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Thailand's HIV/AIDS program after weaning-off the global fund's support

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Abstract

Background: Though 85% of financing HIV/AIDS program was domestic resources, Global Fund (GF) programs played a significant role in prevention interventions and treatment for non-Thai Key Affected Populations (KAP) and migrants. As upper-middle income country, Thailand is not eligible for GF support. This study identified the remaining challenges and funding for prevention interventions for Thai and non-Thai KAP and migrants if GF supports were to curtail.

Methods: Qualitative method was applied including document review and in-depth interviews of 21 key informants who were Principal Recipients, Sub-recipients, provincial level program implementers and policy makers in health financing agencies. A multi-stakeholder consultation workshop was convened to discuss recommendations.

Results: The "public financed public services model" where Principal and Agents were the same entities resulted in less accountability than the "contractual agreement" in GF programs where the Principal Recipients, as the Agents were more accountable to the GF as Principal through results based financing. If GF supports were to curtail, impacts on the current programs would be varied from low to high degree of negative consequences. Scale down the scope and targets, while keeping the most critical components were common coping mechanisms. All three, except one, Principal Recipients had difficulties in fund mobilization. Prevention among non-Thai KAP and migrants were identified as the remaining challenge.

Conclusions: A pooled funding mechanism from multiple domestic sources was proposed. Replacing the conventional public-financed-public-service by a contractual model was preferable. The GF should continue funding the non-Thai KAP and migrant as transition mechanism. Multi-countries or regional programs especially at the border areas were priorities.

Keywords: Principal-Agent relationship, Thailand, Global fund, Key Affected Populations, Migrants

Background

The Global Fund to Fight AIDS, Tuberculosis (TB), and Malaria (GF), founded in 2002, is the largest international funding instrument to support prevention and treatment of HIV/AIDS, TB and Malaria. GF mobilized and disbursed funding to countries with high disease burdens but had limited capacities to address them. In 2011, it disbursed US\$ 2.6 billion to countries based on the technical merits of proposals submitted to and reviewed by the Technical Review Panel, and approved by

the GF Board. In 2011, 57% of total funding was disbursed for HIV and TB/HIV co-infections, 23% for malaria, 15% for TB and the remaining for health systems strengthening [1].

The contributions by GF expanded exponentially; the 2002 grants disbursed to 36 countries [2] has expanded to 151 countries, including Thailand, in 2012 [3]. Application and implementation of GF programs were based on country ownership and participation through multi-stakeholder platform of Country Coordination Mechanisms (CCM) [4].

HIV/AIDS was a major public health problem in Thailand in terms of mortality and Disable Adjusted Life Year loss [5]; rapid and effective responses had turned the 1980s "generalized" to "concentrated" epidemics in

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late 1990s affecting some most at risk populations such as sex workers, men having sex with men and intravenous drug users. In 2003, Thailand introduced a tax-financed universal anti-retroviral therapy (ART) resulting in a significant reduction in HIV/AIDS mortality [6,7].

Government commitment to deal with HIV/AIDS was demonstrated by increased total spending on HIV/AIDS. Prior to 2008 there was no systematic resource tracking on HIV/AIDS. Spending on HIV/AIDS programs increased from 1.9% of Total Health Expenditure in 2008 to 2.4% in 2011; or increased from US\$ 431 to US\$ 675 per capita people living with HIV/AIDS (PLWHA) in the same period. See Table 1. Domestic resource was a majority, up to 85% of total AIDS expenditure during 2008–2011. Of the international sources, GF was the largest contributor, more than 70% of overall international funding [8]. Though international funding was a small fraction; it largely contributed, 41%, to HIV prevention while the majority, 84% of total domestic funding was spent on treatment and care [9].

With reference to the 23rd GF Board meeting in May 2011 [10], a new Eligibility, Counterpart Financing and Prioritization policy was adopted for all funding channels, by taking into account the country's income level, disease burden and recent funding history. GF policy change has affected HIV/AIDS funding opportunities to Thailand. Although burden was high; with a history of recent funding, Thailand is neither eligible to submit a proposal for General nor Targeted Funding Pool, see Table 2.

Policy makers and practitioners were concerned about how Thailand prepared itself given GF policy changes

Table 1 Key indicators on HIV/AIDS financing, Thailand 2008-2011

	2008	2009	2010	2011
Total AIDS expenditure, million Baht	6,928	7,208	7,733	9,922
Total Health Expenditure, million Baht	363,771	383,051	392,368	408,718
Financing sources				
• Domestic, % Total AIDS expenditure	85	93	85	85
• International, % Total AIDS expenditure	15	7	15	15
Total AIDS expenditure				
• per capita population, Baht	110	114	121	154
• per capita PLWHA, Baht	14,275	14,417	15,487	20,594
• per capita population, US\$	3.3	3.3	3.8	5.1
• per capita PLWHA, US\$	430.9	415.2	488.7	675.4
• % of Gross Domestic Product	0.08	0.08	0.08	0.09
• % Total Health Expenditure	1.9	1.9	2.0	2.4

Source: National Expenditure on HIV/AIDS 2008–2009 and 2010–2011 report.

Table 2 Thailand's profiles of eligibility to 2012 GF

	HIV/AIDS	TB	Malaria
<i>Eligibility criteria</i>			
• Income category	UMI	UMI	UMI
• Is the country on the OECD-DAC list of ODA recipients?	Yes	NA	NA
• What is the disease burden of the country for each component?	High	Severe	Severe
• Does the country have a history of recent funding?	Yes	Yes	Yes
<i>General funding</i>			
• Is the country eligible to submit a proposal in the General Funding Pool?	No	No	No
• Partial prioritization score (income level and disease burden, the minimum partial score is 3 and the maximum is 12)	NA	7	7
<i>Targeted funding pool</i>			
• Is the country eligible to submit a proposal in the Targeted Funding pool?	No	No	No

Source: GF Eligibility List.
http://www.theglobalfund.org/documents/core/eligibility/Core_EligibleCountries2012_List_en/ [access on 26 March 2013].
 Note: UMI = Upper Middle Income.

and its significant contributions to HIV prevention. This study, with a scope limited to HIV/AIDS program (excluding TB and Malaria), compared the programmatic and financing natures between the GF and government funded programs, assessed the potential impacts and the coping mechanism by Principal Recipient (PR) if the GF supports were to cease, identified the remaining challenges of prevention interventions for the KAP and finally proposed new funding mechanisms for effective responses to these challenges.

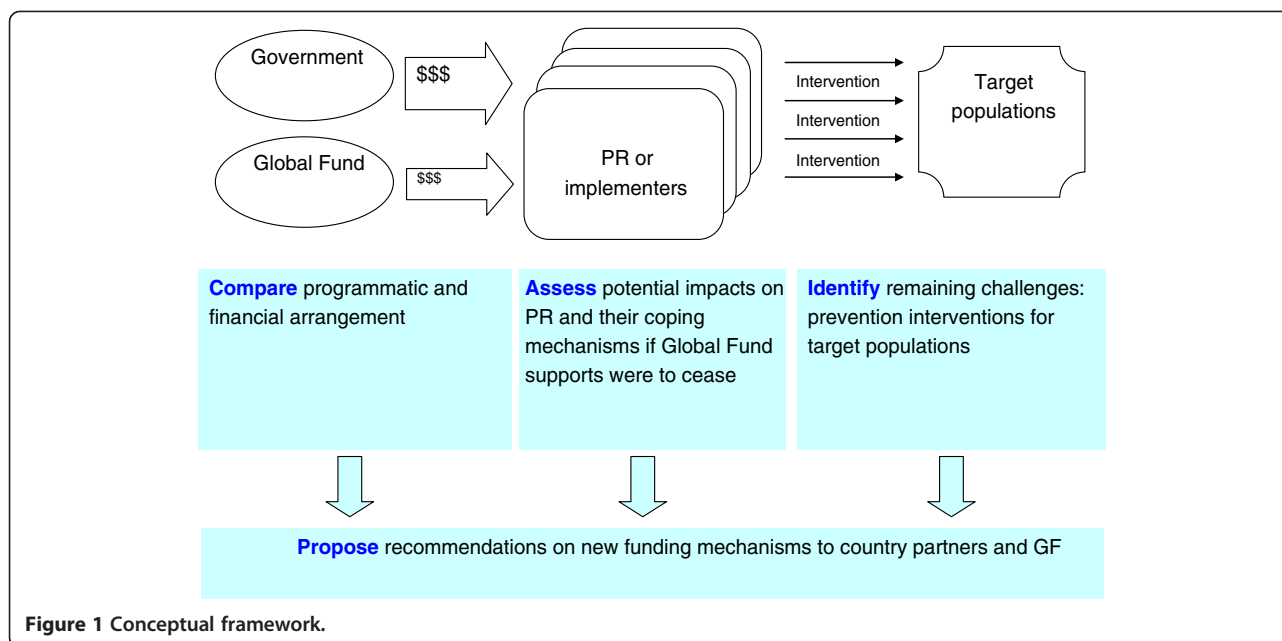
Methods

Conceptual framework

In line with the objectives, a research framework was depicted in Figure 1. The GF differed from the government funded programs in term of programmatic, financial arrangements and targets. Such comparisons informed how difficult it would be if both programs were to harmonize; the greater the difference, the more difficulties in integrating. The assessment of potential impacts on PR and their coping mechanisms and identification of the remaining challenges contributed to recommendations to country partners and GF on financing model which responded effectively to these challenges.

Methodology

Qualitative approach was applied, consisting of document reviews, in-depth interviews of key informants and conducting a brainstorming session.



Reviews of relevant literature, financial documents held by the PR, minutes of the meetings of the CCM and the National AIDS Committee contributed to the understanding of GF program operation and guided the content of the in-depth interviews of key informants (KI).

Three groups of most knowledgeable KI who closely involved with the GF programs were identified and interviewed: first, all four PR and key sub-recipients; second, government program implementers from the top ten provinces having highest HIV prevalence based on the 2009 sero-sentinel; third, selected policy makers and representative from the Universal Health Coverage Scheme (UCS) responsible for HIV prevention for the whole population and treatment for UCS members.

Open-ended questions were used for in-depth interviews focusing on three broad themes:

- The nature of GF and the government sponsored programs.
- The potential impacts on program operation if GF support were curtailed.
- Coping mechanisms both immediate and medium term responses.

Research ethics was approved by the Ethics Committee of Institute for the Development of Human Research Protections (IHRP), the Ministry of Public Health (MOPH). Confidentiality was strictly observed. Data and tape records were kept securely and will be destroyed 2 years after the completion of the work. The interviews were conducted in November 2012 when 21 KI were successfully face-to-face interviewed, except the technical

officers in ten Provincial Health Offices were phone-interviewed, See Table 3. Interviews were recorded with approval and transcribed. Content analysis based on the three thematic topics above was done manually.

The Principal-Agent Theory was applied for the analysis of the relationship and accountability between the principal and the agent. The principal is a party who wishes to secure provision of goods or services but does not have the necessary knowledge and skills to do so. The principal employs an agent to undertake this task and delegates some control to the agent [11]. The information imbalance leads the principal to a difficulty whether or not the agent is acting in the principal's true interests [12].

There was limited accountability framework in the government funded program in an “integrated model”

Table 3 Key informants successfully interviewed

Group	Profiles	Number of KI
Policy makers	Member of the national AIDS committee	1
	Former CCM member	1
Financing agencies	Insurance management division, National Health Security Office	1
Implementation	Directors of primary recipient	3
	Technical officers of the primary recipient	3
	Directors of sub-recipient	2
	Technical officers/implementers in 10 provincial health offices (PHO)*	10
Total key informants		21

Note * Telephone interviews.

where the principal and the agent are the same entity. MOPH, as a principal, does not effectively enforce its own network of health delivery systems, which acted as an agent, to be accountable. Either incentive or sanction mechanisms were seldom applied by MOPH [13,14].

A half-day brainstorming session was conducted on December 17, 2012 to solicit opinion from KI on the way forward after weaning-off the GF support. A total seventeen stakeholders with extensive experiences in HIV/AIDS planning and program implementation participated in the session. These consisted of two national program managers, six civil society organization representatives, six researchers, one MOPH policy maker, one from National Health Security Office who operates the UCS and a Secretariat of GF programs.

Results

Emerging context: increased ART expenditure in response to mature epidemics

At the inception of the UCS in 2002, ART was not included in the benefit packages; as medicines were too costly and unaffordable, neither information on cost-effectiveness nor fiscal impact was available to support policy decision [15,16].

A considerable policy shift towards supporting universal ART took place in November 2001, when the Health Minister pledged to gradually extend treatment to achieve full coverage. It was not until 2003 when the universal ART was formally launched. As a consequence, the public-funded program was dramatically extended, by which the number of treatment recipients reached to over 100,000 in 2007 indicating strong health delivery systems to accommodate scaling up. In the UNGASS country report, in 2007, 52.9% of adult and children with advanced HIV received ART, accounting 84.8% of symptomatic PLWHA [17]. By 2011, ART treatment was scaled to 225,000 receiving services from 943 healthcare facilities of which 96% were governmental hospitals; 97% of those on treatment were adults and 3% were children [18].

Universal ART was encouraged by multiple factors. The success of the Government Pharmaceutical Organization (GPO) in October 2001 in producing a first-line ARV regimen at US\$ 360 per patient year (Exchange rate 40 Baht to US\$); 96% cheaper than the brand products, was the most important contribution to policy change. Also the role of national and international treatment advocates was prominent. The civic networks made use of the information on ARV price reduction to enhance their campaigns. Withholding ART services was no longer justified when medicines became affordable [19].

Universal ART resulted in rapid increase in spending on treatment while the prevention proportion gradually

shrank from 21.7% in 2008 to 13.7% in 2009. Policy makers became complacency when Thailand reversed its epidemics. The 2006 MOPH reform weakened the function of Bureau of AIDS, TB and sexual transmitted infections; transferring financing authority to National Health Security Office resulted in lack of budget line for prevention [20]. GF support was used to fill financial gaps in prevention interventions.

Financing sources and implementing agencies: government and GF program

Financing sources and implementing agencies for three groups of population differed, see Table 4. The GF support focused on prevention and treatment for non-Thai KAP and migrants, with very few GF programs for Thai KAP preventions. Civil Society Organizations (CSO) were the implementing agents for GF supported programs, as they had comparative advantages than government in out-reaching to Thai and non-Thai MSM, IDU and sex workers and migrants. Rigidity was reported in using government budget to supply ART for the non-Thai.

"Our target is IDU. Thai government is reluctant to fund our work, especially for the non-Thai citizens, also uses of illicit drug is illegal. GF is the only source, ensuring continuity for some years. Though it requires lots of audit, time consuming and has less flexibility."
[KI05 PR]

Major proportions of domestic budget were for treatment as GF resources cannot be used to purchase non-WHO-prequalified ARV produced by GPO. For Thai KAP, government outlets and CSO outreaches were applied to improve access.

"...Only delivering medicines (ART) to patients is not adequate for the successful outcome. Patients' participation and adherence are important. We initiated a program to strengthen capacity of patient group. GF money can be used for these purposes while government budget had limitation" [KI01, 02, 03 PR]

Table 5 summarized programmatic and financial nature between government and GF supported programs which were drawn from document reviews, in-depth interviews and the brainstorming session; and also interpretation was made by researchers using Principal-Agent theory.

In a bureaucrat system, priority was given to the control of input, procurement of goods and services by rule and regulation, while effectiveness of implementation and performance was not so much a primary concern. The GF result-based financing better ensured accountability of the

Table 4 Three groups of population and HIV/AIDS interventions: government and GF funded programs

		A. General pop	B. Thai KAP	C. Non-Thai KAP and migrants
Preventions	Financing source	Government budget	Government budget + GF	GF
	Implementer	Government service outlet	Government service outlets + CSO outreach	Mainly CSO
Care and treatment	Financing source	Thai health insurance schemes	Thai health insurance schemes	GF
	Implementer	Government service outlet	Government service outlets + CSO outreach	CSO

PR to the GF; all PR were required to comply with deliverables committed with GF.

“...GF differs from government budget that it can be used as a drive for better performance with clear accountability framework, timeline and deliverables” [KI12 PHO]

The implementers at provincial level also faced difficulties in budget disbursement

“The GF contributes to almost 100% of our prevention budget, whereas budget from the National Health

Security Office and the Ministry of Public Health is small, unpredictable in terms of amount and time to disburse.” [KI21 PHO]

Potential impacts of and responses to weaning off GF supports

All KI were aware of Thailand non-eligible for HIV program of GF. Half of them (11 out of 21 KI) explicitly and strongly supported that Thailand can be and should be financially self-reliance. The GF should support non-Thai KAP program. Thai KAP should be the government responsibilities.

The Provincial Coordinating Mechanism used GF resources to hire additional staffs to co-ordinate all

Table 5 Financing and programmatic nature: government and GF

	Government programs	GF supported programs
Duration of plan	Usually annual plan and budget cycle	Medium term program (often five years) ensures continuity
Financing profile	84% spent on treatment and care	50% or more on prevention interventions
Financing prevention interventions	Cover operational cost, not on human resources incentives	<ul style="list-style-type: none"> Cover all expenditures including human resources. More flexible in procurement than government, such as syringe and needle supplies for IDU and ART for non-Thai KAP and migrants Financial audits are required which can create burden for PR
Accountability framework	<ul style="list-style-type: none"> Integrated model, where MOPH as principal, and its health service network as agent, results in limited accountability framework. Input focus, regulate use of resources in line with procurement rules and regulation, less accountable to outputs and program performance 	<ul style="list-style-type: none"> A proposal-based payment Clear accountability framework: the Principal Recipients as Agents are accountable to the GF as the Principal, through contractual agreement. Non-performance was sanctioned by termination of grants. Focus on result and performance foster accountability and responsiveness
Monitoring and evaluation	<ul style="list-style-type: none"> Not clear on timing and requirement 	<ul style="list-style-type: none"> Regular progress report is required Annual report for monitoring and evaluation
Limitations	<ul style="list-style-type: none"> Allocation of limited annual budget to too many government sectors (e.g. health, education, defence, social development, labour) results in fragmentation and lack of impact Doubtful effectiveness of interventions such as public media Limitation to address preventions among non-Thai population Poor attitude, rigidity and capacity in outsourcing/contracting services to competent non-state actors 	<ul style="list-style-type: none"> It ensures continuity of activities in some certain period (depends on the project lifespan). However, there is uncertainty in long term support beyond five year program grants

activities in the province. If GF funding ceased, program downsizing is inevitable; provincial program would be more affected, as they relied more on GF resources where provincial municipalities had limited resource capacities.

The non-state actors were key GF program implementers, especially in outreaching targeted KAP where the government staffs had limited capacities, either attitude, skill or competency. Curtailing GF support raised concern how to sustain these merits and impacts on migrants.

“GF is good. It adds more money to the program. If we cannot get support from GE, we will have a problem on ART for migrant. ART is very expensive. Apart from this I did not see any negative consequences if GF ceases support. If we can find money for migrant, it should be okay” [KI07 SR]

Document reviews and interviews of KI confirmed that the government funded programs secured adequate funding on generic interventions such as, prevention in schools or in factories, but not on KAP. The GF is the *de facto*, the only funding source targeting KAP, especially non-Thai KAP and migrants through the contributions of non-state actors.

“...Though, we can spend government budget on KAP but we are very stretched by others. We have other routine activities such as detection and treatment of tuberculosis DOTS, huge daily workload from NCD such as diabetes and hypertension, and strengthening our district, so why bother with MSM?” [KI16 PHO]

Table 6 synthesized the potential impacts and coping strategies. A few messages emerged. To prevent program abruption and negative impact on KAP, a transitional financing mechanism to smooth out by phasing in new funding source and phasing out GF support; prioritization and resources planning among key stakeholders were required. Though similar immediate responses across PR and coping strategies emerged, such as mobilizing local government and other international sources; there were variations in financial capacities to sustain program across PR. Some PR could mobilize resources while others had less capacity. Some PR had planned to integrate essential activities into annual activities supported by local government.

“...Funding from GF is one additional to other funding sources, we have good capacities to mobilize from elsewhere.” [KI01 PR; KI02 PR; KI07 SR]

“...Without GF, there is little possibility (for us) to keep the good program going on, GF is the major pot. We do

not have capacities to mobilize funding as the program is not attractive to the Government.” [KI05 PR]

Discussion

A multi-stakeholder consultation was convened where preliminary research findings were presented and extensive discussion followed. A few consensuses emerged.

The remaining challenges were access to prevention, care and treatment by Thai and non-Thai KAP and migrants. Undoubtedly, it was the Thai government legitimate responsibility to fully support the Thai KAP, limitations existed in using government budget to support the non-Thai KAP. Skills and competencies to work effectively for KAP varied across implementing agencies, where the non-state actors had comparative advantages.

It is important to make the case for using budget to support non-Thai KAP; for example, migrant labour contributed to 6.2% of Gross Domestic Product [21]. Financing health services for the non-Thai migrants should be fully covered by the existing employer-financed health insurance scheme, for which annual premium was 1300 Baht per individual. Its benefit package should cover HIV prevention, care and treatment. However, the scheme covered a fraction of migrants who were registered, while a large part were non-registered and hence uninsured [22,23].

The comparative advantages of the GF model, where there was clear accountability framework under the distinct Principal Agent relationship through contractual agreement, should be applied and replaced the current integrated model with limited accountability framework where MOPH played dual role: Principal and Agent.

National pooled domestic fund from national and local governments, private sector and international sources, dedicated for HIV/AIDS prevention (not for ART as it was fully covered in the benefit package by the three public health insurance schemes) was proposed and reached consensus. It can play a strategic temporary measure to meet the prevention challenges for Thai and non-Thai KAP and migrants.

The concept of a national pool funding mechanism was clear. Instead of allocating annual budget to various agencies for broad and ineffective interventions, it should be centrally pooled and used to purchase services targeting the KAP from competent state and non-state actors. Through this mechanism, the contractual agreement will hold the recipients accountable through result-based financing and monitoring of performance.

This can be managed through medium term proposal submission, peer reviews, transparent approval, disbursement based on timely deliverables. Stakeholders were confident that this will bring significant program effectiveness and accountability than the conventional “public

Table 6 Capacity to survive, possible impacts, immediate responses and coping strategies, if GF were to wean-off its support

Principal recipients	Capacity to survive after weaning-off	Possible impacts, immediate responses	Coping strategies
KI 01–03, PR	High, since GF sources play minor role, it has high capacity to mobilize resources	<ul style="list-style-type: none"> • Staff cut, though unknown future funding for IDU and migrants 	<ol style="list-style-type: none"> 1. Merge GF program with existing governance body, mobilize local government budget 2. Transfer ARV finance to National Health Security Office 3. Mobilize other international funders
KI04, PR	Low	<ul style="list-style-type: none"> • Severe impact on IDU and ART for non-Thai migrants • Local staff cut, scale down or termination of some projects. 	<ol style="list-style-type: none"> 1. Scale down GF programme 2. Negotiate with GPO supporting ARV for non-Thai migrants
KI05, PR	Very low	<ul style="list-style-type: none"> • Termination of HIV prevention services for IDU • HIV incidence/prevalence among IDU may increase sharply 	<ol style="list-style-type: none"> 1. Change target KAP to other group that conform to Thai government regulations in order to be eligible to receive funding from other international sources 2. Scale down and prioritize the most affected areas
KI06, PR	Low	<ul style="list-style-type: none"> • Abrupt termination of current program • Interim: use of savings/or remaining budget • May be eligible for a 'ceiling budget' from a single stream funding Round 10 targeting children 	<ol style="list-style-type: none"> 1. A national focal point is essential to manage the new national pooled fund from domestic sources; requiring legislation or regulations 2. Others: public private partnership on HIV/AIDS

Source: assessment by authors from interviews of KI.

financed public provision model". This pooled fund was strongly advocated based on learning experiences from the GF programs in the last decade.

One limitation was identified. A number of participants in the multi-stakeholder consultation were not large and some of them have potential positive bias towards a future pooled fund mechanism; driven by their positive experiences in managing GF result-based-funding mechanisms. However, this idea has yet to check with political and bureaucratic realities, such as institutional territory. An idea of national pooled fund requires strong political support and leadership. It is recommended that opinions from wider stakeholders should be solicited, in particular views from healthcare providers, different ministry agencies, fund managers, civil societies and patients.

Conclusion

A few conclusions were drawn. Effective interventions, access to prevention and treatments were the remaining challenges for Thai and non-Thai KAP and migrants. It is the legitimate responsibility of Thai government to fully finance Thai KAP programs.

Using government budget to support non-Thai is a major contentious political debate, divided opinion remained. The integrated model where MOPH played dual role of Principal and Agent resulted in lack of accountability. The public implementers had limited skill working with KAP. Annual allocation of small budget to various government agencies resulted in fragmentation, ineffective to make the difference, and lack of continuity.

Poor public program performance was a result of focusing on control of procurement, but not on effectiveness and outcome. Monitoring and evaluation were not used to sanction the poor performing implementers. In contrast, contractual agreement held the Agents responsive and accountable to the Principal through result based financing.

If the GF were to curtail its financial support, a transitional phase is needed to prevent program disruption. It is likely that Thailand can mobilize and fill the GF gaps though capacities varied across PR; as the GF finance represents 15% of total AIDS financing in 2010 and 2011.

Recommendations for Thai partners

Mobilizing additional resources is as important as how to spend them effectively and more accountable. It is recommended to establish a national pooled financing mechanism from various sources and centrally managed to purchase preventive services from competent state or non-state actors, through contractual agreement. It believed that the new mechanisms will hold partners accountable and better performed.

Financing for non-Thai should be responsible by employers who benefited from their labour, through expansion coverage of employer financed insurance scheme which should cover HIV prevention and treatment.

A key limitation identified; the proposal for a national pooled funding mechanism, replacing the current budget allocation to government implementing agencies by a contractual arrangement might not be politically feasible, and may face resistance from the bureaucrats.

Recommendations for the GF

A medium term bridging programs for Non-Thai KAP was recommended. It can be programs in Thailand or in neighbouring countries or a joint cross country program. A transitional period according to the country context is needed to prevent program disruption. The duration of transitional period should be flexible based on capacity of the country to mobilize additional resources. The GF should support country to prepare to be financially self-reliant.

Ethics approval

The study was approved by the Ethics Committee of Institute for the Development of Human Research Protections (IHRP), Ministry of Public Health. The Certificate of Approval was issued as IHRP 1728/2555, 29 October 2555 BE (2012 AD). Informed consents were sought and protection of confidentiality was strictly followed.

Abbreviations

AIDS: Acquired Immune Deficiency Syndrome; ART: Anti-retroviral therapy; CCM: Country Coordination Mechanisms; CSO: Civil Society Organizations; GPO: Government Pharmaceutical Organization; GF: Global Fund to fight AIDS, TB and Malaria; HIV: Human immunodeficiency Virus; KAP: Key Affected Populations; IDU: Intravenous drug users; KI: Key informants; MSM: Men having sex with men; PHO: Provincial health offices; PLWHA: People living with HIV/AIDS; PR: Principal Recipient; SR: Sub-Recipient; UCS: Universal Health Coverage Scheme; UNGASS: UN General Assembly Special Session on HIV/AIDS.

Competing interests

The authors declared that they have no competing interests.

Authors' contributions

The study was designed by WP, NT and VT. NT, SK, TT, CT and RS reviewed the literatures and collecting data. Data analysis was done by WP, NP and VT. All authors contributed to drafting, revision and agreed upon manuscript. All authors read and approved the final manuscript.

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