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Controversies in HIV-associated neurocognitive disorders

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Abstract

Cross-sectional studies show that around half of individuals infected with HIV-1 have some degree of cognitive impairment despite the use of antiretroviral drugs. However, prevalence estimates vary depending on the population and methods used to assess cognitive impairment. Whether asymptomatic patients would benefit from routine screening for cognitive difficulties is unclear and the appropriate screening method and subsequent management is the subject of debate. In some patients, HIV-1 RNA can be found at higher concentrations in CSF than in blood, which potentially results from the poor distribution of antiretroviral drugs into the CNS. However, the clinical relevance of so-called CSF viral escape is not well understood. The extent to which antiretroviral drug distribution and toxicity in the CNS affect clinical decision making is also debated.

Introduction

Almost 34 million people worldwide are chronically infected with HIV-1.[1] In the UK more than 90 000 people are infected, a quarter of whom are unaware of their HIV status, and this number continues to rise.[2] Antiretroviral therapy (ART) has revolutionised the treatment of HIV—many individuals now live healthily for decades while receiving treatment, and the life expectancy of patients with access to treatment can approach that for uninfected cohorts.[3] HIV enters the brain early in disease via migrating myeloid and lymphoid cells and

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establishes infection in perivascular macrophages and microglia. Some infection also occurs in astrocytes.[4] Before the widespread use of ART, severe cognitive impairment was common in individuals with HIV infection and affected up to 50% of patients before death.[5] In countries where ART is widely available, the incidence of HIV-associated dementia has dramatically declined along with other AIDS-related conditions.[6] In this era of potent ART, we continue to observe cognitive disorders in individuals infected with HIV, which have several possible underlying pathogenic mechanisms. Distribution of ART in the CNS can be poor, and concentrations in CSF fall below the concentrations needed to inhibit wild-type virus replication for several drugs.[7] This reduced efficacy or distribution might have clinical consequences and explain the finding that some patients have detectable levels of HIV RNA in CSF even when it is undetectable in blood.[8,9] Other potential mechanisms of pathogenesis include a legacy effect of CNS damage due to HIV sustained before the start of ART, persistent immune and glial cell activation, antiretroviral drug neurotoxicity, and indirect effects from comorbid conditions such as cerebrovascular disease and hepatitis C co-infection. HIV-associated neurocognitive disorders, particularly mild forms, persist even in patients with access to treatment.[10,11] Some investigators have suggested that as many as half of those infected with HIV in Europe and the USA might have some cognitive impairment, which in many cases seems to be either asymptomatic or does not cause functional incapacity.[12]

However, controversy exists with respect to several of these findings (table 1). Prevalence estimates for HIV-associated neurocognitive disorders vary depending on the target population and the methods used to assess cognitive impairment.[13–19] Several guidelines now recommend screening all patients for HIV-associated neurocognitive disorders, although the populations to target and the best methods to use have not been determined for every clinical setting.[41–43] The clinical relevance of identifying asymptomatic cognitive impairment is not fully understood and uncertainties surround the most appropriate investigations and manage ment of patients who are identified as cognitively impaired.[34,36,44] Although persistently detec table HIV RNA in CSF might indicate progressive CNS damage, results have not shown that HIV RNA concentrations consistently correlate with impaired cognitive function.[45] Studies also show that some anti retroviral drugs are more effective in the CNS than others,[7] but this finding depends on how their effectiveness is estimated. Studies focusing on the efficacy of antiretroviral drugs on cognitive function have not consistently shown differences, although the methods vary substantially between studies and only a few randomised controlled trials have been done.[20,38,39] In this Review we address common questions that clinicians face in the field of HIV-associated neuro cognitive disorders and suggest approaches to resolving key issues of debate.

How common are HIV-associated neurocognitive disorders?

CNS involvement in HIV infection is a major public health issue in resource-poor settings; however, in this Review we focus on HIV-associated neurocognitive disorders in populations with access to ART. Cross-sectional studies show that HIV-associated neuro-cognitive disorders are common in industrialised countries with widely available ART (figure 1). The largest and most detailed study to examine cognitive impairment in HIV is

the CNS HIV AntiRetroviral Therapy Effects Research (CHARTER) cross-sectional cohort study that showed cognitive impairment in 814 (52%) of 1555 HIV-seropositive patients.[12] This cohort was selected to reflect the HIV-seropositive population receiving treatment in clinics and as such included all causes of impaired cognitive function that occur in people with HIV. Among the 843 people in this cohort who had minimally confounding neuropsychiatric disorders (unrelated to HIV infection) 40% met the criteria for impaired cognitive function. Several other studies estimate the prevalence of HIV-associated neurocognitive disorders in patients with access to ART as 20–50%,[13–19] and some studies estimate that it is as high as 69%.[20] This wide range in prevalence estimates has resulted in uncertainty about the actual prevalence of cognitive impairment due to HIV pathology in populations with access to ART.

Do comorbid disorders affect neurocognitive function?

Several factors might predispose HIV-seropositive individuals to cognitive impairment (figure 2). Cerebrovascular disease[11] can result from the metabolic and systemic effects of HIV and ART on endothelial function and cardiovascular risk factors.[6,12,46,47] These mechanisms might become increasingly important as the HIV-seropositive population ages.[16] Hepatitis C infection[13] is associated with cognitive dysfunction independently of HIV infection,[48] and this effect is compounded in patients with HIV. Patients with HIV and hepatitis C co-infection are almost twice as likely to have cognitive impairment as HIV-seropositive individuals without hepatitis C infection.[49,50] The use of psychoactive drugs,[14] par ticularly methamphetamine, has deleterious effects on cognition, which is more pronounced when combined with HIV infection.[51,52]

Genetic factors in patients,[15] particularly the *APOE ε4* allele, are associated with HIV-associated dementia, but the association with mild impairment is inconsistent.[53,54] Cognitive changes related to ageing[16] might be compounded by HIV infection,[55] and low educational level[17] can contribute to poor cognitive function. Mood disorders[18] might masquerade as, or be caused by, cognitive impairment.[56] The extent to which each factor contributes to the prevalence of cognitive impairment in various populations is unclear.

Immunosuppression before ART is initiated, as estimated by the nadir CD4+ T-cell count, is strongly associated with cognitive impairment.[1,12,16] This might be due to irreversible CNS injury before treatment, a so-called legacy effect.[29] Alternatively there might be a process of immune or glial cell activation that occurs during advanced immunosuppression, which persists after treatment and immune recovery.[3,4]

Comorbidities are important to consider in the clinical assessment of HIV-positive individuals with cognitive impairment and in studies of HIV-associated neuro cognitive disorders. Risk factors, such as a low nadir CD4+ T-cell count, are potentially preventable, whereas others, such as depression and systemic HIV replication might be amenable to treatment. Although comorbidities are linked with impaired cognitive function, they are not strictly the underlying cause of HIV-associated neuro cognitive disorders. The widely used research classification, the Frascati criteria, proposed the terms asymptomatic neurocognitive impair ment and mild neuro cognitive disorder to characterise the neuro cognitive deficits in patients with mild HIV-associated neurocognitive disorders and state

that the diagnosis is possible only if cognitive impairment is not explained by comorbidities (panel and figure 3).[57]

Many patients in the CHARTER cohort had comorbidities; those with cognitive impairment were more likely to have hepatitis C co-infection or AIDS, had a lower nadir CD4+ T-cell count, had more comorbidities, were more likely to engage in recreational drug use or to be depressed, and were usually older and less educated than were patients without impaired cognitive function. 815 (52%) of 1555 patients had impaired cognitive function; however, this percentage varied from 83% of 239 patients with severe neuro-psychiatric comorbidities to 40% of 843 patients with minimal neuropsychiatric comorbidities. Even in the group with minimal neuropsychiatric comorbidities, 71% of patients had a history of drug misuse (16% had recent drug use as shown by a positive breathalyser test or urine test), 16% had current depression or a psychotic disorder, 60% had AIDS, and 60% had detectable levels of HIV RNA in plasma (not all were taking antiretroviral therapy).[12] Findings in this diverse population might be generalisable to the population attending HIV clinics in the USA, but not to a patient who is taking long-term ART that was started at an early stage of infection and who has good immune recovery. Variability in the prevalence and severity of comorbidities might explain some of the differences in the prevalence estimates of HIV-associated neuro cognitive disorders between studies. On the basis of these findings, several conditions should be considered in the assessment of patients with HIV infection and cognitive impairment, and a careful clinical assessment is essential.

Do prevalence estimates vary with demographic characteristics?

HIV-associated neurocognitive disorders are defined by at least one standard deviation from normative neuro-psychological test data derived from a control population that is matched to the target population for at least age and education (panel and figure 3). The Frascati criteria, therefore, depend on how accurately the control population reflects the test population. The socioeconomic, ethnic, and educational diversity of a typical HIV population in Europe and North America makes the use of appropriately matched control data essential to accurately classify cognitive impairment. Variability in demographics can affect the proportion of individuals classified as cognitively impaired, as shown in the results of clinical trials that did not use appropriate normative data. Variability in classification of individuals according to cognitive function has been shown in different countries,[57] and between ethnic groups within a country.[60] Although these differences could be due to disease-related factors (eg, HIV clade), other causes include educational, cultural, and social differences that vary by geographical region and clinical settings.[61]

One of the best opportunities to study a representative control group was provided by a cohort of Chinese plasma donors.[14,62] Farmers in a rural area of China supplemented their income by donating plasma to a local laboratory. Several hundred became infected with HIV because of the use of unsterilised needles. This unfortunate situation provided a rare opportunity to study a well-matched control group by comparing HIV-infected individuals with those who attended the same clinic but did not become infected. The assessment of this population showed cognitive impairment in 37 (34%) of 108 individuals with HIV infection compared with 18 (13%) of 141 individuals who were HIV seronegative.[14] When followed

up over 1 year, 28% of patients with HIV had deterioration in cognitive function compared with only 5% of those without HIV.[62] However, less than half of patients who took ART had undetectable concentrations of HIV RNA in plasma, and most had already progressed to advanced immunosuppression or AIDS, which are known risk factors for HIV-associated neurocognitive disorders.

Studies using comprehensive neuropsychological tests, stringent criteria for the definition of HIV-associated neurocognitive disorders and well-matched control data, have shown a high prevalence of HIV-associated neurocognitive disorders in patients.[12] However, the challenge is to generate the most appropriate normative data for each clinical setting.

The definition of HIV-associated cognitive disorder and diagnostic overestimation

The Frascati criteria emphasise that the essential feature of HIV-associated neurocognitive disorders is cognitive function inferior to that of a matched-control population. The criteria aim to eliminate the possibility of HIV-associated neurocognitive disorders being diagnosed on the basis of HIV comorbidities or non-cognitive psychiatric changes such as changes in personality or mood (panel and figure 3).

Debate about the current approach to HIV-associated neurocognitive disorders classification is ongoing.[63,64] Concerns have been raised that this classification will overestimate the prevalence of HIV-associated neuro-cognitive disorders by inaccurately classifying a proportion of the target population as cognitively impaired as a consequence of the method of the criteria alone. The use of a purely statistical approach, according to the Frascati criteria, will identify 8–13% of the normative population—and, therefore, the target population—as having impaired cognitive function.[57] This value is based on the assumption that two tests are performed per domain (panel). Although the use of two tests is recommended it is not mandatory to fulfil the Frascati criteria and some studies have used a single test per domain.[12] With the use of less conservative criteria[12] the frequency of false positives rises to 16–21%. The lower end of the false-positive estimate is thought by some to be the most accurate and is similar to the 14% prevalence of cognitive impairment in the HIV-sero-negative population.[57] Proponents of this reasoning raise concerns that use of the Frascati criteria in clinical practice will result in misdiagnosis of around 14% of HIV-seropositive patients as having HIV-associated neuro-cognitive disorders, which could lead to costly and potentially unsafe clinical interventions and anxiety and stigma in patients who are misdiagnosed. The counterargument is that low scores on neuropsychological tests reflect impaired cognitive function irrespective of the population tested (HIV-seropositive or HIV-seronegative), and HIV-associated neurocognitive disorders are not solely diagnosed on the basis of neuropsychological tests.

HIV-seronegative individuals who are evaluated as controls will probably have cognitive function that ranges from worse than average to better than average. The individuals in the control population who have the lowest scores on neuropsychological tests are, by definition, those with the lowest cognitive function. Thus, patients in the target population who score similarly on neuropsychological tests to the controls with the lowest scores for cognitive function are themselves the individuals with low cognitive function. The need for individuals to have low scores for at least two cognitive domains (according to the Frascati

criteria) is intended, partly, to reduce the risk of misdiagnosis of cognitive impairment in HIV-seropositive individuals. Importantly, for a diagnosis of HIV-associated neurocognitive disorder the cognitive impairment must not precede HIV infection and severely confounding comorbidities (eg, psychosis or active recreational drug use) and delirium must be absent at the time of diagnosis; diagnostic confidence is further strengthened when a decline in cognitive function has occurred.

Should the HIV-seropositive population be screened for cognitive impairment?

People with asymptomatic neurocognitive impairment have poor performance on cognitive tests but, by definition, do not have symptoms or diminished daily functioning.[57] Estimates of prevalence vary but asymptomatic neurocognitive impairment might occur in 33% to 60% of HIV-seropositive people despite ART.[12, 20] Asymptomatic neurocognitive impairment is a research classification but might have clinical implications both symptomatic and asymptomatic cognitive impairment are associated with poor quality of life, unemployment, low adherence to drug regimens and poor driving ability.[23] Mild neurocognitive disorder has been associated with neuropathological evidence of HIV-encephalitis in some patients.[65] Patients with asymptomatic neuro-cognitive impairment in the CHARTER cohort, had a substantially higher risk of progressing to symptomatic neurocognitive impairment or mild neurocognitive disorder than those with normal cognitive function.[58] These factors have led to questions about the value of routine screening in the HIV-seropositive population for asymptomatic neuro cognitive impairment.

The Mind Exchange Working Group[41] advocate that all patients with HIV should be screened for HIV-associated neurocognitive disorders, regardless of symptoms or risk factors, using sensitive screening tools. The group recommend that patients should be screened early in the disease and then every 6–24 months. The British HIV Association (BHIVA) also states that patients should be screened annually—but they do not give details of which methods should be used or suggest which populations should be targeted.[42] Guidelines from the European AIDS Clinical Society (EACS) recommend that formal neuropsychological tests should be restricted to patients who have symptoms of impaired cognitive function based on a questionnaire.[43]

Several issues should be considered with respect to screening for asymptomatic neurocognitive impairment. For a test to be clinically useful the disease must have a well-defined early stage that would progress to a more severe stage without intervention. An effective intervention should be available, and the distress and subsequent investigation caused by a positive test result must be outweighed by the benefit of early treatment.[66] Since no effective therapy for asymptomatic neuro-cognitive impairment other than ART has been identified, the benefits of screening asymptomatic patients who have normal daily functioning and are already taking ART are debatable, particularly because no single screening method seems to be adequately sensitive and specific enough to diagnose asymptomatic neurocognitive impairment in all clinical settings. In many patients, asymptomatic neurocognitive impairment is not progressive; for instance, around half of individuals with any HIV-associated neurocognitive disorder fluctuate in cognitive functioning over time, with improvement from HIV-associated neurocognitive disorder to

unimpaired cognitive function occurring as frequently as deterioration.[15] This variability might be due to true fluctuations in pathological processes, perhaps reflecting varying degrees of HIV replication in the CNS, or might reflect limitations of the neuro-psychological tests. Importantly, whether or not the poor outcomes reported for those diagnosed with asymptomatic neurocognitive impairment are driven primarily by HIV, by comorbidities, or by both is unclear.

Identification of patients who have early-stage impaired cognitive function might have some merit, so that risk factors can be controlled, treatment adjusted, and disease progression monitored. Changes to antiretroviral drug regimens based on distribution into the CNS, monocyte activation, or neurotoxicity have been posited in the treatment of asymptomatic neurocognitive impairment, but randomised clinical trials to support these or other interventions, such as exercise or cognitive rehabilitation, have not been done. As a result there is no strong consensus on the best course of action for patients who are taking adequately suppressive ART and are diagnosed with asymptomatic neurocognitive impairment, and there is no widely accepted therapeutic framework in which to change ART on the basis of differences in the estimated efficacy or toxicity of antiretroviral drugs in the CNS.[34,36,44] A remaining important consideration is the impact of the screening process on patients; informing an asymptomatic individual that he or she has cognitive impairment could cause psychological distress. For these reasons, routine cognitive screening for asymptomatic neurocognitive impairment has not yet been widely adopted in the clinic.

What is the clinical relevance of HIV RNA concentrations in CSF?

Systemic HIV replication is a risk factor for cognitive impairment, and HIV RNA in blood is independently associated with cognitive impairment.[12] Neurocognitive function typically improves after virological control with ART, even if the patient did not have functional deficits at baseline.[67] This effect has been shown experimentally: rhesus macaque monkeys inoculated with simian immunodeficiency virus had only 70% of the locomotor activity of animals that were uninfected. After ART locomotor activity returned to the same level as before infection.[68]

Only 19% of all HIV infected individuals in the USA are estimated to achieve suppression of HIV in blood;[69] only 80% are aware of their diagnosis and fewer access HIV-specific health care, stay in HIV health care, receive ART, and are able to adhere to their treatment. Although aviraemic patients who are taking ART might be a minority of the total HIV-infected population, the prevalence of HIV-associated neuro cognitive disorder in this population is substantially lower than in those who are either not taking ART, or in whom it is ineffective. A cross-sectional study in the UK of 100 HIV-seropositive individuals, all asymptomatic and aviraemic with ART, showed cognitive impairment in just 19% of patients, similar to the prevalence expected in a HIV-negative population.[21,22] HIV RNA concentrations in plasma often strongly correlate with those in CSF. Whether HIV replication either inside the CNS, outside the CNS, or both, leads to CNS injury is unknown (figure 2).

Can HIV in the CNS escape ART?

Modern ART can control systemic viraemia but concern has arisen that it might not fully control HIV replication in the CNS, in which drug concentrations can be much lower. The occurrence of detectable HIV RNA in CSF when undetectable in plasma has been termed CSF viral escape. In clinical practice this can be seen in around 10% of individuals undergoing lumbar puncture.[8,9,70,71] Results from studies in which a lumbar puncture was done only for research purposes in asymptomatic individuals showed the prevalence of CSF viral escape to be less than 10% (eg, 2% in the CHARTER study).[9,70] The extent to which CSF viral escape leads to CNS injury and HIV-associated neurocognitive disorders is unknown. Direct neurotoxicity occurs from the HIV virus and its proteins, such as the envelope glycoprotein gp120 and the regulatory protein Tat.[7] Chronic sustained immune activation in the CNS leads to the production of neurotoxic products, such as nitric oxide, arachidonic acid, and proinflammatory cytokines.[8,72] In untreated patients in the pre-ART era, high levels of HIV RNA in CSF were associated with HIV-associated dementia.[25–28] However, the association between HIV RNA in CSF and cognitive function in treated patients in the modern era of potent ART is less clear.[26,45,73]

Analysis of CSF from patients in the CHARTER study showed that cognitive performance was not related to the absolute concentration of HIV RNA in CSF but did relate to the presence of discordant virus.[70] This association was shown when an assay was used that can detect HIV RNA at 2 copies per mL, which is a much more sensitive assay than that currently used in clinical practice. Other studies have shown no association between HIV RNA concentrations in CSF and cognitive function but few have used such sensitive assays.[74] The authors of the Mind Exchange Consensus report[41] recommend the use of an assay sensitive enough to quantify HIV RNA at 1·0–2·5 copies per mL in CSF and plasma in individuals with HIV RNA concentrations of less than 50 copies per mL in both CSF and plasma, and who have cognitive impairment confirmed with neuropsychological tests for whom there is no alternative explanation. However, this recommendation is based on preliminary findings in two conference reports and needs further investigation.[70,75]

One explanation for the weakness of the association between HIV RNA concentrations in CSF and impaired cognitive function is that HIV RNA levels in CSF are an imperfect proxy for HIV replication in brain tissue. Although regional viral loads in the brain correlate to some extent with the concentration in CSF, this correlation can be weak, meaning levels of HIV RNA in the CSF may not always be an accurate surrogate for production of HIV virions (and viral proteins) within the brain.[76,77] Another explanation relates to the pathogenetic mechanisms underlying cognitive impairment in HIV-seropositive individuals; if the pathology is a result of immune dysregulation rather than virus-related cytopathy then HIV RNA concentrations in CSF might not be the most accurate biomarker of cognitive impairment. In fact, in large cohorts, cognitive impairment seems to correlate more strongly with the severity of immunosuppression before ART than with HIV RNA concentrations in CSF.[78] In one study, time to progression to HIV-associated dementia in 74 (36%) of 203 patients with advanced HIV infection was independent of plasma or CSF viral load, but was associated with biomarkers plasma TNFα and CSF MCP-1 in plasma and CSF.[74] On the basis of this and other published findings, a combination of biomarkers reflecting neuronal

injury and glial cell or immune activation in combination with HIV RNA concentrations in CSF might be more accurate than HIV RNA in CSF alone.[70,79] However, the clinical validity, reproducibility, and cost-effectiveness of these biomarkers have not been evaluated.

Can HIV drug resistance develop in the CNS?—If HIV can continue to replicate in the CNS in the presence of sub-therapeutic levels of ART, drug resistance could develop. Many studies have shown mutations in HIV which confer resistance to several classes of antiretroviral drugs in the CSF that were not present in blood.[31–33] In two separate case series of patients with newly diagnosed cognitive impairment or other neurological symptoms, and CSF viral escape, most had mutations associated with drug resistance in HIV in CSF.[29,30] Alterations to antiretroviral drug regimens based on drug resistance mutations in HIV in CSF led to clinical improvement and a decrease in HIV RNA concentration in CSF in both series of patients.

HIV might also differ between CSF and plasma in terms of pathogenicity, and tropism for CD4+ T-cells with different coreceptors. These differences might be due to the adaptation of the virus to target cells in the CNS, or to differences between exposure of the virus to antiretroviral drugs in the CNS and in plasma.[37,80] The degree of HIV compartmentalisation is associated with the duration of infection, previous immune suppression, and the risk of HIV-associated neurocognitive disorder. Of note, indicators for compartmentalisation of HIV do not differ between HIV-seropositive individuals with mild neurocognitive disorder and those who are unimpaired. This observation supports the notion that the effect of HIV mutations on pathogenicity in the CNS differs between milder and more severe HIV-associated neurocognitive disorders.[81,82] Another reason for this difference might be that the most severe HIV-associated neurocognitive disorder, HIV-associated dementia, is associated with the most advanced immunosuppression, which might increase viral replication and accelerate viral mutations in the CNS.[81]

Although drug resistance testing of HIV in CSF is not currently recommended in the routine management of asymptomatic patients, it may be useful in those with impaired cognitive function and other neurological disorders, and forms part of recommendations from EACS, BHIVA, and the Mind Exchange group.[41,43,83] More work is needed to determine the clinical applications and cost-effectiveness of drug resistance tests for CSF HIV, and the implications of drug resistant mutations in HIV in the CSF.

Are some antiretroviral drugs more effective than others in the CNS?

Evidence supports the idea that ART generally protects the CNS: current drug regimens decrease HIV RNA concentrations in the CSF[70] in most patients who are adherent to their medication, reduce the incidence of HIV-associated dementia,[84] and improved histopathology findings in brain tissue of patients with HIV infection at post-mortem. A central question is whether some anti-retroviral drugs are more effective in reducing HIV replication in the brain than others.

Several characteristics of antiretroviral drugs affect their distribution into the CNS. These characteristics include molecular weight, protein binding, fat solubility, and interaction with influx or effux drug transporters on brain endothelium.[85] Consequently, there is a wide

range of effective concentrations for antiretroviral drugs in the CNS across different antiretroviral drug classes, and for individual drugs within a class. A hierarchy of drug distribution (or penetration) into the CNS has been proposed by the authors of the CHARTER study based on the chemical properties, pharmacokinetics, and effectiveness of these drugs in clinical studies.[7] The CNS Penetration Effectiveness (CPE) score is used to assign each drug an integer from one to four (table 2), with one indicative of below average estimated effectiveness and four indicative of higher than average estimated effectiveness. The total CPE score is the sum of all antiretroviral drugs in a regimen. The score was devised as a research tool but has been used by some clinicians to guide prescribing for HIV-seropositive individuals with neurological complications; however, the benefits of its use in the clinic are unproven. The Mind Exchange Consensus Report suggests that for patients with persistent or worsening cognitive impairment and detectable HIV RNA in CSF, the modification of therapy according to the CPE score might be an option when other risk factors (eg, poor adherence to medication, virological drug resistance, and comorbidities) have been considered.[41] The CPE score is not included in the EACS guidelines for the treatment of cognitive impairment in HIV-seropositive individuals—instead the guidelines list nine potentially CNS-active antiretroviral drugs, based on either CSF drug concentrations, efficacy as single agents affecting cognitive function or CSF viral load in randomised trials. This approach to the categorisation of ART has some overlap with drugs that are higher than average on the CPE score.[43] The current BHIVA guidelines recommend against the use of the CPE score to guide the prescription of ART.[83]

In cohort studies, the CPE score has been significantly correlated with HIV RNA in CSF; the higher the CPE score the fewer patients with detectable levels of HIV RNA in CSF.[34,86] Evidence linking CPE scores with cognitive performance has been mixed.[20,38,39] The authors of a systematic review[35] concluded that antiretroviral drugs with high estimated levels of CNS penetration effectively improved cognitive function and decreased HIV RNA concentrations in CSF, but only two of the studies included were adequately statistically powered and all were observational studies. To date the only randomised trial of antiretroviral drugs with good penetration into the CNS for the treatment of HIV-associated neurocognitive disorders used a so-called CNS-targeting approach that took the CPE score into account when a new ART regimen was selected. No difference in the neurocognitive outcome at 16 weeks after the change in ART was noted, although the trial was statistically underpowered, with only 49 of the planned 120 patients enrolled.[87] A planned subgroup analysis of patients who entered the trial with suppressed plasma HIV RNA showed a trend towards neurocognitive benefit in those who received CNS-targeted therapy. Patients who received CNS-targeted therapy, however, also had poorer plasma virological suppression at 16 weeks, which supports the idea that the prescription of ART on the basis of estimates of CNS penetration rather than proven efficacy might lead to unacceptable clinical outcomes.

One theory states that antiretroviral drugs with low concentrations in the CSF, estimated by CSF measures or CPE score, could more likely result in resistance mutations in the CNS than in the periphery. Findings in the literature to date are mixed,[88,89] although a high level of genetic diversity suggesting autonomous viral replication in the CNS has been associated with a low CPE score.[90] An adjusted CPE score has been proposed, to take into account drug resistance mutations in the CSF.[30]

One criticism of the CPE score is that it relies heavily on pharmacokinetic data from CSF, not brain tissue. Although CSF is commonly used as a surrogate for brain events, drug concentrations in CSF might not accurately reflect those in brain tissue. Drug concentrations in CSF and brain tissue can differ for several reasons, including the differing characteristics of the blood-brain and blood-CSF barriers.[91] Indeed drug concentrations can differ between the brain tissue and CSF,[92] as well as between different brain regions.[93] Although currently impossible to ascertain in living people, the concentration that might best predict the efficacy of CNS ART in the brain is that in perivascular macrophages, a crucial HIV target cell in the brain.[4] Nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are generally ineffective in chronically infected macrophages and the concentration at which protease inhibitors inhibit viral replication is higher in macrophages than in T lymphocytes.[94,95]

Direct comparisons of individual antiretroviral drugs is difficult because it would need administration of monotherapy to patients—a practice that is uncommon in most clinics. Sidtis and colleagues[96] showed in 1993 that zidovudine was effective in the treatment of HIV-associated dementia. Few drugs have since been assessed as monotherapy in randomised controlled trials. Recently, the simplification of maintenance treatment to a single protease inhibitor was investigated as an approach that might reduce toxicity but still maintain full suppression of viral replication. Concern exists that protease inhibitor monotherapy might not control HIV replication in the brain because concentrations in CSF can be low, perhaps because many are substrates for drug efflux transporters.[97] Despite this concern, protease inhibitor monotherapy was not associated with impaired cognitive function when compared with triple drug ART in a recent observational study of 191 participants.[98]

Do antiretroviral drugs cause neurotoxicity?

Evidence is increasing that at least some modern antiretroviral drugs can cause neurotoxicity (figure 2).[36,99,100] The relation between the drug concentration needed to inhibit HIV replication in the CNS and that needed to cause neurotoxicity probably differs according to the drug used. The drugs that have the greatest penetration into and distribution within the CNS are not necessarily the most neurotoxic. The goal is to identify which drugs offer the best balance between efficacy and neurotoxicity, and to maintain drug concentration in this so-called therapeutic window.

In addition to direct injury of neurons, ART might also indirectly alter brain function via effects on immune, glial, or endothelial cells. One potential mechanism is low-grade immune recon stitution inflammatory syndrome (IRIS) in the absence of an underlying lesion. The resultant chronic lymphocyte activation and persistent inflammation in the CNS[45,101,102] might be more severe in patients who have advanced immuno suppression before the initiation of ART.[12,16] Such events present challenges to neurocognitive recovery and the eradication of HIV from the CNS.

Conclusions and future directions

In our opinion, future studies describing the incidence or prevalence of HIV-associated neurocognitive disorders should address at least two key elements: the identification of the effect of comorbidities on cognitive function and the use of well-matched controls to provide normative data for the diversity of target HIV populations. Ideally, diagnostic methods should be standardised to enable comparisons between studies. When possible, the Frascati criteria for diagnosis should be applied with a conservative approach that requires two impaired tests per cognitive domain to reduce the risk of misclassification.[64] Authors of studies of HIV-associated neurocognitive disorder should be encouraged to publish the demographic characteristics of the control population used to obtain normative data.

The current approach to identify cognitive impairment in HIV-seropositive individuals is focused on the development of a classification system, not on clinical diagnosis. We feel that the 2007 Frascati criteria should be updated to provide practical guidance for clinicians on, for example, how to interpret cognitive function in the context of various demographic factors and comorbidities. Further work is needed to develop clinically useful methods to distinguish HIV-associated neurocognitive disorders (ie, potentially amenable to earlier initiation of ART, more potent ART or CNS-targeted ART) from cognitive impairment related to other factors.

In our opinion, the approach to screening of HIV-seropositive individuals for assymptomatic neuro-cognitive impairment needs evaluation. Few studies have systematically evaluated the progression from asymptom atic neurocognitive impairment to mild neurocognitive disorder in these patients; longitudinal studies are needed to define the natural history of HIV-associated neurocognitive disorders. Despite much evidence evaluating several methods to screen patients for HIV-associated neurocognitive disorders, no single, cost-effective, easy-to-perform test has proven adequately sensitive and specific across all clinical settings.[41] The most appropriate techniques to screen patients for HIV-associated neurocognitive disorders have yet to be determined. Computerised cognitive assessments need further evaluation in people with HIV because these assessments could be administered to patients quickly and inexpensively in clinic.

Although comprehensive neuropsychological tests are appropriate for some patients, they are unlikely to be cost effective if widely adopted as a screening tool. The selection of symptomatic patients on the basis of a questionnaire as suggested by EACS[43] also warrants investigation in prospective studies because self-reporting of symptoms may be unreliable in patients with cognitive difficulties.[103] Other tests have been evaluated for their potential in the diagnosis and prognostication of HIV-associated neurocognitive disorders. Biomarkers in CSF or blood can be found at abnormal concentrations in some patients with HIV despite viral suppression; however, the implications for the development of cognitive impairment in these patients is not well understood.[45] Many of these biomarkers correlate with scores on cognitive tests in cross sectional and longitudinal studies, but none have yet been developed for use in the clinic. Advanced neuroimaging techniques such as nuclear magnetic resonance spectroscopy, amyloid PET, and functional MRI might be useful in some patients, and are the subject of further study.[104,105] Biomarkers and neuro-imaging techniques need to be

evaluated as screening tools, in the monitoring of the response to ART, and as endpoints in clinical trials. Additionally, as the HIV-seropositive population ages, these techniques should be evaluated in older patients so they can distinguish HIV-associated neurocognitive disorders from other causes of cognitive impairment, such as Alzheimer disease.

Whether patients who initiate ART early in the disease are at risk of developing HIV-associated neurocognitive disorders is unclear from existing data. Studies of avireamic patients show HIV-associated neurocognitive disorders prevalence estimates ranging from 19% to 64%.[20,21] These discrepant findings could be attributed to differences in comorbidities and the severity of immunosuppression before the start of ART. More work is needed to identify major risk factors in patients who meet current clinical goals, such as those who began ART with a high CD4+ T-cell count, have long-term aviraemia, and few neuropsychiatric comorbidities.

The extent to which CSF viral escape contributes to the risk of HIV-associated neurocognitive disorders and the activation of immune cells and glial cells in the CNS is unknown. The best approach to identify which patients would benefit from assessment of HIV RNA concentrations in CSF is unclear. Longitudinal studies are needed to follow up patients with CSF viral escape to determine its effect on cognitive function and antiretroviral drug resistance either in the CNS or systemically. Additionally, studies are needed to assess CSF and serum proteins and neuroimaging markers of inflammation to determine where there is an association between CNS viral escape, inflammation, and neuronal or glial cell injury.

Large, prospective, well stratified, randomised trials are needed to examine the effect on cognitive function and CNS distribution of different ART regimens. Cross-sectional studies might not be reliable because some clinicians select CNS-targeted regimens for their patients with evidence of CNS involvement.[106] The number of antiretroviral drug combinations in use and the length of follow-up needed mean that the evaluation of each regimen is a major undertaking.

An alternative strategy is to monitor improvements in cognitive function after the start of ART. In most individuals there is improvement in cognitive function after starting ART,[107,108] which is detectable as early as 3 months,[109] and might continue beyond a year.[110] This effect has been compared for different antiretroviral drug regimes. ART that has good estimated distribution into the CNS has been associated with better cognitive performance in some studies; however, results are inconsistent.[67] This strategy needs further evaluation in randomised clinical trials with large sample sizes.

There are no data for the use of ART to prevent, rather than treat, HIV-associated neurocognitive disorders. Cognitive impairment might develop soon after HIV transmission and whether a mild degree of irreversible cognitive impairment can occur with high CD4+ T-cell counts is unknown.[111] A study of US military personnel who were diagnosed as HIV-seropositive and treated with ART early in the disease course had a low prevalence of cognitive impairment similar to a matched cohort uninfected with HIV.[22] The question of whether to start ART early to prevent cognitive impairment is being investigated as part of

the Strategic Timing of AntiRetroviral Treatment (START) study and in an NIH-funded clinical trial in China (NCT01340950).

Although there is increasing evidence that at least some modern antiretroviral drugs cause neurotoxicity, whether this leads to persistent cognitive impairment has not been systematically studied. The association between effective or toxic drug concentrations, the mecha nisms of neurotoxicity, and approaches to identify patients with neurotoxicity in the clinic need further study.

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Panel: Neurocognitive assessment of patients with HIV-associated neurocognitive disorders according to the Frascati criteria

Assymptomatic neurocognitive impairment and mild neurocognitive dementia

Scores on neuropsychological tests of at least 1 standard deviation below those of age and education matched controls in the normative population in at least two cognitive domains are needed for a diagnosis of asymptomatic neurocognitive impairment or mild neurocognitive dementia. The assessment must include at least these domains (with at least two tests per domain if possible): verbal and language; and attention and working memory; abstraction and executive function; memory (learning, recall); speed of information processing; and sensory-perceptual and motor skills. Cognitive impairment must be acquired, cannot be explained by comorbidities, and there should be no evidence of delirium or a pre-existing cause.

Daily functioning can be formally assessed by Lawton & Brody's modified Activities of Daily Living scale or the Patient's Assessment of Own Functioning Inventory (figure 3).[58,59]

HIV-associated dementia

Scores on neuropsychological tests of at least 2 standard deviations below those of age and education matched controls in the normative population in at least two cognitive domains are needed for a diagnosis of HIV-associated dementia. Typically cognitive impairment is in several cognitive domains, particularly in the learning of new information, speed of information processing, and attention or concentration. The pattern of cognitive impairment does not meet criteria for delirium and there is no evidence of another, pre-existing cause for dementia (figure 3).

Search strategy and selection criteria

We identified references for this Review through searches of PubMed with the search terms “HIV associated neurocognitive disorders”, “HIV dementia”, “asymptomatic neurocognitive impairment”, “mild neurocognitive disorder”, “cognitive”, “cerebrospinal fluid”, “CNS penetration effectiveness”, “antiretroviral resistance” “compartmentalization”, “antiretroviral neurotoxicity”, and specific antiretroviral therapy drug names, for articles from October 1980 to October 2013. Articles were also identified through searches of our own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

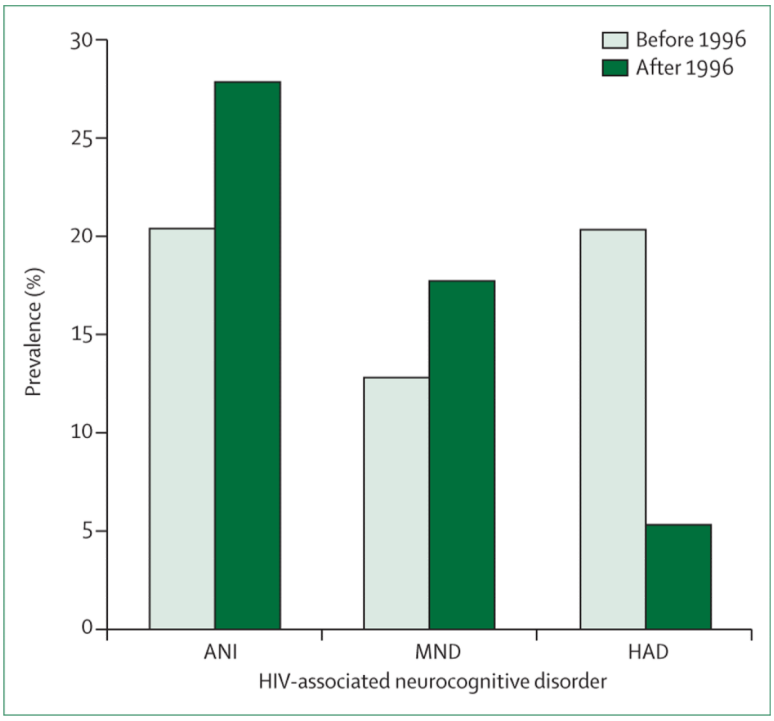

Figure 1.

Changes in the prevalence of HIV-associated neurocognitive disorder in the USA before (HNRC study, N=678)[10] and after (CHARTER study, N=843)[12] the widespread use of HAART[11] ANI=asymptomatic neurocognitive impairment. MND=mild neurocognitive impairment. HAD=HIV-associated dementia. HAART=highly active antiretroviral therapy

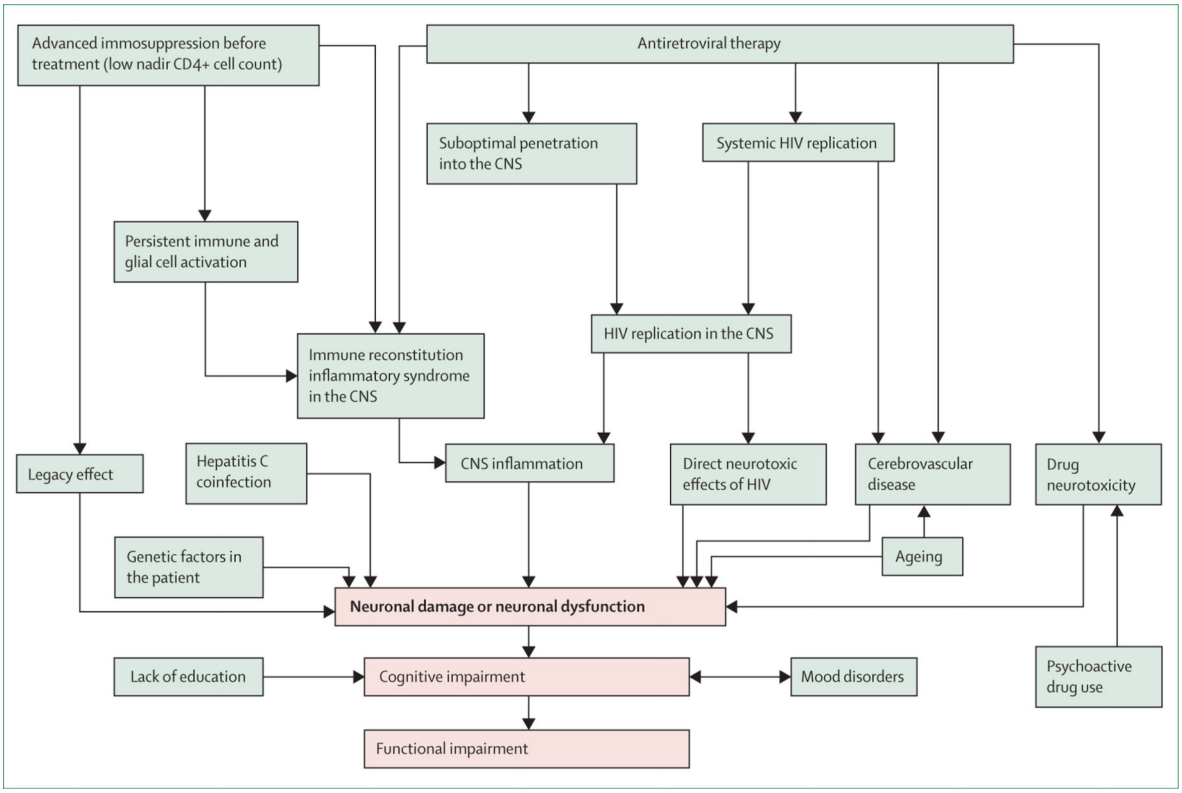

Figure 2.

Overview of proposed pathological mechanisms underlying HIV-associated neurocognitive disorders

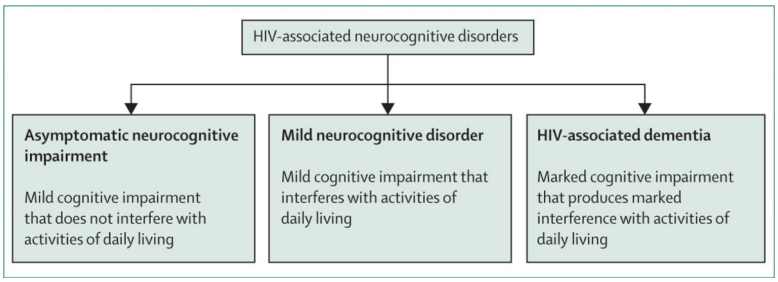

Figure 3.
Summary of the Frascati criteria for HIV-associated neurocognitive disorders[35]

Table 1

Summary of arguments in favour or against controversial clinical statements in HIV-associated neurocognitive disorders

	Arguments in favour	Arguments against
HIV-associated neurocognitive disorders are common in the era of ART	Several statistically well powered, observational studies have shown prevalence of up to 60% in HIV-seropositive populations with access to ART. Most patients might have asymptomatic cognitive impairment[12-20] Some studies that show high prevalence of cognitive impairement used a thorough neurocognitive evaluation and matched control data to key demographic variables[12] Prevalence of cognitive impairment is high in subpopulations with few neuropsychiatric comorbidities[12]	Using current critera approximately 14% of those at the lower end of cognitive functioning in a normative population will be classified as impaired. Cognitive functioning at this level might be of concern but HIV-related neuropathology is not necessarily the cause Prevalence estimates depend on the use of appropriate normative data. Most studies did not have a normative population appropriate to all demographic groups in their cohort Prevalence estimates are often made in HIV-seropositive populations who have other conditions that affect cognition. Prevalence in patients taking long-term ART who do not have other conditions that impair cognitive function is similar to that in HIV uninfected controls[21,22]
People with HIV should be screened for ANI	ANI is typically more common than MND or HAD; therefore, cognitive impairment would go unrecognised without screening ANI is associated with poor quality of life, poor adherence to medication, and unemployment[23] ANI might be associated with an increased risk of progressive neurocognitive disease[24] A negative test result on screening might reassure HIV-seropositive patients who are aware of the high prevalence of ANI	There are no screening tools for ANI with high sensitivity and specificity that can be used in all clinical settings There is no consensus on the therapeutic management of ANI. Patient screening could lead to diagnostic procedures that might be unnecessary, costly, and invasive Worse outcomes in patients with ANI might be related to comorbidities A positive result on screening might cause psychological distress to some patients Screening for ANI uses clinical resources which are limited
HIV RNA in CSF is a useful clinical tool in the assessment of patients who are HIV-seropositive	Before the introduction of ART, high levels of HIV RNA in CSF were associated with HAD in people with advanced immunosuppression[25-28] Case series have shown a link between decreased cognitive impairement and a decrease in HIV RNA in CSF[29,30] One ART era study showed that people with greater HIV RNA in CSF than in blood were more likely to have neurocognitive impairment[26] Persistent HIV RNA in CSF during ART might increase the risk of antiretroviral drug resistance and virological failure[31-33]	In individuals successfully treated with ART, cognitive impairment might be caused by ongoing inflammation in the CNS or comorbidities, rather than ongoing HIV replication HIV RNA levels in CSF may not accurately reflect HIV replication in brain parenchyma Most studies have failed to show an association between HIV RNA in CSF and neurocognitive status since the introduction of ART Longitudinal studies have not shown that people who have CSF viral escape are more likely to develop antiretroviral drug resistance or progress to virological failure
Some antiretroviral drugs are more effective in the CNS than others	Concentrations of some antiretrovirals in CSF do not exceed the inhibitory concentration for wild-type HIV replication Drugs with poor estimated CNS effectiveness are associated with high levels of HIV RNA in CSF[34] Some studies have shown that drugs with high estimated CNS effectiveness are associated with improved cognitive function.[35] Studies have shown that some antiretrovirals are neurotoxic[36] Some observational studies have reported a decline in the levels of HIV RNA in CSF and improvements in cognitive function after changes to ART regimines on the basis of estimated CNS effectiveness[30,37]	CSF viral escape is uncommon with any antiretroviral combination when using routing HIV RNA assays[12] Some observational studies have not shown an association between ART with drugs that have high estimated CNS effectiveness and neurocognitive function[12,20-39,40] Estimates of CNS effectiveness are largely based on the pharmacokinetics of ART in CSF, which might not accurately reflect the pharmacokinetics of antiretroviral drugs in HIV-infected glial cells or brain macrophages

ART=antiretroviral therapy. ANI=asymptomatic neurocognitive impairment. MND=mild neurocognitive disorder. HAD=HIV-associated dementia.

Table 2

CNS penetration effectiveness (CPE) 2010 ranking scale[7]

	4	3	2	1
NRTI	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Zalcitabine Stavudine	Tenofovir Zalcitabine
NNRTI	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease inhibitors	Indinavir*	Darunavir* Fosamprenavir* Indinavir Lopinavir*	Atazanavir Atazanavir* Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir* Tipranavir*
Cell fusion and cell entry inhibitors	..	Maraviroc	..	Enfuvirtide
Integrase inhibitor	..	Raltegravir	..	..

CPE score is the sum of the individual scores of all drugs in the ART regimen. NNRTI=non-nucleoside reverse transcriptase inhibitor.

*Ritonavir boosted. NRTI=non-nucleoside reverse transcriptase inhibitor.