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REVIEW

Cerebrovascular disease in HIV-infected individuals in the era of highly active antiretroviral therapy

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Abstract The widespread use of highly active antiretroviral therapy (HAART) in HIV-infected individuals mostly in developed countries has dramatically improved their prognosis. In such advantaged regions of the world, therefore, many patients are now transitioning from middle into older age, with altered patterns of disease. While previously a rare complication of HIV infection, cerebrovascular disease (particularly that associated with atherosclerosis) is becoming relatively more important in this treated group of individuals. This review summarises the evidence regarding the shifting epidemiology of cerebrovascular diseases affecting HIV-infected individuals. While outlining the association between HIV infection and AIDS and cerebrovascular disease, as well as opportunistic diseases and HIV-associated vasculopathies, the current evidence supporting an increase in atherosclerotic disease in treated HIV-infected individuals is emphasised and a management approach to ischaemic stroke in HIV-infected individuals is presented. Evidence supporting the important role of HAART and HIV infection itself in the pathogenesis of atherosclerotic disease is discussed, together with preventative approaches to this increasingly important disease process as the population ages. Finally, a discussion regarding the significant association between cerebrovascular disease and HIV-associated neurocognitive disorder is presented, together with possible mechanisms behind this relationship.

Keywords Human immunodeficiency virus · Cerebrovascular disease · Highly active antiretroviral therapy HIV-associated neurocognitive disorders

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Introduction

With the widespread use of HAART, the morbidity and mortality associated with HIV infection has improved dramatically. HAART has been demonstrated to reduce morbidity and mortality in HIV-infected individuals (Chen et al. 2007, Murphy et al. 2001) such that HAART-treated HIV infection has now become a chronic illness, with effectively treated patients living longer with improved quality of life. The impact, however, of chronic HIV infection, long term use of HAART, and the effect of older age are converging to alter the pattern of illnesses affecting HIV-infected individuals. Cerebrovascular disease, a previously rare complication of HIV infection, is becoming more prevalent and

changing in aetiology in treated, aging HIV-infected individuals, with the pattern of illnesses more closely resembling that of the elderly general population. Important differences exist, however, between HIV-infected and uninfected individuals with regards to disease aetiology, progression, treatment and risk stratification. For example, as will be discussed below, HAART itself contributes to increased atherosclerotic disease in this population and poses important considerations with regards to risk prediction, investigation and management. Furthermore, HAART has so far failed to fully protect HIV-infected individuals from HIV-associated neurocognitive disorders (HAND); indeed, cerebrovascular disease is a likely contributing factor to the ongoing impact of HAND.

The changing epidemiology and incidence of cerebrovascular diseases in HIV-infected persons

Studies quantifying the observed association between HIV infection and stroke of various types (and indeed further describing these associations) are lacking, although there is emerging evidence that individuals chronically infected with HIV are at greater risk than the general population. Importantly, the HIV-affected population is a heterogeneous group not only with respect to risk factors for stroke, but also current and historical degree of immunosuppression and HIV activity, and prior or current opportunistic infection. All of these factors can contribute to difficulties generalising epidemiological findings in some studies to the population at large. Furthermore, autopsy studies have revealed a high risk of clinically silent strokes in those with advanced HIV infection (Evers et al. 2003), with uncertain clinical significance. Reported prevalence rates of ischaemic stroke (IS) and intracranial haemorrhage (ICH) in autopsy series range widely (6–34%; Ortiz et al. 2007; Evers et al. 2003; Modi et al. 2006; Pinto 2005; Brew 2001; Pinto 1996).

A review of data from retrospective and prospective clinical studies and autopsy studies between 1976 and 1994 demonstrated an overall frequency of stroke syndrome of 1.3%. Definitive conclusions regarding the true association of cerebrovascular disease and AIDS, however, could not be made due to data limitations (Pinto 1996). A similar prevalence was demonstrated in a cohort study across 9 years (1993 to 2001), representing a several fold greater risk than that of the non-HIV population in the region (Evers et al. 2003). In a US-based retrospective study across a three year period (1988–1991), an AIDS diagnosis was strongly associated with ICH and IS, an association that persisted even after controlling for identifiable AIDS-related medical conditions and other causes of stroke (Cole et al. 2004). By comparison, overall stroke incidence in the young (less than 45 years old) general population has been demonstrated at much lower levels; an Australian epidemiological study reported overall stroke incidence of up to 44 cases (per 100,000 people per year (Thrift et al. 2001) and a USA prospective, population-based study revealed an overall rate of stroke of 23 cases per 100,000 people per year (Jacobs et al. 2002).

Overall the majority of studies have revealed a significantly increased risk of stroke in the HIV population, but importantly some retrospective studies have not (reviewed by Pinto 2005, Modi et al. 2006 and Berger 2004; Patel et al. 2005). Possible contributors to this disparity could include relatively small sample size, inherent limitations of retrospective analyses or a lack of data regarding baseline risk (Patel et al. 2005).

Importantly, most of the aforementioned epidemiological studies regarding the frequency of cerebrovascular disease in HIV-affected patients were performed retrospectively and in the pre-HAART era, consisted of a large number of those in advanced stages of HIV infection, and have examined a relatively young (often less than 45 years old) population. These factors make much of the historical information obtained less representative of the current and future HIV epidemic, and clearly have methodological limitations in detecting relevant cerebrovascular damage linked to chronic HIV disease (as evidenced by the much higher prevalence of IS and ICH in autopsy studies when compared with epidemiological studies). In other words, new prospective studies are warranted in the current HAART era and in middle-aged HIV-infected individuals.

Indeed, the epidemiology of HIV infection is changing. Dramatic increases in the proportion of HIV-infected individuals over the age of 65 have been observed after the introduction of HAART, and it has been estimated that by 2015 the proportion of people living with HIV/AIDS over the age of 50 will be 50% (Gebo and Justice 2009; Simioni et al. 2011). An examination of registry data in Australia predicts and increase (by 377% in men and 825% in women) in the number of HIV-infected individuals over the age of 60 (Cysique et al. 2011). In some areas, the incidence of new HIV diagnoses and AIDS cases in individuals older than 50 is also rising, an age group known to be at higher morbidity and mortality associated with HIV/AIDS (Martin et al. 2008; Gebo and Justice 2009). As a result of this shift, the landscape of cerebrovascular disease in HIV-infected individuals is thought to be changing (Pinto 2005). HIV infection and its treatment across the long term contribute directly and indirectly to cerebrovascular and cardiovascular disease, and therefore the pattern of cerebrovascular disease in HIV-infected individuals, the emphasis of this article, will in future likely reflect a much greater burden of more traditional atherosclerotic ischaemic cerebrovascular disease, more in keeping with that of the general aging population. Furthermore, this atherosclerotic disease is suspected to affect HIV-infected individuals at a much younger age, and much more aggressively than in the general population.

There is a lack of reliable data regarding the incidence of atherosclerosis-related IS. A recent nationwide examination of the incidence of stroke in the USA demonstrated an increase, by 60% (to 0.18%), in the proportion of recorded stroke patients with coexisting HIV between 1997 and 2006, despite a decrease in the absolute number of stroke hospitalisations (by 7%). Importantly, the increase was related to IS (as opposed to ICH, which remained stable; Ovbiagele and Nath 2011). The reasons behind this trend are still speculative; with the authors emphasising the role of advancing age (although the median age for stroke in the HIV population was in the fifth decade; lower than in the non-HIV population). Other proposed contributors are a greater proportion of male and African American patients (who are known to be at greater risk for vascular disease) across the study period, longer duration of exposure to HIV itself and importantly antiretroviral exposure through various mechanisms (see below).

A recently published nationwide, population-based cohort study in Denmark has also examined the relative risk of cerebrovascular events in the HIV-infected population when compared with the general population. Rasmussen and colleagues found that HIV infection in the absence of intravenous drug abuse (IVDU) conferred a higher risk of cerebrovascular events with relative risk of 1.6 overall when compared with non-infected controls (predominantly due to a statistically significant increase in IS with adjusted relative risk of 1.63). Even higher risks for cerebrovascular events overall were found among HIV-infected individuals with exposure to IVDU (due to statistically significant increases in IS, together with ICH and subarachnoid haemorrhage). Importantly, patients with cerebral opportunistic (and other) infection, HIV-associated dementia (HAD) or neoplasm were excluded from analysis (Rasmussen et al. 2011). While those with CD4 T-cell count of less than 200 cells/μl without HAART were at greater risk, controlling for identified opportunistic processes may make this study more representative overall of the diseases affecting HAART-treated HIV-infected individuals. HAART itself in this study did not, however, impact on the risk of cerebrovascular events, nor did the initiation of protease inhibitor therapy.

There is also a paucity of studies sub-classifying the mechanism of IS in the HIV-infected population in the post-HAART era. Ortiz and colleagues recently performed a retrospective study of all HIV-infected patients admitted to a large, metropolitan USA hospital between 1997 and 2004 with stroke, identifying a total of 82 patients: 77 patients had IS and five haemorrhagic stroke (HS). Of the former group, applying the TOAST classification, 13% was due to large artery atherosclerosis, 19% cardioembolism, 19% small vessel occlusion, 23% other aetiology and 25% undetermined (17% incompletely evaluated). While this represents the post-HAART era, only 37% was on HAART at the time of the stroke, and 54% of the group had a CD 4 T-cell count less than 100 cells/μl. In addition, the cohort was again relatively young (mean age 42 years) and the prevalence of traditional risk factors for atherosclerosis correspondingly low. Of the ten patients identified with large artery stenosis due to atherosclerosis, the mean age was 45 years. Further examination revealed that four of the ten with large artery stenosis had extracranial internal carotid involvement (5% of the total study group), five had disease of middle cerebral artery (6.5%) and one had vertebrobasilar artery disease (1.3%) (Ortiz et al. 2007).

The pathogenesis of cerebrovascular disease in HIV

HIV infection is associated with IS through diverse mechanisms including opportunistic infections, intracranial malignancies, systemic infection such as infective endocarditis, advanced illness with associated hypercoagulable states (Dobbs and Berger 2009) and perhaps more importantly accelerated atherosclerosis (see Table 1; Rabinstein 2003; Pinto 2005; Chetty 2001; Guillevin 2008; Lynn and Lightman 2004; Adams et al. 1993). Similarly, ICH can occur through various mechanisms and has been found at higher incidence in HIV-infected individuals, particularly in the more advanced stages of disease. Tuberculosis (TB), toxoplasmosis and other opportunistic infections, as well as intracerebral malignancies, have all been associated with ICH. HIV-associated thrombocytopenia (particularly in children) and other disorders of coagulation such as disseminated intravascular coagulation should also be considered (Rabinstein 2003, Pinto 2005 and reviewed by Dobbs and Berger 2009). Use of cocaine and amphetamines, especially with intravenous routes of administration, have been associated with IS and ICH through mechanisms including infective endocarditis, cerebral vasculitis and vasospasm, foreign body embolism (Pinto 1996), acute hypertension or hypotension (Brust 1993).

Mechanisms of cerebrovascular disease specific to HIV

The issue as to whether HIV itself is directly pathogenically linked to IS or HS is not yet fully resolved. Mechanisms that have been proposed include an HIV-induced vasculopathy, Protein S (PS) deficiency and antiphospholipid antibodies (Pinto 1996; Brew 2001). These latter potential coagulopathies have been demonstrated at higher rates in HIV-affected individuals (Brew and Miller 1996; Dobbs and Berger 2009); however, the causal role of this PS deficiency in stroke is debated (Modi et al. 2006; Mochan et al. 2005; Mochan et al. 2003; Qureshi et al. 1997)

Table 1 Some diverse mechanisms of IS in HIV-infected individuals, using TOAST classification

Large artery atherosclerosis
Cardioembolic stroke
Infective endocarditis (with and without IVDU)
Atrial fibrillation
Nonbacterial thrombotic endocarditis (with and without IVDU)
Myxoid valvular degeneration
Kaposi's sarcoma involving the myocardium or valves
Cardiomyopathy including HIV myocarditis and dilated cardiomyopathy with mural thrombus
Small vessel occlusion
Stroke of other determined aetiology
Cerebral opportunistic infection, vasculitis/vasculopathy
Varicella-zoster virus
Syphilis
Cryptococcosis
Mycobacterium tuberculosis
Cytomegalovirus
Mucormycosis
Aspergillosis
Candida albicans
Toxoplasmosis
Coccidiodomycosis
Trypanosomiasis
Cerebral opportunistic neoplasm
Cerebral lymphoma
Prothrombotic states
Protein S deficiency
Antiphospholipid antibody syndrome
Disseminated intravascular coagulation in advanced disease
Intravenous drug abuse
HIV-related vasculopathy
Noninfective vasculitis
Stroke of undetermined aetiology

An HIV-associated cerebral vasculopathy has been described in autopsy studies, associated with clinically silent cortical and sub-cortical infarctions. Histopathological changes described in HIV-infected individuals include a non-vasculitic vasculopathy affecting small vessels, with similarities to changes in aging non-HIV brains (cerebral arteriolosclerosis; Connor et al. 2000). Indirect evidence of this small vessel vasculopathy has been described more recently. Brilla and colleagues demonstrated reduced baseline blood flow and cerebrovascular reserve capacity (and therefore vasoreactivity) in HIV-infected individuals when compared with controls (Brilla et al. 1999). At this stage, the role of this observed vasculopathy in the pathogenesis of cerebrovascular events in the HIV-affected population is uncertain, as is the impact of HAART on this phenomenon.

Far more rarely, HIV itself has also been linked to the presence of a large vessel vasculopathy with ectasia and aneurysm formation, both intra- and extracranially with associated ICH and IS (Ake et al. 2006; Kossorotoff et al. 2006). The aetiological role of HIV itself, an immune or other infectious chronic vasculitis (particularly varicella zoster virus (VZV)) in this disorder remains the topic of debate (Gilden and Nagel 2006; Guillevin 2008). Case reports of true vasculitides of varying histopathological appearances have also been documented in HIV-infected patients with no other identifiable cause (summarised by Rabinstein 2003).

Atherosclerotic disease in HIV

The burden of atherosclerotic disease in HIV-infected persons has been the focus of intensive research recently, as described below. Potential contributors to atherogenesis in this population include an increase in traditional risk factors (related to HAART and possibly HIV itself), direct effects of HIV and/or HAART itself, chronic inflammation and impaired fibrinolysis (Grinspoon and Carr 2005). The relative contribution to atherogenesis in the HIV-infected population by these factors has not yet been defined, but it is likely that individuals have a variable, additive and possibly synergistic contribution of these factors to atherogenesis.

Mechanisms of atherogenesis in HIV: the role of HAART

The D:A:D study (Data Collection on Adverse Events of anti-HIV Drugs), a prospective observational cohort study of 23,468 HIV-positive patients, demonstrated an increased risk of cardio- and cerebrovascular disease events (CCVE; of which 62% was myocardial infarcts (MI)). Over 36,145 person-years of follow-up, the incidence rate of CCVE increased by 26% per additional year of exposure to HAART, after controlling for traditional vascular risk factors. Other studies have also demonstrated a significant association between HAART and vascular events, MI being the outcome most studied. With further analysis of data and longer follow-up, the D:A:D study has demonstrated that the excess risk of myocardial infarction (MI) is associated only with certain antiretroviral agents, specifically the protease inhibitors (PIs) indinavir and ritonavir–lopinavir, and the nucleoside reverse transcriptase-inhibitors (NRTIs) abacavir and didanosine (as opposed to non-nucleoside reverse transcriptase inhibitor exposure; Worm et al. 2010; D:A:D study group 2004). The risk of MI increased with the duration of HAART therapy, and remained significant after adjusting for cholesterol levels, which has led authors and others to conclude that the metabolic effects of these therapies are

only partly responsible for this observed adverse association. Similarly, a large cohort study from the French Hospital Database on HIV found higher rates of MI to be proportional to the duration of exposure to certain antiretroviral drugs (Mary-Krause et al. 2003; Lang et al. 2010). All the PIs studied were associated with an increased risk of MI, with the exception of saquinavir. As in the D:A:D study, the association was particularly strong for lopinavir with ritonavir. In contrast to the D:A:D study, the NRTIs of the thymidine analogue class (zidovudine and stavudine) were associated with a higher risk of MI which was proportional to the cumulative exposure, as was abacavir initiation (though not cumulative exposure; Lang et al. 2010).

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group demonstrated that intermittent HAART (as opposed to continuous therapy) increased the risk of many adverse events including major cardiovascular disease, an unexpected outcome when considering evidence linking cumulative HAART exposure to vascular events (The SMART study group 2006). This suggests that acute arterial and systemic inflammation and/or changes to immune function (particularly in the context of fluctuating degrees of HIV replication) may play a role in these observed events (The SMART study group 2006; The D:A:D study group 2007).

At least part of the HAART-associated increase in atherosclerosis is attributed to its impact on traditional vascular risk factors; HAART induces changes to lipid profile, hyperinsulinaemia, impaired glucose tolerance, overt diabetes mellitus and hypertension (Barbaro 2003; Grinspoon and Carr 2005; d'Arminio Monforte and Bongiovanni 2005). The observed changes to lipid profile induced by HAART consist of an increase in LDL, decrease in HDL and increase in TG. The extent and nature of these changes vary between therapies and individuals; however, PIs as a class are most strongly associated with these changes (Volberding et al. 2003). It has been acknowledged that studies of the true impact of HAART are made more difficult by the fact that symptomatic HIV infection itself is known to decrease levels of HDL and LDL, and increase triglyceride levels; some data suggest that HAART leads to an increase in lipid levels only to pre-infection levels (Kotler 2008, Riddler et al. 2003). Furthermore, PI therapy has been associated with markers of endothelial dysfunction, an association best predicted by PI induced changes to the lipid profile (Stein et al. 2001) and not duration of HIV infection, viral load (VL) or CD4 T cell count. Indeed, several studies in HAART-treated patients have demonstrated that increased carotid intima-media thickness (cIMT) or overt atherosclerotic disease is not independently associated with markers of HIV infection or HAART itself (Delaney et al. 2010; Depairon et al. 2001; Currier et al. 2005; Mercie et al. 2005). These observations argue that it is through the modification of traditional risk factors that HAART influences atherogenesis.

Some evidence on the other hand points towards a direct or alternative mechanism by which HAART promotes atherogenesis. For example, in a cross-sectional study of treated HIV-infected individuals, a strong association between HAART and increased cIMT persisted after controlling for traditional cardiovascular risk factors and Framingham Risk Score itself (Jerico et al. 2006). It is possible that differences in the site of cIMT measurements (internal/bulb region versus common carotid) between studies may account for some of the observed discrepancies, and clearly warrants further evaluation in order to clarify the impact of measured risk factors, parameters of HIV infection and HAART on atherogenesis (Grunfeld et al. 2009). Other potential mechanisms for atherosclerosis include HAART induced coagulopathy, impaired fibrinolysis and thrombocytosis (Grinspoon and Carr 2005; Barbaro 2003; d'Arminio Monforte and Bongiovanni 2005).

Aging and the impact of HAART

Despite the aging population of HIV-infected individuals, patients over the age of 50 have been studied relatively much less, simply because the bulk of the HIV epidemic is only just starting to age. It has been noted in particular that the pharmacokinetic effects of ARV classes and individual drugs on lipid profile and vascular risk have been inadequately studied in the older population (Martin et al. 2008). Indeed, due to inherently increased vascular risk in this group, the metabolic effects of HAART may be more harmful as the treated population ages (Gebo and Justice 2009). It is conceivable, therefore, that many of the measured magnitudes of vascular risk posed by HIV and its treatment will increase as this population ages.

Mechanisms of atherogenesis in HIV: the role of HIV

HIV itself and immunosuppression may further contribute to atherogenesis. Focussing on carotid artery atherosclerosis in particular, an association between HIV infection itself and greater cIMT, together with impaired carotid artery distensibility (and therefore arterial stiffness) has been demonstrated, over and above the effect of traditional vascular risk factors (Shrestha et al. 2010; Hsue et al. 2004; Grunfeld et al. 2009; Seaberg et al. 2010). The magnitude of risk conferred by HIV infection itself on cIMT in one of these studies was similar to that of smoking and diabetes (Grunfeld et al. 2009). An inverse relationship between CD4 T-cell count and cIMT and peripheral vascular disease (Periard et al. 2008) has also been demonstrated. In

one study, a CD4 count less than 200 cells/μl conferred an odds ratio for the presence of carotid lesions in women of 2.0 and men 1.74 (Kaplan et al. 2008). Furthermore, cIMT progression over time has been shown to be accelerated across a 1-year period when compared with age and sex-matched controls (Hsue et al. 2004).

Inflammatory cytokines with an associated procoagulant effect and upregulation of vascular adhesion molecules (Kotler 2008) have been associated with the pathogenesis of atherosclerosis, and are a mechanism by which both treated and untreated HIV could promote atherogenesis. Markers of long-term endothelial activation, and therefore risk of atherosclerosis, have been found in some studies at higher levels in individuals with untreated HIV when compared with healthy controls. Furthermore, plasma levels of these markers seem to correlate with an individual's HIV RNA viral load, and a reduction in certain markers has been demonstrated following HAART initiation (Francisci et al. 2009, Wolf et al. 2002, and de Larranaga et al. 2003). HIV has also been linked to endothelial dysfunction and indeed increased cIMT through direct effects of specific secreted proteins (Shrestha et al. 2010, Modi et al. 2006). Similarly, in a prospective study of HAART-naïve patients with indications for treatment, baseline endothelial dysfunction was demonstrated by brachial artery flow-mediated dilation. Over a period of 24 weeks of HAART, improvement in measures of endothelial dysfunction was seen across all groups, independent of HAART regimen and adverse lipid profile changes, correlating most strongly with the change in HIV-viral load (VL) in these patients (Torriani et al. 2008). Taking these studies into consideration, it therefore appears that HAART is associated with a reduction in HIV infection related inflammatory markers in the relatively short-term. On the other hand, when considering clinical outcomes, traditional risk factors (albeit many associated with HAART itself) appear to exert a greater impact on vascular risk.

It is likely that host factors also influence the propensity for inflammation induced by HIV itself or metabolic changes of therapies to induce atherosclerosis. Monocyte chemoattractant protein-1 (MCP-1), for example, is an activator of monocytes and macrophages, and implicated in the development of atherosclerosis. HIV-infected individuals with the 2518G allele of MCP-1 have a fivefold increased risk of subclinical atherosclerosis and faster rate of progression of cIMT (Alonso-Villaverde et al. 2004). As another example, a genome wide association study has identified a functional single nucleotide polymorphism in the ryanodine receptor 3 (RYR3) gene that is associated with increased common cIMT. RYR3 plays a role in physiological endothelial vasodilation and interestingly the RYR gene family is regulated by the HIV protein Tat (Shrestha et al. 2010). Again, the relative impact of these, and other individual factors, in atherogenesis remain to be established.

Management of stroke in HIV

Acute management and evaluation

The acute management of stroke in HIV-infected individuals should be similar to that of the general population, in accordance with international guidelines (Adams et al. 2007, Fig. 1; (Adams et al. 2007) and Table 2 for summary of relevant differences in the approach to stroke in HIV-infected individuals compared with the general population). The use of IV rtPA for acute thrombolysis in the first 4.5 h (Hacke et al. 2008) after an acute IS has not been evaluated in the HIV-infected population by published case series or prospective studies, however when used according to guidelines for use in the non-HIV setting it is generally considered suitable (Dobbs and Berger 2009). The relative safety and efficacy of intra-arterial fibrinolysis for acute IS affecting large arteries is currently under evaluation in the non-HIV population (Lee et al. 2010); however, the use of this therapy in the HIV population has not been studied adequately for specific recommendations to be made at this time.

Further investigation of acute stroke in HIV-infected individuals differs in some ways to the uninfected general population: a much higher index of suspicion for opportunistic infection, tumours, infectious and immune-mediated vasculopathy, and cardioembolism is required. Initial evaluation, therefore, necessitates rapid risk stratification for opportunistic disease by assessment of CD 4 T-cell count and HIV VL. CSF examination should also be considered in significantly immunocompromised HIV-infected patients with IS or HS to evaluate the possibility of vasculopathy. CSF with lymphocytic pleocytosis, positive VZV DNA polymerase chain reaction (PCR) or more importantly, evidence of intrathecal production of anti-VZV IgG antibodies is strongly suggestive of VZV vasculopathy (Nagel et al. 2008). CSF microscopy, culture and PCR to consider TB are also important, together with treponemal and non-treponemal antibodies for consideration of syphilitic vasculopathy, CMV PCR and evaluation for cryptococcosis.

Evaluation for cardioembolic sources of stroke is essential in HIV-infected patients as it is in the non-HIV setting. Diagnoses to consider in particular are infective endocarditis, marantic endocarditis (the former especially in the context of intravenous drug use), myxoid valvular degeneration, HIV-associated myocarditis or dilated cardiomyopathy with mural thrombi (Rabinstein 2003) and Kaposi's sarcoma.

Secondary prevention

As in the general population, secondary prevention against atheroembolic stroke in the HIV-infected population necessitates the early use of antiplatelet therapy (O'Donnell et al.

2008, Sacco et al. 2008), and aggressive evaluation for, and modification of traditional risk factors (Furie et al. 2011). Patients with significant atherosclerotic stenosis of intra- or extracranial arteries should be evaluated for suitability of vascular intervention in the form of carotid endarterectomy or endovascular techniques (Adams 2009).

HIV-infected individuals with risk factors or overt vascular disease benefit from use of a HAART regimen with low impact on cardiovascular risk profile. As reviewed by Grinspoon and Carr (2005), switching a patient from a PI-based therapy is likely to improve central fat accumulation, hyperlipidaemia and possibly insulin resistance. Ritonavir, together with some other PIs (including indinavir, amprenavir and nelfinavir) are relatively more likely to induce insulin resistance. If PI use is preferred or required, atazanavir or saquinavir have a much more favourable side effect profile, as they are not associated with significant dyslipidaemia or insulin resistance (Grinspoon and Carr 2005). Encouragingly, a recent study has demonstrated that the use of ritonavir-boosted atazanavir therapy is associated with a decrease in cIMT when compared with HIV positive controls. While the authors acknowledged study limitations, including non-randomisation in the study, this provides some evidence that use of a 'low cardiovascular impact HAART regimen' indeed may reduce cerebrovascular disease in HIV-infected individuals (Saint-Martin et al. 2010). The role of newer agents such as darunavir in such a regimen is not yet clear.

The use of lipid lowering therapies must also be used with caution in the treated HIV population. As in the non-HIV population, statin therapy is preferred for cholesterol-lowering, while fibrates are more effective in the treatment of hypertriglyceridaemia. PIs inhibit cytochrome P450 and therefore increase the risk of statin toxicity (and decrease efficacy of the PI) when used in combination. In contrast, statin efficacy is compromised with concomitant use of NNRTI, which induce CYP450 enzymes. Standard dose (20–40 mg) pravastatin seems to the safest choice for use with HAART (Boccara and Cohen 2003). If required for lipid control, the combination of a statin and fibrate should be used only with caution in a patient on HAART (particularly if it includes PI therapy). This requires close monitoring clinically and of creatine kinase and transaminase levels, due to the potential for increased toxicity when used together (Boccara and Cohen 2003; Grinspoon and Carr 2005)

Predicting and reducing vascular risk in HIV patients

Complicating the recognition of increased vascular risk in the HIV-infected population, comes the issue of how best to assess patients at an individual level and thus target investigations and primary prevention measures (Goldstein et al. 2011). Application of the Framingham Risk Score (FRS) has been used in studies and advised in the HIV population (Volberding et al. 2003; Grinspoon and Carr 2005), however clearly this cannot take into consideration the unique contribution of long-term HIV infection or its treatment (Stein 2005). Indeed, the FRS has been shown to underestimate the risk of subclinical atherosclerosis (measured by the cIMT), in HIV-infected individuals who are estimated in the low (<10%) risk group (Parra et al. 2010). Clinical studies confirm the risk of MI is underestimated by application of the FRS in HAART-treated individuals (Law et al. 2006). Screening for the presence of the metabolic syndrome and lipodystrophy have been proposed as a means of more accurately identifying truly higher risk HIV-infected individuals (De Socio et al. 2008; Wand et al. 2007). While the use of some serum markers of inflammation (and therefore increased endothelial activation) has been proposed to provide additional cardiovascular risk stratification in HIV-infected individuals (Lowe 2010), application of inflammatory markers has not yet been validated for use in this manner (Grinspoon and Carr 2005).

At this stage, while risk factor modification should be a priority of clinicians caring for those with HIV, there is insufficient evidence to support using more aggressive targets for intervention. A study evaluating cIMT in HAART-treated HIV-infected individuals, for example, did not demonstrate a significant difference in cIMT progression (across a 12-month period) with use of aggressive interventions compared with standard targets used in the general population (Masia et al. 2009).

HIV-associated neurocognitive disorder and cerebrovascular disease

The burden of HAND is expected to increase as the HIV-infected population ages (Cysique et al. 2011). HAND encompasses HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated minor neurocognitive disorders (MND) and HAD (Antinori et al. 2007); however, it is the milder forms of disease (ANI and MND) which account for the increasing burden of disease in the treated, aging population (Heaton et al. 2010, Cysique and Brew 2011). The converging impact of HIV itself, advancing age (both with preferential impact on prefronto-striato-thalamo-cortical circuits; Valcour et al. 2004; Burke and Barnes 2006; Scott et al. 2011; and reviewed by Simioni et al. 2011) and probably cerebrovascular disease among other risk factors are likely to contribute to a much greater burden of HAND in an older cohort perhaps with an altered phenotype. Moreover, an increased prevalence of Alzheimer's and vascular dementia (VaD), along with other age-linked neurodegenerative disorders can be expected. HAND occurs and can progress in HAART-treated HIV-infected individuals who achieve viral suppression in the plasma and in the CSF (Simioni et al. 2011;

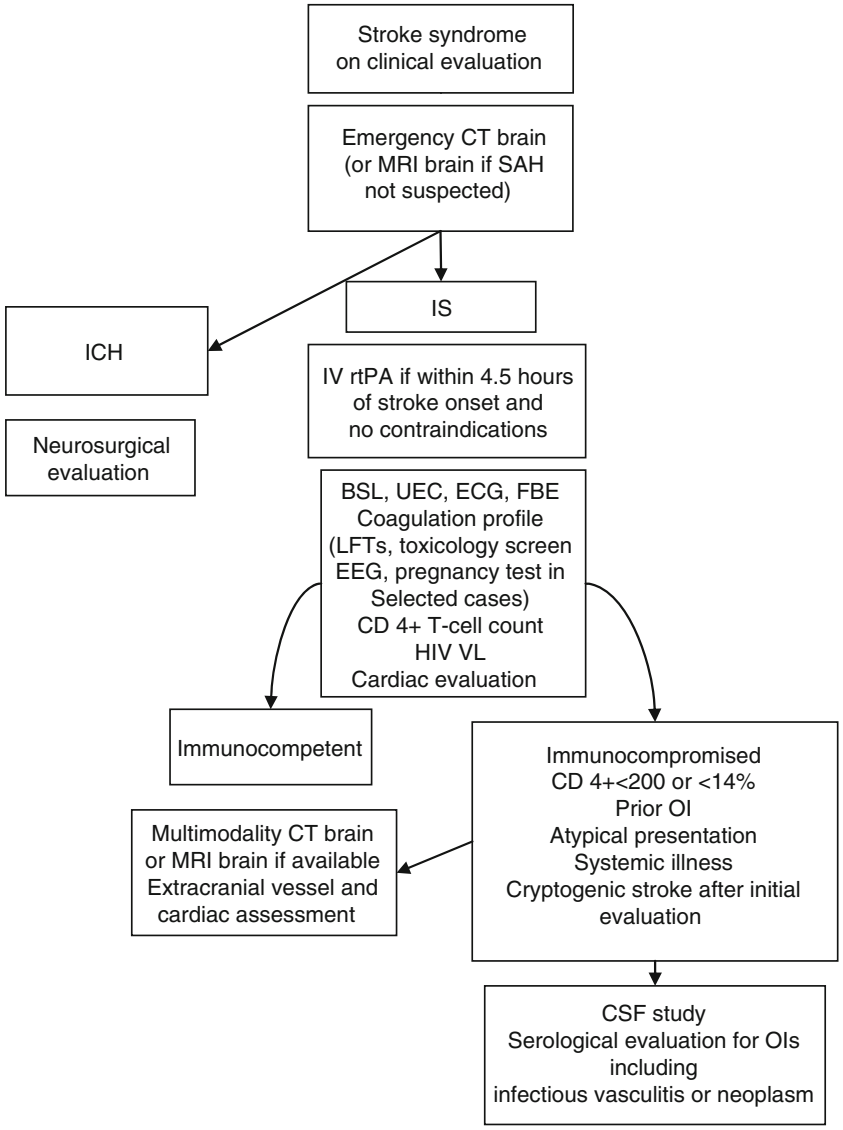

Fig. 1 Investigation and management of acute stroke in HIV-infected individuals. *CT* computed tomography, *MRI* magnetic resonance imaging, *ICH* intracranial haemorrhage, *SAH* subarachnoid haemorrhage, *IV rtPA* intravenous recombinant tissue plasminogen activator, *UEC* urea electrolytes and creatinine, *FBE* full blood examination, *EEG* electroencephalogram, *LP* lumbar puncture, *VL* viral load, *OI* opportunistic infection

Robertson et al. 2007; Cysique and Brew 2011; Cysique et al. 2006). The prevalence of HAND in such cases is estimated at 20–30% after adequately controlling for co-morbid conditions (Cysique and Brew 2011). In these cases especially, cerebrovascular diseases may be an alternate candidate for ongoing brain damage. Notably, in the prevalence study by Cysique and Brew, acute ischaemic events were set as criteria of exclusion, therefore underestimating the real prevalence of brain HIV and cerebrovascular damage.

In relation to cerebrovascular disease, recent literature has identified a clear relationship between vascular risk factors, overt cerebrovascular disease, and cognitive impairment in HIV-infected individuals. In the SMART neurology substudy, reduced neurocognitive performance was associated with prior cardiovascular disease and with vascular risk factors, specifically the use of antihypertensive agents and hypercholesterolaemia (Wright et al. 2010). Similarly, evaluation of the cognitive performance of men enrolled in the Multicenter AIDS Cohort Study demonstrated that cIMT and reduced GFR were significantly associated with reduced psychomotor speed, and the former with memory test performance (Becker et al. 2009). This relationship suggests direct and/or indirect mechanisms by which vascular risk factors and cerebrovascular disease impact upon neurocognitive functions in the HIV-infected population. Additionally, a lack of vascular risk factor modification in HIV-infected individuals is associated with poorer performance on cognitive testing (Foley et al. 2010). It is not yet clear whether risk factor modification reduces or slows neurocognitive decline in affected individuals.

VaD is the second most common type of dementia worldwide, encompassing a clinically heterogenous group of disorders resulting from haemorrhagic or

Table 2 Ischaemic stroke in HIV-infected individuals compared with those uninfected

	General population	HIV-infected population
Causes	• Large-artery atherosclerosis (thrombosis or embolus from aortic arch, carotid bifurcation)	• Atherosclerotic disease is increasing as HIV-infected individuals age
	• Cardioembolism (AF, mural thrombus, AMI, DCM, valvular lesions, paradoxical embolus)	• Unique vascular risk factors (e.g. role of HIV infection itself and HAART-induced metabolic changes in atherogenesis)
	• Small-vessel occlusion (lacune)	• Increased risk of opportunistic infection and neoplasm among those with advanced HIV/AIDS.
	• Other (arterial dissection with embolus, dehydration, hypercoagulable states, autoimmune vasculitis, infectious vasculitis, drug abuse)	• Some non-opportunistic infections are more prevalent in HIV-infected individuals, such as neurosyphilis.
		• HIV itself can contribute (HIV-associated cerebral vasculopathy, haematological abnormalities).
Evaluation	• Emergency imaging to exclude ICH	• As for general population
	• Inflammatory markers	• Specific evaluation of CD4- T cell count and HIV VL
	• Haematological assessment (coagulopathy, contraindications for fibrinolysis)	• Directed evaluation for opportunistic infection and vasculitides in at risk individuals
	• Intra- and extracranial vessel imaging	
	• Cardiac evaluation (rhythm, structural abnormalities, cardioembolic disease)	
	• CSF study in selected cases	
Management	• Acute management in accordance with international guidelines	• Acute and longer term care as for general population
	• Supportive care in dedicated stroke unit and rehabilitation	• Drug interactions with HAART during risk factor modification must be recognised (e.g. certain statins)
	• Secondary prevention with antiplatelet therapy, vascular risk factor modification	• Immune reconstitution with HAART in those with advanced HIV disease
	• Specific therapy directed to aetiology	• Use of HAART regime(s) with lower impact on vascular disease and risk factors should be considered.

ischaemic lesions. In the case of ischaemia, VaD can result from large vessel disease (classically associated with lateralised neurological signs and aphasia) and/or small vessel disease causing microinfarction within the white and deep grey matter of the brain (associated with insidious and more subtle neurological signs including gait disturbance, executive dysfunction with relative sparing of memory; Staekenborg et al. 2008; Roman 2003). This small vessel vascular disease is manifested by lacunar strokes, punctate white matter hyperintensities and periventricular leukoaraiosis on conventional MRI. The same type of white matter damage correlates with frontocortical volume loss in HIV-infected individuals receiving HAART (McMurtray et al. 2008), and poorer performance on cognitive testing (Ovbiagele and Saver 2006; McMurtray et al. 2007), and are present at levels that appear to correlate more strongly with age and vascular risk factors in the aging HIV-infected population than with HIV-related factors (McMurtray et al. 2007; Archibald et al. 2004).

The subcortical form of VaD presents with a very similar neuropsychological profile to that of HAND, especially in its mild form with predominant psychomotor slowing, attentional deficit, mild dysexecutive functions and decrease in new learning capacities, but intact long-term memory storage. More subtle, as yet not understood structural changes secondary to vascular factors have been suggested to also impact on cognition (Viswanathan et al. 2009). Therefore, an increasing proportion of HIV-infected patients with HAND may be displaying what is actually a clinically indistinguishable subcortical VaD when only identified with neuropsychological testing.

Cerebrovascular disease superimposed on degenerative processes in the CNS has been shown to accelerate the clinical manifestations of a patient's underlying disorder (Nakamoto et al. 2011). For example, in the presence of a cerebral infarct, fewer pathological changes of AD are needed to produce clinical dementia (Knopman 2006). Moreover, it has been proposed that AD and VaD be

considered part of a continuum, with most patients affected having a (variable) contribution of neurodegeneration and vascular cerebral lesion burden in their dementia syndrome (Viswanathan et al. 2009; Knopman 2006). A similar relationship may now exist for HAND affected aging patients. Vascular processes may increase the susceptibility of an individual's brain to the neurodegenerative effects of HIV in the long term thereby accelerating the clinical manifestations of HAND or altering the way in which HAND is clinically manifested; a 'tipping' or 'threshold' effect. Alternatively, as outlined above, vascular processes in this aging population may 'mimic' those of HIV itself. That is, while closely related in clinical impact and expression (and in some cases clinically identical), HIV-induced neurodegeneration and vascular processes may in fact represent disease mechanisms operating simultaneously on an individual level or within the HAART-treated, aging HIV population.

Further research regarding the role of vascular risk factors and their modification in the risk and progression of HAND and other neurodegenerative diseases (on an individual and population basis) is required to further clarify this relationship. Indeed this may also assist in establishing potential mechanisms for the relationship between vascular risk factors and HAND. Nevertheless, with the simultaneous impact of HAART on both longevity and vascular risk factors, vascular disease is likely to exert a relatively greater impact on cognitive function in the aging HIV population and possibly clinical manifestations of HAND (Cysique and Brew 2009).

Conclusion

The relative importance of cerebrovascular disease in the treated and ageing HIV-infected population is increasing. Most importantly in this regard are atherosclerotic cerebrovascular disease and the ongoing burden of HAND, with devastating consequences to affected patients and the community at large. The factors that contribute to the burden of these disorders include the advancing age of treated HIV-infected individuals, attendant increases in traditional vascular risk factors and effects of long-term infection with HIV, along with HAART itself. While the treatment-related side effects are clearly outweighed by the extensive benefits of HAART, a proactive approach to these unintended consequences is of utmost importance clinically, with aggressive and ongoing risk factor screening and modification, together with early screening for vascular disease itself in HAART-treated individuals. This must accompany the ongoing efforts to develop antiretroviral agents which minimise or abolish such side effects, while achieving better HIV control, particularly in the CNS where HIV infection continues to result in neurocognitive decline. Furthermore, ongoing research to better define the relative importance of vascular factors in the pathogenesis of HAND will assist in its prevention and the treatment of HAND in affected individuals, and indeed augment research on the interrelationship between vascular and other pathogenic processes in other neurodegenerative diseases.

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