Science of HIV
Last news

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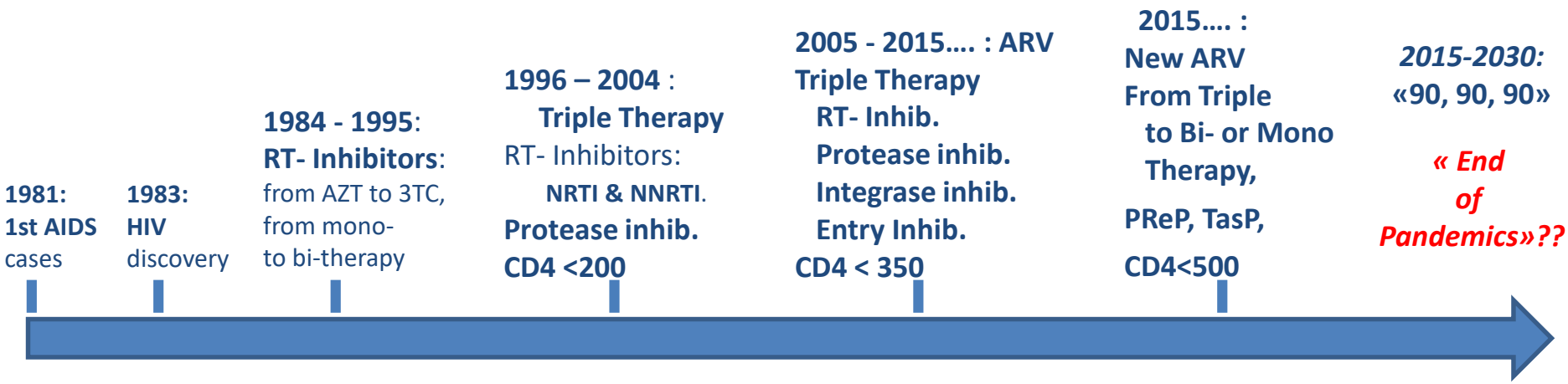
Science of HIV : the ARV revolution: towards the end of AIDS ?



- ✓ Improvement of Immune status & Survival but Persistence of :
  - **Inflammation and Non AIDS related co-morbidities**
- ✓ Improvement of virus control despite **Persistence of :**
  - **Latent HIV reservoirs**
- ✓ Progress in prevention of HIV but :
  - **Lack of HIV vaccine at sight despite intensive researches**

➢ **What's next ?**

HIV infection and immune activation: the role of coinfections

Curr. Op. HIV/AIDS, 2016

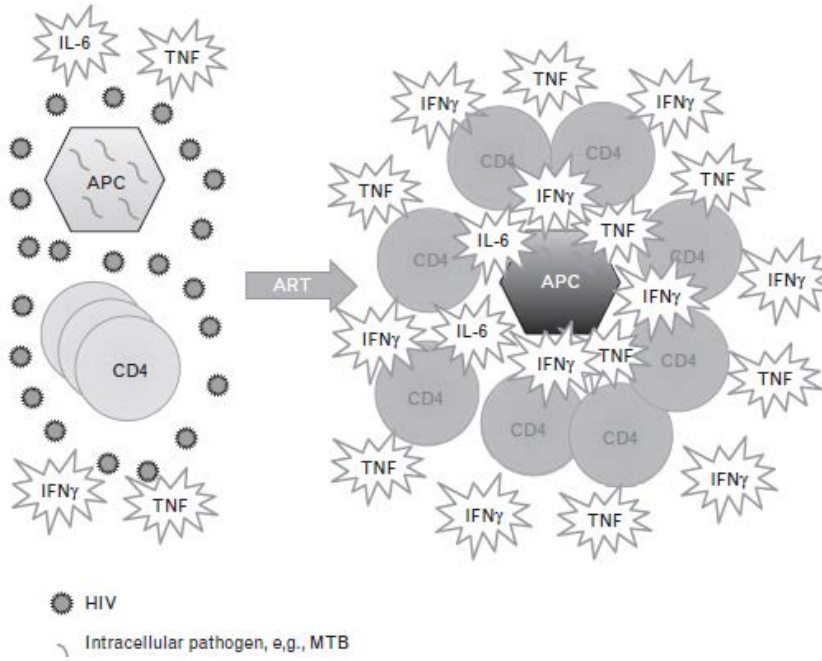
Afroditi Boulougoura and Irini Sereti

- ✓ **Immune Restoration Syndrome (IRS):**

  (M French 1998)

  - **At initiation of ART in low CD4 counts with Opportunistic Infections:**

    - **Tuberculosis** *(A Bourgarit , AIDS 2005)*
    - **Crytococcosis**
    - **CMV** retinitis



- ✓ **Long term persistence of inflammation in ART-suppressed patients**
  - **role of co-infections?**
    - **CMV**
    - **Others?**

Determinants of a Low CD4/CD8 Ratio in HIV-1–Infected Individuals Despite Long-term Viral Suppression

Clin. Inf. Dis. 2016

Fabienne Caby,[1,2] Amélie Guihot,[3,4] Sidonie Lambert-Niclot,[2,5] Marguerite Guiguet,[2] David Boutolleau,[4,5] Rachid Agher,[1,2] Marc-Antoine Valantin,[1,2] Roland Tubiana,[1,2] Vincent Calvez,[2,5] Anne-Geneviève Marcelin,[2,5] Guislaine Carcelain,[3,4] Brigitte Autran,[3,4] Dominique Costagliola,[2] and Christine Katlama[1,2]

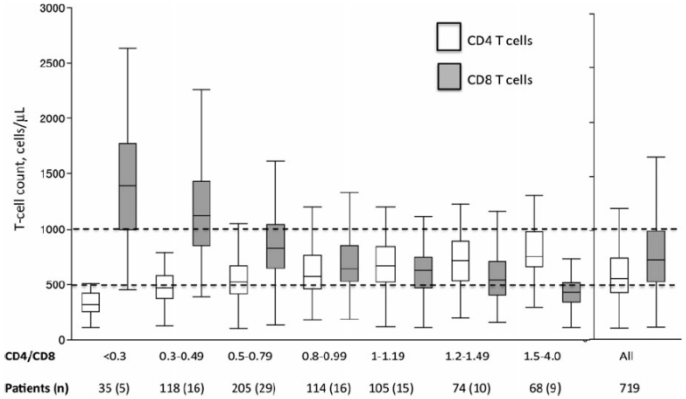
Characteristics	All (n = 719)	Individuals With Available CMV Serology (n = 645)	Individuals With No Available CMV Serology (n = 74)	*P* Value
Age, y	49 (44–56)	49 (44–56)	49 (43–53)	.6905
Male sex	529 (74)	478 (74)	51 (69)	.3386
HIV risk group				.9718
MSM	303 (48)	303(53)	0 (0)	
Heterosexual	250 (40)	222 (39)	28 (38)	
IDU	62 (10)	43 (7)	19 (26)	
Blood transfusion	11 (2)	8 (1)	3 (4)	
Other/unknown	93 (13)	69 (11)	24 (32)	
Body mass index, kg/m^2	24 (21–26)	24 (22–27)	23 (20–25)	.0067
CDC stage C	168 (23)	155 (24)	13 (18)	.2158
CD4 count nadir, cells/μL	183 (80–276)	183 (75–279)	183 (125–245)	.7248
CD8 count zenith, cells/μL	1365 (1032–1843)	1361 (1032–1861)	1446 (920–1788)	.3862
CD4 count, cells/μL	565 (435–742)	576 (432–756)	520 (458–625)	.0843
CD8 count, cells/μL	727 (530–991)	727 (529–986)	717 (570–1097)	.2352
CD4/CD8 ratio	0.8 (0.6–1.1)	0.8 (0.6–1.1)	0.7 (0.5–1.0)	.0864
Duration of viral suppression[a], y	5.4 (3.3–9.1)	5.5 (3.3–9.1)	4.8 (3.0–7.9)	.1248
ART introduction				.0669
2002 or later	218 (30)	203 (31)	15 (20)	
1997–2001	277 (39)	245 (38)	32 (43)	
Before 1997	224 (31)	197 (31)	27 (36)	
Current PI-containing regimen	428 (60)	380 (59)	48 (65)	.3243
Current NNRTI-containing regimen	260 (36)	240 (37)	20 (27)	.0864
Raltegravir-containing regimen	95 (13)	85 (13)	10 (14)	.9357
Maraviroc-containing regimen	15 (2)	13 (2)	2 (3)	.6963
Current NRTI-containing regimen	665 (92)	592 (92)	73 (99)	.743
Positive anti-HCV IgG	105 (15)	94 (15)	11 (15)	.8685
Positive HBsAg	53 (8)	49 (8)	4 (5)	.4898
Positive anti-CMV IgG (n = 645)	NA	564 (87)	NA	

CMV as a major risk factor for persistently low CD4/CD8 ratio

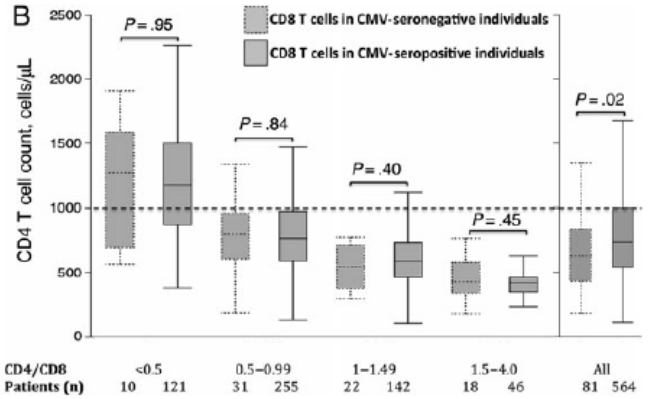
Risk factors for a CD4/CD8 ratio<1 (n=645)

Variable	CD4/CD8 Ratio <1 (n = 416)	CD4/CD8 Ratio ≥1 (n = 229)	Univariable Analysis		Multivariable Analysis[a]	
			Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Age[b], y	48 (42–56)	51 (45–57)	0.8 (.7–.9)	.005	0.8 (.7–1.0)	.064
Male sex	300 (72)	178 (78)	0.7 (.5–1.0)	.061	0.9 (.6–1.5)	
Body mass index, kg/m^2	24 (22–27)	23 (21–26)	1.0 (1.0–1.1)	.418		
HIV risk group						
MSM	186 (45)	117 (51)	1	.226		
Heterosexual	153 (37)	69 (30)	1.4 (1.0–2.1)			
IDU	26 (6)	17 (8)	1.0 (.6–6.5)			
Other/unknown	51 (12)	26 (11)	1.4 (.9–2.4)			
CD4 count nadir[c], cells/μL	153 (56–240)	233 (141–315)	0.7 (.6–.8)	<.001	0.7 (.7–.8)	<.001
Duration of viral suppression[d], y	4.9 (3.1–8.5)	6.3 (3.7–10.1)	0.7 (.5–.8)	<.001	0.6 (.5–.8)	<.001
ART introduction						
2002 or later	123 (30)	80 (35)	1	.004	1	.009
1997–2001	150 (36)	95 (41)	1.1 (.8–1.6)		1.5 (1.0–2.3)	
Before 1997	143 (34)	54 (24)	1.9 (1.2–2.8)		1.9 (1.2–3.0)	
Positive anti-HCV IgG	68 (16)	26 (11)	1.4 (.9–2.2)	.159	1.4 (.8–2.3)	.224
Positive HBsAg	36 (9)	13 (6)	1.5 (.8–2.8)	.21		
Positive anti-CMV IgG	375 (90)	189 (83)	1.9 (1.2–3.1)	.005	1.9 (1.1–3.1)	.003

Altered distribution of CD8 T cells



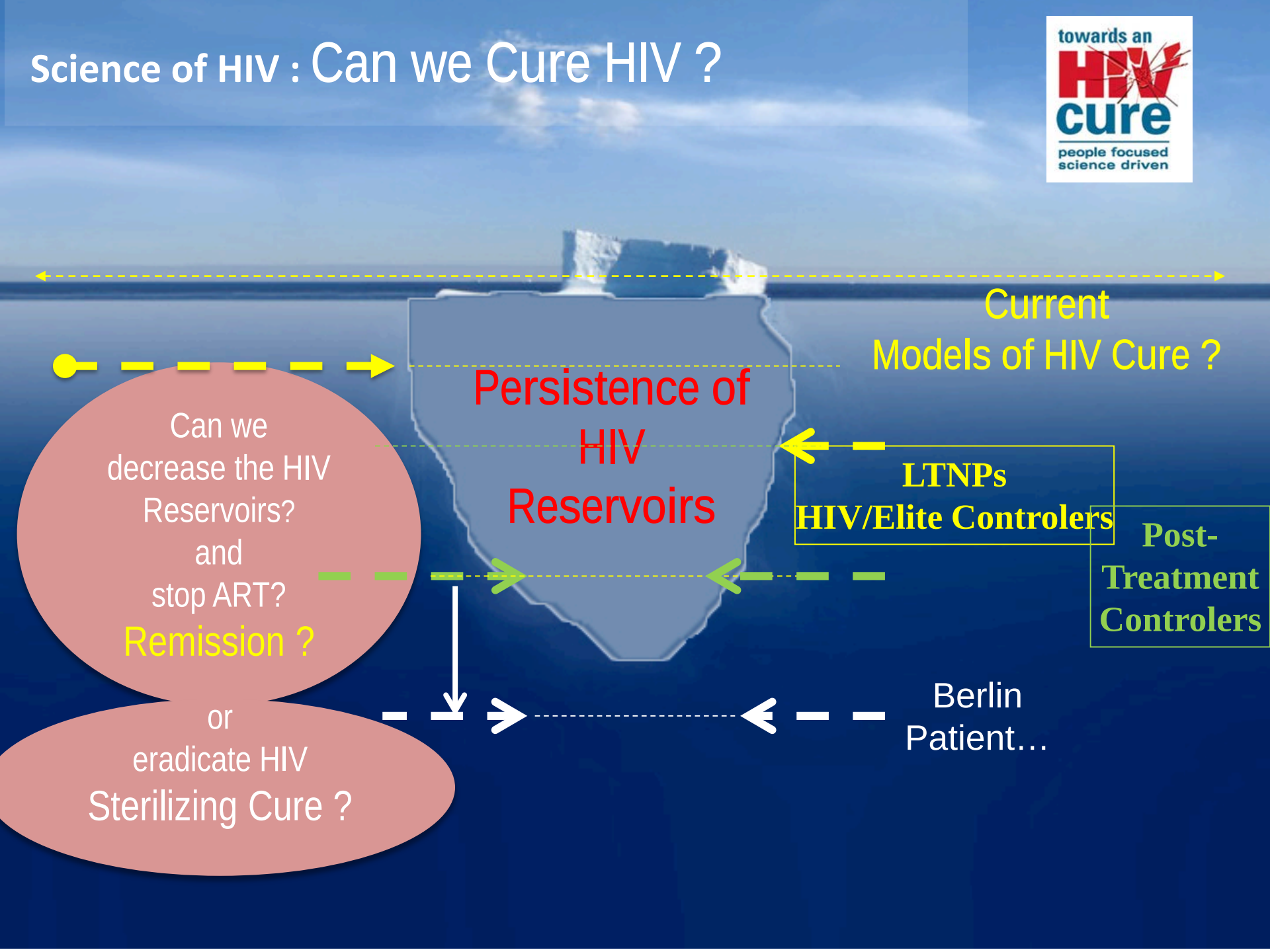
Impact of CMV Infection on CD8 T cells



Risk factors for persistent inflammation and therapeutic implications

- **Persistent inflammation and Role of**
  - **Persistent co-infections** other than CMV**?**
    - **Low or no effect of HCV and HBV in fully suppressed patients :** No abnormal inflammation markers except for I**FN-alpha** and **ISG** (*M Griesbeck AIDS 2017)*
  - **Altered microbiota?**
    - **confounding factors** such as sexual preference *(R. Paredes et al. Ebiomed. 2016)* or diet
    - interfere with mechanisms of inflammation and CD4 recovery *(W Lu et al. Front. Microbiol. 2018)*
- **Therapeutic implications:**
  - **To treat CMV ? Gancyclovir reduces immune activation** *(S Deeks JID,2008)*
    - But short term course => imposes new anti-CMV compounds
  - **To use anti-inflammatory agents?**
    - Poor effect of classical agents
    - **New agents? Blockade of IFN-alpha** or **p38 MAP-Kinases** *(D Douek et al.; A Aldovini et al. PLosPath 2018)*

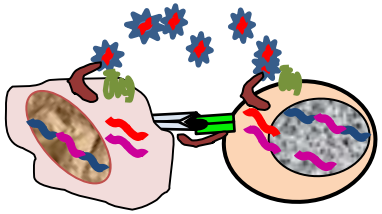
Science of HIV : Can we Cure HIV ?



Establishment & persistence of HIV reservoirs *(J Ghosn et al. Lancet 2018)*

A- Infection

Activation

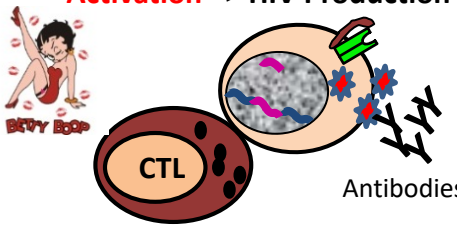


CD4+ antigen-presenting cell

Antigen-**activated** CD4+ T cells

HIV provirus integration
in active regions of memory cell genome

Activation => HIV Production

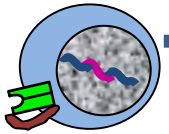


Death of most HIV-producing activated Memory CD4+ T cells: due to HIV cytopathogenicity or immune death

B- Post-integration Latency in HIV reservoirs *the Sleeping Beauty* :

1- Establishment of latency

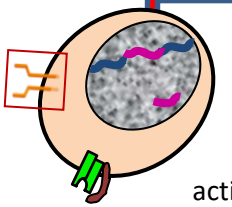
Resting
quiescent HIV-infected Memory CD4 T cells



Escape from death of rare HIV-infected Memory CD4 T cells

Ex: IL-7

+ Ag Activation



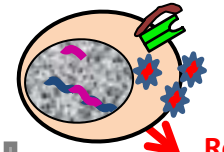
Exhausted
activated HIV-infected Memory CD4 T cells

2- Fate of latently -infected cells

Persistence of latent reservoirs In Resting long-lived Memory HIV-infected cells

Homeostatic proliferation of memory HIV-infected cells

Production of HIV



Re-seeding of reservoirs

PD1 Blockade of
- **T cell functions**
- **HIV production**

Persistence of latent Reservoirs in Short-lived Memory cells

Cell & Reservoir Lifespan

Models and Factors of Remission ???

ow Reservoirs ?

trong Immunity or
eak infection of
ome 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)

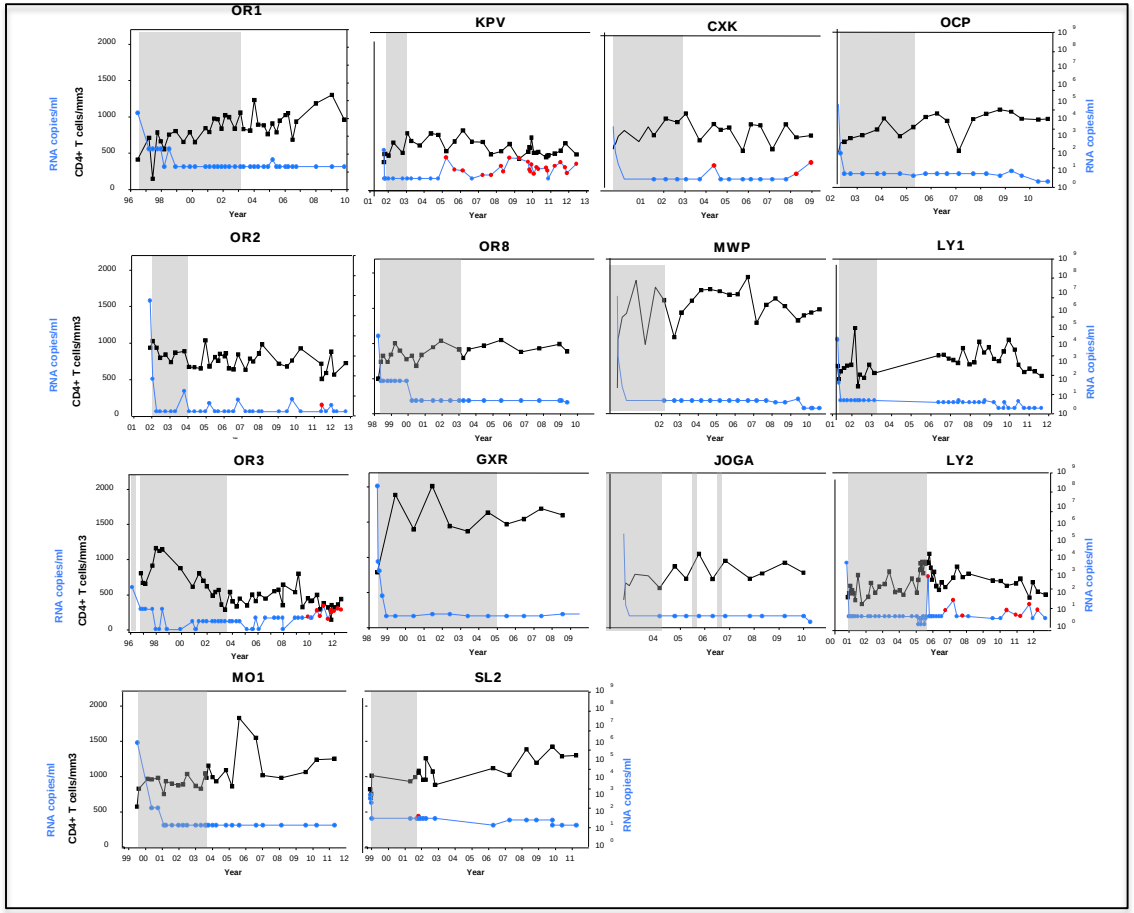
Hoqueloux et al. AIDS 2010, J A C. 2013, Saez-Cirion et al. PLosPathogens, 2013

VISCONTI : Post-Treatment Controllers (PTC)

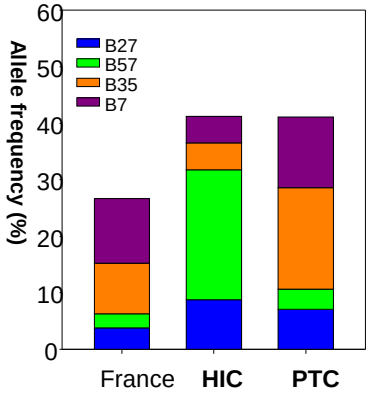
- **Key role of ARV in Primo-Infection:**
- **Reservoirs + low**

- **VISCONTI:**
- **pVL<500cp/ml for 3.5ans,**

after 3-5 ans ARV in early PHI



- **No protective d'HLA**



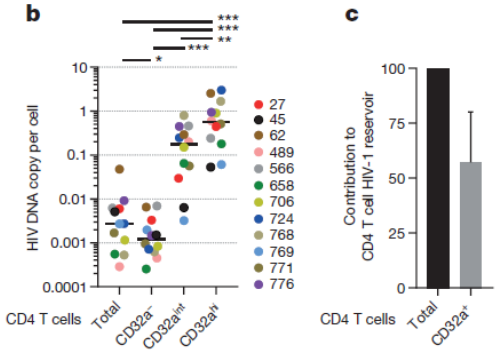
Hoqueloux et al. AIDS 2010,

Saez-Cirion et al. PLosPathogens, 2013

A quest for biomarkers of the HIV reservoirs

- **CD32a ?** (a receptor to the Fc of IgG) (*B Descours et al. Nature 2017)*

  - ***CD32a+ cells harbor 50% of the HIV reservoirs ?***
    and produce faster and more HIV

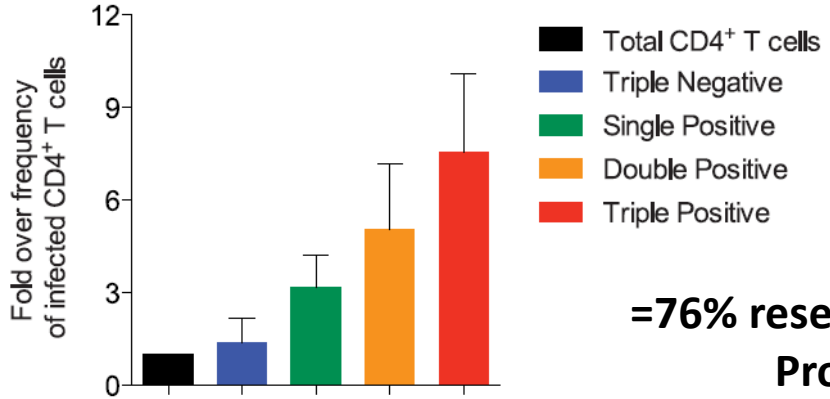


- **BUT Highly controversed :**

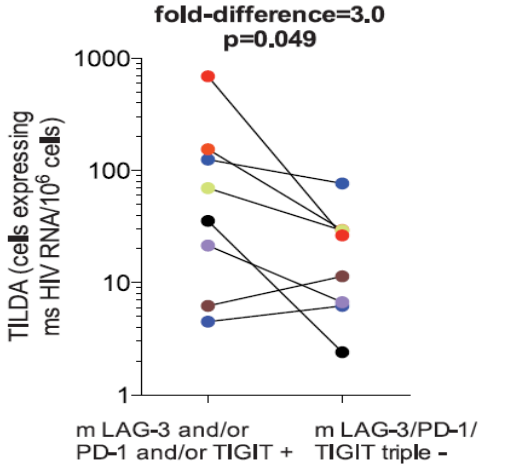
CD32a not a maker of latent reservoir: cells express ingCD32a are all monocytes, macrophages and 1% activated memory CD4 T cells

(*A Noto/G Pantaleo et al, JVI 2018; R Siliciano et al. CROI2018; L Montaner et al. CROI 2018; D Nixon et al. CROI 2018; A Corneau et al, unpublished)*

- **Immune Check-points?** *(R Fromentin et al. PLosPathogens 2016)*

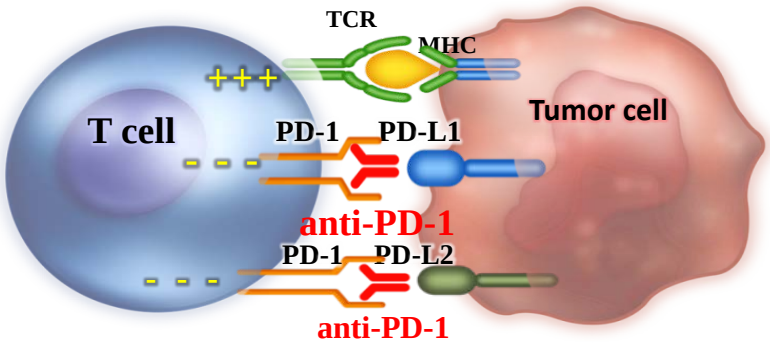


=76% reservoirs Produce HIV



Why are Immune check points interesting for the reservoirs ?

- **Immune check points**
  = PD1, CTLA-4, LAG-3, TIGIT …
  block T cell functions



- **Monoclonal antibodies against the PD-1 axis :** **Successful in Oncology**
  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)*

Therapeutic Strategies for Cure ?

1) To decrease the HIV reservoirs

below a deadly threshold for the virus

- No convinicng results

2) **To target the residual cells**

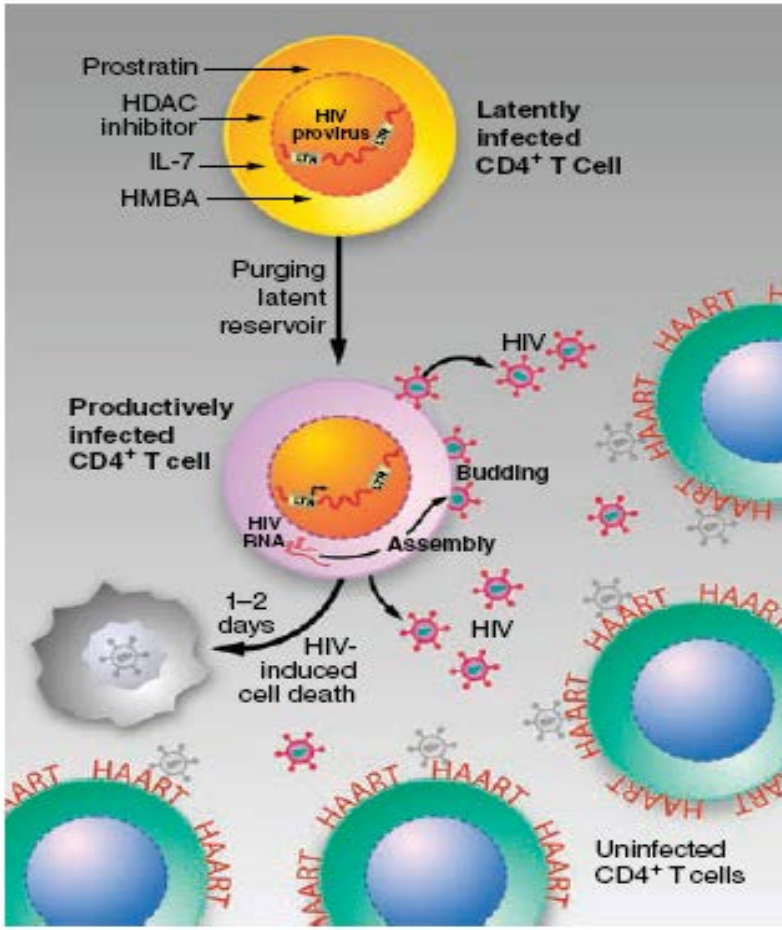
producing HIV with ARV?

- No convinicng results

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

= the shock and kill strategy

combined strategies



4) To change the host cells into HIV-resistant cells:

- The Berlin patient
- Cell & therapy (CCR5-)
- Gene therapy : To exfiltrate HIV genes from the host genome: the Crispr/Cas 9 strategy

1) To decrease the HIV reservoirs with early therapy ???

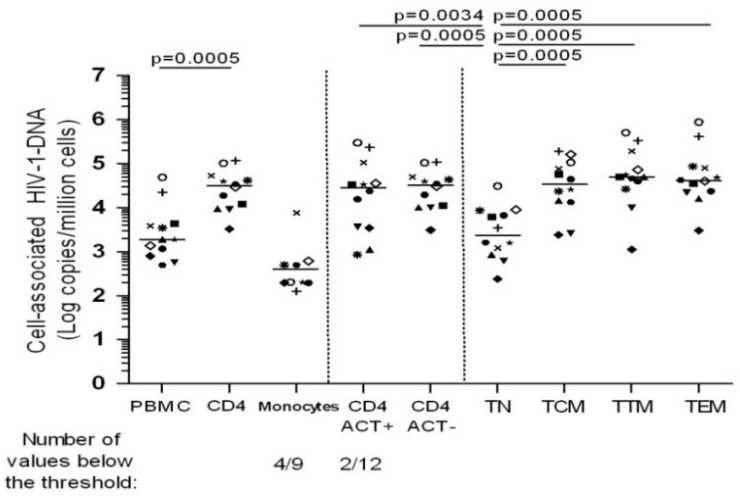
➢ The Optiprim trial:

D0= 30days post-infecton : (Fiebig III)

Bacchus & Chéret et al Plos One 2013

Reservoirs : immediate clonal and massive diffusion of HIV :

3-5 logs/millions long lived CD4+ cells

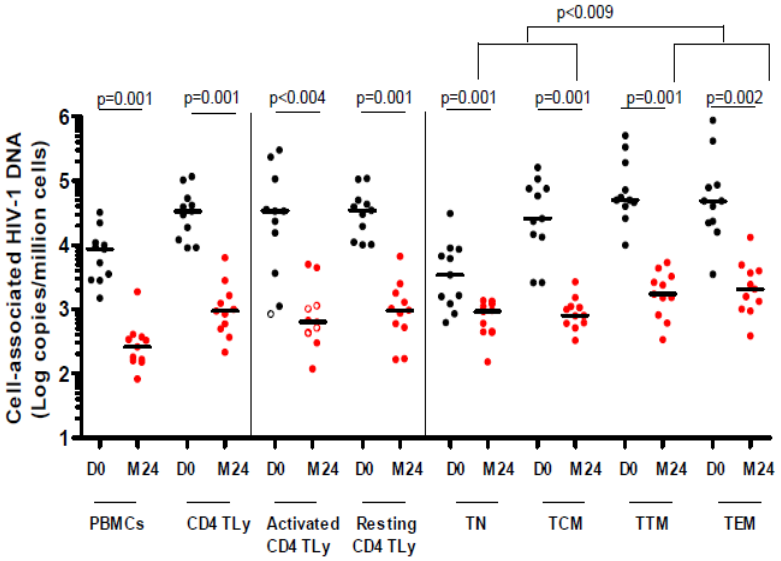


After 2 years of intensified ARV (5 vs 3 drugs)

Chéret & Bacchus et al JAC 2014

Persistence of substantial HIV reservoirs

despite a 2 log decrease in long lived CD4 TCM



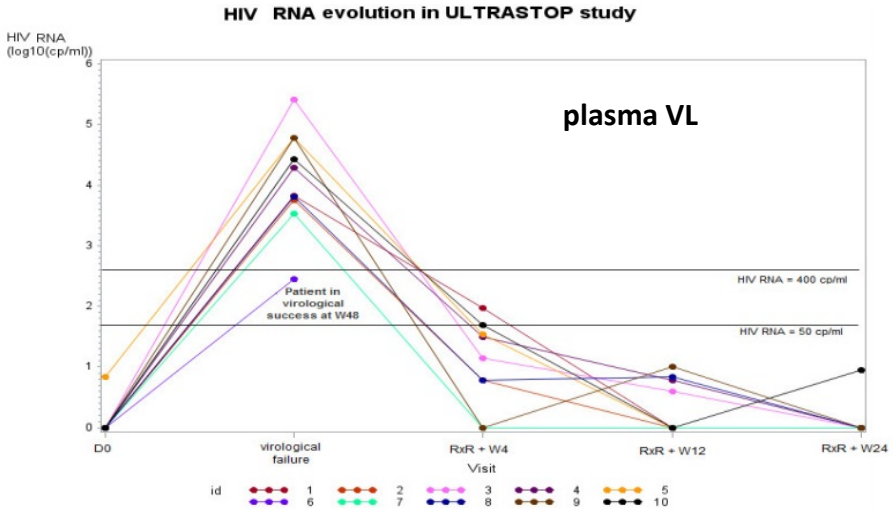
➢ Similar results in Fiebig I stage and rapid HIV rebound after ATI :

(J Ananworanich et al. 2017, 2018)

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

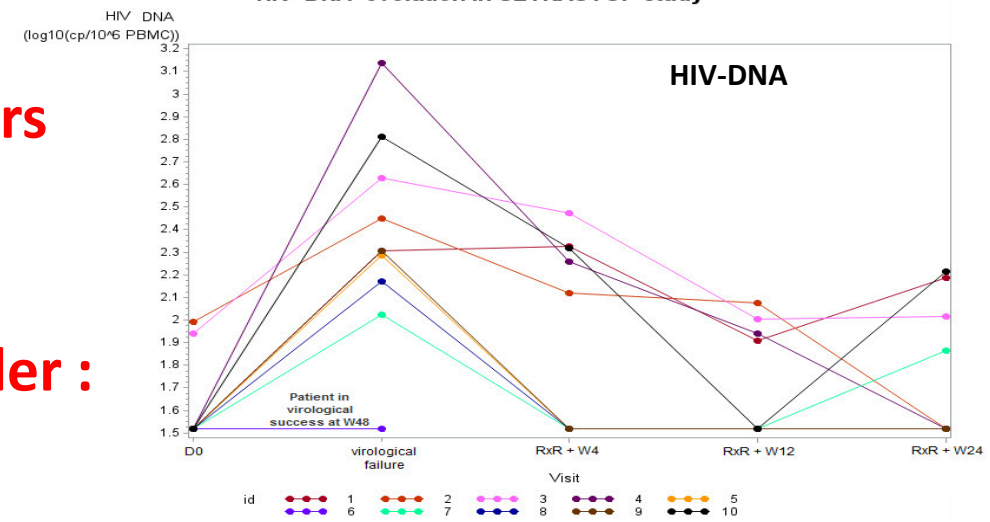


➢ **HIV Rebound in 9/10**

➢ **Rapid Dynamics of HIV reservoirs**

➢ ***Weak immunity to HIV*.**

➢ **1 single Post-treatment controller : 12m**



3) Combined strategies to purge the HIV reservoirs

- **to re-activate HIV in latently infected cells :**
  - **HDAC Inhibitors ? Failure of all trials,**
  - **IL-7?** Failure: Eramune-01 trial *(Katlama et al. AIDS 2016)*
  - Adjuvants ?

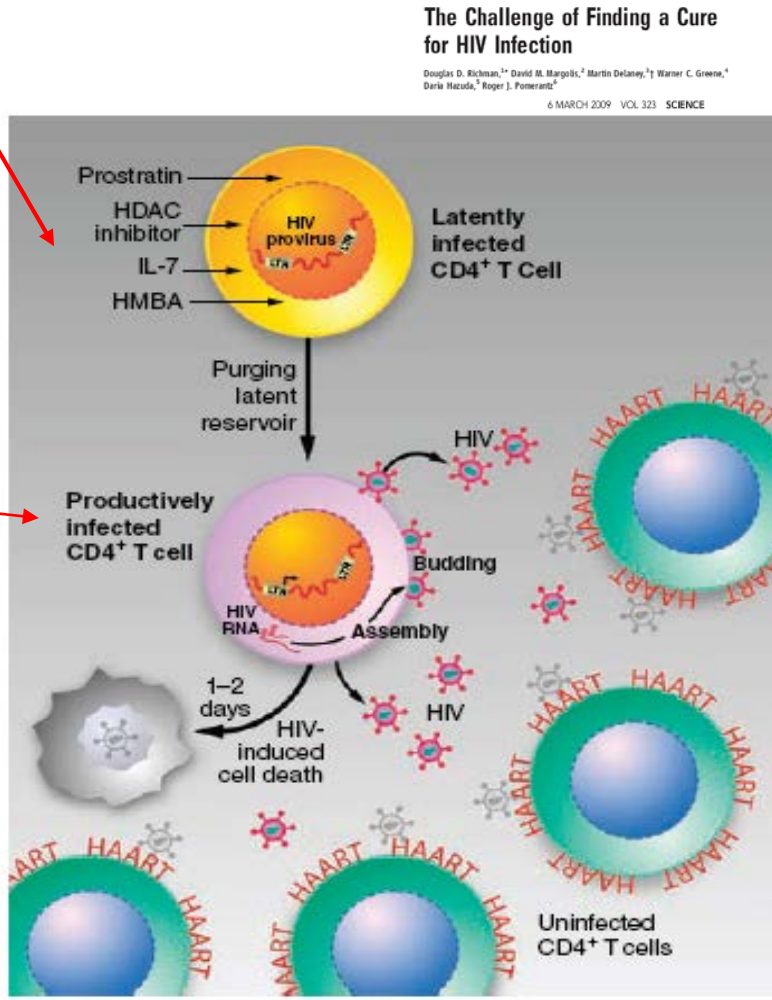
- **and to target HIV producing cells**

  to limit residual virus spreading
  - **Therapeutic vaccines**

    inducing *CTLs ?*

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

    Broadly Neutralizing Abs?



- **Immune check point inhibitors ?**

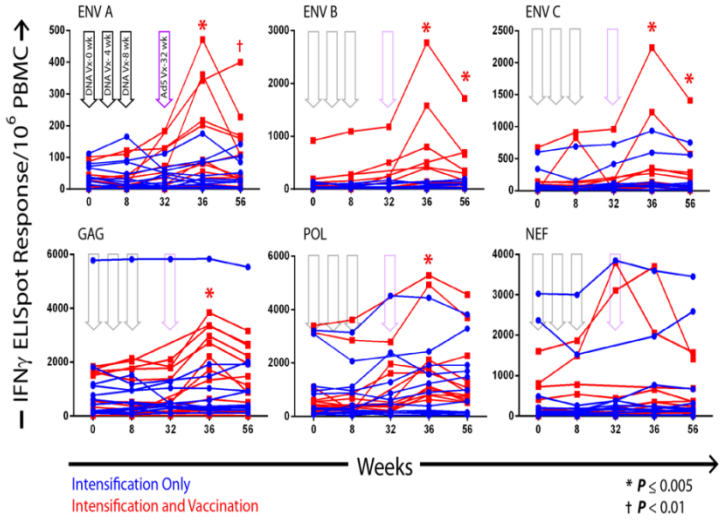
To target the residual cells producing HIV with ARV + Therapeutic vaccine? The Eramune-02 study

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

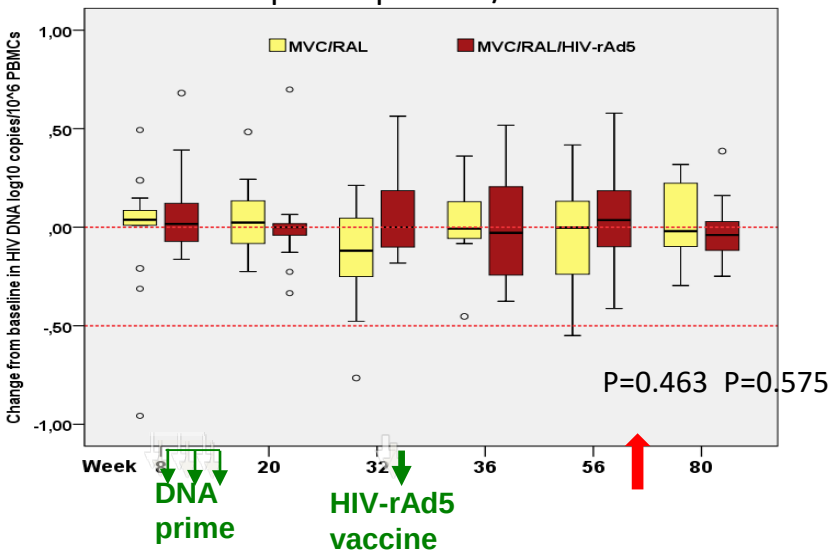
- **Robust induction of HIV-specific T cells**

Ex-vivo Elispot analysis,



- **No change in peripheral HIV reservoirs**

except in 1 patient / 15



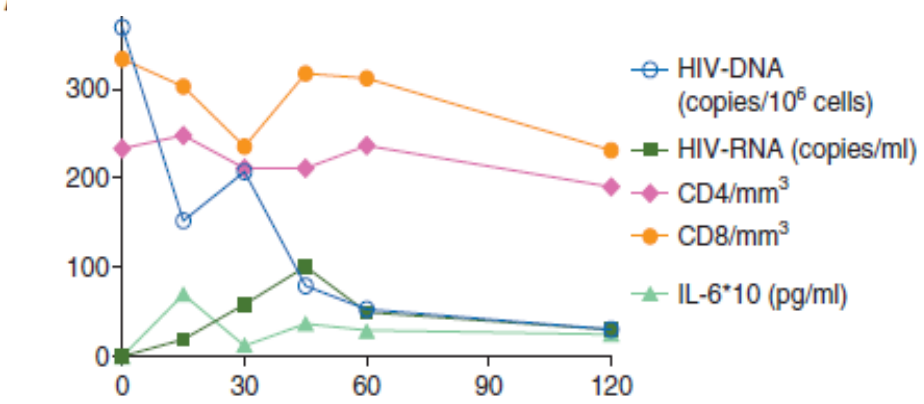
Conclusion:

- **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?*

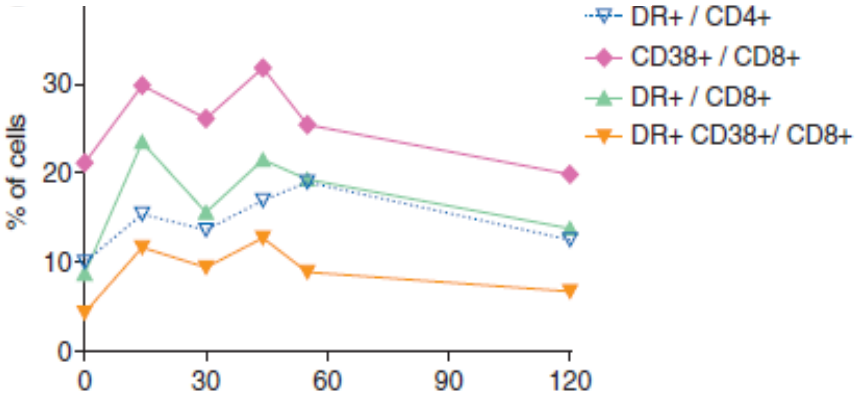
B Autran

Reduction of the HIV reservoirs & restoration of HIV-specific T cells with anti-PD-1 therapy in 1 Patient out of 15 *(A Guihot et al. Ann. Oncol. 2017)*

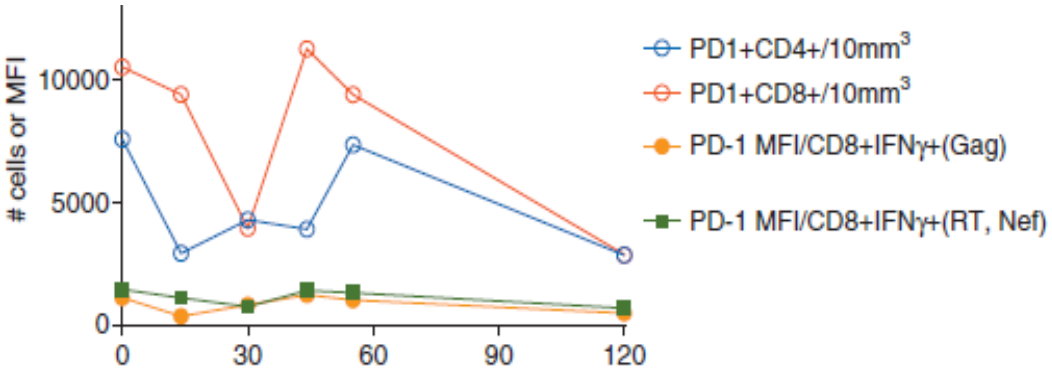
- 3-fold reduction in the HIV reservoirs



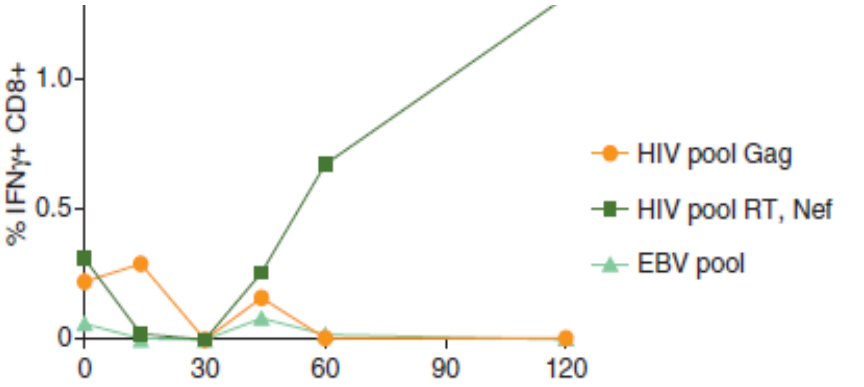
- Transient increase in activation



- Decreased expression of ICP



- Sustained increase in anti-HIV CD8 T cells

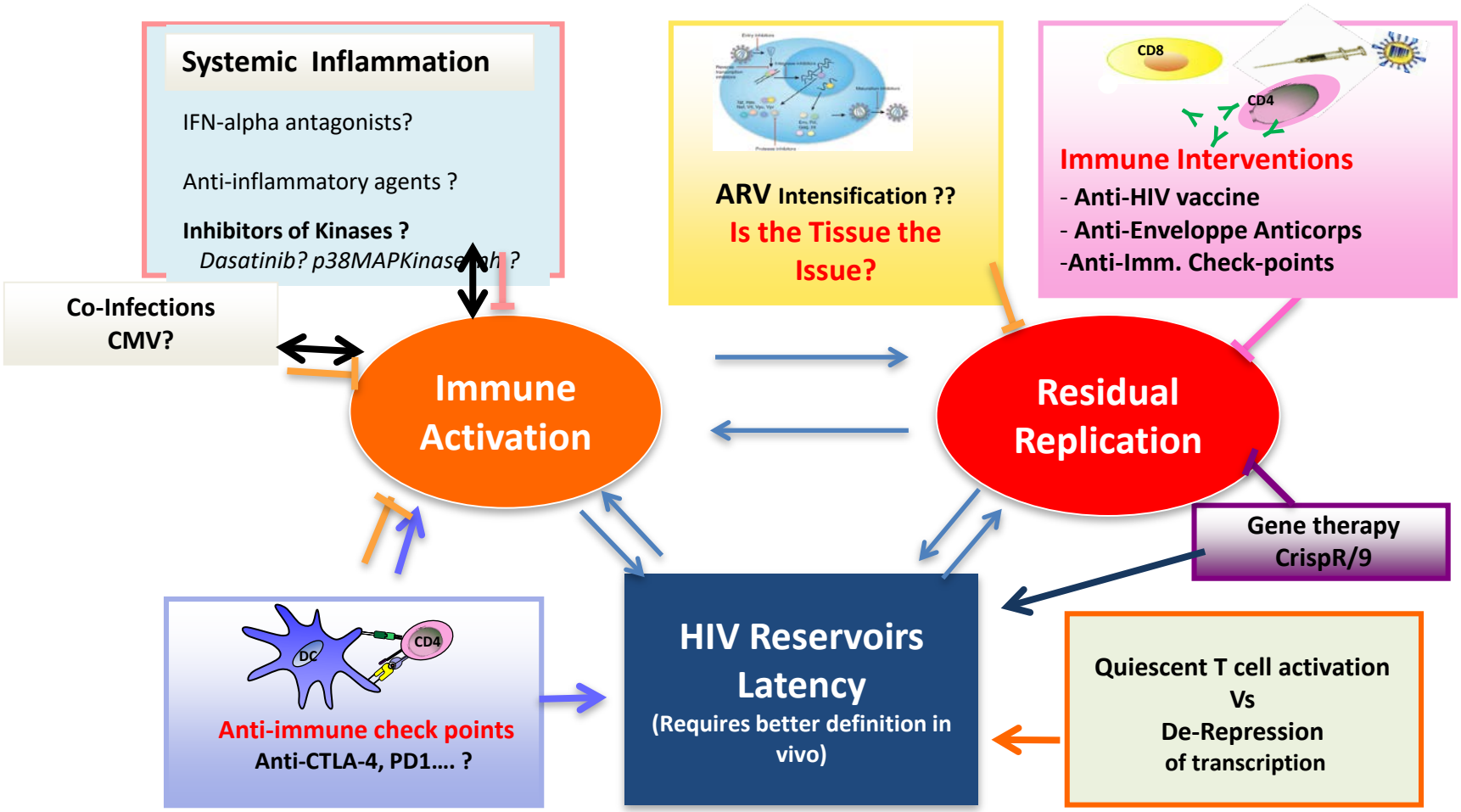


Time since start of treatment (days)

➢ **But effect only transient over 1 year and frequency of success still unknown**

Conclusions

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

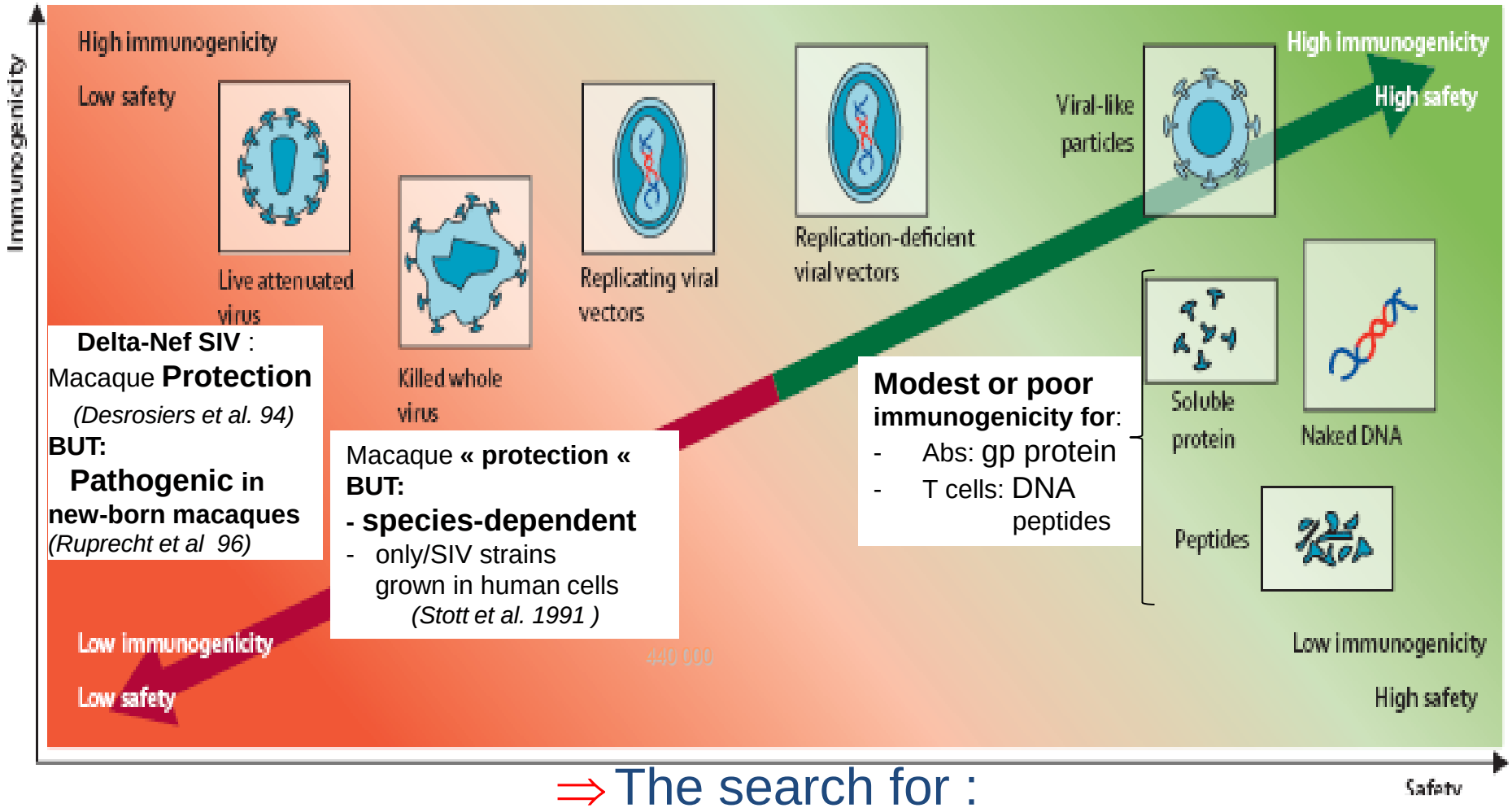


from C Katlama et al. Lancet 2013

Progress towards development of an HIV vaccine

from

Anna Laura Ross, Andreas Bräve, Gabriella Scarlatti, Amapola Manrique, Luiqi Buonaquro *Lancet, 2009*

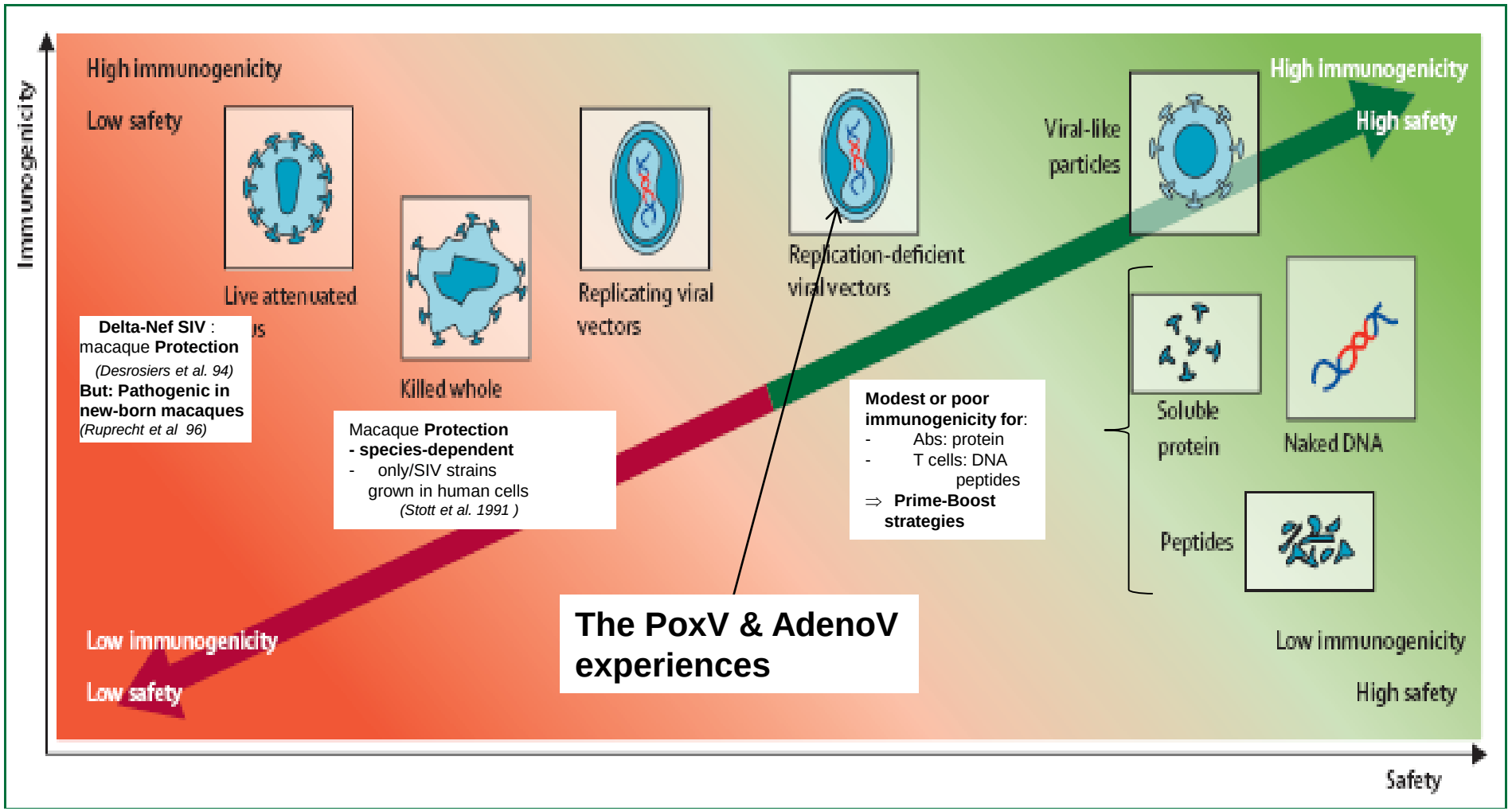


⇒ The search for :

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

Progress towards development of an HIV vaccine

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



⇒ The search for :

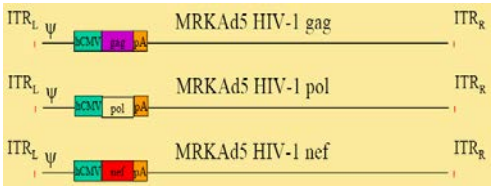
a T cell based HIV vaccine

the Step Study

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

- **Vaccine**:

HIV Rec.Adeno5



- **Controlled trial**:
  - 3,000 High risk volunteers
  - +/- pre-existing anti-Ad5 Abs

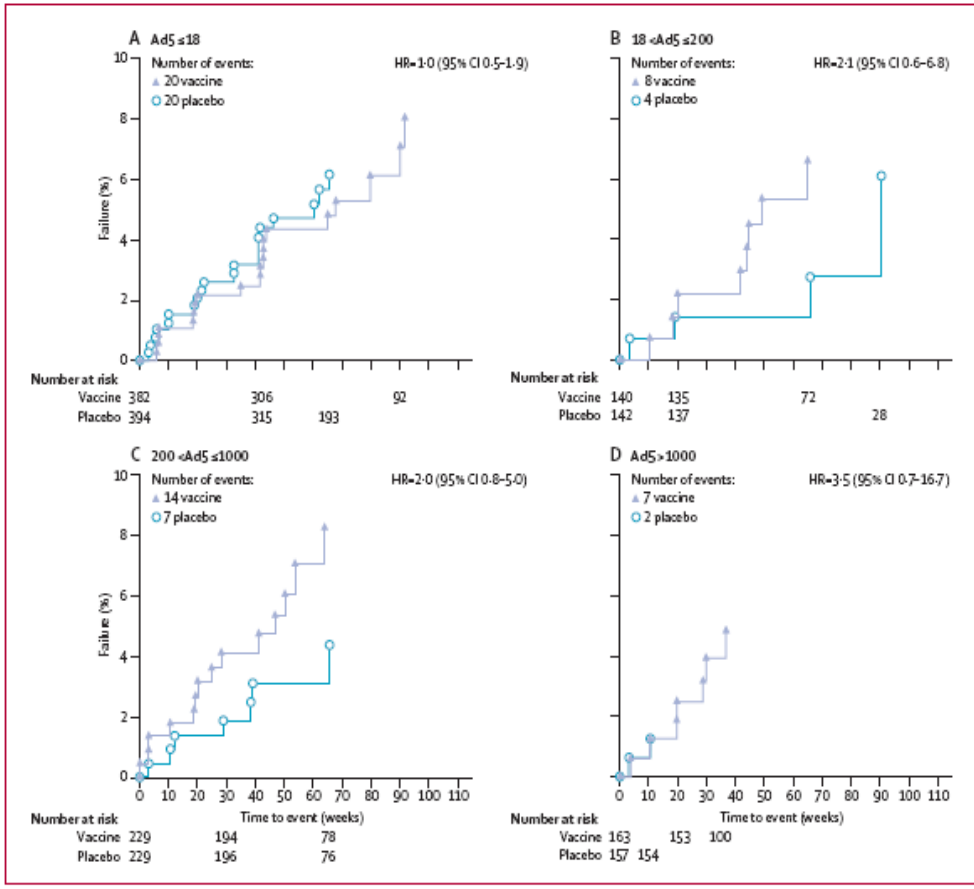


Figure 2: Kaplan-Meier plots of HIV infection for male vaccine and placebo groups by baseline Ad5 antibody titre ≤18 (A); baseline Ad5 antibody titre between >18 and ≤200 (B); baseline Ad5 antibody titre between >200 and ≤1000 (C); and baseline Ad5 antibody titre >1000 (D)
Each hazard ratio (HR) is from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

➢ **DSMB: Definitive arrest of the trial**

=> Increased frequency of HIV infections

in Vaccinees vs Placebo :

Most evident in uncircumcised men with pre-existing Ad5 Abs (HRs: 4.2-4.8)

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

➢ Effect of pre-existing Abs / Ad5?

➢ No differences in vaccine immunogenicity between Cases and Non Cases

B Autran

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.

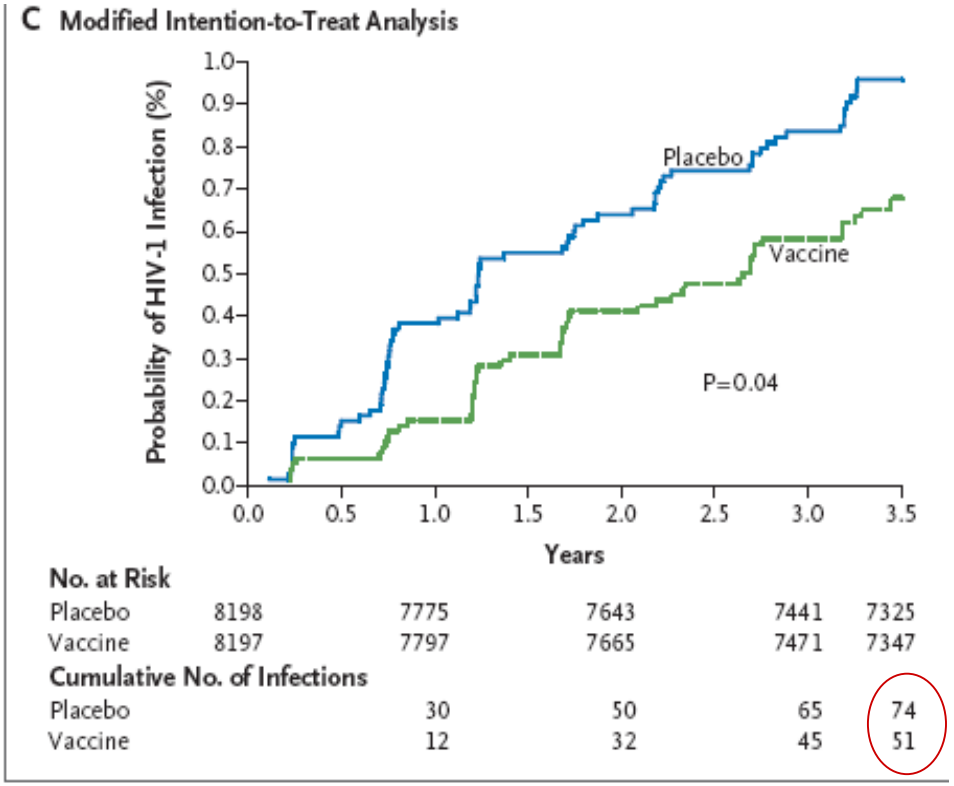
- Study Design :
  - A randomized, multicenter, double-blind, placebo-controlled efficacy trial,
    - in **16,402** healthy men and women 18 and 30 years
    - primarily at **heterosexual risk** for HIV infection,
  - 4 priming injections of a **recombinant canarypox vector vaccine** (ALVAC-HIV [vCP1521])
  - 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:

« ALVAC-HIV + AIDSVAX B/E vaccine regimen may reduce the risk of HIV infection in a community-based population with largely heterosexual risk. »

- But: Vaccination did not affect the viral load or CD4+ count after HIV infection

Immune correlates of protection ??? (No Neut Abs, no IFN-g producing T cells?)

= Non Neutralizing Abs / V1-V2 *(Haynes et al. NEJM 2011)*

Post RV144 HIV vaccine programme :

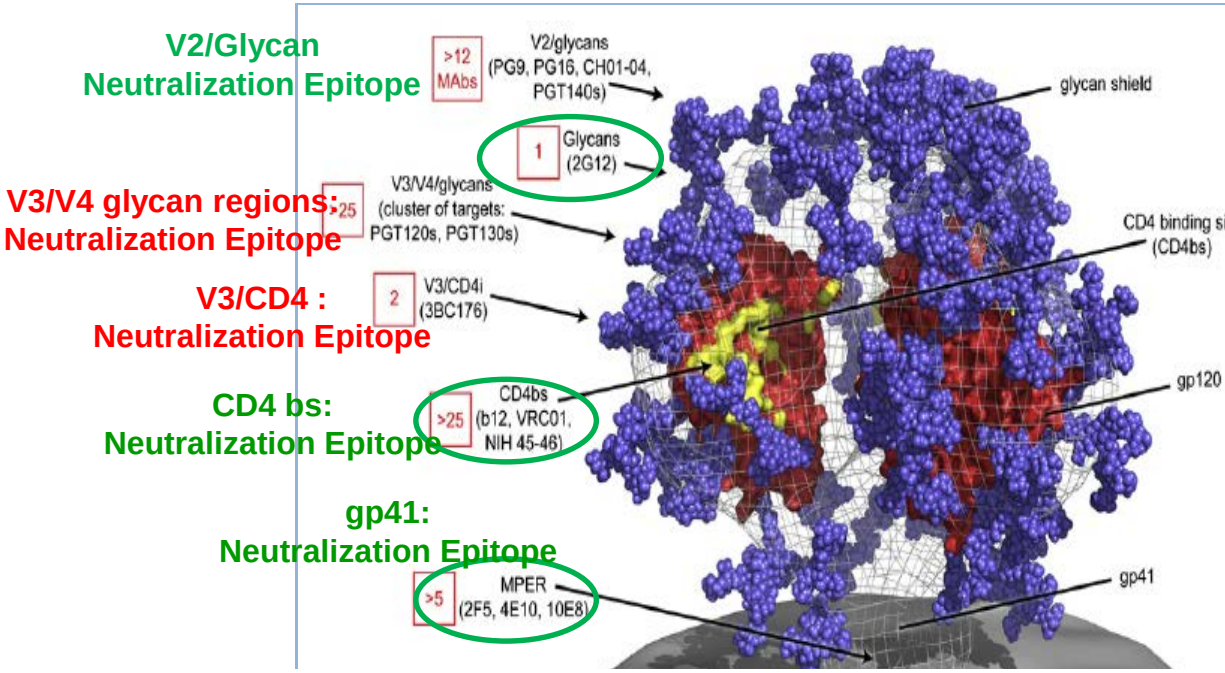
- The single cell antibody cloning approach :
  - **Discovery of Human Broadly Neutralizing Antibodies**

- ✓ **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…)

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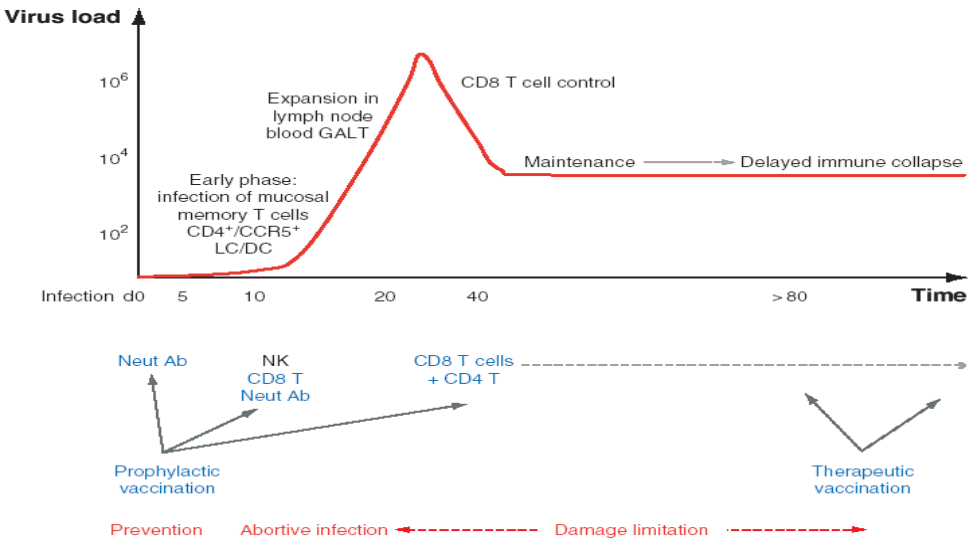
The search for an anti-HIV Vaccine:

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 :**

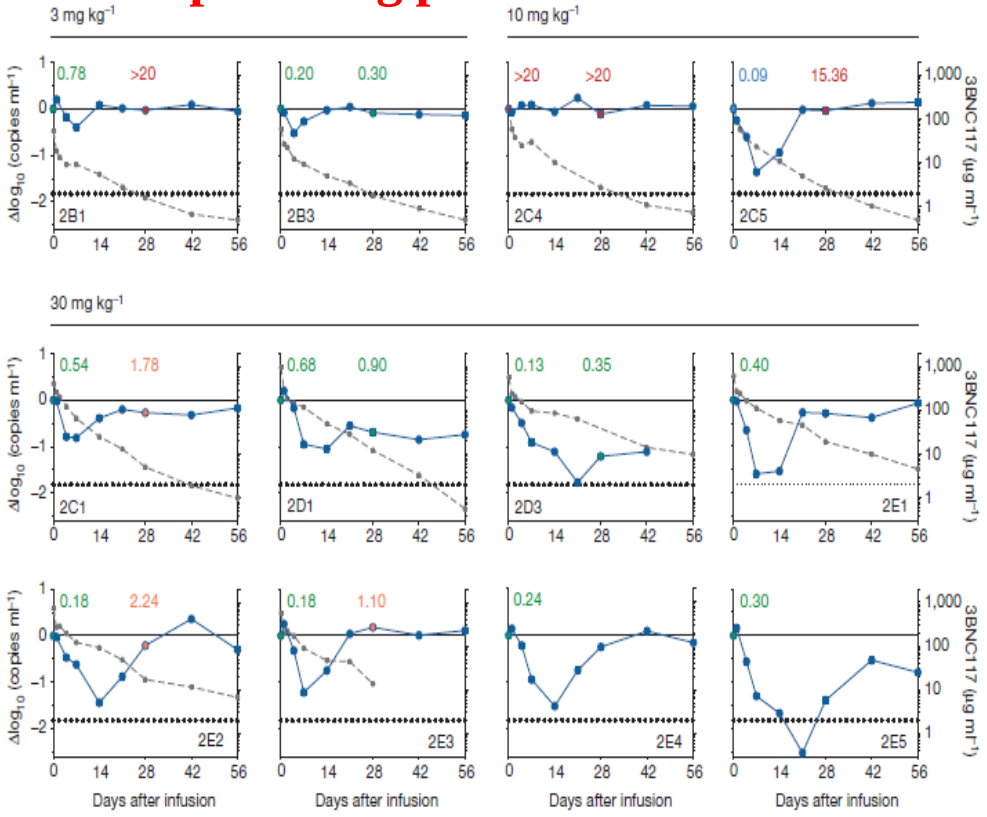
  Mosaic multiclade or Conserved Chimeric Ags

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

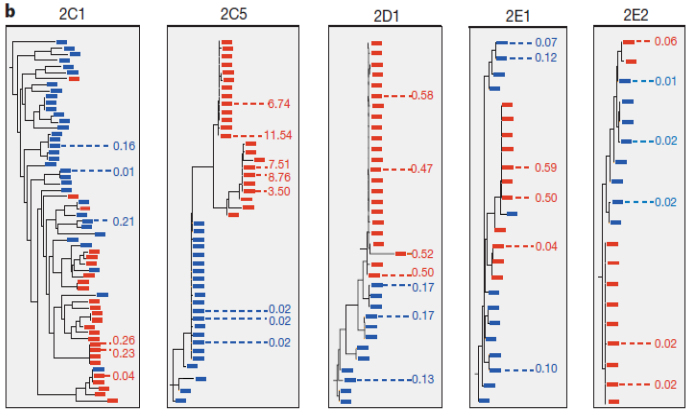
Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117

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**

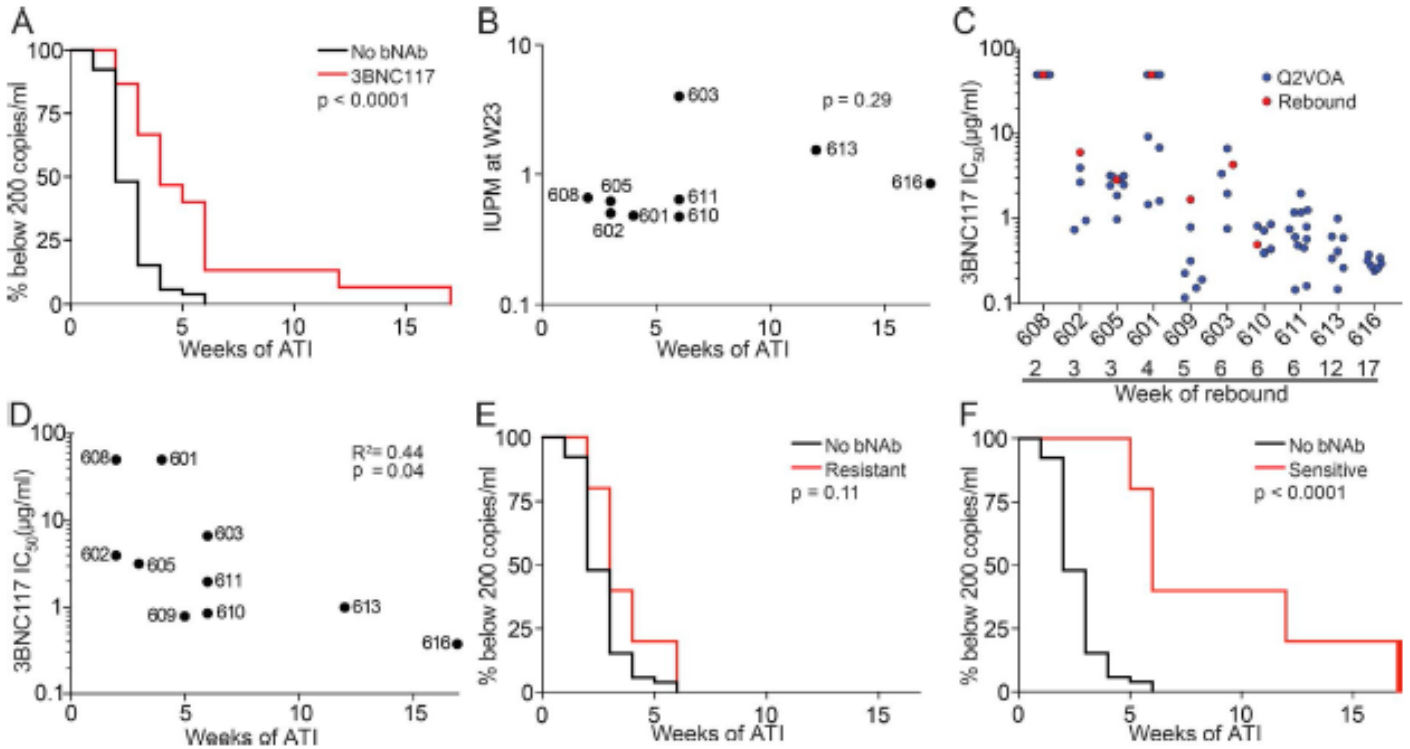
- **Very Encouraging**

BAutran

Relationship between latent and rebound viruses in a clinical trial of anti–HIV-1 antibody 3BNC117

JEM 2018

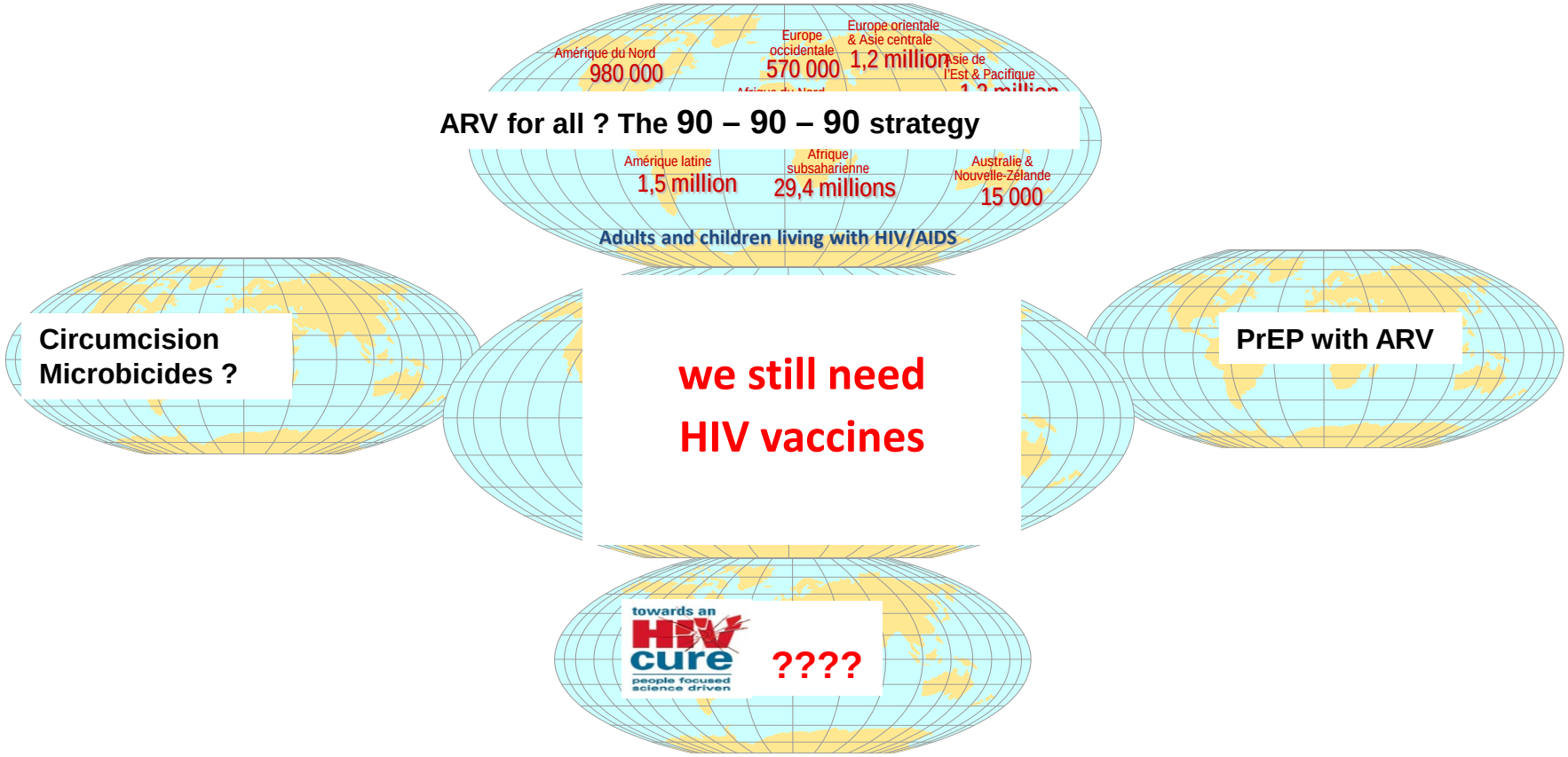
Yehuda Z. Cohen[1*], Julio C.C. Lorenzi[1*], Lisa Krassnig[1], John P. Barton[2], Leah Burke[3], Joy Pai[1], Ching-Lan Lu[1], Pilar Mendoza[1], Thiago Y. Oliveira[1], Christopher Sleckman[1], Katrina Millard[1], Allison L. Butler[1], Juan P. Dizon[1], Shiraz A. Belblidia[1], Maggi Witmer-Pack[1], Irina Shimeliovich[1], Roy M. Gulick[3], Michael S. Seaman[4], Mila Jankovic[1], Marina Caskey[1**], and Michel C. Nussenzweig[1,5**]



BUT:

- **No change in the size of the reservoir**
- **No correlation between circulating HIV clones and sensitivity of the Neut. Ab** BNC117

Success of ARV-based HIV Prevention strategies …
But
no vaccine and no clear strategy for HIV cure yet



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