REVIEW ARTICLE

HIV and its relationship to insulin resistance and lipid abnormalities

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Antiretroviral therapy has revolutionized the care of people with human immunodeficiency virus (HIV) by reducing morbidity and mortality from acquired immunodeficiency syndrome–related conditions. Despite longer life expectancy, however, HIV-infected individuals continue to have a higher risk of death compared with the general population. This has been attributed to the increasing incidence of noncommunicable diseases, in particular, atherosclerotic cardiovascular diseases. This is driven, in part, by the emergence of metabolic disorders, particularly dyslipidemia, insulin resistance, and lipodystrophy, in those on antiretroviral therapy. The pathogenesis of these metabolic derangements is complex and multifactorial, and could be a consequence of an interplay between traditional age-related risk factors, HIV infection, antiretroviral therapy effects, and the inflammatory state and immune activation in this population. Understanding the contributions of each of these factors could not just impact the current management of these individuals and help mitigate the risk for premature cardiovascular disease, but also shape the future direction of research in HIV. (Translational Research 2017;■:1–15)

Abbreviations: ■ = ■■

BACKGROUND

The introduction of very potent and well-tolerated antiretroviral drugs and convenient once daily regimens has changed the natural history of human immunodeficiency virus (HIV)–infected individuals. HIV, an infection associated with the once uniformly fatal acquired immunodeficiency syndrome (AIDS), has now become a chronic condition for individuals on effective combination antiretroviral therapy (cART).[1] With HIV-related deaths on a decline, the life expectancy of newly diagnosed HIV-infected individuals now approach that of the general population. However, the age-dependent mortality of HIV-infected individuals remains higher compared with the general population.[2,3] This is, in a large part, attributable to noncommunicable and non-HIV–related conditions, particularly atherosclerotic cardiovascular diseases, that have been emerging as a significant cause of morbidity and mortality in the well-controlled HIV-infected population.[4,5] The purported mechanism of this increased cardiovascular risk among HIV-infected individuals is multifactorial, and results from traditional age-related cardiovascular risk factors,[6] HIV infection itself,[7,8] metabolic and body composition changes induced by antiretroviral therapy,[9,10] and the inflammatory state induced by HIV infection and other chronic infections that may coexist in this population.[11]

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Central to the pathophysiology of cardiovascular disease in HIV-infected individuals are 2 metabolic derangements—dyslipidemia and insulin resistance (IR)—that may result from the complex interplay between the aging host, the virus, host inflammation, and antiviral therapy.[12]

Before the introduction of antiretroviral therapy, a pattern of dyslipidemia was often seen in uncontrolled HIV-infected individuals characterized by high triglyceride level and low levels of total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C),[13-15] leading to an unfavorable TC/HDL ratio. Both high HIV viremia and lower CD4 lymphocyte count are independently associated with lower HDL-C levels, whereas HIV viremia itself is associated with reduced levels of LDL-C and increased levels of very low-density lipoprotein (VLDL) and triglycerides.[16] How this pattern of dyslipidemia develops in HIV individuals is not yet fully understood but is believed to be from direct effects of HIV infection itself and inflammation. Treatment with cART has led to successful long-term suppression of HIV, reduction in inflammation, and restoration to health. However, a different pattern of dyslipidemia characterized by elevated TC, TG, and LDL-C, and low HDL-C, has emerged with the use of cART. Moreover, IR, a state where the concentration of insulin needed to maintain normal glucose surpasses physiological levels, has also been observed in well-controlled and treated HIV-infected individuals. In those taking older generations of antiretroviral therapy, a specific form of body fat redistribution known as HIV-associated lipodystrophy (increased truncal obesity, buffalo hump, peripheral fat loss, facial atrophy, breast enlargement) was observed. The metabolic syndrome, characterized by a combination of elevated fasting glucose, elevated fasting triglyceride, low HDL, abdominal obesity, and hypertension was also observed, which, in combination with the other aforementioned metabolic and anthropometric abnormalities, may be contributory to the observed increased cardiovascular risk.[17,18] Individuals on newer, more lipid-"friendly" cART are not completely spared from dyslipidemia and diabetes mellitus, as longer lifespans allow a "restoration to health" and development of these age-related metabolic diseases.

In this review, we attempt to summarize our current understanding and knowledge on the interrelationships between the complex processes of HIV, dyslipidemia, and IR, and how they contribute to increased cardiovascular risk in the well-controlled HIV-infected individual.

EPIDEMIOLOGY

Globally, there are an estimated 36.7 million people living with HIV in 2015, and the rate of new infection over the last few years has been stable.[19] In the United States, where an estimated 1.2 million people live with HIV, the overall mortality in all the age groups has decreased, except for those 65 years and older, for which the rates of death have increased.[20,21] This is attributed, at least in part, to an increase in atherosclerotic cardiovascular diseases and a higher risk of death from acute coronary syndrome. HIV-infected men and women have at least twice the risk for acute myocardial infarction (AMI) compared with the equivalent uninfected population.[22,23] Moreover, coronary artery disease appears to be accelerated among young HIV-infected individuals compared with the non-HIV population.[24] This increase is likely from a multitude of factors, including higher rates of traditional risk factors (eg, smoking), but also increased rates of dyslipidemia and diabetes mellitus. The prevalence of any form of dyslipidemia according to the Adult Treatment Panel III guidelines in cART-naïve people is estimated to be at 75%–85%.[25-28] This overall prevalence does not differ from HIV-negative individuals, but the prevalence of elevated TG and low HDL are higher in HIV-infected than uninfected individuals.[25] In cART-experienced individuals, the prevalence of dyslipidemia can be as high as 90%, but the prevalence of severe dyslipidemia requiring treatment is rare (<5%).[28,29] The forms of dyslipidemia are also different between those on treatment and those who are not, with elevated TC and LDL-C found to be significantly higher among HIV-infected individuals on cART than those not taking cART.[30] Furthermore, a recent meta-analysis comprising of 51 observational studies, including more than 37,000 individuals, found that the risks of hypercholesterolemia (pooled odds ratio [OR] 3.8, 95% CI 3.1 to 4.7), and hypertriglyceridemia (OR 2.2, 95% CI 1.7 to 2.9) are also significantly higher among cART-exposed individuals compared with cART-naïve individuals.[31] Individuals who interrupt cART also have increased major cardiovascular events, which could have been partly explained by a reversion of lipid profile toward the pattern seen in HIV-associated dyslipidemia.[32]

There is an overlap between IR and dyslipidemia, as dyslipidemia is found to be more frequent in those individuals with impaired fasting glucose or diabetes mellitus than euglycemic individuals.[33] Studies conducted before the introduction of HAART show that the prevalence of IR in HIV-infected individuals, measured using the hyperinsulinemic euglycemic clamp, was similar or even lower than HIV-uninfected controls.[34,35] Shortly after the introduction of protease inhibitors in 1996, the Food and Drug Administration warned of new-onset diabetes and hyperglycemia and worsening of existing diabetes among HIV-infected individuals taking these medications.[36] The prevalence of the metabolic syndrome, a surrogate for IR, is estimated at 33%