Published in final edited form as:

J Acquir Immune Defic Syndr. 2015 June 1; 69(2): 193–199. doi:10.1097/QAI.0000000000000563.

Early Antiretroviral Therapy is Protective against Epilepsy in Children with Human Immunodeficiency Virus Infection in Botswana

David Bearden, MD^{1,2,3}, Andrew P. Steenhoff, MD^{2,4}, Dennis J. Dlugos, MD, MSCE¹, Dennis Kolson, MD, PhD⁵, Parth Mehta, MD⁶, Sudha Kessler, MD, MSCE^{1,3}, Elizabeth Lowenthal, MD, MSCE^{2,3,7}, Baphaleng Monokwane, MD⁸, Gabriel Anabwani, MBChB, MMed⁹, and Gregory P. Bisson, MD, MSCE^{2,3,10}

¹Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, USA

²Botswana-UPenn Partnership

³Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania

⁴Division of Infectious Disease, Children's Hospital of Philadelphia

⁵Division of Neurology, Hospital of the University of Pennsylvania, Perelman School of Medicine, Philadelphia, USA

⁶Texas Children's Cancer & Hematology Centers, Baylor College of Medicine, Houston, USA

⁷Department of Pediatrics, Children's Hospital of Philadelphia

⁸Department of Pediatrics, University of Botswana

⁹Botswana-Baylor Children's Clinical Centre of Excellence

¹⁰Division of Infectious Disease, Hospital of the University of Pennsylvania, Perelman School of Medicine, Philadelphia, USA

Abstract

Background—Seizures are common among patients with HIV/AIDS in the developing world and are associated with significant morbidity and mortality. Early treatment with combination antiretroviral therapy (cART) may reduce this risk by decreasing rates of central nervous system infections and HIV encephalopathy.

Methods—A case-control study of new onset epilepsy among children age 0-18 years with perinatally acquired HIV/AIDS followed in Gaborone, Botswana during the period 2003-2009 was conducted. Children with epilepsy were identified and compared to age-and-sex-matched controls without epilepsy with respect to timing of cART initiation. Early treatment was defined as

Corresponding author: David Bearden, Phone: (215) 983-9766, Fax (215) 590-1771, 10th Floor Colket Translational Research Building, 3400 Civic Center Blvd, Philadelphia, PA 19104, bearden@email.chop.edu.

Prior Presentation: Preliminary data from this study were presented at the World Federation of Neurology Meeting Annual Meeting September 2013 in Vienna, Austria and the American Academy of Neurology Annual Meeting April 2012, New Orleans, Louisiana.

Conflicts of Interest: All authors report no conflicts of interest.

treatment with cART before the age of twelve months, at a CD4% of greater than 25 in children age 1-5, or at an absolute CD4 count of >350 cell/mm³ in children age 5 and older.

Results—We identified 29 cases of new onset epilepsy and 58 age and sex-matched controls. The most common identified etiologies for epilepsy were CNS infections and direct HIV neurotoxicity. Only 8 (28%) of the children who developed epilepsy received early treatment compared with 31 (53%) controls (OR 0.36, 95% CI 0.14-0.92, $p=0.03$). This effect was primarily driven by differences in rates of epilepsy among children who initiated treatment with cART between the ages of 1-5 years (11% vs. 53%, OR 0.11, 95% CI 0.01-1.1, $p=0.06$).

Conclusions—Earlier initiation of cART may be protective against epilepsy in children with HIV.

Keywords

Epilepsy; Seizures; HIV; Pediatric; Botswana; Antiretroviral Therapy; Highly Active

Introduction

Infection with Human Immunodeficiency Virus (HIV) may lead to seizures through a variety of mechanisms, including vulnerability to central nervous system opportunistic infections (OIs), metabolic disturbances, and neuronal damage induced by HIV replication within the central nervous system (CNS).¹⁻⁶ Seizures are common in children with HIV, with a recent South African study identifying seizures in 7.6% of their cohort.⁷ However, the prevalence of seizures in adults with HIV has declined from 17% in the era prior to the introduction of combination antiretroviral therapy (cART) to 3 to 6% in more recent studies, suggesting that treatment with cART may reduce the risk of seizures.³⁻⁵ Earlier initiation of cART may provide additional protection against factors predisposing to seizures compared to late initiation of cART.⁸

Despite robust debate and investigation, the optimal timing of cART initiation in children has not yet been defined. While initiating therapy in all children younger than 12 months of age and in children with advanced clinical stage clearly reduces mortality,⁹ two recent Cochrane reviews concluded that there was insufficient evidence for early treatment in children age 1-3⁹ or in children age 2-5.¹⁰ The World Health Organization (WHO) recently released guidelines recommending treatment for all children younger than 5 years regardless of CD4 count, and treatment for children over age 5 if their CD4 counts fall below 500 cells/mm³.¹¹ These recommendations have not yet been implemented in most of Sub-Saharan Africa because of cost concerns, and a recent review found that most children in Sub-Saharan Africa are still being treated at CD4 counts below 350 cells/mm³.¹²

Botswana is a sparsely populated country in Southern Africa with one of the highest rates of HIV infection in the world, affecting 18.5% of adults and 2.2 % of all infants.¹³ Botswana was one of the first countries to provide free antiretroviral therapy (ART) to all children, with nearly 100% of all eligible children receiving ART by 2013.¹³ This has resulted in high retention rates in care and a low mortality rate in children with HIV,¹⁴ and facilitates the study of chronic diseases in children with HIV. Antiretroviral drugs first became widely

available for children in Botswana in 2003 and timing of treatment initiation varied depending on national guidelines, which became progressively more aggressive over time. Thus, there was considerable variability in timing of therapy during the period 2003-2009.¹⁴

We performed a case-control study in a large population of children with perinatally acquired HIV followed as outpatients in Gaborone, Botswana, to identify risk factors for epilepsy. We chose to focus on epilepsy rather than on isolated seizures because epilepsy can be ascertained with a high degree of accuracy from retrospective chart review¹⁵ and has a significant and measurable negative effect on both lifespan and quality of life.¹⁶ Our primary hypothesis was that earlier initiation of cART would be protective against the development of epilepsy.

Methods

Overview

We conducted a retrospective case-control study among children ages 0-18 years with a history of perinatally acquired HIV infection followed in the national HIV treatment program and initiating treatment with cART between June 1st, 2003 and June 1st, 2009 at the Botswana-Baylor Children's Clinical Centre of Excellence, in Gaborone, Botswana. We identified children with HIV who developed epilepsy during the study period and compared them with 1:2 age- and sex-matched controls with no history of seizures by the end of the study period.

Population and Setting

The population for the study was comprised of perinatally infected children ages 0-18 years at enrollment and followed as outpatients at the Botswana-Baylor Children's Clinical Centre of Excellence. The clinic is the largest referral center for children with HIV who live in Botswana and has been described in previous publications.^{14,17} At this clinic, records for subjects from 2003-2006 were exclusively kept on paper. Subjects followed after 2006 had both paper and electronic medical records.

Inclusion criteria included 1) HIV infection, as documented by PCR or diagnostic immunoassay, 2) enrollment at the clinic and at least two documented visits at least 6 months apart during the study period, and 3) initiation of cART at the clinic during the period of the study 4) Age less than 19 years. Exclusion criteria included 1) documented infection with HIV through sexual transmission or contaminated blood products and 2) history of seizures documented prior to cART initiation. Patients with seizures prior to cART initiation were excluded to ensure that only incident cases of epilepsy were included.

The study was reviewed and approved by all relevant institutional review boards. Informed consent was waived because there was no more than minimal risk to subjects and the waiver did not adversely affect the rights and welfare of the subjects. Subject information was kept in a double-password protected anonymized database with no identifying information which could be linked to specific individuals.

Definitions

Seizures were defined as present if a clinical seizure was documented in the medical record.

Unprovoked seizures were defined according to International League Against Epilepsy (ILAE) criteria as seizures not due to an immediate precipitating cause such as fever or infection.¹⁸ Subjects who sustained brain injury secondary to an acute central nervous system infection and then went on to have seizures after the acute infection had resolved were considered to have unprovoked seizures.

Epilepsy was defined as two or more unprovoked seizures documented in the medical record occurring at least 24 hours apart.¹⁸

For our primary analysis, **early treatment** was defined according to 2010 WHO consensus criteria¹⁹ as initiation of cART prior to 12 months of age, at a CD4 percentage greater than 25% in children ages 12 months to 59 months, or a CD4 count greater than 350 cell/mm³ for children 60 months or older. We chose to include children age 12-24 months in the stratification by CD4 percentage according to modified recommendations for low resource settings as this was the more relevant criteria for our setting. We did not include absolute CD4 counts for children under 60 months in the criteria due to high variability across the range of ages in this group. We also did not include measures of disease stage in our criteria for early treatment as this would have created a bias in favor of early treatment. In a secondary analysis we evaluated whether changing the definition of early treatment would have an effect on epilepsy rates (See Table 2).

Delayed treatment was defined as all patients not meeting criteria for early treatment as defined above.

A diagnosis of **HIV** was defined as presence, in the medical record, of a positive HIV PCR prior to the age of 18 months or a positive HIV PCR or double-rapid ELISA after the age of 18 months.

Family status was defined as whether the child was living with one or both biological parents or living with other relatives or caretakers.

HIV encephalopathy was defined according to modified CDC criteria as 1) failure to attain or loss of developmental milestones or loss of intellectual ability, 2) present for at least 2 months and 3) in the absence of a concurrent illness other than HIV, with alternative causes of encephalopathy ruled out by history and imaging.²¹ We could not include measures of acquired microcephaly or symmetric motor deficits into our modified definition due to lack of information on these features recorded in the medical records. Developmental assessment was abstracted from standardized evaluations performed for clinical care and recorded in the chart.

Clinical and immunologic staging was defined according to WHO Guidelines.²²

Identification of cases and controls

Cases were defined as individuals meeting the definition of epilepsy during the period of the study after cART initiation. Controls were patients from the same population meeting the same inclusion/exclusion criteria as cases but with no history of seizures by the end of the follow up period. Controls were matched to cases on year of birth and sex. Matching on year of birth was employed to avoid confounding by improvements in the quality of prenatal and perinatal care and changes in HIV care during the period of the study. Matching on sex was employed to avoid confounding by potential differences in epilepsy rates between males and females.

Cases and controls were identified by review of paper and (after 2006) electronic medical records. All electronic charts were searched for the keywords “seizure,” “sz,” s/z,” “convulsion,” “epileptic,” “epilepsy,” “fit,” “phenobarbital,” “phenobarbitone,” “phenytoin,” “carbamazepine,” “valproate,” “valproic,” “lamotrigine” and “gabapentin.” Paper charts were reviewed manually (by a study nurse or student) to identify patients missed by the electronic search and to identify the total population meeting inclusion and exclusion criteria for the study. In potential cases, all available historical records were further reviewed (by study author DB, a child neurologist) to confirm a diagnosis of seizures and epilepsy. Controls were identified as the two patients with the closest date of birth in the database of the same sex as the matched case who were alive at the time that epilepsy developed in the matched case. All eligible subjects who developed epilepsy during the study period were included as cases; patients with only single seizures or provoked seizures (n=43) were excluded from further analysis.

Data Collection

All data were collected by study author (DB) or a research nurse or student trained by DB through record review of electronic and paper medical records during the period 2010-2013. Collected data included subject demographics, clinical history, and laboratory results. For patients who initiated treatment late the reason for delayed treatment was abstracted from chart review. For patients with epilepsy, clinical data were also collected on epilepsy etiology. Missing data were treated by pairwise deletion. All data were collected on paper data collection forms and verified through review of primary source data (by study author DB) before entry into an anonymized Access database. Potential confounders were compiled based on previously described risk factors for seizures and epilepsy in both HIV-infected and HIV-uninfected children. Information on other exposure variables and potential confounders was collected as detailed in Table 1. Data on each of the purported risk factors was collected at the time cART was initiated. Only incident cases of epilepsy occurring after cART initiation were included.

Statistical Analysis

Statistical analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX USA). Comparisons between matched groups were performed using univariate conditional logistic regression or exact logistic regression, while comparison between unmatched groups was performed using standard logistic regression. Significance level was set at $p=0.05$. Optimal matching ratio for controls was determined prior to collection of data based on

simulations of likely numbers of cases. Given the number of cases identified, with 2:1 matching we had >95% power to detect an odds ratio of at least 3 for our primary outcome variable, but only 50% power to detect an odds ratio of 2 or lower for dichotomous variables. Confounding was assessed by evaluating the association of each covariate with the exposure (early treatment) and the outcome (epilepsy). Prior to data collection we pre-specified that covariates with a univariate $P < 0.20$ would be evaluated as potential confounders in a multivariable conditional logistic regression model. Potential confounders whose inclusion in the multivariable model changed the unadjusted association by greater than 15% were considered actual confounders. We excluded measures of disease stage and immunosuppression from the model as these are part of the hypothesized causal pathway modified by early treatment.

Results

Characteristics of Cases and Controls

There were a total of 1244 subjects meeting eligibility criteria for the study. Out of this population we identified 29 cases and 58 matched controls. Missing data were minimal for all reported exposure variables except as documented in Table 1, and there were no missing data on primary exposure or outcome variables. Data were missing at random except for family history of epilepsy and birth complications, which were more likely to be missing in controls than in cases (Chi-Square test or t-test of independence < 0.05 for these variables, > 0.05 for all other variables).

A summary of the demographic characteristics of cases and controls is presented in Table 1. Epilepsy cases included 14 males (48%) and 15 females (52%). Median year of birth was 1998 (IQR 1995-2002). All cases and controls were of black race and were from Botswana, except for one patient who was born in Uganda. As per the inclusion criterion, all cases and controls were started on cART during the period of the study, with the most common regimen being zidovudine, lamivudine, and nevirapine (In 52% of cases, 60% of controls, $p = 0.5$). Median age at cART initiation was similar between cases and controls (72 months vs. 70 months, $p = 0.46$). Median age at epilepsy diagnosis among cases was 7 years (range 1 year to 17 years, IQR 3-9 years).

There were no significant differences between cases and controls in any of the socioeconomic indicators we evaluated including family status, access to running water, and presence of electricity in the home. Conventional epilepsy risk factors such as birth complications and family history of epilepsy were minimal in this cohort and were similar between cases and controls. Cases were more likely than controls to have a history of advanced clinical stage (WHO Stage 4, 66% vs. 38%, OR 3.1, $p = 0.01$) and severe immunosuppression by age-specific WHO criteria (59% vs. 29%, OR 3.8, $p = 0.01$). There were no other significant differences in measured exposure variables (birth history, history of head trauma, and adherence rates) between cases and controls.

Effect of Early Treatment

Information on treatment initiation is provided in Table 2. A total of 39 patients (45%) received early treatment according to our primary definition. Only 8 (28%) of the children who developed epilepsy received early treatment compared with 31 (53%) of controls. Early treatment was associated with a 64% reduction in the odds of epilepsy (OR 0.36, 95% CI 0.14-0.92, $p=0.03$) in the unadjusted analysis. This effect was primarily driven by differences in rates of epilepsy among children who initiated early treatment with cART between the ages of 1-5 years (11% vs. 53%, OR 0.11, 95% CI .01-1.1, $p=0.06$).

In a secondary analysis we evaluated whether defining early treatment according to more aggressive treatment guidelines (Early Treatment Definition 2, requiring treatment for children over 5 at an absolute CD4 count >500) would have an additional effect on epilepsy. In this analysis only 24% of cases compared to 47% of controls received early treatment (OR 0.37, 95% CI 0.14-1.0, $p=0.05$), suggesting an additional protective effect from implementing more aggressive treatment guidelines. Finally we evaluated the effects of very delayed treatment (Early Treatment Definition 3, treatment above vs. below a CD4 % of 15 for children 1-5, and >200 for children 5 and older) and again found significant differences between early and late treated groups (41% vs. 74%, OR .32, 95% CI .13-.76, $p=.01$). We did not identify any confounding variables in this analysis and thus only the unadjusted odds ratio is shown.

Determinants of Delayed Treatment

Given the above results we explored reasons for delayed treatment, defined as all children who did not receive early treatment according to definition 1 above. Whenever possible we attempted to determine the primary reason initiation of treatment was delayed. The most common reason for delayed treatment was delayed presentation to care (in 22 subjects, 46%), followed by loss to follow up after initiation of care (in 5 subjects, 10%), deferred treatment due to care provider decision (in 5 subjects, 10%), and parental or patient preference (in 3 subjects, 6%). In the remaining 13 subjects (27%) no specific reason could be identified. There were insufficient numbers of patients in each subgroup to be able to identify significant differences in subgroups between cases and controls.

Epilepsy etiology

Seizure and epilepsy etiology were determined by study author DB after review of all available clinical, laboratory and imaging information. When epilepsy co-occurred along with HIV encephalopathy and history and imaging ruled out alternative etiologies, a direct neurotoxic effect of HIV was considered to be the etiology of the epilepsy. A summary of the most common epilepsy etiologies is presented in Table 3. Imaging was performed in most patients with 20 subjects having had CT scans and 4 having had MRI. Lumbar puncture had been performed in 15 subjects. EEG was not generally available in Botswana during the period of the study. Central nervous system (CNS) infections accounted for nearly a third of all cases of epilepsy, with the most common specific etiologies being tuberculosis meningitis, cryptococcal meningitis, bacterial meningitis, and toxoplasmosis. HIV neurotoxicity was the second most common identified cause of epilepsy in this cohort accounting for 27% of all cases, with a variety of other causes (1 case each caused by stroke,

prematurity with intraventricular hemorrhage, and congenital brain malformation) accounting for the remainder of identified causes. In nearly a third of cases no specific cause could be identified. Epilepsy etiology varied by whether patients were in early or late treatment groups, with patients treated late more likely to have epilepsy secondary to either CNS infection or HIV neurotoxicity, and patients treated early more likely to have epilepsy of unknown etiology.

Discussion

This study demonstrates decreased rates of early treatment with cART in children with HIV who developed epilepsy. At every cutoff for early treatment considered there continued to be a reduction in the odds of epilepsy, suggesting that there is no absolute threshold for earlier treatment; instead, across the range of thresholds considered, earlier treatment was better than later treatment. CNS infections and HIV neurotoxicity were the most common causes of epilepsy in this population, similar to what has been reported in the adult literature and in the one prior pediatric study.^{1-7; 23, 24} There were notable differences in epilepsy etiology between the early and late treatment groups, supporting the idea that the mechanism by which early treatment reduces epilepsy is through reduction in rates of CNS infections and HIV neurotoxicity.²⁵

The optimal timing of antiretroviral therapy in low resource settings remains unknown and is the subject of ongoing debate. Financially stressed health care systems must weigh the relative benefits of early treatment against the potential costs.¹² Our study suggests that neurologic complications that may result from delaying treatment are potentially significant and should be considered. This finding is in agreement with prior studies of early treatment that have demonstrated a range of benefits including reduced mortality, reduced rates of CNS infections, and reduced rates of HIV encephalopathy.²⁵⁻²⁷ Of note, in our study the most common reason for delayed treatment was delayed presentation to care, suggesting that aggressive outreach to identify and treat children with HIV before they develop neurologic complications may be necessary to realize the benefits of early treatment.

Our study provides a counterpoint to the recent PREDICT study conducted in Thailand and Cambodia that found no difference in rates of cognitive impairment or other serious adverse events between children who were treated early and those who had therapy deferred.²⁸ Of note, in the PREDICT study fewer than 10% of children were under age five, resulting in a very different population from our study. Our study results were driven by decreased rates of epilepsy in children who initiated treatment under age five, suggesting that young children are particularly vulnerable to these complications. Further, the PREDICT study excluded patients with an AIDS-defining illness. Our study results were driven by children with CNS infections and HIV encephalopathy, and thus would have been excluded from the PREDICT study. The PREDICT study results on deferred treatment may therefore only be applicable to a specific subset of healthy older children.

Our study has several limitations. First, specific information on why treatment was delayed in some patients was not documented in the charts and may have been nonrandom, creating the possibility of confounding by indication. Patients may have been started on cART

“early” due to concerns regarding worsening health or the development of developmental issues concerning for early HIV encephalopathy. However, this would only serve to weaken the effect we are seeing from early treatment and thus would be unlikely to change the result. It is also possible that earlier initiation of antiretroviral therapy may represent a “quality” indicator of the provider, that is, that providers that would initiate early therapy were somehow better or more aggressive than providers that initiated therapy late. This is unlikely as the primary driver of delayed treatment was delayed presentation to care. In addition, all patients were managed through a team approach and seen by multiple different providers over time without a single primary provider.

Secondly, this is a retrospective study, and thus subject to the limitations of reliance on clinically collected data. This is unlikely to have affected the accuracy of epilepsy diagnoses, as all patients had multiple clinical seizures documented as witnessed by multiple different witnesses and providers and almost all were treated with anti-epileptic drugs. However, the diagnosis of HIV encephalopathy is likely to have been less accurate and may include patients with developmental regression of other etiologies, for example, secondary to occult seizures, infections or malnutrition. However, neither of these factors would be likely to have a significant effect on our conclusions. In addition, there is the possibility of unmeasured confounders. Socioeconomic status is a potential confounder in the relationship between delayed treatment and development of epilepsy which we were only partially able to account for due to the limitations of retrospectively collected data. Finally, this study is based upon an outpatient cohort at a single center and thus may not be representative of children with HIV as a whole. The Centre provides active case management and adherence support which results in better adherence and less loss to follow up than is likely to be the case in many similar settings.^{14, 17} Other settings with greater loss to follow up or poorer adherence would be likely to see fewer benefits from early treatment.

Conclusion

In summary, early treatment with cART is likely to be protective against epilepsy in children with HIV. Aggressive outreach to identify and treat all children under age five regardless of CD4 count as per new WHO guidelines would likely have the added benefit of reducing rates of epilepsy in this population. Prospective randomized controlled trials are necessary to identify the optimal timing of cART initiation in older children. Our study adds to the growing body of literature that suggests that early identification and treatment of children with HIV is key to preventing neurologic complications in this vulnerable population.

Acknowledgments

Source of Funding: This publication was made possible through the core services and support provided by the Penn Center for AIDS Research (CFAR), an NIH funded program (P30 AI 045008).

References

1. Price RW. Neurological complications of HIV infection. *Lancet*. 1996; 348:445–452. [PubMed: 8709786]
2. Levy RM, Bredeson DE. Central nervous system diseases in HIV infection. *J Acquir Immune Defic Syndr*. 1988; 1:41–64. [PubMed: 3063805]

3. Wong MC, Suite ND, Labar DR. Seizures in human immunodeficiency virus infection. *Arch Neurol*. 1990; 47:640–642. [PubMed: 2346390]
4. Kellinghaus C. Frequency of Seizures and Epilepsy in neurological HIV-infected patients. *Seizure*. 2008; 17(1):27–33. [PubMed: 17618132]
5. Pascual-Sedano B, Iranzo A, Marti-Fabregas J, et al. Prospective study of new-onset seizures in patients with human immunodeficiency virus infection: etiologic and clinical aspects. *Arch Neurol*. 1999; 56:609–612. [PubMed: 10328257]
6. Modi M. New Onset Seizures in HIV. *Epilepsia*. 2009; 50(5):1266–1269. [PubMed: 19374659]
7. Samia P, Petersen R, Walker KG, et al. Prevalence of Seizures in Children with Human Immunodeficiency Virus. *J Child Neurol*. 2013; 28(3):297–302. [PubMed: 22752475]
8. Collins IJ, Judd A, Gibb DM. Immediate antiretroviral therapy in young HIV-infected children. *Current Opinion in HIV and AIDS*. 2014; 9(1):87–94. [PubMed: 24247666]
9. Penazzato M, Prendergast AJ, Muhe LM, et al. Optimisation of antiretroviral therapy in HIV-infected children under 3 years of age. *Cochrane Database of Systematic Reviews*. 2014; 5:CD004772. [PubMed: 24852077]
10. Siegfried N, Davies MA, Penazzato M, et al. Optimal time for initiating antiretroviral therapy (ART) in HIV-infected, treatment-naïve children aged 2 to 5 years old. *Cochrane Database of Systematic Reviews*. 2013; 10:CD010309. [PubMed: 24114324]
11. World Health Organization. [Accessed January 15 2014] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2013. Available at: <http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html>
12. Gupta S, Granich R, Suthar AB, et al. Global policy review of antiretroviral therapy eligibility criteria for treatment and prevention of HIV and tuberculosis in adults, pregnant women, and serodiscordant couples. *J Acquir Immune Defic Syndr*. 2013; 62(3):e87–e97. [PubMed: 23187942]
13. National AIDS Coordinating Agency. [accessed December 4 2014] Botswana 2013 Global AIDS Response Report. Government Publication March 2014 Available at: http://www.unaids.org/sites/default/files/country/documents/BWA_narrative_report_2014.pdf
14. Lowenthal ED, Anabwani GM, Jibril HB, et al. Botswana-Baylor Children's Clinical Centre of Excellence. *South Afr J HIV Med*. 2005; 6(2):42–46.
15. Kang BS, Cheong HK, Jung KY, et al. The Validity and Reliability of Characterizing Epilepsy Based on an External Review of Medical Records. *Epidemiol Health*. 2013; 35:e2013006. [PubMed: 23991344]
16. Baker GA, Nashef L, van Hout BA. Current issues in the management of epilepsy: the impact of frequent seizures on cost of illness, quality of life, and mortality. *Epilepsia*. 1997; 38(Suppl 1):S1–S8. [PubMed: 9092951]
17. Lowenthal ED, Ellenberg JH, Machine E, et al. Association between efavirenz-based compared with nevirapine-based antiretroviral regimens and virological failure in HIV-infected children. *JAMA*. 2013; 309(17):1803–1809. [PubMed: 23632724]
18. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia*. 2010; 51:676–685. [PubMed: 20196795]
19. World Health Organization. [Accessed 10/22/13] Antiretroviral therapy for HIV infection in infants and children: Towards universal access. Available at: <http://www.who.int/hiv/pub/paediatric/infants2010/en/index.html>
20. Doherty M, Ford N, Vitoria M, et al. The 2013 WHO guidelines for antiretroviral therapy: evidence-based recommendations to face new epidemic realities. *Curr Opin HIV AIDS*. 2013; 8:528–534. [PubMed: 24100873]
21. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force. *Neurology*. 1991; 41(6):778–785. [PubMed: 2046917]
22. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. World

Health Organization; Geneva: 2007. Available at: <http://www.who.int/hiv/pub/guidelines/hivstaging/en/> [Accessed 8/1/2014]

23. Weisberg LA. Neurologic abnormalities in human immunodeficiency virus infection. *South Med J*. 2001; 94:266–275. [PubMed: 11284512]
24. Pesola GR, Westfal RE. New-onset generalized seizures in patients with AIDS presenting to an emergency department. *Acad Emerg Med*. 1998; 5:905–911. [PubMed: 9754504]
25. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. 2009; 373:1352–1363. [PubMed: 19361855]
26. Lewis J, Walker AS, Castro H, et al. Age and CD4 count at initiation of antiretroviral therapy in HIV-infected children: effects on long-term T-cell reconstitution. *J Infect Dis*. 2012; 205:548–556. [PubMed: 22205102]
27. Cotton MF, Violari A, Otway K, et al. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. *Lancet*. 2013; 382(9904):1555–1563. [PubMed: 24209829]
28. Puthanakit T, Ananworanich J, Vonthanak S, et al. Cognitive function and neurodevelopmental outcomes in HIV-infected children older than 1 year of age randomized to early versus deferred antiretroviral therapy: the PREDICT neurodevelopmental study. *Pediatr Infect Dis J*. 2013; 32:501–508. [PubMed: 23263176]

Table 1
Baseline Characteristics of Cases and Controls

	Cases (n=29)	Controls (n=58)	P values ^a
<i>Demographics</i>			
Year of birth, median (range)	1998 (1988-2006)	1998 (1989-2006)	N/A
Age at initiation of cART, median, in months (IQR)	72 (24-96)	70 (22-120)	.46
Male sex (% male)	14 (48%)	28 (48%)	N/A
<i>Socioeconomic indicators</i>			
Electricity in home	28 (97%)	53 (92%)	.41
Running water in home	26 (91%)	52 (90%)	1
Parents as primary caretakers ^b	21 (72%)	41 (70%)	.8
<i>HIV-specific Risk Factors</i>			
WHO Clinical Stage ^c			.05
Stage 1	2 (7%)	14 (24%)	
Stage 2	1 (3%)	2 (4%)	
Stage 3	7 (24%)	20 (35%)	
Stage 4	19 (66%)	22 (38%)	
WHO Immunologic Stage ^d			.006
No/mild immunosuppression	6 (21%)	31 (53%)	
Advanced immunosuppression	6 (21%)	10 (17%)	
Severe immunosuppression	17 (59%)	17 (29%)	
<i>Other risk factors</i>			
History of prematurity	1 (3%) n=23	3 (5%) n=50	0.71
History of birth complications	1 (3%) n=27	2 (3%) n=46	1
Family history of epilepsy	1 (3%) n=29	1 (2%) n=35	.61

Abbreviations: cART, combination antiretroviral therapy. WHO, World Health Organization. HIV, Human Immunodeficiency Virus. IQR, Interquartile Range.

^a All variables analyzed by univariable conditional logistic regression controlling for matching

^b Patients cared for at home by one or both parents.

^c Defined by the presence of stage-specific conditions and opportunistic infections, ranging from Stage 1 (least severe) to Stage 4 (most severe).²²

^d Defined by age-specific classifications based on CD4 percentages in children under 5 and absolute CD4 counts in children 5 and older.²²

Table 2

Effects of Early Treatment

	Cases	Controls	OR	95% CI	P-values ^d
Early Treatment Definition 1^a					
	8 (28%)	31 (53%)	.36	.14-.92	.03
Treated before age 12 months	3 (10%)	8 (14%)	.68	.15-3.1	.62
Treated at CD4 % ≥ 25 (age 1-5)	1/9 (11%)	9/17 (53%)	.11	.01-1.1	.06 ^e
Treated at CD4 count above 350 (age >5)	4/17 (24%)	14/33 (42%)	.63	.14-2.8	.54
Early Treatment Definition 2^b					
	7 (24%)	27 (47%)	.37	.14-1.0	.05
Treated at CD4 count above 500 (age >5)	3/17 (18%)	10/33 (30%)	.49	.12-2.1	.34 ^e
Early Treatment Definition 3^c					
	12 (41%)	43 (74%)	.32	.13-.76	.01
Treated at CD4 % >15 (age 1-5)	2/9 (22%)	12/17 (71%)	.12	.02-.79	.03^e
Treated at CD4 count above 200 (age >5)	7/17 (41%)	25/33 (76%)	.34	.10-1.1	.08

Abbreviations: OR, Odds Ratio. 95% CI, 95% Confidence Interval.

^a Early treatment according to definition 1 corresponds to World Health Organization 2010 recommendations and consists of treatment before 12 months of age at any CD4 count, treatment at a CD4% of greater than or equal to 25 for children age 1-5, or treatment at a CD4 count of >350 for children older than age five.

^b Early treatment according to definition 2 consists of treatment before 12 months of age at any CD4 count, treatment at a CD4% of greater than or equal to 25 for children age 1-5, or treatment at a CD4 count of >500 for children older than age five.

^c Early treatment according to definition 3 consists of treatment before 12 months of age, treatment at a CD4% of greater than 15 for children age 1-5, or treatment at a CD4 count of >200 for children older than age five.

^d All p-values calculated using univariable conditional logistic regression accounting for matching unless otherwise specified.

^e Calculated using standard logistic regression due to small numbers of subjects within groups.

Table 3
Epilepsy Etiology, by Treatment Group

	Total Patients (n=29)	Early treatment group (n=8)	Late treatment group (n=21)
CNS infections	9 (31%)	1 (13%)	8 (38%)
TB meningitis	2	1	1
Cryptococcal meningitis	2	0	2
Bacterial meningitis	1	0	1
Unspecified meningitis	2	0	2
Brain abscess	1	0	1
Toxoplasmosis	1	0	1
HIV Neurotoxicity	8 (27%)	1 (13%)	7 (33%)
Unknown	9 (31%)	4 (50%)	5 (24%)
Other, specified cause	3 (9%)	2 (25%)	1 (5%)
Ischemic Stroke	1	0	1
Congenital Malformation	1	1	0
Birth asphyxia	1	1	0

Abbreviations: CNS, Central Nervous System; HIV, Human Immunodeficiency Virus; TB, Tuberculosis.