# PEDIATRIC HIV INFECTION

*New developments in pediatric HIV infection were discussed at the Chicago meeting by Ellen Gould Chadwick, MD, from Northwestern University Medical School and The Children's Memorial Hospital, Chicago, Illinois.*

## ACTG 152: Preliminary Findings

As related by Dr Chadwick, an interim analysis of a large comparative trial (ACTG 152) in children with symptomatic infection and little or no prior experience with antiretroviral treatment has indicated that either didanosine monotherapy or didanosine-zidovudine combination therapy is associated with significantly delayed clinical progression compared with zidovudine monotherapy. In ACTG 152, patients aged 3 months to 18 years with mild to severe symptomatic disease, low age-adjusted CD4+ cell counts, and less than 6 weeks of prior antiretroviral therapy were randomized to receive zidovudine 180 mg/m$^2$ q6h, didanosine 120 mg/m$^2$ q12h, or zidovudine 120 mg/m$^2$ q6h plus didanosine 90 mg/m$^2$ q12h. The primary study end point was defined as time to death or clinical progression, with the latter defined as growth velocity change, neuropsychological deterioration, or at least 2 new or recurrent opportunistic infections.

The fourth scheduled interim analysis involved 831 evaluable patients with a median follow-up of 24 months. At the time of this analysis, 9% of patients had died, 60% remained on initial randomized treatment, 23% had been permanently discontinued from original treatment, and 21% had reached a primary end point. One of the treatment arms—either the didanosine monotherapy arm or the didanosine-zidovudine combination arm—was found to exhibit a significantly longer time to disease progression ($P = 0.0058$) and a longer time to development of hematologic toxicity ($P = 0.0003$) and liver or pancreatic toxicity ($P = 0.034$) compared with the zidovudine monotherapy arm. There was no difference in survival between the zidovudine group and the group exhibiting delayed disease progression ($P = 0.28$). Since the study continues with blinded treatment in the other treatment arms, it is not yet known which treatment was associated with this comparative benefit. On the basis of these findings, it was recommended that the zidovudine monotherapy arm be discontinued, with the patients being offered alternative treatment. Continuation of the study will determine whether there are differences between didanosine monotherapy and combination therapy.

*An interim analysis of ACTG 152 indicated that either didanosine alone or combined didanosine and zidovudine was associated with a significant delay in disease progression compared with zidovudine monotherapy in patients with more than 6 weeks of prior antiretroviral treatment.*

## An Approach to Treatment

It should be remembered that whereas the findings of the study indicate that either didanosine alone or in combination with zidovudine is superior to zidovudine alone in delaying clinical progression, the data do not allow generalizations regarding the efficacy of zidovudine in preventing maternal-fetal/neonatal vertical transmission, the treatment of asymptomatic infants or children, or the treatment of adults.

In stating that there remains no consensus regarding how to use antiretrovirals in the pediatric population at this time, Dr Chadwick noted that many physicians are reluctant to abandon initial use of zidovudine in children in light of the study findings. Since earlier noncomparative data showed that in addition to being very well tolerated, zidovudine treatment was associated with often striking improvements in energy, weight gain, linear growth, and neurocognitive function.

In outlining a treatment strategy based on currently available experience, Dr Chadwick presented the current approach in her own practice, cautioning that the approach is eminently subject to change based on further information. At present, the approach to the asymptomatic patient with moderate immune suppression is to (1) treat with zidovudine monotherapy, (2) monitor for laboratory evidence of zidovudine resistance, and (3) change to another agent as resistance is documented or disease progression occurs. An additional option is to rotate agents in patients without signs of resistance or progression. In symptomatic patients or asymptomatic patients with severe immune suppression, didanosine monotherapy or combination treatment with zidovudine plus didanosine or zalcitabine would be used. Current recommendations suggest that asymptomatic children who do not have immunosuppression should not be treated. However, these recommendations were made prior to findings regarding the rapid turnover of virus in vivo and noted that, given the implication that treatment should be initiated early to keep viral load suppressed, new recommendations regarding treatment in such children would likely be forthcoming.

## PCP Prophylaxis

*Pneumocystis carinii* pneumonia (PCP) remains the most common opportunistic infection and cause of death in pediatric patients. According to Centers for Disease Control and Prevention (CDC) data for 1993, PCP was the most common AIDS-defining diagnosis in children with perinatally acquired infection, accounting for approximately 30% of cases. As shown in Figure 1, the highest incidence of PCP in children with perinatally acquired infection is between 3 and 5 months of age. Many of these infants develop PCP before a diagnosis of HIV infection is made or suspected. The mean survival of patients developing

PCP at this age is approximately 1 month with many dying within a few days of presentation despite maximal antibiotic therapy and ventilatory support. Based on earlier data indicating that CD4+ cell counts in children were approximately twice those in normal adults, the CDC issued guidelines in 1991 that called for initiation of PCP prophylaxis using a CD4+ cell count threshold

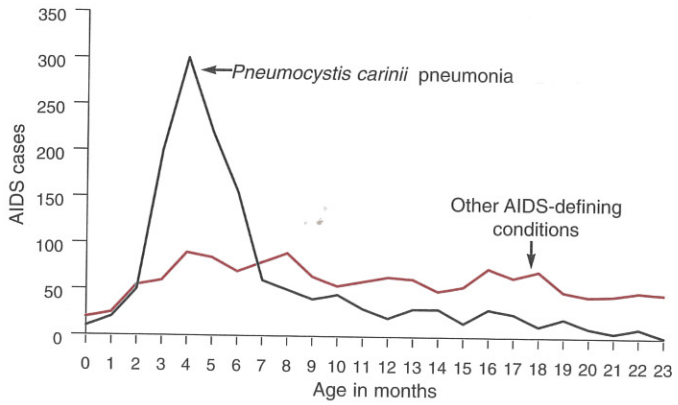


*Figure 1. AIDS-defining condition by age among AIDS patients aged <2 years who acquired infection perinatally. US data through December 1993. Data are from the Centers for Disease Control and Prevention.*

of 1500/µL, which was believed to predict which infants were at highest risk of developing disease. These guidelines failed to significantly reduce the incidence of PCP in the age group with the highest incidence.

One reason for this failure is that infants with HIV infection are probably not being identified early enough to benefit from prophylaxis. In one CDC survey, approximately two thirds of 300 infants had not received prophylaxis prior to PCP onset. In another survey, 59% of infants had not been assessed for HIV infection at more than 30 days prior to onset of PCP. An additional reason for the failure of the guidelines appears to be that the CD4+ cell count threshold of 1500/µL specified in the initial guidelines fails to identify a substantial proportion of patients at high risk for PCP. As shown in Table 1, 22% of children aged 0 to 5 months at the time of PCP onset had counts >1500/µL. In addition, the initial guidelines recommended assessment of cell count every 3 months in children being followed. However, as shown in data presented by Dr Chadwick, CD4+ cell counts in infants could precipitously drop to below the threshold level in a much shorter duration.

*Use of CD4+ cell count of 1500/µL as a threshold for PCP prophylaxis under former guidelines resulted in failure to identify a substantial proportion of patients at risk for disease.*

As a result of the failure of the prior recommendations, new guidelines for PCP prophylaxis in HIV infected or HIV-exposed children have been formulated; these are shown in Table 2. Under these guidelines, no prophylaxis is recommended for children aged up to 4 to 6 weeks, in whom the risk of PCP is exceedingly low. Sulfa-containing drugs are avoided in this age group due to the competitive binding of bilirubin with albumin that can cause jaundice and kernicterus and also, due to the potential for additive toxicity with zidovudine in those infants receiving zidovudine in regimens for prevention of perinatal transmission. From 4 to 6 weeks to 4 months of age, all children known to be HIV infected or who were born to a mother with HIV infection should receive prophylaxis. Prophylaxis should continue until 1 year of age unless absence of HIV infection is documented by at least two negative cultures or PCR assays. Prophylaxis should be maintained or instituted in children aged 1 to 5 years if the CD4+ cell count is lower than 500/µL or the CD4+ cell percentage is less than 15% and for children aged 1 to 2 years in whom the cell count fell below 750/µL in the first year of life. In this age group and in older children, prophylaxis should also be considered if CD4+ cell count is rapidly declining. For children aged 6 to 12 years, prophylaxis is recommended if the CD4+ cell count is less than 200/µL or the proportion is less than 15%. The recom-

**TABLE 1. INFANTS WITH *PNEUMOCYSTIS CARINII* BY AGE AND CD4+ CELL COUNT WITHIN 1 MONTH OF PNEUMONIA**

| CD4+ cell count (cells/µL) | Age at PCP | |
|---|---|---|
| | 0–5 months | 6–11 months |
| ≥1500 | 20 (22%) | 0 (0%) |
| 750–1499 | 24 (26%) | 5 (23%) |
| 500–749 | 9 (10%) | 5 (23%) |
| 200–499 | 19 (21%) | 8 (36%) |
| <200 | 19 (21%) | 4 (18%) |
| Total | 91 (100%) | 22 (100%) |

**TABLE 2. RECOMMENDED *PNEUMOCYSTIS CARINII* PNEUMONIA PROPHYLAXIS FOR HIV-INFECTED AND HIV-EXPOSED CHILDREN**

| Age | PCP prophylaxis |
|---|---|
| Birth to 4–6 weeks | None |
| 4–6 weeks to 4 months | All |
| 4–12 months | |
| HIV-uninfected[1] | None |
| HIV-infected/ indeterminate | All |
| 1–5 years | If CD4+ <500/µL or <15%[2,3] |
| 6–12 years | If CD4+ <200/µL or <15%[3] |

[1] ≥2 negative culture/PCR, both at ≥1 month and one at ≥4 months.

[2] Children aged 1 to 2 years should continue prophylaxis if CD4+ cell count was <750/µL in first year of life.

[3] Prophylaxis also considered for children with rapidly declining CD4+ cell counts/Category C conditions.

**Table 3. Prophylaxis Regimen for *Pneumocystis carinii* Pneumonia in Children**

- Recommended regimen

  TMP-SMX (for children >1 month old)
  - TMP 150 mg/m$^2$/d plus SMX 750 mg/m$^2$/d orally in 2 divided doses 3 d/wk on consecutive days (eg, Monday, Tuesday, Wednesday)

  TMP-SMX alternate schedules
  - Single daily dose 3 d/wk on consecutive days (eg, Monday, Tuesday, Wednesday)
  - 2 divided doses 7 d/wk
  - 2 divided doses 3 d/wk on alternate days (eg, Monday, Wednesday, Friday)

- Alternative agents

  Dapsone 2 mg/kg qd orally
  Pentamidine
  - Aerosolized, for children aged >5 years: 300 mg monthly
  - IV: 4 mg/kg every 2–4 weeks

  Atovaquone: experimental

TMP indicates trimethoprim; SMX indicates sulfamethoxazole.

mended prophylactic regimen consists of trimethoprim/sulfamethoxazole (TMP/SMX) in the standard or alternate regimens shown in Table 3; alternative agents include dapsone in a recently revised regimen of 2 mg/kg/d, aerosolized pentamidine (children older than 5 years) or IV pentamidine, and atovaquone. The single most important feature of successful prophylaxis remains the early identification of infants at risk for HIV infection.

## Rapid and Slow Progression in Perinatally Acquired HIV Infection

It was widely accepted several years ago that children with perinatally acquired HIV infection developed rapidly progressive disease, with an estimated 80% mortality by 3 years of age. However, with further study, it has become clear that the presentation of disease is at least bimodal. Approximately 30% of children acquiring the disease perinatally are rapid progressors, with infection course characterized by early onset of moderate-to-severe symptoms and death often occurring by 3 years of age despite intervention. Rapid progression may correlate with intrauterine transmission. Many of these children are found to be culture- or PCR-positive at birth, suggesting that infection may have been established in the context of an immune system less able to curtail viral replication due to its relative immaturity. Approximately 70% of children appear to be slow progressors, being asymptomatic and without significant physical findings for several years and having a life expectancy of greater than 5 years. Slow progression may correlate with intrapartum transmission, with such children tending to have negative PCR assay and culture findings at birth. Figure 2 shows representative survival curves for children with symptoms during the first year of life and those with symptoms only after 1 year of age. It can be seen that approximately 50% of children with diagnosis within the first year have died by 2 years of age, with more than 50% of those with later onset of symptoms remaining alive after 5 years.

*Approximately 30% of children acquiring HIV perinatally are rapid progressors, with the remainder being slow progressors; rapid progression may correlate with intrauterine transmission and slow progression with intrapartum transmission.*

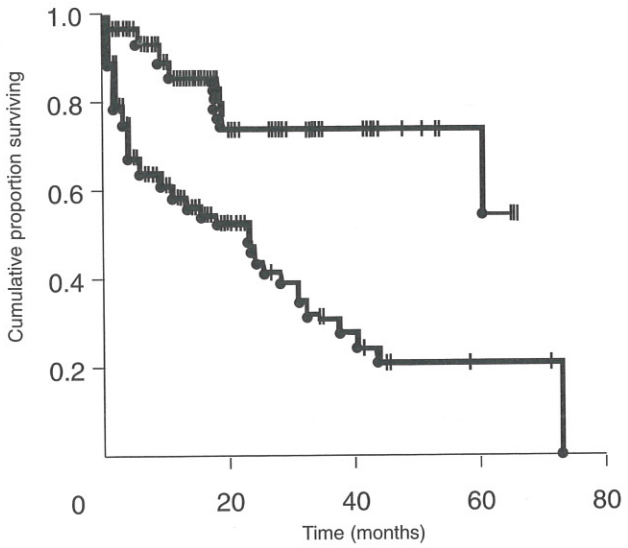


*Figure 2. Survival in children aged <1 year at diagnosis (bottom curve) compared with that in children aged 1 year or older at diagnosis (top curve).*

## Epidemiology of Adolescent AIDS Cases

Dr Chadwick also presented epidemiologic data on adolescent HIV disease. Recent data indicate that adolescents comprise the second most rapidly growing population of newly infected Americans, that 15% of all adult AIDS cases acquired HIV infection during adolescence (assuming 10 years of infection prior to AIDS diagnosis), and that 25% of all patients acquiring infection through heterosexual contact were infected as teenagers. Figures for 1991 indicate that both black and Hispanic adolescents are disproportionately represented among AIDS cases, with the former accounting for 16% of the adolescent population and 36% of adolescent AIDS cases and the latter accounting for 10% of the adolescent population and 21% of adolescent AIDS cases (Figure 3). Updated figures indicate that black teenagers account for 39% of adolescent AIDS cases; 1992 estimates put the highest AIDS rate among black female adolescents, with a rate of 2.6 cases per 100,000 population.

CDC data from 1992 on exposure categories for adolescents and young adults by gender are shown in Table 4. Among females, the most frequently identified route of transmission is heterosexual contact, accounting for nearly half of all AIDS cases. According to Dr Chadwick, the actual proportion of cases attrib-

utable to such transmission is higher, since most of the cases attributed to undetermined exposure are likely to be due to heterosexual contact. For males, the most common exposure category among young teenagers is contaminated clotting factor; homosexual contact is the second most common exposure category in the younger teenagers and is by far the most common exposure category among older teenagers.

Sexual activity is the primary risk factor for HIV infection among adolescents, with there being an increasingly younger age of first intercourse and very inconsistent condom use in this age group. Adolescents often have sexual encounters with older partners, who currently have a much greater prevalence of infection. Adolescents have the highest incidence of other sexually transmitted diseases, which are associated with more effective transmission of HIV. Other risk factors include drug-related behaviors such as sharing of IV drug "works" and a high frequency of unprotected sex because of impaired judgment—behavior particularly associated with the cocaine and alcohol use that is highly prevalent in the adolescent population. Runaways are at particularly high risk of infection, due to resorting to street prostitution for survival and the gravitation toward coastal cities with high prevalence rates of HIV infection.

*Among female adolescents and young adults, the most frequently identified route of HIV transmission is heterosexual sexual activity.*

**TABLE 4. AIDS CASES IN FEMALE AND MALE ADOLESCENTS AND YOUNG ADULTS IN THE UNITED STATES, BY EXPOSURE CATEGORY***

| | No. of cases (%) | |
|---|---|---|
| **Exposure category** | 13–19 years | 20–24 years |
| **Females** | | |
| Injecting drug use | 72 (26) | 659 (37) |
| Hemophilia/coagulation disorder | 4 (1) | 5 (<1) |
| Heterosexual contact | 131 (46) | 872 (49) |
| Receipt of blood transfusion, blood components, or tissue | 29 (11) | 63 (4) |
| Undetermined | 39 (14) | 163 (9) |
| TOTAL | 275 (100) | 1762 (100) |
| **Males** | | |
| Men who have sex with men | 228 (34) | 5141 (66) |
| Injecting drug use | 50 (7) | 986 (13) |
| Men who have sex with men and inject drugs | 37 (6) | 833 (11) |
| Hemophilia/coagulation disorder | 278 (41) | 242 (3) |
| Heterosexual contact | 19 (3) | 262 (3) |
| Receipt of blood transfusion, blood components, or tissue | 28 (4) | 66 (<1) |
| Undetermined | 31 (5) | 290 (4) |
| TOTAL | 671 (100) | 7820 (100) |

*Reported through December 1992.

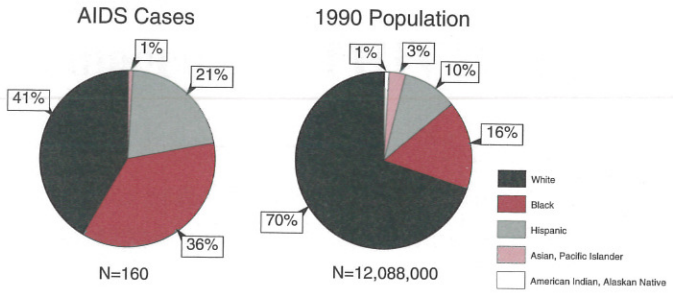


*Figure 3. Comparison of distribution of AIDS cases among adolescents (13- to 19-year-olds) reported in 1991 with 1990 US population estimates of race/ethnicity distribution of adolescent population.*

Finally, Dr Chadwick emphasized that many of the issues of HIV infection and AIDS in adolescents have yet to be appropriately addressed. As a start, improved access to care for HIV-infected teenagers must be developed and new and creative approaches to educating adolescents about HIV disease must be devised and implemented. Although trained educators are probably the most valuable resource for HIV disease prevention efforts among teenagers, physicians have a unique opportunity to implement education efforts in the office setting.

*Ellen Gould Chadwick is Associate Professor of Pediatrics at Northwestern University Medical School and Associate Director of the Section of Pediatric and Maternal HIV Infection in the Division of Infectious Diseases at The Children's Memorial Hospital, Chicago, Illinois.*