

CHAIRE DE MICROBIOLOGIE ET MALADIES INFECTIEUSES  
Année académique 2019-2020

Philippe SANSONETTI

*Ultima Verba...*

Cours les mercredis de 16h à 17h30, suivis des séminaires  
Amphithéâtre Maurice Halbwachs

**Séminaire du 15  
Janvier 2020  
17h30-18h30**

**A vaccine against AIDS: dream or (soon)  
reality?**

**Un vaccin contre le Sida: rêve ou (bientôt)  
réalité?**

**Françoise BARRE-SINOUSI**

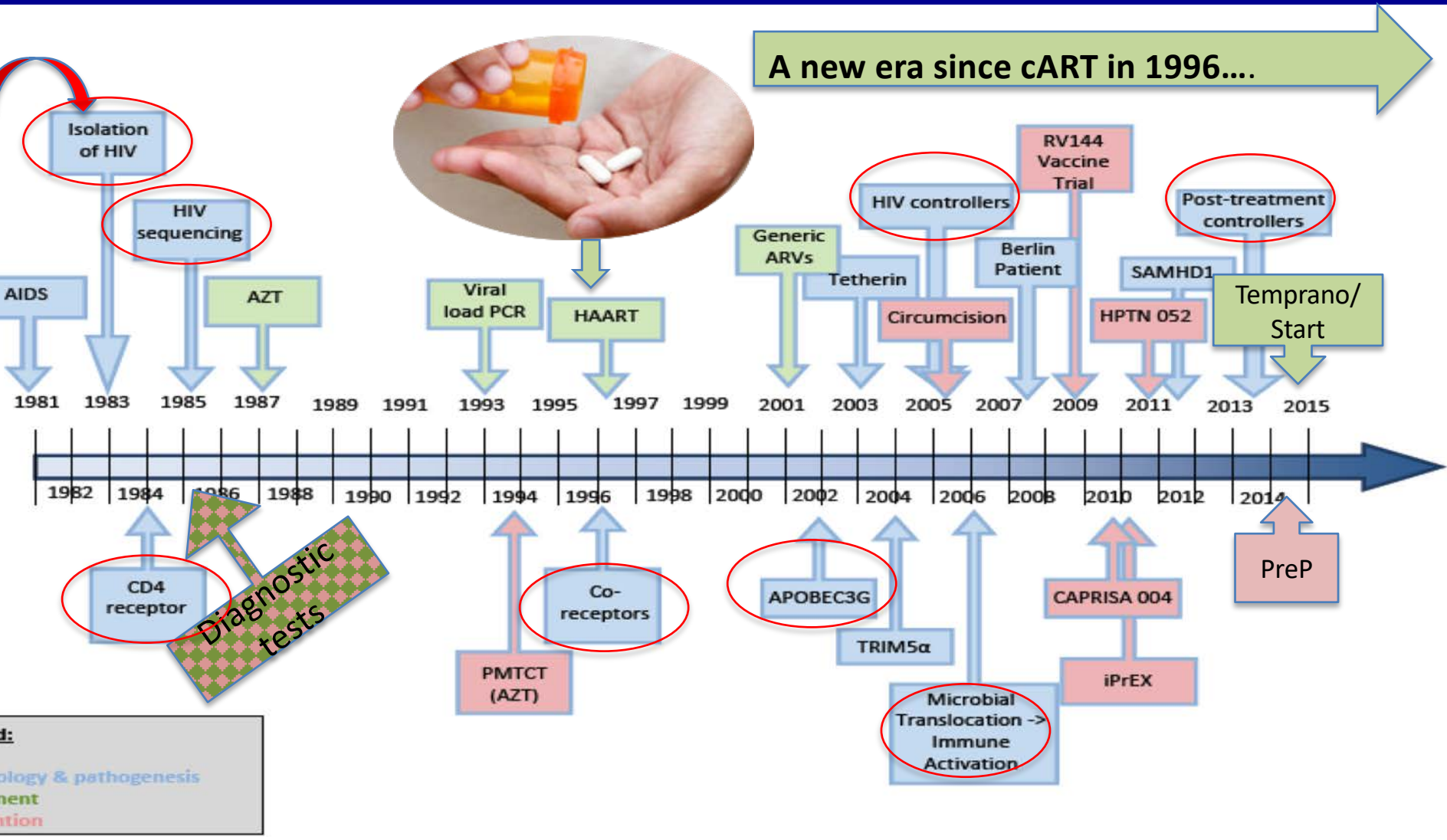
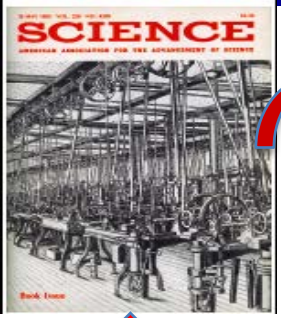


... FOR RESEARCH, FOR HEALTH,  
... **FOR OUR FUTURE**

  
Institut Pasteur

# 37 years of HIV Science

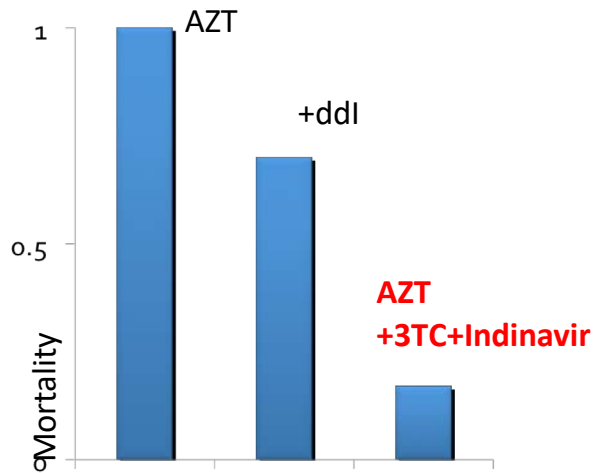
## A good example of translational research



# HIV treatment: 3 Revolutions...

**1996:**

**cART therapeutic revolution...**

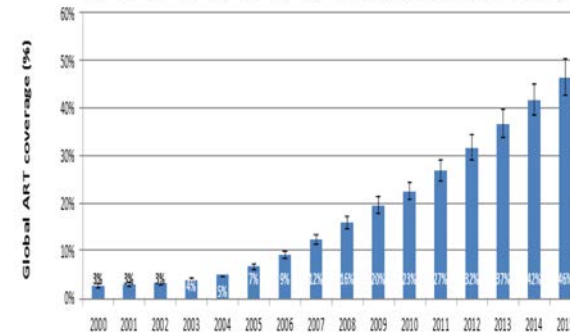


*Fischl MA et al, New Engl J Med 1987,  
Caesar study, Lancet 1997,  
Hammer SM et al, New Engl J Med 1997*

**Since 2003:**

**Universal cART access revolution ...**

Worldwide mass treatment for a chronic emergent viral disease is possible



**3rd Revolution: Therapeutic prophylaxis!**



**Non detectable HIV on cART, no transmission!**

# Combination of tools scientifically validated for prevention



Vaginal/rectal gel  
Vaginal film  
Vaginal ring

Male  
circumcision

Treatment of  
STIs

Female and Male  
Condoms

HIV Counselling  
and Testing

Behavioural  
Intervention

Harm  
Reduction

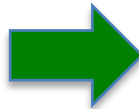
Treatment for  
prevention

Oral pre-exposure  
prophylaxis (PreP)

Post Exposure  
prophylaxis (PEP)

**ARV prophylaxis (0-99% efficacy..)**

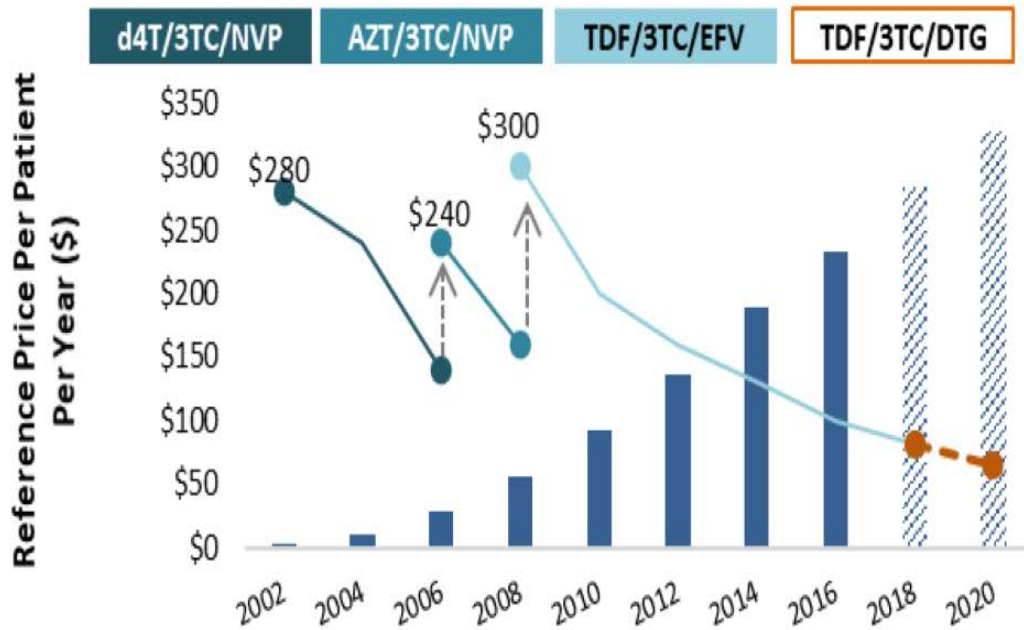
*Future PreP: long-lasting ARVs  
(injectable or implants ou mAbs?)*



# New drugs, new formulations

## Past, present...

HIV | Prices for current key adult first-line products decline and new products drive further cost savings



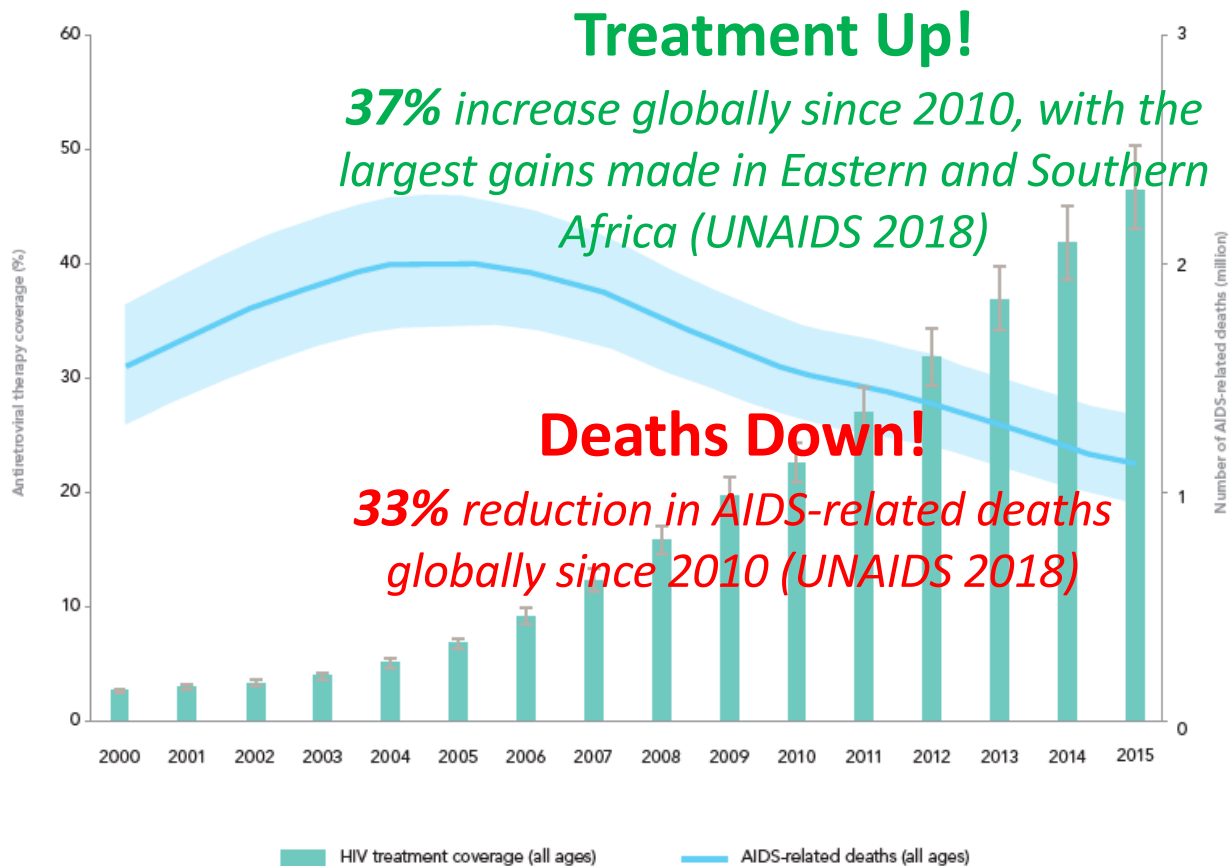
## ...and future



Source: Charlotte Watts, Department for International Development

# Increase of ART coverage since 2000

## Decline in HIV incidence and mortality over time



**But, in 2018:**

- only 62% PLWH on cART,
- 770 000 HIV-related deaths
- 1.7 M people newly infected yearly (180000 infants)
- Increase of Pre-Tx drug resistance in LMIC....

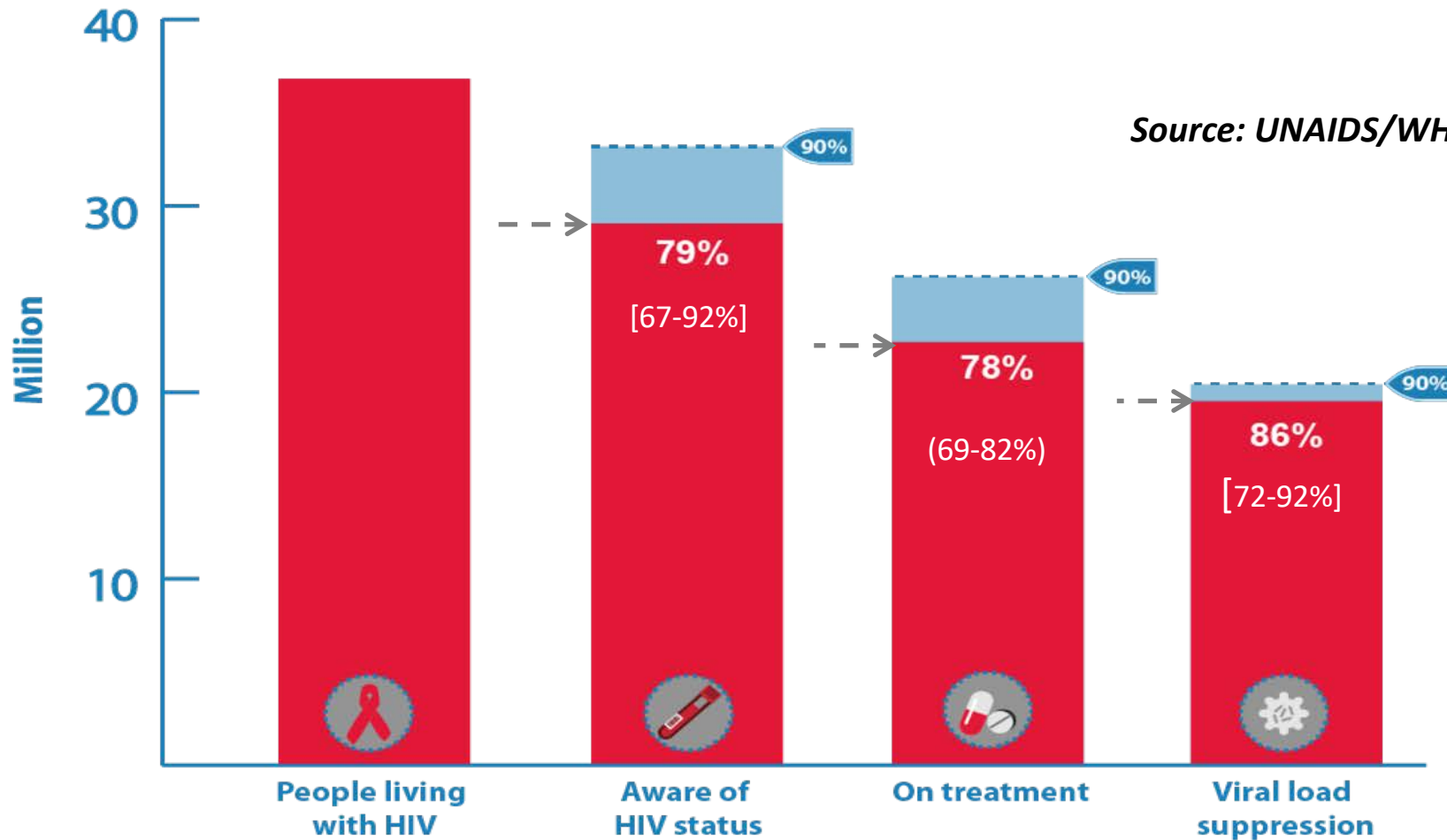
Sources: GA

**37,9 Millions of PLWH (1,7 M infants..)....**



# UNAIDS 90-90-90 targets

## HIV testing and care continuum, global (2018)



= 53% of PLHIV non-transmitters (73% targeted)

# Key Challenges and Priorities in HIV/AIDS today

## Prevent new infections

*(education, condoms, circumcision, risk reduction, PreP...)*

## Test, treat and retain

- 20-25% of HIV+ people ignore their status
- Cascade of continuum of care (79% on ART and 86% of viral suppression...)

- **Political willingness**

- **International Investments**

- **Fighting against repressive legislation/stigma/discrimination (74 countries..): 54% new infections in key populations; 95% in Eastern Europe, Central Asia, Middle East and North Africa.....**

- **Leadership/governance/National integrated policies**

- **Strengthen health systems and services (linking prevention, care and treatment services)**

- **Innovations to optimize prevention, testing, care and treatment (self testing, early test and treat, POC, long acting drugs, community cART delivery and support, digital/mHealth/social media...)**

**Redesign health system and delivery models**

Personalised Home Based & Community Services

Primary Health Care Clinics

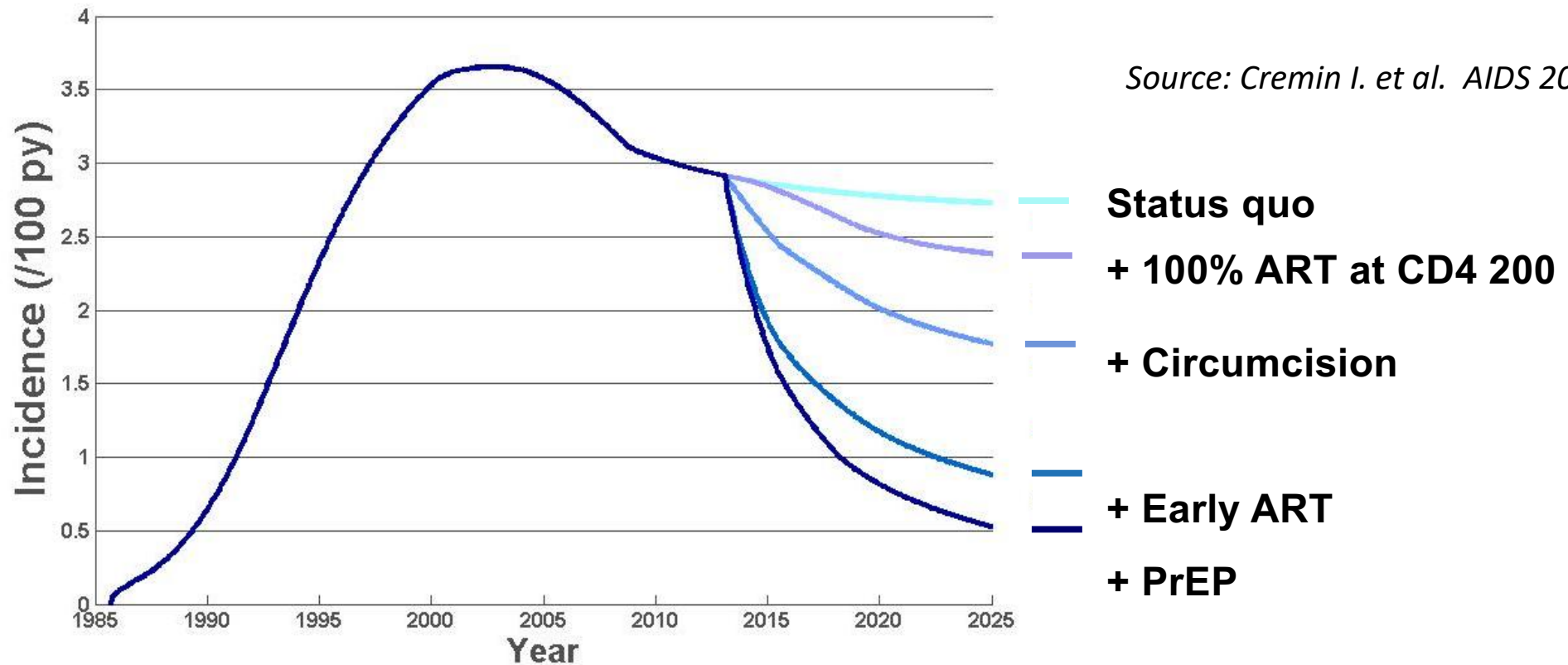
Hospitals

Down-referral

Up-referral



# Ending the HIV epidemic achievable?



**Yes, controlling HIV epidemic control is achievable!  
But HIV vaccine and cure are essential for eradication**

# Key scientific challenges and Priorities in HIV science

## HIV Vaccine discovery

Still no correlates of protection but **significant progresses in HIV vaccine research** since 2009..

## Comorbidities on ART

HIV infection, a chronic condition on life long cART but **non AIDS related comorbidities**

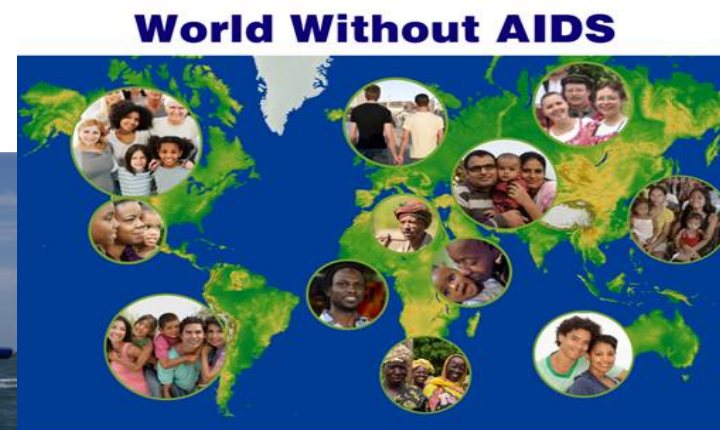
## HIV Cure discovery

Persistent HIV infection on HAART is the main hurdle science must tackle to achieve an HIV "Cure"

Better knowledge on HIV basic science on latency, immunology and pathogenesis

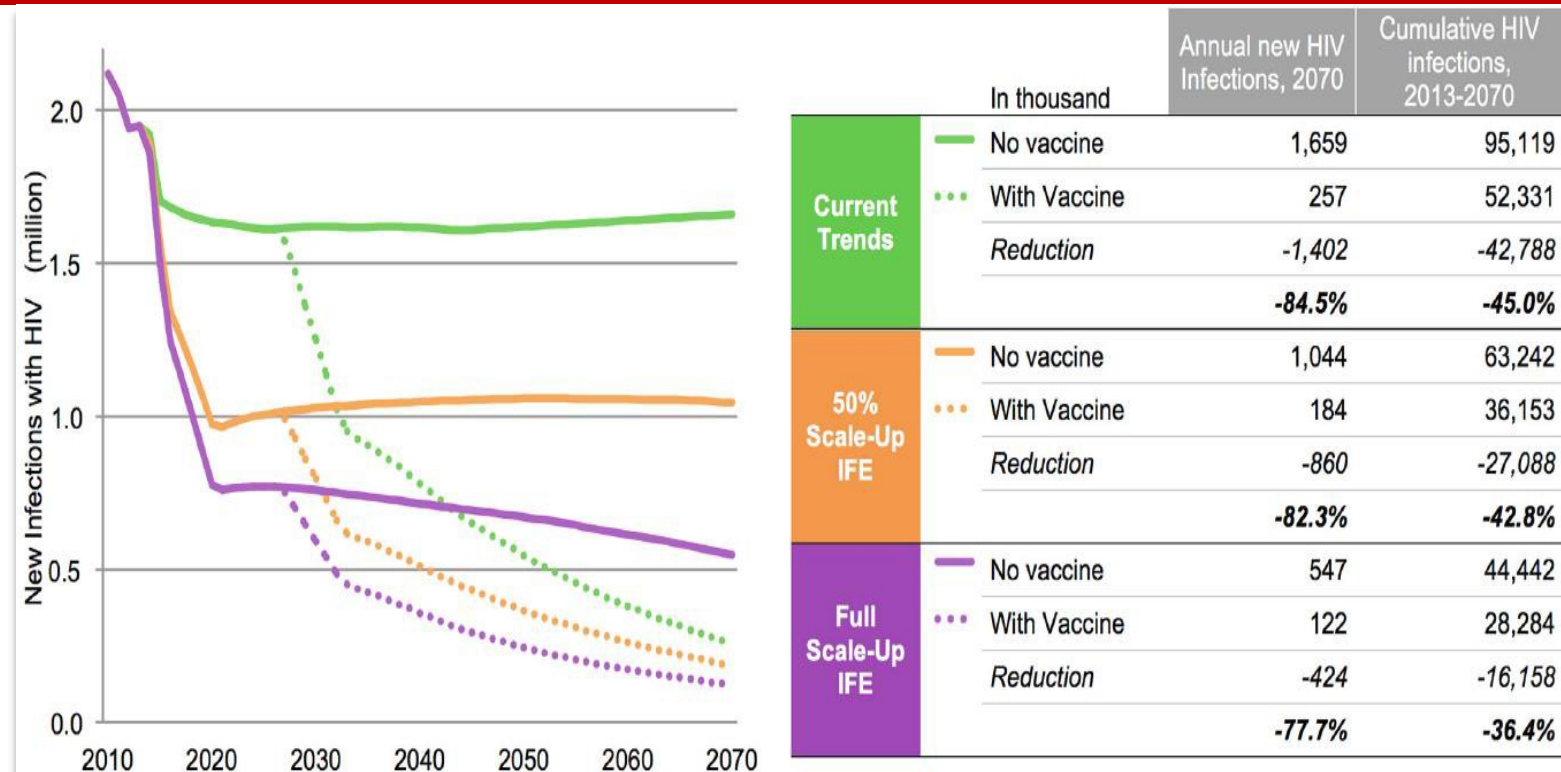


**Novel Vaccine and Therapeutic Strategies?**



# Potential impact of an HIV vaccine

## Reduction of new annual HIV infections with & without a vaccine under different prevention scale-up scenarios



- **Assumptions: Vaccine** introduction in 2027, 50% coverage, 70% efficacy
- **IFE = UNAIDS' Investment Framework Enhanced** includes **scale-up of PrEP, TasP, and other prevention methods** (Harmon, et al. PLOS One. 2016)

# HIV Vaccine Efficacy Results to Date

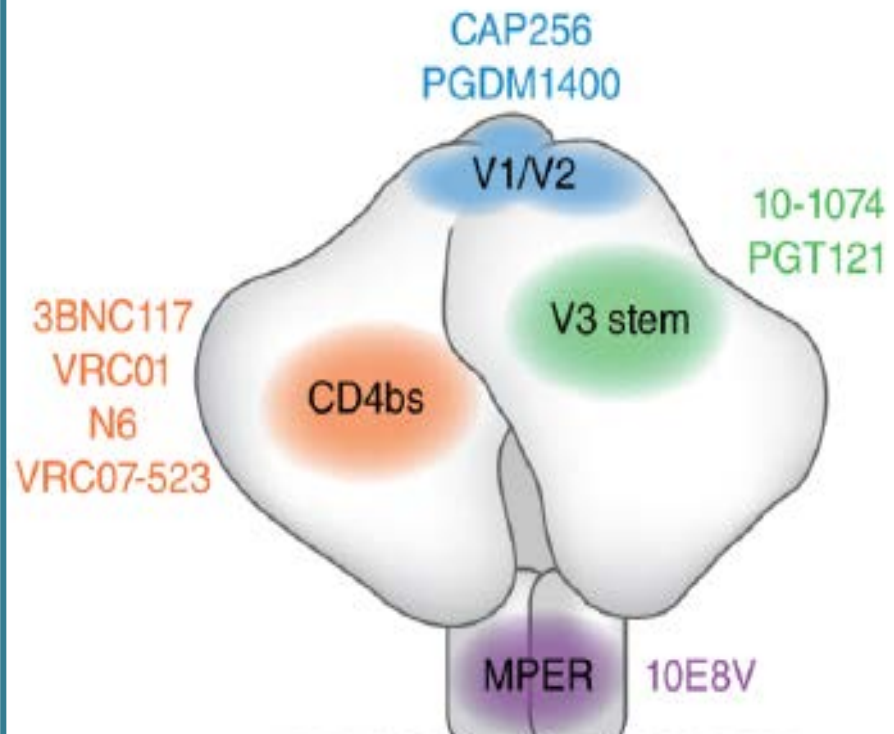
YEAR	TRIAL NAME/ PRODUCT/CLADE	LOCATION	#	RESULT
2003	VAX003 AIDSVAX B/B	Canada, Netherlands, Puerto Rico, US	5,417	No effect
2003	VAX004 AIDSVAX B/E	Thailand	2,546	No effect
2007	STEP MRK-Ad5 B	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US	3,000	Immunizations halted early for futility; subsequent data analysis found potential for increased risk of HIV infection among Ad5- seropositive, uncircumcised men.
2007	Phambili MRK-Ad5 B	South Africa	801	Immunizations halted based on STEP trial result.
2009	Thai Prime-Boost/RV 144 ALVAC-HIV (vCP1521) and AIDSVAX B/E			
2013	HVTN 505 DNA and Ad5 A/B/C			ly for futility; vaccine HIV infection nor reduce viral load among vaccine recipients who became infected with HIV; follow-up continues.

**Correlation with antibodies to the conserved region of V2, previously almost completely ignored by the HIV vaccine field, were highly correlated with efficacy.**

# Since 2009

## New perspectives for both HIV vaccine and cure...

- Non neutralizing but protective antibodies (*ADCC, Fc-mediated, others...*)?
- Identification of new very potent broadly neutralizing antibodies in HIV+ patients (*“elite neutralizers”*), structurally and functionally characterized.
- Identification of new sites of vulnerability of HIV env (*MPER, CD4bs, V1/V2 and V3, glycan side chain on outer domain*)



nature  
medicine

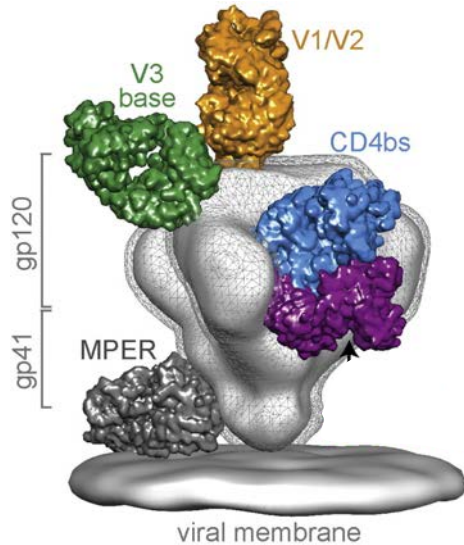
REVIEW ARTICLE

<https://doi.org/10.1038/s41591-019-0412-8>

Broadly neutralizing anti-HIV-1 monoclonal antibodies in the clinic

Marina Caskey<sup>1\*</sup>, Florian Klein<sup>2,3,4\*</sup> and Michel C. Nussenzweig<sup>1,5\*</sup>

## HIV-1 Env vulnerability sites



# Antiviral activities of HIV-1 bNAbs

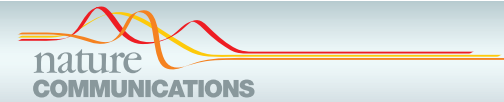
Brief Definitive Report

2013

JEM

## Broadly neutralizing antibodies that inhibit HIV-1 cell to cell transmission

Marine Malbec,<sup>1,3,4</sup> Françoise Porrot,<sup>1,3</sup> Rejane Rua,<sup>1,3,4</sup> Joshua Horwitz,<sup>5</sup> Florian Klein,<sup>5</sup> Ari Halper-Stromberg,<sup>5</sup> Johannes F. Scheid,<sup>5</sup> Caroline Eden,<sup>5</sup> Hugo Mouquet,<sup>2,5,7</sup> Michel C. Nussenzweig,<sup>5,6</sup> and Olivier Schwartz<sup>1,3</sup>



Adapted from:  
Halper-Stromberg  
and Nussenzweig,  
JCI, 2016  
Scharf et al., Cell  
Reports, 2014

ARTICLE

Received 23 Oct 2015 | Accepted 26 Jan 2016 | Published xx xxx 2016

DOI: 10.1038/ncomms10844

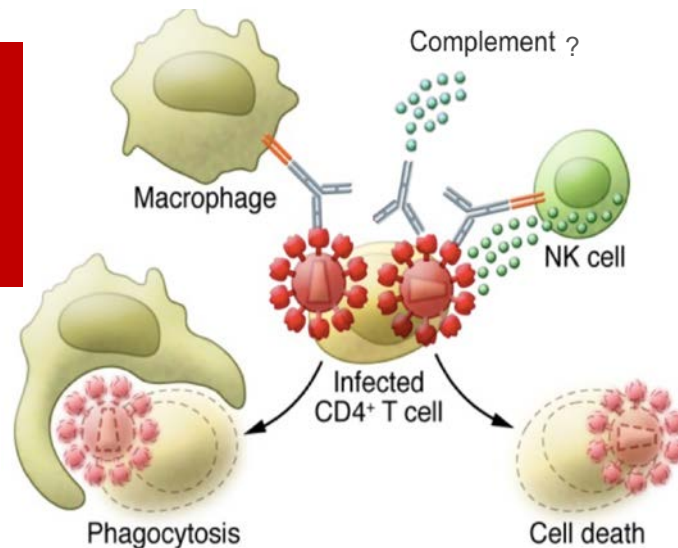
OPEN

2016

## Elimination of HIV-1-infected cells by broadly neutralizing antibodies

Timothée Bruel<sup>1,2</sup>, Florence Guivel-Benhassine<sup>1,2</sup>, Sonia Amraoui<sup>1,2</sup>, Marine Malbec<sup>3,4</sup>, Léa Richard<sup>1,2</sup>, Katia Bourdic<sup>5,6,7,8</sup>, Daniel Aaron Donahue<sup>1,2</sup>, Valérie Lorin<sup>3,4</sup>, Nicoletta Casartelli<sup>1,2</sup>, Nicolas Noël<sup>5,6,7,8</sup>, Olivier Lambotte<sup>5,6,7,8</sup>, Hugo Mouquet<sup>3,4</sup> & Olivier Schwartz<sup>1,2,9</sup>

## Fc-mediated effector functions



VACCINES AND ANTIVIRAL AGENTS



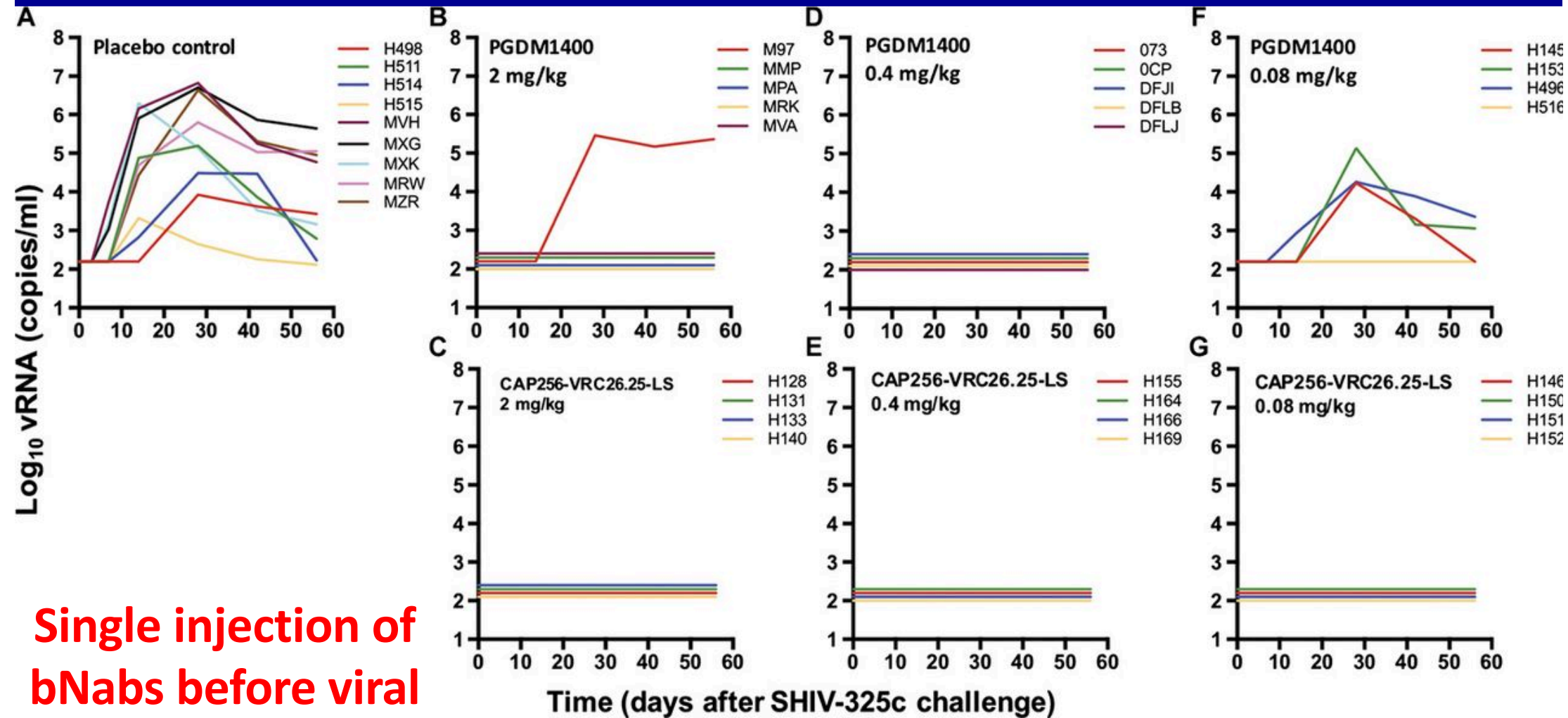
## Lack of ADCC Breadth of Human Nonneutralizing Anti-HIV-1 Antibodies

2017

Timothée Bruel,<sup>a,b,i</sup> Florence Guivel-Benhassine,<sup>a,b</sup> Valérie Lorin,<sup>c,d</sup> Hugues Lortat-Jacob,<sup>j</sup> Françoise Baleux,<sup>k</sup> Katia Bourdic,<sup>e,f,g,h</sup> Nicolas Noël,<sup>e,f,g,h</sup> Olivier Lambotte,<sup>e,f,g,h</sup> Hugo Mouquet,<sup>c,d,i</sup> Olivier Schwartz<sup>a,b,i</sup>

From O. Schwartz

# Protective efficacy of V2 env specific antibodies (PGDM1400 and CAP256-VRC26.25-LS) against SHIV-325c in rhesus macaques.



Single injection of bNabs before viral challenge

Boris Julg et al.,  
*Sci Transl Med* 2017;9:eaal1321



HIV VACCINE  
TRIALS NETWORK

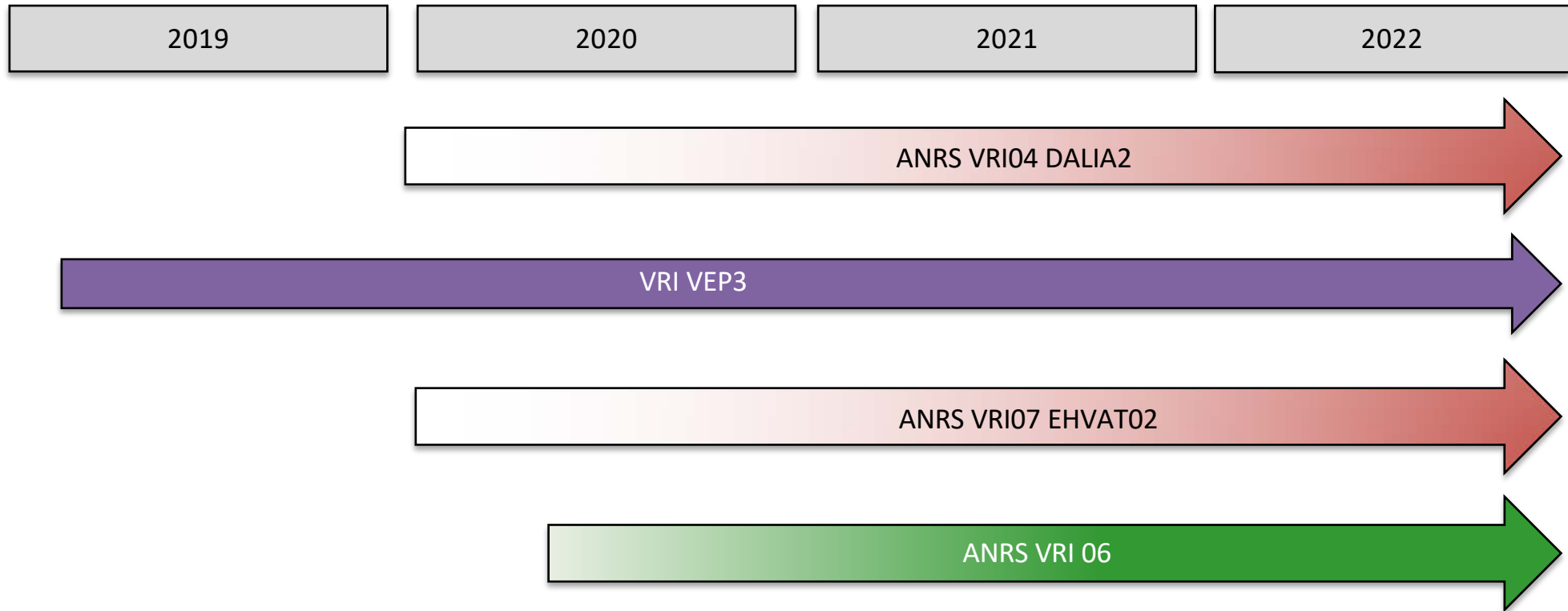


# Ongoing HIV Prevention Efficacy Trials Evaluating Vaccines, Monoclonal Antibodies (mAbs), or PrEP




Trial	Product	Population (Region), Sample Size	End of Study*
HVTN703/HPTN081 HVTN704/HPTN085	<b>AMP</b> mAb: Intravenous infusion of VRC01 vs. placebo	Women (Sub-Saharan Africa), n=1924 MSM+TG (Americas/Europe), n=2701	2020
HVTN 702	<b>Uhambo Vaccine</b> : ALVAC+subtype C gp120/MF59 vs. placebo	Men+Women (South Africa), n=5406	2021
HVTN 705	<b>Imbokodo Vaccine</b> : Ad26.Mos4.HIV + subtype C gp140/alum vs. placebo	Women (Sub-Saharan Africa), n=2600	2021
HVTN 706	<b>Mosaico Vaccine</b> : Ad26.Mos4.HIV + subtype C & Mosaic gp140/alum vs. placebo	MSM+TG (Americas/Europe), n=3800	2023
PrEPVacc	<b>PrEP/Vaccine</b> : oral TAF/FTC vs. TDF/FTC & DNA-HIV-PT123 + AIDSVAX B/E vs. DNA-HIV-PT123 plus CN54gp140/MPLA + MVA-CMDR/CN54gp140/MPLA vs. placebo	Men+Women (Sub-Saharan Africa), n=1688	2023
HPTN 083 HPTN 084	<b>PrEP</b> : Injectable (cabotegravir) vs. oral (TDF-FTC)	MSM+TGW (Americas/Asia/South Africa), n=4500 Women (Sub-Saharan Africa), n=3200	2023 2024



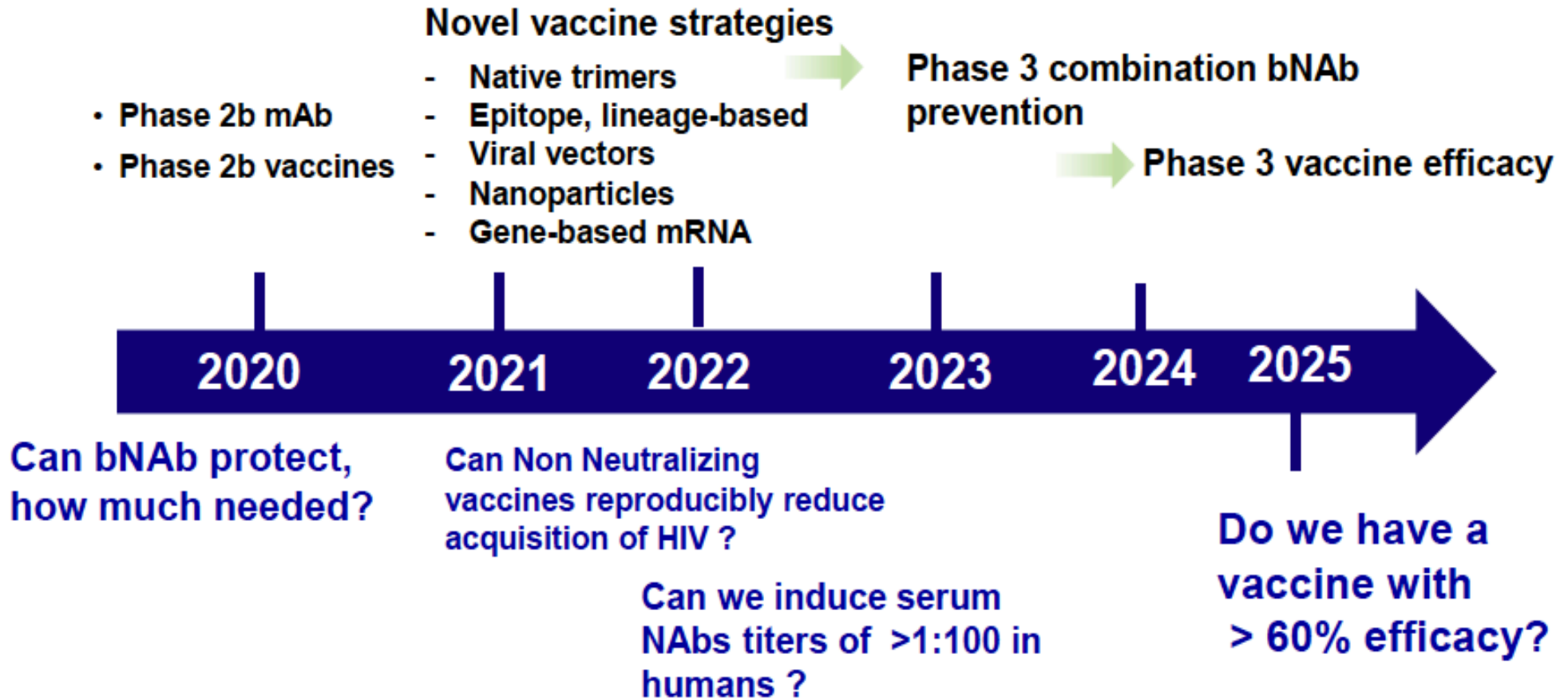
# VRI Ongoing and new Projects 2019-2020 – Clinical trials



**ANRS VRI04-DALIA2:** DC ex vivo+Hiltonol  
**ANRS VRI07 EHVAT02:** DNA/MVA + Vedoluzimab  
(anti  $\alpha 4\beta 7$ )  
**ANRS VRI06:**  $\alpha$ CD40.Env gp140+ DNA-HIV-PT123 HIV

-  Therapeutic
-  Prophylactic
-  Pathophysiology

# Next 5 years....



**Strategy integrating Basic and Clinical Science in the HIV vaccine science agenda using new technologies and innovative concepts**

# “Which kind of “HIV Cure” are we looking for?”

**Cure**

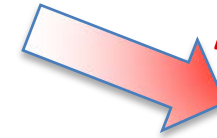


**Elimination of all latently infected cells**



**Berlin Patient  
London Patient?**

**HIV Reservoirs on cART....**



**ART-free durable  
Remission**



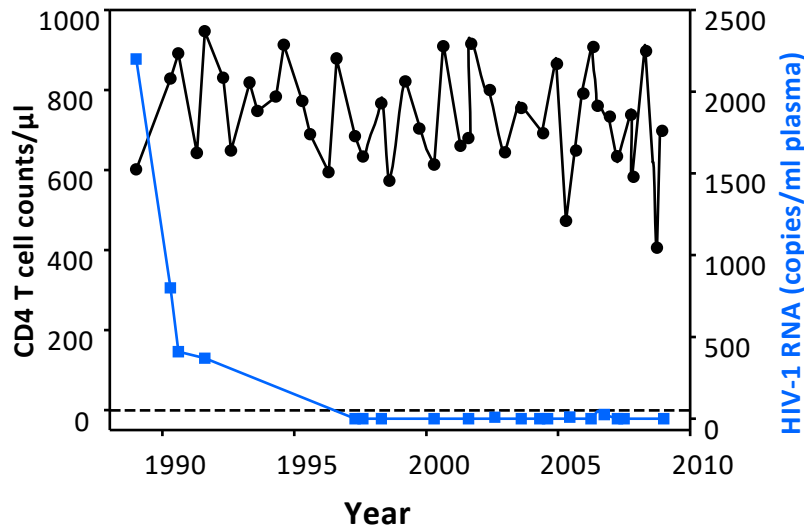
**Persistent control of HIV after ATI  
No disease progression  
No HIV-associated complications  
No risk to transmit**



**Proof of concept...**

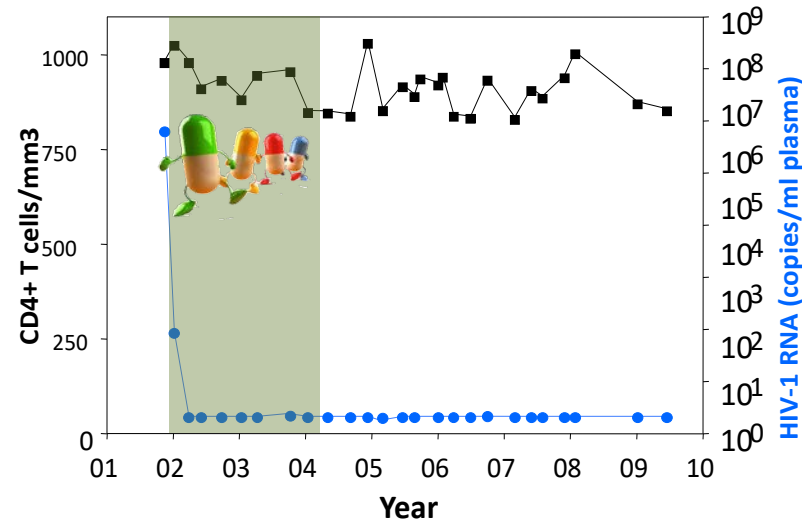
# HIV remission: examples are available

## Natural HIV controllers (HIC)



ANRS CO21 CODEX

## Post-treatment controllers (PTC)



ANRS VISCONTI

Often associated with favorable genetic (MHC) background  
<0.5% of all HIV patients

*Saez-Cirion and Pancino. Immunol Rev 2014*

Therapy started within 10 weeks following Primary Infection (*median 39 days p.i.*)  
~5% of early treated patients

*Saez-Cirion et al PLoS Path 2013, Lancet HIV 2016*

**Understanding the ability to durably contain HIV replication may guide new strategies towards HIV remission**

# Clues emerging from models of HIV remission

**Weak viral reservoirs**



**Optimal mechanisms  
of control**



**Natural HIV controllers**

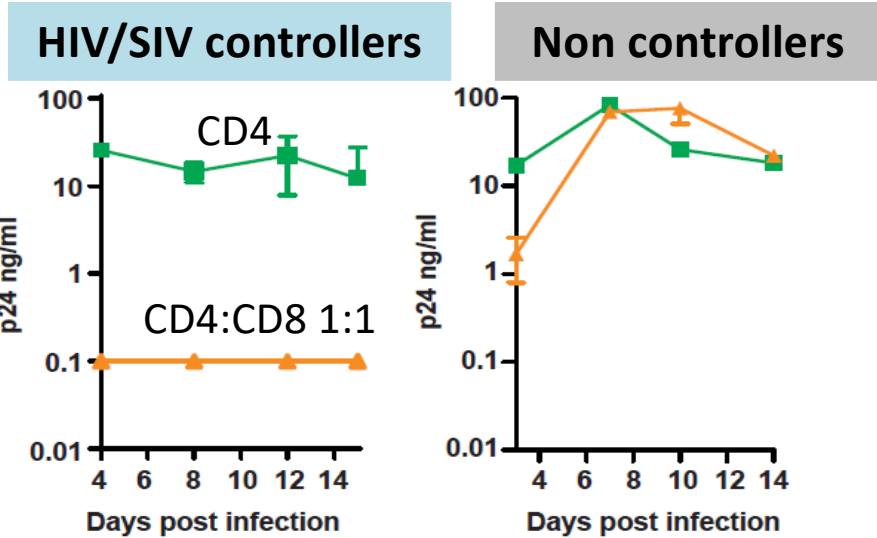
**CD4 T cell function**

**CD8 T cell responses**

**Post-treatment controllers**

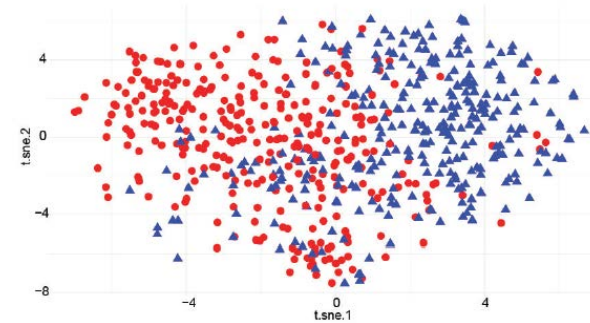
**NK cells**

# Optimal HIV-specific CD8+ T cell memory with superior antiviral potential in HIV Controllers



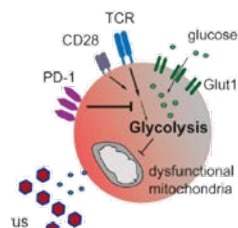
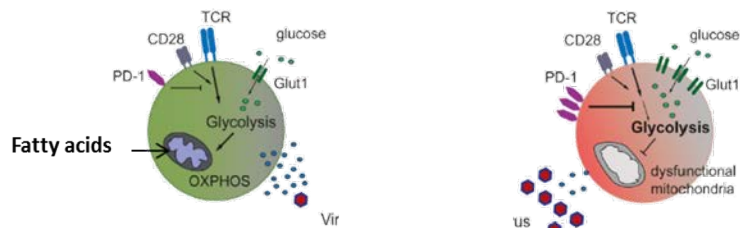
**Distinct single-cell signature of HIV CD8 T cells associated with control**

**controller vs non controller**



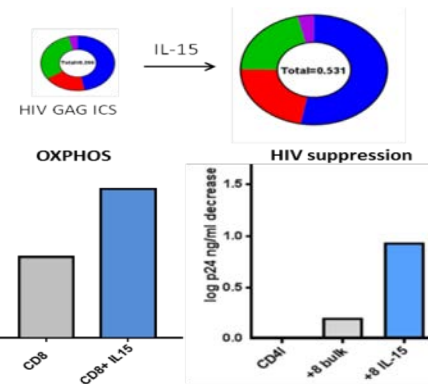
**Metabolic plasticity associated with optimal HIV memory**

**Metabolic reprogramming improves antiviral potential of HIV-specific cells**



**Efficient HIV-specific CD8+ T cells**  
 Effector potential  
 Survival capability  
 metabolic plasticity

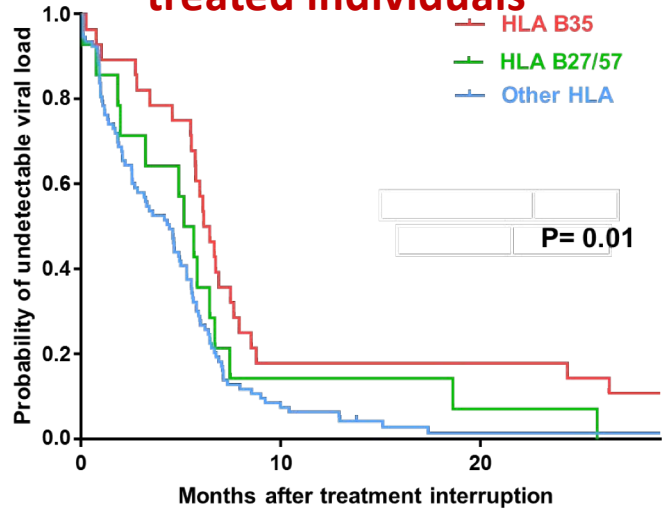
**Skewed HIV-specific CD8+ T cells**  
 Pro-apoptotic  
 Dependency on glycolysis



*Saez-Cirion PNAS 2007, Nat Prot 2010, Angin JI 2016, Passaes submitted, Angin et al Nat Metab*

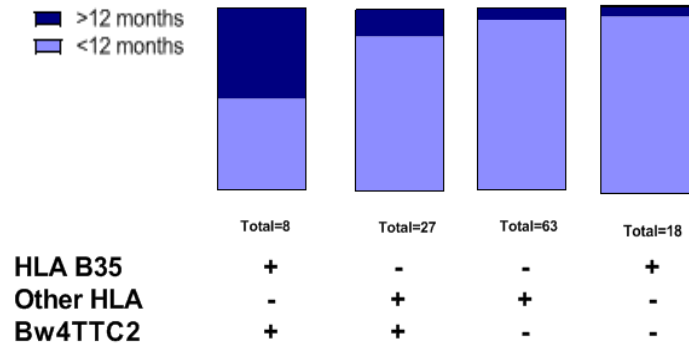
# Immunogenetic traits associated with NK cells contribute to Post-treatment HIV control

## HLA-B35 favors remission among early treated individuals

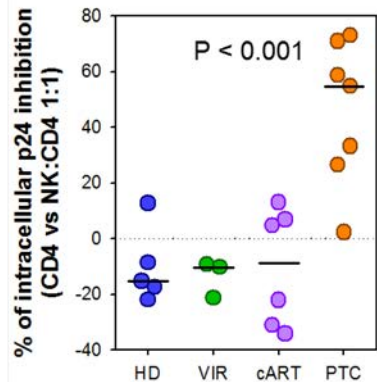
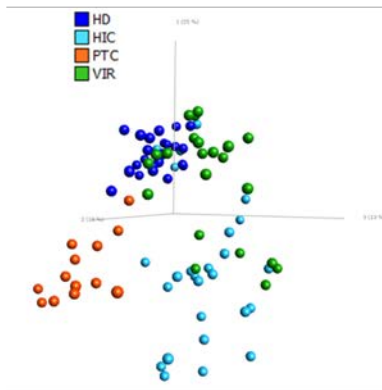


## Identification of a NK cell ligands associated genotype linked with remission

Duration of remission among early treated HIV infected individuals



## NK cells from PTC have a distinct phenotype and enhanced antiviral capacities



Essat, Scott-Algara et al  
unpublished

Coming next: analytic treatment interruption for pre-screened volunteers



# Challenges.....



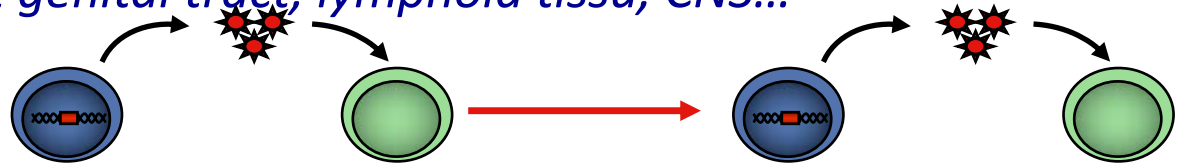
# HIV reservoirs in many cell subsets and lymphatic tissues

✓ **Major reservoirs are resting central & transitional CD4+ memory T cells** (*Persistent and stable on cART for decades*)

✓ **Other reservoir cells:** *naive T cells, memory stem T cells, T follicular helper cells (EC), myeloid cells, astrocytes, hematopoietic progenitor cells, etc...*

✓ **Anatomic reservoirs:** *GI & genital tract, lymphoid tissue, CNS...*

**Residual viral replication**

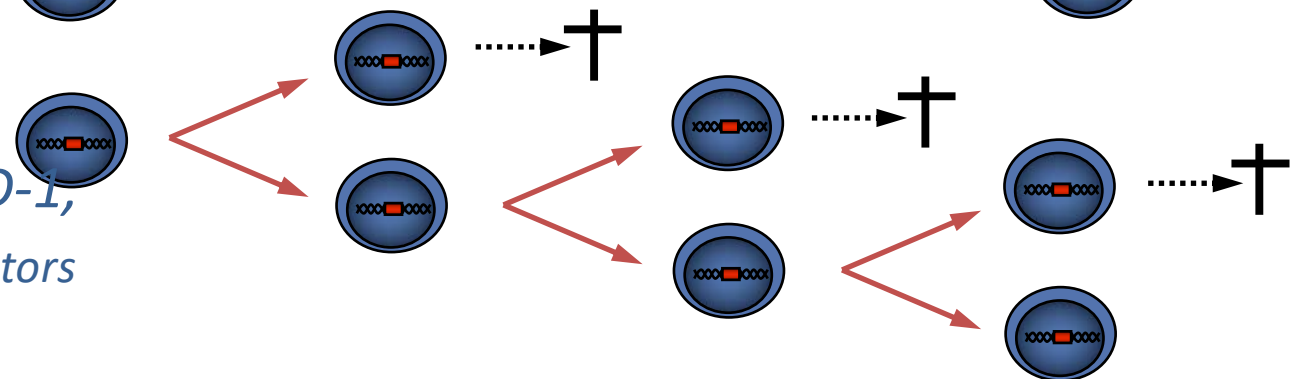


**T cell survival**

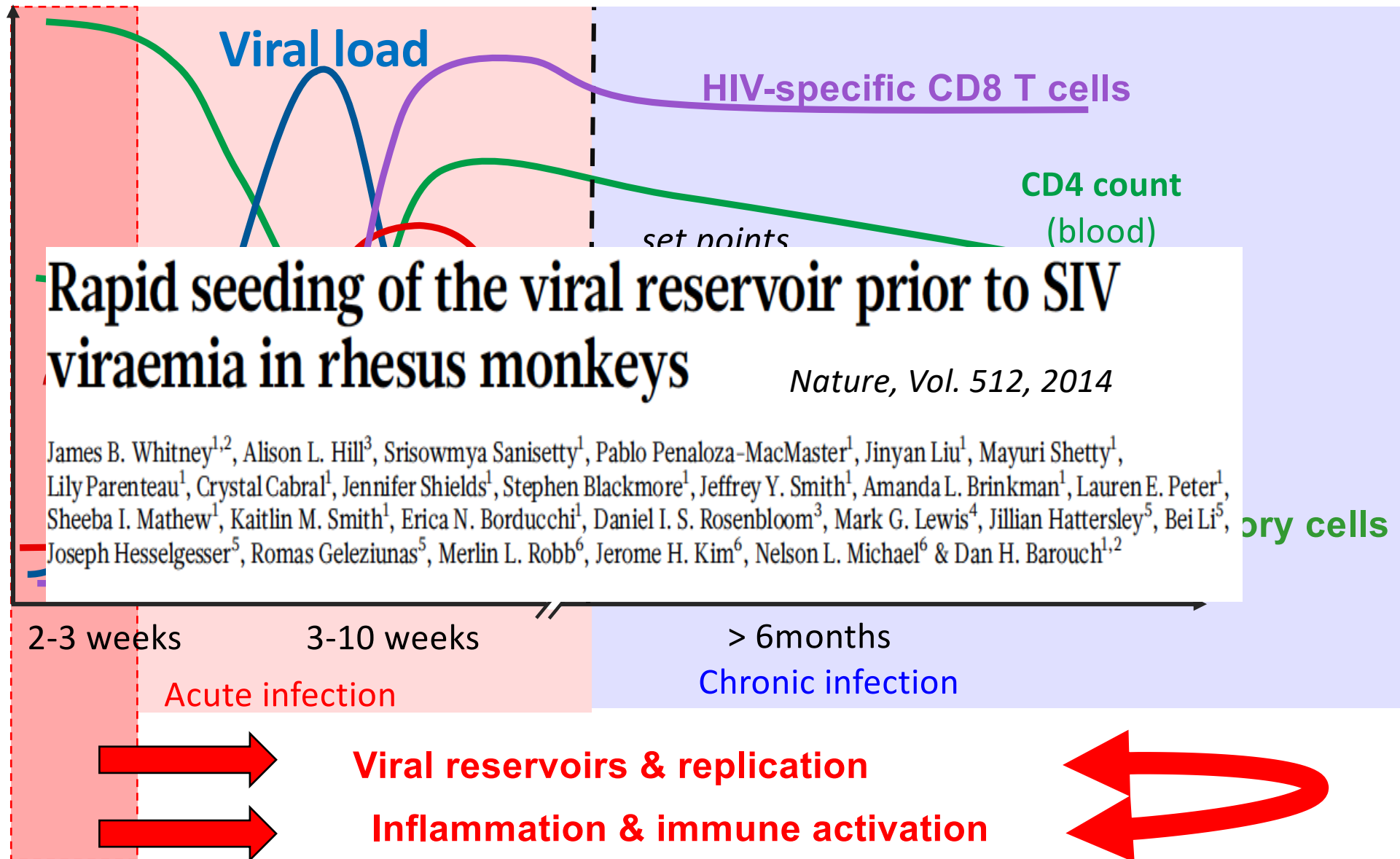


**Homeostatic Proliferation**

*(clonal expansion): expression of Immune checkpoints molecules (PD-1, LAG-3, TIGIT, CTLA-4), negative regulators of T cell responses, contributing to immune exhaustion...*



# HIV Reservoirs and immune activation...



**Opportunities?**

# Killing HIV-infected Cells

Dual-Affinity Re-Targeting Therapy (DART)

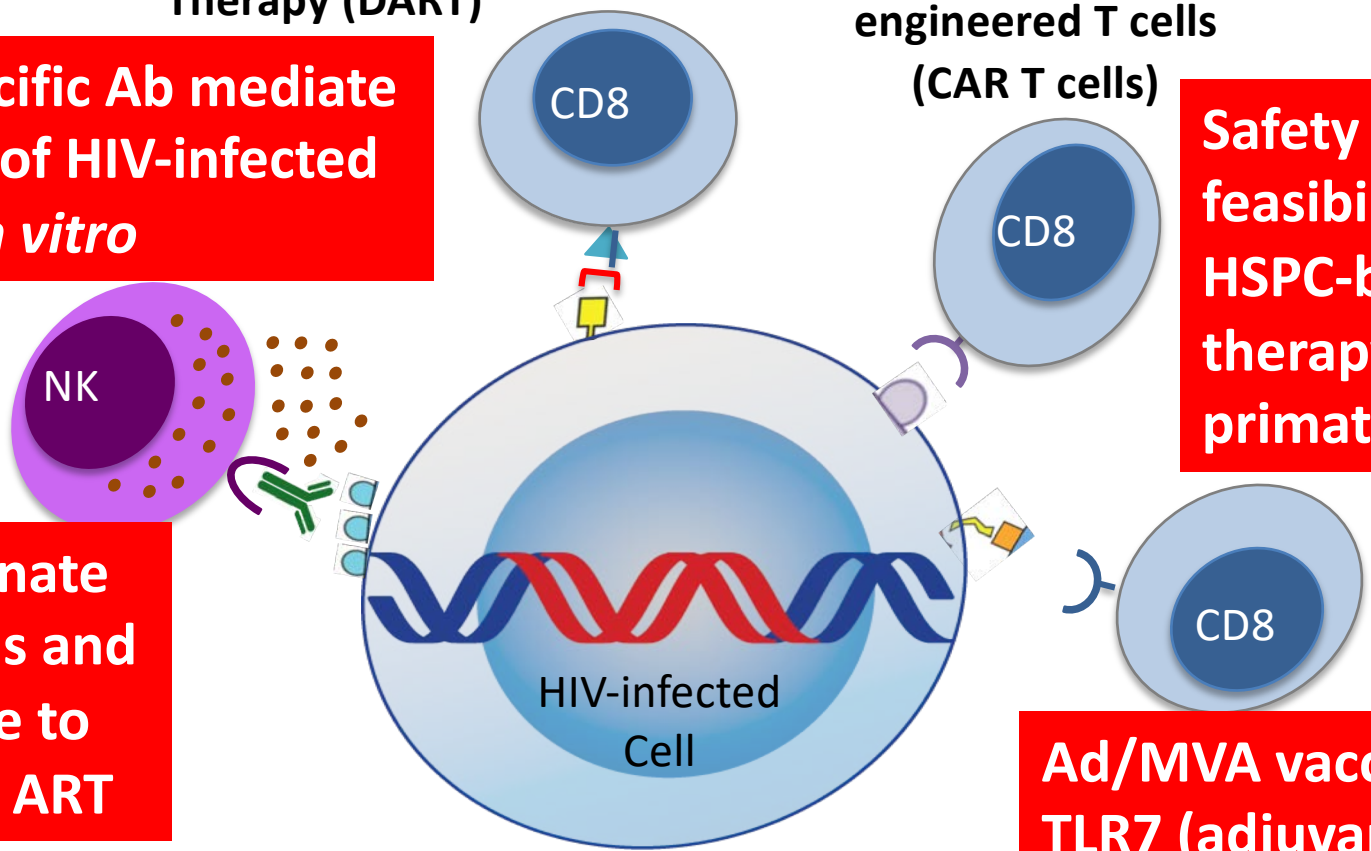
Genetically engineered T cells (CAR T cells)

Bi-specific Ab mediate killing of HIV-infected cells *in vitro*

Safety and feasibility of HSPC-based CAR therapy in primate models

Broadly Neutralizing Antibodies (bNAbs)

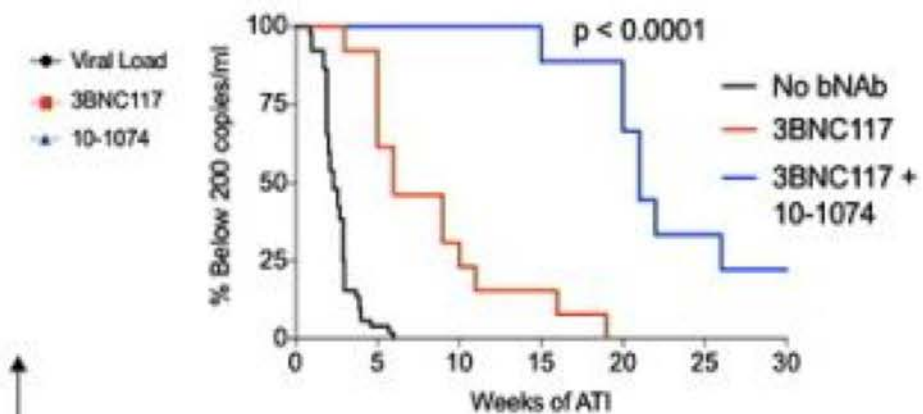
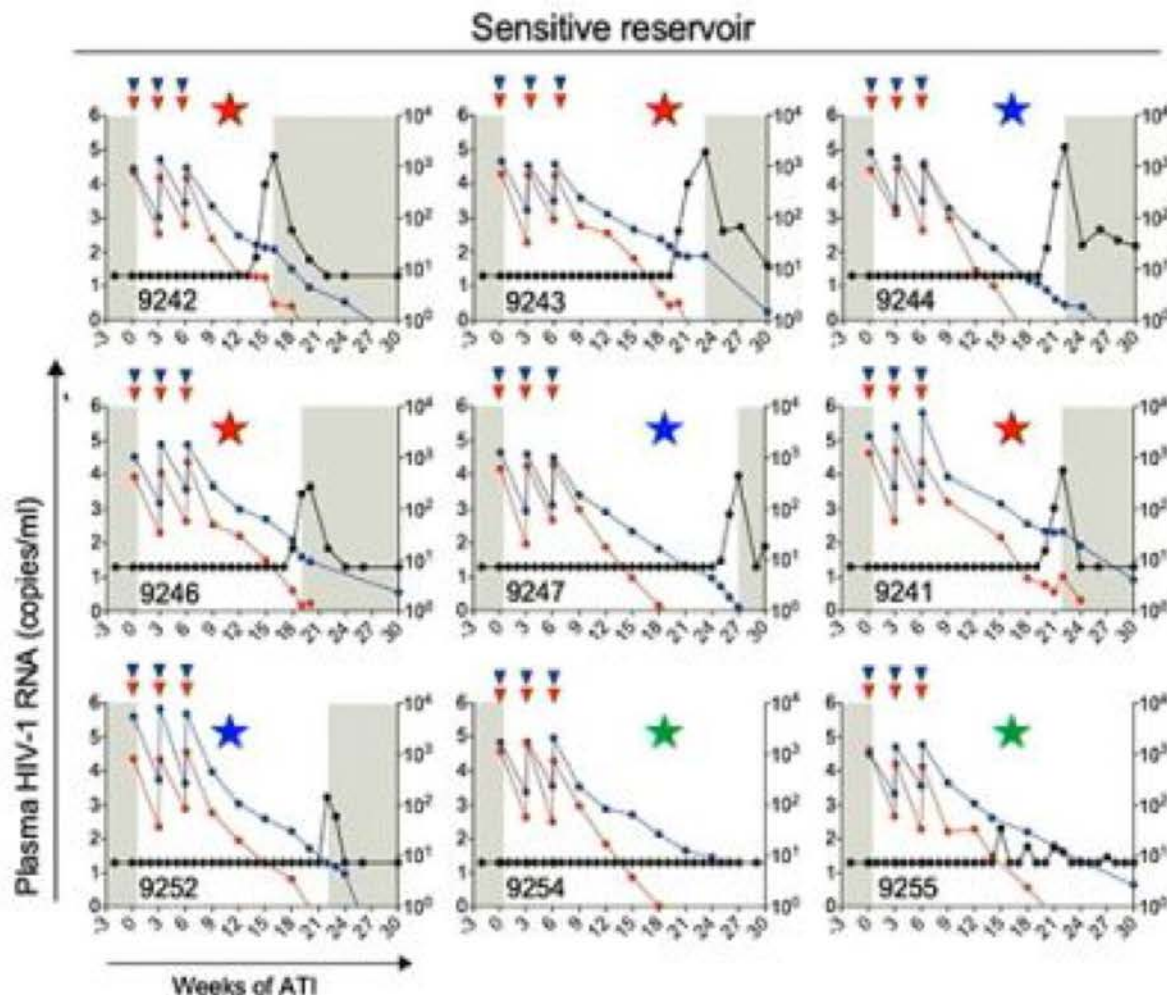
bNabs eliminate infected cells and prolong time to rebound off ART



Ad/MVA vaccination + TLR7 (adjuvant or latency reversal): SIV control off ART

Adapted from Jintanat Ananworanich, Joep Lange Memorial Lecture, IAS 2017, Paris

# Delayed viral rebound with 3BNC117 and 10-1074 combination therapy during ATI.



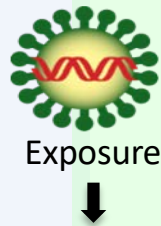
- Median time to rebound was 21 weeks or 15 weeks after last mAb infusion
- Viral rebound only occurred after 3BNC117 levels declined to  $< 10 \mu\text{g/ml}$ , which was followed by a period of 10-1074 monotherapy.



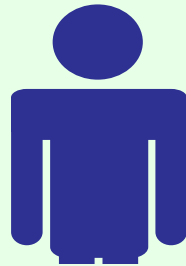
**Where are we going?**

# Future Science: Solutions for the End of AIDS

Prevention



Treatment



HIV Remission/cure?



**New biomarkers => personalized prevention and medicine?**

bNAbs

Vaccines

Long-acting ARV

(Pre-exposure prophylaxis)

New

diagnostic/prognosis

tools

Highly potent ART

Long-acting ART

bNAbs

Therapeutic vaccines

Shock and kill

Cell, Immune and Gene

therapies (*like cancer?*)

**Accès universel? (<\$1400)...**

# Ending the HIV epidemics?

*Still a dream which may become reality....*

Much remains to be done in both  
Implementation and Science !!

Keeping  
in mind...

My only strength is my  
persistence

~ Louis Pasteur ~





# Much thanks.....



**M. Müller-Trutwin  
and A. Saez-Cirion**

**L. Chakrabarti,  
O. Schwartz, H.  
Mouquet,**

**F. Taieb, Y. Madec**



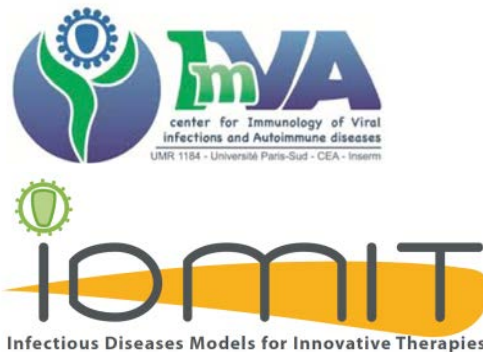
Institut Pasteur

*My apologies to many  
others.....*



**S. Deeks, S. Lewin and all the members of  
the IAS HIV Cure ISWG members**

**To all the patients, researchers and health  
professionals who participate to HIV  
vaccine and cure research...**



Institut national  
de la santé et de la recherche médicale

