Institut Pasteur

HIV: a discovery opening the road to novel scientific achievements and global health improvement

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Nobel Lecture in Physiology or Medicine

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Early 1980s: the world faces the alarming signals of a new epidemic

June 1981

- First clinical and epidemiological observations of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma in homosexual men in the US *(MMWR Weekly)*

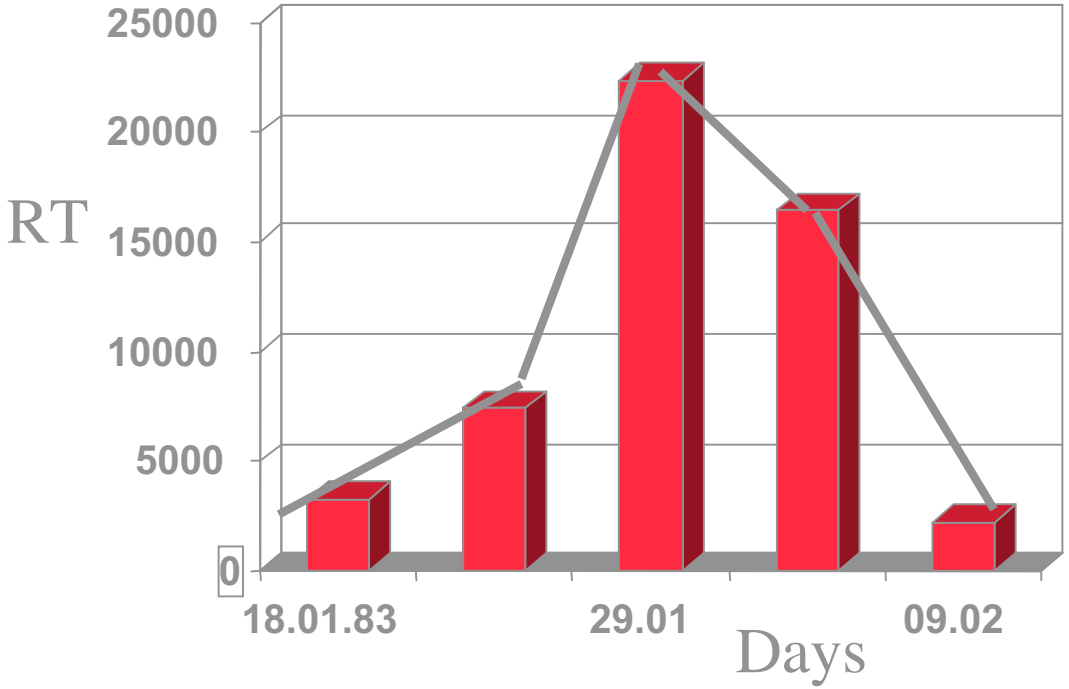
1982

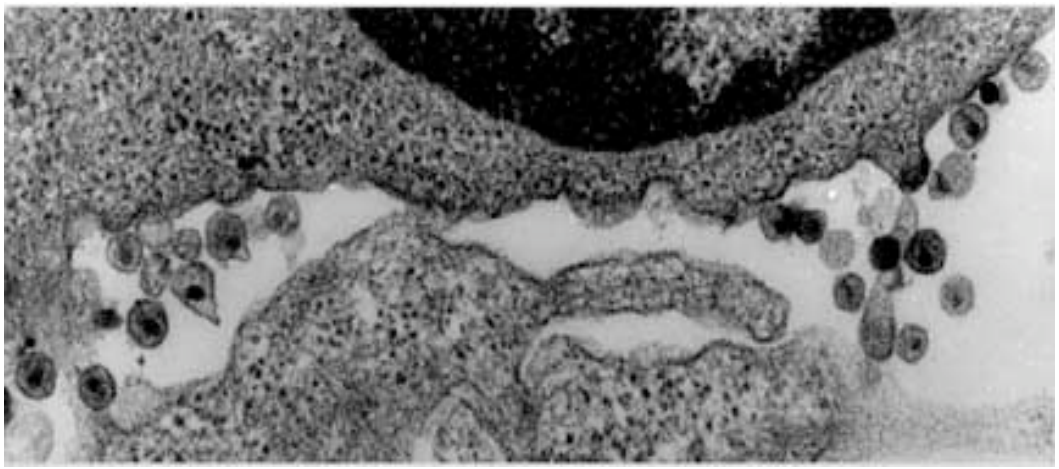
- The term AIDS (acquired immunodeficiency syndrome) is coined.
- First known cases of AIDS in patients having received blood transfusions
- First known cases of AIDS in women, infected by heterosexual transmission

December 1982

- Mobilization of retrovirologists at the Institut Pasteur

Early 1983: Isolation of LAV





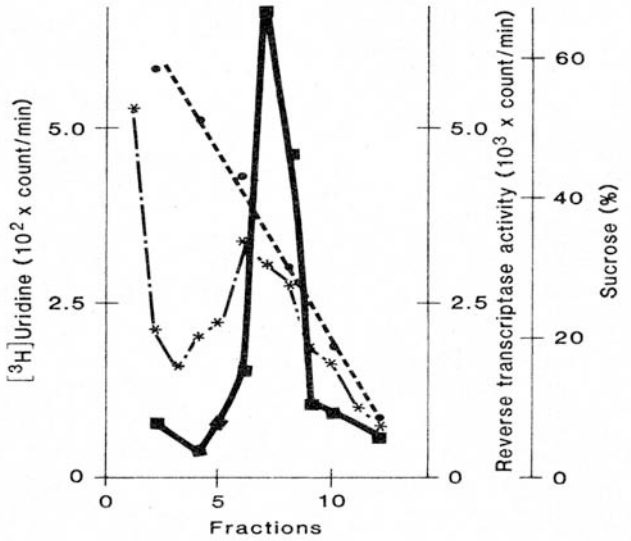


Fig. 1. Analysis of virus from patient 1 on sucrose gradients. Cord blood T lymphocytes infected with virus from patient 1 were labeled for 18 hours with [^{3}H]uridine (28 Ci/mmole, Amersham; 20 μCi/ml). Cell-free supernatant was ultracentrifuged for 1 hour at 50,000 rev/min. The pellet was resuspended in 200 μl of NTE buffer (10 m*M* tris, *p*H 7.4, 100 m*M* NaCl, and 1 m*M* EDTA) and was centrifuged over a 3-ml linear sucrose gradient (10 to 60 percent) at 55,000 rev/min for 90 minutes in an IEC type SB 498 rotor. Fractions (200 μl) were collected, and 30 μl samples of each fraction were assayed for DNA polymerase activity with 5 m*M* Mg^{2+} and poly(A) · oligo-$(dT)_{12-18}$ as template primer; a 20-μl portion of each fraction was precipitated with 10 percent trichloroacetic acid and then filtered on a 0.45-μm Millipore filter. The ^{3}H-labeled acid precipitable material was measured in a Packard β counter.

May 20, 1983: First report on LAV

Science 1983 May 20;220(4599):868-71

Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS).

Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vezinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L.

A retrovirus belonging to the family of recently discovered human T-cell leukemia viruses (HTLV), but clearly distinct from each previous isolate, has been isolated from a Caucasian patient with signs and symptoms that often precede the acquired immune deficiency syndrome (AIDS). This virus is a typical type-C RNA tumor virus, buds from the cell membrane, prefers magnesium for reverse transcriptase activity, and has an internal antigen (p25) similar to HTLV p24. Antibodies from serum of this patient react with proteins from viruses of the HTLV-I subgroup, but type-specific antisera to HTLV-I do not precipitate proteins of the new isolate. The virus from this patient has been transmitted into cord blood lymphocytes, and the virus produced by these cells is similar to the original isolate. From these studies it is concluded that this virus as well as the previous HTLV isolates belong to a general family of T-lymphotropic retroviruses that are horizontally transmitted in humans and may be involved in several pathological syndromes, including AIDS.

- Propagation of LAV on PBMCs and on cord blood lymphocytes
- RT activity detected according to HTLV-1 RT conditions
- Identification of p25: no cross reactivity with HTLV1p24 (IFA& RIA)
- No cross reactivity with HTLV-1 p19
- Presence of LAV Ab in a second patient

May 1983

Urgent need for reactivity and mobilization

1. Further characterization of the virus

2. Convince the scientific community and authorities that LAV was the etiological agent of AIDS by establishing a clear link between the virus and the disease (1983-1984).

⟺

- Stop any other research programs in our lab

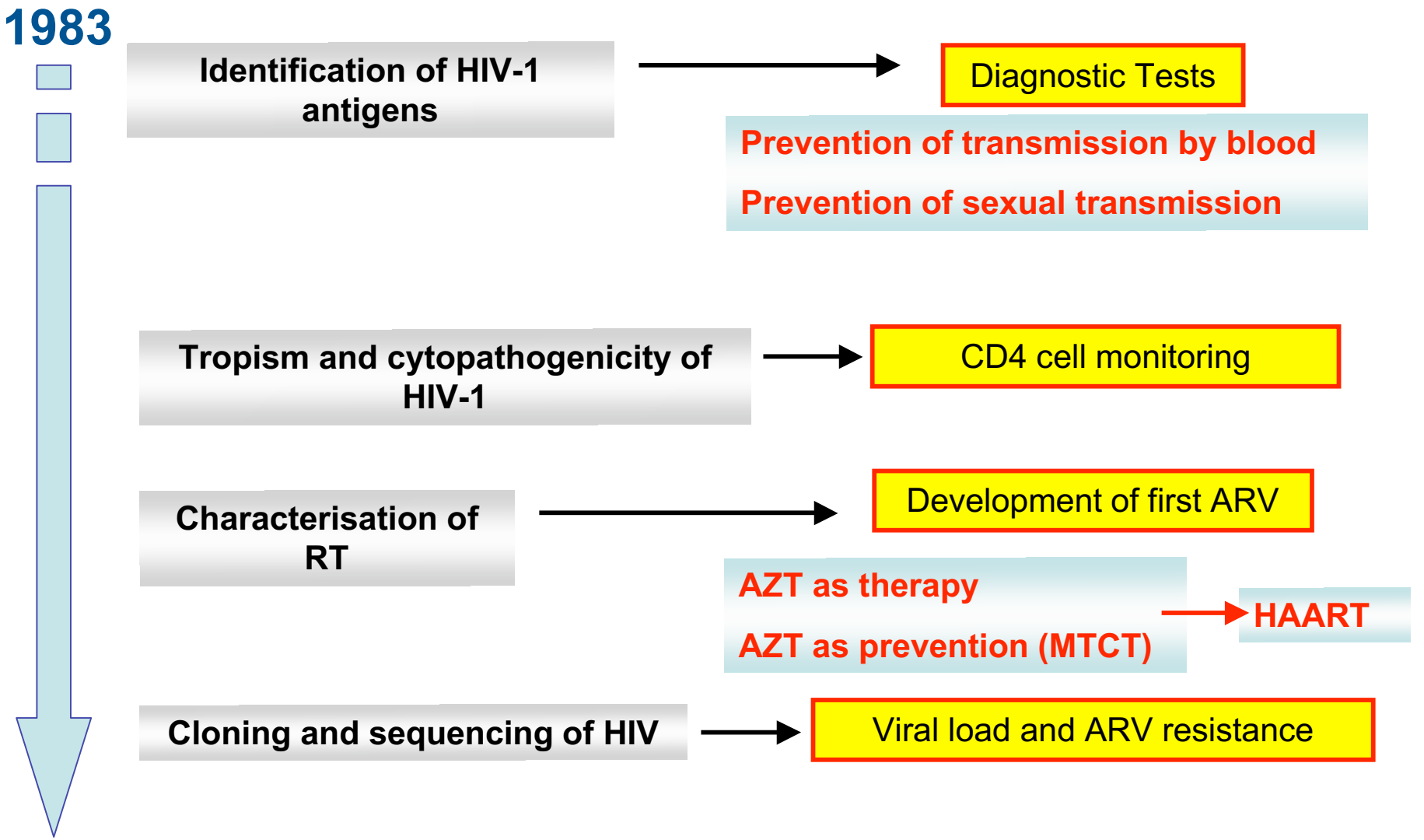
- Mobilization of a network of efficient collaborations

1. Develop serological tests for diagnosis (1983-1985)

⟺

Mobilization of a private company: a strong and efficient partnership with Sanofi Diagnostics Pasteur

HIV research: from bed-side to bench to bed-side



Diversity and origin of HIV

HIV-1

group N

HIV-1

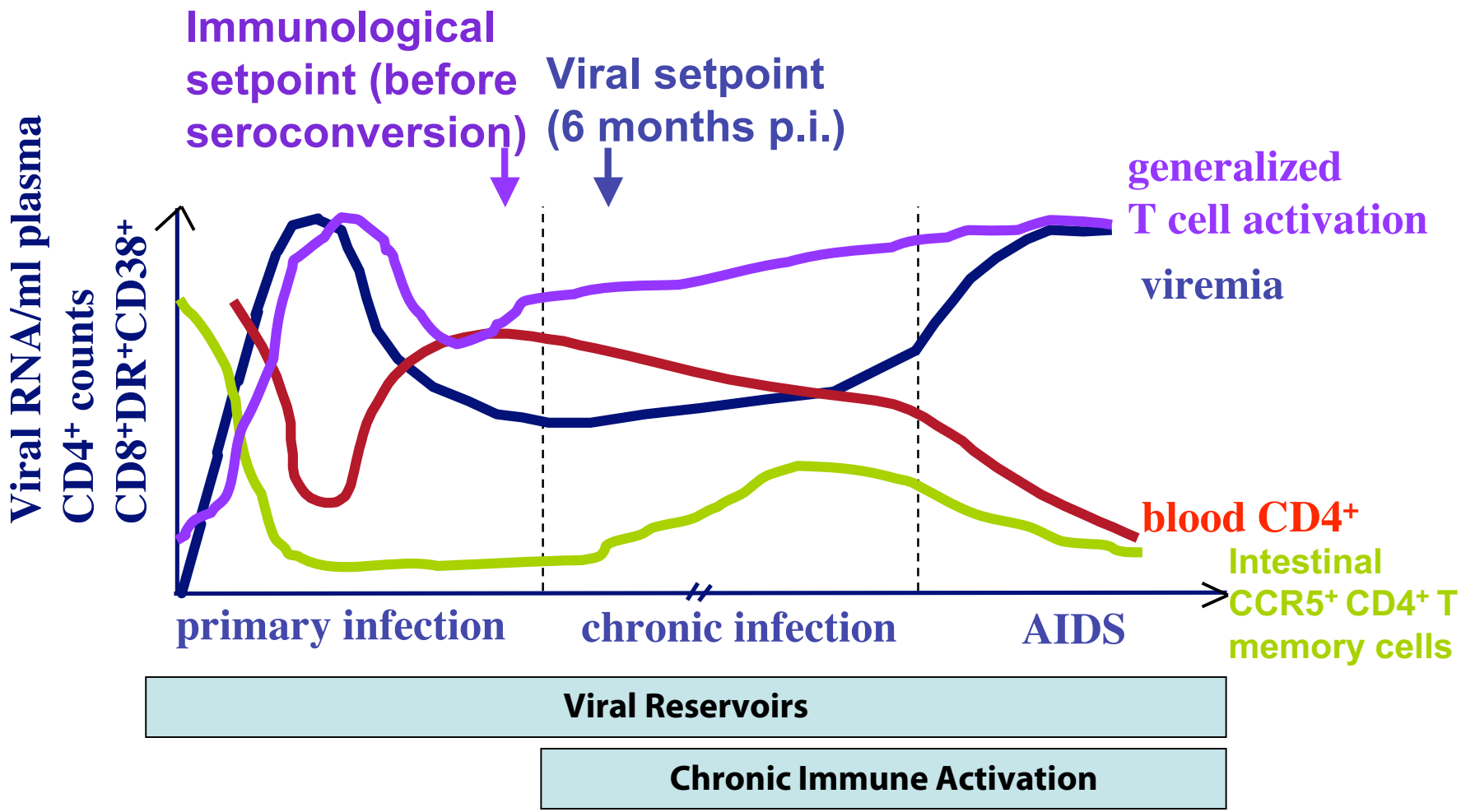
group O

HIV-2

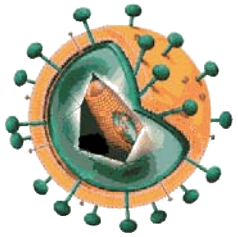
HIV pathogenesis:

what do we know and how can we learn more?

Natural History of HIV infection



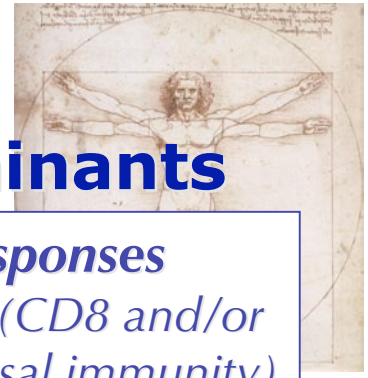
Interplay of host and viral determinants in HIV pathogenesis



Viral factors

(tat, nef, vif, vpr, vpu, gag, pol, env, rev..)

- ***Tropism & Replicative capacity***
- ***Genetic Variations in critical genes***
- ***Immunogenicity***
- ***Immunosuppressive factors***
- ***….***



Host Determinants

- ***Host Immune Responses***
  - ***Adaptive Immunity*** *(CD8 and/or CD4 responses; Mucosal immunity)*
  - ***Innate Immunity*** *(NK; Suppressive factors; Non Cytotoxic CD8 responses; CCR5 antibody…)*
- ***Host genetics and polymorphisms***
  - *HIV coreceptors and ligands*
  - *HLA (B27, B57 alleles…)*
  - *Host restriction factors (APOBEC, TRIM…)*

HIV Pathogenesis

Models to understand protection against HIV/AIDS

1. Resistance to Infection

Exposed Un-infected (EU)

2. Control of HIV infection

HIV Controllers

3. Control of HIV pathogenesis

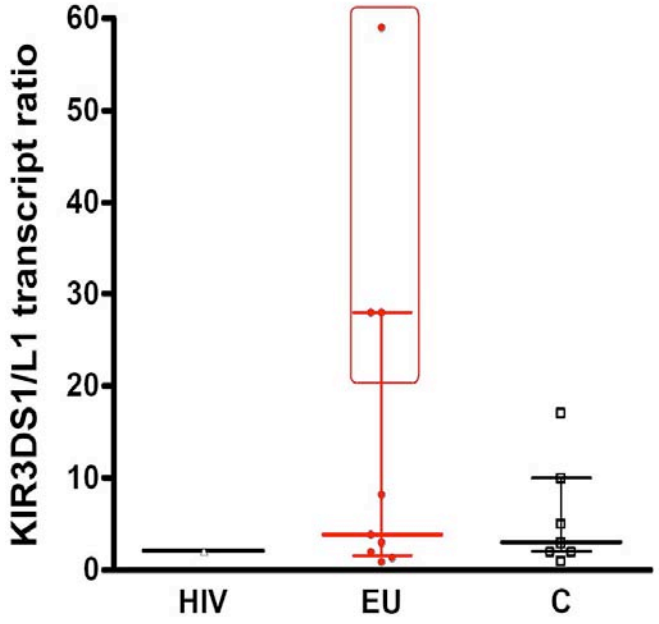
Non-pathogenic SIV model

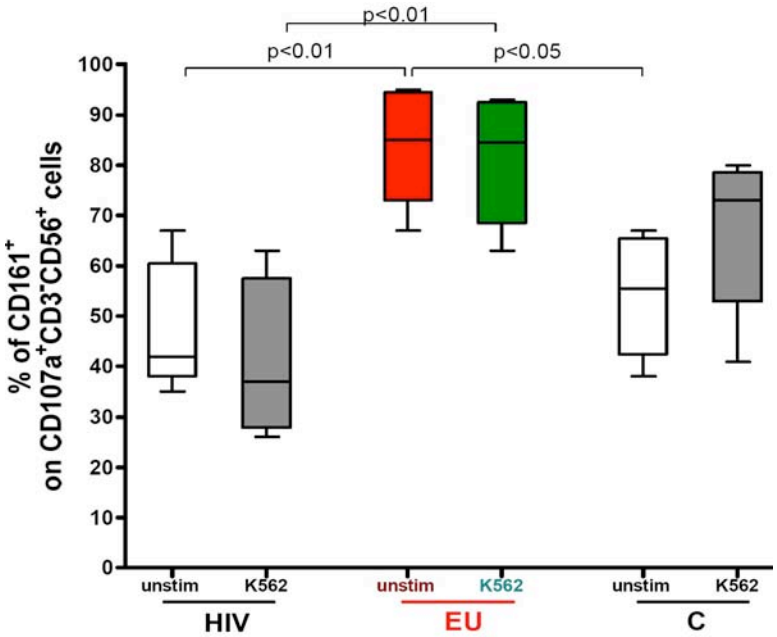
1. Resistance to Infection

EU: HIV-negative by serology and PCR despite repeated exposure to HIV-1

- Sexually exposed (CSW, partners of HIV-1$^+$ patients)
- Systematically exposed (IDU)

✓ **EU: Increased NK cell activity in Vietnamese IDU**





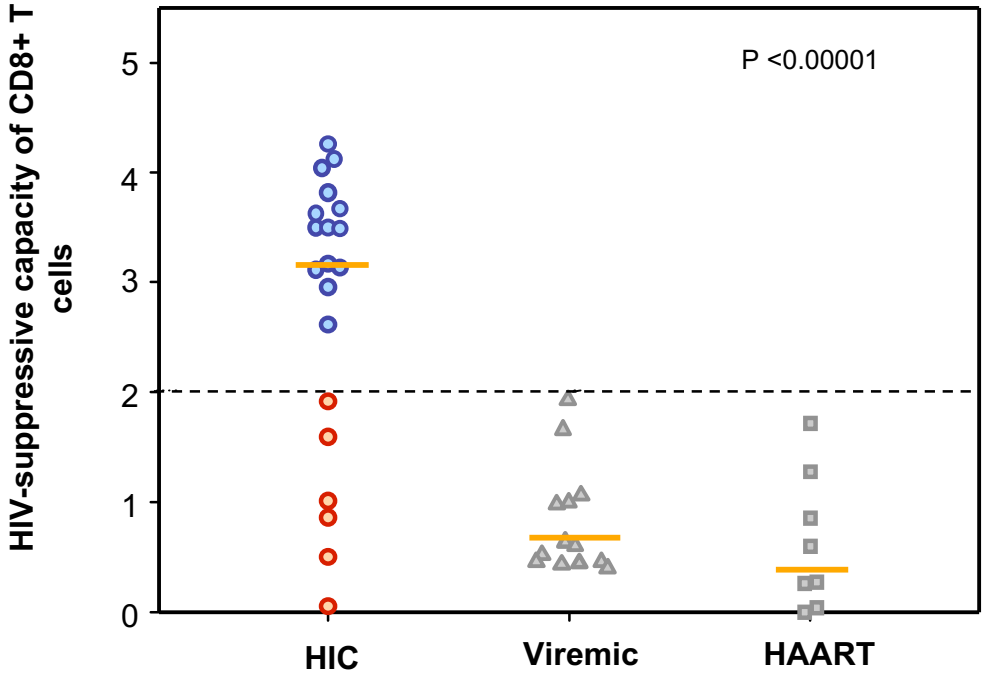
2. HIV Controllers:
Lessons from the lucky few

HIC: Infected individuals spontaneously controlling HIV-1 infection

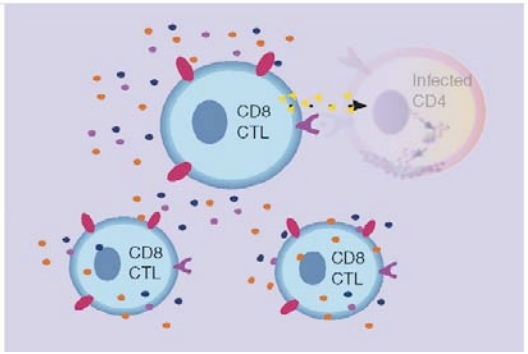
HIV infected for more than 10 years

Undetectable plasma viral RNA

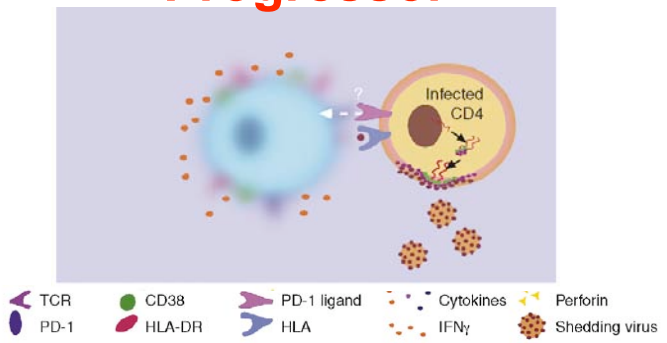
Naïve of antiretroviral treatment



HIV controller



Progressor

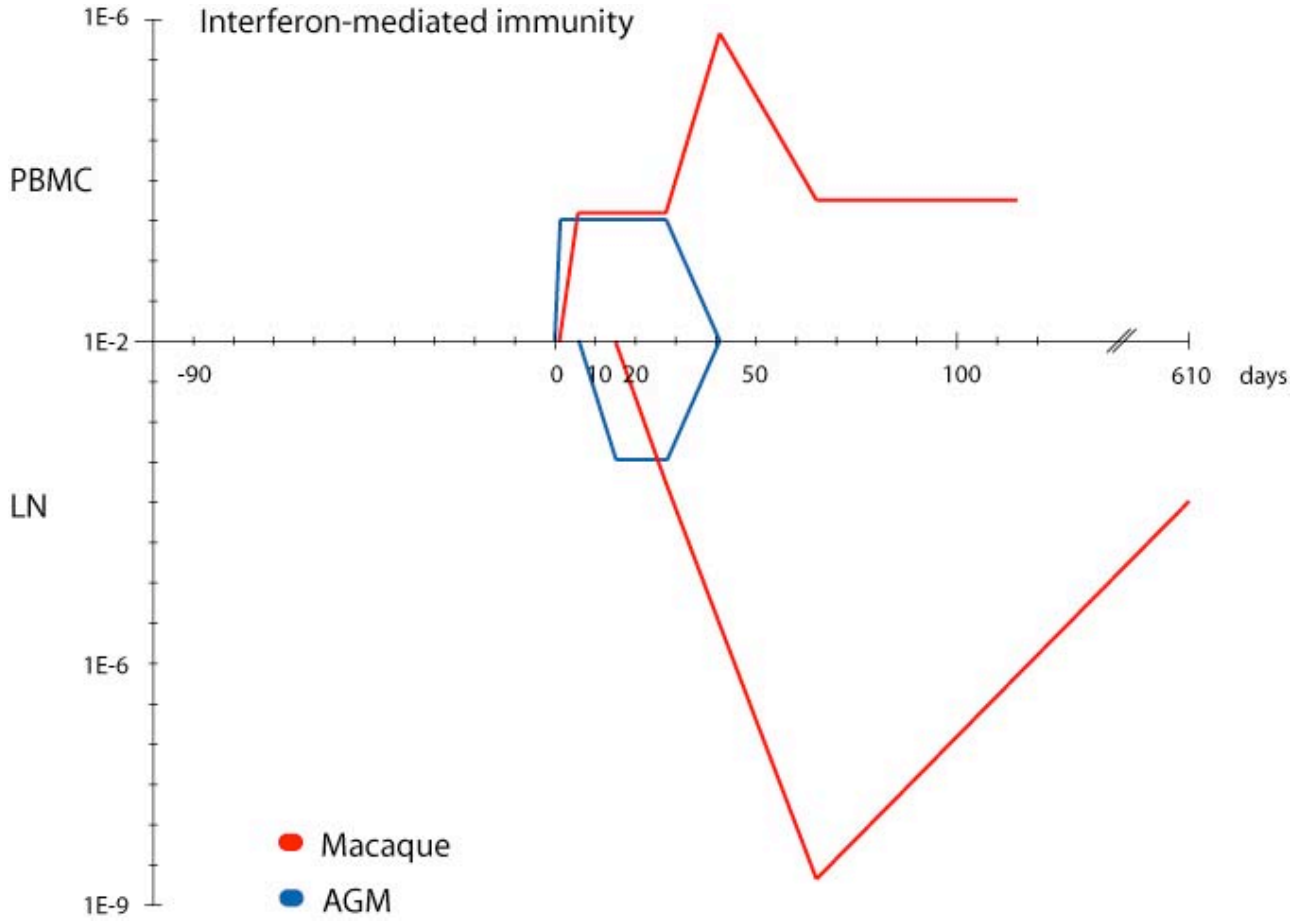


A. Saez-Cirion et al, PNAS 2007 & Trends in Immunol. 2007

3. Control of Pathogenesis:
the simian model

Markers	SIVagm	SIVmac
AIDS	-	+
Viral Load	+++	+++
Chronic Phase		
T cell activation	-	+++
IFN-α	-	+
Interferon Stimulated Genes	-	+++

Gene Profiling of CD4+ T Cells in Non-Pathogenic vs Pathogenic SIV infection



PBMC

LN

Type I interferon pathway is differentially modulated in African Green Monkey and Rhesus Macaque

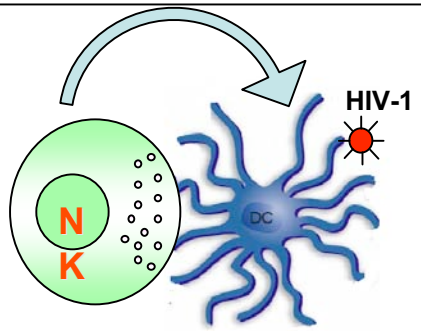
Pathogenic SIVmac vs non-pathogenic SIVagm - Early Acute Phase

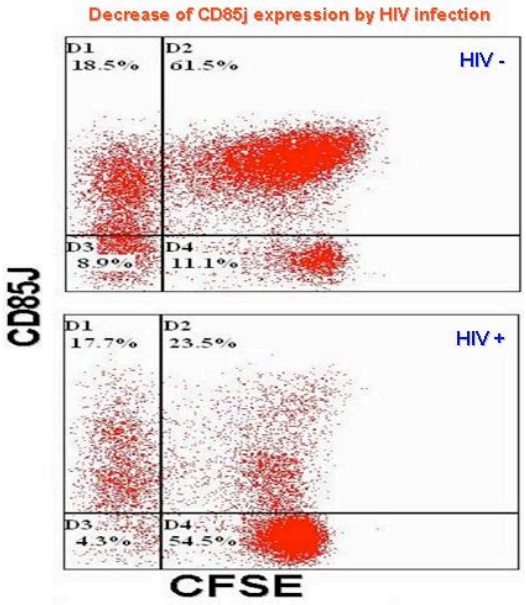
		SIVagm	SIVmac
		Non-pathogenic	Pathogenic
marker			
T cell activation		+	+
Intestinal Mucosa	CCR5+CD4+ depletion	+++	+++
	Microbial translocation	-	+
Cytokines	TNF-α, IL-6, IL-12,	-	++
	TGF-β1	+	+
	Smad7	-	+
Recruitment of PDC to LN		+	++

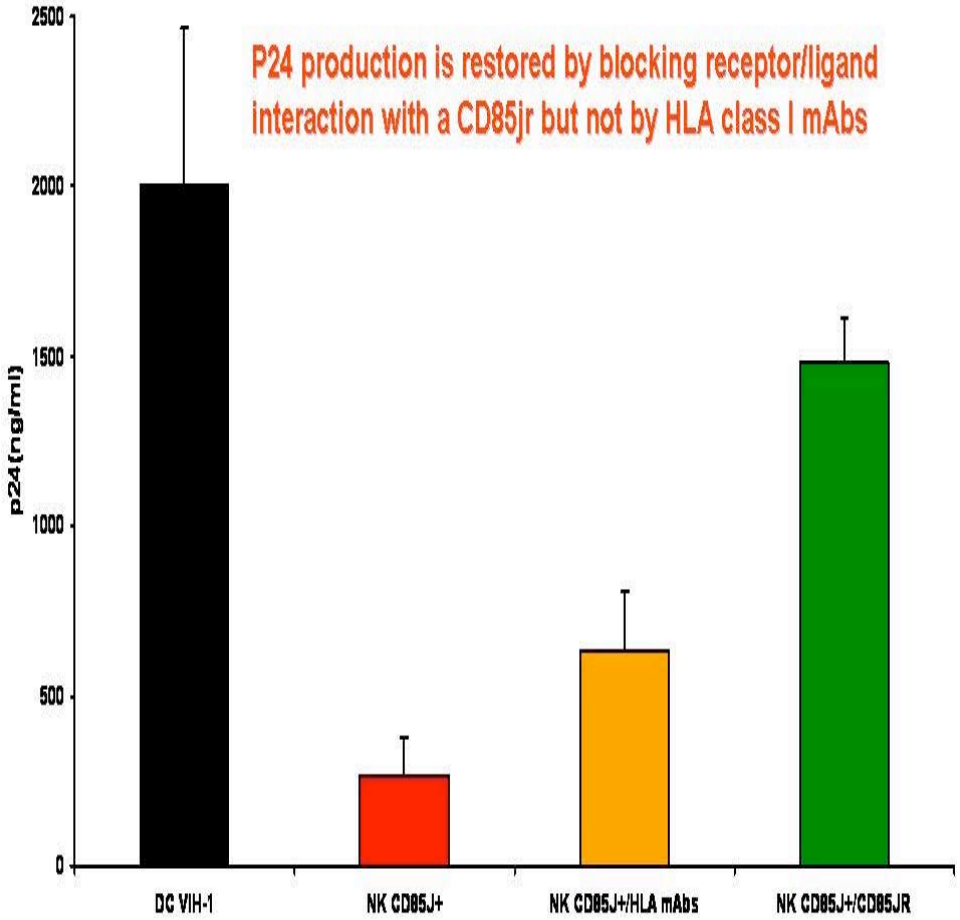
Kornfeld C. et al., JCI, 2005 & Ploquin M. et al. Retrovirol, 2006, Diop et al. J of Virol 2008

CD85j NK cells suppress HIV replication

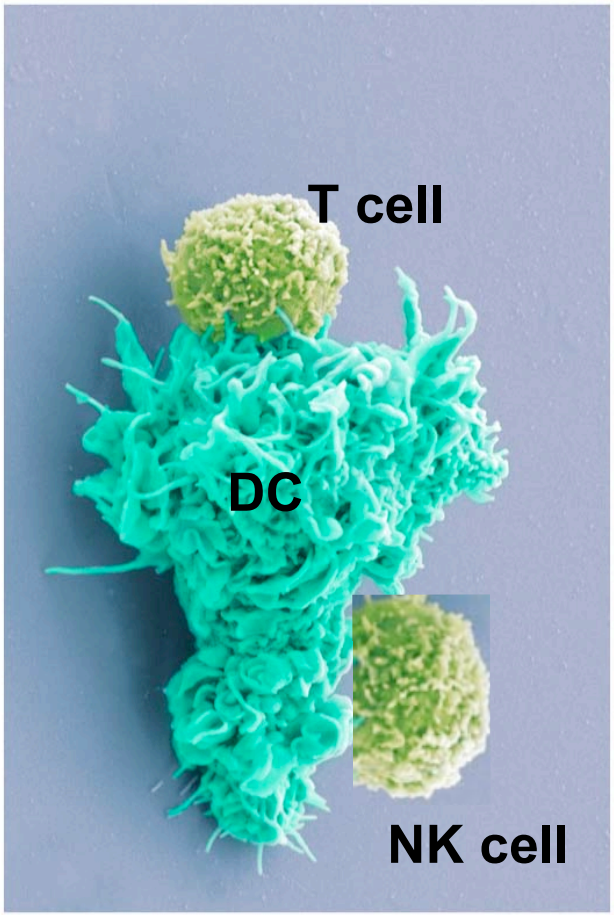
In Vitro **model of NK cell co-culture with HIV-1 infected or uninfected DC**

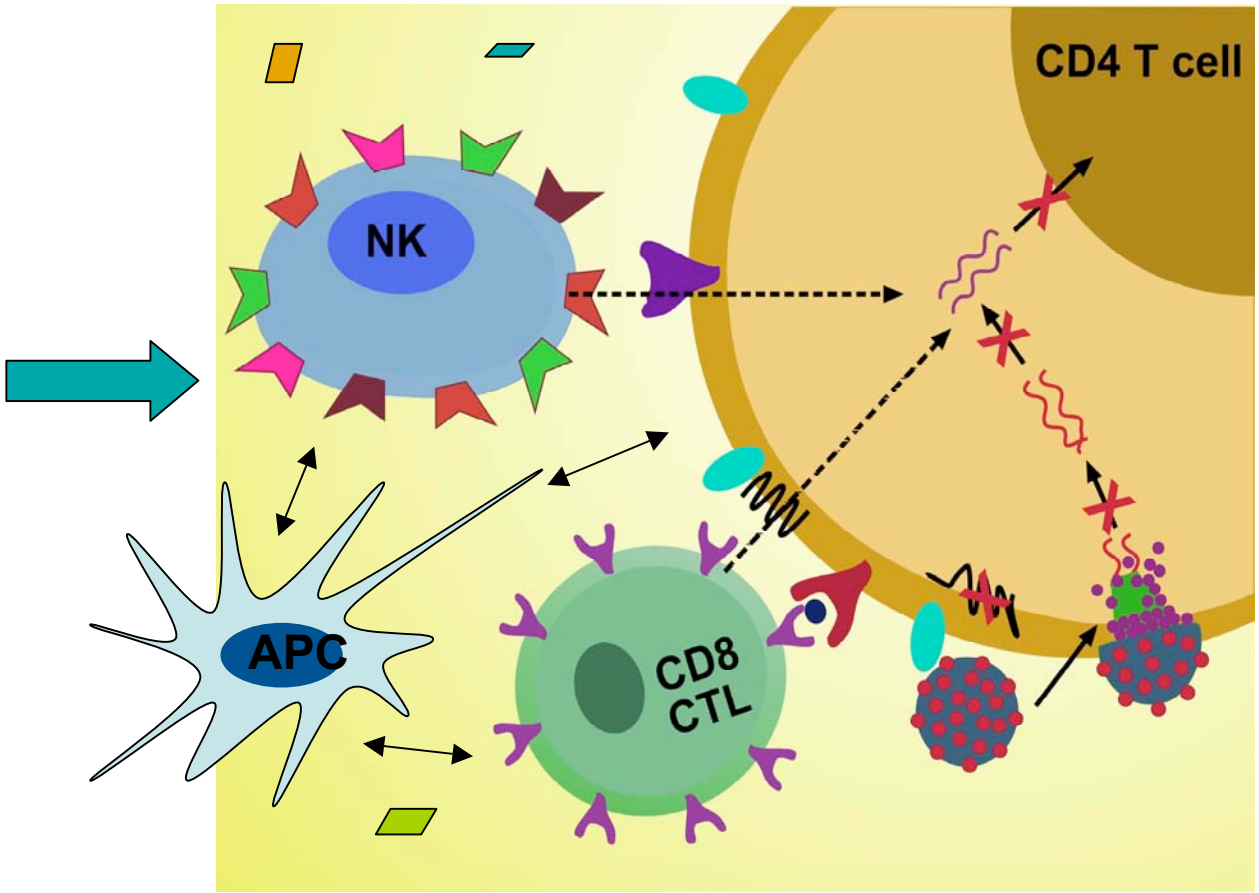






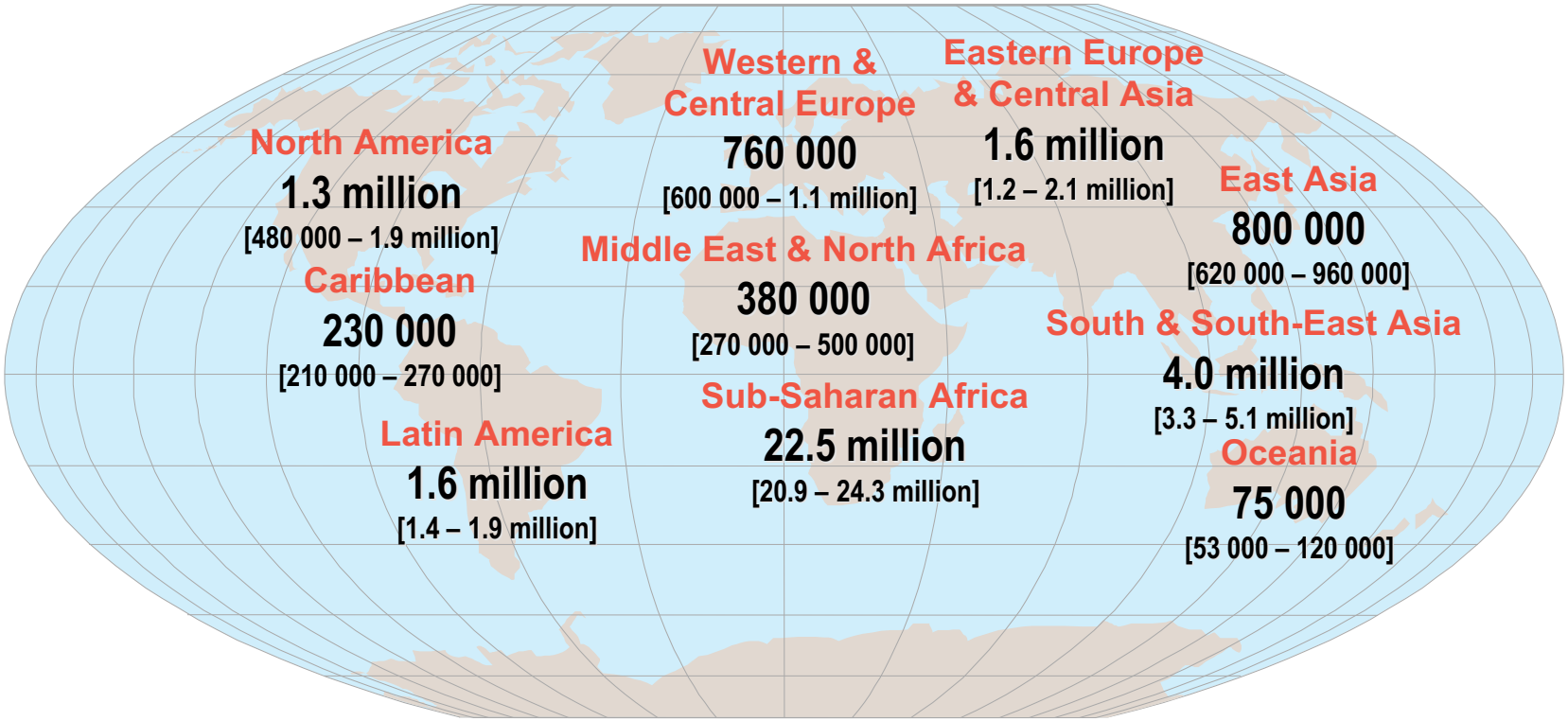
Possible mechanisms of HIV control





HIV/AIDS in 2008: the current situation

HIV/AIDS: the state of the epidemic at the end of 2007

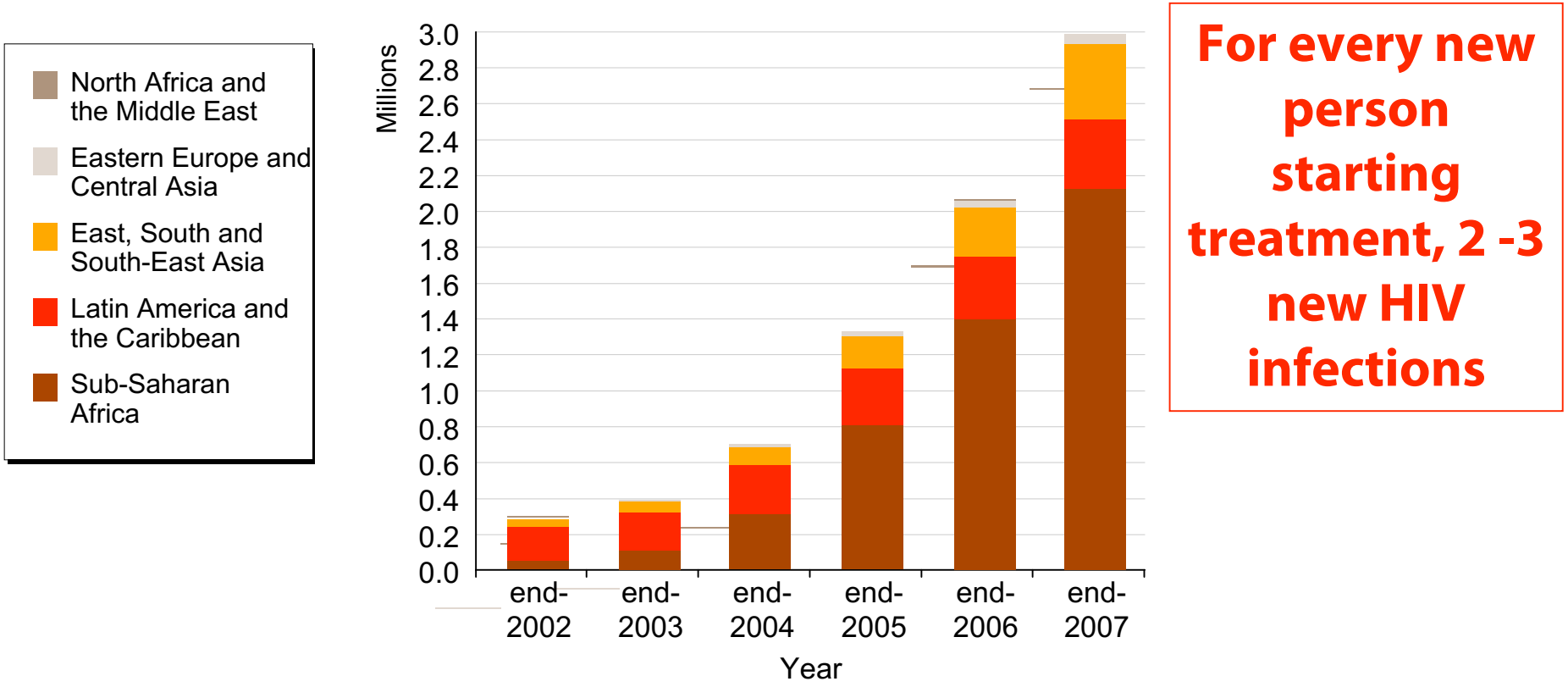


✓ **33 million people** [30.3 – 36.1 million] were living with HIV.
✓ **2.7 million** [2.2 – 3.2 million] new cases of HIV infection
✓ **2 million** [1.8 – 2.3 million] AIDS-related deaths last year.

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

Therapy: Progress in ARV access

Number of people receiving antiretroviral drugs in low- and middle income countries, 2002–2007

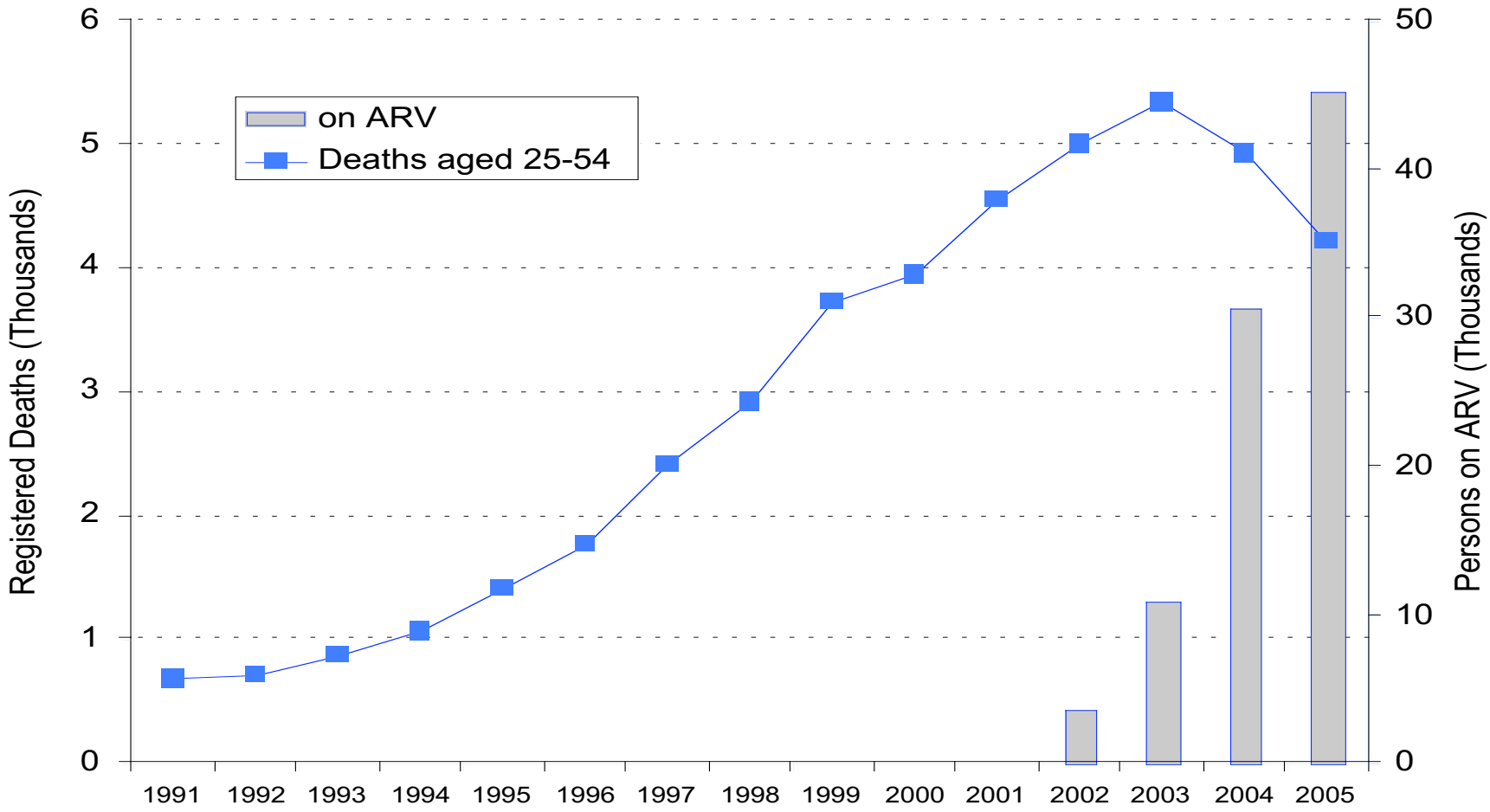


For every new person starting treatment, 2 -3 new HIV infections

Only 30% of people needing treatment receive it

Source: Data provided by UNAIDS & WHO, 2008.

Decline in adult mortality with introduction of ART: Botswana



Investing in our future
The Global Fund
To Fight AIDS, Tuberculosis and Malaria

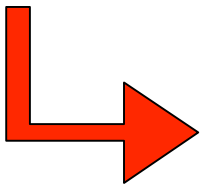
Therapeutic Progress and Challenges

ARV Treatment

- The survival benefits of ARV treatment are immense,

BUT...

- Life-long committment ---> economical limits
- Complications (drug resistance, metabolic disorders...)



Search for a CURE for HIV infection

Prevention Progress and Challenges

- **Prevention of infection: successes....**
  - Prevention of sexual transmission
  - Mother-to-Child transmission
  - Circumcision as part of a comprehensive prevention approach

.... and work in progress....

- Pre and Post-Exposure prophylaxis
- Early diagnosis and treatment
- Specific Microbicides
- Vaccine

Therapy and Vaccines: scientific challenges

- Genetic Variability of HIV
  - Viral evasion of the immune system
- Early establishment of viral reservoirs
- Cell-cell transmission
- Correlates of protection still undefined
- HIV infects, dysregulates and/or depletes key players of immune system
  - Rapid induction of dysfunctions of immune responses
- Animal model limitations

HIV/AIDS research: 25 years on…

Urgent need: CARE, THERAPY and PREVENTION

Priorities for future research:

1. *Early events during acute phase of infection (immune activation, innate and adaptive immune responses, cross-talk between immune cells, mechanisms and correlates of protection, role of host genetics)*
2. *HIV reservoirs (mechanisms of establishment and persistance, depletion of reservoirs)*
3. *Interaction between viral factors and cellular partners*
4. *Co-infections*

New therapeutic & vaccine strategies

New targets

siRNA?

Limitation of microbial translocation?

Therapeutic vaccine?

Vaccine Research: Hope and Progress

- Shift from conventional to novel HIV vaccine strategies in the post-STEP era
- Better understanding of the early events of HIV infection
- Better understanding of the basic immunology in HIV infection (e.g. cross-talk between innate and adaptive immunity)
- International Agenda to promote collaboration and cooperation

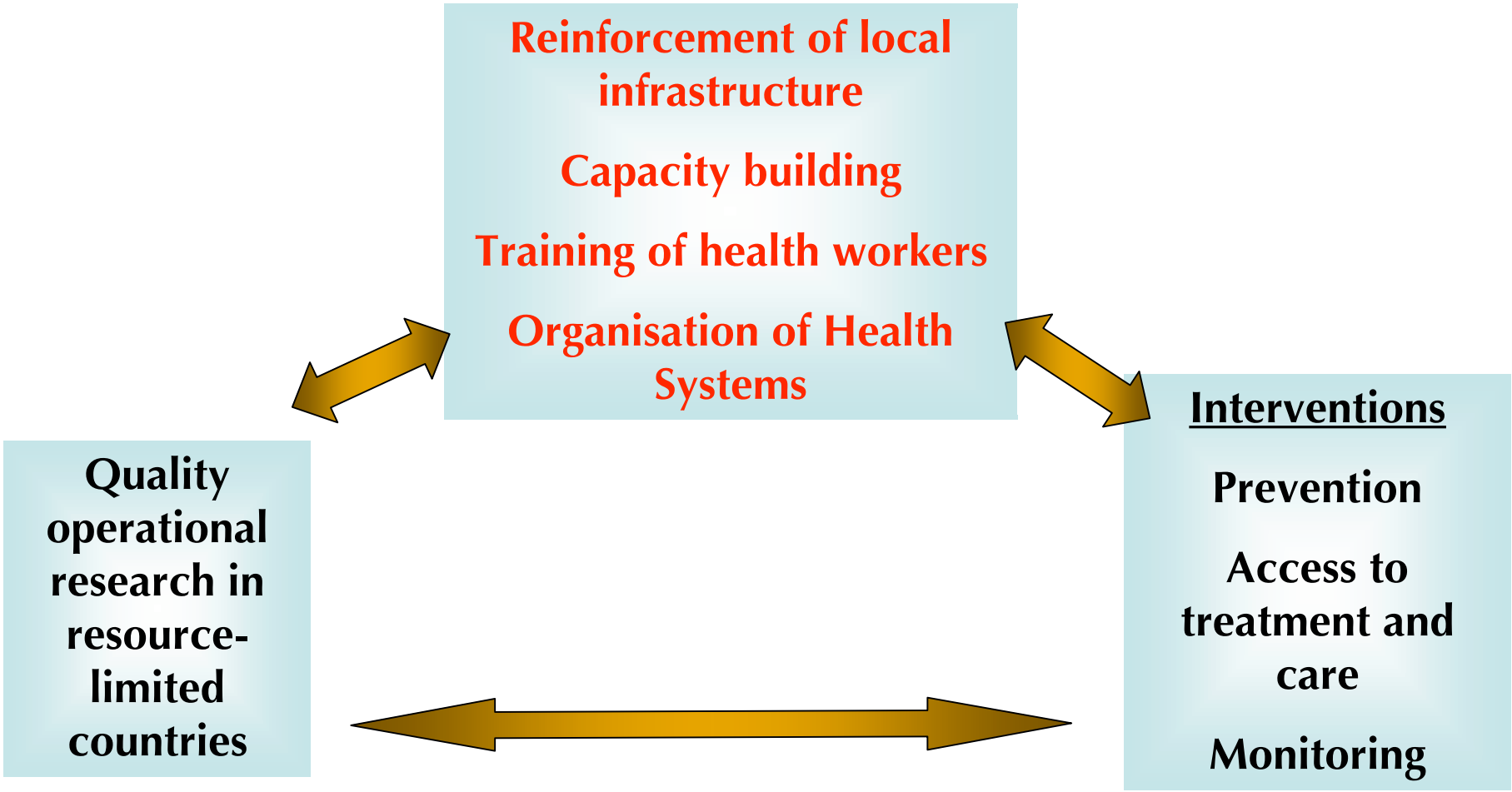
Benefits beyond HIV/AIDS...

HIV: a tool for new scientific knowledge

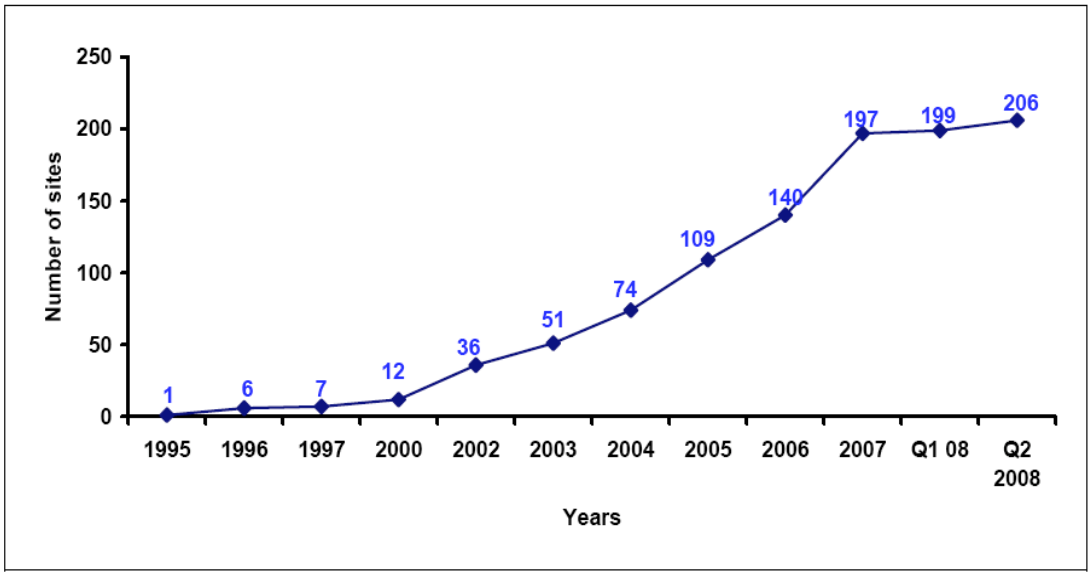
- Better understanding of virus/host interactions
  - Pathways of intracellular innate immunity
  - Identification of novel cellular factors *(high-throughput screening for essential proteins for viral replication)*
- Better understanding of immune responses
  - Identification of new receptors, ligands and signalling pathways
  - Standardised T cell functional test
- Vaccine research
  - Novel concepts and strategies for other diseases
- Lentivirus gene therapy vectors

Global health systems improvement

National Programs with International Collaborations



Reinforcement of the Health System in Cambodia



VCCT sites from 1995 to Q2-2008

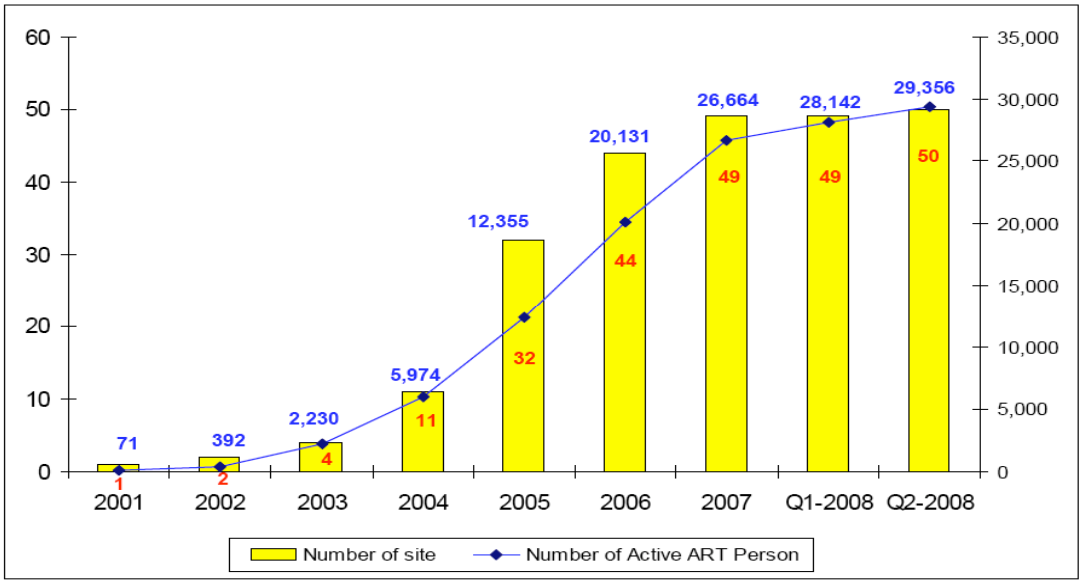


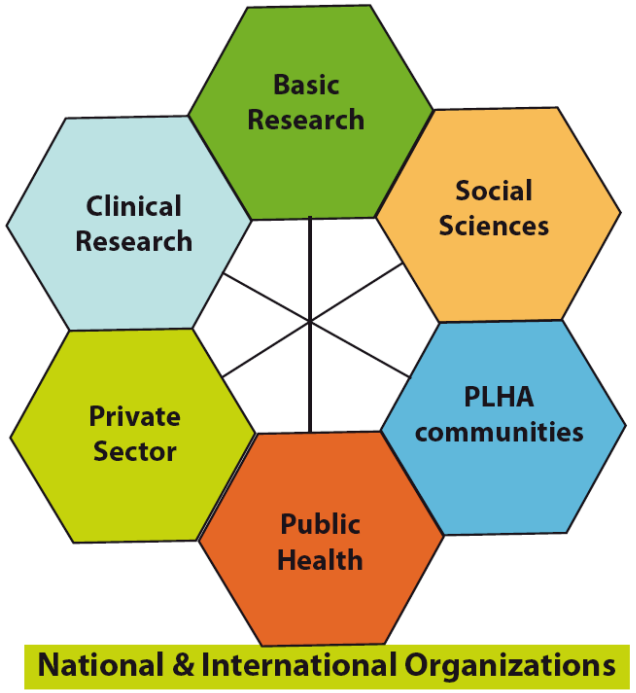
Figure 9: Trend in number of OI/ART sites and active patients on ART from 2001 to Q2-2008

OI/ART sites and active patients on ART from 2001 to Q2-2008

Source: NCHADS, MoH, Cambodia

Towards a world without AIDS and with better global health...

International partnerships and multi-disciplinary approaches



Opposing the fight against HIV to other primary health issues is a total misunderstanding and a major mistake. HIV care, prevention and treatment programs are rather strengthening the global health system. It is time to stop ideological oppositions!

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Inserm

Institut national
de la santé et de la recherche médicale

anRS

Agence nationale de recherches
sur le sida et les hépatites virales

Sidaction

ENSEMBLE CONTRE LE SIDA

International
AIDS Society

Stronger Together