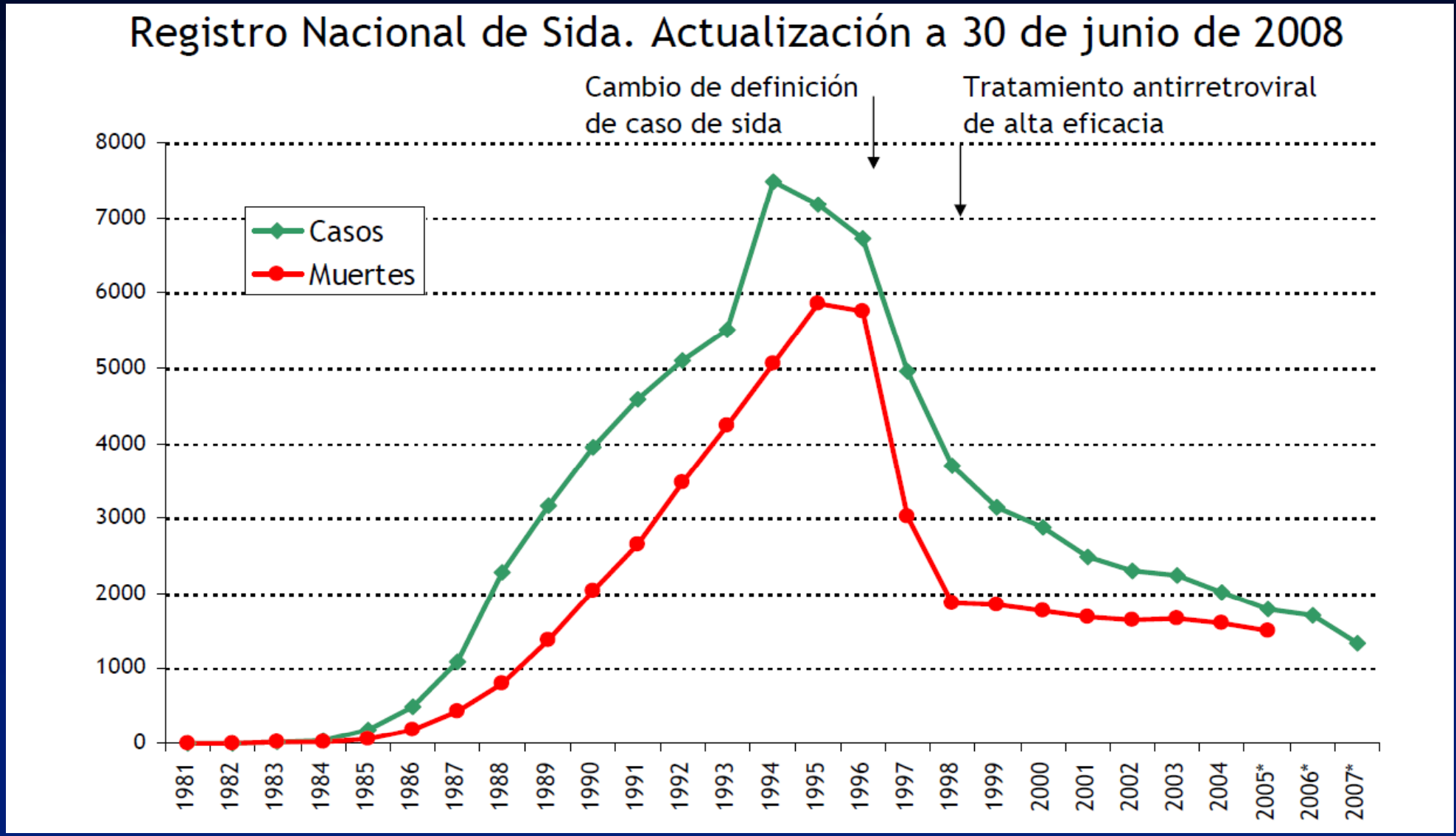
54 Congreso de la S.E.F.H.
Zaragoza, 23 de Septiembre de 2009

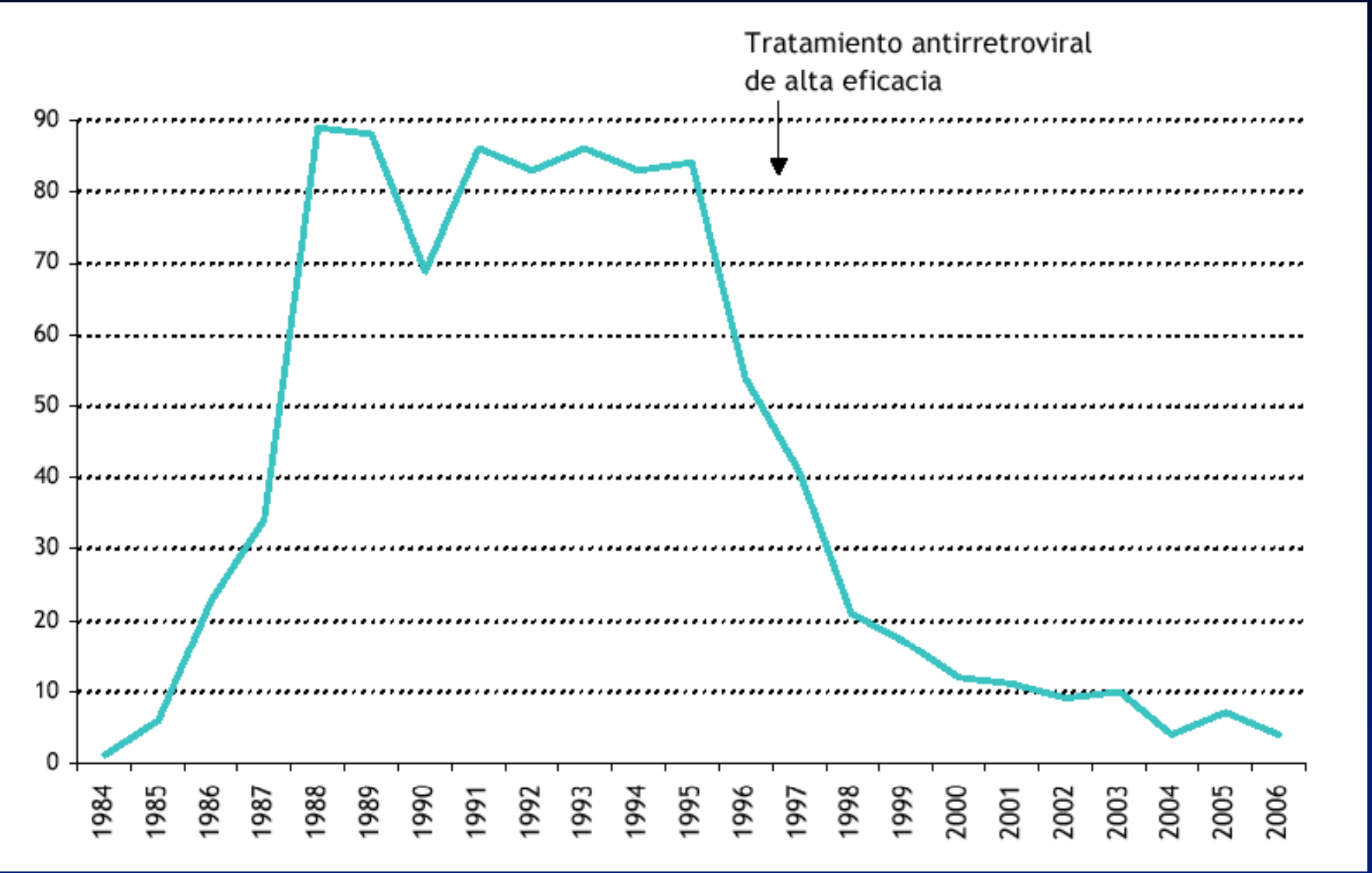
¿Cuándo Iniciar el Tratamiento Antirretroviral?

Santiago Moreno
Hospital Ramón y Cajal. Madrid.

Evolución de la incidencia y mortalidad por sida en España.



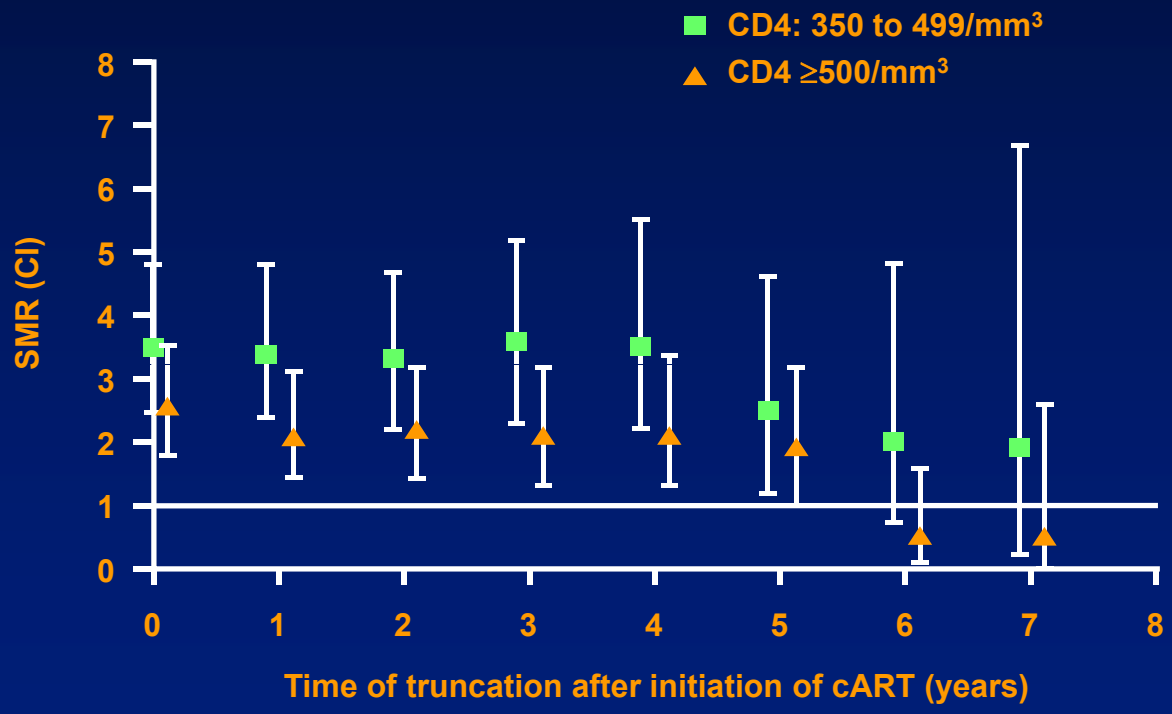
Casos de sida de transmisión madre-hijo en España.



Fuente: Registro Nacional de Sida

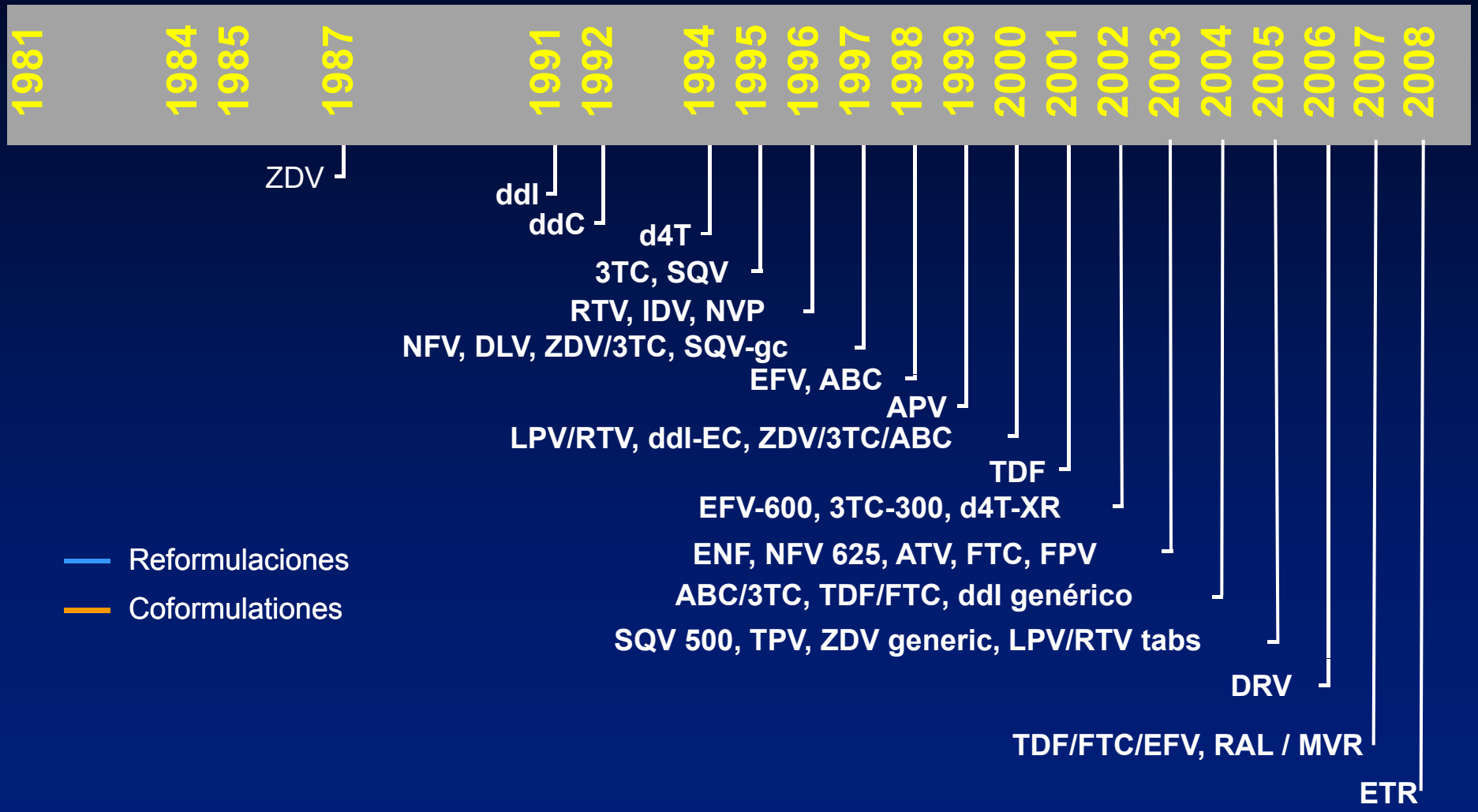
Aumento de la Supervivencia

CD4 count ≥500mm^3 is associated with standard mortality ratio (SMR) similar to general population[1]



Lewden C, et al. J Acquir Immune Defic Syndr 2007;46(1):72–77

Desarrollo de los Antirretrovirales

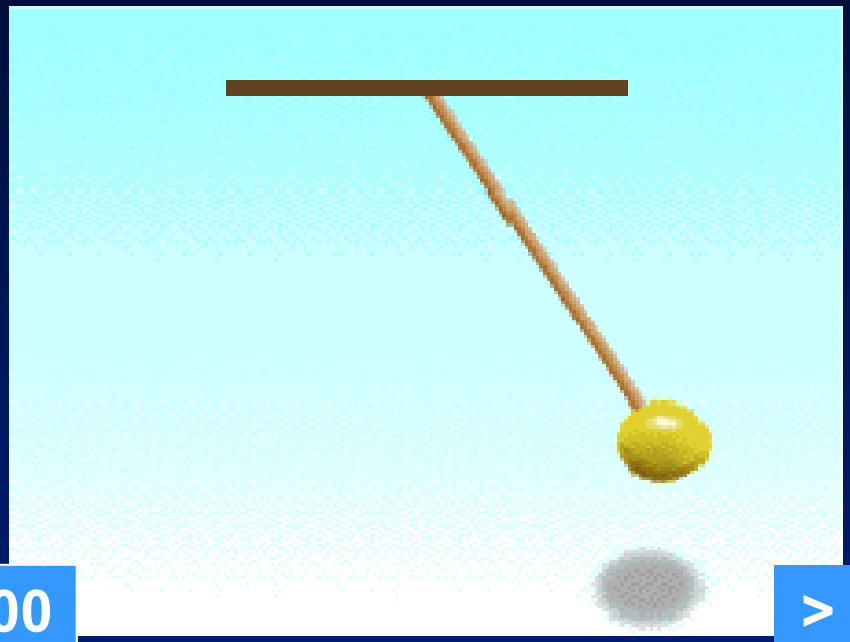


Agentes Antiretrovirales 2009

NRTIs	NNRTIs	IPs
zidovudina (AZT) – *Retrovir*	nevirapina (NVP) – *Viramune*	saquinavir (SQV) – *Invirase*
didanosina (ddI) – *Videx*, *Videx EC*	efavirenz (EFV) - *Sustiva*	indinavir (IDV) – *Crixivan*
zalcitabina (ddC) – *Hivid*	etravirina (DLV) – *Intelence*	ritonavir (RTV) – *Norvir*
estavudina (d4T) – *Zerit, Zerit XR*	Inhibidores de Fusión	nelfinavir (NFV) – *Viracept*
lamivudina (3TC) – *Epivir*	enfuvirtide (ENF, T20) - *Fuzeon*	Fos-amprenavir (APV) – *Telzir*
abacavir (ABC) – *Ziagen*	Inhibidores de Integrasa	lopinavir/ritonavir (LPV/r) - *Kaletra*
emtricitabina (FTC) - *Emtriva*	Raltegravir - *Isentress*	atazanavir (ATV) – *Reyataz*
tenofovir DF (TDF) -*Viread*	Antagonistas CCR5	Tipranavir (TPV) - *Aptivus*
	Maraviroc - *Celsentri*	Darunavir (DRV) - *Prezista*

¿Cuándo iniciar TAR?

Estadíos Clínicos Tardíos



Estadios Clínicos Tempranos

< 200

> 500

200

350

CD4

Carga viral alta

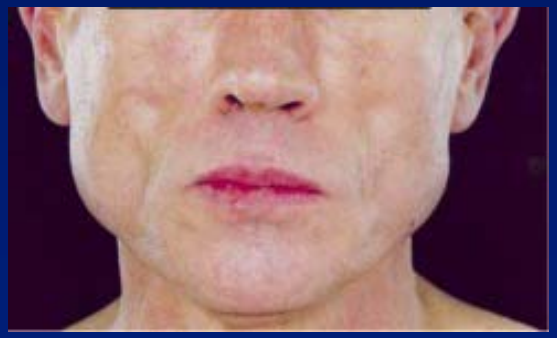
Cualquier carga viral

¿Cuándo iniciar TAR?

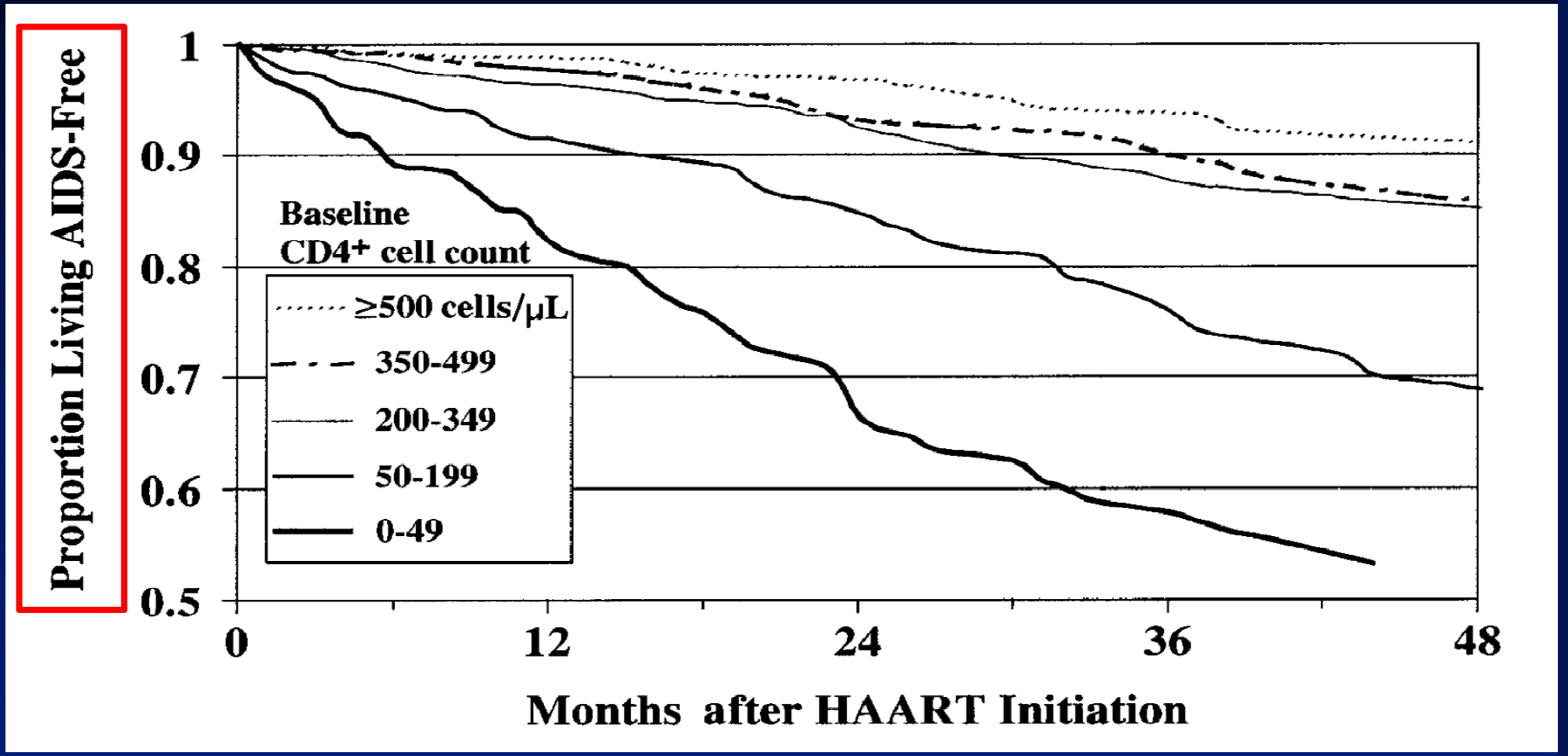
1996

Golpear fuerte y pronto

Hit hard and hit early



Cuándo iniciar TAR



Kaplan J.E et al, Clinical Infectious Diseases 2003; 37:951–8

Recomendaciones para el Inicio de Tratamiento Antirretroviral en Pacientes Asintomáticos : 1998 – 2005

Panel	CD4 Count
US DHHS	
June 1998	< 500
February 2001	< 350
April 2005	< 200
International AIDS Society –USA Panel	
July 1998	Any
January 2000	< 500
July 2004	≤ 200
British HIV Association (BHIVA)	
June 1998	> 350
July 2003	201-350
July 2005	< 200

Cuando iniciar TAR

Guías GESIDA/PNS Enero 2007

Tabla 3. Indicaciones de tratamiento antirretroviral en pacientes asintomáticos con infección crónica por el virus de la inmunodeficiencia humana.

Linfocitos CD4	Pacientes asintomáticos
<200	Recomendar siempre
200-350	Recomendar en la mayoría de ocasiones *
>350	Diferir

* En general a los pacientes con linfocitos CD4+ entre 200 y 350 células/µL se debe recomendar el inicio de TAR sobre todo si la proporción de CD4 es inferior a 14%. Sin embargo en determinadas circunstancias se podría diferir: si los linfocitos CD4 se mantienen de manera estable en una cifra próxima a 350 células/µL y la CVP es baja (inferior a 20.000 copias/mL).

Panel de expertos de GESIDA y PNS. Enferm Infecc Microbiol Clin 2007;25(1):32-53

Razones para retrasar el TAR

- Inability to eradicate HIV
- Long-term toxicity: metabolic changes, neuropathy, lipodystrophy, insulin resistance, etc.
- Side effects
- Complex dosing
- Demanding adherence requirements
- Resistance
- Lack of demonstrated clinical benefit in early cohort studies

DHHS Guidelines 11/2008: Cuándo Iniciar

Clinical Condition and/or CD4 Count	Recommendations
• History of AIDS-defining illness • CD4 ≤ 350 • Pregnant women • HIVAN • HBV coinfection when HBV treatment is indicated	Start ART

US DHHS Guidelines; Revised January 29, 2008. http://.aidsinfo.nih.gov/contentfiles/adultandadolescnetGL.pdf.

DHHS Guidelines 1/2008: Cuándo Iniciar

Clinical Condition and/or CD4 Count	Recommendations
• History of AIDS-defining illness • CD4 ≤ 350 • Pregnant women • HIVAN • HBV coinfection when HBV treatment is indicated	RT
CD4 > 350	• Optimal time to initiate ART not well defined • Consider patient scenarios and comorbidities

High VL
Rapidly declining CD4 (>120 cells/yr)
HIV-negative sexual partner

US DHHS Guidelines; Revised January 29, 2008. http://.aidsinfo.nih.gov/contentfiles/adultandadolescnetGL.pdf

IAS-USA Guidelines 7/2008: Cuándo Iniciar

Clinical Condition and/or CD4 Count	Recommendations
High VL (>100,000) **Rapidly declining CD4 (>100 cells/yr)** **High risk of cardiovascular disease** **Active HBV or HCV disease** **HIVAN**	Start ART
CD4 ≥ 350	ART should be individualized

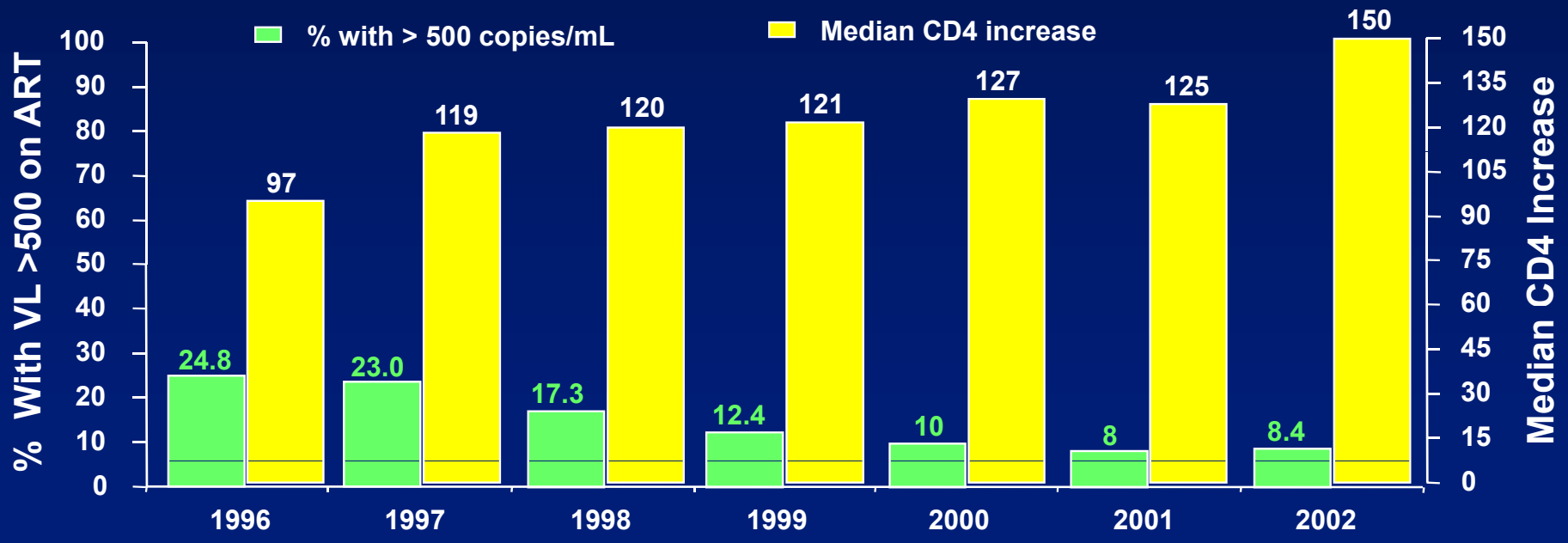
US DHHS Guidelines; Revised January 29, 2008. http://.aidsinfo.nih.gov/contentfiles/adultandadolescnetGL.pdf.

Razones para un Inicio más Precoz

Regímenes más Cómodos y Potentes

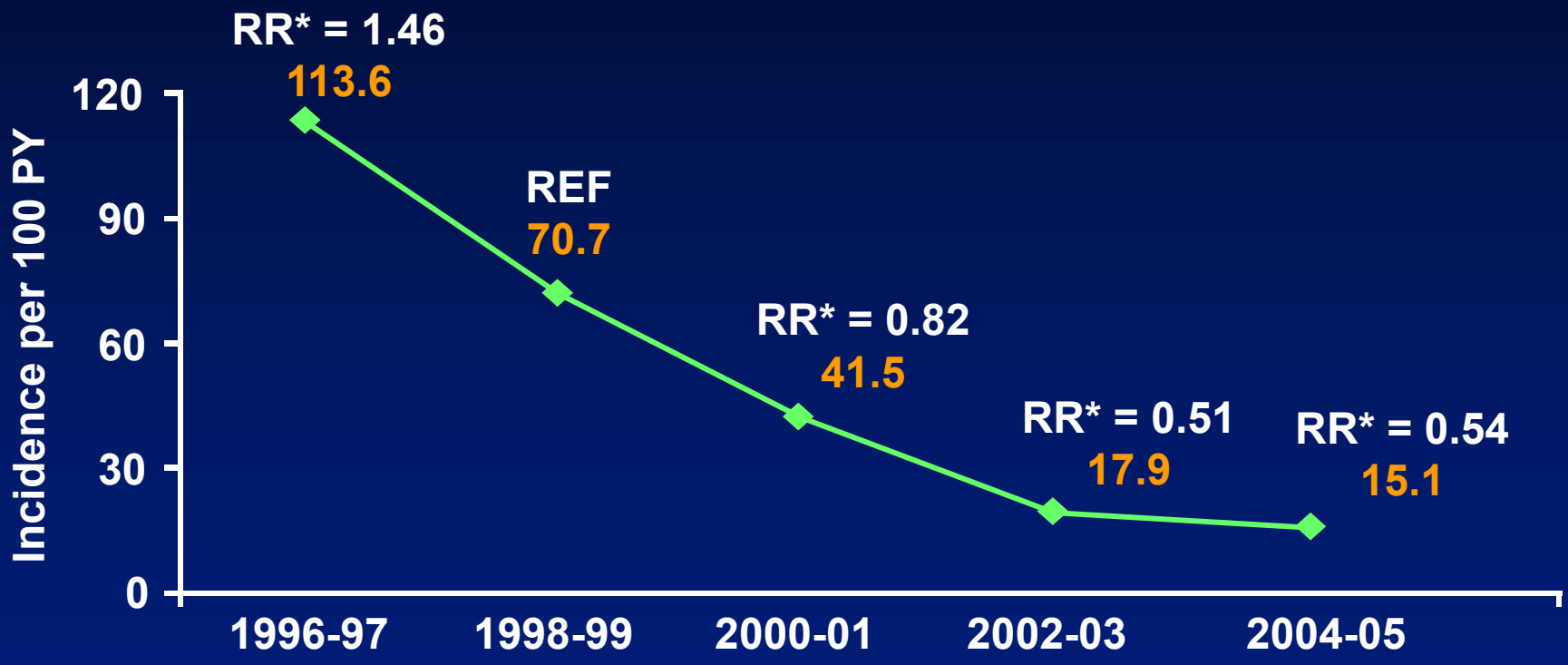
Treatment Responses in 1st Year of HAART Improving Over Time

- 4143 subjects from 5 clinic cohorts in Europe and Canada
- Treatment-naive; started HAART from 1996-2002
- ↓ risk of virologic failure, ↑ med. CD4 count increase in later years
  - Most "failure" now due to loss to follow-up or treatment discontinuation



Lampe F, et al. CROI 2005. Abstract 593

Incidence of Second Virologic Failure Declining Over Time

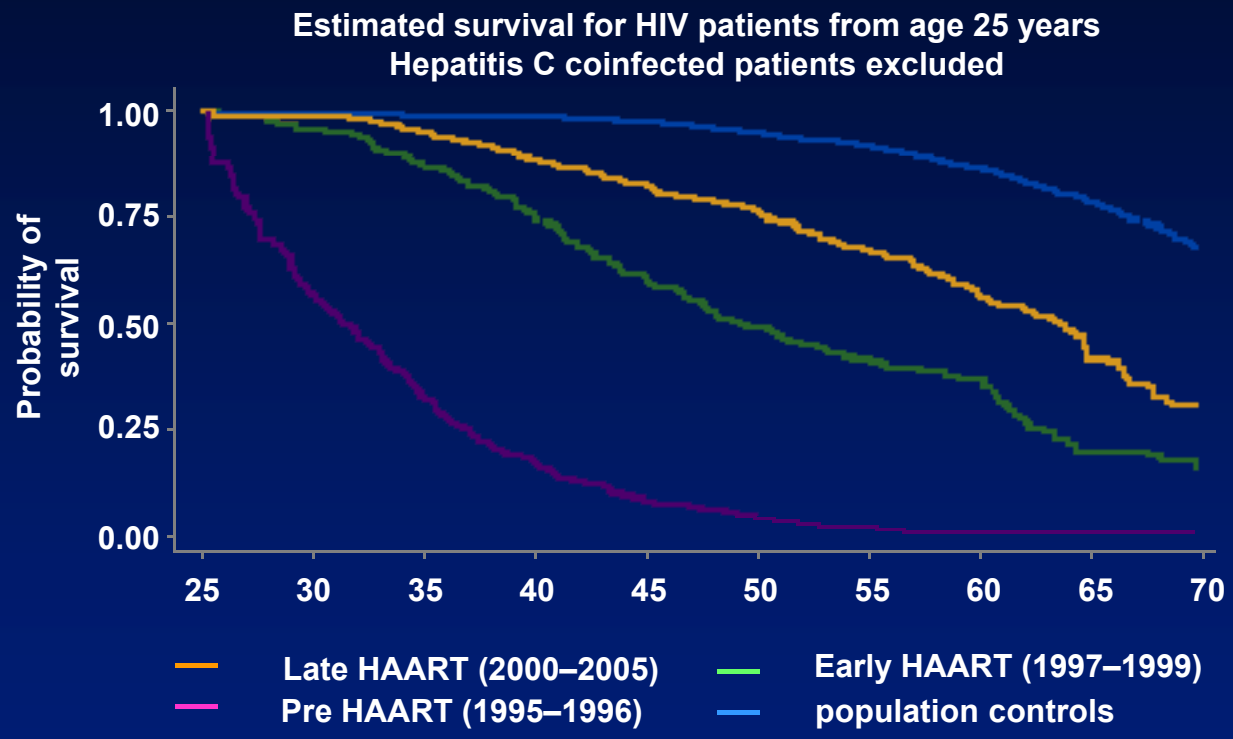


*Adjusted for time from HAART initiation, sex, age, AIDS, CD4 count, VL at HAART initiation and switch, and type of HAART.

Deeks S, et al. CROI 2008. Abstract 41.

Since start of ART, increasing survival rates for people with HIV

- Survival from age 25 years: Cumulative survival curve for HIV-infected individuals and general-population controls
- HIV-infected individuals are divided into three calendar periods of observation



Adapted from Lohse N et al. 16th IAC 2006, Toronto, Canada. Abstract MOPE0310

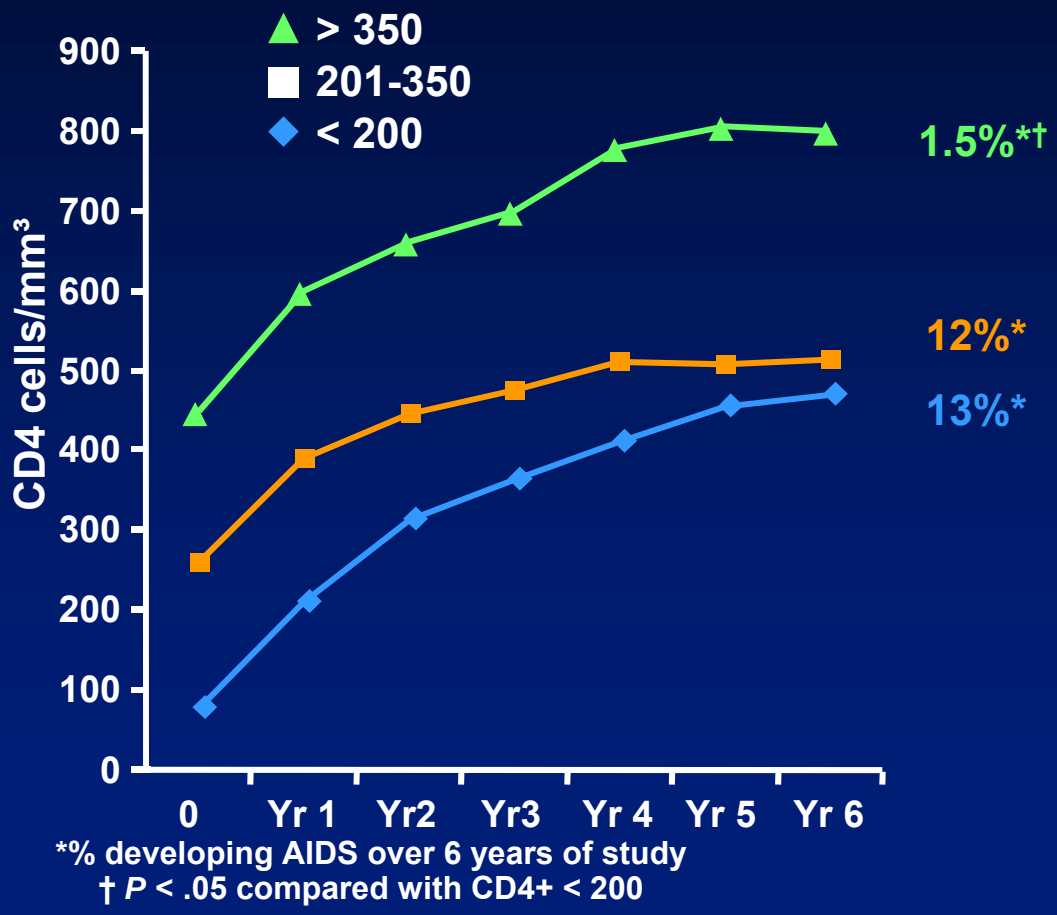
Excellent Safety and Tolerability of Current Regimens

Study	Length	Drug regimen	Discontinuations Due to AEs,* %
AI424-089[1]	96 weeks	ATV + d4T + 3TC	3
		ATV/r + d4T + 3TC	8
GS934[2]	48 weeks	EFV + TDF + FTC	5
		EFV + ZDV/3TC	11
KLEAN[3]	48 weeks	FPV/r + ABC/3TC	12
		LPV/r + ABC/3TC	10
ARTEMIS[4]	48 weeks	DRV/r + TDF/FTC	3
		LPV/r + TDF/FTC	7
CASTLE[5]	48 weeks	ATV/r + TDF/FTC	2
		LPV/r + TDF/FTC	3
HEAT[6]	48 weeks	ABC/3TC + LPV/r	4
		TDF/FTC + LPV/r	6
GEMINI[7]	48 weeks	SQV/r + TDF/FTC	4
		LPV/r + TDF/FTC	7

1. Malan N, et al. IAS 2007. Abstract WEPEB024. 2. Arribas JR, et al. IAS 2007. Abstract WEPEB029. 3. Eron J Jr, et al. Lancet. 2006;368:476-482. 4. DeJesus E, et al. ICAAC 2007. Abstract 718-b. 5. Molina JM, et al. CROI 2008. Abstract 37. 6. Smith K, et al. CROI 2008. Abstract 774. 7. Walmsley SL, et al. EACS 2007. Abstract PS1.4.

Pre-HAART CD4 Predicts Progression to AIDS: Johns Hopkins Cohort

- Johns Hopkins HIV Cohort
- Patients with virologic suppression for up to 6 yrs (N=280)
- Only patients with baseline CD4 >350 returned to near normal CD4 count levels
- Rate of progression to AIDS or death significantly higher over time in patients with CD4 <200 and 201-350 vs. >350

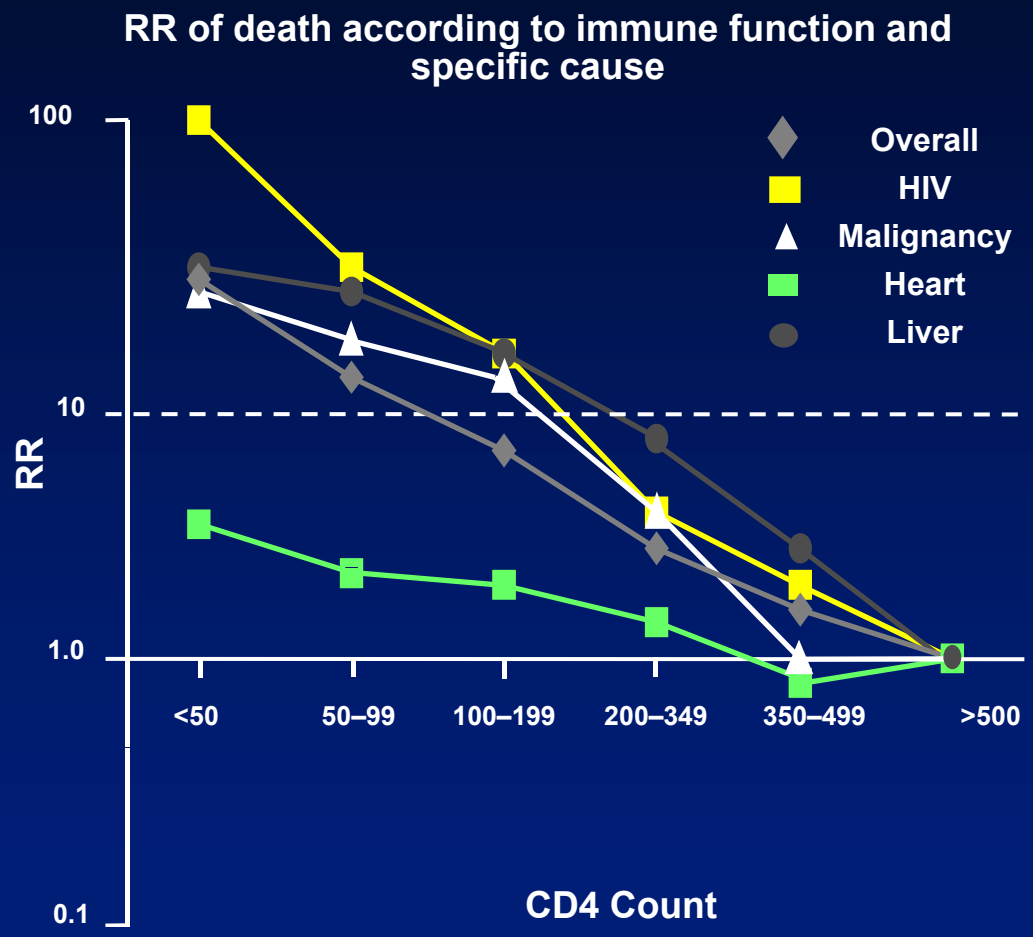


*% developing AIDS over 6 years of study
† *P* < .05 compared with CD4+ < 200

Moore RD, et al. IAC 2006. Abstract THPE0109.

Estudio D:A:D : Relación de CD4 y riesgo de muerte no relacionada con VIH

- Cohort study of >23,000 patients in Europe, Australia, USA
- 1,248 (5.3%) deaths 2000–2004 (1.6/100 person-years)
  - Of these, 82% on ART
- Both HIV- and non-HIV-related mortality were associated with CD4+ cell count depletion, suggesting role for immunosuppression in causes of death typically considered not HIV-related*



**Liver-related: chronic viral hepatitis, liver failure (other); malignancy-related: malignancy, non-AIDS hepatitis; heart-related: MI, other CVD, other heart disease*

Adapted from Weber R, et al. 12th CROI, Boston, USA. February 22–25 2005, Abstract 595

Estudio SMART

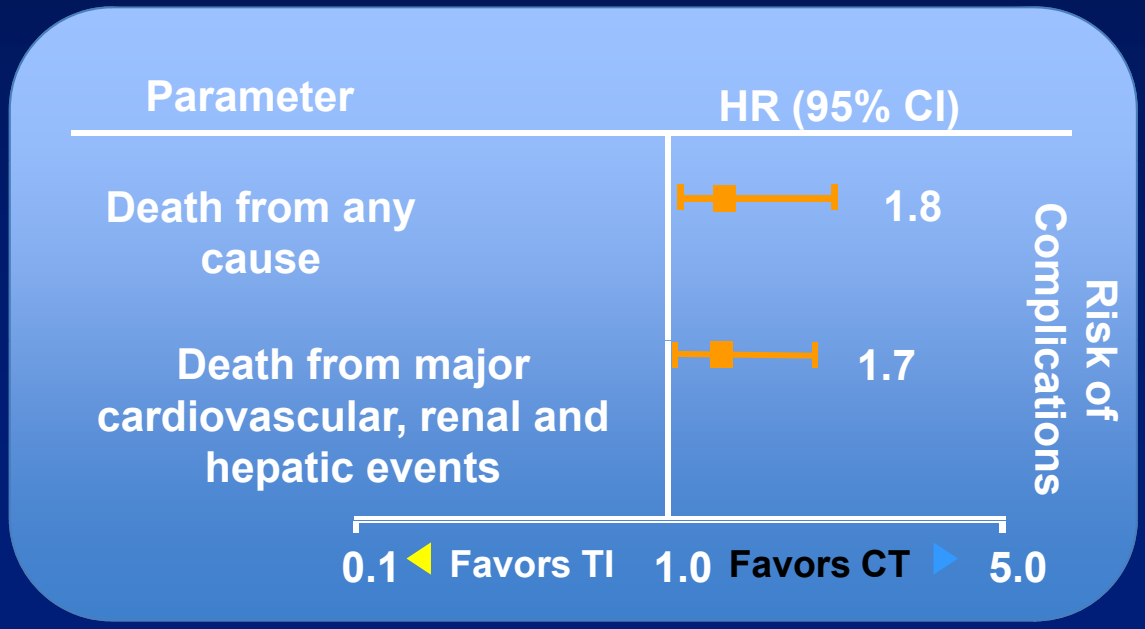
VIH +
CD4 > 350 /mm^3
N = 5472

Random 1:1

Tratamiento continuo

Interrupciones de tratamiento si CD4 >350

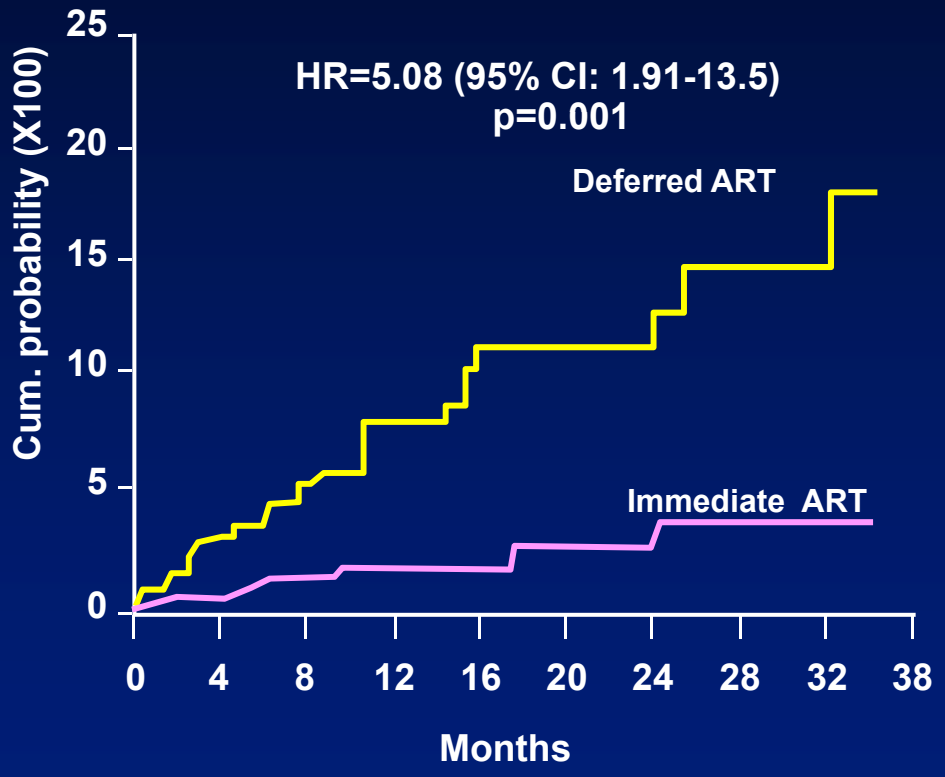
Reiniciar tratamiento si CD4 <250



El-Sadr W, et al. N Engl J Med. 2006;355:2283-2296

SMART: Patients not on ART at Randomization

- Subset: ART-naïve or not on ART at randomization
  - Immediate ART: n=249 (131 naïve)
  - Deferred ART: n=228 (118 naïve)
- Greater risk of OI, OI/death, serious non-AIDS event with deferred ARV
- >5-fold increased risk with deferred ARV



1. Emery S, *et al. 4th IAS*, Sydney 2007, #WEPEB018; 2. Marin B, *et al. ibid*, #WEPEB019

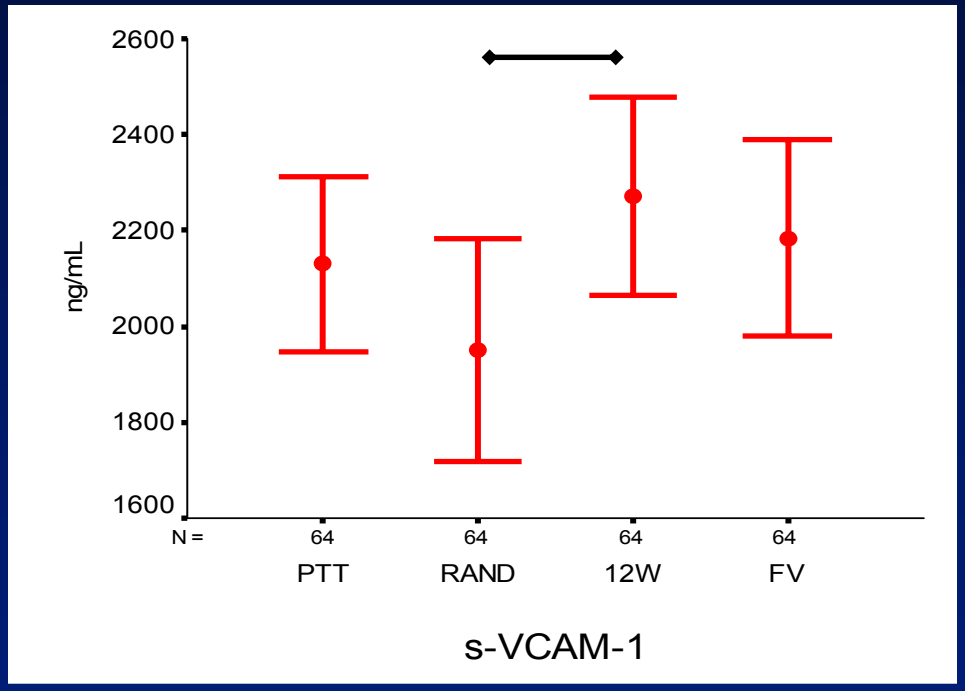
Baseline Marker Level and Odds of Mortality and CVD

	Fatal or Nonfatal CVD			All-Cause Mortality		
Biomarker	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Amyloid A	1.6	0.9 – 2.9	0.12	2.3	0.9 – 5.5	0.08
Amyloid P	2.8	1.4 – 5.3	0.002	1.1	0.5 – 2.4	0.90
D-dimer	2.0	1.0 – 3.9	0.06	13.3	4.4 – 40.3	<0.0001
F1.2	0.8	0.4 – 1.6	0.56	1.4	0.6 – 3.5	0.45
hs-CRP	1.6	0.8 – 3.1	0.20	3.5	1.5 – 8.1	0.004
IL-6	2.8	1.4 – 5.5	0.003	12.6	4.3 – 37.4	<0.0001

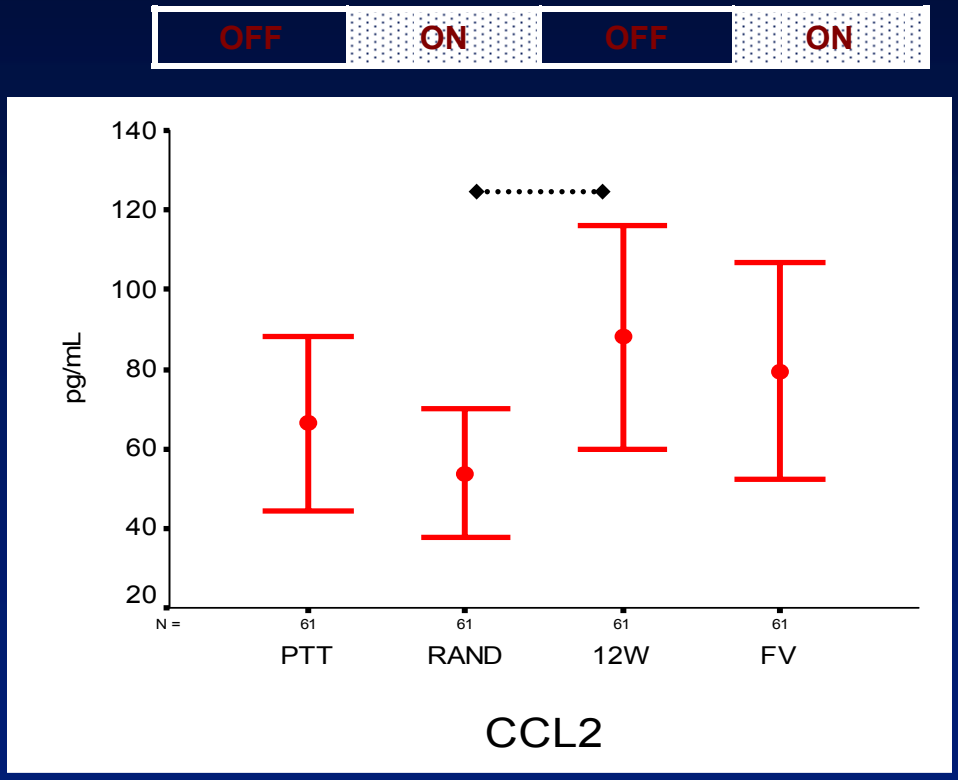
Lewis H. Kuller et al. *PLoS Medicine*. 2008;5(10):e203.

Staccato: endothelial dysfunction and pro-inflamatory markers

s-VCAM-1



MCP-1 [CCL2]

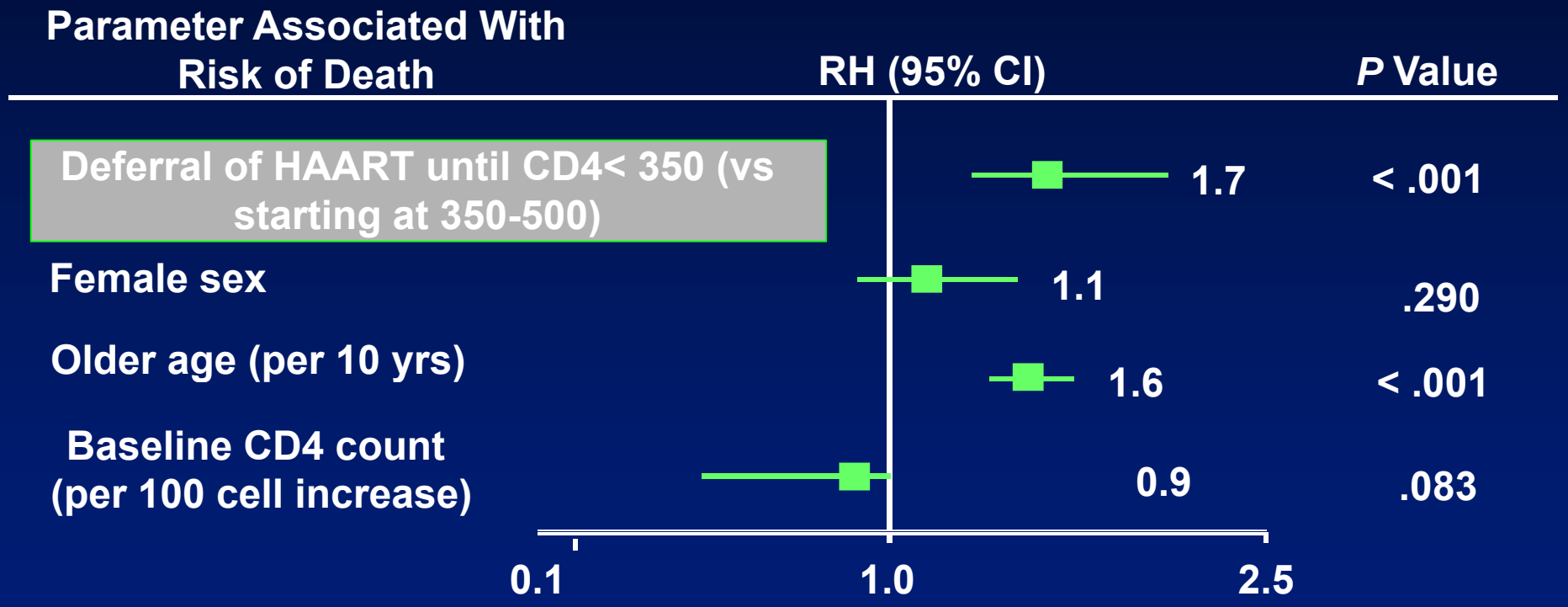


Some effect of retreatment at final visit but not significant

P<0.01 P<0.05

Calmy A, et al. CROI 2008, Boston, abstract 140

NA-ACCORD: Inicio Precoz vs Diferido
(Análisis 350-500 vs. <500)

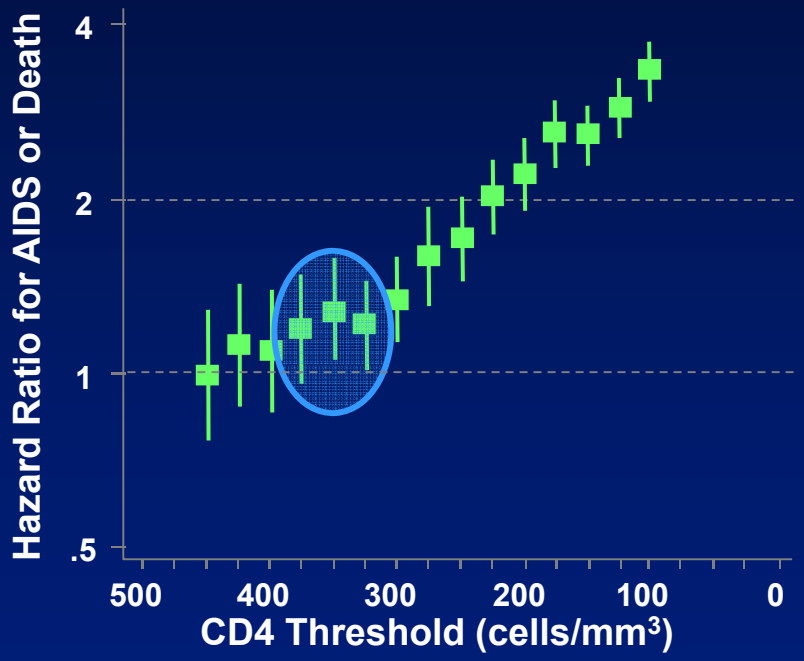


- Increased RH of death with deferral unchanged when adjusted for IDU or for HCV coinfection, both independent predictors of mortality

Kitahata, et al. ICAAC/IDSA 2008. Abstract 896b.

¿Cuándo iniciar el TAR? Datos del ART-CC

- Delaying ART to <350 (but not <375) cells/mm^3 is associated with an increased risk of AIDS or death



Comparison	Hazard Ratio (95% CI)
276–375 vs 376–475	1.19 (0.96 to 1.47)
251–350 vs 351–450	1.28 (1.04 to 1.57)
226–325 vs 326–425	1.21 (1.01 to 1.46)

Adapted from Sterne J, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 72LB.

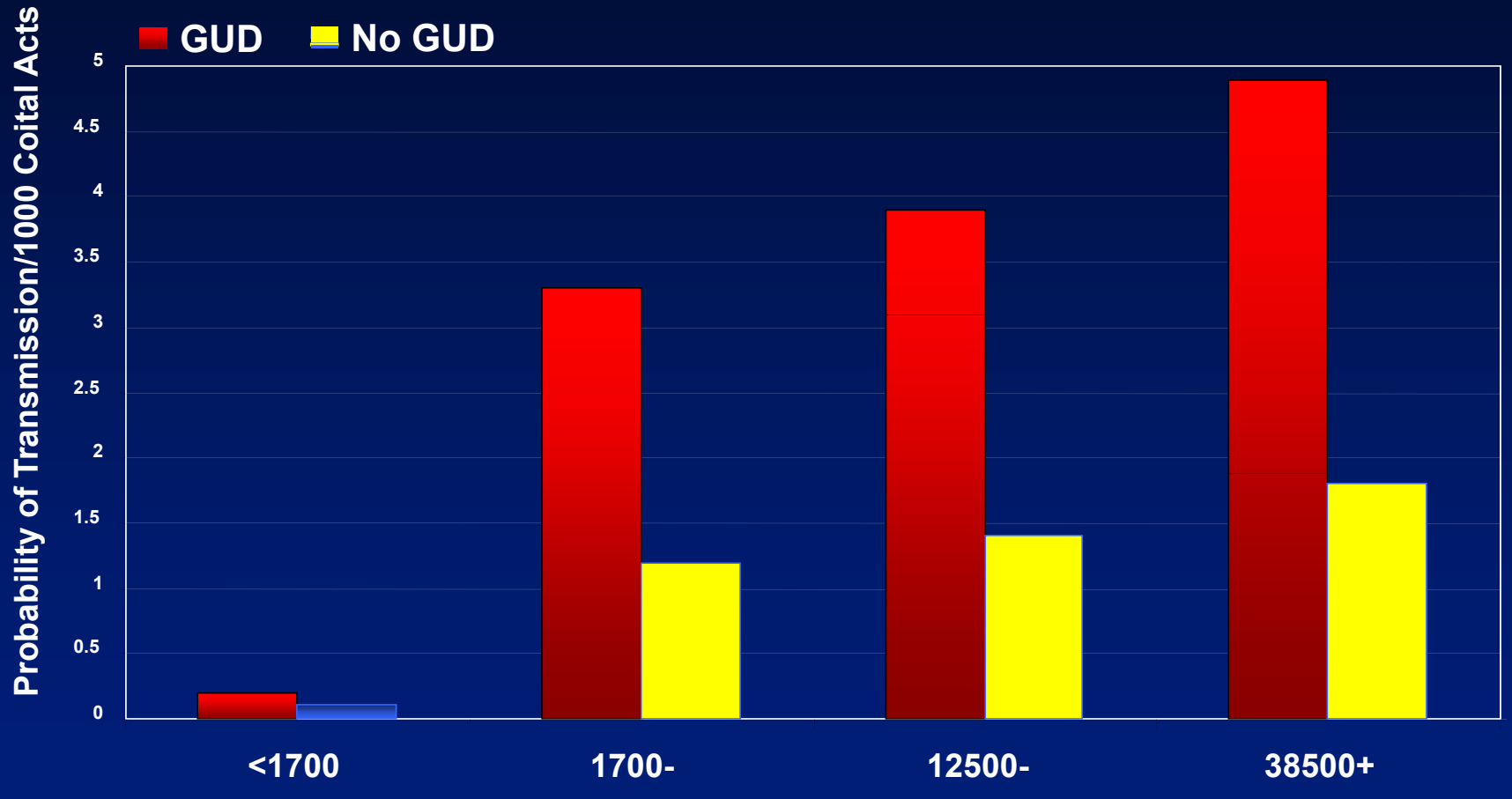
NA-ACCORD: Inicio Precoz vs Diferido (Análisis >500 vs. <500)

Stratified by Cohort and Calendar Year	Relative Hazard (RH)*	95% Confidence Interval	P-value
Deferral of HAART at <500	1.6	1.3, 1.9	<0.001
Female Sex	1.2	0.9, 1.6	0.117
Older Age (per 10 years)	1.6	1.5, 1.7	<0.001
Baseline CD4 count (per 100 cells)	1.0	1.0, 1.1	0.696

-Baseline HIV RNA not independent predictor of mortality
-Increased risk of mortality with deferral similar throughout 10-yr study period

Kitahata, et al. CROI 2009..

Viral Load Affects Probability of HIV Heterosexual Transmission



GUD = genital ulcer disease.

Gray R et al. *Lancet.* 2001;357:1149-1153.

"Our model suggests that massive scale-up of universal voluntary HIV testing with immediate initiation of ART could nearly stop transmission and drive HIV into an elimination phase in a high-burden setting within 1-2 years of reaching 90% of programme coverage."

- **Reuben M Granich, MD, et al. Lancet 2008;**

Pros y Cons de un Ensayo Aleatorizado

PROS

- Could provide the definitive answer about when to start therapy

CONS

- Requires 1000's of patients with CD4 >500 who are willing to be treated based on randomization
- Expensive and time-consuming
- Observational data already compelling
- Changing guidelines during study period could make study unenrollable or unethical
- Will the question or the chosen CD4 thresholds still be relevant by the time the results are available?

When is ART Started?
CD4 Count at Initiation, 2003-5

- 42 countries, 176 sites; n=33,008
- Since 2000, CD4 count at initiation in developed countries stable at ~150–200, increasing in Sub-Saharan Africa from 50 to 100
- In US, CD4 at initiation lower than in many other resource-rich nations

Egger M et al. 14th CROI; 2007; Los Angeles. Abstract 62.

Recomendaciones sobre "HIV Testing" CDC 2006

- *All* patients age 13-64 in *all* health-care settings should be tested
- Patients should be notified that testing will be performed, and can decline ("opt-out")
- Those at high risk should be tested at least annually
- Written consent should not be required; general consent for medical care is sufficient
- Prevention counseling should not be *required*

MMWR Sept 22, 2006;55(RR14):1-17

Conclusiones

- Estudios observacionales coinciden en el inicio de tratamiento antes de <350
- Evidencia creciente en *algunos* estudios para inicio de CD4 >500
- Al contrario de otras enfermedades infecciosas, debe probarse la necesidad del inicio precoz; en ausencia de datos, se elige por defecto el inicio tardío
- Es probable que en el futuro nos preguntemos "¿quién no debe ser tratado?"
  - Pacientes que no quieren o no son adherentes
  - ¿No progesores a largo plazo y *elite controllers*?

Objetivo de iniciar TAR según CD4

- **CD4 200 a 350:**
  - ✓ Enfermedades oportunistas
- **CD4 350-500 (>500 ??)**
  - ✓ Enfermedades no oportunistas
    - ➢ Linfomas y neoplasias
    - ➢ Progresión VHC, tratamiento VHB
    - ➢ Infecciones población general (TB, neumonías)
    - ➢ Eventos cardiovasculares
    - ➢ Alteraciones neuropsiquiátricas

Panel de expertos de GESIDA y PNS.