Appendix

The Thailand setting, overview of mathematical model population groups and presentation of summary data on prevalence levels by population group

There are approximately 530 000 (420 000-660 000) people currently living with HIV in Thailand. The overall prevalence of HIV among the Thai adult (14-49 years old) population has reached a relatively stable plateau of approximately 1.3% (1.0-1.6%) [1] and new HIV infections are occurring at a rate of approximately 10 000 - 12 000 cases per year across the entire population [2]. However, infection levels differ substantially between different sub-population groups in Thailand. Therefore, our model was divided into separate but interacting population groups, each defined by their distinct HIV-related risk behavior. The model was constructed with seven sub-populations: male and female injecting drug users (MIDUs and FIDUs, respectively), female sex workers (FSWs), male clients of FSWs (MCs), men who have sex with men (MSM) and low-risk males (LRM) and females (LRF) who do not fit into one of these categories.

A limitation of this model, along with almost all models based on rates of change in discrete population groups, is its reliance on simplifications regarding the populations involved and their interactions. First, populations are mutually exclusive and grouped only according to their primary risk factor; for example, there is assumed to be no overlap between MIDU and MSM populations, or between MIDUs and MCs. In addition, only those interactions expected to produce the greatest impact are modeled; for example, sexual relationships between MIDUs and FSW are neglected, since the latter are only a small fraction of the total female population. Such assumptions are made for two reasons. First, they reduce the number of parameters that need to be estimated; this is important since every parameter in a model is a potential source of uncertainty and there are no data to inform the parameter. Second, they reduce computation time, allowing more thorough sensitivity and uncertainty analyses than would otherwise be feasible.

The following sub-sections outline evidence for different levels of HIV prevalence among the separate population groups. Figure A illustrates the available data on prevalence in each group along with the range of model simulated prevalence levels; it is observed that the mathematical model was calibrated to accurately reflect the different epidemiology that exists for each sub-population group (Figure A).

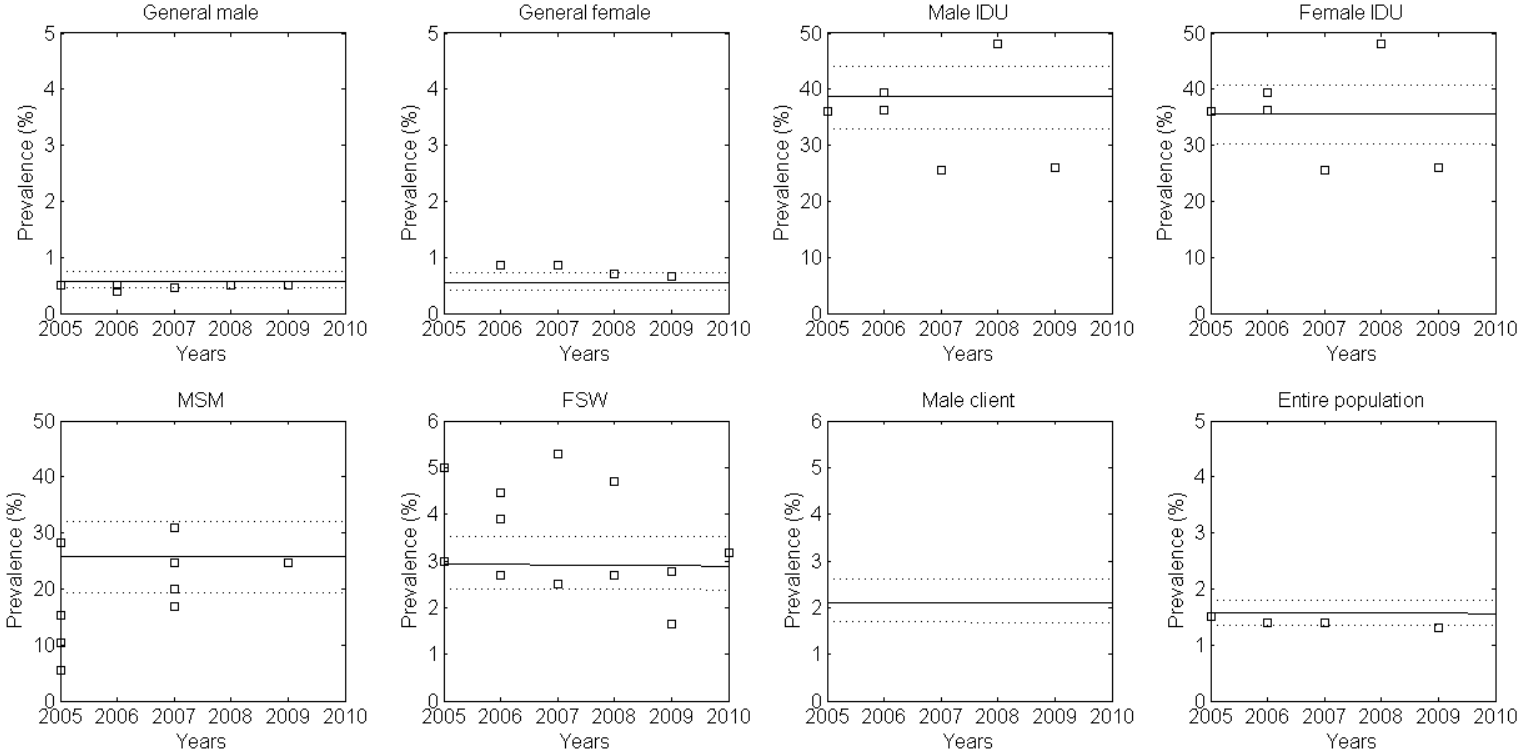
Prevalence among the low-risk population in Thailand

HIV prevalence data obtained from sentinel surveillance sites of ante-natal clinics can be assumed to be an upper estimate of the prevalence of HIV among low-risk females. The HIV prevalence in this population has reached a relatively steady plateau since 2005 of approximately 0.65-0.70% [3]. Similarly, data obtained from new military recruits can be considered roughly representative of young low-risk men. The HIV prevalence among this population has also remained relatively stable since 2005 at approximately 0.5% [3]. Similar estimates are found from data of the population of blood donors at the Red Cross central blood bank of Thailand; these data represent Thai people who believe they are not at risk of HIV infection. The HIV prevalence in this population has reached a level of between <0.1% to 0.45% [3].

Prevalence among IDUs, MSM, FSW and clients of FSW

IDUs are the population group most affected by HIV in Thailand. The prevalence of HIV among IDUs attending detoxification clinics throughout Thailand is currently estimated to range between 30% and 40% [3]. HIV infection among MSM is also markedly higher than that observed in the general population, where HIV prevalence has varied between 17% and 31% during the period between 2007 and 2009. The most recent estimate of HIV prevalence among MSM in Bangkok was 25% during 2009 [3]. Extensive surveillance and HIV prevention strategies have been implemented for FSWs in Thailand and as a result there has been a steady decline in HIV incidence and prevalence in this population. The prevalence of HIV among FSWs is believed to be ~3% for direct FSWs (sex workers who are street- and brothel-based) and ~2% for indirect FSWs (sex workers who are based in entertainment-based establishments (e.g. beer houses, karaoke venues) and will engage in sex work as supplementary income). Less is known about clients of FSWs because they are not a readily identifiable group; as a result only very few HIV prevalence surveys have been conducted in this population. Recently, a study using a modified respondent-driven sampling technique has estimated the prevalence to be approximately 20% [4]. However, our model was calibrated to a lower estimate to account for probable selection bias. A summary of model-produced trajectories of prevalence along with available seroprevalence data for all sub-population groups and the entire population are shown in Figure A.

Figure A. HIV prevalence prior to vaccination in the model. Square points represent HIV seroprevalence data in Thailand where available [1,3,5,6]. Solid and dashed lines represent the median and interquartile ranges of the model-produced HIV prevalence trajectories that were obtained in the absence of vaccination from the set of parameters used in the model.



Model equations

For all population risk groups of people, we constructed a compartmental mathematical model to track the number of people in the relevant population who become infected with HIV and the extent of disease progression in people living with HIV. To monitor the extent of infection in the population and relative transmission levels, as well as accurately reflect antiretroviral treatment (ART) demand and use, the model categorizes the population into those who are not yet infected with HIV but potentially susceptible to acquiring infection and the population of people living with HIV are stratified by CD4 count groupings: CD4>500; 350<CD4<500; 200<CD4<350; CD4<200. People with HIV and a CD4 count below 350 are eligible for ART. The model tracks the number of people who initiate first-line ART, the rate of treatment failure and progression to second-line ART. The model includes rates at which people who are on second-line therapy may experience treatment failure, either through drug resistance or treatment breaks, but then may recommence a different drug regimen of therapy that effectively suppresses viral load. Most importantly for the investigation of vaccination, we further separate the entire population into vaccinated and unvaccinated populations. A schematic diagram of the structure of health states captured by the model is shown in Figure 1 in the main text. HIV/AIDS-related and other causes of death are also included in the model. The schematic diagram of the health states in the model can be translated into mathematical descriptions in the form of a coupled system of ordinary differential equations. One differential equation is developed for each of the 14 health states represented in Figure 1. These 14 equations are then applied (with appropriately different rates of acquiring infection and disease progression; see Table A) to each of the seven population groups, yielding a total of 14×7=98 ordinary differential equations. In all equations, we assume a background death rate (denoted by the symbol μ) and HIV-infected individuals have an additional HIV-related death rate (denoted by δ). The rate at which people enter the model, π, is equal to the total death rate to maintain a constant population size, and the force of infection, λ, is the rate at which individuals become infected (described in detail below).

The 14 base equations of the model that are applied to each of the population groups are provided below. The rate of change in the number of susceptible individuals over time is given by:

$$\frac{dS^{uv}}{dt} = \pi_i + \Omega S^v - (\mu + \lambda_i) S^{uv} \quad (1)$$

$$\frac{dS^{v}}{dt} = \pi_i - (\mu + \lambda_i + \Omega) S^{v} \quad (2)$$

where Ω is the rate at which vaccinated individuals lose protection due to waning, the subscript *i* refers to the population group, and the superscripts *uv* and *v* refer to unvaccinated and vaccinated populations, respectively.

If a previously uninfected person acquired infection, then they transition to a compartment defined as infected with CD4≥500, but untreated. The rate of change in the number of people in this compartment is represented by: ( )

—— (3)

We define the rate at which HIV-infected people with high CD4 counts (≥500) move into a lower CD4 category (350-500) by γ^I. The rate of change in the number of people in the infected with 350≤ CD4<500 but untreated compartment is given by:

( )

—— (4)

Similarly, the model tracks the rate of change in the numbers of people in the lower CD4 categories (200≤ CD4 <350 and CD4<200), which are also treatment eligible compartments, by the following expressions:

( )

—— ( ) (5)

—— (6)

The rate at which treatment is initiated is represented by τ. If viral load is undetectable, then it is assumed that immunological improvement will occur to higher CD4 categories, at rates denoted by γ^T, yielding the following equations for the number of people on treatment:

( ) ( )

—— ( ) ( ) (7)

—— ( ) (8)

—— ( ) (9)

—— (10)

To account for the chance of treatment failure (ϕ), our model tracks the estimated number of people who experience incomplete virological suppression. Additionally, after experiencing effective treatment with undetectable viral load, it is possible for people to experience treatment failure (viral rebound) and move from suppressed viral replication to the corresponding treatment failure compartments (at a rate of ρ). The rates of change in the numbers of people with incomplete virological suppression for each CD4 category are:

( )

—— ( ) (11)

—— ( ) (12)

—— ( ) (13)

—— (14)

It was assumed that people who experienced treatment failure or who stopped therapy were able to commence a second-line therapy and thus were allowed to move back to suppressed virus compartments at rates σ.

Probability of transmission

Each HIV-infection compartment in the model was associated with a viral load range (see Table A), which altered the transmission probability per act of sex (β_a) according to the following relationship,

$\beta_a = 2.45^{\log(a/b)}\beta_b$,

where the viral load associated with a particular HIV-infection compartment is denoted by a and the assumed baseline viral load from the chronic mid-stage of untreated infection is represented by b. Here, β_b represents the baseline transmission probability at the chronic mid-stage of

untreated infection, determined by whether it is male-to-female, female-to-male, male-to-male insertive or male-to-male receptive sex. The probability of infection per act, β_a, was then extended by means of a Bernoulli expression to estimate the probability of acquiring infection per discordant partnership involving n sexual acts and condoms used P % of the time (where condoms have an efficacy of ε_c). This expression for the probability of HIV acquisition per discordant sexual partner is given by

$$\beta_i = 1-(1-(1-q_{cir}\varepsilon_{cir})(1-\varepsilon_v)\beta_a)^{n_i(1-P_i)}((1-(1-\varepsilon_c))(1-q_{cir}\varepsilon_{cir})(1-\varepsilon_v)\beta_a)^{n_iP_i}) .$$

Here, we also add q_{cir} to represent the probability a man is circumcised and ε_{cir} to signify its efficacy in preventing transmission. Also, ε_v represents the efficacy of the vaccine in reducing the probability of HIV acquisition per exposure. The number of sexual acts and condom use varied according to partnership type.

The probability of HIV transmission through injecting practices was based on sharing and cleaning practices and the total annual probability of HIV acquisition over all injecting episodes was similarly modeled by a Bernoulli expression. This is presented by

$$\beta_{inject} = sq_{in}(1-(1-(1-p_{cl}\varepsilon_{cl})\beta_a^{IN}(1-\varepsilon_v))^{n_{in}} ,$$

where s represents the proportion of IDUs who share needles, and q_{in} denotes the proportion of injections that are shared. The baseline probability of transmission through injecting drugs is denoted by β_a^{IN}, and the HIV acquisition rate depends on the probability of cleaning, p_{cl}, and its efficacy, ε_{cl} as well as the vaccine efficacy, ε_v, for vaccinated IDUs. The baseline probability of transmission was assumed to differaccording to differences in viral load, denoted by the subscript, a.

Force of infection

The force of infection, λ, representing the per-capita rate of new HIV infections occurring in the susceptible population, and is expressed by the following equation:

$$\lambda_i = c_i^r \chi_i^r + c_i^c \chi_i^c .$$

The force of infection is based on the average number of casual and regular sexual contacts between the subgroups (denoted by c_i^c and c_i^r) and the chance of interacting with an infected individual and transmission occurring (denoted by χ_i^r and χ_i^c):

$$\chi_i = \frac{\beta_a^{i,vc} N_a^{i,vc}}{N_{tot}} \quad .$$

Here, $\beta_a^{i,vc}$ represents the transmission probability according to viral load, *a*, the partnership type, *i*, and vaccination group, *vc*. The average number of HIV-infected individuals a person interacts with is denoted by $N_a^{i,vc}$ and the total population is represented by N_{tot} .

The force of infection was expanded for IDUs by

$$\lambda_i = c_i^r \chi_i^r + c_i^c \chi_i^c + \chi^{IN} \quad ,$$

where χ^{IN} denotes the chance that a person becomes infected through injecting with a contaminated needle, and is represented by $\chi^{IN} = \frac{\beta_a^{IN} c_a}{c_{tot}^{IN}}$.

Here, *c*, represents the total number of HIV-infected IDUs in the model, and c_{tot}^{IN} the total number IDUs in the model.

Model optimization and calibration

Values for all parameters of the model were sourced from searches across the peer-reviewed literature, available government reports and other grey literature. Ranges of parameters were defined based on limits reported from different data sources and then these ranges were defined as bounds in a mathematical optimization routine. We used a trust-region-reflective algorithm to find the set of parameters within the pre-defined realistic ranges that optimally fits all available epidemiological data (prevalence for all population groups). Briefly, this gradient-descent method varies each parameter by a small amount (the "trust region"), calculates the change in goodness-of-fit resulting from each parameter variation, and keeps those parameter variations which improved the goodness-of-fit. This process is iterated until no changes in parameter values can be found that yield further improvements to the goodness-of-fit. The final set of calibrated parameter values obtained by this method are provided in Table A. To generate uncertainty in model outcomes, we assumed ±20% uncertainty in each parameter value and then sampled

parameter space using Latin hypercube sampling. We then ran 1000 parameter sets, sampled from these ranges and selected all sets that were acceptable fits to the prevalence data. The ranges of all included parameter values are indicated in Table A.

Table A. List of parameters

Abbreviations: low-risk male, LRM; low-risk female, LRF; male injecting drug user, MIDU; female injecting drug user, FIDU; female sex workers, FSW; male clients of sex workers, MC; men who have sex with men, MSM.

Parameter description		**Estimate used in our model**	**Reference**
Vaccine parameters			
Ω	Vaccine waning (per year)	72.24%	[7]
ε_v	Efficacy of vaccine	73.6%	[7]
κ	Vaccine coverage	0-100% (sensitivity analysis)	†
Demographic parameters		**Estimate used for initial model conditions. Median (IQR)**	
Population size	**Total population 15-64**	**46.1 million**	[8]
	Men (15-64 years)	**22.8 million**	[8]
	% MSM among men	5.0% = 1.1 million people	[9-12]
	% IDUs among men	1.1% = 239 892 people (238 411-24 1443)	[13-14]
	% Clients of FSWs among men	11.0% = 2.5 million people	[9, 15,16]
	% Other (low-risk) males	82.9% = 18.9 million people	
	Women (15-64 years)	**23.3 million**	[8]
	% IDUs among women	0.3% = 73 966 people (73 444-74 583)	[13-14]
	% FSWs among women	1.5% = 35 0016 people (34 9962-35 0095)	[9,]
	% Other (low-risk) females	98.2% = 22.9 million people	
q_{cir}	Percentage of men who are circumcised	12.3% (11.6-13.0%)	[17,18]
Biomedical parameters		**Estimate from calibrated parameter set. Median (IQR)**	
Sexual transmission			
β_a^m	Baseline male-to-female transmission probability (per act)	0.071% (0.066-0.075%)	[19-23]
β_a^w	Baseline female-to-male transmission probability (per act)	0.06% (0.057-0.064%)	[19-23]
β_a^{msm}	Baseline male-to-male transmission probability (per act) for insertive sex	0.08% (0.075-0.085%)	[19,21]
$\beta_a^{msm,r}$	Baseline male-to-male transmission probability (per act) for receptive sex	0.8% (0.75-0.85%)	[19,21,24]
w_P	Percentage of time an individual with CD4≥500 and not on treatment has Primary/Acute HIV Infection with higher viral load	10%	[20]
ε_{cir}	Efficacy of circumcision (per act)	0.50 (0.47-0.53)	[25-27]
ε_c	Efficacy of condoms (per act)	0.90 (0.86-0.94)	[28-30]
Rates of disease progression			

$1/\gamma_{500}^{I}$	Average time required for an untreated infected individual to progress from the CD4≥500 compartment to the 350≤CD4<500 compartment.	3.81 (3.58-4.03) years	[31] ‡
$1/\gamma_{350}^{I}$	Average time required for an untreated infected individual to progress from the 350≤CD4<500 compartment to the 200≤CD4<350 compartment.	1.81 (1.71-1.92) years	
$1/\gamma_{200}^{I}$	Average time required for an untreated infected individual to progress from the 200≤CD4<350 compartment to the CD4<200 compartment	1.80 (1.71-1.92) years	
$1/\gamma_{500}^{F}$	Average time required for an infected individual who is failing treatment to progress from the ≥500 compartment to the 350≤CD4<500 compartment.		[32] ¥
	LRM, MSM, MC	8.21 (7.71-8.69) years	
	LRF, FSW	5.81 (5.50-6.17) years	
	MIDU	5.89 (5.58-6.26) years	
	FIDU	4.06 (3.84-4.32) years	
$1/\gamma_{350}^{F}$	Average time required for an infected individual who is failing treatment to progress from the 350≤CD4<500 compartment to the 200≤CD4<350 compartment.		
	LRM, MSM, MC	3.04 (2.88-3.25) years	
	LRF, FSW	2.04 (1.93-2.17) years	
	MIDU	2.22 (2.11-2.37) years	
	FIDU	1.44 (1.37-1.53) years	
$1/\gamma_{200}^{F}$	Average time required for an infected individual who is failing treatment to progress from the 200≤CD4<350 compartment to the CD4<200 compartment.		
	LRM, MSM, MC	3.34 (3.17-3.55) years	
	LRF, FSW	1.43 (1.35-1.51) years	
	MIDU	2.47 (2.33-2.62) years	
	FIDU	1.52 (1.43-1.60) years	
$1/\gamma_{200}^{T}$	Average time required for a treated infected individual with suppressed viral load to progress from the CD4<200 compartment to the 200≤CD4<350 compartment	3.55 (3.36-3.78) years	[33] £
$1/\gamma_{350}^{T}$	Average time required for a treated infected individual with suppressed viral load to progress from the 200≤CD4<350 compartment to the 350≤CD4<500 compartment.	3.01 (2.84-3.20) years	

$1/\gamma_{500}^{T}$	Average time required for a treated infected individual with suppressed viral load to progress from the 350≤CD4<500 compartment to the CD4≥500 compartment	7.31 (6.88-7.74) years	
$\sigma_{<200}$	Percentage of infected individuals in the CD4<200 failed treatment compartment to recommence treatment and suppress virologically (per year).	93% (88-97%)	†
σ_{200}	Percentage of infected individuals in the 200≤CD4<350 failed treatment compartment to recommence treatment and suppress virologically (per year).	80% (75-85%)	
σ_{350}	Percentage of infected individuals in the 350≤CD4<500 failed treatment compartment to recommence treatment and suppress virologically (per year).	~5%	
σ_{500}	Percentage of infected individuals in the CD4≥500 failed treatment compartment to recommence treatment and suppress virologically (per year).	~5%	
ρ	Percentage of treated HIV-infected individuals who experience treatment failure (per year)	5-6%	[34]
ϕ	Percentage of people who receive treatment and experience initial treatment failure (incomplete virological suppression).	~3%	[35-38]
δ_{500}	Percentage of people with CD4≥500 who die each year (HIV-related)	0.035% (0.033-0.037%)	[39]
δ_{350}	Percentage of people with CD4 between 350 and 499 who die each year (HIV-related)	0.1% (0.095-0.106%)	
δ_{200}	Percentage of people with CD4 between 200 and 349 who die each year (HIV-related)	0.825% (0.779-0.87%)	
$\delta_{<200}$	Percentage of people with CD4≤200 who die each year (HIV-related)	7.77% (7.32-8.24%)	
μ	Percentage of people who die of non-HIV related death each year	0.49% (0.52-0.55%)	[5,8,40]
Biological			
v_{PI}	Average viral load at primary infection stage	~$10^{6.00}$ copies/ml	[41-43]
v_{CI}	Average viral load at chronic infection stage	~$10^{4.76}$ copies/ml	[41-44]
v_{TE}	Average viral load at treatment eligible stages	~$10^{5.74}$ copies/ml	[42]
v_{T}	Average viral load throughout treatment	~$10^{1.11}$ copies/ml	[45,46]
v_{F}	Average viral load when on a failed regimen	~$10^{5.74}$ copies/ml	Estimate
Injecting drugs use parameters			
β_{a}^{IN}	Baseline transmission probability of needle sharing (per event), if initial user is HIV-positive	0.50% (0.47-0.53%)	[47,48]

s	Percentage of IDUs who share needles	44.8% (42.3-47.4%)		[3,49]
q_{in}	Percentage of injections that are shared	19.8% (18.7-20.9%)		†
p_{cl}	Percentage of shared needles that are cleaned before re-use	70.2% (66.4-74.3%)		[3,50]
ε_{cl}	Efficacy of cleaning needles	75.7% (70.9-79.8%)		[51,52]
n_{in}	Number of injecting acts per IDU (per year)	237 (223-252)		[50,53]
Behavioural parameters				
P^r_{gm}, P^c_{gm}, P^r_{gf}, P^c_{gf}, P^r_{mc}, P^r_{fsw}	Percentage of acts in which condoms are used in regular and casual partnerships by low-risk male and females, and also by male clients and FSW in their regular partnerships. We assume higher percentage of condom use in all casual partnerships.	LRM (regular partnerships)	39.8% (37.5-42.2%	[3,54-56]
		LRM (casual partnerships)	59.9% (56.3-63.6%)	
		MC (regular partnerships)	39.8% (37.5-42.2%	†
		LRF (regular partnerships)	39.8% (37.5-42.2%	[3,54,57]
		LRF (casual partnerships)	50.0% (47.0-53.0%	
		FSW (regular partnerships)	45.3% (42.5-47.8%)	[3]
P^r_{mIDU}, P^r_{fIDU}, P^c_{mIDU}, P^c_{fIDU}	Percentage of acts in which condoms are used by IDUs	MIDU (regular partnerships)	40.1% (37.7-42.5%	[3]
		FIDU (regular partnerships)	30.2% (28.2-31.9%	
		MIDU (casual partnerships)	49.2% (46.3-52.4%	
		FIDU (casual partnerships)	37.2% (35.1-39.4%)	
P^r_{msm}, P^c_{msm}	Percentage of acts in which condoms are used by MSM	MSM (regular partnerships)	65.2 (61.4-68.9%)	[3,58-60]
		MSM (casual partnerships)	87.9% (83.1-91.5%)	
P^c_{fsw}, P^c_{mc}	Percentage of acts in which condoms are used between FSW and their clients	MC (casual partnerships)	44.8% (41.8-47.7%)	[3]
		FSW (casual partnerships)	74.2 (70.2-78.4%)	[3,61]
c_{gm}	Average number of partnerships (per year) for low-risk males	1.2 (1.13-1.27)		[4,6,12,54,56]
c_{mc}	Average number of partnerships (per year) for male clients	5.38 (5.05-5.67)		
c_{midu}	Average number of partnerships (per year) for male IDUs	1.84 (1.73-1.95)		
c_{msm}	Average number of regular partnerships that involve receptive or insertive sex per year for MSM	0.82 (0.78-0.87)		
n^c_{gm}, n^c_{gf},	Average number of acts per casual partnership (per year)	LRM	1.2 (1.1-1.3)	†
		LRF	1.1 (1.0-1.2)	
		MIDU	2.7 (2.5-2.8)	

n^c_{mIDU}, n^c_{fIDU}, n^c_{msm}, n^c_{fsw}, n^c_{mc}		FIDU	3.2 (3.0-3.4)
		MSM	1.0 (1.0-1.1)
		FSW	5.0 (4.7-5.3)
		MC	6.0 (5.6-6.3)
n^r_{gm}, n^r_{gf}, n^r_{mIDU}, n^r_{fIDU}, n^r_{fIDU}, n^r_{msm}, n^r_{fsw}, n^r_{mc}	Average number of acts per regular partnership (per year)	LRM	51 (48-54)
		LRF	51 (48-54)
		MIDU	93 (88-99)
		FIDU	95 (89-100)
		MSM	26 (25-28)
		FSW	100 (94-106)
		MC	149 (141-158)
$1/\tau_{GM}$, $1/\tau_{GF}$, $1/\tau_{MSM}$, $1/\tau_{FSW}$, $1/\tau_{MC}$	Average time to receive treatment when CD4 count is less than 350. The FSW estimate is based on the high organisation of this group, with several testing options and locations available	LRM	10-50 weeks
		LRF	13-49 weeks
		MSM	10-12 weeks
		FSW	~ 10 weeks
		MC	6-10 weeks
$1/\tau_{mIDU}$	Average time to receive treatment for MIDUs. We assume testing may not occur as regularly for IDUs.	$1/\theta \times 1/\tau_{GM}$	
$1/\tau_{fIDU}$	Average time to receive treatment for FIDUs	$1/\theta \times 1/\tau_{GF}$	
θ	Reduction factor in the rate at which IDUs seek treatment relative to other population groups	0.70 (0.66-0.74)	
$Pr_{GM,GF}$	Percentage of regular partnerships between low-risk males and females	93% (89-96%)	
$Pr_{MIDU,GF}$	Percentage of regular partnerships between MIDU and low-risk females	10% (9-11%)	
$Pr_{MC,GF}$	Percentage of regular partnerships between MC and low-risk females	93% (89-96%)	
$Pc_{GM,GF}$	Percentage of casual sexual mixing between low-risk males and females	93% (89-96%)	
$Pc_{MIDU,GF}$	Percentage of casual sexual mixing between MIDU and low-risk females	10% (9-11%)	
$Pc_{MC,GF}$	Percentage of casual sexual mixing between MC and low-risk females	54% (51-57%)	

† Experimental Parameter

‡ A summary of the relationship between HIV-1 RNA concentration and decline in $CD4^+$ count from the prospective study by Mellors et al. [31] is given below:

Plasma HIV-1 RNA concentration (*copies/mL*)	Mean decrease in $CD4^+$ T cell count per year (*cells/μL*)
≤ 500	-36.3 (-30.4,-42.3)
501-1 000	-44.8 (-39.1,-50.5)
3 001-10 000	-55.2 (-50.7,-59.8)
10 001-30 000	-64.8 (-59.6,□70.0)
> 30 000	-76.5 (-70.5,-82.9)

With these data, and assuming that the average viral load is $\sim 10^{4.87}$ copies per mL for people without treatment, the $CD4^+$ T cell count decreases by an average of 76.5 (70.5, 82.9) every year. To progress from the CD4≥500 compartment to the 350≤CD4<500 compartment we assume that the average CD4 count is 800 cells/μL after the 2-month acute phase of HIV infection and then declines at the constant rate of 76.5 (70.5, 82.9) cells/μL each year. Then the average time to progress through this compartment is 2/12 + 300/(76.5 (70.5, 82.9)) years; that is 4.09 (3.79, 4.42) years.

To progress through the 350≤CD4<500 and 200≤CD4<350 compartments, we assume an average loss of 150 CD4 cells. Then the average time to progress through both compartments is 150/(76.5 (70.5, 82.9)) years; that is 1.96 (1.81, 2.13) years.

¥: The relationship between the CD4 cell slope, and the patient HIV-1 RNA concentration, treatment information and demographic characteristics has been estimated by the PLATO Collaboration [32] and led to the following regression coefficients:

Covariates*	Change (95% CI) in CD4 count slope (cells per μL per year) - multivariate analysis
Age, per 10 years older	-6.7 (-12, -1.2)
Female	16.0 (-2.9, 35.0)
Infection via injecting drug use	-2.7 (-21,16.0)
Current viral load, per $\log_{10}$ copies per mL higher	-25.0 (-29.0, -20.0)
Current CD4 count per 100 cells per μL higher	2.2 (-2.3, 6.6)
Number of drugs, per additional drug	4.8 (0.22, 9.4)
Boosted PI	18.0 (7.0, 28.0)
Receiving ART (NNRTI)	-23.0 (-35.0, -11.0)
Hydroxyurea	-21.0 (-35.0, -5.8)

*Constant term for multivariate model 123(82, 162) cells per μL per year

For Thai people on treatment with detectable viral load, we assume their viral load is $\sim 10^{3.5}$ with a median age of 35 years. Using the multivariate model [32] the average immunological deterioration of an individual with virological failure was determined and applied to the model.

We assumed low-risk males, MSM, and male clients were infected through sexual interaction, and were on a boosted three-drug regimen including an NNRTI but without hydroxyurea. Therefore the following equation can be used to estimate the average CD4 slope from the compartment ≥500

123(82,164) – 6.7(-12.0, -1.2)*3.5 + 16(-2.9, 35.0)*0 – 2.7(-21,16.0)*0 – 25(-29.0, -20.0)*3.5
+ 2.2(-2.3, 6.6)*8 + 4.8(0.22, 9.4)*3 + 18(7.0,28.0)*1 – 23 (-35.0, -11.0)*1 - 21.0 (-35.0, -5.8)*0

That is, an average CD4 slope of approximately 300 $CD4^+$ cells at 39.05 (-107.24, 187.8) cells per μL per year to take approximately 7.68 (1.60, 13.76) years. The lower bound is equated from the distance between the average and the upper bound, because we assume a drop of CD4.

We assumed a similar scenario for low-risk females and FSWs:

123(82,164) – 6.7(-12.0, -1.2)*3.5 + 16(-2.9, 35.0)*1 – 2.7(-21,16.0)*0 – 25 (-29.0, -20.0)*3.5
+ 2.2(-2.3, 6.6)*8 + 4.8 (0.22, 9.4)*3 + 18(7.0,28.0)*1 – 23 (-35.0, 11.0)*1 - 21.0 (-35.0, -5.8)*0

That is, an average CD4 slope of 55.05 (-110.14, 222.8) cells per μL per year to take approximately 5.45 (1.35, 9.55) years to move from ≥500 compartment.

Immunological deterioration among male IDUs was assumed to be based on the following equation:

123(82,164) – 6.7(-12.0, -1.2)*3.5 + 16(-2.9, 35.0)*0 – 2.7(-21,16.0)*1 – 25 (-29.0, -20.0)*3.5
+ 2.2(-2.3, 6.6)*8 + 4.8 (0.22, 9.4)*3 + 18(7.0,28.0)*1 – 23 (-35.0, 11.0)*1 - 21.0 (-35.0, -5.8)*0

That is, an average CD4 slope of 36.35 (-128.24, 203.8) cells per μL per year to take approximately 8.25 (1.47, 15.03) years to move from ≥500 compartment.

Immunological deterioration among female IDUs was assumed to be based on the following equation:

123(82,164) – 6.7(-12.0, -1.2)*3.5 + 16(-2.9, 35.0)*1 – 2.7(-21,16.0)*1 – 25 (-29.0, -20.0)*3.5
+ 2.2(-2.3, 6.6)*8 + 4.8 (0.22, 9.4)*3 + 18(7.0,28.0)*1 – 23 (-35.0, 11.0)*1 - 21.0 (-35.0, -5.8)*0

That is, an average CD4 slope of 52.35(-131.14, 238.8) cells per μL per year to take approximately 5.73 (1.26, 10.20) years to move from ≥500 compartment.

We assumed corresponding CD4 slopes for the remaining compartments while assuming an average drop of 150 cells per μL between transitions.

£: Below is a summary of data from Mocroft et al (2007) [33] for changes in CD4 count over time among people who are on effective cART.

CD4 count at initiation of cART (cells per μL)	**Time since starting cART (years)**	**Rate of CD4 count increases per year (cells per μL) mean (95% CI)**
≤200	<1	76 (53-99)
	1-3	69 (63-76)
	3-5	50 (36-69)
	>5	32 (18-46)
201-350	<1	129 (91-166)
	1-3	50 (25-74)
	3-5	47 (24-69)
	>5	23 (2-44)
>350	<1	90 (37-144)
	1-3	50 (18-82)
	3-5	17 (-17-51)
	>5	21 (-12-54)

We use this data to estimate the average time to progress through our CD4 compartments whilst on effective cART. For people with undetectable viral load:

- For CD4 count increases from 0 to 200 cells per μL, average increases of 76 (53-99) cells per μL can be expected during the first year and then 69 (63-76) cells per μL during the second and third years. Therefore, it can be expected to take 2.80 (2.33-3.58) years to progress through this category.

- For CD4 count increases from 200 to 350 cells per μL, we have a 150 CD4 count increase. In this interval, the

CD4 count increases by 129 (91-166) cells per µL during the first year and then 50 (25-74) CD4 count during the second year. Therefore, it can be expected to take 1.42 (0.9-3.42) years to progress through this category.

- For CD4 count increases from 350 to 500 cells per µL, then we have a 150 CD4 count increase. In this interval, the CD4 count increases by 90 (37-144) cells per µL during the first year and then 50 (18-82) cells per µL during the second year. Therefore, it can be expected to take 2.20 (1.07-7.28) years to progress through this category.

References

[1] UNAIDS. UNAIDS report on the global AIDS epidemic. 2010. Available from: http://www.unaids.org/globalreport/

[2] WHO. Thailand's new condom crusade. *Bulletin of the World Health Organization*. 2010; **88**(6):401-480. Available from: http://www.who.int/bulletin/volumes/88/6/10-010610/en/

[3] National AIDS Prevention and Alleviation Committee. UNGASS Country progress report Thailand. Reporting period January 2008-December 2009. 2010. Available from: http://www.tncathai.org/data/data13.pdf

[4] Shah, N. S., Shiraishi, R. W., Subhachaturas, W., Anand, A., Whitehead, S. J., Tanpradech, S., et al. (2011). Bridging Populations-Sexual Risk Behaviors and HIV Prevalence in Clients and Partners of Female Sex Workers, Bangkok, Thailand 2007. *J Urban Health,* 2011.

[5] UNAIDS/WHO Working Group on Global HIV/AIDS and STI. Epidemiological fact sheet on HIV and AIDS. Core data on epidemiology and response. Thailand. 2008 Update. Geneva: UNAIDS/WHO; 2008. Available from: http://apps.who.int/globalatlas/predefinedReports/EFS2008/full/EFS2008_TH.pdf

[6] National AIDS Prevention and Alleviation Committee. UNGASS Country progress report Thailand. Reporting period January 2006-December 2007. 2008. Available from: http://data.unaids.org/pub/Report/2008/thailand_2008_country_progress_report_en.pdf

[7] Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *N Engl J Med* 2009;**361**(23):2209–20.

[8] Central Intelligency Agency. The World Factbook. Thailand. 2010. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/th.html

[9] Liu A, Kilmarx P, Jenkins RA, Manopaiboon C, Mock PA, Jeeyapunt S, et al. Sexual initiation, substance use, and sexual behavior and knowledge among vocational students in northern Thailand. *Int Fam Plan Perspect* 2006;**32**(3):126–35.

[10] van Griensven F, Kilmarx PH, Jeeyapant S, Manopaiboon C, Korattana S, Jenkins RA et al. The prevalence of bisexual and homosexual orientation and related health risks among adolescents in northern Thailand. *Arch Sex Behav* 2004;**33**(2):137–47.

[11] Beyrer C, Eiumtrakul S, Celentano DD, Nelson KE, Ruckphaopunt S, Khamboonruang C. Same-sex behavior, sexually transmitted diseases and HIV risks among young northern Thai men. *AIDS* 1995;**9**(2):171–6.

[12] Kitsiripornchai S, Markowitz LE, Ungchusak K, Jenkins RA, Leucha W, Limpitaks T, et al Sexual behavior of young men in Thailand: regional differences and evidence of behavior change. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;**18**(3):282–8.

[13] Aceijas C, Friedman SR, Cooper HL, Wiessing L, Stimson GV, Hickman M. Estimates of injecting drug users at the national and local level in developing and transitional countries, and gender and age distribution. *Sex Transm Infect* 2006;**82**(4):344.
[14] Wattana W, van Griensven F, Rhucharoenpornpanich O, Manopaiboon C, Thienkrua W, Bannatham R, et al. Respondent-driven sampling to assess characteristics and estimate the number of injection drug users in Bangkok, Thailand. *Drug Alcohol Depend* 2007;**90**(2-3):228–33.
[15] Kobori E, Visrutaratna S, Kada A, Wongchai S, Ono-Kihara M, Kihara M. Prevalence and Correlates of Sexual Behaviors Among Karen Villagers in Northern Thailand. *AIDS Behav* 2006;**11**(4):611-8.
[16] Jenkins RA, Torugsa K, Mason CJ, Jamroenratana V, Lalang C, Nitayaphan S, et al. HIV Risk Behavior Patterns Among Young Thai Men. *AIDS Behav* 1999;**3**(4):335-46.
[17] Castellsague, X, Peeling RW, Franceschi S, de Sanjose S, Smith, JS, Albero G, et al. Chlamydia trachomatis infection in female partners of circumcised and uncircumcised adult men. *Am J Epidemiol* 2005;**162**(9):907-16.
[18] Tieu HV, Phanuphak N, Ananworanich J, Vatanparast R, Jadwattanakul T, Pharachetsakul N, et al. Acceptability of male circumcision for the prevention of HIV among high-risk heterosexual men in Thailand. *Sex Transm Dis*, 2010;**37**(6):352-5.
[19] Gouws E, White PJ, Stover J, Brown T. Short term estimates of adult HIV incidence by mode of transmission: Kenya and Thailand as examples. *Sex Transm Infect* 2006;**82**(3):iii51-55.
[20] Leynaert B, Downs AM, de Vincenzi I. Heterosexual Transmission of Human Immunodeficiency Virus: Variability of Infectivity throughout the Course of Infection. *Am J Epidemiol* 1998;**148**(1):88-96.
[21] Mastro TD, de Vincenzi I. Probabilities of sexual HIV-1 transmission. *AIDS* 1996;**10**(suppl A):S75-S82.
[22] Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001;**357**(9263):1149-53.
[23] Padian NS, Shiboski SC, Glass SO, Vittinghoff E. Heterosexual transmission of human immunodeficiency virus (HIV) in northern California: results from a ten-year study. *Am J Epidemiol* 1997;**146**(4):350-7.
[24]Grant RM., Wiley JA, Winkelstein W. Infectivity of the Human Immunodeficiency Virus: Estimates from a Prospective Study of Homosexual Men. *The Journal of Infectious Diseases,* 1987;**156**(1):189-93.
[25] Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. *PLoS Medicine* 2005;**2**(11): 1112–22.
[26] Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007;**369**(9562):643–656.
[27] Gray R, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda, F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007;**369**(9562): 657–66.
[28] Cayley WE Jr. Effectiveness of condoms in reducing heterosexual transmission of HIV. *Am Fam Physician* 2004;**70**(7):1268–9.
[29] Weller SC, Davis-Beaty K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database of Systematic Reviews* 2002;**1**. Art. No.: CD003255. DOI: 10.1002/14651858.CD003255.

[30] Varghese B, Maher JE, Peterman TA, Branson BM, Steketee RW. Reducing the risk of sexual HIV transmission: quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. *Sex Transm Dis* 2002;**29**(1): 38–43.
[31] Mellors JW, Muñoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997;**126**(12):946–54.
[32] Ledergerber B, Lundgren JD, Walker AS, Sabin C, Justice A, Reiss P, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet* 2004;**364**(9428):51–62.
[33]Mocroft A, Phillips AN, Gatell J, Ledergerber B, Fisher M, Clumeck N et al. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. *Lancet* 2007;**370**(9585):407–13.
[34] Smith CJ, Phillips AN, Hill T, Fisher M, Gazzard B, Porter K, et al. The Rate of Viral Rebound after Attainment of an HIV Load <50 Copies/mL According to Specific Antiretroviral Drugs in Use: Results from a Multicenter Cohort Study. *Journal of Infectious Diseases,* 205;**192**(8):1387-97.
[35] Badri M, Lawn S, Wood R. Utility of CD4 cell counts for early prediction of virological failure during antiretroviral therapy in a resource-limited setting. *BMC Infect Dis* 2008;**8**(89).
[36] Phillips, A. N., Staszewski, S., Weber, R., Kirk, O., Francioli, P., Miller, V., et al. HIV Viral Load Response to Antiretroviral Therapy According to the Baseline CD4 Cell Count and Viral Load. *JAMA* 2001;**286**(20):2560-67.
[37] Robbins, G. K., Johnson, K. L., Chang, Y., Jackson, K. E., Sax, P. E., Meigs, J. B., et al. Predicting virologic failure in an HIV clinic. *Clin Infect* Dis 2010;**50**(5):779-86.
[38] Ledergerber, B., Egger, M., Opravil, M., Telenti, A., Hirschel, B., Battegay, M., et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. *Lancet* 1999;**353**(9156):863-8.
[39] Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, MacArthur RD, et al. (2008). CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *Aids* 2008;**22**(7):841-8.
[40] World Health Organization. Mortality Country Fact Sheet 2006. Available from: http://www.who.int/whosis/mort/profiles/mort_searo_tha_thailand.pdf
[41] Richardson BA, Mbori-Ngacha D, Lavreys L, John-Stewart GC, Nduati R, Panteleeff DD. Comparison of Human Immunodeficiency Virus Type 1 Viral Loads in Kenyan Women, Men, and Infants during Primary and Early Infection. *J Virol* 2003;**77**(12):7120–3.
[42] Simon V, Ho DD, Karim QA. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* 2006;**368**(9534): 489–504.
[43] Sarr AD, Eisen G, Guèye-Ndiaye A, Mullins C, Traoré I, Dia MC et al. Viral dynamics of primary HIV-1 infection in Senegal, West Africa. *J Infect Dis* 2005;**191**(9):1460–7.
[44] Rangsin R, Chiu J, Khamboonruang C, Sirisopana N, Eiumtrakul S, Brown AE et al. The natural history of HIV-1 infection in young Thai men after seroconversion. *J Acquir Immune Defic Syndr* 2004;**36**(1):622–9.
[45] Anekthananon T, Ratanasuwan W, Techasathit W, Sonjai A, Suwanagool S. Safety and efficacy of a simplified fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIR) for the treatment of advanced HIV-infected patients: a 24-week study. *J Med Assoc Thai* 2004;**87**(7):760–7.
[46] Yozviak JL, Doerfler RE, Woodward WC. Effectiveness and tolerability of nevirapine, stavudine, and lamivudine in clinical practice. *HIV Clin Trials* 2001;**2**(6):474–6.

[47]Hudgens, MG, Longini IM Jr, Halloran ME, Choopanya K, Vanichseni S, Kitayaporn D, et al. Estimating the Transmission Probability of Human Immunodeficiency Virus in Injecting Drug Users in Thailand. *Applied Statistics* 2001;**50**(1):1–14
[48] Kaplan EH, Heimer R. A Model-Based Estimate of HIV Infectivity via Needle Sharing. *JAIDS,* 1992;**5**(11):1116-1118.
[49] Perngmark P, Celentano DD, Kawichai S. Needle sharing among southern Thai drug injectors. *Addiction* 2003;**98**(8):1153–61.
[50] Perngmark P, Celentano DD, Kawichai S. Risk factors for HIV infection among drug injectors in southern Thailand. *Drug Alcohol Depend* 2003;**71**(3):229–38.
[51] Abdala N, Gleghorn AA, Carney JM, Heimer R. Can HIV-1-contaminated syringes be disinfected? Implications for transmission among injection drug users. *J Acquir Immune Defic Syndr* 2001;**28**:487–94.
[52] Abdala N, Crowe M, Tolstov Y, Heimer R. Survival of human immunodeficiency virus type 1 after rinsing injection syringes with different cleaning solutions. *Subst Use Misuse* 2004;**39**:581–600.
[53] Vanichseni S, Kitayaporn D, Mastro TD, Mock PA, Raktham S, Des Jarlais DC, et al. Continued high HIV-1 incidence in a vaccine trial preparatory cohort of injection drug users in Bangkok, Thailand. *AIDS* 2001;**15**(3): 397–405.
[54] Rongkavilit C, Naar-King S, Chuenyam T, Wang B, Wright K, Phanuphak P. Health risk behaviors among HIV-infected youth in Bangkok, Thailand. *J Adolesc Health* 2007;**40**(4):358 e1–8.
[55] Janepanish P, Dancy BL, Park C. (2011). Consistent condom use among Thai heterosexual adult males in Bangkok, Thailand. *AIDS Care* 2011;**23**(4):460-466.
[56] United Nations Development Programme. *Thailand's response to HIV/AIDS: progress and challenges*. New York: UNDP; 2004. Available from: http://www.undp.or.th/download/HIV_AIDS_FullReport_ENG.pdf
[57] Allen DR, Carey JW, Manopaiboon C, Jenkins RA, Uthaivoravit W, Kilmarx PH, et al. Sexual health risks among young Thai women: implications for HIV/STD prevention and contraception. *AIDS Behav.* 2003;**7**(1):9-21.
[58] Centers for Disease Control and Prevention. *HIV prevalence among populations of men who have sex with men--Thailand, 2003 and 2005.* In: MMWR Morb Mortal Wkly. Atlanta: CDC; 2006. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5531a2.htm
[59] Mansergh G, Naorat S, Jommaroeng R, Jenkins RA, Stall R, Jeeyapant S et al. Inconsistent condom use with steady and casual partners and associated factors among sexually-active men who have sex with men in Bangkok, Thailand. *AIDS Behav* 2006;**10**(6):743–51.
[60] Colby DJ. HIV knowledge and risk factors among men who have sex with men in Ho Chi Minh City, Vietnam. *J Acquir Immune Defic Syndr.* 2003;**32**(1):80-85.
[61] Buckingham RW, Moraros J, Bird Y, Meister E, Webb NC. Factors associated with condom use among brothel-based female sex workers in Thailand. *AIDS Care* 2005;**17**(5):640–7.