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Development and Challenge of HIV/AIDS Testing Laboratory Network and Quality Assurance System in China*

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Abstract: This paper describes the development and challenge of HIV/AIDS testing laboratory network and quality assurance system in China. At present, the HIV/AIDS testing laboratories includes three classes, the National AIDS Reference Laboratory, HIV/AIDS confirmatory laboratories and HIV/AIDS screening laboratories. All of them are accredited by the health authorities, and each class of laboratories take charge of their function strictly according to the "National Management of HIV/AIDS Detection (2006)". A complete quality assurance and quality control system for HIV/AIDS testing has been developed, which includes technical training, strict laboratory monitoring and approval, examination or proficiency testing on HIV/AIDS detection, and quality evaluation and supervision of HIV/AIDS diagnostic kits. Besides conduct the routine anti-HIV antibody test, more and more laboratories began to conduct other tests, such as $CD4^+$ T lymphocyte cell counting, HIV viral load, HIV DNA PCR, genotyping, drug resistance, and HIV-1 recent infection test. The primary challenges faced by the HIV/AIDS testing laboratory network are in the areas of laboratory management and quality control. For example, the provincial PT program is inefficient, the internal quality control is conducted perfunctorily, personnel training can not met the needs of the workplace, which need to be improved.

Key words: Human immunodeficiency virus (HIV); Laboratory; Detection; Quality assurance; Quality control

HIV/AIDS testing uses laboratory methods to measure the Human immunodeficiency virus (HIV), anti-HIV antibodies and related immunity index of blood, other body fluids, tissue or organ and blood derivatives etc, and includes the testing conducted for surveillance, inspection and quarantine, voluntary consulting and testing (VCT), clinical diagnosis and blood screening. The HIV/AIDS testing laboratory is a general designation of all laboratories which conduct these tests.

THE FEATURES OF THE HIV/AIDS TESTING LABORATORY

Implementation of the entire accreditation system

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The HIV/AIDS testing laboratory in China performs the entire accreditation process, which includes the laboratory condition, personnel and testing kits. Laboratory accreditation means that the laboratory which has not been accredited by the authority cannot conduct HIV/AIDS diagnostic testing. For personnel to be accredited, they must undergo a series of training on bio-safety, the testing technique, quality control, protection for occupational exposure etc, and then be certificated before they can work in the laboratory. Test kit accreditation means that only kits which are validated and registered by the State Food and Drug Administration (SFDA) and accredited by the National Institute for the Control of Pharmaceutical and Biologic Products (NICPBP) can be used in laboratories. In addition, the recommended kits are those with high sensitivity and specificity by clinical quality evaluation.

Quality assurance and quality control system

According to the regulation of China (7) , the HIV/AIDS screening laboratory must participate in a proficiency testing (PT) program organized by the provincial or higher level of laboratory; and the HIV/AIDS confirmatory laboratory must participate in the program organized by the laboratory of Chinese Center for Disease Control and Prevention (China CDC). Being the appointed organizer for HIV/AIDS proficiency testing by the China National Accreditation Service for Conformity Assessment (CNAS), the National AIDS Reference Laboratory (NARL) organizes the proficiency testing for the confirmatory laboratories every year, which includes the PT program for anti-HIV antibody testing, $CD4^+$ lymphoid cells, HIV viral load, DNA detection, genotyping and drug resistance testing. The PT program organized by the provincial level of confirmatory laboratory primarily focuses on the anti-HIV antibody testing. The national PT program is conducted three times each year. The provincial PT program is generally done once each year (two or three times each year in a few provinces). Furthermore, NARL takes responsibility for inspecting and assessing the quality of all HIV/AIDS testing laboratories in entire country. The provincial level of confirmatory laboratory is responsible for the laboratories within their jurisdiction. All HIV/AIDS testing laboratories must carry out internal quality control according to the "National Guideline for Detection of HIV/AIDS"(1) .

Strict regulations and requirements

The HIV/AIDS testing laboratory should perform all testing work according to the prescribed function, national law and regulation and related guidelines. The testing technology and procedures must be consistent with the "National Guideline for Detection of HIV/AIDS"(1); the management and requirement of detection must fit into the requirements of the "National Management of HIV/AIDS Detection" (7); VCT must be performed according to the "National Management of HIV/AIDS VCT"(8).

Perform the classification, stratification and network construction management

The HIV/AIDS testing laboratories are divided into three classes in China, which are the National AIDS Reference Laboratory (NARL), the HIV/AIDS confirmatory laboratories (including the confirmatory central laboratories and confirmatory laboratories) and the HIV/AIDS screening laboratories (including the screening central laboratories, the screening laboratories and HIV/AIDS testing spots). The National AIDS Reference Laboratory is the HIV/AIDS testing

laboratory appointed by the Ministry of Health (MOH); the HIV/AIDS confirmatory central laboratories are set up in 31 provincial CDCs and 4 institutions from the Chinese People's Liberation Army, the Chinese People's Armed Police Forces, General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China, and Xinjiang Production and Construction Group, respectively; the confirmatory and screening laboratories are approved by provincial health administrative departments and are checked and accredited by the expert group. Each class of laboratory should take charge of their function strictly according to the "National Management of HIV/AIDS Detection"（7）.

BUILDING AND DEVELOPMENT OF HIV/AIDS TESTING LABORATORY NETWORK

The building and development of the HIV/AIDS testing laboratories

In 1985, the first HIV/AIDS testing laboratory in China was built by the Institute for Viral Disease Control (IVDC), Chinese Academy of Preventive Medicine. In 1986, four HIV/AIDS testing labo ratories were built by the Shanghai Municipal CDC, Yunnan Provincial CDC, Beijing Municipality and the Academy of Military Medical Sciences (AMMS) of the Chinese People's Liberation Army, respectively. In 1989, these four laboratories were approved as the HIV/AIDS confirmatory laboratories. Afterwards, new HIV/AIDS confirmatory laboratories were built and approved in every province one after another.

In July of 1998, the MOH established the Center for HIV/AIDS Control and Prevention in the Chinese Academy of Preventive Medicine with the approval of the State Council. NARL was one of the departments of the Center for HIV/AIDS Control and Prevention, whose staff mainly came from the previous laboratory of tumor and HIV/AIDS research of the IVDC. NARL took responsibility for: performing HIV/AIDS detection, training, conducting the technological guidance to some provincial and prefectural laboratories, putting the quality examination and assessment, inspection and supervision, and laboratory quality control into practice for all provincial and prefectural laboratories, and organizing experts community to assess the HIV/AIDS confirmatory laboratories in every provincial center for HIV/AIDS detection, holding all national HIV/AIDS detection conferences, and establishing and revising the "National Guideline for Detection and Management of HIV/AIDS (1997)" (5), which provided the first regulation for HIV/AIDS detection. The MOH expert community of examination and assessment on the HIV/AIDS confirmatory laboratories was set up in 1997, which improved the examination and approval system for the HIV/AIDS confirmatory laboratories.

By 2000, except for the Tibet the HIV/AIDS confirmatory laboratories in 30 provincial CDCs were built and approved. HIV/AIDS screening laboratories covered CDC, blood centers, entry-exit inspection and quarantine departments, hospital, center for women and children's health, army and police etc.

In November 2001, the Chinese Academy of Preventive Medicine was renamed as the Chinese Center for Disease Control and Prevention (China CDC), and the previous Center for HIV/AIDS Control and Prevention of the MOH was replaced by the National Center for AIDS/STD Control and Prevention (NCAIDS). The former NARL was divided into a

reference laboratory and a virology & immunology research laboratory. The new NARL is responsible for the building and developing of the HIV/AIDS testing laboratory network and the quality assurance and quality control system in the whole country.

In May 2003, China CDC published and distributed the "National Guideline for Detection of HIV/AIDS (draft)" with the approval of the MOH (2). The formal edition (2004) was distributed in August 2004 (1). With the HIV/AIDS testing laboratory network being expanded year by year in the whole country, by the end of 2006, over 100 HIV/AIDS confirmatory laboratories and 6066 screening laboratories had been checked and approved. By the end of 2007, it is estimated that the number of HIV/AIDS confirmatory and screening laboratories will exceed 180 and 6500, respectively.

In 2006, to strengthen supervision and management of HIV/AIDS detection in the whole country, to standardize the laboratory setting, checking and approving, and to ensure the quality of HIV/AIDS detection, the MOH distributed the "National Management of HIV/AIDS Detection (June 2006)"(7) according to the "Law of Communicable Disease for Treatment and Prevention of the People's Republic of China" (11), the "Regulation of AIDS for Treatment and Prevention"(13) and the related national laws and rules, which ensure the management of HIV/AIDS testing laboratory standardization.

Construction of the HIV/AIDS testing technology platform

The detection of anti-HIV antibody is the basic technology of the HIV/AIDS testing laboratory with more experience. In recent years, on the basis of carrying out the detection of anti-HIV antibody, more and more laboratories gradually established and developed the detection technology platform of immunology and virology in order to meet the demand of clinical treatment, the detection and monitoring of drug resistance, the early diagnosis of infant HIV infections, the detection of HIV recent infection, etc.

The accurate and reliable detection of $CD4^+$ T lymphocyte cells is an important marker to determine the immunologic condition of people infected with HIV, predict the progress of disease, determine the effect of antiviral drug treatment and estimate prognosis (4). The progressive deterioration of $CD4^+$ T cells correlates with serious clinical symptoms, which signifies a bad prognosis. So, the World Health Organization (WHO) and European/American countries recommend monitoring the level of $CD4^+$ T cells of HIV infections once every three to six months. The number of $CD4^+$ T cells is the key factor to preventing mesenchymal plasma cell pneumonia and other opportunistic infections, and starting antiretroviral treatment (10). According to the definition of monitoring classification system of HIV infections among adult and adolescent AIDS patients reported by U.S. CDC, the level of $CD4^+$ T cells is also the standard to judge HIV related clinical course (15). In China, the "Guideline of AIDS Diagnosis and Treatment" shows that the clinical significance of the detection for $CD4^+$ T cells is to understand the organic immune situation and disease course, to determine the staging of disease and treatment time, and to appraise the treatment effect and the clinical complications of HIV infections. Based on the patient state of illness, the clinician needs to decide the interval of detection for $CD4^+$ T cells. The general suggestion is that HIV infected people without symptoms (CD4 counts＞350

/mm^3) should perform CD4 counts once a year. If CD4 counts are 200～350/mm^3, for the patient without ART, whose CD4 count should be performed once every half a year; For those on ART, once every three months in the first year of treatment and once every half a year for those who have been treated over one year and their condition is stable (3). At present, except for Tibet and Hainan province, the technology platforms of CD4$^+$ cell counts are established in our country. The number of the CD4 count instruments already exceeds 200, which are used directly for the treatment and monitoring of AIDS.

Because of HIV/AIDS spreading quickly in China and in the world, the great attention of leaders and the demand of policy, and the continual development of molecular diagnostic technique, the detection of HIV viral load also developed greatly in China. Having the responsibility of providing technical guidance for the entire laboratory, NARL identifies and introduces various new technologies. The viral load instruments were equipped respectively in 1998, 2003, 2004 and 2005, such as NASBA、RT-PCR、EasyQ and bDNA, etc. At the same time the viral load test method was being established and extended, NARL passed the international PT on viral load testing, which enlarged the test facility and helped diagnose and confirm the questionable HIV samples for the whole country. The methods raised the accuracy of confirming questionable samples, and provided technological support for the problems identified in nucleic acid detection technology performed in some provinces. At present, viral load machines have been installed in most provinces in the country. The detection of viral load has been developed in 20 provinces, with 90 viral load detection instruments.

In recent years, besides doing regular diagnosis and monitoring of HIV/AIDS, NARL researched and evaluated new and recent HIV infection detection methods. The new methods will play an important role in the future surveillance for new HIV infections (14). Furthermore, dried blood spot (DBS) technology was developed, which provides a useful technological platform for early diagnosis of infant HIV infection in our country, and also makes it possible that DBS technology can be used widely in the field for the detection of HIV gene subtype and drug resistance(16). Pooled RT-PCR has been established and can be used to find acute infections. This approach provides a new method for reducing secondary transmission as much as possible (9).

Construction of the Laboratory Information Management System

The management of laboratory information is a key factor in running an efficient laboratory. Building a modernized laboratory needs to use modernized methods. As technology develops quickly worldwide, the internet can be used to improve laboratory management practices. Laboratory Information Management System (LIMS) uses scientific management and advanced technology of computer databases to provide complete laboratory management. Construction of LIMS includes sample management, resource management, affairs management, network management, data management (collection, transmission, handling, output, submission) and report management. All of these comprise a complete system of lab synthetic management and quality monitoring, which meet regular management requirements in the system, and also guarantee strict management and control of lab analysis data. LIMS is a big feature of the laboratory

management in developed countries, where over 80% of laboratories use LIMS. But in China, the LIMS usage rate in laboratories is less than 10%.

The HIV/AIDS testing laboratory has the following features: a lot of screening test work, many documents and network management, etc. The management of samples, disposable materials, test data, documents and the laboratory PT operation utilizes a significant amount of time and manpower. We therefore advocate incorporating LIMS into the HIV/AIDS testing laboratory. China CDC has customized the LIMS to suit the Chinese system of disease prevention and control. Since 2003, laboratories of the NCAIDS have been using this computer management system for specimen collection, reception, storage and sampling, and results reporting. At present, NARL has also established this electronic system to manage laboratory samples and PT. Therefore, the day when LIMS can be fully utilized can be seen in the near future.

THE DEVELOPMENT OF QA & QC SYSTEM

With much trial and effort over many years, a complete Quality Assurance and Quality Control（QA & QC）system for HIV/AIDS detection was developed in China, which includes technical training, strict laboratory monitoring and approval, examination or PT on HIV/AIDS detection, and quality evaluation and supervision of HIV/AIDS diagnostic reagents. In the past 20 years, the development of the laboratory QA & QC system experienced three stages.

The first stage: From 1985 to 1994, the laboratory was established step by step and standardized bit by bit. The laboratories of HIV serology detection were established gradually among the health care institutions, especially within the CDC. In 1990, MOH issued the "National Guideline for Detection and Management of HIV/AIDS (draft)" (6), which prescribed the basic requirement for the HIV/AIDS testing laboratory setting, detection and quality control. The laboratory construction and quality control began to be standardized.

The second stage: From 1995 to 2000, during this stage, the Center for HIV/AIDS Control and Prevention of the MOH was validated formally as an independent legislative institution, and the National AIDS Reference Laboratory was established. At same time, MOH issued the "National Guideline for Detection and Management of HIV/AIDS" in 1997(5), and the monitoring and approval system of HIV/AIDS testing laboratories formally began, which further strengthened the management of the laboratories of HIV serology detection. The National Institute for the Control of Pharmaceutical and Biologic Products examined every batch of anti-HIV antibody screening kits. NCAIDS also began to evaluate the quality of diagnostic kits. The HIV/AIDS detection in health care institutions above the county level became more and more standardized.

The third stage: From 2000 to 2007, the system developed more and more quickly. In this stage, NARL and several HIV/AIDS confirmatory central laboratories passed the assessment and accreditation from CNAS. China CDC issued the "National Guideline for Detection of HIV/AIDS" in 2004, and MOH issued the "National Guideline for Management of HIV/AIDS Detection" in 2006. To strengthen laboratory quality control and attain an international standard, NARL participated in many PT programs organized by well known international institutions (Table 1). NARL increased the frequency of national

serology PT programs from once to three times a year in 2003. Furthermore, NARL initiated the PT programs of $CD4^+$T lymphocyte detection in 2004, viral load in 2005, HIV genotyping in 2006, and anti-HIV rapid test and HIV drug resistance in 2007 (Table 2).

To strengthen the PT program and to improve the efficiency and accuracy of examinations, the NARL, Shanghai CDC and Hunan CDC began to use electronic PT reporting systems since 2004 and 2006, respectively, which increased greatly the efficiency of the PT program for the HIV/AIDS testing laboratory, and also made the examination more objective and just.

CHALLENGES AND FUTURE DEVELOPMENT

The primary challenges faced by the HIV/AIDS testing laboratory network are in the areas of laboratory management and quality control, which include the following aspects:

Table 1. The international PT programs NARL participated in from 2002 to 2007

Program	Organizer #	2002	2003	2004	2005	2006	2007
HIV antigen/antibody test (EIA & WB)	US CAP	Y	Y	Y	Y	Y	Y
HBV, HCV antigen/antibody test	US CAP	Y	Y	Y	Y	Y	Y
$CD4^+/8^+$ T cell count	UK NEQAS	N	Y	Y	Y	Y	Y
HIV viral load test (NASBA)	US VQA	N	Y	Y	Y	Y	Y
HIV viral load test (RT-PCR)	US VQA	N	Y	Y	Y	Y	Y
HIV P24 antigen	US CAP	N	N	Y	Y	Y	Y
HIV, HBV, HCV antigen/antibody test (screening and confirming)	WHO NRL	N	N	N	Y	Y	Y
Syphilis antibody test	US CAP	N	N	N	Y	Y	Y
HTLV 1/2 antibody, HTLV 1/2 WB	US CAP	N	N	N	Y	Y	Y
HBV e antigen, HBVe antibody	US CAP	N	N	N	Y	Y	Y
$CD4^+/8^+$ T cell count	WHO QASI	N	N	N	Y	Y	Y
HIV drug resistance test	US VQA	N	N	N	Y	Y	Y
HIV viral load test (bDNA)	US VQA	N	N	N	Y	Y	Y
HIV DBS-DNA	US CDC	N	N	N	N	Y	Y
HIV viral load test (EasyQ)	US VQA	N	N	N	N	Y	Y
HIV-1 new infectious test (BED)	US CDC	N	N	N	N	Y	Y
HIV antibody rapid test	US CAP	N	N	N	N	N	Y

Note: "Y" indicates participated in, and "N" not.

Table 2. The national PT programs organized by NARL for HIV/AIDS confirmatory laboratories in China from 2003 to 2007

Program	2003	2004	2005	2006	2007
HIV antibody test (EIA)	Y	Y	Y	Y	Y
HIV antibody tes t(WB)	Y	Y	Y	Y	Y
$CD4^+$ T cell count	N	Y	Y	Y	Y
HIV viral load test	N	N	Y	Y	Y
Syphilis non-specific antibody test	N	N	N	Y	Y
Syphilis specific antibody test	N	N	N	Y	Y
HIV-1 new infectious test (BED)	N	N	N	Y	Y
HIV subtype test	N	N	N	Y	Y
HIV DBS-DNA	N	N	N	Y	Y
HBsAg, HCV antibody test	N	N	N	N	Y
HIV antibody rapid test	N	N	N	N	Y
HIV drug resistance test	N	N	N	N	Y

Note: "Y" indicates started, and "N" not.

The provincial PT program is inefficient

There are 21 provinces in whole country which have over 100 HIV/AIDS screening laboratories and 6 provinces which have over 300. Although the laboratory network is very large, the PT is still handled mainly manually and takes two or three months to prepare samples, deal with and feedback examination results for one PT cycle. This requires not only significant time and labor but also allows for mistakes. So it is urgent for us to develop an electronic system to strengthen the management of PT for the screening laboratories. At present, in whole country, only Shanghai electronically manages PT for their screening laboratories. Under the support of international projects, Hunan province started an electronic management system but, because of limited funds, this system has only been used in about 20 project counties in Hunan. To strengthen the PT for the HIV/AIDS testing laboratory and to fulfill the requirement of establishing the electronic PT system for the HIV/AIDS testing laboratories, which is based on the "China Action Plan for AIDS Control and Prevention (2006-2010)" (12), every province should plan to establish its own electronic PT management system. Shanxi province plans to initiate their electronic PT system by the end of 2007.

The internal quality control was conducted perfunctorily

Some confirmatory and screening laboratories did not carry out internal quality control according to the requirements of the "National Guideline for Detection for HIV/AIDS". Even though they conducted the quality control chart, they did not understand how to interpret the QC graph. Therefore they did not make any analysis or correction when the QC chart was out of range.

With many years of effort, the PT program of HIV/AIDS confirmatory laboratories has been developed and improved greatly in China, which has played an important role in promoting laboratory quality control. However, laboratory PT results are not the daily detection results. In other words, good PT results do not prove that your laboratory has no problems. Every laboratory should perform good internal quality control, so that the accuracy and reliability of every detection result can be guaranteed. In the future, NARL will not only strengthen continually the PT for the HIV/AIDS confirmatory laboratories but will also focus on promoting effective internal quality control for the confirmatory laboratories. Every confirmatory central laboratory also should take responsibility for promoting effective internal quality control for screening laboratories to improve continually the detection quality.

Personnel training have not met the needs of the workplace

Every HIV/AIDS confirmatory central laboratory has already carried out staff training for the screening laboratories. Although these trainings have played an important role in detection work, it's not enough. For example, in 2006, there were 154 training workshops for 9801 personnel throughout the country, but this still could not meet the necessary requirements. According to the regulations of the "National Guideline for management of AIDS detection" (7), every screening laboratory should has not less than three technicians, with training for each person occurring less than once each year. In the future, we will try to ensure that each person is trained or retrained at least once a year. At the same time, the standard mana-

gement practices of laboratories will be strengthened greatly and laboratory bio-safety will be reinforced for the safety of personnel and the environment.

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