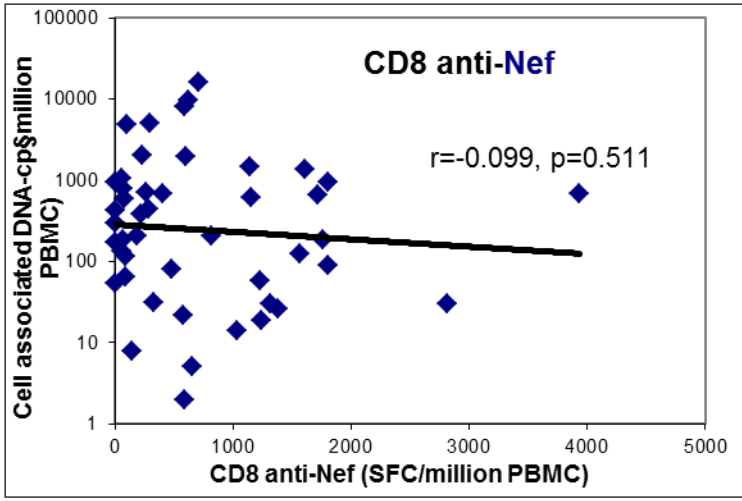


LTNP - ANRS-CO15 cohort: Robust HIV-specific CD8 T cells

- **Strong CD8 T cells against HIV-Gag :**



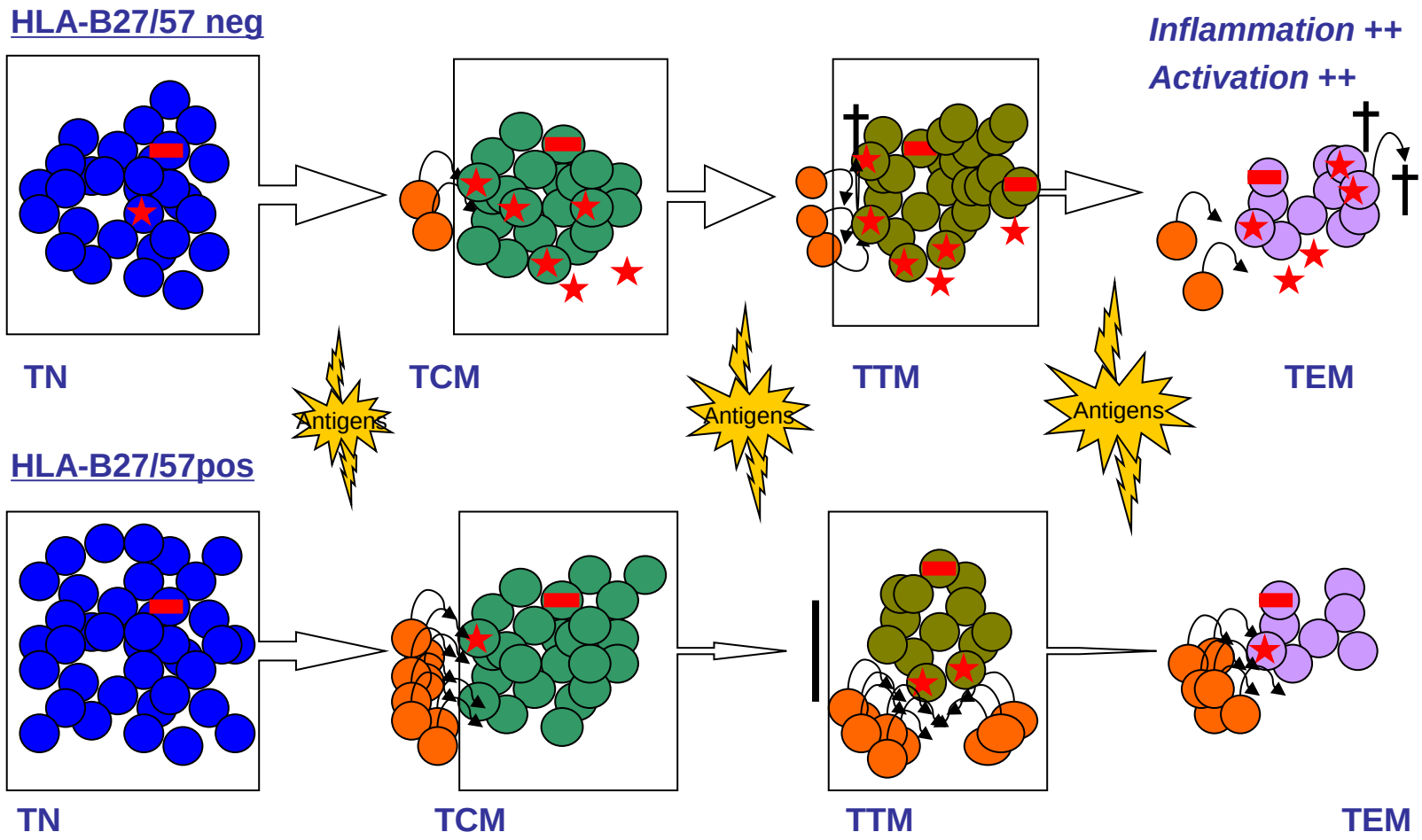




- **CD8 T cells anti-Gag- but not Nef correlate with low HIV reservoirs**

Martinez et al. JID 2005, Jie et al. AIDS 2010

A model for an immune control of the HIV Reservoirs in HLA-B27/57+ LTNPs



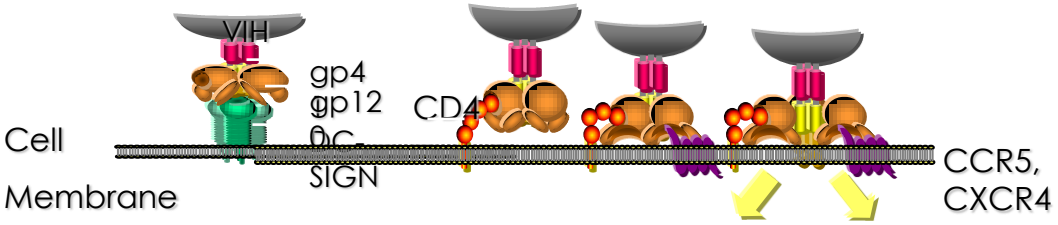
HIV – Elite Controllers, LTNPs

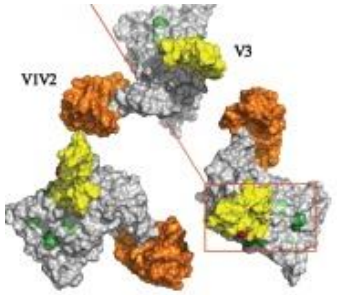
- **The Virus or the Host?**
  - **Is it Immunity ?**
    - **Antibodies ?**
      - **Neutralizing ?**
      - **Others ?**

ANRS CO-15 ALT and antibodies against HIV Env

- **HIV-specific antibodies**: against HIV-enveloppe:
  - Neutralizing Abs::
    - **Positively** correlated to the VL: *N'Go et al, AIDS Res Hum Retrov.2003*
    - Reactivity against the MPER of gp41 *Braibant et al. AIDS 2006*

      2F5-like et 4^{E}10 like Abs in 60% sera *Braibant et al. Virol. 2011*
    - Reactivity against gp120: particular structural characteristics





  - Isotype: **IgG2:** anti-gp41:
    - Best correlate of protection against disease progression

N'Go et al., AIDS Res Hum Retrov. 2003
Martinez et al. J Inf Dis. 2005

  - Inhibition of the NK cell-mediated lysis of CD4 T cells: **Anti-3S** (gp41):
    - Debré et al. block NK cell lysis and correlate with disease progression

Vieillard et al. AIDS 2007

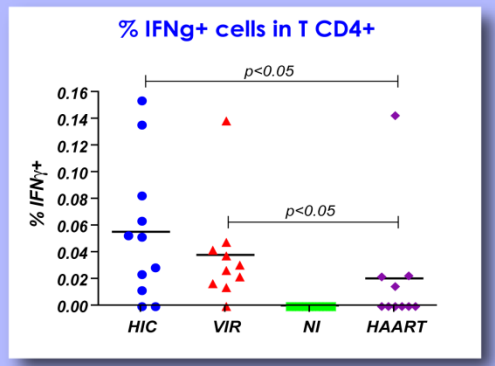
LTNP , HIC and EC: Robust HIV-specific CD4 T cells

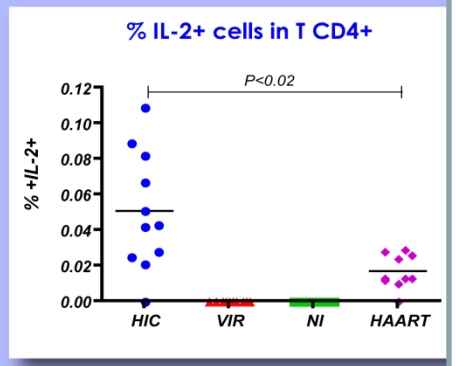
CD4 responses in HIV Controllers

anRS Agence nationale de recherches sur le sida

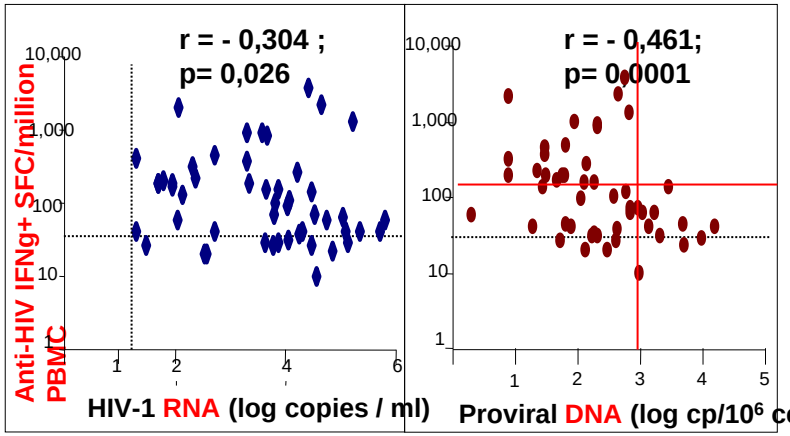
EP3

Cytokine responses to p24 Gag stimulation:





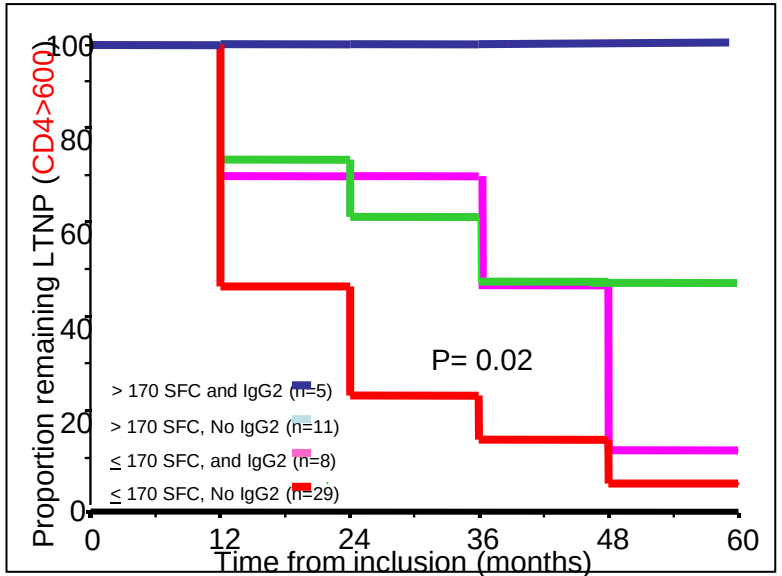
S. Potter / L. Chakrabarti, J. Virol. 2007



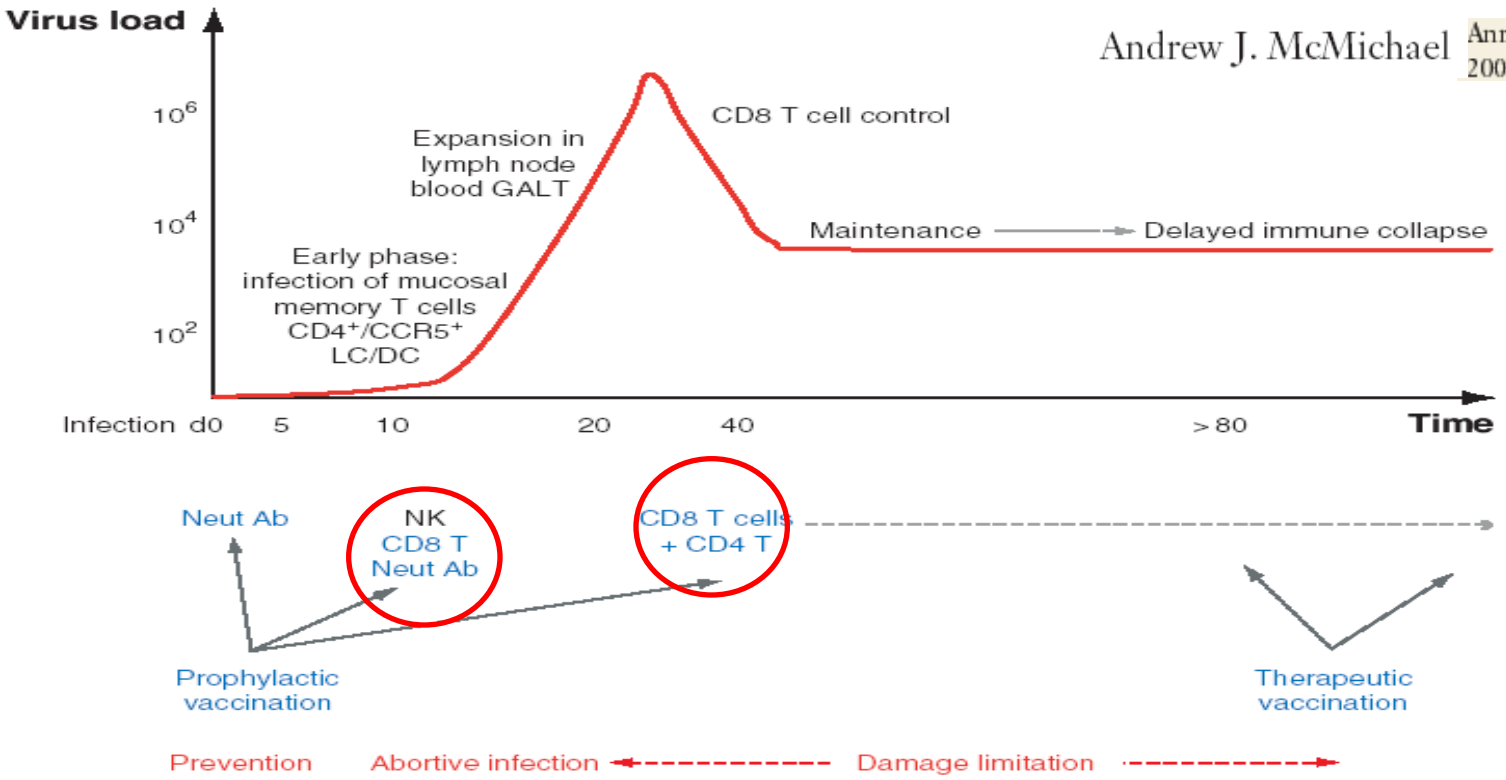
- **LTNPs: Gag-specific Th1 CD4 T cells**
  - **associated with control of HIV & CD4**
  - **The best marker of protection / progression:**

    in association with **anti-gp41 IgG2 Abs**

    Martinez et al. JID 2005

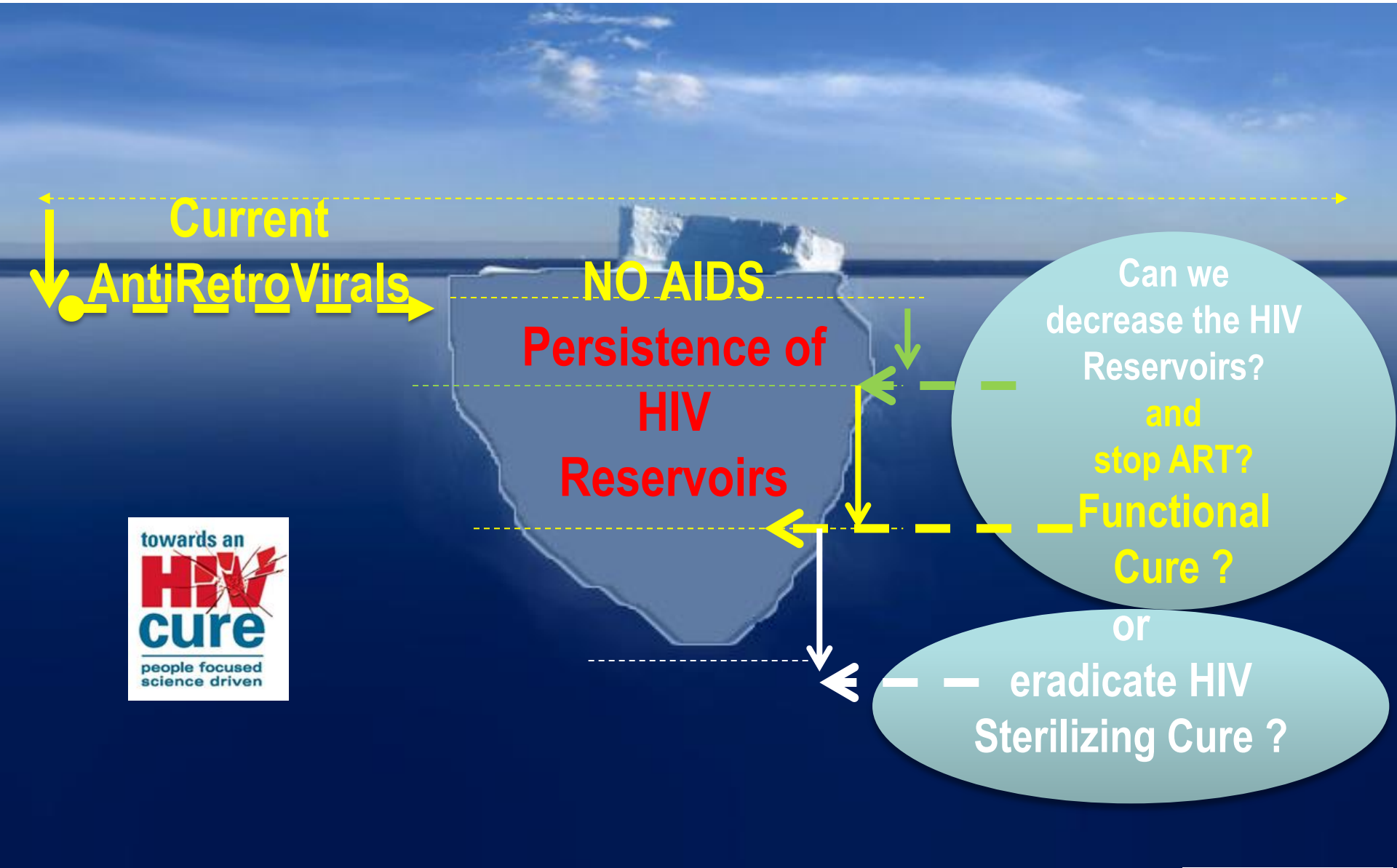


HIV / Elite Controllers, LTNPs
A model for HIV vaccines ?



- **LTNPs, HIC & ECs:**
  - **Strong T cell Immunity to HIV**
  - **Weak Neutralizing Abs but other anti-HIV Abs associated with:**
    - **low VL (IgG2)**
    - **stable CD4 (anti-gp41/3S)**

Are HIV / Elite Controllers, LTNPs a model for HIV Cure?



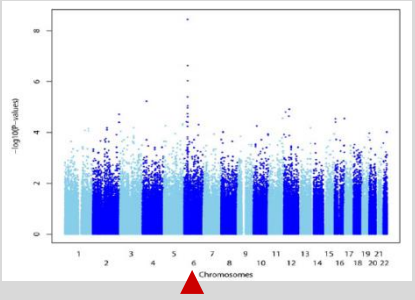
Hot Topic in 2013: Models of Cure ?

Sterilizing cure ?

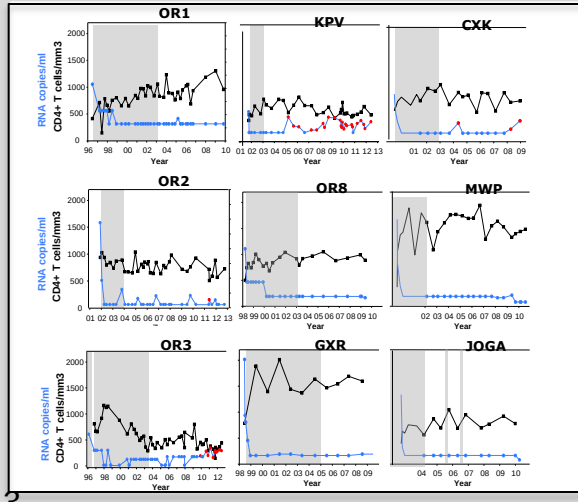
- *CCR5 defective stem cell graft (Berlin patient)*

Models of Functionnal cure

- **Elite Controllers and Long term non progressors**
  - Infected for 10-30 years
  - Never treated ; **Genetic Background**;
  - Strong CD4 and CD8 response/HIV
  - Preserved central-memory CD4 T cells
  - Low immune activation

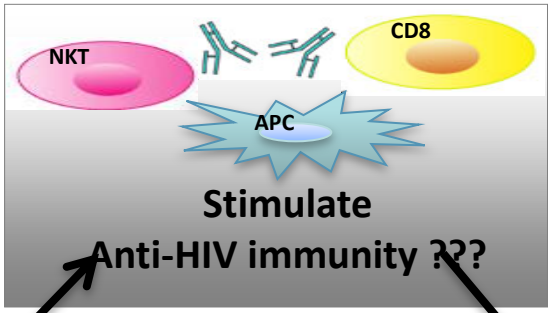


- **Post-Treatment Controlers** (Visconti)
  - ✓ **Control HIV without ARV for median 3.5 years**
  - ✓ After ARV for 5 years started at acute infection
  - ✓ No genetic background; Immunity ???
  - ✓ Preserved central-memory CD4 T cells
  - ✓ Low Immune activation



Hoqueloux et al. AIDS 2010, J Antimicrob. Ther. 2013, Saez-Cirion et al. PLosPathogens, 2013

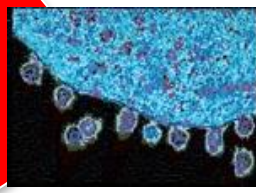
Hot Topic in Sept 2013: Potential strategies to reduce HIV reservoirs: Lessons from LTNPs and HIC /ECs



Reduce Systemic Inflammation

Immune Activation

Residual Replication



HIV Reservoirs Latency

What can we learn from LTNPs, HIC & ECs for Controling Latency ???