Bridges - The International Peace Foundation

05th Aprile 2010 - Bangkok

Future challenges in HIV/AIDS prevention and therapy

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Inserm

Institut national de la santé et de la recherche médicale

Sidaction

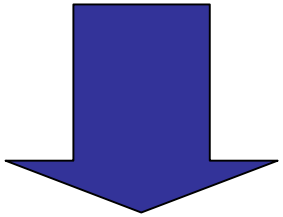
ENSEMBLE CONTRE LE SIDA

Eradication of infectious disease…

the dream of the 60's

" …One can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious disease as a significant factor of social life."

Burnet, 1962.



Interest, curiosity, motivation for other major and lethal human pathologies

Retrovirus, cancers et leukemia…

First alarming signals of an emerging epidemic

➢**June-July 1981: First cases of pneumocystosis associated with immunedepression in homosexual patients in the US.**

MS Gottlieb, HM Schanker, PT Fan, A Saxon, JD Weisman.

MMWR Weekly

June 5, 1981 / Vol. 30/ No. 21

Epidemiologic Notes and Reports

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

➢**July 1982: First cases of AIDS detected in haemophilic patients**
➢**October 1982: First cases of AIDS in women, heterosexual infection**
➢**December 1982: First cases of infected children**

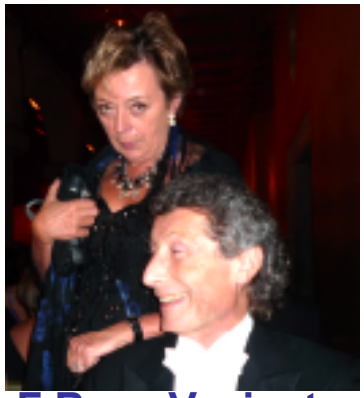
Mobilization of researchers by epidemiologists and clinicians….

The 80's and the years after: a collective adventure

Evolution of technologies and research on retroviruses

- Identification of TCGF or IL2 (1979)
- FeLV and immunodeficiency in cat
- Gallo et Yoshida (1981) - First human retrovirus(HTLV-Human T Cell Leukemia Virus)
- Identification of AIDS in France (1982)

Clinicians mobilized the retrovirologists of the Institut Pasteur



F.Brun-Vezinet
W.Rozenbaum

C. Rouzioux

A decisive meeting

NO DOGMA

May 20th 1983: first report of LAV in Science

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 deatected according to HTLV-1 RT conditions

BUT

- 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 - To face the emergency: reactivity, mobilization

1. *1983-1984: Convince scientific community and authorities that LAV was the etiological agent of AIDS*
   - ✓ *Link between the virus and the AIDS disease (viral isolate, sero-epidemiological investigation)*
   - ✓ *Characterization of LAV and other viral isolates.*

- ➢ *Stop any other research programs in our lab*
- ➢ *Mobilize other clinicians and researchers…*

2. 1983-1985: *Develop serological tests for diagnosis*

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

HIV research: from bed-side to bench to bed-side
An example of translational research

1983

Identification of HIV-1 (*LAV, HTLVIII, ARV)* and viral antigens → **Diagnostic Tests**

Prevention of transmission by blood

Prevention of mother to child infection and of sexual transmission

Tropism and cytopathogenicity of HIV-1 → **CD4 cell monitoring**

Characterisation HIV-1 replication cycle and of RT → **Development of first ARV**

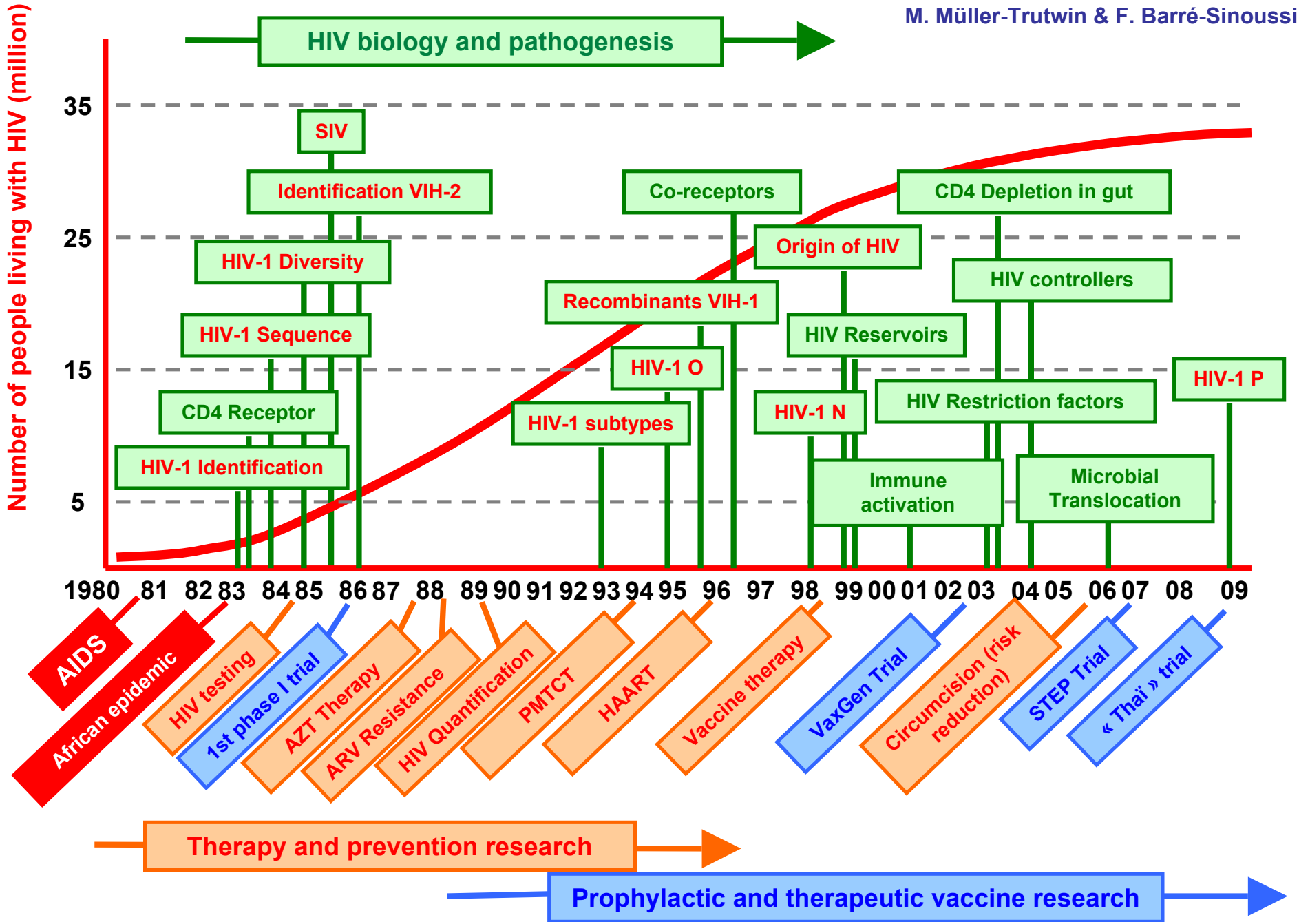
AZT as therapy **HAART**

AZT as prevention (MTCT)

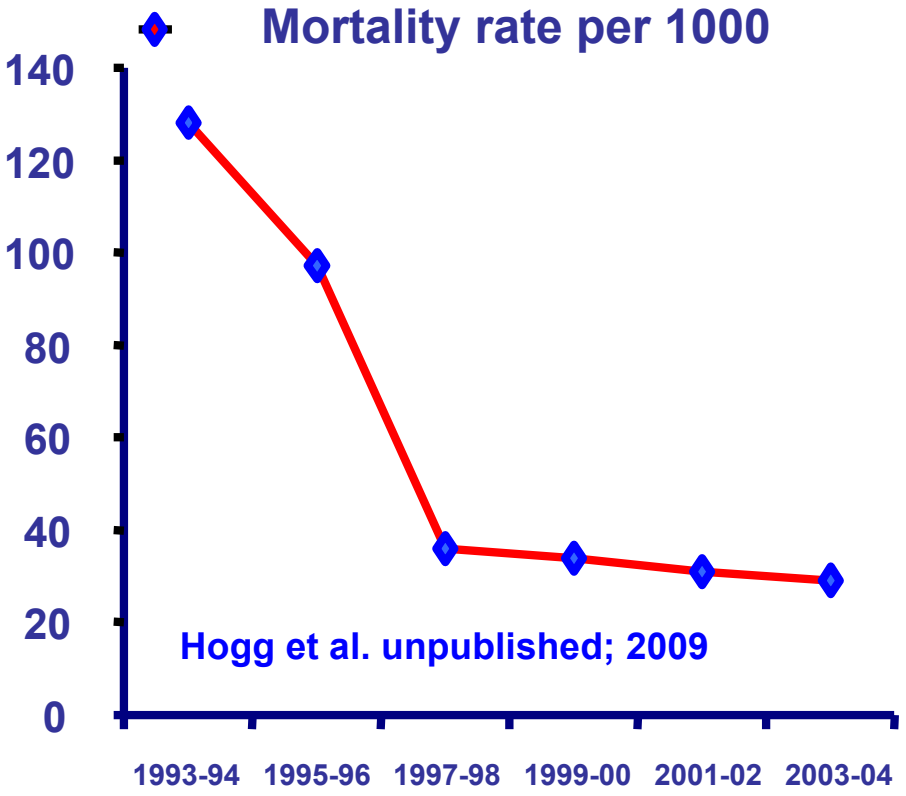
Characterisation HIV-1 genetic material and identification of its diversity → **Monitoring tests for Viral load and ARV resistance**

Main milestones in 27 years of research on HIV

M. Müller-Trutwin & F. Barré-Sinoussi



Today HIV is a chronic infection



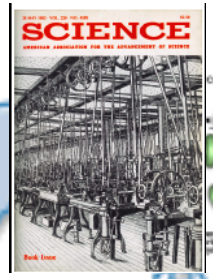
6 therapeutic classes:

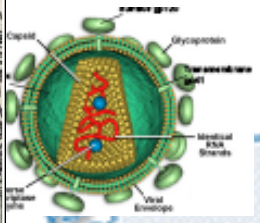
- ✓nucleoside inhibitors of reverse transcriptase
- ✓non nucleoside inhibitors of reverse transcriptase
- ✓Protease inhibitors
- ✓Fusion inhibitors
- ✓Integrase inhibitor
- ✓CCR5 inhibitor

A Panel of about 30 drugs for HAART

More than 85% decrease in treated patients mortality

Responsability and mobilization toward a global scale epidemic





Paris, France
1983

Hanoi, Vietnam
1988

Los Angeles,
USA, 1981

Bangui, Central African
Republic, 1987

« Science has no frontiers because knowledge belongs to humanity and it is the flame that enlightens the world. »

« La science ne connaît pas de frontière parce que la connaissance appartient à l'humanité et que c'est la flamme qui illumine le monde. »

Louis Pasteur
(1822-1895)

Translating Research into large scale public health actions

Main steps and issues

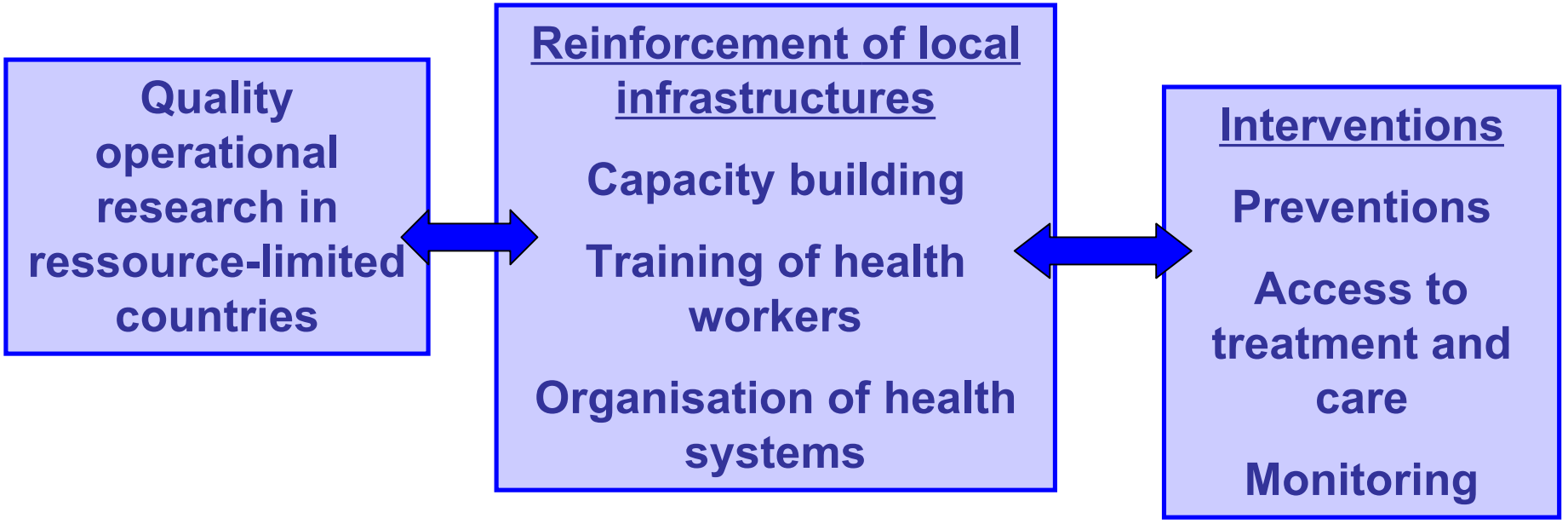
- **Validation of research evidences=> *Credibility***
- Surveillance and epidemiological studies
- Establishment of well characterized cohorts
- Clinical and operational research *(physiopathology, therapeutic trials, strategy evaluation…)*
- Socio-economic research
- Pilot studies
- Scaling up, Implementation & sustainability…

Need of a strong interface and partnerships (policymakers, scientists, health & service providers, patients, civil society, community groups & activists, private and public sectors…)

- Awareness, diffusion & advocacy *(information, communication, education and training)*
- National Programs, Guidelines and decisions
- Coordination of activities
- Evaluation & Updating*(effectiveness and gap identification)*
- Integrated and Permanent research activities ……

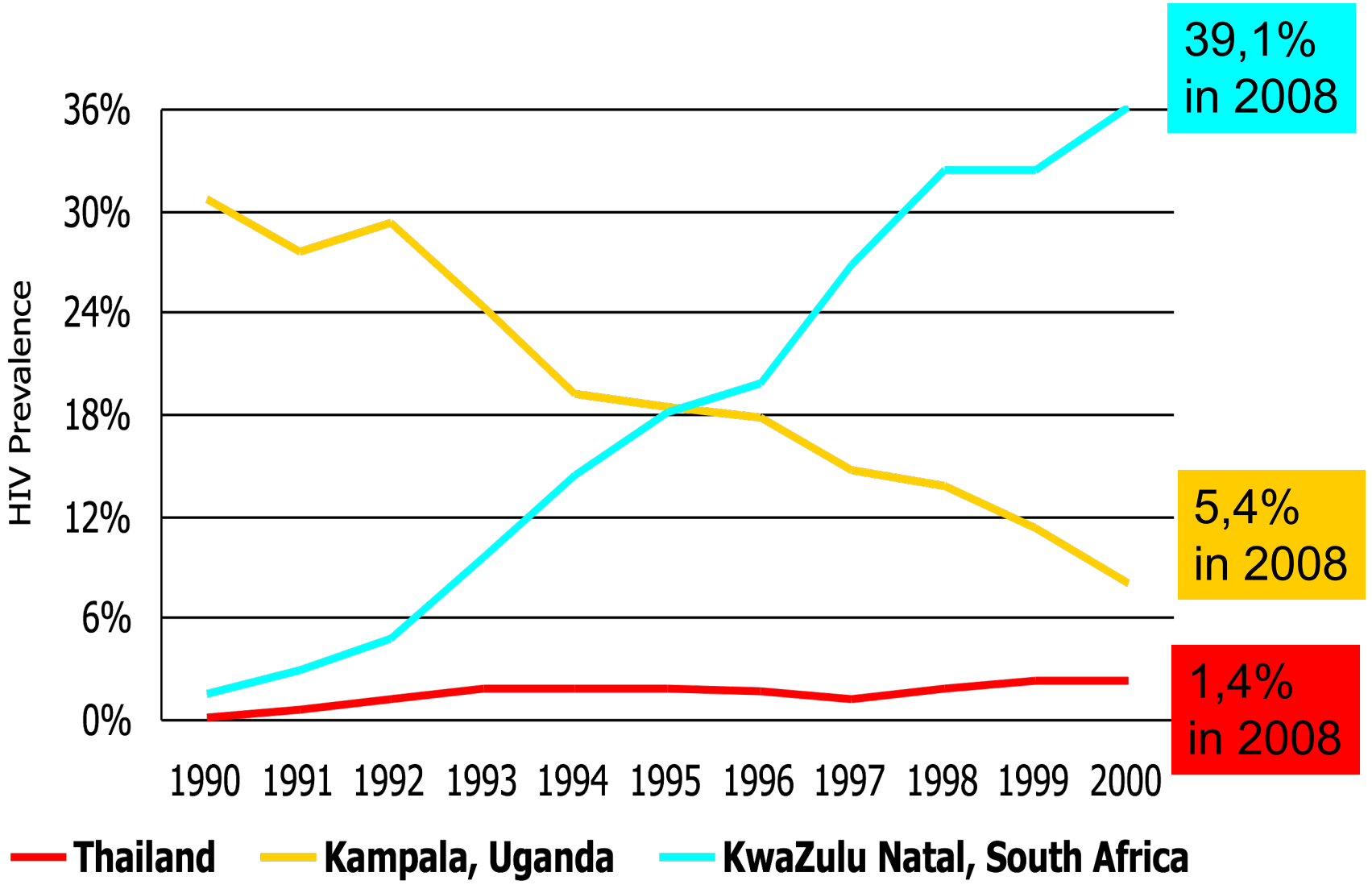
Global health systems improvements

National programs with international collaborations…



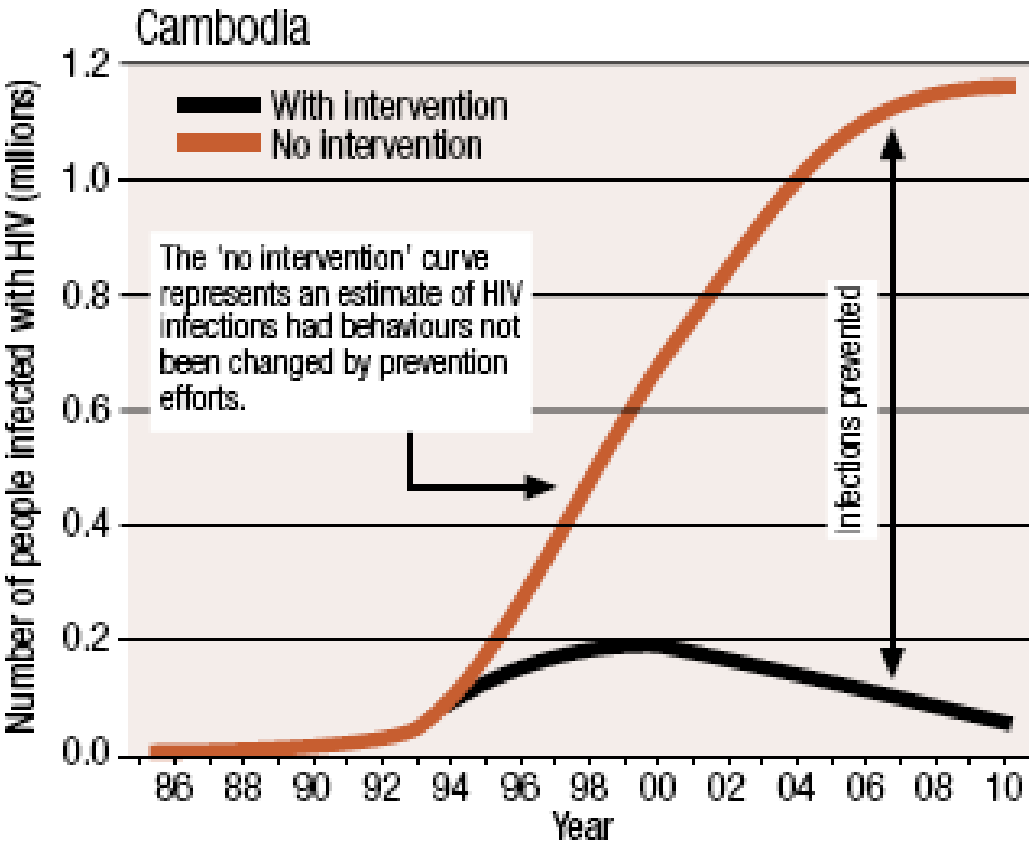
3 compulsory synergetic components…..

Examples of successes and failures: HIV Prevalence in Thailand, Uganda & KwaZulu-Natal: 1990-2000



Translating research into clinical practices: successes and failures

Example of HIV/AIDS issues in Cambodia



-Mobilization and response of national authorities;

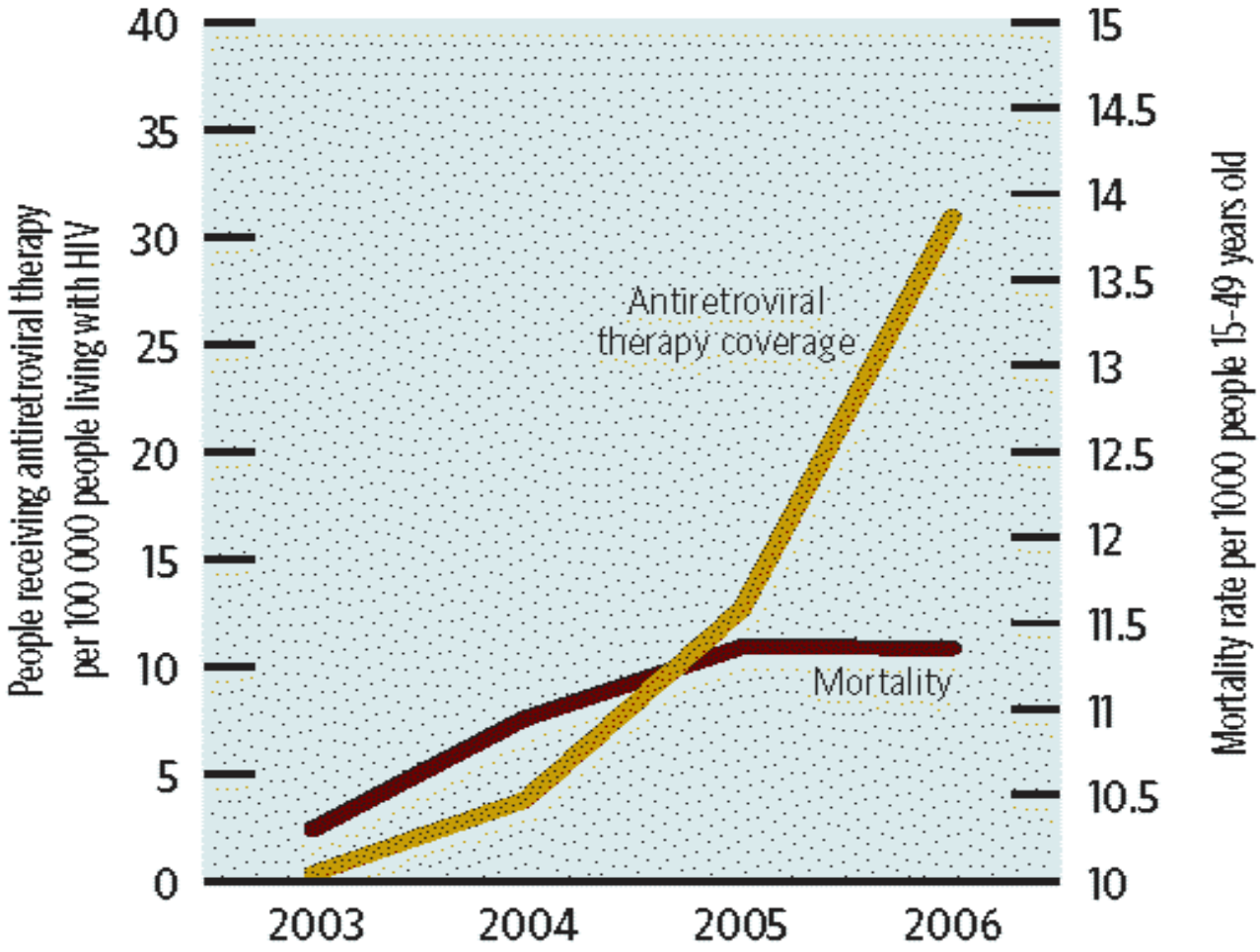
-Supports from international organizations;

-Operational research on site;

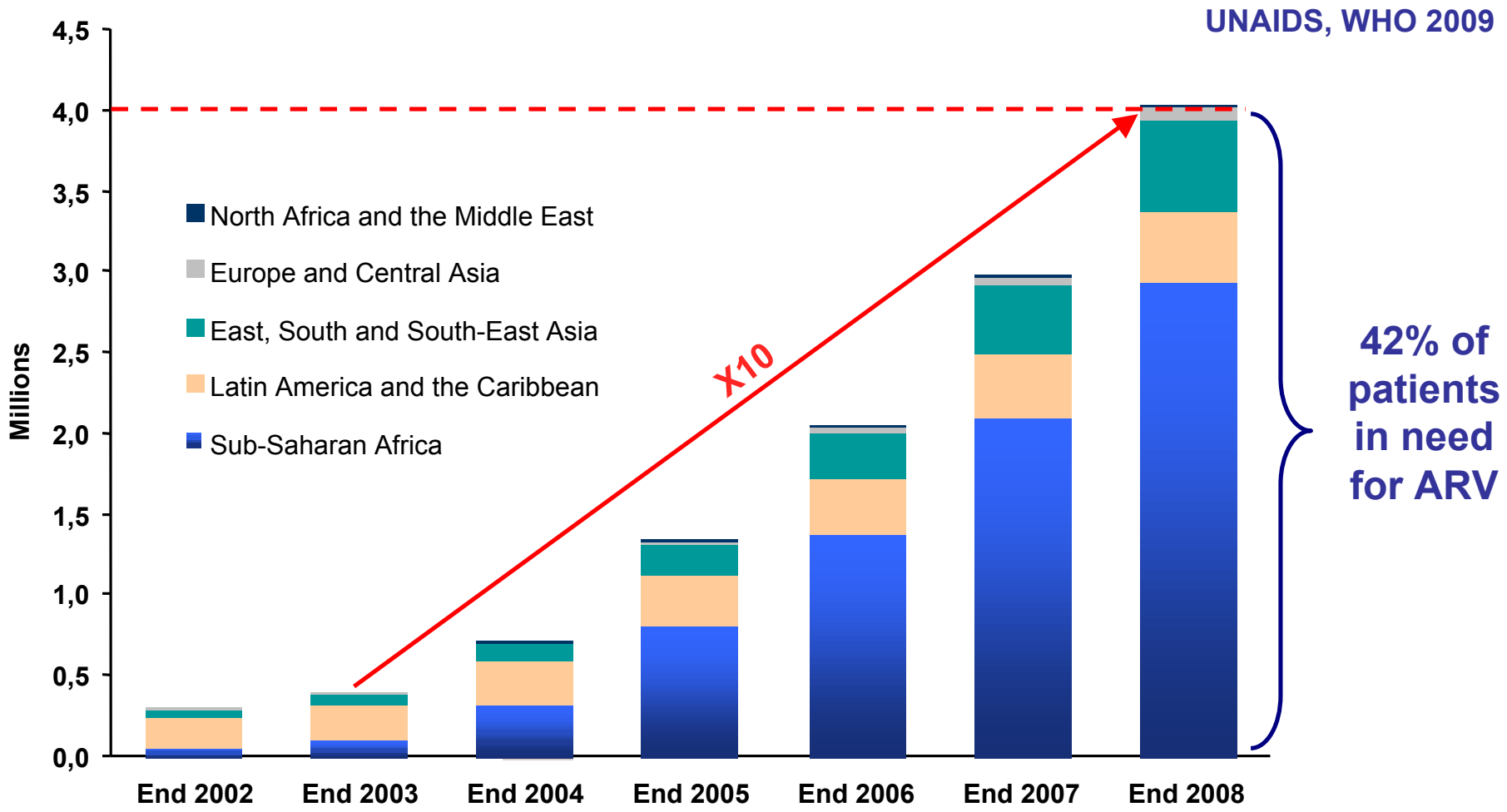
-Evidence: >90% of effectiveness of MSF ARV program after 2 years.

- Today about 35 000 patients on HAART.

Recent progress in translating science into Public health in Southern Africa: Antiretroviral therapy coverage and all-cause mortality, 2003–2006

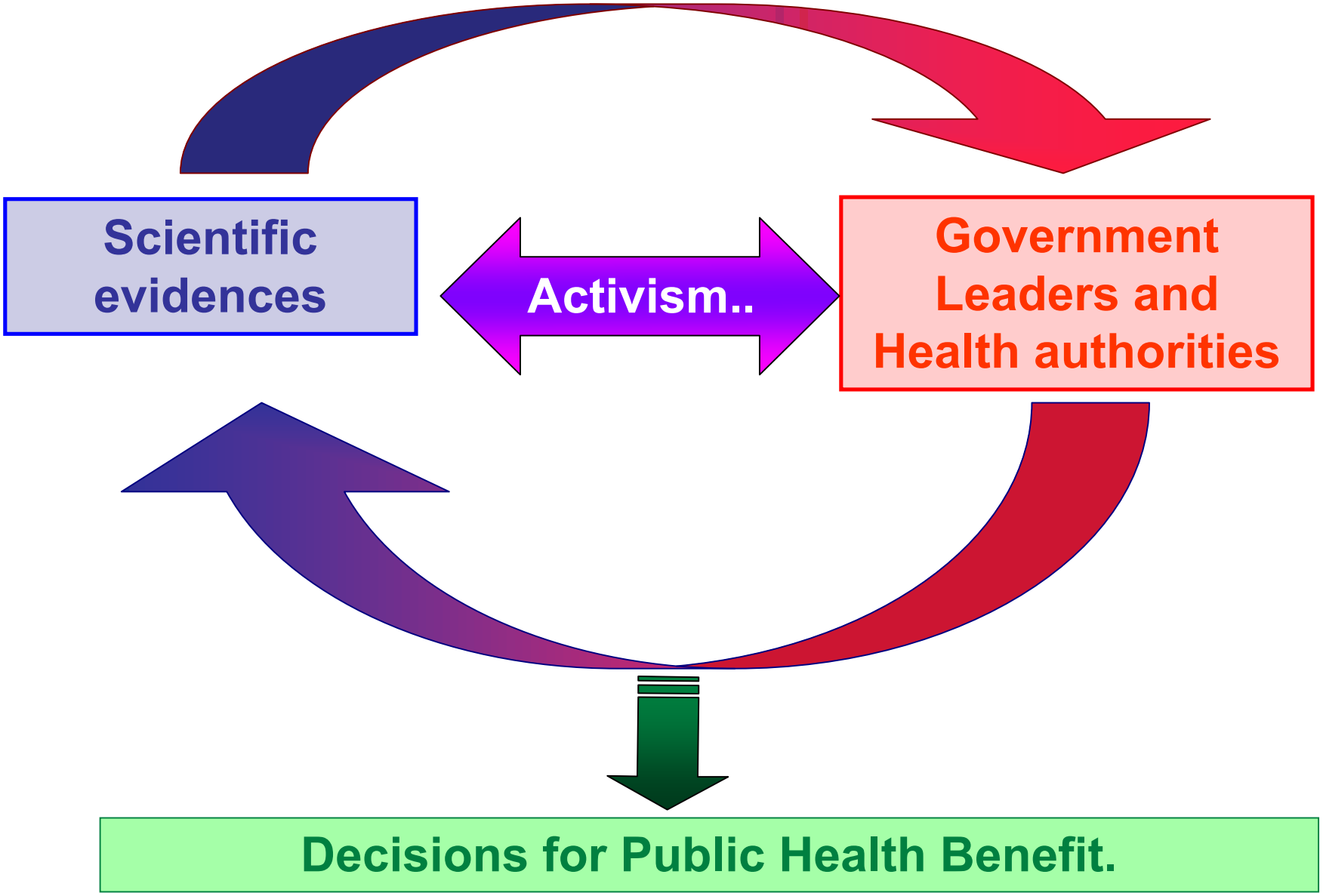


Progress in access to HAART (2002-2008)



For every 2 new persons starting HAART: 5 new infections

Relationship between scientists, health workers, activists and politicians for the benefit of global health...



27 years of HIV/AIDS science and still…

Urgent need for further research….

Priorities:

1) ***Co-infections***
2) ***Complications on long term HAART***
3) ***HIV reservoirs*** *(mechanisms of establishment and persistence, depletion of reservoirs)*
4) ***Early events during acute phase*** *of infection (early signals of immune activation, cross-talk between cells of innate and adaptive immunity, mechanisms of protection, host genetics)*
5) ***Interaction between viral factors and cellular partners***

6) */……*

→ **New therapeutic and vaccine strategies**

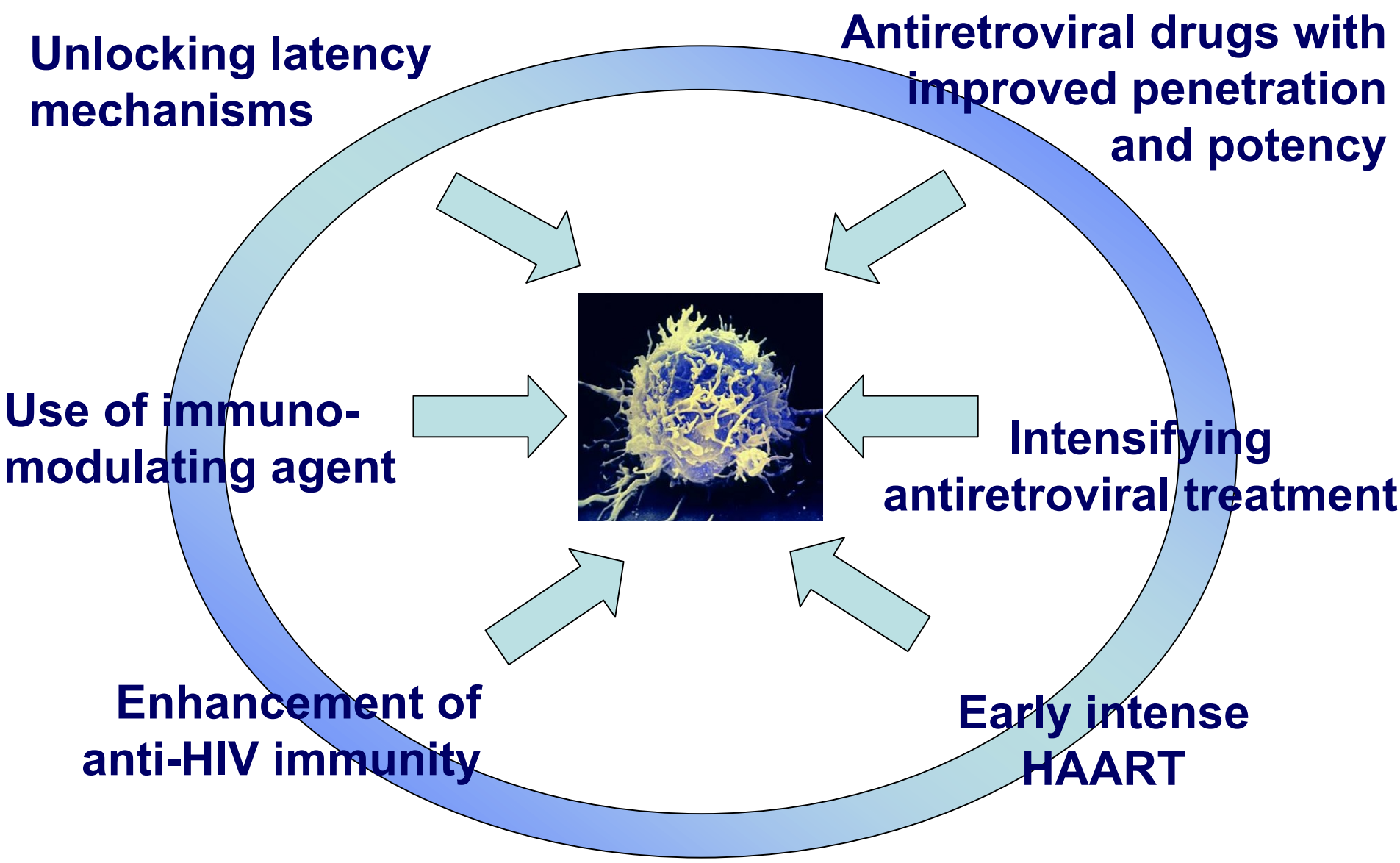
After more than 2nd decade, still gaps in HIV treatment…

- **AIDS associated morbidity in resource limited settings: need to get drugs to people who need them!**

- **Non AIDS associated morbidity in high Complications (resistance, metabolic disorders, including cardiovascular injury, premature aging, cancer…): impact of HAART toxicity, HIV induced persistent inflammation and life style?**

- **Eradication of HIV or at least functional cure…: Not yet there but a renewed effort begun to at least reduce the size of HIV reservoirs…**

Potential strategies targeting HIV reservoirs



Future medical & biomedical preventive strategies

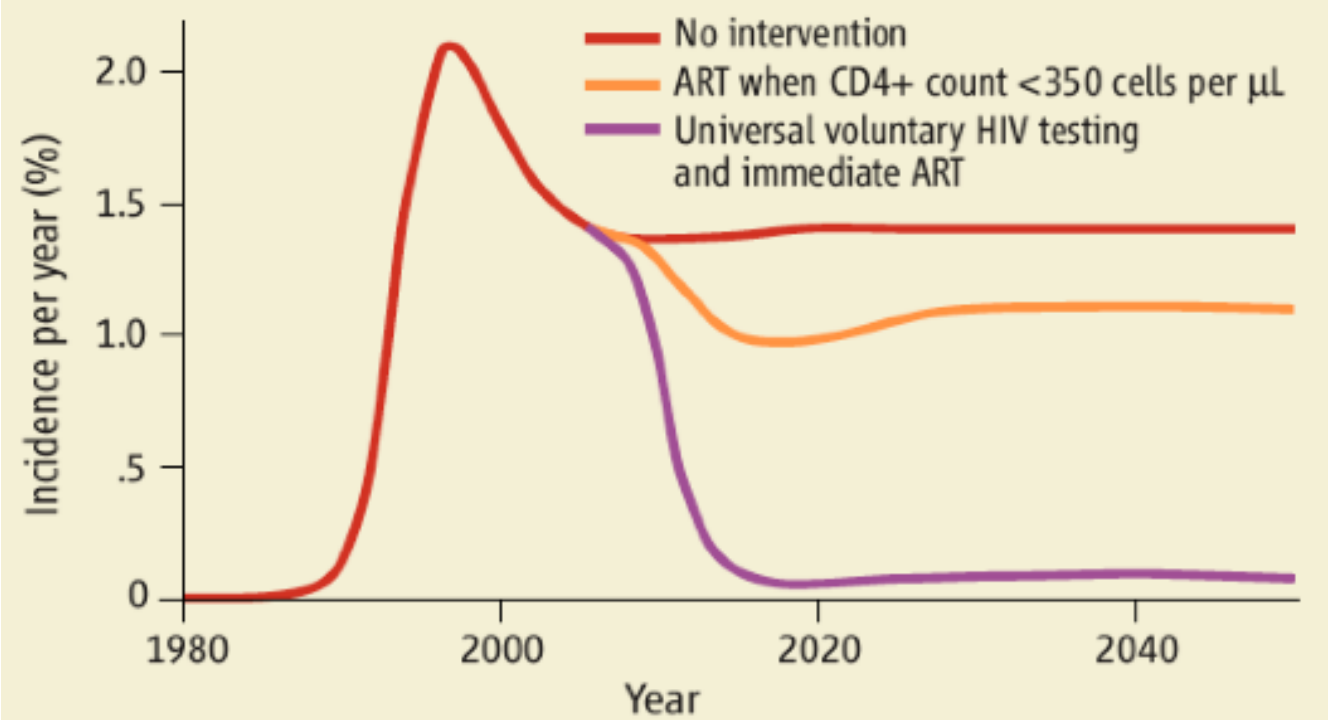
- **ARV in pre- or post-exposition prophylaxis?** ***Test and Treat Concept…***
- **Failure of microbicides =>** ***New specific microbicides?***
- **Circumcision associated to other prevention means?**
- **Vaccine: Failure of the classical approaches** ***(until the Thai RV144 vaccine trial….)***

Toward the eradication of HIV/AIDS? Test and treat concept…

ARV stop viral replication…

Undetectable viral load in blood and genital secretions..

Significant Reduction of HIV transmission…



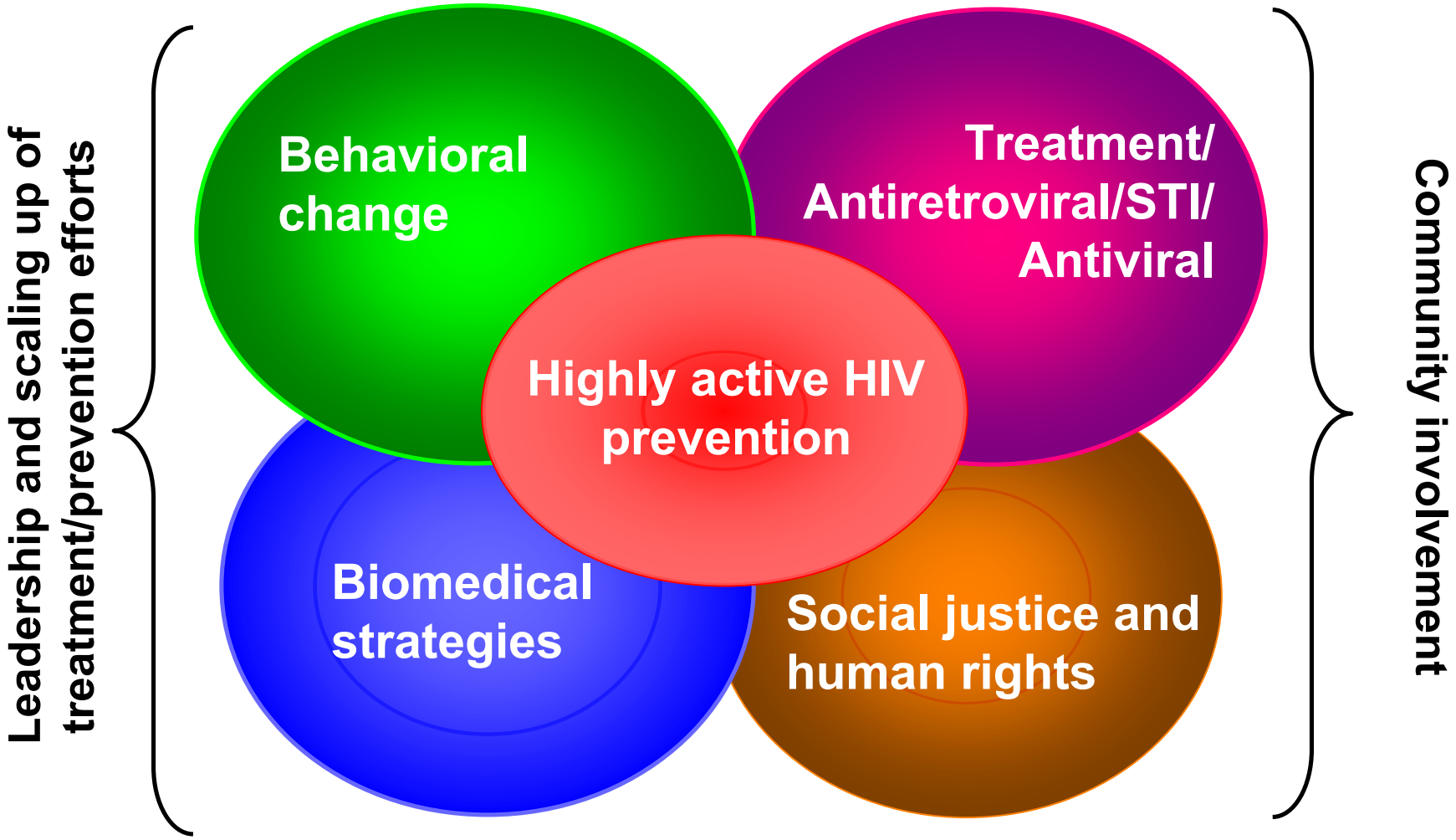
Modelisation:

R Granich, C Gilks, C Dye, K De Cock, B Williams.

Lancet, 2008

Reducing the incidence of HIV-1: A Priority!

A Global Response combining Treatment and Prevention….



Source: Coates TJ, et al. The Lancet 2008

HIV Vaccine history

August 1987 — 1st phase I trial

1987-2007 — > 110 trials (10 Phase II/III) with 67 products (27 500 volunteers)

→ ***Candidate vaccine are usually safe and showed some degree of immunogenicity***

2003 — Data of the 1st phase III efficacy trial VaxGen

→ ***Lack of efficacy of rgp120 definitively proven***

Sept. 2007 — STEP/Phambili phase IIb trial (HIV-1B gag, pol, nef / rAd5)

→ ***Discontinued for lack of efficacy***

Oct. 2009 — RV144 “Thaï”: ALVAC (gag/pol/env) + AidsVax (B/ErGp120)

→ ***Modest Efficacy 31%***

Ongoing phase II trials (DNA+MVA, DNA+NYVAC, lipopeptides…)

Is an AIDS vaccine possible?

Yes, according to the « Thai » RV144 efficacy trial

More than 16 000 volunteers enrolled

125 infections 51 in vaccinees/74 controls

31% of protection => For the 1st time a vaccine shows a modest efficacy in humans

More research are needed:

- ✓Why does this vaccine reduce the risk of HIV infection?
- ✓What are the mechanisms of protection?
- ✓Must we revise/redefine vaccine efficacy endpoints?
- ✓Is the strategy using a “prime” (induction) with an immunogen then “boost” (stimulation) with another immunogen, the right one?
- ✓How can we improve the vaccine efficacy?
- ✓…….

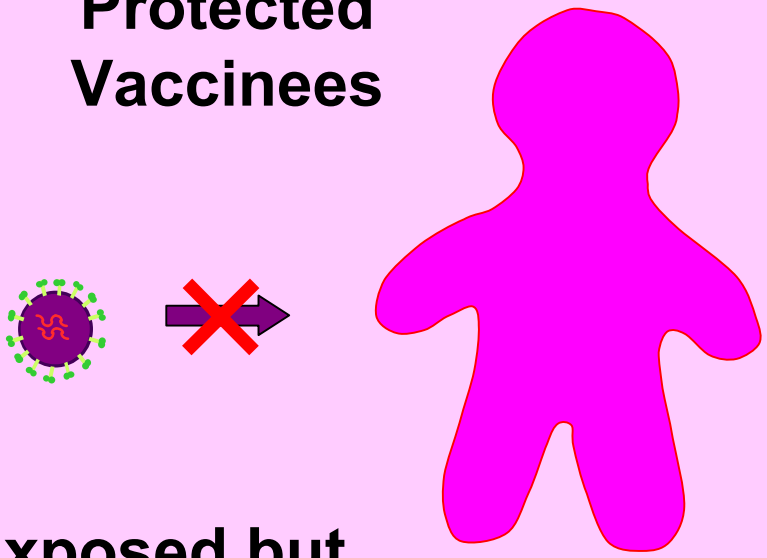
To learn from vaccinees …

New vaccine strategy…

To learn from models of protection

Against HIV infection

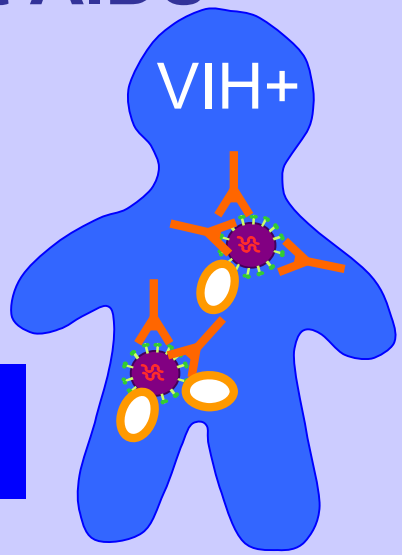
Protected Vaccinees



Exposed but uninfected individuals

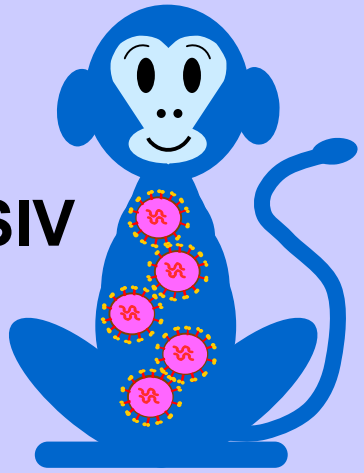
Against AIDS

HIV controllers



Control of HIV replication

African monkeys natural hosts of SIV



Control of abnormal immune activation

Future medical & biomedical preventive strategies

Vaccine Failure

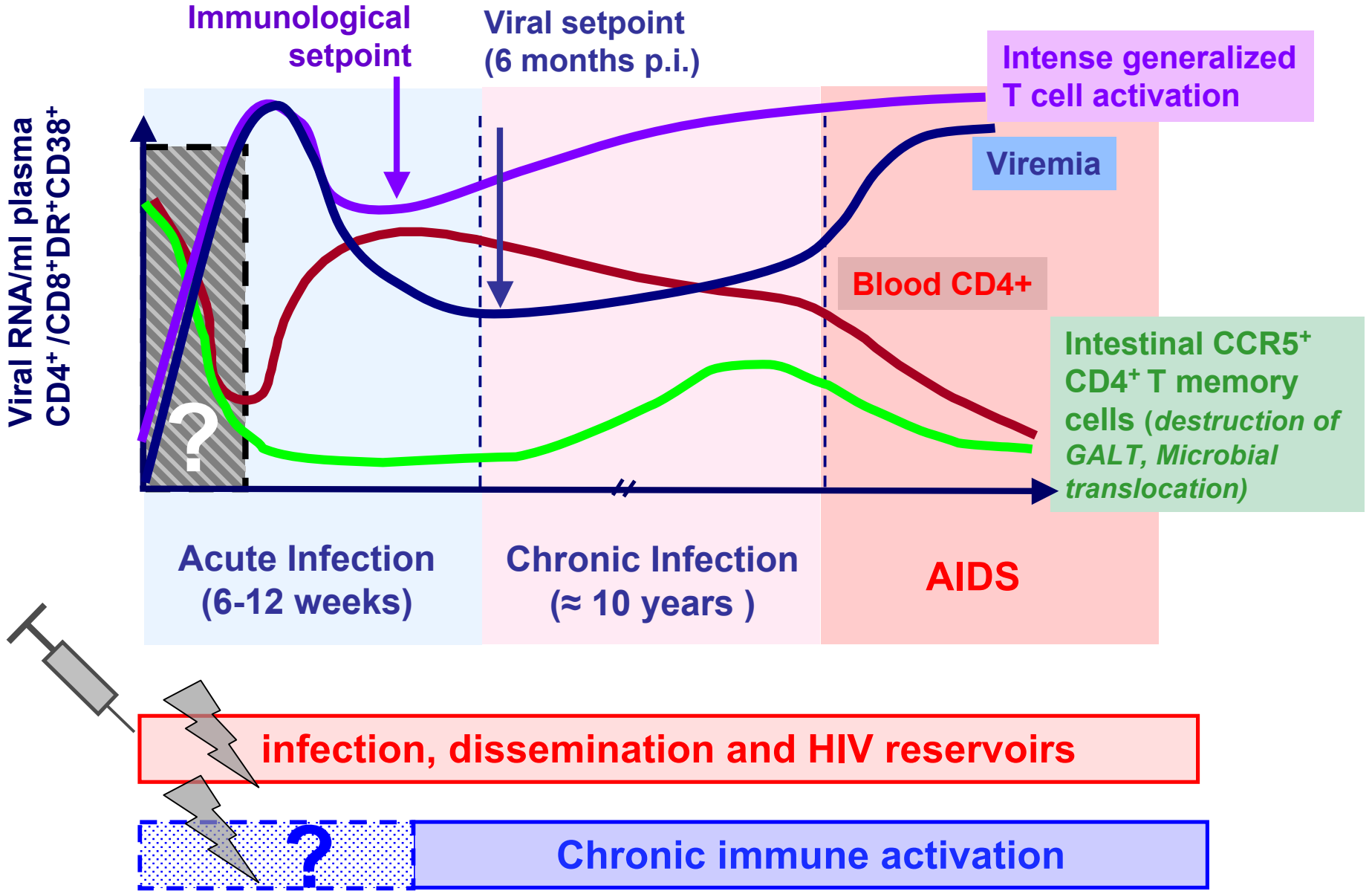
⇒**Why?: Many, many obstacles!**

- ✓ *Transmission by cell to cell infection*
- ✓*Very rapid attack and alteration of key players of the immune response in effector sites.*
- ✓*Latency and thus, no detection of the infection by our defense*
- ✓*HIV diversity and Immune response viral escape*

⇒ **Which solutions?** New innovative concepts based on a better knowledge of early events resulting (or not) in signals required to induce protective immunity, in particular at effector sites..

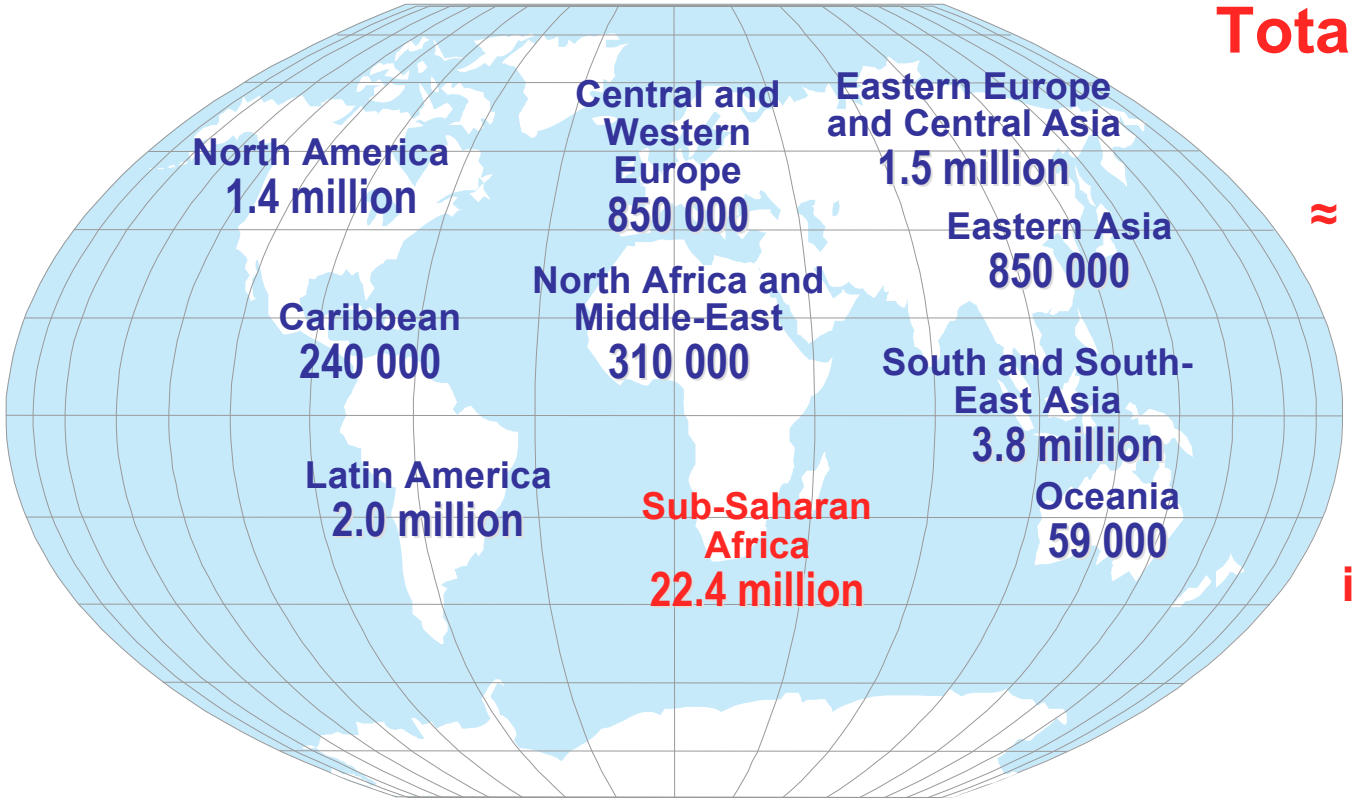
What should a vaccine aim at?

Re-thinking future strategies for an optimal HIV-1 vaccine…



HIV/AIDS, a key challenge in global health equity and development.

UNAIDS, WHO 2009



Total: 33, 4 million

≈ 7400 new infections and 5500 deaths every day

More than 95% in ressource-limited countries

60% of HIV+ persons ignore their serological status

- 2nd position of HIV/AIDS on the list of death caused by infectious diseases.
- Sensitive topic (sex & addiction, stigma, politics, religion,media..)
- Needs for governance & policymakers to understand HIV/AIDS science & socio-economic implications to respond.
- Long term disease requiring very quick policy responses
- Unprecedented international responses with success and failures

Combat HIV/AIDS, One of the Millenium development Goals

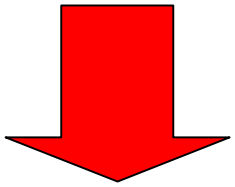
Millenium Development Goal #6

(set at millenium summit 2000 to be reached in 2015)

"Halt and begin to reverse the spread of HIV/AIDS"

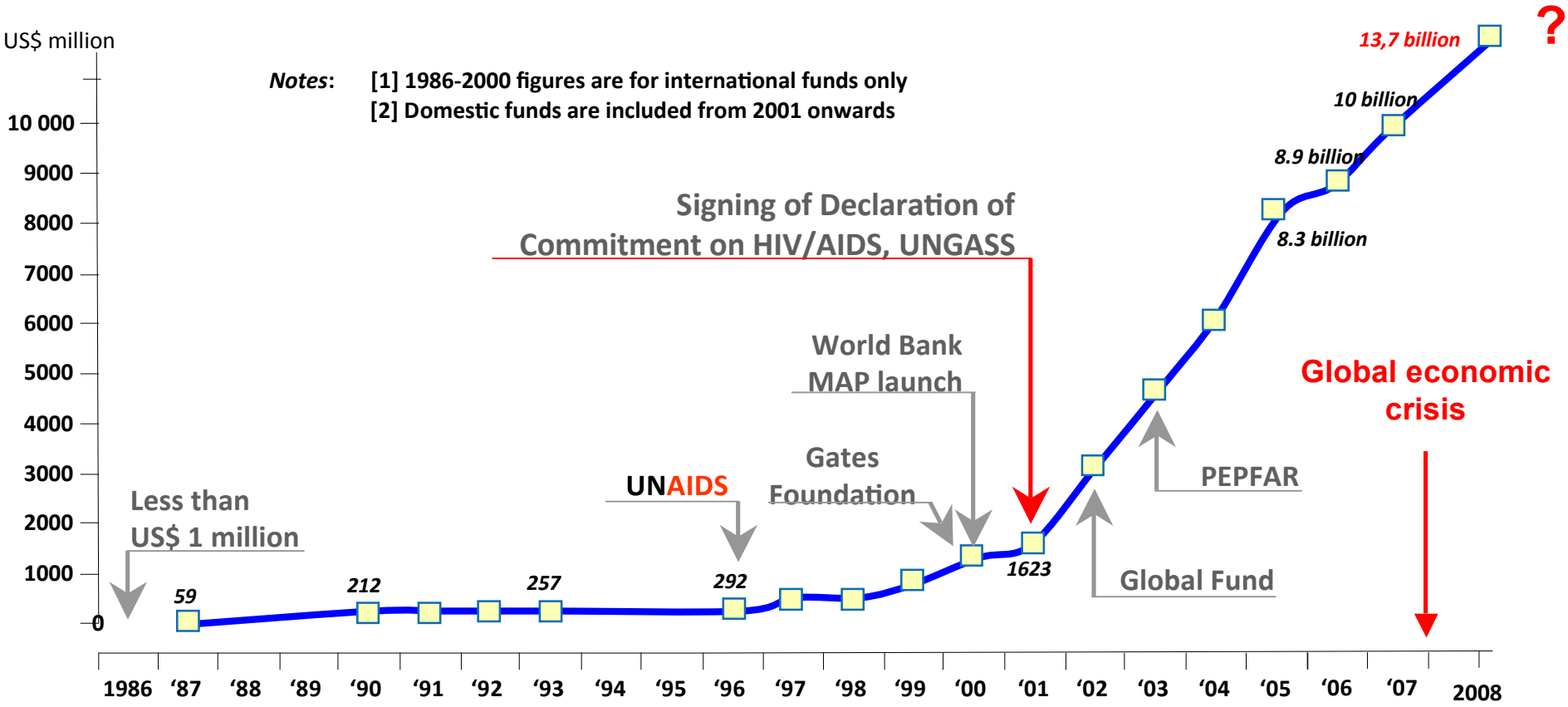
But

"Ensure that the response to HIV/AIDS is further integrated within, and benefits, health systems as a whole"



A unique opportunity to change the course of history in global health equity

Resources available for HIV/AIDS: What's next?

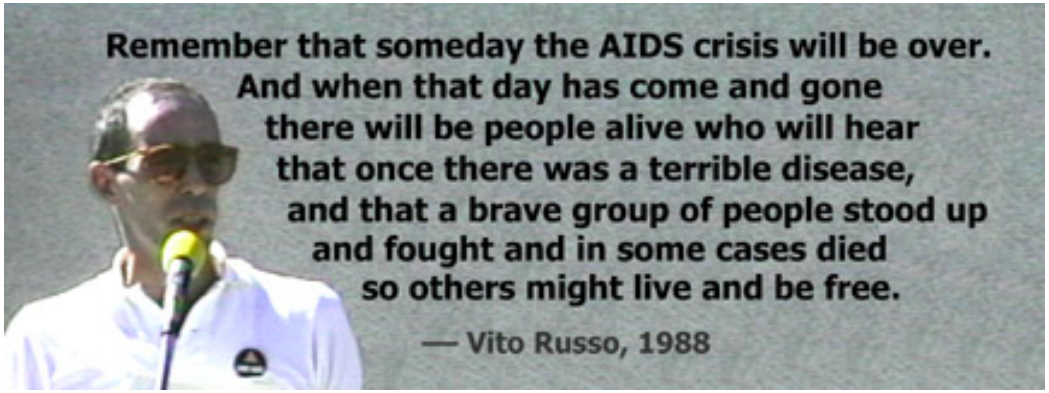


In 2010 an estimated $25.1 billion will be needed, to reach objectives

International leaders must keep their promises

The fight against HIV/AIDS from the beginning up to now: a unique impulse of solidarity

People from different walk of life, raised their voices



Equal access to treatment, care and prevention

Social and legal justice for all

End of stigma and discrimination based on serological status, gender or sexual orientation

…

POLITICAL COMMITEMENT

Fighting for human rights is a part of HIV/AIDS combat

"Today, we know that security means far more than the absence of conflict. (…) We know that lasting peace requires a broader vision encompassing areas such as education and health, democracy and human rights, protection against environmental degradation, and the proliferation of deadly weapons. We know that we cannot build peace without alleviating poverty, and that we cannot build freedom on foundations of injustice. These pillars of what we now understand as the people-centred concept of human security are inter-related and mutually reinforcing". *(Former UN Secretary-General Kofi Annan)*

In a globalized world, health must be considered as a non negotiable right for every human being and equity in access to it, as an international responsibility