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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

# Stimulating High Impact HIV-Related Cardiovascular Research

## Recommendations From a Multidisciplinary NHLBI Working Group on HIV-Related Heart, Lung, and Blood Disease

Monica R. Shah, MD,* Nakela Cook, MD, MPH,* Renee Wong, PhD,* Priscilla Hsue, MD,† Paul Ridker, MD,‡ Judith Currier, MD, MPH,§ Susan Shurin, MD‖

**ABSTRACT**

The clinical challenges confronting patients with human immunodeficiency virus (HIV) have shifted from acquired immunodeficiency syndrome (AIDS)-related illnesses to chronic diseases, such as coronary artery disease, chronic lung disease, and chronic anemia. With the growing burden of HIV-related heart, lung, and blood (HLB) disease, the National Heart, Lung, and Blood Institute (NHLBI) recognizes it must stimulate and support HIV-related HLB research. Because HIV offers a natural, accelerated model of common pathological processes, such as inflammation, HIV-related HLB research may yield important breakthroughs for all patients with HLB disease. This paper summarizes the cardiovascular recommendations of an NHLBI Working Group, Advancing HIV/AIDS Research in Heart, Lung, and Blood Diseases, charged with identifying scientific priorities in HIV-related HLB disease and developing recommendations to promote multidisciplinary collaboration among HIV and HLB investigators. The working group included multidisciplinary sessions, as well as HLB breakout sessions for discussion of disease-specific issues, with common themes about scientific priorities and strategies to stimulate HLB research emerging in all 3 groups. (J Am Coll Cardiol 2015;65:738–44) © 2015 by the American College of Cardiology Foundation.

Tremendous progress in the treatment of human immunodeficiency virus (HIV) has led to increased survival and a dramatic evolution of the disease (1). The clinical challenges confronting the population have now shifted from acquired immunodeficiency syndrome (AIDS)-related illnesses to chronic diseases, such as coronary artery disease, chronic obstructive lung disease, and chronic anemia (2–7). Many studies have demonstrated that the risk of developing cardiovascular (CV) disease in the HIV-positive population is significantly higher, and disease progression may be accelerated compared with in the general population (8–14). Factors that potentially contribute to the pathophysiology of HIV-related CV disease include the HIV virus itself, adverse effects of antiretroviral therapy (ART), and processes such as aging, inflammation, immune activation, microbial translocation, endothelial injury, and disordered coagulation (15–19). These unique features, along with a large burden of traditional risk factors that include cigarette smoking, hypertension, metabolic syndrome, and dyslipidemia, contribute to the increased CV risk in the HIV population (20–26).

From the *National Heart, Lung, and Blood Institute, Bethesda, Maryland; †Division of Cardiology, University of California–San Francisco School of Medicine, San Francisco, California; ‡Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard University School of Medicine, Boston, Massachusetts; §Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine, UCLA, Los Angeles, California; and the ‖National Cancer Institute, Bethesda, Maryland. Dr. Hsue has received consulting fees from Gilead and Amgen. Dr. Ridker is listed as a coinventor on patents held by the Brigham and Women's Hospital and licensed to Seimens and AstraZeneca relating to the use of inflammatory biomarkers in cardiovascular disease and diabetes. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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With the growing burden of HIV-related heart, lung, and blood (HLB) disease, the National Heart, Lung, and Blood Institute (NHLBI) recognizes that it must stimulate and support research that addresses how the chronic phase of HIV affects the HLB systems. Also, because HIV offers a natural, accelerated model of common pathological processes, such as inflammation, HIV-related HLB research has the potential to yield important breakthroughs for all patients with HLB disease. Recently, the NHLBI assessed its AIDS scientific portfolio and determined that it needed to stimulate more peer-reviewed research in HIV-related HLB disease. The first step to encourage more peer-reviewed research was to identify the scientific priorities in the field to guide investigators. Although a small group of investigators has been pioneering this field for years, the NHLBI also recognized the need to develop a larger multidisciplinary scientific community to carry out research in the future. This paper and the Online Appendix summarize the CV recommendations of an NHLBI Working Group (WG), entitled Advancing HIV/AIDS Research in Heart, Lung, and Blood Diseases, which was charged with both identifying scientific priorities in HIV-related HLB disease and developing recommendations to promote multidisciplinary collaboration among HIV and HLB investigators (27).

**OVERVIEW OF THE NHLBI WG.** The WG included basic and clinical researchers with scientific expertise in HIV and HLB disease, as well as representatives from the NHLBI, the National Institutes of Health (NIH) Office of AIDS Research, the Center for Scientific Review, and other NIH institutes and centers. WG participants were asked to identify the top scientific priorities in HIV-related HLB disease, recommend research approaches to address identified critical research gaps, and develop strategies to promote collaboration and partnerships among the HIV and HLB scientific communities.

The group addressed specific HIV-related HLB diseases, as well as on cross-cutting multiorgan and multidisciplinary themes. The CV group focused on HIV-related coronary artery disease (CAD), the pulmonary group centered on HIV-related chronic obstructive pulmonary disease and pulmonary hypertension, and the hematology group addressed HIV-related anemia and the role of hematopoietic stem and progenitor cells, both as potential reservoirs and potential cures for the disease. Common themes that emerged from the conference included the role of inflammation, direct effects of organisms and medications, and barriers to multidisciplinary and cross-institutional collaboration.

The CV group focused on the specific question "Why does CAD occur at such high rates in patients with HIV?" In the following sections, we review the scientific priorities in HIV-related CV disease identified by the WG and the strategies that they proposed to advance research in the field.

## METHODS

During the 2-day meeting, participants were charged with refining the primary question, identifying the related scientific gaps, and developing research approaches to address the gaps. The participants were encouraged to consider basic, clinical, and population science research approaches. The preliminary recommendations were presented to the larger group, and further refined and consolidated into a final set of CV recommendations.

In addition, the WG was asked to provide recommendations on how to stimulate more HIV-related CV research to further develop this emerging field, including identifying operational challenges to multidisciplinary research, developing strategies to enhance collaboration and engage new investigators, and highlighting ways to leverage existing research resources.

## RESULTS

**SCIENTIFIC THEMES.** The top scientific priorities focused on epidemiology, pathogenesis, and prevention and treatment. The scientific recommendations are discussed by category in the following text and listed in the **Central Illustration**.

**Epidemiology.** The WG observed that although there is growing evidence that the incidence and prevalence of CAD in HIV patients may be higher than in noninfected people, the actual rate of CAD in the HIV-infected population, and how it compares with the noninfected population, is still not well established (28–31). Some of the limitations of previous studies included small numbers of HIV-infected patients, a deficiency of rigorously adjudicated of CV events, and inconsistent adjustment for confounding factors, such as smoking, that occur at much higher rates in the HIV population. The WG also noted that there was not enough information to fully understand the contributions to HIV-related CAD of traditional risk factors, such as hyperlipidemia, hypertension, and smoking versus the detrimental effects of the HIV virus itself, associated inflammation, ART, and coinfections (32,33).

The WG identified the following major knowledge gaps in the epidemiology of HIV-related CAD: 1) the

**ABBREVIATIONS AND ACRONYMS**

**AIDS** = acquired immunodeficiency syndrome

**ART** = antiretroviral therapy

**CAD** = coronary artery disease

**CV** = cardiovascular

**HIV** = human immunodeficiency virus

**HLB** = heart, lung, and blood

**NHLBI** = National Heart, Lung, and Blood Institute

**NIH** = National Institutes of Health

**WG** = working group

**CENTRAL ILLUSTRATION** **Identified Scientific Gaps in HIV-Related CAD and Recommended Research Approaches**

| EPIDEMIOLOGY | PATHOPHYSIOLOGY | PREVENTION AND TREATMENT |
|---|---|---|
| **Scientific Gaps**<br>• Incidence and prevalence of coronary artery disease (CAD) in patients with HIV<br>• Interplay of HIV, inflammation, antiretroviral therapy (ART), coinfections, and traditional risk factors on development of CAD<br>• Impact of sex and race on clinical outcomes | **Scientific Gaps**<br>• Mechanisms of the interplay of HIV, inflammation, ART, coinfections, and traditional risk factors in development and progression of CAD<br>• Molecular pathways underlying chronic inflammation in HIV<br>• Impact of microbial translocation, viral reactivation, replication, and production on lipid metabolism, endothelial function, immune senescence, and thrombosis<br>• Synergistic effects of smoking on mechanisms underlying HIV-related CAD<br>• Mechanisms of HIV-related coagulation and platelet abnormalities, and thrombosis<br>• Novel targets for therapy in HIV-related CAD<br>• Need for better animal and molecular models<br>• Characterization of atherosclerotic plaque in HIV patients | **Scientific Gaps**<br>• Potential differences in the prevention and treatment of HIV-related CAD<br>• Efficacy and effectiveness of evidence-based CV therapies in HIV patients<br>• Novel therapies to address unique pathophysiology of HIV-related CAD |
| **Recommended Approaches to Gaps**<br>• Consolidate current knowledge through reviews and meta-analyses<br>• Utilize current HIV and cardiovascular (CV) studies to examine questions about HIV-related CAD<br>• Add and adjudicate CV events (CAD, venous thrombosis, pulmonary embolism) in HIV cohort studies to detect general trends by leveraging cohorts with large numbers of HIV patients<br>• Enrich CV cohort studies with HIV patients to allow for detailed assessment of CAD rates and the relative contributions of traditional and HIV-specific risk factors on the development of CAD<br>• Examine long-term outcomes and determinants of outcomes following CV events<br>• Conduct studies evaluating HIV-related CV disease in women and minorities, and address health disparities | **Recommended Approaches to Gaps**<br>• Combine pre-clinical development of resources with hypothesis-generating research<br>• Develop more robust animal models to explore the relationship between HIV-related inflammation and atherosclerosis<br>• Pursue mechanistic studies evaluating the role of inflammation, microbial translocation, and immune activation in HIV-related CAD | **Recommended Approaches to Gaps**<br>• Add CV outcomes to HIV trials to understand the effects of HIV interventions on CAD<br>• Increase enrollment of HIV patients into CV trials<br>• Collaborate with HIV trial networks early during protocol development to address CV questions<br>• Conduct pilot trials of interventions addressing novel risk factors in HIV-related CAD, which could be further tested in larger studies that include HIV and non-HIV populations<br>• Develop best practices to incorporate HIV testing into clinical trials<br>• Leverage existing CV databases, claims data, and electronic health records to evaluate patterns of care in the prevention, diagnosis, and treatment of HIV-related CAD, post-event outcomes, and implementation of evidence-based CV therapies in the HIV population |

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HIV = human immunodeficiency virus.

actual incidence and prevalence of HIV-related CAD; 2) the contributions of various risk factors to the development of HIV-related CAD; 3) the long-term outcomes and determinants of outcomes following HIV-related CV events; and 4) the unique features of HIV-related CV disease in women and minorities, who are disproportionately affected by HIV. The WG suggested addressing the identified gaps by: 1) pursuing meta-analyses of current studies to fully utilize available data to estimate the incidence and prevalence of HIV-related CV disease; 2) leveraging existing HIV and CV studies to examine the epidemiology of HIV-related CAD; 3) including CV endpoints in existing HIV cohort studies and adjudicating these events—potential cohort studies included CNICS (Centers for AIDS Research Network of Integrated Clinical Systems), MACS (Multi-Center AIDS Cohort Study), the WIHS (Women's Interagency HIV Study), and VACS (Veterans Aging Cohort Study); and 4) actively recruiting HIV-positive patients in future CV cohort studies and identifying patients with HIV who may already have been recruited in current cohorts.

**Pathophysiology.** The WG noted that HIV might alter and potentially accelerate the natural history of the fundamental processes underlying atherosclerosis, endothelial dysfunction, and thrombosis (34-45). The participants also observed that the mechanisms by which HIV and ART may modify these processes have still not been fully elucidated. In their discussions, the WG identified the following critical basic science research gaps: 1) the mechanisms by which HIV, inflammation, ART, coinfections, and traditional risk factors interact in HIV-related CAD; 2) the molecular pathways underlying persistent chronic inflammation in treated HIV, and the

role of microbial translocation and viral reactivation, replication, and production in altering lipid function and metabolism, endothelial function, immune senescence, and thrombosis; 3) understanding whether the unique pathophysiology of HIV-related CAD offered distinct therapeutic targets; 4) the synergistic effects of smoking on the pathophysiological mechanisms contributing to HIV-related CAD, including abnormalities in coagulation and thrombosis; and 5) the characterization of the atherosclerotic plaque in HIV-related CAD through angiography and imaging.

The WG suggested the following approaches to address the identified basic science gaps: 1) develop more robust animal models to better elucidate mechanisms of HIV-related CAD; 2) conduct basic science investigations to understand how inflammation, immune dysfunction, dyslipidemia and other comorbidities, and gut microbial translocation contribute to HIV-related CAD; 3) pursue basic research evaluating how ART may lead to direct and indirect toxic effects on the vascular endothelium; and 4) conduct imaging studies to better understand the pathogenesis of HIV-related CAD.

**PREVENTION AND TREATMENT.** The WG noted that there was an urgent need for evidence from randomized clinical trials to effectively prevent and treat HIV-related CAD (46–50). The WG recommended pursuing both pilot studies with CV surrogate endpoints to provide preliminary data on novel agents, and large-scale randomized trials with clinical outcome endpoints to evaluate evidence-based CAD therapy in the HIV population. The WG identified the following critical scientific priorities in the prevention and treatment of HIV-related CAD: 1) demonstrate the safety, efficacy, and effectiveness of evidence-based therapies for HIV-related CAD; 2) test novel clinical interventions to prevent and treat HIV-related CAD in the HIV population; and 3) conduct pilot studies in the HIV population addressing inflammation and other novel CV risk factors that could be further tested in a larger phase trial that would include both HIV and non-HIV populations. The WG recommended addressing the research gaps in the prevention and treatment of HIV-related CAD by: 1) including CV outcomes in trials testing interventions for HIV to understand the effects of HIV therapies on the development of CAD; 2) collaborating with HIV-related clinical trial networks and investigators early during protocol development to ensure that trials are adequately powered to detect a meaningful difference in CV outcomes; 3) increasing the enrollment of HIV patients into CV intervention trials, to better assess the safety of interventions when performing subgroup analyses; 4) incorporating HIV testing into screening and randomization procedures to ensure that patients with HIV are identified; and 5) leveraging existing CV and HIV databases to pursue outcomes research evaluating patterns of care in the prevention, diagnosis, and treatment of HIV-related CAD, post-event outcomes, and implementation of evidence-based care.

**RESEARCH STRATEGY THEMES.** The WG strongly endorsed enhanced communication, collaboration, and teamwork among investigators from the HIV and HLB scientific communities, as well as among the NIH institutes and centers, to effectively address HIV-related HLB disease. Specific recommendations were as follows:

**Communication; collaboration and teamwork; leveraging resources; and training.** The WG urged engaging both CV and HIV professional societies to raise awareness in their scientific communities about this emerging field. The WG recommended expanding the involvement of CV investigators in current HIV research networks to broaden network expertise and promote multidisciplinary communication. The WG participants also suggested developing a centralized resource for the scientific community to access information about the NHLBI AIDS program and opportunities for research and funding. In addition, the WG advised the NHLBI to promote scientific partnerships by ensuring that any potential funding opportunities included multidisciplinary collaboration as part of the review criteria.

Another major research strategy theme was to leverage available NIH programs, including existing cohort studies, clinical trials, and biorepositories. The WG recommended enriching HIV cohorts with adjudicated CV endpoints and increasing the enrollment of HIV patients into CV studies.

The WG recognized that in order for the field to advance, there needed to be concerted efforts to develop a scientific community with expertise in both HIV and CV disease. The WG encouraged investing resources in training early stage investigators and developing funding opportunities that would encourage multidisciplinary mentorship and collaboration among the HIV and CV scientific communities. The WG suggested that early-stage HIV and CV investigators receive cross-disciplinary training to learn fundamental skills in both fields.

**NHLBI AIDS PROGRAM: EVALUATING PERFORMANCE.** After receiving the WG recommendations, the NHLBI staff recognized the importance of developing a system to evaluate whether the AIDS program effectively stimulates high quality peer-reviewed research

(51,52). The first step in this process was to collectively develop performance measures to gauge how well the AIDS portfolio was being stimulated. The performance measures included the number of new HIV-related HLB peer-reviewed applications and awards, and whether applications and awards addressed the identified scientific gaps. Other performance measures included the number of new investigators entering the field and whether the supported research led to publications, citations, or changes in clinical practice guidelines. The NHLBI AIDS team also determined that regular portfolio analyses and assessment of performance measures were essential to promote a continuous cycle of learning and improvement of the AIDS program. Regular systematic reviews would allow the NHLBI to refine approaches on how best to stimulate peer-reviewed HIV-related HLB research, identify future scientific priorities, and make evidence-based decisions about future research investments.

## CONCLUSIONS AND DISCUSSION

The increased survival of patients with HIV has reshaped the urgent public health needs of this population and triggered new research questions and scientific priorities. The NHLBI has a unique opportunity and an important mandate to take a leadership role in responding to the evolving research demands of HIV-related HLB disease. The WG recommendations laid the foundation for the next phase of the NHLBI AIDS program by identifying the key scientific priorities and strategic gaps that needed to be addressed in order to effectively stimulate HIV-related HLB research. In response to the WG recommendations, the NHLBI has developed an NHLBI AIDS website, made public presentations at professional meetings, such as the American Heart Association and the Conference on Retroviruses and Opportunistic Infections, released broad-based, multidisciplinary basic science and clinical research funding opportunities in HIV-related HLB disease, funded studies in HIV patients that evaluate CV interventions being tested in non-HIV populations, and launched the largest HIV-related CV randomized clinical trial to date (53–60). These collaborative efforts and actions have resulted in growth in the NHLBI AIDS scientific portfolio—including an increase in the number of peer-reviewed HIV-related HLB applications and awards, and a rise in the number of investigators entering the field. Importantly, the NHLBI is funding multidisciplinary partnerships between HIV and HLB investigators and is partnering with other NIH institutes to support large HIV-related HLB scientific programs and clinical trials. Finally, the NHLBI is regularly reviewing and assessing its HIV-related HLB scientific portfolio to assess progress, cultivate new areas for research, and plan for the future.

The WG was a pivotal event in the launch of the next chapter of the NHLBI AIDS program. Guided by the WG recommendations, the NHLBI will continue its efforts to stimulate innovative research, develop multidisciplinary scientific partnerships, and support cutting edge discoveries in HIV-related HLB disease. In making these valuable research investments, the NHLBI looks forward to invaluable returns—improved survival and quality of life, not only for patients with HIV, but for all patients with HLB disease.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Monica R. Shah, National Heart, Lung, and Blood Institute, 6701 Rockledge Drive, Room 8173, Bethesda, Maryland 20892-7956. E-mail: shahmr@nhlbi.nih.gov.

## REFERENCES

**1.** Centers for Disease Control and Prevention. HIV/AIDS statistics overview. Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, Sexual Transmitted Diseases and Tuberculosis Prevention, Centers for Disease Control and Prevention. November 10, 2014. Available at: http://www.cdc.gov/hiv/statistics/basics/index.html. Accessed December 9, 2014.

**2.** Lewden C, May T, Rosenthal E, et al., ANRS EN19 Mortalité Study Group and Mortavic1. Changes in causes of death among adults infected HIV between 2000 and 2005: "the Mortalite 2000 and 2005" surveys (ANRS EN19 and Mortavic). J Acquir Immune Defic Syndr 2008;48:590–8.

**3.** Schwarcz SK, Vu A, Hsu LC, et al. Changes in causes of death among persons with AIDS: San Francisco, California, 1996-2011. AIDS Patient Care STDS 2014;28:517–23.

**4.** Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1 infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis 2010;50:1387–96.

**5.** Palella FJ Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43:27–34.

**6.** Redig AJ, Berliner N. Pathogenesis and clinical implications of HIV-related anemia in 2013. Hematology Am Soc Hematol Educ Program 2013;2013:377–81.

**7.** So-Armah K, Freiberg MS. Cardiovascular disease risk in an aging HIV population: not just a question of biology. Curr Opin HIV AIDS 2014;9:346–54.

**8.** Althoff KN, McGinnis KA, Wyatt CM, et al., for the Veterans Aging Cohort Study (VACS). Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS defining cancer in HIV-infected versus uninfected adults. Clin Infect Dis 2014 Oct 30 [E-pub ahead of print].

**9.** Boccara F, Lang S, Meuleman C, et al. HIV and coronary heart disease: time for a better understanding. J Am Coll Cardiol 2013;61:511–23.

**10.** Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J 2014;35:1373–81.

**11.** Lang S, Mary-Krause M, Cotte L, et al., French Hospital Database on HIV-ANRS CO4. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. AIDS 2010;24:1228–30.

**12.** Triant VA, Lee H, Hadigan C, et al. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab 2007;92:2506–12.

**13.** Frieberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med 2013;173:614–22.

**14.** Baker JV, Lundgren JD. Cardiovascular implications from untreated human immunodeficiency virus infection. Eur Heart J 2011;32:945–51.

**15.** Ho JE, Scherzer R, Hecht FM, et al. The association of CD4+ T-cell counts and cardiovascular risk in treated HIV disease. AIDS 2012;26:1115–20.

**16.** Ipp H, Zemlin A. The paradox of the immune response in HIV infection: when inflammation becomes harmful. Clin Chim Acta 2013;416:96–9.

**17.** de Gaetano Donati K, Rabagliati R, Iacoviello L, et al. HIV infection, HAART, and endothelial adhesion molecules: current perspectives. Lancet Infect Dis 2004;4:213–22.

**18.** Gresele P, Falcinelli E, Sebastiano M, et al. Endothelial and platelet function alterations in HIV-infected patients. Thromb Res 2012;129:301–8.

**19.** Eugenin EA, Morgello S, Klotman ME, et al. Human immunodeficiency virus (HIV) infects human arterial smooth muscle cells in vivo and in vitro: implications for the pathogenesis of HIV-mediated vascular disease. Am J Pathol 2008;172:1100–11.

**20.** Panel of experts from the Metabolic Disorders Study Group (GEAM), National AIDS Plan (SPNS), AIDS Study Group (GeSIDA). Executive summary of the consensus document on metabolic disorders and cardiovascular risk in patients with HIV infection. Enferm Infecc Microbiol Clin 2015;33:41–7.

**21.** Calvo M, Martinez E. Update on metabolic issues in HIV patients. Curr Opin HIV AIDS 2014;9:332–9.

**22.** Niaura R, Chander G, Hutton H, et al. Interventions to address chronic disease and HIV: strategies to promote smoking cessation among HIV-infected individuals. Curr HIV/AIDS Rep 2012;9:375–84.

**23.** Jallow A, Ljunggren G, Wandell P, et al. Prevalence, incidence, mortality and co-morbidities amongst human immunodeficiency virus (HIV) patients in Stockholm County, Sweden: the Greater Stockholm HIV Cohort study. AIDS Care 2014;Oct 3:1–8.

**24.** Nix LM, Tien PC. Metabolic syndrome, diabetes, and cardiovascular risk in HIV. Curr HIV/AIDS Rep 2014;11:271–8.

**25.** Li Vecchi V, Maggi P, Rizzo M, et al. The metabolic syndrome and HIV infection. Curr Pharm Des 2014;20:4975–5003.

**26.** Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. JAMA 2003;289:2978–82.

**27.** NHLBI AIDS Working Group: Advancing HIV/AIDS Research in Heart, Lung, and Blood Diseases. September 6-7, 2012. Available at: http://www.nhlbi.nih.gov/research/reports/2012-aids-working-group.htm. Accessed December 9, 2014.

**28.** Currier JS, Lundgren JD, Carr A, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation 2008;118:e29–35.

**29.** Boccara F. Cardiovascular complications and atherosclerotic manifestations in the HIV-infected population: type, incidence, and associated risk factors. AIDS 2008;22 Suppl 3:S19–26.

**30.** Kaplan RC, Kingsley LA, Sharret AR, et al. Ten-year predicted coronary heart disease risk in HIV-infected men and women. Clin Infect Dis 2007;45:1074–81.

**31.** Grinspoon SK. Metabolic syndrome and cardiovascular disease in patients with human immunodeficiency virus. Am J Med 2005;118 Suppl 2:23S–8S.

**32.** Baekken M, Os I, Sandvik L, et al. Hypertension in an urban HIV-positive population compared with the general population: influence of combination antiretroviral therapy. J Hypertens 2008;26:2126–33.

**33.** Rotger M, Glass TR, Junier T, et al., for the MAGNIFICENT Consortium, INSIGHT, Swiss HIV Cohort Study. Contribution of genetic background, traditional risk factors, and HIV-related factors to coronary artery disease events in HIV-positive persons. Clin Infect Dis 2013;57:112–21.

**34.** Gibellini D, Borderi M, Clo A, et al. HIV-related mechanisms in atherosclerosis and cardiovascular diseases. J Cardiovasc Med (Hagerstown) 2013;14:780–90.

**35.** Klein D, Hurley LB, Quesenberry CP Jr., et al. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1infection? J Acquir Immune Defic Syndr 2002;30:471–7.

**36.** Krikke M, van Lelyveld SF, Tesselaar K, et al. The role of T cells in the development of cardiovascular disease in HIV-infected patients. Atherosclerosis 2014;237:92–8.

**37.** Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis 2012;205 Suppl 3:S375–82.

**38.** Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: causes and consequences. J Pathol 2008;214:231–41.

**39.** Anzinger JJ, Butterfield TR, Angelovich TA, et al. Monocytes as regulators of inflammation and HIV-related comorbidities during cART. J Immunol Res 2014;2014:569819.

**40.** Wong BW, Meredith A, Lin D, et al. The biological role of inflammation in atherosclerosis. Can J Cardiol 2012;28:631–41.

**41.** Lo J, Plutzky J. The biology of atherosclerosis: general paradigms and distinct pathogenic mechanisms among HIV-infected patients. J Infect Dis 2012;205 Suppl 3:S368–74.

**42.** Hsue PY, Hunt PW, Schnell A, et al. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. AIDS 2009;23:1059–67.

**43.** Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El Sadr WM, Lundgren J, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006;355:2283–96.

**44.** Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. JAMA 2012;308:379–86.

**45.** Stein JH, Currier JS, Hsue PY. Arterial disease in patients with human immunodeficiency virus infection: what has imaging taught us? J Am Coll Cardiol Img 2014;5:515–25.

**46.** Dube MP, Stein JH, Aberg JA, et al., Adult AIDS Clinical Trials Group Cardiovascular Subcommittee, HIV Medical Association of the Infectious Disease Society of America. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and Adult AIDS Clinical Trials Group. Clin Infect Dis 2003;37:613–27.

**47.** Lungren JD, Battegay M, Behrens G, et al., EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. HIV Med 2008;9:72–81.

**48.** Boccara F, Teiger E, Cohen A, et al. Percutaneous coronary intervention in HIV infected patients: immediate results and long term prognosis. Heart 2006;92:543–4.

**49.** Ren X, Trilesskaya M, Kwan DM, et al. Comparison of outcomes using bare metal versus drug-eluting stents in coronary artery disease patients with and without human immunodeficiency virus infection. Am J Cardiol 2009;104:216–22.

**50.** Boccara F, Cohen A, Di Angelantonia E, et al., French Italian Study on Coronary Artery Disease in AIDS Patients (FRISCA-2). Coronary artery bypass graft in HIV-infected patients: a multicenter case control study. Curr HIV Res 2008;6:59–64.

**51.** Lauer MS. Thought exercises on accountability and performance measures at the National Heart, Lung, and Blood Institute (NHLBI): an invited commentary for Circulation Research. Circ Res 2011;108:405–9.

**52.** Friedman M. Performance Accountability. Trying Hard Is Not Good Enough. Santa Fe, NM: FPSI Publishing, 2005.

**53.** National Heart, Lung, and Blood Institute. NHLBI AIDS Program. Available at: https://www.nhlbi.nih.gov/research/funding/aids/. Accessed December 9, 2014.

**54.** RFA-HL-14-024: Basic Research in the Pathogenesis of HIV-Related Heart, Lung, and Blood (HLB) Diseases in Adults and Children (R01). October 23, 2014. Available at: http://grants1.nih.gov/grants/guide/rfa-files/RFA-HL-14-024.html. Accessed December 9, 2014.

**55.** RFA-HL-14-029: Basic Research in the Pathogenesis of HIV-Related Heart, Lung, and Blood

(HLB) Diseases in Adults and Children (R21). October 23, 2013. Available at: http://grants1.nih.gov/grants/guide/rfa-files/RFA-HL-14-029.html. Accessed December 9, 2014.

**56.** RFA-HL-14-023: Clinical Research in the Prevention, Diagnosis, and Treatment of HIV-Related Heart, Lung, and Blood (HLB) Diseases in Adults and Children (R01). October 24, 2013. Available at: http://grants1.nih.gov/grants/guide/rfa-files/RFA-HL-14-023.html. Accessed December 9, 2014.

**57.** Everett BM, Pradhan A, Solomon DH, et al. Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. Am Heart J 2013;166:199–207.

**58.** Ridker PM, Thuren T, Zalewski A, et al. Interleukin-1beta inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). Am Heart J 2011;162:597–605.

**59.** Grinspoon S, Douglas PS. Project information U01HL123336: REPRIEVE-Clinical Coordinating Center. 2014. NIH RePORTER. Available at: http://projectreporter.nih.gov/project_info_description.cfm?aid=8730843&icde=22778856&ddparam=&ddvalue=&ddsub=&cr=4&csb=default&cs=ASC. Accessed December 9, 2014.

**60.** Hoffmann U, Ribaudo H. Project information U01HL123339: REPRIEVE-Data Coordinating Center. 2014. NIH RePORTER. Available at: http://projectreporter.nih.gov/project_info_description.cfm?aid=8730997&icde=22778930&ddparam=&ddvalue=&ddsub=&cr=4&csb=default&cs=ASC. Accessed December 9, 2014.

**KEY WORDS** acquired immunodeficiency syndrome, cardiovascular disease, coronary artery disease, disease progression, inflammation, risk factors

**APPENDIX** For expanded information about the NHLBI AIDS Cardiovascular Working Group, please see the online version of this article.