UNIVERSITAT DE BARCELONA

Cardiovascular risk in patients infected by the human immunodeficiency virus compared with that of uninfected patients and general population

Estudio del riesgo cardiovascular en pacientes infectados por el virus de la inmunodeficiencia humana respecto a pacientes no infectados y población general

Marta Calvo Sánchez

TESIS DOCTORAL

CARDIOVASCULAR RISK IN PATIENTS INFECTED BY THE HUMAN IMMUNODEFICIENCY VIRUS COMPARED WITH THAT OF UNINFECTED PATIENTS AND GENERAL POPULATION

ESTUDIO DEL RIESGO CARDIOVASCULAR EN PACIENTES INFECTADOS POR EL VIRUS DE LA INMUNODEFICIENCIA HUMANA RESPECTO A PACIENTES NO INFECTADOS Y POBLACION GENERAL

Marta Calvo Sánchez

Departamento de Medicina

Facultad de Medicina

Universidad de Barcelona

Barcelona, 2014

El **Dr. Esteban Martínez Chamorro**, profesor asociado del Departamento de Medicina de la Facultad de Medicina de la Universidad de Barcelona y médico adjunto consultor del Servicio de Enfermedades Infecciosas del Hospital Clínico de Barcelona

CERTIFICA:

Que la tesis titulada: **"Estudio del riesgo cardiovascular en pacientes infectados por el virus de la inmunodeficiencia humana respecto a pacientes no infectados y población general"** ha sido realizada por **Marta Calvo Sánchez** y dirigida por el que suscribe siendo apta para ser defendida ante el Tribunal correspondiente para optar al grado de Doctor.

Dr. Esteban Martínez Chamorro

Barcelona, 16 septiembre de 2014

Directores de la tesis:

Dr. Esteban Martínez Chamorro	**Dr. Josep Mallolas Masferrer**
Servicio de Enfermedades Infecciosas	Servicio de Enfermedades Infecciosas
Hospital Clínico de Barcelona	Hospital Clínico de Barcelona
Universidad de Barcelona	Universidad de Barcelona

To my friends Padmasree and Gheeta, two brave women

A Padmasree y Gheeta,

dos amigas valientes

Presentación

La presente Tesis doctoral se ha estructurado siguiendo la Normativa Interna de la Universidad de Barcelona para la presentación de Tesis doctorales como compendio de publicaciones.

Los trabajos que conforman esta memoria del proyecto de tesis doctoral pertenecen a una misma línea de investigación, enmarcada en el estudio del riesgo cardiovascular en pacientes infectadas por el virus de la inmunodeficiencia humana. Los resultados de dichos trabajos han sido publicados en 3 artículos originales y 3 artículos de revisión en revistas de amplia difusión internacional con un factor de impacto de 17,8.

"Wir fühlen, daß selbst, wenn alle möglichen wissenschaftlichen Fragen beantwortet sind, unsere Lebensprobleme noch gar nicht berührt sind. Freilich bleibt dann eben keine Frage mehr; und eben dies ist die Antwort."

"Sentimos que aún cuando todas las posibles cuestiones científicas hayan recibido respuesta, nuestros problemas vitales todavía no se han rozado en lo más mínimo. Por supuesto que entonces ya no queda pregunta alguna; y esto es precisamente la respuesta."

"We feel that even when all possible scientific questions have been answered, our vital problems have not yet been touched at all. Of course then I no longer have any questions; and this is precisely the answer".

Ludwig Wittgenstein

Agradecimientos

Deseo expresar mi sincero agradecimiento a todas las personas que han hecho posible la elaboración de esta tesis doctoral, en especial a todos los pacientes que han confiado en mí.

Agradezco a mis directores de tesis su interés por el seguimiento de mi trabajo y su apoyo continuo y cercano.

De forma especial quiero agradecer al Dr. Esteban Martínez la confianza, constancia y buen consejo con los que me ha ayudado durante el desarrollo de esta tesis.

A todos los amigos que he encontrado durante los cuatro años en que he trabajado en el Hospital Clínico. A los compañeros del Hospital de Día, del Helios y de la planta de Enfermedades Infecciosas.

A todas las personas con las que compartí mis inicios en el ámbito de la infección VIH en el proyecto de la Fundación Vicente Ferrer en India. Una experiencia única.

A todos mis amigos, ellos saben quiénes son, cuánto representan para mí y cuánto me ayudan en mi día a día.

A mi familia, en especial a mi abuelo.

A Marcus por su constante apoyo, por todo.

Contents

Abbreviations

HAART	highly active antiretroviral therapy
ICD	ischemic coronary disease
CVR	cardiovascular risk
TCRF	traditional cardiovascular risk factors
PAR	population attributable risk
TGC	triglyceride
HDL-C	high density lipoproteins-cholesterol
LDL-C	low density lipoproteins- cholesterol
VLDL	low-density lipoprotein
LD	lipodystrophy
DM	diabetes mellitus
ROS	reactive oxygen species
IGT	impaired glucose tolerance
cIMT	carotid intima-media thickness
SMC	smooth muscle cells
hsCRP	high-sensitivity C reactive protein
IL-6	inteleukine-6
MMP	matrix-metaloproteinases
CMV	cytomegalovirus
HCV	hepatitis C virus
LPS	lipopolyssacharide
EBV	Epstein-Barr virus
HR	hazard ratio
OR	odds ratio
RR	relative risk
HOMA index	homeostasis model insulin resistance
CYP	cytochrome P
PI	protease inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non nucleoside reverse transcriptase inhibitor

List of original publications

1. **Calvo-Sánchez M**, Perelló R, Pérez I, Mateo MG, Junyent M, Laguno M, Blanco JL, Martínez-Rebollar M, Sánchez M, Mallolas J, Gatell JM, Domingo P, Martínez E.Differences between HIV-infected and uninfected adults in the contributions of smoking, diabetes and hypertension to acute coronary syndrome: two parallel case-control studies. HIV Med. 2013 Jan;14(1):40-8.

2. Perelló R, **Calvo M**, Miró O, Castañeda M, Saubí N, Camón S, Foix A, Gatell JM, Masotti M, Mallolas J, Sánchez M, Martinez E.Clinical presentation of acute coronary syndrome in HIV-1-infected adults: a retrospective analysis of a prospectively collected cohort. Eur J Intern Med. 2011 Oct;22(5):485-8.

3. Egaña-Gorroño L, Martínez E, Escribà T, **Calvo M**, Gatell JM, Arnedo M. Association study of lipoprotein(a) genetic markers, traditional risk factors, and coronary heart disease in HIV-1-infected patients. Front Immunol. 2012 Dec 6;3:367.

4. **Calvo M**, Martinez E. Update on metabolic issues in HIV-1-infected patients. Curr Opin HIV AIDS. 2014 Jul;9(4):332-9.

5. **Calvo M**, Martínez E. How to Address Smoking Cessation in HIV positive patients. HIV Medicine 2014.

6. **Calvo M**, Laguno M, Martínez M, Martínez E. Pathogenic effects of tobacco smoking in HIV-1-infected patients. AIDS Reviews 2014.

Hypothesis

I. Tobacco smoking, diabetes or hypertension have been identified as risk factors for cardiovascular disease in both HIV-uninfected and HIV-infected adults. It is a fact that these three traditional cardiovascular risk factors are more prevalent in HIV-1-infected adults than in the general population. The impact of these traditional cardiovascular risk factors may be modified by additional factors inherent to HIV infection such as chronic inflammation, immuneactivation, hypercoagulability, antiretroviral therapy, co-morbidites or simply by the younger mean age of the HIV community. Hypothesis: the individual contribution of smoking, diabetes or hypertension to acute coronary disease may differ between HIV infected and uninfected adults.

II. As mentioned above, HIV infection implies specific different chronic conditions that may in turn be translated into different clinical symptoms and prognosis of ACS. Hypothesis: Clinical characteristics and prognosis in HIV-1-infected adults presenting with ACS may be different from those in un-infected patients.

III. The size of Apolipoprotein (a) is determined by a copy number variation of the KIV-2 region in LPA gene. In the general population, fewer apo(a) KIV-2 repeats. Several have been associated with atherogenesis and ischemic coronary disease (ICD). Hypothesis: It may occur that in the setting of HIV infection this genetic variation has a different translation.

IV. Physiologic aging implies changes in lipid and glucose metabolisms and in body fat composition. Several endocrinopathies can be diagnosed in the elderly: type 2 diabetes mellitus, testosterone deficiency, sarcopenia, low bone mineral density and thyroid deficiency. HIV infection and its treatment are associated to high prevalence of metabolic abnormalities. HIV population is aging mainly due to the widespread use of HAART. Hypothesis: Aging HIV-1-infected patients may be an specific group with increased susceptibility to develop metabolic changes and diseases.

V. Tobacco smoking prevalence in the HIV community remains higher than in the general population. Some factors have been proposed to explain this higher prevalence. Most of them appear to be also obstacles hindering smoking cessation in this specific group. The number of life years lost due to tobacco consumption is up to twice as much the number lost due to HIV. Hypothesis: Despite the obstacles that HIV-1-infected patients face, smoking cessation is a realistic and achievable objective.

VI. HIV infection impacts on many physiological pathways and so does tobacco-smoke exposure. Hypothesis: Pathophysiology of tobacco-related diseases in HIV-1-infected patients may differ to that in the general population. These differences may confer HIV-1-infected patients greater susceptibility towards tobacco-related health problems.

Objetives

Primary objective

The common main objective of the studies herein presented is to elucidate whether HIV-1-infected patients present with differences in cardiovascular risk relative to un-infected individuals.

Secondary objectives:

1. Epidemiological:

    a. To dissect the relative contribution of smoking, diabetes and hypertension to ACS in HIV-1-infected patients.

    b. To better understand the epidemiological background of HIV-1-infected patients specially focusing on tobacco smoking, aging, metabolic changes.

2. Clinical:

    a. To analyse the clinical characteristics of ACS in HIV-1-infected patients, characteristics of delivery of care for patients presenting with ACS and their prognosis.

    b. To gain insight into the pathogenesis of smoking-related health problems and metabolic disturbances in the aging HIV population.

3. Genetic: To analyse whether genetic variants of Apo (A) may be genetic markers of greater cardiovascular risk in HIV infected persons.

Introduction

Nowadays, life expectancy of HIV-1-infected patients receiving effective antiretroviral therapy is equated to that of the general population. As a consequence of this clinical breakthrough, risk factors and causes of morbidity and mortality in the aging general population such as obesity, metabolic and cardiovascular disease, are emerging as main risk factors and causes of morbidity and mortality among HIV-1-infected patients. However, HIV infection implies a specific epidemiologic, pathophysiological and clinical setting. High prevalence of tobacco, alcohol, illicit drug consumption, persistent immunodeficiency, immune activation and inflammation despite viral suppression and various secondary effects of antiretroviral therapy, are all factors interplaying in the development of cardiovascular disease in HIV-1-infected patients and they may also impact clinical features, symptoms, outcomes after specific cardiologic interventions and prognosis. So far, HIV patients-tailored clinical guidelines, are based on the available recommendations for the general population plus on considering earlier initiation of antiretroviral therapy. This is a basic approach that although correct is likely amenable for optimization. A better understanding of the differences regarding pathogenesis, epidemiology and clinical characteristics of cardiovascular disease between HIV-1-infected patients and uninfected individuals can help to design and develop prevention and clinical interventions to reduce cardiovascular disease risk among HIV-1-infected patients.

Background

1. Contextualizing HIV and cardiovascular disease epidemics.

Two pandemics, infectious and cardiovascular disease, have enlarged worldwide mortality up to date showing along the last century a variable individual impact in public health while remaining closely linked as well. Prior to the widespread use of antibiotic therapy, infectious diseases was the first cause of death worldwide and rheumatic fever secondary to Streptococcus pyogenes provoked most of cardiovascular deaths up to 1940s, being replaced after that by ischemic coronary disease (ICD). ICD overcame all type of infectious diseases as main reason of death in industrialized countries. Thanks to scientific efforts focused on understanding and controlling coronary ischemia, its current associated mortality tends to a progressive decline in western countries in contrast to its rising trend in poorer areas.

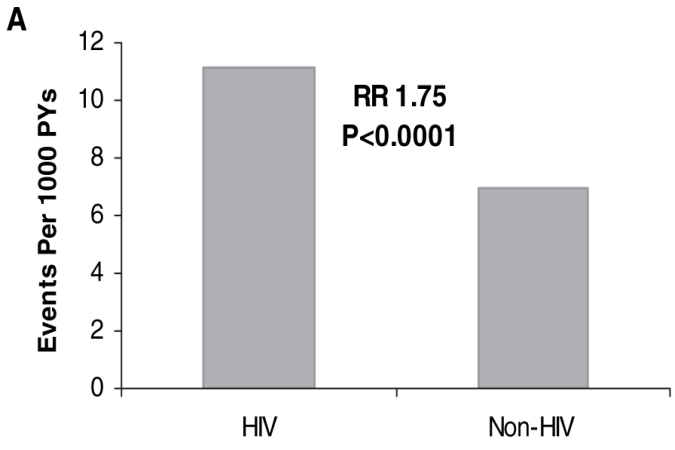
Despite of scientific progress, nowadays the world still faces important infectious epidemics such as the human immunodeficiency virus (HIV), a lentivirus responsible for the life-threatening acquired immunodeficiency syndrome (AIDS). HIV pandemic accounts for an estimated 35.3 (32.2–38.8) million people living with HIV or AIDS (PLWHA) in 2012 (1). This viral infection has become a chronic disease since it is controlled thanks to highly active antiretroviral treatment (HAART). HAART avoids disease progression to AIDS by partially reversing immune-suppression which consequently extends survival but is not able to eradicate HIV. Thus the organism must go on struggling against chronic immune-activation and chronic inflammation triggered by persistent viremia. In addition to these viral conditions, there are host conditions such as aging, health and behavioural aspects more prevalent among HIV-1-infected patients which lead to a variety of medical problems. ICD is currently one of the most remarkable as HIV physicians are witnessing a rebound of serious cardiovascular events in HIV-1-infected patients whereas ICD decreases in the general population (2).

These facts are consistent with latest projections of global mortality published by the World Health Organization in 2006 (3) according to which HIV/AIDS and ICD will become two of the three main causes of death worldwide in 2030. In this report, ICD is considered as one of tobacco-attributable causes of death and will account for up to 50% more deaths than HIV/AIDS. Depressive disorders appear to be another of the three main causes of global deaths, disorders also known to be highly prevalent among HIV-1-infected patients and smokers.

In conclusion, HIV and cardiovascular disease are closely linked epidemics and their control along with smoking cessation strategies, are challenging current and prospective priorities for global health policies.

Cardiovascular risk (CVR) is heightened among HIV-1-infected patients comparing with that in the general population.

First data about a higher incidence of ICD in HIV-1-infected patients comparing with non infected patients were published in 2002 by Klein et al. (4). This study was actually designed to assess a possible implication of protease inhibitors (PI) in the development of ICD and the analysis was not adjusted by traditional cardiovascular risk factors (TCRF). They observed that the ICD-related hospitalization rate (6.5 vs 3.8, p= 0.003) and myocardial infarction rate (4.3 vs 2.9, p=0.07) were both higher among HIV-1-infected patients than in uninfected patients. In 2011 the same authors presented data of a new analysis, this time adjusting by TCRF including smoking. They obtained an adjusted myocardial infarction rate ratio of 1.4 (95% CI 1.3 to 1.7; p <0.001) (5). Consistently, in 2003 Currier et al. observed that ICD incidence was increased among HIV-positive *vs* HIV-negative individuals in a large cohort including 3 million participants. In this work it was newly observed that this increased ICD risk was concentrated on younger men (up to 34) and younger women (up to 44) (6). Till 2007, no more significant data were released. Then, Triant et al. confirmed a higher relative risk (RR) of myocardial infarction (1.75, 95% CI, 1.51–2.02) in a multivariate analysis adjusted by TCRF (excluding tobacco), as well as the first data about an increased risk of myocardial infarction among HIV infected women (RR 2.98, 95% CI 2.33–3.75; P < 0.0001) comparing with men (RR 1.40, 95% CI 1.16–1.67; P = 0.0003) (7).



Myocardial infarction rates and corresponding adjusted RR.

Bars indicate crude rates of AMI events per 1000 PY as determined by ICD coding. RR and associated *P* value are shown *above the bars*. RR was determined from Poisson regression analysis adjusting for age, gender, race, hypertension, diabetes, and dyslipidemia. Associated 95% CIs for RR shown are **1.51–2.02**. Triant V. A. et al. (7)

Obel et. al studied a Danish cohort of patients and found a higher ICD hospitalization rate among HIV-1-infected patients *vs* HIV-negative patients (adjusted RR, 2.12; 95% CI, 1.62–2.76). When focusing on the HIV group, noted that in those patients who had not yet started HAART, the risk of ICD hospitalization was even higher although not

statistically significant. On the other hand, the relative risk of ICD was stable during the first 8 years after HAART initiation (comparing with general population) (8). More recently, the ICD risk in the French Hospital Database on HIV was assessed, comparing with the French general population (9). An increased ICD risk among HIV-positive participants was confirmed. In this HIV group, younger patients (men up to 55 and women up to 45 years of age) and women (*vs* men) showed a higher ICD risk as observed in previous studies (6)(7). An increased risk of ICD in HIV comparing with un-infected individuals was confirmed in the American Veterans Cohort (10). In contrast with the stable ICD incidence in the general population of Canada, this incidence among the HIV-positive community is increasing despite HAART (11).

HIV infection must be considered as an independent cardiovascular risk factor. Since HAART has extended life expectancy of HIV-1-infected patients, they are presenting with a relative increase of non-defining AIDS events such as cardiovascular diseases. However, this heightened ICD risk seems to be not only originated by the aging process. HIV infection itself and other related factors may be also involved in the development of ICD.

2. Pathophysiology of HIV and cardiovascular disease.

2. a. Pathophysiological basis of cardiovascular disease in HIV-1-infected patients.

Pathophysiology of ICD is based on the development of atheromatous plaques in the intima of the arteries induced by different etiologic factors. Additionally, in the setting of HIV infection other etiological factors appear to interact. Different intensity patterns of subclinical atherosclerotic lesions have been widely identified in the vascular system of young and older HIV-1-infected patients (12). From endothelial dysfunction without structural vessel wall changes (13) to vessel wall thickening (14)(15) and further to calcified and non calcified coronary plaques (16). Even if atherogenesis is a chronic process starting in young ages MI is provoked by an acute coronary atherosclerotic plaque rupture with the consequent clot formation which stops blood flow through the artery (17). See Figure 1.

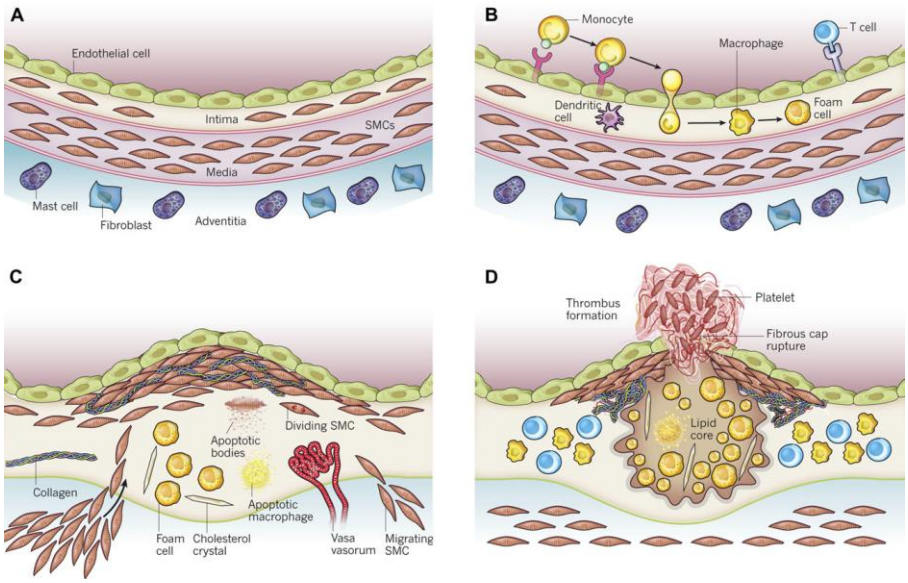


Figure 1. Stages in the developing of atherogenesis. Libby et al. (17).

A). A healthy muscular artery consists of four layers: endothelium, tunica intima, tunica media and adventitia. The monolayer of endothelial cells plays a critical role as it is a kind of barrier or intermediary between blood in the lumen and of vessel wall cells. Likewise endothelium is one of the first steps of defence in the innate immune respond, participates in nutrition and waste excretion, and contributes to control of vascular tone, thrombosis, and coagulation. The tunica intima is the inner layer of the artery and all these physiological events take place through it and within it. The tunica media consists of smooth muscle cells (SMC) and extracellular matrix and its main physiological role is providing physical support to the artery and blood pressure regulation.

B). When endothelial cells are injured by different stimuli (hypertension, hyperglycaemia, dyslipidemia, tobacco consumption, or pro-inflammatory mediators) they become activated, altering their permeability and expressing adhesion molecules on their surface which respectively leads to low-density lipoprotein (LDL) and bound leukocytes (most of them, monocytes) entry into the tunica intima, where monocytes differentiate into macrophage and these endocyte modified LDL becoming foam cells.

C). The complet process promotes that endothelial cells, SMC and leukocytes release chemoattractants which promote migration of additional blood leukocytes and SMC from tunica media to the intima. Other cytokines enhance extracellular matrix synthesis and neovascularisation. Foam cells, SMC and extracellular matrix accumulation result in plaque growth inside the intima deriving in the formation of the fibrous cap. Eventually, apoptosis of foam cells and SMC takes place in the core of the plaque leading to cellular debris and extracellular cholesterol accumulation and its further crystallisation.

D). In order to remove these detritus, signalling between macrophage and T cells foster the release and action of matrix-degrading enzymes like matrix-metaloproteinases (MMP) which destabilize the plaque by degrading the fibrous cap. This rupture of the plaque may occur by erosion of the endothelium as well. When the fibrous cap breaks, blood components contact the tissue factor from the inner artery and the coagulation cascade is triggered. Then, thrombosis occludes blood flow with the subsequent organ infarct (18)(19)(17). Along the whole atherogenesis process, cytokines play the most determinant role. Cytokines are proteins produced by inflammatory and non-inflammatory cells (endothelial cells, SMC and adipocytes) and they coordinate all the different cells involved in each of the sequential steps of atheromatous plaque formation (Fig 2). Some of the biological effects of cytokines belong actually to the sequence of innate and adaptive immune responses, which are nowadays known to be essential contributors to atherogenesis (Table 1)(20).

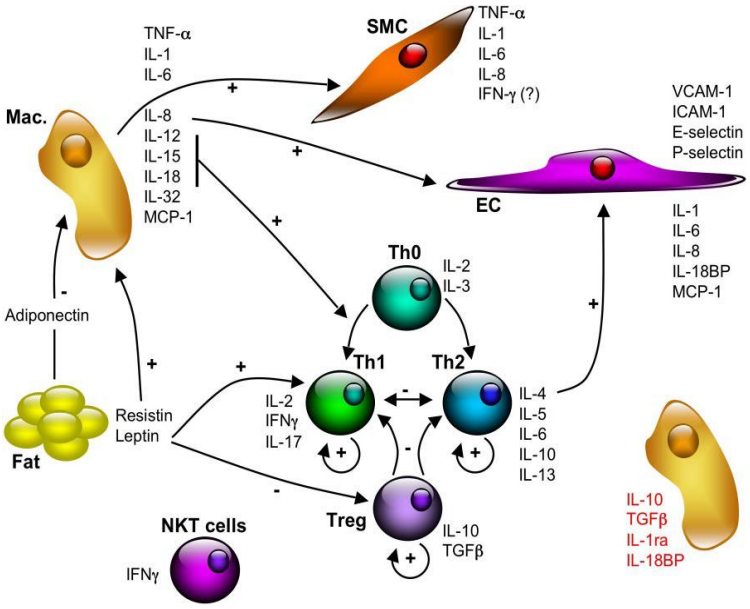


Fig 2. Cytokines involved in atherogenesis. Cytokines are produced by several cell types, including inflammatory and vascular cells, as well as adipocytes. IL-12 and IL-18 produced by macrophages are potent inducers of IFN-_ and promote the differentiation of naive T cells into proatherogenic Th1 cells. Macrophage or macrophage-derived cytokines also activate smooth muscle cells (SMC) and endothelial cells (EC) to produce an array of proinflammatory mediators. On the other hand, the anti-inflammatory cytokines IL-10 and TGF-β, also produced by macrophages, promote antiatherogenic Treg cell differentiation (which also release these cytokines with anti-inflammatory effect). Other anti-inflammatory mediators with potent antiatherogenic properties include IL-1 receptor antagonist (IL-1ra) and IL-18 binding protein (IL-18BP). Interestingly, IL-4, the prototype of Th2 cells, has proinflammatory properties on EC. Adipocytes produce both pro- and anti-inflammatory mediators. Leptin activates Th1 cells but inhibits Treg

Table 1. Effects of cytokines in the atherogenesis.
Adapted from Tedgui A et al. (20)

Effects on endothelial permeability
Activation of adhesion molecule expression
Induction of chemokine release
Modulation of scavenger receptor expression
Modulation of lipid metabolism
Activation of 15-lipoxygenase expression in cultured macrophages
Effect of SMC migration/proliferation
Regulation of immune response (Th1/Th2/Treg)
Conversion of CD4naive T cells into CD4regulatory T cells
Oxidation of LDL (induction cell oxidant stress

The first available evidence of the existence of immunological mechanism in atherogenesis was the finding of macrophage and lymphocytes T in broken atheromatous plaques from autopsies. Results yielded by a number of clinical studies suggest that certain blood inflammatory mediators are associated with increased CVR. Experimental models and *in vitro* studies have demonstrated the vascular cells dysfunction is driven by several proatherogenic factors. From the first stage of atherogenesis with activation of endothelial cells, monocytes migration and differentiation into macrophages which will engulf LDL particles, to the growth of the atheromatous plaque and the rupture of the fibrous cap, there is a continuous activation of pattern recognition receptors that regulate immunological pathways. Innate immune response developed by macrophage, endothelial, dendritic, and mast cells, is deeply implicated in atherogenesis but adaptative immune response also seems to play an important role. It is well known that lymphocytes T-helper type 1 and some of the cytokines that they release like interferon- γ (IFN- γ) foster atherosclerosis. Although lymphocytes B were considered to protect from atherosclerosis by generating antibodies against modified LDL (17), recent studies refute this suggesting that antigen presentation may promote atherogenesis (21). This issue is currently under further investigation. Nevertheless, it is a fact that some immunological cells protect against atherosclerosis such as T regulatory lymphocytes by releasing transforming growth factor β (TGF- β) and interleukin 10 (IL-10); both with anti-inflammatory effects (22).

It is well known that chronic infections are stimuli for atherogenesis by continuous immune-activation triggering inflammation pathways Fig. 3. Therefore HIV infection is considered as an atherosclerosis direct precursor as well as an indirect one since HIV is often associated with other chronic infections. It is a fact that HIV infection is associated to arterial inflammation also when adjusting by TCRFs (23). Additionally HIV infection is often linked to TCRF, such as dyslipidemia and insulin-resistance through visceral fat accumulation and cytokines deregulation as well as with tobacco smoking, twice as prevalent among HIV-1-infected patients as than in the general population. The pro-coagulation status accompanying HIV also promotes the progression of atherosclerosis (24). Autopsies from young HIV-positive individuals show early and severe atherosclerosis (12), findings supported by coronary computed tomography angiography showing more atherosclerosis among HIV-positive than in un-infected participants, even in those HIV-positive younger or scoring lower Framinghan and never had symptoms of ICD (16). Initially calcified atherosclerosis was thought to be associated with use of antiretroviral drugs like protease inhibitors (PI), but further research demonstrated after adjusting for TCRF, that HAART is not associated with the presence of calcified plaques (25)**.** According to these studies, calcified plaques seem to be associated with TCRF, and non-calcified with immune-activation (16)(26). In HIV-

1-infected patients with subclinical atherosclerosis, increased arterial inflammation identified by PET (positron emission tomography) was related to high risk coronary atherosclerotic plaques (27).

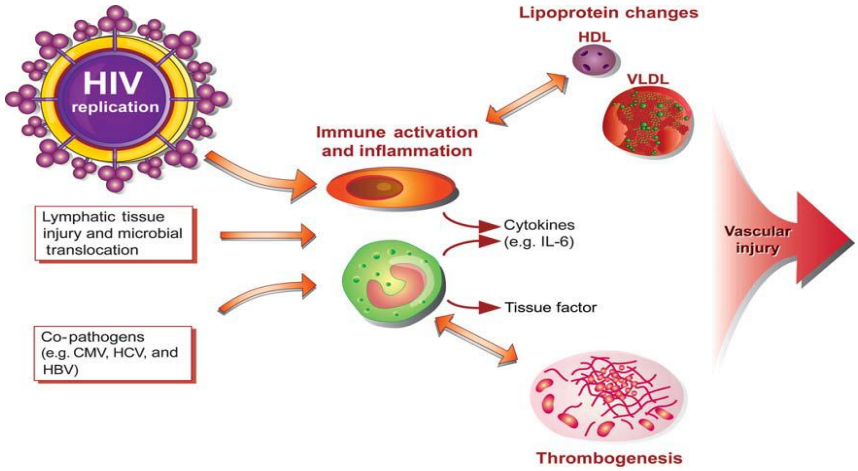


Fig. 3. Pro-atherogenic factors related to untreated human immunodeficiency virus (HIV) infection. Key pro-atherogenic factors amplified in the setting of untreated HIV infection are presented. HIV replication and activation of lymphocytes and monocytes is associated with release of inflammatory cytokines and early vessel dysfunction. Key candidate drivers of immune activation include, but may not be limited to, HIV persistence (including low-level viral replication below level of detection for clinical assays), permanent damage to mucosal lymphatic tissue with increased microbial translocation, and the presence of co-pathogens (e.g. cytomegalovirus). Subsequent coagulation and thrombotic activity, via cell damage and up-regulation of tissue factor pathways, platelet activation, or other mechanisms may contribute to premature atherosclerosis. Pro-atherogenic changes in lipids and lipoprotein metabolism are also consequences of both HIV infection and chronic inflammation. Some of these mechanisms are attenuated, though incompletely, with antiretroviral therapy and suppression of HIV replication. Baker J.V. & Lundgren J.D. (28).

Pathophysiology of cardiovascular disease in the setting of HIV infection is complex and involves several mechanisms; some are host-dependent (e.g. traditional cardiovascular risk factors and genetics) and some directly or indirectly HIV-related (Fig.4.).

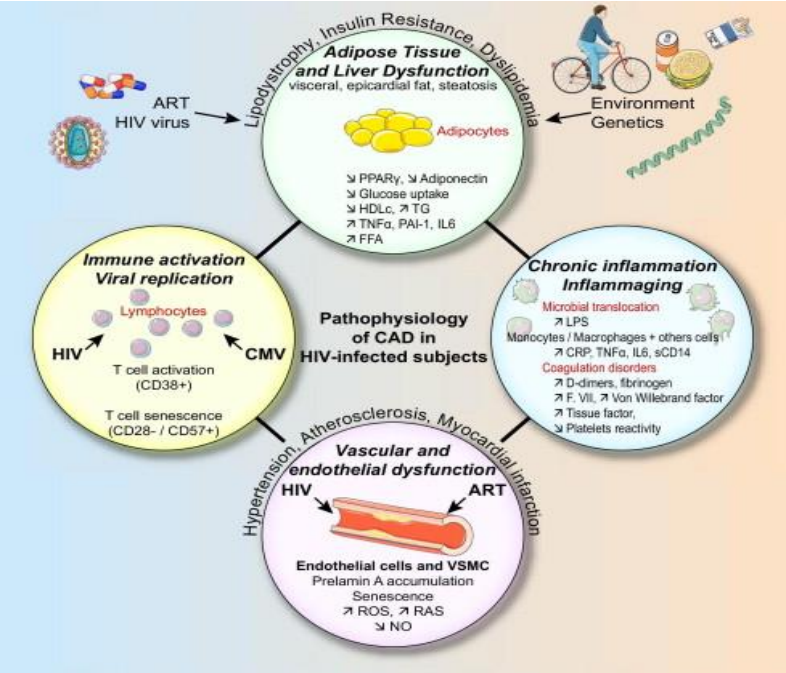


Fig. 4. Hypotheses for the Pathophysiology of Atherosclerotic Coronary Artery Disease in HIV-Infected Patients Taking cART. ART antiretroviral therapy; CRP C-reactive protein; F VII factor VII; FFA free fatty acids; HDLc high-density lipoprotein cholesterol; IL6 interleukin 6; NO nitrogen oxide; PAI-1 plasminogen activator inhibitor type 1; PPAR peroxisome proliferator-activated receptors; RAS Renin angiotensin system; ROS reactive oxygen species; sCD14 soluble CD14; TG triglyceride; TNF tumor necrosis factor; VSMC vascular smooth muscle cells. Figure illustration by Yves Chrétien, INSERM, UMR S 938, Faculté de Médecine Saint Antoine, UPMC, F-75012, Paris, France. Boccara et al. (38).

The so far available scientific evidence addressing the role of the different factors ascribed to pathogenesis of cardiovascular disease in HIV-1-infected patients has been reviewed.

2. b. Traditional cardiovascular risk factor (TCRF).

Non modifiable TCRF such as age, gender and family history, and modifiable TCRF such as smoking, dyslipidemia, diabetes mellitus and hypertension, contribute to the increased cardiovascular risk observed in HIV-1-infected patients.

2.b.1. Aging.

Although atherosclerosis was thought to be an elderly problem, autopsy studies have revealed coronary atherosclerosis lesions in asymptomatic young men in their twenties (29)(30) reaching advance stages with stenosis of ≥ 40% of the lumen in 19% of men in their 30´s, a rate that increases over the age. In women, progression was slower as they showed less severe stenosis than men for a given age (31). HIV infection expedites atherogenesis (32) as it will be further explained here.

Aging of HIV population is the most obvious reason for its increased cardiovascular risk. This is due not only to the aging tissue process but also to the appearance of TCRF at older age (33). It is a fact that for a given age (including younger ages) and similar TCRF profile, the prevalence of cardiovascular disease is greater in HIV-positive than in un-infected individuals (Fig.5) (6)(7)(9)(34)(35)underscoring the role of HIV infection

and its related factors on pathogenic mechanisms of cardiovascular diseases (32). In the large HIV cohort of the DAD Study, the relative risk for myocardial infarction per 5 years increase of age was estimated in 1.32 (95% CI 1.23-1.41) (36). This greater prevalence of cardiovascular disease for a given age in HIV-1-infected patients comparing with the general population may decrease at older ages (33)(34).

On the other hand, it has been suggested that the aging process is anticipated in HIV-1-infected patients since the prevalence of polypathology including cardiovascular disease for a given age stratum, equates that prevalence in 10-15 years older patients from the general population (34). However, other authors have found greater risk for co-morbidities including cardiovascular disease at similar ages in both groups, HIV-positive and HIV-negative (37). Other authors remark that the most frequent mean age at MI occurrence among HIV-positive (48-50 years) may be at least partially due to the youth of the HIV community, whose mean age is still quite less than that of the general population (38).

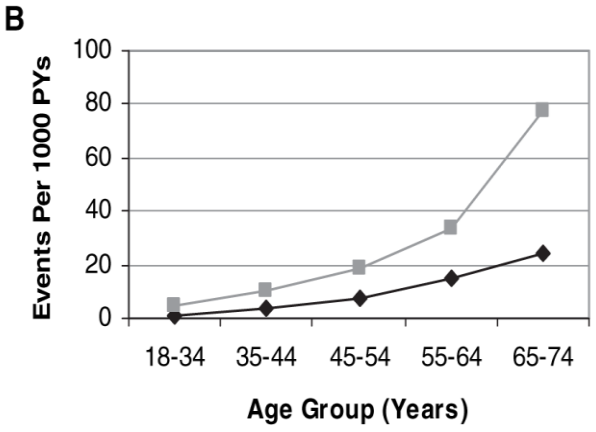


Fig.5. Myocardial infarction rates by age group. *Light line* indicates patients diagnosed with HIV disease. *Dark line* indicates patients not diagnosed with HIV disease. Data shown include both genders. Rates represent number of events per 1000 PY as determined by ICD coding. Triant V.A. et al. (7)

Thanks to the widely use of antiretroviral therapy, demographic changes ensue in the HIV population. In Australia already 25% of the HIV-positive are older than 50 years of age. In U.S.A. half of the HIV population is predicted to be above 50 years in three years and a similar forecast applies to the HIV population in sub-Saharan Africa where in 2007, 14.3% of the 21 million of HIV infected adults were above 50 years (39)(40)(41). HIV physicians and clinical guidelines will need to consider this demographic trend when addressing prevention and treatment of cardiovascular disease in this group of patients.

2.b.2. Gender.

It is a matter of fact that male gender is a cardiovascular risk factor, as premenopausal women have lower risk of ICD and other cardiovascular diseases such as left ventricular hypertrophy (LVH) than age-matched men. This female-gender advantage used to be attributed to differences in body composition and prevalence of risk factors. But studies such as Framingham Heart Study or CARDIA Study yielded data against this hypothesis. In these studies, LVH was more severe in men even after adjusting by body surface area and TCRF, suggesting gender differences in cardiovascular pathophysiology (42)(43). Estrogenic action was suggested and proved to play a role in the female-gender advantage in cardiovascular risk since a number of studies showed that postmenopausal women treated with estrogens presented lower risk of cardiovascular death when comparing with untreated women (44).

Nowadays it is known that there are two estrogens receptors (ERα and ERβ) located in several tissues (endothelial, myocardial, muscle-skeletal, immune system) where estrogenic actions are mediated and regulated by a variety of stimulus (45). Estrogens prevent from atherosclerosis by a vasodilator effect that diminishes endothelial irritation and further SMC proliferation in the tunica intima (46); also by reducing incidence of TCRF since estrogens are implicated in the modulation of blood pressure, LDL, HDL, glucose and insulin plasma levels (47)(48).

Industrialized countries have a higher proportion of men among HIV-positive, correlating with demographic characteristics from populations studies (6)(9)(49) . This implies that an important proportion of HIV-1-infected patients are on higher risk of ICD. Actually HIV-infected men are on greater cardiovascular risk comparing with their counterparts from the general population. Furthermore, in opposition to the observed female-gender cardiovascular advantage in the general population, HIV-infected women exhibit an increased cardiovascular risk comparing with un-infected women. Supporting these data Dolan S et al. observed that HIV-positive women presented greater ICD risk comparing with un-infected women and they suggest that this may be due to the statistically significant greater fat redistribution and higher inflammatory biomarkers (50). Theoretically, this plausible effect of fat redistribution on cardiovascular risk in HIV-positive women could be comparable with that observed in young women with type 1 diabetes (51). In some HIV cohort studies, women exhibit a higher risk than men. Thus, Triant et al. observed a relative risk (RR) of myocardial infarction among women of 2.98 whereas in men was RR 1.40 (7). Saves et al. predicted RR of myocardial infarction of 1.2 in men and 1.6 in women (52) in the HIV French Cohort, but actually real risks were higher according to the analysis by Lang et al. describing myocardial infarction RRs of 1.4 in men and 2.7 and in women (9). These data are consistent with recent findings pointing out a significantly higher presence of

non-calcified coronary atherosclerotic plaques (more prompt to rupture than calcified plaques) and higher levels of sCD63 (marker of monocyte immuneactivation) in young asymptomatic HIV-positive women comparing with HIV-negative women. Immuneactivation (sCD63 levels) was significantly linked to the presence of plaques in HIV-positive women. When comparing also with infected and un-infected men, immuneactivation was associated significantly with gender female, age and HIV infection (53).

In conclusion, because men represent up to 97% of HIV cohorts, in absolute terms there are more men than women affected by ICD among HIV-positive. However it is a fact that HIV-positive women exhibit higher risk of ICD when comparing with HIV-infected men and un-infected women (38).

2.b.3. Tobacco smoking and other vasoactive substance consumption.

Basing on autopsy studies and population studies, smoking has been established as a main TCRF (54)(55) however mechanisms whereby smoking exerts its deleterious effects on the cardiovascular system are still under investigation. These effects consist out of structural changes such as fostering atherosclerosis, functional changes such as vasospasm, impaired oxygen delivery, hypercoagulability, vasoconstriction and endothelial dysfunction due to oxidative stress enhancing endothelin release and inhibiting nitric oxide formation (56)(57). Studies on anatomopathological samples conclude that endothelin receptors are upregulated by smoke molecules triggering both, atherogenesis and endothelial dysfunction (58)(59)(60)(56).

A high prevalence of smoking in the HIV community and the interaction of smoking pathophysiological effects with a vulnerable physiological basis conveyed by HIV infection, result in a significant impact of smoking tobacco on HIV-positive individual´s health. In Spain, the Coris Cohort and the study by Fuster et al. describe smoking prevalence up to 46% and 64% respectively (61)(62) similar to those from U.S.A. and some European countries (63)(64)(65). These smoking prevalence in the HIV population are twice or thrice greater than in the general population since the inception of the HIV epidemic (66)(67). This fact may be due to specific psychosocial conditions in the HIV community (68). Smoking prevalence is higher than those from other TCRF like hypertension, diabetes or dyslipidemia (61)(69). MI risk and major cardiovascular disease risk were twice greater among HIV-positive smokers than in HIV-positive never smokers in the DAD Study and the Strategies for Management of Anti-Retroviral Therapy (SMART) trial respectively (69)(70).

A trend has been observed that shows a decrease in tobacco consumption over time among HIV individuals, with a lower smoking prevalence in the older group (67) but

cardiovascular risk keeps stable in the HIV-positive older group, likely due to a greater contribution of other risk factors over the time (71). A recent study has sought for the relation between cumulative effects of smoking, age and HIV infection on the carotida intima thickness (cIMT) comparing it between HIV infected and uninfected individuals. The cIMT showed statistical association with age and smoking for both groups. The multivariate regression model (adjusted by gender, race and other TCRFs) showed a mutual interaction between age and smoking of greater magnitude in the HIV-positive group. When focusing the analysis on the HIV-positive group (adjusting also by immunological status and use of antiretroviral therapy) the statistical association between increased cIMT, burden of age and smoking remained more intense than in a similar analysis focused on the un-infected group. Authors conclude that HIV infection modulates the interplay of age and smoking on the cardiovascular risk of HIV-positive (Fig.6) (72).

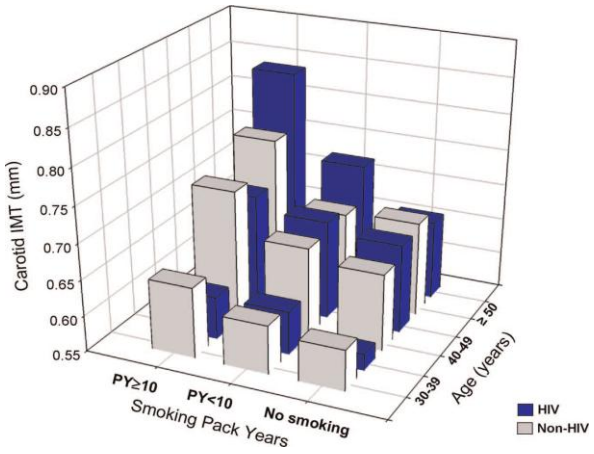


Fig.6. Impact of HIV status, smoking pack years (PY) and age on carotid intima media thickness (cIMT). Three dimensional depiction of cIMT, stratified by smoking pack years, age and HIV status. Fitch K. et al. (72).

In another large collaborative cohort study it was observed that despite the extensive use on antiretroviral therapy, HIV-positive individuals lose more life-years due to smoking than to HIV infection and that smoking-related mortality increases with age and accounts for more life years lost than HIV-related mortality (73).

Along with tobacco use, cocaine and other drug abuse are highly prevalent among smokers in the HIV population (74) also when comparing with general population (68). Cocaine is the substance with the most relevant cardiovascular effect since it blocks the reuptake of norepinephrine by the preganglionic neuron inducing a hyperadrenergic status with excessive myocardial oxygen demand, coronary vasoconstriction, and enhanced pro-coagulability (75). Effects of cocaine use in HIV-1-infected patients include a worse adherence to antiretroviral therapy with subsequent not controlled viremia and immunological decay, both linked to increased cardiovascular risk as it will be explained further down. In the Spanish Coris HIV cohort a 7% cocaine use has recently been described (61) but this prevalence rises up to 20%

and 40% in U.S.A. where cocaine use has been associated to silent coronary disease among African Americans HIV-1-infected patients (76)(77).

2.b.4. Blood pressure.

Increased blood pressure has shown to be a main modifiable cardiovascular risk (78). A reduction of 10 mmHg and 20 mmHg of diastolic or systolic blood pressure, leads to a decrease of a half of cardiovascular deaths (stroke and ICD) (79). Hypertension implies heightened peripheral vascular resistance leading to systolic stress, compromised myocardium exertion and persistent irritation of endothelium. In the Spanish general population, the prevalence of hypertesion has increased about 20 to 47% in individuals aged 20 to 65 years of age and up to a 65% in persons older than 65 years (80).

Hypertension is so far the least studied cardiovascular risk factor in the HIV community. Available data are insufficient and often controversial. This may be due to the disparity in study methodologies, study populations and definitions of blood pressure.

Prevalence estimates of hypertension among HIV-positive subjects may vary depending on the population group studied. Moreover, proper diagnosis of hypertension requires continuous monitoring of blood pressure and in no study in HIV-1-infected patients this diagnostic method has been used. In the Spanish Coris HIV Cohort, hypertension was observed only in 9.4% of participants (61) but it affects up to a 43% of HIV-positive in other cohort studies (67)(81)(82)(83) (84).

Among the HIV community, hypertension has been also linked to an increase in ICD incidence. In the Swiss Cohort Study a group of HIV-positive treated patients affected by a first ICD event were compared with a healthy individuals matched by age, gender and smoking status. In HIV-1-infected patients, blood pressure resulted to be an independent risk factor for ICD (85) and for cardiovascular events (86) . In a recent analysis of the Veterans Aging Cohort Study (VACS) Project Team, low and high prehypertensive patients showed HR for myocardial infarction of 1.60 and 1.81 respectively when comparing with HIV-negative untreated normotensive individuals whereas untreated and treated hypertensive HIV-1-infected patients showed HR of 2.57 and 2.76 respectively (87).

Prevalence of hypertension in patients receiving HAART compared with naïve patients and HIV-negative controls was slightly higher but not statistically significant (88). In this study, increased total cholesterol levels, hypertrygliceridemia and the waist to hip ratio were clear predictors of hypertension. This leads to the notion that developing of hypertension may be mediated by metabolic changes conveyed by HAART. Other

studies have confirmed the association between hypertension, waist to hip ratio and dyslipidemia in patients with LD (mixed phenotypes or only lipohypertrophy) (81)(89)(90)(91). Hypertension has additionally shown significant association with central/peripheral fat mass ratio (92). Body mass index and increasing age are also risk factors for developing hypertension (81)(90)(91)(93)(94). Lower nadir CD4 T-cell counts showed association with hypertension in three studies (81)(94) (95) but not in two others (90)(91).

In a case-control study assessing the relation between blood pressure and metabolic syndrome, the prevalence of hypertension and metabolic syndrome in HIV-positive treated patients were significantly greater in respect of those from age-gender-matched HIV-negative group (hypertension: 34.2 versus 11.9%; $P < 0.0001$; metabolic syndrome: 33.1 versus 2.4%; $P < 0.0001$) for every age rank and respectively. Authors explain that such a big difference may be partially due to the fact that controls were blood donors assumed to be healthier than the general population. In this study metabolic syndrome was a predictor factor for hypertension, along with insulin resistance (HOMA index) and lipodystrophy (96).

In a retrospective study from the Multicenter AIDS Cohort, prevalence of hypertension showed differences from that in the control group in the second year of HAART and onwards, reaching the greatest difference after 5 years of HAART initiation (93). Therefore, duration of exposure to antiviral therapy is a predictor factor for hypertension as confirmed by other studies (81)(95). In the DAD cohort patients on therapy showed higher prevalence of hypertension than naïve patients. However, in the multivariate analysis no association of any type between any antiretroviral drug and greater risk of hypertension was found (97). Similar loss of association between PIs or NNRTI use as third drug and hypertension has been observed in a recent cross-sectional study including 1182 HIV-1-infected patients (81)(86). Nowadays there is not enough scientific evidence to recommend any antiretroviral drug in order to avoid hypertension.

There is little available information about the role that HIV associated nephropathy, nephroangiosclerosis or diabetic microangiopathy may play in the development of hypertension in HIV-1-infected patients.

2.b.5. Dyslipidemia.

Soon after HIV seroconversion, triglyceride (TGC) blood levels increase whereas total cholesterol levels, high density lipoproteins-cholesterol (HDL-C) and low density lipoproteins-cholesterol (LDL-C) levels decrease. These changes in early infected HIV-positive individuals have been attributed to chronic inflammation and its derived

cytokines. Thus, high levels of interferon-alpha inhibit lipase enzyme, responsible for TGC clearing, which explains the increased levels of TGC (98)(99)(100). After HAART initiation significant new changes in the lipid profile ensue: TGC increase even more, LDL-C levels start to increase and HDL-C levels remains low (101)(69). A more accurate analysis revealed that in HIV treated patients (but not in naïve patients), very low-density lipoprotein (VLDL), total LDL-C level and the small LDL-C particles fraction rise, whereas large LDL-C particles decrease (102). The magnitude of the abnormalities observed in the lipid profile after HAART initiation is closely associated to the class of antiretroviral drug used. Nevertheless, irrespective of being or not under HAART, some of the described changes in the lipid profile may be explained by the following mechanisms: insufficient lipolysis suppression by insulin (103), enhanced lipogenesis in the liver (28)(104) and reduced blood fatty acid trapping (105) resulting in an increase blood levels of fatty acid, TGC and VLDL.

When addressing the pathophysiology of dyslipidemia in HIV-1-infected patients it is essential to mention the role of lipodystrophy (LD), which refers to an abnormal body fat distribution. There are two forms: lipoatrophy and lipohypertrophy. The first one consists in a loss of fat in face, buttocks and limbs. Lipohypertrophy consist in an increase of physiological adipose depots such as visceral, breast and cervical fat. These depots may be as well ectopic adipose tissue out of the classical locations, such as lipoma in armpits or suprapubic region (106). Up to 13 to 70% of HIV-positive may experience LD in a different extent in a variable period of time. Interplay of pathogenic mechanisms such as inflammation triggered by viral proteins, gene activation by HIV or HAART and mitochondrial dysfunction secondary to HAART (106) and HIV infection (107) underlay the development of LD. This is more intense and faster when receiving certain antiretroviral drugs as part of HAART combination (i.e thymidine analogues) (106). Duration of exposure to HAART and increasing age and female gender, are predictors of LD development (108). Lipoatrophy becomes clinically evident when the loss of body fat rises up to a 30%. Lipoatrophy and lipohypertrophy may appear alone or concomitantly and both are usually accompanied by dyslipidemia, which is more prevalent among HIV-patients with LD than in those without LD or those HIV-negative (109)(110).

Out of the lipid alterations described above, the most intense and prevalent among HIV-1-infected patients is hypertriglyceridemia. Hypertriglyceridemia has been identified as an independent risk factor for cardiovascular disease in the Data Collection on Adverse Events of Anti-HIV Drugs (*D:A:D*) study. In this study, a 2-fold increase in TGC levels implied an increase of 17% in the risk of myocardial infarction (RR 1.17; 95% CI 1.06–1.29) (111). Hypertrygliceridemia has been also linked to arterial stiffness in HIV-1-infected patients with viral suppression comparing with an un-infected control group (112).

The next most frequent lipid change in HIV-positive is a lower level of HDL-cholesterol which implies a chronic reduction of its anti-proatherogenic functions (28).

In treated HIV-1-infected patients of the Swiss Cohort Study, an increased small LDL-C particles of 1mg/dl and an increase of apolipoprotein B of 10 mg/dl were associated with higher risk of ICD (OR 1.06 and OR 1.16, respectively) (85). LD also impacts on cardiovascular risk since it is not only accompanied usually by dyslipidemia, but also by hypertension, insulin resistance and impaired glucose tolerance which are defining criteria of the metabolic syndrome, known to increase cardiovascular risk (113)(114). LD is more frequent among HIV-1-infected patients with ICD (115). Peripheral lipoatrophy and visceral lipohypertrophy are associated with increased Framingham risk score implying greater cardiovascular risk (116). Peripheral lipoatrophy and visceral fat depot were predictor factors for subclinical atherosclerosis in a study searching for coronary artery calcium by computed tomography after controlling by TCRFs and cumulative antiretroviral use (117). Consistently, recent data link LD defined as fat mass ratio (% of trunk fat mass/% lower limb fat mass) with higher cIMT (118). Moreover, hypertriglyceridemia and an increased waist circumference were highly predictive of greater Framingham Risk Score, diabetes type II, insulin resistance and hypertension in a wide HIV cohort (119).

Elucidating whether the aging process does impact on the lipid metabolism of HIV-positive leading to the appearance or an increase of dyslipidemia is difficult, due to the coexistence of new or persistent confounder factors along aging such as a cumulative use of HAART, the concomitant use of lipid-lowering drugs or other cardiovascular risk factors different than age (106).

2.b.6. Diabetes mellitus.

Diabetes mellitus (DM) is a metabolic disorder consisting in a deficient insulin activity and a subsequent hyperglycaemia. The impairment in insulin physiological action may be due to either pancreas insufficiency or to cellular insulin resistance. Hyperglycemia triggers the generation of reactive oxygen species (ROS) in the mitochondria of endothelium and other vessel cells. This oxidative stress activates in turn cellular pathways leading to endothelium dysfunction implying impairment of its barrier function, increased immune cells and LDL-C molecules adhesion and increased cell proliferation and apoptosis (120).

Global prevalence of DM is 8.3 % and of impaired glucose tolerance (IGT) 6.4% (121) but predictions for year 2025 in industrialized countries state that DM prevalence is expected to rise up to a 42% due to the obesity epidemic (122). Prevalence of DM and IGT in HIV-positive are about 2-14% depending of the cohort studied (123)(124)(69). In

the Multicenter AIDS Cohort Study (MACS), a 4 fold greater incidence (14%) of DM was observed in the HIV-positive group under HAART comparing with an un-infected group (125). Incidence of DM and IGT among HIV-positive is not only influenced by factors affecting the general population (obesity, genetic, ethnic, family history, sedentariness, HCV-coinfection), but also HIV infection related factors such as a low but sustained level of chronic inflammation or LD (secondary to HIV and HAART). Due to the role of these HIV-related factors, a greater incidence of DM may be expectable in HIV-positive (as confirmed in the MAC study) comparing with un-infected counterparts. However this effect on prevalence may not be detected depending on the populations compared (126)(127)(128). For instance, in the study of the Veterans Aging Cohort (VAC) prevalence of DM was significantly lower among HIV-infected subjects than in the control group (19.5 vs 31.8%, p <0.001) (129). In another study a significantly higher incidence of DM and IGT was observed among HIV-positive presenting with LD but not in those without LD when comparing with a healthy control group from Framinghan Offspring Study (109). Similarly to the general population, new onsets of diabetes also rise over time in HIV-positive. Consistently, two HIV cohort studies, the D:A:D Study and the Swiss Cohort, reported an association between aging and cumulative HAART exposure, both risk factors for DM (130)(131). DM incidence increases over time in HIV-1-infected patients and so does their ICD risk, closely linked to duration of DM (132). Furthermore, recently has been detected a relation between diabetes and lower cognitive performance or increased cIMT in HIV-patients with good virological and immune status (133).

2.b.7. Family history of cardiovascular disease.

The impact of family history on the risk of cardiovascular disease due to atherosclerosis is well-known. This impact is conveyed not only by genetics but also by behavioural and environmental aspects. Rasmussen et al. assessed the contribution of the familiar background to the development of ICD in HIV-1-infected patients. An increased risk of myocardial infarction was observed in mothers of HIV-1-infected patients (adjusted IRR, 1.31; 95% CI: 1.08-1.60). In both, mothers (adjusted IRR, 1.63; 95% CI: 1.02-2.60) and fathers (adjusted IRR, 1.42; 95% CI: 1.01-2.00), the greater risk for myocardial infarction was observed when their offspring had acquired HIV infection by intravenous drug use (134).

2. c. Genetic factors.

Unfavorable genetic background linked to cardiovascular disease was tested in a large HIV cohort (Magnificient Consortium, Insight and Swiss HIV Cohort Study) including 1875 patients. Odds ratios for coronary disesase for this unfavorable genetic background was similar to those from TCRFs or current use of lopinavir or abacavir. Furthermore, an unfavorable cardiovasular genetic background showed an additive effect with TCRF and to family history (135).

Genetic regulation in dyslipidemia is better understood than in other TCRFs. In HIV-1-infected patients it has been proposed that HIV infection activity modulates allele-specific apolipoprotein(a) levels. Higher allele-specific apo(a) levels associated with atherogenic small apo(a) sizes may increase cardiovascular risk in those HIV-positive with high CD4 T-cell counts and controlled viremia (136). A Spanish study including 727 HIV naïve patients starting therapy and analyzing 192 single-nucleotide polymorphisms (SNPs), found one SNP in apolipoproteinB associated with increased LDL-C levels. When the initial HAART combination included NNRTI, three other SNPs (in ABCA1/LIPC/CETP) were associated with decreased HDL-C levels (137). Accumulation of intramonocyte cholesterol occurs in HIV-positive untreated and on treatment, suggesting that both, HIV infection and antiviral therapy, modify the expression of genes involved in cholesterol metabolism (138). Longitudinal data from the Multicenter AIDS Cohort Study revealed that biogeographical ancestry plays an important role in the dyslipidemic responses to antiretroviral therapy (139). In an analysis from the study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM), the glucocorticoid receptor Tth111I haplotype was associated with better body composition and metabolic parameters in HIV-positive African-Americans (140).

2. d. HIV-related factors.

2.d.1. HIV infection.

As previously mentioned, the study conducted by Triant et al. described a higher rate of ICD among HIV-1-infected patients comparing with HIV-negative (7). Grundfeld et al. observed a more extent atherosclerosis in carotida (cIMT) in HIV-positive individuals when comparing with HIV-negative. Furthermore, in the HIV-positive group, the association between ICD and cIMT was of the same magnitude than that of ICD and tobacco smoking (141). Both studies conclude that TCRFs do not justify completely the increased cardiovascular risk observed in HIV-1-infected patients, suggesting that other factors directly related to HIV infection, may contribute significantly to this

heightened cardiovascular risk. Supporting this hypothesis, in the Strategies for Management of Antiretroviral Therapy (SMART) trial a greater risk of major cardiovascular events in the discontinuation therapy group comparing with the viral suppression group (HR 1.57 95% CI 1.00-2.46; P=0.05) was unexpectedly observed (the idea was that antiviral therapy would increase cardiovascular risk). However authors emphasized that there was no significant association between the most recent viral load value and risk of CVD events and explained that lipid changes were more unfavorable in the discontinuation group which could confer a higher cardiovascular risk of this group (142).

On the other hand, several studies concluded that HAART contributes significantly to an increase in cardiovascular risk in HIV-1-infected patients. Low level chronic inflammation and immune activation (also those remaining under antiretroviral therapy) play a role in the development of ICD in HIV-positive according to an increasing number of studies. HIV-positive elite controllers are characterized by an undetectable viral load without HAART. Elite controllers show more atherosclerosis (143) and higher levels of inflammation and immune-dysfunction parameters than un-infected controls (144) supporting the contribution of HIV in the increased cardiovascular risk that infected patients exhibit (145).

Other studies found an association between HIV replication and endothelial dysfunction (146) suggesting that high viremia may imply chronic inflammatory activity and changes in lipid metabolism, both effectors of vascular damage (147)(148).

Among immune changes, *immune depletion* is the one with more evident clinical implications and therefore is the most used in clinical practice. CD4 T-cell count (149) (150), nadir CD4 T-cell count and time under low CD4 T-cell count are associated with myocardial infarction (149). In a case-control study within the French Hospital Database on HIV, low CD4 T-cell nadir, higher than >1150 cells/mL CD8 T-cell count and plasma HIV- load >50 copies/mL were identified as independent risk factors for myocardial infarction (151). A major CD4 T-cell decline (≥ 30%) increased significantly the risk of cardiovascular disease (IRR 11.7) in the next six months in the Danish HIV cohort (152). In a recent wide HIV cohort study (153), risk of myocardial infarction for HIV-positive comparing with HIV-negative individuals was 1.4 (95% CI: 1.3 to 1.6), whereas for those HIV-positive with nadir CD4 T-cell count ≥ 500/mL or recent CD4 T-cell count ≥ 500/mL the risk of myocardial infarction equated that of the un-infected counterparts (RR = 0.85; 95% CI: 0.55 to 1.33 and RR = 1.18; 95% CI: 0.96 to 1.45, respectively). In this study, the only HIV factor conferring risk for cardiovascular disease was nadir CD4 T-cell count (RR per 100 cells = 0.88; 95% CI: 0.81 to 0.96); viral load , prior use of HAART or duration of HAART showed no association with risk of myocardial infarction (153).

Immune depletion is independently associated to ICD contributing as much as TCRF (154)(155). The most supported hypothesis is that immune depletion is not directly involve in endothelial injure but actually is a surrogate marker for other immune alterations, chronic inflammation and un-controlled viral load. Thus, in the ESPRIT and SILCAAT trials, patients under HAART and interleukin-2 with sustained viral load and increased CD4 T-cell counts did not show better clinical outcomes than those only receiving active antiretroviral therapy and presenting lower increment of CD4 T-cells (156). These findings underline that immune status by itself does not convey a better clinical outcome.

Other alterations of immunity different to immune depletion and inflammatory processes underlie the development of atherosclerotic plaques in HIV-positive. Nadir CD4 T-cell counts lower than 200 cell/mL are independently associated with cIMT progression (15) and nadir CD4 T-cell counts lower than 350 cells/ml are strongly linked to impaired arterial stiffness (157). A recent lower than 200 cell/mL CD4 T-cell count has been associated to the presence of carotid plaques in the cohorts of the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) (158). The link between inflammation and ICD was strongly supported by a number of studies showing that high levels of inflammation markers, mainly C-reactive protein (CRP), are ICD and mortality risk factors in un-infected patients (159)(160)(160)(161). This fact is consistent with the increased prevalence of ICD among patients affected by diseases with chronic underlying inflammation such as rheumatoid arthritis or gout (162). In HIV-positive, inflammatory marker levels such as hsCRP, IL-6, D-dimer and other endothelial activation markers are significantly higher than in HIV-negative (163)(164). They are predictor factors for all cause mortality and ICD in HIV-infected patients (165). Even elite controllers (patients with undetectable viral load and preserved immune status without therapy) exhibit hsCRP levels higher than un-infected individuals (144). Impact of hsCRP and fibrinogen on mortality was observed under preserved CD4 T-cell counts in the FRAM study (166) as well as in the SMART Study after antiretroviral interruption and its subsequent increase of HIV-RNA levels (165). HIV infection is an independent risk factor for arterial inflammation according to studies on treated patients when assessing arterial inflammation by positron emission tomography and tissue inflammation biomarkers (167) or by cIMT in naïve patients (168) or in elite controllers (143).

The contribution of other chronic infections such as Chlamydia pneumoniae, H pylori, cytomegalovirus (CMV), viral hepatitis and other chronic bacterial and viral infections to the development of cardiovascular disease was hypothesized even before the inception of HIV epidemic. The role of these infections in the pathogenesis of cardiovascular diseases may be driven by the chronic immune activation and subclinical inflammation that these chronic infections may induce (169). But it has not

been possible to established a sure causal relationship between any infection and ICD due to either the impossibility of avoiding confounding factors or the lack of time-sequence between infection and disease onset or the scarcity of patients (169). HIV infection is often accompanied by other chronic infections (a possible confounding factor would be this concomitant condition) that can exert a cumulative detrimental effect on cardiovascular risk. Most of the attention has been focused on microbial translocation occurring in mucosal barriers, CMV and HCV co- infections.

The “leaky gut syndrome” is the result of the tissue damage in gut mucosal epithelium during the acute phase of HIV infection. At this moment, HIV virus destroys CD4+T cells within the gut epithelium leading to: impairment of its barrier function, injured mucosal integrity, continuous gut microbial translocation into the mucosal epithelium and consequent persistent endotoxemia from microbial products such as lipopolysaccharide (LPS). This endotoxemia produces in turn tissue inflammation with further CD4+T cell depletion and gut luminal damage, closing with this last step this pathophysiological loop (170). Thus, the leaky gut syndrome has been directly linked to the poorer immune reconstitution observed in virologically supressed HIV-1-infected patients (171). Furthermore, Sandler et al. found that LPS levels and other biomarkers such as sCD14 (marker of monocyte response to LPS) were associated significantly to an increased incidence of cardiovascular disease, AIDS events and mortality during the SMART trial (172). LPS trigger the release of tissue factor by monocytes promoting a pro-coagulant status and intravascular clotting, eventual precursors of cardiovascular complications (173). Microbial translocation has been independently associated to hypertension in untreated HIV-positive patients (174) as well as with dyslipidemia, impaired insulin sensitivity and greater Framinghan risk score in virologically controlled HIV-patients comparing with un-infected individuals (175).

In HIV-1-infected patients, CMV antibody levels have been independently associated with the number of coronary segments with atherosclerotic plaques (16). Among HIV-infected women from the WIHS Cohort, higher levels of CMV IgGs were linked to a decreased carotid artery distensibility irrespectively whether the HIV viremia was suppressed or not. By contrast, a link between higher CMV IgGs and carotid artery lesions was only significant among virologically suppressed HIV-1-infected patients since in these aviremic group CMV-specific immune-response is more intentse than in HIV-viremic patiensts. Due to this it may lead to chronic subintimal inflammation (176). Whether C hepatitis virus infection (HCV) is a risk factor for cardiovascular disease in the general population and among HIV-1-infected patients is not clear, although consistent data appear to support this hypothesis. Thus, there are a number of large cohort studies in general population (177)(178) and HIV cohorts studies (179)(180) finding significant association between HCV and cardiovascular disease. In a recent study on a large cohort of mono-infected-HIV and co-infected-HCV-HIV or co-infected-

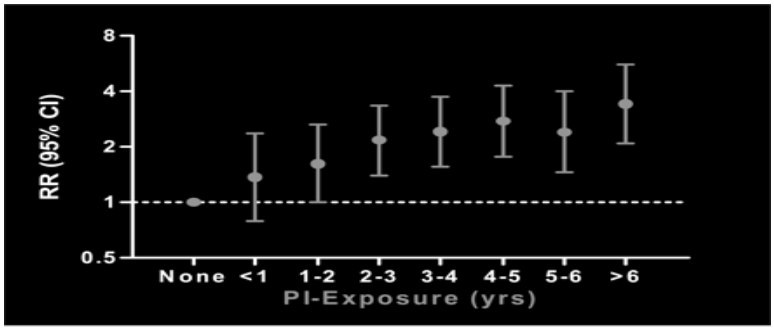
HBV-HIV-1-infected patients, co-infection with HCV was associated to cardiovascular disease approaching the statistically significance, whereas HBV co-infection showed no association (181). However it is noteworthy that the D:A:D Study (a large cohort as well) did not show any association between HCV and myocardial infarction in a wide sample of HIV-1-infected patients (182).

Whatever are the pathophysiological mechanisms triggered by HIV infection and impacting cardiovascular risk, it is currently accepted that HIV infection confers additional risk to that linked to TCRFs, which are overrepresented in the HIV community. Consistently, a three way interaction among HIV infection, age and smoking in their impact on cIMT has been observed in an analysis including HIV-positive and negative after adjustment by gender, race and other TCRFs (72). When focusing on the HIV-positive group, a significant interaction between smoking and age was also observed.

2. d.2. Antiretroviral therapy.

Since HAART appeared in 1996, some speculations about its effect on patients´cardiovascular status arose. Klein et al. (4) and Obel et al. (8) found no significant difference in the number of hospital admissions related to cardiovascular disease when comparing HIV-1-infected patients before and after the introduction of HAART, and with HIV un-infected individuals (4).

However, data yielded by large cohort studies suggested a certain role of HAART on an increased cardiovascular risk in HIV-1-infected patients. For example, in the study conducted in the California Medicaid population, adjusted RR for coronary heart disease of patients on HAART comparing with those not receiving HAART was 2.06 ($P < 0.001$) but only in HIV individuals aged in the range 18 to 33 years old, not finding any association in older patients (6). A statistical association was found between HAART and cardiovascular risk in a case-control study assessing this risk by measuring subclinical atherosclerosis with cIMT ultrasound. In HIV-positive, cIMT was up to 4-14% higher than in controls implying a cardiovascular age 4-5 years older in HIV subjects than in controls (183). In the meanwhile, findings of some studies searching a potential link between certain groups of antiretroviral drugs and cardiovascular risk, were consistent with this hypothesis. Thus, a significant increase in the incidence of cardiovascular events in HIV-1-infected patients receiving protease inhibitors (PI) was found (184)(185). Fig. 7.



PI exposure (yrs)	None	< 1	1-2	2-3	3-4	4-5	5-6	>6	Total
Events/1000 person-years	1.5	2.5	3.0	4.2	4.7	5.3	4.4	6.0	3.7
No of events	33	21	33	57	64	57	33	47	345
No. of person-years	21,623	8,410	10,947	13,616	13,734	10,734	7,576	7,821	94,469

*: Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD, smoking, body-mass index, NNRTI exposure

Fig. 7. Increasing relative rate of MI with cumulative exposure to protease inhibitor. Friis-Møller et al. (186).

PI have been consistenly related with an altered lipid profile leading to an increase in cardiovascular risk. Several *in vitro* studies have identified different phatophysiological pathways of the lipid metabolism impaired by PI exposure. For example, ritonavir fosters lipolysis (187) and combined with other PI such as lopinavir, darunavir or atazanavir, decreases fatty acid oxidation in skeletal muscle cells (188). Adipocyte differentiation and triglyceride storage in adipocytes are both impaired by NRTI, PI and efavirenz (189)(190)(191)(192). These changes in lipid metabolism observed *in vitro*, may explain the hypertriglyceridemia and the increase in the circulating total cholesterol and LDL-C observed in patients receiving PI (97)(101)(193). All these effects on lipid metabolism are less intense with atazanavir.

Antiretroviral drugs can also enhance cardiovascular risk by inducing insulin resistance and diabetes. As it has been previously mentioned the D:A:D Study showed that incidence of DM increased with cumulative HAART exposure to the following drugs (from more to less impact): stavudine, zidovudine, didanosine, ritonavir (130). Similar results were obtained recently in a study searching for 10-year DM-incidence, stratifying by type of antiretroviral drug and duration of exposure. In this study indinavir, showed a similar impact than stavudine (exposure <1 year, HR 2.56 for both drugs) (194).

This dose-dependent detrimental effect of antiretroviral drugs correlates with findings of previous studies conducted in healthy volunteers. Thus, a single dose of 800 mg ritonavir induced acute insulin resistance (195) whereas a single dose of 200 mg did not (196). It has been suggested that HIV-related factors other than antiretroviral therapy may also induce insulin resistance, since in HIV-negative individuals receiving lopinavir/ritonavir 400/100mg twice daily did not alter insulin secretion during hyperglycaemic clamp (197).

HAART contribution to the increased cardiovascular risk in HIV-positive is also driven by LD since it is in turn associated to metabolic syndrome (113) and to an increase incidence of subclinical atherosclerosis (198). NRTI provoke that patients become susceptible to experience progressive fat loss. This effect is fostered when combining NRTI and PI (199). Fat loss takes place slowly once immune restoration process has started, speaking againts a potential link between immunesuppression and LD (200). Stavudine, didanosine and to a lower extent zidovudine (non-nucleoside tymidinic analogs, NRTI) found to be risk factors for LD (199)(201). This effect is mediated via mytochondrial dysfunction (202) with the subsequent oxidative stress, reduction in leptin and adiponectin and the increase expression of chemokines and cytokines (IL-6 and monocyte chemoattractant protein-1) fostering tissue inflammation (203), impairing differentiation of adypocites and inducing apoptosis (191). These last effects on adypocites differentiation and apoptosis are conveyed by PI as well but in this case, not through stressing mitochondrial but endoplasmic reticulum function and through proteasome inhibition (106). On the other hand, NRTI such as didanosine, abacavir or tenofovir had no direct *in vitro* effects on coronary endothelial cell gene transcription and expression of proteins involved in inflammation, apoptosis or oxidative stress (204).

Thus, antiretroviral therapy raises conditions that are cardiovascular risk factors, such dyslipidemia and metabolic syndrome. In contrast no direct link has been found between exposure to PI or NRTI and hypertension (205), only indirectly by the associtiation observed between hypertension and insulin resistance in patients receiving HAART (96). Exposure to NNRTI is linked to a possible protector effect againts hypertension (205).

Noteworthy are other alternative cardiovascular pathophysiological mechanism which have been proposed to be promoted by PIs: vascular senescence (that might be reverse by statins) (206) and overactivation of the adipocyte renin angiotensin system involved in development of hypertension (207).

Detrimental effects of antiretroviral drugs on endothelium has been reported only in *in vitro* studies (208) but they were not reproducible *in vivo* either in healthy volunteers (209) or in HIV-infected individuals (146).

Despite all the information above, when only considering risk of myocardial infarction in patients exposed to HAART within the last 6 months, several meta-analysis of randomized clinical trials did not find a higher risk in relation with use of antiretroviral drugs such as abacavir or PIs (210). In contrast, one meta-analysis perfomed on observational studies did find a RR for abacavir of 1.92 (95% CI 1.51–2.42) and for PI of 2.13 (95% CI 1.06–4.28) (210).

Controversial findings ascribing PI use with prolongation of QT and PR intervals have been reported in case reports and small cohort studies. In the SMART trial, the largest cohort study aimed to elucidate this question, similar minimal changes on QT interval were observed in patients receiving different PIs-based-HAART combinations and those under a NNRTI-based- HAART regimen. On the other hand, PIs showed a significant effect on PR interval and its interruption reduced the prolongation of this interval (211).

3. Clinical implications of the interaction between HIV infection and cardiovascular disease.

3.a. Clinical features.

Few years after the inception of the HIV epidemic, cardiac involvement in AIDS development was diagnosed in the clinical practice and in autopsies from HIV-1-infected patients. Thus, dilated cardiomyopathy, nonspecific myocarditis, pericarditis and primary pulmonary hypertension were directly associated to HIV. Opportunistic infections and neoplasm located in pericardium, myocardium and endocardium were identified and linked to immune suppression (212)(213). After the introduction of HAART in 1996, these cardiovascular features attributable to immune deficiency were better controlled. However, first cases of ICD in HIV-1-infected patients who had been started on PI were published with the subsequent warning and advice to assess lipid profile in patients receiving PIs (214)(215). In 2000 Rickerts et al. concluded that the incidence of myocardial infarction in a wide cohort of HIV-1-infected patients followed over 15 years, had risen after HAART combinations introduction containing PIs from 0.96 myocardial infarctions per 1000 patient-years (before PIs) up to 3.41 (with PIs) (216).

Nowadays we know that HIV-positive patients present with similar features of ICD as un-infected individuals, including more often acute coronary syndrome (from more to less frequent: ST-elevation MI, non–ST-elevation MI and unstable angina), but also silent ischemia and stable angina (38) .

In the SMART trial, frequent electrocardiographic changes of minor and mayor significance were observed and major changes such as isolated ST-abnormalities and major prolongation of QT interval were predictive of cardiovascular disease (217). Furthermore, PI use-related-QT- prolongation has been reported as a predictor factor of complete bundle branch block (218). Since data about sudden death in HIV-infected patients are lacking, these electrocardiographic changes seem not to have serious

clinical implications. However it is advisable to follow electrocardiographically those HIV-1-infected patients affected by any type of cardiovascular disease feature, especially if they are under a PI-based therapy or other QT interval-prolonging medications (e.g. methadone) (219).

As previously explained herein, the most frequent phenotype of HIV-infected patients suffering ICD is: man of 50 year of age , around 10 years since diagnosis of HIV infection, receiving antiretroviral therapy (PIs-60%), smoker (45%) and dyslipidemic (20-60%) (38).

3.b. Treatment of acute coronary ischemic events in HIV-1-infected patients.

HIV-1-infected patients ´coronary atherosclerosis presents in a similar extension when comparing with age-matched-HIV-negative controls. Percoutaneous coronary intervention and coronary artery by-pass grafting are the revascularization methods used and both show similar success rates to those in the general population. Rates of death, reinfarction or heart failure in the acute phase of the coronary event in HIV-positive are similar to those of HIV-negative (220). In HIV-1-infected patients, rates of acute and late stent reestenosis are low (1-4%) (220)(221). However HIV-1-infected patients do present higher rates of recurrent coronary events (222)(220) and recurrent revascularization in the long-term (222) but no higher risk of cardiovascular mortality (220)(223).

In order to reduce the risk of reestenosis, drug-eluting stents have demonstrated to be superior against bare-metal-stents, in both HIV-infected and uninfected patients (221) (223). Outcomes and prognosis after coronary artery by-pass grafting in HIV-1-infected patients do not differ from those from HIV-negative patients.

Primary and secondary prevention of ICD should be a priority for HIV physicians. For that purpose, the first step to assimilate in the routine of the clinical practice is to estimate the cardiovascular risk of every patient before HAART initiation and during treatment. Several HIV clinical guidelines addressed cardiovascular risk reduction (224). Smoking cessation and dyslipidemia are the two more prevalent modifiable cardiovascular risk factors among HIV-1-infected patients, and therefore both must be actively pursued. Although in this specific group none smoking cessation strategy has shown to be better than other, the available strategies can achieve slightly lower abstinence and similar high relapse rates in this community comparing the general population (225), warranting a closer follow-up.

Boccara F. et al. (38) explain the peculiarities that should take into account when addressing the medical control of dyslipidemia, hypertension and platelet function in

HIV-1-infected patients such as: 1) Even in the absence of criteria of dyslipidemia, lipid-lowering therapy is warranted in HIV-infected men older than 45 years and women older than 55 years with hypertension and/or diabetes and/or familial premature CHD are candidates. 2) There is a potential important interaction between statins, fibrates and certain antiretrovirals. Statins are metabolized via the cyto-chrome P450 (CYP) 3A4 pathway. PIs and ritonavir inhibit and NNRTIs induce CYP with a subsequent potential to increase statins plasma level and its toxicity or reduce statins levels impairing its pharmacologic effect. Then statins of choice are: pravastatin, fluvastatin, atorvastatin (low dose) or rosuvastatin (low dose). Pitavastatin, a new statin not metabolized by the CYP 3A4 isozyme could theoretically be an option to avoid pharmacological interaction with PIs but it has not yet been proved. When the recommended statin dose is not sufficient to control LDL-C levels, then adding ezetimibe is a meaningful option due to its good tolerability and safety. The alternative strategy of switching from PI to NNRTI, and integrase inhibitor or a CCR5 receptor antagonist must be considered. 3) Renin-angiotensin-system blockers are the first option to treat hypertension in HIV-1-infected patients due to its lack of significant pharmacological interactions and the protective potential in endothelium, kidney and glucose metabolism. 4) Antiplatelet drugs are recommended in the same cases as in the general population. Ticagrelor is recommended not to combine with PIs due to potential interaction. The efficacy of prasugrel could be compromised by ritonavir.

Basing on their antiinflammatory effect an extensive use of statins in primary prevention of non-AIDS related diseases including ICD (226) and an anticipated HAART initiation before CD4 T-cell count decline below 500 cell/mL (227) have been proposed as strategies for reducing cardiovascular risk in HIV-1-infected patients but supporting data are still insufficient for both of them. Regarding early HAART initiation, data from ongoing clinical trials and wide cohort studies will provide more evidence in the years to come. So far, clinical guidelines recommend to consider HAART initiation above 350 or above 500 CD4 T-cells/mL for patients with an estimated cardiovascular risk in 10 years >20% or for those with a history of cardiovascular disease (224).

Results

I. Two parallel case-control studies assessing the independent impact of smoking, diabetes and hypertension on the development of acute coronary syndrome in HIV-infected patients comparing with un-infected adults. HIV Med. 2013 Jan;14(1):40-8. **Calvo-Sánchez M,** Perelló R, Pérez I, Mateo MG, Junyent M, Laguno M, Blanco JL, Martínez-Rebollar M, Sánchez M, Mallolas J, Gatell JM, Domingo P, Martínez E.

Study summary

Regarding prevention and clinical managment of acute coronary disease HIV clinical guidelines follow the recommendations for the general population. However, HIV-1-infected patients exhibit greater cardiovascular risk than the general population. There are two possible explanations for this greater cardiovascualr risk: 1) The higher prevalence of traditional cardiovascular risk factor (TCRF) among HIV-1-infected patients (i.e. smoking, diabetes mellitus, metabolic syndrome). 2) An additive and/or synergistic impact of TCRFs and HIV-related cardiovascular risk factors (i.e. chronic inflammation, immuneactivation, antiretroviral therapy) coexisting in HIV-1-infected patients. We hypothesize that contribution of traditional cardiovascular risk factors may have a different impact in HIV-infected patients than in un-infected adults. Two parallel case-control studies were conducted. In the first study every HIV-positive adult diagnosed with ACS selected for the HIV+/ACS group was matched with three HIV-positive adults without ACS (HIV+/noACS group). In the second study each participant in the HIV+/ACS group was matched with three HIV-negative individuals diagnosed with ACS (HIV-/ACS group). Each individual in the HIV-/ACS group was then matched for with an HIV-negative adult without ACS (HIV-/noACS group). The matching ratio for individuals in each group (HIV+/ACS, HIV+/noACS, HIV-/ACS and HIV-/noACS) was 1 : 3 : 3 : 3 respectively. Logistic regression analyses were performed in order to identify risk factors for ACS. Population attributable risks (PARs) for smoking, diabetes and hypertension in HIV-positive and HIV-negative individuals were calculated. In order to make calculation of PARs as accurate as possible, participants were adjusted by age and gender in both HIV+ and HIV- participants, by the known duration of HIV infection in HIV+ participants, and by calendar date in HIV- participants. Similar definitions of risk factors and outcomes in both HIV+ and HIV- populations were used.

Conclusions

In this study, the first to our knowledge assessing PARs of common traditional cardiovascular risk factors in the HIV+ population, we found that:

-The contribution of smoking to ACS in HIV-positive adults was almost twice as high as that in un-infected adults.

- Smoking contributes to ACS in HIV-positive adults more than diabetes and hypertension do.

These results support smoking cessation strategies as a priority when addresssing cardiovascular risk reduction in HIV-1-infected patients.

II. A retrospective analysis of a prospective collected cohort of patients presenting with acute coronary syndrome (ACS) comparing the clinical presentation and short-term prognosis of ACS in those who were HIV-infected and those un-infected. Eur J Intern Med. 2011 Oct;22(5):485-8. Perelló R, **Calvo M,** Miró O, Castañeda M, Saubí N, Camón S, Foix A, Gatell JM, Masotti M, Mallolas J, Sánchez M, Martinez E.

Study summary

Clinical characteristics and outcomes of ACS in HIV-1-infected patients are still under research. This study aimed to assess clinical symptoms at acute phase, type of ACS and type of treatment provided, therapy outcome and factors associated to prognosis in a group of HIV-infected patients comparing with an un-infected control group. For that purpose, data from all consecutive patients diagnosed of myocardial infarction or unstable angina in an Emergency Department were registered. Patients were followed at least during one month after discharge.

Conclusions

Comparing with un-infected adults, HIV-infected patients present ACS at younger ages with greater prevalence of traditional cardiovascular risk factors and less symptoms. HIV-1-infected patients present predominantly ST-elevation myocardial infarctions and were treated more frequently with percoutaneous coronary artery intervention. All theses differences lost their significance when controlling by age and gender. Short term prognosis was similar in both groups, HIV-infected and un-infected.

III. Nested case-control study assessing the association of lipoprotein(a) genetic markers with traditional risk factors and with coronary heart disease in HIV-infected individuals. Egaña-Gorroño L, Martínez E, Escribà T, **Calvo M**, Gatell JM, Arnedo M. Front Immunol. 2012 Dec 6;3:367.

Study summary

Lipoprotein (a) is a risk factor for atherosclerotic disease. An association between coronary heart disease and copy-number variation of the LPA gene KIV-2 and single-nucleotide polymorphism in LPA have been described in the general population. This study aims to prove if similar associationin exist HIV-infected patients. HIV-1-infected patients diagnosed of myocardial infarction were matched in a ratio 1:3 with HIV-infected individuals without myocardial infarction. Copy-number variations and single-nucleotide polymorphisms in LPA genes were analyzed by real-time-polymerase reaction. In order to study the association between genetic factors, non-genetic cardiovascular risk factors, and myocardial infarction, a logistic regression analysis was performed.

Conclusions

No association was detected between myocardial infarction and KIV-2 copy-number variation and single-nucleotide polymorphisms in LPA. These two gentetic variants of LPA have not been identified as genetic markers of coronary heart disease in HIV-infected patients. Traditional cardiovascular risk factors and CD4 T-cell count did show significant association with myocardial infarction.

IV. Systematic review of recent scientific evidence regarding HIV infection and body fat redistribution, lipidic and glucose metabolism and their implications in aging patients. **Calvo M**, Martinez E. Curr Opin HIV AIDS. 2014 Jul;9(4):332-9.

Study summary

We report new data supporting inflammation as a cardiovascular risk factor through its direct contribution to hypertriglyceridemia, HDL-cholesterol changes and insulin resistance, well-known atherosclerosis promoters. Recent data found the association of microbial translocation with dyslipidemia, insulin resistance and risk of myocardial infarction. Last generation of antiretroviral drugs may impact less on metabolic abnormalities but cannot reverse them. Genetics may become important when addressing dyslipidemia. Last studies on lipodystrophy report its association to traditional cardiovascular risk factors, inflammation markers and funcitional decline. Since obesity pandemic affects also HIV-1-infected patients, lipodystrophy prevalence is increasing.

Conclusions

Since chronic inflammation and microbial translocation will impact significantly metabolism despite sustained viral suppression in aging HIV- infected persons, new strategies will be required in this increasing group of patients to prevent frailty and comorbidities added to age-related ones.

V. A systemic Review of the available scientific literature addressing smoking cessation in HIV-infected individuals. **Calvo M**, Martínez E. HIV Medicine 2014.

Study summary

Tobacco smoking is the traditional risk factor contributing most to the development of cardiovascular disease and this may be also true for the rest of non-AIDS defining events in HIV-infected persons. Overall and since the inception of the HIV epidemy, the proportion of smokers in the HIV community is at least double than that of the general population. Smoking cessation should be a priority for physicians treating HIV-infected smokers. We reviewed the scientific evidence regarding three main issues with a practical perspective: detection of best candidates to quit, chose of a suitable strategy and follow up during the process.

Conclusions

HIV-positive smokers exhibit greater motivation to quit but lower rates of smoking cessation and similar number of relapses than un-infected smokers with the available anti-smoking strategies. Nonetheless, this evidence is based on few studies with short number HIV infected participants. More studies specifically designed for HIV-1-infected patients are needed but in the meanwhile, the available smoking cessation strategies tailored for the general population should be promoted by HIV physicians. When considering smoking cessation in HIV-1-infected patients, the regularity of their consultations, their trust on HIV physicians and their young mean age favor optimizing the achievable health benefits.

VI. A systematic review of the pathogenic mechanisms and clinical implications of tobacco smoking and HIV infection. **Calvo M**, Laguno M, Martínez M, Martínez E. AIDS Reviews 2014. (under editorial revision).

Study summary

Tobacco-related harm in HIV-1-infected patients may be underestimated. Equating tobacco-related pathophisiological effects in the setting of HIV infection to those in the general population appears at least questionable. The pathogenic mechanisms underlying tobacco-attributed health problems are review in this article.

Conclusions

It is a fact that tobacco smoking exerts greater impact on HIV-1-infected patients´ health than on uninfected smokers´ through cumulative and synergistic effects. It seems reasonable deducing that HIV infection heightens susceptibility to harmful effects of smoking. Understanding the real impact of the pathophysiological interaction between smoking and HIV infection may enhance HIV physicians´ awareness about the potential magnitude of tobacco-related harm and will help to promote smoking cessation among HIV-1-infected patients.

Discussion

Results of the studies presented herein yield insight into the epidemiology, clinical characteristics, genetics and pathogenesis of cardiovascular disease in the setting of HIV infection.

In the general population smoking has been identified as one of the major contributors to cardiovascular disease leading to a heavier weight respect to other risk factors in the equations designed for predicting cardiovascular risk. Consistently, in the first study of this dissertation (I) smoking was the highest contributor to ACS in HIV+ patients as it explained 54% of PAR for ACS compared with 60% of this PAR explained by the combination of the three factors. Furthermore, significant differences between HIV+ and HIV- adults in the PAR due to smoking, diabetes, or hypertension for developing ACS were detected. This finding is also consistent with the notion of a different baseline epidemiologic and pathophysiologic environment in HIV-1-infected patients, in which traditional cardiovascular risk factors may play somehow a different role as in the general population. Most of the HIV cohorts report tobacco-smoking prevalence up to twice higher than that of the background population. Additionally, interplay of factors specific for the HIV population may explain why cardiovascular events are more prevalent among HIV population. Some of these are epidemiological factors such as disclosure of HIV status, experience of disclosure rejection and higher rates of alcohol and illicit drugs misuse. And some other are pathogenic factors such as chronic inflammation and immunreactivation.

PAR is the portion of the incidence of a disease in the population (exposed and unexposed) that is due to exposure. In other words, PAR due to a certain risk factor represents the reduction in incidence that would be expected if exposure to such a factor was completely eliminated. Although different geographical areas may exhibit different PAR for ACS, smoking has always shown the highest PAR among hypertension and diabetes. Thus PAR for smoking, hypertension and diabetes in international INTERHEART study and a cohort of Catalonian adults were 36%, 18%, 10% and 55%, 50% 26% respectively. Our study confirms that the contribution of smoking to ACS in HIV+ adults is even higher (PAR 54.35%), than that in the HIV- population (PAR 17.24%). The advantage is that smoking is a modifiable cardiovascular risk factor and its elimination according to the concept of PAR, is probably the intervention with greatest impact on the risk of cardiovascular disease. This statement is especially meaningful when referring to HIV-1-infected patients, especially since recent consistent data from a large collaborative HIV cohort showed that this group of patients lose more life years through tobacco smoking than through HIV infection. Furthermore this effect is more intense with increasing age (73).

In the last two studies (V, VI) smoking effects and smoking cessation in HIV-1-infected patients are addressed.

Although diabetes and hypertension were more prevalent in HIV+ than in HIV- participants both with and without ACS, our study suggests that their contribution to ACS in HIV+ was actually lower (PAR of DM 6.57%, PAR of HTA 9.07%) than in HIV- adults (PAR of DM 17.24%, PAR of HTA 38.81%). This apparent contradiction may be explained by two facts: firstly, our analysis was adjusted by age and secondly, the mean age of our study population was 53 years, a relative young age whereas prevalence of diabetes or hypertension increases with age and so it might be expected for the ACS-related PAR due to each of them. This fact could diminish the differences in PAR due to diabetes or hypertension between HIV+ and HIV- adults with increasing age. A thorough review of implication of metabolism changes in the aging process of HIV-1-infected patients is addressed in the fourth study of this academic report (IV).

With the 57 cases of myocardial infarction included in our study, its incidence in our cohort would have been estimated in 1.75 cases per 1000 patient-years, not different from that reported in other cohort studies such as the French Hospital Database on HIV ANRS Cohort CO4 (1.24 cases per 1000 patient-years) and the cohort of the study by Triant et al. performed in 2007 (1.75 cases per 1000 patient-years), although it is lower than that from D:A:D Study (3.3 cases per 1000 person-years).

Although a higher relative prevalence of ACS has been described among HIV+ women comparing with HIV+ men and with uninfected women, our prevalence among HIV+ women (42%) is twice higher than that reported in a referral meta-analysis. This might be related to the fact that the 14 patients excluded because of the unavailability of data were all men. Nevertheless, our study was designed to control for age and gender so no biases from these variables should be expected.

Because HIV+ patients had regular follow-up data, some variables were only available in HIV+ participants but no in HIV- ones. Thus, regarding use of cocaine, we only had data from HIV + patients participants. In a cohort from the general population in Barcelona, 25% of persons younger than 30 years and a 5.5% of participants aged 45-50 years reported cocaine consumption. In our study, mean age was 53 years and 11% of HIV+ with ACS admitted use of cocaine whereas only a 3% of HIV+ without ACS did (p= 0,0591).

This prevalence of recent cocaine misuse (11%) in HIV+ with ACS was also reported in our second study (II) and it was 38-fold higher than the prevalence in uninfected patients (in this second study, data about cocaine consumption in the uninfected group were available). Nonetheless, most of these differences disappear when the younger mean age and the most frequent male gender in the HIV+ group was taken into account in the analysis.

These characteristics of our second study population presenting ACS were similar to those described in other cohorts of HIV+ patients presenting with ACS: younger, more frequently men and a higher prevalence of cardiovascular risk factors than uninfected patients.

An interesting finding from this second study was that HIV+ patients complained of less often of chest pain and this was less often oppressive at their arrival in the emergency department. Both angina and pain of acute myocardial infarction derive from nerve fibers in ischemic or injured but not necrotic myocardium. Consistently, patients undergoing procedures to reperfuse the myocardium refer that pain disappears suddenly and completely once blood flow to the infarct territory is restored. Therefore in our study, the lack of pain more frequently reported in HIV+ patients with ACS could be explained by the higher prevalence of myocardial infarction implying transmural necrosis (STEMI, a more advanced and established degree of ischemic disease) and a lesser presentation of unstable angina (myocardial ischemia necrosis) or non-ST segment elevation myocardial infarction (NSTEMI, non-transmural necrosis). These findings are consistent with the higher prevalence of silent myocardial ischemia in HIV-1-infected patients comparing with patients from the general population (11% vs 5%) and similar to that of uninfected diabetics. As patients with diabetes, HIV-infected patients may suffer a loss of integrity of the mediators of cardiac nociception or the sensory pathways. This may be the explanation for the more common atypical manifestation of ACS among HIV+ found in our study. STEMI was the most common ACS diagnosed in our cohort of HIV-1-infected patients, also in accordance with previous results from the French HIV cohort described by Boccara et al. in 2010. A plausible reason for the more intense and established necrosis among HIV-infected patients could be the presence of high-risk coronary plaques in relation to an underlying pro-thrombotic and pro-inflammatory (Tawakol et al. JAIDS, June 2014) environment that may be modulated by other concomitant factors such as illicit vasoactive drugs or tobacco-smoke components.

Percutaneous coronary intervention is the current treatment of choice for STEMI. For this reason, our HIV-infected patients underwent this intervention more often than the HIV-uninfected patients. However, these differences between HIV+ patients and the uninfected control group could be driven by age and gender differences since they disappeared after adjustment by these two variables. The prognosis one month after being discharged was similar in both groups. At present, HIV-infected patients with relatively preserved immunological status and sustained suppression of HIV replication may expect to have a similar survival rate as their uninfected counterparts. Median $CD4^+$ T-cell count in HIV-infected patients presenting with ACS in our study was nearly 500/mm.

Beyond plasma lipoprotein (a) levels, the use of allele-specific apo(A) levels assessing the amount of lipoprotein (a) linked to a defined apo(a) allele size, gives idea of the cardiovascular risk conveyed by lipoprotein (a). In the third study (III) of this dissertation none of the already known associations between LPA, copy number variation KIV-2 (CNVnorrs6415084) and ICD were found in our HIV-infected study group. The association between SNPs in LPA gene and circulating Lp(a)levels and consequently with ICD, may be mediated by various mechanisms: (i) some of the SNPs may be in linkage disequilibrium with the KIV-2 repeat polymorphism which has been shown to explain approximately 50% of the genetic variation in Lp(a)concentrations; (ii) certain SNPs may directly influence the transcriptional and/or translational processes of the LPA gene; and (iii) some non-causal SNPs may be in linkage disequilibrium with SNPs having causal effect on Lp(a) concentrations. Although the power of the study was moderate and this may be the reason why none LPA structural genetic variants were associated to ICD, traditional risk factors including $CD4^{+}$T-cell counts were identified as contributors to the progression of ICD in both study groups. Pathogenesis of HIV- 1-infection and HAART exposure might contribute to ICD to a higher extent than LPA genetic variants do. This hypothesis is supported by a study in which allele-specific apo (a) levels were higher in HIV-infected individuals with high CD4 cell counts or low plasma HIV RNA. This suggests that HIV infection activity might reduce allele-specific apo (a) levels and that in HIV-1-infected patients with a better viroimmunologic control, higher levels of allele-specific apo(a) implying higher levels of atherogenic small apo(a) sizes might increase cardiovascular risk in this patients. Further collaborative studies with a larger number of HIV-infected participants are warranted to address gene implication in cardiovascular risk.

The fourth article (IV) herein presented reviews how aging impacts metabolism also in HIV-1-infected patients. According to recent data, lipodistrophy may be linked to an accelerated age-related functional decline and this has been in turn associated to low muscle mass, low bone mineral density and low insulin growth factor-I. Assessing anthropometric parameters and using metabolically well tolerated antiretroviral drugs are gaining importance in the clinical management of the aging-HIV-1-infected patients group. Besides new strategies such as those developed to attenuate innate immune activation and hepatic function may gain importance as well in the years to come.

In the last two studies (V, VI) smoking effects and Smoking cessation strategies in HIV-infected patients have been reviewed. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study found that the risk of myocardial infarction and cardiovascular disease almost halved after 3 years of quitting. Smoking cessation programs following a similar design as for the general population have been attempted achieving up to 40% rate of success at one year. Specific approaches aimed to improve the

incorporation of smoking cessation strategies by HIV doctors and to obtain better responses given the unique needs of HIV+ adults have been suggested.

Non-AIDS related mortality among HIV-positive smokers is greater than in HIV-negative smokers. Excess of mortality rate among smokers and population attributable risk (PAR%) of smoking related deaths were greater than thrice, for HIV-positive and double for HIV-negative participants respectively. Nowadays with the extensive use of antiretroviral therapy, smoking-related mortality increases with age and accounts for more life years lost than HIV-related mortality.

When reviewing the smoking cessation issue in the HIV population, the most striking fact is HIV-physicians´ reluctance identified as an obstacle for patients´ quitting. Consistently, being a HIV-infected patient is associated to negligent tobacco consumption detection. On the other hand, data reported by the Swiss HIV Cohort are encouraging: patients whose HIV-physicians had been trained in counseling techniques, reduced their tobacco consumption, showed higher rate of nicotine abstinence and fewer relapses. The lower quitting rates among HIV-infected patients comparing with uninfected individual in smoking cessation studies, may be explain by the lower number of HIV-infected patients. Therefore, studies specifically tailored for HIV-infected patients with higher number participants are warranted.

Conclusions and practical applications

I. Smoking contributed to ACS in HIV+ adults almost twice as much as in HIV- adults. The contribution of smoking in the HIV+ population largely exceeds that of diabetes and hypertension. This study demonstrates that if the contribution of smoking disappears, a substantial reduction in the incidence of ACS in HIV+ adults should be expected. Therefore smoking cessation must become a priority among HIV+ adults.

II. Doctors at Emergency Department should take into account that HIV-infected adults presenting with acute coronary disease can be younger, complaining with fewer symptoms but even so exhibiting a more intense cardiac ischemia than uninfected patients. And they should also know that short-term prognosis is similar with the standard therapeutic interventions.

III. Although LPA structural genetic variants are associated to ICD in the general population, they have not shown to be associated with ICD in our cohort of HIV-1-infected patients. However, traditional risk factors did show association in both groups, HIV infected and uninfected. The clinical utility of LPA genetic variants as predictor markers of ICD in HIV-1-infected patients remains unproven.

IV. For the aging HIV population the following interventions addressing reduction of metabolic impairment should be considered: 1) Emphasis on nutrition and exercise. 2). Antiretroviral therapy with the lowest metabolic impact. 3) Assessment, measure, prevention and treatment of lipodystrophy and obesity. 4) To decrease microbial translocation, inflammation, immune deficiency, and abnormal HDL, interventions other than early initiation of antiretroviral therapy will likely gain relevance.

V. It is time for addressing smoking cessation in PLWHA. HIV-1-infected patients present overall and slightly lower rate of success in quitting and more relapses than uninfected individuals do. PLWHA whose HIV physicians are trained on counseling methods achieved higher rates of success in quitting and less relapses than those patients whose doctors are not trained; this rate is positively associated to the duration of the intervention. Awareness of HIV doctors and training them in counseling and motivational techniques may be the first steps pursuing smoking cessation in this specific group.

VI. A better understanding of the pathogenic mechanisms effects of tobacco smoking and HIV infection may help to promote smoking cessation.

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Resumen de la tesis en castellano

ESTUDIO DEL RIESGO CARDIOVASCULAR EN PACIENTES INFECTADOS POR EL VIRUS DE LA INMUNODEFICIENCIA HUMANA RESPECTO A PACIENTES NO INFECTADOS Y POBLACION GENERAL SANA

Introducción

Actualmente, la esperanza de vida de pacientes infectados por VIH que reciben terapia antirretroviral se ha equiparado a la de la población general. Como consecuencia de este avance, factores de riesgo y causales de morbimortalidad en la población general de edad avanzada como la obesidad o la enfermedad metabólica y cardiovascular, emergen como factores de riesgo y causales de morbimortalidad en la población VIH. Sin embargo la infección por VIH continúa implicando un contexto epidemiológico, fisiopatológico y clínico específico.

La alta prevalencia del consumo de tabaco, alcohol y drogas ilícitas, las inmunodeficiencia, inmunoactivación e inflamación persistentes a pesar de una carga viral suprimida, así como algunos efectos secundarios del tratamiento antirretroviral, son factores que intervienen en el desarrollo de le enfermedad cardiovascular en pacientes VIH y que pueden influir también su presentación clínica, evolución y pronóstico tras el tratamiento médico o intervencionista.

Hasta ahora las estrategias preventivas y terapéuticas de la enfermedad cardiovascular en pacientes con infección VIH presentes en las guías clínicas de VIH, se basan en las recomendaciones dirigidas a la población general junto a un inicio temprano de la terapia antirretroviral. Este acercamiento es aunque correcto, susceptible de ser optimizado. Entender mejor las características que diferencian en términos de patogénesis, epidemiología y clínica la enfermedad cardiovascular de pacientes VIH y no infectados, puede contribuir al diseño y desarrollo de intervenciones clínicas y preventivas para disminuir el riesgo de la enfermedad cardiovascular en pacientes VIH.

Objetivos

Objetivo principal

El objetivo común principal de los estudios que se presentan a continuación es investigar las posibles diferencias en el riesgo cardiovascular de los pacientes infectados por VIH frente a pacientes no infectados e individuos sanos de la población general.

Objetivos secundarios

1. Epidemiológico:

    a. Estudiar la contribución relativa del consumo de tabaco, la diabetes y la hipertensión arterial en el desarrollo del síndrome coronario agudo en pacientes VIH.

    b. Profundizar en el conocimiento del contexto epidemiológico relacionado con la enfermedad cardiovascular en la población VIH. En particular se revisarán: tabaquismo, envejecimiento y alteraciones metabólicas.
2. Clínico:

    a. Analizar las características clínicas, del manejo terapéutico y del pronóstico del síndrome coronario agudo en pacientes VIH.

    b. Revisar y sintetizar la evidencia científica disponible referente a la patogénesis de las enfermedades relacionadas con el tabaquismo y con las alteraciones metabólicas durante el envejecimiento.

3. Genético: Analizar el posible papel de variantes genéticas de Apo (A) como marcadores genéticos de riesgo cardiovascular en pacientes VIH.

Resultados

I. Dos estudios casos-controles paralelos. Análisis de la contribución individual del tabaco, la diabetes y la hipertensión arterial en el desarrollo del síndrome coronario agudo en pacientes VIH frente a individuos no infectados. HIV Med. 2013 Jan;14(1):40-8. **Calvo-Sánchez M,** Perelló R, Pérez I, Mateo MG, Junyent M, Laguno M, Blanco JL, Martínez-Rebollar M, Sánchez M, Mallolas J, Gatell JM, Domingo P, Martínez E.

Resumen del estudio

En lo referente a la prevención y el manejo clínico del SCA, las guías clínicas de VIH siguen las directrices consensuadas para la población general. Sin embargo, los pacienes VIH presentan un riesgo cardiovascular más elevado que la población general. Se han descrito dos posibles explicaciones para este mayor riesgo cardiovascular: 1) La mayor prevalencia de factores de riesgo cardiovascular tradicionales (FRCT) en la población VIH (ej. consumo de tabaco, diabetes, síndrome metabólico). 2) Un efecto aditivo y/o sinérgico entre FRCT y factores de riesgo cardiovascular relacionados con la infección VIH (ej. Inflamación crónica, inmunoactivación, terapia antirretroviral). La hipótesis de este estudio sugiere que la contribución de los FRCT en pacientes VIH debe de ser diferente a su impacto en la población general. En este estudio se han llevado a cabo dos modelos casos-control paralelos.

En el primer estudio, cada adulto VIH-positivo diagnosticado con SCA seleccionado en el grupo VIH+/SCA, fue macheado con adultos VIH-positivos sin SCA (VIH+/noSCA group). En el segundo estudio, cada participante en el grupo VIH+/SCA fue macheado con tres individuos VIH-negativos diagnosticados de SCA (VIH-/SCA group). Cada individuo del grupo VIH-/SCA group se macheó con un adulto VIH-negativo sin SCA (VIH-/noACS group). La razón de individuos en cada grupo de estudio (VIH+/SCA, VIH+/noSCA, VIH-/SCA and VIH-/noSCA) fue 1:3:3:3 respectivamente. Con el objetivo de identicar factores de riesgo para SCA, se realizaron análisis de regresión logística. También se calcularon los porcentajes de riesgo poblacional atribuibles a tabaquismo, diabetes e hipertensión arteriral. El modelo fue ajustado por edad y género para los grupos VIH-positivo y VIH-negativo, la duracción de la infección en pacientes VIH-positivos y por fecha de calendario para los individuos VIH-negativos. Se emplearon definiciones similares para los factores de riesgo y las variables de estudio de ambos grupos VIH-positivos y negativos.

Conclusiones

Este estudio, hasta la fecha el primero en analizar el PARs de factores de riesgo cardiovascular tradicionales en la población VIH, concluyó que:

-La contribución del consumo de tabaco al SCA en pacientes VIH-positivo fue más de dos veces mayor que en adultos no infectados.

-El consumo de tabaco contribuye más que la diabetes y la hipertensión arterial al desarrollo de SCA en adultos VIH-positivos.

Nuestros resultados apoyan la prioridad que merecen las estrategias antitabaco en la reducción del riesgo cardiovascular en pacientes VIH.

II. Análisis retrospectivo de una cohorte prospectiva de pacientes con síndrome coronario agudo (SCA) comparando su presentación clínica y pronóstico a corto plazo en pacientes VIH y no infectados. Eur J Intern Med. 2011 Oct;22(5):485-8. Perelló R, **Calvo M,** Miró O, Castañeda M, Saubí N, Camón S, Foix A, Gatell JM, Masotti M, Mallolas J, Sánchez M, Martinez E.

Resumen del estudio

Las caracterísiticas de la presentación clínica, la respuesta al tratamiento y evolución del SCA en pacientes VIH aún requieren ser más investigadas. El objetivo de este estudio es analizar los síntomas de la fase aguda del SCA, el tipo de SCA y el tipo de tratamiento administrado, los resultados del mismo y los factores asociados al pronóstico en un grupo de pacientes infectados por VIH. Para esto se analizaron los datos de pacientes diagnosticados de SCA o angina inestable en un servicio de Urgencias, comparando al grupo de VIH-positivos con un grupo control de no individuos no infectados. Todos los pacientes fueron seguidos al menos durante un mes tras el alta hospitalaria.

Conclusiones

Comparando con adultos no infectados, los pacientes VIH-positivos prsentan SCA a edades más tempranas y muestran entre sus antecedentes mayor prevalencia de factores de riesgo cardiovascular y menos sintomatología en la fase aguda del SCA a su llegada a Urgencias. Los pacientes VIH, presentan con mayor frecuencia infarto miocárdico con elevación del segmento ST requieriendo por lo tanto con más frecuencia angioplastia coronaria transpercutánea. Estas diferencias perdían su

significación estadística al ajustar el modelo por edad y género. El pronóstico resultó similar en ambos grupos, pacientes VIH y no VIH.

III. Estudio casos-controles anidado que evalúa la asociación entre variantes genéticas de la lipoproteína (a) con factores de riesgo cardiovascular tradicionales y el riesgo de presentar infarto de miocardio en pacientes VIH. Egaña-Gorroño L, Martínez E, Escribà T, **Calvo M**, Gatell JM, Arnedo M. Front Immunol. 2012 Dec 6;3:367.

Resumen del estudio

La lipoproteína (a) (LPA) is un factor de riesgo de enfermedad aterosclerótica. En la población general se ha descrito una asociación entre la enfermedad coronaria y variaciones en el número de copias del gen KIV-2 de la LPA así como con polimorfismos de un único nucleótido en dicho gen. El objetivo de este estudio es probar si dicha asociación existe en la población VIH. Se seleccionaron pacientes VIH-positivos que diagnosticados de infarto de miocardio y se machearon a razón de 1:3 con individuos VIH-positivos sin patología coronaria conocida. Mediante reacción en cadena de la polimerasa se analizaron variaciones en el número de copias y polimorfismos de un solo nucleótido en el gen de la LPA de los individuos seleccionados. Se llevó a cabo un análisis de regresión logística para el estudio de la asociación entre factores genéticos, factores no-genéticos de riesgo cardiovascular e infarto de miocardio.

Conclusiones

No se detectó asociación entre haber presentado un infarto de miocardio y variaciones en el número de copias de KIV-2 o con polimorfimos de un solo nucleótidos en el gen LPA. Estas dos variantes genéticas del gen de LPA no se han identificado como marcadores genéticos de enfermedad coronaria en pacientes VIH. Sin embargo los factores de riesgo tradicionales y el recuento de CD4, sí mostraron asociación significativa con el diagnóstico de infarto de miocardio.

IV. Revisión sistemática de la evidencia científica sobre redistribución de la grasa corporal, alteraciones metabólicas y su impacto en pacientes en edades avanzadas infectados por VIH. **Calvo M**, Martinez E. Curr Opin HIV AIDS. 2014 Jul;9(4):332-9.

Resumen del estudio

Se revisan y explican nuevos datos que señalan a la inflamación crónica presente en pacientes VIH como factor de riesgo cardiovascular. Este aumento del riesgo cardiovascular asociado a una mayor inflamación estaría vehiculado por la hipertrigliceridemia, la disminución del HDL-colesterol y la insulin-resistencia, todos ellos promotores ateroscleróticos. También a través de la la translocación microbiana. Las últimas generaciones de antirretrovirales parecen presentar menos alteraciones metabólicas asociadas pero no consiguen revertir la inflamación crónica. Hay factores genéticos que cobrarán relevancia al tratar la dislipedemia. Recientemente varios estudios han demostrados la asociación que existe entre la lipodistrofia y la presencia de factores tradicionales de riesgo cardiovascular, marcadores de inflamación y un declive funcional del paciente. Conocer esta asociación es importante puesto que la pandemia de la obesidad también afecta a los pacientes VIH favoreciendo el desarrollo de lipodistrofia.

Conclusiones

La inflamación crónica y la translocación microbiana impactan sobre el metabolismo de pacientes VIH de edad avanzada a pesar de una supresión virológica mantendia. Será necesario tener lo anterior en cuenta a la hora de diseñar estrategias de prevención de la aparición de una mayor fragilidad y de comorbilidades que se sumen a las ya asociadas a la edad en este grupo de pacientes VIH.

V. Revisión sistemática de la literatura científica sobre el abandono del consumo de tabaco en la población VIH. **Calvo M**, Martínez E. HIV Medicine 2014.

Resumen del estudio

En pacientes VIH, el consumo de tabaco es el factor de riesgo cardiosvascular que más contribuye al desarrollo de enfermedad cardiovascular y probablemente al de otro tipo de eventos no definitorios de SIDA. En general y desde el inicio de la epidemia de VIH, la proporción de fumadores en la comunidad VIH es al menos el doble que en la población general. El abandono del tabaquismo debería ser prioritario para los médicos que tratan pacientes VIH. Desde una perspectiva enfocada en la práctica clínica, se revisa la evidencia científica de tres puntos referentes al cese del tabaquismo en pacientes VIH: detección de los mejores candidatos, elección de una estrategia antitabaco y aspectos importantes en el seguimiento.

Conclusiones

Aunque los pacientes VIH presentan mayor grado de motivación por iniciar una terapia antitabaco que fumadores de la población general, con las estrategias disponibles actualmente, los pacientes VIH presentan una proporción menor de abandonos y similar número de recaídas que individuos no infectados. Sin embargo, esta evidencia se basa en un pequeño número de estudios con un número pequeño de participantes. Se necesita más experiencia que investigue la eficacia de terapias antitabaco específicamente dirigidas a pacientes VIH pero hasta que no se disponga de nueva evidencia, el uso de estrategias antitabaco diseñadas y estudiadas en población general deberían promoverse entre pacientes VIH. Al considerar el abandono tabáquico en pacientes VIH, la regularidad en sus consultas, la confianza que depositan en sus médicos y su media de edad joven, son factores positivos que han de favorecer el logro de un mayor número de abstinencias permanentes y beneficios para la salud a largo plazo.

VI. Revisión de los mecanismos fisiopatológicos e implicaciones clínicas del consumo de tabaco y la infección por VIH. **Calvo M**, Laguno M, Martínez M, Martínez E. AIDS Reviews 2014.

Resumen del estudio

Es muy probable que los perjuicios para la salud que el tabaco provoca en el colectivo VIH se estén subestimando. Equiparar los efectos fisiopatológicos del tabaco en el contexto de la infección por VIH con los observados en la población general, se presume al menos como cuestionable. En este artículo se revisan los mecanismos patogénicos subyacentes a los problemas de salud atribuibles al tabaco y cómo pueden éstos confluir con los mecanismos patogénicos de la infección por VIH.

Conclusiones

La exposición al humo de tabaco daña la salud de los pacientes VIH con mayor intensidad que en individuos no infectados debido a un efecto tanto acumulativo como sinérgico con factores asociados a la infección VIH. La evidencia confirma la intuitiva idea de que la infección por VIH puede aumentar la susceptibilidad a los efectos nocivos del tabaco. Entender el impacto real de la interacción fisiopatológica entre consumo de tabaco e infección por VIH, es importante para que los médicos especialistas en VIH se conciencien y comprometan con la promoción de estrategias antitabaco entre sus pacientes.

Conclusiones e implicaciones prácticas de la tesis

I. El consumo de tabaco contribuye al síndrome coronario agudo (SCA) de pacientes infectados por VIH con una intensidad más de dos veces mayor con la que lo hace en no infectados. Esta contribución supera ampliamente a la de la diabetes o la hipertensión. Estos resultados implican que si la contribución del tabaquismo desapareciese, se podría esperar una reducción sustancial en la incidencia del SCA en pacientes VIH. Por lo tanto, abandonar el consumo de tabaco ha de convertirse en una prioridad para los pacientes VIH.

II. Los especialistas en medicina de urgencias deberían tener en cuenta que los pacientes VIH pueden presentar un SCA a edades más tempranas y presentando menos sintomatología pero acompañada de un mayor grado de isquemia cardiaca que los pacientes no infectados. Estos especialistas deben saber también que el pronóstico a corto plazo tras el tratamiento estándar del SCA es similar para ambos grupos de pacientes.

III. Aunque las variantes genéticas estructurales de la lipoproteína A (LPA) se asocian a enfermedad coronaria isquémica en la población general, no se ha demostrado dicha asociación en la cohorte VIH estudiada. En esta cohorte y en el grupo control, los factores de riesgo tradicionales sí mostraron asociación con la enfermedad isquémica. Según este estudio, no se ha probado utilidad de las variantes genéticas de la LPA como marcador predictivo de enfermedad coronaria isquémica en pacientes VIH.

IV. Para la población VIH en edad avanzada han de considerarse las siguientes medidas dirigidas a reducir el deterioro metabólico: 1) Enfatizar la importancia de una nutrición adecuada y la práctica regular de ejercicio físico. 2) Pauta de una combinación antirretroviral con bajo coste metabólico. 3) Evaluación y medida de la lipodistrofia y la obesidad para plantear estrategias de prevención y tratamiento. 4) Con el fin de reducir el impacto de la translocación microbiana, la inflamación, la inmunodeficiencia y la dislipidemia crónicas, habrán de cobrar relevancia nuevas estrategias diferentes y adicionales a una terapia antirretroviral temprana.

V. Los pacientes VIH presentan una proporción de éxitos en el abandono del tabaco discretamente menor y una proporción de recaídas similares a las de adultos no infectados. Los fumadores infectados cuyos médicos están entrenados en estrategias antitabaco logran la abstinencia y recaen menos que aquéllos cuyos doctores no están entrenados. Esta proporción de éxitos en la abstinencia se asocia con la duración de la intervención antitabaco. La concienciación y el entrenamiento en técnicas de consejo

médico y motivacionales entre los médicos especialistas en VIH son probablemente los pasos más importantes que han de darse para alcanzar el éxito en el abandono del tabaquismo en los pacientes VIH.

VI. Un mejor entendimiento de los efectos de los mecanismos patogénicos activados por el consumo tabáquico y la infección por VIH ayudará a extender la prescripción y seguimiento de terapias antitabaco en la población VIH.

Annex

Other co-authored scientific articles not included in this thesis related to the epidemiology of cardiovascular and other non-AIDS defining events in HIV patients and to new HIV treatment strategies with low metabolic impact.