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Does use of antiretroviral therapy regimens with high central nervous system penetration improve survival in HIV-infected adults?

H McManus[1], **PCK Li**[2], **D Nolan**[3], **M Bloch**[4], **S Kiertiburanakul**[5], **JY Choi**[6], **B Mulhall**[7], **K Petoumenos**[1], **J Zhou**[1], **M Law**[1], **BJ Brew**[8], and **E Wright**[9]

[1]National Centre in HIV Epidemiology and Clinical Research, UNSW, Sydney, NSW, Australia [2]Queen Elizabeth Hospital, Hong Kong, China [3]Department of Clinical Immunology, Royal Perth Hospital, Perth, WA, Australia [4]Holdsworth House General Practice, Sydney, NSW, Australia [5]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand [6]Department of Internal Medicine and AIDS Research Institute, Yonsei University College of Medicine, Seoul, Korea [7]School of Public Health, University of Sydney, Sydney, NSW, Australia [8]Department of Neurology, St Vincent's Hospital, UNSW, Sydney, NSW, Australia [9]The Alfred Hospital/Burnet Institute, Monash University, Melbourne, Victoria, Australia

Abstract

Objectives—The aim of the study was to determine whether combination antiretroviral therapy (cART) with high central nervous system penetration-effectiveness (CPE) rank (neurocART) is associated with increased survival benefit compared with non-neurocART.

Methods—Prospective data were examined for HIV-positive patients in the Asia Pacific HIV Observational Database who had commenced cART. CPE rank was calculated using the 2010 rankings process. NeurocART status was assigned to regimens with a CPE rank of 8 or more. Survival was analysed using Cox proportional hazards models with covariates updated at changes in cART regimen and with deaths up to 90 days after regimen cessation attributed to that regimen. Sensitivity analyses were conducted to examine the robustness of analysis assumptions.

Results—Among 5882 patients, 308 deaths occurred. The hazard ratio (HR) for neurocART use was 0.89 ($P = 0.35$) when data were stratified by cohort and adjusted for age, mode of HIV exposure, hepatitis B virus coinfection, AIDS-defining illness, CD4 count (cells/μL) and regimen count. Sensitivity analyses showed similar nonsignificant results. We also examined a composite endpoint of AIDS-defining illness or death (HR = 0.93; $P = 0.61$), baseline regimen as neurocART (HR = 0.95; $P = 0.69$), CPE category ($P = 0.71$) and prior neurocART duration ($P = 0.16$). No association between CD4 cell count and neurocART use was observed ($P = 0.52$).

Conclusions—Our findings do not show a significant overall survival benefit associated with neurocART compared with cART. The potential benefit associated with neurocART in terms of prevention of neurocognitive impairment did not translate into an improvement in overall survival in this population. These findings were limited by the low incidence of associated mortality. Further studies and more extensive data are needed to address these limitations.

Correspondence: Mr Hamish McManus, University of New South Wales, Cliffbrook Campus, 45 Beach Street, Coogee, NSW 2034, Australia. Tel: + 61 2 9385 0994; fax: + 612 9385 0940; hmcmanus@nchecr.unsw.edu.au.

Keywords

antiretroviral therapy; central nervous system penetration-effectiveness score; combination antiretroviral therapy; HIV; neurocART

Introduction

In a recent study by Patel et al. of over 2272 HIV-infected children, the use of combination antiretroviral therapy (cART) regimens with good central nervous system (CNS) penetration (neurocART) was associated with a significant overall survival benefit (70% risk reduction) compared with use of non-neurocART [1]. In the same study, the use of neurocART was not significantly associated with a reduced incidence of HIV encephalopathy compared with the use of non-neurocART. It is possible that the improved overall survival conferred by neurocART in this paediatric cohort may have been related to better treatment of milder (and probably undiagnosed) HIV-associated neurocognitive impairment (NCI) [2]. In general HIV-positive populations, even mild NCI can affect adherence [3,4], implying a resultant limitation of antiretroviral (ARV) options and an increase in HIV-related complications. In such instances, NCI can be associated with death without the mechanism being through dementia. Further, it is plausible that neurocART regimens afforded improved survival through their being more efficacious at achieving and maintaining an undetectable HIV viral load. However, this association was not evaluable in the study of Patel *et al.* [1] and neurocART has not been associated with greater suppression of plasma HIV viral load in other studies [5].

In Western countries, HIV-associated dementia (HAD) occurs in approximately 15–20% of patients with advanced, untreated HIV infection. In the CASCADE cohort, where patients are recruited from Europe, Canada and Australia, the incidence of HAD was 6.49 per 1000 person-years in the pre-cART era and had fallen to 0.66 by 2003–2006 [6]. In the Asia Pacific region, 12% of HIV-positive out-patients across eight countries had moderate-to-severe NCI compatible with HAD [7]. The prevalence of milder HIV-associated NCI in the Asia and Pacific region is unknown but in a study from India, where HIV-1 clade C predominates, 60% of patients had mild-to-moderate HIV-related neurocognitive deficits [8]. Similarly, a study from Thailand noted a sizeable frequency of mild NCI and the rare occurrence of HAD [9].

HAD *per se* is associated with an increased risk of mortality [10–13], and the reasons for this are probably multifactorial. The optimal antiretroviral treatment for HAD remains controversial but there is evidence to suggest that use of cART regimens with good CNS penetration is superior to the use of regimens with poor CNS penetration [2,14–16]. Recently, Letendre *et al.* have assigned antiretroviral agents individual CNS penetration-effectiveness (CPE) ranks [16,17]. Patients using antiretroviral regimens with a total CPE rank of 8 or more are significantly less likely to have a detectable cerebrospinal fluid HIV viral load than patients using antiretroviral regimens with a total CPE rank below this threshold [17].

The evidence of a strong survival benefit associated with neurocART [1] requires further investigation in a general context regardless of the posited mechanism for survival. Because the reasons for the associated survival benefit are not clear, and because survival may be attributable to the treatment of mild and undiagnosed NCI in particular, the use of NCI as an endpoint rather than survival may underestimate neurocART effects. Further, the beneficial effects of using antiretroviral regimens with high CPE on overall survival in HIV-infected adults has not been evaluated; hence we undertook this study using a combined analysis

from the Australian HIV Observational Database (AHOD) and the TREAT Asia HIV Observational Database (TAHOD).

Methods

Study population

AHOD and TAHOD are observational clinical cohort studies of patients with HIV infection in Australia and countries in Asia and the Pacific region, respectively. As part of the International Epidemiologic Databases to Evaluate AIDS initiative, these databases are combined to form the Asia-Pacific HIV Observational Database (APHOD). APHOD utilizes methodology that has been described in detail elsewhere [18,19].

In AHOD, data are collected from 27 clinical sites throughout Australia, including hospitals, sexual health clinics and general medical practices. Prospective data collection commenced in 1999, with retrospective data provided where available. Written, informed consent is obtained from all patients recruited to AHOD at the time of enrolment. In TAHOD, data are collected from 17 clinical sites in Asia and the Pacific region. Prospective data collection for TAHOD commenced in 2003, with retrospective data provided where available. Written consent was not a requirement of sites in TAHOD unless required by the site's local ethics committee, because data are collected in an anonymous form. Ethics approval for APHOD was obtained from the University of New South Wales, Sydney, Australia, and all other relevant institutional review boards. All APHOD study procedures were developed in accordance with the revised 1975 Helsinki Declaration.

Data for APHOD are transferred electronically to the National Centre in HIV Epidemiology and Clinical Research (NCHECR) every March and September and include the same set of core variables. All data are subject to standardized quality control procedures. We included all patients recruited to APHOD by 31 March 2009, who commenced cART (three or more antiretroviral drugs in combination) after 1 January 1997 and had at least one follow-up visit. All data were analysed centrally at the NCHECR.

Definitions and outcome

Initial baseline was the later date of commencement of cART (defined as the use of three or more antiretrovirals) and enrolment in APHOD. The primary endpoint was mortality, including mortality up to 90 days after cessation of cART. Periods off cART of duration <90 days were considered to be continued cART based on intention-to-treat principles. Periods off cART with a duration of >90 days were omitted from the primary analysis. A new cART regimen was defined as a regimen created from an existing regimen by the addition of one or more new antiretrovirals, or by the replacement of one or more antiretrovirals in the existing regimen with one or more new antiretrovirals. NeurocART status was assigned to those regimens with a CPE rank of 8 or more, with the CPE rank calculated using the 2010 rankings process [17]. CD4 cell counts and viral loads were taken as the latest measurement from up to 90 days prior to regimen commencement. HIV viral load measurements of ≤400 copies/mL were defined as undetectable because more sensitive assays were not uniformly available for all observations. Coinfection with hepatitis B virus (HBV) or hepatitis C virus (HCV) was defined as the detection of HBV surface antigen or HCV antibody, respectively.

A secondary composite endpoint of AIDS or mortality within 90 days of cessation of treatment was also investigated.

Statistical analysis

Follow-up was calculated from the start date of each new cART regimen (or the date of cohort enrolment if later), until cessation of that cART regimen. Loss to follow-up was defined as no clinic visit in the 12 months prior to 31 March 2009 (cohort censoring date). Patients lost to follow-up were censored at their last clinic visit. We used an intention-to-continue treatment approach and ignored any changes to, or interruptions or termination of, treatment after baseline.

For each new cART regimen we created a new set of baseline covariates and assessed the risk of death on that cART regimen adjusted for those baseline covariates. Variables updated at change in cART regimen were neurocART status, CD4 count (<50, 50–99, 100–199, 200–349 and ≥350 cells/μL, or missing), HIV viral load (≤400 or >4400 HIV-1 RNA copies/mL, or missing), prior AIDS-defining illness (ADI), cART regimen count (first, second, third, fourth or more), months of prior neurocART exposure (never, or 1–9, 10–18 or >18 months), and months of prior cART (not neurocART) exposure (never, or 1–18 or >418 months). Additional variables examined were age (<30, 30–39, 40–49 or ≥50 years), sex, mode of HIV exposure [men who have sex with men (MSM), heterosexual, injecting drug use (IDU), other or missing], HCV coinfection, HBV coinfection, and neurocART type prior to entry (naïve, cART and not neurocART, or neurocART). We also analysed the incidence of HAD. As there is some evidence that progressive multifocal leucoencephalopathy (PML) may respond better to neurocART than non-neurocART [20], PML data were also analysed. We did not have data on patients' CD4 cell count nadirs. An administrative censoring date of 31 March 2009 was used. Univariate Cox proportional hazards models were developed for all variables. Multivariate analysis of survival and neurocART status was conducted using Cox proportional hazards models with covariates selected using backward stepwise selection and with forced inclusion of neurocART. All primary analyses were stratified by cohort. Covariates were excluded if there appeared to be collinearity problems. We accounted for the multiple regimens per patient by applying robust standard error estimation to allow for intragroup correlation. Missing data were included as a separate category in all analyses.

The following sensitivity analyses were conducted using multivariate Cox proportional hazards models: separate analyses were conducted for each cohort; for each change in neurocART status a new set of baseline covariates was created; off-cART periods of >90 days were included; all deaths following treatment cessation were excluded; all periods of mono/dual therapy exposures were excluded; and all records with missing CD4 cell counts or viral loads were excluded. A sensitivity analysis was also conducted using Poisson regression as opposed to a Cox regression.

Secondary analyses were conducted as follows: neuro-cART status as a predictor of `ADI or death' within 90 days of cessation of treatment was examined; neurocART as first cART (compared with non-neurocART as first cART) was investigated as a predictor of mortality; CPE score categorized as a four-point variable by quartile (≤6, 7, 8 and ≥9) was investigated as a predictor of mortality; cumulative duration of neurocART use in months prior to the current regimen was also investigated as a predictor of mortality. This was examined as a categorical predictor (never, or 1–29, 10–18 or ≥19 months) with a broad upper category (≥ 19 months) to avoid fitting to patients who survived and had extended follow-up, thereby reducing the potential for bias in survival estimates. This model was compared with the model used in the primary analysis using the Akaike information criterion. In these analyses, covariates used were as for the primary analysis.

Finally, we also assessed CD4 cell count responses according to neurocART status. Log CD4 cell count was analysed using repeated measures regression, with generalized

estimating equations (GEE) methodology, and assumed exchangeable variance structure (but robust calculated variances). CD4 cell counts were recorded for up to 540 days at each 90 days of regimen duration using the closest measurement (taken <90 days before or <30 days after). Additional covariates were included in this analysis: baseline CD4 count (<50, 50–99, 100–199, 200–349 or ≥350 cells/μL or missing), year of cART commencement (1997–1999, 2000–2002 or ≥2003) and time since first cART (≤270, 271–540, 541–810 or >810 days).

Data were analysed using STATA version 10 (Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

Demographic and clinical characteristics by cohort are summarized in Table 1. A total of 5882 patients were included in these analyses (2384 from AHOD and 3498 from TAHOD), contributing 22117 patient-years of follow up. A total of 308 (5%) of patients died during follow-up (195 in AHOD and 113 in TAHOD), with an observed incidence rate of 12.3 deaths per 1000 person-years of follow up [95% confidence interval (CI) 11.0–13.8]. The median age was 43 years [standard deviation (SD) 9.8 years] in AHOD and 38 years (SD 9.6 years) in TAHOD. The majority of patients were male; 94% of patients were male in AHOD compared with 71% of patients in TAHOD. The main exposure category in AHOD was homosexual contact (78%) compared with heterosexual contact (68%) in TAHOD.

Low incidences of HAD were observed: 36 (2%) and five deaths in AHOD and 14 (<1%) and one death in TAHOD. Similarly, low incidences of PML were observed; two (<1%) and no deaths in AHOD and 10 (<1%) and two deaths in TAHOD (Table 1).

The median observed CPE based on treatment time was 8 [interquartile range (IQR) 7–9]. Prior neurocART had been received by 1267 AHOD patients (53%) compared with 2454 TAHOD patients (70%). The average prior cumulative neurocART duration in AHOD was 13 months (SD 20.7 months) compared with 10 months (SD 15.4 months) in TAHOD. Of the patients in AHOD, 1129 (47%) had neurocART as the first cART whereas in TAHOD, 2630 (75%) had neurocART as the first cART.

NeurocART use

There was no significant difference in the risk of mortality between neurocART and non-neurocART groups for either the univariate or the multivariate models (Table 2). The unadjusted hazard ratio (HR) associated with neurocART use was 0.87 (95% CI 0.68–1.12). Variables associated with survival in univariate models were age at entry, HIV exposure category, HBV coinfection, HCV coinfection, ADI, CD4 cell count, HIV viral load, prior treatment, regimen count and duration of prior cART (not neurocART) exposure.

Covariates retained in the final multivariate model were age, HIV exposure category, HBV coinfection, ADI, CD4 cell count and regimen. In this model the adjusted HR associated with neurocART use was 0.89 (95% CI 0.69, 1.14) (Table 2). Covariates associated with increased mortality in this model were age >50 years compared with age <30 years (HR 2.47; 95% CI 1.53–3.99), exposure from IDU compared with MSM (HR 2.01; 95% CI 1.33–3.05), lower CD4 cell count and regimen fourth or more compared with first (HR 1.57; 95% CI 1.13–2.17). Analyses by cohort showed no significant difference in the risk of mortality between neurocART and non-neurocART groups; the adjusted HR associated with neurocART use was 0.81 (95% CI 0.59–1.12) for AHOD and 0.92 (95% CI 0.59–1.43) for

TAHOD. All other sensitivity analyses showed similar, nonsignificant differences in risk of mortality for the neurocART and non-neurocART groups (Table 3).

There was no significant difference in the risk of AIDS or death between the neurocART and non-neurocART groups for either of the univariate or multivariate models (Table 4). The adjusted HR associated with neurocART use was 0.93 (95% CI 0.71–1.23). Similarly, there was no significant difference in the risk of mortality between the group with neurocART as the first cART (neurocART-first cART) and the group with non-neurocART as the first cART (non-neurocART-first cART) for either of the univariate or multivariate models (Table 4). The adjusted HR associated with neurocART-first cART was 0.91 (95% CI 0.70–1.18). CPE as a four-point variable showed no significant association with risk of mortality (P=0.71) (Table 4) for all categories of CPE. Also, there was no significant difference in mortality associated with duration of prior neurocART use when used as a primary independent predictor and adjusted for other covariates (P=0.16) (Table 4). Regimen count was omitted from this analysis because of confounding. This model was less successful than the model used in the primary analysis in describing overall mortality with regard to numbers of covariate levels (Akaike information criterion 4183.7 compared with 4180.4).

No association between CD4 cell count and neurocART was observed (P=0.52) using a GEE model adjusted for age, HIV exposure category, ADI, CD4 cell count at baseline, HIV viral load, HBV coinfection, HCV coinfection, age, regimen count, year of first cART, time since first cART and regimen duration as covariates (Table 4). In this model, a nonsignificant increase in CD4 cell count of 1% (95% CI −2 to 4%) was observed per each 3 months of duration of neurocART regimens compared with non-neurocART regimens and when adjusted for other covariates.

Discussion

In this analysis using data from APHOD, neurocART was not significantly associated with a reduction in survival for HIV-positive patients, and this finding was consistently obtained across a range of sensitivity analyses. Similarly, a nonsignificant association was observed when the first incidence of ADI was incorporated as an endpoint, and no association was found between neurocART use compared with cART use and CD4 cell count. At least in APHOD, a potential benefit associated with neurocART use is not evident in overall population survival.

The use of neurocART has been shown to improve survival after diagnosis of HIV encephalopathy in perinatally infected children and adolescents [1], but survival effects are less clear in general HIV-positive populations [21]. Our analysis does not confirm the association of neurocART use and improved survival in a broader population of HIV-infected adults, with our findings being robust to changes in model assumptions. Further, the independent associations between other population and treatment characteristics and survival in our study were consistent with other findings [18,19,22–24]: higher CD4 cell count was strongly associated with reduced mortality, while increased HIV viral load, increased age, certain modes of exposure (IDU and `other'), hepatitis coinfection, ADI and more extensive treatment history (higher regimen count) were associated with increased mortality. In the multivariate analysis, it was found that higher CD4 cell count, increased age, HBV coinfection, ADI and more extensive treatment history (higher regimen count) were strongly associated with survival after adjustment for other covariates. In terms of survival prediction, neurocART was not very important to the models in comparison with these covariates.

We did not directly examine NCI-associated mortality, although an important rationale for this study was the possible improvement in survival attributable to the beneficial effect of neurocART on mild, and possibly undiagnosed and unmeasured, NCI [1]. Although previous studies have demonstrated a sizeable frequency of mild NCI in certain populations [8,9], we do not have comprehensive data on the incidence of mild NCI-associated mortality in APHOD. To our knowledge, there is no strong existing evidence of survival attributable to the beneficial effects of neurocART on mild NCI. A recent paper by Smurzynski *et al*. [25] showed an adjusted association between increases in CPE score and neuropsychological test scores when accounting for an interaction with the number of ARVs per regimen. While Patel *et al*. did not find a significant association between CNS penetration and the incidence of HIV encephalopathy, they did observe a significant survival benefit associated with CNS penetration in HIV encephalopathy cases [1]. In contrast, while Garvey *et al*. did not observe a significant adjusted association between CPE score and CNS opportunistic diseases, they noted that the lowest and highest CPE scores were associated with increased mortality [21], but suggested that this was a consequence of clinical status affecting prescribing practice. Overall, our findings do not demonstrate the posited association between neurocART-reduced NCI and improved survival in APHOD.

Our findings, which describe prospective data for the period 1999–2009, can be contrasted with those of a recent study by Lanoy *et al*. [20], where all-cause mortality in neuroAIDS diagnoses was associated with CPE score for each of the periods 1992–1995 and 1996–1998 but not for 1999–2004. In that study, the authors attributed the lack of an associated effect in the period 1999–2004 to improved control of plasma viral load (which was not adjusted for in initial models) by cART regimens in general. In the same study, a secondary analysis for the period 1997–2004 showed no change in survival associated with CPE score after including plasma HIV RNA as a covariate. While our results reflect a lack of a differentiable survival effect of neurocART use in the later cART period for all HIV-positive patients, they also suggest that plasma viral load adds little extra descriptive power after the inclusion of CD4 cell count as a covariate in multivariate models when examining neurocART survival outcomes. Similarly, while Patel *et al*. were unable to adjust for viral load in their primary analysis, sensitivity analyses suggested that measured CNS effects were not confounded by the omission of this covariate [1]. In this regard, temporal changes in the measured CPE effect as observed by Lanoy *et al*. are not necessarily reflected by measured HIV RNA suppression in these analyses, at least when also adjusting for CD4 cell counts. Nevertheless, broader changes in therapy, including general increases in cART CPE levels and potency, may reduce the effectiveness of CPE as a measure of neuroAIDS treatment, and wider changes in therapy should be considered in association with CPE measurements to describe the effectiveness of treatments of neuroAIDS.

Of note is the fact that in our study we used the 2010 CPE ranking approach, as presented by Letendre *et al*. [17]. While this approach has not been validated at the time of submission, we have found analysis results to be qualitatively similar to those obtained using the 2008 approach [16] (data not shown). There are acknowledged weaknesses with the CPE scoring system, including scarce information on ARV CNS penetration and pharmacodynamics, including possible insensitivity to drug–drug interactions, the role of blood–brain barrier permeability in CNS drug penetration and the possible effects of ageing. However, the CPE scoring system represents a practical tool with which to assess CNS effectiveness of cART regimens and has been associated with strong measured improvement in overall survival in one study [1]. As stated, a posited reason for this is that treatment of mild undiagnosed NCI with neurocART improves overall survival, although we were not able to evaluate this in our analysis. Furthermore, we were not able to evaluate the relationship between use of neurocART and cerebrospinal fluid HIV viral load results.

In APHOD, HAD and PML events are too rare to be used as statistical endpoints and detailed data on other neurological events are not collected; however, we looked at broader outcomes for neurocART use. The composite endpoint of `ADI or death' showed a weaker association, suggesting that neurocART use does not reduce the incidence of ADI compared with cART. Also of note is the finding that neurocART use was not strongly associated with changes in CD4 cell count compared with cART use. These findings do not demonstrate any additional benefit associated with neurocART use compared with non-neurocART use.

We also examined survival attributable to neurocART across different stages of treatment: for baseline neuro-cART, subsequent neurocART, and cumulative duration of neurocART. We observed a nonsignificant association between neurocART as the first cART and survival, consistent with the findings of Garvey *et al*. [21], where baseline CPE category was categorized as a four-level variable. In the same study, Garvey *et al*. found that the lowest and highest categories of the latest CPE were associated with increased mortality in multivariate models; however, we did not find an equivalent association in APHOD. We also found that models using the latest neurocART showed a stronger, but still nonsignificant, association with survival than equivalent four-level CPE models. Finally, we observed no association between survival and duration of neurocART use when data were adjusted for other patient characteristics. Overall, we were unable to demonstrate a difference in survival associated with neurocART compared with non-neurocART.

There are several limitations to this study. Firstly, our study may have been underpowered to detect a significant association between CPE score and overall survival. Sample size calculations estimate that we would have needed over 1000 events to detect a significant improvement in survival of<15%. The likely low incidence of death associated with NCI further limits the power of analysis. In APHOD, the low incidence of HAD precluded it from being analysed directly, and limited data are collected on other NCI outcomes. Although APHOD comprises relatively large multisite cohorts with good follow-up, these results flag the need for more extensive data for examination of neuro-cART outcomes including associated mortality. In particular, examination of mild CNS events might increase the sensitivity of analyses to general neurocART outcomes including associated mortality, subject to available data and the constraints this places on the power of analyses. Although TAPHOD does not collect these data in any standardized fashion, we are not aware of any other cohorts that do so. In this regard, the routine screening for HIV-associated neurocognitive disorders in relevant cohorts should be considered. Similarly, although previous studies have identified clade-specific differences in HIV neurotoxicity [26], our analysis did not specifically adjust for this. Differences in neurotoxicity by clade may potentially limit the general application of CPE as used in this analysis, and the inclusion of clade as a covariate to examine this should be considered in future analyses. Other limitations include the enrolment of patients in APHOD after the initiation of cART, and the enrolment of patients with mono/dual therapy experience prior to starting cART. To address these concerns, prior treatment experience was factored into analyses including prior treatment type, neurocART-first cART, regimen count and neurocART exposure. Of these covariates, only higher regimen counts (≥4 regimens) were found to contribute significantly to multivariate models.

In summary, our findings do not show a significant overall survival benefit associated with neurocART compared with cART in a population of HIV-positive adult patients (APHOD). In particular, the potential benefit associated with neurocART in terms of prevention of neurocognitive impairment did not translate into an improvement in overall survival in this population. These findings were limited by the likely low incidence of NCI-associated mortality. Further studies and more extensive data are needed to address these limitations.

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Table 1

Demographic and clinical characteristics

	AHOD		TAHOD	
	Patients	**Deaths**	**Patients**	**Deaths**
Total [n (%)]				
Age at entry (years) *n* (%)	2384 (100)	195 (100)	3498 (100)	113 (100)
Mean (SD)	43 (9.8)		38 (9.6)	
<30 years	148 (6)	6 (3)	602 (17)	17 (15)
30–39 years	859 (36)	64 (33)	1641 (47)	37 (33)
40–49 years	829 (35)	61 (31)	860 (25)	26 (23)
≥ 50 years	548 (23)	64 (33)	395 (11)	33 (29)
Gender [*n* (%)]				
Male	2240 (94)	185 (95)	2500 (71)	86 (76)
Female	144 (6)	10 (5)	998 (29)	27 (24)
HIV exposure [*n* (%)]				
MSM	1854 (78)	143 (73)	651 (19)	8 (7)
HET	221 (9)	10 (5)	2370 (68)	82 (73)
IDU	147 (6)	21 (11)	169 (5)	10 (9)
Other	138 (6)	18 (9)	256 (7)	12 (11)
Missing	24 (1)	3 (2)	52 (1)	1 (1)
HBV coinfection [*n* (%)]				
Negative	1882 (79)	151 (77)	2085 (60)	59 (52)
Positive	125 (5)	19 (10)	244 (7)	8 (7)
Missing	377 (16)	25 (13)	1169 (33)	46 (41)
HCV coinfection [*n* (%)]				
Negative	1843 (77)	140 (72)	1856 (53)	51 (45)
Positive	263 (11)	34 (17)	232 (7)	11 (10)
Missing	278 (12)	21 (11)	1410 (40)	51 (45)
HAD ever [*n* (%)]				
No	2348 (98)	190 (97)	3484 (100)	112 (99)
Yes	36 (2)	5 (3)	14 (0)	1 (0)
Progressive multifocal leucoencephalopathy [*n* (%)]				
No	2382 (100)	195 (100)	3488 (100)	111 (98)
Yes	2 (0)	0 (0)	10 (0)	2 (2)
AIDS at entry [*n* (%)]				
No	1901 (80)	136 (70)	1754 (50)	34 (30)
Yes	483 (20)	59 (30)	1744 (50)	79 (70)
CD4 count at entry (cells/|μL) *n* (%)				
Mean (SD)	460 (282.4)		274 (211.4)	
<50 cells/μL	80 (3)	32 (16)	373 (11)	31 (27)
50–99 cells/μL	67 (3)	8 (4)	279 (8)	23 (20)
100–199 cells/μL	249 (10)	31 (16)	650 (19)	23 (20)

	AHOD		TAHOD	
	Patients	**Deaths**	**Patients**	**Deaths**
200–349 cells/μL	515 (22)	44 (23)	914 (26)	14 (12)
≥350cells/μL	1386 (58)	67 (34)	894 (26)	7 (6)
Missing	87 (4)	13 (7)	388 (11)	15 (13)
HIV RNA at entry (copies/mL) *n* (%)				
Median (LQ-UQ)	400 (400–12 900)		400 (400–13100)	
≤400 copies/mL	1270 (53)	81 (42)	1155 (33)	17 (15)
>400 copies/mL	1008 (42)	100 (51)	641 (18)	27 (24)
Missing	106 (4)	14 (7)	1702 (49)	69 (61)
Regimen at entry* [*n* (%)]				
1st	1335 (56)	81 (42)	2737 (78)	93 (82)
2nd	438 (18)	39 (20)	522 (15)	12 (11)
3rd	270 (11)	22 (11)	164 (5)	6 (5)
4th or more	341 (14)	53 (27)	75 (2)	2 (2)
Median CPE over study (IQR)	8 (7–9)		8 (7–9)	
Prior treatment [*n* (%)]				
Naïve	677 (28)	51 (26)	1082 (31)	51 (45)
cART and not neurocART	687 (29)	59 (30)	681 (19)	14 (12)
NeurocART	1020 (43)	85 (44)	1735 (50)	48 (42)
First cART was neurocART [*n* (%)]				
No	1255 (53)	123 (63)	868 (25)	29 (26)
Yes	1129 (47)	72 (37)	2630 (75)	84 (74)
Duration of prior neurocART at entry (months)				
Mean (SD)	13 (20.7)		10 (15.4)	
Duration of prior cART (not neurocART) at entry (months)				
Mean (SD)	13 (17.1)		4 (11.3)	
Complete follow-up (%)	79		86	

cART, combination antiretroviral therapy; CPE, central nervous system penetration-effectiveness; HAD, HIV-associated dementia; HBV, hepatitis B virus; HCV, hepatitis C virus; HET, heterosexual; IDU, injecting drug use; IQR, interquartile range; LQ, lower quartile; MSM, men having sex with men; neurocART, cART with high CPE rank; SD, standard deviation; UQ, upper quartile.

* '1st' regimen at entry includes continuing patients and commencing naïve patients.

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Table 2

Predictors of survival*

	Univariate			Multivariate†		
	Hazard (95% CI)	***P***	***P*‡**	**Hazard (95% CI)**	***P***	***P*‡**
NeurocART						
No	1.00			1.00		
Yes	0.87 (0.68, 1.12)	0.29		0.89 (0.69, 1.14)	0.35	
Age						
<30 years	1.00		**<0.001**	1.00		**<0.001**
30–39 years	0.86 (0.54, 1.37)	0.52		0.92 (0.58, 1.46)	0.73	
40–49 years	1.05 (0.66, 1.69)	0.83		1.26 (0.79, 2.01)	0.34	
≥ 50 years	1.88 (1.17, 3.03)	0.01		2.47 (1.53, 3.99)	<0.001	
Sex						
Male	1.00					
Female	0.83 (0.57, 1.20)	0.32				
HIV exposure						
MSM	1.00		**<0.001**	1.00		**0.01**
HET	1.13 (0.83, 1.53)	0.44		1.05 (0.76, 1.45)	0.76	
IDU	2.52 (1.70, 3.73)	<0.001		2.01 (1.33, 3.05)	<0.01	
Other	1.93 (1.27, 2.93)	<0.01		1.50 (0.97, 2.31)	0.07	
Missing	2.32 (0.84, 6.42)	0.11		1.18 (0.34, 4.11)	0.80	
HBV coinfection						
No	1.00			1.00		
Yes	1.55 (1.03, 2.32)	0.04		1.48 (0.99, 2.20)	0.05	
HCV coinfection						
No	1.00					
Yes	1.76 (1.26, 2.45)	<0.01				
Prior ADI						
No	1.00			1.00		
Yes	2.06 (1.61, 2.64)	<0.001		1.28 (0.98, 1.66)	0.07	
CD4 count						

	Univariate			Multivariate†		
	Hazard (95% CI)	***P***	***P*‡**	**Hazard (95% CI)**	***P***	***P*‡**
<50 cells/μL	1.00		**<0.001**	1.00		**<0.001**
50–99 cells/μL	0.44 (0.28, 0.70)	<0.01		0.44 (0.28, 0.71)	<0.001	
100–199 cells/μL	0.21 (0.14, 0.32)	<0.001		0.21 (0.14, 0.32)	<0.001	
200–349 cells/μL	0.16 (0.11, 0.23)	<0.001		0.18 (0.12, 0.26)	<0.001	
≥350cellsVL	0.07 (0.05, 0.10)	<0.001		0.08 (0.05, 0.12)	<0.001	
Missing	0.27 (0.18, 0.42)	<0.001		0.30 (0.19, 0.47)	<0.001	
HIV RNA						
≤400 copies/mL	1.00		**<0.001**			
>400 copies/mL	1.96 (1.49, 2.59)	<0.001				
Missing	2.17 (1.56, 3.01)	<0.001				
Prior treatment						
Naïve	1.00		**0.04**			
cART and not neurocART	0.70 (0.51, 0.97)	0.03				
NeurocART	0.72 (0.54, 0.95)	0.03				
First cART was neurocART						
No	1.00					
Yes	0.85 (0.67, 1.08)	0.19				
Regimen						
1st	1.00		**<0.001**	1.00		**0.02**
2nd	0.80 (0.56, 1.14)	0.21		0.98 (0.68, 1.40)	0.91	
3rd	0.95 (0.65, 1.38)	0.78		1.10 (0.75, 1.63)	0.62	
4th or more	1.73 (1.29, 2.33)	<0.001		1.57 (1.13, 2.17)	<0.01	
Duration of prior neurocART exposure						
Never	1.00		**0.10**			
1–9 months	1.01 (0.72, 1.42)	0.95				
10–18 months	1.16 (0.79, 1.69)	0.45				
>18 months	0.77 (0.58, 1.03)	0.09				
Duration of prior cART (not neurocART) exposure						
Never	1.00		**<0.01**			
1–18 months	1.55 (1.17, 2.04)	<0.01				

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	Univariate			Multivariate†		
	Hazard (95% CI)	***P***	***P*‡**	**Hazard (95% CI)**	***P***	***P*‡**
≥ 19 months	0.95 (0.72, 1.25)	0.69				

ADI, AIDS-defining illness; cART, combination antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HET, heterosexual; IDU, injecting drug use; LQ, lower quartile; MSM, men having sex with men; neurocART, cART with high central nervous system penetration-effectiveness rank; UQ, upper quartile.

*Models stratified by cohort.

†Akaike information criterion: 4180.4.

‡Wald test for homogeneity for categorical covariates.

Table 3

Sensitivity analyses

Model*	HR (neurocART use)	95% CI	*P*>*z*
New baseline if change in cART changes neurocART status	0.88	(0.68, 1.13)	0.31
Include 'off cART' status	0.95	(0.75, 1.20)	0.65
Deaths following treatment cessation are not counted	0.85	(0.66, 1.09)	0.20
Omit all mono/dual exposures	0.89	(0.69, 1.15)	0.38
Exclude regimens with missing baseline CD4 cell count or viral load	0.84	(0.61, 1.16)	0.29
Poisson model (standard errors adjusted for intra-group correlation)	0.87	(0.67, 1.12)	0.28

cART, combination antiretroviral therapy; CI, confidence interval; HR, hazard ratio; neurocART, cART with high central nervous system penetration-effectiveness rank.

*Models were adjusted for age, mode of exposure, hepatitis B virus coinfection, AIDS-defining illness, CD4 cell count and regimen count, stratified by cohort.

Table 4

Secondary analyses

Model	HR (neurocART use)	95% CI	*P*>*z*	*P**
Cox proportional hazards				
Endpoint: ADI or death†	0.93	(0.71, 1.23)	0.61	
First cART=neurocART†	0.91	(0.70, 1.18)	0.48	
CPE (four-point scale)†				
≤6	1.00			**0.71**
7	1.04	(0.68, 1.59)	0.86	
8	0.90	(0.59, 1.37)	0.62	
≥9	0.88	(0.60, 1.28)	0.50	
Prior neurocART duration§				
Never	1.00			**0.16**
1–9 months	0.89	(0.63, 1.26)	0.52	
10–18 months	1.23	(0.84, 1.80)	0.28	
≥ 19 months	0.82	(0.60, 1.11)	0.19	
GEE – linear §	**Coef.**			
CD4 dependent variable	1.01	(0.98, 1.04)	0.52	

cART, combination antiretroviral therapy; CI, confidence interval; CPE, central nervous system penetration-effectiveness; GEE, generalized estimating equation; HR, hazard ratio; neurocART, cART with high central nervous system penetration-effectiveness rank.

*Wald test for homogeneity for categorical covariates.

†Model adjusted for age, mode of exposure, hepatitis B virus (HBV) coinfection, AIDS-defining illness (ADI), CD4 cell count and regimen count, stratified by cohort.

§Model adjusted for age, mode of exposure, HBV coinfection, ADI and CD4 cell count, stratified by cohort; Akaike information criterion: 4183.7.

§Model adjusted for age, sex, mode of exposure, HBV coinfection, hepatitis C virus (HCV) coinfection, ADI, CD4 baseline cell count, regimen count, year of cART commencement, months of cART and cohort.