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

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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

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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
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:
(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
Table 1. Characteristics of most recent combination antiretroviral therapy failure among individuals with virologic failure after at least 6 months of combination antiretroviral therapy (N = 939)*.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)/median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous cART failures*</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>790 (84%)</td>
</tr>
<tr>
<td>One</td>
<td>138 (15%)</td>
</tr>
<tr>
<td>Two or more</td>
<td>11 (1%)</td>
</tr>
<tr>
<td>cART initiation and failure year</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td></td>
</tr>
<tr>
<td>1993–1997</td>
<td>82 (9%)</td>
</tr>
<tr>
<td>1998–2000</td>
<td>365 (39%)</td>
</tr>
<tr>
<td>2001–2011</td>
<td>492 (52%)</td>
</tr>
<tr>
<td>Type of failed cART: NRTIs +</td>
<td></td>
</tr>
<tr>
<td>One PI*</td>
<td>627 (67%)</td>
</tr>
<tr>
<td>PI and NNRTI</td>
<td>159 (17%)</td>
</tr>
<tr>
<td>NNRTI alone</td>
<td>137 (15%)</td>
</tr>
<tr>
<td>PI and E/INSTI</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>NNRTI and E/INSTI</td>
<td>2 (0%)</td>
</tr>
<tr>
<td>PI in failed cART</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>360 (38%)</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>260 (28%)</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>64 (7%)</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>46 (5%)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>29 (3%)</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>19 (2%)</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Boosted Darunavir</td>
<td>4 (0%)</td>
</tr>
<tr>
<td>NNRTI in failed cART</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>159 (17%)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>143 (15%)</td>
</tr>
<tr>
<td>Etravirine</td>
<td>2 (0%)</td>
</tr>
<tr>
<td>NNRTI and E/INSTI</td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>11 (1%)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>E/INSTI in failed cART</td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>4.2 (3.5, 4.8)</td>
</tr>
<tr>
<td>CD4% at cART initiation*</td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>25 (17, 32)</td>
</tr>
<tr>
<td>Missing</td>
<td>313 (34%)</td>
</tr>
<tr>
<td>Time from cART initiation to failure (months)</td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>23 (14, 38)</td>
</tr>
</tbody>
</table>

*cART, combination antiretroviral therapy; E, entry inhibitor (including fusion inhibitor); INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/tide reverse transcriptase inhibitor; PI, protease inhibitor.

*Virologic failure defined as a consecutive series (at least one month apart) of HIV viral load >1000 copies/ml, at least 6 months after initiation of cART regimen. Date of cART failure defined as date of confirmed viral load >1000 copies/ml.

**Nearest measure up to 6 months prior to or at cART initiation.

*Includes ritonavir boosting where appropriate.

(baseline), their median age was 11 years, their median CD4⁺% was 28% and their median log_{10} 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 protease inhibitor; 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 outcome.
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\(^+\) cells/\(\mu\)l (95% CI \(-3.18\) percentage points 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\(^+\) cells/\(\mu\)l and count with median (range) slopes of \(-0.66\)\% (\(-3.54\) to \(+1.34\)\%) and \(-12.7\) cells/\(\mu\)l (\(-148\) to \(+31\) cells/\(\mu\)l) 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\(^+\) cells/\(\mu\)l compared with lamivudine/emtricitabine \(P = 0.04\). Siberry et al. [18] reported from the overlapping AMP cohort that children who had an unplanned treatment interruption saw a steady decline in CD4\(^+\) cells/\(\mu\)l and count with median (range) slopes of \(-0.66\)\% (\(-3.54\) to \(+1.34\)\%) and \(-12.7\) cells/\(\mu\)l (\(-148\) to \(+31\) cells/\(\mu\)l) 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.

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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 NRTIs 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.

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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.F. 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.

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