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?

Timeline:
- 1981: 1st AIDS cases
- 1983: HIV discovery
- 1984 - 1995: RT-Inhibitors: from AZT to 3TC, from mono- to bi-therapy
- 1996 – 2004: Triple Therapy RT-Inhibitors: NRTI & NNRTI, Protease inhib., CD4 <200
- 2015…. : New ARV From Triple to Bi- or Mono Therapy, PReP, TasP, CD4<500
- 2015-2030: «90, 90, 90» «End of Pandemics»??
Immune Restoration Syndrome (IRS):  
(M French 1998)  

- At initiation of ART in low CD4 counts with Opportunistic Infections:  
  - Tuberculosis (A Bourgarit, AIDS 2005)  
  - Cryptococcosis  
  - 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 719)</th>
<th>Individuals With Available CMV Serology (n = 645)</th>
<th>Individuals With No Available CMV Serology (n = 74)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49 (44–56)</td>
<td>49 (44–56)</td>
<td>49 (43–53)</td>
<td>.6905</td>
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<tr>
<td>Male sex</td>
<td>529 (74)</td>
<td>478 (74)</td>
<td>51 (69)</td>
<td>.3386</td>
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<tr>
<td>HIV risk group</td>
<td></td>
<td></td>
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<tr>
<td>MSM</td>
<td>303 (48)</td>
<td>303 (53)</td>
<td>0 (0)</td>
<td>.9718</td>
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<tr>
<td>Heterosexual</td>
<td>250 (40)</td>
<td>222 (39)</td>
<td>28 (38)</td>
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<td>IDU</td>
<td>62 (10)</td>
<td>43 (7)</td>
<td>19 (26)</td>
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<tr>
<td>Blood transfusion</td>
<td>11 (2)</td>
<td>8 (1)</td>
<td>3 (4)</td>
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<tr>
<td>Other/unknown</td>
<td>93 (13)</td>
<td>69 (11)</td>
<td>24 (32)</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>24 (21–26)</td>
<td>24 (22–27)</td>
<td>23 (20–25)</td>
<td>.0067</td>
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<td>CDC stage C</td>
<td>168 (23)</td>
<td>155 (24)</td>
<td>13 (18)</td>
<td>.2158</td>
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<tr>
<td>CD4 count nadir, cells/µL</td>
<td>183 (80–276)</td>
<td>183 (75–279)</td>
<td>183 (125–245)</td>
<td>.7248</td>
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<td>CD8 count zenith, cells/µL</td>
<td>1365 (1032–1843)</td>
<td>1361 (1032–1861)</td>
<td>1446 (920–1788)</td>
<td>.3862</td>
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<tr>
<td>CD4 count, cells/µL</td>
<td>565 (435–742)</td>
<td>576 (432–756)</td>
<td>520 (458–625)</td>
<td>.0843</td>
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<tr>
<td>CD8 count, cells/µL</td>
<td>727 (530–991)</td>
<td>727 (529–986)</td>
<td>717 (570–1097)</td>
<td>.2352</td>
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<td>CD4/CD8 ratio</td>
<td>0.8 (0.6–1.1)</td>
<td>0.8 (0.6–1.1)</td>
<td>0.7 (0.5–1.0)</td>
<td>.0864</td>
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<td>Duration of viral suppression*, y</td>
<td>5.4 (3.3–9.1)</td>
<td>5.5 (3.3–9.1)</td>
<td>4.8 (3.0–7.9)</td>
<td>.1248</td>
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<td>ART introduction</td>
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<td></td>
<td></td>
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<tr>
<td>2002 or later</td>
<td>218 (30)</td>
<td>203 (31)</td>
<td>15 (20)</td>
<td>.0669</td>
</tr>
<tr>
<td>1997–2001</td>
<td>277 (39)</td>
<td>245 (38)</td>
<td>32 (43)</td>
<td></td>
</tr>
<tr>
<td>Before 1997</td>
<td>224 (31)</td>
<td>197 (31)</td>
<td>27 (36)</td>
<td></td>
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<tr>
<td>Current PI-containing regimen</td>
<td>428 (60)</td>
<td>380 (69)</td>
<td>48 (65)</td>
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<tr>
<td>Current NNRTI-containing regimen</td>
<td>260 (36)</td>
<td>240 (67)</td>
<td>20 (27)</td>
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<tr>
<td>Raltegravir-containing regimen</td>
<td>96 (13)</td>
<td>85 (13)</td>
<td>10 (14)</td>
<td>.9357</td>
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<tr>
<td>Maraviroo-containing regimen</td>
<td>15 (2)</td>
<td>13 (2)</td>
<td>2 (3)</td>
<td>.6963</td>
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<tr>
<td>Current NRTI-containing regimen</td>
<td>665 (92)</td>
<td>562 (82)</td>
<td>73 (99)</td>
<td>.743</td>
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<td>Positive anti-HCV IgG</td>
<td>105 (15)</td>
<td>94 (15)</td>
<td>11 (15)</td>
<td>.8685</td>
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<tr>
<td>Positive HBsAg</td>
<td>53 (8)</td>
<td>49 (8)</td>
<td>4 (5)</td>
<td>.4898</td>
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<tr>
<td>Positive anti-CMV IgG (n = 645)</td>
<td>NA</td>
<td>564 (87)</td>
<td>NA</td>
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</table>
CMV as a major risk factor for persistently low CD4/CD8 ratio

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>CD4/CD8 Ratio &lt;1 (n=416)</th>
<th>CD4/CD8 Ratio ≥1 (n=229)</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Odds Ratio (95% CI)</td>
<td>PValue</td>
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<tr>
<td>Age, y</td>
<td>48 (42–56)</td>
<td>51 (45–57)</td>
<td>0.8 (.7–.9)</td>
<td>.005</td>
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<tr>
<td>Male sex</td>
<td>300 (72)</td>
<td>178 (78)</td>
<td>0.7 (.5–1.0)</td>
<td>.061</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24 (22–27)</td>
<td>23 (21–26)</td>
<td>1.0 (1.0–1.1)</td>
<td>.418</td>
</tr>
<tr>
<td>HIV risk group</td>
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<tr>
<td>MSM</td>
<td>186 (45)</td>
<td>117 (51)</td>
<td>1</td>
<td>.226</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>153 (37)</td>
<td>69 (30)</td>
<td>1.4 (1.0–2.1)</td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>26 (6)</td>
<td>17 (8)</td>
<td>1.0 (0.6–6.5)</td>
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<tr>
<td>Other/unknown</td>
<td>51 (12)</td>
<td>26 (11)</td>
<td>1.4 (0.9–2.4)</td>
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<tr>
<td>CD4 count nadir², cells/μL</td>
<td>153 (56–240)</td>
<td>233 (141–315)</td>
<td>0.7 (.6–8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of viral suppression³, y</td>
<td>4.9 (3.1–8.5)</td>
<td>6.3 (3.7–10.1)</td>
<td>0.7 (.5–8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ART introduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002 or later</td>
<td>123 (30)</td>
<td>80 (35)</td>
<td>1</td>
<td>.004</td>
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<tr>
<td>1997–2001</td>
<td>150 (36)</td>
<td>95 (41)</td>
<td>1.1 (.8–1.6)</td>
<td></td>
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<tr>
<td>Before 1997</td>
<td>143 (34)</td>
<td>54 (24)</td>
<td>1.9 (1.2–2.8)</td>
<td></td>
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<tr>
<td>Positive anti-HCV IgG</td>
<td>68 (16)</td>
<td>26 (11)</td>
<td>1.4 (0.9–2.2)</td>
<td>.159</td>
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<tr>
<td>Positive HBsAg</td>
<td>36 (9)</td>
<td>13 (6)</td>
<td>1.5 (0.8–2.8)</td>
<td>.21</td>
</tr>
<tr>
<td>Positive anti-CMV IgG</td>
<td>375 (90)</td>
<td>189 (83)</td>
<td>1.9 (1.2–3.1)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Impact of CMV Infection on CD8 T cells

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 IFN-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?

Can we decrease the HIV Reservoirs and stop ART? Remission?

or eradicate HIV Sterilizing Cure?

Persistence of HIV Reservoirs

Current Models of HIV Cure:

- LTNPs
- HIV/Elite Controllers
- Post-Treatment Controllers

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

A- Infection

Activation

HIV provirus integration in active regions of memory cell genome

Activation \Rightarrow HIV Production

CD4+ antigen-presenting cell

Antigen-activated CD4+ T cells

HIV-infected CD4+ T cells

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

Persistence of latent reservoirs in Short-lived Memory cells

PD1 Blockade of - T cell functions - HIV production

Cell & Reservoir Lifespan

Antigen-activate d CD4+ T cells

CD4+ antigen-presenting cell

HIV provirus integration in active regions of memory cell genome

Activation \Rightarrow HIV Production

Antibodies

Death of most HIV-producing activated Memory CD4+ T cells: due to HIV cytopathogenicity or immune death
Models and Factors of Remission ???

Low Reservoirs ?

Strong Immunity or Weak infection of some 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 expressing CD32a are all monocytes, macrophages and 1% activated memory CD4 T cells *(A Noto/G Pantaleo et al, JVI 2018; R Siliciano et al. CROI 2018; 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 convincing results

2) To target the residual cells producing HIV with ARV?
   ➢ No convincing 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-infection: (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?

- 3-fold reduction in the HIV reservoirs
- Transient increase in activation
- Decreased expression of ICP
- Sustained increase in anti-HIV CD8 T cells

➢ 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 Monrique, Luigi Buonaguro

Lancet, 2009

Delta-Nef SIV: Macaque Protection (Desrosiers et al. 94)
BUT: Pathogenic in new-born macaques (Ruprecht et al. 96)

Macaque « protection » BUT:
- species-dependent
- only/SIV strains grown in human cells (Stott et al. 1991)

Modest or poor immunogenicity for:
- Abs: gp protein
- T cells: DNA peptides

⇒ The search for:
- Prime-Boost strategies
- a T cell based HIV vaccine
Progress towards development of an HIV vaccine

Macaque Protection - species-dependent - only/SIV strains grown in human cells (Stott et al. 1991)

Delta-Nef SIV: macaque Protection (Desrosiers et al. 94)
But: Pathogenic in new-born macaques (Ruprecht et al. 96)

Modest or poor immunogenicity for:
- Abs: protein
- T cells: DNA peptides
⇒ Prime-Boost strategies

The PoxV & AdenoV experiences

⇒ The search for:

a T cell based HIV vaccine
Vaccine: HIV Rec.Adeno5

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

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


- 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, B Autran)
Post RV144 HIV vaccine programme:

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

- Neutralize x clades at low concentrations (<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
The search for an anti-HIV Vaccine:

The combined Ab + CD8 T cells approach:

- 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

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

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

- Transient effect
- Selection of mutants

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

Yehuda Z. Cohen1, Julio C.C. Lorenzi1*, Lisa Krassnig1, John P. Barton2, Leah Burke3, Joy Pai3, Ching-Lan Lu3, Pilar Mendoza3, Thiago Y. Oliveira3, Christopher Sleckman3, Katrina Millard1, Allison L. Butler1, Juan P. Dizon1, Shiraz A. Belblidia1, Maggi Witmer-Pack1, Irina Shimeliovich3, Roy M. Gulick3, Michael S. Seaman4, Mila Jankovic3, Marina Caskey1**, and Michel C. Nussenzweig3***

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

ARV for all ? The 90 – 90 – 90 strategy

Circumcision Microbicides ?

PrEP with ARV

we still need HIV vaccines

?????
Univ Pierre et Marie Curie, Pitié-Salpêtrière,

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

Immunogenetics
I Theodorou

HIV immunity
V Appay D Sauce

IPLESP Inserm U1136

Clinical research
Virology Epidemiology Oncology
C Katlama V Calvez D Costagliola JP Spano
R Tubiana AG Marcelin
MA Valantin

ALT ANRS CO15, Co21 Cohort, VISCONTI, OPTIPRIM and Reservoir study groups:
C Rouzioux, V Avettand, Univ. Paris-5, H Agut, UPMC & CIMIT