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Review

Biomedical HIV prevention research and epidemic control in Thailand: two sides of the same coin

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Abstract. For a country with a moderate adult HIV prevalence of just over 1% in 2012, Thailand is widely perceived as having made some extraordinary contributions to the global management of the HIV/AIDS pandemic. It has been promoted as a model of effective HIV control and applauded for its leadership in providing access to antiretroviral treatment. Thailand has also received international recognition for its contribution to biomedical HIV prevention research, which is generally perceived as exceptional. In this paper, Thailand's global role model function as an example of effective HIV/AIDS control and high-quality biomedical HIV prevention research is re-evaluated against the background of currently available data and more recent insights. The results indicate that Thailand's initial response in raising the level of the political significance of HIV/AIDS was indeed extraordinary, which probably prevented a much larger epidemic from occurring. However, this response transpired in unusual extraconstitutional circumstances and its effectiveness declined once the country returned to political normalcy. Available data confirm the country's more than exceptional contribution to biomedical HIV prevention research. Thailand has made a huge contribution to the global management and control of the HIV/AIDS pandemic.

Additional keywords: antiretroviral treatment, condom use, injecting drug users, prophylaxis, sex workers, vaccination.

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Background

For a country spending less than 4% of its gross domestic product on health care and ranking 161 out of 190 world countries in health expenditure,[1] Thailand is believed to have made some extraordinary programmatic and research contributions to the global management of the HIV/AIDS pandemic. This nation of 67 million, with a moderate adult HIV prevalence of 1.2% in 2012,[2] has been promoted as an example of effective HIV control and has received international recognition for its high quality biomedical HIV prevention research. In 1991, Thailand started its '100% condom use in commercial sex' program, widely believed to be the first and possibly the only national program having achieved successful control of a generalised HIV epidemic.[3–8] In 1996, Thailand was the world's first country to start hosting its own clinical trials of more affordable antiretroviral regimens for the prevention of mother-to-child HIV transmission (PMTCT);[9] by 2001, close to 100% of pregnant Thai women were tested for HIV and were offered antiretrovirals for them and their newborns if found to be HIV-infected.[10,11] Thailand again served as a role model by introducing its National Access to Antiretroviral Program for People living with HIV/AIDS in 2001, the first nonhigh-income country doing so.[12,13] More recently, in 2006 and 2007, Thailand gained further international respect for its courage in issuing compulsory licences for the import or local production of antiretrovirals to be able to meet the expenses of its program and ensure continued access for its people, despite looming punitive economic measures.[14,15]

The aim of the present review is to revisit and update Thailand's global role model function as an example of effective HIV control and high quality biomedical HIV prevention research using more recent information and new insights. This includes a review of the HIV epidemiology and preventive responses, a description of Thailand's biomedical HIV prevention research infrastructure, and a quantification of its past and future contribution to global biomedical HIV prevention research.

Methods

Scientific publications and reports commissioned by international and national government and non-government organisations, such as the World Health Organisation, the World Bank, the United States Agency for International Development, Family Health International 360 and the National Social and Economic Development Board, were searched and retrieved from PubMed (www.ncbi.nlm.nih.gov/pubmed; accessed March 2014), Google Scholar (www.scholar.google.com; accessed March 2014), and from other available online and offline sources (www.aidsdatahub.org; accessed March 2014), including Thai country progress reports in response to the UN General Assembly Special Session on HIV/AIDS and to the Global Fund to Fight AIDS, Tuberculosis and Malaria.[16] This information was then reviewed, abstracted and summarised to review Thailand's role as an example of effective HIV control and high quality biomedical HIV prevention research.

Results

Epidemiology and prevention

Epidemiology

General population. Since the mid-80s, the cumulative number of HIV-infected Thais is estimated to be 1.1 million.[17,18] At the current time, ~600 000 Thais are believed to have died from AIDS; of the remaining 500 000 (1.2% of the adult population), ~350 000 (70%) are estimated to be eligible for antiretroviral treatment (ART) under Thai national guidelines.[A,19] Of the latter, ~225 000 or 65% are now receiving publicly funded ART.[12,13,20]

Early cases of AIDS and AIDS-related complex. The first known case of AIDS in a Thai citizen was diagnosed in the United States (US) in a young homosexual male who returned to his native country in 1984, seeking solace with his family, and who passed away 2 months later.[21] This case was followed by a string of AIDS-related complex (ARC) and AIDS cases diagnosed in Thai and foreign homo- and bisexual men in 1984 and 1985.[22,23] Two additional heterosexually acquired cases of AIDS-related complex were diagnosed in 1985, one in a Thai male who had returned from the US and one in a female consort to a bisexual male diagnosed earlier.[22]

Early HIV epidemiology. The first specimen testing HIV-positive on Thai soil was taken from a male sex worker (MSW) in the Bangkok Patpong area in 1985 during an *ad hoc* HIV surveillance activity of the Ministry of Public Health (MOPH).[23] During the next few months, several more MSWs tested HIV-reactive from the same area and from Pattaya, a beach resort south of the capital.[23] Through 1986, a small number of female sex workers (FSWs) from the same locations was found to be HIV-infected. By the end of 1987, the first HIV infections were detected among injecting drug users (IDUs) attending drug treatment facilities in greater Bangkok.[23,24] These early HIV cases were followed by an unprecedented outburst of HIV infection among IDUs receiving methadone treatment in Bangkok Metropolitan Administration clinics, in whom HIV prevalence rose from 1.0% by the closure of 1987 to 42.7% by September 1988.[23] This steep increase was confirmed several years later in a retrospective study of stored IDU blood specimens in which the HIV incidence rose from zero to 30 per 100 person years (PY) of follow-up during the first quarter of 1988, climbing to 60 per 100 PY during the second quarter and steadily declining to bottom out at 10 per 100 PY during the second quarter of 1991.[25]

Heterosexuals. In 1988, the MOPH initiated national HIV surveillance among FSWs, MSWs, IDUs and other sentinel populations. Although the system was expanding coverage in 1988, the HIV prevalence in direct[B] FSWs in 20 out of 29 provinces was $\leq$10%, but in the three northernmost provinces (Chiang Mai, Chiang Rai and Phayao), it was 42.7%, 35.0% and 26.0%, respectively.[26]

During the second biannual round in 1989, the national provincial median HIV prevalence among direct FSWs was 11.4%, which increased to 21.6% during the next year and to 29.5% in 1992.[26] During the same period, the direct FSW HIV prevalence in upper northern Thailand and the Gulf of Thailand bordering industrialised provinces had risen into the 60–70% range (Fig. 1). After 1992, the number of FSWs included and the number of provinces submitting HIV surveillance reports declined rapidly, hampering trend analyses over time.[26]

HIV surveillance conducted by the Royal Thai Army among 21-year-old military conscripts[C] showed a triple increase from 0.5% in 1989 to 1.6% in 1990, indicating that HIV had made inroads and was spreading in the youngest age bracket of Thailand's male reproductive population.[16,27,28] In addition, HIV prevalence was higher among conscripts from the upper northernmost provinces, the highest being in 1991 in Phayao (19.8%; Fig. 2).

Even though paediatric HIV/AIDS cases were observed in Bangkok hospitals as early as in 1988,[29] national-level evidence of HIV transmission among reproductive age groups was provided by the 0.7% HIV prevalence in pregnant women

[A]At the time of writing this report, HIV-infected persons with <350 CD4+ cells mm^{-3} or symptomatic HIV infection are eligible for ART. The subcommittee on HIV/AIDS of the Thai Medical Council has resolved that a diagnosis of HIV infection is sufficient for ART initiation. This change will be published in 2014 and will become policy in 2015.

[B]In the Thai commercial sex setting at the time, a distinction was made between 'direct' or brothel-based FSWs in locations where only sexual services would be provided on the premises, versus indirect FSWs based in locations where additional services could be procured, such as companionship for the evening or during leisure activities or travel over multiple days, and where sexual services, if desired, would be provided at another location such as the client's hotel or home, or in an attached luxury room or facility to be paid for separately.

[C]A fairly representative national sample of 21-year-old Thai men drafted into the military during two yearly cycles, with exception of men from usually higher socioeconomic backgrounds, who may exercise the privilege granted to aspiring or young students to complete their military duties part-time stretched out over a number of years while they attend high school or prepare for admission to institutions for higher learning.

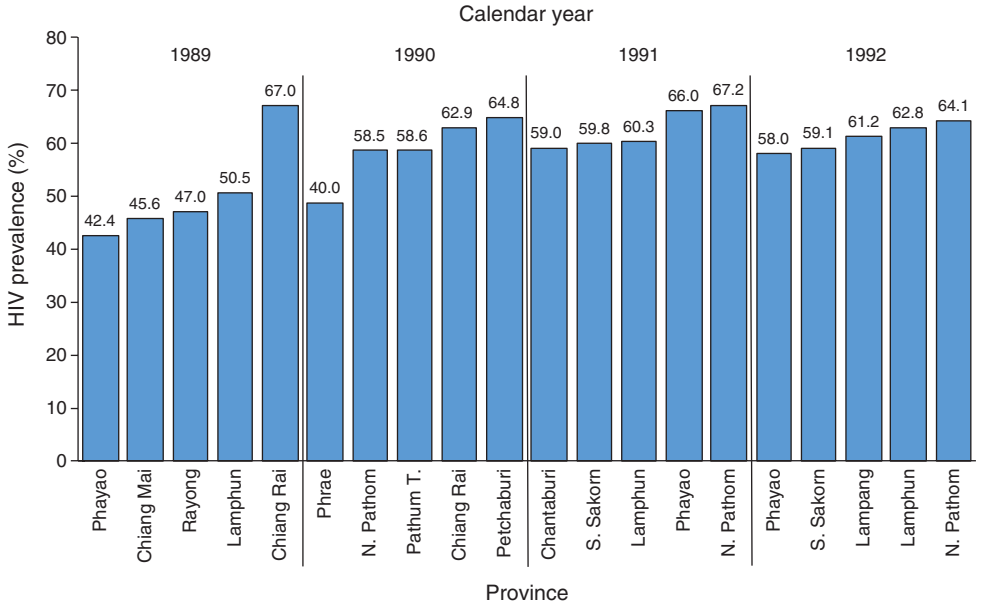

Fig. 1. HIV prevalence among direct female sex workers in selected provinces: sentinel HIV surveillance in Thailand, 1989–92. Data from the Ministry of Public Health.[26]

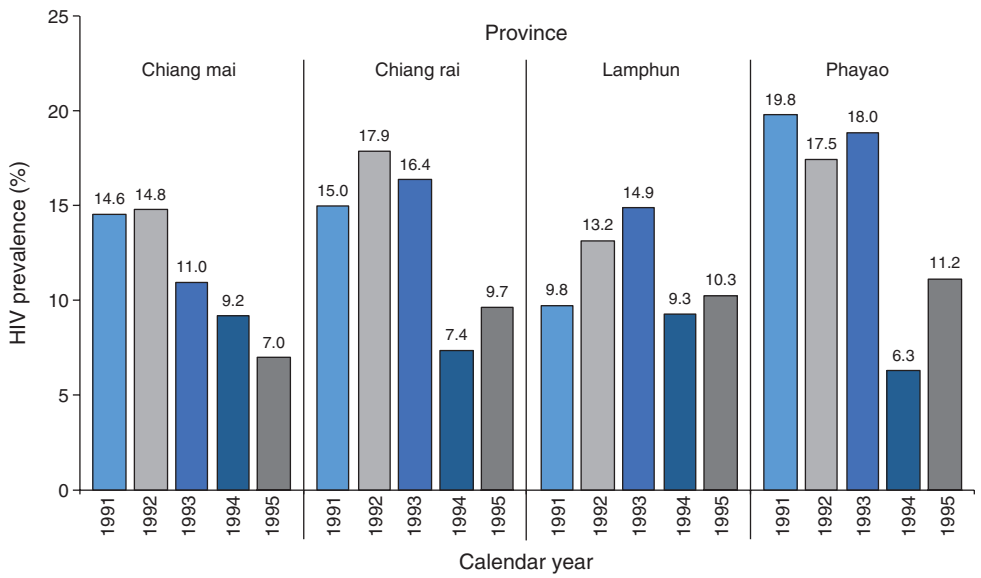

Fig. 2. HIV prevalence among military recruits from selected upper Northern provinces in Thailand, 1991–95. Data from the HIV AIDS Asia Pacific Research Statistical Data Information Resources,[16] and Royal Thai Army.[27]

attending public antenatal care facilities during 1991.[26] Given the untreated mother-to-child transmission probability of 30–40%,[9–11] several newborns started their lives with HIV infection prior to and during 1991 as well. The national HIV prevalence peaked at 4.0% in military conscripts in 1993 and at 2.3% in pregnant women in 1995. By 2004, this prevalence had declined to 1.0% and 0.5%, respectively.[26–28] The national provincial median HIV prevalence among direct FSWs reached its peak in 1994, 35.5%, after which it gradually declined to 7.4% in 2004.[26]

These trends have been corroborated by a large body of independent and partially overlapping research, providing additional evidence of high HIV prevalence and incidence, and subsequent declines in HIV risk behaviour, prevalence and incidence among FSWs, military conscripts, pregnant women, and young adult heterosexual Thai males and females.[30–47] In addition, from 1989 to 1993, the number of five sexually transmissible infections (STI) diagnosed in men at venereal disease clinics operated by the MOPH declined by 79%, in addition to a 23% decrease in the number of FSW

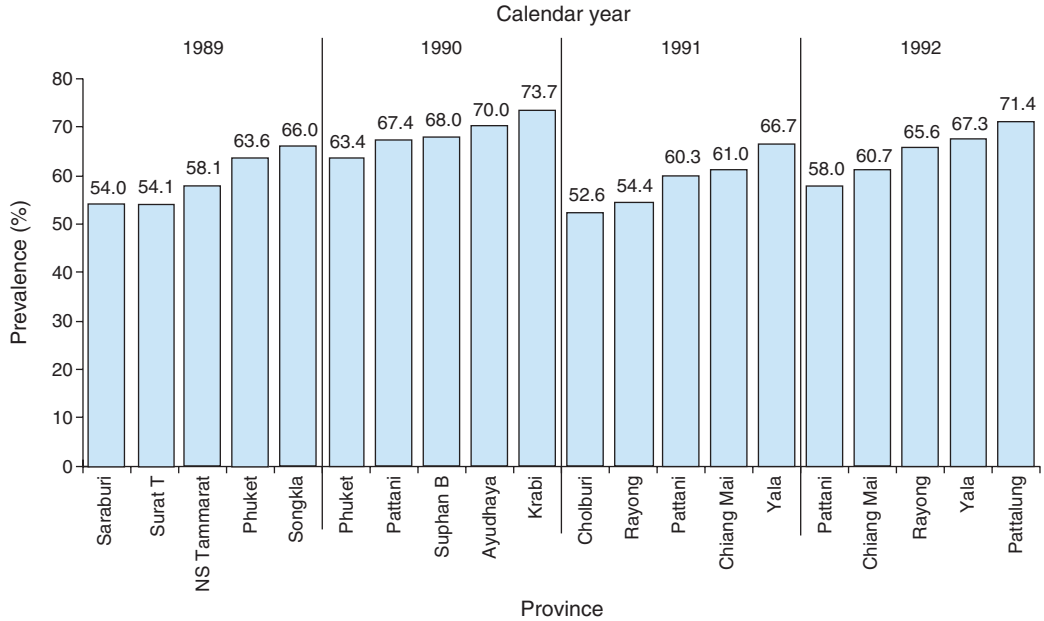

Fig. 3. HIV prevalence among injecting drug users in selected provinces: sentinel HIV surveillance in Thailand, 1989–92. Data from the Ministry of Public Health.[26]

registered with the Venereal Disease Division during the same period.[4,48]

Injecting drug users. Since the initial upsurge in Bangkok IDUs during 1988, routine HIV surveillance data collected from users attending government treatment facilities around Thailand during 1989–2010 showed that the national provincial median HIV prevalence was fluctuating around 40%, with lows of ~30% to highs of >50%.[26] Throughout the Thai HIV epidemic, IDU HIV prevalence has been consistently higher in the southern provinces, close to or exceeding 70% during 1989–92 (Fig. 3). After that year, the number of IDUs included and the number of provinces submitting IDU HIV surveillance reports declined quickly, complicating further analyses and interpretation of trend data.[26] The continuing high HIV prevalence and incidence and HIV risk factors and cofactors in Thai IDUs have been well described and verified by a large body of auxiliary and independent research spanning the past two decades.[49–61]

During that time, the estimated number of IDUs in Bangkok and elsewhere declined,[62–64] probably as a result of increased background[65] and HIV-related mortality,[66] barriers in accessing ART,[58,60] extrajudicial 'law enforcement',[67,68] and a shift in drugs of choice and their administration by novice users.[69,70]

Men who have sex with men. Men who have sex with men (MSM) were the first population in Thailand in which HIV was described[21–23] and surveys have reported the proportion of Thai men engaging in same-sex behaviours to range from 3.3% to 16.3%.[71–75] Since the current Thai adult male population is ~22 million,[76] the number of MSM in Thailand may therefore be large. MSM were initially not considered a population of epidemiologic relevance[77] and were only included in HIV surveillance in 2003. In that year, a cross-sectional assessment by the Thailand MOPH–US Centers for Disease Control and Prevention (CDC) Collaboration (TUC) and the Thai Red Cross AIDS Research Center (TRCARC) among a venue–daytime sample of 1121 MSM in Bangkok revealed an HIV prevalence of 17.3%.[78] During similar assessments in 2005 and 2007, the HIV prevalence had risen to 28.3% and 30.8%, respectively[79] (Fig. 4). Since then, the overall HIV prevalence among MSM has been fluctuating at around 30%[D] (Fig. 4).[80,81]

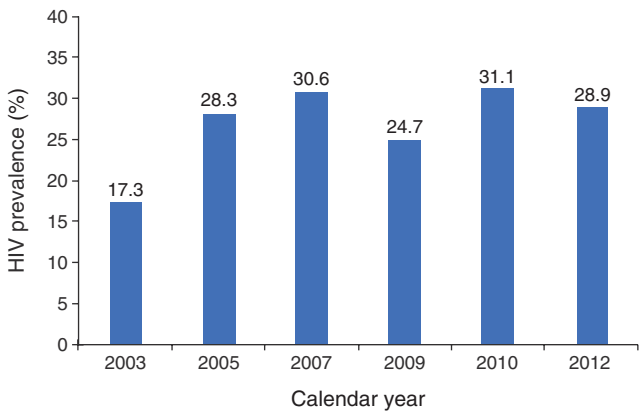

Fig. 4. HIV prevalence among men who have sex with men in Bangkok: sentinel HIV surveillance in Thailand, 2003–12. Data from van Griensven *et al.*,[78,79] Kladsawas *et al.*[80] and the Bureau of Epidemiology.[81]

[D]Both in 2009 and 2010, HIV surveillance data collection in MSM was hindered by ongoing political protests in Bangkok and fewer men could be enrolled from known high-risk urban venues such as public parks and other settings occupied or blocked by protesters. This may have affected the HIV prevalence during these years, possibly explaining the 'dip' in HIV prevalence found in 2009 ($Z_{2007–09} = 1.98$, $P < 0.047$; $Z_{2009–10} = 1.7$, $P < 0.09$, two-tailed tests).

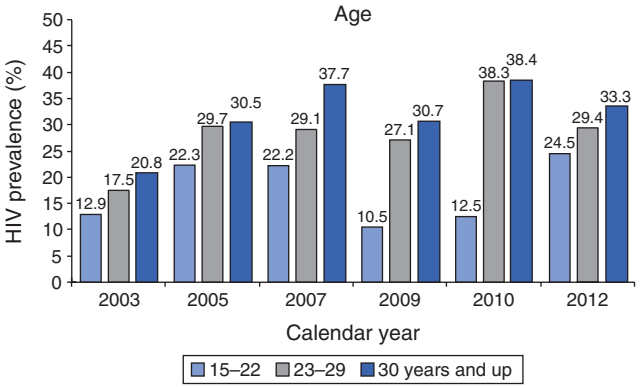

Fig. 5. Age-disaggregated HIV prevalence among men who have sex with men in Bangkok: sentinel HIV surveillance in Thailand, 2003–12. Data from van Griensven *et al.*,[78,79] Kladsawas *et al.*[80] and the Bureau of Epidemiology.[81]

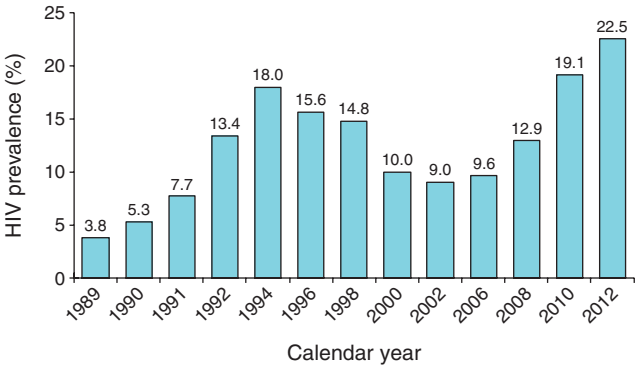

Fig. 6. HIV prevalence in male sex workers: sentinel HIV surveillance in Thailand, 1989–2012. Data from the Ministry of Public Health.[26]

Age-disaggregated HIV prevalence shows ongoing HIV acquisition among the youngest category of MSM, cumulating to ~40% at entry into the fourth decade of life by the year 2010 (Fig. 5).

This high and increasing HIV prevalence was later confirmed from several other sources, notably the Thai Red Cross Anonymous Clinic, where 29.1% of 3485 MSM attending voluntary testing and counselling for HIV during 2006–2009 tested HIV-positive;[82] the Silom Community Clinic, with 28.3% of 4762 MSM attending similar services during 2005–2011 showing evidence of HIV infection;[83] and at baseline in the Bangkok MSM Cohort Study, 2006–2010, with 21.3% of 1744 men being HIV-infected.[84] Lower HIV prevalence was found during assessments among MSM in urban areas outside Bangkok such as Chiang Mai (12.9%, 2008–09),[85] Phuket (20.0%, 2005)[86] and Pattaya (17.6%, 2009–10).[87] Over the years, the MOPH has included MSM from several provincial capitals around the country in their surveillance, showing HIV prevalence to vary between 5% and 15%.[80,81]

Thailand is the only country in South-East Asia for which HIV incidence data among MSM are available. Initially, recent HIV infection among 15- to 22-year-old Bangkok MSM was estimated to have risen from 4.1 to 7.7 per 100 PY during 2003–07.[79] A second estimate was obtained from nucleic acid testing of MSM aged ≥18 years HIV-negative on regular assays during 2006–07 (2.7 per 100 PY).[88] During follow-up among MSM who initially tested HIV-negative at the Silom Community Clinic, HIV incidence was 6.3 per 100 PY but was higher among 15- to 21-year-olds (12.2 per 100 PY).[83] During follow-up in the Bangkok MSM cohort study, from 2006–12, the HIV incidence was 5.9 per 100 PY and was also higher in 18- to 21-year-olds (8.8 per 100 PY).[84] After 60 months of follow-up, the overall cumulative HIV incidence was 23.9%, but was 31.3% in 18- to 21-year-olds.[84] High HIV incidence was also found in cohorts of MSM in Chiang Mai during 2008–09 (8.4 per 100 PY)[85] and Pattaya during 2009–10 (9.7 per 100 PY).[87]

Male sex workers. HIV surveillance data have been collected from venue-based MSWs since 1988 in selected provinces (Bangkok, Chiang Mai, Chonburi (Pattaya), Phuket (Patong) and Song Khla (Had Yai)) where such sex establishments were found.[16,26] During more recent years, inclusion of MSW from these provinces has been inconsistent,[E] whereas MSW active in other provincial capitals were surveyed on an *ad hoc* basis. After an initial increase from 3.8% in 1989 to 18.0% in 1994 and a decline to 9.0% in 2002, the HIV prevalence increased to 22.5% in 2012,[16,26,80,81,86] the highest since 1988 (Fig. 6). Little ancillary epidemiologic research has been conducted in MSWs, except studies among 1172 and 181 MSWs in Chiang Mai during 1989–94[89] and in 2003,[90] respectively. In the first study, the median sex work time was 4 months; most (57.6%) identified themselves as heterosexual and 50% did not use condoms with clients or used them only inconsistently. Although the HIV prevalence was 1.4% in 1989, it was 13.9% in 1990 and 20.1% in 1993. The overall HIV incidence during the 4.5-year study period was 11.9 per 100 PY.[89]

The second study concerned a cross-sectional comparison between Thai and non-Thai (mostly ethnic Shan Burmese) MSWs, in which the overall HIV prevalence was 7.7% (11.8% in Thai *v.* 3.4% in non-Thai). Of these men, 68.8% identified as heterosexual and 36.9% had practiced sex work for less than 6 months; female clients were reported by 24.9% and consistent condom use varied from 22.4% with steady male or female partners to 90.7% with female clients.[90]

Transgender women. Transgender women were first included in Thai HIV surveillance in 2005, and inconsistently and in varying numbers and locations in subsequent years. The HIV prevalence in transgender women from Bangkok, Phuket and Chiang Mai was 13.5% in 2005,[86] 9.8% in 2009[80] and 10.1% in 2010[81] (Fig. 7). However, the latter sample included transgender women from eight additional provincial capitals.[81] HIV prevalence in underlying age groups varied considerably, with more than one-fifth of ≥30-year-old transgender women found to be HIV-infected in 2005 and 2010.

[E]For reasons of consistency and parsimony, the data presented here are limited to those from the cities mentioned above and are presented annually during the first 4 years, and biennially during the remainder of the observation period.

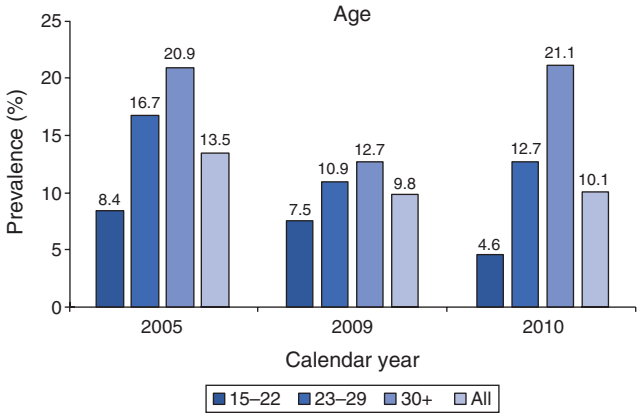

Fig. 7. HIV prevalence in transgender women: sentinel HIV surveillance in Thailand, 2005–10. Data from van Griensven *et al*.,[78,79] Kladsawas *et al*.[80] and the Bureau of Epidemiology.[81]

However, the overall HIV prevalence did not significantly differ between the three years (χ^2 (trend) = 5.23, $P = 0.073$). This HIV prevalence was confirmed by two additional studies among transgender women screened for enrolment in the International Pre-exposure Prophylaxis Study (iPrEx) study in Chiang Mai (9.3%)[85] and in the Early Capture of HIV Infection (ECHO(cohort study in Pattaya (12.9%).[87] In this latter study, the HIV incidence among transgender women testing negative at screening was 9.1 per 100 PY between 2009 and 2010.

Prevention

Thailand's National HIV/AIDS Control Program. During the second half of 1991, the Thai Government started its National HIV/AIDS Control Program, where '100% condom use during commercial sex' was the core component.[3–8,44] A few years after the implementation of the program, indicators of heterosexual HIV transmission started to plateau,[26] indicating that HIV incidence and population replacement rates had reached parity. The subsequent declines in national HIV prevalence indicators in FSWs, pregnant women and military conscripts are generally considered evidence of the effectiveness of the '100% condom use' program.[3–8,44]

The 100% condom use program revisited. The main idea behind this program was that even though prostitution was illegal, such transactions could not be prevented and an inclusive approach would be more effective than a repressive one. By involving multiple government sectors, the program aimed to exert pressure on the provider side to assure and empower FSWs in enforcing condom use with clients, thereby protecting men from acquiring HIV infection and avoiding onward HIV transmission inside and outside the commercial sex setting. Establishments were threatened with closure if evidence was found of noncompliance (e.g. STIs being diagnosed in workers or their clients). The overall population was informed by daily mass media campaign emphasising the importance of condom use during commercial sex and with those frequenting or providing these services, and the physical consequences if this advice was ignored. At the same time, the government flooded FSW establishments with free condoms and educational messages through the public health infrastructure.[3–8,44] The program focussed solely on heterosexual transmission and did not include other risk behaviours. To appreciate the nonmoralistic and nonrepressive approach of the program and to apprehend the rigour with which it was implemented, one needs to be aware of Thailand's successful national fertility control program, from which it emerged, and the political landscape at the time. Those who conceptualised the '100% condom use program' had been closely involved in Thai fertility programming and had a profound understanding of heterosexual behaviour and how to address it. They had successfully desensitised and instilled birth control as a positive value in the Thai public mind during the preceding 20 years, while protecting and promoting the autonomy of women and effectually navigating pronatalist political influence, and moral, ethical and religious convictions interfering with fertility control.[91–95] In the area of reducing the world's population growth at the time, Thailand ranked third, behind China and South Korea, and the changes in Thai fertility were so profound they were labelled 'Thailand's Reproductive Revolution'.[94,95]

In March 1991 and again in June 1992, elder statesman Khun Anand Panyarachun was charged with forming a government after periods of political turbulence. Khun Anand recognised the HIV/AIDS threat and decided to tap the technical expertise developed in the fertility control program to steer Thailand away from a looming public health disaster and the draconian legislative measures being proposed at the time (Draft AIDS Act of 1990).[96] Soon thereafter, Dr Mechai Viravaidya,[97] an outspoken and charismatic population control advocate,[98] was appointed Minister of the Prime Minister's Office in charge of Tourism, Information and AIDS. Dr Mechai, knowing his term was limited, acted swiftly and had the cabinet declare HIV/AIDS a national emergency to be dealt with at the Prime Minister's level. Subsequently, the secretariat of the newly formed National AIDS Commission (chaired by the Prime Minister) and the HIV/AIDS control budget were moved to the Prime Minister's Office, where Dr Mechai and his associates took charge of the nation's HIV/AIDS control. Thus it happened that a fertility control prophylactic, the latex condom, was promoted as Thailand's national response towards the HIV epidemic, even though *in vivo* protective scientific evidence at the time was limited.[99–104] Observational data,[99–104] expert opinion and professional intuition, and the absence of alternatives convinced Dr Mechai the latex condom was the only available remedy. But for it to be effective, it needed to be used 100%. Without further delay, the '100% condom use during commercial sex' program was launched as the national policy in August 1991, supported by the Prime Minister's office as the world's first biomedical HIV prevention program '*avant la lettre*'.

Other national HIV prevention programs. Besides the 100% condom use[46] and PMTCT programs,[11] no national level HIV prevention programs have been carried out in Thailand. In response to the increasing HIV prevalence among MSM, Family Health International implemented a targeted multimedia campaign directed at MSM in Bangkok and Chiang Mai in 2006.[105] During the same period, an adapted version of the peer-opinion leader model[106] was implemented among MSM in Bangkok, with support from the US Global AIDS Program. Next to these two structured and theory-based

interventions, a large of nationally and internationally funded specific programs and interventions for different key affected populations have been implemented and evaluated in Thailand, but none at the national level.

Access to HIV voluntary testing and counselling, STI services, and HIV treatment and care. Access to publicly funded STI services, and HIV voluntary testing and counselling, treatment and care is available to all Thais, including FSWs, IDUs, MSM, MSWs and transgender women as part of Thailand's universal health care coverage scheme.[12] All government-operated hospitals, STI clinics and (drug) dependency treatment centres, and several private sector hospitals (reimbursed by the National Health Security Office) provide such services to the general population and their specific target audiences throughout the country.[12,13,107,108] There are four clinics dedicated to MSM, MSWs and transgender women, two in Bangkok, one in Chiang Mai and one in Pattaya. Three of these were born out of international biomedical HIV prevention research targeting MSM, MSWs and transgender women, and provide HIV voluntary testing and counselling and (some) STI services. These clinics are (a) the Silom Community Clinic, supported by TUC in Bangkok, established 2005;[83] (b) the PIMAN (Prevention in Man) clinic, supported by the Research Institute for Health Sciences (RIHES) in Chiang Mai, established 2008;[85] (c) the ECHO clinic, supported by the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Pattaya, established 2010.[87] The fourth is the Thai Red Cross's Men's Health Clinic in Bangkok (2005),[82] which was established in conjunction to its anonymous HIV clinic. Even though access to publicly funded HIV treatment and care is available for all HIV-infected Thais,[12] knowledge of current HIV status among key populations is still low (<30%) due to various barriers[107] and follow-up or linkage of those HIV infected to treatment and care services is targeted for further improvement.[108]

Recently proven biomedical interventions. In the area of early treatment for prevention, RIHES contributed a site within Thailand for the HIV Prevention Trials Network (HPTN) 052 study, in which early ART in serodiscordant heterosexual couples was shown to decrease HIV transmission by 96%.[109] Alongside free post-trial access to study drugs for trial participants, the MOPH and TRCARC are currently conducting a demonstration project (ClinicalTrials.gov number NCT01869595) regarding the feasibility of early treatment for prevention in MSM and transgender women. This project evaluates the feasibility of regular HIV testing, and the acceptability of immediate ART initiation and subsequent adherence among 800 MSM and transgender women not known to be HIV-infected, regardless of CD4+ cell count, at three different sites. The HIV prevalence among MSM and transgender women at these sites is estimated to be 25%, resulting in ~200 people being estimated eligible for early ART initiation. Next to blood plasma HIV viral load, this project also evaluates seminal and rectal lavage HIV viral load as proxies for HIV infectiousness after the initiation of ART in MSM and transgender women.

In the area of HIV preventive chemoprophylaxis, through its PIMAN clinic, RIHES contributed to the successful evaluation of daily Truvada for the prevention of HIV infection in MSM and transgender women in the iPrEx study.[110] Similarly, the Bangkok Tenofovir Study conducted in IDUs attending Bangkok Metropolitan Administration dependency clinics found daily tenofovir to be efficacious in preventing HIV infection from parenteral exposure.[70] With the exception of post-trial open label access to the study drug for trial participants, no demonstration projects or programs for MSM, transgender women and IDUs are currently being implemented where these biological interventions are being evaluated for external validity and larger scale use in Thailand.

Biomedical HIV prevention research

Thailand's biomedical HIV prevention research infrastructure

The biomedical HIV prevention research landscape in Thailand is populated by five major research organisations: two Thai (TRCARC[111] and RIHES[112]), two Thai–US bilateral collaborations, (AFRIMS[113] and TUC[114]; see Table 1) and a fifth, Programs for HIV Prevention and Treatment,[115] which is a collaboration between Chiang Mai University and the French Institute for Research and Development, involving a large number of Thai and international collaborators and donors. However, given their current focus on clinical HIV epidemiology, pathogenesis and treatment their activities were not included in this review.

TRCARC and RIHES. The TRCARC, earlier known as the Center for AIDS Research and Education (1985) was established in 1989 and is part of the Thai Red Cross, which was founded in 1893 as a relief organisation during the Franco-Siamese war. TRCARC is located in Bangkok and is Thailand's oldest and largest HIV/AIDS nongovernment organisation. TRCARC's core activity is the delivery of high quality diagnostic, treatment and primary HIV care services. The large number of men, women and children attending serve as a pool of potential volunteers in a wide variety of HIV clinical trials. TRCARC also maintains a longstanding involvement in PMTCT, and paediatric and adolescent HIV treatment. In the spirit of the humanitarian Red Cross, TRCARC has been providing a home to organisations of persons living with HIV/AIDS and shelter for the HIV-infected, is engaged in advocacy for the establishment and respect of the rights of people living with HIV, and has been active in a variety of HIV/AIDS-related social and humanitarian causes. TRCARC is engaged in an international (therapeutic) clinical trials collaboration with the Kirby Institute, University of New South Wales, Sydney, Australia, and with the Amsterdam Institute for Global Health and Development, University of Amsterdam, The Netherlands, through its HIV Netherlands Australia Thailand Research Collaboration (1995)[116]. Similarly, it is entertaining a strong partnership in basic science and clinical research with AFRIMS (directly and through its South-East Asia Research Collaboration with Hawaii (SEARCH) research unit (2005)[117]).

The RIHES of Chiang Mai University was first established in 1967 as the Anaemia and Malnutrition Research Center, and HIV became its major focus in 1988 when it was found spreading rapidly in Chiang Mai province. The Bloomberg School of Public Health of Johns Hopkins University has

Table 1. Description of biomedical HIV prevention research organisations in Thailand

ACTG, AIDS Clinical Trials Group; AIGHD, Amsterdam Institute of Global Health Development; AFRIMS, Armed Forces Research Institute of Medical Sciences; amfAR, American Foundation for AIDS Research; BMGF, Bill and Melinda Gates Foundation; CARE, Center for AIDS Research; HIVNAT, HIV Netherlands Australia Thailand Research Collaboration; HPTN, HIV Prevention Trials Network; HVTN, HIV Vaccine Trials Network; IMPAACT, International Maternal and Paediatric Adolescent AIDS Clinical Trials Network; INSIGHT, International Network for Strategic Initiatives in Global HIV Trials; iPrEx , International Pre-exposure Prophylaxis Study; US MHRP, United States Military HIV Research Program; MOPH, Ministry of Public Health; MTN, Microbicide Trials Network; RIHES, Research Institute for Health Sciences; SEARCH, South East Asia Research Collaboration with Hawaii; TRCARC, Thai Red Cross AIDS Research Center; TUC, Thailand MOPH–US Centers for Disease Control and Prevention (CDC) Collaboration; US AMRMC, US Army Medical Research and Material Command; US NIH, United States National Institutes of Health

Name	Location	Year of start	Main collaborators	Primary funding sources	Prevention research areas; past, current and future studies	Accredited facilities
TRCARC	TRCARC–HIVNAT, Bangkok	1989 (CARE, 1985; TRCARC, 1989; HIVNAT, 1995)	Kirby Institute, University of New South Wales, AIGHD, University of Amsterdam, AFRIMS	AFRIMS, amfAR, MOPH, TREAT Asia, US NIH, US MHRP, industry	Heterosexual, homosexual and mother-to-child transmission, human papillomavirus control	Clinical trials unit (US NIH) Clinical research site (INSIGHT, ACTG)
	SEARCH Bangkok	2005	AFRIMS, University of Hawaii	AFRIMS, amfAR, TREAT Asia, US MHRP	Acute HIV infection, neovaginal transmission, RV 254, SEARCH 010, SEARCH 017	–
RIHES	Chiang Mai	1967	Johns Hopkins University, University of California at San Francisco (Gladstone) University of Pittsburgh	US NIH, BMGF	Heterosexual transmission (Phase III), homosexual transmission (Phase III), preventive vaccine (Phases I and II), HVTN 050, HVTN 060, iPrEx, HPTN 052, MTN 017	Clinical trials unit (US NIH) Clinical research site (ACTG, IMPAACT, HVTN, MTN)
AFRIMS	Bangkok	1959	Royal Thai Army,, MOPH, Mahidol University, TRCARC, SEARCH	US AMRMC, US MHRP	Acute HIV infection, preventive vaccine (Phases I, II and III), RV 144, RV 144i, RV 254, RV 305, RV 306, RV 328	–
TUC	Nonthaburi	1980	MOPH, Bangkok Metropolitan Administration	US CDC, US NIH	Heterosexual (Phases I and II), parenteral (Phase III), homosexual (Phase II), mother-to-child transmission (Phase III), preventive vaccine (Phase III), Bangkok Regimen, VAX003, Bangkok Tenofovir Study, HPTN 067, MTN 017	Clinical research site (HPTN, MTN)

been RIHES' main international partner in its HIV/AIDS endeavours ever since, under the Chiang Mai University–Johns Hopkins University Collaboration. In 1992, this collaboration was awarded a Preparation for AIDS Vaccine Evaluation grant, and soon thereafter joined the HIV Network for Prevention Trials. Over the years, the Chiang Mai University–Johns Hopkins University collaboration became a member of the AIDS Clinical Trials Group, the International Maternal and Paediatric Adolescent AIDS Clinical Trials Network (IMPAACT), the HIV Vaccine Trial Network (HVTN), the HPTN and, most recently in 2013, the Microbicide Trials Network (MTN). Currently, RIHES has a fully accredited Clinical Trials Unit with four Clinical Research Site accreditations from IMPAACT, HVTN, HPTN and MTN. By virtue of its geographic location, RIHES is proximate to the majority of the Thai HIV-infected population and is an environment conducive to and in need of continuous HIV prevention research. RIHES took part in early preparatory HIV vaccine cohort studies,[118–120] in clinical evaluation of HIV candidate vaccines[121] and, more recently, in the iPrEx and HPTN 052 efficacy trials[109,110] (Table 2).

AFRIMS and TUC. Both AFRIMS (1959) in Bangkok and TUC (1980) in Nonthaburi have a longstanding presence in Thailand and their operations are codirected by the Royal Thai Army and the Thai MOPH, respectively. AFRIMS's mission is scientific research into the origin, pathogenesis and prevention of (tropical) infectious diseases threatening the health and operations of the American military, such as yellow fever, malaria and HIV. Obviously, successful completion of this mission is also in the interest of the general public. TUC, as a public health-focussed organisation, follows local needs, opportunities and priorities as set out with its MOPH 'hosting' partner. Consequently, TUC has been or is involved in various capacities in biomedical HIV prevention research across most routes of HIV transmission (PMTCT,[9] heterosexual,[122] homosexual[123] and parenteral[70,124]).

The work done and commissioned by AFRIMS focusses on understanding the biology of HIV transmission, particularly virus–host dynamics, and immune-susceptibility versus immunogenicity and ensuing HIV pathogenesis for the purpose of developing and testing a safe and protective HIV vaccine or chemical preventive intervention or cure. Besides the scientific agenda, an essential difference between the native Thai and bilateral organisations is the former having to engage in competitive research grant application processes, be it from the US National Institutes of Health or elsewhere, whereas AFRIMS and TUC follow their internal processes in acquiring and appropriating resources from the overall budget allocated to their mother institutions out of the overall US government financial budget yearly approved by the US Congress. Without going into detail, the structure along which AFRIMS and TUC budgets move before they finally arrive in Thailand is long and complicated, and the use of funds is strictly subject to US government regulations. Since both TUC and AFRIMS are organisations under different departments, coordination between the two is continuous; as soon as activities occur on Thai soil or with Thai human subjects (and their specimens), it also involves the Ministries of Foreign Affairs of both countries and the Thai Ministry of Defence and the MOPH. Within the US Department of Health and Human Services, the US CDC and the US National Institutes of Health operate on separate budget lines. In recent years, signs of a possibly increasing budgetary integration in some areas between the two 'health research pillars' of the Department of Health and Human Services have been observed, with some components of US CDC competing and being awarded US National Institutes of Health funding for clinical HIV prevention research.[123] Disregarding the funding mechanisms, another essential difference between the locals and the bilaterals is that AFRIMS and TUC operate within a command structure (of the US military and the US Public Health Service, respectively) and deploy some of their staff to work and oversee research conducted in Thailand directly on their behalf. All locally employed Thai and other nationals are US government employees or contractors. AFRIMS and TUC maintain strong ties with their US-based mother institutions and their representations in other countries, and locally with public and private entities other than their 'hosting' partners. For example, TUC has been collaborating closely with the Bangkok Metropolitan Administration since 1991 (>20 years) to characterise the epidemiology of HIV infection among Bangkok IDU to inform and assist in the conduct of the VAX003 study[124] (Table 2) and, more recently, in execution of the Bangkok Tenofovir Study, the successful efficacy trial of daily oral tenofovir to prevent parenteral HIV transmission.[70] AFRIMS, in turn, has been working closely with the MOPH and Mahidol University in the Thai AIDS Vaccine Evaluation Group, and with TRCARC and SEARCH for more than 10 years in the preparation and follow-up of the RV 144 vaccine efficacy trial of the prime-boost ALVAC™-HIV vCP1521gp120 AIDSVAX® B/E concept, the first vaccine showing some protective efficacy against HIV infection[125] (Table 2). Interestingly, both AFRIMS and TUC were entertaining research field sites in faith-based private sector health care facilities in Thailand: the River Kwai and Bangkok Christian Hospitals.

Thailand's participation in biomedical HIV prevention research

Thailand participated in seven (23%) out of 30 completed Phase II(b) or III controlled and blinded efficacy trials of biomedical interventions to prevent HIV infection (Table 3).[9,70,124–149] Only South Africa was involved in more trials (11) but had a higher trial nonefficacy rate (7 out of 11 *v.* 2 out of 7). With a record of entirely conducting four Phase III efficacy trials on its own soil, Thailand outnumbered South Africa (three of its own Phase III trials), Uganda (two) and Cameroon (two) (Table 3). Thailand's trial contribution relative to its adult HIV prevalence (7 out of 1.2 = 5.8) ranked third behind the USA (10) and Peru (7.5) (Table 2). Of all 40 countries (out of 150 countries for which this is known) with an adult HIV prevalence of ≥1.2% in 2011,[2] Thailand's relative contribution ranked first. All trials in which Thailand participated (Table 2) were completed and none of its study sites were closed prematurely because of regulatory problems, poor retention or adherence. One site in the COL-1492 study did not transition into the Phase III portion due to low HIV

Table 2. Listing of Phase II and III efficacy biomedical HIV prevention trials conducted in Thailand

AZT, azidothymidine; BTS; Bangkok Tenofovir Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; DOT, directly observed therapy; FTC, emtricitabine; ART, antiretroviral therapy; HPTN, HIV Prevention Trials Network; HR, hazard ratio; IDU injecting drug user; iPrEx, International Pre-exposure Prophylaxis Study; MSM, men who have sex with men; TDF, tenofovir; TGW, transgender women

Study title (period)	Study design (as reported)	Intervention	Population (Thai *n* out of *N*)	% Retention	% Adherence	Effect size or measure (95% CI)	Reference
Mother-to-child transmission							
Short course AZT (Bangkok regimen) (1996–97)	Randomised double-blind placebo-controlled trial	Oral AZT 300 mg twice daily at >36 weeks; once every 3 h in labour	Mothers (397 out of 397), babies (395 out of 395)	99%	>90%	50% (15–71%)	Shaffer *et al.* (1999)[9]
Heterosexual transmission							
COL 1492 (1996–2000)	Randomised placebo-controlled triple-blind Phase II and III trial	52.5 mg precoital nonoxynol-9 gel	High-risk heterosexual women (162 out of 892)	>58% and <88%	79–81% of sex acts	HR = 1.5 (1.0–2.2%)	van Damme *et al.* (2002)[139]
HPTN 052 (2007–10)	Multicontinent randomised controlled trial	Early oral ART (<550 CD4+) in HIV-infected partner	HIV-discordant heterosexual couples (106 out of 1763)	99% (index)	90% (partner)	HR = 0.04 (0.0–0.3%)	Cohen *et al.* (2011)[109]
Homosexual transmission							
IPREX (2007–09)	Two armed randomised placebo controlled multicentre study	Daily oral FTC–TDF (Truvada)	MSM and TGW (114 out of 2499)	84.4%	9–95% (self-report)	44% (15–63%)	Grant *et al.* (2010)[110]
Injecting drug use transmission							
CDC 4370 BTS (2005–11)	Randomised double-blind placebo-controlled Phase III trial	Daily oral tenofovir	IDUs (2413 out of 2413)	88–99% (annual)	83.8% (self-report) 86.9% (DOT)	49% (10–72%)	Choopanya *et al.* (2013)[70]
Preventive vaccine							
VAX003 (1999–03)	Randomised double-blind placebo-controlled efficacy trial	Intramuscular bivalent gp120 AIDSVAX® B/E at Months 0, 6, 12,18, 24 and 36	IDU (2546 out of 2546)	90.1% (2995 36 months f/u)	80.3% (*n* = 2030, all injections)	0.1% (–31% to 24%)	Pitisuttithum *et al.* (2006)[124]
RV 144 Eastern Seaboard HIV vaccine trial (2005–08)	Community-based randomised multicentre double-blind placebo-controlled efficacy trial	Prime ALVAC™-HIV [vCP1521]) at Months 0, 1, 3 and 6; booster gp120 AIDSVAX® B/E at Months 3 and 6	Heterosexual men and women (16 402 out of 16 402)	90.2% (*n* = 14 802)	76.5% (*n* = 12 542)	31.2% (1–52%)	Rerks-Ngarm *et al.* (2009)[125]

Table 3. Listing of completed Phase II(b) and III randomized, placebo-controlled, blinded biomedical HIV prevention efficacy trials, by country

AZT, azidothymidine; TDF, tenofovir; ARV, antiretroviral; ART, antiretroviral therapy; ARNS, Agence Nationale de la Recherche sur le SIDA; CAPRISA, Center for AIDS Programme of Resaearch in South Africa; VOICE, Vaginal and Oral Interventions to Control the Epidemic; MTN, Microbicide Trials Network; HPTN, HIV Prevention Trials Network; CONRAD, Contraception Research and Development; NA, not applicable; BKK, Bangkok; CDC, Centers for Disease Control and Prevention; FHI Family Health International; the shaded 'X' indicates single site studies

Prevention area	Short name	Australia	Benin	Botswana	Brazil	Burkina Faso	Canada	Cameroon	Cote D'Ivoire	Dominican Republic	Ecuador	France	Ghana	Haiti	India	Jamaica	Kenya	Malawi	Netherlands	Nigeria	Peru	South Africa	Tanzania	Thailand	Uganda	USA	Zambia	Zimbabwe	Total of countries	Reference
Efficacious																														
Mother-to-child transmission																														
AZT	PACTG076											X														X			2	126
	BKK regimen																							X					1	9
	DITRAME					X			X																				1	127
	HIVNET-12																								X				1	128
	AFRICAZT								X																				2	129
Heterosexual transmission																														
Male circumcision	ARNS1265																					X							1	130
	Kisumu Trial																X												1	131
	Rakai Study																								X				1	132
Truvada or TDF tablets	PartnersPrep																X								X				2	133
	CDC 4940 TDF-2			X																									1	134
TDF gel	CAPRISA 004																					X							1	135
Early ART	HPTN 052			X	X										X			X				X		X				X	7	109
Homosexual transmission																														
Truvada	iPrEx										X										X	X		X		X			5	110
Injection drug use transmission																														
TDF tablets	CDC 4370 BTS																							X					1	70
Preventive vaccine																														
Prime-boost	RV 144																							X					1	125
Not efficacious																														
Preventive vaccine																														
AIDSVAX B/E AIDSVAX B/B	VAX003																							X					1	128
	VAX004						X												X							X			3	136
Ad5	STEP	X								X				X		X						X				X			6	137
Heterosexual transmission																														
Nonoxynol 9	N-9 film							X																					1	138
	COL-1492		X						X													X		X				4	139
Savvy C31G	Savvy												X																1	140
	Savvy																			X									1	141
Carrageenan	Carreguard																					X							1	142
Cellulose sulfate	CONRAD		X												X							X			X				3	143
	FHI																			X									1	144
PRO 2000	MDP301																					X	X		X		X		4	145
Buffergel & PRO 2000	HPTN 035																	X				X				X	X	X	5	146
ARV gel and tablets	FemPrep																X					X	X						3	147
	MTN 003/VOICE																					X			X			X	3	148
Sexual transmission																														
Aciclovir																					X					X	X		3	149
2011 Adult HIV prevalence %2		0.2	1.2	23.4	0.3	1.1	0.3	4.6	3.0	0.7	0.4	0.4	1.5	1.5	NA	1.8	6.2	10.0	0.2	3.7	0.4	17.3	5.8	1.2	7.2	0.6	12.5	14.9	–		
Ratio studies : prevalence (score)		5.0 (3.5)	0.8 (11.3)	0.1 (15)	3.3 (4.5)	0.9 (10.5)	3.3 (4.5)	2.1 (6)	1.0 (9)	1.4 (8)	2.5 (5.5)	2.5 (5.5)	0.7 (12.5)	0.7 (12.5)	NA	0.9 (10.5)	0.5 (13.5)	0.2	5.0 (3.5)	0.5 (13.5)	7.5 (2)	1.5 (7)	0.8 (11.3)	5.8 (3)	0.8 (11.3)	10 0.0 (1)	0.2 (14.5)	0.2 (14.5)	–		
Number of studies (≥1 site per study)	1		1		1		1		1		1		1		1		2		1		3				6	3	3		68		
Single-site studies				1				1	1				1				1		2			3		4	2				16		

incidence; another site was replaced for similar reasons.[111] However, identical problems occurred elsewhere in COL-1492, in addition to some other 'instances of experiential learning' during this early HIV efficacy trial. The world's second and Thailand's first own successful (50% efficacy) Phase III trial of a biomedical intervention was conducted in 397 mother–child pairs during 1996–97 in Bangkok for PMTCT[9] (Table 2). After the 'azidothymidine (AZT) long course' was shown to be 68% efficacious in 1994 by the Paediatric AIDS Clinical Trials Group (PACTG) 076 study,[96] Thailand's MOPH gave its go-ahead to a placebo-controlled study of a cheaper 'AZT short course', also known as the 'Bangkok Regimen'.[9]

Ongoing and planned biomedical HIV prevention research in Thailand

Open label studies. The currently ongoing biomedical HIV prevention researches in Thailand are the open label extensions of successful trials, HPTN 052,[109] iPrEx[110] and the Bangkok Tenofovir Study.[70] Post-trial access for trial participants to interventions found to be efficacious is one of the fundamental requirements for this type of research. The efficacy of the prime-boost HIV vaccine concept was considered not high enough to warrant open label post-trial access. In the open label extension studies, the safety and efficacy of longer-term exposure to the study products is being evaluated as well, in addition to longer-term behavioural side effects of study participation.

New generation of antiretroviral chemoprophylaxis studies. In addition to the ongoing open label extension studies in Thailand, TUC is currently hosting a site (180 MSM and transgender women) in the HPTN 067,[123] a three-armed randomised Phase II study of the pharmacokinetics and behavioural aspects of intermittent oral Truvada for the prevention of HIV infection among MSM and transgender women and high-risk heterosexual women, with additional sites in Cape Town (180 women) and New York City (180 MSM and transgender women). This study started in 2012, and the Cape Town and Bangkok sites are fully enrolled at this time. Daily intake of antiretroviral drugs for an extended period may be associated with negative bone-density and other side effects in some people, whereas short- and long-term daily adherence has been shown problematic for certain individuals, and high-risk behaviour is usually not permanent.[150,151] Moreover, daily intake of these agents does not seem to be necessary to generate significant levels of protection[70,110,152] and daily antiretroviral for prevention may be too costly in many situations. To address some of these questions, HPTN 067 will evaluate and compare intermittent time-dependent, sexual event-driven and daily dosing of Truvada to assess the feasibility, pharmacokinetics and coverage of sex events by other than daily chemoprophylaxis regimens.[123]

TUC and RIHES are currently preparing their sites for participation in MTN 017, a Phase II randomised crossover trial of the safety and acceptability of daily oral Truvada, and daily or sexual event-driven 1% tenofovir reduced glycerin rectal gel. The total number of participants in MTN 017 is 168, 40–60 of which are expected to be from Thailand. The study includes eight international sites and is slated to start mid-2014.[153]

Novel biomedical HIV prevention research. Recently some novel biomedical HIV prevention research has come to the forefront from TRCARC through its collaboration with AFRIMS in SEARCH. As part of the RV254 SEARCH 010 study of acute HIV infection, ~70 000 specimens testing HIV-negative on regular assays were screened by fourth-generation enzyme immunoassay and by nucleic acid testing. This identified 90 MSM in acute HIV infection who were enrolled in a follow-up study, 88 of whom started immediate ART within an average of 2 days after detection.[154,155] Upon learning about their acute HIV infection, HIV transmission risk behaviour (unprotected anal intercourse with casual and steady partners) in these men fell considerably and was sustained at 1 year after diagnosis. In addition, HIV viral load in peripheral blood, seminal fluid and anal lavage samples fell from the excessively high levels typical for acute HIV infection to undetectable within 4–8 weeks.[155] Phylogenetic studies have shown that undetected and untreated acute HIV infection may be responsible for up to 50% of new infections[156,157] in rising and ongoing MSM HIV epidemics, and this onward fraction of HIV incidence increases further if one or both partners have transmission cofactors, such as STIs, or rectal or genital trauma resulting from intensive or prolonged sexual intercourse with multiple consecutive sexual partners, particularly when using stimulant or erectile dysfunction agents or a combination of both.[158–164] Early ART during acute HIV infection among the same group of MSM has also been shown to considerably improve HIV disease outlook and prognosis, with characteristics similar to the 'Elite HIV Controllers', having a small or undetectable reservoir of integrated HIV RNA.[154] These early-treated men are ideal candidates for further functional cure studies or therapeutic vaccines in combination with chemical agents to help deplete or exhaust the HIV reservoir.[165,166] The combined individual and preventive benefit of ART during acute HIV infection[155] may make this intervention appealing and for inducing high-risk individuals to undergo HIV testing frequently to avoid the long-term progressive immune decay normally seen in HIV infection.

A second area of novel biomedical HIV prevention research by SEARCH pertains to a group that falls between the cracks in the internal and external validity of antiretroviral chemoprophylaxis Phase II and III efficacy trials conducted so far: postoperative transgender women.[167] The American Foundation for AIDS Research and TREAT Asia are supporting TRCARC and SEARCH to change this with the SEARCH 017. Researchers are currently enrolling postoperative transgender women to explore the biodynamics and immune genesis in the surgically created vagina, and to lay the ground work for future studies regarding the safety and pharmacokinetics of oral, topical and other formulations of preventive antiretroviral chemoprophylactic drugs in this population. This study is novel in many aspects, since the neovagina has not been characterised in the context of HIV transmission and little is known about its prevalence, sexual and behavioural aspects, or whether the immune functions of skin and mucosal tissue transported from other body locations retain

their original function or modify themselves in adapting to new aerobic and anaerobic circumstances.

Although the HPTN 067, MTN 017, SEARCH 010 and SEARCH 017 studies address important aspects of antiretroviral chemoprophylaxis, more effective therapeutic and preventive use of antiretrovirals and addressing the needs of the most overlooked and disadvantaged in the HIV epidemic, the future of biomedical HIV prevention research in Thailand seems to be a preventive HIV vaccine. Several studies initiated by the US Military HIV Research Program and AFRIMS in Thailand and in Sub-Saharan Africa to follow-up RV 144 will provide crucial answers to modify the prime-boost concept and hopefully increase its protective efficacy. Protection from the prime-boost concept peaked early and dissipated quickly, with a significantly higher efficacy in lower-risk individuals after completion of the prime-boost vaccine series.[125,168] Higher and longer sustained and challenge-resilient levels of neutralising antibodies need to be produced to increase the efficacy of the prime-boost vaccine concept. This may be possible by altering the active components of the prime in combination with additional boosting by AIDSVAX® B/E alone or with another component. Studies to (more clearly) identify (additional) correlates of protection are currently ongoing in stored specimens obtained during RV 144 (protocol RV 144i) and in volunteers with acute HIV infection recruited in Bangkok, in collaboration with SEARCH and TRCARC (RV 254), and in Pattaya in the dedicated ECHO clinic supported by AFRIMS for this purpose (RV 217). In addition, studies are being done with RIHES and SEARCH in HIV-negative RV 144 and other volunteers by additional boosting and extended follow-up (RV 305) of the expanded immunogenicity of the RV 144 concept (RV 306) and of AIDSVAX® B/E-only immune responses (RV 328). With the results of these studies in hand, the US military expects to be able to move forward to a Phase IIb double-blinded placebo-controlled vaccine efficacy trial (RV 349) by the start of 2016 among 3500 high-risk MSM and transgender women in Thailand. This study is tentatively powered by an HIV incidence of 3% per year, a loss to follow-up of 10% per year, and recruitment from Bangkok, Pattaya and Chiang Mai. Volunteers will be randomised at a ratio of 2 : 1 vaccine versus placebo, and followed for 24 months for the primary endpoint of HIV infection and for an additional 12 months to assess the longer-term effects of vaccination.[168–171]

Discussion

The evolving epidemic of HIV infection in Thailand continues to be one of the most researched and best documented worldwide. Even though the epidemiological picture is not always complete and prevention coverage is not 100%, the Kingdom must be complemented for its supportive and open sociopolitical climate in allowing research to be conducted and data to be collected. Without this information, there would be no way forward.

Although Thailand's national HIV/AIDS control program remains exemplary in terms of raising the significance of HIV/AIDS to the highest political level, the currently available information suggests that its effect may not have been as profound and long-lived as previously thought. The Thai national program was created during unusual political circumstances in which an extraconstitutional cabinet was assembled from the country's best technical experts, including those in public health. Unfortunately, for a national program to be sustainable in the long term, the creation of a wider administrative and more rigid scientific support base would have been necessary to assure its survival beyond the political livelihood of its proponents. For example, after the National AIDS Commission resolved in 1993 to return the responsibility for HIV/AIDS prevention and control and its budget to the MOPH, the ensuing process of transferring and accommodating tasks and duties between government agencies negatively impacted the continuity and expansion of the national program. In this climate, it was not surprising that its main component, 'the 100% condom use' program, gradually lost much of its initial allure. Unsurprisingly, during the years following the transfer, newly identified, emerging, ongoing and rebounding epidemics of HIV infection were observed among FSWs, MSWs, MSM and transgender women in Bangkok and elsewhere,[26,78–90,175,176] while the HIV epidemic among IDUs throughout the country continued unabatedly and remained unaddressed.[26,49–70,124]

In addition, *a priori* scientific and regulatory frameworks documenting pilot and approval trajectories, and definitions of target audiences, expected coverage, milestones, impact and effects of the '100% condom program' would have been helpful for program monitoring and evaluation.[96] Regrettably, this lack of documentation hampered *a posteriori* assessment of the program's impact and effects, which, as a result, were mostly *post hoc*, and described correlations and ecological associations between variables selected on the basis of their ability to serve as 'proof' or evidence of the program's success. In this respect, additional lessons could have been learnt from Thailand's national fertility control program, for the evaluation of which the government created two independent academic population research institutes at its most prestigious universities while opening the doors widely for international scientific collaboration to study the results of the program.[91–95] To remain fair, this would have slowed down program implementation and was justifiably not defined as a priority at the time.

Finally, the noninclusive focus of the program solely on the prevention of heterosexual HIV transmission, despite epidemiologic evidence for substantial IDU and homosexual transmission raises some valid human rights concerns, since access to HIV prevention information and good health in society is not the purview of the heterosexual population alone but belongs equally to all. The absence of IDUs from the program is probably one of the main reasons why the discussion about modification or softening of Thailand's punitive laws on drug use and possession of drug paraphernalia has made little or no progress in the past 25 years. On the positive side, the MOPH recently issued, for the first time in its history, national guidelines for implementing HIV prevention in MSM and transgender women,[177] almost 30 years after the first AIDS case was diagnosed in a Thai MSM citizen.[21] However, this event was already foreshadowed by the initiation of the government-sponsored early ART for

prevention demonstration project among MSM and transgender women in Bangkok and two other provinces in 2012. With the start of this project, the MOPH also implicitly communicated its preference for early ART for prevention in MSM and transgender women over PrEP, even though the supporting evidence was obtained in heterosexuals[109] and the country participated in the successful iPrEx efficacy trial to prevent homosexual transmission.[110]

The second part of this review confirms Thailand's exceptional and disproportionate contribution to biomedical HIV prevention research on a global level. In the early stages of the HIV/AIDS epidemic, Thailand conducted its own trials of cheaper antiretroviral regimens for PMTCT in 1996–97,[4] and from 1999 to 2003, it successfully completed VAX003, the first standalone HIV vaccine efficacy trial conducted ever in a developing country, among IDU in the Bangkok Metropolitan Administration drug treatment system. The trial itself did not show efficacy, but the gp120 concept was later used in the successful RV 144 prime-boost vaccine efficacy trial.[123] In addition, the follow-up rate in the VAX003 IDUs was >90%,[124] much higher than expected, since it was widely believed that such high follow-up rates in IDUs were not possible. Generally speaking, retention and adherence among Thai participants in all Phase III trials has been excellent.

The work of the American military and their perseverance in finding the beginning of a trail towards the efficacy of a vaccine concept, the testing of which had been seriously questioned by several of their scientific peers,[171–174] deserves admiration. The rigor, determination and focus with which the US Military HIV Research Program pursues its goals has all signs of major success in waiting, even though it may have to wait until 2020 or further away before the final result will become visible.

Thailand contributed to more Phase II and III biomedical HIV prevention efficacy trials than did any other country, with the exception of South Africa, but this country had a higher trial nonefficacy rate. Thailand also hosted more single-site efficacy studies on its own soil than did any other country, although the differences were small. Finally, of all 40 countries with an adult HIV prevalence of $\geq$1.2%, Thailand participated in more Phase II and III efficacy trials than did any other nation, both in absolute numbers and relative to its adult HIV prevalence. Among the 30 countries contributing to Phase II and III biomedical HIV prevention research, Thailand ranked third, after the USA and Peru; with respect to the number of trials relative to its adult HIV prevalence in 2011, it ranked first. As the country contributing the most resources and knowledge towards biomedical HIV prevention research than any other nation, the position of the US is beyond dispute. The second-ranked position of Peru – and the third-ranked position of Thailand for that matter – is probably due to its active HIV/AIDS research community, led by several internationally educated, well respected and connected local sociomedical scientists who actively collaborate with foreign academic institutions, often their alma maters. Both countries hold good relationships with the US and welcome international scientific collaboration in a social and political environment supportive of research. In line with Thailand's leadership in epidemic control and providing access to ART and care, its contribution to global biomedical HIV prevention research is truly exceptional, both in volume and quality, and in absolute and relative numbers; thereby, the country has made a huge contribution to the global management and control of the HIV/AIDS pandemic.

Disclaimer

The findings, views and conclusions reported in this paper are those of the authors and do not represent those of the Research Institute of Health Sciences and the Thai Red Cross AIDS Research Center.

Conflicts of interest

None declared.

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