

# HIV Infection In Women: Management Across the Continuum

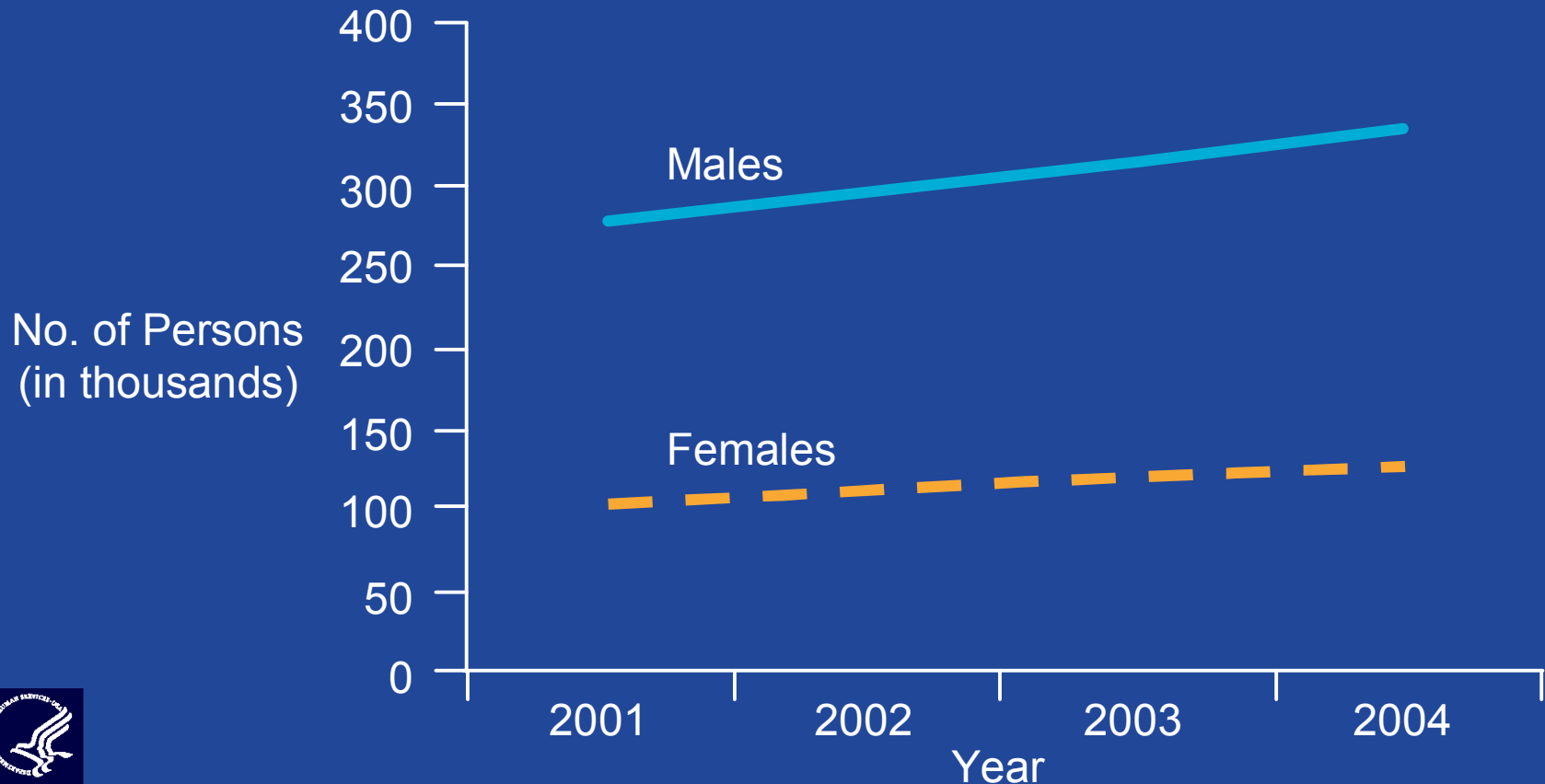
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Division of Infectious Diseases  
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# Global Infection Rates

**~50% of Cases are Women**



# Estimated Number of Adults and Adolescents Living With HIV/AIDS by Sex (2001–2004) – 35 Areas



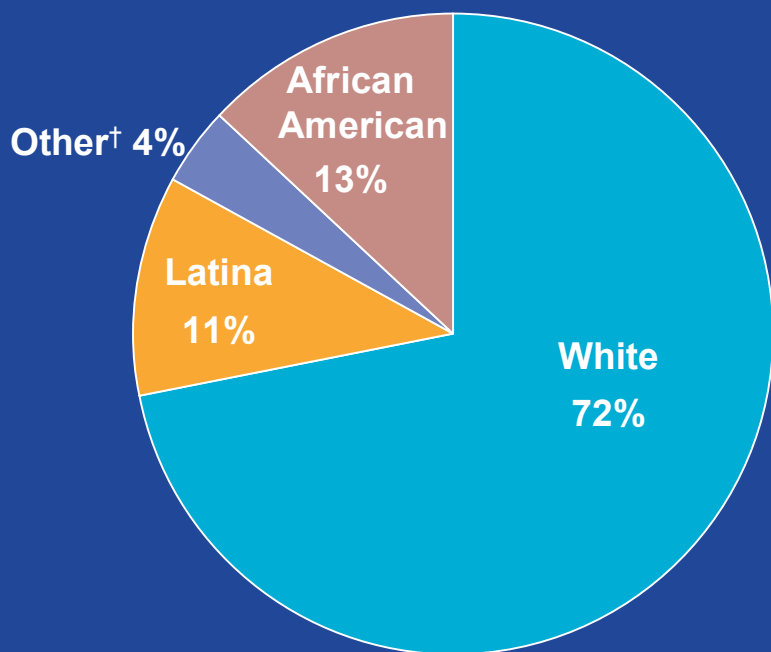
Note: Data include persons with a diagnosis of HIV infection regardless of their AIDS status at diagnosis. Data from 35 areas with confidential name-based HIV infection reporting since at least 2000. Data have been adjusted for reporting delays. Age as of end of year.

Source: CDC. *HIV/AIDS Surveillance General Epidemiology* (through 2004). Available at: <http://www.cdc.gov/hiv/topics/surveillance/resources/slides/general/slides/general.ppt>. Accessed November 15, 2006.

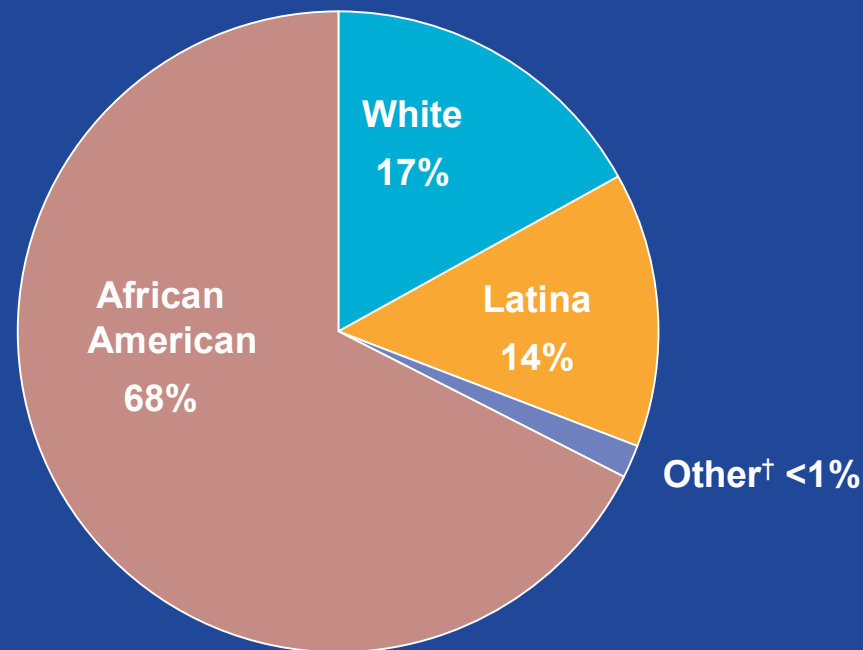
# Female HIV/AIDS Cases, by Race/Ethnicity 2004

Data from 33 states with long-term, confidential name-based HIV reporting

US Female Population  
Total = 78.6 million



HIV/AIDS Cases  
Total\* = 10,391



\*The total HIV/AIDS cases include 49 female adults and adolescents of unknown race or multiple races.

†Other includes Asian/Pacific Islander, Alaskan Native, and Native American women.

# 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

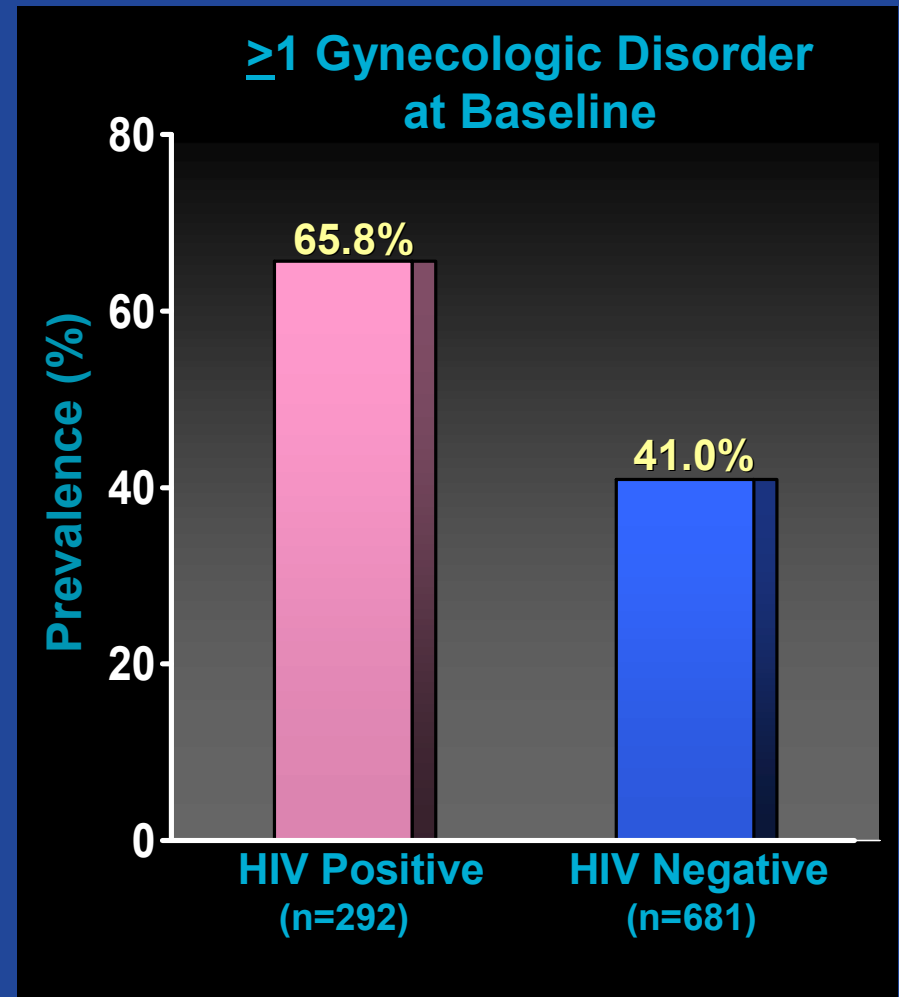
- Laboratory values
  - CD4 64 cells/mm<sup>3</sup>
  - HIV-1 RNA 158,000 copies/mL
  - Medical and social history significant for:
    - partner who 'died of AIDS' 2 years ago
    - recurrent episodes of vaginal candidiasis
    - cervical dysplasia

## Late Diagnosis of HIV Infection: Missed Clues

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

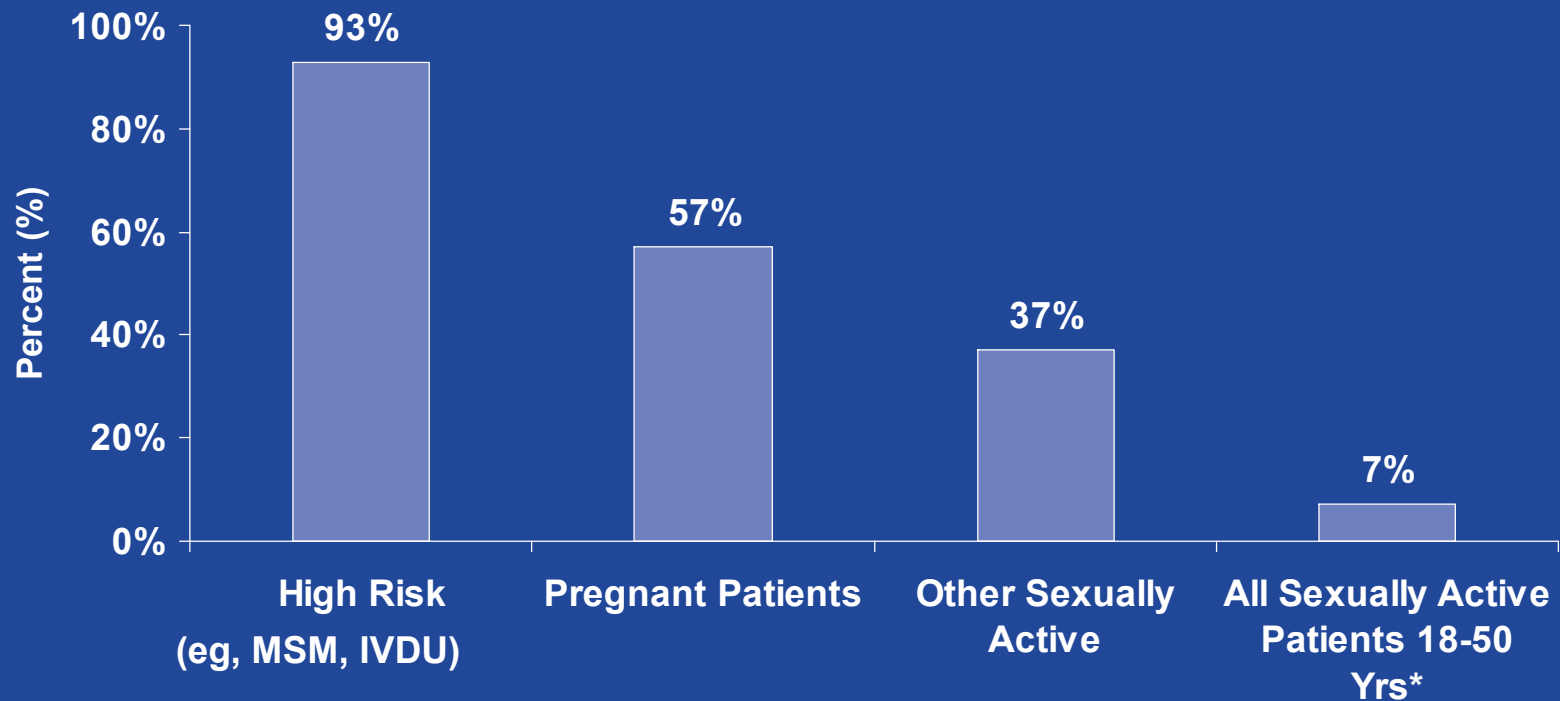
# Prevalence of Gynecologic Disorders Among HIV-Infected Women

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



# HIV Testing in the Primary Care Setting

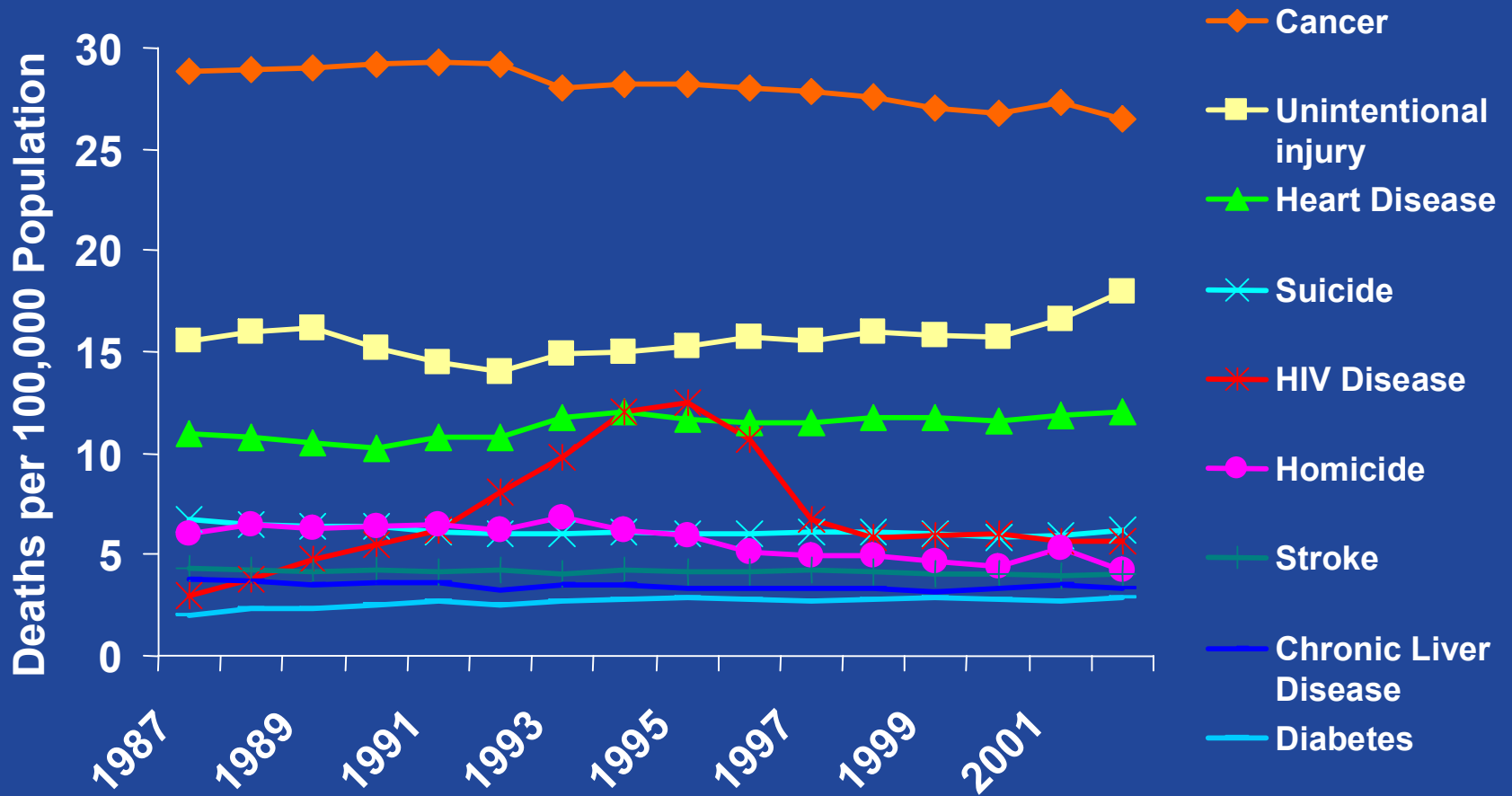
Primary care practitioner recommendations for HIV testing: 2002 survey of family practitioners in Rhode Island and Mississippi



\*Sexually active within the past year.

Simmons E, et al. *AIDS Patient Care STDs*. 2006;20:79-83.

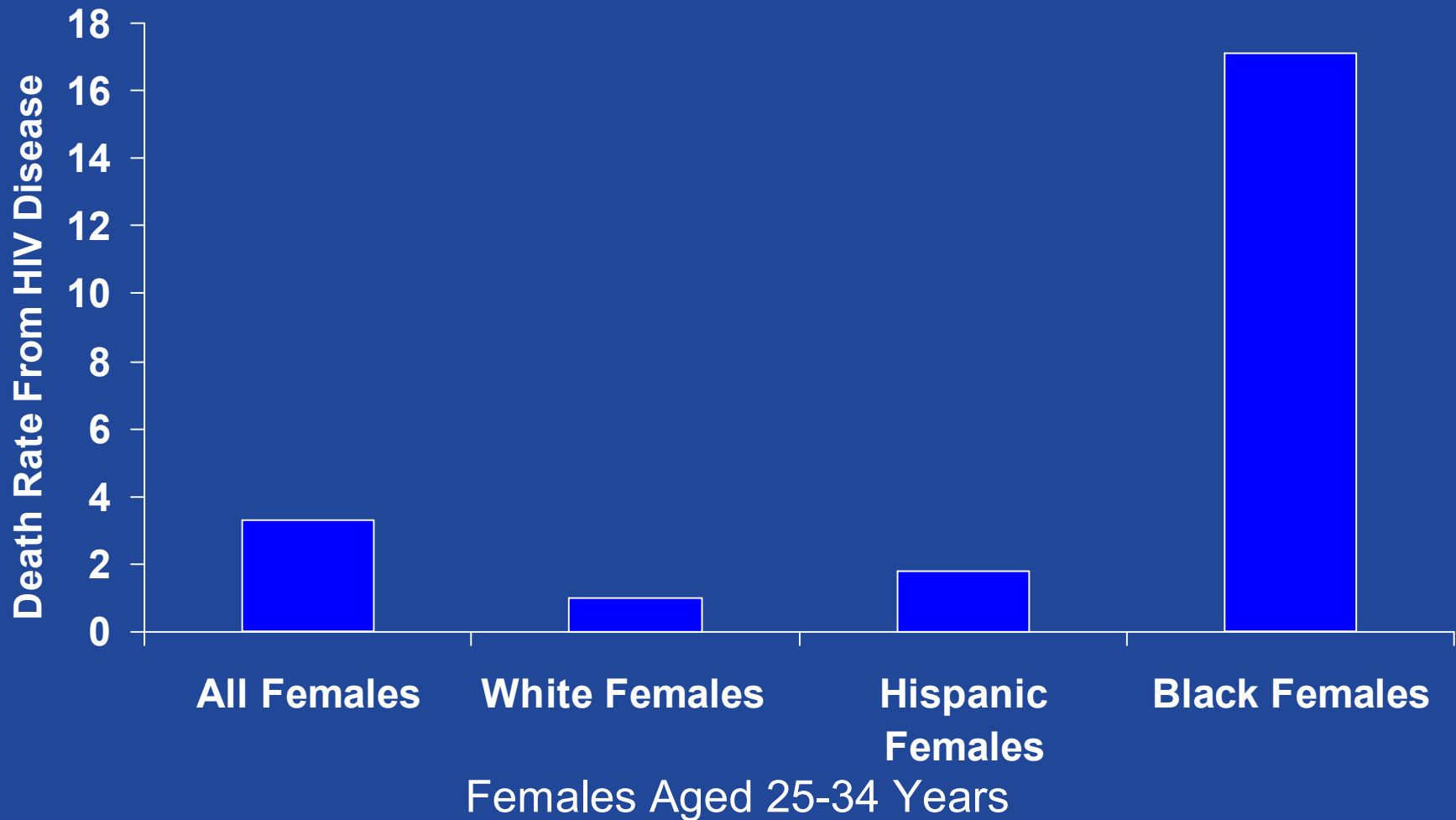
# Trends in Annual Rates of Death Due to the 9 Leading Causes Among Women Aged 25–44, 1987–2002—United States



Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for *ICD-10* rules instead of *ICD-9* rules.

CDC. Available at: [www.cdc.gov/hiv/topics/surveillance/resources/slides/index.htm](http://www.cdc.gov/hiv/topics/surveillance/resources/slides/index.htm). Accessed June 20, 2006.

# HIV Disease Is the Leading Cause of Death for Black Females Aged 25-34 Years



# Reproduction Issues and HIV Infection

- Most HIV-infected women are of reproductive age<sup>1</sup>
- ~29% of HIV-infected women and men desire children in the future<sup>2</sup>
- Pregnancy rate has been estimated at 7.4/100 person-years among HIV+ women (WIHS data)<sup>3</sup>
  - 77% of pregnancies occurred in women reporting contraceptive use
  - Elective abortion was not associated with HIV serostatus
  - Abortion was less likely during HAART era than before HAART
  - Some studies suggest that HIV-infected women may be less fertile<sup>4</sup>

1. Aberg JA et al. *Clin Infect Dis*. 2004;39:609-629.

2. Chen JL et al. *Family Planning Persp*. 2001;33:144-152,165.

3. Massad LS et al. *AIDS*. 2004;18:281-286.

4. Anderson J. *A Guide to the Clinical Care of Women with HIV/AIDS, 2005 edition*. Chapter VII.

- PACTG 367 slide
- Counseling slide
- Contraceptive slides
- Fertility rights slide
- Types of assisted contraception

# Timing of HIV Diagnosis for HIV-Infected Pregnant Women

PACTG 367 n = 1527 pregnancies

During  
pregnancy  
41%



Before  
pregnancy  
59%

# Reproductive Choice

## Helping women make informed decisions



“HIV infection is classified as a chronic disease. It is treatable but not yet curable....Health care providers and HIV-infected persons together share responsibility for the safety of the uninfected partner and potential offspring. When an affected couple requests assistance to have their own genetically related child, they are best advised to seek care at institutions with facilities that can provide the most effective evaluation, treatment, and follow-up. Alternatively, they may be advised to look at other options and consider donor sperm, adoption, or not having children.”

Ethics Committee, American Society for Reproductive Medicine. *Fertility and Sterility*. 2002;77:218-222.

# Reproductive Choice: Principles of Counseling

- Discuss appropriate contraceptive methods to reduce unintended pregnancy
- Consideration of ART if pregnancy is desired:
  - Avoid agents with teratogenic potential
  - Maximize agents effective in reducing transmission
  - Achieve durable suppression of viral load prior to attempting pregnancy
- Education on perinatal transmission and effective intervention strategies

# Reproductive Health: Contraception Choices

- Contraception/STD Prevention
  - Barrier
    - Condoms (male and female)
  - Hormonal
    - Oral contraceptives
      - Newer modalities
        - Transdermal E/P administered as a weekly patch
        - Monthly E/P vaginal ring
    - Depoprovera
  - Intrauterine device (IUD)
  - Sterilization

*E/P, estrogen/progesterone.*

## Reproductive Choice: Principles of Counseling

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## HIV and Pregnancy: Avoiding Transmission in Serodiscordant Partners

- HIV-positive woman/HIV-negative man
  - ART to achieve virologic suppression
  - Artificial insemination
  - Low-cost/ low-tech alternatives
- HIV-negative woman/HIV-positive man
  - Unprotected intercourse
    - ART to achieve virologic suppression and timed insemination
  - Semen processing
  - In vitro fertilization

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# HIV and Pregnancy: Avoiding Transmission in Serodiscordant Partners

- HIV-negative woman/HIV-positive man
  - Unprotected intercourse
    - Male-to-female transmission approximately 1/1000<sup>[1]</sup> (about 8 times more efficient than female to male)
    - ART to achieve virologic suppression and timed insemination
      - APV +/- NRTIs (n = 30)<sup>[2]</sup>
        - Baseline seminal VL: 3.45 log<sub>10</sub> copies/mL (4 had > 6 log<sub>10</sub> copies/mL )
        - Seminal plasma VL reduced to undetectable in 77%
        - 8 men (27%) had measurable HIV-RNA last visit (16 weeks)

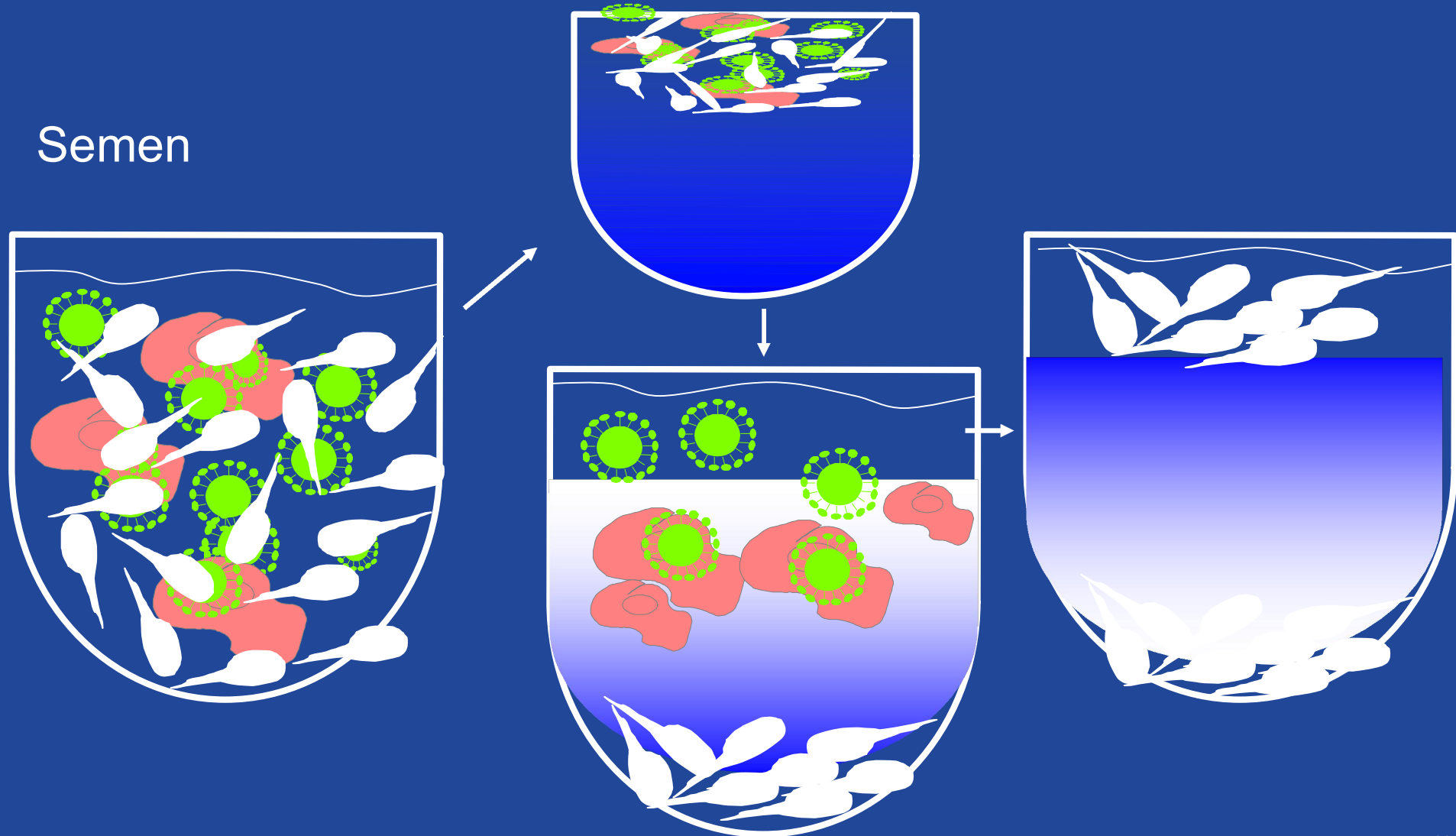
# HIV and Pregnancy:

## Avoiding Transmission in Serodiscordant Partners

- HIV-negative woman/HIV-positive man
  - Unprotected intercourse
    - ART to achieve virologic suppression and timed insemination
  - Semen processing
    - Centrifugation → harvesting sperm → PCR assay → intrauterine insemination
  - In vitro fertilization

# Semen Processing

Semen



# Semen Processing - IUI

Study	Cycles	Pts	Preg	Births	Infect
Semprini	1954	623	272	242	0
Marina	458	233	116	86	0
Tur	155	67	32	--	0
Gilling-Smith	66	27	12	3	0
Vernazza	46	16	5	3	0
Weigel	143	64	19	14	0
Bujan	62	28	14	2	0
Totals	2884	1058	470	350	0

# HIV and Pregnancy:

## Avoiding Transmission in Serodiscordant Partners

- HIV-negative woman/HIV-positive man
  - Unprotected intercourse
    - ART to achieve virologic suppression and timed insemination
  - Semen processing
    - Centrifugation + swim up + PCR + intrauterine insemination
  - In vitro fertilization
    - Hormonal stimulation for oocyte recruitment, egg retrieval under ultrasound guidance, fertilization via intracytoplasmic sperm injection

# Assisted Reproduction: IVF-ICSI

Study	Cycles	Pts	Preg	Births	Infect
Marina	58	40	27	11	0
Jonannet	97	68	33	22	0
Loutradis	2	2	2	2	0
Sauer	55	34	17	17	0
Weigel	32	30	11	4	0
Totals	244	164	90	56	0

## Reproductive Choice: Principles of Counseling

- Discuss appropriate contraceptive methods to reduce unintended pregnancy
- Consideration of ART if pregnancy is desired
  - Avoid agents with teratogenic potential
  - Maximize agents effective in reducing transmission
  - Achieve durable suppression of viral load prior to attempting pregnancy
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# Recommended Antiretroviral Agents for Perinatal Use: DHHS October 2006

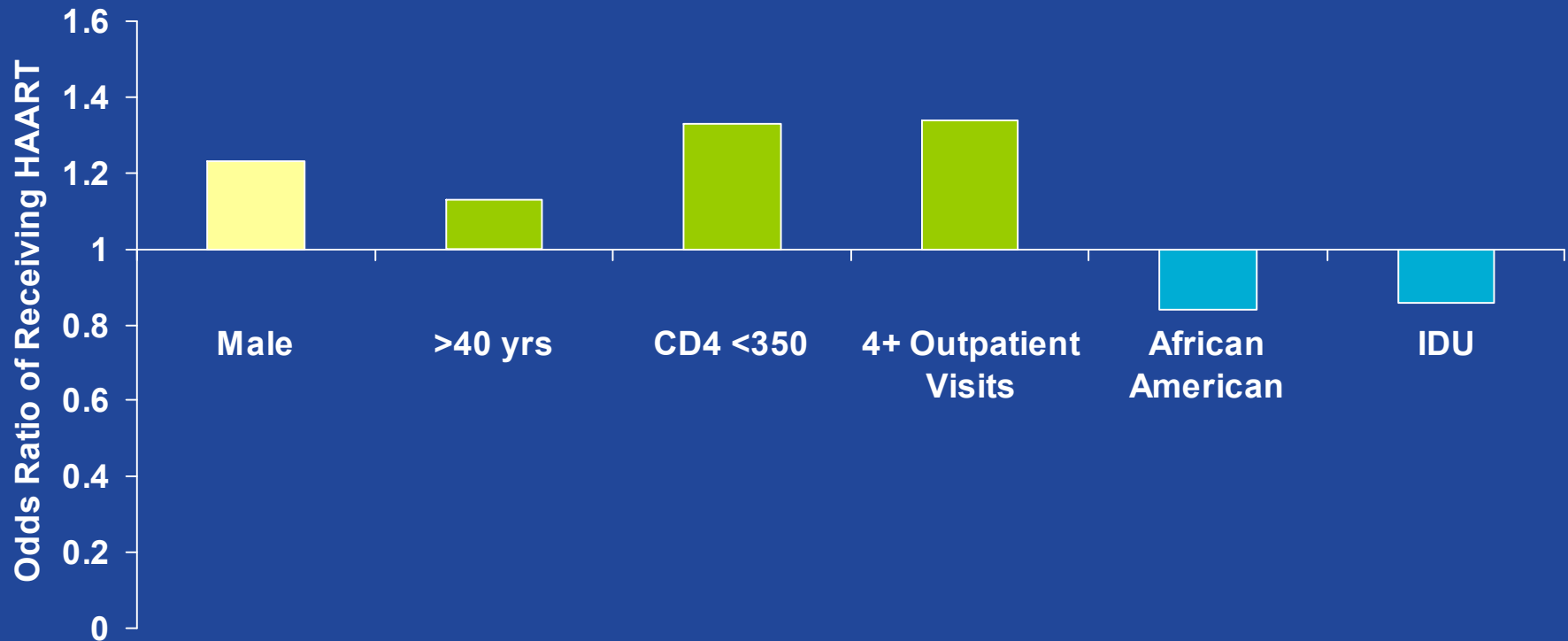
	PIs	NNRTIs	NRTIs	Other
<b>Recommended</b>	Lopinavir/ Nelfinavir	Nevirapine	Zidovudine* Lamivudine*	
<b>Alternative</b>	Indinavir Ritonavir Saquinavir HGC		Abacavir Didanosine Emtricitabine Stavudine	
<b>Insufficient data</b>	Amprenavir Atazanavir Fosamprenavir Darunavir Tipranavir		Tenofovir DF	Enfuvirtide
<b>Not recommended</b>		Efavirenz Delavirdine	Zalcitabine	

\*Zidovudine and lamivudine are included as a fixed-dose combination in Combivir®; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir®.

# Race and Gender Disparities in the Use of HAART

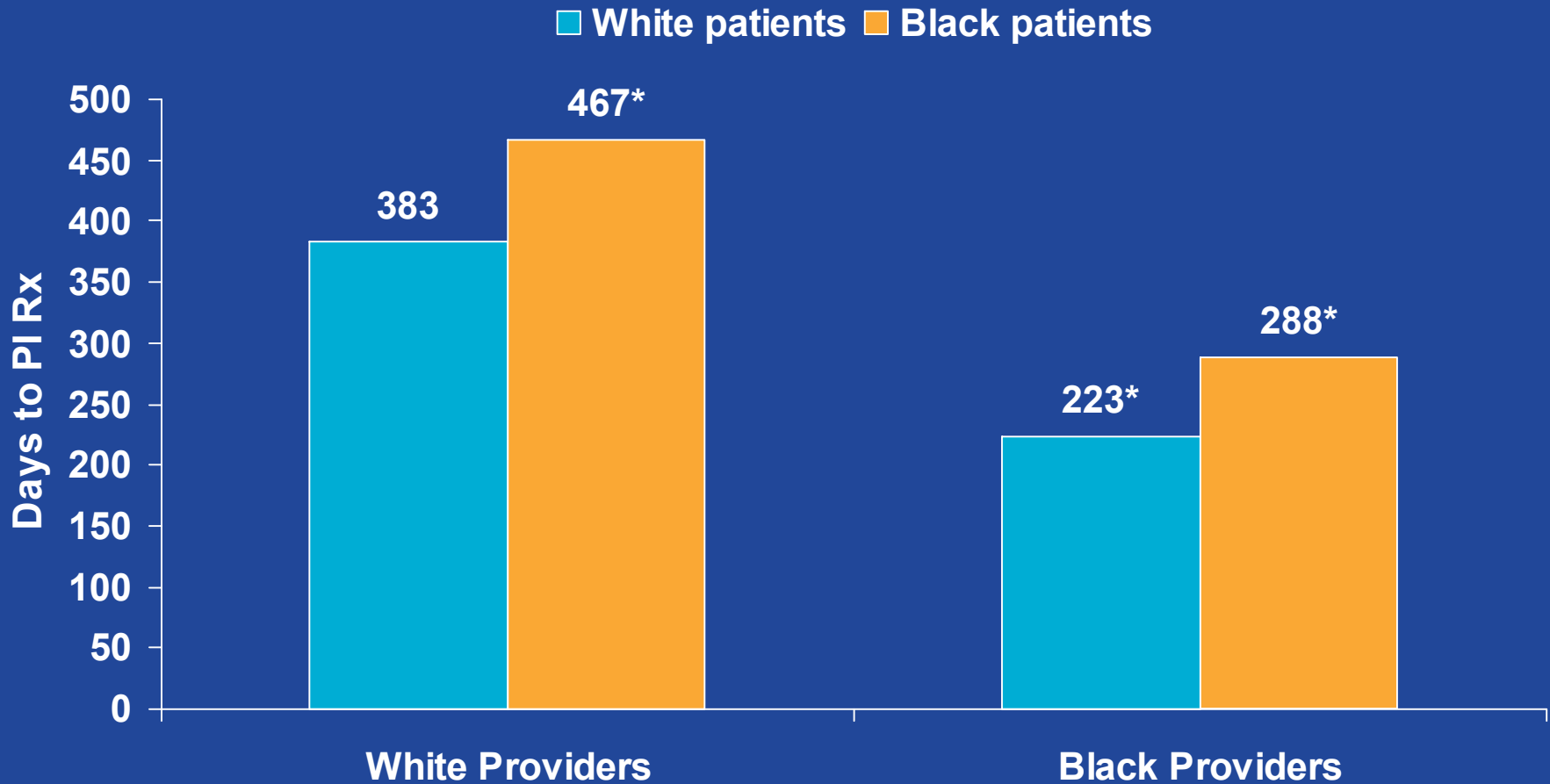
## HIV Research Network (HIVRN)

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

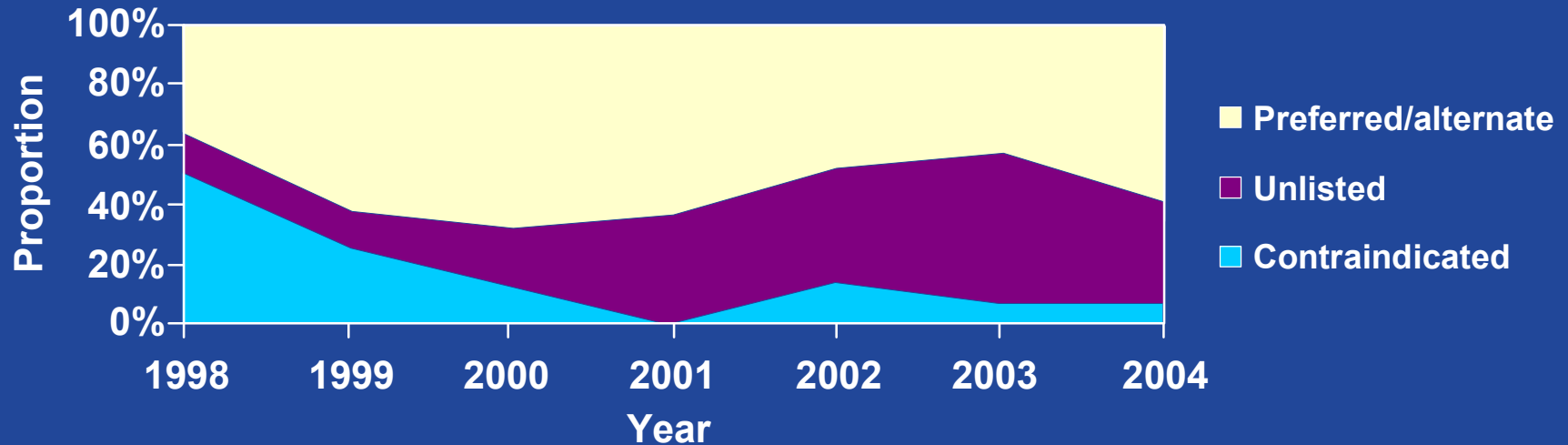


Data from 287 providers of care to 1,241 patients with HIV disease.

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

# 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

# Recommended Regimens for Treatment-Naïve Patients: DHHS 2006

	PI	or	NNRTI	+	2 NRTIs
Preferred	Atazanavir + ritonavir qd Fosamprenavir + ritonavir bid Lopinavir/ritonavir bid				Efavirenz  Tenofovir DF/emtricitabine Zidovudine/lamivudine
Alternative	Atazanavir (unboosted) Fosamprenavir (unboosted) Fosamprenavir + ritonavir qd Lopinavir/ritonavir qd				Nevirapine  Abacavir/lamivudine Didanosine + lamivudine

Choose a PI or NNRTI plus 2 NRTIs.

- 1.Efavirenz is not recommended for use in the first trimester of pregnancy or in sexually active women with child-bearing potential who are not using effective contraception.
- 2.The pivotal study that led to the recommendation of lopinavir/r as a preferred PI component was based on twice-daily dosing. A smaller study has shown similar efficacy with once-daily dosing but also showed a higher incidence of moderate to severe diarrhea with the once-daily regimen (16% vs. 5%).
- 3.FTC may be used in place of 3TC and vice versa.
- 4.Nevirapine should not be initiated in women with CD4+ T cell count >250 cells/mm<sup>3</sup> or in men with CD4+ T cell count >400 cells/mm<sup>3</sup> because of increased risk of symptomatic hepatic events in these patients.
- 5.Atazanavir must be boosted with ritonavir if used in combination with TDF.

# Advantages and Disadvantages of NNRTI-Based HAART<sup>1,2</sup>

## Advantages

- Less dyslipidemia than PI-based regimens
- Low pill burden, especially in co-formulated combinations

## Disadvantages

- Resistance
  - Low genetic barrier (single mutation confers high-level resistance)
  - Class-based cross-resistance
  - Increasing frequency of transmitted (primary) resistance
- Side effects
  - CNS side effects (efavirenz)
  - Hepatotoxicity (nevirapine)
  - Rash

# Treatment Considerations in Women of Child Bearing Potential: NNRTIs<sup>1-3</sup>

- Efavirenz
  - Pregnancy Category D:
    - Not recommended in first trimester of pregnancy or in women with high pregnancy potential due to teratogenicity
- Nevirapine
  - Not recommended for women with CD4 counts >250 cells/mm<sup>3</sup> due to risk of severe hepatotoxicity
  - HLA-DRB 0101 appears to be associated with hypersensitivity to nevirapine, especially at higher CD4 counts
  - Higher incidence of hepatotoxicity and severe rash (5.5-73 times) among women compared with men

1. DHHS Guidelines. Available at: <http://aidsinfo.nih.gov>. Accessed March 1, 2007. 2. Martin A. XV International AIDS Conference; July 11-16, 2004; Bangkok Thailand. Abstract LbOrB13. 3. Bersoff-Matcha SJ, et al. *Clin Infect Dis*. 2001;32:124-129.

# Advantages and Disadvantages of PI-Based HAART

## Advantages

- Demonstrated long-term efficacy
- Potential immune benefit beyond antiviral effect
- High barrier to resistance (boosted)
  - Preservation of both PI and NRTI options upon failure
- Lower rates of transmission of primary PI resistance
- No known teratogenicity; less likely to cross placenta
- No CD4 restrictions
- QD dosing available with LPV/r, ATV, and FPV/r for treatment-naïve patients (alternative regimens)

## Disadvantages

- Lipid and metabolic abnormalities (agent specific)
- Higher pill burden (agent specific)
- CYP3A4 inhibitors and substrates
- Gastrointestinal side effects
- Drug-drug interactions

# Gender Differences in Lopinavir/r Soft-Gel Pharmacokinetics

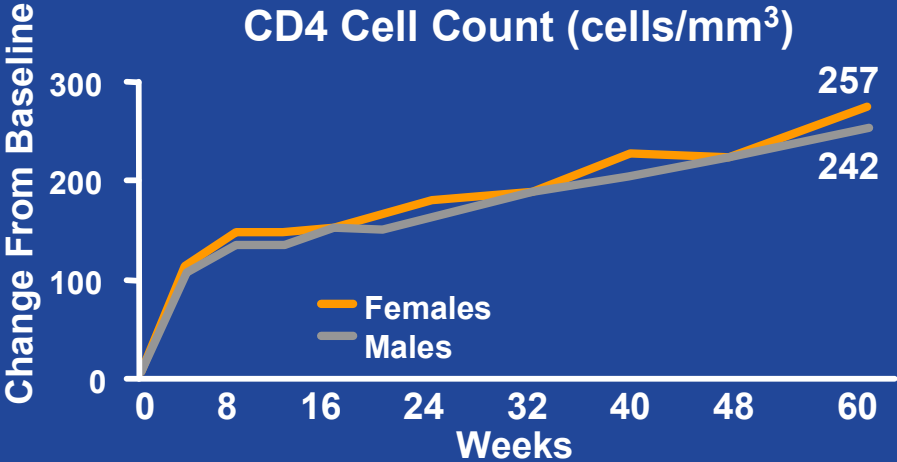
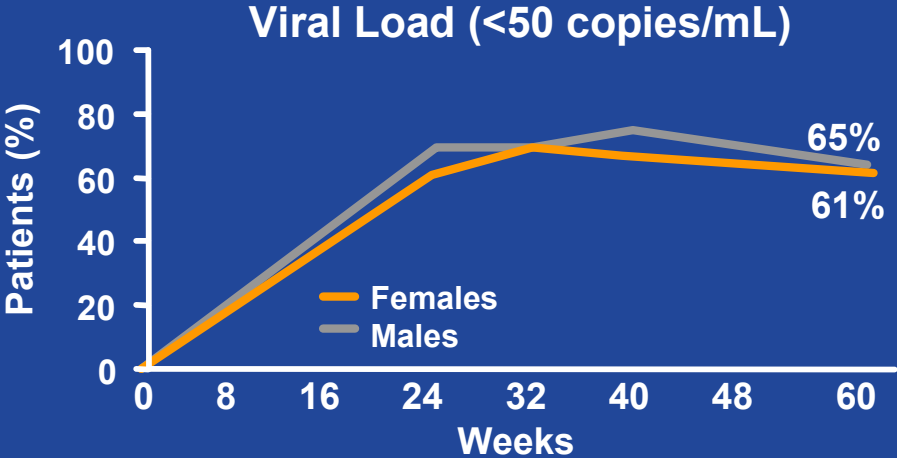
- Pharmacokinetics of lopinavir/r (400/100) soft gel determined in 40 men and 38 women
  - Well balanced as to race
    - 31% white, 31% black, 31% Hispanic, 4% Asian
- Lopinavir pharmacokinetics did not differ between men and women
- Women had 20% higher ritonavir AUC,  $C_{max}$ , and trend toward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



# Treatment of Women With HIV/AIDS: HAART Adverse Events

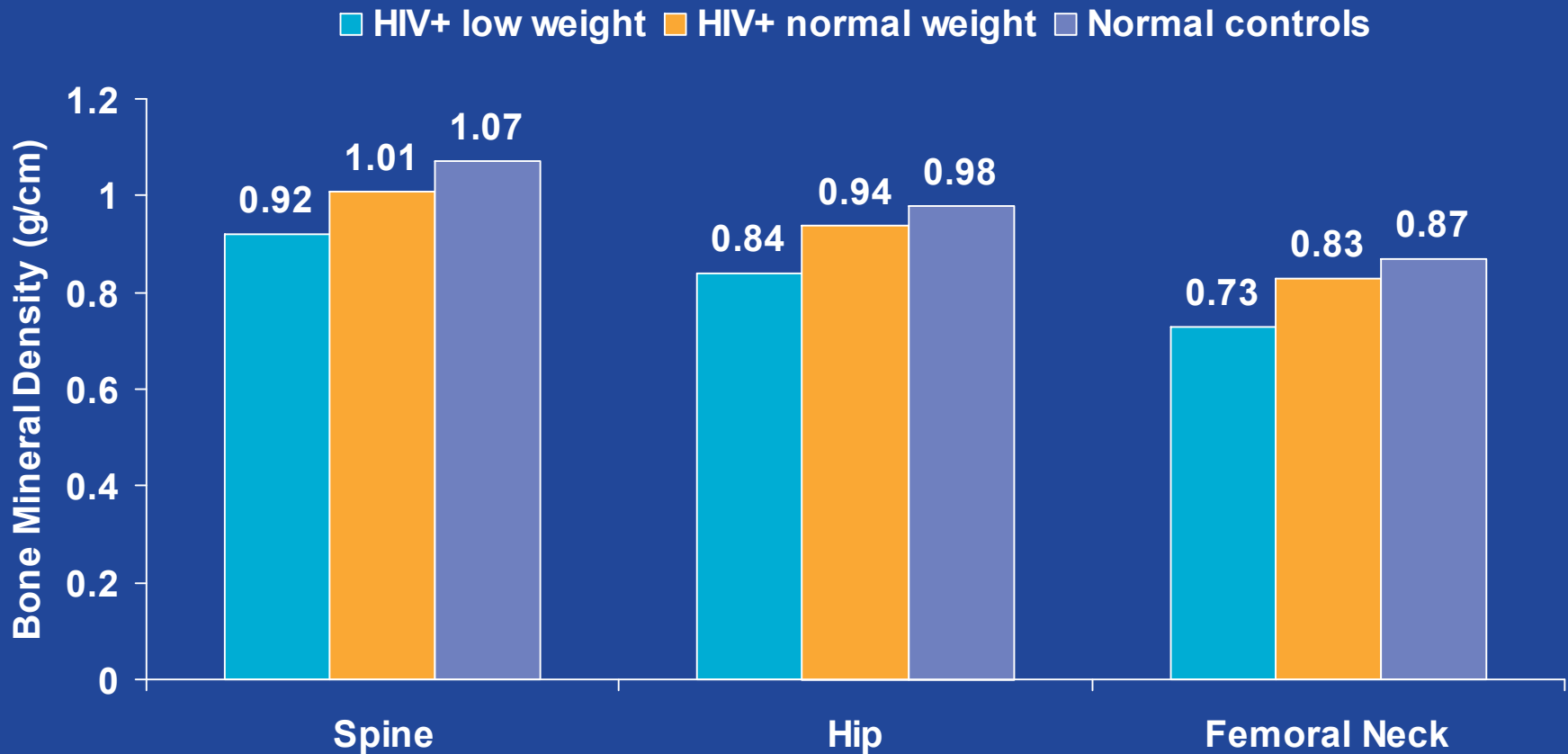
- Higher prevalence of adverse events in women
  - Ritonavir-associated nausea and vomiting: 66% vs 27%<sup>1</sup>
  - Women are also nearly 3 times as likely to have adverse events when treated with ddI<sup>1</sup>
- Some common side effects more prevalent in men (nelfinavir-associated diarrhea 10% vs 23%)
- Side effects have special importance for women
  - When women discontinue HAART medications, it is most frequently because of side effects<sup>2</sup>
    - 2 times as likely as men to discontinue because of side effects<sup>2</sup>

<sup>1</sup> Squires K, et al. 13th IAC; Durban, South Africa. Abstract TuOr54.

<sup>2</sup> Hirschhorn LR, et al. 12th IAC; 1998; Geneva, Switzerland. Abstract 12443.

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

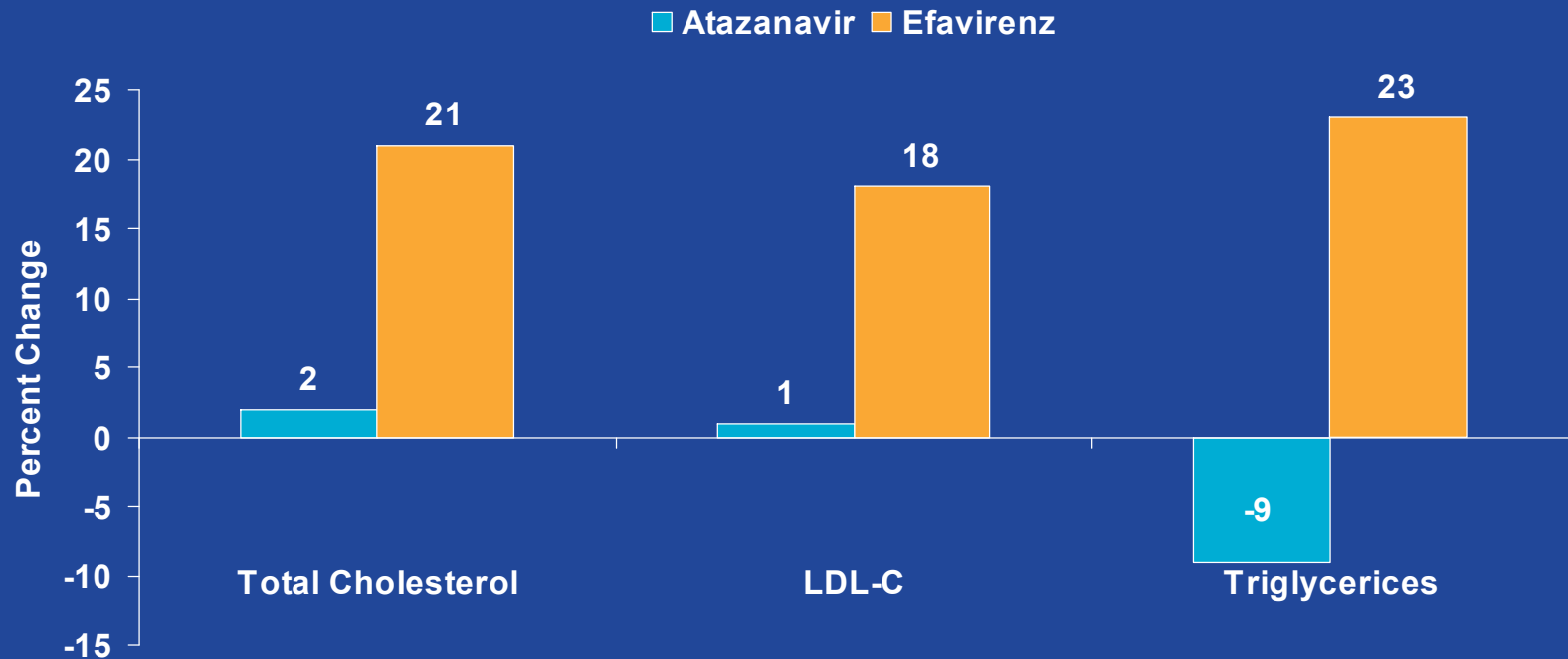
Risk factors for osteoporosis/osteopenia included low free testosterone, low weight, and oligomenorrhea



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

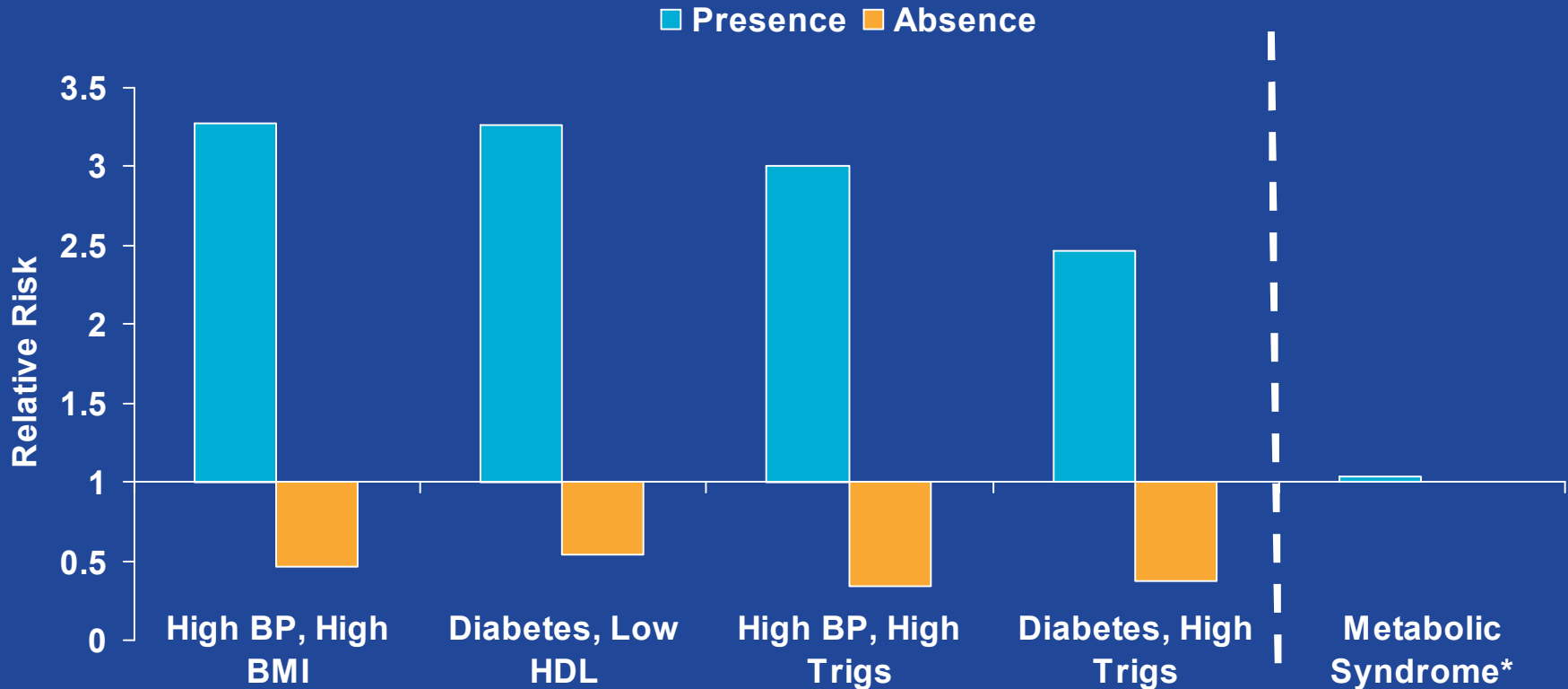
# Comparative Effects of HAART on Lipid Levels

## Changes in Lipids at 48 Weeks



N=810 treatment-naïve patients treated with either atazanavir or efavirenz in a 3-drug regimen. Efficacy equivalent between 2 regimens.

# Relative Risk of CVD in the D:A:D



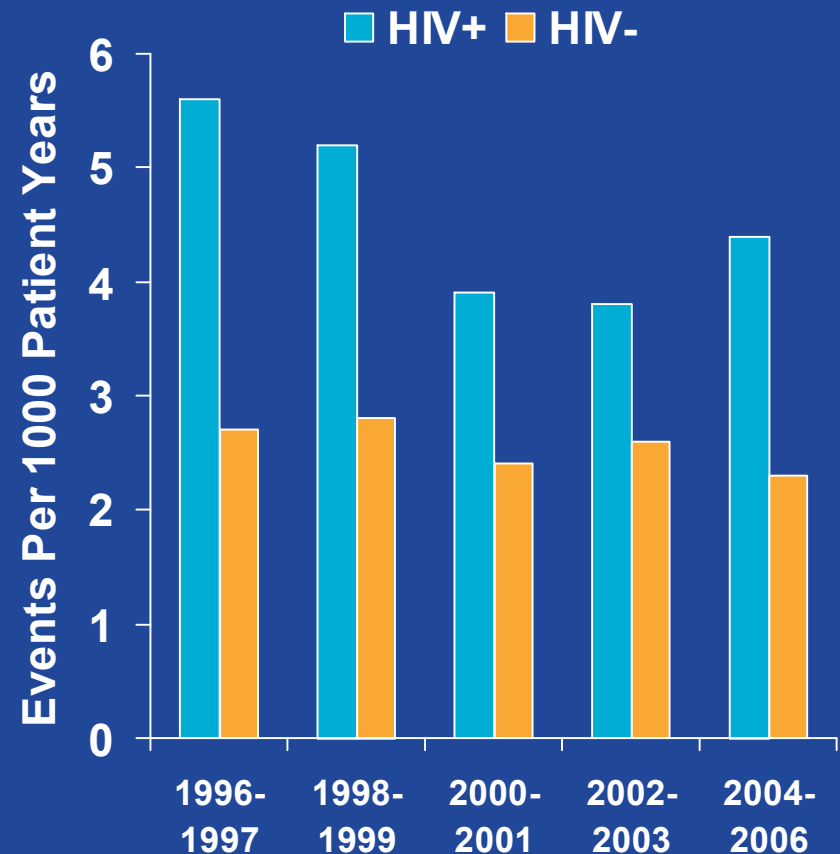
Pairwise comparison: relative risk of CVD based on presence or absence of 2 or more symptoms of metabolic syndrome.

\*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 HIV: A Long-Term Commitment Summary

- 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