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EFFECTIVENESS OF EARLY INITIATION OF PROTEASE INHIBITOR-SPARING ANTIRETROVIRAL REGIMEN IN HUMAN IMMUNODEFICIENCY VIRUS-1 VERTICALLY INFECTED INFANTS

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Abstract: Each of the 17 vertically infected infants born to HIV-1-infected mothers in Belgian HIV reference centers since 1996 was treated with a combination of 3 reverse transcription inhibitors as soon as the diagnosis was established. Treatment was initiated in all patients before 66 days of life. Twelve patients, including 11/13 infants treated with the combination of zidovudine, lamivudine and nevirapine, experienced a complete viral suppression (<50 copies/mL) with their first drug regimen. At last follow-up, 12 patients were asymptomatic, 2 were CDC stage A and 3 were stage B; 15 had HIV-1 RNA levels of <50 copies/mL and 14 had ≥25% CD4 lymphocytes. These results suggest that early initiation of treatment with 3 reverse transcription inhibitors is highly effective to inhibit viral replication and to prevent clinical and immunologic progression of HIV infection in vertically infected infants.

Key Words: infants, highly active antiretroviral therapy, HIV, viral load

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In the absence of treatment about 20% of HIV-1 vertically infected children develop severe manifestations of the disease within the first year of life.[1,2] There are no markers to identify infants who are at risk for rapid disease progression. When highly active antiretroviral therapy (HAART) became available, early treatment of vertically infected infants to avoid rapid progression was advocated[3,4] and this approach has been supported by a reduction in disease progression observed in cohorts of HIV-1-infected infants followed since birth.[5,6] The limited number of studies that have assessed the efficacy of HAART initiated before 3 months of age have confirmed the absence of major clinical or immunologic progression, but have reported a low rate of virologic success.[7,8]

In 1996, we decided to treat all vertically HIV-1-infected infants as soon as the diagnosis was established with a regimen including 3 reverse transcription inhibitors (RTI). Between 1996 and 2003 each of the 17 infected infants followed in 3 Belgian pediatric HIV reference centers were treated accordingly. We report the ability of these protease inhibitor (PI)-sparing regimen initiated early in life to inhibit viral replication, and to prevent clinical and immunologic progression of HIV infection.

MATERIALS AND METHODS

Vertical transmission of HIV-1 infection was established on the basis of 2 positive virologic tests (DNA or RNA PCR) performed on 2 separate blood samples. For this purpose, blood samples were taken from all infants born to known HIV-1-infected mothers before 48 hours of life and at 1, 2 and 3 months. Plasma HIV-1 RNA copies were measured using the Amplicor HIV-1 monitor test, version 1.5 (Roche) from December 1996 to June 2002. From June 2002 onwards the Cobas Ampliprep/Cobas Amplicor HIV-1 monitor test version 1.5 was used.

A PI-sparing combination of 3 antiretroviral agents was administered as soon as feasible after the confirmation of infection. At the time of initiation of this protocol only nucleoside reverse transcription inhibitors (NRTIs) were available for use in young children and the infants were treated with a combination of zidovudine (ZDV), didanosine (ddI) and lamivudine (3TC). When non-nucleoside reverse transcription inhibitors (NNRTIs) became available, the first line regimen was ZDV + 3TC + nevirapine (NVP). These 3 drugs were chosen because they are easily administered to infants and pharmacokinetic data were available for young age groups. Other drugs were considered as second line in case of suspected resistance.

Children were assessed at the time of initiation of therapy, at months 1 and 3 and then at least every 3 months. Assessment included physical examination, tolerability and blood sampling for laboratory assessment. Data collection ended in June 2005.

RESULTS

Patient Characteristics. Seventeen infected infants were born between December 1996 and April 2003: 14 in Brussels, 2 in Liège and 1 in Antwerp. Ten of the 17 were born by cesarean delivery. Four were premature (gestational ages from 30 to 35 weeks). Nine of the 17 infants had received complete antiretroviral prophylaxis (antenatal, peripartal and postnatal). All but 4 were treated prophylactically postnatally with at least ZDV. The age at first detection of HIV-1 suggests in utero transmission in 8 patients, peripartal transmission in 4 patients and was indeterminate for 5 patients (Table 1). T1, AQ: 1

At initiation of therapy, 1 infant (Table 1, ID3) was classified in CDC clinical category B and the 16 others were asymptomatic (stage N). The time elapsed between diagnosis of vertical transmission and the initiation of treatment was less than 30 days in 13/17. Treatment was initiated in all patients within 66 days of life. Treatment characteristics and outcome are summarized in the table.

Initial Antiretroviral Therapy. Two infants born in 1996 were treated with ZDV + ddI + 3TC and 13 infants received ZDV + 3TC + NVP. Two infants received stavudine (d4T) + ddI + NVP because of concern about baseline resistance.

Viral suppression (<50 copies/mL) with the first antiretroviral regimen was achieved in 12/17 infants. Eleven of these 12 infants had plasma HIV-1 RNA <400 copies/mL 17 weeks after initiation of HAART (median: 8 weeks, range: 3–17), and a plasma HIV-1 RNA level <50 copies/mL after 42 weeks (median: 16 weeks, range: 6–42). One patient (ID 16) had a much slower response (plasma HIV-1 RNA level <400 and <50 copies/mL after 47 and 65 weeks, respectively). Among the 12 patients who experienced virologic success with their first line therapy, 11 were treated with the combination of ZDV + 3TC + NVP and 1 with ZDV + 3TC + ddI.

Five of the 17 patients failed to reach plasma HIV-1 RNA of <50 copies/ml with the initial therapy. One (ID 6) was born at 33 weeks of gestation after 6 weeks of maternal therapy with ZDV + 3TC + NVP + NFV and pharmacokinetic factors relating to prematurity as well as prior resistance could explain the poor response. Another patient (ID 7) had received prolonged ZDV + 3TC prophylaxis, and was then treated with d4T + ddI + NVP initiated at 60 days of life. Although baseline resistance testing showed only a single mutation (M184V) associated to 3TC resistance, his lowest viral load with the regimen was 413 copies/mL despite an apparent good compliance. Periods of major lack of compliance were acknowledged by the parents of the other 3 patients (ID 1, 10 and 15).

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TABLE 1. Initial and Current Antiretroviral Regimen and Long-Term Outcome of the 17 Children Included in the Study

ID	Age at Diagnosis (d)	Age at Initiation of Therapy (d)	First Antiretroviral Regimen	Lowest VL with Initial ART	Age (y) at Last FU	VL at Last FU	CDC Classification	CD4 (%) at Last FU	ART at Last FU
1	35	60	ZDV-3TC-ddI	24,000		<50	N	33	Lop/rito-TDF-ABC
2	29	51	ZDV-3TC-ddI	<50	8	<50	N	30	Unchanged
3	2	29	ZDV-3TC-NVP	<50	7	<50	B	46	Unchanged
4	2	23	ZDV-3TC-NVP	<50	6.5	<50	N	41	Unchanged
5	35	61	ZDV-3TC-NVP	<50	5.5	<50	N	35	Unchanged
6	1	15	ZDV-3TC-NVP	619	v.5	<50	N	27	ZDV-ABC-NVP
7	46	62	d4T-ddI-NVP	413	5	<50	N	37	ZDV-3TC-ABC
8	1	33	ZDV-3TC-NVP	<50	5	<50	A	24	Unchanged
9	12	37	ZDV-3TC-NVP	<50	4.5	<50	B	26	ZDV-NVP-NFV
10	2	66	d4T-ddI-NVP	2160	4.5	378	B	22	d4T-ddI-ABC
11	5	7	ZDV-3TC-NVP	<50	4.5	<50	A	36	Unchanged
12	6	13	ZDV-3TC-NVP	<50	3	<50	N	16	Unchanged
13	35	55	ZDV-3TC-NVP	<50	3	<50	N	34	Unchanged
14	24	30	ZDV-3TC-NVP	<50	3	<50	N	46	Unchanged
15	1	8	ZDV-3TC-NVP	110	3	37000	N	28	ZDV-3TC-ABC
16	1	48	ZDV-3TC-NVP	<50	2	<50	N	34	Unchanged
17	1	10	ZDV-3TC-NVP	<50	2	<50	N	49	Unchanged

ID, patient identification number; VL, viral load; ART, antiretroviral therapy; FU, follow-up.

Treatment Modifications. Eleven of the 17 patients remain treated with their initial regimen at last follow-up: 10 with ZDV + 3TC + NVP and 1 with ZDV + 3TC + ddI. One patient had a change in treatment regimen to decrease the pill burden. Five other patients had 6 changes of therapy because of failure. Three children have received a PI (nelfinavir (NFV) or lopinavir/ritonavir) after their initial therapy.

Follow-up and Long-Term Virologic Outcome. Median follow-up duration on June 2005 was 56 months (range 26–103). All patients were alive and treated with HAART. None had developed AIDS-associated events since initiation of therapy. Two patients had progressed from CDC stage N to A (multiple adenopathies) during a period of interrupted therapy and 2 patients progressed to stage B (severe bacterial infection). The viral load of 15/17 patients was <50 copies/mL at last follow-up.

Among the 12 infants who had viral suppression with their initial regimen, 5 had plasma HIV-1 RNA permanently <50 copies/mL (all treated with ZDV + 3TC + NVP) and 7 had 1 or several rebounds but had undetectable viral load at last follow-up.

Among the 5 patients who did not achieve viral suppression with the initial therapy, 3 eventually had plasma HIV-1 RNA <50 copies/mL with second or third line regimens and maintained undetectable plasma viral load at last follow-up.

Tolerance of Antiretroviral Therapy. One patient had severe side effects (nonregenerative anemia and pancreatitis) when his treatment was simplified to crushed tablets of Trizivir (association of ZDV + 3TC + ABC) to decrease the number of pills. One patient treated for the last 4 years with d4T + ddI + ABC developed clinical signs of lipodystrophy. Hypercholesterolemia and hypertriglyceridaemia were observed in 4 patients. Prevalence of febrile seizures in this cohort was 23.5% with multiple events in 2 patients.

Production of Antibodies. Among the 12 patients who achieved viral suppression with their initial regimen, 6 (50%) became seronegative for HIV-1 before the age of 19 months, among whom 5 remained seronegative at last follow up (ID 2, 3, 5, 12, 13).[9]

DISCUSSION

No randomized trials have investigated the benefit of beginning HAART in asymptomatic infants diagnosed very early in life. Such trials are now difficult to perform in industrialized countries, because prophylaxis with these drugs has markedly reduced the rate of vertical transmission. Two prospective open-labeled non comparative trials of antiretroviral treatments with at least 3 drugs administered in the first months of life to asymptomatic infected infants have been reported by European (PENTA) and North American (PACTG) collaborative groups.[7,8] The clinical outcomes in these 2 trials were good, confirming the information obtained from cohorts follow up but suppression of viral replication was difficult to obtain. In the PENTA trial, only 4/20 infants treated with a combination of d4T, ddI and NFV achieved suppression of plasma HIV-1 RNA to <50 copies/mL.[7] In PACTG 356, 15/25 infants treated before 3 months of age had <400 HIV-1 RNA copies/mL at 48 weeks. Triple or quadruple PI-sparing regimens were inferior to a quadruple therapy including a PI.

In our cohort, treatment with a regimen including 3 RTI initiated before 2.5 months of age reduced plasma HIV-1 RNA to <50 copies/mL in 70% of the infants, an efficacy comparable to that obtained with a 4 drugs regimen including 2 NRTI, 1 NNRTI and 1 PI in PACTG 356.

Lack of compliance of the parents to treatment might be an explanation for the disappointing results observed in earlier studies. If HAART is initiated very early in the life of HIV vertically infected infants, the time to build a relationship between the pediatric team and the parents to obtain their adhesion to treatment is short. In our centers, the multidisciplinary pediatric team is involved in the care as soon as possible during pregnancy, to help the parents to cope with the diagnosis, to break the social barriers to treatment and to support them in the care of the infant if vertical transmission occurs.

Among other explanations that might explain the high rate of virologic failure in PENTA 7 was the poor pharmacokinetic profile of NFV in infants, and the fact that ddI has to be administered on an empty stomach, adding an additional constraint during early life. The absence of food restriction of the association of ZDV + 3TC + NVP, its tolerability and well established pharmacokinetic data for use in infants make it an attractive option in this setting, as indicated by our data. However this regimen has a low genetic barrier to resistance and would not be suitable in case of baseline resistance to any of its component.

In conclusion, a 3 drugs regimen including only RTI initiated during the first few weeks of life in HIV-1 vertically infected infants

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is easy to administer, well tolerated and can inhibit HIV-1 replication in the long term. It prevents clinical and immunologic progression and in some patients specific antibody production. Parental adhesion to therapy is crucial. Close follow up of these children to detect the occurrence of metabolic abnormalities is important.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES **1**

AQ1—Please note that the "perpartal transmission" has been changed to "peripartal transmission" - OK?

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