CD4+ and viral load outcomes of antiretroviral therapy switch strategies after virologic failure of combination antiretroviral therapy in perinatally HIV-infected youth in the United States

Citation
Fairlie, Lee, Brad Karalius, Kunjal Patel, Russell B. van Dyke, Rohan Hazra, Miguel A. Hernán, George K. Siberry, George R. Seage, Allison Agwu, and Andrew Wiznia. 2015. “CD4+ and viral load outcomes of antiretroviral therapy switch strategies after virologic failure of combination antiretroviral therapy in perinatally HIV-infected youth in the United States.” AIDS (London, England) 29 (16): 2109-2119. doi:10.1097/QAD.0000000000000809. http://dx.doi.org/10.1097/QAD.0000000000000809.

Published Version
doi:10.1097/QAD.0000000000000809

Permanent link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:23845375

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

Share Your Story
The Harvard community has made this article openly available. Please share how this access benefits you. Submit a story.

Accessibility
CD4⁺ and viral load outcomes of antiretroviral therapy switch strategies after virologic failure of combination antiretroviral therapy in perinatally HIV-infected youth in the United States

Lee Fairlie⁵, Brad Karalius⁴, Kunjal Patel⁶, Russell B. van Dyke⁷, Rohan Hazra⁸, Miguel A. Hernán⁶, George K. Siberry⁸, George R. Seage III⁴, Allison Agwu⁹, Andrew Wiznia¹⁰, for the Pediatric HIV AIDS Cohort Study (PHACS), The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)

Objective: This study compared 12-month CD4⁺ and viral load outcomes in HIV-infected children and adolescents with virological failure, managed with four treatment switch strategies.

Design: This observational study included perinatally HIV-infected (PHIV) children in the Pediatric HIV/AIDS Cohort Study (PHACS) and Pediatric AIDS Clinical Trials (PACTG) Protocol 219C.

Methods: Treatment strategies among children with virologic failure were compared: continue failing combination antiretroviral therapy (cART); switch to new cART; switch to drug-sparing regimen; and discontinue all ART. Mean changes in CD4⁺% and viral load from baseline (time of virologic failure) to 12 months follow-up in each group were evaluated using weighted linear regression models.

Results: Virologic failure occurred in 939 out of 2373 (40%) children. At 12 months, children switching to new cART (16%) had a nonsignificant increase in CD4⁺% from baseline, 0.59 percentage points [95% confidence interval (95% CI) −1.01 to 2.19], not different than those who continued failing cART (71%) (0.64 percentage points, P = 0.15) or switched to a drug-sparing regimen (5%) (1.40 percentage points, P = 0.64). Children discontinuing all ART (7%) experienced significant CD4⁺% decline −3.18 percentage points (95% CI −5.25 to −1.11) compared with those initiating new cART (P = 0.04). All treatment strategies except discontinuing ART yielded significant mean decreases in log₁₀VL by 12 months, the new cART group having the largest drop (−1.15 log₁₀VL).

Conclusion: In PHIV children with virologic failure, switching to new cART was associated with the best virological response, while stopping all ART resulted in the
worst immunologic and virologic outcomes and should be avoided. Drug-sparing regimens and continuing failing regimens may be considered with careful monitoring.

Introduction

The benefits of early combination antiretroviral therapy (cART) in HIV-infected children are well described and include improvement in virologic and immunologic parameters and reductions in mortality, hospital admissions and comorbidities such as HIV encephalopathy and cardiomyopathy [1–6]. The WHO recommends initiation of cART in all HIV-infected children under 5 years of age [1,7]. However, sustaining the benefits of early treatment requires lifelong adherence to cART, which is hampered by dependence on caregivers for cART administration, poor palatability of drugs, pill burden and frequency of administration, drug toxicities and developmental changes, especially during adolescence [8–10].

Globally, excellent virologic suppression rates in children receiving cART have been described with over 80% viral suppression at 36-month follow-up [11,12]. However, 30–40% of children develop virologic failure over time [13]. In children who develop virologic failure, switching to a new cART regimen on the basis of viral drug resistance testing can lead to virologic suppression. Success of this approach relies on overcoming adherence barriers and on the availability of potent drugs to construct a new cART regimen to which the child's virus is susceptible. In resource-limited settings, highly treatment-experienced children with prior exposure to numerous antiretroviral drugs are presented with the challenges of multiresistant HIV and lack of active drugs [14]. In resource-limited settings, in which financial and structural constraints limit access to new drugs, it is often difficult to access potent new cART regimens for children with virologic failure on first-line therapy.

As more children access cART globally, challenges around optimal management of virologic failure are likely to intensify. Treatment options explored by various studies include optimizing therapy with a new CART regimen [15]; continuing with a failing regimen [16]; switching to a simplified, non-cART drug-sparing regimen [17]; and treatment interruption [18]. No studies to date have directly compared immunological and virologic outcomes with these treatment options in children with virologic failure.

We used observational data from two large US-based prospective cohorts of perinatally infected children and adolescents (PHIV) to address this question. Among PHIV with virologic failure after at least 6 months of cART, we compared immunological and virologic outcomes 12 months after virologic failure in children managed with the following treatment options: continue with current failing cART; switch to a new cART; switch to a non-cART, drug-sparing regimen and discontinue all ART.

Materials and methods

Study population

The source populations were the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS) and the Pediatric AIDS Clinical Trials (PACTG) Protocol 219C. These prospective cohort studies were designed to evaluate the impact of HIV infection and cART on children with perinatal infection and enrolled over 2700 PHIV children and adolescents from 1993 to 2009. The protocols were approved by Institutional Review Boards at each participating site: written informed consent was obtained from each participant or participant’s parent or legal guardian, as appropriate. For the final study population, we selected PHIV children with documented virologic failure after at least 6 months of cART who had covariate information available at the time of virologic failure. The most recent virologic failure event was included in the analysis.

Study definitions

cART was defined as a regimen consisting of at least three antiretroviral drugs from at least two different drug classes. Virologic failure was defined as an HIV plasma viral load more than 1000 copies/ml on at least two consecutive occasions at least 1 month apart, with no intervening values of 1000 copies/ml or less, after receiving at least 6 months of cART. The date of confirmed virologic failure was defined as the date of the second elevated virologic failure and used as baseline.

The treatment strategies after documented virologic failure on cART were defined as follows:
Virological failure in HIV-infected youth Fairlie et al. 2111

(1) Continue failing cART: continuation of the same failing cART regimen or addition, subtraction or substitution of a single antiretroviral drug, with no change in drug classes, still meeting the definition of cART

(2) Switch to new cART: the addition, subtraction or substitution of at least two antiretroviral drugs and/or addition of at least one antiretroviral drug from a new drug class, while still meeting the definition of cART

(3) Switch to a drug-sparing regimen: a regimen not meeting the above definition of cART (one or more drugs from a single class or one drug from each of two classes)

(4) Discontinuation of all antiretroviral drugs

All decisions regarding changes in treatment regimen were made by the patient, the family and clinician. PHIV children in our study population were followed from baseline to 12 months after virologic failure, death or loss to follow-up, whichever came first. The outcomes of interest were change in CD4\% and viral load from baseline to 12 months after virologic failure. Covariates considered as potential confounders of the association between treatment switch strategies and the immunologic and virologic outcomes included age at baseline, sex, calendar year of cART failure, having a previous cART failure, nadir CD4\%, CD4\% (baseline and time-varying), viral load (baseline and time-varying), Centers for Disease Control and Prevention (CDC) classification at baseline, antiretroviral drug adherence (self/caregiver-reported at baseline and time-varying), height (HAZ) and weight (WAZ) for age z-scores (baseline and time-varying), and increases in toxicity grade of the following laboratory measures (time-varying): creatinine, alanine aminotransferase, lipase, absolute neutrophil count, haemoglobin, platelets and white blood cell count.

Statistical analysis

For each outcome, we estimated the mean change from baseline to 12 months for each of the four treatment strategies initiated within 6 months of cART failure. A weighted linear regression model for change from baseline was fit for each outcome, including treatment strategy, sex, cART failure year, previous cART failure and baseline measures of age, nadir CD4\%, CDC class, antiretroviral drug adherence, HAZ, and WAZ. Baseline CD4\% was only included in the change in viral load outcome model and baseline viral load was only included in the change in CD4\% outcome model. Toxicity was graded according to Division of AIDS (DAIDS) toxicity tables [19]. Robust standard errors were calculated to compute 95% confidence intervals around the parameter estimates.

To adjust for prognostic factors that may have influenced clinical decision to choose one of the four treatment strategies after virologic failure, we implemented a statistical modelling approach that has been previously described to evaluate when to start strategies in HIV-infected adults [20]. Briefly, this strategy creates exact copies of each child and assigns one copy to each of the four treatment strategies. Each child copy is censored if and when the child’s data were no longer consistent with the strategy assigned to the copy. To adjust for the potential bias resulting from this censoring, inverse probability weights were estimated using multinomial logistic models for the time-varying probability of each treatment strategy in the original study population. The models included the covariates previously listed along with time-varying antiretroviral drug adherence, HAZ, WAZ, CD4\%, viral load and interval of follow-up time. Inverse probability weights for censoring due to loss-to-follow-up were also estimated using logistic regression models including treatment and the previously listed baseline and time-varying covariates. Consistent with previous studies, inverse probability weights were truncated at a maximum value of 10 [20]. The estimated weights were then applied to the outcome models described previously. Under our assumptions, the parameters of the weighted model validly estimate the parameters of a marginal structural model. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA).

Results

There were 2747 PHIV children in the AMP and 219C cohorts. Of these, 2433 (89\%) were ever on cART with 2373 (98\%) receiving cART for at least 6 months. Virologic failure was observed in 939 (40\%) of the children receiving cART for at least 6 months after a median of 23 months [interquartile range (IQR) 14–38]. Among these 939 children, 15\% experienced one and 1\% experienced two or more prior episodes of virologic failure (Table 1). The majority (90\%) of virologic failure occurred prior to 2007. Of the failing cART regimens, 85\% (n = 800) contained a protease inhibitor, of which 20\% (n = 164) also contained a nonnucleoside reverse transcriptase inhibitor (NNRTI). Nelfinavir was included in 45\% and lopinavir/ritonavir in 33\% of failing protease inhibitor based cART regimens. Of failing cART regimens, 32\% included NNRTIs, either efavirenz (52\%) or nevirapine (47\%). (Table 1)

Observed treatment strategies for children with virologic failure

Of the 939 children who failed cART, 735 (78\%) had complete baseline covariate information for analyses comparing immunologic and virologic outcomes by treatment strategy after virologic failure. Half of this analytic population was female and 63\% were black, non-Hispanic (Table 2) [21,22]. At the time of virologic failure...
their median age was 11 years, their median CD4⁺% was 28% and their median log₁₀ viral load was 3.8. Thirty-six percent had a previous AIDS-defining condition. Eighty percent reported 100% adherence at the time of virologic failure.

Figure 1 presents the proportion of children following each treatment strategy after cART failure by time since virologic failure. At 6 and 12 months after virologic failure, 84 and 71%, respectively, of children had not switched from their failing regimen. New cART regimens were initiated in 8% at 6 months and in 16% at 12 months. Few children switched to a drug-sparing regimen (5%) or discontinued all antiretroviral drugs (7%) by 12 months after virologic failure.

Thirty-one children with virologic failure switched to a drug-sparing regimen within 6 months of follow-up (Supplementary Table 1S, http://links.lww.com/QAD/A752). Antiretroviral drugs included in drug-sparing regimens were variable, but the majority (68%) included NRTIs only [single (23.8%), double (28.6%) or triple (47.6%)]; 19% included a protease inhibitor and single NRTI; 3% a single NNRTI and 6% a protease inhibitor and NNRTI combination. Only one child received emtricitabine monotherapy and none lamivudine.

Mean change from baseline CD4⁺% at 12 months after virologic failure

Children who switched to new cART and to a drug-sparing regimen both had a nonsignificant mean increase in CD4⁺% from baseline (0.6 and 1.4 percentage points, respectively) (Table 3). Children continuing a failing cART regimen had a significant mean decrease in CD4⁺% by month 12. These changes in CD4⁺% did not differ significantly from those of children who switched to new cART. Faring the worst were children who discontinued all antiretroviral drugs, with a significant mean decrease in CD4⁺% of 3.2 percentage points from...
baseline levels, which differed significantly from that of those who switched to a new cART regimen.

Mean change from baseline viral load at 12 months after virologic failure
All four treatment strategies yielded mean decreases in $\log_{10}$VL from baseline to 12 months after virologic failure, and these decreases were significant for all but the antiretroviral drug discontinuation group (Table 3). Children who switched to new cART saw the largest reduction in $\log_{10}$ viral load, followed by those who switched to a drug-sparing regimen, and finally, those who stayed on their failing cART. The decrease in viral load for children who switched to new cART did not differ significantly from that of the drug-sparing group but was significantly larger than for those who made no change from their failing cART and those who discontinued antiretroviral drugs entirely.

All above estimates were derived from weighted outcome models. The estimates did not materially change when we used unweighted models with or without baseline covariates (data not shown).

Discussion
Our study provides evidence that in children with virologic failure, stopping all ART results in the worst

Table 3. Mean change from baseline CD4+ % and $\log_{10}$ viral load at 12 months after combination antiretroviral therapy failure (N = 735).

| Characteristics                  | Continue failing cART | New cART | Drug-sparing regimen | Discontinue ARVs |
|----------------------------------|------------------------|----------|----------------------|------------------|
| Person-time (years)              | 612                    | 324      | 293                  | 306              |
| CD4+ % changes                   |                        |          |                      |                  |
| Parameter estimate               | -0.64                  | 0.59     | 1.40                 | -3.18            |
| 95% confidence interval          | -1.10 to -0.17          | -1.01 to 2.19 | -1.56 to 4.37       | -5.25 to -1.11  |
| $\log_{10}$ viral load change    | 0.15                   | Ref      | 0.64                 | 0.004            |
| Parameter estimate               | -0.27                  | -1.15    | -0.85                | -0.20            |
| 95% confidence interval          | -0.34 to -0.20          | -1.41 to -0.88 | -1.35 to -0.34       | -0.65 to 0.26   |
| $P$                              | <0.001                 | Ref      | 0.30                 | <0.001           |

ARVs, antiretrovirals; cART, combination antiretroviral therapy.
immunologic and virologic outcomes at 12 months and should be avoided. We found that children who stopped ART had a significantly greater decline in CD4+ (% [−3.18 percentage points (95% CI −5.25 to −1.11)] at 12 months after virologic failure than those who switched to new cART (P = 0.04). Siberry et al. [18] reported from the overlapping AMP cohort that children who had an unplanned treatment interruption saw a steady decline in CD4+ and count with median (range) slopes of −0.66% (−3.54 to +1.34%) and −12.7 cells/μl (−148 to +31 cells/μl) per month, with no comparison group included in this report. Gibb et al. [23] found a similar rate of CD4+% decline with unplanned treatment interruptions in a cohort from the United Kingdom, Ireland and Rotterdam. The Paediatric European Network for Treatment of AIDS (PENTA) 11 Trial Team study reported that even in children with good immunological recovery and virologic suppression, planned treatment interruptions resulted in rapid CD4+ cell count decline, particularly in the first 12 weeks, stabilizing through 48 weeks [24]. These findings, together with our study, suggest that where possible, treatment interruptions should be avoided in HIV-infected children with virologic failure.

We found that the majority of children (73%) with virologic failure remained on failing cART through 12 months, a decision made by the patient, the family and their clinicians. Continuing a failing cART regimen resulted in a significant decrease in CD4+% from baseline, but this change was not significantly different from the group starting new cART. Children who switched to new cART, however, had significantly higher viral load suppression at 12 months than those remaining on a failing cART regimen. Delayed switching of cART in children, adolescents and adults is not uncommon in large observational cohorts. The Collaborative HIV Paediatric Study (CHIPS) cohort report from 2005 that of 22% children who switched to second-line therapy for virologic failure, children who never achieved virologic suppression (<400 copies/ml) switched at a median of 3.2 years after cART initiation [25]. From resource-limited settings, Davies et al. [11], from the Southern African IeDEA cohort including seven South African Paediatric HIV Treatment sites between 1999–2008, report that of 254 children identified with virologic failure on first-line ART and at least 1 year of follow-up, only 38% switched to second line. Given that ART rollout in South Africa began in April 2004 with limited access to ART for some children between 2001 and 2003, we can assume that most of these children remained on failing ART in an era when second-line drugs were available in South Africa [11]. Similarly, in a South African adult cohort between 2003 and 2008 with confirmed virologic failure on first-line ART, after 6 months of follow-up, only 21.6% were switched to second-line therapy [26]. The reasons for this are multiple and include availability of second and third-line regimens, treating clinician experience and most importantly concerns about switching a child or adolescent to a new regimen when adherence remains suboptimal. The PENTA and the Pediatric AIDS Clinical Trials Group (PACTG/IMPAACT) (PENPACT-1) study randomized children with virologic failure receiving either protease inhibitor based or NNRTI-based cART to switch to a new cART at either a low (viral load >1000 copies/ml) or a high threshold (viral load >30 000 copies/ml) [16]. This study found that immunological outcomes in children receiving a protease inhibitor based regimen did not differ between low and high-threshold groups at the time of switch. Adult studies have also shown that immunological well being is maintained on a failing protease inhibitor based regimen [27]. More specifically, Peterson et al. [28] found that a delayed switch from a failing protease inhibitor-based regimen in adults was not associated with an increase in mortality and immunological deterioration, but with NNRTI-based therapy, a switch beyond 3 months from virologic failure was associated with such increases. Our study was not able to directly compare outcomes after delayed switch from protease inhibitor or NNRTI-based regimens. Concern about ongoing accumulation of viral resistance mutations during continuation of a failing cART regimen may influence decisions regarding this strategy in children with virologic failure. In the PENPACT-1 study, although the M184V mutation was most common in both groups, there was no accumulation of NRTI resistance mutations in the protease inhibitor based high-threshold group [16]. In children receiving an NNRTI-based regimen, there was an accumulation of resistance mutations, particularly NRTI mutations, in the high-threshold group conferring high-level resistance to zidovudine, didanosine, stavudine and abacavir [16]. Therefore, on the basis of these studies, children failing NNRTI-based regimens should be switched early, although there may be less urgency in those failing boosted protease inhibitor based regimens.

Data to support the evaluation of drug-sparing strategies in this study are limited, as only 5% of our study population were receiving a drug-sparing regimen at 12 months of follow-up after virologic failure. Evaluation was difficult due to the small number of children receiving this strategy and the heterogeneity of selected holding regimens, although 68% of children received one or more NRTIs, only one child received emtricitabine monotherapy and a number of children in the drug-sparing regimen group received potentially suppressive ART with two drug classes included. When developing this study, our criterion defining cART was strict and it is possible that children classified in the ‘drug-sparing regimen’ group received potentially robust regimens that may have improved their outcomes. Few studies have evaluated drug-sparing regimens in children. Most recently, the IMPAACT P1094 study, a randomized controlled study evaluated continuing a failing ART regimen compared with lamivudine/emtricitabine
(3TC/FTC) monotherapy in poorly adherent 8 to 24 year olds. The study was halted early due to slow recruitment and only 33 children were enrolled (16 continued a failing regimen, 17 switched to 3TC/FTC monotherapy). After 28 weeks on study, those switched to 3TC/FTC were more likely to sustain a 30% decline in absolute CD4$^+$ [29]. Abadi et al. [17] demonstrated that children who stopped their protease inhibitor-based therapy and continued with an NRTI-based regimen, that is partial treatment interruption, did not progress clinically and remained relatively stable immunologically. The ARROW study reported that after induction with protease inhibitor or NNRTI-based regimens, children switched to triple NRTI maintained virological suppression in the short term (24 weeks) but by 144 weeks, virological suppression rates were significantly lower [30]. A small South African study (23 children) showed a 23% reduction in CD4$^+$ cell count at 6 months of follow-up in children who switched to lamivudine monotherapy; 30% restarted a cART regimen [31]. Adult studies have shown that immunologic stability can be maintained with lamivudine monotherapy, albeit with larger declines in CD4$^+$ cell count among those previously treated with protease inhibitor based regimens [32]. Drug-sparing regimens might, therefore, serve as a useful stopgap treatment approach when there are significant barriers to starting new cART (such as persistent adherence problems and/or lack of availability of active drugs or toxicity), as they may be easier to administer, have less side effects than cART, have lower risk of resistance mutation accumulation and stability might persist in the presence of incomplete adherence. However, considering the lack of available data, children continuing this strategy require careful follow-up [8,33,34].

Resolving adherence issues remains the most important, yet most difficult factor in managing children with virologic failure. Adherence problems may be related to patient/caregiver and/or healthcare provider factors [35,36]. We found that most children who experienced virologic failure initiated cART prior to 2006 and that nelfinavir was the most commonly prescribed failing cART drug, followed by lopinavir/ritonavir. It is likely that poor palatability of these drugs, side effects such as nausea and vomiting and a large pill burden contributed to poor adherence and subsequent virologic failure in this cohort. Ongoing efforts to increase the palatability of paediatric drugs and to simplify regimens with fixed-dose combination drugs are hoped to increase adherence. Adherence interventions in children and adolescents need to be tailored to the personal circumstances of the index case and their family and caregivers and require a multidisciplinary, dynamic approach. Interventions may include, but are not limited to simplification of ART regimens as far as possible; treating associated side effects; reminders to trigger adherence such as alarms; psychosocial interventions that may be individual or group-based; mental health screening and management; appropriate disclosure of HIV status to the child; minimizing transport costs for clinic attendance and directly observed therapy in children and adolescents taking cART in extreme cases [36]. Although this study was based in a resource-rich setting, as increasing numbers of children in low and middle-income countries start cART early, a proportion will experience virologic failure and clinicians will require access to second and third-line cART, currently scarce in these settings, creating treatment dilemmas for this increasing population.

**Limitations**

This study has limitations. The validity of our estimates of change in immunologic and virologic outcomes by treatment strategy after virologic failure is based on the assumption that we appropriately accounted for all confounders. Although we collected information on prognostic characteristics we believe would strongly predict choosing one treatment strategy over the alternatives, we did not have information on resistance, a key variable that may be associated with choosing a particular treatment strategy and immunologic and virologic outcomes. Adherence data were also not uniformly collected in this study population, although we were able to utilize all available data. Lastly, the period of follow-up after virologic failure was relatively brief. However, this study provides detailed analysis on a robust number of participants and our results remained stable across the crude, baseline-adjusted and weighted models as well as with several sensitivity analyses.

**Conclusion**

Managing virologic failure in children remains challenging. Compared with switching to new cART, which requires optimized adherence and available cART, continuing a failing cART regimen results in similar 12-month immunologic outcomes while discontinuing ART is the worst option immunologically and virologically and should be avoided in children with virologic failure. Switching to a drug-sparing regimen may be a well tolerated option in the short-term, but data regarding the sustainability of this strategy remain scarce and careful follow-up is required.

**Acknowledgements**

We thank the children and families for their participation in PHACS and IMPAACT 219C, and the individuals and institutions involved in the conduct of these studies.

R.V.D., R.H., K.P., G.K.S., L.F. and A.W. conceived and designed the study. K.P. and B.K. collected and cleaned data and performed the statistical analysis with an additional input from M.H. and G.R.S. R.V.D., K.P., R.H., B.K., L.F. and A.W. drafted the manuscript with
additional content contributions from G.K.S., A.A. L.E. coordinated the drafting of the manuscript and revisions to the manuscript. All authors contributed to review of the manuscript and all authors read and approved the final manuscript.

The following institutions, clinical site investigators and staff participated in conducting PHACS AMP in 2012, in an alphabetical order: Baylor College of Medicine: William Shearer, Mary Paul, Norma Cooper, Lynette Harris; Bronx Lebanon Hospital Center: Murli Purswani, Mahboobullah Baig, Anna Cintron; Children’s Diagnostic & Treatment Center: Ana Puga, Sandra Navarro, Doyle Patton, Deyana Leon; Children’s Hospital, Boston: Sandra Burchett, Nancy Karthas, Betsy Kammerer; Ann & Robert H. Lurie Children’s Hospital of Chicago: Ram Yoge, Margaret Ann Sanders, Kathleen Malee, Scott Hunter; Jacobi Medical Center: Andrew Wiznia, Marlene Burey, Molly Nozyce; St. Christopher’s Hospital for Children: Janet Chen, Latrecia Ivey, Maria Garcia Bulkley, Mitzie Grant; St. Jude Children’s Research Hospital: Katherine Knapp, Kim Allison, Megan Wilkins; San Juan Hospital/Department of Pediatrics: Midnella Acevedo-Flores, Heida Rios, Vivian Olvera; Tulane University Health Sciences Center: Margarita Silio, Medea Jones, Patricia Sirios; University of California, San Diego: Stephen Spector, Kim Norris, Sharon Nichols; University of Colorado Denver Health Sciences Center: Elizabeth McFarland, Emily Barr, Robin McEvoy; University of Medicine and Dentistry of New Jersey: Aray Dieudonne, Linda Bettica, Susan Adubato; University of Miami: Gwendolyn Scott, Patricia Bryan, Elizabeth Willen.

The following institutions, clinical site investigators and staff participated in conducting IMPAACT 219C: University of New Jersey Medical and Dental School, Department of Pediatrics, Division of Allergy, Immunology & Infectious Diseases: Arlene Bardeguay, Aray Dieudonne, Linda Bettica, Juliette Johnson; Boston Medical Center, Division of Pediatric Infectious Diseases: Stephen I. Pelton, Ellen R. Cooper, Lauren Kay, Ann Marie Regan; Children’s Hospital LA, Department of Pediatrics, Division of Clinical Immunology & Allergy: Joseph A. Church, Theresa Dunaway; Long Beach Memorial Medical Center, Miller Children’s Hospital: Audra Deveikis, Jagmohan Batra, Susan Marks, Ilaisanee Fineanganofo; Harbor - UCLA Medical Center, Department of Pediatrics, Division of Infectious Diseases: Margaret A. Keller, Nasser Redjal, Spring Wetten, Sheryl Sullivan; Johns Hopkins Hospital & Health System, Department of Pediatrics, Division of Infectious Diseases: Nancy Hutton, Beth Griffith, Mary Joyner, Carolyn Keifer; University of Maryland Medical Center, Division of Pediatric Immunology & Rheumatology: Douglas Watson, John Farley; Texas Children’s Hospital, Allergy & Immunology Clinic: Mary E. Paul, Chivon D. Jackson, Faith Minglana, Dr Heidi Schwarzwald; Cook County Hospital: Kenneth M. Boyer, Jamie Martinez, James B. McAuley, Maureen Haak; Children’s Hospital of Columbus, Ohio: Michael Brady, Katalin Koranyi, Jane Hunkler, Charon Callaway; University of Miami Miller School of Medicine, Division of Pediatric Immunology & Infectious Disease: Gwendolyn B. Scott, Charles D. Mitchell, Claudia Florez, Joan Gamber; University of California San Francisco School of Medicine, Department of Pediatrics: Diane W. Wára, Ann Petru, Nicole Tilton, Mica Muscat; Children’s Hospital & Research Center Oakland, Pediatric Clinical Research Center & Research Lab: Ann Petru, Teresa Courville, Karen Gold, Katherine Eng; University of California San Diego Mother, Child & Adolescent HIV Programme: Stephen A. Spector, Rolando M. Viani, Mary Caffery, Kimberly Norris; Duke University School of Medicine, Department of Pediatrics, Children’s Health Center: Margaret Donnelly, Kathleen McGann, Carole Mathison, John Swetnam; University of North Carolina at Chapel Hill School of Medicine, Department of Pediatrics, Division of Immunology and Infectious Diseases: Tom Belhorn, Jean Eddleman, Betsy Pitkin; Schneider Children’s Hospital: Vincent R. Bonagura, Susan Schuval, Blanka Kaplan, Constance Colter; Harlem Hospital Center: Elaine J. Abrams, Maxine Frere, Delia Calo; New York University School of Medicine, Division of Pediatric Infectious Diseases: William Borkowsky, Nagamah Deygoo, Maryam Minter, Seham Akleh; Children’s National Medical Center, ACT: Diana Dobbins, Deidre Wimble, Lawrence D’Angelo, Hans Spiegel; University of Washington School of Medicine, Children’s Hospital and Regional Medical Center: Ann J. Melvin, Kathleen M. Mohan, Michele Acker, Suzanne Phelps; University of Illinois College of Medicine at Chicago, Department of Pediatrics: Kenneth C. Rich, Karen Hayani, Julia Camacho; Yale University School of Medicine, Department of Pediatrics, Division of Infectious Disease: Warren A. Andiman, Leslie Hurst, 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: Sohail Rana, Helga Finke, Patricia Yu, Jhoanna Roa; LA County/University of Southern California Medical Center: Andrea Kovacs, James Homans, Michael Neely, LaShonda Spencer; University of Florida Health Science Center Jacksonville, Division of Pediatric Infectious Disease & Immunology: Mobeen H. Rathore, Ayesha Mirza, Kathy Thoma, Almer Mendoza; North Broward Hospital District, Children’s Diagnostic & Treatment Center: Ana M. Puga, Guillermo Talero, James Blood, Stefanie Juliano; University of Rochester Medical Center, Golisano Children’s Hospital: Geoffrey A. Weinberg, Barbra Murante, Susan Laverty, Francis Gigliotti; Medical College of Virginia: Suzanne R. Lavoie, Tina Y. Smith; St. Jude Children’s Research Hospital, Department of Infectious Diseases: Aditya Gaur, Katherine Knapp, Nehali Patel, Marion Donohoe;
University of Puerto Rico, U. Children's Hospital AIDS: Irma L. Febo, Licette Lugo, Ruth Santos, Ibet Heyer; Children's Hospital of Philadelphia, Center for Pediatric & Adolescent AIDS: Steven D. Douglas, Richard M. Rutstein, Carol A. Vincent, Patricia C. Coburn; St. Christopher's Hospital for Children/Drexel University College of Medicine: Jill Foster, Janet Chen, Daniel Conway, Roberta Laguerre; Bronx-Lebanon Hospital Center, Infectious Diseases: Emma Stuard, Caroline Nubel, Stefan Hagmann, Murli Purswani; New York Medical College/Metropolitan Hospital Center: Mahrukh Banji, Indu Pathak, Savita Manwani, Ekti Patel; University of Massachusetts Memorial Children's Medical School, Department of Pediatrics: Katherine Luzuriaga, Richard Moriarit; Baystate Health, Baystate Medical Center: Barbara W. Stechenberg, Donna J. Fisher, Alicia M. Johnston, Maripat Toye; Connecticut Children's Medical Center: Juan C. Salazar, Kirsten Fullerton, Gail Karas; Medical College of Georgia School of Medicine, Department of Pediatrics, Division of Infectious Disease: Stuart Foshee, Chitra S. Mani, Denis L. Murray, Christopher White; University of South Alabama College of Medicine, Southeast Pediatric ACTU: Mary Y. Mancao, Benjamin Estrada; LSU Health Sciences Center: Ronald D. Wilcox; Tulane University Health Sciences Center: Margarita Silto, Thomas Alchediak, Cheryl Borne, Shelia Bradford; St. Joseph's 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 Programme; 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 (Paediatric); 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; 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; 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.

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) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI06716 (IMPAACT LC), with funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

PHACS was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) with funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases (NIAID), the Office of AIDS Research, the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard University School of Public Health (HD052102, 3 U01 HD052102-05S1, 3 U01 HD052102-06S3) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104, 3U01 HD052104-06S1) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Kenneth Rich; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research.
References

1. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med 2008; 359:2233.

2. Meyers TM, Dranowisk A, Schneider H, Gardiner N, Kuhn L, Moor D. Changes in pediatric HIV-related hospital admissions and mortality in Soweto, South Africa, 1996-2011: light at the end of the tunnel? J Acquir Immune Defic Syndr 2012; 60:503–510.

3. Viani RM, Araneta MRG, Deville JG, Spector SA. Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. Clin Infect Dis 2004; 39:725–731.

4. Laughton B, Cornell M, Grove D, Kidd M, Springer PE, Dobbels E, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. AIDS Behav 2012; 16:1685–1690.

5. Patel K, Van Dyke RB, Mittelman MA, Colan SD, Oleske MJ, Seage GR 3rd, et al. The impact of HAART on cardiomyopathy among children and adolescents perinatally infected with HIV-1. AIDS Behav 2012; 26:2027–2037.

6. Lipshultz SE, Williams PT, Wilkinson ID, Leister E, Van Dyke R, Shearer WT, et al. Cardiac status of HIV-infected children treated with long-term combination antiretroviral therapy: results from the Adolescent Master Protocol of the NIH multicentre Pediatric HIV/AIDS cohort study. JAMA Pediatr 2013; 167:520–527.

7. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommendations for a public health approach. Geneva, Switzerland: WHO Press; 2013.

8. Hazra R, Siberry G, Molenson AL. Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection. Ann Rev Med 2010; 61:169–185.

9. Williams PT, Storn D, Montepiedra G, Nichols S, Kamberer B, Sirisai PA, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. Pediatrics 2006; 118:e1745–e1757.

10. Nacheja JB, Hislop M, Nguyen H, Dowdy DW, Chaisson RE, Regensberg L, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in Southern Africa. J Acquir Immune Defic Syndr 2009; 51:65–71.

11. Davies MA, Keiser O, Techau K, Eley B, Rabie H, Cutsem GV, et al. Virologic failure and second-line antiretroviral therapy in children in South Africa: the iDeA South Africa Collaboration. J Acquir Immune Defic Syndr 2011; 56:270–278.

12. Musoke P, Mudirope P, Barlow-Mosha LN, Ajuma P, Bagenda D, Mulatu MM, et al. Growth, immune and viral responses in HIV-infected African children receiving highly active antiretroviral therapy: a prospective cohort study. BMC Pediatr 2010; 10:36.

13. Van Dyke RB, Patel K, Siberry GK, Burchett SK, Spector SA, Chernoff MC, et al. Antiretroviral treatment of U.S. children with perinatally-acquired HIV infection: temporal changes in therapy between 1991 and 2009 and predictors of immunologic and virologic outcomes. J Acquir Immune Defic Syndr 2011; 57:165–173.

14. Wong FL, Hsu AJ, Pham PA, Siberry GK, Hutton N, Agwu AA. Antiretroviral therapy interventions in highly treatment-experienced perinatally HIV-infected youth. Pediatr Infect Dis J 2012; 31:1279–1283.

15. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at http://aidsinfo.nih.gov/ContentFiles/lguidelines/PediatricGuidelines.pdf. [Accessed 13 December 2012]

16. The PENPACT-1 (PENTA 9/PECTG 390) Study Team. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. Lancet Infect Dis 2011; 11:273–283.

17. Abadi J, Sprecher E, Rosenberg MG, Dobroszycki J, Sansary J, Fennelly G, et al. Partial treatment interruption of protease inhibitor based highly active antiretroviral therapy regimens in HIV-infected children. J Acquir Immune Defic Syndr 2006; 41:289–303.

18. Siberry GK, Patel K, Dyke RBV, Hazra R, Burchett SK, Spector SA, et al. CD4+ lymphocyte-based immunologic outcomes of perinatally HIV-infected children during antiretroviral therapy interruption. J Acquir Immune Defic Syndr 2011; 57:223–229.

19. Division of AIDS. Table for grading the severity of adult and pediatric adverse events version 1.0. December 2004; Clarification August 2009. Available at http://www.niaid.nih.gov/lab-sand-resources/resources/daidsclinresrch/documents/daidsaegis/daidsaegisvingitable.pdf. [Accessed 12 December 2012]

20. The HIV Causal Collaboration. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. Ann Intern Med 2011; 154:509–515.

21. Centres for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1993. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm. [Accessed 12 December 2012].

22. Centres for Disease Control and Prevention. 1994 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1994. Available at http://www.cdc.gov/mmwr/PDF/rr/rr4312.pdf. [Accessed 12 December 2012].

23. Gibb DM, Duong T, Leclercio VA, Walker AS, Verweel G, Dunn DT, et al. Immunologic changes during unplanned treatment interruptions of highly active antiretroviral therapy in children with human immunodeficiency virus type 1 infection. Pediatr Infect Dis J 2004; 23:465–472.

24. Klein N, Sefe D, Mosconi I, Zanchetta M, Castro H, Jacobsen M, et al. The immunological and virological consequences of planned treatment interruptions in children with HIV infection. Pediatr Clin North Am 2013; 60:765–782.

25. Lee KJ, Lyall EG, Walker AS, Sharland M, Judd A, Gibb DM, et al. Wide disparity in switch to second-line therapy in HIV infected children in CHIPs. Eighth International Congress on Drug Therapy in HIV infection; 12 November 2006; Glasgow, Scotland.

26. Johnston V, Fielding KL, Charalambous S, Churchyard G, Lips A, Grant AD. Outcomes following virological failure and predictors of switching to second-line antiretroviral therapy in a South African treatment programme. J Acquir Immune Defic Syndr 2012; 61:370–380.

27. Deeks SG, Barbour JD, Martin JN, Swann MS, Grant RM. Sustained CD4+ T cell response after virologic failure of protease inhibitor–based regimens in patients with human immunodeficiency virus infection. J Infect Dis 2000; 181:946–953.
28. Petersen ML, van der Laan MJ, Napravnik S, Eron JJ, Moore RD, Deeks SG. Long term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification. AIDS 2008; 22:2097–2106.

29. Agwu A, Warshaw M, Siberry G, Melvin A, McFarland E, Wiznia A, et al. 3TC/FTC monotherapy vs. continuing failing cART as a bridging ART strategy in persistently nonadherent HIV-infected youth with M184 V resistance: results of IMPAACT P1094. 6th International Workshop on HIV Pediatrics; 18 July 2014; Melbourne, Australia, oral presentation.

30. ARROW Trial team. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. Lancet 2013; 381:1391–1403.

31. Lazarus EM, Otowombe K, Fairlie L, Untiedt S, Violari A, Laher F, et al. Lamivudine monotherapy as a holding strategy in HIV-infected children in South Africa. J AIDS Clin Res 2013; 4:246–251.

32. Opravil M, Klimkait T, Louvel S, Wolf E, Battegay M, Fux CA, et al. Prior therapy influences the efficacy of lamivudine monotherapy in patients with lamivudine-resistant HIV-1 infection. J Acquir Immune Defic Syndr 2010; 54:51–58.

33. Palmer M, Chersich M, Moultrie H, Kuhn L, Fairlie L, Meyers T. Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa. AIDS 2012; 27:781–785.

34. Giaquinto C, Morelli E, Fregonese F, Rampon O, Penazzato M, de Rossi A, et al. Current and future antiretroviral treatment options in paediatric HIV infection. Clin Drug Invest 2008; 28:375–397.

35. Scanlon ML, Vreeman RC. Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. HIV/AIDS 2013; 5:1–17.

36. Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. J Int AIDS Soc 2013; 16:18579.