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Update on Perinatally Acquired Human Immunodeficiency Virus Infection in Children Followed at One Centre in Hong Kong

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Abstract To date, 17 children with perinatally-acquired human immunodeficiency virus (HIV) infection have been diagnosed and reported in Hong Kong. We reported on our experience at Queen Mary Hospital with 8 of the 11 children diagnosed in 2000. Since then, 4 more children have been referred to us. This study reports on these new patients as well as provides an update on the existing patients from May 2000 to May 2006. Two of the four new patients had AIDS at the time of diagnosis. All patients were given highly active antiretroviral therapy. Over 80% of the infected children had long-term undetectable HIV viral load after initiation of treatment, the longest duration being 7 years to date. Changes in management as a result of immune reconstitution in these children included the discontinuation of monthly IVIG infusion in some children and the discontinuation of primary prophylaxis against *Pneumocystis jirovecii* pneumonia, formerly *Pneumocystis carinii* pneumonia (PCP). Disclosure was an important issue as the children were growing older. With the exception of one 4 years old boy who was too young, full disclosure was achieved in half of the patients with a mean age of 8.9 years. As these medically well children enter adolescence, additional services including support with disclosure to others, self acceptance, therapy and sexual health would be needed.

Key words Perinatal human immunodeficiency virus infection

Introduction

To date, there have been 17 children with perinatally-acquired human immunodeficiency virus (HIV) infection diagnosed and reported in Hong Kong.[1] We reported on eight children with perinatally-acquired HIV infection followed in our centre in 2000.[2] Since the last report, we have witnessed some changes in the prevention and treatment of HIV. In September 2001, universal antenatal screening for HIV was implemented in all public maternity clinics in Hong Kong. A few more new and potent drugs with pediatric preparations have been available since 2000, the most notable being lopinavir/ritonavir (kaletra). New knowledge has been gained in regards to the association of lipodystrophy and certain antiretroviral agents which has affected our selection of drugs. More importantly, the children are growing up and are beginning to deal with issues other than drugs and adverse effects.

Objectives

The objective of this review is to update on Hong Kong children perinatally-infected with HIV followed in our centre with reference to their response to anti-retroviral treatment, adverse effects, complications, social situation and support.

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Methods

A retrospective chart review was conducted of all the HIV infected children followed in the HIV clinic at Queen Mary Hospital since the last report period, from May 2000 to May 2006. Inclusion criteria included the absence of other risk factors like transfusion and a history or documentation of maternal HIV infection. Haemophiliac patients infected with HIV through blood products were excluded.

Results

In addition to the 8 cases reported in the original report, 4 more children were diagnosed and referred to Queen Mary Hospital.

Detailed information on these children is tabulated in Tables 1 and 2.

Presentation and Course of the Four New Patients

Patient 9 was a 28 month old boy referred by his private practitioner for a 3 month history of fever. He had gingivostomatitis, hepatosplenomagaly, multiple adenopathy, anaemia and developmental regression on examination. His CD4 counts were extremely low: 14/μL (0.6%) and HIV viral load was high at 6.6 x 10^5 copies/ml. Clinically and immunologically, he satisfied the AIDS diagnosis.[3] He was started on d4T, 3TC and the protease inhibitor nelfinavir, an effective protease inhibitor newly available at the time that came in powder form and therefore children friendly. Incidentally, he also had G6PD deficiency of the Canton type. After discussion with our haematologist, the decision was to initiate trimethroprim/sulfamoxazole (TMP/SMX) prophylaxis for *Pneumocystis jirovecii* pneumonia, formerly *Pneumocystis carinii* pneumonia (PCP), since the risk of haemolysis was deemed very small. He tolerated TMP/SMX for 6 years without any problem. His parents were subsequently referred to the Special Prevention Unit. His mother tested HIV positive but his father was not infected. The child's HIV viral load decreased by 2 logs after a month of treatment and became undetectable in 3 months.

Patient 10 was a 22 month old boy with AIDS who was referred to us from another hospital to which he presented with recurrent pneumonia, chronic draining otitis media, chronic HSV gingivostomatitis, expressive speech delay and wasting syndrome (chronic diarrhoea and crossing weight percentiles from 75-90th percentile to 5-10th percentile). His CD4 counts were 22/μL (1.31%) and HIV RNA was 6.5 x 10^5 copies/ml. He was treated with d4T, 3TC and nelfinavir, as well as TMP/SMX prophylaxis. His HIV RNA became undetectable in 6 weeks, his CD4 cell count, growth and development normalised over 12 months.

Patient 11 was diagnosed at 5 years of age when her pregnant single mother underwent universal antenatal HIV screening in September 2001 and tested positive. She underwent termination of pregnancy and her two sons were tested for HIV. Our patient tested positive while his older brother was negative. He was noted to have hepatomegaly and growing at 10th percentile for weight and height. Despite not meeting the clinical criteria for symptomatic HIV, his CD4 cell count showed severe immune suppression and his HIV viral load was high, at 5.6 x 10^5 copies/ml. He was treated with 3TC, d4T and nelfinavir. His viral load became undetectable in 3 months and his weight and height improved to the 25th percentile.

Patient 12 was an 8 month old boy who was born in another hospital after the implementation of universal antenatal screening. His mother, however, declined the test. Several days after he was born, his mother requested to be tested for HIV and was found to be positive. The infant was tested with HIV RNA PCR on day 11 but the result was negative. He was discharged with followup for repeat testing. However, they were lost to followup until the infant was 8 months of age. The social situation was extremely poor. He did not even have a birth certificate at that time and he had not had any vaccination except for BCG given at birth. His mother, a single woman, also had another 5 years old son by a different father. This child subsequently tested negative for HIV infection. Our patient at diagnosis was found to have diffuse lymphadenopathy at the occipital, cervical and inguinal areas, hepatomegaly and candidiasis. He was also found to have global developmental delay with hypotonia, no tripod sitting and no babbling. His HIV RNA was 5.3 x 10^5 copies/ml but his CD4 cell count showed no immune suppression. He was also put on d4T, 3Tc and nelfinavir and his viral load became undetectable in 2 months. He was referred for neurodevelopmental assessment, occupational therapy, physical therapy and early training centre enrollment. Two months after his diagnosis, his mother was arrested and sentenced to imprisonment for criminal offence and he was sent to an institution where he has been staying until now, since despite release from jail, the social situation at home is still unstable.

Table 1 Epidemiologic data and baseline conditions of the perinatally-acquired HIV- infected children

Patient	Sex/Age	Age & date of diagnosis	Ethnicity (father/mother)	Reason for HIV testing	Manifestations at time of diagnosis	Baseline HIV load (RNA copies/mL)	Baseline CD4 (%), CD4/CD8 ratio	CDC Classification
1.	F/11y	18m/Nov, 96	British/Filipino	Father tested positive	Multiple occipital, cervical, axillary lymphadenopathy	4×10^5	2267 (36%), ratio 1.42	B1
2.	F/8y6m	5.5m/Apr, 98	Filipino/Thai	Symptomatic	PCP Strep. Viridans meningitis Hepatitis FTT Developmental delay and cerebral atrophy	5×10^5	94/μL (21.7%), ratio 0.74	C3
3.	Died of EBV associated T/NK lymphoma at 2y 5m	18m/Jun, 98	Chinese/Chinese	Symptomatic	Pancytopenia Haemophagocytic syndrome EBV infection Pulmonary TB Recurrent Pseudomonas thigh abscess FTT Developmental regression and progressive multifocal leukoencephalopathy (PML)	2.3×10^5	756/μL(29.6%), ratio 0.6	C2
4.	M/12y1m	4y10m/Mar, 99	Chinese/Chinese	Symptomatic	Disseminated Penicillium marnefeii infection FTT	2.4×10^5	17/μL (1.9%), ratio 0.05	C3
5.	F/9y10m	2y10m/May, 99	Chinese/Chinese	Mother tested positive	Cervical and axillary lymphadenopathy Thrombocytopenia	1.7×10^5	430/μL (23.5%), ratio 0.74	B3
6.	M/12y5m	5y2m/May, 99	Chinese/Chinese	Mother tested positive	FTT Cervical, axillary lymphadenopathy, hepatomegaly	1.1×10^5	103/μL (5%), ratio 0.11	B3
7.	M/9y7m	3y/Oct, 99	Chinese/Burmese	Mother died of AIDS	FTT Cevical, axillary, inguinal lymphadenopathy Anaemia	5×10^5	66/μL (6.3%), ratio 0.13	B3

Table 1 Epidemiologic data and baseline conditions of the perinatally-acquired HIV- infected children (cont.)

Patient	Sex/Age	Age & date of diagnosis	Ethnicity (father/mother)	Reason for HIV testing	Manifestations at time of diagnosis	Baseline HIV load (RNA copies/mL)	Baseline CD4 (%), CD4/CD8 ratio	CDC Classification
8.	M/6y5m	3m/Mar, 00	Thai/Thai	Mother tested positive	Occipital and cervical lymphadenopathy Hepatomegaly, slightly deranged transaminases	1.3×10^6	2284/μL (26.8%), ratio 1.06	B1
9.	M/7y10m	2y3m/Nov, 00	Chinese/Thai	Symptomatic	Prolonged fever for 3 months HSV gingivostomatitis Hepatosplenomegaly Developmental regression	6.6×10^5	14/μL (0.6%), ratio 0.04	C3
10.	M/6y11m	22m/Mar, 01	Chinese/Chinese	Symptomatic	Recurrent pneumonia Chronic draining otitis media Chronic HSV gingivostomatitis Oral candiasis Wasting (weight dropped from 75-90th percentile to 5-10th percentile)	6.5×10^5	22/μL (1.31%), ratio 0.02	C3
11.	M/9y7m	5y/Oct, 01	Chinese/Chinese	Mother tested positive	Hepatomegaly	5.6×10^5	378/μL (18.7%), ratio 0.31	A3
12.	M/4y5m	8m/Aug, 02	Pakistanian/ Filipino	Mother tested positive	Hepatosplenomegaly, hepatitis Diffuse lymphadenopathy Global developmental delay	5.3×10^5	5073 (38.7%), ratio 1.28	B1

PCP = *pneumocystis jirovecii* pneumonia; FTT = failure to thrive; EBV = Epstein-Barr virus; TB = Tuberculosis; NK = Natural killer cell

Table 2 Current situation of illness, disclosure status and psychosocial issues of the perinatally-acquired HIV infected children

Patient	Sex/Age	Current antiretroviral regimen	Most recent HIV load (RNA copies/mL)	Most recent CD4 (%), CD4/CD8 ratio	Disclosure status/ caretaker attitude	Psychosocial issues
1.	F/11y	D4T 3TC Nevirapine	2.7 x 10^3	1916 (38.9%), 0.96	Disclosed by both parents at 10y	Mother died of lymphoma in 2005 Living with aunt, new drug adherence issue
2.	F/8y6m	AZT 3TC Kaletra	2 x 10^3	822/μL (49.2%), 1.33	Not disclosed to child Disclosed to school but not relatives	Parents separated; Living with father
3.	Deceased	N/A	N/A	N/A	N/A	N/A
4.	M/12y1m	AZT 3TC Kaletra	Undetectable for 84m	490 (29.1%), 0.93	Disclosed by father at 10y without explanation or support	Parents divorced Father not caring; Living with aunt Longstanding adherence issue resolved On CSSA NGO Nome care RN support
5.	F/9y10m	AZT 3TC Nelfinavir	Undetectable for 77m	743 (35.6%), 1.23	Disclosed by mother with counselling support from home care nurse	Debt problem On CSSA NGO Home care RN support
6.	M/12y5m	AZT 3TC Nelfinavir	Undetectable for 77m	756 (28.2%), 0.84	Disclosed by mother with counselling support from home care nurse	Debt problem On CSSA NGO Home care RN support
7.	M9y7m	AZT 3TC Kaletra	Undetectable for 79m	451 (27.3%), 0.7	Disclosed by father at 9y	Mother died in 1998 Living in China
8.	M/6y5m	AZT 3TC Kaletra	Undetectable for 63m	676 (27%), 0.88	Not disclosed/Getting exposed to information on HIV	Parents not married Mother abandoned him in hospital Adopted by grandparents Living in Thailand
9.	M/7y10m	AZT 3TC Kaletra	Undetectable for 52m	836 (29.8%), 0.83	Not disclosed/Not willing	Debt problem from father's gambling Mother attempted suicide On CSSA NGO Home care RN support
10.	M/6y11m	AZT 3TC Nelfinavir	Undetectable for 59m	778 (32.3%), 0.89	Not disclosed/Not willing	On CSSA NGO Home care RN support
11.	M/9y7m	AZT 3TC Nelfinavir	Undetectable for 51m	559 (29.9%), 0.72	Not disclosed/Not willing	Single mother On CSSA NGO Home care RN support
12.	M/4y5m	AZT 3TC Nelfinavir	Undetectable for 41m	971 (41.3%), 1.26	Not disclosed (child too young)	Single mother On CSSA Child living in institution NGO Home care RN support

AZT=zidovudine; 3TC= lamivudine; d4T= stavudine; TMP/SMX= trimethoprim/sulfamethoxazole

Update on Previously Reported Patients

Other than the child who died of lymphoma reported in the last study, all the children have stayed medically well.[4] Their HIV RNA have been continually suppressed, many since the initiation of HAART. The longest duration of viral suppression to date is 7 years in a child. Two children remain virally nonsuppressed. One is the 11 year old girl whose mother was adamant in keeping her off of protease inhibitors for fear of lipodystrophy. Ironically, her regimen contains stavudine (d4T) which has recently been shown to be associated with the development of lipodystrophy. Her mother recently died of lymphoma and resistance testing for the child is underway with plans to switch her to a protease inhibitor containing regimen according to her viral resistance pattern. The other patient is an 8 year old girl who presented at 5 months with PCP and AIDS and has done remarkably well clinically. With a kaletra containing regimen, her viral load had been undetectable for over a year before having a recent rebound at low levels. Since she is heavily antiretroviral experienced, resistance testing will be performed to see if there is still a more effective regimen available to her.

Changes in Management Over the Past 5 years

Monthly intravenous immunoglobulin (IVIG) therapy is recommended for children with humoral immunodeficiency manifested as: 1) hypogammaglobulinaemia (IgG <250 mg/dL); 2) recurrent, serious bacterial infection; 3) children who fail to form antibodies to common antigens; 4) treatment of parvovirus B19 infection; 5) treatment of thrombocytopenia. Four children required monthly IVIG infusion at the start of the review period, but excellent response to HAART in all the children has made this practice unnecessary since 2002. All have remained healthy with no serious bacterial infection.

All the children with initial abnormal CD4 counts were put on TMP/SMX prophylaxis for PCP. With HAART, reconstitution of the immune system with increasing CD4 cell counts in children is possible.[5] Prospective studies in adults have shown that after an increase of CD4 cell count above the threshold of immunosuppression of 200/μL both primary and secondary PCP prophylaxis can be safely discontinued. This led to a change in the recent adult guidelines for PCP prophylaxis, permitting discontinuation after an increase of the CD4 cell count above 200/μL for at least 3 months.[6] Although there is no similar official recommendations available for children as reflected by a lack of change in the 2003 CDC recommendations for prophylaxis of opportunistic infections in HIV-infected children, there have been emerging data from retrospective and prospective studies that indicate for HIV-infected children whose CD4 cell count were above the age-appropriate threshold, discontinuation of PCP prophylaxis was safe.[7-9] More and more centres, including ours, discontinue PCP prophylaxis after immune constitution above the age-related thresholds in HIV-infected children. Due to the relative paucity of data in the discontinuation of secondary PCP prophylaxis in children, children requiring secondary prophylaxis are currently continued on prophylaxis until more data are available. Therefore, of our 11 surviving patients, only the girl who presented with PCP at 5 months of age is continued on TMP/SMX prophylaxis.

It has been said that HIV-infected individuals are benefiting from long-term HAART at the expense of potentially serious metabolic complications such as lipodystrophy, insulin resistance and dyslipidemia.[10] There are few reports documenting these complications in HIV-infected children. Lipodystrophy syndrome is characterised by peripheral fat wasting, central fat accumulation and metabolic changes. There is no consensus on case definition of HIV-associated lipodystrophy, although two types are described. Lipoatrophy, is characterised by localised fat loss in limbs, face and buttocks. Lipohypertrophy, is characterised by central fat accumulation in abdomen, breasts in women and in the posterior neck (buffalo hump). The diagnosis is not easy in children with changing adiposity with normal physiologic growth and it is not surprising that estimates of its prevalence range from 1% to 43%. Protease inhibitors are implicated in the development of lipodystrophy but newer data found the use of stavudine (d4T) and didanosine (DDI) to be associated with an increased risk.[11,12] Fasting blood glucose, lipid profile, blood gas and urine glucose are monitored in our patients every clinic visit. Other than an occasional borderline increase in triglyceride or cholesterol in a few patients, no abnormalities have been detected. No child has obvious habitus change. However, with newer data available, children who were on stavudine were changed to receive zidovudine.

Psychosocial and Disclosure Issues

The majority of HIV infected children come from a low income and unstable family. Sixty-four percent of the families are on public assistance. Two children had one parent die of HIV. One child was abandoned and subsequently adopted by his grandmother. One child lives in an institution.

Since the time of diagnosis, psychosocial issues have been difficult to address and manage. Pychological counselling is offered to all the family members of a newly diagnosed child. Many parents refused the offer while a small number went for an initial session but were reluctant to continue further followup. The diagnosis of HIV in a child and at least one parent in a family has enormous, long-lasting and on-going psychosocial stress to the family. Both parents of patient 10 are infected, but his older brother and sister are not. After the diagnosis of the family, the father sent the two older children to live with their grandmother for many months fearing close contact with them. Even after reassurance and education when they brought the uninfected children home, the children were not allowed to hug and kiss their infected brother, and the father prepared their meals in separate woks and had them use separate utensils for a couple of years.

With the growing up of the children, the need of disclosure of the child's own diagnosis, that of the infected parents to the infected child and that of the infected family members to other uninfected family members have been a forefront issue of care of these children and their families in the recent few years. Studies suggest that children who know their HIV status have higher self-esteem than children who are not aware of their diagnosis, and patents who have disclosed to their children experience less depression than those who do not. It is the policy of our clinic that we do not lie to our patients. Honest sharing of information is critical even if they do not know the exact name of the diagnosis. Partial disclosure is practiced from the time of diagnosis in that all the children older than 3 or 4 years are told that they have a problem with their immune system ('ability to fight germs') and therefore have to be good with taking medication and returning for blood tests and followup. Full disclosure, however, is a problem and parents are the main barrier. Excluding the 4 year old child who is too young to understand, only 5 of the 10 surviving infected children have been told of their HIV diagnosis. Several children older than 8 or 9 years of age are still not told.

Discussion

There are many challenges in taking care of HIV infected children. The issues and problems that arise from an HIV infected child are both medical and social. The availability of HAART has resulted in HIV-infected children who are essentially free of opportunistic infections or other medical problems. PCP and IVIG prophylaxis have been safely discontinued. Nonadherence to therapy is of utmost importance in treatment response. A study on adherence to HAART in HIV infected children in the US showed that the level of adherence was only 58%, with adherence defined as filling ≥75% of all prescribed antiretrovirals from the pharmacy.[13] This same study also reported that only 35% of patients were able to maintain an undetectable viral load, much less than that reported in adults, but comparable to other small reports of HAART in children. With the exception of patient 4, our children and their families have done very well with no problems. The good adherence of our group of children may partially explain why viral suppression can be achieved and maintained in over 80% of our surviving patients despite their having multiple problems at presentation. This high rate of viral suppression is remarkable when compared to anywhere in the world. Modeling after the treatment of tuberculosis, there has been much interest in Direct Observed Therapy in HIV infected adults. In our group of Hong Kong children, DOT is essentially being practiced by parents. This is extremely remarkable because even parents of some of the children are nonadherent in their own treatment or even clinic followup, they are diligent in administering medications to their children.

There is no arbitrary age of disclosure but the American Academy of Pediatrics recommends disclosure to school age children.[14] However, concrete guidelines are not available.[15] The appropriate time should be determined jointly with the parents and when the child is deemed mature enough. Unfortunately but not surprisingly, parents are the barrier to disclosure. Commonly cited reasons across culture include stigma, lack of knowledge and skills, emotional unpreparedness, and the fear that the child is too young and the inability for them to keep the diagnosis confidential, thereby exposing self and family to potential stigmatisation, discrimination and predjudice.[16,17] The difficulties these parents face in disclosure to their children likely involve dealing with the guilt of transmitting the illness to their child, fear of being asked about their own infection and how they had acquired it, the wish to preserve status quo and feeling that they do not know how to disclose and how to deal with their children after disclosure. Our disclosure rate of 50% in school age children is comparable to data from several US centres that indicate that between 25% and 90% of school age children with HIV infection have not been told that they are infected.[14] Much work is being

done to help these parents to understand the need for disclosure, empower them and train them. For those more receptive parents, clinical psychologist referrals are arranged again. It has to be emphasised that disclosure of HIV infection should be perceived as an ongoing process as the cognitive and emotional awareness about the impact of the disease develops and evolves as he or she enters into different stages of life.

Without an HIV specialist nurse in our clinic, support from the Society for AIDS Care (SAC), a non-Government Organisation, has been an integral part in caring for these children and their families. Half of our children and their families are served by the Society. Their home care nurses have provided services like accompanying them to clinic and medical appointments, home visits, medicine checking and organising, round-the-clock counselling. Trust and friendship have also been built. The centre also provides social and parenting activities and classes for the families. Tackling family issues and drug adherence issues would not have been possible without their support. Recently, we have met with HIV specialists from Kowloon Bay Integrated Clinic who care for the parents of our children, together with the home care nurse representative from SAC, to discuss families under our care. Sharing of information by different caretakers is extremely useful and provides better understanding of the dynamics and difficulties of the families, as well as devising strategies to work with the family as a whole. We currently have an ongoing dialogue amongst all three parties to alert one another when issues and crises arise.

Conclusion

In conclusion, the great majority of children with perinatally-acquired HIV infection cared for in our centre is medically well and living a healthy and normal lifestyle. Diligent adherence to therapy by parents and caretakers is the main reason for the remarkable long-term viral suppression in a remarkably high proportion of these children. However, the majority of these children also live in families that are unstable social and economically. With these children becoming older and entering adolescence, additional services are needed including support with disclosure to others, self acceptance, therapy and sexual health.

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