ORIGINAL RESEARCH ARTICLE

Hypogonadism among HIV-infected men in Thailand

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Summary: This study assessed prevalence and associated factors of hypogonadism among 491 HIV-infected Thai men who visited the HIV outpatient clinic. All participants were interviewed and data were collected from medical records, including demographic and HIV-related illness characteristics. They also completed questionnaires relevant to hypogonadal symptoms, sexual function and depression. All participants' blood samples were obtained to check for total testosterone, sex hormone-binding globulin (SHBG) and albumin levels, and free testosterone (cFT) was calculated. Hypogonadism was diagnosed if a cFT level of <0.225 nmol/L was detected. The median age of the participants was 37 years old (ranging from 34 to 44 years old). HIV infection was diagnosed for a median of 77 (47–99) months. Eight of 491 participants (2%) had hypertension and 1% had diabetes mellitus (DM). Fourteen (3%) used methadone and 23% had SHBG level over 70 nmol/L. Of the 491 participants, 123 (25%) men were diagnosed with hypogonadism. The univariate analyses indicated that DM, hypertension, methadone use, SHBG level >70 nmol/L group and lack of antiretroviral therapy were associated with hypogonadism. In multivariate analysis, a SHBG level >70 nmol/L was the only factor that was significantly associated with hypogonadism (odds ratio [OR] $= 1.922$, $P = 0.007$).

Keywords: HIV, AIDS, men, hypogonadism, prevalence, free testosterone, SHBG, Thailand

INTRODUCTION

Hypogonadism has previously been studied among HIV-infected men, as well as other endocrine disorders including hypothyroidism, adrenal insufficiency, hypercortisolism, diabetes mellitus (DM) or dyslipidaemia. Hypogonadism can cause bothersome clinical manifestations for HIV-infected men such as sexual dysfunction, fatigue, depressive mood, sleep problems, decrease in muscular strength and lean body mass, diminished bone mineral density, dyslipidaemia and anaemia.[1] Some studies reported that hypogonadism was the most frequent endocrine disorder in men with AIDS.[2,3] Hypogonadism was found in up to 50% of AIDS patients in the pre-highly active antiretroviral therapy (pre-HAART) era and was related to HIV-associated wasting and advanced stage of AIDS.[2,4] During the era after HAART, the prevalence of hypogonadism decreased to 19–25% but it still remained higher than the previous reports in American men of the same age.[3,5,6] The predictors of hypogonadism in HIV-infected men are not well defined and may be HIV infection itself, concurrent opportunistic infections, malnutrition or medications such as methadone, morphine sulphate, ketoconazole, megestrol acetate, glucocorticoids and anabolic steroid.[3,7,8] Determining the prevalence and associated factors for hypogonadism among HIV-infected men is important, because it results in many clinical sequelae and deterioration in the quality of life.[1] The aim of the present study was to determine the prevalence and associated factors of hypogonadism among HIV-infected Thai men.

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MATERIALS AND METHODS

The design of the present study was an observational descriptive cross-sectional study. The sample size for prevalence estimation was calculated by the following formula:

$$n = \frac{(Z_{\alpha/2})^2 pq}{d^2}$$

where n is the minimum sample size required; P the estimated prevalence of hypogonadism $= 0.25$; $q = 1 - P = 0.75$; d the acceptable error $= 0.04$; and α is the probability of type I error $= 0.05$.

$Z_{\alpha/2} = Z_{0.025} = 1.96$

$$\frac{(1.96)^2 \times 0.25 \times 0.75}{(0.04)^2}$$

$n = 450$ cases.

After obtaining approval from the Ethics Committee for Research in Human Subjects, Department of Disease Control, the present study was carried out between August 2007 and May 2008 at Bamrasnaradura Infectious Diseases Institute. The study sample included 491 HIV-infected Thai men (age ≥18 years) who visited the HIV outpatient clinic with evidence of HIV infection (confirmed positive ELISA and documented history of measureable HIV-RNA) during the period of this study. Patients were excluded if they had a learning disability (including dyslexia), acute severe illness, or androgen replacement therapy prior to or during the study period. After obtaining informed consent, each participant was interviewed and the information was recorded in the designed record forms, including age, current tobacco use, current alcohol use, physical exercise, current illicit drug use and current psychiatric illness.

The enroled patients' medical records were retrieved and reviewed for data including duration of HIV infection, current fasting cholesterol and triglyceride levels, current CD4 cell count, current plasma HIV-1 RNA, peak HIV-1 RNA, Center for Disease Control (CDC) clinical category, current medical history (DM, hypertension, stroke, seizure, myocardial infarction), any previous HIV-related illness, current opportunistic infection-related drug use, current receipt of antiretroviral therapy (ART), current body mass index (BMI) and the diagnosis of lipodystrophy (when the participants and treating physician agreed that peripheral lipoatrophy and central lipohypertrophy had occurred). Participants who had history of abnormal symptoms or signs of the testes were examined for further investigation if indicated by the physicians or urologists and the report returned to the authors.

Participants were asked to complete questionnaires that consisted of three parts. The first part was an aging males' symptom (AMS) questionnaire, which was developed to assess severity of symptoms of hypogonadism or partial androgen deficiency in ageing men (PADAM). The total score over 26 indicated positive hypogonadism symptoms.[9] The AMS questionnaire was culturally and linguistically validated from English into Thai with good correlation.[10] The second part was a bridged five-item version of the International Index of Erectile Function (IIEF), also known as the Sexual Health Inventory for Men (SHIM). A classification-tree analysis suggested an optimal cut-off score of 21 or less for diagnosis of erectile dysfunction (ED) (sensitivity = 0.98, specificity = 0.88) for the clinical trial patients from the USA and UK.[11] The participants were classified as having ED if they had an SHIM total score less than 22.[11] The Thai version of IIEF was used similar to the study of prevalence of ED in Thailand by Thai ED epidemiological study group.[12] The third part was a Thai Hospital Anxiety and Depression Scale (Thai HADS) for evaluation of depression. The participants who had a total score higher than 10 calculated from all the even numbered questions of the 14 measurement items were considered to be depressed.[13]

Blood samples were obtained between 8:00 and 11:00 hours to measure total testosterone, sex hormone-binding globulin (SHBG) and albumin levels. The assays were performed all in the laboratory of the King Chulalongkorn memorial hospital. The electrochemiluminescence immunoassay (ECLIA) was intended for use on Elecsys and Cobas Immunoassay Analyzers (Roche Diagnostic Systems, Indianapolis, IN, USA) to determine serum total testosterone (normal range 9.6–28.8 nmol/L) and SHBG levels (normal range 14.5–48.4 nmol/L). Calculated value of free testosterone (cFT) was derived by putting the data of serum total testosterone, SHBG and albumin levels into the calculator in www.issam.ch/freetesto.htm. Hypogonadism was diagnosed as a calculated free testosterone level of less than 0.225 nmol/L according to the standards, guidelines and recommendations of The International Society for the Study of the Aging Men (ISSAM).[14,15] According to ISSAM, a deficiency in serum testosterone levels is defined by the level below the young healthy adult male reference range. This is the same definition for diagnosis of hypogonadism according to the Endocrine Society clinical practice guideline by Bhasin *et al.*[16]

The prevalence of hypogonadism was reported. Descriptive statistics were presented in contingency tables for categorical variables and continuous variables. For non-normally distributed data of continuous variables, median and range were reported. Univariate analysis to compare variables between the patients with and without hypogonadism was performed using Chi-squared or Fisher's exact test as appropriate. For continuous variables, *t*-tests or non-parametric counterparts were used depending upon observed distributions. Multivariable logistic regression analysis was used to assess the strength of association of potential associated factors for hypogonadism. The variables in the multivariable logistic regression analysis comprised the variables with a P value ≤ 0.05 from the univariate analysis. The P value < 0.05 indicates statistical significance.

RESULTS

A total of 491 HIV-infected Thai men were enroled. The descriptive characteristics of the participants are shown in Table 1. The median age of the participants was 37 (range 34–44) years of age. Participants had known of their seropositivity for a median of 77 (range 47–99) months. Of 491 participants, 0.8% had DM, 1.6% had hypertension and 25.5% had diagnosed lipodystrophy. Fourteen of 491 participants (2.9%) used methadone and 2.6% used antidepressant drugs. Of 491 participants, 114 (23.2%) had a SHBG level over 70 nmol/L. Among the 491 HIV-infected participants, 459 (93.5%) men were receiving ART.

Out of the 491 participants in this study, 123 (25.0%, 95% confidence interval (CI) 21.3–29.2) were diagnosed with hypogonadism due to a cFT level ≤0.225 nmol/L. The median (range) of serum total testosterone was 19.1 (13.4–25.5) nmol/L. The univariate analyses of factors associated with hypogonadism are also shown in Table 1. The factors, including DM, hypertension, methadone use, SHBG level >70 nmol/L group and not currently receiving ART were associated with hypogonadism ($P \leq 0.05$). The authors also examined currently receiving ART according to non-nucleoside reverse transcriptase inhibitors-based (NNRTI-based), protease inhibitor-based (PI-based) and individual ARV drugs such as ritonavir, indinavir, lopinavir, efavirenz, nevirapine, didanosine, tenofovir, zidovudine, lamivudine or stavudine but found no correlation ($P > 0.05$). HIV-related illnesses were studied and categorized into pulmonary tuberculosis, extra-pulmonary tuberculosis, *Pneumocystis jiroveci* pneumonia, cytomegalovirus disease or toxoplasmosis of the brain. However, the results showed that such illnesses had no relation to hypogonadism. Almost all of these illnesses were inactive conditions. Current opportunistic infection-related drug use including fluconazole,

Table 1 **Characteristics and univariate analyses of HIV-infected Thai men with or without hypogonadism**

Factor	Total (n = 491)	Hypogonadism (n = 123)	Non-hypogonadism (n = 368)	P value
Age, years; median (range)	37 (34–44)	39 (35–43)	38 (34–44)	0.516
Duration of known HIV infection, month; median (range)	77 (47–99)	80 (47–100)	77 (45–99)	0.765
Body mass index, kg/m^2; median (range)	21.9 (20.1–23.9)	22.1 (19.9–23.5)	21.8 (20.1–24)	0.645
Current tobacco use; n (%)	162 (32.9)	44 (35.8)	118 (32.1)	0.258
Current alcohol consumption; n (%)	151 (30.8)	31 (25.2)	120 (32.6)	0.075
Current physical exercise; n (%)	369 (75.2)	88 (71.5)	281 (76.4)	0.171
Illicit drug use; n (%)	30 (6.1)	6 (4.9)	24 (6.5)	0.339
Methadone use; n (%)	14 (2.9)	9 (7.3)	5 (1.4)	0.002
Antidepressant use; n (%)	13 (2.6)	3 (2.4)	10 (2.7)	0.583
DM; n (%)	4 (0.8)	3 (2.4)	1 (0.3)	0.050
Hypertension; n (%)	8 (1.6)	5 (4.1)	3 (0.8)	0.026
Psychiatric illness; n (%)	15 (3.1)	6 (4.9)	9 (2.4)	0.146
Lipodystrophy; n (%)	125 (25.5)	37 (30.1)	88 (23.9)	0.108
Cholesterol, mg/dL; median (range); $n = 13$	193 (168–223)	211 (175–241)	221 (206–295)	0.414
Triglycerides, mg/dL; median (range); $n = 13$	168 (105–266)	263 (232–323)	313 (213–452)	0.940
Current CD4 cell count; median (range); $n = 468$	320 (200–462)	321 (189–456)	318 (207–460)	0.811
Current CD4 cell count <200 cells/mm^3; n (%), $n = 468$	113 (24.1)	29 (25.4)	84 (23.7)	0.399
Current plasma HIV-1 RNA <50 copies/mL; n (%), $n = 417$	364 (87.3)	79 (84.0)	285 (88.2)	0.183
Peak plasma HIV-1 RNA level; median (range), $n = 417$	157 (50–105,000)	54 (50–75,700)	281 (50–130,000)	0.296
SHBG level median (range)	42.0 (29.4–67.1)	46.0 (30.6–85.1)	41.8 (29.3–64.2)	0.059
SHBG level >70 nmol/L; n (%)	114 (23.2)	43 (35.0)	71 (19.3)	<0.001
CDC				0.095
				0.005
Stage A; n (%)	184 (37.5)	56 (45.5)	128 (34.8)	
Stage B; n (%)	99 (20.1)	20 (16.3)	79 (21.5)	
Stage C; n (%)	208 (42.4)	47 (38.2)	161 (43.8)	
Currently receiving ART; n (%)	459 (93.5)	108 (87.8)	351 (95.4)	
HIV-related illness; n (%)	254 (51.7)	56 (45.5)	198 (53.8)	0.069
Current opportunistic infection-related drug use; n (%)	42 (8.5)	7 (5.7)	35 (9.5)	0.128
Hypogonadism by total score of AMS > 26; n (%)	357 (72.7)	96 (78.0)	261 (70.9)	0.076
ED by total score of SHIM <22; n (%)	130 (26.5)	30 (24.4)	100 (27.2)	0.315
Depression by positive Thai HADS; n (%)	22 (4.5)	7 (5.7)	15 (4.1)	0.300

DM = diabetes mellitus; SHBG = sex hormone-binding globulin; CDC = Centers for Disease Control and Prevention; ART = antiretroviral therapy; AMS = ageing mens' symptom; ED = erectile dysfunction; SHIM = Sexual Health Inventory for Men; HADS = Hospital Anxiety and Depression Scale

cotrimoxazole and antituberculosis drugs (isoniazid, rifampicin pyrazinamide, ethambutol) were separately analysed and also indicated no association with hypogonadism.

The multivariate analyses of the selected factors with their odds ratio (OR), 95% CI and P values are shown in Table 2. The SHBG level >70 nmol/L was the only factor that was significantly associated with hypogonadism (OR = 1.922, $P = 0.007$).

The data collection by using the AMS questionnaire indicated that 72.7% of all participants had hypogonadism symptoms, with a sensitivity level of 78.0%, specificity of 29.1%, positive predictive value of 26.9% and negative predictive value of 79.9%. There was no correlation between hypogonadism and positive hypogonadism symptoms.

Out of 491 participants, 130 (26.5%) were diagnosed with ED by total score of SHIM <22. There was no correlation between ED and hypogonadism. Of 491 participants, 22 (4.5%) had depression indicated by positive Thai HADS but no correlation was found between depression and hypogonadism.

DISCUSSION

The prevalence of hypogonadism among HIV-infected Thai men in the present study is 25%. This rate of hypogonadism in the HAART era is lower than the rates in the previous studies conducted in the pre-HAART era by Dobs *et al.* (50%),[4] Raffi *et al.* (29%)[17] and Grinspoon *et al.* (49%).[18] The first two aforementioned studies diagnosed hypogonadism by determining total testosterone levels which might even underestimate the prevalence of hypogonadism[3] but Grinspoon *et al.*[18] used free testosterone levels which were recommended according to increased SHBG levels in HIV-infected patients.[3] The reduction in the prevalence of hypogonadism in the present study is comparable with the findings of other studies in the HAART era, including studies by Berger *et al.* (17%),[5] Rietschel *et al.* (19%),[3] Fisher *et al.* (20%),[6] Crum *et al.* (17%)[19] and Rochira *et al.* (16%).[20] The availability of HAART leading to a lower prevalence of hypogonadism is expected to be related to the reduction in the number of patients with advanced HIV/AIDS. However, hypogonadism remains a significant problem even among the patients in the early stages of HIV infection, particularly when the prevalence is still higher than the average rate for the general population.[1] Kaufman and Vermeulen[21] found only one subnormal serum testosterone in 105 non HIV-infected men aged 20–40 years old. Araujo *et al.*[22] reported 4.1% of the age-specific prevalence of hypogonadism in general population aged 40–49 years old. By comparison, the present study indicated that the prevalence of hypogonadism in HIV-infected men was higher than that of the general population at the same age. These findings propose that serum testosterone might begin to decrease at an early age in HIV-infected men. This conclusion is similar to the finding of Rochira *et al.*[20]

In the present study, although the median SHBG level (42 nmol/L) of the participants was within the normal range;

Table 2 **Multivariate analyses of HIV-infected Thai men with or without hypogonadism**

Factors	Univariate analysis			Multivariate analysis		
	COR	95% CI	*P* value	AOR	95% CI	*P* value
SHBG level >70 nmol/L	2.248	1.431–3.534	<0.001	1.922	1.200–3.080	0.007
Methadone use	5.732	1.883–17.449	0.002	2.971	0.880–10.026	0.079
Currently receiving ART	0.349	0.169–0.721	0.005	0.472	0.212–1.054	0.067
Hypertension	5.155	1.214–21.897	0.026	3.855	0.823–18.065	0.087
DM	9.175	0.945–89.034	0.050	7.469	0.702–79.495	0.096

COR = crude odds ratio; AOR = adjusted odds ratio; CI = confidence interval; SHBG = sex hormone-binding globulin; ART = antiretroviral therapy; DM = diabetes mellitus

however, 23.2% of participants were found to have the SHBG level over 70 nmol/L, which was significantly a predictive factor for hypogonadism in HIV-infected Thai men. SHBG is the major binding protein for testosterone, primarily synthesized in the liver as well as in breast or prostatic tissue and it renders testosterone unavailable to most tissues. In total, 60–69% of total testosterone is tightly bound to SHBG, 30–38% of total testosterone is loosely bound to albumin and 1–2% of testosterone is unbound (free testosterone). The last two previously stated types of testosterone (albumin-bound and free testosterone) are called bioavailable testosterone, which is metabolically active.[23] Specifically, SHBG levels increase with ageing, hepatic cirrhosis, hyperthyroidism, anticonvulsant use and HIV infection, causing decline of circulating albumin-bound and free testosterone, resulting in hypogonadism.[24] This result of increase in SHBG level in the present study is supported by Martin *et al.*[25] The participants with SHBG levels over 70 nmol/L had 1.9 times the risk of being diagnosed with hypogonadism than those participants without.

The study by Martin *et al.*[25] reported increased SHBG levels among HIV-infected men. Based on the study, they advised the measurement of free testosterone or bioavailable testosterone in these patients. The previous study of Rietschel *et al.*[3] reported that SHBG level was highly associated with total testosterone level but not with free testosterone level and they found no association between SHBG levels and free testosterone levels. In contrast, Wasserman *et al.*[26] reported reduction in testosterone and SHBG levels in three men with AIDS wasting and hypogonadism after prolonged exposure to testosterone and oxandrolone. They concluded that first pass metabolism of orally administered oxandrolone might decrease hepatic synthesis of SHBG, allowing exogenously supplied testosterone to be excreted. The reduction in SHBG levels was the oxandrolone side-effect.

There were 14 participants with positive HBsAg, 21 participants with positive anti-HCV and only one participant with positive HCV RNA in this study. SHBG levels were grouped according to these hepatitis profiles. In analysis, the authors found no correlation between SHBG levels and hepatitis profiles. The present study also assessed possible predictors of high SHBG levels in HIV-infected men and found that a low body mass index (BMI) was the only significant predictive factor. Further studies should be required for identification of the potential associated factors of high SHBG levels in HIV-infected men.

In the general population, the most widely accepted parameter to establish the presence of hypogonadism is the measurement of serum total testosterone (TT). But serum TT level would not be adequate in the diagnosis of hypogonadism in HIV-infected men. This is because the present study reported a significant association between high SHBG levels and hypogonadism. The median (range) of SHBG levels of all participants (42.0 [29.4–67.1] nmol/L) was significantly ($P < 0.001$) higher than the median (range) of SHBG levels of the laboratory reference range of healthy men (29.9 [14.5–48.4] nmol/L). The rise in SHBG levels among these men made it impossible to identify a decrease in TT level, resulting in an underestimation of hypogonadism diagnosis. This study also assessed prevalence and associated factors of hypogonadism using a TT level of less than 10.4 nmol/L as the reference method. The median (range) of SHBG levels in hypogonadal men (30.3 [20.2–37.8] nmol/L) was significantly ($P < 0.001$) lower than the median (range) of SHBG levels of eugonadal men (45.8 [31.7–71.0] nmol/L). When grouping the patients with SHBG levels of more than 70 nmol/L, we found six of 58 cases or 10.3% of the patients had hypogonadism and 108 of 433 cases (24.9%) had eugonadism. We also found that SHBG levels increase significantly in association with rising TT levels. These findings caused a reduction in hypogonadal cases from 123 cases to 58 cases and the prevalence of hypogonadism decreased from 25% to 12%. In multivariate analysis, SHBG levels were the only significant protective factors of hypogonadism. (OR = 0.766, $P < 0.001$). Then if TT levels were used in the diagnosis of hypogonadism among HIV-infected men, physicians should be cautious about underestimation of the prevalence of hypogonadism and unusual SHBG hypogonadism correlation. In 2010, Moreno-Pérez *et al.*[27] found that the median SHBG level among HIV-infected men was significantly higher than the reference population of eugonadal healthy men. They also validated the determination of serum TT level of less than 10.4 nmol/L for hypogonadism diagnosis in HIV-infected men using calculation of free testosterone (cFT) as the reference method, and TT levels had a sensitivity of 25% in the diagnosis of hypogonadism. They concluded that TT level was not useful in the diagnosis of hypogonadism in HIV-infected men. The present study also validated the determination of serum TT level of less than 10.4 nmol/L for hypogonadism diagnosis in similar patients using cFT as the reference method and found a sensitivity of 43.9%. According to the result, TT levels might not be useful in the diagnosis of hypogonadism in HIV-infected men. Dubé *et al.*[28] studied effects of potent ART on free testosterone levels and fat-free mass in HIV-infected men. Their data support obtainment of free testosterone levels when hypogonadism is suspected in patients with conditions such as HIV infection, which SHBG levels are commonly elevated.

There was no association between CDC clinical category, CD4 cell count or HIV-related illness and hypogonadism. This result is similar to the other studies in the HAART era.[3,5,6] The advent of HAART might result in the reduction of cases associated with end-stage AIDS such as low CD4 cell count, HIV-related illness and advanced CDC clinical category.

In 2007, Crum *et al.* found that increasing age and BMI were risk factors and smoking was protective factor of hypogonadism in HIV-infected men.[19] These results were different from the present study and cannot be comparable because Crum *et al.* used total testosterone level for diagnosing hypogonadism. In contrast with the report of Moreno-Pérez *et al.*,[27] increasing age in this study had no correlation with hypogonadism. This might be affected by the range of age (34–44 years) in our study which was narrower than the range of age (25–68 years) in the study of Moreno-Pérez *et al.*[27]

The AMS questionnaire used in the present study was not helpful for hypogonadism diagnosis because there was no correlation between hypogonadism and positive hypogonadism symptoms. Furthermore, this questionnaire yielded quite low sensitivity (78.0%) and low specificity (29.1%) that was comparable with the finding of Moreno-Pérez *et al.*[27] which showed quite low sensitivity (66.7%) and low specificity (37.7%). These findings suggest that the AMS questionnaire can only be used as a self-evaluation screening questionnaire but not diagnostic test for hypogonadism in HIV-infected men. Even in the general population, the AMS questionnaire is not recommended for making the diagnosis of hypogonadism due to its low specificity.

There was no correlation between hypogonadism and ED in the present study; this is similar to other studies in the HAART era.[19,20] Crum *et al.*[19] found increasing age to be a significant predictor of both ED and hypogonadism. These results suggest a non-hormonal aetiology of ED in HIV-infected men. On the one hand, ED is not very useful as a sign of hypogonadism in the setting of HIV-infected men whose symptoms are different from those of HIV-negative men. On the other hand, ED is frequent in HIV-infected men due to other factors that are different from hypogonadism. In addition, depression was also evaluated in this study and we found that it had no correlation with hypogonadism, similar to a previous study.[19]

The present study has a number of limitations. Firstly, the study was an observational cross-sectional descriptive study so the authors could only observe the prevalence and temporally associated factors. Approximately 35% of persons with hypogonadism in this study had an increased SHBG level, suggesting that other mechanisms such as DM, hypertension, methadone use and lack of ART may be at play. Further prospective analytical study is required for determination of the potential pathogenesis of hypogonadism among HIV-infected men. More analytical or experimental studies are also warranted for determination of therapeutic or adverse effects of testosterone supplementation. Secondly, the present study collected just single serum samples of cFT without assessment of luteinizing hormone (LH), prolactin and follicle stimulating hormone (FSH). The lack of results on serum gonadotropins limited the ability of our study to establish the cause of hypogonadism. ISSAM recommends that if testosterone levels are at the lower limit of or below the accepted normal values, it is sensible to confirm the results with a second serum sample together with prolactin, FSH and LH. Thirdly, signs and symptoms related to hypogonadism and testicular pathology were assessed by different physicians and the reports were returned to the authors. This might limit the strength of the results. Fourthly, The AMS questionnaire was developed to assess severity of symptoms of hypogonadism in ageing men. The questionnaires used were not validated for young/middle-aged men. This limitation might account for underestimating the signs and symptoms of hypogonadism in this study. Fifthly, this study used the SHIM questionnaire because it has been proved to possess favourable statistical properties in diagnosing the presence and severity of ED in many prevalence and intervention studies.[29] It is a convenient and reliable tool to rapidly identify patients with ED who should be further assessed. This might limit the strength of the results. The original 15-item version of the IIEF was developed for use in determining efficacy of treatment in controlled clinical trials. The IIEF-15 has high sensitivity for detecting real treatment effects and has been adopted as the gold standard treatment outcome measure for clinical trials in ED.[29] Finally, the present study could not accurately determine the free testosterone level by the equilibrium dialysis method, which is the ideal method,[14] because it is not available in a laboratory in Thailand and is very costly.

However, the present study had several benefits. Firstly, the optimum sample size by statistical calculation enabled accurate determination of the prevalence of hypogonadism in HIV-infected Thai men. Secondly, the authors diagnosed hypogonadism by using cFT level that is more accepted by the ISSAM than using the total testosterone level.[14] Thirdly, widely available information technology, the authors demonstrated the procedure to obtain the cFT for diagnosis of hypogonadism in a way that was practical for most Thai provincial hospitals. Finally, the authors did not request for free testosterone level determination by the equilibrium dialysis method from abroad but instead opted for the use of the cFT level for identification of hypogonadism due to its cost-effectiveness. In the USA, the costs of measuring and reporting free testosterone level by equilibrium dialysis, cFT level and total testosterone level are estimated at $30.58, $5.93 and $3, respectively.[30] However, the costs are proportionately much higher in Thailand (cFT level measurement costs $20 and total testosterone level measurement costs $10).

In conclusion, the prevalence of hypogonadism among HIV-infected Thai men in the present study was comparable to other HAART era studies[3,5,6,19,20] but still remained higher than the average prevalence for men in general. The only important significant risk factor for hypogonadism was a SHBG level >70 nmol/L, indicating a high tendency towards with hypogonadism. As a result, the authors recommend the use of cFT for the diagnosis of hypogonadism in HIV-infected Thai men.

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