Antiretroviral Treatment in Pediatric HIV Infection in the United States
From Clinical Trials to Clinical Practice

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Antiretroviral therapy (ART) for pediatric human immunodeficiency virus (HIV) infection has evolved from simple nucleoside reverse transcriptase inhibitor (NRTI) regimens of the 1980s and early 1990s to today’s complex regimens of NRTI in combination with protease inhibitors (PIs) and/or nonnucleoside reverse transcriptase inhibitors (NNRTIs). Changes in the treatment of pediatric HIV infection were driven by evidence from randomized controlled trials in HIV-infected adults, a small number of pediatric trials, and nonexperimental pediatric studies. No studies have examined how novel therapies have been integrated into the clinical care of pediatric HIV infection.

Since 1998, the US Working Group on Antiretroviral Therapy and the Medical Management of HIV-Infected Children has published guidelines for the use of combination ART for pediatric HIV infection. Current pediatric guidelines recommend a regimen of 2 NRTIs in

See also pp 2221 and 2272.
combination with a PI or an NNRTI. These guidelines exist to aid the practicing physician and are not meant to supplant clinical decision-making. To date, concordance between the US pediatric guidelines and treatment in clinical practice has not been assessed.

As HIV becomes a treatable disease, it is becoming increasingly important to take a long-term strategic approach to initial and subsequent ART. Quantifying the frequency of treatment switches provides an estimate of the rate at which regimens are failing or not tolerated. We identified only 1 study of ART use in HIV-infected children from 6 US sites that reported increases in use of highly active antiretroviral therapy (HAART) and frequent regimen changes from 1998 through 2000. The objectives of this study were to describe changes in the treatment of pediatric HIV in the United States from 1987 to 2003; to determine initial treatment choices, including the concordance between the US pediatric ART guidelines and clinical practice; and to identify predictors of first regimen switch.

**METHODS**

The source population for this study was the Pediatric AIDS Clinical Trials Group (PACTG) 219C cohort. All children born to an HIV-positive mother, whether infected or uninfected, younger than 24 years, and receiving care at a PACTG site were eligible. The PACTG 219C cohort has been enrolling and following up children since September 2000. PACTG 219C was a revised version of PACTG 219—a protocol initiated in 1993 to study the long-term effects of in utero ART exposure and complications of HIV infection in children. Children eligible for the present study must have been perinatally HIV infected, born before January 1, 2004, and must not have participated in an ART clinical trial at 219C enrollment or during follow-up. Although the latter criterion excluded roughly two thirds of perinatally infected children, it was essential to allow investigation of trends in the treatment of pediatric HIV infection in clinical practice. The institutions obtained approval from their respective review boards for human research, and each child’s parent or guardian provided written informed consent.

At 219C enrollment, medical and clinical histories and lifetime ART use including start and stop dates were abstracted from clinical records, CD4 T lymphocyte percentages and HIV viral loads were measured, and sociodemographic information was obtained. Information on race/ethnicity was volunteered by each child and/or guardian. Use of ART, HIV immunological and virological parameters, and clinical diagnoses were recorded at follow-up visits every 3 months. CD4 percentages and HIV viral load at ART initiation and by calendar year also were obtained from PACTG 219 when available; most children initiated ART before 219C enrollment and the 219C protocol did not collect information on CD4 percentages or viral load prior to enrollment. Thus, measures at ART initiation were unavailable for many children.

We used the following ART regimen classification: 1 NRTI, 2 NRTIs, 3 or more NRTIs, HAART (3 or more drugs from at least 2 classes) including a PI, HAART including an NNRTI, HAART including a PI plus an NNRTI, and other. Zidovudine prophylaxis taken in the first 6 weeks of life to prevent HIV infection was not counted as a regimen. The duration of use of each regimen was constructed from the start and stop dates of lifetime ART use. When examining the number of unique drug regimens, individual drugs rather than drug classes were considered. To examine trends in ART use by calendar time, the proportion of children receiving each of the above regimens from 1987 (the earliest date of ART use in the study population) through 2003 was determined. If a child used more than 1 regimen in a given year, 1 regimen was randomly selected. The use of specific drugs, CD4 percentages, and viral load by calendar year also were identified.

Concordance between first regimens and US pediatric guidelines was assessed in children who initiated ART at 11 years or younger and on or after April 17, 1998—the date on which the pediatric guidelines for HIV infection in the HAART era were published (Table 1). The upper age limit was used to ensure children were treated according to pediatric, not adult and adolescent, guidelines. The first regimen was classified according to the pediatric guidelines in effect at the time each child started therapy. The guidelines classified initial regimens as “strongly
recommended,” “alternative,” “secondary alternative,” “special circumstance,” and “not recommended.” The proportion of children who initiated therapy in each regimen category was reported. Children who started with a regimen that did not correspond to one of the pediatric guideline categories were classified as “other.”

To identify trends in the first, second, and third ART regimens and to account for the temporal availability of ART, children were classified into 4 birth cohorts. Birth cohort 1980-1990 was the period during which zidovudine was the only US Food and Drug Administration (FDA)–approved ART for HIV or AIDS; birth cohort 1991-1995 was the period during which additional NRTIs became available; birth cohort 1996-1999 reflected the advent of HAART, when PIs and NNRTIs were approved and began to be used; and birth cohort 2000-2003 reflected widespread use of PIs and NNRTIs. Dates of FDA approval of initial drugs in each class are provided in Table 1. The first, second, and third regimens and duration of use of each regimen by birth cohort were determined.

Multivariate Cox proportional hazards regression was used to identify predictors of time to first regimen switch. Variables considered included sex, race/ethnicity, age at ART initiation, calendar year of ART initiation, the first ART regimen, ART adherence at cohort enrollment, and whether the child lived in a state with an AIDS Drug Assistance Program. Additional models were constructed including CD4 percentages at the time of ART initiation for children for whom these data were available. There were too few children with HIV viral load measured at ART initiation to include this variable. The validity of the proportional hazards assumption was assessed, and no marked violations were identified. Analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC); P<.05 was used to determine statistical significance.

RESULTS

Of 2399 perinatally HIV-infected children enrolled in PACTG 219C between September 2000 and April 2004, 1633 (68.1%) participated in an ART clinical trial and thus were excluded. The remaining 766 children in the study population were recruited from 79 institutions in 25 states across the United States. The study population was significantly younger, more likely to be non-Hispanic black and less likely to be Hispanic, and less likely to have CD4 lymphocyte percentages in the lower range than ART trial participants (Table 2). At 219C enrollment, the participants’ ages ranged from 1.2 months to 21.9 years, with a mean age of 8.1 years.

FIGURE 1 provides the proportion of children receiving each ART regimen by year. Dual NRTI regimens began to be used in 1993 and became the most frequently used regimens in 1996-1997. In 1998—2 years after the implementation of PIs for adult HIV infection—regimens of HAART including a PI became the most frequently used. In 2000, the most frequently used regimens included lamivudine, stavudine, and nevirapine or combination lamivudine, zidovudine, and nevirapine, with 18.7% and 13.6% of children taking one of these regimens in 2000 and 2003, respectively. The increased proportion of children receiving HAART was accompanied by increases in CD4 percentages (<15: 20.0%, 20.0%, 18.3%, 9.7%, and 7.4% in 1997, 1998, 1999, 2000, and 2003, respectively) and by decreases in HIV viral load (>10 000 copies/mL: 75.0%, 60.0%, 77.8%, 32.1%, and 23.2%).

Trends in individual drug use by calendar time are shown in FIGURE 2. Zidovudine was the most frequently used NRTI in the early years of the epidemic, reaching a peak of 90.4% in 1991 and decreasing to around 35% in 1999 as other NRTIs became available. The use of didanosine also decreased after its peak of 51.3% in 1996. Stavudine and lamivudine were the most frequently used NNRTIs (approximately 55%) from 1998 onward. The use of both nevirapine and efavirenz steadily increased following FDA approval in 1996 and 1998, respectively, with efavirenz being the most frequently used NNRTI.
virenz becoming the most frequently used NNRTI in 2002. However, less than 20% of children were receiving either drug. The uptake of PIs was steady; nelfinavir was the most frequently used PI from 1998-2002 but declined after its peak of 38.4% in 1999. In 2003, boosted lopinavir was the most frequently used PI (28.4%), followed in frequency by nelfinavir (27.3%). In 2000, 20% of children initiated ART with combination lamivudine, zidovudine, and nelfinavir, and 20% initiated ART with combination lamivudine, stavudine, and nelfinavir. The proportion who initiated ART with combination lamivudine, zidovudine, and boosted lopinavir has increased since 2001 (5.3%) to become the most frequent initial regimen (30.0%) in 2003.

Concordance between the first regimens of the study population and pediatric guidelines was assessed in 261 children who started therapy after the guidelines were published (Table 1). These 261 children initiated therapy with the following pediatric guideline-classified regimens: “strongly recommended” (49.0%), “alternative” (14.6%), “secondary alternative” (8.8%), “special circumstance” (5.4%), “not recommended” (7.3%), and “other” (14.9%). The regimens of the 19 children who initiated a “not recommended” regimen included 1 NRTI (84.2%), 1 NNRTI (5.3%), 3 NRTIs (including both zidovudine and stavudine) (5.2%), and 1 PI (5.3%). The regimens of the 39 children who initiated a regimen classified as “other” included HAART with a PI plus an NNRTI (66.7%), HAART with an NNRTI but not the recommended one (10.3%), HAART with a PI but not the recommended one (7.7%), 1 PI (5.1%), 3 NRTIs but not the recommended combination (5.1%), 1 NRTI and 1 NNRTI (2.6%), and 1 NNRTI and 1 PI (2.6%).

Among the 4 birth cohorts, 0.5% of cohort 1980-1990, 7.3% of cohort 1991-1995, 27.7% of cohort 1996-1999, and 50.0% of cohort 2000-2003 used zidovudine prophylaxis in the first 6 weeks of life. The first, second, and third regimens of each birth cohort were examined, and key findings are summarized in Figure 3. Most of birth cohort 1980-1990 initiated therapy with 1 NRTI (66.1%), mainly zidovudine, which gradually decreased to 11.5% in birth cohort 2000-2003 (Figure 3A). HAART including a PI became the most frequently used first regimen in birth cohort 1996-1999 (37.4%), increasing to 61.5% of birth cohort 2000-2003. In the earlier birth cohorts, children frequently switched between single and/or dual NRTI regimens, with a
small number returning to single or dual NRTI regimens after HAART. In contrast, none of birth cohort 2000-2003 switched to single or dual NRTIs after HAART. Forty-one percent of birth cohort 1980-1990 used HAART including a PI by their third regimen, which increased to almost 90% of birth cohort 2000-2003 (Figure 3B). The median age at the initiation of ART decreased from 5.8 years in the 1980-1990 birth cohort to 2.4 months in the 2000-2003 cohort, as did the median age at initiation of HAART including a PI. Age at ART initiation decreased irrespective of the availability of ART, but the decrease in age at first PI use was affected by the availability of PIs. The median number of regimens used was 4 (10th, 90th percentiles: 1, 9) in birth cohort 1980-1990, 4 (10th, 90th: 1, 10) in birth cohort 1991-1995, 2 (10th, 90th: 1, 6) in birth cohort 1996-1999, and 2 (10th, 90th: 1, 3) in birth cohort 2000-2003. Five children (2.2%) of birth cohort 1980-1990, 5 children (1.8%) of birth cohort 1991-1995, 1 child (0.5%) of birth cohort 1996-1999, and 2 children (2.5%) of birth cohort 2000-2003 never initiated ART.

Eleven children died from HIV infection or a related diagnosis, 10 from birth cohort 1980-1990 and 1 from birth cohort 1991-1995. The median age of death was 14.6 years (10th, 90th percentiles: 11.9, 19.2). All 11 children were ART experienced, with a median age of ART initiation of 7.1 years (10th, 90th: 0.5, 14.0).

Six hundred six (80.5%) of the 753 children receiving ART switched from a first to a second regimen. The median time to first regimen switch decreased from 31.3 months in the 1980-1990 birth cohort to 13.8 months in the 2000-2003 cohort. The unadjusted hazard ratio (HR) for a first regimen of 1 NRTI, 2 NRTIs, or other ART (TABLE 3) dramatically increased when adjusted for other covariates in the multivariate model, primarily because of confounding by year of ART initiation. Thus, we focus on the multivariate results. As shown, male participants had a higher risk of switching—or shorter time to switch—than female participants (HR, 1.17; 95% confidence interval [CI], 1.00-1.38). Risk of switching significantly decreased (ie, a significantly longer time to switch) with age (years) at ART initiation (HR, 0.96; 95% CI, 0.94-0.99) and significantly increased (ie, a significantly shorter time to switch) with calendar year of ART initiation (HR, 1.28; 95% CI, 1.23-1.33). The first regimen was associated with the likelihood of switching: children who initiated therapy with 1 or 2 NRTIs or an unconventional regimen had a significantly higher risk of switching (ie, shorter...
time to switch) than those who initiated therapy with HAART including a PI. There was no significant difference in the risk of switching among children who initiated ART with 3 or more NRTIs or HAART including an NNRTI or a PI plus an NNRTI vs those who initiated therapy with HAART including a PI. Adherence to ART and living in a state with an AIDS Drug Assistance Program were not associated with switching, did not change the other parameter estimates, and therefore were not retained in the model.

The likelihood of switching was examined in 39 children for whom CD4 percentages were available at ART initiation. In this multivariate model (adjusted for a first regimen of 1 NRTI, 2 NRTIs vs other, and ART initiation at 3 years or younger vs other), children who initiated ART at CD4 percentages less than 15 had a significantly higher risk of switching (ie, a shorter time to switch) than did children who initiated ART with CD4 percentages of 15 or greater (HR, 2.90; 95% CI, 1.03-8.13).

**COMMENT**

This study describes changes in the treatment of pediatric HIV infection in the United States from 1987 through 2003. There was a short lag between the identification of novel ART—including new drugs and drug combinations—and its adoption in the pediatric community; both ritonavir and nelfinavir were approved for children in 1997 and were in widespread use the following year. Pediatricians involved in ART clinical trials treated the children in our study population, which probably enhanced the transfer of research to clinical practice. Some children who initiated dual NRTI before the HAART era continued to have good immunological and clinical profiles, which thwarted the need to switch to a more potent regimen. Further, the uptake of PIs in 1998 corresponded to the publication of the pediatric guidelines for combination ART. Thus, the clinicians, patients, and caregivers may have been reluctant to use novel treatment in the absence of recommendations for use in children.

To our knowledge, this is the first study to examine concordance between the US pediatric ART guidelines and clinical practice. We found a...
that most clinicians of the collaborating institutions—of which the majority were university affiliated HIV clinics—followed pediatric guidelines. However, since publication of the pediatric guidelines in 1998, 22% of children initiated therapy with a regimen not recommended by the guidelines, and a small proportion was receiving unorthodox treatment at any time in therapy. Children who initiated therapy with these unorthodox regimens had a shorter time to switch than did those who initiated therapy with HAART plus a PI. A shorter time to switch might affect prognosis because of the increased exposure to multiple drugs and drug classes, the consequent development of resistance, and the reduction of future therapy options. The relatively common use of nonstandard regimens may reflect some children’s intolerance of standard therapy or the willingness of this group of physicians to try unorthodox regimens.

Because a key objective of this study was to describe and assess the treatment of pediatric HIV infection in clinical practice, the study population was restricted to children in the PACTG 219C cohort who were not participants in ART clinical trials. Although there was no difference in the virological status of the 2 groups, the study population was younger, more likely to be black and less likely to be Hispanic, and less likely to have CD4 lymphocyte percentages in the lower range than were children who participated in ART clinical trials. Furthermore, the clinical sites were university-affiliated institutions, which may differ from other HIV clinics. As a result, our findings may not be generalizable to all HIV-infected children. Nonetheless, 766 children from 79 institutions in 25 states across the United States constituted our study population, and therefore their ART experience should validly characterize clinical practice in these university settings.

Although not statistically significant, time to first regimen switch was shorter in male vs female participants. Studies in HIV-infected adults have found that women have lower HIV RNA levels than men with comparable CD4 cell counts, and this was observed in a study of HIV-infected infants. If this phenomenon is in fact true of the pediatric population and clinicians primarily are basing treatment initiation and switches on HIV RNA levels, then this could explain our observed association. Levels of HIV RNA at ART initiation were unavailable for most of the study population, and therefore we were unable to examine this association. The role of sex, HIV RNA, and ART should be studied further; the adult guidelines propose considering lower HIV RNA thresholds when initiating therapy in women with CD4 cell counts greater than 350 cells/µL.

Others have reported that poor ART adherence is associated with an increased likelihood of virological failure and disease progression, which could warrant a change in therapy. In our study, we found no association between switching and ART adherence. Our adherence data concerned missed doses in the past 3 days and was measured at cohort enrollment, which was after ART initiation for many children and may have misclassified ART adherence prior to switching.

Time to first regimen switch decreased with calendar year of ART initiation. Children who initiated ART in the era of viral load monitoring, a larger selection of treatments, and more potent therapies had a shorter time to first regimen switch. Unfortunately, the 219C protocol did not record reasons for treatment switch. While we have speculated that most switches were due to virological, immunological, or clinical failure, other reasons such as drug toxicity and palatability, age appropriateness of formulations, number of pills or volume of liquid, frequency of dosing, and availability of new ART also may have prompted a regimen switch.

A European survey conducted in 1998 found that most pediatric HIV physicians delayed therapy until disease progression—evident through symptoms, low CD4 cell counts, or high viral load—was apparent. In our study, children who began ART when severely immunosuppressed (CD4 percentages <15) had a significantly shorter time to first regimen switch than children who were immunocompetent or moderately immunosuppressed at initiation. Studies conducted in adults also have found that lower CD4 cell counts and higher viral load have been associated with switching. Although our analysis included children from all birth cohorts and who initiated ART at varying ages, our findings on CD4 percentages were based on a small number of children and may not be generalizable to the larger pediatric population.

In sum, this study describes changes in the treatment of pediatric HIV infection in US children from 1987 through 2003. We identified demographic differences in children who were participating in ART clinical trials and in those who were not, as well as a short lag in the uptake of novel therapies in this latter group of children. The use of unorthodox regimens not recommended by the US pediatric guidelines was relatively common, and was related to a shorter time to first regimen switch. Younger age at ART initiation, recent ART initiation, immunosuppression at ART initiation, and initial therapy of 1 or 2 NRTIs were significantly associated with a shorter time to first regimen switch. Monitoring and documenting ART use in HIV-infected children can provide important insight regarding the clinical care of this population.

Author Contributions: Dr Brogly 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; critical revision of the manuscript for important intellectual content: Brogly, Williams, Seage, Oleske, Van Dyke, McIntosh.

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22.0 infection.

Preliminary study of ritonavir, an inhibitor of HIV-1 protease, to treat HIV-1 infection.


23. Does patient sex affect human immunodeficiency virus levels?


24. Patterns of adherence to highly active antiretroviral combination therapy in HIV-infected adults.


25. European Collaborative Study. Level and pattern of HIV-1 viral load over age: differences between girls and boys?


