AEEMT

Asociación Española de Especialistas en Medicina del Trabajo

I Simposio de Vacunación en el Ámbito Laboral
Madrid 17 de junio de 2016

UNA VACUNA FRENTE AL VIH/SIDA SITUACION ACTUAL Y DESAFIOS PLANTEADOS

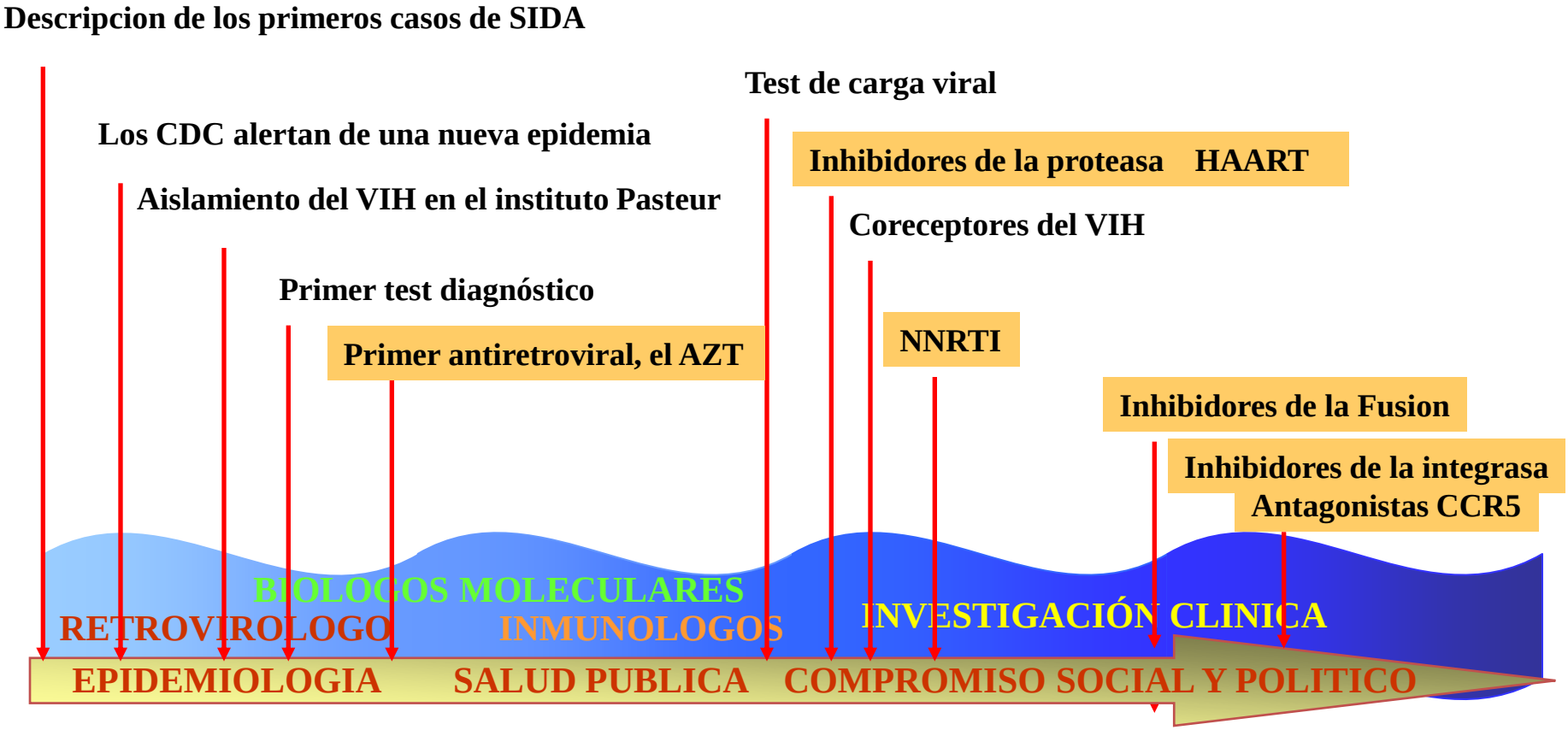
Dr José Alcamí
Unidad de Inmunopatología del SIDA
Instituto de Salud Carlos III
Coordinador de la Red de Investigación en SIDA

RETIC-RIS

I.P.

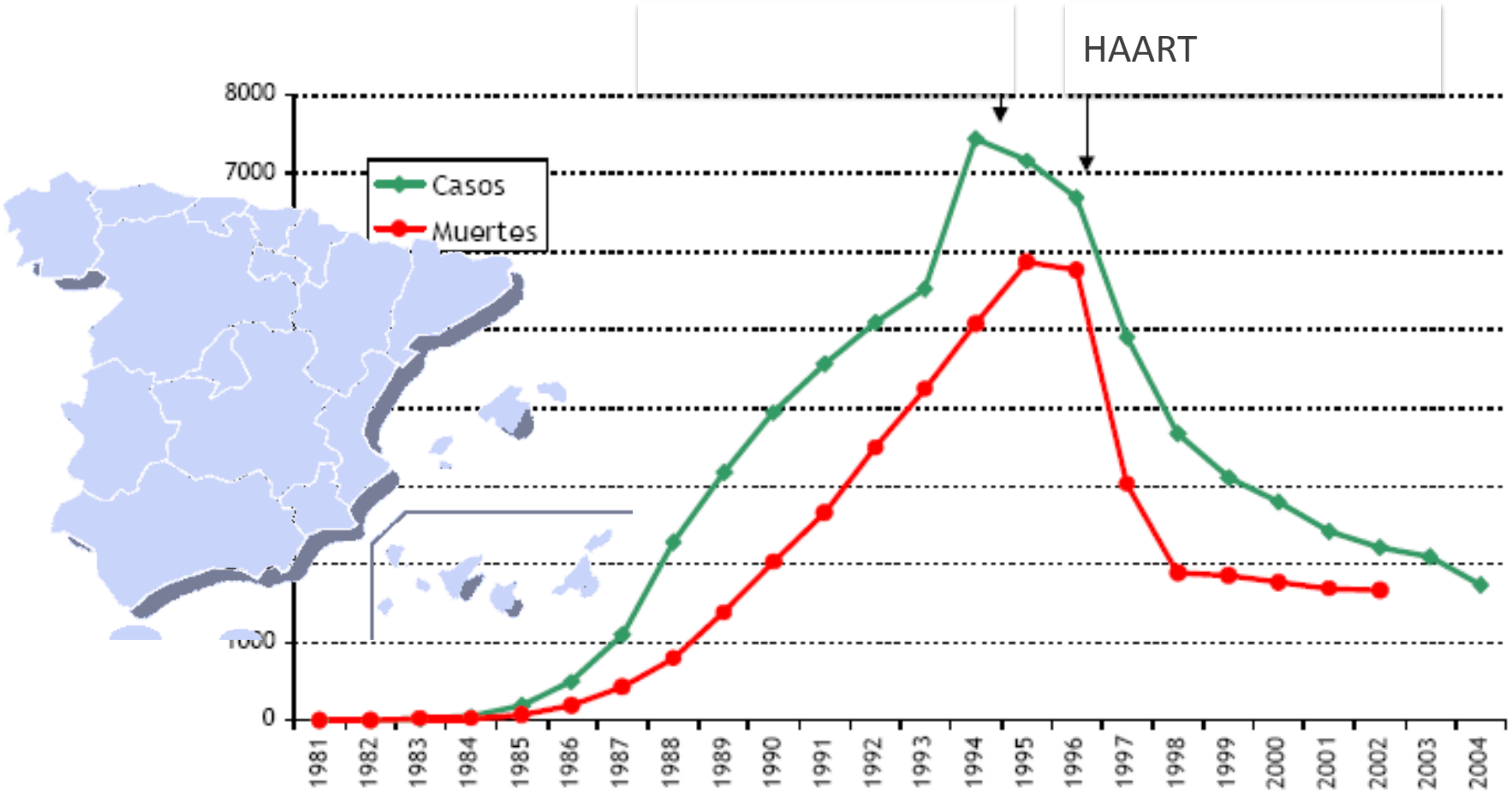
Instituto de Salud Carlos III

35 AÑOS DE HISTORIA. EL SKI LINE DEL SIDA



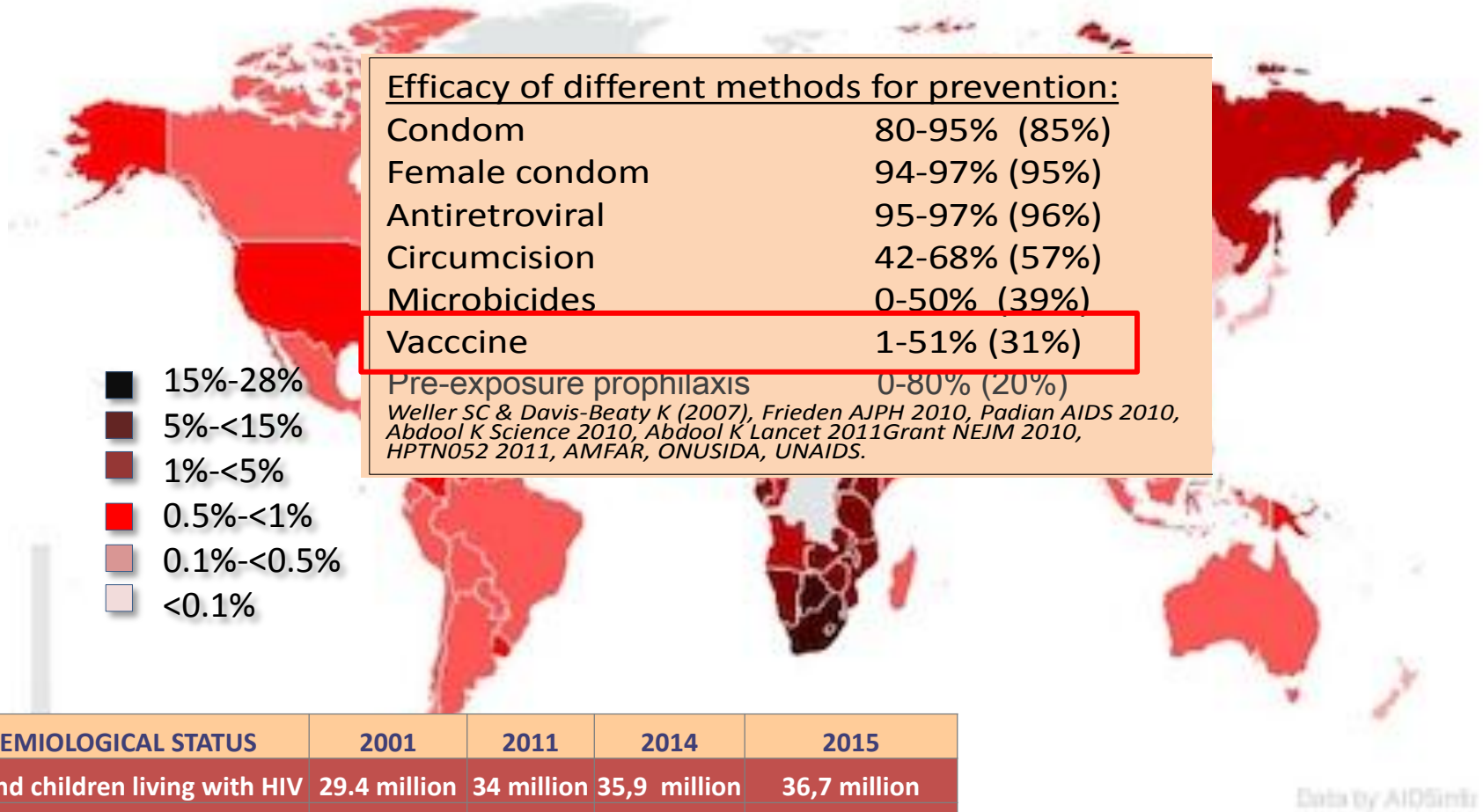
35 AÑOS DE VIH/SIDA

HISTORIA DE EXITO → TRATAMIENTO



35 AÑOS DE VIH/SIDA

HISTORIA DE FRACASOS → LA EPIDEMIA NO HA SIDO CONTROLADA



Efficacy of different methods for prevention:

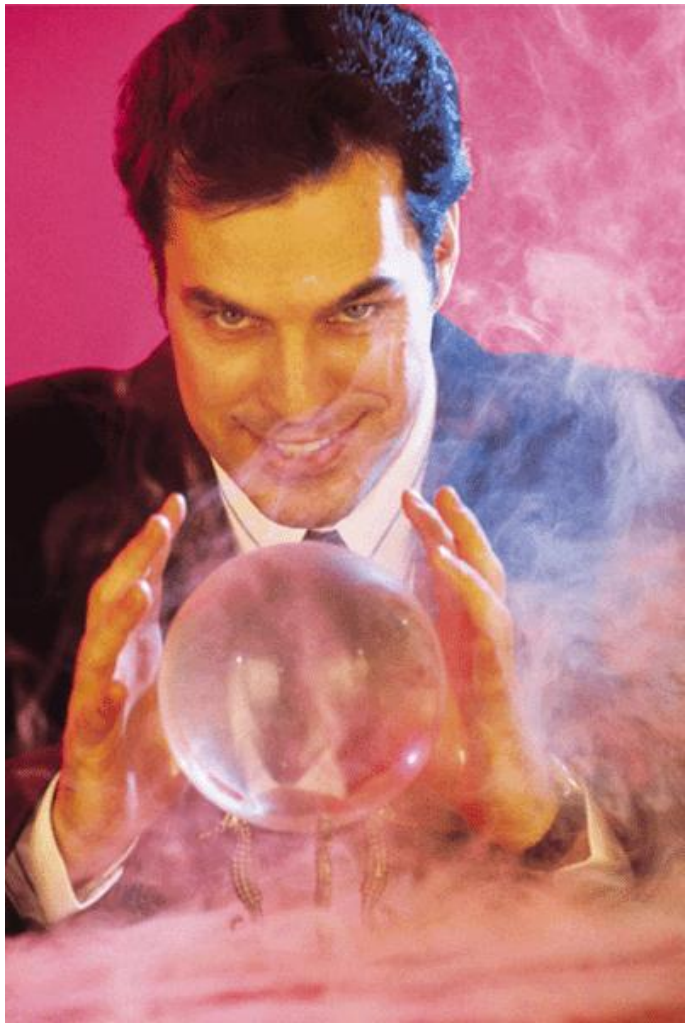
Condom	80-95% (85%)
Female condom	94-97% (95%)
Antiretroviral	95-97% (96%)
Circumcision	42-68% (57%)
Microbicides	0-50% (39%)
Vacccine	1-51% (31%)
Pre-exposure prophilaxis	0-80% (20%)

Weller SC & Davis-Beaty K (2007), Frieden AJPH 2010, Padian AIDS 2010, Abdool K Science 2010, Abdool K Lancet 2011Grant NEJM 2010, HPTN052 2011, AMFAR, ONUSIDA, UNAIDS.

EPIDEMIOLOGICAL STATUS	2001	2011	2014	2015
Adults and children living with HIV	29.4 million	34 million	35,9 million	36,7 million
Adults and children newly infected	3.2 million	2.5 million	2,1 million	2,1 million
% Adult prevalence	0,8	0.8	0,8	0,8
Adult and child deaths due to AIDS	1.7 million	1.4 million	1,2 million	1,1 million

El SIDA COMO PARADIGMA Y DESAFIO
LA OBTENCION DE UNA VACUNA PREVENTIVA

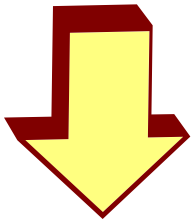
¿CUANDO TENDREMOS UNA VACUNA FRENTE AL VIH?



El SIDA COMO PARADIGMA Y DESAFIO
LA OBTENCION DE UNA VACUNA PREVENTIVA

~~¿CUANDO TENDREMOS UNA VACUNA FRENTE AL VIH?~~

¿ES POSIBLE UNA VACUNA FRENTE AL VIH?



NO LO SABEMOS

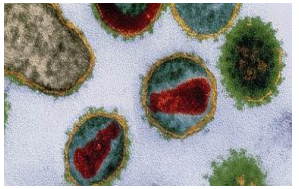
EL DESAFIO DE CONSEGUIR UNA VACUNA PREVENTIVA

1. Diferentes fases en el desarrollo de una vacuna preventiva
2. Los ensayos clínicos críticos en cada fase
3. Aprendiendo de los fracasos. Mecanismos de escape viral a la respuesta inmune
4. ¿Alguna buena noticia?

Conclusion.

- El VIH es un virus diferente
- Nos enfrentamos a un nuevo desafío

LA BUSQUEDA DE UNA VACUNA FRENTE AL VIH

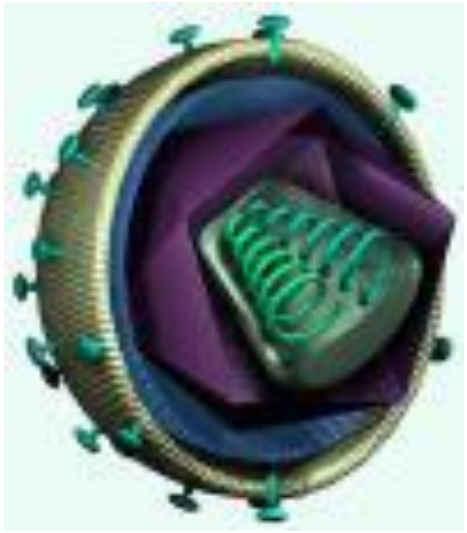


1984 1990 2000 2005 2010 2015

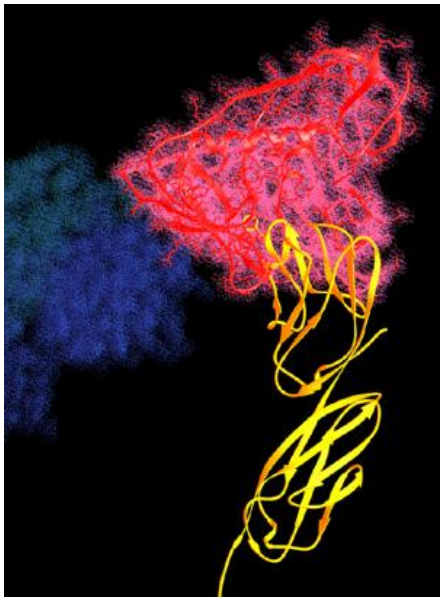
1984-2004.
FRACASO DE LOS MODELOS CLASICOS

- **Vacunas inactivadas → Demasiado peligrosas**
- **Vacunas inactivadas → Demasiado débiles**
- **Vacunas recombinantes gp120 →Ineficaces**

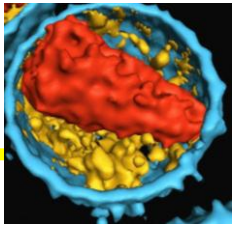
Objetivo
Inducir anticuerpos neutralizantes



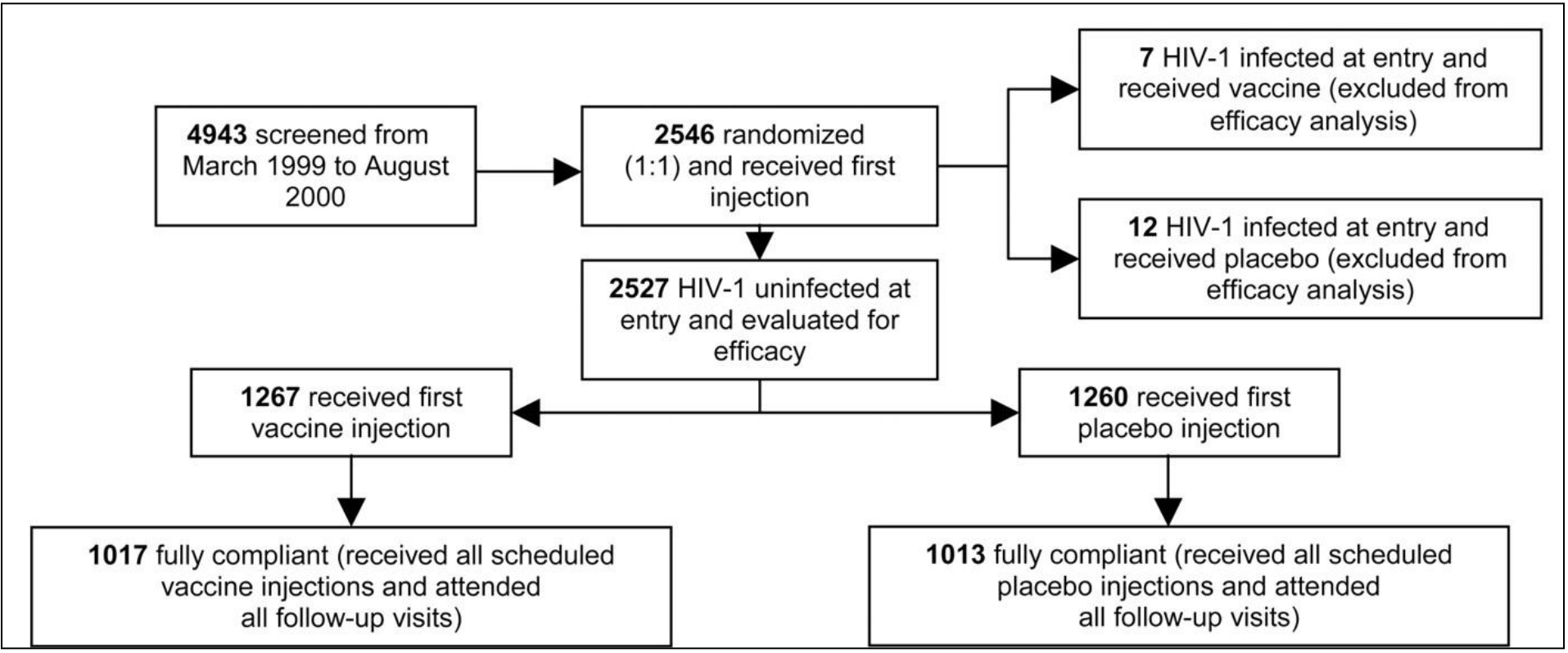
EL MODELO DE LA HEPATITIS B
- Fuerte respuesta humoral
- Anticuerpos de larga vida
- Alto nivel de protecciónn



Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand.



Pitisuttithum P et al. J Infect Dis. 2006;194:1661-71



-IVDU

- AIDSVAX B/E contains 2 rgp120 HIV-1 envelope antigens: 1 from a CXCR4-dependent laboratory-adapted subtype B strain (MN), and 1 from a CCR5-dependent primary subtype CRF01_AE isolate (A244), each produced from stable, transfected CHO cell lines

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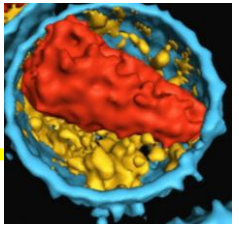

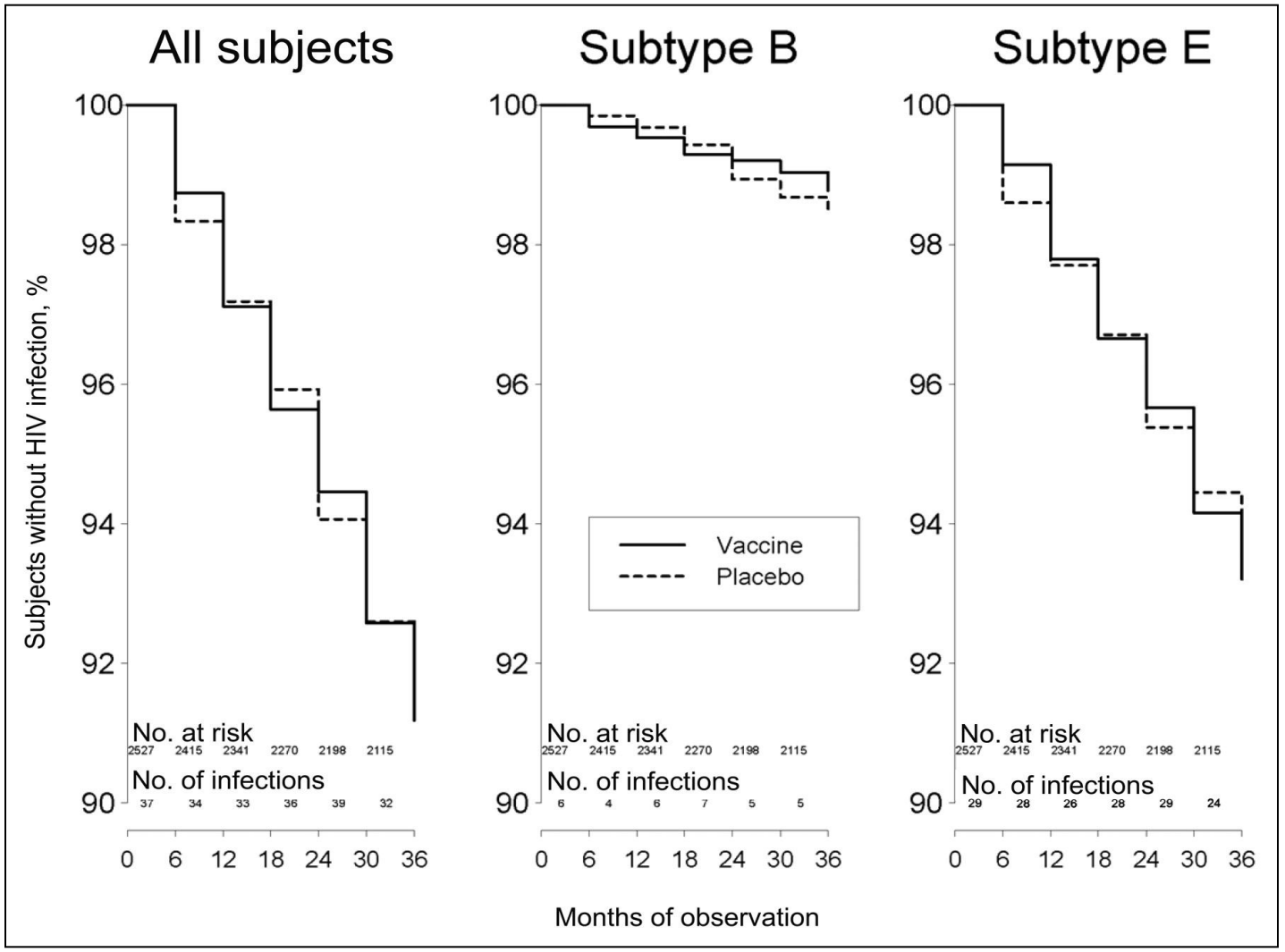

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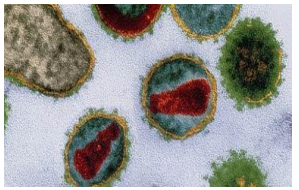
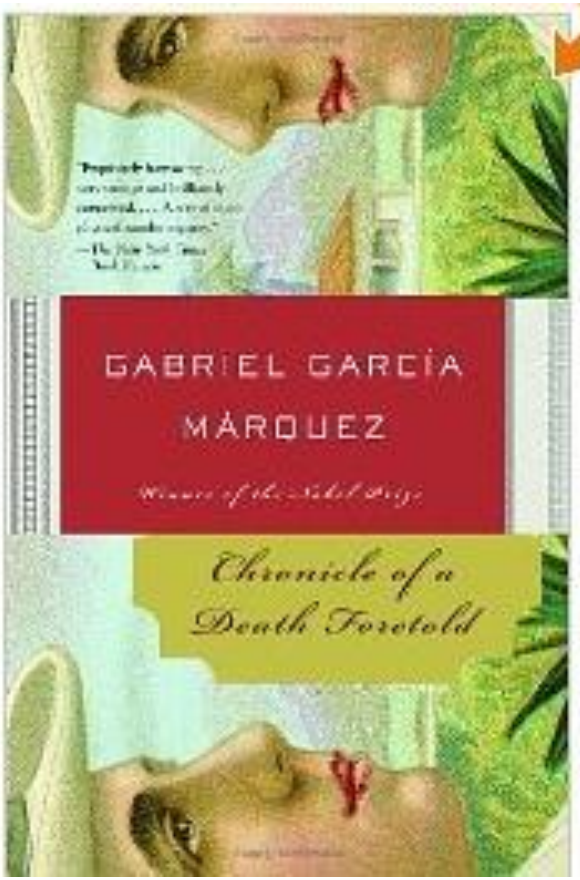
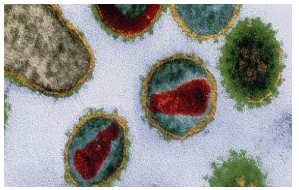




Gp120 recombinante

FALTA DE EFICACIA

THE SEARCH FOR AN HIV VACCINE



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Objetivo
Inducir anticuerpos neutralizantes

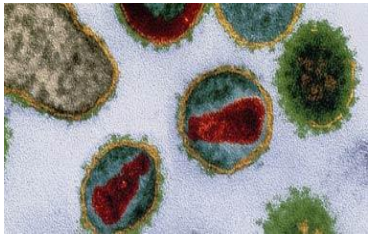
Las respuestas celulares se han asociado con control de la replicación del VIHl

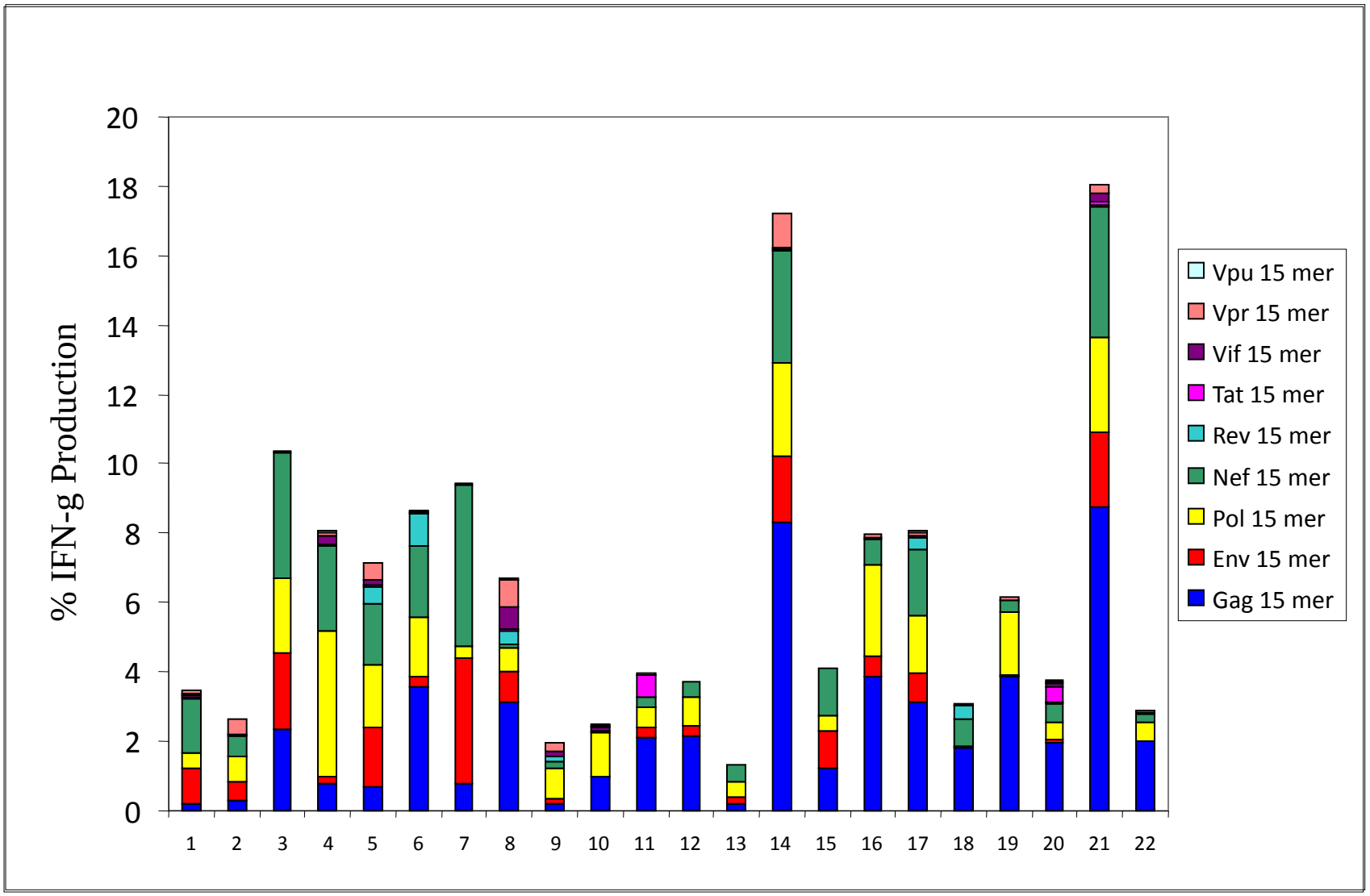
- LTNP y controladores de élite
- Infección primaria
- Interrupciones de tratamiento
- Modelos animales

2000-2008 (2014) VACUNAS CELULARES

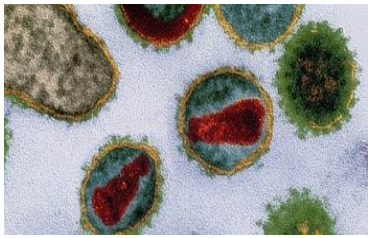
Objetivo
Inducir respuestas celulares

Total HIV-specific CD8 Response

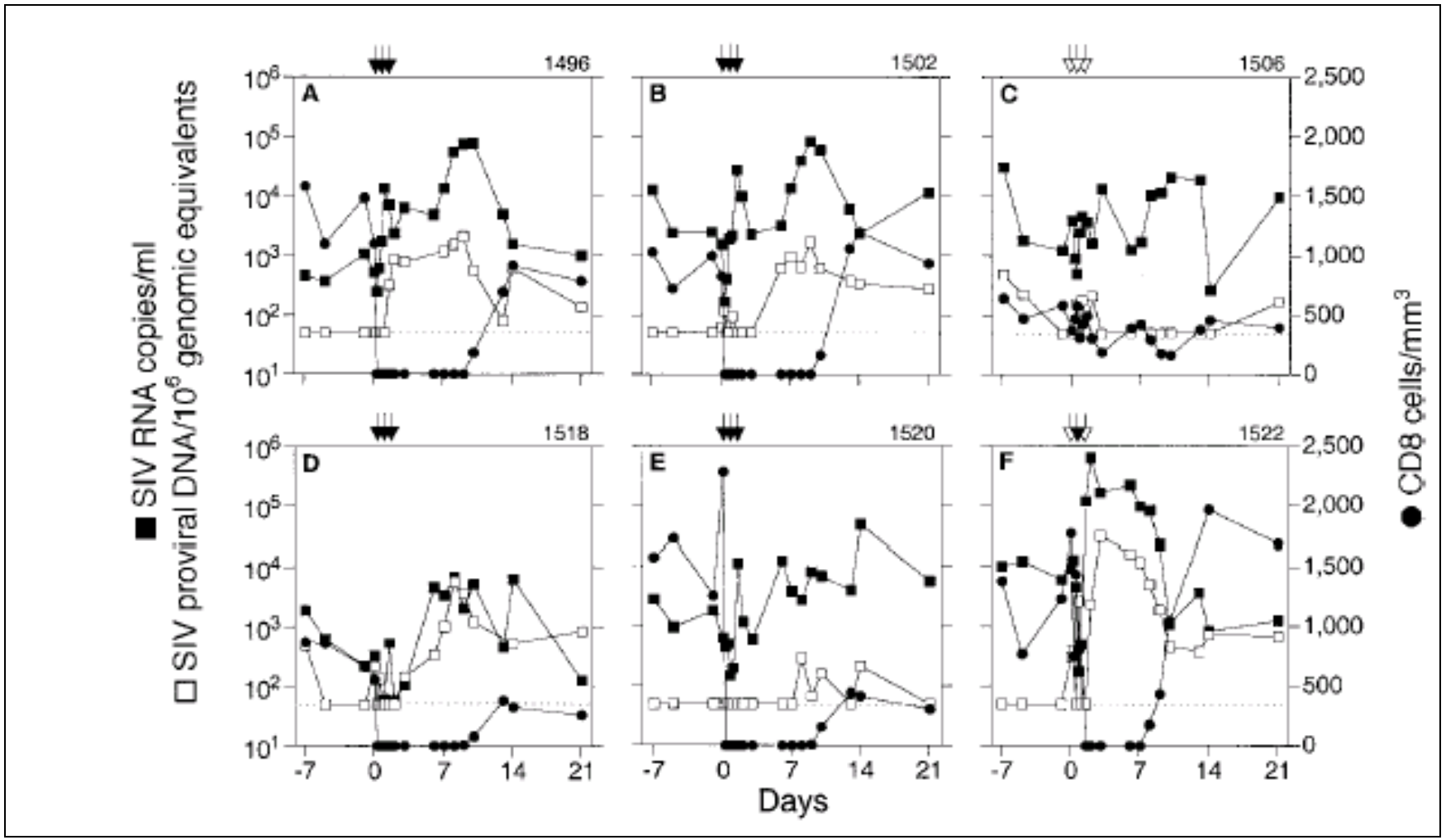




VACUNAS CELULARES FRENTE AL VIH

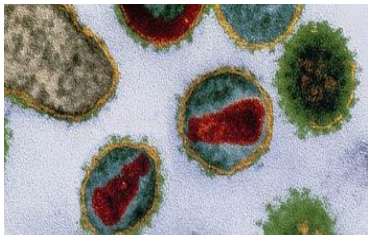


Effects of In Vivo CD8+ T Cell Depletion on Virus Replication in Rhesus Macaques Immunized with a Live, Attenuated Simian Immunodeficiency Virus Vaccine

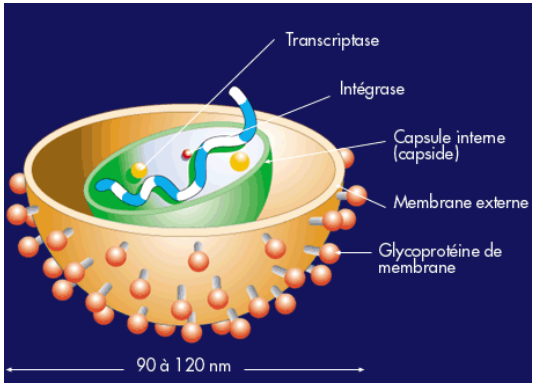


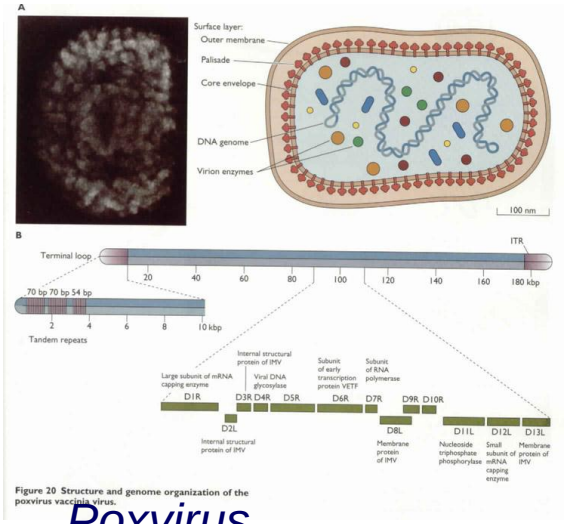
J Exp Med 2000;191:1921-1931

VACUNAS CELULARES FRENTE AL VIH

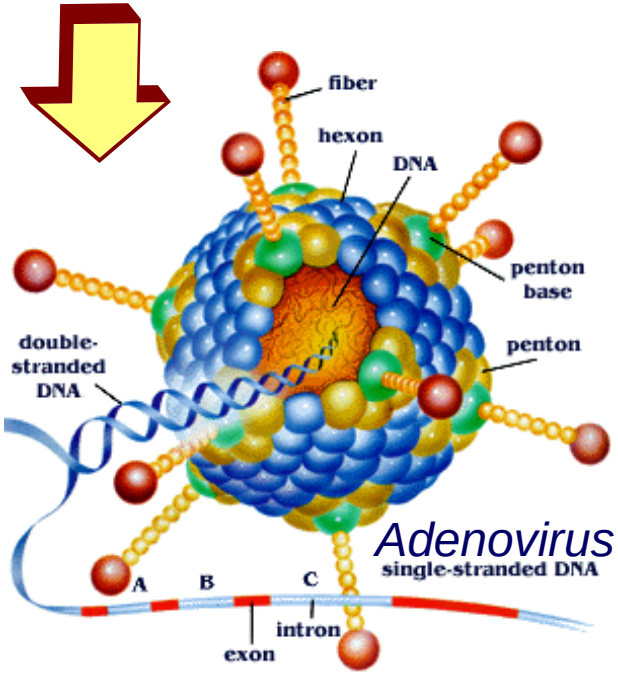


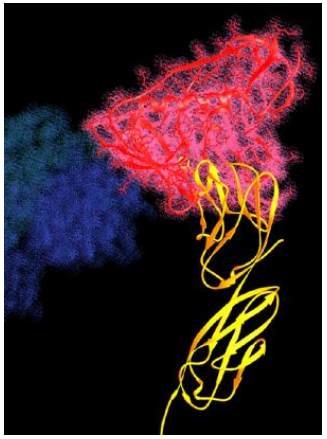
EXPRESION DE GENES DEL VIH POR VECTORES VIRALES





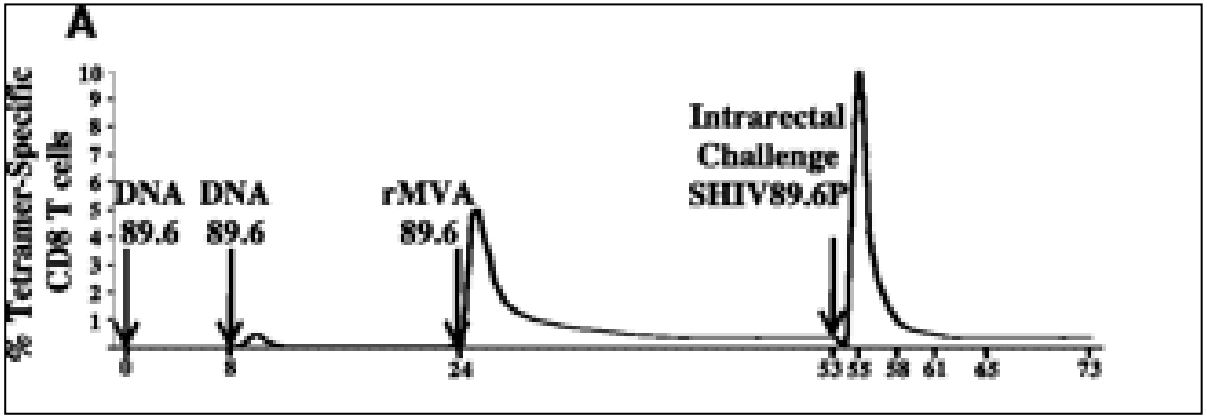
Poxvirus

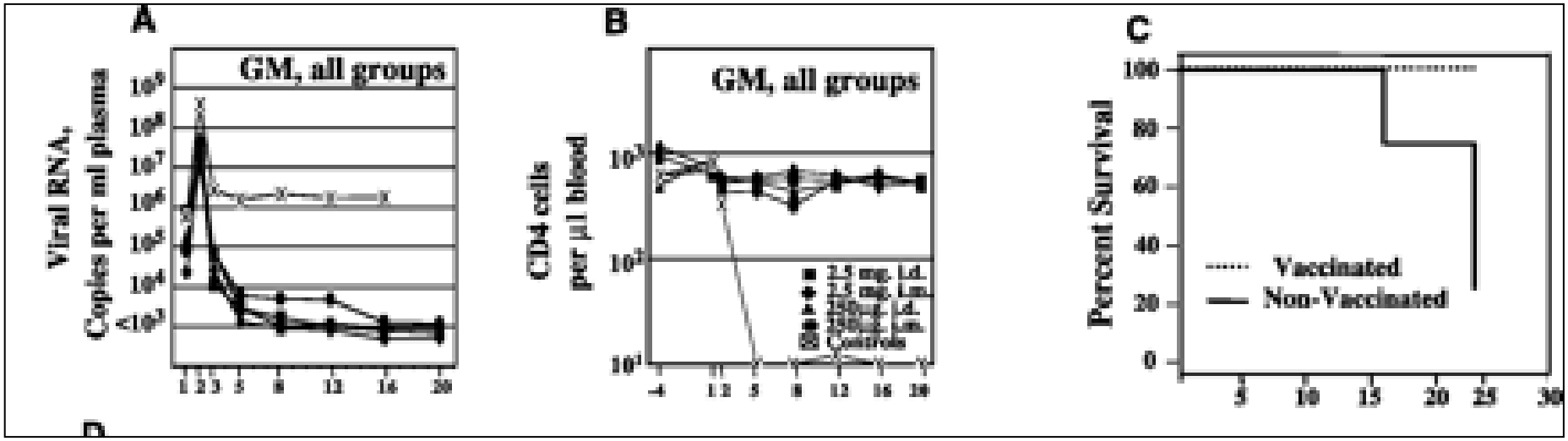




VACUNAS CELULARES

Control of a Mucosal Challenge and Prevention of AIDS by a Multiprotein DNA/MVA Vaccine (Science 2001;292:69-74)

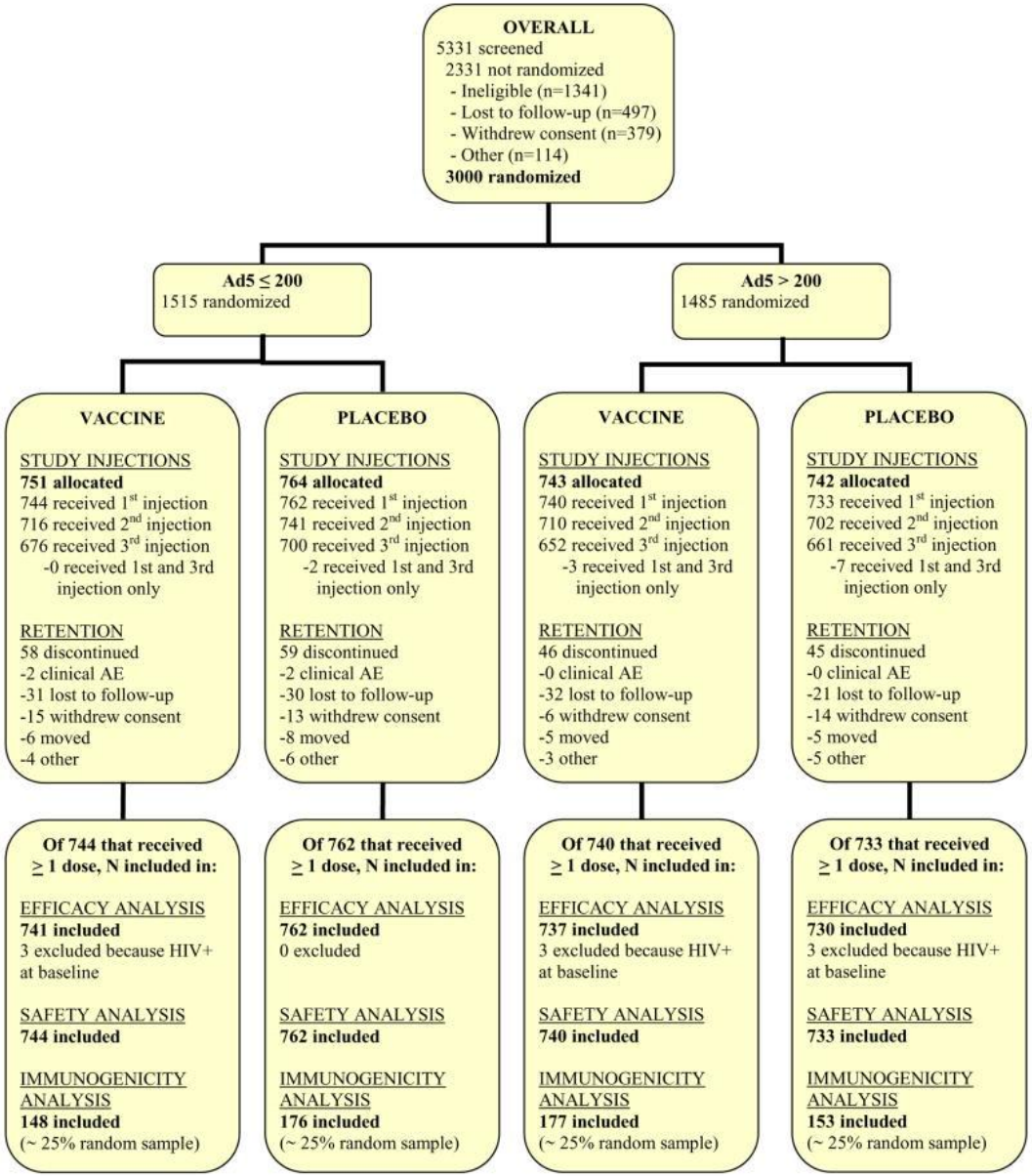




Control de carga viral, niveles de CD4 y mejor superviviencia en macacos vacunados
Correlación con la inducción de respuestas celulares
PERO NUNCA SE CONSIGUE PROTECIÓN

EL ENSAYO STEP (MERCK V520 Protocolo 023/HVTN 502)

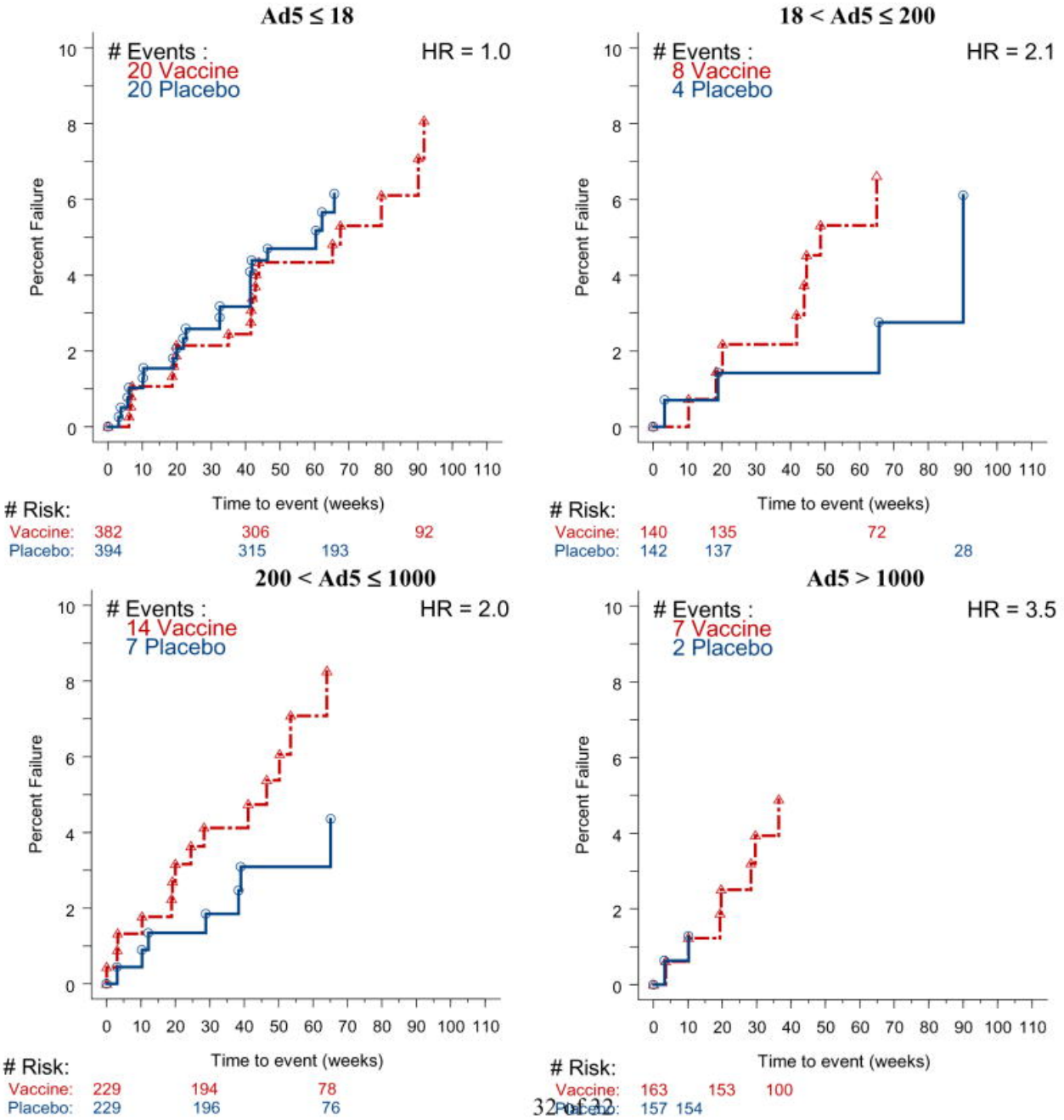
Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial Susan P Buchbinder et al. Lancet 2008;372:1881-93



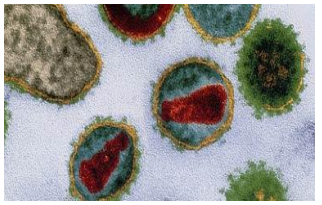
EL ENSAYO STEP (MERCK V520 Protocolo 023/HVTN 502)

RESULTADOS

- Las cargas virales en los sujetos infectados fueron similares independiente de que estuvieran vacunados o no
- La incidencia de la infección VIH **fue superior en el subgrupo de vacunados con anticuerpos frente a Ad5 que en el grupo control (5.1% versus 2.2% por año)**



MOTIVOS PARA EL FRACASO DEL ESTUDIO STEP DIFERENTES HIPÓTESIS



Proc Natl Acad Sci U S A;109:E3503-12Merck Ad5/HIV induces broad innate immune activation that predicts $CD8^+$ T-cell responses but is attenuated by preexisting Ad5 immunity

Table 1

Pre-existing anti-Ad5 neutralizing antibodies reduced immune responses generated by MRKAd5 HIV-1 gag/pol/nef vaccine, especially HIV-specific CD8+ immune responses.

Specific T cells		IFN-γ^+ and/or IL-2^+ Median Frequency (%) Ad5 seronegative (n = 36–39)	Ad5 seropositive (n = 66–75)	p value
Gag	CD4	0.064 (0.041–0.083)	0.060 (0.032–0.099)	0.4
	CD8	0.088 (0.051–0.236)	0.017 (0.000–0.090)	<0.0001***
Nef	CD4	0.040 (0.015–0.071)	0.018 (0.003–0.036)	0.007***
	CD8	0.271 (0.121–0.819)	0.080 (0.009–0.307)	0.0005***
Pol	CD4	0.017 (0.003–0.041)	0.012 (0.000–0.030)	0.3
	CD8	0.112 (0.044–0.316)	0.042 (0.009–0.106)	0.001**

Median (25%–75% percentile),
*: p<0.05;
**: p<0.01,
***

Decreased Pre-existing Ad5 Capsid and Ad35 Neutralizing Antibodies Increase HIV-1 Infection Risk in the Step Trial Independent of Vaccination *Cheng C. et al Plos One 2012*

Conclusions: Together, these findings suggest that the case subjects were less immunologically responsive prior to infection. Subjects infected during the Step trial had qualitative differences in immunity that increased their risk of HIV-infection independent of vaccination.

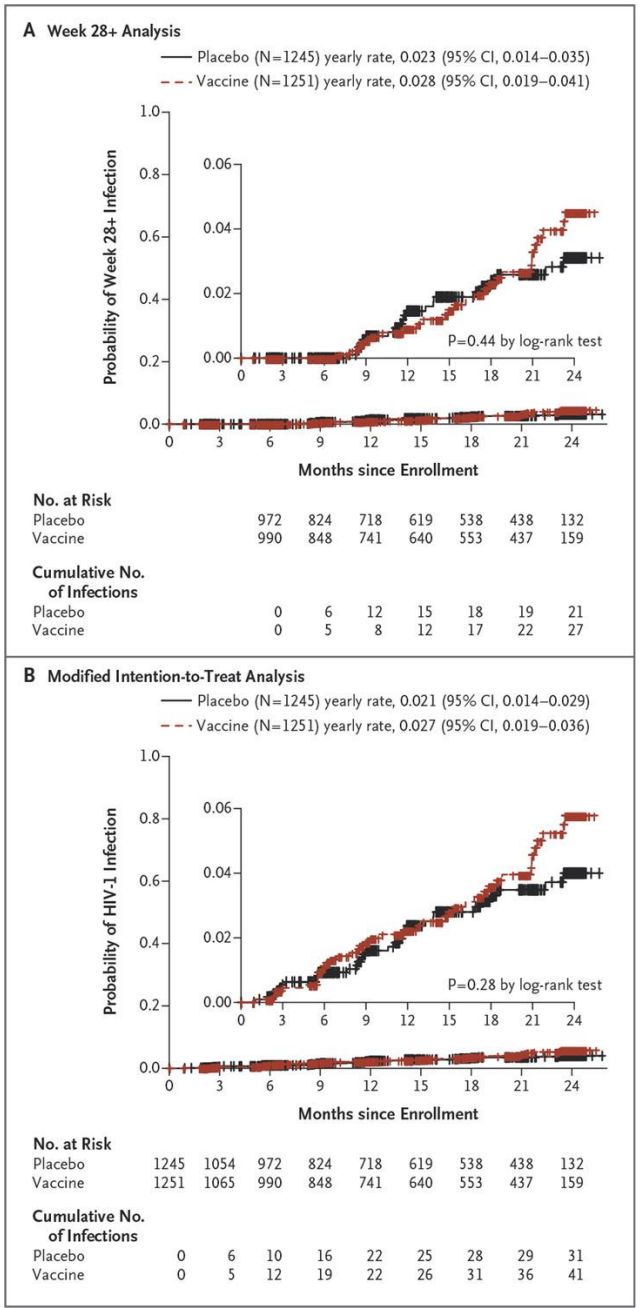
MALAS NOTICIAS CONFIRMADAS EN EL ESTUDIO 505

NIH halts trial of HIV prevention vaccine on lack of efficacy. April 2013

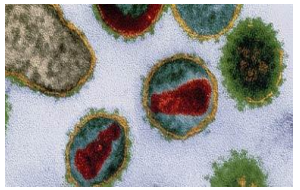
NIH's National Institute of Allergy and Infectious Diseases (NIAID) discontinued the Phase IIb HVTN 505 trial to prevent HIV infection after an interim analysis showed a lack of efficacy of the vaccine regimen in the trial. An independent DSMB found that the VRC DNA/rAd5 HIV vaccine regimen did not prevent HIV infection nor reduce viral load in vaccine recipients who became infected with HIV. The double-blind, placebo-controlled, U.S. trial enrolled 2,504 HIV-uninfected circumcised men who have sex with men and transgender people who have sex with men. All subjects received HIV risk-reduction counseling

A scheduled safety review on April 22 found that slightly more volunteers who had received the vaccine later became infected with HIV. Overall, 41 cases of HIV infection occurred in the volunteers who received the experimental vaccine and 30 cases of HIV infection occurred among the recipients who received the dummy injection.

Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine
Scott M. Hammer. NEJM 2013 N Engl J Med 2013; 369:2083-2092



UNA VACUNA FRENTE AL VIH



ETAPAS EN EL DESARROLLO DE UNA VACUNA FRENTE AL VIH

1984 1990 2000 2005 2010

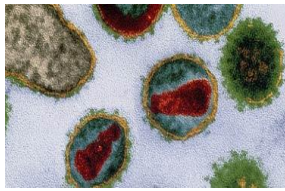
FRACASO DE LOS MODELOS CLÁSICOS
-Virus atenuados: la gran decepción
-Fracaso de vacunas inactivadas
-El espejismo de la hepatitis B
-Decepción de los anticuerpos

DESARROLLO DE NUEVOS VECTORES
-Inducción de respuestas celulares
-Ausencia de protección
-Control de la replicación
-Ensayos decepcionantes en el paso a humanos

¿HAY UN PAPEL PARA VACUNAS CELULARES POST-STEP

- ✓ **Utilizar vectores poxvirales, otros vectores**
- ✓ **Utilizar vacunas que combinen respuesta celular y Ac**
- ✓ **Vacunas celulares como vacunas terapeúticas**

COMBINACION DE VACUNAS CELULARES Y HUMORALES: canarypox+gp120

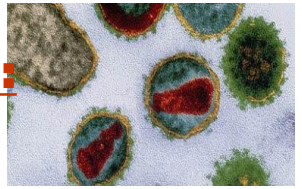


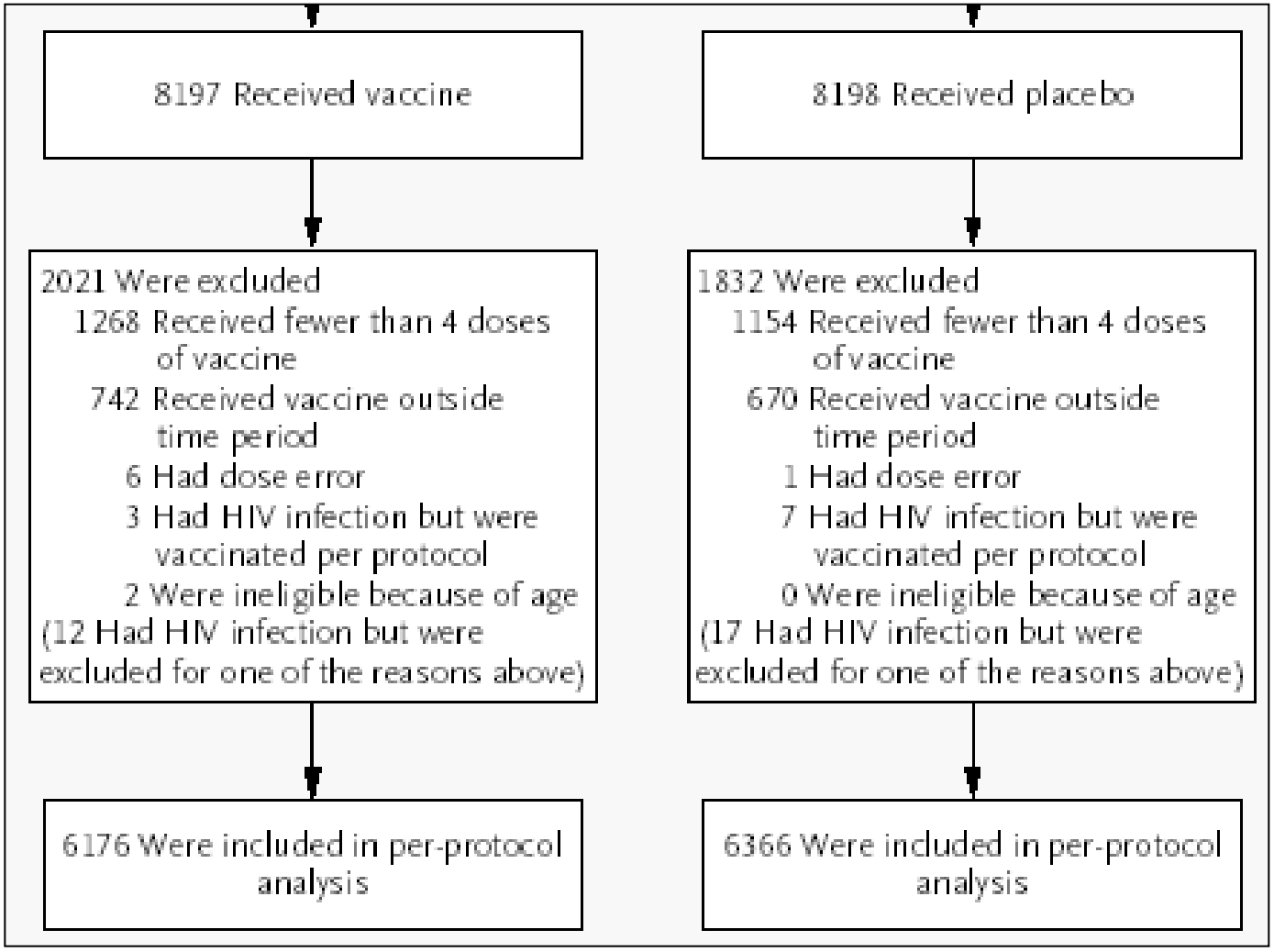
The NEW ENGLAND JOURNAL of MEDICINE

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

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

COMBINACION DE VACUNAS CELULARES Y HUMORALES: canarypox+gp120





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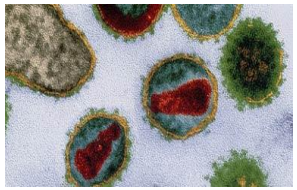
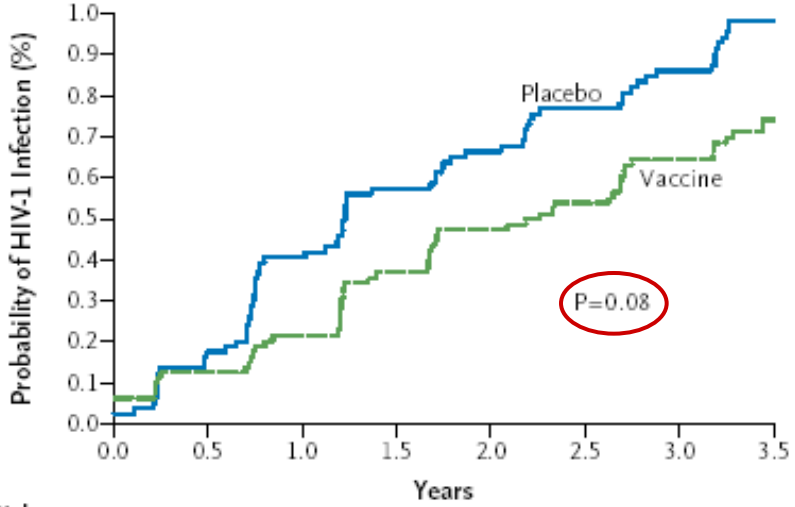
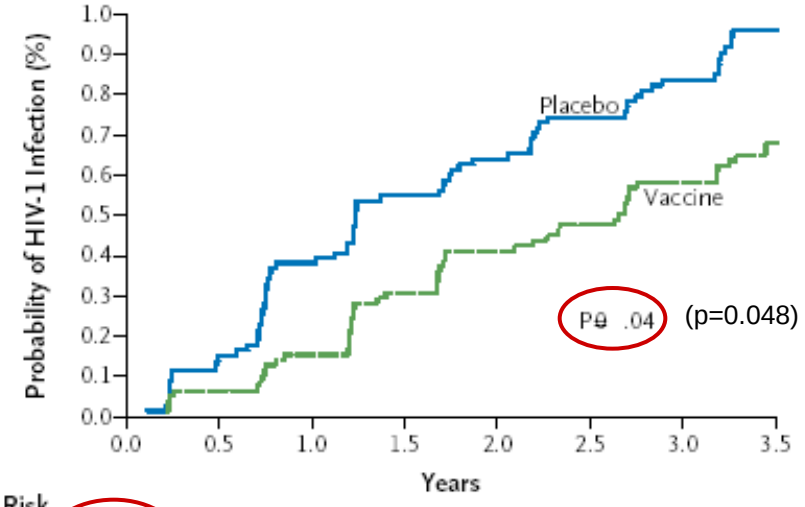


A Intention-to-Treat Analysis



No. at Risk					
Placebo	8200	7775	7643	7441	7325
Vaccine	8202	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		32	52	67	76
Vaccine		17	37	50	56

C Modified Intention-to-Treat Analysis



(p=0.048)

No. at Risk					
Placebo	8198	7775	7643	7441	7325
Vaccine	8197	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		30	50	65	74
Vaccine		12	32	45	51

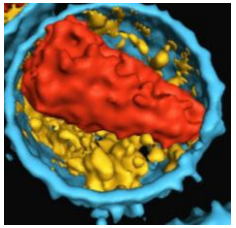
Cumulative No. of Infections

Placebo	30	50	65	74
Vaccine	12	32	45	51

Cumulative No. of Infections

Placebo	32	52	67	76
Vaccine	17	37	50	56

IMMUNE-CORRELATES ANALYSIS OF RV144 TRIAL



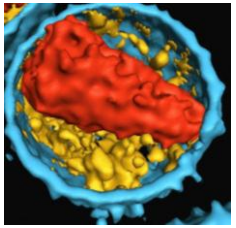
ANALISIS MULTIVARIABLE

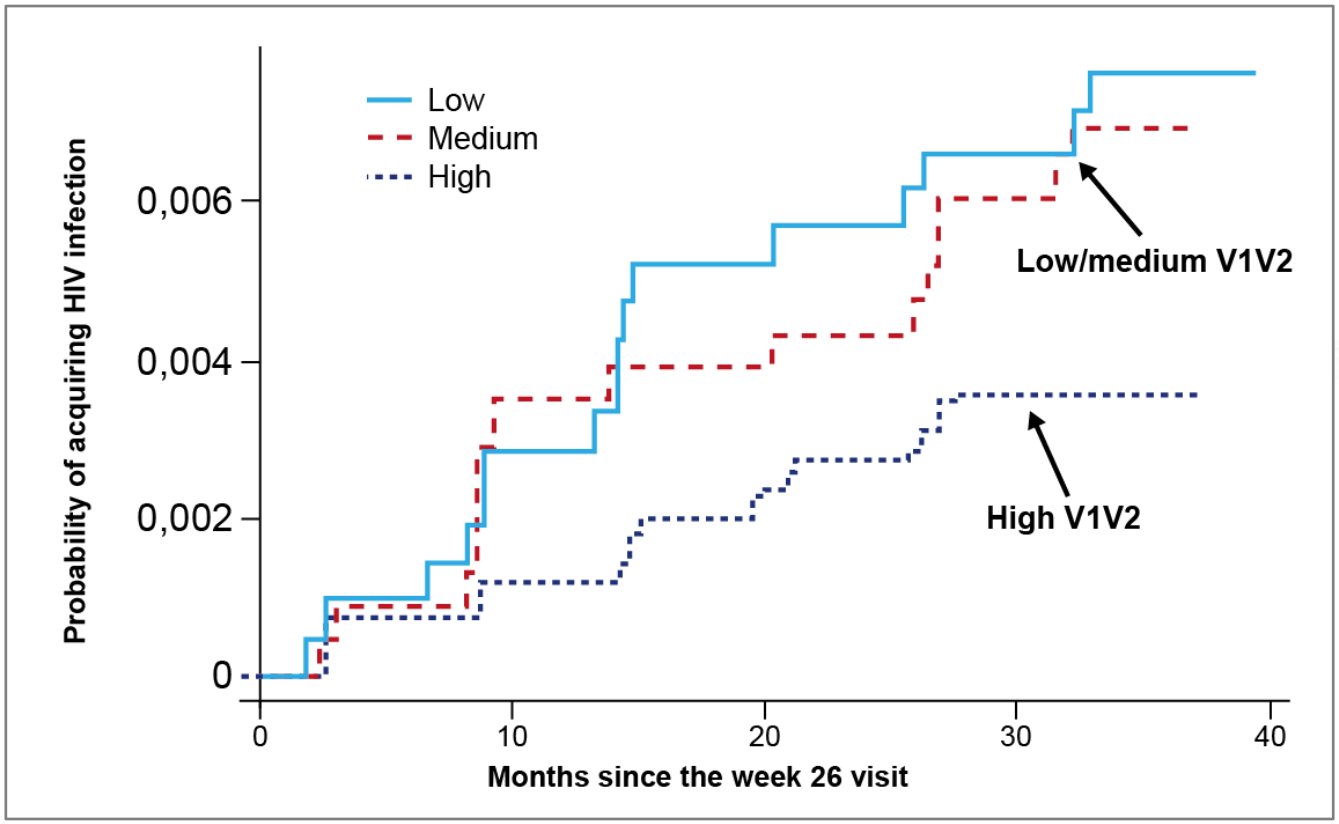
Variable	Relative risk	P-value	Q-value
IgA Binding to Envelope Panel	1.54	0.027	0.08
IgG Avidity A244 gp120	0.81	0.37	0.56
ADCC AE.HIV-1 Infected CD4 Cells	0.92	0.68	0.68
Tier 1 Neutralizing Antibodies	1.37	0.22	0.45
IgG Binding to gp70-V1V2	0.57	0.015	0.08
CD4+ T Cell Intracellular Cytokines	1.09	0.61	0.68

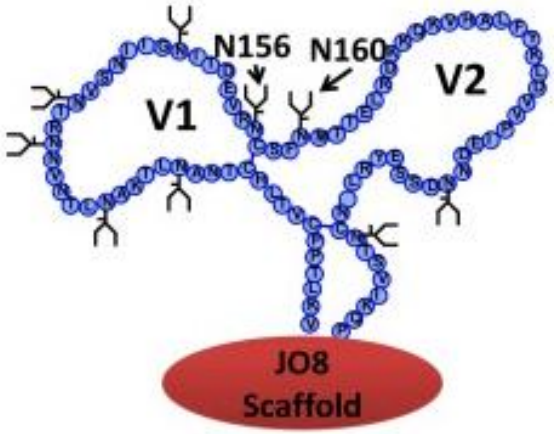
Haynes BF. N Engl J Med. 2012;366:1275-86

IMMUNE-CORRELATES ANALYSIS OF RV144 TRIAL

Haynes BF N Engl J Med. 2012;366:1275-86



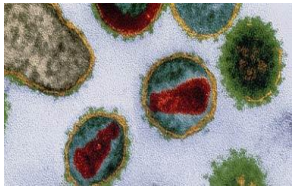




- El grado de protección de los pacientes con altos niveles de anticuerpos que unían la proteína recombinante gp70-V1V2 fue del 60%.
- ¿Es este un parámetro sustitutivo de protección o es únicamente un marcador de aquellos pacientes que desarrollaron una respuesta eficaz?

Haynes BF. N Engl J Med. 2012;366:1275-86

LA BUSQUEDA DE UNA VACUNA FRENTE AL VIH



1984 1990 2000 2005 2010 2015

1984-2004. FRACASO DE LOS MODELOS CLASICOS

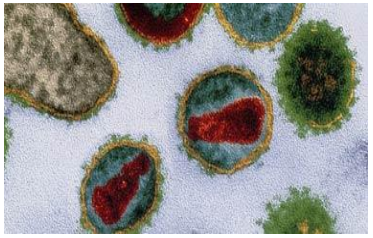
2000-2008 (2014) VACUNAS CELULARES

2005-2013
ESTUDIOS SOBRE ANTICUERPOS NEUTRALIZANTES
NUEVA GENERACION DE VACUNAS HUMORALES

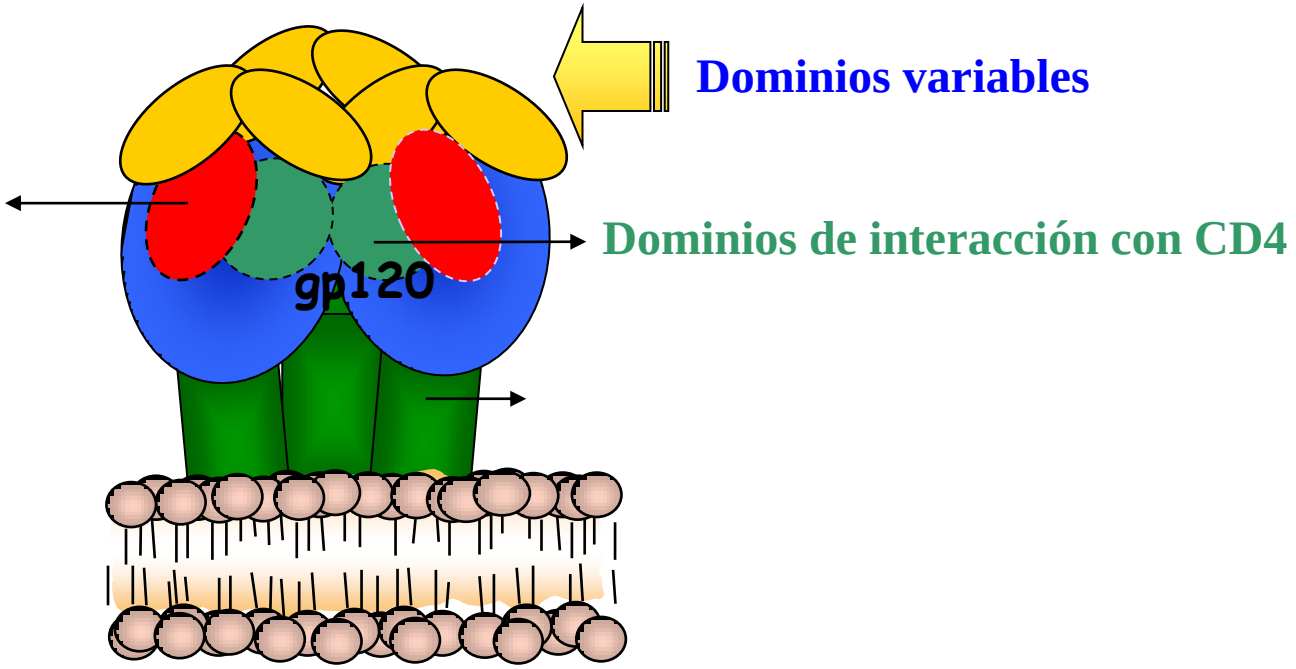
DOS GRANDES DESAFIOS
1. **GENERAR ANTICUERPOS DE AMPLIO ESPECTRO**
2. **GENERAR ANTICUERPOS DE ALTA AFINIDAD**

GENERAMOS ANTICUERPOS DE MALA CALIDAD
- **ESPECTRO DE NEUTRALIZACION REDUCIDO**
- **BAJA AFINIDAD**

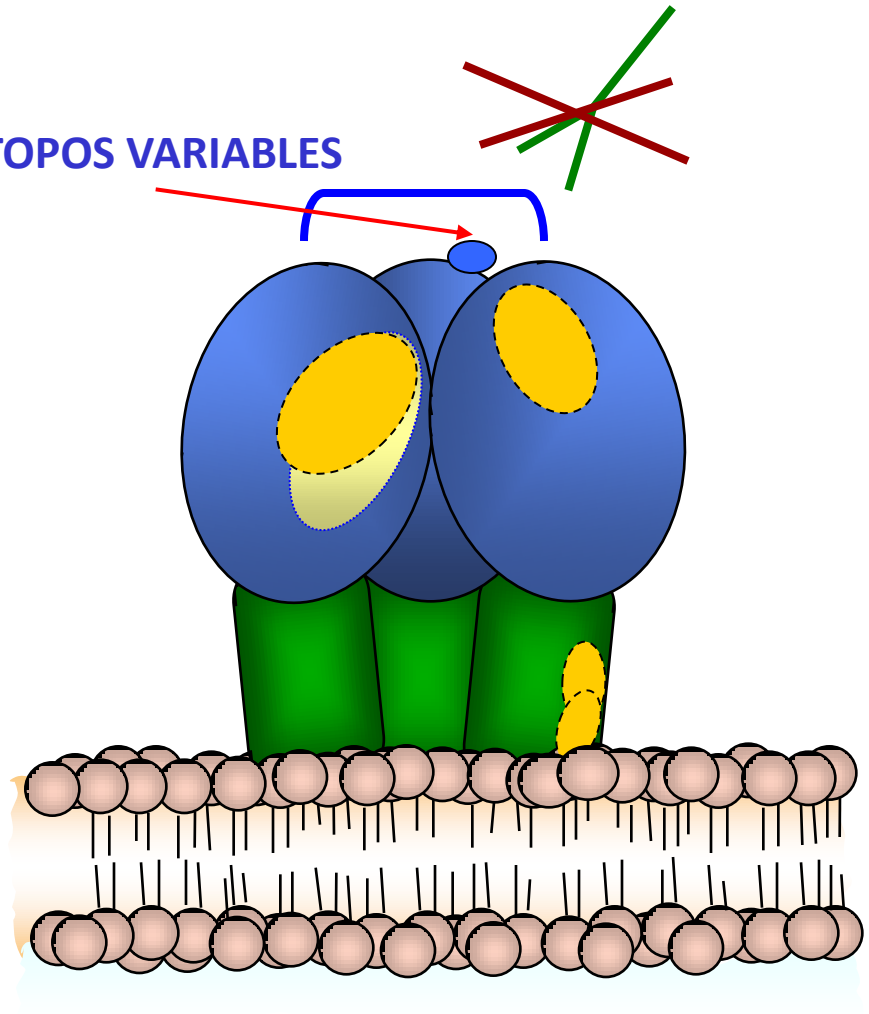
MECANISMOS DE ESCAPE A LOS ANTICUERPOS



1- ESTRUCTURA DE LA ENVUELTA VIRAL
2- MUTACION DE LOS DOMINIOS VARIABLES
3. GLICOSILACIÓN



2. MUTACION DE LOS DOMINIOS VARIABLES

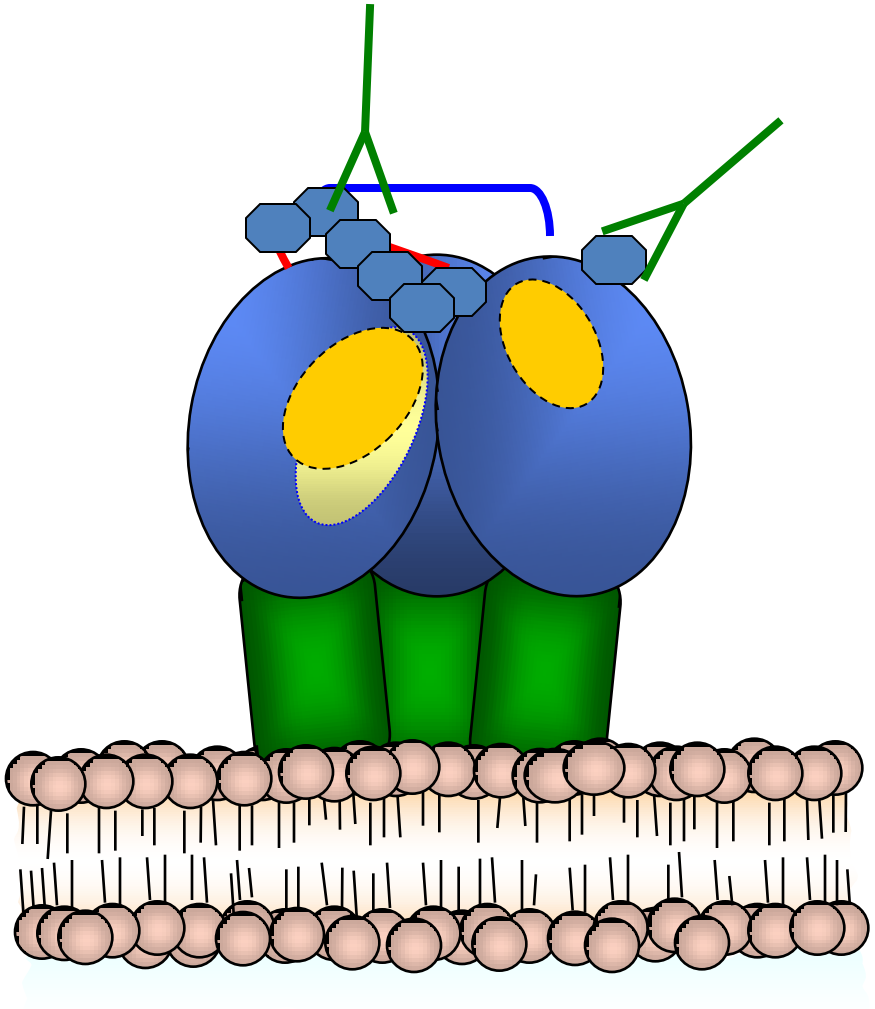


(Burton D. Human neutralizing antibodies and a vaccine for HIV-1. XIV International AIDS Conference [Abstract nº201])

MECANISMOS DE ESCAPE A LOS ANTICUERPOS

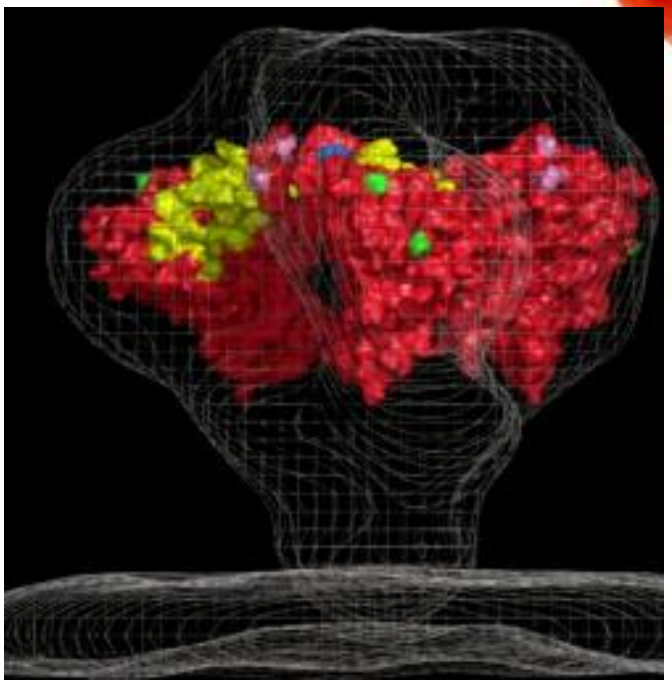
3. GLICOSILACION

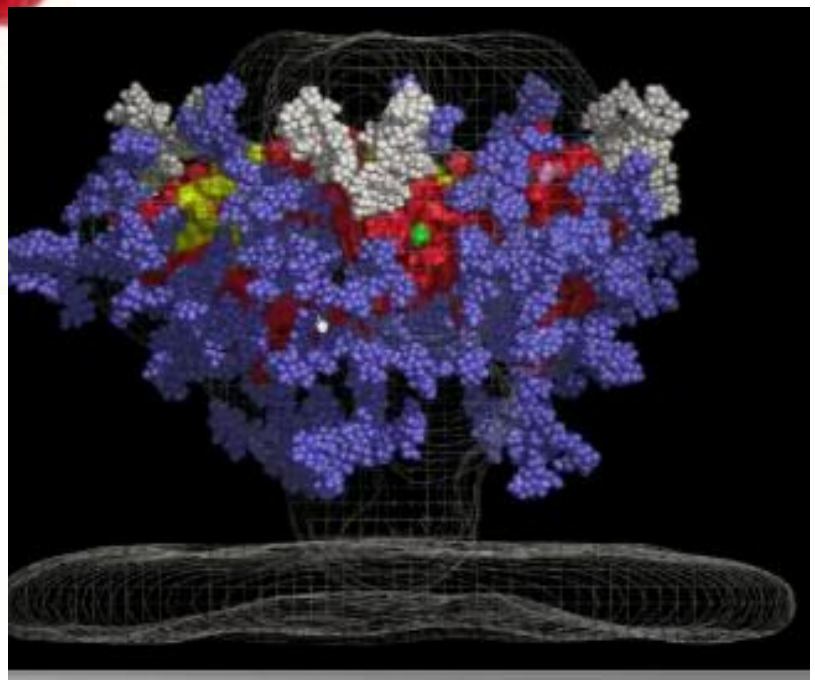
Viral envelope



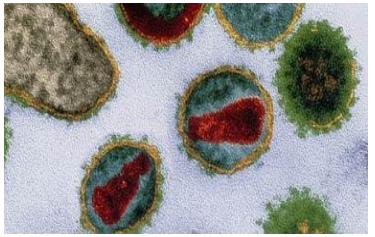
MECANISMOS DE ESCAPE A LOS ANTICUERPOS

3. GLICOSILACION





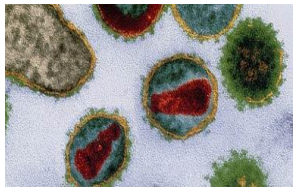
UNA VACUNA FRENTE AL VIH
EL DESAFIO: GENERAR ANTICUERPOS



Mecanismos de escape viral de anticuerpos neutralizantes

-**Enmascaramiento epitópico**
  variación epitópica
-**Glicosilación residuos**
  enmascaramiento por glicosilación
-**Inaccesibilidad en la forma trimérica de la proteína**
  exclusión oligomérica
-**Ocultamiento por la conformación de la proteína nativa**
  enmascaramiento entrópico
-**Enmascaramiento por carbohidratos de residuos adyacentes**
  escudo glicano

LA BUSQUEDA DE UNA VACUNA FRENTE AL VIH



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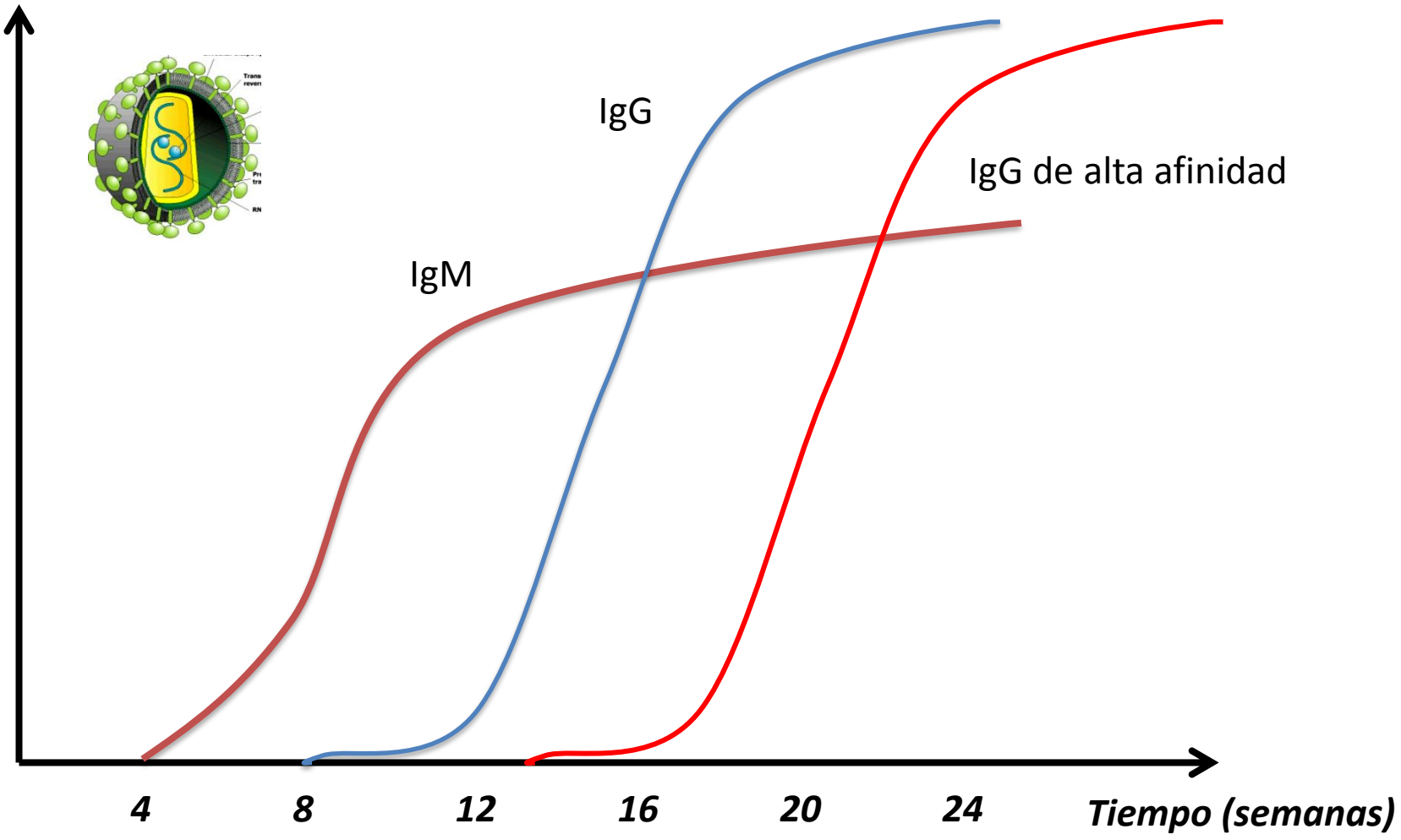
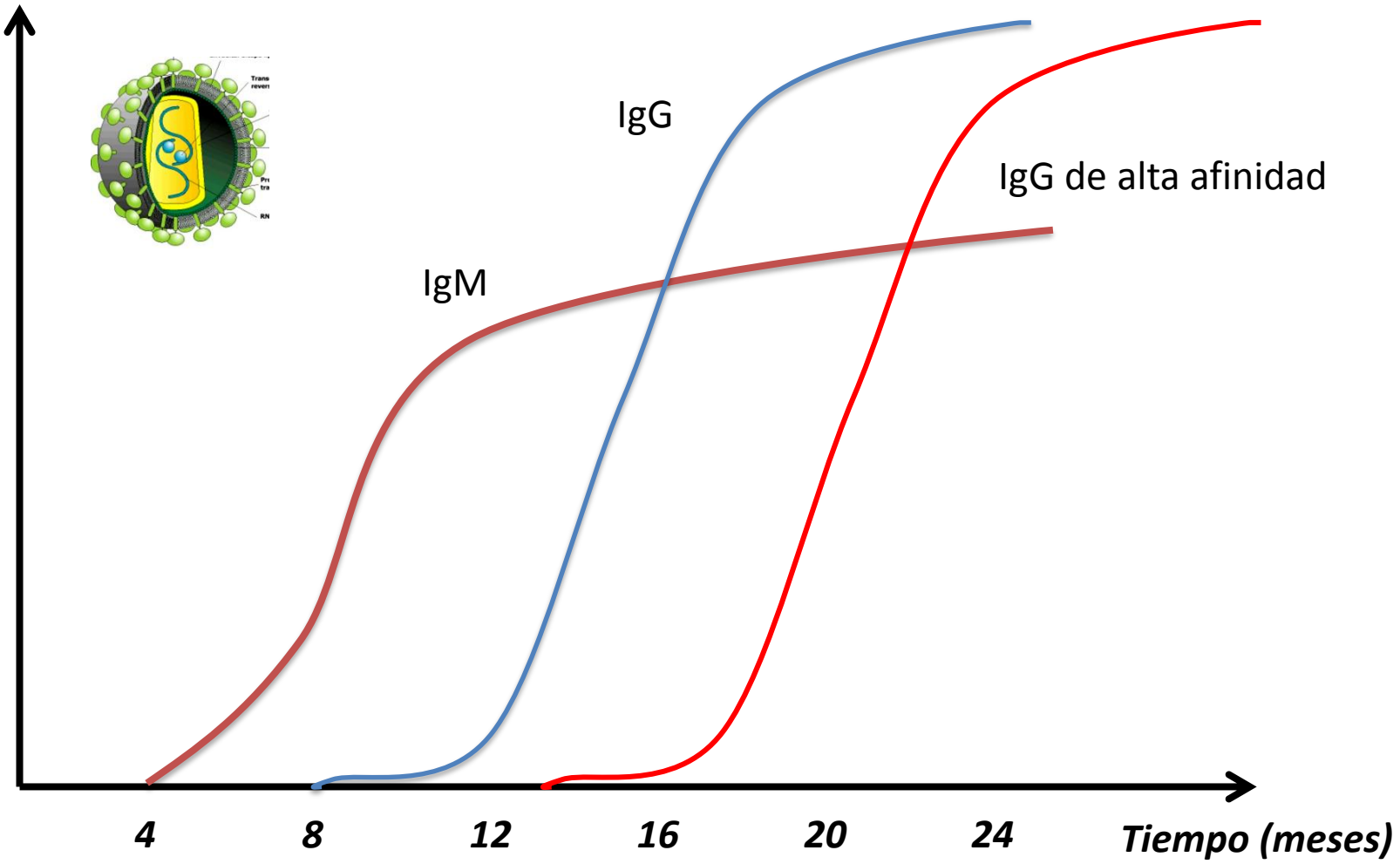
GENERAMOS ANTICUERPOS DE MALA CALIDAD
- **ESPECTRO REDUCIDO**
- **BAJA AFINIDAD**

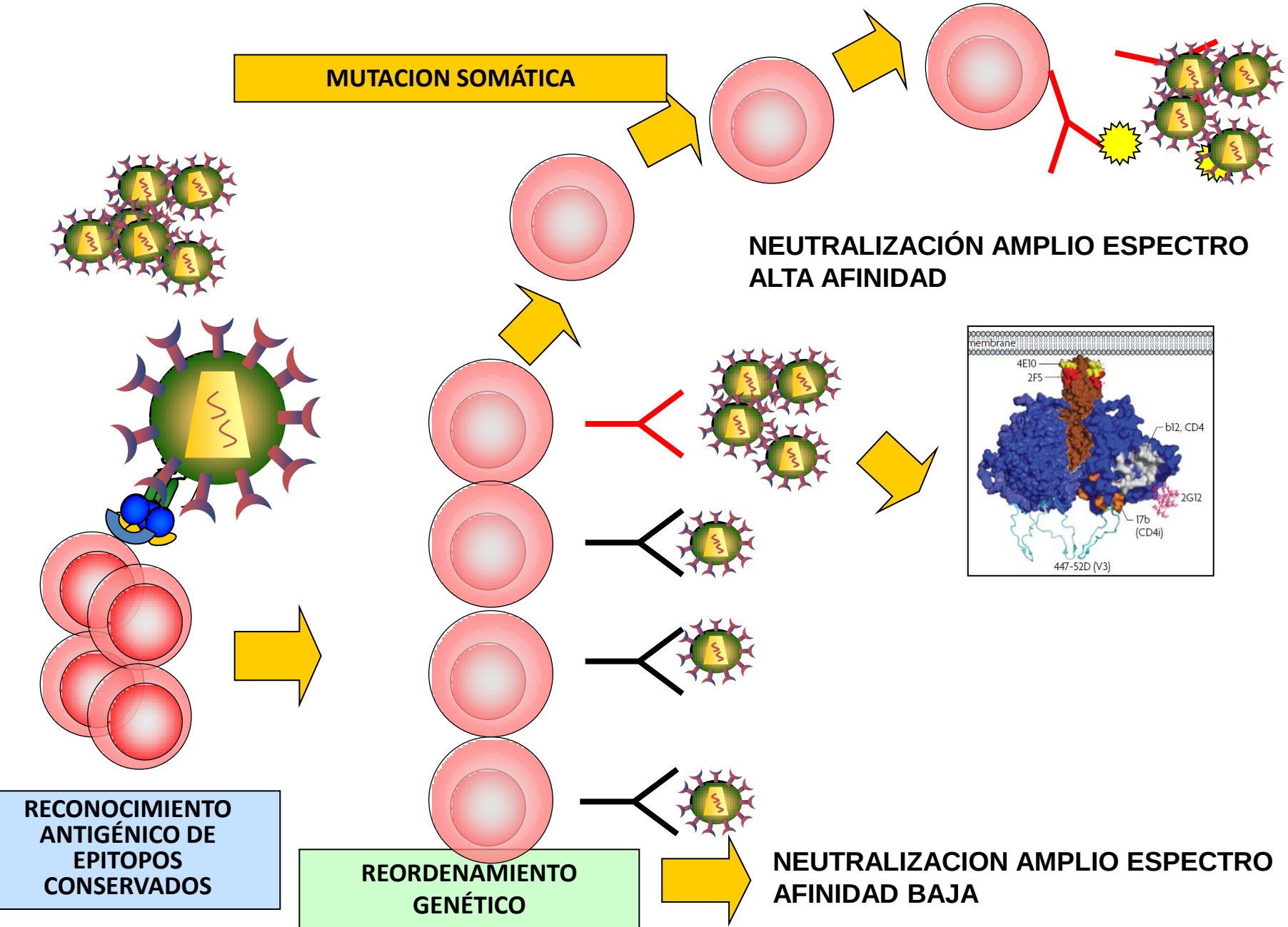
2. DINAMICA DE GENERACION DE ANTICUERPOS DE ALTA AFINIDAD EN INFECCIONES VIRICAS



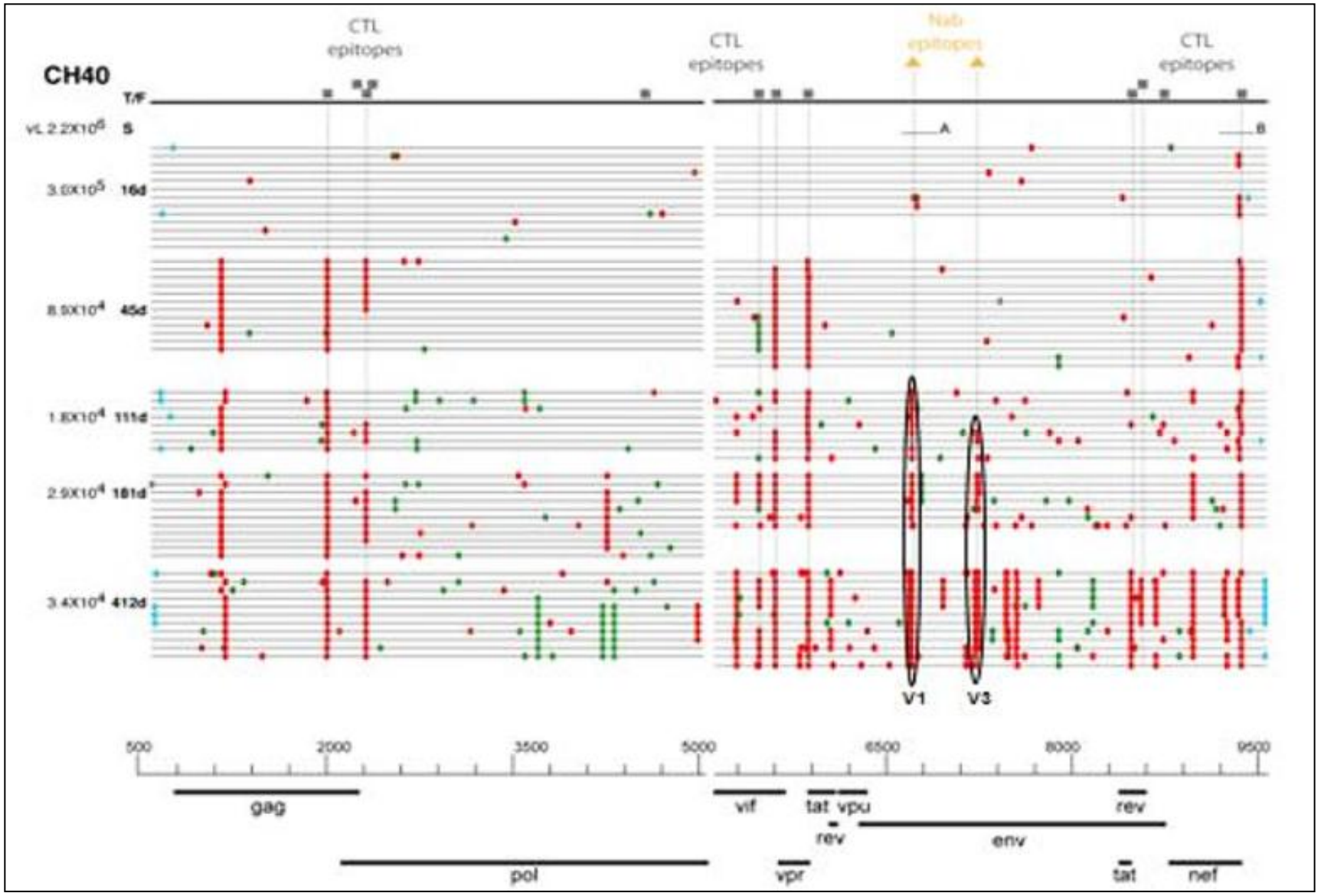
2. GENERACION LENTA DE ANTICUERPOS DE ALTA AFINIDAD EN LA INFECCION POR VIH



DESAFIO DE LA RESPUESTA HUMORAL Y DE TODA VACUNA
GENERACION DE ANTICUERPOS DE AMPLIO ESPECTRO Y ALTA AFINIDAD

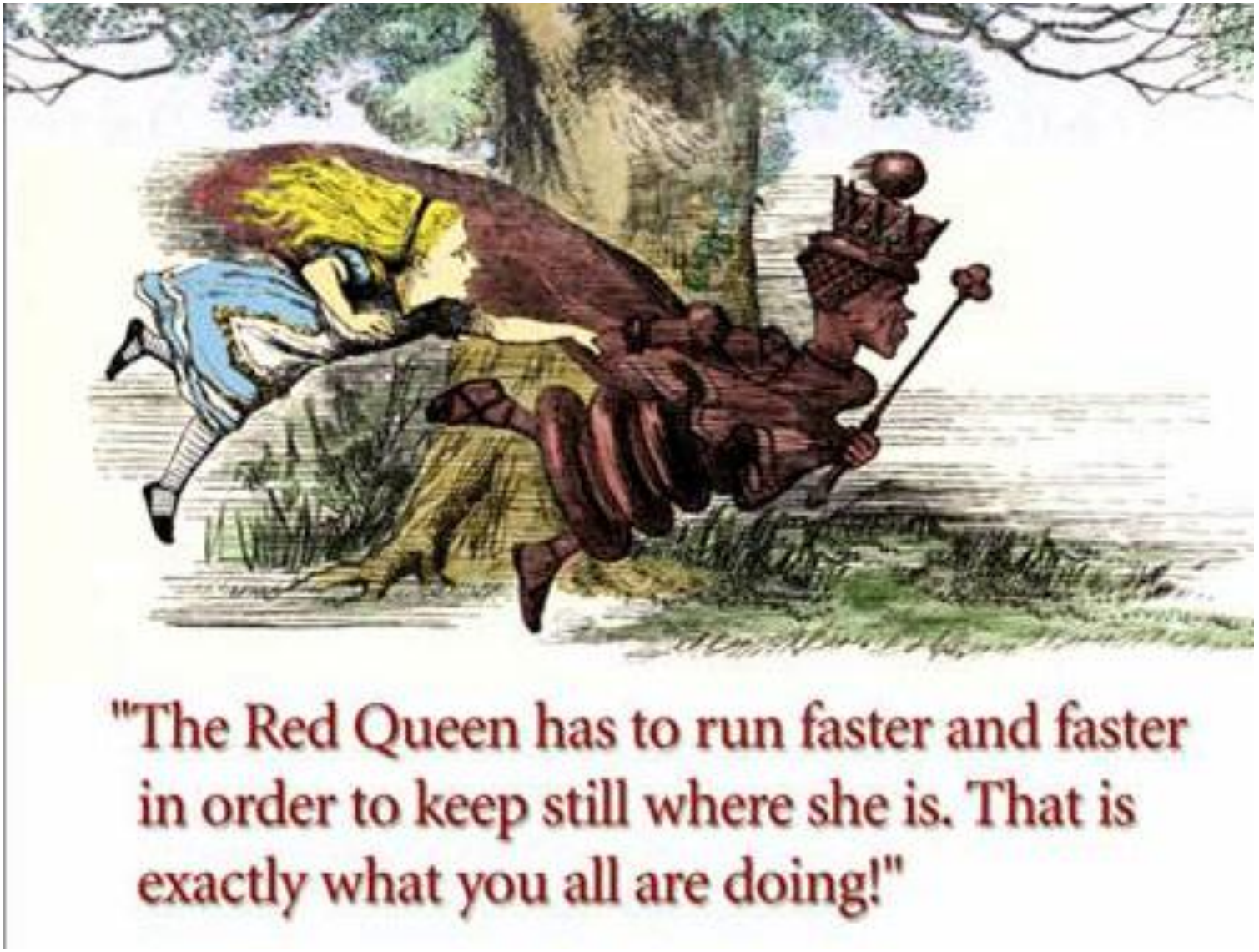


LA ENVUELTA SE MODIFICA A MEDIDA QUE SE INDUCEN AC

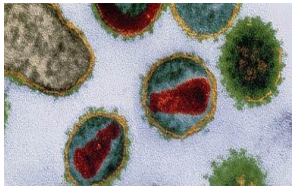


Salazar-Gonzalez JF, et al. J Exp Med. 2009 ;206:1273-89. Keele BF, et al. PNAS 2008;105:7552-7

Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. *Liao HX et al. Nature 2013*



UNA VACUNA FRENTE AL VIH



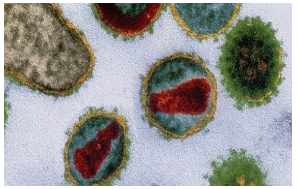
2014

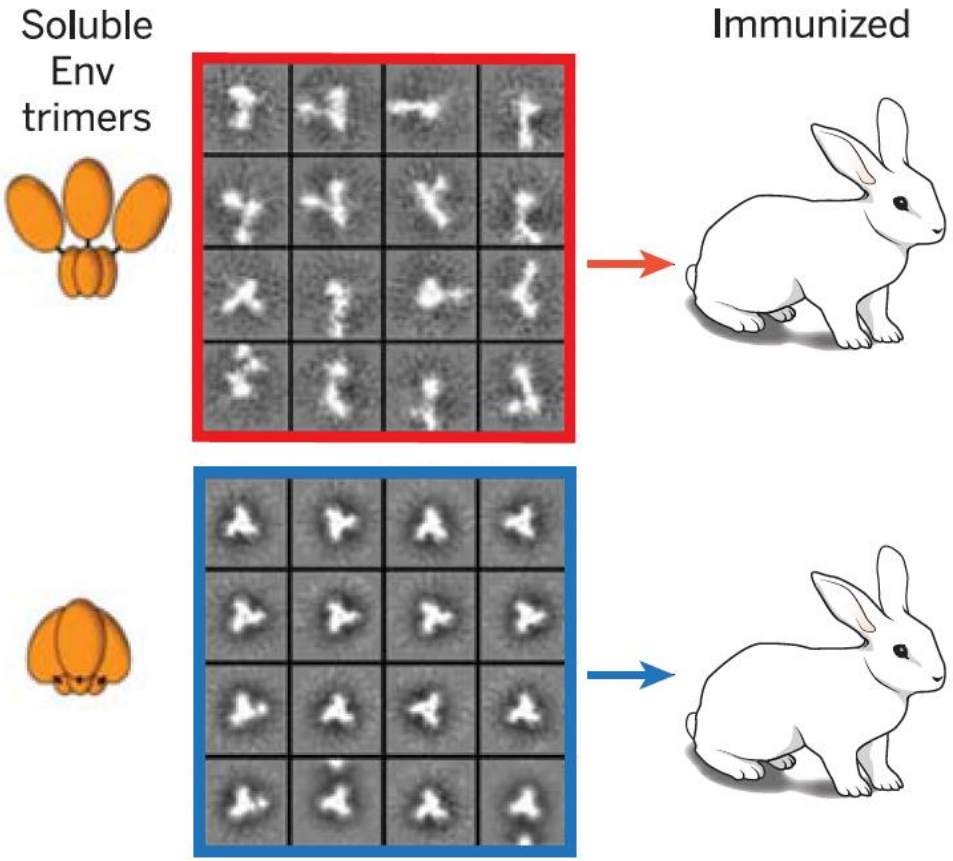
NUEVAS ESTRATEGIAS

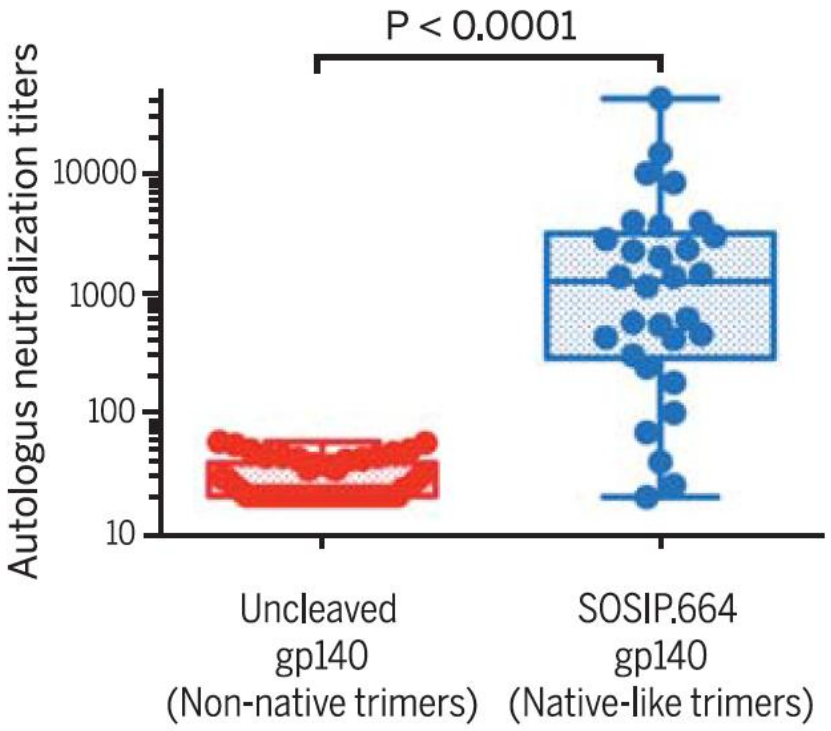
VACUNAS PREVENTIVAS
- **UTILIZAR ENVUELTAS TRIMERICAS**
- **SI NO PUEDES INDUCIR ANTICUERPOS REGALASELOS**

VACUNAS TERAPEUTICAS
- **COMBINACION CON FARMACOS ANTILATENCIA**

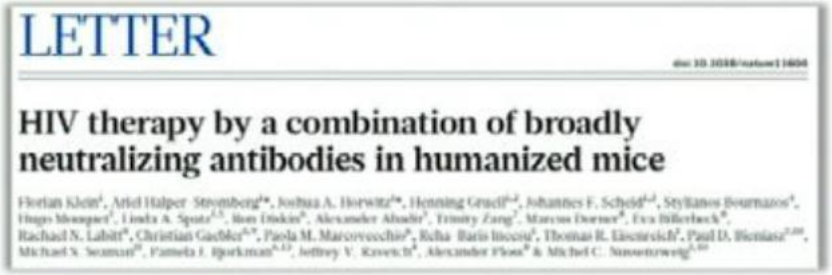
ENVUELTAS TRIMERICAS







Antibodies Work Therapeutically in Animal Models

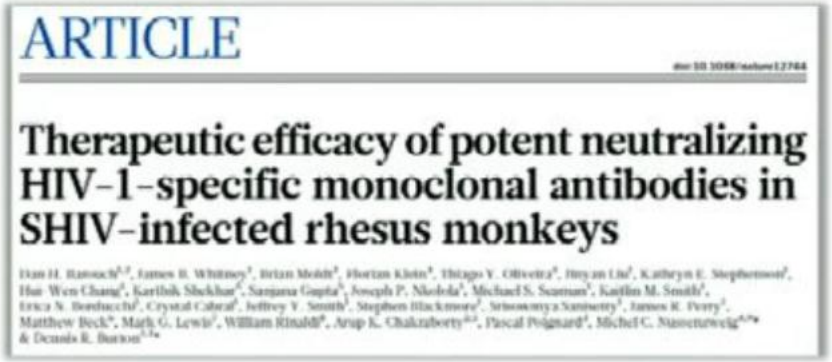


LETTER

HIV therapy by a combination of broadly neutralizing antibodies in humanized mice

Florian Klein[1], Ariel Halper-Stromberg[2]*, Joshua A. Horwitz[3]*, Henning Gruell[1,2], Johannes F. Scheid[1,2], Stylianos Bournazos[3], Hugo Mouquet[1], Linda A. Spatz[1,3], Ron Diskin[3], Alexander Abadir[3], Timothy Zang[3], Marcus Dorner[4], Eva Billerbeck[4], Rachael N. Labitt[4], Christian Gaebler[4,5], Paola M. Marcovecchio[4], Reha-Baris Incesu[3], Thomas R. Eisenreich[2], Paul D. Bieniasz[2,6], Michael S. Seaman[6], Pamela J. Bjorkman[4,12], Jeffrey V. Ravetch[3], Alexander Ploss[4] & Michel C. Nussenzweig[1,6]*

Nature 492:118-122 (2012)

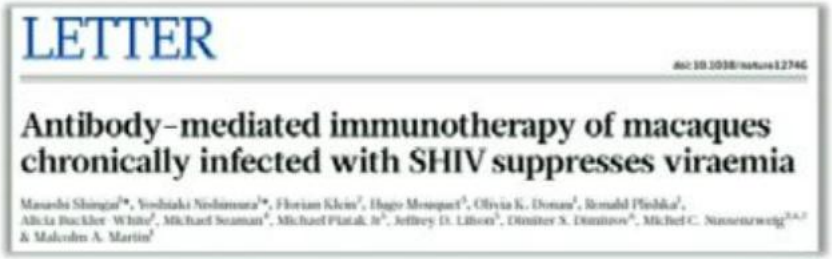


ARTICLE

Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys

Dan H. Barouch[1,2], James B. Whitney[3], Brian Moldt[4], Florian Klein[5], Thiago Y. Oliveira[6], Jinyan Liu[1], Kathryn E. Stephenson[1], Hui-Wen Chang[1], Karthik Shekhar[7], Sanjana Gupta[3], Joseph P. Nkolola[1], Michael S. Seaman[3], Kaitlin M. Smith[1], Erica N. Borducchi[1], Crystal Cabral[1], Jeffrey Y. Smith[1], Stephen Blackmore[1], Srisowmya Sanisetty[1], James R. Perry[1], Matthew Beck[8], Mark G. Lewis[3], William Rinaldi[9], Arup K. Chakraborty[6,7], Pascal Poignard[4], Michel C. Nussenzweig[6,7]* & Dennis R. Burton[3,7]*

Nature 503:224-228 (2013)



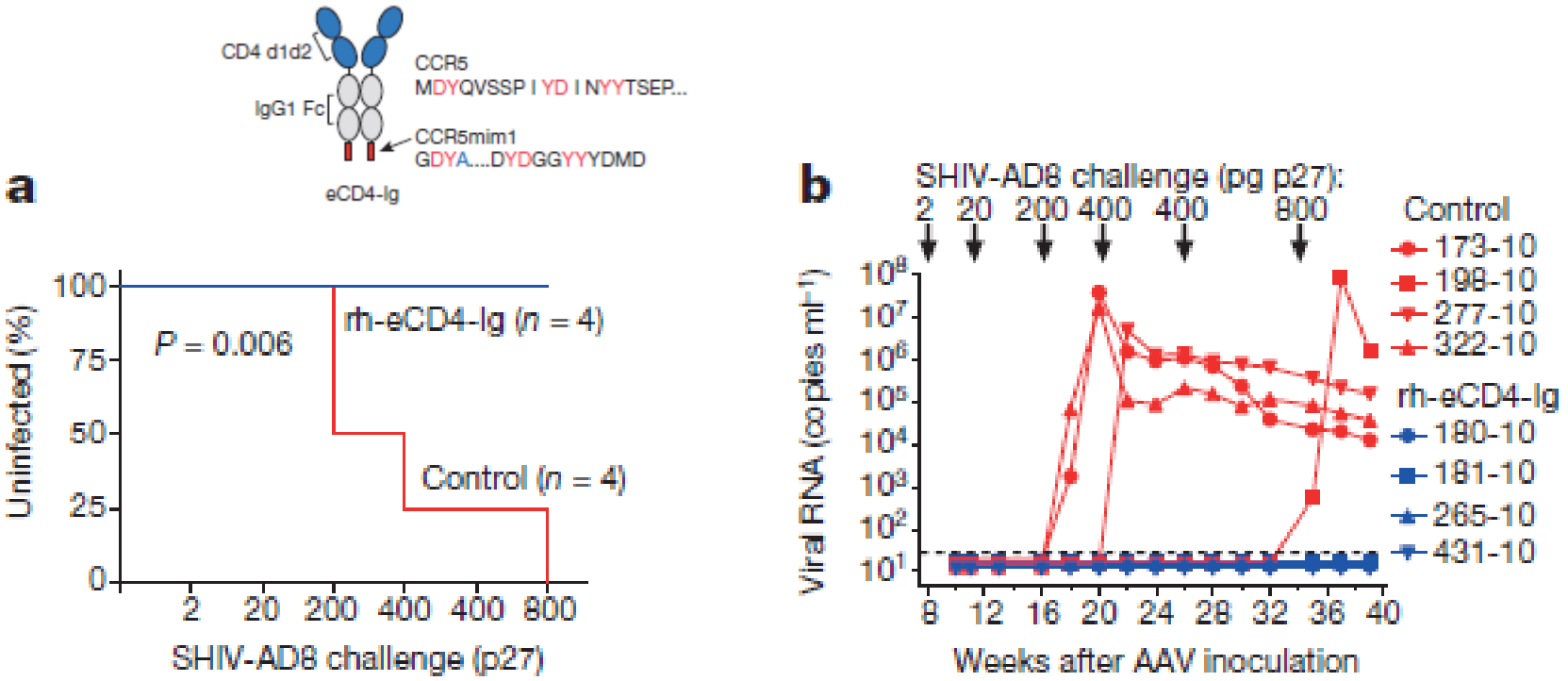
LETTER

Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia

Masashi Shingai[1]*, Yoshiaki Nishimura[1]*, Florian Klein[2], Hugo Mouquet[3], Olivia K. Donau[1], Ronald Plishka[1], Alicia Buckler-White[1], Michael Seaman[4], Michael Piatak Jr[5], Jeffrey D. Lifson[5], Dimiter S. Dimitrov[6], Michel C. Nussenzweig[2,3,7] & Malcolm A. Martin[1]

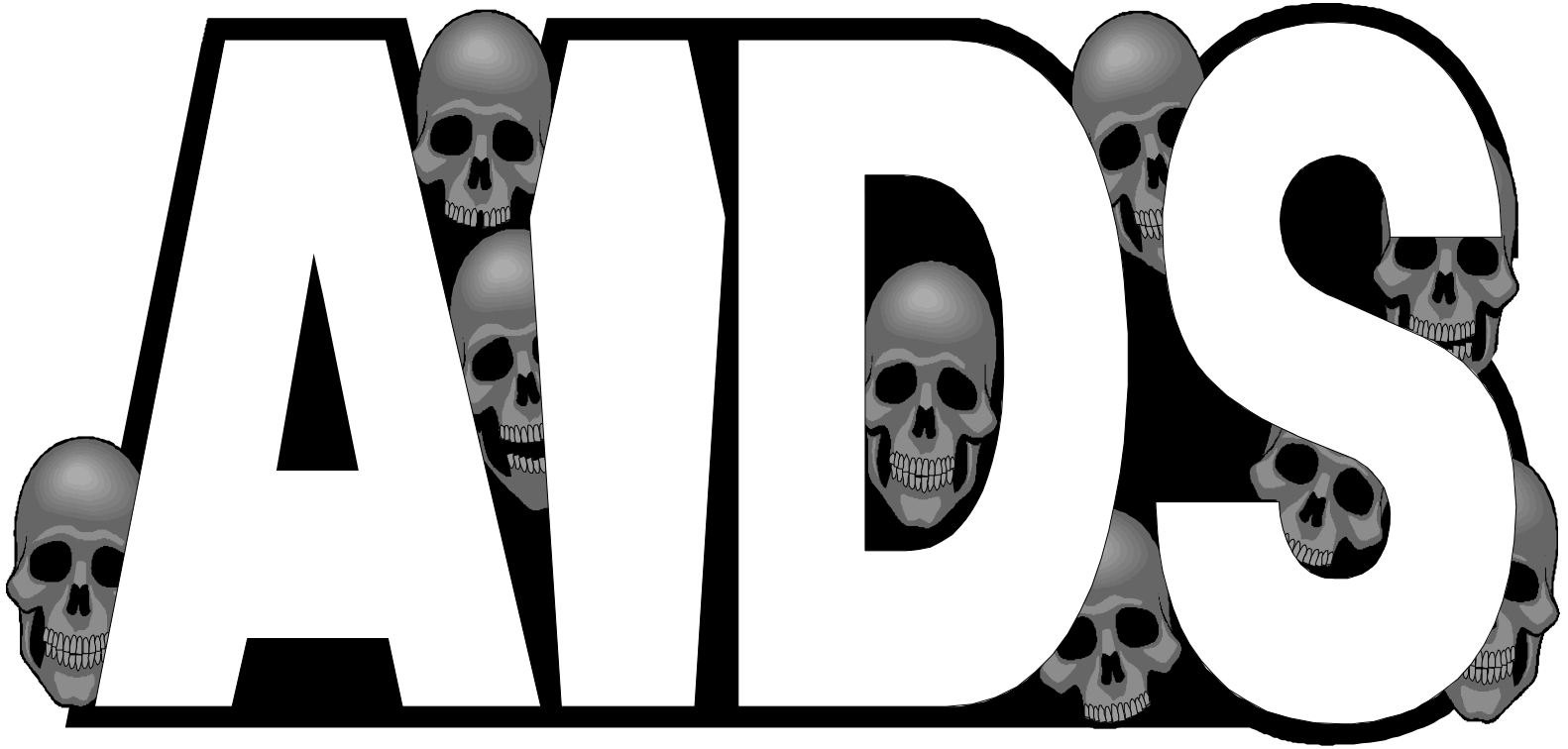
Nature 503:277-280 (2013)

GENE THERAPY. CHIMERIC PROTEINS



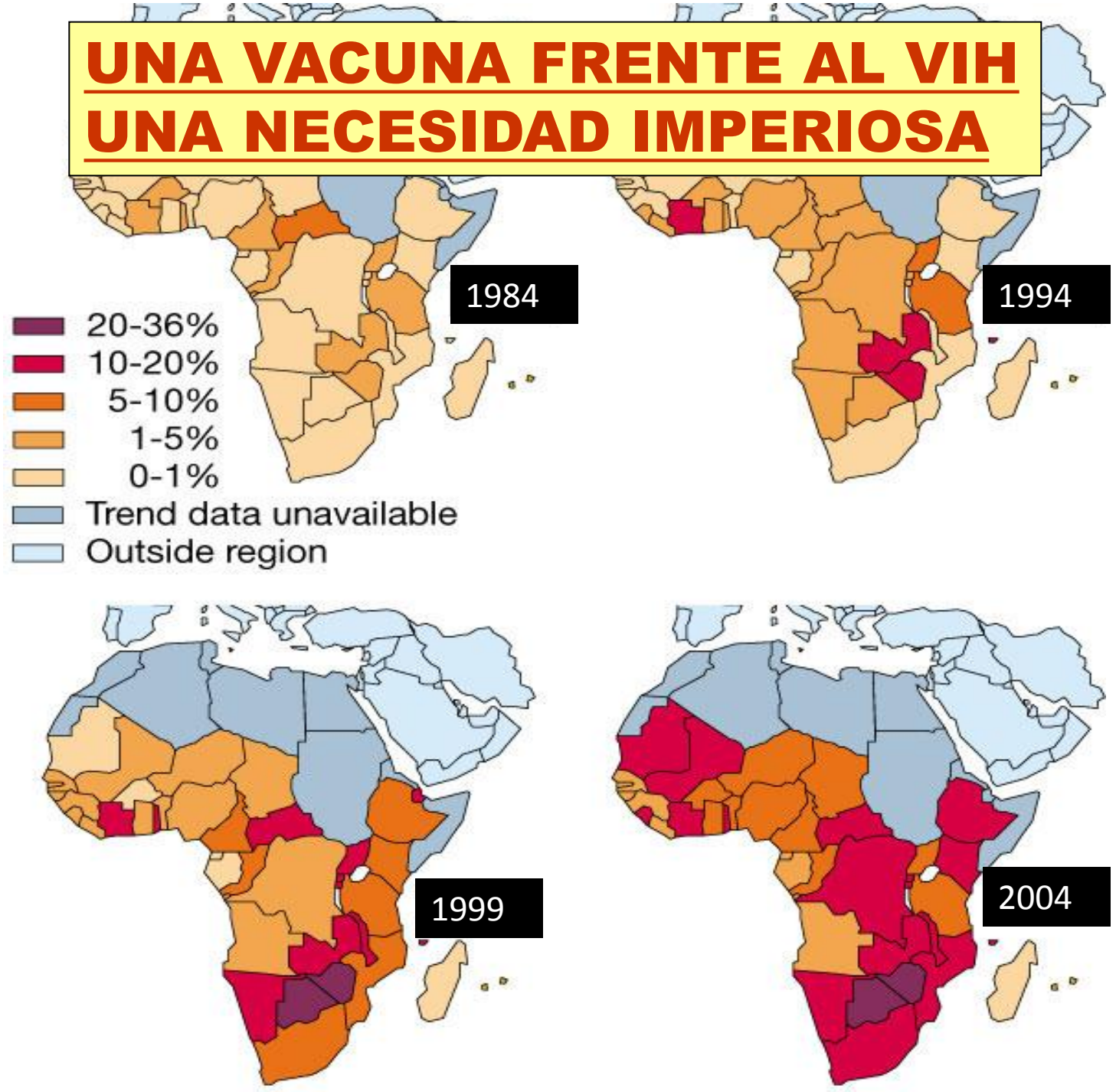
AAV-rh-eCD4-Ig protects rhesus macaques from SHIV-AD8.
a, Infection analysis comparing four male Indian-origin rhesus macaques inoculated intramuscularly with 231013 AAV particles delivering rh-eCD4-Ig (blue) and four age- and gender-matched controls (red). At 8, 11, 16, 20, 26 and 34 weeks after inoculation, macaques were challenged with the indicated p27 titres of SHIV-AD8. Significant protection (P50.006; Mantel–Cox test) was observed in the AAV-rh-eCD4-Ig-treated group. b, Viral loads of inoculated (blue) and control (red) macaques are shown, with the time and titre of challenge indicated above the graph.

Gardner et al. Nature 2015;519:87-91

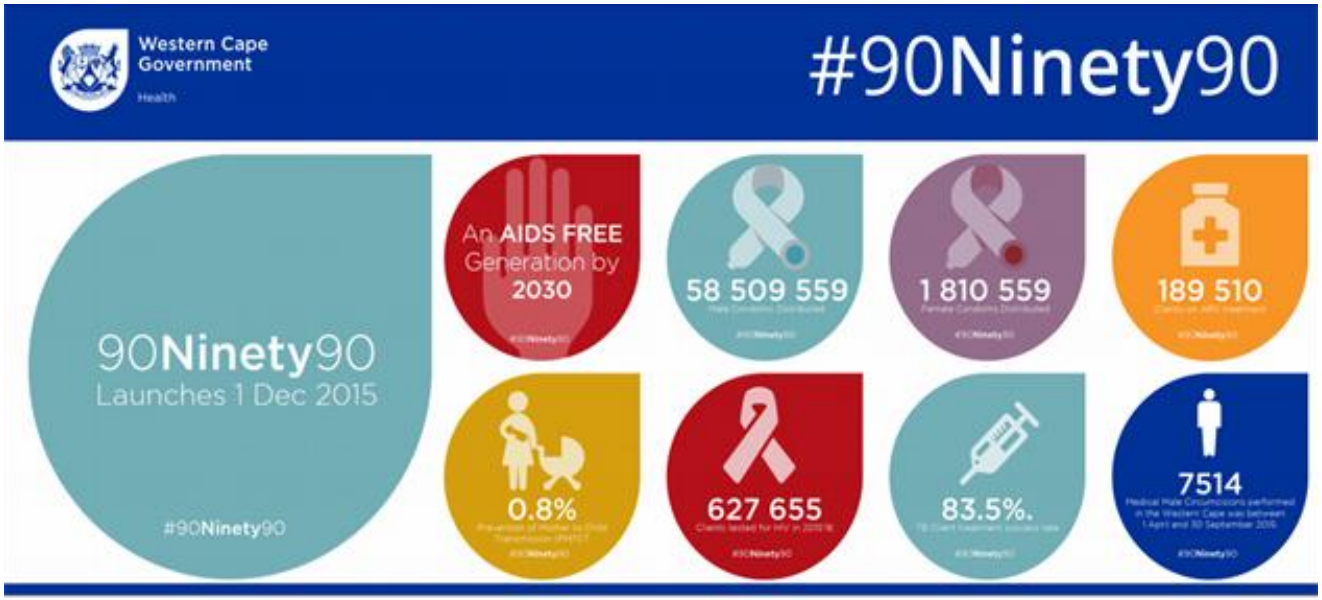

AIDS


AIDS

UNA VACUNA FRENTE AL VIH
UNA NECESIDAD IMPERIOSA



¿ESTRATEGIAS ALTERNATIVAS?



90%

of all

living with HIV will know their HIV status

90%

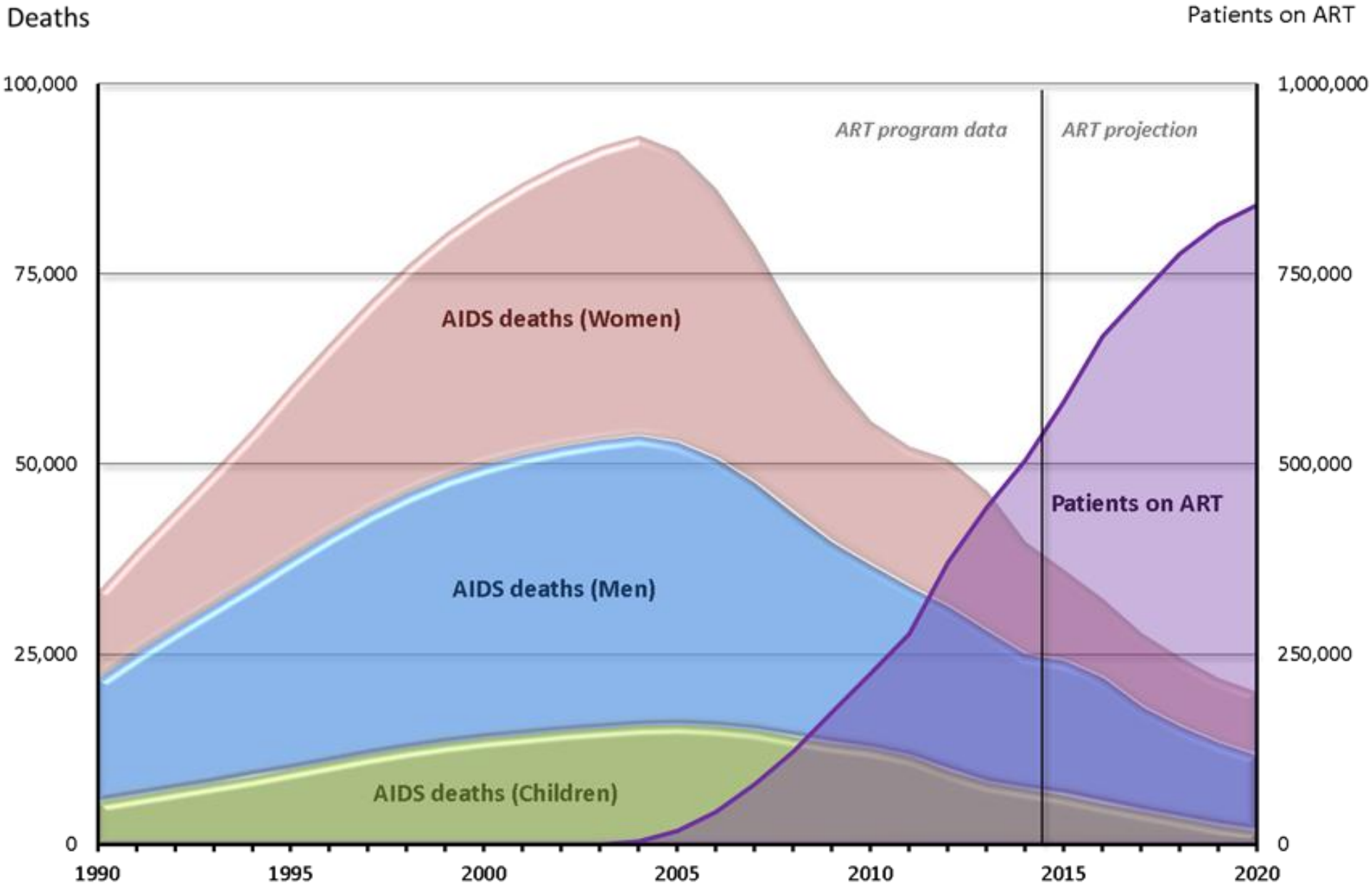
of all

living with HIV will receive antiretroviral therapy

90%

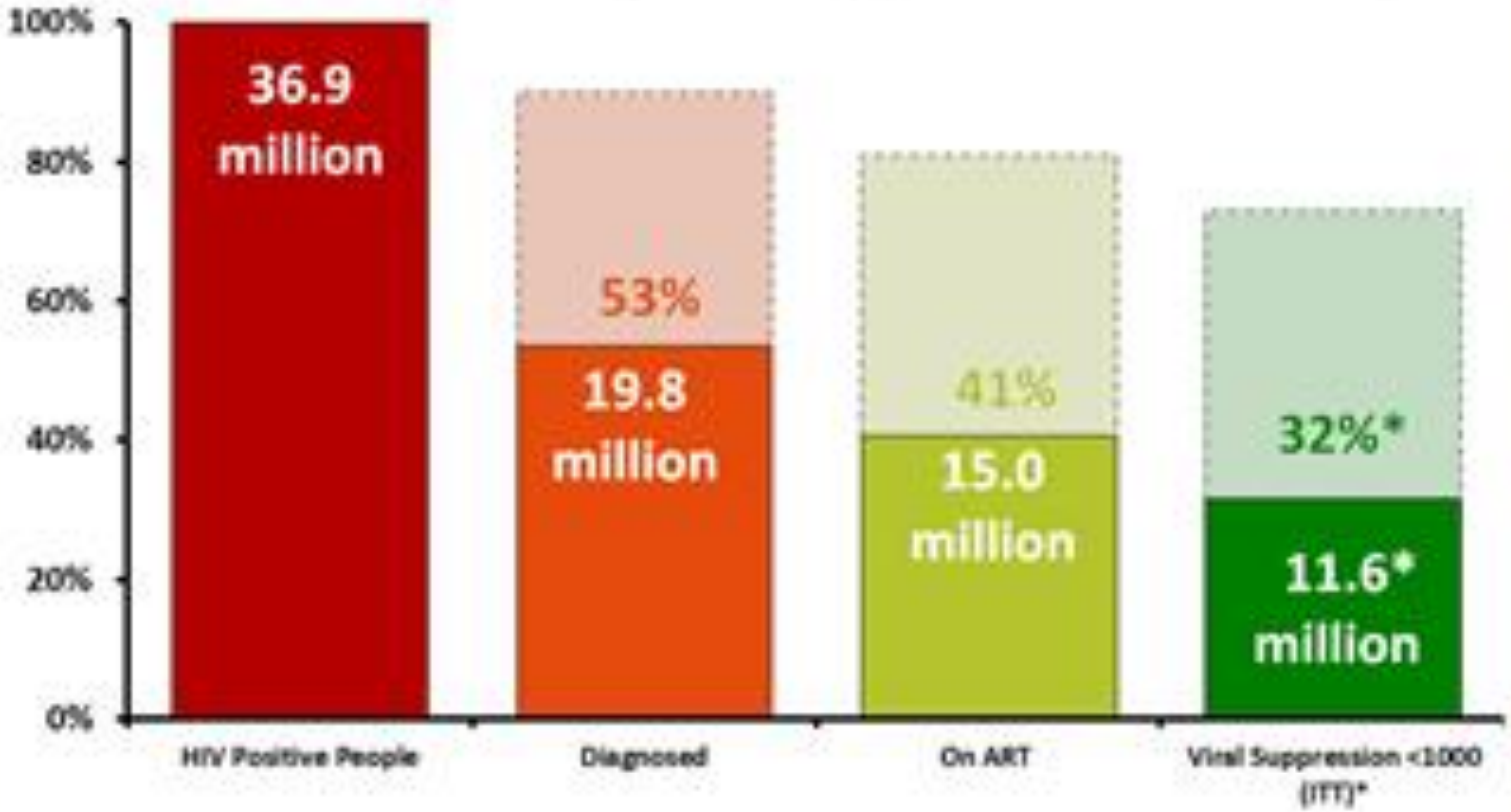
of all

receiving antiretroviral therapy will have viral suppression

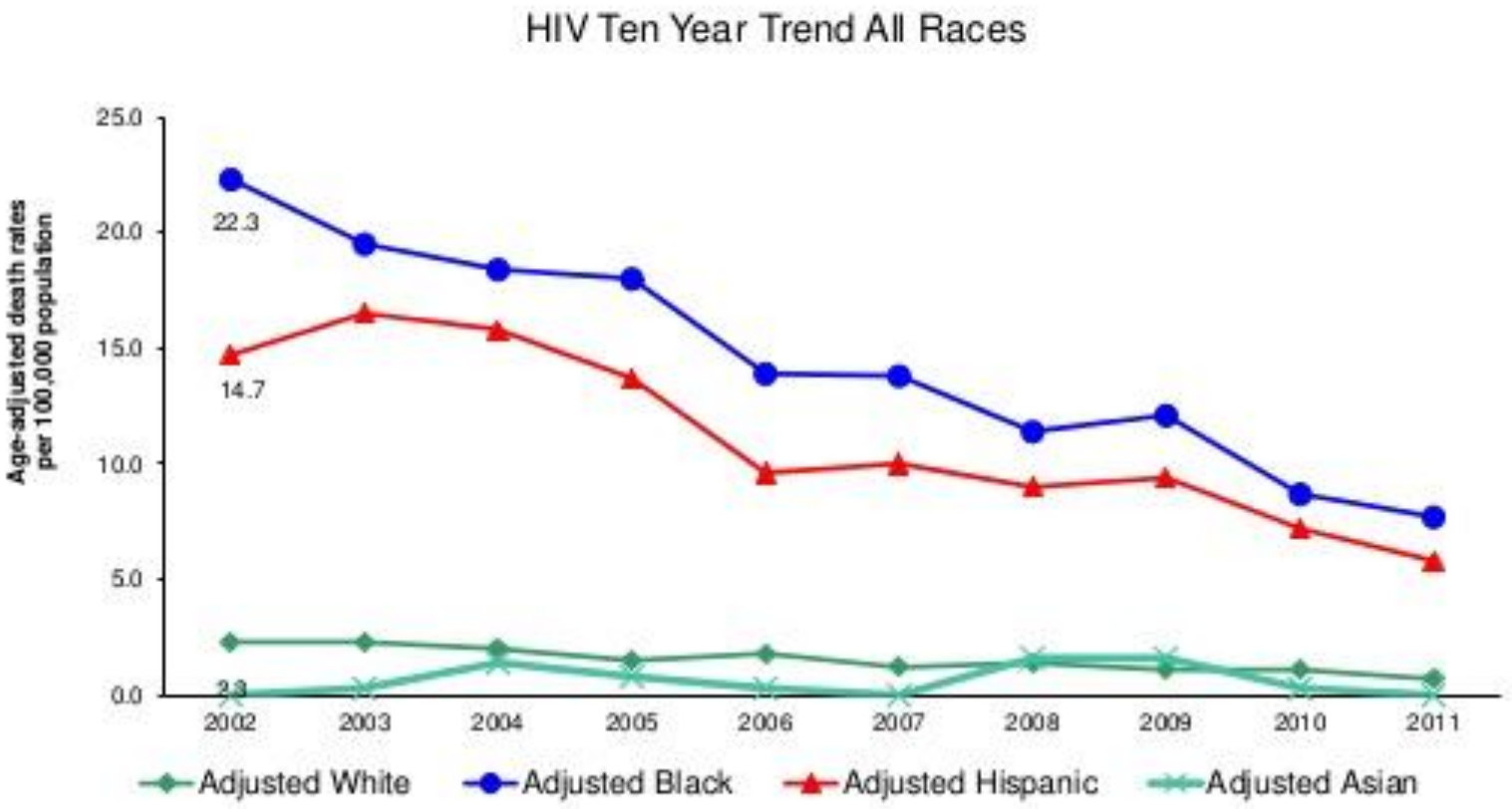

Deaths
Patients on ART
100,000
75,000
50,000
25,000
0
1,000,000
750,000
500,000
250,000
0
ART program data
ART projection
AIDS deaths (Women)
AIDS deaths (Men)
AIDS deaths (Children)
Patients on ART
1990
1995
2000
2005
2010
2015
2020

IAS 2015

Global Estimates (2014-15) vs the Gap to reach 90-90-90 Targets



What trends exist in HIV Mortality?



EL VIH COMO LOCOMOTORA CIENTÍFICA