

Top 10 HIV Issues of Past Year to 2010

Douglas G. Fish, MD
Albany Medical College
March, 2010

Cali, Colombia
March 26, 2010



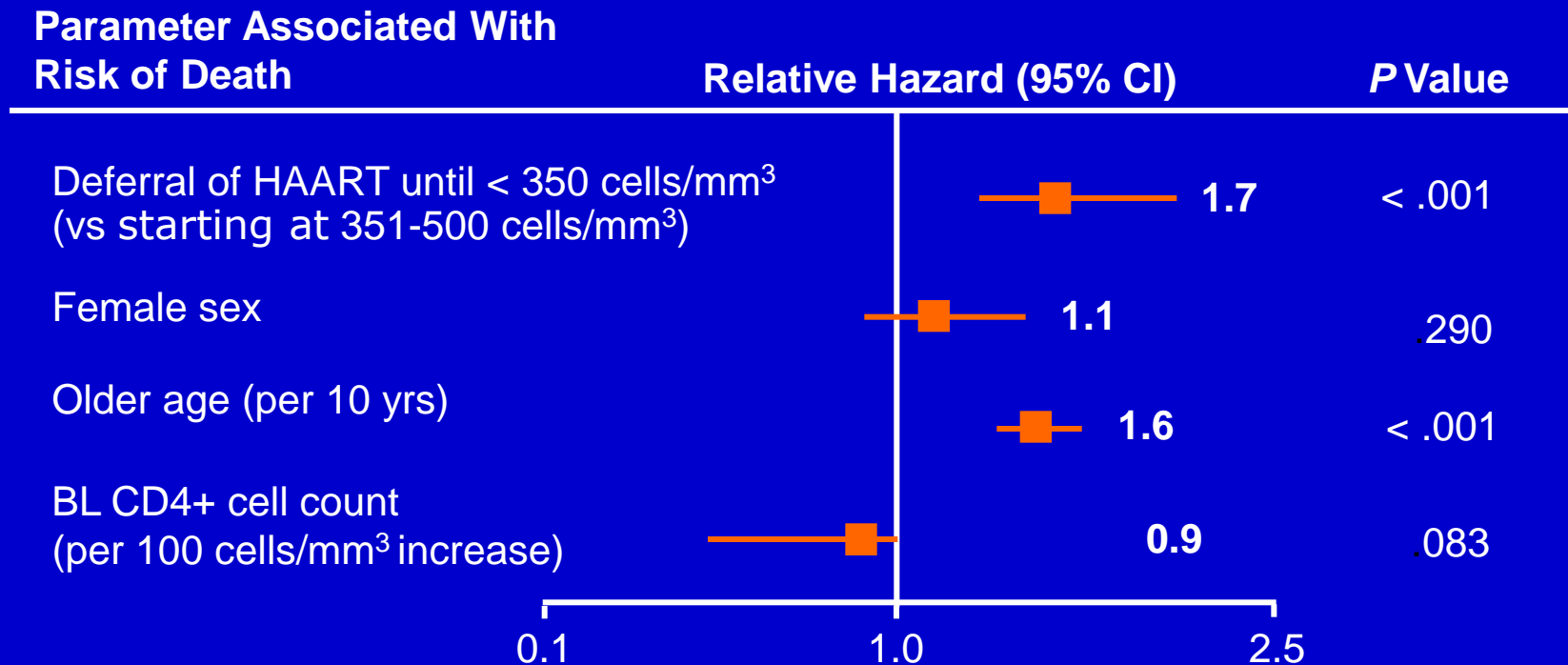
Top 10 HIV Issues

- 1) When to Start
- 2) Acute HIV Infection– If to Start
- 3) Cardiovascular Risk
- 4) Other Metabolic Concerns
- 5) Adverse Effects of HAART
- 6) Central Nervous System and HIV
- 7) Viral Tropism
- 8) HIV Vaccines
- 9) H1N1 Influenza A
- 10) HIV & U.S. Travel

NA-ACCORD: Earlier vs Deferred HAART

- NA-ACCORD, established in 2006, includes 22 HIV research cohorts
 - Current analysis includes patients with CD4+ cell count 351-500 cells/mm³ at study visit between 1996-2006
- Compared outcomes based on treatment according to following definitions:
 - Immediate treatment: initiated HAART within 1.5 years of first CD4+ cell count in 351-500 cells/mm³ range
 - Deferred treatment: did not initiate HAART within 1.5 years of first CD4+ cell count in 351-500 cells/mm³ range
 - Included patients who did not initiate treatment after reaching CD4+ cell count < 350 cell/mm³
- Primary outcome: Death from any cause

NA-ACCORD: Survival Benefit With Earlier vs Deferred HAART

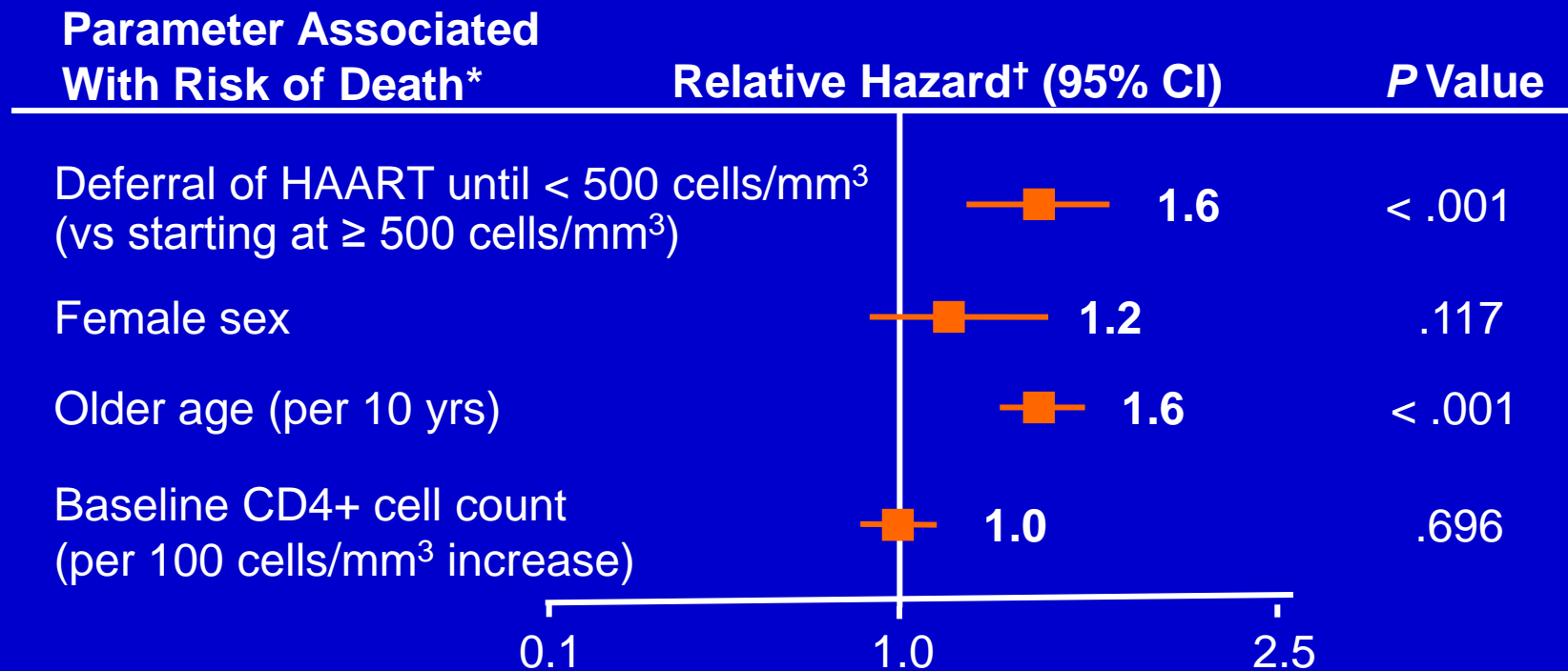


- Increased relative hazard of death with deferral of HAART remained unchanged when adjusted for IDU or for HCV coinfection, which were both independent predictors of mortality.

NA-ACCORD: Earlier vs Deferred HAART

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

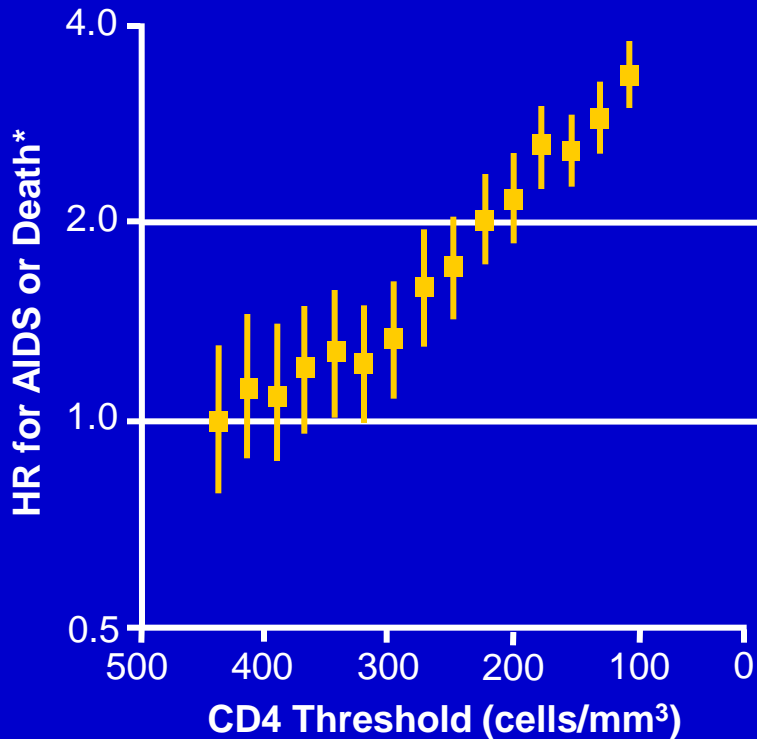
NA-ACCORD: Survival Benefit of Earlier HAART by Baseline Factor



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

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

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



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

*Adjusted for lead-time and unobserved events.

Sterne J, et al. CROI 2009. Abstract 72LB.

Graphic reproduced with permission for educational use only.

Clinicaloptions.com/hiv

2009 DHHS Indications for Initiating ART: Chronic HIV Infection

Clinical Category and/or CD4 Count	Recommendation
<ul style="list-style-type: none"> •History of AIDS-defining illness (AI) •CD4 <350 cells/mm³ •Pregnant women (AI) •HIV-associated nephropathy (AII) •Hepatitis B coinfection, when HBV treatment is indicated* (AIII) 	Initiate therapy
<ul style="list-style-type: none"> •CD4 count 350 – 500 cells/cmm (A/B-II) 	Antiretroviral therapy is recommended
<ul style="list-style-type: none"> •CD4 count > 500 cells/cmm (B/C-III) 	50% of panel favor; 50% optional

*Treatment with fully suppressive drugs active against both HIV and HBV recommended. DHHS Guidelines; Dec. 1, 2009 <http://AIDSinfo.nih.gov>.

Summary of Observational Cohort Analyses: When to Initiate HAART

- NA-ACCORD^[1]: initiating HAART at CD4+ cell count ≥ 500 cells/mm³ provided 60% survival benefit over deferring HAART to CD4+ count < 500 cells/mm³
- ART Cohort Collaboration^[2]: analysis supports initiating HAART at CD4+ cell count threshold of 350 cells/mm³
 - Smaller absolute risk of AIDS or death and mortality observed at CD4+ cell counts > 350 cells/mm³

1. Kitahata MM, et al. CROI 2009. Abstract 71.

2. Sterne J, et al. CROI 2009. Abstract 72LB.

Summary of Observational Cohort Analyses: When to Initiate HAART

- NA-ACCORD adjustment for lead-time bias: allowed HAART to be initiated within 1.5 years after BL CD4+ cell count
- ART CC adjustment for lead-time bias: events prior to HAART initiation derived from 7 different cohort studies (not ART CC) obtained between 1989 and 1996
 - Unobserved events during lead time imputed from historical observational data
 - Multiple imputation adjustments for error in lead time and unseen event estimation

Acute HIV:

If to Start?

The Prospective, Randomized Primo-SHM Study

- Randomized, open-label triple arm study for pts with primary HIV infection
- Temporary HAART :
 - 24 weeks (n=19) or
 - 60 weeks (n=18) vs
 - No therapy (n=11)
- HAART: Zidovudine/lamivudine + efavirenz + lopinavir/r
- Objective: Plasma viral load 36 weeks after seroconversion in no-therapy arm, or 36 weeks after therapy interruption in the treatment arm

Radjin Steingrover*^{1,2,3}, I Schellens⁴, A Verbon⁵, K Brinkman⁶, A Zwinderman⁴, S Jurriaans², F Miedema⁴, J Lange⁴, D van Baarle⁴, and J Prins^{1,2} *1*Ctr for Infection and Immunity Amsterdam, The Netherlands; *2*Academic Med Ctr, Amsterdam, The Netherlands; *3*Intl Antiviral Therapy Evaluation Ctr, Amsterdam, The Netherlands; *4*Univ Med Ctr, Utrecht, The Netherlands; *5*Academic Hosp Maastricht, The Netherlands; and *6*Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands. CROI 2008, Abstract 698b.

Temporary Antiretroviral Therapy During Primary HIV-1 Infection Lowers The Viral Set-point:

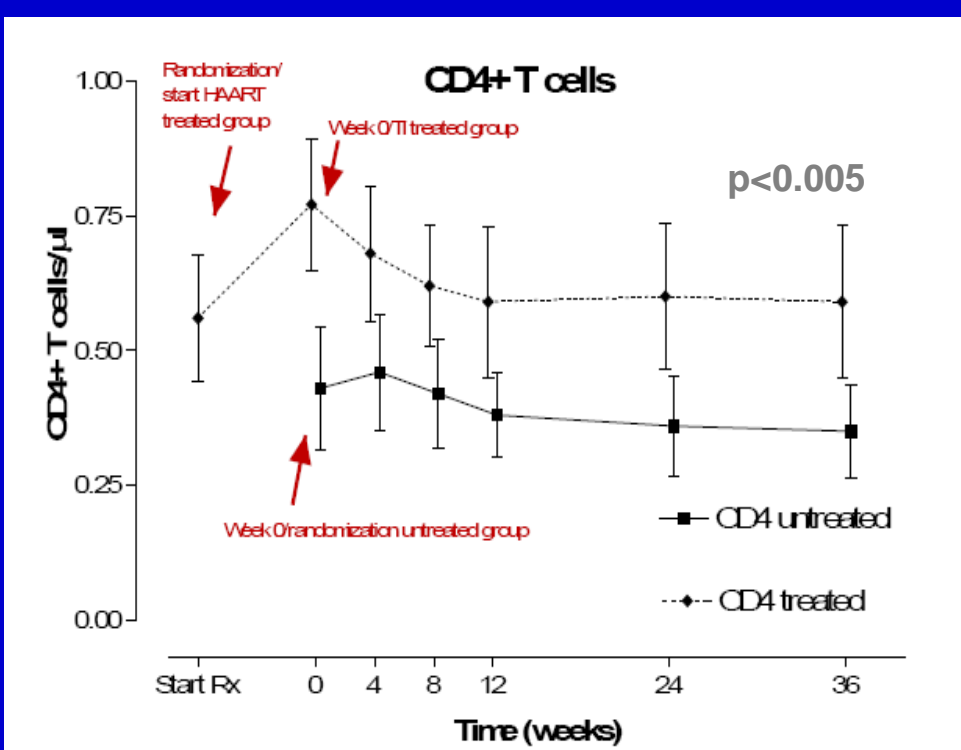
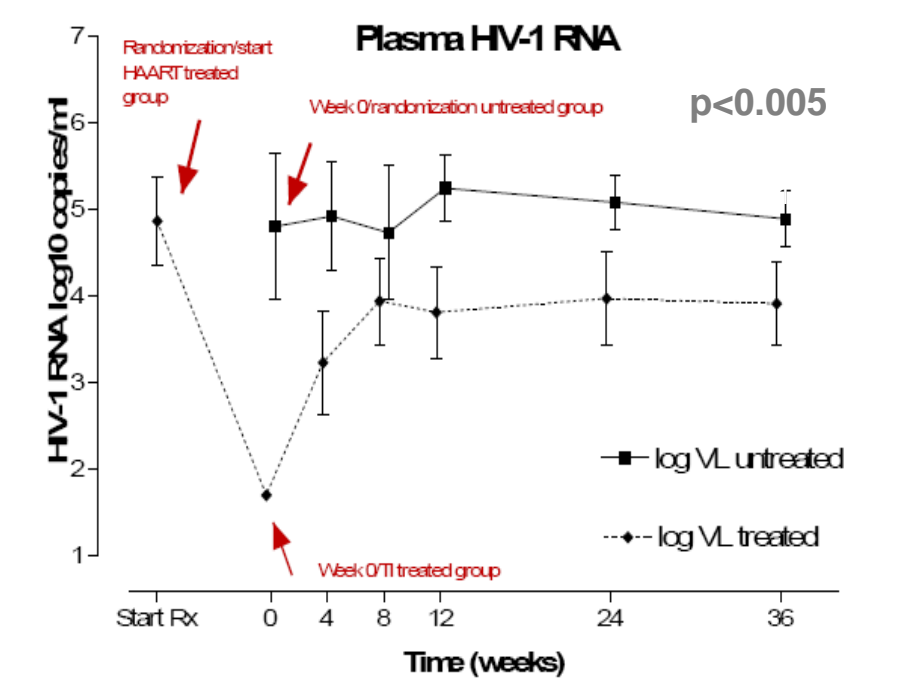
The Prospective, Randomized Primo-SHM Study

Radjin Steingrover^{1,2}, Ingrid Schellens³, Annelies Verbon⁴, Kees Brinkman⁵, Aeilko Zwinderman⁶, Suzanne Jurriaans⁷, Frank Miedema⁸, Joep Lange⁹, Debbie van Baarle³, Jan M. Prins¹



¹Dept. of Internal Medicine, Division of Infectious Diseases, Tropical Medicine and AIDS, and Center for Infection and Immunity Amsterdam (CIINA), Academic Medical Center, Amsterdam; ²International Antiviral Therapy Evaluation Center, Amsterdam; ³Department of Immunology, University Medical Center, Utrecht; ⁴Dept. of Internal Medicine, Academic Hospital Maastricht, Maastricht; ⁵Dept. of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam; ⁶Dept. of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam; ⁷Dept. of Medical Microbiology, Academic Medical Center, Amsterdam, all in The Netherlands

Results: treated vs. untreated



Conclusions: Primo-SHM Study

- “Both 24 and 60 weeks of HAART during PHI lower the plasma HIV-RNA set point after treatment interruption compared to no early treatment.”

Radjin Steingrover*^{1,2,3}, I Schellens⁴, A Verbon⁵, K Brinkman⁶, A Zwinderman⁴, S Jurriaans², F Miedema⁴, J Lange⁴, D van Baarle⁴, and J Prins^{1,2} *1Ctr for Infection and Immunity Amsterdam, The Netherlands; 2Academic Med Ctr, Amsterdam, The Netherlands; 3Intl Antiviral Therapy Evaluation Ctr, Amsterdam, The Netherlands; 4Univ Med Ctr, Utrecht, The Netherlands; 5Academic Hosp Maastricht, The Netherlands; and 6Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands. CROI 2008, Abstract 698b.*

Effect of ART of Different Durations in Primary HIV Infection

- ARVs initiated within first 6 months of HIV seroconversion
- 348 early treated patients; 675 deferred therapy
 - 147 received ART of limited duration
- Duration of HAART:
 - < 6 months: n = 38
 - 6 – 12 months: n = 40
 - > 12 months: n = 69

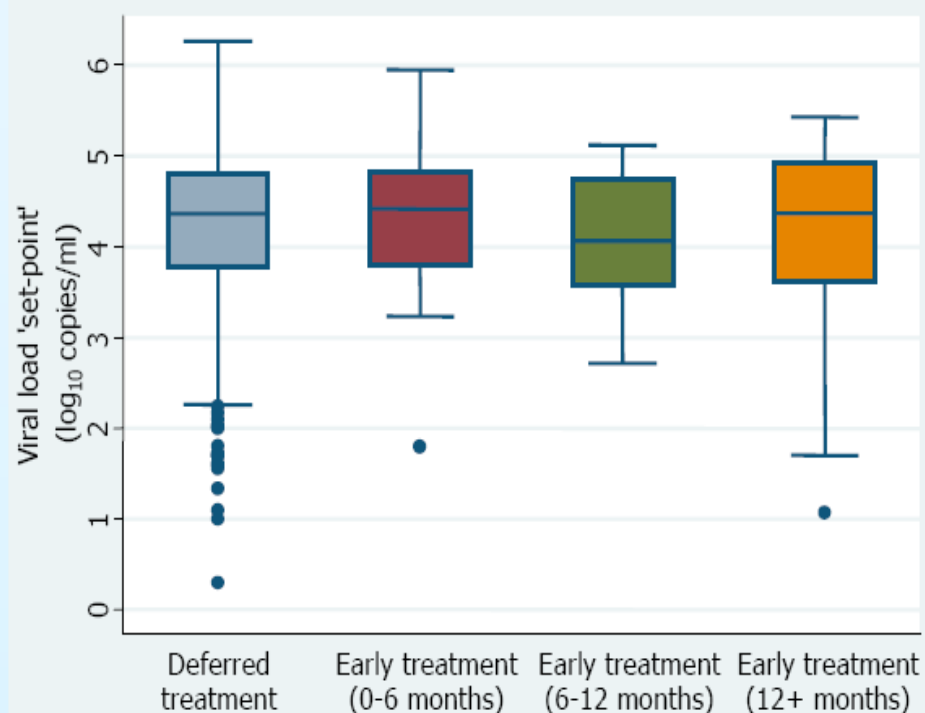
N Pantazis¹, Giota Touloumi*¹, P Vanhems², J Gill³, K Porter⁴, and CASCADE Collaboration
1Athens Univ Med Sch, Greece; 2CNRS UMR 5558, Univ Lyon 1, France;
3Southern Alberta HIV Clin, Calgary, Canada; and 4Med Res Council Clinical Trials Unit,
London, UK. CROI 2008, Abstract 697.

The effect of antiretroviral treatment of different durations in primary HIV infection

Nikos Pantazis¹, Giota Touloumi¹, Philippe Vanhems², John Gill³, Kholoud Porter⁴ and the CASCADE collaboration

1: Athens University Medical School, Athens, Greece; 2: Hospices Civils de Lyon, Hôpital Edouard Herriot, Département d'Hygiène, Epidémiologie et Prévention; Université de Lyon; université Lyon 1; CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Lyon, France; 3: Southern Alberta HIV Clinic, Calgary, Alberta, Canada; 4: MRC Clinical Trials Unit, London, UK

Figure 4. Viral load "set-point" (average of all viral load measurements/individual taken >1 year after SC and while both groups were off ART and "Early treatment" individuals had stopped HAART for at >6 months) and duration of "early" HAART.



Effect of ART of Different Durations in Primary HIV Infection

- “No difference in HIV RNA set-points between the early and deferred groups ($p = 0.43$).”
- “AIDS rates were similar but death rates were higher in the deferred group ($p = 0.05$), mainly due to an increased number of non-AIDS deaths in this group.”

Guideline Recommendations on Treating Acute Infection

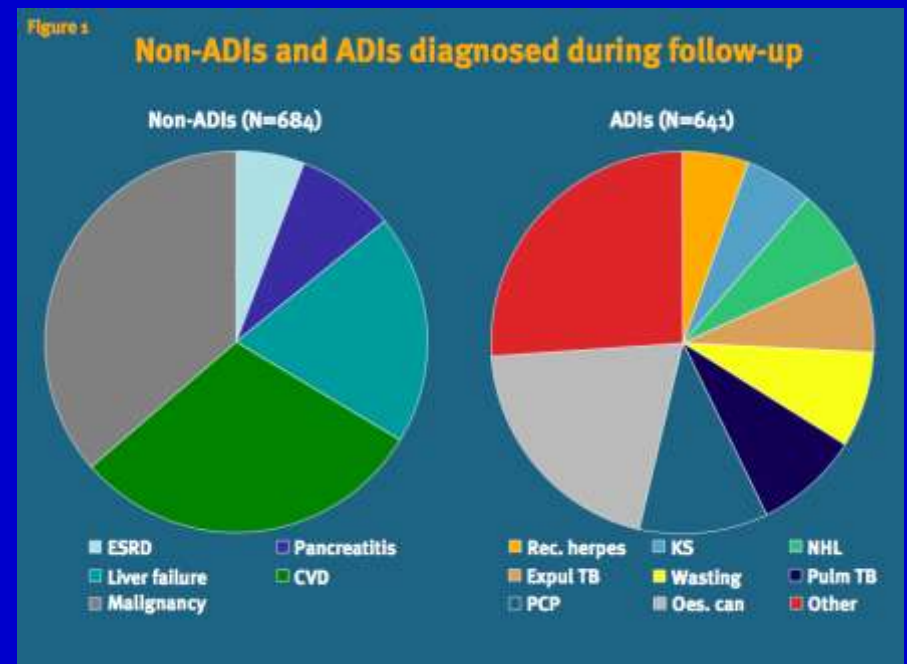
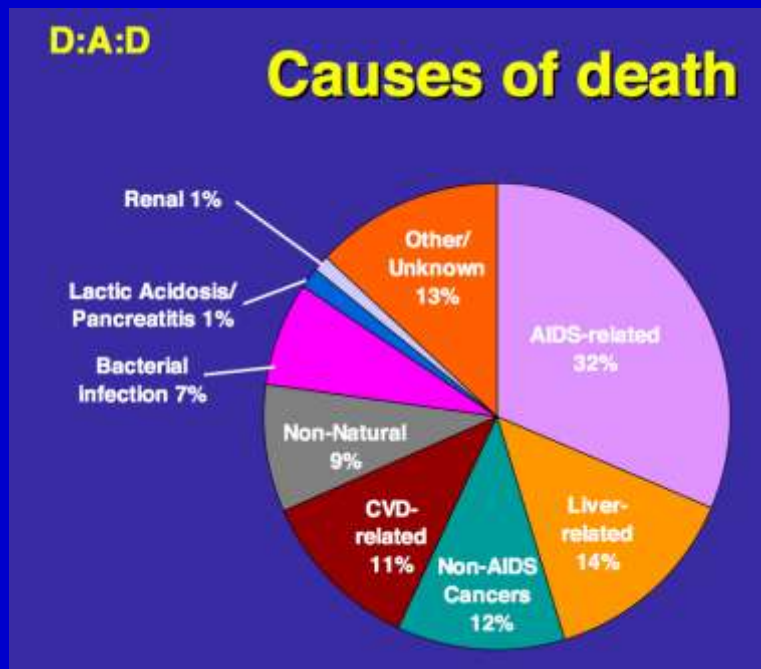
DHHS ^[1] 2009	IAS-USA ^[2] 2008
<p>“Whether treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown; treatment should be considered optional at this time”</p>	<p>“Although knowledge continues to evolve regarding the pathogenesis of primary HIV infection, no definitive evidence has emerged that supports routine initiation of antiretroviral therapy in primary HIV infection”</p>

1. DHHS guidelines. Available at: <http://www.aidsinfo.nih.gov>. Accessed March 14, 2010. 2. Hammer SM *et al.* *JAMA*. 2008;300:555-570.

3. Cardiovascular Risk

How Much CHD is There?

- D:A:D - 2,192 deaths/158,959 person-years = death rate of 13.8 per 1000 person years (95% CI 13.2 -14.4)¹



- EuroSIDA – Non-AIDS events more common and of these large proportion were due to CVD ²

¹Smith C, et al. CROI 2009 #145; ²Mocroft A, et al CROI 2009 #707.

Slide courtesy of Marshall Glesby, MD. Cornell University. NY/NJ AETC.

SMART Study and CV Events

- SMART: 5472 patients (84% on ART) randomized to continuation (viral suppression; VS) or CD4-guided treatment interruption (drug conservation; DC)

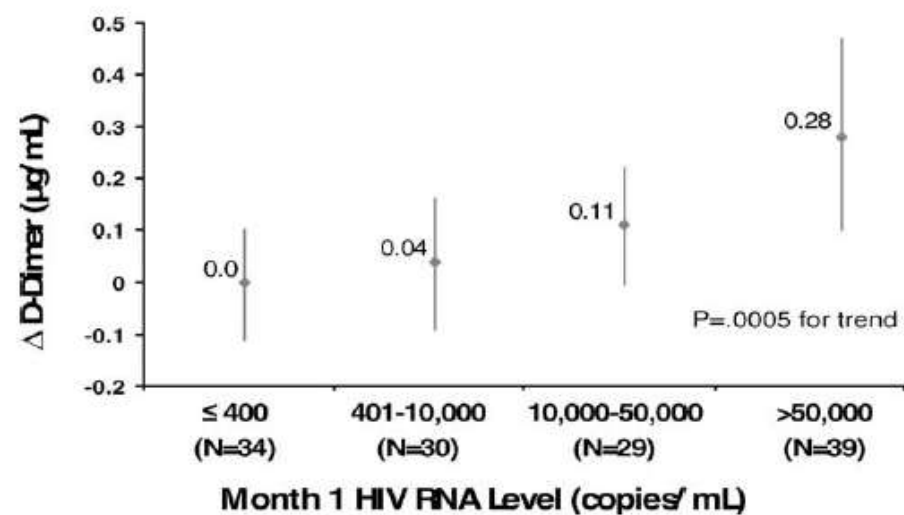
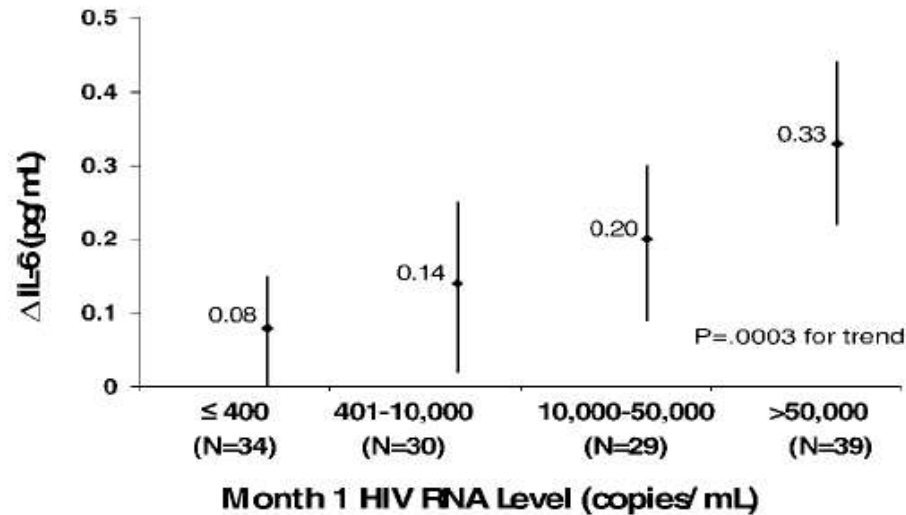
Events	DC	VS	RH (DC/VS)	95% CI	p-value
Clinical MI, silent MI, CAD requiring invasive procedure or surgery, CVD death	48	31	1.57	1.00–2.46	0.05
+ Peripheral vascular disease, CHF, CAD requiring medication	76	52	1.49	1.04–2.11	0.03
+ Unobserved death from unknown cause	84	54	1.58	1.12–2.22	0.009

Conclusion

- Discontinuation strategy associated with higher risk of CV disease

El-Sadr WM, et al. N Engl J Med. 2006;355:2283-2296. Phillips A, et al. 14th CROI, Los Angeles 2007, #41. Slide courtesy of Marshall Glesby, MD. Cornell University. NY/NJ AETC.

SMART: Inflammatory & Coagulation Markers Associated with Mortality



Subjects in Drug Conservation arm on ART at baseline with HIV-1 RNA ≤ 400 copies/mL (n = 132)

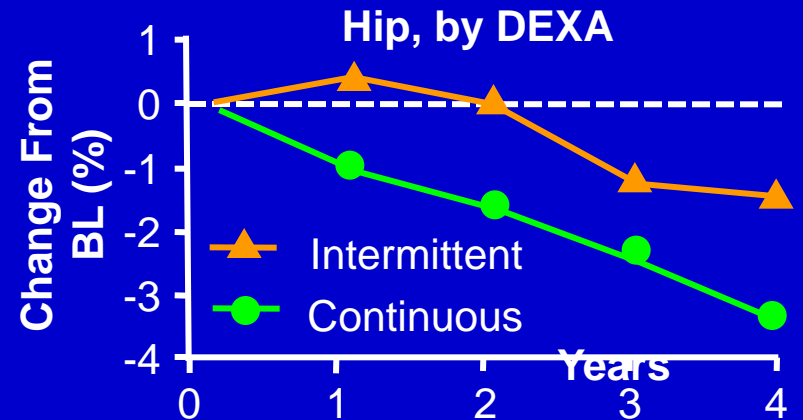
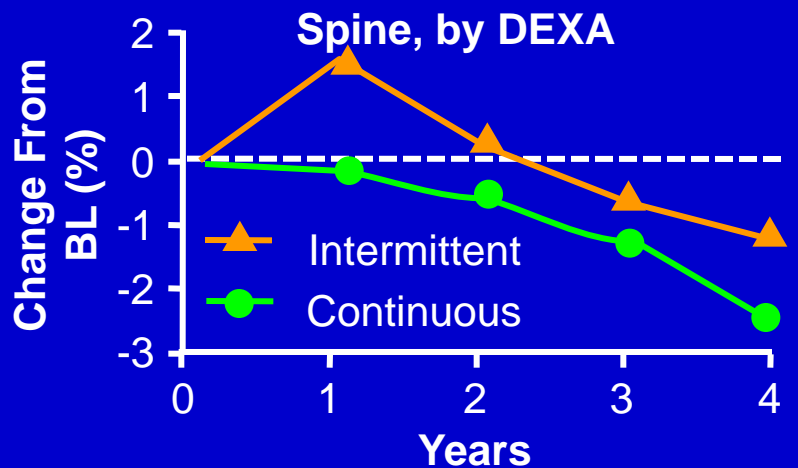
Kuller L et al, *PLoS Med.* 2008; 21:e203.

Slide courtesy of Marshall Glesby, MD. Cornell University. NY/NJ AETC.

4. HIV and Other Metabolic Concerns

SMART: BMD Loss With Continuous vs Intermittent ART

- Continuous ART associated with significantly larger BMD decline than intermittent ART; only observed disadvantage of continuous treatment in study
 - By year, differences in BMD between arms are statistically significant only in the first 1-2 years of follow-up; few patients included in analysis in Years 3-4



	1	2	3	4
n =	112	88	54	10
n =	96	77	47	15
Est diff:	1.7	0.8	0.5	2.1
P values:	.003	.26	.64	.40

	1	2	3	4
n =	109	86	51	9
n =	95	75	47	15
Est diff:	1.3	1.7	1.0	2.5
P values:	.002	.005	.27	.21

Grund B, et al. ICAAC/IDSA 2008. Abstract 2312a.

Permission granted to CCO for use of these graphics. Clinicaloptions.com/hiv

Bone Fractures

- **A5224s (n=269)**



- 5.6% had ≥ 1 fracture (all traumatic)
- No statistically significant differences between NRTI components or NNRTI/PI components in fracture rate (Fisher's exact) or time to first fracture (log-rank test)

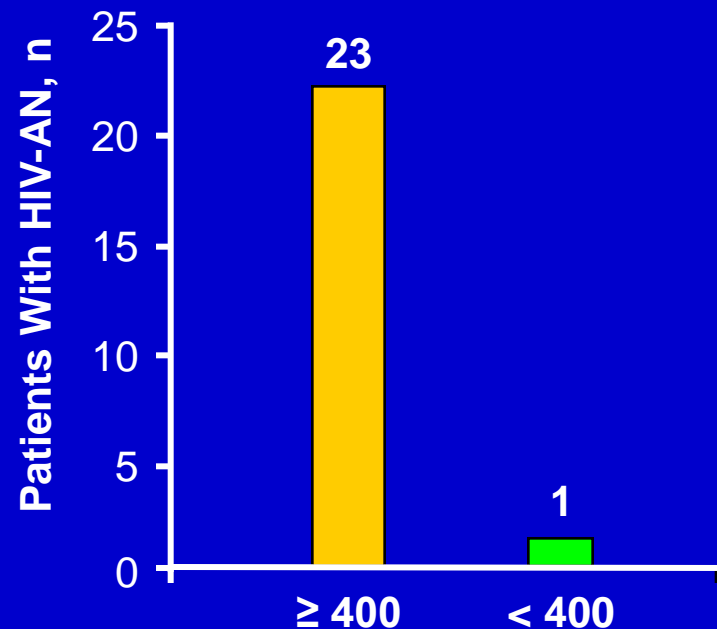
- **A5202 (n=1857)**

- 4.3% fracture rate (12.7% of those atraumatic)
- No statistically significant differences between NRTI components or NNRTI/PI components in fracture rate (Fisher's exact), incidence or time to first fracture (log-rank test)

	TDF/FTC +EFV (n=464)	TDF/FTC +ATV/r (n=465)	ABC/3TC +EFV (n=465)	ABC/3TC +ATV/r (n=463)	Total (n=1857)
% with ≥ 1 fractures	4.5%	4.5%	4.7%	3.4%	4.3%
Incidence per 100 pt-year	1.8	1.8	1.9	1.4	1.7

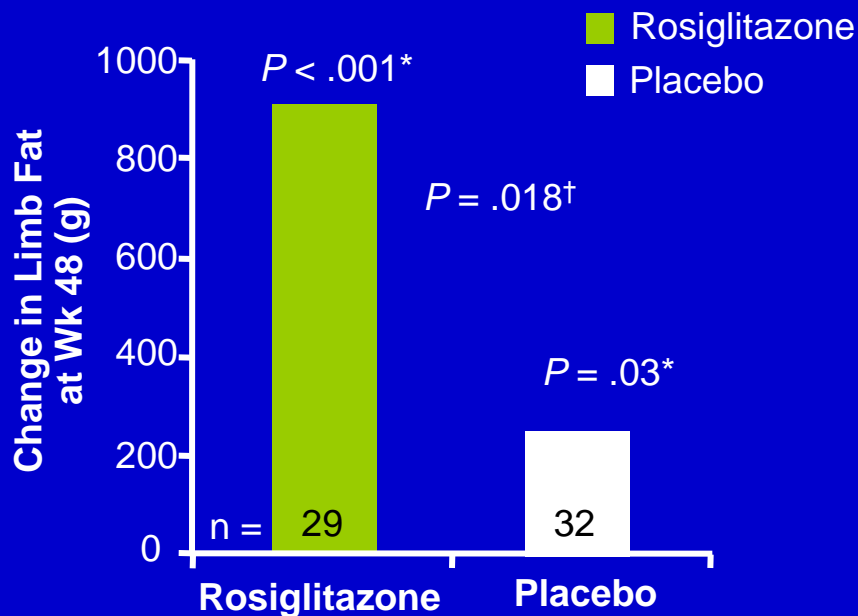
HIV-AN and Viral Load

- Retrospective comparison of renal biopsies on 86 HIV-infected patients according to HIV-1 RNA
 - HIV-1 RNA < 400, n = 23
 - HIV-1 RNA ≥ 400, n = 63
- Lower viral load group had greater proportion of patients with diabetes (35% vs 16%) and patients receiving HAART (96% vs 76%)
- High VL group had higher mean serum creatinine (4.3 mg/dL vs. 2.3 mg/dL; $P < .01$)
- HIV-AN rare in patients with lower viral load



- Hypertensive vascular disease most common abnormality (n = 15 in high VL group; n = 10 in lower VL group)
- HIV-1 RNA did not correlate with renal survival

Rosiglitazone Improves Lipoatrophy in Previous Zidovudine or Stavudine Recipients



*Intragroup comparison. †Intergroup comparison.

- Patients with clinical lipoatrophy, ≥ 12 mos' cumulative exposure to d4T or ZDV, discontinued d4T or ZDV from current HAART regimen for ≥ 24 wks prior to study
 - Randomized to receive rosiglitazone 4 mg BID (n = 34) or placebo (n = 37) in addition to current regimen
- Rosiglitazone associated with significant increases in TC (22 vs -8 mg/dL, respectively; $P = .008$) but not TG (19 vs -1 mg/dL, respectively; $P = .19$)

EI-Bajjani D, et al. CROI 2009. Abstract 42LB. Graphic reproduced with permission.

Clinicaloptions.com/hiv

5. Adverse Effects of Antiretroviral Therapy

FDA Alert: Didanosine

- Reports of non-cirrhotic portal hypertension
 - Risk for death from bleeding from esophageal varices
 - Hepatitis C and alcohol-related cirrhosis excluded

Patient – 4 Years of Didanosine

- 40 year old male – No chronic hepatitis B or C
- Presented with pleural effusion, tense ascites and peripheral edema
- Cytology of ascitic and pleural fluid benign
- Liver biopsy X 2 – mild inflammation only, without fibrosis
- Albumin low at 3.1 gm/dL
- Developed portal vein thrombosis
 - Variceal bleed when anti-coagulated
- Being evaluated for possible liver transplantation

FDA Alert:

Ritonavir-boosted Saquinavir

- Reports of QT prolongation
 - Risk for torsades de pointes, which may progress to ventricular fibrillation
- Reports of PR interval prolongation
 - Risk for heart block
- Actually a class effect with protease inhibitors

6. Central Nervous System and HIV Infection

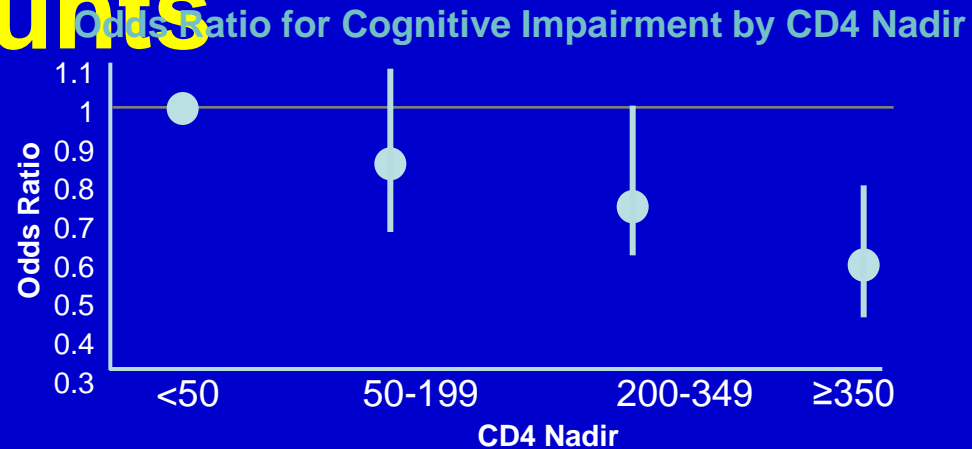
CNS Penetration of Antiretrovirals

- 4. Best penetrators:
 - Zidovudine, nevirapine, indinavir/ritonavir
- 3. Moderately good penetrators:
 - Abacavir, emtricitabine, delavirdine, efavirenz, darunavir/ritonavir, fosamprenavir/ritonavir, unboosted indinavir, lopinavir/ritonavir, maraviroc, raltegravir
- 2. Moderately poor penetrators:
 - Didanosine, lamivudine, stavudine, etravirine, atazanavir/ritonavir, unboosted atazanavir, unboosted fosamprenavir
- 1. Poor penetrators:
 - Tenofovir, zalcitabine, nelfinavir, ritonavir, saquinavir/ritonavir, unboosted saquinavir, tipranavir/ritonavir, enfuvirtide

Neurocognitive Disorders Associated with Nadir CD4 Counts

- Multicenter cohort study (CHARTER) of 1526 pts evaluating HIV-associated Neurocognitive Disorders (HAND)
- Complex testing consistent with defined criteria used to determine HAND
 - 603 had HAND (without a substantial confounder); 726 not impaired
 - Most with HAND (n=428) were asymptomatic and only a few (n=27) had frank dementia
- Multivariate analysis: Higher CD4 nadir associated with lower risk of HAND

Counts



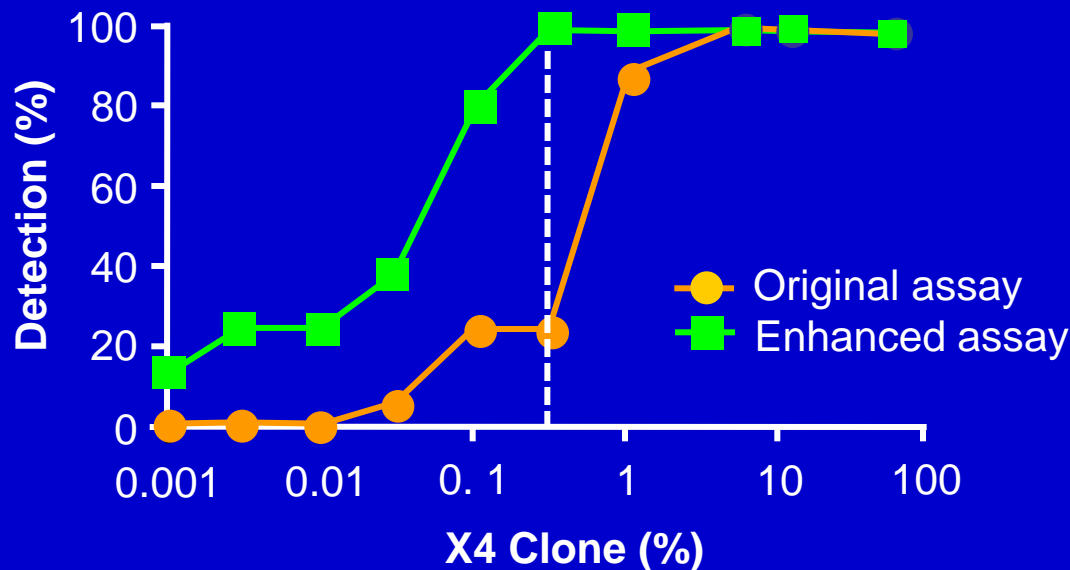
Odds Ratios for NP Impairment

	N	Impaired	Unimpaired	OR (95% CI)
All	1525	799	726	
Nadir CD4 < 50	387	222	165	1.00 (reference)
Nadir CD4 50-199	481	258	223	0.86 [0.66, 1.13]
Nadir CD4 200-349	370	189	181	0.78 [0.58, 1.03]
Nadir CD4 ≥350	287	130	157	0.62 [0.45, 0.84]
On ART, Plasma VL <50c/ml	589	320	269	
Nadir CD4 < 50	185	112	73	1.00 (reference)
Nadir CD4 50-199	214	118	96	0.80 [0.54, 1.19]
Nadir CD4 200-349	133	64	69	0.60 [0.39, 0.95]
Nadir CD4 ≥350	57	26	31	0.55 [0.30, 0.99]

7. Viral Tropism

Enhanced Phenotypic Tropism Assay for Detection of CXCR4-Using Virus

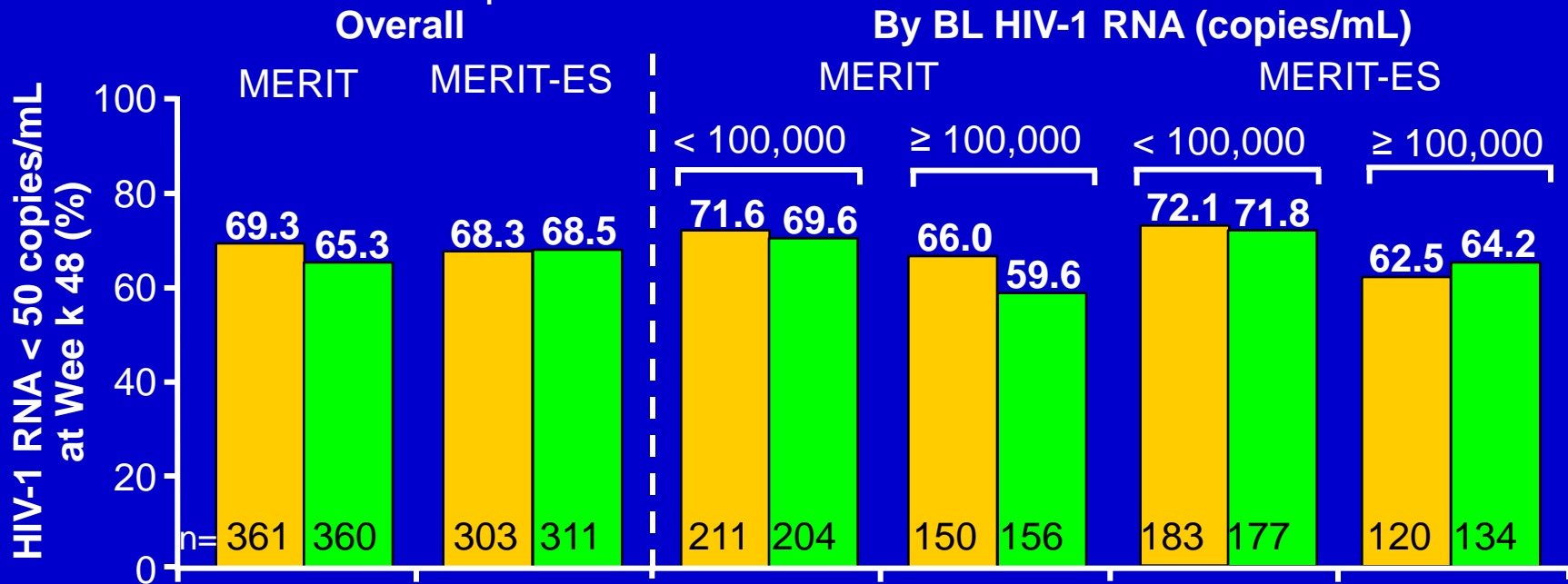
- Enhanced assay highly sensitive in detecting CXCR4-using HIV variants comprising 0.3% of viral populations



Reanalysis of Virologic Efficacy in MERIT With Enhanced Tropism Assay

- Enhanced phenotypic tropism assay resulted in reclassification of 15% of patients from R5 to D/M at screening

- Noninferiority criteria (rates of HIV-1 RNA < 50 copies/mL) met when D/M patients excluded
 - EFV + ZDV/3TC
 - MVC + ZDV/3TC



HIV Tropism Affects Clinical Progression but Not Response to ART

- Antiretroviral naive-patients (N = 422) assessed for viral tropism
 - R5, n = 326; X4 or D/M, n = 76
- CD4+ cell count decrease prior to therapy significantly greater in patients with X4 or D/M virus at 12 months ($P = .026$)
- Upon HAART initiation, time to virologic suppression and proportion of patients achieving virologic suppression similar between 2 groups at 6, 12, 24 months
- Clinical events occurred in 23/326 R5 patients and 17/76 X4 or D/M patients (RR, 2.56; 95% CI, 1.37-4.76, $P = .003$)

8. HIV Vaccine News

“HIV Vaccine Regimen Demonstrates Modest Preventive Effect in Thailand Clinical Study”

- 16,000 adult participants in Thailand
- Phase III prime-boost investigational vaccine (RV144) strategy
 - ALVAC-HIV vaccine (**the primer dose**), a modified canarypox vaccine developed by Sanofi Pasteur, based in Lyon, France;
 - AIDSVAX B/E vaccine (**the booster dose**), a glycoprotein 120 vaccine in the United States
 - based on the subtype B and E HIV strains that commonly circulate in Thailand.

Prime-Boost Investigational HIV Vaccine

- Primer Vaccine vs. Placebo given at entry and 1, 3 and 6 months
- Booster vaccine vs. Placebo given at 3 and 6 months
- Vaccine was **safe**
- 74 of 8,198 placebo recipients became infected with HIV, compared with 51 of 8,197 participants who received the vaccine regimen
 - Vaccine was **31% effective in preventing HIV transmission**
 - Vaccine regimen had no effect on the amount of virus in the blood of volunteers who acquired HIV infection during the study.

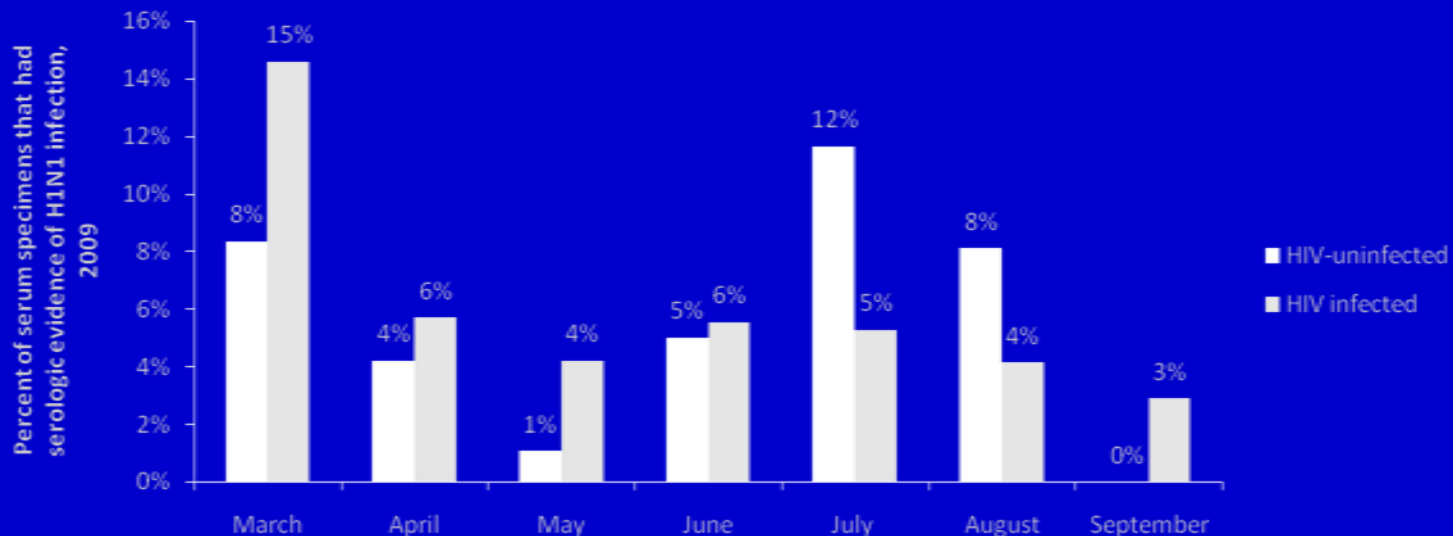
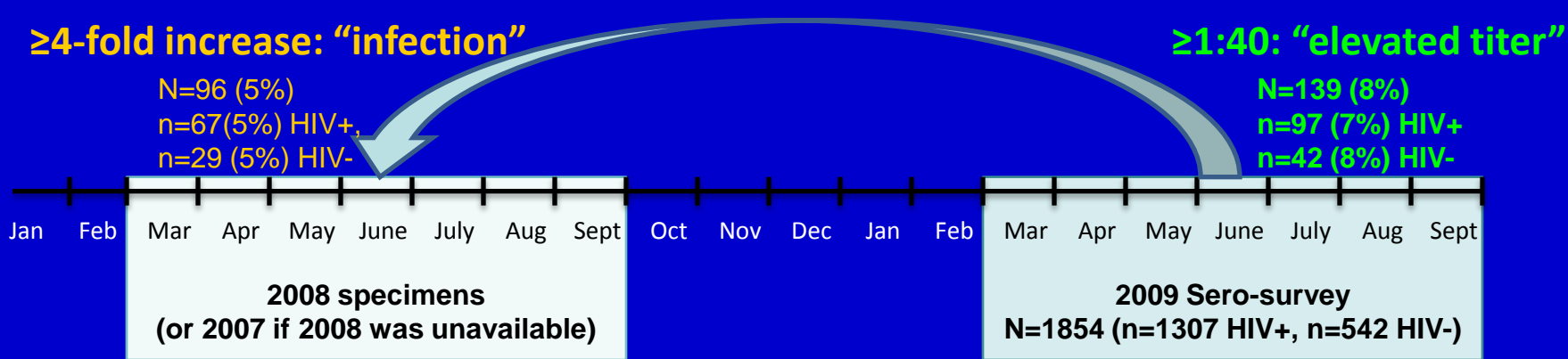
9. HIV and H1N1 Virus

807LB: Elevated 2009 H1N1 Antibody Titers and Serologic Evidence of Infection in HIV-infected and –uninfected Women: A Sero-study conducted March 1 – September 30, 2009



Keri N. Althoff, Stephen J. Gange, Gerald B. Sharp, Maryna Eichelberger, Jin Gao, Marshall Glesby, Mary Young, Ruth Greenblatt, Audrey French and Howard Minkoff for the Women's Interagency HIV Study (WIHS)

- Women's Interagency HIV study (WIHS) is an ongoing, prospective cohort study of HIV-infected and similar uninfected women in 5 US cities; est. 1994.
- Hemagglutination inhibition assays for 2009 H1N1 antibody titers on stored serum



807LB: Elevated 2009 H1N1 Antibody Titers and Serologic Evidence of Infection in HIV-infected and –uninfected Women: A Sero-study conducted March 1 – September 30, 2009
 Keri N. Althoff, Stephen J. Gange, Gerald B. Sharp, Maryna Eichelberger, Jin Gao, Marshall Glesby, Mary Young, Ruth Greenblatt, Audrey French and Howard Minkoff for the Women’s Interagency HIV Study (WIHS)



- Infections found in March (HIV+: 7/48, HIV-: 2/24)
- Overall infection rate: 17.1 [14.0, 20.9] infections per 100 person years
- Infection rates did not differ by HIV status

	IR	aIRR
HIV-uninfected	18.0 [12.5, 25.9]	REF
HIV-infected	16.8 [13.2, 21.3]	0.91 [0.58, 1.42]

- Infection rates differed by age, as seen in other studies of 2009 H1N1

	IR	aIRR
<30 years	27.0 [14.5, 50.1]	REF
30-<50 years	14.5 [11.0, 18.9]	0.33 [0.20, 0.55]
50-<65 years	21.4 [15.0, 30.4]	0.41 [0.24, 0.70]
≥65 years	17.4 [4.3, 39.5]	0.40 [0.09, 1.72]

- Infection rates differed by HIV-1 RNA in the year prior to the pandemic

	IR	aIRR
≤80 copies/mL	23.6 [18.1, 30.8]	REF
80-<10,000 copies/mL	7.2 [3.5, 15.2]	0.31 [0.13, 0.73]
≥10,000 copies/mL	8.4 [3.5, 20.1]	0.37 [0.12, 1.16]

Ongoing, prospective cohort studies are an important resource.

H1N1 CDC Recommendations for People with HIV Infection

- Patients with HIV infection may be at higher risk of complications
 - Especially for patients with low CD4 cell counts
- Patients with HIV should receive the injectable, inactivated form of H1N1 vaccine
- Over 20 cases of confirmed Influenza A in HIV-infected patients at AMC in 2009
 - H1N1 inferred from local surveillance data

1. U.S. CDC Updated Interim Recommendations—HIV-Infected Adults and Adolescents: Considerations for Clinicians Regarding 2009 H1N1 Influenza ; October 21, 2009.

2. Jain S *et al.* *N Engl J Med* 2009;361.

Hand Sanitizing



10. HIV and U.S. Travel



January 4, 2010 President Obama's order to end ban on travel to the U.S. for people with HIV/AIDS went into effect!