1. 特別講演：タイ王国における HIV 抗原検査導入の成果と問題点

Results and Issues of HIV Antigen Screening for Blood Donors in Thailand

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Since 1981, HIV has made a great concern over every national blood program in the world. It creates not only a major medical impact, but also a major social issue. No other diseases except HIV/AIDS has ever received such a strong support for human right. The knowledge of HIV, however, is still at the tip of an iceberg. Decision making upon HIV/AIDS issue has always been caught in the dilemma, especially in transfusion area. One example is whether to inform the donor when test result of a donor is positive for anti-HIV. On the one hand, sympathy to the donor must be given, then the test result must be kept confidential. On the other hand safety of blood supply must be maintained, then the donor's test result must be informed so that future donation is permanently deferred. Another example is whether HIV antigen screening should be implemented concurrently with anti-HIV in order to maximize blood safety. Cost effectiveness then becomes an issue.

In Thailand new HIV infection as well as total infection is high. Transfusion associated HIV from screened blood during window period is evident. HIV antigen screening is therefore mandatory. In fact, we began HIV antigen screening since September 1991, few years before it was adopted as blood screening policy in the United States. We therefore would like to take this opportunity to share our experience.

Thailand's Health Care Profile (Table 1)

Thailand is the country of 60 million population.

Table 1 Health Care Profile

Population (1997)	60 million
Physicians	20,965
Nurses	61,478
Hospital-University based	8
Regional	17
Provincial	76
District	581
Total beds	100,100

Health services are provided through a governmental as well as a non-governmental system. There are 100,100 hospital beds throughout the country, 24,000 of which are in Bangkok (1993 census). Of 24,000 beds in Bangkok 7,000 are privately owned. The Ministry of Public Health provides most of the medical services, free of charge or at nominal charges. Private medical service is much more expensive; charges are based on fee for service. Only Medical benefits are provided for governmental employee. Health insurance is also provided by Workman Compensation Fund. National health insurance are not yet available.

The National Blood Program and Blood Program Policy

The National Blood Program in Thailand is run by the National Blood Centre, Thai Red Cross Society and its 76 provincial blood transfusion service throughout the country. The mission is designated by the Government in formulating and carrying out the program activities with closed collaboration and support from Ministry of Public Health. The National Blood Centre serves as the national head-quarter and co-ordinator of the national blood program.

The formulation of National Blood Program Policy is set forth as follows:

1. The National Blood Centre, Thai Red Cross Society is responsible for the national blood program with government support.
2. Blood collection should come from voluntary non-paid basis and self-sufficiency should be aimed at provincial level.
3. Before dispatch for use, every unit of blood must be tested according to the set standard to maximize the safety of blood.
4. Appropriate use of blood must be encouraged.
5. User (clinicians) and providers (BTS) must be mutually cooperative to maximize blood collection and minimize wastage.

The National Blood Centre

The National Blood Centre was established in 1966 by the Cabinet's approval with technical assistance from the French Government. In the first decade of operation (1966-75), the emphasis was on recruitment of unpaid donors, the establishment of provincial transfusion services in every province and the availability of 5 basic blood components i.e. whole blood, packed red cells, platelet concentrates, cryoprecipitates and fresh frozen plasma. By the end of the second decade (1976-1985) specialized products such as single donor platelets, frozen red cells and fractionated plasma products such as albumin, immunoglobulin were available. In the third decade (1985-present), plasma apheresis program was initiated to collect additional plasma for pilot scale fractionation at the Centre and blood group reagents by monoclonal hybridoma technique were produced. In 1995 a factory was set up to produce plastic blood collection bags to replace the bottles. Production at the National Blood Centre is shown in Table 2.

Each provincial blood transfusion service is responsible for the supply of blood and blood components in the province where National Blood Centre is responsible for such activity in Bangkok. The National Blood Centre also provides essential blood components as a back up service to other provinces when necessary.

The Blood Collection

During the past 30 years of operation, blood collection by the National Blood Centre has increased from about 20,000 units in 1966 to 335,893 units in 1996. From 1987 onwards, all donors in Bangkok are non-paid. About 50% of total whole blood collection is separated into other four basic blood components, i.e. packed red cells, platelet concentrates, cryoprecipitates and fresh frozen plasma. Expansion of blood components preparation are being done with the increased use of plastic bags produced by National Blood Centre's own factory. Blood

Table 2 Production at NBC, 1996

Blood Collection	335,893
Component Preparation	47%
Plasmapheresis	5,557 liters
Plasma Fractionation	8,000 liters
Blood Grouping Reagents(10 ml.)	103,859 bottles
Plastic Blood Bags	100,000

collection in 1996 is shown in Table 3.

AIDS Epidemiology in Thailand

A domestic AIDS case in Thailand was first recognized in late 1984. The country's surveillance program has been implemented ever since, which consisted of AIDS Voluntary Reporting System, and Semi-annual Sentinel Sero-prevalence System. The AIDS Voluntary Reporting System provides information on the number of persons affected with AIDS and/or other symptomatic HIV infection. Whilst the Sentinel Seroprevalence Surveillance System monitors the trends of the HIV/AIDS epidemic. In AIDS Voluntary Reporting System, health institutions and physicians are encouraged to report the specific details of AIDS cases anonymously to public health authority. In Sentinel Sero-prevalence Surveillance System, cross sectional HIV serosurvey among prostitutes, male attending sexually transmissible diseases (STD) clinics, pregnant women and blood donors, were conducted twice a year (June and December).

In the first 4 years (1984-88), there had been only 19 AIDS cases reported to the Ministry of Public Health. By the end of 1995, a total of 36,500 cumulative AIDS cases have been reported, 14,951 of which occurred in 1995 alone, which is an explosive situation. Most frequent age group is 25-29 among the male and 20-24 among the female. The sex ratio,

Table 3 Blood Collection, 1996

Whole Country	1,113,415 units
Bangkok(NBC)	335,893 units
Volume : First time	350 ml.
Repeat < 50 kg	350 ml.
> 50 kg	450 ml.
Interval	3 months

Table 4 AIDS Patients by Risk Factors

(Sept. 1984-Dec. 1996)

Risk Factor	Numbers	Per Cent
Sexual	44,753	80.72
Unknwn	4,840	7.47
IVDU	3,549	6.40
Vertical	3,012	5.43
Transfusion	45	0.08
Total	55,443	100

Fig. 1 AIDS Cases, 1984-1996.

male:female, is 5.4:1. The most common route of infection is sexual transmission (78.60%) and the least common was blood transfusion (0.12%). All transfusion associated AIDS cases received blood and blood product prior to the implementation of anti-HIV screening program in 1989.

Epidemiologically, HIV infection in Thailand in 1988 was classified as a "Pattern III" country, signifying that small number of AIDS cases has been reported and that introduction of HIV occurred relatively late in the AIDS pandemic. In 1988, however, an evidence of explosive increase in HIV prevalence was noted; first, among injecting drug users (IVDU). In a survey study of 4,495 blood donors in late 1986 at the National Blood Center, six cases of anti-HIV positives were found only in prison inmates; all were drug addicts. HIV rate climbed from about 1% at the start of 1988 to 32-43% by August-September, 1988 among heroin users, mostly men (96%) attending methadone treatment clinics in Bangkok. This was the first wave of HIV epidemic scene in this country. Of HIV positive drug users (IVDU), one quarter reported continuing to have sex despite their sero-positivity, mostly without condom usage. From May 1985 through May 1989, all reported sero-surveys of female prostitutes in Thailand detected nil HIV infection. In June 1989—one year after the explosive spread of HIV among IVDU—the first national sentinel sero-survey detected HIV infection in 44% of brothel-

based in Chiangmai, a northern city of Thailand. This was the second wave of HIV spread; from IVDU to female prostitutes.

The third wave of HIV spread, was among heterosexual non-IVDU. HIV rate was first detected at 0.5% in public sexually transmitted disease (STD) clinics in 1988. By June 1991, male STD patients had a national median provincial HIV rate of 5%. Unprotected sex with female prostitutes is the primary factor contributing to HIV transmission³⁾.

Finally HIV spread occurs through heterosexual transmission among non-IVDU male and female as evidenced by a figure of 2.29% HIV positive among pregnant women (1995).

An estimated total HIV infection was 800,000 in 1995. The government budget allocated for the AIDS/HIV prevention program in 1995 was nearly 2,300 million Bahts (US\$ 90 million).

Through active campaign and public education by the government agencies, such as 100 percent condom usage project, avoid unsafe sex project, etc., as well as many other educational activities, there is an evidence that new HIV infection has reached its peak and began to decline. Study at the National Blood Centre has observed that anti-HIV sero-conversion rate among repeated blood donors climbed up from 0.06% annually in 1988, reached the peak of 0.41% in 1991 and then declined to 0.19% in 1994. The total infection, as evidenced by anti-HIV sero-positive among new donors, also declines; the

rate rose from 0.06% in 1988 to its peak of 1.13% in 1992 and then declined to 0.93% in 1994.

Transfusion Associated HIV

Blood transfusion is the most effective way in transmitting HIV infection. The infectivity is related to the large volume of virus infused. It is, on the other hand, the most easily preventable means of HIV transmission, provided that an effective anti-HIV screening program is in place.

In May 1987, the first case of transfusion associated HIV appeared on the press. The recipient received 8 units of unscreened whole blood for the treatment of his gastrointestinal hemorrhage in November 1986. He developed full blown AIDS later and died. By the end of 1996, a total of 45 transfusion associated AIDS cases have been reported to the Ministry of Public Health²⁾, all of whom had received unscreened blood. Unfortunately, detailed clinical information was not available.

In addition to 45 cases of transfusion associated HIV infection from unscreened blood, cases of HIV infection from screened blood have also been reported. The first report of transfusion associated HIV infection from screened (sero-negative) blood was in 1990 in three thalassemic children who received multiple transfusion. The report came from Chiang-mai, a city which has the highest HIV prevalence in the country⁴⁾. It was believed that the donor donated his blood during the "window" period of early HIV infection, when antibody to the virus has not yet been formed; thus his blood escaped anti-HIV detection and the result was negative. Thus far, a total of 32 cases of transfusion associated HIV from screened blood has been discoverable.

In Western countries where unheated purified factor VIII concentrates had been used for the treatment of hemophilia, HIV infection among hemophiliacs were high, up to 70%. On the contrary, HIV infection among Thai hemophiliacs was low. Only 3 of 76 Thai hemophiliacs (3.9%) have been reported to have HIV infection, all of whom sero-converted in 1987 and later, one from the un-screened and two from the screened cryoprecipitates. Imported factor concentrates were used in a very limited numbers, due to high price of the imported product. Most Thai hemophiliacs therefore received only locally produced cryoprecipitates supplied from the National Blood Centre, Thai Red Cross Society. Using domestic product thus contributes to the find-

ing of low HIV infection rate among the hemophiliacs in Thailand. The imported heat treated factor VIII has been registered in 1991 and became available for use in the country since.

Safety Measures

After the blow out of HIV infection in 1981, safety of blood became an important issue. Safety measures implemented at the National Blood Centre are as follows:

1. Safe blood donation, through pre-donation counseling and voluntary self exclusion
2. Laboratory screening for transmissible diseases
3. Inactivation (viral) wherever possible; it is presently available only for non-cellular products

Safe Blood Donation

For safe blood donation, we promote the concept of non-remunerated voluntary general donation rather than replacement (or family) donation. Every measure to retain regular donor is also encouraged. In addition to conventional donor recruitment activities, we put extra effort to motivate more female donors since positive rate for infectious disease markers are much lower among female donors comparing to the male counterpart. Donor with high risk behaviour such as drug addicts, prisoners, homosexuals, commercial sex workers and their partners are deferred or excluded from blood donation. One-to-one interview is carried out by nursing staff at pre-donation counseling clinic. It is, however, not conveniently done at mobile station where private room is not available. Those who are positive for infectious disease markers such as HBsAg, anti-HCV, VDRL, are also excluded from donating blood.

Voluntary self exclusion is another measure for safe blood donation. New as well as regular donors are asked to indicate whether their blood are "safe" or "unsafe". The result at our center is interesting (Table 5). Those who answer "unsafe" have significant higher positive rate for anti-HIV than those who answer "safe" (1.01% vs. 0.3%). Pre-donation counseling as well as voluntary self exclusion alone, however, cannot be substituted for HIV antigen screening. It does help to reduce further chance of HIV infection during window period.

Laboratory Screening for Transmissible Disease

Emphasis on the safety of blood against HIV

infection has always been the main interest of the National Blood Centre. Routine screening for transmissible disease is done on every unit of donated blood which includes syphilis, hepatitis B, hepatitis C and HIV. For other diseases such as malaria, we rely on medical history of blood donors since no laboratory screening for malaria is available yet. Prevalence of transmissible disease markers in 1996 are shown in Table 6. With an emphasis on HIV, Anti-HIV as well as HIV antigen screening is carried out at the National Blood Centre.

Anti-HIV Screening

This measure is regarded as the foremost important measure to be taken at the National Blood Centre. The test was first become commercially available in 1985 and has been improved continuously through the improvement of antigen used in the production. The test is now in its third generation. The anti-HIV test detects antibody to HIV virus in human body, which usually became positive 4-6 weeks after acquiring an infection. It therefore does not detect an early infection during the so-called "window period". Two types of test, i.e. ELISA and agglutination, are used for blood screening. Positive anti-HIV screening must be confirmed by Western blot test before labeling as anti-HIV positive.

In late 1986 an anti-HIV sero-survey was initiated at the National Blood Centre⁹⁾. The study included 4,495 donors of various groups, e.g. students, govern-

ment officials, military men, prison inmates and general public. Six cases of anti-HIV positive were found only among prison inmates; all were drug addicts. Anti-HIV screening was subsequently initiated at the National Blood Centre in January 1987. But screened blood was issued only to those hospitals who agreed to pay for the reagent costs. About 50% of blood were screened in the first half of 1987. After a case of transfusion associated HIV being recognized in May 1987, then compulsory anti-HIV screening at NBC began in September that year. The Public Health authority subsequently adopted the anti-HIV screening on every unit of blood as a national policy in February 1989, after having full budget allocation for the cost of reagents from the government.

The current scheme of anti-HIV testing at the NBC is as follows:

1. Initial screening was done with sandwich ELISA HIV1+2, which will detect both IgG and IgM.
2. If reactive, a duplicate test was repeated with another ELISA and particle agglutination (PA).
3. It is then confirmed with Western Blot (WB) if any of the repeat test is positive.

Note: When the repeat tests are both positive (ELISA and PA), WB is almost always positive; thus WB is not necessary in this case, since it is an expensive test.

4. Results are transferred to computer with a flag, to alert our staff not to accept future donation and also to keep the donor's result confidential.

All units of blood which are positive for anti-HIV screening are discarded. They are, however, subjected to further repeat testing and confirmation, as described above. Those with negative Western Blot may be put on the lists for re-entry evaluation. Donors with positive results will be notified with consent (optional), and be advised not to donate blood. We also provide counseling to them.

Anti-HIV positive rate in 1996 is as follows;

0.22% for all donations (which decreases from 0.32% in 1994)

1.01% for first time male donors and 0.37% for first time females

0.19% for repeat male donors and 0.09% for repeat females

The anti-HIV positive rate in donated blood was

Table 5 Donor Self Exclusion (NBC)

Year	Answer	Donation	HIV +	%HIV +
1993	Safe	249,951	925	0.40
	Unsafe	6,295	63	1.01
1994	Safe	254,504	784	0.3
	Unsafe	6,005	63	1.07

Table 6 Infectious Markers

Donation	HBsAg	Anti-HCV	VDRL	Anti-HIV
	(%)	(%)	(%)	(%)
Total	1.38	0.47	0.12	0.22
First time: M	6.55	2.29	0.51	1.01
F	3.41	0.77	0.21	0.37
Repeat: M	0.86	0.51	0.25	0.19
F	0.41	0.23	0.12	0.09

0.048% in 1988, increased rapidly, reaching its peak rate of 0.42% in 1992, then declined.

HIV Antigen Screening

This test was implemented at the National Blood Centre in September 1991 after having discovered that 2 cases of hemophiliacs who received multiple units of fully screened cryoprecipitates had sero-converted and developed AIDS⁶⁾. Also, in a cohort study of 10,165 anti-HIV negative donors who subsequently donated blood 3 to 6 months later, 10 were found to be sero-converted. These 10 donors' serum were traced back and tested for HIV-antigen; one was found positive. That unit of blood which was antibody negative but antigen positive had unfortunately been transfused and the recipient, an 85-year-old woman who had no other risk for HIV, subsequently sero-converted. Additional study at the NBC, testing a total of 125,472 units from voluntary donors for anti-HIV and HIV-antigen, showed a significant results of 1 antigen positive among 18,000 anti-HIV negatives⁷⁾.

The current scheme of HIV-antigen screening is as follows:

1. Abbot HIV Ag-1 monoclonal or Coulter HIV Ag Assay ELISA was used for initial screening.
2. If reactive, they are re-tested in duplicate with the same reagent, but with neutralization. Confirmation of positive result required more than 50% neutralization as compared to control.

During 1991-1996, there were a total of 1,536,396 cumulative units of blood tested for HIV antigen in concurrence with anti-HIV. Of these, 114 units were positive for HIV antigen; 81 were also anti-HIV positive and 33 were anti-HIV negative. The total HIV antigen positive rate was 7.45 per 100,000 donations. Nearly equal positive rate (52% v.s. 48%) were from first-time donors and repeat donors.

There were a total of 33 HIV-antigen positive but anti-HIV negative (infectious window) among 1,536,396 donations. An average infectious window prevalence was 2.15 per 100,000 donations. It was highest (3.1 per 100,000) in 1991-92 when anti-HIV sero-conversion rate was also highest (355/100,000 person-year). The prevalence slowly came down each year in concordance with the lower anti-HIV sero-conversion rate. The prevalence was 1.49/100,000 in 1996 when anti-HIV sero-conversion rate was 165/

Table 7 Seroconversion and Infectious Window

Year	Seroconversion (/100,000)	Window (/100,000)
1991-92	355	3.10
1993	250	2.96
1994	192	1.47
1995	183	1.67
1996	165	1.49
Average	245	2.15

100,000 person-year. Young male donor was the most predominant group (88%). Associated infectious disease markers were positive at a rather insignificant rate which is unlikely to be useful to use as surrogate markers. Busch⁸⁾ recently reported a very low anti-HIV sero-conversion in the United States of 3.4/100,000 person-year comparing to our experience in Thailand. This would explain the absence of HIV antigen positive-antibody negative in earlier US study.

With an estimated figure of 80,000-100,000 new HIV infection a year⁹⁾ in our country, the presence of HIV infectious "window" is therefore expected and the use of HIV-antigen screening is thus definitely useful in our situation, although it costs more. It has been a debating issue whether HIV-antigen screening is cost effective. We consider that cost effectiveness lies not upon the test and its result, but upon the appropriate use of blood. Nevertheless, our analysis⁹⁾ did show that the addition of HIV-antigen test for the prevention of HIV transmission, even at such low rate of 2.15 per 100,000, is cost benefit in terms of medical care expense, productivity loss and loss of future earnings. Moreover, it prevents the psycho-social cost of pain, suffering, and social stigmatization of the patient.

Risk of transfusion associated HIV in Thailand has significantly decreased after the implementation of HIV antigen screening along with the anti-HIV screening. The risk decreased from 35 to 0.2 per 100,000 (Table 8)

Conclusion

In Thailand where HIV infection rate is high, the use of HIV antigen screening in addition to anti HIV has objectively shown to decrease the risk of transfusion associated HIV. Thus, HIV antigen test helps save the economical loss of the country. It also

Table 8 Transfusion Associated HIV

Period	Units transfused	Number of HIV-positive recipients	Rate/100,000 Units
1987-91 (before HIVAg)	919,359	32	35
1991-96 (After HIVAg)	1,536,359	3	0.2

prevents the psychological costs of pain and suffering, the adverse effect on personal and family relationship as well as social stigmatization.

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