Update in HIV Medicine for the Generalist

Society of General Internal Medicine
33rd Annual Meeting
Minneapolis, Minnesota
April 30, 2010

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SGIM HIV/AIDS Interest Group

Disclosures

- Dr. Cofrancesco has been a consultant for Gilead Sciences
- No other disclosures

Learning Objectives

At the end of this session, participants will be able to:

1. Describe the most recent data on HIV prevention, including an update on HIV vaccine development.

2. Discuss the recommendations and emerging evidence for routine HIV testing, particularly in community-based settings.

3. Interpret the most recent data on initiation and selection of antiretroviral therapy and HIV management.

4. Apply these findings to their own clinical practice.

Methodology

- Literature review of peer-reviewed studies dealing with the management of HIV as relevant to the generalist physician, published since March 2008
  - PUBMED Medical Subject Heading (MeSH) search limited to articles published on or after March 2008
  - Review of published studies in the major peer-reviewed general medicine and HIV journals since March 2008
- Final articles were selected by group consensus of HIV experts and practicing clinicians

Agenda

- Prevention update Chaudhry
- Testing update: Gifford
- Treatment update: Berkenblit

Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission

Lut Van Damme, M.D., Roshini Govinden, Ph.D., Florence M. Mirembe, Ph.D., Fernand Guédou, M.D., Suniti Solomon, M.D., Marissa L. Becker, M.D., B.S. Pradeep, M.D., A.K. Krishnan, B.A., Michel Alary, M.D., Bina Pande, M.D., Gita Ramjee, Ph.D., Jennifer Deese, M.P.H., Tania Crucitti, M.S., Doug Taylor, Ph.D., for the CS Study Group

NEJM. 2008. 359:463-472

Cellulose Sulfate and HIV Transmission

- More than half of all adults living with HIV/AIDS in sub-Saharan Africa are women
- Strides have been made in prevention (condoms, male circumcision) but these depend largely on men
- Topical microbicides are a potential woman-initiated method that have been investigated for prevention
- Cellulose sulfate is an entry inhibitor with in-vitro activity against HIV, *N. gonrrhoeae*, and *C. trachomatis whose s*afety and tolerability have been demonstrated
- This is a randomized, double-blind, placebo-controlled trial that was prematurely halted

Van Damme L et al. N Engl J Med 2008;359:463-472

Methods

- Women were recruited from 5 sites (Cotonou, Benin; Chennai, India; Durban, South Africa; Kampala, Uganda; Karnataka, India)
- Eligibility: Age ≥18; negative HIV-antibody test, ≥ 3 acts of vaginal intercourse/week, ≥ 3 different partners in previous 3 months
- Intervention: 6% cellulose sulfate gel vs. placebo
- At all study visits: counseling, free condoms, and treatment for curable STI
- Primary outcome: incident HIV-1 or HIV-2 infection
- Secondary outcome: incident *N. gonrrhoeae* or *C. trachomatis*

Van Damme L et al. N Engl J Med 2008;359:463-472

Results

- The two groups were similar in terms of demographics, medical history and baseline sexual behavior (self-reported)
- Sexual activity significantly higher in Benin and Uganda
- 1398 women included in the primary effectiveness analysis

Study group	N	Median No. partners	Median No. sexual acts	Gel use (% of all acts)	Condom use (% of all acts)	Gel use when condom not used (% of acts without condom
Cellulose Sulfate	702	3.5	6.7	87.4	95.3	45.9
Placebo	691	3.3	6.5	86.7	96.1	45.7

Adapted from Van Damme L et al. N Engl J Med 2008;359:463-472

Halting the Trial

- Data monitoring board reviewed the data according to predetermined specifications (when approximately half of expected HIV infections occurred)
- At the interim analysis, there were 35 new HIV infections: 24 in the cellulose sulfate group and 11 in the placebo group (estimated HR 2.23 p=0.02)
- The trial was stopped per recommendations of the data monitoring committee
- Final effectiveness analysis was performed

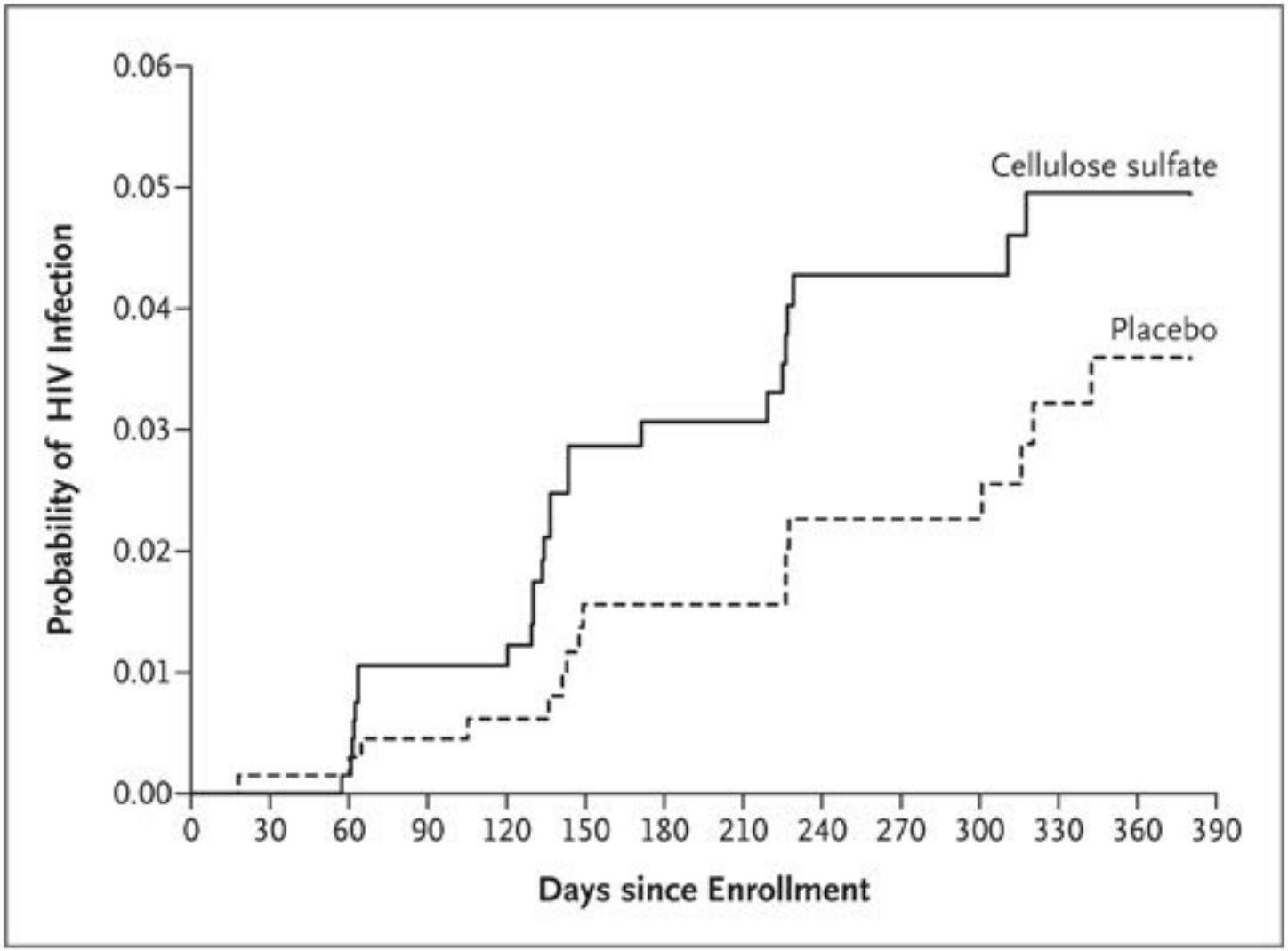
Van Damme L et al. N Engl J Med 2008;359:463-472

Results

Analysis	Cellulose sulfate (n=706)		Placebo (N=692)		Hazard Ratio (95% CI)	P value
	No. with event	rate	No. with event	Rate		
Primary	25	5.29	16	3.33	1.61 (0.86-3.01)	0.13
Per-Protocol	21	5.11	11	2.59	2.02 (0.97-4.18)	0.05
Interim	24	6.75	11	3.03	2.23 (1.05-5.03)	0.02

Adapted from Van Damme L et al. N Engl J Med 2008;359:463-472

Kaplan-Meier Estimates of the Cumulative Probability of HIV Infection



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Van Damme L et al. N Engl J Med 2008;359:463-472

Implications

- There was a higher incidence of HIV in the cellulose sulfate group: however this did not reach significance in the primary analysis
- There were non-differential pregnancy rates in the 2 groups, suggesting that non-adherence might be an issue
- Cellulose sulfate is not effective in the prevention of vaginal HIV transmission
- There is a critical need for identifying woman-initiated and controlled HIV prevention methods

Van Damme L et al. N Engl J Med 2008;359:463-472

Acyclovir and Transmission of HIV-1 from Persons Infected with HIV-1 and HSV-2

C. Celum, A. Wald, J.R. Lingappa, A.S. Magaret, R.S. Wang, N. Mugo, A. Mujugira, J.M. Baeten, J.I. Mullins, J.P. Hughes, E.A. Bukusi, C.R. Cohen, E. Katabira, A. Ronald, J. Kiarie, C. Farquhar, G.J. Stewart, J. Makhema, M. Essex, E. Were, K.H. Fife, G. de Bruyn, G.E. Gray, J.A. McIntyre, R. Manongi, S. Kapiga, D. Coetzee, S. Allen, M. Inambao, K. Kayitenkore, E. Karita, W. Kanweka, S. Delany, H. Rees, B. Vwalika, W. Stevens, M.S. Campbell, K.K. Thomas, R.W. Coombs, R. Morrow, W.L.H. Whittington, M.J. McElrath, L. Barnes, R. Ridzon, L. Corey, for the Partners in Prevention HSV/HIV Transmission Study Team

NEJM. 2010. 362:427-439

Acyclovir and HIV Transmission

- In HIV-1 infected populations, the seroprevalence of HSV ranges from 60-90%

- Studies suggest that HSV may increase HIV infectiousness
  - In coinfected cells, HSV proteins bind HIV and promote transcription
  - In coinfected individuals, HSV reactivation is associated with increased HIV in blood and genital tract
  - Rates of sexual HIV transmission are markedly higher from persons with genital ulcers
  - Several RCTs have demonstrated that anti-HSV therapy decreases plasma HIV levels

- This study is an RCT designed to evaluate the effect of daily acyclovir therapy on HIV transmission

Celum C et al. N Engl J Med 2010;362:427-439

Methods

- HIV serodiscordant heterosexual couples from 7 sites in southern Africa and 7 sites in eastern Africa.
- HIV-infected partner seropositive for HSV, CD4 ≥ 250, no AIDS-related conditions, no current ARV therapy, no persistent genital ulcers. HIV-negative partner HSV negative or positive
- Intervention: acyclovir 400 mg twice daily vs. placebo
- All persons received intensive counseling, condoms and were treated for STI (including HSV) at all study visits
- Primary outcome: HIV incidence. HIV sequencing was used to classify the transmission as ‘linked’ or ‘unlinked’

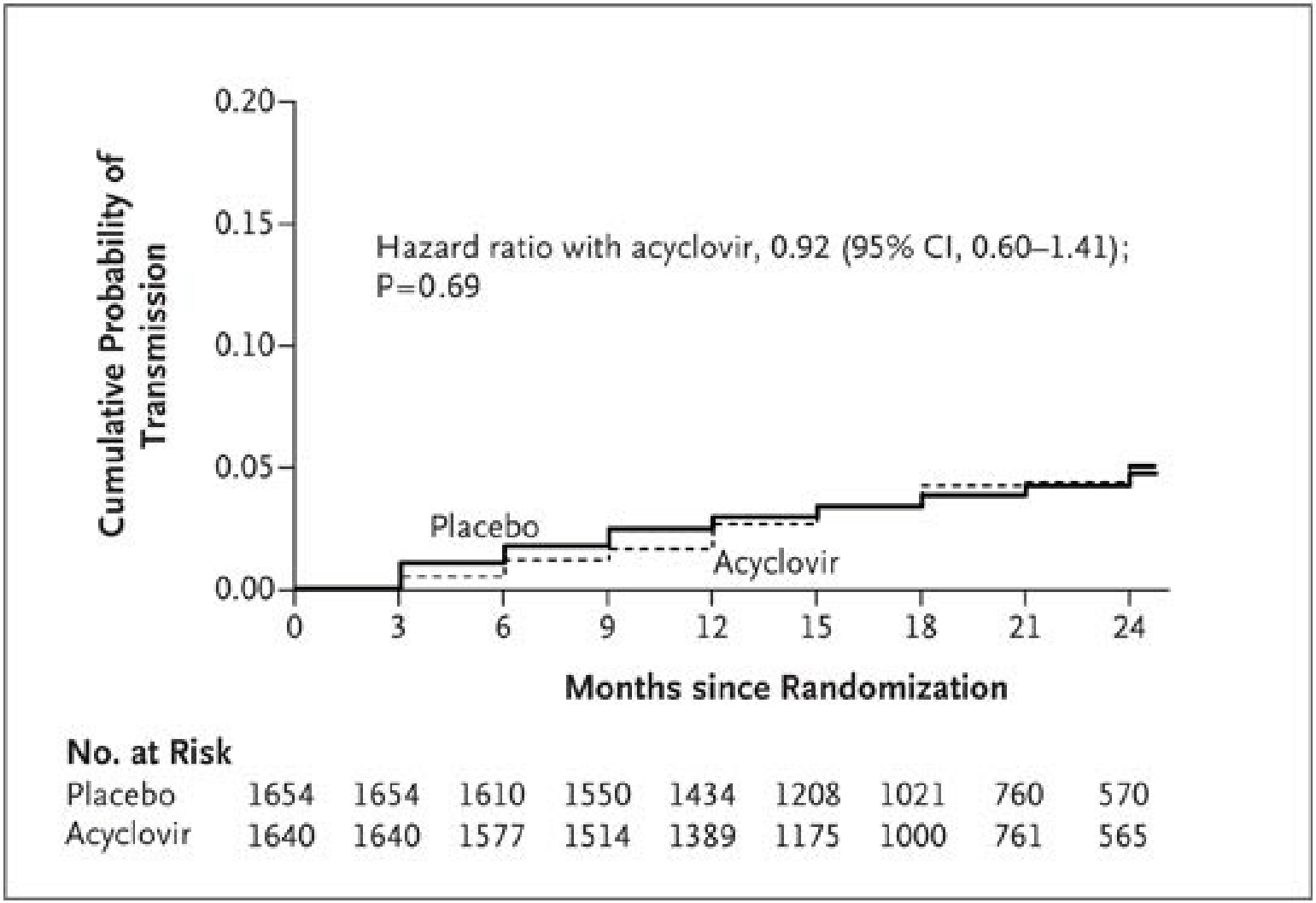
Celum C et al. N Engl J Med 2010;362:427-439

Results

- 3408 discordant couples randomized. 24 couples in each arm were excluded. 3360 included in the final analysis
- Baseline characteristics similar. In 68% of couples, the woman was HIV-infected. Median CD4 count was 462 cells/$mm^{3.}$ 68% of HIV-negative partners had HSV-2
- 132 new HIV infections, an incidence of 2.7 per 100 person-years (95% CI: 2.3 to 3.2)
- 84 linked transmissions included in the analysis
  - 41 in the acyclovir group, 43 in the placebo group
  - HR 0.92 (95% CI: 0.60-1.41)

Celum C et al. N Engl J Med 2010;362:427-439

Kaplan-Meier Curves for the Modified Intention-to-Treat Analysis



No. at Risk

Placebo	1654	1654	1610	1550	1434	1208	1021	760	570
Acyclovir	1640	1640	1577	1514	1389	1175	1000	761	565

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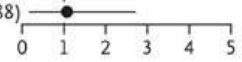
Celum C et al. N Engl J Med 2010;362:427-439

HIV-1 Seroconversion Events, Overall and within Subgroups

Cohort	Acyclovir				Placebo				Total		Hazard Ratio (95% CI)	P Value
	No.	No. of HIV-1 Seroconversion Events	Person-Yr of Follow-up	Rate per Person-Yr	No.	No. of HIV-1 Seroconversion Events	Person-Yr of Follow-up	Rate per Person-Yr	No.	No. of HIV-1 Seroconversion Events		
Overall												
Modified intention-to-treat analysis	1654	41	2323	0.018	1640	43	2290	0.019	3294	84	0.92 (0.60–1.41)	0.69
Intention-to-treat analysis	1657	67	2459	0.027	1645	64	2409	0.027	3302	131	0.99 (0.71–1.40)	0.97
HIV-1–infected partners												
Sex												0.88
Female	1101	21	1507	0.014	1117	23	1502	0.015	2218	44	0.94 (0.51–1.76)	
Male	553	20	816	0.025	523	20	788	0.025	1076	40	0.88 (0.49–1.60)	
HIV-1 plasma viral load at baseline												0.69
<10,000 copies/ml	758	5	1058	0.005	782	6	1092	0.005	1540	11	0.88 (0.27–2.88)	
10,000–49,999 copies/ml	474	12	678	0.018	458	16	654	0.024	932	28	0.68 (0.32–1.43)	
50,000–99,999 copies/ml	159	11	220	0.050	162	7	215	0.033	321	18	1.42 (0.55–3.67)	
≥100,000 copies/ml	247	13	341	0.038	224	14	311	0.045	471	27	0.82 (0.39–1.75)	
Genital ulcer disease in 3 mo before enrollment												0.24
Symptoms	379	12	541	0.022	368	8	528	0.015	747	20	1.46 (0.60–3.59)	
No symptoms	1275	29	1782	0.016	1272	35	1763	0.020	2547	64	0.79 (0.48–1.29)	
Adherence to study drug												0.36
<90%	284	10	328	0.030	277	5	350	0.014	561	15	1.80 (0.61–5.28)	
≥90%	1196	25	1776	0.014	1167	32	1715	0.019	2363	57	0.76 (0.45–1.28)	
HIV-1–uninfected partners												
Male circumcision status												0.21
Circumcised	601	11	851	0.013	621	9	861	0.010	1222	20	1.31 (0.54–3.18)	
Uncircumcised	500	10	656	0.015	496	14	641	0.022	996	24	0.61 (0.27–1.38)	
HSV-2 serologic status												0.79
Seropositive	1131	33	1596	0.021	1114	36	1587	0.023	2245	69	0.90 (0.56–1.44)	
Seronegative	523	8	726	0.011	526	7	704	0.010	1049	15	1.05 (0.38–2.88)	



Celum C et al. N Engl J Med 2010;362:427-439

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Implications

- Suppressive doses of acyclovir given up to 2 years did not reduce HIV transmission in this population, despite
  - Decreased HIV viremia
  - Decreased symptomatic genital ulcers

- Further strategies to decrease HIV transmission among serodiscordant couples are necessary

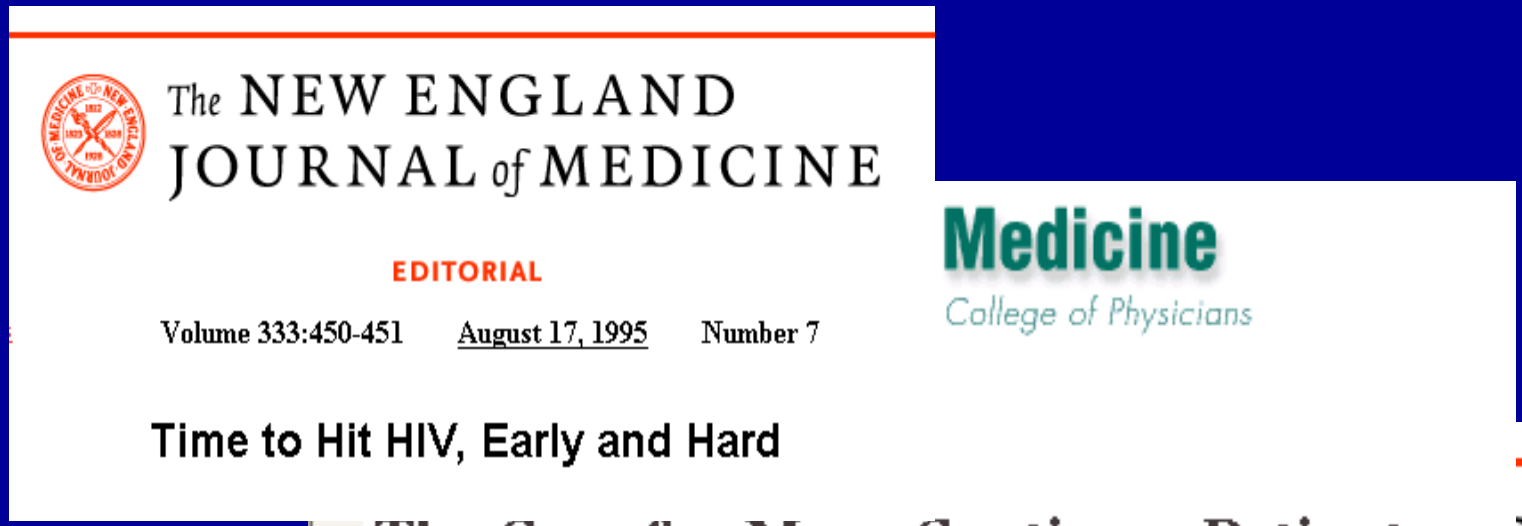
Celum C et al. N Engl J Med 2010;362:427-439

Additional Prevention Studies of Note

Rerks-Ngarm et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009; 361:2209-2220

Wawer et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet* 2009;374:229-37

When to Start?



The SMART Study: Subgroup Analysis of Naïve and Untreated Patients

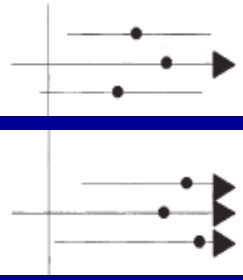
n = 2752 total
n = 249 subgroup

[Continuous Treatment]
Virologic Suppression (VS)

n = 2720 total
n = 228 subgroup

[Treatment interruptions]
Drug Conservation (DC)

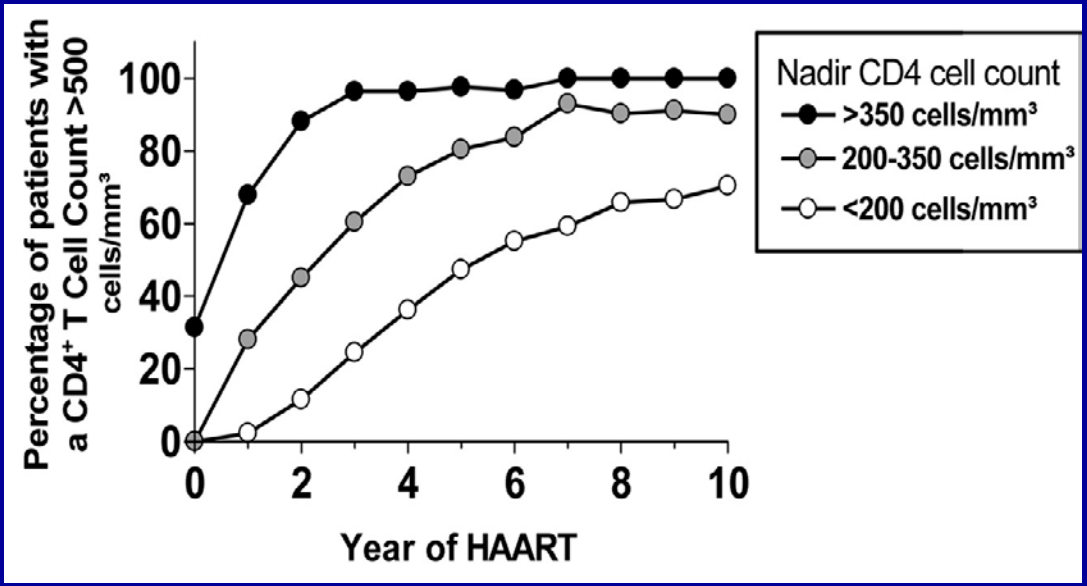
	No. Events (rate per 100 person years)			Hazard Ratio (DC/VS) and 95% Confidence Interval		
	DC	VS	HR (DC/VS)		P-value	P-value for Interaction
OD/Death						
Overall	15 (4.8)	5 (1.3)	3.5		0.02	
ART naïve	4 (2.7)	1 (0.5)	5.3		0.13	0.63
Off ART	11 (6.8)	4 (2.2)	2.7		0.09	
Serious Non-AIDS						
Overall	12 (3.9)	2 (0.5)	7.0		0.01	
ART naïve	4 (2.8)	1 (0.5)	5.1		0.15	0.76
Off ART	8 (4.8)	1 (0.5)	8.4		0.04	



SMART Study Group, JID 2008: 197

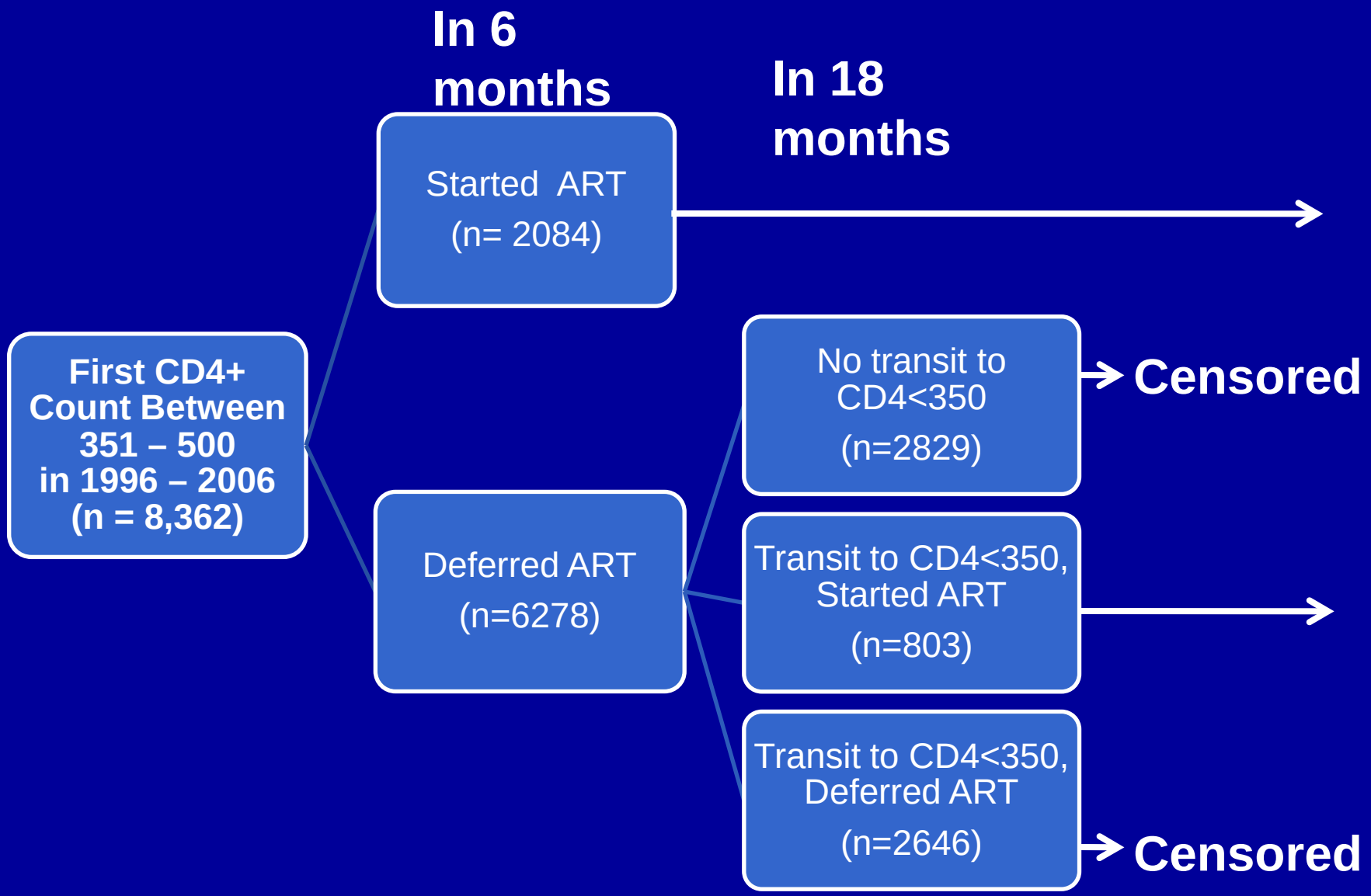
CD4 Count & Immune Reconstitution

- 365 patients from 5 clinical cohorts
- Maintained VL < 1000 over at least 4 years, median 7.5 yrs
- 83% men , median age 47, 12% HepC coinfection
- Regimens: Unboosted PI (64%), NNRTI (24%), boosted PI (6%)
- Bottom line: Median time to and likelihood of achieving CD4 ≥ 500 depends on starting CD4



Kelley, C et al, CID, 2009; 48: 787-94

NA-ACCORD Analysis



NA-ACCORD Baseline Characteristics

	Defer HAART n = 5,901	Initiate HAART n = 2,473
Follow Up Person-Years	16,636	8,358
Hepatitis C Virus Infection (%)*	34	27
History of Injection Drug Use (%)*	21	16
Males (%)	75	83
Median Age Years (IQR)	38 (32, 45)	40 (34, 48)
Median CD4+ Count Cells/mm^3 (IQR)	432 (391, 468)	421 (386, 459)
Median log_{10} HIV RNA Copies/mL (IQR)*	4.1 (3.3, 4.6)	4.3 (3.1, 4.9)
White (%)	38	39

*Among patients with known status

Adapted from Mari Kitahata et al. ICAAC/IDSA 2008; abstract H-896b

NA-ACCORD: Early versus Deferred ART

	Defer HAART & Initiate 200 – 350 n = 1,220	Initiate HAART 351 – 500 n = 2,473
Median (IQR) CD4+ Count Cells/mm^3 Prior to HAART Initiation	275 (210, 317)	421 (386, 459)
Median (IQR) Time in Months From First CD4+ Count in the Interval to HAART	2 (< 1 – 7)	1 (< 1 – 3)
Median Month/Year HAART Initiation (IQR)	5/01 (1/99, 5/03)	1/00 (5/98, 1/02)
Type of Initial HAART Regimen (%)		
NNRTI-Based	39	34
PI-Based (Boosted)	12	9
PI-Based (Non-Boosted)	37	46
NNRTI & PI-Based	3	4
≥ 3 NRTIs	8	7

NA-ACCORD: Early vs. Deferred ART

Risk of Death With Deferral of ART

CD4 Count	Relative Risk (95% CI)	*P* Value
351-500	1.69 (1.26-2.26)	<0.001
>500	1.94 (1.37-2.79)	<0.001

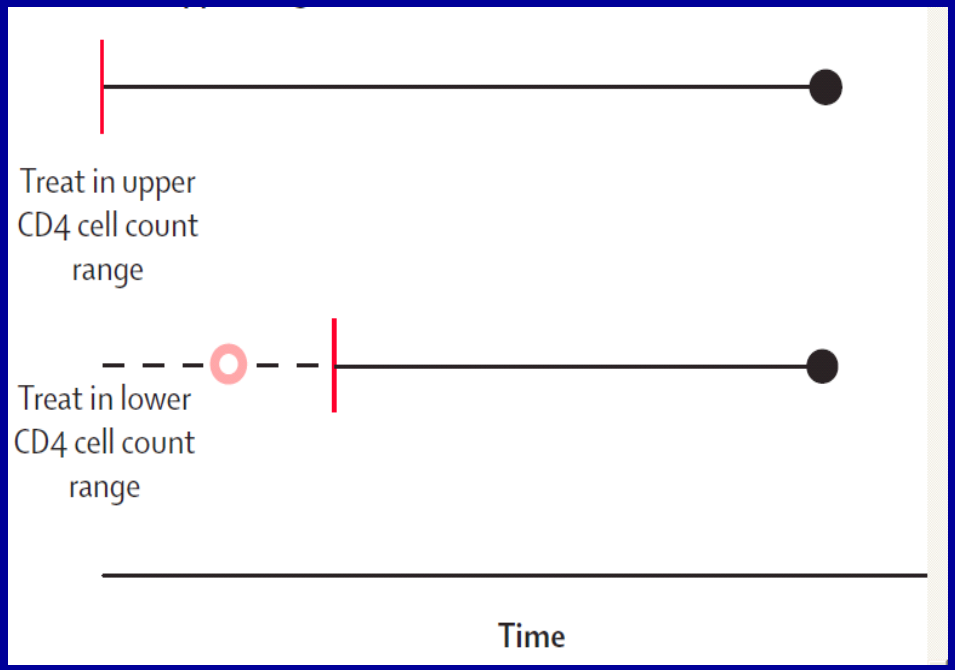
- Study controlled for factors that could affect decision to defer ART
  - Adjustment for sex, age, and CD4 counts at baseline
- VL response similar in early vs. deferred arms
- Results similar when IDUs excluded

- Limitations: observational study with potential for unmeasured confounding

Adapted from Kitahata MM, et al. *N Engl J Med.* 2009;360:1815-1826

ART-CC Analysis: Lead Time Adjustment

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

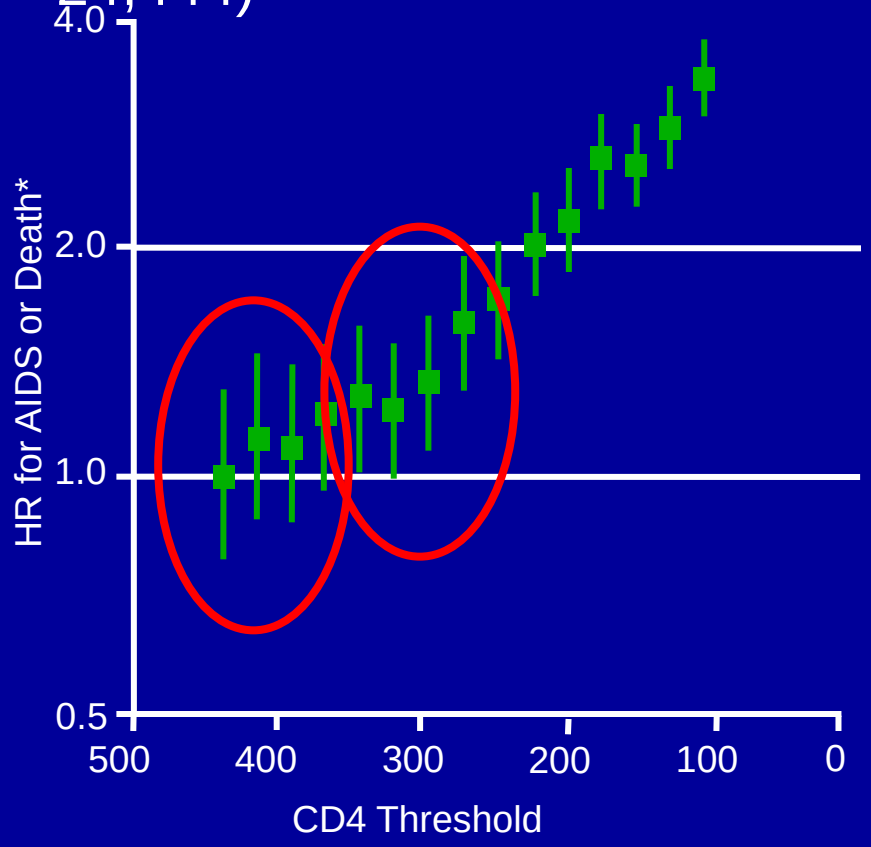


	Pre-HAART Era	Study Patients
Median Age	34 (28-41)	37 (31-45)
Male	77%	71%
MSM	56%	38%
Yrs of Enrollment	1989-1995	1998-2006

Adapted from When to Start Consortium, Lancet, 2009; 373:1352 – 63.

ART-CC: Prognosis based on CD4 count at initiation of ART

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



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

*Adjusted for lead-time and unobserved events.

Sterne J, et al. CROI 2009. Abstract 72LB. Graphic reproduced with permission for educational use only.

IDSA Guidelines

Initiation of Antiretroviral Therapy

In this updated version of the guidelines, the Panel recommends earlier initiation of antiretroviral therapy with the following specific recommendations:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with CD4 count < 350 cells/mm^3 (**AI**).
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy (**AI**), HIV-associated nephropathy (**AII**), and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (**AIII**).
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm^3. The Panel was divided on the strength of this recommendation: 55% of Panel members for strong recommendation (A) and 45% for moderate recommendation (B) (**A/B-II**).
- For patients with CD4 counts >500 cells/mm^3, 50% of Panel members favor starting antiretroviral therapy (B); the other 50% of members view treatment as optional (C) in this setting (**B/C-III**).

Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (**AIII**). Patients may choose to postpone therapy, and providers may elect to defer therapy, based on clinical and/or psychosocial factors on a case-by-case basis.

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents - December 1, 2009

Panel's Recommendations:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm3 (AI)

- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm3. The Panel was divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) (A/B-II)

- For patients with CD4 counts >500 cells/mm3, the Panel was evenly divided: 50% favor starting antiretroviral therapy at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III)

- Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

TAKE HOME POINTS

- 2 large cohort studies show benefit in starting above 350
- IDSA changed guidelines reflect
- Cohort studies are subject to bias, watch for RCT

- But…most people present at CD4 <350
  - *The question may not be when to start, but how to get people into care earlier*