Lipid Management in Human Immunodeficiency Virus

Merle Myerson, MD, EdD, FACC, FNLA

KEYWORDS

• HIV • Dyslipidemia • Cardiovascular risk factors • Antiretroviral therapy • Infectious diseases

KEY POINTS

- Antiretroviral therapy has changed human immunodeficiency virus (HIV) from a fatal disease to a chronic disease whereby extended and productive life spans are possible.
- People living with HIV are at increased risk for cardiovascular disease partly because of the HIV itself, the use of antiretroviral therapy (ART), and because people are living to an age when cardiovascular disease is more prevalent.
- HIV produces metabolic abnormalities, including dyslipidemia, that are exacerbated by ART.
- Diagnosis and management of dyslipidemia for patients living with HIV are needed to help prevent manifest cardiovascular disease.
- There are no comprehensive guidelines for the treatment of dyslipidemia specific to this population. Existing guidelines for the general population are currently used with modification for use with patients living with HIV.

INTRODUCTION

On June 5, 1981, the *Morbidity and Mortality Weekly Report* published by the Centers for Disease Control and Prevention provided the first report on young, gay men with a rare lung infection, *Pneumocystis carinii* pneumonia, as well as other abnormalities attributed to immune system deficiency.[1] By 1982, the disease had a name, Acquired Immune Deficiency Syndrome (AIDS). Two separate research groups, one led by Dr Robert Gallo of the National Institutes of Health (NIH) and Dr Luc Montagnier of the Pasteur Institute in France, independently reported that a retrovirus could be the cause of AIDS. The virus that each group identified was the same and in 1986 it was given the name *human immunodeficiency virus* (HIV). It was thought that the virus originated in nonhuman primates in West-Central Africa and jumped to humans in the early 1900s.

There was no cure or treatment of HIV, large numbers of those who became infected, mostly gay men, hemophiliacs, Haitians, and intravenous drug users, did not live. In 1987, the Food and Drug Administration (FDA) approved the first antiretroviral drug, zidovudine, which began a new era for those infected with HIV. Opportunistic infections and death were no longer inevitable, and longer and productive life spans were possible. HIV was becoming a chronic disease.

With the advent of antiretroviral therapy (ART) also came a new spectrum of diseases for patients living with HIV. These included diseases related to the metabolic changes brought about by the virus itself, side effects of ART, and that people infected

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Cardiovascular Disease Prevention Program & Lipid Clinic, Cardiology Section, Institute for Advanced Medicine (HIV), Mount Sinai St. Luke's, Mount Sinai Roosevelt, 1111 Amsterdam Avenue, New York, NY 10025, USA
E-mail address: myersonm@optonline.net

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with HIV were living to ages when other diseases, such as cardiovascular disease (CVD), were more prevalent.[2–4]

In response to this, the American Heart Association (AHA) convened a multidisciplinary State of the Science Conference in June of 2007: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS. This conference summarized existing knowledge and outlined key questions and areas where more information was needed to provide optimal care for this patient population.[5]

More recent epidemiologic studies have shown that people infected with HIV have an increased risk of CVD at all ages compared with the general population, which remains even after control of traditional risk factors.[2] This population also has higher rates of smoking and behavioral and social factors that increase the risk.[6,7] It is anticipated that CVD will be the leading cause of morbidity and mortality in this patient population making diagnosis and management of CVD risk factors, in particular dyslipidemia, essential to patient care.[2,3] It is important to note that this need is not yet universal, as access to the more basic needs of diagnosis and treatment with ART remain limited in areas such as Sub-Saharan Africa and many parts of Asia.

This review is intended to provide a brief overview of HIV and ART with a focus on how the virus and the treatment impact on cardiovascular risk, in particular dyslipidemia. Currently, there are no specific and comprehensive guidelines or risk stratification schemes for the management of dyslipidemia in patients infected with HIV; but existing recommendations as well as those for the general population are discussed with suggestions as to how they may be applied to this patient population. Recommendations for the clinician who is taking care of these patients are presented based on established guidelines, evidence from epidemiologic and clinical trials, as well as the clinical experience of this author. Issues for which there is little or no information available are noted to highlight the many gaps in our knowledge regarding cardiovascular care for patients living with HIV.

BACKGROUND

Human Immunodeficiency Virus

The virus infects cells in the immune system, specifically $CD4^+$ T cells, which are white blood cells. After entering the $CD4^+$ T cell, the viral RNA genome is converted (known as reverse transcription) into double-stranded DNA that becomes integrated into the cell nucleus and rapidly replicates. The virus has a high mutation rate making treatment and finding a vaccine challenging.[8,9]

Human Immunodeficiency Virus and Risk for Cardiovascular Disease

Infection with HIV produces a cardiometabolic syndrome consisting of insulin resistance, lipodystrophy (fat maldistribution including increase in abdominal visceral fat), and abnormal lipids (elevated triglycerides and low high-density lipoprotein cholesterol [HDL-C]). Therapy with ART may exacerbate these abnormalities.[5,10,11] The mechanisms of these metabolic abnormalities are complex and interdependent with the impaired glucose metabolism and dyslipidemia partly due to abnormal fat distribution (especially abdominal fat) and inflammation.[12,13]

The role of inflammation in the pathogenesis of atherosclerosis is well known in the general population[14] and is thought to play a significant and unique role in the development of CVD and increased risk in patients infected with HIV.

In the Strategies for Management of Antiretroviral Therapy (SMART) study, patients with CD4 cell counts greater than 350 cells per microliter were randomized to either continuous or intermittent ART. The trial was stopped early as those in the intermittent group had greater opportunistic disease, death from any cause, and major CVD.[15] Follow-up analysis of stored samples from the SMART study showed that inflammatory and coagulation biomarkers, interleukin 6 and D-dimer levels were significantly increased in the intermittent compared with the continuous therapy group and that these levels were strongly related to all-cause mortality.[16] It was hypothesized that therapies that reduce the inflammation response to HIV may be relevant to the care for patients infected with HIV.[16]

Mangili and colleagues[17] examined the association of all-cause mortality in patients infected with HIV and carotid intima-media thickness (cIMT) and high-sensitivity C-reactive protein (hsCRP). The median follow-up time was 3 years; although ART regimens were similar in all, those who died (11.6%) had higher cIMT (>75th percentile) and higher hsCRP. The investigators conclude that abnormal cIMT and elevated hsCRP suggest that inflammation, subclinical atherosclerosis, and immune activation may identify those at higher risk.

Subramanian and colleagues[18] investigated arterial inflammation in 27 HIV-infected people without known cardiac disease. They used PET with ^{18}fluorine-2-deoxy-D-glucose, an imaging method that can measure inflammation in the arterial wall. All participants with HIV were on