Early versus Deferred Antiretroviral Multidrug Therapy in Infants Infected with HIV Type 1

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Background. The clinical impact of early antiretroviral multidrug therapy on the risk of early-onset severe human immunodeficiency virus (HIV) disease has not been evaluated on a large scale.

Methods. We evaluated the risk of early-onset events associated with acquired immunodeficiency syndrome (AIDS), particularly the risk of encephalopathy, among infants in the French Perinatal Cohort, according to whether antiretroviral multidrug therapy was initiated before or after the age of 6 months.

Results. Of 83 HIV-infected infants born in 1996 (when HAART became available) or later, 40 received early treatment on or before the age of 6 months, and 43 received deferred multidrug therapy after the age of 6 months. In the group that received early multidrug therapy, no child developed an opportunistic infection or an encephalopathy during the first 24 months of life. In the deferred multidrug therapy group, 6 infants presented with a total of 7 AIDS-associated events (P \(\leq .01\)), 3 of which were encephalopathies (P \(\leq .08\)). The small number of events prevented the identification of clinical and biological markers that accurately predict progression of early-onset severe HIV disease.

Conclusion. In this observational study, infants who received multidrug therapy before 6 months of age did not have the early-onset severe form of childhood HIV disease. Further studies are needed to find accurate early markers of disease progression in this age group.

The time at which antiretroviral therapy should be initiated to HIV-infected infants remains a major issue. Before the widespread use of multidrug antiretroviral therapy in children, 15%–20% of infected infants developed severe disease early during the course of illness [1–4]. This form of HIV disease is associated with 2 major risks: high mortality and morbidity associated with opportunistic infections and encephalopathy [5, 6]. Although several clinical or immunovirological factors predictive of severe forms of infection have been described, it is still difficult to accurately identify those infants who will develop a severe form, particularly encephalopathy [7–9]. The HIV RNA load is higher among HIV-infected infants with early disease progression, compared with those without disease progression [10–12]. However, there is a large overlap between the distribution of viral loads in the 2 groups. Moreover, for infants <1 year of age, the risk of short-term progression is high, even if the CD4+ cell percentage is high [13]. In a recent study, low CD8+ cell count has been reported to be a risk factor for encephalopathy, but this observation has not been confirmed in large cohorts [14]. Thus, none of these factors can accurately predict a poor clinical progression in a given infant.

The situation for infected infants is similar to that for infected adults during the so-called primo-infection phase, in which the use of early antiretroviral treatment remains controversial [15]. The long-term immunological and clinical benefits of early suppression of viral
replication are counterbalanced by the potential toxicity and risk of resistance associated with currently available antiretroviral treatments. The same issues are pertinent for children, but the notable difference is that infected infants, unlike infected adults, are at risk for early and severe encephalopathy.

Several experiments involving early treatment of newborn infants have been reported, with good clinical and immunological results but with variable virological results [16–18]. However, the effects of such treatment on the incidence of encephalopathy have not been evaluated. Moreover, antiretroviral treatment is complex and difficult to administer to very young children and may result in only partial control of viral replication, with a serious risk of the emergence of resistant viral strains [17–22]. The aim of our study was therefore to compare early and deferred multidrug therapy in HIV-infected infants in the French Perinatal Cohort. After assessment of the overall AIDS-related morbidity and incidence of encephalopathy according to date of birth, we examined the impact on disease progression of antiretroviral multidrug therapy initiated before the age of 6 months in infants born during 1996–2001. We also investigated the prognostic value of a few baseline clinical and immunovirological characteristics of infants in the cohort.

METHODS

Study population. The French Perinatal Cohort is an ongoing, nationwide, prospective longitudinal cohort in France that was set up in 1986 and includes 94 centers. Indirect but concordant independent evaluation estimates that, since the beginning of the 1990s, a total of 70% of all French HIV-seropositive women have participated in the cohort. The recruitment of HIV-seropositive mothers is exhaustive at each center. The investigators at each center are free to choose the therapeutic strategies for prophylaxis against mother-to-child HIV transmission and for treatment of the children. The mother’s informed consent for data collection is obtained in every case, according to French Ethics Committee rules.

From January 1986 through December 2001, a total of 7947 HIV-seropositive pregnant women were included in the French Perinatal Cohort. Of these, a total of 2168 subjects were included before January 1994, a total of 894 were included from January 1994 through December 1995, and a total of 4885 were included from January 1996 through December 2001. The numbers of HIV-infected infants born during these 3 periods were 348, 55, and 83, respectively (with mother-to-child transmission rates of 16%, 6.1%, and 1.7%, respectively). HIV-infected infants were included in the study and, as such, were observed for 24 months. Demographic data concerning the mother (drug addiction status and clinical stage of HIV disease) and baseline characteristics of the infants at birth were collected. Clinical events were prospectively collected at regular intervals. CD4+ cell counts and HIV RNA loads were determined for the mothers during the month before delivery and for the infants at birth and every 3 months thereafter.

Study definitions. HIV infection was diagnosed in infants on the basis of PCR detection of proviral HIV DNA and/or by determination of plasma HIV RNA load in 2 separate blood specimens. In utero infection was defined as the isolation of virus during the first week of life, rather than as detection of virus during the first 3 days, because of missing data during this early period. For patients born during 1996–2001, two groups of infants were compared: those in the “early” multidrug therapy group (EMG) and those in the “deferred” multidrug therapy group (DMG). Multidrug therapy was defined as treatment that included at least 3 antiretroviral agents that were given simultaneously for at least 1 month. The postnatal phase of mother-to-child-transmission prophylaxis was excluded from this definition of treatment. Early multidrug therapy was defined as treatment initiated on or before the age of 6 months. The DMG included all infants who did not receive multidrug therapy during the first 6 months of life.

The choice of early or deferred treatment was made by the attending physician according to recommendations of the French Ministry of Health, published in 1998, for care of HIV-infected individuals [23]. These recommendations suggest early treatment for infants who, at birth, have the following risk factors for the onset of a severe form of HIV disease: hepatosplenomegaly, early detection of virus, and CD4+ cell percentage <30%. The recommendations allow either early or deferred treatment of asymptomatic infants. Furthermore, the possibility in France of directly observed therapy in the context of home-based care minimizes the delays in treatment that can be associated with social difficulties or with problems of observance.

Infants were defined as having met a study end point if, within the first 24 months of life, they received a diagnosis of category C illness specified in the revised 1994 pediatric Centers for Disease Control and Prevention (CDC) classification [24]. Encephalopathy was defined as the presence, before the age of 2 years, of 3 of the following clinical criteria: failure to attain or loss of developmental milestones or loss of intellectual ability or impaired brain growth; an acquired microcephaly; or an acquired symmetrical motor deficit [25]. Any other cause of encephalopathy, including active CNS opportunistic infection or malignancy, had to be ruled out for HIV-associated encephalopathy to be scored.

Statistical analysis. The Kaplan-Meier method was used to establish the survival curve for events under consideration (i.e., AIDS-associated events [according to the CDC classification] and encephalopathy). Log-rank tests were used for comparisons. To compare the maternal and child characteristics for
the EMG and the DMG, we used χ² and Fisher’s exact tests for expected values <5 for qualitative variables and Student’s t tests for quantitative variables. Wilcoxon tests were used to compare immunological variables (CD4° and CD8° cell counts and percentages) and virological variables (plasma HIV RNA load) at birth and at 3 months of age between infants who developed AIDS and those who did not. These comparisons were made on the basis of data for infants who had not received previous antiretroviral multidrug therapy before the time of measurement. Analyses were performed with SAS software (SAS Institute).

RESULTS

Survival without AIDS-associated events and encephalopathy in the French Perinatal Cohort, according to birth period. The group of 83 HIV-infected infants who were born during 1996–2001 was compared with the groups of 55 and 348 HIV-infected infants who were born during 1994–1995 and before 1994, respectively. Overall survival without AIDS-associated events and without encephalopathy was significantly higher in the 1996–2001 group, compared with the 1994–1995 and pre-1994 groups (P = .006 and P = .04, respectively) (figures 1A and 1B). Survival to 24 months of age without AIDS-associated events was 76% for the pre-1994 group, 74% for the 1994–1995 group, and 92% for the 1996–2001 group, and survival without encephalopathy was 88%, 83%, and 96%, respectively. Although the number of AIDS-associated events in the 1996–2001 group was low, there was nevertheless residual morbidity, mostly during the first 7 months of life.

Overall mortality and morbidity in HIV-infected infants born during 1996–2001. Among the 83 HIV-infected infants included at birth in the prospective French Perinatal Cohort during 1996–2001, a total of 4 deaths were reported: 3 were not associated with HIV infection (all were due to prematurity), and only 1 occurred in a child with an AIDS-associated event. Seven AIDS-associated events were diagnosed in 6 infants: 3 cases of encephalopathy, diagnosed at 2, 6, and 7 months of age; 3 cases of opportunistic infection, diagnosed at 2 (pneumocystis infection), 5 (pneumocystis infection), and 9 (CMV infection) months of age; and 1 case of severe recurrent bacterial infection, diagnosed at 23 months of age.

Characteristics of early and deferred therapy. Of the 83 HIV-infected infants studied, 40 received early multidrug therapy (i.e., before the age of 6 months). Most (74%) of the infants treated early received a combination that included 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and a protease inhibitor (PI). Ten percent received 3 NRTIs, and 3% received 2 NRTIs and a nonnucleoside reverse-transcriptase inhibitor (NNRTI). Quadruple therapy that included NRTIs and 1 PI, with or without 1 NNRTI, was given to 13% of these infants. Forty-three infants received deferred multidrug therapy: 18 received multidrug therapy between the ages of 6 and 24 months, 14 received bitherapy before the age of 24 months, and 11 received no treatment (other than the mother-to-child transmission prophylaxis) up to the age of 24 months.

More than one-half of the infants in the DMG (23 of 43) were born in 1996. Thirteen of the 40 infants in the EMG were born in 1999. The median year of birth was 1996 in the DMG, compared with 1999 in the EMG.

The case data used to decide the time at which to start therapy were not available for either group. However, these decisions were made on the basis of the French recommendations of 1998, which encourage treatment of an infant presenting with risk factors for early and severe disease. None of the decisions for deferred treatment resulted in delays in the initiation of treatment until after the disease had progressed excessively. The percentages of infants who were receiving
trimethoprim-sulfamethoxazole prophylaxis at 3, 6, and 12 months of age to prevent opportunistic infections were similar in both groups: 55%, 66%, and 81%, respectively, in the DMG and 50%, 71%, and 74%, respectively, in the EMG (P = .60).

**Baseline characteristics of mothers and infants.** Among mothers, there were no differences between the EMG and DMG with respect to the percentage of mothers with AIDS or a CD4+ cell count <200 cells/mm³ during the month before delivery (table 1). There was also no difference between the maternal HIV RNA loads at delivery for the 2 groups. There were no significant differences between the EMG and DMG with respect to social and demographic data, including geographic origin and drug addiction status. The percentage of mothers who had not received prophylaxis, compared with the percentage of those treated with bitherapy, did not differ between the 2 groups. However, the proportion of mothers treated with multidrug therapy that included at least 3 antiretroviral drugs was higher in the EMG, compared with the DMG (35.9% vs. 7.5%; P = .008). Similarly, monotherapy was less prevalent in the EMG, compared with the DMG (20.5% vs. 47.5%). There were no significant differences between the groups with respect to the relative proportions of vaginal delivery and cesarean section. However, the percentage of elective cesarean section procedures (i.e., cesarean section performed before labor and membrane rupture) was higher in the EMG, compared with the DMG (25.6% vs. 5.1%; P < .05).

Among infants, frequency of premature birth, mean birth weight, and mean cranial circumference in the DMG were similar to those in the EMG (table 2). There was no difference between the groups with respect to CD4+ and CD8+ cell counts and percentages during the first week of life. The percentage of in utero infections was the same in the 2 groups.

**AIDS-associated events and encephalopathy.** By the age of 24 months, there were no AIDS-associated events among infants in the EMG. In contrast, there were 7 AIDS-associated events, including 3 encephalopathies, in the DMG. Despite the small number of events, survival among infants without AIDS-associated events was significantly higher in the EMG, compared with the DMG (P = .01) (figure 2A). Similarly, at 24 months of age, there were no cases of encephalopathy in the EMG, whereas there were 3 cases in the DMG (P = .08) (figure 2B). It is important to note that all of these events occurred among infants in the DMG before the initiation of treatment.

**Predictive factors of disease progression.** We compared the 6 infants who developed early-onset AIDS-associated events with infants who did not to identify factors that were potentially...
Figure 2. Survival without AIDS-associated events (A) and survival without encephalopathy (B) among 40 infants who received early multidrug therapy (dotted line) and 43 infants who received deferred therapy (solid line) for HIV-1 infection. Log-rank analysis revealed P values of .01 (A) and .08 (B).

DISCUSSION

Independent of the timing of treatment, the evidence from this cohort is that antiretroviral multidrug therapy has a large, positive overall impact. Since the introduction of this type of multidrug therapy in 1996, the incidence of AIDS-associated events before the age of 24 months among infants in the French Perinatal Cohort has been reduced by ~70%, which accords with the findings of other large national cohorts [26, 27]. However, despite the widespread use of multidrug therapy since 1996, there is a residual risk of severe morbidity among infants <24 months of age. Our observations suggest that early-onset severe HIV disease with encephalopathy might be prevented by the initiation of antiretroviral multidrug therapy before the age of 6 months. There were no cases of AIDS-associated events or encephalopathy in the EMG, whereas there were such cases in the DMG. Despite the small number of AIDS-associated events in the DMG, the difference in the number of such events between the 2 study groups was significant.

Our study was observational and not randomized. Consequently, the findings must be interpreted with caution. There were several possible biases. Although all children were born during or after 1996, the majority in the DMG were born at the beginning of the study period. Therefore the possibility of a “calendar effect” during the short duration of the study cannot be excluded. Because of the small number of infants involved, it was not statistically possible to distinguish between calendar effects associated with age at initiation of the multidrug therapy and calendar effects associated with year of birth. However, this study was exhaustive, given that it involved a large national cohort comprised of ~70% of the children born to HIV-seropositive mothers in France; these children were prospectively followed since birth. Both these factors tend to diminish the risk of a calendar effect.

During the study period, decisions concerning whether to initiate early or deferred therapy were left to the discretion of the attending investigators, and French recommendations allow either option. The baseline characteristics of both the mothers and children studied, particularly characteristics concerning risk factors of disease progression in infants, were remarkably similar in the EMG and DMG. In particular, it is important for the validity of the comparison of the EMG and DMG that the proportions of cases of in utero infection were similar between the 2 groups, which was the case in our study.

Another possible bias is that the multidrug therapies used in the DMG (which were mostly given during the early part of the study) were less effective and/or more toxic than the multidrug therapies given more recently. This cannot, however, have been the cause of the AIDS-associated events that were observed, because all infants in the DMG who experienced such events did so before the start of treatment. It is also possible that the quality of care for the infants was subject to a major
Table 3. Baseline risk factors of disease progression for infants with and infants without AIDS-associated events.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Infant group, median value (range)</th>
<th>With AIDS-associated events (n = 6)</th>
<th>Without AIDS-associated events (n = 77)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>T cell value at birth&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; Cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1514 (1097–2972)</td>
<td>2127 (337–4312)</td>
<td>.19</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>42 (16–61)</td>
<td>54 (20–81)</td>
<td>.19</td>
<td></td>
</tr>
<tr>
<td>CD8&lt;sup&gt;+&lt;/sup&gt; Cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>799 (520–2060)</td>
<td>809 (316–2031)</td>
<td>.58</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>19 (14–36)</td>
<td>20 (5–35)</td>
<td>.71</td>
<td></td>
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<tr>
<td>T cell value at 3 months of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; Cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1725 (416–2812)</td>
<td>2531 (400–4610)</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>24 (17–38)</td>
<td>37 (18–61)</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>CD8&lt;sup&gt;+&lt;/sup&gt; Cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1748 (510–3901)</td>
<td>1558 (450–6280)</td>
<td>.85</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>26 (23–53)</td>
<td>24 (9–45)</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>HIV RNA load at 3 months of age, log copies/mL</td>
<td>6.2 (5.7–6.6)</td>
<td>5.4 (1.4–6.4)</td>
<td>.008</td>
<td></td>
</tr>
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</table>

<sup>a</sup> Recorded during the first week of life.

calendar effect. Although such an effect (e.g., morbidity associated with opportunistic infections) is plausible, it is unlikely to affect the occurrence of events such as encephalopathy. Furthermore, there was no difference in the strategy used for prevention of opportunistic infections (i.e., trimethoprim-sulfamethoxazole treatment) between the EMG and DMG.

Finally, the only difference between the 2 groups was the higher frequency of prophylactic multidrug therapy administered to mothers of infants in the EMG during pregnancy. The consequences of subsequent disease progression in infants after prophylactic treatment of mothers is not well established: it could paradoxically increase the risk of early-onset AIDS-associated events. Indeed, a more severe evolution of disease in infants born to mothers treated with antiretrovirals has been suggested elsewhere [28, 29].

However, early treatment is only beneficial for the small number of children likely to have early-onset severe HIV disease. Factors involved in the accurate prediction of progression to severe disease remain to be identified. The viral load and CD4<sup>+</sup> cell percentage at 3 months of age are both predictive of disease progression [10–12], but for both markers there is overlap between the individuals with progression and those without progression. Recently, a large meta-analysis has shown that the predictive value of CD4<sup>+</sup> cell percentage for short-term disease progression is lower for children <1 year of age than it is for older children [13]. The CD4<sup>+</sup> cell count and percentage at birth and the CD4<sup>+</sup> cell count at 3 months of age were not predictive of disease progression in our study, probably because of the small number of events. Thus, although some of these markers may have some predictive value, none can reliably predict the absence of risk of progression. Further effort is therefore required to identify specific early markers of progression for this particular age group.

This study was not designed to assess issues of toxicity and genotypic resistance associated with antiretroviral therapy in HIV-infected infants. Some studies have reported good short-term tolerance of the treatment in infants, but data concerning the long-term tolerance and the impact of HIV on diverse organs and biological systems are insufficient [30]. Indeed, adapted and effective multidisciplinary support is undoubtedly needed for the families of HIV-infected children, to ensure optimal and prolonged adherence. The optimal therapeutic strategy for newborn infants awaits more accurate and rigorous definition, which will require large international studies that involve both observational and prospective methodologies.

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References


2. Natural history of vertically acquired human immunodeficiency vi-


