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Effects of Tobacco Smoking on HIV-Infected Individuals

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Abstract

A longer life expectancy and a high prevalence of tobacco smoking among HIV patients have led to an increasing cumulative exposure to tobacco in this community. Clinical recommendations for smoking cessation in HIV patients are mainly based on the body of evidence from the general population plus few available data from HIV cohort studies. The assumption that the pathophysiology of tobacco-related diseases in HIV-infected patients is similar to that in the general population may be questionable. This article reviews the pathophysiological mechanisms underlying health problems attributable to tobacco in HIV patients, and how these mechanisms may interact with those of HIV infection.

Tobacco smoking exerts a greater health impact on HIV-infected patients than on uninfected smokers. Components of tobacco smoke and HIV infection induce complex interrelated pathophysiological changes through different pathways, affecting various organ systems with a cumulative or synergistic effect. This review supports the contention that HIV infection may confer an increased susceptibility to the harmful effects of smoking. Tobacco-related harm in the setting of HIV infection is still underestimated. A better understanding of the pathophysiological interaction between tobacco smoking and HIV will help to promote smoking cessation in this specific population. **(AIDS Rev. 2015;17:47-55)**

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Key words

Tobacco cigarette smoking. HIV infection. Nicotine. Oxidative stress. Cancer. Cardiovascular disease.

Magnitude of the problem

Since the beginning of the HIV pandemic, the prevalence of smoking in HIV-infected patients has been estimated at up to two and three times higher than that in the general population[1]. Smokers account for up to 40-70% of the individuals in different HIV cohorts of developed countries[2,3]. In the USA, the burden of smoking-attributable mortality in the general population in one year (480,000 persons)[4] is closer to that of HIV-related deaths since the origin of the HIV epidemic (600,000 persons)[5].

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Consequences of cigarette smoking in HIV-infected patients

There is reasonable scientific evidence about the lack of relation between smoking and risk of HIV seroconversion[6]. Available data addressing the impact of smoking on HIV infection progression may seem to be conflicting due to differences in study population, design, and endpoints among studies. Nonetheless, significant data indicate the impact of smoking on HIV disease progression[6].

With the introduction of HAART, AIDS mortality has sharply declined[7], leading to an increase in mortality related to non-AIDS-defining diseases such as cancer, cardiovascular diseases, or bacterial infections[8]. Most of these diseases are also tobacco-related[2]. Non-AIDS-related mortality among HIV-positive smokers is greater than in HIV-negative smokers[9]. Smoking-associated mortality increases with age and accounts for more life years lost than HIV-associated mortality[10]. In the Strategies for Management of Antiretroviral Therapy (SMART) study, the risk for serious coronary events or non-AIDS-defining neoplasia was twice as high for smokers than for non-smokers. The risk of pulmonary cancer was nine times higher among smokers than non-smokers[2]. In the Swiss HIV Cohort, former and current smoking was associated with death of any cause[11]. In another cohort study, when comparing HIV-positive smokers versus non-smokers, mortality secondary to non-AIDS events was significantly higher than all-cause mortality. Excess of mortality rate among smokers and population attributable risk (PAR%) of smoking-related deaths were greater than threefold for HIV-positive and twofold for HIV-negative participants, respectively[12].

Some authors have found a worse HAART compliance among smokers[13] along with greater risk of virologic failure[14]. Alcohol abuse, which is highly prevalent among smokers[15], has also been linked to neglected antiretroviral therapy (ART) adherence and a subsequent worse immune response[16].

Recent data confirm that nicotine metabolism is enhanced in HIV smokers[17], although more research is necessary to understand its pathological implications. Potential drug-drug interactions between nicotine and antiretroviral drugs have been proposed since nicotine[17], protease inhibitors, and nonnucleoside reverse transcriptase analogs are metabolized by cytochrome P450 enzymes. These interactions may lead to subtherapeutic antiretroviral plasma levels as well as overproduction of reactive oxygen species (ROS) enhancing viral replication[18,19] (Fig. 1).

Pathophysiological basis of tobacco smoking effects on clinical health

More than 5,000 different chemical compounds have been identified among solid particles of tobacco or its smoke constituents[20]. Some of them are gases like carbon monoxide and carbon dioxide, nitrogen-based and sulfur-based compounds. Others are volatile components of the liquid part of the smoke aerosol like formaldehyde, aniline, acrolein, benzene, arsenic, cadmium, and plumb. Lastly, others are solid particles of the smoke such as nicotine and polyaromatic hydrocarbons. Nicotine is an alkaloid from tobacco smoke responsible for its most relevant and immediate physiological effects. It mimics the endogenous neurotransmitter acetylcholine (ACh) and exerts most of its physiological effects as an agonist of the Ach receptors (nAChR)[21]. This group of receptors is not only expressed on the surface of neural cells but also on cells in the immune system[22].

Cigarette smoke impairs redox homeostasis by both increasing levels of ROS derived from combustion and decreasing intracellular antioxidant defenses.

This imbalance fosters the activation of redox-sensitive signaling pathways, leading to altered cellular responses and cellular damage (Fig. 1). One of these pathways is inflammation, which induces generation of endogenous free radicals, leading to tissue lesion within central nervous[23], respiratory[24], and cardiovascular[25] systems. Tobacco smoke through oxidative stress induces mitochondrial dysfunction, with a systemic impact affecting cardiovascular[25], respiratory[26], brain, and nervous[27] systems. Mitochondrial oxidative injury among smokers might be important when caring for HIV patients, since several antiretroviral drugs[28] as well as HIV infection itself[29] can also induce mitochondrial toxicity. Smoking may expedite the aging process through oxidative stress and telomere shortening[30] (Fig. 1).

Effects on immune system

Cigarette smoke also contains chemical compounds other than nicotine, and traces of microbial components, which exert changes in the innate and adaptive immunity. This immune modulation results in a combination of pro-inflammation and immune suppression whose balance depends on factors associated to tobacco exposure (type and duration) and basal conditions of the immune system. The effects of these alterations may consist of: promotion of colonization and infection, apoptosis, tissue damage, autoimmunity, and impaired antineoplastic cell mechanisms[31].

Nicotine displays its cholinergic immunomodulatory effects on macrophages, T lymphocytes, and B lymphocyte-derived cell lines, not by interacting with nAChRs but in the intracellular compartment. Here, nicotine modifies signaling pathways involved in the regulation of the inflammatory response[22]. Figure 2 shows immunologic effects of nicotine and tobacco smoke extract identified so far.

In HIV-infected patients, tobacco consumption's immunologic effects may differ from those among the general population. For instance, smoking-related leukocytosis is

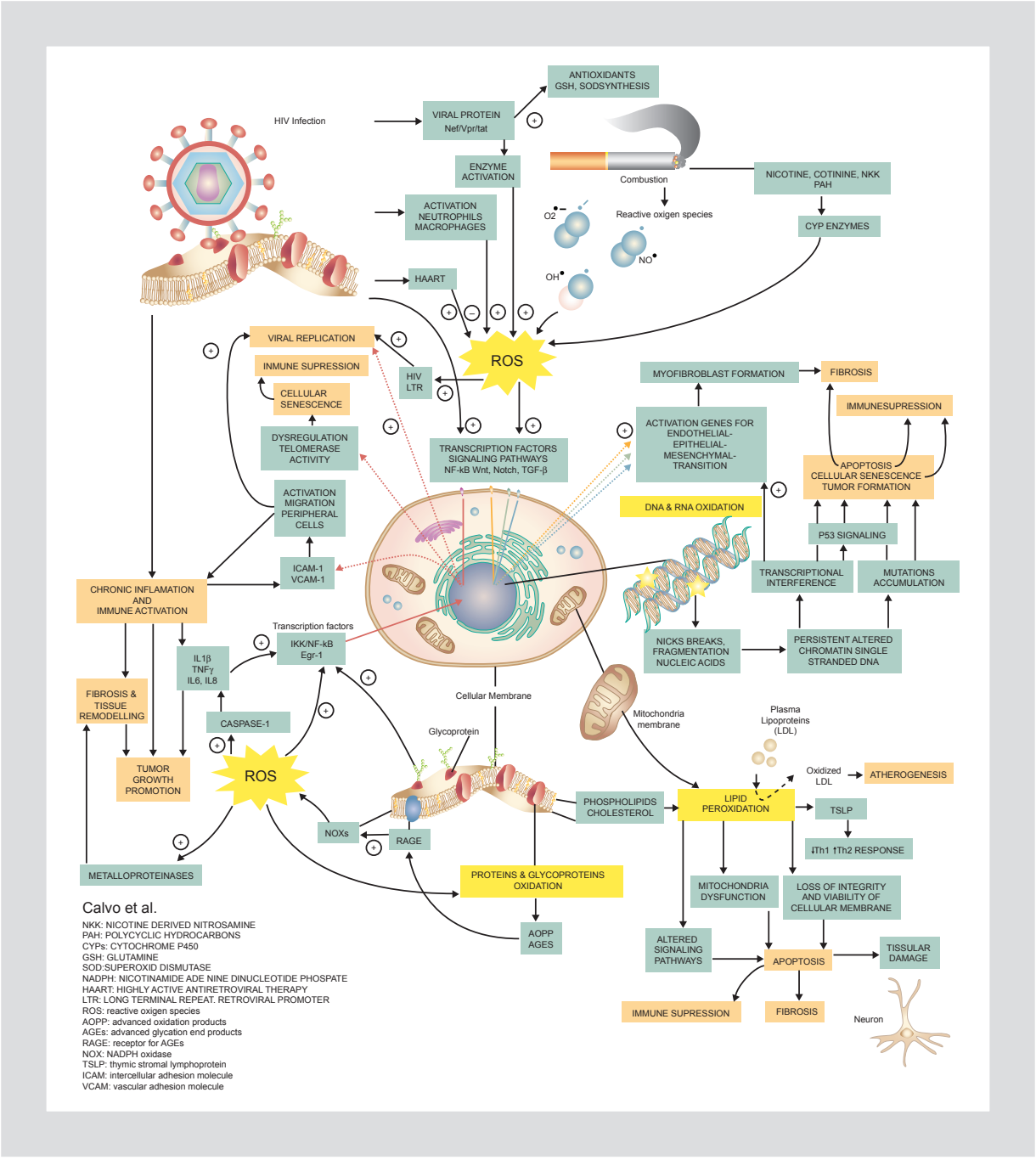

Figure 1. *Oxidative stress induced by tobacco smoke and HIV infection.This scheme depicts: (1) Pathways by which reactive oxygen species (ROS) are generated in the context of HIV infection and tobacco smoking. (2) Pathways by which ROS induces cellular damage such as chronic inflammation, altered immune response, cellular senescence, and apoptosis along with tissue damage such as organ fibrosis, tissue remodeling, atherosclerosis, and tumor formation.*

less pronounced in HIV-positive smokers[32]. In the San Francisco Men's Health Study[33], smoking showed an association with increased CD4+ cell counts in all men, but the effect was attenuated in HIV-seropositive men (85 cells/mcl difference in median counts when non-smokers were compared with smokers) compared with HIV-seronegative men (230 cells/mcl difference in median counts); analysis of data from HIV seroconverters suggested that smokers' counts fall faster than those of non-smokers after HIV infection acquisition. The smoking effects on CD4 counts in seroconverters were later confirmed in the Multicenter AIDS Cohort Study[32], which

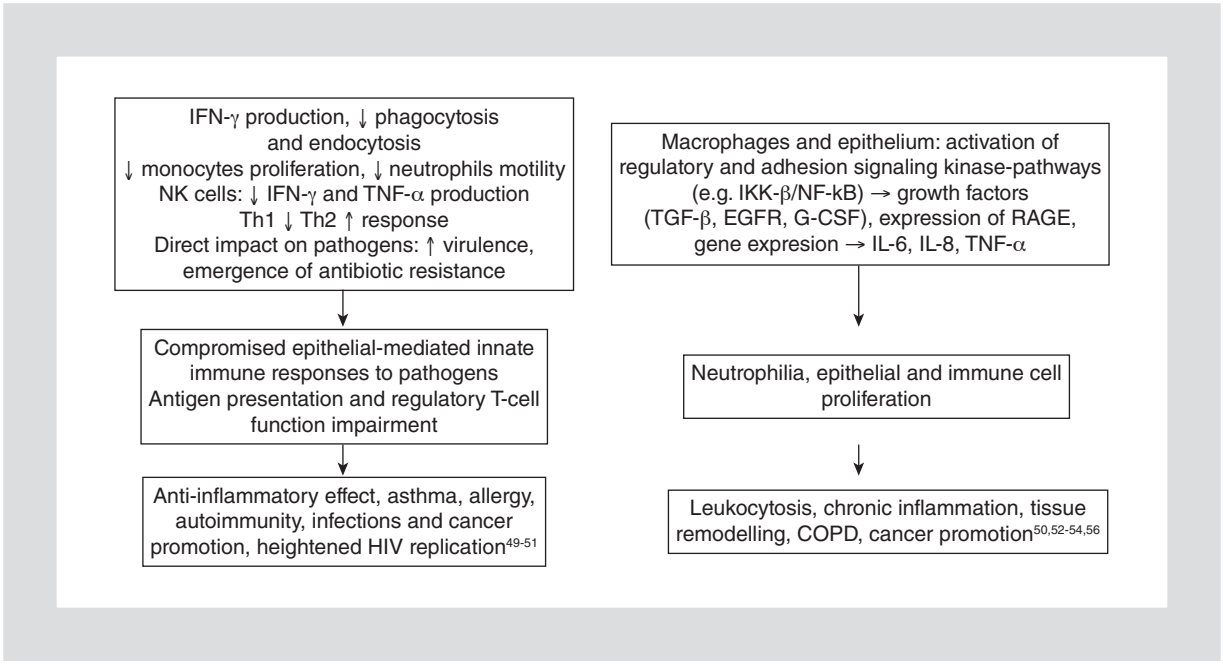

Figure 2. *Effects of nicotine and/or other components of cigarette smoke on immune system.The RAGE receptor is a multi-ligand receptor on the surface of macrophages that, when activated, triggers inflammation; IKK kinase complex proteins such as IKK β trigger the transcription factor NF-κB signaling. IL: interleukin; IFN-γ: interferon gamma, NK: natural killer; TNF-α:tumor necrosis factor alpha; Th1: T helper type 1; Th2: T helper type 2; RAGE: receptor for advanced glycation end products (AGE); IKK-β: I kappa B kinase; NF-κB: nuclear factor kappa B; TGF-β: transforming growth factor beta; EGFR: epidermal growth factor receptor; G-CSF: granulocyte colony stimulating factor.*

additionally showed the reversibility upon smoking cessation. HIV-positive smokers have been reported to have a worse immunological[14,34] and virological[14] response to ART, and a higher risk of AIDS[14]. Other authors have failed to detect any immunological impact of smoking in HIV patients[6]. Local immune suppression affecting the respiratory epithelium of HIV patients aggravated by smoking may contribute to respiratory diseases among otherwise healthy HIV-positive smokers[35].

HIV replication is enhanced by nicotine and other smoke constituents through activation of cellular gene expression[36,37]. Nicotine is involved in viral replication through its *CYP2A6* metabolism and the subsequent induction of oxidative stress in macrophages[38] (Fig. 1). Recent data confirm the association between HIV and smoking and leukocyte telomere shortening leading to immune senescence[39] (Fig. 1).

Effects on cancer risk

The International Agency for Research on Cancer classifies 73 compounds identified in tobacco smoke as carcinogens and cigarette smoke as class 1 human carcinogen[20]. So far, the role of nicotine as carcinogen has not yet been ruled out due to an increasing amount of supporting data. Tobacco-derived carcinogens are involved in the following malignancies: lung, oral cavity, pharynx, larynx, pancreas, nasal cavities and sinuses, esophagus, stomach, liver, urinary bladder, kidney and uterine cervix as well as leukemia. Carcinogenic pathways need further investigation, but some of them have been identified (Table 1).

HIV patients may develop AIDS-related and non-AIDS-related malignancies. Whereas immunodeficiency is a key factor in the pathogenesis of AIDS-malignancies, the carcinogenic effect of their corresponding risk factors seems more critical for non-AIDS malignancies[49,50]. The HIV patients on HAART exhibit an increased risk of non-AIDS cancer compared to the general population. This is due to the significantly higher prevalence of smoking-related and virological cancers in HIV-infected patients[50].

The contribution of HIV infection to cancer is double that of smoking in terms of PAF[50]. Impaired antitumoral immune response associated with tobacco smoking acts synergistically with HIV infection by enhancing human papillomavirus in the pathogenesis of uterine cervix[47], anal, and head and neck cancer[51,52]. Lung cancer is one of the most prevalent non-AIDS malignancies among HIV patients and the only one in which both tobacco and HIV have clearly shown an

Table 1. Tobacco involvement in cancer promotion

Carcinogenic agent	Carcinogenic via	Type of cancer
CS-derived genotoxic carcinogens	– DNA adduction and mutagenicity: genotoxic carcinogens bind DNA forming DNA adducts that, if not repaired, will elicit errors during DNA polymerase replication → mutations → ↑ oncogene or ↓ tumor suppressor gene – Mutations in gene codifying for the ↓ tumor suppressor p53 – Mutations in oncogene KRAS	– Bladder carcinoma[41] – Lung and pancreatic cancer – (PAH and NNK)[20,42,43] – Lung cancer[44] – Lung and pancreatic cancer[43,44]
CS → cell receptors and regulatory and adhesion signaling k-pathways (e.g. NF-kB) activation	– Chronic inflammation, oxidative stress (Fig. 1), epigenetic changes (e.g. DNA methylation) → cell proliferation, migration and transformation, angiogenesis and apoptosis → tissue damage	– COPD or chronic pancreatitis → lung and pancreatic cancer[42,43,45]
Nicotine	– Upregulation α7-nAChRs triggering tumor growth pathways – Tumor promoter: angiogenic effect (nAChR activation), increases proliferation and reduces apoptosis (NF-kB regulation)	– Lung cancer[46] – Pancreatic cancer[43]
ROS	– Synergistic effect of tobacco enhancing HPV infection, its persistence and its carcinogenic effect[40]	Uterine cervix[47], head and neck cancer[48]

CS: cigarette smoke; PAH: polycyclic aromatic hydrocarbons; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1- abutanone; COPD: chronic obstructive pulmonary disease; nAChR: nicotinic acetylcholinergic receptor; NF-kB: nuclear factor kappa B; ROS: reactive oxygen species; HPV: human papillomavirus.

independent etiopathological role[53]. Due to the genomic instability conveyed by microsatellite alterations detected in lung cancer samples from HIV patients, HIV infection has been proposed as a mechanism for amplifying the effect of cigarette smoke genotoxic carcinogens on lung cancer[54]. However, HIV infection and the effects of tobacco smoking appear to be cumulative rather than synergistic according to epidemiological analysis[53]. HIV-related immune suppression seems not to be related to the risk of developing lung cancer[49,50]. Consistently, ART use has not proved to lower lung cancer prevalence[49]. This supports the role on cancer promotion of other HIV-related mechanisms such as local chronic inflammation that favors repeated pulmonary infections and tissue damage[45]. Although HIV itself has also been suggested to exert an oncogenic action[49], some facts argue against this hypothesis. For instance, the risk of lung cancer in HIV-positive patients is high for all histopathological subtypes, weakening the hypothesis of a single oncogenic virus involved in its pathogenesis[49].

Effects on cardiovascular system and metabolism

For more than 60 years, the strong association between tobacco abuse and cardiovascular disease and its associated mortality (70% greater in smokers than in non-smokers)[55] has been well known. In current smokers, adjusted hazard ratios for myocardial infarction, stroke, and cardiovascular disease respectively are 2.25, 2.12, and 2.45 when compared with never smokers[56].

After smoking a cigarette, hemodynamic effects such as increased heart rate and blood pressure are not only secondary to nicotine-dependent cholinergic stimulation, but also to oxidative stress in brainstem induced by tobacco smoke. Both mechanisms lead to deregulation of the sympathetic and parasympathetic responses involving catecholamine[57]. In the long term, tobacco smoke promotes atherosclerosis through endothelial dysfunction and lipid metabolic changes, and by fostering hypercoagulation (Table 2).

Different complex nicotine-mediated mechanisms underlie glucose metabolism changes along with central fat accumulation observed in heavy smokers[60]. Consistently, epidemiological evidence supports smoking as an independent risk factor for diabetes. The observed dose-dependent link between tobacco use and risk of diabetes correlates with recent findings implicating cytochrome p450 2A6, responsible for nicotine metabolism[61].

Several HIV-associated factors convey an increased risk of cardiovascular disease. High HIV viremia is

Table 2. Phatophysiological effects of cigarette smoke on cardiovascular system

Mechanism	Pathologic effect	Clinical feature
LDL oxidation (Fig. 1) and endothelial inflammation → impairment in cellular responses (such as cytokines) to proatherogenic factors e.g.: ↑ CRP and endothelin-1, ↓ nitric oxide and prostacyclin[25]	Vasoconstriction → cytoplasmic vacuolation, mitochondrial and sub-endothelial edema, less complex intercellular unions → endothelial permeability and dysfunction	Atherosclerotic and vasospastic ischemia
nAChR → growth factors[58]	Angiogenesis → endothelial dysfunction	Atherosclerosis COPD Tumor vascularization
Combustion → CO → cHb → hypoxia	↓ Respiratory enzymes, ↓ inotropism ↓ fibrillation threshold Endothelial dysfunction	Atherosclerosis Heart insufficiency Cardiac arrhythmia
nAchR → ↑ sympathoadrenal axis → lipolysis and hormonal modulation in CNS	Proatherogenic lipid profile (↑ total, LDL and VLDL-C, ↓ HDL-C and ApoA-protein)[59], glucose intolerance, insulin resistance, central obesity[60]	Atherosclerosis Metabolic syndrome, type 2 diabetes[61] → atherosclerosis
Inhibition of platelet NTPDase → ↓ adenine nucleotide degradation → platelet activation ↑ nAchR → platelet catecholaminergic receptors → platelet and arachidonate pathway activation, aggregation[62]	Hypercoagulability	Thrombosis may occur, heightening the risk of ischemic coronary events

LDL: low density lipoprotein; HDL: high density lipoprotein; CRP: C reactive protein; nAChR: nicotinic acetylcholinergic receptor; CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; cHb: carboxihemoglobin; NTPDase: nucleoside triphosphate diphosphohydrolase.

associated with chronic subclinical inflammation and deleterious changes in lipid metabolism[63]. HIV immune depletion is an independent risk factor for ischemic coronary disease, contributing as much as traditional risk factors do[64]. Antiretroviral therapy is linked to arterial inflammation[65] since it, and mainly protease inhibitors, convey a pro-atherogenic lipid profile[66].

The contributions of smoking and HIV infection in the development of atherosclerosis[67] and cardiovascular disease[68] are independent but comparable in intensity. The PAR% of smoking for acute coronary disease in HIV-positive patients has shown to be double that in HIV-negative patients, and it is several times higher than that of diabetes or hypertension[69]. A triple interaction between smoking, age, and HIV infection on carotid intima media thickness[70], and between duration of smoking, of ART, and coronary vessel thickness[71] have been found when comparing HIV-positive versus HIV-negative healthy individuals.

Effects on central nervous system

In the general population, current smoking is an independent risk factor for multiple sclerosis and Alzheimer's disease, and has also been linked to the development of vascular dementia, unspecified dementia, and cognitive impairment[27].

Through nAchR stimulation, nicotine stimulates cognitive functions such as alertness, reaction time, and memory in the short term[72]. Cigarette smoking constituents, including nicotine, may induce sustained cellular oxidative stress and neuroinflammation, leading to endothelial injury with blood brain barrier disruption[27], abnormalities that lie beneath the pathogenesis of multiple sclerosis[73], Alzheimer's, and Parkinson's disease[27].

Despite the sharp reduction of HIV-associated dementia and other AIDS-related diseases since the introduction of HAART, neurocognitive impairment still affects up to 50% of HIV patients[74]. Low nadir CD4 counts and older age are well established risk factors[75]. Traditional cardiovascular risk factors induce brain microvessel and blood-brain barrier damage, resulting in ischemia and inflammation[27]. Consistently, traditional cardiovascular risk factors including smoking show strong association with lower cognitive performance in those HIV positive[76]. Nicotine and the protease inhibitor saquinavir may cause blood-brain barrier disruption through an additive oxidative stress burden[77]. Further-

Table 3. Deleterious effects of tobacco and HIV infection on the bone

Effects of tobacco smoking[79]
Lower body fat → lower body weight → weaker osteogenic stimulus
Altered estrogen production metabolism and clearance → lower estrogen bioavailability → anticipated premenopausal ovarian dysfunction
Increased serum levels of adrenal steroid hormones
Enhanced hepatic vitamin D precursors metabolism → lower levels of 25-hydroxycholecalciferol
Intestinal atherosclerosis → lower calcium enteric absorption
Oxidative stress (Fig. 1) → ↓ parathyroid hormone levels and ↑ bone resorption
Inhibition of *in vitro* osteogenesis
Effects of HIV infection[80]
Untreated HIV-positive exhibit high levels of bone resorption markers
– HIV viral proteins and inflammatory cytokines (TNF and IL-6) favor osteoclastogenesis and apoptosis and suppress osteoblastogenesis in *in vitro* studies
HAART ↑ bone resorption reaching up to 6% of loss of BMD after two years of therapy
– Bone resorption is more intense the lower the CD4 count is before HAART initiation and irrespective of the type of HAART
– Protease inhibitors and tenofovir have been linked to osteoporosis and risk of fractures
• Exposure to boosted lopinavir increases this risk by 17%
• Tenofovir elicits greater BMD loss than other backbone drugs by an altered renal phosphate handling
Traditional risk factors for bone loss frequent in HIV-positive subjects
– Smoking is the most prevalent
– Vitamin D deficiency
– Hypogonadism
– Low body weight
– Alcohol and opiate abuse
– Sedentary lifestyle

TNF: tumor necrosis factor; IL-6: interleukin-6; BMD: bone marrow density.

more, nicotine enhances protease inhibitor penetration into the central nervous system. This may convey a better suppression of HIV viral load in this reservoir, but an increase in the risk for neurotoxicity as well[77]. Alcohol abuse may potentiate the negative effects of chronic smoking on the nervous system in HIV-infected patients. Heavy drinking HIV-positive smokers exhibited worse learning, memory, and cognition along with reduced neocortical volumes when compared with heavy drinking HIV-positive non-smokers and with light drinking HIV-negative non-smokers[78].

Effects on bone metabolism

Smoking is an independent risk factor for osteoporosis and major site osteoporotic fractures both in general[79] and HIV-infected populations[80]. Smoking effects on bone are dose-dependent and partially reversible. Lower bone mineral density, osteoporosis, and fragility fractures are more prevalent among HIV-positive patients[81]. This may be due at least in part to HIV infection itself, immune reconstitution after starting effective ART, specific antiretroviral drugs, and a higher prevalence of risk factors common to the general population including tobacco smoking[80]. Table 3 summarizes the deleterious effects of tobacco and HIV infection on the bone.

Effects on reproductive health

HIV-infected patients have lower fertility rates than uninfected controls[82]. HIV and genitourinary coinfections may result in hypogonadism, oligospermia, teratozoospermia, or uterin implantation problems. It is also well known that immune depression may decrease fertility rates[83]. Psychosocial factors (e.g. drug abuse) and mitochondrial toxicity mediated by antiretroviral drugs have been linked to low fertility or infertility[84]. Cigarette smoking, through oxidative stress[85] and subsequent DNA damage, may alter many physiological processes involved in fertility: maturation of ovarian follicle, uterine implantation, and sperm production and quality[86].

Conclusions

Tobacco smoking is probably the best described risk factor for a number of health problems affecting different organs and systems. Nicotine and other components of

tobacco smoke induce complex pathophysiological changes that still require further research.

In the HIV-infected community, smoking is at least twice as prevalent as in the general population worldwide. Although smoking has been invariably recognized as a risk factor for almost all comorbidities in HIV-infected patients, it is less clear how smoking may exert its negative health effects. This comprehensive review summarizes current knowledge on this issue, since a better understanding of smoking pathophysiology may be critical for encouraging more effective efforts towards smoking cessation in HIV-positive patients, an objective that every physician should be committed to.

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