

Review Article

Cardiovascular Complications of HIV-Associated Immune Dysfunction

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Prolonged survival in HIV infection is accompanied by an increased frequency of non-HIV-related comorbidities. It is suggested that cardiovascular diseases (CVD) occur earlier among HIV-positive patients compared with HIV-negative patients, and at a higher rate. Several factors have been proposed which can be categorized into traditional and nontraditional risk factors. Immune dysfunction is a nontraditional risk factor that contributes significantly to cardiovascular pathology. Markers of inflammation are elevated in HIV-infected patients, and elevations in markers such as high-sensitivity C-reactive protein, D-dimer, and interleukin-6 (IL-6) have been associated with increased risk for cardiovascular disease. However, the data currently suggest the most practical advice is to start antiretroviral therapy early and to manage traditional risk factors for CVD aggressively. A better understanding of the mechanisms of CVD in this population and further efforts to modify chronic inflammation remain an important research area.

1. Introduction

The reduction of human immunodeficiency virus- (HIV-) related deaths by introduction of antiretroviral therapy (ART) [1] has been challenged by increasing incidence of non-HIV-related mortality [2] that is mainly attributed to cardiovascular diseases [3]. Multiple studies suggest increased risk of cardiovascular disease (CVD) in HIV-infected versus non-HIV-infected patients [4–6]. Although traditional risk factors such as advanced age, smoking, and dyslipidemia [7] have contributed significantly to CVD, nontraditional risk factors such as immune dysfunction have been accused [8]. Through a focused literature search, this review aims to shed light on the cardiovascular complications of persistent immune dysfunction in HIV patients receiving ART as a public health concern and potential preventive strategies to reduce its impact.

2. The Burden of Cardiovascular Diseases in HIV Population

Globally, an estimated 35.3 (32.2–38.8) million people were living with HIV in 2012 [9]. More than 95% of HIV infections are in developing countries, two-thirds of them in sub-Saharan Africa [9]. In 2012, 65% of the target group has access to ART; it is up from 54% at the end of 2011 [10]. With increasing access to ART, the life expectancy of HIV-infected individuals is improving. Consequently, mortality from non-HIV-related illness is increasing. Despite the demographic differences of HIV patients between developed and developing countries, CVD remains a major cause of non-HIV-related mortality.

In developed countries, about 9–20% of HIV-positive patients have moderate to high 10-year risk of myocardial infarction (MI) [11, 12]. It is estimated that, by 2015, 50% of HIV-positive patients in the United States of America

will be over the age of 50 [13]. Studies have shown that aging HIV-infected patients exhibit significantly increased rates of CVD, including coronary artery disease, MI, and peripheral arterial diseases [4]. Also, traditional risk factors such as smoking, HIV-associated lipodystrophy syndrome (HALS), diabetes mellitus, and hypertension are common among HIV-positive patients [14]. Whereas national estimates indicate that approximately 21% of the adult population smokes [15], the prevalence of active smoking in HIV-positive individuals ranged from 40 to 84% in various studies [16, 17]. Compared with nonsmokers, smokers have a twofold or greater increased risk of CVD [18]. 9–83% of HIV-infected patients suffer from HALS [19]. It represents morphological (lipoatrophy, lipohypertrophy) and metabolic changes in ART treated patients. Patients on ART are exposed to alterations of cholesterol and triglyceride profiles associated with increased risk of atherogenic progression and CVD [19, 20].

In developing countries, about 20% of the daily deaths due to HIV/AIDS are attributed to CVD [21]. This is complicated by rapid epidemiological transition promoted by prolonged survival of HIV-infected individuals, urbanization, and nutritional transition. The percentage of HIV-infected individuals over the age of 50 in South Africa is now higher than in the 15–24-year-old age group [22]. Also this is further increased by the growing number of HIV survivors, now estimated at 5.8% of the population older than 50 years [22]. Urbanization and dietary and lifestyle changes result in conditions such as excessive weight gain, dyslipidemia, and hypertension to become prominent. The rapid epidemiological transition compresses the time available to adopt new strategies and impacts the economy of these countries. In 2010, the total cost of major CVD in the World Health Organization (WHO), Africa subregion, was estimated to be \$11.6 billion, including \$4.7 billion due to loss of productivity [23]. Therefore, the rapidly increasing CVD in developing countries, with unmatched growth in economy and wealth, will quickly shift these conditions beyond the coping capacities of countries.

3. Immune Dysfunction as Nontraditional Risk Factor for CVD

In addition to previously mentioned traditional risk factors for CVD, HIV-induced immune dysfunction might partially explain the increased risk of CVD (Table 1). HIV-induced inflammation might explain the increased risk of CVD in part; particularly it is well established that inflammation is a major factor in the development of atherosclerosis in the general population [24]. Inflammation as a complex biological process represents interplay of multiple cellular and inflammatory mediators that are affected by both HIV and ART [5, 14, 25–27].

4. CD4⁺ T-Cells

The association between CD4⁺ cell count and CVD has been reported by multiple studies. Although in Data Collection on

TABLE 1: Factors that might confer an increased risk of cardiovascular diseases in HIV patients.

Traditional	Nontraditional
Age	Systemic inflammation
Smoking	Low CD4 ⁺ T-cells count
Obesity	Elevated C-reactive protein (CRP)
Diabetes mellitus	Elevated interleukin-6 (IL-6)
Hypertension	Elevated D-dimer
HIV-associated lipodystrophy syndrome (HALS)	Elevated HIV RNA level
	Role of drugs [protease inhibitors (PIs)]

Adverse Events of Anti-HIV Drugs (D:A:D) study the CD4⁺ cell count below 500 cells/ μ L was associated with increased risk of non-AIDS-related deaths [28], HIV Outpatient Study (HOPS) cohort reported 28% increased risk of CVD in patients with CD4⁺ count <500 cells/ μ L, regardless of the class of ART used [29]. In addition, failure to restore a normal peripheral CD4⁺ cell count is associated with an increased risk of morbidity and mortality of CVD [30]. Interestingly, a significant subset of patients who delay therapy until their CD4⁺ cell count is <200 cells/ μ L may not achieve a normal CD4⁺ cell count, even after >10 years of otherwise effective therapy [31]. These individuals likely remain at risk for developing significant CVD (Figure 1).

5. Inflammatory Mediators

Elevated C-reactive protein (CRP), interleukin-6 (IL-6), and D-dimer are predictors of CVD events in the general population [32]. However, the associations between IL-6 and D-dimer levels in HIV-positive individuals with all-cause mortality were much stronger than in studies of non-HIV-infected populations that usually focused on CVD morbidity and mortality [25]. Strategies for Management of Antiretroviral Therapy (SMART) study showed higher levels of the inflammatory or coagulation markers such as high sensitivity CRP, IL-6, D-dimer, and cystatin C in patients with treated HIV disease than in uninfected control subjects. Also it was successfully reported that, one month after stopping treatment, HIV RNA levels were correlated with increases in D-dimer and IL-6 levels and were subsequently associated with an increased risk of all-cause mortality [25]. Furthermore, the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) showed an increase in serum fibrinogen level compared with HIV-negative patients which contributes to increased risk of atherosclerosis in HIV-infected patients [33] (Figure 1).

The underlying mechanism of immune activation is poorly understood; however, multiple studies investigated the potential causes. *HIV replication* below the clinically detectable levels might contribute to persistent immune activation [34]. However, ART intensification trials did not

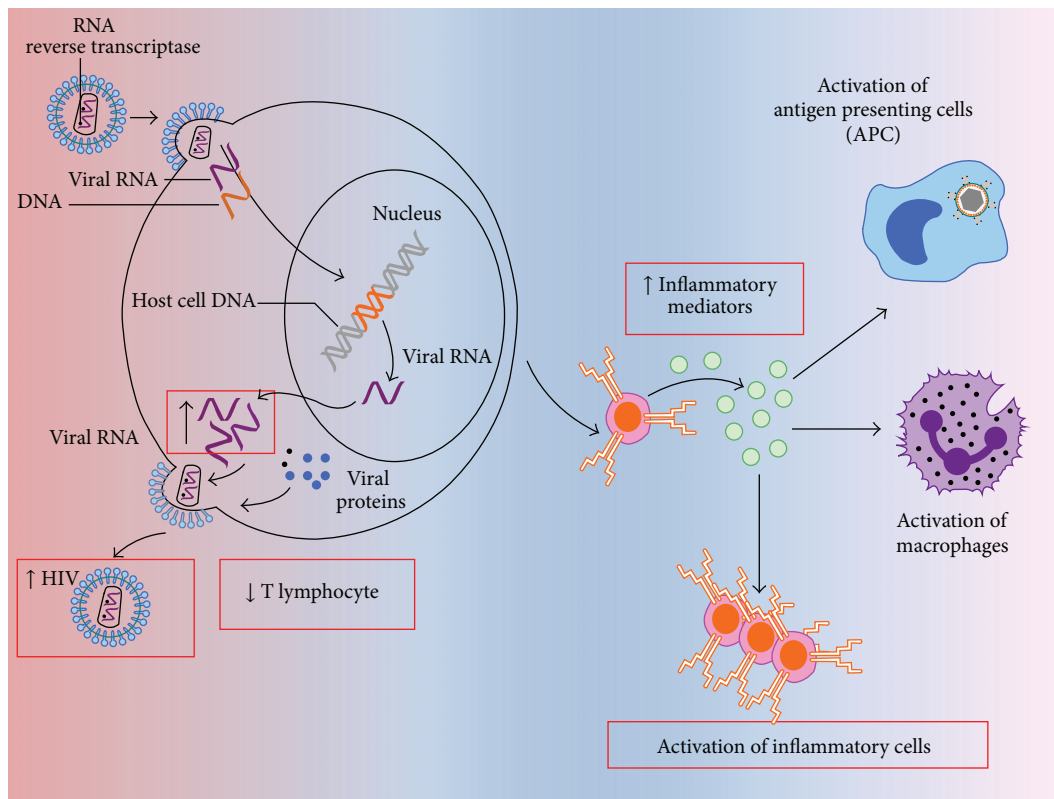


FIGURE 1: Nontraditional risk factors for cardiovascular diseases in human immunodeficiency virus- (HIV-) infected patients. HIV infection is associated with consumption of CD4⁺ T-cells due to viral replication as indicated by increased viral RNA load (left panel). Subsequently, the increased production of inflammatory mediators such as interleukin-6 (IL-6) indicates a status of dysregulated immune response which precipitates cardiovascular pathology (right panel).

show consistent results which eliminate the role of HIV replication in persistent immune activation [35]. *Microbial translocation* as facilitated by HIV-induced depletion of CD4 T-cells from the gut-associated lymphoid tissue and intestinal barrier dysfunction has been proposed as potential cause for persistent immune activation [36, 37]. Even after initiation of ART, microbial translocation does not normalize and continues to be associated with T-cell activation [38]. Majority of HIV-infected individuals are prone to *coinfection* with subsequent immune activation [39]. Cytomegalovirus (CMV) coinfection is highly prevalent in the setting of HIV infection and elicits CMV-specific T-cell responses in HIV-infected individuals [40].

In a study conducted on 49 HIV-infected children with evidence of cardiomyopathy, giving intravenous immunoglobulin (IVIG) was associated with improvement of left ventricular (LV) structure and function as demonstrated by serial echocardiograms [41]. Although the actual mechanism of action of IVIG remains unclear, immunomodulation is proposed as a potential theory. IVIG has been shown to inhibit the production of TNF- α via downregulation in at least one study [42].

6. Antiretroviral Therapy and Immune Dysfunction

The increasing rates of dyslipidemia and other metabolic changes among HIV-positive patients receiving ART have led

to many studies investigating the link between ART use and CVD. In 2003, the D:A:D study demonstrated 26% relative risk increase in rate of MI per year of exposure during the first 4–6 years of use [43]. In a subsequent study, the D:A:D group demonstrated that the rate of MI was 1.53 per 1000 person-years among patients not exposed to protease inhibitors (PIs) and 6.01 per 1000 person-years for patients exposed to PIs for more than 6 years [28]. After adjustment for exposure to the other drug classes and established cardiovascular risk factors (excluding lipid levels), the relative rate of MI per year of PIs exposure was 1.16. The conclusion of the study is that increased exposure to PIs is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidemia.

In an earlier HOPS study, the investigators found an increased risk of MI in patients receiving a PI compared with those who were not. A multivariate statistical analysis showed that PI use was still strongly, although not significantly, associated with the incidence of MI [44]. In a study assessing carotid intima-media thickness (IMT), the investigators found premature atherosclerosis that correlated with usual risk factors, but also with PIs, especially that of lopinavir [45]. The D:A:D study demonstrated that the effect of PIs depends on the time of exposure, hence the need for long follow-up period to detect the actual MI risk [28]. In HOPS study, the exclusion of dyslipidemia made the interpretation of

the differences insignificant, although it might reflect casual association between PIs and MI [44].

There are inconsistencies in the literature regarding the risk of MI associated with abacavir usage. Although multiple observational studies point towards an increase in MI risk, the evidence is not consistent [46–51]. However, it is known that even well-conducted observational studies are subject to bias. For instance, in the D:A:D study most patients were not naïve to antiretroviral therapy when enrolled; therefore there was a degree of selection bias which could have affected the patients' survival [52]. On the other hand, three meta-analyses of randomized clinical trials reported no evidence of an association between abacavir use and MI [53–55]. Nevertheless, in a study conducted to evaluate the inflammatory mediators in patients receiving abacavir, there was an associated induction of proinflammatory mediators [CD4 ligand, interleukin-8 (IL-8), and lymphotoxin alpha (LTA)] [56] and these findings might support the concept of a potential MI risk.

7. Prevention of Cardiovascular Complications in HIV Patients

Despite the available data on immune dysfunction in HIV-infected patients, it is still unclear how patients should be treated on the basis of this information or whether these markers should be used to assess and guide CVD risk management. Currently, early control of the HIV disease activity and managing the risk factors for CVD might partially modulate the immune dysfunction and subsequently reduce cardiovascular complications.

Initiation and maintaining HIV viral suppression through ART are crucial for prevention of CVD. In spite of the increased risk of CVD in the population receiving ART, it is known from D:A:D study that the absolute risk is small and the benefits of ART outweigh the risks [43]. Also, SMART study concluded that after one month of stopping ART, there is increased level of D-dimer and IL-6 with associated high risk for all-cause mortality [25]. However, changing ART regimen from PIs to nonnucleoside reverse transcriptase inhibitors (NNRTIs) may improve the lipid profile by increasing HDL cholesterol levels [57]. There are several barriers governing ART regimen selection such as economic burden of the drugs, limited availability of laboratory monitoring, and individual patient management. For instance, in Africa the cost of first line treatment is around \$175 per year; the costs of the second line drugs can be ten times higher. In addition, effectiveness depends on high levels of adherence (at least 85 to 90 percent), for which counseling and follow-up to ensure adherence are required [58]. In conclusion while selection of ART regimen depends on the individual CVD risk and the duration of ART exposure, it might not be suitable strategy in low income countries to adopt certain ART regimens such as NNRTIs. Nevertheless, frequent monitoring of traditional risk factors such as dyslipidemia might help overcoming such a challenge [59].

Assessment of CVD risk for ART population is fundamental to guide risk management. However, utilizing conventional tools such as Framingham equation might inaccurately estimate the CVD risk. That is mainly because Framingham equation is used for non-HIV individuals and predicts the risk over a relatively long period. As previously mentioned HIV-infected individuals have significant CVD risk by 6 years' period [43]. Recently, several cardiovascular risk equations have been developed for HIV-positive patients. In a European multicenter study, conducted on 22,625 HIV-infected patients, an HIV specific model was able to accurately predict CVD better than conventional risk prediction models [60]. Thus, utilizing HIV specific model incorporating both routine CVD risk parameters and exposure to individual ART is useful in estimating CVD risks in HIV-infected persons compared with conventional risk prediction models [60]. The currently available recommendations for screening for the presence of CVD risk factors in persons with HIV infection take into account the evidence for dyslipidemia, insulin resistance, and changes in body fat distribution that have been shown to occur with HAART [61]. Nevertheless, referral for diagnostic testing should be assessed in light of the underlying disease or any comorbidity that might limit the life expectancy of the HIV patient [62].

To date, there is no evidence to suggest that HIV-positive patients need to be offered more aggressive management of dyslipidemia than those used in the general population. In 2013, the American College of Cardiology (ACC)/American Heart Association (AHA) issued updated practice guidelines for the treatment of blood cholesterol to reduce atherosclerotic CVD risk in adults [63, 64]. These guidelines recommend offering statin therapy of different intensity based on an individual's absolute risk (new calculator of risk provided in the recommendations) rather than aiming for a specific low-density lipoprotein (LDL) target level [64]. Accordingly, patients with the highest CVD risk are treated with high intensity statins and both primary and secondary prevention are addressed [63, 64]. Selected lipid-lowering drugs, such as pravastatin or atorvastatin, appear to be safely used in ART-treated patients [65]. Also, statins are known to have anti-inflammatory effects that are particularly beneficial to CVD [66]. In Intervention Trial Evaluating Rosuvastatin (JUPITER) study, anti-inflammatory treatment with rosuvastatin statistically significantly reduced mortality and risk of venous thrombotic disease in apparently healthy subjects with elevated hs-CRP (>2 mg/dL) and "normal" LDL cholesterol (<130 mg/dL) [67].

The prevalence of hypertension in HIV population has not been established with certainty [68]; however, hypertension remains a powerful predictor of CVD events as in the general population [69]. The prevalence of hypertension is expected to increase with improved survival of HIV patients and increased prevalence of HIV among patients in certain high risk ethnic subgroups [70]. Guidelines for the effective diagnosis and management of hypertension in non-HIV patients should be applied to patients with HIV until further data are available [68]. Also, impaired glucose tolerance is increased in patients with HIV and is associated with ART

exposure [71]. In patients with HIV, intensive lifestyle intervention, metformin, and thiazolidinediones tend to reduce insulin resistance; however, the long-term effectiveness of these agents for the prevention and treatment of diabetes mellitus in patients with HIV is not known [68, 72]. Patients initiating ART should be screened for impaired fasting glucose and diabetes mellitus by measurement of fasting glucose levels or hemoglobin A1C levels at baseline, annually, and after changes are made to ART regimens [68].

Smoking is a classic risk factor for CVD, and in the general population, the risk of coronary heart disease and mortality considerably reduced within the first 2 years of stopping smoking [73]. Data from HIV-infected subjects in the D:A:D study showed that cessation of smoking decreases the risk of CVD, with increasing years of having stopped smoking [74]. In addition to obstacles to cessation known for the general population, substance abuse, psychiatric disorders, low socioeconomic status, poor access to care, and resulting low utilization of cessation programs are more prevalent with HIV and present significant risks for continued smoking and barriers to cessation [75].

There are several small studies conducted to address the impact of smoking cessation programs on HIV population [76–79]. One randomized clinical trial comparing a program of nicotine replacement therapy (NRT), self-help materials, and phone counseling with a usual care program comprised only of self-help materials and NRT found that HIV-infected smokers in the phone counseling group had abstinence rates of 36.8%, compared with 10.3% in the usual care group [80]. Limited data are available regarding pharmacologic therapy other than NRT for smoking cessation in HIV-infected populations. Nevertheless, there are several potential interactions between ART and smoking cessation pharmacotherapy. For example, ritonavir combined with lopinavir can significantly decrease plasma concentrations of bupropion [81]. It is essential to conduct more aggressive interventions to increase the efficacy and generality of smoking cessation programs in HIV-positive patients.

8. Conclusion

As HIV-positive patients live longer CVD risk is increasing. The risk of CVD in HIV-positive patients is a complex mix of the traditional cardiovascular risk factors and nontraditional risk factors such as immune dysfunction. The evaluation of an individual's CVD risk should be assessed routinely, and the prevention of CVD should therefore be considered in terms of the patient's overall CVD risk and HIV disease stage. Early initiation of ART, close monitoring of the drugs toxicity, and ensuring high level of adherence are fundamental for CVD risk modification. In addition, control of traditional risk factors such as smoking and dyslipidemia is greatly needed for HIV-positive population.

Abbreviations

HIV: Human immunodeficiency virus
 ART: Antiretroviral therapy
 CVD: Cardiovascular disease

MI: Myocardial infarction
 HALS: HIV-associated lipodystrophy syndrome
 CRP: C-reactive protein
 IL-6: Interleukin-6
 CMV: Cytomegalovirus
 PIs: Protease inhibitors
 NNRTIs: Nonnucleoside reverse transcriptase inhibitors
 NRT: Nicotine replacement therapy.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] F. J. Palella Jr., K. M. Delaney, A. C. Moorman et al., “Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators,” *The New England Journal of Medicine*, vol. 338, pp. 853–860, 1998.
- [2] J. E. Sackoff, D. B. Hanna, M. R. Pfeiffer, and L. V. Torian, “Causes of death among persons with aids in the era of highly active antiretroviral therapy: New York City,” *Annals of Internal Medicine*, vol. 145, no. 6, pp. 397–406, 2006.
- [3] F. J. Palella Jr., R. K. Baker, A. C. Moorman et al., “Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 43, no. 1, pp. 27–34, 2006.
- [4] S. K. Grinspoon, C. Grunfeld, D. P. Kotler et al., “State of the science conference: initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary,” *Circulation*, vol. 118, no. 2, pp. 198–210, 2008.
- [5] J. S. Currier, A. Taylor, F. Boyd et al., “Coronary heart disease in HIV-infected individuals,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 33, no. 4, pp. 506–512, 2003.
- [6] V. A. Triant, H. Lee, C. Hadigan, and S. K. Grinspoon, “Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease,” *The Journal of Clinical Endocrinology & Metabolism*, vol. 92, no. 7, pp. 2506–2512, 2007.
- [7] O. Galescu, A. Bhangoo, and S. Ten, “Insulin resistance, lipodystrophy and cardiometabolic syndrome in HIV/AIDS,” *Reviews in Endocrine and Metabolic Disorders*, vol. 14, no. 2, pp. 133–140, 2013.
- [8] J. A. Aberg, “Aging, inflammation, and HIV infection,” *Topics in Antiviral Medicine*, vol. 20, no. 3, pp. 101–105, 2012.
- [9] “UNAIDS report on the global AIDS epidemic 2013,” 2013.
- [10] WHO, *Global Update on HIV Treatment 2013: Results, Impact and Opportunities*. WHO Report in Partnership with UNICEF and UNAIDS, WHO, 2013.
- [11] M. G. Law, N. Friis-Møller, W. M. El-Sadr et al., “The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study,” *HIV Medicine*, vol. 7, no. 4, pp. 218–230, 2006.
- [12] J. Santos, R. Palacios, M. González, J. Ruiz, and M. Márquez, “Atherogenic lipid profile and cardiovascular risk factors in HIV-infected patients (Nétar study),” *International Journal of STD & AIDS*, vol. 16, no. 10, pp. 677–680, 2005.

- [13] R. B. Effros, C. V. Fletcher, K. Gebo et al., "Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions," *Clinical Infectious Diseases*, vol. 47, no. 4, pp. 542–553, 2008.
- [14] V. A. Triant, H. Lee, C. Hadigan, and S. K. Grinspoon, "Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease," *The Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 7, pp. 2506–2512, 2007.
- [15] "Cigarette smoking among adults—United States, 2006," *Morbidity and Mortality Weekly Report*, vol. 56, pp. 1157–1161, 2006.
- [16] K. K. Browning, M. E. Wewers, A. K. Ferketich, and P. Diaz, "Tobacco use and cessation in HIV-infected individuals," *Clinics in Chest Medicine*, vol. 34, no. 2, pp. 181–190, 2013.
- [17] J. M. Tesoriero, S. M. Gieryc, A. Carrascal, and H. E. Lavigne, "Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation," *AIDS and Behavior*, vol. 14, no. 4, pp. 824–835, 2010.
- [18] A. R. Lifson, J. Neuhaus, J. R. Arribas, M. D. van Berg-Wolf, A. M. Labriola, and T. R. H. Read, "Smoking-related health risks among persons with HIV in the strategies for management of antiretroviral therapy clinical trial," *The American Journal of Public Health*, vol. 100, no. 10, pp. 1896–1903, 2010.
- [19] C. R. Loonam and A. Mullen, "Nutrition and the HIV-Associated lipodystrophy syndrome," *Nutrition Research Reviews*, vol. 25, no. 2, pp. 267–287, 2012.
- [20] K. Samaras, H. Wand, M. Law, S. Emery, D. Cooper, and A. Carr, "Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia," *Diabetes Care*, vol. 30, pp. 113–119, 2007.
- [21] A. P. Kengne, Z. June-Rose Mchiza, A. G. B. Amoah, and J. C. Mbanya, "Cardiovascular diseases and diabetes as economic and developmental challenges in Africa," *Progress in Cardiovascular Diseases*, vol. 56, no. 3, pp. 302–313, 2013.
- [22] S. Arie, "HIV infection is rising among over 50s across the world, figures show," *British Medical Journal*, vol. 341, Article ID c4064, 2010.
- [23] J. M. Kirigia, H. B. Sambo, L. G. Sambo, and S. P. Barry, "Economic burden of diabetes mellitus in the WHO African region," *BMC International Health and Human Rights*, vol. 9, article 6, 2009.
- [24] G. K. Hansson, "Inflammation, atherosclerosis, and coronary artery disease," *The New England Journal of Medicine*, vol. 352, no. 16, pp. 1626–1695, 2005.
- [25] L. H. Kuller, R. Tracy, W. Belloso et al., "Inflammatory and coagulation biomarkers and mortality in patients with HIV infection," *PLoS Medicine*, vol. 5, no. 10, article e203, 2008.
- [26] C. Grunfeld, J. A. Delaney, C. Wanke et al., "Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study," *AIDS*, vol. 23, no. 14, pp. 1841–1849, 2009.
- [27] D. Klein, L. B. Hurley, C. P. Quesenberry Jr., and S. Sidney, "Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection?" *Journal of Acquired Immune Deficiency Syndromes*, vol. 30, no. 5, pp. 471–477, 2002.
- [28] N. Friis-Møller, P. Reiss, C. A. Sabin et al., "Class of antiretroviral drugs and the risk of myocardial infarction," *The New England Journal of Medicine*, vol. 356, no. 17, pp. 1723–1735, 2007.
- [29] K. A. Lichtenstein, C. Armon, K. Buchacz et al., "Low CD4⁺ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study," *Clinical Infectious Diseases*, vol. 51, no. 4, pp. 435–447, 2010.
- [30] A. Mocroft, A. N. Phillips, J. Gatell et al., "Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study," *The Lancet*, vol. 370, no. 9585, pp. 407–413, 2007.
- [31] C. F. Kelley, C. M. R. Kitchen, P. W. Hunt et al., "Incomplete peripheral CD4⁺ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment," *Clinical Infectious Diseases*, vol. 48, no. 6, pp. 787–794, 2009.
- [32] J. Danesh, S. Kaptoge, A. G. Mann et al., "Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review," *PLoS Medicine*, vol. 5, no. 4, article e78, 2008.
- [33] E. Madden, G. Lee, D. P. Kotler et al., "Association of antiretroviral therapy with fibrinogen levels in HIV-infection," *AIDS*, vol. 22, no. 6, pp. 707–715, 2008.
- [34] F. Maldarelli, S. Palmer, M. S. King et al., "ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia," *PLoS Pathogens*, vol. 3, no. 4, article e46, 2007.
- [35] M. J. Buzón, M. Massanella, J. M. Llibre et al., "HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects," *Nature Medicine*, vol. 16, no. 4, pp. 460–465, 2010.
- [36] R. S. Veazey, M. DeMaria, L. V. Chalifoux et al., "Gastrointestinal tract as a major site of CD4⁺ T cell depletion and viral replication in SIV infection," *Science*, vol. 280, no. 5362, pp. 427–431, 1998.
- [37] Q. Li, J. D. Estes, L. Duan et al., "Simian immunodeficiency virus-induced intestinal cell apoptosis is the underlying mechanism of the regenerative enteropathy of early infection," *The Journal of Infectious Diseases*, vol. 197, no. 3, pp. 420–429, 2008.
- [38] E. Cassol, S. Malfeld, P. Mahasha et al., "Persistent microbial translocation and immune activation in HIV-1-infected south africans receiving combination antiretroviral therapy," *Journal of Infectious Diseases*, vol. 202, no. 5, pp. 723–733, 2010.
- [39] A. W. Sylwester, B. L. Mitchell, J. B. Edgar et al., "Broadly targeted human cytomegalovirus-specific CD4⁺ and CD8⁺ T cells dominate the memory compartments of exposed subjects," *The Journal of Experimental Medicine*, vol. 202, no. 5, pp. 673–685, 2005.
- [40] D. M. Naeger, J. N. Martin, E. Sinclair et al., "Cytomegalovirus-specific T cells persist at very high levels during long-term antiretroviral treatment of HIV disease," *PLoS ONE*, vol. 5, no. 1, Article ID e8886, 2010.
- [41] S. E. Lipshultz, E. J. Orav, S. P. Sanders, and S. D. Colan, "Immunoglobulins and left ventricular structure and function in pediatric HIV infection," *Circulation*, vol. 92, no. 8, pp. 2220–2225, 1995.
- [42] A. Achiron, R. Margalit, R. Hershkoviz et al., "Intravenous immunoglobulin treatment of experimental T cell-mediated autoimmune disease: upregulation of T cell proliferation and downregulation of tumor necrosis factor α secretion," *Journal of Clinical Investigation*, vol. 93, no. 2, pp. 600–605, 1994.
- [43] N. Friis-Møller, C. A. Sabin, R. Weber et al., "Combination antiretroviral therapy and the risk of myocardial infarction," *The New England Journal of Medicine*, vol. 349, pp. 1993–2003, 2003.

- [44] S. D. Holmberg, A. C. Moorman, J. M. Williamson et al., "Protease inhibitors and cardiovascular outcomes in patients with HIV-1," *The Lancet*, vol. 360, no. 9347, pp. 1747–1748, 2002.
- [45] M. L. de Saint, O. Vandhuick, P. Guillo et al., "Premature atherosclerosis in HIV positive patients and cumulated time of exposure to antiretroviral therapy (SHIVA study)," *Atherosclerosis*, vol. 185, no. 2, pp. 361–367, 2006.
- [46] The SMART/INSIGHT and the D:A:D Study Groups, "Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients," *Aids*, vol. 22, no. 14, pp. F17–F24, 2008.
- [47] S. Lang, M. Mary-Krause, L. Cotte et al., "Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French hospital database on HIV ANRS cohort CO4," *Archives of Internal Medicine*, vol. 170, no. 14, pp. 1228–1238, 2010.
- [48] C. A. Sabin, S. W. Worm, R. Weber et al., "Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration," *The Lancet*, vol. 371, no. 9622, pp. 1417–1426, 2008.
- [49] T. Antoniou, J. Gillis, M. R. Loutfy et al., "Impact of the data collection on adverse events of Anti-HIV drugs cohort study on abacavir prescription among treatment-naive, HIV-infected patients in Canada," *Journal of the International Association of Providers of AIDS Care*, vol. 13, no. 2, pp. 153–159, 2014.
- [50] P. Dellamonica, C. Katlama, L. Lévy-Bachelot, J.-P. Daures, and L. Finkielstein, "Abacavir (Ziagen) use between 2003 and 2008 in France according to the electronic medical record NADIS," *Medecine et Maladies Infectieuses*, vol. 43, no. 11-12, pp. 467–474, 2013.
- [51] E. S. Brouwer, S. Napravnik, J. J. Eron Jr. et al., "Effects of combination antiretroviral therapies on the risk of myocardial infarction among HIV patients," *Epidemiology*, vol. 25, no. 3, pp. 406–417, 2014.
- [52] C. Smith, C. A. Sabin, J. D. Lundgren et al., "Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study," *AIDS*, vol. 24, no. 10, pp. 1537–1548, 2010.
- [53] C. H. Brothers, J. E. Hernandez, A. G. Cutrell et al., "Risk of myocardial infarction and abacavir therapy: No increased risk across 52 glaxosmithkline-sponsored clinical trials in adult subjects," *Journal of Acquired Immune Deficiency Syndromes*, vol. 51, no. 1, pp. 20–28, 2009.
- [54] H. J. Ribaud, C. A. Benson, Y. Zheng et al., "No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT," *Clinical Infectious Diseases*, vol. 52, no. 7, pp. 929–940, 2011.
- [55] X. Ding, E. Andraca-Carrera, C. Cooper et al., "No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis," *Journal of Acquired Immune Deficiency Syndromes*, vol. 61, no. 4, pp. 441–447, 2012.
- [56] I. J. MacLeod, C. F. Rowley, S. Lockman et al., "Abacavir alters the transcription of inflammatory cytokines in virologically suppressed, HIV-infected women," *Journal of the International AIDS Society*, vol. 15, no. 2, Article ID 17393, 2012.
- [57] B. M. Bergersen, S. Tonstad, L. Sandvik, and J. N. Bruun, "Low prevalence of high-density lipoprotein cholesterol level < 1 mmol/L in non-nucleoside reverse transcriptase inhibitor recipients," *International Journal of STD & AIDS*, vol. 16, no. 5, pp. 365–369, 2005.
- [58] D. Canning, "The economics of HIV/AIDS in low-income countries: the case for prevention," *Journal of Economic Perspectives*, vol. 20, no. 3, pp. 121–142, 2006.
- [59] S. D. Fisher, B. S. Kanda, T. L. Miller, and S. E. Lipshultz, "Cardiovascular disease and therapeutic drug-related cardiovascular consequences in HIV-infected patients," *American Journal of Cardiovascular Drugs*, vol. 11, no. 6, pp. 383–394, 2011.
- [60] N. Friis-Møller, R. Thiébaud, P. Reiss et al., "Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 17, no. 5, pp. 491–501, 2010.
- [61] P. Y. Hsue, K. Squires, A. F. Bolger et al., "Screening and assessment of coronary heart disease in HIV-infected patients," *Circulation*, vol. 118, no. 2, pp. e41–e47, 2008.
- [62] Gibbons R. J., G. J. Balady, J. T. Bricker et al., "ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines)," *Journal of the American College of Cardiology*, vol. 40, no. 8, pp. 1531–1540, 2002.
- [63] N. J. Stone, J. G. Robinson, A. H. Lichtenstein et al., "2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American college of cardiology/American heart association task force on practice guidelines," *Circulation*, vol. 129, pp. S1–S45, 2014.
- [64] S. C. Smith Jr. and S. M. Grundy, "2013 ACC/AHA guideline recommends fixed-dose strategies instead of targeted goals to lower blood cholesterol," *Journal of the American College of Cardiology*, vol. 64, no. 6, pp. 601–612, 2014.
- [65] M. Schambelan, C. A. Benson, A. Carr et al., "Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA Panel," *Journal of Acquired Immune Deficiency Syndromes*, vol. 31, no. 3, pp. 257–275, 2002.
- [66] M. P. Dubé, "Will statins be an effective anti-inflammatory intervention for prevention of cardiovascular disease in patients with HIV?" *Journal of Infectious Diseases*, vol. 209, no. 8, pp. 1149–1150, 2014.
- [67] P. M. Ridker, E. Danielson, F. A. H. Fonseca et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein," *The New England Journal of Medicine*, vol. 359, no. 21, pp. 2195–2207, 2008.
- [68] J. H. Stein, C. M. Hadigan, T. T. Brown et al., "Prevention strategies for cardiovascular disease in HIV-infected patients," *Circulation*, vol. 118, no. 2, pp. e54–e60, 2008.
- [69] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "The seventh report of the joint National Committee on prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 report," *Evidence-Based Eye Care*, vol. 4, no. 3, pp. 179–180, 2003.
- [70] R. C. Kaplan, L. A. Kingsley, A. R. Sharrett et al., "Ten-year predicted coronary heart disease risk in HIV-infected men and women," *Clinical Infectious Diseases*, vol. 45, no. 8, pp. 1074–1081, 2007.
- [71] C. Hadigan, "Diabetes, insulin resistance, and HIV," *Current Infectious Disease Reports*, vol. 8, no. 1, pp. 69–75, 2006.
- [72] A. Gavrilu, S. Tsiordas, J. Doweiko et al., "Exercise and vitamin E intake are independently associated with metabolic abnormalities in human immunodeficiency virus—positive subjects: a

- cross-sectional study,” *Clinical Infectious Diseases*, vol. 36, no. 12, pp. 1593–1601, 2003.
- [73] R. Doll, R. Peto, J. Boreham, and I. Sutherland, “Mortality in relation to smoking: 50 Years’ observations on male British doctors,” *British Medical Journal*, vol. 328, no. 7455, pp. 1519–1528, 2004.
- [74] K. Petoumenos, S. Worm, P. Reiss et al., “Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study,” *HIV Medicine*, vol. 12, no. 7, pp. 412–421, 2011.
- [75] G. L. Humfleet, K. Delucchi, K. Kelley, S. M. Hall, J. Dilley, and G. Harrison, “Characteristics of HIV-positive cigarette smokers: a sample of smokers facing multiple challenges,” *AIDS Education and Prevention*, vol. 21, no. 3, pp. 54–64, 2009.
- [76] D. J. Vidrine, R. C. Arduino, and E. R. Gritz, “The effects of smoking abstinence on symptom burden and quality of life among persons living with HIV/AIDS,” *AIDS Patient Care and STDs*, vol. 21, no. 9, pp. 659–666, 2007.
- [77] D. J. Vidrine, R. M. Marks, R. C. Arduino, and E. R. Gritz, “Efficacy of cell phone-delivered smoking cessation counseling for persons living with HIV/AIDS: 3-month outcomes,” *Nicotine & Tobacco Research*, vol. 14, no. 1, pp. 106–110, 2012.
- [78] A. B. Lazev, D. J. Vidrine, R. C. Arduino, and E. R. Gritz, “Increasing access to smoking cessation treatment in a low-income, HIV-positive population: the feasibility of using cellular telephones,” *Nicotine and Tobacco Research*, vol. 6, no. 2, pp. 281–286, 2004.
- [79] J. E. Burkhalter, C. M. Springer, R. Chhabra, J. S. Ostroff, and B. D. Rapkin, “Tobacco use and readiness to quit smoking in low-income HIV-infected persons,” *Nicotine and Tobacco Research*, vol. 7, no. 4, pp. 511–522, 2005.
- [80] D. J. Vidrine, R. C. Arduino, and E. R. Gritz, “Impact of a cell phone intervention on mediating mechanisms of smoking cessation in individuals living with HIV/AIDS,” *Nicotine and Tobacco Research*, vol. 8, no. supplement 1, pp. S103–S108, 2006.
- [81] L. Y. Park-Wyllie and T. Antoniou, “Concurrent use of bupropion with CYP2B6 inhibitors, nelfinavir, ritonavir and efavirenz: a case series,” *AIDS*, vol. 17, no. 4, pp. 638–640, 2003.



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