



Anemia and HIV/AIDS

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National Anemia Action Council

www.anemia.org

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NAAC Mission



The National Anemia Action Council, Inc. (NAAC) is dedicated to raising the awareness of health care professionals and the public regarding the prevalence, symptoms, consequences, and treatment options of anemia.

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NAAC's Online Resources for Medical Professionals



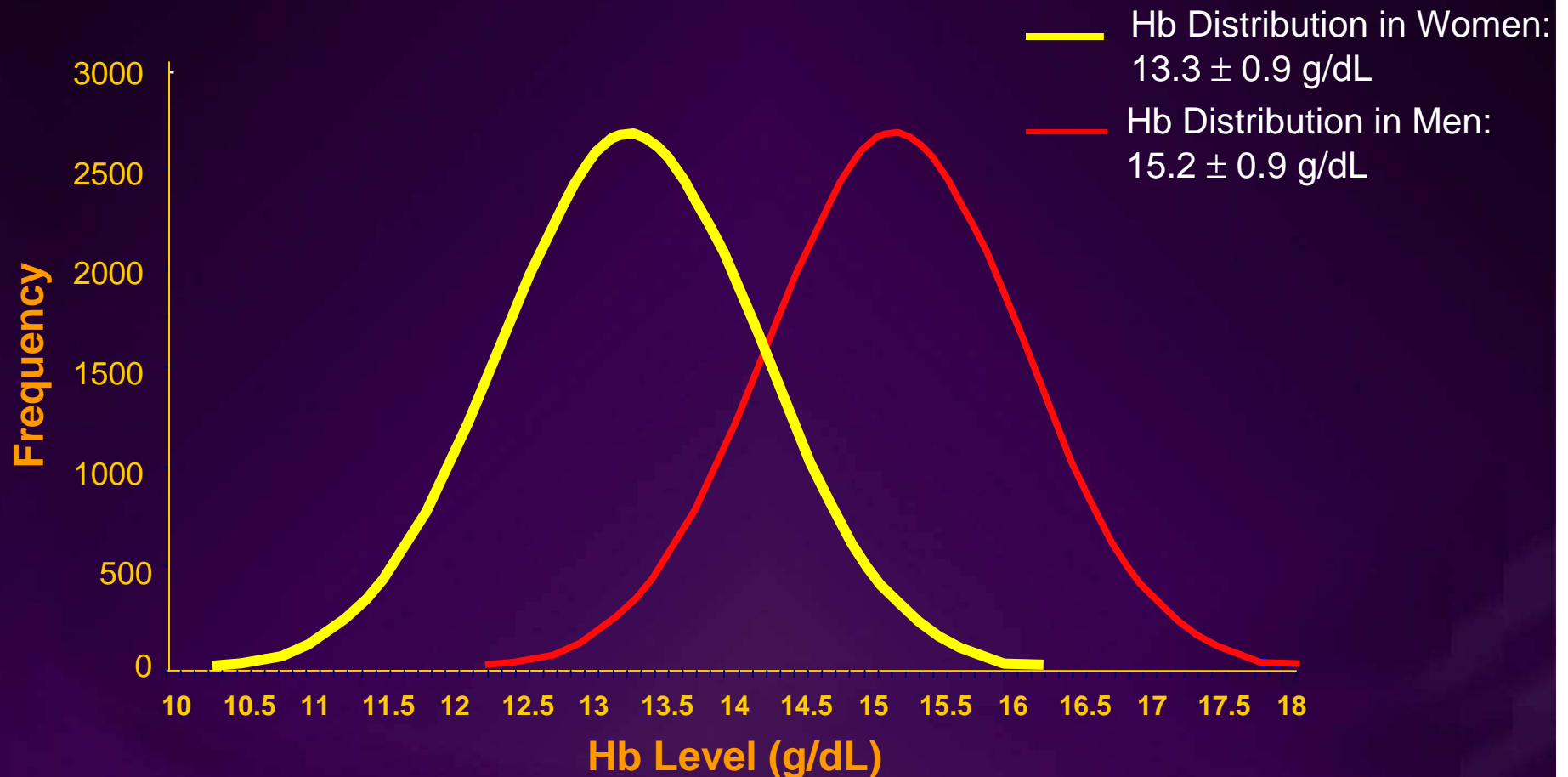
- Research Reviews - Recent clinical trials reviewed
- Ask the Expert - Your anemia questions answered
- Monograph - In-office handbook on anemia
- Feature Articles - Anemia related news and research
- Anemia Alert - Free monthly e-newsletter
- Slide Sets - Educational presentations about anemia
- We have materials for your patients too!

Key Points



- Anemia during HIV infection can be caused by disease-related factors and treatment-related factors.
- Anemia prevalence is higher in patients with severe HIV disease
- Anemia is associated with increased mortality and morbidity
- Anemia management may improve survival and quality of life

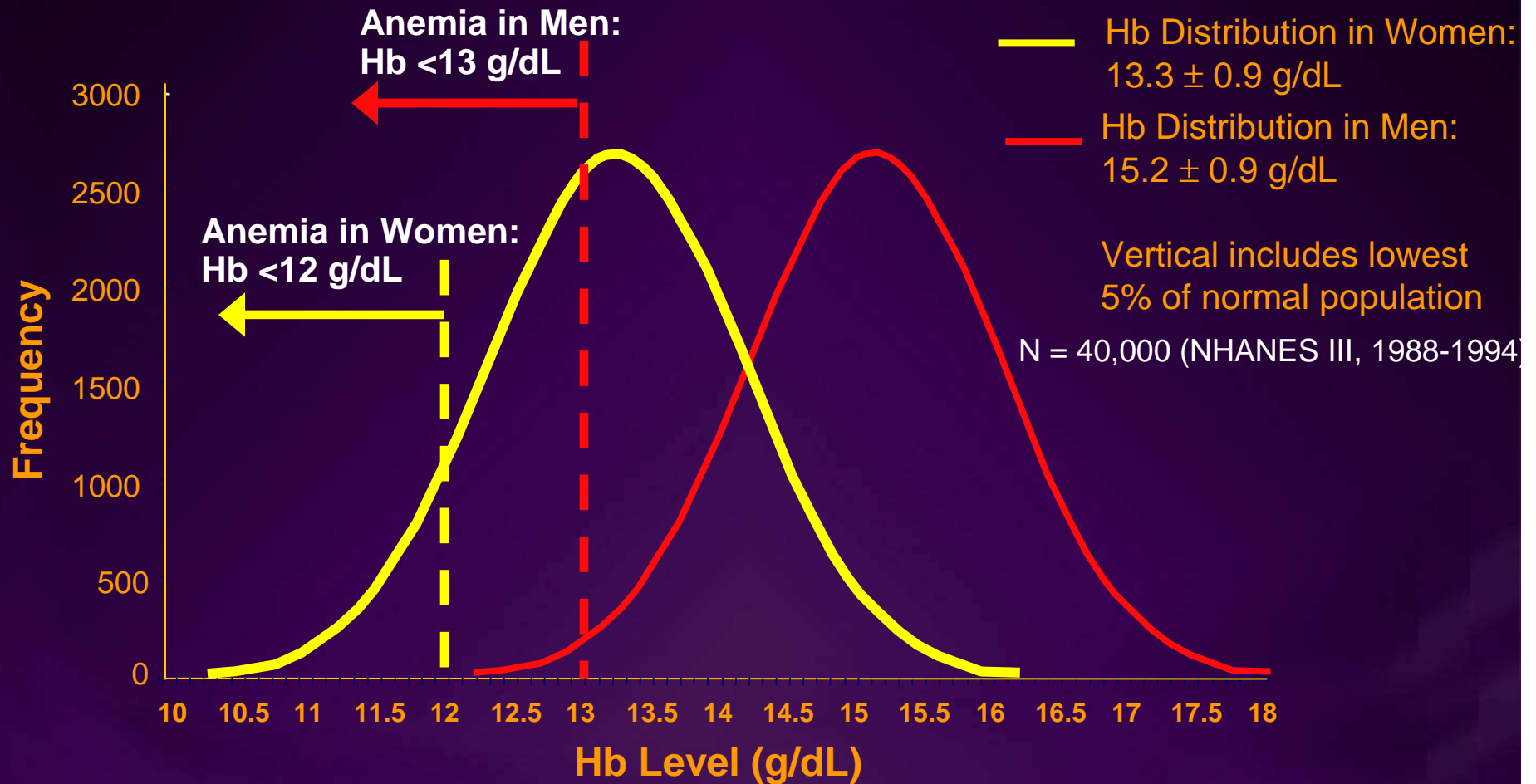
Hemoglobin Distribution in the Normal Population



N = 40,000 (NHANES III, 1988-1994)

Dallman PR, et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

WHO Definition of Anemia vs. Hb Distribution in General Population



World Health Organization. Geneva, Switzerland; 2001.

Dallman PR, et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

Laboratory Reference Ranges



Parameter	Male	Female
Hb (g/dL)	14.0 – 17.4	12.3 – 15.3
Hct (%)	41.5 – 50.4	36.0 – 45.0
RBC count ($10^6/\mu\text{L}$)	4.5 – 5.9	4.5 – 5.1
Reticulocyte count (% of RBC count)		0.5 – 2.5
Mean corpuscular volume (fL)		80 – 96
Mean corpuscular Hb (MCH) (pg)		27.5 – 33.2
MCH concentration (g/dL)		33.4 – 35.5

Hb = hemoglobin; Hct = hematocrit; RBC = red blood cell

Perkins S. In: Lee G, et al, eds. *Wintrobe's Clinical Hematology*. Vol 2. 10th ed. Baltimore, Md: Lippincott, Williams & Wilkins; 1998:2738.

Anemia Signs and Symptoms



Central nervous system

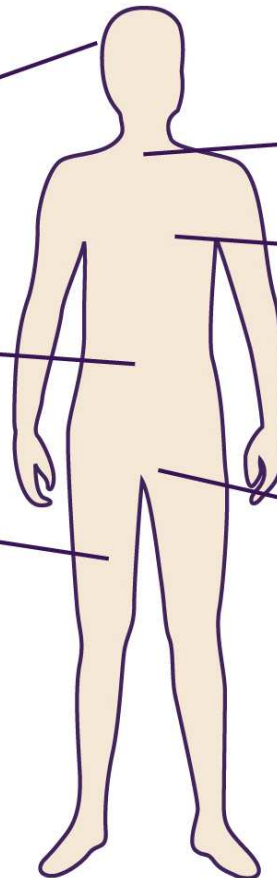
- Fatigue
- Depression
- Impaired cognitive function

Gastrointestinal system

- Anorexia
- Nausea

Vascular system

- Low skin temperature
- Pallor of skin, mucous membranes, and conjunctivae



Immune system

- Impaired T-cell and macrophage function

Cardiorespiratory system

- Exertional dyspnea
- Tachycardia, palpitations
- Cardiac enlargement, hypertrophy
- Increased pulse pressure, systolic ejection murmur
- Risk of cardiac failure

Genital Tract

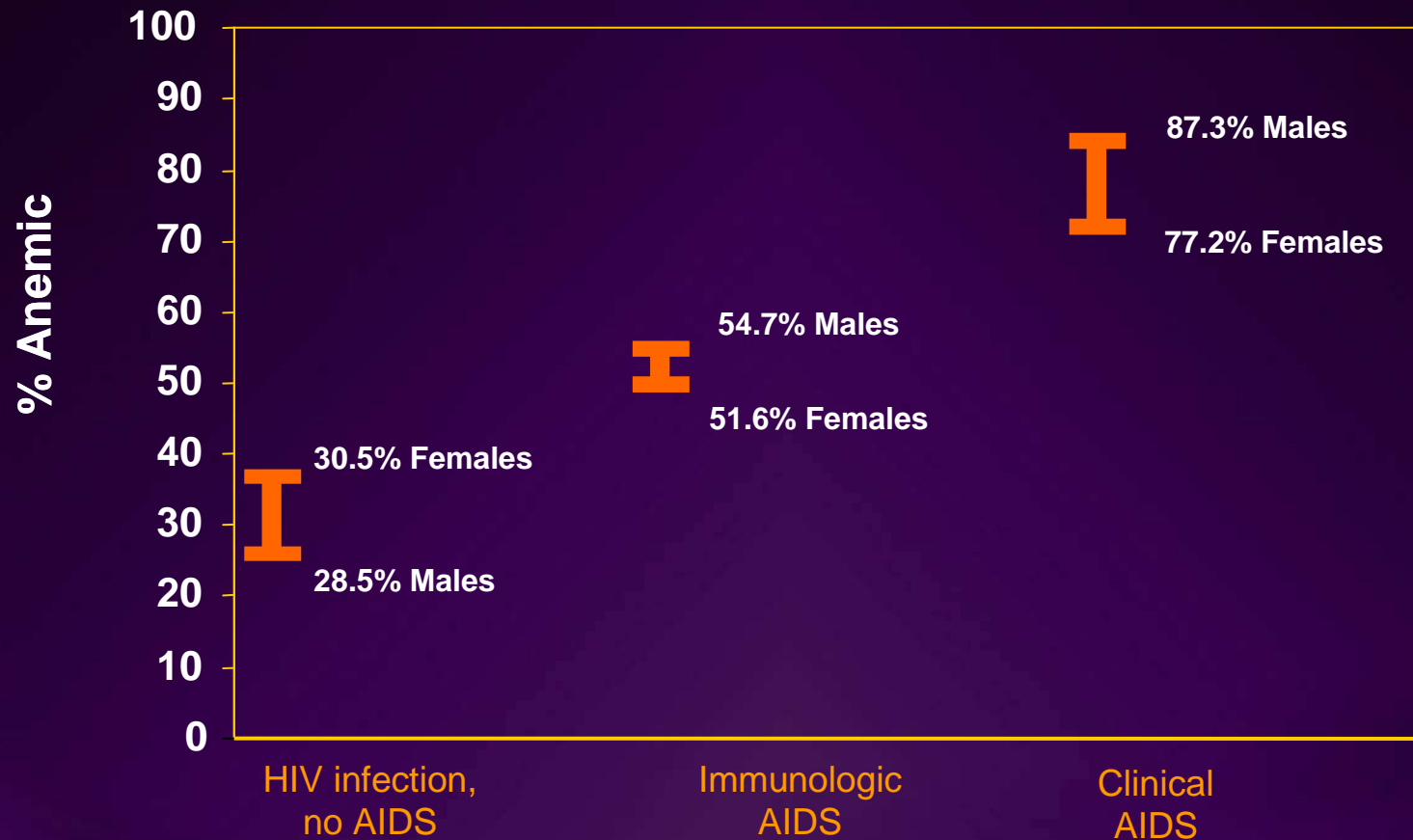
- Menstrual problems
- Loss of libido

Adapted from Ludwig H, et al. *Semin Oncol.* 2001;28(suppl 8):7-14.



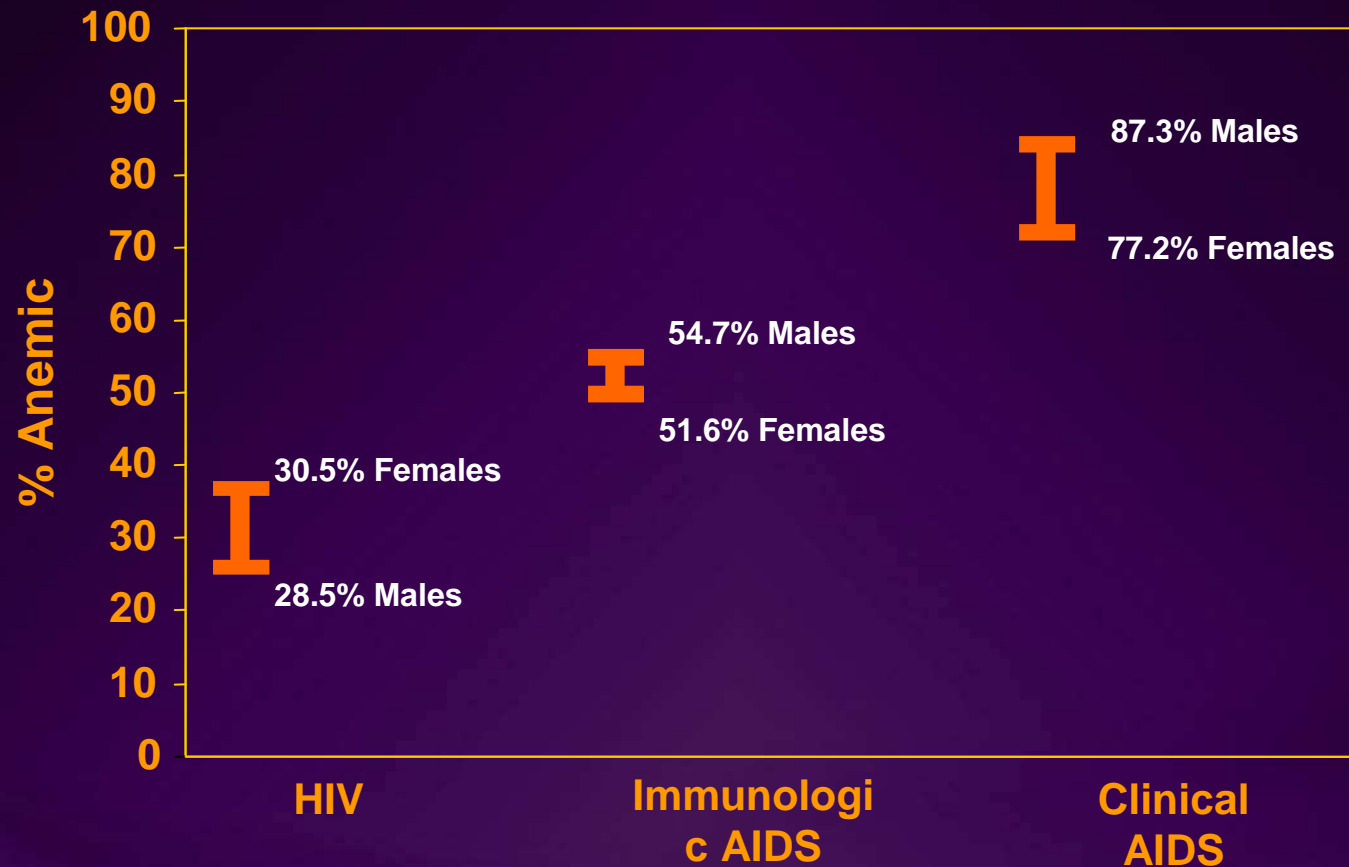
Anemia Prevalence

Prevalence of Anemia in HIV Patients: Stages of Disease



Sullivan PS, et al. *Blood*. 1998;91:301-308.

Prevalence of Anemia in HIV Patients: Women with HIV



Sullivan PS, et al. *Blood*. 1998;91:301-308.

Causes of Anemia in HIV Patients: Disease Related



- Cytokine production suppresses hematopoiesis
- Erythropoietin concentrations are decreased
- Opportunistic infections and malignancies affecting bone marrow
- Vitamin and mineral (Fe) deficiencies
- Blood loss; gastrointestinal most common
- Hemolysis (uncommon)

Causes of Anemia: Treatment Related



- Studies have shown HIV therapies have myelotoxic side effects
 - Zidovudine
 - Adjunctive therapies: Gancyclovir, trimethoprim-sulfamethoxazole, dapsone in patients with G6PD deficiency
 - Lamivudine (3TC) may cause anemia, but evidence is much weaker

Anemia Prevalence Rates



- Prevalence rates vary based on multiple variables
 - Subpopulations studied
 - Disease stage
 - Patient age
 - Definition of anemia (e.g., hemoglobin threshold)

Belperio PS, Rhew DC. *Am J Med* 2004 Apr 5;116 Suppl 7A:27S-43S

Anemia Prevalence: Subpopulations



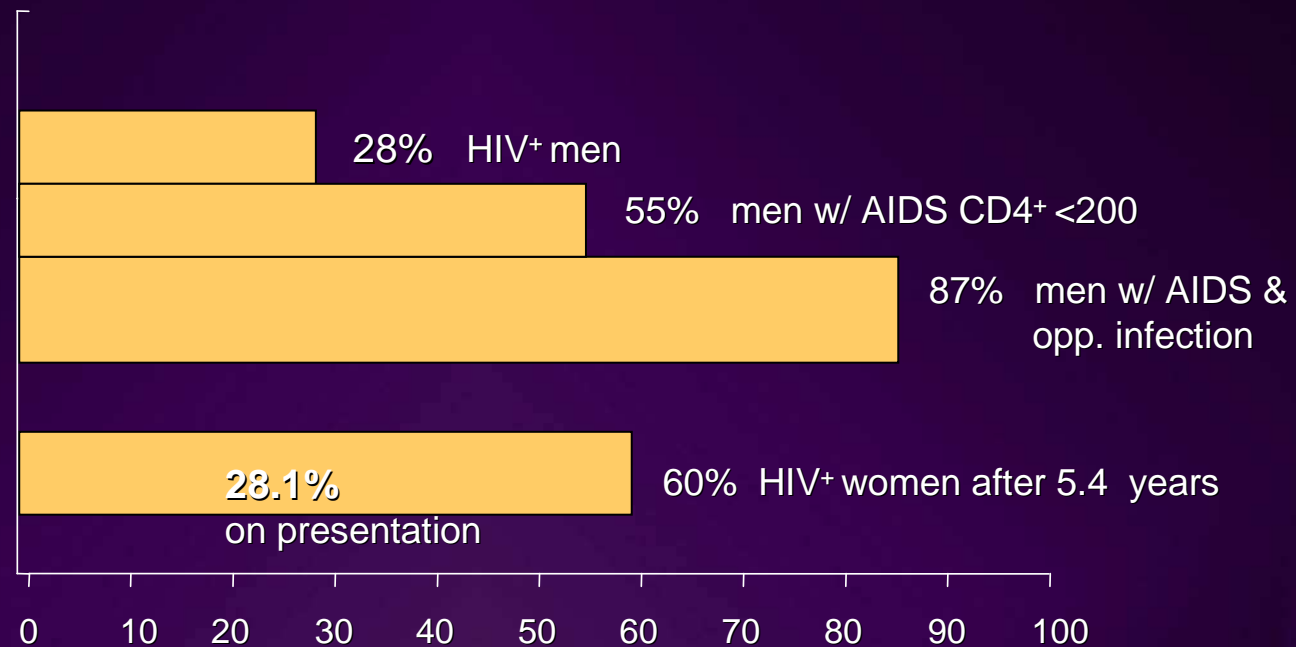
- Certain factors in HIV positive patients are associated with an increased risk of anemia
 - **African-American race**
 - **Women**
 - **Older age**
 - **Lower body mass index**
 - **History of fever or pneumonia**
 - **Oral candidiasis**
 - **CD4⁺ count <200 cells/ μ L**
 - **Use of zidovudine**

Belperio PS, Rhew DC. *Am J Med* 2004 Apr 5;116 Suppl 7A:27S-43S

Anemia Prevalence Rates in HIV/AIDS Patients



Sullivan PS, et al.
Blood 1998;91:301-308



Percentage of HIV/AIDS Patients With Anemia



Disease Progression

Disease Progression



- Three studies provide support for an association between disease progression to AIDS and anemia
 - Moore et al.
 - Graham et al.
 - Morfeldt-Manson

Disease Progression: Results of Moore et al.



- In 1987, 886 patients receiving zidovudine with AIDS or ARC
- Anemia development significant prognostic association with early death
- Increased risk of disease progression to AIDS with hematocrit concentration <35 ($P = 0.05$).

Moore RD, et al. *Arch Intern Med* 1991;151:981-6.

Disease Progression: Results of Graham et al.



- Group of 747 AIDS-free HIV-infected patients observed
- Hemoglobin level changes over 6 months not significantly predictive of AIDS
- Proportional hazards analysis demonstrated baseline hemoglobin level associated with disease progression to AIDS ($P = 0.0001$)

Graham NM, et al. *J Acquir Immune Defic Syndr* 1993;6:1258-66

Disease Progression: Results of Morfeldt-Manson et al.



- 89 HIV positive patients treated with antiretroviral therapy observed
- Cox bivariate regression analysis revealed hemoglobin level to < 10 g/dL associated with increased risk of disease progression to AIDS ($P = 0.01$)

Morfeldt-Manson L, et al. *Scand J Infect Dis* 1991;23:443-9.



Anemia & Mortality

Anemia and Mortality



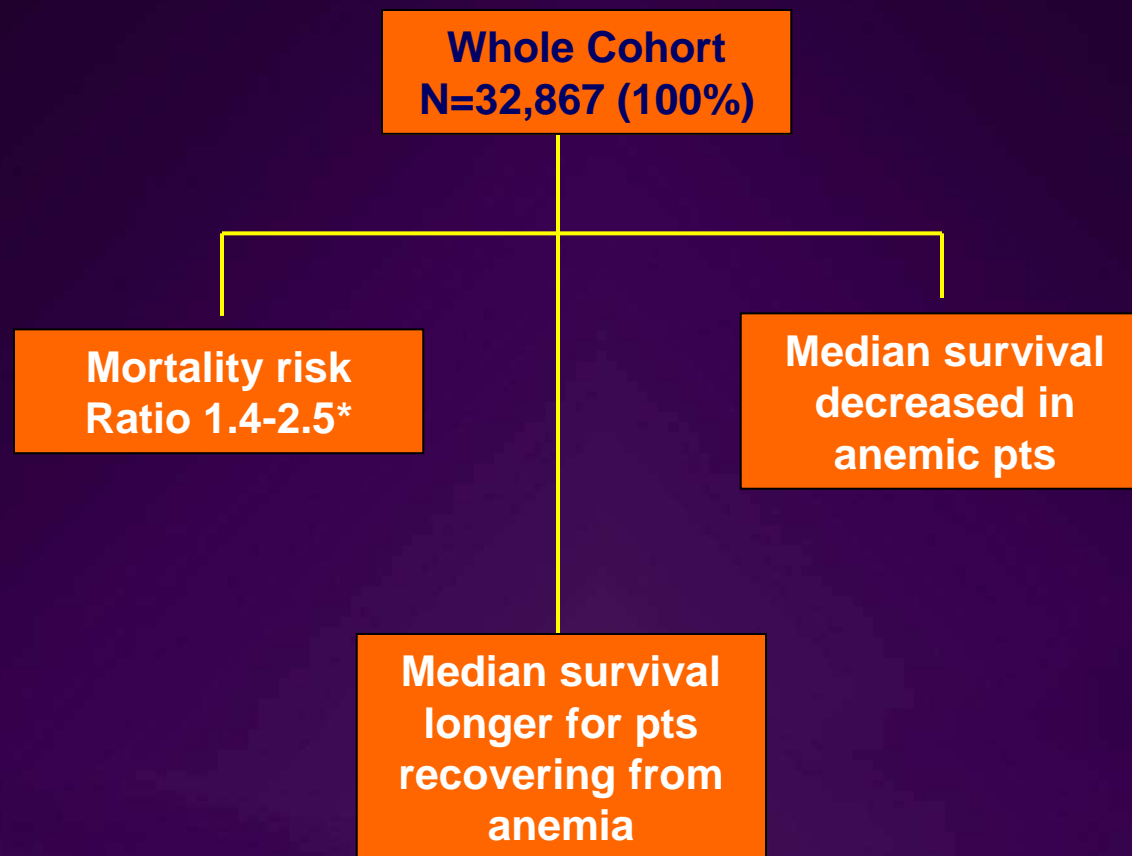
Anemia may be independently associated with increased mortality risk in patients with HIV infection or AIDS

Anemia in HIV Disease and Mortality Rates



- Shorter survival times have been associated with anemia in HIV disease
 - Spectrum of HIV Disease Surveillance Project
 - Multicenter AIDS Cohort Study
 - EuroSIDA
 - Moore et al.
 - Creagh-Kirk et al.

Mortality: Results of Sullivan et al.



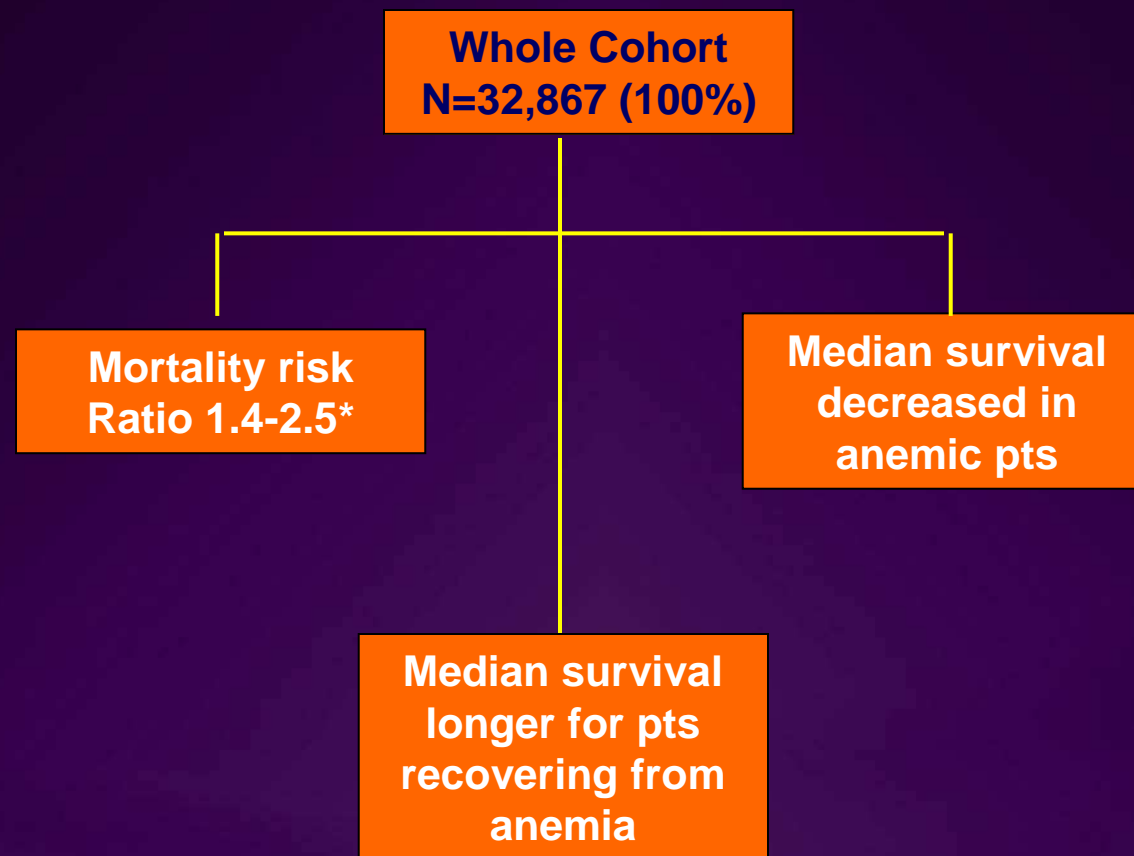
Mortality: Results Spectrum of HIV Disease Surveillance Project



- Medical record analysis of 32,867 HIV-infected patients (13,654 excluded)
- Median survival decreased for patients with anemia as compared to patients without anemia
- Mortality risk ratio ranged from 1.4 (patients with CD4⁺ counts 100-149 x 10⁶/L) to 2.5 (patients with CD4⁺ counts \geq 200 x 10⁶/L)
- Median survival longer for patients recovering from anemia than those that did not recover

Sullivan PS et al. *Blood* 1998;91:301-8.

Mortality: Results of Saah AJ, et al.



Mortality: Results of Multicenter AIDS Cohort Study



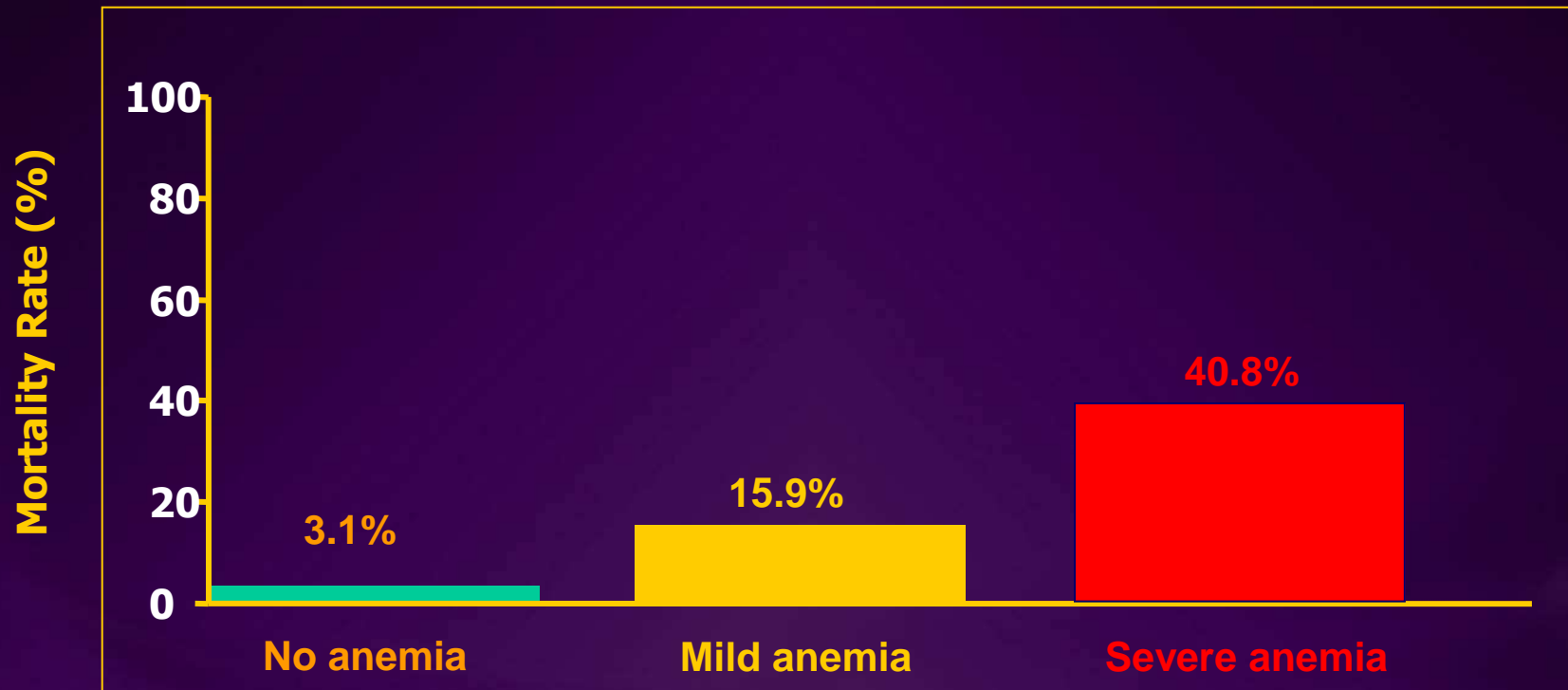
- Hemoglobin data gathered on 603 male patients (cohort HIV positive homosexual men)
- Univariate analysis revealed shorter survival period after diagnosis associated with hemoglobin level <13.0 g/dL
- Hemoglobin level predictor of mortality in multivariate proportional hazards model

Saah AJ et al. *J Acquir Immune Defic Syndr* 1994;7:287-95.

Mortality: Results of EuroSIDA



Patients in 3 categories:
No anemia; mild anemia; severe anemia



Mocroft A, et al. *AIDS* 1999;13:943-50

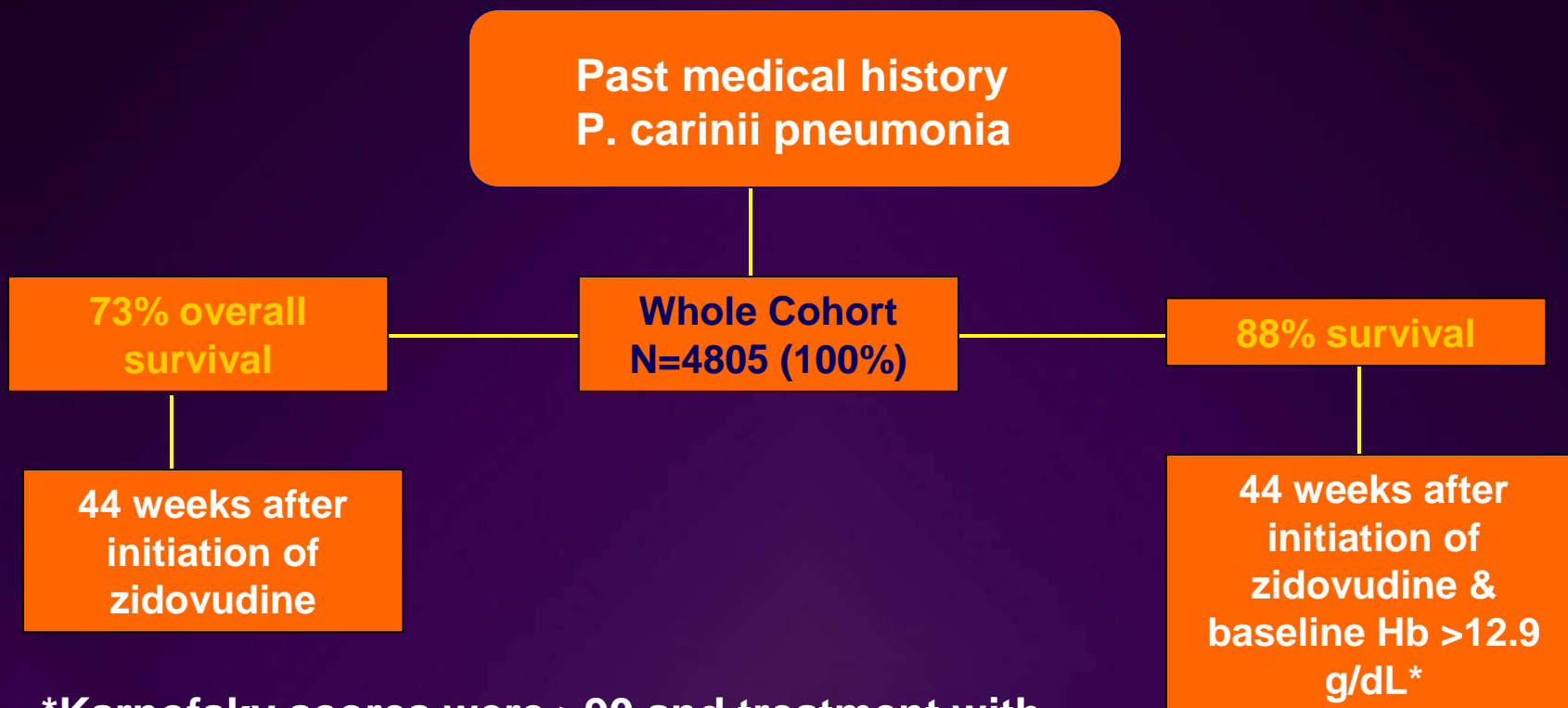
Mortality: Results EuroSIDA Study



- Prospective European cohort study 6,725 patients analyzed relation between mortality and Hb levels in 3 groups:
 - 1) no anemia; 2) mild anemia; 3) severe anemia
- Kaplan-Meier analyses demonstrated mortality rates differed significantly between all 3 groups
- Death occurred in **3.1%** of patients without anemia, **15.9%** of patients with mild anemia, and **40.8%** with severe anemia
- Hazard ratio for death 1.39 (associated with 1g/dL Hb decrease)

Mocroft A, et al. *AIDS* 1999;13:943-50

Mortality: Results of Creagh-Kirk, et al



*Karnofsky scores were ≥ 90 and treatment with zidovudine was initiated within 90 days of *P. carinii* pneumonia

Creagh-Kirk T, et al. *JAMA* 1988;260:3009-15

Mortality: Results of Creagh-Kirk et al.



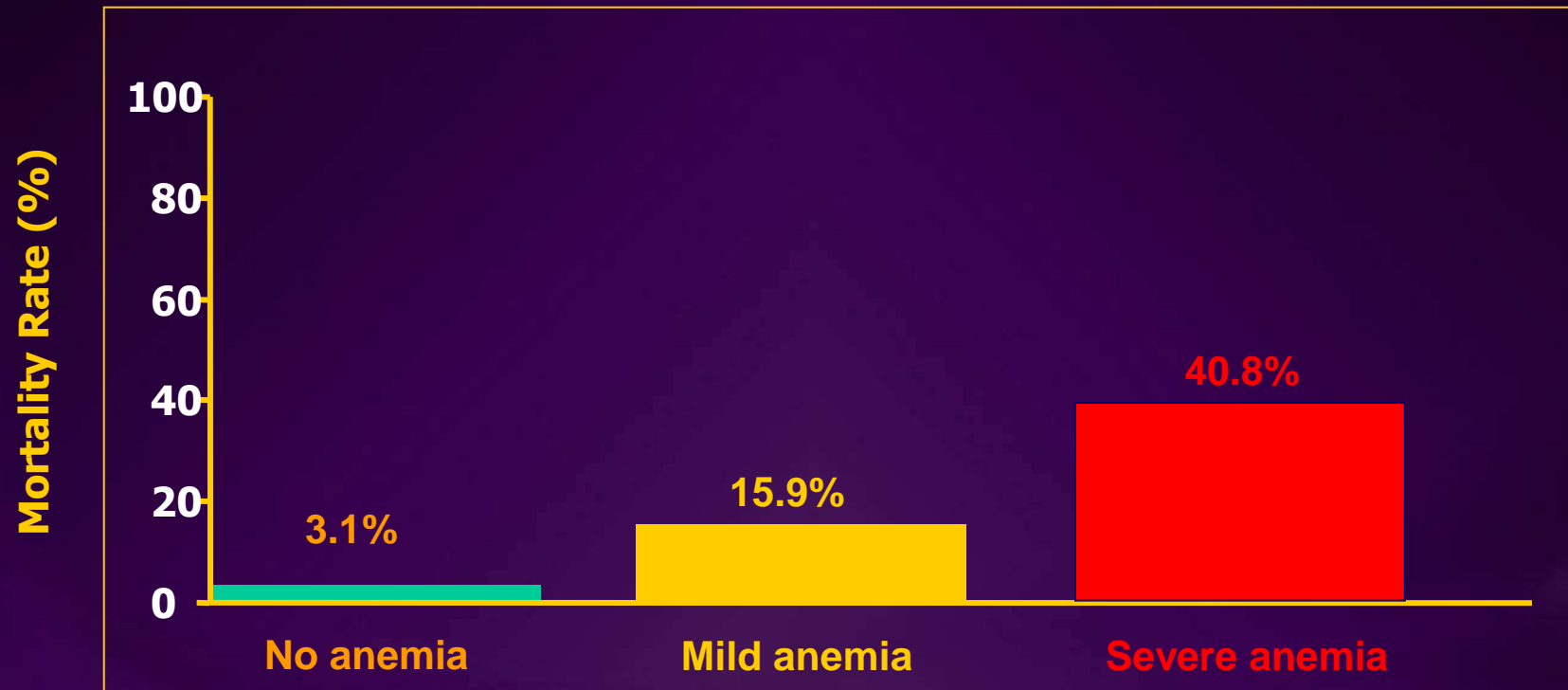
- 4805 AIDS patients with prior *Pneumocystis carinii* pneumonia [receiving zidovudine] evaluated
- **Overall survival 73% (+2.1%)** at 44 weeks after initiation of zidovudine
- 88% survival at 44 weeks in patients with baseline Hb ≥ 12.0 g/dL, Karnofsky scores ≥ 90 , treatment with zidovudine within 90 days of *P. carinii* pneumonia diagnosis

Creagh-Kirk T, et al. *JAMA* 1988;260:3009-15

Mortality: Results Moore, et al.



Patients in 3 categories:
No anemia; mild anemia; severe anemia



Moore RD, et al. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19:29-33

Mortality: Results of Moore et al.



- Cohort of 2,343 HIV-infected patients with anemia – anemia stratified in grades 1-4
- Median time to death 113 days with grade 4* anemia
- Median time to death 265 days with grade 1* anemia
- Cox proportional hazards model showed each successive grade of anemia increased mortality risk

Moore RD, et al. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19:29-33



Transfusion

Allogeneic Blood Transfusion Current Guidance



Red-cell containing components should not be used to treat anemia that can be corrected with specific medications such as iron, vitamin B₁₂, folic acid, or recombinant erythropoietin, except when the patient's symptoms require immediate enhancement of oxygen-carrying capacity.

–American Association of Blood Banks, America's Blood Centers, and the American Red Cross

Some Risks of Allogeneic Blood Transfusion



Blood Transfusion Risk	No. Deaths per Million Units	Estimated Frequency per Unit
VIRUS		
Hepatitis B		1/60,000-1/200,000
Hepatitis C	0.5-17	1/800,000-1/1.6 x 10 ⁶
HIV	0.5-5	1/1.4-2.4 x 10 ⁶
BACTERIA		
Red cells		1/500,000
Platelets		1/2000
ACUTE HEMOLYTIC REACTIONS	0.67	1/250,000-1,000,000
DELAYED HEMOLYTIC REACTIONS		1/1000
TRANSFUSION-RELATED ACUTE LUNG INJURY		1/8000
ABO CLERICAL ERROR ²		1/16,000

Modified with permission from Goodnough LT, et al. *N Engl J Med.* 1999;340:438-447.
Krombach J, et al. *Anesth Anal.* 2002;94:154-156.

Immune Effects of Blood



- Immunologic effects of autologous/allogeneic blood transfusion:
 - Decreased T-cell proliferation
 - Decreased CD3⁺, CD4⁺, CD8⁺ T cells
 - Increased soluble cytokine receptor
 - sTNF-R, sIL-2R
 - Increased serum neopterin
 - Increased cell-mediated lympholysis
 - Increased TNF- α
 - Increased suppressor T-cell activity
 - Reduced natural killer cell activity

1. McAlister FA, et al. *Br J Surg*. 1998;85:171-178.
 2. Innerhofer P, et al. *Transfusion*. 1999;39:1089-1096.
- Slide courtesy of Aryeh Shander, MD.

Transfusion: Problems With Oxygen Delivery



- Storage of RBCs can lead to:^{1,2}
 - Impaired ability of RBCs to distribute oxygen
 - Microcirculatory occlusion
- Greater age of blood has been linked to increased risk of death,² pneumonia,² and splanchnic ischemia³
- In patients with sepsis, transfusion does not appear to increase oxygen uptake³⁻⁵

1. Corwin HL, et al. *Crit Care Med.* 1999;27:2346-2350.

2. Carson J. *JAMA.* 2002;288:2884-2886.

3. Marik P, et al. *JAMA.* 1993;269:3024-3029.

4. Lorente JA, et al. *Crit Care Med.* 1993;21:1312-1317.

5. Gramm J, et al. *Shock.* 1996;5:190-193.

Potential Risks Associated With Transfusion



- Transfused patients have
 - Longer ICU stays
 - Higher mortality
 - Risk of death increased by factor of 1.4 in transfused patients
 - Diminished organ function
 - Increased risk of infection

1. Vincent JL, et al. *JAMA*. 2002;288:1499-1507.

2. Taylor RW, et al. *Crit Care Med*. 2002;30:2249-2254.

Transfusion Requirements: Anemia and HIV Disease



The impact of anemia on transfusion requirements in HIV patients has been evaluated

- Abrams et al.
- Henry et al.
- Buchanan et al.

Transfusion Requirements: Results of Abrams et al.



- Open-label trial in 221 HIV patients with anemia on zidovudine
- Percentage of patients requiring transfusion dropped from 20% to 5% by the fourth month with epoietin- α
- Mean number of transfused units went from 0.5 units to 0.14 units

Abrams DI, et al. *JAMA* 1988;260:3009-15. *Int J STD AIDS* 2000;11:659-65.

Transfusion Requirements: Results of Henry et al.



- Meta-analysis of 4 randomized, double-blind, placebo-controlled multicenter US trials; 255 patients with AIDS on zidovudine met inclusion criteria
- Lower mean number of units transfused with epoietin- α therapy vs. placebo
- 43% of baseline transfusion-dependent population became transfusion-independent with epoietin- α therapy (vs. 18% on placebo)

Henry DH, et al. *Ann Intern Med* 1992;117:739-48

Transfusion Requirements: Results of Balfour et al.



- 523 patients with AIDS not on zidovudine (open-label epoietin- α study)
- Mean Hb increased from baseline of 9.1 g/dL to 10.6 g/dL by week 6
- 43% at baseline required ≥ 1 transfusion; decreased to 18% between weeks 18 & 24 of epoietin- α therapy

Balfour Jr HH. *Int J Antimicrob Agents* 1997;8:189-92.



Anemia & Morbidity

Anemia and Morbidity



The impact of anemia on morbidity in HIV/AIDS patients has been evaluated

- Breitbart et al.
- Steinberg et al.
- Buchanan et al.

Anemia and Morbidity: Results of Breitbart et al



- 427 ambulatory patients with AIDS
 - Primary study focus: impact of fatigue
 - Patients with fatigue more likely to have lower Hb levels (mean Hb 12.4 g/dL in fatigued population vs. Hb 13.1 g/dL in non-fatigued population)

Breitbart W. *J Pain Symptom Manage* 1998;15:159-67.

Anemia and Morbidity: Results of Steinberg et al.



- 58 AIDS cases studied
 - Examined predictors of outcome in patients on zidovudine
 - Low baseline Hb predictor of poor outcomes ($P = 0.001$).
 - 13% of patients with low Hb levels <10.5 g/dL were able to complete 12 weeks of therapy vs. 86% able to complete 12 weeks of therapy with Hb values >13.0 g/dL

Steinberg JP, et al. *J Acquir Immune Defic Syndr* 1989;2:229-34.

Anemia and Morbidity: Results of Buchanan et al.



Admission assessments made on HIV
residents (nursing home):

1281 anemic, 3832 nonanemic

- Nonanemic residents (35.1%) more likely than anemic residents (30.8%) to be physically independent
- Anemic patients were more likely to have certain comorbidities

Buchanan RJ, et al. *AIDS Patient Care STDS* 2001;15:373-83.



Anemia & Outcomes

Study Results: Functional Outcomes



Functional capacity and quality of life are important factors in disease management in light of medical therapies that allow patients to live longer.

The following 3 studies suggest treatment of anemia may enhance quality of life.

Anemia & Functional Outcomes: Abrams et al.



- QOL measured by Functional Assessment of HIV Infection scale
- Significant improvement in health-related quality of life scoring was associated with Hb increases of >2.0 g/dL
- Regression analyses demonstrated total QOL scores associated with increased Hb levels independent of CD4⁺ count changes

Abrams DI, et al. *JAMA* 1988;260:3009-15. *Int J STD AIDS* 2000;11:659-65.

Anemia & Functional Outcomes: Revicki et al.



- Revicki et al. analyzed 12 QOL indicators
- Improvements in energy and fatigue, health satisfaction, global health, and home management apparent in patients whose anemia resolved
- Patients whose anemia resolved had better QOL scores than patients with unresolved anemia

Revicki DA, et al. *J Acquir Immune Defic Syndr* 1994;7:474-84.

Anemia & Functional Outcomes: Wilson et al.



- Cross-sectional analysis 305 people with AIDS
- Regression equations
 - Association between low Hb levels and worsened physical functioning
 - Low Hb levels independent correlates of worsened health

Wilson IB, Cleary PD. *Med Care* 1996;34:610-23.

Anemia Management: Treating Underlying Cause



- Management of anemia may improve healthcare outcomes in patients with HIV/AIDS
- Anemia etiology will vary and must be treated as necessary (infection, hemolysis, tumor)
- Anemia management must continue past this phase



Anemia Management

Anemia Management: HAART Therapy



- HAART may prevent anemia in HIV positive patients
- HAART regimens containing a minimum of one protease inhibitor may improve HIV-associated anemia
- Improvements in anemia have been negated in some studies, but not all, when zidovudine was included in the HAART regimen

Anemia Management: Therapeutic Options



- Treat specific etiologies such as vitamin and mineral deficiencies, opportunistic illness
- Treat blood loss
- Discontinue anemia-causing medications if possible
- Use hematopoietic growth factors (i.e., epoietin- α)
- RBC transfusion if severe anemia threatening health

Summary



- Anemia during HIV infection can be caused by disease-related factors and treatment-related factors.
- Anemia prevalence is higher in patients with severe disease, and in patients with certain characteristics
- Anemia is associated with increased mortality and morbidity
- Anemia management may improve survival and quality of life

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