AIDS Rev. 2014;16:75-89

Morbidity in Older HIV-Infected Patients: Impact of Long-Term Antiretroviral Use

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Abstract

The introduction of HAART has represented a major advance in the care of people with HIV. By markedly increasing life expectancy, HAART has significantly changed the pattern of HIV infection in developed countries, the "graying" of the HIV-infected population being a powerful testament to its success. However, this has presented physicians with new challenges relating to the care of older patients with HIV, many of whom exhibit a "frailty syndrome" associated with increased comorbidity and chronic low-grade inflammation in a process which has recently been termed "inflammaging". This paper reviews the pattern of morbidity seen in older HIV-infected patients and examines the effects, both beneficial and deleterious, of antiretroviral therapy. The efficacy and tolerability of antiretroviral therapy is of particular importance in older patients, given the likelihood that increased frailty may magnify the consequences both of suboptimal viral suppression and of toxicity, and in view of the complications that may arise from the presence of comorbidities and resultant polypharmacy. The challenge is to maximize antiviral efficacy and minimize toxicity, while taking into account the often complex web of comorbidities that may be present in these patients. This challenge is being met through the refinement of existing antiretroviral therapy regimens, the development of new agents, and a growing focus on a more holistic approach to care, which acknowledges the importance of the overall "health picture" and of good communication and cooperation between treating physicians and patients. **(AIDS Rev. 2014;16:75-89)**

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Key words

Aging. Frailty. Multimorbidity.

Introduction

Significant improvements in antiretroviral therapy (ART) over the past 15 years have resulted in markedly improved life expectancy for HIV-infected adults in industrialized countries. About 20% of HIV-infected patients accessing care in the UK are now aged ≥ 50 years[1], while in the USA about 30% of people living with HIV/AIDS are aged ≥ 50 years[2]. A recent study has calculated a projected life expectancy of 75 years for HIV-positive men who have sex with men living in a developed country with good access to HIV care, assuming an early rate of diagnosis (median CD4 cell count: 432 cells/mm^3)[3].

While this "graying" of the HIV-infected population is to be welcomed as an indication of improved treatment and survival, the increase in the number of older patients with a higher rate of comorbidities compared with younger patients presents new challenges for patient care. Care concerns for this population relate not only to the increased incidence of comorbidities in older patients, but also to the way in which HIV disease is now thought to affect the biology of aging itself. While aging makes everyone more susceptible to disease and the manifestation of various morbidities, there is growing evidence of what might be termed an "early aging" process in HIV-infected individuals[4], with early immune

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senescence accompanied by chronic inflammatory processes that are linked with the pathogenesis of various morbidities. In addition to this, there is evidence that the absolute risk of HIV disease progression is significantly greater for a given CD4 cell count in older patients[5].

In this paper we review the pattern of morbidity seen in older HIV-infected patients and examine the impact, both beneficial and deleterious, of ART.

Immunosenescence, chronic inflammation, frailty, and increased morbidity in aging HIV-infected patients: inflammaging

It is well established that aging, through a decline in the ability of body tissues to renew and repair themselves and the accumulation of tissue damage and proliferative errors, increases the risk of diseases such as atherosclerosis, hypertension, cancer, osteoporosis, and neurodegenerative diseases. A common mechanism for the development of many such chronic diseases with increasing age is their association with chronic low-grade inflammation in a process that has been termed "inflammaging". While increased frailty and comorbidity are well-recognized features of aging in the non-HIV population, a "frailty syndrome" is increasingly being recognized in patients who have contracted HIV.

Frailty syndrome and HIV infection

In HIV infection, in addition to changes in immunity and host defense, infection may accelerate several age-related conditions. Infected patients can therefore experience what might be termed "accelerated frailty", with patients in their 50s developing illnesses more typically associated with more advanced age. Current literature suggests that HIV infection is a risk factor for frailty in both men and women, particularly in patients with a low CD4 count and high viral load[6,7]. Desquilbet, et al.[6] identified a frailty related phenotype in HIV-infected patients, with the CD4 count predicting the phenotype's development[8], and later showed that having a persistent frailty-like phenotype predicted a worse prognosis after HAART initiation[9]. In the Multicenter AIDS Cohort Study (MACS), age-specific prevalence rates of frailty (assessed using components of the Fried system for defining frailty[10]) in HIV-infected men were higher than in age-matched controls, with HIV infection being associated with a shift to an approximately 10-year earlier emergence of frailty phenotypes[6]. Secondly, lower CD4 cell counts and higher viral loads were significantly associated with frailty, although there was substantial variability[8]. Interestingly, it was found that the prevalence of frailty in the HIV-positive population appeared to decrease, moving from the early days of the HAART era in 1996-1999 to the era of more advanced therapy in 2000-2005[8]. In an urban outpatient setting, Onen, et al. found that HIV infection was associated with premature frailty, and patients who had been on ART for a longer time were more likely to be frail[11]. More recently, data from the MACS showed that, for patients aged 50-70 years, the prevalence of frailty among HIV-infected men receiving ART was twice that of HIV-negative controls, with CD4 count < 500 µl and viral load > 50 copies/ml both associated with increased prevalence[12]. After correction for viral load, the prevalence of frailty increased with age similar to what is seen in the general population, suggesting that aging and HIV infection have additive effects on the risk of frailty.

The role of ART remains unclear. The finding of an increased prevalence of frailty among ART-naive patients suggests that the effect of HIV on frailty is at least in part independent of ART. However, while ART (by suppressing HIV) limits the pro-frail effects of infection, some data suggest that cumulative exposure to ART may contribute to some of the frailty phenotypes, including lipodystrophy, ectopic fat changes, atherosclerosis, and sarcopenia[13-17]. Moreover, it is as yet unclear to what extent behavioral factors, previous exposure to risk factors, such as smoking or recreational drugs and previous coinfections such as syphilis, may contribute to the frailty phenotype seen in HIV infection. Associations with African American ethnicity and with lower socioeconomic and educational status also have to be taken into account[10].

Frailty is strongly associated with comorbidity and disability and is a sensitive indicator of changed medical care needs in HIV-infected patients (better than CD4 count or high viral load)[18]. Thus, frailty may represent an important marker for the inflammaging process in HIV-infected patients. Studies are needed to improve our understanding of the complex interrelationship between HIV infection, frailty, and comorbidity and to assess if the frailty phenotype portends adverse outcomes in HIV-infected patients. This would make the evaluation of frailty a useful clinical tool and a possible endpoint in clinical trials.

The pattern of frailty seen in older HIV-infected patients represents a serious management concern and in this regard, the US HIV and Aging Consensus Project 2011 stated that "older" in the context of HIV infection means aged over 50 years[19].

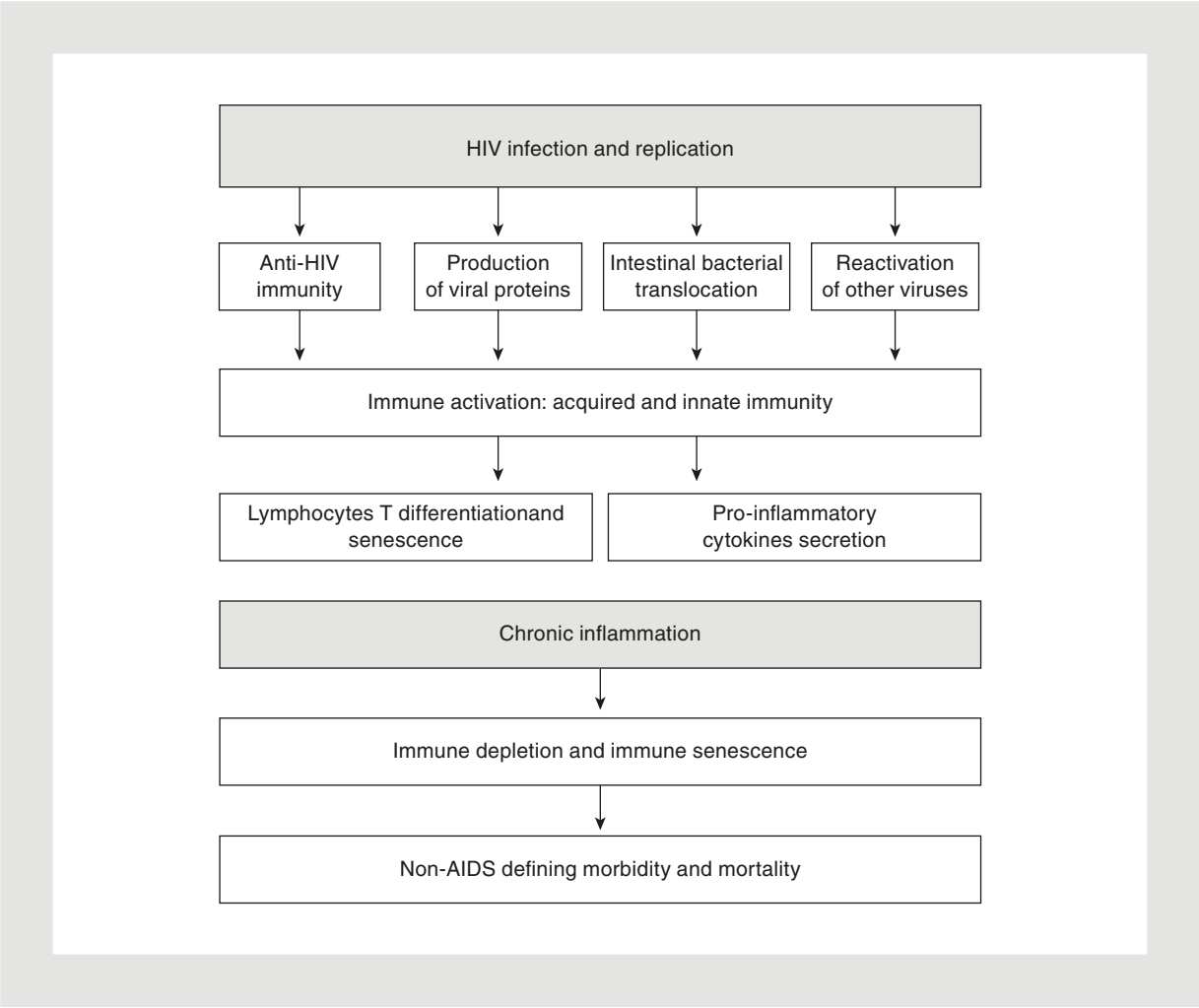

Figure 1. *Putative factors involved in the development of accelerated frailty and increased morbidity seen in HIV-infected individuals[23].*

Mechanisms and consequences of inflammaging in HIV-infected patients

During the aging process, changes occur in body systems that have a major effect upon the immune system in all individuals, with and without HIV infection. In addition to reductions in circulating growth hormones, increases are seen in the baseline levels of inflammatory cytokines[20,21]. Furthermore, chronic diseases and atherosclerosis increase the overall state of chronic inflammation (inflammaging).

In addition, it is known that aging influences the interaction between HIV infection and the immune system[22]. The situation is multifactorial, involving immune activation through the chronic infection, immunosenescence, chronic inflammation[4], and the effects of ART (Fig. 1)[23]. Evidence exists of increased expression of proinflammatory markers in HIV-positive patients compared with the general population[24], with higher levels of these biomarkers independently predicting risk for opportunistic diseases[25] and mortality[26]. Analyses of the SOCA and SCOPE studies have shown that immune activation and inflammation predict mortality, adjusting for CD4 count[27]. Other factors, such as exposure to nephrotoxic drugs, steroids, recreational drugs, lifestyle factors etc., and the effects of other sexually transmitted diseases, may also exert an influence in HIV-infected patients.

Whatever the mechanism(s) involved, it is clear that there is a significant issue relating to increased morbidity and mortality in older HIV-infected patients[28-31]. Data from 7,746 patients in the Swiss Cohort Study show a significantly higher incidence of clinical AIDS

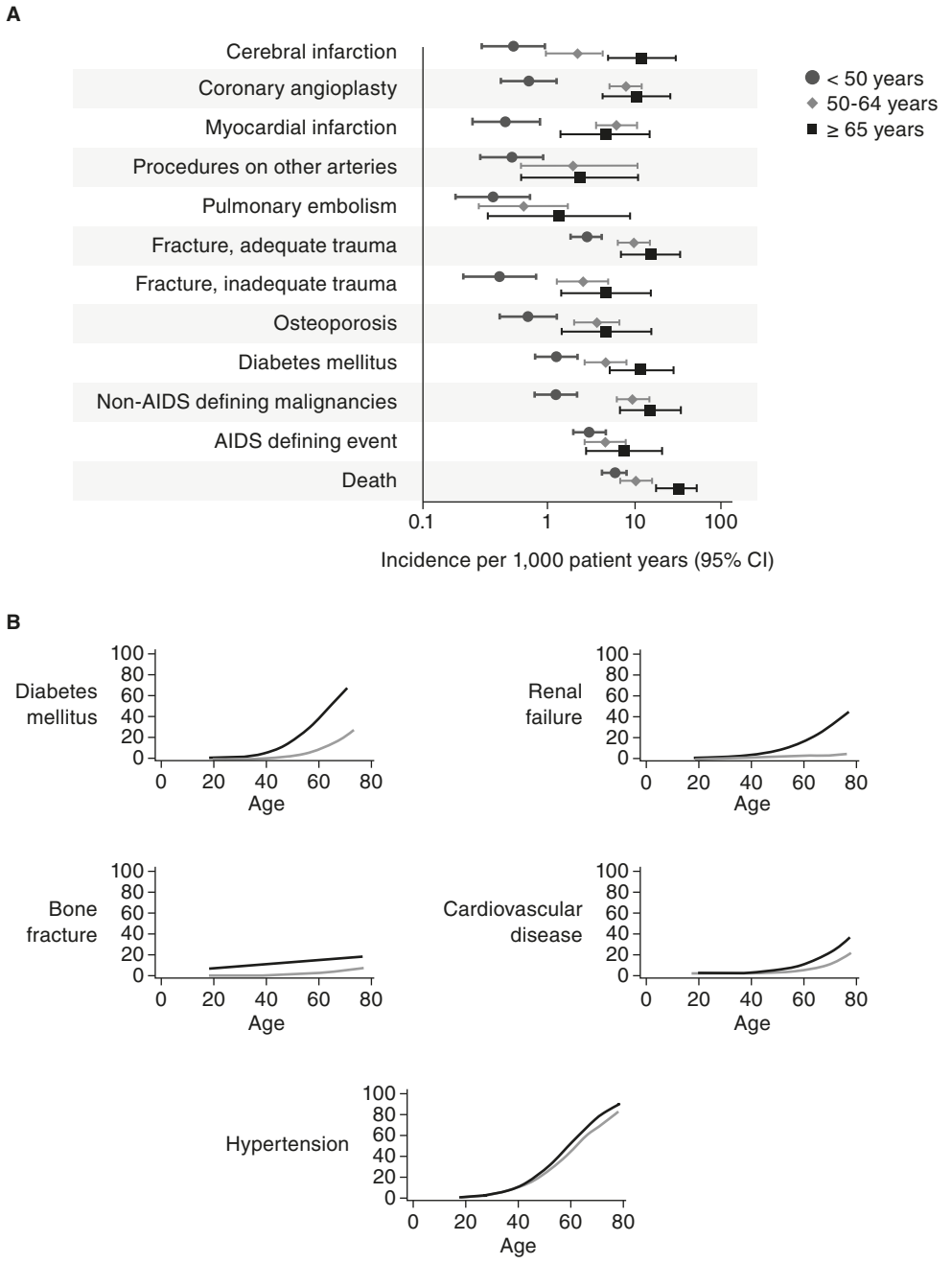

Figure 2. *Increased morbidity in older HIV-infected individuals in* ***(A)*** *the Swiss Cohort Study*[30] *and* ***(B)*** *the Modena cohort*[29].

and mortality, and of some morbidities including stroke, myocardial infarction, diabetes, bone fractures, and non-AIDS-defining malignancies in HIV-infected patients aged > 50 years compared with younger patients (Fig. 2 A)[30]. In the Modena cohort of 2,854 HIV-infected patients, specific age-related, noninfectious comorbidities were more common than in the general population, with the prevalence of polypathology anticipated observed among patients aged 10 years older in the general population (Fig. 2 B)[29].

It should be noted that the emergence of non-AIDS-related morbidity and mortality as an increasing proportion of the serious morbidity observed in HIV-infected patients[32-34] reflects the success of ART in suppressing HIV and increasing survival. Moreover, ART itself plays a role in the pattern of morbidity that may be seen in older patients, as discussed below.

Morbidities and the effects of antiretroviral therapy in older HIV-infected patients

As with any form of pharmacotherapy, ART is associated with both beneficial and deleterious effects, and it is important to weigh any negative effects against the overwhelming positive consequences of viral suppression.

HIV infection and metabolic complications

Metabolic complications, commonly manifesting as cardiovascular disease (CVD) and diabetes, are common in older HIV-infected patients. The etiology of CVD in HIV-infected patients reflects the complex interaction of factors associated with the aging of this population, a high prevalence of CVD risk factors such as smoking and cocaine use in this group, the effects of HIV infection itself, and the effects of ART[35,36].

Lipid changes in older HIV-infected patients, including hypertriglyceridemia, raised low-density lipoprotein (LDL) cholesterol and reduced high-density lipoprotein (HDL) cholesterol, with the associated atherosclerotic risk, are a growing concern. The HIV infection itself may be a direct causal factor in the development of accelerated atherosclerosis and decreased HDL levels[37], possibly mediated through the actions of proinflammatory populations of T-cells to produce functional or structural vascular changes linked with increased arterial stiffness[38].

Metabolic complications associated with antiretroviral therapy

Both lipodystrophy and ART have been shown to be predictive factors for the development of atherosclerotic lesions in HIV-infected patients[15]. Lipodystrophy is a known side effect of some forms of ART, associated with altered circulating levels and adipose tissue mRNA expression of proinflammatory cytokines, interleukin-6, tumor necrosis factor-α and adiponectin[39,40]. Lipodystrophy appears to be less of a problem with nonnucleoside reverse transcriptase inhibitors (NNRTI), integrase inhibitors, and chemokine receptor-5 (CCR-5) antagonists than with protease inhibitors (PI) or thymidine nucleoside reverse transcriptase inhibitors (NRTI); however, within each class, individual agents exhibit differing risk profiles for dyslipidemic/atherogenic effects. Correlations between lipodystrophy and changes in other laboratory parameters and clinical outcome and their association with drugs or drug classes are sometimes difficult to interpret as the syndrome may be associated with lipoatrophy as well as lipoaccumulation and the clinical diagnosis and objective measurements of fat distribution are not always tightly connected.

Nonnucleoside reverse transcriptase inhibitors

Some NNRTIs, such as nevirapine, appear to have less of a negative impact on lipids. *In vitro*, among NNRTIs, efavirenz but not nevirapine has been shown to inhibit adipocyte differentiation[41]. Similarly, efavirenz but not nevirapine was demonstrated to increase the release of proinflammatory cytokines including interleukin-6[41]. Rilpivirine has been shown to affect adipocyte differentiation, but higher concentrations are needed than with efavirenz[41]. A 192-week follow-up of study MC278-C204 found that increases in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were significantly lower with rilpivirine compared with efavirenz[42]. The use of efavirenz was also associated with more grade 3-4 lipid elevations than with etravirine in the SENSE study[43].

While use of nucleotide reverse transcriptase inhibitors (N[t]RTI) appears to be mainly associated with peripheral lipoatrophy (with nucleoside analogues principally involved), PIs are associated with fat hypertrophy, dyslipidemia, and metabolic complications[36]. Assessing the true impact of individual ART agents on lipid metabolism can be difficult, as in clinical trials improvement in lipoatrophy is frequently accompanied by lipoaccumulation. The atherosclerotic risk profile associated with PI vs. NNRTI treatment also appears to be more unfavorable with respect to their effects on carotid intima-media thickness[44].

Although NNRTIs appear to have less effect on lipids than PIs, individual agents within this class show differing profiles with respect to lipid effects and associated CVD risk profile. Hence, it is important to consider the profile for individual agents when selecting ART for a given patient. Use of ART agents with more favorable lipid profiles is particularly important for the growing number of patients with diabetes and when trying to achieve LDL targets in the secondary prevention of CVD. While use of lipid-lowering agents can decrease the atherosclerotic risk in patients receiving ART, the potential for drug interactions must be considered.

The NNRTIs appear to have a relatively favorable risk profile in terms of risk for myocardial infarction, as demonstrated by the D:A:D cohort study[45]. With regard to diabetes, the US Veterans Aging Cohort Study did not show any association between HIV infection and increased risk of diabetes; however, increasing age, HCV coinfection, and body mass index had a greater effect on risk in HIV-infected patients[46]. A study of diabetes incidence over 10 years in a cohort of 1,046 patients in France found that the incidence of diabetes was associated with older age (hazard ratio [HR]: 2.13 for age 40-49 years; HR: 3.63 for age ≥ 50 years), time-updated lipoatrophy (HR: 2.14), and with short-term exposure to indinavir (0-1 year, HR: 2.53), stavudine (0-1 year, HR: 2.56; 1-2 years, HR: 2.65) and didanosine (2-3 years, HR: 3.16)[47]. While use of PIs, NRTIs and N(t)RTIs has been associated with increased risk for type 2 diabetes[48] and PIs have been shown to reduce glucose tolerance[49], the D:A:D and Swiss Cohort Studies have shown no association between NNRTI therapy and diabetes risk.

Integrase inhibitors

Raltegravir has fewer effects on lipids than efavirenz and PIs[50,51]. Raltegravir has been shown to increase total cholesterol and triglycerides, but has had no effect on the total:HDL cholesterol ratio[52-54]. Data from a metabolic substudy from STARTMRK showed that treatment-naive patients receiving raltegravir (n = 55) had significantly lower levels of total cholesterol, HDL-C, LDL-C, and triglycerides than those (n = 57) receiving the efavirenz-based combination[55]. Moreover, two randomized studies, both examining raltegravir combinations versus PI combinations in virologically controlled patients (SPIRAL-LIP substudy in 74 patients; KITE study in 60 patients) have reported no changes in body fat[53,56].

However, in treatment-experienced patients failing treatment, switching to a raltegravir-based N(t)RTI-sparing regimen (raltegravir plus lopinavir/r) showed a 20% increase in limb fat and CVD risk over 48 weeks[57]. Similar increases in body fat were seen in the control arm (lopinavir /r plus NRTIs), but raltegravir plus lopinavir/r was associated with a less favorable lipid (total:HDL-C ratio) profile. Characteristics of the metabolic syndrome were comparable, with fat accumulation being seen in the limbs, trunk, and over the total body to a similar extent in both treatment arms. Glucose, insulin, and Homeostasis Model Assessment were also not significantly different between the treatment arms.

Some metabolic changes have also been associated with the use of raltegravir in treatment-naive patients. The STARTMRK study reported a fat gain of 19% raltegravir patients (n = 25) and 31% efavirenz patients (n = 32) at week 156[55]. In addition, PROGRESS in 206 treatment-naive patients also showed that patients receiving raltegravir plus lopinavir/r had an increase in limb fat, but no changes were seen in trunk fat[52]. The differences in each of these findings may be the result of the different patient populations, particularly as both treatment arms experienced similar increases in limb fat mass.

Clinical studies with dolutegravir have shown similar findings to studies with raltegravir. In the SPRING-1 study, treatment-naive HIV patients who received dolutegravir had more favorable changes in lipids than in those receiving efavirenz-based treatment (both regimens given with either tenofovir plus emtricitabine or abacavir plus lamivudine)[58]. Lower mean increases in fasting LDL cholesterol from baseline were reported with dolutegravir than with efavirenz (0.6 vs. 15.9 mg/dl); however, there were no differences either from baseline or between drugs in the total/HDL cholesterol ratio at week 48 (likely due efavirenz's effect of increasing HDL[59]. In the randomized phase III study SPRING-2, which compared once-daily dolutegravir (n = 403) to twice-daily raltegravir (n = 405) among treatment-naive, HIV-infected patients, there were no clinically significant differences in fasting lipid profiles in either group (total cholesterol increases: 6.7 vs. 8.3 mg/dl, respectively; triglyceride increases: 7.7 vs. 9.8 mg/dl)[60]. Dolutegravir and raltegravir were also shown to have similar lipid profiles at 48 weeks in antiretroviral-experienced, integrase inhibitor-naive adults with HIV[61]. However, as yet no metabolic studies have been presented examining the changes in body fat composition with dolutegravir.

In a randomized, phase III study of elvitegravir, co-formulated with cobicistat, emtricitabine, and tenofovir DF, median changes in fasting lipid concentrations in treatment-naive patients were similar to the control arm (atazanavir/r plus co-formulated emtricitabine and tenofovir DF); however the elvitegravir arm showed a significantly lower elevation of triglycerides (0.09 vs. 0.26 mg/dl; p = 0.006)[62].

Chemokine receptor-5 inhibitors

Use of maraviroc has shown beneficial effects on lipids in both treatment-naive and experienced patients, and may be beneficial in patients with an elevated risk of CVD. In the randomized, phase III MERIT trial, examining

Table 1. Reported nephrotoxicity of antiretroviral agents[67]

Drug	Nephrotoxicity
NRTIs and N(t)RTIs	
– Abacavir	Acute renal failure, interstitial nephritis also rarely seen
– Didanosine	Tubular dysfunction (rarely seen)
– Lamivudine	Tubular dysfunction (rarely seen)
– Stavudine	Tubular dysfunction (rarely seen)
– Tenofovir	Tubular toxicity, Fanconi syndrome (rare), eGFR Patients with low bodyweight, impaired baseline renal function, or receiving concomitant treatment with potentially nephrotoxic drugs are considered at greater risk
Protease inhibitors	
– Atazanavir	Case reports of nephrolithiasis, interstitial nephritis, reversible renal failure
– Indinavir	Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute renal failure Patients with low lean body mass, chronic infection with HCV/HBV and those living in warm environmental temperatures are considered at greater risk
– Ritonavir	Reversible renal failure, but nephrotoxicity not definitely established
NNRTIs	
– Efavirenz	Single report of hypersensitivity reaction
Fusion inhibitor	
– Enfuvirtide	Single report of glomerulonephritis

NRTI: nucleoside reverse transcriptase inhibitor; N(t)RTI: nucleotide reverse transcriptase inhibitor; eGFR: estimated glomerular filtration rate; NNRTI: nonnucleoside reverse transcriptase inhibitor.

maraviroc versus efavirenz in treatment-naive patients (both in combination with zidovudine/lamivudine), patients who received maraviroc had smaller elevations in total cholesterol, LDL-cholesterol and triglycerides than those receiving efavirenz[63]. The benefits were also seen in the subsets of patients with baseline dyslipidemia and patients with elevated total cholesterol upon treatment initiation. A phase III, 96-week, comparative study in approximately 800 antiretroviral-naive patients infected with CCR5-tropic HIV-1 is examining the effects of maraviroc on peripheral fat distribution and the ratio of trunk to limb fat (NCT01345630).

Taking all these studies together, we can assume a progressive advantage in metabolic parameters is present in drugs that came to market after 2009 when compared to previous ones. Nevertheless, this "lipid-friendly" benefit will not necessarily translate to a CVD risk reduction in HIV-infected patients; in fact, the size of ART's effect on cardiovascular risk, in absolute terms, is mediated by the underlying cardiovascular risk, with aging being its major driver.

HIV infection and renal toxicity

Both acute renal failure and chronic kidney disease (CKD) are more common in HIV-infected patients[64-66] than in the general population, with age being an important risk factor (amongst other factors such as black race, hypertension, diabetes, and high viral load)[67,68]. Renal toxicity in HIV-infected patients is multifactorial and individuals may suffer from renal damage related to the HIV infection itself, coinfections, hypertension, diabetes, and nephrotoxic drugs including ART[69]. Several glomerular disorders are associated with HIV infection, including HIV immune complex kidney disease and the more common HIV-associated nephropathy (HIVAN), known to occur almost exclusively in patients with an African genetic background[70,71]. Nephrotoxicity as a result of HIV infection is thought to result both from infection of renal parenchymal cells and from the effects of immune activation and chronic production of proinflammatory cytokines[70].

Renal toxicity associated with antiretroviral therapy

Suppression of HIV replication with ART can prevent the development or halt the progression of HIVAN[72,73], with studies showing preservation of renal function with ART and declining renal function with treatment interruption[74-78]. There is also evidence that ART may improve kidney function in patients with renal impairment[79-81], an effect that may be mediated through viral suppression and other immune mechanisms.

Use of some ART agents, notably tenofovir, has been associated with nephrotoxicity (Table 1[67])[59,82,83]. While some studies have suggested a low overall nephrotoxicity profile[84], there have been numerous case reports of tenofovir-associated renal tubular dysfunction, with the proximal tubule mainly affected (in severe cases renal Fanconi syndrome may develop)[83]. In a UK study, exposure to indinavir or tenofovir was associated with accelerated declines in renal function (4.6-fold and 3.7-fold, respectively) in patients with CKD (prevalence 2.4% in this cohort)[85]. Notably, age ≥ 50 years increased the risk of CKD in patients starting indinavir (odds ratio [OR]: 4.9) or tenofovir (OR: 5.4). A meta-analysis of 17 studies concluded that while tenofovir treatment was associated with a statistically significant reduction in renal function, the clinical magnitude of the effect was modest[86]. A recent analysis of D:A:D study data showed that among HIV-infected patients with a normal baseline glomerular filtration rate (eGFR), the cumulative use of tenofovir, atazanavir with low dose ritonavir (/r), and lopinavir/r was associated with a fast decline in eGFR[87]. Over 4.5 years of follow-up, the rates of antiretroviral-associated progression to GFR values below which treatment switches would be considered were low, but this may be a more significant issue for the long-term use of ART. When interpreting such data on eGFR decline, it should be considered that glomerular function is only estimated by the formulas used (e.g., modification of diet in renal disease, Cockcroft-Gault, CKD-epidemiology collaboration) and may be underestimated if secretion of creatinine in the proximal tubule is blocked (e.g., by drugs such as cimetidine, cobicistat, and dolutegravir). Trial data for newer classes of antiretrovirals suggest no significant concerns regarding nephrotoxicity (for example, SPRING-2 and STARTMRK for dolutegravir and raltegravir, respectively)[50,60]. However, the potential for any long-term effects on renal function requires follow-up, as one small trial has suggested a decline in renal function when patients were switched from an efavirenz-based to a raltegravir-based regimen (both given with a tenofovir/emtricitabine backbone)[88].

HIV infection and hepatotoxicity

Liver disease has emerged as one of the main non-AIDS-related causes of death in HIV-infected patients[89,90], accounting for 14-18% of deaths[89]. Reflecting the impact of ART, the pattern of liver disease seen in HIV-infected patients has changed. Whereas the most common causes of liver dysfunction before the introduction of ART were opportunistic infections and AIDS-related neoplasms, now they are HCV/HBV infections[91], medication-related toxicity[92], alcohol abuse, and non-alcoholic fatty liver disease[88]. Increasing evidence suggests that HIV infection itself and immunosuppression also contribute to liver damage[93]. The ART-related hepatotoxicity may be mediated through direct toxicity/drug metabolism, hypersensitivity reactions, mitochondrial toxicity, and immune reconstitution inflammatory syndrome[94,95].

Hepatotoxicity associated with antiretroviral therapy

Different classes of ART are associated with characteristic patterns of hepatotoxicity. With PIs, hepatotoxicity normally occurs some months after starting treatment. Full-dose ritonavir, being strongly associated with hepatotoxicity, is no longer used and the low dose used to boost levels of other PIs does not appear to increase the toxicity risk[96], though clinical hepatitis and liver failure have been reported with tipranavir boosted by ritonavir[95]. Both atazanavir and indinavir can cause indirect hyperbilirubinemia, but this is not associated with liver injury and does not require discontinuation[97].

Hepatic steatosis and lactic acidosis typically manifest some weeks or months after starting NRTI treatment, with stavudine, didanosine, and zidovudine being most commonly associated with this toxicity. Prolonged treatment with didanosine has also been associated with cryptogenic liver disease and has been linked with non-cirrhotic portal hypertension[98,99]. A Spanish study found that, amongst other factors including older age, exposure to didanosine or stavudine was associated with development of advanced liver fibrosis[100]. Abacavir is less associated with mitochondrial toxicity but can cause hypersensitivity reactions, while treatment with lamivudine, emtricitabine, and the N(t)RTI tenofovir can result in HBV reactivation and severe acute hepatitis if they are withdrawn in infected patients or if resistance develops[89].

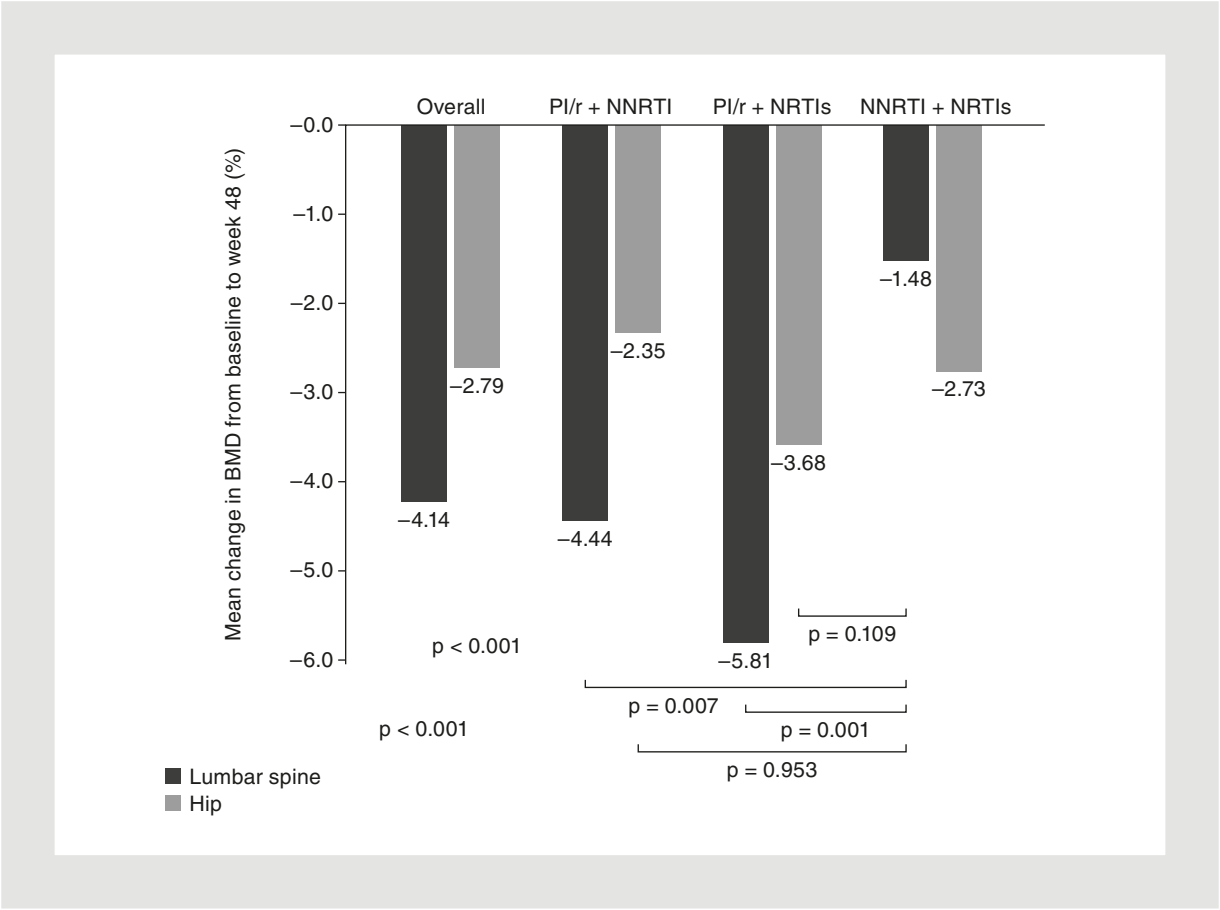

Figure 3. *Comparative effects of protease inhibitor-based vs. nonnucleoside reverse transcriptase inhibitor-based treatment on bone mineral density[107]. BMD: bone mineral density; PI/r: ritonavir boosted protease inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor.*

The NNRTIs most commonly cause hypersensitivity reactions (typically soon after starting treatment) or direct drug toxicity (usually apparent months later)[95]. The NNRTI most associated with hepatotoxicity is nevirapine[101].

With regard to other types of ART, the fusion inhibitor enfuvirtide has been rarely associated with hypersensitivity reactions, while maraviroc has a "black box" warning for hepatotoxicity due to hypersensitivity reactions. In contrast, hepatotoxicity has not been identified as a significant issue in the phase IIb/III trials for the integrase inhibitors, although elevated liver enzymes leading to study discontinuation have been observed in a small percentage of patients (SPRING-1 and SPRING-2 for dolutegravir[58,60]).

HIV infection and the effects on bone

While decreased bone mineral density (BMD) and increased risk of fracture are features of normal aging, HIV-infected patients, particularly when older, may be at increased risk due to the effects of HIV infection and ART. Low BMD and fractures are more common among HIV-infected patients[102] and, while the etiology is multifactorial with socioeconomic and lifestyle factors also involved (drug use leading to falls, smoking, physical inactivity, exposure to violence, etc.), HIV infection and ART are established as independent risk factors for osteoporosis[103]. A 2006 meta-analysis showed the prevalence of osteoporosis in HIV-infected patients to be > 3-times greater than that in uninfected volunteers[104]. It has been postulated that the associated inflammatory state in HIV infection may disturb the immuno-skeletal interface (common cells and cytokines regulating both the skeletal and immune systems), resulting in imbalanced bone turnover, bone loss, and osteoporosis[103,105].

Effects on bone and vitamin D associated with antiretroviral therapy

Combination ART is associated with low BMD[106], with bone loss appearing to be a particular feature on starting

therapy[102]. This may, in part, reflect a decrease in bone turnover from its previous immune activation-heightened state as the effects of ART on viral load become manifest. The AIDS Clinical Trial Group (ACTG) study A5224s showed significantly greater losses in spine and hip BMD with tenofovir/emtricitabine vs. abacavir/lamivudine treatment, while atazanavir/r was associated with more significant bone loss in spine but not hip BMD vs. efavirenz[107]. The Agence Nationale de Recherche sur le Sida (ANRS) 121 trial substudy showed greater loss of lumbar spine BMD in patients on PI/r-containing regimens compared with those containing NNRTIs or NRTIs (Fig. 3)[108]. It is notable that 34% of the ART-naive patients entering this study (median age 40 years) showed loss of BMD before starting treatment. Data from the PROGRESS study showed that ART-naive patients treated with lopinavir/r plus raltegravir had no significant loss in total body BMD and a significantly smaller reduction in spine BMD compared with patients who received lopinavir/r plus tenofovir/emtricitabine[109], while the TROP study found that switching from tenofovir to raltegravir treatment improved BMD and reduced bone turnover in the spine and hip[110]. A trial of another integrase inhibitor, elvitegravir, has shown long-term decreases in both spine and hip BMD that were similar between elvitegravir- and atazanavir/r-based ART[111]. Trials evaluating the effect of maraviroc on BMD are ongoing.

Given the expense and specialist equipment required for DEXA analyses, interest is growing in the potential use of bone turnover markers, such as osteocalcin, as surrogates for changes in BMD. The SINGLE trial showed rises in bone turnover markers in both the dolutegravir/abacavir/lamivudine and the efavirenz/tenofovir/emtricitabine arms, but with significantly greater increases in the latter; the authors suggest this may correlate with the known deleterious effects of tenofovir on BMD[112]. A separate prospective study evaluating bone turnover markers has suggested it may be desirable to have stricter monitoring of bone health for patients receiving atazanavir/ritonavir than for those receiving efavirenz, as well as for older patients in general[113].

Antiretroviral therapy can also affect vitamin D levels. Use of efavirenz and of zidovudine have been associated with reductions in vitamin D[106,114,115], while use of tenofovir appeared to protect against vitamin D deficiency in patients also receiving efavirenz[114]. Furthermore, patients receiving tenofovir/emtricitabine plus either efavirenz or atazanavir/r maintained stable vitamin D levels over 48 weeks[113]. In the MONET[115] study, switching from efavirenz and/or zidovudine to darunavir/r led to increased vitamin D levels. Data from the EuroSIDA study showed that when stratified into tertiles by vitamin D level, patients receiving PIs were at lower risk of having low vitamin D levels[116]. Vitamin D (25-[OH]-D) inadequacy or deficiency was reported in 83% of patients on combined ART, and was independently associated with higher risk of mortality[116]. With regard to newer agents, the ECHO study showed that while efavirenz-based ART significantly decreased 25-(OH)-D levels, rilpivirine-based ART had no significant effect; patients with 25-(OH)-D deficiency at baseline have a significantly lower risk of developing severe deficiency with rilpivirine- vs. efavirenz-based ART[116]. Another trial reported no significant effect on vitamin D levels after switching from an efavirenz-based regimen to raltegravir-based therapy, although these are relatively short-term data (24 weeks)[88]. Similarly, dolutegravir-based therapy was associated with a 7% drop in vitamin D levels over 48 weeks, comparable to the 10% reduction in the efavirenz arm[112].

In acknowledging the impacts of HIV infection and ART on BMD and vitamin D levels, it is important to note that, at present, the clinical significance of these effects, in terms of their contributions to the incidence of fractures and subsequent mortality in HIV-infected patients, is uncertain[106]. Nevertheless, in patients with known risk factors for osteoporosis, it is recommended that long-term use of proton pump inhibitors or corticosteroids should be avoided if possible.

HIV infection and central nervous system/nervous system toxicity

Both HIV infection and aging are independently associated with neuropathological changes, and in combination may have additive or even synergistic effects on the central nervous system (CNS)[118]. The changes associated with HIV and aging both preferentially affect the same brain circuits[119,120].

Neuroimaging studies in HIV-infected patients[121,122] have shown an association of older age with marked alterations (including decreased gray matter volumes and markers of metabolic changes) in frontal systems known to be highly vulnerable to HIV-associated neuropathologies[123]. This suggests that there may be increased cerebral and subcortical damage in older HIV-infected patients, increasing the risk of cognitive impairment[124]. A recent neuroimaging study in 84 HIV-positive men and 76 seronegative controls all aged ≥ 50 years showed that both age and HIV infection had a significant effect

on gray and white matter volume[125]. In all patients, performance on neuropsychological tests was related to the volume of both the gray and white matter.

Older patients with HIV are more likely to develop HIV-associated neurocognitive disorders (HAND) than their younger counterparts, including HIV-associated dementia (HAD) and minor neurocognitive disorder[126-129]. Additionally, the prevalence of milder forms of neuropsychological impairment is disproportionately high among older patients without dementia and with HIV[130-132]. In a cross-sectional substudy of the CHARTER cohort, neurocognitive impairment was diagnosed in 40% of patients and univariate analyses showed associations between neurocognitive impairment and age and longer duration of HIV infection[132,133]. As with other morbidities found in older HIV-infected patients, the etiology of HAND is multifactorial, being associated with persistent systemic and CNS inflammation (possibly related to HIV infection), aging, enhanced neuronal injury due to substance abuse, syphilis, and possibly with HCV infection and ART[134].

Central nervous system/nervous system toxicity associated with antiretroviral therapy

The introduction of HAART dramatically reduced the incidence of HAD[135] and has reduced the overall severity of HAND, though its prevalence remains high[136]. Some studies have suggested CNS-penetrating HAART (neuro-HAART) regimens improve cognitive outcomes in HIV-infected patients[137]. However, other data do not support CNS-penetrating HAART regimens providing additional improvement of cognitive outcomes in HIV-infected patients[138,139]. Further, very few modern ART regimens actually have low CNS penetration effectiveness scores, clearly demonstrating the need for further study in this area. A recent study showed that HIV-associated volumetric reductions in the amygdala, caudate, and corpus callosum were not prevented by HAART[140]. The ART itself can be associated with neurocognitive/psychiatric complications, with efavirenz being the agent most notably involved[141-143].

Peripheral neuropathy (PN) is also associated with HIV infection and with combination ART[144,145]. In the ACTG study in 2,141 HIV-infected patients, PN/symptomatic PN were reported in 32.1/8.6%[144]. In the DELTA study, treatment with zidovudine plus zalcitabine was associated with a higher incidence of PN compared with zidovudine monotherapy (6.2 vs. 3.0 cases/100 person-years) or zidovudine plus didanosine (2.2 cases)[145]. Peripheral neuropathy was also associated with patients' ages at study entry (HR: 2.35 for patients aged 35-44 years compared with those aged < 30).

Care of older HIV-infected patients

Management of older patients is of growing importance and this is now being reflected in clinical guidelines, with the British HIV Association (BHIVA) 2011 guidelines for investigation and monitoring of HIV-infected patients containing a specific subsection on "Older Age", while the latest Department of Health and Social Services (DHHS) guidelines for the use of antiretrovirals in adults have a new section on "HIV and the Older Patient"[146,147].

Older HIV-infected patients, who often have a long history of HIV therapy, tend to have lower CD4 counts, a higher viral load, and to be more frequently symptomatic at the time of diagnosis, with the infection progressing more rapidly with higher morbidity and mortality rates[22]. This increased clinical risk and the importance of achieving effective viral suppression in older patients are reflected in the new DHHS guidelines[147], which recommend ART for patients aged > 50 years regardless of their CD4 count as the immunologic response to ART may be reduced in older patients and because the risk of non-AIDS-related complications may be increased. Similarly, the BHIVA 2012 guidelines state that consideration should be given to starting ART at CD4 counts > 350 cells/μl in older people as the risk of disease progression is significantly higher for a given CD4 count[5]. There is no evidence that the virologic response to ART is worse in older versus younger patients, but CD4 cell recovery after starting treatment is generally less robust than in younger individuals[148-151]. In the European multi-cohort study, patients aged 55-59 and ≥ 60 years had worse clinical outcomes after adjusting for CD4 count[150].

Management of older patients is complicated by the likelihood of comorbidities requiring treatment, resultant problems with drug toxicity and interactions on polypharmacy, and changes in pharmacokinetics (potential for drug accumulation and toxicity) as hepatic and renal function often decline with age. In view of this, the DHHS guidelines recommend close monitoring of cardiovascular, metabolic, liver, kidney, and bone health in older patients. The guidelines also recommend that the risk of drug interactions between ART and concomitant medications be assessed regularly, especially when starting or switching drugs. The BHIVA 2011 guidelines also recommend close monitoring for

drug-related toxicities in older patients[146]. Nevertheless, no recommendations of preferred ART regimens in older patients have been made.

While it might be expected that treatment adherence may be a problem in older HIV-infected patients, as in the wider geriatric population where factors such as high pill burden, neurocognitive impairment, and diminished ability to follow complex dosing schemes are a problem, some data suggest that older HIV-infected patients may actually be more adherent to ART than younger patients[152-155].

The delivery of improved care for older patients will require HIV experts and primary care providers to work together to optimize ART and other pharmacotherapy, to monitor relevant health indices regularly, and to minimize toxicity. While care is likely to require the input of a range of different medical specialists on a case-by-case basis, the HIV-treating physician will remain central to care and must balance the often competing demands of maintaining effective viral suppression while managing comorbidities, treatment side effects, and drug interactions. Further, education and involvement of the patient remains vital for the success of any treatment plan to ensure it meets the varying needs of individual patients.

Future perspectives

While HAART does not completely restore health in HIV-infected individuals, it has dramatically reduced morbidity and improved survival such that the normalization of life expectancy is now seen as a realistic goal of treatment. The complications of ART must be viewed against this background. Moreover, those consequences of uncontrolled HIV replication preceding ART, which are not fully reversed within years of treatment and which contribute to persistent immune deficiency and/or activation, raise the issue of the timing of ART and whether patients might benefit from its earlier initiation.

Future strategies to minimize ART complications might include the development of more "metabolically friendly" ART agents or regimens, and the increased use of treatment switching/substitution (e.g., replace PI/r with second generation NNRTI to improve lipid profile), simplification (apparent body fat and BMD benefits of switching from darunavir/r plus two NRTIs to darunavir/r in the MONOI and MONARCH studies[156,157]) and intensification strategies. In addition to improving ART, toxicity and morbidity might be reduced by increased physician awareness of potential pharmacokinetic and drug interaction issues in older patients, and by the regular monitoring of patients and administration of lipid-lowering agents and other appropriate medication for comorbidities. Patient education and the modification of lifestyle factors may also be beneficial.

Future developments may include new treatments to combat HIV-associated inflammation and immunosenescence (CCR-5/CCR-2 inhibitors, cytokine inhibitors, antivirals, agents preventing microbial translocation, etc.), while our growing knowledge of the genes involved in the metabolic complications of HAART may one day result in the introduction of personalized therapy regimens for individual patients, based upon their genetic profile.

Conclusions

The success of HAART has significantly changed the pattern of HIV infection in developed countries, with the "graying" of the HIV-infected population testament to its success. This has provided new challenges relating to the care of older patients, particularly with regard to the management of comorbidities and ART toxicity, which scientists and physicians are addressing through the refinement of existing ART, the development of new agents, and a growing focus on a more holistic approach to care involving the integration of concepts from general internal medicine into HIV care. A trustful patient-physician relationship established in HIV care may provide an excellent starting point for the management of these complex problems.

Acknowledgments

The authors would like to thank Patrick Hoggard (Medical Writer, Gardiner-Caldwell Communications, Macclesfield, UK) for his assistance in developing the preliminary draft of the manuscript. This was funded by Janssen Pharmaceutica N.V.

Author disclosures

G. Guaraldi has received research funding or honoraria for lectures or consultancy from both academia and a number of pharmaceutical companies including: Gilead Sciences, Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag and Merck. H-J. Stellbrink is a member of advisory boards for ViiV Healthcare, Abbott Labs, Gilead Sciences, Janssen-Cilag, Boehringer Ingelheim, and Bristol-Myers Squibb, and has received honoraria for scientific presentation by the abovementioned companies and payment for expert testimony by Bristol-Myers Squibb; travel grants were provided at some point in the last three years by each of those companies, mostly for participation in company-sponsored symposia. M. Prakash and C. Moecklinghoff are both full-time employees of Janssen Pharmaceuticals.

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