Published in final edited form as:

AIDS. 2012 October 23; 26(16): 2027–2037. doi:10.1097/QAD.0b013e3283578bfa.

The Impact of HAART on Cardiomyopathy among Children and Adolescents Perinatally Infected with HIV-1

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Abstract

Objective—Previous studies of cardiomyopathy among children perinatally infected with HIV were conducted before the routine use of highly active antiretroviral therapy (HAART). Nucleoside analogues (NRTIs), the backbone of HAART, have been associated with mitochondrial toxicity, which can lead to cardiomyopathy. We evaluated the association of HAART and specific NRTIs associated with mitochondrial toxicity, on development of cardiomyopathy among perinatally HIV-infected children.

Design—3,035 perinatally HIV-infected children enrolled in a US-based multicenter prospective cohort study, were followed for cardiomyopathy, defined as a clinical diagnosis or initiation of digoxin, from 1993–2007.

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Conflicts of interest

None declared.

Financial Disclosures: None reported.

Previous Presentations: Presented in part at XVIII International AIDS Conference, Vienna, Austria, July 2010.

Author Contributions: Dr Patel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Patel, Van Dyke, Mittleman, Colan, Oleske, Seage.

Acquisition of data: Van Dyke, Oleske.

Analysis and interpretation of data: Patel, Van Dyke, Mittleman, Colan, Oleske, Seage.

Drafting of the manuscript: Patel, Van Dyke, Seage.

Critical revision of the manuscript for important intellectual content: Patel, Van Dyke, Mittleman, Colan, Oleske, Seage.

Statistical analysis: Patel, Seage.

Obtained funding: Oleske, Van Dyke, Seage.

Administrative, technical, or material support: Seage.

Study supervision: Patel, Van Dyke, Mittleman, Colan, Oleske, Seage.

Methods—Cox models were used to estimate the effects of HAART and NRTIs on cardiomyopathy, identify predictors of cardiomyopathy among HAART users, and estimate the association between development of cardiomyopathy and mortality.

Results—99 cases of cardiomyopathy were identified over follow-up (incidence rate: 5.6 cases per 1,000 person-years) at a median age of 9.4 years. HAART was associated with a 50% lower incidence of cardiomyopathy compared to no HAART use (95% confidence interval: 20%, 70%). Zalcitabine (ddC) use, however, was associated with an 80% higher incidence of cardiomyopathy. Among HAART users, older age at HAART initiation, ddC use before HAART initiation, initiating a HAART regimen containing zidovudine (ZDV), and a nadir CD4<15% were independently associated with a higher rate of cardiomyopathy. Cardiomyopathy was associated with a 6-fold higher mortality rate.

Conclusions—HAART has dramatically decreased the incidence of cardiomyopathy among perinatally HIV-infected children. However, they remain at increased risk for cardiomyopathy and ongoing ZDV exposure may increase this risk.

Keywords

cardiomyopathy; HAART; mortality; perinatally HIV-infected children; zidovudine

Introduction

Since the first pediatric cases of HIV-associated cardiomyopathy were reported in the late 1980s, cardiomyopathy has been the leading non-infectious cause of death among HIV-infected children [1–4]. It is a Centers for Disease Control (CDC) Category B condition and a World Health Organization HIV clinical stage 4 disease [5,6].

Numerous studies have evaluated cardiac function among HIV-infected children [7–18]. The United States (US)-based Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study (P2C2) reported an incidence of poor left ventricular (LV) function, heart failure, and/or use of cardiac medications, of 18–30% [11–15]. This is similar to the prevalence of cardiac dysfunction found among HIV-infected children from Uganda, Nigeria, and South Africa [17–19]. Although symptomatic cardiac dysfunction was rarely diagnosed among the P2C2 children, mild LV dysfunction was associated with mortality [12,15].

Several mechanisms of HIV-associated cardiomyopathy have been proposed. The presence of HIV within the heart initially suggested that cardiac damage resulted from direct infection of cardiac myocytes [20–22]. HIV, however, does not replicate within myocytes [23,24]. Increased production of pro-inflammatory cytokines by infected inflammatory cells within the myocardium may be an alternative mechanism. Cytokine activation results in cardiomyocyte apoptosis, eventually leading to ventricular remodeling [24–26]. Another proposed mechanism for cardiomyopathy is nucleoside reverse transcriptase inhibitor (NRTI) induced mitochondrial toxicity [27–29]. NRTIs, which inhibit HIV reverse transcriptase, also inhibit DNA polymerase gamma, the enzyme responsible for mitochondrial DNA (mtDNA) replication [27–34]. NRTIs inhibit DNA polymerase gamma in varying degrees within different human tissues [30–34]. The rank order of the effects of NRTIs on mitochondria however, is relatively consistent, with zalcitabine (ddC), an NRTI that is no longer in use, associated with the greatest degree of mitochondrial toxicity, followed by didanosine (ddI), stavudine (D4T), and zidovudine (ZDV) [30–34]. Lamivudine (3TC), abacavir (ABC), and tenofovir (TDF) have relatively limited effects on mitochondria [30,31]. However, an adult study did find an association between current ABC use and left ventricular hypertrophy [35].

NRTIs constitute the backbone of highly active antiretroviral therapy (HAART). Survival among perinatally-infected children has increased with HAART [36], generating questions about the long-term effect of HAART on cardiac disease. A few studies have examined the association between antiretroviral (ARV) use and cardiac function among HIV-infected children, but they were all conducted in the pre-HAART era [8,10,13]. Two studies found no toxicity with ZDV [8,13], while one found an 8-fold increased risk of cardiomyopathy with ZDV [10]. With these conflicting results and increased HAART use, including ZDV, among HIV-infected children, there is a need to assess the effect of HAART on cardiomyopathy. We described the incidence of cardiomyopathy from 1993–2007 in a large US-based cohort of perinatally HIV-infected children, and evaluated the effects of HAART and specific NRTIs (ddC, ddI, D4T, ZDV, and ABC) on cardiomyopathy incidence. We also identified predictors of cardiomyopathy among HAART initiators and the effect of HAART on survival after cardiomyopathy development. Finally, we examined the clinical significance of cardiomyopathy by estimating its effect on overall survival.

Methods

The eligible study population included 3,209 perinatally HIV-infected children enrolled in Pediatric AIDS Clinical Trials Group (PACTG) Protocols 219 and 219C, which were consecutive prospective studies evaluating the long-term effects of HIV infection and ARVs. HIV-infected and HIV-exposed but uninfected children were enrolled between 1993 and 2006 from more than 80 study sites across the US and Puerto Rico. The protocols were approved by human subjects review boards at each participating institution and written informed consent was obtained from each child's parent or legal guardian.

At each study visit, sociodemographic and clinical characteristics were collected. HIV-RNA quantification was not routinely performed before 2000 and thus viral loads were available for only 59% of our incident study population. Nadir CD4% and peak viral load were defined as the lowest CD4% and the highest viral load documented prior to and at study entry.

HAART was defined as concomitant use of at least 3 drugs from at least 2 classes of ARVs. The calendar years prior to 1996 were considered to be the pre-HAART era since this time span predates protease inhibitor use in clinical practice. The HAART era included all calendar years from 1996 onwards. In analyses, once a child initiated HAART, they were assumed to remain on HAART. A similar approach was used to estimate effects of ddC, ddI, D4T, ZDV, and ABC. Medication start and stop dates were unavailable within PACTG 219. Therefore, the midpoint between the first visit at which treatment was documented and the preceding visit was considered the date of treatment initiation [36].

Cardiomyopathy was defined as having a diagnosis based on clinician report of meeting the criteria for cardiomyopathy or initiating digoxin. The study specified criteria for cardiomyopathy were having ventricular diastolic/ systolic dimensions ≥ 2 standard deviations above the mean for body surface area or abnormal fractional shortening index ≥ 2 standard deviations below the mean. No validation with actual echocardiogram results was conducted. For analyses, the date of cardiomyopathy was defined as the earliest of the date of cardiomyopathy diagnosis or date of initiation of digoxin.

Prevalent cases of cardiomyopathy were identified at entry and excluded from subsequent analyses. For incident cardiomyopathy, children were followed from entry to cardiomyopathy, death, or their last visit, whichever came first. For incident cardiomyopathy among HAART initiators, children were followed from HAART initiation to cardiomyopathy, death, or their last visit. Children who initiated HAART prior to entry were

followed from entry. For survival after cardiomyopathy, children were followed from their cardiomyopathy date to their date of death or censored at their last visit. For overall survival, all children were followed from entry to their date of death, or censored at their last visit.

An extended Cox regression model was used to estimate the effects of time-varying HAART, ddC, ddI, D4T, ZDV, and ABC on cardiomyopathy incidence. Age at entry, birth cohort, sex, race/ethnicity, maternal ARV use during pregnancy, birth weight, CDC clinical category at entry, nadir CD4%, and peak viral load were considered as potential confounders. All confounders of the association between any of the ARVs of interest and cardiomyopathy were included in the final multivariable model. A Cox regression model was used to identify predictors of cardiomyopathy among those receiving HAART. Age at HAART initiation, sex, race/ethnicity, CDC clinical category at HAART initiation, nadir CD4%, peak viral load, use of individual NRTIs prior to HAART initiation and in the first HAART regimen were considered as potential predictors. All univariable predictors of cardiomyopathy at the $p < 0.05$ significance level were included in the final multivariable model. Given our prior hypothesis that nadir CD4% (as a proxy for pro-inflammatory response to viral load) and ZDV would be associated with cardiomyopathy via different pathogenic mechanisms, we additionally evaluated their potential interaction. To further explore the effects of ZDV we also compared incidence rates by ZDV use prior to HAART initiation and initiating ZDV-containing HAART. Extended Cox regression models were also used to estimate the effect of time-varying HAART use on survival after cardiomyopathy diagnosis and the effects of time-varying HAART and cardiomyopathy on overall survival. Analyses were conducted using SAS version 9 (SAS Institute, Cary, NC).

Results

Of the 3,209 perinatally infected children enrolled in PACTG 219 and 219C, 7 children immediately went off-study and were excluded. Thirteen children exposed to doxorubicin, 2 children who underwent radiation therapy, 10 diabetic children, and 8 children with Kawasaki disease were further excluded due to their independent risk of cardiomyopathy. No children were identified with hyperthyroidism, Barth Syndrome, or muscular dystrophy. Of the 3,169 children remaining in the study population, 134 entered PACTG 219 or 219C with cardiomyopathy, resulting in a prevalence of 4.2% (95% confidence interval (CI): 3.6%, 5.0%). Their median age at cardiomyopathy diagnosis was 4.5 years. Seventy-two percent of the cases had initiated ARVs prior to diagnosis but only 12% had initiated HAART. There were 18 deaths (13.0%) observed among the prevalent cases with a median time from diagnosis to death of 1.8 years.

Table 1 outlines characteristics of the 3,035 children followed for incident cardiomyopathy. At entry, 44% were ≤ 5 years of age (81% born prior to 1996), 26% were CDC category C, and 27% had a nadir CD4 $< 15\%$. Of the 1,795 children with viral load information, 34% had a peak viral load $\geq 100,000$ copies/ml at entry. The children exposed to HAART were more likely to be born in the HAART era, more likely to be Black, and more likely to be exposed to ARVs in-utero than children who never initiated HAART.

Over a median of 5.5 years of follow-up, 99 incident cases of cardiomyopathy were observed, yielding an incidence rate (IR) of 5.6 cases per 1,000 person-years (95% CI: 4.6, 6.8; person years: 17,603). The majority (80%) of the incident cases had only on a clinical diagnosis of cardiomyopathy. Five (5%) of the incident cases only had exposure to digoxin, and 15 (15%) of the incident cases had both a clinical diagnosis of cardiomyopathy and exposure to digoxin. The median age at diagnosis of cardiomyopathy was 9.4 years and increased in the HAART era compared to the pre-HAART era (pre-HAART era: 6.7 years, HAART era: 10.3 years, $p = 0.005$). Sixty-three percent of the incident cases were male. The

incidence of cardiomyopathy decreased substantially over time from 25.6 cases per 1,000 person-years in the pre-HAART era, to 3.9 cases per 1,000 person-years in the HAART era (Fig. 1). In more recent years (2001–2005), the incidence of cardiomyopathy ranged from 0.5 to 4.8 cases per 1,000 person-years.

In multivariable analyses, HAART was associated with a 50% lower rate of cardiomyopathy compared to no HAART (Table 2). In contrast, the rate of cardiomyopathy was 1.8 times higher among children exposed to ddC. Although none of the other NRTIs were significantly associated with cardiomyopathy, there was a suggestion of an almost 2-fold higher rate of cardiomyopathy with any use of ZDV.

Among the 2,515 children exposed to HAART in the study population, the median age at HAART initiation was 6.1 years. Over a median of 5.1 years, 45 (1.8%) HAART initiators developed cardiomyopathy. In multivariable analyses (Table 3), significant predictors of cardiomyopathy development during HAART included older age at HAART initiation, male sex, Hispanic ethnicity, ddC use prior to HAART initiation, first initiating a HAART regimen containing ZDV, and a lower nadir CD4%. There was a multiplicative interaction between initiating a HAART regimen containing ZDV and nadir CD4%. Children who first initiated ZDV-containing HAART and had a nadir CD4 <15% had a substantially higher subsequent incidence of cardiomyopathy compared to children with either of these exposures alone (i.e. children who initiated HAART not containing ZDV but had a nadir CD4 <15% and children who did first initiate ZDV-containing HAART but had a nadir CD4 ≥15%) (Table 3).

Table 4 compares the crude IRs of cardiomyopathy by exposure to ZDV prior to HAART and initiating HAART including ZDV among the 2,515 children exposed to HAART in the study population. Children exposed to ZDV prior to HAART with continued exposure through initiation of a HAART regimen including ZDV, and children who initiated HAART including ZDV, had substantially higher rates of cardiomyopathy compared to children who discontinued ZDV exposure by initiating a HAART regimen without ZDV and children who were not exposed to ZDV prior to or with HAART. The majority of the cases who were exposed to ZDV prior to HAART and initiated HAART including ZDV (N=25) were on a PI-based HAART regimen (72%), while the majority of cases who were not exposed to ZDV prior to HAART but initiated HAART including ZDV (N=10) were on an NNRTI-based HAART regimen (60%). Seven out of the 8 (88%) cases exposed to ZDV prior to HAART and initiated a HAART regimen without ZDV were on a PI-based HAART regimen including D4T and 3TC. Both of the cases who were never exposed to ZDV initiated a PI-based HAART regimen including D4T.

Over a median follow-up of 5.6 years from entry until death, an overall mortality rate of 12.1 per 1,000 person-years (95% CI: 10.6, 13.8; 219 deaths; 18,060 person-years) was observed. Thirty-six deaths occurred among the 99 incident cases of cardiomyopathy with a median time from diagnosis to death of 0.8 years and a mortality rate after diagnosis of 78.7 per 1,000 person-years (95% CI: 55.1, 108.9; person-years: 458). In multivariable analyses, having a diagnosis of cardiomyopathy was significantly associated with a 6-fold higher rate of mortality compared to not having a diagnosis of cardiomyopathy (95% CI: 4.0, 8.8), while HAART use was associated with 60% lower rate of mortality compared to no HAART exposure (95% CI: 50%, 70%). In contrast, there was no association between HAART and survival after cardiomyopathy development (hazard ratio: 1.3, 95% CI: 0.6, 2.7).

Discussion

We found a 6-fold decrease in the incidence of cardiomyopathy among children perinatally infected with HIV in the HAART era (1996–2007) compared to the pre-HAART era (1993–1995), likely reflecting improved virologic control with HAART reducing the risks of opportunistic infections and cytokine activation leading to cardiomyopathy. However, the observed annual incidence of cardiomyopathy in recent years ranged from 0.5 to 4.8 per 1,000 children, over 40 times higher than the reported annual incidence of 1.13 per 100,000 children from the US-based Pediatric Cardiomyopathy Registry [37]. Though the definition of cardiomyopathy in the Pediatric Cardiomyopathy Registry was more specific, the substantially increased incidence among perinatally infected children, suggests that even with HAART, HIV infection and/or its treatment still increases the risk of cardiomyopathy in children.

While HAART was associated with a significantly lower rate of cardiomyopathy, ddC use was associated with an 80% higher rate of cardiomyopathy. This may be due to the effect of ddC on the mitochondria of cardiomyocytes, similar to the effect of ddC on mtDNA of nerve cells leading to peripheral neuropathy [38]. Advanced HIV infection, as indicated by a nadir CD4 <15%, was also independently associated with a higher rate of cardiomyopathy. Again, activation of a pro-inflammatory cytokines in response to viral infection of lymphocytes within the heart may be the mechanism by which HIV causes cardiomyopathy [24–26]. Similar to the effects observed in the Pediatric Cardiomyopathy Registry, we found males to have a higher rate of cardiomyopathy than females. Our observed higher rate of cardiomyopathy among Hispanics compared to white children also seems to be consistent with results from the Pediatric Cardiomyopathy Registry, though a formal comparison of Hispanics to whites could not be conducted within the Registry population [37].

Stronger associations of male sex, Hispanic ethnicity, and use of ddC prior to HAART with cardiomyopathy were observed among children who initiated HAART. An older age at HAART initiation was also associated with a higher rate of cardiomyopathy, perhaps indicating the effects of greater exposure to replicating virus during prior non-suppressive therapy or a longer duration of exposure to NRTIs. Although ever having received ZDV was not significantly associated with cardiomyopathy in our entire study population, among those who initiated HAART, continued or new exposure to ZDV as a component of HAART was associated with a higher rate of cardiomyopathy. There was a multiplicative interaction between this association and nadir CD4% supporting the theory of a multi-factorial pathogenesis of HIV-associated cardiomyopathy, combining inflammatory mediators and NRTI-associated cardiac damage perhaps mediated through mtDNA depletion [28].

Our reported incidence of cardiomyopathy may be underestimated if young children with cardiac cardiomyopathy died prior to enrolling in PACTG 219 or 219C. The greater median age of the incident cases of cardiomyopathy compared to the median age of the prevalent cases identified at entry suggest that a ‘survivor’ cohort of children may have been followed for incident analyses. The majority of our prevalent cases were diagnosed in the pre-HAART era. If covariate information prior to entry were available, inclusion of all prevalent cases in incident analyses would likely have strengthened our observed association of HAART use with cardiomyopathy. Since viral load information was missing for 59% of the study population, we were not able to adjust for it in our analyses. Sensitivity analyses conducted among the subset of children with viral load information, however, suggest that stronger associations of HAART and cardiomyopathy with survival would be observed with adjustment for viral load. Lack of sufficient viral load data also limited our ability to explore the mechanisms underlying our observed association between ZDV as a component of HAART and rate of cardiomyopathy. The specific hypothesis of mitochondrial toxicity

associated with ZDV exposure leading to cardiomyopathy was therefore not tested. There may be an alternative mechanism explaining the observed association between HAART with ZDV and cardiomyopathy. Echocardiographic studies were not recorded and kept as part of PACTG 219 and 219C so cardiomyopathy classification could not be confirmed. There may therefore be some outcome misclassification of our cardiomyopathy outcome. Assuming that this misclassification is non-differential with respect to treatment, our observed associations of HAART and individual NRTIs with incidence of cardiomyopathy are likely conservative.

In conclusion, we found a strong protective association of HAART with cardiomyopathy among children and adolescents perinatally-infected with HIV. We also demonstrated that early initiation of HAART is associated with a lower incidence of cardiomyopathy, adding to earlier studies showing the benefits of early HAART initiation on maintaining immunocompetence among perinatally-infected children [39]. In choosing therapy, however, the benefit of specific medications must be weighed against their potential toxicities [40]. Our study is the first to see a multiplicative effect of a low nadir CD4% and initiating a ZDV-containing HAART regimen on cardiomyopathy. This association needs to be confirmed in future studies but is consistent with the theory of a multi-factorial pathogenesis of HIV-associated cardiac damage [27–29]. Even with the significant declines in mortality observed with improved ARV therapy, this study highlights the ongoing problem of cardiomyopathy among HIV-infected children. ZDV may cause progression to cardiomyopathy and thus its risks and benefits should be carefully balanced for each child, and alternative NRTI's may be considered. Additionally, long-term monitoring of cardiac function among HIV-infected children may be warranted.

Acknowledgments

We thank the children and families for their participation in PACTG 219C, and the individuals and institutions involved in the conduct of 219C as well as the leadership and participants of the P219/219C protocol team. *We are grateful for the contributions of Joyce Kraimer, Barbara Heckman, Shirley Traite, and Nathan Tryon. We also thank the individual staff members and sites who have participated in the conduct of this study, as provided in Appendix I.

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Funding/Support: Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) [U01 AI068632], the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH) [AI068632]. The content is solely the responsibility of the authors and

does not necessarily represent the official views of the NIH. This work was supported by the Statistical and Data Analysis Center at Harvard School of Public Health, under the National Institute of Allergy and Infectious Diseases cooperative agreement #5 U01 AI41110 with the Pediatric AIDS Clinical Trials Group (PACTG) and #1 U01 AI068616 with the IMPAACT Group. Support of the sites was provided by the National Institute of Allergy and Infectious Diseases (NIAID) and the NICHD International and Domestic Pediatric and Maternal HIV Clinical Trials Network funded by NICHD (contract number N01-DK-9-001/ HHSN267200800001C). Additional data for a subset of the study population was collected under the Eunice Kennedy Shriver National Institute of Child Health and Human Development cooperative agreement #3 U01 HD052102-06S3 with the Pediatric HIV/AIDS Cohort Study Data and Operations Center (PHACS-DOC).

Role of the Sponsor: The National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development were involved in the design, data collection, and conduct of protocol 219/ 219C but were not involved in the present analysis, the interpretation of the data, the writing of the manuscript, or decision to submit for publication.

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Appendix I: Participating institutions and clinical site investigators in the U.S.-based multisite cohort study, PACTG 219/219C

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Delia Calo, New York University School of Medicine, Division of Pediatric Infectious Diseases: Dr. William Borkowsky, Nagamah Deygoo, Maryam Minter, Seham Akleh, Children's National Medical Center, ACT: Diana Dobbins, Deidre Wimbley, Dr. Lawrence D'Angelo, Hans Spiegel, University of Washington School of Medicine - Children's Hospital and Regional Medical Center: Dr. Ann J. Melvin, Kathleen M. Mohan, Michele Acker, Suzanne Phelps, University of Illinois College of Medicine at Chicago, Department of Pediatrics: Dr. Kenneth C. Rich, Dr. Karen Hayani, Julia Camacho, Yale University School of Medicine - Department of Pediatrics, Division of Infectious Disease: Dr. Warren A. Andiman, Leslie Hurst, Dr. Janette de Jesus, Donna Schroeder, SUNY at Stony Brook School of Medicine, Division of Pediatric Infectious Diseases: Denise Ferraro, Jane Perillo, Michele Kelly, Howard University Hospital, Department of Pediatrics & Child Health: Dr. Sohail Rana, Dr. Helga Finke, Patricia Yu, Dr. Jhoanna Roa, LA County/University of Southern California Medical Center: Dr. Andrea Kovacs, Dr. James Homans, Dr. Michael Neely, Dr. LaShonda Spencer, University of Florida Health Science Center Jacksonville, Division of Pediatric Infectious Disease & Immunology: Dr. Mobeen H. Rathore, Dr. Ayesha Mirza, Kathy Thoma, Almer Mendoza, North Broward Hospital District, Children's Diagnostic & Treatment Center: Dr. Ana M. Puga, Dr. Guillermo Talero, James Blood, Stefanie Juliano, University of Rochester Medical Center, Golisano Children's Hospital: Dr. Geoffrey A. Weinberg, Barbra Murante, Susan Lavery, Dr. Francis Gigliotti, Medical College of Virginia: Dr. Suzanne R. Lavoie, Tima Y. Smith, St. Jude Children's Research Hospital, Department of Infectious Diseases: Dr. Aditya Gaur, Dr. Katherine Knapp, Dr. Nehali Patel, Marion Donohoe, University of Puerto Rico, U. Children's Hospital AIDS: Dr. Irma L. Febo, Dr. Licette Lugo, Ruth Santos, Ibet Heyer, Children's Hospital of Philadelphia, Center for Pediatric & Adolescent AIDS: Dr. Steven D. Douglas, Dr. Richard M. Rutstein, Carol A. Vincent, Patricia C. Coburn, St. Christopher's Hospital for Children/Drexel University College of Medicine: Dr. Jill Foster, Dr. Janet Chen, Dr. Daniel Conway, Dr. Roberta Laguerre, Bronx-Lebanon Hospital Center, Infectious Diseases: Dr. Emma Stuard, Caroline Nubel, Dr. Stefan Hagmann, Dr. Murli Purswani, New York Medical College/Metropolitan Hospital Center: Dr. Mahrukh Bamji, Dr. Indu Pathak, Dr. Savita Manwani, Dr. Ekta Patel, University of Massachusetts Memorial Children's Medical School, Department of Pediatrics: Dr. Katherine Luzuriaga, Dr. Richard Moriarty, Baystate Health, Baystate Medical Center: Dr. Barbara W. Stechenberg, Dr. Donna J. Fisher, Dr. Alicia M. Johnston, Maripat Toyé, Connecticut Children's Medical Center: Dr. Juan C. Salazar, Kirsten Fullerton, Gail Karas, Medical College of Georgia School of Medicine, Department of Pediatrics, Division of Infectious Disease: Dr. Stuart Foshee, Dr. Chitra S. Mani, Dr. Denis L. Murray, Dr. Christopher White, University of South Alabama College of Medicine, Southeast Pediatric ACTU: Dr. Mary Y. Mancao, Dr. Benjamin Estrada, LSU Health Sciences Center: Dr. Ronald D. Wilcox, Tulane University Health Sciences Center: Dr. Margarita Silio, Dr. Thomas Alchediak, Cheryl Borne, Shelia Bradford, St. Josephs Hospital and Medical Center, Cooper University Hospital - Children's Hospital Boston, Division of Infectious Diseases, David Geffen School of Medicine at UCLA - Department of Pediatrics, Division of Infectious Diseases, Children's Hospital of Orange County, Children's Memorial Hospital - Department of Pediatrics, Division of Infectious Disease, University of Chicago -Department of Pediatrics, Division of Infectious Disease, Mt. Sinai Hospital Medical Center - Chicago, Women's & Children's HIV Program, Columbia University Medical Center, Pediatric ACTU, Incarnation Children's Center, Cornell University, Division of Pediatric Infectious Diseases & Immunology, University of Miami Miller School of Medicine - Jackson Memorial Hospital, Bellevue Hospital (Pediatric), San Francisco General (Pediatric), Phoenix Children's Hospital, Metropolitan Hospital Center (N.Y.), University of Cincinnati, SUNY Downstate Medical Center, Children's Hospital at Downstate, North Shore University Hospital, Jacobi Medical Center, University of South Florida - Department of Pediatrics, Division of Infectious Diseases, Cornell University, Oregon Health & Science University - Department of Pediatrics, Division of Infectious

Diseases, Children's Hospital of the King's Daughters, Infectious Disease, Lincoln Medical & Mental Health Center, Mt. Sinai School of Medicine, Division of Pediatric Infectious Diseases, Emory University Hospital, San Juan City Hospital, UMDNJ - Robert Wood Johnson, Ramon Ruiz Arnau University Hospital, Medical University of South Carolina, SUNY Upstate Medical University, Department of Pediatrics, Wayne State University School of Medicine, Children's Hospital of Michigan, Children's Hospital at Albany Medical Center, Children's Medical Center of Dallas, Children's Hospital - University of Colorado at Denver and Health Sciences, Center, Pediatric Infectious Diseases, Columbus Children's Hospital, University of Florida College of Medicine - Department of Pediatrics, Division of Immunology, Infectious Diseases & Allergy, University of Mississippi Medical Center, Palm Beach County Health Department, Children's Hospital LA - Department of Pediatrics, Division of Adolescent Medicine, Vanderbilt University Medical Center, Division of Pediatric Infectious Diseases, Washington University School of Medicine at St. Louis, St. Louis Children's Hospital, Children's Hospital & Medical Center, Seattle ACTU, Oregon Health Sciences University, St. Luke's-Roosevelt Hospital Center, Montefiore Medical Center -Albert Einstein College of Medicine, Children's Hospital, Washington, D.C., Children's Hospital of the King's Daughters, University of Alabama at Birmingham, Department of Pediatrics, Division of Infectious Diseases, Columbus Regional HealthCare System, The Medical Center, Sacred Heart Children's Hospital/CMS of Florida, Bronx Municipal Hospital Center/Jacobi Medical Center.

Fig. 1. Incidence rates of cardiomyopathy in the pre-HAART era (1993–1995), HAART era (1996–2007), and recent years of follow-up, PACTG 219/219C, 1993–2007.

Table 1

Demographic and clinical characteristics of the incident cardiomyopathy study population (N =3,035) according to HAART initiation by end of follow-up, PACTG 219/219C, 1993–2007.

Characteristic	Total N (%)	Initiated HAART N (%)	Never initiated HAART N (%)	P-value
	3035 (100)	2515 (83)	520 (17)	
Age (years)				0.02
1	338 (11)	281 (11)	57 (11)	
2–5	997 (33)	796 (32)	201 (38)	
6–10	1086 (36)	916 (36)	170 (33)	
>10	614 (20)	522 (21)	92 (18)	
Birth cohort				<0.001
1975–1989	992 (33)	766 (30)	226 (43)	
1990–1995	1475 (48)	1207 (48)	268 (52)	
1996–2005	568 (19)	542 (22)	26 (5)	
Sex				0.23
Male	1485 (49)	1243 (49)	242 (47)	
Female	1550 (51)	1272 (51)	278 (53)	
Race/Ethnicity				<0.001
White/Other	470 (16)	377 (15)	93 (18)	
Black	1770 (58)	1509 (60)	261 (50)	
Hispanic	795 (26)	629 (25)	166 (32)	
Maternal ARV use during pregnancy				0.02
Yes	310 (10)	271 (11)	39 (8)	
No	2457 (81)	2014 (80)	443 (85)	
Missing	268 (9)	230 (9)	38 (7)	
Birth Weight				0.83
< 2500 grams	746 (25)	615 (25)	131 (25)	
2500 grams	2167 (71)	1794 (71)	373 (72)	
Missing	122 (4)	106 (4)	16 (3)	
CDC clinical category				0.68
Not C	2237 (74)	1850 (74)	387 (74)	
C	798 (26)	665 (26)	133 (26)	
Nadir CD4%				0.24
< 15	809 (27)	657 (26)	152 (29)	
15–24	878 (29)	740 (30)	138 (26)	
25	1188 (39)	987 (39)	201 (39)	
Missing	160 (5)	131 (5)	29 (6)	
Peak Viral load (copies/ml)				0.02
< 10,000	720 (24)	643 (26)	77 (15)	
10,000–99,999	464 (15)	397 (16)	67 (13)	
100,000	611 (20)	556 (22)	55 (10)	
Missing	1240 (41)	919 (36)	321 (62)	

Table 2

Independent associations between HAART, ddC, ddI, D4T, ZDV, and ABC and incident cardiomyopathy (N =3,035), PACTG 219/ 219C, 1993–2007.

Characteristic	N (%) ^a	N (%) ^a incident cases	Multivariable Hazard Ratio (95% CI) ^b	P-value
HAART use				
Yes	2515 (83)	45 (45)	0.5 (0.3, 0.8)	0.01
No	520 (17)	54 (55)	Referent	--
Zalcitabine (ddC) use				
Yes	297 (10)	24 (24)	1.8 (1.1, 3.0)	0.03
No	2738 (90)	75 (76)	Referent	--
Didanosine (ddI) use				
Yes	2280 (75)	71 (72)	1.0 (0.6, 1.6)	0.96
No	755 (25)	28 (28)	Referent	--
Stavudine (D4T) use				
Yes	2161 (71)	41 (41)	0.8 (0.5, 1.5)	0.51
No	874 (29)	58 (59)	Referent	--
Zidovudine (ZDV) use				
Yes	2660 (88)	89 (90)	1.9 (0.9, 4.3)	0.10
No	375 (12)	10 (10)	Referent	--
Abacavir (ABC) use				
Yes	789 (26)	8 (8)	0.7 (0.3, 1.5)	0.36
No	2246 (74)	91 (92)	Referent	--
Birth cohort				
1973–1989	992 (33)	62 (63)	1.7 (1.1, 2.6)	0.03
1990–2005	2043 (67)	37 (37)	Referent	--
Maternal ARV use during pregnancy				
Yes	310 (10)	3 (3)	0.6 (0.2, 1.8)	0.33
No	2457 (81)	93 (97)	Referent	--
Nadir CD4%				
< 15	809 (27)	54 (55)	3.6 (2.1, 6.3)	<0.001
15–24	878 (29)	21 (21)	1.1 (0.6, 2.1)	0.76
25	1188 (39)	18 (18)	Referent	--

^aBy end of follow-up.

^bMultivariable results from one extended Cox model including all variables in the table.

Table 3

Independent predictors of incident cardiomyopathy among children who received HAART (N =2,515), PACTG 219/219C, 1993–2007.

Characteristic	N (%)	N (%) incident cases	Multivariable Hazard Ratio (95% CI)	P-value
Age at HAART initiation (years)				
5	999 (40)	5 (11)	Referent	--
6–10	1019 (40)	24 (53)	3.3 (1.2, 8.7)	0.02
>10	497 (20)	16 (36)	5.1 (1.8, 14.2)	0.002
Sex				
Male	1243 (49)	35 (78)	3.6 (1.7, 7.5)	<0.001
Female	1272 (51)	10 (22)	Referent	--
Race/Ethnicity				
White/Other	377 (15)	2 (4)	Referent	--
Black	1509 (60)	21 (47)	3.0 (0.7, 12.9)	0.14
Hispanic	629 (25)	22 (49)	5.7 (1.3, 24.4)	0.02
Zalcitabine (ddC) use prior to HAART				
Yes	157 (6)	10 (22)	2.3 (1.1, 4.9)	0.02
No	2358 (94)	35 (78)	Referent	--
Initiated ZDV-containing HAART /Nadir CD4%				
Yes/CD4<15	370 (15)	24 (55)	6.8 (2.6, 18.1)	<0.001
No/CD4<15	287 (11)	5 (11)	2.0 (0.6, 7.1)	0.27
Yes/CD4 15	848 (34)	10 (23)	1.9 (0.7, 5.6)	0.24
No/CD4 15	879 (35)	5 (11)	Referent	--

Table 4

Incidence rates of cardiomyopathy by zidovudine (ZDV) use prior to HAART and initiating a HAART regimen including ZDV among children who received HAART (N =2,515), PACTG 219/219C, 1993–2007.

	ZDV use prior to HAART (N =1822)		No ZDV use prior to HAART (N =693)	
	Initiated HAART including ZDV (N =911)	Initiated HAART not including ZDV (N =911)	Initiated HAART including ZDV (N =374)	Initiated HAART not including ZDV (N =319)
Cardiomyopathy				
Cases	25	8	10	2
Person-years	5491	4641	1605	1356
Incidence rate/1,000 person-years (95% confidence interval)	4.6 (2.9, 6.7)	1.7 (0.7, 3.4)	6.2 (3.0, 11.5)	1.5 (0.2, 5.3)