Rapid disease progression in HIV-1 perinatally infected children born to mothers receiving zidovudine monotherapy during pregnancy

The Italian Register for HIV Infection in Children*

Objective: To investigate the outcome in children perinatally infected with HIV-1 whose mothers received zidovudine (ZDV) monotherapy in pregnancy.

Design: Observational retrospective study of a prospectively recruited cohort.

Setting: Italian Register for HIV Infection in Children.


Main outcome measures: The estimated probability of developing severe disease or severe immune suppression, survival probability [95% confidence interval (CI)] within 3 years, and the hazard ratio (95% CI), adjusted for year of birth, maternal clinical condition at delivery, birthweight and treatments (Pneumocystis carinii pneumonia chemoprophylaxis and/or antiretroviral therapy before the onset of severe disease, severe immune suppression or death) were compared.

Results: Comparison of HIV-1-infected children whose mothers were treated with ZDV with children whose mothers were not treated showed that the former group had a higher probability of developing severe disease [57.3% (95% CI 40.9–74.3) versus 37.2% (95% CI 30.0–45.4); log-rank test 7.83, \(P = 0.005\); adjusted hazard ratio 1.8 (95% CI 1.1–3.1)] or severe immune suppression [53.9% (95% CI 36.3–73.5) versus 37.5% (95% CI 30.0–46.2); log-rank test 5.58, \(P = 0.018\); adjusted hazard ratio 2.4, (95% CI: 1.3–4.3)] and a lower survival [72.2% (95% CI 50.4–85.7) versus 81.0% (95% CI 73.7–86.5); log-rank test 4.23, \(P = 0.039\); adjusted hazard ratio of death 1.9 (95% CI 1.1–3.6)].

Conclusions: This epidemiological observation could stimulate virologic studies to elucidate whether this rapid progression depends on in utero infection or transmission of resistant virus. Findings may suggest a need to hasten HIV-1 diagnosis in infants of ZDV-treated mothers and undertake an aggressive antiretroviral therapy in those found to be infected.

Keywords: disease progression, perinatal infection, zidovudine, zidovudine in pregnancy

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Introduction

The Pediatric AIDS Clinical Trial Group (PACTG) protocol 076 clearly showed that a three-part regimen of zidovudine (ZDV) during pregnancy, labour and the newborn period decreases the mother-to-child transmission of HIV-1 by about 70% [1]. In the past few years the extension of the protocol into practice has indeed decreased perinatal infection both in the United States and in Europe [2–4].

A sizeable number of HIV-1-infected mothers in Italy were given ZDV during pregnancy since 1992. As in other European countries and the United States [3,5,6], a number of centres in Italy were giving pregnant women ZDV during the early 1990s [7,8]. Subsequently, the three-part regimen of ZDV was implemented as the results from the PACTG protocol 076 became available. Little is known about the outcome in those children who acquired the infection despite this maternal treatment. Consequently, we selected from HIV-1-infected children enrolled in our multicentre study and derived prospectively from birth those born since 1992 and compared the disease progression in children born to mothers receiving ZDV monotherapy (ZDV⁺) with that of children born to mothers receiving no antiretroviral drug (ZDV⁻) during pregnancy.

Materials and methods

Data collection

The Italian Register for HIV Infection in Children is a nationwide multicentre study of children exposed perinatally to HIV-1; it was instituted in 1985 by the Italian Association of Paediatrics [9–14]. The Register involves a network of 103 paediatric centres that participate voluntarily and forward data to two coordinating centres at the Departments of Paediatrics in Florence and Turin. The centres undertake to enrol all exposed children and the data set is representative of the overall population of exposed children in Italy [10]. Children derived prospectively from birth or retrospectively are enrolled but only those derived prospectively are taken into account when studies on risk factors or course of infection are designed [11–14].

Data regarding mother–child pairs are collected through specific registration and follow-up forms as previously described [9–14]. In particular, the registration form includes specific questions concerning the child’s demographic data, age at first observation, maternal antiretroviral treatment during pregnancy, antiretroviral drug(s) used, gestational age at the beginning and end of treatment, application of the PACTG protocol 076, maternal clinical condition at the time of delivery, gestational age, birthweight and type of infant’s feeding. Both the registration and follow-up forms include information concerning infection status, HIV-1 antibodies, virus markers (proviral DNA, virus culture, free and complexed p24 antigenemia), laboratory tests, the Centers for Disease Control and Prevention (CDC) classification [15], CD4-positive cell numbers (measured by standardized fluorescent-activated cell sorting technique [9]), HIV-1-related signs and age at the appearance of single signs, age at entrance into the clinical and immunological categories of the CDC paediatric classification system or at death, Pneumocystis carinii pneumonia (PCP) chemoprophylaxis, drug used for PCP chemoprophylaxis, date at the beginning and end of chemoprophylaxis with each drug, antiretroviral therapy, antiretroviral drug(s) used, date at the beginning and end of therapy with each antiretroviral drug, date at last check-up or at death (with causes). The paediatric register has no information available concerning maternal viral load at the time of delivery, concomitant infections and treatments prior to pregnancy; maternal immunological condition at the time of delivery is known in a few cases.

Forms are filled in every 6 months by the appointed paediatrician at each centre [11]. Paediatricians from participating centres meet at least once a year to audit proceedings and to standardize procedures. According to these, infected children are examined at least every 2 months, and any clinical or immunological changes are reported in the follow-up form. For this study, any information concerning the antiretroviral treatment in pregnancy was confirmed by reviewing medical records from the adults’ infectious disease centres and/or obstetric wards and/or services for drug addiction.

Case definition

Inclusion criteria were prospective follow-up from birth, year of birth between 1 January 1992 and 31 December 1997, ascertained perinatal HIV-1 infection and confirmed history of maternal ZDV monotherapy or no antiretroviral treatment during pregnancy. Children derived prospectively from birth were defined as previously reported [10,14]. The CDC paediatric classification system defined the infection status and the clinical and immunological condition [15]. Infection was diagnosed through detection (on at least two occasions) of proviral DNA by polymerase chain reaction, positive virus culture and free and complexed p24 antigenemia. Definitions of preterm delivery (gestational age ≤ 36 weeks) and low birthweight (≤ 2500 g) have already been reported [10,13,14]. The criteria for disease definition have been previously described [11–13]. Severe disease and severe immune suppression were defined according to the CDC clinical category C and immunological category 3, respectively. The status of each subject at last analysis was the one attributed at the date of last clinical check.
or death. Only HIV-1-related deaths were considered when survival was estimated, and subjects whose death
was not directly attributable to HIV-1 infection were
censored at last check [11–13]. Mothers considered to
be ZDV+ were those with a confirmed history of ZDV
monotherapy (according to the PACTG protocol 076
or taking antenatal oral ZDV alone) during pregnancy
up to delivery. Mothers considered to be ZDV− were
those with a confirmed history of no antiretroviral
treatment during pregnancy. The CDC classification
for HIV-1 infection in adults was used in defining the
mothers’ clinical condition at the time of delivery [16].

Data set
The study comprised 221 children perinatally infected
with HIV-1, born between 1 January 1992 and 31
December 1997 and derived prospectively from birth
from the database of the Italian Register for HIV
Infection in Children. Four children were not taken
into account as they were born to mothers whose anti-
retroviral history in pregnancy was unknown. One
additional child was excluded because his mother had
received combined treatment (ZDV and lamivudine) in
pregnancy. Consequently, 216 children were included
in this study.

Chemoprophylaxis for PCP (oral trimethoprim–sul-
phamethoxazole or aerosolised pentamidine isethionate)
was prescribed to 118 (54.6%) children and 144
(66.6%) were given antiretroviral therapy (ZDV,
didanosine, lamivudine, stavudine, zalcitabine,
saquinavir, indinavir, or ritonavir) during the first 3
years of life. Only children given the PACTG protocol
076 three-part regimen [1] had received ZDV prophy-
laxis in the newborn period before HIV-1 diagnosis.
Decisions regarding therapies were the concern of the
contributing centres.

Figure 1 shows the distribution of children studied
according to the year of birth and maternal ZDV treat-
ment or no antiretroviral treatment during pregnancy.
There were 38 children [25 females and 13 males;
median age at last follow-up or death 25 months (range
2–69)] born to ZDV+ mothers; the three-part ZDV
regimen according to the PACTG protocol 076 [1] had
been given to 12 mother–child pairs whereas 26 pairs
were prescribed antenatal oral ZDV alone starting at
5 months of gestation [median (range 1–8)] and contin-
uing to delivery. All 18 children born to ZDV+ mothers
before 1995 were only exposed to ZDV in utero; out of
20 children born subsequently, 12 received the PACTG
protocol 076 three-part regimen, whereas eight were
only exposed to ZDV in utero because the protocol was
not universally and simultaneously carried out in all
centres. There were 178 children [81 females and 97
males; median age at last follow-up or death 32 months
(range 2–72)] born to ZDV− mothers. Before the
PACTG protocol 076, ZDV had been administered to
pregnant women in selected centres in our country
[7,8]; thereafter, the prophylactic regimen was intro-
duced (not universally and simultaneously), but some
women refused prophylaxis and other women were
diagnosed with HIV-1 infection late in pregnancy. As
infected children entered the present analysis, obviously
a sizeable proportion comprised children born to ZDV−
mothers.

Statistical analysis
Data was processed through SPSS™ (SPSS Inc.,
Chicago, IL) statistical package. The Student’s t test or
the non-parametric Mann–whitney U test (according
to normal or non-normal data distribution) were used
for quantitative variables whereas the \( \chi^2 \) test or the
Fisher exact test were used for nominal variables.
Analyses looked at the endpoint of reaching severe dis-
ease, severe immune suppression or dying. The esti-
mated probability of developing severe disease or
severe immune suppression and estimated survival
[with 95% confidence limits (CI)] were calculated by
the Kaplan–Meier product-limit method. Differences
in curves were tested by the log-rank test. The Cox
model was used to evaluate the adjusted hazard ratio.
As the outcome in children perinatally infected with
HIV-1 may be associated with year of birth [17], birth-
weight [13], maternal clinical condition at the time of
delivery [18], and treatments [17], covariates such as
year of birth (as a continuous variable), birthweight
(> 2400 g versus \( \leq 2400 \) g), asymptomatic (CDC cate-
gory A) versus symptomatic (CDC categories B and C)
mother at the time of delivery, and treatments (PCP
chemoprophylaxis versus no chemoprophylaxis and
antiretroviral therapy versus no antiretroviral therapy
before the onset of severe disease, severe immune sup-
pression or death) were introduced into the model.
Because there was a rapid death rate in children born to
ZDV+ mothers, analyses were limited to the first
3 years of life in order to maintain the reliability of later
parts of the probability curves. All statistical tests were two sided. Values of $P > 0.05$ were defined as not significant.

**Results**

**Perinatal data**
The frequency of birth of children to ZDV$^+$ mothers did not statistically differ over the years ($P = 0.317$, $\chi^2$ test). The ZDV$^+$ mothers were not more likely to be symptomatic at the time of delivery than ZDV$^-$ mothers [6/37 (one missing) (16.2%) versus 19/142 (36 missing) (13.3%) ($P = 0.860$, $\chi^2$ test)]. There was a similar frequency of preterm deliveries of children born to ZDV$^+$ or ZDV$^-$ mothers [6/38 (15.8%) versus 34/170 (8.8%) ($P = 0.653$, $\chi^2$ test)], low birthweight [7/37 (one missing) (18.9%) versus 33/177 (18.6%) ($P = 0.847$, $\chi^2$ test)] and even of breast feeding [1/38 (2.6%) versus 7/178 (3.9%) ($P = 1.0$, Fisher exact test)]. The two groups did not significantly differ in overall gestational age [median 39 weeks (range 30–42) versus 39 weeks (range 24–42) ($P = 0.120$, Mann–Whitney U test)] or birthweight [mean ± standard deviation: 2813 ± 536 g versus 2880 ± 564 g ($P = 0.560$, Student’s t test)].

**Treatments**
The proportion of children receiving PCP chemoprophylaxis within the first 3 years of life was similar in those with ZDV$^+$ and ZDV$^-$ mothers [25/38 (65.8%) versus 93/178 (52.2%) ($P = 0.179$, $\chi^2$ test)]; however, the chemoprophylaxis was started earlier in the former group of children [median 3.4 months (range 0.8–16.8) versus 5.9 months (range 0.3–33.1) ($P = 0.025$, Mann–Whitney U test)]. The history of antiretroviral therapy within the first 3 years of life in children of ZDV$^+$ or ZDV$^-$ mothers is reported in Table 1: the two groups did not differ in the frequency of children receiving antiretroviral drugs, age at the beginning of therapy and type of antiretroviral drug regimens. Similar proportions of children born to ZDV$^+$ or ZDV$^-$ mothers received ZDV as the initial treatment [ZDV monotherapy 20/21 (95.2%) versus 86/89 (96.6%); two combined nucleoside analogue reverse transcriptase inhibitors including ZDV 5/5 versus 27/27; highly aggressive antiretroviral therapy (HAART) including ZDV 0/1 versus 1/1].

**Outcome**
The probability of developing severe disease at 3 years of life (Fig. 2) was significantly higher in children born to ZDV$^+$ mothers (57.3%; 95% CI 40.9–74.3) than in those born to ZDV$^-$ mothers (37.2%; 95% CI 30.0–45.4) (log-rank test 7.83; $P = 0.005$). The number of at-risk children from ZDV$^+$ or ZDV$^-$ mothers is reported at individual time points.

![Fig. 2. Kaplan–Meier estimate of the probability of developing severe disease in children of mothers receiving zidovudine monotherapy (ZDV$^+$) or no antiretroviral treatment (ZDV$^-$) during pregnancy (log-rank test 7.83; $P = 0.005$). The number of at-risk children from ZDV$^+$ or ZDV$^-$ mothers is reported at individual time points.](image)

Table 1. Antiretroviral therapy in children born to mothers receiving zidovudine monotherapy (ZDV$^+$) or no antiretroviral treatment (ZDV$^-$) during pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>ZDV$^+$</th>
<th>ZDV$^-$</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Children receiving</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapy</td>
<td>27/38</td>
<td>117/178</td>
<td>0.658$^a$</td>
</tr>
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<td>Age at the beginning of</td>
<td>6.8 (1.3–25.4)</td>
<td>8.6 (0.99–35.9)</td>
<td>0.208$^b$</td>
</tr>
<tr>
<td>therapy (months, median and range)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Initial regimens$^c$</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NRTI monotherapy</td>
<td>21/27</td>
<td>89/177</td>
<td>0.950$^a$</td>
</tr>
<tr>
<td>Two combined NRTI</td>
<td>5/27</td>
<td>27/177</td>
<td>0.797$^a$</td>
</tr>
<tr>
<td>HAART</td>
<td>1/27</td>
<td>1/117</td>
<td>0.820$^a$</td>
</tr>
<tr>
<td>Subsequent regimens in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>some children (replacing</td>
<td>9/27</td>
<td>39/117</td>
<td>0.821$^a$</td>
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<td>the initial one)</td>
<td></td>
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<tr>
<td>Two combined NRTI</td>
<td>4/27</td>
<td>10/117</td>
<td>0.528$^a$</td>
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<tr>
<td>HAART</td>
<td></td>
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$^a$ $\chi^2$ test; $^b$ Mann–Whitney U test. $^c$ Drug regimens: NRTI, nucleoside analogue reverse transcriptase inhibitor; HAART, highly active antiretroviral therapy (two NRTI and one protease inhibitor).
higher in the children born to ZDV+ mothers (53.9%; 95% CI 36.3–73.5) than in the children born to ZDV− mothers (37.5%; 95% CI 30.0–46.2) (log-rank test 5.58; \( P = 0.018 \)) and the adjusted hazard ratio of severe immune suppression was 2.4 (95% CI 1.3–4.3; \( P = 0.003 \)). Finally, survival probability (Fig. 4) was lower in children born to ZDV+ mothers [72.2% (95% CI 50.4–85.7)] compared with children born to ZDV− mothers [81.0% (95% CI 73.7–86.5)] (log-rank test 4.23; \( P = 0.039 \)), and the adjusted hazard ratio of death in children born to ZDV+ mothers was 3.2 (95% CI 1.5–7.0; \( P = 0.002 \)). Only one child (of ZDV− mother) died of disease that was not related to HIV-1 infection.

**Discussion**

Our study suggests that children who fail ZDV prophylaxis are more likely to have a rapid course of HIV-1 infection compared with children born to untreated mothers, as disease progression and immunological deterioration are significantly more rapid and the risk of death is actually increased during the first 3 years of life.

Mechanisms by which ZDV treatment reduces mother-to-child HIV-1 transmission are not fully understood [19] and the mechanisms of treatment failure even less so. A strong association exists between high maternal viral load and an increased risk of transmission [20,21]. Inability to reduce maternal viral load might explain both treatment failure and rapid disease progression in infected children [22]. The mothers with a high viral load may transmit more virus to their infants [22], and infants with a high viral load during the first months of life are more likely to undergo a rapid progression of disease [22–24]. In addition, a ZDV-resistant HIV-1 transmitted by the mother could determine a poor outcome in the child [25]. However, it is uncertain whether an absent virological response and a ZDV-resistant HIV-1 in the mother determines prophylaxis failure [19,26,27], and factors other than inoculum size may affect outcome in the infants [22]. Infants with rapid disease progression [9,12,28] are likely to be those who have been infected by an intrauterine infection [29], which is marginally affected by ZDV prophylaxis [30]. If most HIV-1-infected children born to ZDV+ mothers acquire the virus in utero, they are more likely to be rapid progressors.

Our findings have the potential biases owing to the unmeasured variables and limitations of retrospective cohort studies. Such information as the maternal antiretroviral history before pregnancy, concomitant infections, viral load and CD4-positive lymphocyte counts at the time of delivery was not available in our data set; virologic markers immediately after birth (to distinguish intrauterine and intrapartum infection [29,30]) were not routinely investigated by all participating centres, and maternal and infant HIV-1 samples (to assay for
mutations associated with ZDV resistance) were unavailable.

We cannot rule out, a priori, the possibility that some women received HAART prior to pregnancy, which could bias the results because certain genotypic changes have been associated with multidrug resistance [31]. However, very few women were involved (if it did occur), considering the distribution of deliveries by year and timing of HAART introduction in our country. No women received HAART in the first months of pregnancy with therapy terminated when the pregnancy was diagnosed and then ZDV prophylaxis initiated in the second trimester. A few patients underwent the PACTG protocol 076 and in others ZDV treatment was not part of a formal protocol, hence compliance could not be fully monitored in all mothers. Our data set included only 12 children treated with the three-part regimen, no mother received combined treatment during pregnancy, and only one child received HAART. It is possible that the postnatal treatment included in the PACTG protocol 076 [1], combined antiretroviral treatments in mothers [19], or HAART in children [32] determine a different outcome.

However, similar retrospective cohort studies [5,6] already provided reliable and useful information on the efficiency of antenatal ZDV prophylaxis [19]. The design of our study was a retrospective one, but the cohort was recruited prospectively and followed-up from birth according to standardized criteria [9–14]. The association between ZDV treatment in pregnancy and the children’s outcome was significant after adjustment for factors possibly biasing the results. The two groups of children were similar as all variables were taken into account apart from age at the beginning of PCP chemoprophylaxis, which was undertaken prospectively and followed-up from birth according to standardized criteria [9–14]. The association between ZDV treatment in pregnancy and the children’s outcome was significant after adjustment for factors possibly biasing the results. The two groups of children were similar as all variables were taken into account apart from age at the beginning of PCP chemoprophylaxis, which was undertaken prospectively and followed-up from birth according to standardized criteria [9–14]. The association between ZDV treatment in pregnancy and the children’s outcome was significant after adjustment for factors possibly biasing the results. The two groups of children were similar as all variables were taken into account apart from age at the beginning of PCP chemoprophylaxis, which was undertaken prospectively and followed-up from birth according to standardized criteria [9–14]. The association between ZDV treatment in pregnancy and the children’s outcome was significant after adjustment for factors possibly biasing the results. The two groups of children were similar as all variables were taken into account apart from age at the beginning of PCP chemoprophylaxis, which was undertaken prospectively and followed-up from birth according to standardized criteria [9–14]. The association between ZDV treatment in pregnancy and the children’s outcome was significant after adjustment for factors possibly biasing the results. The two groups of children were similar as all variables were taken into account apart from age at the beginning of PCP chemoprophylaxis, which was undertaken prospectively and followed-up from birth according to standardized criteria [9–14].

Our study suggests that disease progression may be rapid in those children who fail prophylaxis with maternal ZDV monotherapy. This observation needs to be better understood and requires further investigation in other settings with shorter and more variable antiretroviral regimens, but is biologically plausible, is worth confirming through virologic studies (on timing of infection, viral load, HIV-1 genotype, phenotype, and antiretroviral drug resistance) in mother–child pairs who fail prophylaxis and is potentially important for clinicians. Probably HIV-1 diagnosis should be hastened in infants whose mothers are treated with ZDV monotherapy in pregnancy; those found to be infected should be candidates for aggressive antiretroviral therapy and HIV-1 genotyping should be carried out during the neonatal period before deciding treatment regimen. Our findings should not be misinterpreted as a reason not to use ZDV prophylaxis, which is effective in preventing perinatal HIV-1 infection [1–8].

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References

HIV-positive children of ZDV-treated mothers de Martino et al.


Appendix

Participants for this analysis