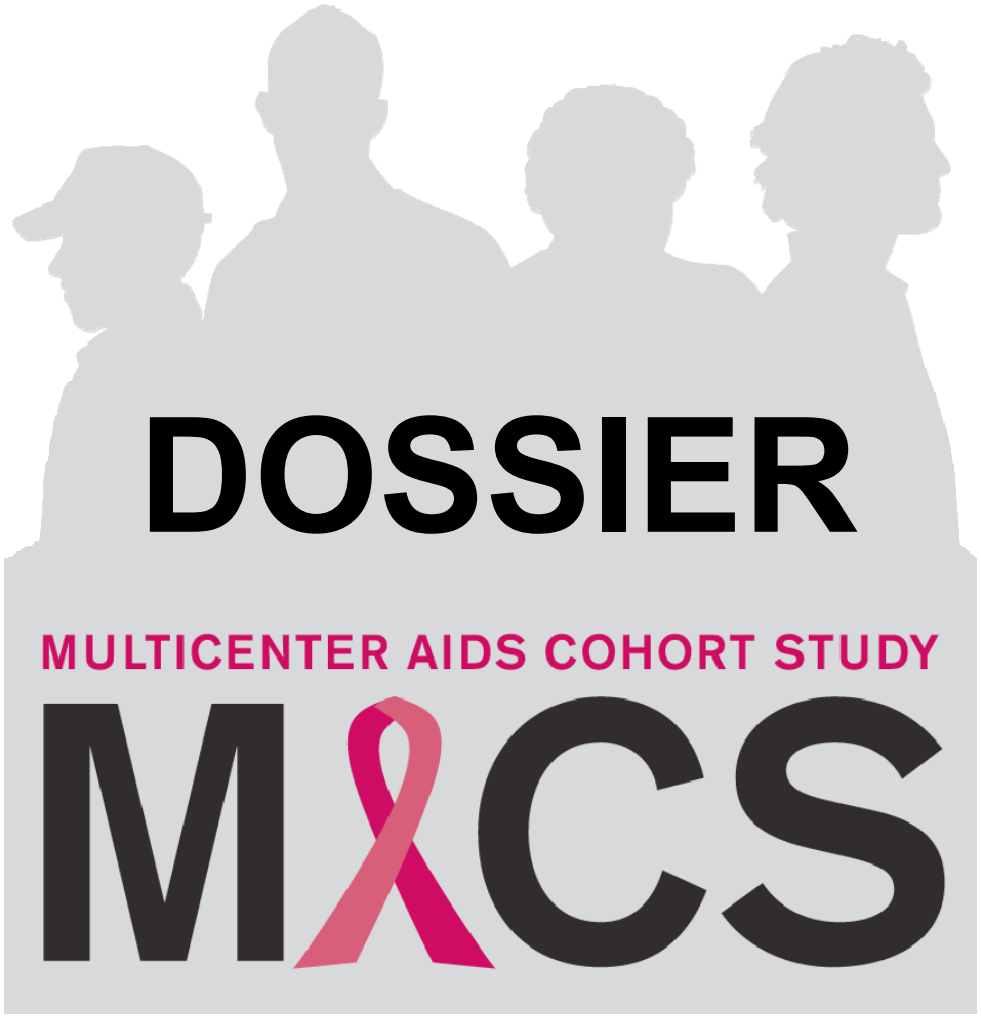


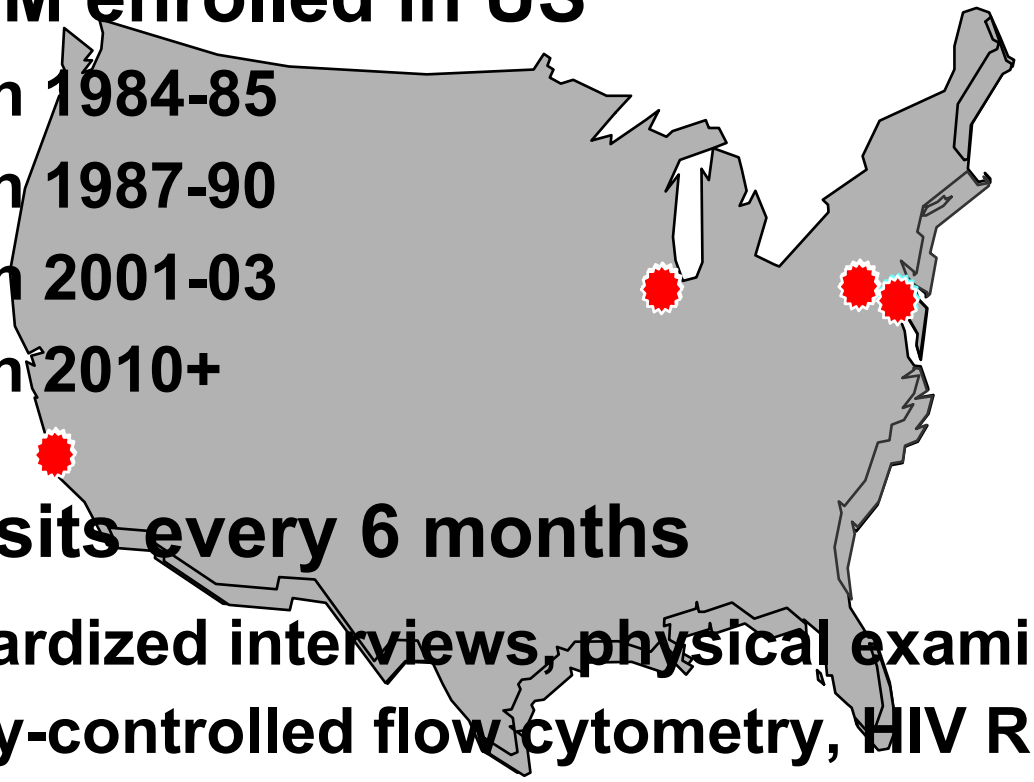
Web site: http://statepi.jhsph.edu/macs/macs.html
Prepared by CAMACS
Fax: 410-955-7587

The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute and the National Heart, Lung and Blood Institute. UO1-AI-35039, UO1-AI-35040, UO1-AI-35041, UO1-AI-35042, UM1-AI-35043, UL1-RR025005, (NCATS).

December 2013

Multicenter AIDS Cohort Study (MACS)

- 7087 MSM enrolled in US
  - 4954 in 1984-85
  - 668 in 1987-90
  - 1350 in 2001-03
  - 115 in 2010+



- Study visits every 6 months
  - Standardized interviews, physical examination
  - Quality-controlled flow cytometry, HIV RNA quantification
- Storage of biospecimens in local/national repositories

MACS
Principal Investigators and Sites

Roger Detels, Los Angeles

Otto Martinez-Maza, Los Angeles

Lisa Jacobson, CAMACS

Charles Rinaldo, Pittsburgh

Joe Margolick, Baltimore

Steven Wolinsky, Chicago

December 2013

MACS Sites and Principal Investigators

- **Sites:**
  - **Baltimore, MD (J. Margolick)**
  - **Chicago, IL (S. Wolinsky)**
  - **Los Angeles, CA (R. Detels, O. Martinez-Maza)**
  - **Pittsburgh (C. Rinaldo)**
- **Data Coordinating Center (CAMACS):**
  - **Baltimore, MD (L. Jacobson)**

MACS Working Groups

- Aging (J. Margolick)
- Behavioral (R. Stall)
- Biomarkers (J. Bream)
- Cardiovascular (W. Post)
- Clinical (F. Palella)
- Core Laboratory (B. Jamieson)
- Data (A. Abraham)
- Genetics (J. Martinson)
- Liver (C. Thio)
- Malignancy/Pathology (E. Breen)
- Metabolic (T. Brown)
- Neuropsychology (N. Sacktor)
- Renal (M. Estrella / F. Palella)
- Viral Immune Pathogenesis (J. Margolick)

Semiannual Visit

- **Questionnaire / ACASI**
  - Medical History, Health Services, Behavior
  - Medications: Antiretrovirals, OI-specific, Adherence
- **Labs**
  - T-cells, HIV RNA, HBV & HCV serology
  - Lipids, liver and kidney function tests / anal cytology
- **Banked Specimens**
  - Plasma, Serum, Cells
  - B-cell lines
  - PBMC pellets
- **Demographics**
- **Physical Examination / Lipodystrophy / Frailty**
- **Psychosocial**
  - Quality of Life (SF36)
  - Depression (CESD)
  - Activities of Daily Living (IADL)
- **Neuropsychological Screening**

Continuous Outcome Ascertainment

- Seroconversion
- Clinical Outcomes (medical records confirmation)
  - AIDS diagnoses
  - Non-AIDS diagnoses
    - Cardiovascular disease
    - Cerebrovascular disease
    - Kidney disease
    - Liver disease
    - Lung infection, bacterima, septicemia
    - Malignancies
    - Neurologic
  - Mortality

Data Collection Forms

- Drug Form 1 (*anti-virals*)
- Antiretroviral Medication Adherence
- Section 2* (*demographics, depression (CESD)*)
- Physical Exam / Lipodystrophy Exam
- Section 4 (*medical history, health services, behavior**)
- Quality of Life* (SF36)
- Neuropsychological
- HIV Seroconversion
- Clinical Diagnostic Outcomes

*** Administered using Audio Computer Assisted Structured Interview (ACASI)**

Administrative Forms

- Data Set Transmission
- Study Investigator Registration for using MACS Specimens
- Restricted Use of MACS Specimens

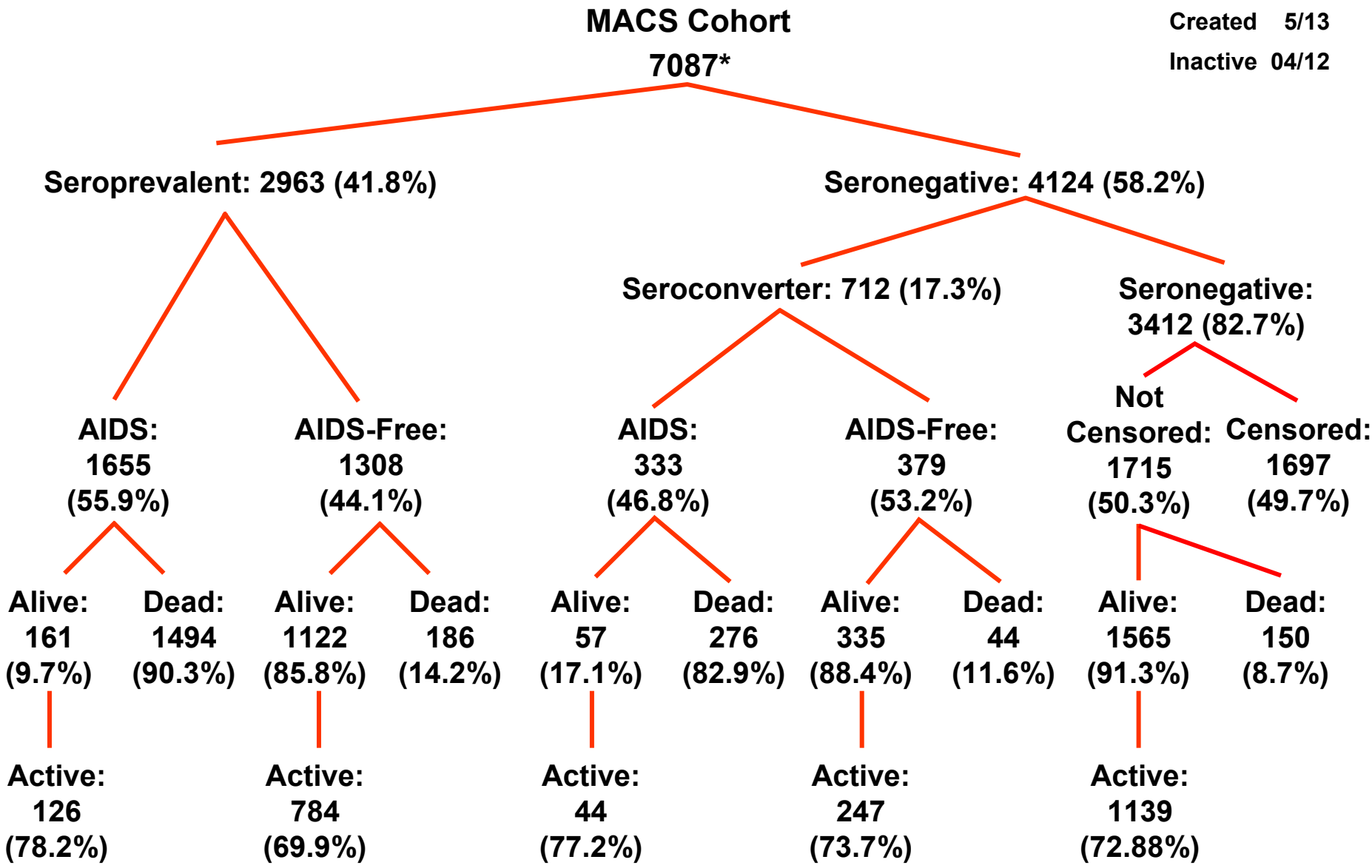
CAMACS

- Planning and design of studies
- Coordination of data acquisition
  - Form development
  - Codebooks
  - Data transfer
- Standardization and data management
  - Edits and updates
  - Data security
- Data analysis, statistical computing and methodological research

MACS Database
(as of October 2013)

Publications (published & in press)	**1,306**
Participants	**7,087**
Person-Years	**93,710**
Variables	**12,357**
Repository aliquots (plasma, serum, cells, urine)	**1,743,937**

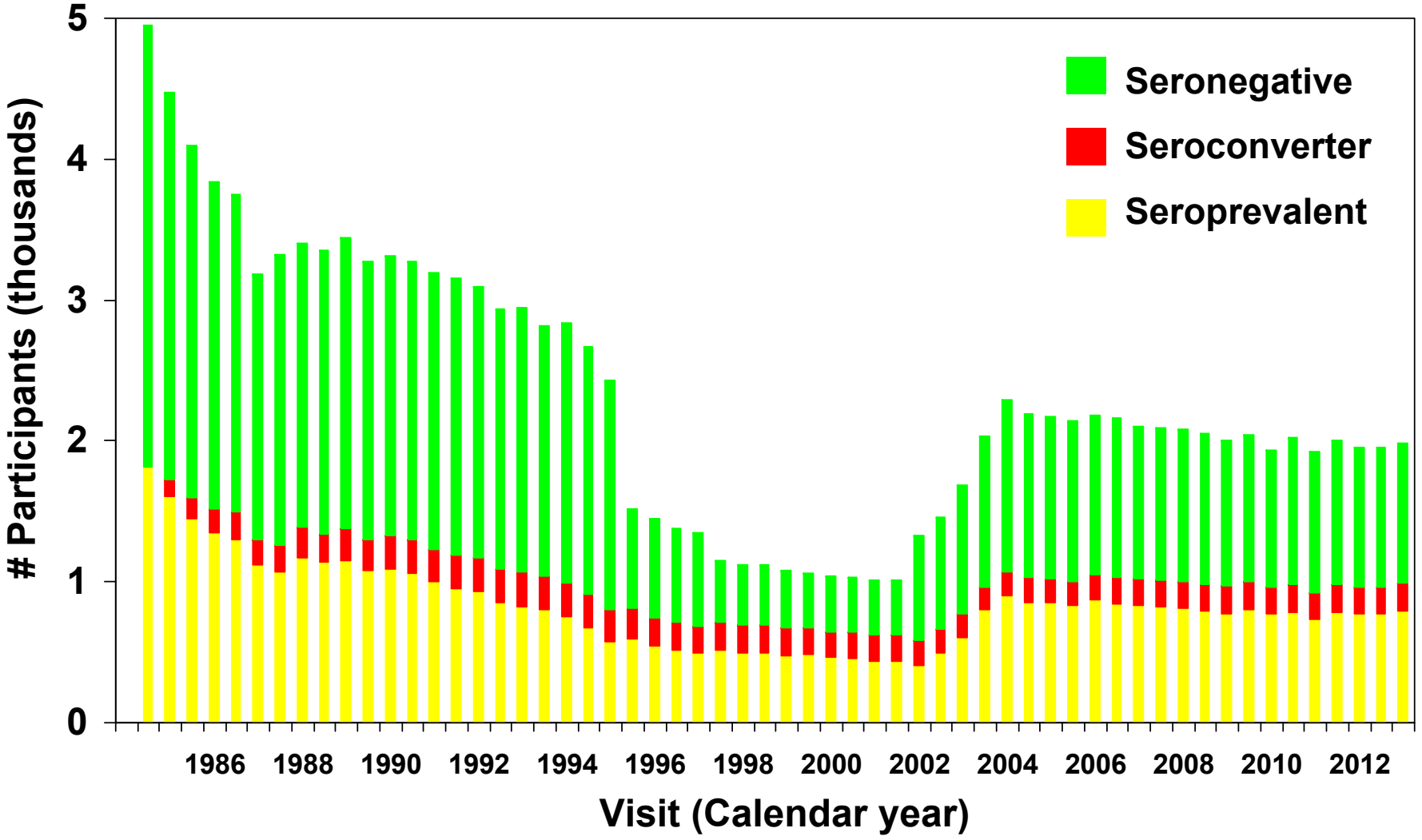
	HIV+	HIV-
Person-Visits	**61,357**	**77,577**
CD4 Measurements	**56,144**	**62,252**
HIV RNA Measurements	**38,503**	**1,222**



* Includes 115 additional men (12 seronegatives, 103 seroprevalent, 24 with known seroconversion dates prior to entry) enrolled in the MACS per the 2010 recruitment protocol

November 2013

Composition & Size of Cohort



*** 1710 have been administratively censored**

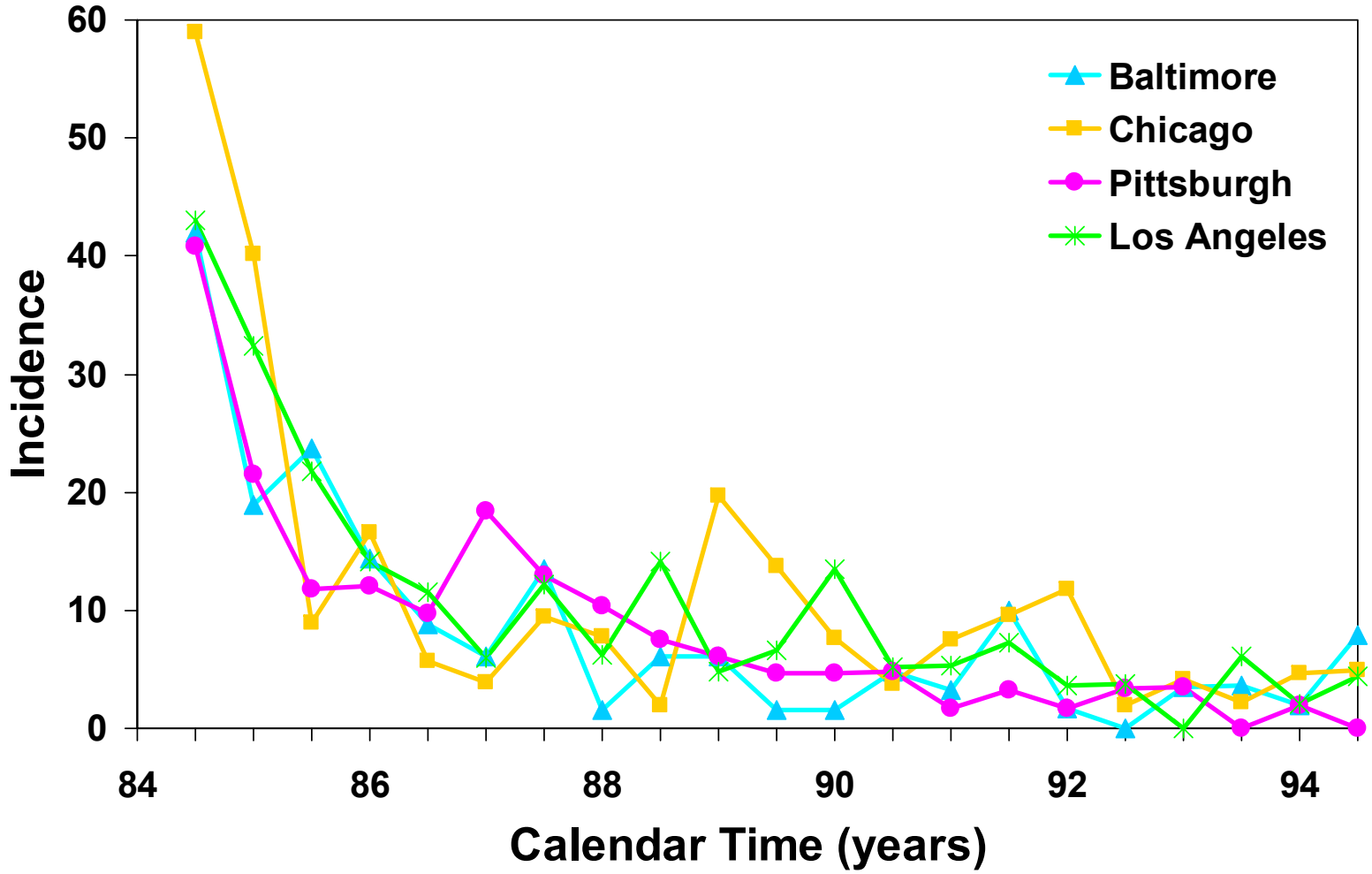
November 2013

Total # of CD4 and HIV RNA Measurements by Serostatus

# per individual	Seronegative CD4	Seropositive (CD4 ; HIV RNA)	
0	5	6 ;	326
1 – 4	711	804 ;	1412
5 – 8	373	594 ;	499
9 – 12	579	476 ;	263
13 – 16	459	385 ;	222
17 – 20	336	402 ;	227
21 – 24	146	330 ;	254
25 – 28	82	72 ;	63
29 – 32	128	75 ;	61
33 – 36	185	75 ;	93
37 – 40	104	70 ;	119
41 – 44	70	64 ;	49
45 – 48	70	68 ;	33
49 – 52	61	81 ;	32
53 – 54	32	44 ;	13
55 – 56	48	62 ;	7
57 - 58	23	67 ;	2

Incidence* of Seroconversion in the MACS by Center

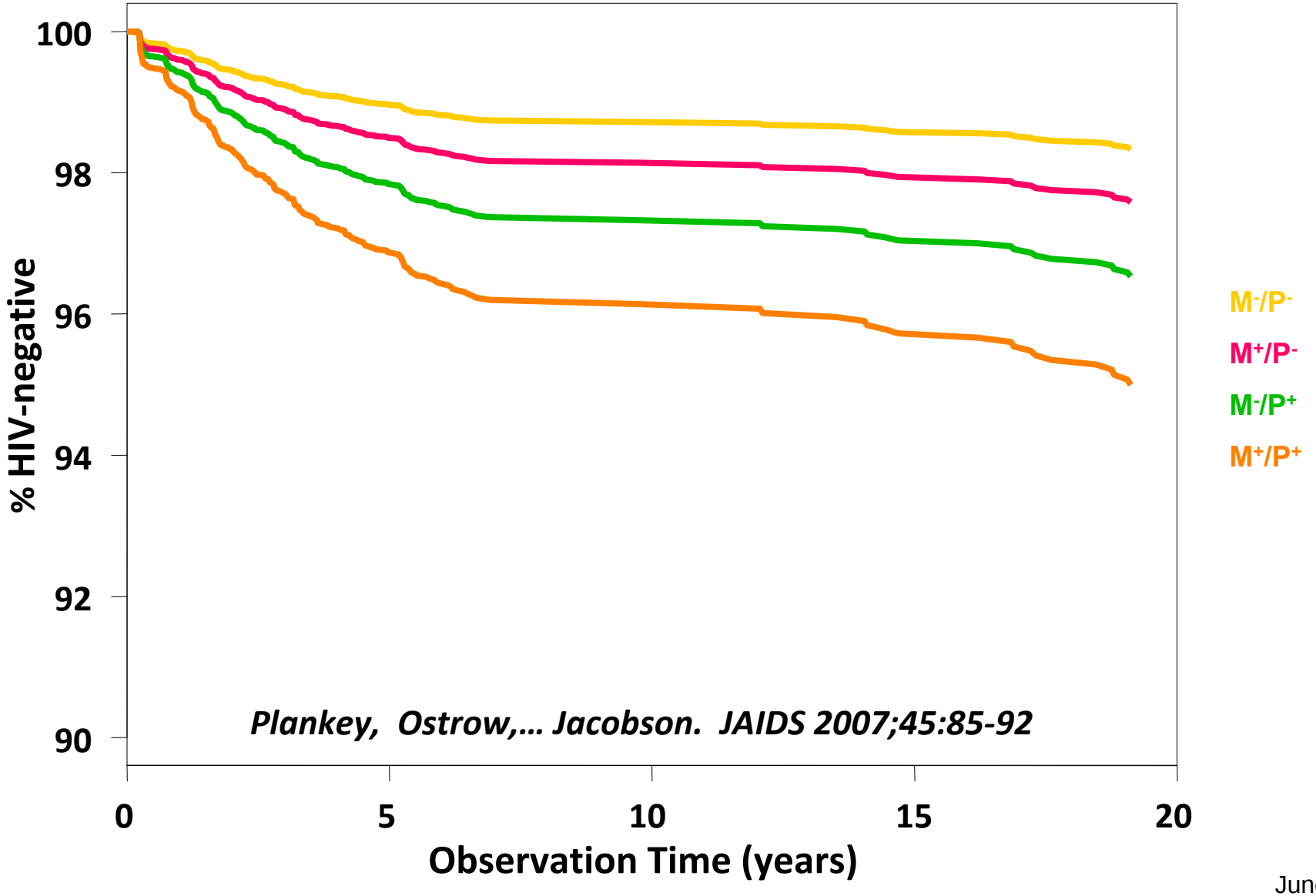
Kingsley, Zhou, . . ., Muñoz - AJE 1991 (update)



* Incidence = # of seroconverters per 1,000 person-semesters

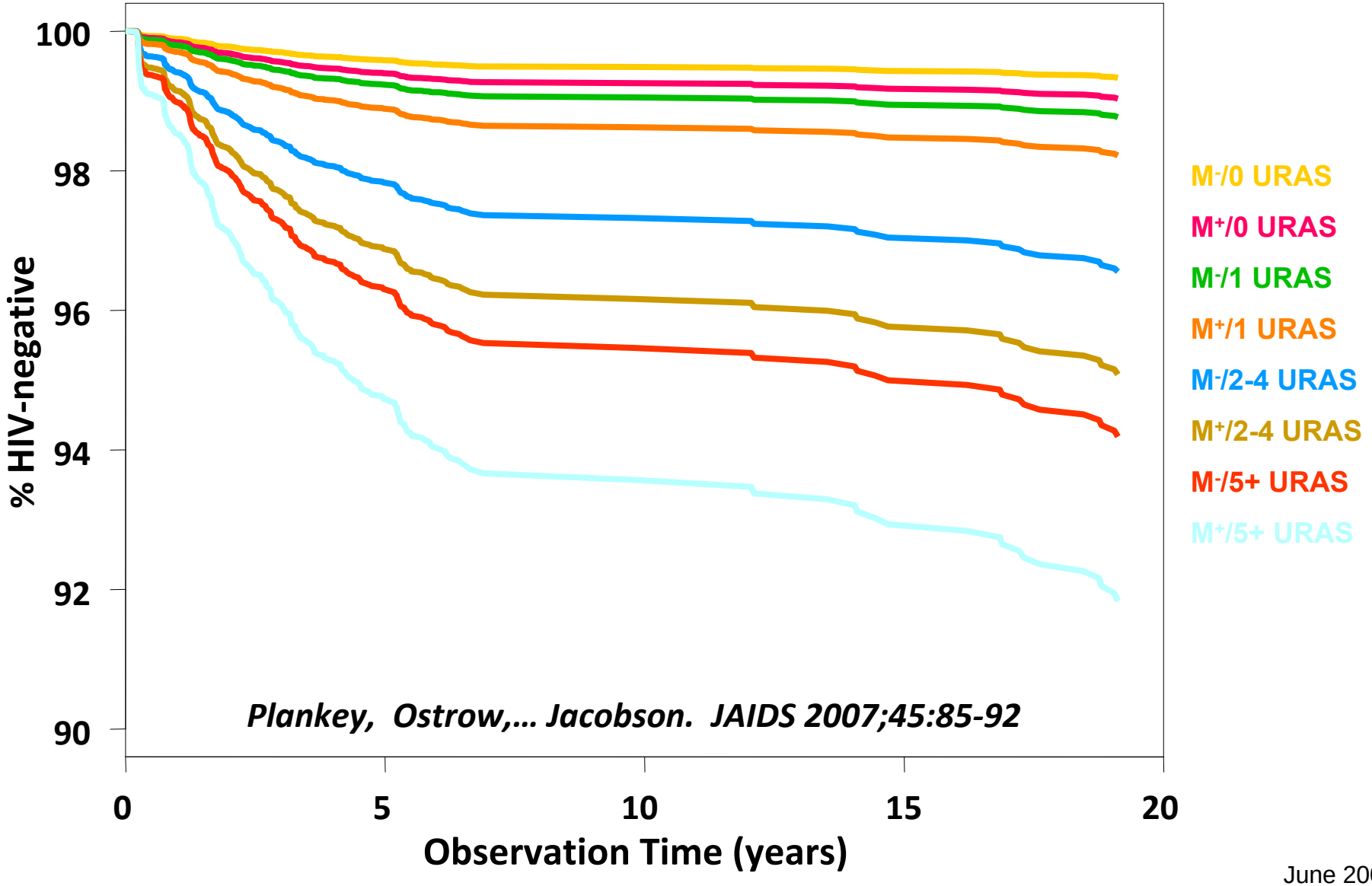
September 1995

Adjusted Time to HIV Seroconversion by Methamphetamine (M) and Popper Use (P)



June 2008

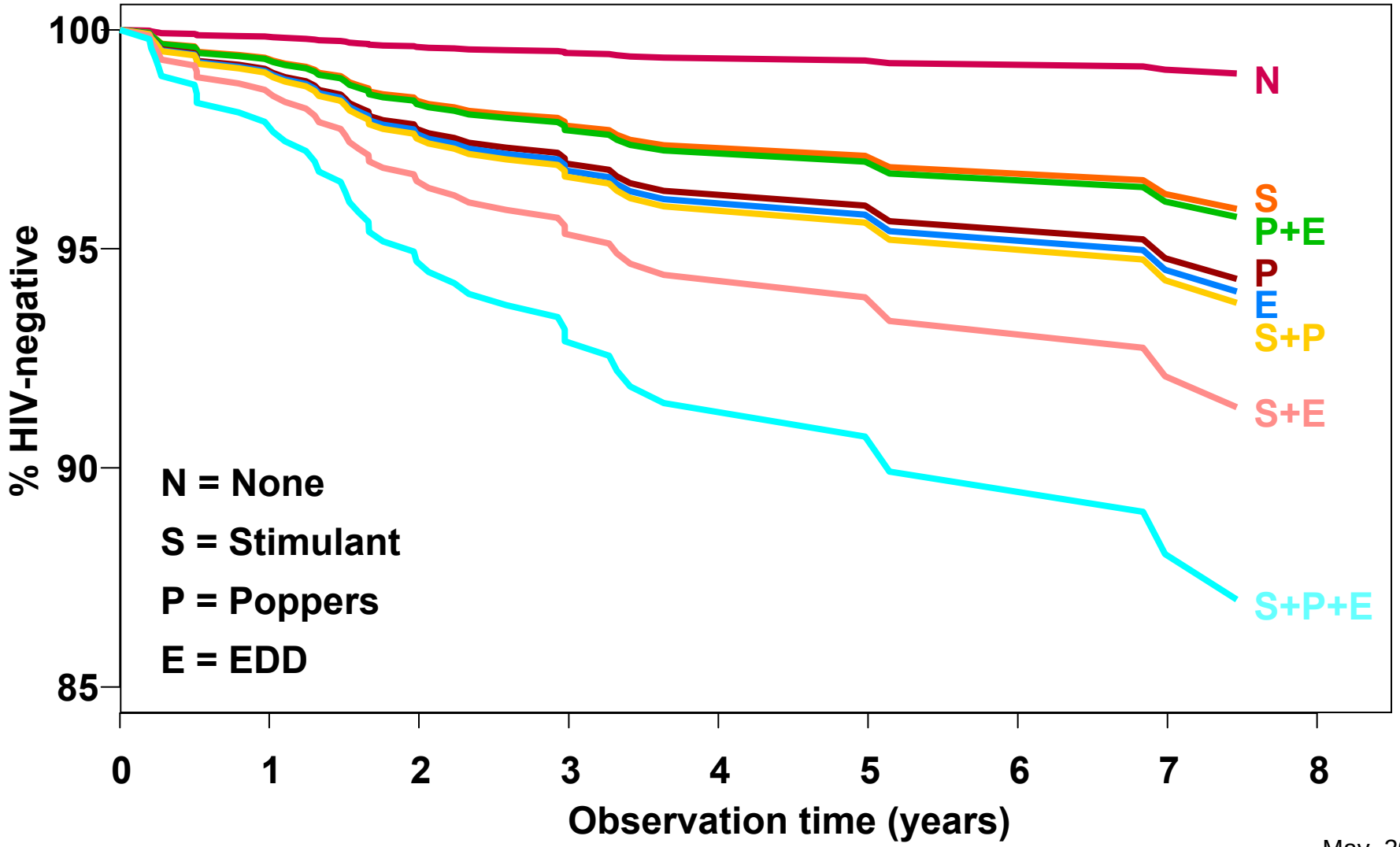
Adjusted Time to HIV Seroconversion by Methamphetamine (M) Use and Number of Unprotected Receptive Anal Sex (URAS) Partners



June 2008

Adjusted Time to Recent HIV Seroconversion by Combinations of Sex-Drug Use

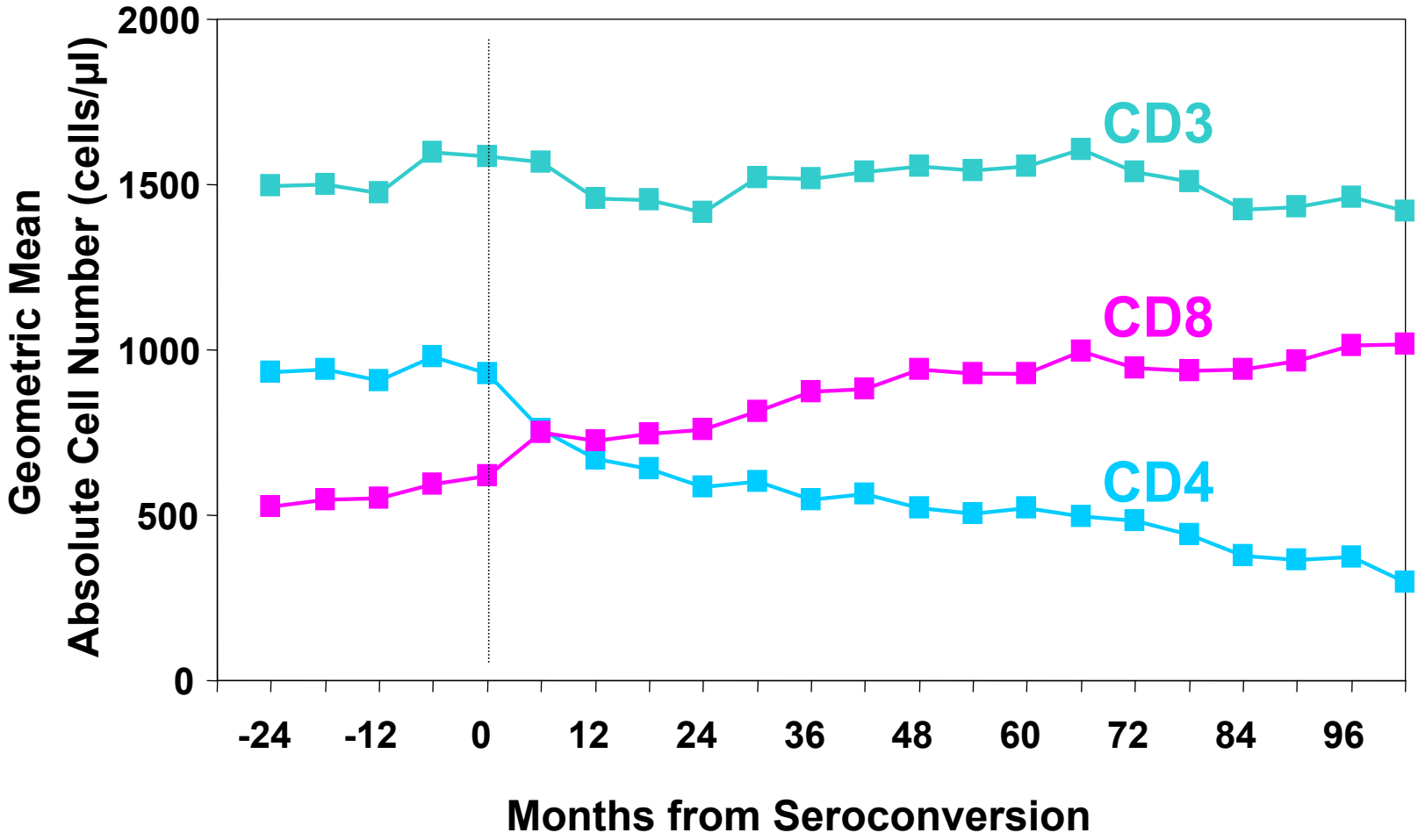
Ostrow, Plankey, …, Stall. JAIDS 2009



May 2010

T-Cell Subset Changes and Homeostasis in AIDS-Free MACS Seroconverters

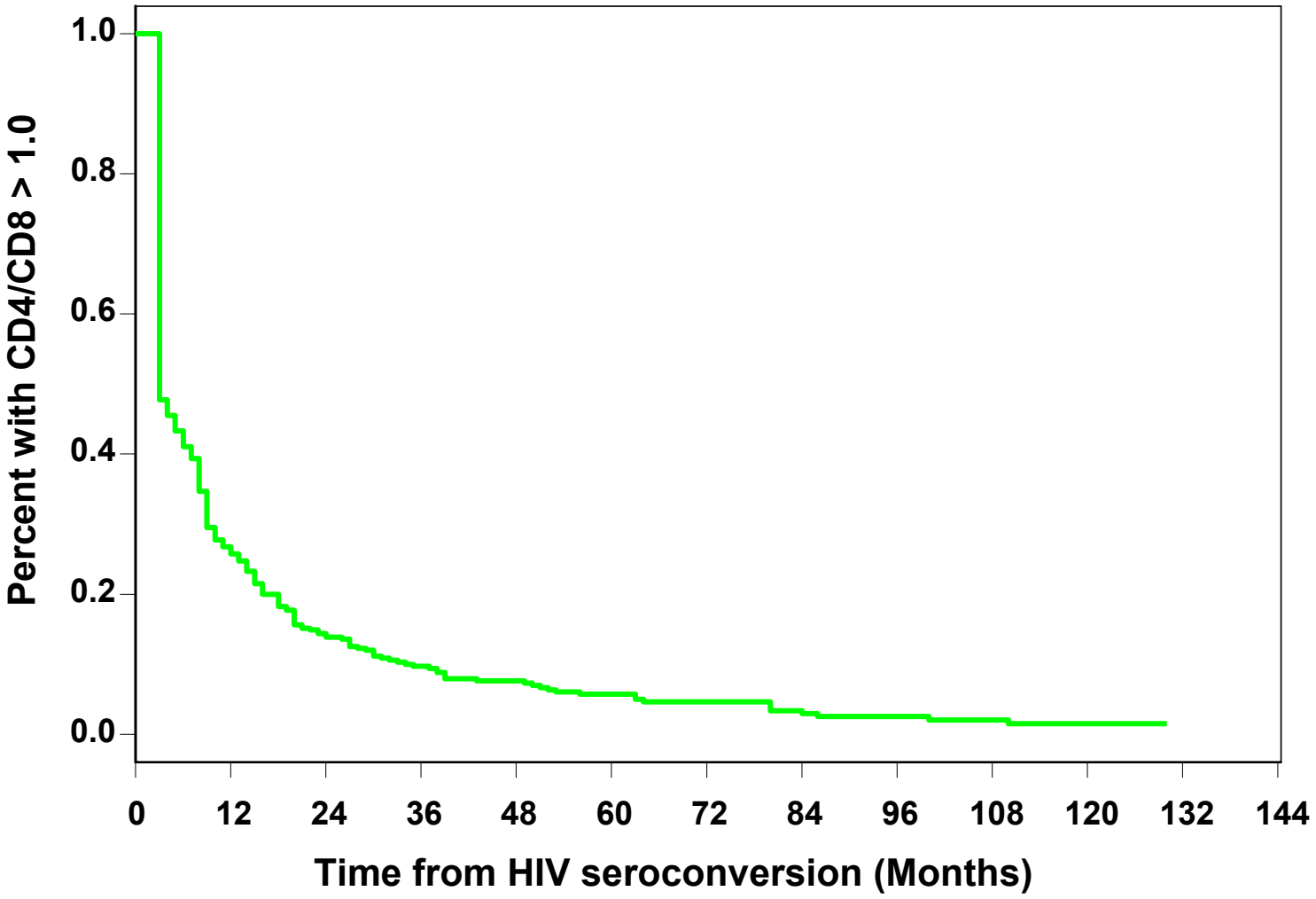
Margolick, Muñoz, . . ., Ferbas – Nat Med 1995



October 1997

Kaplan-Meier Survival Curve for Inversion of the CD4/CD8 Ratio after the Estimated Time of HIV-1 Seroconversion

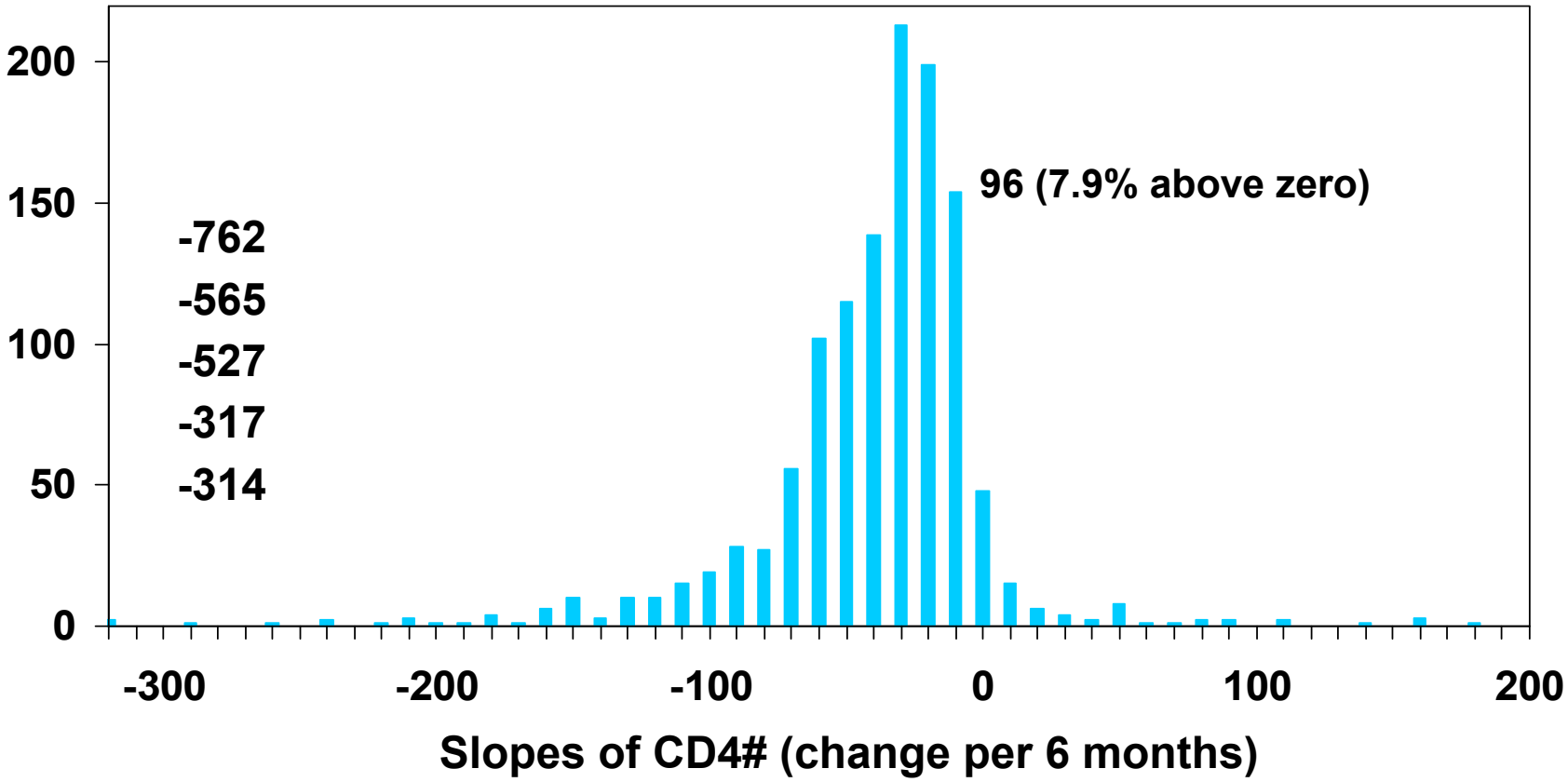
Margolick, Gange, …, Lai. JAIDS 2006



May 2007

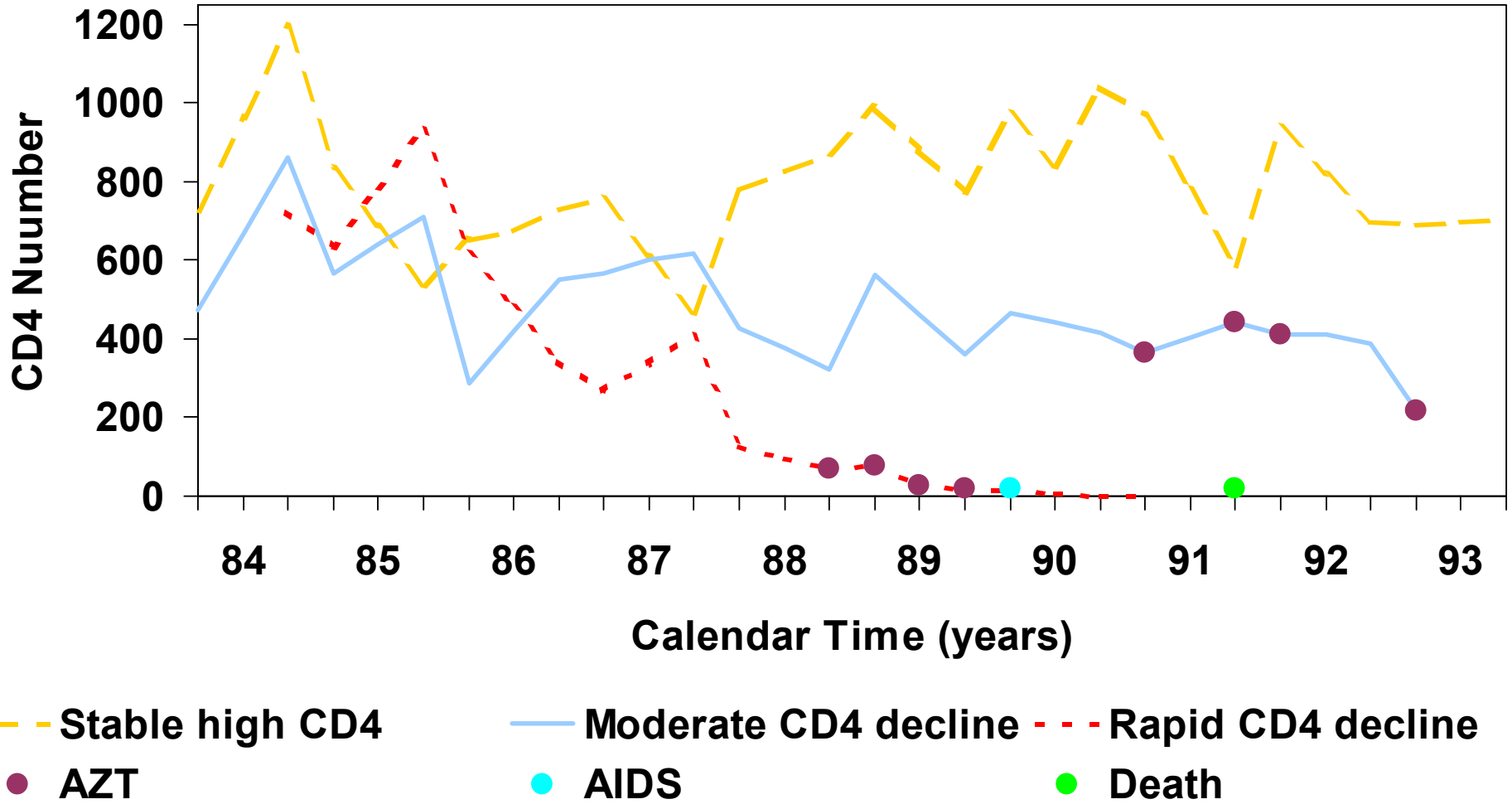
Histogram of 1222 CD4+ Regression Slopes Among HIV-1 Seropositive Men, 1984-1996

Muñoz, Kirby, . . ., Phair. JAIDS 1995 (update)



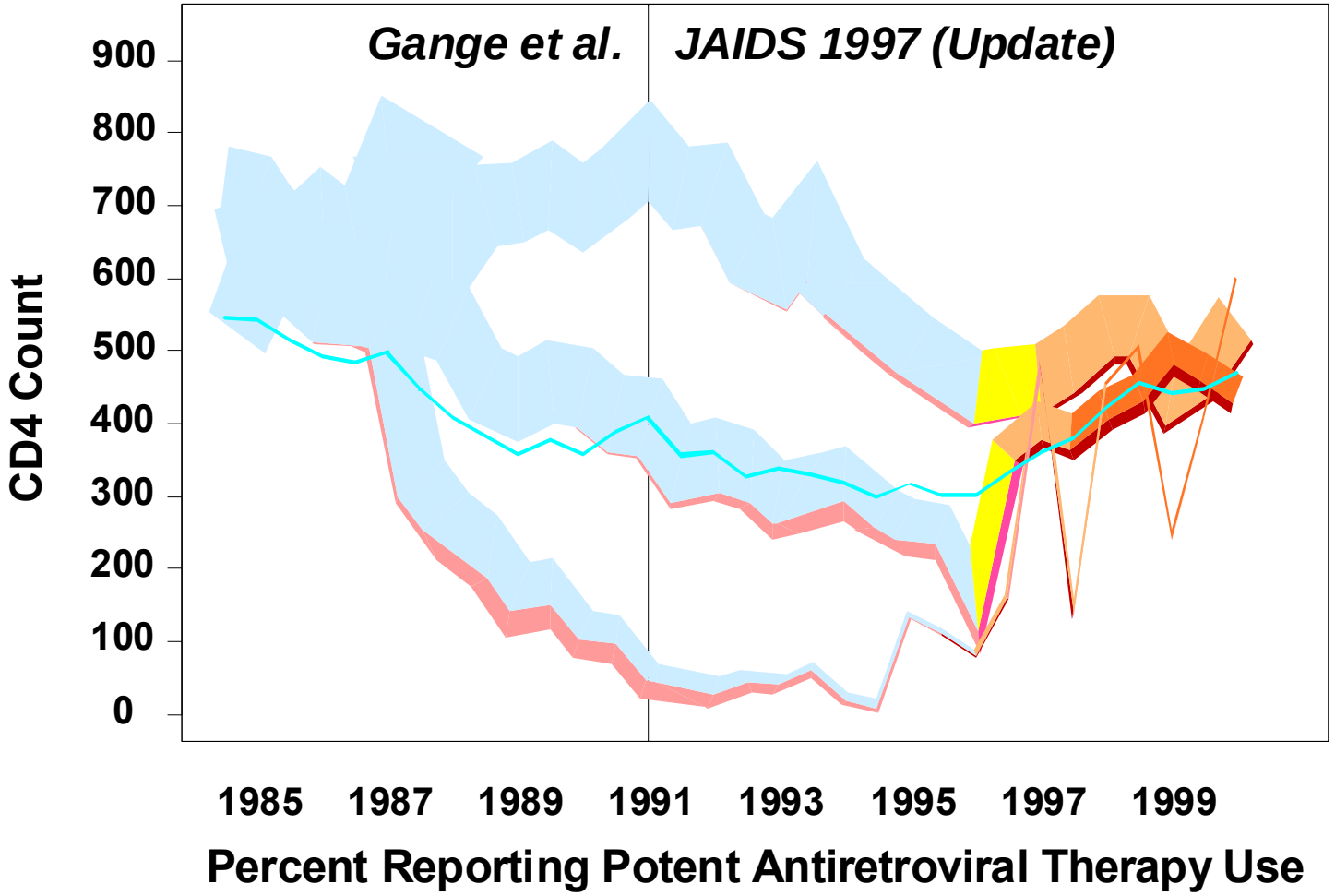
June 1997

A Seropositive Triplet with Distinct Profiles



September 1995

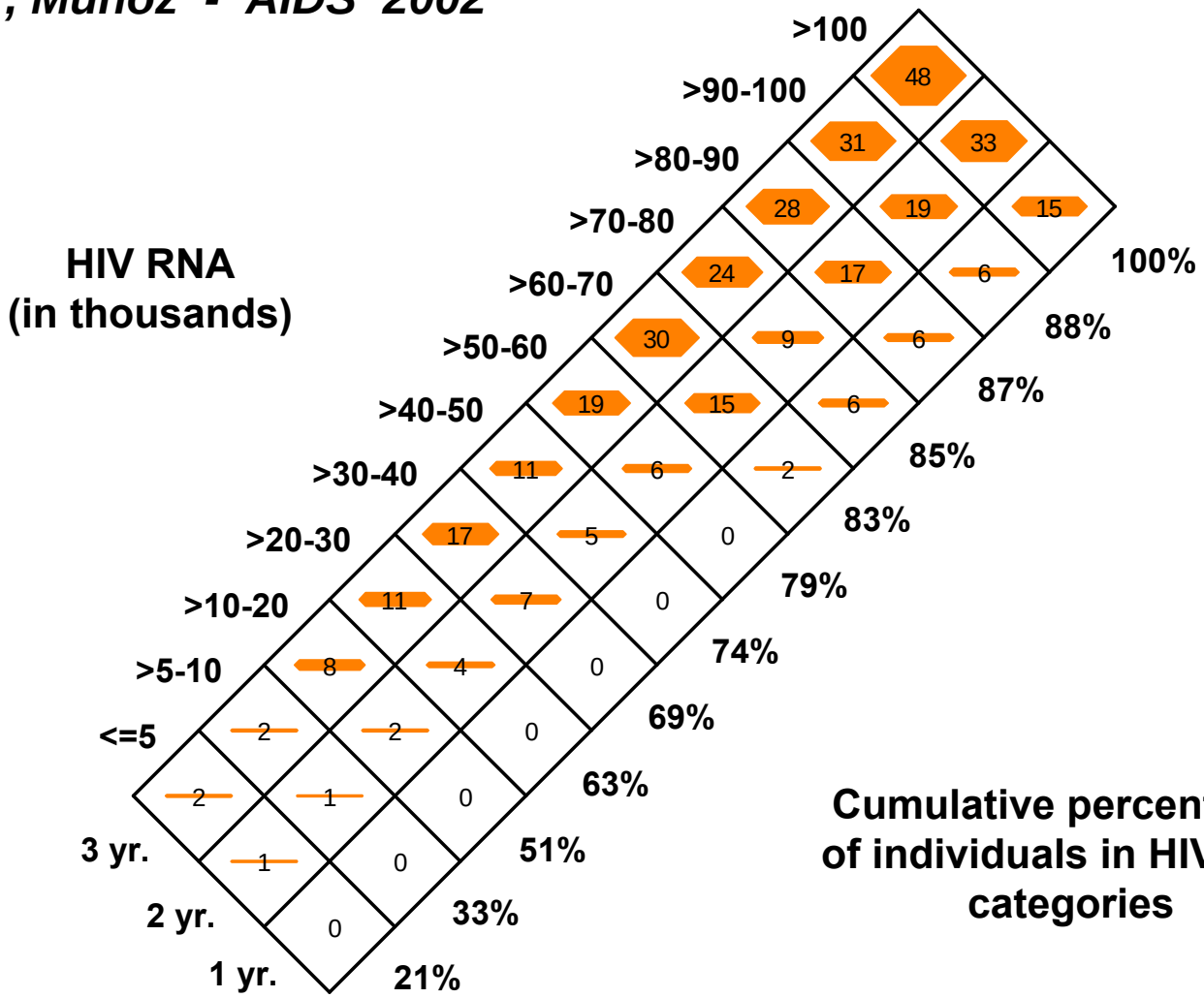
Disease Progression Among Triplets of HIV- Infected Men with Distinct CD4 Trajectories



October 2000

Likelihood of Developing AIDS in HIV Infected Individuals with CD4 > 350 in the Non-HAART Era

Phair, Mellors,…, Muñoz - AIDS 2002

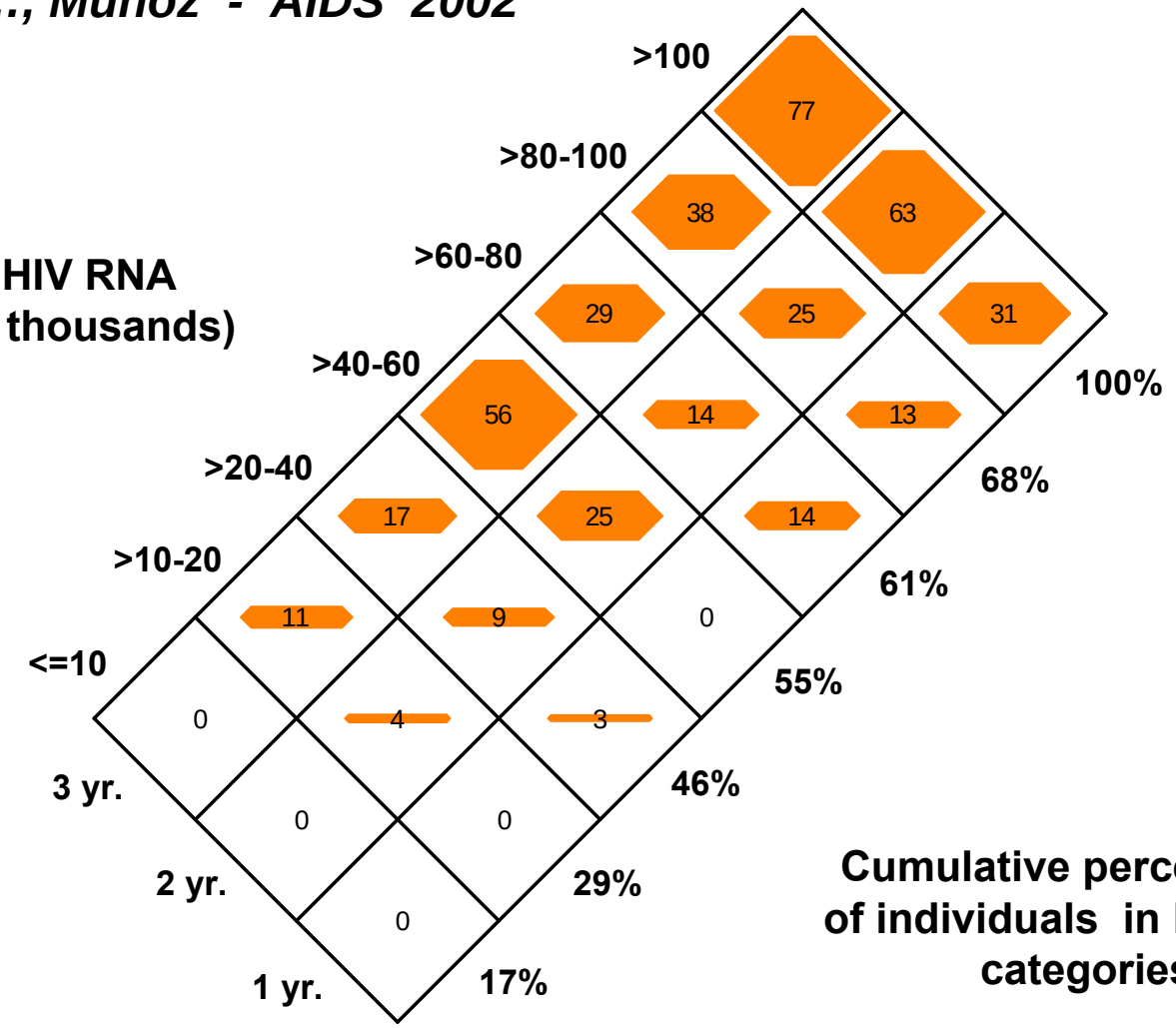


Graphical Reference: Li, Buechner, …, Muñoz - Am Statistician 2003

November 2004

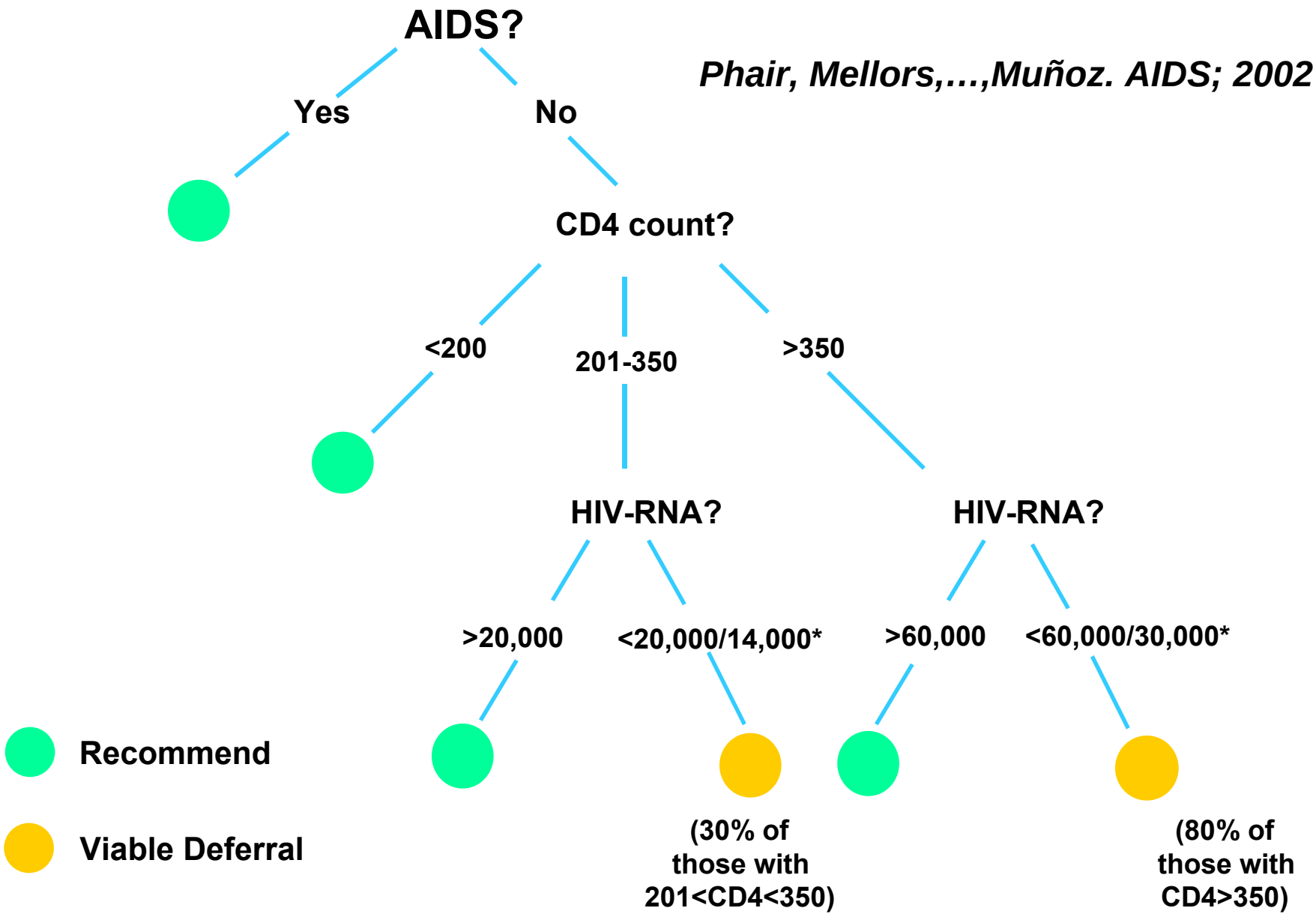
Likelihood of Developing AIDS in HIV Infected Individuals with 200 < CD4 < 350 in the Non-HAART Era

Phair, Mellors,…, Muñoz - AIDS 2002



Graphical Reference: Li, Buechner, …, Muñoz - Am Statistician 2003

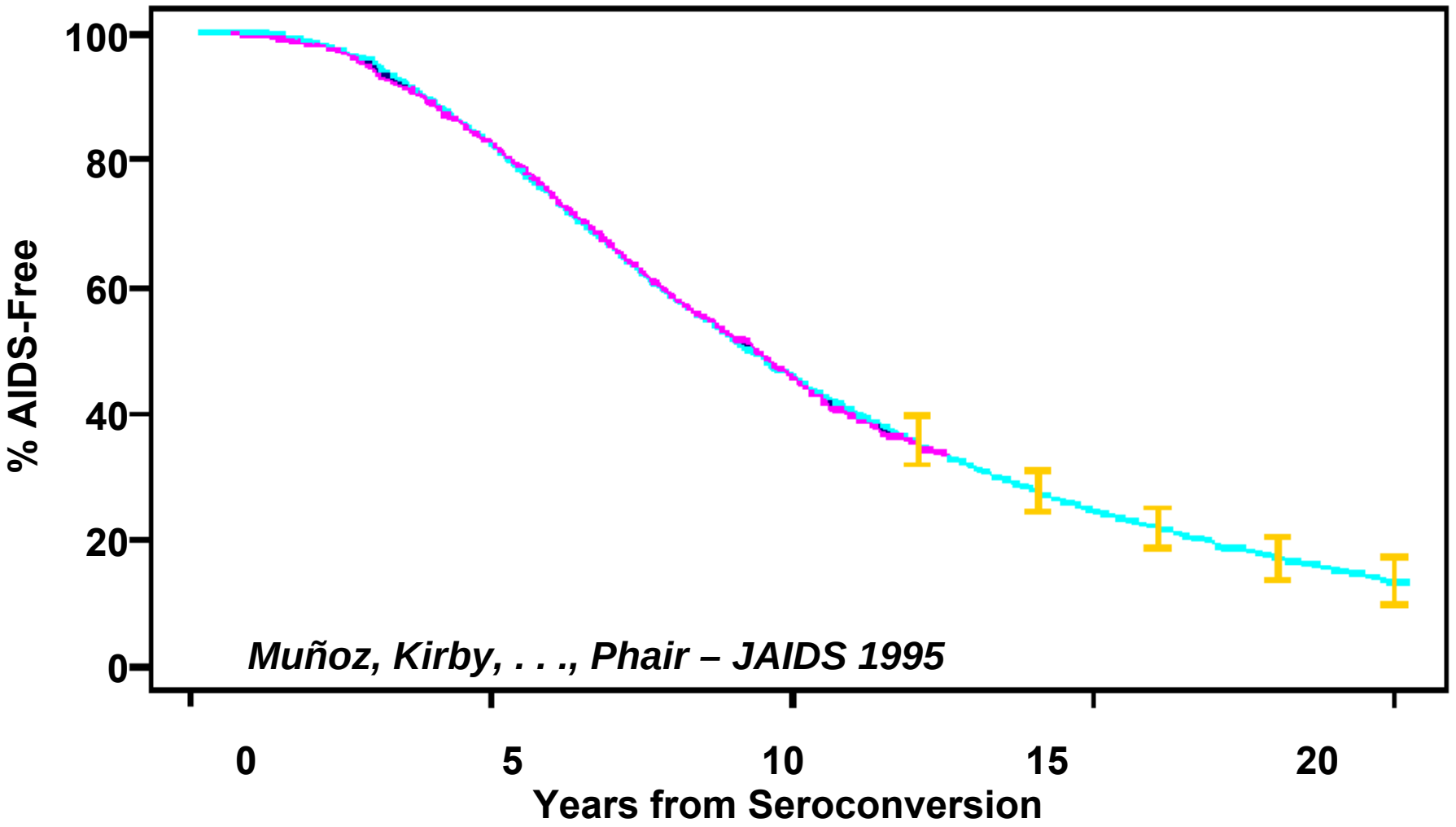
November 2004



Phair, Mellors,…,Muñoz. AIDS; 2002

Men/Women equivalence by Anastos, Gange, Lau et al., *JAIDS* 2000.
Source: Multicenter AIDS Cohort Study

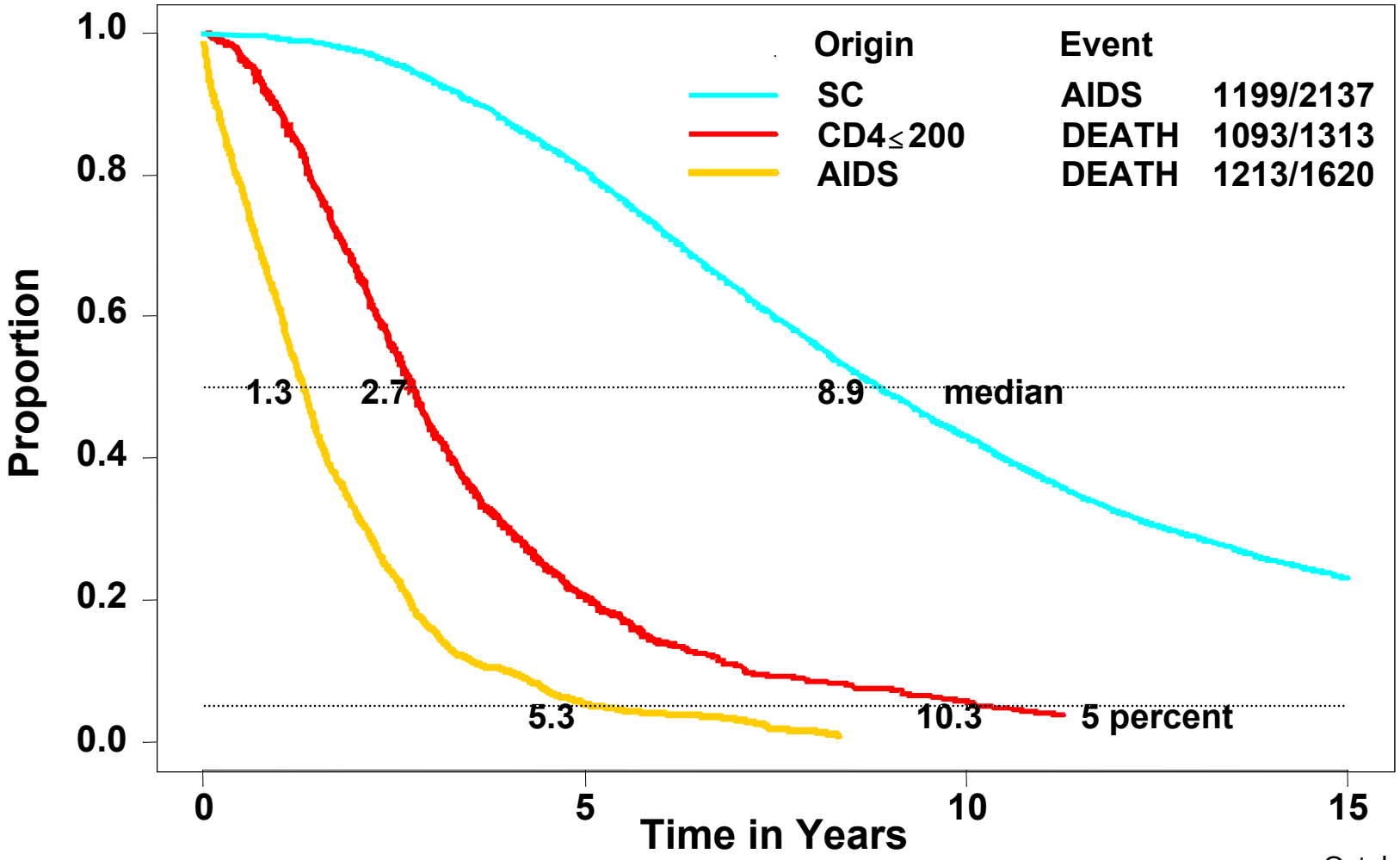
Estimated Long Term AIDS-Free Proportions Prior to Potent Antiretroviral Therapies



October 1998

Progression of HIV-1 Infection Prior to Potent Antiretroviral Therapy

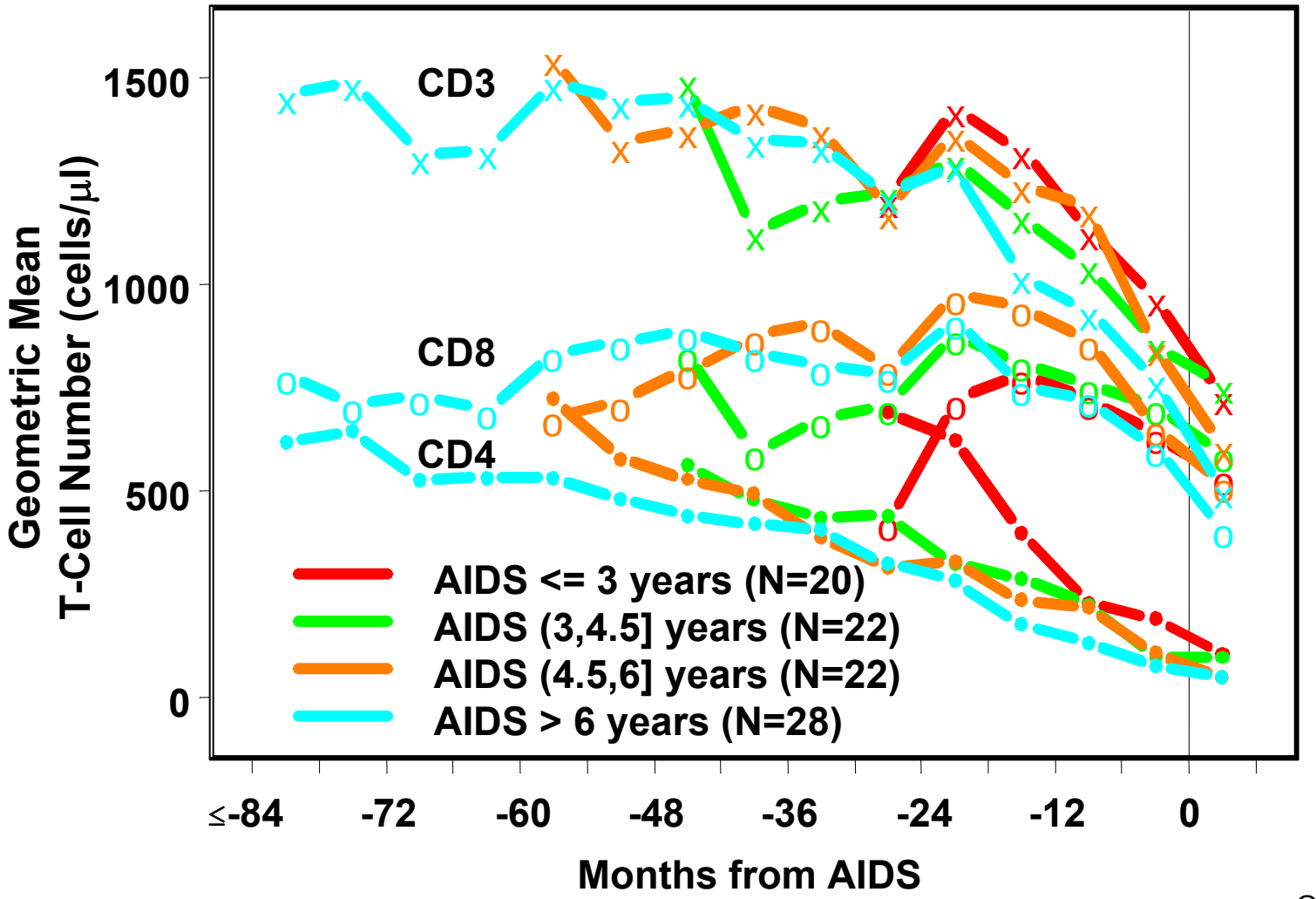
Muñoz, Xu. Stat Med 1996; Enger et al. JAMA 1996; Jacobson et al. AJE 1993 (update)



October 1998

Circulating T-Cell Lymphocyte Levels Relative to the Onset of AIDS

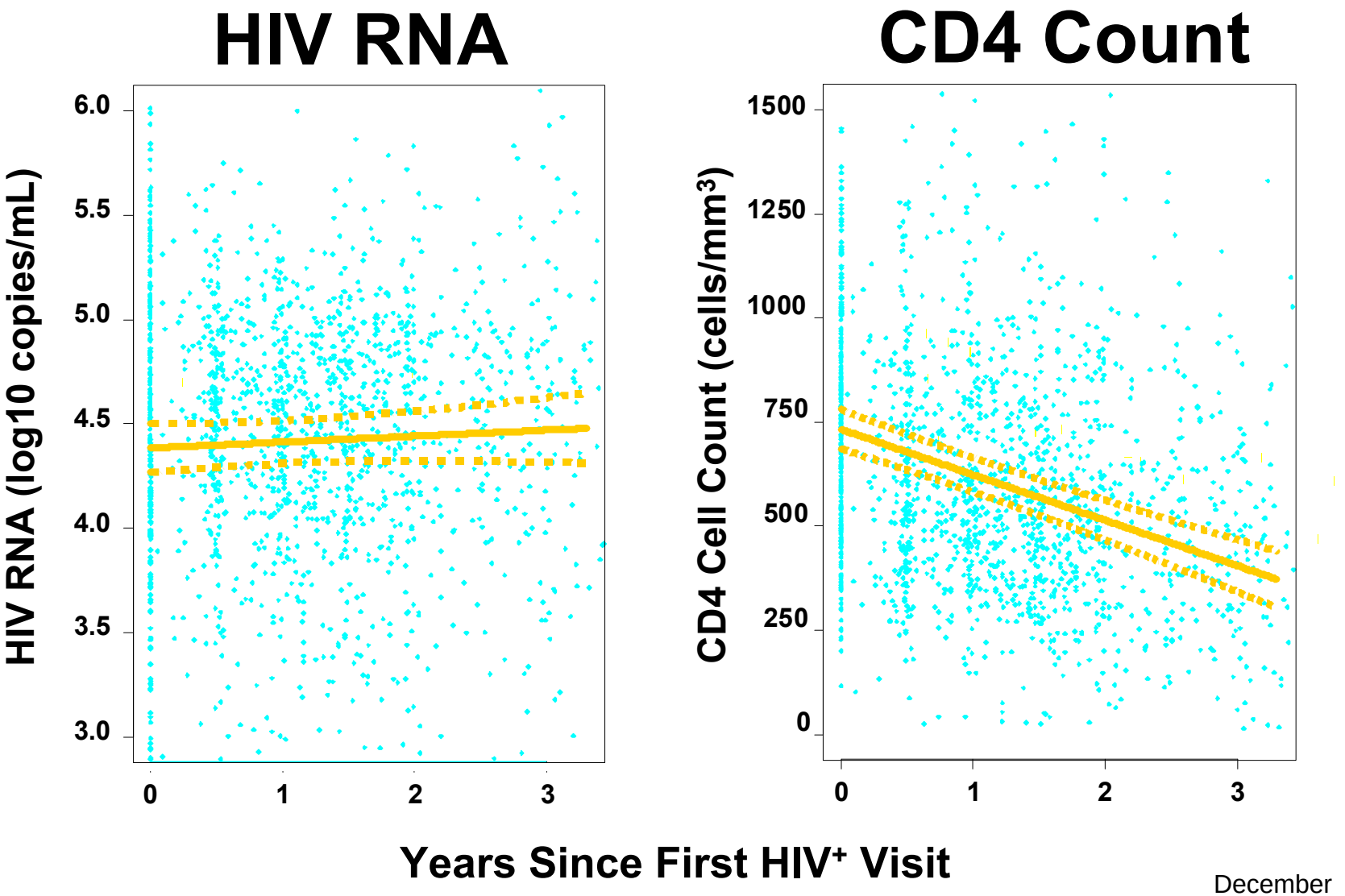
Margolick, Muñoz, . . ., Ferbas - Nat Med 1995



October 1996

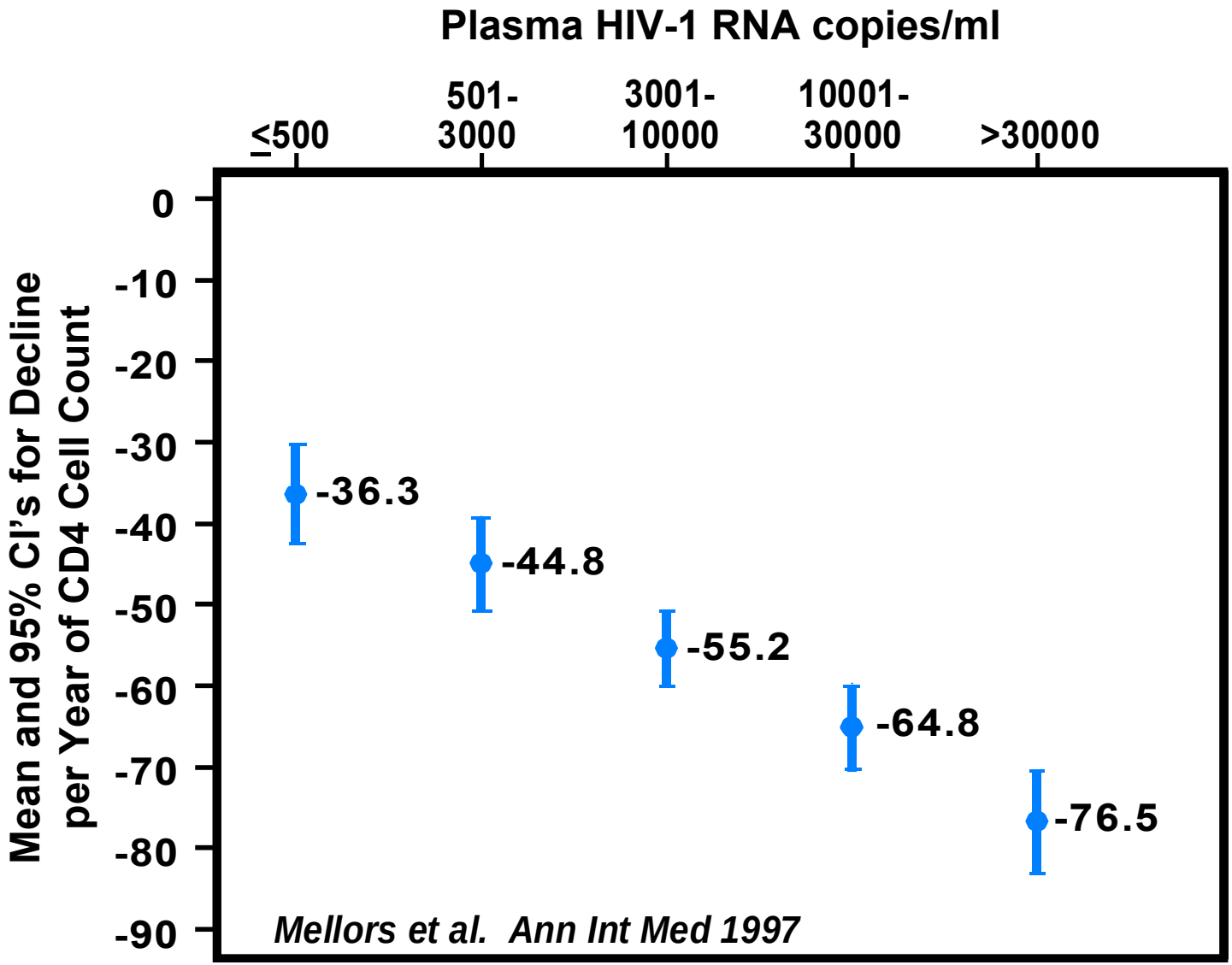
HIV Markers after Seroconversion Prior to HAART

Lyles, Muñoz, . . ., Mellors - JID 2000



December 2001

Decline in CD4 Count per Year by Plasma HIV-1 RNA



June 1997

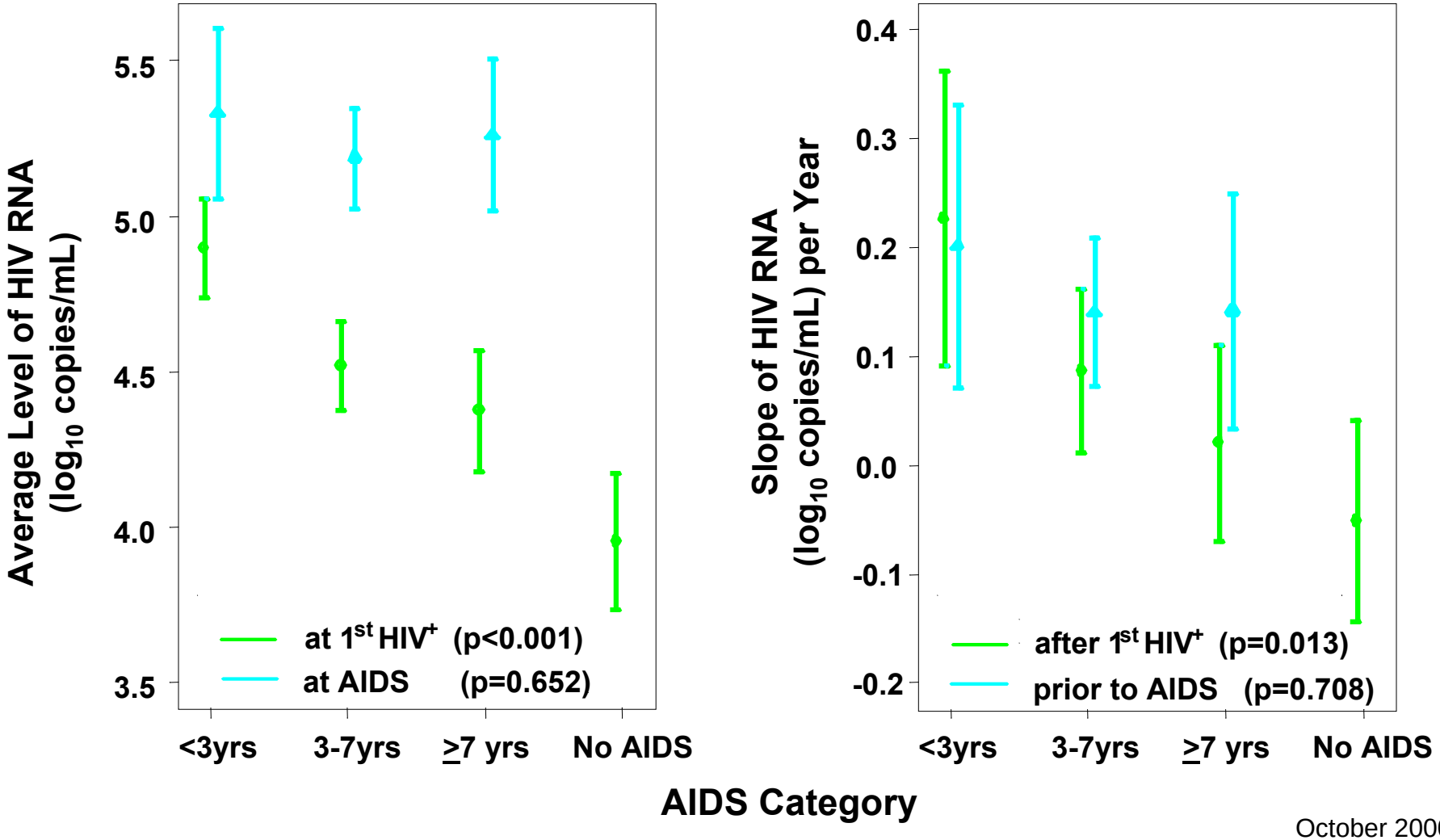
X4 Emergence Prior to Clinical Event According to Time of Events After Seroconversion

Shepherd, Jacobson, . . ., Margolick - JID 2009

	Progression Groups			
	Rapid	Moderate	Slow	Very Slow
CD4 < 200 cells/μℓ				
n (%)	7 (54%)	11 (79%)	4 (50%)	3 (19%)
OR	5.1	15.9	4.3	1.0
AIDS Illness				
n (%)	4 (57%)	17 (77%)	4 (57%)	4 (25%)
OR	4.0	10.2	4.0	1.0

HIV-1 Viremia after Seroconversion and Proximal to AIDS

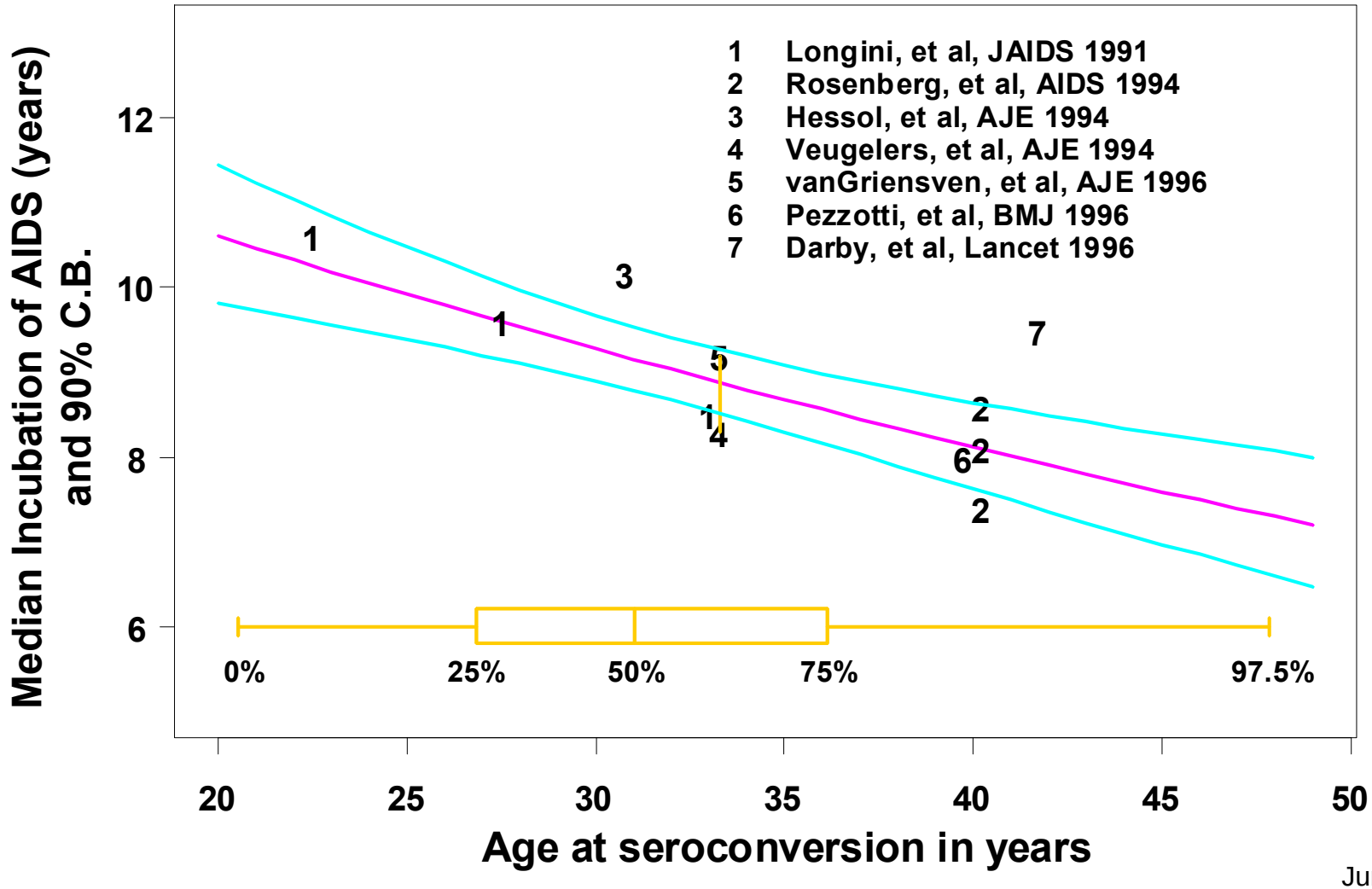
Lyles, Muñoz, . . ., Mellors - JID 2000



October 2000

Estimates from Lognormal Model
Multicenter AIDS Cohort Study

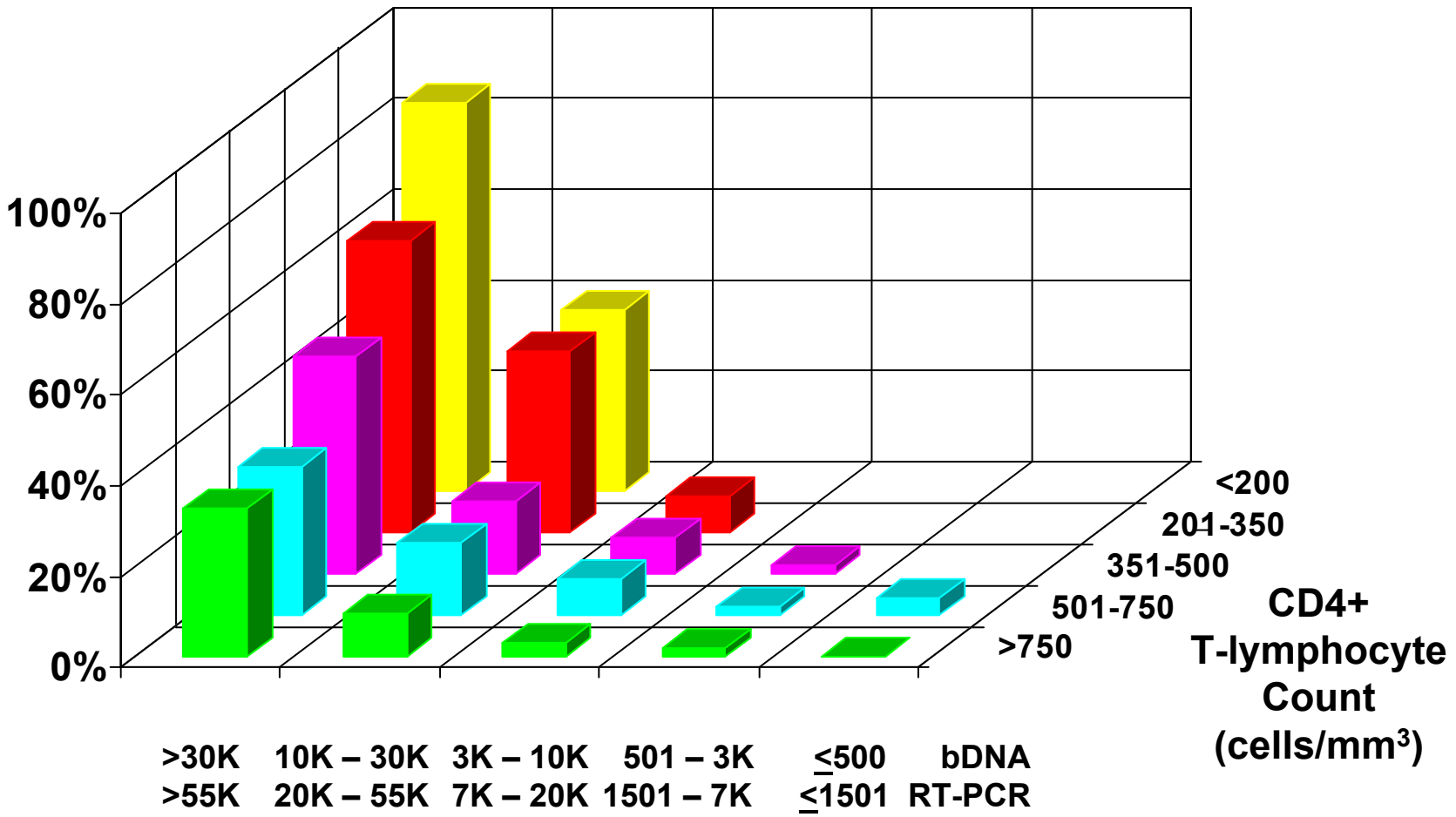
Muñoz, Sabin, Phillips. AIDS 1997



June 1997

Likelihood of Developing AIDS in Three Years

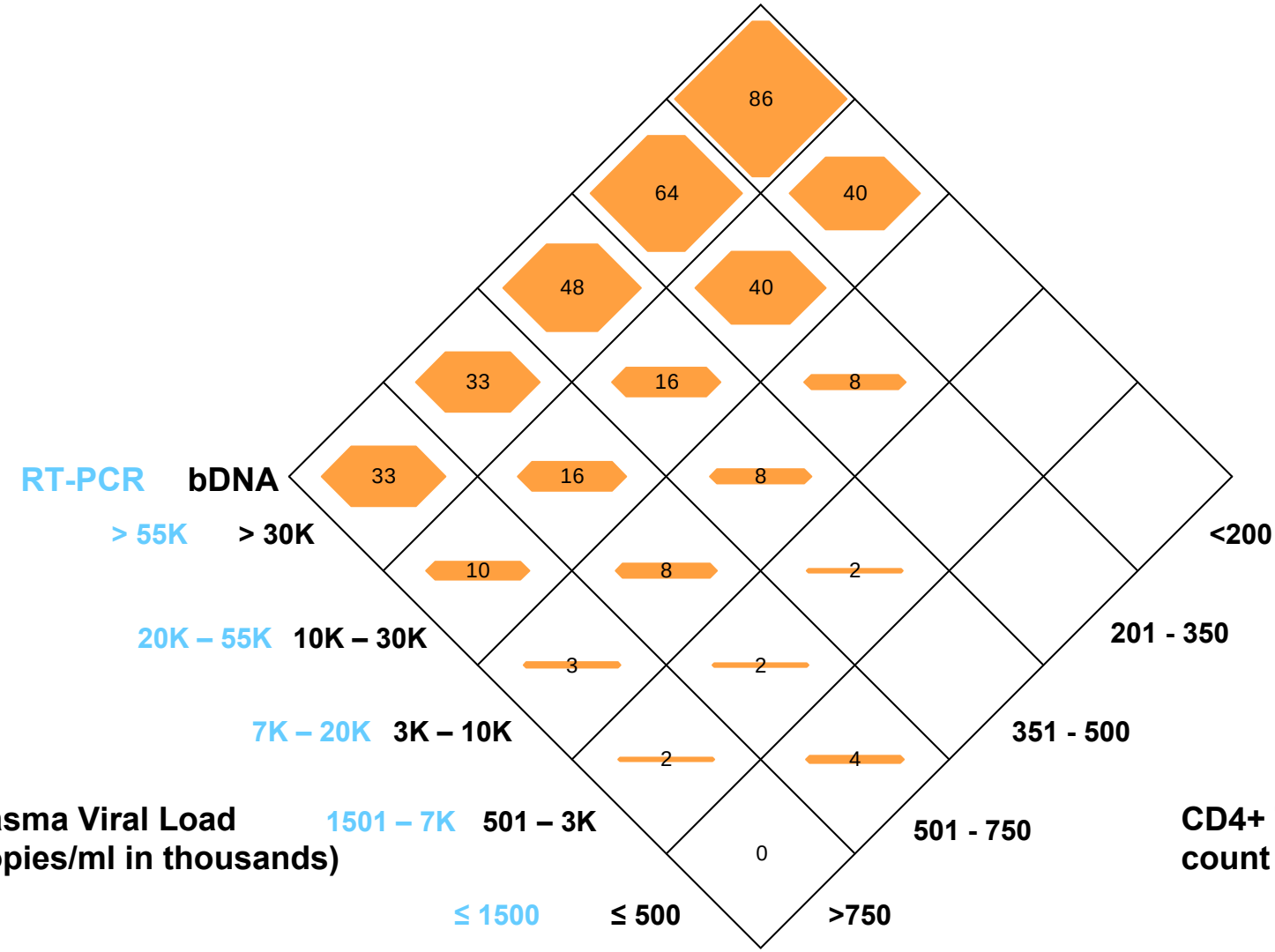
Mellors, Muñoz, . . ., Rinaldo - Ann Int Med 1997



June 1997

Likelihood of Developing AIDS in Three Years

Mellors, Muñoz, ..., Rinaldo – Ann Int Med 1997

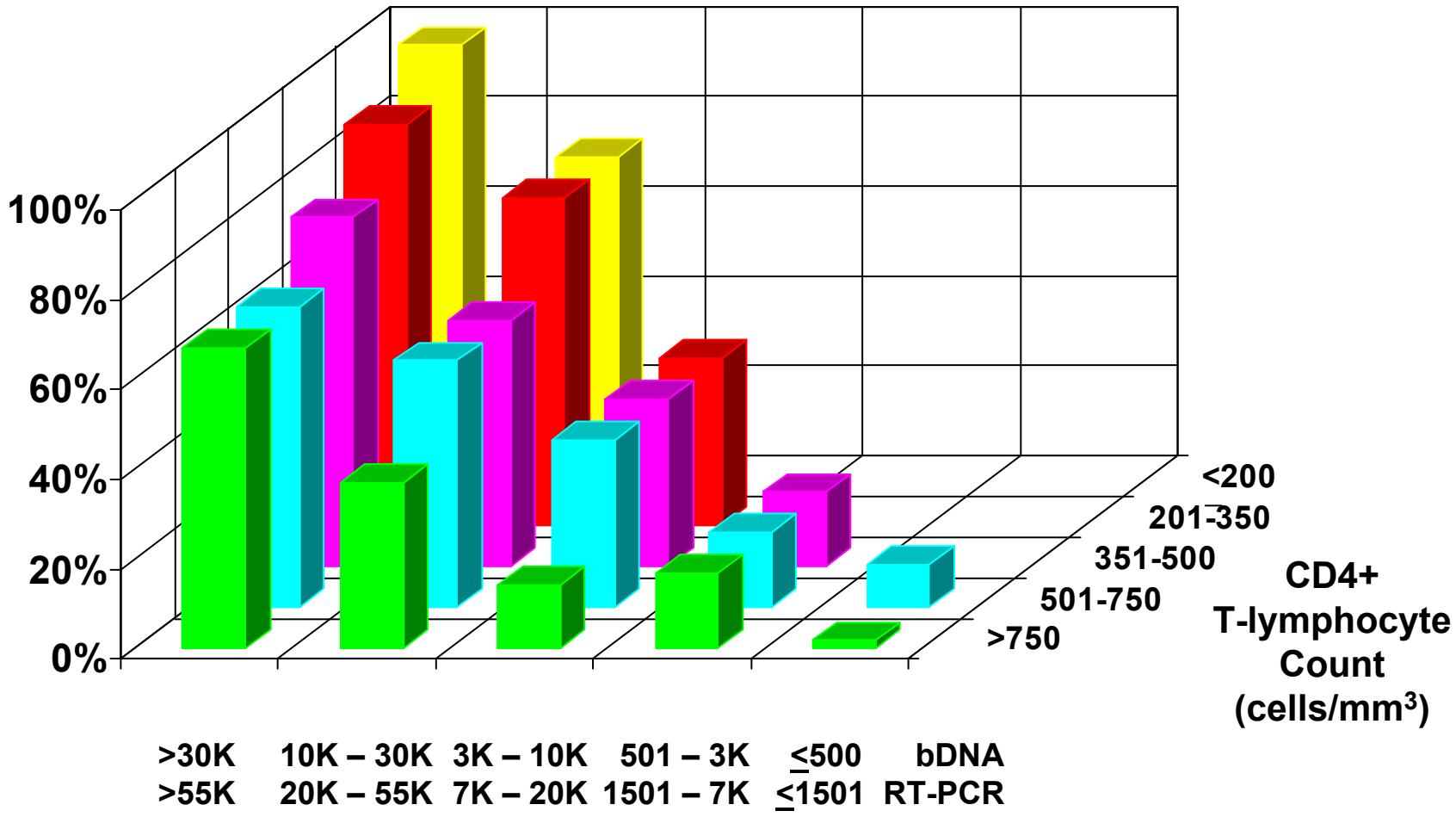


Graphical Reference: Li, Buechner, …, Muñoz - Am Statistician 2003

November 2003

Likelihood of Developing AIDS in Six Years

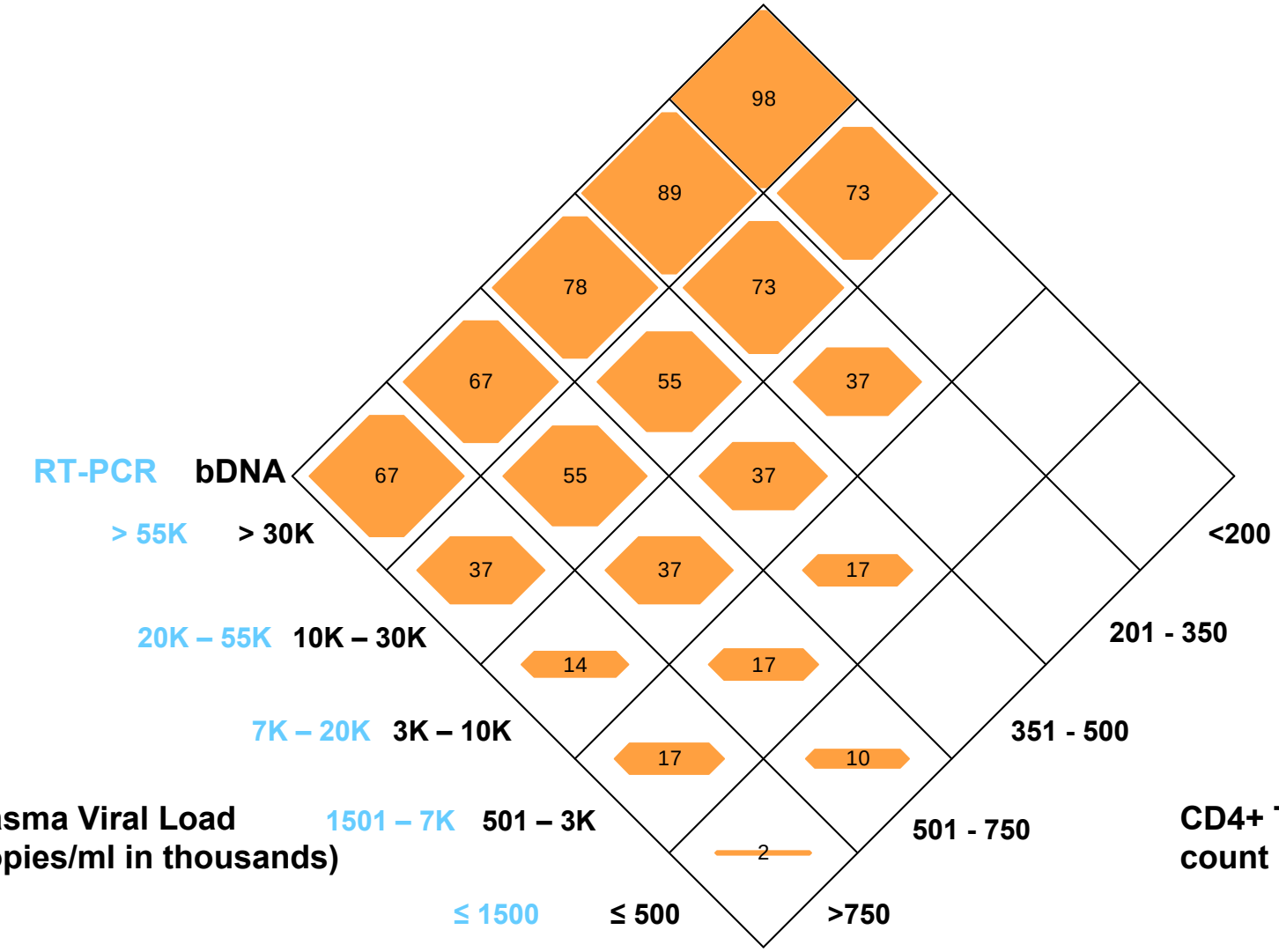
Mellors, Muñoz, . . ., Rinaldo - Ann Int Med 1997



June 1997

Likelihood of Developing AIDS in Six Years

Mellors, Muñoz, ..., Rinaldo – Ann Int Med 1997

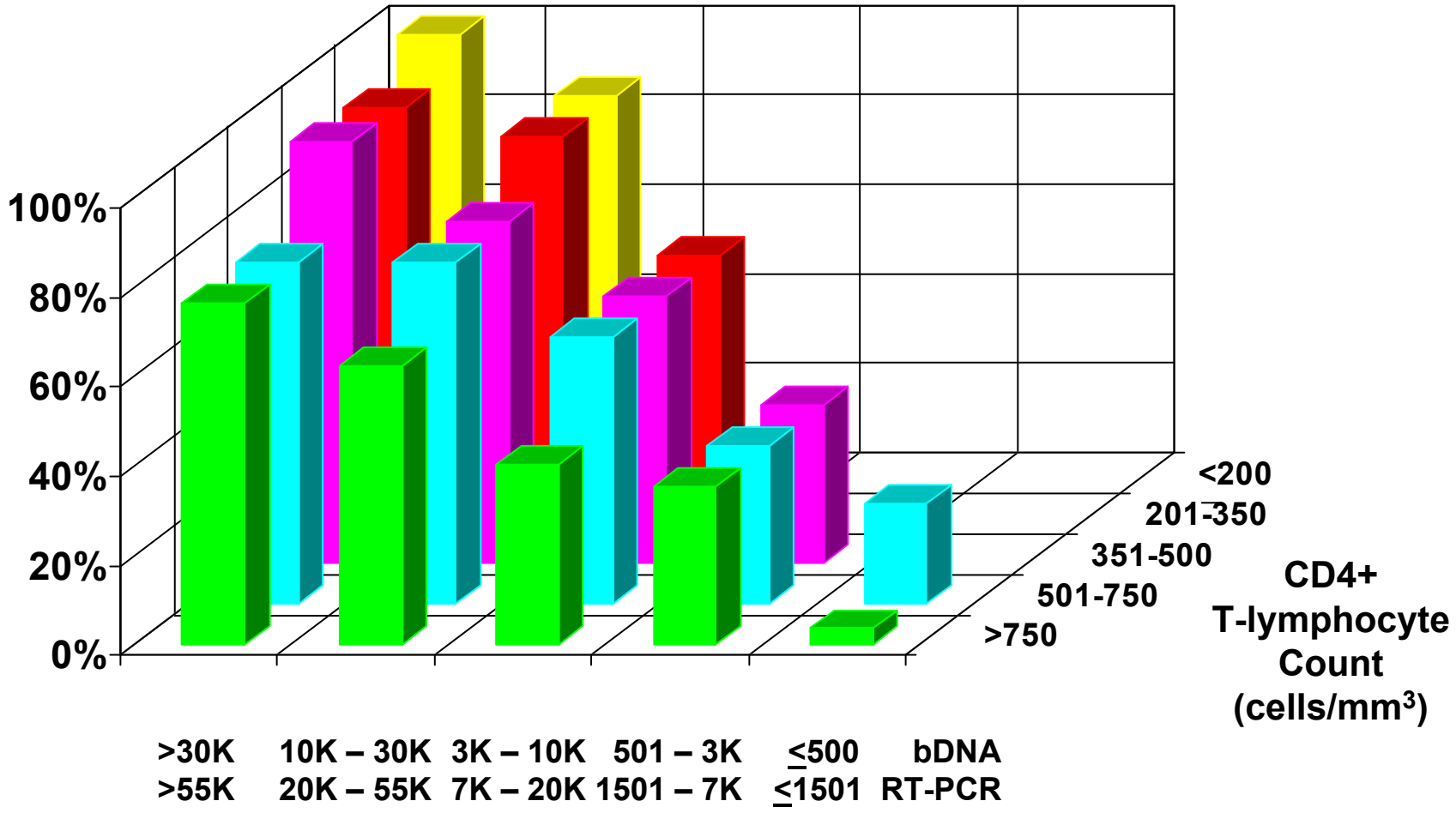


Graphical Reference: Li, Buechner, …, Muñoz - Am Statistician 2003

November 2003

Likelihood of Developing AIDS in Nine Years

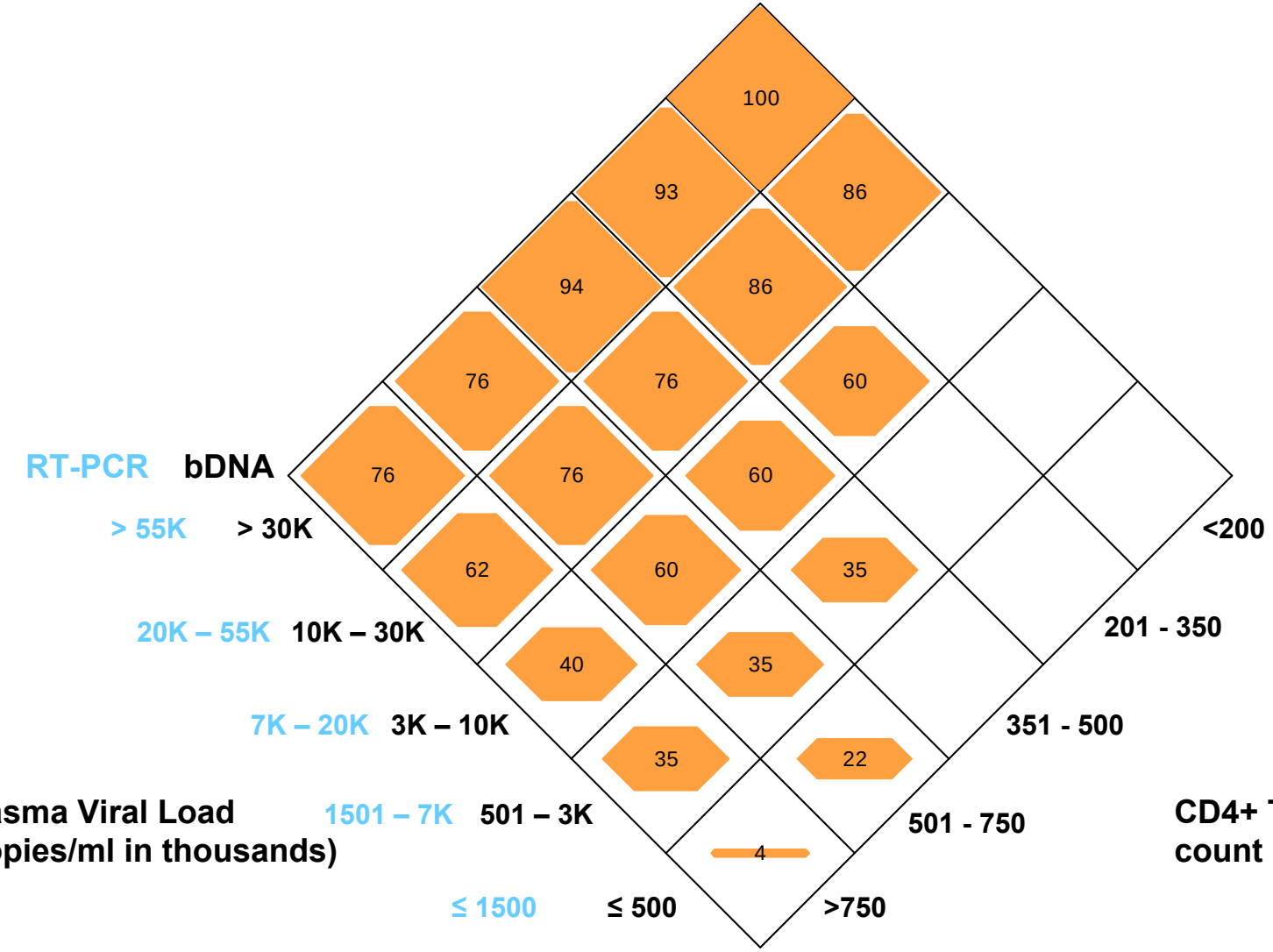
Mellors, Muñoz, . . ., Rinaldo - Ann Int Med 1997



June 1997

Likelihood of Developing AIDS in Nine Years

Mellors, Muñoz, ..., Rinaldo – Ann Int Med 1997

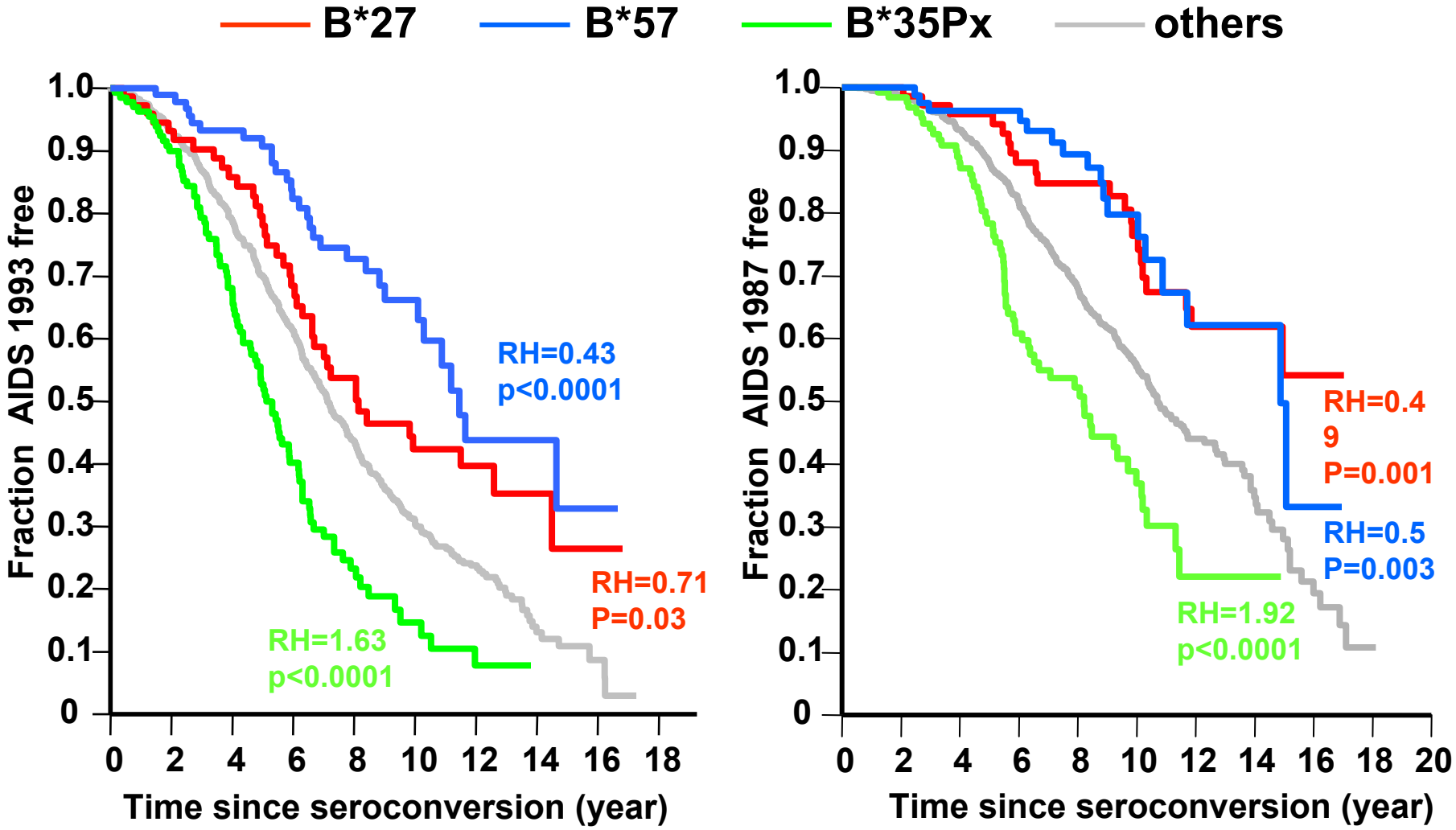


Graphical Reference: Li, Buechner, …, Muñoz - Am Statistician 2003

November 2003

Effect of HLA-B Alleles on AIDS Progression (N=1,089)

Gao, Bashirova, …, Carrington. Nat Med 2005



May 2006

HLA Allotypes are Distinct in Terms of the Timing at Which They Influence AIDS Progression

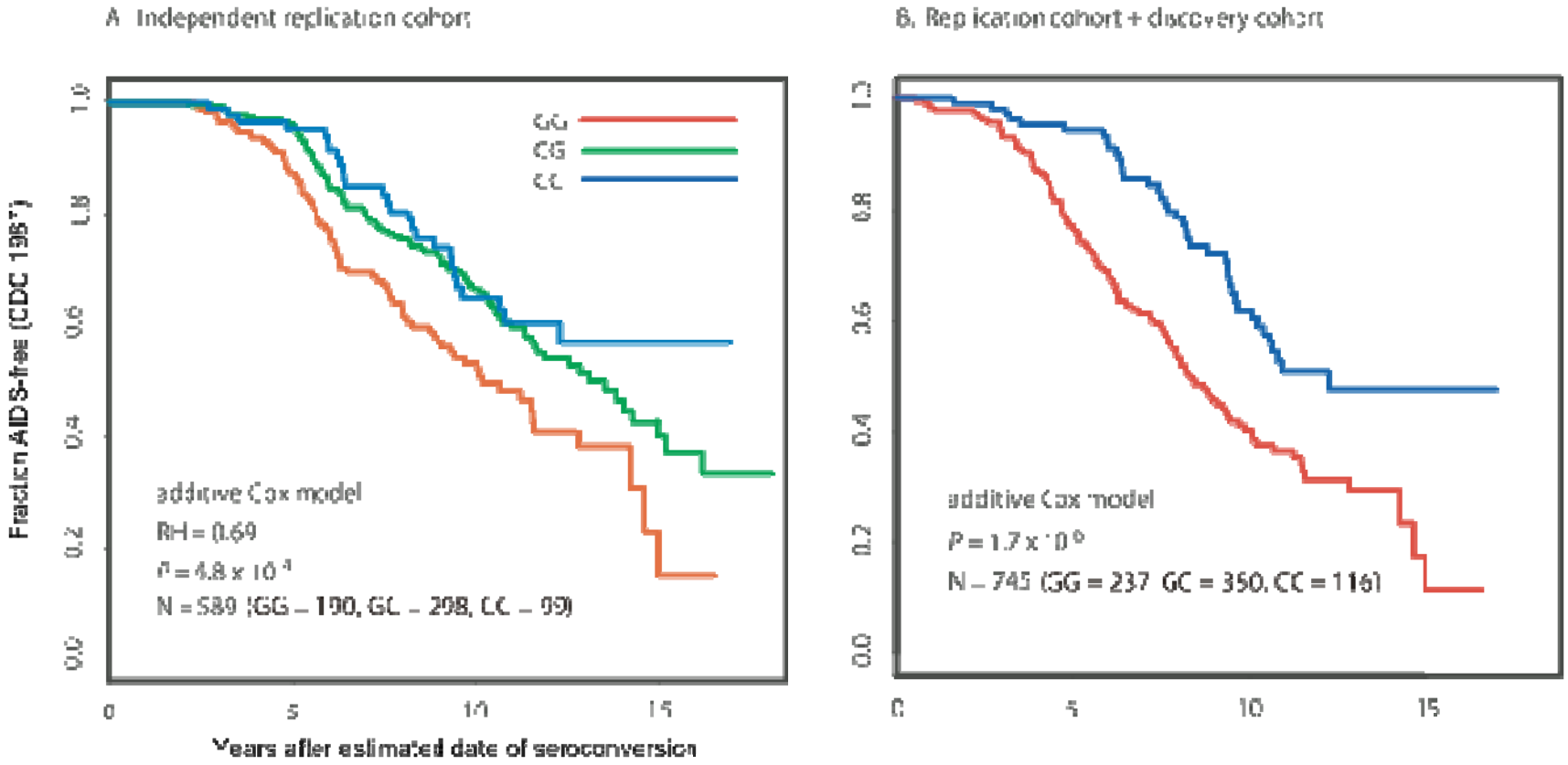
Gao, Bashirova, …, Carrington. Nat Med 2005

All Races

	Serocon. → CD4<200		CD4<200 → AIDS 87		AIDS 87 → death	
	RH	p value	RH	p value	RH	p value
	N = 1089		N = 1934		N = 1529	
B27	0.77	0.12	0.55	0.0001	0.77	0.08
B57	0.41	<0.0001	0.7	0.01	0.85	0.28
B35 Px	1.43	0.004	1.09	0.35	0.91	0.29

Kaplan-Meier Survival Curves for Genotypes of SNP rs17762192, Representing a Haplotype Located 36kb Upstream of *PROX1* and Chromosome 1, Showing Strong Associations with Differing Rates of Progression to Clinical AIDS

Herbeck, Gottlieb, … Mullins. J Infect Dis 2010



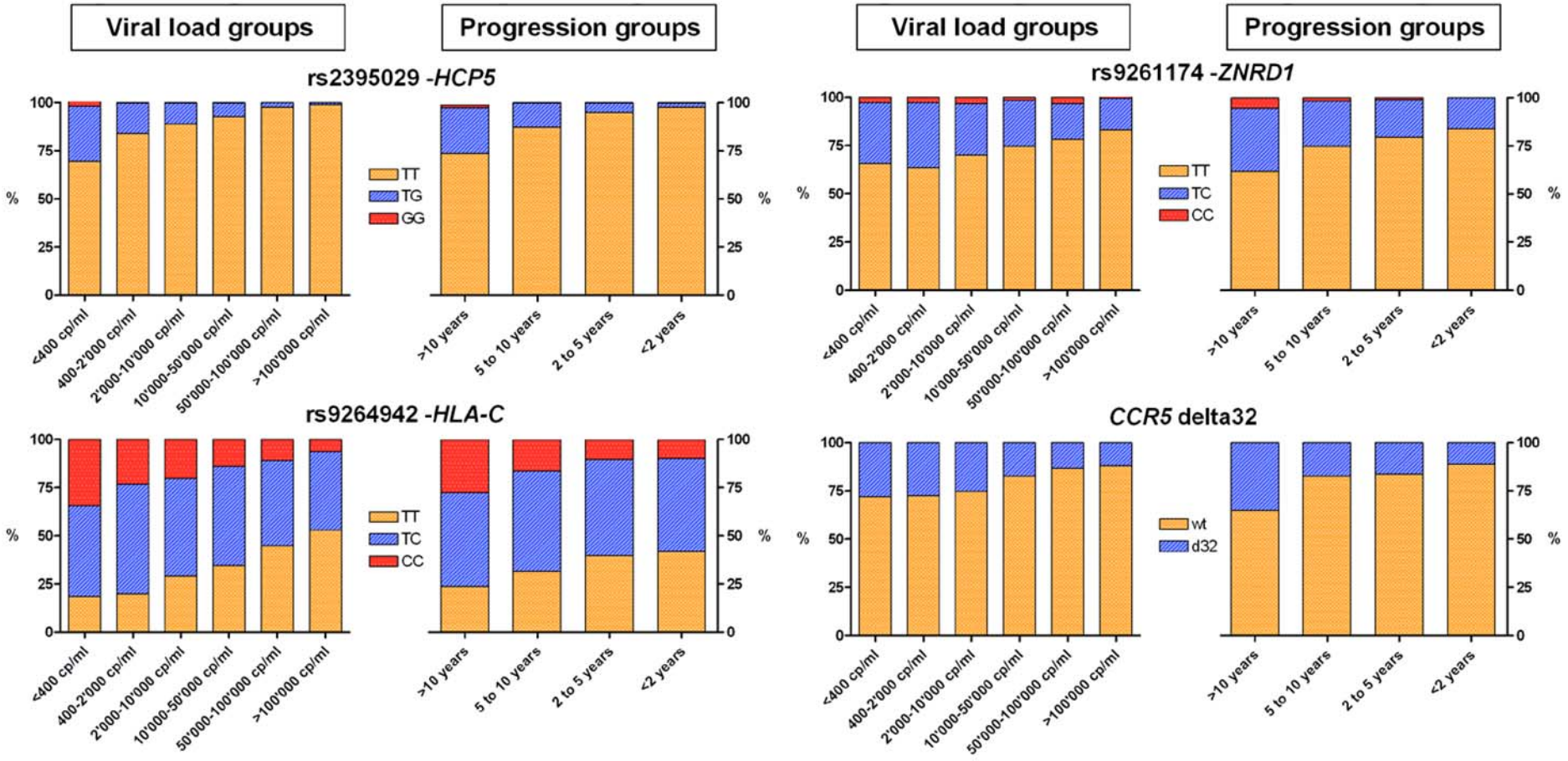
A. Replication cohort (ALIVE, MACS, MHCS, SFCC, individuals genotyped by Steve O'Brien

B. Combined analysis of replication and discovery cohorts (156 MACS individuals enriched with rapid progressors and long-term non-progressors.

May 2010

Allelic Distribution of the Significant Variants in Subsets of the Study Population

Fellay, Ge, …, Goldstein. PLoS Genet 2009



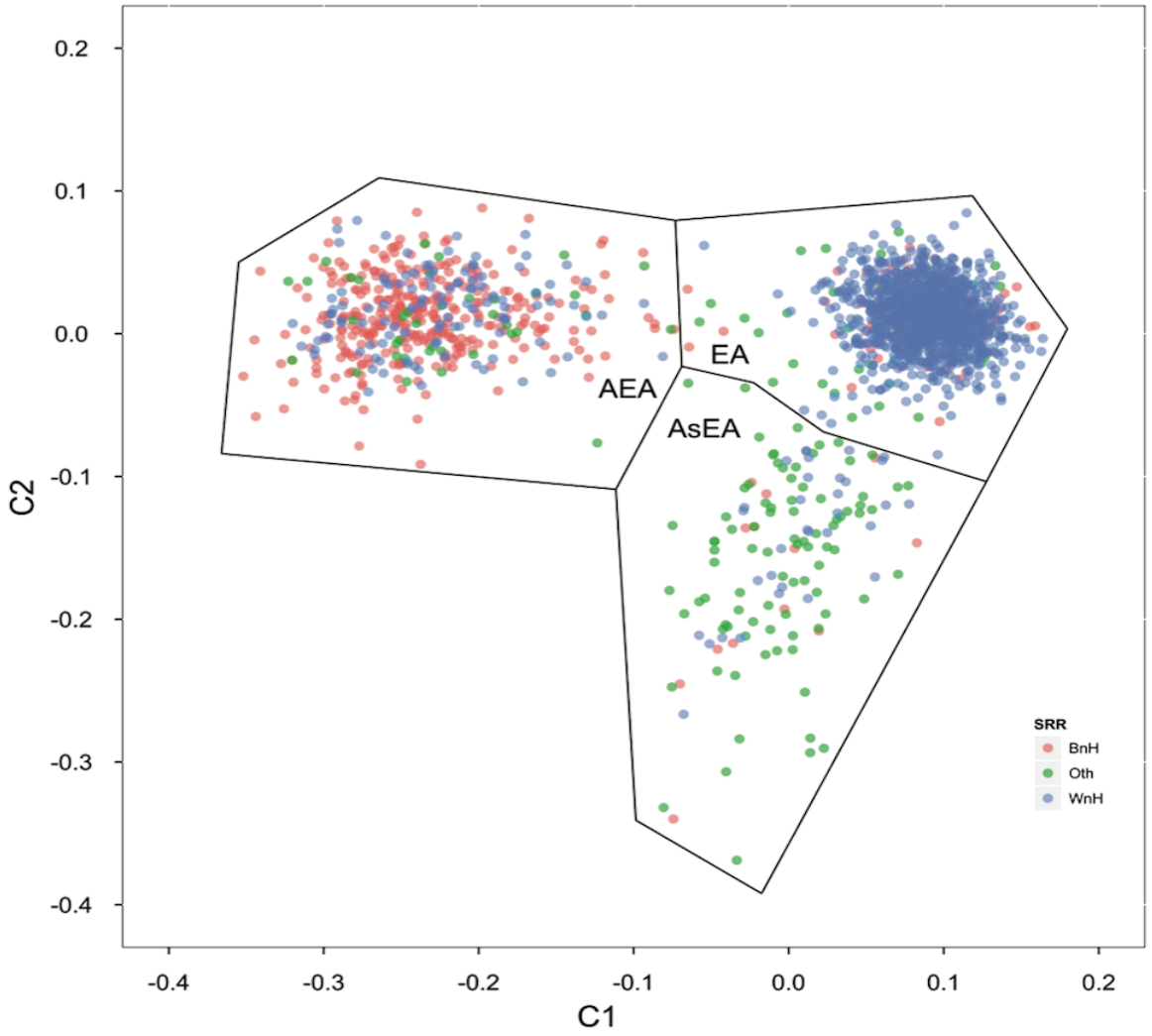
The bar graphs show the allelic distribution of the 4 variants that have a genome-wide significant association with HIV-1 set point and/or disease progression in subsets of the study population. Groups were defined according to HIV-1 set point (left-hand side graphs) and to progression time (right-hand side graphs)

May 2010

Self-Reported Race Varies by Genetically Defined Biogeographical Ancestry

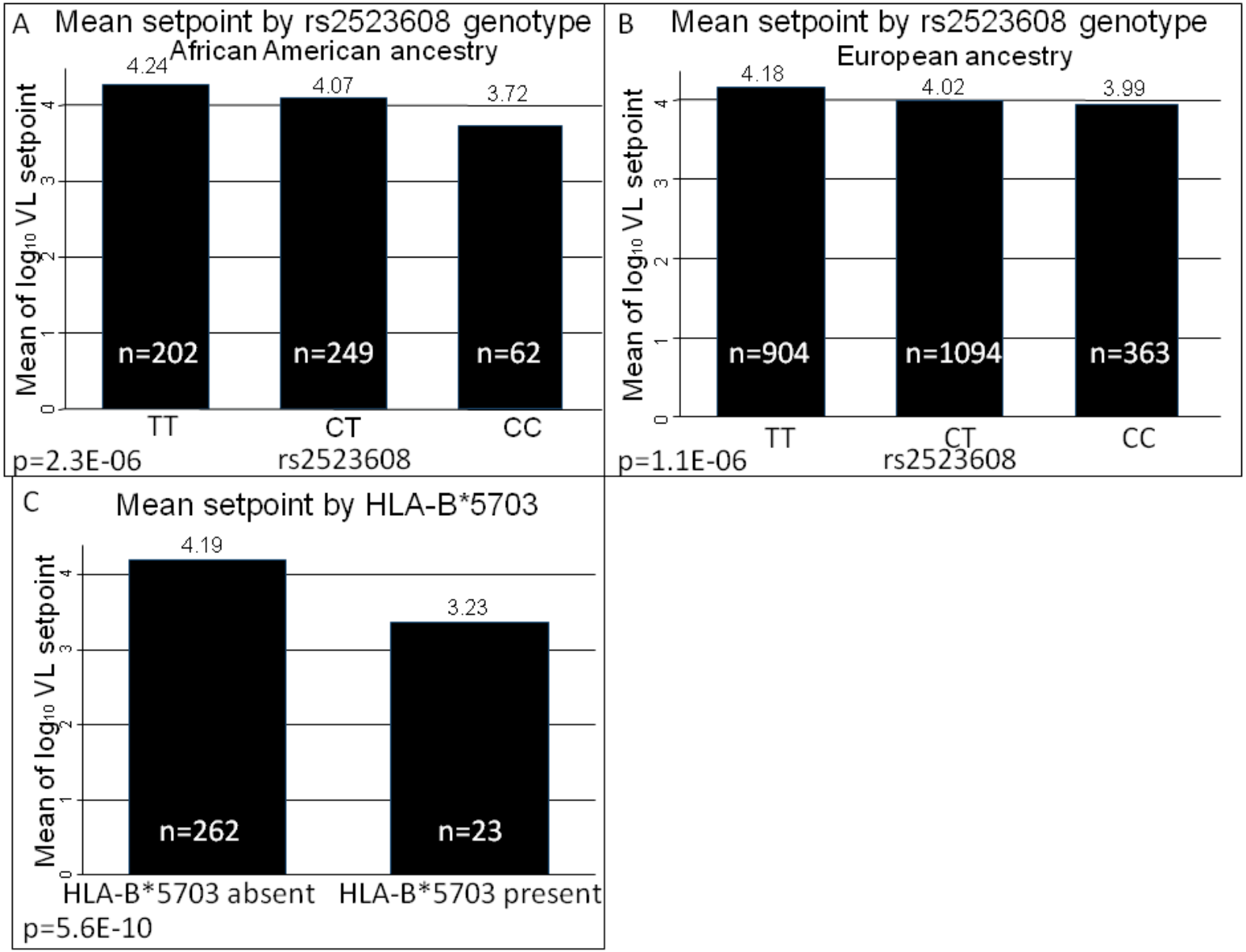
Nicholaou, Martinson, …, Kingsley - AIDS Res Hum Retroviruses 2013;29:871-9

The scatter plot shows the first two principal components from the multi dimensional scaling (MDS) procedure, performed on the ancestry informative markers (AIMs) data. Each dot represents an individual who was genotyped in the MACS cohort (n=1914). Colors represent self-reported race (SRR) (red = BnH, blue = WnH, green = other) and boundaries of biogeographical ancestry (BGA) populations (EA, AEA, and AsEA) were defined by a *k*-means clustering procedure.

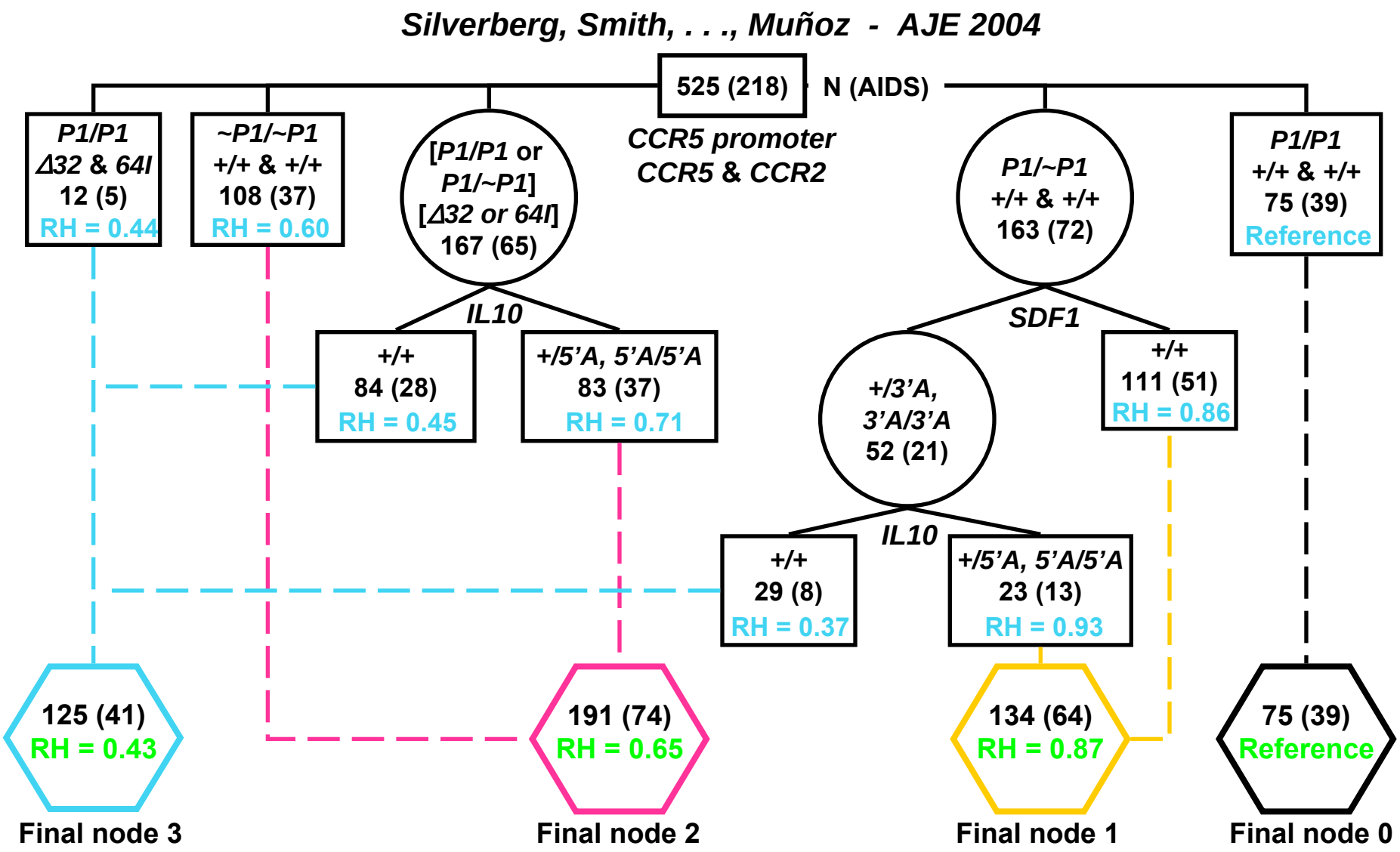


Distribution of Mean HIV-1 Set Point According to Patient Genotype

Pelak, Goldstein,…, Weintrob. J Infect Dis 2010



AIDS Prevented Fraction Among Seroconverters



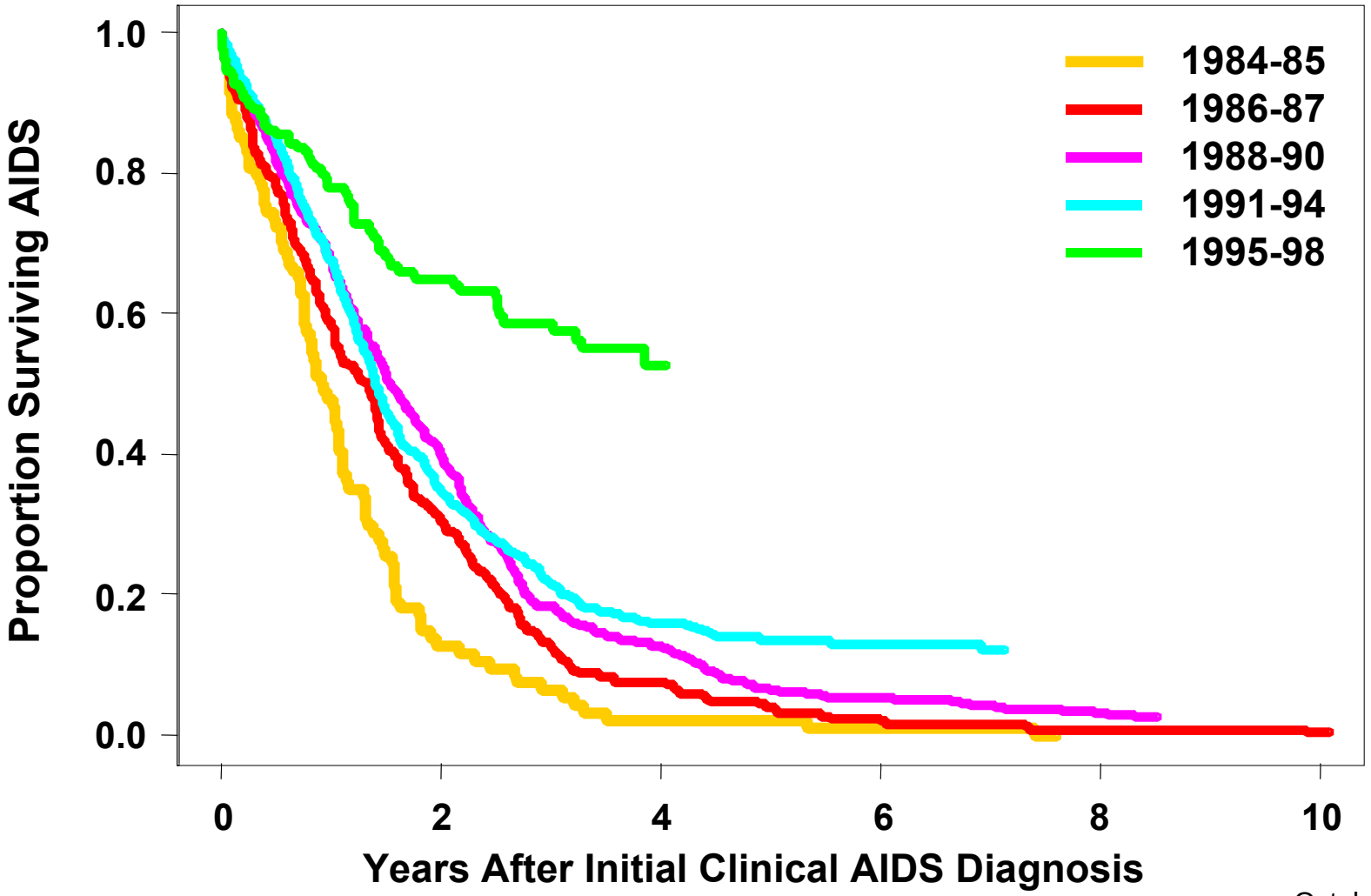
Fraction of AIDS prevented by nodes 1, 2, and 3: 0.30 (95% CI: 0.07, 0.47)

November 2004

Proportion Surviving AIDS by Year of Diagnosis

Assumed currently alive at 6/30/99 if contacted since 6/30/98

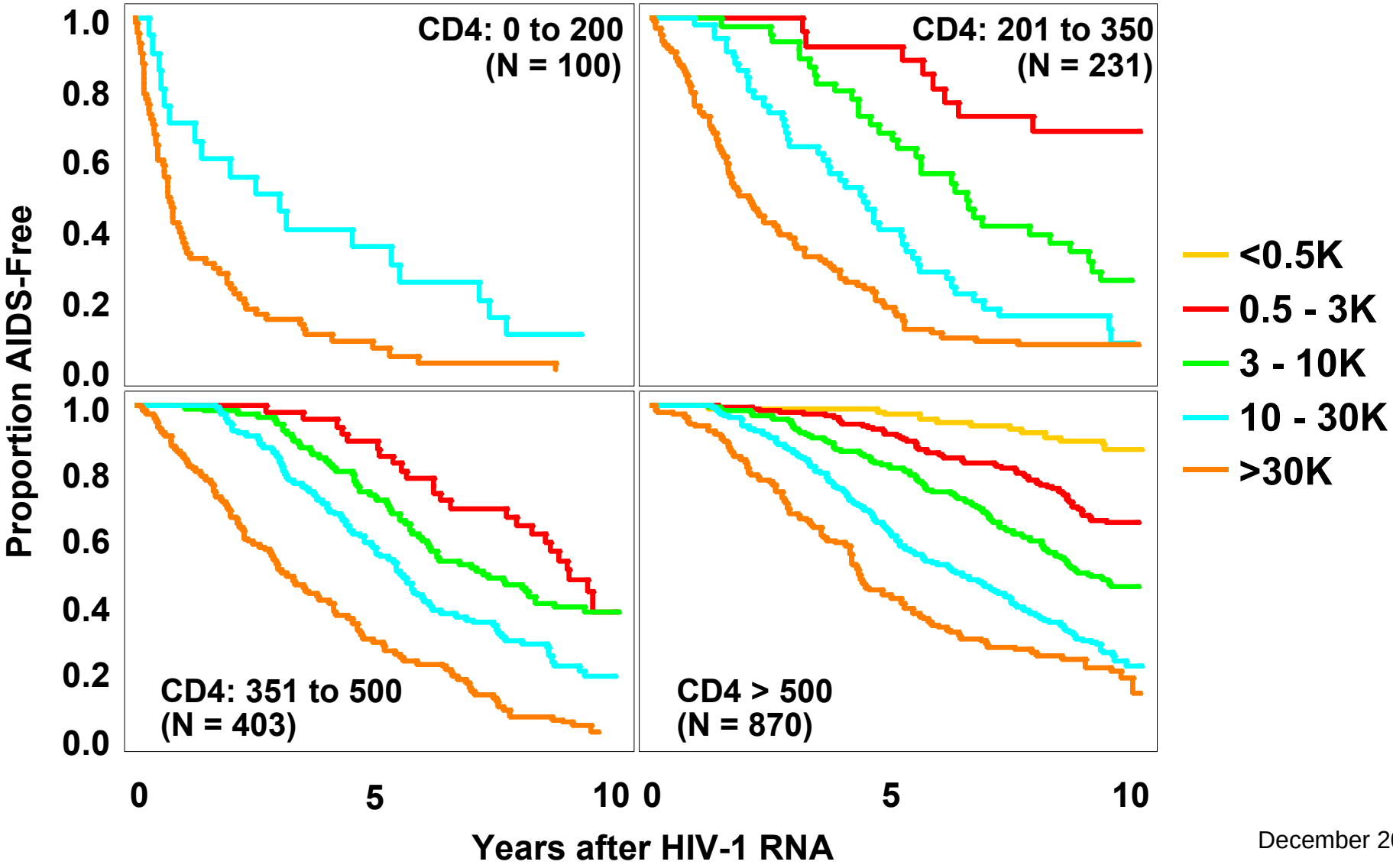
Jacobson, Kirby, . . ., Schrager - AJE 1993 (update)



October 1999

Effect of HIV-1 RNA within CD4 Category Prior to HAART

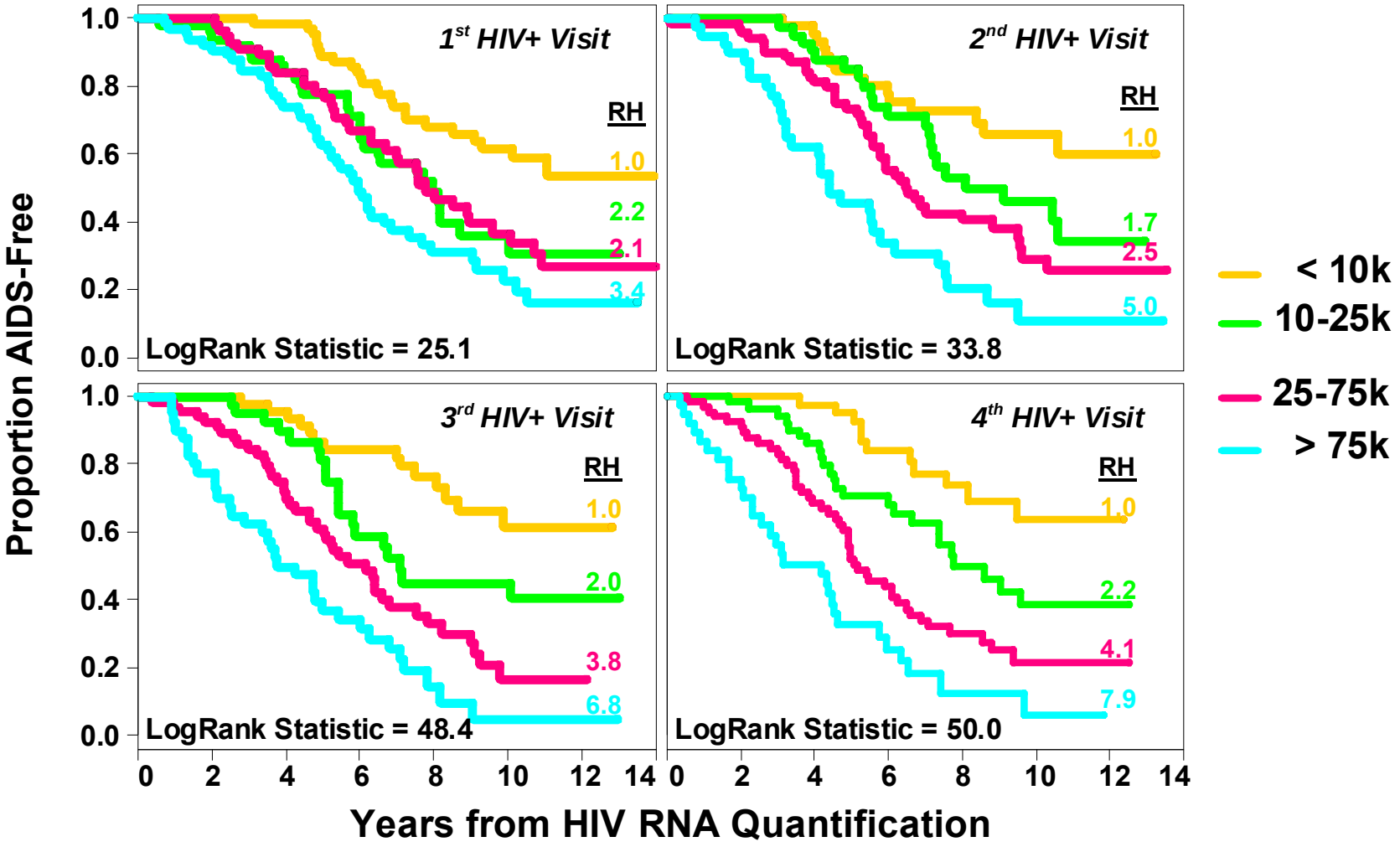
Mellors et al. Ann Int Med 1997



December 2001

Predictive Value of HIV RNA (copies/ml) by Time Since Seroconversion

Lyles, Muñoz, . . ., Mellors - JID 2000



October 2000

Extension of Time to Events by Reducing HIV RNA Setpoint

Gupta, Jacobson, …, Straus. J Infect Dis 2007

	Outcome			
	AIDS		CD4 <350 cells/μl	
HIV RNA copies/ml	Relative Time	Median Time (Years)	Relative Time	Median Time (Years)
30,000	1	8.4	1	3.4
9,487 (0.5 log)	1.4	11.9	1.3	4.5
3,000 (1 log)	2.0	16.9	1.7	5.9
300 (2 log)	4.1	34.4	3.0	10.3

Prognostic Value of HIV-1 RNA, CD4 Cell Count and CD4 Cell Count Slope for Progression to AIDS and Death in Untreated HIV-1 Infection

Mellors, Margolick, …, Jacobson. JAMA 2007;297:2349-50

Percent (95% CI) Variability in Outcomes Explained by Predictor

Baseline Predictors	AIDS	Death	CD4 cell count <200/µL
(Events/Total N)	(598/1640)	(421/1640)	(648/1472)
HIV-1 RNA	47 (40-55)	50 (41-62)	34 (25-42)
CD4 cell count	29 (25-34)	26 (21-32)	26 (21-31)
Age	1 (0-2)	3 (1-5)	1 (0-3)
HIV-1 RNA and CD4 cell count	54 (47-61)	56 (48-67)	46 (37-52)

Prognostic Value of HIV-1 RNA, CD4 Cell Count and CD4 Cell Count Slope for Progression to AIDS and Death in Untreated HIV-1 Infection

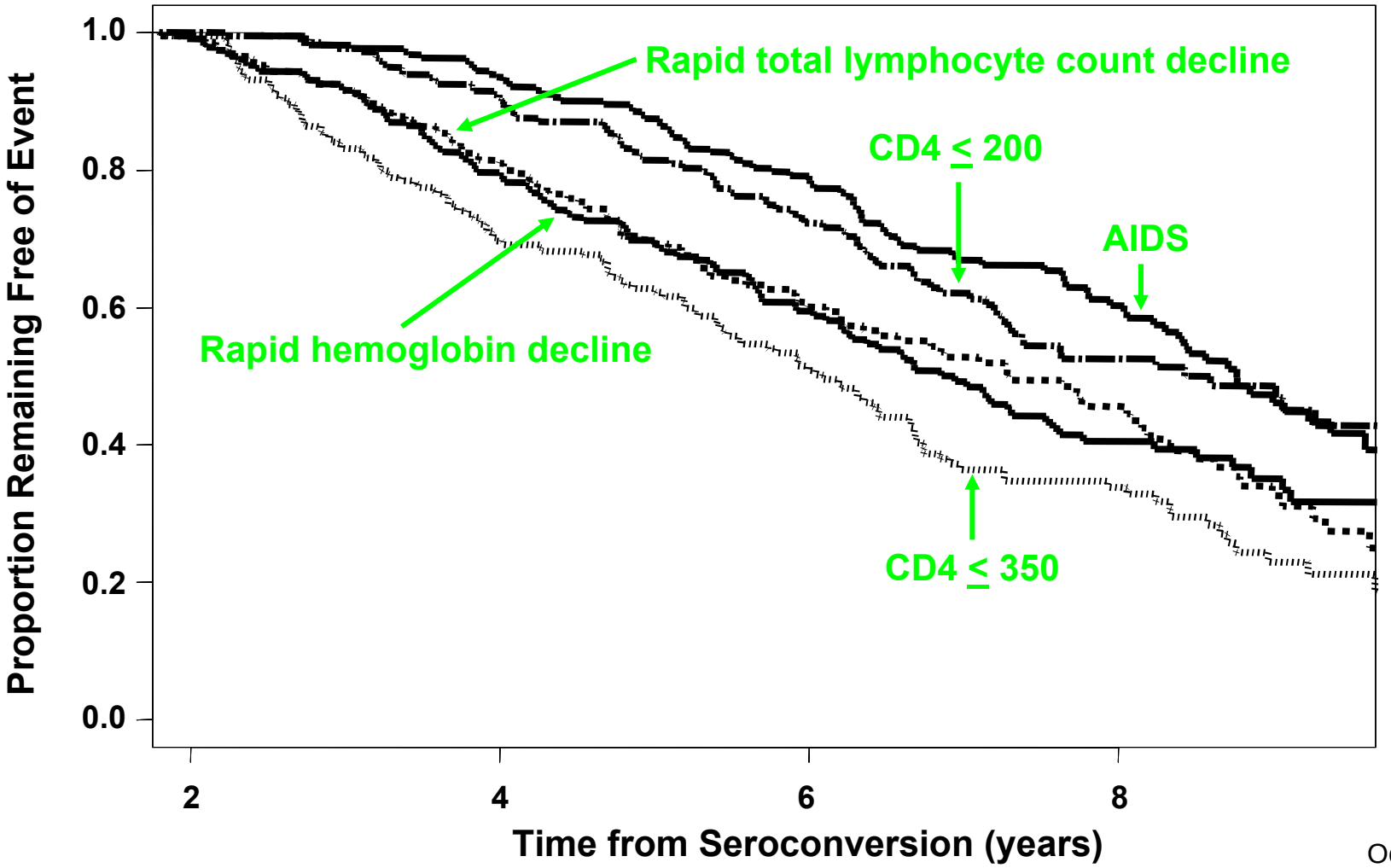
Mellors, Margolick, …, Jacobson. JAMA 2007;297:2349-50

Percent (95% CI) Variability in Outcomes Explained by Predictor

Longitudinal Predictors (1984-1988)	AIDS	Death	CD4 cell count <200/µL
(Events/Total N)	(302/1303)	(285/1490)	(206/870)
Median HIV-1 RNA	51 (38-64)	58 (47-69)	39 (24-60)
Median CD4 cell count	29 (22-38)	35 (29-43)	24 (15-35)
CD4 cell count slope	3 (1-7)	7 (4-12)	4 (1-8)
Age in June 1988	1 (0-4)	2 (0-3)	2 (1-4)
Median HIV-1 RNA and CD4 cell count	58 (46-69)	63 (54-73)	48 (31-79)

Kaplan-Meier Estimates of the Time from Seroconversion to AIDS, CD4+ Lymphocyte Count <200 cells/mm3, Rapid TLC Decline, and CD4+ Lymphocyte Count <350 cells/mm3

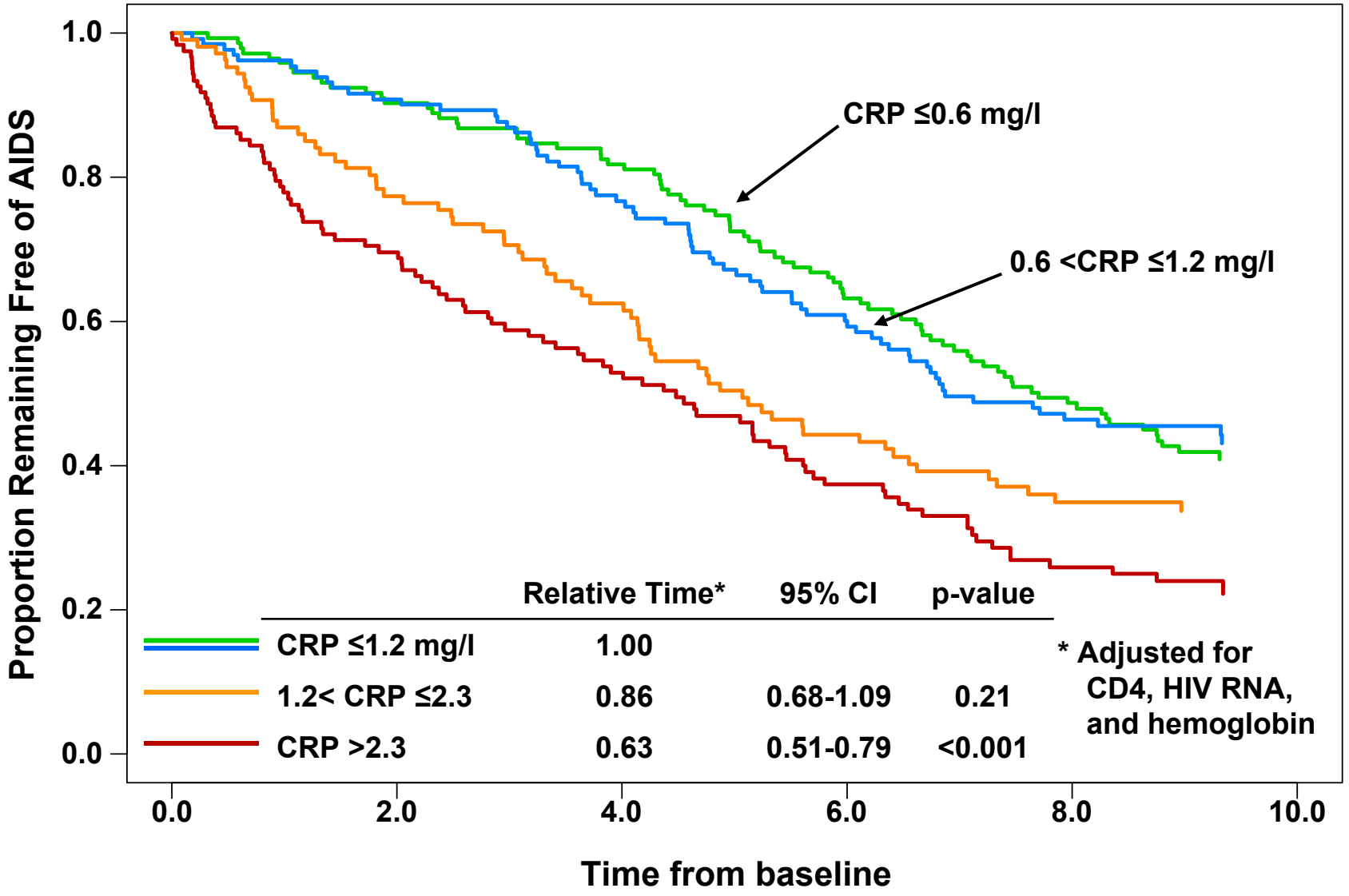
Lau, Gange, … , Margolick - JAIDS 2005



October 2005

HIV Disease Progression to AIDS by CRP Level

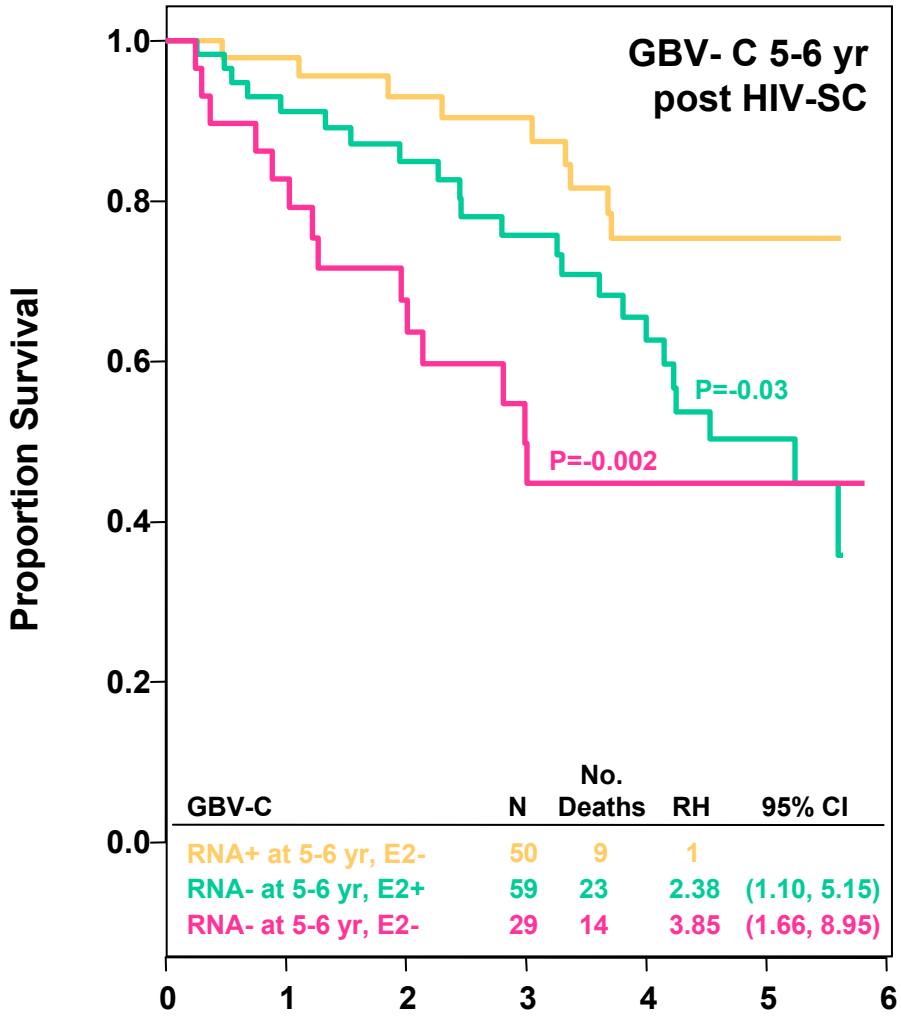
Lau, Sharrett, …, Gange. Ann Intern Med 2006

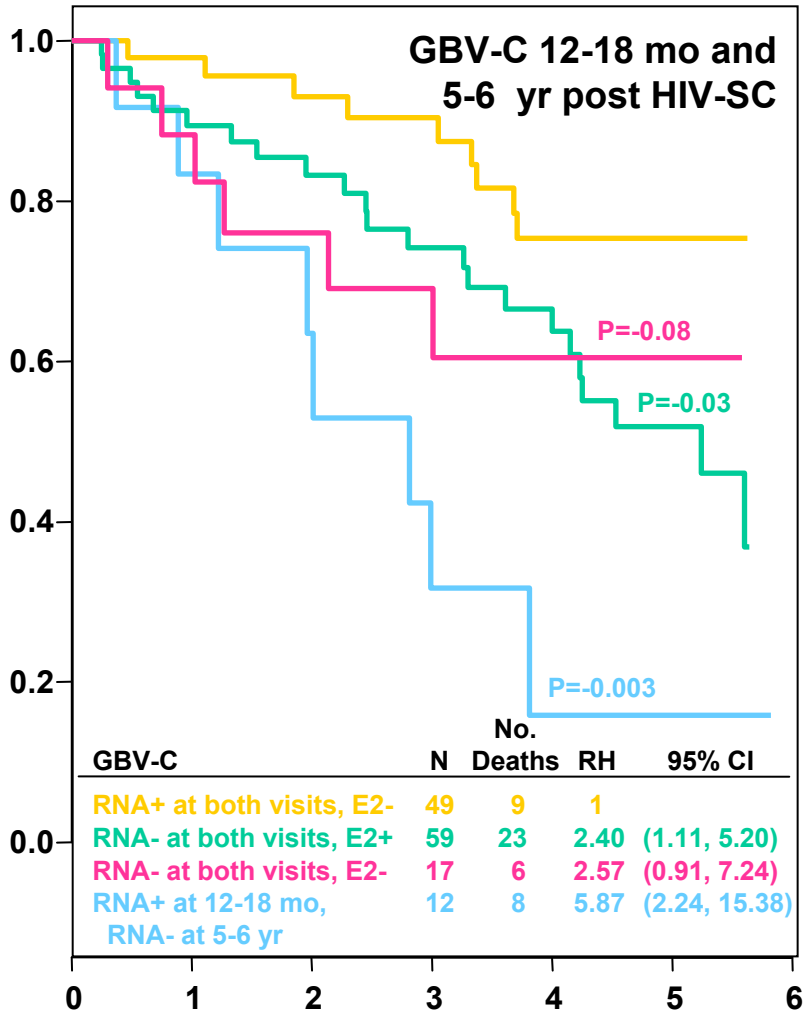


May 2006

Time to Death According to GBV-C Serostatus Early and Late in HIV Infection

Williams, Klinzman, …, Stapleton - N Engl J Med 2004

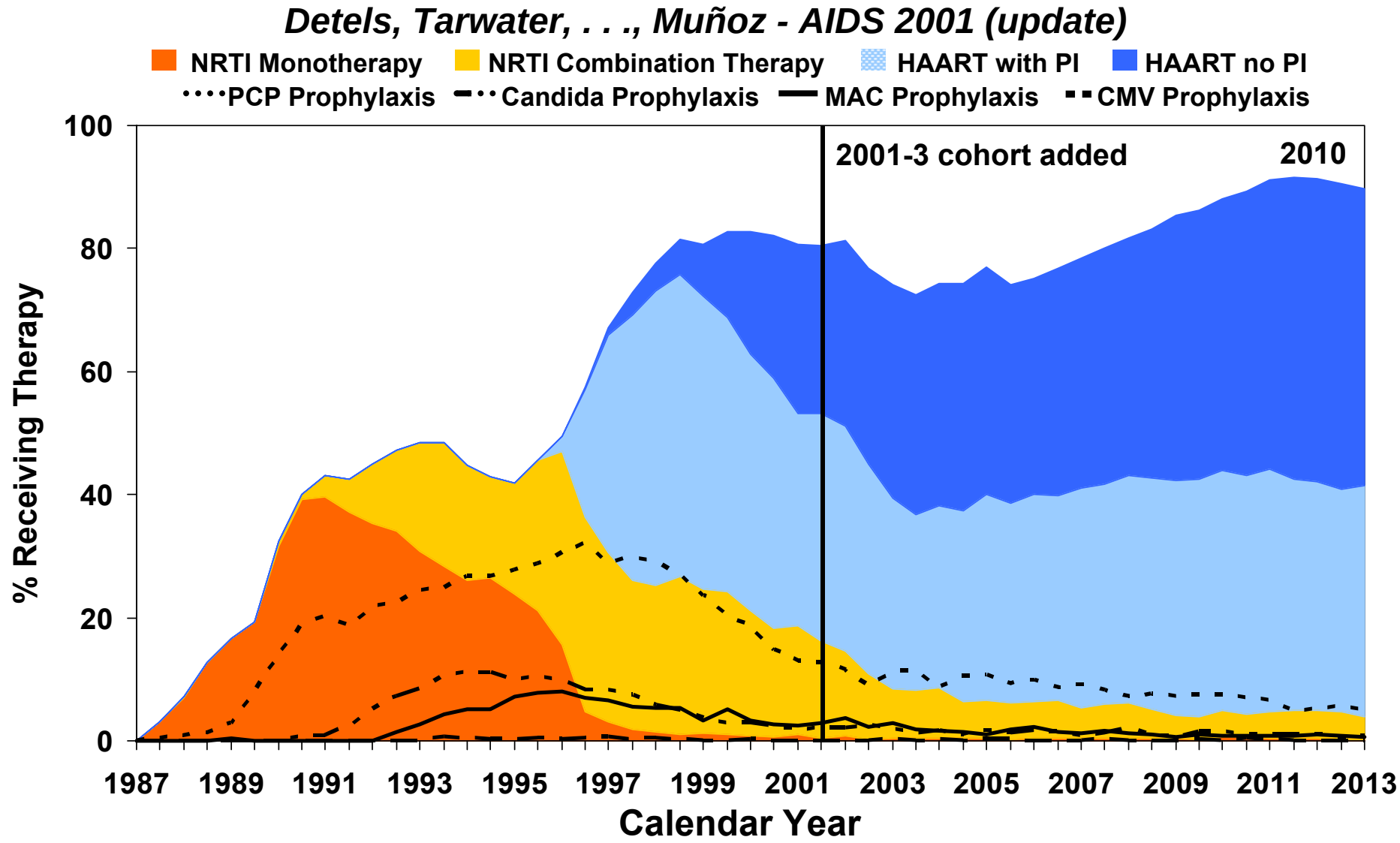




Years from Late Visit

November 2004

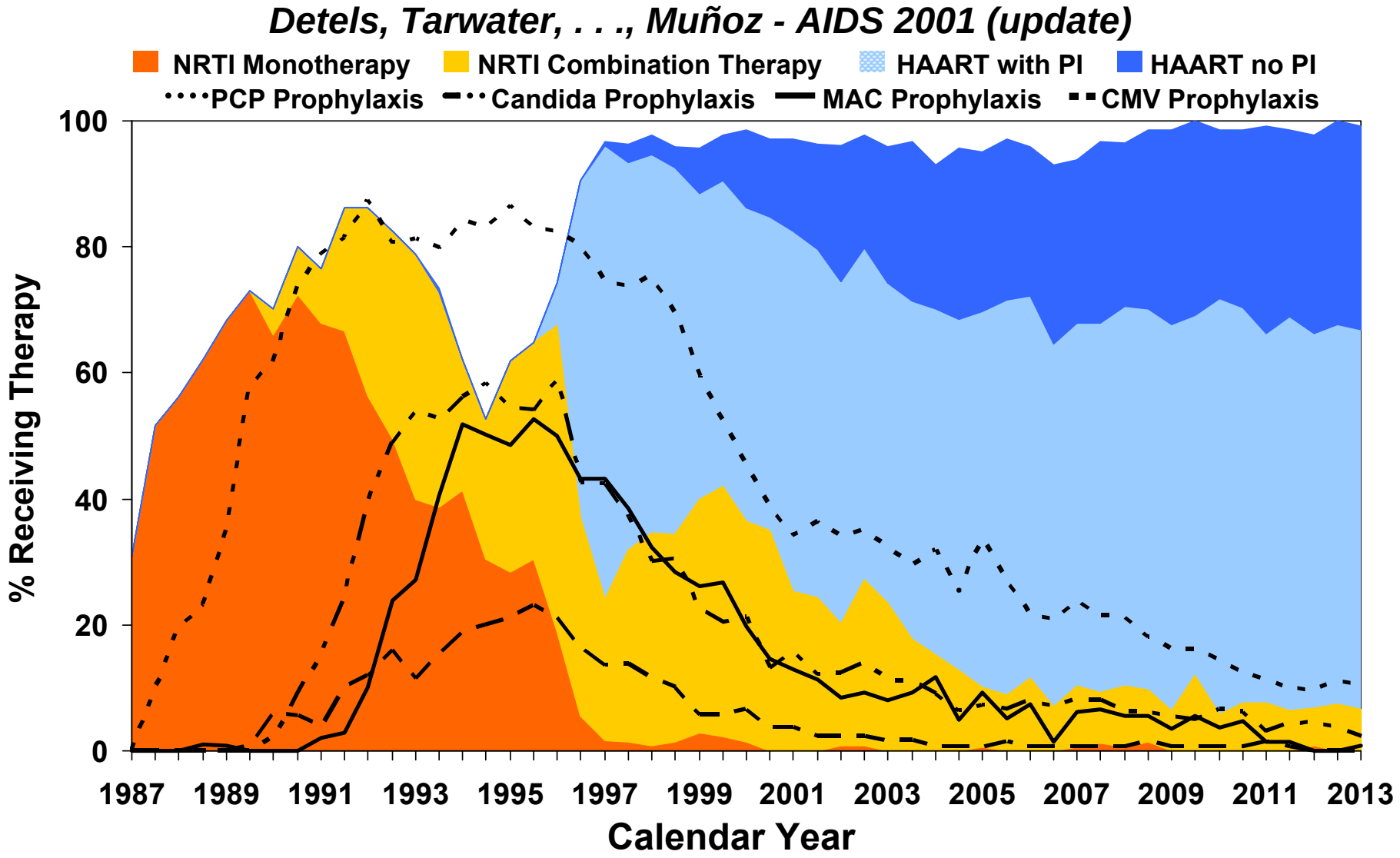
Use of Antiretroviral Therapy by Seropositive MACS Participants without Clinical AIDS



** Based on November 2008 HAART definition*

November 2013

Use of Antiretroviral Therapy by Seropositive MACS Participants with Clinical AIDS



** Based on November 2008 HAART definition*

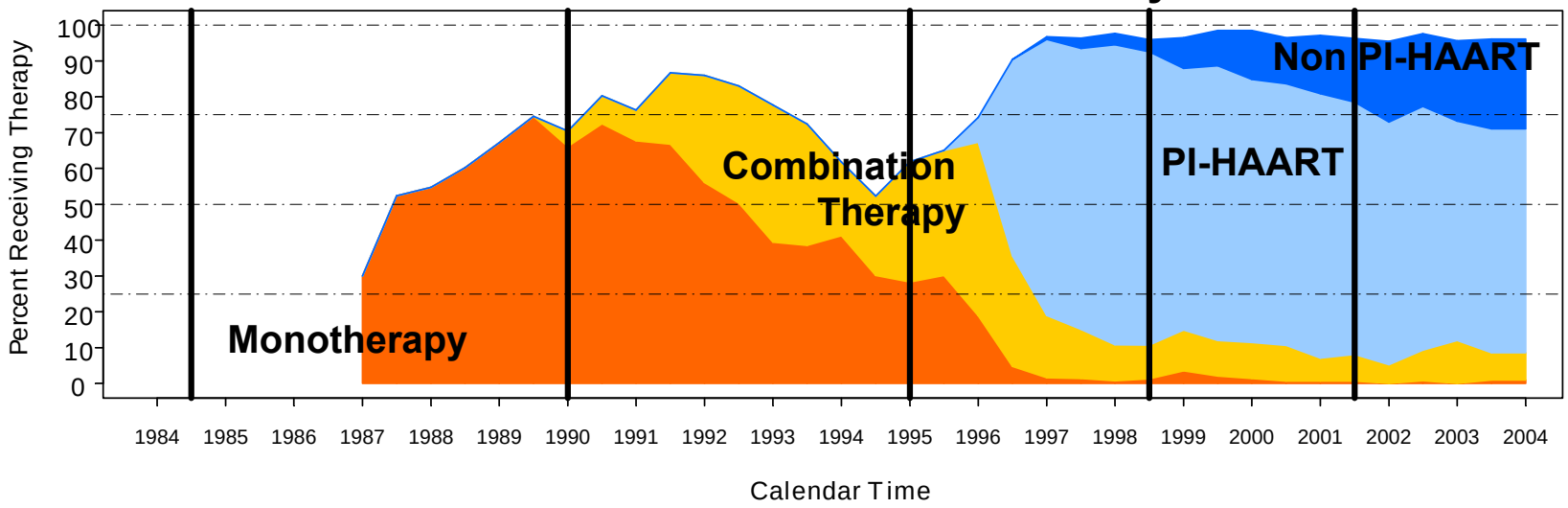
November 2013

Use of ART by Participants with AIDS

Schneider, Gange, …, Muñoz. AIDS 2005

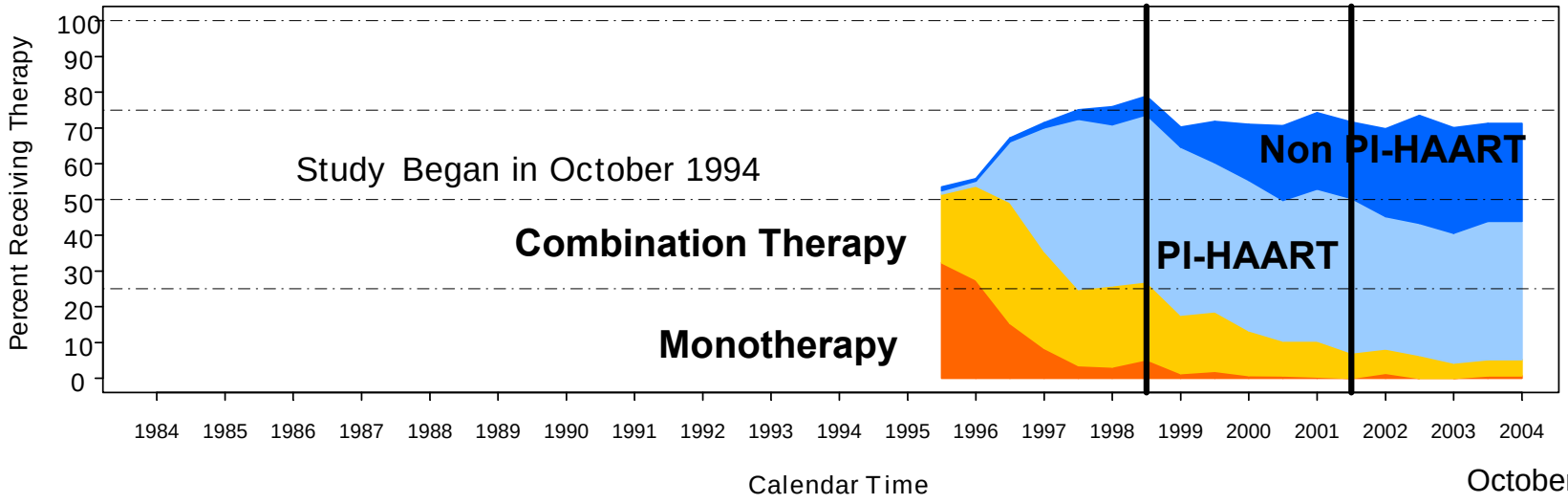
A

Multicenter AIDS Cohort Study



B

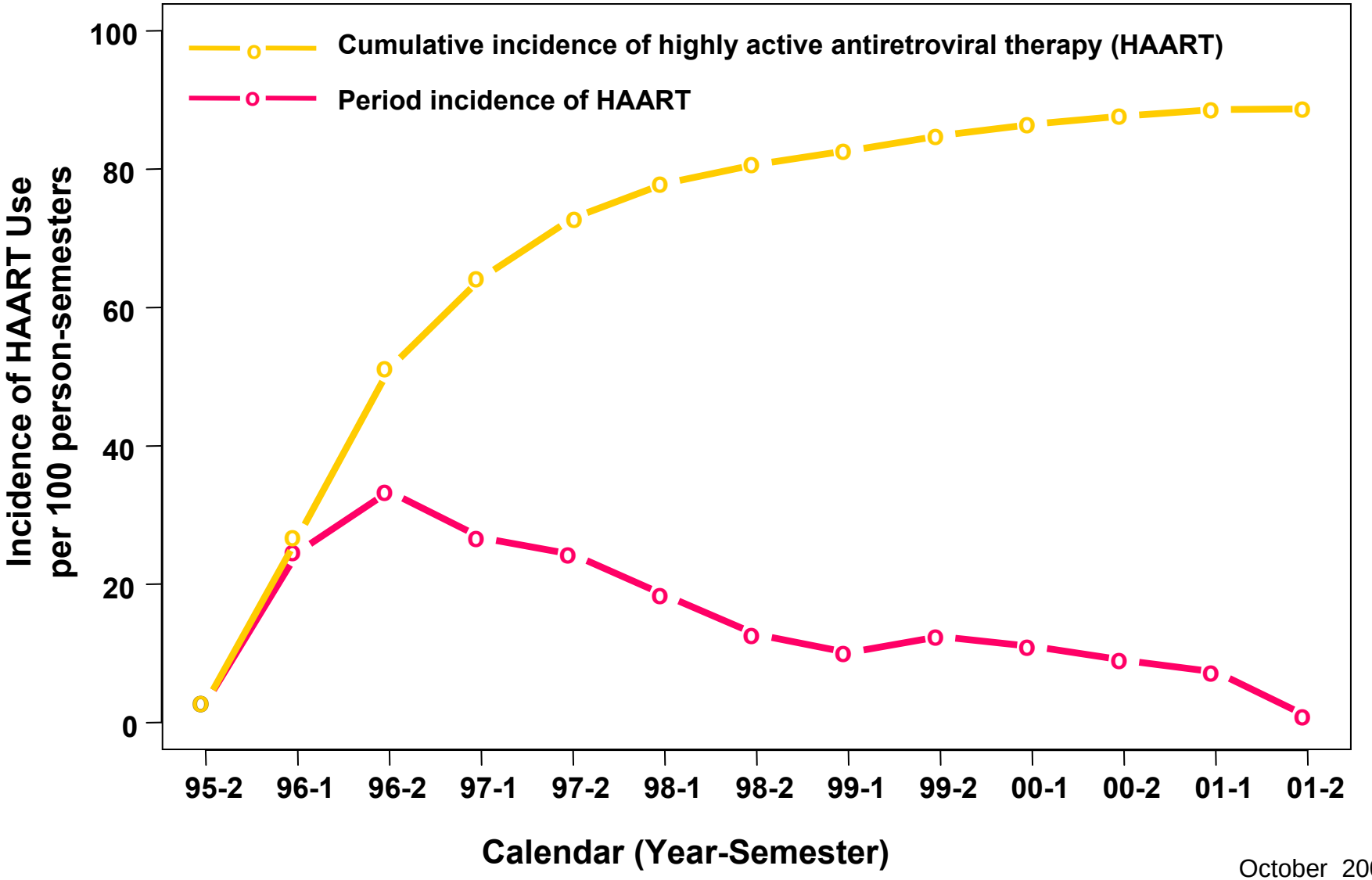
Women's Interagency HIV Cohort Study



October 2005

HAART Use in the Multicenter AIDS Cohort Study

Jacobson, Li, …, Muñoz - Am J Epidemiol 2002 [update]



October 2002

Adherence to HIV-Antiretroviral Therapies

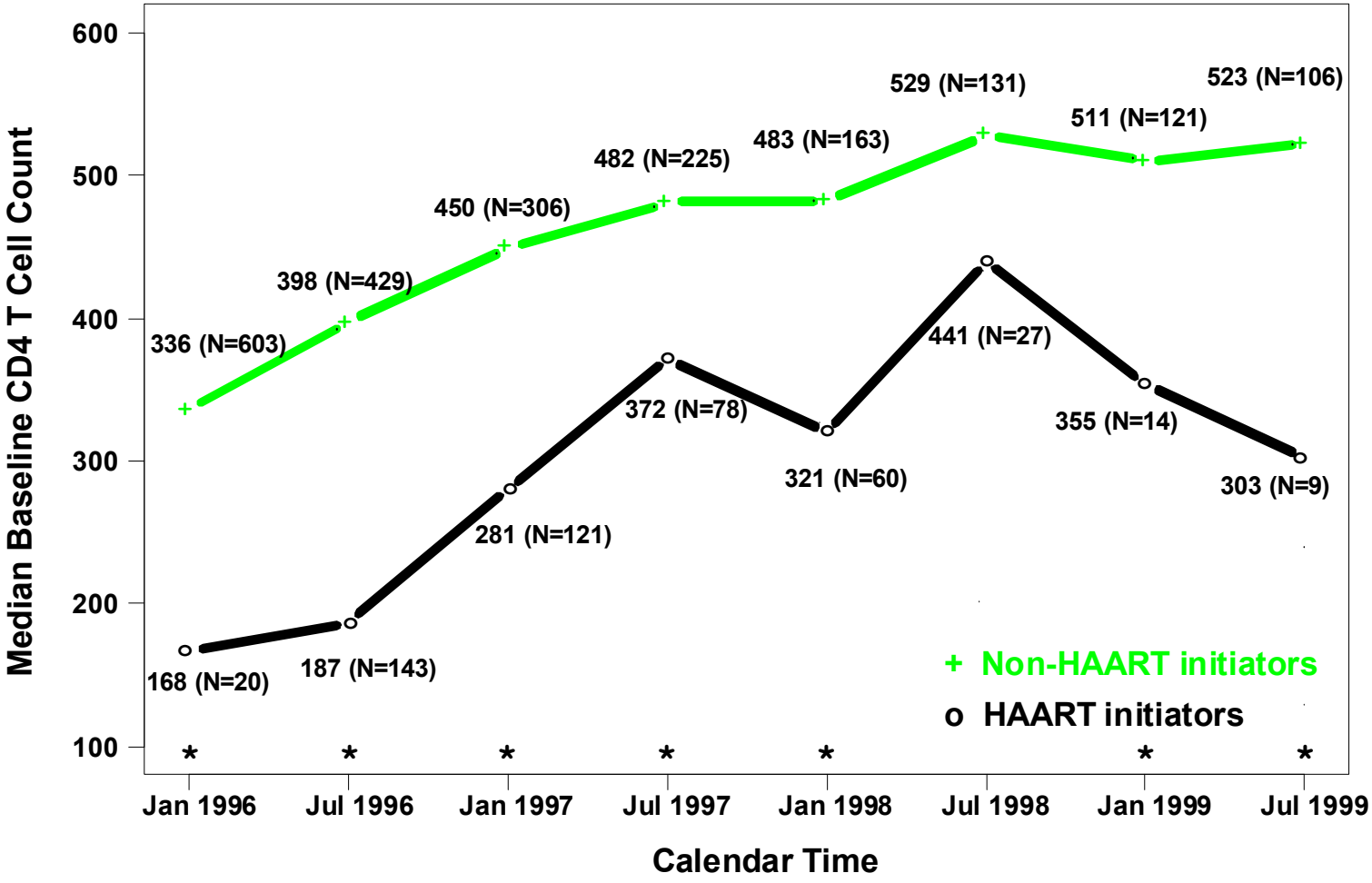
Kleeberger, Phair, . . ., Jacobson - JAIDS 2001

	% (N)	Percent with <50 HIV RNA copies/mL
100% Adherent	77.7 (419)	48.2
<100% Adherent	22.3 (120)	33.7*

*p=0.01

CD4 Cell Count in HAART Initiation and Non-Initiation

Yamashita, Phair, . . ., Jacobson - AIDS 2001

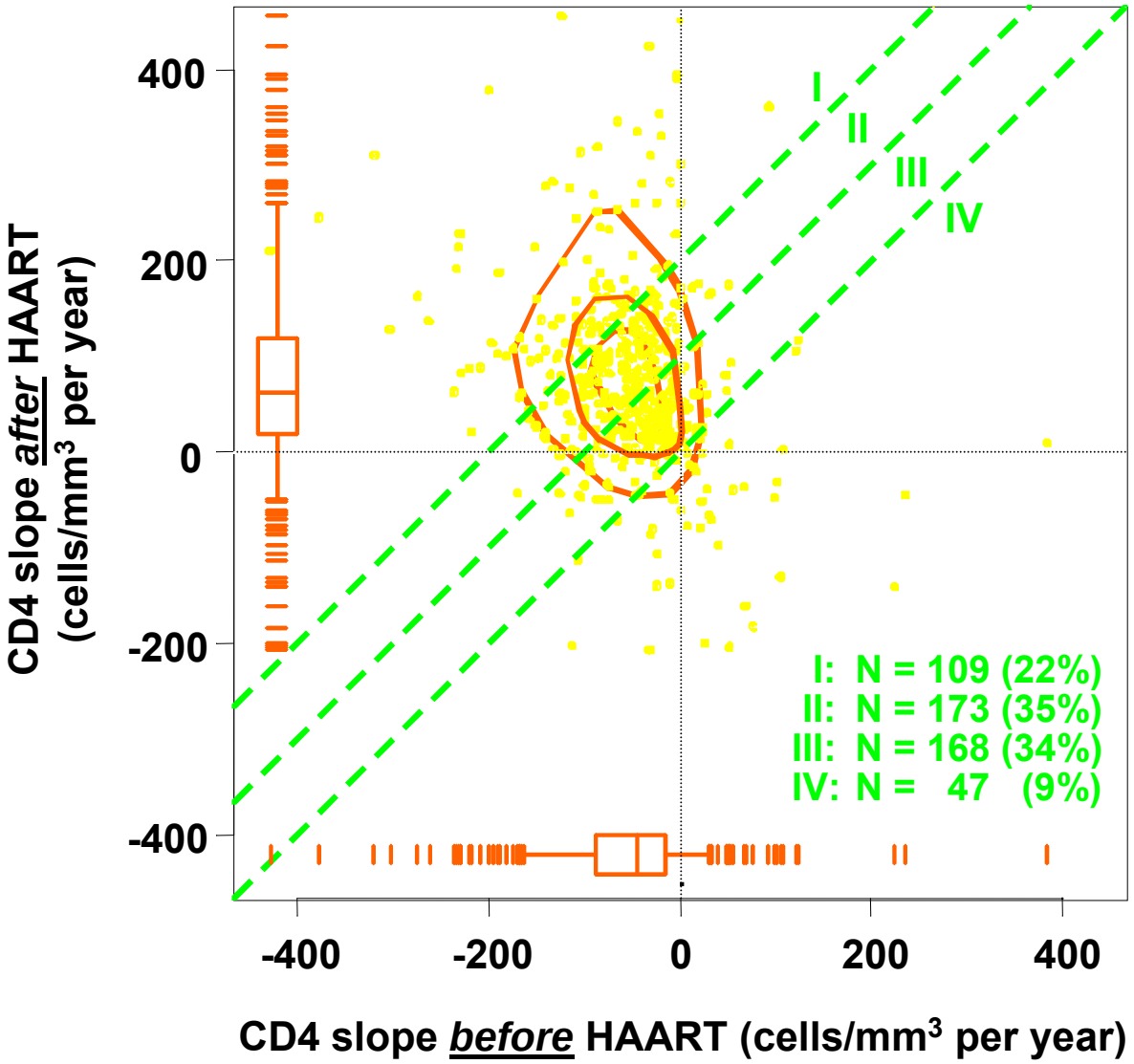


* significant difference between HAART initiators and non-initiators ($p<0.05$)

October 2000

Comparison of CD4 Slope Before and After HAART Use

Yamashita, Phair, . . ., Jacobson - AIDS 2001



I: Increased by ≥ 200

II: Increased by 100-199

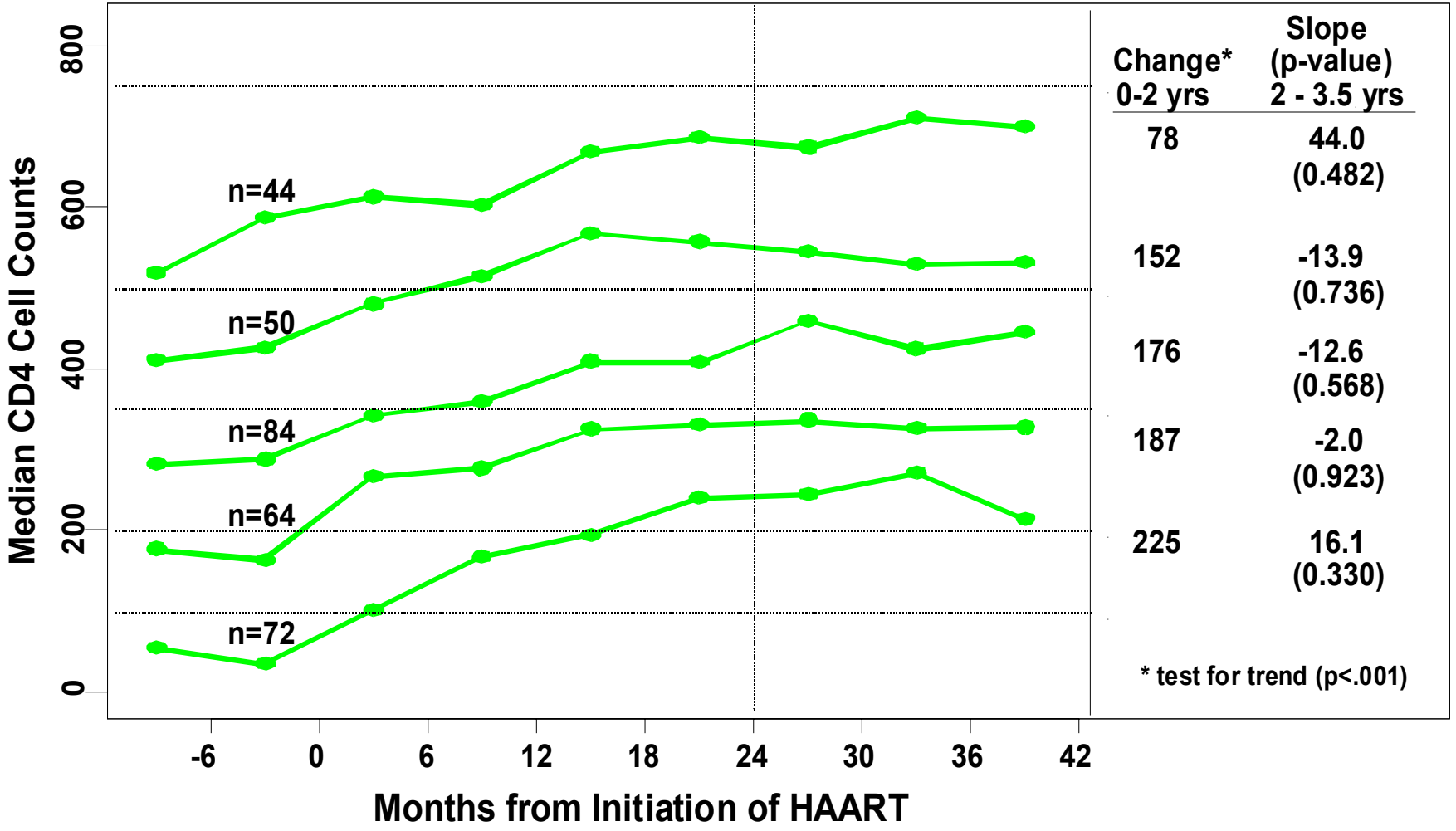
III: Increased by ≤ 99

IV: Decreased

May 2001

Trajectories of Median CD4 Cell Counts over 3.5 Years after Initiation of HAART

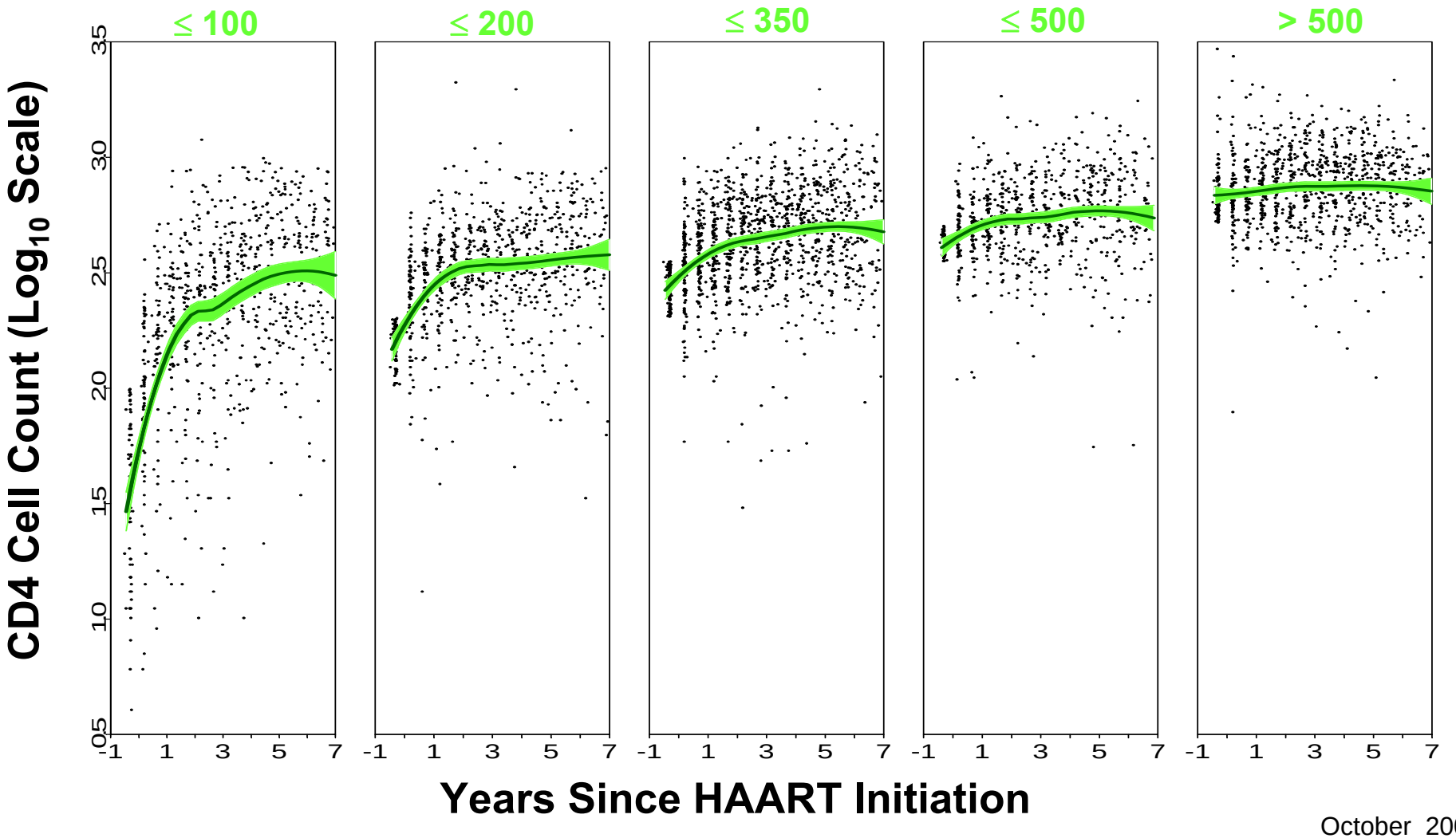
Tarwater, Margolick, . . ., Muñoz - JAIDS 2001



May 2001

Individual Variation of CD4 T-Cell Trajectory among HIV+ on Long Term HAART

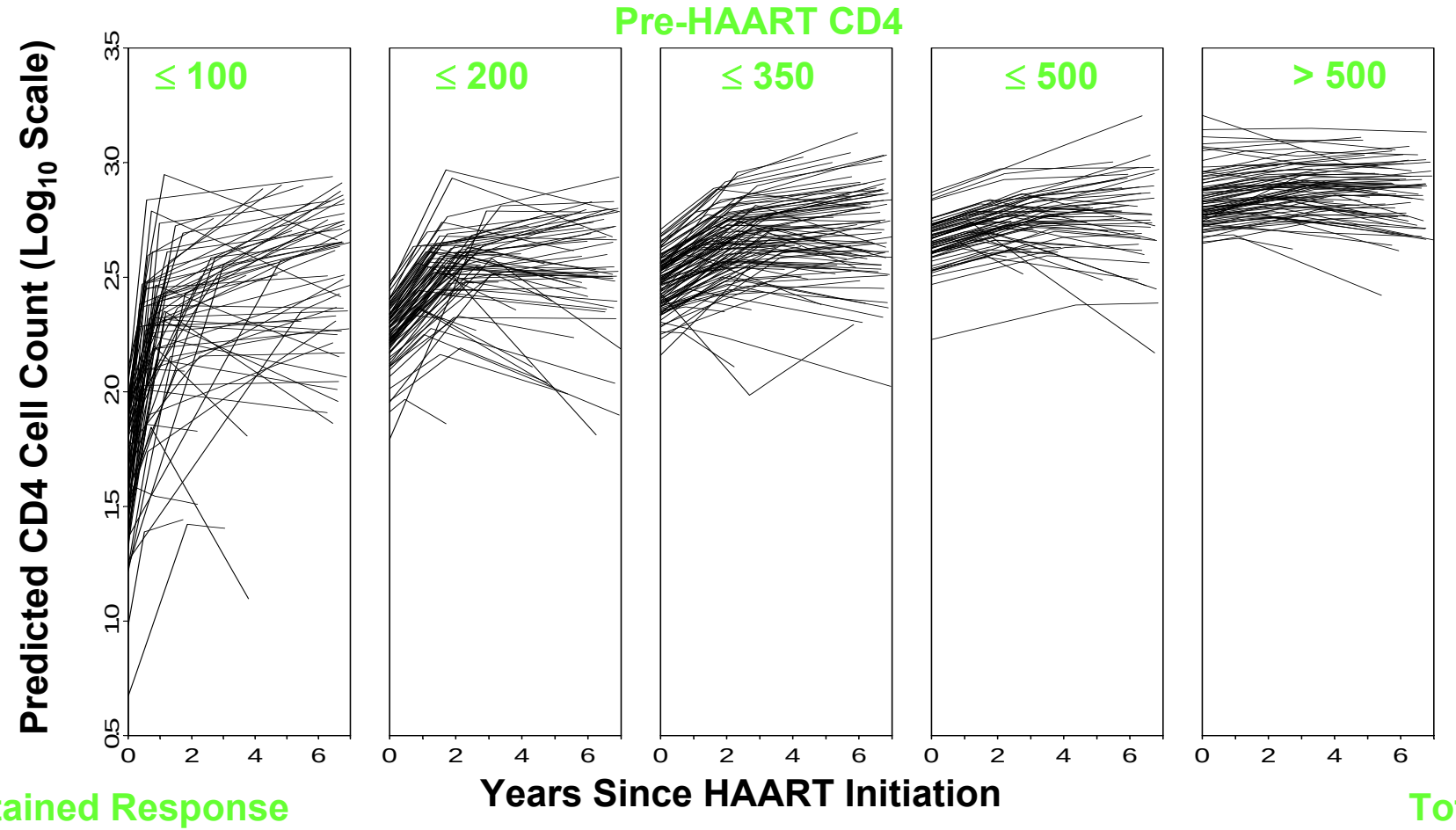
Chu, Gange, … , Jacobson - Am J Epidemiol 2005



October 2005

Individual Variation of CD4 T-Cell Trajectory among HIV+ on Long Term HAART

Chu, Gange, … , Jacobson - Am J Epidemiol 2005

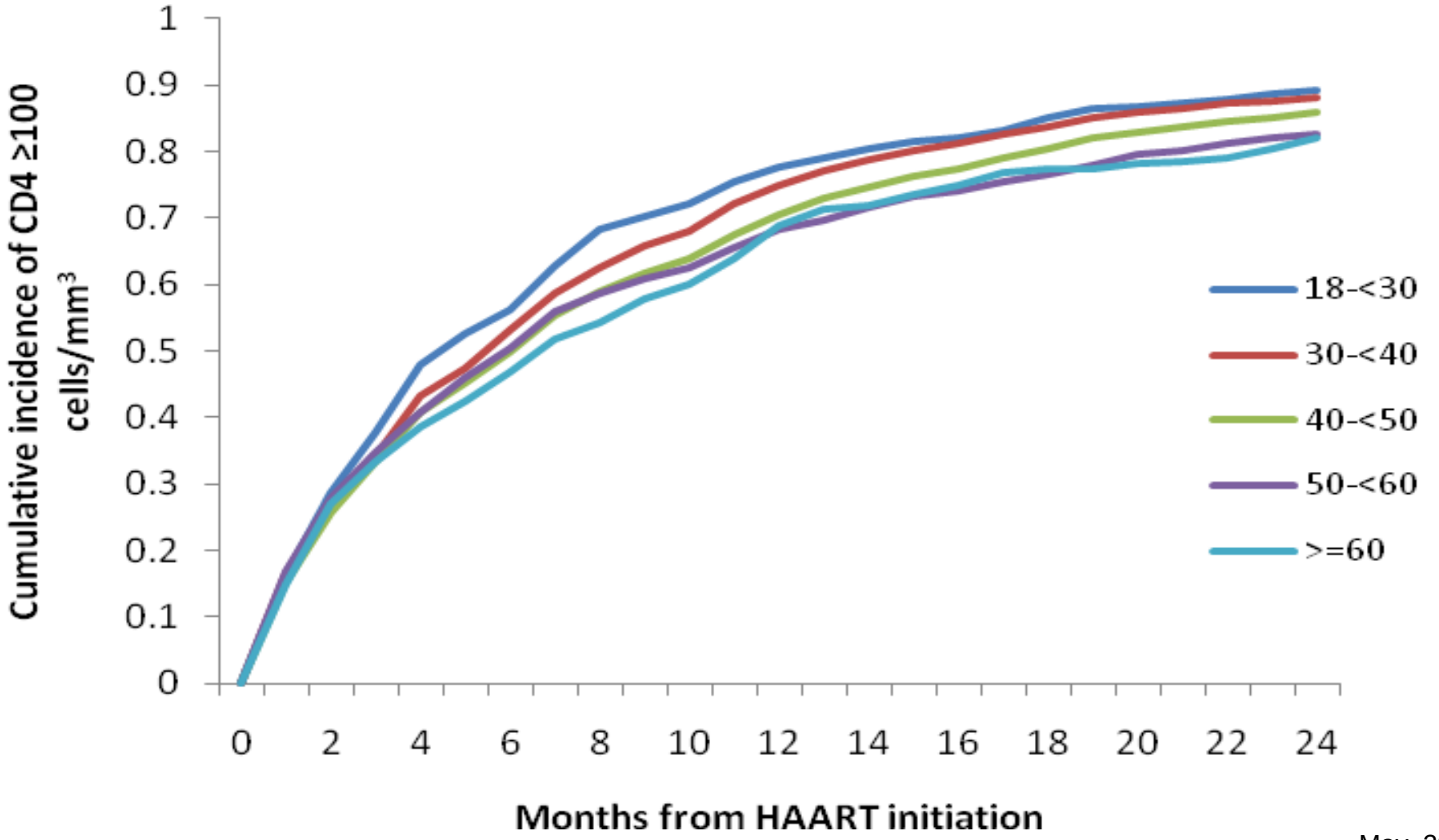


Sustained Response						Total
Yes	31(47%)	42(56%)	88(81%)	66(92%)	82(99%)	309(76%)
No	35(53%)	33(44%)	20(19%)	6(8%)	1(1%)	95(24%)

October 2005

Overall Cumulative Incidence of an Increase in CD4 Cells of ≥100 cells/mm³ in the First Two Years after HAART Initiation, by Age Group and Initial HAART Regimen Class

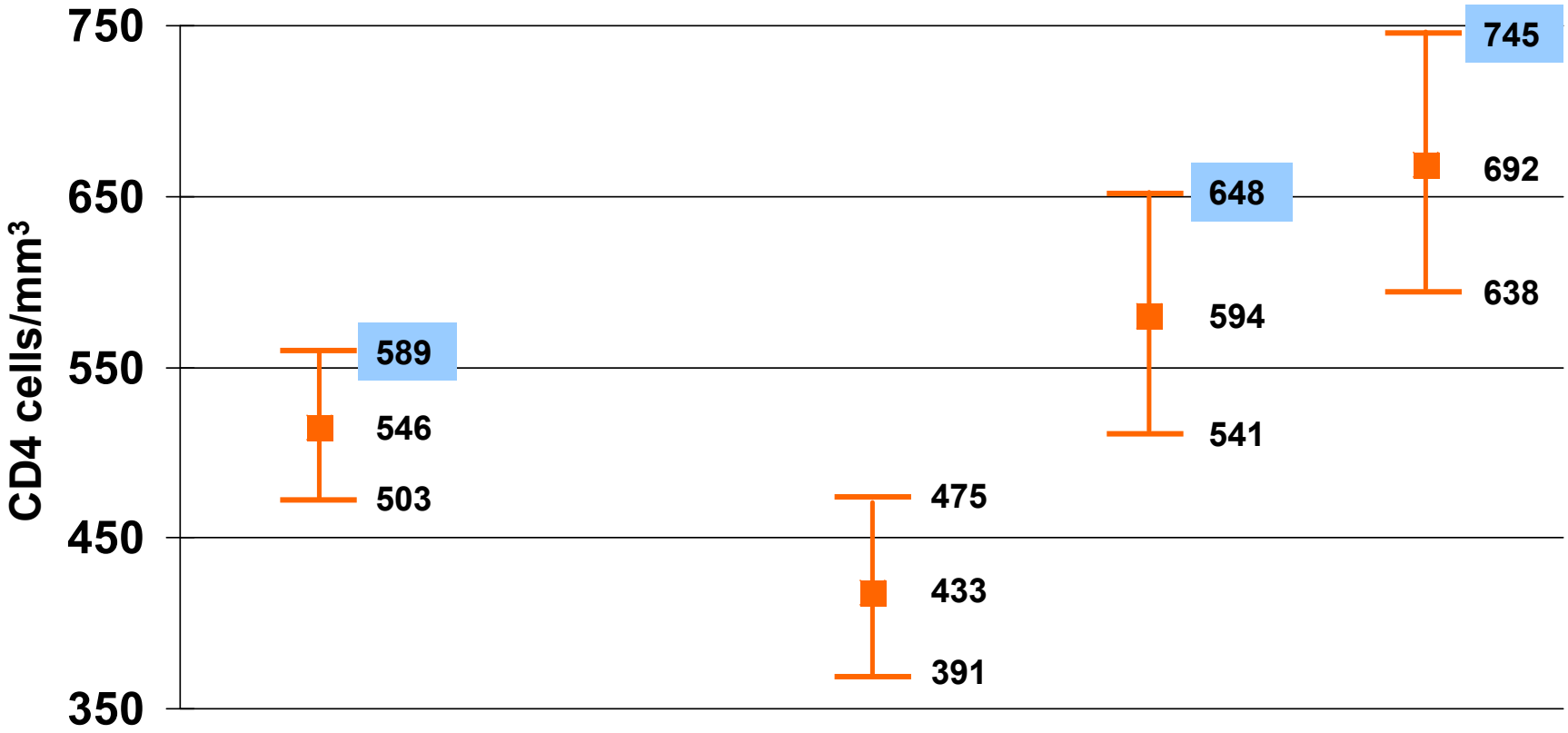
Althoff, Justice, . . . , Gebo. AIDS 2010



May 2011

CD4 Cell Count 5-10 Years After HAART Initiation

Li, Margolick, …, Jacobson. J Acquir Immune Defic Syndr 2011



Pre-HAART

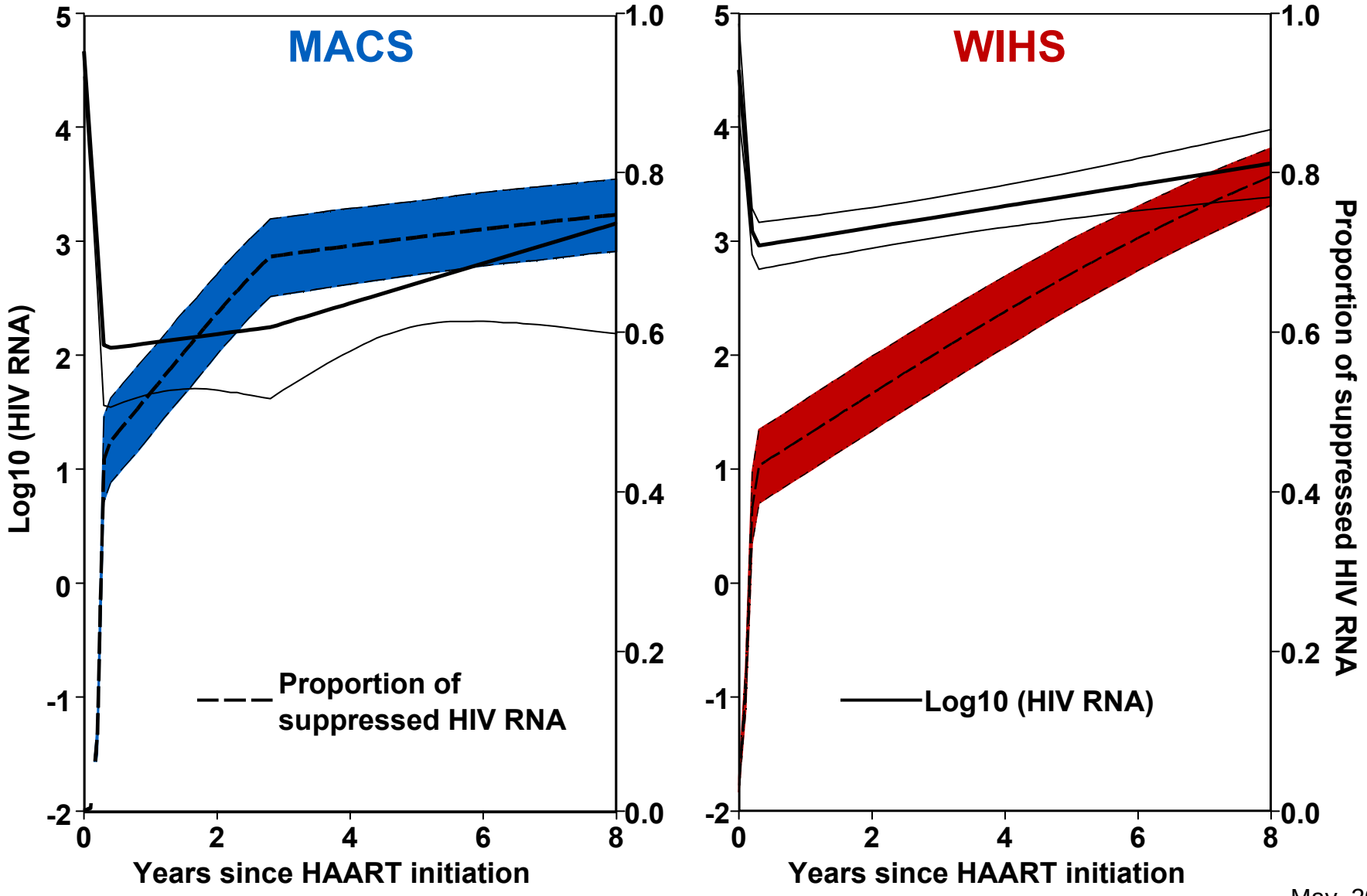
CD4 cells: <350 <350 350-499 ≥500

Age: <35 years ≥50 years

May 2012

Mixture Model of Predicted HIV Viral Load Trajectory among HIV Positive on Long Term HAART

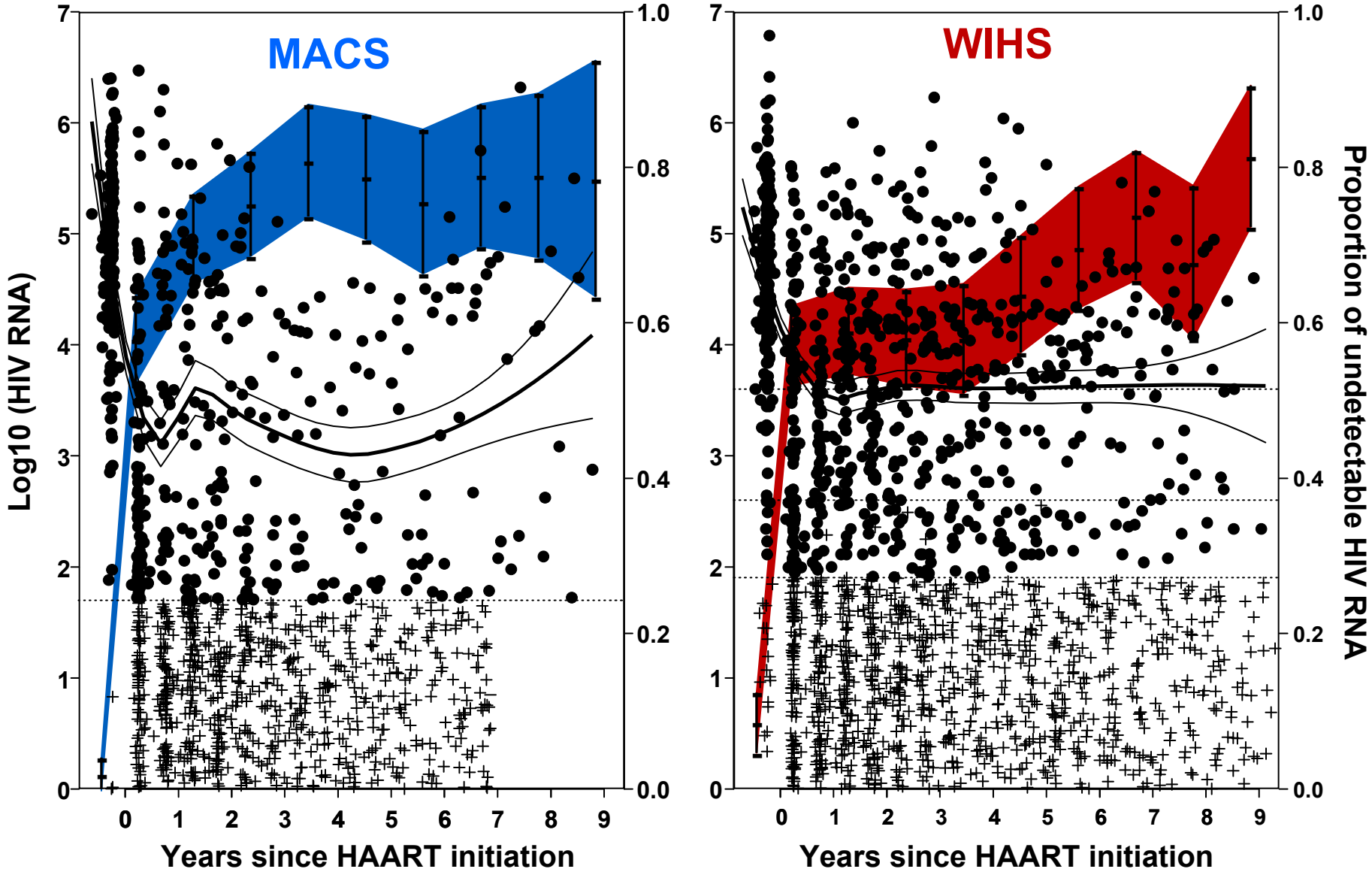
Chu, Gange, Li. Epidemiology 2010



May 2011

Longitudinal Measurement of HIV RNA

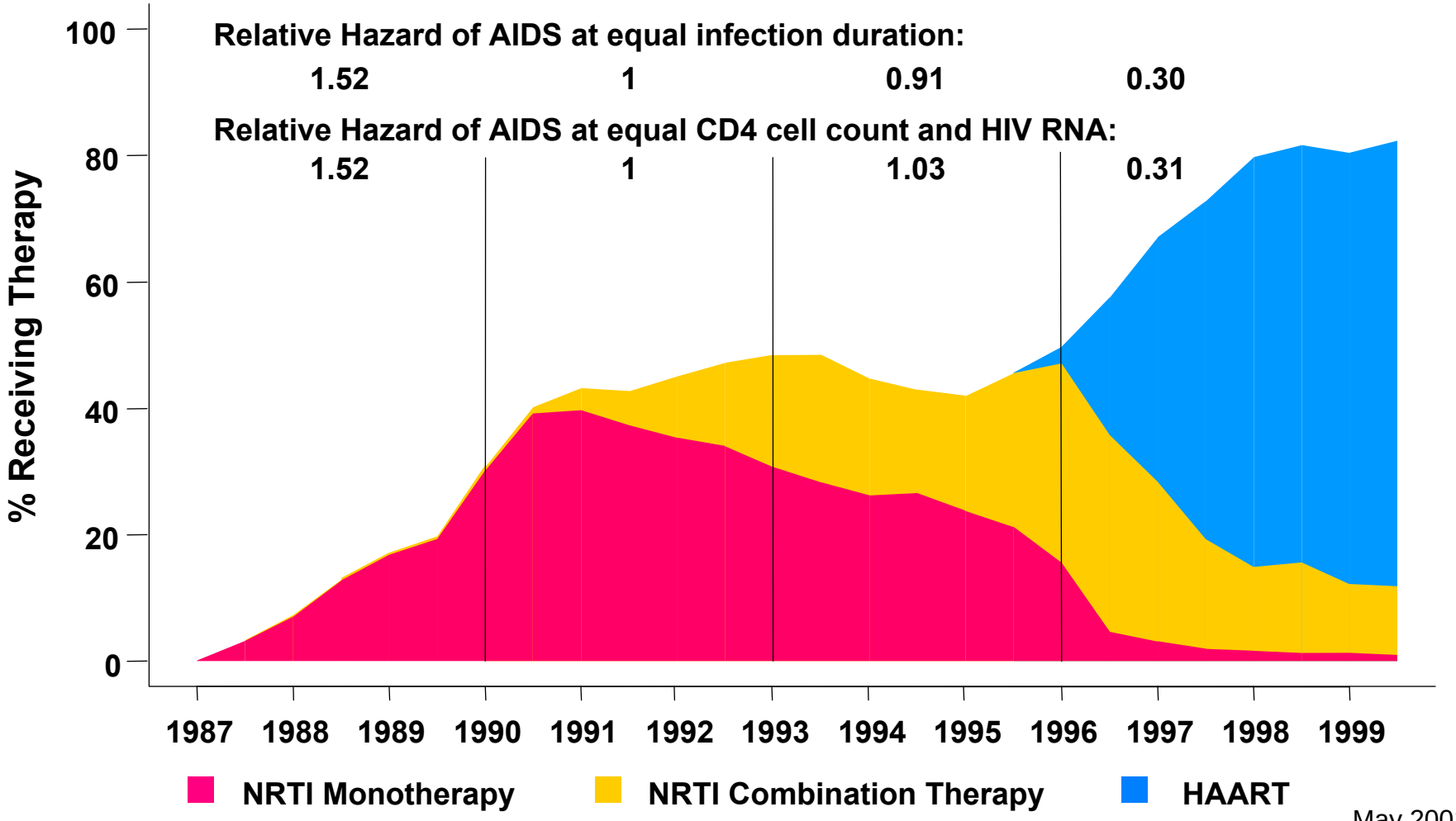
Chu, Gange, Li. Epidemiology 2010



May 2011

Use of Antiretroviral Therapy and Effectiveness at the Population Level

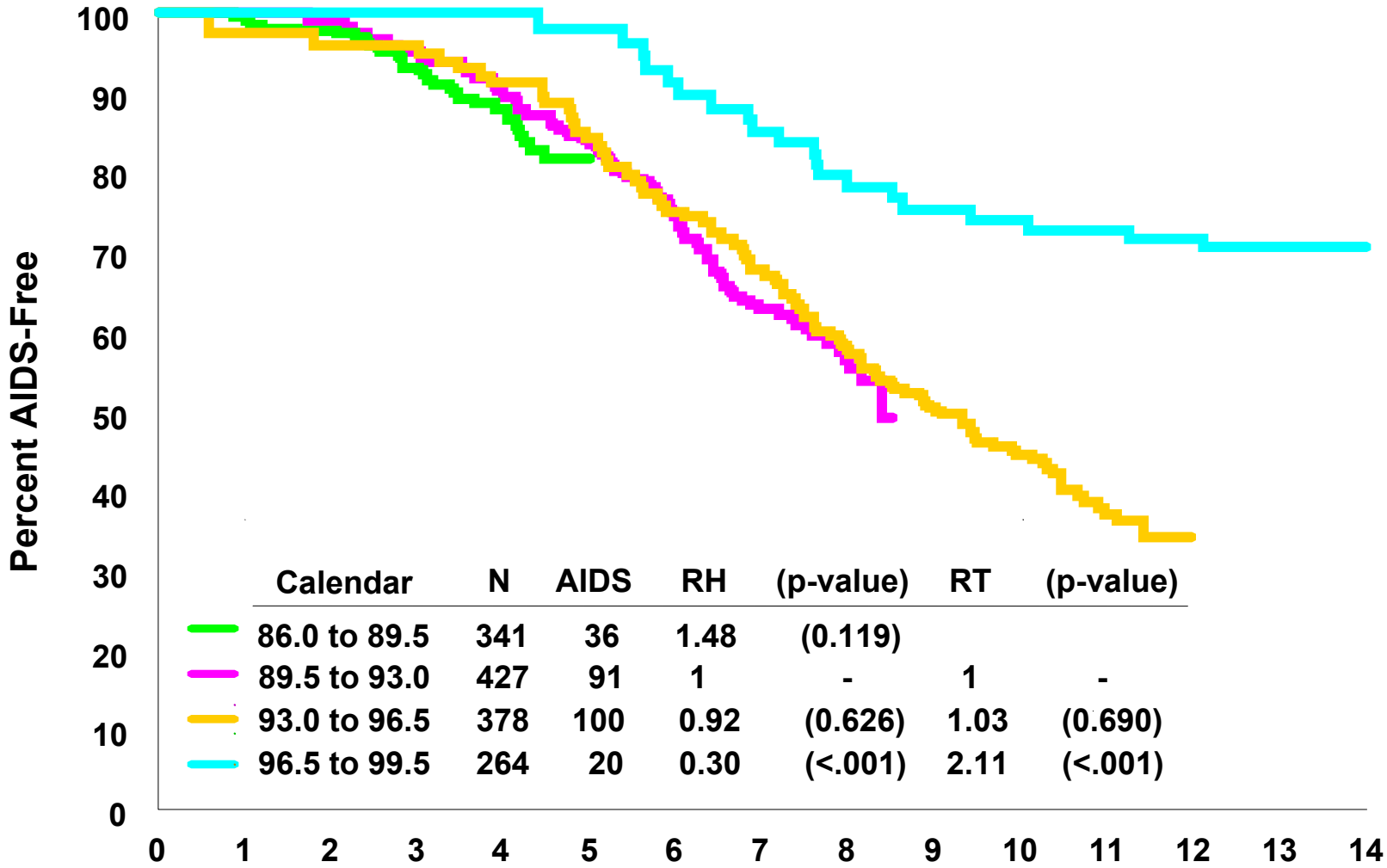
Tarwater, Mellors, . . ., Muñoz - AJE 2001
Detels, Muñoz, . . ., Phair - JAMA 1998 (update)



May 2001

AIDS-Free Time by Calendar

Detels, Muñoz, . . ., Phair - JAMA 1998 (update)

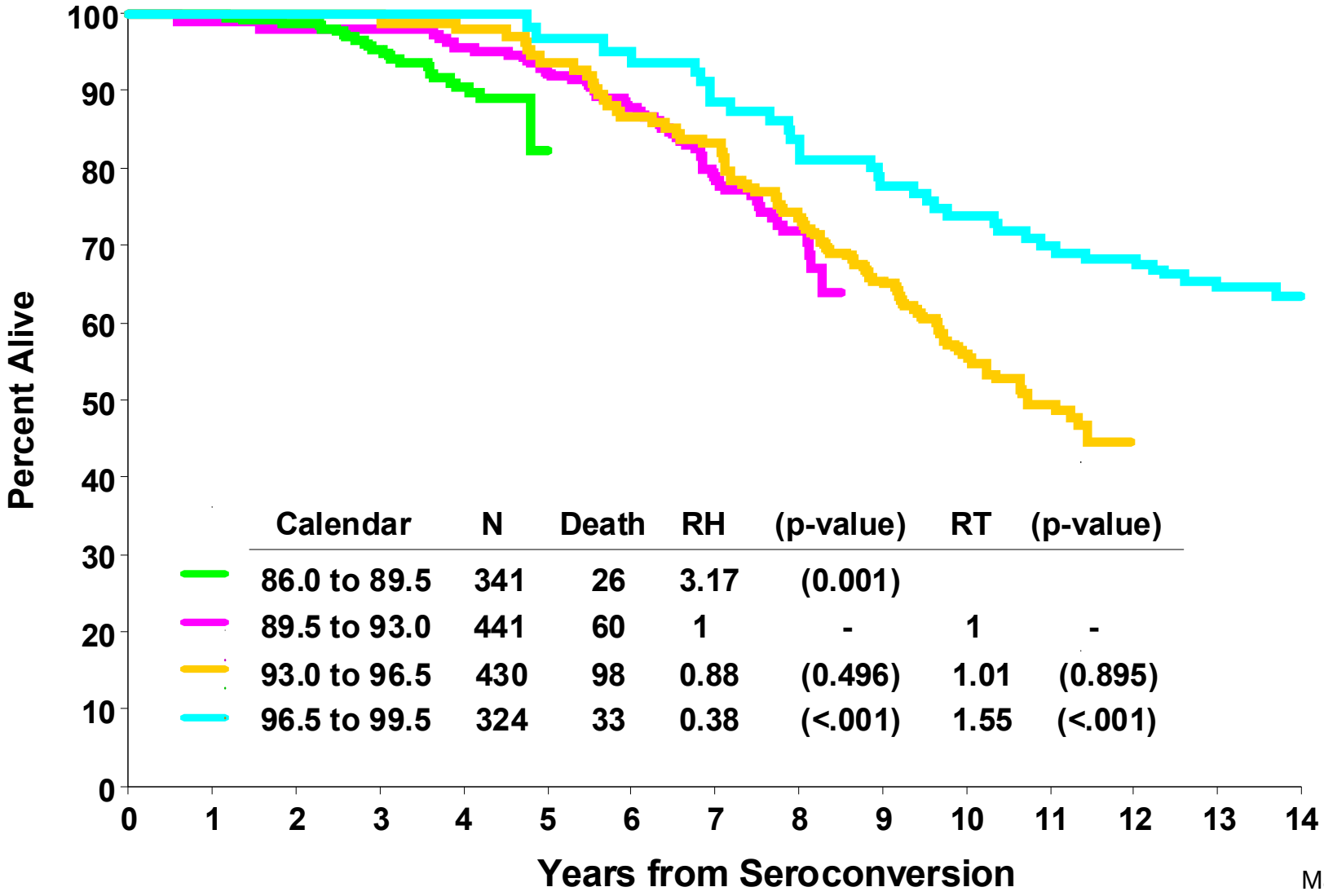


Calendar	N	AIDS	RH	(p-value)	RT	(p-value)
86.0 to 89.5	341	36	1.48	(0.119)		
89.5 to 93.0	427	91	1	-	1	-
93.0 to 96.5	378	100	0.92	(0.626)	1.03	(0.690)
96.5 to 99.5	264	20	0.30	(<.001)	2.11	(<.001)

May 2000

Survival Time by Calendar

Detels, Muñoz, . . ., Phair - JAMA 1998 (update)

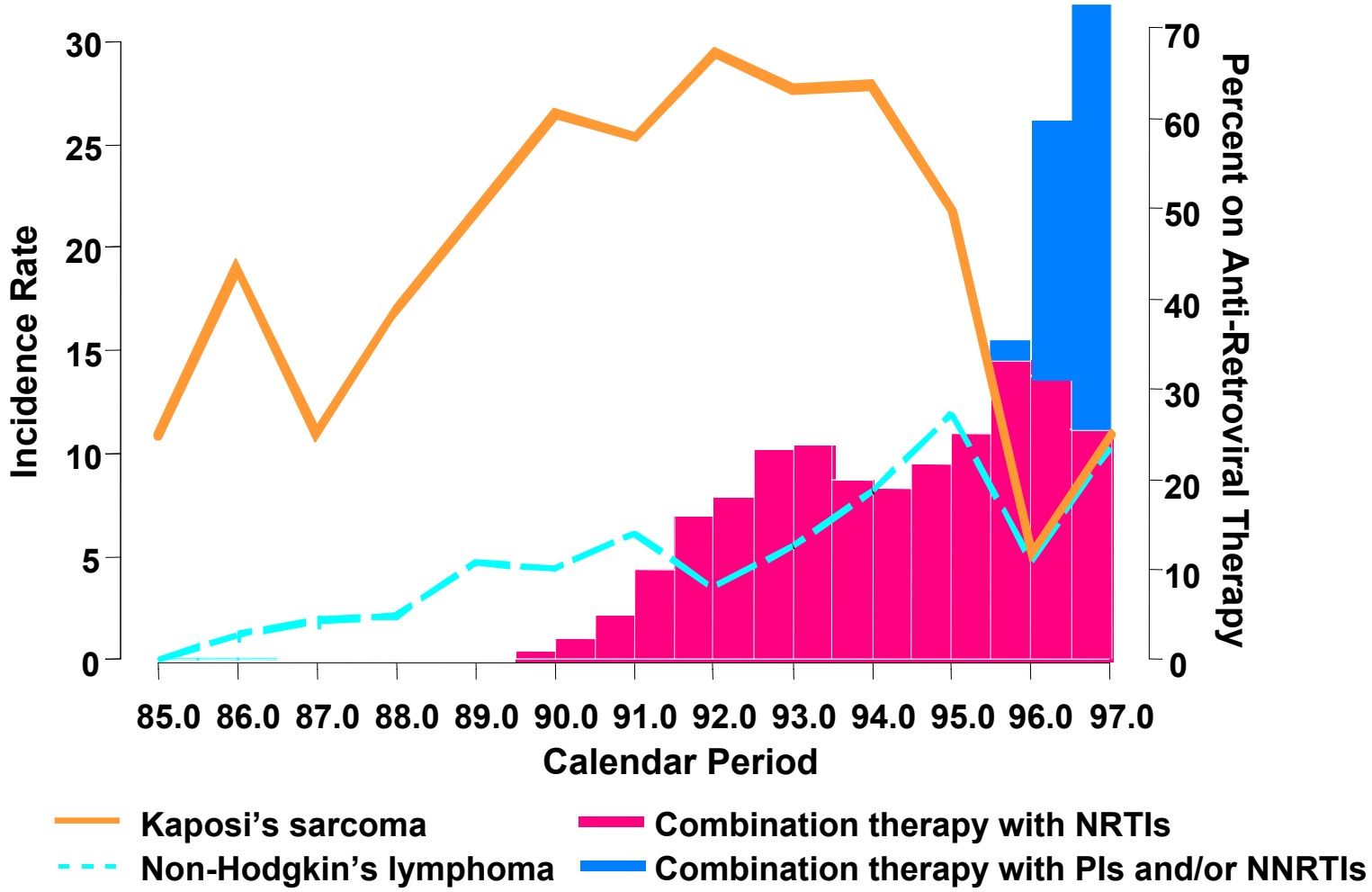


Calendar	N	Death	RH	(p-value)	RT	(p-value)
86.0 to 89.5	341	26	3.17	(0.001)		
89.5 to 93.0	441	60	1	-	1	-
93.0 to 96.5	430	98	0.88	(0.496)	1.01	(0.895)
96.5 to 99.5	324	33	0.38	(<.001)	1.55	(<.001)

May 2000

Lymphoma and Kaposi's Sarcoma Incidence per 1000 Seropositive Person Years (1/98)

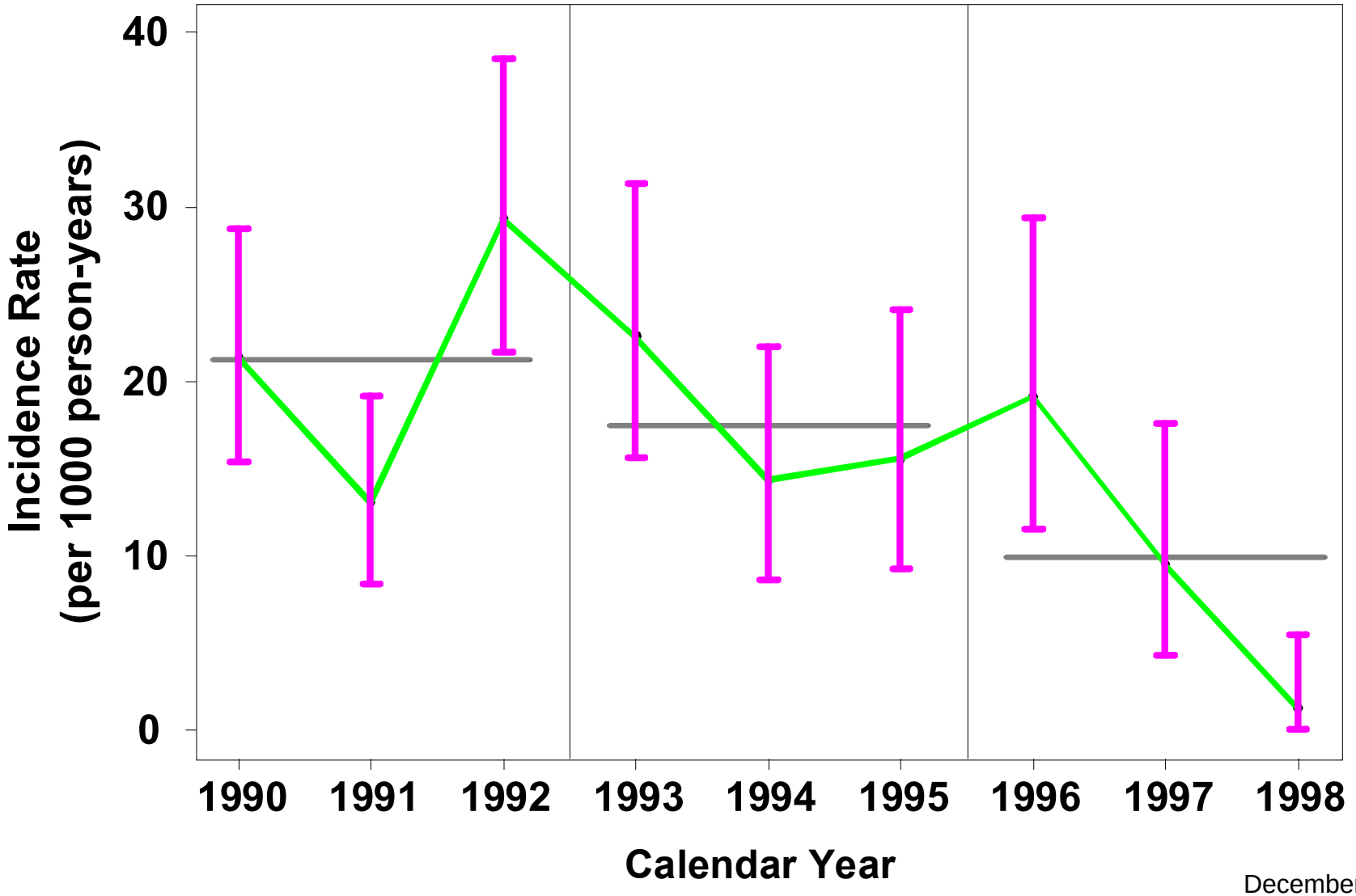
Jacobson, Yamashita, . . ., Muñoz - JAIDS 1999



October 1999

Incidence of HIV Dementia in the Multicenter AIDS Cohort Study

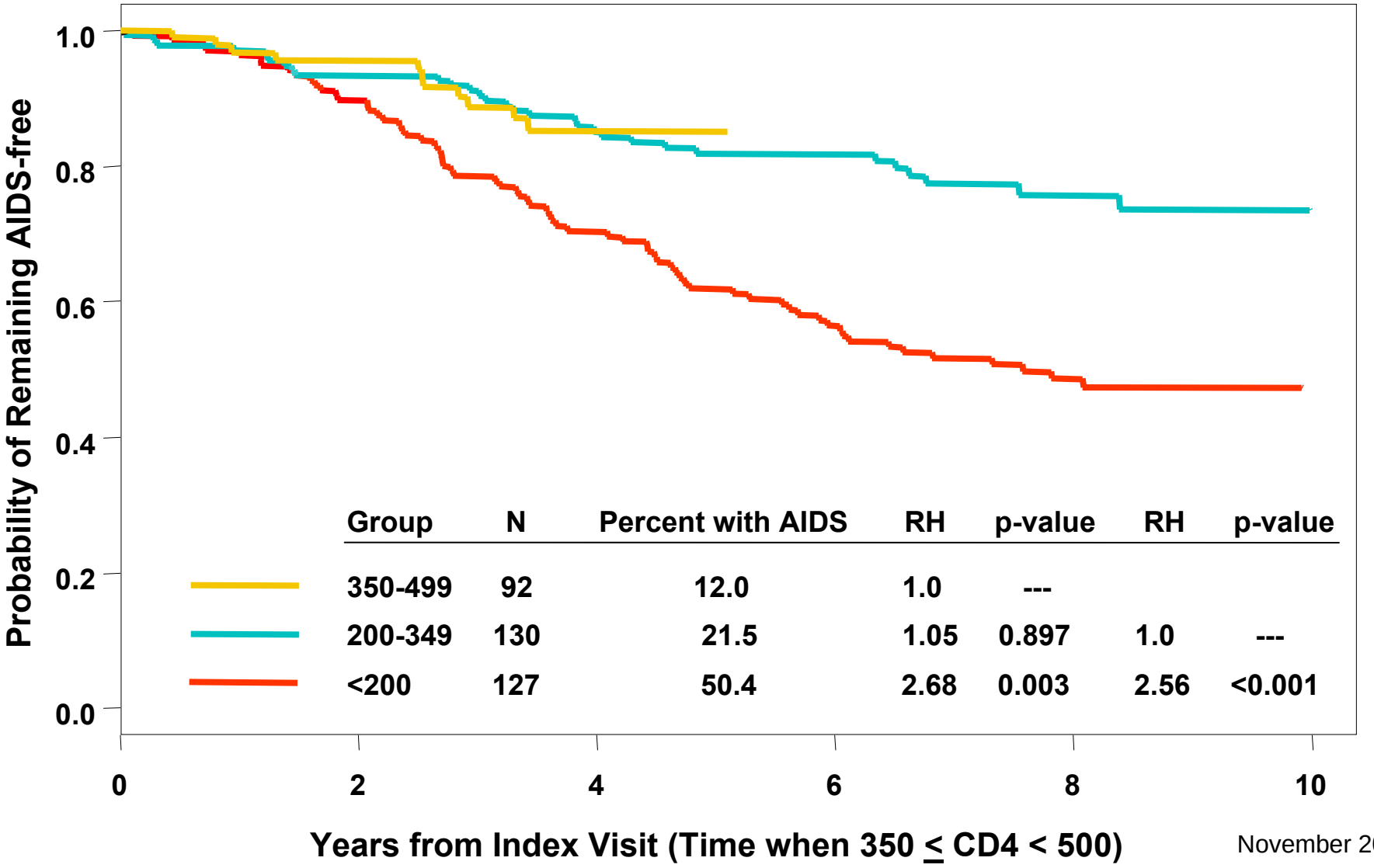
Sacktor, Lyles, …, McArthur - Neurology 2001



December 2001

Time to AIDS by CD4 Cell Count at Time of Treatment Adjusting for Individual Lead Time

Ahdieh-Grant, Yamashita, …, Jacobson - Am J Epidemiol 2003

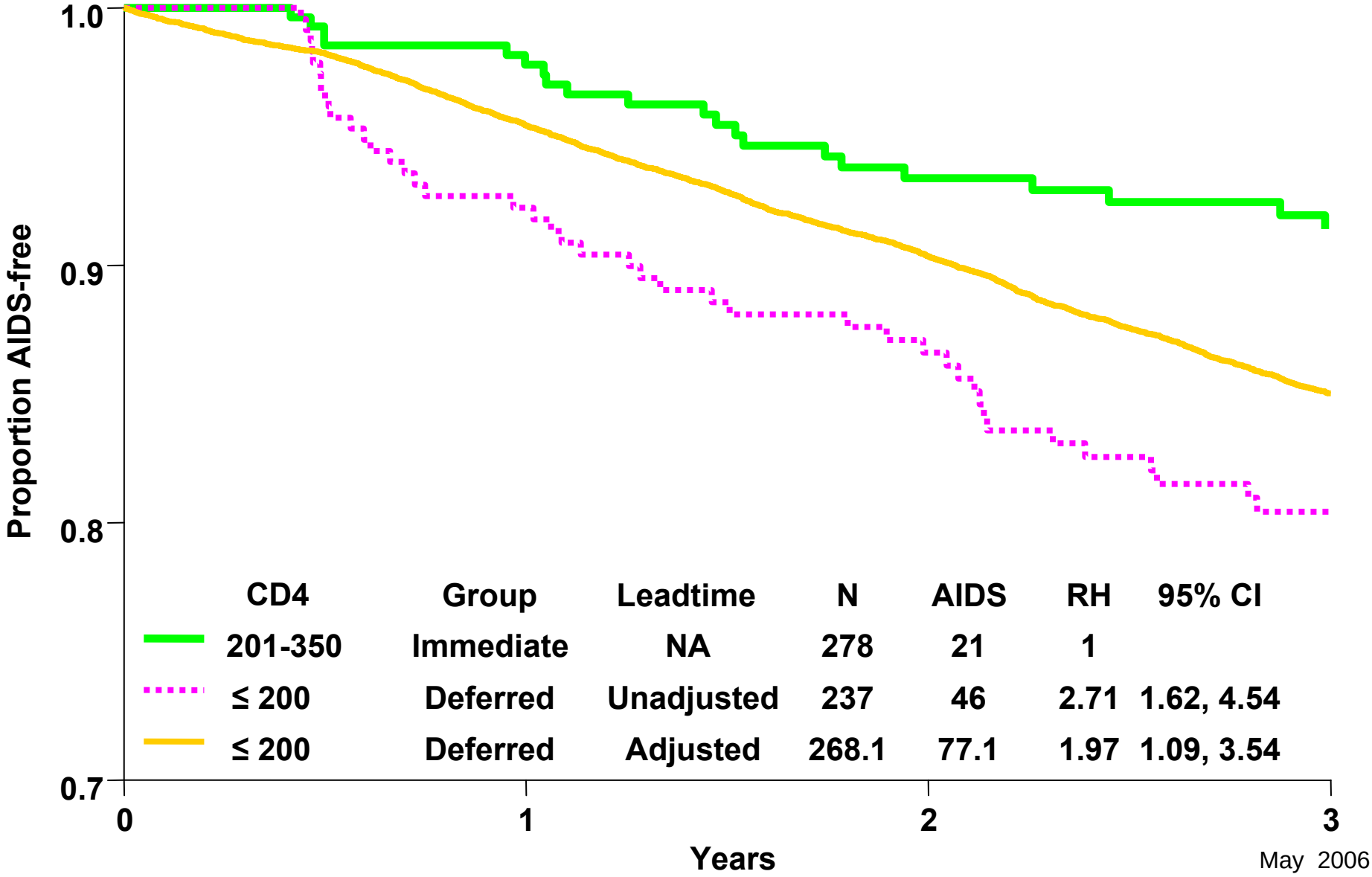


Group	N	Percent with AIDS	RH	p-value	RH	p-value
350-499	92	12.0	1.0	---		
200-349	130	21.5	1.05	0.897	1.0	---
<200	127	50.4	2.68	0.003	2.56	<0.001

November 2004

Percent AIDS-free after HAART Initiation (MACS & WIHS)

Cole, Li,…, Muñoz - Stat Med 2004

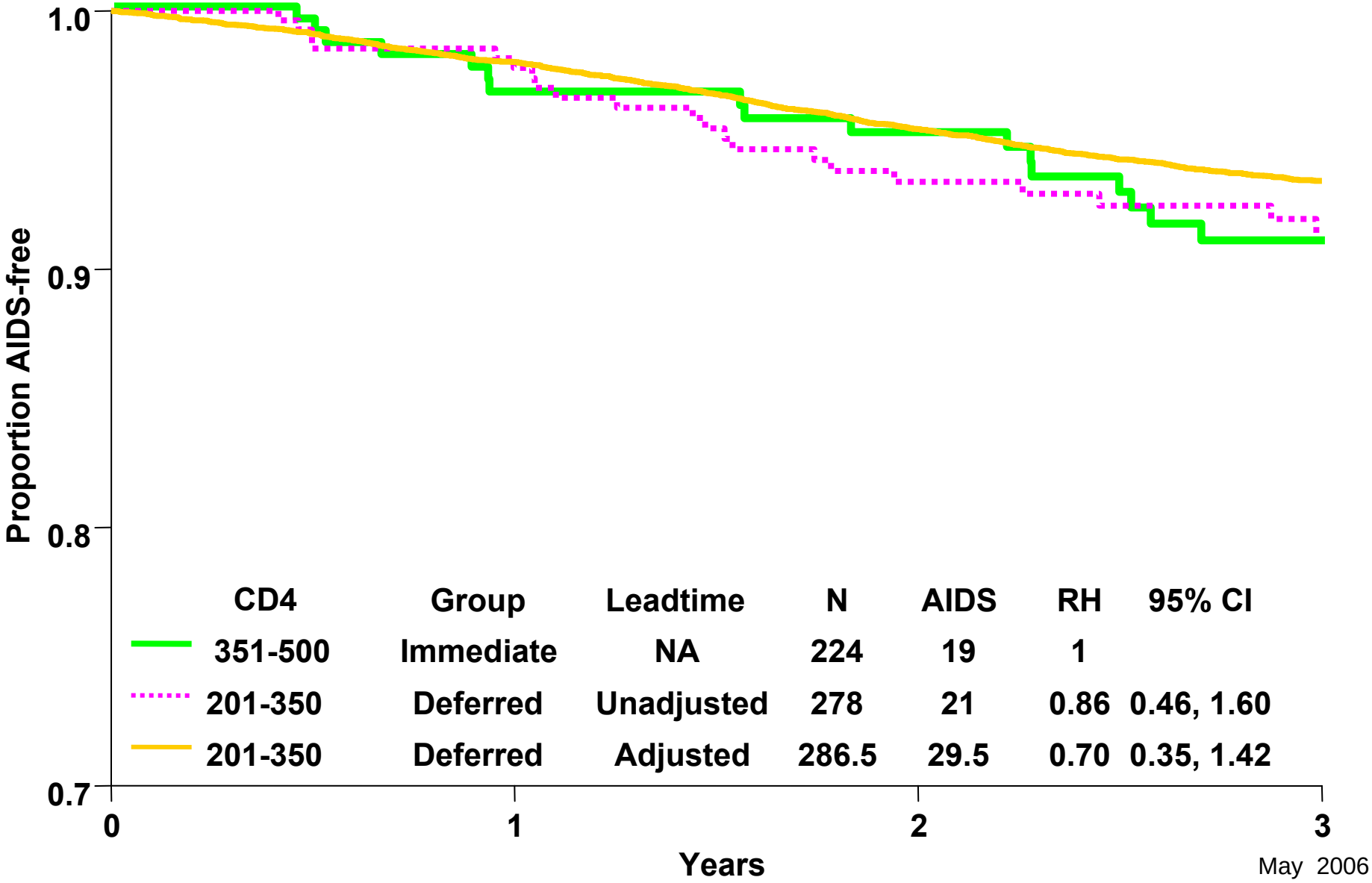


CD4	Group	Leadtime	N	AIDS	RH	95% CI
201-350	Immediate	NA	278	21	1	
≤ 200	Deferred	Unadjusted	237	46	2.71	1.62, 4.54
≤ 200	Deferred	Adjusted	268.1	77.1	1.97	1.09, 3.54

May 2006

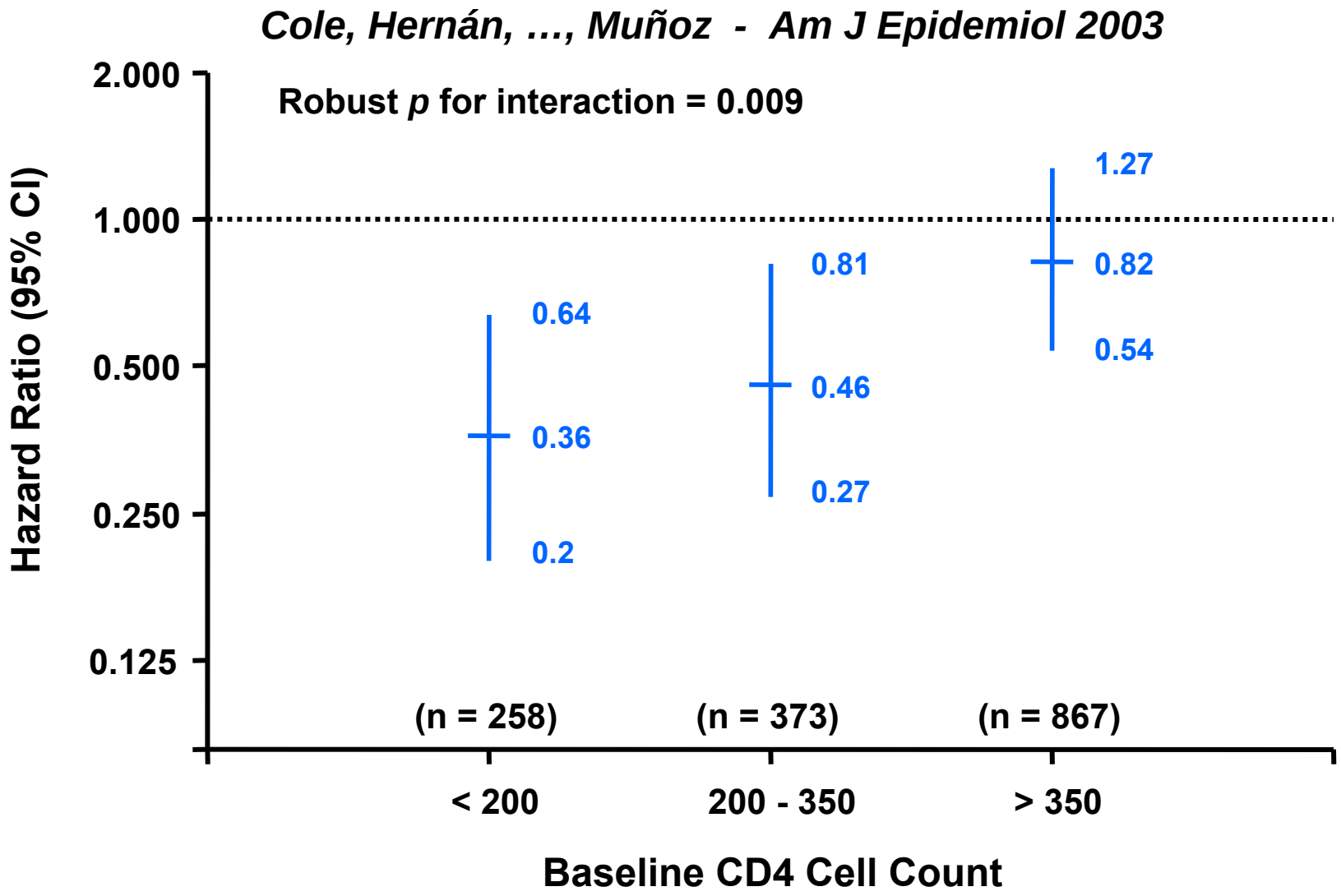
Percent AIDS-free after HAART Initiation (MACS & WIHS)

Cole, Li,…, Muñoz - Stat Med 2004



May 2006

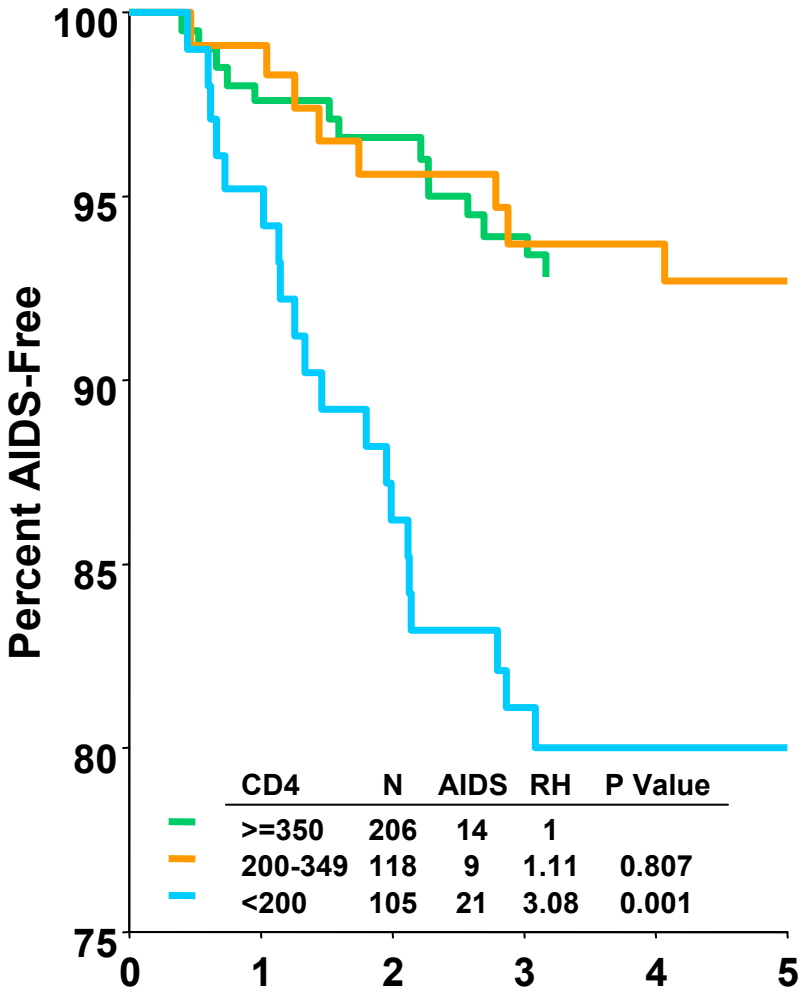
Individual Effect of HAART on AIDS or Death

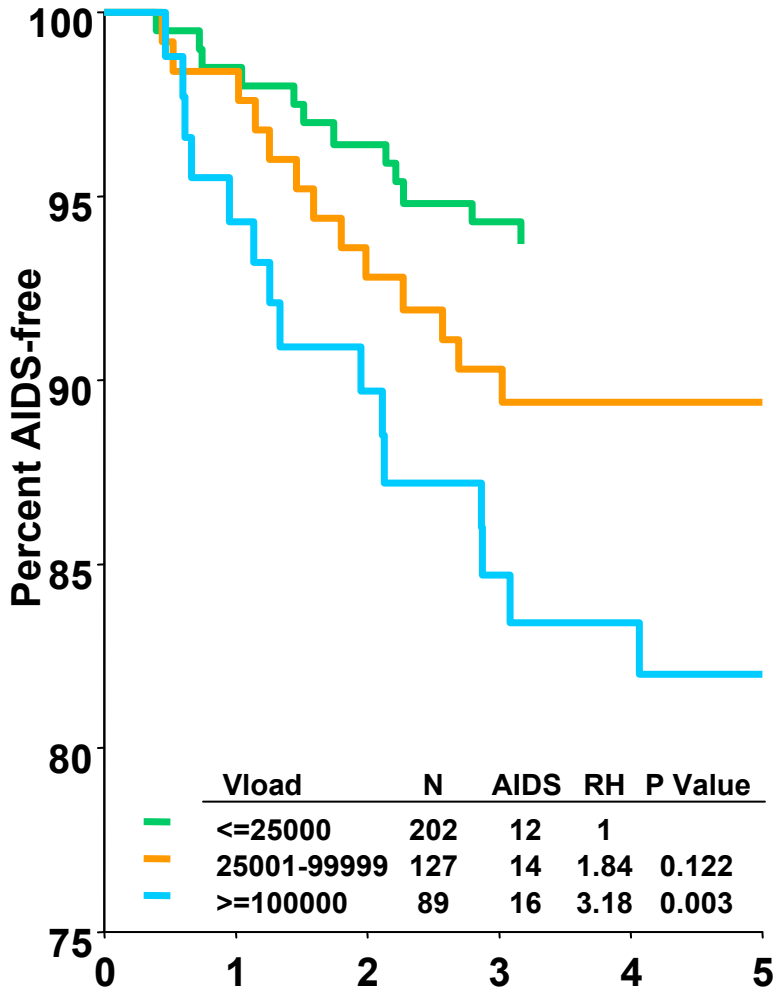


November 2003

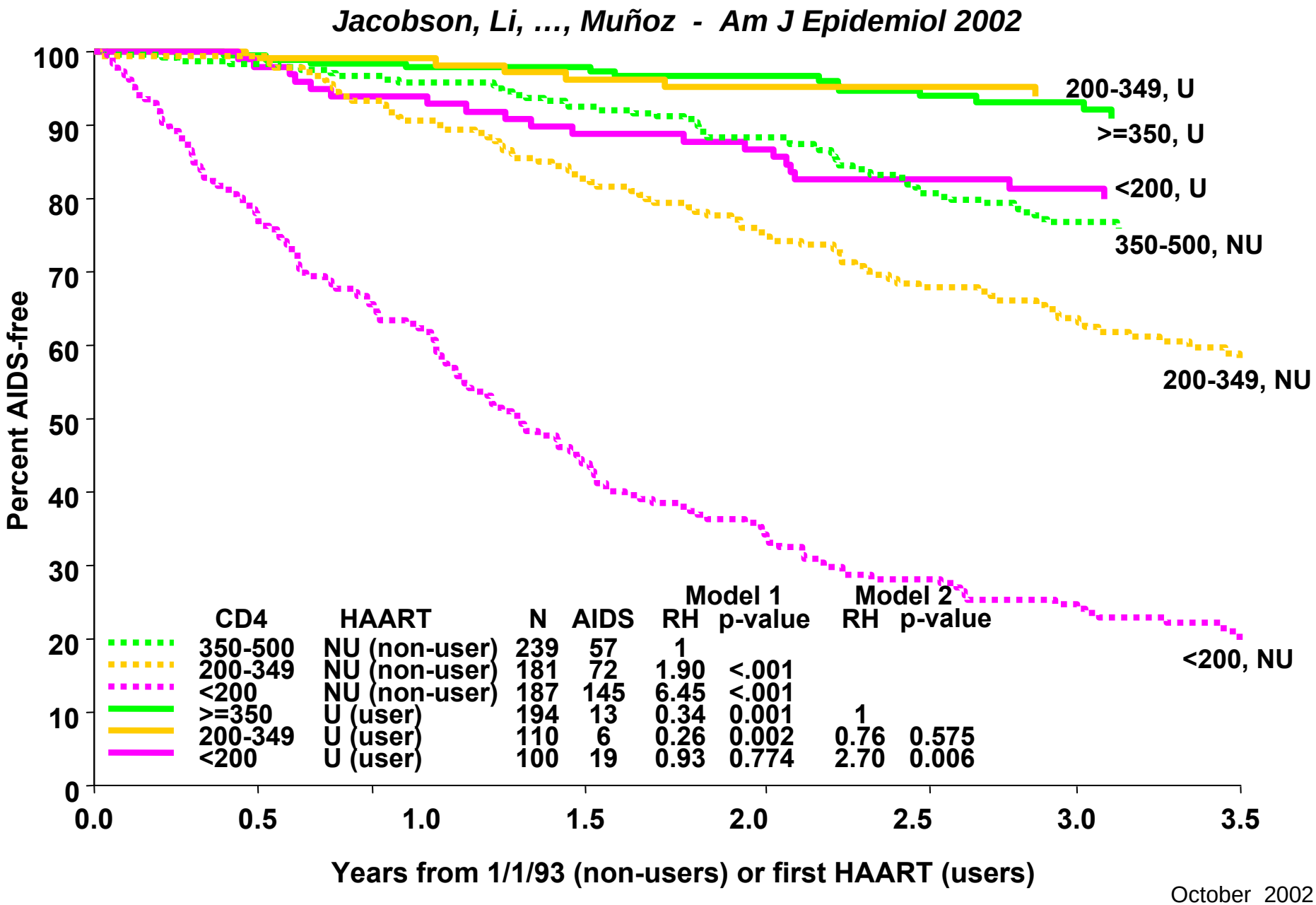
Percent AIDS Free among HAART Users by CD4 T-cell Count and HIV RNA

Jacobson, Li, …, Muñoz - Am J Epidemiol 2002 [update]



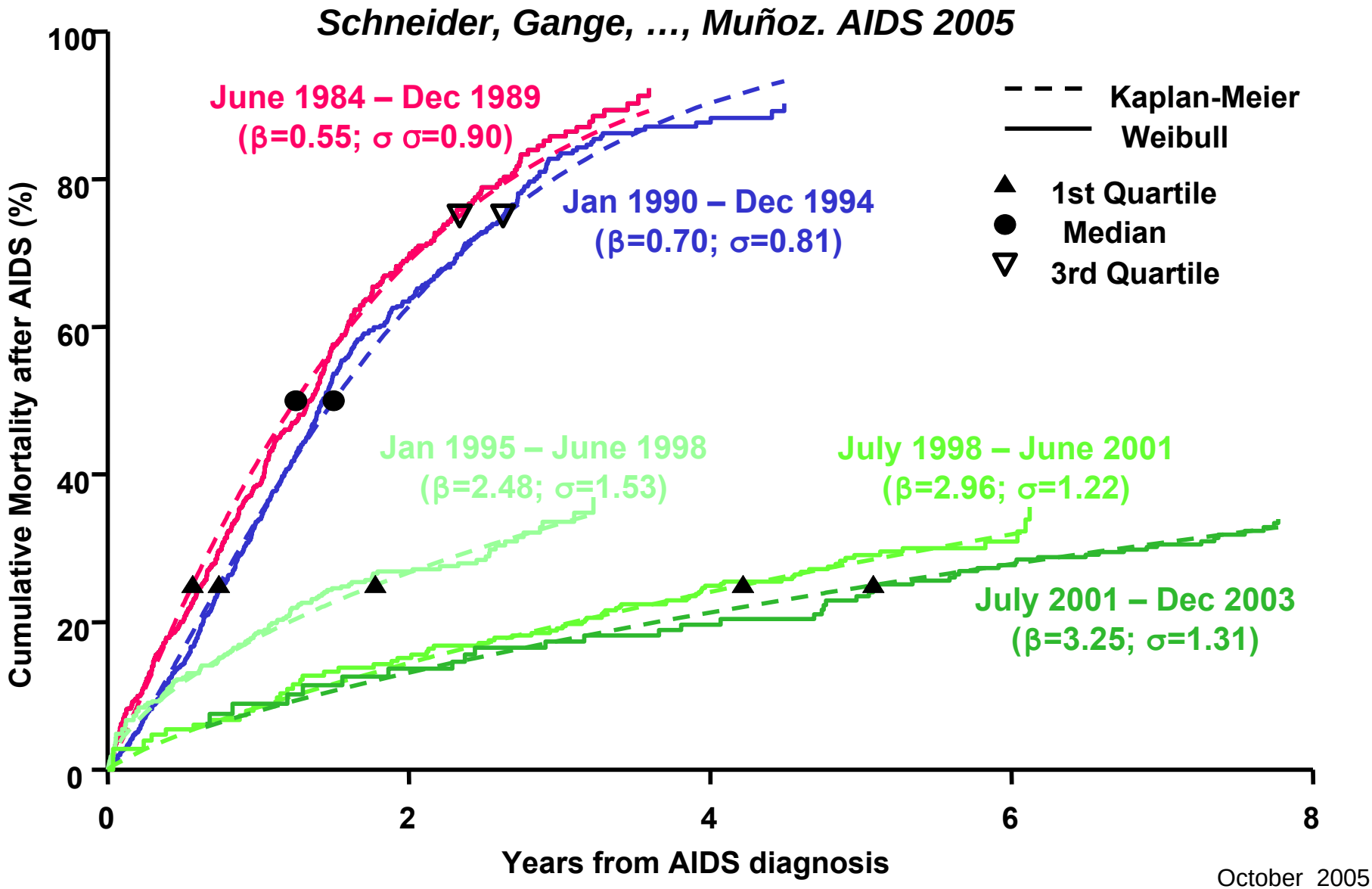


Percent AIDS Free According to HAART Use and CD4 Tcell Count



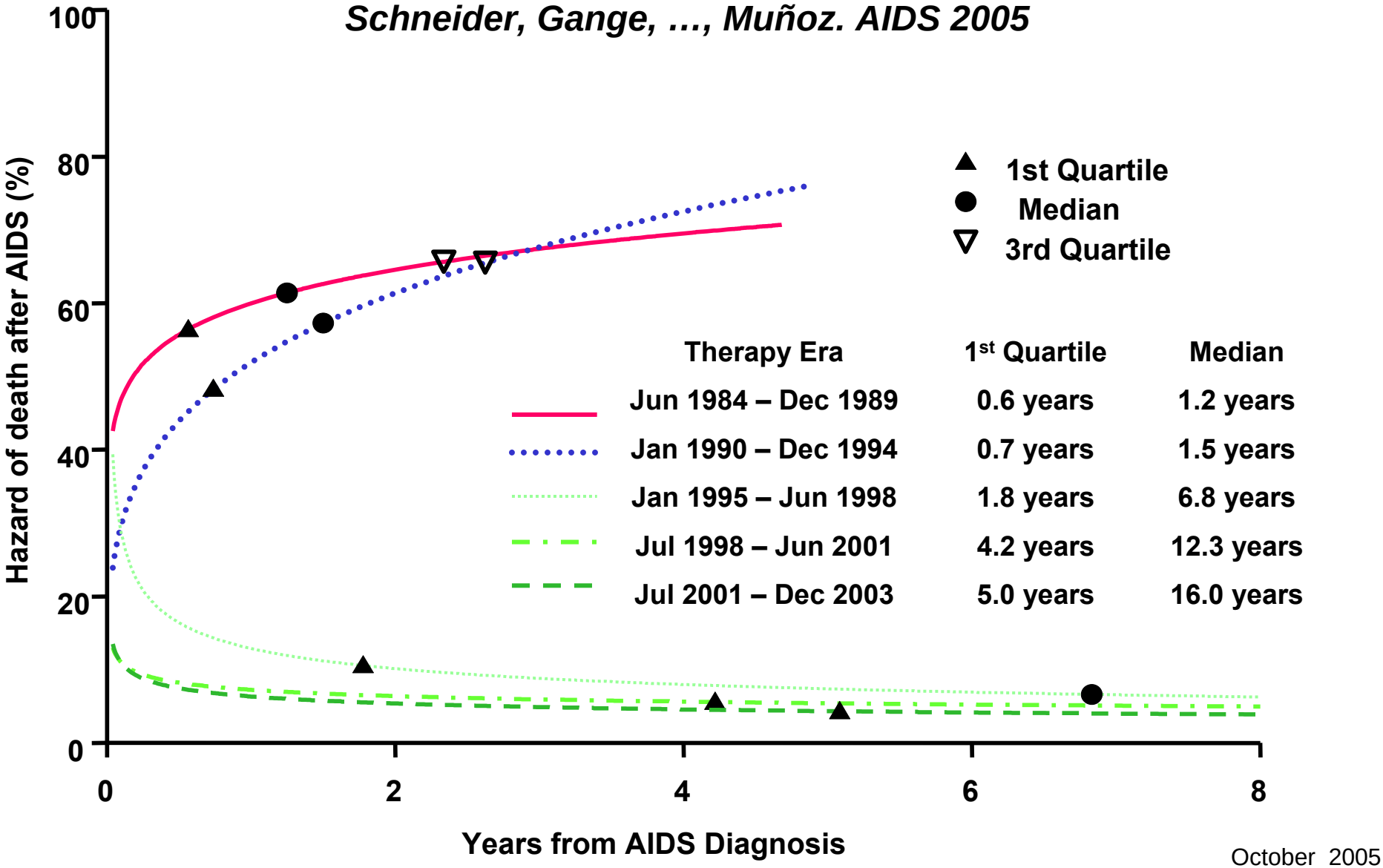
October 2002

Cumulative Mortality and Appropriateness of Weibull Model for Five Therapy Eras



October 2005

Corresponding Hazards of Death after AIDS Diagnosis from Weibull Models



October 2005

Risk of Death Associated with Deferral of Antiretroviral Therapy, According to CD4+ Count at Baseline, with Adjustment for HIV RNA Level, Age, and Sex*

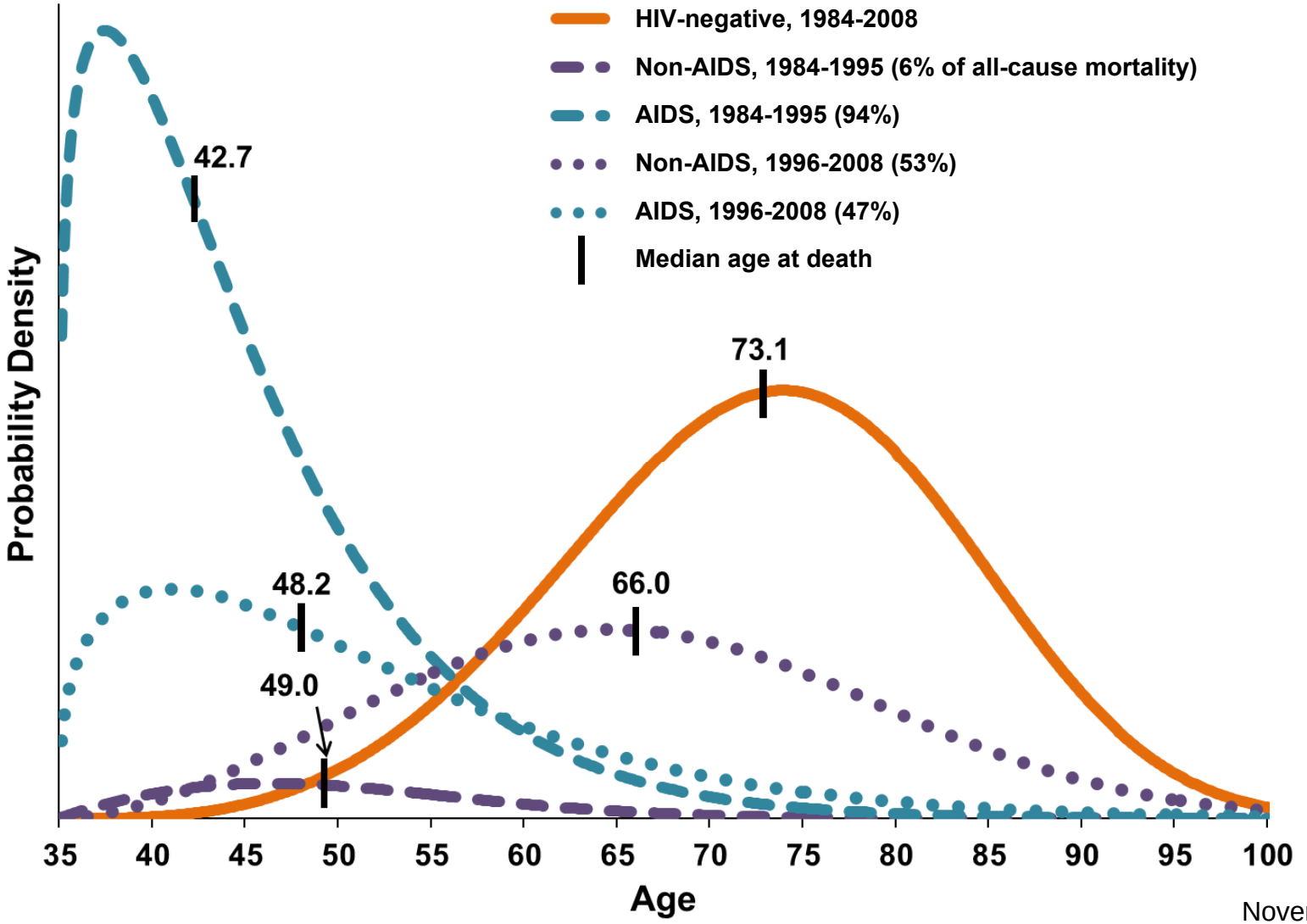
Kitahata, Gange, …, Moore. N Engl J Med 2009

Variable	351 – 500 CD4+ Count		> 500 CD4+ Count	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Without inclusion of HIV RNA data				
Deferral of antiretrovial therapy	1.69 (1.26-2.26)	<0.001	1.94 (1.37-2.79)	<0.001
Female sex	1.21 (0.89-1.64)	0.24	1.85 (1.33-2.59)	<0.001
Older age (per 10-yr increment)	1.68 (1.48-1.91)	<0.001	1.83 (1.62-2.06)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	1.13 (0.72-1.78)	0.59	0.93 (0.87-0.99)	0.03
With inclusion of HIV RNA data				
Deferral of antiretrovial therapy	1.63 (1.21-2.19)	0.002	1.85 (1.20-2.86)	0.006
Female sex	1.47 (1.02-2.12)	0.04	1.35 (0.85-2.15)	0.20
Older age (per 10-yr increment)	1.89 (1.69-2.11)	<0.001	1.81 (1.58-2.07)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	0.74 (0.55-1.00)	0.06	0.97 (0.89-1.05)	0.45
Baseline HIV RNA level (per $\log_{10}$ copies/ml)	1.11 (0.96-1.28)	0.15	1.13 (0.96-1.33)	0.14

* The CD4+ count was measured in cells per cubic millimeter. Results were calculated with the use of Cox regression analyses with inverse probability-of-censoring weights.

Estimated Cause-Specific Mortality after 35 Years of Age by HAART Era in the MACS, 1984-2008

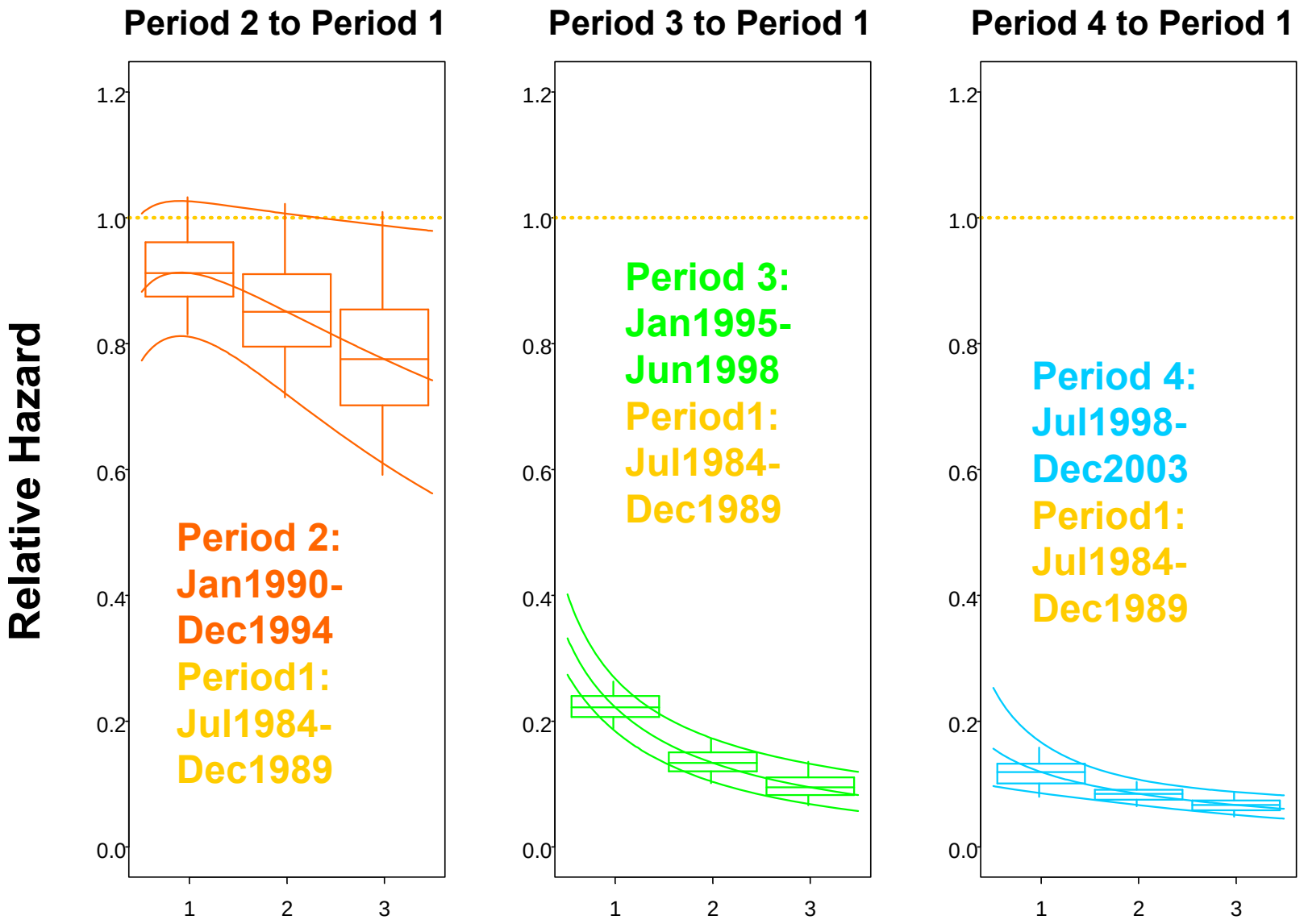
Wada, Jacobson, …, Muñoz - Am J Epidemiol 2013;177:116-25



November 2013

Relative Hazards

Cox, Chu, …, Muñoz. Stat Med 2007

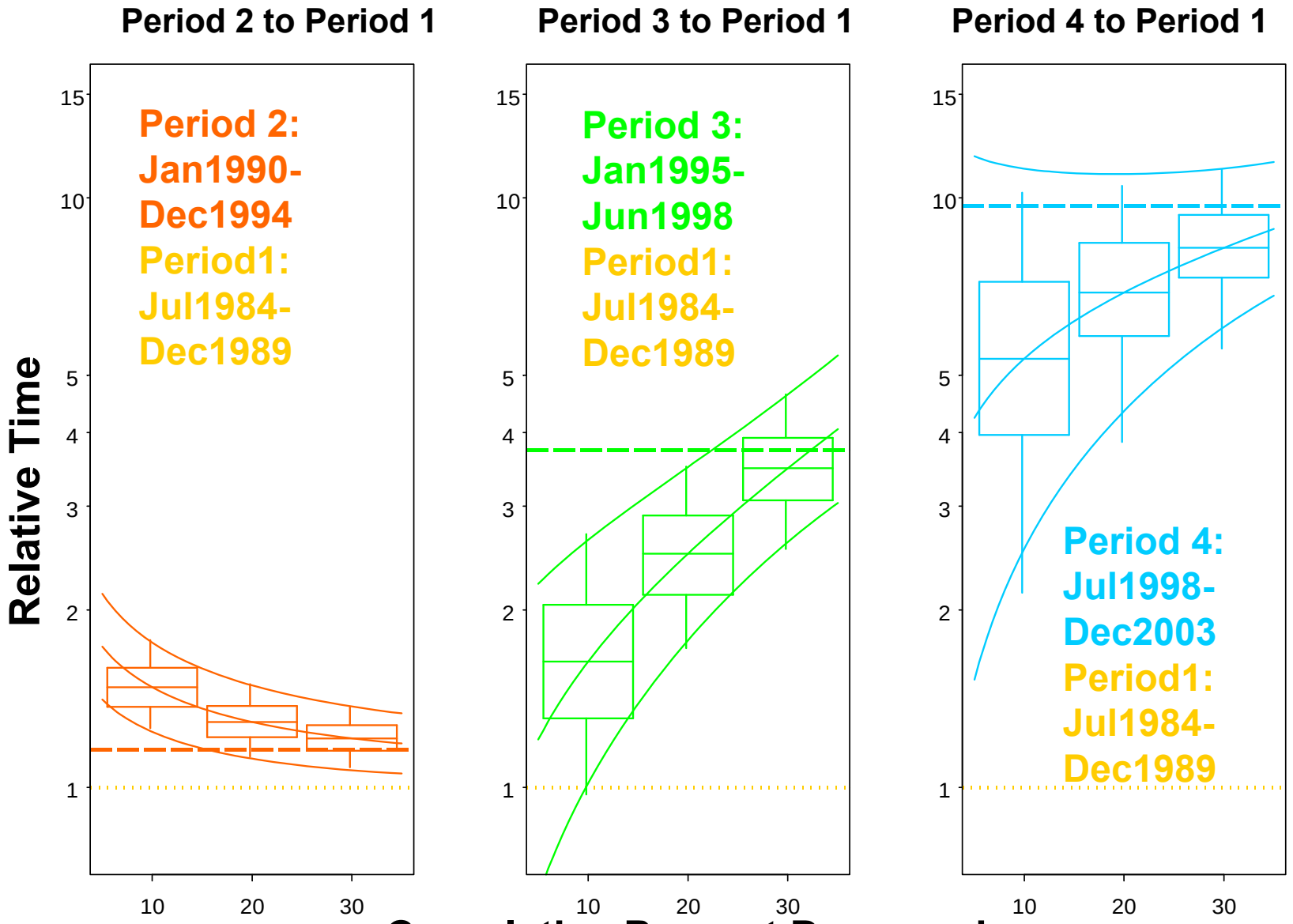


Years since AIDS Diagnosis

(Hazard at 1, 2, 3 years for Period 1 : 0.59, 0.71, 0.82)

Relative Times

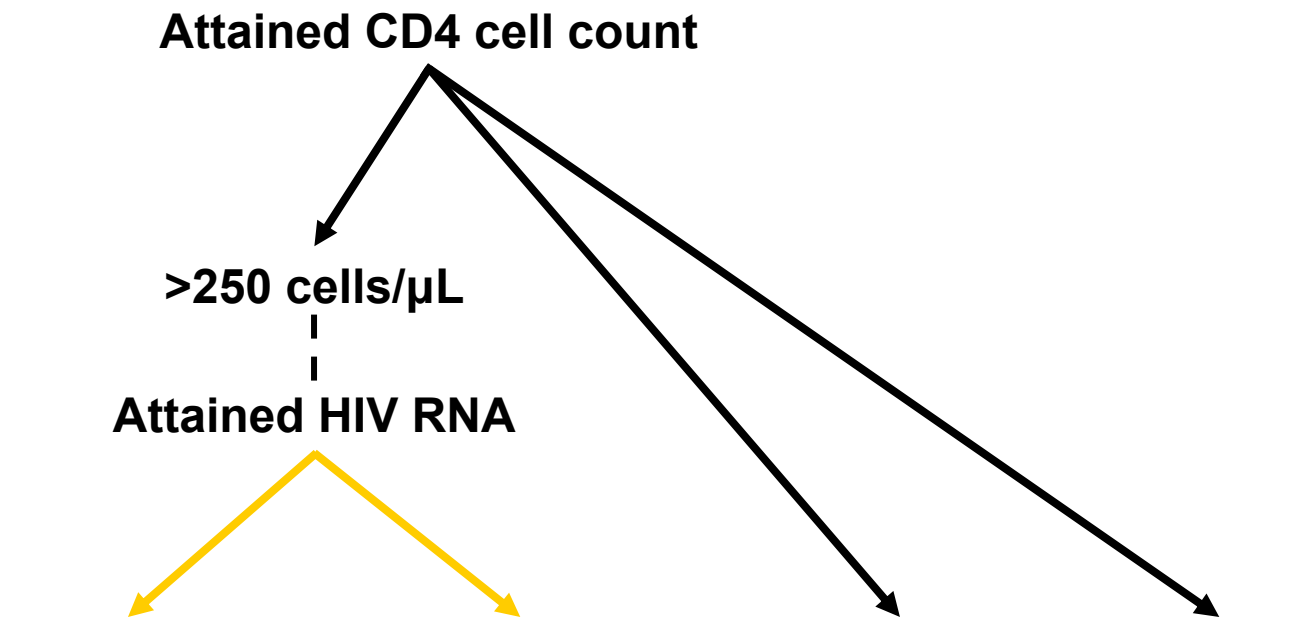
Cox, Chu, …, Muñoz. Stat Med 2007



August 2007

Prognostic Value of the CD4 Cell Count and HIV RNA attained by HAART-Treated Individuals

Tarwater, Gallant, …Muñoz. AIDS, 2004

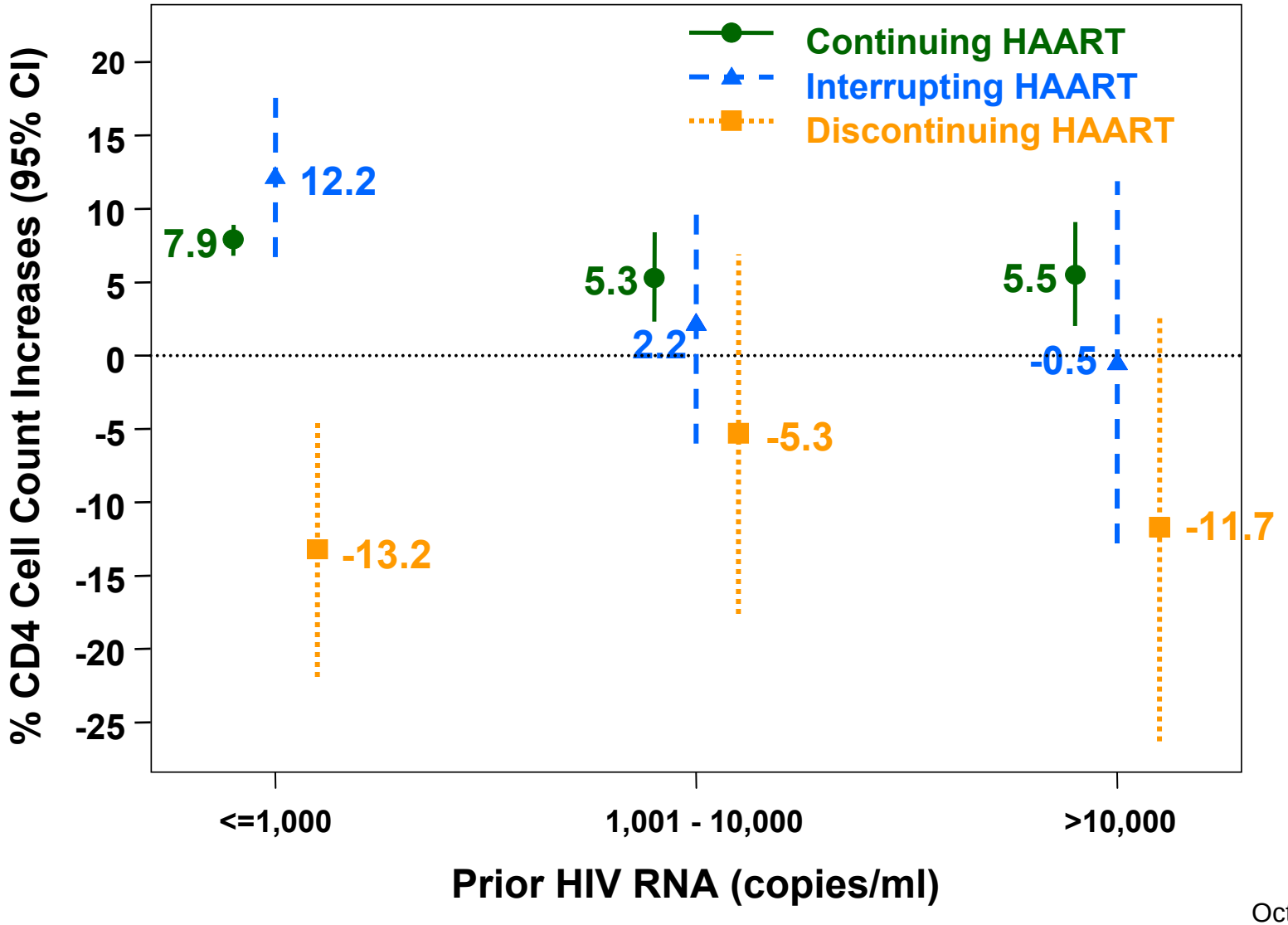


	≤1000 copies/mL	>1000 copies/mL	101–250 cells/ µL	≤100 cell/ µL
Person-years at risk	739	295	140	44
Number of AIDS cases	5	9	12	10
Relative Hazard of AIDS	1	4.6	12.1	33.1
95% CI		(1.5, 13.6)	(4.2, 34.5)	(11.2, 97.7)

November 2004

Effect of Interrupting and Discontinuing HAART on % CD4 Cell Count Increases in 6 months According to Prior HIV RNA Level

Li, Margolick, …, Jacobson - JAIDS 2005



October 2005

Risk of AIDS or Death by CD4 Cell Count while Plasma Viral Load was <50 HIV RNA copies/mL

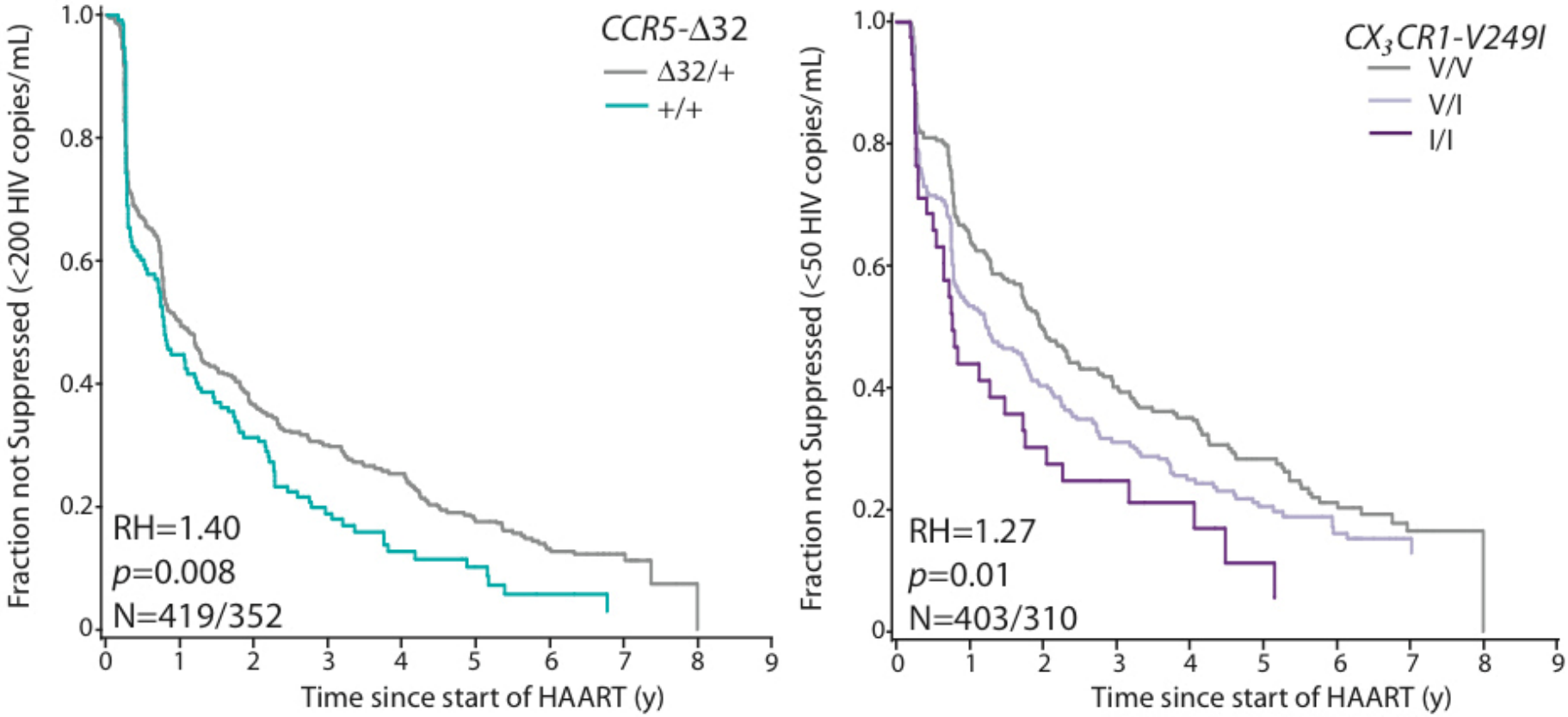
Taiwo, Li, …, Phair. HIV Med 2009

CD4 cell count	Hazard ratio (95% CI) AIDS* (P value)	Death* (P value)	AIDS or Death* (P value)
≤ 200 cells/μL	5.96 (0.40, 87.8) (0.194)	22.8 (1.89, 275) (0.014)	10.7 (1.65, 70.0) (0.013)
201-350 cells/μL	5.44 (0.47, 63.4) (0.176)	10.8 (0.92, 127) (0.059)	8.54 (1.54, 47.2) (0.014)

* Compared to having CD4 cell count > 350 cells/μL while plasma viral load was <50 copies/m:

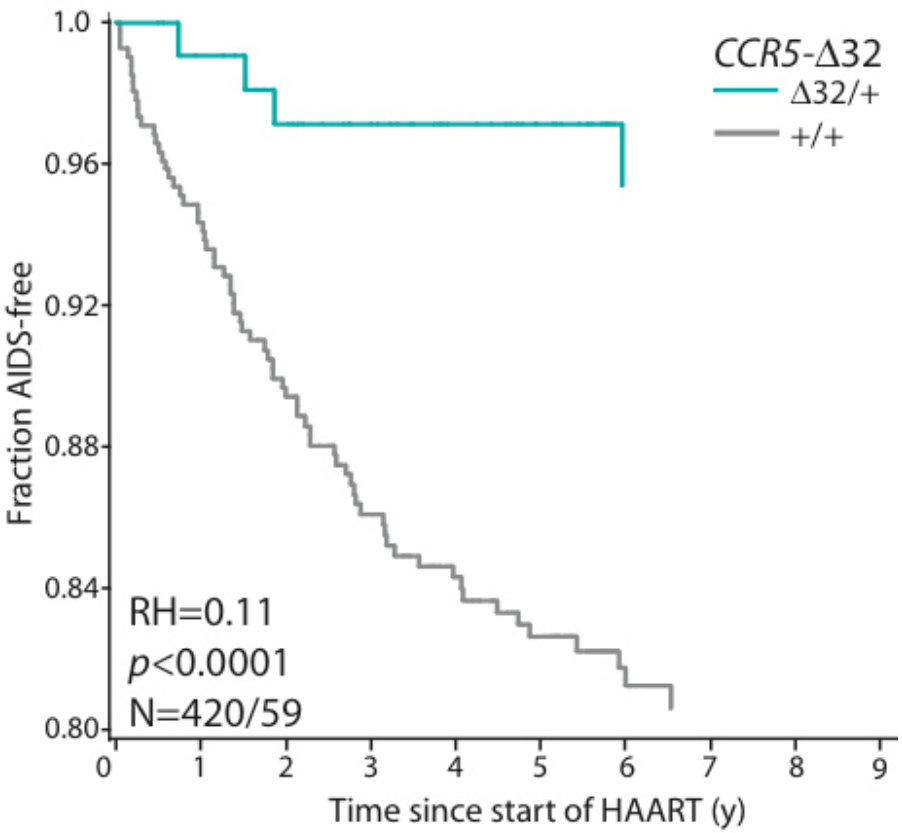
Time to Viral Suppression Following HAART According to Selected Genotypings

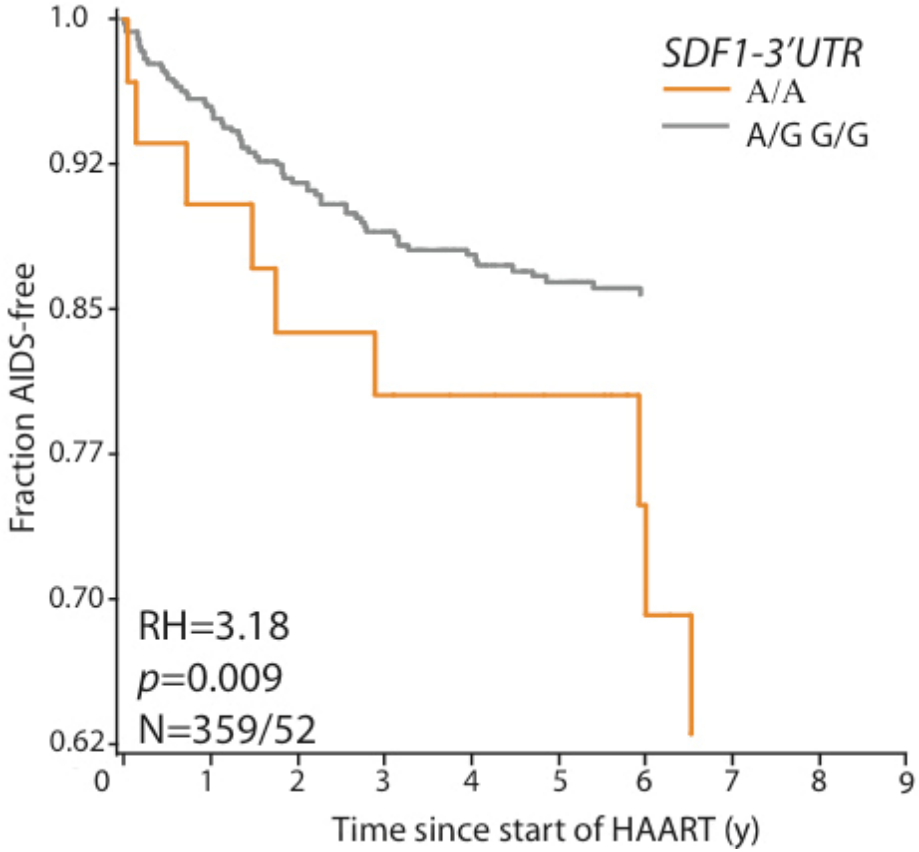
Hendrickson, Jacobson, . . ., O'Brien - JAIDS 2008



Time to AIDS Following HAART According to Selected Genotypings

Hendrickson, Jacobson, . . ., O'Brien - JAIDS 2008



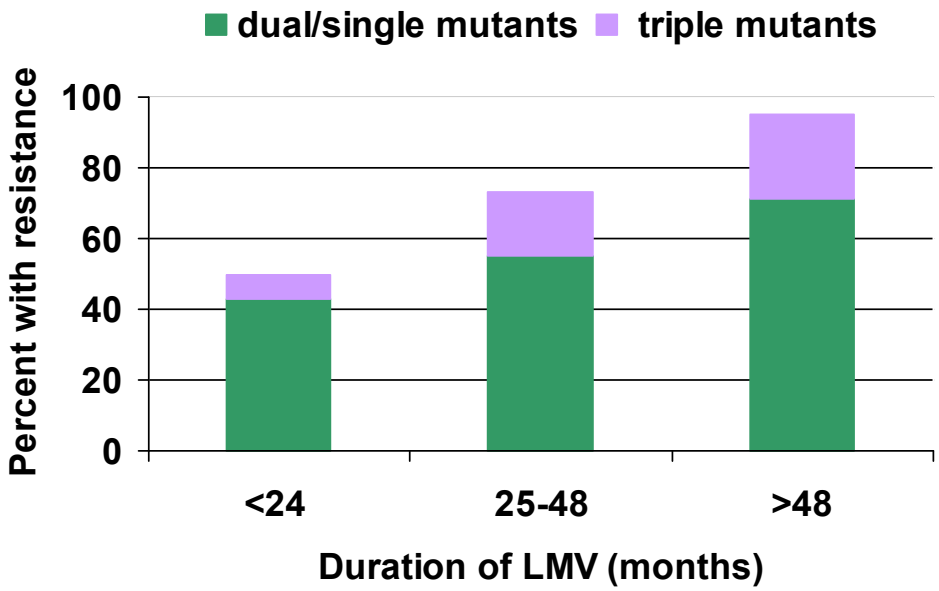


Lamivudine (LMV) Resistance in HIV-HBV Coinfected Cohort

Matthews, Bartholomeusz, …, Thio. AIDS 2006

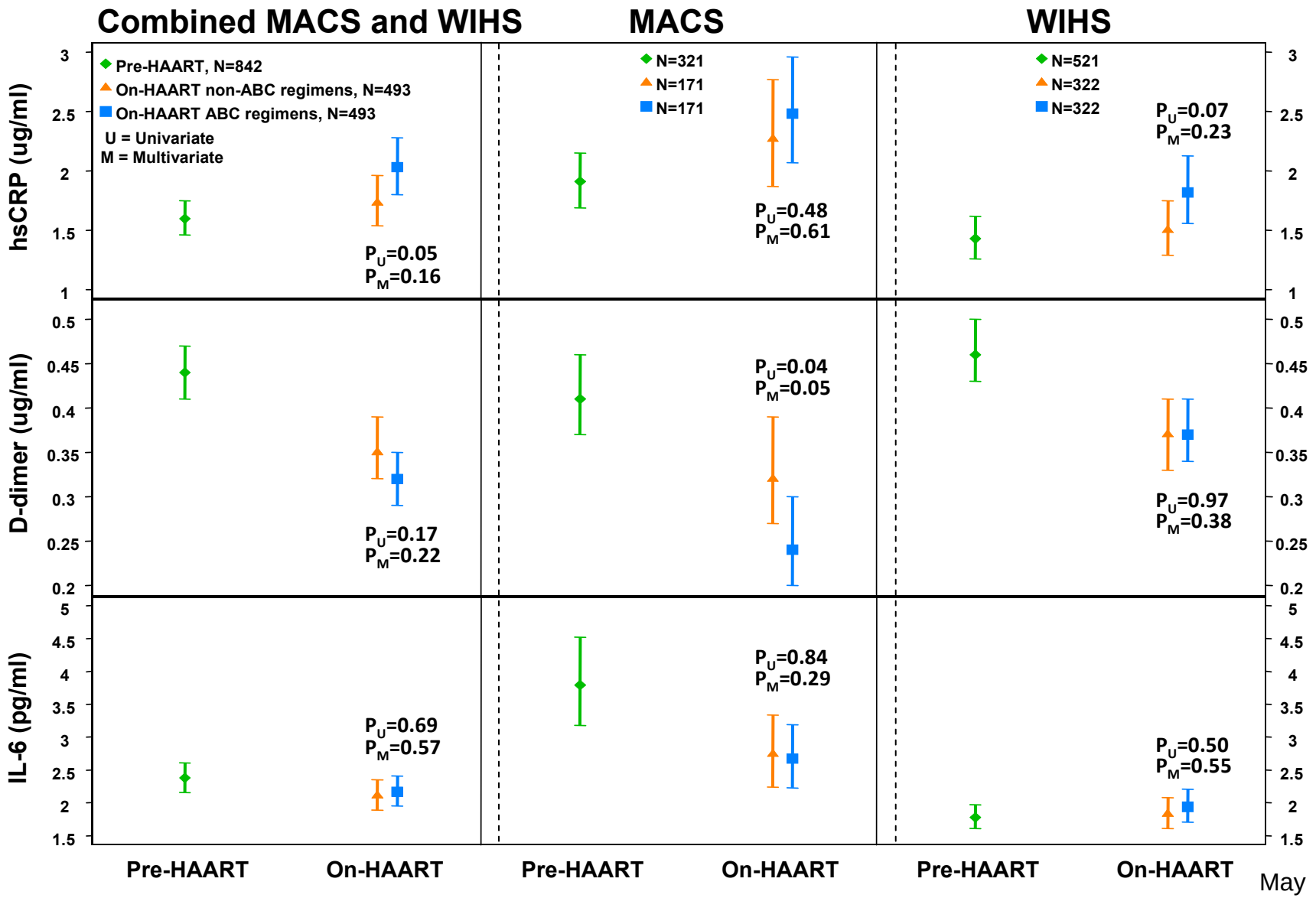
Sequenced Pol in 53 viremic persons > 6 mos LMV

- **39 (74%) LMV-R HBV**
- **After 4 yrs, 94% with LMV-R HBV**
- **Factors associated with developing resistance**
  - **Longer LMV, HAART**
  - **Higher CD4 count at time of resistance testing**
- **9 (17%) with triple mutant**
  - **2x the prevalence of monoinfected persons**



Pre- and On-HAART Biomarker Geometric Means and 95% Confidence Intervals Overall and Stratified by Cohort

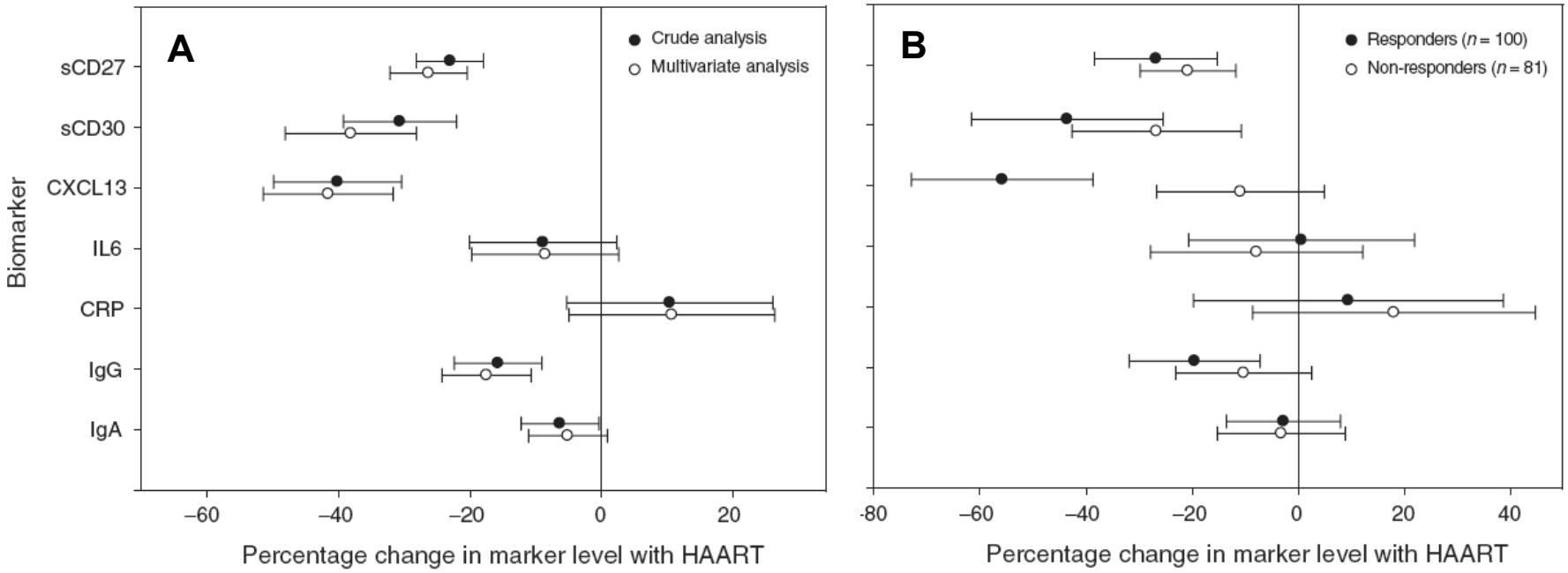
Palella, Gange, . . . , Elion, AIDS 2010



May 2011

Effect of HAART on Biomarkers of Inflammation and Immune Activation

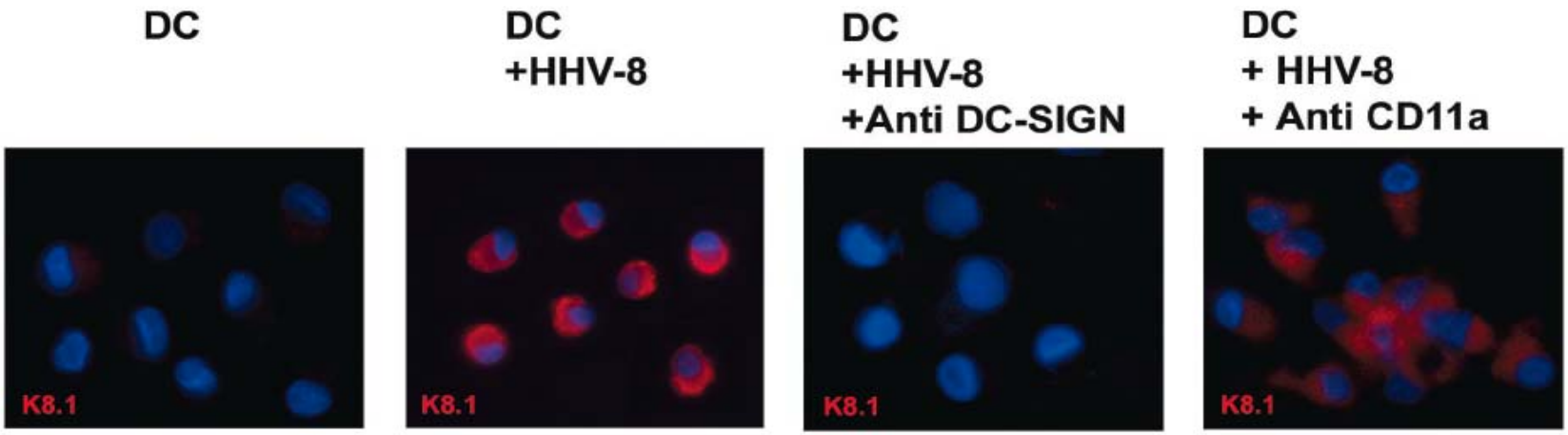
Regidor, Detels, . . . , Martinez-Maza. AIDS 2011



a) Total population; *;* b) Stratified by viral load response (<50 copies within 1.5 years after HAART initiation and sustained 1.5 – 3 years post HAART, if measurement was available)

Infection of Dendritic Cells with HHV-8 is Blocked by anti-DC-SIGN mAb

Rappocciolo, Jenkins, …, Rinaldo. J Immunol 2006

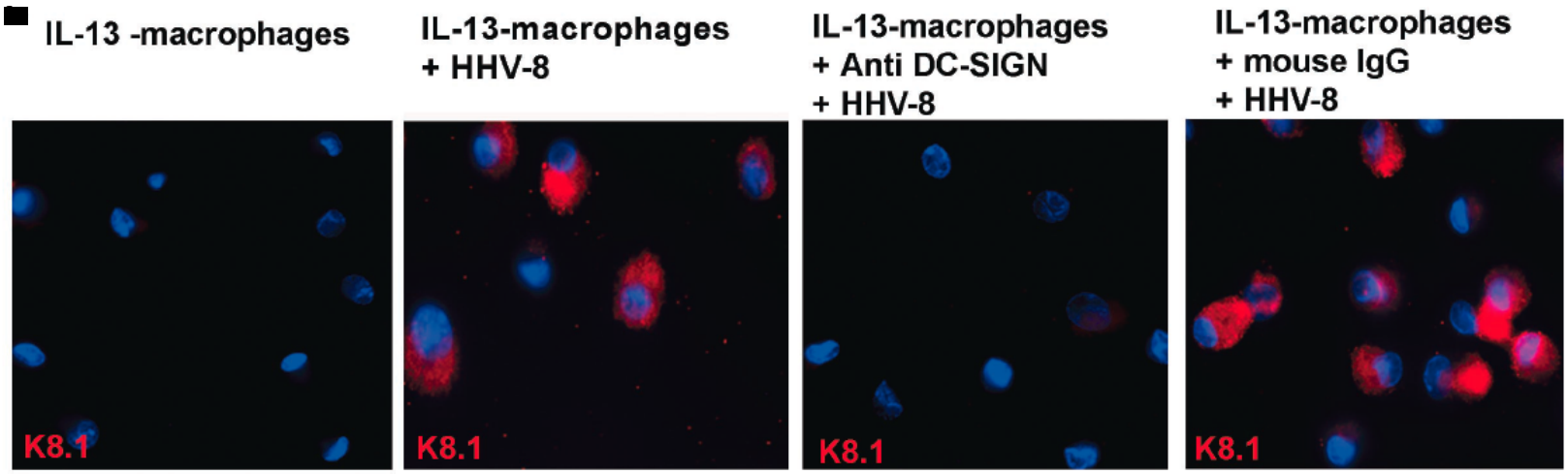


J Immunol 2006;176:1741-1749 – Figure 3A

May 2006

Infection of Macrophages with HHV-8 is Blocked by anti-DC-SIGN mAb

Rappocciolo, Jenkins, …, Rinaldo. J Immunol 2006

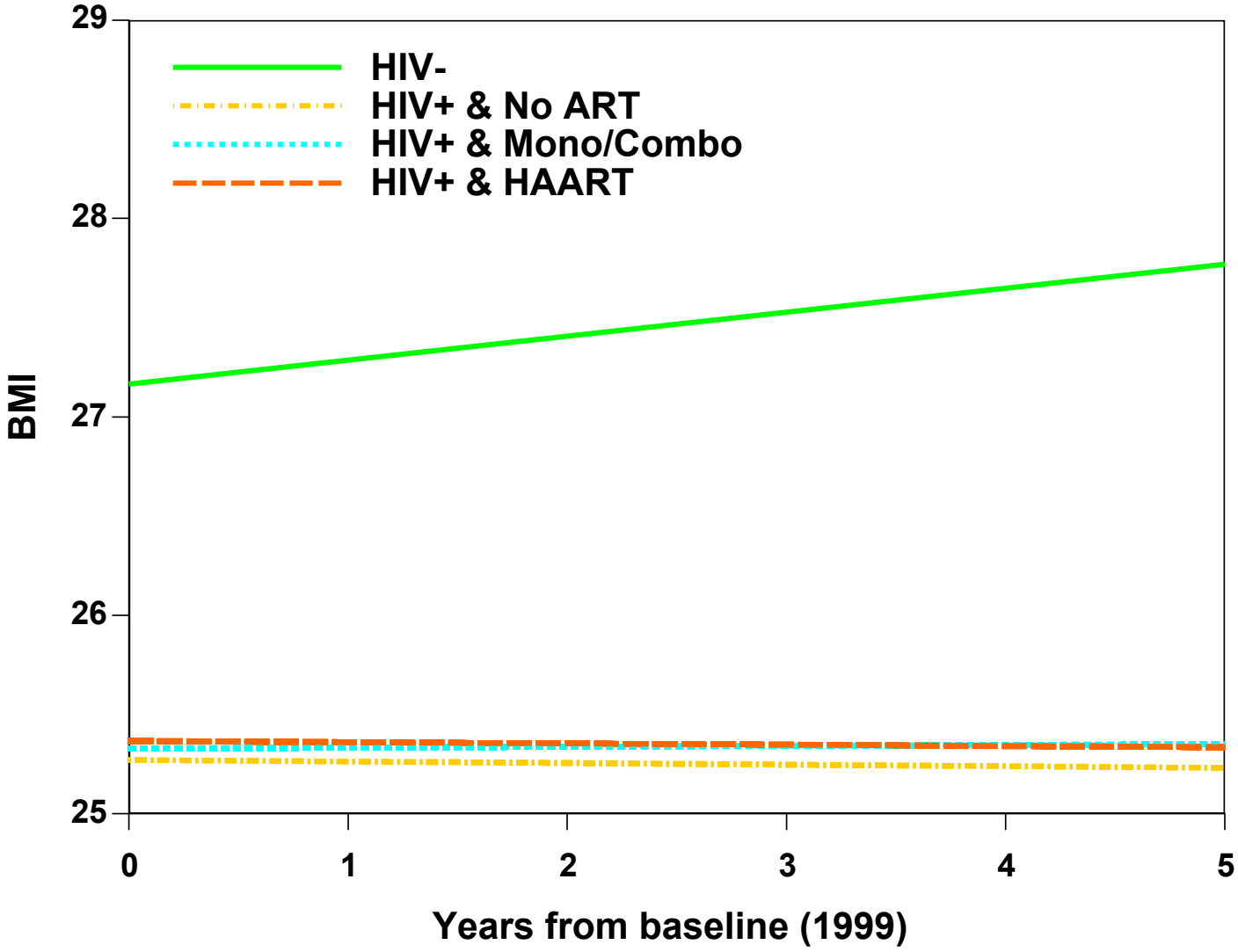


J Immunol 2006;176:1741-1749 – Figure 6C

May 2006

Annual Mean Change over a 4-year Interval in BMI in 4 Groups

Brown, Wang, …, Dobs. JAIDS 2006

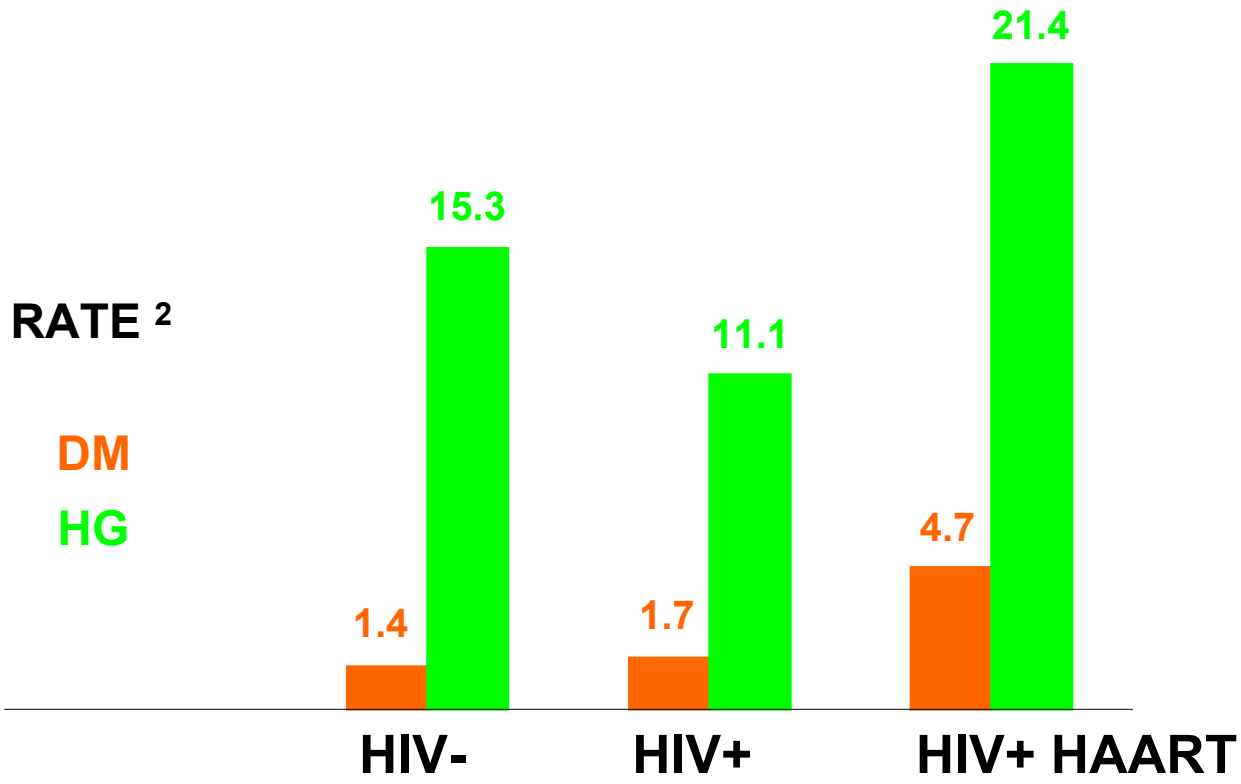


May 2007

Diabetes Mellitus and Hyperglycemia

Brown, Cole, …, Dobs - Arch Intern Med 2005

RATE RATIO [1]	**1**	**1**	**NA**	**4.1 (1.9, 9.2)** **1.6 (1.2, 2.3)**



[1] Adjusted for age and BMI
[2] Rate per 100 person-years

May 2007

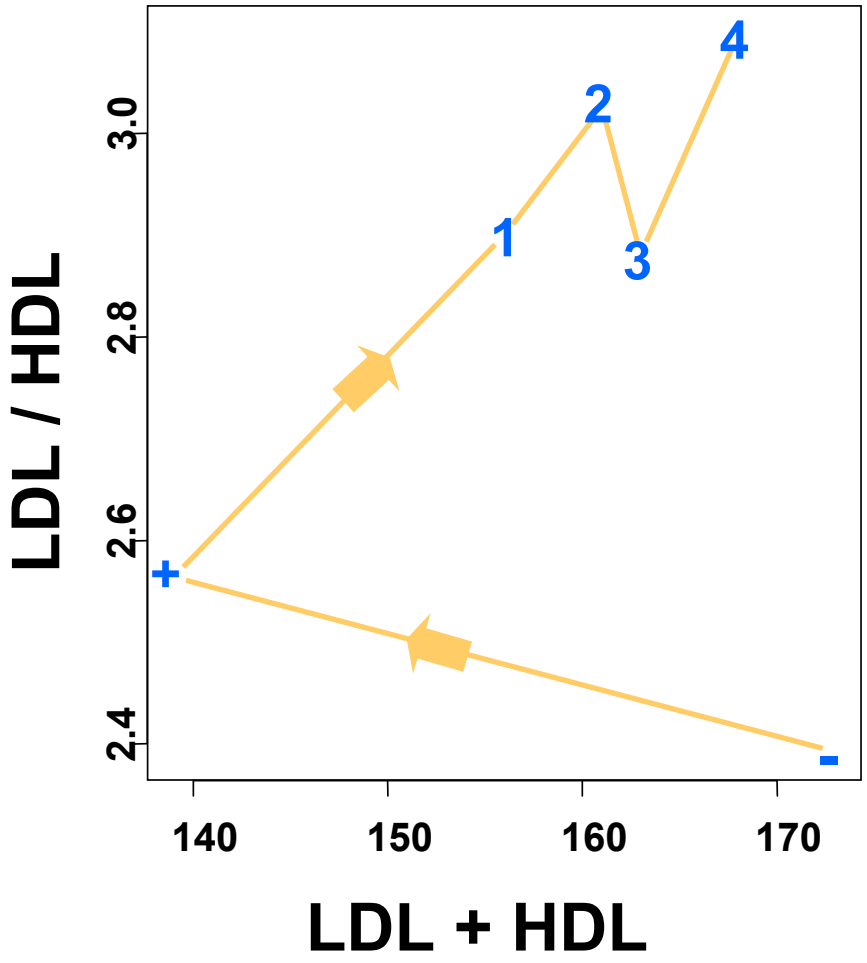
Mean Change in Blood Lipids Over Time for 50 Seroconverters Who Initiate HAART

Riddler, Smit, …, Kingsley - JAMA 2003

		Mean change from Pre-Seroconversion Values (95% CI)				
Lipids, mg/dL:	Pre-seroconversion (n=50)	Last Visit before HAART (n=50)	1st Visit after HAART (n=49)	2nd Visit after HAART (n=49)	3rd Visit after HAART (n=43)	4th Visit after HAART (n=38)
Total cholesterol	201 (179, 222)	-30 (-52, -9)	4 (-17, 25)	9 (-16, 34)	20 (-1, 41)	18 (-7, 42)
HDL-C	51 (46, 57)	-12 (-19, -6)	-11 (-16, -6)	-11 (-16, -6)	-9 (-16, -2)	-10 (-16, -3)
LDL-C	122 (102, 143)	-22 (-45, 1)	-6 (-29, 17)	-1 (-24, 22)	-1 (-25, 22)	5 (-20, 30)

Serum Lipids in HIV Seroconverters Who Initiated HAART

Riddler, Smit, …, Kingsley - JAMA 2003



	N	TC	LDL	HDL
-	(50)	201	122	51
+	(50)	171	100	39
1	(49)	205	116	40
2	(49)	210	121	40
3	(43)	221	121	42
4	(38)	219	127	41

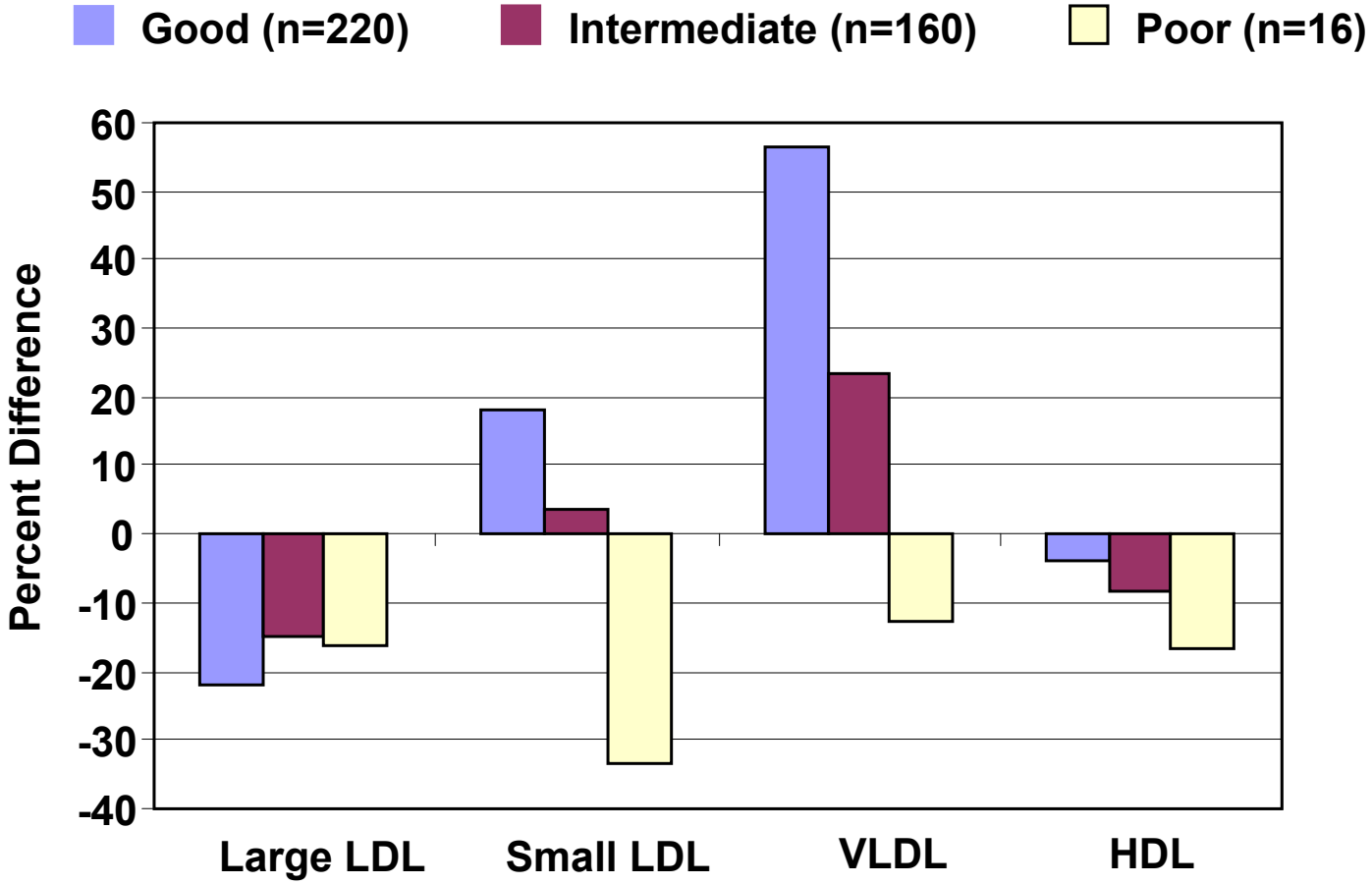
TC - total cholesterol

LDL - low density lipids

HDL - high density lipids

Percent Difference in Lipoprotein Concentrations Among HAART Treated According to Clinical Status, Compared to Uninfected

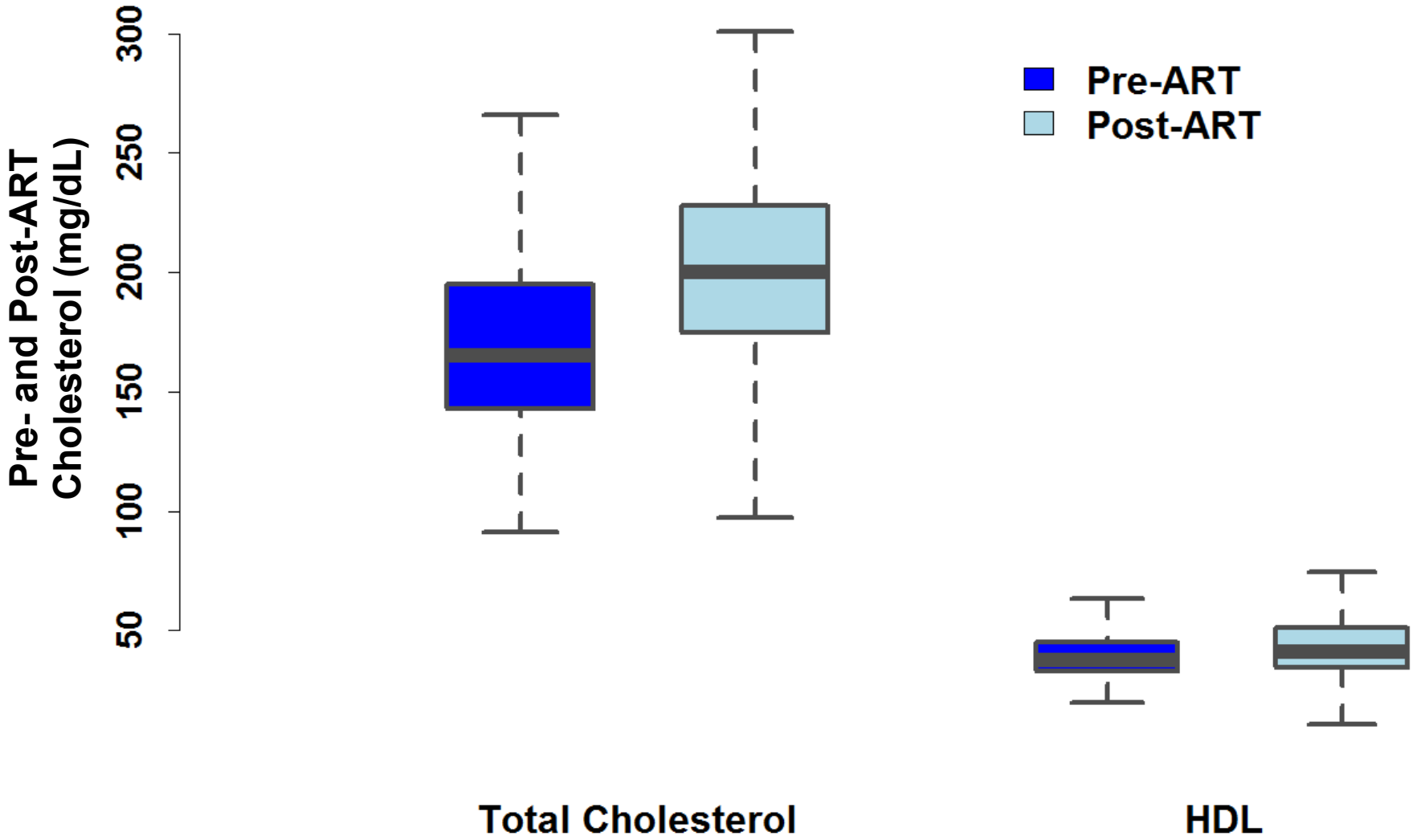
Riddler, Li, . . ., Sharrett - JAIDS 2008



May 2009

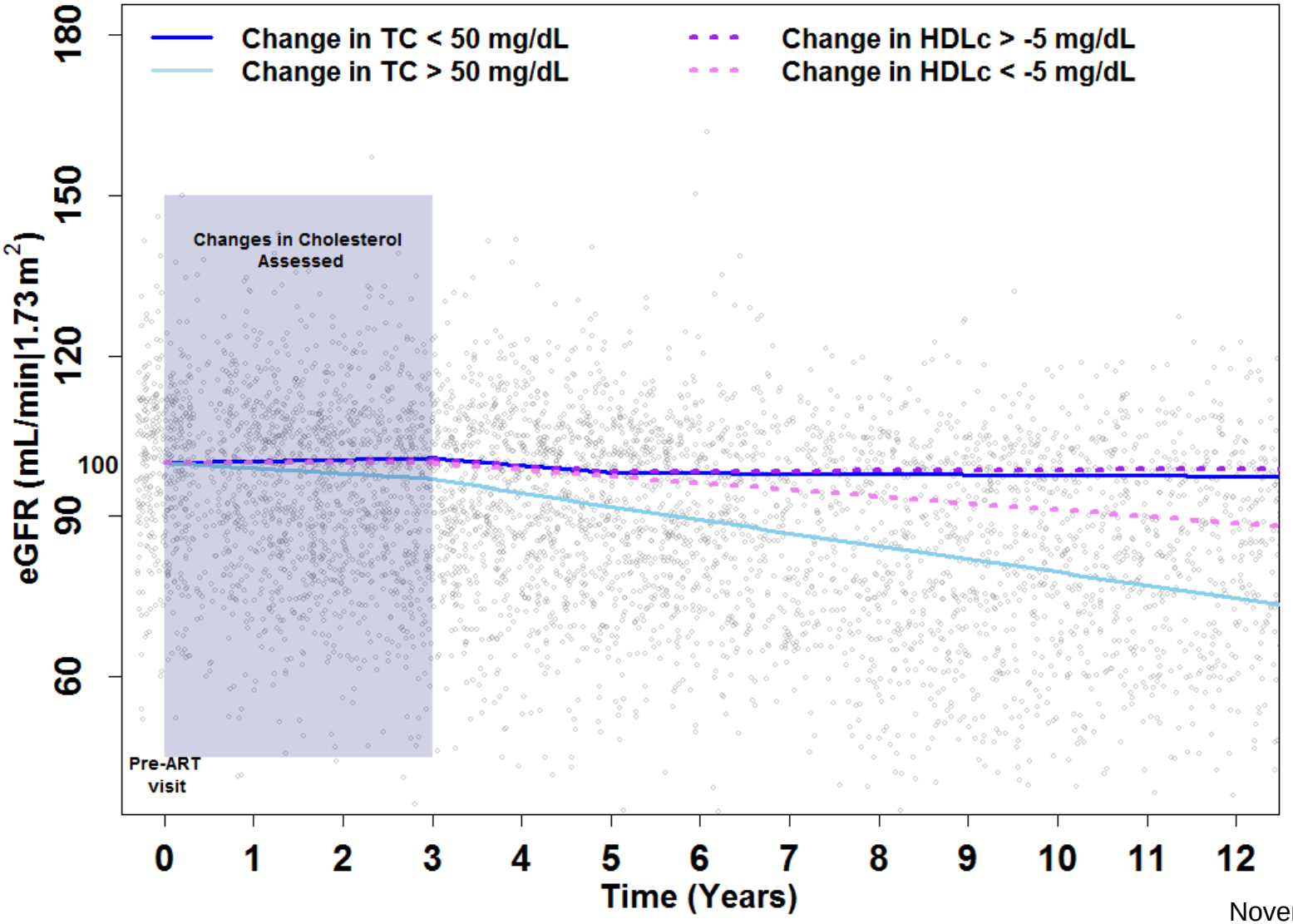
Distribution of Total Cholesterol and High-Density Lipid Levels in HIV-Infected Men

Abraham, Li, …, Phair - AIDS Res Hum Retroviruses 2013;29:1346-52



Estimated GFR after cART Initiation According to Total Cholesterol Change

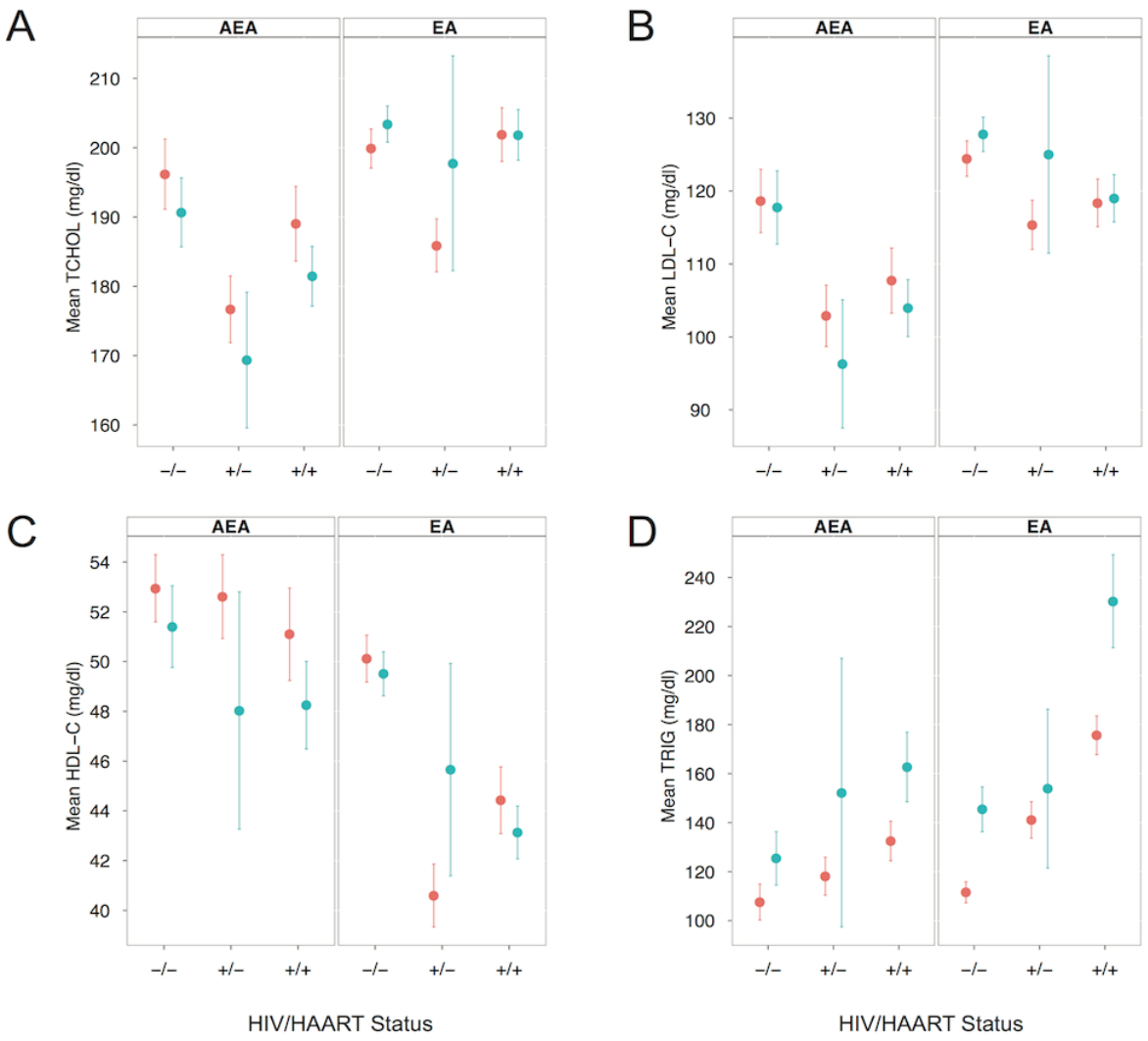
Abraham, Li, …, Phair - AIDS Res Hum Retroviruses 2013;29:1346-52



November 2013

Mean Serum Lipids Vary by Biogeographical Ancestry and HIV/HAART Status

Nicholaou, Martinson, …, Kingsley - AIDS Res Hum Retroviruses 2013;29:871-9



A: Mean total cholesterol (TCHOL) by HIV/HAART status (-/- = HIV negative; +/- = HIV/HAART naïve, +/+ = HIV/HAART).

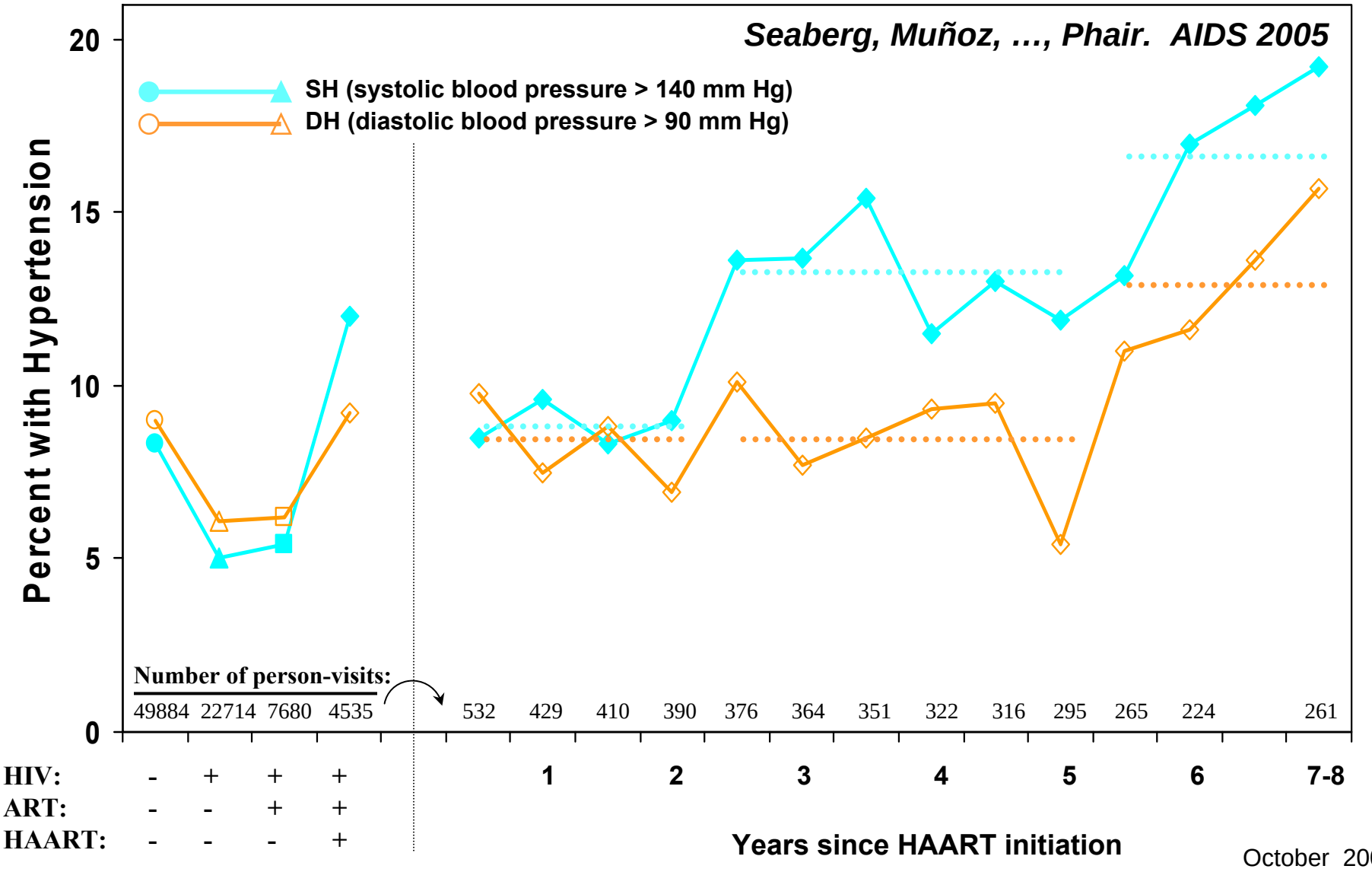
B: Mean low density lipoprotein cholesterol (LDL-C).

C: Mean high-density lipoprotein cholesterol (HDL-C).

D: Mean triglyceride (TRIG).

AEA = African/European ancestry population; EA = European ancestral populations. Raw calculated means are shown in blue and adjusted means are shown in red. Bars indicate 95% confidence intervals of the mean.

Prevalence of Systolic Hypertension (SH) and Diastolic Hypertension (DH) by HIV Sero-status and Therapy, and Relative to the Time of HAART Initiation



October 2005

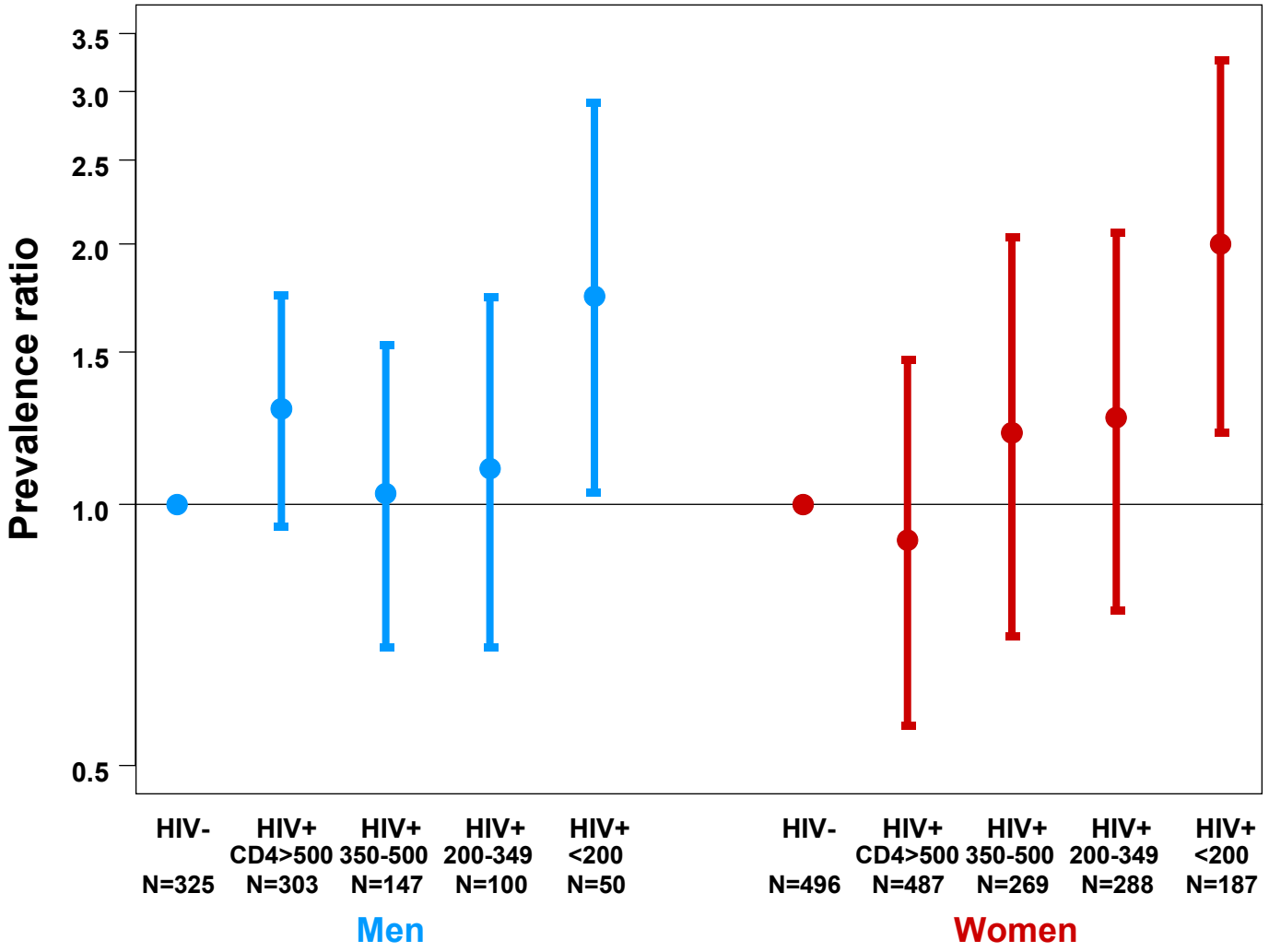
Multiple Regression Analyses: Systolic Hypertension and Diastolic Hypertension

Seaberg, Muñoz, …, Phair. AIDS 2005

Characteristics				Systolic Hypertension OR	Systolic Hypertension 95% CI	Diastolic Hypertension OR	Diastolic Hypertension 95% CI
Age (years)							
<30				1		1	
30-39				1.21	1.06, 1.37	1.67	1.47, 1.90
40-49				1.69	1.46, 1.96	2.36	2.05, 2.73
≥50				3.23	2.73, 3.82	3.05	2.58, 3.62
Race/ethinicity							
Caucasian				1		1	
African-American				1.42	1.16, 1.72	1.67	1.40, 1.99
All others				0.90	0.68, 1.18	1.01	0.79, 1.29
Body mass index (kg/m^2)							
<20				1		1	
20-24.9				1.66	1.36, 2.01	1.46	1.23, 1.74
25-29.9				2.83	2.31, 3.47	2.46	2.05, 2.96
≥30				5.20	4.15, 6.51	4.43	3.62, 5.43
Cigarette Smoking history							
Never smoked				1		1	
Former smoker				1.21	1.08, 1.35	1.04	0.93, 1.15
Current smoker				1.17	1.03, 1.33	0.93	0.82, 1.05
HIV	**/**	**ART**	**/ HAART (years since HAART initiation)**				
-		no		1		1	
+		no	naive	0.79	0.70, 0.89	0.84	0.76, 0.94
+		yes	naive	0.69	0.59, 0.80	0.73	0.63, 0.84
+		yes	yes (<2 years)	1.06	0.87, 1.30	0.84	0.68, 1.03
+		yes	yes (2-5 years)	1.51	1.25, 1.82	0.78	0.63, 0.96
+		yes	yes (>5 years)	1.70	1.34, 2.16	1.21	0.94, 1.56
+		discontinued HAART		1.32	0.91, 1.90	1.02	0.69, 1.49

Association between CD4+ T-cell Count (cells/μℓ) and Prevalence of Carotid Lesions among Participants in Men (MACS) and Women (WIHS)

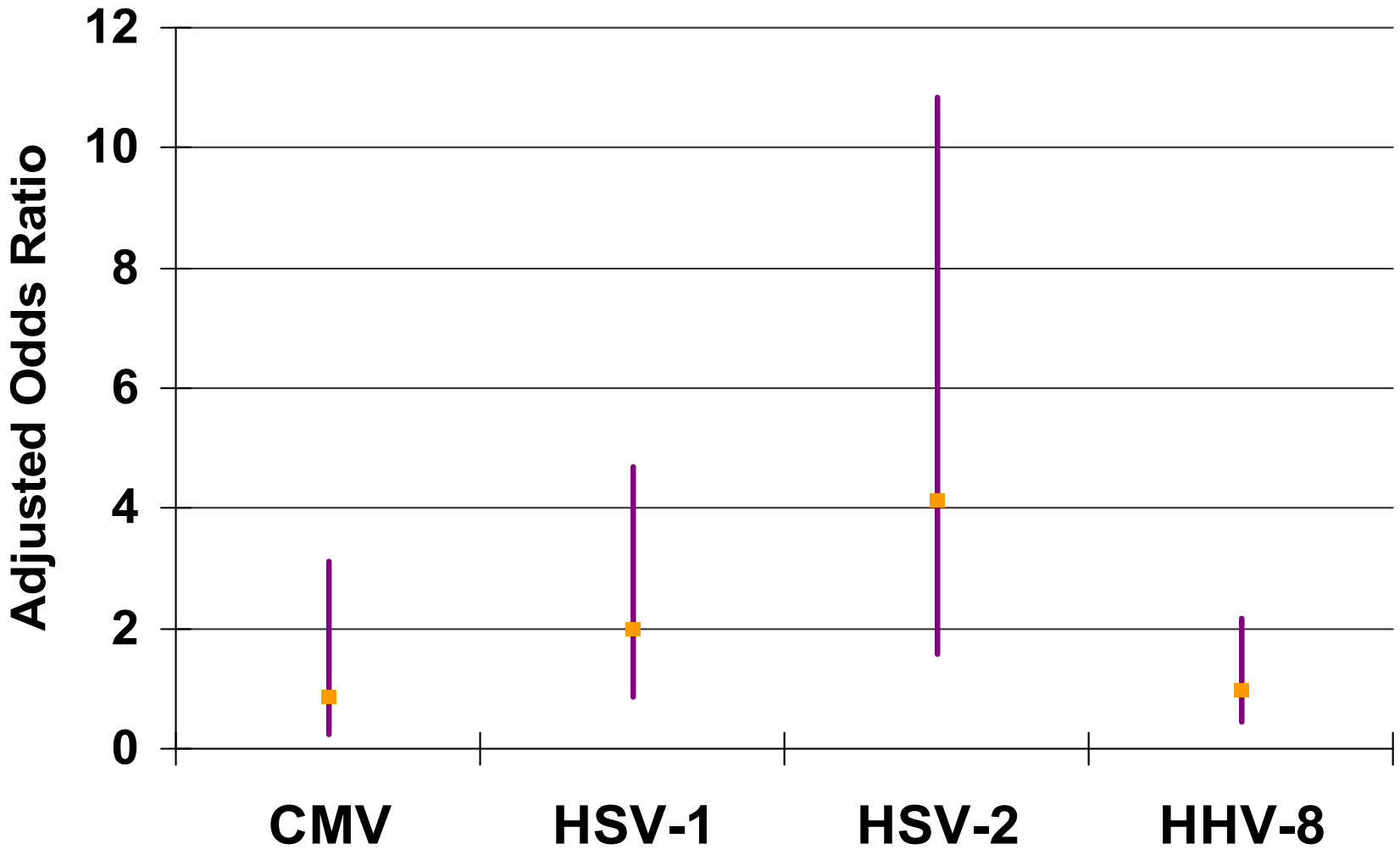
Kaplan, Kingsley, . . ., Hodis - AIDS 2008



May 2009

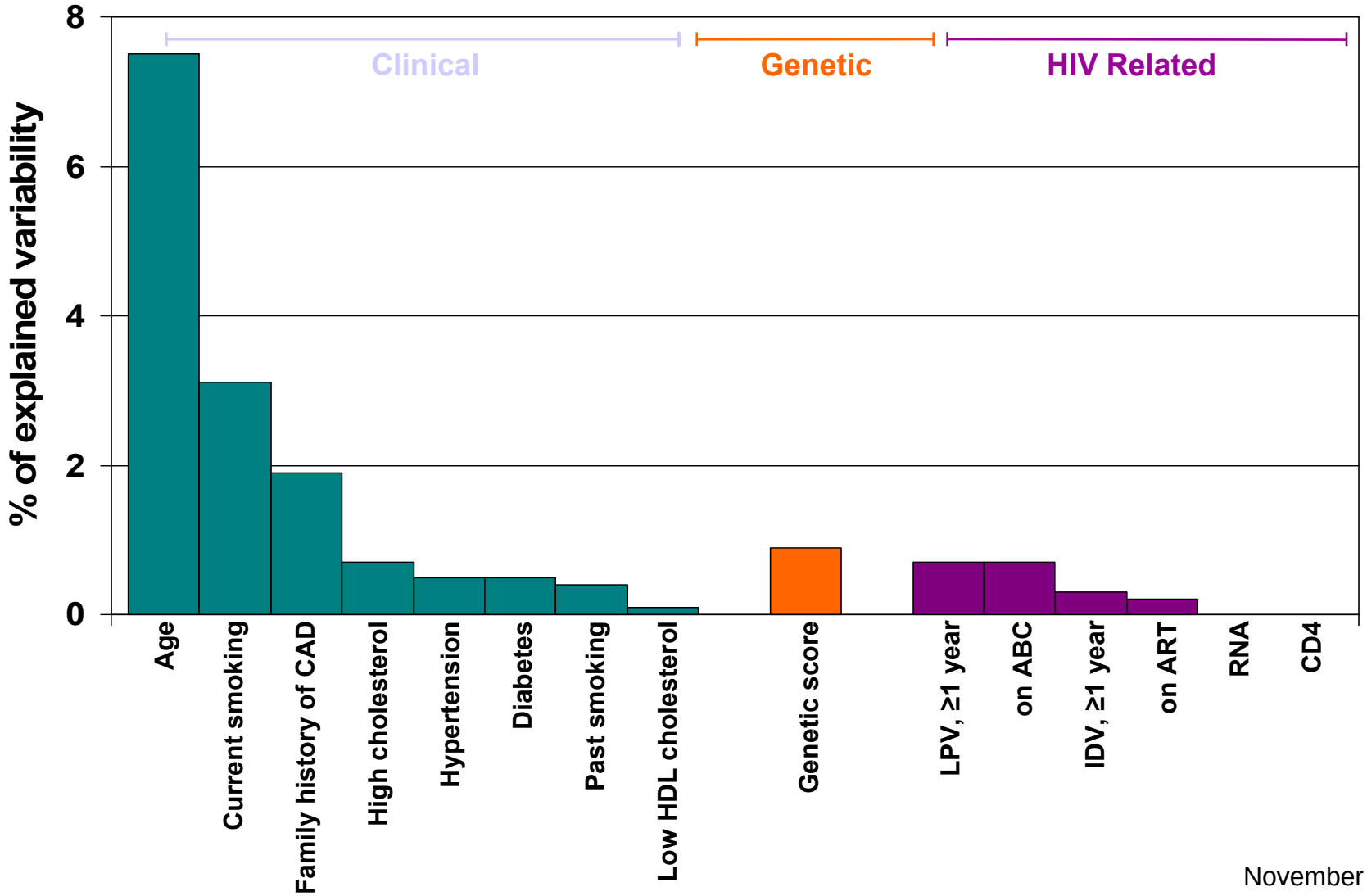
Association of Subclinical Atherosclerosis with Presence of Plasma CMV DNA, and Antibodies to HSV-1, HSV-2 and HHV-8 in HIV-Infected Men Who have Sex with Men

Hechter, Budoff, …, Detels - Atherosclerosis 2012;223:433-6



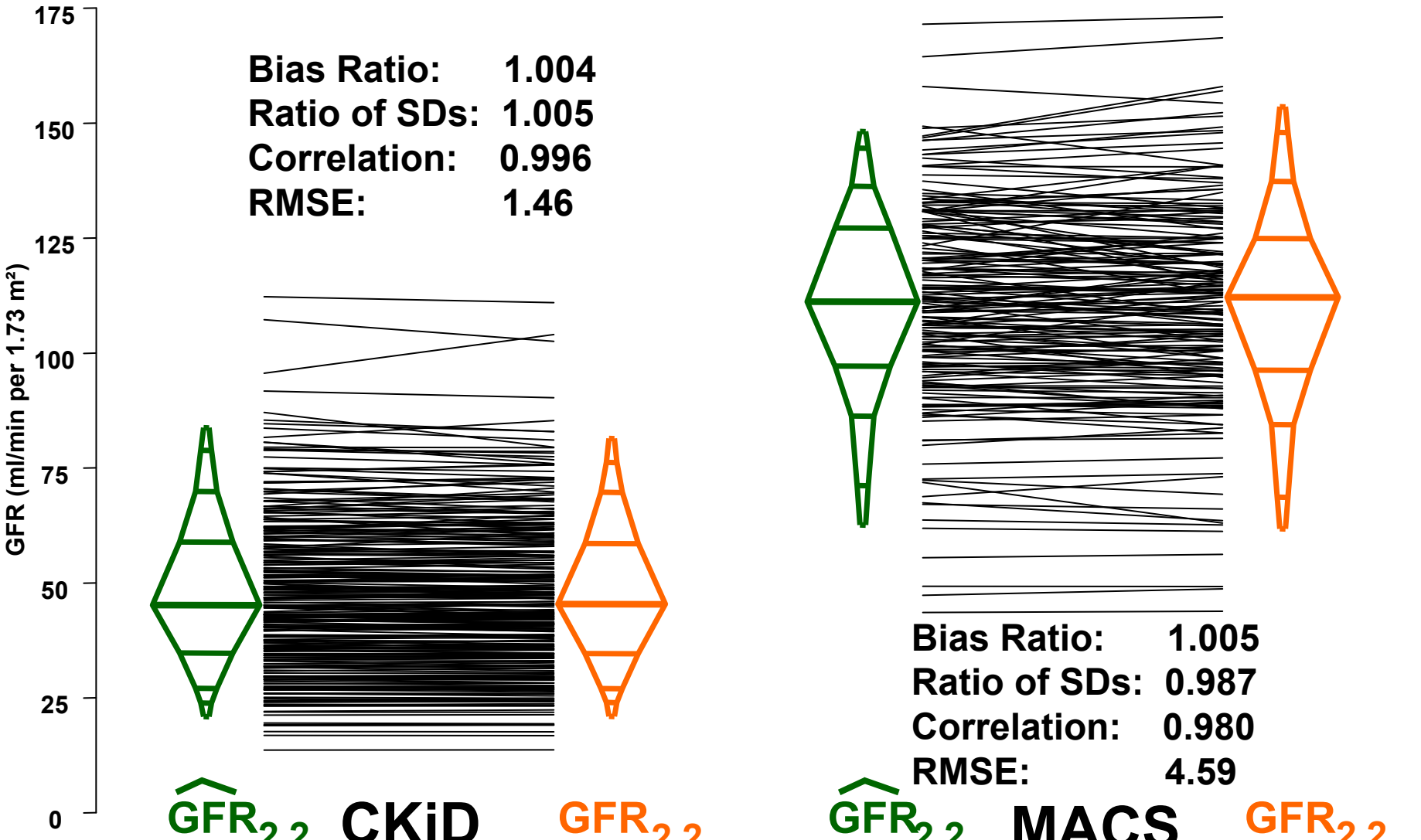
Coronary Artery Disease (CAD) Variability Explained by Traditional Risk Factors, HIV-Related Factors and Genetic Background

Rotger, Glass, …, Tarr - Clin Infect Dis 2013;57:112-21



Agreement Between $\widehat{GFR}$ and Observed GFR

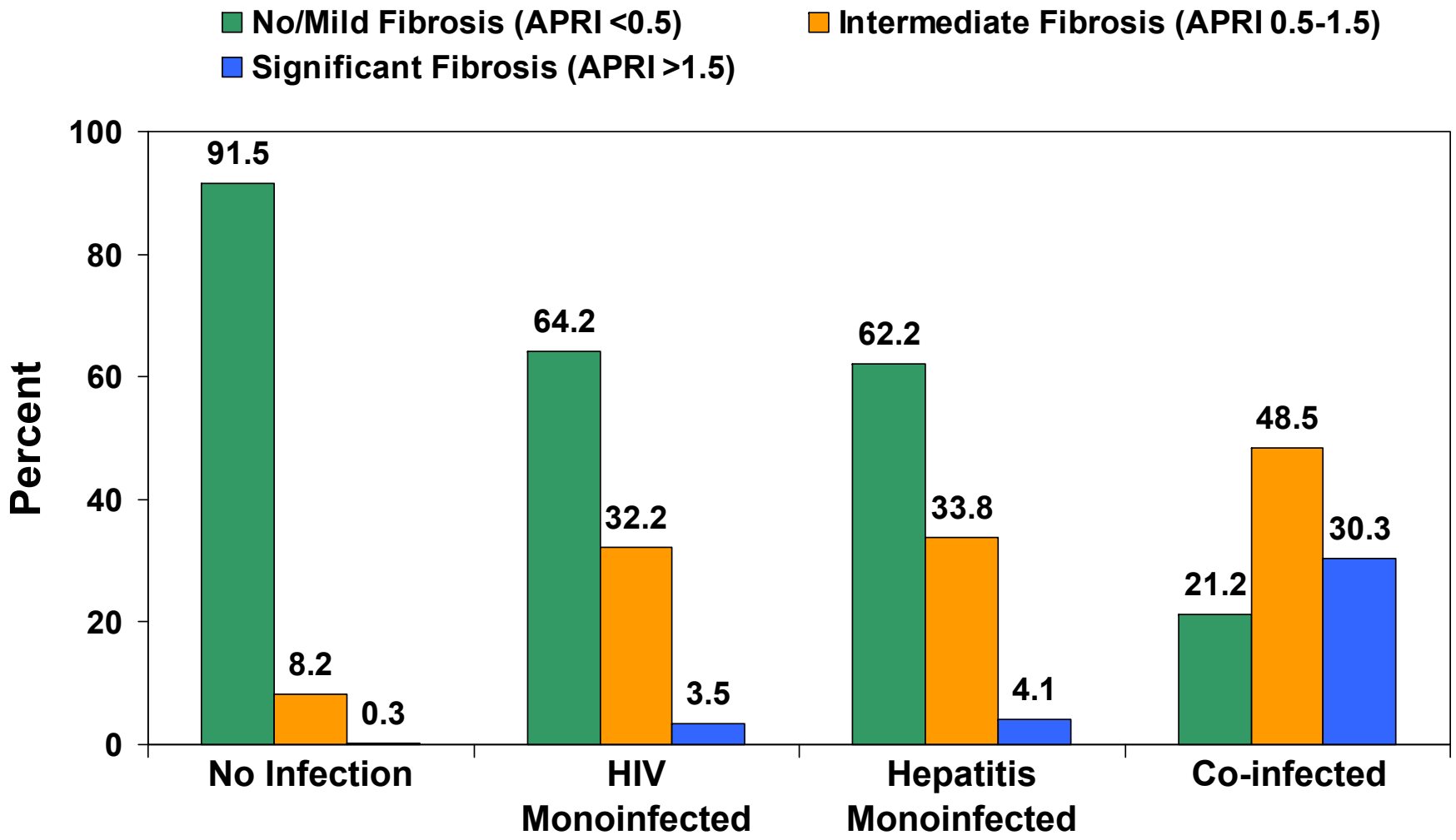
Ng, Schwartz, …, Muñoz. Kidney Int 2011



May 2012

Categorization of Hepatic Fibrosis by HIV and Viral Hepatitis Disease Category

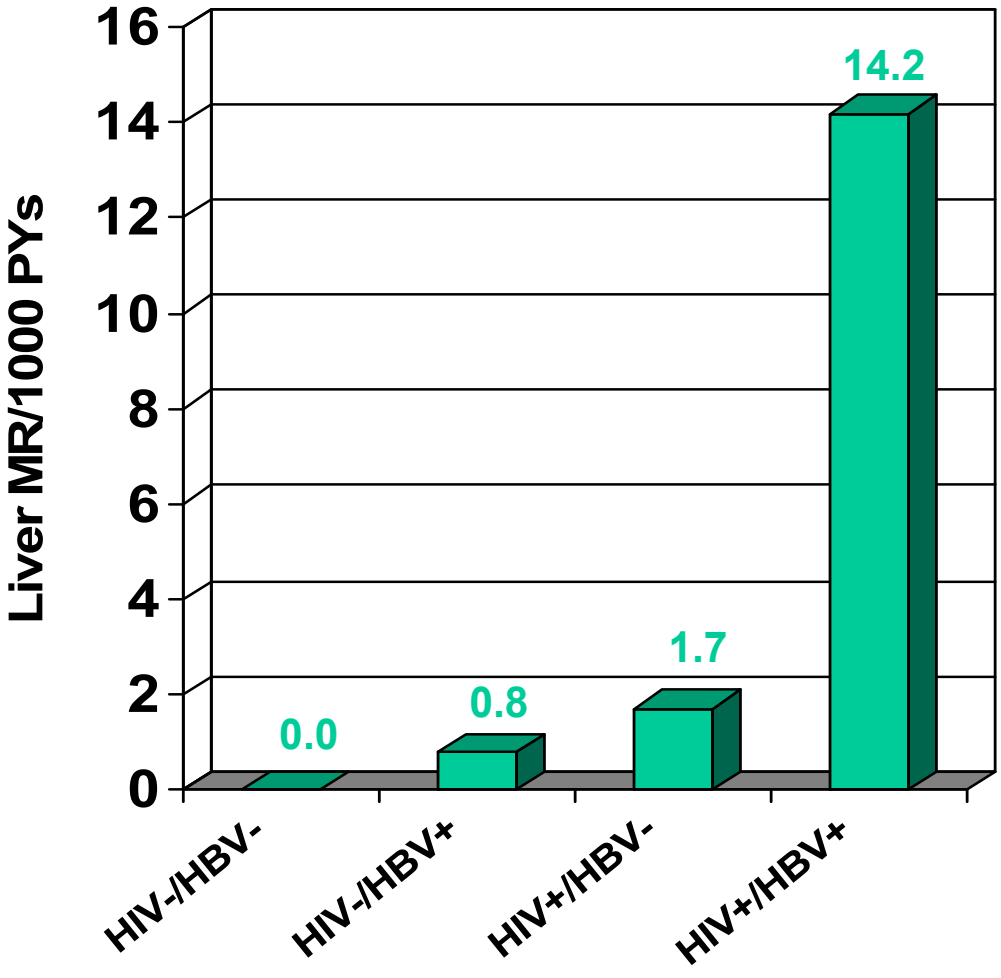
Price, Seaberg, …, Thio. J Infect Dis 2012



May 2012

Increased Liver Mortality in HIV-HBV Co-infected Men: MACS

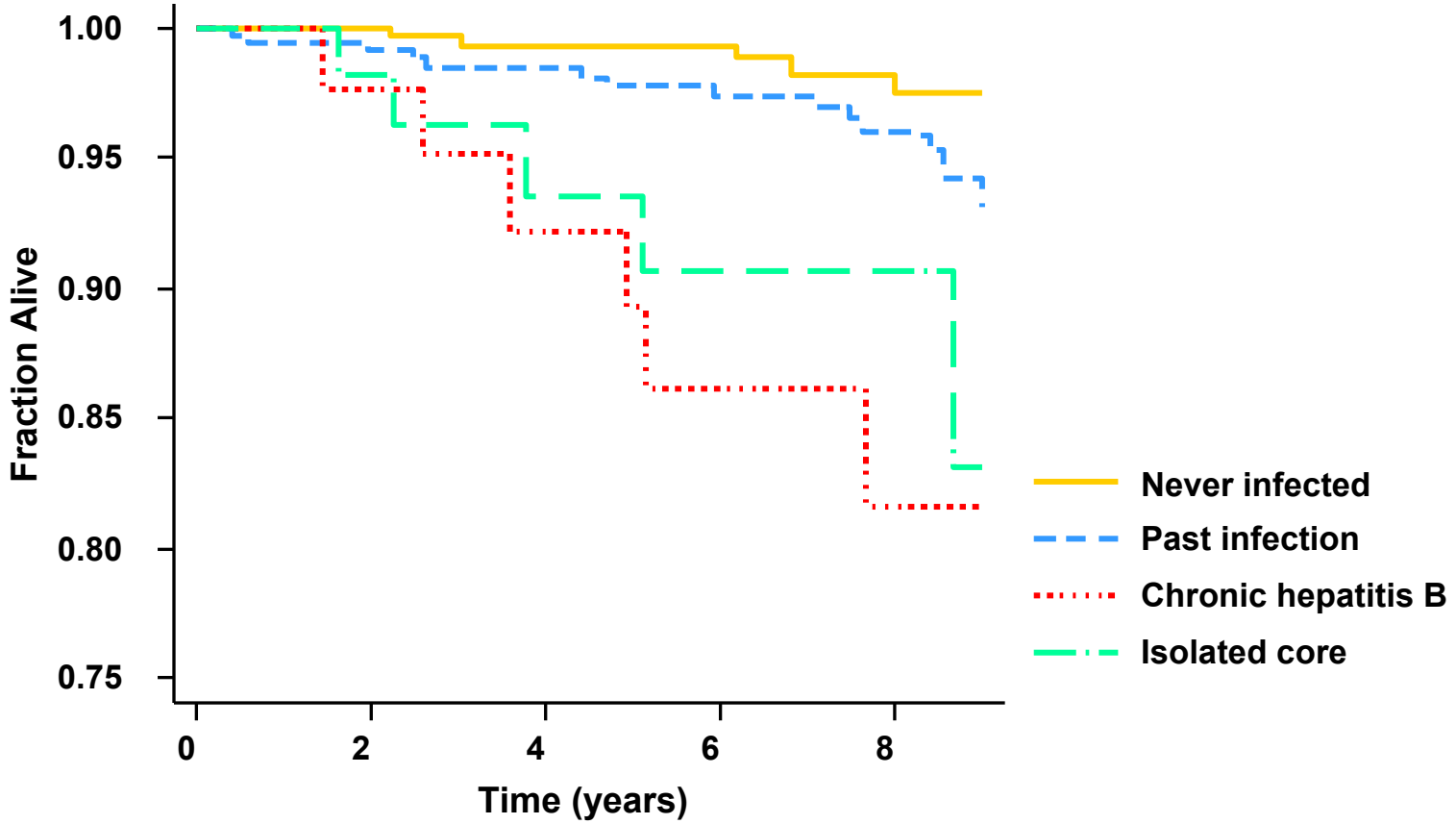
Thio, Seaberg, …, Thomas - Lancet 2002



- 5293 men (326 HBsAg+ baseline) followed 10.5 years
- RR of liver death 18.7 in coinfected vs. only HBsAg+

Kaplan-Meier Curve of Non-AIDS Mortality by Hepatitis B Virus Status as Determined at Time of HAART Initiation

Hoffmann, Seaberg, …, Thio. AIDS 2009

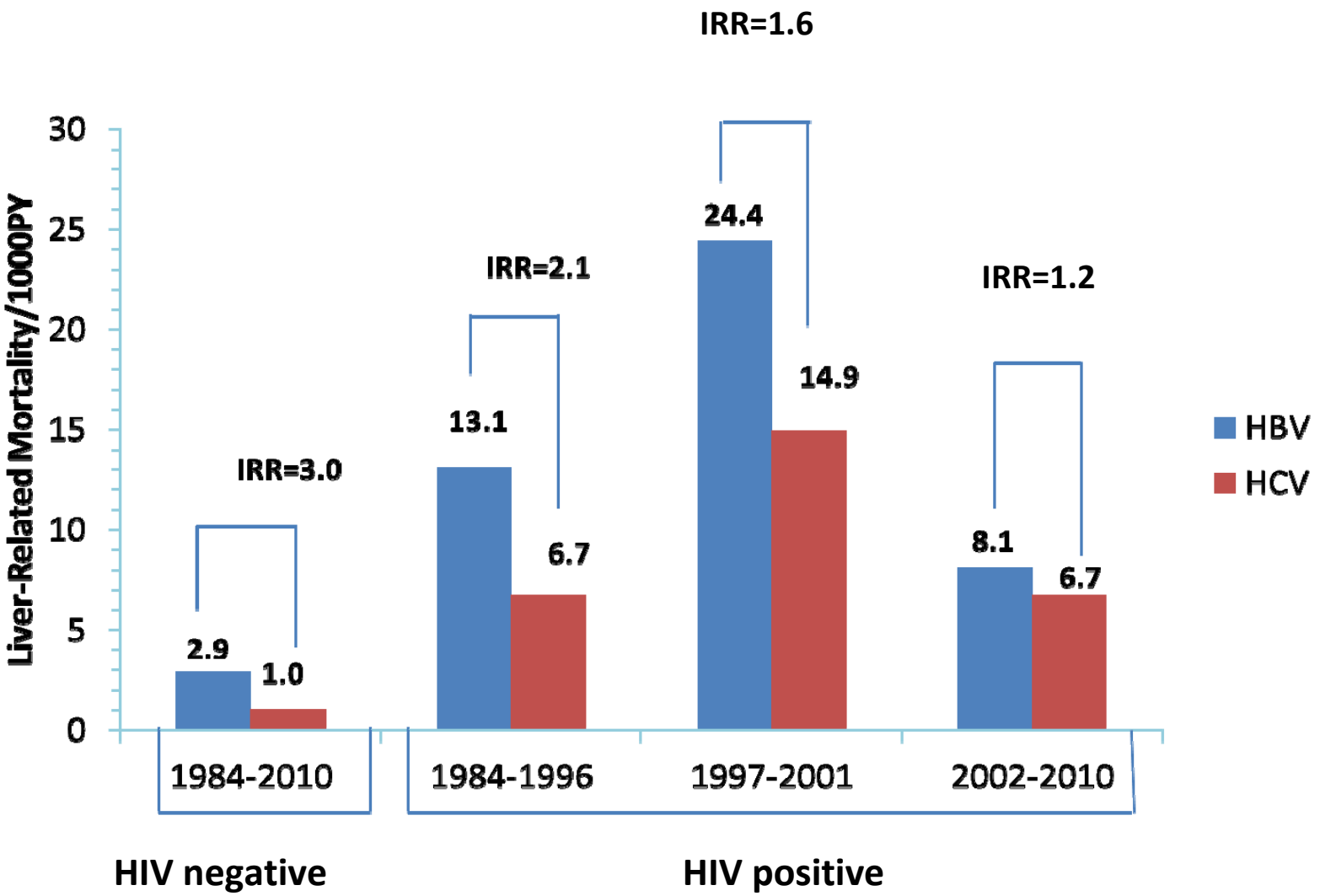


Number at Risk

Never infected	350	326	250	191	125
Past infection	357	324	278	246	193
Chronic hepatitis B	45	41	31	27	16
Isolated core	64	53	35	31	23

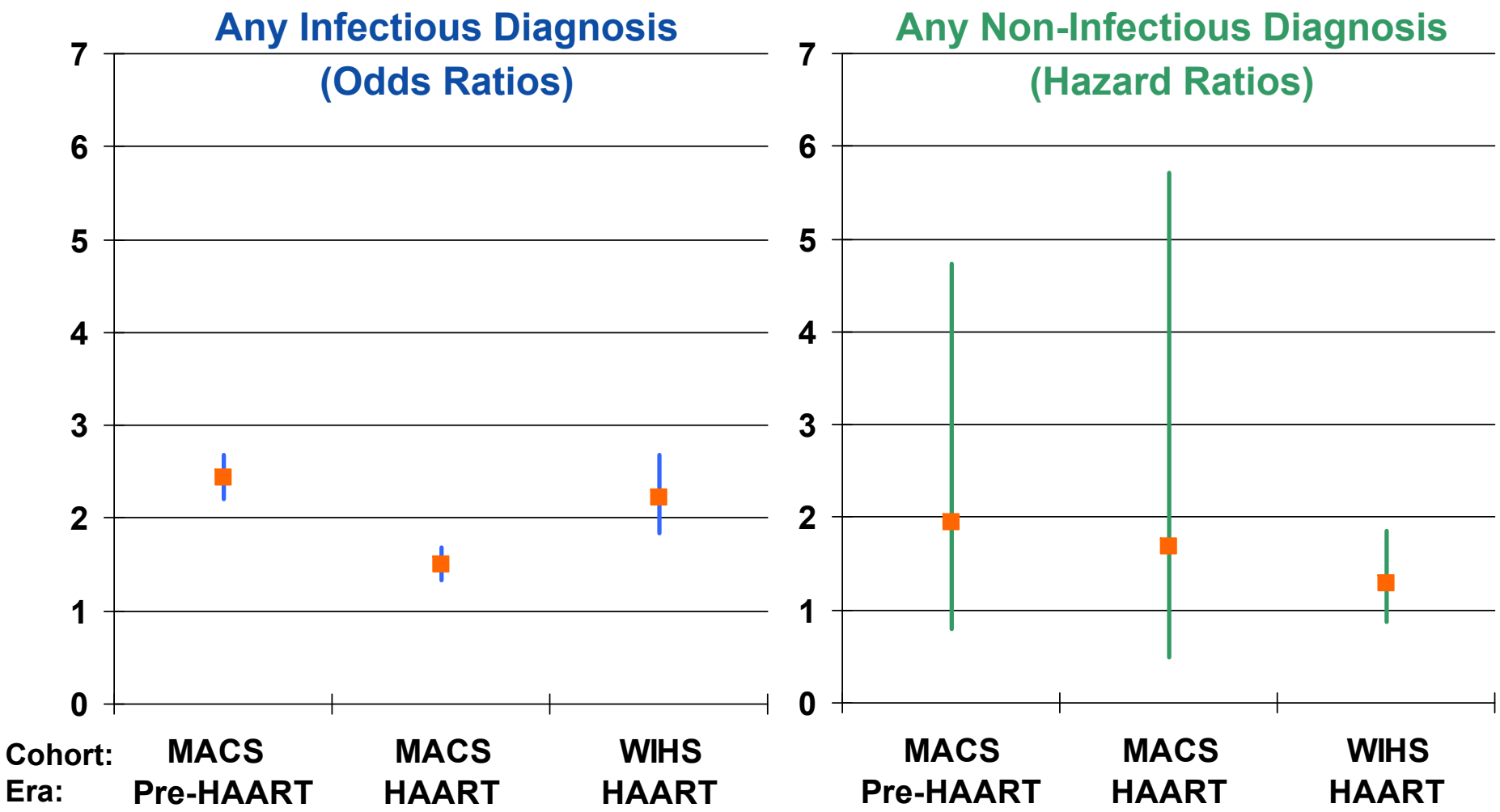
Time Trend in Liver-Related Mortality Rates by Hepatitis and HIV-1 Status

Falade-Nwulia, Seaberg, …, Thio - Clin Infect Dis 2012;55:507-13



Infectious and Non-Infectious Respiratory Complications in HIV-Infected Compared to Uninfected Persons

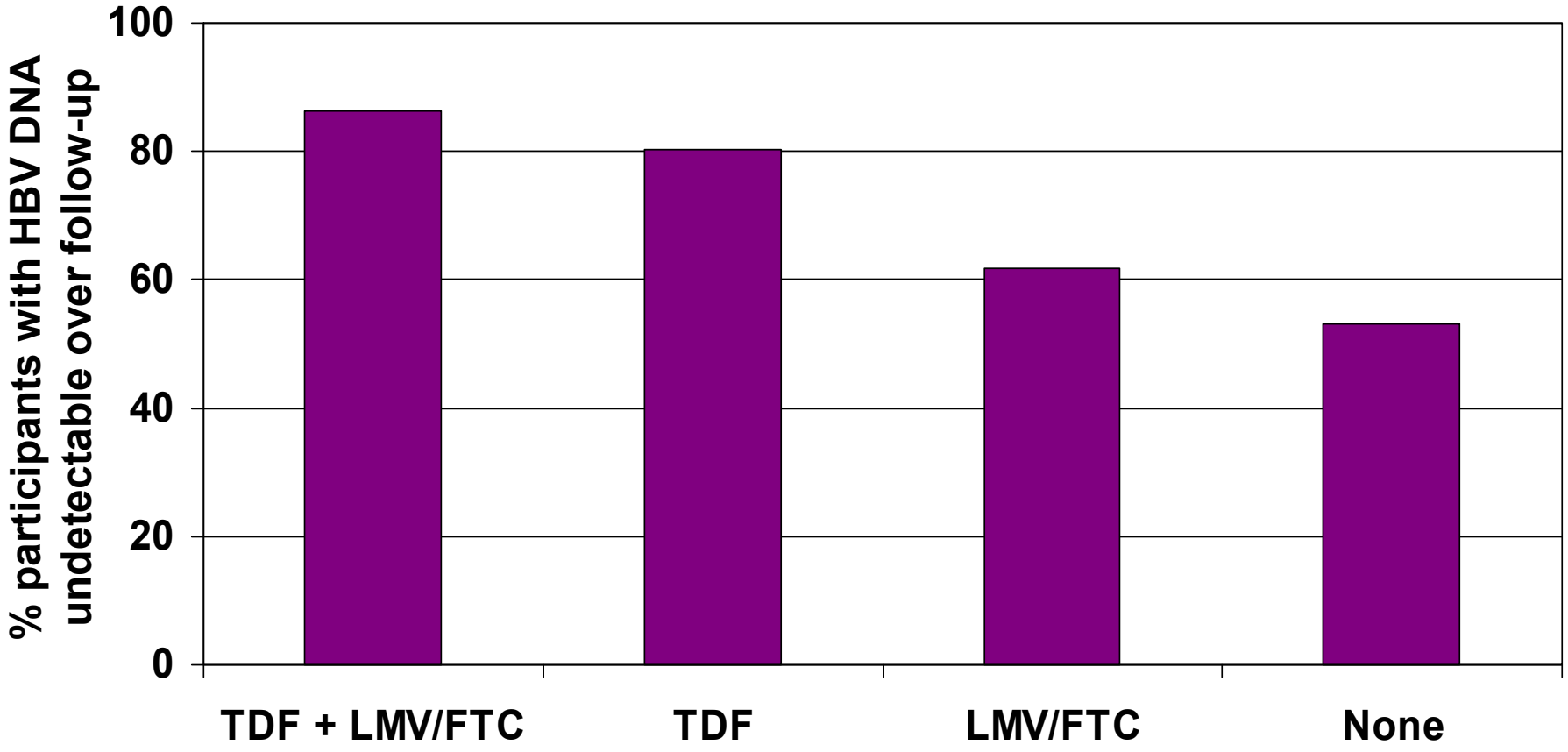
Gingo, Balasubramani, …, Morris - PLoS ONE 2013;8:e58812



November 2013

Proportion of Participants HBV DNA Undetectable by HBV Regimen

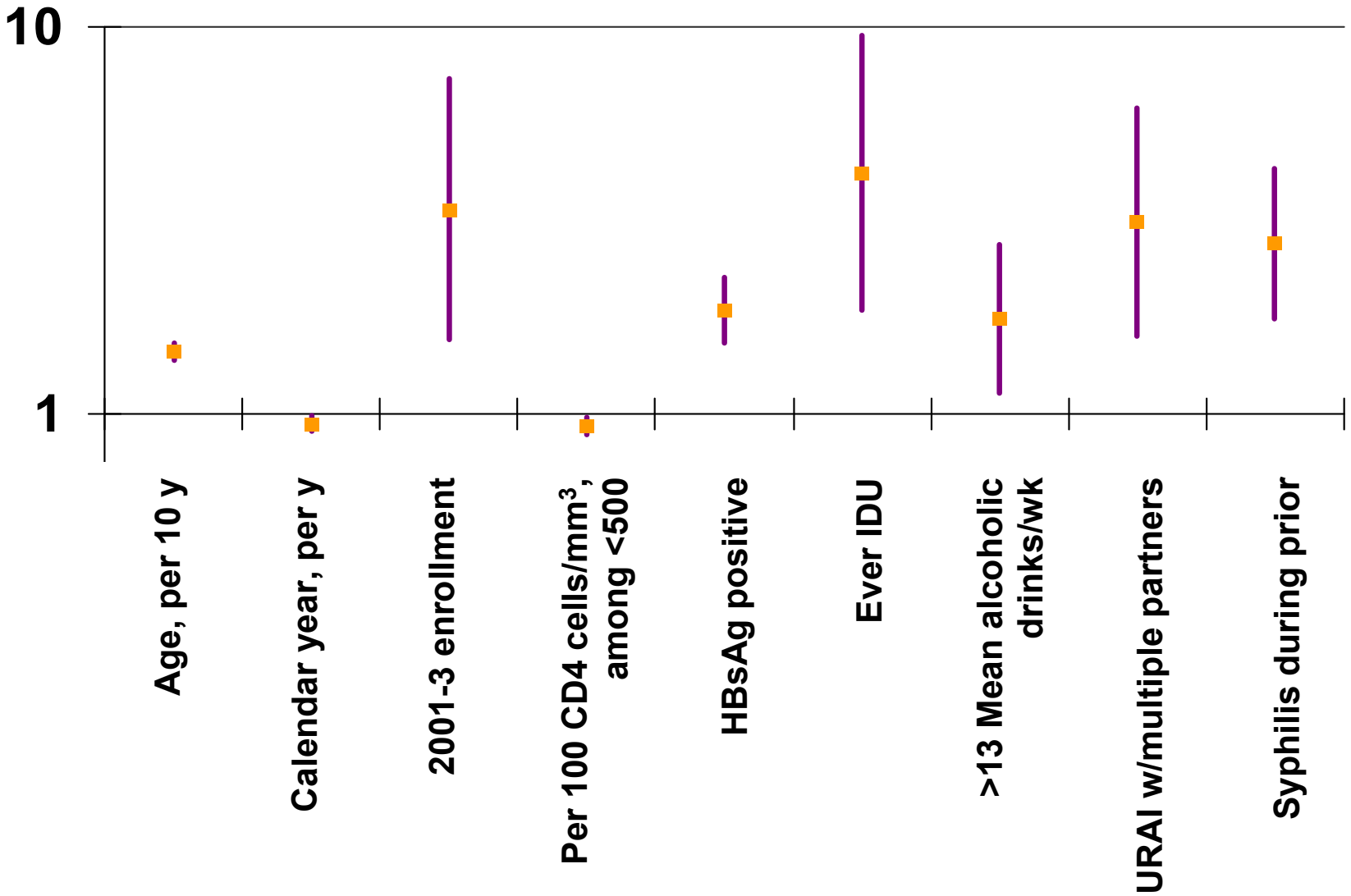
Matthews, Seaberg, …, Thio - Clin Infect Dis 2013;56:e87-e94



Proportion of individuals coinfected with HIV and HBV with undetectable HBV DNA by HBV active regimen.
Abbreviations: FTC = emtricitabine; LMV = lamivudine; TDF = tenofovir

Incident Rate Ratios for Incident HCV Infection in HIV + Subjects

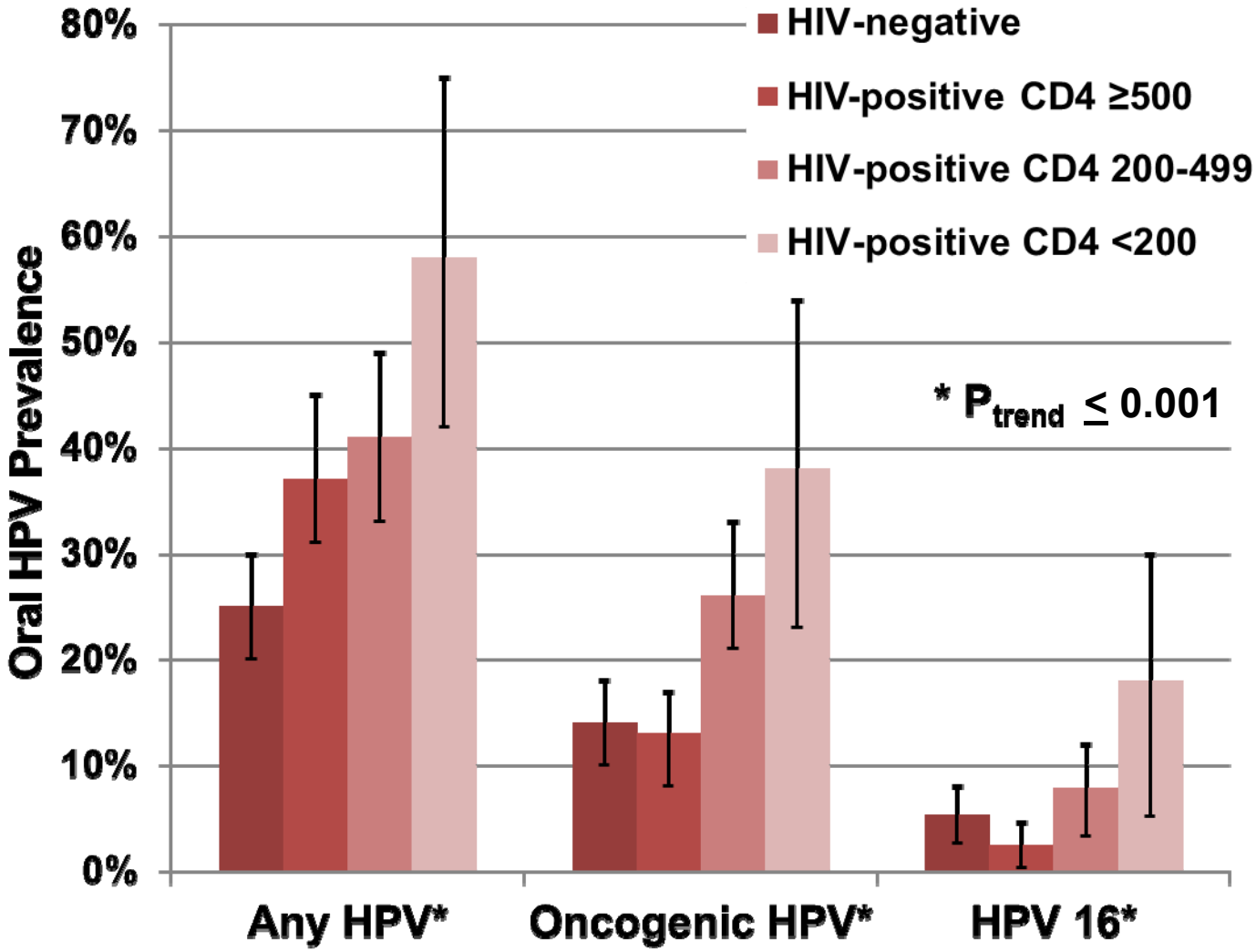
Witt, Seaberg, …, Thio - Clin Infect Dis 2013;57:77-84



- HCV incident rate per 1000 PY: 4.22 for HIV^{+} and 0.50 for HIV^{-}

Oral HPV Prevalence (Unadjusted) by HIV Status and Current CD4 T-cell Count Among 370 HIV-Positive Individuals

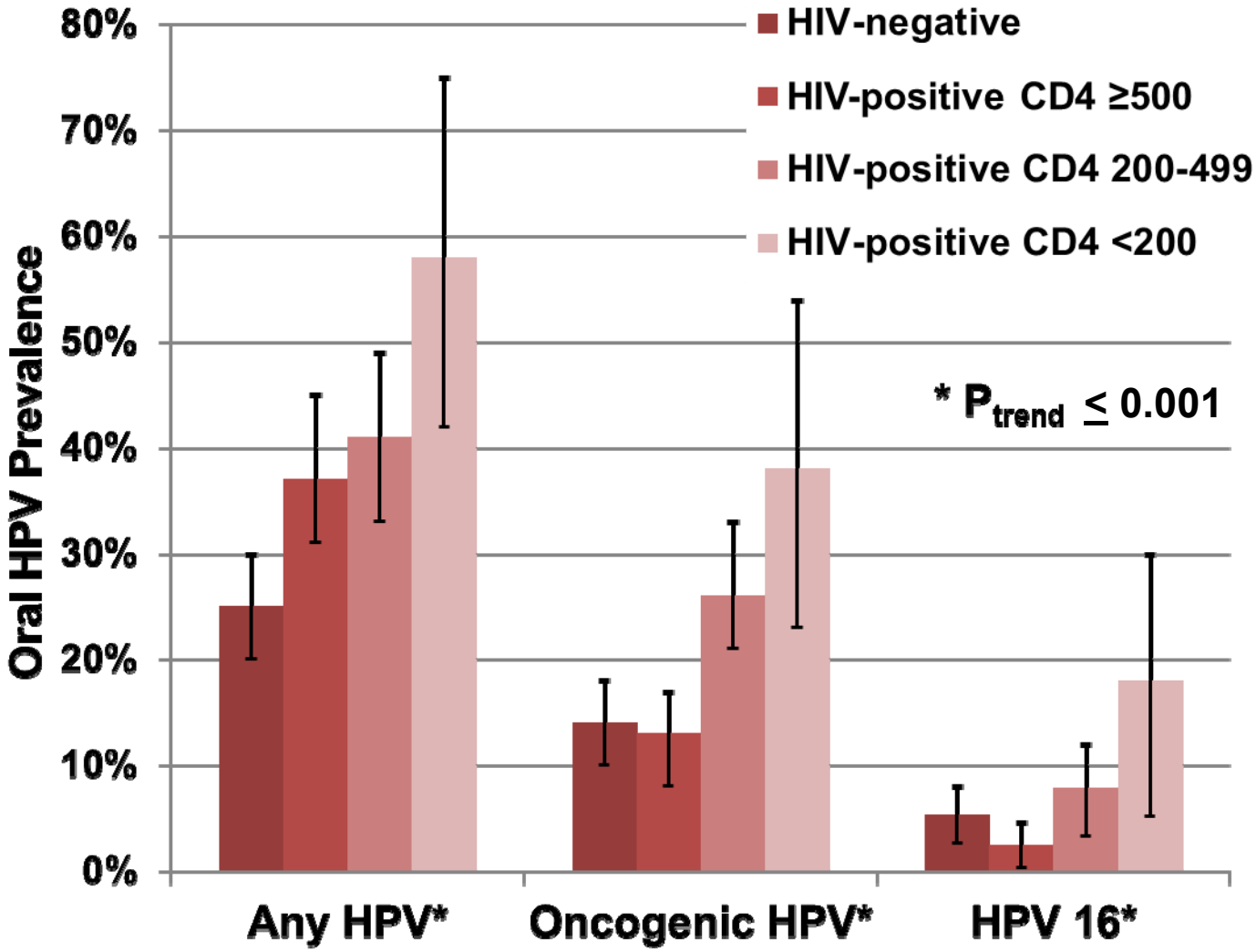
Beachler, Weber, …, D'Souza. Cancer Epidemiol Biomarkers Prev 2012



May 2012

Oral HPV Prevalence (Unadjusted) by HIV Status and Current CD4 T-cell Count Among 370 HIV-Positive Individuals

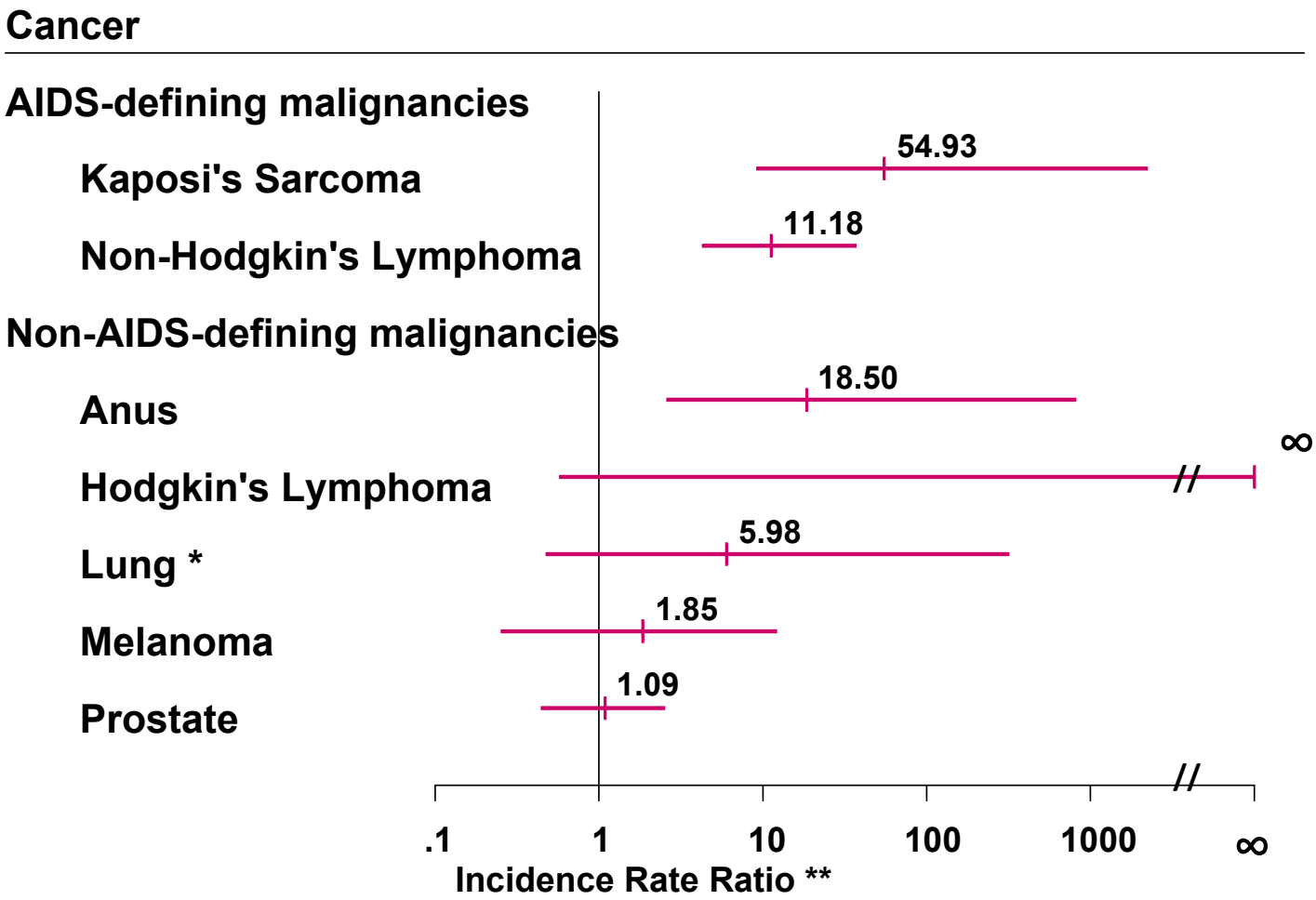
Beachler, Weber, …, D'Souza. Cancer Epidemiol Biomarkers Prev 2012



May 2012

Cancer Incidence among HIV-infected vs. HIV-uninfected MACS Participants in the HAART Era

Seaberg, Wiley, …, Jacobson. Cancer 2010



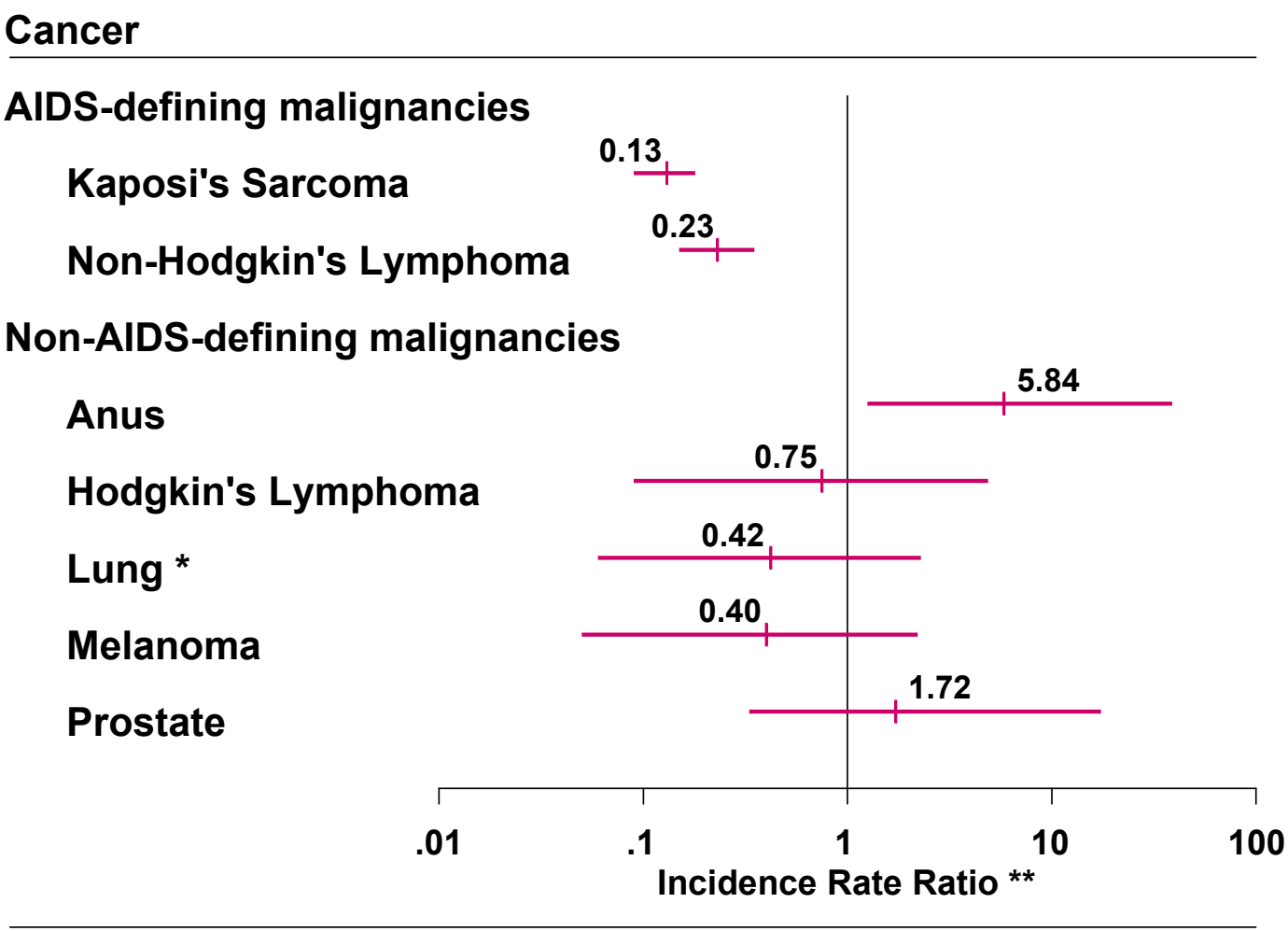
* Among participants with a history of smoking.

** Adjusted for age and race.

May 2011

Cancer Incidence in the HAART Era vs. the Pre-HAART Era among HIV-infected MACS Participants

Seaberg, Wiley, …, Jacobson. Cancer 2010



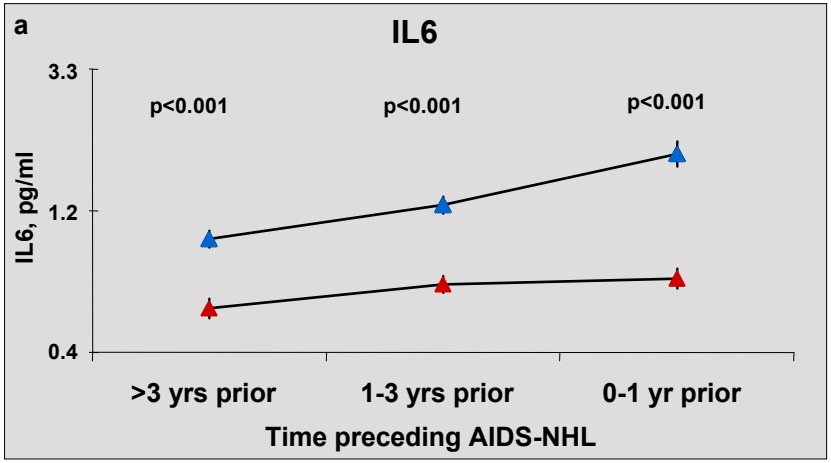
* Among participants with a history of smoking.

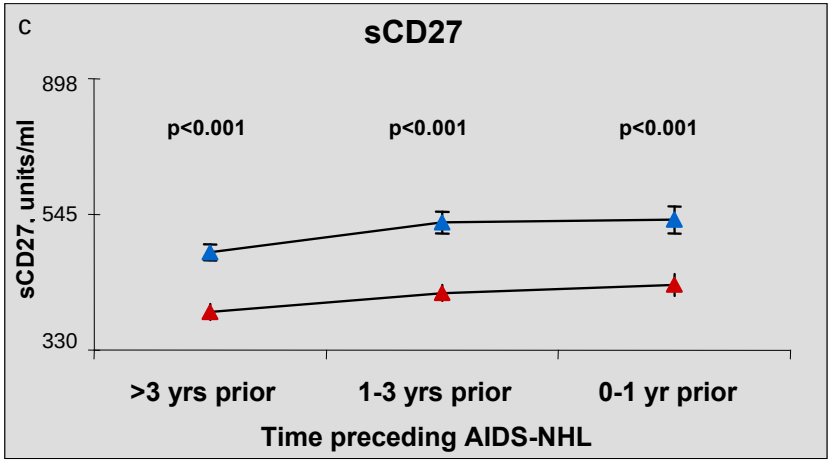
** Adjusted for age and race.

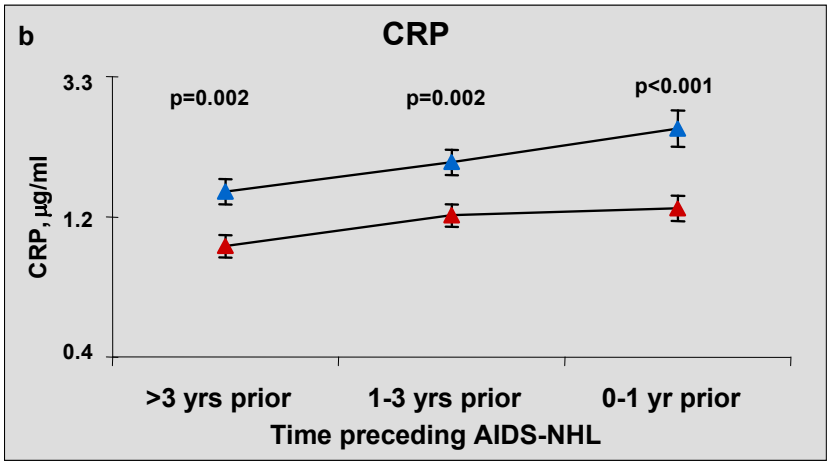
May 2011

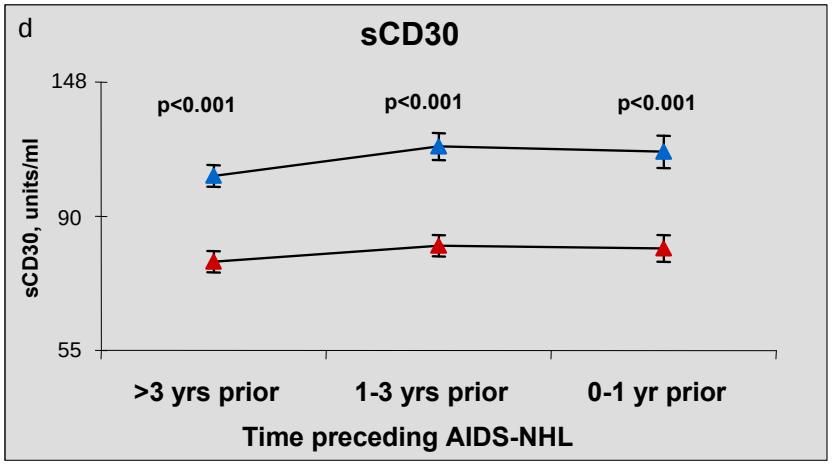
Mean Serum Levels of Several B Cell Activation-associated Molecules are Consistently Elevated More than 3 Years Preceding AIDS-associated Lymphoma Diagnosis

Breen, Hussain, …, Martínez-Maza. Cancer Epidemiol Biomarkers Prev 2011







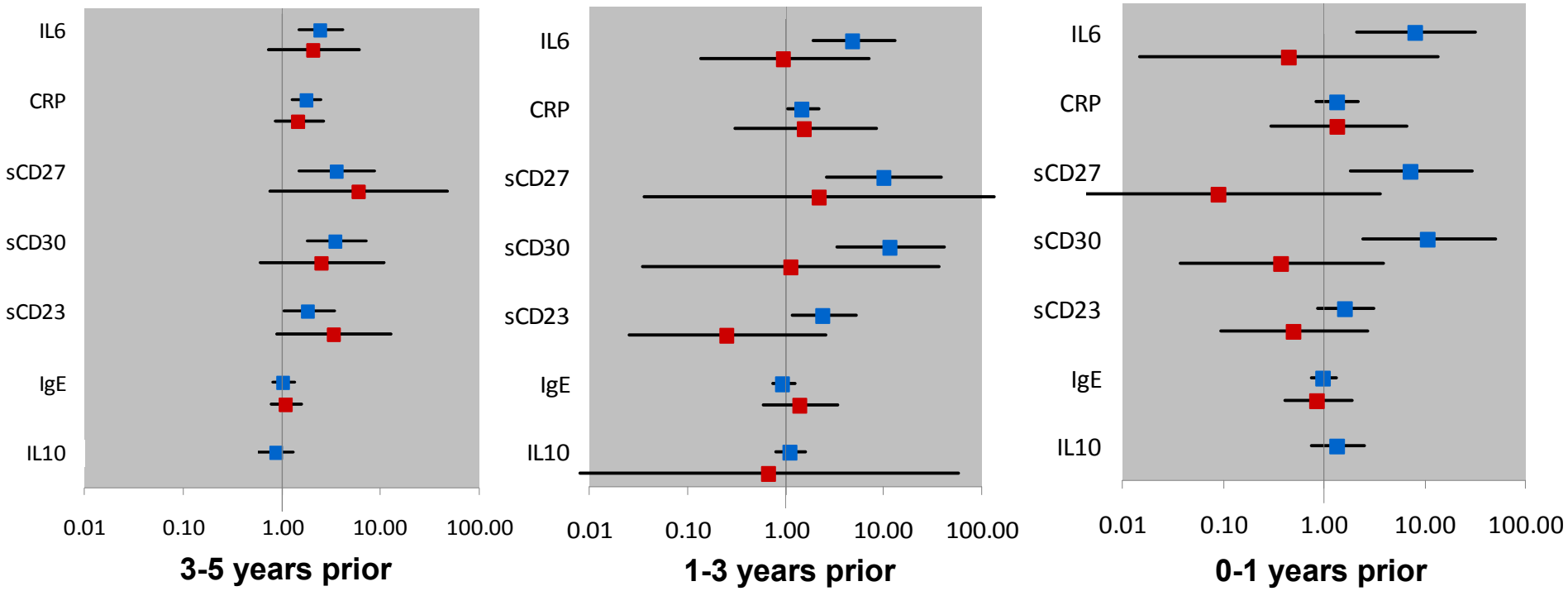


Natural log-transformed mean values (± s.e.m.) for HIV-infected subjects who went on to develop AIDS-NHL (▲) and HIV-infected controls without lymphoma (▲)

May 2012

Elevated Levels of B Cell Activation Markers Prior to AIDS-NHL are Seen Only in Those Subjects Who Develop Systemic Lymphoma

Breen, Hussain, …, Martínez-Maza. Cancer Epidemiol Biomarkers Prev 2011

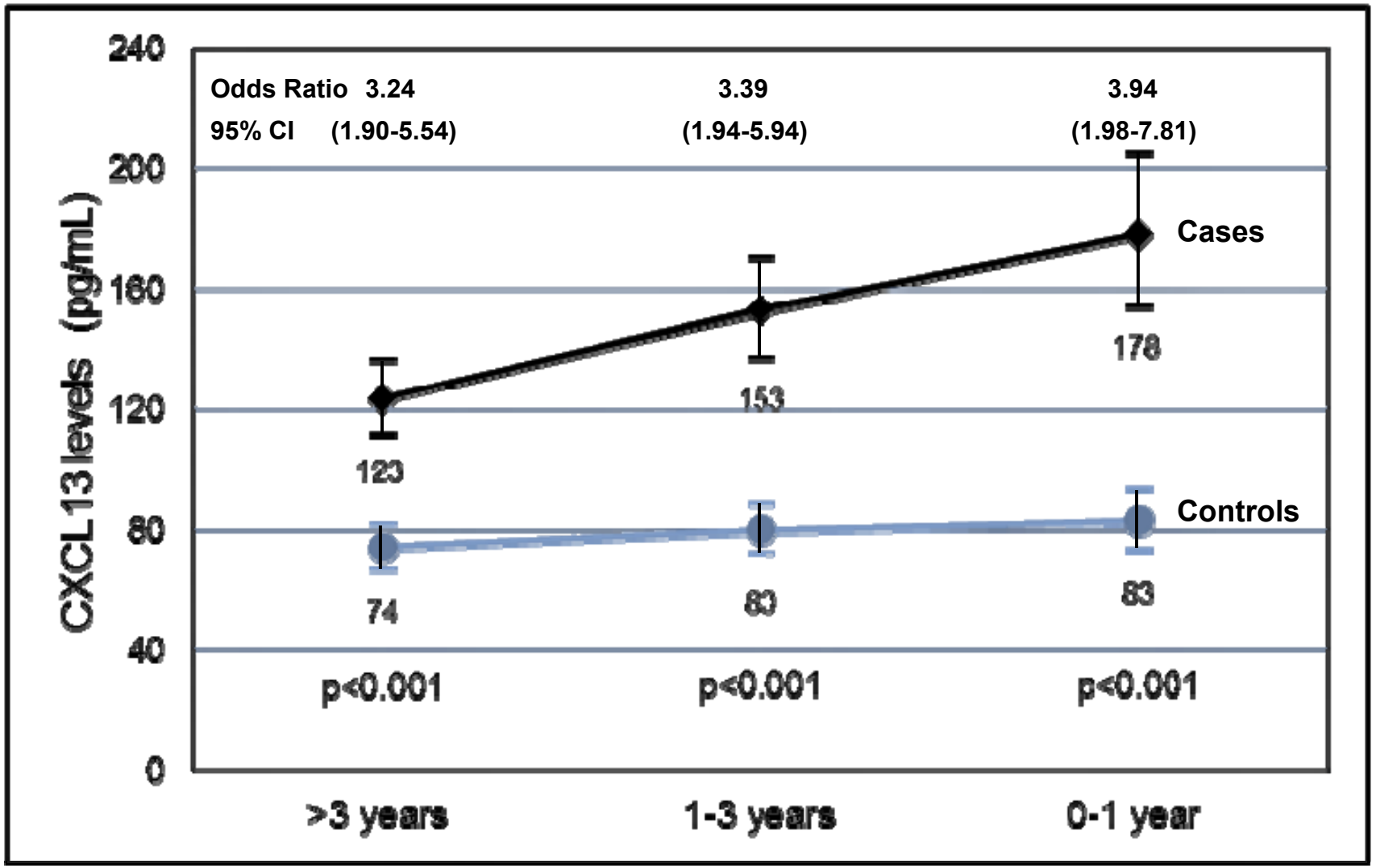


CD4-adjusted odds ratios (OR) ± 95% confidence intervals (CI) for increased serum cytokine levels are shown for AIDS-NHL cases compared to matched HIV+ controls, stratified according to primary tumor location outside of the central nervous system (systemic, ■) or within the central nervous system (CNS, ■). For all markers except IL10, ORs are in terms of one unit increase in natural log-transformed values; for IL10, ORs are in terms of detectable vs. undetectable. ORs are missing for IL10 for CNS tumors at two time-points (>3 years and 0-1 year) due to failure of the logistic regression model to converge on account of sparse data.

May 2012

CXCL13 Levels in HIV-Positive Non-Hodgkin Lymphoma Cases and Controls

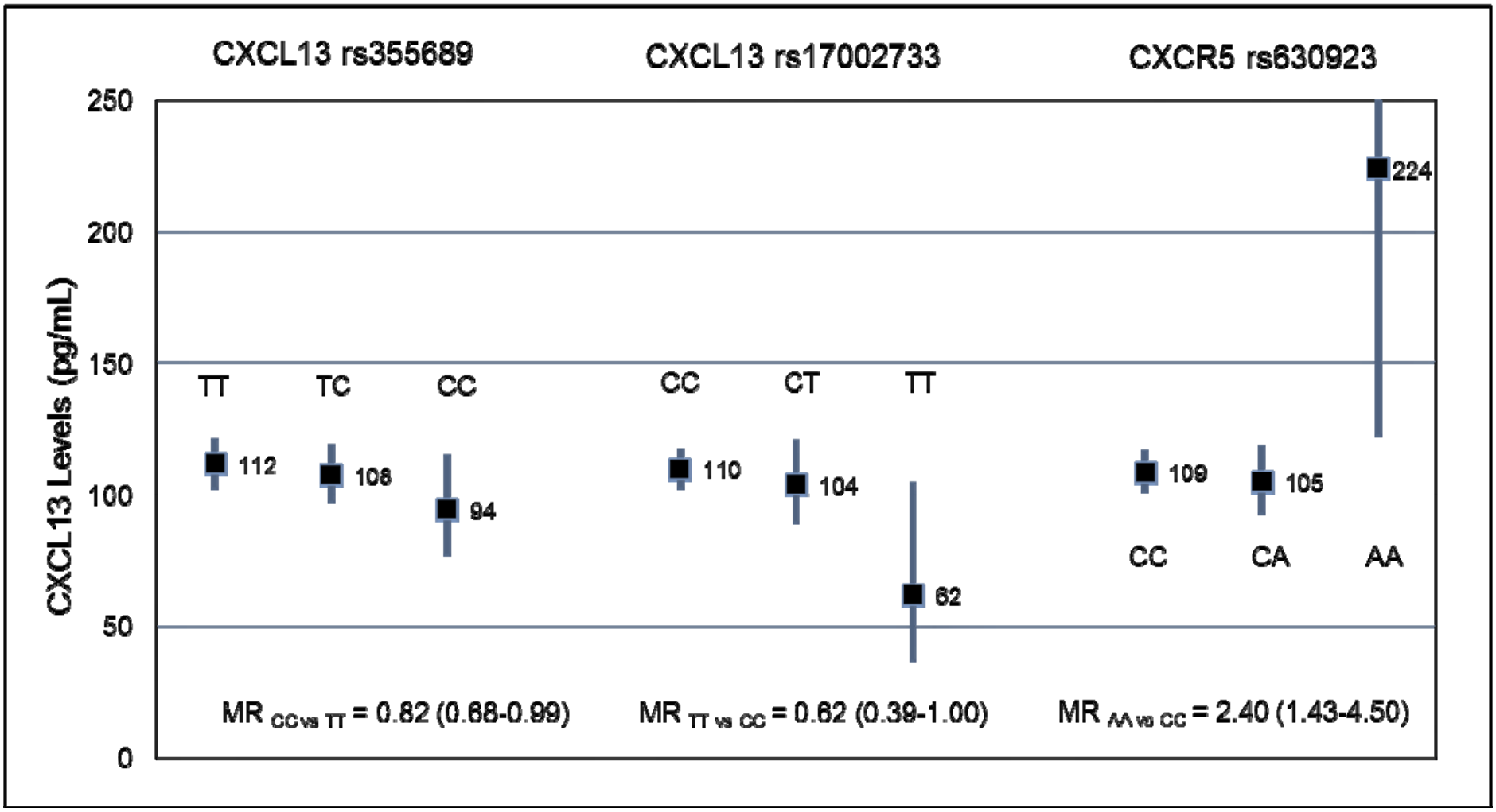
Hussain, Zhu, …, Martinez-Maza - Cancer Epidemiol Biomarkers Prev 2013;22:295-307



November 2013

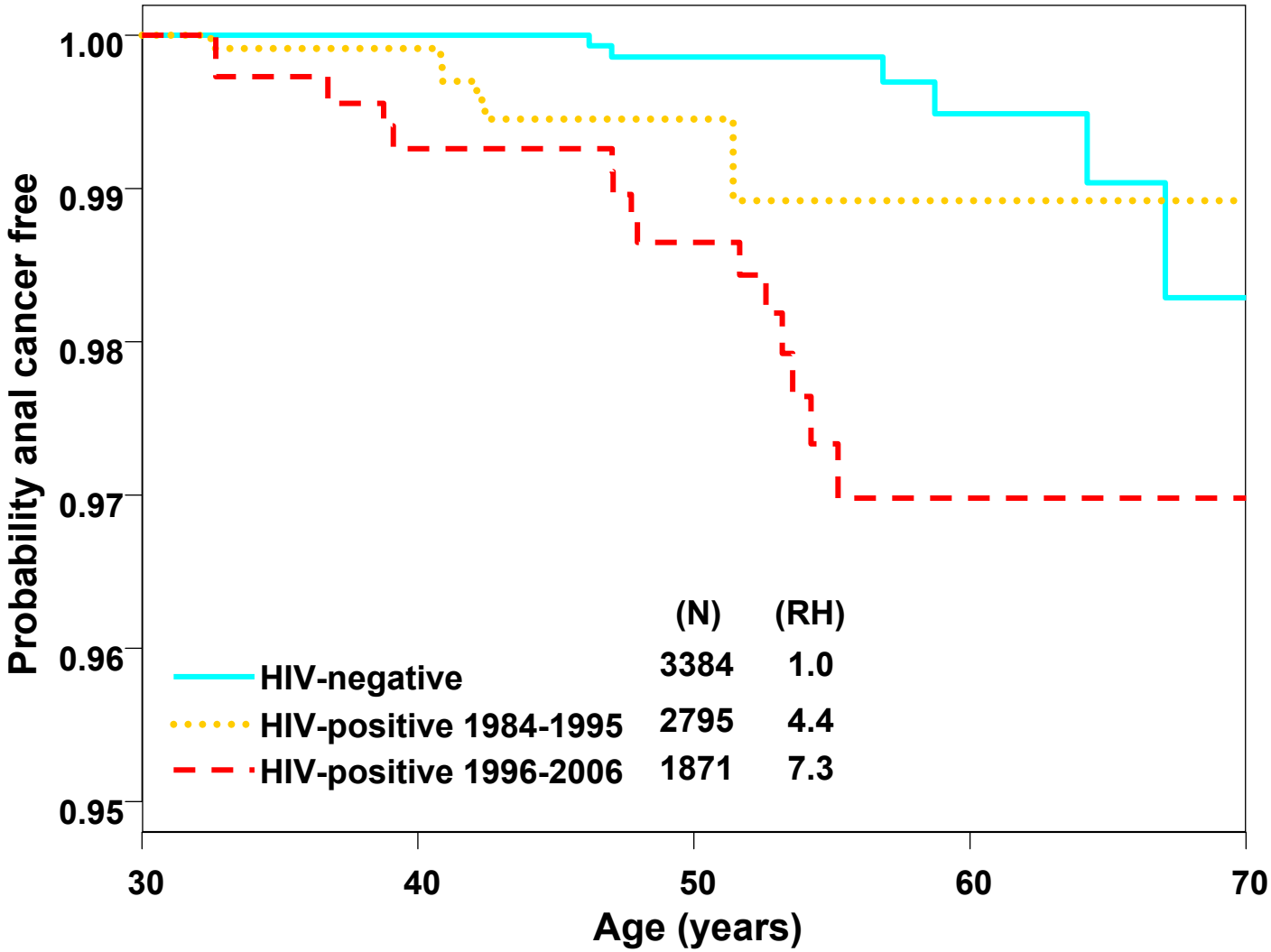
CXCL13 Levels by CXCL13 and CXCR5 tagSNPs

Hussain, Zhu, …, Martinez-Maza - Cancer Epidemiol Biomarkers Prev 2013;22:295-307



Time Free of Anal Cancer
HIV+ Men Pre-HAART and HAART Era
vs HIV- Men

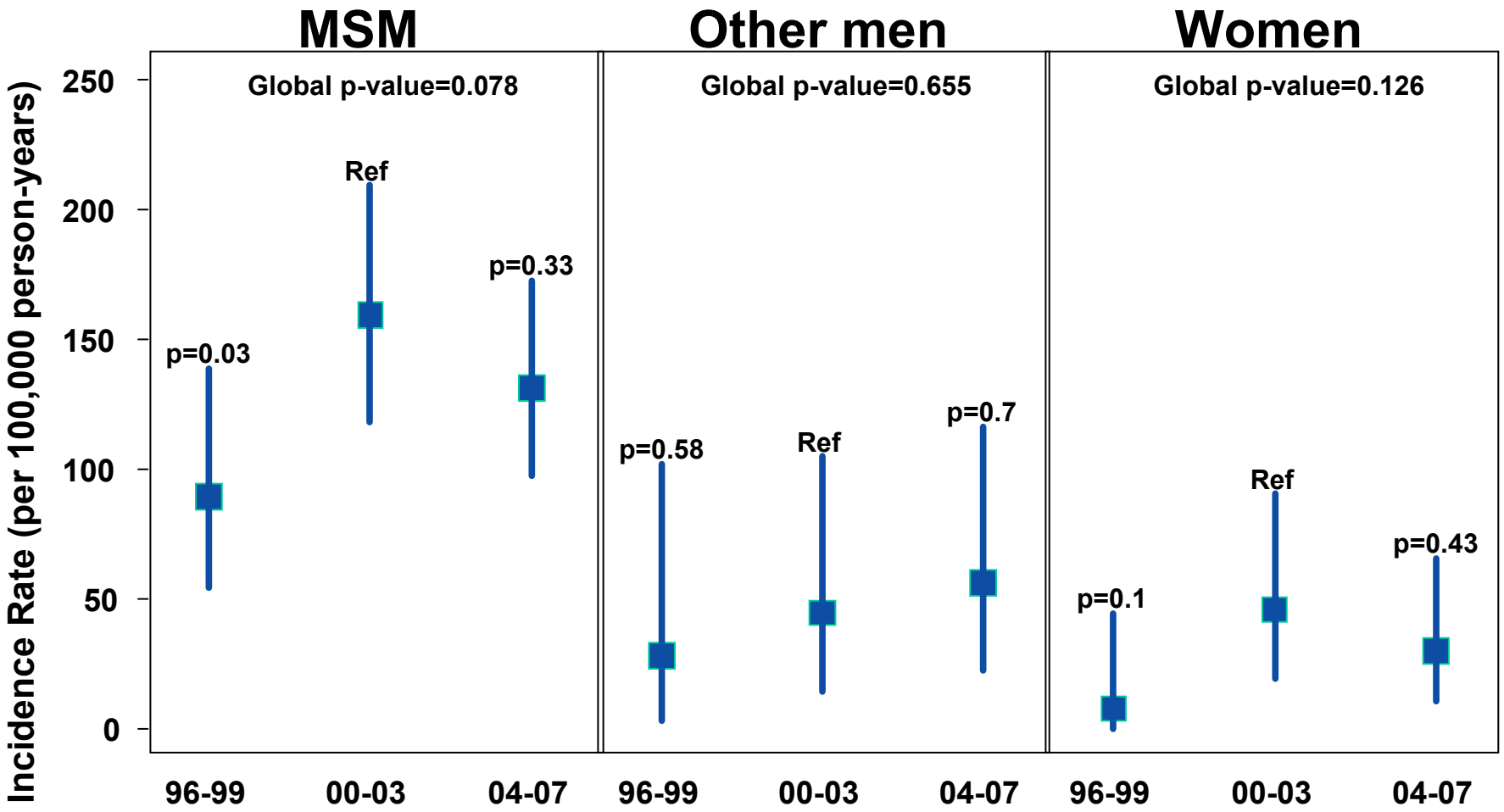
D'Souza, Wiley, . . ., Jacobson - JAIDS 2008



May 2009

Anal Cancer Incidence Rates by Calendar Era for HIV+ Men Who have Sex with Men, Other Men, and Women, NA-ACCORD, Years 1996-2007

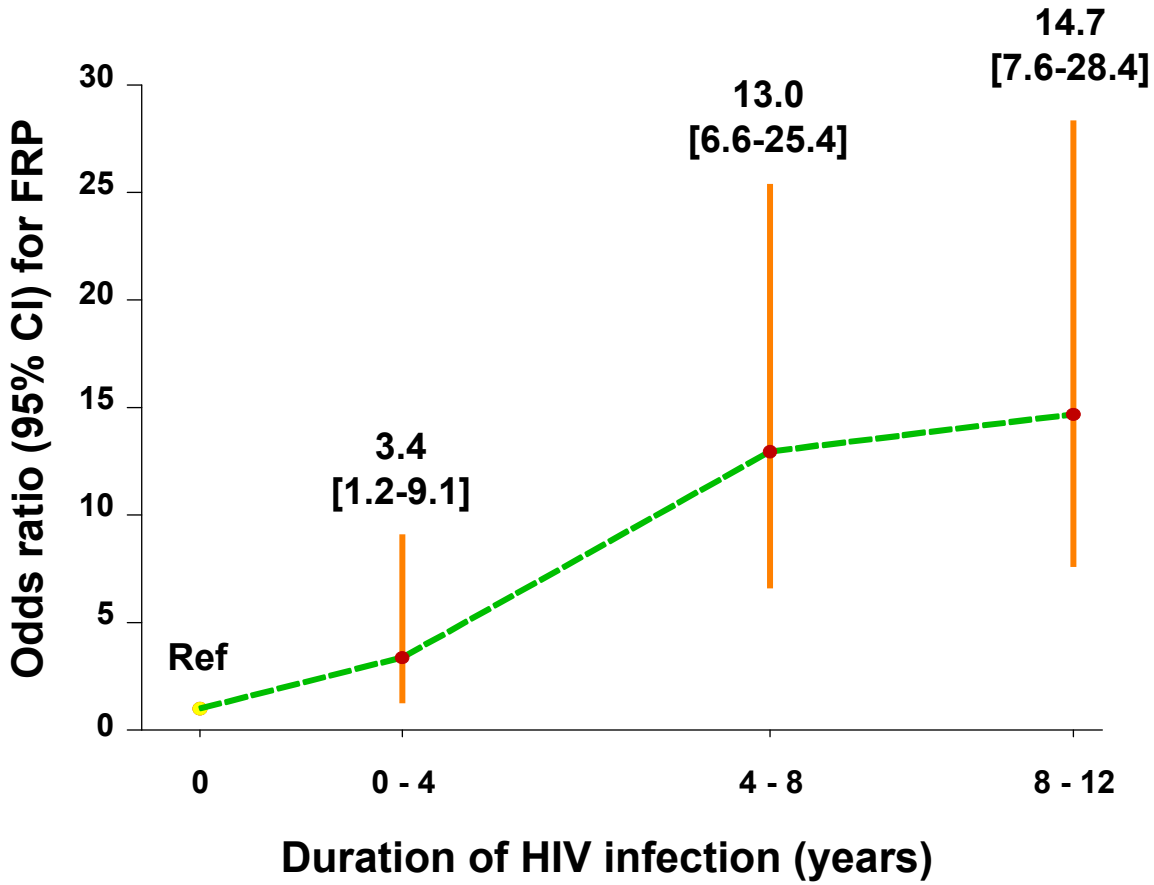
Silverberg, Lau, …Dubrow, Clinical Infectious Diseases, 2012;54:1026–34.



November 2013

Frailty-Related Phenotype (FRP) by Duration of HIV Infection (Pre-HAART)

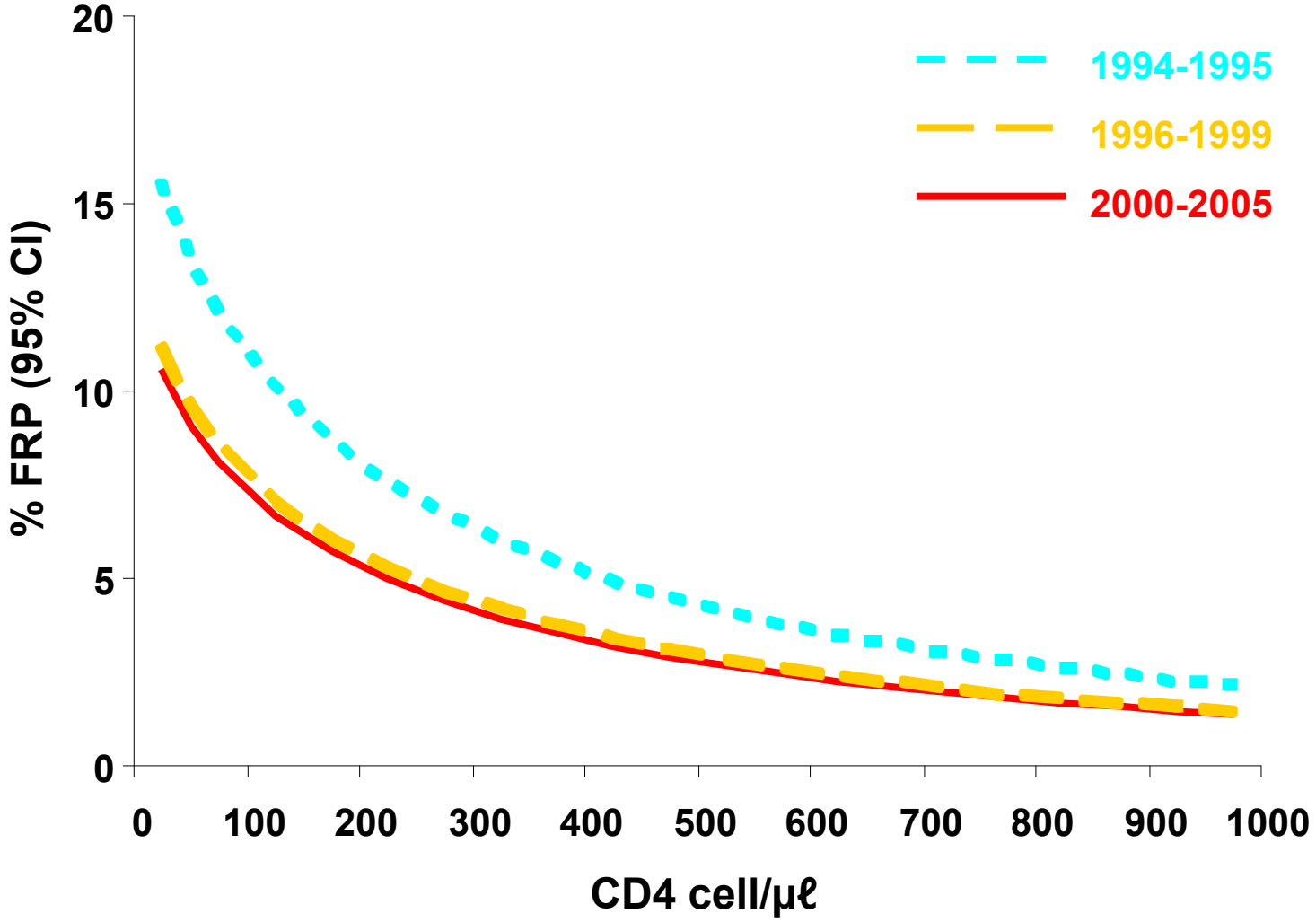
Desquilbet, Jacobson, …, Margolick.
J Gerontol A Biol Sci Med Sci 2007;62a:1279-86



- **Same FRP prevalence between a 55-year old man infected < 4 years and a >65-year old uninfected man**

Estimated Prevalence of Frailty Phenotype (FRP) According to CD4+ Cell Count and Calendar Period (Age = 45 years)

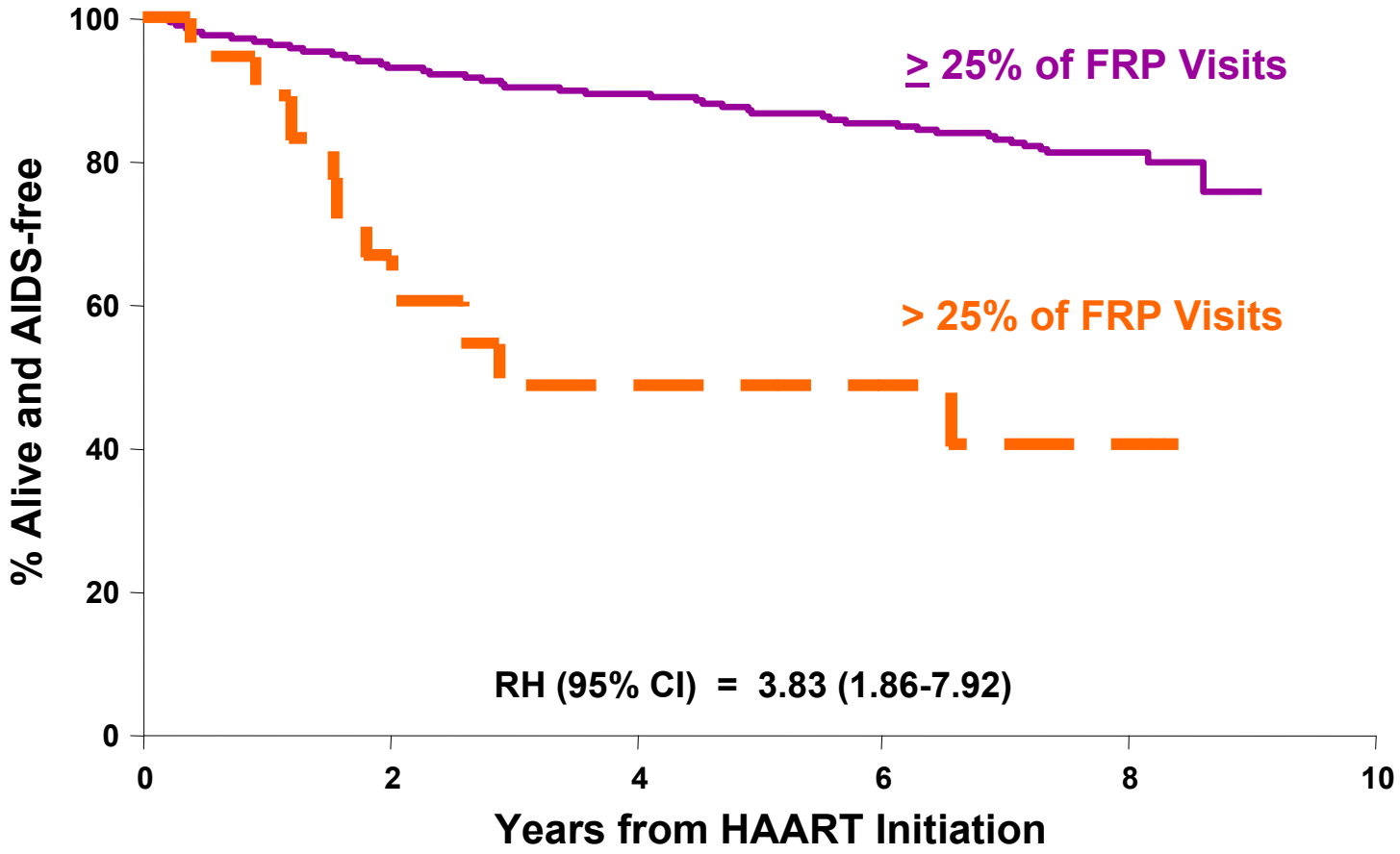
Desquilbet, Margolick, . . ., Jacobson - JAIDS 2009



May 2009

Prognostic Effect of Persistent Frailty-related Phenotype (FRP) per-HAART on AIDS/Death Following HAART Initiation

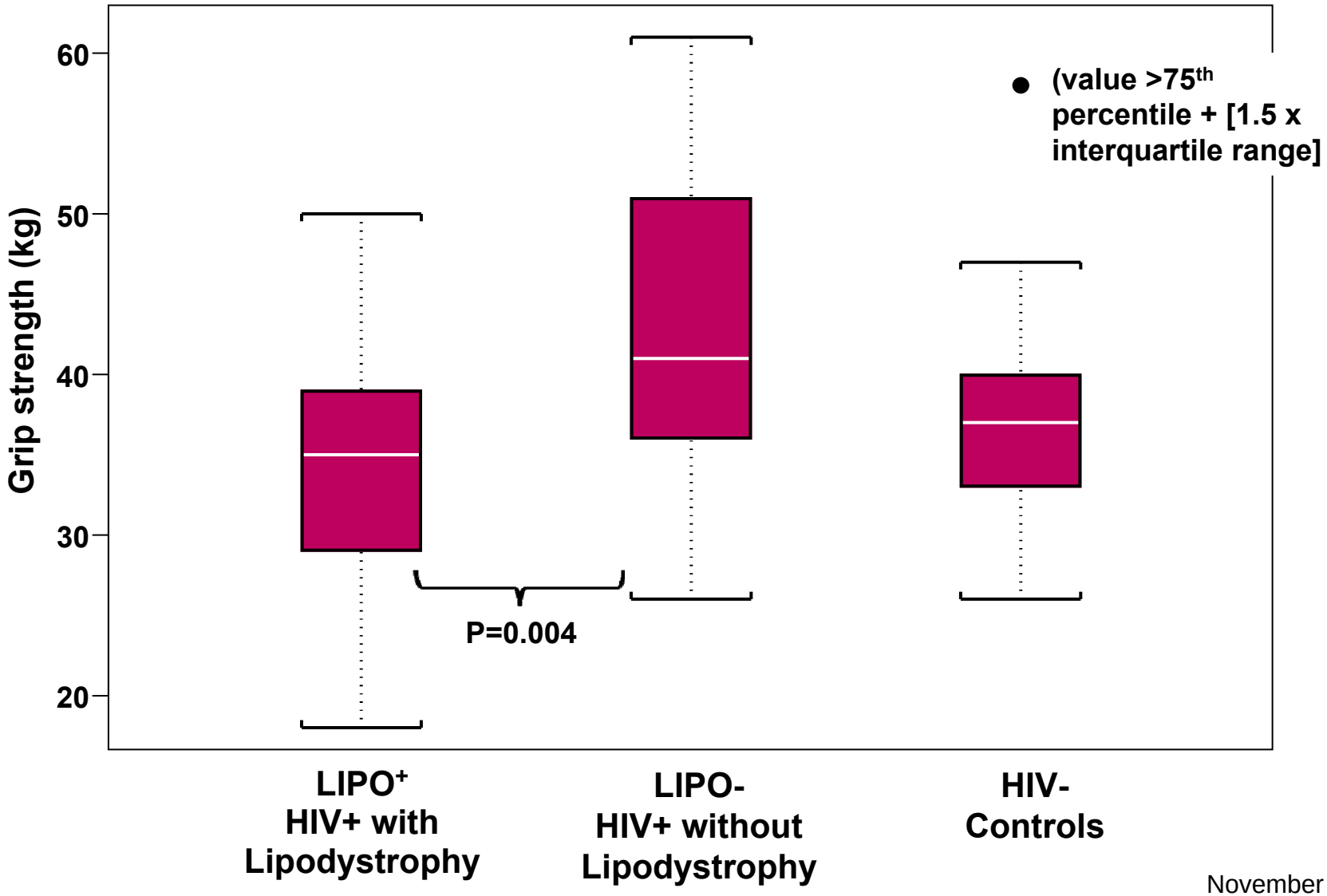
Desquilbet, Jacobson, …, Margolick. J Gerontol Med Sci 2011



N men at risk	0	2	4	6	8
≥25% of FRP visits	454	401	353	287	127
>25% of FRP visits	18	13	8	7	3

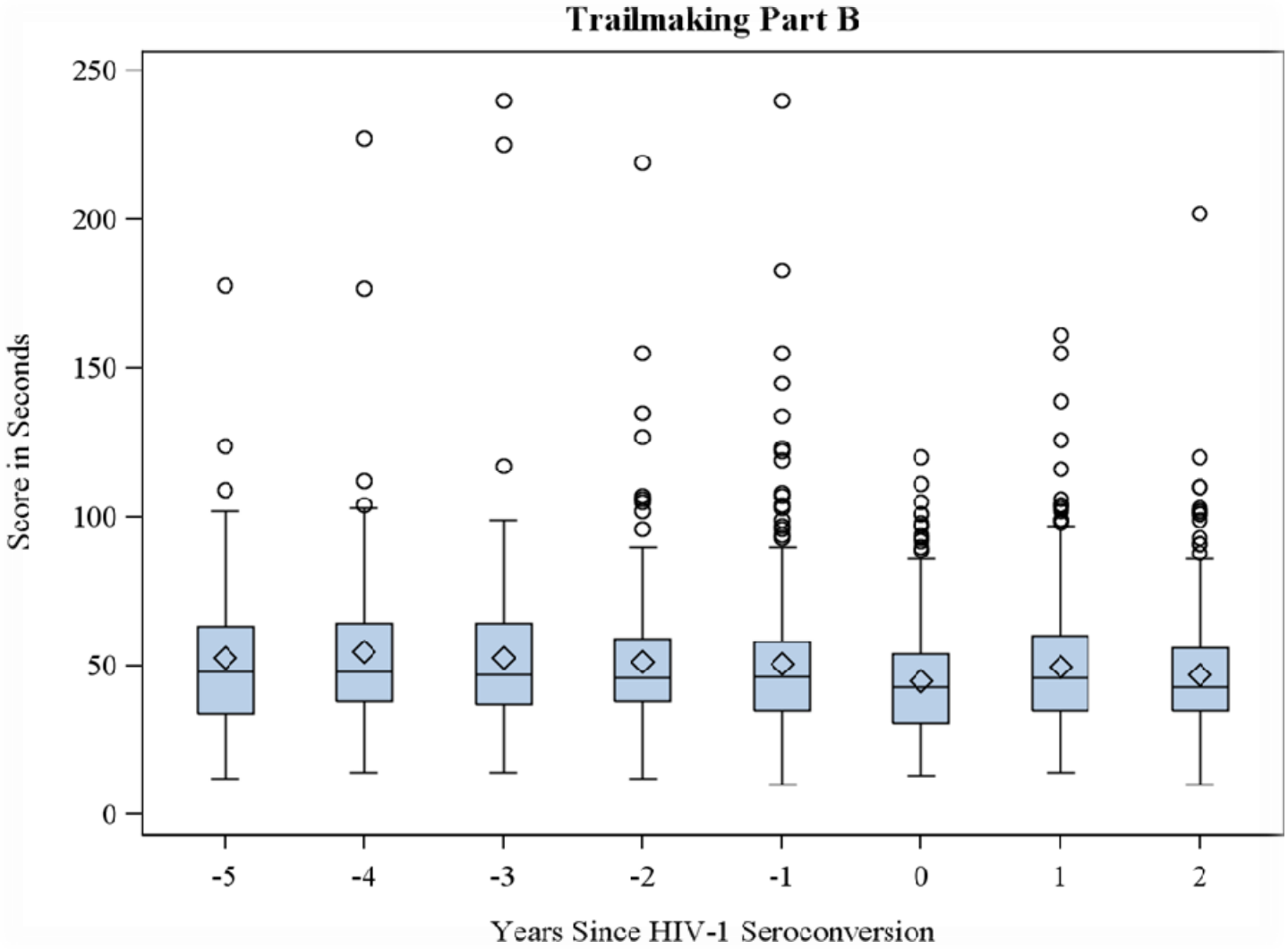
Distribution of Grip Strength in HIV-Infected Men with and without Lipodystrophy, and HIV-Uninfected Controls

Crawford, Li, …, Brown - AIDS Res Hum Retroviruses 2013;29:1138-45



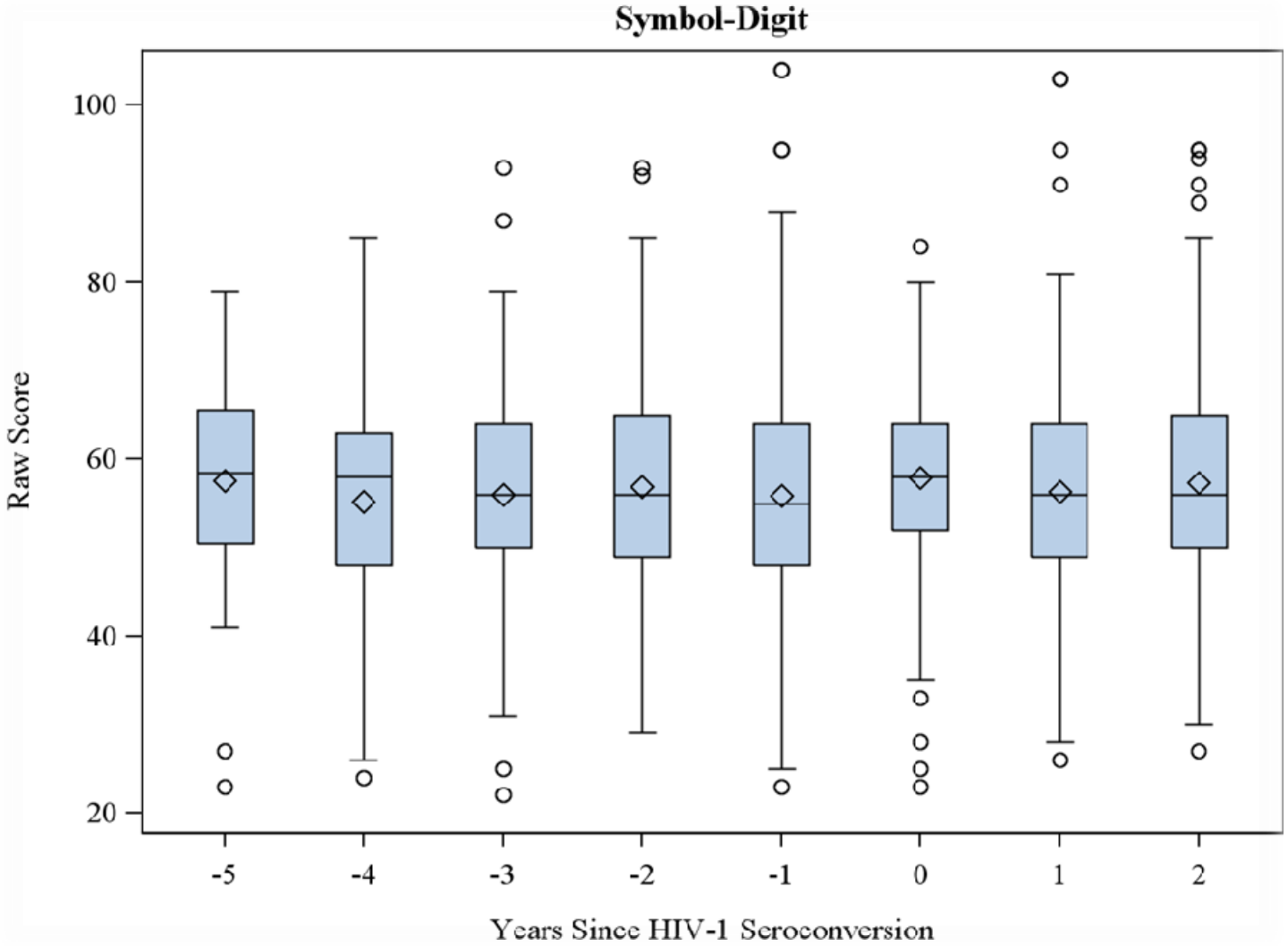
Mean Trail-Making B Scores Around HIV-1 Seroconversion

Vo, Cox, …, Miller - J Neurovirol 2013;19:24-31



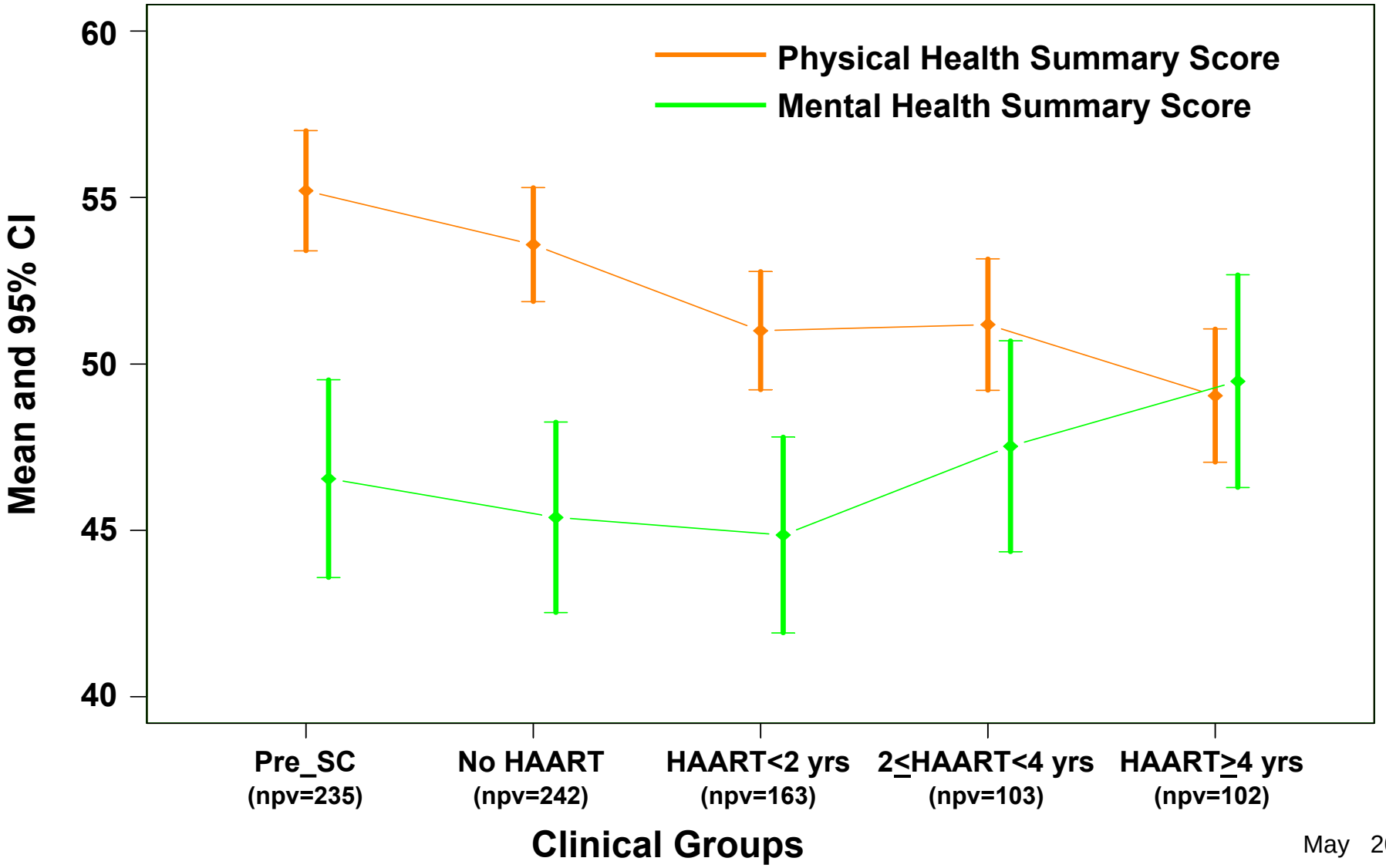
Mean Symbol-Digit Scores Around HIV-1 Seroconversion

Vo, Cox, …, Miller - J Neurovirol 2013;19:24-31



Mental and Physical Health Summary Score Change over the Course of HIV Disease Progression

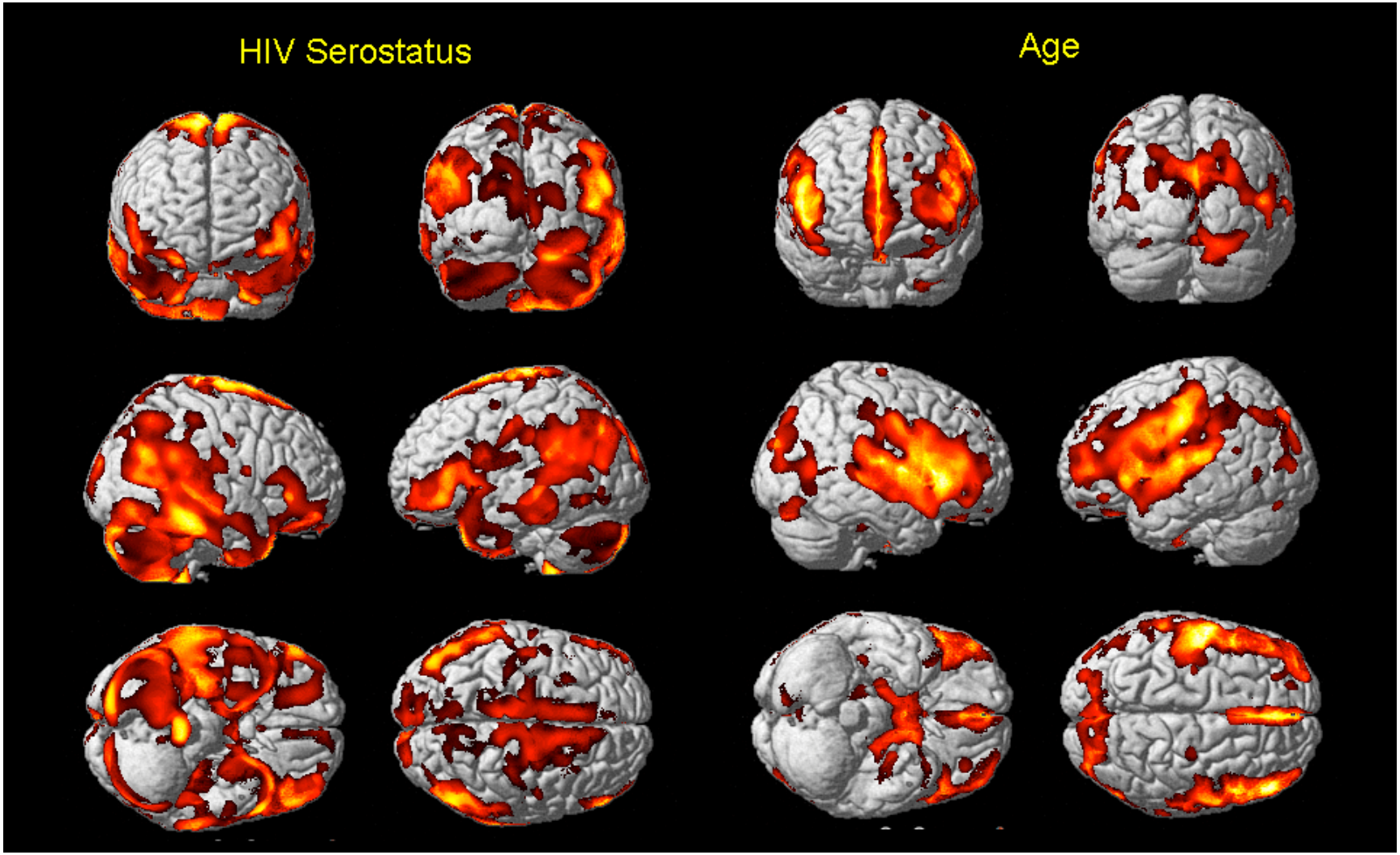
Liu, Ostrow, …, Jacobson. Qual Life Res 2006



May 2007

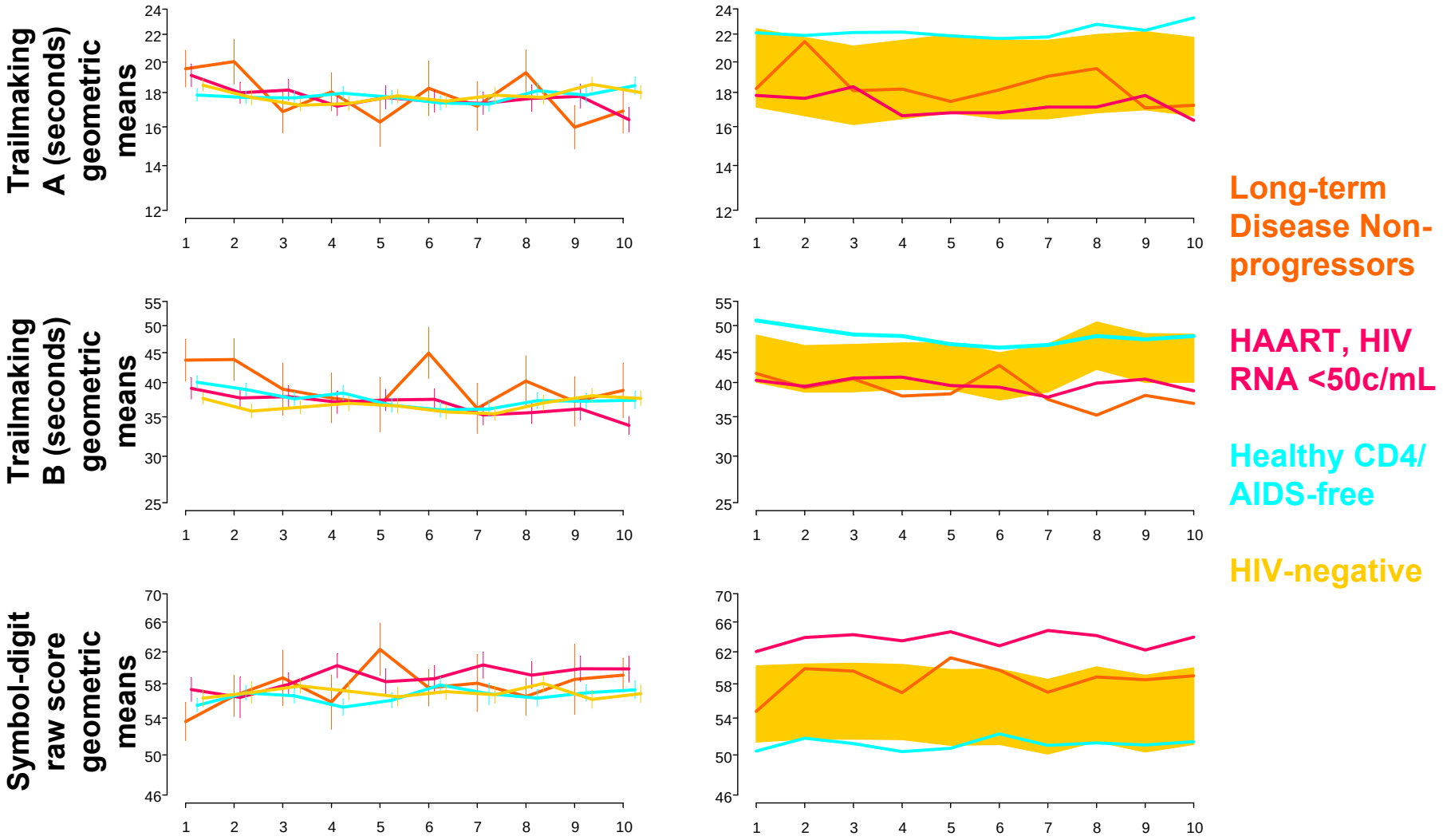
Surface Rendering of the Independent Effects of HIV Serostatus and Age on Grey Matter Volume

Becker, Maruca, …, Selnes - Neuroradiology 2012;54:113-21



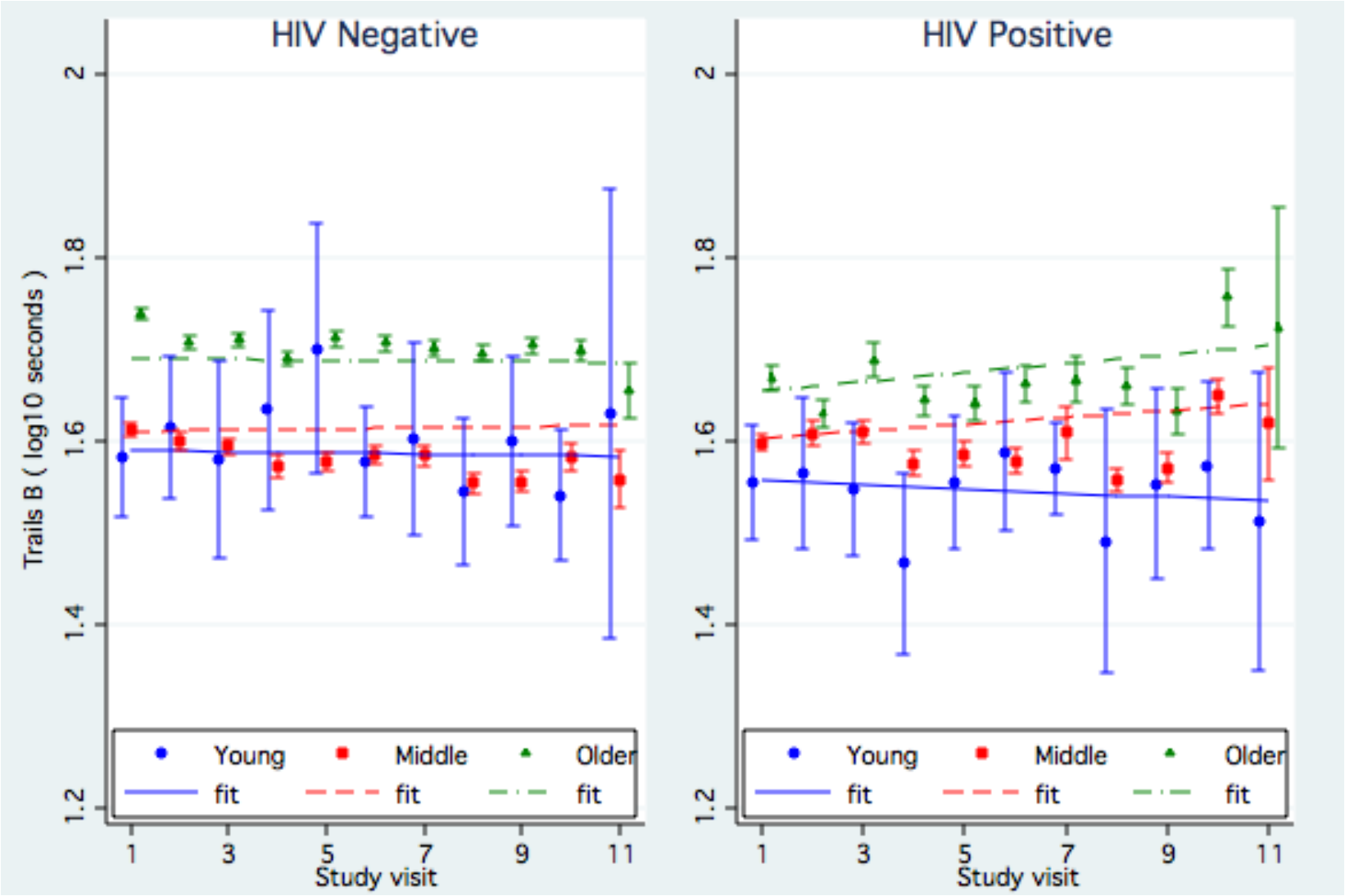
Longitudinally Preserved Psychomotor Performance in Long-Term Asymptomatic HIV-Infected Individuals

Cole, Margolick, …, Miller. Neurology 2007;69:2213-20



Trail Making Performance Over Time by HIV Status and Age HAART Era

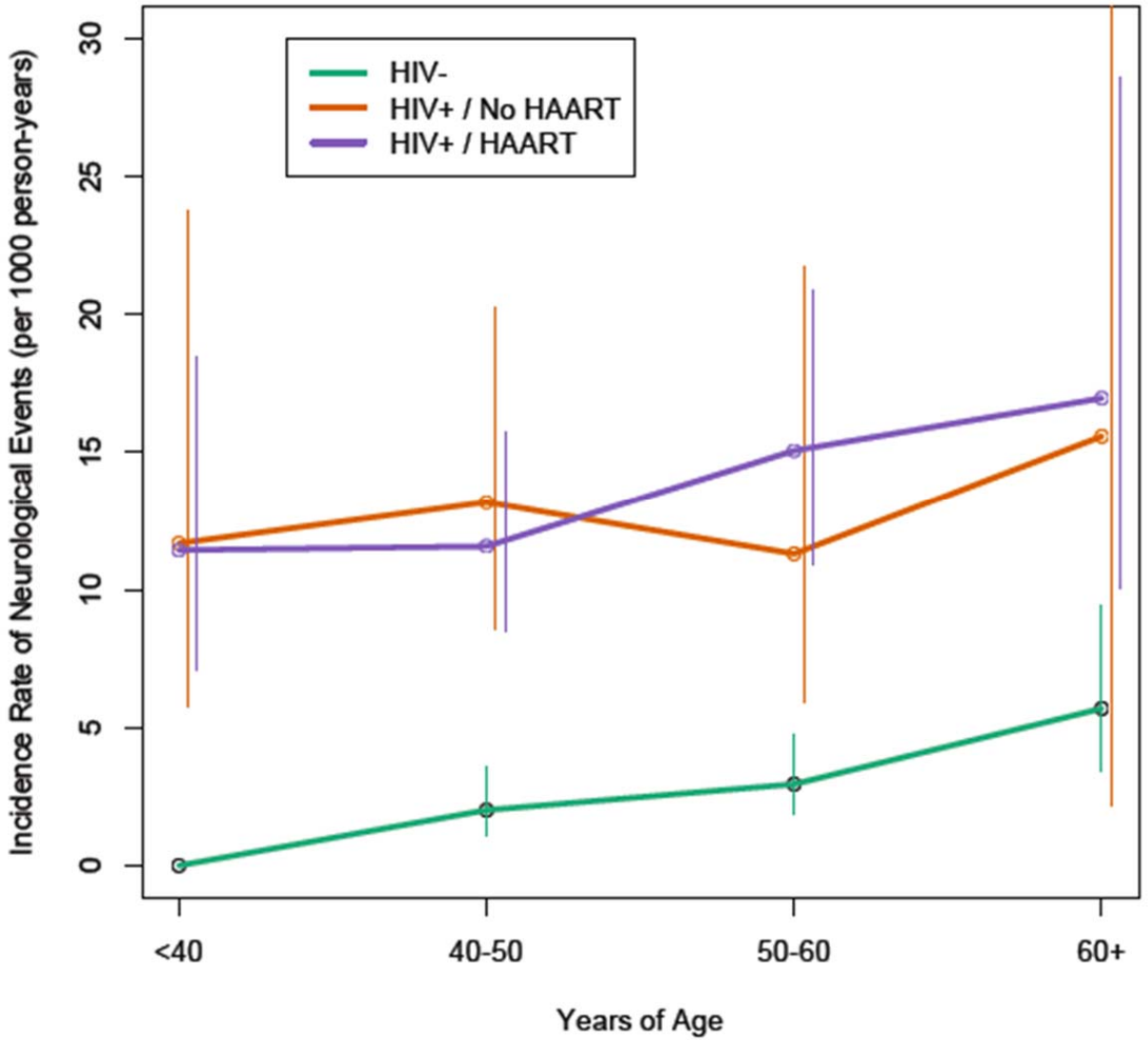
Sacktor, Skolasky,…, Miller. J NeuroVirol 2010



May 2011

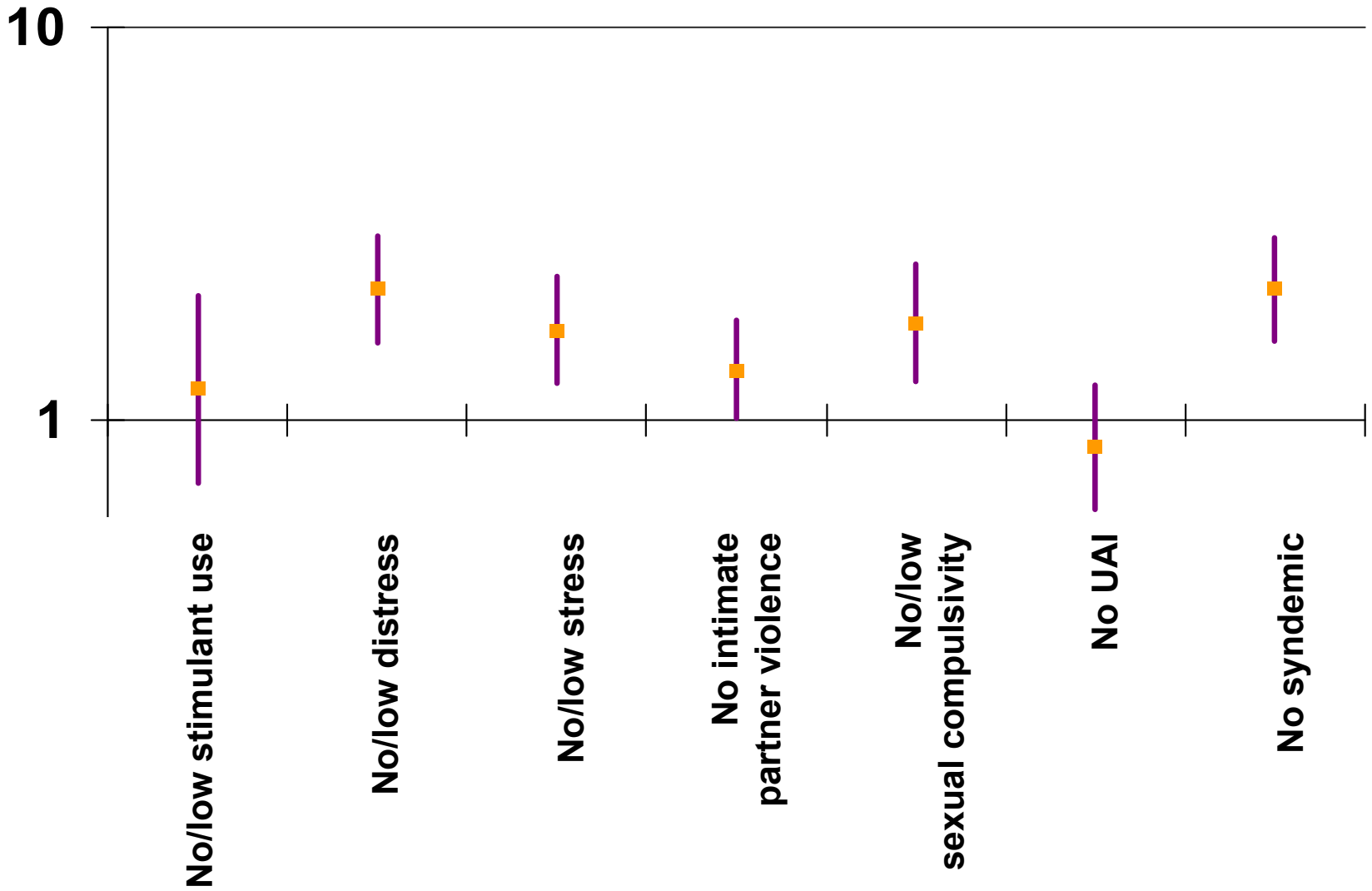
Incidence of Neurologic Events in the MACS by HIV and HAART Status

Mateen, Shinohara, …, Sacktor - Neurology 2012;79:1873-80



Adjusted Associations of Internalized Homophobia Resolution and Health Outcomes Among Men Who had Early Internalized Homophobia

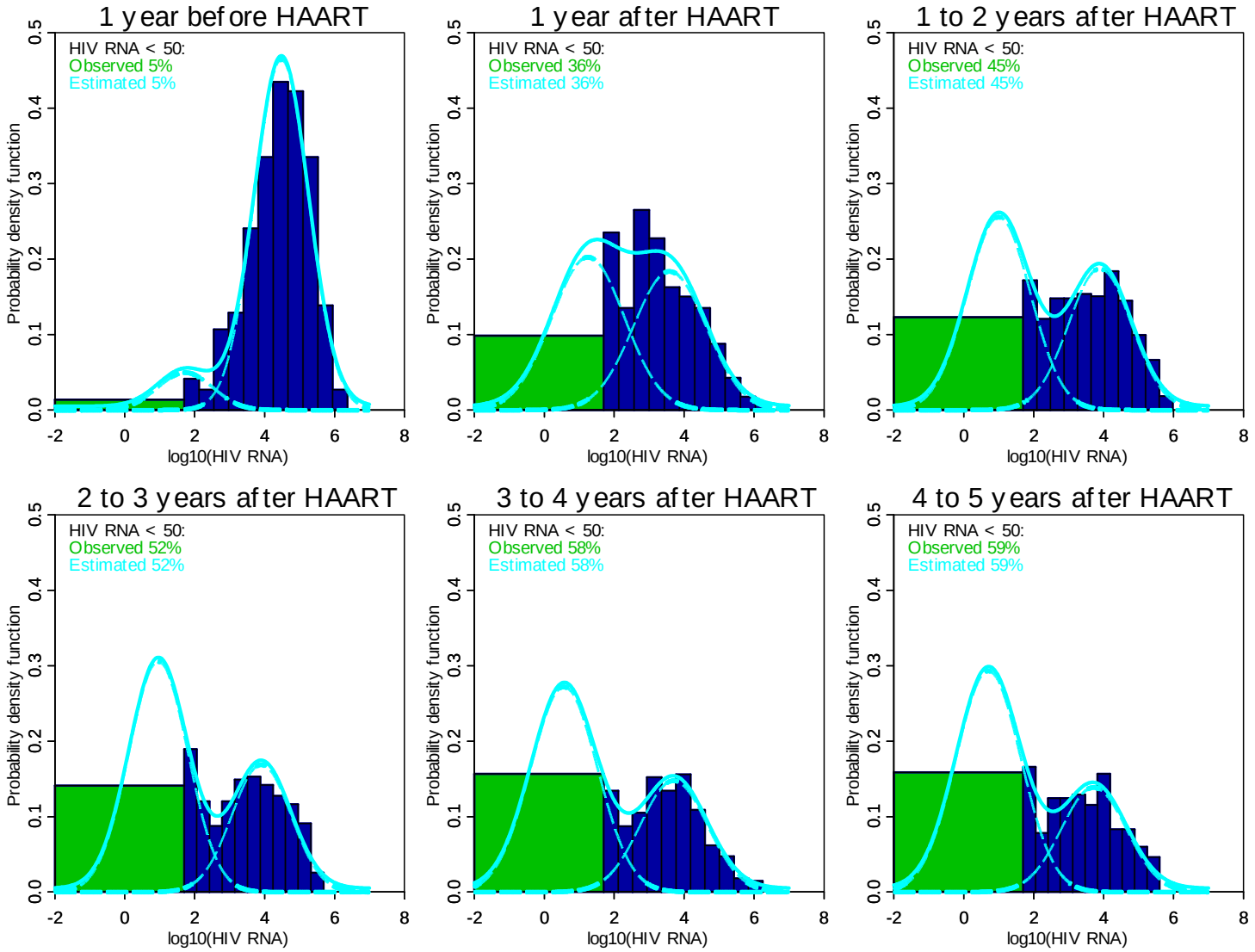
Herrick, Stall, …, Plankey - AIDS Behav 2013;17:1423-30



November 2013

Goodness of Fit for $\log_{10}$(HIV NRA) as a Mixture of Two Normal Distributions - MACS

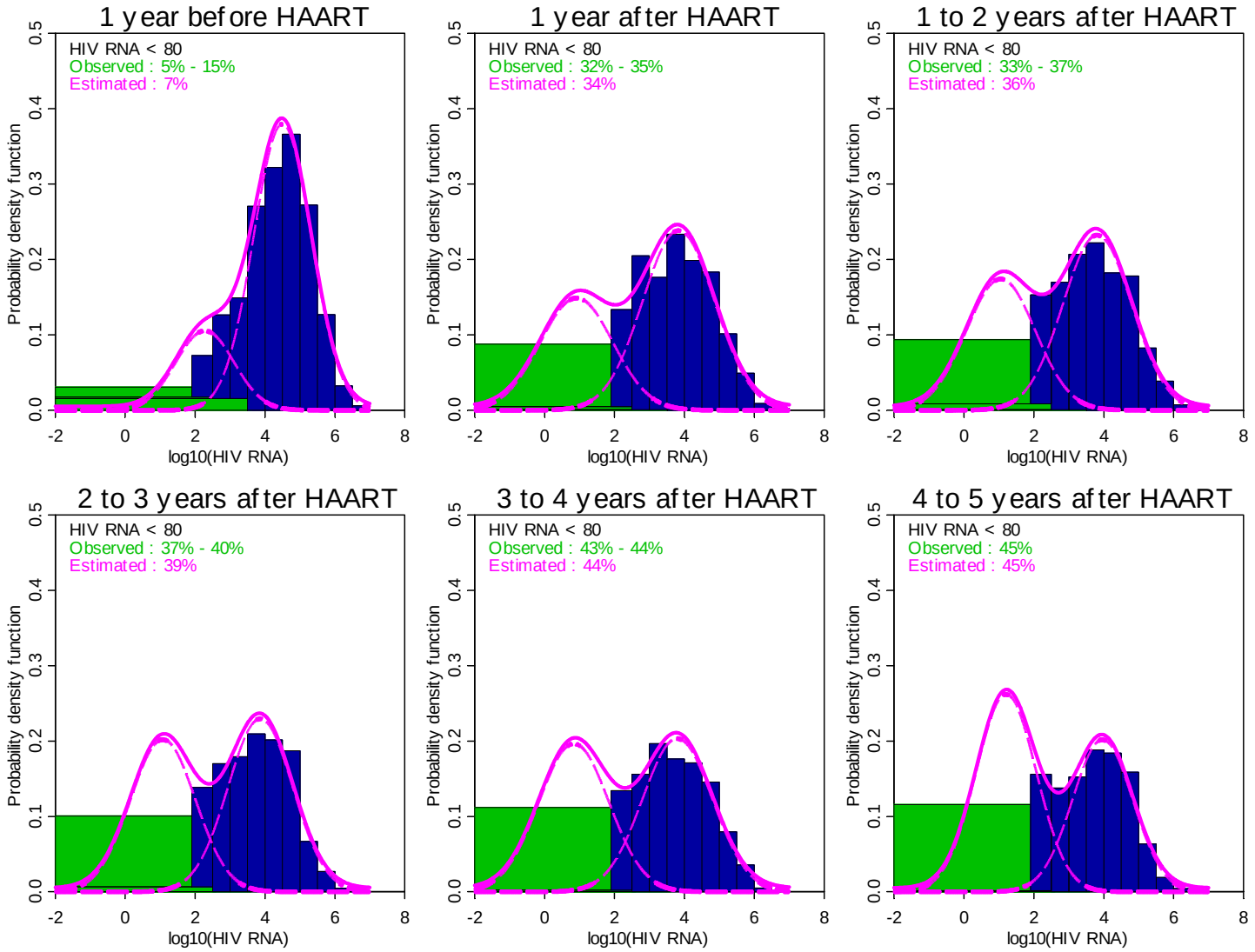
Li, Chu, …, Muñoz. J Epidemiol Community Health 2006



May 2006

Goodness of Fit for $\log_{10}$(HIV NRA) as a Mixture of Two Normal Distributions - WIHS

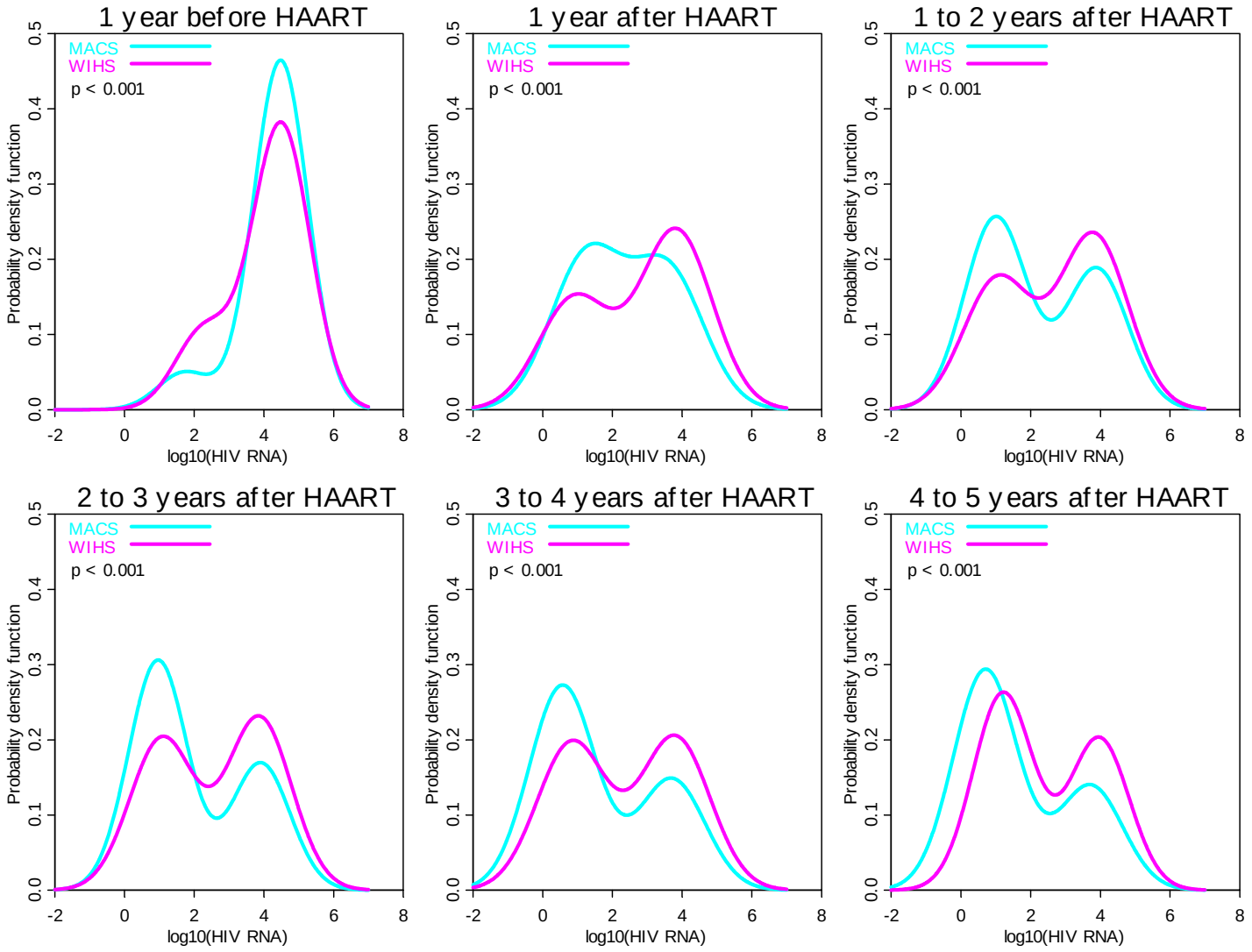
Li, Chu, …, Muñoz. J Epidemiol Community Health 2006



May 2006

Bimodel Distributions of $\log_{10}$(HIV RNA in copies/ml) for the MACS and WIHS

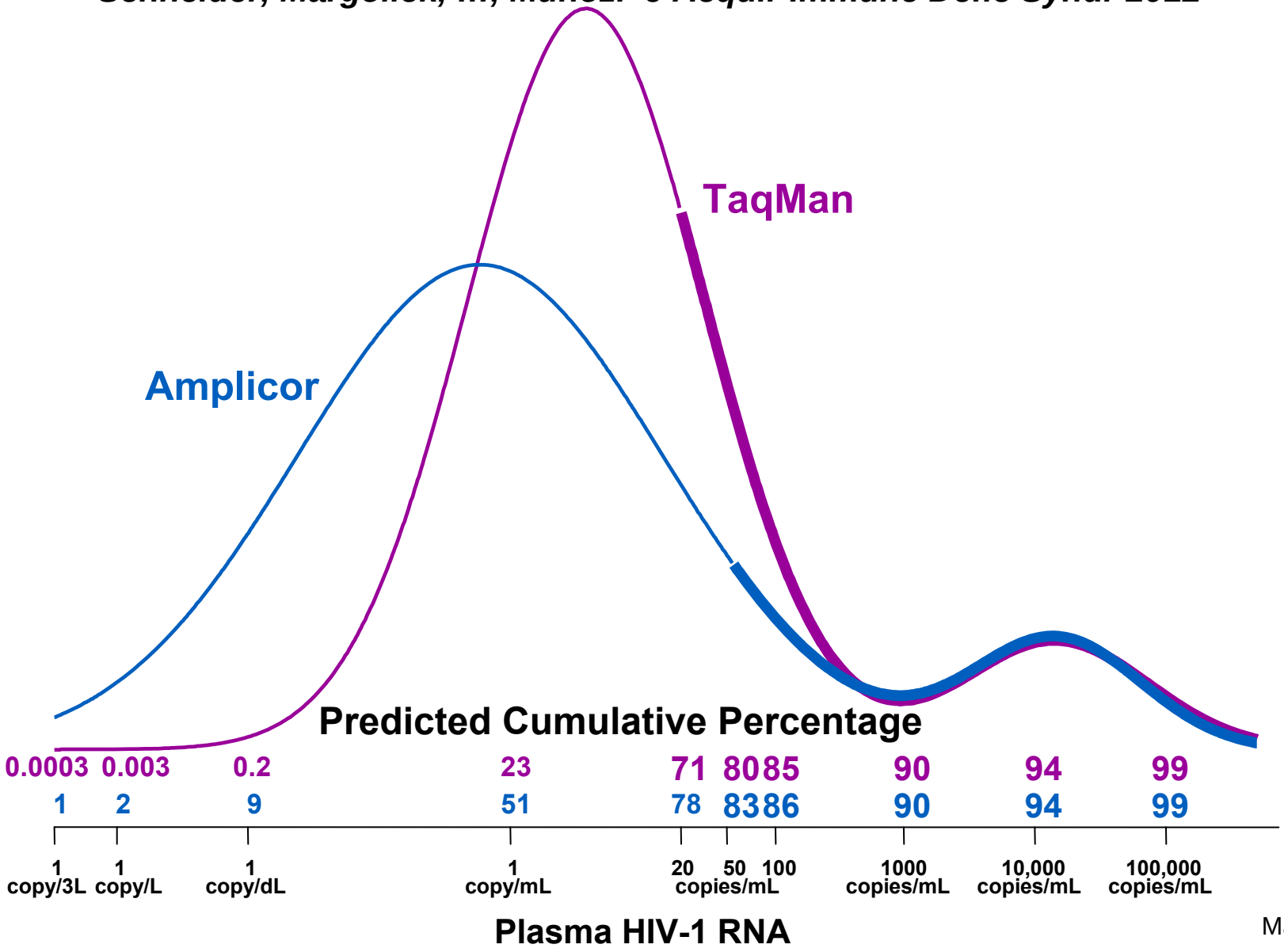
Li, Chu, …, Muñoz. J Epidemiol Community Health 2006



May 2006

Bimodal Mixture Distributions Summarizing the HIV-1 RNA Distributions Derived from 2 Assays Used to Measure HIV-1 RNA

Schneider, Margolick, …, Muñoz. J Acquir Immune Defic Syndr 2012



May 2012

Risk and Survival Attributable to an Exposure

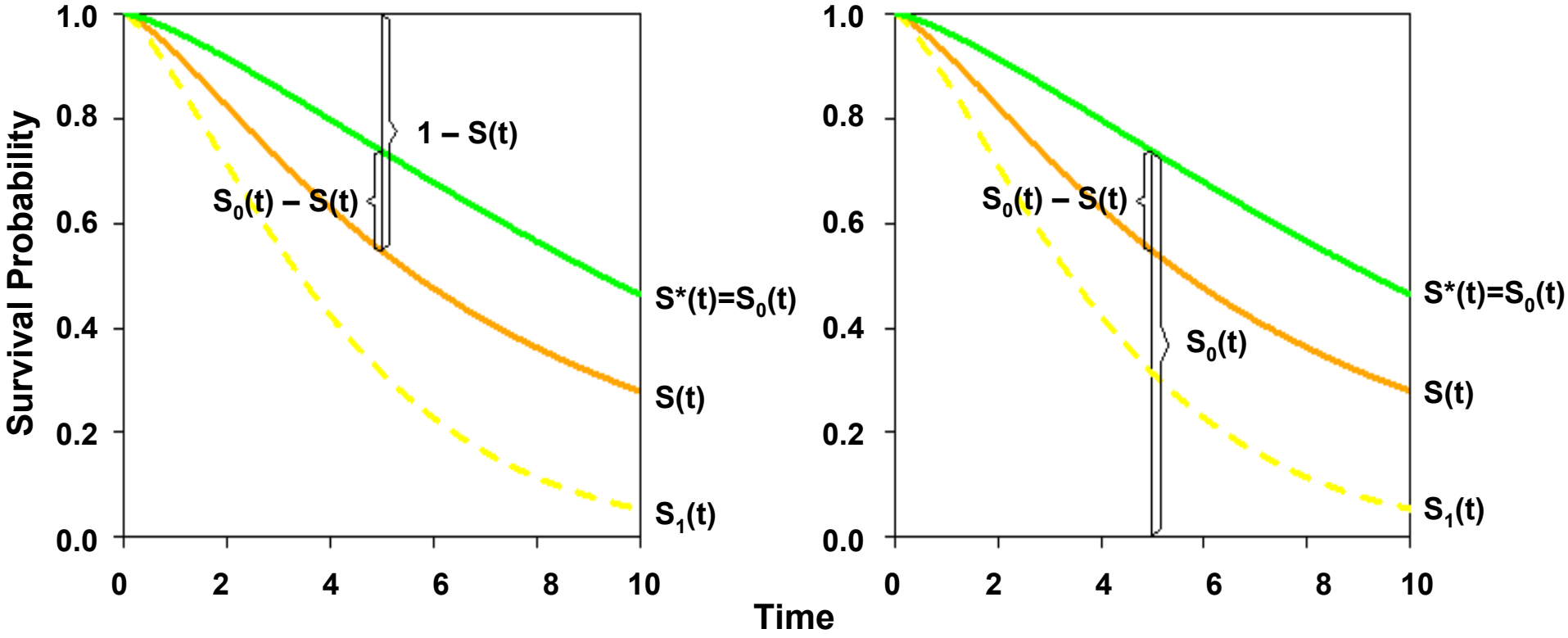
Cox, Chu, Muñoz. Stat Med 2009

Attributable Risk

$$AR(t) = \frac{S_0(t) - S(t)}{1 - S(t)}$$

Attributable Survival

$$AS(t) = \frac{S_0(t) - S(t)}{S_0(t)}$$



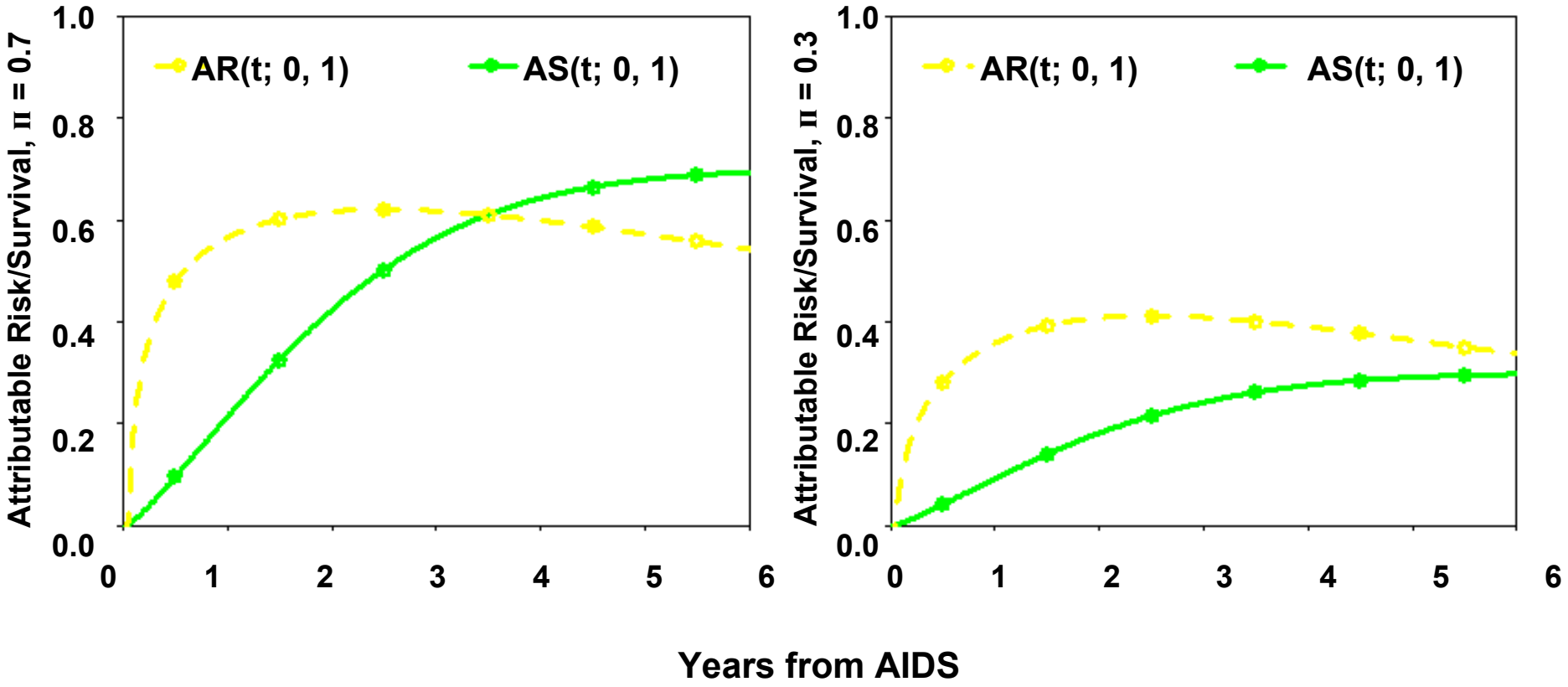
Π = proportion exposed; $S_0(t)$ = survival unexposed; $S_1(t)$ = survival exposed

$S(t) = \Pi S_1(t) + (1-\Pi)S_0(t)$ = survival in population

May 2010

Risk and Survival Attributable to the Absence of HAART

Cox, Chu, Muñoz. Stat Med 2009



May 2010

Number of Pre-2010 Participants with Specimens Available* in the National Repository Relative to the Time of Seroconversion**

Specimen Type	Last Seronegative Visit	First Seropositive Visit
Plasma	472	515
Serum	496	493
Cells	455	450

* 2 or more tubes according to repository inventory as of 10/1/13

** A total of 651 pre-2010 participants have a known seroconversion date

Number of Pre-2010 Participants with Specimens Available* in the National Repository Relative to the Development of AIDS**

Specimen Type	Within 1 Year Pre-AIDS	Within 6 Months Post AIDS	After 6 Months Post AIDS
Plasma	1268	640	641
Serum	1205	553	594
Cells	808	296	386

*** 2 or more tubes according to repository inventory as of 10/1/13**
**** A total of 1988 pre-2010 participants have developed AIDS**

November 2013

Number of Pre-2010 Participants with Specimens Available* in the National Repository Relative to HAART Use**

Specimen Type	Within 1 Year Prior to HAART	Within 6 Months Post HAART	After 6 Months Post HAART	All 3
Plasma	813	673	1368	532
Serum	781	642	1367	481
Cells	643	525	1266	366

* 2 or more tubes according to repository inventory as of 10/1/13

** A total of 1530 pre-2010 participants have initiated HAART

November 2013