Special Article

HIV Vaccine Trials in Thailand and Path to HIV Cure

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Thailand has had over 30 years of experiences and development in fighting HIV/AIDS with successful results in terms of providing access to prevention, testing, antiretroviral treatment (ART) and care for over 90% of the affected patients. As a consequence, approximately 400,000 patients on ART currently have undetectable viral load, lead normal lives, and are untransmittable. However, ART must remain in place forever or else the viral load in blood will rebound. Recent advance in stem cell transplant, gene editing, and therapeutic HIV vaccine development yields hope on designing novel approach for an HIV elimination or functional cure. The National AIDS Prevention and Alleviation Committee of Thailand has set up the Subcommittee on HIV Vaccine Trials to oversee and endorse experimental vaccine regimen with sound and adequate scientific background to be tested in Thailand. So far, at least 23 small and large studies have been conducted in collaboration with the international organizations and at least 10 articles were published after the studies ended and cited over 2,726 times. One landmarked trial using notable vaccine regimen, evaluated in the RV144 trial, has shown effectiveness in reducing new infections by 31.2%. The conduction of these research in Thailand have facilitated the development of infrastructure, networking, and experience sufficiently to further support future field trial with a notable HIV cure approach. Since there are over 400,000 HIV cases with undetectable viral load in Thailand, this condition poses an excellent opportunity for testing a novel HIV cure approaches to eliminate HIV or functional HIV cure. The Subcommittee has reviewed current novel methods in this regard and strongly welcomed international organizations with similar aim, to test an innovative therapeutic HIV vaccine or a combination therapy to finally end HIV/AIDS in Thailand by the year 2030.

Keywords: HIV vaccine; HIV cure; Latent HIV reservoir; mRNA vaccine; Gene therapy; Stem cell transplantation

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Thailand has served as the co-host country of many high-quality HIV/AIDS research collaborated with several international organizations for more than 30 years. Several Infectious Disease Clinical Trials Units have been set up in Thailand at Mahidol University, Thai Red Cross AIDS Research Center in Chulalongkorn University, Chiang Mai University, Royal Thai Army (RTA) with Armed Forces Research Institute of Medical Sciences (AFRIMS), and Ministry of Public Health to conduct research and have published a large number of high-impact original articles that received widespread attention in policy documents and the media. The success of conducting HIV research in Thailand reflects the strong research infra-structure units that include the health villager volunteers and peers under supervisions of these trial units that facilitate the present study research with no significant obstacles. A SCOPUS search using keyword "HIV AIDS original article published by Thai researchers" on August 26, 2022, showed the overall results of 50,384 articles including 7,806 webpages, 39,005 books, and 2,854 journals (Figure 1), thus, demonstrating that Thailand has actively participated in HIV/AIDS research and published numerous respectable articles searchable in international database. In short, Thailand has

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Figure 1. Result of SCOPUS Search using keywords "HIV/AIDS original articles published by Thai researchers" on August 26, 2022.

Figure 2. A consultative meeting both online (in small pictures above and below) and onsite at the Department of Disease Control, Ministry of Public Health, Thailand between the researchers from an international institute and the Subcommittee members to discuss the upcoming HIV vaccine projects anticipated to be conducted in Thailand.

had a remarkable success in its response to the HIV epidemic, and this achievement is recognized around the world.

As a consequence, HIV/AIDS management by healthcare sector in Thailand has been globally accepted as high standard. The national data in the year 2020 showed Thai people living with HIV (PLHIV) were estimated to be 500,000 cases with 94% of PLHIV knew their status, 84% of PLHIV who knew their status received antiretroviral treatment (ART), and 97% of PLHIV that received ART were subsequently virally suppressed. In addition, 98% of pregnant women living with HIV received ARTs to prevent mother-to-child transmission of HIV, and 97.7% of the infants born to HIV-infected mothers received a virological test for HIV within two months of birth. Accordingly, HIV infection rate in newborn babies has gradually declined to less than 50 children per year at present, and hence, saving up to 3,500 children from being infected with HIV from their mothers annually. At the governmental level, after Thailand's national strategy for prevention and response to AIDS between 2014 and 2016 succeeded, the National AIDS Management Center has coordinated with the various partners in the public and private sectors, civil society, and relevant international organizations to produce the latest national strategy for ending AIDS between 2017 and 2030 with the following three targets, reduction of new HIV infections to less than 1,000 cases per year, reduction of AIDS mortality to less than 4,000 cases per year, and reduction of negative discrimination related to HIV and sexual orientation by 90%. This national strategy was approved by the Thai government on January 17, 2017, and the relevant agencies were assigned to use the strategy as a framework for implementation of the prevention and response to HIV going forward. This national strategy is a long-term strategy that sets the goal to successfully eliminate HIV problems in Thailand by 2030.

Though the transmission of HIV can be interrupted by physical preventive means, the final step of HIV eradication was initially anticipated to be achieved with a reliable effective HIV vaccine as demonstrable in the smallpox eradication. The first HIV vaccine trial in Thailand dated back to 1991 when an AIDS vaccine using GP-160 protein began making the headlines that Thailand was one of the six or seven countries selected by the World Health Organization as a testing ground for an AIDS vaccine. Six months later, at a conference on AIDS, the United States proposed that Uganda, Rwanda, Brazil, and Thailand served as test sites for a first AIDS vaccine. In doing this, Thailand maintained three principles, first, the vaccine to be tested must first be approved by the Food and Drug Administration in the country where it was produced. Second, the vaccine must have been tested on people in the country where it was produced. Third, the vaccine must be produced in laboratories based on those standards. Hence the National Committee on AIDS Control and Prevention has had the policy to enable Thailand to conduct research with sound scientific background to control HIV infection. The trial needed cooperation with experts and relevant organizations both domestically and internationally to help develop the HIV vaccines that were most suitable to the subtypes of HIV endemic in Thailand (Figure 2). Hopefully, the desired vaccines would be tested in Thailand with adequate domestic infrastructure to oversight and coordinate the necessary research undertaken at all levels by the local relevant agencies, by both public and private sectors. Subsequently, a Subcommittee on HIV Vaccine Trials was appointed

to guide and supervise the HIV vaccine testing projects. Thailand had also declared its position as one of the global pioneers to clinically test any HIV vaccines from phase-1 onward providing that they had adequate scientific backgrounds and preclinical results. So far, numerous HIV vaccine studies have been successfully conducted in Thailand as shown in Table 1 and at least ten related articles were published[1-10] after the studies had been complete. After searching for the number of citations of these ten articles that were reported to the Subcommittee from the above trials, total citation was 2,726 (30 + 38 + 23 + 21 + 2,395 + 27 + 27 + 34 + 87 + 44 citations), which reflected the high quality and good impact on HIV vaccine research in Thailand and publications.

One of the notable studies that demonstrated Thailand determination of finding a safe and effective vaccine against the HIV-1 was the publication of an article in NEJM entitled "Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand"[5]. The finding demonstrated that the "ALVAC-HIV and AIDSVAX B/E" vaccine regimen could reduce the risk of HIV infection in a community-based population with heterosexual risk. Although the results showed only a modest benefit, they offered significant insight for future research, which is critical to end the pandemic. More importantly, this phase-3 trial was performed in the eastern provinces of Rayong and Chon Buri of Thailand for at least six years. However, the interim analysis of the study result by an independent blinded statistical group at the third year of the study suggested that even if the trial would have been conducted for another two years, the end result would not provide any benefit difference between the control and the intervention groups. Therefore, it was suggested by this independent monitoring group to terminate the study to save all the resource needed to continue the trial for another two years. However, at the consultation meeting with the Thai members of the Subcommittee on HIV Vaccine Trials, the subcommittee disagreed with the advice to end the trial and encouraged the trial groups to continue since the beneficial result might be seen after two or three years of the priming and boosted vaccination strategy. Finally, the trial was continued and ended up with the first-ever-shown benefit of the prime-boosted vaccination program of the two types of vaccines and created new hypotheses. The authors would like to stress that if this trial would have been prematurely terminated as recommended, the researchers would not have been able to entertain successful final results and conclusion.

HIV cure: is it on the near horizon?

Thailand and UNAID have the same goal of ending global HIV epidemics by the year 2030. Currently, the combination antiretroviral therapy (cART) has reduced morbidity and mortality from HIV to nearly zero and significantly extended life expectancy of HIV-infected patients. However, the HIV cure is still not achieved because the virus is only suppressed and needs life-long usage of cART with potential adverse side effect. The ART resistance poses another potential problem in those who need lifelong treatment. The authors need a novel method that eliminate HIV persistent infection or viral latency, despite effective cART and host antiviral immune responses. If the viral latency in the host cannot be eliminated, another method namely, the "functional cures" of HIV infection that aims to terminate HIV replication in the absence of cART may be the present study target instead of "sterilizing cures" that aims for complete eradication of all viral reservoir.

So far, recent advance in molecular biology has provided us with novel ways and means to successfully tackle this problem or HIV cure, as shown in three representative cases with bone marrow or umbilical cord cell transplants. Though cord blood is more widely available than the adult stem cells used in the bone marrow transplants that cured the first two patients, it does not need to be matched as closely to the recipient. A key factor from the donor in the third case, is that the "delta32" mutation on the CCR5 receptor and homozygous CCR5 mutation in recipient are resistant to HIV cell entry, which enables the host not to progress to AIDS. However, this stem cell transplant method is limited to patients with underlying lymphoma or leukemia so that the benefit of the transplantation overcomes the risk of subsequent superimposed infection and failure of the transplantation if it occurred. The authors still need a less invasive and simpler method with high success rate. Since Thailand has had vast experience in successfully conducting several field trials containing 10 to more than 10,000 volunteers and with the infrastructure for conducting clinical trial remains in place, this kind of experience position Thailand as an interesting site to conduct such trial if an innovative vaccine or strategy to eliminate the HIV latent infection is seen on the horizon. Currently, there are more than 400,000 HIV-infected patients who can maintain the complete virologic suppression with cART and are a valuable pool of material to jointly initiate any novel elimination method (Figure 3, 4). Since the initial HIV elimination step lies

Table 1. Summary of some HIV vaccine research titles with corresponding principal investigators conducted in Thailand

No.	Phase	Project Title	Principal Investigator & number of cases (n)	TSHAVD approved/ finish dates
1	I	Phase I, Safety and Immunogenicity Trial of HIV-1 MN Synthetic Peptide Prototype Vaccine. (UBI)	Praphan Phanuphak, et al. Chulalongkorn University and the Thai Red Cross Society. (n=30)	17 Jan 1994/ 23 Jan 1995
2	I/II	Phase I/II, Evaluation of Safety and Immunogenicity of MN rgp 120/ HIV-1 Alum Adjuvant Candidate Vaccine (Genentech) in Recovering Intravenous Drug Users in Bangkok.	Sricharoen Migasena. Vaccine Trial Center, Faculty of Tropical Medicine, Mahidol University. (n=33)	6 Jan 1995/ 25 Jun 1996
3	I	Phase I, Trial of HIV SF2 gp120/MF59 Vaccine (Biocine) in Seronegative Volunteers.	Sorachai Nitayaphan, et al. RTA-AFRIMS. (n=54)	13 Jul 1995/ 29 Nov 1996
4	I	Phase I, Double-Blind, Adjuvant Controlled Study of the HIV-1 Immunogen (Immune Response) on Safety and Immunogenicity in HIV-1 Infected Subjects. (2101A)	Vina Churdboonchart, et al. Faculty of Science, Mahidol University. (n=30)	27 Mar 1996/ 24 Jul 1996
5	II	Phase II, Double-Blind, Adjuvant Controlled Study of the HIV-1 Immunogen (Immune Response) on Safety and Immunogenicity in HIV-1 Infected Subjects. (2101B)	Vina Churdboonchart, et al. Faculty of Science, Mahidol University. (n=297)	25 Jun 1997/ 18 Aug 1999
6	I/II	Phase I/II, Double-blind, Placebo-controlled Study of the Chiron Biocine HIV Thai E gp 120/MF59 Vaccine Administered Alone or Combined with the Chiron Biocine HIV SF2 gp120 Antigen in Healthy HIV-Seronegative Thai Adults. (V26V6P1)	Sorachai Nitayaphan, et al. RTA-AFRIMS. (n=380)	29 Aug 1997/ 8 Jan 1999
7	I/II	Phase I/II, Evaluate the Safety and Immunogenicity of AIDSVAXTM B/E Vaccine (VaxGen) in Bangkok. (V001)	Punnee Pitisuttithum, et al. Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University. (n=92)	25 Dec 1997/ 5 Aug 1999
8	III	Phase III, Determine the Efficacy of AIDSVAXTM B/E Vaccine (VaxGen) in Intravenous Drug Users in Bangkok. (V003)	Kachit Choopanya, et al. Bangkok Tenofovir Study Group, Bangkok, Thailand. (n=2,500)	8 Dec 1998/ 25 Jun 2003
9	I/II	Phase I/II Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming with either Oligomeric gp160 THO23/LAI-DID or Chiron Vaccines HIV Thai E (CM235) gp120 plus SF2 gp120 Boosting in Thai HIV - Seronegative Adults. (WRAIR No. RV132, HSRRB No. A-8603)	Prasert Thongcharoen, et al. Depart of Microbiology, Faculty of Medicine Siriraj Hospital. (n=130)	2 Aug 1999/ 31 Jan 2000
10	I/II	Phase I/II Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (v1521) Priming with VaxGen gp 120 B/E (AIDSVAXTM B/E) Boost in Thai HIV-Seronegative Adults. (RV135)	Punnee Pitisuttithum, et al. Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University. (n=125)	11 Jan 2000/ final report
11	III	Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming with VaxGen gp120 B/E (AIDSVAX B/E) Boosting in HIV-uninfected Thai Adults -2003. (RV144)	Supachai Rerks-Ngam, et al. Department of Disease Control, Ministry of Public Health. (n=16,402), Efficacy=31.2%	5 Jul 2003/ 28 May 2020
12	I	A Worldwide, Phase I, Dose-Escalating Study of the Safety, Tolerability, and Immunogenicity of a 3-Dose Regimen of the MRKAd5 HIV-1 gag Vaccine in Healthy Adults. (HVTN 050/Merck 018)	Punnee Pitisuttithum, et al. Faculty of Tropical Medicine, Mahidol University; with RTA- AFRIMS, Bangkok; RIHES, Chiang Mai. (n=87)	3 Sep 2003/ final report
13	I	A Randomized, Placebo-Control, Double-Blind, Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of a Candidate Prophylactic pHIS-HIV-AE (DNA) Prime and rFPV-HIV-AE Boost HIV Vaccination Strategy. (HIV-NAT 064/Vaccine)	Kiat Ruxrungtham, et al. Chula Vaccine Research Center, Department of Medicine Chulalongkorn University. (n=24)	20 Mar 2005/ 2 Jun 2009
14	I	A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of an HIV-1 gag DNA Vaccine with or without IL-12 DNA Adjuvant, Boosted with Homologous Plasmids or with HIV CTL Multi-epitope Peptide Vaccine/RC529-SE plus GM-CSF, in Healthy, HIV-1 Uninfected Adult Participants. (HVTN 060)	Vinai Suriyanon, et al. Research Institute for Health Sciences (RIHES), Chiang Mai. (n=12)	13 Sep 2006/ 16 Oct 2012
15	I	A Phase I Double-Blind, Randomized, Dose Escalating, Placebo-Controlled, Study of Safety and Immunogenicity of WRAIR/NIH Live Recombinant MVA-CMDR (HIV-1 CM235 env/CM240 gag/pol) Administered by Intramuscular (IM) or Intradermal (ID) Route in HIV-Uninfected Adults. (RV158)	Prasert Thongcharoen, et al. Mahidol University; and RTA-AFRIMS Bangkok. (complete follow-up in 12 cases)	23 Mar 2007/ 18 Jul 2014
16	II	Phase II, Randomized, Double Blind Evaluation of Late Boost Strategies for HIV-uninfected Participants in the HIV Vaccine Efficacy Trial RV 144: Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) with VaxGen gp120 B/E (AIDSVAX®B/E) Boosting in HIV-uninfected Thai Adults. (RV305)	Supachai Rerks-Ngam, et al. Department of Disease Control, Ministry of Public Health. (n=161) (complete follow-up in 63 cases)	13 Dec 2011/ 25 May 2017
17	II	Randomized, Double Blind Evaluation of Different One-Year Boosts after Sanofi Pasteur Live Recombinant ALVAC-HIV (vCP1521) and Global Solutions for Infectious Diseases (GSID) gp120 B/E (AIDSVAX® B/E) Prime-Boost Regimen in HIV-uninfected Thai Adults. (RV306)	Punnee Pitisuttithum, et al. Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University. (n=367) (complete follow-up in 347 cases)	5 Jun 2013/ 23 Dec 2016
18	II	Randomized, Double Blind Evaluation of Sequential Administration of gp120 B/E (AIDSVAX® B/E) (GSID) with 1-year Boosting in HIV-uninfected Thai Adults. (RV328/SEARCH016)	Nittaya Phanuphak, et al. Institute of HIV Research and Innovation Foundation (IHRI). (n=40) (complete follow-up in 40 cases)	12 Dec 2013/ 24 May 2016
19	I	A Phase I Prime-Boost Combinations Using Modified Vaccinia Ankara and Adenovirus Type 26 Vectors with Mosaic and Natural Inserts in Healthy, HIV Uninfected Adults. (RV307)	LTG Sorachai Nitayaphan. RTA-AFRIMS Site-Principal Investigator.	29 May 2013/ Study was terminated before enrollment due to vaccine problem

Table 1. (continued)

No.	Phase	Project Title	Principal Investigator & number of cases (n)	TSHAVD approved/ finish dates
20	I/IIa	A Phase 1/2a Study to Evaluate the Safety/Tolerability and Immunogenicity of Homologous Ad26 Mosaic Vector Vaccine Regimens or Ad26 Mosaic and MVA Mosaic Heterologous Vector Vaccine Regimens, with High-Dose, Low-Dose or No Clade C gp140 Protein Plus Adjuvant for HIV Prevention. (HIV-V-A004)	1. LTG Sorachai Nitayaphan. RTA-AFRIMS Site-Principal Investigator 2. Punnee Pitisuttithum. Vaccine Trial Center, Faculty of Tropical Medicine, Mahidol University. Site-Principal Investigator (n=58) (complete follow-up in 48 cases)	30 Jun 2015/ 11 Aug 2022
21	I/IIa	A Combined Phase I/2a, Exploratory Study of a Therapeutic Vaccine Using an Adenovirus Type 26 Vector Prime and Modified Vaccinia Ankara Boost Combination with Mosaic Inserts in HIV-1 Infected Adults Who Initiated Antiretroviral Treatment during Acute HIV Infection. (RV405/VAC892220HTX1001/SEARCH023)	Nittaya Phanuphak, et al. Institute of HIV Research and Innovation Foundation (IHRI). (n=27) (complete follow-up in 25 cases)	7 Apr 2016/ 16 Nov 2018
22	I	Phase I, Proof of Concept, Open-Label, Randomized Clinical Trial to Evaluate the Safety and Effects of Using Prime-boost HIVIS DNA and MVA-CMDR Vaccine Regimens with or without Toll-like Receptor 4 Agonist on HIV Reservoirs in Perinatally HIV infected Children and Youth. (RV534/HVRRICANE)	Thanyawee Puthanakit, et al. Center of Excellence for Pediatric Infectious Diseases and Vaccines, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University.	30 Oct 2020/ Study was terminated before enrollment due to expired HIVIS DNA vaccine
23	I	Randomized, Double Blind Evaluation of Late Boost Strategies with IHV01 (FLSC in aluminum phosphate) and A244 with or without ALFQ for HIV-uninfected Participants in the HIV Vaccine Trial RV306/WRAIR 1920. (RV546)	1. Punnee Pitisuttithum, et al. Vaccine Trial Centre, Mahidol University. 2. LTG Sorachai Nitayaphan RTA-AFRIMS Site-Principal Investigator (n=120)	18 Dec 2021/ ongoing

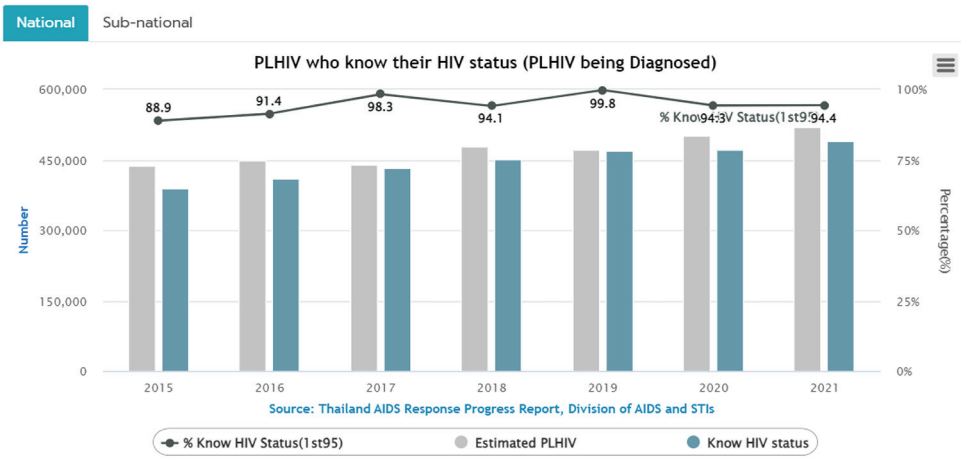

Figure 3. HIV statistics in Thailand: number of cases.

PLHIV=people living with HIV People Living with HIV/AIDS

Source: Division of AIDS and STI, Department of Disease Control, Ministry of Public Health, Thailand (August 2022)

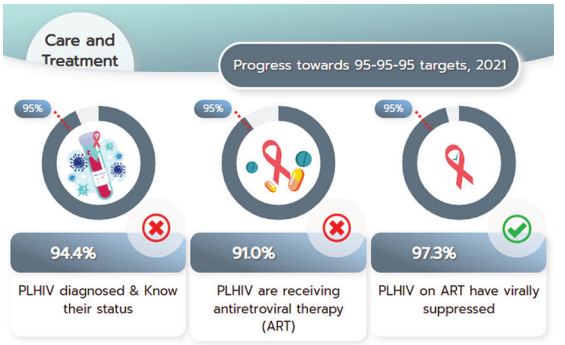

Figure 4. HIV-known status and success rate of ART.

PLHIV=people living with HIV People Living with HIV/AIDS

on a successful combination of ART with complete virologic suppression for a certain period such as six to twelve months, this group of patients will serve as material pool ready for the second step, which is designed to kill all cells harboring latent HIV inside the body. To support Thailand's national strategy to end AIDS, with a vision defined as "Thailand is jointly free from AIDS problems by 2030 with due consideration to the principles of human rights and gender equality", the authors will update their readers with some essential background on molecular genetics and molecular biology related to HIV-infected cell killing and latent HIV infection elimination in

human. Any study focused in this direction would be most welcomed by the Subcommittee on HIV Trials to study in Thailand, especially in the phase-3 randomized controlled trial.

Barrier for HIV eradication

HIV persistent and envelope diversity

A major obstacle for the HIV cure is a latent HIV reservoir formed shortly after acute HIV infection, even after early ART initiation. Following suppression by ART, HIV persistence remains in latency in resting memory CD4+ T cells with half-life of about 44 months and it may need as long as 73 years for HIV patients on ART to completely eliminate these latency cells[11]. HIV proviral DNA in the CD4+ T cells have also been found in gut-associated lymphoid tissue (GALT) at a magnitude five times higher than that found in the blood[12]. A major source of rebound viremia after ART interruption is from reservoirs in lymph nodes. There are two types of latent reservoir, deep latency with no RNA produced, and active reservoir in which the viral RNA is produced, but mostly as defective proviruses in about 98%[13].

Another problem on HIV eradication is associated with its envelope diversity. HIV trimeric gp120-gp41 heterodimers envelope glycoprotein is the only known target that induces neutralizing antibodies (NAbs), which are the key success of efficient preventive vaccine. High antigenic variation of the envelop that are heavily glycosylated often interfere with the generation of broadly neutralizing antibodies (bNAbs) [14-16]. So far, the HIV Env-based candidate vaccines that have been developed to induce non-neutralizing antibodies (nNAbs) and NAs only against Tier 1 viruses as HIV-1 lab strains are most sensitive to neutralization, and not against Tier 2 viruses as HIV-1 circulating strains, or Tier 3 viruses as HIV strains that resist neutralization[17,18]. Only bNAbs isolated from HIV-infected individuals, or long-term non-progressors, LTNPs, and elite controllers (ECs) can neutralize Tier2 and Tier 3 viruses[18].

T cell exhaustion and dysfunction

Prolonged exposure of T-cells to HIV antigens, mostly from defective viruses, continuously induced high levels of activate T-cell, even under ART, which result in chronic inflammation and progressive dysfunctional or exhaustion. T-cell exhaustion with sustained expression of ICs is known to have reduced effector functions and poor recall responses, a phenomenon that is distinct from functional effector or memory T-cells[19,20]. The defective cytotoxic capabilities of HIV-specific CD8+ T cells have been found in almost all HIV patients such as chronic progressor and CP[21]. The defective proviruses that are often produced from HIV reservoirs at higher level than the replication competent proviruses can also produce new chimeric viral proteins, which can serve as a decoy for CTL. Although the T cell exhaustion induced in HIV specific CD8 T cells may have broader function, it is less effective in eliminating HIV infected cells[22].

HIV eradication strategy

Less than 0.1% to 1% of individuals can naturally control HIV infection without any treatment and are often referred to as elite controllers (ECs). These patients have high CD4+ T cells and low viral load or less than 50 copies/mL[23]. The other HIV functional cure is found in "post-treatment control" (PTC). A small number or 5% to 15% of these individuals have undetectable viral load after stopping the ART[24]. Factors that can influence a functional cure in ECs and PTC are high number of HIV-specific CD8+ T cells, high level of broadly neutralizing antibodies (bNAbs), strong innate immunity (TLR7 & TLR8), and less inflammatory immune responses[25]. These ECs and PTC are good model for HIV functional cures. In conclusion, potential strategy to cure HIV infection is how to eliminate latent HIV as outlined below.

Gene therapy

Gene therapy is a medical approach that treats or prevents disease by correcting the underlying genetic problem. HIV gene therapy concept aims to change host or viral genes to eradicate HIV from infected patients. The targeted cells for HIV gene therapy might be CD4+ T lymphocytes and hematopoietic stem cells (HSCs). The most widely used gene targets in HIV gene therapy are the host genes including monocyte chemoattractant protein-1 (MCP-1, also known as CCL2), human lymphocyte antigen class II (HLA class II), CXCR, CCR2, CCR5, CCL3, stromal cell-derived factor 1 (SDF1), and the HIV genes coding for structural proteins such as Gag, Pol, Nef, Tat, and CCR5 co-receptor[26]. Most gene-based clinical trials for HIV cure are still in its early stage with about 106 clinical trials worldwide[27].

RNA interference (RNAi) is the process that double-stranded small RNA molecules complementarily bind targeted mRNAs to inhibit translation. These small RNA molecules are short, at 21 to 23 nucleotides, interfering RNAs (siRNAs) and short hairpin RNAs (shRNA) that are delivered into

mammalian cells by plasmid or viral vectors to inhibit gene expression or translation by binding to targeted mRNA molecules[28]. U1 interference (U1i) RNA is a modified small nuclear ribonucleoprotein (U1 snRNP) that can bind to downstream or terminal exon of target transcript to stop the translation process[29]. U1i combination with RNAi synergistically induce HIV gene silencing[29]. HIV-1 genes such as LTR, TAR, gag, vif, pol, tat, and rev, host genes for HIV transcription such as HIV Tat specific factor 1, transcription elongation factor SPT5, and cyclin T1, and essential host genes for HIV cell entry such as CCR5, CXCR4, LEDGF/p75, CD4 receptor, and importin-7, can be suppressed by RNAi[26].

A variety of lentiviral vectors have been constructed to express siRNAs targeting HIV genes such as tat and rev, and host genes such as C46 peptide and a CCR5 shRNA-LVsh5[30]. The anti-HIV lentiviral vector, LVsh5/C46, to inhibit HIV fusion, has been developed by Calimmune Inc, USA, and has undergone a phase I and II clinical trial (NCT01734850)[31]. The LVsh5/C46 transduced CD4+ T lymphocytes (Ttn) and LVsh5/C46 transduced CD34+ HSPC (HSPCtn) were transplanted back to the patients and shown to have potential to control HIV infection and stop disease progression[31]. Further development of SiRNAs in vivo delivery systems such as nanoparticles, aptamer, and peptides, would certainly enhance transferring of SiRNAs into the infected cells[32].

Aptamers are small single-stranded RNAs with ability to bind target proteins or nucleic acids via three-dimensional conformations[26]. Because of its function similar to that of monoclonal antibodies, the aptamers are sometimes known as "nucleic acid antibodies"[27]. Many HIV proteins and receptors have been used for aptamer construction such as pseudoknot RNA aptamers, which would then bind to Rev, RT, IN, gp120, Gag, or nucleocapsid (NC) to inhibit HIV replication[26].

Ribozymes are RNA enzymes that can cleave RNA target and inactivate its activity. Together with shRNAs, ribozymes can be specifically targeted at any specific HIV nucleotide sequences[26]. Phase II clinical trial of tat-vpr-specific anti-HIV ribozyme (OZ1) has been administered to 74 HIV patients, and the study showed that the OZ1 was safe and induced high CD4+ lymphocyte counts in the OZ1 group[33].

Due to low gene-editing efficiency, high off-target rate, cost, and time-consuming vector construction of the first generation of gene-editing technologies such as ZFNs and TALENs, they were subsequently replaced by a novel CRISPR/Cas 9 system that is now a powerful tool to eliminate latent HIV reservoirs[34]. Gene-editing using the CRISPR/Cas9 in HIV-1 patients can target the HIV-1 genome to remove regulatory genes and host factors such as host chemokine receptor CCR5 and CXCR4[35,36]. Preliminary results from preclinical studies showed that the CRISPR/Cas9 strategy may not only decrease HIV replication, but it may also continuously reduce latent HIV reservoir by removing integrated proviral DNA[37].

Immunotherapy for HIV cure

Hematopoietic stem-cell transplantation

Modifying hematopoietic stem cells (HSC) by gene therapy (CCR5Δ32/Δ32) can improve the function of HSC in HIV treatment. The "Berlin patient" was the first successful functional cure of HIV-1 infection in humans. In 1995, this patient with acute myeloid leukemia and HIV-1 infection received transplantation of stem cells from a donor who was homozygous for CCR5Δ32/Δ32. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy[38]. The second case of the functional cure of HIV-1 infection was the "London patient". This HIV-1 infected Caucasian male received allogeneic hematopoietic stem-cell transplantation (HSCT) for Hodgkin's lymphoma using cells from a CCR5Δ32/Δ32 donor[39]. The patient achieved full remission and remained HIV negative for 28 months after a single transplantation and no viral rebound after ART interruption. The third case, the "Dusseldorf patient", also demonstrated a functional cure after receiving CCR5 Δ32/Δ32 homozygous deletion mutation harboring allogeneic hematopoietic stem cells[40]. Another clinical trial with allogeneic stem-cell transplantation in 36 patients resulted in undetectable HIV-1 viral load in plasma, CSF, intestine, and lymphoid tissue up to 30 months[41].

CAR-T cell therapy

Chimeric antigen receptor (CAR)-T cells are T cells constructed from an scFv derived from variable domains of antibodies as an extracellular domain that recognizes antigens and the intracellular domain consists of CD3ζ, a signal transduction part of T-cell antigen receptor, which mediate signaling pathways after antigen recognition and activation[42]. The autologous CAR-expressed CD8+ T cells, in vitro construct, recognizing HIV antigens can kill HIV infected cells with better binding and specificity[43].

The bNAbs-based CARs are one of the most important CARs in HIV cure, allowing it to bind to the trimeric viral envelope of HIV infected cells[44]. The results from two phase II clinical trials of CD4+ CAR T therapy in HIV infected patients were found to be safe and well-tolerated[45]. There are another two approved ongoing clinical trials that apply CAR T cell-based therapy for HIV treatment[46].

Therapeutic HIV vaccine

Even with the effective ART to control HIV infection, HIV virological failure still occurred due to HIV persistence and emergence of drug resistant variants. To achieve a better functional cure, one needs not only to optimize ways and means to improve ART to control latent reservoir reactivation, but also improving immune stimulation, either by active or passive immunization to induce effective broadly neutralizing antibodies (bNAbs) and strong T cells (CD4 and CD8) response. These immunotherapeutic approaches include therapeutic HIV vaccines to induce strong T cell immunity such as DCs-based vaccine, DNA vaccine, mRNA vaccine, viral vector vaccine such as vaccinia virus, MVA, adenovirus-Ad5, Ad26, chimpanzee adenovirus, and cytomegalovirus and high level of bNAbs response[47]. Among these HIV therapeutic vaccine, the DCs-based HIV vaccine was most promising, inducing polyfunctional CD4+ and CD8+ T cell immunity specific for HIV and virus control[48,49].

HIV mRNA vaccine

Of the seven HIV vaccine efficacy trials worldwide, only the RV144 efficacy trial in Thailand has given efficacy results of 31.2% protection, showing the level of V1/V2 IgG-binding antibodies inversely correlated with the degree of HIV infection. However, the plasma Env-specific IgA-binding antibodies that were simultaneously generated after immunization were found to have opposite effect, as its level be directly correlated with the magnitude of HIV infection by interfering with protection effect of ADCC and Nabs[50,51].

After decades of study, correlation of specific immunity to prevent HIV infection has rarely been demonstrated. Because broadly neutralizing anti-HIV antibodies are poorly induced following natural infection or vaccination, the ultimate goal of the future HIV vaccine development is to induce bnAbs. Since mRNA-based COVID-19 vaccine has been shown to be capable of inducing broadly neutralizing antibodies against SARS-CoV-2, this approach will certainly be used to develop future HIV vaccine candidate. With the success of COVID-19 mRNA vaccine, the first phase I randomized, open-label clinical trial of mRNA-based HIV vaccine [eOD-GT8 60mer mRNA Vaccine (mRNA-1644) and Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core), Moderna) has been administered to 56 healthy HIV seronegative participants aged 18 to 56 years in October 2021 to evaluate its safety and immunogenicity (https://clinicaltrials.gov/ct2/show/NCT05414786).

bNAbs immunization

Apart from the antiretroviral drugs, ART, HIV broadly neutralizing antibodies (bNAbs) may be another effective promising prophylaxis and therapeutic agents for HIV infection/AIDS[52]. Neutralizing antibodies (NAbs) against HIV Env are produced in chronic HIV infection with multiple maturation of memory B cells that recognize HIV quasispecies antigens emerge over time. However, bNAbs are rarely found in natural HIV infection at only 1%[53]. In addition, active immunization with HIV vaccine candidate scarcely induces bNAbs due to the presence of trimeric structure and high genetic diversity of Env glycoprotein and low number of bNAbs precursor naïve B cells in normal individuals[54]. HIV envelope protein has been modified in some HIV vaccine candidates to more effectively stimulate bNAbs, and these include HIV Env trimer immunogens, Env consensus ancestral protein, and replicating Env-CD4 fusion intermediates. However, none of these Env-modified HIV vaccine candidate induces bNAbs[55]. Therefore, another approach has been developed using germline-targeting (GT) immunogens[56].

Passive immunization in non-human primate with bNAbs has been shown to induce significant degree of protection against SHIV challenge[57]. The success of this animal study paves way to explore and test antibody-mediated prevention approach in HIV infection human clinical trial. Among the single bNAbs human phase I clinical trials for HIV infection prophylaxis, the VRC01 trial showed protective efficacy similar to the RV144 phase III clinical trial[58,59]. To combat emerged HIV resistant strains in single bNAbs passive immunization, a combination of bNAbs therapy such as anti-CD4bs (VRC07), -V3 glycan site (PGT121), and -V2 glycan site (PGDM1400), has been shown to improve efficacy and reduce resistance[60].

Ibalizumab, anti-CD4 humanized IgG4 monoclonal bNAbs, has been approved by FDA

for HIV-1 therapy, especially in multidrug resistant HIV infection cases with ART failure[61]. In a phase 3 clinical trial, Ibalizumab could reduce HIV viral load at least 0.5 log10 copies/mL and 63% maintain viral load to less than 200 copies/mL[62]. Gene transfer using recombinant adeno-associated virus (rAAV) as a vector carrying bNAb genes such as VRC01, 4E10, and PG9 has also been shown to induce bNAbs production within six weeks in Balb/c mice[63].

Shock (or kick) and kill

Shock (or kick) and kill strategy for HIV eradication was proposed in 2012[64] with the aims of reducing the size of latent reservoirs of the virus by first reactivating the latent proviruses in cellular reservoir ("shock" or "kick") with Latent Reversing Agents (LRAs), thus allowing it to express HIV proteins that can then be detected and eliminated by immune-mediated mechanisms like CTL or NK cells or antibody to ("kill")[65]. More than 300 potential chemical and biological compounds have been explored and those with LRA activity have now been categorized as 1) chromatin modulation, 2) transcription activators, 3) transcriptional elongation, 4) immune checkpoint inhibitors, and 5) post-transcriptional modification[66]. Therapeutic HIV vaccines may be administered to enhance CTL and NK activities after the LRAs administration. Vorinostat was the first LRA shown to have the ability of shock and kill to eliminate infected cells in a primary-cell model of latency[67,68]. However, despite these promising results, a single LRA might not be enough to reactivate all latent reservoir. Moreover, these potential LRAs may have undesirable side effects like impairment of host immunity, which will limit their use in shock and kill strategy. Therapeutic HIV vaccines are critical in the "shock and kill" and functional cure strategies because reactivated virally infected cells must be removed as soon as they become visible to the immune system[69].

Block and lock

Block and lock strategy aims to permanently stop virus transcription from latent reservoir by suppressing viral reactivation through transcriptional and post-transcriptional gene silencing, thus allowing deep latency state to remain in the cellular reservoir in HIV-1-positive patients without having to take ART similar to that found in elite controllers[70]. A functional cure via transcriptional silencing of the proviruses could be achieved by latency-promoting agents (LPA), as 1) small interfering RNAs (siRNAs) and short hairpin RNAs (shRNAs), 2) Tat inhibitors e.g., didehydro-cortistatin A (dCA), levosimendan, 3) mTOR (serine/threonine kinase complex) inhibitors e.g., rapamycin, INK128, and 4) heat shock protein 90 inhibitors e.g., AUY922, 17-AAG[68,71].

As shown in Table 1, there have been many HIV vaccine trials conducted in Thailand for over 25 years and the country success rate of ART in achieving the untransmittable HIV status among people living with HIV, together with the current scientific advance and knowledge in HIV cure as reviewed above, all of these render Thailand a suitable site to test an innovative method in that aims at HIV cure for people living with HIV/AIDS. The Subcommittee still maintain the authors' commitment to ending HIV infection to provide a fulfilling and harmonious lives for this group and their friends. Although more than forty years have passed since the discovery of HIV, at present, the authors admit that a cure for HIV infection is still far from the horizon. ART has continuously evolved and while a highly active combination of safe drugs is available, it is still not a curative method. Though much knowledge has been gained through recent advance of molecular medicine and immunology as reviewed above, it is still far from what the authors expect to achieve an "HIV cure". However, the authors believe the advanced knowledge is essential and still holds promise for the ultimate cure of HIV infection that will certainly improve the quality of life of people living with HIV. Though HIV infection can be simply prevented by physical barriers or behavior risk avoidance, those who have been infected, now mostly falls into clinical "latency" period. The successful ART in Thailand has kept individuals with HIV-completely suppressed waiting for the groundbreaking studies of novel strategies to achieve HIV cure. The advances in molecular genetics and biology, genome editing, embryonic stem cells, and induced pluripotent stem cells have drastically stimulated the present study intention to search for more novel technology that will bring us closer and faster to the HIV cure approach. The authors believe the solution to ending the HIV epidemic among those already infected is to have regular HIV test in routine health check-up. Those with positive HIV test should then take anti-retroviral drugs until the HIV viral load is suppressed to undetectable level for six months. These steps should then be followed by another step that deploys through therapeutic vaccine, monoclonal antibody, gene editing drug, immune checkpoints modulator, or the combination of these agents or HIV-cytolysis method to reverse the proviral

quiescence and remove latently infected cells, leading to a complete or functional cure. The final step is to follow the cases until a treatment-free remission and viral eradication has been achieved beyond question.

In conclusion, the authors strongly believe that Thailand has emerged as an appropriate study site that can facilitate identification and implementation of an innovative, simple, and safe technique to be used globally with either single or combination methods. The subcommittee does welcome any collaboration from international organizations in conducting the clinical research aiming at the HIV cure direction. Since Thailand has adequate material, superb infrastructure, and human resource with experience to conduct a high-quality field research, the authors believe the present study country can serve a key role in the field trial to achieve a breakthrough strategy that would cure HIV and end AIDS epidemic in the country. Together, the entire world will also realistically achieve the HIV-zero by the year 2030.

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Conflicts of interest

The authors declare no conflict of interest.

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งานวิจัยวัคซีนเอดส์ในประเทศไทยและหนทางสู่การหายขาดจากการติดเชื้อ HIV

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ประเทศไทยประสบความสำเร็จอย่างดียิ่งมายาวนานกว่า 30 ปี ในการป้องกันและจัดระบบบริการทำให้ผู้ติดเชื้อ HIV ทราบสถานะการติดเชื้อตนเองและรับการรักษาด้วยยาต้านไวรัส HIV ได้มากกว่าร้อยละ 90 ความสำเร็จดังกล่าวทำให้ผู้ติดเชื้อประมาณกว่า 400,000 ราย ในประเทศไทย กินยาต้านไวรัส HIV สม่ำเสมอจนทำให้ระดับ viral load ในเลือดลดลงจนถึงระดับที่ตรวจไม่พบและทำให้ผู้ติดเชื้อรายนั้นไม่สามารถแพร่เชื้อ HIV ได้อีกต่อไป อย่างไรก็ตาม การหยุดกินยายังทำให้เชื้อไวรัส HIV เพิ่มจำนวนกลับขึ้นมาใหม่ได้ ขณะนี้ วิทยาการการกำจัดเชื้อโรคมีความก้าวหน้าถึงการปรับเปลี่ยนรหัสพันธกรรม การปลูกถ่ายเซลล์ต้นกำเนิดและใช้ความรู้ในระดับชีวโมเลกุล ทำให้เกิดการรักษาวิธีใหม่มากมายที่คาดว่าจะนำมาประยุกต์ใช้ในการกำจัดเชื้อ HIV ที่หลบซ่อนในเซลล์ของผู้ติดเชื้อได้ วิธีใหม่นี้จะกำจัดทั้งเซลล์ที่ติดเชื้อ HIV หรือ กำจัดเฉพาะยีนไวรัส HIV ที่หลบซ่อนอยู่มิให้เพิ่มจำนวนได้อีกตลอดไป ประเทศไทยมีคณะกรรมการแห่งชาติว่าด้วยการป้องกันและแก้ไขปัญหาเอดส์มานานและได้แต่งตั้งคณะอนุกรรมการวิชาการการทดลองวัคซีนเอดส์ เพื่อให้ข้อเสนอนโยบาย และสนับสนุน กำกับดูแลโครงการวิจัยเรื่องวัคซีน HIV จนถึงปัจจุบันได้มีโครงการวิจัยวัคซีนเอดส์มากกว่า 23 เรื่อง ที่มาทำวิจัยในประเทศไทยและเป็นการทำวิจัยร่วมกับองค์กรระดับนานาชาติจนประเทศไทยมีผลงานวิจัยตีพิมพ์อย่างน้อย 10 เรื่อง (อ้างอิงไปถึง 2,726 ครั้ง) และมีผลงานวิจัยหนึ่งเรื่องที่ประสบความสำเร็จเป็นครั้งแรกในโลกที่พบว่าวัคซีนมีประสิทธิภาพในการป้องกันการติดเชื้อ HIV ได้ถึงร้อยละ 31.2 การทำวิจัยทำให้เกิดโครงสร้าง เครือข่ายและประสบการณ์มากเพียงพอที่จะรองรับการวิจัยในเรื่องนี้ต่อไปในอนาคตได้เป็นอย่างดี เนื่องจากขณะนี้ประเทศไทยมีผู้ติดเชื้อ HIV จำนวนมากกว่า 400,000 ราย ที่กินยา ARV จนควบคุมโรคได้ดีและมีคุณสมบัติที่จะเข้าร่วมงานวิจัยในเรื่อง HIV cure ได้ คณะอนุกรรมการจึงได้ทบทวนวิชาการในเรื่องวัคซีน HIV และ HIV cure เพื่อเตรียมความพร้อม เพราะมีความหวังอย่างแรงกล้าที่จะประยุกต์นำความรู้ดังกล่าวร่วมกับหน่วยงานนานาชาติมาใช้กำจัดทั้งเชื้อ HIV ที่หลบซ่อนในร่างกายและเซลล์ที่ติดเชื้อให้หมดไป เพื่อนำประเทศไทยไปสู่ประเทศแรกๆ ที่สามารถยุติปัญหาเอดส์ได้ภายในปี พ.ศ. 2573