Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents

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Abstract

Objectives—Prior to antiretroviral treatment, HIV-infected children frequently developed encephalopathy, resulting in debilitating morbidity and mortality. This is the first large study to evaluate the impact of HAART and central nervous system (CNS)-penetrating antiretroviral regimens on the incidence of HIV encephalopathy and survival after diagnosis of HIV encephalopathy among perinatally infected children.

Design—A total of 2398 perinatally HIV-infected children with at least one neurological examination were followed in a US-based prospective cohort study conducted from 1993 to 2007.

Methods—Trends in incidence rates over calendar time were described and Cox regression models were used to estimate the effects of time-varying HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy and on survival after diagnosis of HIV encephalopathy.

Results—During a median of 6.4 years of follow-up, 77 incident cases of HIV encephalopathy occurred [incidence rate 5.1 cases per 1000 person-years, 95% confidence interval (CI) 4.0–6.3]. A 10-fold decline in incidence was observed beginning in 1996, followed by a stable incidence rate after 2002. HAART regimens were associated with a 50% decrease (95% CI 14–71%) in the incidence of HIV encephalopathy compared with non-HAART regimens. High CNS-penetrating regimens were associated with a substantial survival benefit (74% reduction in the risk of death, 95% CI 39–89%) after HIV encephalopathy diagnosis compared with low CNS-penetrating regimens.

Conclusion—A dramatic decrease in the incidence of HIV encephalopathy occurred after the introduction of HAART. The use of HAART was highly effective in reducing the incidence of HIV encephalopathy among perinatally infected children and adolescents. Effective CNS-penetrating antiretroviral regimens are important in affecting survival after diagnosis of HIV encephalopathy.

Keywords

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Introduction

The first pediatric cases of HIV encephalopathy were reported in 1985 among children with

AIDS [1–3]. The prevalence of HIVencephalopathy among this population varied from 30 to 50% and latency to HIV encephalopathy ranged from 2 months to 5 years [3,4]. Clinical features of HIV encephalopathy include loss of or failure to attain developmental milestones, impaired brain growth, and motor deficits [1–4]. Some children present with rapidly progressive fatal disease, whereas others have stable phases interspersed with short periods of neurological deterioration [1–3]. Given the level of morbidity and mortality associated with this disease, HIV encephalopathy was added as an AIDS-defining condition in 1987 [5].

Studies of cerebrospinal fluid (CSF) from children with HIV encephalopathy found active and persistent brain infection with HIV suggesting a need for antivirals that penetrate the blood–brain barrier [3,6]. Drug manufacturers and independent studies have evaluated the penetration of specific antiretroviral drugs into CSF [7]. To aid clinicians in antiretroviral therapy decision-making for patients with neurological symptoms, this information has recently been used to develop a drug ranking system based on a drug's ability to penetrate the central nervous system (CNS) [7]. The clinical utility of these CNS-penetration-effectiveness ranks still needs to be validated in pediatric populations and clinical studies examining neurological outcomes such as HIV encephalopathy [7].

With yje advent of HAART, survival has increased [8,9]. The effect of such therapy on neurological disease such as HIVencephalopathy, however, is less clear. Several studies [10–13] have suggested a decreasing incidence of HIV encephalopathy. However, heterogeneity in the time scales and study populations used make it difficult to assess trends and attribute them to antiretroviral use.

The majority of studies examining the association between antiretroviral use and HIV encephalopathy [14–17] have focused on the effect of antiretroviral therapy on improving neuropsychological functioning after diagnosis of encephalopathy. One study [18] examined the effect of antiretroviral therapy before diagnosis of encephalopathy but restricted their study population to children with an eventual diagnosis of HIVencephalopathy. It found antiretroviral therapy to be associated with a later age at diagnosis. Another study compared 13 children ever diagnosed with HIV encephalopathy with 113 children never diagnosed with HIV encephalopathy and found a significantly greater proportion of HAART use among the children with a diagnosis of HIV encephalopathy [13]. The temporal relationship between HAART use and diagnosis is unclear in this study and no multivariate analyses were conducted to adjust for confounding by indication. Three recent studies [19–21] compared effect of early versus deferred antiretroviral therapy on AIDS progression and/or mortality and found a higher number of HIV encephalopathy cases among the groups that deferred therapy. Each of these studies, however, only had a few HIV encephalopathy cases (range 3–9 cases) to compare between their early and deferred treatment groups. No studies to date have quantified the effect of antiretroviral use on the risk of HIV encephalopathy. Our study describes the incidence of HIV encephalopathy between 1994 and 2006 among a cohort of perinatally HIV-infected children enrolled in a large multicenter cohort study in the United States and evaluates the effects of HAART and CNS-penetrating antiretroviral regimens on the incidence of encephalopathy. It further assesses the effects of HAART and CNS-penetrating antiretroviral therapy on overall survival and survival after diagnosis of HIV encephalopathy.

Methods

The study population included participants from Pediatric AIDS Clinical Trials Group (PACTG) Protocols 219 and 219C, which were prospective studies designed to evaluate the long-term effects of HIV infection and inutero and postnatal exposure to antiretroviral therapy. Between April 1993 and September 2000, infected and uninfected children from more than 80 study sites in the United States were eligible for enrollment in PACTG 219 if they were born

to HIV-infected mothers enrolled in PACTG perinatal trials or were themselves enrolled in PACTG perinatal or clinical trials and were younger than 21 years of age at entry. In September 2000, all children in PACTG 219 were encouraged to enroll into PACTG 219C, which expanded entry criteria to allow all HIV-infected children at the study sites to enroll into the cohort. These studies were approved by the human subjects review boards at each participating institution and written informed consent was obtained from each child's parent or legal guardian. The population eligible for this study included 2398 perinatally HIV-infected children enrolled in PACTG 219 and 219C between 1993 and 2006 who had at least one neurological examination.

At each study visit, data on sociodemographic characteristics, clinical diagnoses, antiretroviral therapies, and CD4 cell measurements were collected. HIV-RNA measurements, however, were not routinely collected or available before 2000 and were available for only 46% of the population. We, therefore, could only adjust for HIV-RNA viral load as a potential confounder in secondary analyses restricted to that subset. Baseline CD4 cell percentage and viral load were defined as the closest CD4 cell and HIV-RNA measurement recorded either prior to or a week after the first neurological examination. Neurological diagnoses reported on neurological examination and diagnoses forms were reviewed by the study pediatric neurologist, and dates of HIV encephalopathy diagnoses were confirmed. Only HIV encephalopathy diagnoses assumed to be progressive based on the best available information for review were included as cases.

HAART exposure was defined as the concomitant use of at least three drugs from at least two classes of HIV drugs. HIV drugs were classified into three main categories: nucleoside/ nucleotide reverse-transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors. In analyses, children could switch from no HAART to HAART when they initiated a HAART regimen. However, for statistical simplicity, children were considered to remain on HAART for the length of follow-up after HAART initiation. In the earlier PACTG 219 cohort, actual dates of initiation of medication or dates of changes in the use of medications were not available. Following previous evaluations of HAART using data from PACTG 219 [7–8], we assumed the midpoint between the visit date at which use of treatment was recorded and the date of the prior visit to be the date of treatment initiation.

To rank antiretroviral regimens according to their ability to penetrate the CNS, a modified version of the CNS-penetration-effectiveness rank developed by Letendre *et al.* [7] was used. The modification accounts for the total number of antiretroviral drugs in a regimen and has been used to predict change in CSF HIV-RNA levels [22]. A scale of 1 (lowest penetration) to 3 (highest penetration) was used to rank each antiretroviral drug (Table 1). A CNS-penetration score was calculated for each antiretroviral regimen by summing the individual ranks of each antiretroviral drug included in the regimen. Antiretroviral regimens with scores less than 4 were classified as low CNS-penetrating regimens, scores of 4–5 were classified as medium CNS-penetrating regimens, and scores greater than or equal to 6 were classified as high CNS-penetrating regimens. In analyses, children could switch from low CNS-penetrating regimens to higher CNS-penetrating regimens. However, for statistical simplicity, once a child initiated his/her highest CNS-penetrating regimen, he/she was considered to remain on that regimen for the length of follow-up.

The baseline date for all children was defined as the date of their first neurological examination. Prevalent cases of HIV encephalopathy were identified as of this baseline date and removed from subsequent analyses. However, age at diagnosis and subsequent mortality are presented descriptively for prevalent diagnoses. For the analyses of incident HIV encephalopathy, each child was followed from his/her baseline date to the date of HIV encephalopathy diagnosis, death, or his/her last visit before 31 May 2007 (date of closure of PACTG 219C), whichever

came first. For overall survival analyses, each child was followed from his/her baseline date to date of death, or censored as of his/her last visit before study closure. For analyses of survival after HIVencephalopathy diagnosis, all children with an incident diagnosis of HIV encephalopathy were followed from their date of HIV encephalopathy diagnosis to their date of death or censored as of their last study visit. The rate of loss to follow-up in the HIV-infected children enrolled in the PACTG 219C study was 3–4% per year [23].

Extended Cox regression models were used to estimate the effects of time-varying HAART versus no HAART on the incidence of HIVencephalopathy, overall survival, and survival after HIV encephalopathy diagnosis. Extended Cox regression models were also used to estimate the effects of time-varying medium and high CNS-penetrating regimens versus low CNS-penetrating regimens on the incidence of HIVencephalopathy, overall survival, and survival after HIVencephalopathy diagnosis. Age at baseline, sex, race/ethnicity, birth weight, and baseline CD4 cell percentage were included as covariates in all models. In secondary analyses, extended Cox models were used to evaluate the effect of HAART and CNS-penetrating regimens on HIV encephalopathy adjusting also for HIV-RNA and to investigate the effect of HIV encephalopathy diagnosis on mortality. Analyses were conducted using SAS version 9 (SAS Institute, Cary, North Carolina, USA).

Results

Of the 3553 HIV-infected children enrolled in PACTG 219 and 219C, 3193 were perinatally infected and 2398 of these (75%) had at least one neurological examination. The perinatally HIV-infected children with a neurological examination were generally similar to the 795 without, although those excluded were more likely to be female children, of older age, and to have higher CD4 cell percentage levels. At baseline, 126 cases of HIV encephalopathy were identified among 2398 children with a neurological examination, resulting in a prevalence of 5.3% [95% confidence interval (CI) 4.4–6.2%]. The median age at diagnosis of these prevalent cases was 1.7 years (Q1, Q3: 0.9, 3.9). Twenty of the 126 prevalent cases (16%) had initiated HAART before diagnosis, 60 (48%) had initiated non-HAART regimens, and 46 (36%) had not initiated any antiretroviral therapy before diagnosis of HIV encephalopathy. There were 42 deaths among the 126 prevalent cases with a median survival after diagnosis of 1.4 years (Q1, Q3: 0.7, 2.9). The majority of the deaths (62%) occurred among children who never initiated HAART during their lifetime.

The baseline characteristics of the 2272 children followed for incident HIV encephalopathy and overall survival analyses are provided in Table 2. Half of the children were female, 48% were less than or equal to 5 years of age at the time of their first neurological examination, 82% were born prior to 1995, 55% were black, 24% were classified as having low birth weight (<2500 g), and 19% had severe immunosuppression (CD4 cell <15%). Of the 1044 children with HIV-RNA information at baseline, 16% had viral load of at least 100 000 copies/ml. At the time of their first neurological examination, 35% of the children were on a HAART regimen and 27% were on a high CNS-penetrating regimen.

Over a median duration of 6.4 years of follow-up, (Q1, Q3: 3.6, 9.9), 77 incident cases of HIV encephalopathy occurred, yielding an incidence rate of 5.1 cases per 1000 person-years (95% CI 4.0–6.3, person years: 15 178). The median age at diagnosis of the 77 incident cases was 6.3 years (Q1, Q3: 3.3, 11.4). In Fig. 1, the incidence rates and the percentage of children on HAART in the study population are summarized from 1994–2006. Beginning in 1996, there was a 10-fold decrease in the incidence of HIVencephalopathy followed by a relatively stable incidence rate after 2002. Conversely, there was a significant increase in the percentage of children on HAART regimens after 1996, suggesting an impact of HAART on the decreased incidence of HIV encephalopathy over time. By the end follow-up, 1806 children (79%) had

initiated HAART and 31 of the 77 HIV encephalopathy cases (40%) were observed among them. Four hundred and sixty-six children never initiated HAART with 46 of the 77 HIV encephalopathy cases (60%) observed among them. Of the 1741 children who had initiated a high CNS-penetrating antiretroviral regimen by end of follow-up, 34 (2%) had a diagnosis of HIV encephalopathy. Twenty-four (9%) of the 267 children who ended follow-up on a medium CNS-penetrating regimen had a diagnosis of HIV encephalopathy, and 19 (7%) of the 264 children on a low CNS-penetrating regimen had a diagnosis of HIV encephalopathy by end of follow-up.

Over a median follow-up of 6.5 years (Q1, Q3: 3.9, 10) from the first neurologic examination until death or censoring, 207 deaths were reported, resulting in a mortality rate of 13.5 per 1000 person-years (95% CI 11.7–15.4, person-years = 15 389). By the end of follow-up, 1826 children had initiated HAART and 101 deaths (6%) were observed among them. The number initiating HAART is higher than that reported above for the HIV encephalopathy incidence analysis as some children initiated HAART after their diagnosis. Four hundred and forty-six children never initiated HAART and 106 deaths (24%) were observed among them. Of the 1756 children who had initiated a high CNS-penetrating regimen, 111 (6%) had died by the end of follow-up. Twenty-six deaths (10%) were observed among 255 children on a medium CNS-penetrating regimen and 70 deaths (27%) were observed among 261 children on a low CNS-penetrating regimen.

The total person-time accrued for the 77 incident cases followed for survival was 219 person-years. Forty-three deaths were observed during follow-up resulting in a mortality rate of 196.3 per 1000 person-years (95% CI 142.1–264.5). Median survival after diagnosis was 2.0 years (Q1, Q3: 0.1, –). By the end of follow-up, 51 of the 77 children with a diagnosis of HIV encephalopathy had initiated HAART and 18 deaths were observed among them, as compared with 25 deaths among the 26 children who never initiated HAART. The numbers of deaths occurring by level of CNS-penetrating regimen were 19, 11, and 13 among 50, 12, and 15 children ending follow-up on a high, medium, or low-penetrating regimen.

Children who initiated HAART had a 50% lower risk of developing HIV encephalopathy compared with those who were not on HAART (hazard ratio 0.50, 95% CI 0.29–0.86) (Table 3). Baseline CD4 cell values less than 15% were associated with a greater than eight-fold increased risk of HIV encephalopathy (hazard ratio 8.41, 95% CI 4.79–14.76). Age less than or equal to 1 year at first neurologic examination was also independently associated with a greater than three-fold increase in HIV encephalopathy with a hazard ratio of 3.38 (95% CI 1.36–8.44). In the secondary analysis restricted to the subset of the population with HIV-RNA measurements, the HIV encephalopathy hazard ratio comparing HAART to no HAART was even stronger, 0.32 (95% CI 0.12–0.85) after adjustment for viral load. We also considered adjustment for calendar year, but treatment effects were attenuated and became nonsignificant due to the high correlation between calendar year and introduction of HAART (analyses not presented).

High CNS-penetrating regimens, as defined by CNS-penetrating scores, were associated with a 41% reduced incidence of HIV encephalopathy compared with low-penetrating regimens, although this association was not statistically significant (hazard ratio 0.59, 95% CI 0.31–1.10; Table 3). After adjustment for viral load, the effect of high CNS-penetrating regimens on incidence of HIV encephalopathy was even stronger compared with low CNS-penetrating regimens (hazard ratio 0.41, 95% CI 0.13–1.29). Given the restricted sample size in this subanalysis, this large protective association was not statistically significant. Similar to the HAART analyses, these treatment effects were attenuated with adjustment for calendar year due to the correlation between calendar year and introduction of effective CNS-penetrating regimens (analyses not presented).

In the overall population, HAART and effective CNS-penetrating regimens were associated with increased survival compared with no HAART and low CNS-penetrating regimens, respectively (Table 4). Children with a diagnosis of HIVencephalopathy, however, had 12 times the risk of death compared with children without a diagnosis of encephalopathy (hazard ratio 12.42, 95% CI 8.46–18.24). Among the 77 children with an incident diagnosis of HIVencephalopathy, HAART use halved the risk of death after diagnosis compared with non-HAART regimens (hazard ratio 0.51, 95% CI 0.25–1.05), but use of high CNS-penetrating regimens conferred a larger survival benefit (74% reduction in risk of death) after HIV encephalopathy diagnosis compared with low CNS-penetrating regimens (hazard ratio 0.26, 95% CI 0.11–0.61; Table 4).

Discussion

The present study describes a 10-fold decrease in the incidence of HIV encephalopathy among a large prospective cohort of perinatally infected children enrolled over a 14-year period, 1993–2006. This dramatic decline in incidence occurred with a concurrent increase in use of HAART, proposing an association between HAART use and risk of HIV encephalopathy. Although this hypothesis has been suggested by previous studies [13,24], this is the first study to quantify the impact of HAART on the incidence of HIV encephalopathy.

We found HAART use to decrease the risk of HIV encephalopathy by 50% compared with no HAART use. Similar to previous studies [8,9], we also found HAART use to be associated with improved overall survival compared with no HAART use. HAART also resulted in an improvement in survival after diagnosis of HIV encephalopathy, although this association was not statistically stable due to the small sample size of incident cases. These results suggest that HAART inhibits or delays HIV dissemination in the CNS and may also decrease viral replication if an active and persistent infection is already established in the brain.

One study found a significant decrease in CNS viral load with increasing numbers of CNS-penetrating antiretroviral drugs independent of HAART alone [25]. We evaluated the effect of CNS-penetrating regimens on the risk of HIV encephalopathy and found effective CNS-penetrating regimens to be associated with a lower incidence of HIV encephalopathy, although not statistically significant. However, we did observe a significant survival benefit of using high CNS-penetrating regimens after diagnosis of HIV encephalopathy. Optimal levels of antiretroviral drugs within the CNS, over what some HAART regimens provide, are likely needed to stop the active replication of HIV within the brain that can lead to further neurological decline and eventually death. Although the utility of effective CNS-penetrating antiretroviral drugs is clear in improving survival after diagnosis of HIV encephalopathy, a study assessing the impact of such drugs on cognitive impairment was equivocal [26]. Further research is required to assess the impact of antiretroviral CNS-penetration effectiveness on the various pathogenic mechanisms leading to neurological deterioration and disease.

A recent study evaluating the ability of the protease inhibitor atazanavir to penetrate the CNS [27] found cerebrospinal concentrations of atazanavir to be highly variable even when boosted with ritonavir. This result suggests a modification of the CNS-penetration-effectiveness ranks proposed by Letendre *et al.* [7]. Given that only 1% of the children classified as initiating a high CNS-penetrating regimen in our study used atazanavir boosted with ritonavir, any future modification of the ranking system is unlikely to change our results.

Our study population only included children with at least one neurological examination in PACTG 219 or 219C. This inclusion criterion allowed identification of preexisting diagnoses of HIV encephalopathy by a pediatric neurologist and subsequent follow-up after the first examination of confirmed 'disease-free' children at risk for incident HIVencephalopathy.

However, this inclusion criterion did exclude 795 perinatally infected children who did not have a neurological examination in PACTG 219 or 219C. This excluded population had significantly more female children and higher CD4 cell percentage compared with the study population. They also were significantly older than the study population. Although sex was not associated with risk of HIVencephalopathy in our analyses, the associations of age and CD4 cell percentage with risk of HIVencephalopathy suggest that the excluded population would have a lower risk of HIVencephalopathy compared with the study population.

The children in our study population were not followed from birth. Therefore, early fatal cases of HIV encephalopathy may have been missed leading to an underestimation of the incidence of HIV encephalopathy. The median age of the incident cases of HIV encephalopathy identified during follow-up was also greater than the median age of the prevalent cases of HIV encephalopathy identified at baseline, suggesting that a 'survivor' cohort of children was followed for incident analyses. If these 'survivors' were at lower risk of HIV encephalopathy compared with the general pediatric HIV-infected population, then the estimated incidence rates of HIV encephalopathy may also be underestimated. Our interest in the trend in incidence of HIV encephalopathy over time, however, would not be affected by this potential survivor effect.

As viral load information was missing for 46% of the study population, we were not able to adjust for this important confounder in our primary analyses. Sensitivity analyses conducted among the subset of children with viral load information suggest that stronger protective effects of HAART and high CNS-penetrating regimens on risk of HIV encephalopathy and survival after diagnosis of HIV encephalopathy would have been estimated with adjustment of viral load. However, as clinicians did not have viral load information to make treatment decisions in the early years of follow-up, viral load could not be a confounder in these time periods.

Diagnoses of HIV encephalopathy were collected in the study population either from chart abstraction or from neurological examination forms. It is unclear whether diagnoses collected from chart abstraction were made by treating clinicians or pediatric neurologists. Given the wide spectrum of neurological disease experienced by perinatally infected children, there may be some outcome misclassification of HIV encephalopathy. Assuming that this misclassification is nondifferential with respect to treatment, our observed protective effects of HAART and CNS-penetrating antiretroviral regimens on risk of HIV encephalopathy and survival after diagnosis of HIV encephalopathy, respectively, are conservative estimates.

In conclusion, HAART use was highly effective in reducing the risk of HIV encephalopathy among perinatally infected children and adolescents. Among children with a diagnosis of HIVencephalopathy, treatment decisions should consider the effectiveness of antiretroviral drugs in penetrating the CNS. Highly CNS-penetrating regimens conferred a substantial survival benefit to children with HIV encephalopathy compared with low CNS-penetrating regimens. Of course, any potential toxicity of individual or combination antiretroviral drugs [28] must be weighed with their ability to penetrate the CNS when making treatment decisions in pediatric HIV-infected populations.
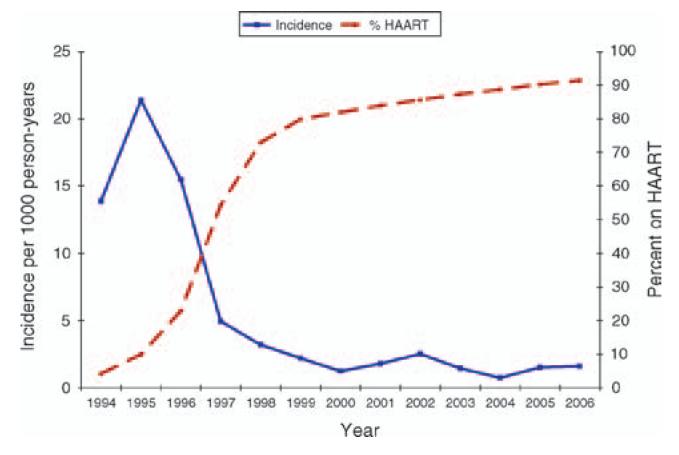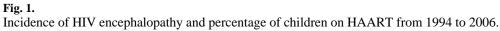
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Fig. 1.
Incidence of HIV encephalopathy and percentage of children on HAART from 1994 to 2006.

Table 1

Central nervous system penetration scale for antiretroviral drugs.

1 (lowest penetration)	2 (medium penetration)	3 (highest penetration)
Didanosine (ddI)	Emtricitabine (FTC)	Abacavir (ABC)
Tenofovir (TFV)	Lamivudine (3TC)	Zidovudine (ZDV)
Zalcitabine (ddC)	Stavudine (d4T)	Delavirdine (DLV)
Nelfinavir (NFV)	Efavirenz (EFV)	Nevirapine (NVP)
Ritonavir (RTV)	Amprenavir (APV)	Amprenavir/ritonavir (APV-r)
Saquinavir (SQV)	Atazanavir (ATV)	Atazanavir/ritonavir (ATV-r)
Saquinavir/ritonavir (SQV-r)	Fosamprenavir (f-APV)	Fosamprenavir/ritonavir (f-APV-r)
Tipranavir/ritonavir (TPV-r)	Indinavir (IDV)	Indinavir/ritonavir (IDV-r)
Enfuvirtide (T-20)		Lopinavir/ritonavir (LPV-r)

Table 2

Characteristics of study population followed for incident HIV encephalopathy and overall survival at time of first neurologic examination (*N* = 2272).

Characteristic	*N* (%)
Sex	
Male	1136 (50)
Female	1136 (50)
Age	
≤1 year	268 (12)
2–5 years	828 (36)
6–10 years	833 (37)
>10 years	343 (15)
Birth year	
<1990	874 (38)
1990–1994	996 (44)
>1995	402 (18)
Race/ethnicity	
White, Non-Hispanic[a]	342 (15)
Black, Non-Hispanic	1247 (55)
Hispanic	683 (30)
Birth weight	
<2500 g	551 (24)
≥2500 g	1640 (72)
Unknown	81 (4)
CD4 cell percentage	
<15	433 (19)
15–24	505 (22)
≥25	1271 (56)
Missing	63 (3)
HIV-RNA load (copies/ml)	
≤400	327 (14)
401–99 999	550 (24)
≥100 000	167 (7)
Missing	1228 (54)
Antiretroviral therapy	
HAART	786 (35)
Non-HAART	1486 (65)
CNS-penetrating regimens	
Low	896 (39)
Medium	765 (34)
High	611 (27)

CNS, central nervous system.

[a]Other race/ethnicity ($N = 36$) included in White, Non-Hispanic category.

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Table 3

Estimated effects of HAART and central nervous system-penetrating antiretroviral regimens on incident HIV encephalopathy.

Characteristic	Hazard ratio[a] (95% CI)	P
Antiretroviral therapy		
HAART	0.50 (0.29, 0.86)	0.01
Non-HAART	Referent	
CNS-penetrating regimens		
Low	Referent	
Medium	0.86 (0.46, 1.62)	0.64
High	0.59 (0.31, 1.10)	0.10

CI, confidence interval; CNS, central nervous system.

[a]Multivariate hazard ratios adjusted for age, sex, race, birth weight, and CD4 cell percentage at baseline.

Table 4

Estimated effects of HAART and central nervous system-penetrating antiretroviral regimens on overall survival and survival after diagnosis of incident HIV encephalopathy.

Characteristic	Hazard ratio[a] (95% CI)	P
Effect on overall survival in the entire cohort ($N = 2272$)		
Antiretroviral therapy		
HAART	0.41 (0.29, 0.58)	<0.0001
Non-HAART	Referent	
CNS-penetrating regimens		
Low	Referent	
Medium	0.25 (0.16, 0.40)	<0.0001
High	0.31 (0.22, 0.45)	<0.0001
Effect on survival after diagnosis of HIV encephalopathy ($N = 77$)		
Antiretroviral therapy		
HAART	0.51 (0.25, 1.05)	0.07
Non-HAART	Referent	
CNS-penetrating regimens		
Low	Referent	
Medium	0.51 (0.20, 1.33)	0.17
High	0.26 (0.11, 0.61)	0.002

CI, confidence interval; CNS, central nervous system.

[a]Each adjusted for age, sex, race, birth weight, and CD4 cell percentage.