Progress of the National Pediatric Free Antiretroviral Therapy program in China

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In 2003, the Chinese Government initiated a free antiretroviral therapy (ART) program focusing on adult AIDS patients. Pediatric antiretroviral (ARV) formulations were yet unavailable. It was not until July 2005, with the initiation of a two-stage program implemented by the Chinese Ministry of Health, that pediatric formulations became accessible in China. Initially, the pediatric ART program was piloted in six provinces with the highest incidences of pediatric HIV/AIDS. The pilot stage allowed the Chinese Center for Disease Control and Prevention (CCDC) to finalize entry criteria, treatment regimen, and patient monitoring and follow-up procedures. The second stage commenced at the end of 2006 when the program was scaled-up nationally. In order to guarantee treatment of pediatric patients, extensive training in the selection of appropriate ARV drug regimen and dosage was provided to doctors, often through on-site collaboration with domestic and international experts. The CCDC simultaneously established a pediatric ARV management system and a pediatric ART information system. CD4 count and other laboratory tests are being routinely performed on these pediatric patients. By the end of June 2009, 1529 pediatric patients had received ARV under the national program. However, challenges remain. Firstly, many children infected with HIV/AIDS live in rural areas where the treatment quality is hindered by the limited number of medical facilities and skilled medical workers. Secondly, much of the pediatric ARV drug supply depends on donation. An effort needs to be made by the Chinese Government to establish China’s own drug procurement and supply system.

**Keywords:** children; HIV; ART; HAART

**Introduction**

There were an estimated 2.1 million children living with HIV/AIDS worldwide at the end of 2007, of which two million live in sub-Saharan Africa, and approximately 1500 children are infected with HIV daily. The number of children receiving antiretroviral therapy (ART) has increased from approximately 75,000 in 2005 to almost 2,00,000 in 2007 (The Joint United Nations Programme on AIDS, 2008). China has a low prevalence of HIV nationally but with pockets of high prevalence among specific high-risk populations and in certain geographic locations. By the end of 2007, an estimated 7,00,000 were infected with HIV, and 1.2% of them were infected through mother-to-child transmission (State Council AIDS Working Committee Office, UN Theme Group on AIDS in China, 2007). The first HIV(+) case under the age of 15 in China was diagnosed in 1985. Between 1985 and 2003, only a total of 637 pediatric patients were diagnosed; however, the number of newly diagnosed pediatric patients has risen steadily since then. By the end of June 2009, the cumulative number of pediatric patients ever identified rose to 5162 (see Figure 1).

Pediatric HIV/AIDS cases are present in all 31 provinces of China. However, 85% of these cases are concentrated in only eight provinces. The pediatric HIV epidemic distribution characteristic parallels that of the adults. These high-prevalence provinces can be divided into two major groups: those located in central China and were mostly affected by unsafe commercial plasma collection, including Henan, Anhui, and Shanxi; and those where HIV infection has spread mostly through injection drug use and the commercial sex behaviour, including Xinjiang in the northwest and Yunnan, Guangdong, Sichuan, and Guangxi in the southwest (Zhao et al., 2006; see Figure 2).
The World Health Organization (WHO) has proposed a public-health approach to ART in order to enable the scale up of access to treatment for AIDS patients in developing countries (Gilks et al., 2006). In 2003, China introduced the National Free ART policy, dramatically increasing the number of people living with HIV and AIDS (PLWHA) who are able to receive treatment. Through this policy, PLWHA are able to receive access to free ARV drugs and CD4 count testing, as well as subsidies for treatment of certain opportunistic infections (OI; Zhang et al., 2005). However, as the initial policy specifically targeted adult patients, improving pediatric access to ART has been slower (Zhang et al., 2007a). China lacked access to pediatric ART formulations and therefore had no standardized treatment guidelines for children. As a result, 288 children with AIDS were initially treated using adult ARV formulations. This issue has been corrected gradually since 2005; however, limited human resources and barriers due to patients’ location in economically underdeveloped regions are continual challenges. The following is a review of the current situation of pediatric ART care in China, the achievements which have been made and the challenges remaining.

The National Pediatric Free Antiretroviral Therapy (ART) program

The National Pediatric Free ART program was officially launched in July 2005, and is managed by the National Center for AIDS/STD Control and
Prevention (NCAIDS), Chinese Center for Disease Control and Prevention (CCDC) under the auspices of the Ministry of Health (MOH). Within NCAIDS, the Division of Treatment and Care (DTC) is responsible for operational and strategic planning. DTC’s primary duty is to facilitate the nationwide implementation of pediatric treatment and provide technical support to HIV/AIDS hospitals. Additional areas of oversight include physician training, drug supply, and data collection and analysis.

In July 2005, based on existing central database information which identified provinces with the highest prevalence of pediatric HIV/AIDS cases, the program was piloted in Henan, Anhui, Hubei, Yunnan, ShanXi, and Guangxi. After finalizing entry criteria, treatment regimens, and patient monitoring and follow-up procedures during the pilot study, the program was expanded nationally at the end of 2006. By the end of June 2009, the number of pediatric patients receiving treatment had grown to 1529 (see Figure 3). The median age of patients enrolled into the program was 7.1 ± 4.1 years, with 31.6% of children younger than 60 months, and 68.4% of them 60 months or older. A total of 905 (59.2%) were males. A 60.1% of them were in the WHO Stages III and IV. The median baseline CD4 count was 194/μL (IQR, 70–391/μL).

The treatment system

Provinces with higher HIV prevalence have hospitals or clinics designated to treat children with HIV/AIDS. In most cases, these are county-level hospitals which have been chosen to maximize access for rural patients. Each enrolled pediatric patient is treated by a designated doctor who is primarily responsible for the administration of treatment, conducting regular clinical care, administration of treatment and follow-up, monitoring toxicity, and completing the patient case file. Based on need, national or provincial-level doctors provide guidance in prevention and treatment of serious OI, as well as monitoring for adverse drug reactions and adjusting the treatment regimen accordingly. In high-pediatric HIV prevalence areas, upper level doctors assist with follow-up work for special cases. To date, 240 facilities all over the country are able to administer pediatric ART.

Management of the pediatric ARV drug supply system

When the pediatric ART treatment program began in 2005, China lacked the ability to import or manufacture pediatric ARV drugs. The Clinton Foundation assisted in the interim by providing imported pediatric ARV drugs. The currently available regimens are listed in Table 1. Increasing the availability of drugs, for example, fixed-dose combinations and drug dosing, and category options remain challenges.

Currently, all pediatric ARV drugs are provided by NCAIDS to provincial-level drug management departments, who are also responsible for managing adult formulations. To ensure a continuous supply of drugs, drug management departments at the provincial level and below establish a mechanism for drug demand forecasting and early warning of inventory depletion. At the same time, drug control departments at all levels establish a strict registration system for drug storage to avoid unnecessary losses. The provincial departments in charge of pediatric antiretroviral drug administration distribute drugs to treatment facilities, which in turn declare drug demand every quarter. Demand is then reported to NCAIDS by each province, enabling accurate forecasting of drug supplies for the following quarter. As pediatric formulations are more complex due to multiple dosage options, additional

Figure 3. Annual cases of pediatric HIV patients receiving treatment in China, 2002–June 2009.
training is provided to these departments prior to assuming pediatric drug management responsibilities. The Chinese MOH is planning to establish its own pediatric ARV drugs supply system through a combination of domestic manufacturing of generic and importation of brand-name drugs.

**Strengthening of the professional staff**

Prior to the roll-out of the pediatric treatment program in 2005, expertise in the treatment of pediatric HIV/AIDS was inadequate nationally. Physicians treating HIV/AIDS patients were often inexperienced in treating children, and pediatricians were unfamiliar with managing ART. In preparation for the nationwide program expansion, extensive training with the assistance of international experts and consultants, was provided in the six pilot provinces to local program managers, clinicians, nurses, and laboratory technicians.

A national medical team was also created to provide training and on-site clinical demonstrations. Members of this team have received considerable training overseas in preparation to becoming a critical training unit domestically.

The support network system, which allows local physicians to consult provincial and national-level doctors, also provides opportunities for skills training and improved care. However, despite these efforts, challenges remain with regard to proper training of physicians caring for children with HIV/AIDS.

The current healthcare system in rural China, where the majority of patients reside, is often inadequate due to a lack of qualified medical personnel. Urban doctors who are better equipped are reluctant to assist in rural treatment due to a lack of incentive mechanisms. Limited medical facilities and resources in such areas also greatly impact quality of care. Since pediatric AIDS treatment is a highly specialized field, pediatricians with a background in HIV care are few and scattered throughout the expansive country. This makes it particularly difficult for expertise in pediatric HIV/AIDS to penetrate the rural communities.

To address the current deficiency in human resources, and to ensure the quality of pediatric ART, all localities should continue to work toward increasing pediatric clinical staff and providing such clinicians with proper training in pediatric HIV care.

From 2005 to 2008, DTC organized two pediatric HIV treatment training programs every year for physician. Nearly 500 physicians benefited from them, and more pediatricians should be encouraged to join the program.

**Pediatric ARV treatment, procedures, and practices**

Guidelines for the initiation of pediatric ART in China were established by the DTC and NCAIDS and were published in the National China Free ART Manual. They incorporate many of the WHO recommendations while taking China’s national situation into consideration. The most recently revised version of the Manual was issued in December 2007 and detailed the enrollment, regimen, and treatment recommendations for pediatric HIV/AIDS patients.

Prior to enrollment in ART, all pediatric patients undergo an evaluation based on a combination of clinical and baseline laboratory criteria. Each must be evaluated according to their medical records and a physical examination. Laboratory criteria are primarily assessed through CD4+ T lymphocyte count or percentage testing. In accordance with the WHO’s 2007 recommendations, treatment is recommended for all children who meet the following criteria (The AIDS Clinical working group, 2007):

1. children who manifest symptoms and signs of WHO Stages III or IV;
2. children with a CD4 count of <350/ml (for children older than five years), CD4 count <350/ml; or
3. CD4% <15% (three–five years), CD4 count <750/ml, or CD4% <20% (one–three years),
and all virologically diagnosed infants within one year of diagnosis.

Once ART has been initiated, Chinese pediatric HIV/AIDS guidelines recommend that follow-up visits should occur at two weeks, one–three months, and every three months thereafter, though physicians may perform additional follow-ups at their discretion.

**First-line treatment regimens**

The current recommended first-line ART regimen for HIV-positive children/infants is AZT/d4T+3TC+NVP/EFV. NVP is used for children under three years of age or under 10 kg in weight. Standardized dosage tables based on patient weight and body surface area are provided to physicians to streamline the drug administration process (WHO, 2006).

**Second-line treatment regimen**

Second-line pediatric drugs became available in 2008 but have not yet become fully implemented due to physicians’ inexperience and insufficient laboratory support in providing second-line therapy. Training is being scaled-up and promoted. Currently, all second-line regimens are approved and distributed at the national level. The recommended pediatric second-line treatment is ABC+3TC/ddI + Kaletra. The availability of second-line treatment is a priority as some children who were originally prescribed incorrect adult medications have become non-responsive to their first-line regimens.

**Cotrimaxazole prophylaxis**

Pediatric cotrimaxazole prophylaxis procedures were established in 2004, prior to pediatric treatment program initiation. These have remained the same and are recommended as follows:

1. All infants born to an HIV-positive mother should be started on sulfamethoxazole from four to six weeks after birth until exclusion of HIV infection status, to prevent *Pneumocystis jiroveci* pneumonia.
2. Children between one and five years old who are diagnosed as HIV positive and have CD4+ T lymphocyte count <500/μl or CD4+ T lymphocyte percentage <15%.
3. Children older than five years old who are diagnosed as HIV positive with CD4+ T lymphocyte count <200/μl or CD4+ T lymphocyte percentage <15%.

**Laboratory testing**

Currently, the most commonly used test for determining HIV status in China is antibody testing. However, this is inconclusive in children younger than 18 months. For children born to known HIV-positive mothers, aside from a few high-prevalence regions where HIV DNA diagnosis is specifically available, many infants were not diagnosed by antibody assays until 18 months of age.

It is very important to strengthen monitoring and evaluation after treatment initiation. CD4 cell count testing, recommended for all pediatric patients, is presently performed nationwide at baseline, three, six, and every six months thereafter. However, providing CD4 percentage calculations is still limited by testing equipment shortages, which is an especially important issue for patients under five years of age. Since 2008, children receiving treatment under the National Free ART program are eligible for annual free viral load testing. In actuality, viral load testing is not required nationwide due to limited technical capability.

**Establishing a pediatric ART information system**

The CDC and all lower CDCs are responsible for the collection and analysis of the pediatric treatment data. During the roll-out of the pediatric treatment program, a full-scale database specifically for collecting pediatric treatment information was established. It is modeled after and has the same capabilities as the National ART Database for adults, which collects the data via DATAFAX (Clinical DataFax Systems Inc., Hamilton, ON, Canada). Based on experiences with the adult information system, the pediatric system is now functioning well. Provincial disease control and prevention centers are responsible for local data collection, reporting, and management. Local doctors are responsible for completing DATAFAX forms. The DATAFAX System records patient information at treatment initiation, follow-up, and various treatment termination events. It includes:

1. At ART initiation: demographics, medical history, baseline laboratory results (CD4 cell count and CD4%, viral load, hematology, chemistries), WHO clinical stage information, need for sulfamethoxazole (SMZ), and initial regimen.
2. At each follow-up: laboratory results, self-reported adherence, adverse side effects, and regimen changes.
At termination: whether termination is due to treatment discontinuation, lost to follow-up, mortality, transfer of care, or other causes.

This comprehensive information system is then utilized at all levels to better facilitate the development of pediatric HIV/AIDS care and treatment in China. At the national level, it has also been used to assess the effectiveness of the overall program, and to guide future recommendations (Ma et al., 2009). Now NCAIDS are changing their DATA-FAX systems to a new internet pattern system.

**International cooperation**

There has been strong international support for China’s pediatric AIDS control efforts. Supporters and national program partners include the WHO, United Nations Children’s Fund, the Clinton Foundation, the United States Centers for Disease Control and Prevention and Médecins Sans Frontières. International cooperations support many aspects of the national program, including procurement and donations of pediatric ARV drugs, technical program development, staff training, on-site technical guidance, and establishment of treatment modalities.

**Operational research**

China established the first Pediatric Highly active antiretroviral therapy (HAART) cohort of 83 children in a high-HIV prevalence, rural county supported by the Chinese Ministry of Science and Technology Grant in July 2005. Fifty-one children were ART naive at enrollment, and 32 were ART experienced. The cohort data indicated that weight and CD4 cell counts improved, and 58% of previously ART-naive patients had undetectable viral loads at 1 year. The prevalence of drug resistance was high, with at least 62.5% of ART experienced and 27.5% of previously ART-naive children showing resistance to one or more drugs after one year of HAART (Zhang et al., 2007b, 2009). Future efforts should focus on improving virologic suppression. Operational research should strive for ways of achieving a more successful treatment outcome. Another important National Science and Technology Specific Project has already been launched last year to improve the pediatric HAART status.

**Program challenges**

While China’s pediatric HIV/AIDS program has made great strides in a relatively short period of time, challenges remain.

In our cohort, the average age was 7.1 years old, and 68.4% of them were older than five years old. There are several reasons contributing to the higher average age of AIDS children in China. Early infant diagnosis through DNA PCR is not yet widely available. Thus, the HIV-status of children born to HIV-positive mothers often remains in question until they reach 18 months. Whenever possible we have used HIV RNA tests to confirm HIV infection in children less than 18 months. A significant portion of the children in our program is from central China, where the majority of the HIV positive adults were former plasma donors infected in the mid-1990s. Children born around that time have raised the average age of our cohort. In addition, the scaling-up of a PMTCT program in the past few years may have decreased the number of children born with HIV, further skewing the average age.

It is recommended that immunodeficiency in children should be evaluated using CD4%. The Chinese Government has provided CD4 count detection apparatus for high-HIV prevalence areas after 2005 to enable better assessment and monitoring of patient conditions and to facilitate the scale-up of the ART program. However, most sites only have access to FACS COUNT, and CD4% tests are still not widely available. For sites with access to only FACS COUNT and not to CD4% tests, CD4 absolute count is used based on the children’s age. We found that only 31.6% patients obtained the CD4% test at baseline. In addition, accessibility to viral load tests is also low. Only 15.4% of children have viral load as part of their baseline data. Although viral load is not a crucial ART initiation criterion, it is an important index for determining treatment success. There is a great need for strengthening the capability for CD4% and viral load testing in China’s Pediatric Free ART program.

As the majority of children living with HIV/AIDS come from economically underdeveloped rural regions, they have limited access to medical resources including knowledgeable HIV/AIDS specialists. These limitations have obvious impact on patient care. Adherence rate in the treatment of pediatric HIV/AIDS is unclear. Little has been done in the realm of psychosocial support for children living with HIV/AIDS. Overcoming these difficulties will be the focus of further research.

Currently most of the pediatric formulations depend on donation from the Clinton foundation. Complicated import procedures impact the drug supply chain. The Chinese Government should make an effort to establish China’s own drug procurement and supply system.
Conclusion

Although China began its pediatric HIV/AIDS treatment program rather late and its experience with pediatric AIDS ARV is limited, the scope of its national program remains impressive. Many children and their families have benefited from the Chinese national program. Through support from the state, community, and family, in combination with continuous exploration and research, a more suitable HIV/AIDS management and control program can be established for China’s children.

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