

ARV Treatment in HIV+ Women: Sex/Gender Considerations That Inform Regimen Selection

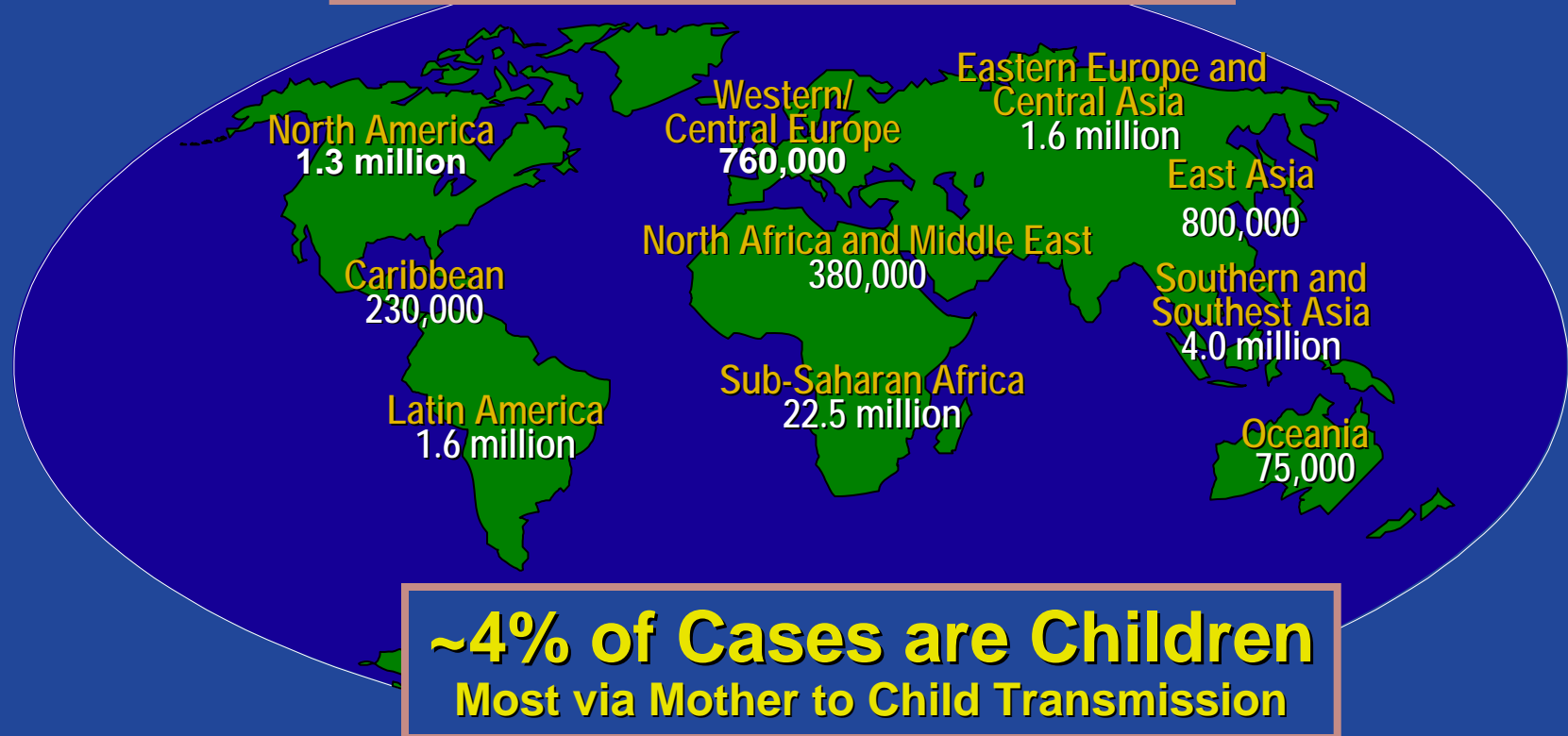
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Educational Objectives:

- Review sex/gender differences in biology of HIV infection and pharmacokinetics and disposition of antiretroviral agents
- Review data supporting initial preferred antiretroviral regimens
- Discuss sex/gender differences in efficacy and safety of antiretroviral agents and combination regimens

Adults and Children Estimated to Be Living With HIV, 2007

50% of Cases are Women



~4% of Cases are Children
Most via Mother to Child Transmission

Clinical Case

- 38 year-old African-American woman presents for evaluation and management of newly diagnosed HIV infection
- Discharged from 3-week hospital admission
 - complicated by ***Streptococcus pneumoniae*** meningitis, pneumonia, respiratory failure and intubation

Clinical case: HIV diagnosis

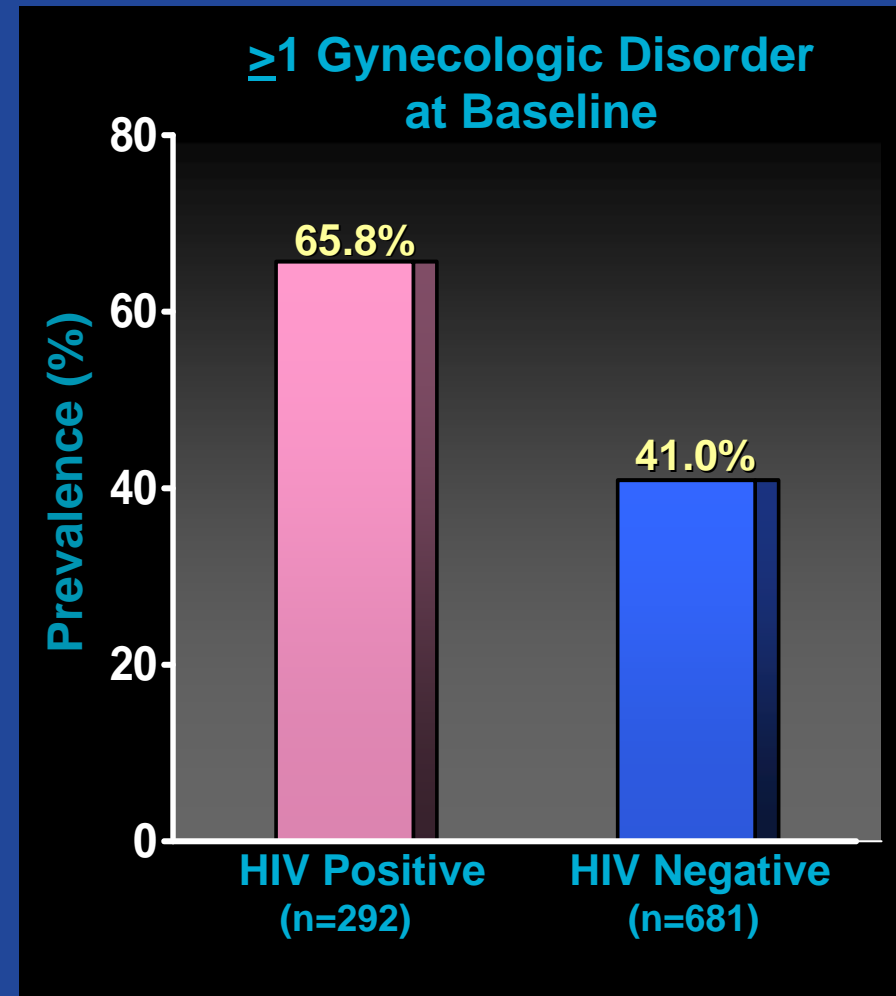
- Laboratory values
 - CD4 64 cells/mm³
 - HIV-1 RNA 158,000 copies/mL
 - Medical and social history significant for:
 - partner who 'died of AIDS' 2 years ago
 - recurrent episodes of vaginal candidiasis
 - cervical dysplasia

Late Diagnosis of HIV Infection: Missed Clues

- A. Sexually active
- B. Vaginal candidiasis
- C. Cervical dysplasia
- D. Partner with HIV infection

Prevalence of Gynecologic Disorders Among HIV-Infected Women

- NYC community hospitals
 - 1991-1994
 - Serial assessment
- Selected gynecologic disorders
 - Candidiasis
 - Oncogenic HPV
 - HSV shedding
 - Abnormal Papanicolaou smear
 - Positive TPHA result
 - Warts
 - CMV

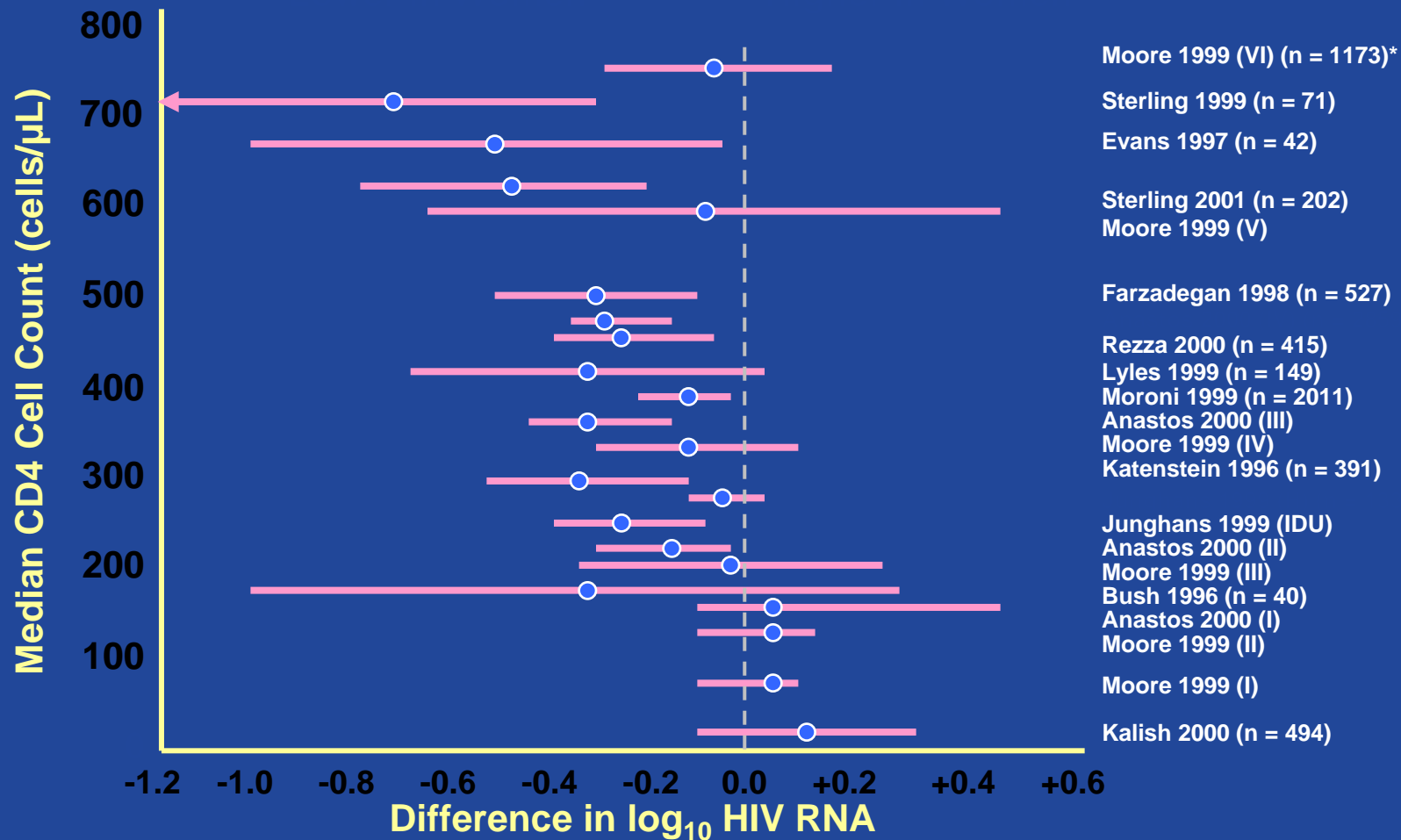


Sex/Gender Differences: Natural History

Biologic Differences: *Compared to Men, Women Have...*

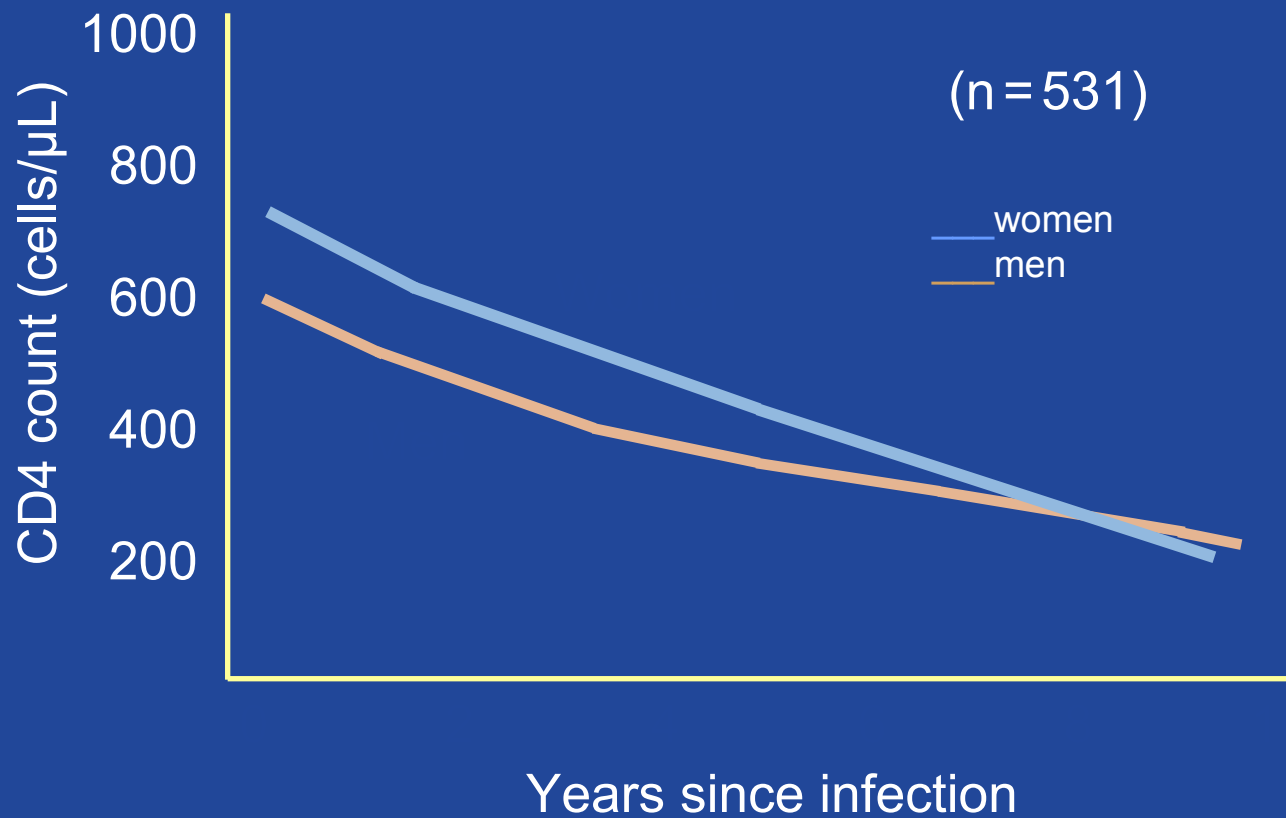
- 2x-6x lower viral load in early disease; the difference disappears within 5-15 years
- Higher CD4⁺ cell counts earlier in disease process
- But women have a similar disease progression rate!

Women vs Men: HIV RNA Levels by CD4 Cell Count



*n values for total population, not strata.
 Gandhi M, et al. *Clin Infect Dis.* 2002;35:313–322.

Women Have Higher CD4⁺ Cell Counts



Natural History: How Gender and Viral Load Affect The Development of AIDS

Median baseline HIV RNA (copies/mL)

	All	Progression to AIDS	No Progression to AIDS
Female	15,103	17,149	12,043
n =	46	15 (32.6%)	31 (67.4%)
Male	50,766	77,822	40,634
n =	156	29 (18.6%)	127 (81.4%)

Sterling et al. *N Engl J Med.* 2001;344:720-725.

Sex/Gender Differences: Biology , Social Factors and Pharmacokinetics/Pharmacodynamics

Women Are Different From Men

Issues common to women

Specific psycho-sexual issues

Gynecologic problems¹

STDs that increase HIV transmission²

Use of more support systems than men

Diagnosed later than men

Decreased bone mineral density with PI use³

Issues common to women and men

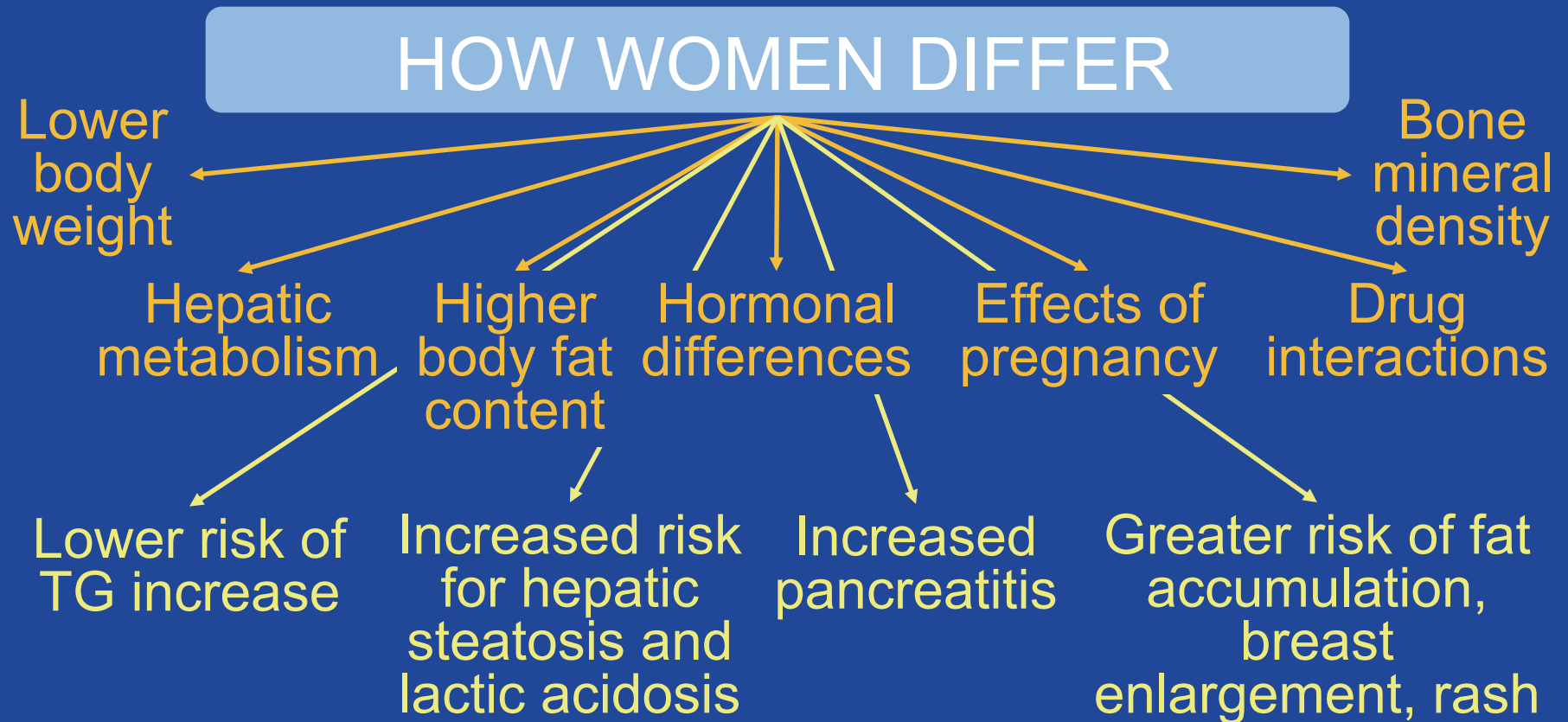
Depression

Substance use

Lack of social support

¹Minkoff et al. *Am J Obstet Gynecol.* 1999;180:824-836; ²Wasserheit. *Sex Transm Dis.* 1992;19:61-77; ³Arsten. CROI, 2002. Abstract #717-T.

Factors Affecting Treatment



Arnsten et al. 9th Conference on Retroviruses and Opportunistic Infections; No. 717-T; DHHS guidelines. March 23, 2004; Garcia et al. *N Engl J Med.* 1999;341:394-402. Hader et al. *JAMA.* 2001;285:1186-1192; Mirochnick. *Ann NY Acad Sci.*, 2000.

Pharmacokinetic Differences: *Compared to Men, Women...*

- Saquinavir¹: 50% ↓ clearance
- Tipranavir/r²: ↑ plasma concentrations
- Darunavir³: ↑ AUC
- Ritonavir³: ↑ AUC
- Nevirapine⁴: ↑ drug levels
- Zidovudine, ↑ intercellular concentrations
lamivudine⁵

²Walmsley et al. 4th International AIDS Society Conference on HIV Pathogenesis and Treatment; July 22-25, 2007; Sydney, Australia. Abstract MOPDB04.

³Sekar et al. 9th International Workshop on Clinical Pharmacology of HIV Therapy; April 7-9, 2008; New Orleans, LA. Abstract O16.

⁴Clark. *Drug Saf.* 2005;28(12):1075-1083.

⁵Anderson et al. *AIDS.* 2003;17(15):2159-2168.

Tolerability Differences: *Compared to Men, Women...*

- Darunavir/r¹: ↑ nausea, ↑ headache, ↓ fatigue
- Didanosine²: ↑ pancreatitis
- Fosamprenavir³: ↑ upper respiratory tract infections,
 ↑ headache, ↓ diarrhea
- Nelfinavir⁴: ↓ diarrhea
- Nevirapine⁵: ↑ hepatotoxicity
- Ritonavir⁶: ↑ peak concentration
 ↑ abdominal pain, nausea, vomiting

¹Collier et al. 46th ICAAC; September 27-30, 2006; San Francisco, CA. Abstract H-1396.

²Moore et al. *AIDS*. 2001;15(5):617-620.

³Currier et al. 46th ICAAC; September 27-30, 2006; San Francisco, CA. Abstract A-2593.

⁴Gerstein et al. National Conference on Women and HIV; May 4-7, 1997; Los Angeles, CA. Abstract 304.1.

⁵Bersoff-Matcha et al. *Clin Infect Dis*. 2001;32(1):124-129.

⁶Gatti et al. 39th ICAAC; September 26-29, 1999; San Francisco, CA. Abstract 2210.

Antiretroviral Treatment: Should It Be Gender/Sex Specific?

Clinical Case: Decision Point

- Which antiretroviral regimen would you recommend?
 - A. 2 NRTIs + NNRTI
 - B. 2 NRTIs + boosted PI
 - C. Other

NRTIs = nucleoside reverse transcriptase inhibitors; NNRTI = nonnucleoside reverse transcriptase inhibitors.

Currently Approved Drugs for Antiretroviral Therapy (ART) 1/2008

■ Nucleoside RTIs

- Zidovudine (Retrovir®, ZDV) 1987
- Didanosine (Videx®, ddI) 1991
- Zalcitabine (Hivid®, ddC) 1992
- Stavudine (Zerit®, d4T) 1994
- Lamivudine (Epivir®, 3TC) 1995
- Abacavir (Ziagen®, ABC) 1998
- Emtricitabine (Emtriva®, FTC) 2003

■ Nucleotide RTI

- Tenofovir (Viread®, TDF) 2001

■ Nonnucleoside RTIs

- Nevirapine (NVP) (Viramune®, NVP) 1996
- Delavirdine (Rescriptor®, DLV) 1997
- Efavirenz (EFV) (Sustiva®, EFV) 1998
- Etravirine (Intelence, TMC 125) 2008

RTIs = reverse transcriptase inhibitors.

Currently Approved Drugs for Antiretroviral Therapy (ART) 1/2008

■ **Protease Inhibitors**

- Saquinavir (Invirase®, SQV.hgc) 1995
- Ritonavir (Norvir®, RTV) 1996
- Indinavir (Crixivan®, IDV) 1996
- Nelfinavir (Viracept®, NFV) 1997
- Amprenavir (Agenerase®, APV) 1999
- Lopinavir/r (Kaletra®, LPV/r) 2000
- Atazanavir(Reyataz®, ATV) 2003
- Fosamprenavir (Lexiva®, FPV) 2003
- Tipranavir (Aptivus®, TPV) 2005
- Darunavir (Prezista™, TMC114) 2006

■ **Entry Inhibitors**

- Enfuvirtide (Fuzeon , T-20) 2003 (Fusion Inhibitor)
- Maraviroc (Selzentry) 2007 (CCR5 Inhibitor)

■ **Integrase Inhibitors**

- Raltegravir (Isentress) 2007

■ **Fixed-Dose Combinations**

- ZDV/3TC (Combivir®) 1997
- ZDV/3TC/ABC (Trizivir®) 2000
- ABC/3TC (Epzicom™) 2004
- TDF/FTC (Truvada®) 2004
- EFV/TDF/FTC (Atripla™) 2006

DHHS Guidelines: When To Start 2008

Clinical Condition and/or CD4 Count	Recommendations
<ul style="list-style-type: none">• History of AIDS-defining Illness• CD4 count <350 cells/mm³• Pregnant women• Persons with HIV-associated nephropathy• Persons co infected with HBV, when HBV treatment is indicated	<p>Initiate ARV Therapy</p>
<p>Patients with CD4 > 350 cells/mm³</p>	<ul style="list-style-type: none">• Optimal time to initiate ARV therapy not well defined• Consider patient scenarios and co morbidities

Available at: <http://aidsinfo.nih.gov/Default.aspx>. Revision January 29, 2008.

Female Gender: Lessons Learned From Clinical Trials?

- 6.7% of 11,909 ACTG participants from 1987–1990 were women¹
- Despite increased representation by women, studies since 1990 lack the statistical power to definitively answer the questions:
 - Is ART more or less efficacious in women?
 - Are ART adverse effects significantly different in women?

ARV = acquired immunodeficiency syndrome-related virus.

1. Cotton DJ, et al. *J Acquir Immune Defic Syndr*. 1993;12:1322–1328.

NNRTI-Based HAART

■ Advantages

- Low pill burden
- Demonstrated potency in multiple clinical trials
- Few metabolic effects

■ Disadvantages

- Teratogenicity (EFV)
- Low resistance barrier
- Cross-class resistance
- Increasing frequency of transmitted resistance
- Side effects
 - CNS side effects (EFV)
 - Hepatotoxicity (NVP)
 - Rash

Treatment Considerations in Women: NNRTIs

- **EFV¹**
 - Not recommended in 1st trimester of pregnancy or in women with high pregnancy potential due to teratogenicity
- **NVP¹⁻³**
 - Not recommended for women with CD4 counts greater than 250 cells/mm³ at initiation of or switching to NVP because of severe hepatotoxicity risk
 - HLA-DRB* 0101 appears to be associated with hypersensitivity to NVP, especially at higher CD4 counts²
 - Higher incidence of hepatotoxicity and rash³ among women

1. DHHS. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; January 29, 2008. Available at: <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=7&ClassID=1>. Accessed March 21, 2008 [Evidence Level C]; 2. Martin AM, et al. *Antiretroviral Therapy: Metabolic Complications and Cardiovascular Risk*. 15th International AIDS Conference. 2004; Bangkok, Thailand. Abstract LbOrB13; 3. Bersoff-Matcha SJ, et al. *Clin Infect Dis*. 2001;32:124-129.

PI-Based HAART

■ Advantages

- Demonstrated long-term efficacy
- Potential immune benefit beyond antiviral effect
- High barrier to resistance (boosted)
- Lower rates of transmission of PI resistance mutation
- No known teratogenicity
- No CD4 restrictions
- Convenient QD dosing with LPV/r, ATV, and FPV/r in treatment-naive patients

■ Disadvantages

- Higher pill burden (agent specific)
- Lipid and metabolic abnormalities (agent specific)
- Gastrointestinal side effects

Gender Differences in Lopinavir/r Soft-Gel Pharmacokinetics

- Pharmacokinetics of lopinavir/r (400/100) soft gel determined in 40 men and 38 women
 - Well balanced as to race
 - 31% white, 31% black, 31% Hispanic, 4% Asian
- Lopinavir pharmacokinetics did not differ between men and women
- Women had 20% higher ritonavir AUC, C_{max} , and trend toward faster oral clearance
- Clinical significance of differences unclear

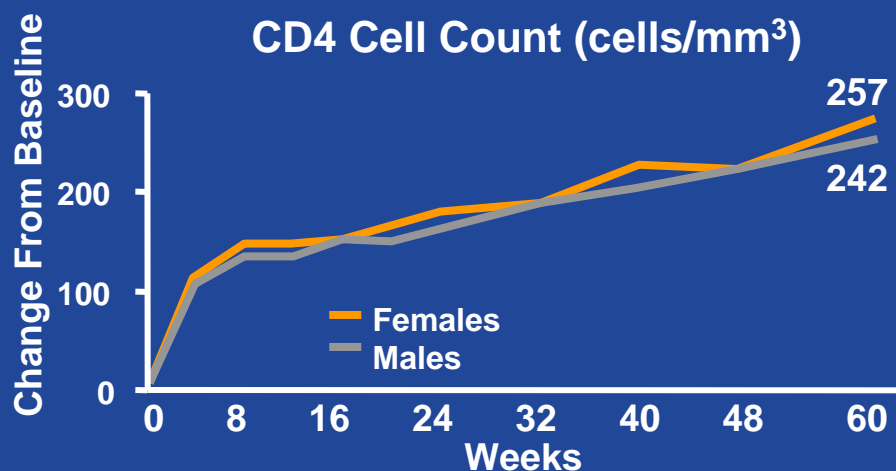
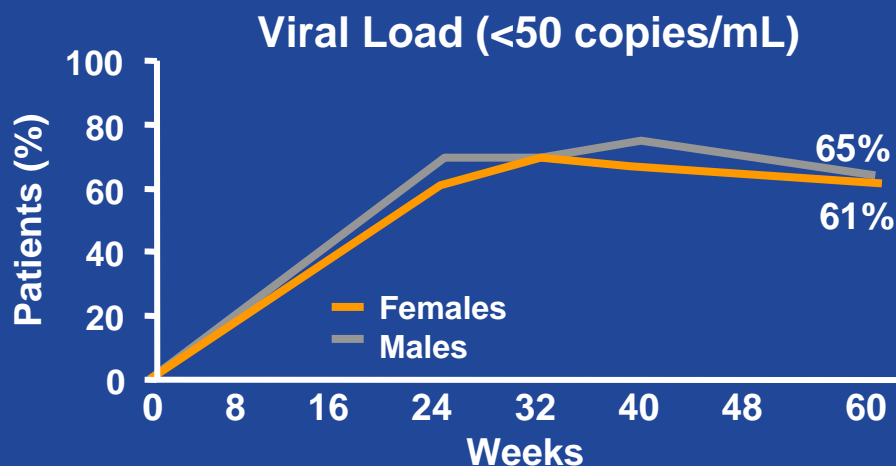
Lopinavir/Ritonavir Virologic and Immunologic Outcomes Do Not Differ by Gender

- 326 lopinavir/ritonavir patients (soft-gel formulation)
 - Female/male: 20% vs 80%
 - African American: 50% vs 18%
 - Caucasian: 33% vs 62%
 - Hispanic: 15% each
- Grade 3/4 adverse events
 - Female/male
 - Diarrhea: 11% vs 18%
 - Nausea: 14%* vs 6%
 - Dyspepsia: 8%* vs 2%
 - Vomiting: 6% vs 2%
 - Triglycerides >750 mg/dL: 2%* vs 13%

* $P < 0.05$ vs males.

Intent-to-treat analysis (missing values=failure).

Cernohous P, et al. 14th IAC; 2002, Barcelona, Spain. Abstract WePeB5972.



Women Are at Increased Risk for a Number of ART Short-Term Adverse Effects

- Increased risk of hepatic steatosis and lactic acidosis and pancreatitis² with older NRTIs¹
- Increased report of abdominal pain, pruritus, and rash with nelfinavir⁴
 - Less diarrhea
- Higher rates in women than in men of moderate to severe nausea (14% vs 6%) and dyspepsia (8% vs 2%) with lopinavir/r⁴
- Side effects have special importance for women
 - When women discontinue HAART medications, it is most frequently because of side effects⁵
 - 2 times as likely as men to discontinue because of side effects

1. Boxwell DE, et al. 39th ICAAC. San Francisco 1999. Abstract 1284; 2. Moore RD, et al. *AIDS*. 2001;15:617–620 3. Gersten M, et al. 1st NCHIVW. Pasadena, 1997. Abstract 304.1;4. Cernohous P, et al. 14th IAC. Barcelona, 2002. Abstract WePeB5972, 5. Hirschhorn LR, et al. 12th IAC. Geneva 1998. Abstract 12443.

ARV Long-Term Adverse Effects in Women: Fat Redistribution and Lipids

- Early data suggested women at higher risk of fat accumulation (truncal, breast)
 - WIHS¹ (605 HIV+, 210 HIV–)
 - Higher incidence of central and peripheral lipoatrophy in HIV+ women
 - Howard et al 2003² (105 HIV+, 120 HIV–)
 - Truncal fat higher in HIV+ women
 - Decreased truncal fat in black women
 - Multivariate analysis: PI use not independently associated with increased truncal fat
- Women on lopinavir/r noted to have lower risk of grade 3–4 triglyceride elevation (2% vs 13%—statistically significant)³

1. Tien PC, et al. *J Acquir Immune Defic Syndr*. 2003; 34:461–466; 2. Howard AA, et al. 10th CROI. Boston 2003. Abstract 735; 3. Cernohous P, et al. 14th IAC. Barcelona 2002. Abstract WePeB5972.

ARV Long-Term Adverse Effects in Women: Diabetes

- Glucose tolerance study of 125 HIV+ and 90 HIV– women¹
 - Glucose intolerance and DM associated with traditional risk factors for DM
 - Among HIV+ women, non-PI HAART associated with greater insulin resistance
- In WIHS cohort,² rate of DM higher among women on PI-based therapy (3%) than in women on non-PI-based therapy (1%) or HIV– women (1.4%)
 - In multivariate model, PI use, age, and BMI independent predictors of developing DM
- Obesity in women with HIV: cross-sectional study of people with HIV infection in urban Philadelphia³
 - Women were more obese than men (28% vs 11%, $P < .001$)
 - Among women, being African American associated with **overweight/obesity**

DM = diabetes mellitus; PI = protease inhibitor.

1. Howard AA, et al. 11th CROI. San Francisco 2004. Abstract 701; 2. Justman JE, et al. *J Acquir Immune Defic Syndr.* 2003; 32:298–302 ; 3. Amorosa V, et al. *J Acquir Immune Defic Syndr.* 2005;39:557–561.

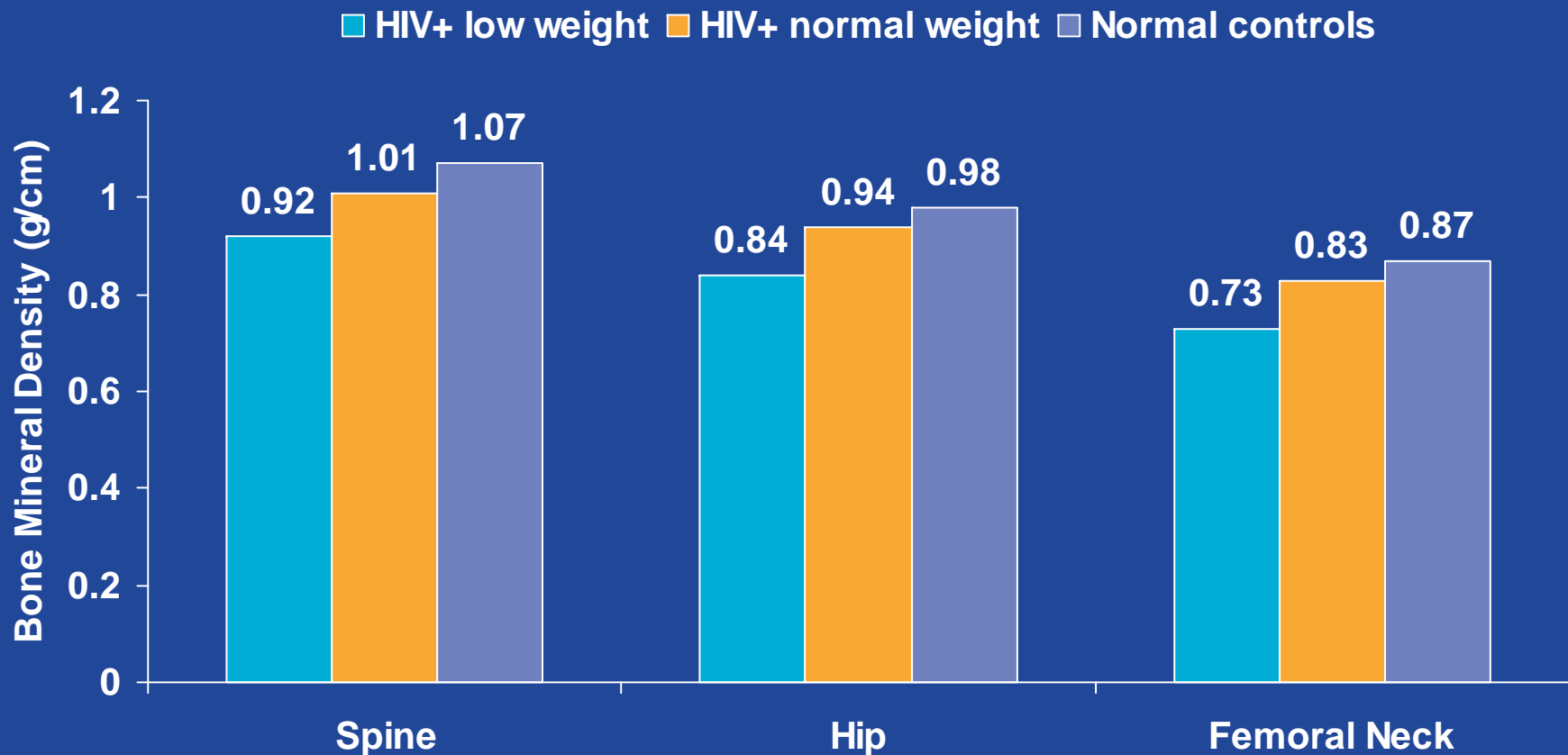
Bone Loss in HIV-Infected Women

- Prospective study of HIV+ and HIV- women
 - 2000–2003
 - Matched for age, weight, race
- HIV+ women
 - >50% had mild bone loss
 - 2.5 times as likely to have bone loss as HIV- women
 - Bone density correlated with body weight
 - Bone loss did not correlate to PI, NRTI, or NNRTI use

	Incidence (%)	
	HIV+ (n = 84)	HIV- (n = 63)
Osteopenia		
Lumbar spine	28	14
Femoral neck	33	17
Hip total	27	8
Hip or spine	54	30
Osteoporosis		
Lumbar spine	6	5
Femoral neck	0	2
Hip total	1	0
Hip or spine	10	5

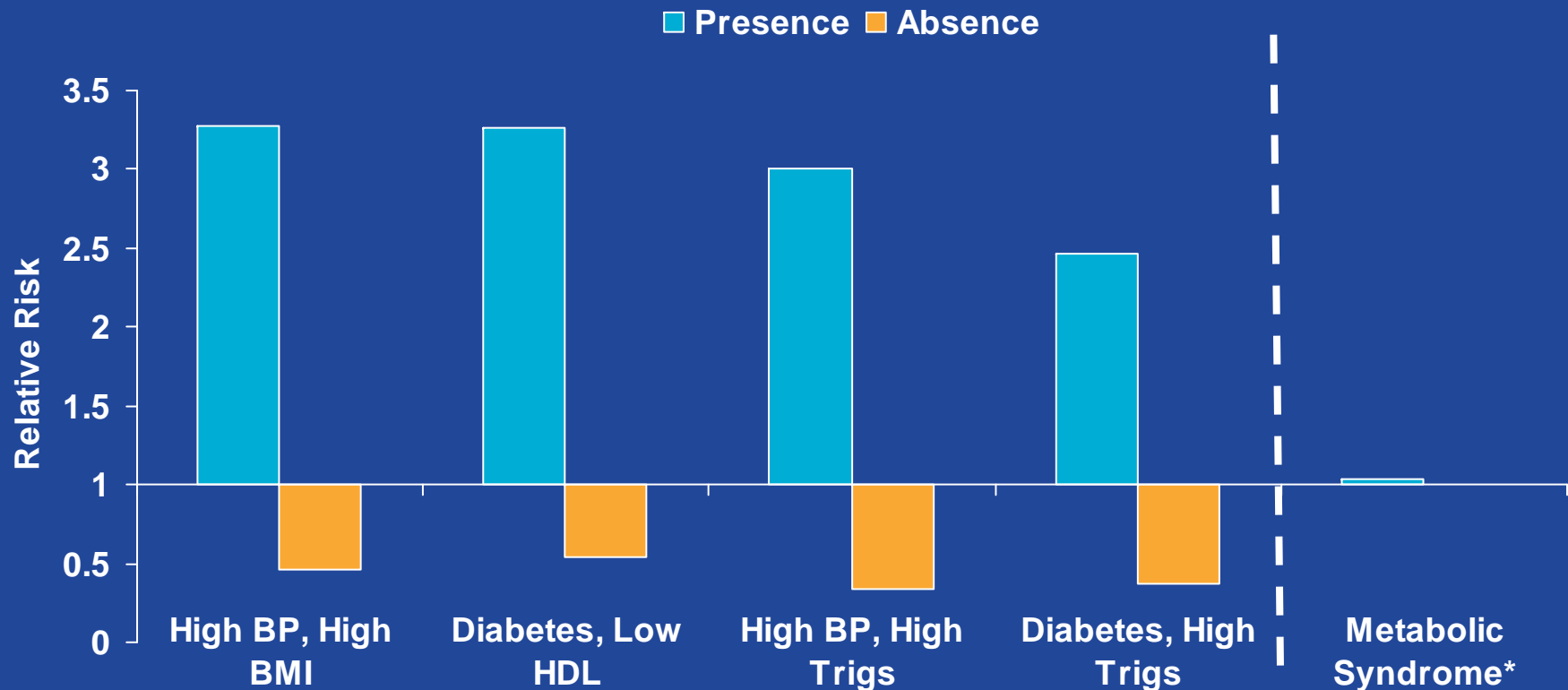
Low Weight, Oligomenorrhea Associated With Low Bone Mineral Density in HIV+ Women

Risk factors for osteoporosis/osteopenia included low free testosterone, low weight, and oligomenorrhea



$P < 0.0001$ HIV+ low weight versus all comparisons.

Relative Risk of CVD in the D:A:D



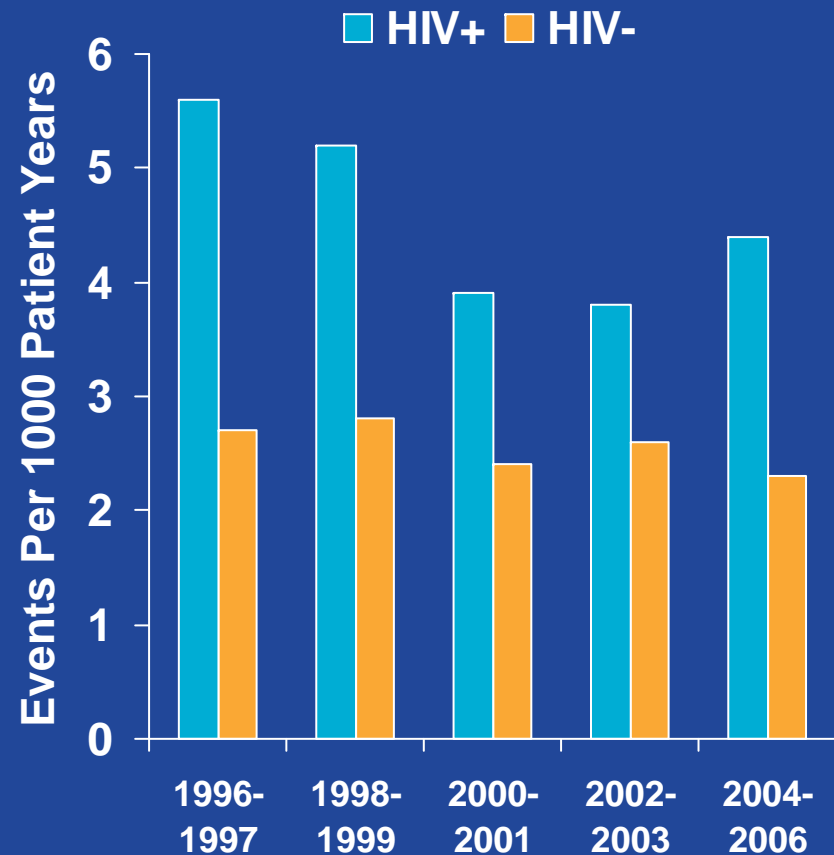
Pairwise comparison: relative risk of CVD based on presence or absence of 2 or more symptoms of metabolic syndrome.

*Excess risk of CVD with diagnosis of metabolic syndrome compared with individual symptoms.

Risk of Myocardial Infarction Hospitalization Higher in HIV+ Women

Kaiser Permanente Northern California Surveillance Cohort

- MI hospitalizations significantly higher among HIV+ patients compared with HIV- health plan members
- HIV+ women had 3.99 times relative risk of MI hospitalization

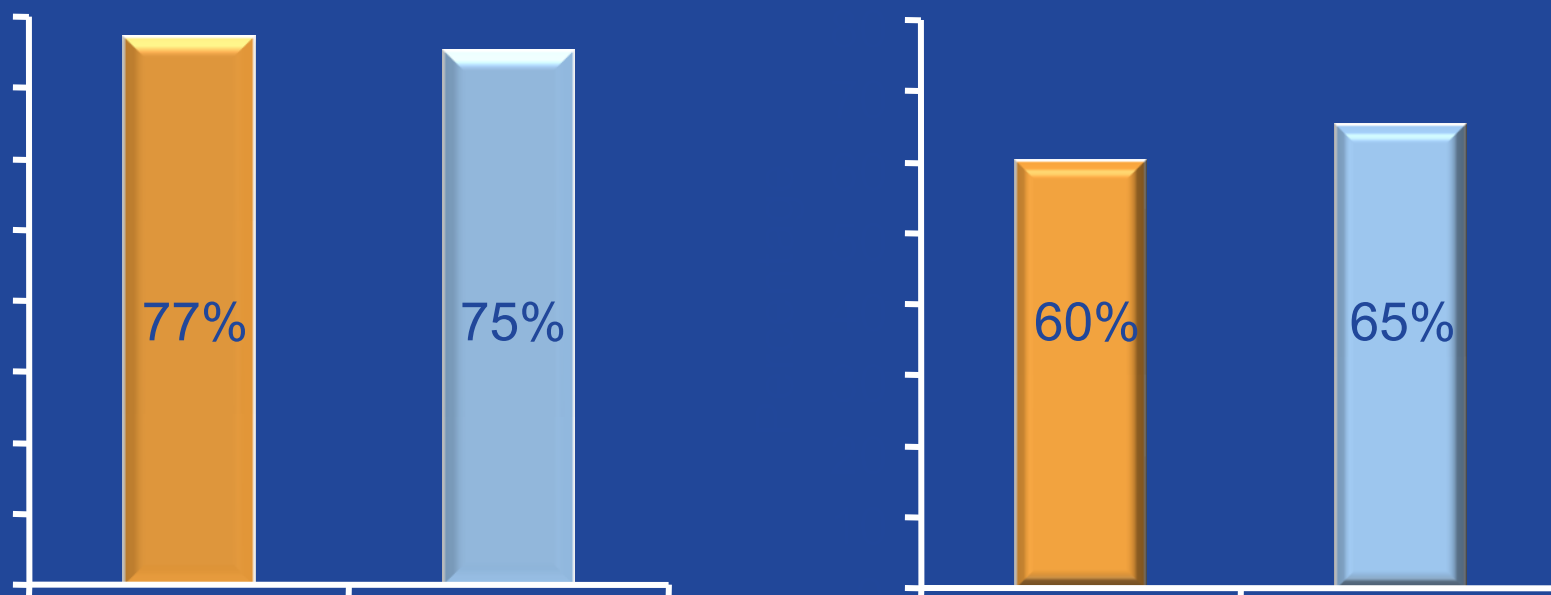


Women and Adherence to Treatment

- Factors associated with nonadherence
 - Depression
 - Active substance use
 - Active alcohol use
 - Lack of trust in provider
 - Lack of self-esteem
 - Lack of support
- Potential contributors to non-adherence in women
 - Partner or family unaware of patient's HIV status
 - Economic status/dependence
 - Caregiving role in family
 - Stigma
- Pregnancy and adherence
 - Adherence during pregnancy is often excellent, but may decline postpartum
 - Postpartum depression
 - Increased caregiving demands
 - Less motivation to continue medication for prevention
 - Changes in family dynamics, privacy
 - Increased doctor visits

PI-HAART Equally Effective for Women and Men

% <400 copies/ml at most recent visit nelfinavir-based HAART taken for mean 52.2 (men) or 47.8 (women) months

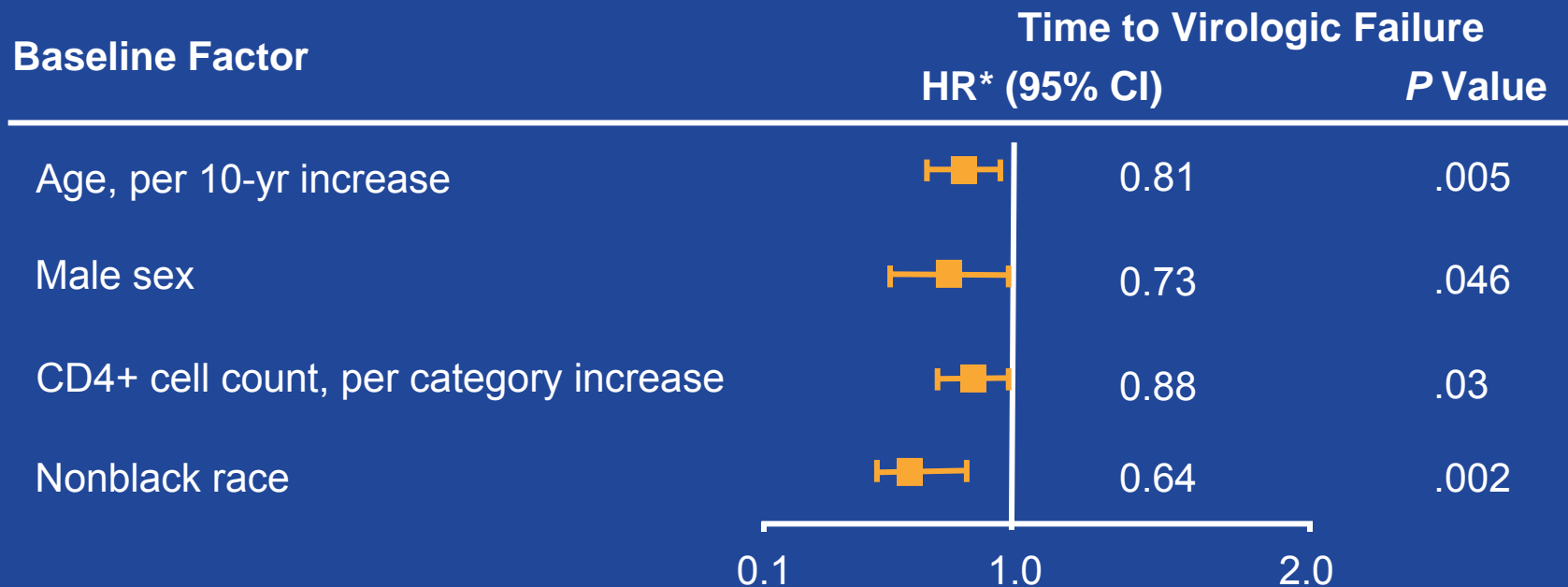


$P > .3$ for men vs women

Palella et al. XIV Int AIDS Conf, 2002; poster WePeB5967.

ACTG 5142: Sex and Race Associated With Time to Virologic Failure

- ACTG 5142: BL factors associated with virologic failure include: younger age, female sex, lower CD4+ cell count, black race



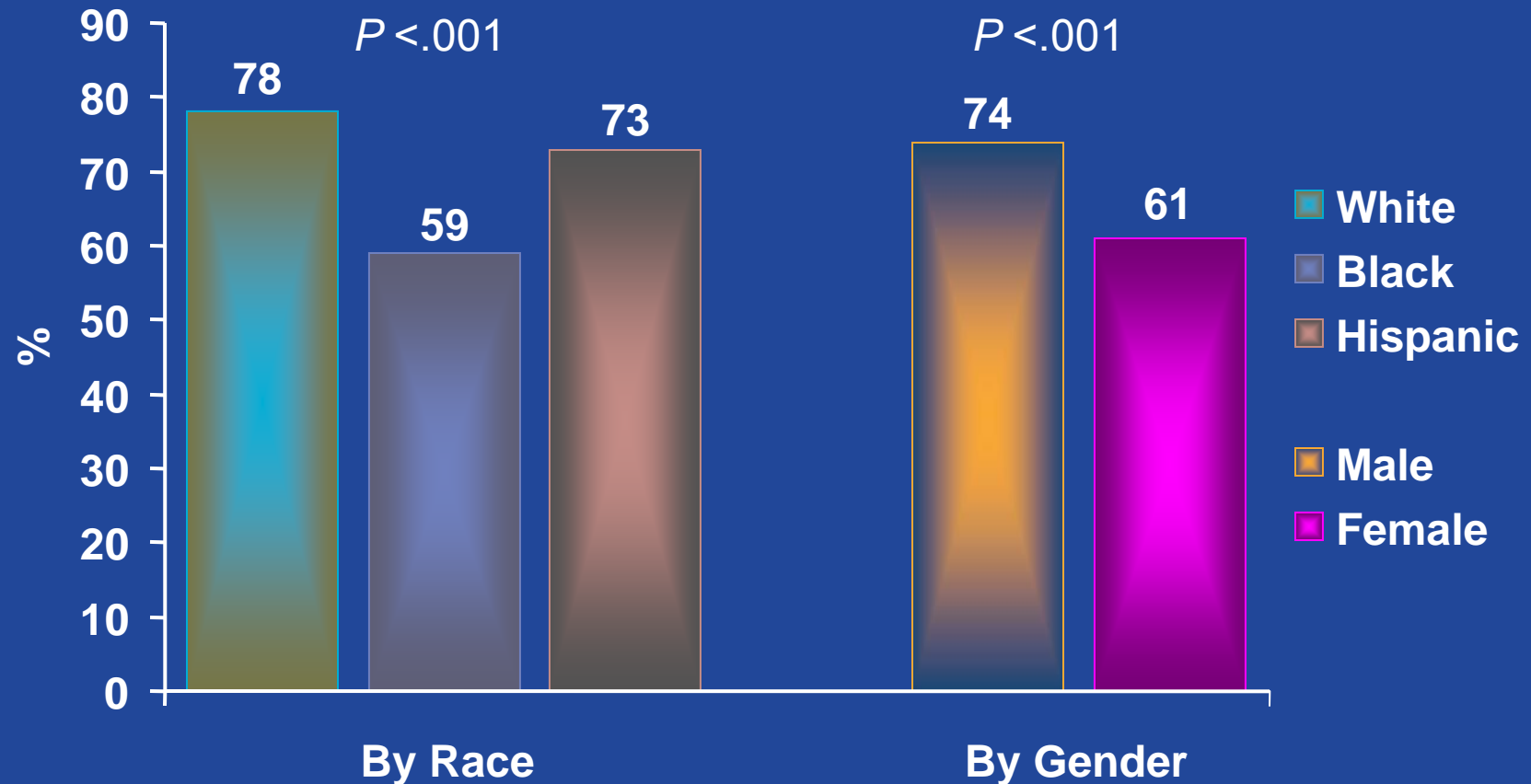
*Multivariate hazard ratio stratified by screening HIV-1 RNA level, presence of hepatitis, NRTI used.

EuroSIDA: No Gender Differences in Outcomes on HAART

- Prospective study
- 2547 Treatment-naive patients
 - Male: 2036
 - Female: 511
- Median HAART start date
 - 1997 (range: 1995–2000)
- Virologic, immunologic, and clinical response to HAART
 - No significant gender differences were found

	Achieving Success (% Patients)		
	All	Men	Women
HIV RNA <500 c/mL	89	89	88
Viral rebound	33	31	40
CD4 rise ≥100 cells/mm ³	83	84	80
AIDS	8	8	7
Death	5	5	5

Use of HAART in the US by Race and Gender

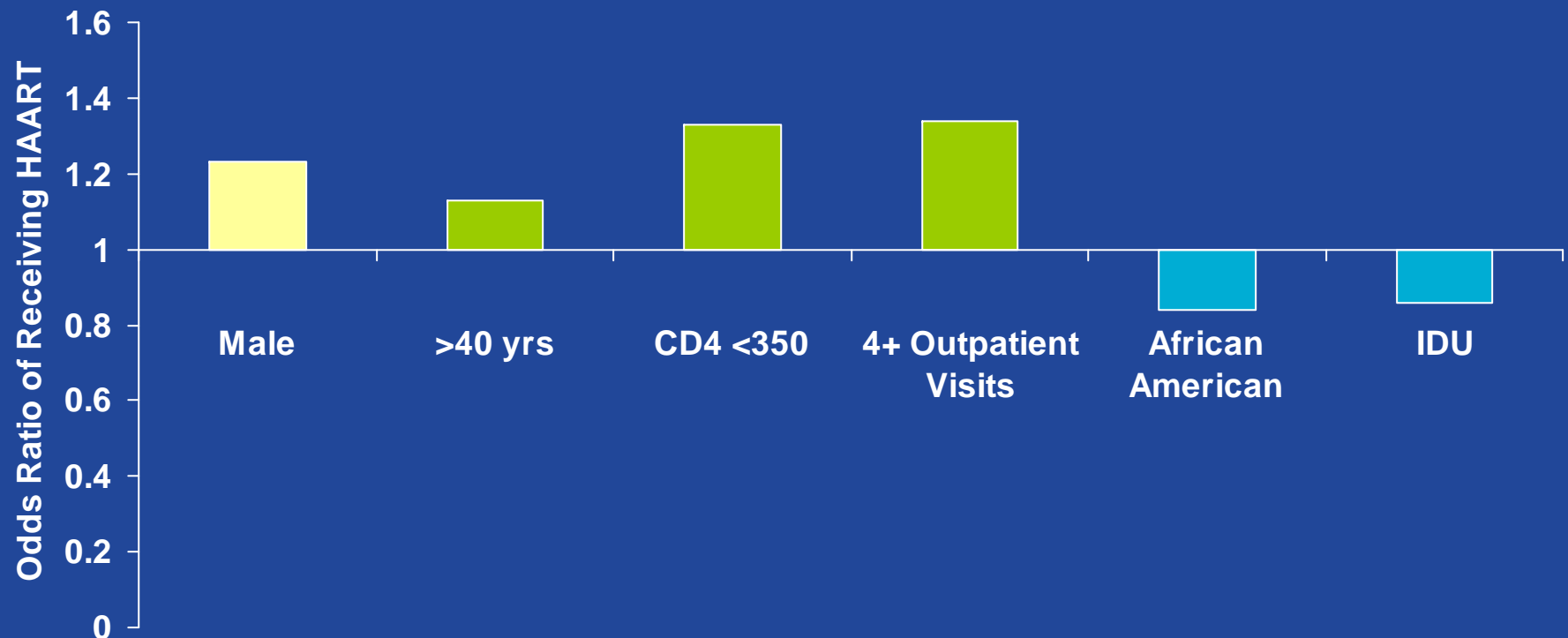


Cunningham WE, et al. *J Acquir Immune Defic Syndr.* 2000;25:115-123; McNaghten AD, et al. *J Acquir Immune Defic Syndr.* 2003;32:499-505.

Race and Gender Disparities in the Use of HAART

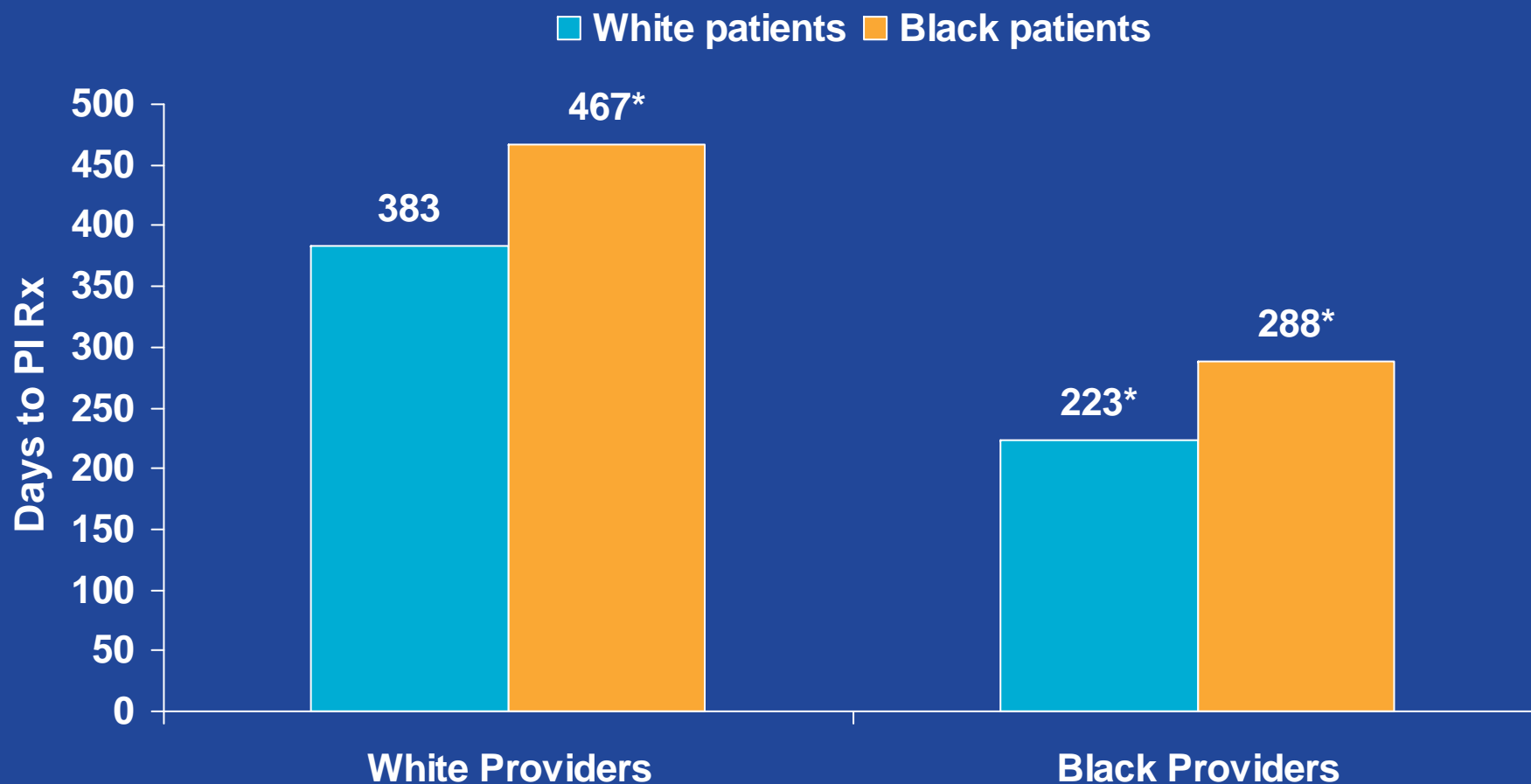
HIV Research Network (HIVRN)

Persistent differences exist in access to HAART by gender, race, and use of injection drugs



Multivariate analysis odds ratio of receiving HAART at 10 primary care sites.

Delayed Initiation of Protease Inhibitors: Racial Discordance Between Physician and Patient



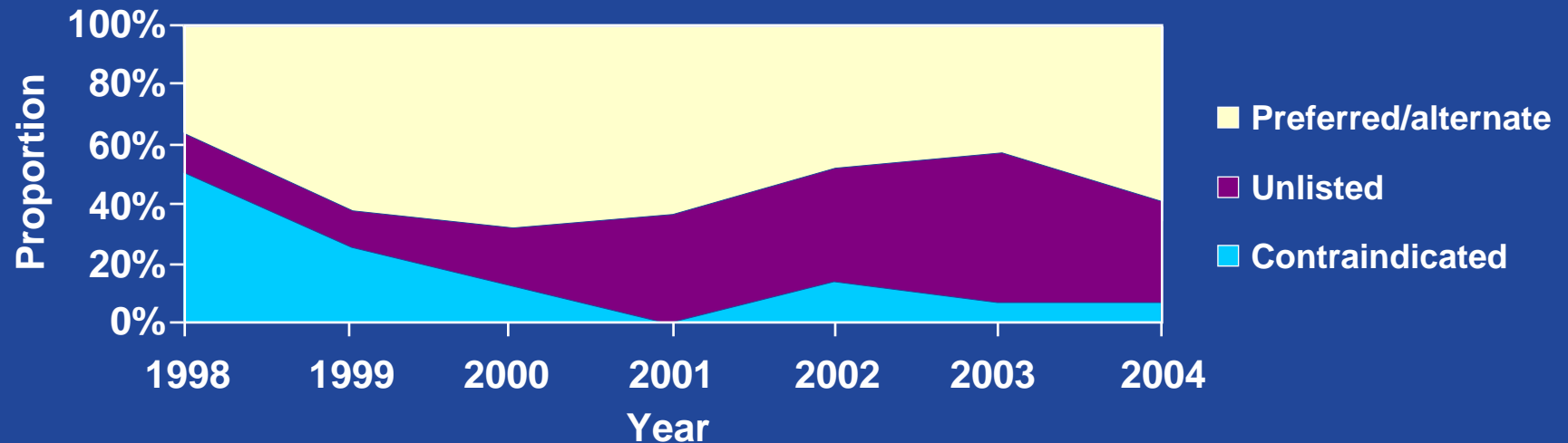
Data from 287 providers of care to 1,241 patients with HIV disease.

* $P < 0.05$ versus white patients/white providers. Adjusted for patient, provider, and attitude characteristics.

King WD, et al. *J Gen Intern Med.* 2004;19:1146-1153.

Trends in the Use of Suboptimal Therapy in Women

DHHS Category of Initial Regimens in WIHS by Year



WIHS Report

- Inappropriate use of ART regimens, contrary to USPH guidelines, persists
- Inappropriate therapy results in suboptimal response

Women and HIV: Initial Antiretroviral Regimen Considerations

- Women comprise at least half of total burden of human HIV infection
- HIV is an STI in the majority of women, most frequently acquired early in life
- Episodic pregnancy-related ART, delayed initiation of therapy and sub-optimal ART common
 - Clinical implication and/or effect on long-term outcome unknown at this time
- Significant medical complications pertinent to women-heart disease and osteoporosis-may become significant management issues and causes of morbidity and mortality for women living with chronic HIV infection
- Optimal management strategies for this patient population must address HIV infection over the continuum
 - Reproduction options
 - Management of pregnancy
 - Selection and modification of ART regimens based on reproductive choices, sex/gender specific issues and inter-current conditions
 - Screening for and management of long term complications