HIV Infection 2013
New Challenges-Opportunities for Translational Research

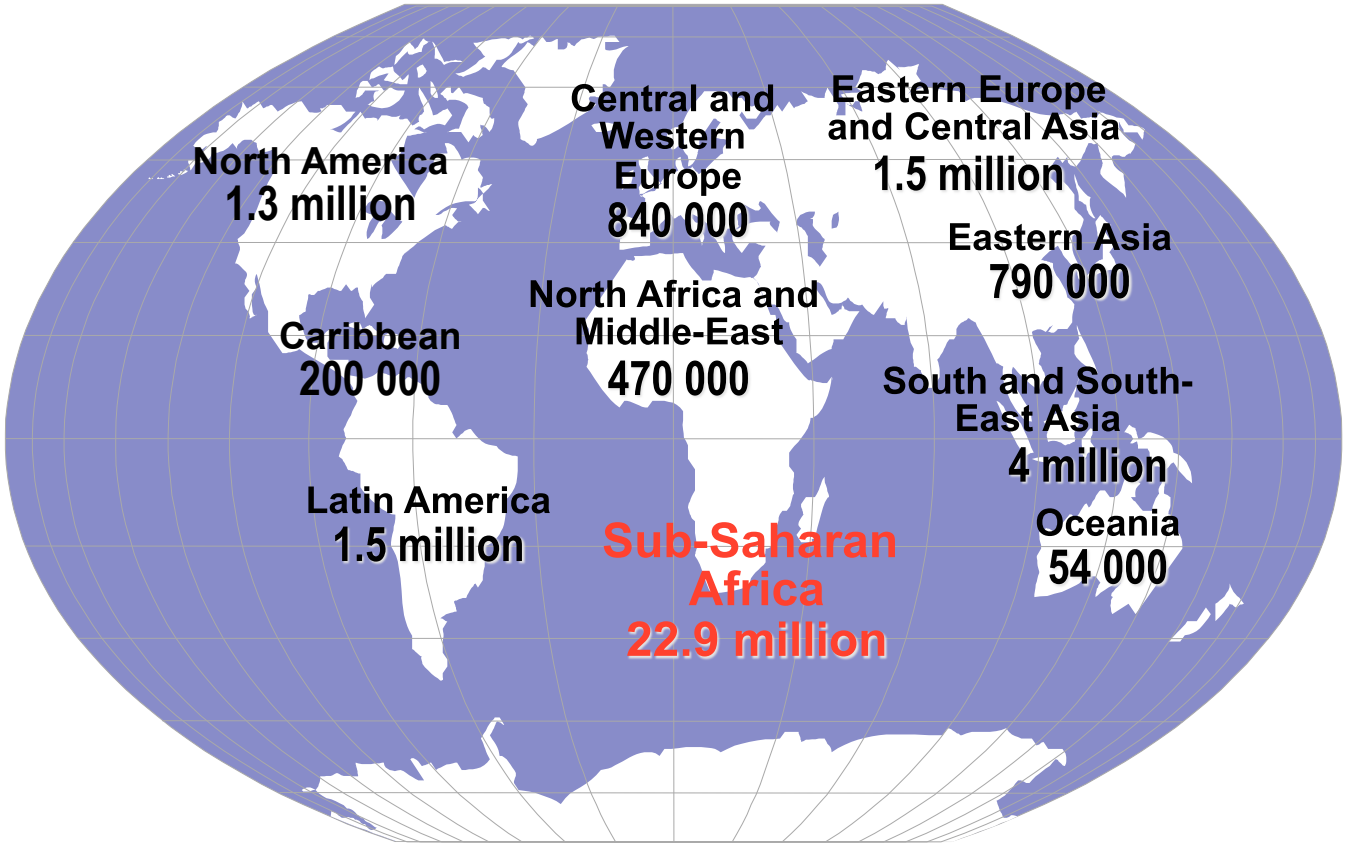
Pr. Jean François DELFRAISSY
Service de Médecine Interne
CHU Bicêtre – Paris XI – INSERM U.1012
Director of ANRS

Collège de France – 30 Janvier 2013

HIV INFECTION
1983-2013/ 30 years

- Key issues in pathogenesis
- Limits of HAART
- Towards a cure ?
- New opportunities in Prevention
- Challenges and priorities in/for develloping countries

Despite unprecedented international efforts, HIV/AIDS remains a key challenge in global health equity and development.



UNAIDS, WHO 2012

33 million of PLWH

- **HIV/AIDS remains at the 2nd position on the list of death caused by infectious diseases with 5500 deaths and ≈ 7400 new infections every day**
- **More than 95% in resource-limited countries**
- **About 60% of HIV+ persons ignore their serological status (15 to 50% in Europe…)**
- **Still a sensitive topic (sex & addiction, stigma, politics, religion,media..)**

AGENDA of the ANRS : 4 main priorities for HIV

- **Study reservoirs with the objective of eradication or functional cure**
- **Testing: Novel methods; Early and better treatment**
- **Prevention of new infection with a biomedical approach**
- **Develop new vaccine strategies**

With a NORTH ← → SOUTH vision

Integrating economic aspects

1981…1er signes alarmants d'une épidémie émergente

- **Juin-Juillet 1981: Premiers cas de pneumocystoses associés à un déficit Immunitaire chez des patients homosexuels aux USA**

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

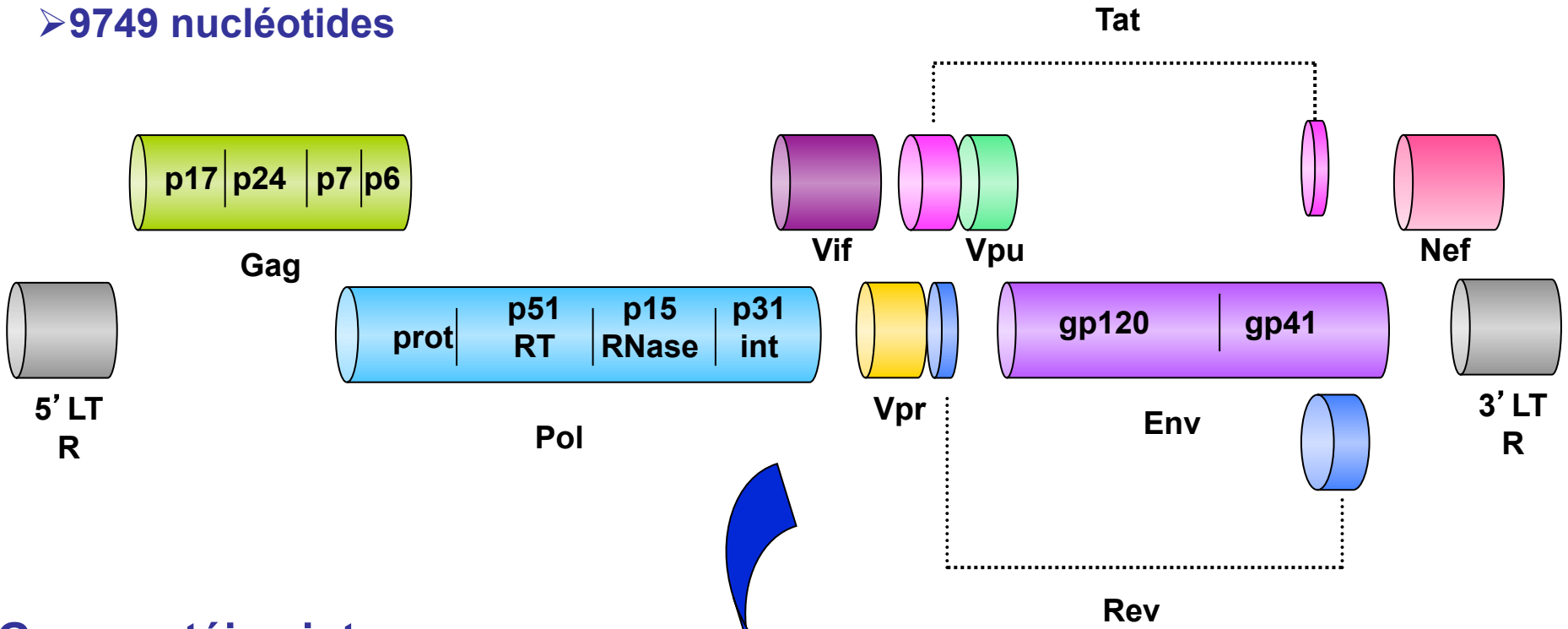
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV)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

- **Juillet 1982: Premiers cas de SIDA chez les patients hémophiles**
- **Octobre 1982: Premiers cas de SIDA chez les femmes, infection hétérosexuelle**
- **Décembre 1982: Premiers cas d'enfants infectés**

Mobilisation des chercheurs par les épidémiologistes et les cliniciens…

1984-1985: clonage et séquençage du génome du VIH-1

- 1ere séquence complète en 1985 (un génome unique complexe, distinct du HTLV-1, mais une organisation similaire à Visna-Maedi)
- 9749 nucléotides



Gag: protéine interne
Pol: Enzymes virales
Env: Glycoproteines de l'enveloppe
Genes de regulation (Tat, Rev, Nef, Vpr, Vpu, Vif)

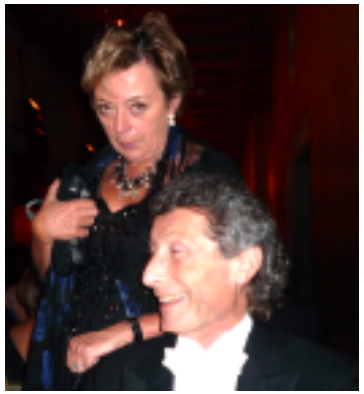
Diversité et origine du VIH…

Les années 1980 : Histoire d'une aventure partagée

Evolution des connaissances des technologies en rétrovirologie…

- **Identification du SIDA en France (1982)**
- **Gallo et Yoshida (1981) - Premier rétrovirus humain (HTLV ou Human T Cell Leukemia Virus)**
- **FeLV et immunodéficience chez le chat**
- **Identification du TCGF ou IL2 (1979)**

Des cliniciens mobilisent les rétrovirologues de l'Institut Pasteur



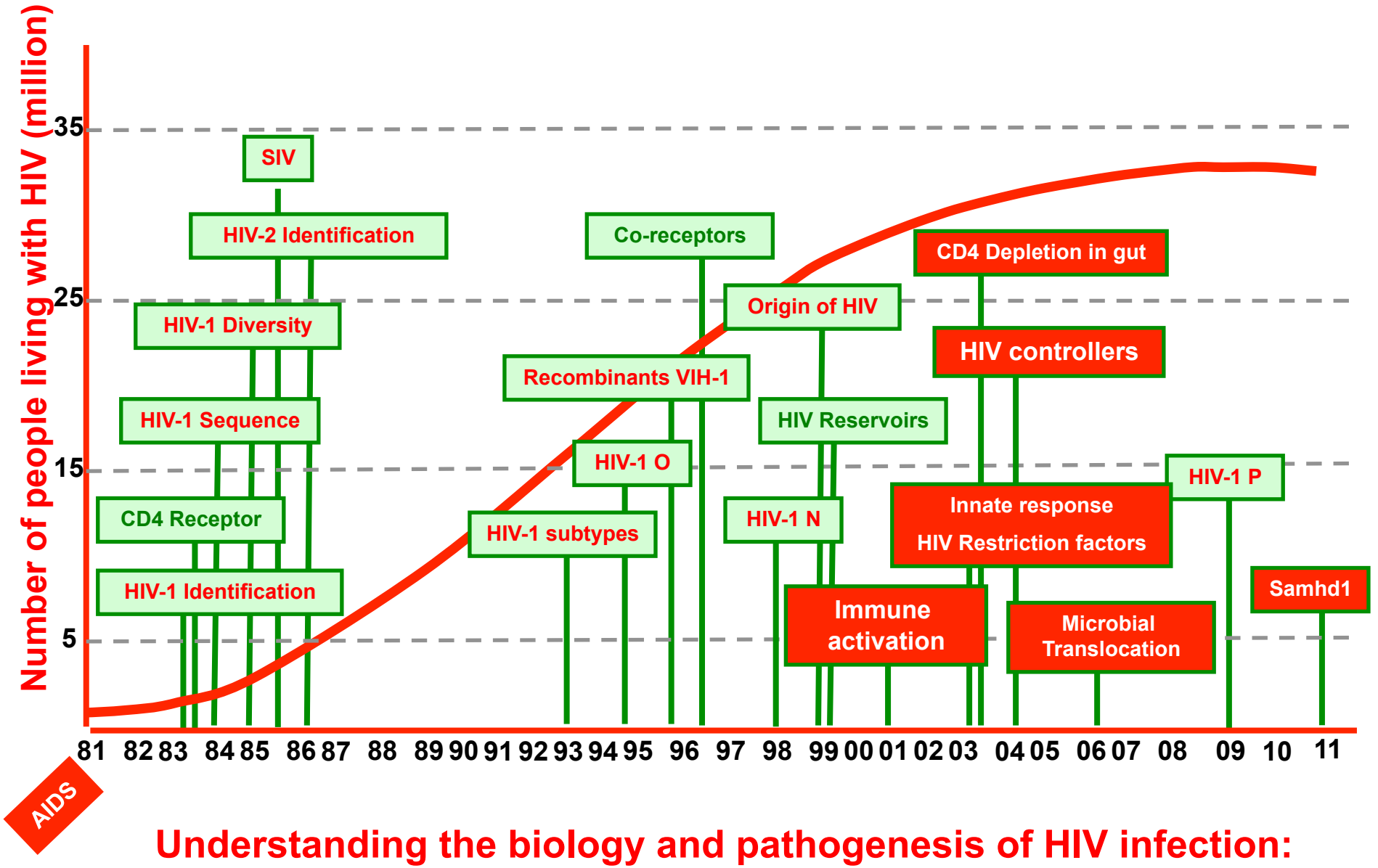
F.Brun-Vezinet
W.Rozenbaum

C. Rouzioux

Une rencontre décisive

Quel virus? Quand? Où? Comment?
Pas de DOGME….

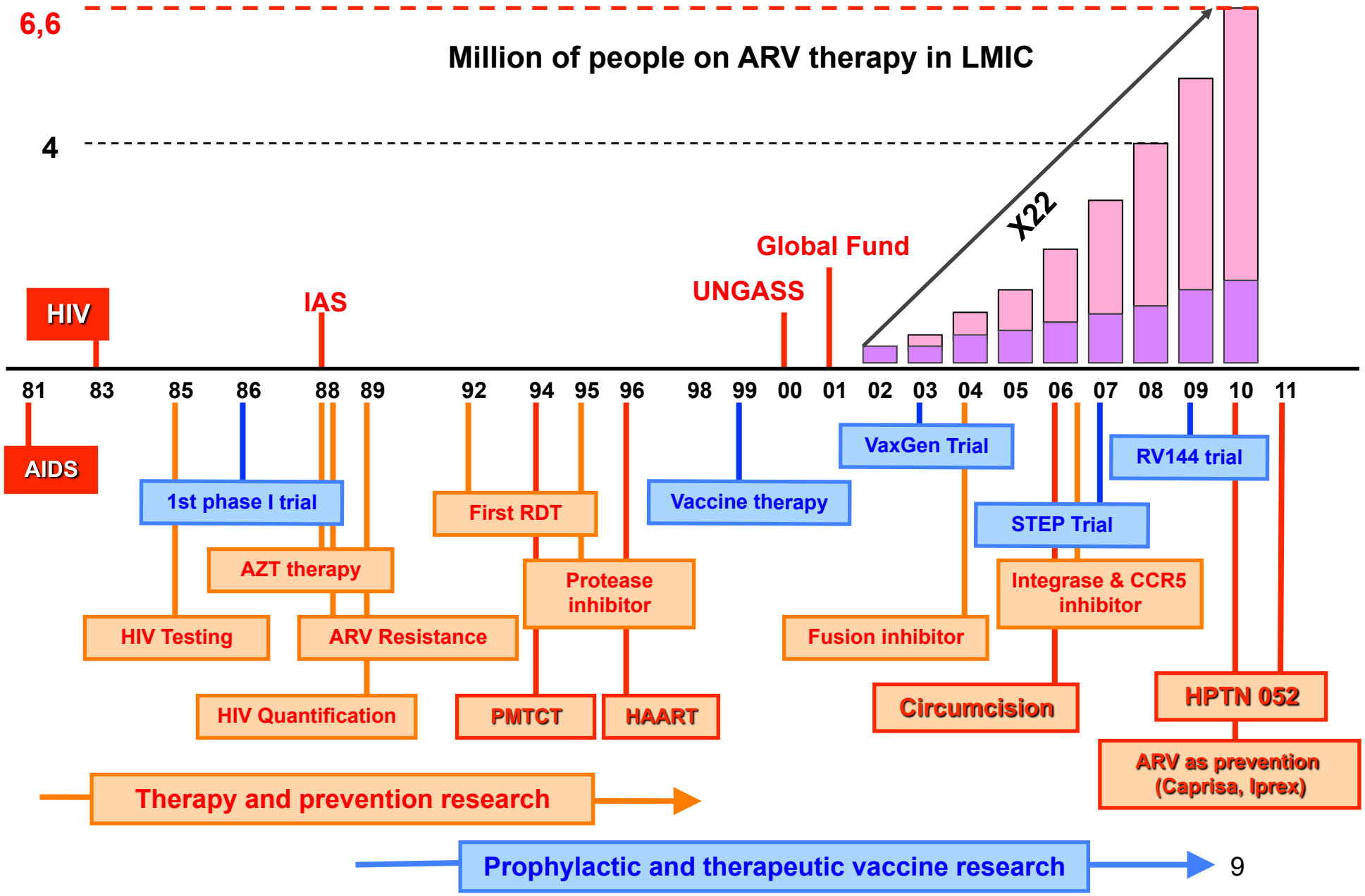
30 years of HIV/AIDS Science: Main milestones



Understanding the biology and pathogenesis of HIV infection:

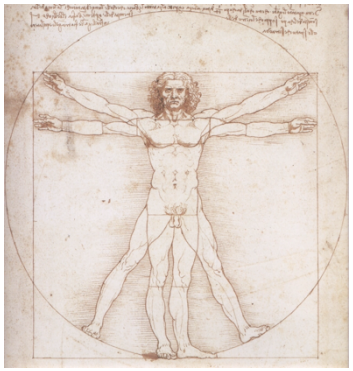
First step toward prevention and treatment strategies….

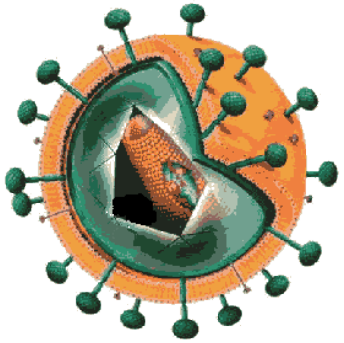
30 years of HIV/AIDS translational science…



HIV transmission and pathogenesis:

A complex interplay between the virus and its host





Host Determinants

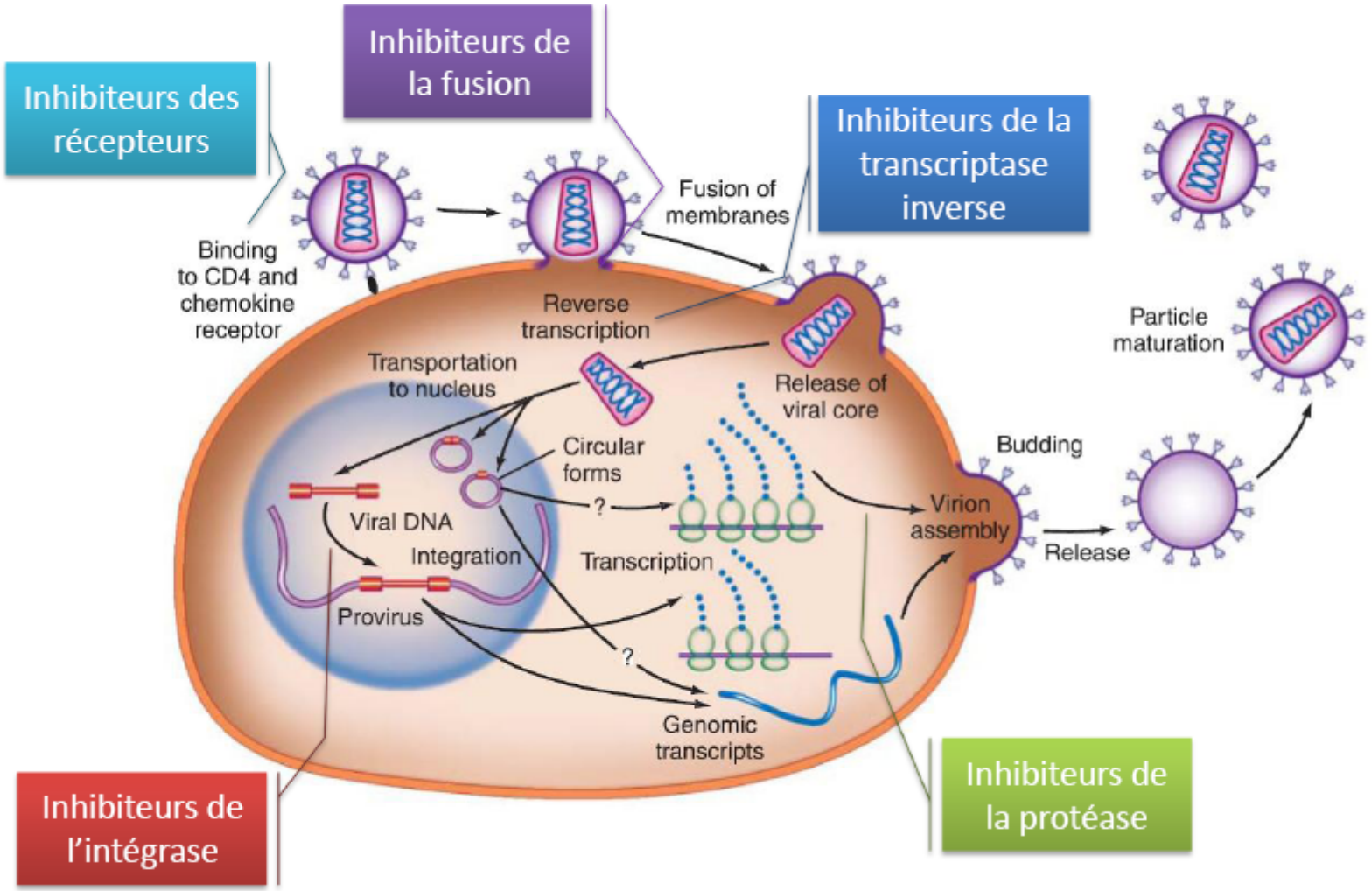
- Host Cell factors invoved in virus life cycle
- Intrinsic cellular defense (restriction factors APOBEC, TRIM5α, Tetherin/BST2, SAMHD1, p21, others…)
- Mediators of Host Innate and Adaptive Immunity

Viral Determinants

- Tropism & replicative capacity in host cells *(CD4 T lymphocytes, macrophages, DCs)*
- Immunosuppressive capacity
- Abnormal activation signaling pathways

Impact of host and viral genetic diversity ….

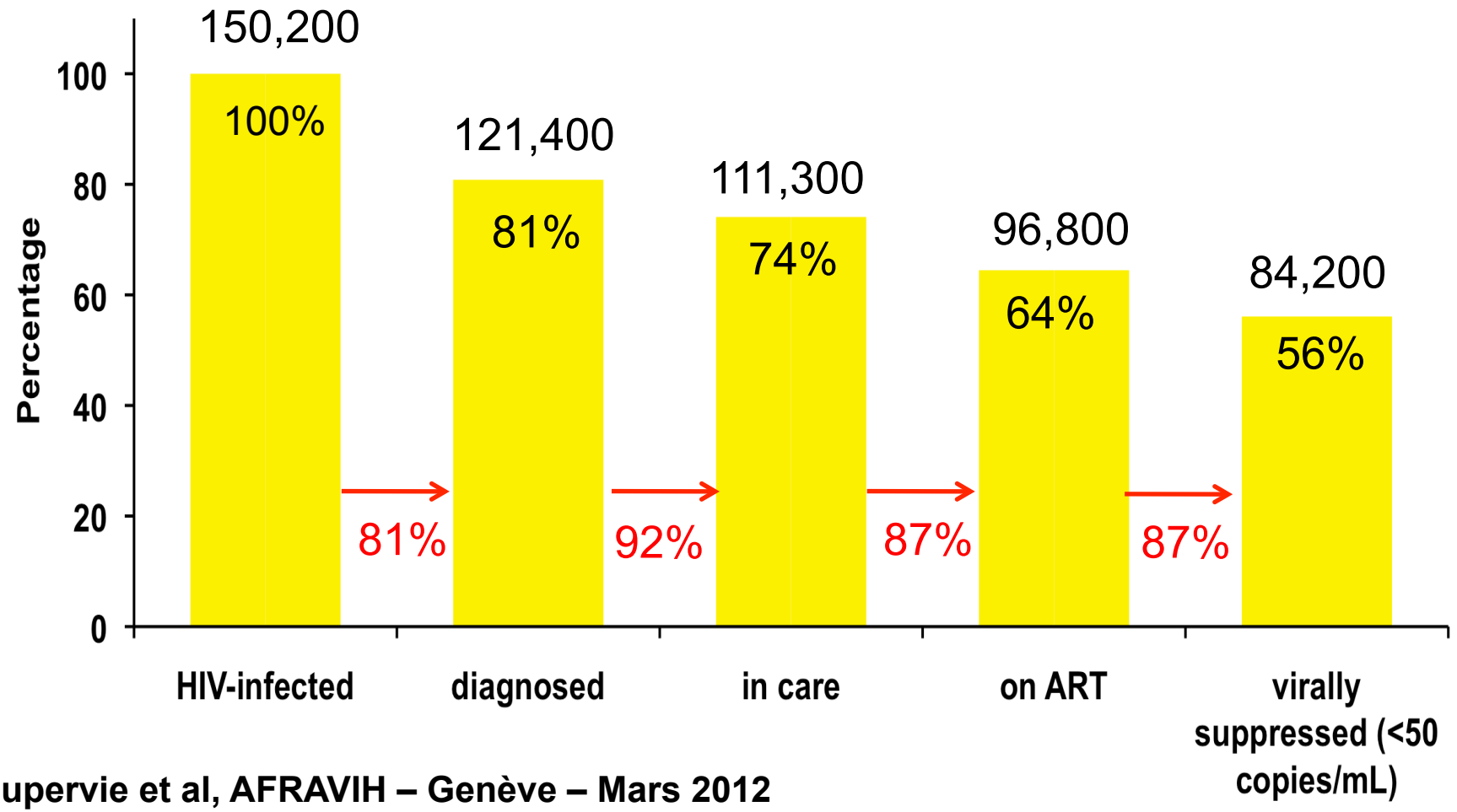
Cycle de Réplication du VIH-1



Plus de 25 moléculesantiretrovirales et plus de 35 combinaisonsthérapeutiquesapprouvées et disponibles..

New Challenges:HIV and emerging new diseases…

Estimation du nombre et du pourcentage de personnes infectées par le VIH dans les différents stades de la cascade d'une prise en charge effective en France en 2010

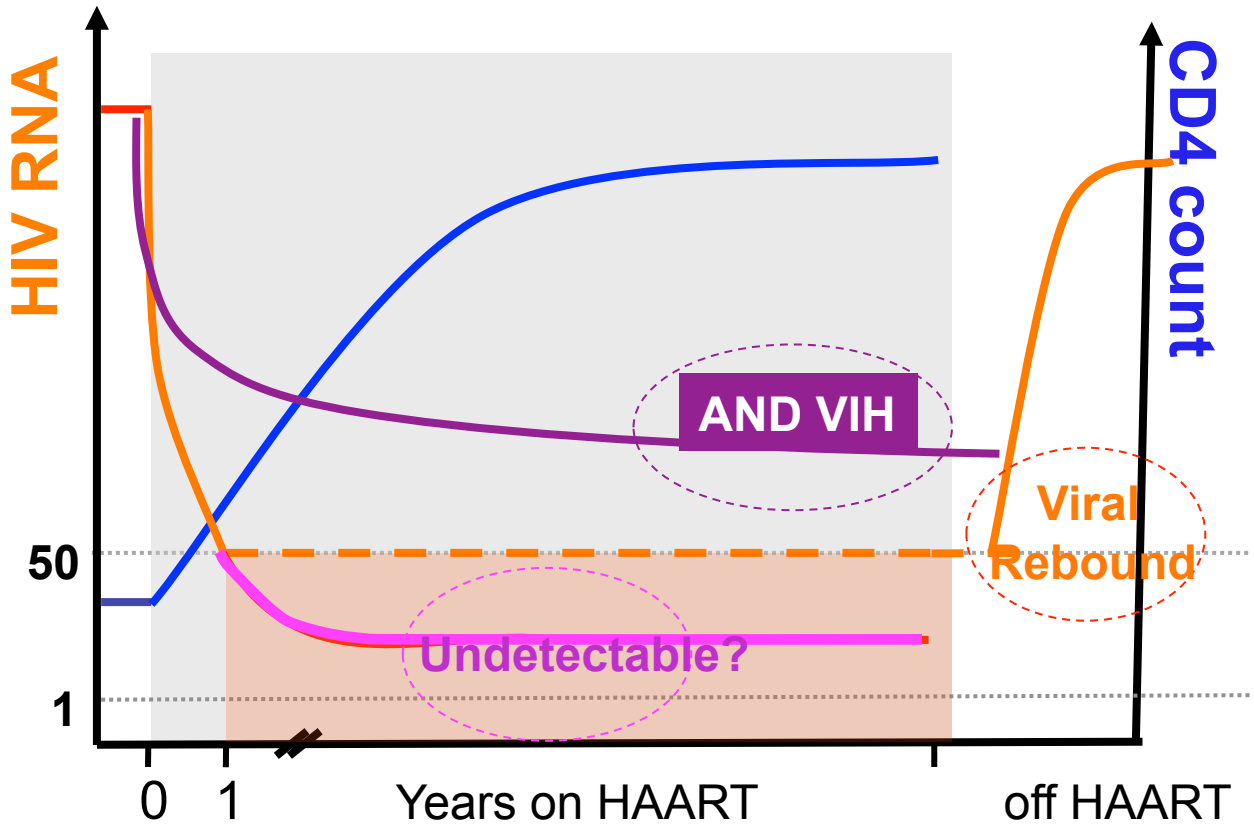


V Supervie et al, AFRAVIH – Genève – Mars 2012

LIMITS OF ANTIRETROVIRAL THERAPY

- Viral eradication is not possible with currently available drug combinations
- Treatment should be maintained for years or decades
- Toxicity of ARVs
- Adherence to therapy is a major issue in antiretroviral therapy and explains occurrence of resistance
- Immune restoration is limited (CD4 < 500 in 40% of patients)

Pourquoi l'infection VIH persiste sous ARV?



Obstacles:

- Infection latente de cellules T
- Replication virale residuelle en lien avec l'inflammation/ activation immunitaire
- Reservoirs anatomiques
- Pénétration des ARV dans les tissus

Palmer et al., *Proc Natl Acad Sci U S A*. 2008;105:3879-84
Maldarelli et al., *Plos Pathogens* 2007; 3:484

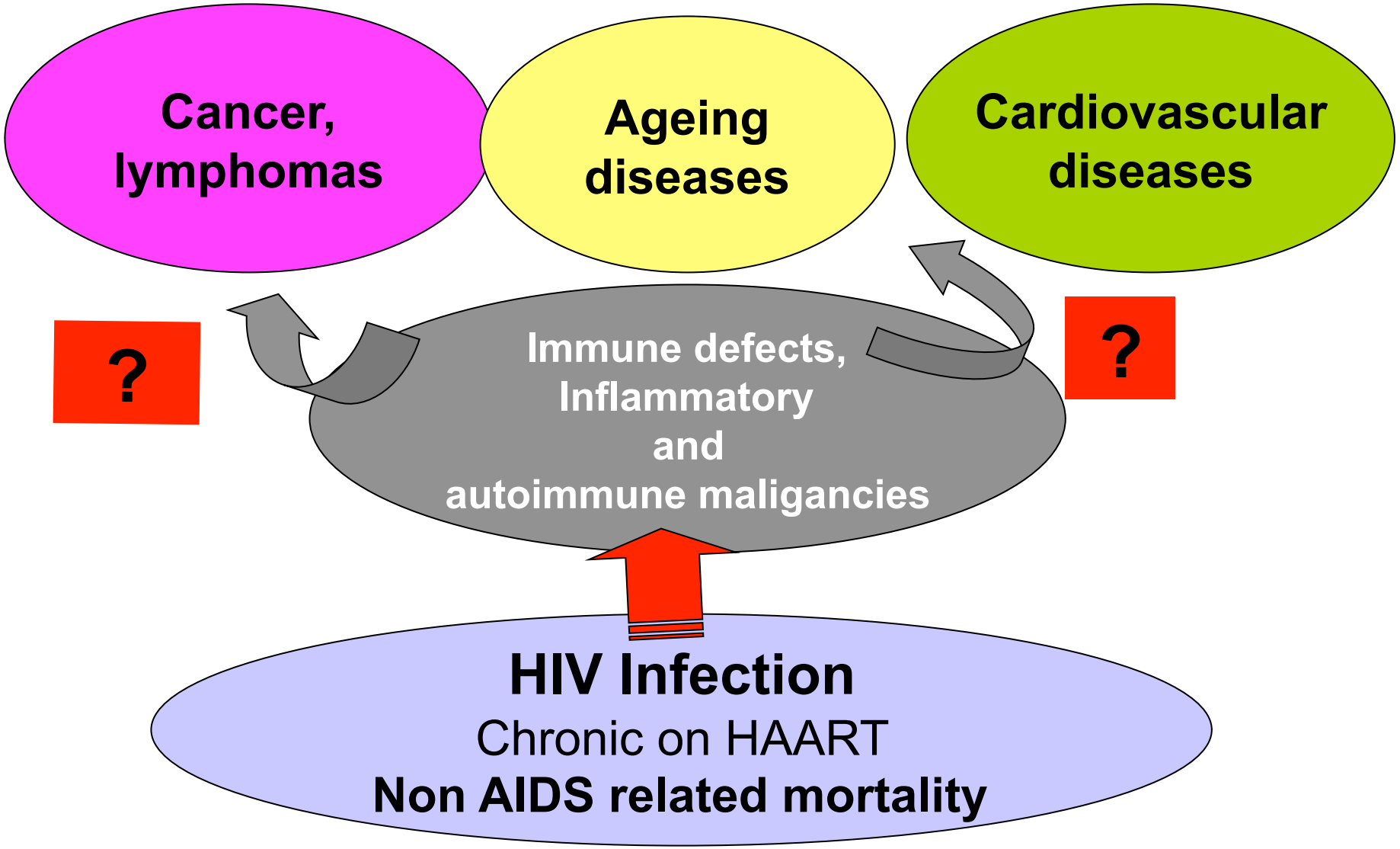
SCIENTIFIC PRIORITIES FOR FUTURE TRIALS

- **Prevention and treatment of cancers**
  - Viral-induced Cancers (HCV, HPV, EBV)
- **Improvement of immune reconstitution**
  - Early treatment, treatment intensification, cytokines, role of chronic inflammation
- **Prevention/treatment of drug-induced toxicities**
  - Role of chronic inflammation
  - bone, renal, cardiovascular toxicities
- **Control/eradication of HIV-infection**
  - New drugs, immune-based therapies
- **Prevention of new infections**
  - Use antiretroviral treatment for prevention
- **Keep opportunities to implement innovative/timely studies**

Complementary, non ARV-containing,therapy : Treatment of immune dysfunction and of chronic inflammation

- Immune dysfunction and/or chronic inflammation are not fully reversed by HAART and are implicated as causally related to the premature onset of cardiovascular disease, cancer, osteoporosis,..
- Examples of strategies developed to minimize immune dysfunction and/or chronic inflammation in patients with controlled HIV replication:
  - r-hIL-7. Maraviroc, rifaximin
  - Drugs with anti-inflammatory activity (aspirin, statins, etc..)
  - Inhibition of the TOx pathway
  - Other approaches (telomerase-based, anti-fibrosis, etc..)

New Challenges:HIV and emerging new diseases…



Learning from each others beyond HIV/AIDS…..

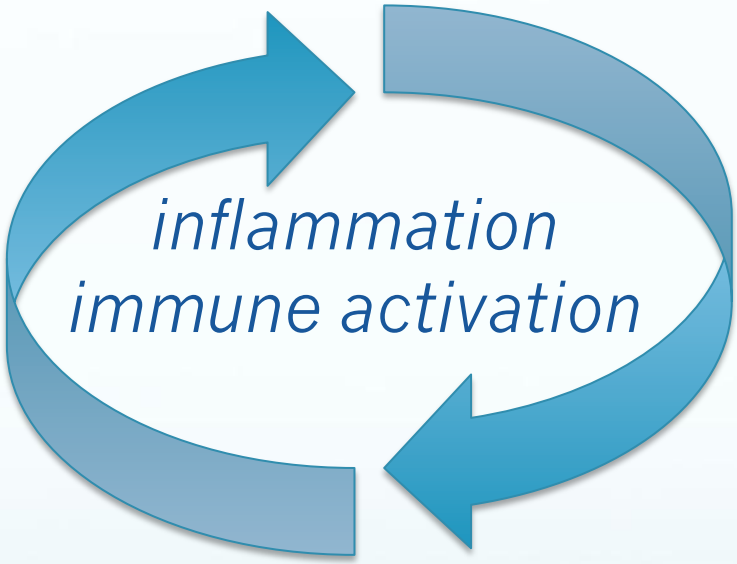
Towards a functional cure ?

The Reservoirs

Barriers to cure HIV infection

Where is the virus and how is it maintained in the face of suppressive therapy?

Residual replication



Latent infection

Approaches to an HIV Cure

Eradication → **"Purge" virus**

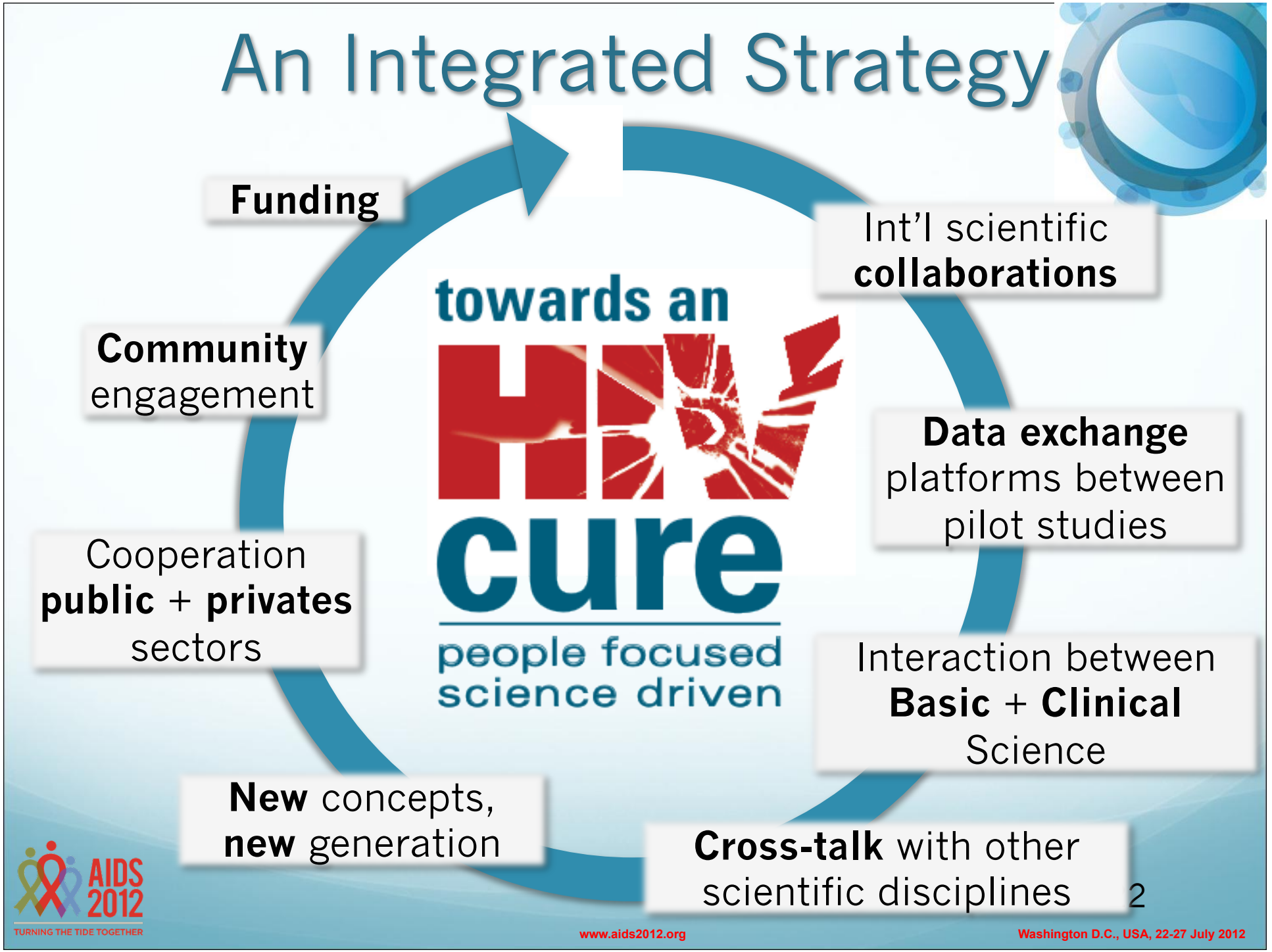
Functional Cure

- **Enhance HIV-specific immunity**
- **Modify host cells to be resistant to HIV infection**

HIV cure: 2-models

Eradication	Remission
Sterilizing cure	Functional cure
Elimination of all HIV-infected cells	Long-term health without cART
HIV RNA < 1 cop/mL	HIV RNA <50 cop/mL
Berlin Patient post-BMT	Elite controllers Post-cART controllers

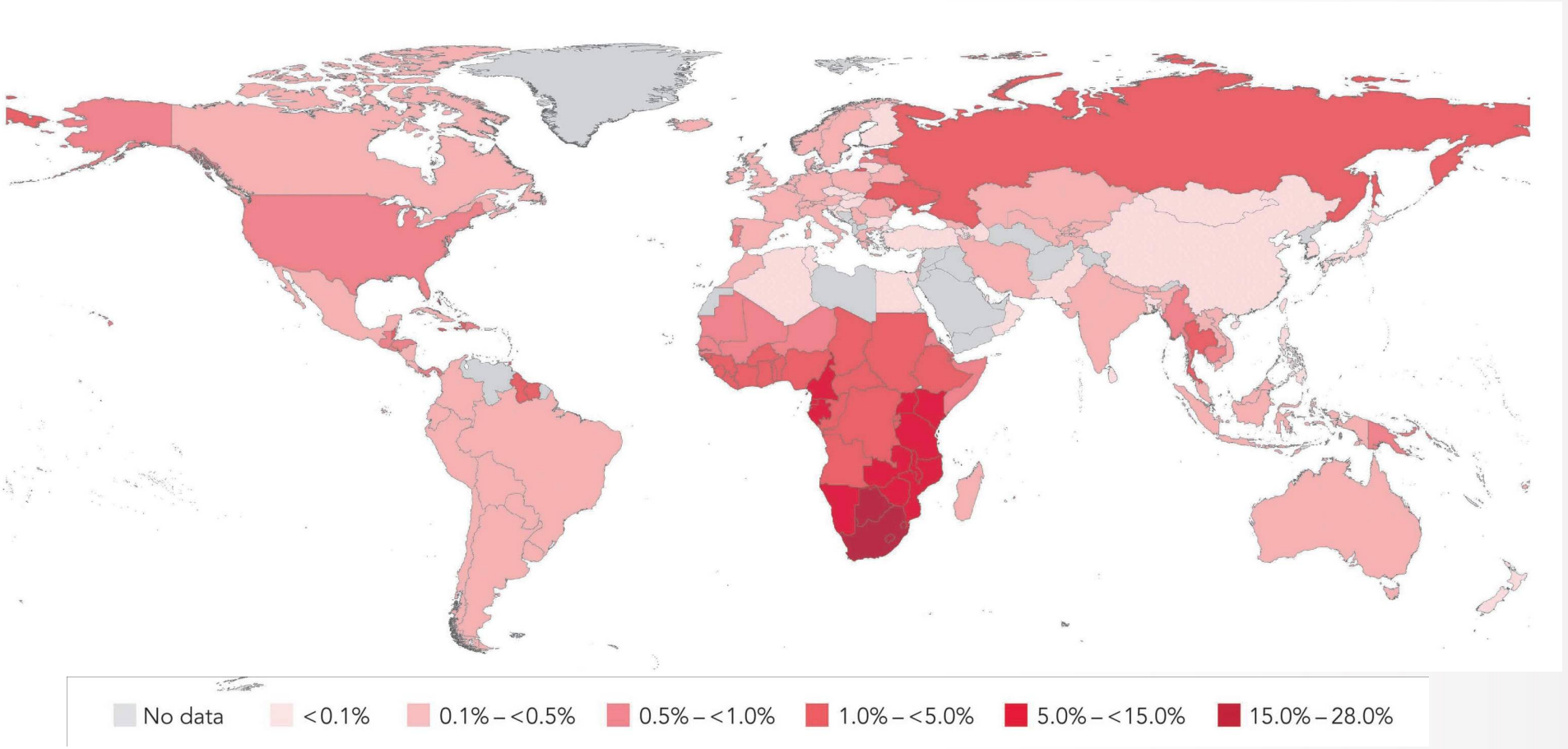
An Integrated Strategy



New opportunities in prevention

Treatment and prevention

2012 : A Global View of HIV Infection



- *>33 million HIV-infected worldwide*
- *~6.5 million currently on ARV therapy*

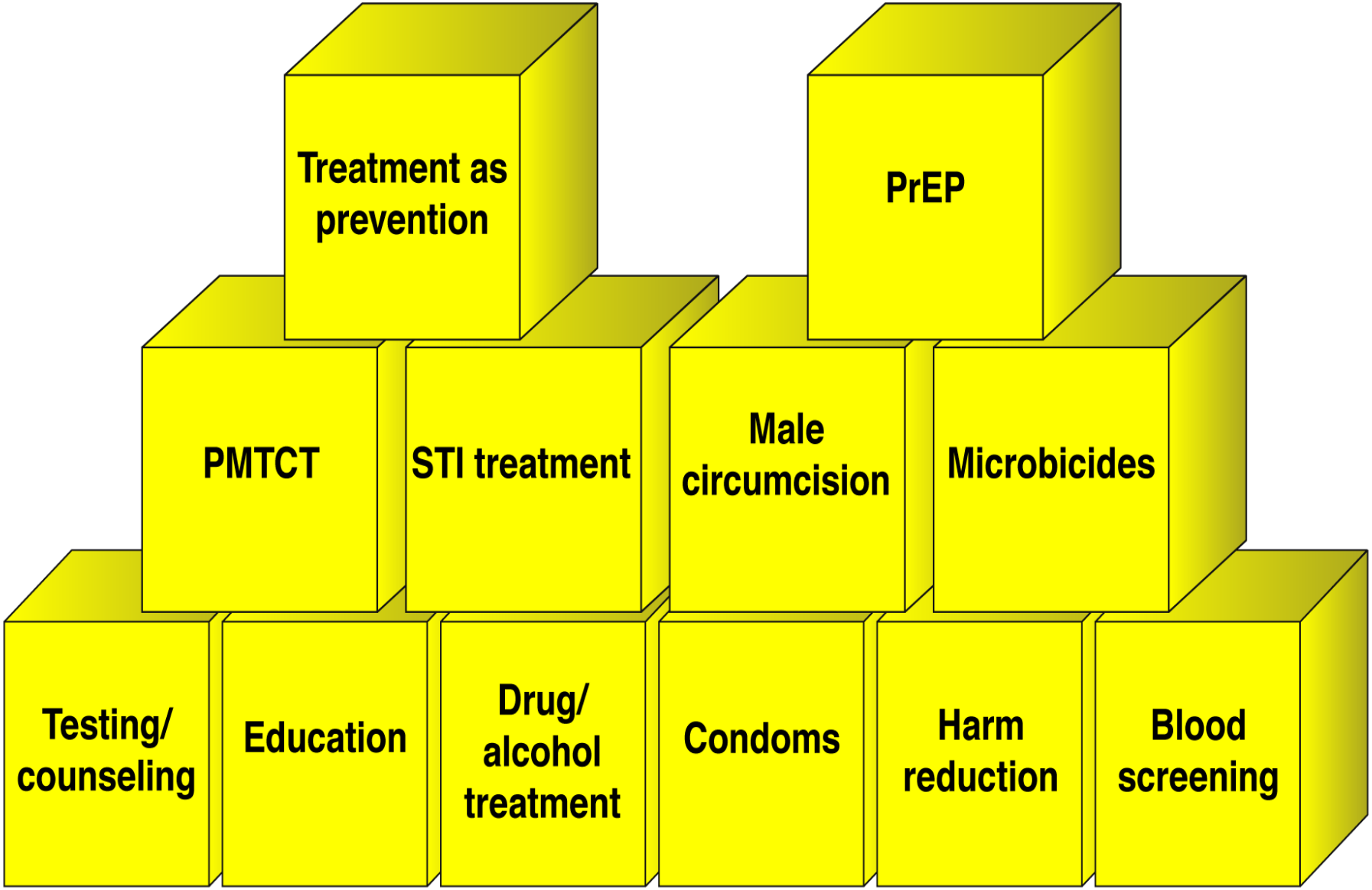
Recent HIV-infection in France (2011)

- ✓ New enzyme immunoassay able to differentiate recent (< 6 months) from non-recent HIV-infection has been implemented as part of the national HIV case surveillance since 2003
- ✓ Global incidence of 17/100.000 in 2009, slow decrease since 2003
- ✓ 48% of recent infections occur in MSM with a stable incidence of 1% (200x general population)
- ✓ Prevagay study (886 MSM in Paris) : HIV prevalence 17.7%, annual incidence: 5%, 20% do not know they are infected

Failure of current preventive strategies

Le Vu S et al, Lancet Infect Dis 2010

Combination HIV Prevention



Adult Male Circumcision Significantly Reduces Men's Risk of Acquiring HIV

PLoS MEDICINE
a peer-reviewed, open-access journal
PUBLIC LIBRARY of SCIENCE
Volume 2 Issue 1 November 2005

Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial

Bertran Auvert et al.

– **South Africa**

THE LANCET
Founded 1823 Published weekly
Volume 369 Isssue 9562 24 February 2007

Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya: A Randomised Controlled Trial

RC Bailey et al.

Male Circumcision for HIV Prevention in Men in Rakai, Uganda: A Randomised Trial

RH Gray et al.

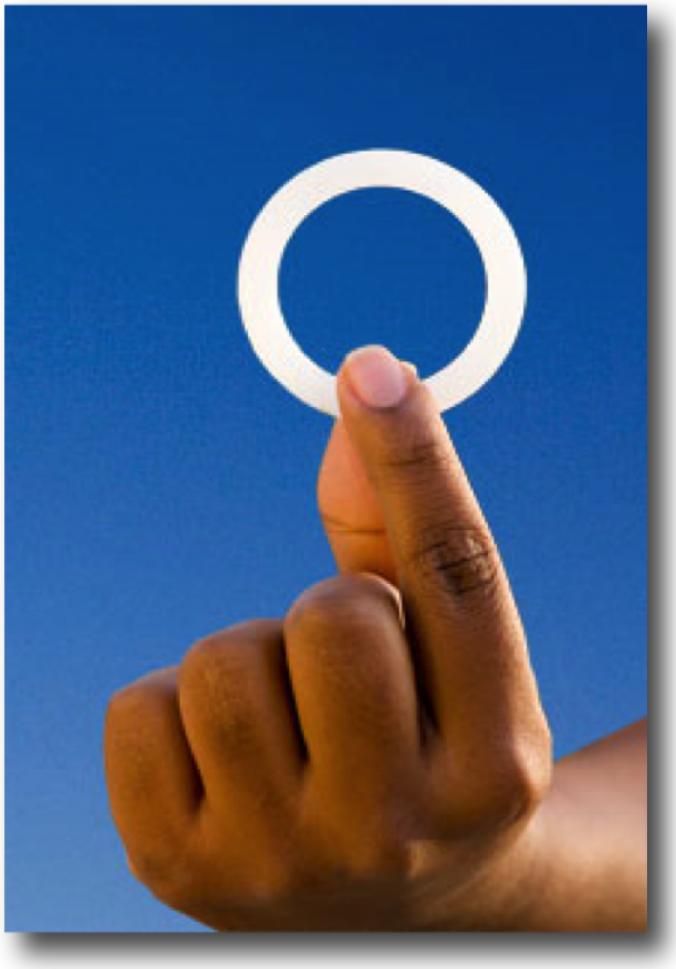
Microbicides: Mixed Results

- **CAPRISA 004** – 1% tenofovir gel before and after intercourse reduced incidence by 39%; with adherence > 80%, incidence reduced by 54%

- **VOICE** – 1% tenofovir gel daily. Study arm discontinued due to futility

- **FACTS 001** – Ongoing study in South Africa of 1% tenofovir gel before and after intercourse

Dapivirine Microbicide Rings



- Monthly use
- Two large-scale trials in 2012
  - **ASPIRE** ~3500 women in Malawi, South Africa, Uganda, Zambia, and Zimbabwe
  - **The Ring Study (IPM 027)** ~1,650 women in South Africa, Rwanda, and Malawi

Oral PrEP: Mixed Results

	Efficacy
MSM – iPrEx (Americas, Thailand, SA)	42%
Heterosexual discordant couples – Partners PrEP (Kenya, Uganda)	75%
Heterosexual men and women – TDF2 (Botswana)	62%
Women – FEM-PrEP (Kenya, SA, Tanzania)	0%
Women – VOICE (SA, Uganda, Zimbabwe)	0%

Voluntary "Test and Treat" Concept

THE LANCET

Available online November 27, 2008

Universal Voluntary HIV Testing with Immediate Antiretroviral Therapy as a Strategy for Elimination of HIV Transmission: a Mathematical Model

RM Granich et al.

- Model indicates that universal and annual voluntary HIV testing followed by immediate antiretroviral therapy treatment (irrespective of clinical stage or CD4 count) could reduce new HIV cases by 95% within 10 years
- Concerns: feasibility, protection of individual rights, drug resistance, toxicity, financing

The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Volume 365 August 11, 2011 Number 6

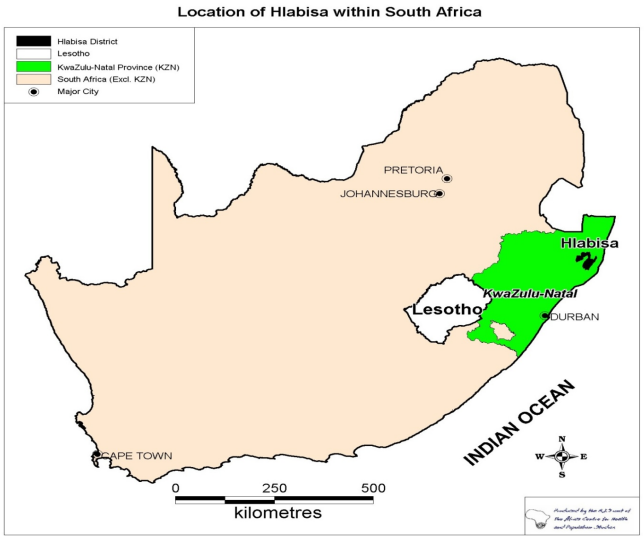
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

HPTN 052 Study Team

- 1,763 HIV-serodiscordant couples in 9 countries
- 96% reduction in HIV transmission when ART started in HIV-infected partner at CD4 count of 350-550 compared to <250
- Dramatic decreases in disseminated TB in infected partners treated early

TasP Protocol

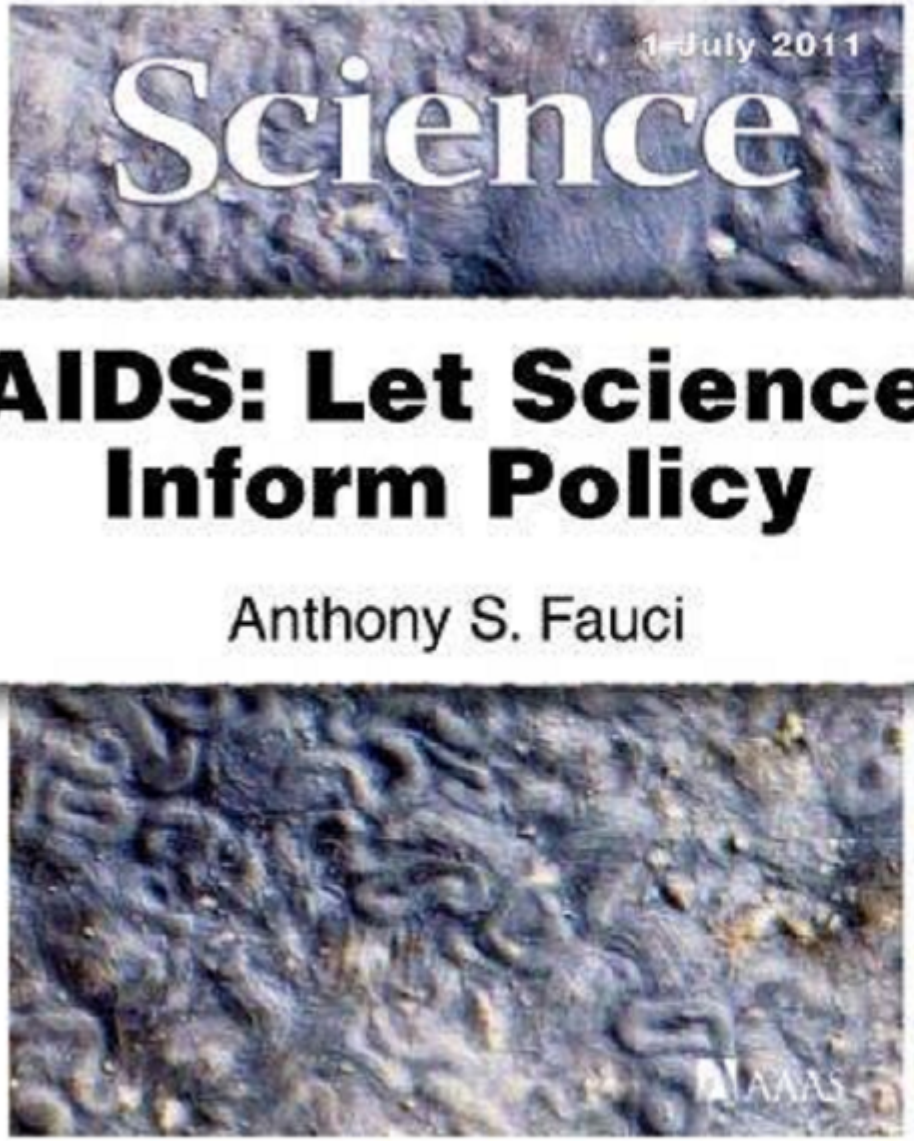
- **Objective : to reduce HIV incidence**
- **Method :**
  - ➔ **To test all HIV+ individuals whatever the CD4 number**
  - ➔ **To compare with a HIV population treating according standard guidelines**
  - ➔ **Cluster-based randomization**
- **Outcomes**
  - ➔ **HIV incidence +++**
  - ➔ **Cost-effectiveness**
  - ➔ **Toxicity**
  - ➔ **Behaviors : adherence, sexual behavior**
  - ➔ **Quality of life**



Agence nationale de recherches sur le sida et les hépatites virales

The ANRS TasP programme

- **Initiated in january 2009**
- **Partnership established with the Africa Center and health authorities (Kwazulu Natal, South Africa)**
- **A « step by step » programme: Pilot Study then….**
- **Multidisciplinary working groups**
- **PI: F. Dabis (France), ML Newell (SA)**
- **Scientific Board directed by B. Hirschel**
- **First inclusions : March 2012**



"We now have an unprecedented opportunity, based on solid scientific data, to control and ultimately end the AIDS pandemic.

. . .Major investments in implementation now will save even greater expenditures in the future; and in the meantime, countless lives can be saved."

VACCINE
A long story ….

30 years after the discovery of AIDS, no HIV vaccine yet…

- *Animal model limitations*
- *Genetic Variability of HIV and viral evasion of the host immune response*
- *Cell to cell transmission of the virus*
- *HIV infects and very rapidely alters the functions of key players of both innate and adaptative immune responses*
- *Pathways to elicit protective responses through vaccination?*
- *Immune mechanisms of protection against acquisition of HIV infection and/or disease progression (correlates of protection??)*
- …/

BUT…

• One vaccine prime -boost strategy showed for a first time a modest efficacy *(31% of protection in the Thai-RV144 vaccine efficacy trial)*

•Very few individuals are naturally protected against HIV-1 infection (*e.g. exposed non-infected subjects)*

• Some experimental vaccines confer protection to monkeys infected with SIV

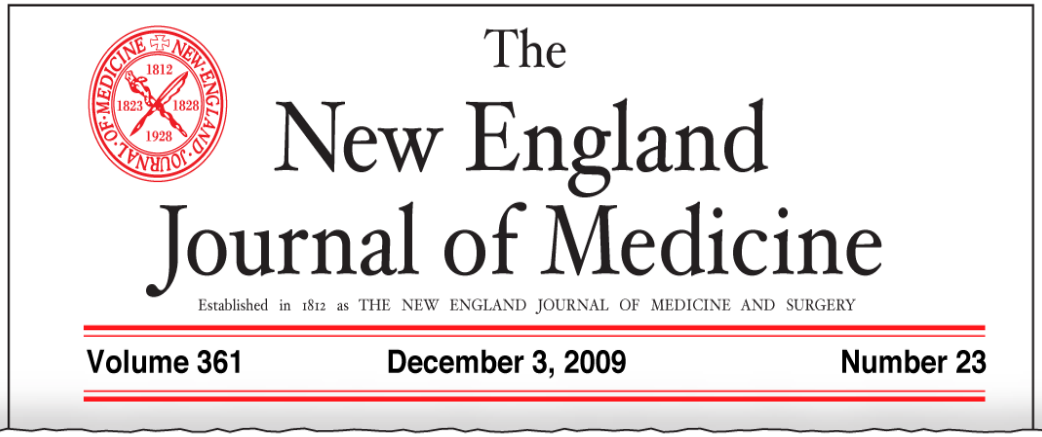
• Recent identification of new very potent (80-90%) and broadly reactive neutralizing antibodies targeting V2/V3 or CD4bs *env*

Leçons des essais d'efficacité

Dates	Clinical efficacy studies	Strategy	Viral targets	Immune response	Efficacy
1999-2003	AidsVax	Protein subunit (AIDSVAX)	monomeric rgp120	Type specific binding Ab	NO
2005-2007	Step Phambili	Viral vector (Ad5)	gag/pol/nef	CD8+T (+++)	NO
2003- 2009	RV144 (Thai trial)	Prime: ALVAC-vCP152 + Boost: AIDSVAX	gag/pol/env + Monomeric rgp120 B/E	CD4+ T cell (+/-) + Type specific binding Ab	31% reduction

Quels sont les corrélats de protection?

First Signal of Efficacy in an HIV Vaccine Clinical Trial



The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Volume 361 December 3, 2009 Number 23

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

S Rerks-Ngarm, JH Kim, NL Michael et al. for the MOPH–TAVEG Investigators

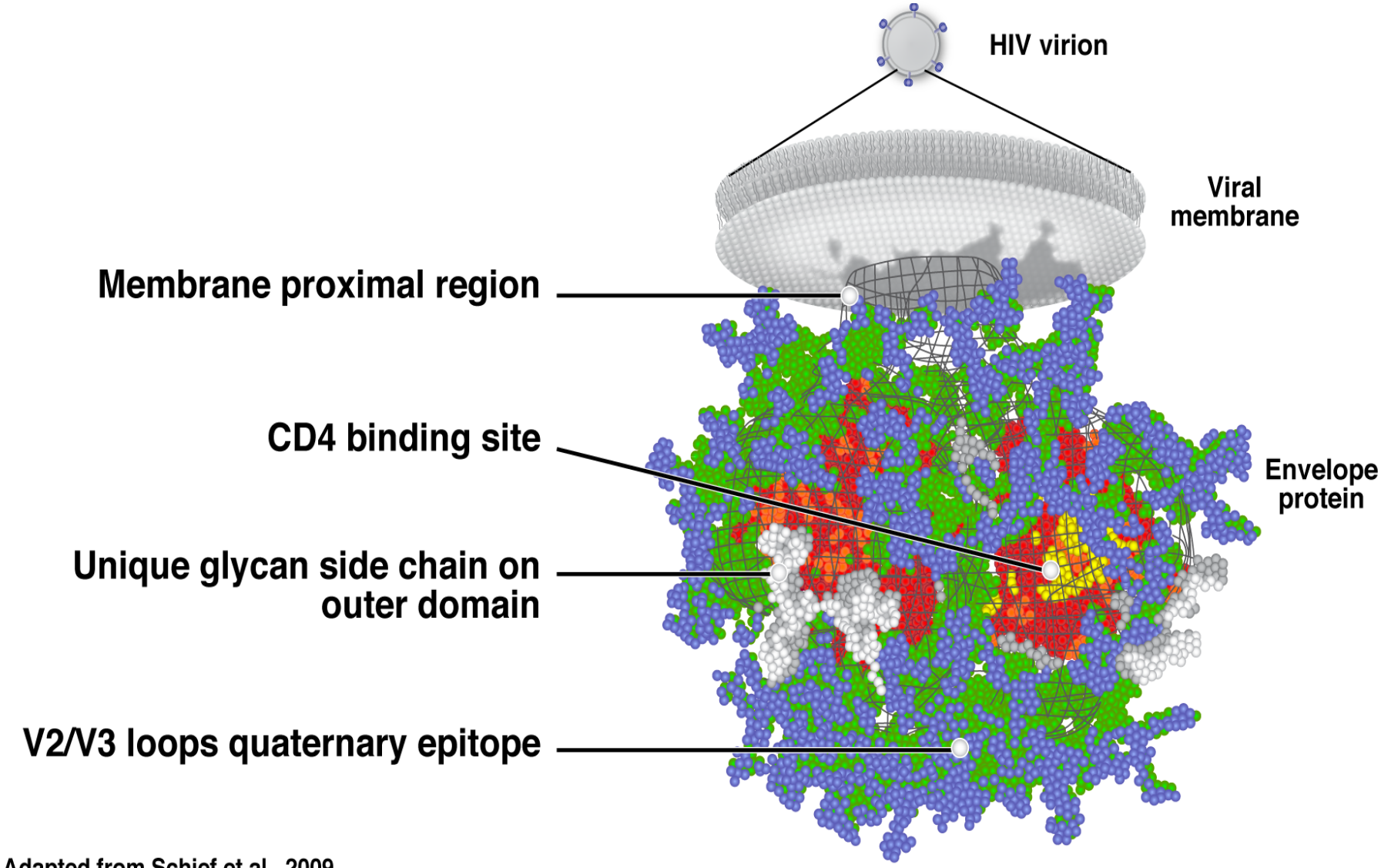
The New England Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
VOLUME 366 APRIL 5, 2012 NUMBER 14

Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

BF Haynes et al.

- IgG antibodies to V1V2 region of Env may have contributed to protection against HIV-1 infection
- High levels of Env-specific IgA antibodies may have mitigated the effects of protective antibodies

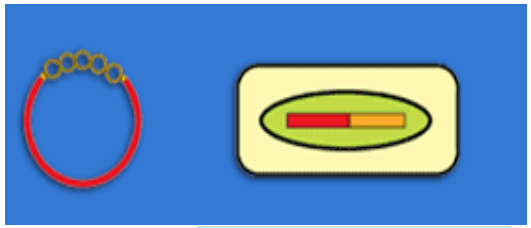
Structure-Based HIV Vaccine Design: Conserved Targets Defined by Neutralizing Antibodies



Adapted from Schief et al., 2009

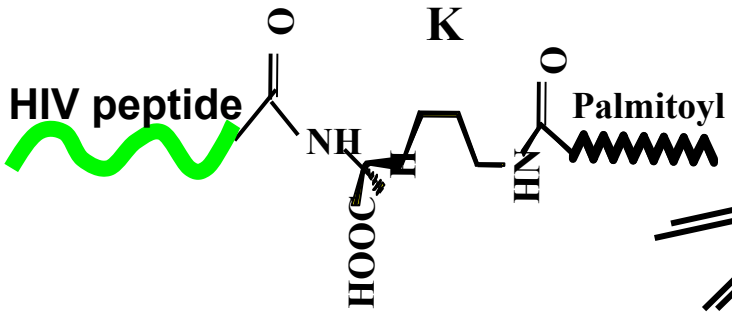
anRS HIV Vaccine Network

Development of an epitope-based vaccine approache that could be employed in prime-boost strategy combined with recombinant viruses aimed to elicit strong, long lasting, polyepitopic T-cell responses focused on highly conserved epitopes

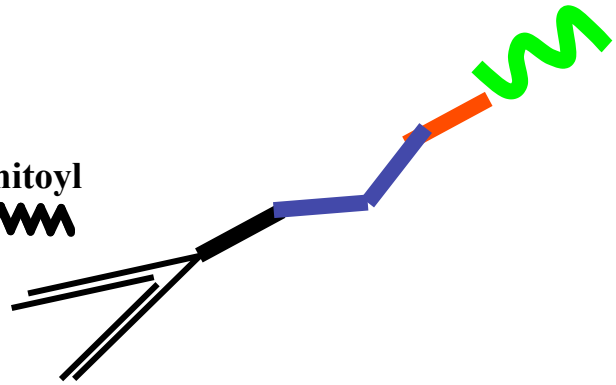


ADN

NYVAC (B/C)
MVA (B)



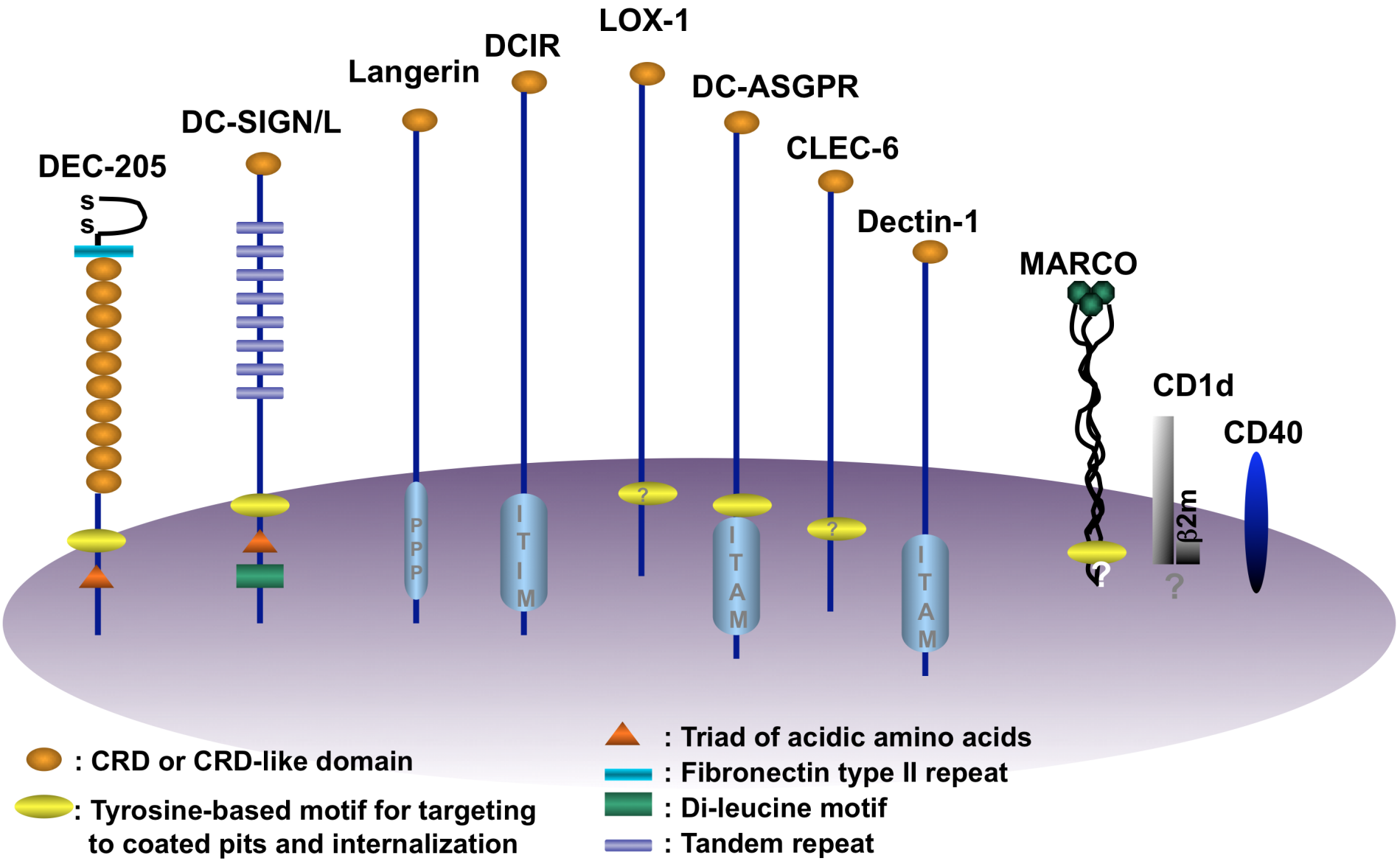
LIPO5



Peptide-anti-DC

EuroVacc anRS transgene BAYLOR Institute for Immunology Research
A Service of Baylor Research Institute

DC receptors for antigen-targeting



AGENDA of the ANRS : 4 main priorities for HIV

- **Study reservoirs with the objective of eradication or functional cure**
- **Testing: Novel methods; Early and better treatment**
- **Prevention of new infection with a biomedical approach**
- **Develop new vaccine strategies**

With a NORTH ← → SOUTH vision

Integrating economic aspects

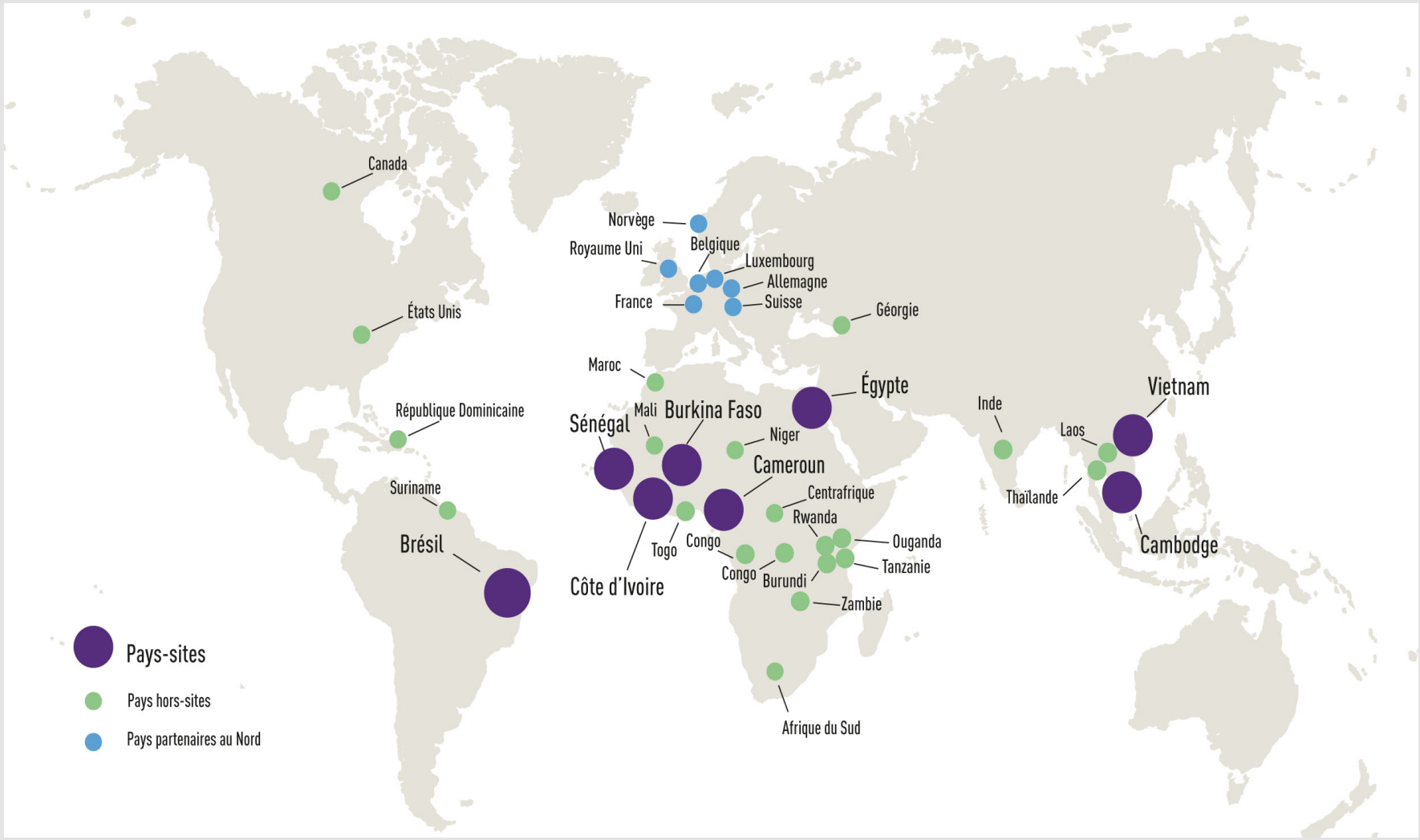
L'ANRS au Sud

- Animer et financer les recherches sur le VIH et les hépatites dans toutes les disciplines

  (biologie fondamentale, recherche clinique et thérapeutique, épidémiologie, santé publique, économie, sciences humaines et sociales, vaccin)

- A partir de 1998 : politique incitative : budget dédié, création du service PED, développement des sites au Sud

Les Sites ANRS (N=8) et les Pays partenaires



Structuration de la recherche au Sud

- Une politique stratégique de partenariat : les sites ANRS
- Une politique scientifique
  - « Top to bottom » : Actions Coordonnées (définition de thèmes prioritaires)
  - « Bottom to top »: appels d'offres(blancs++)

Les sites : principes généraux

Agence nationale de recherches sur le sida et les hépatites virales | *French National Agency for Research on AIDS and Viral Hepatitis*

Articulation avec les programmes nationaux

HCV risk factors
-Iatrogenic
-Intra-familial

Factors associated with HCV clearance
-epidemiology
-lipids
-virology
-immunology

Treatment efficacy
- Acute phase
- Chronic infection

Mathematical modeling
-Prediction
-cost-effectiveness

EGYPTIAN NATIONAL CONTROL STRATEGY FOR VIRAL HEPATITIS 2008-2012

April 2008

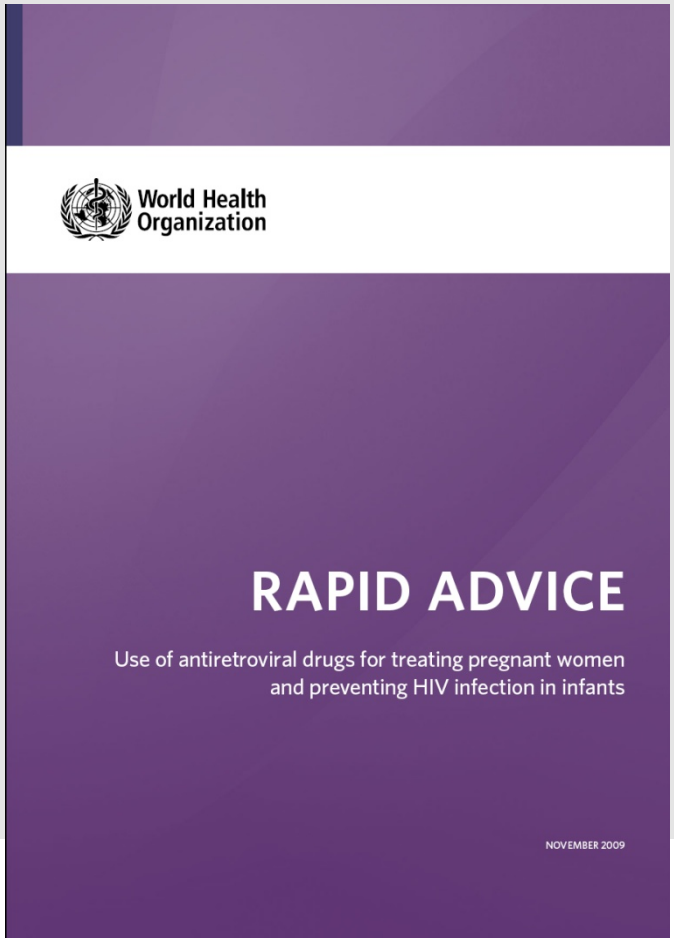
Arab Republic of Egypt, Ministry of Health and Population
National Committee for the Control of Viral Hepatitis

Les sites : principes généraux

Agence nationale de recherches sur le sida et les hépatites virales | *French National Agency for Research on AIDS and Viral Hepatitis*

Articulation avec les directives OMS

Essais PTME



Option A	Option B
Mother • **Antepartum AZT** (from 14 weeks) • sd-NVP at onset of labour* • **AZT + 3TC** during labour & delivery* • AZT + 3TC for 7 days postpartum*	**Mother** • Triple ARV (from 14 wks until one wk after all exposure to breast milk has ended) • AZT + 3TC + LPV-r • AZT + 3TC + ABC • AZT + 3TC + EFV • TDF + XTC + EFV
Infant **Breastfeeding population** • Daily NVP (from birth until one wk after all exposure to breast milk had ended) **Non-breastfeeding population** • AZT for 6 weeks OR • NVP for 6 weeks	**Infant** **Breastfeeding population** • Daily NVP from birth to 6 weeks **Non-breastfeeding population** • AZT for 6 weeks OR • NVP for 6 weeks

http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf

Les sites : principes généraux

Intégration aux structures nationales

Site ANRS du Sénégal, CRCF, Hôpital FANN, Dakar

Les sites : principes généraux

Intégration aux structures nationales

Site ANRS au Cameroun, Hôpital Central, Yaoundé

Les sites : principes généraux

Intégration aux structures nationales

Caractéristiques des programmes sur les sites

Multidisciplinarité

Prise en charge précoce de l'infection VIH de l'adulte en Côte d'Ivoire

Temprano Résistance

(ANRS 12253)

Temprano Quantiféron

(ANRS 12224)

Variabilité génétique de l'hépatite B :

(ANRS 12240)

Essai Temprano

ANRS 12136

Bénéfices et risques d'un traitement antirétroviral précoce chez des adultes infectés par le VIH

Temprano Social

(ANRS 12239)

Freins au Dépistage

(ANRS 12245)

Temprano Anthropologique

(ANRS 12242)

Les sites : principes généraux

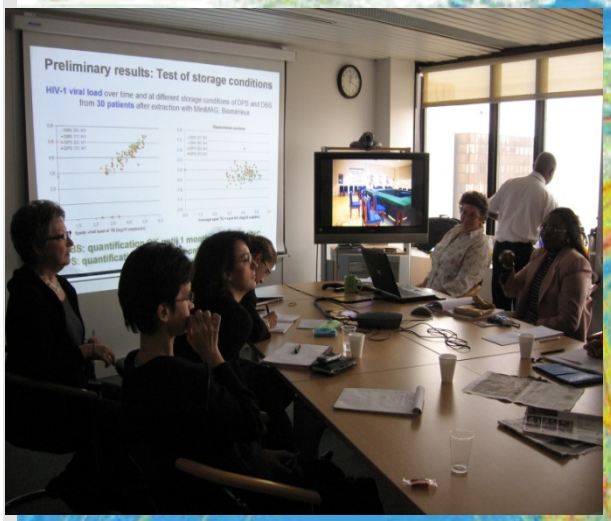
Coordination bilatérale

Animation scientifique périodique conjointe ANRS/pays sur site

Caractéristiques des programmes sur les sites

Travail en réseau (projets multi-sites)

Groupe de travail nord/sud en virologie (quantification VIH et résistance)



Necker
Montpellier
Bordeaux
Rouen

Sénégal
Côte d'Ivoire
Cameroun
Burkina Faso

Togo

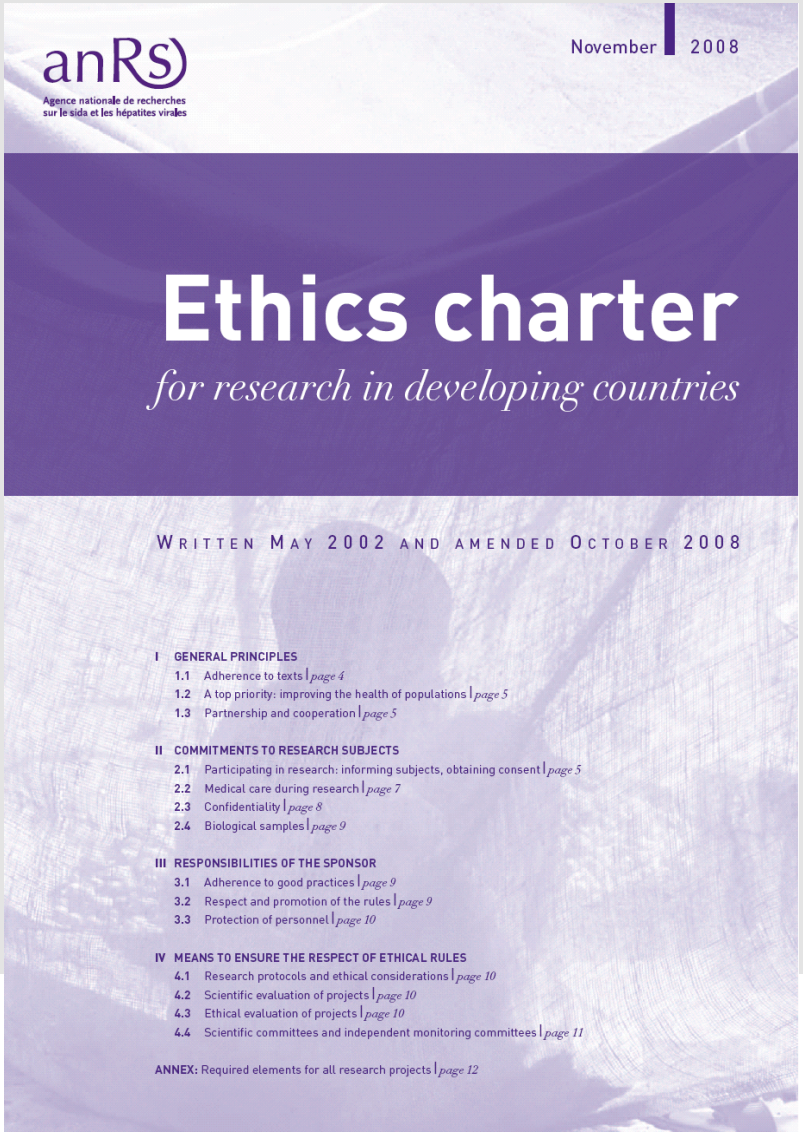
Thaïlande

Vietnam
Cambodge

Quality Control: viral load and genotyping

1) ANRS 12134: primary résistance survey
2) ANRS 12 186: resistance to ARV in HIV + patients in national programmes
3) ANRS 12 235: Comparison DBS/plasma (viral load, genotyping…)

Les sites : principes généraux
Engagements de l'ANRS



Projets en cours en 2011, pays en développement

91 projets

- VIH : 85%
- hépatites et co-infections /VIH : 15 %

- 17 % Recherche fondamentale
- 40% Recherche clinique et multidisciplinaire
- 43 % Science sociale et santé publique

Diminution des ressourcesdisponiblescontre le VIH/sida

- **Les financements internationaux n'ont pas augmenté depuis 2008 et ont même diminué à 6,9 b$ en 2010 (7,6 b$ en 2009)**
- **Annulation du 11ème round de financement du Fonds Mondial par manque de ressources!!!**
- **Proposition de budget 2013 du PEPFAR: -11% dans l'aide internationale directe des programmes VIH**

- **Des millions de vie dépendent de ces ressources**
- **Rapport de la Banque Mondiale (mars 2012) appelle à un accroissement des efforts de prévention VIH en Afrique**
- **Retour sur investissement positif de l'accès aux traitements (R*esch S et al, PloSOne 2011)***
- **Impact positif des programmes VIH/sida sur la santé globale (B*endavid E, CROI 2012*)**

Les nations privilégiées doivent tenir leurs promesses…

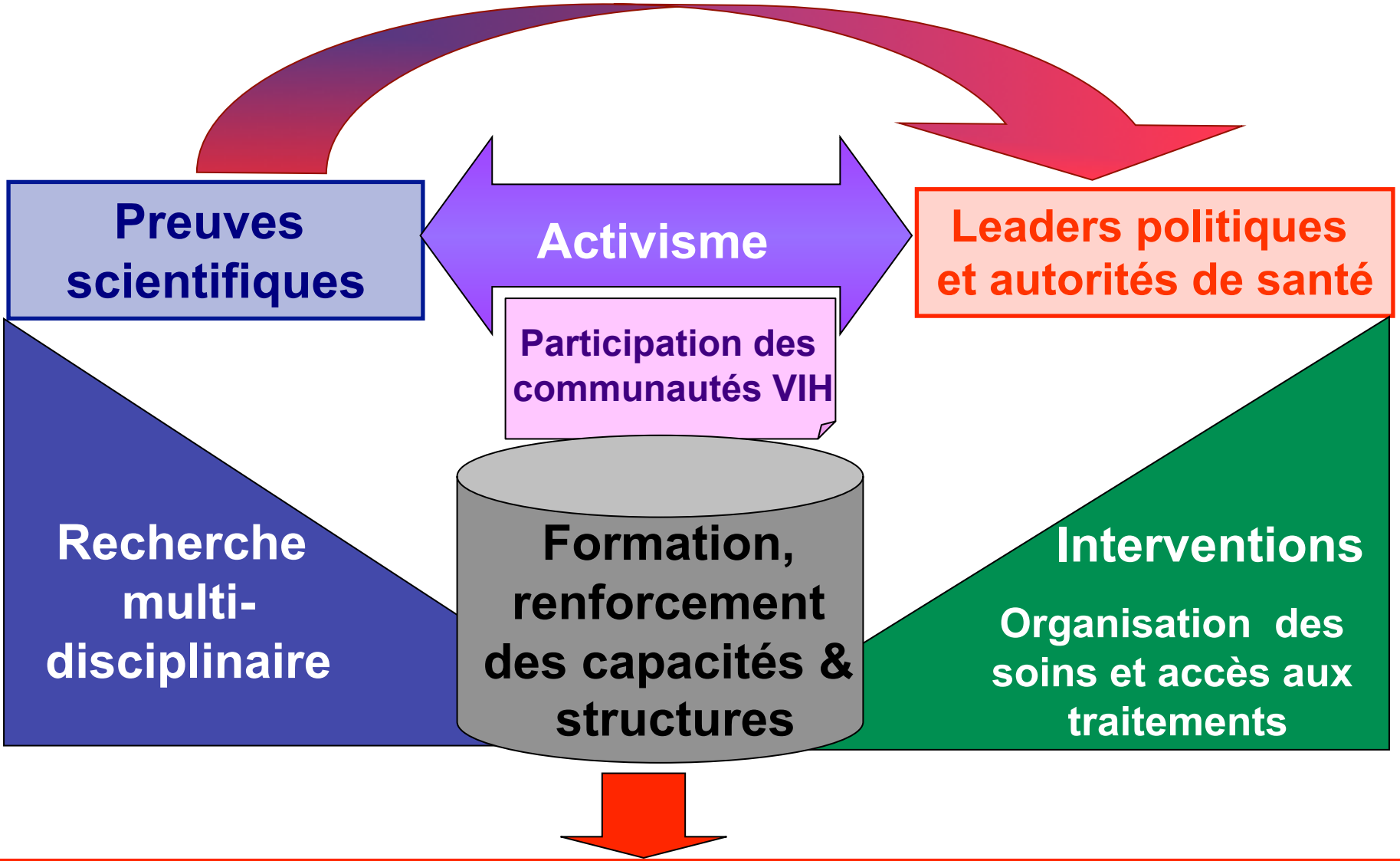
Malgré des efforts internationaux sans précédent, le VIH/SIDA reste un défi majeur pour la santé globale

2,5 millions de nouvellesinfections et 1,7 millions de mortschaqueannée

Assurer l'accès équitable à la prévention, au dépistage et aux traitements

- **Prévention: éducation, préservatif, circoncision, ARV…**
- **Dépistage précoce: environ50% des personnes VIH+ ignorentleurstatutsérologique**
- **Luttecontre les discriminations qui restent un obstacle majeur au dépistage et aux soins (orientation sexuelle, prostitution, usagers de drogue…)**
- **Accès à toutes les molécules y compris de 2nd et 3ème lignes (de 2 à 15 fois plus chers que les traitements de 1ère ligne)**
- **330 000 enfants infectés par an et 57% des femmes enceintes reçoivent un traitement pour prévenir la transmission à leur bébé = INADMISSIBLE la PTME date des années 90!!!**
- **Qualité du suivi: monitorage des patients sous traitement (accès à la charge virale, tests de résistance)**
- **Former du personnel soignant**
- **Organiser les systèmes de santé et décentraliser les soins**

Mobilisationinternationale pour la recherche et l'action



Décisions au bénéfice de TOUTES les populations où qu'elles soient…

ACKNOWLEDGMENTS

- Clinical and research teams
- Chairs of Coordinated working groups
- ANRS staff
- Patients NGOs, more specifically TRT5, AIDES, Sidaction
- INSERM, Institut Pasteur, IRD, CNRS, Hospitals
- Pharmaceutical companies
- Foundations
- Patients

FIN