Cognitive disorders in people living with HIV

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High rates of cognitive disorders in antiretroviral-treated people living with HIV have been described worldwide. The exact prevalence of such cognitive disorders is determined by the definitions used, and the presence of these cognitive disorders significantly impacts the overall wellbeing of people with HIV. With the cohort of people with HIV becoming increasingly older, and having high rates of comorbidities and concomitant medication use, rates of cognitive disorders are likely to increase. Conversely, interventions are being sought to reduce the size of the latent HIV reservoir. If successful, such interventions are likely to also reduce the HIV reservoir in the brain compartment, which could result in improvements in cognitive function and reduced rates of impairment.

Introduction

During the first decade of the HIV pandemic, prior to any antiretroviral therapies (ARTs) becoming available, the natural history of HIV infection was documented, with many acquired immunodeficiency syndromes described. One of the early AIDS-defining illnesses to be recognised was HIV-associated dementia. In individuals with advanced HIV, the prevalence of HIV-associated dementia was around 15%, with an incidence rate of 7% per year.[1]

With the development of virologically suppressive ART, and the resulting immune restoration and preservation, AIDS-defining illnesses, including HIV-associated dementia, are now rarely seen in people with HIV who have access to ART. Indeed, life expectancy on suppressive ART is now almost equal to that of the general population.[2]

Although frank HIV-associated dementia is now rarely seen, apart from in people with HIV presenting late with significant immunosuppression, milder forms of cognitive disorders continue to be described in those otherwise effectively treated. These cognitive disorders were recognised soon after the advent of virologically suppressive ART,[3] and continue to be described in more recent years.[4,5] Notably, this finding is not an occurrence linked to specific geographical regions or specific healthcare settings, with high rates of cognitive disorders reported in people with HIV in North America,[4] South America,[6] Europe,[7] Australia,[8] Asia,[9] and Africa.[10]

As this field has evolved over the preceding decades, several areas of debate have arisen, including how to optimally define cognitive impairment in people with HIV, who to screen for cognitive disorders and whether there should be screening programmes, and what management strategies should be used. Although definitive answers to many of these debated topics might not be possible, some of the underlying reasons as to why such controversies have arisen are outlined. Potential causes of cognitive impairment in effectively-treated people with HIV are described, highlighting the contribution of HIV-related factors as well as lifestyle factors. Taking these contributions into account, recommendations on how to optimally manage people with HIV who have cognitive impairment are delineated. Finally, we address emerging considerations for cognitive health in HIV, including potential challenges surrounding efficacy and effects of HIV cure interventions related to HIV infection in the brain.

Prevalence of cognitive disorders

Many cohort studies have reported the prevalence of cognitive disorders in people with HIV.[9,11] Although determining the prevalence of a condition, such as cognitive impairment, in a well-designed cohort study might at first appear simple, many challenges arise in interpreting data relating to cognitive function.

One of the first challenges is to determine so-called cognitive normality, or the expected cognitive performance in a given population. Many populations of people with HIV differ substantially in several aspects from their control populations or the general population. Differences that might be present between populations include lifestyle differences, such as rates of tobacco smoking and recreational drug use, and differences in the prevalence of other non-infectious medical conditions.[12] These factors can impact cognitive testing results, and therefore impact the prevalence of reported cognitive disorders, if control populations are utilised as cognitive norms where the control populations differ from the people with HIV.

A second challenge is how to analyse cognitive testing results. Formal cognitive batteries involve tests covering several different cognitive domains, such as language, learning and memory, attention, executive function, and motor function. Interpretation of these cognitive results can be undertaken in many ways. Often, results are dichotomised into normal and abnormal, but deciding the cut-off for determining this dichotomisation can be challenging.

Dichotomisation of results can also occur at differing levels. For instance, overall average cognitive testing scores can be calculated, often known as a cognitive T score, and then a cut-off for this average cognitive score determined to assess if an individual has cognitive impairment or not. Or, each cognitive score can be individually dichotomised and then rules applied to determine if an individual meets a definition of cognitive impairment.

In 2007, a research definition of cognitive disorder in people with HIV was proposed, which has been widely used in this field. This definition is known as the HIV-associated neurocognitive disorders (HAND) criteria, or sometimes called the Frascati criteria.[13] The main aim of this definition at the time of its development was to recognise the more minor cognitive deficits that

were apparent in people with HIV on ART, and move away from definitions that were more focused on a severe dementia phenotype. The HAND definition is proposed for research studies with cognitive disorders including asymptomatic neurocognitive impairment, mild neurocognitive disorders, and HIV-associated dementia. For all three categories, an individual's performance in cognitive testing is required to be below expected by at least one standard deviation in at least two cognitive domains. Symptomatology and impact on activities of daily living determine the difference between asymptomatic neurocognitive impairment, in those with no symptoms, mild neurocognitive disorders, in those with mild symptoms and limited impact on daily living, or HIV-associated dementia, in those with symptoms that have substantial impact on daily living.

The HAND criteria have over time led to several areas of controversy. Questions remain on the clinical significance of defining cognitive impairment in otherwise asymptomatic individuals. Although some studies have suggested people with HIV with asymptomatic neurocognitive impairment are more likely to progress to symptomatic cognitive disorders,[14] confounders that might affect cognitive performance, such as the presence of non-infectious comorbidities, were often more prevalent in individuals whose cognitive classification deteriorated. Progression of asymptomatic neurocognitive impairment to mild neurocognitive disorder can also occur if symptomatology develops, which might not always be formed of cognitive symptoms. These issues have led to the relevance of this asymptomatic category being questioned.

Questions also remain regarding the high rates of cognitive impairment observed in cohort studies that have used the HAND criteria. Rates of cognitive impairment of up to 50% are widely reported when the HAND criteria are applied. The relevance of this finding can therefore be questioned, given that such high rates of cognitive impairment are generally not apparent in clinical practice.[15] Furthermore, in HIV-negative control populations, the HAND criteria classify a high percentage of individuals as having a cognitive disorder, which clearly cannot be related to HIV, given that the controls are HIV-negative. In addition, heterogeneity is likely to exist in cognitive profiles across different populations and cultures. As with many criteria for defining cognitive disorders, the HAND criteria do not differentiate individuals on the basis of specific cognitive domain types that are deemed to be impaired, but rather the total number of cognitive domains deemed impaired.

To address some of these potential limitations of the HAND criteria, several other definitions of cognitive disorders in people with HIV have been proposed (table 1). These include revisions to the HAND criteria (Gisslén criteria),[16] the global deficit score criteria,[17] and, more recently, a multivariate normative comparison score.[18] These criteria do appear to categorise substantially lower numbers of people with HIV as having cognitive impairment,[20] with further clinical validation required.

	Details	Considerations
HIV-associated neurocognitive disorders (HAND)[13]	Also known as the Frascati criteria; three categories: asymptomatic neurocognitive impairment, mild neurocognitive disorders, and HIV-associated dementia; cognitive impairment defined if two or more cognitive domain scores are at least one standard deviation below expected	One of the first classifications proposed in the effective ART era; disadvantages are a lack of clinical significance of asymptomatic neurocognitive impairment and high rates of cognitive disorders reported due to high rates of asymptomatic neurocognitive impairment (ie, false positive cases are probably being observed)
Gisslén criteria[16]	More stringent definition of the HAND criteria, whereby domain scores are required to be 1·5 standard deviations lower than expected to fulfil the HAND criteria	This definition assists in reducing the high rates of cognitive disorders reported with the HAND criteria
Global deficit score[17]	The average deficit score of all demographically adjusted cognitive domain scores is calculated, with impairment defined using a prespecified threshold	Might be more comparable to a clinical rating as all domains are taken into consideration
Multivariate normative comparison[18]	Using a study-specific control group as a reference, a multivariate statistic (Hotelling's T^2) is calculated utilising all cognitive domains	Disadvantage is that a study-specific control group is required
Novel multivariate method[19]	As multivariate normative comparison but using the Mahalanobis distance as statistical correction	As cognitive testing is multidimensional (many measurements), a multidimensional measure of deviation from the mean is utilised (the Mahalanobis distance)

ART=antiretroviral therapy.

Table 1: **Research definitions of cognitive impairment**

Clinical diagnosis

A diagnosis of HIV-associated cognitive impairment is a diagnosis of exclusion, where other contributing factors have either been excluded or optimally managed, and a clinical diagnosis of the condition should also be based on results from formal neuropsychiatric testing.

As outlined previously, people with HIV frequently have concurrent medical conditions and lifestyle factors that can affect overall cognitive function. Medical conditions that can affect cognitive function include depression, anxiety and other mental health illnesses, liver disease, and cardiovascular disease.[21] The treatments for these medical conditions, which might include psychoactive medications that impact cognition, are also potential factors in cognitive impairment in this population. Lifestyle factors that can affect cognition include excessive alcohol intake, the use of recreational drugs, and tobacco smoking.

Screening

Outside of the field of HIV medicine and HIV-related cognitive impairment, the role of screening programmes for cognitive disorders is a hotly debated topic. Advocates for cognitive screening programmes argue that they are necessary because not all individuals recognise the early symptoms of cognitive decline, and that individuals can be asymptomatic in the early stages. Also, the early recognition of cognitive disorders

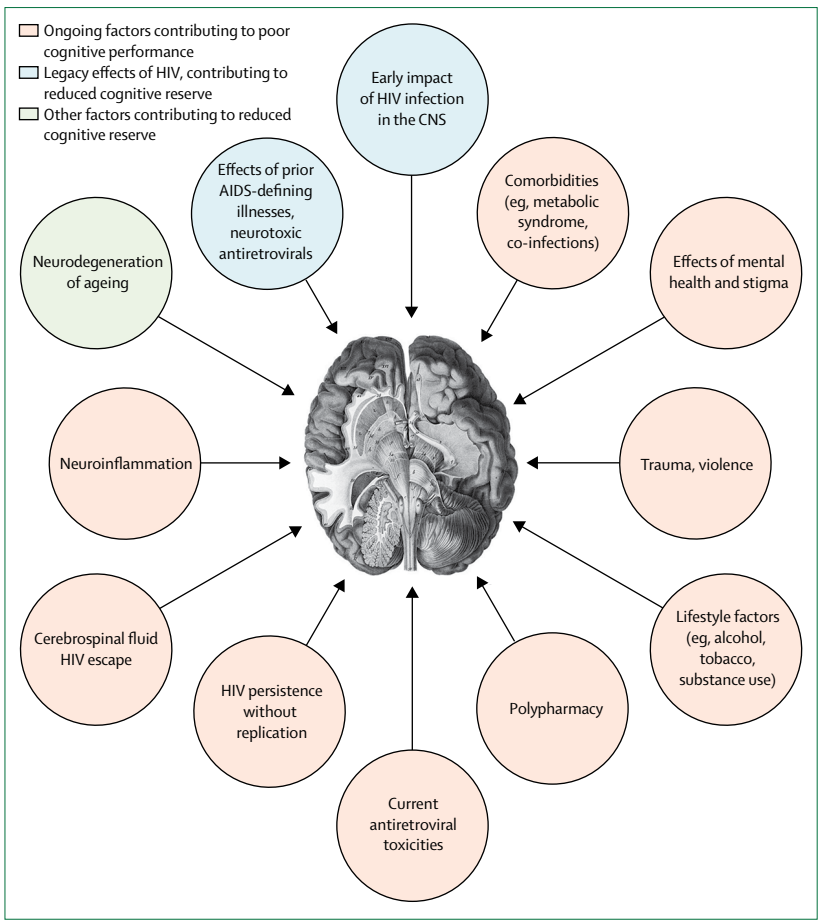

Figure: **Potential contributing factors to cognitive impairment in people with HIV**
No single definitive pathogenic mechanism underlying cognitive disorders in people with HIV has been proposed. Rather, several mechanisms have been considered, with the underlying pathogenesis in many individuals likely to be multifactorial. These mechanisms can be considered as active or ongoing insults to cognitive function, or historical. Several contributing aetiologies directly associate with HIV infection and treatment, while others, such as mood disorders, substance use, and polypharmacy are conditions that may commonly affect people with HIV rates than those without HIV.

permits interventions to be established which might halt or slow the progression of the disease. Arguments against the mass screening programmes for cognitive impairment include the health-care anxiety that screening programmes in general create, the health-care anxiety of patients being told they have a cognitive disorder when they are otherwise asymptomatic, and the lack of interventions that are currently available to prevent disease progression.

The arguments for and against mass screening for cognitive disorders in the context of HIV do not differ greatly from the aforementioned arguments, however a few disease-specific aspects to consider exist. For example, are screening tools sensitive for HIV-associated cognitive impairment? The phenotype of HIV-associated cognitive impairment in the suppressive ART era is one where the subcortical domains of attention, fine movement, learning, and executive function are predominantly affected, and therefore screening batteries that focus on such domains might have a higher sensitivity for HIV-related cognitive disorders. Several such batteries have been developed, including the International HIV Dementia Scale,[22] and the HIV Dementia Scale. Several studies have also compared the utility of screening with different cognitive batteries. Importantly, these studies have focused on the utility of screening batteries in resource-limited settings, where formal neuropsychiatric assessment and mental health assessments might not be widely available.[23]

Pathogenesis and contributing factors

Legacy effects from HIV and its complications

Advances in HIV management over the past 20 years have been unprecedented. Prior to these advances, people with HIV experienced many conditions which may have had long-term effects on brain health, such as clinically evident AIDS-defining CNS infections and cancers, and toxicities from the initial generations of antiretroviral drugs. Additionally, processes associated with cognitive disorders in HIV, including neuroinflammation,[24,25] brain atrophy,[26,27] and injury to neurons, as detected via the cerebrospinal fluid and neuroimaging,[28] can be initiated and progressively worsen during early untreated HIV infection. While these processes appear to be attenuated once ART is started and viral suppression is achieved, the lengthy duration of HIV infection in many people with HIV prior to initiation of therapy might lead to a subtle but lasting neural dysfunction. Although these legacies are not ongoing or necessarily progressive during modern stable treatment regimens, the resultant detrimental effects on cognitive reserve, which does not recover, may be apparent several decades later. For individuals who have experienced these so-called legacy effects and therefore have a reduced cognitive reserve, current insults to the CNS, including natural changes with ageing, might have a greater impact (figure).

Neuroinflammation

Activation of the innate and adaptive immune systems, immunosenescence, and chronic inflammation are widely reported features of ART-treated HIV disease.[29] This persistent immune activation and inflammation in people with HIV on otherwise suppressive ART is postulated to be a major driver of many age-related non-infectious comorbidities, and a major driver of cognitive disorders.

Activated immune cells, some of which are HIV-infected, invade the CNS and can result in neuroinflammation and propagation of HIV infection to resident cells within the brain and adjacent nervous system tissues. Elevated concentrations of soluble markers of monocyte activation and inflammation in the cerebrospinal fluid in people with HIV on suppressive ART provides evidence of such neuroinflammation.[30] The association between

elevated concentrations of inflammatory markers and cognitive impairment in people with HIV on ART suggests that cognitive disorders might be in part a consequence of persistent neuroinflammation despite ART.[31] Imaging studies utilising PET have also suggested increased binding of PET ligands, which bind to activated microglial cells, in otherwise effectively treated people with HIV, and suggested an association between increased microglial activation in some brain regions and reduced performance on cognitive tests.[32,33]

Unlike the legacy effects of HIV, which are unlikely to be causing progressive damage to the CNS or progressive cognitive decline, neuroinflammation could be causing persistent damage, and could result in an accelerated decline in cognitive performance.

Antiretroviral toxicities

Given the sharp decline in frank HIV-dementia since the availability of virologically effective ART, there can be little doubt that, in general, ART is beneficial with regard to cognitive function and brain health in people with HIV on a population level. Nonetheless, several antiretroviral drugs have known central nervous system toxicities that might have an impact on cognitive health.

The non-nucleoside reverse transcriptase inhibitor efavirenz has a wide array of neuropsychiatric side effects, with effects on sleep, abnormal dreams, and anxiety recognised early in the drug's development as being associated with the drug.[34] Awareness of these toxicities allowed clinicians to inform people with HIV commencing efavirenz of these frequently observed adverse events. It was not until several years later that studies reported poorer cognitive performance in cohorts of people with HIV receiving efavirenz-based ART than those on other regimens.[35] Improvement in cognitive function has been observed in people with HIV who have ceased taking efavirenz-based ART.[36,37]

Neuropsychiatric side effects are reported with the integrase-strand transfer inhibitors. These neuropsychiatric side-effects differ markedly in several aspects from the adverse events reported with efavirenz. First, during the licensing studies no specific neuropsychiatric toxicities were observed with these drugs, with reports instead occurring in postlicensing cohort data.[38] Why such effects were not apparent in phase 3 development programmes is unclear, but might be due to differences in the characteristics of participants who enter drug development programmes compared with the characteristics of the wider population of people with HIV, or due to a lack of ascertainment of such toxicities in phase 3 programmes. Second, unlike efavirenz, the integrase-strand transfer inhibitor toxicities are not apparent in most individuals, but rather only in specific at-risk populations, such as those with underlying depression or anxiety, and older individuals. This could also help explain why these adverse events were not observed within the clinical trials, as this phenotype of participant might have been less likely to enter a clinical trial (the predominant phenotype of people with HIV in drug development studies has traditionally been young white men). Third, the reported toxicities from integrase-strand transfer inhibitors are predominantly insomnia and anxiety, with no reports thus far describing a specific effect on cognition. However, vigilance for potential effects of the integrase-strand transfer inhibitors on cognitive performance would be prudent, given it took several years to recognise such an effect from efavirenz use.

In addition to clinical evidence of CNS toxicities caused by antiretroviral drugs outlined previously, laboratory and imaging studies have suggested potential mechanisms whereby antiretroviral drugs could have neuronal toxicities. Neuronal cell culture studies have observed toxicities from several of the antiretroviral drugs in current clinical use.[39] Potential proposed toxicities include mitochondrial toxicities and direct neuronal toxicities. MRI spectroscopy and functional imaging studies have also provided insight into potential toxicities, with reductions in neuronal integrity metabolites observed in people with HIV receiving older nucleoside reverse transcriptase inhibitors on spectroscopy, and differing effects on blood oxygen dependent contrast between different antiretroviral combinations on functional MRI.[40]

Cerebrospinal fluid HIV RNA escape and HIV persistence

With modern antiretroviral regimens, suppression of plasma HIV RNA is achievable in most treated individuals. Systemic ART is also very effective at suppressing HIV RNA in other body compartments, including suppressing cerebrospinal fluid HIV RNA. However, rarely, cerebrospinal fluid HIV RNA can be detectable when plasma HIV RNA is not detectable, or cerebrospinal fluid HIV RNA levels might be greater than plasma HIV RNA ones. This scenario is generally termed cerebrospinal fluid HIV RNA escape.[41,42]

In cases where detectable cerebrospinal fluid HIV RNA is an incidental finding, a conservative approach is generally recommended, with ongoing clinical monitoring of the individual to ensure symptoms do not develop. Such scenarios would include people with HIV, who are otherwise asymptomatic, undergoing lumbar puncture examination for research programmes.

In the context of symptomatic individuals, and, of relevance here, in individuals with new or worsening cognitive symptoms, cerebrospinal fluid HIV RNA should generally not be ignored, with detailed management described later on.

Risk factors for cerebrospinal fluid HIV RNA escape include a prior history of antiretroviral drug resistance, which can lead to ART treatment failure in the CNS compartment, often without evidence of such failure in the plasma compartment, and a low nadir CD4 lymphocyte count. It is plausible that advanced immunosuppression and prolonged untreated HIV results in more extensive CNS HIV infection and inflammation,

which could lead to compartmentalised replication and emergence of drug resistance during ART. The exposure and effect of antiretroviral drugs within sanctuary sites of the body might also have impact on cerebrospinal fluid escape. Indeed, reports have described the use of ART regimens containing boosted protease inhibitors as a significant risk factor for cerebrospinal fluid HIV RNA escape.[43] Boosted protease inhibitors have a relatively low cerebrospinal fluid inhibitory quotient (concentration of free drug compared to the inhibitory concentration required to suppress HIV replication) providing credence to this hypothesis. However, it should be noted that ART regimens based on boosted protease inhibitors are generally reserved for people with HIV with drug-resistant HIV strains, and teasing out whether it is the presence of HIV drug resistance, or pharmacokinetic and pharmacodynamics drivers that cause the cerebrospinal fluid HIV RNA escape is challenging.

More recently, detection of HIV infected cells[44] and HIV proteins[45] in cerebrospinal fluid from people with HIV on sustained effective ART has been associated with reduced cognitive performance, although further studies are needed to determine whether HIV persistence in the CNS without viral replication is causally related to ongoing cognitive impairment.

Lifestyle factors

Factors that might predispose to cognitive disorders, particularly cigarette smoking, substance abuse, and alcohol misuse, are highly prevalent in people with HIV. Over the past 10 years, substantial changes in recreational drug use have been seen, especially in men who have sex with men, including so-called chemsex, which refers to drug use to facilitate sexual intercourse and includes the use of mephedrone and crystallised methamphetamine.[46] Not only can substance use directly affect cognitive health via the direct toxicities to the CNS, but also via pharmacological interactions with antiretroviral drugs and concomitant medication.

Ageing and comorbidities

Many cohort studies have reported the prevalence of non-infectious comorbidities to be more highly prevalent in people with HIV than those without HIV, even when compared with lifestyle-similar HIV-negative controls.[12] It is well documented in the literature that the presence of non-infectious comorbidities can impact negatively on cognitive function, with this observation replicated in HIV cohorts.[47] Infectious comorbidities are also more frequent in people with HIV, including sexually transmitted infections. Cytomegalovirus,[48] syphilis,[49] and *Mycobacterium tuberculosis*[50] infection have each been associated with poorer cognitive function, although whether this association results from direct effects of pathogens, immune responses, or unrecognised factors that increase risk of coinfections and cognitive impairment is unknown.[51]

How the ageing process will affect people with HIV and how such effects will impact on cognitive performance over time is an area of controversy. Another area of debate is whether an accelerated ageing phenotype exists in people with HIV on ART. With regards to cognitive performance and the context of an accelerated ageing phenotype, the question is whether the natural decline in cognitive performance observed with ageing, is more marked, or accelerated, in people with HIV than in the general population. Some longitudinal studies have suggested an accelerated cognitive ageing phenotype to be present in people with HIV,[52–54] with other studies suggesting that age-related cognitive decline is similar in people with HIV and lifestyle-similar controls.[55] Differences in the characteristics of the cohorts and study design might explain these inconsistencies, with further longitudinal studies with closely and carefully matched control groups required to evaluate this important question.

The management of older individuals with multiple comorbidities often involves polypharmacy. Cognitive decline associated with concomitant medication use and polypharmacy is well described, and is probably an important factor driving cognitive disorders in older people with HIV.[56] Different concomitant medications can have differing impacts on cognitive performance, with data suggesting anticholinergic, anxiolytic, anticonvulsant, and opioid medication has a greater impact than other types of medication.[57]

Mental health and stigma

High rates of depression and other mental health conditions have been described in people with HIV since the start of the epidemic. Prior to the advent of effective ART, with the very poor prognosis associated with HIV disease, such high rates of depression were not unexpected. However, why such high rates of depression continue to exist in people with HIV with otherwise effectively treated HIV disease remains unclear. Potential explanations include heightened rates of mood disorders in individuals at risk of acquiring HIV; living with a medical condition that remains highly stigmatised, with this stigma manifesting clinically as anxiety and depression; the neuropsychiatric toxicities of ART, manifesting as depressive symptoms; and residual or progressive neuroinflammation leading to depressive symptoms. For some individuals, the heightened rates of mood disorders might relate to historical events such as childhood trauma and violence, and a history of post-traumatic stress disorder, rates of which may be higher in people with HIV.[58]

Whatever the underlying pathogenesis of depression and other mental health conditions in people with HIV, these conditions are probably relevant when considering cognitive disorders. Depression can manifest as concentration difficulties and significantly affect overall cognitive performance. Over recent years, the impact of

	Mechanism of action	Study population (people living with HIV)	Result
OPC-14117[59]	Lipophilic antioxidant	Cognitive impairment (n=30)	No change in cognitive scores
Thioctic acid and selegiline[60]	Antioxidant and monoamine oxidase B inhibitor	Cognitive impairment (n=36)	Thioctic acid had no effect on cognitive performance; and selegiline was associated with improvement in tests of verbal memory
Peptide T[61]	Block envelope protein gp120 binding to brain	Cognitive impairment (n=215)	Improved cognitive performance in those with global deficit score of at least 0·5
Nimodipine[62]	Calcium channel blocker	HIV-associated dementia (n=41)	No significant change in global cognitive score
Selegiline[63,64]	Monoamine oxidase B inhibitor	Cognitive impairment (n=30)[63] and (n=125)[64]	Selegiline group performed better on delayed recall and grooved pegboard than control group; no significant change in global cognitive performance
CPI-1189[65]	Antioxidant and TNF-α blocker	Mild to moderate cognitive impairment (n=64)	No effect on cognitive performance
Valproic acid[66]	Histone deacetylase inhibitor	With and without cognitive impairment (n=22)	No significant improvement in cognitive function
Memantine[67]	NMDA receptor antagonist	Cognitive impairment (n=99)	Improvement in cognitive function over 12 weeks; however, not sustained over 48 weeks
Minocycline[68]	Tetracycline antibiotic	Cognitive impairment (n=107)	No significant improvement in overall cognitive function
Rivastigmine[69]	Acetylcholinesterase inhibitor	Cognitive impairment (n=17)	Improvement in one measure of attention
Paroxetine and fluconazole[70]	Antidepressant and antifungal	Cognitive impairment (n=45)	Improvements in some measures of cognitive function with paroxetine

TNF=tumor necrosis factor. NMDA=N-methyl-D-aspartate. Interventions were compared with baseline performance, or control group with no drug.

Table 2: **Trialled interventions to improve cognitive function in people with HIV**

mental health on cognitive health has gained increasing attention, with several studies clearly describing a close association between depressive symptoms and overall cognitive function.[51]

Management

ART is the mainstay of treatment for cognitive disorders in HIV. Clinical trials of adjunctive therapeutic interventions, intended to reduce cognitive impairment in people with HIV, have in general shown no effect to date (table 2). As highlighted in table 2, adjunctive therapies that have been trialled have had several mechanisms of action, highlighting the lack of an individual known pathogenic mechanism underlying cognitive disorders in people with HIV.

Several randomised clinical trials of interventions to improve cognition in people with HIV on ART are underway, investigating the effects of ART intensification with maraviroc and dolutegravir (NCT02519777), adjunctive therapy with tesamorelin to address metabolic abnormalities (NCT02572323), and adjunctive therapy with intranasal insulin as a neuroprotective agent (NCT03081117 and NCT03277222). To date, however, the evidence base is lacking and no specific proven intervention for the management of cognitive disorders in people with HIV exists. Thus, management is based on best clinical practice, with several important strategies for consideration.

Management of cerebrospinal fluid HIV RNA escape is an example of an important strategy. Although the evidence is from case series and case reports, it suggests active management of cerebrospinal fluid HIV RNA in neurologically symptomatic individuals can result in substantial clinical improvement.[71] Management comprises of modification of ART on the basis of both historical and current HIV resistance test results from the plasma and cerebrospinal fluid. Given this syndrome is manageable, with evidence for clinical improvement ensuing from active management, the important message is to always actively assess for cerebrospinal fluid HIV RNA escape with cerebrospinal fluid sampling.

Other antiretroviral strategies include assessing and reviewing for toxicities. Individuals on efavirenz-containing ART without other explanations for the cognitive symptoms should be switched to other ART regimens, and vigilance for emerging toxicities from newer antiretroviral agents and classes is required.

In any Review of cognitive disorders in people with HIV, the clinical penetration effectiveness score needs to be mentioned. The clinical penetration effectiveness score is a pharmacokinetic and pharmacodynamic scoring system, which rates antiretroviral agents based on their hypothetical antiviral activity in the central nervous system.[72] Although in principle, pharmacokinetic and pharmacodynamic scoring systems are of interest, the evidence base to determine ART for an individual on the basis of such scoring systems is lacking, and basic evidence-based principles for determining optimal ART should always prevail. Such principles include using guideline-based ART regimens, as these are the regimens with the greatest evidence base, and regimens based on HIV drug resistance testing.

In addition to antiretroviral management, consideration should also be given to the optimal management of other

Search strategy and selection criteria

References for this Review were identified via searches on PubMed with search terms "cognitive", "neurocognitive", "HIV", "dementia", from Jan 1, 1990, until Feb 29, 2020. Only manuscripts published in English were included. A systematic review of all publications was not undertaken; rather we included relevant references for each topic and, where possible, references from more recent calendar years were included.

non-infectious comorbidities and depressive conditions when optimising treatment for people with HIV with cognitive disorders.

Prevention of cognitive disorders

Several of the risk factors for cognitive disorders in people with HIV are avoidable or could be reduced. Regarding the legacy effects of HIV disease, such risk factors are likely to decline in future years. ART is now recommended for all people with HIV, irrespective of disease status or CD4 lymphocyte measurements. Commencing ART early will reduce the duration of time that the brain tissue is exposed to uncontrolled HIV replication, and therefore might reduce CNS damage, neuroinflammation, and potentially rates of cognitive disorders. Benefit of ART irrespective of CD4 lymphocyte count was observed within the Strategic Timing of Antiretroviral Therapy study.[73] Although a neurology substudy of this research did not observe cognitive benefits in patients randomly assigned to immediately commence antiretroviral therapy, such potential benefits could have been mitigated by the majority of participants in the primary study receiving efavirenz-based combination ART regimens (whereby efavirenz use could have mitigated cognitive benefits).[74]

Some recent studies, designed to examine rates of cognitive impairment in people with HIV starting ART early after acquisition of HIV, have suggested rates of cognitive impairment to be similar to the rate in people without HIV.[75,76] Important questions here are how early is early enough, in terms of starting ART, to gain this potential benefit, and whether these findings are durable after many years of ART treatment, which will require additional studies with extended follow-up. Widespread so-called immediate ART treatment schemes, based on likely clinical and public health benefits of starting ART as early as possible after HIV diagnosis,[77] might additionally benefit the brain, especially in individuals identified with acute or recent HIV infection. However, adherence in vulnerable populations started on ART through such programmes will be of critical importance as a determinant of long-term cognitive outcomes.

Future considerations

HIV cure, encompassing HIV eradication (complete elimination of all latent HIV within the host) or the more realistic goal of remission (ability to maintain plasma viral load below the limit of detection without ART), is a desirable goal for people with HIV, given current lifelong challenges of medication adherence, non-AIDS related comorbidities, and stigma, even in those with access to antiretroviral treatment who achieve optimal immune recovery. Controversy exists as to whether the CNS is a barrier to HIV cure efforts, perhaps requiring specific approaches that effectively target the CNS, in addition to systemic sites of HIV latency.[78,79] While varied methods have demonstrated HIV DNA in the cerebrospinal fluid and brains of people with HIV on suppressive ART, it is uncertain whether these virions are capable of replication, and thus able to serve as a source of HIV rebound that would prevent HIV remission if not directly eliminated.

Similarly, it is unclear whether interventions to study HIV cure could be injurious for the brain, given the specific risks of inflammation, neuronal injury, and viral escape in the CNS compartment. ART treatment interruption, undertaken to assess the impact of therapeutic interventions on the potential of ART-free remission, is particularly controversial, since old studies of prolonged interruption showed biomarker evidence of inflammation and injury in the CNS.[80] However, modern interventions typically involve brief and tightly monitored ART interruption, which might not have such deleterious effects in the brain.[81]

Conclusions

Challenges remain in defining, understanding, and treating cognitive dysfunction in people with HIV on ART. Cognitive impairment in the setting of well treated HIV is heterogeneous, and can be due to either or both legacy effects and active processes. In order to optimally develop effective therapies to improve symptoms, it is necessary to differentiate prior versus progressive injury. Clinical trials may need to define so-called biotypes of cognitive impairment on the basis of clinical assessments as well as other biomarkers for correct aetiological diagnosis. Additionally, systemic and central nervous system disease are linked, such that in most cases targeted CNS therapy is probably not necessary and systemic management is sufficient. Exceptions include cases of cerebrospinal fluid HIV RNA escape, where adjustment of ART to address antiretroviral drug resistance or inadequate drug efficacy in the CNS appears to be important. Early initiation of ART may protect the brain, however just how early is necessary remains unknown. The extent to which HIV persistence (latent or active infection) in the CNS relates to clinical symptoms and might present a barrier to HIV cure efforts is uncertain.

Despite these challenges, it is clear that virologically suppressive ART and optimisation of confounding conditions (such as treatment of mood disorders and reduction of lifestyle factors that worsen cognition) are

key aspects of clinical management of cognitive impairment in people with HIV. Additionally, investigation and clinical trials of cognitive impairment in under-resourced settings, where the burden of HIV worldwide is highest, and demographics, lifestyle factors, and treatment options might be different from well-resourced settings that have generated most existing data, is an emerging priority.

Contributors

AW wrote the initial version of the manuscript. SS produced the figure and undertook substantial review of the initial manuscript. Both authors undertook the literature search and approved the final version of the manuscript.

Declaration of interests

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References

1 McArthur JC, Hoover DR, Bacellar H, et al. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. *Neurology* 1993; **43:** 2245–52.

2 May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS* 2014; **28:** 1193–202.

3 Starace F, Bartoli L, Aloisi MS, et al. Cognitive and affective disorders associated to HIV infection in the HAART era: findings from the NeuroICONA study. Cognitive impairment and depression in HIV/AIDS. The NeuroICONA study. *Acta Psychiatr Scand* 2002; **106:** 20–26.

4 Heaton RK, Franklin DR Jr, Deutsch R, et al. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *Clin Infect Dis* 2015; **60:** 473–80.

5 De Francesco D, Underwood J, Post FA, et al. Defining cognitive impairment in people-living-with-HIV: the POPPY study. *BMC Infect Dis* 2016; **16:** 617.

6 Gascón MRP, Vidal JE, Mazzaro YM, et al. Neuropsychological Assessment of 412 HIV-Infected Individuals in São Paulo, Brazil. *AIDS Patient Care STDS* 2018; **32:** 1–8.

7 Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 2010; **24:** 1243–50.

8 Dore GJ, Correll PK, Li Y, Kaldor JM, Cooper DA, Brew BJ. Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS* 1999; **13:** 1249–53.

9 Ian E, Gwen CL, Soo CT, et al. The burden of HIV-associated neurocognitive disorder (HAND) in the Asia-Pacific region and recommendations for screening. *Asian J Psychiatr* 2016; **22:** 182–89.

10 Debalkie Animut M, Sorrie MB, Birhanu YW, Teshale MY. High prevalence of neurocognitive disorders observed among adult people living with HIV/AIDS in Southern Ethiopia: a cross-sectional study. *PLoS One* 2019; **14:** e0204636.

11 d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol* 2004; **55:** 320–28.

12 Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* 2014; **59:** 1787–97.

13 Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; **69:** 1789–99.

14 Grant I, Franklin DR Jr, Deutsch R, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology* 2014; **82:** 2055–62.

15 Ferretti F, Mora-Peris B, Underwood J, Waldman A, Everitt A, Winston A. Cognitive impairment in a clinical setting. *J Acquir Immune Defic Syndr* 2018; **77:** e10–13.

16 Gisslén M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? *BMC Infect Dis* 2011; **11:** 356.

17 Carey CL, Woods SP, Gonzalez R, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *J Clin Exp Neuropsychol* 2004; **26:** 307–19.

18 Huizenga HM, Smeding H, Grasman RP, Schmand B. Multivariate normative comparisons. *Neuropsychologia* 2007; **45:** 2534–42.

19 Underwood J, De Francesco D, Leech R, Sabin CA, Winston A. Medicalising normality? Using a simulated dataset to assess the performance of different diagnostic criteria of HIV-associated cognitive impairment. *PLoS One* 2018; **13:** e0194760.

20 Underwood J, De Francesco D, Cole JH, et al. Validation of a novel multivariate method of defining HIV-associated cognitive impairment. *Open Forum Infect Dis* 2019; **6:** ofz198.

21 Guaraldi G, Malagoli A, Calcagno A, et al. The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65–74 years and more than 75 years. *BMC Geriatr* 2018; **18:** 99.

22 Sacktor NC, Wong M, Nakasujja N, et al. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. *AIDS* 2005; **19:** 1367–74.

23 Robbins RN, Joska JA, Thomas KG, et al. Exploring the utility of the Montreal Cognitive Assessment to detect HIV-associated neurocognitive disorder: the challenge and need for culturally valid screening tests in South Africa. *Clin Neuropsychol* 2013; **27:** 437–54.

24 Young AC, Yiannoutsos CT, Hegde M, et al. Cerebral metabolite changes prior to and after antiretroviral therapy in primary HIV infection. *Neurology* 2014; **83:** 1592–600.

25 Suh J, Sinclair E, Peterson J, et al. Progressive increase in central nervous system immune activation in untreated primary HIV-1 infection. *J Neuroinflammation* 2014; **11:** 199.

26 Ragin AB, Wu Y, Gao Y, et al. Brain alterations within the first 100 days of HIV infection. *Ann Clin Transl Neurol* 2015; **2:** 12–21.

27 Sanford R, Ances BM, Meyerhoff DJ, et al. Longitudinal trajectories of brain volume and cortical thickness in treated and untreated primary human immunodeficiency virus infection. *Clin Infect Dis* 2018; **67:** 1697–704.

28 Peluso MJ, Meyerhoff DJ, Price RW, et al. Cerebrospinal fluid and neuroimaging biomarker abnormalities suggest early neurological injury in a subset of individuals during primary HIV infection. *J Infect Dis* 2013; **207:** 1703–12.

29 Duffau P, Ozanne A, Bonnet F, et al. Multimorbidity, age-related comorbidities and mortality: association of activation, senescence and inflammation markers in HIV adults. *AIDS* 2018; **32:** 1651–60.

30 Hagberg L, Cinque P, Gisslen M, et al. Cerebrospinal fluid neopterin: an informative biomarker of central nervous system immune activation in HIV-1 infection. *AIDS Res Ther* 2010; **7:** 15.

31 Edén A, Marcotte TD, Heaton RK, et al. Increased intrathecal immune activation in virally suppressed HIV-1 infected patients with neurocognitive impairment. *PLoS One* 2016; **11:** e0157160.

32 Vera JH, Guo Q, Cole JH, et al. Neuroinflammation in treated HIV-positive individuals: A TSPO PET study. *Neurology* 2016; **86:** 1425–32.

33 Rubin LH, Sacktor N, Creighton J, et al. Microglial activation is inversely associated with cognition in individuals living with HIV on effective antiretroviral therapy. *AIDS* 2018; **32:** 1661–67.

34 Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 1999; **341:** 1865–73.

35 Ciccarelli N, Fabbiani M, Di Giambenedetto S, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology* 2011; **76:** 1403–09.

36 Hakkers CS, Arends JE, van den Berk GE, et al. Objective and subjective improvement of cognition after discontinuing efavirenz in asymptomatic patients: a randomized controlled trial. *J Acquir Immune Defic Syndr* 2019; **80:** e14–22.

37 Vera JH, Bracchi M, Alagaratnam J, et al. Improved central nervous system symptoms in people with HIV without objective neuropsychiatric complaints switching from efavirenz to rilpivirine containing cART. *Brain Sci* 2019; **9:** E195.

38 de Boer MG, van den Berk GE, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. *AIDS* 2016; **30:** 2831–34.

39 Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. *J Neurovirol* 2012; **18:** 388–99.

40 Underwood J, Robertson KR, Winston A. Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease? *AIDS* 2015; **29:** 253–61.

41 Ferretti F, Gisslen M, Cinque P, Price RW. Cerebrospinal fluid HIV escape from antiretroviral therapy. *Curr HIV/AIDS Rep* 2015; **12:** 280–88.

42 Winston A, Antinori A, Cinque P, et al. Defining cerebrospinal fluid HIV RNA escape: editorial review AIDS. *AIDS* 2019; **33** (suppl 2)**:** S107–11.

43 Pérez-Valero I, Ellis R, Heaton R, et al. Cerebrospinal fluid viral escape in aviremic HIV-infected patients receiving antiretroviral therapy: prevalence, risk factors and neurocognitive effects. *AIDS* 2019; **33:** 475–81.

44 Spudich S, Robertson KR, Bosch RJ, et al. Persistent HIV-infected cells in cerebrospinal fluid are associated with poorer neurocognitive performance. *J Clin Invest* 2019; **129:** 3339–46.

45 Henderson LJ, Johnson TP, Smith BR, et al. Presence of Tat and transactivation response element in spinal fluid despite antiretroviral therapy. *AIDS* 2019; **33** (suppl 2)**:** S145–57.

46 McCall H, Adams N, Mason D, Willis J. What is chemsex and why does it matter? *BMJ* 2015; **351:** h5790.

47 Wright EJ, Grund B, Robertson K, et al. Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. *Neurology* 2010; **75:** 864–73.

48 Letendre S, Bharti A, Perez-Valero I, et al. Higher anti-cytomegalovirus immunoglobulin G concentrations are associated with worse neurocognitive performance during suppressive antiretroviral therapy. *Clin Infect Dis* 2018; **67:** 770–77.

49 Marra CM, Deutsch R, Collier AC, et al. Neurocognitive impairment in HIV-infected individuals with previous syphilis. *Int J STD AIDS* 2013; **24:** 351–55.

50 Robertson KR, Oladeji B, Jiang H, et al. Human immunodeficiency virus type 1 and tuberculosis coinfection in multinational, resource-limited settings: increased neurological dysfunction. *Clin Infect Dis* 2019; **68:** 1739–46.

51 De Francesco D, Winston A, Underwood J, et al. Cognitive function, depressive symptoms and syphilis in HIV-positive and HIV-negative individuals. *Int J STD AIDS* 2019; **30:** 440–46.

52 Clifford KM, Samboju V, Cobigo Y, et al. Progressive brain atrophy despite persistent viral suppression in HIV patients older than 60 years. *J Acquir Immune Defic Syndr* 2017; **76:** 289–97.

53 Sheppard DP, Iudicello JE, Morgan EE, et al. Accelerated and accentuated neurocognitive aging in HIV infection. *J Neurovirol* 2017; **23:** 492–500.

54 Goodkin K, Miller EN, Cox C, et al. Effect of ageing on neurocognitive function by stage of HIV infection: evidence from the Multicenter AIDS Cohort Study. *Lancet HIV* 2017; **4:** e411–22.

55 Cole JH, Caan MWA, Underwood J, et al. No evidence for accelerated aging-related brain pathology in treated human immunodeficiency virus: longitudinal neuroimaging results from the comorbidity in relation to AIDS (COBRA) project. *Clin Infect Dis* 2018; **66:** 1899–909.

56 Falutz J, Kirkland S, Guaraldi G. Geriatric syndromes in people living with HIV associated with ageing and increasing comorbidities: implications for neurocognitive complications of HIV infection. *Curr Top Behav Neurosci* 2020; published online Jan 7. DOI:10.1007/7854_2019_119.

57 Rubin LH, Radtke KK, Eum S, et al. Cognitive burden of common non-antiretroviral medications in HIV-infected women. *J Acquir Immune Defic Syndr* 2018; **79:** 83–91.

58 Rubin LH, Pyra M, Cook JA, et al. Post-traumatic stress is associated with verbal learning, memory, and psychomotor speed in HIV-infected and HIV-uninfected women. *J Neurovirol* 2016; **22:** 159–69.

59 The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders. Safety and tolerability of the antioxidant OPC-14117 in HIV-associated cognitive impairment. *Neurology* 1997; **49:** 142–46.

60 The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders. A randomized, double-blind, placebo-controlled trial of deprenyl and thioctic acid in human immunodeficiency virus-associated cognitive impairment. *Neurology* 1998; **50:** 645–51.

61 Heseltine PN, Goodkin K, Atkinson JH, et al. Randomized double-blind placebo-controlled trial of peptide T for HIV-associated cognitive impairment. *Arch Neurol* 1998; **55:** 41–51.

62 Navia BA, Dafni U, Simpson D, et al. A phase I/II trial of nimodipine for HIV-related neurologic complications. *Neurology* 1998; **51:** 221–28.

63 Sacktor N, Schifitto G, McDermott MP, Marder K, McArthur JC, Kieburtz K. Transdermal selegiline in HIV-associated cognitive impairment: pilot, placebo-controlled study. *Neurology* 2000; **54:** 233–35.

64 Schifitto G, Zhang J, Evans SR, et al. A multicenter trial of selegiline transdermal system for HIV-associated cognitive impairment. *Neurology* 2007; **69:** 1314–21.

65 Clifford DB, McArthur JC, Schifitto G, et al. A randomized clinical trial of CPI-1189 for HIV-associated cognitive-motor impairment. *Neurology* 2002; **59:** 1568–73.

66 Schifitto G, Peterson DR, Zhong J, et al. Valproic acid adjunctive therapy for HIV-associated cognitive impairment: a first report. *Neurology* 2006; **66:** 919–21.

67 Zhao Y, Navia BA, Marra CM, et al. Memantine for AIDS dementia complex: open-label report of ACTG 301. *HIV Clin Trials* 2010; **11:** 59–67.

68 Nakasujja N, Miyahara S, Evans S, et al. Randomized trial of minocycline in the treatment of HIV-associated cognitive impairment. *Neurology* 2013; **80:** 196–202.

69 Simioni S, Cavassini M, Annoni JM, et al. Rivastigmine for HIV-associated neurocognitive disorders: a randomized crossover pilot study. *Neurology* 2013; **80:** 553–60.

70 Sacktor N, Skolasky RL, Moxley R, et al. Paroxetine and fluconazole therapy for HIV-associated neurocognitive impairment: results from a double-blind, placebo-controlled trial. *J Neurovirol* 2018; **24:** 16–27.

71 Soulié C, Fourati S, Lambert-Niclot S, et al. HIV genetic diversity between plasma and cerebrospinal fluid in patients with HIV encephalitis. *AIDS* 2010; **24:** 2412–14.

72 Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol* 2008; **65:** 65–70.

73 Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373:** 795–807.

74 Wright EJ, Grund B, Robertson KR, et al. No neurocognitive advantage for immediate antiretroviral treatment in adults with greater than 500 CD4+ T-cell counts. *AIDS* 2018; **32:** 985–97.

75 Crum-Cianflone NF, Moore DJ, Letendre S, et al. Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. *Neurology* 2013; **80:** 371–79.

76 Evering TH, Applebaum A, La Mar M, Garmon D, Dorfman D, Markowitz M. Rates of non-confounded HIV-associated neurocognitive disorders in men initiating combination antiretroviral therapy during primary infection. *AIDS* 2016; **30:** 203–10.

77 Coffey S, Bacchetti P, Sachdev D, et al. RAPID antiretroviral therapy: high virologic suppression rates with immediate antiretroviral therapy initiation in a vulnerable urban clinic population. *AIDS* 2019; **33:** 825–32.

78 Nath A, Clements JE. Eradication of HIV from the brain: reasons for pause. *AIDS* 2011; **25:** 577–80.

79 Hellmuth J, Valcour V, Spudich S. CNS reservoirs for HIV: implications for eradication. *J Virus Erad* 2015; **1:** 67–71.

80 Gisslén M, Rosengren L, Hagberg L, Deeks SG, Price RW. Cerebrospinal fluid signs of neuronal damage after antiretroviral treatment interruption in HIV-1 infection. *AIDS Res Ther* 2005; **2:** 6.

81 Julg B, Dee L, Ananworanich J, et al. Recommendations for analytical antiretroviral treatment interruptions in HIV research trials-report of a consensus meeting. *Lancet HIV* 2019; **6:** e259–68.