

HIV and Cardiovascular Disease:
Getting to the Heart of the Matter

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Case Study - Kenneth

- 48-year old HIV-infected male
- Dx: 2001
- ART: PI-based regimen
- BMI: 26.5
- Smoker: 1 ppx20 yrs
- FMH: father had angina & stents placed at age 56
- BP: 128/84
- FBG: 111
- Tchol: 240
- HDL: 30
- LDL: 132
- Trigs: 240
- CD4: 870
- Viral Load: undetectable

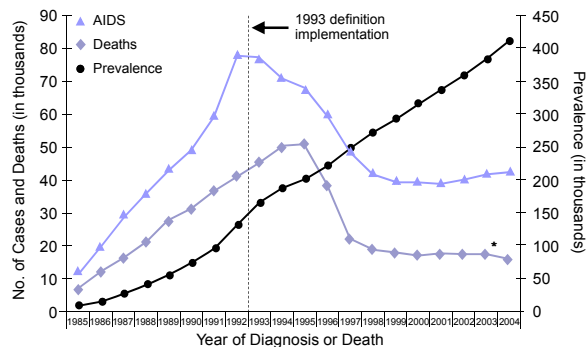
Questions to Consider

- Is Kenneth at risk for CVD?
- What is his level of risk?
- Is his risk affected by his HIV status?
- What does he know about CVD risk factors?
- What can we do to help him reduce his risk of having a CV event?

Objectives

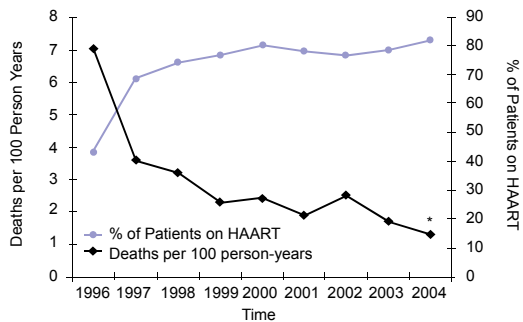
- To briefly review the epidemiology of HIV infection in the United States
- To describe the prevalence of cardiovascular disease (CVD) in HIV-infected adults
- To identify the traditional and nontraditional risk factors associated with CVD in this population
- To present data related to CVD risk factor knowledge and risk perception in HIV-infected adults
- To discuss potential strategies that nurses can implement to reduce the risk of CVD in patients

AIDS Cases, Deaths, and Persons Living with AIDS, 1985-2004, United States



Note: Data have been adjusted for reporting delays. Centers for Disease Control and Prevention. <http://www.cdc.gov/hiv/topics/surveillance/resources/slides/trends/index.htm>

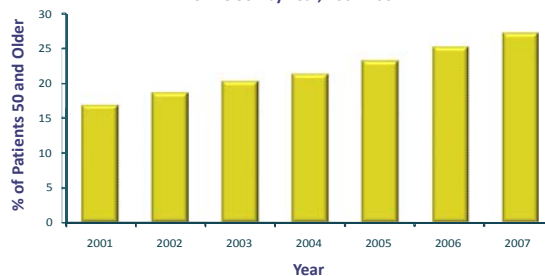
Mortality and HAART Over Time



*P<0.008 for trend. Palella FJ et al. J Acquir Immune Defic Syndr. 2006;43:27-34.

Growing Older: HIV and Aging

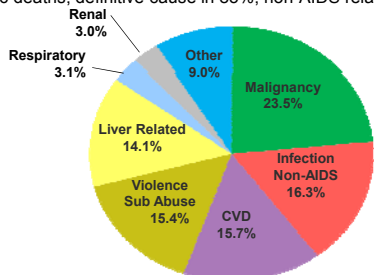
Estimated Percentage of Persons Living with HIV/AIDS Who Are 50+ by Year, 2001-2007*



*For years 2001-2003, data are based on 33 states and US dependent areas with confidential name-based HIV infection reporting. CDC HIV/AIDS Surveillance Report, 2005. For years 2004-2007, data are based on 34 states and 5 US dependent areas with confidential name-based HIV infection reporting. CDC HIV/AIDS Surveillance Report, 2007. Gay Men's Health Crisis. Growing Older With the Epidemic: HIV and Aging, 2010.

Causes of Death In HIV+ Persons Treated With ART (1996-2006)

- Assessed deaths in 13 HIV-1 cohorts comprised of 39,727 persons
- 1876 deaths; definitive cause in 85%; non-AIDS related 50.5%



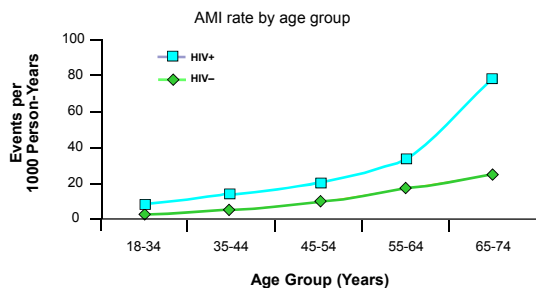
Antiretroviral Therapy Cohort Collaboration (ART-CC). *Clin Infect Dis.* 2010;50(10):1387-1396.

9

HIV and Cardiovascular Disease

- CVD is leading cause of death in U.S. (American Heart Association, 2009)
- CVD has emerged as a major cause of morbidity & mortality in HIV-infected persons
- CVD accounts for 23.8% of all non-HIV-related deaths in HIV-infected persons (Sackoff et al., 2006)
- RR for MI in HIV-infected is 1.75 (p< .0001) compared to negative controls (Triant et al., 2007)

MI Rates in HIV-infected and HIV-uninfected individuals

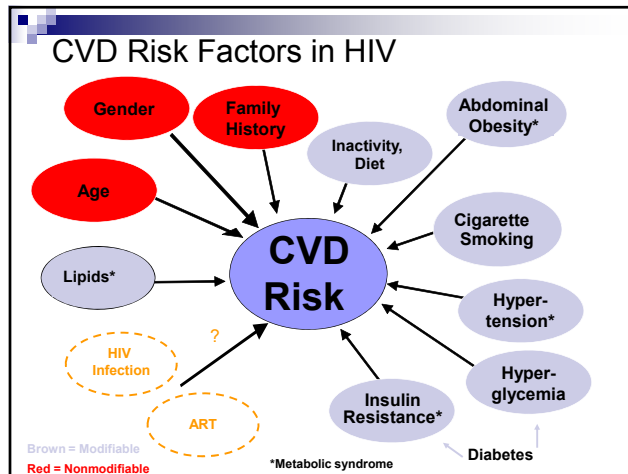
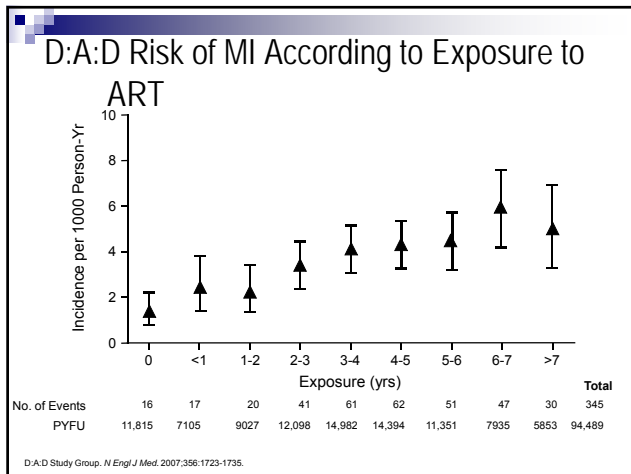


Cohorts (HIV+ =3851, HIV- =1,044,589) were identified in the Research Patient Data Registry. The primary outcome was AMI.

Triant VA, et al. *J Clin Endocrinol Metab.* 2007;92:2506-2512.

D:A:D Study

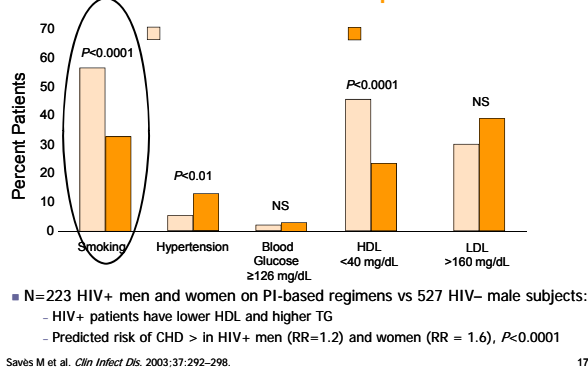
- Large, prospective, longitudinal study with 11 cohorts in Europe, Australia and the U.S.
- Designed to determine if ART was assoc with increased risk of MI
- Over 33,000 participants enrolled and followed since '99
- Baseline median age = 39 years, 76% male
- 82% exposed to ART; median duration of ART 6.9 years
- 345 participants experienced an MI
- Incidence 3.65/1000 person-years
- Data showed a 26% increase in rate of MI per year of exposure to ART (p<0.001; 1.09-1.23) (Fris-Moller et al., 2003)
- Certain HIV drug classes were found to be associated with a higher risk of MI



- ### Cardiovascular Risk Factors in HIV
- **Traditional**
 - Age
 - Male gender
 - Smoking
 - Dyslipidemia
 - Insulin resistance/diabetes
 - **Non-Traditional**
 - Inflammation/persistent viremia
 - Specific ART medication effects AND class effects
 - Elevated Biomarkers - IL-6, d-dimer, hsCRP
 - Endothelial dysfunction - brachial artery flow-mediated dilatation (FMD)
 - Preclinical atherosclerosis - elevated cIMT
 - Fat redistribution (lipoatrophy, lipohypertrophy)

- ### Smoking and HIV
- higher prevalence compared to the general population
 - DAD cohort: 56% prevalence
 - RR for MI increased 2-fold (p=0.007) (Fris-Moller et al., 2003)
 - Swiss Cohort: 57% prevalence (Glass et al., 2006)
 - Kaplan study: 35-40% prevalence
 - significant difference when compared to non-HIV-infected (p<0.001) (Kaplan et al., 2007)

Incidence of Smoking Is Increased Among HIV-Infected vs General Population



Dyslipidemia

- Generally related to the use of protease inhibitors (PIs) – first reported in '95 with ritonavir (Colagreco, 2004)
- PIs stimulate cholesterol and triglyceride synthesis
- Hyperlipidemia occurs in 74% of pts on PIs compared to 28% in pts not on PIs (Carr et al., 1999)
- D:A:D Study – progressive increase in MI risk related to drug class
 - PI-based therapy > NNRTI based therapy

Lipoatrophy/lipohypertrophy

- Prospective cross-sectional case control (3:1) study
- 91 HIV-infected; self-reported LD; and 273 controls, matched for age, sex, and BMI
- 30 HIV-infected w/o LD and 90 matched controls
- Framingham Risk Equation
- Patients w/LD had increased 10-year risk compared to controls 7.4% vs. 5.3% (p=0.002)
- Patients w/LA had highest level of risk 9.2% (p=0.043) (Hadigan et al., 2001; 23: 130 & Hadigan et al., 2003; 36: 909)

Diabetes

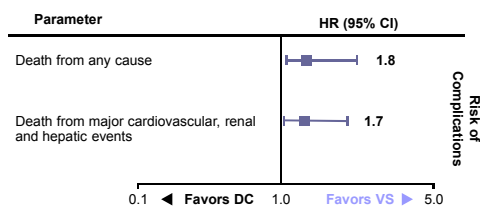
- An increased prevalence of insulin resistance and diabetes has been reported in HIV-infected patients in the ART era
- In 1 study, the prevalence of diabetes was 4 times greater in HIV-infected men with ART exposure than in matched HIV-negative men (Brown, T., 2005)

Inflammation/Persistent Viremia

- SMART Study: RCT >5000 participants
- Compared treatment interruption vs. continuous therapy
- Primary endpoint was opportunistic infection or death; secondary endpoint was major cardiovascular, renal, or hepatic event
- Treatment interruption associated with an increased risk of MI (HR 1.70; 1.0-2.5, $p=0.05$)
- Persistent viremia (inflammation) confers additional risk for MI
- Treatment is associated with lower levels of vascular adhesion molecules and pro-coagulant molecules (Kuller, LH et al, 2008)

SMART: Treatment Interruption Associated With Increased CV Risk

- Treatment interruption in the drug conservation (DC) group was associated with significantly greater disease progression or death, compared with continuous virologic suppression (VS): RR: 2.5 (95% CI: 1.8-3.6; $P < .001$)



El-Sadr W, et al. N Engl J Med. 2006;355:2283-2296.

Effect of Antiretroviral Therapy on MI Risk

- Class effect
 - DAD Study
 - MI incidence increased from 1.53/1000PY to 6.01/1000PY in pts exposed to PIs >6 years
 - Adjusted (for other CVD RFs) RR 1.16 per yr of exposure
- Specific medications
 - DAD and SMART studies
 - recent (but not cumulative) use of abacavir was related to increased in rate of MI

Specific Biomarkers

- Biomarkers:
 - Elevated IL-6 and D-dimer levels related to all-cause mortality (Kuller et al., 2006)
 - hsCRP independently associated with AMI after controlling for conventional risk factors (OR 2.13, 1.92-2.37, $p < 0.001$) (Triant et al., 2009)

SMART Study: Association of IL-6 and D-dimer with Mortality / CVD in HIV+ Patients

- Analysis of changes in inflammatory and coagulation markers
 - N=250 from DC and VS arms, 85 who died and 136 with CVD
- IL-6 and D-dimer levels related to mortality and CVD
 - IL-6: All cause OR 12.6 (p<0.0001); CVD OR 2.8 (p=0.003)
 - D-dimer: All cause OR 13.3 (p<0.00001); CVD OR 2.0 (p=0.06)
- HIV RNA may increase CVD risk by increasing tissue factor transcription (via IL-6) which initiates a coagulation cascade (via D-dimer) in vascular endothelium

* DC patients on ART at baseline with HIV RNA ≤ 400 copies/mL.

Kuller L, et al. 15th CROI; Boston, MA (2008); Abst. 139.

Preclinical Atherosclerosis

- HIV infection was associated with greater cIMT (p< 0.0001), even after adjusting for traditional CVD risk factors and demographic variables
- similar to changes usually seen in smokers (Grunfeld et al., 2009)
- cIMT increased progressively over time after ART initiation and did not differ by regimen prescribed (Van Vonderen et al., 2009)

FRAM 2 cIMT¹ Study

HIV Infection is an Independent Risk for Atherosclerosis Similar in Magnitude to Traditional CVD Risk Factors

- Cross-sectional study
- Evidence of pre-clinical atherosclerosis

	HIV+ (n=433)	Controls (n=5479)
Internal cIMT (mm)	1.17	1.06 (P<0.0001)

- After adjusting for demographics and CVD risk factors, HIV infection has more atherosclerosis than controls
 - Difference 0.15 mm (P=0.0001)
- HIV infection similar to traditional CV risk factors (Table)

Estimated Effect of	Difference in Internal cIMT (mm)*
HIV infection	0.15
Current smoker	0.17
Past smoker	0.09
Age (per 10 yr)	0.16
Male [†]	0.13
Diabetes	0.12
Systolic BP	0.05

* P < 0.001 for all values
[†] Significant gender interaction (women > men)

"Independent association of HIV infection with atherosclerosis should be taken into account when counseling HIV-infected patients with regard to their CVD risk factors."

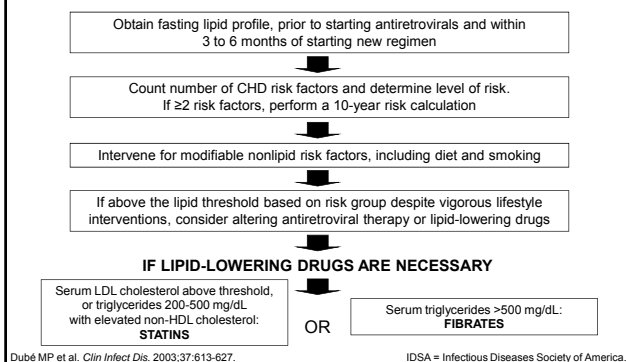
¹ Carotid intima medial thickness

Grunfeld C., CROI 2009; 146

Clinical Management of HIV Patients with CVD Risk

- Maintaining HIV viral suppression may be a critical aspect of CVD risk management
- Traditional CVD risk factors need to be identified and addressed
- ART modification may be considered, while maintaining virologic suppression

IDSA Guidelines: General Approach to CV Risk in HIV Positive Patients



Calculating Framingham Risk

NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The risk assessment tool below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age: years
 Gender: Female Male
 Total Cholesterol: mg/dL
 HDL Cholesterol: mg/dL
 Smoker: No Yes
 Systolic Blood Pressure: mm/Hg
 Currently on any medication to treat high blood pressure: No Yes

Available at: <http://ho2010.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof>, Accessed September 25, 2008.

Strategies for Managing CVD Risk

- Lifestyle changes
 - Smoking cessation
 - Diet and weight management
- Earlier initiation of ART
 - Current guidelines reflect this change
- ASA as primary prevention??
 - No evidence to support this in HIV-infected patients

Strategies for Managing CVD Risk

- Use of Lipid-lowering Agents
 - Statins must be used carefully as drug-drug interactions may occur
 - One retrospective study (N=700)
 - Atorvastatin, pravastatin, rosuvastatin

NCEP ATP III Lipid Management Goals

Risk Category	CHD Risk Factors or Equivalents	LDL Goal, mg/dL	Non-HDL Goal, mg/dL
Very high	High risk + recent acute coronary syndrome, diabetes, smoking, metabolic syndrome*	< 70	< 100
High	CAD or risk equivalent (10-yr risk > 20%)	< 100 (optional < 70)	< 130
Moderately high	≥ 2 risk factors + (10-yr risk 10% to 20%)	< 130	< 160
Moderate	≥ 2 risk factors + (10-yr risk < 10%)	< 130	< 160
Low	0-1 risk factor	< 160	< 190

National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III final report. Circulation. 2002;106:3143-3421. Grundy SM, et al. Circulation. 2004;110:227-239.

Case Study: Kenneth

CVD Risk Factors

- Male gender, smoking, glucose intolerance, elevated BMI, elevated cholesterol, family history, ?ART, ?HIV

Estimated Risk

- Framingham Risk Score
- Moderate Risk: 16%

CVD Risk Reduction

- Smoking cessation, exercise, weight loss, ?statin, ?daily ASA, ?regimen change



Cardiovascular Risk Factor Knowledge, Perceived Risk and Actual Risk in HIV-infected Adults

(Cioe, 2012)

Purpose

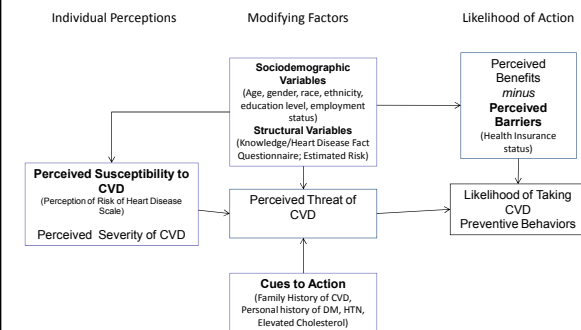
- To describe cardiovascular risk factor knowledge and CVD risk perception in a cohort of HIV-infected adults

Specific Aims

- 1. to describe: the estimated risk of CVD; the perceived risk of CVD; and, the level of risk factor knowledge in HIV-infected adults
- 2. to describe the relationship between estimated and perceived risk of CVD in HIV-infected adults
- 3. to examine the influence of CVD risk factor knowledge on perceived risk of CVD in a sample of HIV-infected adults

Theoretical Framework: Health Belief Model

(Adapted from Stetcher, V. & Rosenstock, IM., 1997)



Design & Procedures

- Descriptive study, cross-sectional design
- One study visit - face-to-face interviews
- Laboratory data were obtained from the medical record
- IRB approval was obtained at UMMS and at RI Hospital
- Study procedure and instruments were piloted with 9 participants

Sample and Setting

- Convenience sample – 130 adult participants
- Recruited from 2 hospital-based HIV clinics in RI
- Recruitment took place as patients presented to clinic for their scheduled appointments
- 40 individuals were screened but not recruited for participation

Inclusion & Exclusion Criteria

- Inclusion Criteria:
 1. males & females over age 18
 2. HIV-infected per the medical record
 3. able to read and speak English
 4. ability to give written informed consent
- Exclusion Criteria:
 1. unable to read and understand English
 2. Had an established dx of CVD (AMI or CVA) in medical record
 3. Had a past CVD event (MI or stroke) or intervention (CABG, stent placement, vascular surgery)

Measures/Instruments

- **Perceived Susceptibility:**
 - Perception of Risk of Heart Disease Scale; alpha = .78 in this sample (Amour & Neuberger, 2008)
- **Structural Variables:**
 - **Knowledge:** Heart Disease Fact Questionnaire; alpha = .74 in this sample (Wagner, Lacey, Chyun, & Abbott, 2006)
 - Estimated Risk: Framingham Risk Score
- **Sociodemographic Variables:**
 - Age, gender, race, ethnicity, education level, employment status
- **HIV Clinical Variables:**
 - Duration of HIV infection, antiretroviral medications, CD4, viral load, Nadir CD4
- **Cues to Action:**
 - FH of CVD, Personal History of DM, HTN, Elevated cholesterol
- **Perceived Barriers:**
 - Health insurance status

Data Analysis

- Descriptive stats (frequencies, means, SDs, percentages) were calculated for all demographic data
- Pearson correlation statistic was used to describe the relationship between estimated and perceived risk of CVD
- Linear regression was used to examine the influence of RF knowledge on perceived risk of CVD
- Statistical significance was accepted at the 95% confidence interval level ($p < .05$)
- All statistics were performed using SPSS Version 17.0

Demographics of Sample (N=130)

Mean Age (in years)	48.0 (range 22-67, SD 8.4)
Race/Ethnicity	
White	54 (41.5%)
Black	41 (31.5%)
Hispanic	31 (23.8%)
Gender	
female	48 (36.9%)
male	82 (63.1%)
Years of Education, mean	11.8 (range 4-19; SD 2.7)
Years since HIV diagnosis	14.7 (range 1-30; SD 8.0)
Current Smokers	74 (56.9%)

Clinical Variables

- Clinical Variables:
 - Currently on ART: 87%
 - Mean CD4: 546
 - Undetectable viral load: 71.5%
 - HCV AB+: 49%
 - Taking methadone or suboxone: 12%
- CVD Risk Factor Variables:
 - 48.5% had a mean BP consistent with a diagnosis of pre-hypertension (120 -139 systolic or 80 - 89 diastolic)
 - Only 7% of participants were involved in smoking cessation efforts
 - 76.2% of participants reported never discussing CVD risk with their HCP

Results

■ T chol	170	(SD 36)	■ Daily ASA	7%
■ LDL	97	(SD33)	■ Diabetes Dx	10%
■ HDL	44	(SD 17)	■ Taking a statin	8.5%
■ FPG	96	(SD 25)		
■ BMI	27	(SD 5.5)		

Estimated and Perceived Risk Risk Factor Knowledge

- Framingham risk score
 - Mean FRS = 7.87 (SD 6.0, range 1-25)
 - 1/3 of participants had FRS in moderate or high risk categories (>10% risk)
- Perceived risk of heart disease
 - Mean = 53.1 (SD 5.8, range 27-68)
- Heart Disease Fact Questionnaire
 - Mean = 19.0 (SD 3.5, range 6-25)

CVD Risk Factor Knowledge

97.7%

- Being overweight increases a person's risk for heart disease

96.9%

- Smoking is a risk factor for heart disease

91.5%

- High cholesterol is a risk factor for developing heart disease

90.8%

- Regular physical activity will lower a person's chance of getting heart disease

Correlation and Prediction

Estimated and perceived risk were significantly correlated, though weakly

$$(r(126) = .24, p = .01)$$

Controlling for age, risk factor knowledge was not predictive of perceived risk

$$(F(1, 117) = .13, p > .05)$$

Limitations and Strengths

Limitations of Study

- Convenience sample
- Cross-sectional analysis
- Self-report/interview format
- Generalizability
- Instruments used

Strengths of Study

- First study to measure CVD risk factor knowledge and perceived risk in HIV infected adults
- Low level of missing data (<5%)

Conclusions

- HIV-infected patients in the U.S. are living longer due to the efficacy of antiretroviral therapy
- CVD has emerged as an important cause of death in this population
- Increased lifespan of HIV-infected patients has increased focus on management of comorbid conditions, including CVD
- Increasing evidence suggests a relationship between HIV infection, ART, and traditional risk factors, leading to an increased risk in this population

Conclusions/Implications

- Traditional risk factors (smoking, prehypertension, and being overweight) are highly prevalent
- Despite a fair level of RF knowledge, knowledge did not inform perception of risk
- Research and efforts to improve CV risk perception and risk factor knowledge are needed
- Innovative interventions to reduce risk in this population need to be developed
- Nurses are in a pivotal position to optimize the management and reduction of CVD risk in this population

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Acknowledgments

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Thank you!

Questions/Comments??