
Women's Interagency HIV Study (WIHS)

*Range of Data, specimens and analyses available to
researchers investigating drug use and its
ramifications*

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Women's Interagency HIV Study (WIHS)



WIHS Sites and Principal Investigators

▶ Consortia:

- Bronx, NY (K. Anastos)
- Brooklyn, NY (H. Minkoff)
- Chicago, IL (M. Cohen)
- Los Angeles, CA (A. Levine)
- Northern California (R. Greenblatt)
- Washington, DC (M. Young)

▶ Data Coordinating Center (WDMAC):

- Johns Hopkins University, Baltimore, MD (S. Gange)



WIHS Sponsoring Institutions (Project Officers)

- National Institute of Allergy and Infectious Diseases (G. Sharp; C. Williams – Epidemiology Branch Chief)
 - National Cancer Institute (G. Dominguez)
 - National Institute of Child Health and Human Development (H. Watts)
 - National Institute on Drug Abuse (K. Davenny)



Areas of Focused Scientific Research in the WIHS

- Neurocognition
- Cancer
- Cardiovascular Disease
- Drug Use & Behavior
- Genetics
- Pharmacology
- Gynecology/Menopause
- HPV
- Immunology/Pathogenesis
- Metabolic
- Hepatitis / Liver Disease
- Epidemiology



WIHS Major Active Substudies

- **Cardiovascular Disease:** Assessment of aspects of cardiovascular disease among HIV+ and HIV- women, including cardiovascular risk factors, carotid artery intima-media thickness (IMT), and clinical cardiovascular events
- **Genetics and Disease Progression:** Interaction between genetic factors, substance abuse, mood, cognitive impairment, and progression of HIV disease
- **Neurocognition:** Interaction between aging and HIV/AIDS on neurocognitive functioning among HIV+ and HIV at-risk women
- **Physical Functioning:** Cross-sectional assessment to identify and characterize physical impairment and frailty among HIV+ and HIV at-risk women



WIHS Major Active Substudies cont'd.

- **Metabolic** : Cross-sectional and longitudinal assessment of metabolic parameters including fat distribution, lipoprotein levels, bone density and glucose tolerance determined via DXA scan, glucose tolerance testing (GTT), and MRI
- **Intensive Pharmacokinetics (PK)**: Bioavailability and clearance rates for five target antiretroviral medications
- **Sex Steroid**: Effect of HIV infection on age of onset of diminished ovarian reserve



Semi-Annual Visit

Interview Administered Questionnaires:

- Medical and OB/GYN History
- Health Services
- Demographics/Psychosocial
- Behavior

Physical and Gynecological Examination

Body Habitus Exam (anthropometrics, BIA)

Medication use (ART, OI prophylaxis, hepatitis, etc.)

Participant Samples:

- Blood (virologic, immunologic, fasting lipodystrophy markers, liver/renal function, etc.)
- Other (CVL, saliva, hair)
- Local and National Repositories

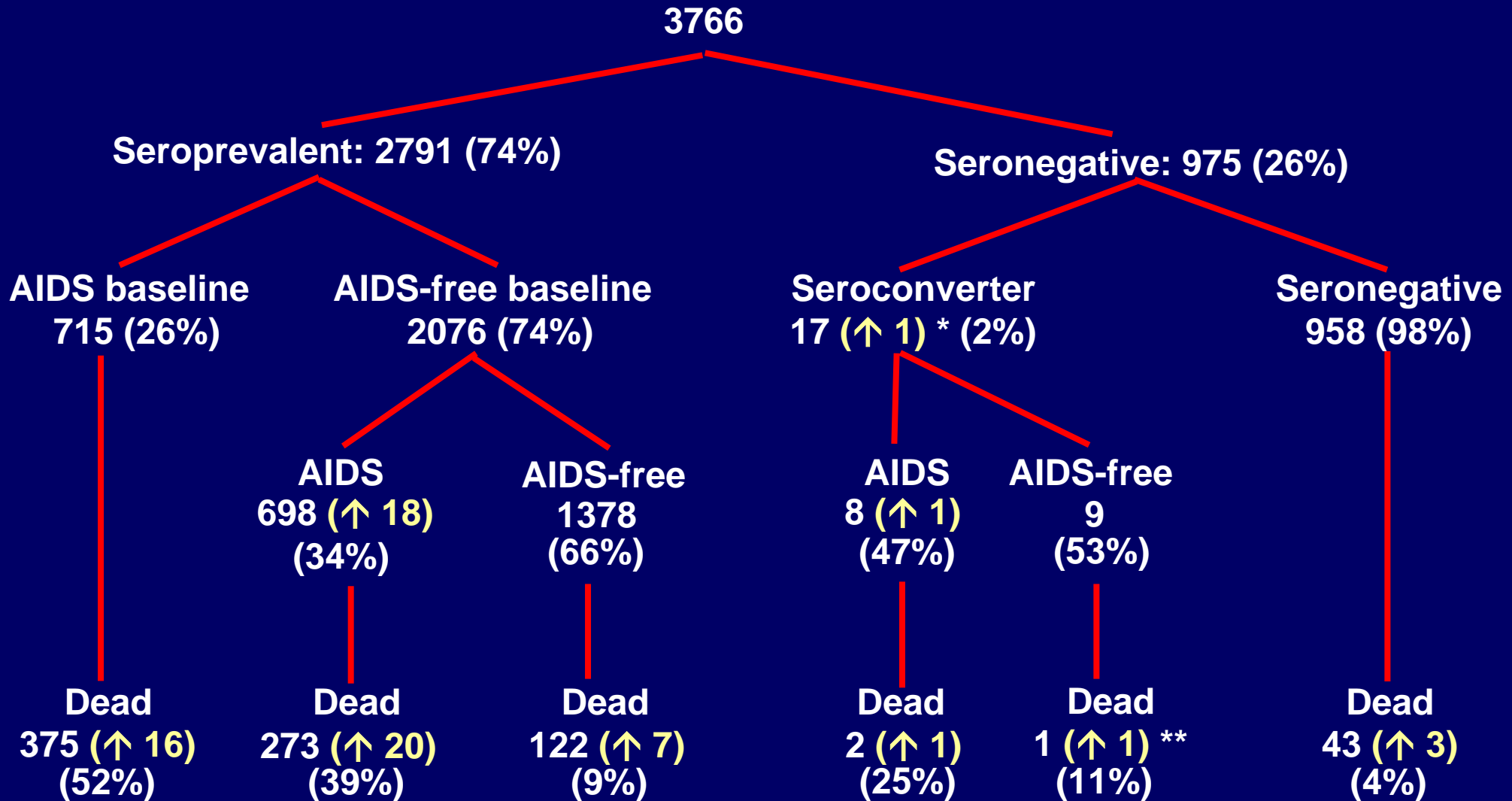


Continuous Outcome Ascertainment

- Seroconversion
- Clinical Outcomes:
 - AIDS Diagnoses
 - Malignancies
 - Mortality
 - Tuberculosis
 - Cardiovascular Diagnoses
 - Liver biopsies
 - Hysterectomies
- Sources:
 - Medical Record Abstractions
 - Registries (Cancer, AIDS, TB)
 - National Death Index



WIHS Cohort (as of 3/06) *



*HIV and AIDS status as of the of visit 23 (3/31/06). Deaths reflect those ascertained through 12/31/04 using the National Death Index and through 4/7/06 using other reports.

10 **One seroconverter found at death.



Baseline Characteristics (1)

(Barkan, Melnick, . . . , Feldman, *Epidemiology* 1998; 9:117-125)**

	94/95 Cohort		01/02 Cohort	
	HIV+	HIV-	HIV+	HIV-
Median age	36	34	33	29
Race/ethnicity:				
African-American	56%	54%	60%	61%
Latina	23%	28%	32%	28%
Exposure Category:				
Intravenous drug use	34%	28%	10%	13%
Heterosexual risk	42%	26%	41%	24%
Transfusion risk	4%	3%	--*	--*
No identified risk	20%	43%	48%	63%



Baseline Characteristics (2)

(Barkan, Melnick, . . . , Feldman, *Epidemiology* 1998; 9:117-125)*

	94/95 Cohort		01/02 Cohort	
	<u>HIV+</u>	<u>HIV-</u>	<u>HIV+</u>	<u>HIV-</u>
Median per capita household income	\$4,500	\$5,000	\$4,500	\$4,500
No health insurance	18%	41%	15%	39%
History of physical/sexual abuse	66%	67%	9%	16%
Median CD4+ count (cells/mm ³)	330	1028	493	984
Median viral load (copies/ml, NASBA assay)	22,000	---	610	---



Baseline Characteristics (3)

(Bacon, Von Wyl, . . . , Young, *CDLI* 2005; 12:1013-1019)

Parameter or condition	Percent with comorbidity	
	94/95 Cohort	01/02 Cohort
HBV core antibodies	43	19
HBV surface antigen	2.6	1.4
HCV antibodies	39	13
SIL on Pap test*	13	8
Diabetes	4.4	4.6
Hypertension	17	12
Obesity	53	65
Smoking	58	42

*Low-grade SIL, high-grade SIL, or carcinomas were detected in situ on initial Pap smear.

HBV, hepatitis B virus; HCV, hepatitis C virus; SIL, squamous intraepithelial lesion.



WIHS Database (as of 3/06)

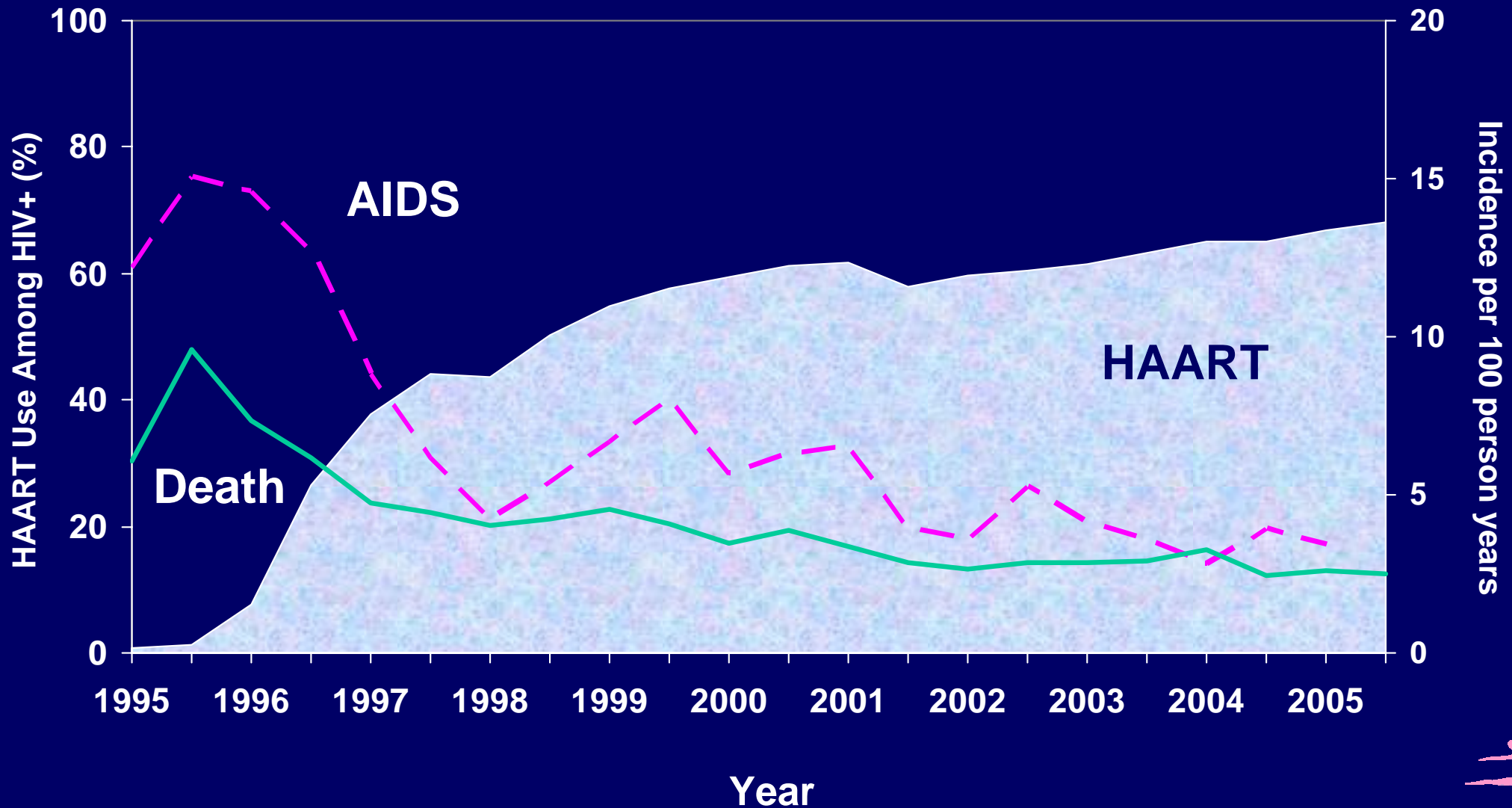
Total number of PARTICIPANTS enrolled	2807 959	HIV+ HIV-
Total number of PERSON-YEARS	17,659 5,627	HIV+ HIV-
Median FOLLOW-UP TIME in years	10.10 3.59	94/95 01/02
Total number of PERSON-VISITS	34,233 11,010	HIV+ HIV-
Total number of CD4 MEASUREMENTS	32,436 6,978	HIV+ HIV-
Total number of VIRAL LOAD MEASUREMENTS	32,368	
Total number of REPOSITORY ALIQUOTS*	1,842,688	

* Available as of 11/14/2006



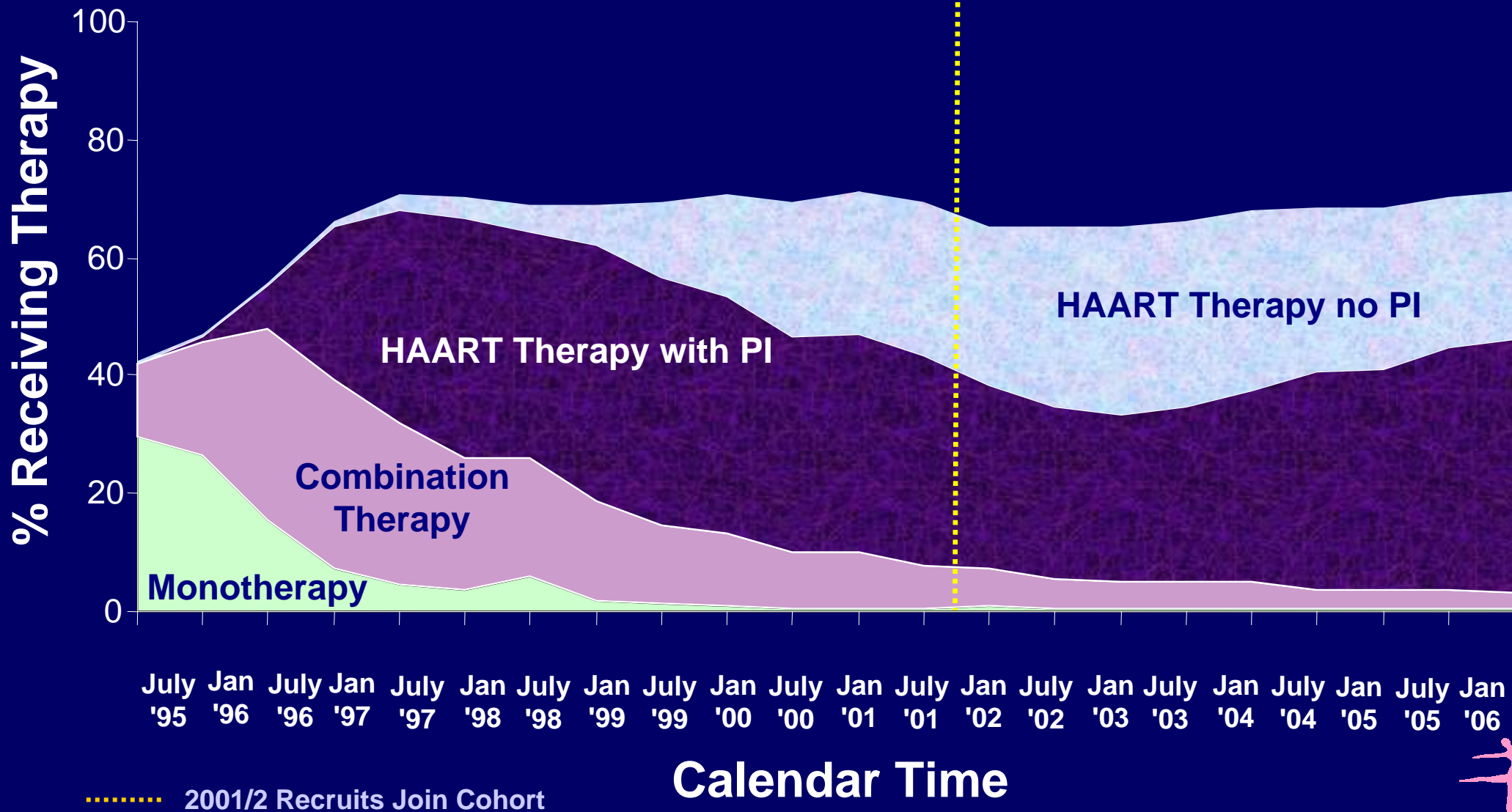
WIHS Self-Reported AIDS Incidence, Mortality and Use of HAART

(Gange, Barrón, . . . , Muñoz, *J Epi Comm Health* 2002; 56:153-159) (as of 3/06)



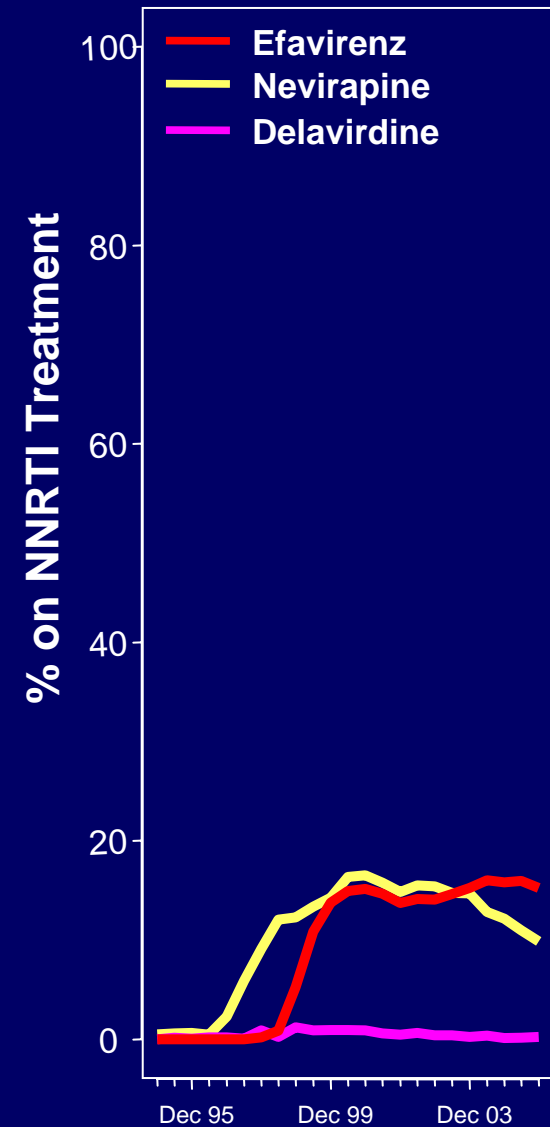
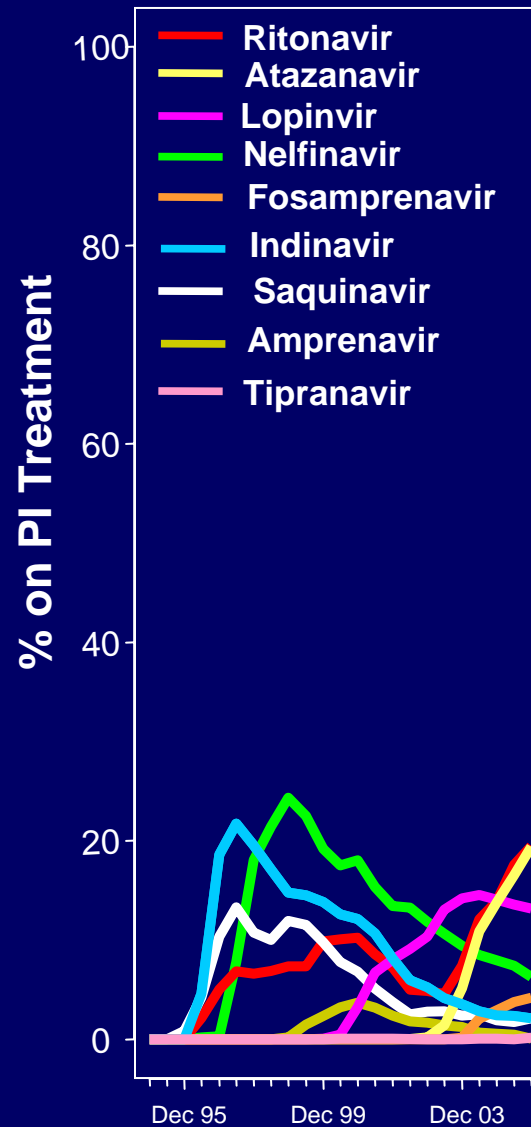
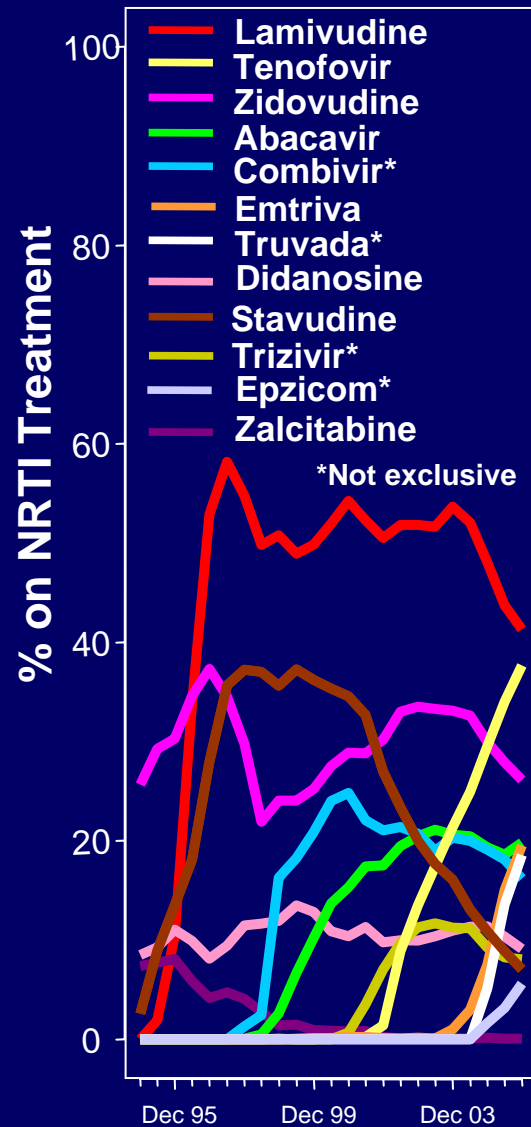
Antiretroviral Therapy Use Among WIHS HIV+

(Cook, Cohen, . . . , Young, *AJPH* 2001, 92:82-87) (as of 3/06)



Antiretroviral Use Among WIHS HIV+

(Kirstein, Greenblatt, ..., Gange, *JAIDS* 2002, 29:495) (as of 3/06)

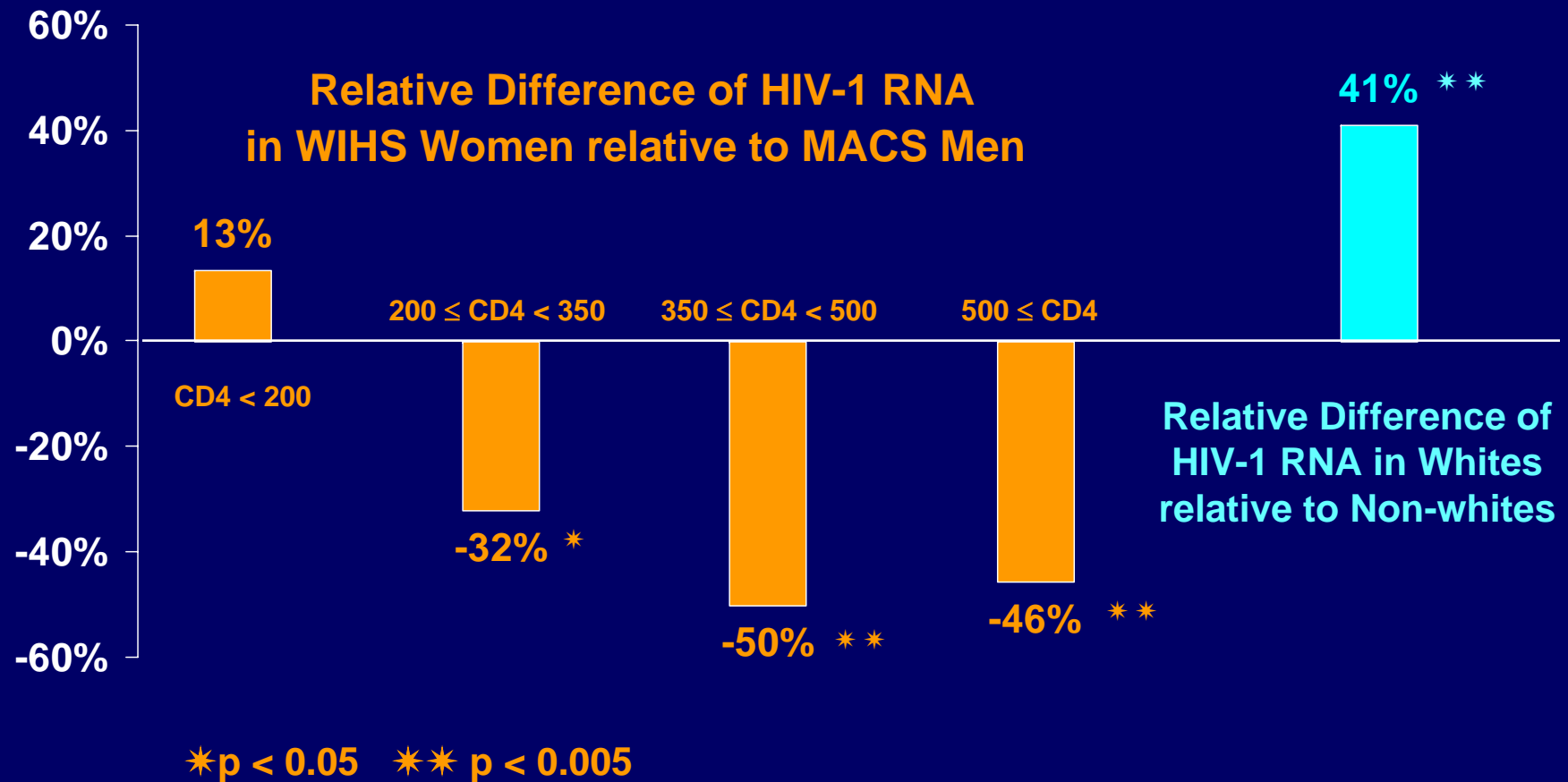


Effect of Substance Use on HIV disease progression

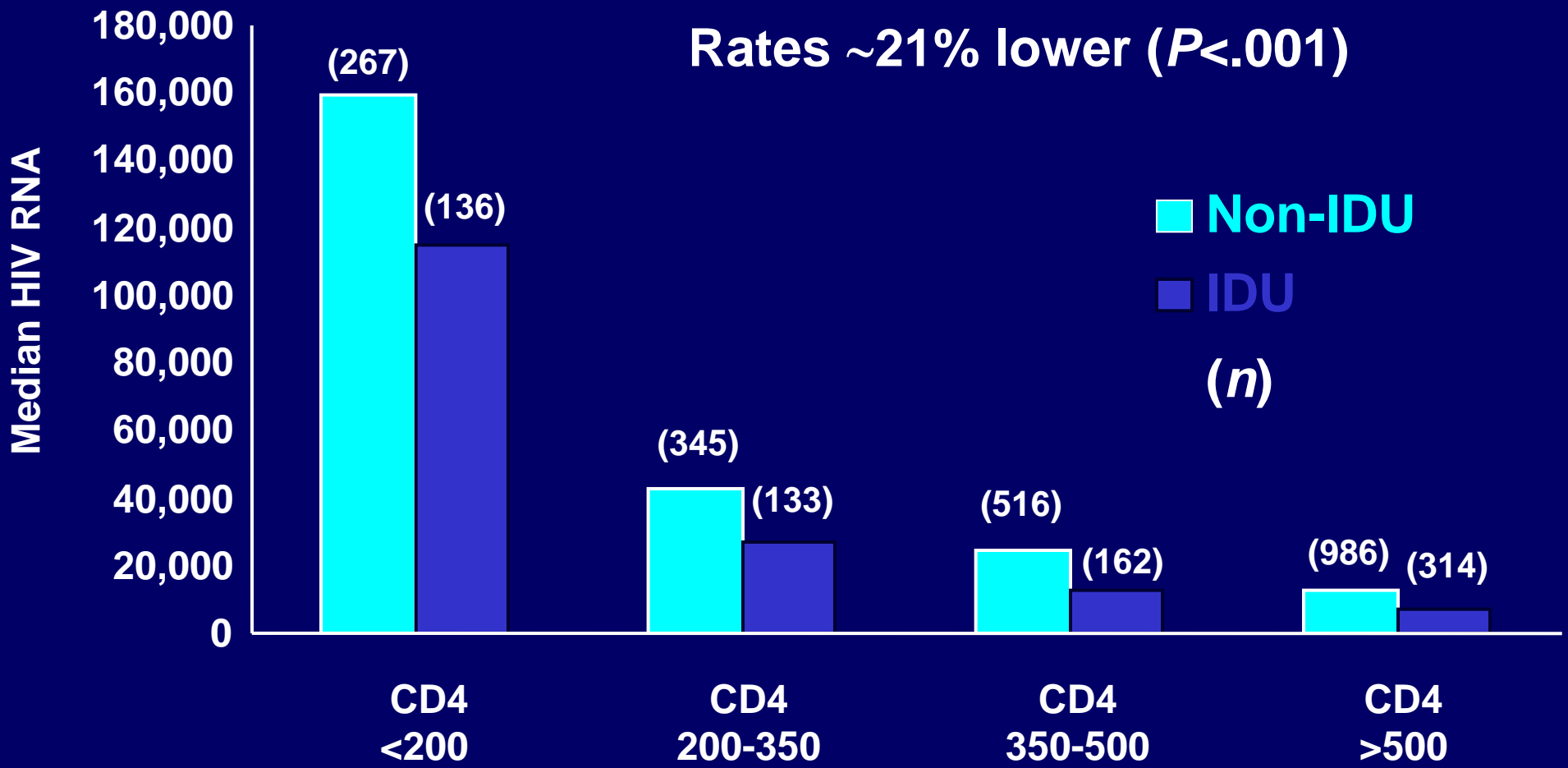


Association of Race and Gender with HIV-1 RNA

(Anastos, Gange, . . . , Greenblatt, *JAIDS* 2000; 24:218-226)

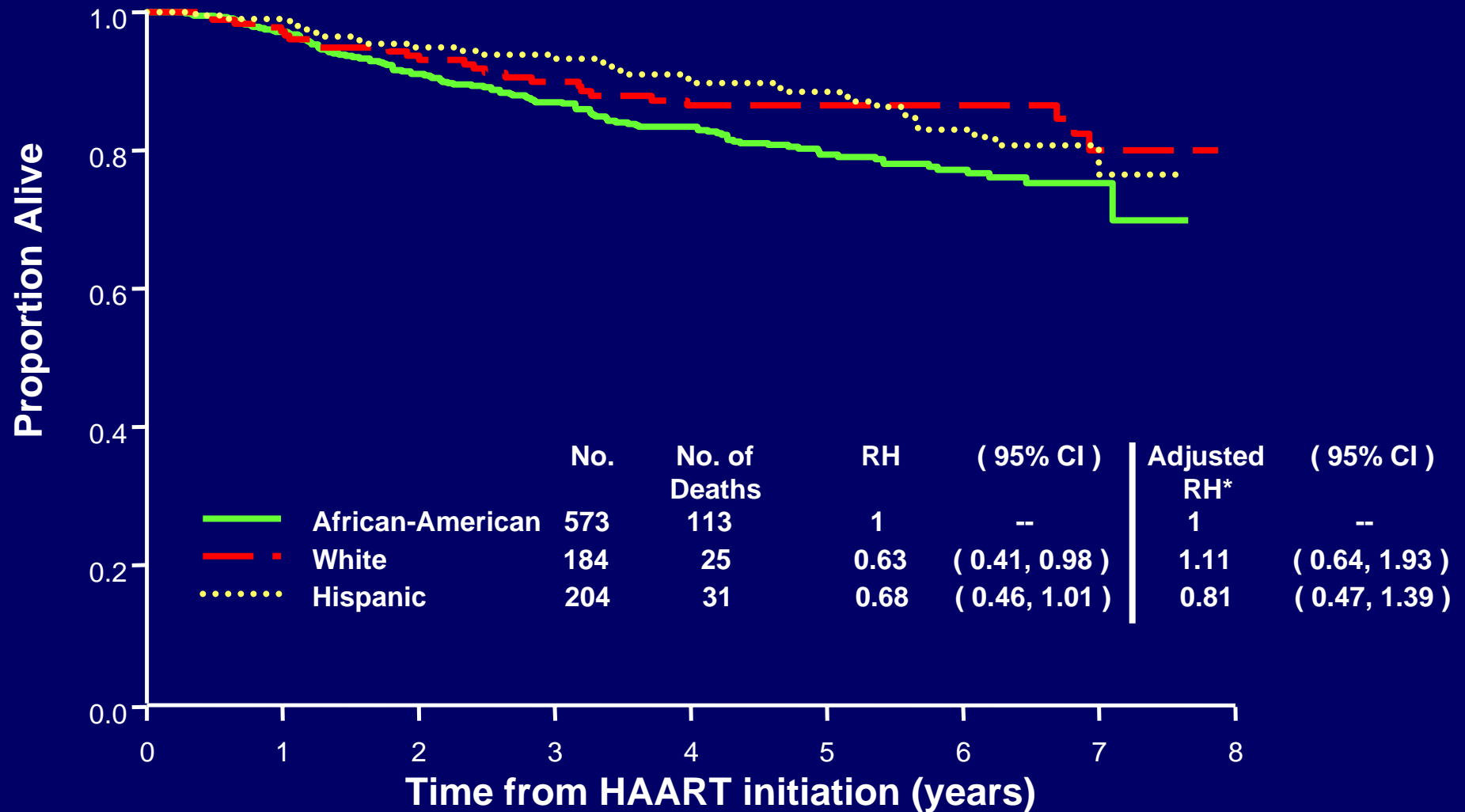


Association of HIV-1 RNA with history of Injection Drug Use with



Factors Associated with Response to HAART (1)

(Anastos, Schneider, . . . , Cohen, *JAIDS* 2005; 39,5:537-544)



* Adjusted for ART use prior to HAART initiation, age at last pre-HAART visit, pre-HAART AIDS status, pre-HAART nadir CD4⁺ cell count, pre-HAART peak HIV-1 RNA, self-reported baseline HIV-1 exposure category, depression, current drug use, cigarette smoking, income, ART used following HAART initiation.



Factors Associated with Response to HAART (2)

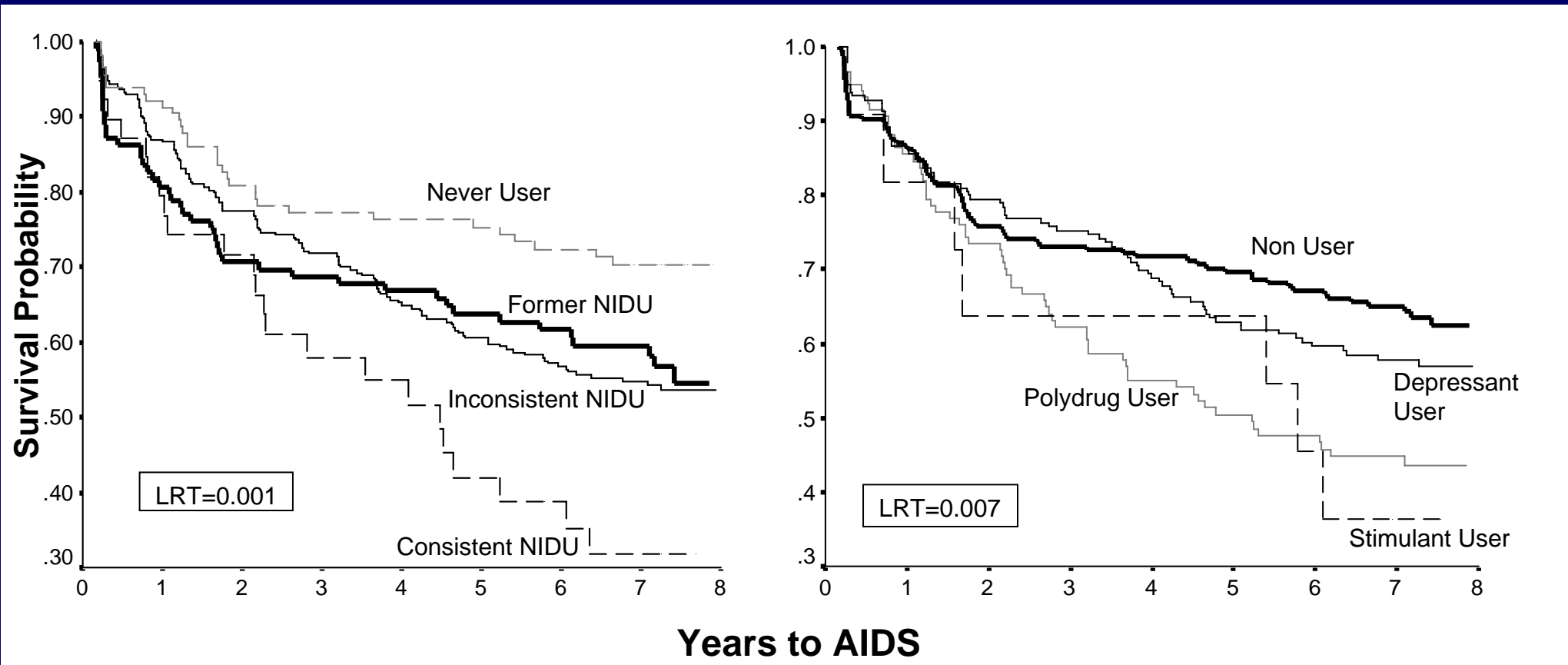
(Anastos, Schneider, . . . , Cohen, *JAIDS* 2005; 39,5:537-544)

Exposure	Virologic Response	Virologic Rebound	Immunologic Response	Immunologic Failure	Incident ADI	Death	AIDS Death
ART naïve prior to HAART	1.77	0.82	0.96	0.72	1.29	0.94	1.41
Age at last pre-HAART visit (per 10 years)	1.19	0.91	1.12	1.00	0.98	1.36	1.18
Pre-HAART AIDS	0.98	1.04	0.93	0.92	2.19	1.35	1.62
Pre-HAART nadir CD4 ⁺ count (per 100 cells)	1.08	1.02	1.09	1.27	0.86	0.61	0.30
Pre-HAART peak HIV-1 RNA (per log ₁₀)	0.62	1.48	1.02	0.89	1.38	1.61	1.63
Therapy used after HAART							
No therapy	1	1	1	1	1	1	1
Mono/combo	8.55	0.30	4.07	0.59	0.72	0.53	0.71
HAART	16.14	0.26	7.04	0.31	0.74	0.46	0.33
Depression (CES-D > 16)	0.81	1.22	0.96	1.98	1.62	1.65	1.06
Current drug use	0.89	1.23	0.85	1.11	1.49	1.04	2.35
Currently smoke cigarettes	0.72	1.30	1.04	0.93	1.18	1.38	1.05
Income <\$12,000	0.91	1.25	0.98	1.45	1.19	1.64	1.39
Adherence	2.19	0.37	1.47	0.66	0.65	0.67	0.53

Note: Adjusted for HIV-1 exposure and race. Significant values are in bold and yellow.

Time to AIDS Among Non-injecting Drug Users (NIDU) in the HAART Era

(Kapadia, Cook, . . . , Vlahov, *Addiction* 2005; 100:990-1002)

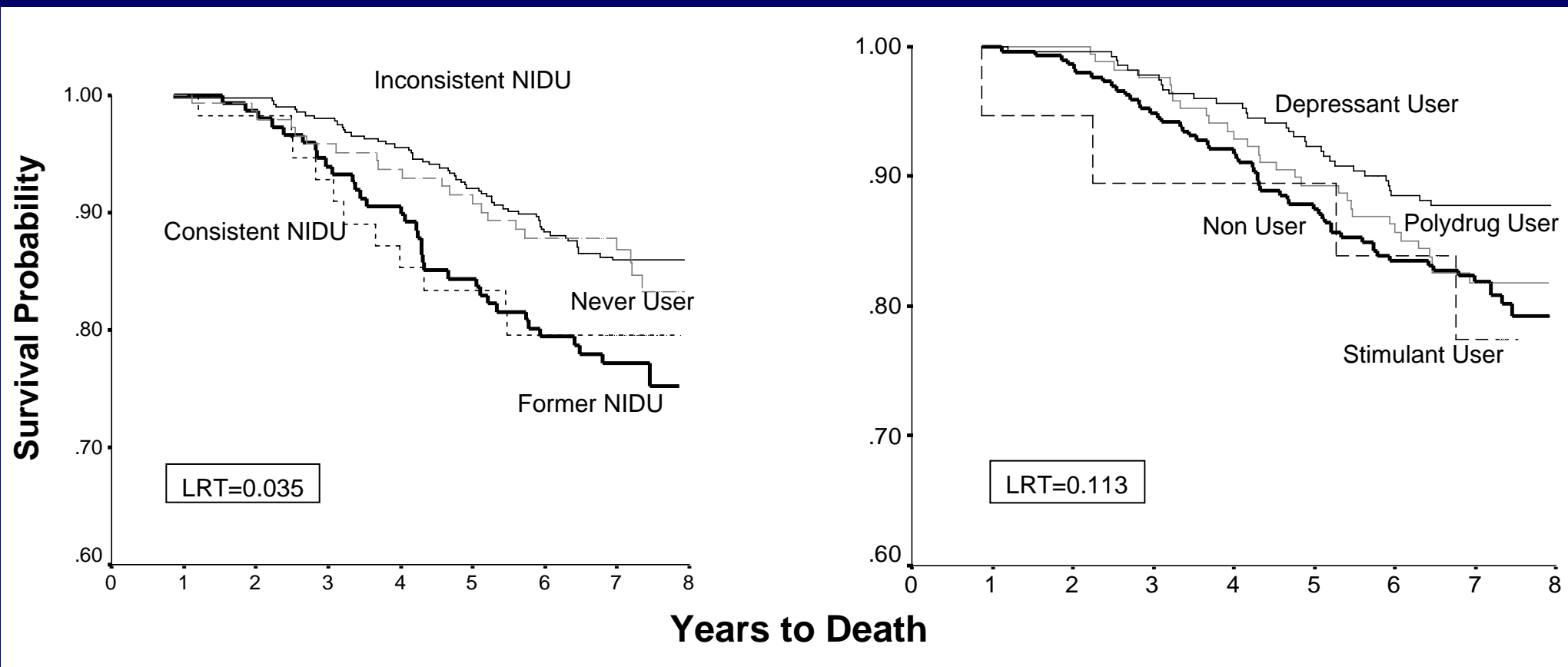


Kaplan-Meier curves of cumulative probabilities of survival for AIDS by pattern and type of NIDU among HAART users, WIHS (n=1046).



Time to Death Among Non-injecting Drug Users (NIDU) in the HAART Era

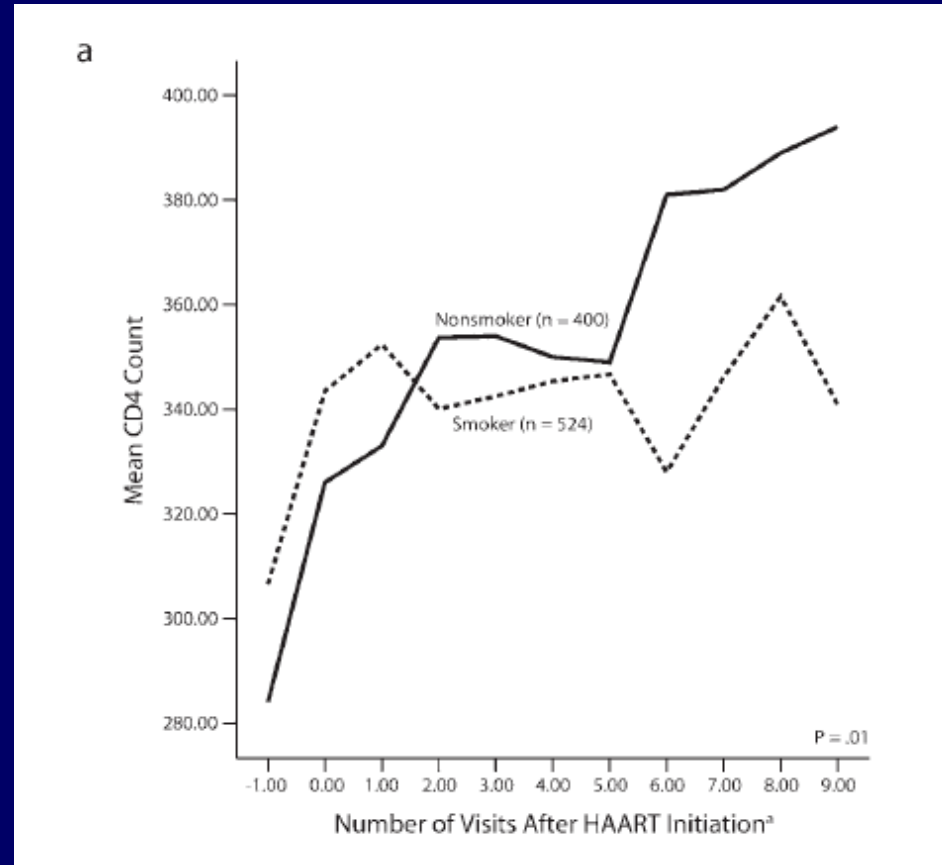
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Kaplan-Meier curves of cumulative probabilities of survival for death by pattern and type of NIDU among HAART users, WIHS (n=1046).



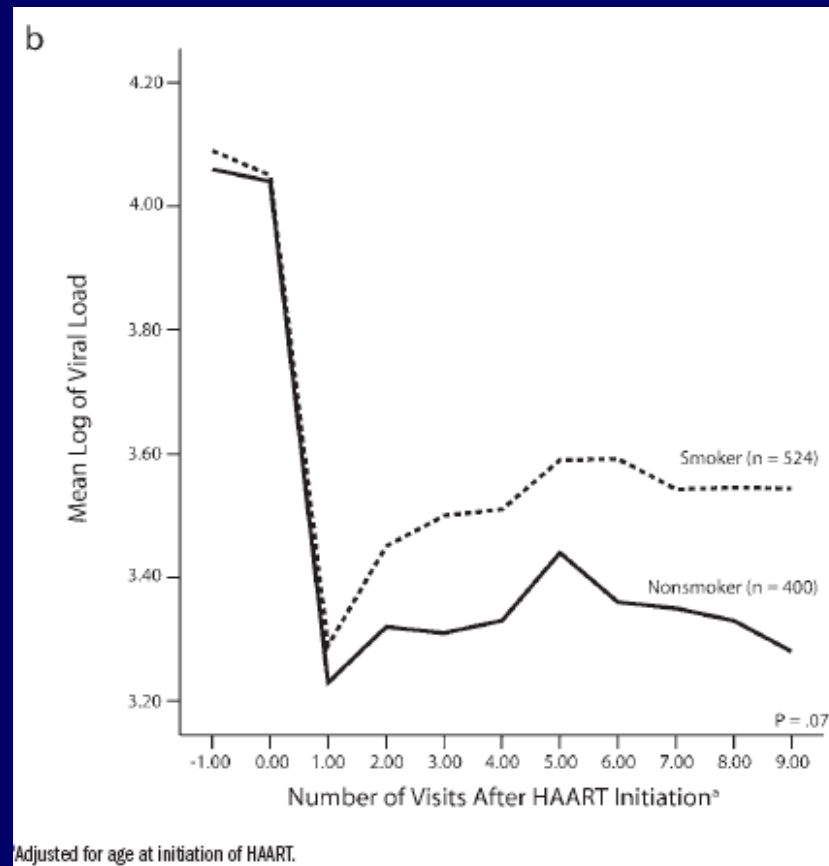
Association of Smoking with CD4 response to HAART



Feldman J, Schneider M, Gange S, Cohen M, Watts H, Gandhi M, Young M, Mocharnuk R, and Anastos K. Impact of Cigarette Smoking on HIV Prognosis Among Women in the HAART Era- A Report from the WIHS. *Am J Public Health* 2006



Association of Smoking with HIV-1 RNA response to HAART



Feldman J, Schneider M, Gange S, Cohen M, Watts H, Gandhi M, Young M, Mocharnuk R, and Anastos K. Impact of Cigarette Smoking on HIV Prognosis Among Women in the HAART Era- A Report from the WIHS. *Am J Public Health* 2006



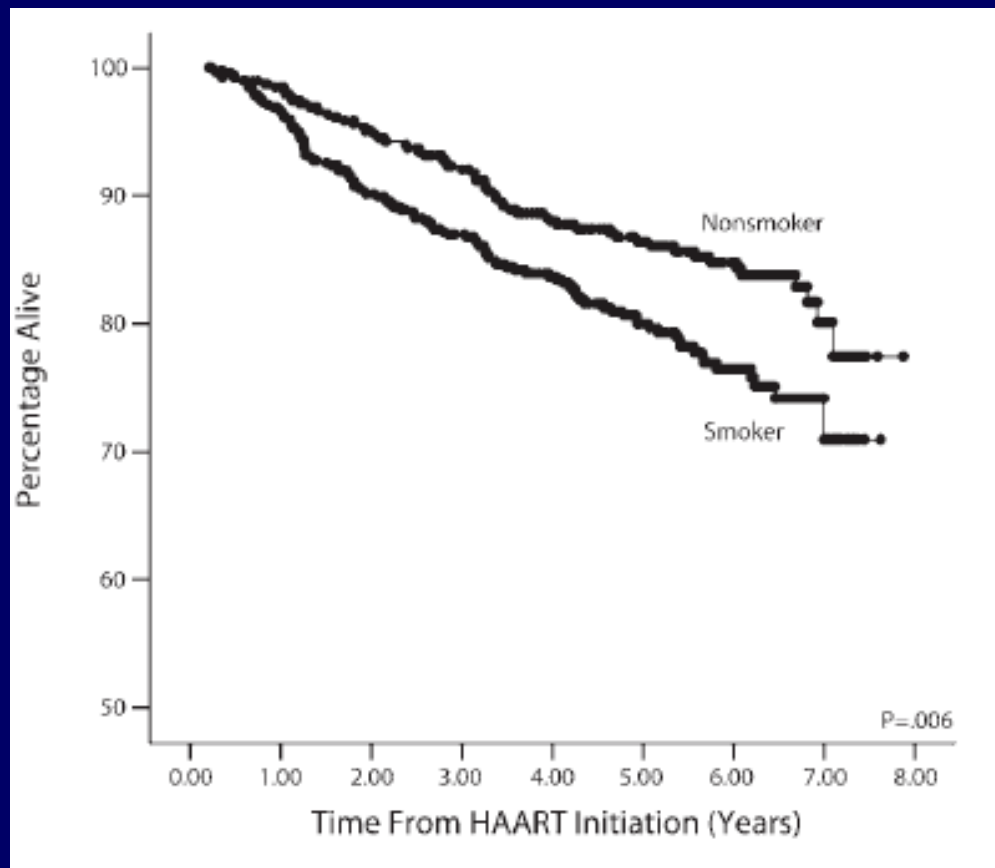
Progression to AIDS-defining condition by smoking

QuickTime™ and a
TIFF (Uncompressed) decompressor
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Feldman J, Schneider M, Gange S, Cohen M, Watts H, Gandhi M, Young M, Mocharnuk R, and Anastos K. Impact of Cigarette Smoking on HIV Prognosis Among Women in the HAART Era- A Report from the WIHS. *Am J Public Health* 2006



All-cause mortality by smoking



Feldman J, Schneider M, Gange S, Cohen M, Watts H, Gandhi M, Young M, Mocharnuk R, and Anastos K. Impact of Cigarette Smoking on HIV Prognosis Among Women in the HAART Era- A Report from the WIHS. *Am J Public Health* 2006



Association of Substance Use with Other Outcomes



Relative Hazard for New HPV Infection in HIV+ Women

(Minkoff, Feldman, . . . , Anastos, *JID* 2004; 189:1821-1828)

	<i>RH (95% CI)</i>	<i>P</i>
Monotherapy vs. none	0.81 (0.49 – 1.32)	.40
Combination therapy vs. none	1.06 (0.64 – 1.75)	.83
HAART vs. none	1.08 (0.66 – 1.77)	.76
Oral contraceptive use (yes vs. no)	1.09 (0.69 – 1.72)	.72
Log CD4+ cell count	0.90 (0.83 – 0.97)	.008
Log viral load	1.06 (1.01 – 1.11)	.01
Smoking status (yes vs. no)	1.33 (1.10 – 1.60)	.003
Parity	1.02 (0.98 – 1.06)	.34
No. sex partners, recent or lifetime	0.99 (0.97 – 1.03)	.80
Age at baseline	0.988 (0.97 – 1.00)	.04
Age at first intercourse	1.00 (0.97 – 1.03)	.79

Parity and age at first intercourse are fixed variables; smoking, number of sex partners, oral contraceptive use, CD4+ cell count, and viral load are time-dependent variables.



Accidental Death in WIHS and MACS

- ❑ IDU and smoking each independently associated with higher likelihood of accidental death:
 - IDU: OR=2.6, p=0.0007
 - Smoking: OR=1.63, p=0.027



Predictors of Menopause and Amenorrhea

- Opiate use predicted amenorrhea, but not menopause
- Menopause also predicted by age, BMI
- Menopause *not* predicted by HIV status, or any HIV related parameter (CD4, Viral load)



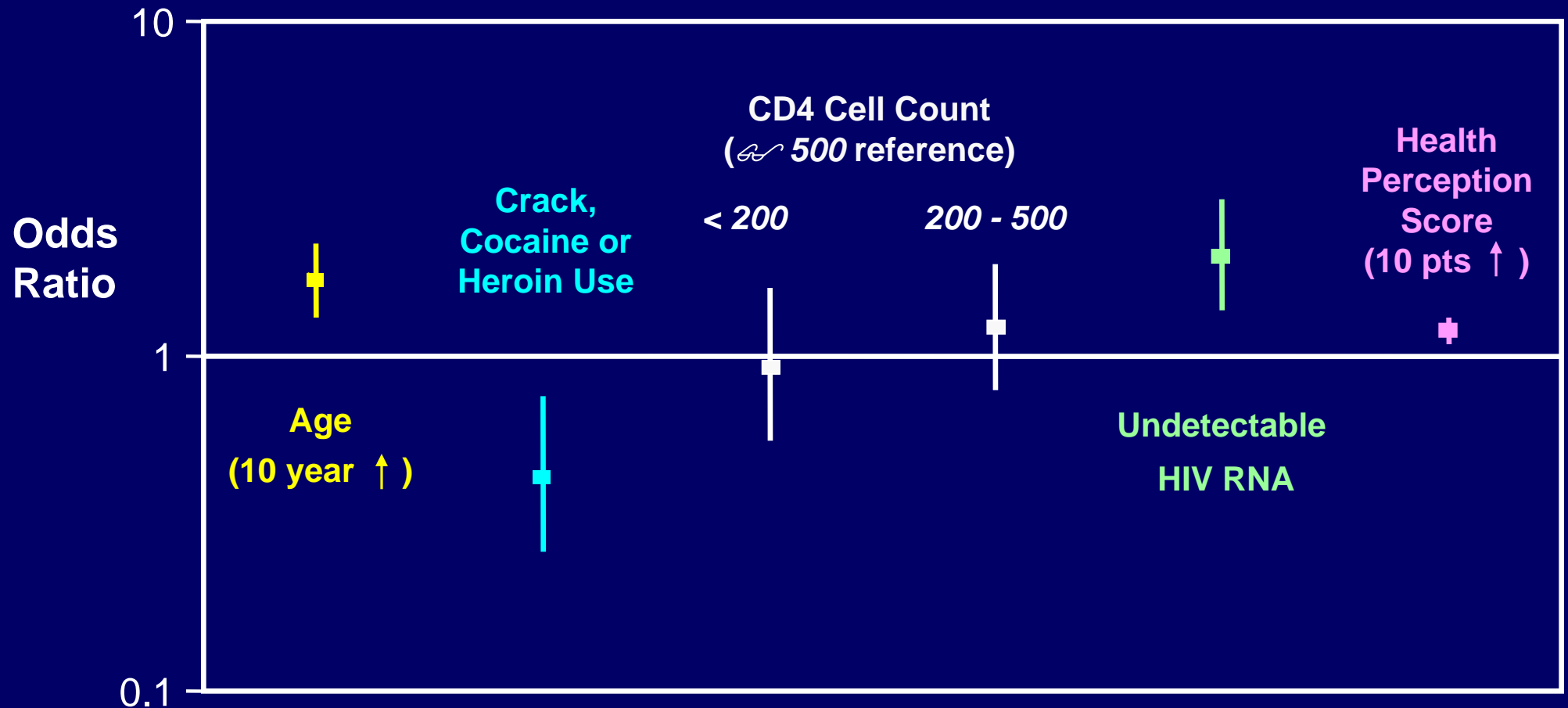
Association of Substance Use with Behaviors

Including Adherence



Correlates of ART Adherence in the Women's Interagency HIV Study

(Wilson, Barrón, . . . , Young, *Clin Infect Dis* 2002; 34:529-534)



Drug Use and Sexual Behavior

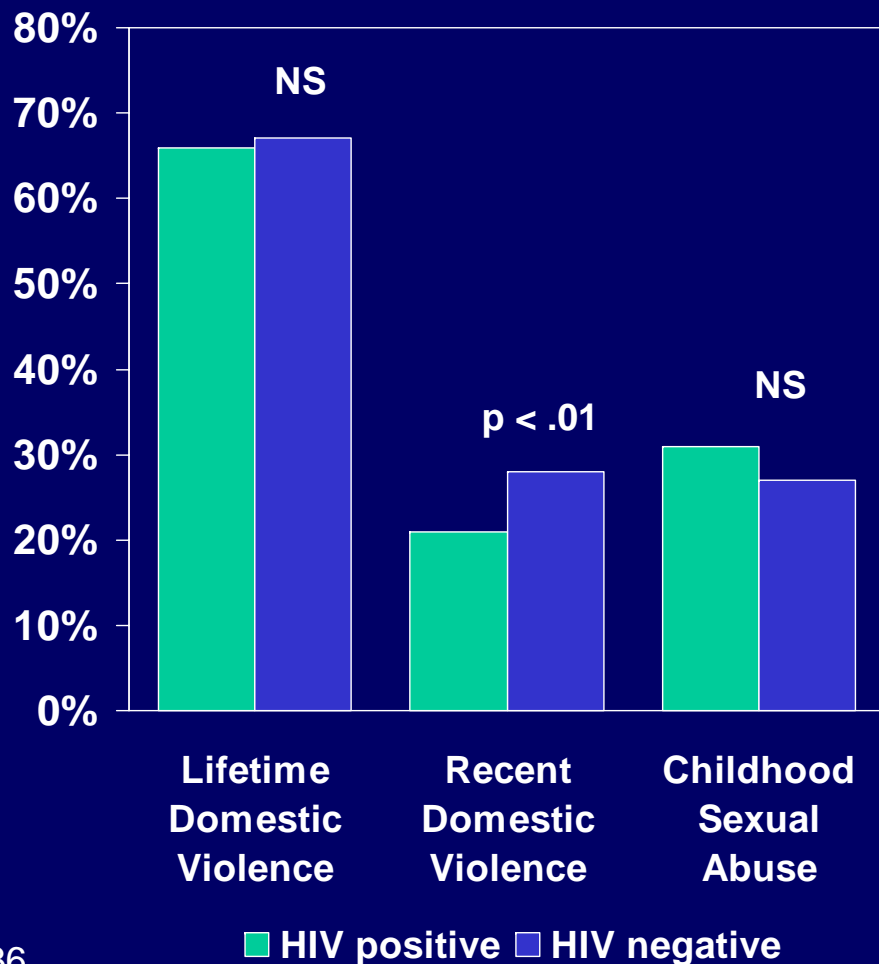
- Women using crack, cocaine or heroin less likely to use condoms: $OR=0.63$, $p<0.001$ ¹
- Women who undergoing treatment for drug use were less likely to be sexually active: $OR=0.83$, $p=0.0001$ ²



Domestic Violence and Childhood Sexual Abuse in WIHS Women

(Cohen, Deamant, . . . , Melnick, *Am J Public Health* 2000; 90:560-565)

Baseline Prevalence



Multivariate Behavioral Correlates of Childhood Sexual Abuse

- **Drug use, ever**
(OR* = 4.25, p < .001)
- **Male partner w/HIV risk**
(OR* = 2.07, p < .001)
- **Lifetime male sex partners (>10)**
(OR* = 2.29, p < .001)
- **Sex for drugs, money or shelter**
(OR* = 2.62, p < .001)

*OR adjusted for HIV serostatus, age, race/ethnicity and annual household income



Hepatitis C



Association between Renal Disease and Outcomes in HIV-Infected Women Receiving HAART

(Szczech, Hoover, . . . , Anastos, *Clin Infect Dis* 2004; 39:1199–1206)

Table 3. Multivariable predictors of the development of AIDS-defining illness (ADI) and death among women, after the initiation of HAART, in a multivariate model.

Class of predictor, variable	Hazard ratio (95% CI)	P
Predictor of ADI		
Inverse creatinine level, per 1-dL/mg decrease	1.42 (0.97–2.08)	.07
Prior history of ADI	2.29 (1.75–2.99)	<.0001
Hepatitis C virus infection	1.58 (1.23–2.04)	.0004
CD4 lymphocyte count, per 100-cells/mL decrease	1.09 (1.02–1.17)	.02
Log viral load, ^a per 1-log increase	1.17 (1.03–1.33)	.02
Albumin level, per 1-mg/dL decrease	1.32 (0.98–1.77)	.07
Predictor of death		
Proteinuria, presence vs. absence	2.21 (1.33–3.67)	.002
CD4 lymphocyte count, per 100-cells/mL decrease	1.36 (1.15–1.60)	.0003
History of hypertension	2.25 (1.37–3.68)	.001
Hepatitis C virus infection	2.13 (1.34–3.39)	.001
Albumin level, per 1-mg/dL decrease	2.04 (1.26–3.29)	.004
Prior history of ADI	1.81 (1.09–3.01)	.02

^a Log₁₀ HIV RNA copies/mL.



Predictors of HCV viremia in adjusted models

- Age (>35 years) OR= 1.6, p=0.005
- African Ancestry OR= 1.6, p=0.04
- Crack/cocaine use OR= 1.7, p=0.02
- HBV viremia OR= 0.3 p=0.006
- Current smoking OR= 1.7, p=0.009



Opiate Use, HCV and incident Diabetes

Table 4. Unadjusted and adjusted relative hazards of incident diabetes among 2,016 women^a

Variable	Unadjusted RH (95% CI)	Adjusted RH (95% CI) ^b		
		Model 1	Model 2	Model 3
HCV infected	2.02 (1.43, 2.87) ^c	1.52 (1.02, 2.27) ^d	--- ^e	1.30 (0.82, 2.06)
History of opiate use	1.99 (1.39, 2.84) ^c	--- ^e	1.57 (1.06, 2.32) ^d	1.39 (0.88, 2.17)
Age (per year) ^f	1.05 (1.03, 1.07) ^f	--- ^e	--- ^e	--- ^e
Race				
African American	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Hispanic	0.79 (0.53, 1.17)	0.86 (0.56, 1.30)	0.82 (0.54, 1.24)	0.83 (0.55, 1.26)
Caucasian	1.09 (0.68, 1.76)	1.22 (0.74, 2.00)	1.20 (0.73, 1.97)	1.21 (0.74, 2.00)
Other	0.17 (0.02, 1.24)	0.22 (0.03, 1.59)	0.22 (0.03, 1.55)	0.22 (0.03, 1.56)
Family history of diabetes	1.91 (1.37, 2.66) ^c	1.78 (1.26, 2.50) ^d	1.80 (1.28, 2.54) ^c	1.79 (1.27, 2.52) ^c



Opiate Use, HCV and incident Diabetes, cont'd.

Body mass index				
Lean/normal (<25.0 kg/m ²)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Overweight (25.0-29.9 kg/m ²)	0.89 (0.56, 1.41)	0.93 (0.58, 1.48)	0.91 (0.57, 1.45)	0.92 (0.58, 1.47)
Obese (≥ 30 kg/m ²)	1.70 (1.15, 2.51) ^a	1.88 (1.25, 2.80) ^a	1.83 (1.23, 2.72) ^a	1.87 (1.25, 2.80) ^a
HIV infected	1.22 (0.83, 1.79)	1.02 (0.68, 1.53)	1.06 (0.71, 1.59)	1.04 (0.69, 1.57)

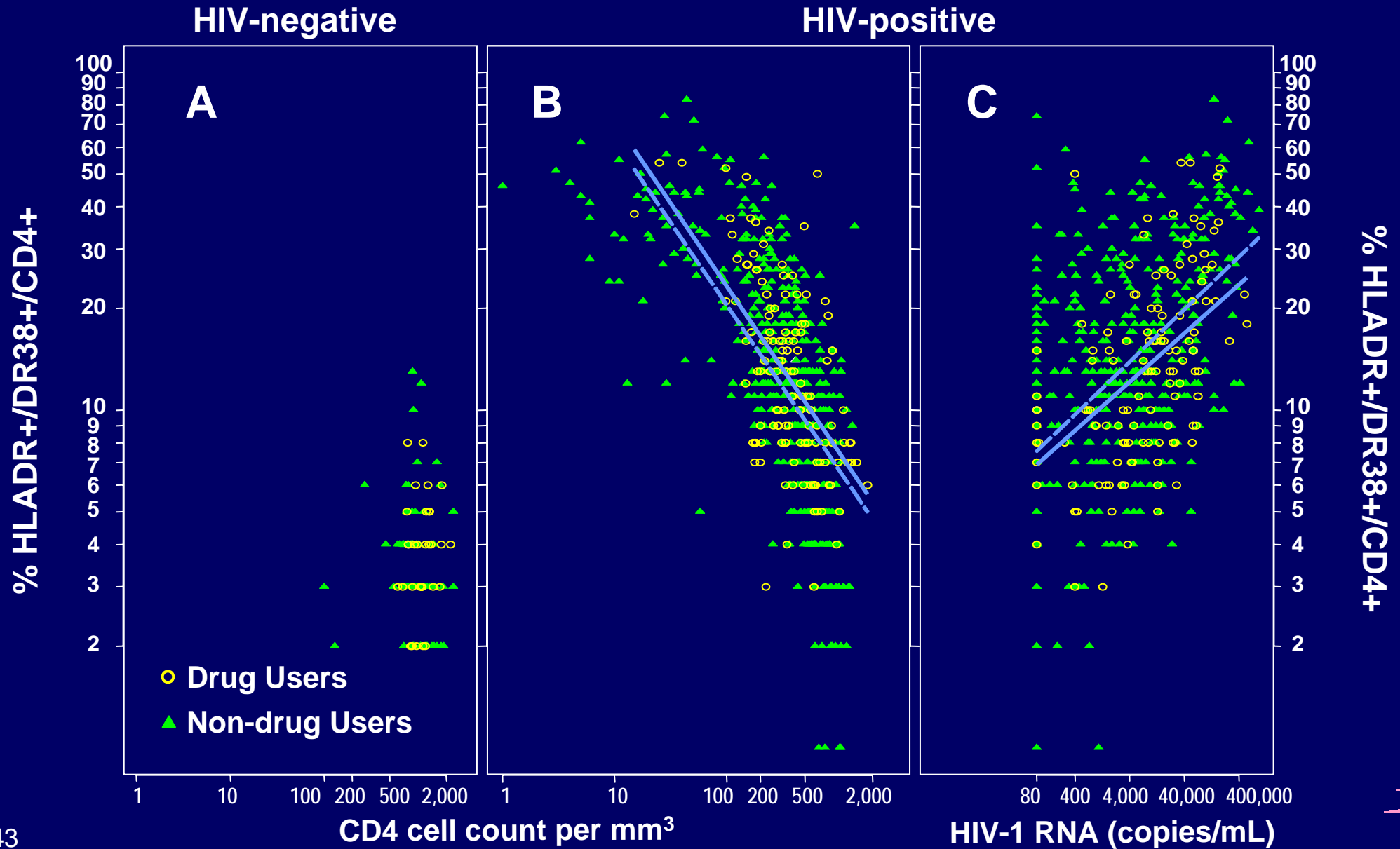


Translational Studies



Impact of Drug Use on CD4 Cell Activation

(Landay, Benning, . . . , Kovacs, *JID* 2003; 188:209-218)



HCV quasispecies

- Women with active IDU more likely to experience shift in quasispecies of HCV over time: OR=5.12, p=0.004



QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.



Cohort Composition

- 935 participants
 - 715 HIV infected women
 - 221 HIV negative women
- ~50% of each group are women who survived genocidal rape
- At 1.5 years follow-up 410 HIV+ women have initiated ART
- No tobacco or drug use
- 20% use alcohol





