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Lipid Metabolism and Cardiovascular Risk in HIV Infection: New Perspectives and the Role of Nevirapine

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Abstract

Effective antiretroviral regimens allow patients to successfully manage their HIV infection for decades. Both HIV infection and treatment elevate the incidence and progression of cardiovascular disease, as evidenced by higher rates of myocardial infarction. Traditional cardiovascular disease risk factors, including elevated serum lipids, lipoprotein and triglyceride levels, hypertension, and smoking, may play a role. In addition, factors directly related to HIV infection (chronic inflammation and persistent immune activation due to viral replication) further elevate risk, while some antiretrovirals adversely affect serum lipids and promote inflammation.

Recent epidemiological studies report that HIV-infection rates in patients aged 50 years or greater are rising. Since HIV patients experience decades of elevated cardiovascular disease risk, and many patients are infected later in life, older patients are generally at even greater cardiovascular disease risk. Treatment guidelines recommend antiretroviral regimen initiation soon after initial diagnosis, with continuous adherence to minimize long-term consequences of HIV infection. Also, appropriate selection when initiating or switching antiretroviral regimens can play a major role in managing cardiovascular disease risk. Antiretroviral drugs with favorable lipid profiles may help. Close adherence to the NCEP guidelines for managing hyperlipidemias and other cardiovascular risk factors further reduces cardiovascular disease risk.

Recent awareness of other patient factors, such as the impact of vitamin D deficiencies on cardiovascular disease risk, especially in the HIV-infected population, raises important questions with regard to the potential benefits of vitamin D repletion via supplementation. Fortunately, these and other important cardiovascular disease risk management questions designed to improve patient care are currently being addressed in large, well-controlled clinical trials **(AIDS Rev. 2013;15:195-203).**

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Key words

HIV infection. Serum lipid metabolism. Chronic inflammation. ARV regimen selection. Vitamin D repletion.

Introduction

The incidence and progression of cardiovascular disease (CVD) are both increased in the HIV-infected patient population. The underlying causes driving these trends are diverse and complex, and include traditional CVD risk factors, HIV infection-associated inflammation and immune activation, and the direct effects of antiretroviral (ARV) medications themselves[1,2]. Now that HIV-infected patients are living much longer in the setting of effective antiretroviral therapy (ART) and are being treated for decades instead of years, the long-term consequences of HIV infection and treatment on a patient's CVD risk profile are increasingly important. It is well-established that CVD risk increases with age for all patients, and epidemiologic trends indicate that individuals aged 50 years or older make up a rising percentage of newly HIV-infected

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patients[3,4]. As a result of these trends, HIV-infected patients generally have higher CVD risk profiles compared with non-HIV-infected age-matched controls, and these risks need to be managed with proper therapy and long-term care[4,5].

In the last few years it has become apparent that early initiation and non-interrupted use of ART may be useful for decreasing CVD in HIV-infected patients. However, at the same time, traditional CVD risk factors such as smoking or hypertension should be properly managed in this population. Finally, taking into account that some ARV drugs increase CVD risks, the selection of appropriate ARV when initiating or switching ART can be very important.

Factors underlying increased cardiovascular risk in HIV-infected patients

In a large cohort study, acute myocardial infarction (MI) rates were determined from a healthcare system data registry with 3,851 HIV-infected and 1,044,589 non-HIV-infected patients. The primary outcome was MI, as defined by the International Classification of Diseases coding criteria[2]. The overall rates of acute MI per 1,000 person-years were significantly higher in HIV-infected patients; 11.13 (95% [confidence interval] CI: 9.58-12.68) vs. non-HIV-infected 6.98 (95% CI: 6.89-7.06), with a relative risk of 1.75 (95% CI: 1.51-2.02; $p < 0.0001$), after adjusting for age, sex, race, hypertension, diabetes, and dyslipidemia[2]. After stratification by sex, the relative risk (for HIV vs. non-HIV) was 2.98 (95% CI: 2.33-3.75; $p < 0.0001$) for women and 1.40 (95% CI: 1.16-1.67; $p = 0.0003$) for men, adjusting for age, race, hypertension, diabetes, and dyslipidemia[2]. It should be noted that the HIV cohort had significantly higher proportions of hypertension (21.2 vs. 15.9%), diabetes (11.5 vs. 6.6%), and dyslipidemia (23.3 vs. 17.6%) than the non-HIV cohort ($p < 0.0001$ for each comparison)[2].

Clinical studies have shown that the increase in CVD risk in HIV-infected individuals results from a variety of host, viral, and ARV factors, which exert their pro-atherosclerotic effects on activated macrophages and smooth muscle cells. These effects are varied and far-ranging, beginning with viral replication that leads to chronic inflammation, which adversely impacts endothelial function, thereby promoting atherosclerosis and hypertension[3].

Endothelial dysfunction is a fundamental process in the development of atherosclerosis, which can be assayed via flow-mediated dilation of the brachial artery[6]. The median flow-mediated dilation was lower in HIV-infected patients, indicating that endothelial function is impaired, even in ARV-treated patients with undetectable viral loads[6]. In a prospective observational cohort of adults infected with HIV (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy, n = 389), common carotid artery intima-media thickness (CIMT), another key measure of atherosclerotic change, was assessed by ultrasound at baseline, and at year 2[7]. The median increase over two years in the CIMT was 0.016 mm (interquartile range, –0.003 to 0.033 mm; $p < 0.001$)[7]. In patients with suppressed viral load at baseline, progression of CIMT was reduced (–0.009 mm change; $p = 0.015$), especially in those who remained virologically suppressed throughout follow-up (–0.011 mm change; $p < 0.001$)[7]. Virologic control was associated with a reduced rate of progression of atherosclerosis.

In the Strategies for Management of Anti-Retroviral Therapy (SMART) trial, all-cause mortality was higher for participants randomized to intermittent, CD4-guided ARV treatment (drug conservation) than continuous ARV treatment (viral suppression)[8]. To test the hypothesis that increased HIV-RNA levels because of interrupted ART lead to chronic inflammation and markers of coagulation commonly associated with progressive CVD and death[8], six biomarkers, including high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), amyloid A, amyloid P, D-dimer, and prothrombin fragment 1+2 were assayed in drug conservation patients (n = 249), and viral suppression patients (n = 250) at baseline and at one month following randomization[8]. Higher levels of hsCRP, IL-6, and D-dimer at baseline were significantly associated with a greater risk of all-cause mortality[8].

In a separate report from the SMART study, patients randomized to the interrupted ARV regimen demonstrated a CVD event hazard ratio (HR) of 1.57 (1.00-2.46; $p = 0.05$) compared with patients receiving continuous therapy[9]. Increases were seen in deaths from CVD (7 vs. 4), non-fatal silent MI (11 vs. 5), non-fatal strokes (8 vs. 3), and coronary artery disease requiring invasive procedures (22 vs. 14) in drug conservation vs. viral suppression patients, respectively[9].

While it has been well established that patient factors such as elevated total cholesterol (TC) and triglycerides (TG), a family history of chronic heart disease[1], high rates of smoking in the HIV-infected community[1,3], and elevated rates of hypertension may all contribute to accelerated atherosclerotic disease, the data discussed above support the notion that HIV infection, and subsequent therapeutic interventions, can elevate the CVD risk in HIV-infected patients.

Antiretrovirals may also increase cardiovascular disease risk in HIV-infected patients

In addition to the established increase in CVD risk associated with HIV infection and viral replication, certain ARV drugs have been associated with increased risk for the progression of CVD.

An atherogenic lipid profile is a long-recognized and associated CVD risk factor. However, several underlying mechanisms may also play a role in the association between protease inhibitors and CVD, such as the formation of foam cells via upregulation of CD36 cell surface receptors[10], or a prothrombotic stimulus resulting from increased PAI-1 levels[11]. Moreover, abnormal fat redistribution in the form of peripheral lipoatrophy or central/visceral lipohypertrophy may also contribute to an increased CVD risk through insulin resistance, altered cytokines, and lipid disturbances[12].

In the DAD study, the relative risk of MI by cumulative exposure to various protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) were compared. Except for ritonavir-boosted atazanavir (ATV/r)[13], PI, including indinavir (IDV), nelfinavir (NFV), ritonavir-boosted lopinavir (LPV/r), and saquinavir each had a relative risk of MI per year > 1[4]. Indinavir and LPV/r in particular showed the highest relative risk. On the other hand, the NNRTIs efavirenz (EFV) and nevirapine (NVP) demonstrated much lower relative risk/year, with NVP in particular showing a relative risk < 1[4].

The CIMT from baseline has been shown to vary by drug class. For all ARVs, the two-year change in CIMT was 0.014 mm. A comparison of NNRTI vs. PI demonstrated a significant difference in the two-year change in CIMT of 0.011 vs. 0.019 mm, p = 0.01 (NNRTI and PI, respectively)[7].

Among nucleoside reverse transcriptase inhibitors (NRTIs), results from the DAD study indicated that 2',3'-dideoxyinosine (ddI), and especially abacavir (ABC), were associated with an increased risk of MI. Since ABC is considered to have a relatively good lipid profile, these results were surprising, and several mechanisms were subsequently proposed, including the induction of a proinflammatory cytokine profile[14], and increased platelet reactivity resulting from the competitive inhibition of soluble guanylyl cyclase by ABC[15].

Several recent studies designed to test these findings have generated conflicting results. Two recent meta-analyses that analyzed data from 9,000 patients between them, did not report any association between the use of ABC and an increase in CVD risk[16,17]. Nevertheless, some experts continue to recommend individualizing ABC therapy and potentially avoiding its use in patients with high CVD risk.

Serum lipids and cardiovascular disease risk

Elevated serum lipids are associated with increased CVD risk in uninfected people. Treatments that lower low-density lipoprotein cholesterol (LDL-c), TG, and increased high-density lipoprotein cholesterol (HDL-c), have been shown to lower overall CVD risk (Table 1). It is well established that serum lipids are altered in ARV-naive HIV-infected patients, and that ARV treatment further modifies serum lipid levels and the final profile can depend on the interactions between the individual ARV treatment regimen and a patient's background (Table 2)[18]. The thymidine analogues stavudine (d4T) and zidovudine (AZT), the NNRTI EFV, and the PI (and among these, especially LPV/r, IDV, and fosamprenavir) are associated with atherogenic changes in serum lipid profiles.

In a randomized and placebo-controlled trial of 2,531 patients receiving either gemfibrozil or placebo, HDL-c was increased by 6% ($p < 0.001$) and TG were decreased by 31% ($p < 0.001$) vs. placebo after one year[19]. These changes resulted in a 22% reduction in the relative risk of MI or death from CVD[19]. The relative risk of CVD events was reduced by 11% for a 5 mg/dl increase in HDL-c seen with gemfibrozil treatment[20].

Cox proportional-hazards regression was used to test the hypothesis that increases in circulating HDL-c because of lipid therapy were independently associated with a reduction in cardiovascular (CV) events in The Framingham Offspring Study (1975-2003)[21]. After adjusting for changes in LDL-c, plasma TG, and pretreatment blood lipid levels, the independent effect of HDL-c levels on future CV risk was estimated (with an average follow-up of eight years)[21]. A 5 mg/dl increase in HDL-c was associated with a HR for CV events of 0.79. Each 1% increase in HDL-c was associated with a 2% drop in CV risk[21]. The HDL-c and TG levels affect all-cause mortality in HIV-infected patients.

The INTERHEART study was a standardized case-control examination of acute MI in patients from 52 countries. Key plasma lipids, lipoproteins, and apolipoproteins were assayed in 9,345 cases and 12,120 controls (age- and sex-matched)[22]. Of all the parameters measured or determined, the apolipoprotein B100 (apo-B)/apolipoprotein A1 (apo-A1) ratio had the highest

Table 1. Serum lipid changes observed in treatment-naive patients in clinical trials

Trial	Background	TC (%)		LDL (%)		HDL (%)		TG (%)		TC:HDL (Change in ratio from baseline)	
KLEAN[52*]	n = 887	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r	LPV/r
LPV/r vs. FPV/r	48 weeks + ABC/3TC	33	39	23	29	41	39	66	60	0.0	–0.2
CASTLE[53†]	n = 883	LPV/r	ATV/r	LPV/r	ATV/r	LPV/r	ATV/r	LPV/r	ATV/r	LPV/r	ATV/r
LPV/r vs. ATV/r	48 weeks + TDF/FTC	24	12[‡]	15	12	32	27	51	13[‡]	–0.2	–0.5
GEMINI[54§]	n = 337	LPV/r	SQV/r	LPV/r	SQV/r	LPV/r	SQV/r	LPV/r	SQV/r	LPV/r	SQV/r
LPV/r vs. SQV/r	48 weeks + TDF/FTC	20	16	18	20	29	26	47	12[¶]	–0.13	–0.27
ARTEMIS[55**]	n = 689	LPV/r	DRV/r	LPV/r	DRV/r	LPV/r	DRV/r	LPV/r	DRV/r	LPV/r	DRV/r
LPV/r vs. DRV/r	48 weeks + TDF/FTC	19	14	11	11	17	10	49	20	NSD	NSD
089[56††]	n = 200	ATV/r	ATV	ATV/r	ATV	ATV/r	ATV	ATV/r	ATV	ATV/r	ATV
ATV/r vs. ATV	48 weeks + 3TC/d4T XR	16	7	24	16	24	25	11	–11	–0.3	–0.6
2NN[27‡‡]	n = 1,216	EFV	NVP	EFV	NVP	EFV	NVP	EFV	NVP	EFV	NVP
EFV vs. NVP	48 weeks + d4T + 3TC	31	27	40	35	34	43	49	20	6.6%	–4.3%
ArTEN[29§§]	n = 569	NVP	ATZ/r	NVP	ATZ/r	NVP	ATZ/r	NVP	ATZ/r	NVP	ATZ/r
NVP vs. ATV/r	48 weeks	24	20	15	10	10	4	0	28	–0.24	0.13
MERIT[57¶¶]	n = 679	EFV	MVC	EFV	MVC	EFV	MVC	EFV	MVC	EFV	MVC
EFV vs. MVC	48 weeks + Combivir	36	2	21	–9	14	7	21	–9	–0.43	–0.54
ECHO and THRIVE[58***]	n = 1,368	RPV	EFV	RPV	EFV	RPV	EFV	RPV	EFV	RPV	EFV
RPV vs. EFV	96 weeks + FTC/TDF	1	27	0	14	4	11	–13	8	NA	NA

3TC: lamivudine; ABC: abacavir; ATV: atazanavir; ATV/r: atazanavir/ritonavir; DAIDS: Division of Acquired Immunodeficiency Syndrome; DRV/r: darunavir/ritonavir; d4T: stavudine; EFV: efavirenz; FPV/r: fosamprenavir/ritonavir; FTC: emtricitabine; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LPV/r: lopinavir/ritonavir; MVC: maraviroc; NVP: nevirapine; RPV: rilpivirine; SQV/r: saquinavir/ritonavir; TC: total cholesterol; TDF: tenofovir; TG: triglyceride; XR: extended release; NSD = no significant difference; NA = not available; NS = not significant.

Unless otherwise noted, data represent mean change from baseline in fasting lipid values (%).

*Comparisons between treatment arms were non-significant for all lipid parameters in the KLEAN trial.

†In the CASTLE trial, the observed changes in the non-HDL cholesterol levels were 21 vs. 7% ($p < 0.0001$).

‡($p < 0.0001$).

§TC:HDL –0.27 vs. –0.13 ($p = 0.47$).

¶($p = 0.002$).

**TC:HDL +0.1 vs. +0.1 (NS); DAIDS grade 2-4 toxicities (TG: 13 vs. 3%; TC: 23 vs. 11%).

††Non-HDL cholesterol (10 vs. 2%).

‡‡HDL, $p < 0.05$; TG, $p < 0.001$ (EFV vs. pooled NVP).

§§TC, $p = 0.041$; LDL-c, $p = 0.001$; HDL-c, $p = 0.0001$; TG, $p < 0.0001$; TC/HDL-c, $p = 0.001$ (NVP vs. ATV/r).

¶¶TC, $p < 0.0001$; LDL-c, $p < 0.0001$; HDL-c, $p < 0.0001$; TG, $p = 0.0002$; TC/HDL-c, $p = 0.005$ (EFV vs. MVC).

***$p < 0.001$ for all comparisons using Wilcoxon rank-sum test (RPV vs. EFV).

Table 2. Cardiovascular risk factors in HIV-infected patients

Host	HIV	Antiretroviral treatment
Male gender	Viral load	Metabolic disturbances (lipids, insulin resistance, vitamin D)
Age	CD4 cells	Abnormal fat redistribution
Family history of CVD	Chronic inflammation	Other*
Sedentary lifestyle	Immune activation	
Smoking		
Dyslipidemia		
Hypertension		
Diabetes		
Vitamin D		

CVD: cardiovascular disease.
*Abacavir has been related to an increase in CVD risk through different potential mechanisms in cohort studies, but this was not confirmed in two recent large meta-analyses[16,17].

population attributable risk and the highest odds ratio (OR) with each 1 standard deviation difference (1.59; 95% CI: 1.53-1.64)[22]. This study demonstrated that the non-fasting apo-B/apo-A1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute MI in all patients regardless of ethnic group, sex, or age[22].

Nutritional and metabolic risk factors were examined in 557 HIV-infected patients in a cohort study (1995-2005)[23]. Only low serum HDL-c and elevated serum TG were found to be associated with an increased risk of all-cause mortality, after adjusting for age, serum albumin, current smoking status, and $CD4^+$ T-cell counts < 200 cells/mm^3 [23].

The effects of tenofovir (TDF)/emtricitabine (FTC) vs. ABC/lamivudine (3TC) based ARV regimens on LDL size, cholesterol content, and lipoprotein-associated phospholipase activity in virologically controlled patients were studied by comparing changes in serum lipids at week 48. The ABC/3TC arm was associated with a more atherogenic profile than TDF/FTC, as reflected by an increase in the cholesterol content of small, dense LDL subfractions (0.48 mmol/l; p = 0.003), and a decrease in LDL size (–2.6 nm; p = 0.011)[24]. However, in another substudy of the BICOMBO trial evaluating several inflammatory and proatherogenic markers (including C-reactive protein, IL-6, IL-10, tumor necrosis factor-α, insulin, adiponectin, and D-dimer), no significant differences were found between ABC/3TC and TDF/FTC treated patients in endothelial function, insulin resistance, or hypercoagulability[25].

Nevirapine effects on serum lipids emerge from key clinical trials

As the long-term significance of CVD risk factors in HIV-infected patients became more apparent, the potential effects of ARVs on serum lipids came under greater scrutiny. As a consequence, the "lipid-friendly effects" of NVP were initially recognized in some early clinical trials.

The ATLANTIC Study compared plasma lipids in patients receiving NVP, IDV, or 3TC, each on a backbone of d4T and ddI at weeks 0, 6, and 24[26]. At the week 24 time point, NVP-treated patients (n = 34) demonstrated dramatic increases in HDL-c (49%), apo-A1 (19%), lipoprotein A1 (38%), and HDL-c particle size (3%)[26]. However, patients receiving 3TC (n = 39) and IDV (n = 41) demonstrated more modest changes in these parameters[26]. The LDL-c increased significantly in both the NVP and the IDV arms; however, the TC/HDL-c ratio was reduced by 14% in the NVP arm[26]. The NVP-based regimen resulted in changes in plasma lipids and lipoproteins that have been associated with a lower CVD risk profile in other settings[26].

In a seminal study, Fisac, et al. compared metabolic changes in 43 patients after 6-12 months of either NFV- (n = 20) or NVP- (n = 23) based ARV regimens[18]. Metabolic parameters under study in serum included TC, HDL-c, lipoprotein cholesterol, TG, glucose, and insulin, and all measured parameters were equivalent at baseline[18]. The TC increased in both arms (NVP, 11%; NFV, 17%) and HDL-c also increased more in the NVP arm vs. the NFV arm (44 vs. 20%, respectively)[18]. These changes resulted in a TC/HDL-c ratio that was reduced by 22% in the NVP arm, while remaining stable in the NFV-treated patients[18].

In a substudy of 2NN, serum lipids and lipoproteins were prospectively analyzed through 48 weeks of follow-up in patients on NVP (n = 417) or EFV (n = 289), each on a background of d4T and 3TC[27]. The percentage change in various serum lipid measures over the 48-week follow-up period was the primary endpoint of

the study. The increase of HDL-c was greater in the NVP arm (42.5%) vs. the EFV arm (33.7%; p = 0.036), while the rise in TC was lower in the NVP arm (26.9%) vs. the EFV arm (31.1%; p = 0.073)[27]. These changes resulted in a lower TC/HDL-c ratio for patients in the NVP arm (–4.1%), and a larger ratio for patients in the EFV arm (+5.9%; p < 0.001)[27]. Smaller increases in non-HDL-c were seen in the NVP arm (24.7%) vs. EFV (33.6%; p = 0.007). The authors concluded that the NVP-containing regimen showed larger increases in HDL-c, and greater reductions in the TC/HDL-c ratio than the EFV-containing regimen at 48 weeks[27].

As previously mentioned, increased apo-A1 production has been shown to increase HDL levels in plasma. To test the hypothesis that NVP increases HDL-c levels in serum by increasing apo-A1, production kinetics and circulating levels of this key protein were measured at baseline, six weeks, and 24 weeks after NVP was added to the regimens of patients who were virologically stable[28]. By 24 weeks of NVP treatment, levels of each key plasma component increased significantly, apo-A1 rose by 13 ± 4% (p = 0.01) and HDL-c rose by 16 ± 6% (p = 0.015)[28]. The rate of apo-A1 production rose by 17 ± 7% (p = 0.0424) at 24 weeks, while its rate of catabolism did not change[28]. In this group of patients, NVP treatment increased apo-A1 production, which was associated with an increase in circulating HDL-c; this effect most likely contributes to the more favorable effect on serum lipids overall that accompanies NVP therapy[28].

The international ArTEN study prospectively compared ATV/r with immediate release NVP, each on a background of fixed-dose TDF/FTC in 569 ARV-naive HIV-1-infected patients[29]. At week 48, the following increases were measured in key serum lipids; TC (24.4 vs. 19.6 mg/dl; p = 0.038), HDL-c (9.7 vs. 3.9 mg/dl; p < 0.0001), LDL-c (15.0 vs. 10.4 mg/dl; p = 0.011), and apo-A1 (0.18 vs. 0.08 g/l; p < 0.0001) for NVP vs. ATV/r, respectively[29]. Increases in apo-B levels were the same in both groups (0.02 vs. 0.02 g/l). Increases in TG levels were much greater in the ATV/r arm, 27.80 mg/dl vs. 0.02 mg/dl for NVP (p = 0.0001)[29]. The apo-B/apo-A1 ratio was significantly lower at week 48 with NVP vs. ATV/r (p = 0.008), reflecting a significantly greater increase in apo-A1 in the NVP arm (0.18 vs. 0.08 g/ml; p <0.0001)[29].

The consensus of data that has emerged from an extensive collection of randomized clinical trials is that individual ARV regimens can have significantly different effects on serum lipid profiles, and some NVP-based regimens can lead to lipid profiles that are potentially less atherogenic than those seen with other regimens.

Newer antiretrovirals and serum lipid effects

The emergence of newer ARVs, including second-generation NNRTIs, integrase inhibitors, and CC chemokine receptor 5 (CCR5) inhibitors, are adding important options to the overall ARV armamentarium. Each of these newer medications has important benefits over first-generation NNRTIs, including different resistance profiles, unique mechanisms of action, and greater flexibility in regimen design.

Raltegravir (RAL) was the first integrase inhibitor to be approved for use in treatment-naive HIV-infected patients. A 96-week follow-up of the ongoing START-MRK study, comparing RAL and EFV, both on a background of TDF/FTC, showed that RAL had a better lipid profile compared with EFV, which included a lower increase in TG and LDL[30]. In patients already on an ARV regimen, switching to RAL has been associated with more favorable changes in serum lipids, such as significant decreases in TC, TG, and LDL, as reported in the SWITCHMRK[31] and SPIRAL[32] randomized clinical trials.

The CCR5 inhibitor maraviroc has also been associated with a better lipid profile when compared with EFV[33], and may also have an anti-inflammatory effect by blocking the trafficking and recirculation of macrophages and monocyte-derived dendritic cells[34].

The effects of the new NNRTIs on serum lipids are an open question. In the SENSE trial, 157 treatment-naive patients were randomized 1:1 to either ETV once daily (n = 79) or EFV once daily (n = 78), each on a backbone of either ABC/3TC, ZDV/3TC, or TDF/FTC for 48 weeks[35]. At week 48, significantly larger increases in HDL (+0.15 mmol/l; p = 0.004), LDL (+0.35 mmol/l; p = 0.005), TC (+0.61 mmol/l; p < 0.0001), and TG (+0.33 mmol/l; p = 0.03) were seen in EFV-treated patients compared with the ETV-treated patients[35]. Overall, there were fewer grade 3/4 elevations in TC, LDL, and TG in the ETV arm compared with the EFV arm[35]. Rilpivirine (RPV) has also been associated with a better lipid profile when compared with EFV in both the ECHO and THRIVE trials[36].

Overall, these new ARV drugs have favorable lipid profiles, with minimal effects on TC and TG. However, it should be noted that they do not increase HDL levels and are not associated with a decrease in the TC/HDL ratio, an important marker ratio of overall CVD risk.

Nevirapine, inflammatory markers, and subclinical atherosclerosis

The identification of sensitive biomarkers of inflammation and subclinical atherosclerosis are areas of active investigation, to serve as early warning signs of subclinical disease and sensitive markers for reversal of CVD risk. These markers include coronary artery calcium and CIMT[37]. Additional studies have identified an association between higher adiponectin plasma concentrations and, (i) favorable lipid profiles, (ii) decreased subclinical inflammation, (iii) decreased markers of atherosclerosis, and (iv) improved endothelial function[38].

In a comparison of the levels of inflammatory/immune markers and residual HIV-viremia in patients receiving either NVP or EFV on a backbone of TDF/FTC, adiponectin (an anti-inflammatory protein) was higher (6.7 vs. 5.6 mg/ml; p = 0.04) and sCD14 was lower (1,503 vs. 1,663 pg/ml; p = 0.05; NVP vs. EFV, respectively), indicating a lower inflammatory profile with NVP treatment[39]. Also, 81% of the patients on NVP had viral loads < 1 copy/ml vs. 62% of the patients on EFV[39].

The independent effects that NVP or EFV might have on the terminal differentiation, gene expression, and release of adipokines and cytokines were examined in differentiating human adipocytes[40]. In this model system, EFV treatment led to a significant increase in the release of numerous proinflammatory markers, including IL-8, IL-6, monocyte chemoattractant protein-1, plasminogen activator inhibitor type-1, and hepatocyte growth factor (HGF). However, NVP either had no effect on these proinflammatory factors or decreased their release (IL-6 and HGF)[40]. Interestingly, NVP treatment did significantly increase the release of adiponectin, which was strongly inhibited by EFV. Furthermore, EFV demonstrated profound anti-adipogenic and proinflammatory effects in this model system, whereas NVP did not appear to inhibit adipogenesis[40].

In a separate study, color-Doppler ultrasonography was used to measure the percentage of patients with normal CIMT at baseline and after at least five years of follow-up in patients receiving either NVP (n = 156) or EFV (n = 120)[5]. In the NVP-treated patients, the percentage with normal CIMT fell only slightly from 69 to 64% (p = 0.8029), whereas the percentage of patients with normal CIMT who were being treated with EFV fell dramatically from 77 to 26% (p < 0.0001)[5].

Taken together, these studies demonstrate a relationship between choice of NNRTI-based regimens and markers of subclinical inflammation and atherosclerosis, such as proinflammatory cytokines and CIMT, over time.

Impact of antiretroviral therapy on vitamin D levels in HIV-infected patients

Vitamin D is an essential vitamin and a key regulator of many metabolic pathways, including inflammation and immunity. If present at sufficient levels, vitamin D has been reported to play a role in reducing the risk of chronic illness, including certain cancers and infectious diseases[41]. While optimal levels of circulating vitamin D are still an area of active investigation and debate, cross-sectional surveys suggest that many people in the general population have suboptimal levels of vitamin D, which may lead to an increased risk for osteoporosis, bone fractures, and CVD[41].

A retrospective chart review of 2,992 HIV-infected adults in New York City identified 274 patients whose vitamin D levels were quantified by radioimmunoassay and none were taking supplemental vitamin D[42]. Black race (OR: 4.11; 95% CI: 1.46-11.54; p = 0.007) and HIV viral load > 50 copies/ml (OR: 2.40; 95% CI: 1.12-5.13; p = 0.024) were each significantly associated with vitamin D deficiency. Vitamin D deficiency was highly prevalent in HIV-infected patients[42].

In the EuroSIDA study, vitamin D 25(OH)D_3 deficiency was seen in 83% of HIV-infected patients on ART, and independently associated with greater risk of developing AIDS and risk of death[43].

In a systematic review of the literature, vitamin D deficiency, secondary hyperparathyroidism, and low bone mineral density (BMD) were found to be common in HIV-positive patients[44]. EFV treatment is associated with a reduction in 25(OH) vitamin D levels, and TDF treatment is associated with secondary hyperparathyroidism[44]. Moreover, ARV was associated with low BMD and increased bone turnover[44]. What role these findings play in the increased incidence of bone fractures reported in this population is still under study.

The MONET trial included 256 European patients taking either NNRTI- or PI-based ARV regimens, with HIV RNA < 50 copies/ml at screening. Patients were switched to ritonavir-boosted darunavir 800/100 mg once-daily, either as monotherapy or with two NRTIs[45]. At baseline, 77% of patients had vitamin D deficiency (< 50 nmol/l), and lower vitamin D levels were significantly associated with calendar month (p = 0.0067), black ethnicity (p = 0.013), EFV (p = 0.0062), and use of AZT (p = 0.015)[45]. Discontinuation of either EFV or ZDV resulted in increased vitamin D levels[45].

Vitamin D levels were found to be suboptimal in 91% of 1,077 patients assayed at a London HIV clinic[46]. Approximately one-third of patients had severe vitamin D

deficiency, which was associated with Black ethnicity, nadir CD4+ cell count < 200 cells/mm^3, sampling during the winter months, and combination ART exposure[46]. This later effect was most significantly associated with current EFV use (OR: 2.0; 95% CI: 1.5-2.7) by multivariate analysis, while no association was seen with current NVP use[46].

The effect of EFV on circulating vitamin D levels results from the inhibition of CYP2R1 by EFV[47]. This is a key enzyme in the metabolism of 25(OH)D_3 into calcitriol, the active metabolite of vitamin D. In addition, EFV induces CYP24R1, an enzyme that oxidizes 25(OH)D_3 into 24,25(OH)$_2D_3$, further reducing the levels of calcitriol[47].

In an analysis of the prospective Dat'AIDS cohort of HIV-infected adult patients in five French centers, vitamin D deficiency/insufficiency was observed in 86.7% of the 2,994 patients, with 55.6% presenting with vitamin D insufficiency, and 31.1% presenting with deficiency. Interestingly, EFV was the only ARV to be significantly associated with deficiency (OR: 1.89; 95% CI: 1.45-2.47)[48].

The effect of EFV on vitamin D seems to be drug-specific, rather than a class effect, as has been suggested by Welz, et al., who found EFV but not NVP to be associated with serious vitamin D deficiency[46]. Of the newer NNRTIs, RPV has a significantly lower impact on serum vitamin D concentrations than EFV[49], while no differences were observed between ETV and EFV in the SENSE trial[50].

Recent studies have demonstrated that vitamin D deficiency and insufficiency are common in HIV-infected patients, and that these metabolic states appear to play a role in the development of various non-infectious comorbidities, including low BMD, immune dysfunction, and advanced CVD. Preliminary data showed that a higher CIMT and vitamin D insufficiency were associated in a cross-sectional analysis of 139 HIV-infected patients. Mean CIMT rose from 0.8 to > 1 mm as vitamin D levels were stratified from normal (> 30 ng/dl) to deficient (< 15 ng/dl)[51].

A number of clinical trials are currently underway to determine the potential benefits of vitamin D supplementation in the HIV-infected population. Therefore, close attention to the data that emerges from these studies will be warranted.

Implications for clinical practice

Circulating lipid and lipoprotein levels, particularly HDL-c and TG, as well as changes in inflammatory markers, may have a significant impact on overall CVD risks[2,8,20]. In this context, early initiation of ARV treatment is now recommended and may be helpful in decreasing CVD risk in HIV-infected patients. In addition, a strict adherence to the National Cholesterol Education Program guidelines for the therapy of hyperlipidemia and other CVD risk factors is warranted. With the increase in CVD risks associated with HIV infection, the potential for some ARV regimens to adversely affect serum lipid profiles can augment a patient's composite CVD profile. Therefore, the selection of appropriate ARV regimens takes on added meaning, since these may have very different effects on serum lipid and inflammatory marker levels, both of which are closely linked to overall CVD risk[28]. The impact of newly described alterations in HIV-infected individuals, such as vitamin D deficiencies, and the potential benefits of their management should be addressed in large prospective clinical trials.

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