When to Start

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Disclosures

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Consultant/Advisor: BMS, Gilead, ViiV, Merck
DHHS Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (volunteer position)

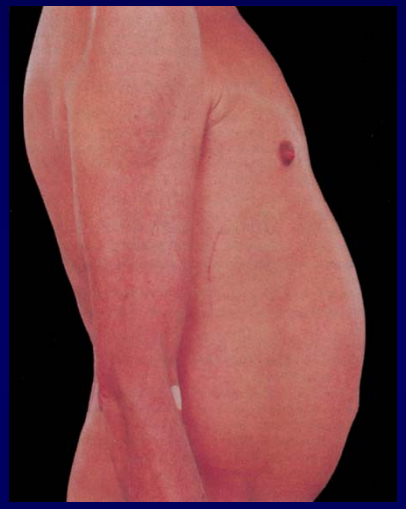
Objectives

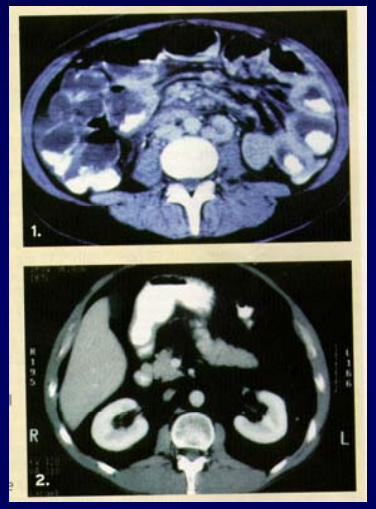
- Summarize the reasons for a debate related to the optimal time to initiate therapy
- Current data that informs the decision as to when therapy should be initiated
- Summarize DHHS and IAS-USA treatment guidelines
- Discussion regarding how existing data and guidelines influence practice in LA County

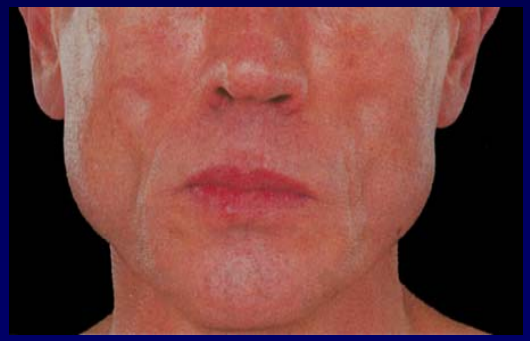
Case for delaying therapy

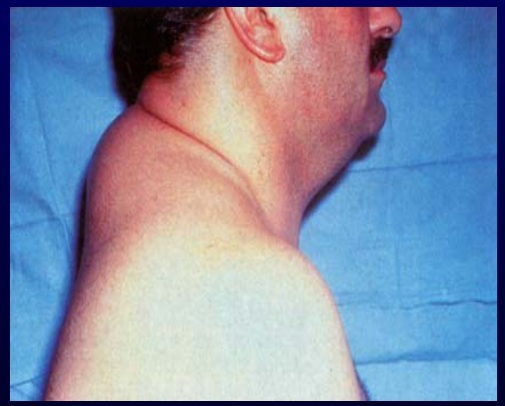
- Short-term and long-term toxicity
- Need for life long therapy
- Risk of virologic failure, resistance and cross-resistance
- Limited evidence for earlier therapy being associated with better outcomes than delayed therapy

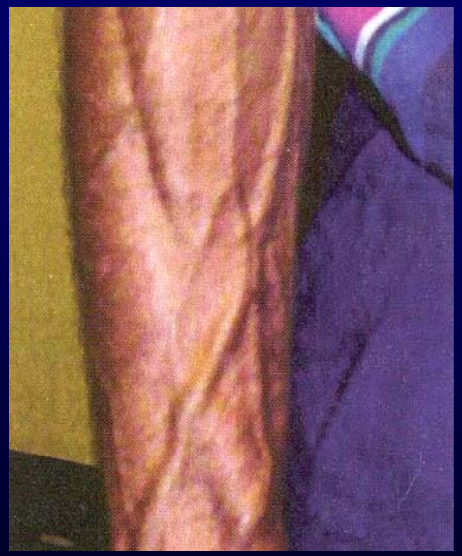
Physical Manifestations of Fat Redistribution Syndromes



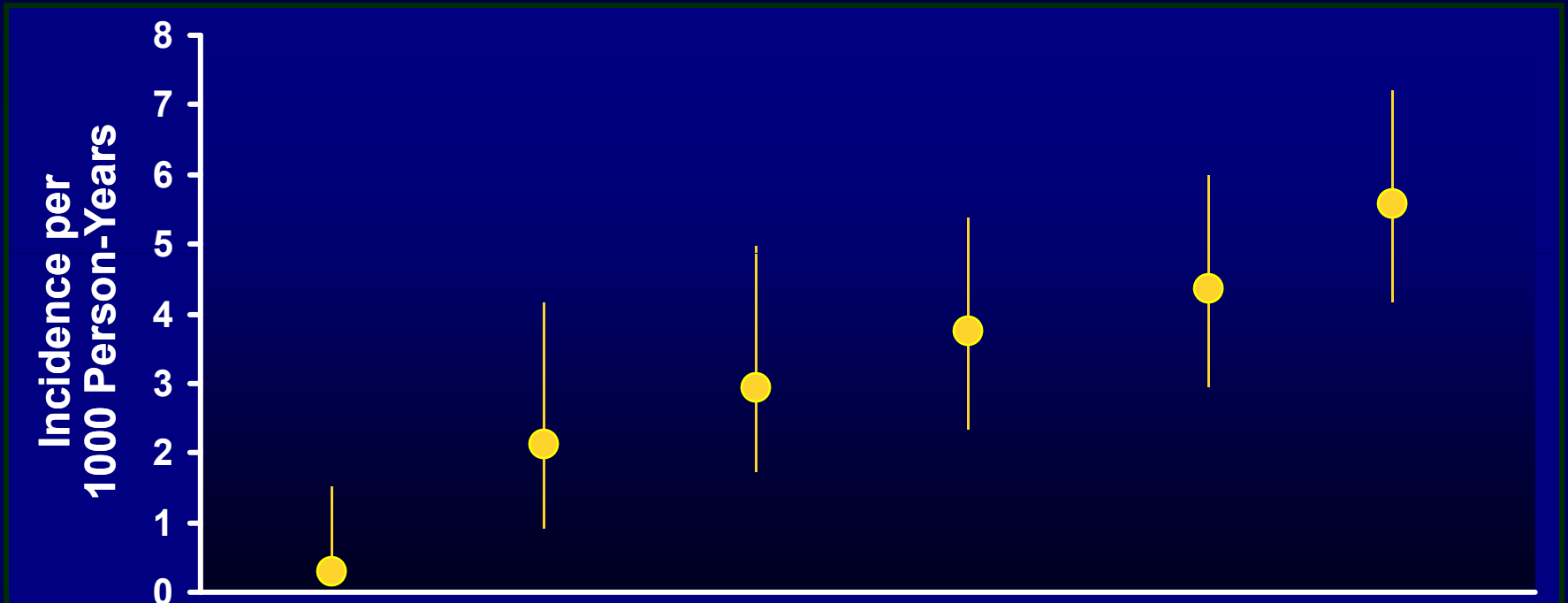








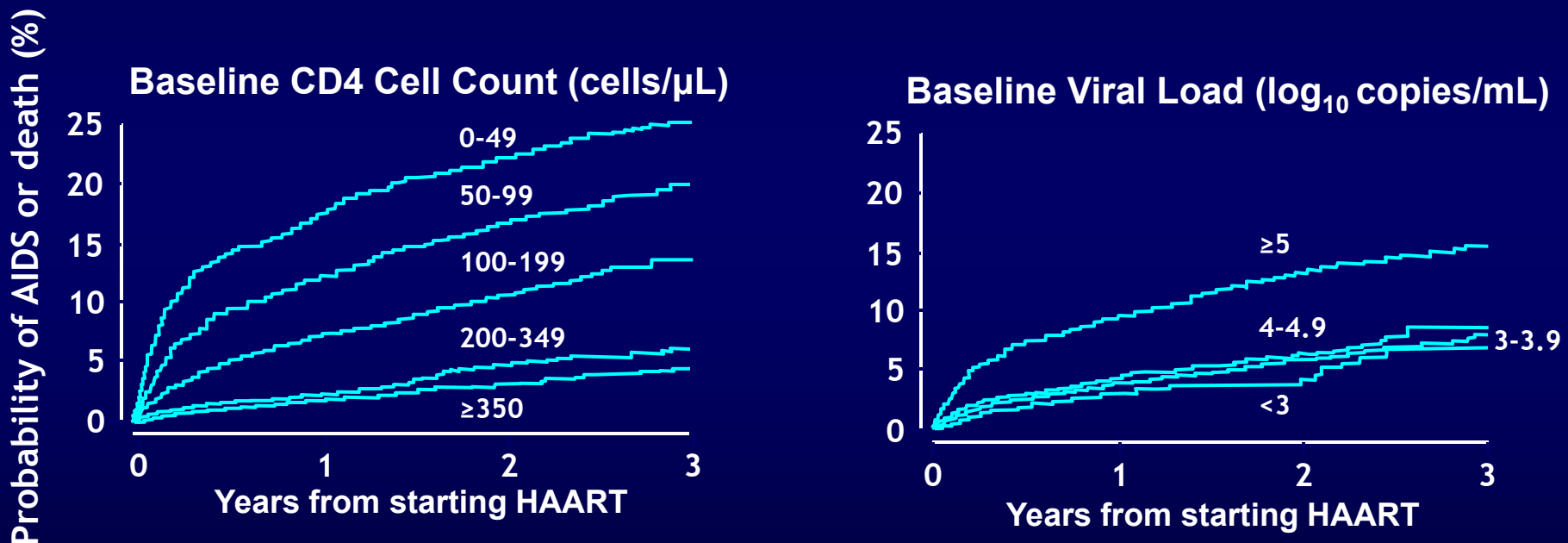
Myocardial Infarction and Duration of Combination ART (D:A:D Study)



Exposure (y):	None	<1	1-2	2-3	3-4	>4
Relative Risk:	1.0	0.24	1.34	1.73	1.98	2.25
No. of events	3	9	14	22	31	47
No. of person-y	5714	4140	4801	5847	7220	8477

Friis-Møller N et al. *N Engl J Med*. 2003;349:1993-2003.

When to Initiate ARV Therapy: Effect of Baseline CD4 and HIV RNA Level



HAART=highly active antiretroviral therapy.

Egger M et al. *Lancet.* 2002;360:119-129.

Case for Earlier Therapy

CIPRAHT001: Randomized Trial of When to Start ART in Haiti

Randomized clinical endpoint study of when to start therapy

- Treatment-naive
- No hx AIDS-defining illness
- CD4 200-350

Early Treatment
(Immediate ZDV/3TC + EFV)

Standard Treatment
(Delay until CD4+ <200 or AIDS

Primary endpoint: Survival

Baseline Characteristics	Early (n=408)	Standard (n=408)
Median age (years)	40	40
Male (%)	41%	44%
Median CD4+ (cells/mm^3)	280	282
Body Mass Index (kg/m^2)	21.4	21.0

May 2009: DSMB review stopped study due to excess deaths in Defer Treatment arm

Severe P, et al. NEJM 2010 363:257-265.

CIPRAHT001: Clinical Endpoints

May 2009: DSMB review stopped study due to excess deaths in Defer Treatment arm

Clinical Endpoints	Early	Standard	Hazards Ratio (p value)
Death	6	23	4.0 (.0011)
Incident Tuberculosis	18	36	2.0 (.0125)

- Infectious causes of death
  - Early: 1 (gastroenteritis)
  - Standard: 17 (7 gastroenteritis, 5 TB, 4 pneumonia, 1 cholangitis/sepsis)
- More toxicity from ART and intensive need for lab f/u for deferred grp
- WHO start guidelines now modified to <350 cells/uL

Severe P, et al. NEJM 2010 363:257-265.

Consequences of Stopping ART: SMART Trial

HIV-1-infected patients with CD4+ cell count > 350 cells/mm^3

(N = 5472)

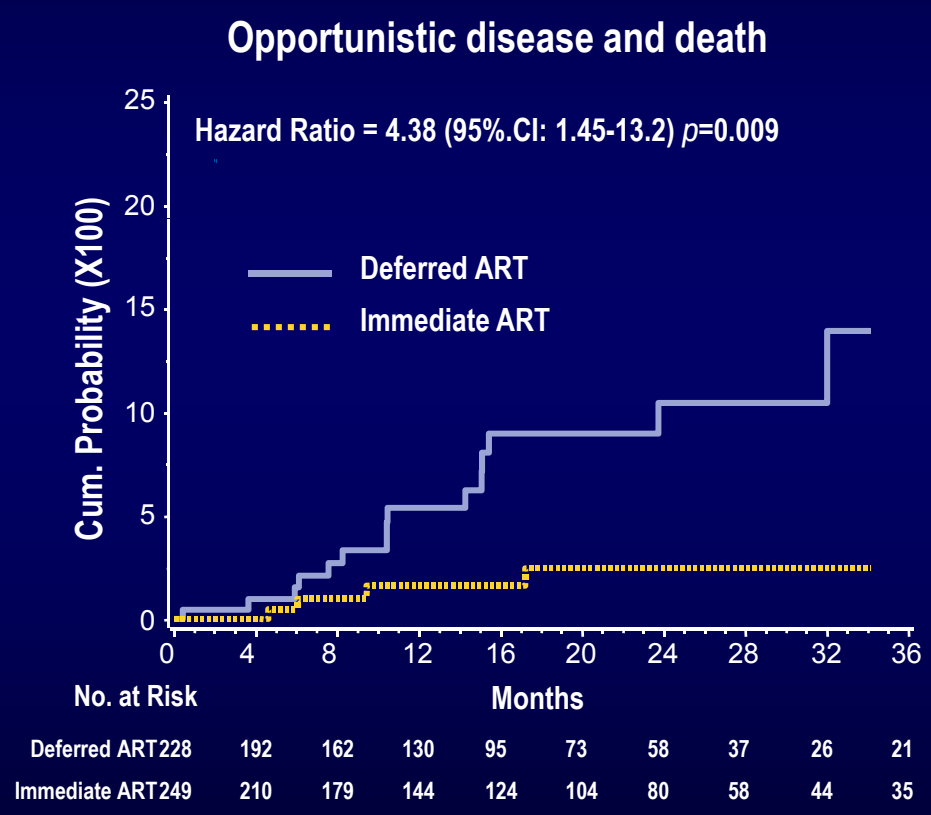
95.4% treatment experienced

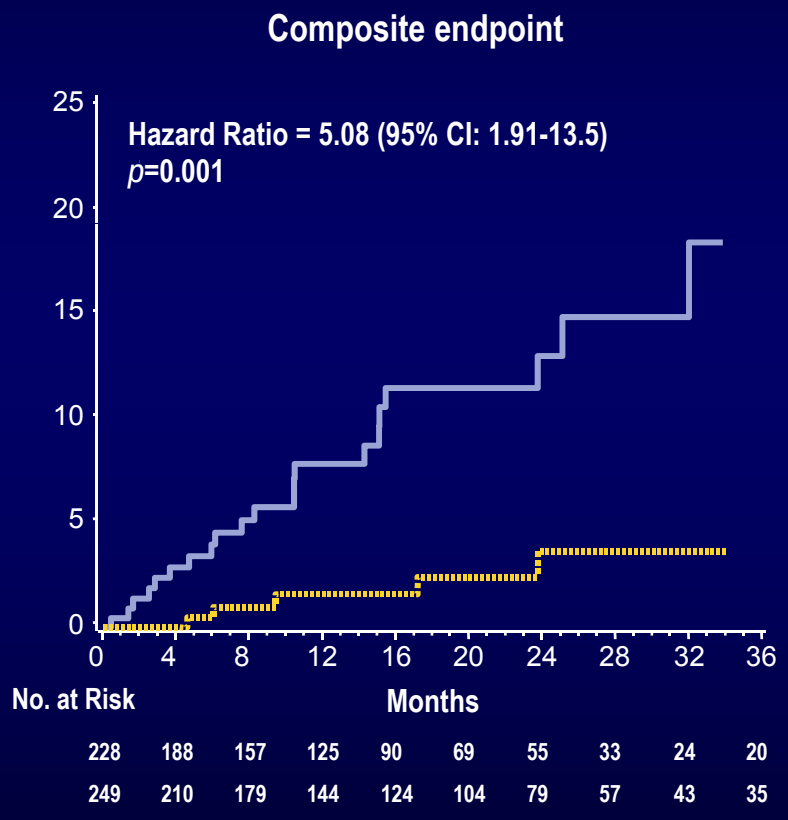
Continuous antiretroviral therapy throughout follow-up (n = 2752)

ART stopped/deferred until CD4+ <250 cells/mm^3 then started to increase CD4+ to >350 cells/mm^3 (n = 2720)

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

SMART: Treatment Naïve Patients





Emery S, et al. JID 2008; 197: 1133–1144.

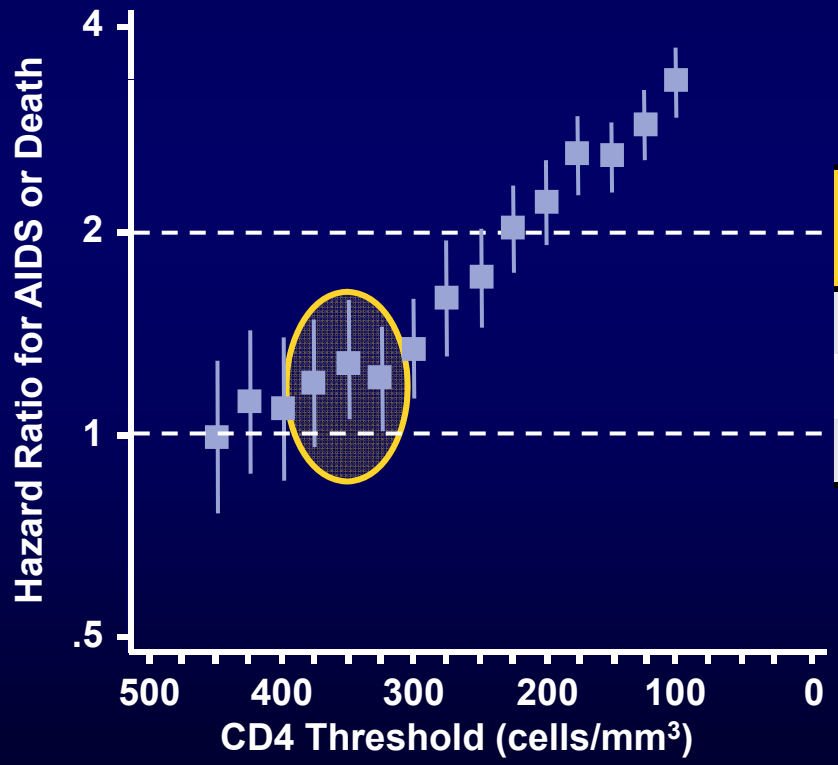
NA-ACCORD: Risk of Death with ART Deferral

	351-500 CD4+			>500 CD4+		
	RR	95% CI	*P*	RR	95% CI	*P*
Deferral of ART	**1.7**	**1.3, 2.3**	**<0.001**	**1.9**	**1.4, 2.8**	**<0.001**
Female Sex	1.2	0.9, 1.6	0.24	1.9	1.3, 2.6	<0.001
Older Age (per 10 years)	1.7	1.5, 1.9	<0.001	1.8	1.6, 2.1	<0.001
Baseline CD4 count (per 100 cells/mm^3)	1.1	0.7, 1.8	0.59	0.9	0.9, 1.0	0.03

Kitahata M, et al. New Engl J Med 2009;360:1815-26.

ART-CC: When Should ART be Started?

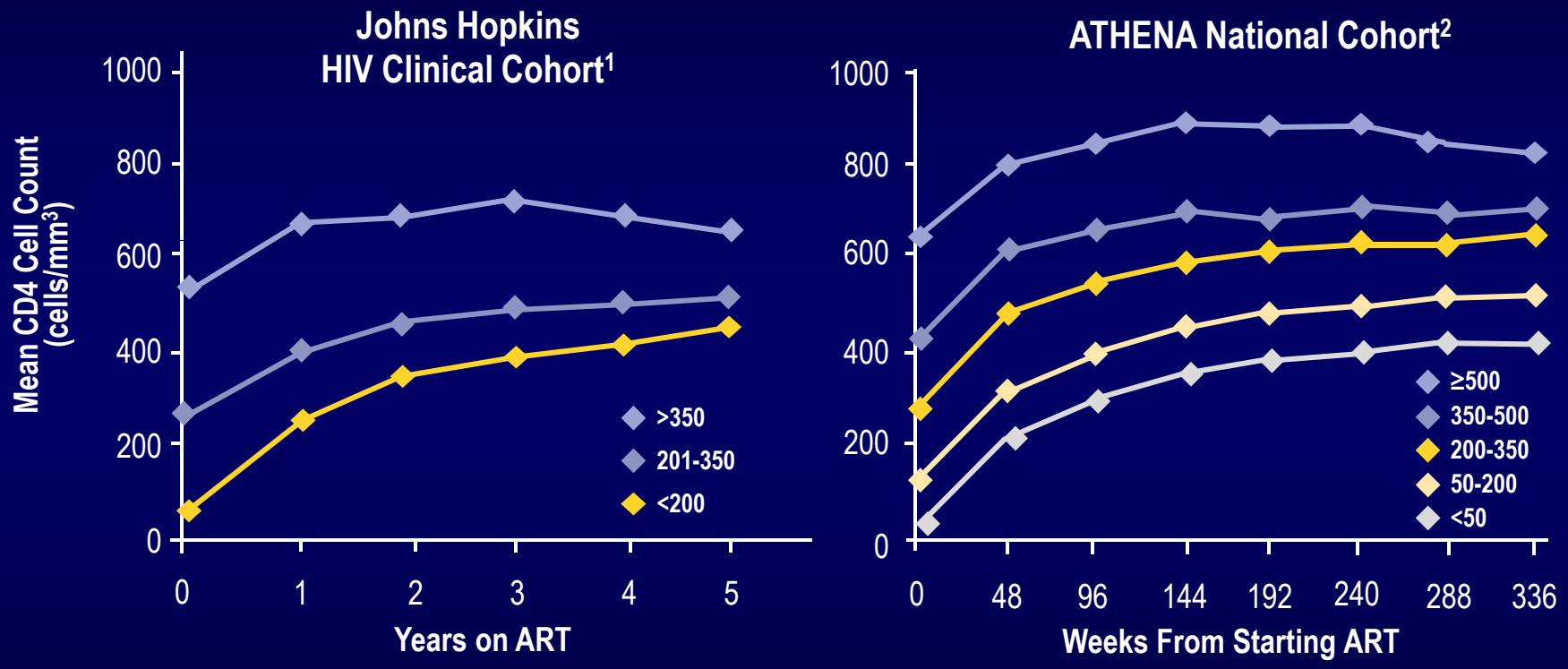
- Hazard ratios for AIDS or death, adjusted for lead time/unseen events



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

Ledergerber B, et al. Lancet 2009; 373:1352-63

Ultimate CD4 Cell Count Depends on Where You Start



Magnitude of increase in CD4 cell count greatest if therapy started at low CD4 cell counts, but greater likelihood of CD4 cell count normalization with earlier therapy

1. Moore R, et al. Clin Infect Dis. 2007;44(3):441-446; 2. Gras L, et al. J Acquir Immune Defic Syndr. 2007;45(2):183-192.

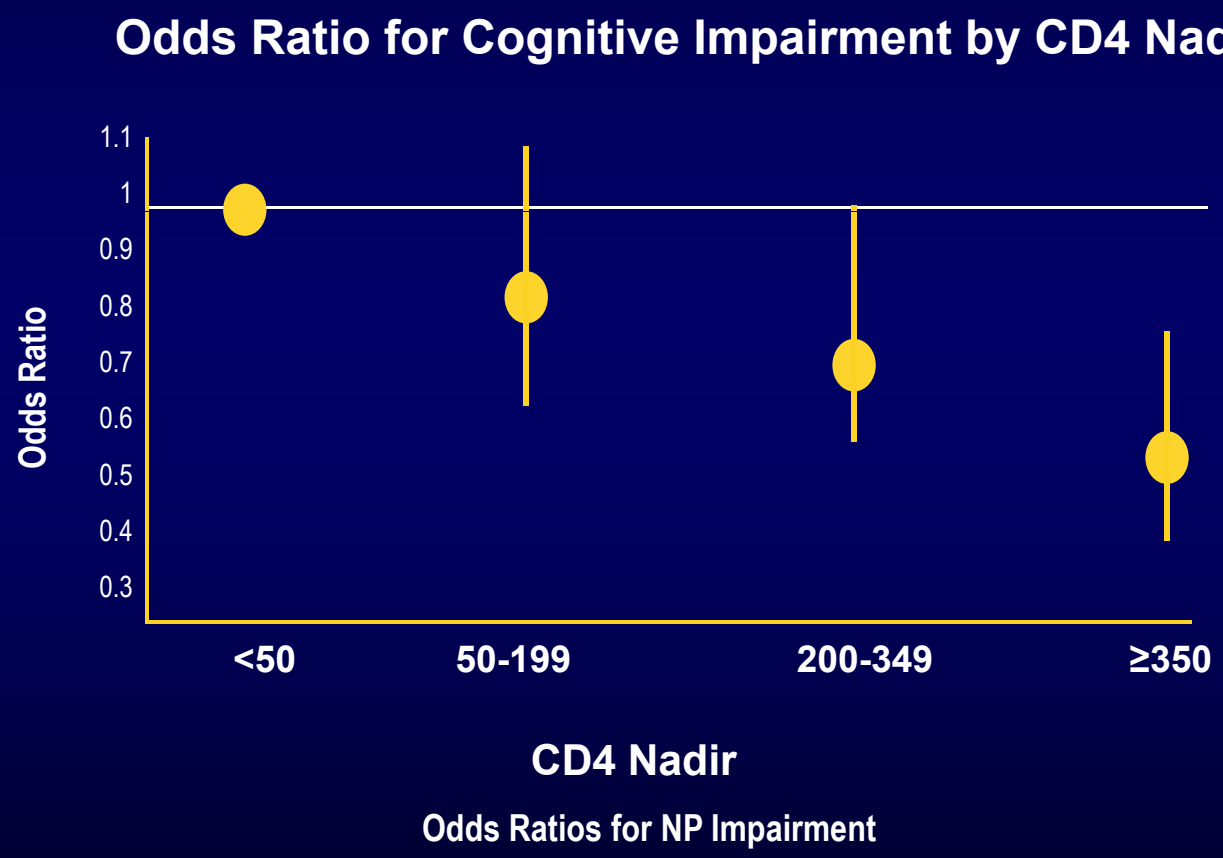
Association Between Current CD4 Cell Count and Non-AIDS Complications

Is Lower Current CD4 Cell Count Significantly Associated With Increased Risk of non-AIDS Events?

Study	Non-AIDS malignancies	Renal disease/death	CVD events/death	Liver disease/ death
FIRST	Yes	Yes	Trend, NS	No
D:A:D	Yes	Yes	Trend, NS	Yes
CASCADE	Yes	NA	Yes	Yes
SMART	Trend, NS	Trend, NS	Trend, NS	Yes

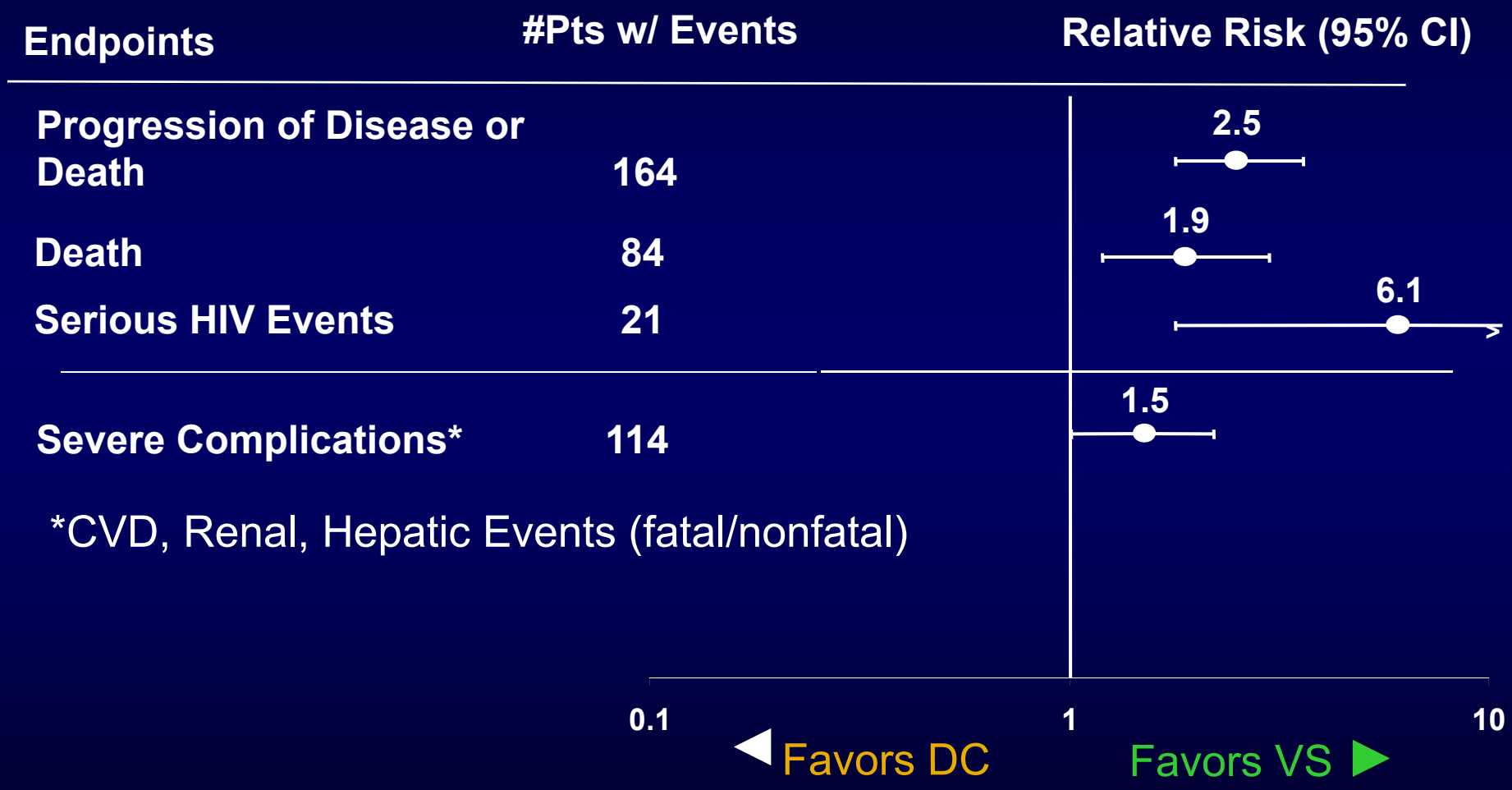
Phillips A, et al. 15th CROI; 2008; Boston. Abstract 8.

Neurocognitive Disorders Associated with Nadir CD4 Counts



Ellis R, et al. AIDS, July 6, 2011, Epub ahead of print

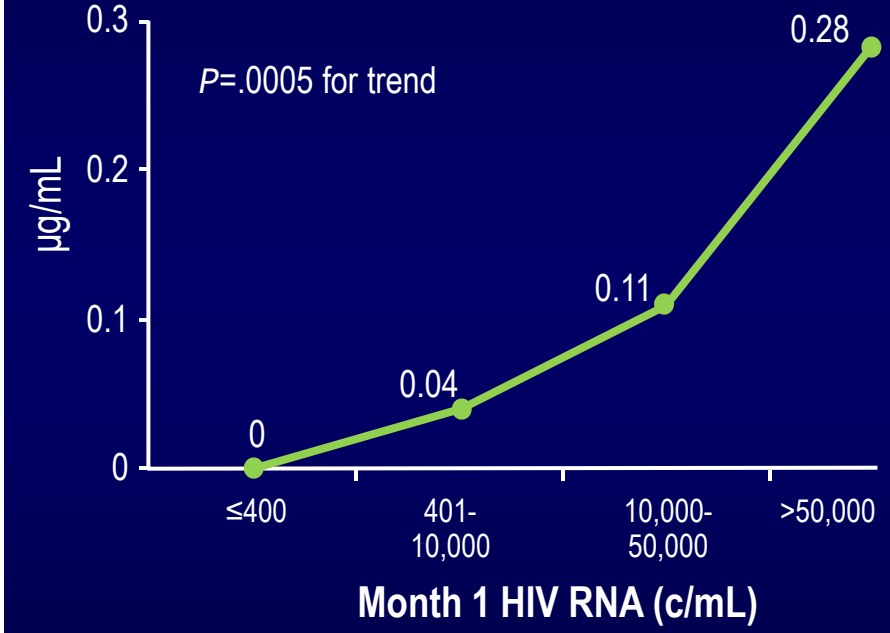
SMART: Primary Endpoint and Components



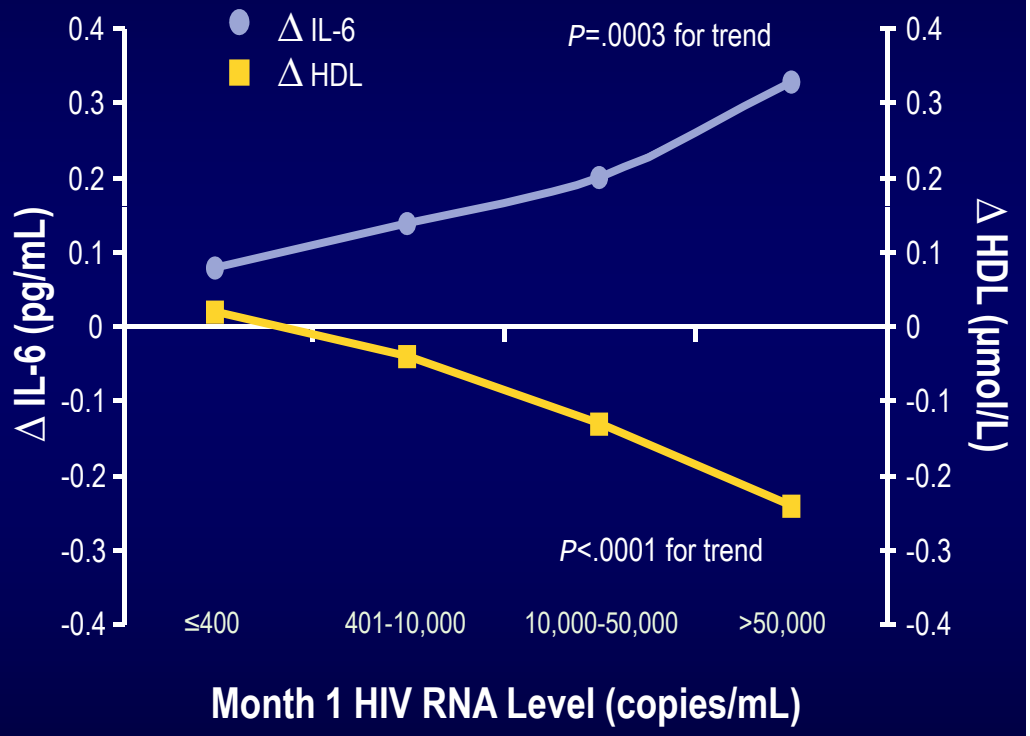
El-Sadr W et al. *N Engl J Med.* 2006; 355:2283-2296.

SMART: Changes in D-Dimer and IL-6 Levels

Change in D-Dimer*, BL to 1 Month



Change in Log IL-6 (pg/mL) and HDL (µmol/L) BL to 1 Month[2]*



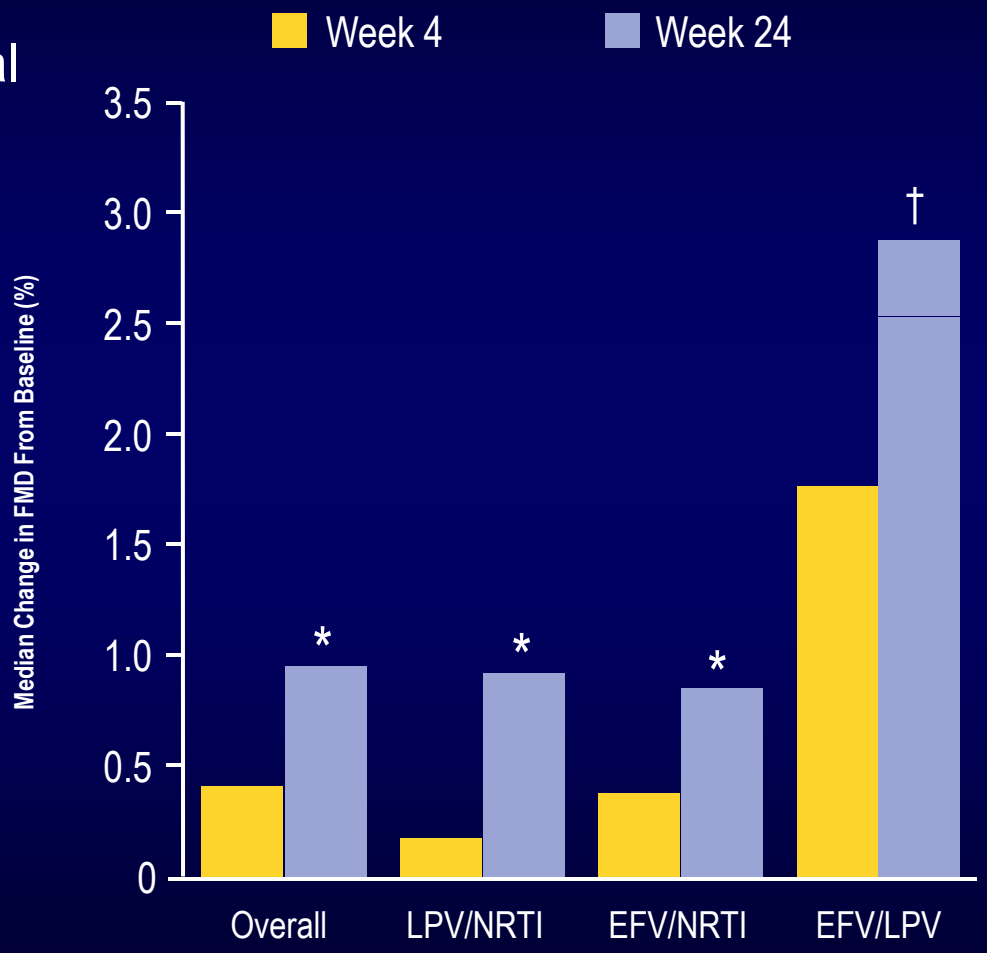
- Suggests HIV viremia effect on endothelium, leading to increased tissue factors and initiation of coagulation cascade

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

[1]Kuller L, et al. PLoS 2008;10:1496-1508. [2]SMART/INSIGHT: Duprez et al, CROI, 2009.

A5152s: VL Decrease Associated With Improved Endothelial Function

- HIV infection affected endothelial function
  - Baseline FMD: 3.7%
- FMD improved during HAART
- No consistent correlations between changes in FMD and changes in any lipids or glycemic parameter
- Improvement in FMD significantly associated with decrease in VL at Week 24
  - No relationship with baseline VL



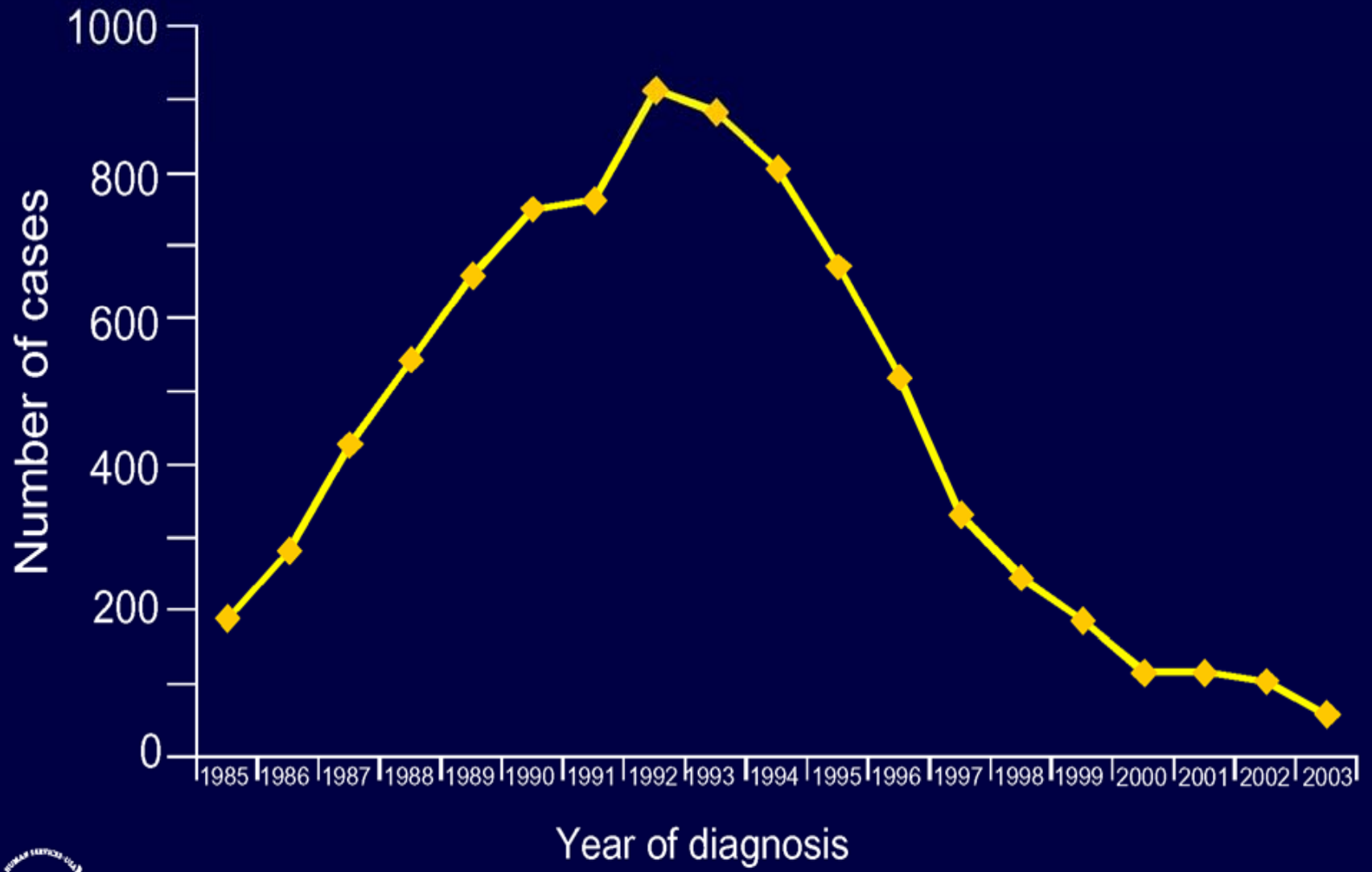
*P<0.01 compared with baseline.

†P<0.01 compared with baseline and within group.

Torriani F, et al. J Am Coll Cardio 2008;52:569.

Effect on Transmission

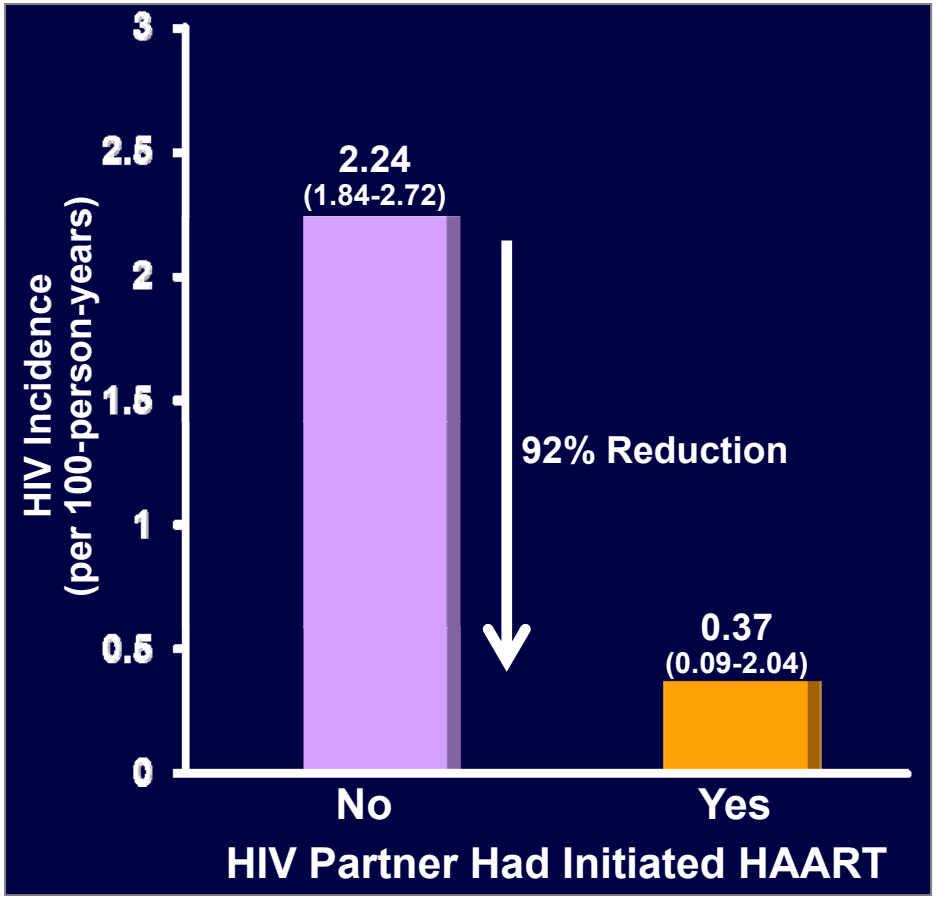
Estimated perinatally acquired AIDS cases- United States



Note: Data adjusted for reporting delays and for estimated proportional redistribution of cases in persons Initially reported without an identified risk factor.

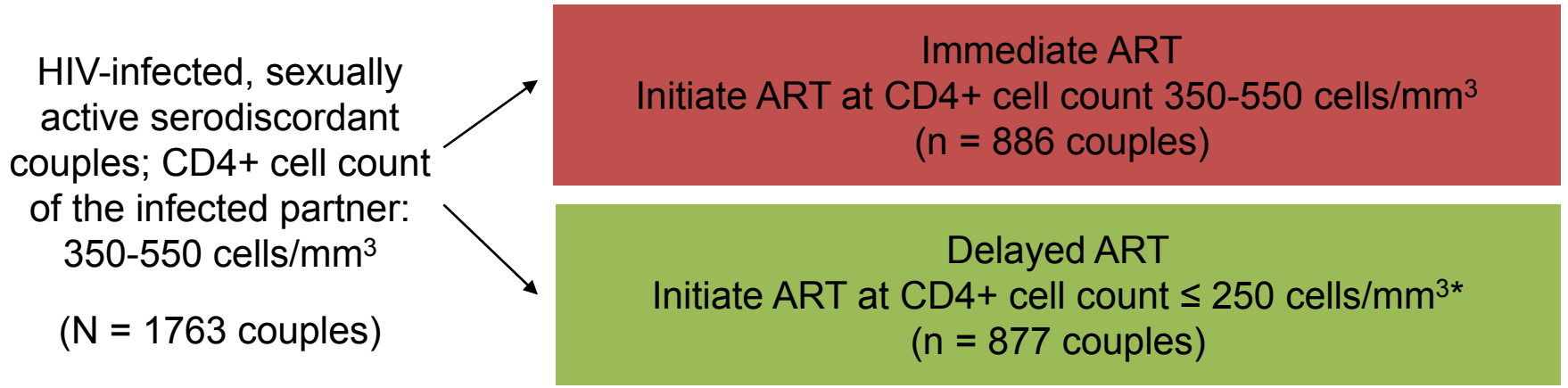
Heterosexual HIV Transmission After ART Initiation in Discordant Couples

- Partners for the Prevention of HSV/HIV Transmission study
  - Prospective cohort analysis of discordant couples (n=3381)
  - 7 African countries
- HIV-infected partners starting HAART (n=349)
  - Genetically linked HIV transmission (n=103)
- Follow-up
  - Up to 24 months



Donnell D, et al. *Lancet.* 2010;375:2092-2098.

HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples



*Based on 2 consecutive values ≤ 250 cells/mm^3.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

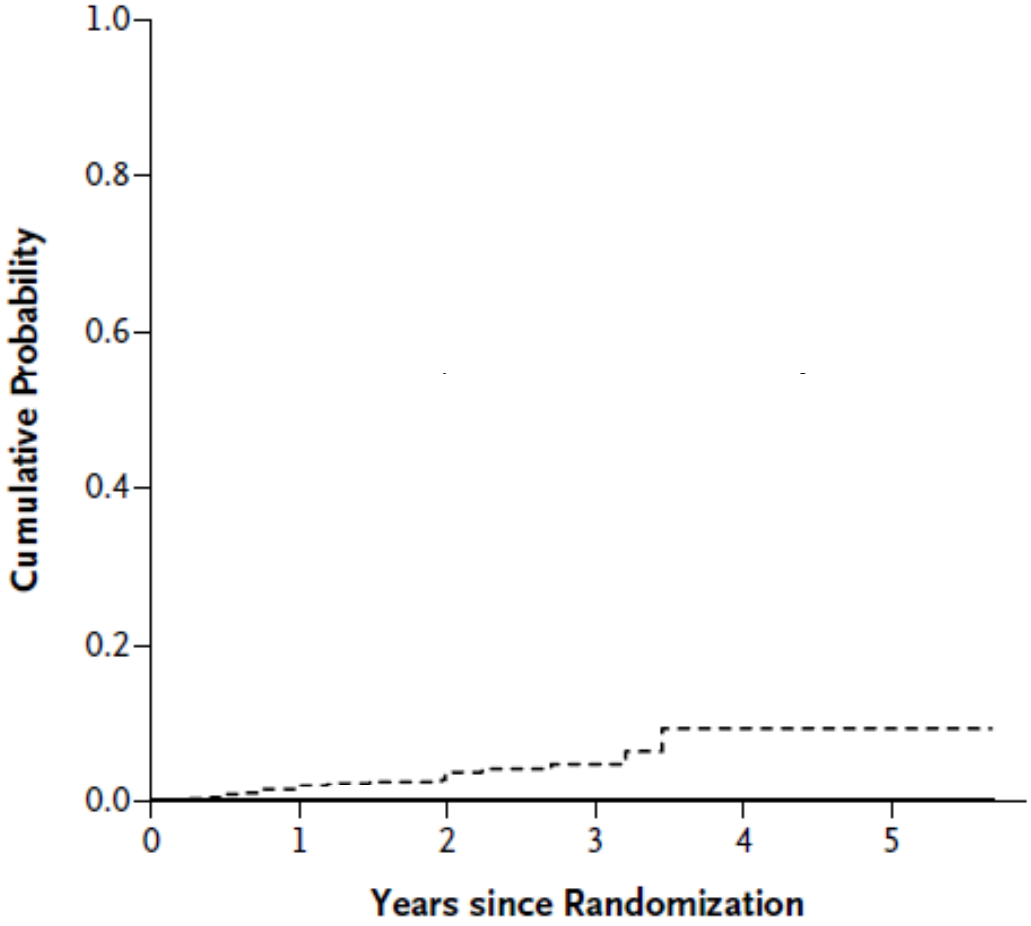
Cohen MS, et al. IAS 2011. Abstract MOAX0102.
Cohen MS, et al. N Engl J Med. 2011 Jul 18. [Epub ahead of print]

HPTN 052: ARV in Discordant Couples

- Study began April 2005 in Africa, Asia, Brazil, India, US; planned f/u through 2015
- N=1763 couples (97% heterosexual) CD4 350-550 cells/uL and sex with partner >2 times in last 3 months (50% HIV-infected were men)
  - Immediate ART vs. starting with symptoms or CD4<250 cells/uL
- DSMB reviewed on April 28, 2011 and found that study met stopping rules for both transmission and clinical events (median f/u 1.7 yrs)
- DSMB recommended closure of study

Cohen M, et al. NEJM July 18, 2011.

Linked HIV Transmission Events

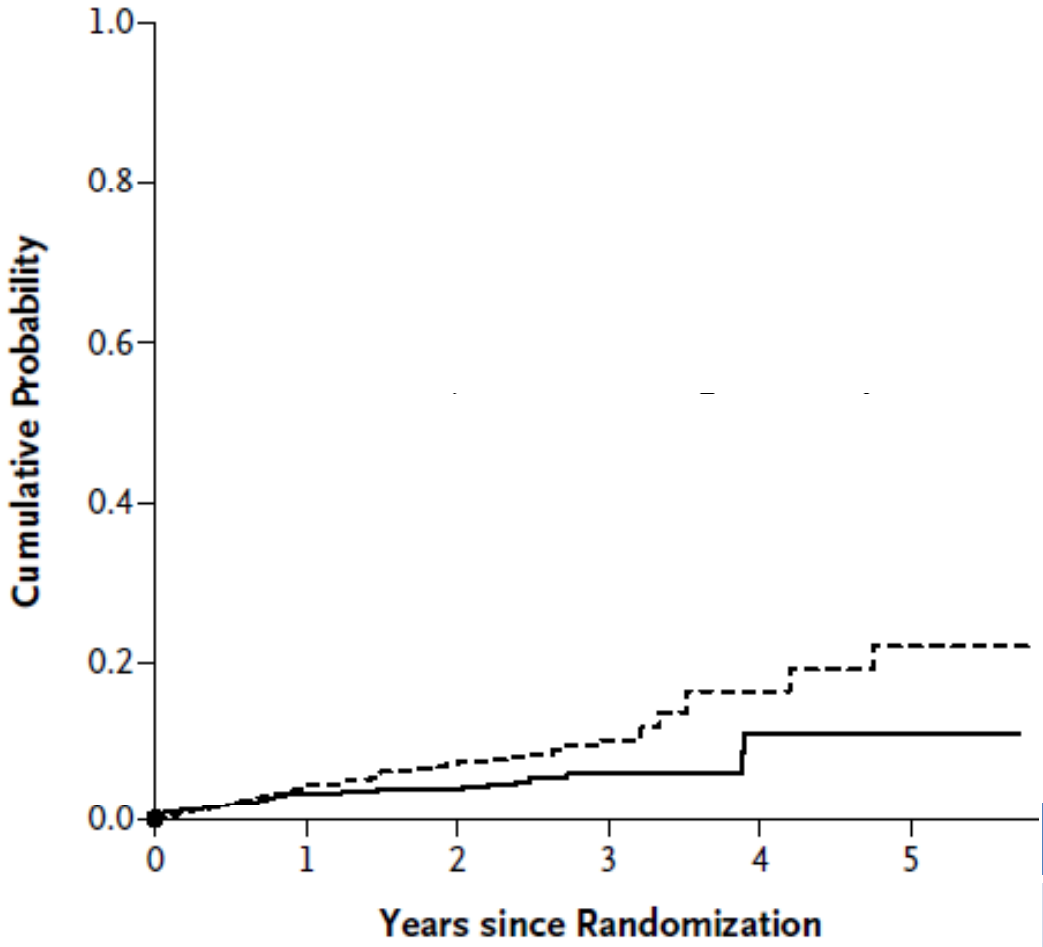


No. at Risk						
Early	893	658	298	79	31	24
Delayed	882	655	297	80	26	22

- 61% transmitters had CD4>350 cells/uL at time of Tx with 67% being women
- Tx in early group within 1 month of enrollment
- All Txs in delayed group prior to starting ARVs
- 82% of Tx at African sites

Cohen M, et al. NEJM July 18, 2011.

Clinical Events



No. at Risk						
Early	886	700	333	85	36	29
Delayed	877	701	317	86	32	25

Event	Delayed (n)	Early (n)
Extrapul TB	17	3
Pul. TB	15	13
Deaths	13	10

Cohen M, et al. NEJM July 18, 2011.

When to Start: 2011 DHHS Guidelines

CD4+ Cell Count	Recommendation
▪ CD4+ cell count < 350 cells/mm³	▪ Start ART
▪ CD4+ cell count 350-500 cells/mm³	▪ Start ART*
▪ CD4+ cell count > 500 cells/mm³	▪ Panel divided†
Clinical Conditions Favoring Initiation of Therapy Regardless of CD4+ Cell Count	
▪ History of AIDS-defining illness ▪ Certain acute opportunistic infections ▪ Pregnancy ▪ HIVAN ▪ HBV coinfection when HBV treatment is indicated ▪ CD4+ count decline > 100 cells/mm³ per yr ▪ HIV-1 RNA > 100,000 copies/mL	

*Panel divided: 55% strongly recommend and 45% moderately recommend. †50% favor initiating therapy at this stage. 50% view initiating therapy at this stage as optional.

Adapted from US Department of Health and Human Services Guidelines; Revised January 10, 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

IAS-USA Guidelines 2010: When to Start

Asymptomatic Infection	Recommendation
▪ CD4+ cell count < 500 cells/mm³	▪ Start HAART
▪ CD4+ cell count > 500 cells/mm³	▪ Should be considered*

Clinical Conditions Favoring Initiation of Therapy Regardless of CD4+ Cell Count

- Symptomatic HIV disease
- Acute opportunistic infection
- Pregnant women
- Older than 60 yrs of age
- HIV-1 RNA > 100,000 copies/mL
- Rapid decline in CD4+ cell count (> 100 cells/mm³/yr)
- Active HBV or HCV infection
- Active or high risk for CV disease
- Symptomatic primary HIV infection
- HIVAN
- Serodiscordant couples

*Unless patient is elite controller or has stable CD4+ cell count and low HIV-1 RNA in absence of antiretroviral therapy.

Thompson MA, et al. JAMA. 2010;304;321-333.

Rationale for Recommending Therapy for Those with >350 CD4 cells/uL

- Recent cohort studies (4 for 350-500 cells/uL and 1 for >500 cells/uL)
- HIV replication associated with non-AIDS-defining diseases (e.g. cardiovascular, renal, liver, malignancy)
- Evidence that ARVs may reduce risk of transmission
- ARV more effective, convenient, better tolerated than in the past

US Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/Guidelines.

Discussion

- What do people think of current guidelines related to when to start therapy?
- How do existing data and guidelines influence current practice?
- If you promote the idea of early therapy (e.g. >500 CD4 cells), how receptive are patients?
- How does prevention message/data influence practices and fit into discussion with patients?