

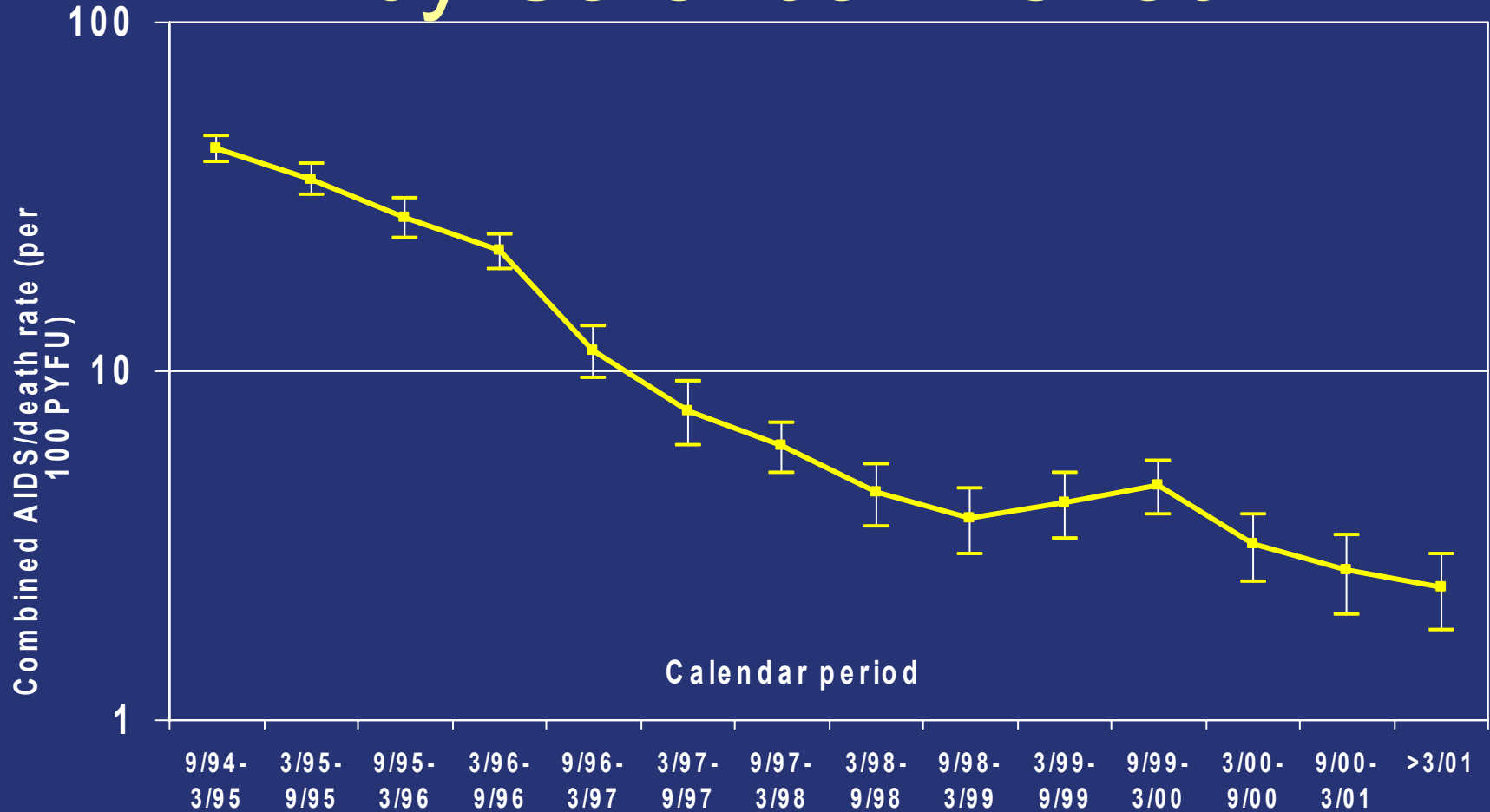
Treatment of Early HIV Disease

Changing Patterns of Morbidity and Mortality in HIV Disease

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EuroSIDA: AIDS/Death Rates by Calendar Period



Lancet 2003:362:22-29

Cascade: Causes of Death, Pre- and Post- HAART

	<u>Pre-HAART</u> <u>(before 1997)</u>	<u>Post-HAART</u> <u>(1997 onwards)</u>
No. Deaths	1424	514
% AIDS	48.2	28.2
% Non-AIDS	25.0	48.5
% Unknown	26.8	23.3
	100.0	100.0
	51.8	71.8

AIDS 2006; 20: 741-749.

HOPS: Causes of Death by CD4+ Count at Start of HAART

	<u>CD4+ cell count (cells/mm³)</u>	
	<u><200</u>	<u>200+</u>
No. Deaths	239	95
% AIDS	60.7	36.8
% Non-AIDS	23.0	45.3
% Unknown	<u>16.3</u>	<u>17.9</u>
	100.0	100.0

Brackets indicating combined percentages:

 For <200: 23.0 + 16.3 = 39.3

 For 200+: 45.3 + 17.9 = 63.2

Reasons for Changes in Causes of Death

- Competing risks
- Risk factors for other diseases (e.g., smoking)
- Effects of HAART
- Effects of HIV

Possibly all of the above. Whatever, focus on non-AIDS morbidity is important from a clinical and public health point of view.

SMART Study Design

CD4+ cell count >350 cells/mm³

n = 2752

n = 2720

Virologic Suppression (VS) Strategy

[Use of ART to maintain viral load as low as possible throughout follow-up]

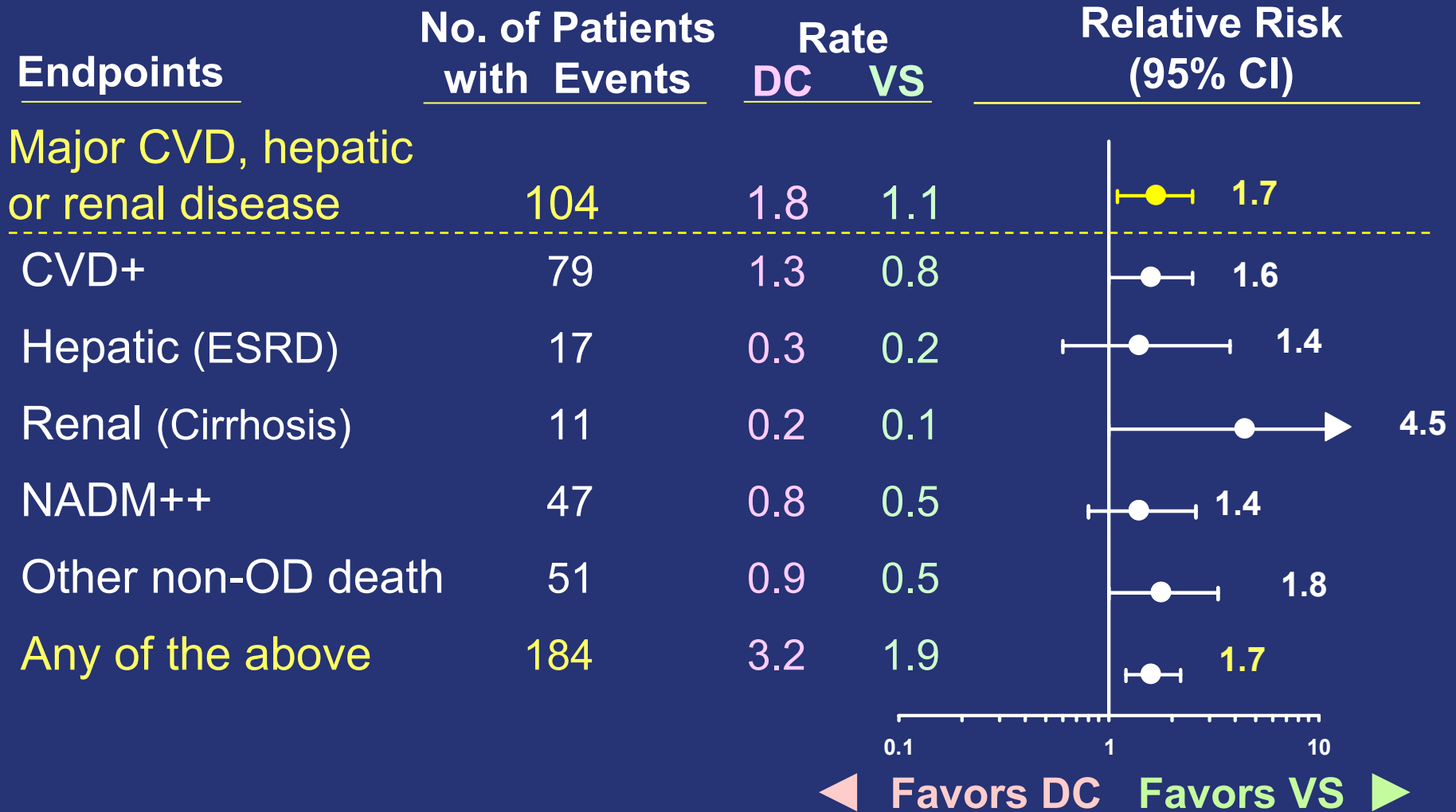
Drug Conservation (DC) Strategy

[Stop or defer ART until CD4+ < 250 ; then *episodic* ART based on CD4+ cell count to increase counts to > 350]

SMART Primary and Supportive Endpoint Results

	DC Group		VS Group		HR (DC/VS)	
	N	Rate	N	Rate	[95% CI]	P-value
OD or death (primary endpoint)	120	3.3	47	1.3	2.6 [1.9, 3.7]	<0.001
CVD, Renal, Liver	65	1.8	39	1.1	1.7 [1.1, 2.5]	0.009
CVD	48	1.3	31	0.8	1.6 [1.0, 2.5]	0.05
Renal	9	0.2	2	0.1	4.5 [1.0, 20.9]	0.05
Liver	10	0.3	7	0.2	1.4 [0.6, 3.8]	0.46

Serious Non-AIDS Outcomes in SMART



+ MI (clinical or silent), stroke, surgery for CAD

++ Except non-melanoma skin

SMART Subgroup Finding: ART Naïve Patients and Patients Not Taking ART for 6 months Prior to Randomization

	DC Group		VS Group		HR (DC/VS) Deferred vs. Early	
	N	Rate	N	Rate	[95% CI]	P-value
OD or death	15	4.8	4	1.1	4.4 [1.5, 13.2]	0.009
OD (fatal or non-fatal)	11	3.5	3	0.8	4.4 [1.2, 15.8]	0.02
Serious Non-AIDS	12	3.9	2	0.5	7.1 [1.6, 31.5]	0.01
Composite	21	7.0	5	1.3	5.1 [1.9, 13.5]	0.001

Serious AIDS and Serious non-AIDS Outcomes in SMART

<u>Outcome</u>	<u>DC arm No. events</u>	<u>VS arm No. events</u>	<u>HR (P-value)</u>
Serious AIDS+	46	12	3.9 (<0.0001)
Serious non-AIDS	115	69	1.7 (0.0007)

Overall more than 3X more serious non-AIDS than AIDS events

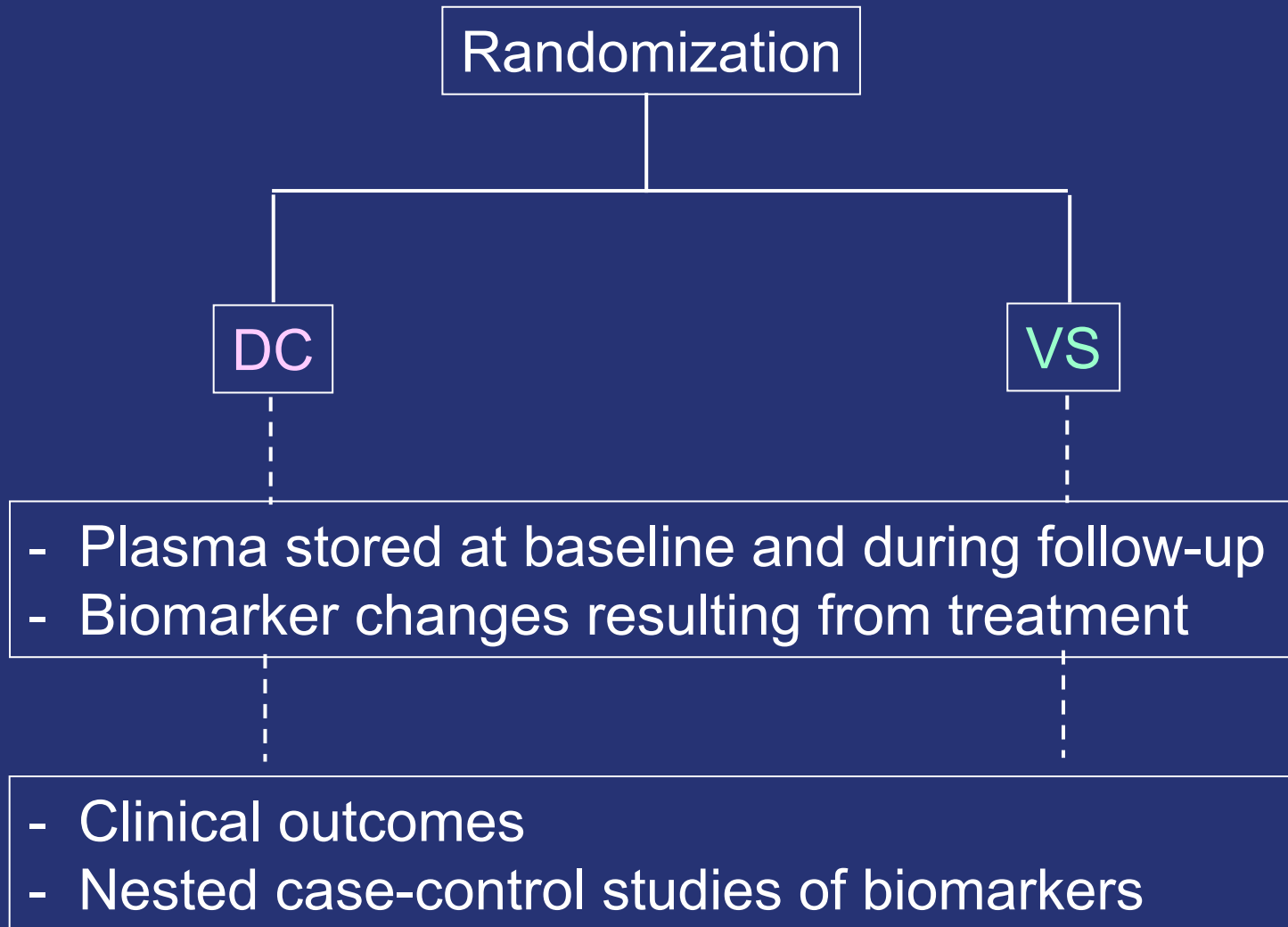
+ Excludes esophageal candidiasis and herpes simplex

Hypothesis: HIV and Non-AIDS Disease Risk

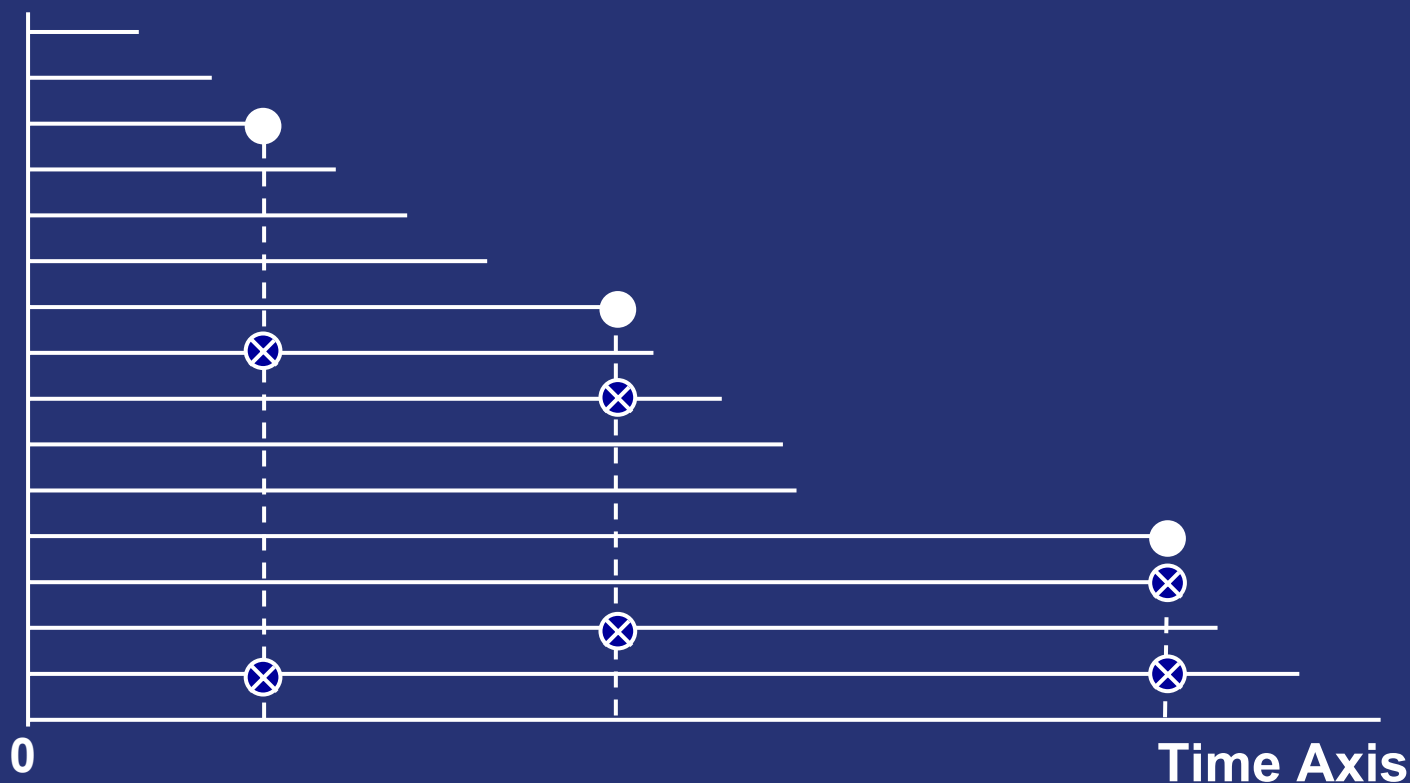


Magnitude of absolute risk ↑ depends on other factors

The Strength of Randomized Studies with Clinical Outcomes



SMART: Nested Case Control Design



Two controls (circle with X) for every case (solid circle) were randomly chosen after matching (vertical dashed lines). Follow-up for all members of the cohort (horizontal white lines) begins at randomization (zero-time axis).

Sampling Plan for Biomarkers

- 250 DC and 250 VS patients without CVD, randomly chosen from those with 1 month specimens (baseline and 1 month levels)
- AIDS, death, CVD, renal and liver events (280 patients) and 2 controls (560) matched on age, gender, site and date of randomization (baseline and recent follow-up levels)

Inflammatory and Coagulation Markers Initially Evaluated

- Inflammatory
 - hs C-reactive protein (hs-CRP)
 - IL-6
 - Serum amyloid A
 - Serum amyloid P
- Coagulation
 - D-dimer
 - PA1-1
 - Prothrombin fragment 1+2 (F1.2)

D-dimer and Mortality in SMART

- D-dimer is a fibrin degradation product that reflects ongoing activation of blood coagulation and fibronolytic systems
- A useful diagnostic tool for venous thromboembolism
- Related to CVD in several cohort studies of non-HIV-infected individuals
- Studied to a more limited extent in HIV:
 - D-dimer was higher in HIV+ patients than HIV- controls and was reduced with ART (41 HIV+ patients in the Swiss Cohort Study and 21 HIV- controls) **JID 2002**
 - Coagulation markers increased with advancing HIV disease and were greater than HIV- controls in women (144 participants in WIHS) **JAIDS 2006**

D-Dimer Level ($\mu\text{g}/\text{mL}$) by ART Status at Baseline

<u>Baseline ART</u>	<u>No.</u>	<u>Mean (SD)</u>	
No ART	128	0.69 (0.95)	} P=0.02
ART	368	0.48 (0.78)	
Total	496	0.53 (0.83)	

Normal range: 0 – 0.3 or 0.5 ($\mu\text{g}/\text{mL}$); 34% > 0.5

Change in D-Dimer ($\mu\text{g/mL}$) from Baseline to 1 Month by Treatment Group

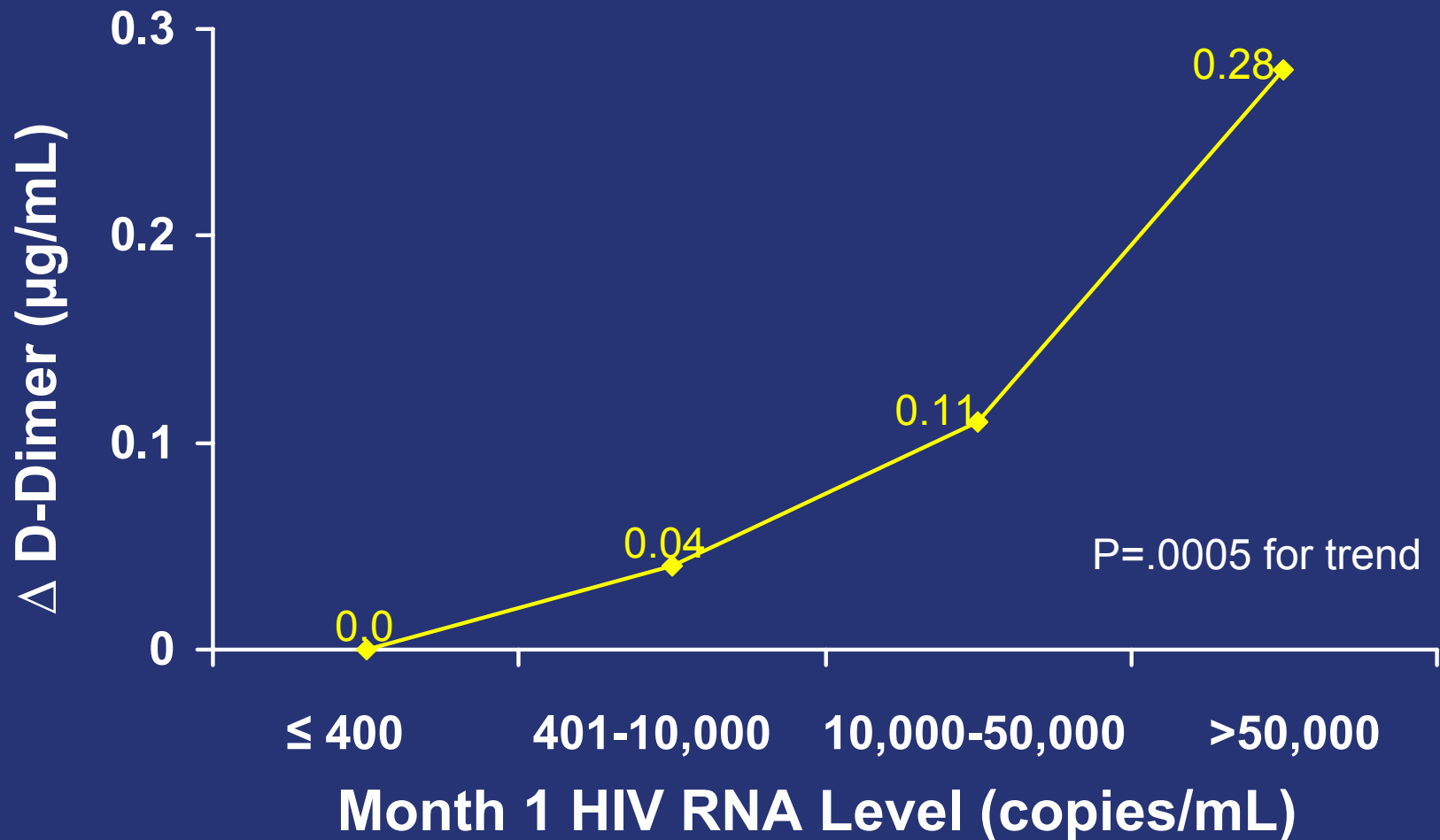
	DC		VS		Adj. Diff.	P-value
	<u>No.</u>	<u>Mean</u>	<u>No.</u>	<u>Mean</u>		
No ART	67	0.02	61	<u>-0.22</u>	0.14	0.052
ART	181	<u>0.10</u>	187	-0.03	0.14	<0.001
Total	248	0.08	248	-0.08	0.15	<0.001

Change in D-Dimer ($\mu\text{g/mL}$) from Baseline to 1 Month by Treatment Group and Baseline HIV RNA Level*

	DC		VS		Adj. Diff.	P-value
	<u>No.</u>	<u>Mean</u>	<u>No.</u>	<u>Mean</u>		
HIV RNA ≤ 400	134	0.13	127	-0.05	0.18	<0.001
HIV RNA > 400	47	0.03	60	0.00	0.04	0.54

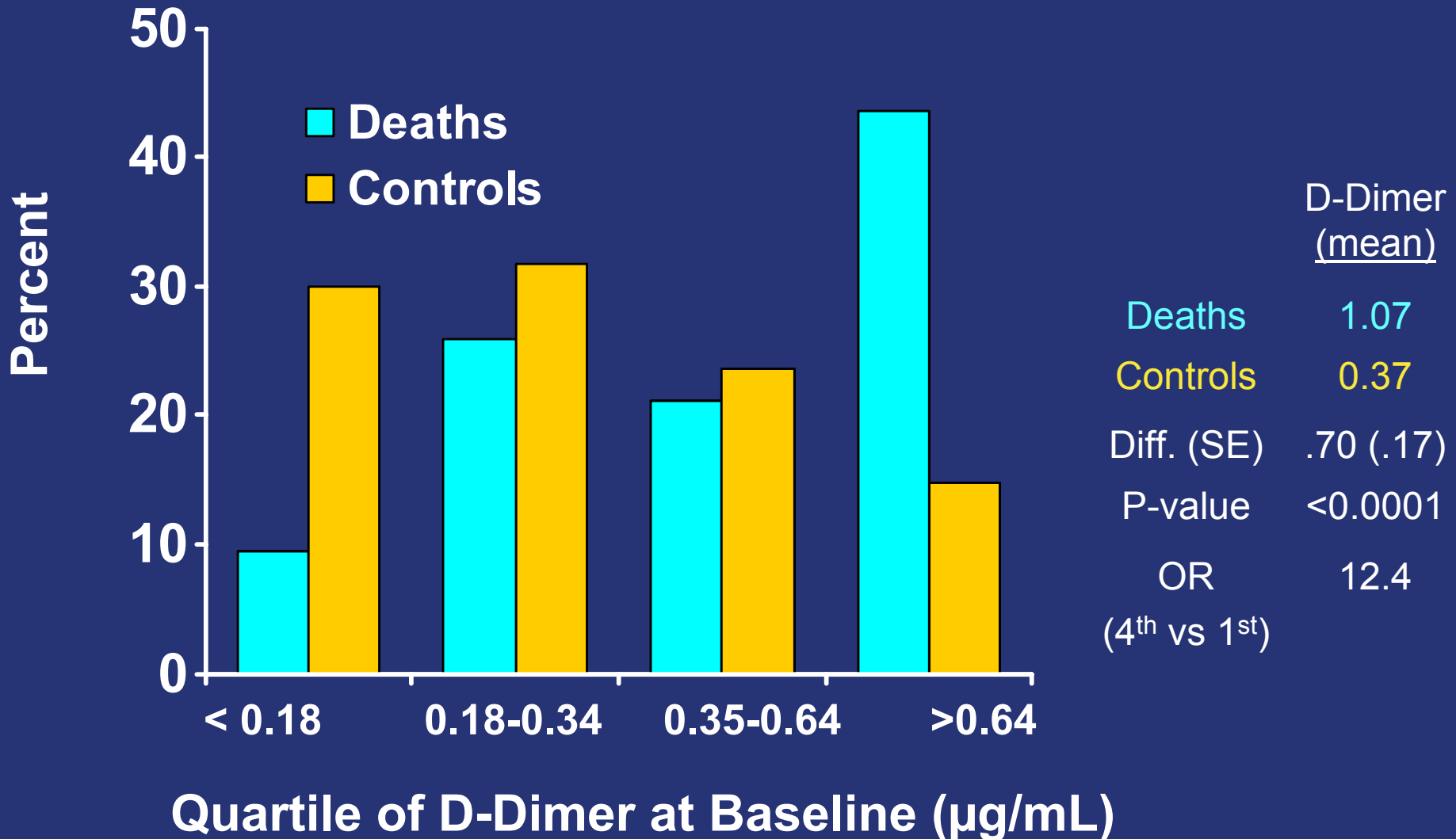
* Patients taking ART at entry

Change in D-Dimer* ($\mu\text{g/mL}$) from Baseline to 1 Month

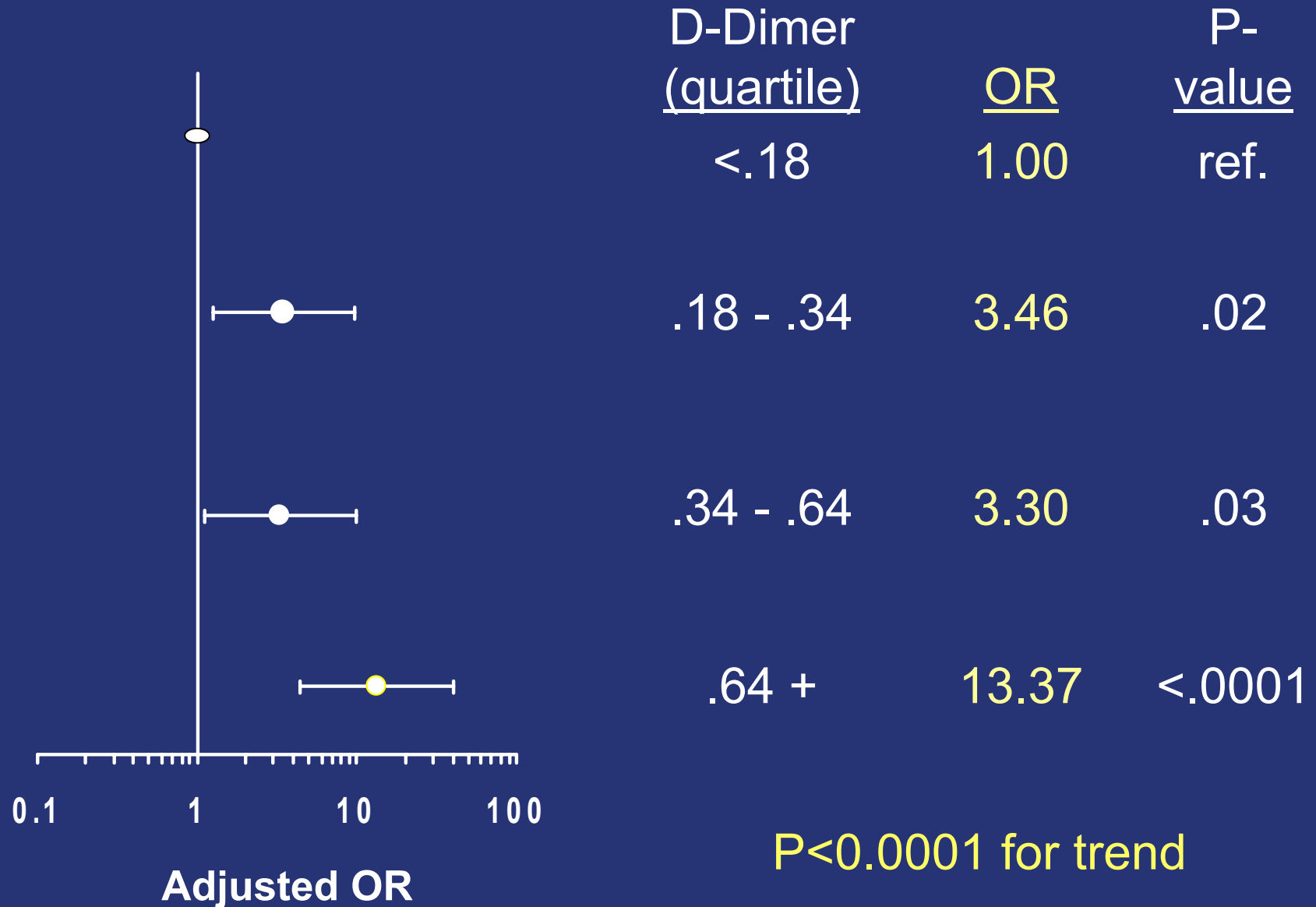


* DC patients on ART at baseline with HIV RNA ≤ 400 copies/mL

Nested Case-Control Study in SMART: 85 Deaths and 170 Matched Controls



Adj. Odds Ratios for Death by Baseline D-dimer



Adjusted Odds Ratios Associated with a 0.15 $\mu\text{g}/\text{mL}$ Increase in D-dimer

<u>Event</u>	<u>No. Events</u>	<u>Adj. OR</u>	<u>95% CI</u>	<u>P- value</u>
All Deaths	74	1.23	1.07-1.42	.004
Major CVD	59	1.12	1.01-1.24	.04
AIDS	75	1.40	1.19-1.66	.0001

Conclusions

- Data from SMART provide a strong scientific rationale for studying the effect of early ART on mortality and serious morbidity from AIDS and non-AIDS conditions
 - Serious non-AIDS conditions occur 3-4 times more frequently than serious AIDS events at high CD4+ counts
 - Treatment differences (DC/VS) are consistent among those on and off ART at entry
 - Biomarker data provide additional evidence for the potential benefit of early ART

Acknowledgements

SMART patients

INSIGHT investigators

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