HIV-associated cognitive disorders: Scientific discoveries through international collaborations in Thailand
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Chapter 1
General Introduction
HIV/AIDS AND COGNITIVE OUTCOMES IN THAILAND

The first diagnosed case of HIV in Thailand occurred in February of 1985; by 2000, one million Thais had become infected with the virus. The epidemic started slowly; but explosive growth began in the early 1990s despite aggressive government preventative efforts. By the mid 1990s, 3.6% of drafted Thai military recruits tested positive for HIV, a percentage representative of young males in Thailand. Arguably, the most bleak period of the Thai epidemic occurred in the late 1990s, when mortality was high and treatments were not available. It was estimated that the population growth rate would slow from 1.3% to 0.9% by 2005 due to HIV.

The Thai government has been widely credited for novel and assertive public health strategies aimed at curbing the epidemic. Intravenous drug use and sex with prostitutes in brothels were identified as primary early sources of spread within Thailand, and each was addressed by aggressive government campaigns. Beginning in Ratchaburi province in 1989, the “100% condom campaign” mandated safe sex practices in brothels. This mandate was supported by education and HIV testing for sex workers, but also enforced with threats to close down establishments that were not compliant. The government monitored these efforts by questioning sex workers and their clients who developed sexually transmitted diseases (STDs) and through routine HIV testing. Once demonstrating success, the program was expanded and by 1992, it was implemented in all Thai provinces.

Among military recruits in northern Thailand, self-reported condom use at last sexual encounter rose from 61% to 93% between 1990 and 1995 while sexually transmitted diseases decreased from 42% to 15%. Among military conscripts, the HIV prevalence declined, most notably in northern provinces, where it dropped from over 12% in 1992 to just less than 8% in 1994. The most recently available data (May 2012) noted a prevalence of 0.6% (n = 40,842, personal communication Colonel Nitayapan Sorachai, Armed Forces Research Institute of Medical Sciences (AFRIMS) – Royal Thai Army). Public information campaigns were also credited with impacting transmission rates. Operating out of the Office of the Prime Minister, Mechai Viravaidya directed these campaigns that included a focus of removing the taboo of condom contraception.

The HIV virus circulating in Thailand has a few distinctive features from that engulfing the international pandemic. The predominant subtype is circulating recombinant form (CRF) 01_AE (“subtype E”), a virus originating from central Africa. Clade B has been identified in lesser frequency and clade E/B recombinants have emerged. Compared to clade B virus, clade E has been associated with more rapid disease progression. This study completed in Thai military conscripts, where the date of seroconversion is known, demonstrated that it took a median of 6.5 years to achieve a CD4 T-lymphocyte drop to <200 cells in the absence of treatment. The median time to death was 7.8 years. Both were considerably faster than that reported in other settings. For example, the median time to developing clinical AIDS was 7.2 years compared to 11 years described in the CASCADE cohort, a meta-analysis of studies from high-income countries (presumably predominantly clade B). Others have refuted these data as confounded by environmental and other biases.

In vitro studies identify distinctive features with subtype E transactivator of transcription (Tat) protein inhibiting tissue necrosis factor (TNF) gene and protein production compared to no inhibition seen in subtypes B and C. This may have implications for neurological outcomes given knowledge of TNF expression in brains of HIV dementia patients; but, clinically, differences in neurological outcomes compared to other subtypes have not been demonstrated. Most studies that have attempted to identify cognitive impairment in Thailand find few differences in frequency when compared to other international settings.

In resource-rich settings, the outlook for an individual with HIV infection changed remarkably in the 1990s. While progressive immunodeficiency
with opportunistic infections, AIDS-related malignancies and death had been the hallmark features of HIV/AIDS, by the mid-1990s combinations of antiretroviral medications emerged that could produce durable reductions in morbidity and mortality. Initially termed highly active antiretroviral therapy (HAART), these combinations led to increased CD4 T-lymphocyte counts and suppressed viral replication resulting in blood levels of HIV RNA that were not detectable by laboratory assays. The enthusiasm was somewhat dampened when it was quickly learned that chronic treatment would be needed since viral detection quickly returned when halting these medications. Cure remained elusive. Over the following decade, medication improvements led to greater tolerability and reduced pill burden, facilitating adherence with sustained immunologic and virologic responses. By 2005, a 20 year-old HIV+ non-injection drug user from a high-income country could expect to live to age 65 years.

But, the picture remained dismal for most resource-limited settings where the vast majority of HIV infections exist, but resources in which to implement broad treatment access were limited. Early in the 2000s, international and local government efforts were launched in earnest to make antiretroviral medications accessible to all. As a middle-income country, Thailand benefited to a lesser extent from international aid, but instituted a national campaign to provide universal access. This work began in 1996 with Dr. Praphan at the Thai Red Cross AIDS Research Center through a donation program developed to provide zidovudine therapy to pregnant women (personal communication, Jintanat Ananworanich). In 1997, the Bangkok Collaborative Perinatal HIV Transmission Study Group demonstrated that a short-course of zidovudine combined with no breast-feeding could reduce vertical transmission rates by one-half. By the late 1990s, it was implemented throughout Thailand.

In 2001, at considerable financial cost, the Thai government re-invigorated its commitment to HIV/AIDS treatment by pledging nationwide access to therapies for all who required it. The National Access to Antiretroviral Program for People living with HIV/AIDS (NAPHA) was a major public health undertaking with components aimed at developing national treatment guidelines, health care education, laboratory development and identifying a long-term monitoring plan. By 2004, over 50,000 patients were receiving anti-retroviral therapy; yet, with over 500,000 estimated to be living with HIV/AIDS, much more work was needed (Figure 1). The Thai government’s rapid scale-up became feasible with the development of generic versions of antiretroviral medications by the Thai Government Pharmaceutical Organization, including fixed combinations such as GPOvir (stavudine, lamivudine, and nevirapine). In all, this work required tremendous national effort and the dedication of many medical pioneers, including people I have had the privilege to work with. Over time, universal access became available and the Thai epidemic has transformed, in many ways, to mirror that seen in settings with more resources.
this thesis. A review of the role of monocytes is discussed in greater detail in Chapters 5-7.

The proportion of neuroAIDS studies that present data captured from populations outside of the US and Europe is proportionally meager when compared to the distribution of the pandemic. From a clinical standpoint, evaluating cognitive disorders in resource-limited settings is fraught with methodological challenges. Some complexities include the use of neuropsychological tests designed for use in English-speaking settings from the US or Europe, the lack of normative data for interpretation and poor or no access to brain imaging. Culture, education, nutrition, and a multitude of other environmental factors confound cross-site comparisons, making it difficult to understand the mechanistic basis for any differences that may emerge across settings. Thailand has state-of-the-art imaging capabilities that facilitate neurological research. Normative data for neuropsychological testing was developed within our collaboration, as presented in Chapter 9. Working with our international collaborators, we were able to develop advanced research imaging capabilities and the neuropsychological testing infrastructure required to pursue new research ideas.

For our cognitive work, we utilized a neuropsychological testing battery which was designed for HIV with the intent of minimizing cultural influences. Bangkok, Thailand was one of five sites used to develop this international battery in collaboration with the World Health Organization (WHO) and the US National Institutes of Mental Health (NIMH), first published in 1991.28 Requiring about one hour to administer, the tests evaluate visual and verbal memory, psychomotor speed, higher cognitive abilities and motor speed. The first study utilizing this battery, in 1994, identified the presence of cognitive impairment within the five sites (including Bangkok) and noted poorer neuropsychological testing performance in symptomatic HIV-infected Thais.29 In contrast, asymptomatic HIV-infected patients had only limited differences in comparison to controls. These findings were similar to those emerging in the US where most impairment was noted in medically symptomatic subjects, particularly if they met criteria for AIDS.29,30 Our early work similarly identified profound differences in neuropsychological performance among symptomatic HIV-infected Thais who were naïve to HAART (Chapter 3) and work from our colleagues note that over one-third of Thai HIV patients will continue to have mildly impaired performance on these tests five years after continuous HAART with viral suppression.15,17 This concurs with findings from a survey of cognition among HIV patients throughout Southeast Asia.31

The work presented in this thesis represents fruitful collaborations with individuals and organizations in Thailand that began in 2003. Our studies first evaluated cognition in advanced HIV disease before and after treatment. The work became possible because of the setting of rapid antiretroviral medication access scale-up in Thailand among individuals with advanced disease and with the availability of both highly technical immunological capabilities provided by the US Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok and the exceptional expertise of our lead neurologist collaborators. Together, we gained a stronger appreciation for the impact of HIV on the brain in advanced disease and in the absence of treatment. We chronicled the profound improvements that occur when antiretroviral therapies are introduced; although many subjects continued to have mild impairment despite treatment (Chapter 3). Throughout this work, we maintained a commitment to improving clinical care in Thailand by obtaining normative neuro-psychological data for HIV cognitive disorders (Chapter 9) and the developing of a screening tool for HIV-associated cognitive impairment in Thailand (Chapter 10). As our program matured, we were able to tackle more complex studies, including characterizing brain involvement during the first few weeks after infection (Chapter 4) and the identifying intramonocyte HIV DNA as a predictor and mechanistic link to cognitive impairment in HIV (Chapter 6) with subsequent validation of this biomarker as a predictor of HIV-associated neurocognitive disorders (Chapter 7). At the same time, Thai colleagues began to complete independent research in this field, resulting in several
Our work now includes multimodal imaging and we have started to investigate the impact of HIV on neurodevelopment in children throughout Thailand and Cambodia.

UNAIDS estimates 530,000 Thais are currently living with HIV/AIDS and about one-half are on antiretroviral therapy. This estimate is slightly lower than that reported by Thai Ministry of Public Health (610,000), which concludes a national prevalence rate of 1.4%. The remarkable success of curbing the epidemic understates the challenges that lie ahead. Chronic antiretroviral treatment and other health care costs associated with life-long infection will stretch the resources needed for broad comprehensive care. AIDS stigma continues to be problematic and the aging-up of 10,000-15,000 HIV+ youth will pose unique and unknown difficulties.

I am indebted to collaborators at the Thai Red Cross AIDS Research Centre, Phramongkutklao Hospital and King Chulalongkorn Memorial Hospital who made this work possible. Among the countless friends and colleagues I have made in this process, I am particularly grateful for the assistance of Dr. Pasiri Sithinamsuwan, Associate Professor Jintanat Ananworanich, Colonel Jerome Kim, and Professor Praphan Phanuphak, without whom this work would not have been possible. I thank the Thai people for their hospitality and our study subjects for their dedication. Together, this has allowed us to gain a greater understanding of the epidemic in resource-constrained settings, which will ultimately support our long-term goal of decreasing the morbidity of HIV/AIDS in Thailand.

LITERATURE CITED

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