Update on HIV/AIDS vaccine development

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IrsiCaixa
Institut de Recerca de la Sida

HIVACAT
Projecte de Recerca de la Vacuna de la Sida

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Jornades Catalanes de Salut Internacional i Medicina Tropical
Barcelona, 7 i 8 de maig 2015

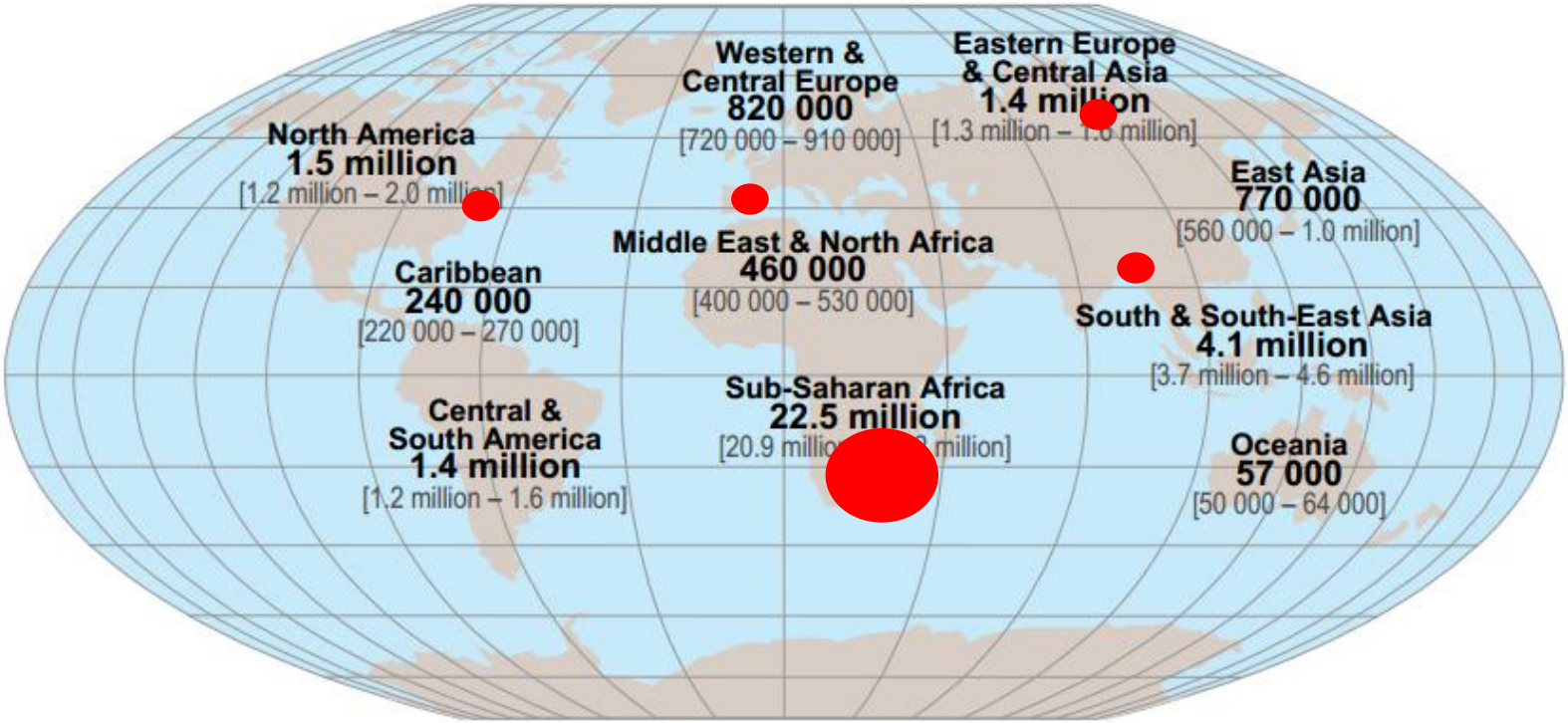
1. **INTRO**
- Do we still need an HIV vaccine?

2. VACCINE DEVELOPMENT
- Main hurdles
- Most relevant past vaccine trials. Any optimism?

3. Vaccine Research Plan at IrsiCaixa. HIVACAT T-cell Candidate

GLOBAL REPORT

Adults and children estimated to be living with HIV | 2009



Total: 33.3 million [31.4 million – 35.3 million]

World Health Organization

UNAIDS

1

		Adults and children living with HIV	Adults and children newly infected with HIV
SUB-SAHARAN AFRICA	2011	23.5 million [22 100 000–24 800 000]	1.8 million [1 600 000–2 000 000]
	2001	20.9 million [19 300 000–22 500 000]	2.4 million [2 200 000–2 500 000]
SOUTH AND SOUTH-EAST ASIA	2011	4.0 million [3 100 000–4 600 000]	280 000 [170 000–370 000]
	2001	3.7 million [3 200 000–5 100 000]	370 000 [250 000–450 000]
EASTERN EUROPE AND CENTRAL ASIA	2011	1.4 million [1 100 000–1800 000]	140 000 [91 000–210 000]
	2001	970 000 [760 000–1 200 000]	130 000 [99 000–170 000]
WESTERN AND CENTRAL EUROPE	2011	900 000 [830 000–1 00 000]	30 000 [21 000–40 000]
	2001	640 000 [590 000–710 000]	29 000 [26 000–34 000]
NORTH AMERICA	2011	1.4 million [1 100 000–2 000 000]	51 000 [19 000–120 000]
	2001	1.1 million [850 000–1 300 000]	50 000 [35 000–71 000]
GLOBAL	2011	34.0 million [31 400 000–35 900 000]	2.5 million [2 200 000–2 800 000]
	2001	29.4 million [27 200 000–32 100 000]	3.2 million [2 900 000–3 400 000]

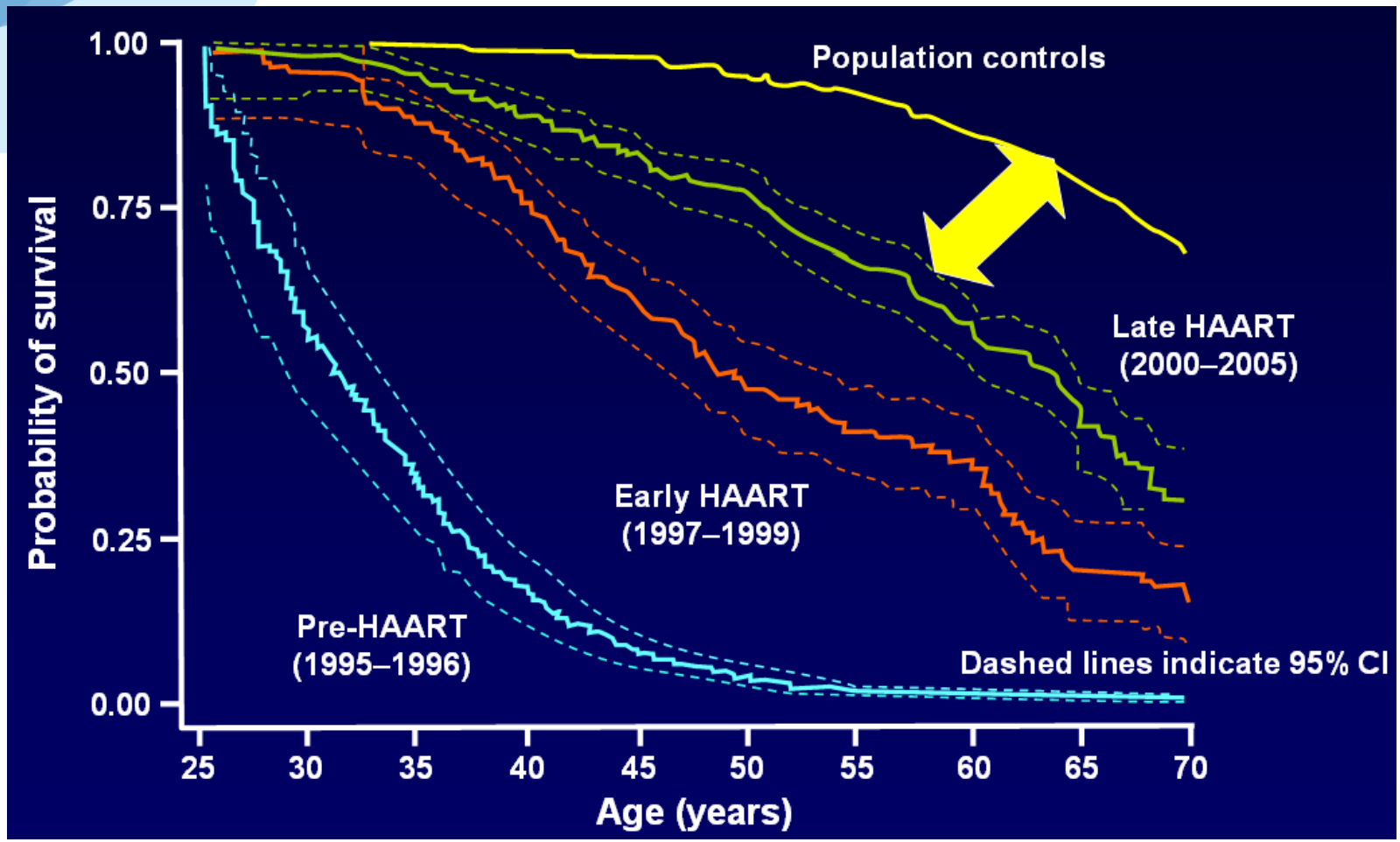
1.7
MILLION DIED

In 2011, 1.7 million people worldwide died from AIDS-related causes, down 24% from the peak in 2005.

nates.

1

One every 4 individuals HIV infected does NOT know it.

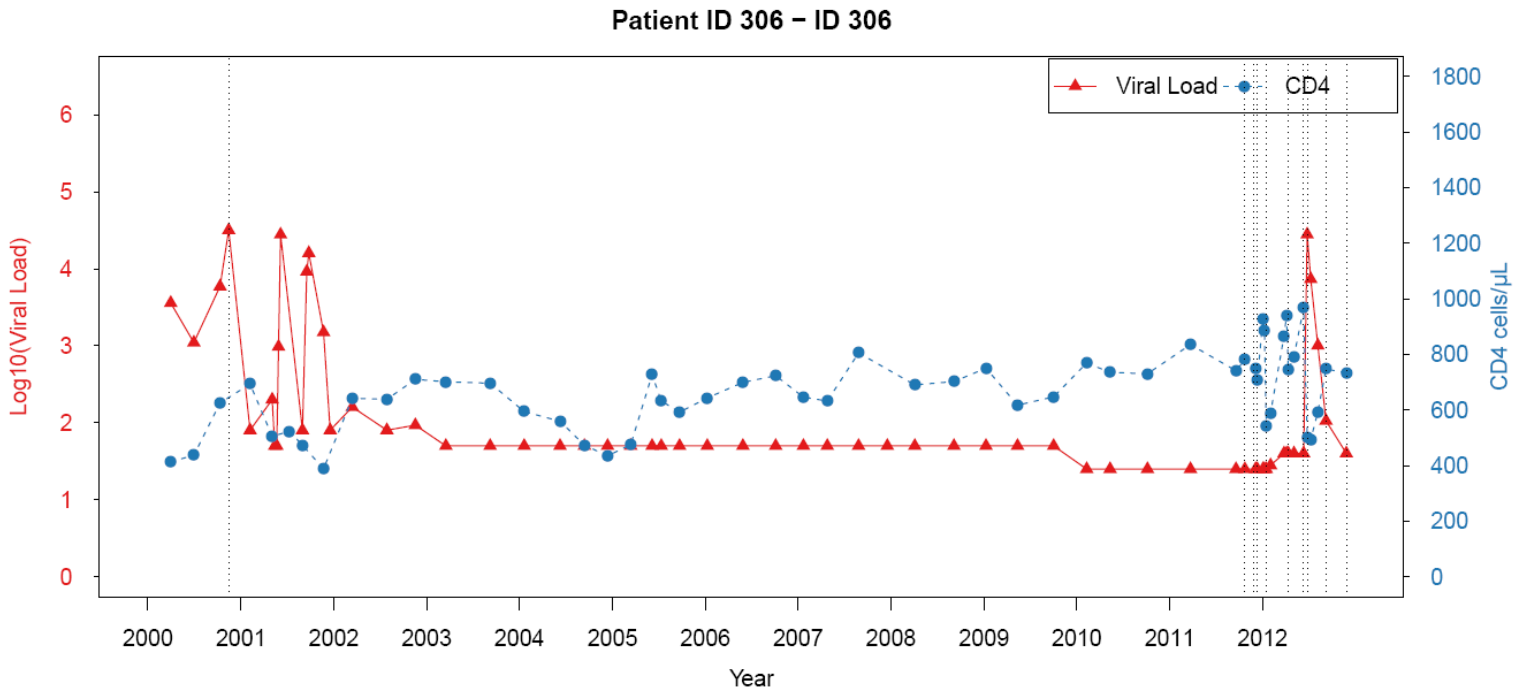


Lohse N, Ann Intern Med 2007

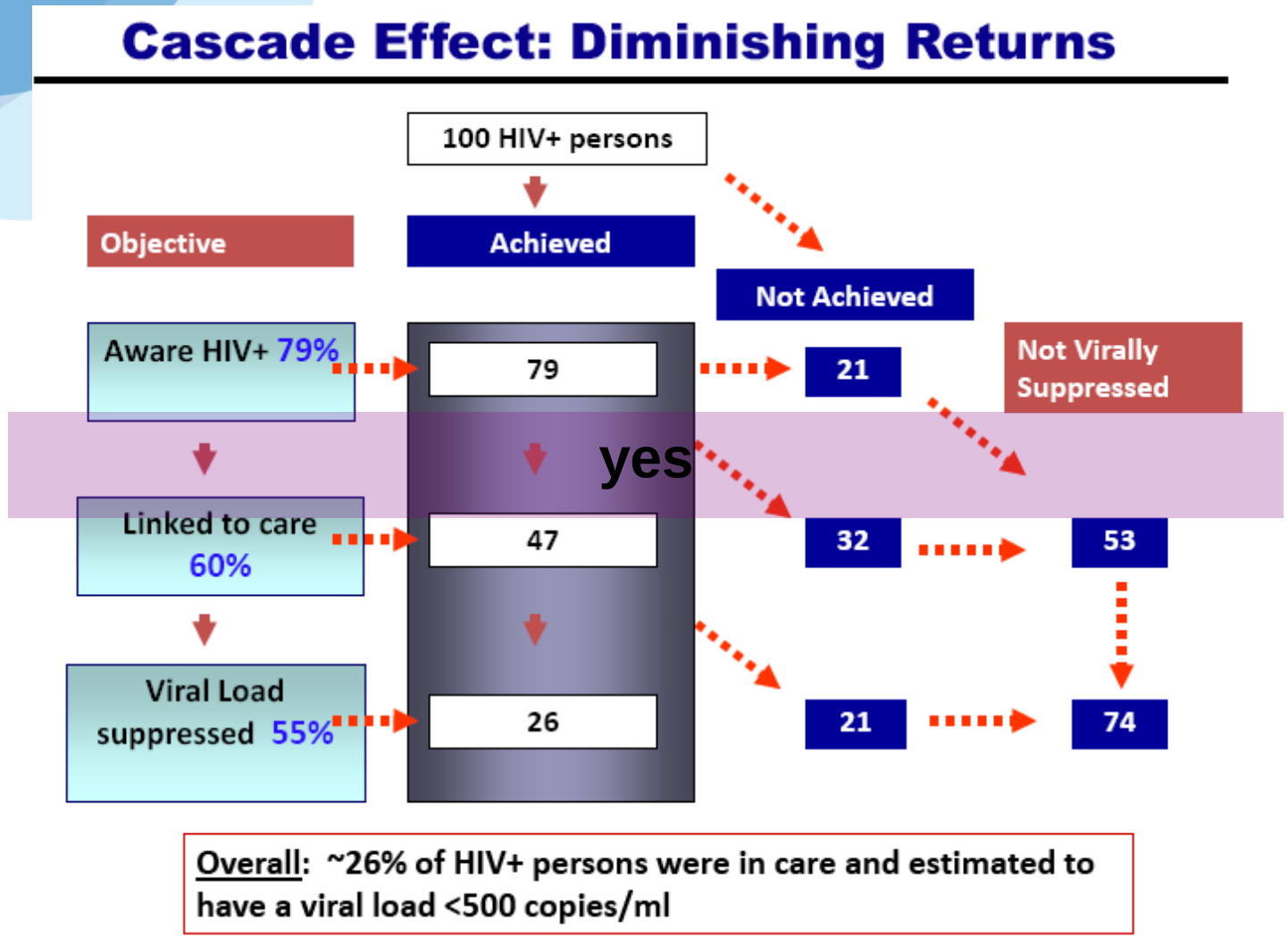
1

Require high adherence

Long-term Toxicity → High Cost → Do Not Cure HIV infection

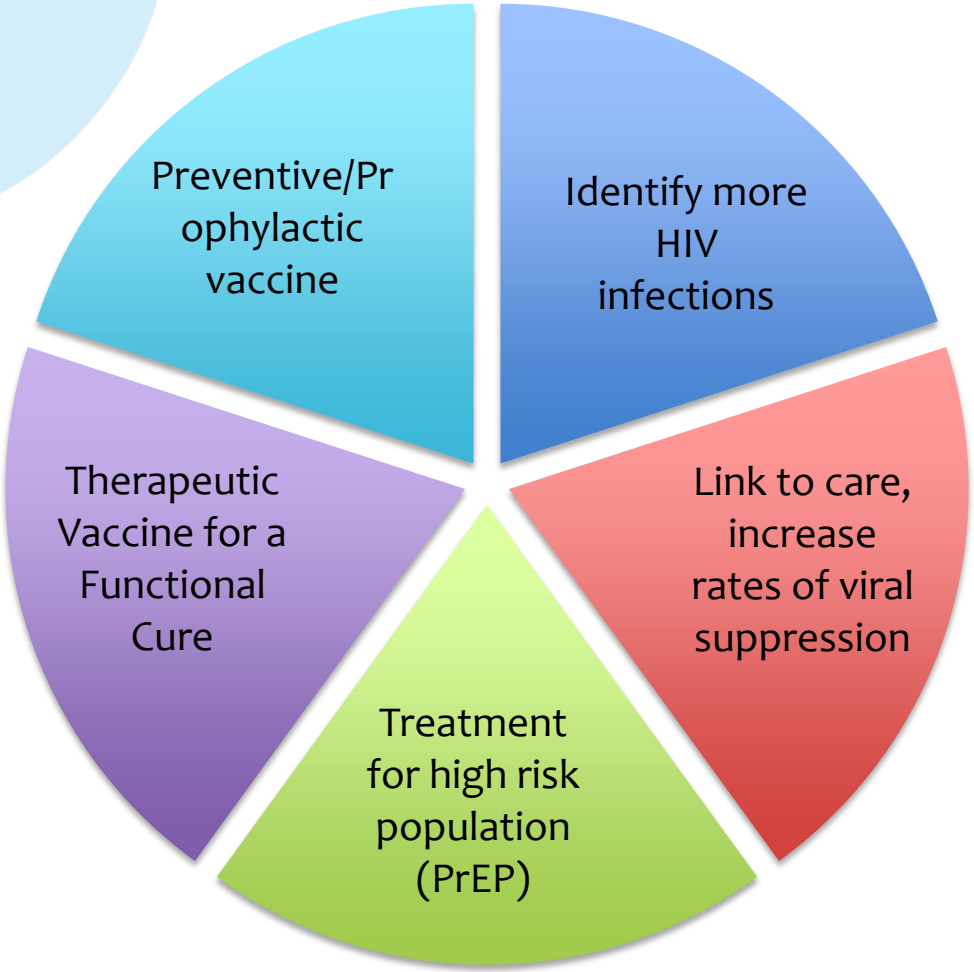


‘diagnostic → link to care →adherence →supression’



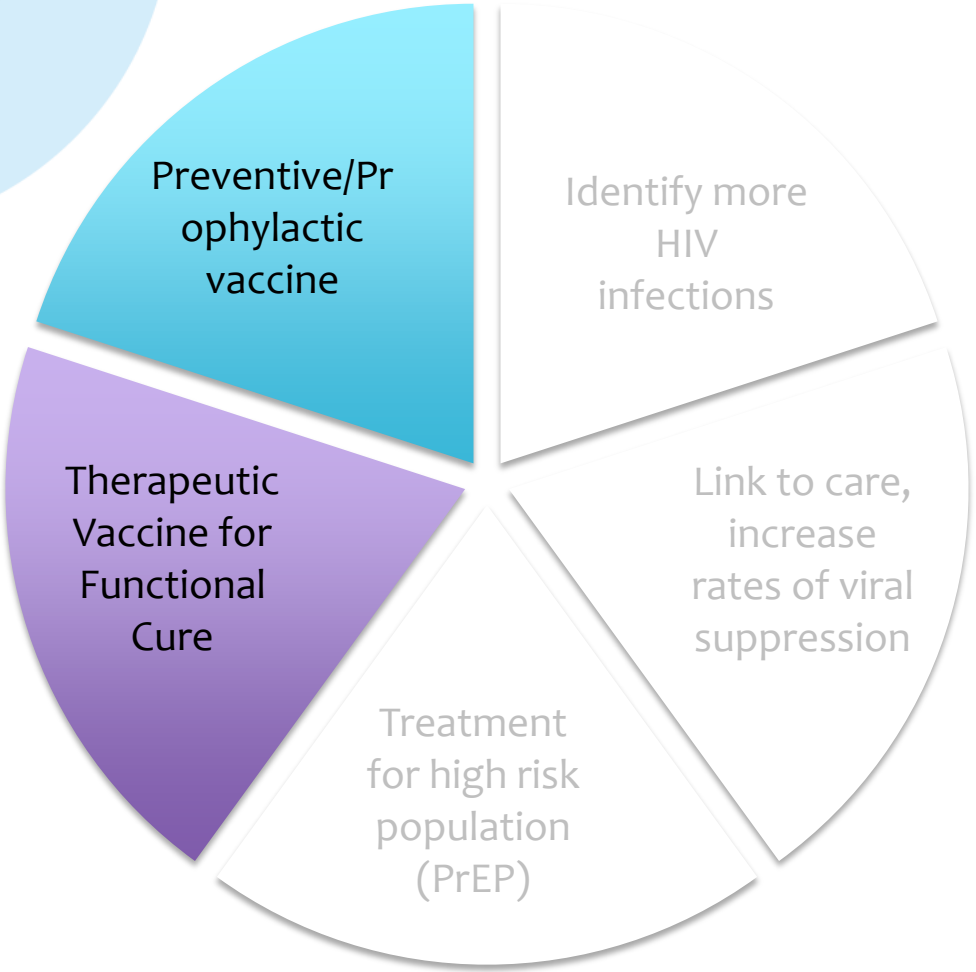
Johnsonn. Arch Intern Med. 2011

How to stop the HIV pandemia



Dieffenbach, Fauci. Arch Intern Med. 2011

How to stop the HIV pandemia



General view of HIV Vaccine Strategies

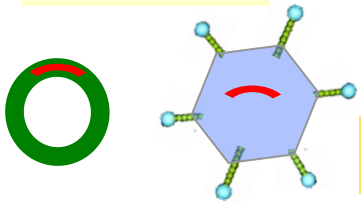
HIV/AIDS

Vaccine Candidate

Vector

+

Safety
Anti-vector Immunity
Feasible (scalability)



Immunogen

+/-

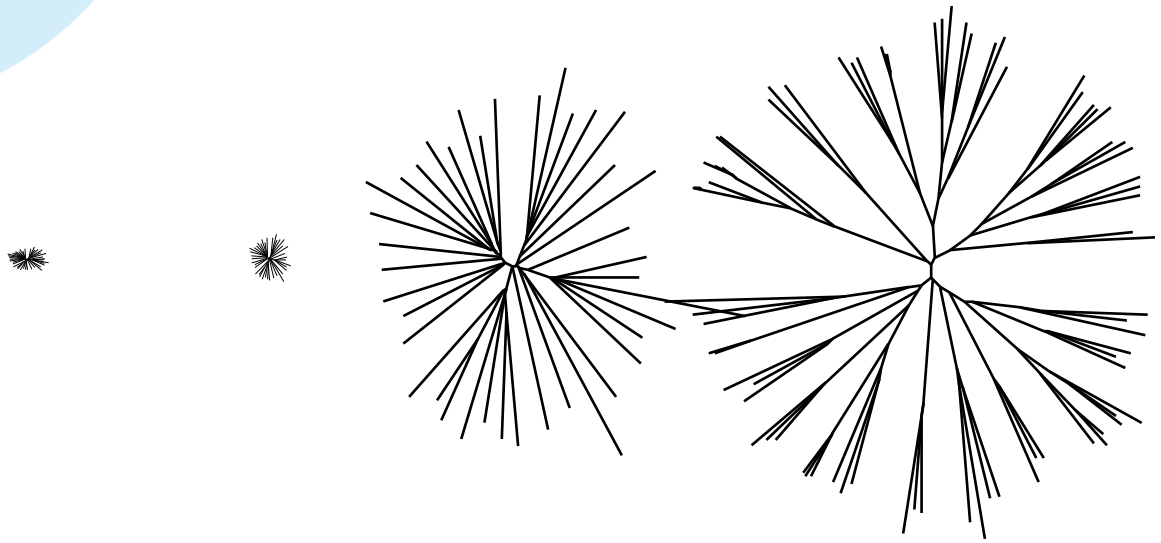
Combined Immune Response (CTL + Ab)
Tackle Viral diversity and Ability to immune escape

Adyuvants

2

understand main hurdles in HIV vaccine development
Immunopathogenesis of HIV

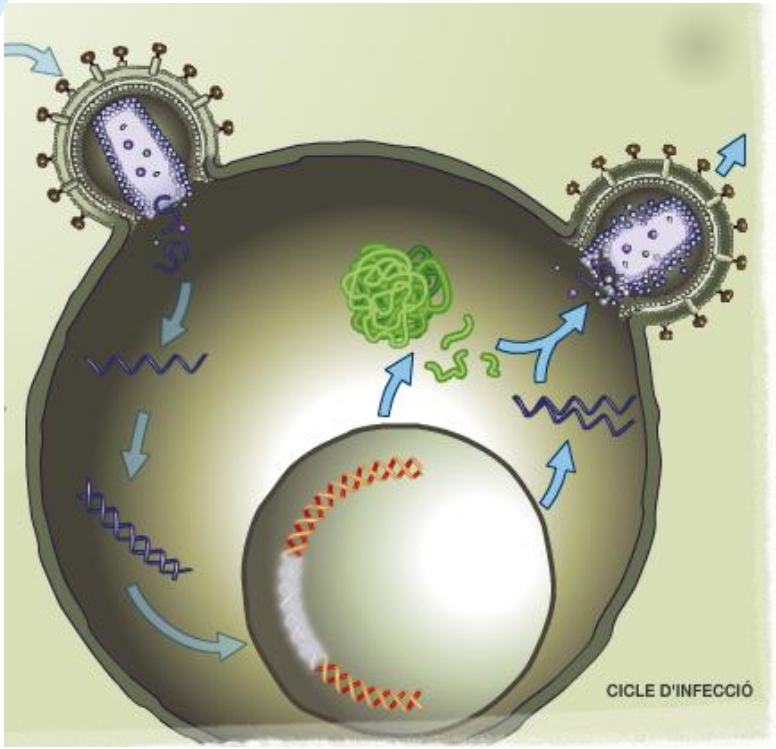
Global Viral Diversity



Adapted from McCutchan F. and Korber B., Brit Med Bull 2001

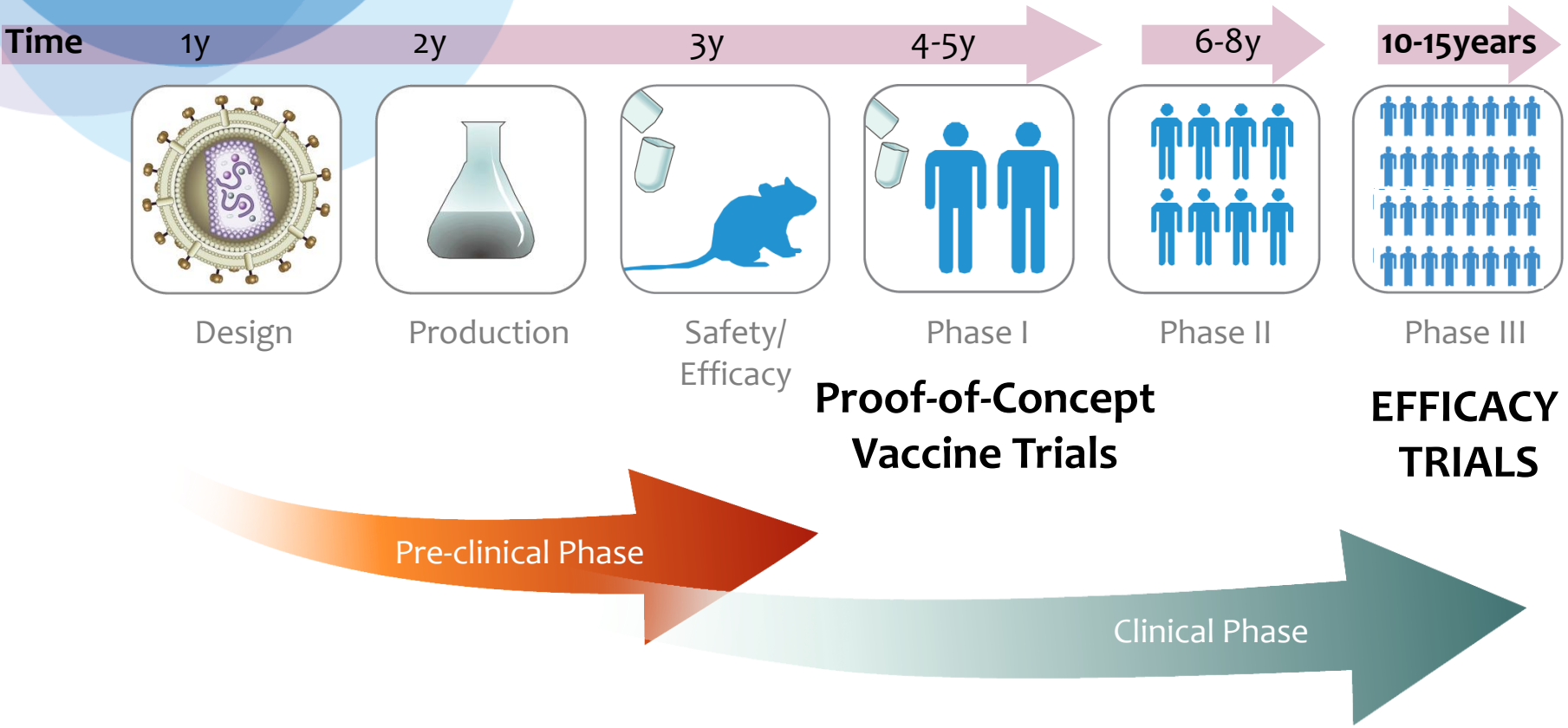
HIV vaccine research HURDLES

Early Establishment of a Viral Reservoir in resting memory cells. LATENCY



Integration of the virus genome into the host cell chromosomes → Latency of the virus in resting memory cells → not accessible to drug/immune system if not reactivated.
'Kick & Kill' Strategies

Learn from clinical trials
Failures → help to improve



Past History of Vaccine Clinical Trials

1987

first preventive HIV vaccine candidate testing gp160 subunit entered into clinical trial

...more than 40 vaccines have been evaluated in safety and immunogenicity trials

...more than 40,000 HIV-uninfected volunteers have participated in CT

...2 phase IIb trials were terminated prematurely in 2007, 1 in 2013

...only 3 phase III trials have been completed

...only 1 has demonstrated a very modest vaccine efficacy

2014

Available Database of AIDS Vaccine Candidates in Clinical Trials
www.iavireport.org
www.hvtn.org
www.clinicaltrials.gov

Past History of Vaccine Clinical Trials

Prematurely stopped phase IIb clinical trials

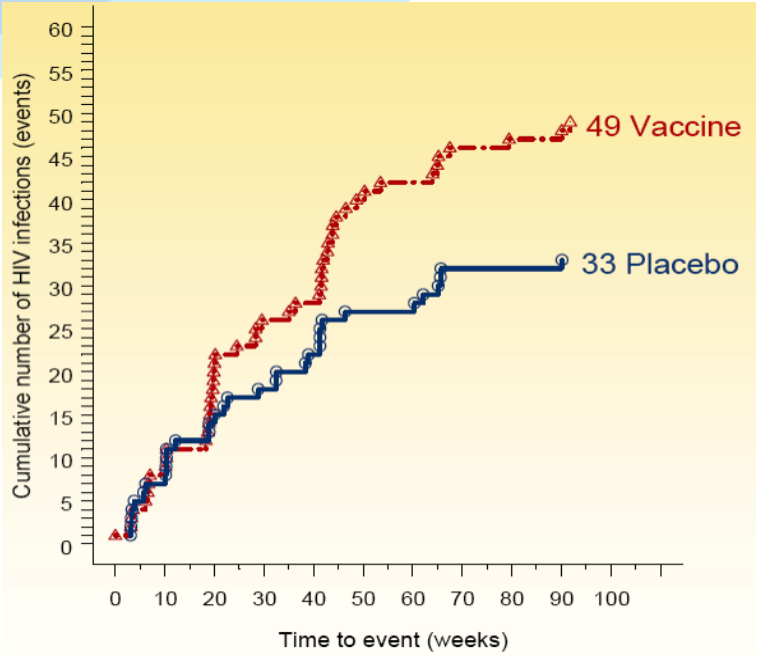
Phase	Trial ID	Strategy	Candidate	# target
IIb	HVTN 502/Merck 023 (Step Study)	Viral Vector - Adeno	MRKAd5 HIV-1 gag/pol/nef	3,000
IIb	HVTN 503 (Phambili)	Viral Vector - Adeno	MRKAd5 HIV-1 gag/pol/nef	3,000
IIb	HVTN 505	DNA – Viral Vector Adeno	VRC-HIVDNA016-00-VP / VRC HIVADV014-00-VP	2504

Completed phase III clinical trials

Phase	Trial ID	Strategy	Candidate	#
III	RV 144	Viral Vector - Pox/Protein	ALVAC-HIV vCP1521/AIDSVAX gp120 B/E	16,403

Past History of Vaccine Clinical Trials: 'Failures' → Opportunities

STEP Trial (2007)



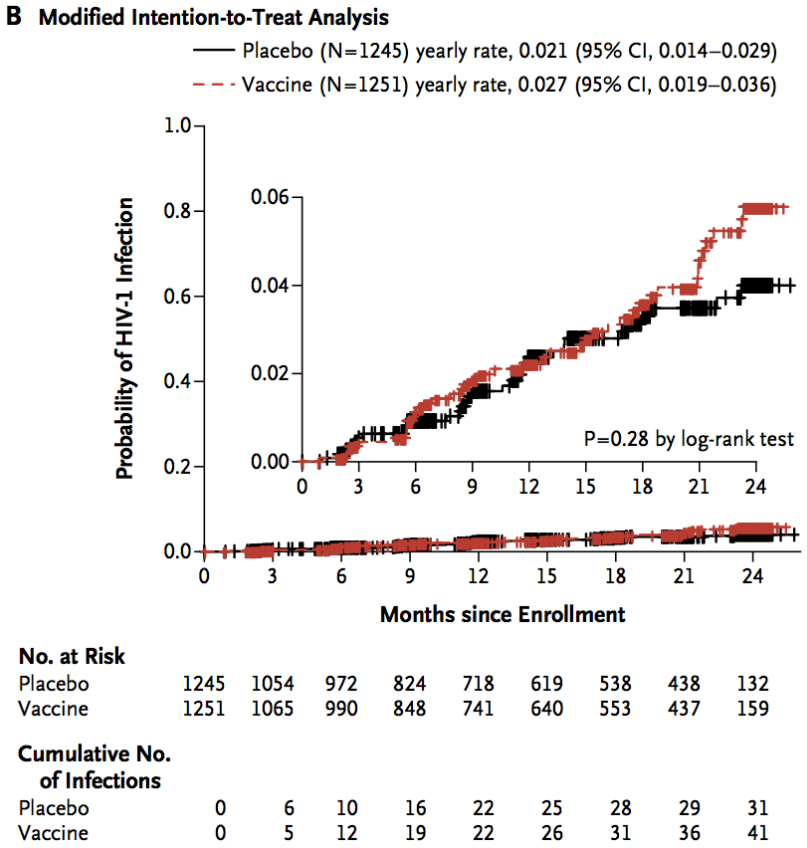
1-tailed p-value = 0.044 (for $VE_{INF} < 0$)

2-tailed p-value = 0.077 (for $VE_{INF} \neq 0$)

'Sieve Effect'

Buchbinder, NEJM 2008
Mullins/Rolland Nat Med. 2011

HVTN 505 (2013)

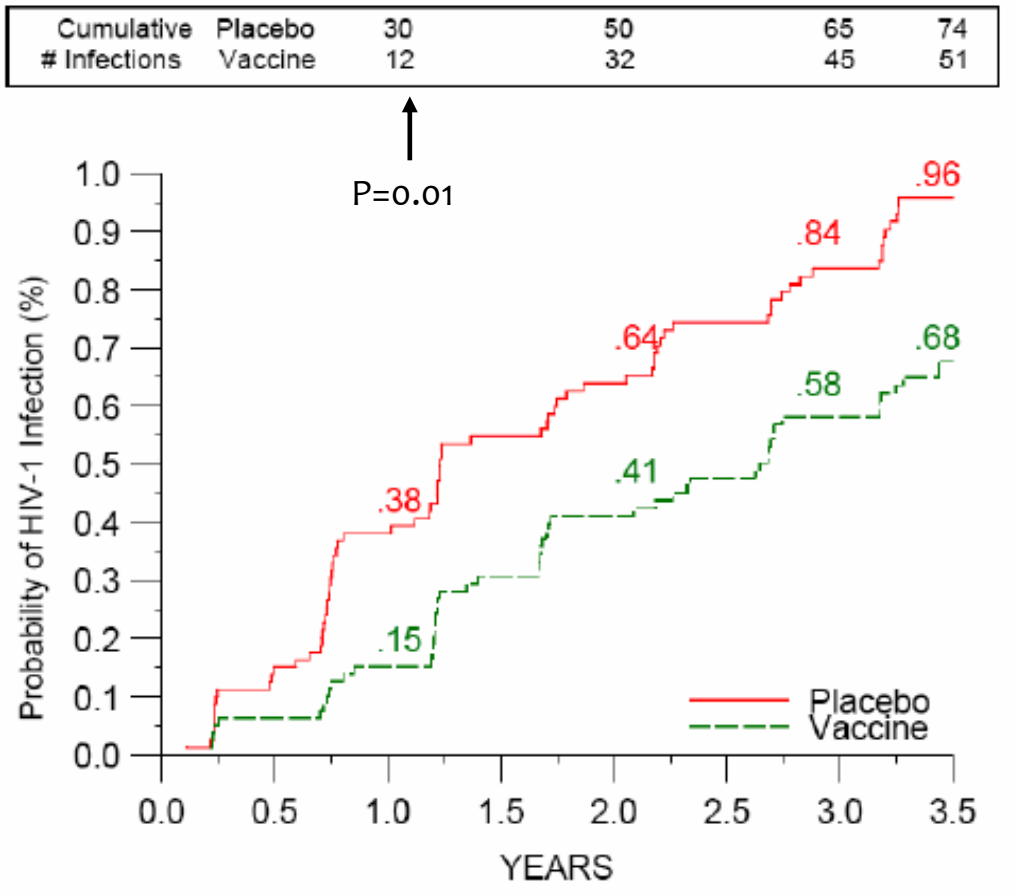


Ad5-mediated increased risk?

Hammer, NEJM 2013

Past History of Vaccine Clinical Trials: Modest 'success' → Opportunities: Immune Correlates

RV144 'Thai' Trial (2009)



CORRELATES OF PROTECTION

Haynes B, NEJM 2012

Early effect??

52,985 person-years

125 infections

Vaccine infections: 51
Placebo infections: 74

VE: 31.2%
p=0.04
95% CI: 1.1, 52.1
(O'Brien-Fleming-adjusted)

Rerks-Ngarm NEJM 2009

Ongoing phase II clinical trials

Phase	Trial ID	Strategy	Candidate	#
I/II	IPCAVD009	Viral Vector - Ad26 + Pox / Protein / adjuvant	Ad26.Mos.HIV/MVA-Mosaic, gp140 DB, Alumn	400
II	RV 305	Viral Vector - Pox / Protein	ALVAC-HIV vCP1521 / AIDSVAX B/E (RV144 reboost)	162
II	RV 328	Protein	AIDSVAX B/E (RV144 substudy mucosa)	40
II	TaMoVac II	DNA / Viral Vector - Pox	HIVIS-DNA / MVA-CMDR (ID electroporation)	198
II	Tiantan vaccinia HIV Vaccine and DNA	DNA / Viral Vector - Replicating Pox	Chinese DNA (clade B/C) / Tiantan vaccinia	150

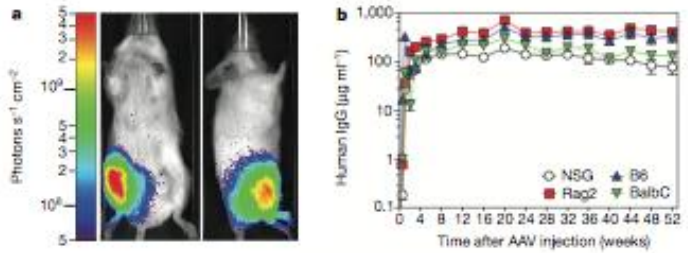
Ongoing phase III clinical trials

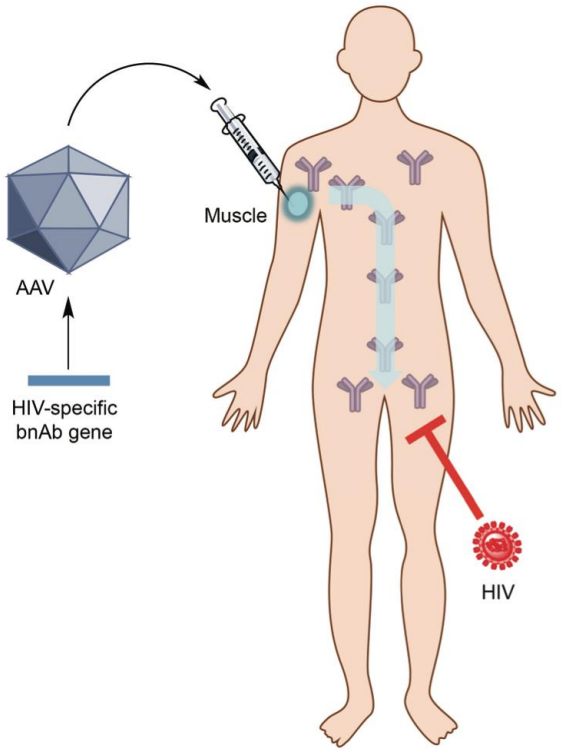
.....

Most Promising New strategies (preclinical): (a) Induction of Ab through VIP

Antibody-based Protection Against HIV Infection by Vectored ImmunoProphylaxis

Alejandro B. Balazs†, Joyce Chen†, Christin M. Hong†, Dinesh S. Rao‡, Lili Yang†, and David Baltimore†,§





LETTERS

nature medicine

Vectored immunoprophylaxis protects humanized mice from mucosal HIV transmission

Alejandro B Balazs[1,4], Yong Ouyang[1], Christin M Hong[1,4], Joyce Chen[1], Steven M Nguyen[1], Dinesh S Rao[2], Dong Sung An[3] & David Baltimore[1]

- Specialized adeno-associated virus (AAV) vector optimized for the production of full-length antibody from muscle tissue
- Humanized mice
- High titer AAV8 stocks
- Coding for mAbs

Balazs, Nature 2011, 2014

2

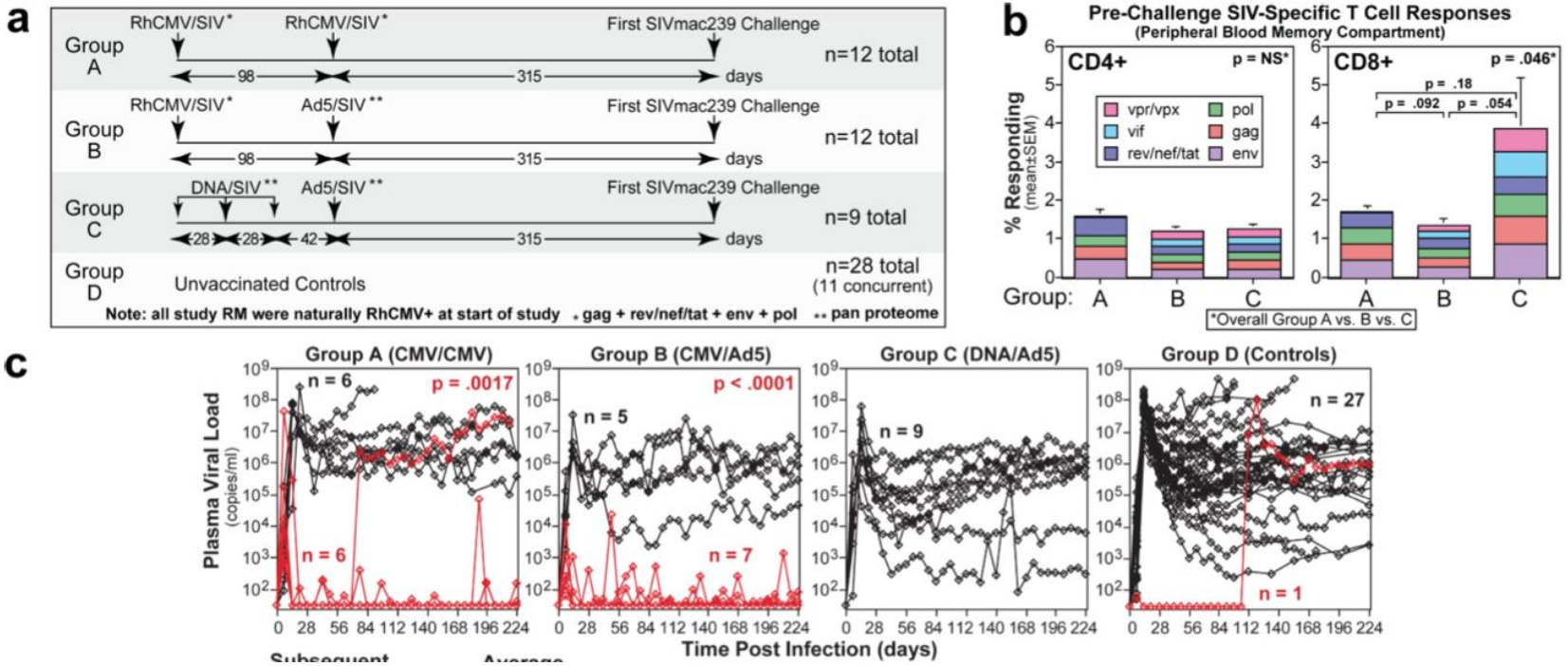
Most Promising New strategies (preclinical): (b) CMV as a vector: CTL responses able to control/cure

Effector-memory T cell responses are associated with protection of rhesus monkeys from mucosal SIV challenge

Scott G. Hansen[1], **Cassandra Vieville**[1], **Nathan Whizin**[1], **Lia Coyne-Johnson**[1], **Don C. Siess**[1], **Derek D. Drummond**[1], **Alfred W. Legasse**[1], **Michael K. Axthelm**[1], **Kelli Oswald**[2], **Charles M. Trubey**[2], **Michael Piatak Jr.**[2], **Jeffrey D. Lifson**[2], **Jay A. Nelson**[1], **Michael A. Jarvis**[1], and **Louis J. Picker**[1]

[1]Vaccine and Gene Therapy Institute, Departments of Molecular Microbiology and Immunology and Pathology, and the Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR 97006

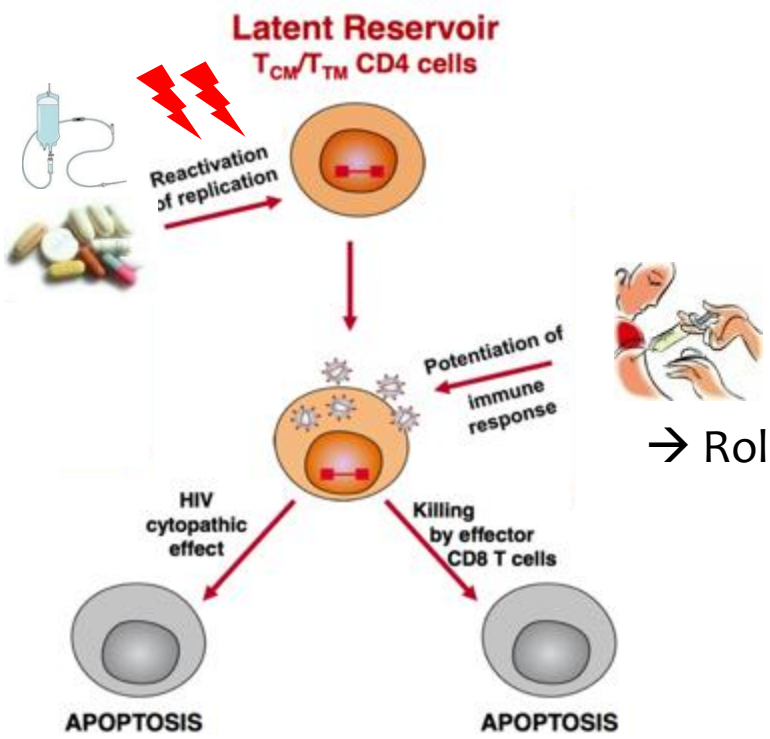
[2]AIDS and Cancer Virus Program, SAIC Frederick, Inc., National Cancer Institute-Frederick, Frederick, MD 21702



Hansen Nature 2011, Science 2013, Nature 2013

Most Promising New strategies (clinical): (c) Exploring new therapies to reactivate the virus (purge reservoir) for a functional cure

'Kick and Kill' strategies



→ Role of **Therapeutic Vaccines**

Hansen Nature 2011, Science 2013, Nature 2013

2

Most Promising New strategies (clinical): (c) Exploring new therapies to reactivate the virus (purge reservoir) for a functional cure

Nature. ; 487(7408): 482–485. doi:10.1038/nature11286.

HDACi as potential latency-reversal agents

Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

NM Archin[1], AL Liberty[1], AD Kashuba[1], SK Choudhary[1], JD Kuruc[1], AM Crooks[1], DC Parker[1], EM Anderson[2], MF Kearney[2], MC Strain[3], DD Richman[3], MG Hudgens[1], RJ Bosch[4], JM Coffin[2], JJ Eron[1], DJ Hazuda[5], and DM Margolis[1,*]

Kick-and-kill strategies

Immunity
Article

Stimulation of HIV-1-Specific Cytolytic T Lymphocytes Facilitates Elimination of Latent Viral Reservoir after Virus Reactivation

Liang Shan,[1,2] Kai Deng,[1] Neeta S. Shroff,[1] Christine M. Durand,[1] S. Alireza. Rabi,[1] Hung-Chih Yang,[3] Hao Zhang,[4] Joseph B. Margolick,[4] Joel N. Blankson,[1] and Robert F. Siliciano[1,5,*]

RMD as potent viral replication inducer

OPEN ACCESS Freely available online
PLOS | PATHOGENS

Histone Deacetylase Inhibitor Romidepsin Induces HIV Expression in CD4 T Cells from Patients on Suppressive Antiretroviral Therapy at Concentrations Achieved by Clinical Dosing

Datsen George Wei[1], Vicki Chiang[1], Elizabeth Fyne[2], Mini Balakrishnan[1], Tiffany Barnes[1], Michael Graupe[1], Joseph Hesselgesser[1], Alivelu Irrinki[1], Jeffrey P. Murry[1], George Stepan[1], Kirsten M. Stray[1], Angela Tsai[1], Helen Yu[1], Jonathan Spindler[3], Mary Kearney[3], Celsa A. Spina[4], Deborah McMahon[2], Jacob Lalezari[5], Derek Sloan[1], John Mellors[2], Romas Geleziunas[1], Tomas Cihlar[1]*

HDACi can impair CTL function?

OPEN ACCESS Freely available online
PLOS | PATHOGENS

Histone Deacetylase Inhibitors Impair the Elimination of HIV-Infected Cells by Cytotoxic T-Lymphocytes

Richard Brad Jones[1,2], Rachel O'Connor[1], Stefanie Mueller[1,2], Maria Foley[2,3], Gregory L. Szeto[2,3], Dan Karel[1], Mathias Lichterfeld[4], Colin Kovacs[5,6], Mario A. Ostrowski[5,6,7], Alicja Trocha[1], Darrell J. Irvine[1,2,3,8], Bruce D. Walker[1,4,8]*

HIVACAT

Projecte de Recerca de la Vacuna de la Sida

HIVACAT Program for HIV Vaccine Research

www.hivacat.org

Dr. Clotet, *HIVACAT codirector* | ***Dr. Gatell,*** *HIVACAT codirector* | ***Dr. Brander,*** *HIVACAT scientific director*

IrsiCaixa Institut de Recerca de la Sida

ESTEVE

FUNDACIÓ CLÍNIC BARCELONA

Generalitat de Catalunya Departament d'Innovació, Universitats i Empresa

Obra Social "la Caixa"

Generalitat de Catalunya Departament de Salut

Developed by a **joint public and private sector consortium** unprecedented in Spain. It is composed of Catalonia's two longest established and **leading AIDS research centres** based in **Barcelona, in conjunction with leading public and private institutions**

60 investigators and staff, with broad and complementary expertise in humoral, cellular and mucosal innate and adaptive immunology and focus on viral entry, transmission and diversity
HGTIP + Hclínic: Cohort of >6000 HIV-infected population

AIDS vaccine Barcelona 2013

Multidisciplinary Approach of the HIV management
Collaborations with Community to increase HIV diagnosis - Prevention
Translational Research at IrsiCaixa

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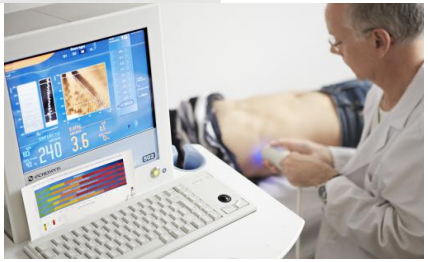
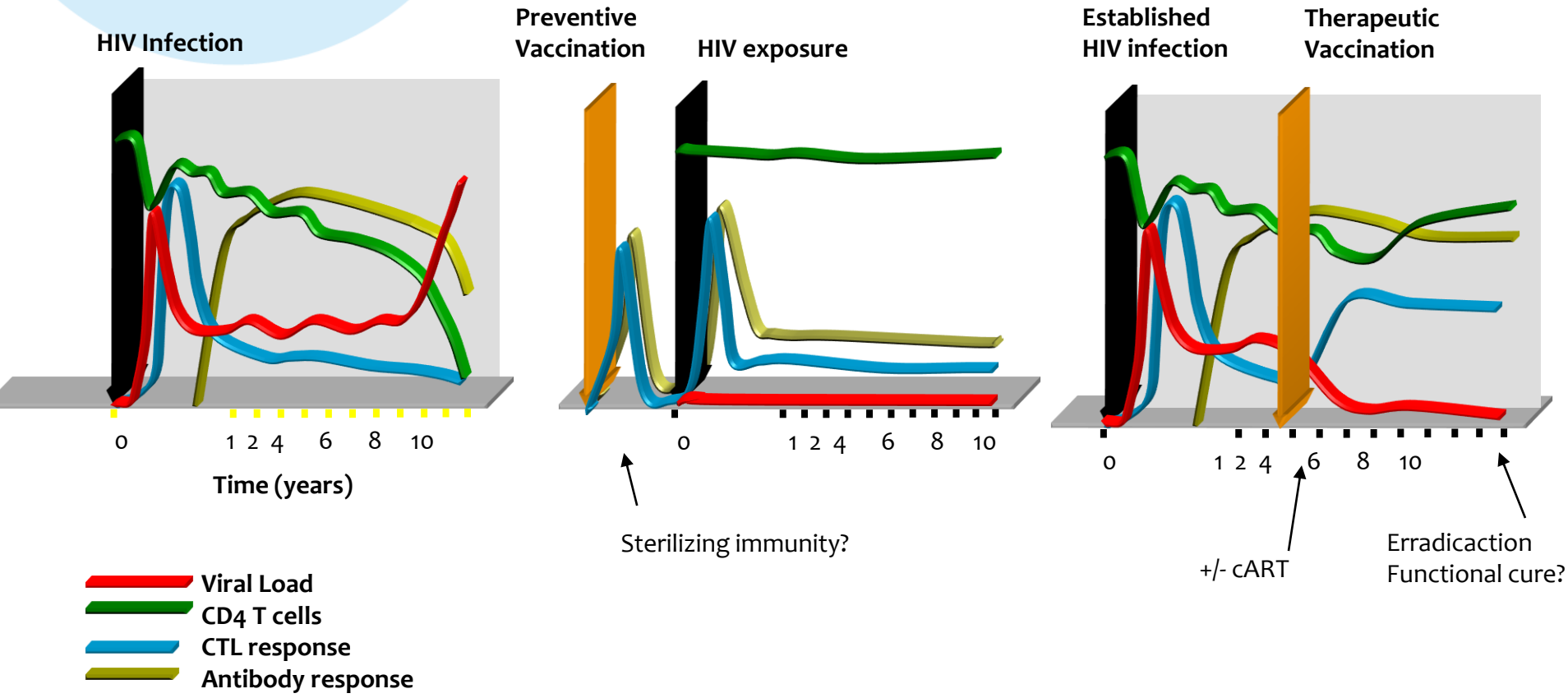


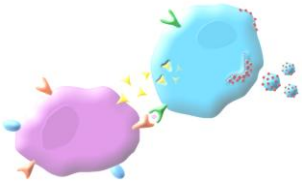
CLINIC – BENCH - CLINIC

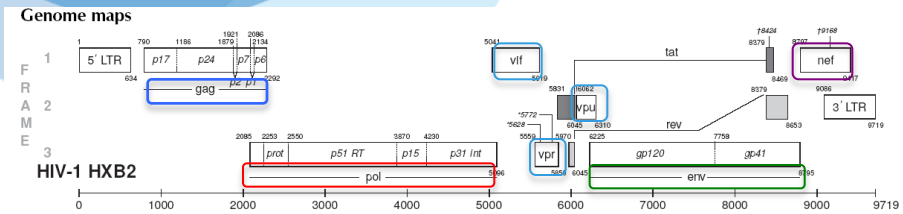
3 Knowledge of response to HIV → Improve HIV Vaccine design?

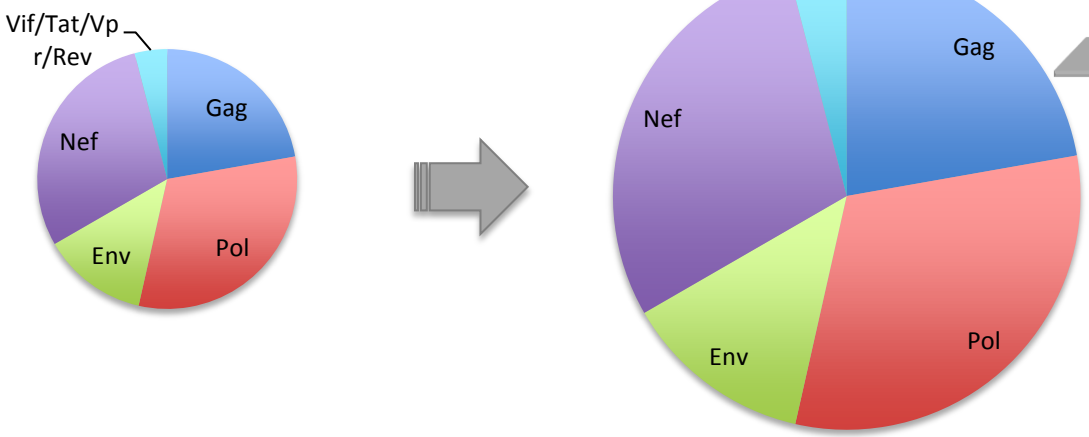


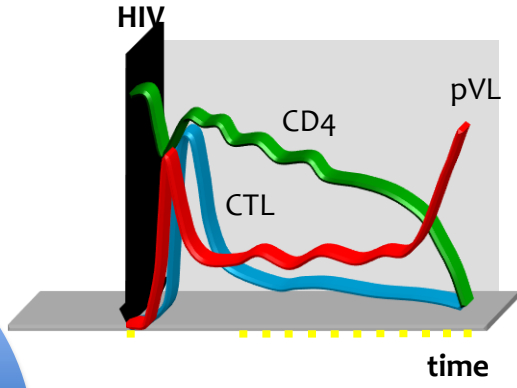
HIVACAT T-cell Immunogen (HTI)

T-cell Candidate







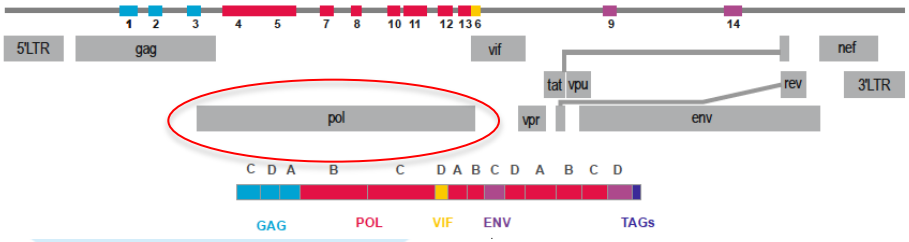


- T cell immunogen design may profit from a focus on SELECT HIV viral targets where the virus is most vulnerable and to avoid inducing responses to potential decoy targets.

[1]Buchbinder SP et al, Lancet 2008; [2]Hammer et al, NEJM 2013

HIVACAT T-cell Immunogen (HTI)

- FOCUS of responses to SELECT HIV viral targets



Highly conserved regions of the viral genome (CE[3,4,5,6] & HIVconsv[7,8,9]).

[3]Rolland M et al, PLos Pathog 2007
[4]Mothe B et al, Plos One 2012
[5]Kulkarni V et al PLos One 2013
[6]Kulkarni et al, PLos One 2014
[7]Letourneau S et al, PLos One 2007
[8]Borthwick N et al, Mol Ther 2014
[9]Hayon E et al, PLos One 2014
[10]Rolland M et al, JVI 2013

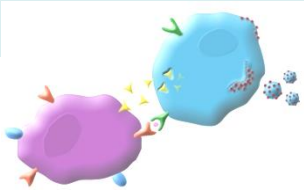
* Very immunogenic in HIVneg ← → NOT in natural HIV-1 infection
Conservation alone does NOT define vulnerability[10]

Guide the selection by human immunogenicity data[11,12]

1) To identify the major vulnerable sites for protective HIV-1 specific T cell responses

2) Break immunodominance to non-beneficial targets

3) Ensure a broad HLA class I and II coverage



[11]Mothe B et al, JTM 2011
[12]Pereyra F et al, JVI 2014

HIVACAT T-cell Immunogen (HTI)

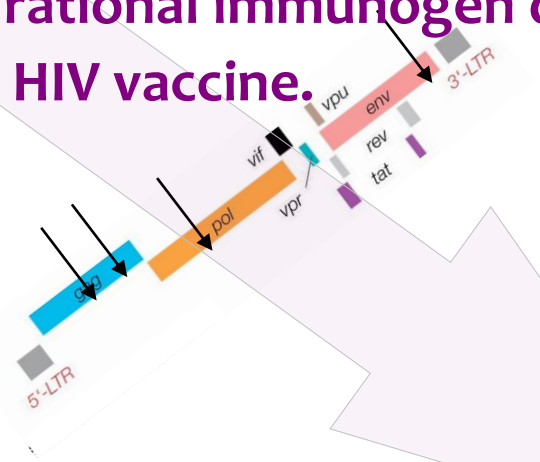
3

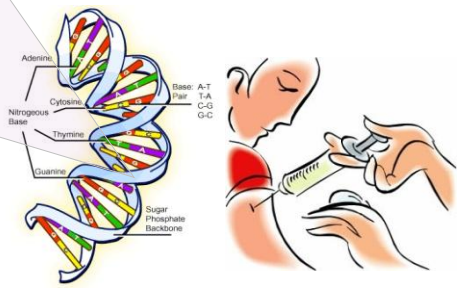
Long-term non progressors

HIV controllers

Elite controllers

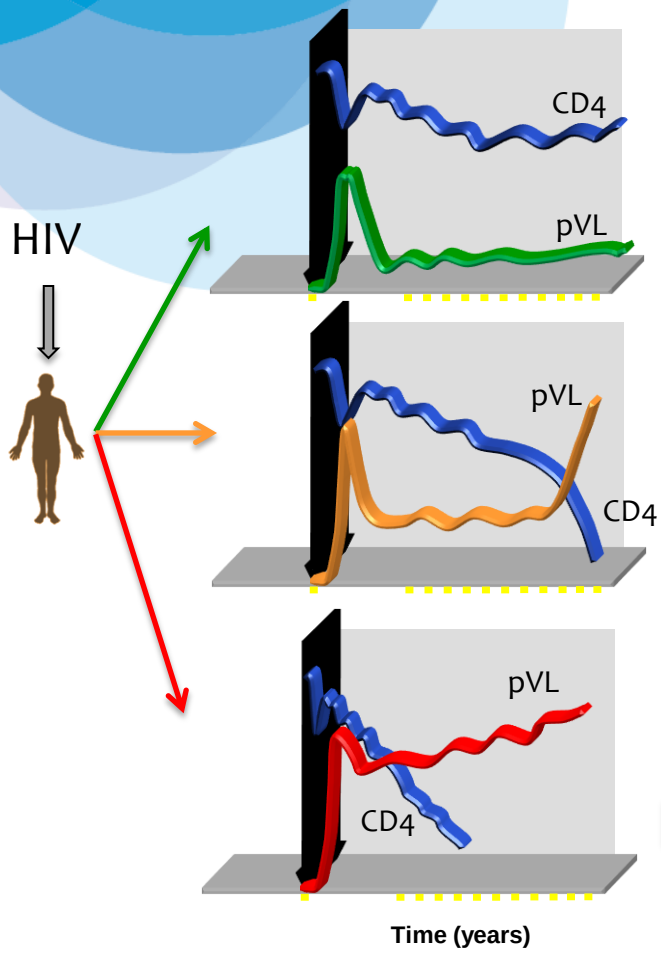
identify the viral targets that intervene most consistently in mediating viral control in vivo and address how this information can be incorporated into a rational immunogen design for a global HIV vaccine.

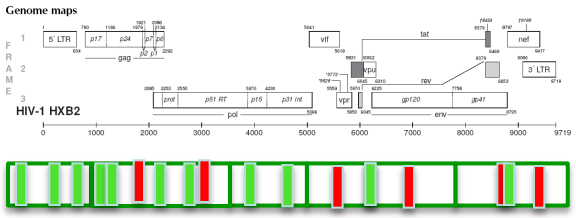


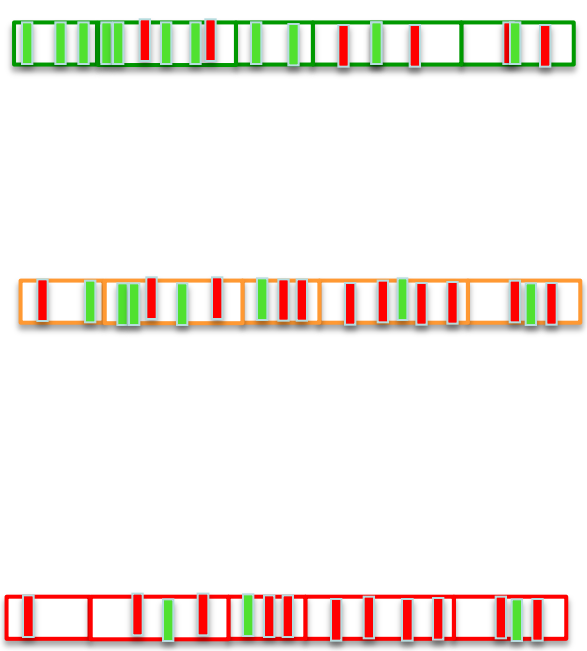


HIVACAT T-cell Immunogen (HTI)

Screens in >1000 infected individuals to the entire HIV proteome





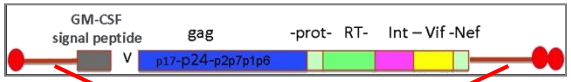


26 BENEFICIAL **regions**

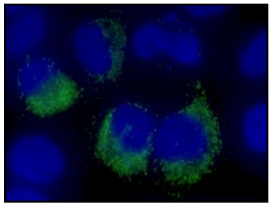
Mothe B et al, PLos One 2012
Mothe B et al, JTM 2011

HIVACAT T-cell Immunogen (HTI)

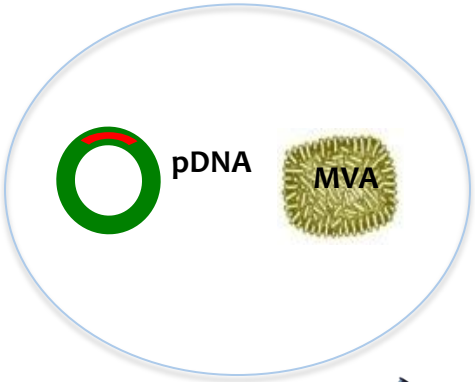
HTI (16 segments, 529 aa)



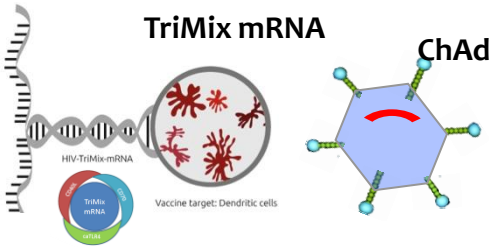
Cloned into a CMV basic DNA plasmid



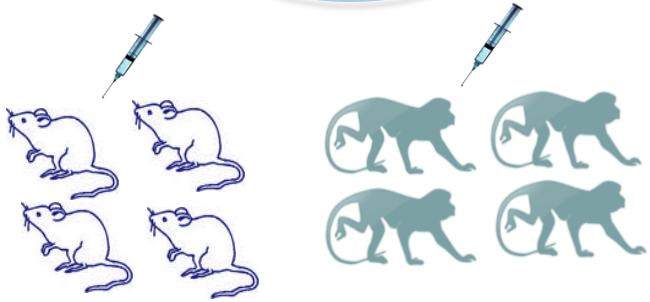
In vitro expression



Expressed in different vector systems



IMMUNOGENICITY



HTI development plan

2014	2015				2016			
4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q

DNA.HTI

Inicio de la Producción GMP

Viales del 1er Lote Clínico DNA.HTI

Estudios de toxicidad Biodistribución y Estabilidad

MVA.HTI

Inicio de la Producción GMP

Estudios de toxicidad Biodistribución y Estabilidad

Viales del 1er Lote Clínico MVA.HTI

Inicio Ensayo en voluntarios sanos DNA.HTI + MVA.HTI (Phase I/IIa safety)

Preparativos para Phase II/PoC
En VIH positivos con Interrupción TTM

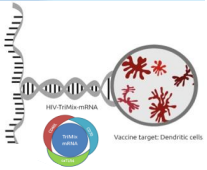
Proceso Regulatorio con Agencia Española del Medicamento (AEMPS)

- Advisory Meeting AEMPS
- Comités éticos
- Datos Tox y Estabilidad
- OK finales

HTI development plan

2014	2015				2016			
4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q

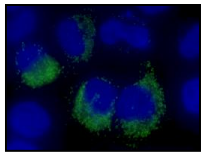
iHIVARNA Trimix.HTI

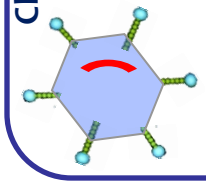


Inicio Ensayo en HIV+
(Phase I/IIa safety)

Inicio Ensayo en HIV+
Phase II/PoC (interrupción de TTM – 5 sites

ChAd.HTI





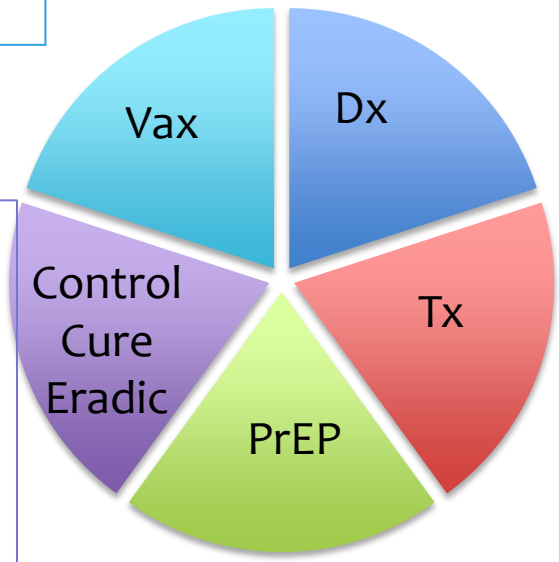
Estudios de inmunogenicidad en animales
Combinación de DDD-ChAd-MVA

Inicio de la
Producción GMP

HIV / AIDS agenda

1) Discovery of new bNAb past years
2) Massive increased knowledge on Ab structure
3) VIP (gene-therapy strategy using AAV to produce Ab

1) Changes in CDC diagnose algorithms
2) Inclusion of new rapid tests - NAT
3) Self-diagnose



1) Berlin, Boston, Mississipi cases
2) Promising CMV-vax in monkeys
3) New drugs with potential to reactivate virus from latent reservoir (HDACis, a-PD1...)
4) New vaccine concepts for a T-cell vaccine concept for a kick-and-kill strategy

1) Permanent updates in treatment guidelines -→ towards Universal
2) Renewed focus in acute infection and early treatment. Impact on inflammation, reservoir...
3) Reduce cascade gaps

1) FDA approval of PrEP
2) Long-lasting ART for PrEP Numerous studies ongoing of PrEP
3) HIV R4P meetings to combine prevention – vaccine research agenda

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iHIVARNA
EC-FP7-602570

CUT HIVAC Cutaneous HIV Vaccination
EC-FP7-241904

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HIVACAT
Projecte de Recerca de la Vacuna de la Sida

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