

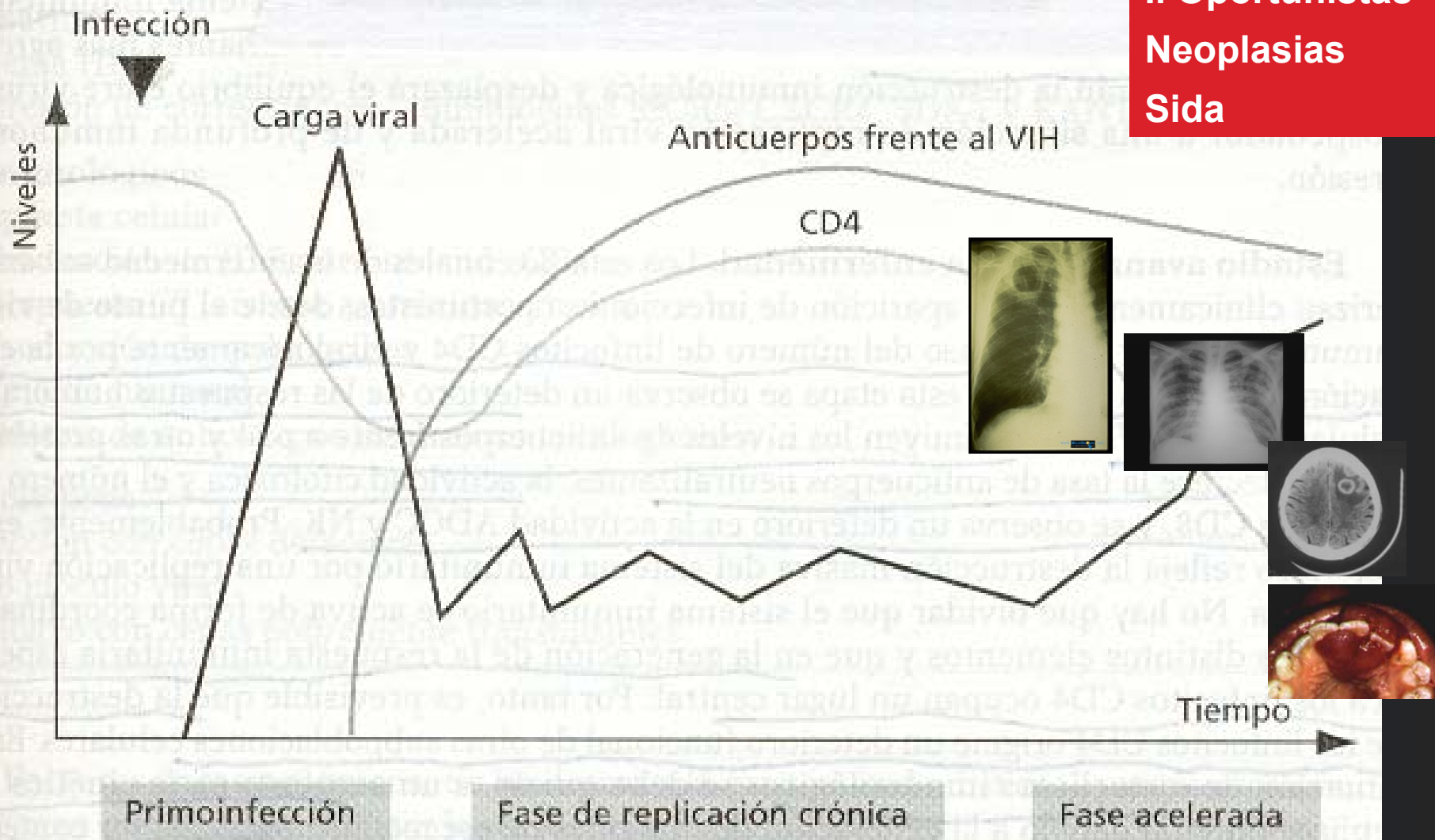
Diagnóstico y tratamiento precoz de la infección por VIH

- Importancia pronóstica
- Papel del médico internista

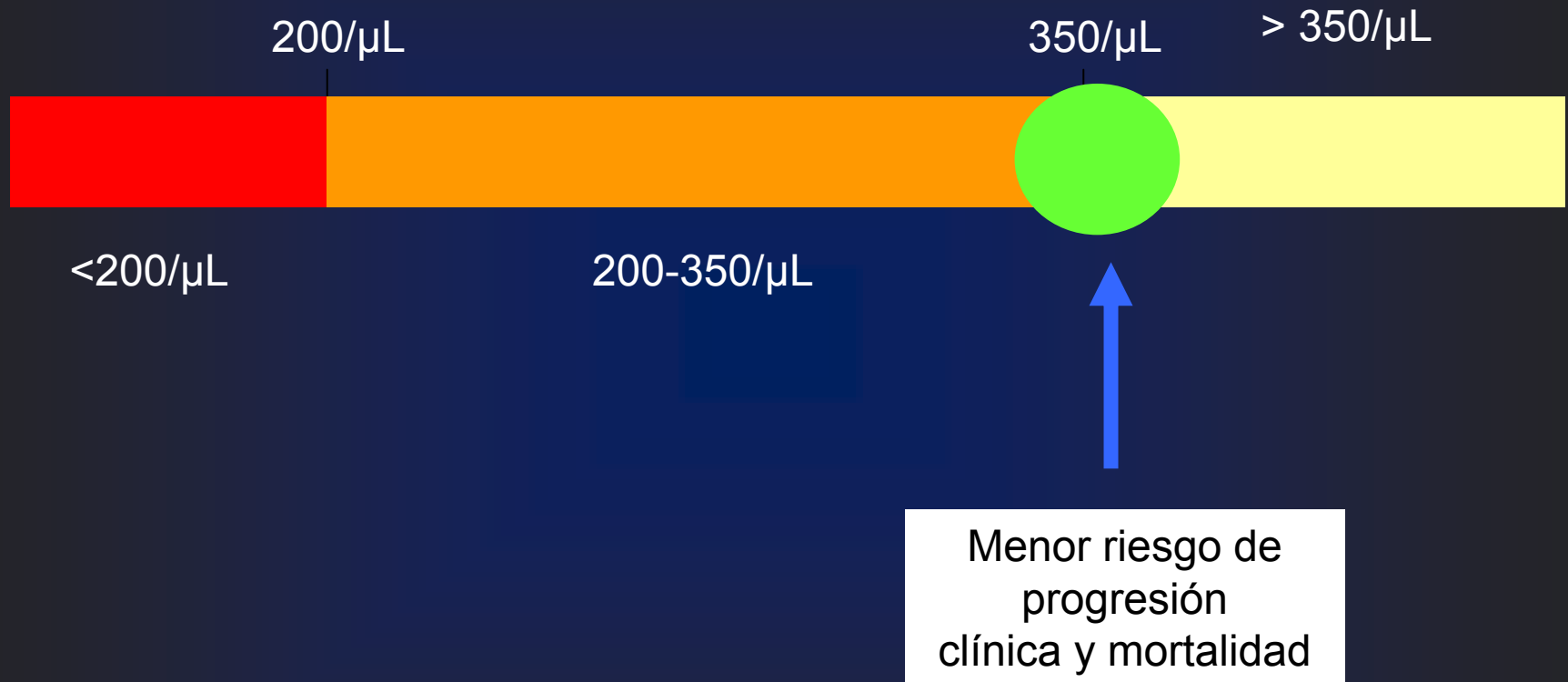
Joaquín Portilla
Hospital Gral Univ. Alicante

Hª natural de la infección por VIH:

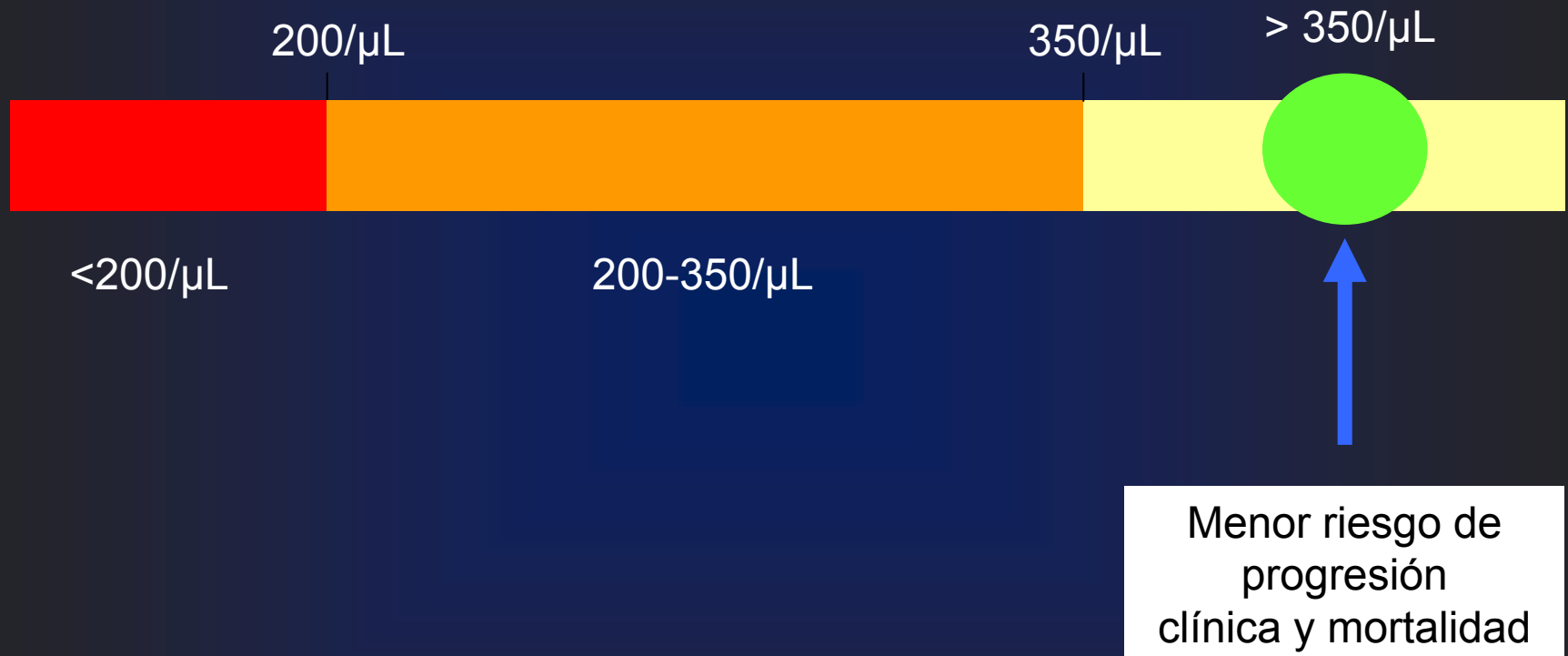
Síntomas B
I. Oportunistas
Neoplasias
Sida



¿Cuándo iniciar el TAR?



¿Cuándo iniciar el TAR?



Recomendaciones GESIDA/PNS (2009/2010)

Indicaciones de TARV en pacientes asintomáticos con infección crónica por VIH

Linfocitos CD4	Pacientes asintomáticos	Nivel evidencia
≤ 350	Recomendar	A*, B**
350-500	Recomendar en determinadas ocasiones***	B
>500	Diferir en general. Considerar en determinadas ocasiones***	B

* < 200; ** 200-350

*** Cirrosis hepática, hepatitis crónica por VHC; CVP-VIH $>10^5$ cop.;proporción de CD4 $<14\%$; edad >55 años; riesgo cardiovascular elevado; nefropatía VIH. Si hepatitis B que requiere tratamiento, se recomienda iniciar el TARV

***Se puede considerar iniciar el tratamiento en pacientes con alto riesgo de transmisión (Nivel B)

DHHS Guidelines: When to Start

Clinical Condition and/or CD4+ Count	Recommendations
• History of AIDS-defining illness • CD4+ count ≤ 350 cells/mm³ • Pregnant women • HIV-associated nephropathy • HBV coinfection when HBV treatment is indicated	Start antiretroviral therapy
CD4+ cell count > 350 cells/mm ³	Considerations: ▪ Older age ▪ Comorbidities ▪ CD4+ count decline > 120 cells/yr ▪ Serodiscordant relationships

IAS-USA Guidelines: When to Start

Clinical Condition and/or CD4+ Count	Recommendations
Symptomatic HIV infection Asymptomatic, CD4+ cell count < 350 cells/mm ³	Start antiretroviral therapy
CD4+ count ≥ 350 cells/mm ³	Considerations: - HIV-1 RNA > 100,000 copies/mL - CD4+ count decline > 100 cells/yr - HBV or HCV infection - Cardiovascular disease - HIV-associated nephropathy - Mother-to-child transmission - Serodiscordant relationships

2009 European Guidelines: When to Start

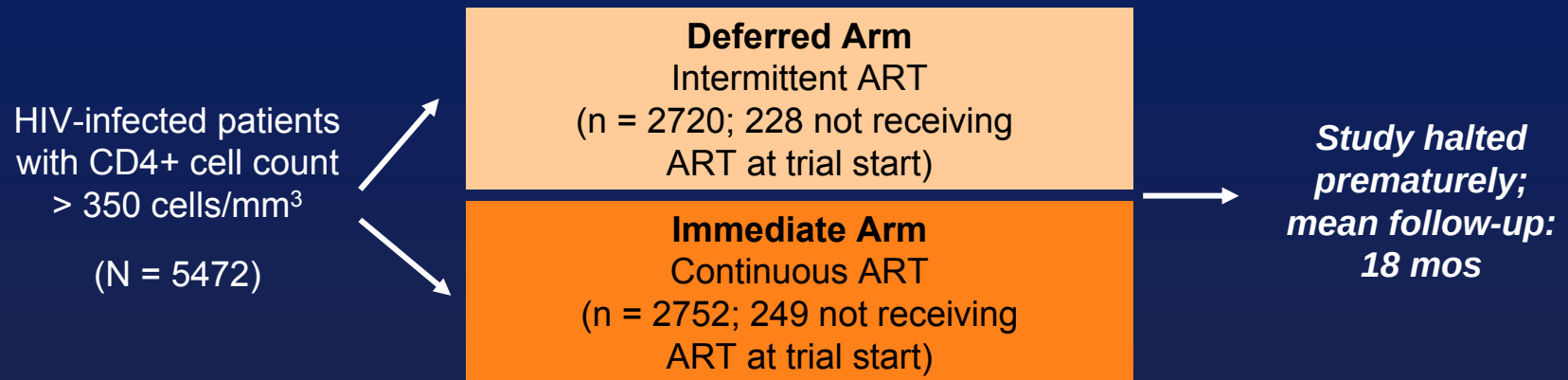
Guideline	Recommendation to Begin Immediate Therapy	Optimal Time Not Well Defined
EACS 2009 ^[1]	• Symptomatic HIV or active AIDS • CD4 < 200 cells/mm³ count (without delay) • CD4+ cell count < 350 cells/mm³ (recommended) • CD4+ cell count from 350-500 cells/mm³ with HCV or HBV, HIV associated nephropathy or other specific organ deficiency. Consider if HIV-1 RNA > 100,000 copies/mL, CD4+ decline > 50-100 cells/mm³/yr, pregnancy, high cardiovascular risk or malignancy • CD4+ cell count > 500 cells/mm³ . Offer if presence of ≥ 1 of the above co-morbid conditions. • Whatever CD4 and plasma HIV-RNA on an individual basis, if patient is seeking and ready for ARV therapy	• CD4+ cell count > 500 cells/mm³

1. EACS. Available at: http://www.eacs.eu/guide/1_Treatment_of_HIV_Infected_Adults.pdf.

Motivos para iniciar precozmente el TARV

- Evitar la progresión a sida y muerte
- Favorecer la recuperación inmunológica
- Disminuir la incidencia de enfermedades no relacionadas con el VIH
- Disminuir la toxicidad por TARV
- Evitar la transmisión del VIH

SMART: Subgroup Analysis in Patients Not Receiving ART at Study Entry



- Treatment definitions for subanalysis
 - Deferred: ART initiated when CD4+ cell count < 250 cells/mm³, CD4+ cell percentage < 15%, or HIV symptoms
 - Immediate: ART initiated immediately after randomization
- **Primary endpoints:**
 - OD or death from any cause
 - Fatal or nonfatal OD
 - Serious non-AIDS events
 - Fatal and nonfatal OD plus serious non-AIDS events

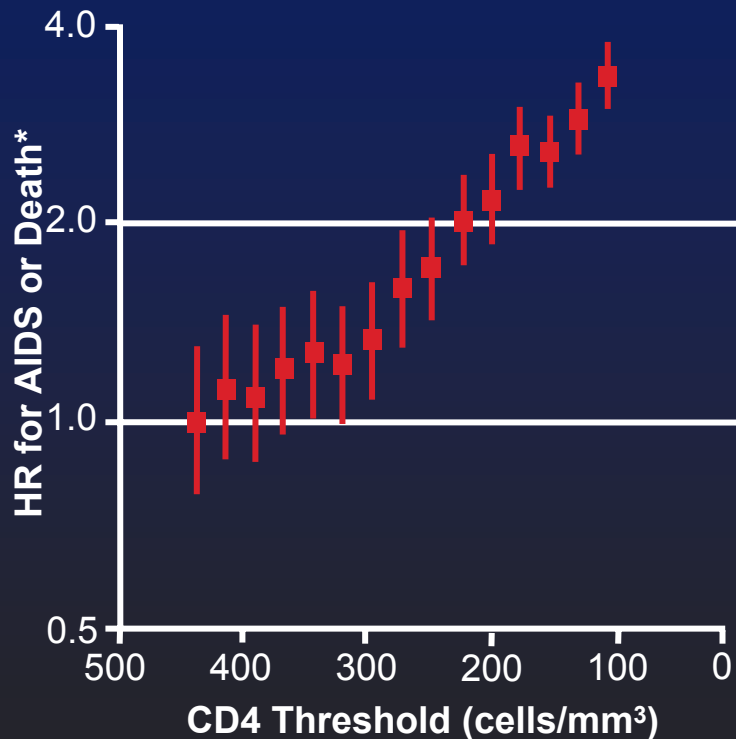
SMART: Immediate Therapy Reduces Risk of OD, Serious Non-AIDS Events

- Immediate group experienced substantially fewer events compared with deferred group
 - Excess risk associated with deferring therapy: 5.4 events/100 person-yrs

Event, n (Rate per 100 Person-Yrs)	Deferred Arm (n = 228)	Immediate Arm (n = 249)	HR (DC/VS)	95% CI	P Value
OD/death	15 (4.8)	5 (1.3)	3.5	1.3-9.6	.02
OD only	11 (3.5)	4 (1.1)	3.3	1.0-10.3	.04
Serious non-AIDS events	12 (3.9)	2 (0.5)	7.0	1.6-31.4	.01
Composite	21 (7.0)	6 (1.6)	4.2	1.7-10.4	.002

ART CC: Supports Initiating ART at CD4 Threshold of 350 cells/mm³

- Analysis of 15 cohorts from US and Europe (ART Cohort Collaboration) N = 24,444



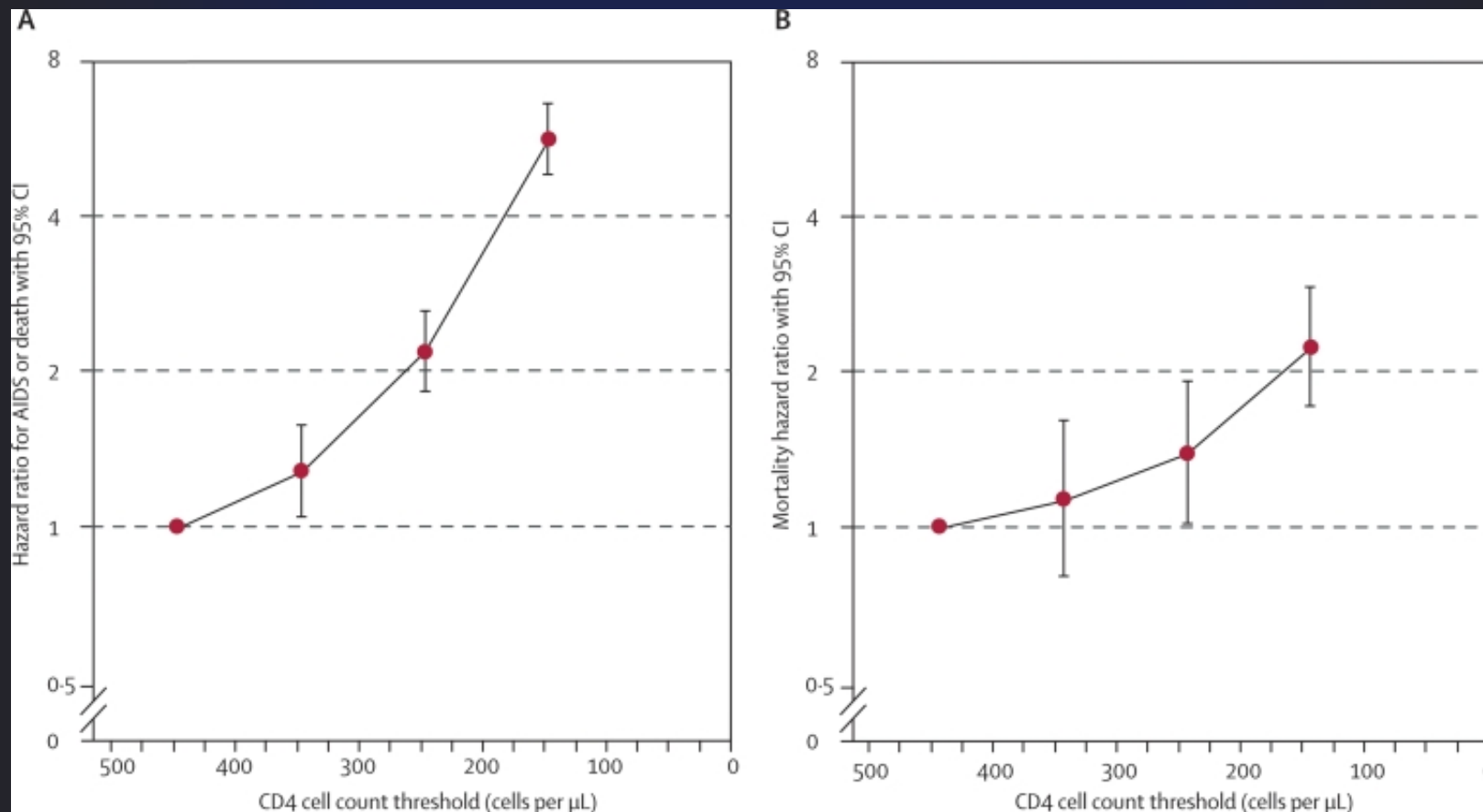
Comparison	HR* (95% CI)
1-100 vs 101-200	3.35 (2.99-3.75)
101-200 vs 201-300	2.21 (1.91-2.56)
201-300 vs 301-400	1.34 (1.12-1.61)
251-350 vs 351-450	1.28 (1.04-1.57)
351-450 vs 451-550	0.99 (0.76-1.29)

*Adjusted for lead-time and unobserved events.

Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies

When To Start Consortium†

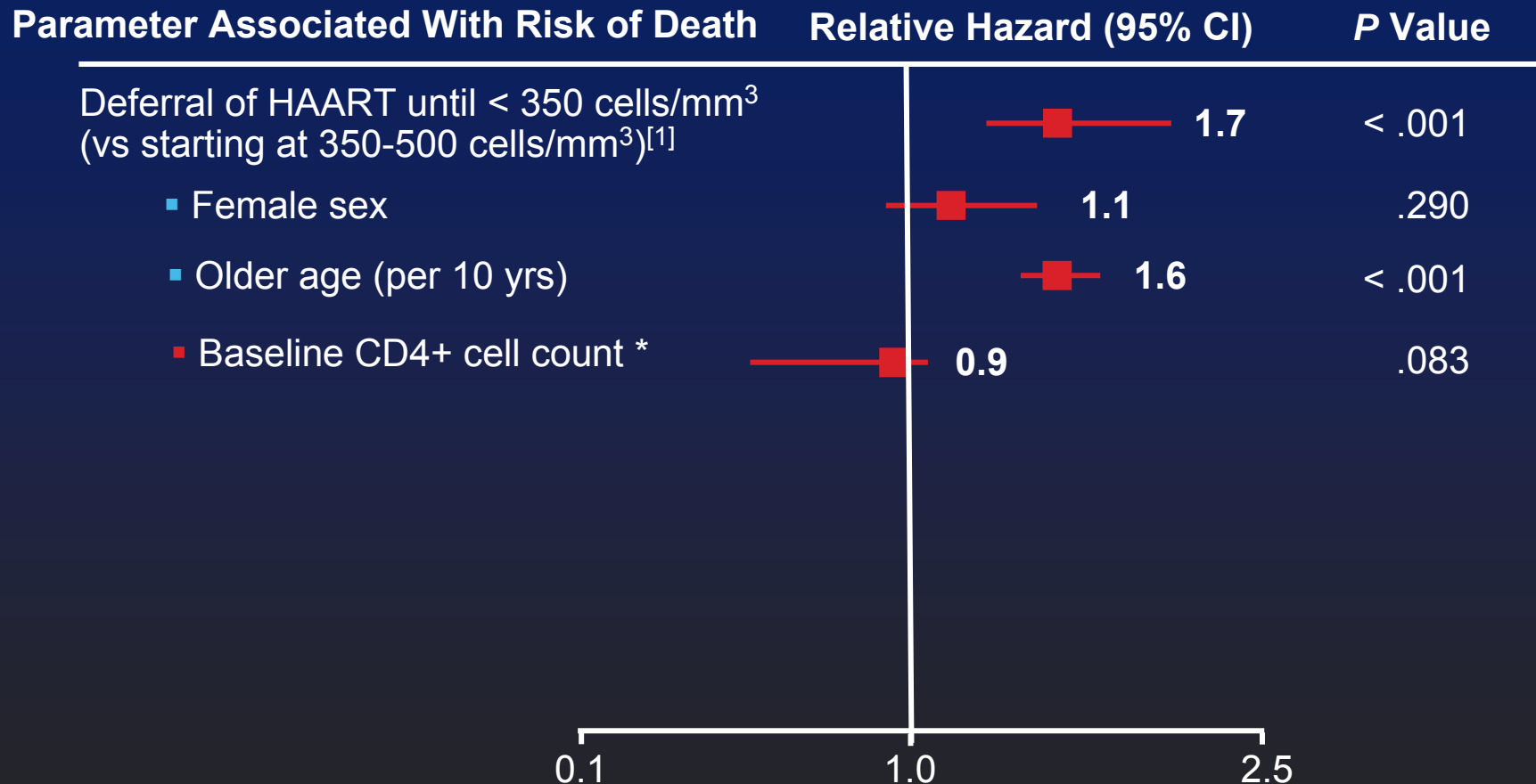
Hazard ratios for the cumulative effect of deferred initiation of combination antiretroviral therapy for (A) AIDS or death and (B) death alone, compared with starting treatment at CD4 cell count range 351–450 cells per μL



NA-ACCORD: Earlier vs Deferred HAART

- NA-ACCORD, established in 2006, includes 22 HIV research cohorts (US, Canada)
 - Current analysis includes 9174 asymptomatic patients with CD4+ cell count ≥ 500 cells/mm³ at study visit between 1996-2006
- Compared outcomes based on treatment according to following definitions
 - Immediate treatment: initiated HAART within 1.5 years of first CD4+ cell count of ≥ 500 cells/mm³
 - Deferred treatment: did not initiate HAART within 1.5 years of first CD4+ cell count of ≥ 500 cells/mm³ but did initiate HAART within 1.5 years of first CD4+ cell count of < 500 cells/mm³
- Primary outcome: death from any cause

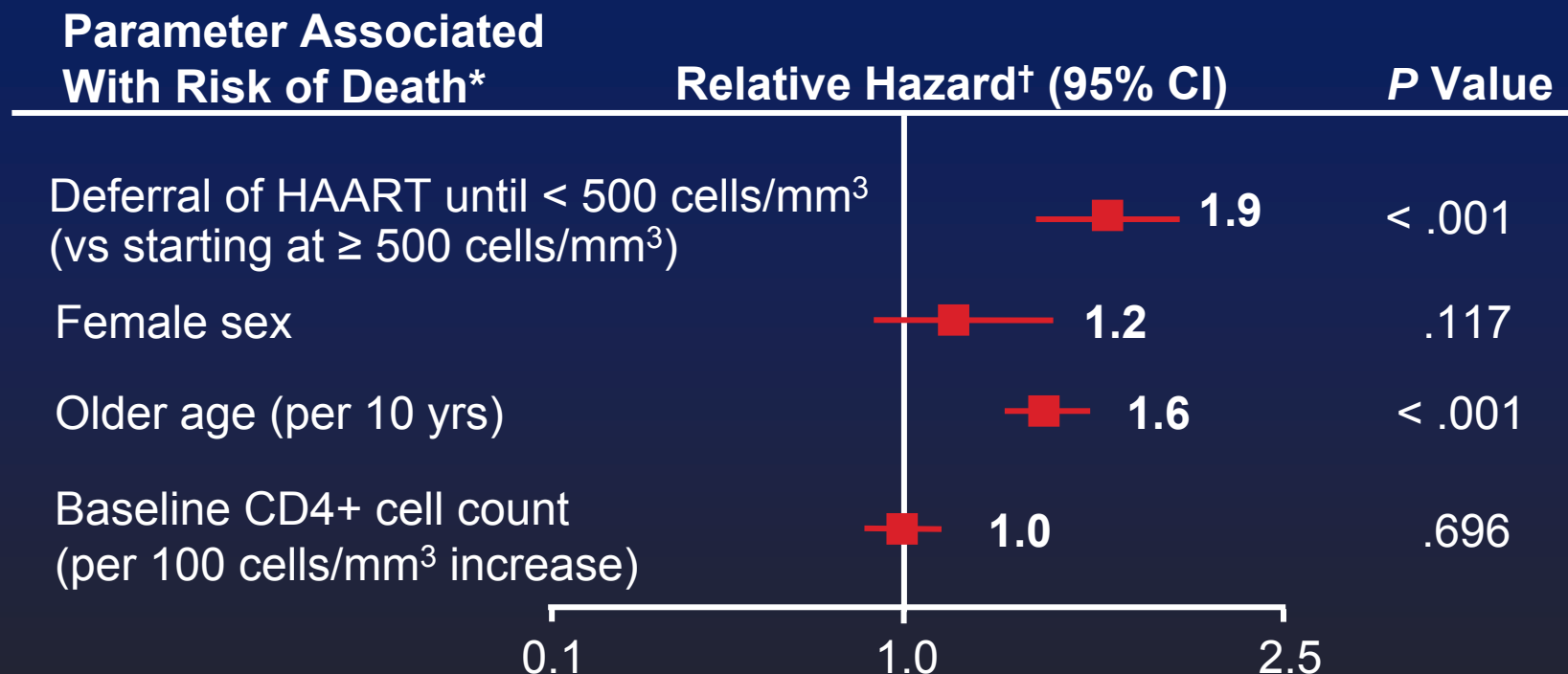
NA-ACCORD: Survival Benefit With Earlier vs Deferred HAART



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

2. Kitahata MM, et al. CROI 2009. Abstract 71. N Eng J Med 2009

NA-ACCORD: Survival Benefit of Earlier HAART by Baseline Factor



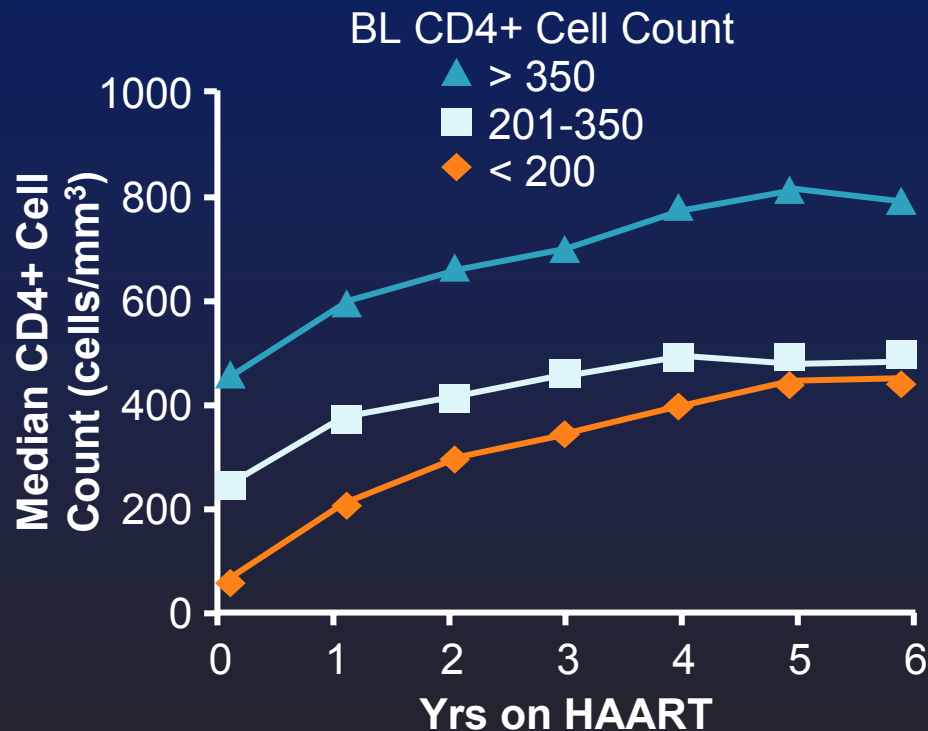
*All causes of death unspecified. †Stratified by cohort and calendar year.

Motivos para iniciar precozmente el TARV

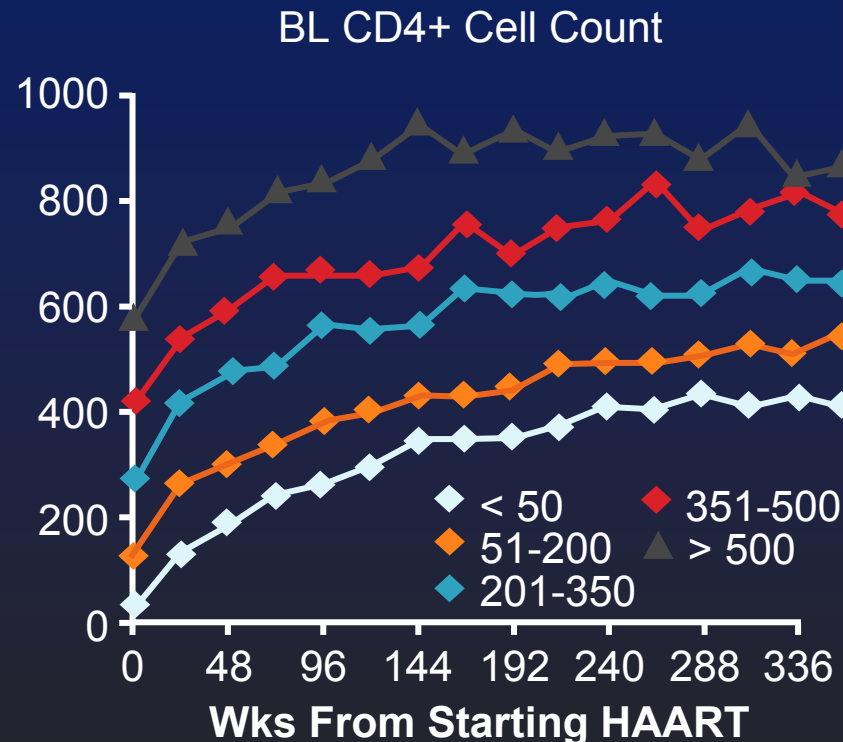
- Evitar la progresión a sida y muerte
- Favorecer la recuperación inmunológica
- Disminuir la incidencia de enfermedades no relacionadas con el VIH
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Likelihood of Achieving Normal CD4+ Cell Count Depends on BL Level

Johns Hopkins HIV Clinical Cohort^[1]



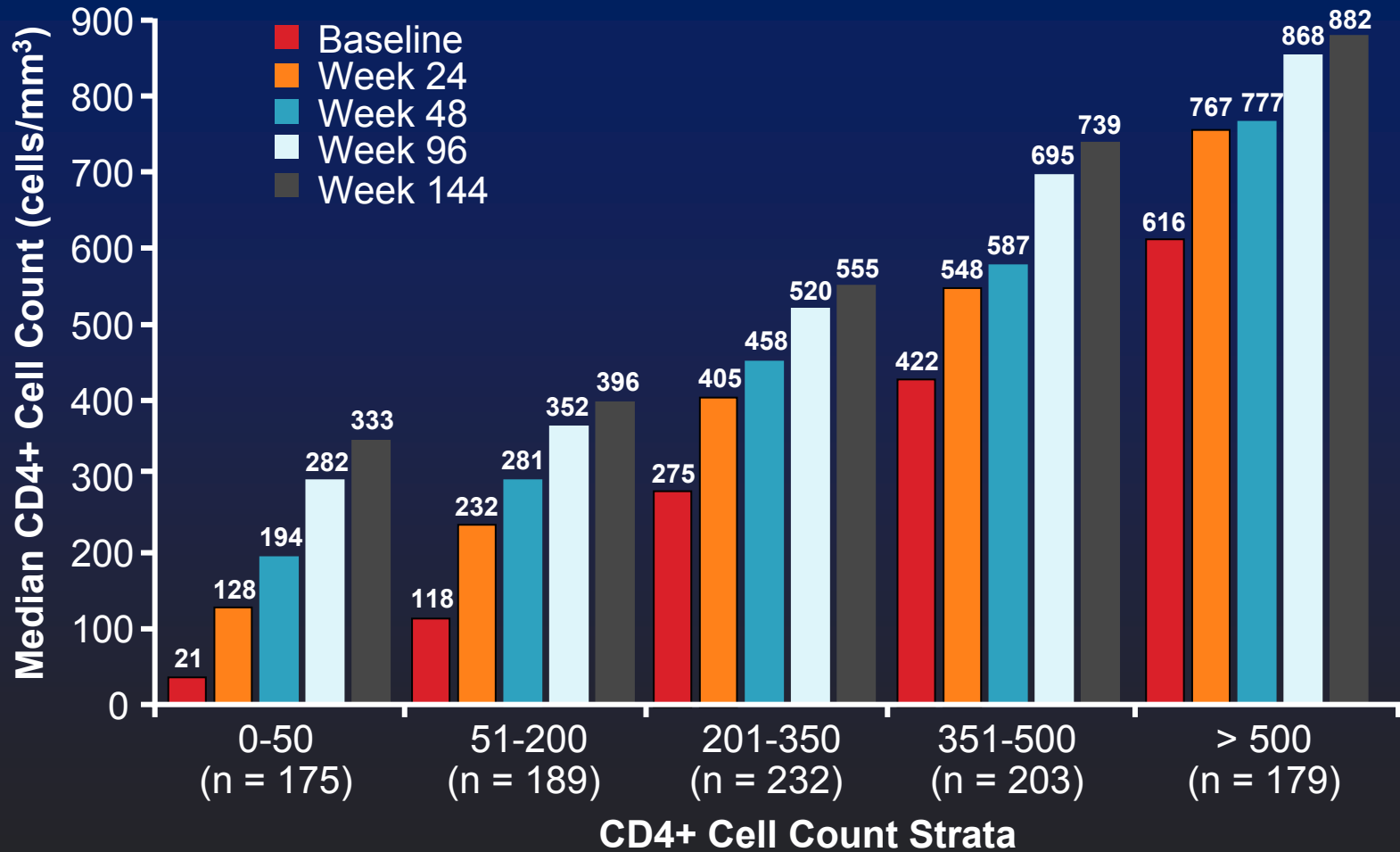
ATHENA National Cohort^[2]



Initiation of HAART in Patients With Baseline CD4+ Cell Count ≤ 350 cells/mm³ Does Not Completely Restore Absolute T-Cell Counts to Normal Levels After 3 Years of Treatment

- ACTG 384: large, international, randomized trial that compared 6 different HAART strategies in treatment-naïve individuals
- Patients classified into 5 strata based on baseline CD4+ cell count (≤ 50 , 51-200, 201-350, 351-500, and > 500 cells/mm³)
- All analyses based on available data regardless of whether patients had virologic suppression (HIV-1 RNA < 50 copies/mL)
- Reference ranges for immune cell subsets calculated from data from 48 healthy HIV-uninfected patients who participated in ACTG A5113
 - 50% of individuals aged 18-30 years, 50% aged 45 years or older
 - 25th-75th percentiles for these individuals used for comparison of T-cell subsets in HIV-infected individuals

Results



Robbins GK, et al. Clin Infect Dis. 2009;48:350-361.

Results

- Compared with uninfected controls, patients with baseline CD4+ cell counts > 350 cells/mm³ had normalized CD4+ naive and memory cell counts by Week 48
 - Reference value of CD4+ naive:memory cell ratio in HIV-uninfected controls: 0.87

Median CD4+ Naive: Memory Cell Ratios	CD4+ Cell Count Stratum, cells/mm ³				
	0-50	51-200	201-350	351-500	> 500
Week 0	0.21	0.45	0.57	0.66	0.81
Week 24	0.23	0.40	0.71	0.79	0.87
Week 48	0.41	0.55	0.72	0.95	0.96
Week 96	0.51	0.53	0.65	0.80	0.80
Week 144	0.43	0.50	0.68	0.80	0.69

Other results

- Median time to virologic suppression (HIV-1 RNA < 50 copies/mL) differed significantly based on baseline CD4+ cell count

Outcome	CD4+ Cell Count Stratum, cells/mm ³					P Value
	0-50	51-200	201-350	351-500	> 500	
Median time to virologic suppression, wks	16	16	12	12	12	< .001

- Median time to virologic suppression also differed significantly based on baseline HIV-1 RNA ($P < .001$)
 - HIV-1 RNA < 35,000 copies/mL: 8 weeks
 - HIV-1 RNA 35,000-100,000 copies/mL: 12 weeks
 - HIV-1 RNA > 100,000 copies/mL: 16 weeks

Mortality in HIV+ Pts Similar to General Population When CD4 > 500 for 5-7 Yrs

- Overall mortality in HIV-infected patients 7-fold higher than general population
- After 6th year of follow-up, mortality among patients with CD4+ cell counts ≥ 500 cells/mm³ comparable to that of the general population

Truncation for Duration of Follow-up, Yrs	Median Time Spent With CD4+ Cell Count ≥ 500 cells/mm ³ After Truncated Duration of Follow-up, Yrs (IQR)	Deaths, n	SMR (95% CI)
0 (n = 1208)	4.5 (2.1-7.0)	37	2.5 (1.8-3.5)
1 (n = 1156)	4.2 (2.1-6.4)	29	2.1 (1.4-3.1)
2 (n = 1083)	4.0 (2.1-5.6)	26	2.2 (1.4-3.2)
3 (n = 1031)	3.5 (1.8-4.8)	22	2.1 (1.3-3.2)
4 (n = 967)	3.0 (1.5-3.8)	18	2.1 (1.3-3.4)
5 (n = 864)	2.4 (1.4-3.0)	12	1.9 (1.0-3.2)
6 (n = 763)	1.6 (1.0-2.2)	2	0.5 (0.1-1.6)
7 (n = 610)	0.9 (0.5-1.3)	1	0.5 (0.0-2.6)

SMR: Standardized mortality ratios (were computed in relation to 2002 French population rates)

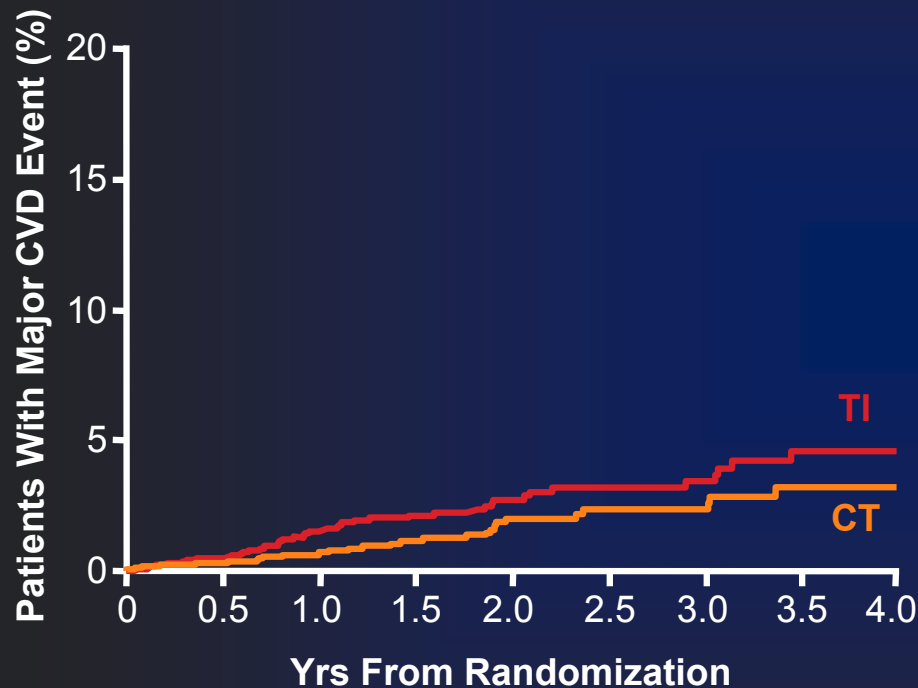
Motivos para iniciar precozmente el TARV

- Evitar la progresión a sida y muerte
- Favorecer la recuperación inmunológica
- Disminuir la incidencia de enfermedades no relacionadas con el VIH
- Disminuir la toxicidad por TARV
- Evitar la transmisión del VIH

Motivos para iniciar precozmente el TARV

- Disminuir la incidencia de enfermedades no relacionadas con el VIH:
 - Enfermedad cardiovascular
 - Nefropatía por VIH
 - Cirrosis e insuficiencia hepática en ptes co-infectados por VHC ó B
 - Cánceres no definitorios de sida

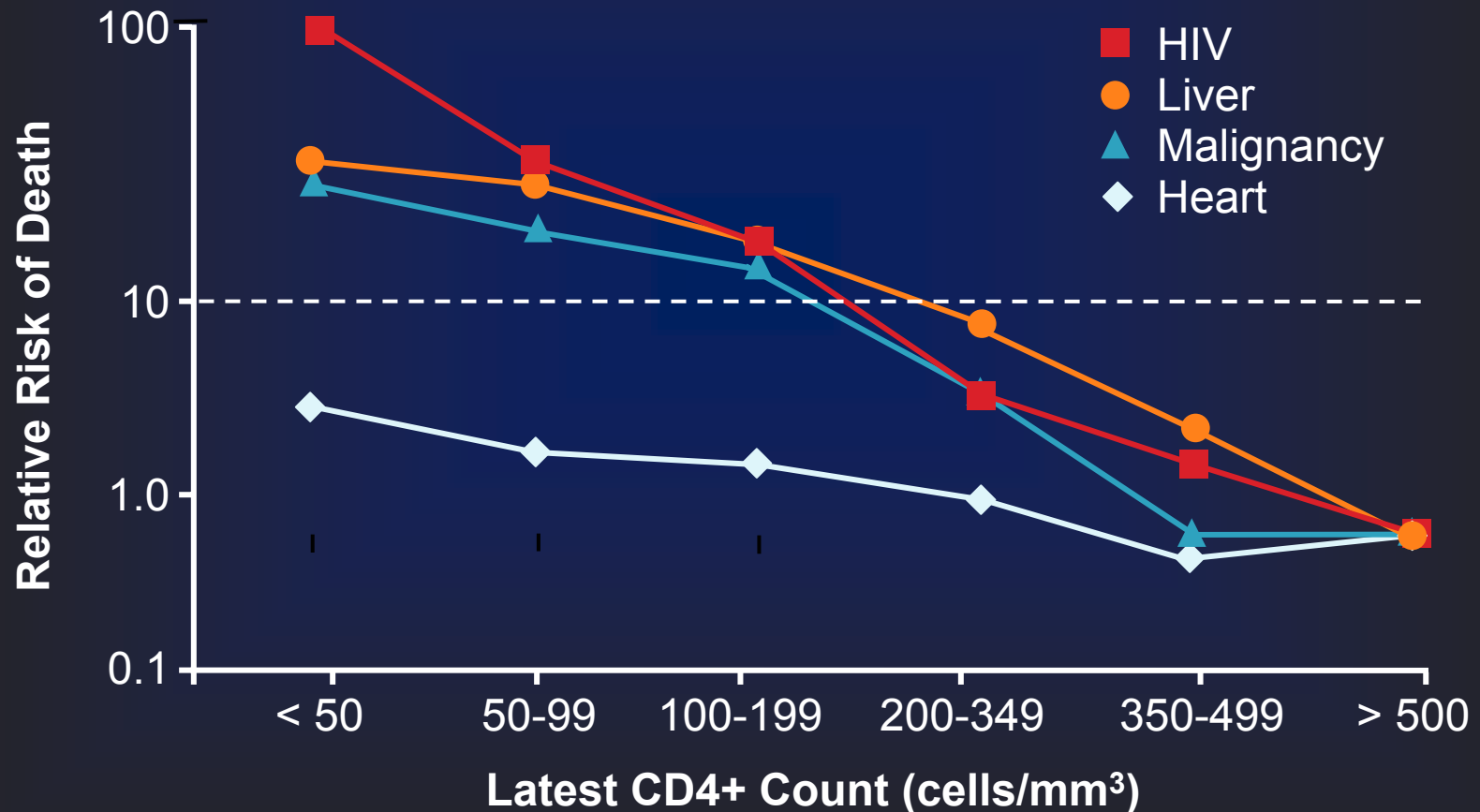
SMART: Risk of Major CVD Events as Function of TI



TI	2752	1306	713	379	10
CT	2720	1292	696	377	10

Relative Hazard of Expanded CVD Events ^[1]		
Event	RR (TI/CT) (95% CI)	P Value
Clinical MI, silent MI, CAD requiring invasive procedure or surgery, death from CVD	1.57 (1.00-2.46)	.05
+ PVD, CHF, CAD requiring drugs	1.49 (1.04-2.11)	.03
+ unobserved death from unknown cause	1.58 (1.12-2.22)	.009

D:A:D: Higher CD4+ Count Associated With Lower Risk of Non-HIV Death



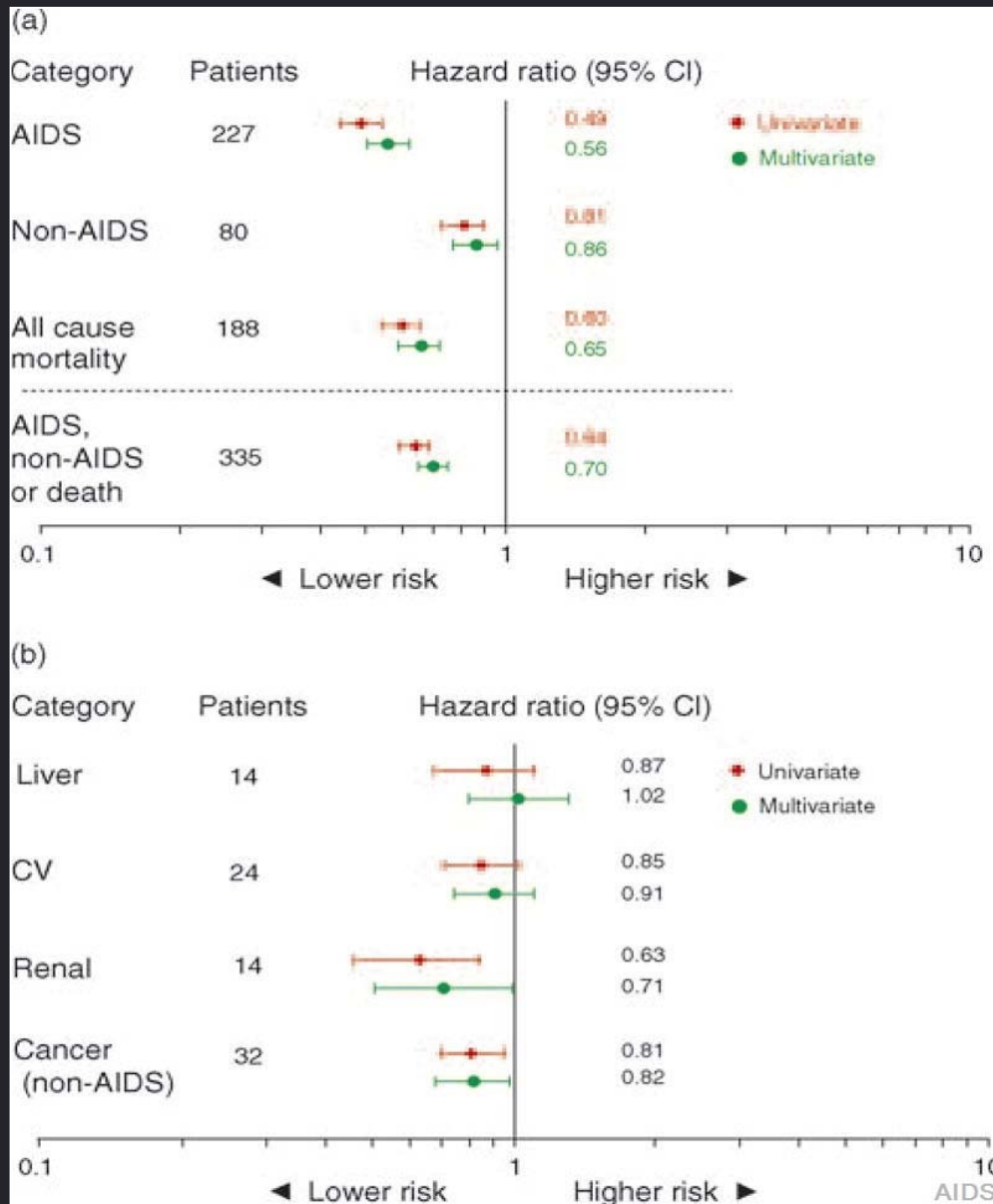
CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. FIRST Study

Table 1. Baseline characteristics of FIRST cohort and by selected outcomes.

	Outcome						
Group	FIRST	AIDS	Non-AIDS	Liver	Cardiovascular	Renal	Cancer (non-AIDS)
Patients	1397	227	80	14	24	14	32
Deaths	188	89	27	8	5	4	10
Age (median)	38	38	41	41	44	40	41
Sex (% female)	21	23	16	7	21	14	16
Race/ethnicity							
Black (%)	54	59	56	21	58	93	53
Latino (%)	17	20	9	21	4	0	9
White (%)	26	19	33	57	38	0	34
Other (%)	3	2	3	0	0	7	3
Intravenous drug use (%)	15	18	24	36	25	21	19
Hepatitis B or C (%)	25	32	40	79	29	50	31
Prior AIDS (%)	38	67	48	57	50	57	34
Baseline CD4 (cells/ μ l)	163	43	114	170	82	30	146
Median/IQR	36–332	14–132	24–257	37–288	19–248	11–251	45–266
Baseline RNA (log ₁₀ copies/ml)	5.2	5.5	5.3	5.1	5.4	5.2	5.3
Median/IQR	4.6–5.6	5.0–5.9	4.8–5.7	4.8–5.3	4.7–5.7	4.8–5.7	4.6–5.8

Non-AIDS: non-fatal and fatal events related to liver, cardiovascular, and renal diseases and non-AIDS defining cancers. AIDS: non-fatal and fatal events adapted from 1993 CDC AIDS criteria to include additional conditions: invasive aspergillosis, bartonellosis, Chaga's disease (American trypanosomiasis) of the central nervous system, disseminated herpes zoster, visceral Leishmaniasis (Kala-Azar), Hodgkin lymphoma, non-Hodgkin's lymphoma (all cell types), chronic intestinal microsporidiosis (>1 month), Nocardiosis, extrapulmonary *Penicillium marneffii*, extrapulmonary *Pneumocystis jirovecii*, and *Rhodococcus equi* disease. IQR, interquartile range.

Baker, Jason V et al. AIDS. 2008.



Risk of event by latest CD4+ count. Univariate and multivariate hazard ratio (HR) estimates of risk for events are plotted **per 100 cells/ μ l higher CD4+ count** (a). 'Non-AIDS' includes nonfatal and fatal events related to liver, cardiovascular, and renal diseases and non-AIDS defining cancers. 'All-cause mortality' is death from any cause: 'AIDS, non-AIDS, or Death' is any non-fatal AIDS or non-AIDS event plus death from any cause. Multivariate HR are adjusted for latest HIV RNA and baseline covariates: age, sex, race/ethnicity, prior AIDS, and hepatitis B or C virus coinfection. Risk for individual non-AIDS diseases per 100 cells/ μ l higher CD4+ count are also presented (b).

Baker, Jason V et al.
AIDS. 22:841-848, 2008

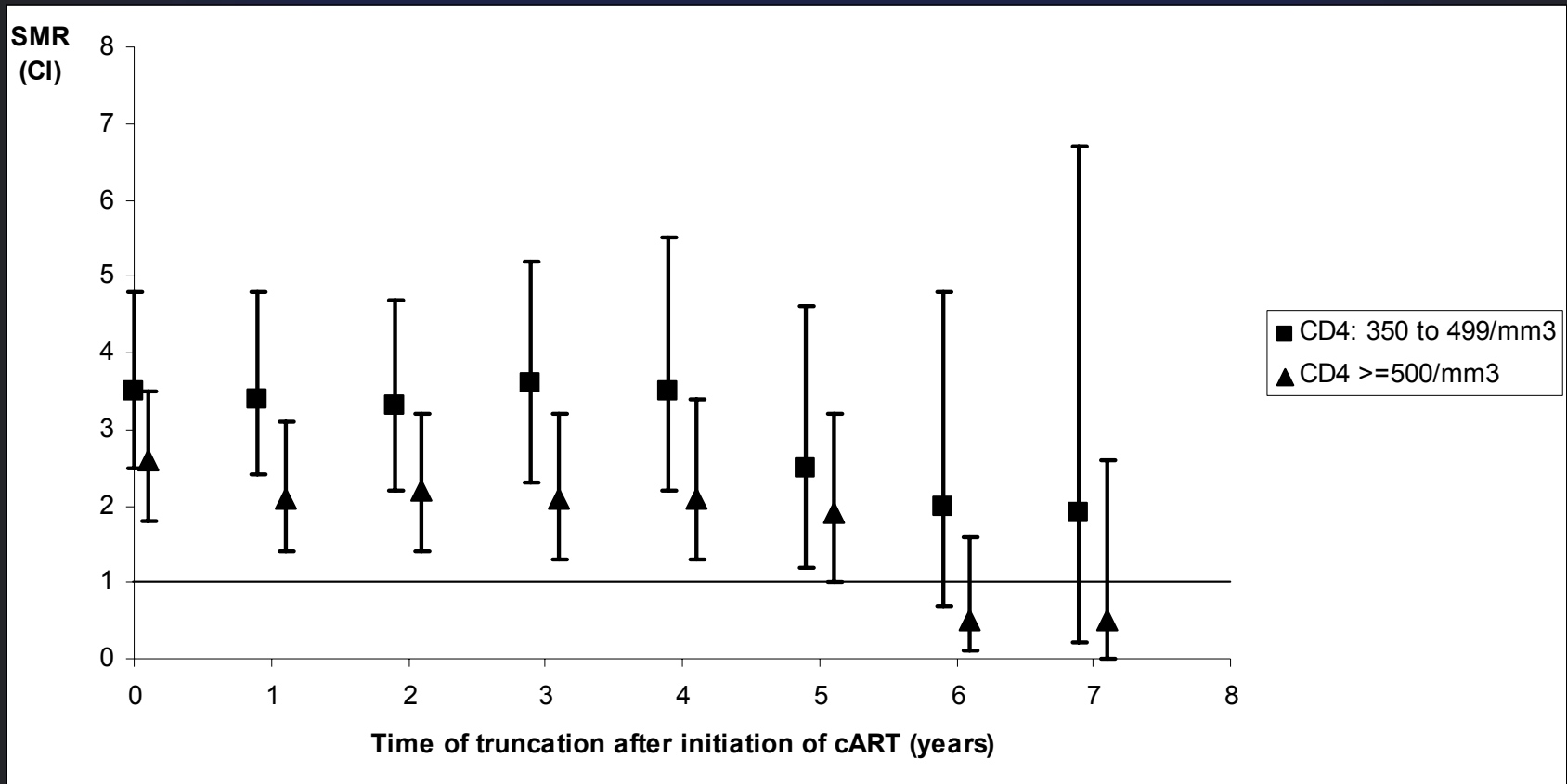
Incidence of Non-AIDS–Defining Cancers Increasing, Constituting Majority of Cancer Cases Despite the Use of HAART

- 4498 HIV-infected US military beneficiaries (33.486 person-years of follow-up)

- Multivariate analysis revealed several cancer predictors

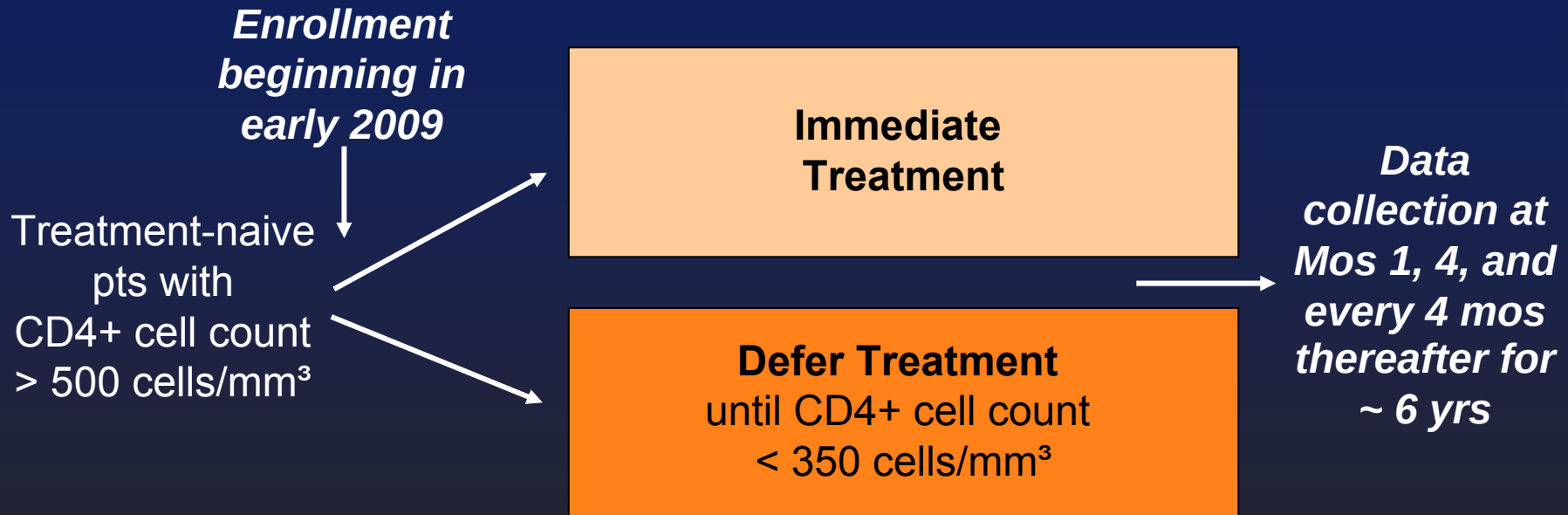
Predictor	Any Cancer		AIDS		nADC	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Male sex	2.37 (1.39-4.05)	.002	3.23 (1.64-6.73)	.001	1.44 (0.63-3.30)	.38
Noncancer AIDS event*	2.34 (1.86-2.97)	<.001	2.11 (1.62-2.77)	<.001	1.29 (0.78-2.16)	.33
Age at HIV-1 diagnosis, per 10-yr increase	1.37 (1.22-1.53)	<.001	1.10 (0.94-1.28)	.23	1.99 (1.67-2.36)	<.001
CD4+cell count, per 50 cells/mm ³ increase*	0.86 (0.84-0.88)	<.001	0.76 (0.73-0.80)	<.001	0.99 (0.96-1.03)	.69
HAART use*	0.53 (0.38-0.75)	<.001	0.40 (0.25-0.65)	<.001	0.74 (0.44-1.25)	.26
Black race (vs white)	0.58 (0.47-0.71)	<.001	0.68 (0.54-0.87)	.002	0.33 (0.21-0.50)	<.001
Other race (vs white)	0.68 (0.48-0.96)	.03	0.83 (0.56-1.24)	.36	0.44 (0.22-0.88)	.002

Standardized mortality ratio (SMR) in 2435 HIV-infected adults, ANRS CO8 APROCO-COPILOTE and ANRS CO3 AQUITAINE cohorts, 1997-2005, according to cumulated time spent with CD4 cell count between 350 and 499 /mm³ and ≥ 500 /mm³, after the time of truncation



START Study: Proposed Study Design

- Early treatment pilot study, estimated enrollment: 4000 patients

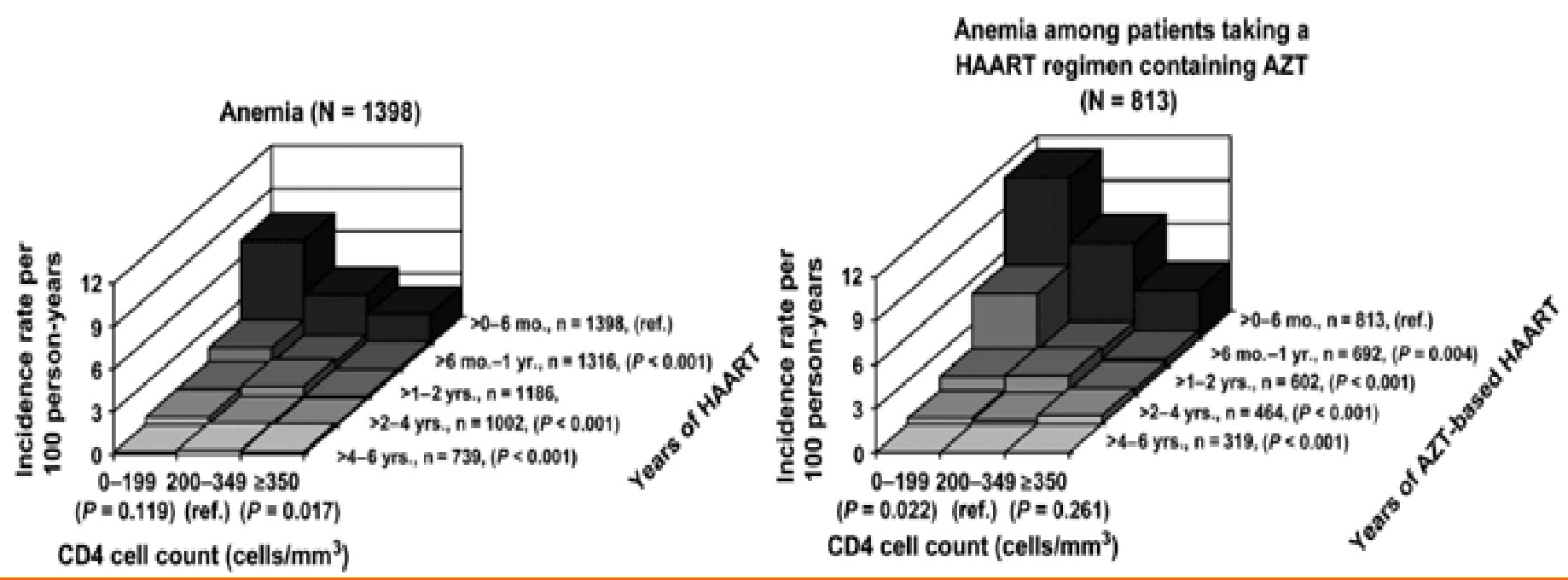


Study endpoints: fatal AIDS or nonfatal serious AIDS events (cardiovascular, liver, renal, and cancer), and non-AIDS–related deaths

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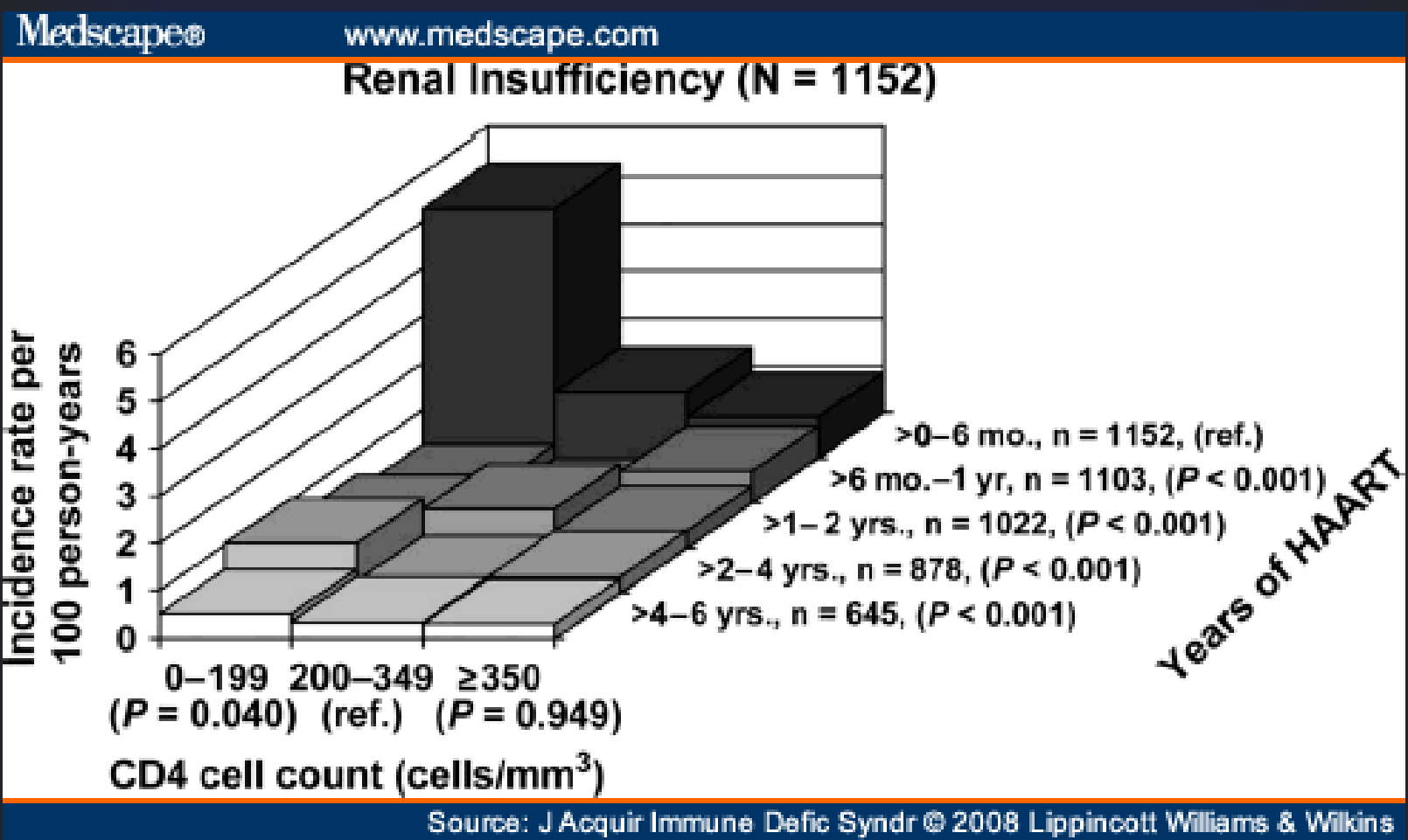
Initiation of antiretroviral therapy at CD4 cell counts ≥ 350 cells/mm³ does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency



Source: J Acquir Immune Defic Syndr © 2008 Lippincott Williams & Wilkins

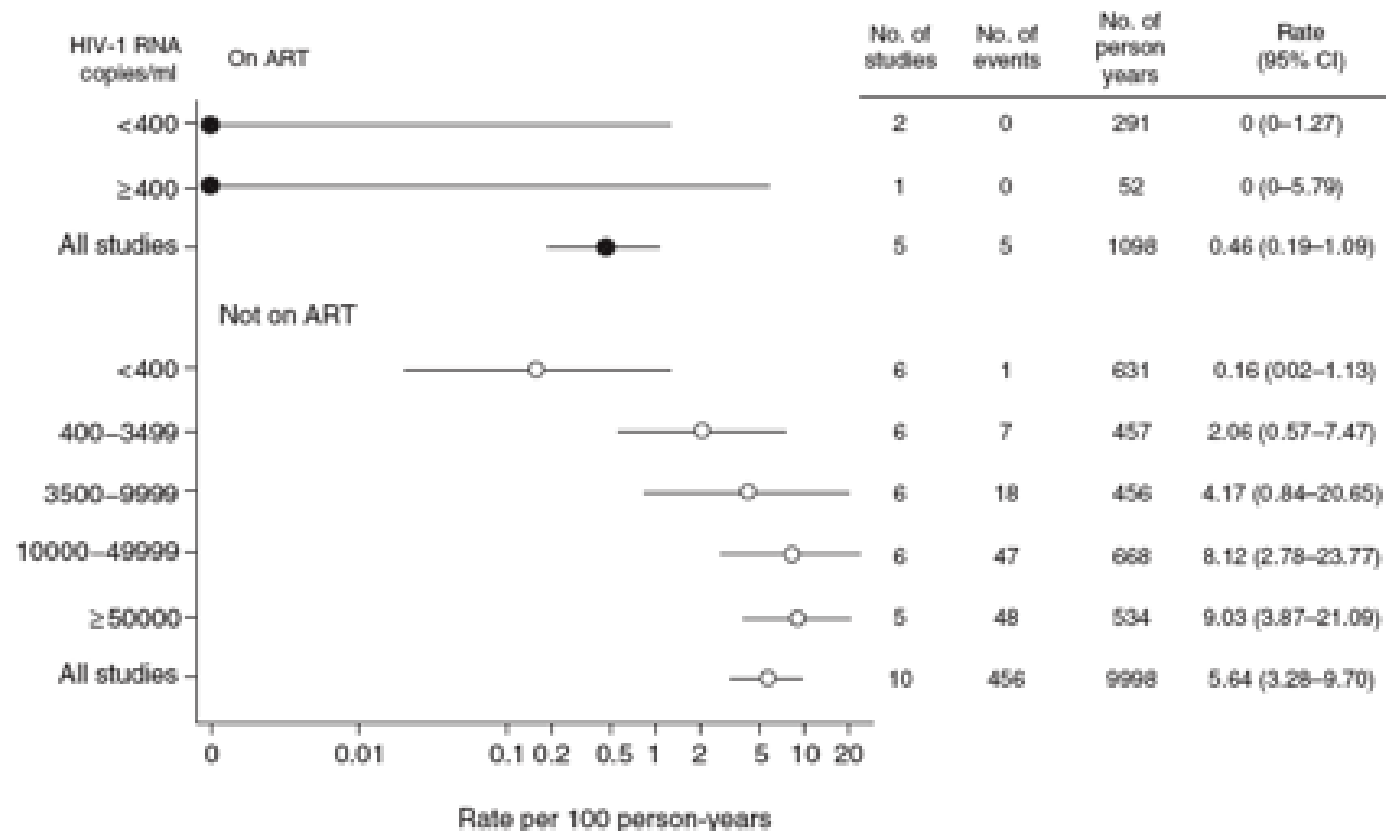
Lichtenstein KA, et al (HIV Outpatient Study –HOPS-)
J Acquir Immune Defic Syndr. 2008

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Lichtenstein KA, et al (HIV Outpatient Study –HOPS-)
J Acquir Immune Defic Syndr. 2008

Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis



Diagnóstico y tratamiento precoz de la infección por VIH

**¿Estamos diagnosticando de forma
precoz la infección por VIH en nuestro
país?**

Cohorte CoRIS, 2004-2008

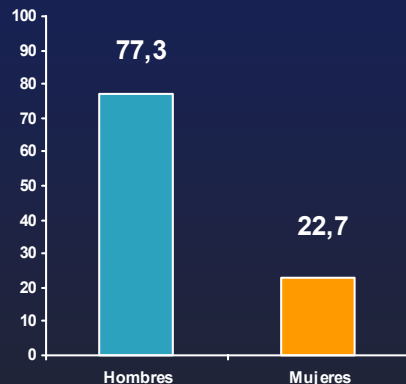
- Cohorte abierta, prospectiva y multicéntrica
- Participan 28 grupos asistenciales de 13 CCAA
- Personas con infección VIH, >13 años de edad, sin TARV y que inician seguimiento por 1ª vez
- Retraso diagnóstico:
 - Enfermedad definitoria de sida, ó
 - $< \text{CD4}^+ / 200 / \mu\text{L}$ al diagnóstico de la infección

Cohorte CoRIS, 2004-2008

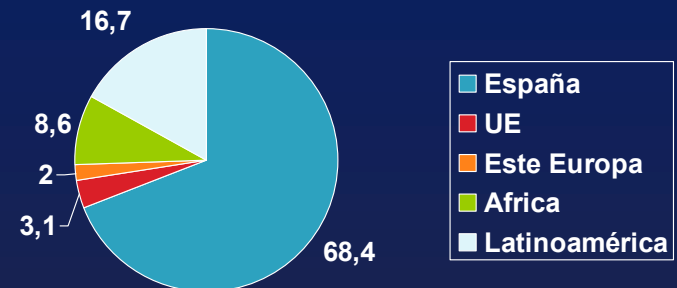
Características sociodemográficas y epidemiológicas (n=4.418):

Mediana edad al diagnóstico: 33 (2-79)

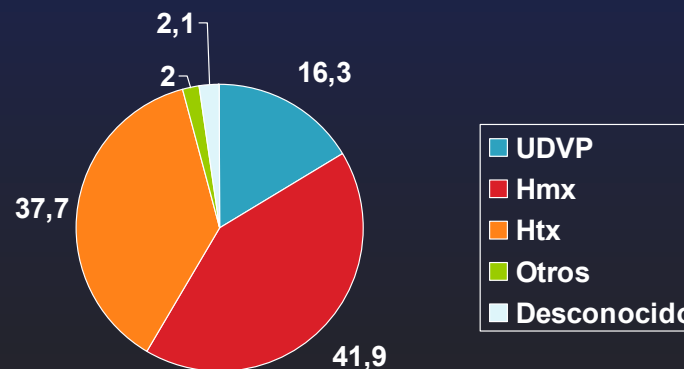
Porcentaje dx según género



Porcentaje dx según lugar origen



Porcentaje dx según categoría transmisión



Cohorte CoRIS, 2004-2008

Características clínicas al diagnóstico:

	N=4.418
Estadio clínico: • Asintomático • Síntomas B • Sida • Desconocido	72,8% (3.217) 11,5% (506) 15,2% (671) 0,5% (24)
Nivel CD4+/μL: • ≤ 50 • 51-200 • 201-350 • 351-500 • >500 • Desconocido	11% (485) 19,1% (844) 20,8% (918) 18,6% (821) 27,9% (1.232) 2,7% (118)
Coinfección por VHB	5,8%
Coinfección por VHC	21,8%

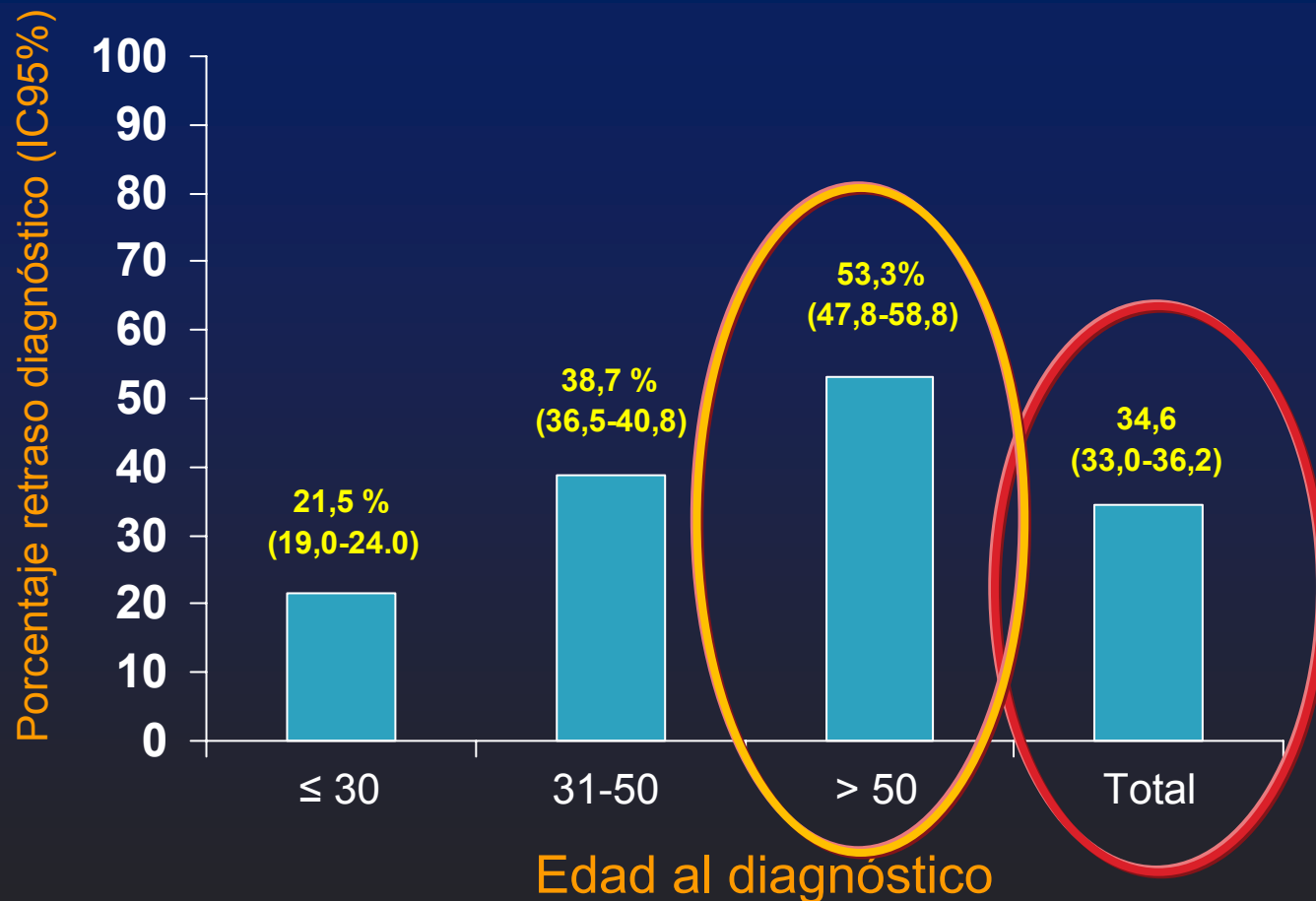
Cohorte CoRIS, 2004-2008

Enfermedades definitorias de sida al diagnóstico:

	N=4.418	
	%	N
Total ptes con enfermedad	19	839
Neumonía por <i>P jirovecii</i>	27,9	234
TBC pulmonar	16,8	141
Candidiasis esofágica	15,6	131
TBC extrapulmonar	14,8	124
S Kaposi	10,7	90
Caquexia por VIH	8,3	70
Toxoplasmosis cerebral	6,1	51
Linfoma no Hodgkin	4,2	35

Cohorte CoRIS, 2004-2008

Porcentaje de pacientes con retraso diagnóstico según edad:



Delayed Diagnosis of HIV Infection in a Multicenter Cohort: Prevalence, Risk Factors, Response to HAART and Impact on Mortality

Table 3. Virological and CD4 Cell Responses to Highly Active Antiretroviral Treatment (HAART), and Mortality, According to Delayed HIV Diagnosis (Baseline Definition)

Virological Response				
	Respondents /n	% (CI95%)	OR * (CI 95%)	P
DHD	220 / 321	68.5 (63.3 – 73.8)	1.17 (0.77-1.8)	0.448
No DHD	161 / 234	68.8 (62.7 – 75.0)	1	
Total	381 / 555	68.6 (64.7 – 72.6)		
CD4 Cell Response				
	Respondents /n	% (CI95%)	OR ** (CI 95.0%)	P
DHD	289/354	81.6 (77.5 – 85.8)	1.11 (0.67-1.84)	0.683
No DHD	210/259	81.1 (76.1 – 86.0)	1	
Total	499/613	81.4 (78.2 – 84.6)		
Mortality				
	Death/Person-Years	Rate (CI95%)	HR *** (CI 95.0%)	P
DHD	22 / 683	3.22 (2.02 – 4.88)	5.22 (1.88-14.5)	0.002
No DHD	5 / 1192	0.42 (0.14 – 0.98)	1	
Total	27 / 1875	1.44 (0.95 – 2.10)		

Papel del internista:

- Diagnóstico precoz
- Educación sanitaria
- Prevención de la infección
- *Counselling*
- Tratamiento (si tiene experiencia)

Cómo podemos diagnosticar precozmente la infección:

- El patrón epidemiológico de la infección ha cambiado en España:
 - la vía sexual es la principal vía de transmisión sexual
- El porcentaje de pacientes que se diagnostican con > 55 años es importante: 9%
- Un 35% de los pacientes que se diagnostican en la actualidad presentan infección sintomática o riesgo elevado de desarrollar sida o muerte

Qué pacientes serían candidatos a diagnóstico de infección por VIH:

- Cualquier persona que lo solicite de forma voluntaria
- Personas sexualmente activas (u otras prácticas de riesgo) con clínica sugestiva de infección por VIH
- Personas con ETS
- Mujeres embarazadas
- Personas de origen subsahariano

Qué pacientes serían candidatos a diagnóstico de infección por VIH:

- Eventos B/C relacionados con la infección VIH:
 - Enfermedad tuberculosa
 - Linfomas
 - Neumonías bacteriana recurrente
 - Infecciones bacterianas recurrentes
 - Carcinoma de cérvix
 - Trombocitopenia de origen inmune
 - Herpes zoster recurrente o multidermatómico
 - Displasia de cérvix
 - Enfermedad pélvica inflamatoria

Qué pacientes serían candidatos a diagnóstico de infección por VIH:

Patologías asociadas:

- Hepatitis C ó B
- Displasia/carcinoma anal (infección por HPV)
- Enfermedad cardiovascular en adultos jóvenes (¿?) o con prácticas de riesgo
- Enfermedad neurológica: deterioro neurocognitivo, mielopatía o neuropatía periférica
- Nefropatía de origen incierto

Patología del internista:

- Fiebre de origen desconocido
- Sd. Constitucional: pérdida de peso progresiva
- Diarrea crónica
- Sd. linfadenopático
- Sd. malabsorción

- Meningomielitis aguda
- Sd. Mononucleósico
- Hepatitis aguda



Infección aguda

Resumen. Ventajas del TARV precoz:

- El inicio precoz ($\text{CD4}^+ > 350/\mu\text{L}$) se asocia a un descenso en la incidencia de sida, muerte y otras enfermedades no asociadas a inmunodeficiencia
- La recuperación mantenida de la inmunidad celular ($\text{CD4}^+ > 500/\mu\text{L}$) asegura una supervivencia probablemente similar a la población general
- Menor toxicidad
- Disminución transmisión sexual VIH

Resumen. Desventajas del TARV precoz:

- Medicalización de pacientes jóvenes asintomáticos
- Mala adherencia (tratamiento crónico que exige tasas de cumplimiento >95%)
- Riesgo de toxicidad crónica no conocida
- Aumento de resistencias a los fármacos antirretrovirales en casos de mala adherencia
- Mayor coste económico

Diagnóstico y tratamiento precoz de la infección por VIH

CONCLUSIONES:

- El inicio precoz del TARV ($CD4^+ > 350/500$) aumenta la supervivencia de los pacientes con infección por VIH
- Para conseguirse este objetivo debe diagnosticarse de forma precoz a los pacientes
- El inicio del TARV precoz ($CD4^+ > 350/500$) exige una valoración individual y un compromiso de adherencia del paciente
- Deben plantearse pautas de TARV eficaces, seguras y de coste razonable