Retos del futuro en la infección VIH: Vacuna y curación

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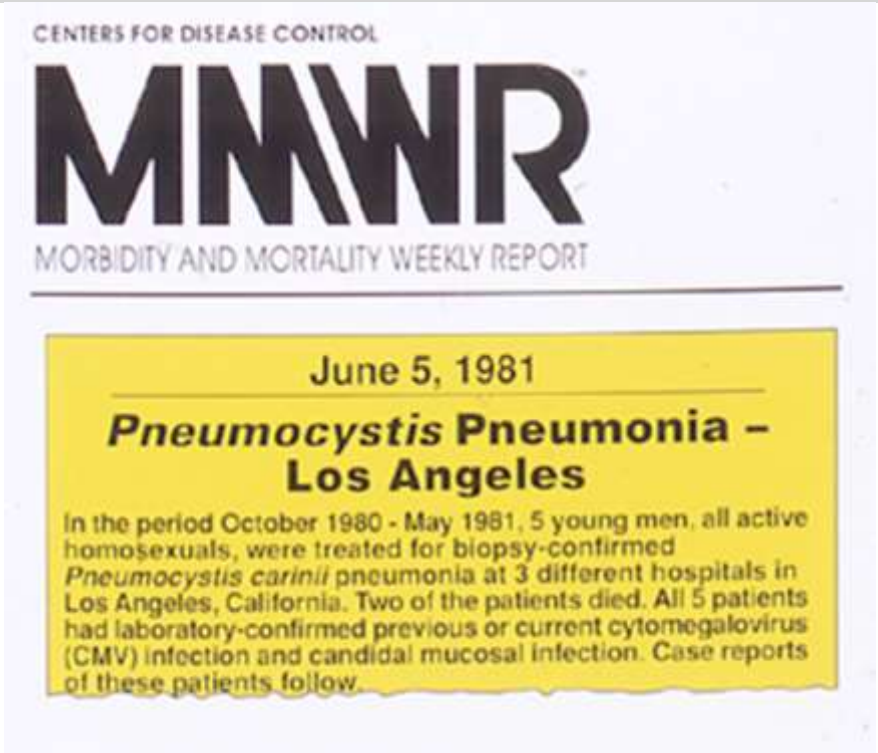
El principio…



CENTERS FOR DISEASE CONTROL

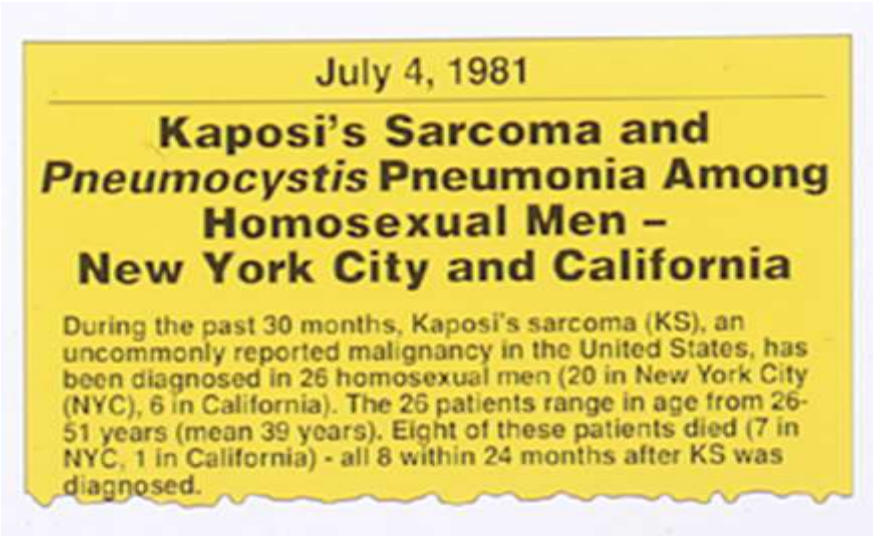
MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

June 5, 1981

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.

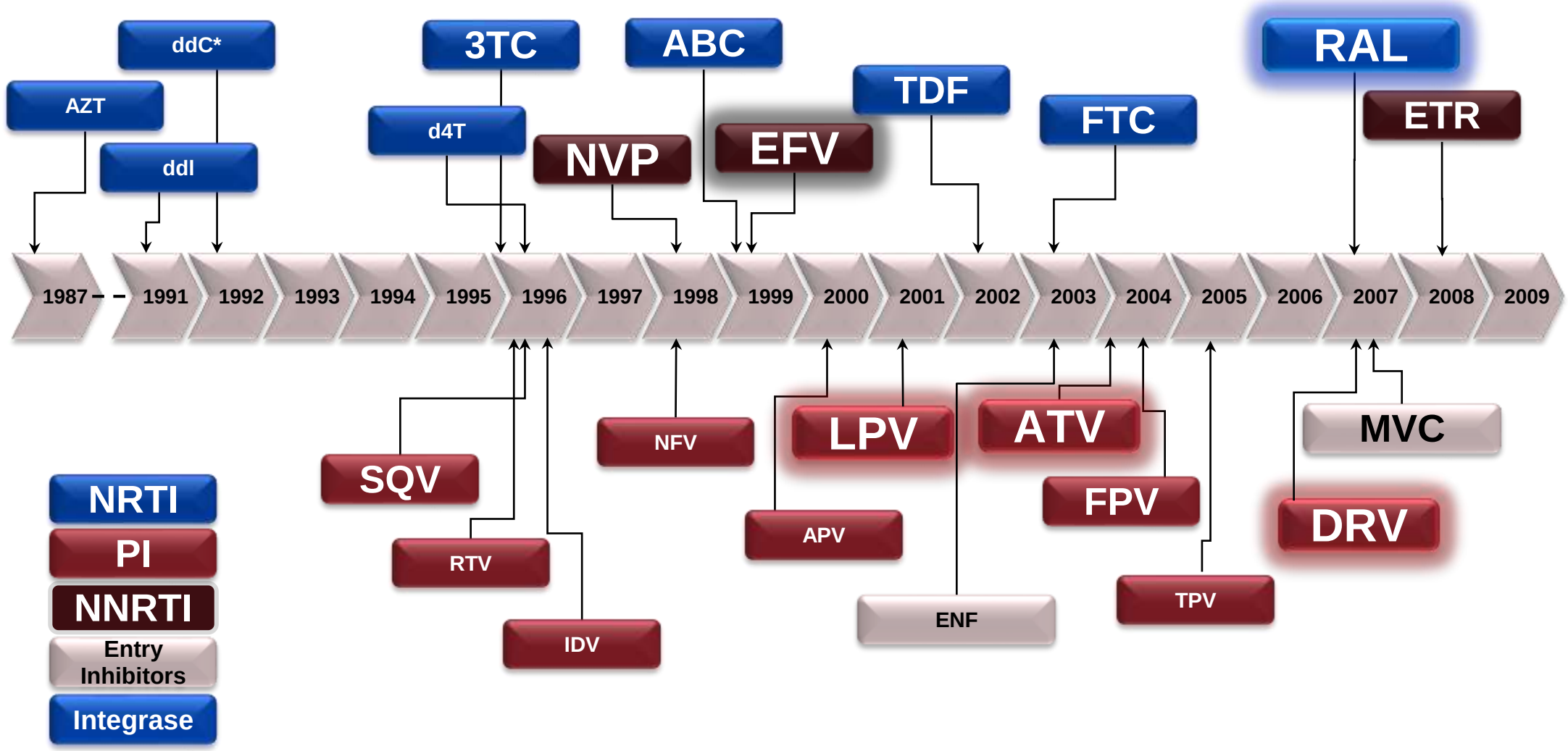


July 4, 1981

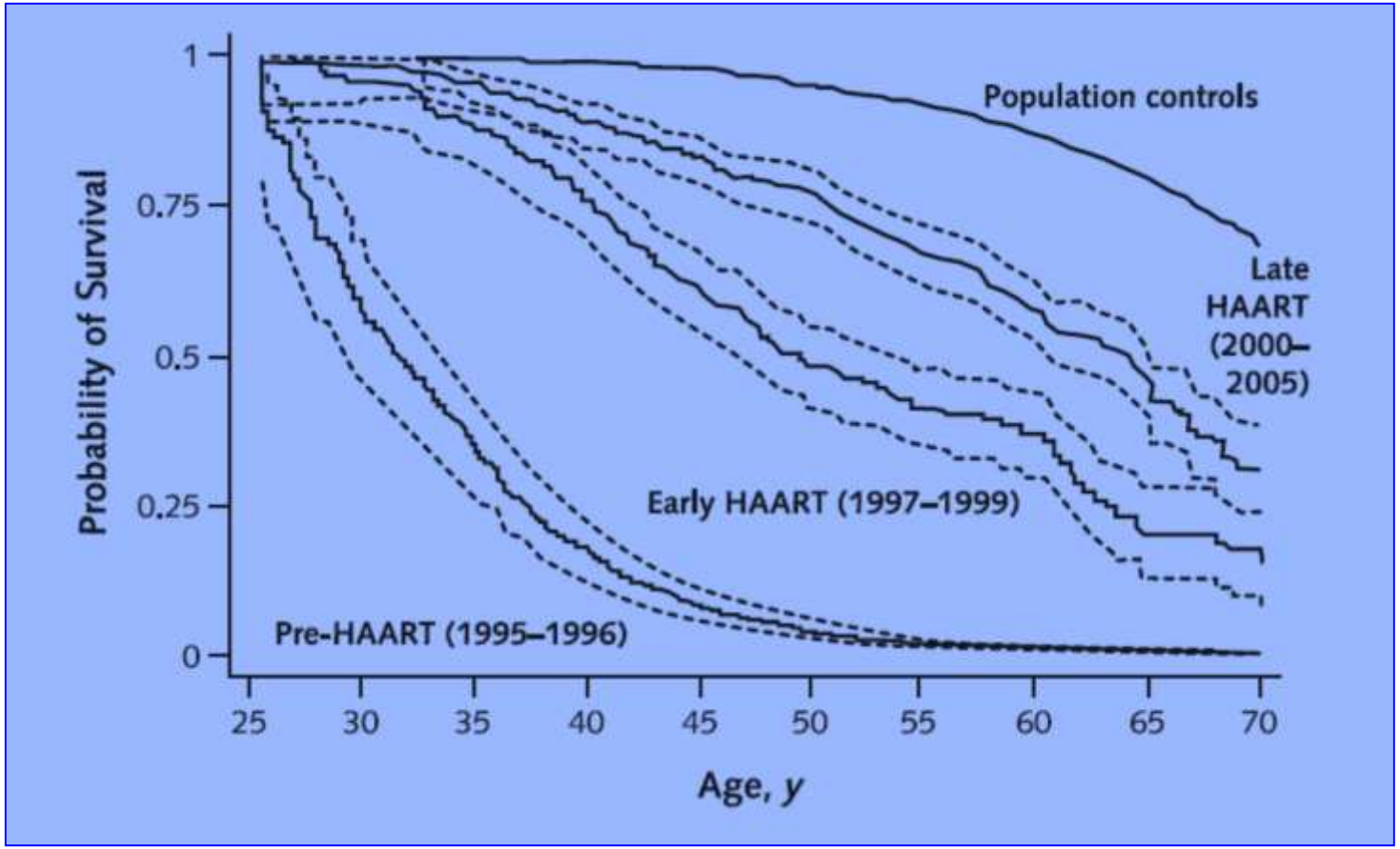
Kaposi's Sarcoma and _Pneumocystis_ Pneumonia Among Homosexual Men – New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City (NYC), 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California) - all 8 within 24 months after KS was diagnosed.

Nuevos fármacos y familias; nuevas posologías



TAR. Supervivencia



Lohse N et al. Ann Intern Med 2007

Los retos del futuro en la infección por el VIH

- …
- …
- Vacuna
- Curación

¿por qué no interesará tener una vacuna…?

El principio…

1981 June 5;30:250–2

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.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30-year-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed, and he was again given Amphotericin B. The CMV complement-fixation titer in March 1981 was 8. Material from an esophageal biopsy was positive for CMV.

Patient 4: A 29-year-old man developed *P. carinii* pneumonia in February 1981. He had had Hodgkins disease 3 years earlier, but had been successfully treated with radiation

1983. Se descubre la causa del sida

Premio Nobel en 2008

Luc Montagnier & Françoise Barré-Sinoussi
LAV (1983)

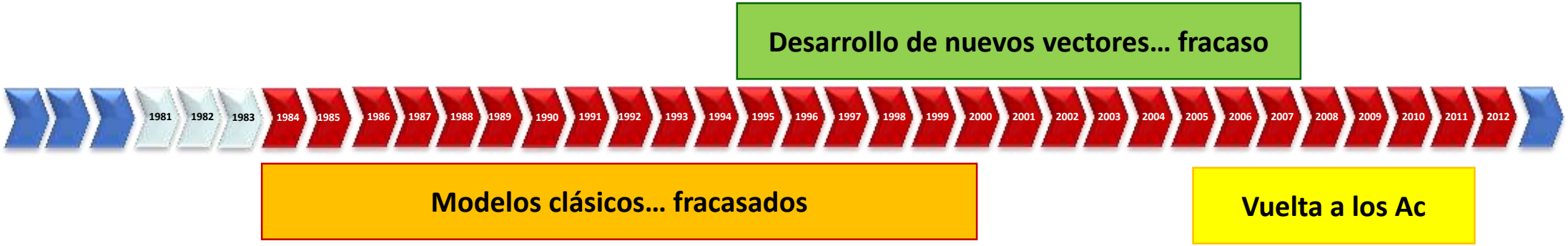
Y en plena euforia… La vacuna preventiva

Robert Gallo, investigador de los CDC y Margaret Hecker, secretaria del HSS

“Esperamos tener la vacuna en unos dos años”

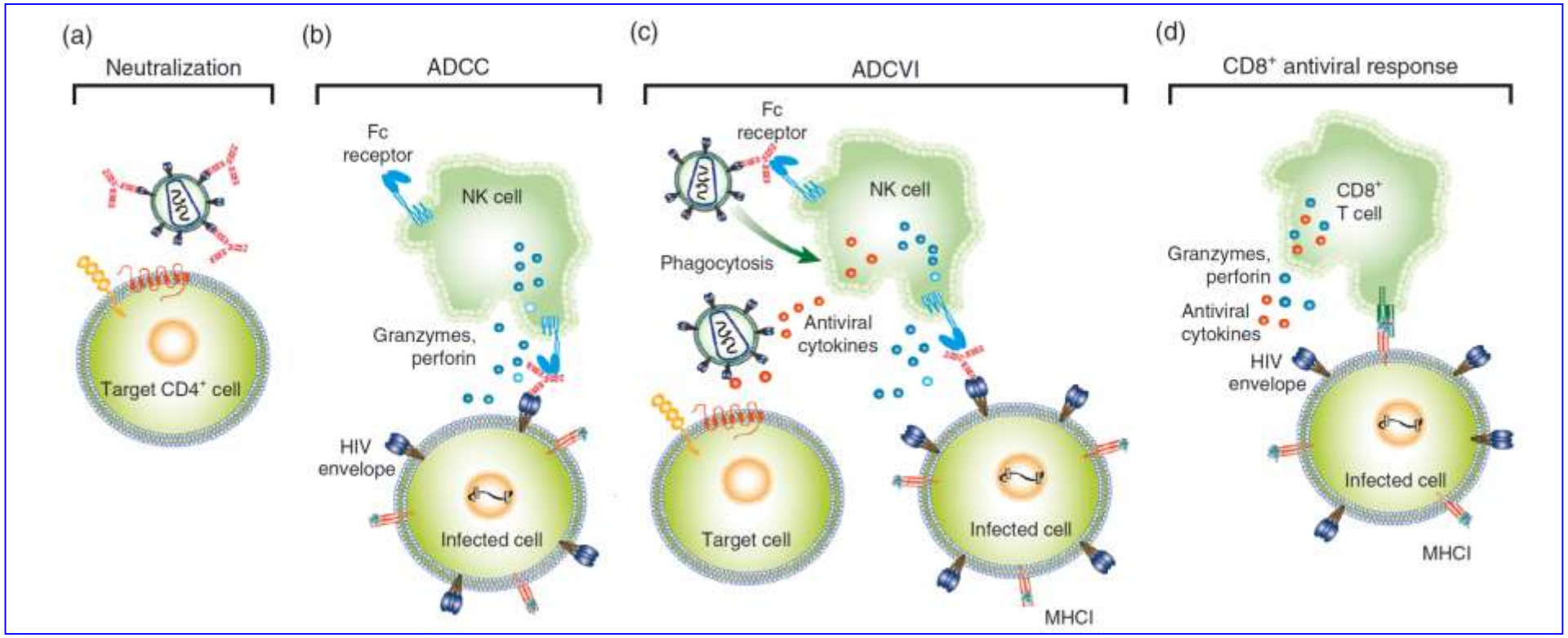
(Margaret Heckler Secretaria del Human and Heathl Service, 23.04.84)

Vacunas. Una carrera… ¿en la dirección correcta?



Modificado de J. Alcamí

Mecanismos de inhibición del VIH



Saunders KO et al. AIDS 2012

Propiedades ideales de la vacuna contra el VIH

- Anticuerpos neutralizantes a todos los subtipos del VIH
- Inmunidad humoral y celular contra células infectadas
- Inmunidad a células con infección latente
- No induzca anticuerpos facilitadores
- No induzca respuestas autoinmunes
- Inmunidad local en todos los sitios de entrada del VIH
- Segura, sin efectos tóxicos, potente, y durabilidad

Tipos de Vacunas VIH

- Virus muertos (enteros, inactivados)
- Virus vivos atenuados
- Subunidades glicoproteínas recombinantes
- Vectores vivos(vaccinia, MVA, Canarypox, VEE, Ad5)
- Plasmidios DNA
- Combinación de vacunas (prime-boost)

Historia de las vacunas

History of HIV Vaccine Research

1981	HIV was identified as the cause of AID
1987	The first HIV vaccine clinical trial open (NIH) Clinical Center in Bethesda, Mar healthy, uninfected volunteers. The gr adverse effects.
1988	The NIAID AIDS Vaccine Evaluation C HIV vaccine clinical trials group, begar
1992	NIAID launched the first Phase II HIV uninfected volunteers with a history of multiple sex partners, or sexually trans counseled repeatedly to avoid any beh infection.
1998	• First annual HIV Vaccine Awar volunteers. • First large scale vaccine trial b AIDSVAX in North America an
1999	• NIAID begins first African prev • First large scale vaccine trial ir initiates Phase III trial of AIDS' • Dedication of the Dale and Bet (VRC).
2000	• NIAID formed the HIV Vaccine Trials Network (HVTN), a network of clinical sites in the United States and abroad dedicated to developing a preventive HIV vaccine by testing and evaluating candidate vaccines in all phases of clinical trials. The network included more than 25 sites in the United States, Africa, Asia, South America, and the Caribbean • First African vaccine trial completed in Uganda.
2003	• U.S. and Royal Thai governments jointly initiated RV144, a Phase III trial to evaluate a novel HIV vaccine strategy commonly referred to as "prime-boost." • Formation of Global HIV Vaccine Enterprise proposed in *Science*
2004	VaxGen candidate failed in Phase III trials.
2007	NIAID halted the Phase II Step and Phambili studies due to safety concerns.
2009	• Phase II HVTN 505 study initiated to evaluate a “prime-boost” vaccine regimen developed by the NIAID Vaccine Research Center (VRC). • Results of Phase III Thai Trial (RV144) show vaccine combination is first to demonstrate modest preventive effect in humans. The trial enrolled more than 16,000 volunteers.
2010	• Two potent antibodies that prevent most strains of HIV identified by the VRC (VRC01 and VRC02). • Establishment of Pox-Protein Public-Private Partnership (P5)
2011	• HVTN 505 expanded to include protection from HIV as primary endpoint.
2012	• Additional analyses of samples from RV144 provide insight about what type of immune response may be needed for an effective vaccine.

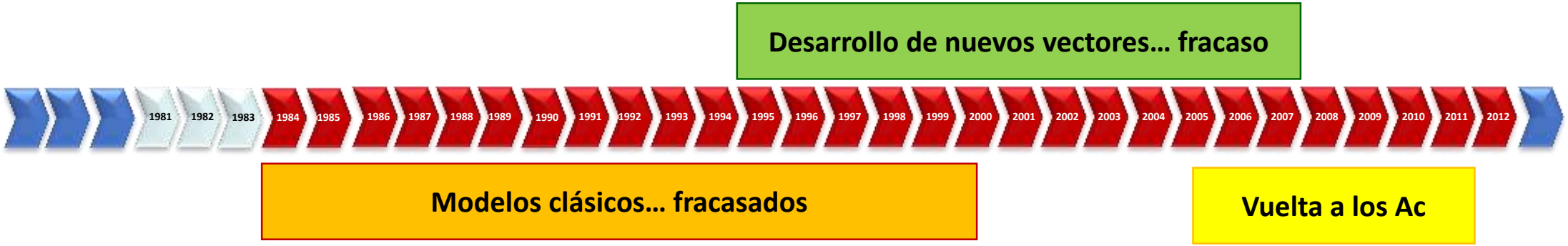
Ac neutralizantes
El continuo escape del virus

Sequential Plasma Specimens against Autologous Virus

Virus (months)	Plasma (months)								
	0	3	6	9	12	15	18	21	25
0	26	219	675	1403	2670	2089	2190	2363	2411
3	29	179	1024	2151	3733	3152	2808	2953	3086
6	27	35	78	358	1769	1939	2247	3112	4345
9	36	67	82	200	795	1078	1371	2208	3375
12	19	48	36	64	76	166	556	937	1407
15	29	43	64	76	90	119	374	721	1234
18	42	65	61	152	117	134	122	289	526
21	41	66	82	84	85	113	78	107	296
25	42	62	56	62	85	77	55	61	95

Richman D, et al. PNAS 2003; 100:4144

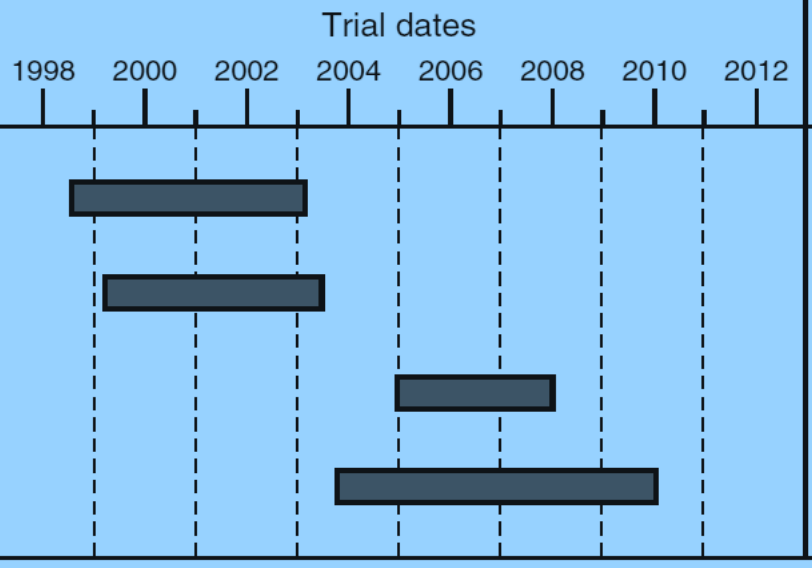
Vacunas. Una carrera… ¿en la dirección correcta?



Modificado de J. Alcamí

Vacunas VIH con "nuevos vectores"
Resultados de 4 ensayos

Trial	Immunity	Vaccine components	Trial dates	Efficacy
VAX 004	gp120 Ab	Recombinant gp 120		No
VAX 003	gp120 Ab	Recombinant gp 120		No
Step	T cell	rAd5 (gag, pol, nef)		No
RV144	T + B cell	Canarypox (gag, pol, env) + recombinant gp 120 B/S		Yes (31%)



Saunders KO et al. AIDS 2012

Magnitud de la respuesta inmune según el inmunógeno utilizado

Vaccine platform	$CD4^+$ T cell	$CD8^+$ T cell	Humoral	Clinical evaluation
Whole inactivated virus	+++	–	+++	None
Live-attenuated virus	++	++	++	None
Viral protein	++	–	+++	Phase III
HIV peptide	++	++	–	Phase II
Viral vector	+++	+++	+++	Phase III
Plasmid DNA	++	+	+	Phase II

Saunders KO et al. AIDS 2012

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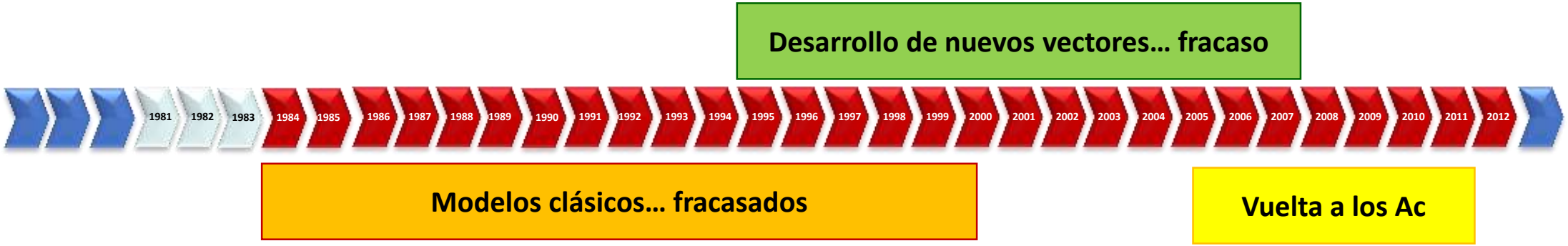
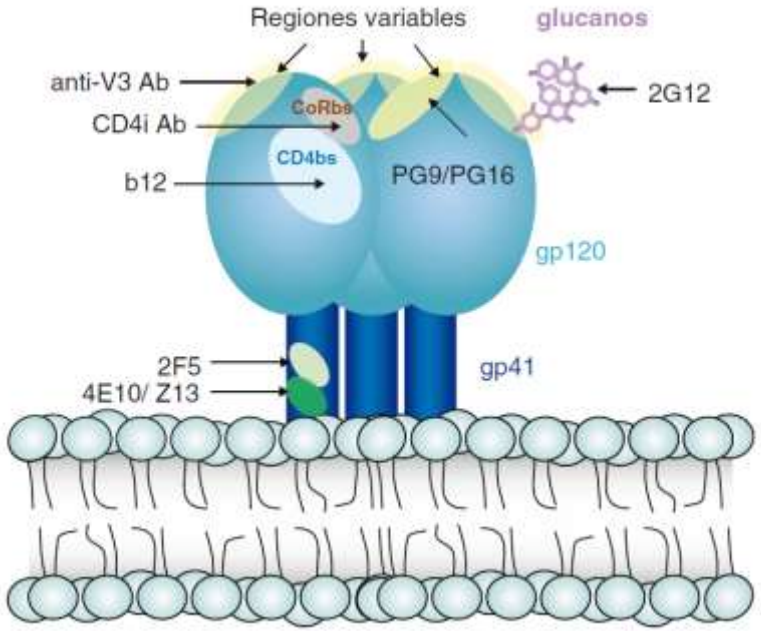


Modificado de J. Alcamí

Anticuerpos neutralizantes de alta eficacia

- ✓ *Se han identificado Ac neutralizantes de amplio espectro*
- ✓ *"Neutralizadores de élite"*
- ✓ ***Hallazgo esperanzador** desde el punto de vista de la obtención de una vacuna*



Alcami J & Coira M. EIMC 2011