Impact of HIV on Tuberculosis in Northern Thailand

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November 2000

Abstract

Introduction: The risk of tuberculosis is greatly increased in those with HIV infection, but the relative risk will vary over time, depending on the proportion of HIV-infected individuals with different levels of immunosuppression. This study in Chiang Rai, Thailand, assesses how this relative risk changes, investigates any interaction with age, and estimates the TB burden attributable to HIV infection now and in the future.

Methods: We conducted a case-control study using retrospective data from Chiang Rai hospital. Cases were all newly diagnosed TB patients during 1990-1998. Controls were antenatal clinic attenders (ANC), delivery patients, surgical patients, blood donors and military conscripts. Odds ratios (OR) were calculated separately by year, age group and gender, using each control group separately. The population attributable fraction (PAF) was calculated by year. A mathematical model was developed to recalculate the PAF taking account of the time lag between HIV infection and TB, and to predict PAF in the future.

Results: During the study period, the number of new TB cases in Chiang Rai hospital increased more than 3-fold. HIV prevalence peaked at 17.4% in 1992 in male military recruits before declining dramatically. The peak was later and lower in women. The OR for the association of TB and HIV infection increased markedly over time but there was no consistent pattern by age. Age-adjusted PAFs, rose to around 70% by 1998. Modelling suggested that a true difference in ORs by age is masked by the lower proportion of individuals with more advanced HIV infection in younger age groups. The model gave slightly lower estimates for the PAF than those calculated directly, and predicted that the PAF would decline earlier in younger individuals. For older adults PAFs will remain very high throughout this decade.

Conclusion: The HIV epidemic has a profound and prolonged impact on TB burden despite the marked reduction in HIV incidence already seen in Chiang Rai. Besides HIV prevention, we need additional TB control measures to reduce the burden among HIV positives.

Acknowledgements

The completion of this thesis and my doctoral study would not been possible without the great support from my supervisor, Dr Judith Glynn, who has been very encouraging and enormously supportive of me. I would like to express my sincere gratitude to her. Special thanks also go to Dr Emilia Vynnycky, who is in my supervisory committee, for her very kind support, comments and time available, Professor Richard Hayes for his valuable comments, and to other staff of the London School of Hygiene & Tropical Medical for their assistance.

The work leading to this dissertation would not have been at this level of accomplishment without kind support from Dr Hideki Yanai and all staff of the Research Institute of Tuberculosis in Chiang Rai, including the funding for data collection in Chiang Rai. I am indebted to my collaborators in Chiang Rai: Dr Wat Uthaivoravit for his assistance and suggestion of my collecting data in Chiang Rai hospital, Dr Supak Pitipakorn for a nice collaboration with the surgical wards, Dr Renu Srismith, and Dr Peter Kilmarx and the staff of the HIV/AIDS Collaboration office in Chiang Rai for kindly allowing the use of data from Chiang Rai hospital. I would like to express my thanks to Dr Pasakorn Akarasewi, Dr Pawongsak Rientrirak, Dr Thapanok Rattanadilok na Phuket, Dr Vallop Payanandana of TB division, Ministry of Public Health, for overseeing the plan of my thesis.

I am also indebted to the Armed Force Research Institute of Medical Sciences for the permission to use data from the military conscripts.

I would like to express my gratitude to Dr Kumnuan Ungchusak, who is the programme manager in my office and gave me the opportunity to come here with very kind support for my study. I also would like to give my special appreciation to all of my colleagues, including all trainees in Field Epidemiology Training Programme, Division of Epidemiology, for their strong support and encouragement in my study. I would like to thank Dr Somsak Wattananasri, Director of Division of Epidemiology and all supporting staff, for the allowance of their resources and time and their kind support.

I would like to express my appreciation to the World Health Organization for the funding of my study during the first and last year. Without this starting point, it is almost impossible to come to this programme. My doctoral study and thesis could not possibly have been finished without the financial support from GTZ, British Council and the Trust fund of London School of Hygiene and Tropical Medicine.

Most of all, I would like to express my deep gratitude to my mum and dad for the love and moral support they give to me, and to my brother for being nice company throughout my life.

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AFB	Acid fast bacilli
ANC	Antenatal care
CI	confidence interval
CSWs	Commercial sex workers
DOTS	Directly observed therapy, short course
HIV	Human Immunodeficiency Virus
IDUs	Intravenous drug users
IPT	Isoniazid preventive therapy
MS1	Male surgery ward 1
MS2	Male surgery ward 2
NTP	National Tuberculosis Programme
OR	Odds ratio
PAF	Population attributable fraction
RIT	Research Institute of Tuberculosis
RR	Relative risk or relative rate
STD	Sexually transmitted disease

TB	Tuberculosis
WHO	World Health Organization

The re-emergence of tuberculosis

About a century after Koch's discovery of *M.tuberculosis* bacilli the tuberculosis epidemic which had appeared under control was again recognized as a major global health threat [Kochi 1994]. In the United States, tuberculosis incidence reached its nadir in 1985 when there were 22,201 cases (9.3 per 100,000 population) before an increase in the number of reported cases during 1986-1992 [Kaye et al. 1996]. In other industrialized countries, the trends were varied. Between 1974 and 1992, tuberculosis case notification rates in western Europe continued to decline in Belgium, Finland, France, Germany and Portugal. Cases rates leveled off in Austria, Ireland, Sweden and the United Kingdom, and increases were recorded in Denmark, the Netherlands, Norway, Switzerland, Italy and Spain although decreases were observed in Switzerland after 1990 [Raviglione et al. 1995]. Tuberculosis rates are higher in countries in eastern Europe and the former Soviet Union than in western industrialized nations and the quality of surveillance is variable [Raviglione et al. 1994].

In developing countries, where the rate of decline has been relatively slow in middle-income countries, and negligible in low-income countries, increases have also been observed since the mid 1980s in many countries, especially those in sub-Saharan Africa [Kochi 1991, Cantwell et al. 1996]. The reasons for this reemergence are many. They include population migration and increasing urban poverty in some western European countries and the USA [Zolopa et al. 1994, Fujiwara et al. 1996, Kane et al. 1996]. Another important factor is the failure of control programmes, with low rates of case finding and cure, and increasing rates of drug resistance [Brudney et al. 1991, Hamburg et al. 1994]. However, on a world scale, the main factor increasing the incidence of TB is HIV infection [Rieder et al. 1989, Cantwell et al. 1996]. In sub-Saharan Africa, HIV probably accounts for almost all of the increase in TB cases, and there are early indications

that previous long term declining trends in the annual risk of tuberculous infection are beginning to reverse [Cantwell et al.1996, Odhiambo et al. 1999].

In terms of public health, tuberculosis must be one of the very highest priority diseases because of its tremendous burden and the existence of interventions of proven efficacy that are some of the most cost-effective in the international public health armamentarium [Murray et al.1990]. From the global perspective the position of TB as a major killer has not changed in the last 100 years [Kochi 1994]. Among adults, tuberculosis is the world's foremost cause of death from a single infectious agent [Raviglione et al. 1995]. In terms of illness, tuberculosis is a leading cause of morbidity in developing countries, where 95% of tuberculosis cases occur. Eighty percent of these cases involve persons who are in their economically productive years (15 to 59 years). The highest prevalence of tuberculosis infection and the highest estimated annual risk of infection are in sub-Saharan Africa and Southeast Asia. Overall, almost 3.8 million notification cases of tuberculosis in the world were reported to WHO in 1990, of which 49% were in Southeast Asia [Raviglione et al. 1995], where the HIV epidemic is growing rapidly in many countries. It has been suggested that the elimination of tuberculosis in most developed countries will not be substantially influenced by AIDS because of the low prevalence of TB in the population aged 20 to 50 years in whom HIV infection is most frequent [Murray et al. 1990]. In contrast, HIV infection will result in a considerable increase of tuberculosis cases in those developing countries where both tuberculosis and HIV are prevalent.

Biological interaction of tuberculosis and HIV infection

The main mechanism of natural immunity against TB is cell-mediated immunity, leading to the formation of granulomas to localize the tubercle bacilli within a discrete region of the lung to prevent further spread of the disease [Scharer and McAdam, 1995]. This involves macrophages and T lymphocytes. In the process of HIV infection, the virus invades and destroys T lymphocytes with the CD4+ surface marker. The loss of T-cell function reduces lymphokine production, which in turn compromises macrophage function.

The interaction of HIV infection on TB disease can occur through all mechanisms of disease progression: primary infection, reinfection and reactivation. In general, the risk of developing active TB among persons with latent infection has been estimated to be no greater than 10% in their entire lifetime [Sutherland 1976]. This is in sharp contrast with studies among HIV-infected persons with latent TB infection, which have mostly shown an incidence of tuberculosis ranging from 5 to 10% per year of observation [Girardi et al. 2000]. Moreover, the risk of re-activation among HIV-infected persons appears to be correlated with the level of immunosuppression. In a cohort study from Italy [Antonucci et al. 1995], the annual incidence of tuberculosis among tuberculin-positive HIV-infected persons was 2.59 per 100 person-years among those with a CD4 cell count above 350/μl, 6.54 among those with CD4 cell count between 200 and 350/μl, and 13.3 among persons with CD4 cell counts less than 200/μl. For the progression of recently acquired *M tuberculosis* infection in HIV negative individuals, the risk of disease is highest during the first two years after primary infection: approximately 5% of newly *M tuberculosis* infected HIVnegative individuals will develop TB disease within two years [Comstock 1982, Styblo 1991]. For HIV-infected individuals the risk of tuberculous disease ranges from 5.4 per 100 person years among HIV-infected tuberculin converters in the general population in the USA, to 35 per 100 person years among those in a hospital ward in the US [Coronado et al. 1993, Markowitz et al. 1997].

Most cases of TB seen in patients infected with HIV have been assumed to be due to reactivation of latent tuberculosis because these cases occurred among members of groups with a high prevalence of underlying *M tuberculosis* infection, such as intravenous drug users and people in developing countries [Scharer and McAdam. 1995]. However many studies during the past decade have demonstrated a high proportion of HIV-associated TB cases that were attributed to recent infection [Girardi et al. 2000]. No studies examing the relative importance of reactivation and recent infection in tuberculosis have been conducted in Thailand.

The association between HIV and tuberculosis

There are many studies of the association between HIV and TB. All studies have shown an increased risk of developing TB among HIV-infected persons compared to those who are not HIV-infected, but the magnitude of this relative risk has varied from less than 5 to more than 20. Some of this variation is a result of differences in study design, especially in the types of TB case included (HIV prevalence is higher in those with extrapulmonary TB, and where bacteriological confirmation is not available, misdiagnosis of other HIV-related illness as TB is likely), or in control selection in case-control studies, but there may be true differences in the relative risk in different populations with different experiences of both TB and HIV [Glynn et al. 1997].

It is likely that the strength of the association between HIV and TB will change in a population as the HIV epidemic progresses and an increasing proportion of HIV-infected individuals becomes immunosuppressed. Reviewing studies conducted in developing countries in the general population, suggests that the relative risk varies with age (table 1). Some studies reported highest odds ratio (OR) among TB cases aged 25-34 years [Van Den Broek at al.1993, Van Cleeff and Chum 1995, Chum et al. 1996]. All of these studies had the lowest OR in the oldest age group (45 years or more in 2 studies and 55 years or more in the remaining study). Other studies divided the age group in different ways. A study from rural Haiti in 1988 found a much higher OR among those aged 20-39 years, compared to 40-59 years, while a study in Kenya during the same period had a different highest age group among males and females (table 1). A study in Zimbabwe (1988-1989), used a matched case-control design but used the relative risk (RR) for the calculation [Houston et al. 1994]. When we re-calculat d the results using unmatched OR, the highest value was among aged 25-44 year olds. Cohort studies generally had higher RR than the case-control studies. Most studied young adult women of childbearing age. Therefore if the relative risk varies with age, with young adults having higher risk of developing TB than older people in HIV-infected populations, the RR in these cohort studies should be higher than in the case-control studies that used subjects from a wider range of age. However, there

were also some studies that did not find different ORs by age and then presented only the overall OR (table 1).

The biological difference between males and females in developing TB disease has been debated for many years. Comparison of infection rates with disease rates in some settings suggested that women may have a higher rate of progression to disease in their reproductive years, whereas men have higher rates of progression at older ages [Murray 1991, Fine 1993]. There are several explanations regarding these findings, covering both biological and socioecon. mic aspects such as pregnancy-induced breakdown of immune response and women being more likely to use health services during their reproductive years [Holmes et al. 1998]. If the biological explanation is correct, it is also possible that the risk of developing TB disease in HIV-infected people might be different between sexes. There are few previous studies that separately reported the results by sex. The study in Western Kenya during 1989-1990, using community controls, matched for age, sex and area of residence, found highest OR among males aged 10-29 years (OR=8.1, 95%CI: 2.9-22.3) and among females aged 29-49 years (OR=19.6, 95%CI: 2.5-154) [Orege et al. 1993]. However this study used a very wide age grouping, which might obscure effects on their subgroup OR in each sex. A case-control study in Tanzania in 1991, using community controls found only slightly different ORs between males and females, which were 8.9 (6.1-12.9) and 7.7 (5.1-11.7), respectively [Van den Broek et al. 1993]. Another study from Tanzania between 1991-1993 found an overall OR of 7.1 (95% CI 6.6-7.5) with no marked difference by sex [Chum et al.1996].

Given the variation seen between studies, and the variation expected as the HIV epidemic develops, we cannot assume that the pattern of disease in one country or region will be mirrored in others, and local studies become imperative. If the relative risk for the association between HIV and TB and the prevalence of HIV among TB patients or the general population are known, then the proportion of TB attributable to HIV can be calculated and the future excess burden of TB predicted.

To date most studies have been conducted in sub-Saharan Africa, or in Western countries particularly among high-risk groups such as intravenous drug users. Relatively little is known about the combined epidemic in Asia although there have been reports of increasing HIV prevalence among TB patients in some countries [Akarasewi et al.1991, Wiriyakitjar et al.1992, Ibopishak Sing 1993, Mohanty et al.1993,]. All studies to date have been in areas of increasing or stable HIV prevalence. The HIV epidemic in Thailand varies considerably in extent from area to area, and shows a unique pattern of rapid incidence followed by a rapid decrease and then apparent stabilisation. It has been unusually well documented.

In conclusion, it is known that HIV infection increases the risk of tuberculosis. This makes biological sense, and the risk increases with increasing immunosuppression. It is, however, unknown how the RR of the association between HIV and TB changes with duration of HIV infection, and what this means at the population level at different stages of the HIV epidemic. We also know little about whether and how the association between HIV infection and TB varies by age or sex, or whether there are differences in the effect of HIV on the risk of getting TB disease following primary infection or reinfection or by reactivation. Any differences seen by age may be a reflection of differences in the effect of HIV on these three different pathways to disease. In this study we explore the changing RR over time and variations by age.

HIV/AIDS epidemic in Thailand

Thailand is a country in Southeast Asia with a population of 60 million in 1997 [National Statistical Office 1997] and an area of 513,115 square kilometers. The whole area is divided into four geographical regions: northern, northeastern, central and southern region. During the past 30 years, the population structure changed from wide based (high proportion of children) to narrower based. The proportion of children aged less than 15 years decreased from 45.1% in 1970 to 27.9% in1995 while the proportion of those aged, 15-54 years, increased from 47.7% to 60.2% in 1970 and 1995 respectively [Central Statistical Office, Bureau of Health Policy and Planning]. The life expectancy increased from 57.7 and 61.6 in males and females respectively in 1970 to 65.3 and 69.8 respectively in 1995

[Public Health Statistics A.D.1992]. More than 75% of the population live in rural areas and work in agriculture although rapid industrialization and modernization have occurred since the 1960s [World Health Organization, 1998]. The disease pattern of the country reflects a mixture of both developing and developed countries [Ministry of Public Health, 1992].

The country was among the first 3-4 nations in the Asia and Pacific region to experience the explosion in HIV infections [Kaldor et al.1994]. However, when compared to the epidemic in Africa or Western countries it is still considered as a recent origin [Weninger et al.1991]. The first cases of AIDS in Thailand were reported in 1984 [Phanupak et al.1985, Limsuwan et al. 1986]. In 1988 Thailand experienced an explosive increase in HIV prevalence among injecting drug users attending methadone treatment in Thanyarak hospital and the Bangkok Metropolitan Administration drug treatment clinics [Uneklabh et al. 1988, Vanichseni et al. 1989, Vanichseni et al. 1990]. The HIV rate in injecting drug users in Bangkok climbed from about 1% at the start of 1988 to 32-43% by August-September 1988 [Phanupak et al.1989a, Phanupak et al.1989b]. Only a year later, the first national sentinel serosurvey detected HIV infection in 44% (44/100) of lower class brothel-based prostitutes in Chiang Mai, after reports of zero or less than 1% HIV infection from sero-surveys among female prostitutes during 1985-1988 [Weninger et al. 1991, Division of Epidemiology 1989, Ungchusak et al 1989b]. National median provincial HIV prevalence rates for brothel-based prostitutes increased steadily from 3.5% (range 0-44%, in 13 provinces) in June 1989 to 15% (range 2-63%, in 60 provinces) in June 1991 and 33.2% in 1994 [Ungchusak et al.1997a]. Rates for brothel-based prostitutes have been consistently highest in the northern tier of provinces bordering Myanmar and Laos such as Chiang Mai, Chiang Rai and Payao. The study among commercial sex workers (CSW) in Chiang Mai (1989) and Chiang Rai (1991) showed the HIV prevalence among brothel-based CSW as 36.5% and 47%, respectively [Siraprapasiri et al.1991, Limpakarnjanarat et al.1999]. Another study performed in 1992 reported HIV prevalence in Chiang Mai among CSW at 65% [Celentano et al. 1994]. A longitudinal study among female CSW in a big province in northeastern region during 1990-1991 showed an average seroprevalence of HIV of 12.5% [Ungchusak et al. 1996a]. A serial cross-sectional study in female CSW

in Bangkok in 1989 and 1990 reported HIV seroprevalence of 10.2% and 16.8% respectively [Sumnavadi et al. 1990].

The third wave of the epidemic was seen in sexually-active heterosexual men. This was not as explosive as the first two groups (drug users and CSWs), but they played an important role as a bridge population between the core group (female prostitutes) and the general population [Morris et al. 1996]. The HIV infection among non-IDU heterosexual men was first detected at public sexually transmitted disease (STD) clinics in 1988 at a rate of 0.2% (31/20061) [Mangkalaviraj 1990]. By June 1991, male STD patients had a median national provincial HIV rate of 5% and this increased up to 8.5% in June 1994 [Ungchusak et al. 1997a]. In the general population HIV prevalence in men has been monitored using HIV sero-surveillance of military conscripts. In November 1989, 0.5% of 19131 men were HIV-positive (by Western blot) and the rate rose up to a peak of 4.0% in June 1993 [Ungchusak et al. 1997b]. Conscripts from the northern tier of provinces of the northern region have had consistently higher HIV rates than elsewhere. Men aged 21 from the five provinces of Chiang Mai, Chiang Rai, Lampang, Payao, and Phrae (upper north) had an overall rate in November 1990 of 10.3% of the 2100 men tested, compared with 2.4% of 1234 men from the remaining six provinces (lower north) of the northern region [Nopkesorn et al. 1991]. The November 1990 regional rates were 6.2% of 3989 men in the northern region, 3% of 1810 in the southern region, 1.1% of 4743 in the northeastern region and 1.1% of 13730 men in the central region.

From these men HIV infection has been transferred to the general female population, spouses and their newborn children. In 1991 the median provincial rate among women attending public antenatal care clinics was 0.8% and gradually increased to its peak of 2.3% in 1995 [Ungchusak et al.1999].

The main route of HIV infection in Thailand is heterosexual transmission although homosexual men and intravenous drug users were the main groups at the very early period of the epidemic [Weninger et al.1991]. These two risk behaviors are not very common in Thai society. From a behavioral study in randomly selected men aged 15-49 years nationwide, injecting drug use was reported by

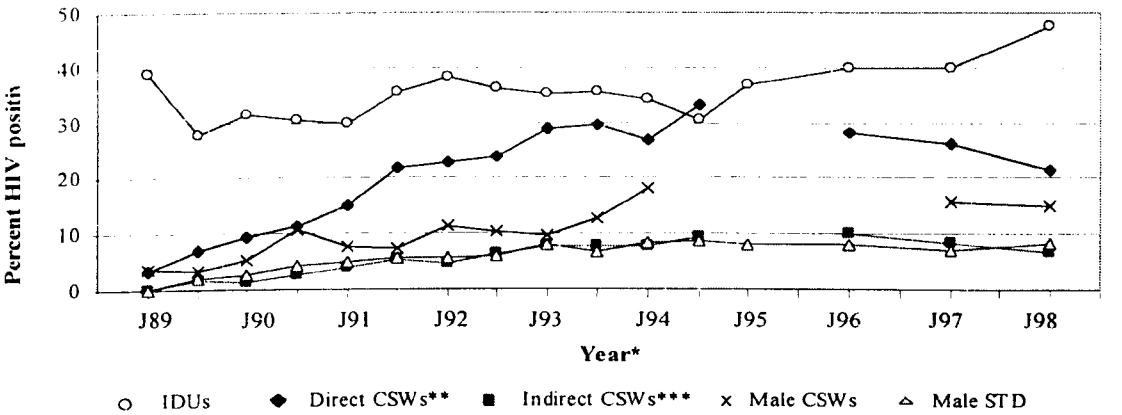
only 0.9% while 3.3% reported ever having had a homosexual experience, and 0.2% were exclusively homosexual [Sittitrai et al. 1991]. A survey among military conscripts reported 1.6% of injecting drug use [Nopkesorn et al.1991]. However, the rate of homosexuality in this group was much higher than in the first study: 26% reported ever having had one or more homosexual encounters. Data from the national sentinel behavior surveillance in factory workers found that about 6% of males aged 15-29 years reported homosexual experiences [Ungchusak et al. 1996b].

From the report of the first 500 AIDS cases in Thailand between 1984-1992, the male to female ratio was 7:1 [Wattanasri et al.1992]. The highest number of cases came from the 25-29 year age group (21.0%), followed by 30-34 years (20.0%), 35-39 years (14.5%) and 20-24 years (12.6%) respectively. The number of cases by region was highest in the northern region (61.5%), followed by central region (29.7%), northeastern region (7.5%) and southern region (1.3%). The province that had the highest number of cases was Chiang Mai 188 cases, Bangkok 110 cases and Chiang Rai 107 cases. The most common route of transmission was heterosexual (76.5%), followed by vertical transmission (10.9%), intravenous drug use (10.3%) and homosexual transmission (1.2%). Compared to the characteristics of AIDS cases in the latest year, 1998-1999, the main difference is the male to female ratio. For the reported AIDS cases in 1999 (the data was up to March 31) this ratio was markedly decreased to 2.5:1 while for the 1998 reported cases it was 2.9:1 [Division of Epidemiology, 1999]. The main route of transmission is still heterosexual (80.8%), followed by vertical transmission (9.1%), intravenous drug use (3.5%) and homosexual transmission (0.1%) in 1999 AIDS cases.

In 1989, the Thai Ministry of Public Health created a sero-sentinel surveillance system for HIV infection in 6 risk groups in 14 provinces and covered all 76 provinces in later years. The initial surveys were performed biannually, in June and December but were switched to annual surveys since 1995, after the improvement of the disease situation [Ungchusak et al.1997a]. These six risk groups comprise intravenous drug users (IDUs), female commercial sex workers (CSW), male commercial sex workers, male clients of public sexually transmitted

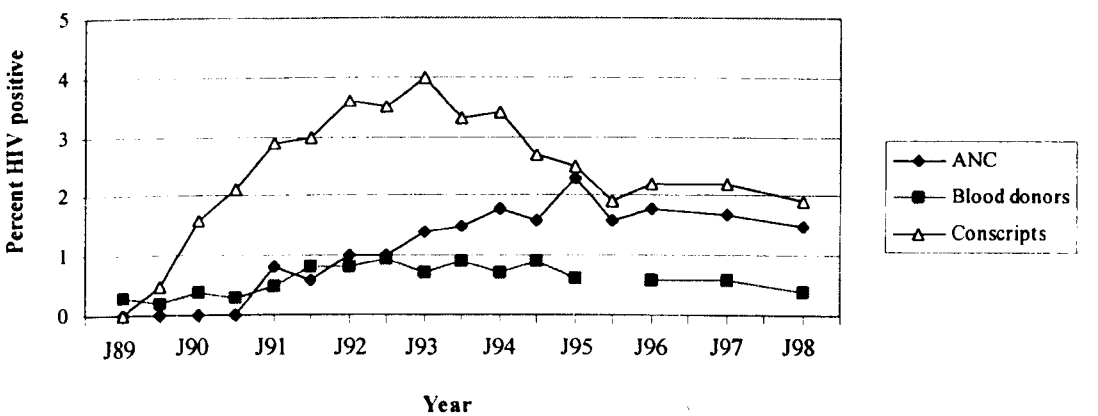
disease (STD) clinics, pregnant women who attended public ante-natal care (ANC) clinics and blood donors. The results of this survey are shown in figure 1. In the same year, the Royal Thai Army initiated another HIV sero-surveillance among 21-year-olds chosen by lottery for conscription in every May and November. This was the first group that directly showed a decrease in HIV prevalence, starting since 1993 (figure 1.1.1, 1.1.2).

Figure 1.1.1: HIV prevalence in various sentinel groups in Thailand in high-risk populations, 1989-1998.



* During 1989-1994 the survey was done twice a year in June and December then changed to be once a year since 1995.
** Sex workers who work in brothels
** * Sex workers who work in other sex establishments such as massage parlours, bars, karaoke. Etc.

Figure 1.1.2: HIV prevalence in various sentinel groups in Thailand in normal or low risk populations, 1989-1998.



Source: Sentinel serosurveillance, Division of Epidemiology Army Institute of Pathology, Royal Thai Army

The 100% condom use campaign of the Thai Ministry of Public Health, instituted in 1991, was claimed as the main factor responsible for this decrease in HIV infection [Rojanapithayakorn et al. 1996, Mastro et al. 1995]. The first sign of the response to this was seen from the downward trend of reported STD cases from the government STD clinics. Since 1994 onward, the HIV infection rates have been slowing down in many risk groups [Ungchusak K, 1999].

TB situation and the control program in Thailand

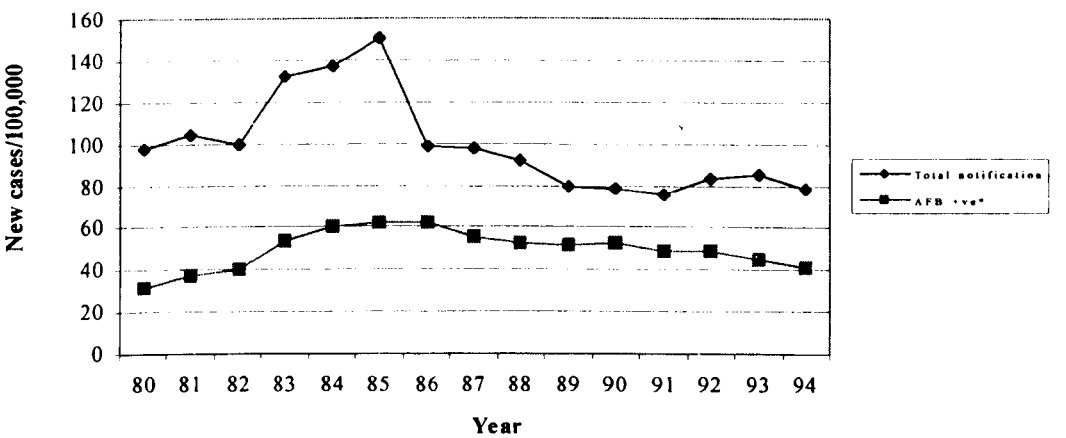
After the end of the Second World War, tuberculosis was recognized by the government as a major public health problem, ranking second only to malaria as one of the most important causes of death in the population [Sriyabhaya et al. 1993]. The tuberculosis control program in Thailand was initiated in 1949. During its early years control measures emphasized BCG vaccination [Payanandana et al.1995]. The real concept of the National Tuberculosis Programme (NTP) was formulated during 1966-1967, following WHO recommendations of 1964 for developing countries. It was agreed that the NTP must be integrated with the network of the existing general health service, in order to attain countrywide coverage, and as a permanent programme acceptable and accessible to the population. However the early control programme which focussed on case finding and treatment by targeting infectious (smear positive) TB patients as the first priority suffered from an immature health infrastructure. Until 1982 when the health infrastructure was strengthened by setting up a large number of hospitals in district level and upgrading hospitals in provincial level, tuberculosis services were implemented through existing health facilities [Payanandana et al.1999]. After a period of field trials short course chemotherapy (SCC) was adapted for use in the NTP in 1983, and the systematic implementation of SCC was begun in 1991 to cover all smear-positive cases detected [Sriyabhaya et al. 1993]. From 1992 SCC has been extended to smear-negative and x-ray cases with suspected active TB.

Studies of annual rate of tuberculosis infection (ARI) were performed four times in Thailand but the most recent in 1987, was considered invalid because the

coverage rate of BCG vaccine in children aged 0-1 year was already very high, at 96.2% [Tuberculosis Division 1992]. For the previous three surveys, the ARI was never less than 2: 3.8% in 1962, 4.9% in 1977 and 2.3% in 1983.

The first national TB epidemiological survey conducted in 1960-1964 revealed an average TB case rate for all age groups of 2100 per 100,000 population as suspected by x-ray and 500 per 100,000 population infectious tuberculosis [Sunakorn et al. 1969]. The prevalence of TB infection was estimated to be 49%. The morbidity and infection rate was higher in urban areas, especially Bangkok, the capital city of the country. From the result of the second epidemiological survey in 1977, it appeared that the trend of tuberculosis morbidity had already declined to 300 per 100,000 population for infectious tuberculosis [Daramas et al. 1981]. Until 1985, after the improvement of health infrastructure throughout the country, the number of new TB cases notified increased to 150 per 100,000 population before markedly decreasing in 1986. The overall decline has continued since then [figure 1.2]. Given the ageing population the age-adjusted rates are likely to show a greater decline than the overall rates shown here. Nevertheless, the situation has been different in the upper north where HIV was most severe. The annual increase in TB case rates in upper North is up to 10%.

Figure 1.2: Trends in new TB case notification rates in Thailand, 1980-1994.



*** Sputum smear positive for acid fast bacilli in at least two microscopic examinations or positive in one microscopic examination plus abnormal chest x-ray or plus positive culture for tuberculosis.**

Source: Tuberculosis Division, Ministry of Public Health

Tuberculosis mortality rate had steadily declined from 31.9 per 100,000 population in 1962 down to 5.9 in 1994, when it still ranked among the top 10 leading causes of death and the first among the infectious diseases of the general population [Bureau of Health Policy and Planning, 1962-1997]. However, during 1995-1996 the mortality started to increase to 7.0 and 7.7 per 100,000 population in 1995 and 1996 respectively [Payanandana et al. 1999].

The demographic distribution of tuberculosis patients also showed some interesting changes. The result of the third tuberculosis prevalence survey during 1991-1992 showed an increased prevalence of tuberculosis in urban areas and Bangkok compared to the second prevalence survey in 1979 although the overall prevalence decreased [Tuberculosis Division 1992]. In terms of age structure, although the results from the third survey still had nearly 60% of patients aged at least 55 years, the data from the annual report 4 years later showed shifting age patterns at the national level [Tuberculosis Division, 1997]. In 1996, the highest proportion came from 25-34 years in males and more than 64 years in females. Detailed analysis by each regional center showed this shifting age pattern in all geographical regions except the northeastern region (where there was highest tuberculosis rate) and one center in the lower north area. However, apart from Bangkok tuberculosis treatment clinic, 3 out of 4 central regional centers, 1 out of 2 southern region centers and the regional center in the upper north area, the remaining 8 regional centers still did not show age shifts in female patients [Tuberculosis Division, 1997].

The data from HIV surveillance in newly diagnosed TB cases which is performed twice a year in May and November since 1989 showed high HIV prevalence in the upper north regional center since it began and this area has consistently had the highest HIV prevalence among TB patients so far [Payanandana et al. 1999]. In this center (located in Chiang Mai province) the HIV prevalence among TB patients increased from 5.4% in 1989 to 45.7% in 1995 and has been stable at between 30-40% since then. The HIV prevalence in TB patients increased in all regional centers but has not exceeded 30% in other centers. At the national level, the prevalence increased from 3.1% in 1989 to a peak of 18.9% in 1996 before decreasing to 16.8% and 15.8% in 1997 and 1998 respectively.

From the evaluation of the World Health Organization, the Tuberculosis Control Programme in Thailand is still considered ineffective [World Health Organization, 1999b]. Despite the introduction of short course therapy in 1986, the treatment is largely unsupervised and fixed drug combinations are not used. National statistics on treatment outcome reveals that the cure rate is currently less than 50%. Recent WHO publicity for World TB Day identified Thailand as among 22 world trouble spots in TB control which have not made progress in implementing Directly Observed Treatment, Short course (DOTS) [Payanandana et al.1999]. The implementation of DOTS was started in 1996 in 8 demonstration districts. The expansion in 1997 was hampered by the country's economic crisis, and then the expansion of DOTS achieved only 44% of the plan. However, the Government gives high priority to the Tuberculosis Control program and even increased the budget in 1998 while many other programmes were severely cut. The achievement of DOTS expansion reached 96% of the plan in 1998 but the quality seems to be decreasing. The smear conversion rate and cure rate decreased from 86% and 80% respectively in 1996 in the demonstration area to 76% and 68% respectively in 1998 [Payanandana et al.1999].

As a result of low cure rates in the past, and with the increasing number of dual infections with HIV, the TB control programme is threatened by the emergence of multi-drug resistant (MDR) strains. Data from the Central Chest Clinic in Bangkok indicate that the percentage of new cases with MDR-TB has risen substantially during recent years [World Health Organization, 1999b]. At the time that the evaluation by WHO was performed, there was not yet systematic surveillance of drug resistance. However, with the support of WHO, there is a "Drug Resistance Surveillance" project since 1996 in some key treatment centers. The result up to October 1998 revealed primary MDR-TB 2.3% at the national level and around 3 times higher in the data from upper north province such as Chiang Rai, 6-7% [Payanandana et al.1999].

Outline of the thesis

We have divided the study into two main parts, a case-control study and modelling. In chapter 2, we describe the overall methods used in the study. Chapters 3-8 describe the cases and the different control groups. The case-control analysis is in chapter 9, including the PAF calculation. The development, structure and results of the model are in chapter 10. The last chapter, chapter 11, discusses the findings and the public health implications.

Table 1: Review of published studies from developing countries which have measured the association of tuberculosis and HIV-1 infection

I) Cohort studies

PLACES/ YEAR	EXPOSED GROUP	NON EXPOSED GROUP	TB OUTCOME	HIV prevalence in population	RESULT	COMMENT
Zaire 1987-1989 (Bruan et al. 1991)	- HIV positive mothers giving birth at a large public hospital (from a perinatal HIV transmission project)	- HIV negative mothers from the same ward - Matched for age (within 2 years), parity and day of admission.	- Proven pulmonary TB (sputum smear positive) or clinically diagnosed TB, including extra-pulmonary TB	6% (in childbearing women)	**All pulmonary TB** **Rate** HIV + women = 3.1/100PY HIV - = 0.12/100PY **Rate ratio** = 26 (5-125) **Proven pulmonary TB** **Rate** HIV + women = 1.2/100PY HIV - = 0.12/100PY **Rate ratio** = 10 (1.5-47)	- Mothers whose babies died were much less motivated to present for follow-up at the first year after enrollment. This group has a higher risk of having depressed immune function and therefore was probably at higher risk of TB. - Diagnostic criteria for TB did not include culture or biopsies, therefore TB cases in this study may have been misclassified with other opportunistic infections. - The design was mixed between retrospective cohort (for the first year after enrolment) and prospective with 2 months follow up (for physical examination) for the next 2 years. From the retrospective study, 80 HIV-positive and 27 HIV negative were lost to follow-up. This could cause bias toward lower estimation of RR because of those HIV-positives who died from TB before the time of data collection.
Kigali Rwanda 1988-1990 (Allen et al. 1992)	- Women aged 17-38 years, attending OPD pediatric and prenatal care at the only community hospital, as part of a prospective cohort for natural history and predictors of HIV infection.	- HIV negative women from the same cohort - Same age restriction with HIV positive group but unmatched	- TB diagnosis based on both clinical and confirmed cases (culture or sputum positive), including extra-pulmonary TB.	32% (1988, in childbearing women)	**Rate** HIV + = 2.4/100PY HIV - = 0.1/100PY **Rate ratio** = 21.8 (5.1-92.9) **Risk** HIV + = 5.0% HIV - = 0.2% **Risk ratio** = 22.9 (5.4-97.6)	- The measure of outcome (TB disease) in this study was more accurate than the previous study but it also included clinical diagnosis plus response to treatment. - Low proportion of loss follow up, 6% (24/425) in HIV-positive and 8% (78/995) in HIV-negative

PLACES/ YEAR	EXPOSED GROUP	NON EXPOSED GROUP	TB OUTCOME	HIV prevalence in population	RESULT	COMMENT
Kigali, Rwanda 1989-1993 (Leroy et al 1995)	- Study groups were enrolled at delivery at the same hospital as the second study. - Inclusion criteria was delivery of a live birth, and living permanently within the city limits.	- HIV negative mothers from the same ward - Matched for maternal age, parity and living in the same city.	- TB diagnosis based on both clinical and bacteriologically confirmed cases (sputum smear positive or culture positive), including extra-pulmonary diseases.	32% (the paper did not provide this information but it is likely to be similar to the above study).	**Rate** HIV + = 2.86/100PY HIV - = 0.16/100PY **RR** = 18.2 (2.4-137.0)	- 176/431 women were lost to clinical follow up before the end of the fourth year. The paper did not separate this group by HIV status.
South Africa 1986-1996 (Wood et al. 2000)	- Adult patients attending HIV clinics of 2 referral hospitals	- TB incidence of general population in the study area was used as a comparison group	- TB diagnosis had 3 levels: definite (culture or autopsy diagnosis), probable (smear or histology) and possible (clinical response to drug therapy), including extra-pulmonary diseases.	7 % (1995, ANC)	**Rate** HIV+ = 10.4/100PY **RR** (by WHO staging of HIV) WHO 1&2 / 3&4 White 140 / 304 Coloured 10.1 / 64.4 African 10.3 / 81.5	- TB was diagnosed by passive case finding. - This study was not initially design to be a cohort study but used a cohort of hospital-based HIV clinics as a study population. Therefore it did not have a system to follow patients who disappeared or died. So, the TB incidence is likely to be under estimated. - This study used the TB incidence rate in the general population for the calculation of RR. This is not adjusted for confounding factors such as age or sex - This study had the highest TB incidence among HIV-positive patients compared to all cohort studies in this review. There is a very high TB case rate in the study area (670/100,000 per annum).

II) Case-control studies with community controls

PLACES/ YEAR	CASE	CONTROL	HIV prevalence in population	RESULT	COMMENT
Rural Malawi 1988-1995 (Glynn et al. 1997)	- Incident cases of TB, pulmonary and extra-pulmonary aged 14 years or more, diagnosed actively and passively - TB was classified as certain or probable (positive culture or smear for pulmonary TB and positive biopsy or culture for extra-pulmonary TB)	- Matched age (within 5 years up to age 35 and within 10 years thereafter), sex and area of residence) - Randomly selected from computer database from the previous survey (1986-1989).	3.0% in 1988/1989 5.3% in 1990/1991 10.8% in 1992/1995 (sampling from general population)	**Matched OR** All types = 7.4 (4.4-12.4) Pulm. AFB+ = 6.3 (3.6-11.0)	- Selection of controls may bias toward underestimate of HIV prevalence since it is based on people who stayed in the study area for a long time (from the previous survey, 1986-1989, to the study period) and did not refuse to be tested. - OR in this study may underestimate the real situation because of very rapid increase of HIV prevalence in controls while there is a time lag from exposure to disease in cases.
Rural Malawi 1989 (Ponnighaus et al. 1991)	- All incident pulmonary TB cases diagnosed in the district and admitted to the district hospital, aged 15 years or more. - Only microscopic or culture positive TB cases were included.	- Randomly selected from computer database (matched to leprosy cases) - Analysis adjusted for age, sex and area	2.4% (from controls)	**OR** Pulmonary = 7.4 (3.3-16.7)	- HIV prevalence in the study area was rising, therefore this OR may be underestimated because of the time lag between HIV infection and TB development in cases. - This OR also may underestimate the real association between TB and HIV because only pulmonary TB was included - 27% of computer-selected controls either could not be found or refused to provide blood
Kenya 1989-90 (Orege et al. 1993)	- Newly diagnosed pulmonary TB in health facilities, age 15-44 years and resident in the study area during the time of study. - Diagnosis of TB was separated into 2 levels: certain (positive repeated smear or culture) and possible (positive only one smear at the time of screening).	- Selected from neighbouring households - Matched for age and sex - Excluded those with history of chronic cough and females who were sexually related to cases	17% (from "matched" controls)	**Matched OR** Overall = 4.9 (2.6-6.8) Male 10-29 = 8.1 (2.9-22.3) 29-49 = 2.6 (0.9-7.5) Female 10-29 = 2.8 (1.1-7.1) 29-49 = 19.6 (2.5-154)	- The OR in this study should be lower than the studies that use all type of TB as cases since HIV-positives TB cases are more likely to be extra-pulmonary and smear negative. - Age grouping in this study was very wide (20 year age band). It can mask or dilute some age affect on the OR, if there is any. - Age range given in the result (10-49 years) was inconsistent with the inclusion criteria (15-44 years).

PLACES/ YEAR	CASE	CONTROL	HIV prevalence in population	RESULT	COMMENT
Tanzania 1991 (Van Den Broek et al. 1993)	- Newly diagnosed TB cases, all types from all 9 hospitals of Mwanza region. Recurrent cases included. - Age 15-54 years and resident in Mwanza region	- General population from stratified cluster sample from urban, roadside settlement and rural area, unmatched	3.4% in rural area 7.2% in roadside 12.1% in urban area	**OR** 15-24 = 5.7 (3.1-10.4) 25-34 = 13.4 (8.8-20.7) 35-44 = 7.3 (4.1-13.2) 45-54 = 2.9 (1.0-7.9) Overall OR = 8.3 (6.4-11.0) Male = 8.9 (6.1-12.9) Female = 7.7 (5.1-11.7)	- Case definition included clinically suspected TB which may lead to inclusion of some HIV-positive cases without TB, and recurrence cases, which may bias the OR towards overestimation if HIV increases the risk of recurrence

III) Other case-control studies

PLACES/ YEAR	CASE	CONTROL	HIV prevalence in population	RESULT	COMMENT
Tanzania 1985-1990 (Van Cleeff and Chum 1995)	- All newly registered TB patients aged more than 16 years - Divided into 4 groups: New smear positive pulmonary TB, new smear negative pulmonary TB, extra-pulmonary and relapse cases.	- Blood donors, donating blood in the same districts as the cases during the study period	3% in 1987 6% in 1990 (estimated for general population aged 15 years or more)	**OR** All TB cases All ages = 11.8 (7.9-18.3) 15-24 = 5.7 (2.1-15.2) 25-34 = 22.6 (11.8-46.2) 35-44 = 13.4 (5.2-34.7) 45+ = 4.2 (1.1-16.2) Smear positive pulmonary TB All ages = 8.1 (4.4-16.3) 15-24 = 6.6 (1.3-31.6) 25-34 = 11.7 (4.2-33.3) 35-44 = 16.3 (3.3-76.7) 45+ = 1.3 (1.3-11.6)	- Cases were not restricted to incident cases. - HIV prevalence in blood donors did not vary significantly by age and sex, indicating that the blood donors controls in this setting were not representative of the general population.
Rural Haiti 1988 (Long et al. 1991)	- All pulmonary TB cases treated in the district hospital in the study area, all ages. - Restricted to smear or culture positive; excluded cases who had received anti-TB drugs within 1 year.	- OPD cases of all diagnoses except active TB or AIDS - Matched for age (±5yrs), sex, residence	3.0% (in general population)	**Matched OR** , 20-39 =15.7 (4.8-50.0) 40-59 = 3.0 (0.8-11.1)	- Cases were did not restricted to only newly diagnosed, so the estimation of OR was most likely to be biased. - Cases limited to pulmonary, bacteriological confirmed, therefore should compare with the studies that used the same type of TB. - Using hospital controls, which is likely to have higher HIV prevalence than the general population.

PLACES/ YEAR	CASE	CONTROL	HIV prevalence in population	RESULT	COMMENT
Zimbabwe 1988-89 (Houston et al. 1994)	- All patients treated for TB in the tuberculosis service responsible for all TB treatment in the study area - Cases included all types of TB, both clinical diagnosis and bacteriologically confirmed (smear or histology but no culture). - No age restriction but the analysis was limited to age 15 years or more.	- Age and sex matched from ANC, hypertension clinic, trauma, employment medical examination - Excluded if known active TB or presented with STD symptoms.	8.8% : first 6 months 10.1% :second 6 months 24.6%: third 6 months (in controls)	**re-calculated OR (unmatched)** 15-24 = 4.8 (2.5-9.4) 25-34 = 7.2 (4.8-10.8) 35-44 = 8.3 (4.3-16.3) 45-54 = 6.0 (2.1-17.9) 55+ = 1.3 (0.5-3.6)	- This study used a matched case-control design but was analysed using risk ratios. We have calculated odds ratios from the data provided but cannot do a matched analysis as properly required - These hospital controls are likely to have higher HIV prevalence than general population (except ANC), therefore it can underestimate the OR - The rapid increase in HIV prevalence among controls might reflect real changes in the HIV situation among control groups, or bias in the selection of controls in each period. - Cases were not restricted to newly diagnosed, and the data showed that relapse cases were more likely to be HIV negative.
Ivory Coast 1989-90 (De Cock et al. 1991)	- All types TB patients in 2 TB treatment centres in Abijan - TB was divided into 3 types: confirmed pulmonary TB (smear positive), presumed pulmonary TB (clinical and radiological) and extra-pulmonary TB.	- Volunteer blood donors	8.5% (in controls)	**OR*** All types = 5.9 (0.5-65.6) Pulmonary = 5.3 (4.3-7.2) Smear positive pulmonary TB 20-29 = 6.45 (4.6-9.1) 30-39 = 5.5 (3.5-8.8) 40-49 = 2.5 (1.1-5.9) 50-59 = 3.6 (0.4-81) * All ORs in this table are crude OR, calculated by using available data in the paper, grouping HIV1 and HIV1&2 together	- Not limited to newly diagnosed cases of TB - Blood donors are likely to bias toward under-estimation of HIV prevalence

PLACES/ YEAR	CASE	CONTROL	HIV prevalence in population	RESULT	COMMENT
Kenya 1990-1994 (Van Gorkom et al. 1999)	- New TB cases (all types) and smear positive relapse cases from the district TB registers. - Age 15 years or more - Exclude refugees, and patients registered as transfer in, treatment resumed or failure.	- ANC patients in the same district as cases.	3.5% in 1990 5.7% in 1993 (estimated adult HIV seroprevalence)	**OR** = 5.58 (4.5-6.92) (- calculated by using HIV prevalence in female TB cases aged 15-44 years and ANC - OR was not adjusted for age due to lack of data)	- This OR was not adjusted for age. ANC attenders are likely to be younger than TB patients - ANC attenders tend to have lower HIV prevalence than the general population of the same age - Control group probably had an urban bias (within districts) - Rising trend of HIV prevalence in general population - Not restricted to incident TB cases
Tanzania 1991-1993 (Chum et al. 1996)	- All new TB (all types) and relapse cases (smear positive pulmonary TB), aged 15 years or more. - Each region, all over the country collected data for 6 months during the 3 year study period. - Patients were asked to volunteer to take part in the study. - For each pulmonary TB case, one sputum specimen was obtained at the time of enrolment.	- Data from blood donors throughout the country during 1991-1993.	4.3% in 1992 (estimated HIV prevalence in general population)	**RR** * New smear positive cases = 7.1 (6.6-7.5) with no marked difference by sex RR for age 25-34 years male = 9.6 female = 9.3 significantly higher than other age groups * it should be OR rather than RR	- The relative risk was presented not the odds ratio and insufficient data were presented to allow re-calculation - The proportion of HIV testing among cases varied from 28-83% (average 52%)in each region which may bias the HIV prevalence. - Only one sputum examination for pulmonary TB should cause lower yield of smear positive cases, therefore a higher chance of misclassification. - Cases were not restricted to incident cases.

PLACES/ YEAR	CASE	CONTROL	HIV prevalence in population	RESULT	COMMENT
South Africa, gold miner population 1993-96 (Corbett et al. 1999)	- First episode of culture positive TB disease, attending the study hospital, which provides tertiary care for a gold mining company. - Excluded patients who had previously been HIV tested.	- Admitted with trauma or surgical conditions unrelated to HIV infection, in the same hospital as cases - Had HIV test record - Excluded patients who previously had been HIV tested.	5.6% in controls	**OR** Adjusted, all years = 4.5 (2.12-9.57) OR by year* 1993 = 1.11 1994 = 2.23 1995 = 3.46 1996 = 3.29 (*calculated from available data in the paper, unadjusted)	- Cases were restricted to culture positive - Control were selected only from those patients who had HIV results, which probably differed from other patients - The use of hospital controls, especially from ill people, is likely to overestimate the HIV prevalence. - HIV prevalence in population was rising fast, leading to under-estimation of the OR - The restriction to men who had not previously been HIV tested seems to introduce selection bias away from known HIV positive men, causing lower estimates of HIV prevalence in both case and control groups.

Chapter 2: Study outline

Purpose of the study

Chiang Rai province has been one of the areas most effected by the HIV epidemic in Thailand. The objective of our study was to assess the strength of association between TB and HIV in this province and to explore how the pattern of this association varies by year, age and sex; to use this to calculate the population attributable fraction in the study area by year; and to predict the future burden of TB attributable to the HIV epidemic.

Study Setting

Chiang Rai Province and the HIV/AIDS situation

Chiang Rai province is in the northernmost area of Thailand, 829 kilometres from Bangkok, close to the Myanmar and Laos borders, in an area known as the Golden Triangle. The population was about 1.2 million in 1996 [Chiang Rai Provincial Public Health Office, 1997]. It is claimed to have the largest number of different ethnic groups in the country, both from the mixture of sub-ethnic local Thai people, many groups of hill tribes, and people of many nationalities. Chiang Rai is one of the most popular tourist places in the northern region, next to Chiang Mai, and was also the main route of opium exports, in the past, from the Golden triangle.

In Chiang Rai, like other provinces in Thailand, every district has at least one public hospital. These are generally small (10 to 30 beds with 2-5 medical doctors) except for some large districts in which the hospital can be as big as 120 beds. Every province has a Muang district, the central urban district that contains almost all of the government main offices. This usually has the largest hospital in the province as a referral center for other smaller districts. In general the public hospital in Muang district is called the provincial hospital, and those hospitals in other districts are called community hospitals. Hospitals that are larger than 500 beds are called regional

hospitals. For Chiang Rai, the main hospital in Muang district is the regional hospital with 720 beds. There are 4 private hospitals in Chiang Rai, of which 2 are located in Muang district [Chiang Rai Provincial Public Health Office, 1997].

The first HIV case in Chiang Rai was reported in 1988 [Division of Epidemiology,1989b] and an explosive epidemic among intravenous drug users (IDUs) and female commercial sex workers (CSWs) was found only a year later (HIV prevalence 60.7% in IDUs and 36.7% in CSWs in 1989) [Limpakarnjanarat K, 1991]. In 1990, the data from the HIV sero-sentinel surveillance in this province showed very high prevalence in female CSWs, up to 54.0%. As in other parts of the country, this group is claimed to be a major factor in spread of HIV to the population, especially to young men [Weninger B, et al. 1991]. In Chiang Rai province the HIV prevalence in military conscripts to the Royal Thai Army (RTA) peaked in 1993 at 16.5% and then declined rapidly, followed by a decline in HIV prevalence measured in pregnant women after 1994 [Kilmarx P, et al. 2000]. The result of HIV sero-sentinel surveillance in 1998 showed HIV prevalence equal to 1.14% in blood donors, 30.0% in IDUs, 5.39% in antenatal clinic (ANC) attenders, 5.0% in male clients of STD clinic, 33.33% in brothel-based CSWs and 9.96% in non-brothel-based CSWs [Division of Epidemiology, 1999].

This study uses data collected in Chiang Rai Hospital from 1990-1998: HIV testing in most of the patient groups studied started in 1990. The HIV antibody testing in Chiang Rai hospital began first among blood donors in 1989, following national policies [Sawanpanyalert, 1996a]. In late 1989 HIV testing was started in TB patients, and from 1990 all ANC and delivery patients are routinely HIV tested. In all surgical wards (including trauma and orthopedic wards), HIV tests are performed for those who will undergo surgery, though after the Thai economic crisis in 1997, the universal testing in surgical wards was not done, and it was restricted to those suspected to be HIV infected [Dr Supak, personal communication]. In general, each serum specimen was tested for HIV antibody by two different types of enzyme immunoassay (EIA). During the study period the EIA from many different manufacturers were used in Chiang Rai hospital [Bunnell et al. 1999].

Outline of Study design

Study design

A case-control study was conducted to compare HIV prevalence in TB patients and various control groups overtime.

Cases were all newly diagnosed TB patients aged at least 15 years who resided in Chiang Rai province. Information was collected on the site of TB (pulmonary or extra-pulmonary) and sputum smear results. Controls were groups of patients who are likely to be similar to the general population: blood donors, antenatal clinic attenders, delivery patients, surgical patients and military conscripts. Information on age, gender, place of residence and some necessary information in each set of data were collected (such as gravida in ANC and delivery patients or number of donations in blood donors, etc.). The full characterisitics of each dataset are considered in detail below.

Computerised data for various groups of patients in Chiang Rai hospital were extracted from 1990-1998 where available. These were TB cases, blood donors and delivery patients. For the other groups of patients information was extracted from the original ward registers and data entry was performed. Data were separately keyed in by 2 different data entry clerks. Validation of data was performed by the double entry program in Epi Info version 6.2 and cross-tabulation of related variables.

In addition to the data from Chiang Rai hospital, the individual records from military conscripts who stayed mainly in Chiang Rai before the year of their conscription were extracted from the Royal Thai Army. In all provinces of Thailand, there are HIV surveys among 21 year-old men who are recruited to join as military conscripts [Mason et al. 1995, Sirisopana et al. 1996]. The process of recruitment uses a lottery and all those selected are tested for serum HIV antibodies.

Outline of Statistical methods

Data were analysed using STATA 5.0 software and Excel. Initial analyses were carried out to explore the particular biases likely to be present among the cases and in each control group and to make decisions about the final case and control groups to be compared. (For example, policies on who to test varied over time: this is discussed below.) HIV prevalence in each control group were compared in 5 year age bands for each year. In general, any unknown data were treated by exclusion from the analysis. However, in case-control analysis, the cases that had unknown HIV status were treated as HIV negative. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association of HIV and TB were calculated for each year and age group using each control group. Logistic regression was used for multivariate analysis and to explore any interaction of age with the association between HIV and TB. The variables included in the model were age, year of diagnosis and area of residence (urban/rural). Separate analyses were conducted for men and women.

The proportion of TB attributable to HIV infection (the population attributable fraction, PAF) was calculated by using the formula: $PAF = (RR-1)\, p'/RR$ when p' is the prevalence of HIV infection in TB cases. However, because our study design was a case-control study, we used OR as an estimate of the RR. This was done both overall and weighted by age. Estimates from this simple formula may, however, be misleading. In Thailand the HIV prevalence in the population increased and decreased very rapidly over time. In this dynamic situation the proportion of HIV infected individuals with different levels of immunosuppression will also have changed rapidly over time. A model was developed to calculate the proportion of HIV infected individuals immunosuppressed in each year and hence to recalculate the PAFs and to predict the future burden of TB (assuming the HIV epidemic stays at a low level).

In the following sections I will describe details of each of the study groups (the TB cases and each group of controls). For each I will describe the source of the data, HIV prevalence and trends, and any limitations of the data set, and decisions on which parts of the data to include in the case control analysis. This is followed by an analysis and discussion of the case-control study. The final part models the HIV epidemic in Chiang Rai to re-estimate the PAF.

Chapter 3: Tuberculosis data

Methods

Information on tuberculosis patients in Chiang Rai Province has been collected as part of a provincial database. This was collected from all public hospitals in the province since 1987, as an initiative of the tuberculosis zonal center in Chiang Mai (TB 10th), which covers Chiang Rai. Since mid-1995 the TB 10th stopped collecting individual data from all provinces. The Research Institute of Tuberculosis (RIT) from Japan has been researching drug resistance of tuberculosis from this provincial database. They have continued the data collection from 1995 until now. Since 1996, RIT has supported the cost of HIV testing for all smear positive TB [Research Institute of Tuberculosis , 1998]. Some other TB cases are also HIV tested.

In Chiang Rai hospital, HIV testing has been more consistent. Confidential HIV antibody testing was begun in almost all newly diagnosed TB patients since October 1989. Almost all TB patients have been tested since then, and there has been supported by RIT since 1996. The test kits used for determination of HIV antibody are Enzygnost, Anti-HIV1/HIV2 (Behring, Germany) or Genelavia Mixt (Sanofi Diagnostics Pasteur, France). The former test is based on synthetically-produced HIV peptides which represent glycoprotein (gp) 41 for HIV-1 and gp36 for HIV-2 . The latter is developed from purified antigens (gp160), recombinant protein, and peptide mimicking the immunodominant epitopes of the HIV-1 and HIV-2. The two tests are used interchangably. Two repeated positive results by either kit are considered "HIV-positive." Usually no immunoblotting confirmation is done except when the serum is positive with only one of the tests.

In Chiang Rai hospital, computerised data for TB patients have been collected since 1988, by the Department of Social and Preventive Medicine. However, the data collection of Chiang Rai provincial database (by RIT personnel) does not use the existing computerized data but collects data from the registry of TB patients logbook from the Department of Social and Preventive Medicine and the sputum smear logbook in the laboratory room. The data are validated and counterchecked between

these two sources. The patients' name and day of treatment are checked with other hospitals in Chiang Rai province in order to identify those cases who have already received treatment but come to Chiang Rai hospital stating that they are new cases. Timing of data entry is after patients have received a full course of treatment (so should be at least 6 months later, except for those who default or die).

The variables collected are hospital name, gender, age, body weight, address, ethnicity, TB site, CXR, patient type (previous TB, new, relapse, etc.), transfer hospital, AFB status, HIV antibody test result, DOTS, register date, year, regimen, AFB result at 2 months, 5 months and at the end of treatment, outcome, discharge date, final status (dead or alive), and if dead, the date and cause of death.

Results

From 1987 –1998 data was collected on 13,579 TB patients. Most hospitals started collecting this data since 1987, except for 5 new hospitals that were not yet opened at that time. The last hospital started collecting their data in 1996.

The ratio of males to females was 2.1:1. Median age of this group was 40 years (range 1-98 years). Most TB patients (84.0%) reside in Chiang Rai province, while the second highest proportion come from neighboring countries (Myanmar 3.2%, Laos 1.1%) and Payao, the adjacent province (1.9%). From all of these TB cases, 43.7% came from the provincial hospital as shown in table 3.1.

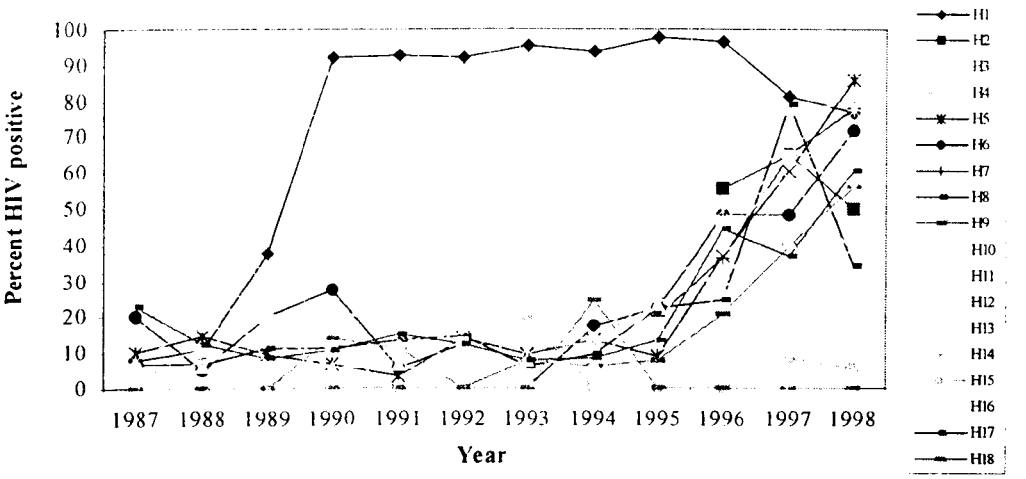
Table 3.1: Number of TB cases in all public hospitals in Chiang Rai from 1987 to 1998.

Hospital (Number of bed)	TB cases	HIV Negative	HIV Positive	Unknown HIV result
1. Chiang Rai hospital (759)	5935	2468	2236	1231 (20.7%)
2. Mae Lao (10)	64	16	20	28 (43.8%)
3. Wieng Chiang Rung (30)	109	25	29	55 (50.5%)
4. Somdej-pra-sang-kla-raj Wieng Chai (10)	25	0	7	18 (72.0%)
5. Tueng (60)	644	64	117	463 (71.9%)
6. Praya Mengrai (30)	248	16	66	166 (66.9%)
7. Khuntan (30)	90	22	30	38 (42.2%)
8. Chaing Khong (60)	606	27	66	513 (84.7%)
9. Wieng Kaen (30)	122	9	16	97 (79.5%)
10.Phan (90)	1152	101	227	824 (71.5%)
11.Pa Dad (30)	154	15	27	112 (72.7%)
12.Mae Saruay (30)	465	42	56	367 (78.9%)
13.Wieng Pa Pao (60)	438	63	97	278 (63.5%)
14.Mae Jan (90)	1622	176	338	1108 (68.3%)
15.Mae Pha Luang (10)	223	7	5	211 (94.6%)
16.Mae Sai (90)	1098	102	53	943 (85.8%)
17.Chiang San (30)	572	56	97	419 (73.3%)
18.TB 10th *	12	1	2	9 (75.0%)
Total	**13579**	**3210**	**3489**	**6880**

* These data come from the tuberculosis zonal center 10th in Chiang Mai.

For most hospitals, HIV testing was not widely performed during the first 7-8 years. The proportion of TB patients HIV tested in most hospitals started to exceed 50% only after 1996. In contrast, in the provincial hospital, where almost all TB patients were tested for HIV antibody since 1990, the proportion HIV tested began decreasing since 1997, as shown in figure 3.1.

Figure 3.1: Proportion of HIV testing in each public hospital in Chiang Rai by year, 1987-1998. (Hospital number as in table 3.1)



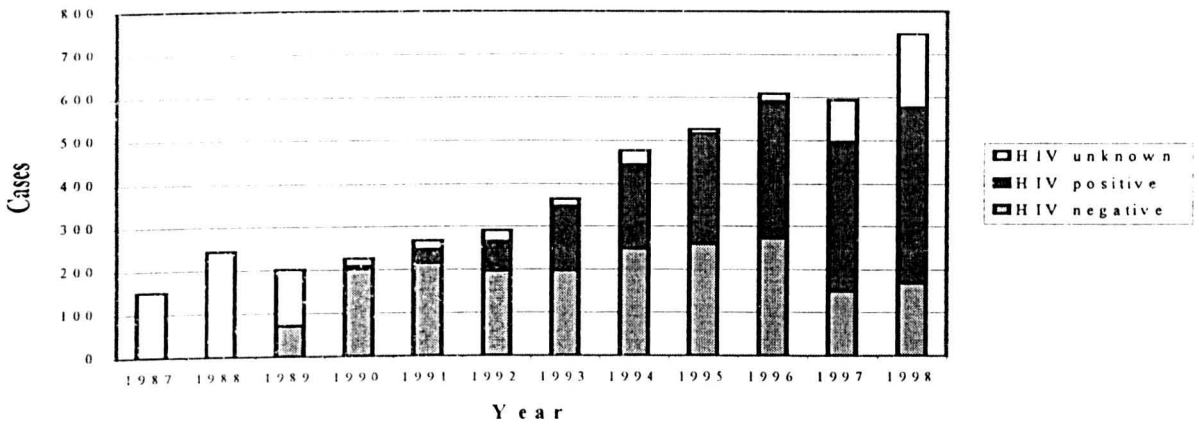
Because of the very high proportion of unknown HIV results in district hospitals, especially before 1997, HIV testing is likely to have been selected for those who were suspected to be HIV positive. These data are therefore likely to be biased and any trends in HIV infection in these hospitals cannot be measured. Further detailed analysis is therefore restricted to the TB patients in Chiang Rai hospital (provincial hospital) since 1990-1998. However, the HIV prevalence in TB patients of those hospitals which had not too few cases and a low proportion of unknown HIV results, are compared with the HIV prevalence in Chiang Rai hospital, to examine the extent to which the results from Chiang Rai hospital are likely to be representative (see below).

1. Chiang Rai hospital

From 1987-1998 there were a total of 5935 TB cases. From this number 5445 (91.7 %) lived in Chiang Rai province. Of these, 5319 (97.7%) were aged at least 15 years and 4260 (80.1%) were new patients. In addition, during 1987-1994 there were 435 cases that were most likely to be new cases but lacked confirmation.

When we combined the number of these two categories ("new cases" and "likely to be new cases") and stratified by year, we saw that the number of cases increased since 1992 (figure 3.2).

Figure 3.2: Number of new TB cases in Chiang Rai hospital from 1987-1998 (n=4695 cases)



Because systematic HIV testing began after 1989, the first 3 years (1987-1989) have been excluded from further analysis. In addition, we excluded those 435 of "not confirmed" new cases from the analysis. From figure 3.2, as mentioned earlier, it is clear that the proportion of unknown HIV results increased in the last 2 years. This is mainly due to decreased testing of older patients in those years, especially women (Figure 3.3.1 and 3.3.2).

Figure 3.3.1: Proportion of unknown HIV results in female TB patients, Chiang Rai hospital, by age group, 1990-1998

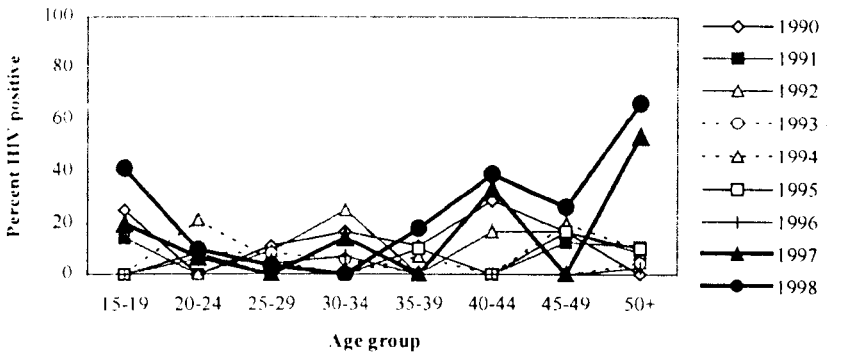
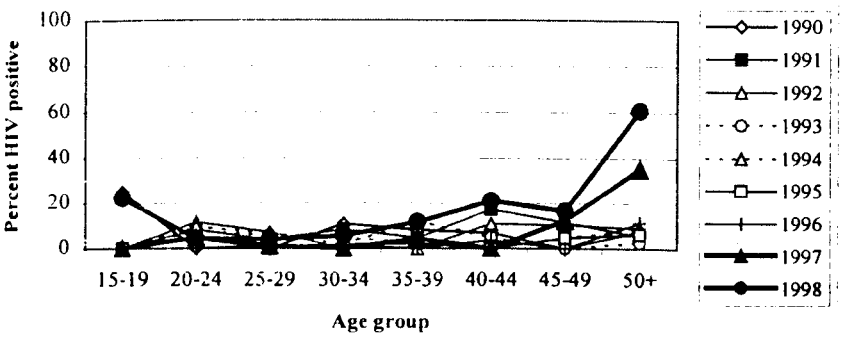


Figure 3.3.2: Proportion of unknown HIV results in male TB patients, Chiang Rai hospital, by age group, 1990-1998



Initially the proportion of TB cases classified as pulmonary was around 90% but this proportion has decreased each year after 1993 (table 3.2).

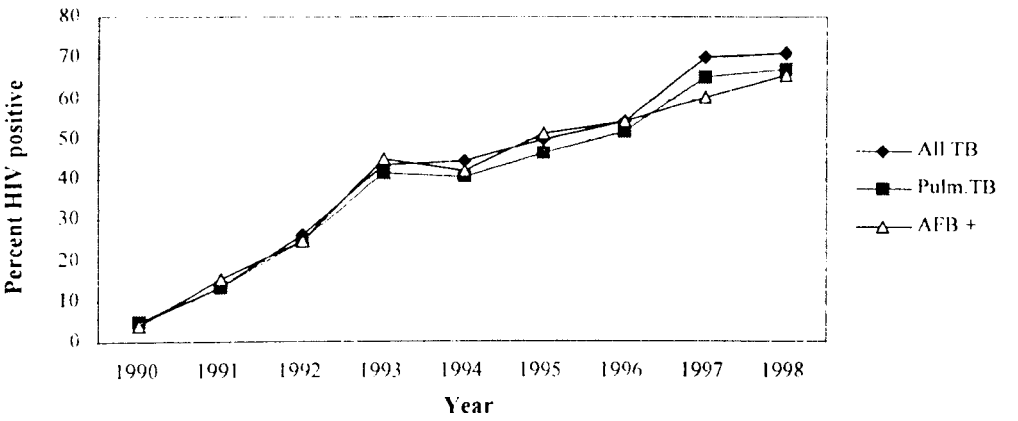
Table 3.2: Proportion of pulmonary TB from all types of TB cases in Chiang Rai hospital, from 1990-1998.

Year	% Pulmonary TB
1990	89.4% (177/198)
1991	89.6% (207/231)
1992	90.3% (262/290)
1993	93.1% (337/362)
1994	85.3% (405/475)
1995	83.3% (438/526)
1996	81.1% (493/608)
1997	76.3% (453/594)
1998	66.8% (499/747)
Total	**81.2% (3271/4031)**

For those who were diagnosed as having pulmonary TB, about 50% were sputum smear (acid fast bacilli, AFB) positive. This proportion has also varied slightly in each year but with a less clear trend.

For all types of TB cases in Chiang Rai hospital, the proportion HIV positive increased sharply since 1991. HIV prevalence among all types of TB cases, pulmonary TB cases and those who were smear positive, were very similar, especially in the earlier years (figure 3.4).

Figure 3.4: HIV prevalence in all types of TB cases, all pulmonary TB cases and AFB positive pulmonary cases, by year of treatment



Overall, the male to female ratio in TB cases was 2.5:1. The HIV prevalence in females was 44.3% (441/996) compared to 51.1% (1347/2635) in males, though this varied by age. When we stratified the HIV prevalence in 5-year age groups we found that the peak age of HIV prevalence among both genders changed overtime. In males the peak of HIV prevalence started with 20-24 years in 1990 and then moved to 25-29 in most of the years before further moving to 30-34 age group in the last year, 1998 (table 3.3). For females a similar pattern is seen but because there were smaller numbers of cases, the trend of shifting age groups was less clear compared to the male data. In general, the peak of female HIV prevalence was in age 20-24 years (table 3.4). For both genders there were very few cases in the 15-19 age group, even in the later years when the overall number of cases was much increased.

Table 3.3: HIV prevalence in male TB patients in Chiang Rai hospital, by age group and year.

Age group	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50+	Total
1990	0% (0/2)	57.1% (4/7)	11.1% (1/9)	9.1% (1/11)	25.0% (2/8)	0% (0/10)	0% (0/11)	0% (0/68)	**6.4% (8/126)**
1991	0% (0/3)	22.2% (2/9)	41.2% (7/17)	43.8% (7/16)	20% (3/15)	14.3% (2/14)	14.3 (1/7)	6.4% (5/78)	**17.0% (27/159)**
1992	16.7% (1/6)	46.7% (7/15)	54.6% (12/22)	69.2% (18/26)	38.5% (5/13)	14.3% (2/14)	31.3% (5/16)	9.1% (8/88)	**29.0% (58/200)**
1993	50% (2/4)	76.2% (16/21)	78.6% (33/42)	57.8% (26/45)	68.0% (17/25)	41.2% (7/17)	16.7% (2/12)	16.9% (15/89)	**46.3% (118/255)**
1994	28.6% (2/7)	80.8% (21/26)	76.2% (48/63)	76.8% (43/56)	75.0% (21/28)	51.4% (18/35)	35.3% (6/17)	10.9% (12/110)	**50.0% (171/342)**
1995	50.0% (1/2)	63.0% (17/27)	80.5% (62/77)	78.7% (48/61)	62.8% (27/43)	50.0% (21/42)	37.5% (9/24)	17.3% (18/104)	**53.4% (203/380)**
1996	25.0% (2/8)	61.5% (24/39)	84.8% (78/92)	76.4% (55/72)	60.4% (32/53)	41.4% (12/29)	47.6% (10/21)	12.2% (12/99)	**54.5% (225/413)**
1997	0% (0/5)	73.7% (28/38)	87.9% (80/91)	85.9% (61/71)	81.8% (45/55)	57.7% (15/26)	42.1% (8/19)	25.0% (15/60)	**69.0% (252/365)**
1998	28.6% (2/7)	80.6% (29/36)	86.7% (65/75)	90.0% (99/110)	77.6% (45/58)	60.0% (24/40)	56.5% (13/23)	18.2% (8/44)	**72.5% (285/393)**

Table 3.4: HIV prevalence in female TB patients in Chiang Rai hospital, by age group and year.

Age group	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50+	Total
1990	0% (0/2)	0% (0/2)	0% (0/6)	0% (0/5)	0% (0/7)	0% (0/3)	0% (0/4)	0% (0/25)	**0% (0/54)**
1991	0% (0/6)	0% (0/4)	0% (0/6)	0% (0/2)	25.0% (1/4)	0% (0/2)	0% (0/5)	0% (0/23)	**1.9% (1/52)**
1992	33.3% (1/3)	50.0% (3/6)	37.5% (3/8)	20.0% (1/5)	16.7% (1/6)	0% (0/5)	20% (1/5)	3.7% (1/27)	**16.9% (11/65)**
1993	75% (3/4)	66.7% (12/18)	70.0% (7/10)	33.3% (5/15)	60% (3/5)	33.3% (1/3)	50.0% (1/2)	2.9% (1/34)	**36.3% (33/91)**
1994	60% (3/5)	45.5% (5/11)	47.1% (8/17)	42.9% (6/14)	18.2% (2/11)	0% (0/3)	25% (1/4)	2.6% (1/38)	**25.2% (26/103)**
1995	20.0% (1/5)	70.4% (19/27)	60.0% (15/25)	66.7% (10/15)	36.4% (4/11)	37.5% (3/8)	0% (0/6)	7.9% (3/38)	**40.7% (55/135)**
1996	33.3% (3/9)	77.5% (31/40)	77.5% (31/40)	66.7% (10/15)	58.3% (7/12)	37.5% (6/16)	42.9% (3/7)	10.0% (4/40)	**53.1% (95/179)**
1997	40% (2/5)	83.3% (25/30)	85.4% (35/41)	86.7% (13/15)	72.7% (8/11)	85.7% (6/7)	40.0% (2/5)	26.3% (5/19)	**72.2% (96/133)**
1998	44.4% (4/9)	85.3% (29/34)	75.0% (36/48)	81.8% (27/33)	80.0% (12/15)	36.4% (4/11)	45.5% (5/11)	30.4% (7/23)	**67.4% (124/184)**

This current age distribution of TB patients is very different to the picture of TB cases before the epidemic of HIV infection. For those TB cases with HIV negative results, almost half of them were aged 50 years or older.

2. Other hospitals

For the other 16 district hospitals (ie excluding Chiang Rai hospital and the tuberculosis zonal center 10th in Chiang Mai) there were few HIV data available before 1997. Moreover many of the hospitals are small and therefore have few TB cases each year. For comparison with the data from Chiang Rai hospital we have selected only those that had a total of more than 10 TB cases for a particular year and gender, and for which the proportion of unknown HIV results was not more than 35%. We found that none of the hospitals met our criteria for the data in 1997. This analysis, therefore, is limited to 1998 only.

Table 3.5: HIV prevalence in selected district hospitals in Chiang Rai province in 1998, for age 15-39 years

	CR hospital (1)	Teung (5)	Praya Mengrai (6)	Wieng Pa Pao (13)	Mae Jan (14)
Male					
- HIV (%)	83.9 (240/286)	90.0 (9/10)	87.5 (14/16)	84.6 (11/13)	88.2 (30/34)
- Unk. (%)	6.2 (19/305)	16.7 (2/12)	5.9 (1/17)	7.1 (1/14)	15.0 (6/40)
Female					
- HIV (%)	77.7 (108/139)	83.3 (5/6)	88.9 (8/9)	87.5 (7/8)	71.4 (15/21)
- Unk. (%)	10.9 (17/156)	0 (0/6)	10.0 (1/10)	11.1 (1/9)	12.5 (3/24)

In addition, Phan hospital had a high proportion of unknown HIV results for age group 35-39 years but the total number in age group 15-34 years was still higher than 10. So we decided to compare HIV prevalence of Phan hospital with Chiang Rai hospital for the age group 15-34 years.

Table 3.6: HIV prevalence in Phan hospital in 1998, for age 15-34 years

	CR hospital (1)	Phan (10)
Male		
- HIV (%)	85.5 (195/228)	87.5 (21/24)
- Unk. (%)	4.2 (10/238)	22.6 (7/31)
Female		
- HIV (%)	77.4 (96/124)	84.2 (16/19)
- Unk. (%)	10.1 (14/138)	9.5 (2/21)

These results, though limited, suggest that the very high HIV prevalence measured in TB patients in Chiang Rai Hospital in 1998 was similar to that measured elsewhere in the districts.

Discussion

Chiang Rai province is the only province in Thailand that has HIV testing in TB patients for all public hospitals. Although there are 4 private hospitals in the province, very few TB patients have their full course treatment in the private sector, due to the long period of high cost treatment. Among all public hospitals, Chiang Rai hospital is the most complete source of TB and HIV data in Chiang Rai. Its many years of HIV testing in almost all of the TB cases, together with the large number of TB patients make it an interesting place to study the HIV dynamic over time in TB patients.

Since 1997, Thailand experienced a severe economic crisis, which led to the increased proportion of patients that were not HIV tested. From the characteristics of those who were not tested (higher proportion of women and elderly) it is likely that the doctors selected to test only high risk persons, particularly young and male gender. Therefore the HIV prevalence in TB patients for the last 2 years is likely to be biased towards overestimation, especially in patients older than 35 years old and also 15-19 years. From the characteristic of this "unknown HIV" cases, we believe that most of them were HIV negative. The data that support our hypothesis was the trend of new TB cases in Chiang Rai hospital by year, stratified by HIV status (figure 3.2). When we grouped unknown HIV cases as HIV negative, it gives relatively stable trend among HIV negative TB cases (there is no reason for the decreased trend among HIV negative-TB cases, which will happen if we separate some part of unknown HIV cases into HIV positive group). In addition, the data from an on going study about mortality rate in 6-month cohort analysis in AFB-positive pulmonary TB cases in Chaing Rai province during 1995-1999 also supports our hypothesis. The case fatality ratio (CFR) of HIV positive, HIV negative and HIV unknown in male patients were 49.6%, 14.1%, and 18.3% respectively. For female, these figures were 49.0%, 11.6% and 11.2% [Yanai H, unpublished data].

During this 9 year study period, we are not aware of any major changes in the method of diagnosis or of doctors who were responsible for TB treatment. Therefore we assume that the decreased proportion of pulmonary TB in the later years should be mainly due to the effect of HIV [Sepkowitz, 1995].

Because Chiang Rai hospital functions as a main referral center for other districts and neighboring provinces, it has good facilities for both diagnosis and treatment. Therefore it tends to receive any complicated patients such as extra-pulmonary TB or suspected HIV infection with TB cases. Moreover, it is possible that patients who have already been treated somewhere else can go to Chiang Rai hospital as new cases (by hiding the fact that they were already treated). Although this problem was minimized by the validation of patient records in other hospitals from the provincial database, these did not cover treatment outside the province or in private clinics. Therefore our high HIV prevalence in TB patients could be partly affected by referral bias toward overestimation.

However from our results, the HIV prevalence in TB patients from other hospitals were not much different from the HIV prevalence in Chiang Rai hospital. Therefore, the hypothesis that Chiang Rai hospital, which is located in the most urban area of the province should have the highest HIV prevalence was not confirmed, and any referral bias in Chiang Rai hospital in new TB patients is unlikely to have been important.

For deciding which type of TB should be the primary interest of our analysis, we had to judge between increasing specificity of the study by using the most certain TB cases (AFB positive, pulmonary TB) and loss of power of the study by dropping a large proportion of cases from the analysis. We were concerned that including extra pulmonary TB patients might bias the study because some HIV related opportunistic infections can be misdiagnosed as extra pulmonary TB. This would lead to an overestimation of HIV prevalence in TB patients. However, in this setting we found that the HIV prevalence of all type TB patients was very close to the HIV prevalence of pulmonary TB cases (figure 3.4). Therefore, we decided to use all types of TB patients as the main focus of our analysis.

So, in summary, the TB cases included in further analyses were:

- New TB patients (all types) in Chiang Rai hospital between 1990 and 1998
- Aged at least 15 years
- Resident in Chiang Rai province

The most complete data were available for those aged 20-39.

Chapter 4: Military conscripts

Methods

The data come from routine surveillance of the Royal Thai Army among young men who were conscripted to the army. The ages of these men ranged from 19-29 years, and varied in each year, but most of them (more than 90%) were aged 21 years. In our data, we selected only those Thai men who spent most of their time in Chiang Rai during the 2 years before conscription. In general, men become eligible for conscription on their 21st birthday and are chosen by a random lottery system based on legal registration address. Conscription is conducted annually in April, with induction taking place semi-annually in May and November [Celentano et al. 2000]. Exemption was granted for university students, skilled workers, handicapped individuals, certain religious personnel, individuals who completed a course of military instruction (offered in most secondary schools) and individuals who participate in alternative military service [Celentano et al. 1995, Mason et al. 1995]. Therefore these conscripts represent socioeconomically the lower four-fifths or so of the nation's men aged 21 years [Weninger et al 1991]. However, HIV infection, drug use and sexual orientation were not grounds for exemption.

Within a few weeks of their conscription, each man gave a serum specimen, which was tested for HIV by enzyme-linked immunosorbent assay using standardized methods and licensed commercial reagents (Behring Co Ltd, Somerville, New Jersey, or Organon-Teknica Co, Durham, North Carolina). Specimens reacting positive on initial testing were retested in duplicate by enzyme-linked immunosorbent assay and confirmed with Western blot using commercially licensed reagents (Biotech-Dupont Inc, Wilmington, Delaware). Serum samples were also tested for syphilis antibodies using a licensed assay (VDRL test) and standard methods [Nelson et al. 1993].

Since 1991information on age, education level, marital status, place of conscription, place of residence during 2 years before enrollment and place of birth have been collected and the reports are analyzed by the time of induction (May or November round) to the Royal Thai Army.

Results

From 1991-1998 the total number of conscripts who spent most of the previous 2 years before their enrolment in Chiang Rai was 6340. The number enrolled at each time was remarkably varied as in table 4.1.

Table 4.1: Number of conscripts who lived in Chiang Rai during 2 years before the time of enrolment in each period.

Year	May	November
1991	-	587
1992	565	543
1993	401	-*
1994	-*	448
1995	155	707
1996	136	857
1997	135	965
1998	142	699

*No HIV testing was performed due to budget restraints for these 2 rounds.

95% of the conscripts were 21 years old. 29 individuals aged more than 24 years were excluded, leaving 6310.

For our analysis of the trend of HIV prevalence, we decided to group both May and November rounds together. The result showed highest prevalence in 1992 and followed by abrupt decrease since 1994 (table 4.2). This data set had only one case with unknown HIV status (from 1998).

Table 4.2: HIV prevalence among military conscripts aged less than 25 years in Chiang Rai, by year.

Year	Number tested	HIV prevalence
1991	587	15.0%
1992	1101	17.4%
1993	399	16.5%
1994	448	7.4%
1995	859	6.6%
1996	989	5.9%
1997	1094	3.4%
1998	833	2.9%

Discussion

Military conscript data were the first data from the general population to show a decrease in HIV prevalence after the implementation of the intervention program in 1991 [Mason et al. 1995]. Compared to other regions of the country, the upper North and Bangkok had the earlier declines, between 1992 and 1993, while the decline in HIV prevalence started after 1993 in the rest of the country [Mason et al. 1995]. It was thought that this was due to the early and severe epidemic pattern of the upper North region that meant that the area received higher attention for the control measures. Therefore it is likely that there was also earlier access to information and more intensive control programs in the upper North and Bangkok.

The sharp decrease in HIV prevalence in 1994, following the slight decline of 1993 showed that the incidence reduced markedly very soon after the nationwide implementation of the 100% Condom Program in 1991 [Rojanapithayakorn et al. 1996]. There has been some argument about the current large number of deaths from AIDS in some communities that might have an impact on behavior change [Mason et al. 1995]. However the dramatic increase in symptomatic HIV and deaths from AIDS occurred in 1993 [Ministry of Public Health 1995], therefore this is unlikely to be a major factor explaining this behavior change.

Studies from Thai military conscripts have noted that the conscripts are biased towards low socioeconomic groups. The risk factor studies from this population also almost always show that less educated conscripts have higher risk for HIV infection [Nelson et al. 1993, Sirisopana et al 1996, AFRIMS 1996, 1997]. The exemption criteria for conscription will tend to the bias towards an overestimation of HIV prevalence compared to the general population. However, because of its large sample size and random selection methods, despite the exclusion of the upper classes and the narrowness of the age group, this sample is the most comprehensive and reliable indicator available of HIV prevalence in the general young adult male population [Weninger et al. 1991].

Interestingly, from a study of demographic risk factors for HIV infection of military conscripts in the whole country during 1991-1993, all regions showed significantly higher HIV prevalence among urban residents than rural residents, except the upper North where there were no significant difference and even a slightly higher HIV prevalence in rural conscripts [Sirisopana et al. 1996].

In our data we selected place of residence during 2 years before the time of conscription, as the key indicator of having exposure in Chiang Rai because the place of conscription is not necessarily related to the area of recent residence but to the place of birth.

In summary, the military conscripts data that were included in further analysis were:

- Aged 19-24 years
- Spent most of the time in Chiang Rai province during the 2 years before conscription

Chapter 5: ANC attenders

Methods

Like the patients in other wards of Chiang Rai hospital, the women who come to have their antenatal care at the hospital are primarily lower-to-middle class. However, one difference is that the ANC attenders are more likely to live in the nearby area rather than come from other districts, since antenatal care is expected to be a basic service that all level of health services have to provide.

Chiang Rai hospital has had HIV counselling and testing for women who receive antenatal care at the hospital since 1990. This process takes place on the first ANC visit and at a third-trimester ANC visit. Serum specimens at Chiang Rai hospital were tested for HIV-1 antibodies by HIV tests described in chapter 3. HIV positive pregnant women are provided with infant formula and counselled to avoid breastfeeding. They are also offered effective contraception postpartum such as tubal ligation or depo-medroxyprogesterone acetate injection, which they accept at a high rate [Wiwatwongwana 1996]. Since 1997, HIV infected pregnant women in Chiang Rai have had access to perinatal zidovudine treatment to prevent vertical transmission, either as a participant in a research study or through a regional government program [Thaineua et al. 1998].

Data were collected from the ANC logbooks which contain date of the first ANC visit, age, gravidity, parity, gestational age, area of residence (province and district), hematocrit, blood group, HIV and VDRL results for both first and second times. These data have been routinely collected in a computerized form since the latter half of 1990 for general purposes. We created double entry of this data using Epi Info version 6 and performed further cleaning by examining frequencies and looking at consistency of some linked variables (eg gravidity and parity) and went back to see the total records of original data in the logbooks for any inconsistent records. For the HIV status, only the first result (taken at the time of the first visit) was used.

Results

During 1990-1998, 10,628 women came to the ANC clinic in Chiang Rai hospital. Of these, 42 (0.4%) women were aged less than 15 years. Among those aged equal or more than 15 years, 10372 women (98.1%) lived in Chiang Rai province, of whom 62.2% resided in Muang district. In general, the number of ANC cases is around 1,000 per year but this started to increase since 1997 (table 4.1). The patients' ages ranged from 13-49 years (median 25 years). Median gestational age when they first came to ANC was 14 weeks, (interquartile range 10 to 22 weeks).

The overall HIV prevalence was 6.4% (645 cases from 10,041 cases). The peak of HIV infection among the ANC group was in 1994. For the ANC data, there were women with unknown HIV results in each year, ranging from less than 1% before 1994 to around 2-4% since 1994. The age distribution of ANC patients showed the highest number of cases in 20-24 years with very few women aged more than 35 years. The proportion of HIV tested was similar over different age groups. The peak HIV prevalence shifted to the older age group in later years, as shown in table 5.1.

Table 5.1: HIV prevalence in ANC attenders of Chiang Rai hospital in each age group, from 1990 to 1998.

Year	15-19	20-24	25-29	30-34	35-39	40-44	45-49	Total
1990	6.8% (6/88)	5.7% (10/175)	1.4% (2/148)	0% (0/50)	0% (0/10)	0% (0/3)	-	3.8% (18/474)
1991	10.7% (19/178)	6.6% (26/395)	4.2% (14/332)	1.4% (2/139)	3.0% (1/33)	20% (1/5)	-	5.8% (63/1082)
1992	10.7% (17/159)	7.6% (29/380)	5.1% (17/335)	4.1% (6/145)	0% (0/41)	0% (0/3)	-	6.5% (69/1063)
1993	8.5% (15/177)	9.6% (32/335)	3.8% (12/317)	4.3% (6/140)	0% (0/40)	0% (0/6)	-	6.4% (65/1015)
1994	8.6% (12/140)	11.2% (36/321)	6.2% (21/339)	5.6% (9/162)	4.7% (2/43)	0% (0/3)	-	7.9% (80/1008)
1995	8.2% (14/170)	9.0% (35/388)	4.2% (16/379)	2.8% (5/179)	0% (0/46)	0% (0/7)	0% (0/2)	6.0% (70/1171)
1996	7.8% (13/166)	10.7% (34/318)	5.6% (15/269)	2.2% (4/183)	10.0% (6/60)	0% (0/7)	0% (0/1)	7.2% (72/1004)
1997	6.2% (17/275)	9.8% (46/472)	7.3% (28/386)	2.9% (7/242)	4.9% (4/82)	6.7% (1/15)	0% (0/1)	7.0% (103/1473)
1998	7.0% (25/355)	7.0% (38/542)	6.3% (30/473)	3.8% (10/262)	2.1% (2/97)	0% (0/21)	0% (0/1)	6.0% (105/1751)
Total	8.1% (138/1708)	8.6% (286/3326)	5.2% (155/2978)	3.3% (49/1502)	3.3% (15/452)	2.9% (2/70)	0% (0/5)	6.4% (645/10041)

Because the pregnant women who are found to be HIV positive receive counseling, and are provided choice of effective contraception after delivery, the prevalence of HIV infection in multigravida is likely to be lower than in primigravida. This phenomenon was shown in Chiang Rai hospital as in table 5.2.

Table 5.2: HIV prevalence by gravidity among ANC attenders of Chiang Rai hospital, 1990-1998.

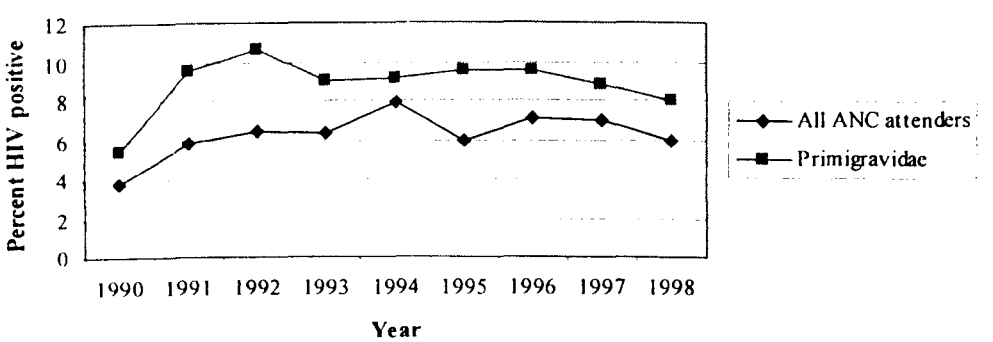
Gravidity	Cases	Percent HIV positive
1	4263	9.0
2	4000	5.0
3	1260	3.7
4	320	3.4
More than 4	111	3.6
Total	**9954***	**6.4**

* 87 women did not have information about gravidity

Since the HIV prevalence by gravidity must be highly confounded by age, we calculated the HIV prevalence by gravidity in a selected age group. For ANC women aged 20-24 years (which is the peak age group in the ANC), HIV prevalence was 11.4% (142/1246) for the women who had first time pregnancy and 6.6% (58/883) for the second time pregnancy. The higher number of pregnancies gave even lower levels of HIV prevalence.

When comparing the trend of HIV prevalence between all ANC cases and the primigravid cases we found higher prevalence among primigravidae every year and the peak changed to be highest in 1992 and HIV prevalence became stable for several years afterward (figure 5.1).

Figure 5.1: HIV prevalence among women who lived in Chiang Rai province and came to ANC at Chiang Rai hospital by year



Among primigravidae as for all ANC attenders, the highest HIV prevalence was in those aged 15-19 years in the first three years since data collection began, before moving to age 20-24 years in the later years (table 5.3).

Table 5.3: HIV prevalence in primigravida ANC patients of Chiang Rai hospital in each age group, from 1990 to 1998.

Year	15-19	20-24	25-29	30-34	35-39	40-44	45-49	Total
1990	7.8% (5/64)	7.1% (7/99)	0% (0/43)	0% (0/12)	0% (0/2)	0% (0/2)	-	5.4% (12/222)
1991	12.4% (16/129)	9.2% (19/206)	8.0% (9/112)	0% (0/29)	16.7% (1/6)	50% (1/2)	-	9.5% (46/484)
1992	12.4% (14/113)	10.9% (21/192)	8.8% (10/114)	13.3% (4/30)	0% (0/7)	0% (0/0)	-	10.8% (49/456)
1993	7.6% (10/131)	12.9% (22/170)	6.9% (7/102)	3.2% (1/31)	0% (0/9)	0% (0/2)	-	9.0% (40/445)
1994	8.6% (9/105)	10.0% (17/170)	8.8% (9/102)	9.7% (3/31)	0% (0/9)	0% (0/1)	-	9.1% (38/418)
1995	8.8% (12/136)	12.3% (26/211)	8.4% (10/119)	0% (0/31)	0% (0/4)	0% (0/2)	-	9.5% (48/503)
1996	7.2% (10/139)	13.2% (22/167)	8.7% (6/69)	4.4% (1/23)	0% (0/9)	0% (0/1)	-	9.6% (39/408)
1997	6.5% (14/215)	10.3% (24/234)	11.3% (11/97)	3.1% (1/32)	18.2% (2/11)	-	0% (0/1)	8.8% (52/590)
1998	7.8% (21/270)	8.5% (24/282)	8.2% (11/135)	5.9% (2/34)	7.7% (1/13)	0% (0/3)	-	8.0% (59/737)
Total	**8.5% (111/1302)**	**10.5% (182/1731)**	**8.2% (73/893)**	**4.7% (12/253)**	**5.7% (4/70)**	**7.7% (1/13)**	**0% (0/1)**	**9.0% (383/4263)**

Discussion

HIV sentinel surveillance in ANC attenders is widely used as an indicator to assess the magnitude and trend of the HIV epidemic in the general population. In some countries, the results of sentinel surveillance in pregnant women are taken to be representative of all women of child bearing age, or both men and women aged 15-49, [Colebunders et al. 1990, Giesecke et al. 1994, Karon et al. 1996b]. To directly apply the sentinel seroprevalence to the population makes the assumption that HIV-infected women have the same opportunity of becoming, and staying pregnant as do uninfected women [Ades 1995, Boisson et al. 1996, Karon 1996a]. There have been a number of studies in sub-Saharan Africa which have compared the HIV prevalence in pregnant women with that in the population or, on the other hand, compared fertility between HIV infected women and those in the general population of the same age. The results from these studies showed the same pattern that HIV positive women have higher fertility rate in age 15-19 years , but at older age HIV-positive women have markedly lower fertility than their HIV negative counterparts [Zaba et al 1998]. This was explained by selection effects that in a population with low rates of contraceptive use, women who begin sexual activity at an early age are exposed both to the risk of pregnancy and HIV. In contrast, in the older age groups, HIV positive women are more likely to be sexually inactive and less fertile because of the effect of sickness, separation and widowhood [Zaba et al 1998]. The most direct effects of HIV on fertility arise because the virus can lower a woman's fecundity and ability to bear a pregnancy to term. Since HIV and other STD infections are closely associated and some STD such as syphilis are risk factors for intrauterine foetal death [Temmerman et al. 1990, Miotti et al. 1990], that can be an additional factor to affect the fertility rate in HIV positive women. In sub-Saharan Africa, there have also been reports about behavior change that can effect the fertility in HIV-positive women. An attitude survey in rural Zimbabwe showed that better knowledge of the mechanism of HIV infection and family experience of AIDS were associated with increased use of condoms and that persons who felt at risk of HIV had a lower than usually desired family size [Gregson et al. 1997]. In Rakai, HIV-positive women were marginally more likely to use some form of contraception (OR 1.3, including abstinence) although this result was not statistically significant [Gray et al. 1998].

In Thailand the result of ANC sentinel surveillance can be more complicated to interpret because some hospitals have a policy to offer permanent or semi-permanent contraceptive methods to HIV-infected pregnant women after the termination of pregnancy or even induce abortion at an early gestational age [Pinchun 1994, Piya-Anant et al. 1995, Tancepanichskul et al 1995]. In a university in Bangkok, 74.3% and 88.3% of the HIV-infected women requested female sterilization after the pregnancy, in 1992 and 1993 respectively. For the remaining group, 17.6% and 10% of all HIV infected women accepted Norplant, respectively [Piya-Anant et al. 1995]. The husbands of these HIV-infected women were advised to use condoms regardless of the contraceptive method their wives received. The tubal ligation rate was lower in a report from a provincial hospital in a central province during 1990-1993: 31 out of 133 women (23.3%) of HIV-positive in this hospital accepted tubal resection. However, all of the remaining HIV-positive women accepted use of contraceptives such as pills, injection and Norplant [Pinchun 1994]. In Chiang Rai hospital the HIV positive pregnant women are also advised and discuss about family planning especially tubal ligation. From a study among women attending labour room during February and September 1996, 75 out of 150 (50%) HIV-infected women underwent tubal ligation, 18 (12%) had hormonal implant and the other 57 (38%) refused contraception. Although the hospital does not offer induced abortion to HIV-positive pregnant women who have low gestational age, anecdotal information suggests that abortion rates among HIV-infected women may be increasing [Bunnell et al. 1999].

With these biological, behavioral and medical factors which all tend to decrease the possibility for HIV-infected women who come to ANC at Chiang Rai hospital to be pregnant again, it is better to exclude the multigravida group from our further analysis. The inclusion of all ANC cases not only underestimates HIV prevalence but also masks recent changes. From the comparison of HIV prevalence in each year, the point that started to have downward trend was after 1994 in all cases of ANC women while the peak for primigravidae was in 1992, the same year as the peak in military conscript groups. Since primigravidae are likely to be younger, their HIV prevalence rate is closer to the incidence, as also seen in the military conscripts.

Despite the differences from the general population as discussed above, HIV prevalence data from pregnant women remain immensely valuable for the study of

HIV situation especially in women of child-bearing age. The information from additional studies can also provide a guide to the magnitude and direction of these differences. One useful source of information is studies about HIV risk behavior. It is widely known that almost all African women are sexually active after age 20 years [Carael et al. 1991]. In Thailand, this figure is different: the data from HIV behavioural surveillance showed that at age 15-19 years only 20% of females are sexually active. For women age 20-24 years, slightly more than half (58-60%) reported ever having had sexual experience, while at the age 25-29 years, around 80-85% reported ever having been sexually active [Division of Epidemiology 1995-1998, unpublished data]. This different proportion sexually active should affect the "cross-over" pattern of the fertility rate between HIV-positive and HIV-negative we mentioned earlier. If 40% of Thai women aged 20-24 years never have sexual experience, it is more likely that in the Thai population the pregnant women aged 20-24 years also have higher HIV prevalence compared to women in general population, unlike the African studies in which overestimation of HIV prevalence occurs only under 20 years.

In Thailand many middle class and almost all upper class women do not use the ANC service in public hospitals because it is overcrowded and time consuming. With the characteristic of the Thai epidemic that low socioeconomic people have higher risk to develop HIV, the data from public hospitals tend to over estimate the HIV prevalence in the general population. Atikij et al reported the HIV prevalence in women who gave birth in 5 private hospitals in Bangkok during 1992-1993. Only 1/1000 had an HIV positive result (0.1%, 95% CI 0.003-0.56%) [Atikij et al. 1996]. This was less than 10 times lower than HIV prevalence reported from public hospitals in Bangkok during the same period. In a public university teaching hospital in Bangkok, the HIV prevalence among low to middle class women in 1992 was 1.4% (67/4689) and 1.7% (77/4629) in the third and forth quarters, respectively [Roongpisuthipong et al. 1993]. A similarly large public government hospital in Bangkok found HIV prevalence of 1.3% and 1.4% in the last two quarters of 1992 among women who received prenatal care and 3.1% and 4.4% among those who had not [Siriwasin et al. 1993].

With our intention to restrict to the primigravidae ANC cases, we have to keep in mind about some special characteristic of primigravida. It is more likely that this

group is on average younger than all ANC cases. On the other hand, for those women aged more than 30, and especially more than 35 years, but have a first time pregnancy, it should be questioned how far these women represent the population in their age. In Thailand most people prefer to have children within 2-3 years after marriage. Therefore the middle age primigravidae should be the group that have late marriage, which are more likely to have higher socioeconomic status or came from couples with infertility problems. Hence this can induce the bias in both under and overestimation HIV prevalence.

The effect of AZT research since 1997 onward can induce more referral bias for HIV positive women from other districts or other provinces, in order to get treatment to their baby. This coincides with the markedly increased number of ANC attenders since 1997. Therefore, this project can introduce another bias to our data. However when we compared the proportion of ANC attenders who lived in Muang district in each year, we did not find a lower proportion from Muang district after 1997. This suggests that referral bias after the AZT trial should not be a big problem in our setting.

In conclusion, the ANC attenders included in further analysis were:

- primigravidae
- seen in Chiang Rai hospital between 1990-1998
- aged at least 15 years
- resident in Chiang Rai province

Chapter 6: Delivery patients

Methods

About one-third of the 15000-16000 total live births each year in Chiang Rai province take place at Chiang Rai hospital. Since 1990, women giving birth at Chiang Rai hospital have been routinely counselled and tested for HIV-1 antibodies, and nearly all women have been tested. Women who receive their antenatal care at the Chiang Rai hospital have HIV counseling and testing at their first ANC visit and again at a third-trimester ANC visit. Women without a well-documented third trimester HIV test result from CRH were retested in the delivery ward, and HIV positivity together with key maternal and infant characteristics were recorded in delivery-ward log books by delivery ward nurses. Serum specimens were tested for HIV-1 antibodies by enzyme immunoassay (EIA) as previously described for TB patients.

These data come mainly from the existing data of the HIV/AIDS Collaboration, which is a joint program between the Centers for Disease Control and Prevention (CDC), US and Ministry of Public Health, Thailand. They started collecting the data from logbooks of delivery room in Chiang Rai hospital since 1990 to mid 1997 when they closed their project about HIV trends in delivery patients. The data were already cleaned by the CDC personnel. However, for the purposes of our study, these data were insufficient since they did not contain the area of residence (province and district). We, therefore, decided to merge these data with the postpartum logbook, to add these 2 variables. Nevertheless, there were many records with missing information on patient's identity such as name, surname hospital number and ANC number. In those cases, we tried to match with date of delivery, age, gravidity, infant's gender, weight and apgar score. The postpartum logbook of the general obstetric ward was well kept for nearly 15 years. However for those patients who came from a special ward (who can afford to pay for the cost of private rooms), most of the logbooks were not available. Overall, we found the matching records for 86.6%. For those for whom we found matching records, there were some variables such as age and weight and gender of infant that are not identical between the 2 data sources. In this analysis we used the original CDC data for the age of delivery patients

because the data about patient's age in postpartum ward are likely to be less accurate. For instance, in cases of Caesarian section, or in the situation that the mother was too fatigued, their relative might be the source of this information instead of the patients themselves. The data for the latter half of 1997 was added to the original file, using the postpartum logbook as the only source of information.

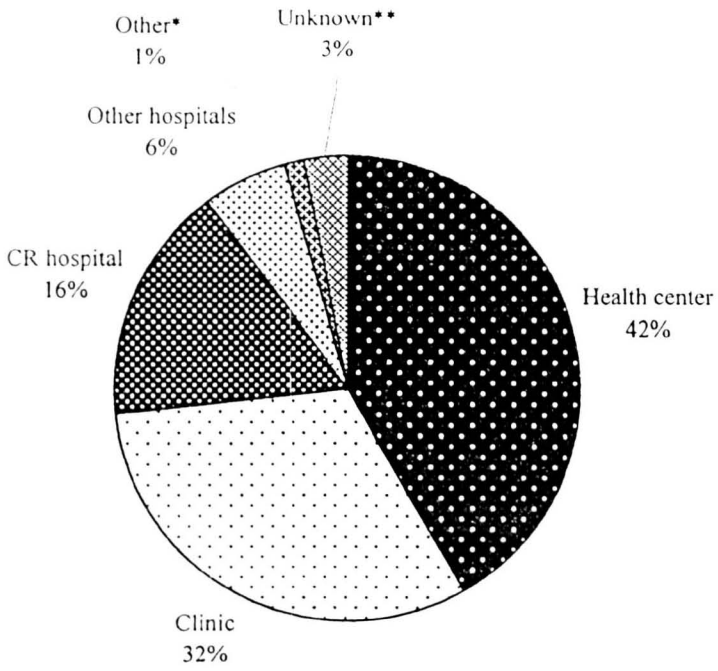
The data contain age, gravidity, parity, gestational age, number of pregnancy, place of residence (province and district), place of ANC, date of delivery, method of delivery, blood group, HIV infection, Hepatitis B antigen and syphilis positivity measured by VDRL test, and infant information (weight, gender, apgar score).

During the first 7 years (1990-1996) there was no record of negative HIV results in the delivery ward log books. Therefore, it was not possible to separate the unknown and negative HIV results. Just in 1997, they started to record HIV negative. In that year there were 28 unknown cases from a total of 4922 women.

Results

From 1990-1997 there were 43,326 women who gave birth in Chiang Rai hospital. The number of patients peaked at 1991 and then slightly decreased over time. The median age was 25 years (range 12-49 years). Nearly half of them (41.8%) had their ANC in health centers, while only 16.4% had ANC care at Chiang Rai hospital (figure 6.1).

Figure 6.1: Place of ANC among delivery patients of Chiang Rai hospital, 1990-1997



* Health center is a public health service in sub-district level. It has average 2-3 personnel but no bed and no doctor.

** Such as municipal health service which is under the Interior Ministry, large district hospitals and private hospitals.

The overall HIV prevalence among delivery patients in Chiang Rai hospital during the study period was 4.6%. Comparing the HIV prevalence between those who had antenatal care from different sources, the lowest prevalence come from private clinics while Chiang Rai hospital had the second lowest rank, next to private clinics, lower than both health centers and other hospitals as in table 6.1. This rank varied from year to year in most of the groups but private clinics always gave the lowest and distinct HIV prevalence.

Table 6.1: HIV prevalence in delivery patients who gave birth in Chiang Rai hospital during 1990-1997, by place of ANC.

Place of ANC	HIV positive	Total cases	Percent
Health center	1063	18099	5.9
Chiang Rai hospital	375	7080	5.3
Private clinic	298	13716	2.2
District hospitals	137	2468	5.6
Other health service	47	595	7.9
Total	**2009**	**43297**	**4.6**

Among all women delivering in Chiang Rai hospital, 40 (0.09%) were aged less than 15 years and 77 women did not have information about age. For the remaining 43209 women, 36244 (83.9%) of them lived in Chiang Rai province. HIV prevalence among women delivering in CR hospital who were aged at least 15 years and lived in Chiang Rai province increased to a peak of 6.8% in 1994 and then gradually decreased (table 6.2).

Table 6.2: HIV prevalence in delivery patients of Chiang Rai hospital by year of delivery. (Restricted to those aged at least 15 years and resident in Chiang Rai province)

Year	HIV positive	Total cases	Percent
1990	70	5005	1.4
1991	177	4994	3.5
1992	247	5181	4.8
1993	290	4720	6.1
1994	326	4769	6.8
1995	255	4026	6.3
1996	247	4286	5.8
1997	174	3244	5.4
Total	**1786**	**36225**	**4.9**

*There were 19 unknown HIV results in 1997.

For all delivery patients, the highest HIV prevalence came from the 15-24 years age group (table 6.3).

Table 6.3: HIV prevalence in delivery patients, Chiang Rai hospital, by age group.

Age	Cases	Percent of HIV positive
15-19	4385	6.9 (301)
20-24	11623	6.9 (800)
25-29	11353	4.1 (467)
30-34	6647	2.7 (178)
35-39	1906	1.9 (36)
40-44	281	1.4 (4)
45+	30	0 (0)
Total	**36225**	**4.9 (1786)**

Because there were many reports about the fertility effect of HIV infection, and because of the hospital policy to offer contraception for HIV infected pregnant women, HIV prevalence in multigravidae should not reflect the true magnitude in this population. Like the ANC data, HIV prevalence in our delivery patients was highest among primigravidae, 6.6% (table 6.4).

Table 6.4: HIV prevalence in delivery patients of Chiang Rai hospital by gravidity.*

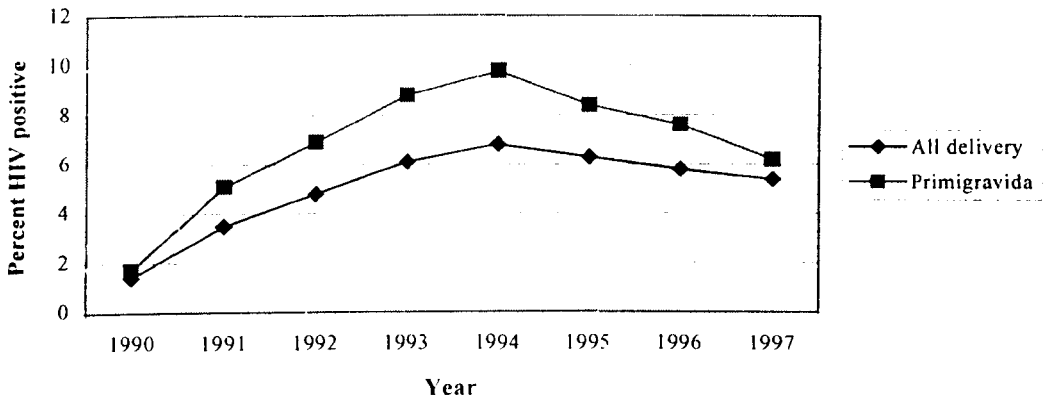
Gravidity	Total cases	Percent of HIV positive
1	15455	6.6
2	13881	3.8
3	4301	3.7
4	1218	2.1
More than 4	608	1.5
Total	**35463**	**4.9**

* There were 762 cases that do not have data about gravidity and 19 cases that did not have an HIV test.

As discussed earlier in the ANC section, these data are likely to be highly confounded by age. Therefore, we compared the data for women aged 20-24 years who gave birth at Chiang Rai hospital by gravidity. HIV prevalence among the women who gave birth for their first pregancy was 7.7% (536/6993) and for the second pregnancy was 5.8% (204/3545).

For the HIV prevalence over time, both all cases and primigravid cases had the same pattern of having maximum prevalence in 1994, before slowly decreasing (figure 6.2).

Figure 6.2: HIV prevalence of women who gave birth in Chiang Rai hospital by year, compared between all delivery cases and primigravid cases,



The pattern of HIV prevalence by year in each age group, in all cases and primigravid cases was similar, despite generally higher prevalence among primigravidae (table 6.5).

Table 6.5: HIV prevalence in primigravid delivery patients in Chiang Rai hospital in each age group, from 1990 to 1997.

Year	Age							
	15-19	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**Total**
1990	2.2% (11/502)	1.6% (18/1101)	1.4% (8/559)	1.4% (2/147)	0% (0/34)	0% (0/8)	-	1.7% (39/2351)
1991	7.0% (34/488)	5.3% (57/1070)	3.6% (19/527)	3.1% (4/130)	0% (0/16)	0% (0/2)	-	5.1% (114/2233)
1992	7.5% (38/507)	8.3% (85/1030)	5.3% (28/525)	3.7% (6/163)	0% (0/43)	0% (0/9)	0% (0/1)	6.9% (157/2278)
1993	9.3% (43/463)	12.3% (110/898)	7.7% (35/452)	4.7% (6/129)	10.5% (4/38)	0% (0/7)	0% (0/1)	8.8% (172/1949)
1994	9.3% (43/463)	12.3% (110/898)	7.9% (38/479)	5.1% (8/158)	2.7% (1/37)	0% (0/6)	-	9.8% (200/2041)
1995	7.5% (26/348)	10.7% (71/664)	6.4% (22/343)	4.4% (5/113)	5.6% (1/18)	0% (0/5)	-	8.4% (125/1491)
1996	7.1% (32/448)	8.2% (64/779)	7.7% (28/366)	6.8% (10/148)	3.5% (1/29)	0% (0/5)	-	7.6% (135/1175)
1997	5.2% (20/383)	6.8% (38/563)	7.6% (20/262)	4.4% (4/92)	2.9% (1/35)	0% (0/1)	0% (0/1)	6.2% (83/1337)

Discussion

Although almost all public hospitals in Thailand serve primarily lower to middle class people, this varies in different wards, depending on the popularity of doctors and availability of private hospitals in the nearby area. The delivery ward covers a greater range of people than the ANC because there are some types of health service that do not have facilities to admit people but can offer antenatal care services, such as health centers and private clinics. Many middle class women prefer to have ANC in private clinics because they believe they will get better care and also not waste time, but they choose to give birth in public hospital because the delivery in a private hospital is far more expensive. For some women who live in other areas that do not have any hospital it is more convenient to attend an ANC in a health center close to their homes. Therefore, delivery data should be more representative of general population than ANC data and there is a larger sample size.

However, as we discussed in chapter 5 (our ANC section), these groups of women (ANC and delivery patients) do not cover the sexually inactive and infertile people while HIV infection can relate with many biological and behavioral changes such as amenorrhea, decreased fecundity or increased use of condoms. These data should have the same direction of bias as the ANC data. However, there are some additional problems in using the HIV prevalence in delivery patients. With the effect of HIV infection itself and also additional risk from other STD infection (which is common in HIV-positive people), some pregnant women will have miscarriages [Zaba et al. 1998]. Moreover there is some anecdotal information about intentional abortion in pregnant women who discover that they are HIV positive (abortion is illegal in Thailand). Some hospitals offer induced abortion to HIV positive pregnant women with early gestational age, and the proportion accepting abortion is quite high. A study from one university teaching hospital reported that 90.9% of HIV positive pregnant adolescents during 1991-1995 underwent induced abortion [Taneepanichkul et al. 1995]. After pregnancy 36.4% accepted contraceptive injection, 27.3% did not accept any contraception and 4.5% accepted condom. A study from another university hospital in Bangkok that allowed HIV-positive pregnant women to have abortion if their gestational age was not more than 20 weeks showed that 15% of HIV positive pregnant women underwent induced abortion, 1.6% had spontaneous abortion and

another 1.6% had illegal abortion in 1992. The proportion was also similar in 1993, with 19.7% having induce abortion, 1.7 spontaneous abortion and 1.7% illegal abortion [Piya-Anan et al. 1995]. Another provincial hospital in a central province offered abortion for HIV-positive pregnant women who had gestational age less than 24 weeks and all of that group decided to have abortion [Pinchun 1994]. Although this option was not formally allowed in Chiang Rai hospital, so that the proportion of women who go for abortion should be less than that in these other hospitals, the information in those reports show that HIV positive pregnant women have a high tendency to decide for abortion. After the beginning of AZT trial, this proportion might decrease but the practice probably still continues.

Therefore if we can compare the HIV prevalence among ANC data and delivery case that had their antenatal care in Chiang Rai hospital, we should expect to see higher prevalence in ANC cases in the same year. Unfortunately, because the data are incomplete, many delivery records did not have hospital numbers or ANC numbers. Therefore, we could not match these two files together. So these two groups are not completely the same because there will have been some cases that had antenatal care at the CRH but went on to give birth at other places.

In conclusion, the delivery patients included in further analysis were:

- primigravidae
- seen in Chiang Rai hospital between 1990-1998
- aged at least 15 years
- resident in Chiang Rai province

Chapter 7: Surgical patients

Methods

The data on surgical patients came from admission logbooks in different wards. The wards involved were general surgery, neuro-surgery, plastic surgery, uro-surgery and orthopedics. Logbooks were not available in all wards or for all years. HIV testing was routinely used for all admitted surgical patients from 1990, so logbooks before 1990 are excluded. After 1997, the year of economic crisis, HIV testing was restricted to suspected high-risk patients. Therefore, we have limited our data collection up to 1997.

The HIV testing in surgical patients used the same testing protocol as described for TB patients. However, for surgical patients, the test was compulsory in all patients that went on to have surgery and no pre and post counseling was done.

These data have not previously been computerised or analysed. Data entry was performed for this study separately by two different clerks who were trained for coding and entering these data by using Epi Info version 6.0, using double entry functions. The completion of the double entry was checked by the principle investigator. The data were further cleaned by checking the frequency distributions of variables such as age, sex, province, district and HIV result. In addition some linking variables such as province and district were examined. Initially information about the diagnosis was not entered. However after completion of data entry and preliminary analysis we found some possible biases in HIV prevalence from different surgical wards. So, we made a decision to add the information about diagnosis as one of the variables for this control group to allow exclusion of patients with diagnoses, which might be related to HIV. Unfortunately by the time of this second round entry, some of the logbooks had already been thrown away in 2 wards (uro-surgery and the General Surgery I).

At the end of the data entry, there were 9 variables in this data set: ward, month and year of admission, age, gender, province and district of residence, HIV result and the diagnosis.

Results

There were 57,817 cases that had information available during 1991-1997 from different wards as shown in table 7.1.

Table 7.1: Data available from surgical ward patients in Chiang Rai hospital (including all those for whom the logbook was available initially).

Ward	Year	Number of cases
Male general surgery I (MS I)	1992-1997	13,952
Male general surgery II (MS II)	1991-1997	12,688
Urology - Male - Female	1992-1997	 9,138 4,317
Female general surgery	1994-1997	10,868
Female orthopedic ward - Male (mostly children) - Female	1991-1995	 1,255 5,599
Total	**1991-1997**	**57,817**

Ward MS I and urology are the two wards for which we could not find the logbook in some years at the time of adding diagnosis as a variable. The data thus lost was 10342 cases from 1992-1997 in ward MS1 and 1708 cases from the urology ward. Therefore, there were only 3610 cases left in MS1 and 11747 cases in urology ward.

MS I, although called general surgery, includes neuro-surgery and plastic surgery patients. The female orthopedic ward includes children of both genders and a few cases of adult males. Because each ward contains patients with different

characteristics, the age distributions between the wards were markedly different, with the median age ranging from 34 in MS I to 50 in urology.

Because in all wards the data were not complete in some periods, the number of cases in each year varied, as shown in table 7.2.

Table 7.2: Number of surgical cases with available data by ward and year of treatment.

Year	MS1	MS2	Uro-surgery	Female surgery	Female orthopedic
1991	-	795	-	-	167
1992	388	1234	862	-	1583
1993	3263	2535	3547	-	1427
1994	1983	1617	2206	2516	1407
1995	2686	2727	2303	2995	1015
1996	2350	2937	2295	3060	-
1997	3282	843	2242	2297	-
Total	**13952**	**12688**	**13455**	**10868**	**5599**

HIV prevalence was examined in those aged more than 14 years who lived in Chiang Rai province. The HIV prevalence varied by ward and was generally low in female wards. Among males the HIV prevalence varied from more than 7% in MS I and MS II to less than 3% in urology. After stratifying by age group and year the HIV prevalence in male general surgery ward was still much higher than male urology

The exclusion of some potential HIV associated cases

To explore the differences in HIV prevalence between the general surgery and urology wards, we looked at the diagnoses and found that a high proportion of cases in general surgery had conditions related to infection such as acute appendicitis or abscess. Therefore, we divided the patients into 3 groups; group 1 is the patients who had a diagnosis that is likely to be associated with HIV, group 2 is diagnoses that

might be associated with HIV, and group 3 is those diagnoses that are not likely to be associated with HIV. The list of diseases related with HIV was defined following a literature review of HIV-related surgical conditions. The details of this list are in Appendix 1.

After excluding those in group1 and 2 categories, and also excluding the records for which we did not know the diagnosis because of missing log books, the HIV prevalence in each wards changed very little (table 7.3).

Table 7.3: HIV prevalence in surgical patients, Chiang Rai hospital before and after excluding the cases that might be related with HIV infection, by year of treatment.

7.3.1 Male general surgery

Age group	MS1			MS2		
	All case	Drop group 1	Drop group 1&2	All case	Drop group 1	Drop group 1&2
15-19	1.8% (40/2247)	1.8% (10/563)	1.8% (10/562)	2.8% (23/834)	2.7% (15/557)	2.4% (13/533)
20-24	11.3% (251/2221)	12.4% (65/525)	12.4% (65/524)	13.6% (129/952)	12.2% (82/673)	12.4% (79/637)
25-29	16.1% (288/1790)	15.9% (71/446)	16.3% (71/437)	23.7% (258/1087)	22.1% (159/719)	21.3% (138/647)
30-34	11.9% (185/1557)	13.6% (54/396)	13.9% (54/390)	14.3% (174/1215)	14.0% (117/835)	14.1% (103/733)
35-39	8.5% (122/1442)	7.2% (24/334)	7.3% (24/330)	9.0% (113/1262)	9.3% (86/929)	9.7% (76/787)
40-44	4.9% (57/1157)	5.6% (15/270)	5.6% (15/267)	5.6% (65/1163)	5.2% (45/866)	5.9% (41/695)
45-49	3.8% (29/757)	2.1% (4/188)	2.2% (4/186)	4.8% (45/948)	4.5% (33/731)	5.4% (31/573)
50+	1.2% (29/2527)	1.3% (8/599)	1.4% (8/575)	1.7% (89/5126)	1.7% (74/4304)	1.7% (54/3312)
Total	**7.3% (1001/13719)**	**7.5% (251/3329)**	**7.7% (251/3279)**	**7.1% (896/12587)**	**6.4% (611/9614)**	**6.9% (535/7771)**

7.3.2 Urology male and female

Age group	Male			Female		
	All case	Drop group 1	Drop group 1&2	All case	Drop group 1	Drop group 1&2
15-19	0% (0/158)	0% (0/93)	0 % (0/93)	1.5% (1/66)	0% (0/48)	0% (0/48)
20-24	3.4% (9/262)	3.8% (6/158)	3.8% (6/157)	1.6% (2/122)	2.9% (2/69)	2.9% (2/69)
25-29	10.5% (59/564)	10.1% (41/405)	10.3% (41/398)	2.9% (7/238)	2.6% (5/193)	2.6% (5/193)
30-34	4.1% (32/788)	4.2% (26/614)	4.3% (26/606)	2.2% (8/370)	1.7% (5/287)	1.8% (5/281)
35-39	3.0% (30/999)	2.5% (20/797)	2.6% (20/780)	1.2% (6/515)	0.5% (2/409)	0.5% (2/403)
40-44	1.7% (15/860)	1.9% (14/722)	2.0% (14/715)	0.4% (2/495)	0.5% (2/430)	0.5% (2/421)
45-49	2.3% (17/742)	1.9% (12/627)	1.6% (10/608)	0% (0/475)	0% (0/394)	0% (0/388)
50+	1.2% (56/4731)	1.0% (39/3926)	1.0% (39/3750)	0.5% (9/2017)	0.5% (9/1655)	0.5% (8/1601)
Total	**2.4% (218/9104)**	**2.2% (158/7342)**	**2.2% (156/7107)**	**0.8% (35/4302)**	**0.7% (25/3460)**	**0.7% (24/3408)**

7.3.3 Female general surgery and orthopedic

Age group	Female general surgery			Female orthopedic		
	All case	Drop group 1	Drop group 1&2	All case	Drop group 1	Drop group 1&2
15-19	2.4% (19/786)	2% (10/500)	1.7% (8/462)	3.3% (17/517)	3.4% (16/468)	3.5% (16/458)
20-24	10.4% (68/652)	9.7% (38/390)	9.9% (35/355)	4.2% (14/332)	4.5% (13/291)	4.5% (13/288)
25-29	10.5% (77/731)	8.3% (38/460)	7.8% (32/411)	5.0% (17/343)	5.1% (16/316)	5.1% (16/313)
30-34	3.6% (34/936)	3.9% (26/666)	4.3% (23/535)	1.3% (5/376)	1.5% (5/342)	1.5% (5/339)
35-39	4.2% (46/1089)	3.8% (29/765)	3.1% (18/586)	1.9% (8/414)	2.1% (8/378)	1.9% (7/374)
40-44	2.1% (22/1032)	2.3% (18/776)	2.4% (13/545)	0% (0/323)	0% (0/309)	0% (0/303)
45-49	1.0% (9/879)	1.0% (7/670)	0.9% (4/454)	0.4% (1/258)	0.4% (1/227)	0.4% (0/225)
50+	0 7% (31/4614)	0.6% (21/3586)	0.7% (16/2226)	0% (0/2339)	0% (0/2125)	0% (0/2086)
Total	**2.9% (306/10719)**	**2.4% (187/7813)**	**2.7% (149/5574)**	**1.3% (62/4902)**	**1.3% (59/4456)**	**1.3% (58/4386)**

From the similarity of HIV prevalence after excluding group 1 category alone compared to exclude both group 1 and group 2 categories, we decided to exclude only group 1. The trend of HIV prevalence by year in each surgical ward, after excluding group 1 category disease and the records for which we did not know the diagnosis because of missing log books, are shown in figure 7.1.1 and 7.1.2.

Figure 7.1.1: Trends of HIV prevalence in female surgical wards by year of treatment, after excluded group 1 category

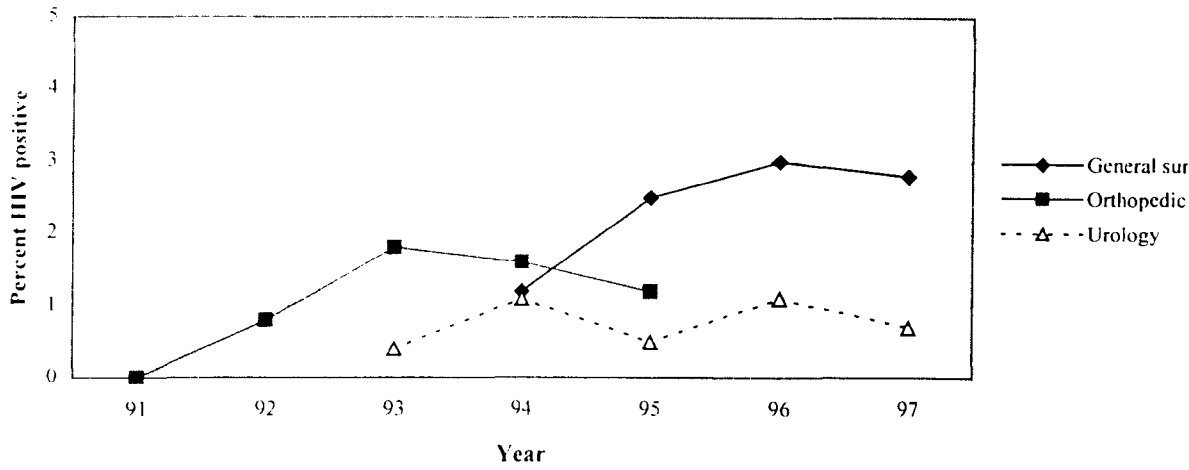
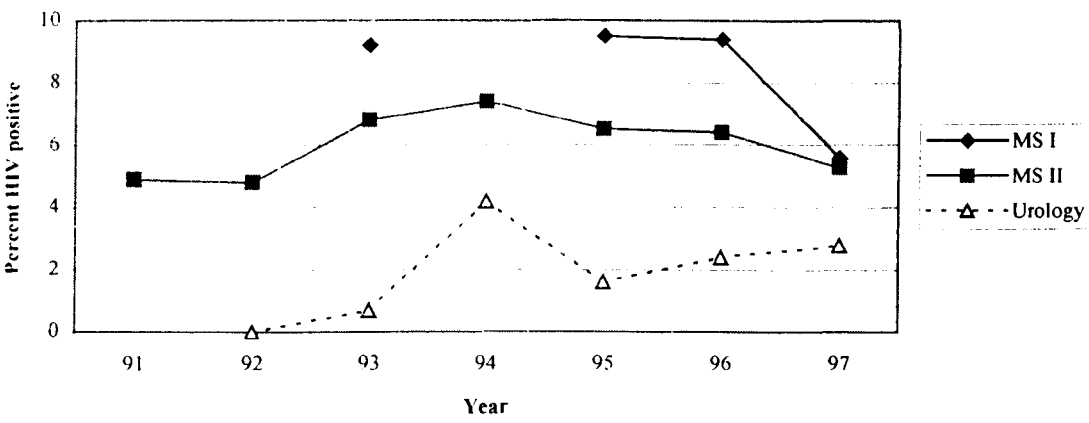


Figure 7.1.2: Trends of HIV prevalence in male surgical wards by year of treatment, after excluded group 1 category



The HIV prevalence by age group in each ward had a similar pattern to that in the other control groups: it started with peak prevalence in aged 20-24 years in the earliest years, the peak moved to aged 25-29 years in the middle years and to age 30-34 in the latest years in males, while females had the peak of HIV prevalence in their aged 20-24 years in most years. Overall, the highest HIV prevalence in males was in 25-29 year olds and in females in 20-24 year olds (figure 7.2.1 and 7.2.2).

Figure 7.2.1: HIV prevalence in female surgical wards by age group, excluding group 1

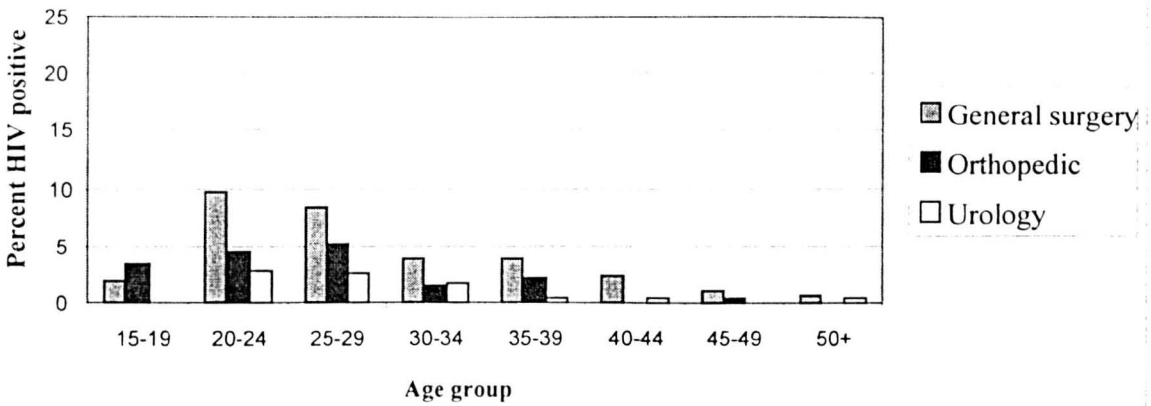
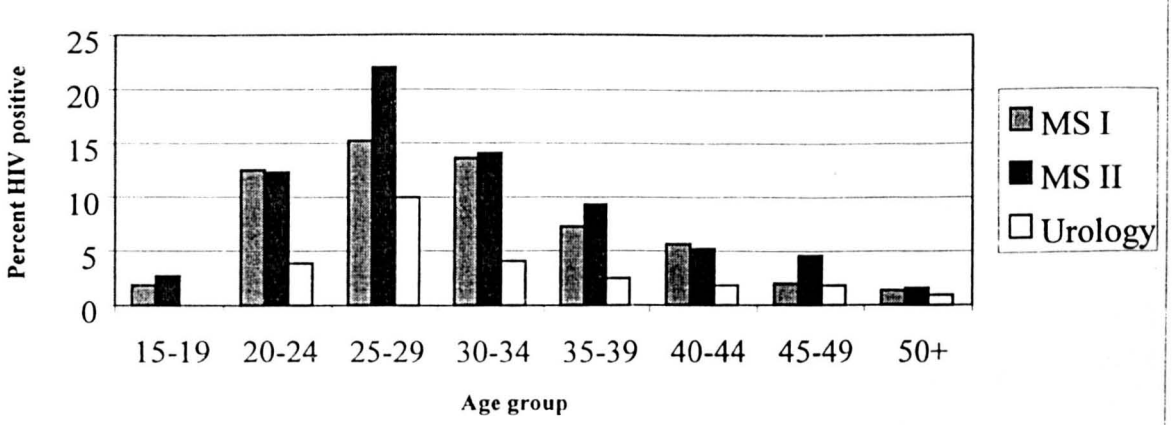


Figure 7.2.2: HIV prevalence in male surgical wards by age group, excluding group 1



Discussion

Among all of the 5 control groups in our study, the surgical ward group is the only group consisting of ill people (the other groups being blood donors, ANC attenders, delivery cases and military conscripts). Although HIV is known to cause more medical than surgical problems, there are many reports about HIV related surgical condition, of both infectious and non-infectious origins. Since AIDS is a multisystem disease, patients can present to the surgeon with a wide range of pathologies including Kaposi's sarcoma, lymphadenopathy and sepsis. The more common sites of sepsis are the female genital tract, anorectum, pleural cavity, soft tissue (necrotizing fasciitis) and bone and joint [Watters 1994]. A study in a rural South African hospital of admission trends during the early years of the HIV epidemic showed that among ANC women HIV prevalence was 4% in 1992, 14% in 1995 and 29% in 1998. During this period the largest increase in hospital admissions was in the adult tuberculosis ward (360%) and there was also an upward trend in adult medical-non tuberculosis ward and pediatric medical admission and, to a lesser extent, female surgical ward [Floyd K et al. 1999]. However, male surgical ward and the other remaining wards had relatively erratic patterns and there was no convincing evidence that any trend existed. The authors did not discuss in detail about the different types of disease or conditions between female and male surgical wards in this setting. Another study from Quebec, about sentinel hospital surveillance of HIV infection, used data from patients attending the outpatient surgical service as a proxy indicator for general population HIV prevalence [Alary et al. 1994]. The calculation of number of HIV infected people using the adjusted sero-prevalence rate (for age, sex and geographic distribution) from these surgical outpatients was close to a previous estimation using back-calculation methods. However, this study used data from outpatients group, which might be less related to HIV infection compared to the data from admitted patients.

In our data, we observed a relatively high HIV prevalence in the male general surgery 2 ward, which has a higher proportion of infection-related surgical conditions such as acute appendicitis or abscess, etc. Therefore, we decided to group all patients into 3 levels by the degree of relatedness to HIV infection, based on their diagnosis. Although almost all of these groupings were based on the knowledge of HIV-related condition from the literature review, and the grouping was done blind to the HIV

results, it contains a degree of subjectivity by the researcher's judgement. For instance, we decided to group all of the infection-related conditions such as abscess, acute appendicitis, acute cholecystitis in the "highly-related" to HIV group (group 1). For some conditions that are usually multifactorial but have also been reported as HIV related condition such as cancer, gangrene, fasciitis etc. we coded them as the "less-related" to HIV group.

Since the HIV prevalence after excluding group 1 only and group 1& 2 was very similar, we decided to keep group 2 in our analysis in order not to have too small a sample size in each group. With the exclusion of only group 1 from the analysis, we hope, the bias from this subjective selection of exclusion should not be very high.

Although we tried to reduce the possible bias in our data, some degree of bias may have remained. As well as keeping some HIV related conditions in our data (those in group 2), other factors that make the difference between ill (enough to admit) people and general population might also be related to HIV infection, such as alcohol. It is widely known that in Thailand alcohol is one risk factor to enhance the HIV risk behavior [Macqueen et al. 1996]. At the same time alcohol is also a well-known factor for traffic injury in this country. Therefore, to some extent, the non-HIV related group (group 3) such as trauma patients can also be related with HIV infection via confounding factors. However, it is very difficult to estimate the size of this bias. Among our male control group, surgical patients and blood donors were the only data we have to see the problem in other age groups, outside the young men who are well represented by the military data. While the data from blood donors are widely accepted to be an underestimate of the general population HIV prevalence, our surgical data should give us some clue about the upper bound of the prevalence.

One main limitation of our surgical data is that they were originally collected for routine use only, not for research purposes like most of our study groups. Therefore we were faced with a lot of lost data in some years, including some further loss when we tried to enter these data for a second time to examine the diagnosis. With this limitation, and with the consideration that the data from each surgical ward may have a different level and direction of bias, and that the proportion of data from each ward varied over time we decided to separate each ward as different sources of data

because we were afraid that if we mix all surgical wards together the level and direction of bias will change overtime, making the results difficult to interpret.

Even after the exclusions and allowing for age and year, the discrepancy in HIV prevalence between urology and the other wards remained. Although it was policy to test all patients, only HIV positive results were recorded in the logbooks and it was assumed that all others were negative. We suspect that the low numbers of positive results from urology compared to the other wards may have arisen due to failure to test all individuals. Results from the urology wards have therefore been excluded from further analysis

In summary, the data included in further analyses were:

- Surgical patients admitted in Chiang Rai hospital between 1991-1997 with available data in all wards except uro-surgery
- Aged at least 15 years
- Resident in Chiang Rai province
- Excluding patients with diagnoses likely to be linked to HIV and patients for whom logbooks were not available at the time of data entry of the diagnosis variable

Chapter 8: Blood bank data

Methods

HIV testing has been a part of the screening test in Thailand's central blood bank since 1987. Since 1989, this scheme has been implemented in the blood banks throughout the country, including Chiang Rai hospital.

In Chiang Rai province there are 3 public hospitals that have their own blood bank, Chiang Rai hospital, Mae Chan and Phan hospitals, but the latter 2 have very small blood banks for their own use. Therefore Chiang Rai hospital blood bank is the major supplier and collects blood from all over the province. About 1000 units of blood are collected per month by the hospital blood bank. Approximately half of the donations are made at the hospital and the remainder at remote donation sites. Apart from going to different districts, mobile teams visit institutions. Before HIV infection was widespread, prison was one of the most frequent sources of blood donation for the mobile team but prison has been excluded from the schedule of Chiang Rai blood bank since wide recognition of the HIV epidemic in Thailand, around 1989. For the hospital sites, relatives or friends of admitted patients are one of the main groups of donors.

In general blood donors must be 17 to 60 years old, weigh more than 45 kg, have haemoglobin level greater than 12 g per dL, and have a blood pressure of more than 100 over 60 mmHg. However, the age criterion is usually waived for regular donors who are in good health. All blood units are tested for HIV antibody, HbsAg and VDRL as a marker of Treponema pallidum infection. The tests are performed simultaneously. Blood that reacts to any of the three infectious agents is discarded. In 1994 the HIV antigen (p24) was added to increase the safety of the blood supply for seronegative window period HIV-infected donors [Sawanpanyalert 1996b].
Blood was not routinely tested for hepatitis C virus antibody until early 1998. HIV test was the same as previously described in chapter 3.

During September 1993 to August 1994 there was a study of donor exclusion criteria for a research degree thesis in Chiang Rai hospital [Sawanpanyalert et al. 1996a]. During that period, the research provided for subsequent testing by Western Blot (BIO-RAD) for all HIV positive blood at the HIV/AIDS collaboration laboratory in Nonthaburi province.

After early 1998 all tests for infectious markers were done in a regional blood center located in a major province (Chiang Mai) about 183 km away, as a part of the National blood center's policy to standardize laboratory tests in Thai blood banking system. Blood specimens are shipped via plane to the center and laboratory results are transmitted back via facsimile [Khaisuwan et al. 1999].

In 1991 the implementation of donor self exclusion (DSE) began in the National Blood Center [Kitsuwannakul et al. 1994] and some hospitals. The primary purpose of donor deferral criteria is to exclude donors who are HIV-infected but still in the seronegative window period [Sawanpanyalert et al. 1997]. Prospective blood donors were presented with a list of behavioral risk factors, such as a history of prostitute visits or homosexual practice without condom in the past 3 months, history of injecting drug use or commercial sex worker and history of sexually transmitted disease in the last 12 months, etc. Chiang Rai hospital is one of the hospitals that had early implementation of this DSE and the practice was still used throughout the period of the blood donor research project. After 1994 the questionnaire-form DSE and also the new adapted DSE from the project was no longer used in routine practice. In practice, current blood donors do not receive any counseling. Those who have positive HIV results are informed and are not accepted to donate again. Nevertheless, for the HIV positive donors seen by the mobile team, there is no mechanism to tell the person of their results unless that person inquires directly to the hospital. Hence there are some repeat mobile donors who are HIV-positive and keep on donating.

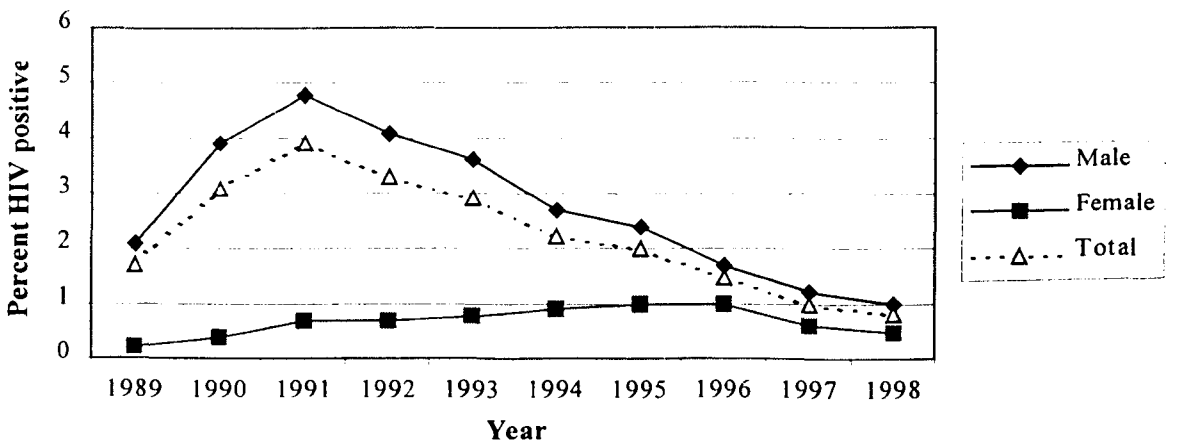
The blood donor data are extracted from the computerized source in the blood bank. These data have been kept in computer since 1994 for research purposes. Since then the RIT has sponsored data entry cost as a part of their on-going project in collaboration with Chiang Rai hospital. The data are double entered by 2 data entry clerks and validated and cleaned by RIT personnel.

Results

From 1989 to 1998 there were 148,782 donations in Chiang Rai hospital, with the annual number increasing slightly over time (from 11,976 in 1989 to 19,027 in 1998). The overall male to female ratio was 3:1. The mean age was 33.6 years (range 15-78 years). About one third (31.5%) of this group was first time donors while median number of donation times was 3 (range 1-120).

The overall HIV prevalence was 2.1% (2.6% in male and 0.7% in female). When looking at the HIV prevalence overtime we can see a continuous decreasing after 1991. However the peak in female blood donors came much later (1995-1996) as in figure 8.1.

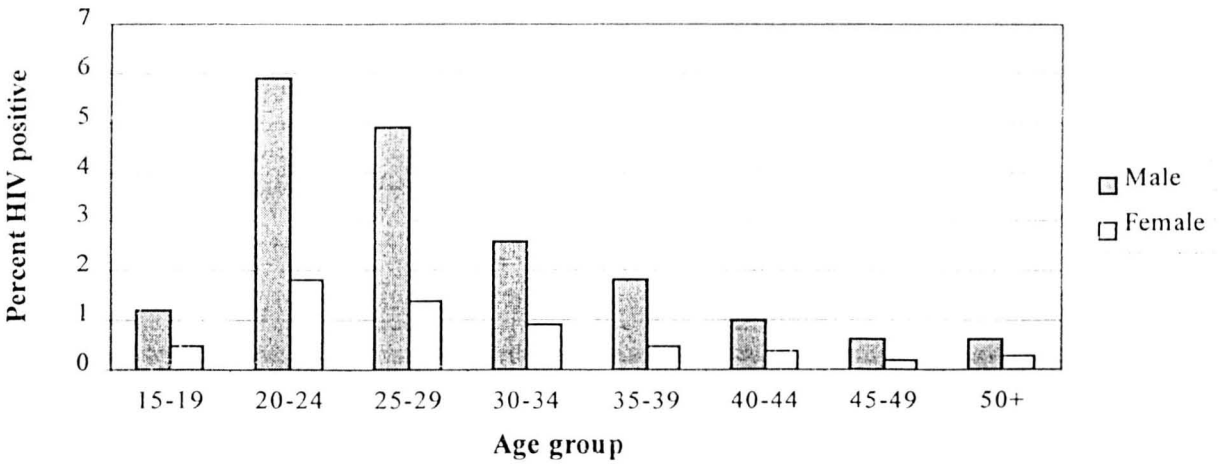
Figure 8.1: HIV prevalence among blood donors in Chiang Rai hospital by sex, 1989-1998.



During the study period, there were 68 cases that did not have HIV results recorded, of which 75% (51 cases) were from 1998. This was because after the HIV tests for blood donors was moved to the regional blood center in Chiang Mai province, there were more undetermined HIV results than previous results from the test in Chiang Rai hospital.

The highest HIV prevalence in both genders was among 20-24 years (figure 8.2).

Figure 8.2: HIV prevalence in each age group, by gender, Chiang Rai hospital, 1989-1998.



Because the HIV prevalence of repeated donors is more likely to underestimate HIV prevalence due to the exclusion of known HIV positive cases from the test, we should separately analyze the first time donors from the whole data set.

After excluding 11976 donors in 1989, there were 130,901 donors (95.7%) who lived in Chiang Rai province. Among 39170 first time donors, there were 28710 men and 10457 women (3 unknown), with a male to female ratio of 2.7:1. This group has younger average age than the total blood donors (mean age 29.3 years, range from 15-78 years). The average number of first time blood donors did not increase during this 10 year period.

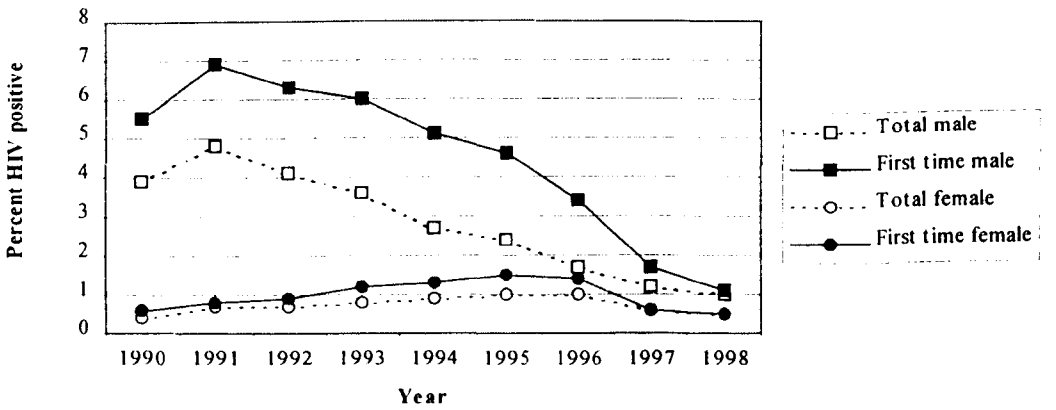
After the wide awareness of HIV infection via blood transfusion, the geographic distribution of donors has changed to include a higher proportion of first time donors from rural sites (table 8.1).

Table 8.1: Geographical distribution of the first time blood donors in Chiang Rai hospital by year.

Year	Number of donors from the Muang District (urban district) of Chiang Rai province
1990	1,161 (29.4%)
1991	1,435 (30.5%)
1992	1,209 (29.3%)
1993	970 (24.7%)
1994	1,000 (21.9%)
1995	800 (17.1%)
1996	883 (19.5%)
1997	856 (20.2%)
1998	968 (22.1%)
Total	**9282 (23.7%)**

As expected, the HIV prevalence in both genders of first time blood donors was higher than HIV prevalence overall (4.3 % vs 2.1% in males and 1.0 % vs 0.7% in females). For the HIV prevalence overtime, the pattern between the total blood donors and the first time donors was the same (figure 8.3).

Figure 8.3: HIV prevalence of blood donor in Chiang Rai hospital compared between the first time and total blood donor



The age distribution of HIV prevalence by year for the first time donors had a similar pattern as that in all donors. The highest prevalence was found in 20-24 years during the initial years in both genders before it shifted to older age group in the later years in males while females did not show a shift to older ages (table 8.2-8.3).

Table 8.2: HIV prevalence of male first time blood donors in Chiang Rai hospital, by age group and year of donation

Year	Age group								All ages
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50+	
1990	3.3% (16/485)	11.4% (88/773)	7.1% (36/510)	3.3% (17/520)	2.1% (8/374)	1.4% (3/212)	0% (0/92)	0% (0/100)	**5.5% (188/3066)**
1991	3.0% (20/661)	15.0% (128/855)	9.3% (57/611)	4.4% (24/547)	2.7% (11/403)	1.5% (4/274)	0.8% (1/128)	1.1% (1/88)	**6.9% (246/3567)**
1992	1.7% (8/475)	10.4% (76/734)	11.0% (61/557)	4.6% (21/458)	4.7% (21/448)	2.5% (6/239)	1.7% (2/120)	0% (0/76)	**6.3% (195/3107)**
1993	0.8% (5/628)	11.6% (64/552)	11.9% (58/486)	6.2% (28/455	3.8% (16/420)	1.6% (4/247)	2% (2/100)	0% (0/67)	**6.0% (177/2955)**
1994	1.2% (6/522)	9% (61/675)	8.7% (45/516)	3.7% (20/547)	4.8% (23/484)	2.1% (6/287)	2.3% (4/173)	1.5% (1/65)	**5.1% (166/3269)**
1995	0.9% (4/433)	6.6% (40/611)	9.2% (49/531)	4.2% (22/528)	4.4% (23/519)	1.6% (6/365)	2.1% (4/192)	1.0% (1/97)	**4.6% (149/3276)**
1996	0.2% (1/656)	3.4% (21/622)	8.0% (34/425)	5.4% (27/501)	3.2% (15/464)	3.1% (10/325)	0.6% (1/170)	0% (0/78)	**3.4% (109/3241)**
1997	0.4% (3/757)	2.3% (13/574)	3.2% (12/372)	5.0% (19/384)	1.0% (4/397)	0.3% (1/350)	0.6% (1/177)	0% (0/67)	**1.7% (53/3078)**
1998	0% (0/766)	1.1% (7/633)	2.8% (9/327)	2.3% (9/395)	2.3% (9/388)	0.3% (1/326)	0% (0/162)	0% (0/61)	**1.1% (35/3058)**

Table 8.3: HIV prevalence of female first time blood donors in Chiang Rai hospital, by age group and year of donation

Year	Age group								All ages
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50+	
1990	0.7% (1/149)	1.6% (2/126)	0% (0/148)	0.6% (1/164)	0% (0/151)	0% (0/88)	0% (0/40)	6.7% (1/15)	**0.6% (5/881)**
1991	0.5% (1/223)	2.5% (3/118)	1.8% (3/171)	0.9% (2/231)	0% (0/181)	0% (0/128)	0% (0/59)	0% (0/16)	**0.8% (9/1127)**
1992	0.5% (1/213)	1.8% (2/112)	0.6% (1/159)	0.6% (1/181)	1.1% (2/180)	0% (0/101)	2.6% (1/38)	5.6% (1/18)	**0.9% (9/1002)**
1993	0% (0/197)	3.6% (4/110)	3.1% (5/162)	0% (0/174)	0.6% (1/172)	1.8% (2/110)	0% (0/33)	0% (0/5)	**1.3% (12/963)**
1994	1.5% (4/261)	2.7% (4/150)	1.9% (4/206)	1.2% (3/262)	0.5% (1/212)	0.8% (1/131)	0% (0/52)	0% (0/9)	**1.3% (17/1283)**
1995	0.5% (1/209)	5.0% (8/159)	3.9% (8/208)	1.0% (3/292)	0.4% (1/253)	0% (0/189)	0% (0/71)	0% (0/19)	**1.5% (21/1400)**
1996	2.4% (7/288)	3.0% (4/135)	2.1% (4/194)	0% (0/231)	0.9% (2/214)	0.7% (1/155)	0% (0/63)	0% (0/10)	**1.4% (14/1290)**
1997	0% (0/269)	2.9% (4/140)	1.3% (2/153)	0.5% (1/217)	0% (0/201)	0% (0/124)	0% (0/58)	0% (0/6)	**0.6% (7/1668)**
1998	0.2% (1/469)	2.5% (3/119)	1.4% (2/142)	0% (0/196)	0.6% (1/178)	0% (0/139)	0% (0/54)	0% (0/5)	**0.5% (7/1302)**

Discussion

Although blood donors come from the general population, the blood bank has aimed to get donors from a low risk population since the beginning of the HIV epidemic. The condition of good weight, normal hemoglobin level and normal blood pressure is expected to prevent some ill people from donating. Moreover, in the process of recruitment some donors who had recognized risk factors (e.g., they were known from their previous donation records to be HBsAg-positive or VDRL-reactive, or they reported an active genital ulcer) were refused. Therefore some people with high HIV risk behavior are already excluded.

After the spread of the HIV epidemic in Thailand, many strategies were used to increase the safety of donated blood. Apart from using the test for HIV Ag (p24) and the donor self- exclusion criteria, the proportion of regular donation sites (3 or more visits a year) increased steadily over time especially after 1992 [Khaisuwan et al. 1999]. This can encourage repeat donors who are generally at less risk for HIV infection. Therefore, the data from blood donors should represent the low risk group of the population.

It is interesting to see how these various efforts to get low risk donors affected the trend of HIV infection from these data. From the overall trend, the peak of blood bank data was in 1991, the same year of the beginning of the well known government control measure "100% Condon Program" [Rojanapithayakorn et al. 1996]. Because the data we get from blood donors is HIV prevalence (not incidence) which should not be very sensitive to the new changes and since the first year of the implementation should not have made an abrupt impact on behavioral change, this decrease can not come from this control measure. Compared to other control groups, this change in the blood donors was the earliest group before the downward trend in the military conscripts in 1993 and followed by ANC and delivery groups in 1995. Therefore the main reason for the change among blood donors should come from the various efforts to reduce the risk for HIV infection in donated blood. Although the evaluation of the DSE process in Chiang Rai hospital showed only 9.9% sensitivity and 6.6 percent positive predictive value for HIV infection [Kitsuwannakul et al. 1994], the implementation of DSE process, combined with the changing process to seek the safe

blood should be the key factors for this change. However, it is noteworthy to observe that most of the targets (both DSE questions and the repeat donor groups) were focussed in males. From figure 1 we can see that while the HIV prevalence in males started to decrease since 1992, the prevalence in females kept rising until reaching its peak in 1995, before gradually decreasing since 1997. This peak in females was consistent with the data from ANC and delivery group that also had the peak in 1995. At the national level, a similar trend was observed [Nuchprayoon et al. 1995].

The HIV-positive donors are informed about their HIV status, for the hospital site donors and also some of mobile site donor who want to know the test result, and HIV positive individuals are not allowed to donate blood again. Therefore the HIV prevalence among the repeat donors should be lower than the first time donor which we saw in our data. It is therefore necessary to exclude repeat donors from our further analysis.

In summary, the data included in further analyses were:

- First time blood donors who gave blood to Chiang Rai hospital during 1990-1998
- Aged at least 15 years
- Resident in Chiang Rai province

Chapter 9: Case-control study

Methods

In chapter 3, I described the cases and the final case definition. The various control groups and their definitions and exclusions are described in chapters 4-8. To further validate the control groups we compared the HIV prevalence in each of the different control groups, stratified by age and year of study. To control for the different age structure in each control group, the age standardized HIV prevalence (using direct standardization method, based on Chiang Rai population structure in 1996) in each control group was compared for each year. This allowed identification of biased control groups.

The remaining groups were used in the study, using all types of TB patients as cases for separate comparison with each of the remaining control groups. Because we considered time after the beginning of the HIV epidemic as one of the major factors affecting the odds ratio (OR) for the association between HIV and TB, we stratified our analysis by year of TB treatment. Age and place of residence were also treated as potential confounders. The district variable (place of residence) was classified into 2 categories, Muang district and other districts because Muang district is more urban and likely to have higher risk of both HIV and TB than the others. Since the control groups for men and women were different, with different biases, we conducted separate analyses for men and women. In order to reduce the problem of small sample size, especially in the case group, we used 2 year intervals in our analysis. Age was grouped into 5 year age bands in the younger groups and then 35-44, 45-54 and 55 years or more. Interaction with age was explored.

The ORs calculated using the control groups that were likely to be the least biased were used to calculate the proportion of TB in the population that can be attributed to HIV - the population attributable fraction (PAF). This was calculated for each time period, separately for males and females. Since we are concerned about the bias in our

control groups, particularly in the age specific estimates of HIV prevalence, we decided to use the formula

$$PAF = p' (RR-1)/RR$$

where p' is the proportion of exposed (HIV positive) among the cases, to avoid using the prevalence of HIV among controls as required by the more frequently used PAF formula, and substituting RR by OR using the rare disease assumption. Because of the changing age structure among TB patients (cases) during the study period, with a higher proportion of young adults in the later years, age-adjusted PAFs were calculated [Schlesselman 1982].

Results

Comparison of control group HIV prevalence

The number and main characteristics of the case and control groups after exclusion of data as described in the previous chapters are shown in table 9.1.

Table 9.1: The characteristics of cases and controls

Study group	Number		Reasons for exclusion*	Mean age (SD)	Gender (% male)	Residence (% living in Muang district)
	At the beginning	After exclusion of some data				
Case						
TB patients	13579 (provincial database)	4031	1. Old or relapse cases 2. Data from other hospitals	41.5 (16.9)	71.4%	45.4%
Control						
Blood donor	148782	M=28,710 F=10,457	Multiple time donors	29.3 (9.5)	73.3%	23.7%
ANC	10,628	4,417	1. Multigravida 2. Age >44 years	22.4 (4.7)	0%	61.1%
Delivery	43326	15,454	1. Multigravida 2. Age >44 years	22.9 (4.5)	0%	44.0%
Surgical**						
- female orthopedic	5599	3,859	1. Patients diagnosed with HIV related conditions 2. Patients without diagnosis information	48.5 (20.8)	0%	28.3%
- female general surgery	10,868	7,029		47.8 (17.6)	0%	25.4%
- male general surgery1	13,952	2,702		35.0 (15.8)	100%	30.9%
- male general surgery2	12,688	8,758		47.0 (17.9)	100%	26.7%
Conscript	6,340	6,310	Age more than 24 years	21.1 (0.5)	100%	-

* In all groups, the exclusion of patients aged less than 15 years and those who lived outside Chiang Rai province were applied.
**Urology was excluded as describe in the surgical section

We compared the HIV prevalence among all groups of controls in 5 year age groups for each 2 year interval, separately for males and females, to look for any outlier control groups (figure 9.1 and 9.2). The results showed very low HIV prevalence in blood donors in both genders while ANC and delivery patients consistently had the highest HIV prevalence among female control groups.

Figure 9.1.1: HIV prevalence in male control groups, by year, by age group

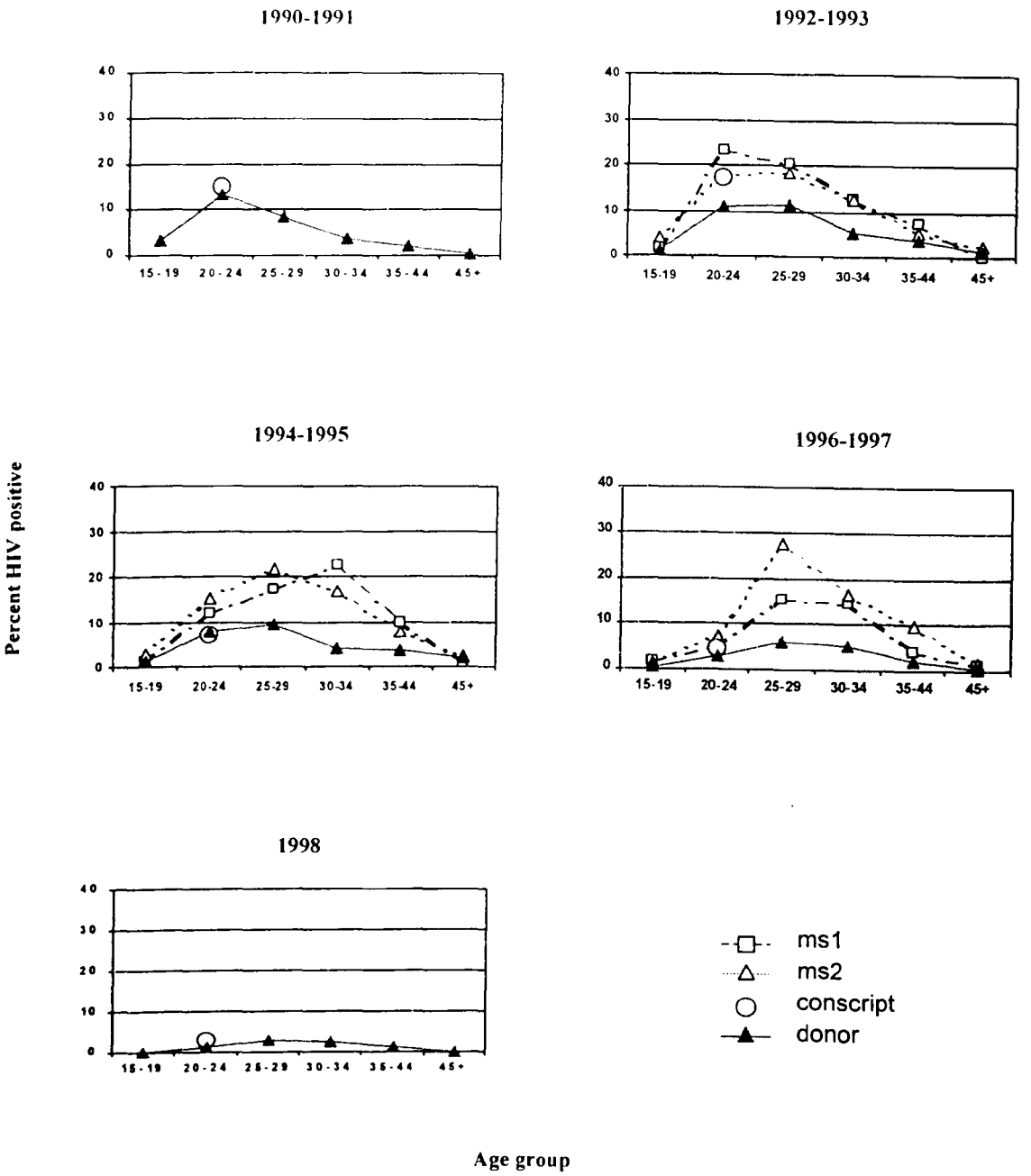
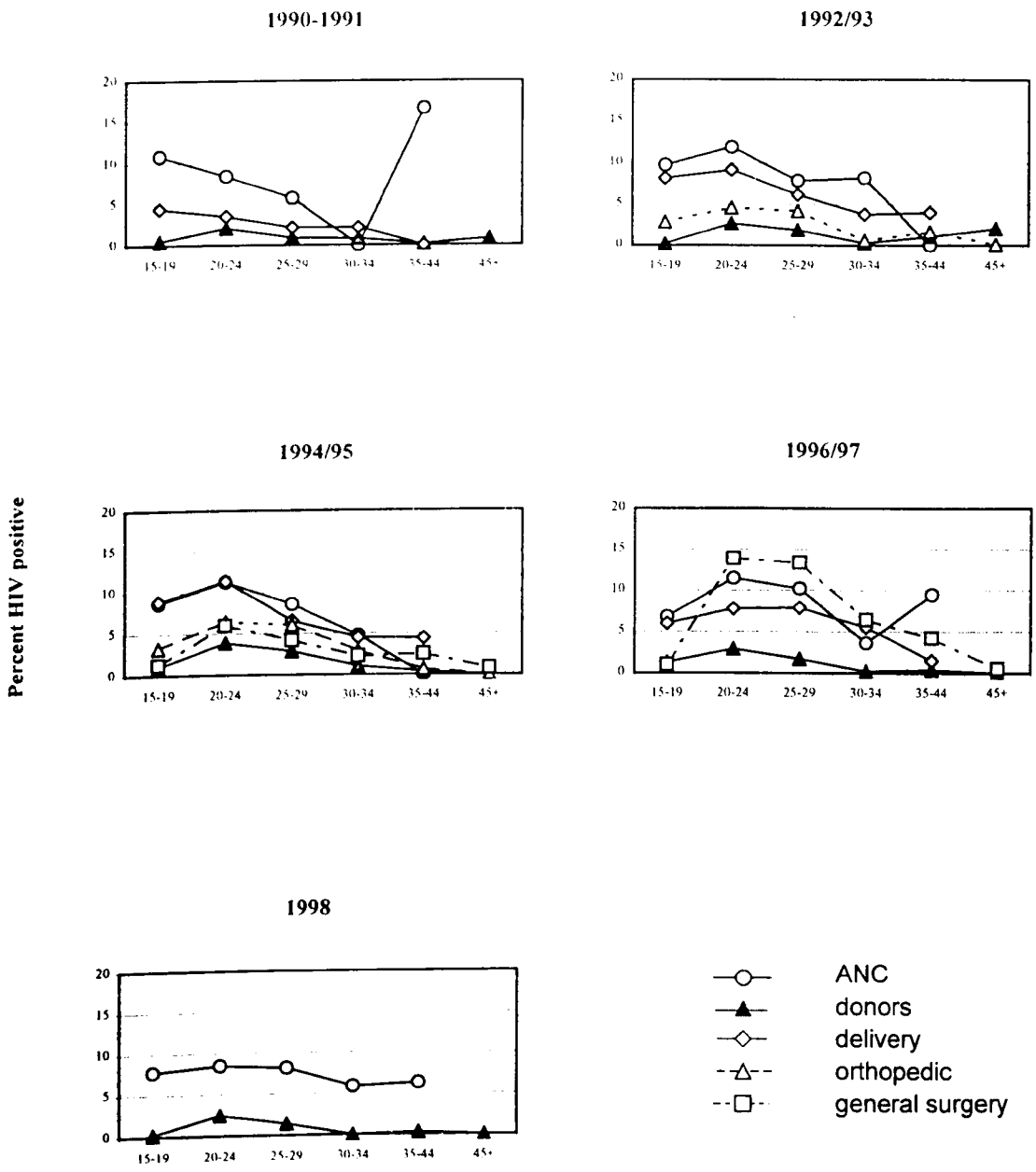


Figure 9.1.2: HIV prevalence in female control groups, by year, by age group



To further investigate the effect of different age structure on the HIV prevalence, we compared the HIV prevalence in the control groups after standardizing. The same biases are still apparent (table 9.2).

Table 9.2.1: Age standardized HIV prevalence in male control groups (except the military conscript)

Year	Blood donors	General surgery I	General surgery II
1990/1991	4.0%	-	-*
1992/1993	4.7%	8.9%	8.5%
1994/1995	4.1%	9.3%	9.5%
1996/1997	2.4%	6.1%	9.5%
1998	1.1%	-	-

* data in 1991 were excluded because of small numbers.

Table 9.2.2: Age standardized HIV prevalence in female control groups

Year	Blood donors	ANC	Delivery	General surgery	Female orthopedics
1990/1991	0.8%	9.3%	2.0%	-	-*
1992/1993	1.5%	6.4%	5.3%	-	1.8%
1994/1995	1.2%	5.6%	6.6%	2.5%	2.4%
1996/1997	0.8%	8.5%	5.1%	5.5%	-
1998	0.6%	7.1%	-	-	-

* data in 1991 were excluded because of small numbers.

HIV prevalence in the ANC and delivery ward is likely to overestimate that in the population in the younger age groups since only a proportion of women in these groups have ever been sexually active as already discussed in ANC section. To explore this, data on age at sexual debut was taken from the behavioural surveillance survey [Ungchusak et al. 1996]. In this survey only 20% of female factory workers aged between 15-19 years reported that they had ever had sexual experience,

compared to around 60% between 20-24 years and 80% aged 25-29 years. This behaviour surveillance survey started in 1995 and studies only 3 groups of women (factory workers, secondary school students and pregnant women) as well as male military conscripts. Information is only available on those aged 15-29. Of the three groups available for the women, factory workers are likely to be the most representative of women in the general population in terms of age at sexual debut. From the result of this surveillance we considered that our HIV prevalence among ANC and delivery groups are overestimated in younger women because only half or fewer are sexually active in general population, while all of ANC and delivery women have been sexually active. Therefore, we adjusted the HIV prevalence in these 2 groups by using the proportion of women who had already been sexually active in each age group. For the women aged 30 or more we left the proportion unchanged: most are sexually active by then and by this age there is a higher probability to have HIV-associated reduced fertility. Following this adjustment the HIV prevalence in both ANC and delivery patients became close to the surgical control groups (table 9.3) suggesting that this explains the discrepancy.

Table 9.3: Comparing HIV prevalence of each female control group by 5 year age groups in 2 year intervals, after adjustment for proportion sexually active for ANC and delivery control groups

Year	General surgery	Orthopedic	Blood donors	ANC	Delivery	Adjusted ANC	Adjusted Delivery
1990/91							
- 15-19	-	-	0.5%	10.9%	4.5%	2.1%	0.9%
- 20-24			2.0%	8.5%	3.6%	5.0%	2.1%
- 25-29			0.9%	5.8%	2.2%	4.6%	1.8%
1992/93							
- 15-19	-	2.9%	0.2%	9.8%	8.2%	1.9%	1.6%
- 20-24		4.6%	2.7%	11.9%	9.2%	7.0%	5.4%
- 25-29		4.2%	1.9%	7.9%	6.2%	6.3%	5.0%
1994/95							
- 15-19	1.3%	3.3%	1.1%	8.7%	8.9%	1.7%	1.7%
- 20-24	6.0%	6.5%	3.9%	11.3%	11.4%	6.7%	6.7%
- 25-29	4.1%	6.1%	2.9%	8.6%	6.6%	6.9%	5.3%
1996/97							
- 15-19	1.0%	-	1.3%	6.8%	6.0%	1.3%	1.2%
- 20-24	13.9%		2.9%	11.5%	7.8%	6.8%	4.6%
- 25-29	13.4%		1.7%	10.2%	7.9%	8.2%	6.3%
1998							
- 15-19	-	-	0.2%	7.8%	-	1.5%	-
- 20-24			2.5%	8.5%		5.0%	
- 25-29			1.4%	8.1%		6.5%	

Comparison of odds ratio using each control group

The odds ratios for the association of HIV and TB calculated using the various control groups are shown in table 9.4.1 and 9.4.2. As previously mentioned (chapter 3) there was an increasing proportion of unknown HIV results among TB patients in the later 2 years of the study period, but these cases with unknown HIV status are more likely to be HIV negative and we have treated them as HIV negative cases in our analysis. Calculations were done separately for males and females. For comparison with the conscripts only TB patients aged 20-24 were used, and for comparison with the ANC and delivery control groups the age range 15-44 was used.

Table 9.4.1: OR for the association of TB and HIV using different control groups of male patients. TB patients with unknown HIV results are treated as HIV negative.

Ward	Blood donor	Conscript*	MS1**	MS2***
Crude OR	18.5 (16.9-20.3)	19.7 (14.7-26.3)	14.4 (12.1-17.2)	12.7 (11.3-14.3)
Adjusted for age, year, district	34.8 (30.7-39.3)	27.2 (20.0-37.0)	19.6 (15.9-24.1)	11.6 (10.2-13.3)
Adjusted for age, district				
- 1990/1991	4.8 (3.1-7.5)	1.4 (0.3-6.8)	-	3.3 (1.8-6.3)
- 1992/1993	17.6 (13.4-23.3)	6.5 (3.4-12.4)	12.5 (8.1-19.1)	8.6 (6.5-11.2)
- 1994/1995	35.4 (27.9-44.9)	28.5 (15.7-52.0)	16.1 (10.1-25.6)	12.2 (9.7-15.3)
- 1996/1997	79.5 (61.1-103.4)	41.9 (25.0-70.0)	28.2 (20.9-37.9)	16.2 (12.8-20.7)
- 1998	206.8 (130.3-327.9)	139.8 (55.7-350.8)	-	-
Adjusted for year, district				
- 15/19	32.1 (14.4-71.3)	-	26.5 (6.4-109.0)	10.0 (3.7-27.0)
- 20/24	32.0 (23.2-44.1)	27.2 (20.0-37.0)	19.6 (11.4-33.5)	11.8 (7.9-17.7)
- 25/29	37.8 (28.0-48.7)	-	24.0 (15.8-36.4)	10.2 (7.5-13.7)
- 30/34	54.3 (41.8-70.7)	-	15.5 (10.1-23.9)	15.0 (10.9-20.7)
- 35/44	37.0 (28.9-47.2)	-	22.7 (14.4-35.8)	15.4 (11.6-20.3)
- 45+	15.5 (9.3-25.7)	-	22.9 (9.9-53.2)	7.6 (5.7-10.0)

* no information available about district
** MS1 = male general surgery ward 1
*** MS2= male general surgery ward 2

Table 9.4.2: OR for the association of TB and HIV using different control groups of female patients. TB patients with unknown HIV results are treated as HIV negative.

Ward	Blood donor	Delivery *	ANC*	General surgery	Orthopedic
Crude OR	61.1 (48.7-76.5)	15.3 (12.9-18.3)	13.0 (10.8-15.5)	32.0 (25.7-39.9)	31.4 (22.2-44.4)
Adjusted for age, year, district	92.1 (71.0-119.7)	17.7 (14.4-21.8)	14.4 (11.7-17.8)	22.2 (17.3-28.4)	29.2 (19.8-43.2)
Adjusted for age, district					
- 1990/1991	1.2 (0.1-13.8)	0.7 (0.1-5.2)	0.1 (0.0-1.2)	-	-
- 1992/1993	59.3 (31.1-113.1)	12.9 (8.0-20.8)	10.3 (5.9-17.8)	-	32.6 (17.9-59.2)
- 1994/1995	55.9 (33.9-92.0)	13.1 (9.0-19.1)	12.3 (7.9-19.1)	18.1 (12.3-26.8)	28.3 (16.8-47.8)
- 1996/1997	180.0 (108.5-298.6)	35.6 (25.3-50.2)	23.8 (16.0-35.3)	25.8 (18.6-35.8)	-
- 1998	283.8 (122.5-657.4)	-	22.5 (14.1-35.9)	-	-
Adjusted for year, district					
- 15/19	64.7 (29.5-141.9)	5.9 (3.0-11.4)	4.2 (2.3-7.6)	38.7 (11.1-134.5)	28.5 (9.3-87.8)
- 20/24	66.1 (40.3-108.3)	19.1 (13.3-27.3)	17.0 (12.0-24.2)	22.0 (12.5-38.6)	26.3 (12.0-57.3)
- 25/29	77.4 (47.3-126.6)	21.9 (15.2-31.6)	17.8 (12.1-26.2)	24.5 (14.2-42.1)	19.1 (8.9-40.8)
- 30/34	237.7 (112.4-502.9)	21.0 (12.4-35.5)	26.2 (12.9-53.3)	40.8 (20.4-81.3)	45.7 (15.5-134.2)
- 35/44	126.9 (62.5-257.5)	16.4 (7.2-37.2)	9.8 (3.7-25.9)	17.4 (10.1-30.0)	37.9 (13.3-108.5)
- 45+	13.8 (4.1-46.2)	-	-	14.4 (7.8-26.7)	113.9 (14.0-926.3)

* This calculation used individual level data. It is therefore not adjusted for the proportion sexually active in each age group.

The data from table 9.4 showed that adjusted odds ratio in both sexes increased with year reaching extremely high levels. Odds ratio by age group had no consistent trend although there was an interesting observation of low OR among elderly in some control groups.

Calculation of PAF

Since there was no evidence that the association of HIV and TB varied by age we used a single odds ratio for all age groups for the calculation of the PAF. The selected odds ratio for each time period was that which we felt likely to be least biased: that from the comparison with the military conscripts for males and with ANC attenders aged 20-29 years for females. We chose age 20-29 years as the least biased group for ANC attenders because highest proportion of ANC attenders came from these 2 age groups and the underestimate due to some population being sexually inactive may be balanced by the association of HIV and lower fertality. An age-adjusted PAF in each time period was calculated to counter the problem of different age structures in TB cases over time. The results show a continuous increase in PAF overtime in all age groups (except age 15-19 years in which the number of TB cases is very small) (table 9.5).

Table 9.5.1: Population attributable fraction (PAF) of HIV infection to tuberculosis in males* in Chiang Rai, 1990-1998

Age group	15-19	20-24	25-29	30-34	35-44	45+	Adjusted PAF
1990-91	0	10.7%	8.8%	8.5%	4.3%	1.0%	3.5%
1992/93	25.4%	54.1%	59.5%	52.4%	38.0%	12.4%	32.7%
1994/95	32.2%	69.2%	75.8%	75.0%	56.7%	17.0%	50.0%
1996/97	15.0%	65.9%	84.3%	79.2%	62.3%	22.1%	59.8%
1998	28.4%	80.0%	86.0%	89.4%	69.9%	31.1%	72.0%

* Calculated by using the OR of military conscripts

Table 9.5.2: Population attributable fraction (PAF) of HIV infection to tuberculosis in females* in Chiang Rai, 1990-1998

Age group	15-19	20-24	25-29	30-34	35-44	45+	Adjusted PAF
1990-91	-	-	-	-	-	-	-
1992/93	52.6%	57.5%	51.1%	27.6%	24.2%	5.4%	26.0%
1994/95	37.1%	58.6%	50.8%	51.2%	25.3%	5.4%	32.0%
1996/97	34.7%	77.7%	79.1%	74.4%	57.0%	19.1%	59.4%
1998	43.4%	83.3%	73.3%	79.9%	60.1%	34.5%	65.8%

*Calculated by using the OR of ANC age 20-29 years, adjusted for individual age within the age group but not adjusted for the proportion sexually active in each age group.

Discussion

We found increasing ORs for the association between HIV and TB over time in all control groups while the pattern of OR in different age groups was less clear. The PAF calculation showed almost 80-90% of TB in young adults was attributable to HIV in the latest year of the study. The overall PAF calculation in each year, adjusted for the changing age structure in TB cases, was more than 50% since 1996/1997 period.

Our study design has both advantages and disadvantages of having multiple control groups. In the situation in which ideal controls (randomly selected from the true general population) are lacking, the result of multiple control groups can support one another in determining exposure trends, or provide some information that lacks in other groups. Moreover if we know the direction of bias in each group, the data from these different groups can provide some guidance of the true exposure prevalence. However because of the different directions and levels of bias, it sometime creates difficulties in interpreting the results. From the comparison of the HIV prevalence among control groups, we found that the difference in HIV prevalence in each control group was not explained by differences in age structure or year of study. For ANC and delivery women, the main cause of bias was most likely to be the high proportion

sexually inactive among young women. Apart from these, we can see that blood donors had markedly low prevalence, as expected.

In terms of HIV trends, the data from all control groups, except surgical patients, showed similar trends among women, with the HIV prevalence gradually rising until 1995 and then starting to decrease. For males the data from military conscripts and blood donors showed different turning points: 1991 in blood donors and 1993 in military conscripts. In surgical patients, there was no clear trend in any male wards. However from the background knowledge of the recruitment process in blood donors and military conscripts, we tend to believe more in the conscript data as a reflection of population HIV prevalence because of its randomly selected nature, especially since there was not any special strategy to avoid high HIV risk people as there was for the blood donors. The other factor is that the conscripts, being young, reflect incidence more closely. We would not expect prevalence to go down so fast in the older age group. In addition, the turning point of 1993 can possibly explained by the full implementation of the 100% condom program in 1992 [Rojanapithayakorn et al.1996]. Moreover, it is consistent with the downward trend among females 2 years later (because it takes a couple of years for this cohort of high risk men to get married and have children, which is reflected in the HIV prevalence in ANC and delivery patients).

The high OR in the later years reflects the rapid decrease in HIV prevalence and the changing proportion of infected individuals with different levels of immunosuppression. In general, the OR from surgical patient controls in males and ANC and delivery controls in female were lower than the remaining groups.

One main problem of the case-control analysis is the small sample size in each strata although we merged the data to 2 year intervals. This results in very wide confidence intervals on some of the estimates.

In our logistic regression model, we adjusted for age, sex and residence. The proportion of patients who live in Muang district was very different in each control

group. This is the effect of referral bias of our study site. Some specialities are not catered for in small hospitals, such as surgery or blood donation, so most of the patients come from other districts. Even among similar groups like ANC and delivery this proportion of referral bias is still very different because the antenatal care can easily be performed in any small size-health services even private clinics but the delivery process needs more comprehensive facilities. The differences in place of residence can effect our results in different way. From the behavioural study comparing HIV risk behaviour between urban and rural Thais, there were indications that the percentage with a history of sex with CSW may be lower in rural area [Sittitrai et al 1994]. This may be related with decreased anonymity, more restrictive local norms or lower income, making commercial sex less affordable. However, the previous study in military conscripts showed no significant difference of HIV prevalence between urban and rural conscripts from the upper north region while the data from other regions showed higher HIV prevalence in the conscripts from urban areas [Sirisopana et al. 1996]. Since the main route of transmission of HIV epidemic in Thailand is heterosexual and these sexually active men play an important role as a bridge population between high risk group (CSW) to general population (their spouses and children), this finding might imply that there is no significant difference between HIV prevalence in rural and urban areas in the upper north region, including Chiang Rai. Other reviews about epidemiology of HIV and AIDS in Thailand in 1994 also concluded that one distinguishing characteristic of the Thai epidemic is that urban and rural infection levels do not radically differ, as is the case in most African and Western settings [Brown et al. 1994]. However the other possibility of the referral bias which can correlate to HIV infection is the pattern of referred patients from other health services for reasons that are directly related to the patients' HIV status. Since HIV positive patients are more likely to develop extra-pulmonary tuberculosis or sputum negative pulmonary tuberculosis, these patients are more likely to be referred to Chiang Rai hospitals because other sectors (such as district hospitals and private clinics) have less advanced diagnostic materials, fewer specialists in medicine and radiology, etc. Therefore it is possible that the HIV prevalence among TB cases in Chiang Rai hospital is an overestimation of the prevalence among TB patients in general population although we found no evidence of this in the available data from

other hospitals. Among the control groups, the AZT trial among ANC attenders since 1997 is an example of possible referral bias that directly correlates with HIV status.

One objective of the study was to explore the interaction of the association of HIV and TB with age. The ORs for those aged equal or more than 45 years were lower than the other age groups, but there was no trend in the other age groups. Different ORs among different age groups have previously been reported in some studies [Long et al.1991, Orege et al.1993, Van Den Broek et al.1993, Houston et al.1994, Van Cleeff et al. 1995, Chum et al.1996]. Age grouping in each of the studies was different and the age groups that had the highest ORs were not all exactly the same [table in chapter 1]. Nevertheless, all of these studies showed higher ORs in the groups of young adult to middle age patients and lower ORs in the elderly. Moreover, some prospective studies among women of child-bearing age also had relatively high RR, compared to other studies (case-control or cross-sectional studies) that included all ages [Miles Bruan et al.1991, Allen et al.1992, Leroy et al. 1995]. The association between HIV and TB could be different for the different mechanisms of disease development, ie, primary infection, reinfection and reactivation. Since most elderly TB cases develop the disease via reactivation, while a higher proportion of young adults develop TB by primary infection, this might result in different ORs between young adults and elderly cases. In our study we found significantly different ORs for males aged 45 years or more and the younger age group (aged 35-44 years) in almost all controls except the ward MS1. For ward MS1, the sample size was small after we excluded the group with no diagnostic information (table 9.1). Unfortunately the most reliable male control group in our study, the military conscripts, provides information on only one age group. The interpretation of this difference in females is even more difficult. Both ANC and delivery data do not have any information for women aged equal or more than 50 years, and even those aged 35+ are non representative of the population and the association of HIV with decreased fertility will tend to increase at older ages. For the remaining female control groups, the blood donors and surgical patients, they generally have lower numbers compared to the male counterparts, despite their already low HIV prevalence, so there was little power to detect a difference. However this does not explain the lack of difference by age among female

surgical patients. With the limitations in our data, in particular the possibilities of different biases operating at different ages, we cannot make solid conclusions about the interaction of age in the association of HIV and TB, but there was no evidence of any difference under 45 years of age.

Although we initially planned to investigate the interaction of sex with the association of HIV and TB, we were unable to do this. Among all of our control groups, only blood donors contained data of both genders that were collected in the same way. However blood donor data had some different biases in the enrolment criteria such as the selection of persons for using the self deferral criteria was more concentrated in young males, therefore it was not equally implemented between genders. In addition, the minimum weight for blood donation at 45 kilograms may have excluded many women with HIV infection

In our calculation of the population attributable fraction (PAF), we chose the formula that uses the prevalence of exposure among cases rather than the formula that uses the prevalence of the exposure among controls, which is more widely use. This can reduce the problem of bias that we face in our control groups. For the selection of OR to use with the formula, we decided to use only the OR from the least biased controls as being representative of the general population. Therefore this calculation still relies on how much these selected control groups represent the general population. From our previous discussion we feel that our choice may be an overestimation of the HIV prevalence in general population in both sexes. The bias in military conscripts is due to selection bias towards low socioeconomic population, that has higher HIV risk in Thai context. The main bias of ANC group should be the low proportion of sexually active women in young adult female, although we already exclude the 15-19 age group from our reference. This potential bias leads to underestimation of the OR and thus underestimate of the PAF in both sexes. The use of a constant OR for different age groups may also have led to inaccuracies.

Since we used OR from different control groups for the calculation of the PAF, which therefore have different level of bias, this creates difficulty to compare the PAF

between genders. However it is interesting to observe that while the PAF in females was generally lower than in males, this was not true in 15-19 age group. However, the number of TB patients in this age group is very small.

Our PAF calculation result is difficult to compare with the results from other studies because ours was stratified by time. In addition, we also tried to minimize its different age structure in each period by adjusting for age. However there were some studies that have reported the PAF by year of the study period but all of them use the same OR for the calculation in each year [Van Gorkom et al. 1999]. Glynn et al. [1998] also reported the age-sex adjusted PAF compared to the crude PAF by year of study, however, the same OR was used to calculate the PAF in all years.

Compared to other studies in the past, our OR (overall) is markedly high even when we looked at the most reliable control groups, military recruits and ANC attenders. This should partly come from the relatively long study period of this study, having a higher proportion of immunocompromised people from HIV infection in the advanced stage of the epidemic. However this should not be the only reason because although most of the studies from sub-Saharan Africa were performed during 1989-1990 or until 2-3 years later, many of these countries started to have HIV epidemic earlier than Thailand. Therefore at the time of those studies, the proportion of immunocompromised people should already be high. The other reason is the pattern of HIV infection in Thailand that had very rapid increase and then showed a rapid decline in a relatively short period. Therefore the magnitude of difference between the HIV prevalence among cases and controls especially at the point that the prevalence in the general population had already declined is enormous. This high OR in the later years can contribute to a very high PAF although in reality the proportion of TB attributable to HIV in particular years might not reach that high. The proportion of TB that is attributable to HIV infection in one year actually depends on the HIV situation over the preceeding years rather than the current prevalence. However, in the calculation of PAF, we have to use the OR calculated from HIV prevalence among cases and controls in that particular year. Hence if the current HIV status among controls is different from that a few years before, for example if the HIV prevalence is

still increasing as in many African countries, the OR and PAF will be underestimated. On the other hand, if the HIV prevalence among controls is much lower than a few years before both OR and PAF should be very high because of the wide gap between the prevalence among cases and controls. In all of these circumstances, the PAF will be overestimated. Therefore, the calculation of PAF by using cross-sectional data suffers from the time lag of the long incubation period disease such as HIV. This problem can be explored using mathematical modelling.

Chapter 10: Mathematical modelling for prediction of the future TB burden

Introduction

For health service planning, it is very useful to estimate the future burden of disease in order to prepare appropriate resources to deal with the caseload. Since the peak of the HIV epidemic in the study area has already passed but the number of TB patients has not yet shown any sign of decreasing, it is necessary to develop a model to predict the burden of disease in the future and also its turning point. Moreover with the biases inherent in calculating the OR and PAF using cross-sectional data in a dynamic situation, the result of the model should also provide a better estimation of the "true" OR and PAF.

Previous studies have proposed models to predict the burden of TB attributable to HIV infection [Schulzer 1992, Schulzer 1994, Heymann 1993]. Schulzer et al developed a model to describe and predict the accelerated annual incidence rate of tuberculosis disease due to HIV infection in a sexually active population (15-49 years) followed cross-sectionally over a period of time. Schulzer's model needs data about incidence of TB infection, prevalence before the HIV epidemic, annual incidence and prevalence rate of HIV infection in the study population, proportion of smear positive TB cases in HIV negatives and HIV positives (since this is the core group for spreading TB), probability of developing TB disease after infection with *M. tuberculosis* in each year, separately for HIV positive and HIV negative individuals, and probability of dying in each year after infection with HIV. The main outputs are annual risk and annual prevalence of TB infection and incidence rate of TB disease in each year for smear-positive and negative cases without HIV and with HIV infection. This model assumes that the risk of TB in those HIV infected is the same as that in those uninfected for the first 7 years of infection and then increases sharply. This does not appear to be the case in our data: in the early years of the epidemic increases in HIV-associated TB were clearly seen long before anyone was infected for 7 years.

Moreover, although the model used different HIV incidence for each year, those data came from the transformation of a point prevalence in 1989, not from the kind of dynamic prevalence situation seen in Chiang Rai.

Heymann et al developed a model to predict TB burden attributable to HIV infection, and the effect of intervention on TB prevalence and mortality both in the current situation and over the next decade [Heymann et al. 1993]. The model was used to look at the effect of the following variables on rate of TB infection, active TB and TB death: HIV prevalence and incidence, TB diagnosis and treatment rates and TB preventive therapy. The model used various different assumptions for HIV prevalence but assumed a stable epidemic.

The more recent models in the TB and HIV area were focused on interventions, although all of them included HIV as an important factor accounting for the differing TB burden between regions. A model developed by Murray et al. aimed to evaluate a range of extensions to global control strategies in terms of their potential effects on tuberculosis incidence and mortality by region from 1998 to 2030 [Murray and Solomon 1998]. The model was composed of an uninfectious stage, an infectious stage (primary and secondary TB), re-infection, isoniazid recipients subject to slow breakdown, active disease stage (treated and untreated), and relapse. The model had 2 submodels, one for HIV-negative populations and one for HIV-positive populations. In the HIV-positive submodel, many of the transfer rates are different because of the effects of HIV on the immune system. There was no detail about the source of HIV incidence data used in the initial model but for sensitivity analysis three different Global Programme on AIDS projection scenarios for HIV incidence were used. The first assumed that the number of incident cases per year would stabilise once incidence fell to half of the peak incidence for the baseline scenario. The equilibrium incidence was assumed to be 75% of peak incidence for the pessimistic projection and 20% for the optimistic projection [Murray and Lopez 1997]. However since this projection was made for the global level, the data used for the input came from various situation of HIV epidemics, and therefore cannot be compared directly with our situation.

A model by Dye et al. was created to predict the potential effect of DOTS on the improvement in case detection rate and cure rate for each WHO region [Dye et al. 1998]. Most parameters in this model had different values for those aged 15 years or less and those aged more than 15 years and separate values for HIV positive people. However, for some parameters such as relapse rate, rate of natural cure, rate of smear conversion from non-infectious to infectious, etc there were no special categories for HIV-positive populations. They used separate HIV/AIDS models to calculate HIV incidence rate by age.

Our model was developed to cope with the specific situation of rapidly changing HIV incidence and also in order to use actual data as far as possible. In Chiang Rai, the incidence of HIV has changed dramatically. This is reflected in the ORs, which increase to very high levels. The true relative risk for TB given HIV depends on the duration of infection [Glynn et al. 1997, Wood et al. 1999]. A **deterministic model** was developed to estimate the proportion of HIV infected individuals who had been infected for different periods of time, by age and sex. Constant odds ratios for TB among those infected for fixed periods of time were then applied to these estimates to calculate the age and sex specific PAF in different time periods.

Methods

Overview of the model

We started with a hypothetical initial population of one hundred thousand people for each year of age. The reason for not trying to base it on any real population structure was because the model is used to predict the OR and PAF by 5 year age groups, so variations in the true population by age are unimportant. Since the first AIDS case in Thailand was reported in 1984 [Limsuwan et al. 1986] and the first HIV case reported in Chiang Rai province was in 1988 we started our model at 1980, assuming no HIV infection in the population at that time. The 3 inputs we used were (i) the incidence of

HIV infection in the study population in each year for a reference age group, (ii) the relative probability of infection in each age compared to the reference age, and (iii) the annual mortality rate after HIV infection. The main output is the HIV prevalence in each age and year, by duration of HIV infection. We then estimated the OR of developing TB disease associated with HIV infection. We allowed constant odds ratios for those infected 0-4 years, 5-9 years and at least 10 years, with variation between these groups such that the odds ratio in those infected for longer could not be less than that in those infected for shorter periods and the maximum odds ratio was 100. We then found the best fit to the observed OR (based on the military recruits for men and on the ANC data for women) for different periods.

To estimate the incidence of HIV infection by age we first estimated the incidence in a baseline age group, separately for men and women, and estimated the relative probability of infection at each age, compared to the reference age. The incidence in the baseline age group varied by year, but the age-specific relative risks of infection were constant from year to year. (This is probably an over-simplification because of increasing saturation of high-risk individuals in older age groups over time.) We could thus estimate the number of new infections in each year for each age. By using the estimated mortality rate from HIV infection in this population, we can calculate the numbers remaining in the population as our denominator. Non HIV-attributable mortality was ignored as it will not affect the proportions in the different groups. The total number of HIV-infected people in each year (by adding newly infected individuals to those previously infected in each age group, and removing those who died) provides the numerator for the calculation of prevalence of HIV infection in each year for each age. The summary of this model is in table 10.1.

Table 10.1: Assumptions and summary of the model

Category	Summary
Assumptions	1. Risk of HIV infection at each age is different but the relative risk compared to a reference age is the same in each year. 2. Risk of HIV infection is different in different years, and the risk in males and females is not necessarily the same. 3. The mortality rate from HIV infection by year after infection in this population should be similar to the mortality rate in studies from other developing countries.
Input variables	1. HIV incidence: using HIV prevalence data of the military conscripts from 1991-1998 in males and ANC 20-24 years in females, transformed to incidence by using the ARI formula (see text) 2. Relative risk of HIV infection at each age compared to the reference age (19 years in male and 21 years in female): using the data from nation-wide behavioural studies [Sittitrai et al. 1992, Thongchai et al. 1995] and the incidence study from village population [Nelson et al. 1994]. Peak of HIV risk behaviour was in 19-21 years in male and 21 years in female. 3. Mortality rate: Use the data from Ugandan cohort study of natural history and survival time of HIV-1 infection, in which the cumulative survival after 1, 3 and 5 years of follow up was 100%, 95% and 83% respectively. The longest survival was assumed to be 19 years.
Output variable	HIV prevalence by each calendar year and each year of age stratified by sex and duration of infection
Estimation of the model odds ratio	The relative risk of TB in HIV infected individuals should be less for those infected for 0-4 years than for those infected for 5-9 years, which in turn is less than for those infected for 10 years or more. From literature review, we restricted the OR for 0-4 years ≥ 1 and the OR for 10+ years ≤ 100.
PAF calculation	1. Use the formula PAF= p' (RR-1)/RR by using constant OR for each duration of infection from the above estimation. 2. Overall PAF taking account of duration of infection. Calculated separately for each 5-year age group. 3. Age-adjusted PAF

Estimating HIV incidence

To estimate the HIV incidence in males, we compared 3 sources of data. The first came from a cohort study of a village population [Nelson, 1994]. This study was performed during 1990-1992 in 5 villages in Chiang Mai province, another northern province adjacent to Chiang Rai, which also suffers from a severe HIV epidemic. The advantage of this data source is it provides HIV incidence in a wide range of age groups, from 15 to more than 60 years old, in both sexes. However, because it came from a rural area and the study was done early in the epidemic, it differs from our study group. For instance, the incidence among females aged 15-19 was zero in the

village while our data showed high prevalence in this age group among ANC and delivery patients; or the incidence in older males in this paper was higher than the group of middle age males. Moreover, the short period of follow up (2 years) did not provide information on what was going on in the later years. Our second source of information came from the incidence data of military conscripts in northern Thailand [Celentano, 1998, Nopkesorn 1998]. During the early HIV epidemic in this country, there were many papers from military conscript data, some of which provided incidence data. There were 2 periods of follow up, from 1991-1993 and from 1993-1995. This group provided incidence data from a large sample. However in the military setting, especially in the northern provinces, there was an ongoing intervention study along with the incidence study [Celentano et al. 2000]. Although these incidence data came from the placebo group of that intervention, this group might have been influenced by the intervention groups. Therefore, this source of data should have some potential to underestimate the HIV incidence compared to young Thai men in the general population. In addition, it also provided data for relatively short periods of time and the data come only from young adult men. For the third source of data, we used the data from HIV surveillance of military conscripts (our data in the case-control study), which is the prevalence data from 1991-1998 at the time of recruitment (i.e. before specific health education messages). We estimated incidence by calculating the average annual risk of infection in each year since onset of sexual activity (using a formula analogous to that used to calculate the incidence of the annual risk of infection of tuberculosis [Styblo et al. 1969]) as shown below:

$$\text{Average annual risk of infection} = 1-(1-\text{prevalence})^{1/t}$$

Where t is the period between the average age at onset of sexual activity and current age at the time of testing.

The age at onset of sexual activity was taken from that reported by military recruits in Chiang Rai interviewed in nationally conducted sexual behaviour surveys [Division of Epidemiology Ministry of Public health 1995-1998, unpublished data]. This average risk applies to the time period between sexual debut and current age, not to the risk at

the current age. Since onset of sexual behaviour was on average at age 17 and recruits have a mean age of 21, this risk of infection was taken as applying to men aged 19 and to a period two years before the date of testing.

The results based on these 3 data sources are shown in table 10.2. From the comparison of the actual HIV prevalence and the output HIV prevalence from the model, we decided to use the 3rd data source – the calculated incidence using the prevalence data in the military recruits - as our incidence data for males.

Table 10.2: Comparison of actual HIV prevalence for males age 21 years, with the model prevalence using input incidence data from 3 different sources.

Year	Actual HIV Prevalence military conscript (1991-1998)	Prevalence estimated from the model, using input incidence data from 3 differed source		
		Village population, (1990-1992)*	Incidence studies of military conscript (1991-1993. 1993-1995)*	HIV surveillance of military conscript (1991-1998)
1990	-	15.1%	9.3%	14.6%
1991	15%	18.9%	11.7%	16.9%
1992	17.4%	20.4%	11.7%	15.9%
1993	16.5%	19.1%	10.7%	14.0%
1994	7.4%	17.0%	9.1%	11.5%
1995	6.6%	13.8%	6.9%	8.4%
1996	5.9%	10.2%	4.8%	6.9%
1997	3.4%	6.8%	3.3%	4.6%
1998	2.9%	4.6%	2.2%	3.3%

* Data beyond the years of studies were estimated by using the number that gave the closest output (HIV prevalence) to the actual data.

For females we also used the ARI formula to estimate HIV incidence. Because the formula will be less accurate if we choose a reference group that is too far from the age of sexual debut, we used the HIV prevalence of primigravid women seen in the ANC aged 20-24 years as our reference group, adjusted to allow for the proportion of women in that age group who are not yet sexually active. The proportion of women

sexually active at age 20-24 and the age of sexual debut were taken from the sexual behaviour survey results from Chiang Rai. [Division of Epidemiology 1995-1998, unpublished data].

From the sexual behaviour surveys, the mean age of sexual debut in women seen in the ANC was about 19 years and the mean age of HIV testing for our reference group (primigravid ANC 20-24 years old) was 22 years, so risk of infection calculated refers to an age in this interval. We took the risk as applying to those aged 21 for the time period one year before the date of the test. In addition we also adjusted for the proportion sexually active in this age group by multiplying our calculated incidence by 0.58, the proportion ever sexually active among Chiang Rai female factory workers aged 20-24 years.

The result of the incidence calculation is shown in table 10.3.

Table 10.3: Estimated HIV incidence from the HIV prevalence data in each gender.

Year	Male		Female	
	Prevalence data In military conscripts	Estimated incidence	Prevalence data in ANC aged 20-24 years	Estimated incidence*
1990	-	-	7.1%	1.37%
1991	15.0%	3.98%	9.2%	1.78%
1992	17.4%	4.55%	10.9%	2.19%
1993	16.5%	4.27%	12.9%	2.61%
1994	7.4%	1.80%	10.0%	1.98%
1995	6.6%	1.80%	12.3%	2.40%
1996	5.9%	1.53%	13.2%	2.61%
1997	3.4%	0.76%	10.3%	1.98%
1998	2.9%	0.76%	8.5%	1.78%

* After adjusting for the proportion sexually active in 20-24 years age group.

After estimating the incidence for each year we changed the numbers slightly to produce a smooth curve (eliminating the dip in 1994 for the women).

For the estimation of HIV incidence before this period, we used the information that the first HIV case in Chiang Rai was detected in 1988 [Limpakarnjanrat et al. 1991]. We assumed that the first HIV infection in Chiang Rai occurred in 1985 and that the incidence gradually increased. To predict the future we have assumed that HIV incidence will gradually decrease and then be stable, at 0.001 in males from 2000 and 0.0008 in females from 2001. These are very low estimates but allow us to predict TB trends when HIV incidence is low.

It was assumed that the relative risk of HIV infection by age compared to the baseline age group in those of the same sex was constant from year to year. These relative risks were estimated using the village data and the data from 2 cross-sectional nation-wide behavioural surveys of those aged15-49 years in the general population [Sittitrai et al. 1992, Thongthai et al. 1995]. The relative risks were adjusted to improve the fit of the model to the observed HIV prevalence in the population. From these nation-wide behavioural studies, the peak of high-risk behaviour was in 20-24 years age group. Additional data from the report of the first 500 AIDS cases in Thailand showed that the highest proportion of full blown AIDS was among age 25-29 years while the highest proportion of the ARC (AIDS related complex) patients was in 20-24 years [Wattanasri et al. 1992]. Therefore, we assume that the peak of HIV incidence in males was 19-21 years old (because most of the cases in the beginning of the epidemic were male). In Thai society, these young men who are not yet married usually have the highest risk of having unsafe sex, especially with commercial sex workers because the tradition of virginity at marriage among women is still strong. In a nation-wide behavioural study in 1990 among 2801 men and women aged between 15 and 49 years, they found 46.6% of single men reported having had sex within the past 12 months while only 4% of single women reported doing so [Sittitrai et al. 1992]. In a study among young Thai men who were recruited to be military conscripts, the HIV incidence among those recruited who were married at the time of enlistment was significantly lower than among those who were single (adjusted RR = 4.7, 95%CI =

2.19-10.08 for single recruits) [Carr et al. 1994]. By age 25 years or more, many young men are already married and have changed their behaviour to be less exposed to commercial sex workers. For females, most of them start to have risk of HIV after their marriage, from their husband. Since, in general, both Thai men and women get married after 20 years and men are usually the same age or older than the women, we assume that the age with highest HIV risk in women should be 21 years. Then, the risk decreases when they are older (since their husbands are at lower risk).

To estimate the youngest age of having HIV risk behaviour, we used data from the literature, national behaviour surveillance and the data from our case-control study. From the study in military conscripts from northern provinces, 22.1%-29.8% of them reported having their first sexual relation at age 15 years or less [Nelson et al. 1996]. The minimum age of sexual debut among military conscripts from Chiang Rai province from the behavioural surveillance data ranged from 12-15 years [Division of Epidemiology 1995-1998, unpublished data]. Therefore, we assumed that the risk of HIV infection started from 14 years in men. Although the female data from the same source also had the range of minimum age for sexual debut at 12-15 years, we decided to use 12 years old in female. This decision came from the comparison of HIV prevalence among TB cases. We found higher HIV prevalence among female TB patients aged 15-19 years compared to males in the same age group while in other age groups males had higher HIV prevalence in almost all years. It is possible that those HIV positive young women who are seen with TB this early at come from the group of commercial sex workers, some of whom start their work at 12 years old. Women from the upper north area, especially Chiang Rai and Phayao, are widely believed to be over-represented in proportion to their provincial population among prostitutes working throughout the country [Weniger et al.1991]. Although the proportion of this group should not be very high compared to all women, this group could be a large proportion of those sexually active at a very young age.

Estimating HIV associated mortality

In the absence of data from Thailand, we used data from the cohort study of natural history and survival time of HIV-1 infection in rural Uganda [Morgan et al 1997]. The

overall (all ages) cumulative survival after 1 year of follow up was 100% in incident cases of HIV-1 infection [Morgan et al 1997]. At 3 and 5 years after infection, the proportion surviving was equal to 95% and 83% respectively. We used this information as our guide to estimate the cumulative survival in each year after infection. So far, there is no sero-incidence cohort in a developing country that has reported the median survival following HIV infection from a general population. Recent results from the ongoing study in rural Uganda show the cumulative survival at 9 years as 65% [Morgan et al. 2000]. Previous studies from sub-Saharan Africa usually came from high-risk groups such as commercial sex workers while the survival study in Thailand came from a tertiary referral center [Grant et al. 1997, Kitayaporn et al. 1996]. In developed countries, the studies conducted at the time before widespread use of highly-active antiretroviral therapy showed the median survival varied from 12.5 years for those aged 15-24 years at seroconversion to 7.9 years for those aged 45-54 years at seroconversion [Collaborative group on AIDS incubation and HIV survival. 2000]. Therefore, we assumed that at 19 years after infection all of the HIV infected population would have died and a median survival of 10 years. From the cumulative survival we calculated annual risk of dying using the formula below.

Annual risk of dying = $1 - S_i / S_{i-1}$

When S_i and S_{i-1} = cumulative survival at year i and year i-1 after HIV infection or we might call it the proportion of original cohort surviving by time since HIV infection.

Estimation of the model odds ratio

We expect that the OR of association between TB and HIV should increase by time since HIV infection [Glynn et al. 1997, Wood et al 1999]. The main factor that causes this increase should be the proportion of patients that already have immunosuppression. Therefore, we hypothesised that the OR for developing TB associated with HIV infection in each time period should be the same but for the

difference in the proportion of immunosuppressed patients. For example, those people who have HIV infection for 0-4 years in 1990 should have the same OR for developing TB as the patients infected for 0-4 years in 1995. Likewise the patients who were infected for more than 5 years in 1990 should also have the same OR as patients infected more than 5 years in 1995. However, because in 1995 the HIV epidemic was more advanced the proportion of those infected for more than 5 years should be higher than in 1990. The other condition is that the OR for infection at 0-4 years should be less than the OR for more than 5 years. The overall RR (relative risk) is a weighted average of the subgroup RRs, the weights depending on the proportion of people that were infected for that particular duration (0-4, 5-9 and 10 years or more), as in the formula below:

$$\textbf{Overall } RR_a = (Pa_{0-4} * RR_{0-4}) + (Pa_{5-9} * RR_{5-9}) + (Pa_{10+} * RR_{10+}) \quad (1)$$

Where

RR_a = relative risk of developing TB from HIV infection in year A

Pa_{0-4} = proportion of people infected for 0-4 years in year A

Pa_{5-9} = proportion of people infected for 5-9 years in year A

Pa_{10+} = proportion of people infected for 10+ years in year A

RR_{0-4} = constant relative risk associated with being HIV-infected for 0-4 years

RR_{5-9} = constant relative risk associated with being HIV-infected for 5-9 years

RR_{10+} = constant relative risk associated with being HIV-infected for 10 years or more

Since TB is rare, we can directly substitute RR by OR in the formula. If we already know the overall OR by year (from the case-control result) and also the proportion of HIV infection in each duration in each year from the model, we should be able to estimate the constant OR relating to each duration of HIV infection. To do this we, put the actual OR we got from our case-control study as the overall OR, using 2 years intervals; 1990-1991, 1992-1993, 1994-1995, 1996-1997 and 1998. For males we used the OR from our military conscript data compared to our cases aged 19-23 years

(not 20-24 years as in our case-control result). The OR of ANC 20-29 years was used as the goal for comparison for our calculation for females. Because we did not find consistent differences between ORs in each age group from our case control results, and because the other control groups were more subject to bias, we decided to use the same actual OR for our calculation in all age groups. The overall OR from the model was calculated separately by calendar years and age group using a range of estimator, to compare with the actual OR. To calculate the discrepancy between actual and model OR, we used the square of the difference between actual and model OR divided by the actual OR. Different values of the odds ratios for those infected for different lengths of time were explored to obtain the best fit of the model OR to the actual OR (i.e. the fit which minimised the discrepancy). For this calculation the assumptions are as below.

1. The OR for the association of HIV and TB for those infected by HIV for a particular duration should be the same in each calendar year
2. The OR for those infected by HIV for a particular duration should be the same in each age group
3. The OR for 0-4 years should not less than 1 because none of the OR in previous studies were less than 1
4. The OR of 5-9 years should be higher than OR for 0-4 years.
5. The OR for 10 years or more should be higher than OR for 5-9 years
6. The OR for 10 years or more should not higher than 100, from data of the only study that reported the OR in late stage of HIV infection and found ORs of 64.4 in coloured population and 81.5 in the black population [Wood et al 1999].
7. The OR for males and females should be more or less the same. From the previous studies that compared the OR between genders, none reported significant differences between these OR [Orege et al. 1993, Chum et al. 1996].

Apart from the values that gave the best fit for our estimation of constant OR for those infected for different lengths of time, we also chose other possible values of our constant ORs to obtain upper and lower limits for our prediction. We used these estimates to calculate the population attributable fraction (PAF), to predict the possible PAF in the future and predict the turning point of PAF in each age group.

PAF calculation, taking time lag into account

We used the same formula as for our PAF calculation in the case-control section, i.e., PAF = p'(RR-1)/RR when p' is the proportion of cases that come from the exposed group. This formula is easier to use in situations in which we need to calculate PAF from an exposure with multiple levels, as in our study. We defined the duration of HIV infection (0-4, 5-9 and 10+ years) as 3 levels of exposure, compared to the HIV negative group. The proportions of cases that come from each exposed group were obtained by using the model output for the proportion of population that do not have HIV infection and for those infected for 0-4, 5-9 and 10 years or more, multiplied by the best fit OR in each level. The overall PAF was directly calculated by summing these exposures group specific PAFs together. We separately estimated PAF by calendar years and age groups. The equations of our PAF calculation are shown below:

$$\mathbf{PAF_{ai}} = \mathbf{p_{ai} * (RR_i - 1)/RR_i} \quad (2)$$

when i = HIV infection duration 0-4, 5-9 and 10+ years

PAF_{ai} = PAF for duration i in year A

p_{ai} = proportion of cases that have HIV infection of duration i in year A

RR_i = constant RR for HIV infection duration i (estimated from the duration-specific OR)

$$\textbf{Age specific PAF in year A} = \sum \mathbf{PAF_{ai}} = \sum \mathbf{p_{ai} *(RR_i-1)/RR_i} \quad (3)$$

An example of the estimation of "p_{ai}" and PAF is shown in table 10.4. In this example, we take a population with HIV prevalence equal to 10% in year A. Among those 10% HIV infected people, 5% were infected for 0-4 years, 3% infected for 5-9 years and 2% infected for 10 or more years (column II). Suppose the constant RR that we estimated from the model for the risk of developing TB in people infected with HIV for 0-4, 5-9 and 10 or more years, equals 2, 10 and 50 respectively (column I). Then the number of disease cases (d) in each level of exposure is given by the proportion of people at each level multiplied by the RR of developing TB at the same

level (column III in the table). The "p_{ai}" (column III) is the proportion of cases in each level, compared to total cases, which were 2.3 in this table. The last column gives the result of PAF calculation for each level of exposure and also the total PAF in year A. We calculated this PAF separately for each age group, by year.

Table 10.4: Method of estimating the proportion of cases in each exposed group and the PAF calculation.

Column	I	II	III	IV	V
Exposure	**RR**	**Proportion of people in each level in the population**	**D**	**p_{ai}**	**PAF**
HIV negative	1	0.9	0.9	0.391	0
HIV infected 0-4 years	2	0.05	0.1	0.043	2.2%
HIV infected 5-9 years	10	0.03	0.3	0.130	11.7%
HIV infected 10 or more years	50	0.02	1.0	0.435	42.6%
Total	-	1	2.3	1	56.5%

Estimation of TB burden attributable to HIV infection by year, using Chiang Rai population structure

The number of TB cases attributable to HIV infection for each age group in each year was calculated by using age-specific PAFs, result from the above calculation, multiplied by the number of new TB cases in Chiang Rai province in the same year and age group. The total number of TB cases attributable to HIV was obtained by summing these estimates The overall PAF estimated from the model for each year was calculated by dividing this TB burden from HIV infection by the total TB cases of the same year.

Results

Estimation of HIV prevalence in general population

From the model, the main output is HIV prevalence in each age, by year. We compared this model prevalence with the actual HIV prevalence in our control groups, (except uro-surgery) (figure 10.1). The result showed a good fit between the model prevalence and the most valid control group, which is the military conscript in male, and the ANC group, after adjusting for proportion of sexual activity in females. For the period or age group that these 2 control groups were not available, the model prevalence lay between the range of HIV prevalence measured in the other control groups.

Estimation of the constant value of the OR for each duration after HIV infection

Using the methods described above, we estimated the OR for the association of HIV and TB for those infected with HIV for 0-4 years, 5-9 years and more than 10 years. Since there was only one HIV positive case among female TB patients in 1990-1991, the actual OR could not be calculated for the whole female group for this period. When we tried to estimate the constant OR for each duration, which gave the best fit to the data for each gender, we did not find the same value between males and females. Hence, we used the values that lay between these two groups, which made the least discrepancy of the actual and model OR for both genders. The values we estimated for constant OR in each interval were 3, 30 and 100 for patients infected for 0-4, 5-9 and 10 or more years. The results of the overall ORs that were calculated by using these best fit OR in each gender are shown in table 10.5.1 and 10.5.2. A sensitivity analysis using other values is given below.

Figure 10.1.1: HIV prevalence in male control groups, compared with the model result

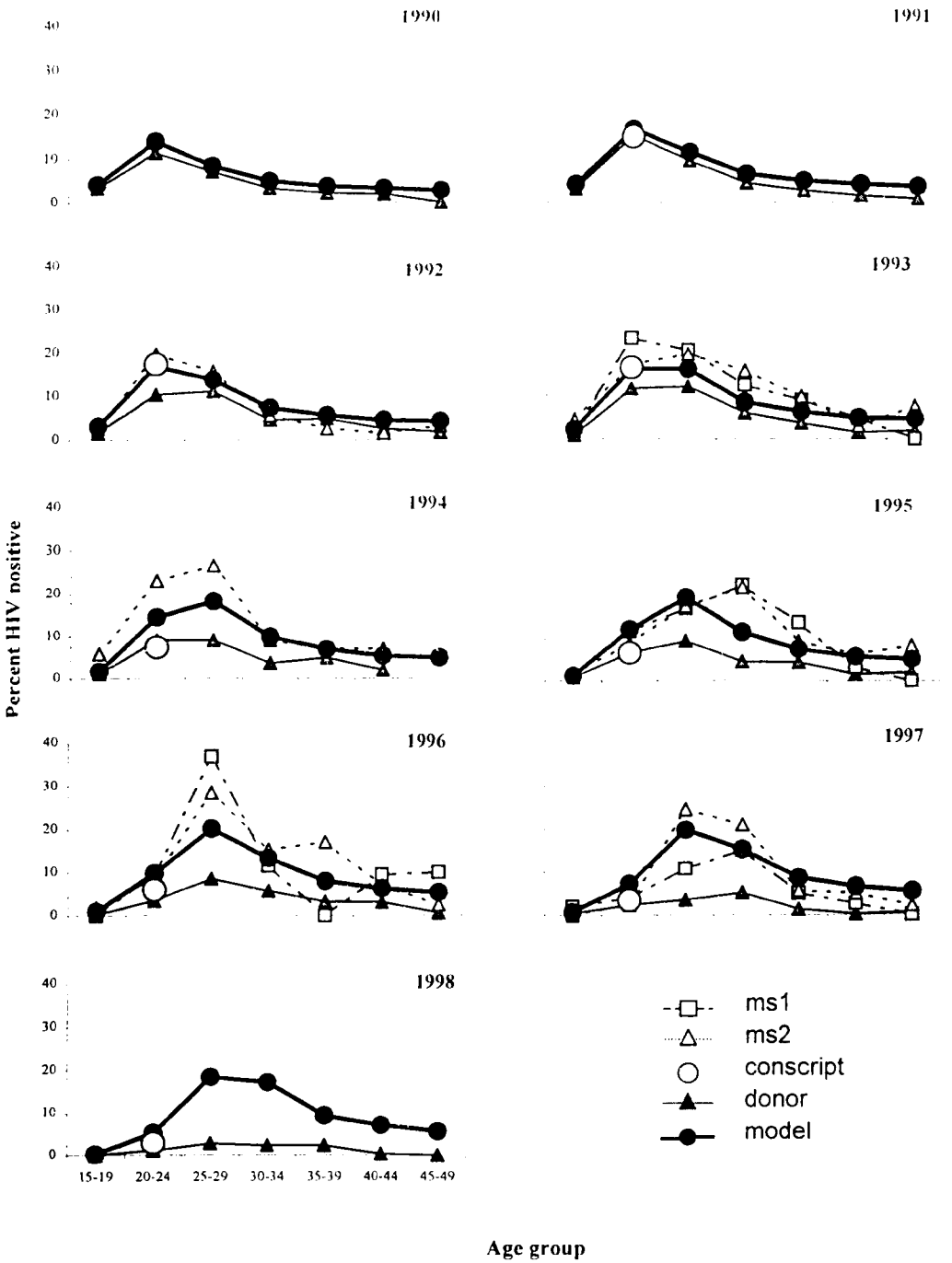
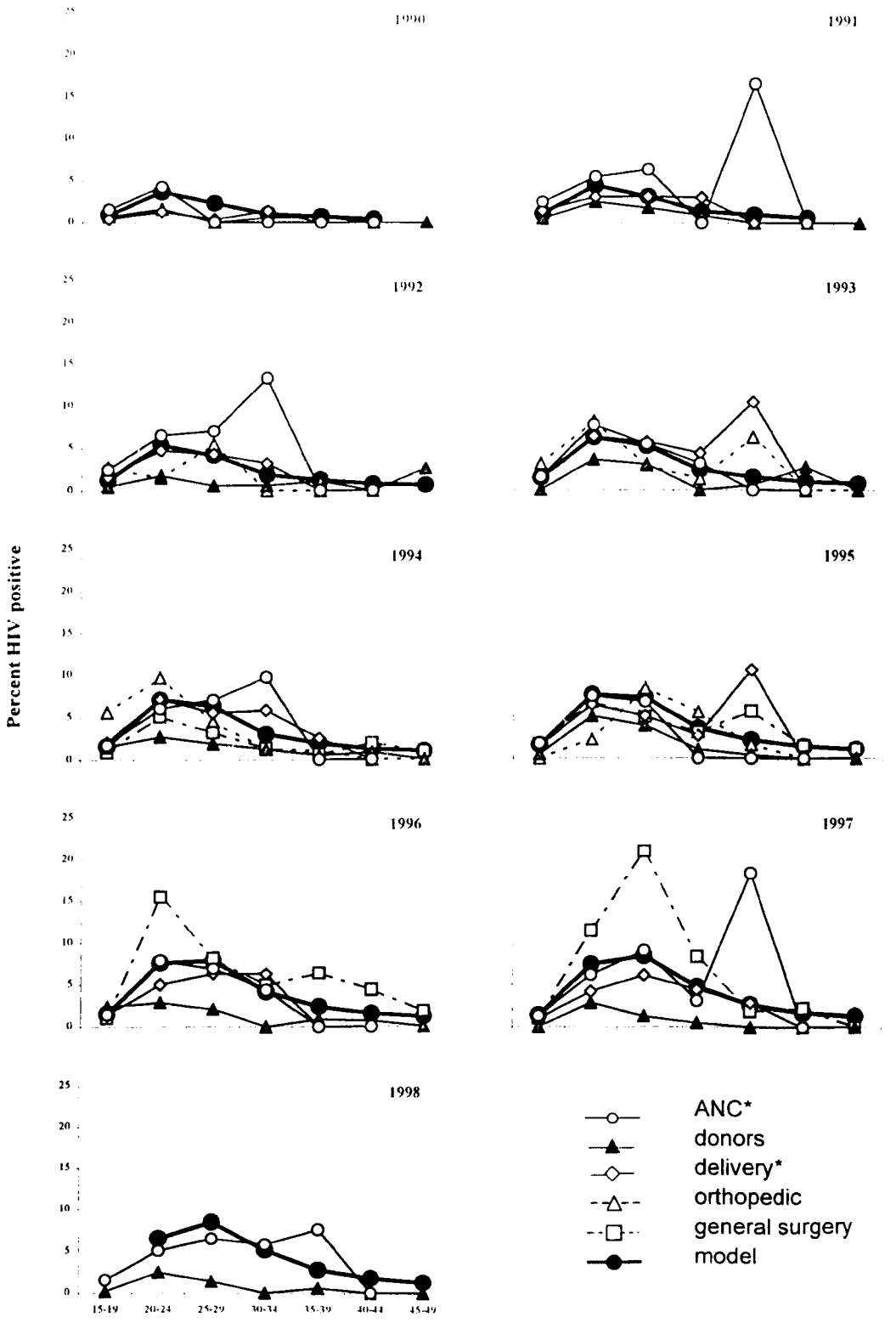


Figure 10.1.2: HIV prevalence in female control groups, compared with the model result



*HIV prevalence in ANC and delivery were adjusted for the proportion sexually active in the population

Table 10.5.1: Comparing the overall odds ratio for males between the results of actual data and the model

Year	Actual OR for male*	Model OR						
		15-19	20-24	25-29	30-34	35-39	40-44	45-49
1990/91	1.1	3.0	3.8	5.4	4.9	4.8	4.5	4.7
1992/93	5.6	3.0	6.6	12.4	11.9	10.9	10.1	10.2
1994/95	25.8	3.1	10.9	20.9	22.3	20.0	19.5	18.8
1996/97	24.4	3.1	14.8	29.9	38.7	35.3	34.1	32.0
1998	60.3	-	14.2	37.7	55.8	52.9	49.8	46.9

* Using the data of military conscripts

Table 10.5.2: Comparing the overall odds ratio for females between the results of actual data and the model

Year	Actual OR for female*	Model OR						
		15-19	20-24	25-29	30-34	35-39	40-44	45-49
1990/91	-	3.1	3.5	5.0	5.1	4.3	4.8	-
1992/93	12.6	3.3	4.7	9.4	10.1	7.8	9.0	7.4
1994/95	13.9	3.4	5.3	12.3	14.4	11.0	12.3	10.3
1996/97	34.4	3.6	6.1	15.4	22.7	18.5	18.1	16.4
1998	42.9	-	7.5	18.8	31.3	27.7	24.9	24.1

* Using the data of ANC 20-29 years

The results of this model showed large differences between actual and model OR in young adults but this difference was less in age groups above 25 years.

Estimation of HIV prevalence in TB patients from the model

To counter check the validation of this model OR, we estimated the HIV prevalence among TB patients by using the result of the model (HIV prevalence in general population and estimated OR). Because the OR comes from odds of having the exposure among those with disease divided by odds of having exposure among the general population, if we know the OR and odds of having exposure among the general population we can calculate the remaining number. Therefore, we use this concept in our calculation as an example below.

HIV prevalence in males age 30-34 years in 1994 to 1995 was 0.102, which is equal to 10.2/100. Therefore, the odds of having HIV infection in males age 30-34 in 1994-1995 is equal to 10.2/(100-10.2), or 10.2/89.8. Using this number and the estimated OR of 22.3, we can substitute in the formula below.

$$\text{OR} = \frac{\text{odds of exposed in disease population}}{\text{odds of exposed in general population}}$$

Odds of exposed in disease population = OR* odds of exposed in general population

$$= 22.3 * 10.2/89.8$$

$$= 227.5/89.8$$

Therefore, prevalence of HIV in TB $= 227.5/(89.8+227.5)$

$$= 0.72$$

This can be compared to the actual HIV prevalence in TB patients aged 30-34 years during the year 1994 to 1995, which was equal to 0.78.

The result of the comparison between actual HIV prevalence in TB cases and the calculated HIV prevalence in TB cases is shown in figure 10.2. In males, the

Figure 10.2.1:Comparison of HIV prevalence among male TB cases between model estimation and actual data

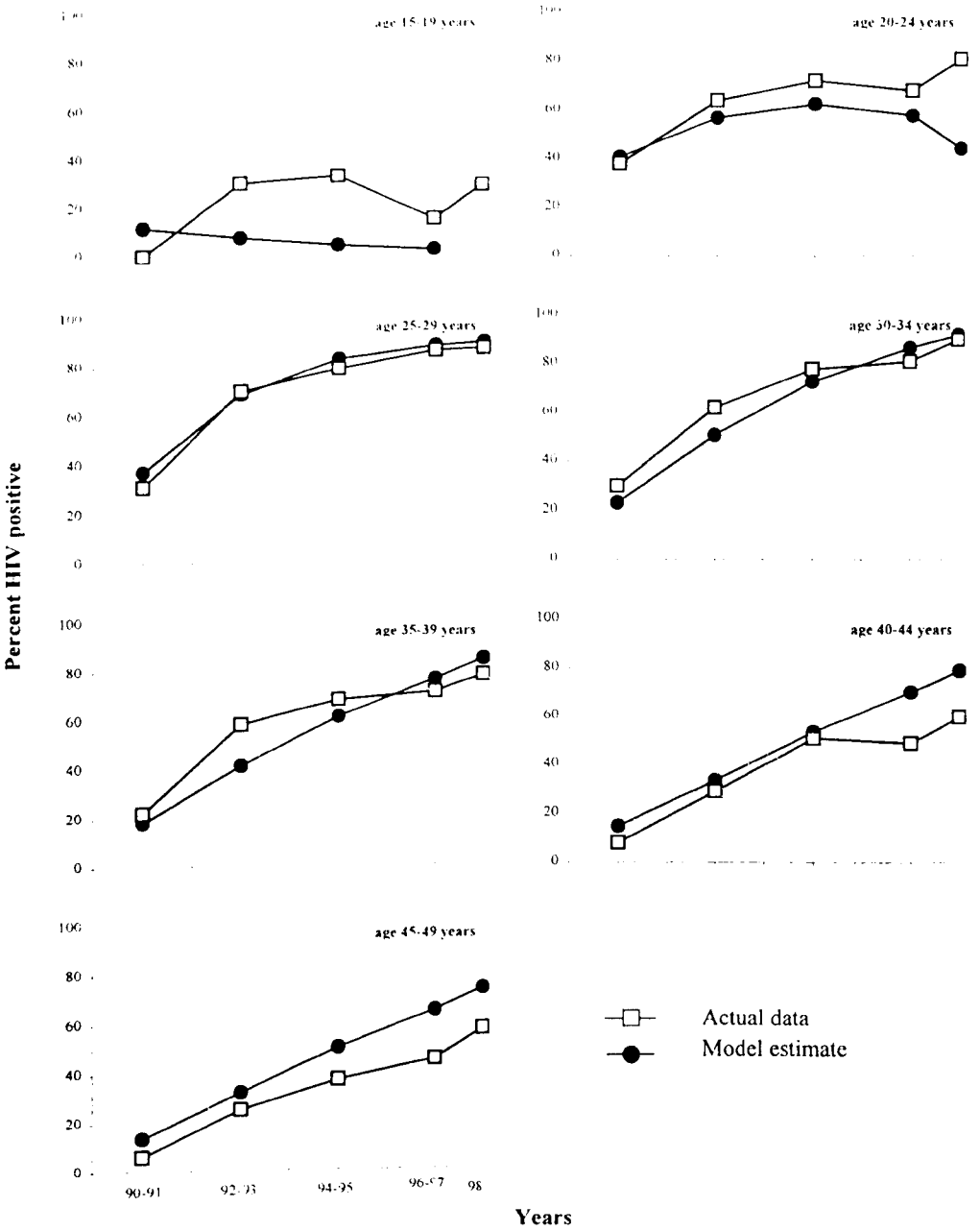
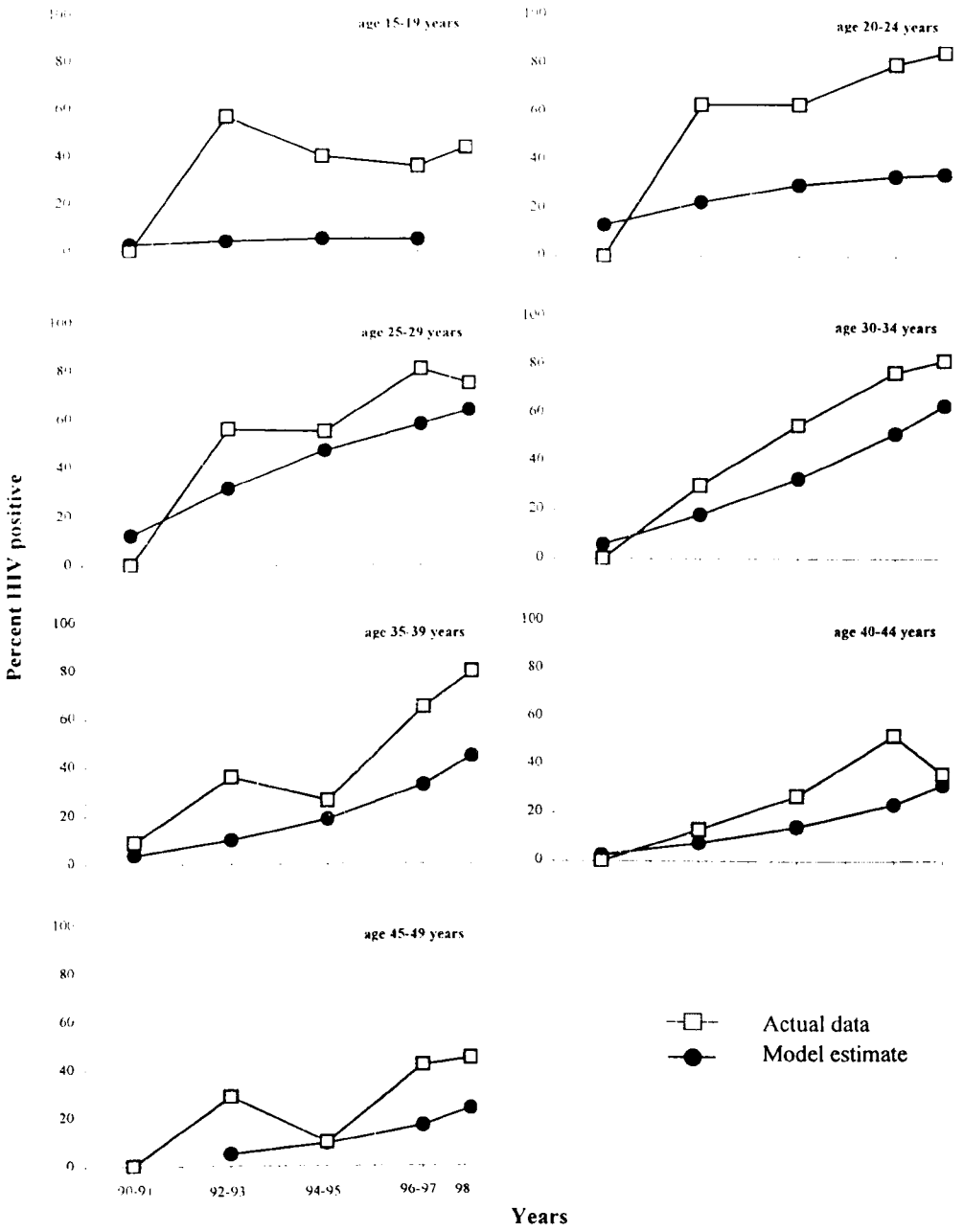


Figure 10.2.2:Comparison of HIV prevalence among female TB cases between model estimation and actual data



estimated HIV prevalence was much lower than the actual data among TB patients aged 15-19 years and becomes very close for age 25-34 years. In the elderly, the model estimated HIV prevalence became higher than the actual data. In females, the discrepancies between the two lines were higher than in males in all age groups. Moreover, the estimated prevalence was consistently lower than the actual data in all age groups.

Age-specific PAF calculation, taking time lag into account

With equation (2) and (3) described in the methodology part and the method used in table 10.4, we calculated the PAF from the model for each age group and year. The results are shown in figure 10.3. They show a different turning point in each age group. For the younger group, the PAF peak earlier. In all of the 4 age groups younger than 35 years old, the PAF peaked before the year 2003 but moved toward later years for the older age group. For people aged older than 35 years, the peak varied little by age and was around 2003-2004 in males and 2005-2006 in female.

Sensitivity analysis of the OR of different duration after HIV infection

As well as calculating PAF using the best fit OR from the model, we explained the effect of using different subgroup OR. The choice of OR in each subgroup for both genders is shown in table 10.6.

Table 10.6: Alternative value of subgroup OR in each gender

	Duration of HIV infection		
	0-4 years	5-9 years	10+ years
Estimate OR	2, 3, 5	5, 30, 50	20, 100

The choice of each value came from the OR of previous studies and the results of our case-control study and the best fit for males and females separately (table 9.4.1 and

9.4.2). The results from this sensitivity analysis showed the same year of PAF peak in each age group for the different values of our subgroup OR, despite the change in magnitude of the PAF (figure 10.4).

Estimation of TB burden, attributable to HIV infection.

With the method described above, the overall PAF for each 2-year interval for males and females was calculated, as shown in table 10.7.

Table 10.7: Overall PAF and age standardised PAF for Chiang Rai population structure by 2-year interval

Year	Male		Female	
	Age-standardized PAF	TB cases attributable to HIV	Age-standardized PAF	Number of TB cases attributable to HIV
1990/91	17.4%	64	4.3%	8
1992/93	42.8%	216	14.3%	28
1994/95	62.1%	538	24.6%	86
1996/97	73.2%	885	34.7%	199
1998*	78.1%	1025	41.9%	286
Total	-	2729	-	607

* Number of cases in 1998 was multiplied by 2, to make it comparable with other years that have 2-year intervals.

Using the PAF to assess the impact of HIV on TB, we feel that the calculated number of TB cases that were not attributable to HIV infection was stable in males and increased in females, (figure 10.5). For males all, and for females most, of the increase in TB was directly attributable to HIV.

Figure 10.3.1: Model-estimated PAF and crude PAF from actual data in male TB cases

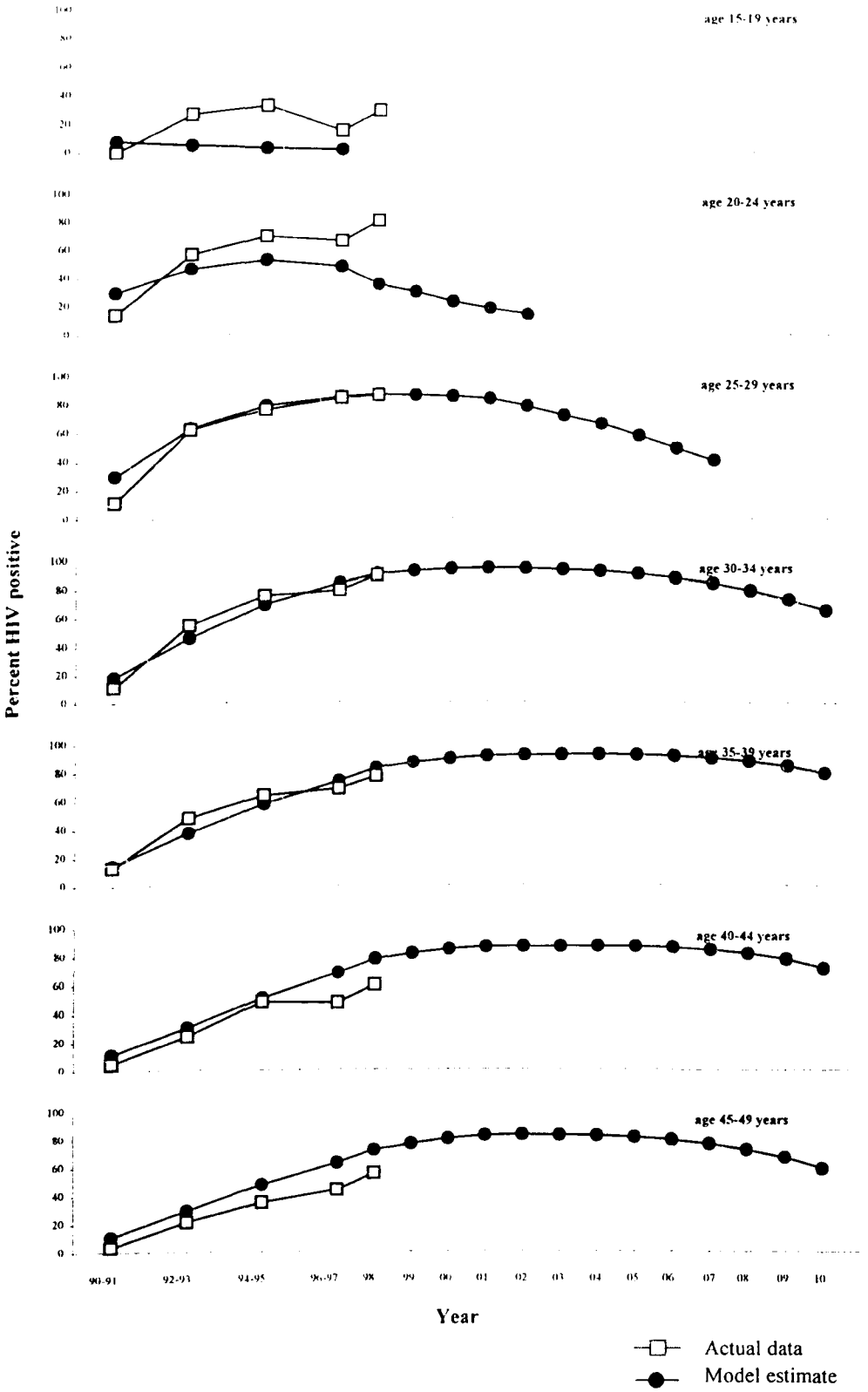


Figure 10.3.2: Model-estimated PAF and crude PAF from actual data in female TB cases

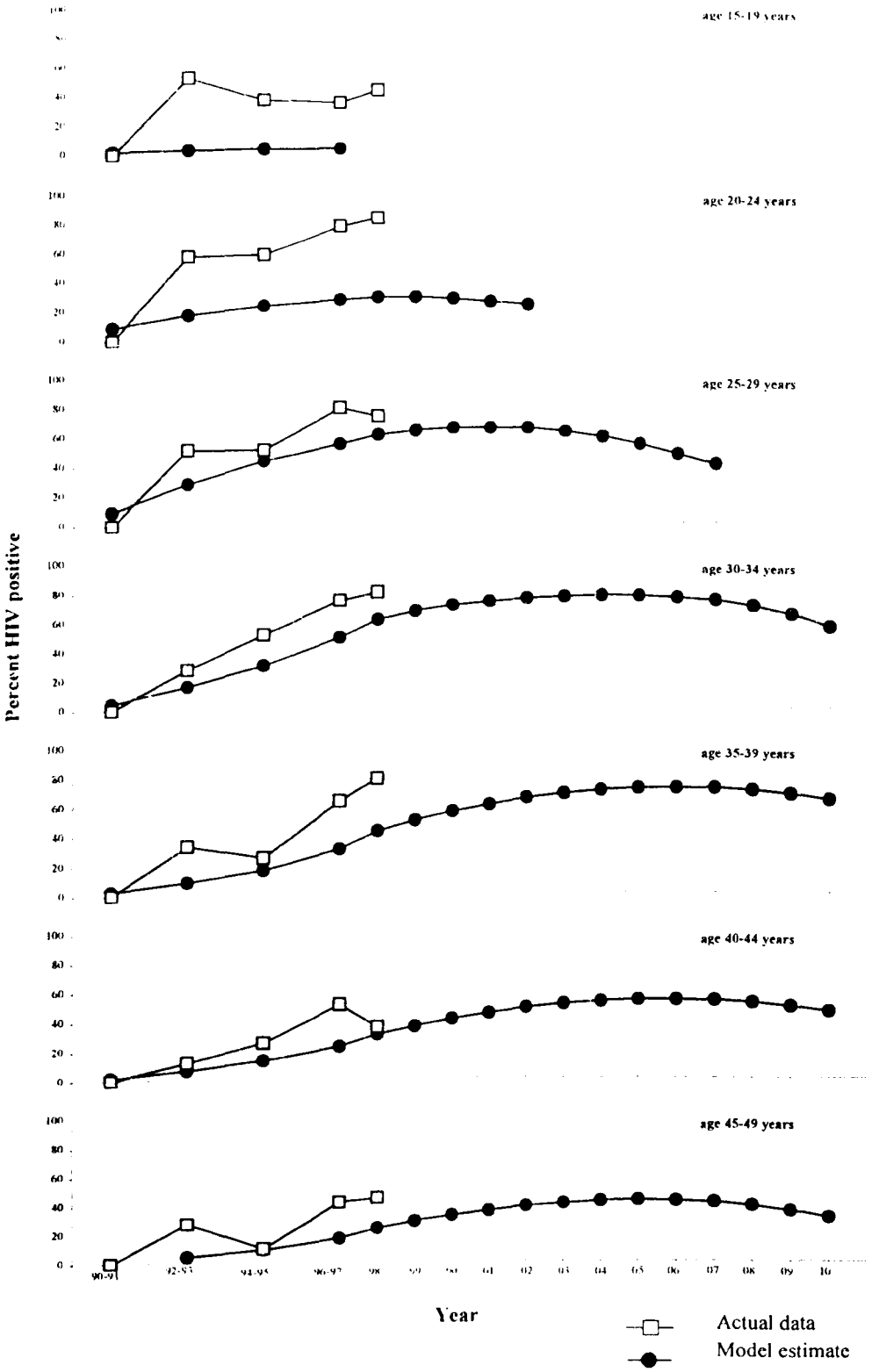


Figure 10.4.1: Sensitivity analysis of estimated PAF in male population, using different OR for people infected for 0-4, 5-9 and 10 or more years

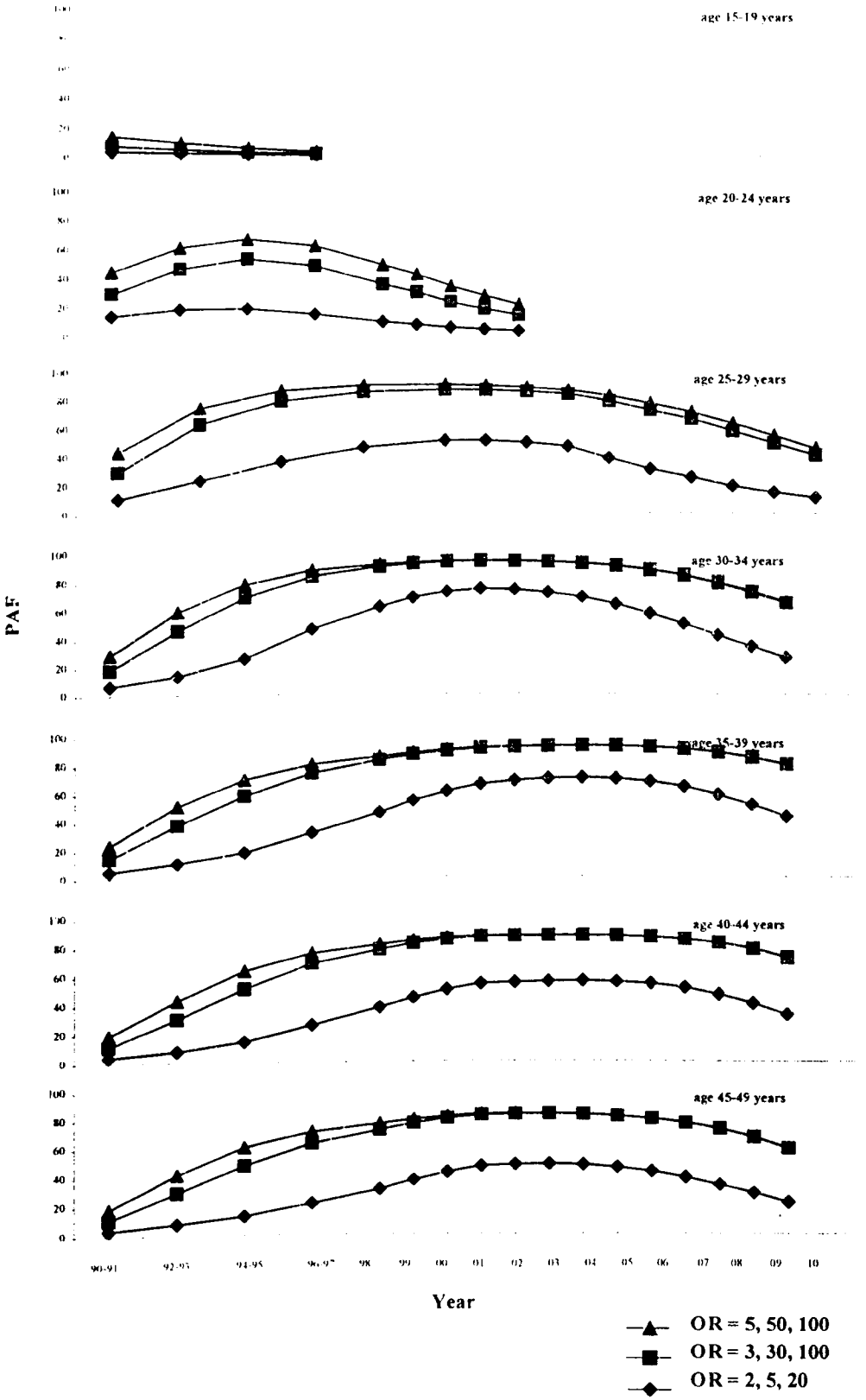


Figure 10.4.2: Sensitivity analysis of estimated PAF in female populaiton, using different OR for people infected for 0-4, 5-9 and 10 or more years

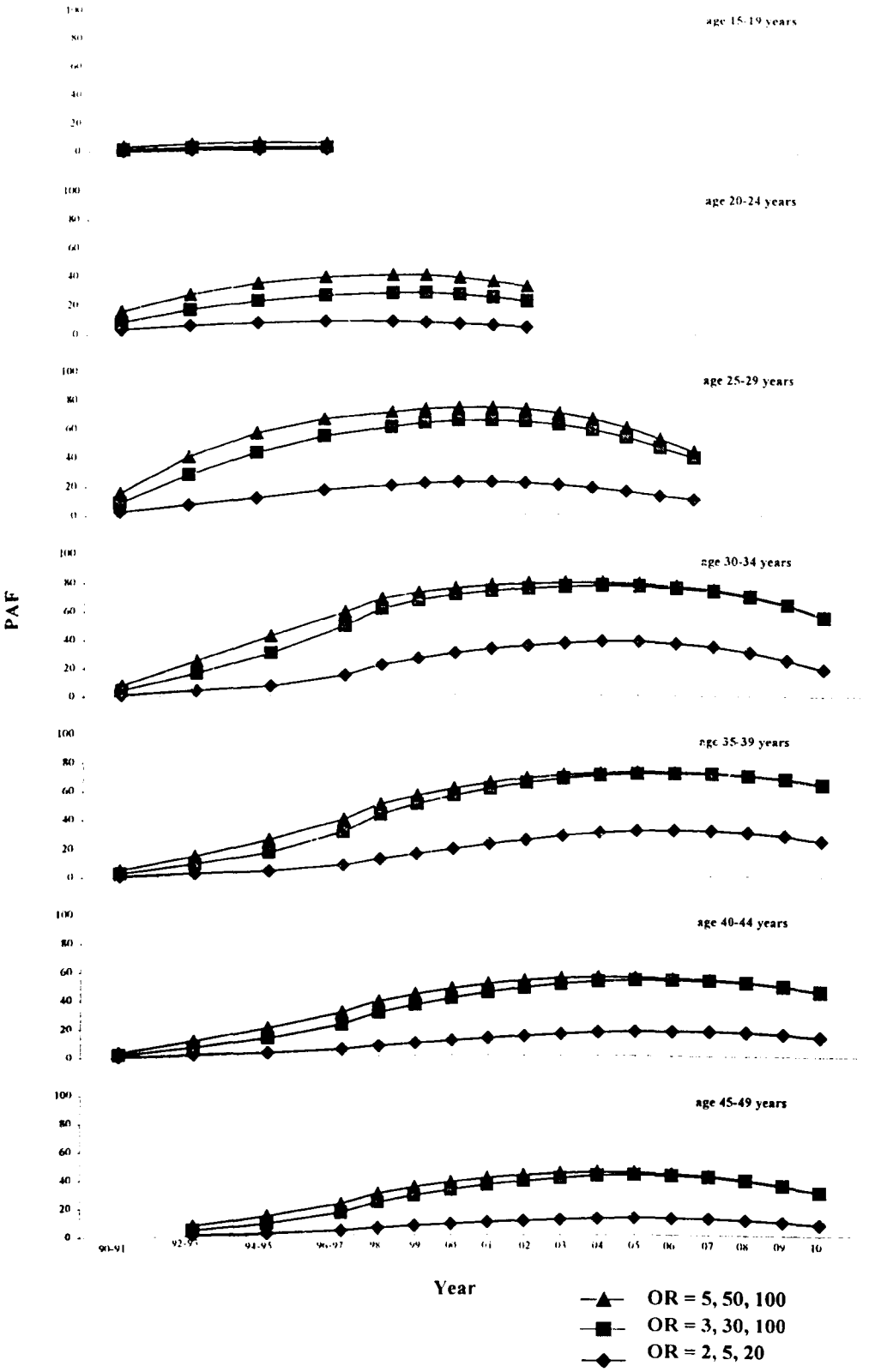


Figure 10.5.1: Number of male TB cases in Chiang Rai province, attributable to HIV infection, estimated from the model

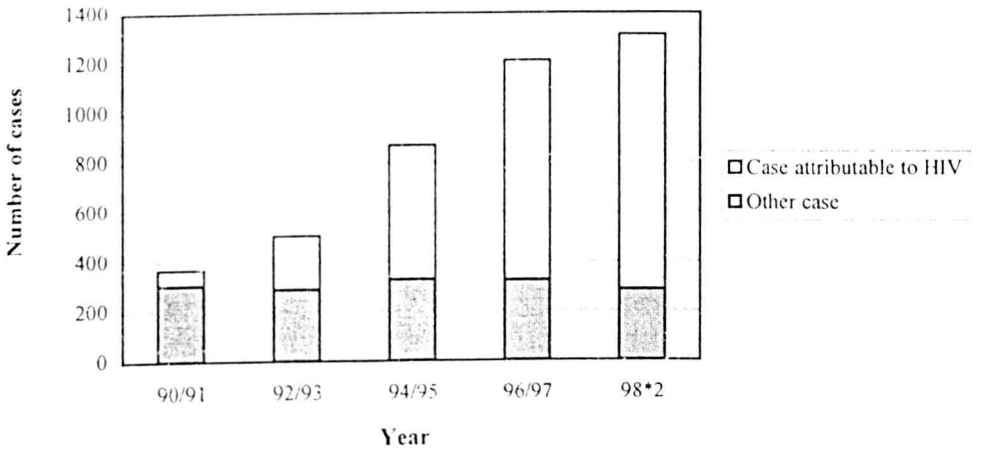
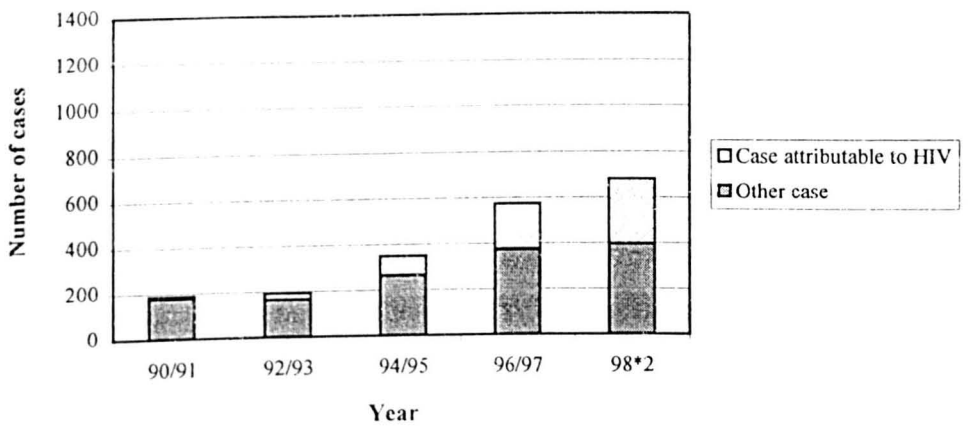


Figure 10.5.2: Number of female TB cases in Chiang Rai province, attributable to HIV infection, estimated from the model



Discussion

Our model differed from previous models in the TB/HIV area, in that it does not use data about the TB infection rate and the probability to develop TB disease as direct inputs. Instead we apply the relationship of TB and HIV as the main linkage to the prediction of TB in the population. This method, therefore, is highly dependent on the validity of OR we use as the input of the second step in the model. In addition, it also relies on the validity of assumptions we used for the calculation of the HIV prevalence, OR and PAF.

The model predicted well the HIV prevalence within the range of our various control groups. However for the further step of the calculation of odds ratio, it failed to give a close prediction in younger age groups, especially among those groups with people that had a low proportion infected for 10 years or more. A possible reason for this is that our assumption about the same level of OR in different age groups might not be correct. Most previous studies have not shown statistically significant differences in the OR by age, but most have shown the same trend, with the highest OR in young adults to middle age patients while elderly patients almost always had the lowest OR [Houston et al.1994, Long et al.1991, Orege et al.1993, Van Den Broek et al.1993, Van Cleeff and Chum 1995, Chum et al.1996].

The estimated OR from the model, which differs by age only depending on the proportion of people with different duration of HIV infection, increased by age group until reaching a peak in middle age, before decreasing slightly in the elderly. This pattern of increasing OR by age did not come up in the result of our actual data or in other studies. Instead, the OR is level between different age groups or higher in young adults. This discrepancy between the pattern of OR from actual data and the model suggests that the *true* OR with infection of a given duration varies with age, being higher in young adults, but that this is hidden in the observed data due to younger adults having a relatively small proportion of individuals HIV infected for long periods. A true difference in the OR by age might result from the different duration of

M. tuberculosis infection and differing relative risks of primary and post primary disease in association with HIV.

To get a good fit it may therefore be necessary to use different levels of OR over time in different age groups, but our case-control data are too limited to test this. We regarded the ANC as our most valid data in females and military conscript in males, but these selected groups only tell us about limited age ranges and subjects to various biases as discussed above. Therefore to improve the model would require better estimates of population HIV prevalence at different ages. Another problem may be the assumption of similar odds ratios for males and females. Better fits were observed when calculation was done separately for males and females (not shown).

Our model assumed the same relative risk of HIV infection in each age, compared to the referent age in each time period. However this will not be true in an epidemic situation. At the beginning of the epidemic those people with high-risk behaviour in various age groups are the ones who first get infected. As the epidemic begins to mature, infection rate in older age groups become saturated while most newly infected people come from new cohorts of young adults. Therefore the mean age of new infection will shift to younger ages in the later years. In the epidemic, this shifting age pattern should have some effect on the turning point of PAF.

For HIV incidence in the future, we put a very low level of HIV incidence in both genders. This might be not realistic for the epidemic. However it has an advantage in that we can see how far the TB patients will increase even with this situation of very low level of new HIV infection.

In different stages of the HIV epidemic, the proportion of people with different levels of immune suppression is not the same. For the first few years after the commencement of the epidemic, the proportion immunosuppressed should be low. In the advanced stage, however, it will depend on the current trend of HIV prevalence. For areas with stable epidemics, the proportion of those infected for 0-4, 5-9 and equal or more than 10 years should be similar over time. However, as the epidemic declines,

the proportion of those people with recent infection should decrease. Since the development of TB disease mainly occurs in this immunocompromised group, if we do not take this factor into account we will underestimate our PAF in the early years and overestimate them in the later years.

The phenomenon of different peaks of estimated PAF in each age group, can be explained by a birth cohort effect, which depends on 2 factors; the changing incidence of HIV in different years and the different level of risk behaviour in different ages. In those people younger than 35 years, the peak of estimated PAF depends on the moving of the group that had highest HIV prevalence across age groups in different years. As we saw in the prevalence data and also incidence studies among the military conscripts, the peak of this HIV epidemic in males should be around 1991-1992 and then the incidence decreased sharply. As we saw, the highest HIV risk behaviour in men is around 19-21 years old. Therefore, the people who were aged 19-21 years during 1991-1992 should contribute the highest PAF in every period they moved to. For example, these people should move to age 27 years in 1998 and age 32 in 2003. This corresponds to the peak of our model PAF at 1998 for age group 25-29 years and in 2002 among those aged 30-34 years. However at age 35 years, most of them are already infected for at least 15 years and many will have died. Therefore, we could no longer see the effect of this group in older age groups. Instead what is seen in the result is that the peak PAF in age group 35 years or more comes directly from the effect of the high prevalence during 1991-1992 across all ages. However since HIV risk is different in different ages, the cohort of 40 year olds in 1991 should have lower HIV level than the cohorts of 30 years old of the same period. That should explain why the peak PAF after 35 years are at increasingly low levels in the later age groups. Until 2006 when all cohorts that were infected during 1991-1992 pass to the point of around 15 years after infection, that is when we see the turning point of PAF curve in all middle to elderly age groups. In practice the turning point may be earlier than this in the older age groups since the model did not allow for shorter median survival in those infected with HIV at older ages [Collaborative Groups on AIDS Incubation and HIV survival. 2000].

From our findings, the turning point of estimated PAF does not change when we used different levels of OR (figure 10.4). This is because the timing depends on the underlying changes in HIV prevalence and on the assumptions of the divisions of individuals into those infected 0-4, 5-9 and 10+ years. Moreover, although the main limitation of all modelling is that we don't know how close our assumptions are to the truth, our most uncertain assumption, which is the same OR in different age group, should not effect our prediction of the turning point of estimated PAF within age groups. If the OR were higher in the younger groups it would effect the magnitude of the PAF but not the time of the turning point within each age group.

The different level of discrepancy between the actual data and model predicted HIV prevalence in TB patients in males and females may be explained by the different level of bias in our different sources of data we used to calculate OR in males and females, the military conscripts and ANC data. In general, ANC data should be less representative of the general population compared to the male control group, not only because of those who are sexually inactive but also because of those who use contraceptives or have fertility problems. Since the high proportion sexually inactive seems to be the main bias for ANC data, our OR for ANC aged 20-29 years that we used for the calculation of this estimated HIV prevalence should be an underestimate. This fits with the consistently low HIV prevalence among female TB patients from the model estimation, compared to the actual data.

Our model gave only the direct effect of HIV on the burden of TB disease. The increasing number of TB cases due to the transmission from the larger pool of TB cases (due to the effect of HIV infection), was not included in our model. However this group should be a smaller proportion compared to the burden of TB cases from the direct effect of HIV. Nevertheless, for the future improvement of the model to estimate TB burden attributable to HIV infection, this indirect effect should be included [Lienhardt and Rodrigues. 1997].

Although we initially did not create the model based on any population structure, in the application of the model to predict the burden in our study area we have to adjust

the PAF by the population structure of Chiang Rai province. The overall PAF after adjustment for Chiang Rai population structure was higher than the PAF from actual data in males while it was lower than the actual PAF in females (figure 9.5 and 10.6). This has occurred because of the use of the average "best fit" values between males and females. For the male data, the best fit ORs have 2, 20, and 100 while they were 10, 50, and 100 in females for the OR_{0-4}, OR_{5-9}, OR_{10+}, respectively. Therefore, using the average values of 3, 30, and 100 for both sexes should give an overestimation among males and underestimation among females.

In conclusion, we have 3 main findings from our model:

1. First was the earlier turning point of PAF in younger age groups especially in 15-19 years. The TB programme should study trends in HIV in TB patients by age in order to detect the earliest changes in the epidemic.

2. Second the assumption that the association between HIV and TB is the same in different age groups appears not to be correct. It is most likely that OR is higher in young adults, especially those aged less than 30 years but because this group is also HIV-infected for a shorter period of time, the effect of the higher OR is hidden by the low proportion of immuno-compromised people.

3. Third, the turning point of PAF within each age group does not change by different levels of the estimated OR.

Our model was developed to answer some specific questions. While not achieving a perfect fit to the data, it has allowed us to gain a better understanding of the interaction of HIV and TB in this complex dynamic situation.

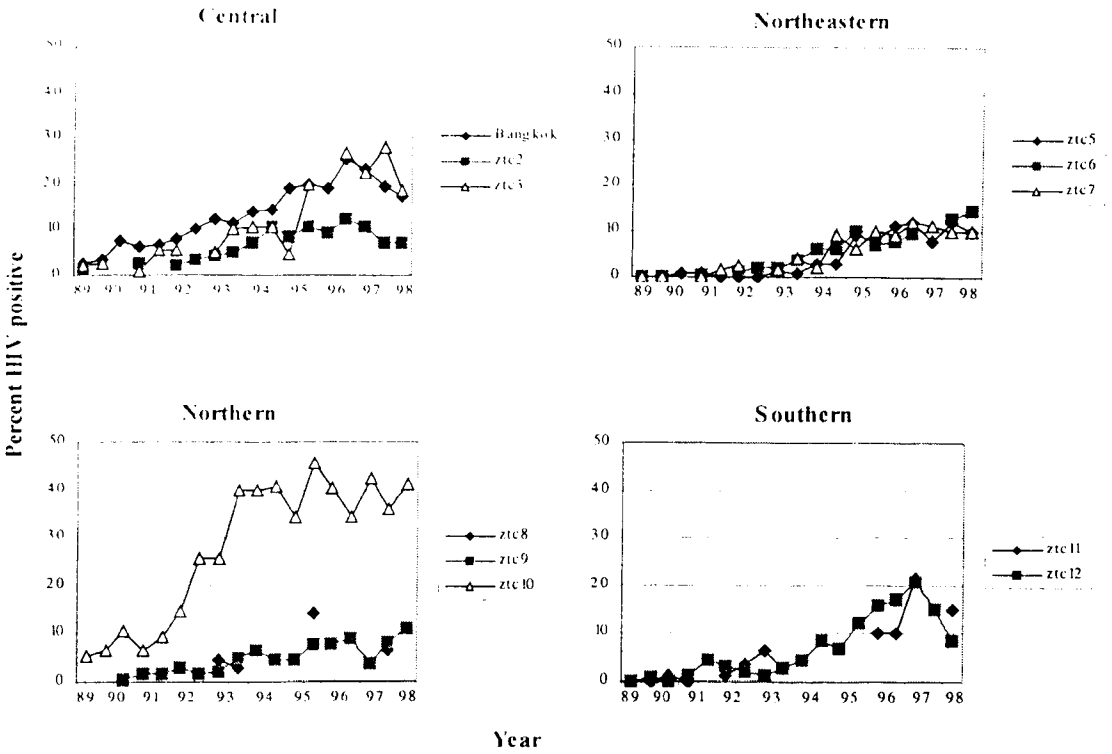
Chapter 11: General Discussion

This chapter addresses the impact of HIV on tuberculosis in Thailand and the current problems of the TB control programme in relation to the findings from our study. The application of our findings for public health interventions is also discussed.

Existing TB burden and the impact of HIV on the burden of disease

The World Health Organisation report in 1999 for Global Tuberculosis Control included Thailand as one among the 22 countries in the world that account for 80% of all new TB cases [World Health Organization 1999b]. Although the reported number of cases of new smear positive TB patients at the national level had not yet increased by 1997, according to reports from the TB division [Payanandana et al. 1999], the trend of increasing HIV prevalence among TB patients in all regions is a warning sign of increasing TB burden in the near future (figure 11.1). However, the impact of HIV on TB from other parts of the country should be less than that we have seen in our study area, and other provinces of the upper northern region (seen in ZTC 10 of figure 11.1). The result from our model showed that this increasing number of TB cases is likely to continue for another 5-6 years, when the PAF will probably start to decrease, but the decrease will happen gradually. This prolonged increase of TB cases after the turning point of HIV prevalence is due to the time lag between HIV infection and the development of TB.

Figure 11.1: HIV prevalence in new TB patients by region (1989-1998)



*** ZTC is zonal tuberculosis center**

Source: Tuberculosis Division, Ministry of Public Health

We calculated the PAF by two different methods: a direct calculation based on the results of the case-control study (chapter 9) and a method based on the model to allow for the different proportions of people HIV-infected for different lengths of time (chapter 10). It is the model PAF which we can use to make predictions about the future, but we need to be cautious in interpreting them because of the problems in the model discussed above. As previously discussed in chapter 10, the fit of the model to the observed odds ratios can be improved by calculating the fixed odds ratios for each duration of HIV infection separately for men and women. The PAF using these sex-specific estimates is lower than the direct estimate for both sexes, as expected. The number of TB cases attributable to HIV using these recalculated PAFs are shown in figures 11.2.1 and 11.2.2.

Figure 11.2.1: Number of male TB cases in Chiang Rai province, attributable to HIV infection, compared between model estimation and the estimation from case-control study

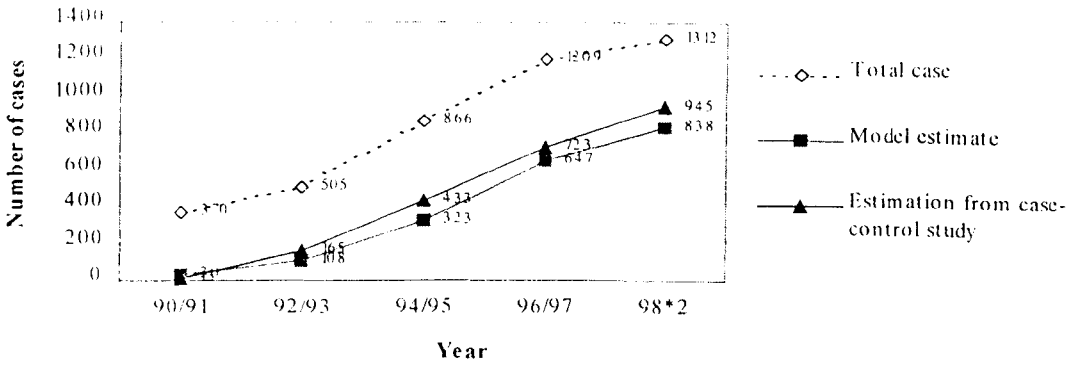
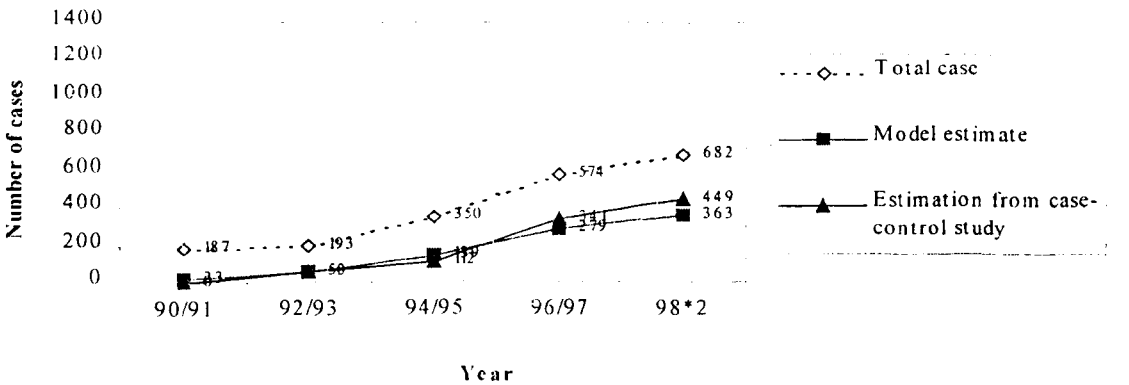


Figure 11.2.2: Number of female TB cases in Chiang Rai province, attributable to HIV infection, compared between model estimation and the estimation from case-control study



*** The number of estimated TB cases in 1998 was multiplied by 2, to make it comparable with other 2 year interval data.**

Given that the estimate based on the actual data is likely to be an overestimate and that our model underestimated the odds ratio in younger age groups, the true number is likely to lie between these two estimates.

The increased number of TB cases attributable to the HIV epidemic for the next 5-6 years only tells part of the story when considering the full consequences of the HIV epidemic on the TB burden in this area. As well as the bio-medical aspects, changes in social structure, the stigma of TB/HIV patients, psychological consequences and economic problems due to loss of working time have to be included. These factors

add to the challenges facing the TB control programme in the study area and in Thailand.

A recent study about the economic impact of tuberculosis at the household level in Thailand showed that people who have income below the poverty line have to spend about 15.3% of their household income for direct patient costs such as drugs, travel costs, and the cost of investigation for diagnosis [Kamolratanakul et al. 1999]. The current low case detection and treatment completion rates may partly be due to the inability of poor patients to cope with the economic consequences of diagnosis and treatment. According to the study, a proportion of these patients has to sell some of their property (15.9%) and some have to take out loans (11.8%). These TB cases also lose money from absence from work due to their illness. TB patients who are HIV infected are mainly young to middle age adults and have a high case fatality rate (around 40%) [Research Institute of Tuberculosis 1999]. These patients are the main group who are responsible for family income. Therefore the indirect costs due to loss of working time or, in the worst case, from death of these patients in their productive age is likely to have even worse consequences on the economics of the affected families, communities and eventually the country. Moreover, the lower socio-economic status of these affected families might lead to a higher possibility of infection with *M. tuberculosis* or development of TB disease. TB has been associated with poverty in many studies although the extent to which this is due to malnutrition or to overcrowding, particularly in cold climates, is not clear.

Control and prevention of TB burden from the impact of the HIV epidemic.

Given the obvious impact of HIV on tuberculosis seen in this and many other studies, the major method of controlling the increase in TB due to HIV is to control the HIV epidemic itself.

Thailand has made good progress with reducing HIV and is frequently used as an example of a success story in HIV control. In contrast to many countries in which government leaders distance themselves from HIV/AIDS issues, in Thailand the Prime Minister chaired the National AIDS Prevention and Control Committee in 1991 [Phoolcharoen et al. 1998]. Thailand was also one of very few low or lower-middle

income countries in which substantial national (rather than donor-derived) resources were committed to HIV/AIDS prevention [Kilmarx et al. 2000]. Following the initiation of the prevention programme, male patronage of female CSWs declined and condom use during commercial sex increased substantially, especially in the upper north. This prevention programme had a remarkable effect. In Chiang Rai, STD rates declined steeply from 726 reported cases per 100,000 population in 1990 to only 12 per 100,000 population in 1999. The seroprevalence of HIV among the military conscripts also declined more than eight fold, to only 2.0% in 1999.

However, we have shown that TB will increase and remain high for some time even if HIV incidence remains very low. As predicted by our model, although the PAF among young adults will decrease quite soon, the PAF in older adults will remain high until the end of this decade even though a gradual decline should start within the next 5-6 years (figure 10.4.1 and 10.4.2). Therefore there is a strong need to strengthen the TB control programme.

The current TB control strategy is composed of 4 elements; 1) Preventive therapy 2) Case-finding and treatment 3) BCG vaccination and 4) Environmental control. The vaccine efficacy of BCG in Thailand is not known and results from other countries are highly variable. It is likely that it has its main impact in prevention of severe disease among children. Environmental control aims to prevent *M tuberculosis* infection, not the disease, so will be similar for HIV negative and HIV positive individuals. However attention should be paid to the evidence of transmission of TB within HIV/AIDS care facilities that has been documented in other countries. The major components for prevention and control of TB cases du to HIV infection, however, are the remaining 2 strategies: preventive therapy (in HIV-infected persons) and case finding and treatment.

Isoniazid (INH) preventive therapy

The effectiveness of INH preventive therapy (IPT) in reducing the risk of active tuberculosis in infected individuals has been demonstrated in a series of controlled trials [Bucher et al. 1999, World Health Organization 1999]. However, the altered immune state of HIV-infected patients, differences in the underlying risk for TB

infection, and differences in susceptibility to drug toxicity make generalization of the utility of IPT to the HIV-infected population questionable. A recent meta-analysis of 7 randomised controlled trials of the overall efficacy of IPT in HIV-infected persons shows that preventive therapy with IPT effectively reduces the incidence of TB in HIV-infected people, RR=0.58 (95%CI 0.43-0.80) [Bucher et al, 1999]. However, the mortality rate was not significantly different between the groups receiving IPT or placebo or control regimens (RR=0.94, 95%CI=0.83-1.07). In the groups of tuberculin skin test-positive and negative persons, the risk ratios for tuberculosis were 0.4 (95%CI, 0.24-0.65) and 0.84 (95%CI, 0.54-1.30), respectively. A recent study in a cohort of HIV-infected Zambian adults also showed similar results. The cumulative risk of TB in the INH or rifampicin plus pyrazinamide group in the first 2.5 years after preventive therapy was significantly lower than the placebo group (RR 0.55, 95%CI=0.32-0.93) while there was no significant effect of preventive therapy on mortality [Quigley et al. 2001].

In Chiang Rai hospital an isoniazid preventive therapy program started since November 1993. The program recruited HIV-infected persons from 4 sources: 1) blood donors; 2) an anonymous clinic conducting HIV/AIDS counselling and blood testing; 3) The Out-Patient Department; and 4) HIV-infected female commercial sex workers who were referred from a cohort study. Except the blood donors, all participants were provided with post-test counselling and information about the IPT program before they were referred for enrolment in the program. The hospital provided the IPT service free of charge. The study during 1994-1995 reported the adherence rate at 67.5% (278 cases out of 412 cases) during the initial 9 months [Ngamvithayapong et al. 1997]. The IPT program in Chiang Rai was stopped after enrolling 996 HIV-positive cases in mid 1997 due to lack of political commitment although it had a relatively high success rate compared to the IPT programmes in other parts of the country [Yanai H, personal communication].

Another study from Chiang Rai province demonstrated the possibility of implementing IPT via an existing AIDS care programme. A retrospective cohort study of IPT in people living with HIV during 1995-1999 in a district hospital in Chiang Rai province showed a reduction in default rates over time [Piyaworawong et al. 2000]. During the study period, the IPT service changed from a special clinic in the hospital's

TB clinic to the hospital's day care centre for People Living with HIV. Registration and counselling at the day care centre are the key processes to promote the acceptance of HIV-positive status and allow higher adherence. Step-wise integration of TB prevention activities from TB clinic to the day care centre promoted the co-operation between TB and HIV/AIDS control activities while securing the resources for TB control. The RR for reduction of default rates associated with enrolment at the day care centre at the beginning compared to participants who were initially enrolled at the hospital's TB clinic was 0.57 (95%CI 0.44-0.75).

However, since IPT is not highly cost-effective compared to curative treatment of infectious tuberculosis cases, it has to have a lower priority in situations in which resources and health personnel are limited. Moreover, studies of the feasibility of IPT demonstrate that the processes required to target appropriate individuals, to exclude active tuberculosis, to deliver IPT and to achieve adherence are complex and inefficient. Therefore, IPT is not widely used due to its operational complexity and the high risk of promoting drug resistance, but needs to have careful consideration for each setting under specific prerequisites [World Health Organization 1999]. Nevertheless, since IPT has been shown to be feasible in Chiang Rai [Ngamvithayapong et al. 1997, Piyaworawong et al. 2000] and since there are several population groups with known HIV status, it would be worth reconsidering the programme.

Case finding and treatment

The WHO strategy for controlling TB is based on DOTS: Directly Observed Therapy, Short Course. DOTS has been advocated by the WHO as an effective strategy to control TB, and reduce drug resistance, following the successful experience in New York City. In its widest interpretation this also includes recommendations on the importance of good case finding, which should be as complete as possible with minimal delay [De Cock and Chaisson, 1999].

Estimating the completeness of case finding is difficult. A study in Thailand gave an estimate of 41.2% coverage of case-finding for smear positive patients.[Payanandana et al.1999]. However this was based on the annual risk of infection calculated from

the series of tuberculin surveys conducted in school children until 1983. This is unreliable because the data were too old, and so the calculations relied on assumptions about the continuing rate of decline in infection rates. In addition, the traditional methods used to estimate the number of smear positive cases expected from the annual risk of infection are no longer valid in the presence of HIV [Rieder, 1995]. In the presence of HIV the annual risk of infection is likely to have declined less quickly than predicted and HIV infected individuals are more likely to progress from infection to disease, so the predicted number of cases is likely to have been underestimated and therefore the completeness of case finding overestimated.

Further evidence that the completeness of case finding is likely to be low comes from a qualitative study about perception of TB in Chiang Rai. This showed that all participants were well informed about AIDS patients and symptoms but knew very little about TB [Ngamvithayapong et al. 1999]. The community defined persons losing weight with fever and cough as having AIDS rather than TB. This resulted in delay seeking care among patients who suspected themselves as having AIDS, and were afraid of AIDS detection.

In general active case finding is not promoted. It is hoped that a successful treatment programme will act to encourage symptomatic individuals to present to the services. The core of DOTS is directly observed therapy. Before implementation of a DOTS programme in Chiang Rai, a focus group discussion among health care providers and clients showed both groups perceived health center-based DOTS to be impractical [Ngamvithayapong et al. 1999]. While most clients preferred home-based DOTS, all female and half of the male providers felt it was impractical. Nevertheless, home-based DOTS may be feasible through building awareness among health staff about multiple drug resistance, and about intermittent DOTS and combined with maternal and child health home visits and provision of fuel and staff incentives.

In 1996, a pilot district was selected to implement DOTS in Chiang Rai and the programme was later introduced in a stepwise fashion to other districts. It now has provincial coverage [Saisorn et al. 1999]. Initially the DOTS system at the district level was either facility- based or home-based. Each district was encouraged to adjust this to suit its own setting. The encouragement of health officers to serve as case

managers and treatment supervisors became more intense later and replaced this role of family members.

During the period of promotion of DOTS, default rates of new smear positive cases decreased over time, i.e., 25.2%, 20.9%, 15.6%, 11.6% and 4.5% in 1995, 1996, 1997, 1998 and 1999, respectively [Saisorn et al. 1999]. The rate of transfer out, however, increased over the same period, i.e., 4.6%, 6.5%, 7.4%, 9.9% and 12.2%, respectively. Out of the 241 transferred out AFB-positive pulmonary TB cases in 1995-1999, 19.1% did not show up at the referred hospital and were therefore probably also defaulters.

For the TB control program in Chiang Rai, the high case fatality rate of TB patients during treatment is a major problem, not only among HIV-positive cases (40%) but also HIV-negative cases (18.6%) [Research Institute of Tuberculosis 1999]. The experience from 2 community hospitals, Wiang Pa Pao and Phan showed that DOTS does not seem to improve mortality. In Wiang Pa Pao mortality before and after DOTS was 14.3% and 16.3% in AFB positive and 25% and 34.4% in AFB negative patients. In Phan, mortality before and after DOTS was 8.5% and 13.9% at 2 months and 22.7% and 25% at 6 months. This could be related to the high proportion of AIDS cases in advanced stage in Chiang Rai province. The results are not available separately by HIV status.

From the experience of many countries in Africa, DOTS alone is unlikely to control tuberculosis in situations in which HIV is prevalent. A recent paper suggested that the TB control strategy in areas of high and low HIV prevalence should be different [De Cock and Chaisson, 1999]. The authors suggested new approaches to TB control in areas with high rates of HIV infection, many of which should suit our study area.

- Active case finding for TB, especially among and around HIV-positive persons should allow earlier case detection and treatment among the group that has the highest risk of developing TB. Spouses of HIV infected people are often infected with HIV themselves. Therefore spouses of HIV positive TB patients are likely to be at particularly high risk of developing active TB. For the spouses that do not already have active TB, preventive therapy should be implemented.

• In some institutions such as prisons, where both TB and HIV are highly prevalent and easily spread, voluntary HIV antibody testing and early detection and treatment of TB among HIV-infected people should be promoted. However the usefulness of INH prophylaxis in these settings may be limited by the high rates of drug resistant strains circulating in the prisons.

• For HIV-infected people in general, a minimum package of care should include TB prevention and early diagnosis. Therefore, programmatic co-ordination between HIV/AIDS and TB needs to be strengthened. Community involvement in TB control is also useful and should be addressed and emphasized in the TB control programme in our study area.

Antiretroviral therapy

Although antiretroviral therapy was reported to decrease incidence of some HIV-associated conditions, until recently there was little information about any effect on TB [Kaplan et al. 2000]. A recent study from 17 European countries reported a marked decrease in incidence of TB after the introduction of highly active antiretroviral therapy (HAART) [Kirk et al. 2000]. This study is a multicenter observational cohort of more than 7000 patients. The incidence of TB decreased from 1.8/100 person-years before September 1995 to 0.3/100 person-years after March 1997 [Kirk et al. 2000].

Even though antiretroviral therapy is not widely used in Thailand currently, due to its cost, there is a potential for decreasing this cost for developing countries, which might make this strategy possible to implement. So far, some drug companies have tried to cut the price of anti-HIV drugs for resource poor countries, such as a reduction of domestic prices for triple drug therapy for AIDS by a drug company in India, a fund raising effort to buy HIV-related drugs and distribute them for free in Africa by a small US firm, and Glaxo-Smith-Kline's offer of 90% discount on HIV drugs to Africa [Reuters Health a, b and c, 2001]. In terms of the feasibility of the health infrastructure in Thailand to cope with administering and monitoring antiretrovirals, there is evidence that this could succeed. The experience with INH prophylaxis has shown that there is the capacity to deal with a follow up system and

monitoring in some places, such as Chaing Rai hospital. And the widespread ANC based HIV testing already in place would help identify HIV-infected individuals

Monitoring impact of control programs

When changes are introduced in the control programme it is important to monitor their impact , but monitoring the impact of these control programmes on mitigating the impact of the HIV epidemic on the TB case rate is difficult. A decline in the TB case rate is expected because of changes in HIV incidence, so it is difficult to know whether changes seen in TB case rates are due to the impact of TB control programmes or to secular trends. Our model should help in differentiating these factors since it allows us to predict when a decline would be expected due to changes in the HIV epidemic alone, and the extent of this decline. Broadly, a decline greater than that predicted would suggest improvements in TB control. Monitoring the different times of decline in different age groups in relation to those predicted by the model may also be useful in differentiating these two causes. The model is too crude to detect small differences, but a continued rise in the PAF for many more years than predicted, or a fall within the next 2-3 years would suggest real change. Continued monitoring of the HIV status of TB patients and population groups in Chiang Rai is thus recommended to help interpretation of future trends. Monitoring of HIV prevalence in the general population can continue to use the sentinel surveillance procedures that are already in place, based on ANC and military conscripts. ANC testing is a priority anyway because of the availability of antiretrovirals to decrease vertical transmission. The regular provision of proper and adequate counselling before and after the test has to be maintained.

Priority of additional strategies to strengthen TB control programme

Based on the current knowledge of TB control, and in the context of the health sector and economic situation in Thailand, we would like to recommend priority strategies to strengthen the TB control programme. These are listed by their importance and feasibility of implementation, in terms of structure and resources.

1. Early detection and treatment of existing cases.

1.1 For the general population, basic knowledge about TB symptoms and treatment should be promoted to encourage early diagnosis and treatment, since many people misunderstand TB symptoms as AIDS, which leads to a delay in seeking treatment

1.2 For some institutional settings, such as prisons or hospitals, that have high risk of spreading TB infection, systems should be implemented to ensure early detection and treatment

2. Improving the cure rate

Studies of risk factors and qualitative studies in different areas about the cause of default and the reason that referred patients do not go to referral hospitals should guide a strategy to improve the cure rate of TB treatment in Thailand. Improving DOTS implementation is required especially in big hospital to increase the cure rate

3. Active case finding

Active case finding should be considered for spouses of HIV-positive persons. In the future, active case finding might be promoted among other groups at high risk, such as immigrant communities in urban areas.

4. Preventive therapy

4.1 IPT in HIV-infected patients should be reconsidered in Chiang Rai hospital and in other appropriate health sectors. This should be integrated into the existing AIDS care programme

4.2 Consideration should be given to giving IPT to families of HIV-infected patients

5. Strengthen programatic co-ordination of TB/HIV

The co-ordination of the programmes would aid th strategies of case finding and prophylaxis described above

6. Antiretroviral therapy

Provision of antiretroviral therapy might be possible in the future, depending on costs.

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Appendix

Group 1= diseases or condition that are most likely to be associated with HIV

Group 2= diseases or condition that are possibly associated with HIV

File MS1 (general surgery, neuro-surgery, plastic surgery and dental surgery)

Group 1

- Abscess
- TB
- Infected wound
- Chronic infection
- Cellulitis

Group 2

- Cancer
- Gangrene
- Myositis
- Osteomyelitis

Except those with underlying diseases such as burn with infected wound.

Group 1

- Abscess
- Acute appendicitis
- Acute cholecystitis
- AIDS, ARC with any condition
- TB with any condition
- Cellulitis
- Empyema
- Infected wound
- Necrotizing fasciitis
- Peritonitis
- Pleural effusion
- Sepsis
- Segmental ilitis
- Zoster

Group 2

- Acute cholangitis
- Ascitis
- Biliary obstruction
- Bowel ileus
- CA
- Chronic appendicitis
- Chronic cholecystitis
- Chronic ulcer (this is not known whether it is in the stomach or in the limb)
- Chronic wound
- Fasciitis
- Gangrene
- Mass

- Gut obstruction
- Pericardial effusion
- Pyomyositis
- Tropical pyomyositis

Except those with all of above with underlying diseases such as DM with infected wound, gall stone with cholecystitis, peritonitis with blunt trauma, peritonitis with peptic perforate, etc.

File male and female urology

Group 1

- Abscess
- Acute pyelonephritis
- Cellulitis
- Infected wound
- Orchitis
- Stricture urethra
- TB orchitis
- UTI

Group 2

- Cancer
- Mass
- Gangrene

Except those with underlying diseases such as renal stone with UTI

File female orthopedic

Group 1

- Abscess
- Cellulitis
- Infected wound
- Septic arthritis
- TB spine

Group 2

- Arthritis
- CA, tumour
- Chronic wound, chronic ulcer
- Gangrene
- Osteomyelitis

Reference: Deziel et al. 1990, Lowy et al. 1994, Luzzi 1994, Watters 1994, Evans et al. 1995, Mueller et al. 1995, Saab et al.1996, Major 1997, Cello 1998, Coburn M 1998, Monkemuller et al. 1998, Greenblatt et al. 1999.