Science of HIV ?
Last news

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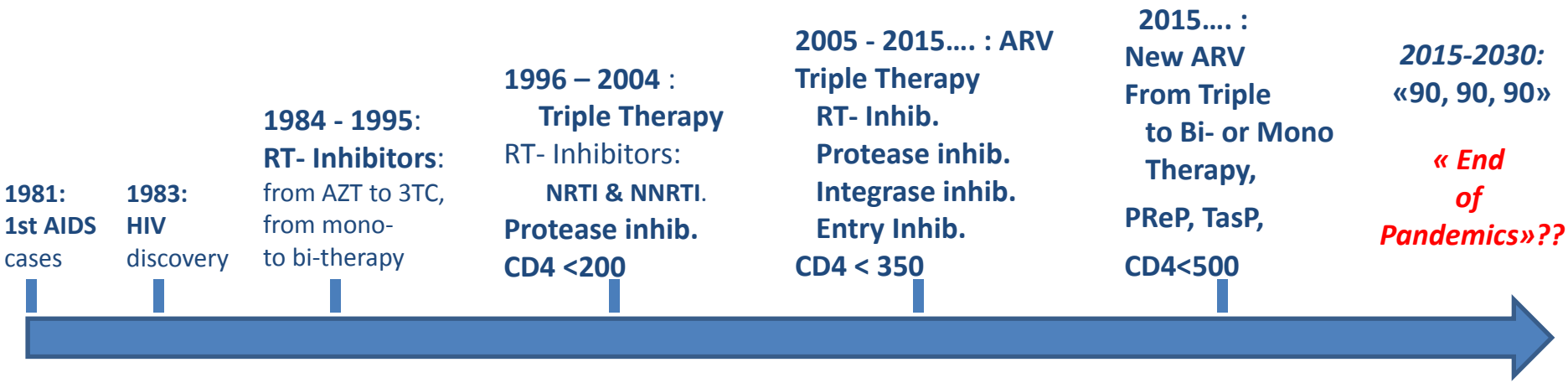
Science of HIV : the ARV revolution: towards the end of AIDS ?



- ✓ Improvement of virus control despite

  Persistence of Latent HIV reservoirs

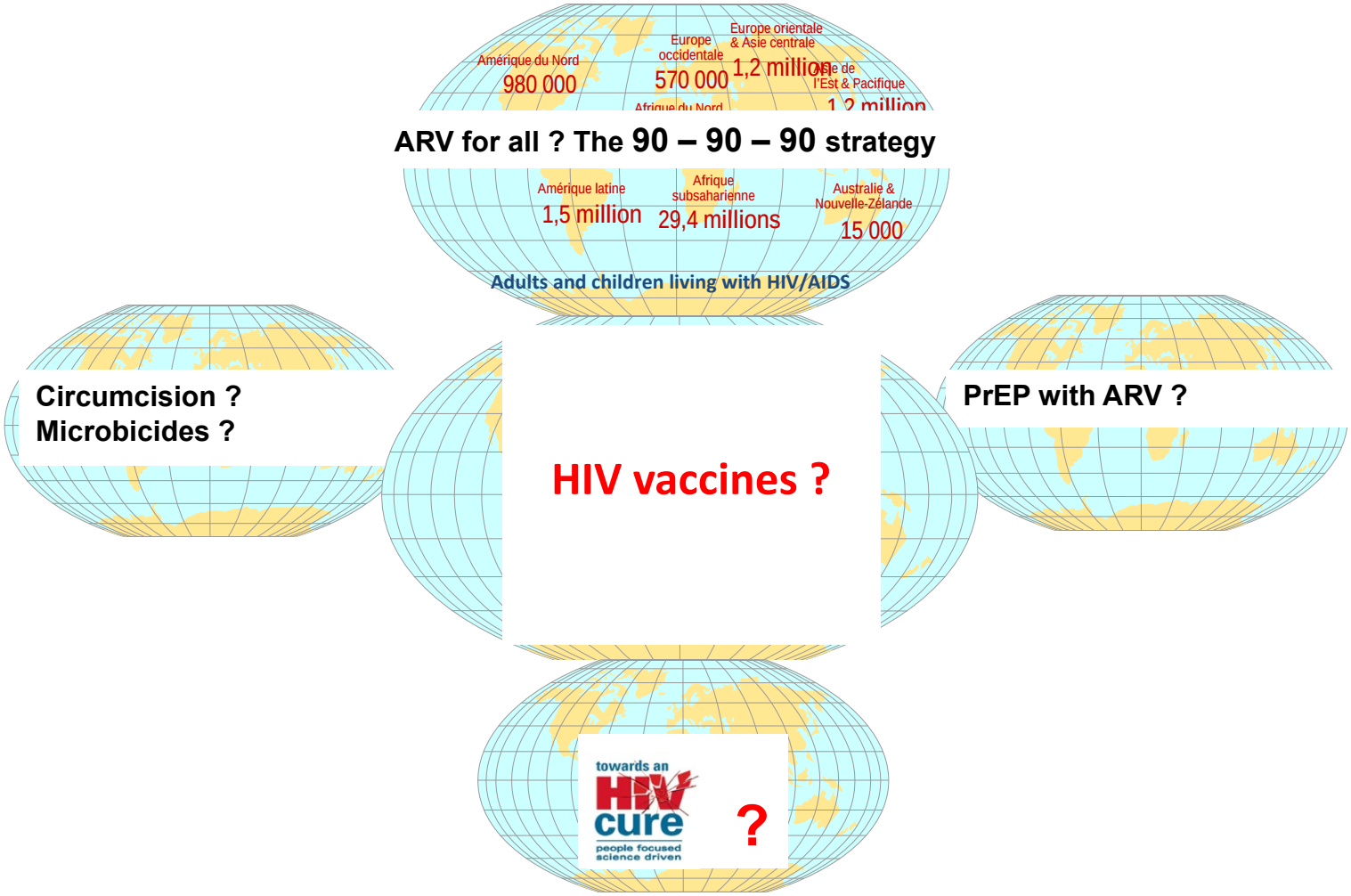
- ✓ Improvement of Survival and Reduction of AIDS-related Deaths **but**

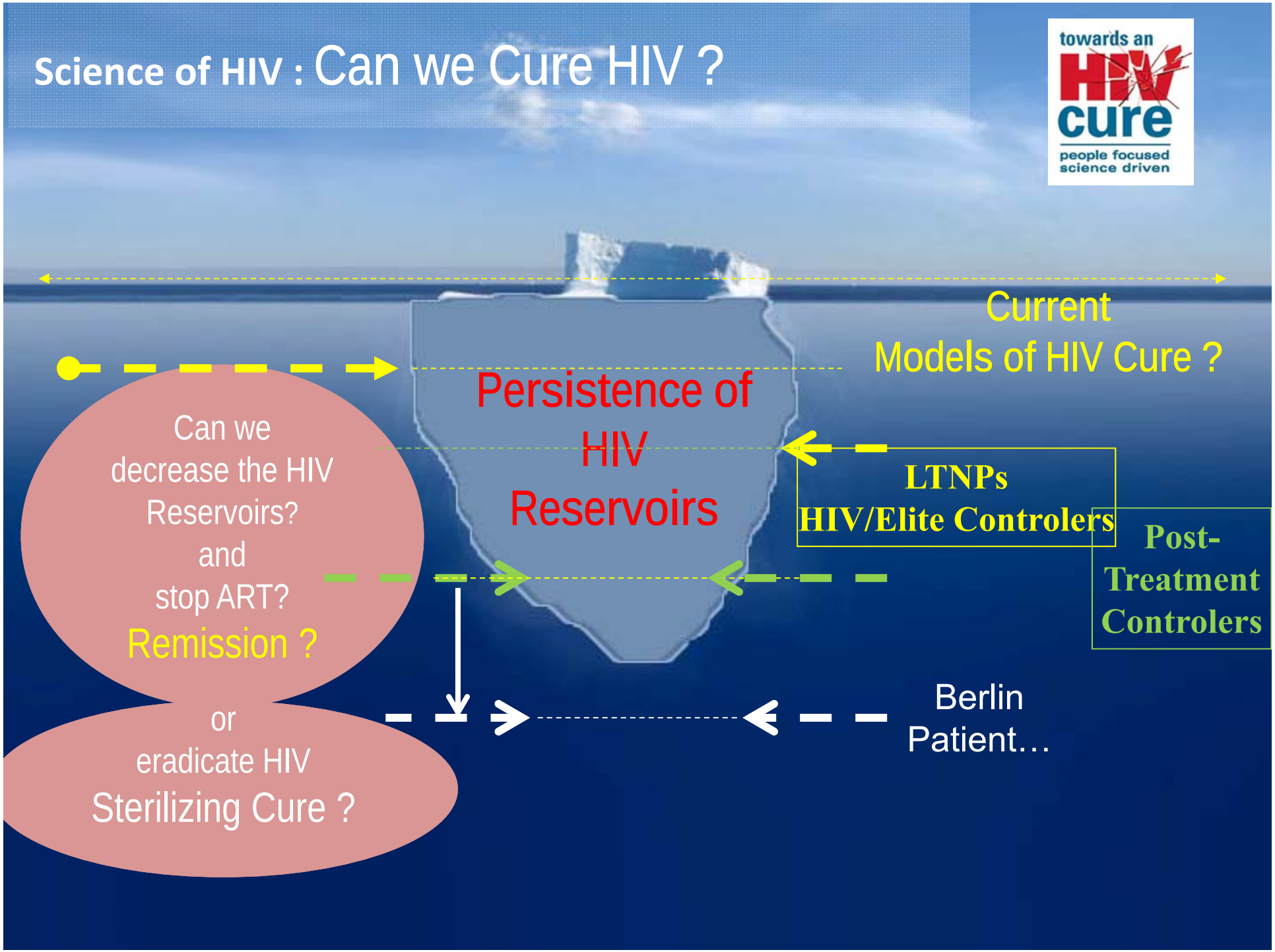
  Persistence of non AIDS related co-morbidities

- ✓ Improvement of immune status despite

  Persistence of Incomplete reduction of Inflammation

➢ **What's next ?**


Amérique du Nord
980 000
Europe occidentale
570 000
Europe orientale & Asie centrale
1,2 million
Asie de l'Est & Pacifique
1,2 million
Afrique du Nord
ARV for all ? The 90 – 90 – 90 strategy
Amérique latine
1,5 million
Afrique subsaharienne
29,4 millions
Australie & Nouvelle-Zélande
15 000
Adults and children living with HIV/AIDS
Circumcision ?
Microbicides ?
HIV vaccines ?
PrEP with ARV ?
towards an HIV cure
people focused science driven
?


Science of HIV : Can we Cure HIV ?
towards an HIV cure
people focused science driven
Current Models of HIV Cure ?
Persistence of HIV Reservoirs
LTNPs HIV/Elite Controlers
Post-Treatment Controlers
Can we decrease the HIV Reservoirs? and stop ART? Remission ?
or eradicate HIV Sterilizing Cure ?
Berlin Patient…

Towards an HIV cure:
a global scientific strategy

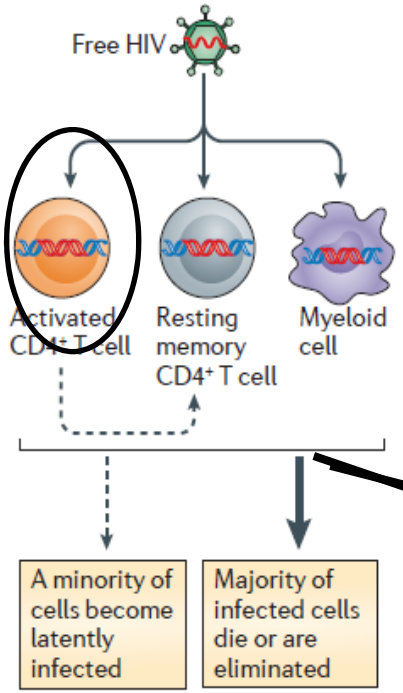
The International AIDS Society Scientific Working Group on HIV Cure

NATURE REVIEWS | IMMUNOLOGY VOLUME 12 | AUGUST 2012 | 607

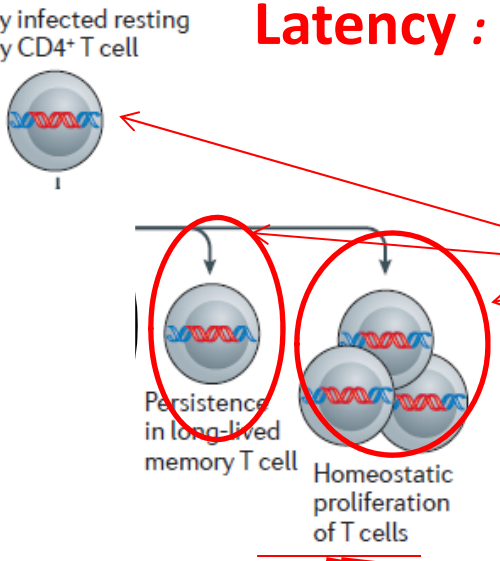
Science of HIV : Why HIV reservoirs persist despite ART and immunity ?

Establishment of latency | **Fate of latently infected cells**

Activation :

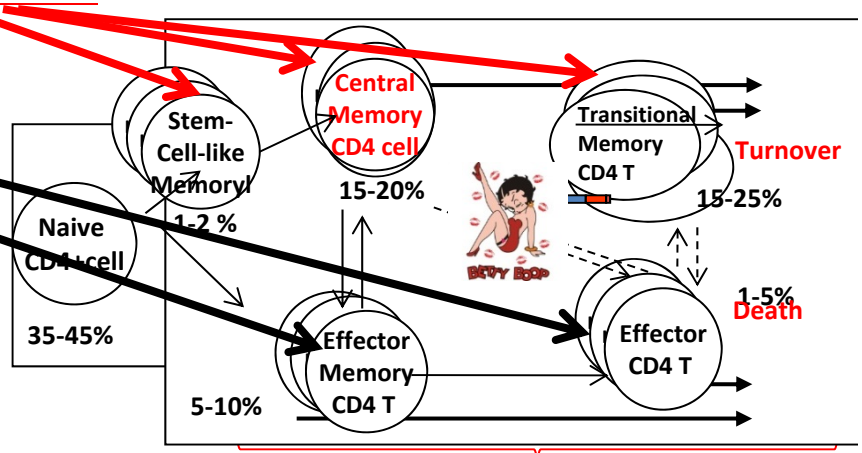


Latency :



Obstacles :

the Sleeping Beauty



Cellules productrices ciblées / ARV

CTL anti-VIH

Ac anti-VIH

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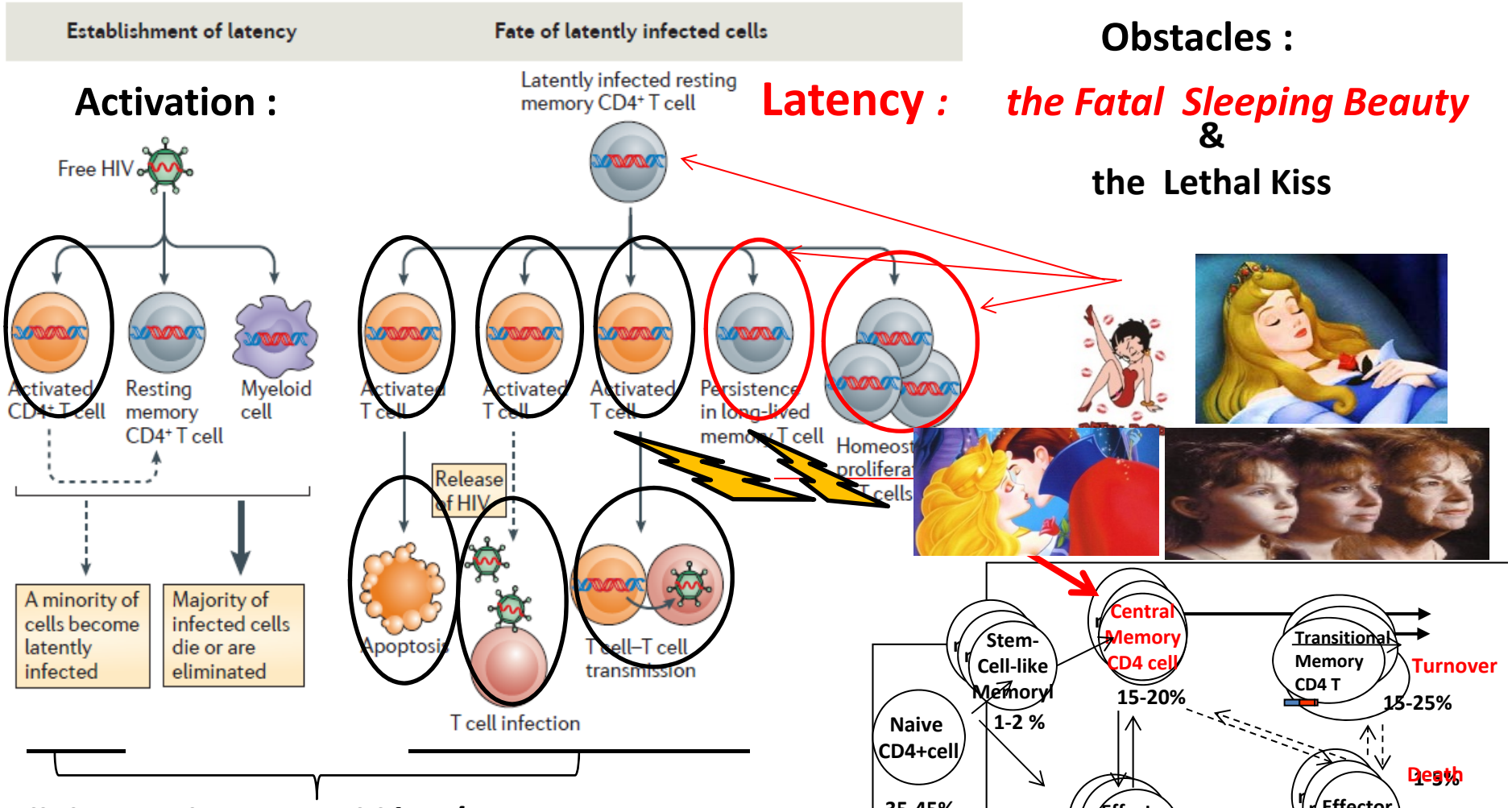
Science of HIV : Why HIV reservoirs persist despite ART and immunity ?

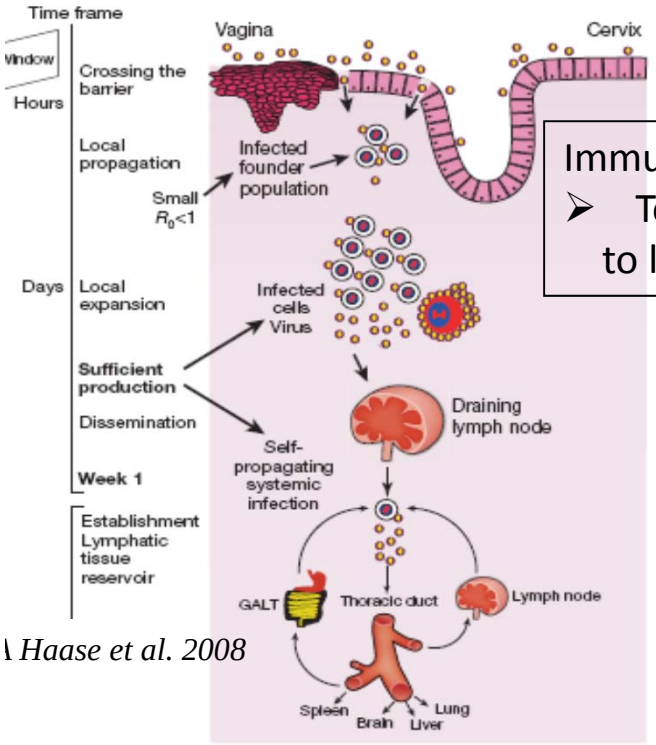


Cellules productrices ciblées / ARV

CTL anti-VIH

Ac anti-VIH

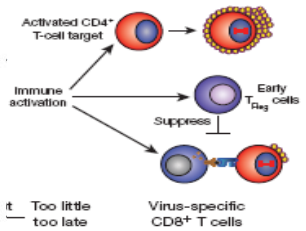
How early are set the HIV reservoirs ?



\ Haase et al. 2008

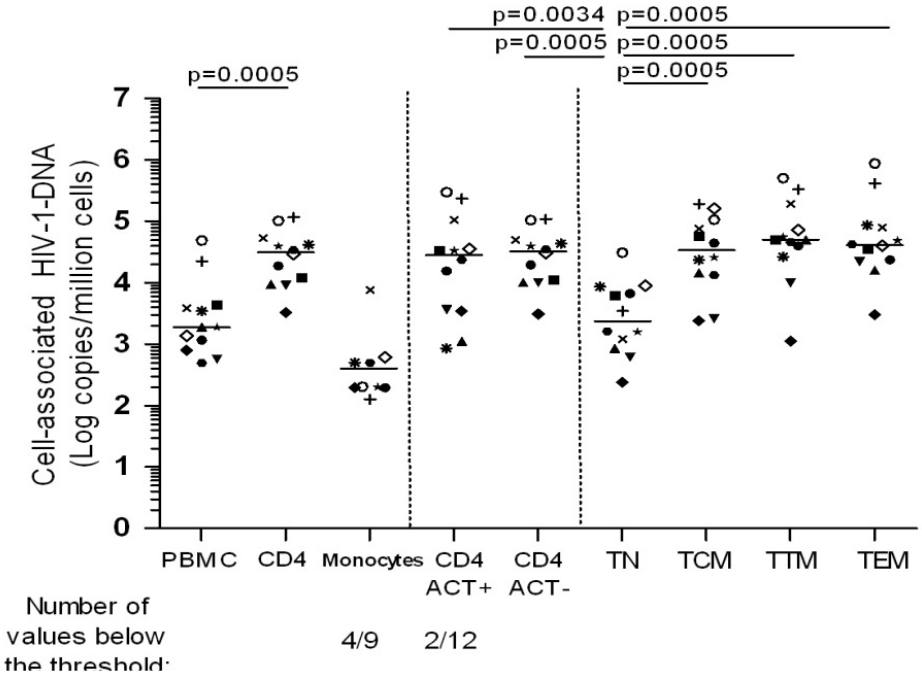
Immune Responses to HIV:

- Too little, too late to limit dissemination



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

Huge infection in short and long-lived CD4+ cells

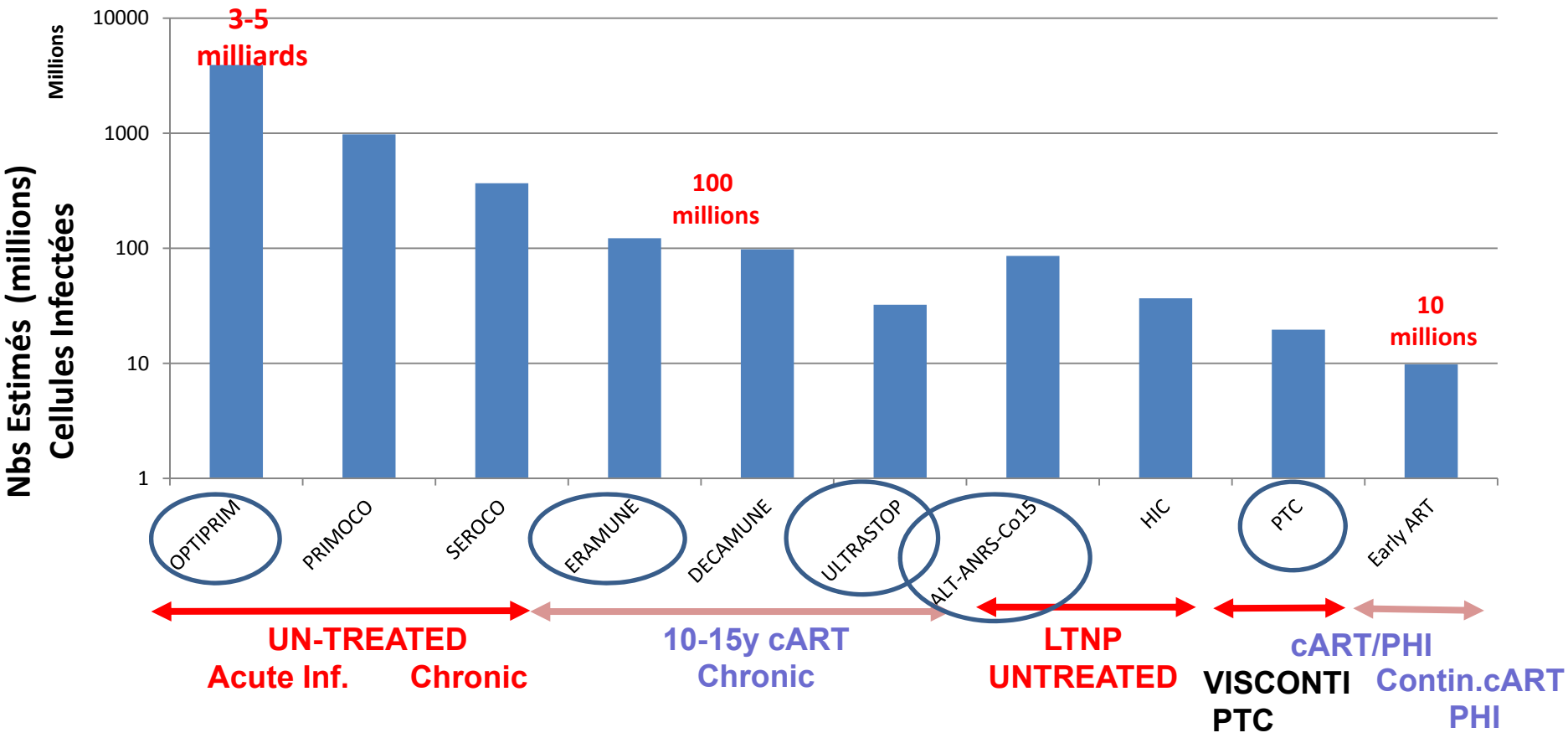


Early Establishment of the HIV Reservoirs in CD4 cells

Bacchus&Cheret et al Plos One 2013

How big are the HIV RESERVOIRS ?

Estimation of total numbers of HIV-infected cells *(d'après C Rouzioux et autres)*



Hypothesis: *1 infected cell contains 1 or 2 copies HIV-DNA (S Palmer)*
1 mL of blood = 1 million PBMCs with about 5 litres of blood
Correlation between blood and rectal reservoirs (Avettand, Descours,Yukl…)
Blood Lymphocytes = about 2% total Lymphocytes

BA, CR, VCalvez

Why and How can we better define the cells hosting the reservoirs ?

- **Why ?**
  - **To try better target and eliminate them**

- **How ?**
  - **To detect cell surface molecules defining small CD4 T cell subsets enriched in HIV reservoirs**

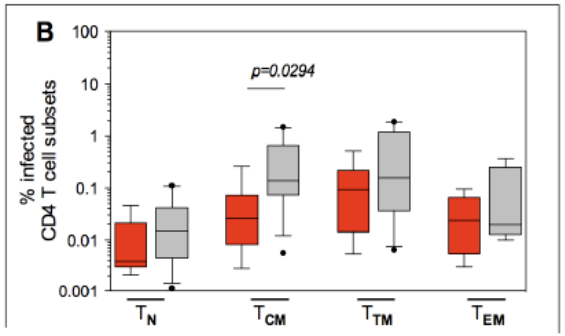
    - **Central-memory (TCM) and Transitional-memoryTTM**
      N Chomont et al; 2009, B Descours et al. 2012, A Saez-Cirion 2013…

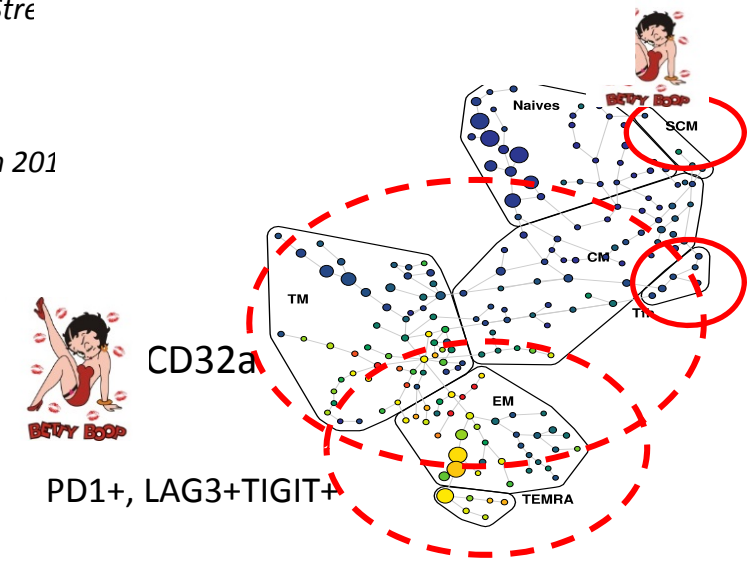
      =70% of the reservoirs

    - **T follicular helper cells (Tfh) :** *J Zaunders 2012, H Stre*
      = 50% of the TCM reservoirs

    - **Stem cell memory CD4 T cells (SCM) :** *M Buzon 201*
      % unknown

    - **PD1+, LAG-3+, TIGIT+ CD4 T cells** :
      R Fromentin, 2016
      = 76% reservoirs
    - **CD32a+ CD4 T cells** *: (B Descours et al. 2017)*
      = 50% reservoirs





CD32a is a marker of a CD4 T-cell HIV reservoir harbouring replication-competent proviruses

Nature 2017

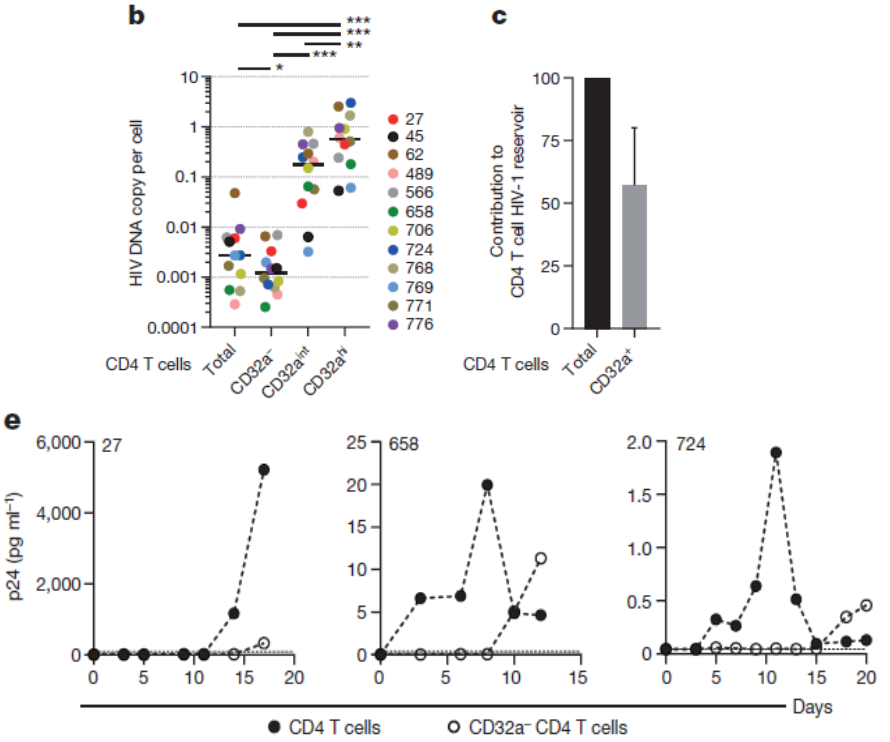
Benjamin Descours[1]*, Gaël Petitjean[1]*, José-Luis López-Zaragoza[2,3,4], Timothée Bruel[2,5], Raoul Raffel[1], Christina Psomas[6], Jacques Reynes[6], Christine Lacabaratz[2,3,4], Yves Levy[2,3,4], Olivier Schwartz[2,5], Jean Daniel Lelievre[2,3,4] & Monsef Benkirane[1]

- **Cells displaying CD32a**

  (a receptor to the Fc of IgG Abs)

  - **Harbor 50% of the HIV reservoirs**

  - **Produce faster and more HIV**



- **Can we use CD32a to target the HIV reservoirs ???**

  Which cells express CD32a:

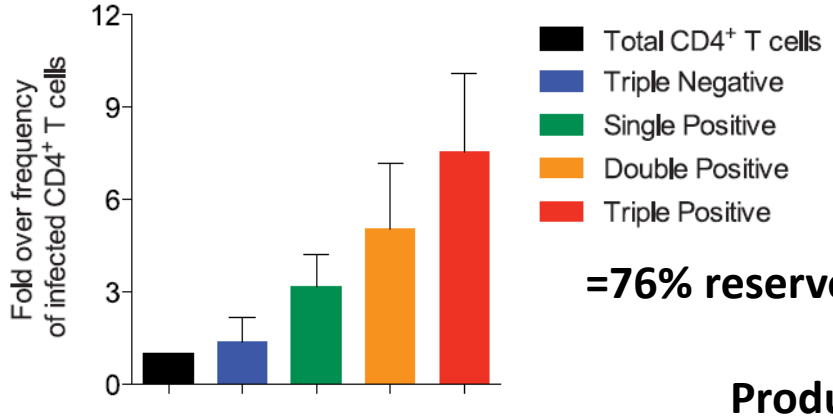
  - 100% of monocytes, macrophages :
    - can we eliminate all ???
  - 1% CD4 T cells = mostly activated mature memory T cells (TEM, TEMRA)

A Corneau et al, unpublished

CD4⁺ T Cells Expressing PD-1, TIGIT and LAG-3 Contribute to HIV Persistence during ART

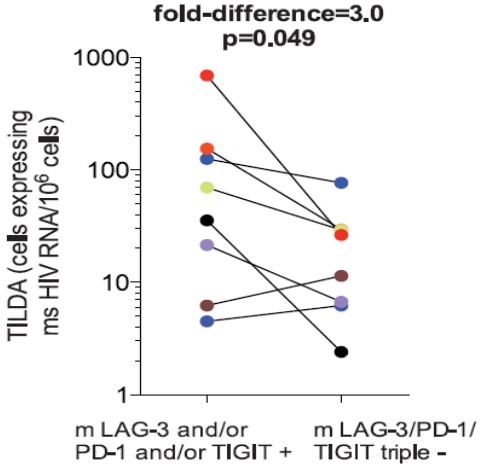
Rémi Fromentin[1], Wendy Bakeman[2], Mariam B. Lawani[2], Gabriela Khoury[3,4], Wendy Hartogensis[5], Sandrina DaFonseca[2], Marisela Killian[6], Lorrie Epling[6], Rebecca Hoh[6], Elizabeth Sinclair[6], Frederick M. Hecht[6], Peter Bacchetti[5], Steven G. Deeks[6], Sharon R. Lewin[3,4], Rafick-Pierre Sékaly[7], Nicolas Chomont[1,2,8]*

PLosPathogens 2016



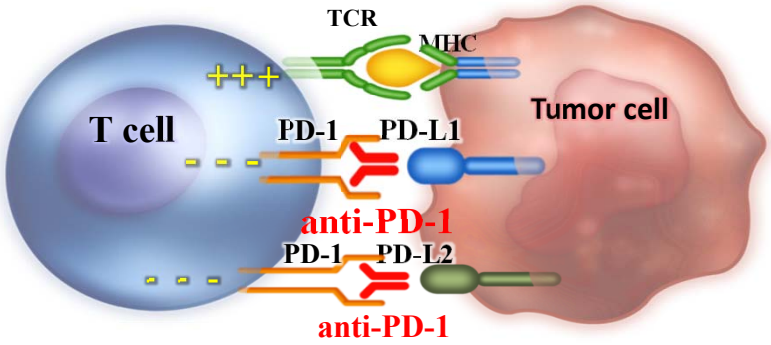
=76% reservoirs

Produce HIV



➢ Why are those findings interesting?

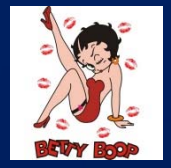
- **PD1, LAG-3, TIGIT … = Immune check points block T cell functions**
- **Monoclonal antibodies against PD-1 :**
  - **antagonize the negative signals induced by PD-1 in exhausted T cells**
  - **Used in Oncology**



Models and Factors of Remission ???

w Reservoirs ?

rong Immunity or eak infection of me key cells ?



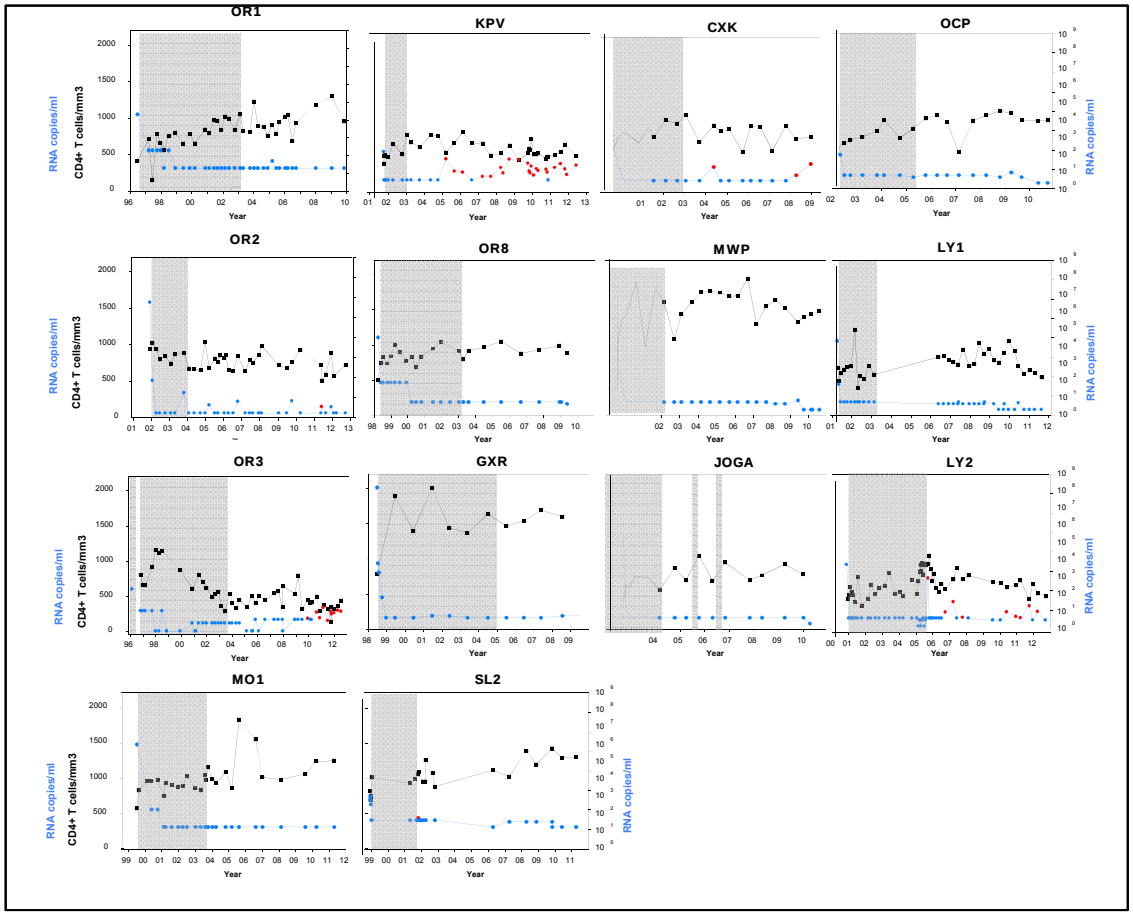
- **Elite Controllers & Long Term Non Progressors**
  - **Infectéed since 12-30 ys, HIV <500, CD4 Nx**
  - **Genetics (HLA-B*57 ou B*27)**
  - **Strong CD4 & CD8 T cells /HIV**
  - **Low infection of some CD4 T cells= TCM if HLA-B*57/27** *(Descours et al. C.I.D. 2012); Klatt et al; PlosPathog. 2014*
- **Post-Treatment Controlers (Visconti)**
  - **Control HIV without ARV for 5-10 yrs after 3-5 yrs ARV at primary infection**
  - **No special genetics (HLA)**

Hoqueloux et al. AIDS 2010, J A C. 2013, Saez-Cirion et al. PLosPathogens, 2013

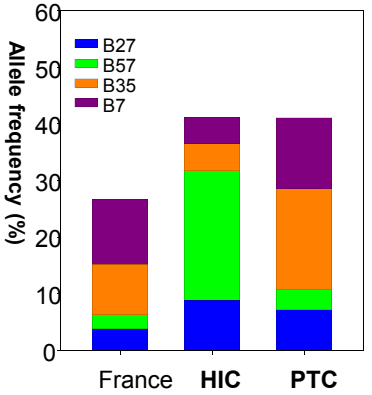
VISCONTI : Post-Treatment Controllers (PTC)

- **Key role of ARV in Primo-Infection:**
- **Reservoirs + low**

- **VISCONTI:**
- **pVL<500cp/ml for 3.5ans,**
  after 3-5 ans ARV in early PHI



- **No protective d'HLA**

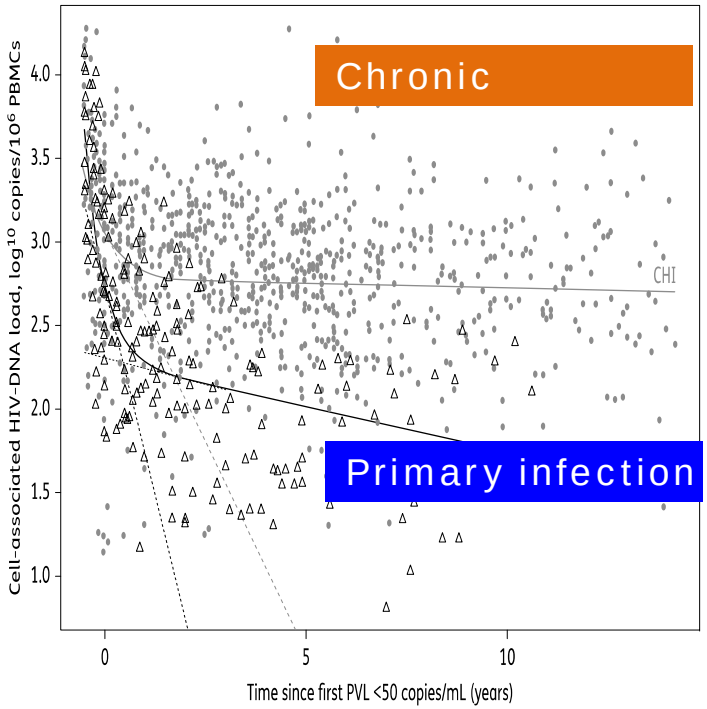


Hoqueloux et al. AIDS 2010,

Saez-Cirion et al. PLosPathogens, 2013

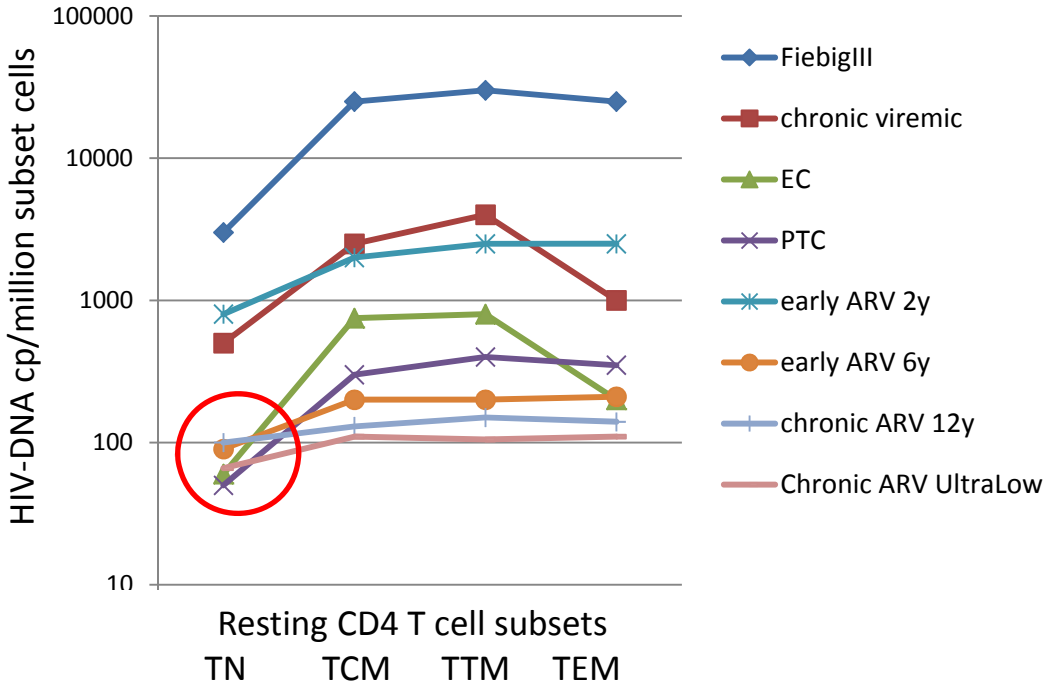
Comparison of HIV reservoirs distribution

Hocqueloux L, et al. J Antimicrob Chemother. 2013



Primary infection
=
- **Lower Reservoirs**
- **More reactive to ARV**

Descours 2012, Bacchus 2013, Saez-Cirion2013, Cheret 2014, Pogliaghi et al. 2014, Chiraz unpublished



- Equivalent distribution of HIV Reservoirs
- **Lowest Reservoirs levels = Late ARV Initiation + long term (≥12 y) ARV** (UltraStop)
- **Models of remission & Long term ARV**

=> Lowest HIV levels in Long lived Naive T cells

Therapeutic Strategies for Cure ?

1) To decrease the HIV reservoirs

below a deadly threshold for the virus

2) **To target the residual cells**

producing HIV with ARV?

3) **To purge the latent reservoirs:**

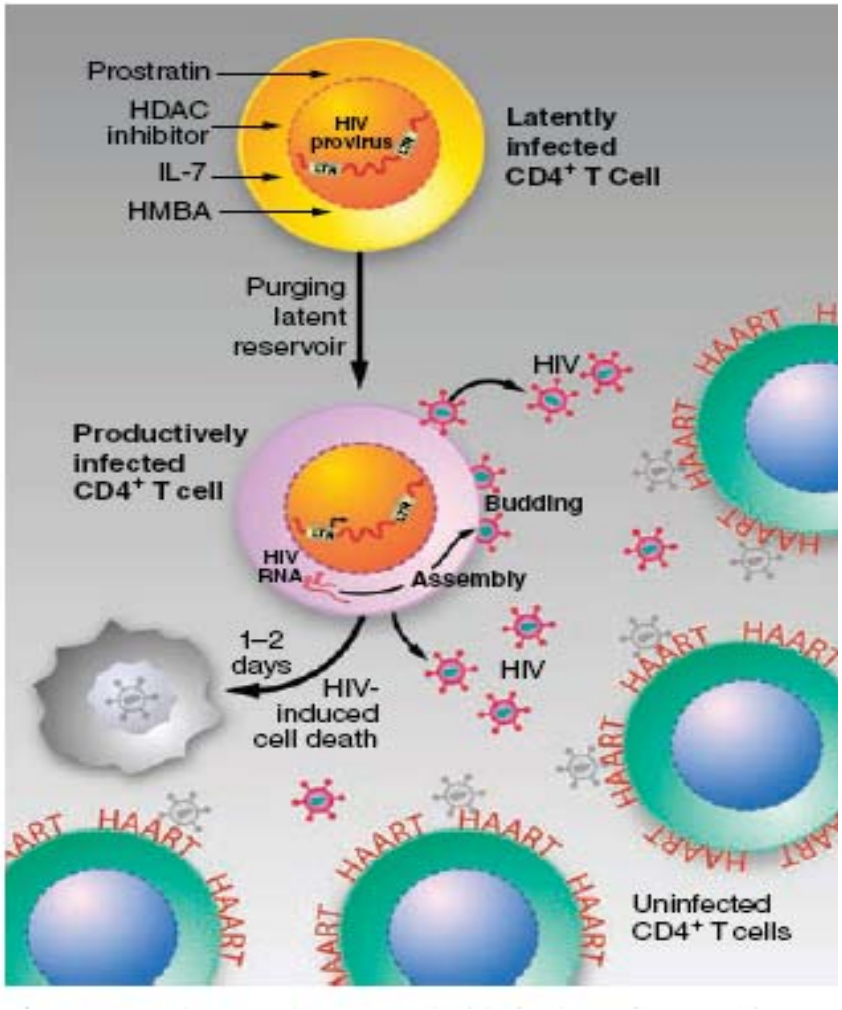
= the shock and kill strategy

combined strateies

4) **To change the host cells**

into HIV-resistant cells:

- **The Berlin patient**
- **Cell & therapy (CCR5-)**

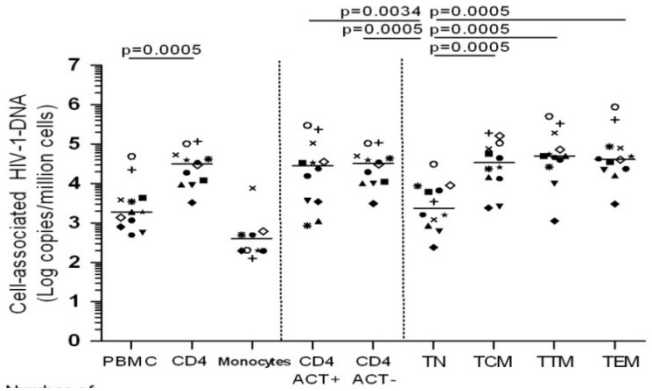


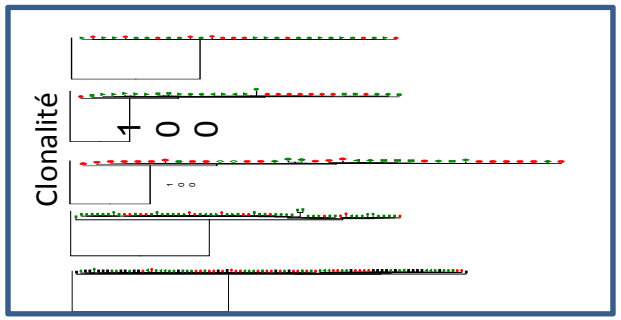
5) To exfiltrate HIV genes from the host genome: the Crispr/Cas 9 strategy : Gene therapy

1) To decrease the HIV reservoirs with early therapy: The Optiprim trial:

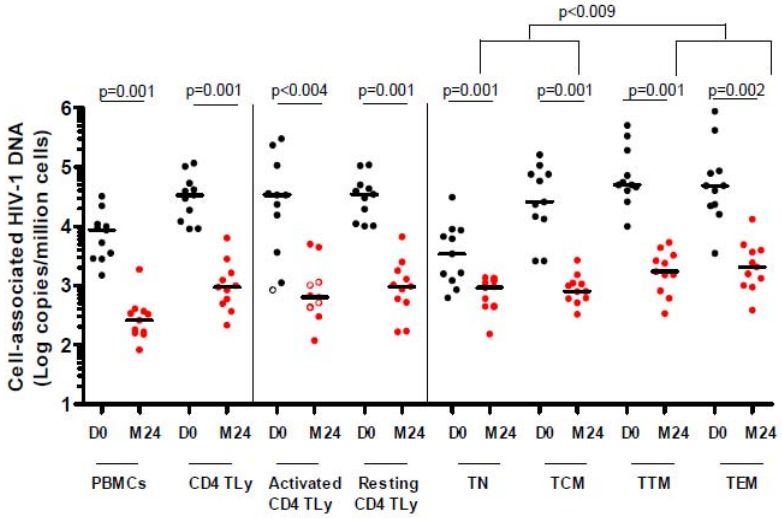
D0= 30days post-infecton : *Bacchus & Chéret et al Plos One 2013*

Reservoirs : immediate clonal and massive diffusion of HIV :
3-5 logs/millions CD4+ cells with long lifespan





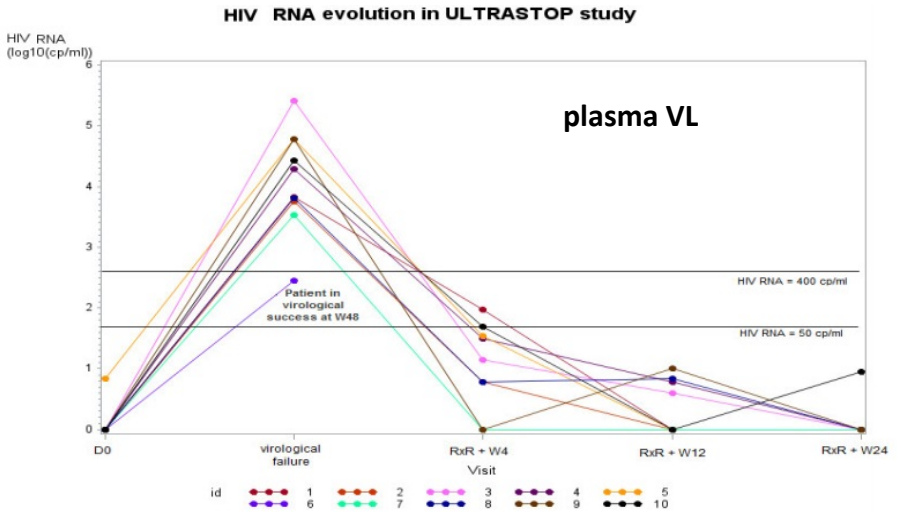
After 2 years of intensified ARV (5 vs 3 drugs) *Chéret & Bacchus et al JAC 2014*

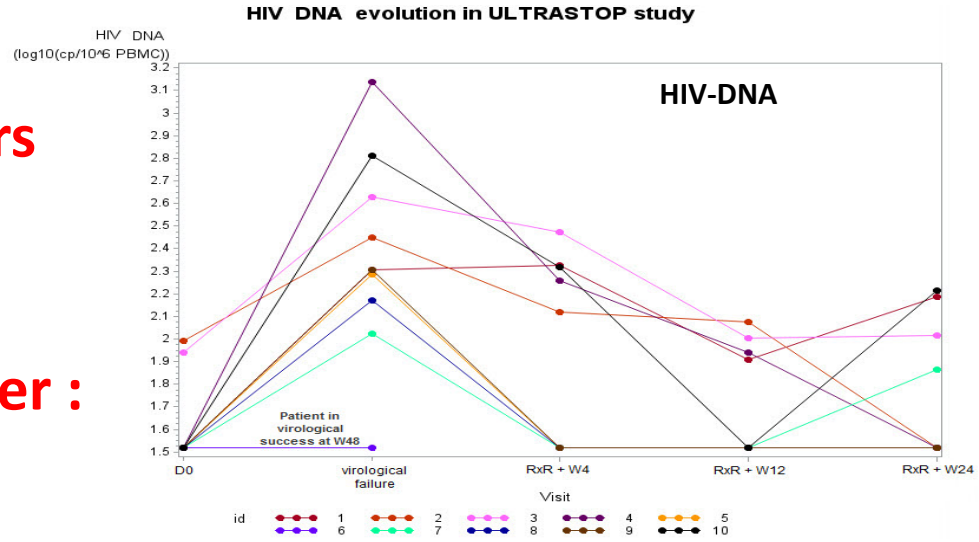


- **Persistence of substantial HIV reservoirs despite a 2 log decrease In long lifespan TCM**

1) To test whether low HIV reservoirs in chronic ARV-treated patients ensure remission: The ULTRA-STOP study (*R Calin, C Hamimi, S Lambert et al AIDS, 2017.)*

- Long term ARV-treated
- Early (Nadir CD4>350)
- Ultra-low HIV reservoirs : at threshold





- **HIV Rebound in 9/10**
- **Rapid Dynamics of HIV reservoirs**
- ***Weak immunity to HIV*.**
- **1 single Post-treatment controller : 12m**

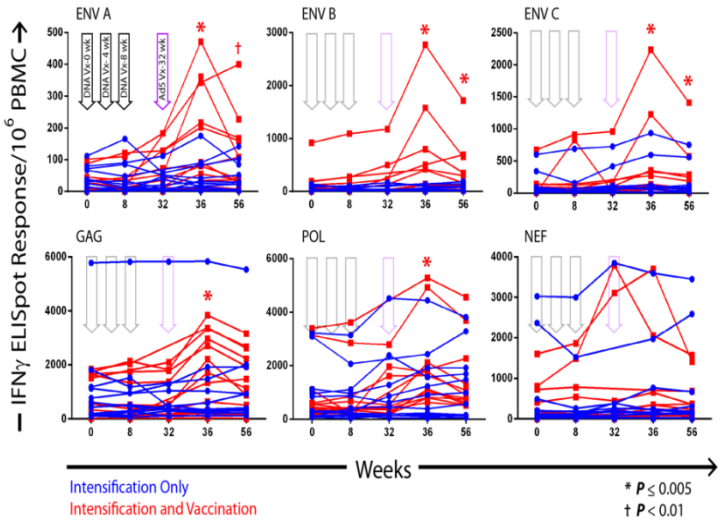
2) **To target the residual cells** producing HIV with ARV + **Therapeutic vaccine? The Eramune-02 study**

C Achenbach et al. Lancet HIV, 2015

- Randomized 2 arms trial in 2 x 15 patients durably suppressed with cART:
  W0: 2 ARV drug intensification +/- Wk8-Wk32 : vaccine immunisation

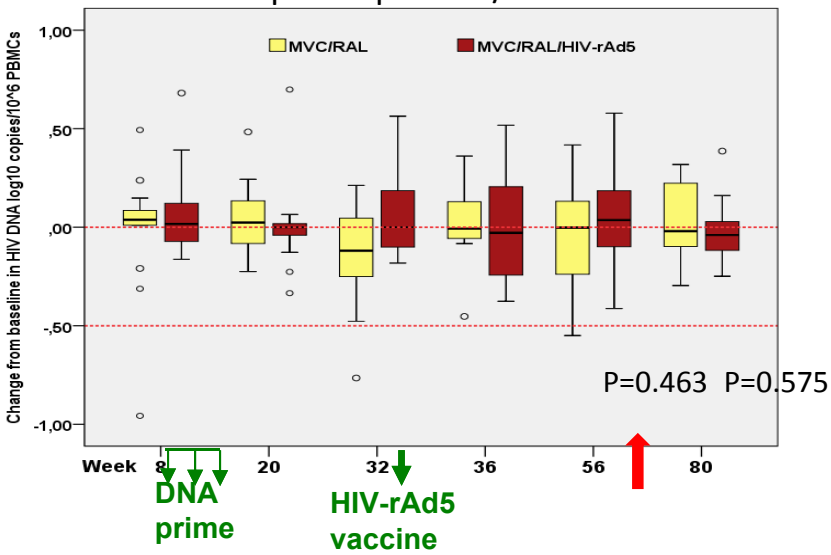
- **Robust induction of HIV-specific T cells**

Ex-vivo Elispot analysis,



- **No change in peripheral HIV reservoirs**

except in 1 patient / 15



Conclusion:

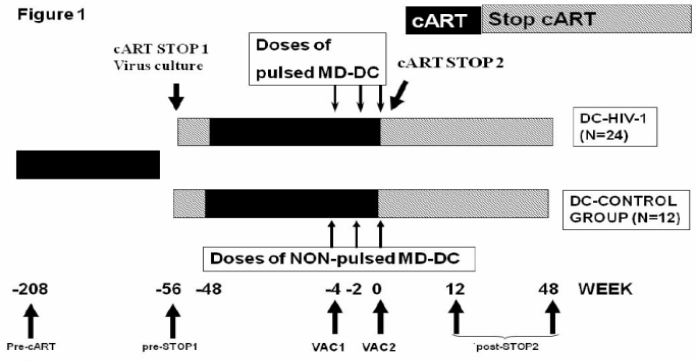
- **VRC vaccine** + intensified ARV did not **decrease HIV reservoirs** despite **strong T cell responses,**
- **Causes ? « *Futility* »?**
  - ***Too low*** *(ARV intensification ?) or* ***inaccessible*** *(Follicular Th cells?)* ***HIV reservoirs*** *?*
  - ***Archived Escape variants*** *in reservoirs?*

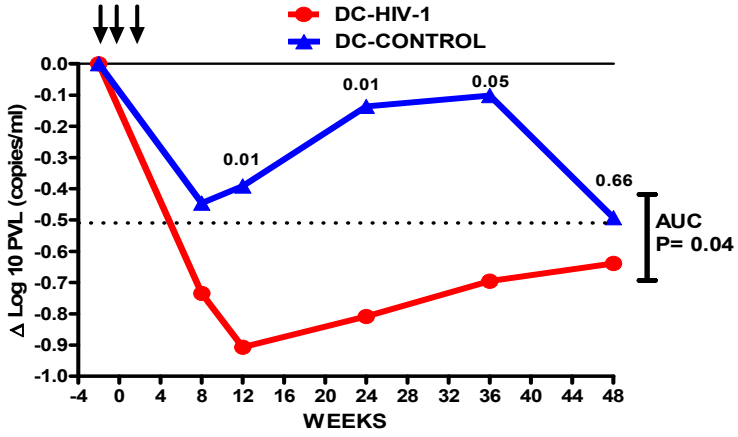
B Autran

HOPE ? Dendritic–cell based Therapeutic Vaccines against HIV:

- **Autologous DC loaded with Inactivated** (ditreithiol or heat) **autologous HIV**

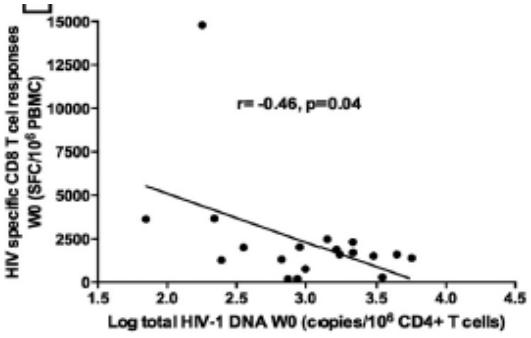
(Garcia et al. J.I.D. 2009, Science Transl. Med. 2012 ; J Virol. 2015)

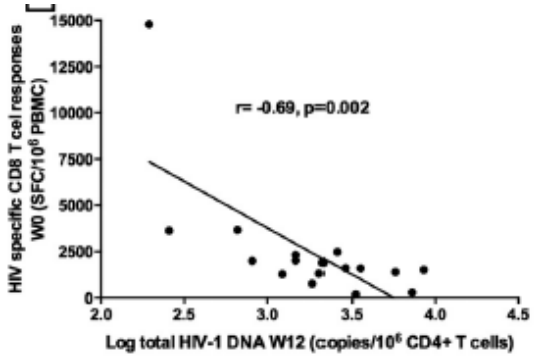




DC-HIV-1	24	23	22	21	20	17
DC-CONTROL	11	11	11	10	9	6

- **Successful induction of anti-HIV CD8 T cells,**
- **Transient control of HIV Production** after stopping cART: *F Garcia et al. Sc Transl. Med. 2013*
- **Lack of control of HIV Reservoirs but HIV-specific CD8 T cells correlate with the reservoir size** pre- and post –vaccination : *Andres et al. J Virol. 2015*





ORVACS

3) Combined strategies to purge the HIV reservoirs

1- to re-activate HIV

in latently infected cells :

- **HDAC Inhibitors ?** Failure of all trials,
- **IL-7?**

  Failure of the Eramune-01 trial *(Katlama et al. AIDS 2016)*
- Adjuvants ?
- **Immune check point inhibitors ?**

2- to target HIV producing cells

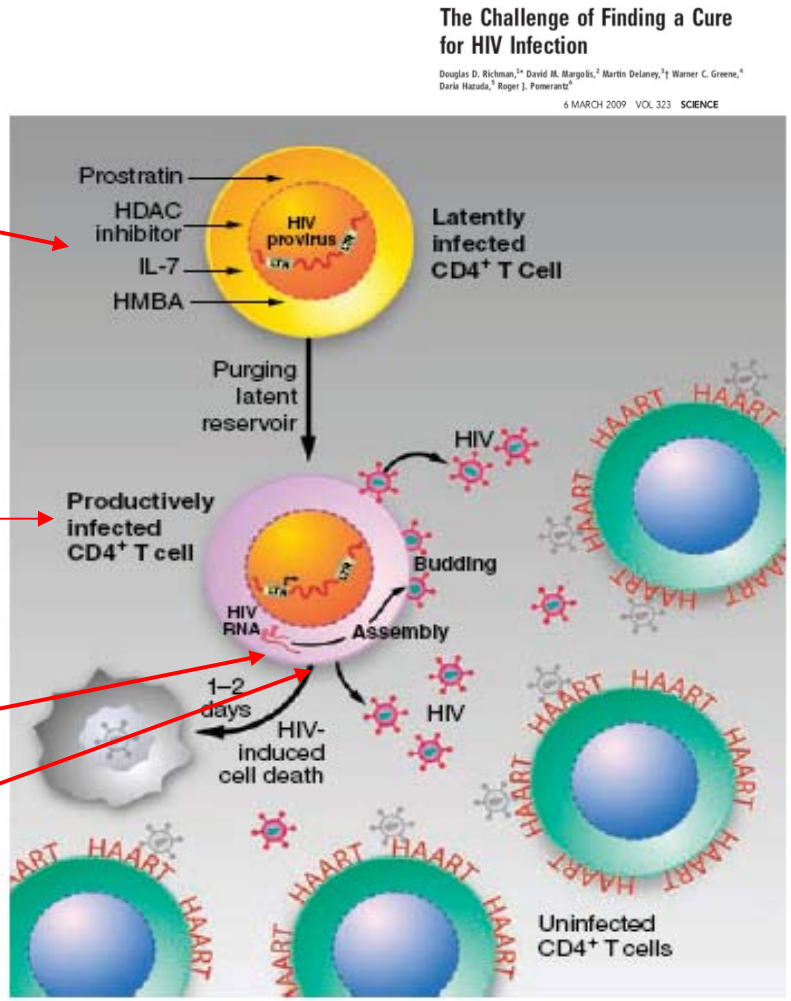
to limit residual virus spreading

- **Therapeutic vaccines**

  inducing ***CTLs ?***

  Abs ???
- **Therapeutic Antibodies ?**

  Broadly Neutralizing Abs?



- **For functional cure of HIV**

Can Therapeutic vaccines synergize with anti-latency agents?

- ***In vitro* combination of:**
  - **HIV re-activation** with : HDAC-Inh (**SAHA**),
  - **CD8 T cells Stimulation** with **HIV peptides**
  - **Co-culture of CD4+CD8 T cells**

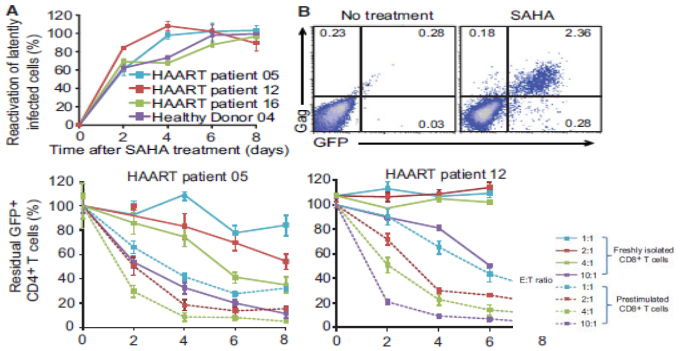
- ***1st HIV re-activation in vivo* :**
  - **IL-7** *(Katlama et al. AIDS 2015 in press)*
  - **1st HDAC-Inh phase I/II trials :**
    - SAHA*: Archin, Nature 2013; Lewin 2014:*
      = Little efficacy
    - **Romidepsin***: Sogaard, AIDS 2014*
      = **Detectable HIV re-activation**

  - **which Vaccine ?**
    - **HIV-specific CD4 T cells ?**
      - Multiple HIV-Gag conserved peptides to be combined with Romidepsin
    - **CD8 T Cells + CD4 T cells ?**
    - **Antibodies ?**
    - **Both ???**

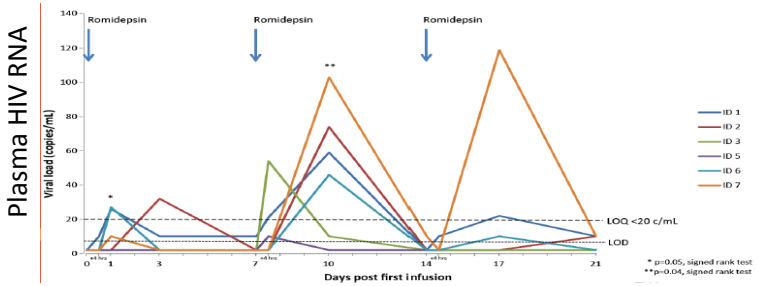
Stimulation of HIV-1-Specific Cytolytic T Lymphocytes Facilitates Elimination of Latent Viral Reservoir after Virus Reactivation

Immunity *36*, 491–501, March 23, 2012

Liang Shan,[1,2] Kai Deng,[1] Neeta S. Shroff,[1] Christine M. Durand,[1] S. Alireza. Rabi,[1] Hung-Chih Yang,[3] Hao Zhang,[4] Joseph B. Margolick,[4] Joel N. Blankson,[1] and Robert F. Siliciano[1,5,*]



Romidepsin trial, Sogaard et al.



Vac4x,

Pollard et al. Lancet ID, 2014

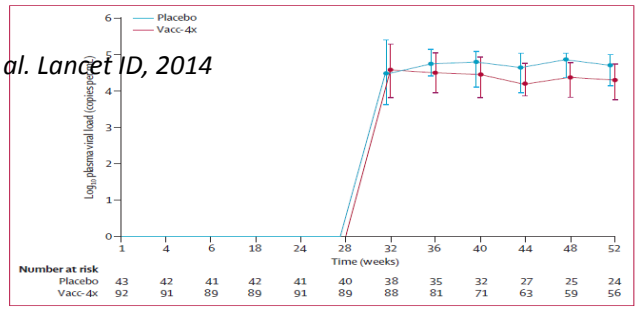


Figure 3: Viral load over time in the intention-to-treat population

VIRAL CONTROL INDUCED BY HIVCONSV VACCINES & ROMIDEPSIN IN EARLY TREATED INDIVIDUALS

Beatriz Mothe[1], José Moltó[2], Christian Manzardo[3], Josep Coll[1], Maria C. Puertas[1], Javier Martinez-Picado[1], Tomas Hanke[4], Bonaventura Clotet[1], Christian Brander[1], Romi Study Group

[1]IrsiCaixa AIDS Rsr Inst, Badalona, Spain, [2]Fundació Lluita Contra la Sida, Badalona, Spain, [3]Univ of Barcelona, Barcelona, Spain, [4]The Jenner Inst, Oxford, UK

CROI 2017

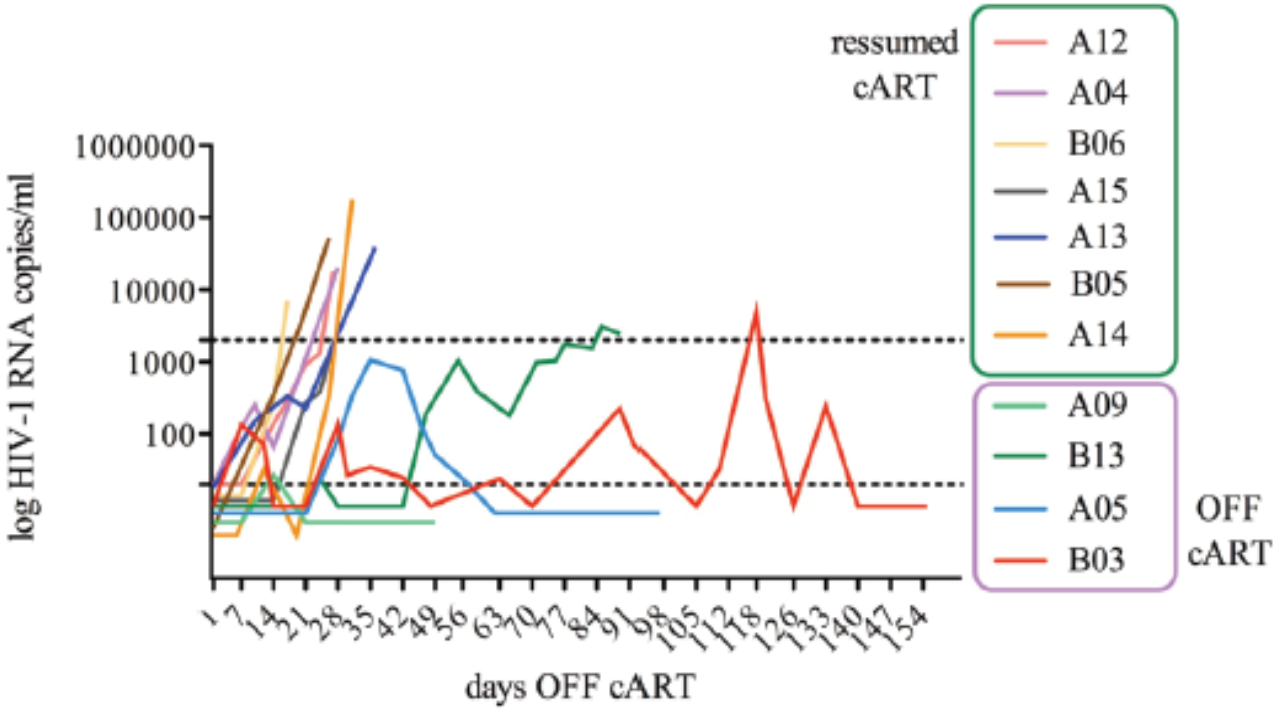
Hope ?

Vaccine: MVA-HIVconsv (2x10>8pfu) + Romidepsin (HDAC Inhib.) 1/wkx3 + MVA-HIVconsv.

Patients: 15 long term ARV-treated with controlled viremia.
Treatment interruption post-immunisation

- Viremia detectable in all patients
- Increase in HIV-specific T cells
- **11 patients stop ARV:**
  - **7 resumed at M+1**
  - **4 off ARV 7- 22 wks**

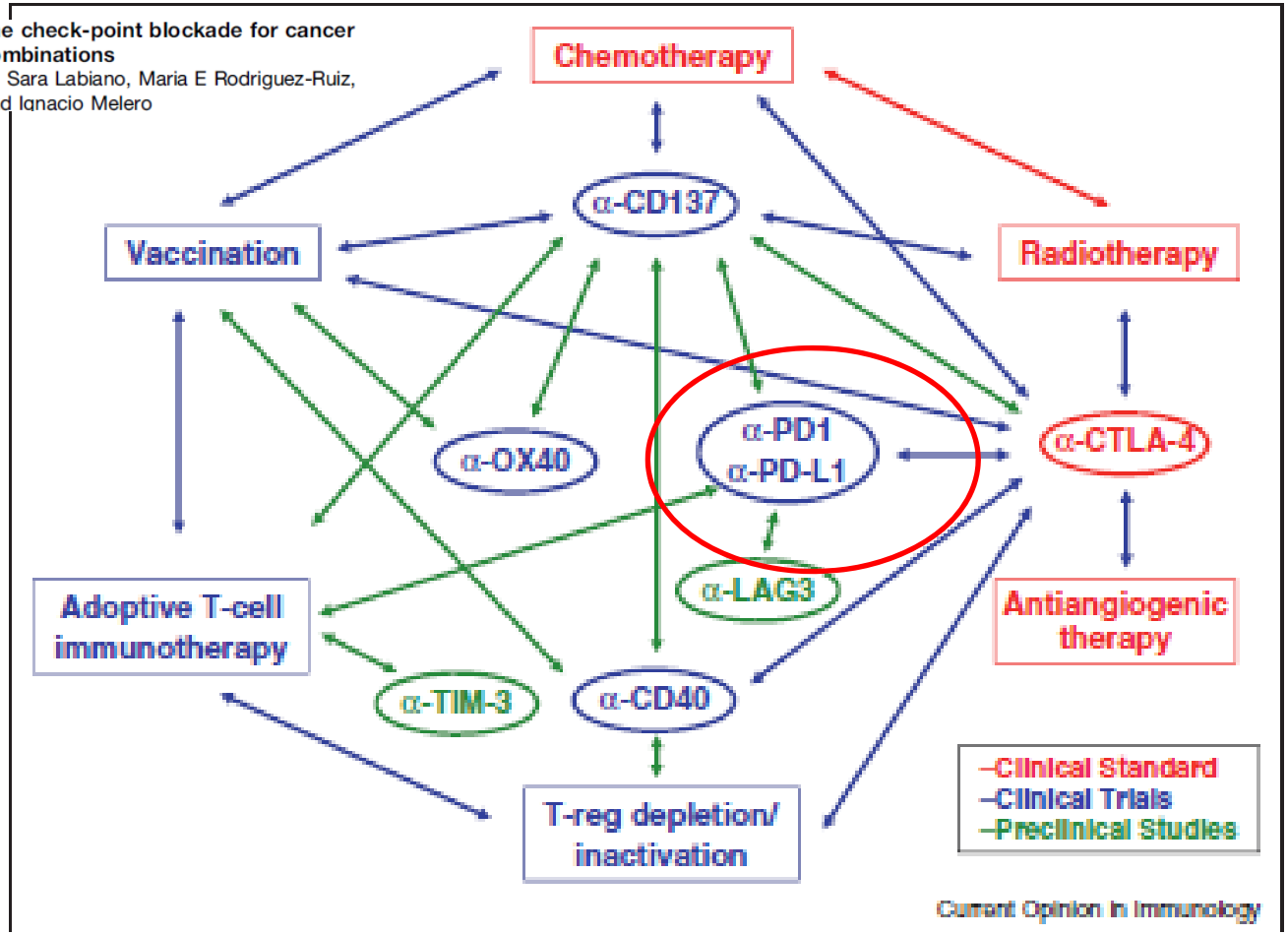
  But no control group



Can blocking Immune check-points help purging the HIV reservoirs ?

A strategy derived from the cancer field

Orchestrating immune check-point blockade for cancer immunotherapy in combinations
Jose Luis Perez-Gracia, Sara Labiano, Maria E Rodriguez-Ruiz, Miguel F Sanmamed and Ignacio Melero



Curr Opin 2014

Development status of immunostimulatory monoclonal antibodies and their combinations. Monotherapies as circles surrounding the name of the antibody target and combinations as arrows connecting the targets are color coded for the developmental preclinical or clinical status. This figure is an update from Ref. [4] published in 2007.

Anti-PD1 therapy in HIV+ patients with cancer

➢ Monoclonal antibodies against the PD-1 axis :

- Antagonize the negative signals induced by PD-1 in exhausted T cells

- **The new standard of care for NSCLC** *(Brahmer 2015, Herbst 2016)*

  by enhancing anti-tumor T cell activity

  but no published data on anti-tumor efficacy in PLWHA (excluded from clinical trials)

- **Restore exhausted anti-HIV T cell activity :**
  - ***in vitro*** *(Trautmann, 2006; Day 2006)*
  - ***in vivo : one case report*** *(Le Garff, AIDS 2017)* but still few data available

- **Proposed as a strategy to purge latent HIV reservoirs** *(Katlama, 2013)*
  - **enriched in PD1+ CD4+ T cells** *(Fromentin 2016)*
  - although **CD4+CD32+ cells not enriched in PD1+ cells :**

    while enriched in Tim3+ cells*(Corneau et al. Ms in prep.)*

A 1st series of anti-PD1 usage in HIV+ patients from the CANCERVIH network

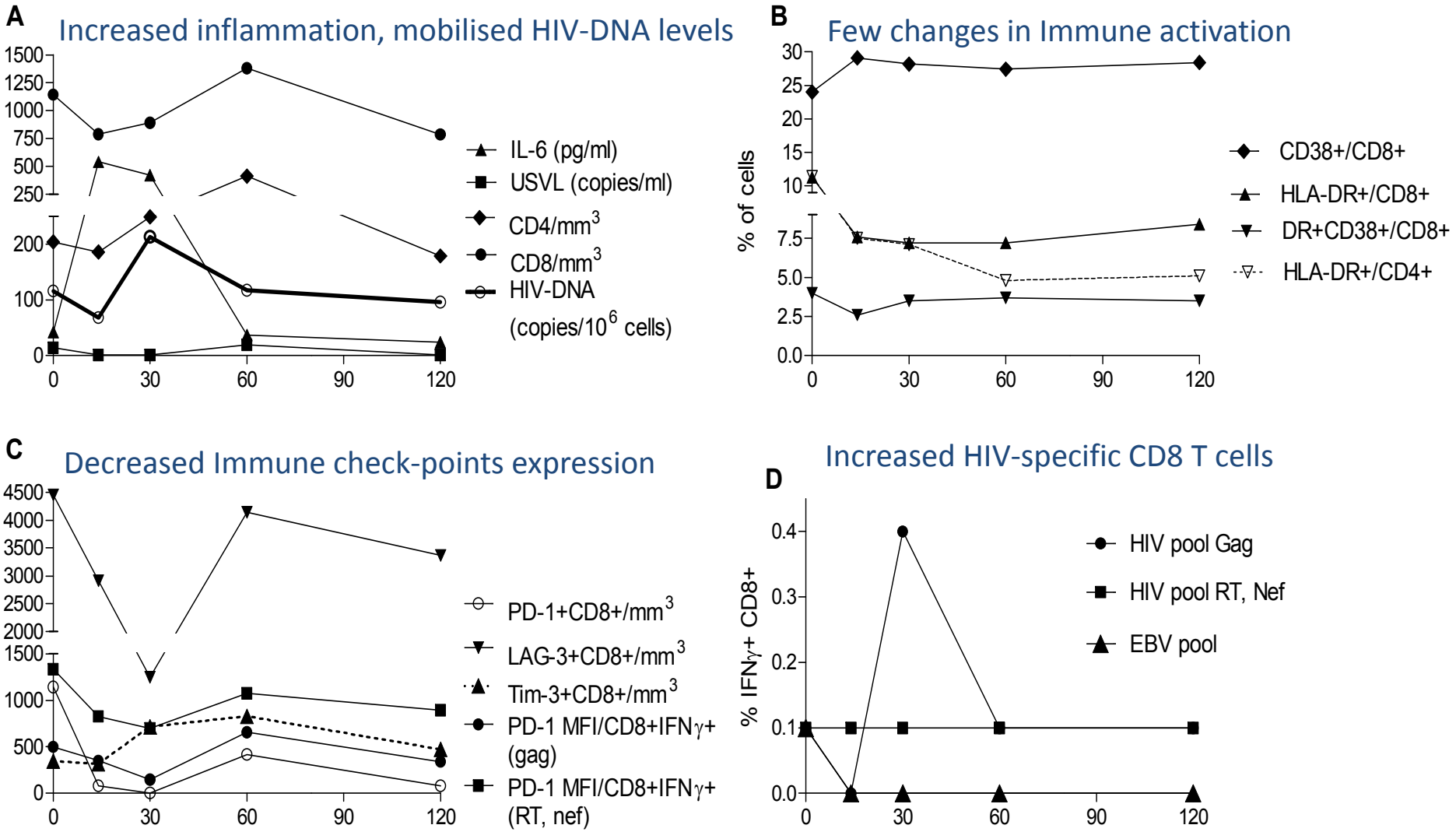
- **Non small cell lung cancers (NSCLC) in HIV+ patients :**
  - The most common non-AIDS-related malignancy ;
  - Chemotherapy : poor efficacy and higher toxicity than in the general population
  - Leading cause of cancer-related death in PLWHA *(Spano Ann Oncol 2016)*

- **CANCERVIH: A national French multidisciplinary network dedicated to PLWHA with cancer**
  - Coordinated by Pr JP Spano, Pitié-Salpétrière, Paris, France
  - Funded by the French national cancer institute (Inca)
  - CANCERVIH recommendation: to discuss all new cases of PLWHAs with cancer

- **Data from 12 HIV+ patients treated for NSCLC by anti-PD1 mAb** (Nivolumab)
  - extracted from a prospective CANCERVIH cohort of 270 HIV+ patients with cancer
  - allow evaluating:
    - **Immunological and Immune Tolerance of anti-PD1 in HIV-infected patients**
    - ***In vivo* effects on anti-HIV immunity and HIV reservoirs**

A Guihot et al. , Towards an HIV Cure 2017; IAS 2017

Transient restoration of HIV-specific T cells and peak of inflammation after anti-PD-1 therapy in Patient #1 *(G. Le Garff et al., AIDS 2017)*



Conclusion : Effects of anti-PD1 in a series of 12 PLWHA treated for NSCLC

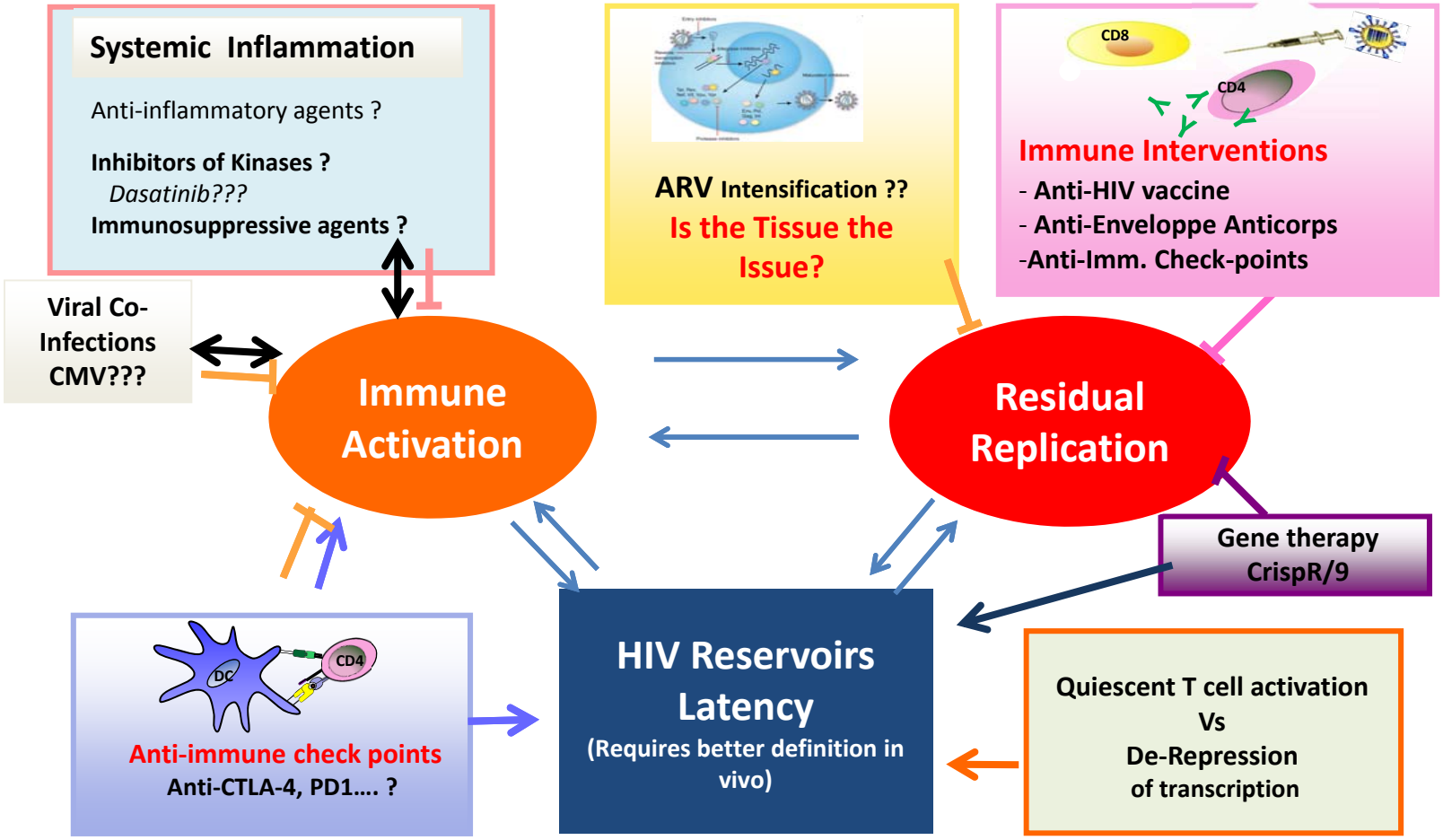
- **Clinical outcome** : some efficacy in 6/12 patients, as in the general population

- **Tolerance** :
  - **Few clinical side effects** except 1 neurosyphilis and 1 hepatitis re-activation
  - Transient **increase** of **Inflammation** or **immune activation** after 1 injection
  - **No changes of plasma HIV viral load nor CD4 or CD8 cell counts**

- **Comprehensive Immuno-virological analysis in 2 patients :**
  - **Transient increase in HIV-specific CD8 T cells** after 1 or 2 injections, with **decrease in immune check points** expression on **CD4 & CD8 T cells**
  - **Effects on HIV Reservoirs ?**
    - Transient weak mobilisation of HIV-DNA levels in PBMcs from one patient,
    - **Drastic decrease of the total HIV-DNA levels** for another patient (more investigations in progress)
      - **open the way for future HIV cure therapeutic strategies**

Conclusions

- **The lack of frequent Remission despite Ultra-Low Reservoirs in the ULTRASTOP study:**
  - **Indicate a Low, even replication uncompetent, Reservoir is NOT enough**
  - **Impose Supplementary Strategies for Remission : What's next ??**

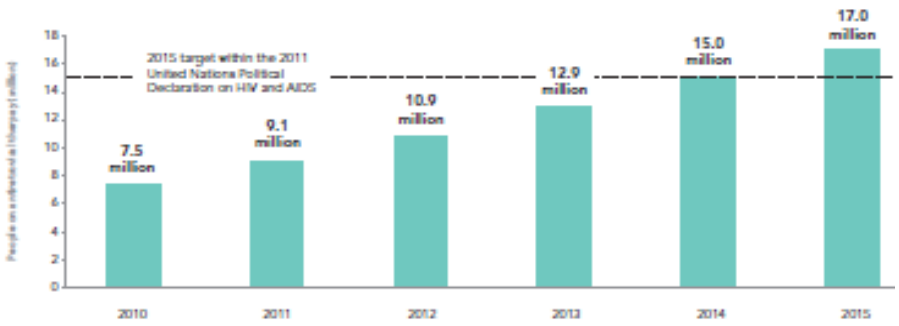


from C Katlama et al. Lancet 2013

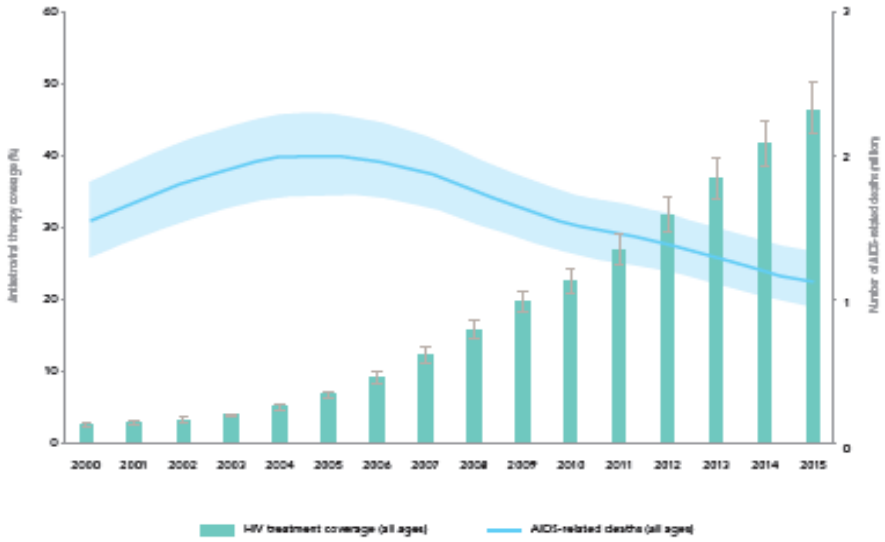
Success of ARV-based HIV Prevention strategies … But no vaccine yet

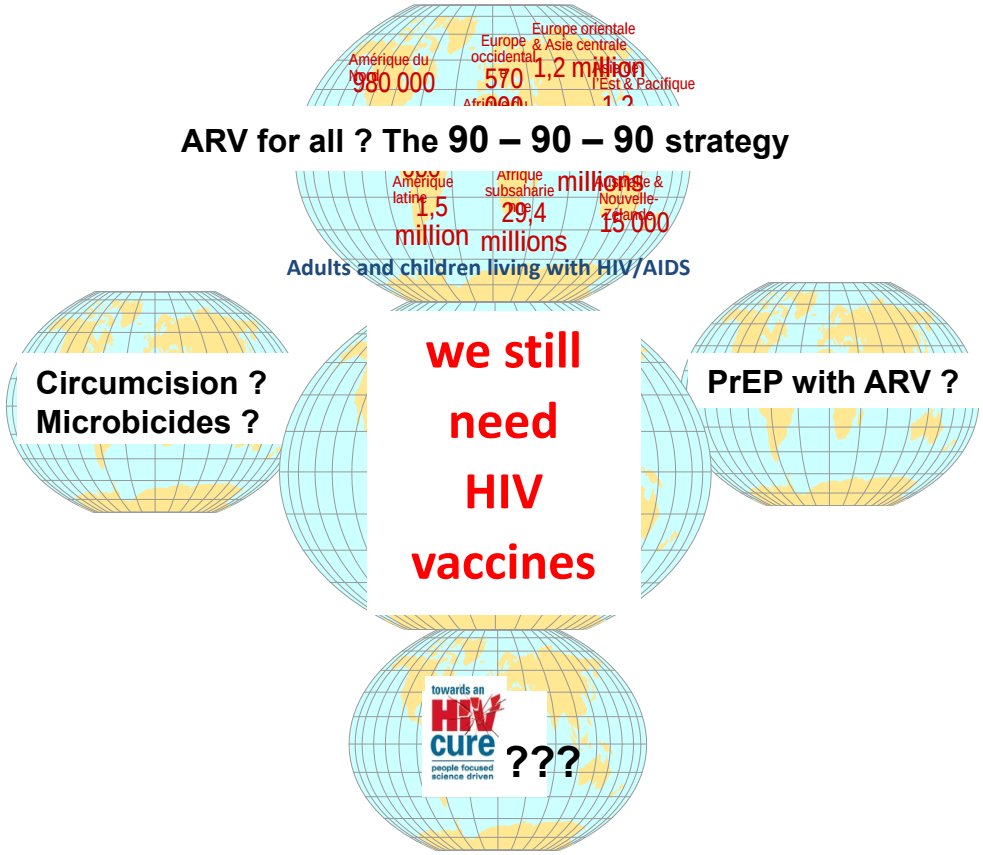
Global UNAIDS 2016 Statistics :

Number of people living with HIV on antiretroviral therapy, global, 2010–2015



Antiretroviral therapy coverage and number of AIDS-related deaths, global, 2000–2015

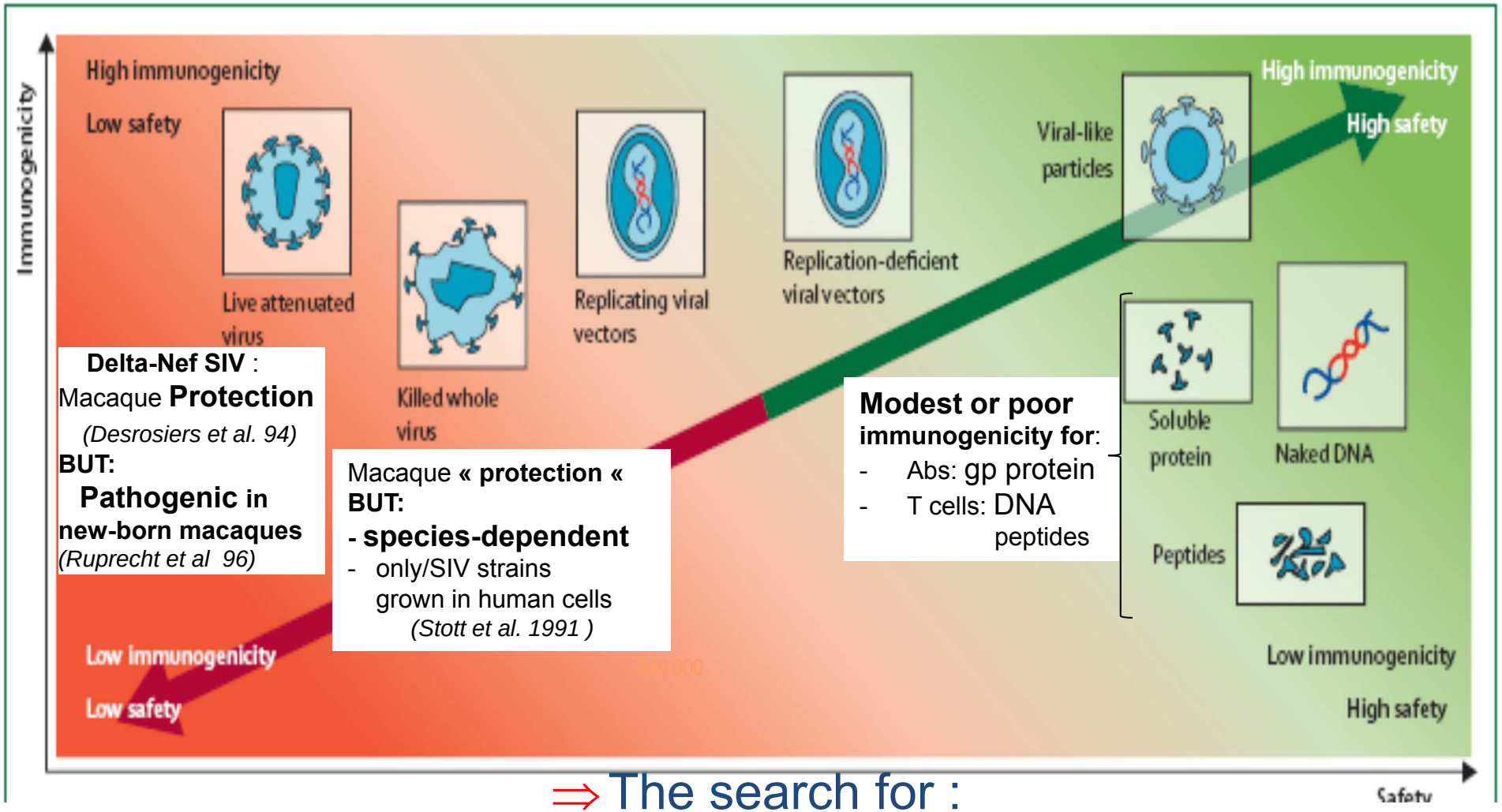




Progress towards development of an HIV vaccine

from

Anna Laura Ross, Andreas Bråve, Gabriella Scarlatti, Amapola Manrique, Luigi Buonaguro *Lancet, 2009*

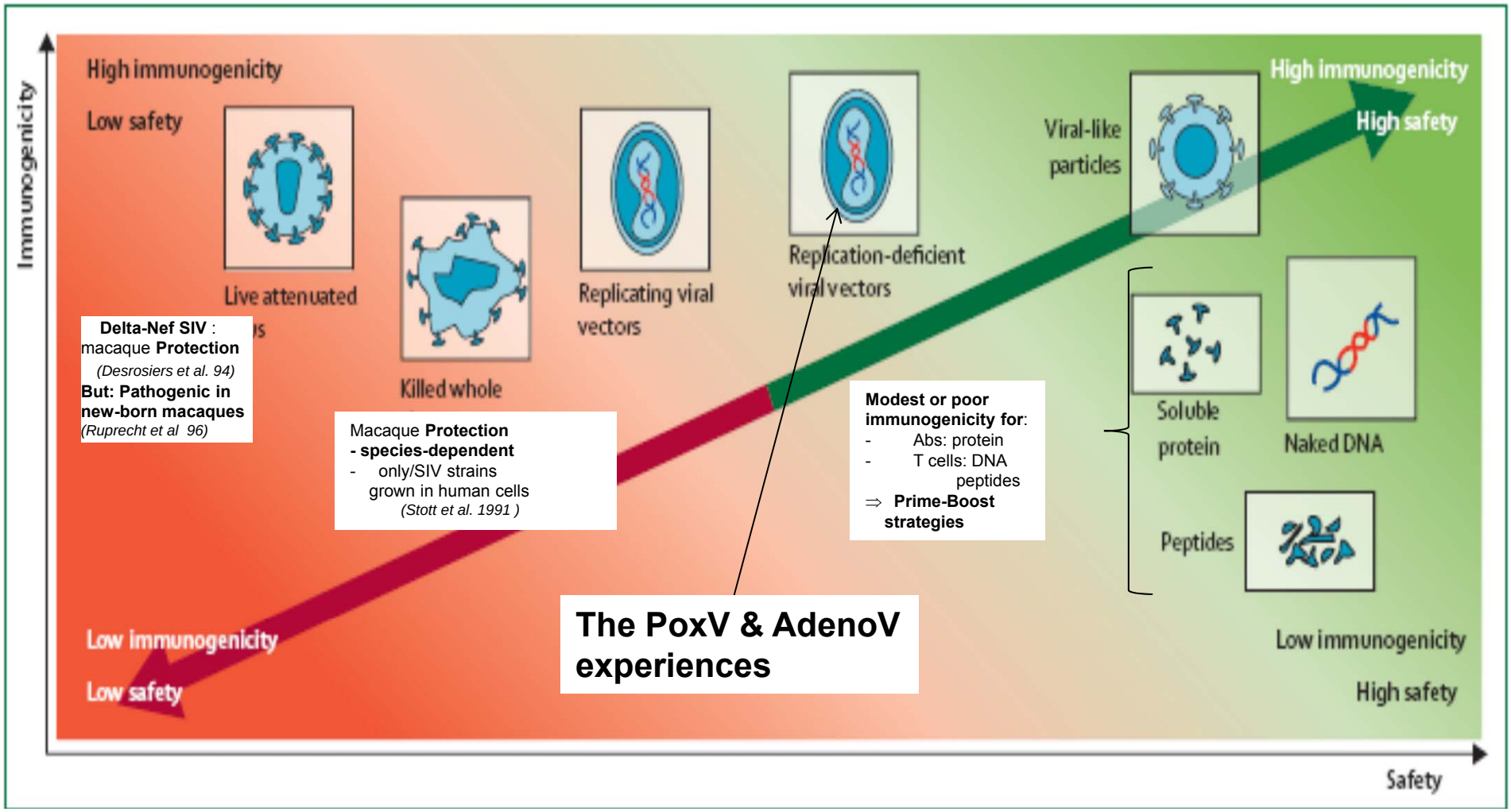


⇒ The search for :

- Prime-Boost strategies
  - a T cell based HIV vaccine

Progress towards development of an HIV vaccine

Anna Laura Ross, Andreas Bräve, Gabriella Scarlatti, Amapola Manrique, Luigi Buonaguro *Lancet, 2009*



⇒ The search for :

a T cell based HIV vaccine

the Step Study

A Phase II Test-of-Concept Trial of the MRKAd5 HIV-1 Gag/Pol/Nef Trivalent Vaccine

(Merck V520 Protocol 023/HVTN 502)

S Buchbinder et al. Lancet 2008

Trial Design

- 3000 high-risk HIV uninfected men and women
  - Initial study: 1500 pts w/ Ad5 NAb ≤200 (Dec 2004)
  - Modification: additional 1500 w/ Ad5 NAb >200 (July 2005)
  - Randomization stratified by Ad5 ≤18, 19-200, 201-1000, >1000

Primary hypotheses: Ad5 ≤200 subset

- Decrease in HIV acquisition and/or
- Lower viral load setpoint (~3 months post-diagnosis)

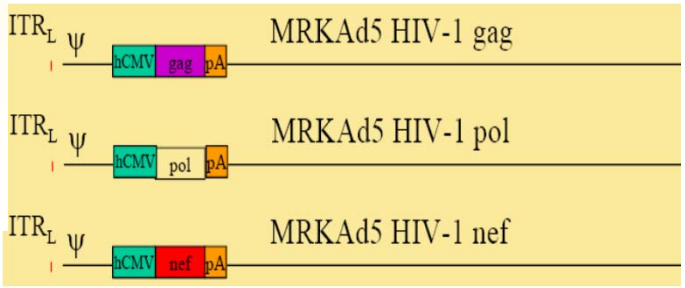
Secondary hypotheses: Total population

- Same as primary (Ad5 ≤200 and Ad5 >200 combined)

Vaccine: 1:1:1 admixture of 3 Ad5 vectors

- Encoded transgenes: codon-optimized, near-consensus clade B HIV-1 sequences

Placebo: vaccine dilution buffer without Ad5



the Step Study

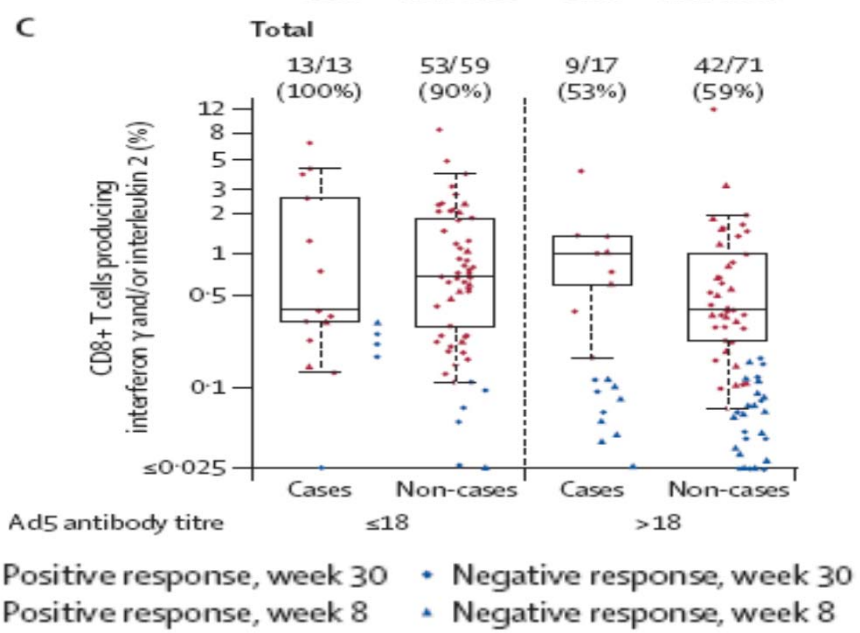
S Buchbinder et al. thelancet.com Vol 372 November 29, 2008

- **DSMB: Definitive arrest of the trial**
  - **Increased frequency of HIV infections**

    in Vaccinees vs Placebo

Increased risk of HIV infection is most evident in uncircumcised men with pre-existing Ad5 immunity [estimated vaccine HRs 4.2 to 4.8].

  - **No reduction in Viral Load after HIV infection**



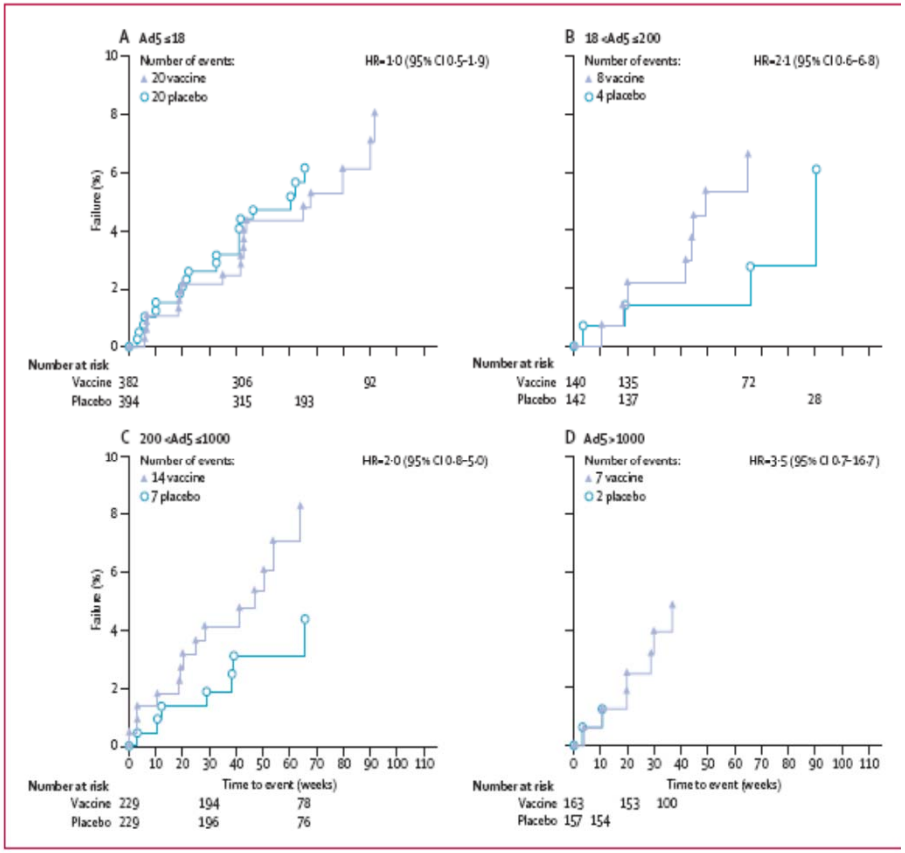


Figure 2: Kaplan-Meier plots of HIV infection for male vaccine and placebo groups by baseline Ad5 antibody titre ≤18 (A); baseline Ad5 antibody titre between >18 and ≤200 (B); baseline Ad5 antibody titre between >200 and ≤1000 (C); and baseline Ad5 antibody titre >1000 (D)
Each hazard ratio (HR) is from a univariate Cox regression model.

- **Effect of pre-existing Abs / Ad5?**
- **No differences in vaccine immunogenic between Cases and Non Cases**

N Engl J Med. 2009 Nov 9

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; the MOPH–TAVEG Investigators.

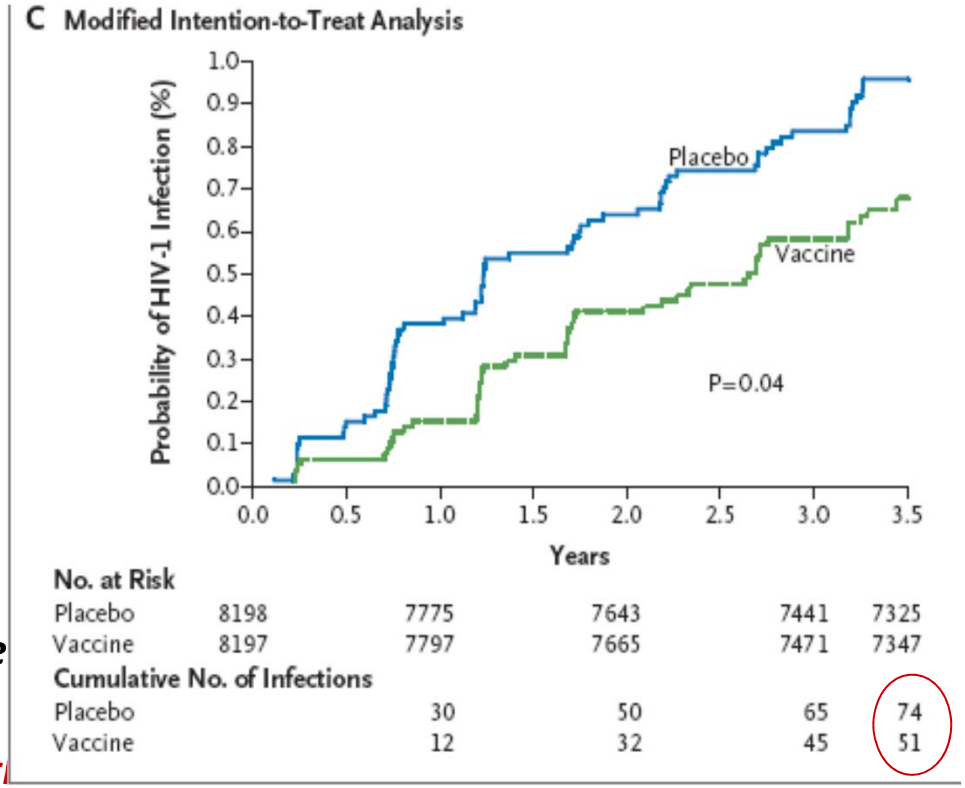
- Study Design :
  - A randomized, multicenter, double-blind, placebo-controlled efficacy trial,
    - in **16,402** healthy men and women 18 and 30 years
    - primarily at **heterosexual risk** for HIV infection,
  - 4 priming injections of a **recombinant canarypox vector vaccine** (ALVAC-HIV [vCP1521])
  - 2 booster injections of a **recombinant glycoprotein 120** vaccine (AIDSVAX B/E).
  - Coprimary end points: at 6-month post vaccinations and every 6 months for 3 years.
    - **HIV-1 infection** and
    - **early HIV-1 viremia**,

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand.

A modest but significant benefit :

- RESULTS:
  - Intention-to-treat analysis:
    - vaccine efficacy: 26.4% (p=0.08).
  - **Modified intention-to-treat analysis:**
    - excluding 7 subjects HIV+ at baseline,
    - **vaccine efficacy :**

      31.2% (P=0.04).



- CONCLUSIONS:

  « ***This ALVAC-HIV and AIDSVAX B/E vaccine re***

  - ➢ ***may reduce the risk of HIV infection***
  - ➢ ***in a community-based population wit***
  - But: Vaccination did not affect the viral load or CD4+ count after HIV infection
    Immune correlates of protection ??? (Neut Abs?, IFN-g producing T cells?)

Post RV144 HIV vaccine programme :

- The single cell antibody cloning approach :
  - **Discovery of Human Broadly Neutralizing Antibodies**

- ✓ **Neutralize x clades**

  at low concentations (<1ng/ml)

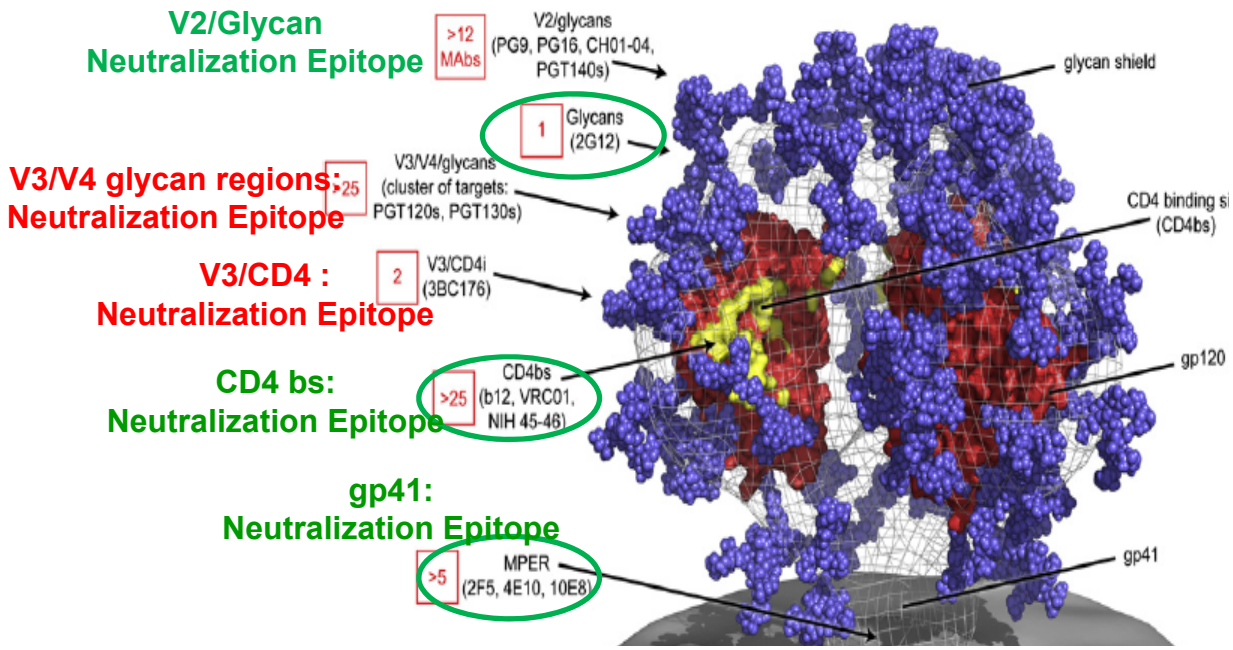
- ✓ **far broader than prior NAbs:**

  Tier 1, 2 and 3 bNAbs

- ✓ **Frequent**

  Tier 3: 1% Elite Neutralizers

  Tier 2: 20% HIV+ subjects



But

- **late** (> 0.5-3 years), and **in viremic patients : not correlated to disease protection**

- **Complex structure : Require long maturation (somatic hypermutations [SHM] + rare structural motifs as a result of chronic B cell stimulation by successive HIV variants**

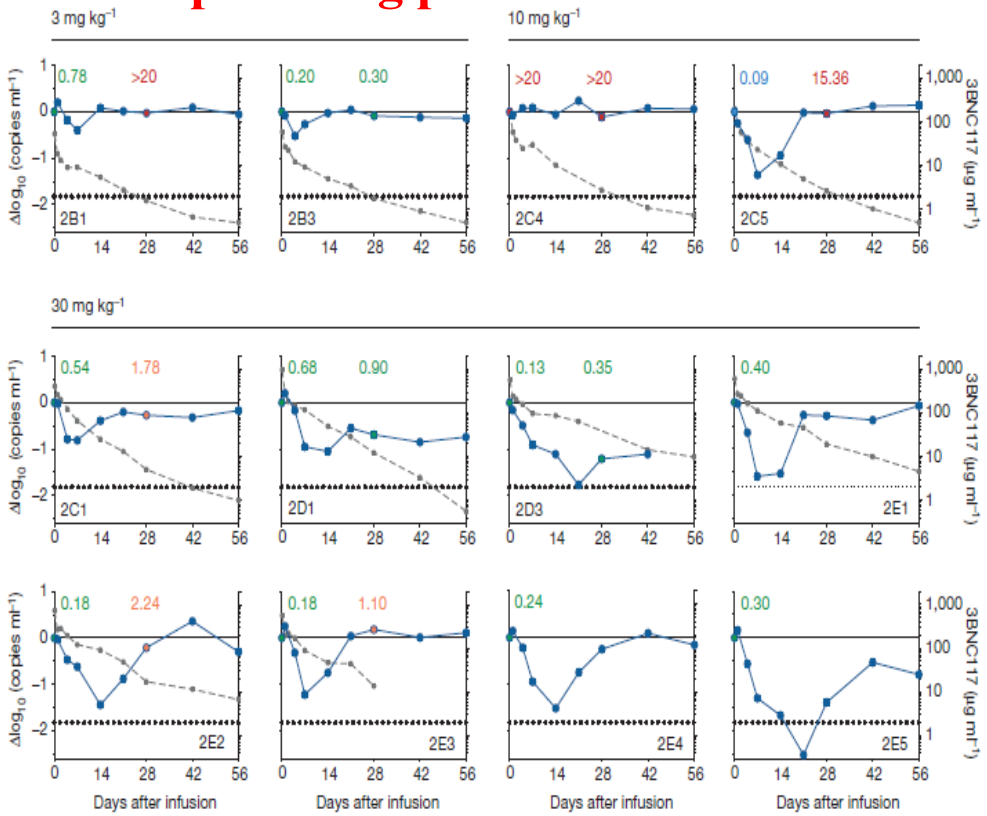
  (request multiple rounds of germinal center selection and hundreds of cell division cycles…)

BA utran

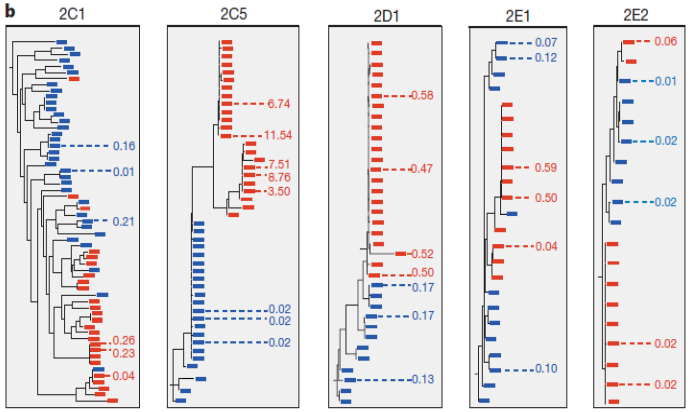
Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117

Caskey et al. Nature 2015

- **Passive transfers of Neutralizing Abs:**
  - 1st clinical trial
  - **Escalating dose**
  - **Up to 2-log plasma HIV load reduction**



	Uninfected (n = 12)	HIV-1-infected (n = 17)
Gender (% male)	83%	76%
Mean age (range)	43 (22–58)	37 (20–54)
Race/ethnicity		
White	42%	29%
Black or African American	50%	53%
Hispanic	8%	18%
ART status		
On ART n (%)	–	2 (12%)
Off ART n (%)	–	15 (88%)
Mean absolute CD4$^+$ count (cells μl^{-1}; day 0)	–	655 (245–1,129)
Mean % CD4$^+$ count (day 0)	–	29% (20–42%)
Mean HIV-1 RNA level (copies ml^{-1}; day 0)*	–	9,420 (640–53,470)



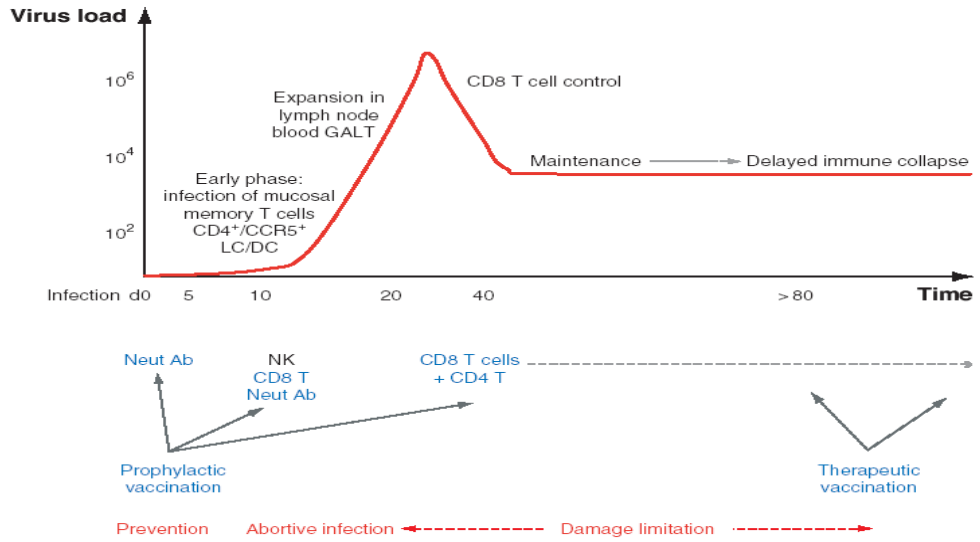
- **Transient effect**
- **Selection of mutants**

- **Very Encouraging**

BAutran

The search for an anti-HIV Vaccine:

The combined Ab +:CD8 T cells approach:



Main Stakeholders :

- NIAID, VRC and HVTN (HPTN)
- IAVI (International AIDS Vaccine Initiative)
- USMHRP (US Military HIV Research Program)
- P5 Poxvirus-Protein Public Private partnership
- B. & M. Gates Foundation
- AVAC (AIDS Vaccine Advocacy Coalition)
- Global HIV Vaccine Enterprise
- Eurovacc Foundation, ANRS, and others

➢ Antibody-based vaccine approach :

➢ The only strategy able to prevent HIV infection based on:

- **Broadly Neutralizing Abs:**
  - **to help immunogen design**
  - **New Env vaccine candidates**
    - **with promising results in animal models**
    - **Clinical trials starting**
- **Non-Neutralizing Abs approaches:**

➢ T cell based Vaccines complementary approach to control Neut.Ab. escape mutants ?

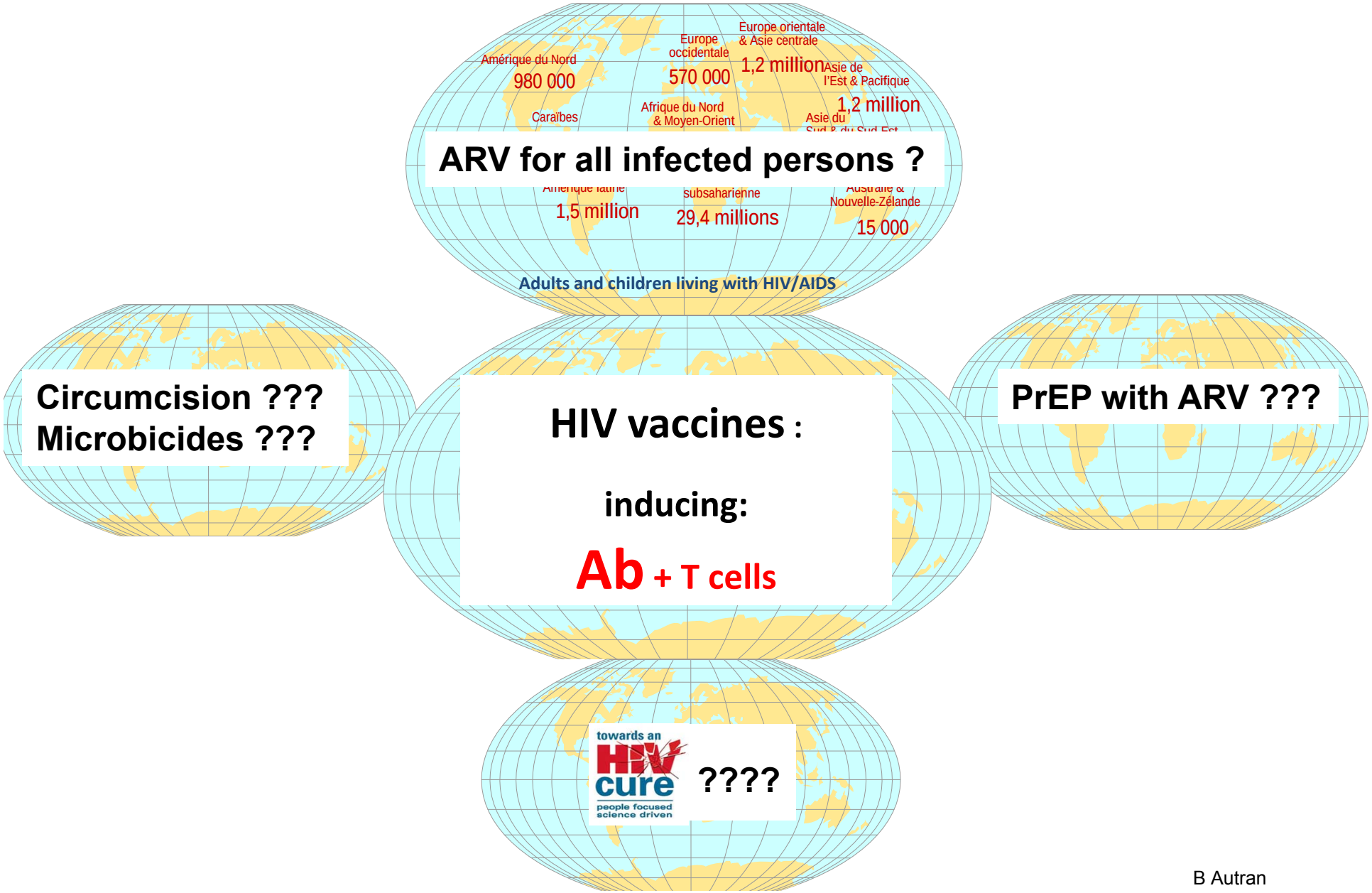
- **Conserved HIV antigens for broader Immunity :**

  Mosaic multiclade or Conserved Chimeric Ags

- **New Vectors :**
  - **Chimeric or AdenoVirus**: Ad26, -35, or ChimpAd
  - **New PoxViruses**
  - **Live replicating** Vectors? the CMV approach

B Autran

Which HIV Prevention strategies for the Future?



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Immunity to viruses
A Samri
A Guihot
G Carcelain
B Descours
C Hamimi
C Bacchus

Immunogenetics
I Theodorou

HIV immunity
V Appay
D Sauce

IPLESP Inserm U1136

Clinical research
C Katlama
R Tubiana
MA Valantin

Virology
V Calvez
AG Marcelin

Epidemiology
D Costagliola

Oncology
JP Spano

ALT ANRS CO15, Co21 Cohort, VISCONTI, OPTIPRIM and Reservoir study groups:

C Rouzioux, V Avettand , Univ. Paris-5, H Agut, UPMC & CIMI;