Metabolic Challenges and Possible Solutions in the HIV-infected Patient

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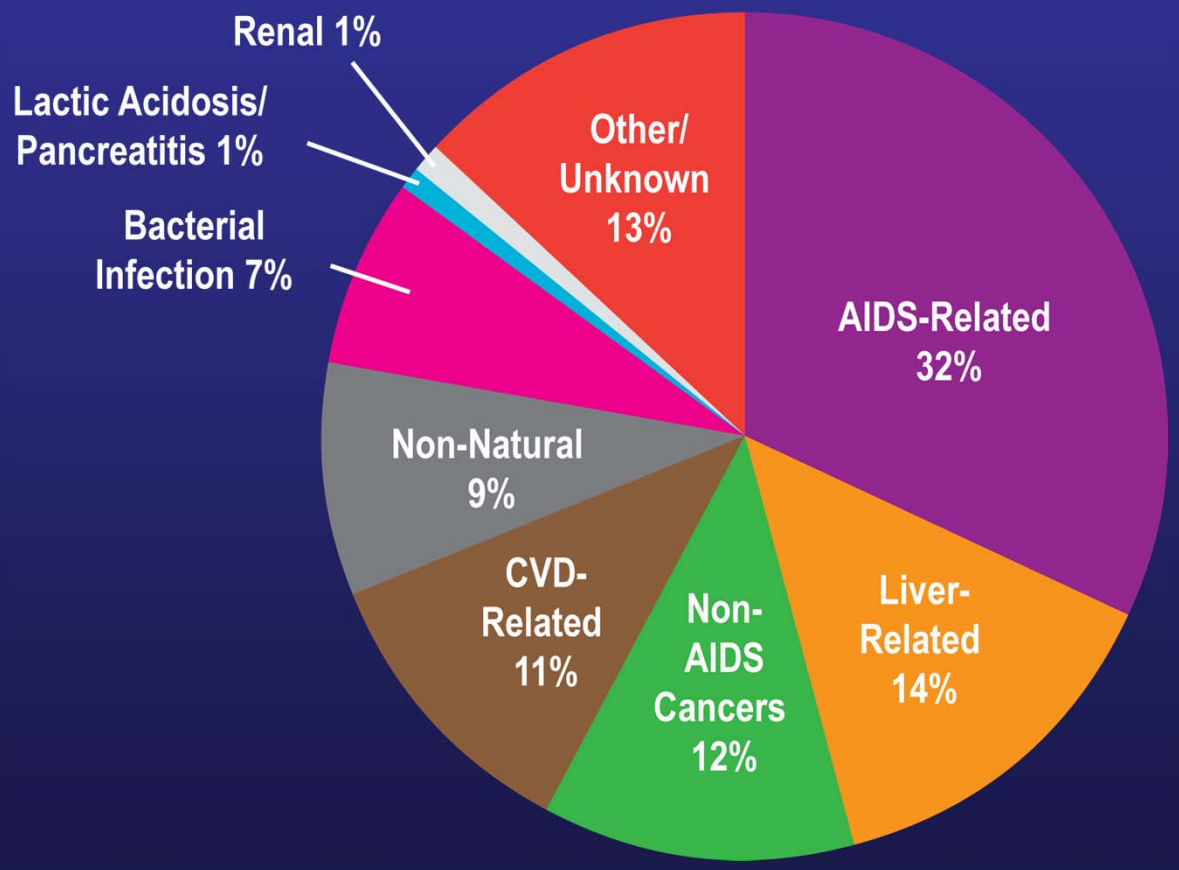
Non-HIV Co-morbidities Account for More Deaths in HIV-Infected Persons Than HIV1

D:A:D database, N = 33,347 HIV-infected; 2,192 Deaths/158,959 Person-Years

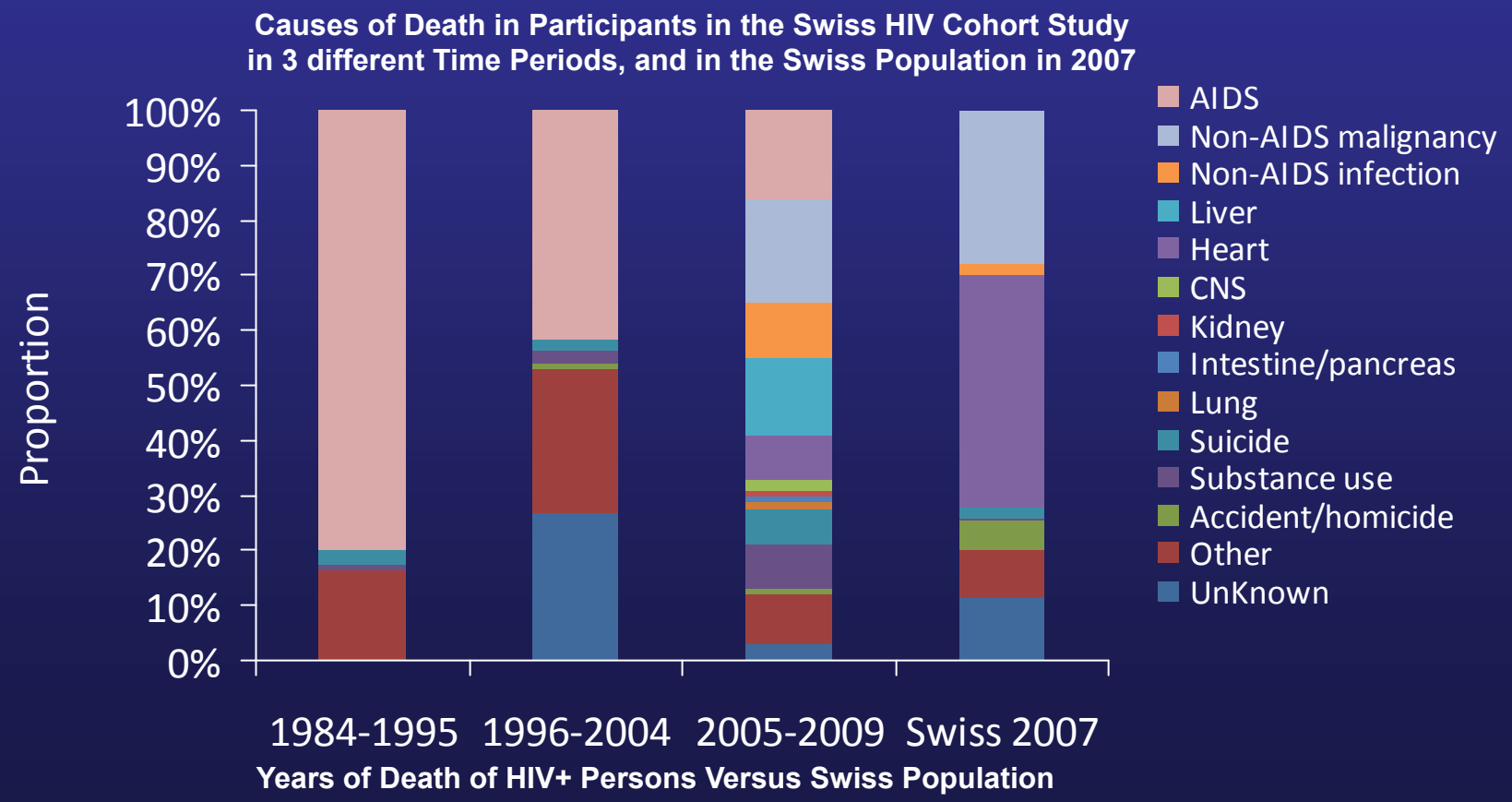


CVD = cardiovascular disease; D:A:D = data collection on adverse events of anti-HIV drugs.

1. Smith C et al. 16th CROI; February 8–11, 2009, Montreal, Canada. Oral presentation. http://www.natap.org/2009/CROI/croi_28.htm. Accessed June 16, 2009.

Changing Patterns of the Causes of Death in a Swiss Cohort (SHCS)

- SHCS is a prospective observational cohort
- Characteristics of participants that died from 2005-2009
- 459 deaths/9,053 participants (5.1%)

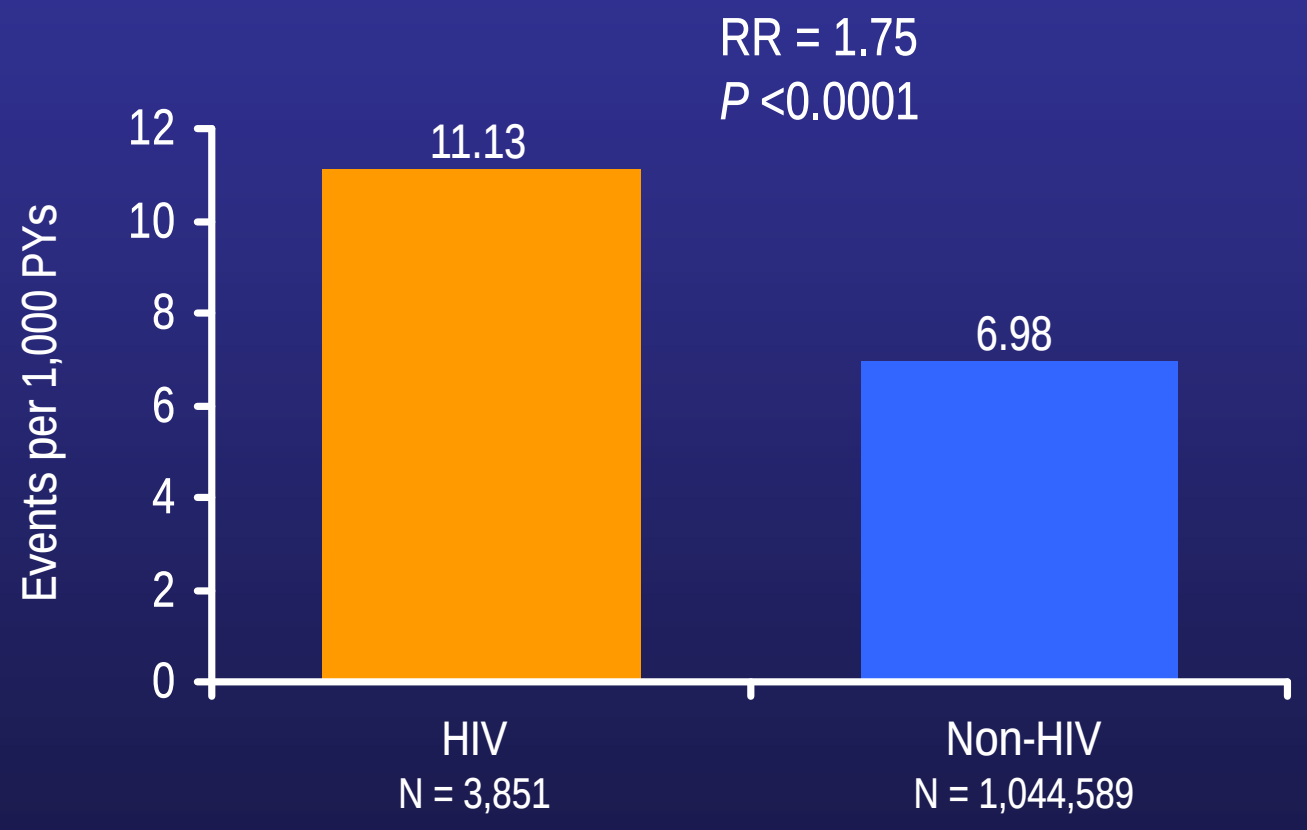


Ruppik M, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 789.

- Cardiovascular Complications
- Hepatic Complications
- Diabetes Mellitus
- Body Fat Changes
- Bone Disorders

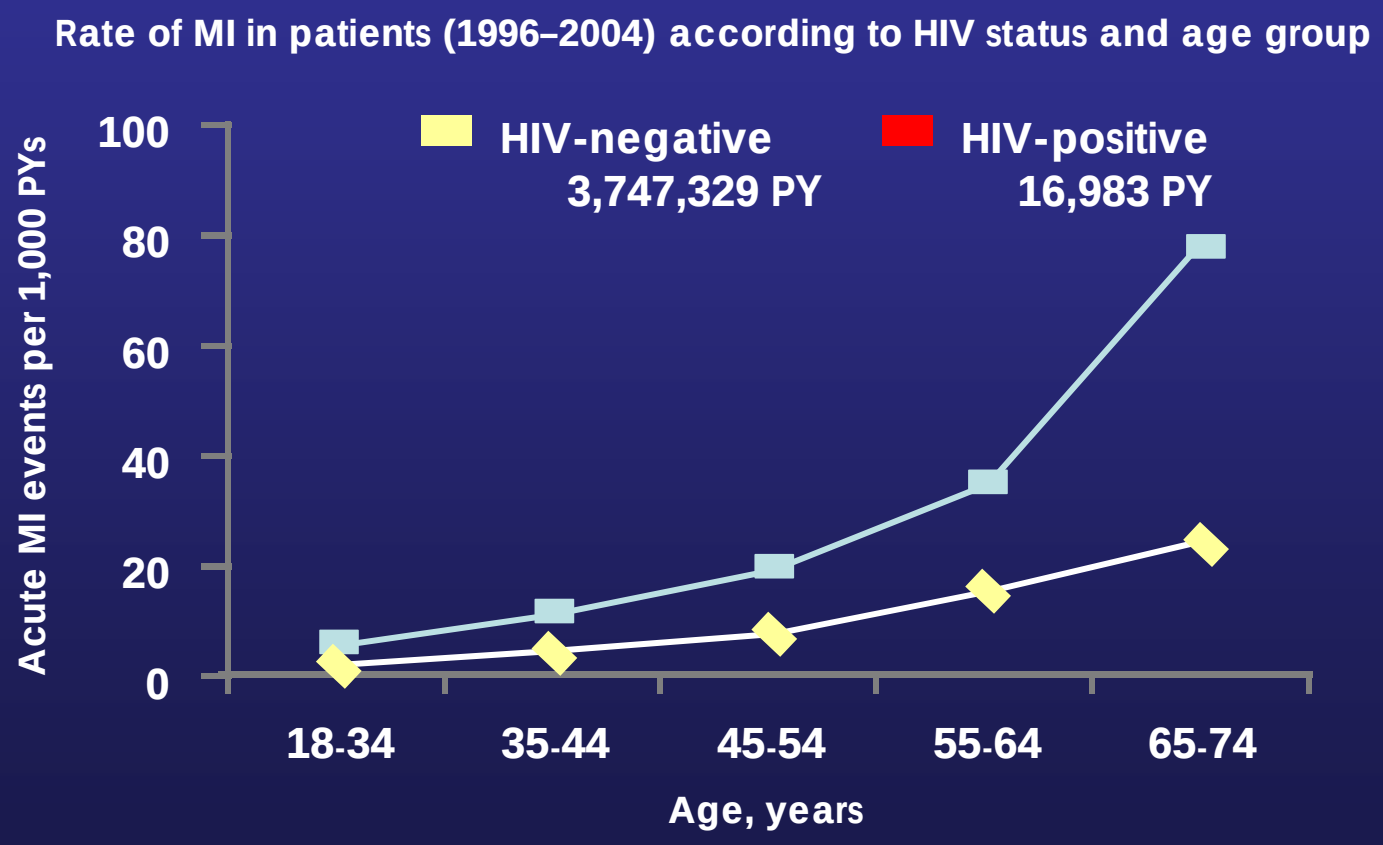
Cardiovascular Complications

Higher Acute Myocardial Infarction Rates in HIV-Infected vs Uninfected Patients



PYs = person-years; RR = relative risk.
Adapted with permission from Triant VA et al. *J Clin Endocrinol Metab*. 2007;92:2506–2512.

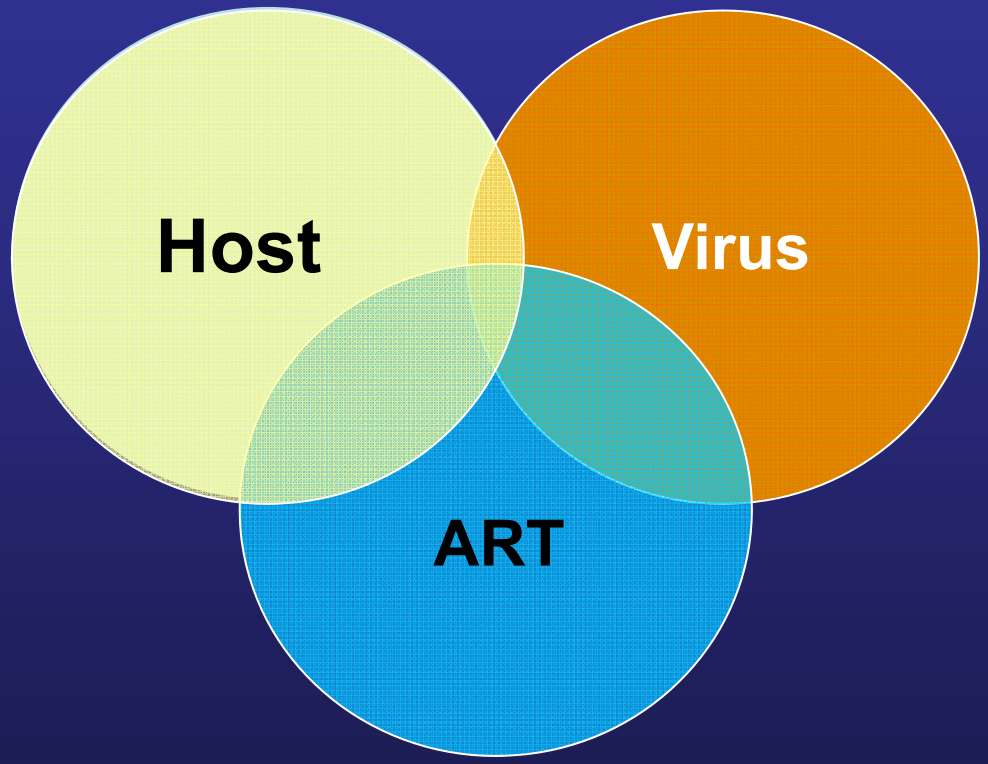
Prevalence of Myocardial Infarction Increases with Advancing Age and HIV Infection



PY = patient-year.

Adapted from Triant VA, *et al. J Clin Endocrinol Metab* 2007; 92:2506–2225.

Cardiovascular Risk and HIV1



These factors interact and affect each other to raise cardiovascular risk

ART = antiretroviral therapy.

1. Currier J. 17th IAC; August 3–8, 2008, Mexico City, Mexico. Oral presentation. http://img.thebody.com/confs/aids2008/slides/WEAB0102%20Currier%20J%20slides.ppt. Accessed June 20, 2009.

Host Factors of CV Risk[1,2]

Traditional CV Risk Factors Are Associated With CV Death in HIV Patients

- Nonmodifiable
  - Age
  - Gender
- Modifiable non-HIV-specific risk factors
  - Smoking
  - Diabetes mellitus
  - Hypertension
  - Body mass index
- Modifiable HIV-specific risk factors
  - Viral load
  - CD4 count

CV = cardiovascular.

1. Smith C et al. 16th CROI; February 8–11, 2009, Montreal, Canada. Oral presentation. http://www.natap.org/2009/CROI/croi_28.htm. Accessed June 16, 2009. 2. Mocroft A et al. 16th CROI; February 8–11, 2009, Montreal, Canada. Oral presentation. http://www.natap.org/2009/CROI/croi_28.htm. Accessed June 16, 2009.

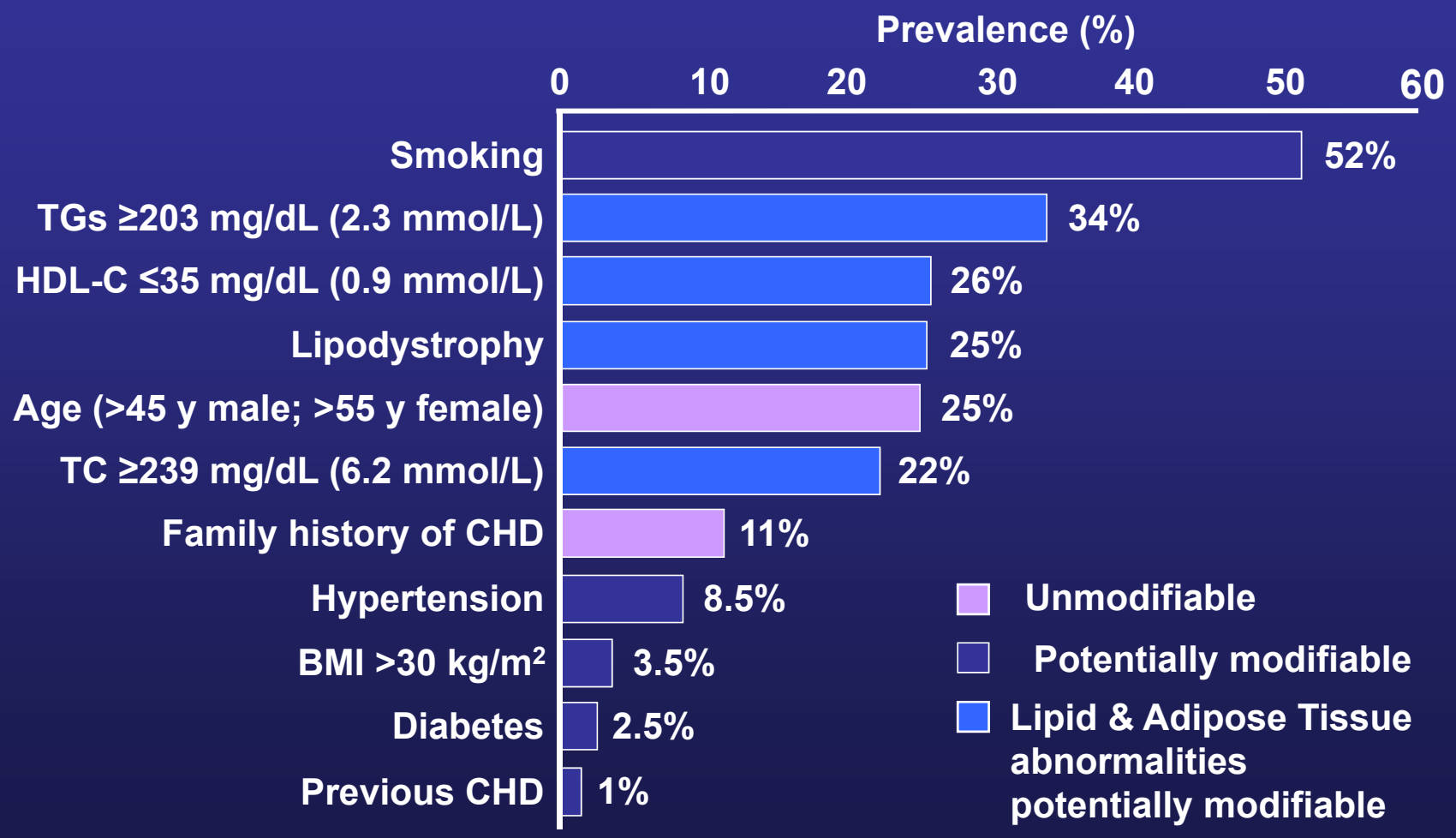
Host Factors of CV Risk: Is the Effect of Traditional CV Risk Factors the Same in HIV?

Increased Risk per Unit, %

Risk Factor (Unit)	HIV-Positive Iloeje 2005	HIV-Positive Friis-Møller 2007	HIV-Negative (Number of Studies)
Age (per 1 year older)	9%	6%	6% to 9% (7)
Sex (male vs female)	NS	110%	110% to 160% (2)
Diabetes mellitus (yes vs no)	260%	90%	140% to 252% (3)
Smoking (yes vs no)	140%	290%	70% to 290% (3)
Hypertension (yes vs no)	30%	80%	80% to 90% (3)

CV = cardiovascular; NS = not significant.
Adapted with permission from Currier JS et al. *Circulation.*2008;118:198–210.

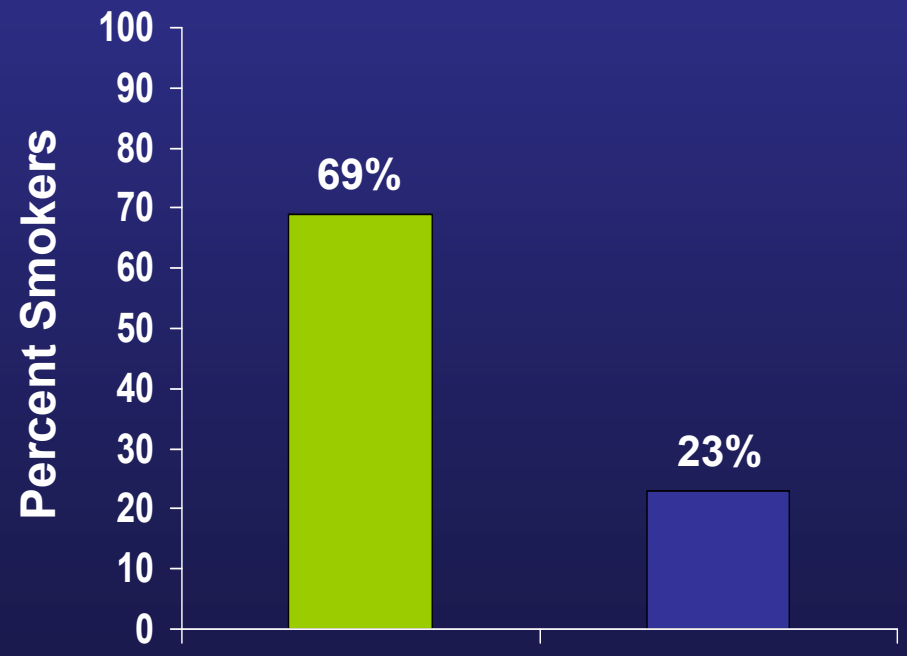
CV Risk Factors in an HIV-Infected Population: the DAD Study



CHD: coronary heart disease; BMI: body mass index; DAD: Data Collection of Adverse Events

Friis-Moller N et al. AIDS 2003; 17: 1179–1193

A Higher Percentage of HIV-infected Individuals Smoke as Compared to the General Population



Smoking habits reported by HIV-infected individuals who were current smokers when entering HIV treatment (69% of total):

- ≤1/2 pack/day (31%)
- 1 pack/day (41%)
- 1-2 packs/day (17%)
- ≥2 packs/day (11%)

Engels EA, et al. *J Clin Oncol.* 2006;1383-1388.

VA Study: HIV is an Independent Risk for MI

- 81,229 veterans (33% HIV+) from the Veterans Aging Cohort Study Virtual Cohort (VACS)
- Case Matched 2:1 age, gender, race/ethnicity, and clinical site
- Variables included HIV status, age, race/ethnicity, hypertension, diabetes, alcohol and cocaine use, self-reported smoking, hepatitis C, lipids, CD4 count, HIV-1 RNA, class of ART
- During a median 4.6 years, there were 497 MI events (44% HIV^+)

Rates of MI were higher for HIV^+ (21.7, 95%CI 19.0 to 24.7) per 10,000 person-years) than uninfected veterans (13.1, 95%CI 11.7 to 14.8 per 10,000 person-years)

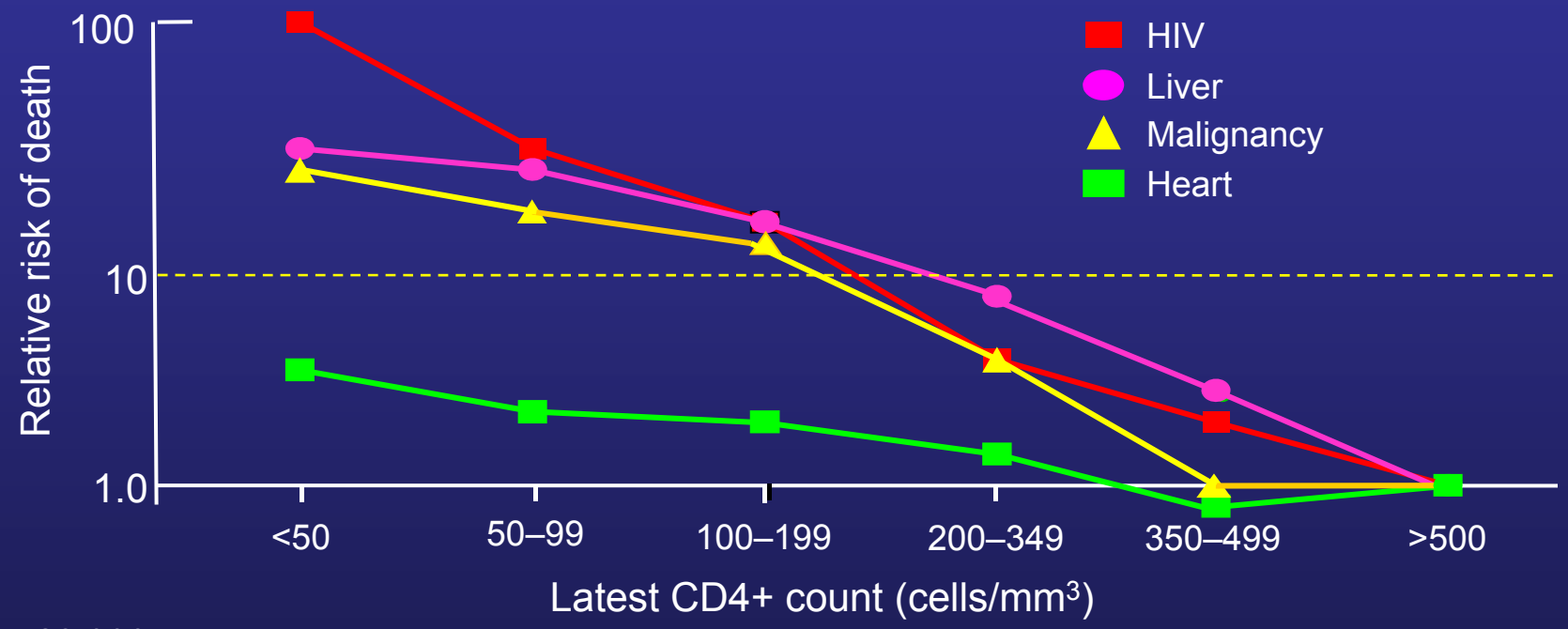
Risk Factor	Hazard Ratio (HR)	95% CI
HIV	1.86	1.54 – 2.26
Age	1.04	1.03 - 1.05
Hispanic ethnicity	1.35	1.01 - 1.80
Hypertension	1.40	1.15 - 1.70
Hyperlipidemia	1.29	1.07 - 1.56
Diabetes	2.06	1.69 - 2.50
Smoking	1.48	1.14 - 1.93

Among HIV-infected participants, baseline CD4 counts, HIV-1 RNA levels, and class of ART were not associated with MI after adjustment for established risk factors (p>0.2)

Freiberg M, et al. 18th CROI 2011;Abstarct 809.

D:A:D Study: Relative Risk of Death according to Immune Function and Specific Cause

Improved Immune function decreases the risk of non–HIV-related death



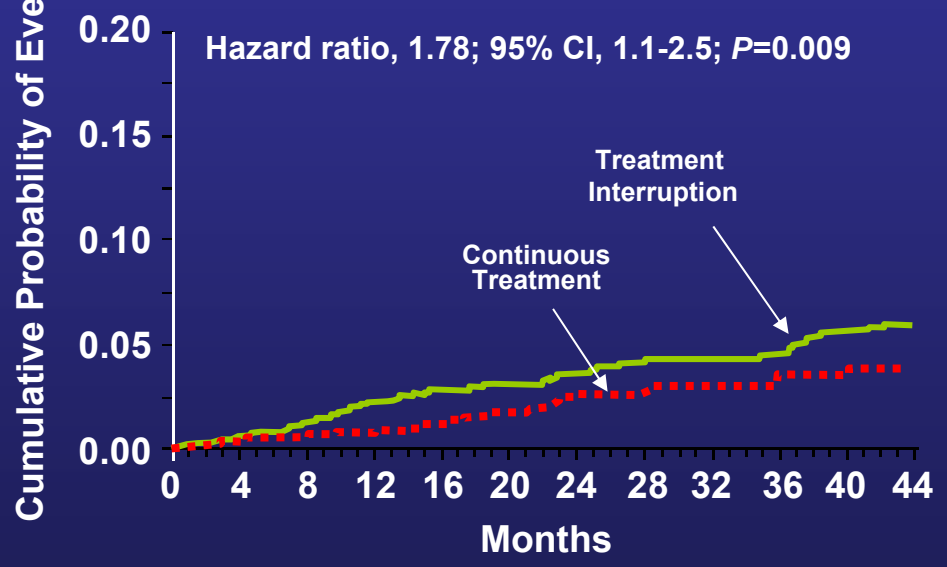
- n=23,000+
- 1,248 (5.3%) deaths 2000–2004 (1.6/100 person-years)
  - Of these, 82% on ART
- Incidence of CV-related mortality lower than other non–HIV-related deaths

Weber R, *et al. 12th CROI*, Boston 2005, #595

SMART Study: HIV Viremia Can Contribute to CV Risk

N=5472 HIV-infected patients with a CD4+ cell count >350mm^3

Major Cardiovascular, Renal, or Hepatic Disease



No. at Risk												
Treatment Interruption	2720	2070	1663	1292	1041	867	693	543	443	375	273	157
Continuous Treatment	2752	2077	1692	1307	1070	899	713	563	462	380	282	165

Endpoint	Hazard Ratio (95%CI)*	*P* Value
Death, any cause	1.8 (1.2-2.9)	0.007
Major cardiovascular, renal or hepatic disease	1.7 (1.1-2.5)	0.009
Fatal or non-fatal CVD	1.6 (1.0-2.5)	0.05

*Treatment Interruption vs. Continuous Treatment

SMART Study Group. N Eng J Med. 2006;355: 2283-2296.

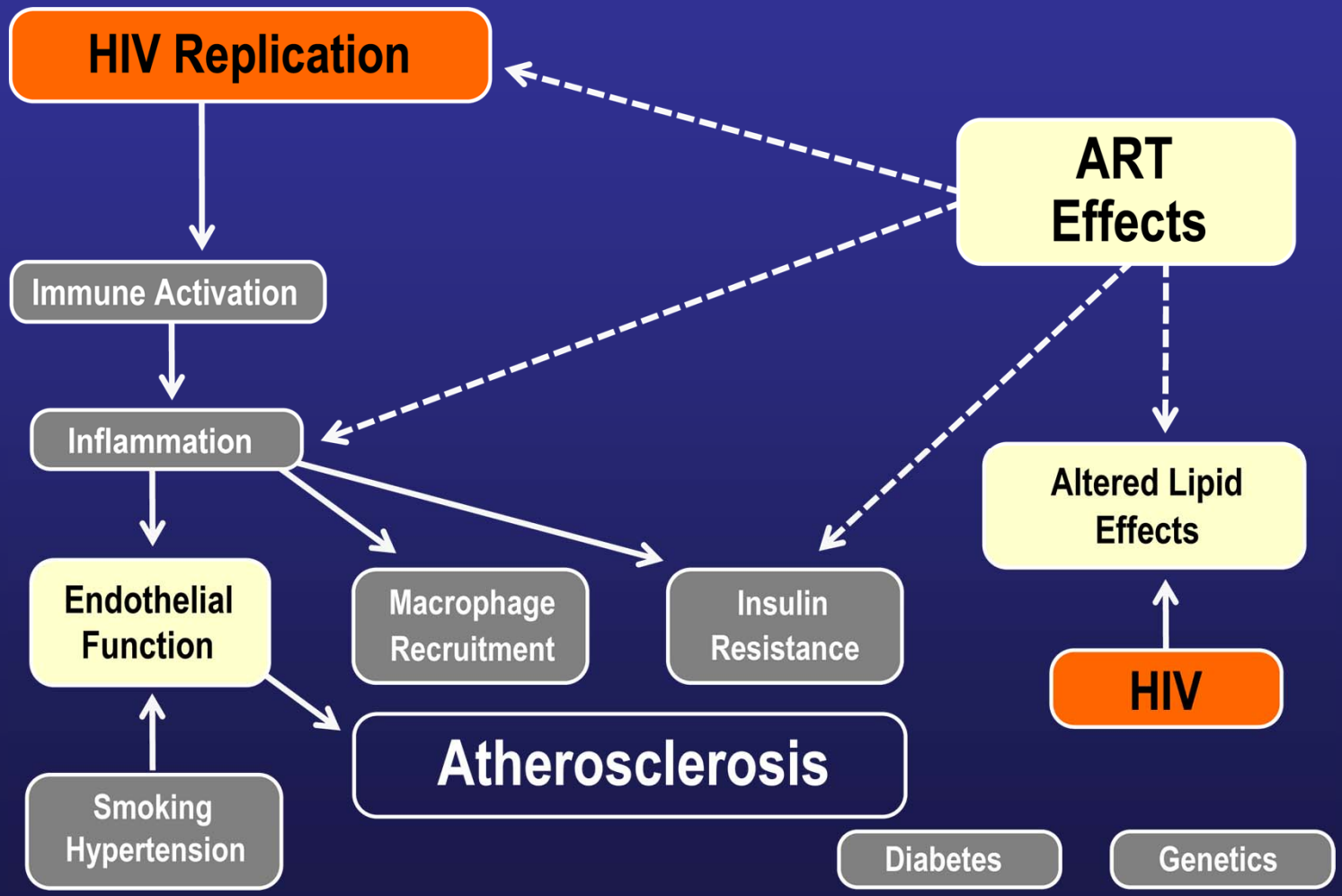
Impact of HIV on CVD[1]

- HIV and ART can contribute to an altered risk of CVD in 3 ways:
  - HIV may serve as a marker to identify a subgroup of the general population with an altered prevalence of traditional cardiovascular risk factors, unrelated to HIV or ART
  - HIV or ART may affect the risk of developing a traditional cardiovascular risk factor
  - HIV or ART may affect the pathogenetic process that leads to CVD in ways other than by an effect on traditional risk factors
- There is substantial evidence to suggest that all 3 mechanisms are in operation and affect the risk of CVD in patients infected with HIV

ART = antiretroviral therapy; CVD = cardiovascular disease.

1. Currier JS et al. *Circulation.* 2008;118:198–210.

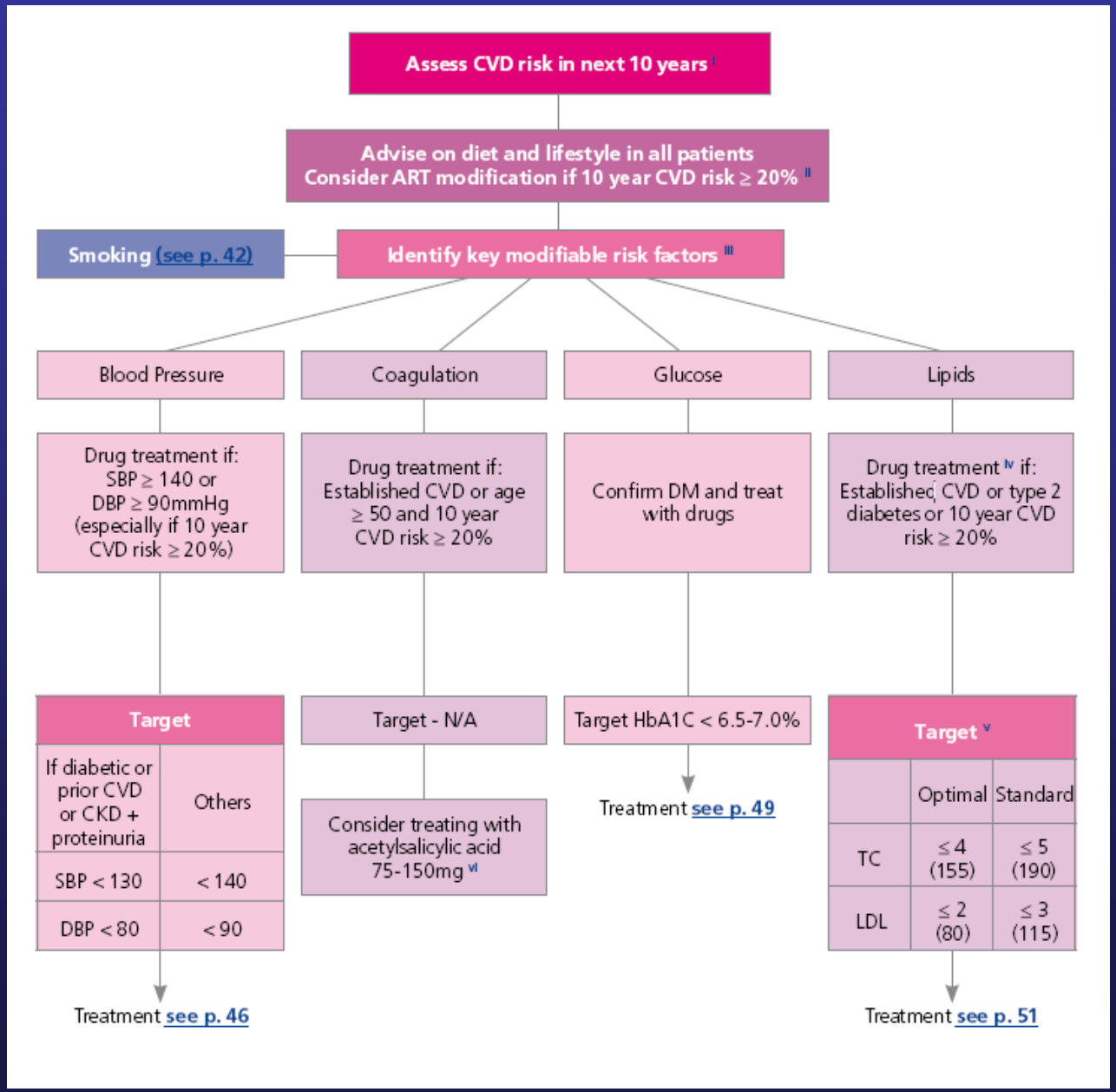
Summary of HIV, Host, and ART Effects[1]



ART = antiretroviral therapy.

1. Currier J et al. 17th IAC; August 3–8, 2008, Mexico City, Mexico. Oral presentation. http://img.thebody.com/confs/aids2008/slides/WEAB0102%20Currier%20J%20slides.ppt. Accessed July 6, 2009.

Prevention and management of CV disease: EACS guidelines



EACS Guidelines 2011. Available at: http://www.europeanaidsclinicalsociety.org/guidelines/(accessed Nov 2011).

Hepatic Complications

Incidence and Epidemiology of HCV Coinfection[1]

- Approximately 25% of HIV-infected individuals are coinfected with HCV
- 50% to 90% of HIV-infected injection drug users are coinfected with HCV

HCV = hepatitis C virus.

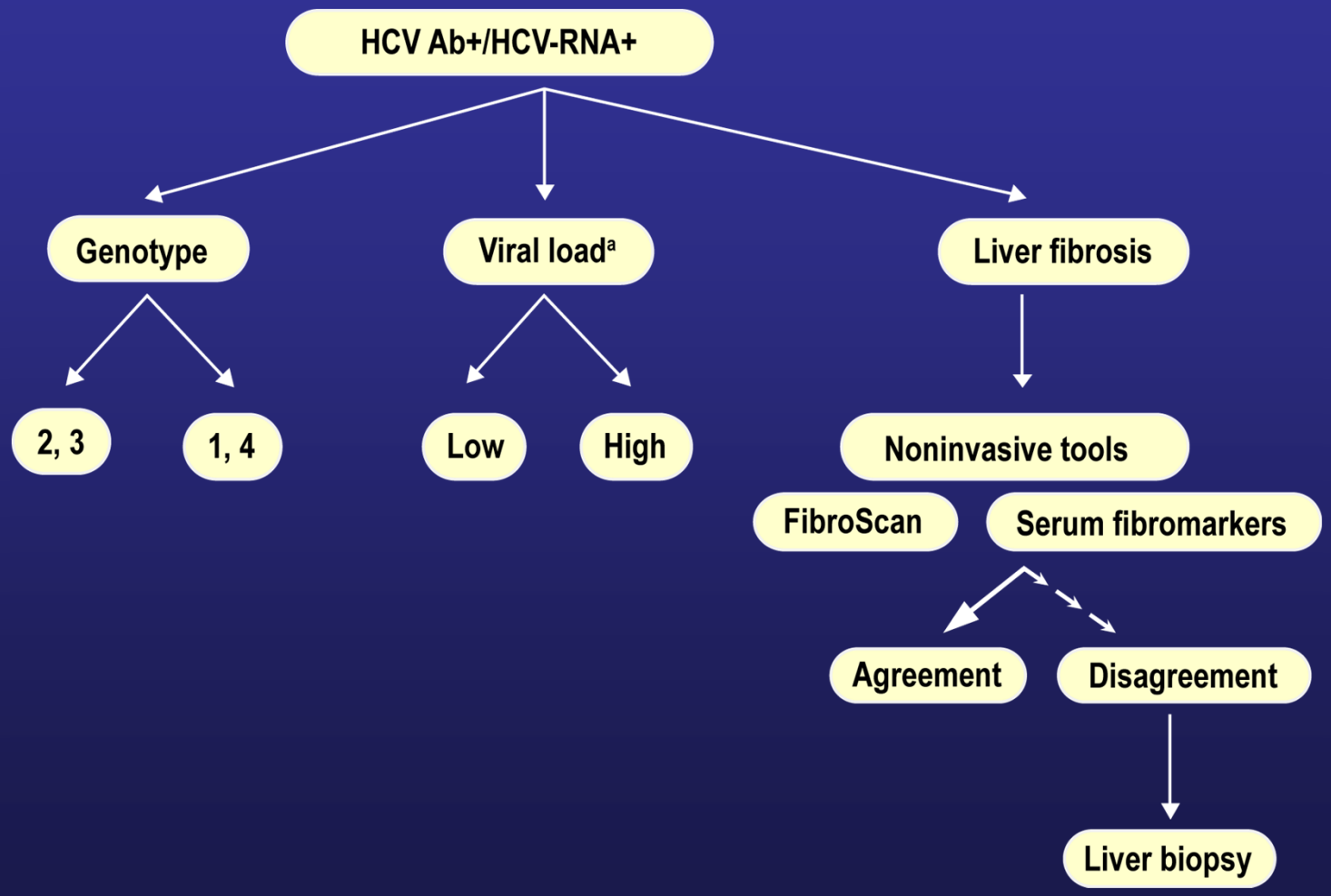
1. Centers for Disease Control and Prevention. http://www.cdc.gov/hepatitis/Populations/hiv.htm. Accessed June 22, 2009.

Liver Fibrosis Assessment

- Best prognostic factor for liver disease progression in chronic HCV[1]
- Especially important in patients with low likelihood of achieving SVR[2]
- Biopsy not needed in every patient[1]
  - Disadvantages: invasive, rare serious complications, subject to sampling error, poor patient acceptance, cost
  - Noninvasive options
    - Imaging techniques (eg, elastometry, FibroScan)
    - Serum biochemical markers (eg, Fibrotest[a], FIB-4[b])
  - A combination of noninvasive markers generally is sufficient

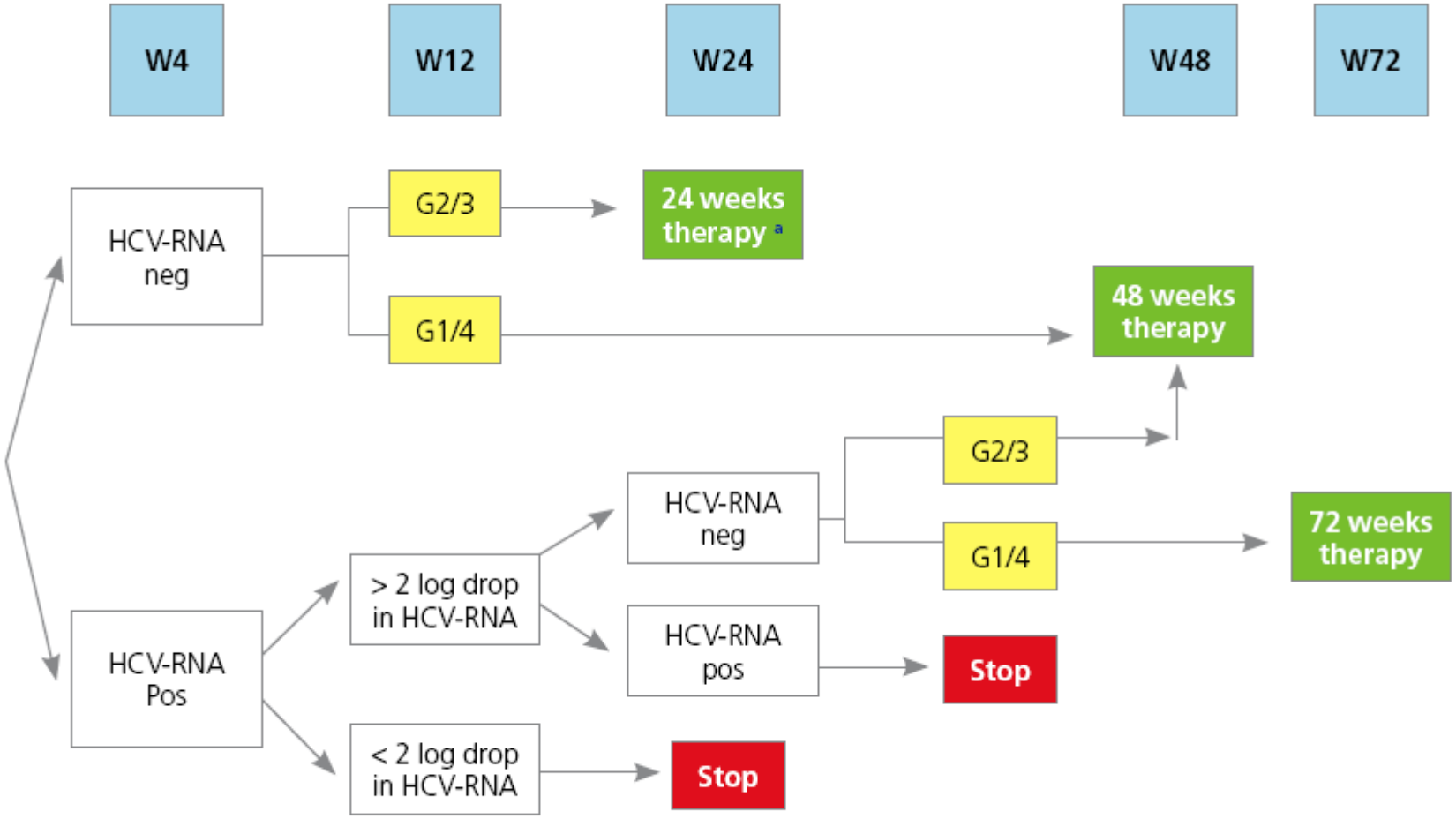
HCV = hepatitis C virus; SVR = sustained virologic response.
[a]Fibrotest considers α2-macroglobulin, haptoglobulin, gamma globulin, apolipoprotein, bilirubin.
[b]FIB-4 considers age, platelet count, alanine aminotransferase, aspartate aminotransferase.
1. Soriano V et al. *AIDS.* 2007; 21:1073–1089. 2. European AIDS Clinical Society. http://www.europeanaidsclinicalsociety.org/guidelinespdf/3_Treatment_chronic_hepatitis_co_infection.pdf. Accessed June 22, 2009.

Main Variables to Assess in HIV/HCV Coinfected Patients



Ab = antibody; HCV = hepatitis C virus.
[a]Low viral load is <400,000 IU/mL and is associated with higher likelihood of achieving sustained virologic response.
Adapted with permission from Soriano V et al. *AIDS.* 2007; 21:1073–1089.

Proposed Treatment, EACS



a) In patients with baseline low viral load (< 400,000 IU/ml) and minimal liver fibrosis.

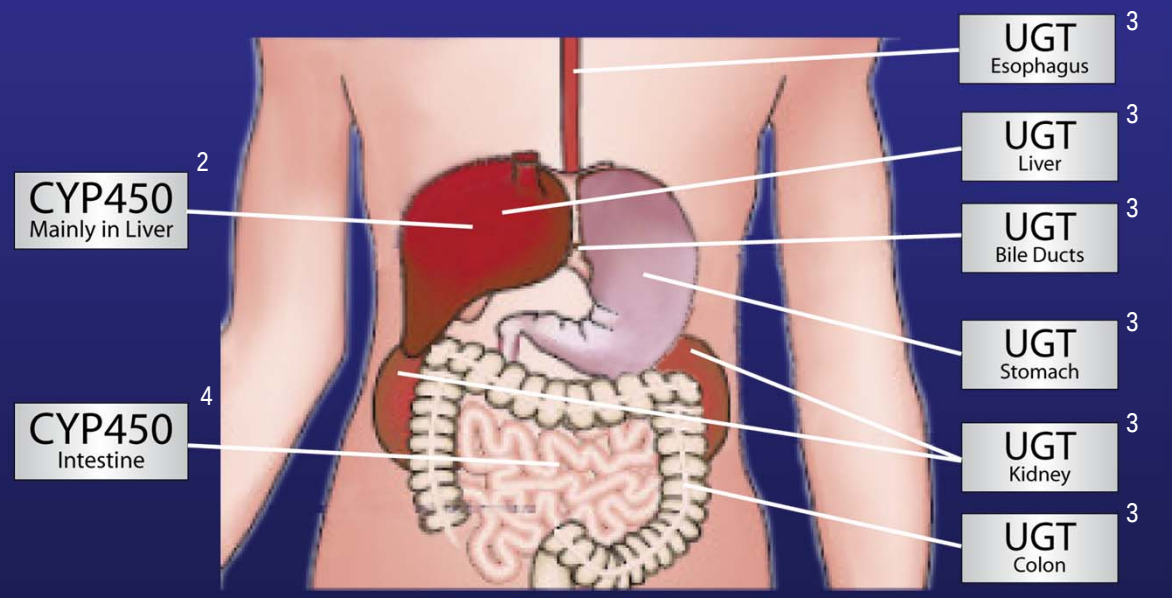
EACS = European AIDS Clinical Society; HCV = hepatitis C virus.

EACS Guidelines 2011. Available at: http://www.europeanaidsclinicalsociety.org/guidelines/(accessed Nov 2011).

Pharmacokinetic Factors Affecting Treatment Success

2/3 of the top 200 drugs utilize CYP450 as a contributor to clearance[1]

1/7 of the top 200 drugs prescribed are cleared by UGT pathways[1]



CYP450 = cytochrome P450; UGT = uridine diphosphate-glucuronosyltransferase.

1. Williams JA et al. *Drug Metab Disp.* 2004;32:1201–1208. 2. Young B. *AIDS Patient Care STDs.* 2005;19:286–297. 3. Tukey RH et al. *Annu Rev Pharmacol Toxicol.* 2000;40:581–616. 4. Piscitelli SC et al. *N Engl J Med.* 2001;344:984–996.

Effects of Liver Disease on Hepatic Drug Metabolism[1]

- Cirrhosis can affect drug clearance in 2 ways:
  - Decreased blood flow due to fibrosis reduces first-pass effects and produces high systemic concentrations of some drugs (eg, terfenadine)
  - Decrease in functional hepatocytes can reduce capacity for some (but not all) Phase I (P450) reactions
- Generally very late complications
  - Excellent capacity for eliminating xenobiotics
- Phase I enzymes (P450s)
  - 0.5 to 1.5% decrease in hepatic blood flow per year after age 25
  - Elderly may have reduced liver blood flow and/or reduced activity of some (CYP2C9 and CYP2D6) enzymes as a consequence of aging or underlying liver disease
- Phase II enzymes (eg, UGTs)
  - Relatively well-preserved, even in patients with end-stage liver disease

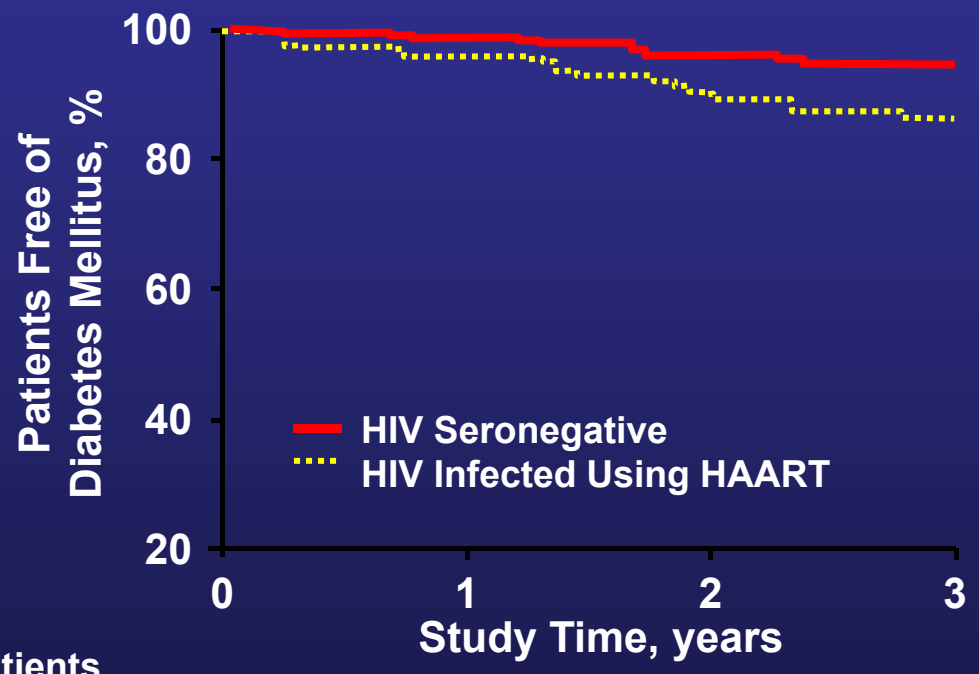
CYP2C9 = cytochrome 2C9; CYP2D6 = cytochrome 2D6; P450 = cytochrome P450; UGT = uridine diphosphate-glucuronyltransferase.

1. Kashuba A. University of North Carolina HIV Care 2009: Antiretroviral Therapy, Hepatitis B/C, Addiction, and Adherence; May 4, 2009, Chapel Hill, NC. Oral presentation. Accessed June 29, 2009.

Diabetes Mellitus

Diabetes Mellitus Incidence is Increased in HIV-infected Patients on HAART

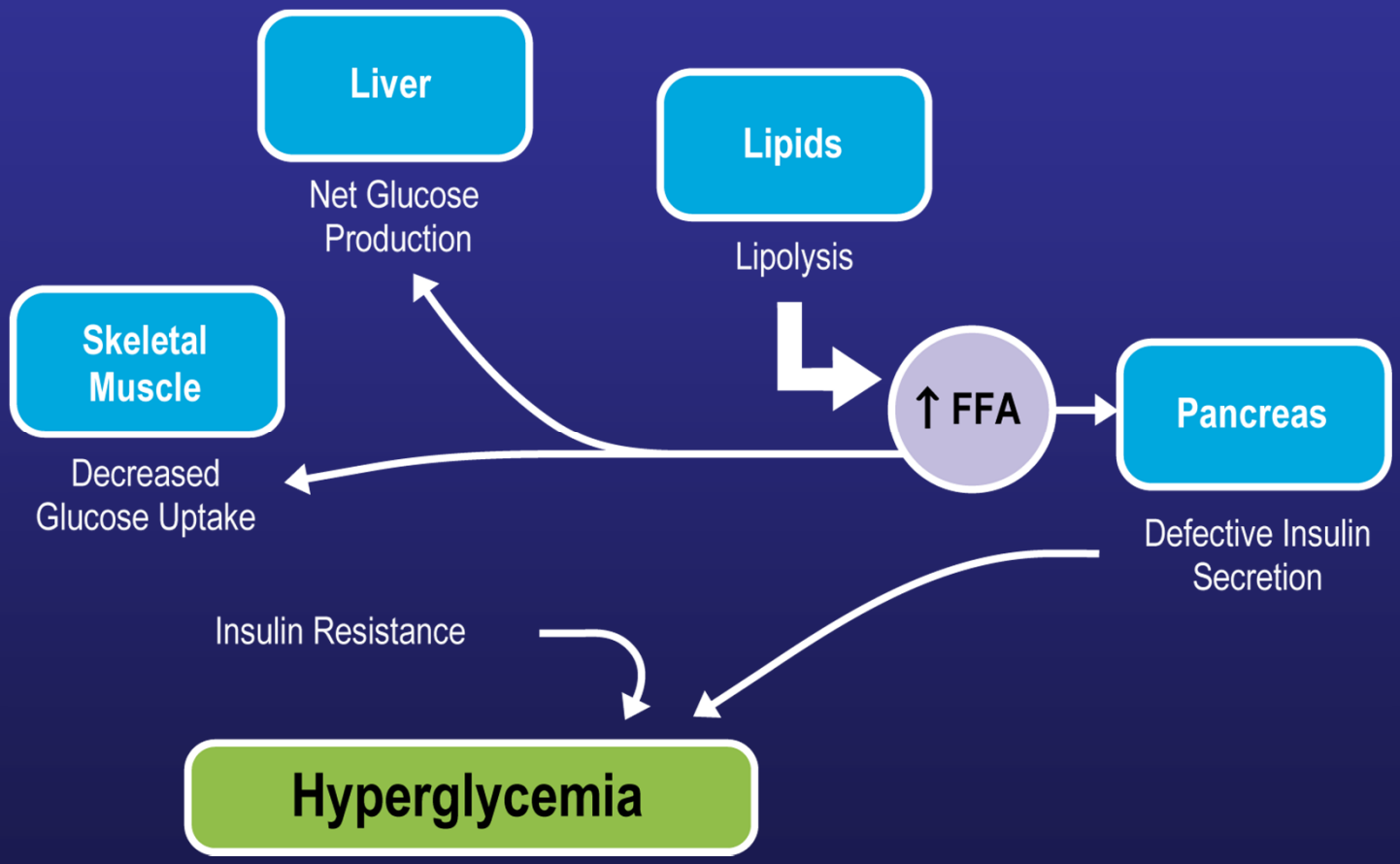
Diabetes Mellitus is more than 4 times higher in HIV-infected patients on HAART as compared to the general population



No. of Patients				
HIV Seronegative	361	265	177	89
HIV Infected Using HAART	229	204	145	62

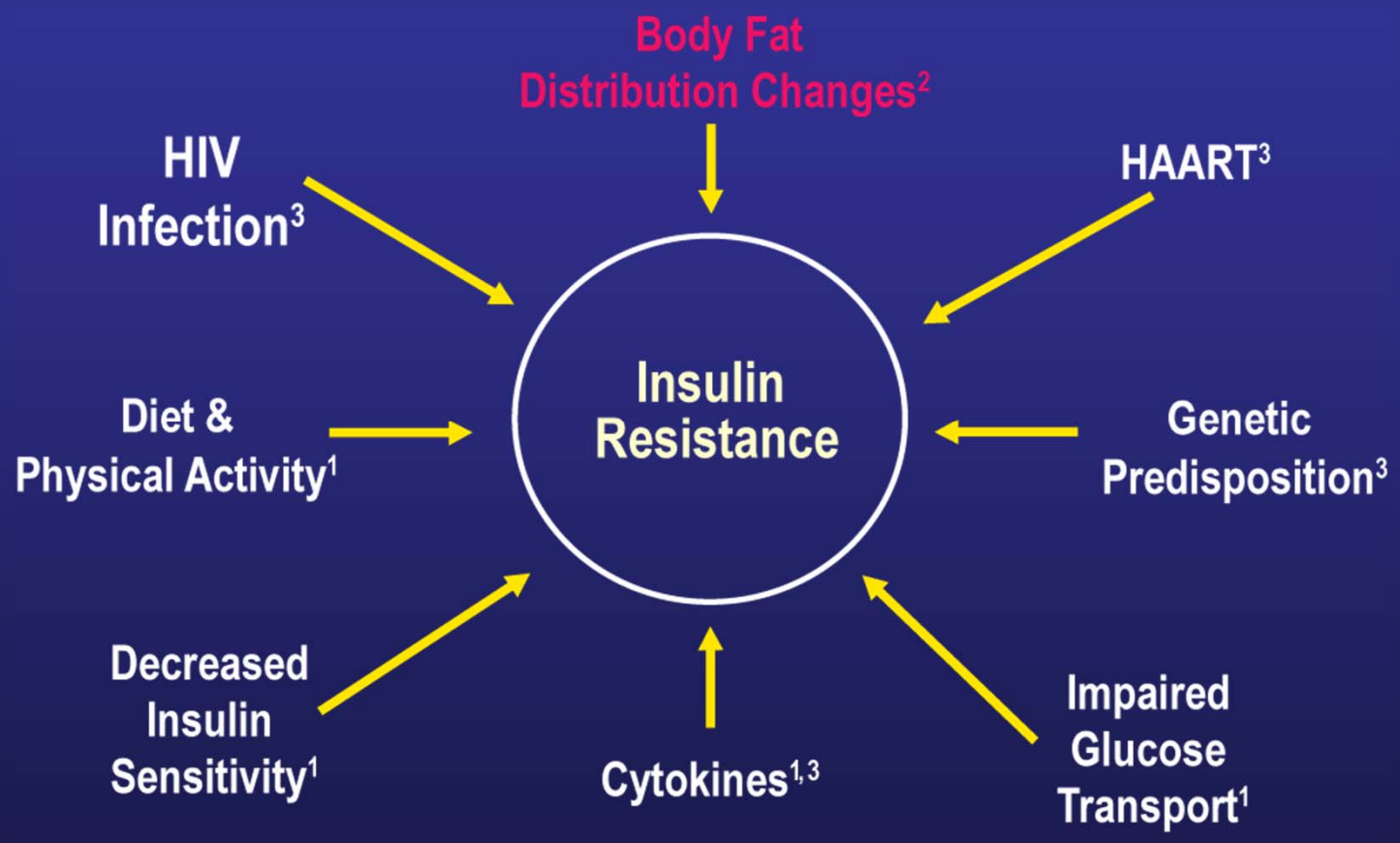
Brown TT, et al. *Arch Int Med.* 2005;165:1179-1184.

Effects of Insulin Resistance



FFA = free fatty acids.
Adapted with permission from Brown TT. Clinical Care Options HIV 2008. http://www.clinicaloptions.com/HIV/treatment%20updates/Insulin%20Resistance.aspx. Accessed June 24, 2009.

Factors That May Contribute to IR in HIV-Infected Patients



HAART = highly-active antiretroviral therapy; IR = insulin resistance.

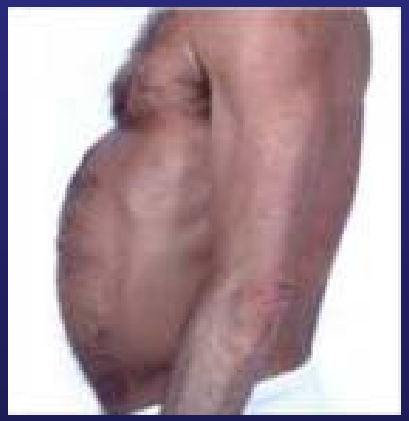
1. Hruz PW. *Am J Infect Dis*. 2006;2:187–192. 2. Van Wijk JP et al. *J Clin Endocrinol Metab*. 2005; 90:3575–3582. 3. Brown TT. Clinical Care Options HIV 2008. http://www.clinicaloptions.com/HIV/treatment%20updates/Insilin%20Resistance.aspx. Accessed June 24, 2009.

Body Fat Changes

Body Fat Changes: Physical Characteristics

Lipoatrophy of face

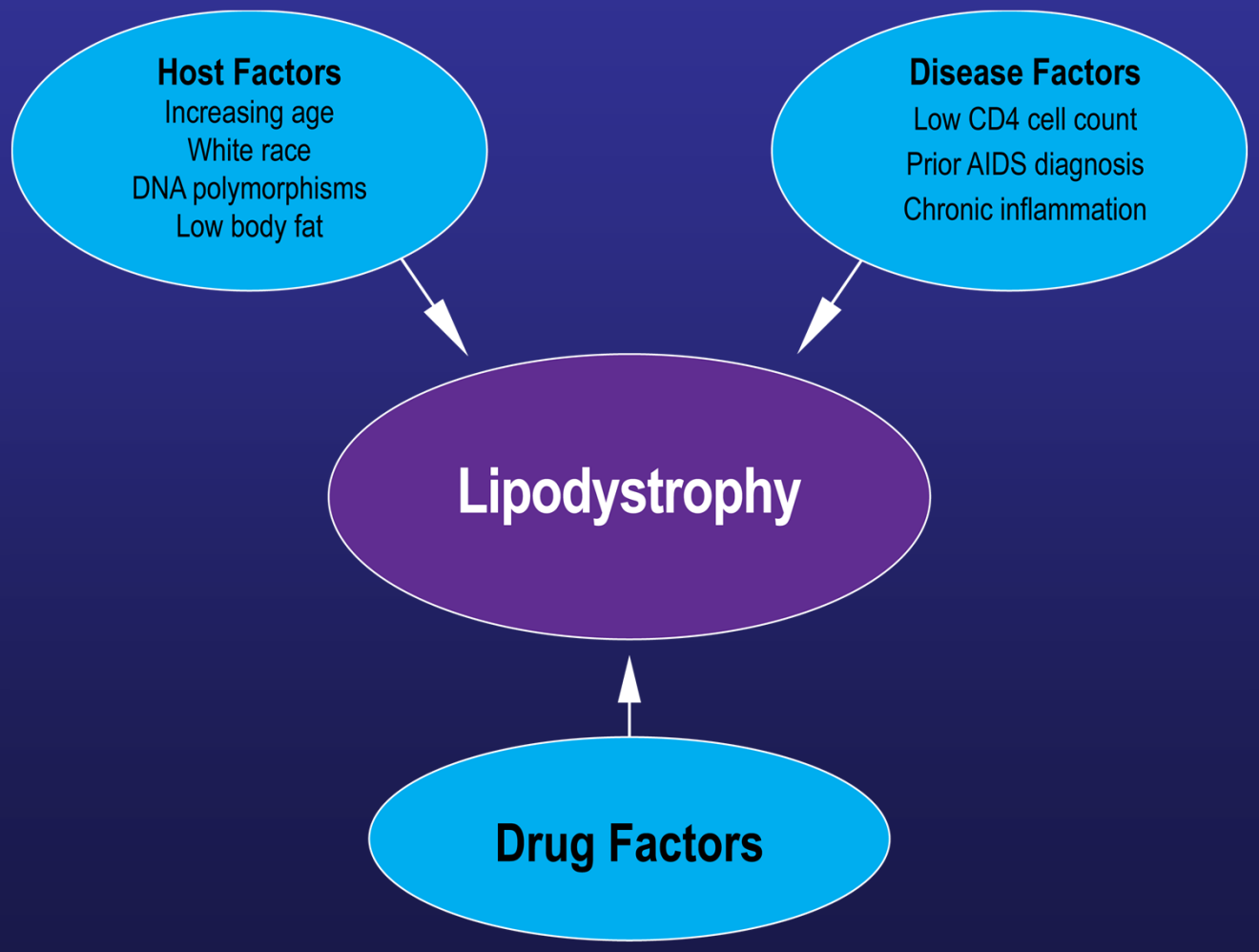
Dorsal cervical fat pad
(“buffalo hump”)



Abdominal distension with visceral fat

Adapted with permission from Morse CG et al. *JAMA*. 2006;296:844–854.

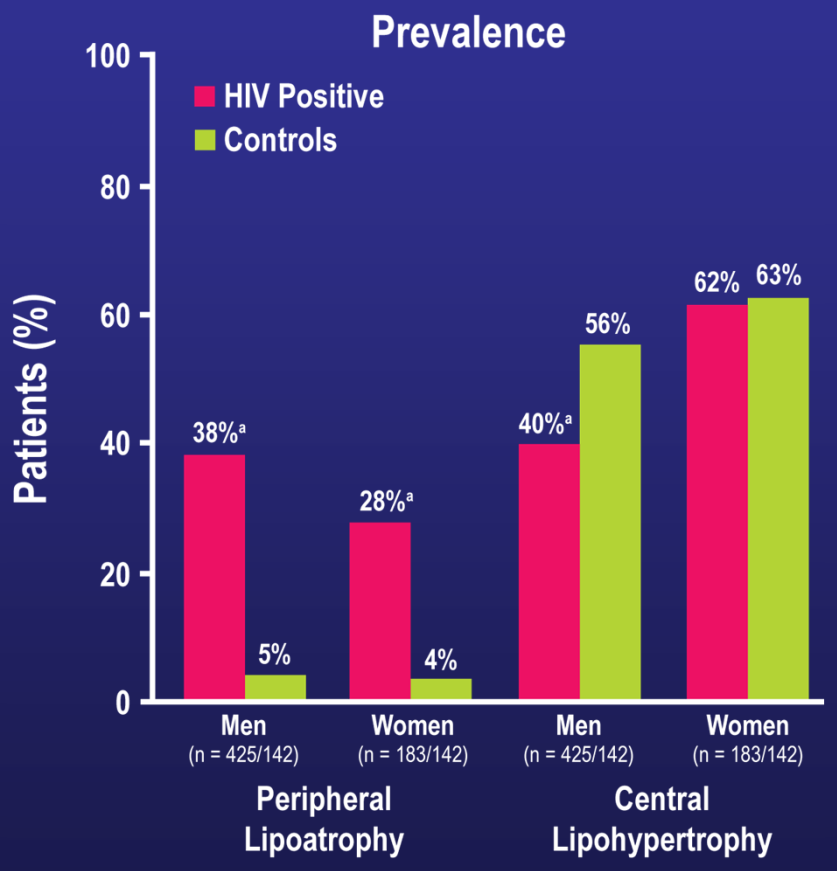
Fat Distribution Changes: Associated Factors[1,2]



1. Fat Redistribution and Metabolic Change. *J Acquir Immune Defic Syndr*. 2005;40:121–131. 2. Fat Redistribution and Metabolic Change. *J Acquir Immune Defic Syndr*. 2006;42:562–571.

FRAM Cohort: Cross-Sectional Analysis of Fat Redistribution[1,2]

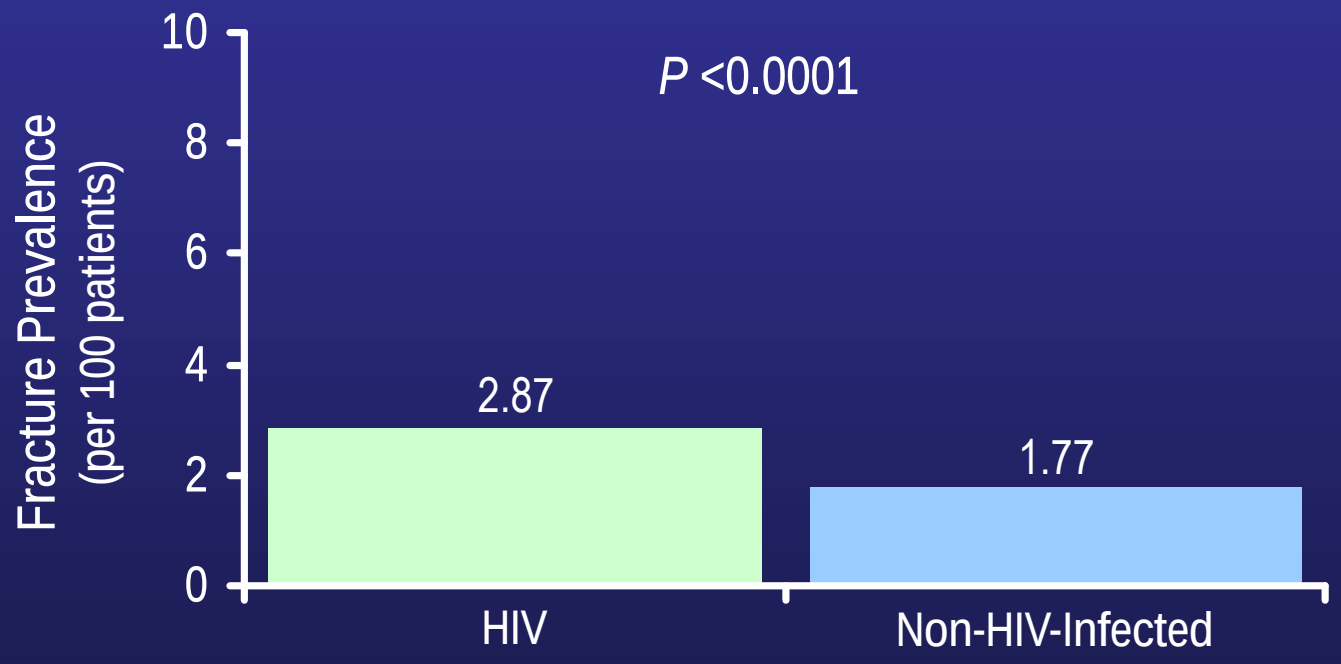
- Lipoatrophy or lipohypertrophy
  - Concordance between subject report of fat change and clinical examination
  - Whole-body MRI measured regional adipose tissue volume
- Subjects 33 to 45 years of age (2000–2002)
  - HIV-infected men and women
    - Duration of HIV infection: 8.5 years
  - Contols: HIV-negative subjects from 2 centers from the CARDIA cohort
- Peripheral lipoatrophy was not linked to central lipohypertrophy
  - Odds ratio
    - Men: 0.71 (0.47–1.06); $P = 0.10$
    - Women: 0.39 (0.20–0.75); $P = 0.006$



CARDIA = Coronary Artery Risk Development in Young Adults; FRAM = Fat Redistribution and Metabolic Change in HIV Infection; MRI = magnetic resonance imaging.
[a]P <0.001 vs controls.
1. Fat Redistribution and Metabolic Change. *J Acquir Immune Defic Syndr*. 2005;40:121–131. 2. FRAM. *J Acquir Immune Defic Syndr*. 2006;42:562–571.

Bone Disorders

Bone Disorders: Increased Fracture Prevalence in HIV[1]



1. Triant VA et al. *J Clin Endocrinol Metab.* 2008;93:3499–3504.

Bone Disorders: Patient-Related Factors[1]

- Smoking
- Alcohol use
- Low body weight
- Hypogonadism
- Low vitamin D
- Sedentary lifestyle
- Opiate use
- Hepatitis coinfection (HIV-infected women)
- Inadequate calcium consumption
- Low peak bone mass
- Corticosteroid use

1. Brown T. 16th CROI; February 8–11, 2009, Montreal, Canada. Update. http://www.natap.org/2009/CROI/croi_139.htm. Accessed June 24, 2009.

Bone Disorders: Treatment Recommendations[1]

- Treat underlying causes
  - Vitamin D deficiency
  - Smoking
  - Excess alcohol consumption
  - Hypogonadism
  - Low BMI (−1.5)
- Calcium and Vitamin D

BMI = body mass index.

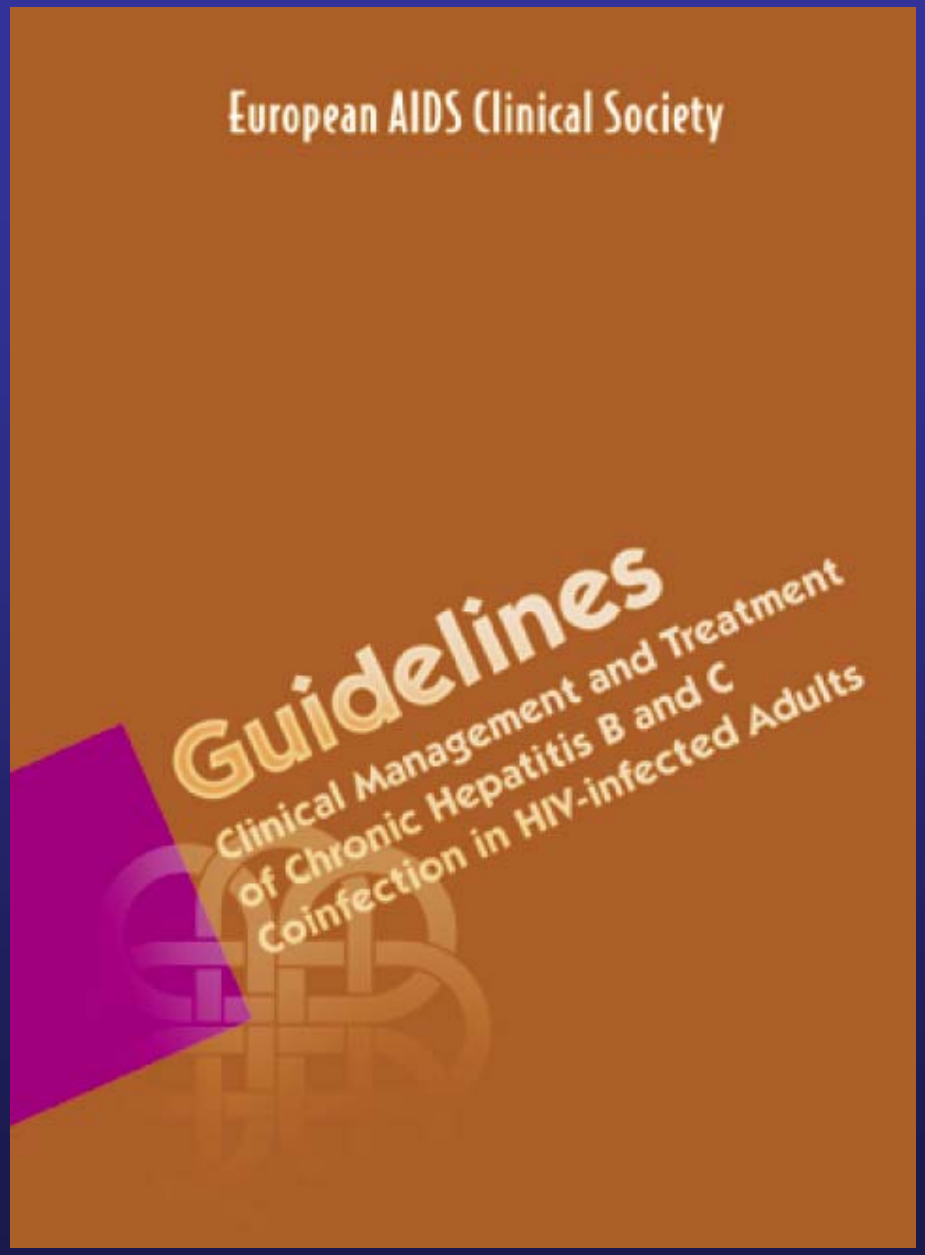
1. Brown T. 16th CROI; February 8–11, 2009, Montreal, Canada. Update. http://www.natap.org/2009/CROI/croi_139.htm. Accessed June 24, 2009.

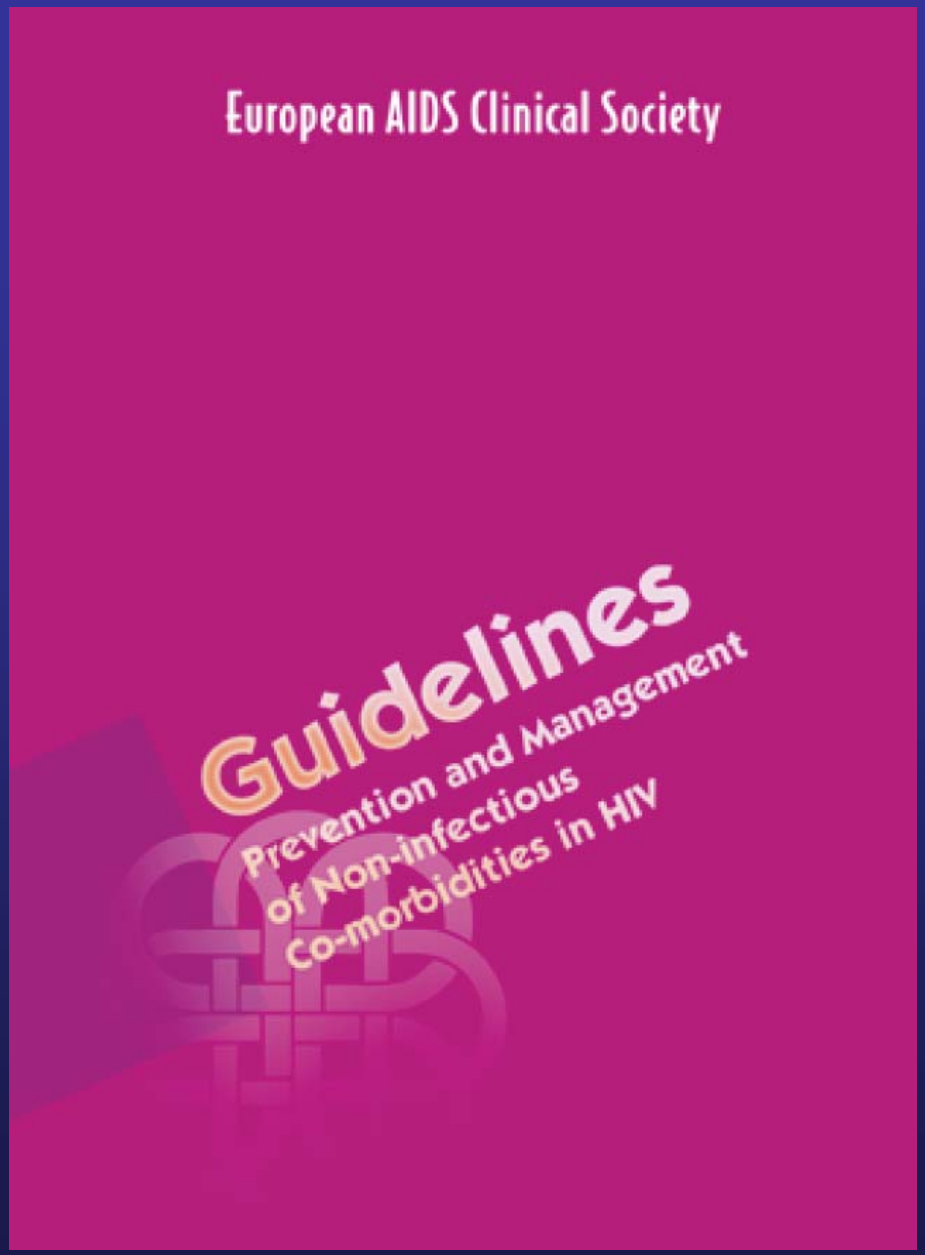
Summary

- As the HIV population continues to age and patients are living longer, physicians must take into account various comorbidities, such as:
  - Cardiovascular disease
  - Renal dysfunction
  - Hepatic diseases (HBV, HCV)
  - Metabolic disorders
  - Substance abuse
- The continued care of pre-existing and developing conditions is of paramount importance for the health of the HIV patient

HBV = hepatitis B virus; HCV = hepatitis C virus.

Where to find Information and Help!





EACS Guidelines 2011. Available at: http://www.europeanaidsclinicalsociety.org/guidelines/(accessed Nov 2011).

Prevention and Management of Non-Infectious Co-Morbidities in HIV

Screening for non-infectious co-morbidities

	Assessment	At HIV diag-nosis	Prior to starting cART	Follow-up frequency		Comment	See page
				with cART	without cART		
History	• Past and current co-morbidities • Family history (e.g. premature CVD, diabetes, hypertension, CKD) • Concomitant medications [i] • Current lifestyle (alcohol use, smoking, diet, aerobic exercise)	+ + + +	+ + + +	every visit 6-12 m	every visit annual	On transfer of care repeat assessment Premature CVD: Cardiovascular events in a first degree relative: male < 55, female < 65 years Adverse lifestyle habits should be addressed more frequently	44 42
Body composition	• Body-mass index • Clinical lipodystrophy assessment	+ +	+ +	annual annual	annual		61
Cardiovascular disease	• Risk assessment (Framingham score [ii]) • ECG	+ +	+	annual	annual	Should be performed in every older patient without CVD (Men > 40 years; women > 50 years)	44
Hypertension	• Blood pressure	+	+	annual	annual		46
Dyslipidaemia	• TC, HDL-c, LDL-c, TG[iii]	+	+	annual		Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	51
Diabetes mellitus	• Serum glucose	+	+	6-12 m		Consider oral glucose tolerance test if repeated fasting glucose levels of 6.1-6.9 mmol/L (110-125 mg/dL)	49
Liver disease	• Risk assessment [iv] • ALT/AST, ALP	+ +	+ +	annual 3-6 m	annual 6-12 m	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs	62
Renal disease	• Risk assessment [v] • eGFR (aMDRD) [vi] • Urine dipstick analysis [vii]	+ + +	+ + +	annual 3-6 m annual	annual 6-12 m annual	More frequent monitoring if CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs [viii] Every 6 months if eGFR < 60 ml/min; If proteinuria ≥ 1+ and/or eGFR < 60 ml/min perform UP/C or UA/C [vii]	59
Bone disease	• Risk assessment [ix] FRAX® [x] in patients > 40 years) • 25-OH vitamin D	+ +	+	2 yrs	2 yrs	If not using FRAX®, consider DXA of spine and hip in specific patients Repeat according to risk factors	52
Neurocognitive impairment	• Questionnaire	+	+	1-2 yrs	1-2 yrs	Screen risk patients	64
Depression	• Questionnaire	+	+	1-2 yrs	1-2 yrs	Screen risk patients	56
Cancer	• Mammography • Cervical PAP • Others			1-3 yrs 1-3 yrs	1-3 yrs 1-3 yrs	Women 50-70 years Sexually active women, frequency depending on CD4 Controversial	37

EACS Guidelines 2011. Available at: http://www.europeanaidsclinicalsociety.org/guidelines/(accessed Nov 2011).