INTRODUCTION

Affecting 38 million individuals worldwide, with 1.7 million newly infected patients in 2019, the global burden imposed by HIV cannot be overstated. Although HIV is notorious for its devastating impact on the cellular immune system, it also instigates direct pathology in the central nervous system (CNS), culminating in a group of syndromes of impaired cognition and functionality, known collectively as HIV-associated neurocognitive disorders (HAND). The implementation of combination antiretroviral therapy (cART) since 1996 has greatly revolutionized HIV prognosis, transforming it to a chronic disease where patient life expectancy resembles that of uninfected cohorts. The combination of multiple antiretroviral agents from different classes targeting the viral life cycle at distinct points reduces the risk of developing resistance to a...
single agent, as well as potently suppressing viral replication. In addition to decreasing mortality attributed to opportunistic infections, cART has more than halved the incidence of HIV-associated dementia (HAD), the most severe form of HAND, from around 20% in the pre-cART era to below 5% [1]. Nevertheless, the milder forms of HAND, asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), not only persist in the cART era but also numerous studies have observed higher rates and severity of ANI following the introduction of cART [1,2]. In addition to the devastating repercussions on the quality of life, the endurance of cognitive disorders also perturbs cART adherence which has serious implications for increased mortality and the development of cART resistance [3]. The explanations proposed for this phenomenon range from persistent CNS HIV replication, ineffective CNS penetration of cART, to the long-term neurotoxicity of cART regimens. Despite a plethora of preclinical and clinical studies, these conflicting hypotheses have proved challenging to reconcile. This review will examine the role of cART in the endurance of HAND by evaluating several of the factors implicated in persistent HAND pathogenesis†.

CONTROVERSIES IN HAND PREVALENCE

Highly potent cART has transformed the nature of HAND. In the pre-cART era, a progressive subcortical dementia was most commonly observed, whereas cortical impairments now comprise the most frequently affected domains in the cART era [4]. Evidently the concept of HAND has evolved which has necessitated a revision of the diagnostic criteria, which previously failed to emphasize these cognitive deficits alongside the presence of cognitive impairment without overt functional decline. The pre-eminent methodology for classifying HAND is the Frascati criteria, outlined in Table 1 [5].

The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study is the largest cross-sectional study to investigate the prevalence of HAND in HIV-infected adults in the era of cART [2]. Using standardized neuropsychological examinations and classification according to the Frascati criteria, the study demonstrated cognitive impairment rates of 52%. A subsequent smaller-scale investigation of 200 HIV patients undergoing cART estimated the prevalence of HAND to be as high as 69% despite plasma aviraemia, implying the insufficiency of current cART regimens for eradicating HAND [6]. Nonetheless, given the significant discrepancy between the HAND rates posited by these two studies, the actual prevalence of HAND in the cART era has been challenged. Although the CHARTER study had a broad inclusion criteria to facilitate a large sample size, the study is limited as patients had highly variable levels of HIV suppression and many had comorbidities including major depression and Hepatitis C, whereas the aviraemic investigation excluded these comorbidities. Thus, inconsistencies in the severity and presence of comorbidities could underlie the differential rates of HAND. The Frascati criteria itself have been criticized as the accuracy of HAND classification is centred upon how faithfully the normative population reflects the test population. In developing nations where HIV is most prevalent, the lack of appropriate normative data severely limits the validity of the conclusions drawn. Moreover, the Frascati criteria have been implicated in inflating cognitive impairment rates as the definition of ANI may be too inclusive, resulting in a false-positive rate of 16–21% [7]. Although the Frascati criteria recommend the use of two neuropsychological tests per cognitive domain, it is not mandatory; the CHARTER study used only a single test per domain which may further inflate the false-positive rate.

Evidently, a more uniform exclusion criterion of confounding comorbidities needs to be enforced, alongside collection of locally derived normative data. A more consistent selection and number of neuropsychological tests for each domain will also increase the comparability of trial results, while the use of biological markers and neuroimaging techniques, notably functional magnetic resonance imaging and positron emission tomography, would strengthen the conclusions drawn to aid HAND classification [8-11]. Finally, the

| Neurocognitive status | Functional Status |
|-----------------------|------------------|
| HIV-associated dementia | 2 standard deviations below the demographically corrected mean in two cognitive domains | Marked interference with daily functioning |
| Mild neurocognitive disorder | 1 standard deviation below the demographically corrected mean in two cognitive domains | Mild interference with daily functioning |
| Asymptomatic neurocognitive impairment | 1 standard deviation below the demographically corrected mean in two cognitive domains | No interference with daily functioning |

Neurocognitive status determined by assessing attention/working memory, speed of information processing, language, memory, abstraction/executive and sensory-perceptual/motor skill domains. Neuropsychological test scores compared with those of education/age matched controls in a normative population. Functional status determined by self-reporting. Diagnosis of HAND requires the exclusion of any confounding factors/comorbidities which could account for the cognitive impairment.
Frascati definition of ANI should be modulated to reduce the false-positive rate, for instance by increasing the cut-off to below 1.5 SD.

**HIV CEREBROSPINAL FLUID VIRAL ESCAPE IMPLICATIONS FOR CNS cART RESISTANCE AND TIMING OF cART INITIATION**

The phenomenon of HIV discordance, also known as cerebrospinal fluid (CSF) viral escape, describes the occurrence of detectable HIV RNA in the CSF with undetectable HIV replication in the plasma. Given that concentrations of cART in the CNS ((cART)\textsubscript{CNS}) are much lower than those in the plasma, suboptimal (cART)\textsubscript{CNS} may allow continued HIV replication in the CNS with subsequent evolution of drug resistance [12]. Notably, a study using HIV-infected human macrophages and patient CSF demonstrated that despite effective cART, persistent low-level viraemia culminates in the production of viral RNA and protein which is packaged and released from extracellular vesicles [13]. Although the use of human-induced pluripotent stem cell (hiPSC)-derived microglia and perivascular macrophages (only CNS cells capable of productive infection) would strengthen the relevance to HAND, the implication of cART inadequacy in controlling viraemia is evident. Whilst HIV discordance is estimated to affect only 10% of patients, [14] the recent genotypic and phenotypic characterization of viral reservoirs in asymptomatic patients with HIV discordance identified distinct mechanisms of how the reservoirs are established [15]. Although the small sample size of three patient reservoirs limits the conclusions drawn, elucidating the origin of viral escape will certainly aid its eradication. Retrospective analyses have also identified viral escape in patients with progressive neurological dysfunction. Notably, resistance to at least one drug in the cART regimen was common, where most patients showed neurological improvements with reduced CSF viral replication when the cART regimen was adjusted with respect to both CNS penetration and resistance [12,16]. Although these findings support the introduction of CSF HIV drug resistance testing in patients with persistent neurological dysfunction, the follow-up data are incomplete, as studies were stopped when symptoms resolved [16]. Manifestly, the dynamics and consequences of residual CNS HIV replication need to be more thoroughly investigated using longitudinal trials incorporating phylogenetic evaluations.

Strikingly, both retrospective studies observed patient histories of advanced immunosuppression, with many reporting nadir CD4 T-cell counts $< 100$ cells/µL [12,16]. Likewise, the CHARTER cohort demonstrated that lower nadir CD4 is associated with greater odds of neuropsychological impairment [17]. Given that low nadir CD4 is a robust predictor of cognitive impairment in both the pre-cART and cART eras, this suggests that severe immunosuppression could represent a ‘legacy event’ which increases the risk of enhanced CNS infection and compartmentalization, where earlier initiation of cART may reduce the risk of developing HAND [4]. However, these studies are limited as nadir CD4 was determined by self-report and is thus susceptible to recall bias. Nevertheless, the significance of nadir CD4 was reinstated by the pivotal Strategic Timing of Antiretroviral Therapy (START) study, which established that commencing cART in HIV patients with CD4 counts > 500 cells/µL (vs. delaying cART initiation to when the CD4 decreased to 350 cells/µL) conferred net benefits for both serious AIDS-related and non-AIDS-related events [18]. Nonetheless, a neurology sub-study of the START cohort used neuropsychological tests to evaluate changes in neurocognitive performance over 3.4 years, and found that immediate initiation of cART conferred no neurocognitive advantage or disadvantage [19]. Although this disputes the claims of previous investigations suggesting the neurological benefits of cART, [20,21] these prospective studies lacked controls and adjustment for practice effects on neuropsychological tests. However, the follow-up period in the neurology sub-study is short, given that patients require cART for the rest of their lives and that the neurological benefits could precipitate after longer periods of treatment. Moreover, results may have been confounded by the high use of efavirenz, and the neuropsychological test battery may be insufficient to capture the neurological benefits of cART. As the participants were younger than expected, age itself could incur neuropsychological protection against HIV. A truly longitudinal analysis of the cohort with the inclusion of older participants would definitively elucidate cART’s effects on people ageing with HIV, while the measurement of neuronal injury biomarkers and the size of the HIV CSF reservoir could provide more sensitive and comprehensive indicators of neurological benefit.

**CNS PENETRATION EFFECTIVENESS**

Although the blood–brain barrier ensures isolation of the CNS from potentially toxic molecules, the clinical significance of cART penetration across the CNS remains highly disputed. Given that CNS ART penetration is highly variable, it is probable that cART regimens with the greatest CNS penetration effectiveness (CPE) will be more efficacious [22]. Subsequently a CPE ranking system was devised (Table 2). Although studies have consistently demonstrated that cART regimens with higher CPE are associated with lower CSF HIV RNA, the correlation between CPE and neurological benefits remains tenuous [23,24]. Several studies have identified associations between higher CPE cART
regimens and improved neuropsychological performance, which has been corroborated by a cross-sectional analysis demonstrating that each point increase in CPE was accompanied by a 17% reduction in the odds of neuropsychological impairment [25-27]. Nonetheless, the study was limited given its failure to exclude confounding comorbidities, and the cross-sectional design prevented the deduction of temporal links between CPE and neuropsychological performance. By contrast, other studies have failed to demonstrate an association between higher CPE regimens and improved neuropsychological performance while others have even implicated worse neuropsychological performance [24,28,29]. Given the extensive limitations of cross-sectional analyses, randomized trials are crucial for dissecting these conflicting hypotheses; a randomized controlled trial (RCT) found that CNS-targeted cART with higher CPE scores conferred no neuropsychological benefit [30]. However, the trial was statistically underpowered as only 49 patients were assessed, and end-point neuropsychological assessment was conducted after 16 weeks of therapy, which is clearly inadequate given that neurocognitive improvement peaks between 24 and 36 weeks [20].

The lack of consensus could be attributed to the limitations of the CPE system which fail to consider ART-ART interactions or ART neurotoxicity. The consequences of HIV-induced disruption of the blood–brain barrier and the subsequent effects on cART delivery are also not addressed. Furthermore, the CPE system relies upon CSF data so is unable to account for ART efficacy in neural tissue. Notably, in vitro models of astrocytic infection have demonstrated that some nucleoside-analogue reverse transcriptase inhibitor cART regimens are ineffective in suppressing HIV replication at concentrations achieved in the CNS [31]; although this needs to be confirmed by in vivo models, this implies that certain cART regimens are unable to target all HIV-infected cells despite high CPE scores, underscoring an imminent need to understand the effect of cART on cellular CNS HIV reservoirs.

As macrophages and microglia are the main sources of productive HIV infection, a monocyte efficacy (ME) score assessing the effectiveness of cART regimens against infected macrophages has been devised and correlates with neuropsychological performance [32]. However, the score is based on in vitro efficacy data and the patient cohort observed did not include any novel ARTs in their cART regimens, and thus data from in vivo models alongside prospective studies on populations on more current cART regimens are required to validate the efficacy of this ME score. Considering the inconsistency of observations, perhaps a shift is required away from theoretical scores towards measurement of individual [cART]_CSF, which in combination with CSF HIV RNA recordings and drug resistance testing could be used to guide the modification of cART regimens for maximal neuropsychological benefits. Nevertheless, it is important to note that none of the current ARTs directly perturb transcription, thus potentially allowing continued production of viral components such as Trans-Activator of Transcription (Tat) which have known in vitro toxicity. Therefore, the CNS effects of these viral components also form a vital consideration which is yet to be adequately addressed.

**cART NEUROTOXICITY**

Evidence is mounting for the neurotoxicity of certain cART regimens which could mitigate the apparent benefit of higher CPE regimens. The observation that discontinuation of cART resulted in improved neurocognition sustained over a 96-week period, where resumption of cART failed to improve neurocognition, lends support to the implication of cART neurotoxicity in HAND endurance [33]. Moreover, an observational study of almost 62 000 HIV patients estimated that the initiation of a high CPE cART regimen (vs. one with low CPE) increases the risk of HAD by > 70%. Although these conclusions need to be interpreted with caution, as the

**TABLE 2 Central nervous system (CNS) penetration effectiveness (CPE) ranking adapted from Letendre et al. [23]**

| ART drug class                        | CPE score |
|--------------------------------------|-----------|
|                                       | 4         | 3         | 2         | 1         |
| Nucleoside analogue reverse           |           |           |           |           |
| transcriptase inhibitors              |           |           |           |           |
| Zidovudine                           |           |           |           |           |
| Abacavir, emtricitabine               |           |           |           |           |
| Didanosine, lamivudine, stavudine     |           |           |           |           |
| Tenofovir, zalcitabine                |           |           |           |           |
| Nonnucleoside analogue reverse        |           |           |           |           |
| transcriptase inhibitors              |           |           |           |           |
| Nevirapine                           |           |           |           |           |
| Delavirdine, efavirenz                |           |           |           |           |
| Etravirine                           |           |           |           |           |
| Protease inhibitors                  |           |           |           |           |
| Indinavir*                           |           |           |           |           |
| Darunavir*, fosamprenavir*,           |           |           |           |           |
| indinavir, lopinavir*                |           |           |           |           |
| Atazanavir, atazanavir*,             |           |           |           |           |
| fosamprenavir                         |           |           |           |           |
| Nelfinavir, ritonavir, saquinavir,    |           |           |           |           |
| saquinavir*, tipranavir*             |           |           |           |           |
| Entry/fusion inhibitors              |           |           |           |           |
| Maraviroc                            |           |           |           |           |
| Enfuvirtide                          |           |           |           |           |
| Integrase inhibitors                 |           |           |           |           |
| Dolutegravir                         |           |           |           |           |
| Raltegravir                          |           |           |           |           |
| Elvitegravir                         |           |           |           |           |

*Ritonavir-boosted regimen. CPE score calculated from antiretroviral therapy (ART) characteristics (drug chemical properties, [CSF], effectiveness in reducing CSF viraemia). Higher CPE scores are associated with better CNS availability. CPE of combination ART regimen is the sum of each individual ART’s CPE.*
follow-up period is only 3 years, and the Frascati criteria for HAD classification were not used, the use of CPE to select therapy is evidently premature where cART neurotoxicity could underlie shortcomings.

The literature demonstrating cART neurotoxicity is extensive, ranging from perturbed metabolism to enhanced oxidative stress. Metabolic alterations, notably dyslipidaemia and insulin resistance, are prevalent amongst HIV patients where the emerging significance of cART in mediating metabolic derangements forms a compelling aspect of cART neurotoxicity [34]. Given that insulin in the CNS is paramount for neuronal survival and neurogenesis, numerous studies illustrate how ARTs, particularly protease inhibitors (PIs), mediate insulin resistance via diverse mechanisms [35,36]. To strengthen the association between insulin resistance and neurotoxicity, in vivo murine models of ART-induced insulin resistance could be investigated for neurocognitive impairment. Nonetheless, a recent retrospective analysis characterizing the plasma samples of HIV patients before and after 12 months of cART, found that cART failed significantly to attenuate metabolic dysfunction [37]. Although 1 year of follow-up is insufficient to infer causality, and the authors failed to exclude confounding factors such as smoking, a longitudinal analysis evaluating the exposure to cART and metabolic dysregulation will be paramount for dissecting their association and the introduction of adjunct therapies to alleviate metabolic perturbations.

Class and drug-specific mechanisms of direct neurotoxicity have been demonstrated where the new-generation PI, lopinavir, mediated in vitro neurotoxicity via oxidative stress [38]. While highlighting the significance of dissecting the neurotoxicity profiles of novel ARTs, the extremely supraphysiological doses (333-fold higher cf. [drug] CSF in patients), alongside the in vitro rodent cultures, severely limits the relevance of these findings. Nonetheless previous in vitro studies confirm oxidative stress-induced PI neurotoxicity at clinically relevant doses, where in vivo macaque and murine models both illustrated synaptic injury following the administration of common cART regimens at therapeutic concentrations [39]. Given that these effects were mediated after only 7 days of treatment, this certainly necessitates the longitudinal investigation of neurotoxicity. Protease inhibitors also perturb oligodendrocyte maturation, where administration at therapeutic doses reduced cortical myelin protein which was corroborated by post-mortem analysis of cortical tissue derived from HIV patients on cART [40]. Notably, the neurotoxicity of efavirenz is extensively demonstrated by both in vitro analysis and an RCT illustrating that efavirenz discontinuation resulted in neurocognitive improvement in cognitively asymptomatic participants following efavirenz therapy for a mean period of 57.8 months [41,42]. Although longitudinal neuropsychological assessments with the inclusion of patients who have experienced short periods of efavirenz therapy would strengthen the conclusions drawn, the demonstration of efavirenz's neurocognitive side effects even in asymptomatic patients warrants the rationale for removing ARTs with known neurotoxicity.

Nonetheless, prospective studies evaluating the impact of cART regimens on paediatric cognitive impairment have demonstrated that prolonged durations of cART are associated with reduced impairment in several neurodevelopmental cognitive domains [43]. Although the studies have not accounted for the effect of differences between the cART regimens implemented, and have not controlled for the effect of other neurodevelopmental risk factors such as malaria, these findings highlight the overall positive impact of cART regimens and question the significance of cART neurotoxicity on neurodevelopment.

The objective of cART is to establish a therapeutic window, where the [cART] CNS is sufficiently high to suppress viraemia without instigating excessive neurotoxicity. Nevertheless, it is probable that chronic cART regimens incorporating neurotoxic ARTs instigate insidious neuronal disturbances which could underlie HAND endurance. Consequently, in vivo studies are critical for elucidating cART neurotoxicity profiles, where cART regimens could be adjusted accordingly to ensure attainment of an optimal therapeutic window.

**ADJUVANT NEUROPROTECTIVE THERAPIES**

Although cART remains the only therapy to significantly alter the clinical course of HAND, the persistence of cognitive impairment reiterates the insufficiency of current cART regimens. Not only is HAND pathogenesis mediated by the direct viral effects of HIV targeted by cART, but the complex interplay between indirect mechanisms of immune dysregulation and neuroinflammation has also become increasingly significant [44]. Moreover, the pervasive neurotoxicity of several cART regimens further strengthens the rationale for neuroprotective adjuvant therapies. As evidenced by Table 3, although numerous medication classes have been investigated, no clinical trial has illustrated robust cognitive benefits and thus no adjuvant therapies are currently in routine clinical use. Nevertheless, substantial inconsistencies in clinical trial design, including varying primary outcomes, HAND classification, inclusion of confounding factors, duration of < 1 year, and dose selection based on in vitro studies failing to consider interactions with cART regimens, all significantly impair the deduction of efficacy. A two-step trial process has been proposed; a ‘learning phase’ identifies optimal doses and target populations, while the ‘confirming phase’ employs a rigorous longitudinal RCT of cohorts selected after the exclusion of confounding factors [45]. Evidently, the concerted implementation of consistent trial designs will be paramount.
to definitively assessing efficacy. Notably, therapies targeting metabolic perturbations remain relatively unexplored, where the effect of combining adjuvant therapies should also be investigated, and the incorporation of neuroimaging and CSF biomarkers would strengthen the sensitivity of detecting neurological changes.

CONCLUSIONS

The endurance of HAND despite widespread implementation of cART confirms that although cART has immensely ameliorated the prognosis for HIV patients, it remains inadequate in achieving complete functional preservation of the nervous system. As even mild cognitive impairment has significant cumulative effects on independence and quality of life, optimization of cART is paramount. Notably, several of the studies we evaluated falsely presume that all patients are at risk of developing HAND, where including these patients requires large sample sizes that have not been achieved. Progress necessitates the use of large-scale longitudinal RCT designs with the incorporation of biomarkers and neuroimaging to assess the neurological manifestations with enhanced sensitivity. Therapeutic frontiers include interrogating the toxicity of persistent viral proteins unaffected by current cART regimens and the chronic neurotoxicity of cART, as well as detecting HIV discordance and cART resistance testing. The failure of trials evaluating single adjuvant therapies implies the redundancy inherent in HAND pathogenesis, as several mechanisms contribute. Thus, the combination of multiple adjuvant classes represents a promising therapeutic avenue yet to be explored.

ORCID

Ishta Sharma https://orcid.org/0000-0001-9228-9603

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