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Effectiveness of antiretroviral therapy initiated before the age of 2 months in infants vertically infected with human immunodeficiency virus type 1

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Abstract The effectiveness and tolerance of antiretroviral therapy with a combination of three reverse transcriptase inhibitors starting at the time of diagnosis (before 2 months of age) was evaluated in four infants with vertically acquired HIV-1 infection. Plasma HIV-1 RNA levels ranged from 230,000 to 1,000,000 copies/ml before onset of triple therapy and fell below 50 copies/ml at 12 to 33 weeks of life in three of the infants. These three children, currently aged 158, 105 and 72 weeks, are asymptomatic, have normal lymphocyte subsets and no hypergammaglobulinaemia. Two children experienced a profound reduction in the amount of proviral DNA detected in blood and have become HIV-1 seronegative, although one of them has had HIV-1 RNA detectable on a single occasion at 114 weeks of life (303 copies/ml). Transient interruption of therapy resulted in a rapid but reversible increase in HIV-1 RNA levels in the third child and was associated with the production of HIV-specific antibodies. The fourth child whose parents were not compliant to treatment and follow-up had a poor virological response.

Conclusion Early treatment of vertically acquired human immunodeficiency virus type 1 infection with three reverse transcriptase inhibitors is well tolerated and can result in such suppression of viral replication that specific antibodies are not produced, that proviral DNA falls to the lower limit of quantitation in blood and that all clinical and immunological manifestations of infection are avoided. Parental adhesion is crucial to the effectiveness of therapy.

Key words Paediatrics · Antiretroviral therapy · HIV-1 infection · Reverse transcriptase inhibitors

Abbreviations ddl didanosine · NRTI nucleoside reverse transcriptase inhibitor · NVP nevirapine · PBMCs peripheral blood mononuclear cells · 3TC lamivudine · ZDV zidovudine

Introduction

In most HIV-1 vertically infected infants, diagnostic assays currently can establish the diagnosis by the age of 1 month [7]. This opens the possibility to begin antiretroviral therapy during primary infection, as the majority of vertically infected infants acquire the virus late in pregnancy or in the peripartal period [12]. However, there is limited experience on the effectiveness and
tolerance of combined antiretroviral therapy initiated during the first weeks of life [8, 9].

In December 1996 we elected to treat HIV-1 vertically infected infants with a combination of antiretroviral agents as soon as the diagnosis was established. At that time only nucleoside reverse transcriptase inhibitors (NRTIs) were available to us for use in young infants and the regimen selected was zidovudine (ZDV) + didanosine (ddI) + lamivudine (3TC). When nevirapine (NVP) became available, the regimen was changed to ZDV + 3TC + NVP. Treatment with one of these combinations of antiretroviral agents was initiated before 2 months of life in four vertically infected infants aged 72 to 158 weeks at the last visit. We report the ability of these well tolerated regimens to profoundly and durably inhibit viral replication and reduce the amount of proviral DNA in blood, provided parents adhere to therapy, and to prevent all clinical and immunological manifestations of infection.

Patients and methods

Patients

Infants born to HIV-1 infected mothers are followed to establish at the earliest the diagnosis of vertical transmission. A blood sample is obtained at 48 h of life and monthly until the age of 3 months for the detection of HIV-1 DNA by a qualitative PCR assay [14]. Vertical transmission is considered to be established when HIV-1 DNA is detected in at least two samples. Since February 1994, ZDV prophylaxis has been offered to HIV-1 infected women and their infants according to the ACTG 076 protocol [3]. In September 1997, 3TC was used in addition to ZDV. Since April 1998, an elective caesarean section has been proposed to all HIV-1 infected pregnant women.

Antiretroviral agents

The antiretroviral drugs used for prophylaxis during the first 6 weeks of life are given at the following dosage: 2 mg of ZDV/kg every 6 h and 2 mg of 3TC/kg every 12 h. The dosages in infected infants are: 360 mg of ZDV/m² of body-surface area per day (divided in three doses), 180 mg of ddI/m² per day (divided in two doses), 8 mg of 3TC/kg per day (divided in two doses) and 120 mg of NVP/m² given once daily for 14 days, then 150–200 mg/m² every 12 h.

Plasma HIV-1 RNA

Plasma HIV-1 RNA levels were measured using the Amplicor HIV-1 Monitor test, version 1.5 (Roche). The lower limit of detection of the assay is 400 HIV-1 RNA copies/ml plasma. When levels below this cut-off were obtained with therapy, the ultrasensitive version of the Amplicor HIV-1 Monitor test with a detection limit of 50 copies HIV-1 RNA/ml was used.

Quantitation of proviral DNA in blood

DNA concentrations in blood were retrospectively measured using a home-made competitive HIV-1 DNA PCR assay adapted from a qualitative PCR technique with pol primers [14] with a truncated HIV-1 DNA sequence as competitor (internal standard). DNA was extracted from whole blood with the Amplicor whole blood specimen preparation kit and results have therefore been expressed both as the number of HIV-1 DNA copies/ml blood and as the number of HIV-1 DNA copies/10⁶ peripheral blood mononuclear cells (PBMCs) by extrapolation from the blood formula. The sensitivity of the assay as assessed with serial dilutions of the internal standard was 40 HIV-1 DNA copies/ml blood.

Results

Patient characteristics

Of the 63 infants born to HIV-1 infected women followed in our centre since December 1996, 4 (6.3%) were infected. Their mothers were naive to antiretroviral therapy before pregnancy. Table 1 describes the antiretroviral prophylaxis regimen used in these four infants, the mode of delivery and their baseline characteristics. The age at first detection of HIV-1 DNA suggests perpartal transmission in patients 1 and 2, and in utero transmission in patients 3 and 4 [1]. At the time of diagnosis, only patient 3 had abnormal clinical findings, namely hypotonia and generalised lymphadenopathy.

Antiretroviral treatment

Therapy with three NRTIs was initiated respectively on weeks 8 and 7 of life in patients 1 and 2. In patients 3 and 4, the diagnosis of infection was established while prophylaxis with ZDV and 3TC was still ongoing and NVP was added to this regimen respectively on weeks 4 and 3 of life. The drugs were easily administered and well tolerated. There were no side-effects.

Response to treatment

Patient 1 experienced a limited and transient reduction in plasma viral load during the 1st year of life (Fig. 1). His parents acknowledged having discontinued therapy on multiple occasions during this period. When adher-